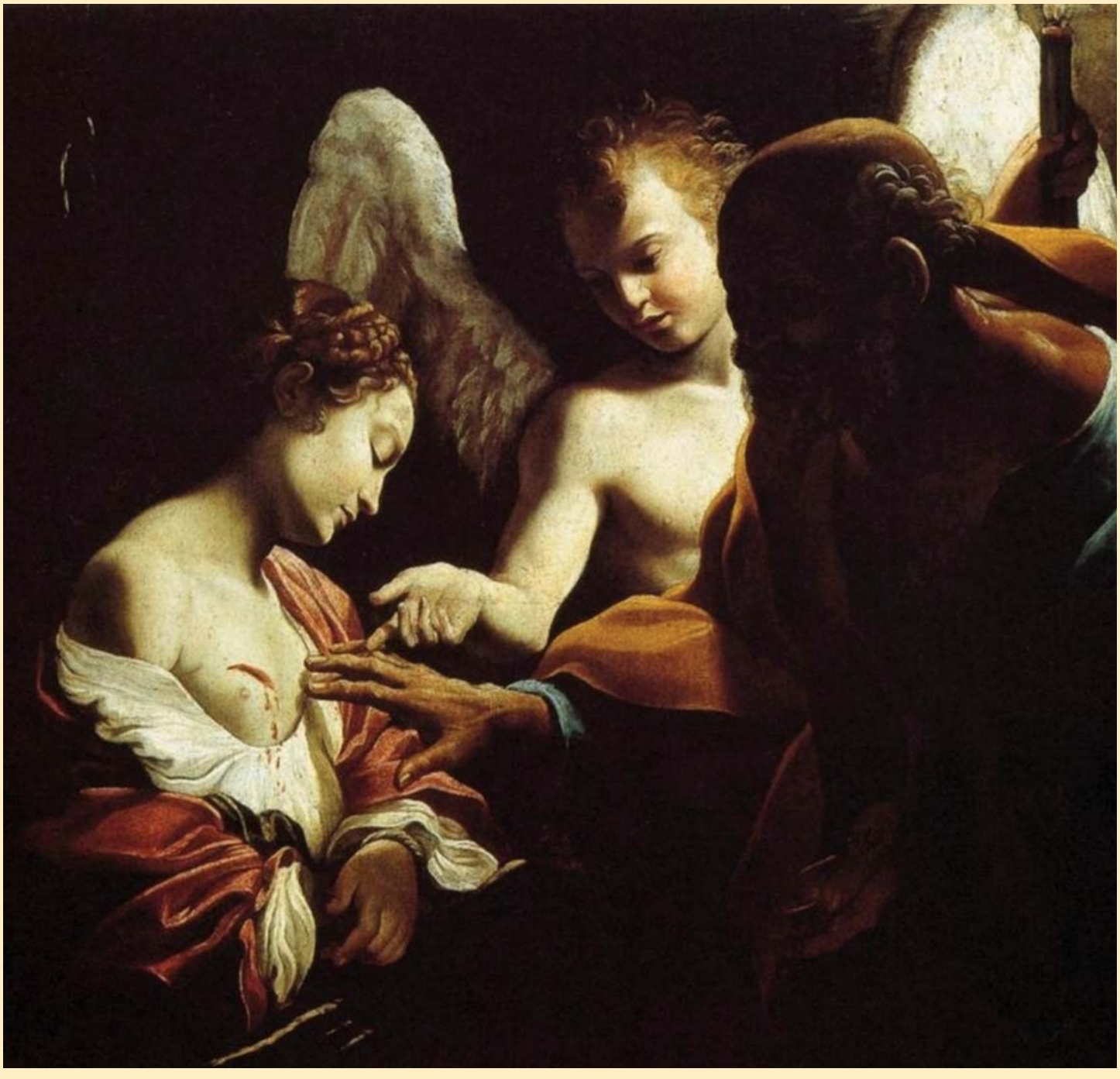
IRE

ISTITUTO NAZIONALE TUMORI

REGINA ELENA

ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO



Scientific Report 2012/2013

In copertina:
Giovanni Lanfranco (1582-1647)
Sant'Agata in carcere curata da San Pietro

IRE
ISTITUTO NAZIONALE TUMORI
REGINA ELENA
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SCIENTIFIC REPORT 2012-2013

Contents

Special Commissioner

Valerio Fabio Alberti

The Regina Elena National Cancer Institute has a long-standing history in the diagnosis and treatment of oncological diseases, as well as being a pioneer in cancer prevention, diagnosis and treatment.
Our innovative research activities are focused on improving all the most up-to-date strategies for the management of cancer patients as well as exploring novel and cutting edge methodologies. We are thus committed to implementing multidisciplinary groups made up of different medical specialists in order to give patients the best treatment care plans available.
This type of multidisciplinary approach favours professional adherence to the current national and international diagnostic and therapeutic guidelines. The professional skills, facilities and resources offered at the Institute are used to define the guidelines and disciplines applied in medical practice nationwide. Each study group consists of a team of medical professionals from across different disciplines.
Disease management teams (DMTs) that have been created at the Institute, are multi-disciplinary study groups each devoted to neoplastic diseases from different origins. This kind of specialized approach not only fosters and cultivates the functional activity of clinical research, but also improves the quality of patient-care services.

These teams meet weekly to discuss all the new emerging cases as well as the more complex ones that require further attention. DMT outputs constitute an integral part of the patient medical records.
An inter-departmental organization system such as this one, promotes a multi-disciplinary approach (more skills combined, in different diagnostic and therapeutic sectors), ultimately resulting in benefitting patients by optimizing and integrating prevention, early diagnosis and treatment.
In 2013, Translational Groups (TG) were established. TGs aim to encourage a combination of multidisciplinary and synergistic clinical research applications, with the aim to make a swift transition from experimental data to clinical management. TGs provide a support system network for the Scientific Office in the strategic decision making process.
To date, six TGs have been activated, i.e. those concerning ovary, gastrointestinal tract, lung and urological cancers (kidney and prostate), as well as sarcomas and brain tumors.
As Special Commissioner of IFO (Istituti Fisioterapici Ospitalieri), which comprises the Regina Elena National Cancer Institute, it is very important for me to introduce this 2012-2013 Clinical-Scientific Report, because it represents a vital milestone in its history as an IRCCS (Comprehensive Cancer Center) since its

foundation in 1939. Given that many things have changed since then, the Institute still maintains a central role in cancer research and therapy on a national and international scale.
Indeed, the Institute is now going through a major turning point, and several changes are occurring. These include the establishment and inauguration of the new research laboratories, now equipped with the most advanced technology and resource tools. Thus, all research activities will be soon carried out in these brand-new labs, which will now host all the research groups of our Institution, (previously located on another building site), in the central location of Mostacciano, Rome, where all the clinical activities and part of the research laboratories are already situated.

The Health Medical Office is working very closely with the Scientific Office of the Institute, in order to review the current research organization and propose the creation of a new system aimed at enhancing the scientific division.
This clearly means that our Institute will be able to significantly improve translational research pathways through the optimization of the spaces and resources available, regardless of the ongoing regional plan of the cost-cutting review, not only favouring clinical research, but also patient care. As a result, patients will receive more efficient and focused innovative cancer management, including personalized therapies at the single-patient level.

IRE Scientific Director

Ruggero De Maria

Scientific Direction Secretariat: Pina Gioffré Carmela Matrascia, Tania Merlino, Catia Minutiello
Grant Office: Maria Guttinger, Fabrizio Marcucci, Barbara Matrascia
Clinical Trial Office: Federica Falcioni
Transfer Office: Letizia Ciancio
Administrative Research Office: Anna Maria Bianchi, Piera Brugnoli, Giovanni Cavallotti, Maria Vittoria Greco, Silvia Malvezzi, Doriana Salvati Federica Struglia, Armando Vitolo
Library: Gaetana Cognetti, Manuela Dimiziani, Fabio D'Orsogna, Francesca Servoli, Domenico Verbicaro
Scientific Art Work: Mauro Di Giovanni, Ivana Zardin
Informatic Support: Marco Canfora, Mario Carbone
Statistic Unit: Diana Giannarelli, Francesca Sperati, Isabella Sperduti, Irene Terrenato

Our institute is presently employing:	
MD and PhD (Faculty)	232
PhD Students and Post-Docs	107
Technicians	86
Administrative personnel	48

Since November 2011, the Scientific Directorate is conveying the activity of the institute on the topic of the translational medicine, with greater attention toward personalized medicine. The aim is to improve the performances of the clinical activity through innovative molecular approaches.

In contrast with the economic crisis known to involve the National Health System, our Institute is strongly investing in cutting edge research activities to support the patient with the added value of the translational research. This will allow a swift transition from laboratory data to preclinical experimentation, which is then translated to clinical applications. Such a conversion required an exceptional effort to reorganize the institutional research activities, improve the use of available resources and overall productivity.

From a scientific point of view, the foremost goals of the Scientific Director, employing state-of-the-art molecular high-throughput technologies, are the establishment of new taxonomic procedures for tumors, thus implementing agreed systems for patient diagnosis, prognosis and the identification of new specific therapeutic targets. This will safely accompany the patient along the road of personalized medicine. To this end, the Scientific Director has identified four research areas to be fostered in the years 2014-2016.

Domain 1: Molecular and cellular bases for translational research in oncology. These activities include 27 projects.

Domain 2: Innovative approaches for the diagnostic and prognostic staging of oncologic patients. These activities include 17 projects.

Domain 3: Innovative cancer treatments. These activities include 31 projects.

Domain 4: Primary and secondary prevention and quality of life. These activities include 15 projects.

In the same context, in 2013 the Scientific Director has established also 6 Translational Groups (TG) with the objective to promote the synergy between basic and clinical research, thereby allowing an efficient translation of the novel knowledge in the clinical setting. The TG staff members had been invited to submit research projects that have been examined by external experts. The funded research projects are the following:

Lung Cancer TG program. Identification of novel genomic alterations in smoking-related NSCLC by analyzing tumor and stromal-associated cells.

Colorectal Cancer TG program. Exploiting next-generation sequencing and loss-of-function genetic screens for discovering novel molecular predictors and therapeutic targets in colorectal cancer.

Neuro-Oncology TG program. Biomolecular characterization and advanced imaging modalities in the diagnosis of brain gliomas: validation of prognostic and predictive factors.

Ovarian Cancer TG program. Exploring biomarkers and pathways driving disease outcome in high-grade serous ovarian carcinoma.

Sarcoma TG program. Identification of prognostic factors and definition of predictive drug response elements in selected sarcoma patients.

Urologic Cancer TG program. New tools for individual risk assessment and treatment assignment in prostate cancer patients; evaluation of in vitro/in vivo-drug sensitivity and phosphoproteomic expression profiles in renal cancer patients: stem cells models and

new molecular biomarkers for personalized therapy.
In support of the activities of all the TGs, after the approval of the Ethical Committee, a database is being created for the management for statistical purposes of all the patient data. The final goal is the intra- and inter-departmental sharing of the clinical and biological traits for each patient. In the next future, the database will be shared with related Italian institutions.
During the years 2012-2013, most of the scientists have been relocated from the CRS campus to laboratories in the headquarters of Mostacciano. This is quite a fundamental achievement, because, after almost 30 years of physical separation between the experimental laboratories and the clinical departments, these vital branches of the Institute are now gathered in the same place, with enormous advantages for all the translational research activities.
Concerning the scientific achievements, the scientific productivity of our institute has significantly increased over the year 2013. The overall, normalized impact factor of the peer-reviewed scientific publications has increased by 20% compared to 2012 and has now attained 1,000.2 points, and the estimates for 2014 confirm such a positive trend. A noticeable contribution to this success has come from the translational activities and the increase of the multicenter clinical studies. Regarding the citations of articles from our Institute, these have been well over 8,000 in 2013.
During this year, there has been the establishment of the HPV Unit, which comprises a task of experts devoted to the management of any Human Papillomavirus-related diseases, from infection to dysplasia and, finally, cancer. The emerging role of HPV in pathologies other than those involving the female genital tract is kept in great consideration. In this perspective, all the services offered by the Unit, in the context of the Public Health System, provide also an opportunity to promote appropriate interventions and reduce disparities across the population in terms of prevention, diagnosis and therapy of HPV-related diseases.
As to the funding raised in 2013, IRE scientists have been granted 8 new projects funded by the AIRC (Italian Association for Cancer Research), which, together with those awarded in previous years and still ongoing, sum now up to 3.1 million Euro. AIRC funds also a limited number of projects within the "Special Program Molecular Oncology", dedicated to the identification of new diagnostic and therapeutic tools in oncology.
The Scientific Director has been appointed since 2010 as the director and coordinator of a five-year project entitled "Development of effective cancer therapies based on functional proteomics and cancer stem cell targeting", which includes ten research groups over the entire national territory. The funding for IRE is 1.4 million Euro/year and foresees activities aimed at identifying new therapies for colon and lung cancer. The Ministry of Health has funded also for 800,000 Euro a project entitled "Bioimaging at high and advanced technology using SPECT and SPECT-CT aiming at the morpho-functional identification of the pathologies through a patient dose reduction and optimization".
Within the ERANET program, IRE has been funded also 125,000 Euro by the Ministry of Health for its participation to the TRANSCAN project.

Research perspectives

The new Scientific Director, since its inception in Novembre 2011, began several activities that are aimed at improving the quality and overall productivity of preclinical and clinical research at IRE
One initiative has been to encourage young scientists to participate at invitations to tender of the Italian government for scientists

aged less than 40, and to guarantee to the winners a research contract. This activity has allowed to increase the number of young group leaders at IRE. This is a fundamental opportunity to boost up the whole research scenario at IRE, because of the natural capability of young people to generate enthusiasm and produce innovation.

Efforts have also been done to improve the technological platforms. For this purpose, a unit for the analysis of cellular metabolism has been established. Moreover, several scientific instruments have been acquired using the overheads from the applied research and some of the grants to projects of the Scientific Director. IRE has entered a collaborative agreement with the Department of Hematology, Oncology and Molecular Medicine of the Italian Institute of Health, which has available some highly innovative facilities such as a biobank for cancer stem cells, high-content imaging, reverse-phase proteomic analysis (RPPA), Mass Cytometry, and fluorescence-activated cell sorting.

Regarding the laboratories and animal facilities, the plan is to centralize all IRE laboratories at the headquarters . Moreover, a biobank of tumor tissue samples will be established. Another project bears on the building of a new animal facility. Fundings for the acquisition of the instrumentation necessary for the animal facilities and imaging in preclinical models have been already obtained.

The activity of the TGs will be supported by four technical-scientific units that have been established *ad hoc*. In the following a brief summary of the activities and mission of these units

- Oncogenomics and epigenomics. This unit will have available the most advanced technologies in genomics, transcriptomics and epigenomics. These technologies are expected to represent a fundamental support for the oncological therapies of the future. The activities of this structure will be in support of research and molecular diagnostics. The latter application should allow IRE to gain a leadership in oncological diagnostics at the regional level.
- Tumor immunology and immunotherapy. In recent year, immune checkpoint inhibitors have proven to be a formidable weapon to improve the cytotoxic activity against tumors. The creation of a technical-scientific structure in the immunological domain will allow the scientists and clinicians at IRE to have a reliable reference in order to fully exploit the innovations introduced by immunologically active molecules. This structure should also take care of immunological monitoring in support of the immunotherapy.
- Molecular networks, cellular metabolism and new therapeutic agents. The molecular pathways that can be targeted with personalized oncological therapies are constituted of oncogenic signals, as well as biochemical and metabolic events that derive from genetic and epigenetic alteration that characterize tumor cells. The structure active in this domain should support scientists in promoting research projects that should end up in investigator-driven clinical trials. It should also support scientists involved in the development of new biomarkers and therapeutic agents
- Preclinical oncology models. These models represent the core for the preclinical development of novel therapies. It has been shown that the use of primary cancer stem cells and transplants of patient-derived fresh tumor tissues is able to reproduce quite reliably the patient tumor in models currently referred to as Avatar. Therefore, the availability of a collection of cells and tissues able to produce Avatar could allow to mimick clinical trials

in the laboratory and foster the planning of investigator-driven clinical trials.

Also an unit for biostatistics and bioinformatics has been created. This unit includes 4 biostatisticians, 1 bioinformatician and 2 coders. This unit now represents a key support for scientists and clinicians at IRE since it is in charge of the biostatistical and bioinformatical supervision at IRE, and also of the creation and implementations of databases of those patients for whom biological samples are available. This database will play a key role in the translational and clinical research at IRE.

In order to foster personalized medicine at IRE, the Scientific Directorate has bought an instrument for Next Generation Sequencing (NGS) and has started several projects on the use of NGS in the diagnosis, preclinical and clinical research. A low-cost NGS panel for the identification of mutations in colon cancer has been set up and a similar project has been started for lung cancer. The Scientific Director, who is also president of the Italian Alliance Against Cancer has also started a national program in order to create preclinical synergies with the other Italian cancer institutes that belong to the IRCCS network.

A final goal is to improve the quality of the personnel working at IRE. For this purpose, several activities are foreseen. Thus, it is planned to increase the number of Group Leaders in order to foster the translational research at IRE. In order to make IRE more attractive for external scientists, it is intended to improve the efficiency of the research administration and renew the laboratory equipment. Regarding PhD students and Postdoctoral fellows, it is planned to establish new rules for their education and training. In general, it is intended to avoid the "inbreeding" phenomenon, i.e. a training limited to a single laboratory, while it is encouraged the recruitment of competitive trainees from external intitutions.

Scientific and Technical Board

President
Prof. Ruggero De Maria

Members
Prof. Francesco Cognetti
Dr. Francesco Facciolo
Prof. Cinzia Marchese
Prof. Edoardo Pescarmona
Dr. Silvia Soddu
Prof. Mario Stefanini
Prof. Maria Rosaria Torrisi

Library

Digital Library - Knowledge Center "R. Maceratini" (BDCC-IRE) and Patient Library (BP-IRE)

Gaetana Cognetti

Head

STAFF

Librarians: Fabio D'Orsogna
Administrative Staff: Francesca Servoli, Domenico Verbicaro
Trainees: 2012: Antonio Lucon, Laura Grossi; 2013: Francesca Berardi, Angela Gagliarde, Sara Tonarelli

Activities 2012-13

The library of the Regina Elena Cancer Institute provides support to the clinical research activities of the Institute by offering scientific information and documentation. The aim of the Library is to guarantee easy access to the latest scientific material. Apart from acting as a library, it is also a Knowledge Centre which facilitates access to relevant documentation in order to favour clinical practices and patients' choices. The library offers its services to the medical staff, patients and their relatives.

The Knowledge Centre aims to contribute to computerised institutional information systems promoting the exchange of data across different professional areas. The library is easy to find. It is situated near the main entrance of the Institute and offers a multimedia room equipped with 15 computers. A special room, known as the patient library, is located within the library from 2005. It provides information through our professional staff members using the most up-to-date health-care databases and quality websites.

In 2012-2013, the Digital Library registered about 700 members. Obviously, most services can be obtained on-line through purchasing and organising electronic resources (e.g. scientific periodicals), which are directly accessible from the workstation of each single researcher.

The main activities of the library consists in the management of monographs, periodicals and databases (inventory, cataloguing, collection management) following international standards and guidelines; updating union catalogues; managing reference desk also through the personalized service called "Book a librarian" that is a tailored course on demand by the users (n. 30 meetings in 2012 and n. 26 in 2013); consulting the main biomedical databases**;** document delivery through an interlibrary exchange system, called NILDE; organising training courses; study and research on the problems of biomedical information.

The library also organizes the institutional repositories for the publications produced by the Regina Elena National Cancer Institute.

Patient Library

The Patient Library offers information through the latest and most up-to-date health-care databases and quality websites. It also offers a multimedia room with Internet connection and a library room for recreational reading.

In 2012 alone, 150 patients and/or family members asked for information (42 bibliographic research and about 800 information booklets delivered). In 2013, 80 patients sought information (10 bibliographic research and about 100 information booklets delivered). Activity decreased during the periods in which the national civil service volunteers who cooperate with the Patient Library were not assigned. The Patient Library remained without volunteers from January to June 2012 and from June 2013 to March 2014.

Library Holdings

The library contains 8.000 monographs and approximately 1.000 periodical titles in print. In 2012 and 2013, electronic packages for around 6.000 periodicals and important databases were purchased such as Scopus, Web of Science, Journal Citation Reports, Best-Practice, Cochrane Library, Faculty 1000, Biology Image Library thanks also to the Bibliosan network.

All library activities have been automated thanks to the use of electronic systems, which are available for free on line through the voluntary or institutional cooperation of the libraries present throughout Italy. In particular, the IRE clinical library participates in:

1. National Library Service (SBN) The Library's books are catalogued following the MeSH (Medical Subject Headings) and the National Library of Medicine (NLM) Classification. About 2.000 volumes are catalogued by the Library in the SBN to date;
2. Network Inter-Library Document Exchange (NILDE) document delivery service for exchanging scientific articles. NILDE automated system is available on the WEB, managing requests on-line (year 2012: total materials borrowed 575; total materials lent 415; year 2013: total materials borrowed 558; total materials lent 361);
3. National Union Catalogue of Periodicals (ACNP) for cataloguing and managing (Techlib software) periodicals on the web;
4. Library Network of Biomedical Research Institutes (Bibliosan) purchases electronic periodicals, medical databases and other electronic information systems and software making them available to the research library networks, and promoting the free exchange of scientific articles between research libraries of the National Healthcare Service;

Vocational training courses and Meetings

The Digital Library organised training and ECM courses in 2012/13. The library staff was involved in teaching and tutoring all the courses. Since 2011, the Library has organised weekly meetings for professionals updating them on the latest electronic information tools, entitled "Documentation Pills" (Pillole di documentazione).

In 2012, the Library organized 21 brief weekly meetings (77 participants), a course for nurse students attending the Nursing school at "La Sapienza" University (66 participants) and a course for the AMSO volunteers (80 participants). In 2013, the Library also organized 5 ECM courses, where each course offered 20.4 credits (total participants: 113), courses for students of the Nursing School - La Sapienza University (66 participants) and courses for AMSO volunteers (80 participants).

Scientific research activities 2012-2013

The activities of the Library involve research activities, meetings and publications regarding health-care information and the use of new technologies. In 2011, the Library took part in a National project called "InformaCancro" which was dedicated to patients. It was coordinated by the Federation of Cancer Volunteer Associations (F.A.V.O.) and "Information as first medicine" ("L'informazione come prima medicina"), coordinated by the National Health Institute. In the past, the Library coordinated some national research projects granted by the Ministry of Health these included: Azalea, data base for patient and their relatives, and National information system for oncology communication to patients (SICOP).

Future trends

- Develop the European Licence "*ECDL HealthDoc"* a certificate certifying skills in the field of biomedical documentation in collaboration with AICA (Associazione Italiana per l'Informatica ed il Calcolo Automatico),;
- Develop Interdisciplinary ECM courses;
- Develop the role of the "adviser" or "clinical librarian", providing evidence-based answers to the clinical questions;
- Produce the book entitled "book crossing" for patients who began their medical course in 2012 and expand the use of ANOBII in order to manage the recreational activities of the Library;
- Develop the use of Web 2.0 tools for improving communication with the users (researchers and patients);
- Producing a Web site integrating information on several diseases of cancer for lay people and healthcare personnel;
- Developing the institutional archives.

Publications 2012-2013

Della Seta M, Cognetti G, Napolitani F, Trends in biomedical libraries of the National Health Service (NHS) in Italy. In: International perspectives and initiatives, *Health Information and Libraries Journal* 2012, 29(4): 338-43

Cognetti G. Il grano e il loglio: viaggio nell'informazione sulla salute in internet per i cittadini. Roma, SEU, 2012

Cognetti G, Tra informatica medica e telemedicina: la gestione delle conoscenze nell'universo della documentazione. In: Dall'informatica medica alla sanità elettronica: lezioni dal passato e prospettive per il futuro, a cura di Fabrizio L. Ricci, Domenico M. Pisanelli e Francesco Sicurello. Roma, Edisef, 2012: 61-74

Poltronieri E, Bravo E, Camerini T, Ferri M, Rizzo R, Solimini R, Cognetti G, Where on earth to publish? A sample survey comparing traditional and open access publishing in the oncological field. *Journal of Experimental & Clinical Cancer Research*. 2013, 32(1):4

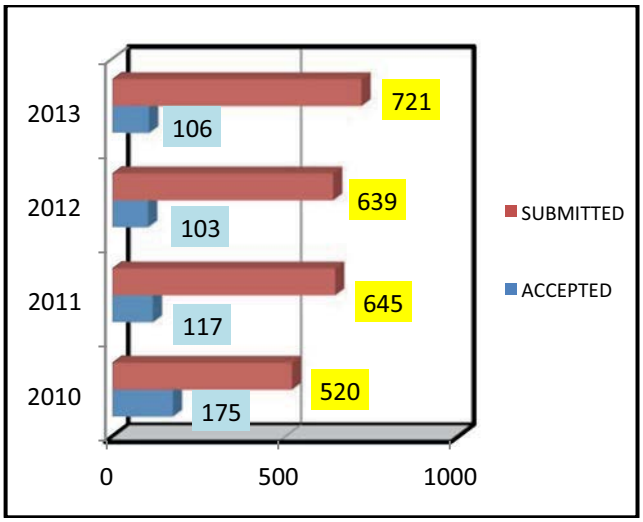
Journal of Experimental & Clinical Cancer Research

Mauro Castelli, PhD

Editor-in-Chief

The Journal of Experimental & Clinical Cancer Research (JECCR), the official scientific journal of the "Regina Elena" National Cancer Institute in Rome, Italy, has continued its publishing activity with the support, of the publisher BioMed Central since 2008.
Our greatest achievement accomplished in this period was increasing the Institute's Impact Factor (I.F.) from an index of 1.1 in 2008 to 3.07 in 2012. Consequently, this optimal result attracted great interest from the international scientific community toward the Journal of Experimental & Clinical Cancer Research, significantly improving the number and quality of submitted manuscripts.
Despite the number of submitted manuscripts drastically increasing in the period from 2010 to 2013, from 520 to 721, the number of accepted manuscripts did not rise. Furthermore, the JECCR maintained an invariable average time of accepting submitted papers (about 80 days).
The software application Google Analytics has been used since 2011 to obtain deeper insight into our website trafficking and monitoring regarding the topics of interest of the international scientific community on the research we have published.
Our goal for the future is to increase areas still under-represented in our publications in JECCR.
In 2013, 721 manuscripts were submitted for publication, with 106 being accepted by referees. Their place of origin was Europe (30%), Asia-Pacific (55%), and USA-America (15%).

Year	*Impact Factor* (IF)
2012	**3,066**
2011	2,148
2010	1,921
2009	1,274
2008	1,184



A monthly report from Google Analytics for JECCR

Visits by Country/Territory

Country Territory	Visits
United States	**2,903**
China	**1,904**
India	**932**
Italy	**903**
United Kingdom	**824**
Japan	**633**
South Korea	**478**
Germany	**419**
Canada	**391**
Taiwan	**315**

Board of Governors

Decrees sanctioned by the President of the Lazio Region n. T00238 8.08.2013, n. T00368 20.11.2013 and approval from Health Minister (Prot. 8474 24.10.2013), active since december 2013 (IFO decree n.959 5.12.2013)

President
Prof. Paolo Marchetti

Members
Dr. Tommaso Antonucci
Prof. Angela Santoni
Dr. Roberto Scrivo
Prof. Maria Rosaria Torrisi

Press Office

Lorella Salce

Chief Press Officer

STAFF: Simona Barbato, Francesco Bianchini, Daniela Renna

PRESS OFFICE ACTIVITIES

- Communication strategies and planning
- Corporate identity and brand communication;
- Public Relation
- Media relations management: press releases, press conferences;
- Website: managing content, updating press section and news;
- Managing TV, radio and press interviews;
- New media communication (Facebook, Twitter, Youtube);
- Digital press review

ANNUAL ACTIVITIES REPORT

Press releases 2012	24
Press releases 2013	22
Agency launches 2012	118
Agency launches 2013	100
Mass media presences 2012	600
Mass media presences 2013	685
News items 2012	500
News items 2013	520
Facebook	840 post; 1 million views
Youtube	110.000 views; 245.000 minutes watched
Twitter	1000 tweet; 180 mentions; 140 retweets

HONORS & AWARDS

- "5 x1000 video campaign" won prestigious award: "La PA che si vede" (2012)
- Second edition of the O.Ma.R. Journalis Award devoted to rare diseases and rare cancers held (2013)

Ethics Committee

As from December 2013

Chairman
Prof. Francesco D'Agostino
Expert in Bioethics

Vice Chairman
Prof. Agata Amato Mangiameli
Expert in Legal Matters

Secretary
Anna D'Ambrosio

Secretariat
Diana Giannarelli, Maria Cecilia Ciacchella

Members

Bioethics: Dr. Emira Aloe Spiriti
Clinicians: Dr. Enzo Maria Ruggeri, Prof. Stefano Bonini, Prof. Ketty Peris, Prof. Daniele Santini
General Medicine: Dr. Mario Falconi
Pedritician: Dr. Raffaele Cozza
Biostatistics: Prof. Annarita Vestri
Pharmacologist: Prof. Lucia Negri
Pharmacists: Dr.ssa Antonia Marina la Malfa, Dr.ssa Silvia Murachelli, Dr.ssa Nicoletta Onori
Genetist: Prof. Giovanni Neri
Volonteer Representative: Elisabetta Iannelli, Lawyer
Health Areas Representative : Dr. Laura Iacorossi
IRE Scientific Director: Prof. Ruggero De Maria
ISG Scientific Director: Prof. Aldo Di Carlo
IFO Chief Medical Officer: Dr. Marina Cerimele
Bietti Foud. Scientific Director: Dr. Monica Varano
Bietti Foud. Chief Medical Officer: Dr. Angela Mastromatteo
Clinical Engineer: Dr. Raoul Paolini
Nutrition Expert: Prof. Marcello Ticca
Veterinarian: Dr. Maria Guttinger

During years 2012-2013 the Central Ethics Commitee IRCCS Lazio examined and expressed its opinion on 257 studies including clinical trial protocols, observational studies and research projects.
Relatively to these items the ethics committee analyzed ethical and scientific aspects, the adequacy of the investigators and the structures involved and, above all, the methods and documents to be used to inform patients and obtain their informed consent.
The Ethics Committee meetings are held monthly and, if necessary and urgent, the opinion of their members on a particular case such as the use of drugs not commercially available is obtained by mail.

General IFO Medical Office

Marina Cerimele, MD

Chief Medical Officer

Activities 2012-13

Objectives:

- Defining specific pathways for the assistance of cancer patients, a necessary condition for a "Good Quality Assistance" that foresees the taking in charge of the cancer patient during all phases of the disease, as well as the full integration of surgical and medical therapies, radiotherapy and nuclear medicine.
- Promoting an appropriate use of the Day hospital.
- Expanding surgical activities in the Day Surgery, through the strengthening of the existing routine surgery in favor of categories A and B.
- Starting the activities that aim at the functional recovery of cancer patients that have ridden out the acute phase, but who need further diagnostic and intensive therapeutic interventions that are not easily deliverable in alternative recovery regimens.

The clinical healthcare program in 2012-13 was based on the reformulation of the healthcare services in accordance with the national and regional guidelines. It aimed at further improving the appropriateness of the healthcare services, encouraging 'virtuous' organizational models both as regards the patient care as well as a more rationale use of the resources.
In fact, it appears obvious that the sustainability of the system is directly linked to actions aiming at the recovery of efficiency in the delivery of the services: appropriateness as guiding principle within the system in order to deliver to the patient the best possible cures using the "right" resources; retraining the hospital assistance through the transfer of part of the activities related to the ordinary recovery to more appropriate ways of delivery, and towards regimes that allow a greater efficiency in the use of the resources, from ordinary recovery towards the day hospital e from the latter towards the practice. The use of Day Service has been significantly increased (Ambulatory Health–Care Service Packages CAP together with Ambulatory Service Performance APA) through the introduction of new Diagnostic packages.

The activities carried out during 2013 were supported by procedures implementing a centralized integrated patient record database system with the main softwares used by the institutes, the Galileo-ADT procedure (Admission-Discharge and Transfer) in the patient wards, the Computerized Medical Record in the Oncology A department and a database for managing interventions in the Operating Block that has replaced paper records.

Moreover, a systematic clinical audit process has been started in collaboration with the heads of the hospital wards, representatives of the SIO department, the Medical Health Service Directorate, the SIO and the Medical Health Department Offices. The goal is to assess the activities and the problems that have emerged during the ASL health inspections.

In spite of an effective control and rationalization of healthcare and pharmaceutical hospitale spending an, this remains a major issue in the financial balance statement of our Institutes that is difficult to reduce further in view of the mission of our two institutes.

General IFO Medical Offices

Unit of Epidemiology

Valerio Ramazzotti, MD
Maria Cecilia Cercato, MD

Activities 2012-13

Public Health In Cancer

POPULATION-BASED CANCER REGISTRY The main activity was the collaboration with the Population Based Cancer Registry of the Latina Province and the Italian Network of Cancer Registries (AIRTUM) in order to estimate the occurrence of cancer in Italy. Cancer incidence, mortality, survival and prevalence are available for a relevant coverage of the Italian population. In 2013 a further indicator was estimated: the occurrence of multiple tumours, i.e. the risk of developing a second cancer in subjects who have already had a previous cancer diagnosis in comparison with the general population.
The results in a cohort of 1.635,060 cancer patients diagnosed between 1976 and 2010 pointed out an overall increased risk of about 10%.

SKIN CANCER PREVENTION PROGRAM IN SCHOOL-AGE CHILDREN Skin Cancer Prevention Program for children in the pre-school and primary-school setting has been carried out by the Department of Epidemiology since 1997, first in Italy and then in several foreign Countries (Belgium, Spain, Hungary, Bulgaria, Tunisia, Russia). Over 180,000 children and their parents were surveyed employing a self-administered questionnaire investigating sun sensitivity characteristics and sun protection practices. The analysis of data collected during more than 15 years of activity allowed us to: a) process and send personalized sun-protection guidelines to all the children involved, in cooperation with the Dermatologists of the "Santa Maria e San Gallicano" Institute; b) describe the prevalence of skin cancer risks factors in a huge sample of children from a wide variety of ethnic and cultural populations; c) explore predictors of sunburns and determinants of sun-protection behaviour.
An educational intervention was conducted in Valencia, Spain through a self-administered basal and post- intervention questionnaire. The aim of the study was to investigate "knowledge" about the risks related to sun exposure, "attitude" towards sun protection, and sun protection behaviour in parents and in their school-age children. The results showed that despite a high level of parents' knowledge, sun protection in children is still not adequate, and sunburns are not uncommon. Unfavourable beliefs and attitudes emerged pointing out the barriers that need to be overcome to achieve sun-safe exposure in children.

Evaluative Epidemiology

REGIONAL OUTCOME EVALUATION PROGRAM (P.Re.Val.E) The Epidemiology Department was the reference unit for the internal audit of IFO in the framework of the P.Re.Val.E. Project carried out in the Lazio Region. The main objectives of this project are as follows: observational assessment of the "theoretical" efficacy of health-care interventions that cannot be or have not been assessed in experimental studies (RCTs); observational assessment of the "operative" efficacy (effectiveness) of the health-care interventions whose theoretical efficacy has already been assessed in experimental studies; comparative assessment of different health-care providers and/or professionals; comparative analysis of different population subgroups (i.e., those defined by socioeconomic level, residence, etc.); identification of factors within the health-care delivery process that affect outcomes; internal and external auditing; monitoring levels of care.
Further activities were:
Collaborative Department in the HPV Unit-IFO
Members of the Comitato Infezioni Ospedaliere - IFO

Narrative Medicine in the multidisciplinary *"Narrative Biomedicine Working Group".*
Teaching activities - IFO in: Bachelor in Nursing, training courses for health professionals.

Publications 2012-2013

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General IFO Medical Offices

Unit of Pharmacovigilance and AIFA Registers Service

Felice Musicco, Pharmacist

STAFF Pharmacist: Elisa Marchesini,
Elisabetta Umana

Activities 2012-13

Pharmacovigilance activities

-Supporting and promoting reports of suspected drug adverse reactions (ADR); periodical visits to clinical wards to meet doctors, nurses, technicians, etc.

-Monitoring the safety of medicine: collect, assess, report, and analyze adverse events

-Register and update ADR reports in the National Network of Pharmacovigilance (Rete Nazionale di Farmacovigilanza RNF- AIFA):

Number of ADR reports registered in RNF:

2012: 63 ADR reports

2013: 145 ADR reports (best practice in Regional Pharmacovigilance objectives)

-Drug safety information to doctors: send drug safety email alerts published by regulatory agencies (EMA, AIFA)

-Hospital reports and guidelines:

-Report suspected adverse drug reactions that occurred in the “Istituti Fisioterapici Ospitalieri” in 2011-2012.

-Procedures for reporting adverse drug reactions in clinical trials.

Drug Reimbursement

-Monitoring drug spending (FileF) and sending monthly data to the Lazio Region by the FarmED flow.

-Reporting reimbursements data to the internal Economic Resources Service.

AIFA Drug Monitoring Registers

-Monitoring prescriptions of new, expensive anticancer drugs

-Supporting clinicians in resolving issues regarding on-line registers.

-Sending information and news to the clinicians about drugs under on-line monitoring (news drugs, indications, safety, etc.).

-Continuous updating on new conditional reimbursement systems (Pay Back, Cost Sharing, Risk Sharing, Payment by Result).

-Managing reimbursement requests and reporting to the DSA and Economic Resources Service.

Publications 2012

Solivetti FM, Elia F, Musicco F, Bonagura AC, Di Leo N, Iera J, Drudi F. Anaphylactic Shock Induced by Sulphur Hexafluoride in an Individual with no History of Heart Disease: Case Report and Literature review. *Ultraschall Med*. 2012 Aug 24

CLINICAL RESEARCH

Department of Surgical Oncology

Unit of Gastro-Intestinal and Peritoneum Surgery

Alfredo Garofalo, MD

Director

STAFF Clinical Activity Coordinator: Mario Valle
Surgeons: Fabio Carboni, Orietta Federici, Franco Graziano
Nursing Coordinator: Giovanna Grazioli
PhD Student: Tania Frixa

Activities 2012-13

Clinical Activities

In 2012-2013, 568 patients underwent surgery in our department: 166 had colorectal cancer, 54 gastric cancer, 3 esophageal carcinoma, 13 carcinoma of the pancreas, liver and bile ducts, 3 genitourinary cancer, 4 pelvectomies; 12 lymphadenectomies; 12 major resections for small bowel tumors; plus other miscellaneous major abdominal operations and reoperations. Peritoneal carcinomatosis was observed and staged in 148 patients, where 50 of them were treated with peritonectomy and Hypertermic IntraPeritoneal Chemotherapy (HIPEC).

Research Activities

Gastric cancer

The working group for the upper GI tumors definitively codified the general strategy of integrated treatment of gastric cancer. In cooperation with the Translational Oncogenomic Group our translational research showed the following results:

1a. Retrospective study with RNA microarrays on the histological samples of the operated patients in the last four years were matched with gastric cancer tissue samples obtained from a different institute of the southern part of Italy: the molecular signature of the two different series gives clearly similar bitmaps. Four microRNAs which show up or down regulation if compared with healthy tissue were individualized, particularly the microRNA 204.

Responsible researchers of the Unit: Orietta Federici, MD; Fabio Carboni, MD

1b. Biological characterization of gastric cancer with RNA microarrays inserted in a multicenter perspective European randomized trial, entitled GASTRICHIP TRIAL: D2 RADICAL RESECTION AND INTRAOPERATIVE HYPERTHERMIC CHEMOPERFUSION IN GASTRIC CARCINOMA PATIENTS AT HIGH RISK OF PERITONEAL RECURRENCE

Randomized multicenter phase III study

Registered EUDRACT n. 2009-011518-98 - Passed at the IRE CE on December 2009.

Study Center: Regina Elena National Cancer Institute (I.R.E.) - I.F.O.

Study Coordinator: A. Garofalo, MD,FACS

1.c The study on Gastric Cancer Stem Cells is based on cancer heterogeneity: functionally distinct cell types that compose the bulk of the tumor which has been conceptually correlated to the radioresistance and/or chemoresistance of many solid and non- solid tumors, the latter representing a major challenge of any current therapeutic approach. Accumulating evidence in recent years strongly indicates the existence of cancer stem cells in solid tumors of a wide variety of organs. The gastric mucosa is lined by an epithelium that is continually renewed and likely sustained by a population of multipotent stem cells.

There are two main approaches that are typically used to identify CSCs in published studies. One is an in vitro method termed “spheroid colony formation” and the other is an *in vivo* method. The former method involves culturing candidate

CSCs in culture dishes specially coated for non-cell attachment with serum-free media

containing, among the others, epidermal growth factor (EGF) and basic fibroblast growth factor(bFGF). The growth of spherical colonies after a few weeks is considered indicative of self-renewal ability, and would be consistent with a CSC phenotype. The latter method growth of cells in immunodeficient mice is needed to demonstrate true tumorigenicity and is generally regarded as a standard for proving existence of CSC. A number of studies have suggested that these two approaches generally provide similar results in evaluating candidate CSCs for many solid tumours. CSCs can be radio and chemioresistant: such a property has been ascribed to the existence of membrane transporters (ABCG2 etc), to the relative quiescence of CSCs within the tumour mass and, recently, to relative lower level of Reactive Oxygen Species within CSCs (Diehn et al, 2009). As a consequence of such properties, surviving CSCs reconstitute the bulk of the tumour, possibly triggering tumour relapse. It is therefore our aim to treat and select the enriched Gastric Cancer Stem Cell subpopulations with commonly used chemos (such as fluorouracil, paclitaxel and oxaliplatin). We predict to find a great survival rate among the gastric cancer stem cell lines derived from gastric spheres. Further analysis by gene expression profiling and microRNA profiling among chemo-selected and untreated samples would be of help to further elucidate mechanisms of chemoresistance and tumour relapse. The putative gastric stem cells were isolated from different samples, kept in culture and finally inoculated in the mouse to establish the reproducibility of the tumour.

Responsible researchers of the Unit: Orietta Federici, MD; Fabio Carboni, MD

Peritoneal Carcinomatosis

The Surgical Unit has gained extensive experience as far as Peritoneal Carcinomatosis is concerned, becoming the first group in the world to systematically apply the staging laparoscopy to all the patients observed. This allowed us to select, for the integrate treatment, only patients with an affordable Peritoneal Cancer Index, avoiding useless and dangerous laparatomies. These patients come from all over Italy and are mainly affected with peritoneal carcinomatosis, ovarian, colonic, appendiceal, and gastric tumors.

We also work together with a group from the Istituto Tumori Milano for the National Registry of Peritoneal Carcinomatosis SICO – SITILO and with Oncologists from AIOM, thus establishing a task force for the national study regarding a wide range collection of cases treated with systemic chemo or with peritonectomy + HIPEC, in order to publish the different outcomes.
Three studies that are currently ongoing are:
In vivo chemoresponsivity of peritoneal cancer cells based on microRNA assays.
Tumor polimorphic profiles in patients who had HIPEC with Cisplatin and Doxorubicin.
Modifications of tumor gene expression profiles in patients who undewent HIPEC.
Responsible Researchers of the Unit: Mario Valle, MD; Franco Graziano, MD

Minimal Invasive Techniques in Surgical Oncology
The surgical unit in recent years has dealt with mini-invasive approaches toward treating different cancers of the digestive tract: colorectal, small bowel, stomach, distal pancreas and liver (minor resections).
The procedure of videolaparoscopic staging of peritoneal carcinomatosis was developed and up to now is the most published approaches in the international literature. Moreover, the treatment of intractable neoplastic ascites with totally laparoscopic chemo hyperthermia has been widely accepted and recognized by the international scientific community and published several times (see The Cancer Journal 2009, EJSO 2009). The group has gained over 15 years of experience in advanced mini-invasive surgery in which also includes splenectomy for hematologic disease, adrenalectomy and nephrectomy.
Responsible Researchers of the Unit: Mario Valle, MD; Orietta Federici, MD

Publications 2012-2013

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Department of Surgical Oncology

Division of General Surgery "A"

Franco Di Filippo, MD

Director

STAFF MD Assistants: Michele Anzà, Claudio Botti, Pietro Lucio Bruno, Rosa Garinei, Loredana Piarulli MD, Fabio Massimo Sega MD.
Fellow: Ioanna Galanou MD
Surgery PhDs : Francesca Centanini, Elsa Iallonardi, Roberto Greco, Luigi Losco, Fabio Pelle.
Nurse Coordinator: Rossella Leonardi
Nurses: Agostino Castaldo, Monica Ceciarelli, Gianni Chiarabini, Nadia D'Antoni, Antonietta Di Ceglie, Giuseppina Gemma, Fiorella Molinari, Maria Antonietta Picano, Viviana Ruspolini, Aurelio Tirimagni.

Activities 2012-13

Clinical Activities

The activities of our department focused on 3 areas: breast cancer, melanoma, soft tissue sarcoma.

BREAST CANCERS

Nipple Skin Sparing Mastectomy (NSM)

By the end of December 2013, 1000 patients had been treated with NSM. At a median follow-up of 37 months the incidence of recurrence is 1,7%. That is rather similar to that of radical mastectomy. Moreover the incidence of complete NAC necrosis or other minor complications such as depigmentation occurred in 1,6%. These results seem to indicate the NSM is a safe procedure having better cosmetic results than radical mastectomy. All the patients must now undergo a psychological evaluation to determine and verify their compliance with this operation. The first 600 patients examined thus far have expressed high levels of satisfaction both from the psychological and aesthetic point of view. Thirty-six% of the patients maintained the nipple sensitivity.

Factors correlated to NAC involvement in patients submitted to NSM.

The fundamental prerequisite for nipple sparing mastectomy is the non involvement of nipple-areola complex. It is for this reason that during the surgical procedure frozen section examination of sub-areolar tissue is carried out.
In fifty-six patients an involvement of sub-areolar breast parenchyma has been found. We have analyzed the prognostic factors correlated with NAC involvement. In our experience distance of tumor from NAC (< 2cm), presence of lympho-vascular invasion, grading as well as the involvement of axillary nodes were the parameters that mostly correlated to NAC involvement.

Multicentric randomized study: IORT vs. external radiotherapy

Our department is participating in a prospective randomized trial that compares the effectiveness of IORT to external radiotherapy. The aim of the study is to demonstrate an equivalence in the two techniques in terms of efficacy as well as cosmetic result. So far, six hundred patients have been enrolled, half of them have been submitted to IORT.

Evaluation of lymphangiogenesis as a potential predictor of sentinel node status

The identification of intratumoral and peri-tumoral lymphatics is carried out by immunohistochemistry using an antibody antipodoplanin. One hundred patients with SN positive and one hundred patients with SN negative were evaluated.

There is a clear correlation between LVD (lympho- vascular density) and sentinel node status, with a mean and median LVD values higher in positive than in negative sentinel nodes. In a multivariate analysis, LVD has been shown to have an independent value in predicting the positivity of both sentinel and non sentinel nodes. Therefore, this parameter may be taken into consideration when elaborating a nomogram

able to predict the non sentinel node status which may help in deciding whether or not to perform an axillary node dissection.

Intra-Operative Sentinel Node Examination by One Step Nucleic Acid Amplification (Osna)

From February 2008 to December 2011, we referred 709 patients to undergo intra-operative OSNA sentinel node analysis for breast cancer, with a total of 901 lymph nodes. The technique is able to identify micro or macrometastases within 35-40 minutes, allowing the surgeon to perform an axillary node dissection in the same surgical session. One hundred and fifty four patients were found positive, an axillary node dissection was immediately carried out and a second operation was avoided.

Intra-Operative Sentinel Node Examination by One Step Nucleic Acid Amplification (Osna): validation of four slices protocol

From February 2008 to December 2011, a total of 901 sentinel nodes from 709 breast cancer patients were analyzed. The sentinel node is divided into four parts, two slices (one peripheral and one central) were analyzed by OSNA method and the other two slices were assessed with conventional histopathology. There were a total of 32 discordant cases. Fourteen OSNA negative nodes were found positive to conventional histopathology, whereas OSNA was able to recover 28 nodes found negative in pathological examination (4 macro and 24 micro-metastasis). The discordant cases were due to a tissue allocation bias, that is, different parts of the same sentinel node were examined by two different methods. The overall sensitivity, specificity and concordance were 94%, 96%, 95% respectively, therefore these values demonstrated that this technique is highly reliable and suitable for intra-operative sentinel node.

Intraoperative sentinel node examination by One Step Nucleic Acid amplifications (OSNA): validation of whole sentinel node examination .

From January 2012 to December 2013, 366 patients entered this study. The sentinel node was entirely examined with OSNA method. The comparison among sentinel node examined with four slices protocol and whole sentinel node showed that the latter procedure is able to identify a greater percentage of macrometastases and avoid a second operation in patients that were treated with the 4 slice protocol, negative to conventional histopathology due to tumour allocation bias.

Protocol	NEGATIVE	OSNA +	OSNA++
Protocol 4 slices 297 pTs	225 (76%)	42 (14%)	30 (10%)
Protocol whole sentinel 336 PTs	336 (75%)	40 (12%)	43 (13%)

Intra-Operative Sentinel Node Examination by Osna: correlation between tumor and sentinel node prognostic factors and non sentinel node status

At the present time one of the most debated arguments is the decision on whether to perform an axillary node dissection in case of positive sentinel node. At our institute, a series of prognostic factors both related to tumor, sentinel node characteristics, and the non sentinel node status were correlated. The multiple correspondence analysis (MCA) showed that axillary node positive dissection is strictly correlated with presence of sentinel node macrometastasis, positive lymphovascular invasion, G3, high KI 67 values and Luminal B cancer. In our experience, no patients with a

number of copies ≤ 2000 and Luminal A cancer tested positive no SN metastases.

Conservative Breast Cancer Surgery, Sentinel Node Biopsy and IORT in Day Surgery

In 2011, a feasibility study that foresaw wide breast cancer excision, intra-operative OSNA sentinel node analysis and IORT was carried out.
Fifteen patients had been treated up to December 2013, only patients with menopause and tumors ≤2,5 cm were eligible.
The first procedure was the removal of sentinel node to be examined in the pathological department. Thereafter a wide tumor excision was performed with an intra-operative examination of the resection margins (that must be negative).
IORT was delivered according to the protocol of our institute and axillary node dissection was performed only in case of sentinel node positivity.
The results obtained thus far indicated that this approach is feasible having a great advantage for the patients who can complete in just one session the surgical and radio-therapeutic treatment in only one day.

Treatment of Breast Cancer patients in Day Surgery

In 2008, we began operating on patients with breast cancer in day surgery, who were also candidates for breast conservative surgery and sentinel node biopsy. Up until now a total of 400 patients have been operated on. The eligibility criteria included: T1, absences of lymph-node metastasis at ultrasonography and good general health according to ASA classification.
The injection of albumin labeled with technetium 99 has generally been carried out the afternoon before operation. A higher than usual radiation dose was delivered in order to maintain the amount of sentinel node radioactivity in order to identify it the day after. Patients underwent breast conservative surgery with intra-operative OSNA sentinel node biopsy. If the sentinel node was found positive, an axillary node dissection was carried out. Among these last patients only few remained hospitalized until the following morning, in case of suspicions bleeding.
Our results demonstrate that this approach has two advantages:

- It permits patients to return home on the same day of operation
- It allows to save money for the public health.

Electrochemotherapy in the treatment of primary breast cancer

Electroporation is able to produce an increase in cancer cell membrane permeability allowing a greater penetration of antineoplastic drugs. For Bleomycin this phenomenon can reach an increase of up to 15.000 fold. Electrochemiotherapy has proven to be an effective treatment for superficial primary and recurrent tumors. Recently the development of new technology has permitted the treatment of deep-seated tumors, thus we have designed a clinical protocol for the treatment of primary breast cancer at our institute. Patients with primary palpable tumors up to 3cm were considered eligible. Under general anesthesia 15mg/m^2 of Bleomycin is administered intravenously. Four electrodes are played at periphery of the tumor and one in its center.
Eight minutes after iv drug administration, the tumor is electroporated and sentinel node biopsy is carried out. Axillary node dissection is carried out only in case of positive sentinel nodes. (osna method) .
After 1 month, the tumor is removed for pathological examination. So far, three patients have been treated and only partial responses have been observed. A mathematical model has been developed to improve the homogeneity of electroporation, hence the following patients will be treated according to the new protocol.

Elaboration of a nomogram to predict Non Sentinel Node Status (NSN) in Breast Cancer (BC) with positive Sentinel Node, intraoperatively assessed with OSNA (One Step Nucleic Acid Amplification) method.

We have developed a European database with positive SN detected by OSNA method, able to identify intraoperatively patients with micro (CK 19 mRNA copies 250-5000) or macrometastases (number of copies > 5000). A total of 2000 patients have been enrolled so far. Multivariate logistic regression analysis demonstrated that the number of copies ($p<0.0001$) T size ($p<0.0001$) and LVI were the parameters that strongly correlated with positive NSN, therefore they will be employed to develop a nomogram that allows the surgeon to decide intraoperatively which patients benefit from ALND.

Sentimag study: Sentinel Lymph Node Biopsy with supermagnetic ironoxide (SPIO) vs. Radioisotope

The aim of this study was to evaluate the potential equivalency of the new sentimag technique in comparison to radiotrace (99m) Tc. With this prospective in mind, we conduced a non inferiority study including 60 patients, (99m) Tc was compared with the magnetic technique, using super magnetic ironoxide particles (SIENNA) for localisation of SLNs. The results showed a detection rate per patient of 97% for (99m) Tc vs 98% for SIENNA with a similar average in the number SLNs removed per patient and a higher malignancy detection rate per patient for the SPIO tracer. We obtained convincing results that magnetic SLNB can be performed easily, safely and equivalently well in comparison to the radiotracer method.

MELANOMA

Prognostic Factors Influencing Tumor Response, Locoregional Control and Survival, in Melanoma Patients with Multiple Limb In-transit Metastases Treated with TNF α-based Isolated Limb Perfusion

In isolated limb perfusion (ILP) with tumor necrosis factor-alpha (TNF α) and interferon (IFN) –γ, pioneered by Lienard and Lejenne in 1988, TNFα was empirically employed at a dosage (3-4mg) ten times higher than the systemic maximum tolerable dose (MTD). We previously conducted a phase I/II study in 20 patients with in-transit melanoma metastases, using a combination of melphalan and TNFα at dosage ranging from 0.5 to 3.3mg.

The dose of 1mg of TNFα was identified as optimal in terms of both efficacy and toxicity. The aim of the present study was to describe our experience with 113 stage IIIA/IIIB melanoma patients treated with a TNFα-based ILP and identify prognostic factors for response, locoregional control and survival.

Patients at stage IIIA/IIIB (presence of in-transit metastases and/or regional node involvement) were considered eligible. The disease was bulky (≥10 nodules ≤3 cm or fewer nodules with a diameter >3cm) in 42.5% of the patients and unresectable in 33%.

Forty patients were treated with a TNFα dosage of >1mg and 73 with 1mg. Patients with tumors in the upper and lower limbs underwent ILP via axillary and iliac vessels, respectively. TNFα was injected in the arterial line of an extracorporeal circuit at the pre-established dose, followed by melphalan (13 and 10 mg /of limb volume for the upper and lower limbs, respectively) 30 minutes later.

Complete responses (CR) and partial responses (PR) were 63 and 24.5%, respectively with objective response (OR) of 87.5%. No change (NC) was observed in only 12.5% of the patients. Upon multivariate analysis, only bulky disease maintained its independent value for tumor response with an odds ratio of 4.07 and a p-value of 0.02.

The 5-years locoregional disease–free survival was 42.7. Upon multivariate analysis, the only prognostic factors were stage, age and bulky disease. The 5 year overall survival was 49%. Multivariate analysis showed that only sex, stage and CR maintained their independent values. TNFα based ILP was proven to be an effective treatment for melanoma patients with in-transit metastases. The TNFα dosage of 1mg was as effective as 3-4 mg, with the lower toxicity an cost. We propose that the TNFα and melphalan based ILP should be employed for bulky tumors or after failure of melphalan-based ILP.

SOFT TISSUE SARCOMA

Hyperthermic Isolated Perfusion with Tumor Necrosis Factor-alpha and Doxorubicin for the Treatment of Limb-Threatening Soft Tissue Sarcoma: The Experience of the Italian Society of Integrated Locoregional Treatment in Oncology (SITILO)

Tumor necrosis factor-alpha (TNFα) based hyperthermic isolated limb perfusion (HILP) is routinely carried out at most oncological institutions in the treatment of locally advanced soft tissue limb sarcoma (STS), employing high TNFα dosages. After a phase I-II study, the SITILO (Italian Society of Integrated Locoregional Thertapies in Oncology) centres began to employ the lower dose of 1 mg of TNFα. The aim of this study is to report on the results obtained in 75 patients with limb- threatening STS treated with a low TNF α dose and Doxorubicin (Dx). HILP with TNFα (at a dosage of either≤1 mg or >1 mg) and Dx was administered to 75 patients with limb-threatening STS: 37 males and 38 females; median age 50 years; tumor in the lower and upper limbs in 58 and 17 patients, respectively; primary and recurrent tumors in 45 and 30 patients, respectively. Most tumors (77%) were high grade. Tumor resection was carried out 6 to 8 weeks after HILP. The grade of limb toxicity was

mild to moderate in the vast majority of patients (76%). Grades IV and V were observed, but only when high muscle temperatures were recorded and high TNFα dosages were employed. Systemic toxicity was also mild to moderate and there were no post-operative deaths. Complete and partial tumor responses were 34% and 48%, respectively with an overall response of 82%. Limb sparing surgery was carried out in 85.3% of patients. At a median follow-up of 28 months, 16 recurrences (21.3%) were recorded, with a 5-year locoregional disease-free survival of 63%. The 5-year disease-free survival and overall survival were 36.7% and 61.6%, respectively. HILP with 1 mg of TNFα is an effective neoadjuvant therapy resulting in a high rate of limb sparing in limb-threatening STS, with acceptable local reactions and negligible systemic toxicity.

Publications 2012-2013

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Testori A, Chiarion-Sileni V, Stanganelli I, Rossi CR, Di Filippo F, Ridolfi R, Parmiani G, Gandini S, Soteldo J. Surgical treatment of melanoma: a survey of Italian hospitals. *Dermatology*. 2013;226 Suppl 1:28-31.

Buglioni S, Di Filippo F, Terrenato I, Casini B, Gallo E, Marandino F, Maini CL, Pasqualoni R, Botti C, Di Filippo S, Pescarmona E, Mottolese M. Quantitative molecular analysis of sentinel lymph node may be predictive of axillary node status in breast cancer classified by molecular subtypes. *PLoS One*. 2013;8(3):e58823

Department of Surgical Oncology

Unit of Hepato-Pancreato-Biliary Surgery

Gian Luca Grazi, MD

Director

STAFF MD Assistants: Maurizio Cosimelli, Marco D'Annibale, Andrea Oddi, Pasquale Perri

Activities 2012-13

Clinical Activities

The Unit of General and Hepato-Pancreato-Biliary (HPB) Surgery is mainly engaged in liver and pancreatic cancer surgery, secondly in gastrointestinal cancer surgery, with particular reference to colorectal tumors. About 80 patients with primary (HCC, cholangiocarcinoma, gall bladder) liver tumors or metastatic cancer, mostly deriving from colorectal primary sites, undergo surgical procedures with radical intent every year. Twenty five patients with pancreatic cancer undergo pancreatoduodenectomy or distal pancreatectomy while the other 70 undergo colorectal surgery for large bowel cancer with/without synchronous liver metastases. Finally, a selection of about 80-90 patients with gastric cancer, metastatic lymph nodes or abdominal soft tissue sarcoma also undergo surgery at our Unit. Several major or minor hepatectomies are carried out after a clinical response to i.v. neoadjuvant chemotherapy, above all for colorectal liver metastases. Furthermore, a major liver surgery (resection of 3 or more segments) is carried out following a lobar angiographic portal embolization in selected patients, in order to guarantee adequate liver hypertrophy and postsurgical function. During every procedure of liver surgery, an intraoperative liver sonogram is routinely performed to detect other metastatic seedings. After surgery all patients are then included in follow-up protocols. The multidisciplinary approach for each patient is discussed within the hepato-pancreatobiliary and gastrointestinal Disease Management Team of our Institute, including all the oncological specialties.

Research Activities

Isolation and characterization of tumor stem cells in intra- and extrahepatic cholangiocarcinoma.

Differential analysis of microRNA expression profiles in cholangiocarcinoma, HCC and liver metastases.

Associating intraoperative Indocyanine Green (ICG) Fluorescence imaging and ultrasound to detect microscopic liver cancer lesions during hepatic surgery.

Enhanced recovery after liver resection in a newly established HPB surgical Unit.

Quality of Life after curative liver resection.

Evaluation of chemotherapy-induced liver damage in patients with colorectal liver metastases using non invasive tools.

Local excision of rectal cancer in complete or near complete responders to neoadjuvant chemoradiation: a phase II clinical trial.

A phase II randomized, multicentric trial on second-line liver-directed radioembolization with microspheres (SIRT) with/without i.v. chemotherapy in patients with unresectable, KRAS- mutant colorectal liver metastases.

Publications 2012-2013

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Melucci E, Cosimelli M, Carpanese L, Pizzi G, Izzo F, Fiore F, Golfieri R,Giampalma E, Sperduti I, Ercolani C, Sciuto R, Mancini R, Garufi C, Diodoro MG, Mottolese M. Decrease of survivin, p53 and Bcl-2 expression in chemorefractory colorectal liver metastases may be predictive of radiosensivity after radioembolization with yttrium-90 resin microspheres. *Journal of Experimental & Clinical Cancer Research* 2013, 32:13 doi:10.1186/1756-9966-32-13.

Department of Surgical Oncology

Unit of Gynecologic Oncology

Enrico Vizza, MD

Director

STAFF MD Assistants: Mario Congiu, Giacomo Corrado, Giuseppe Cutillo, Emanuela Mancini, Luciano Mariani, Domenica Mazza, Roberto Sindico, Cristina Vicenzoni, Giuseppe Vocaturo
Fellows: Giulia Pomati, Stefano Sindico
Medical student: Fabiola Patani

Activities 2012-13

Clinical Activities

The Division of Gynecology Oncology provides all services involving the diagnosis, treatment and follow-up of gynecologic oncology patients. Each staff member is a fully-trained gynecologic oncologist responsible for various activities within the Division, including surgery (minor, major and mini-invasive), research, clinical trials, early diagnosis, and teaching (2 Tumor Boards weekly, International meetings; 3 surgical master courses yearly). All surgical and medical treatments are coordinated on a weekly basis meeting by a multidisciplinary team involving surgeons, medical oncologists, pathologists, and radiotherapists. The ward has 16 in-patient beds, two of which are totally dedicated to day surgery activities. During 2013, 386 patients were admitted and 386 underwent surgery. Of these, 80% for neoplastic disease. The average hospital stay was 3.48 days and an average weight of DRG 1.3.

The Division of Gynecologic Oncology also provides a Day Surgery service where patients requiring minor surgery (conization, LLETZ, operative hysteroscopy, laser therapy, diagnostic laparoscopy), can be easily completed in a short time and does not require hospitalization for more of 6-8 hours. During 2013, 300 patients were operated in day surgery.

Among the surgical activities particular attention is devoted to minimally invasive surgery (traditional laparoscopic surgery and single incision laparoscopic surgery (SILS), robotic surgery and robotic single-site surgery), fertility preserving surgery in young patients with borderline ovarian tumors or early stage ovarian cancer. The division has also the facilities and the experience to perform major surgery such us extensive cytoreduction in patients with advanced ovarian cancer and pelvic exenteration in patients with recurrent cervical cancer.

Moreover, the Division includes a very active out-patient clinic mainly dedicated to diagnosis and treatment of genital cancer precursors. One clinic is dedicated to patients with first entry gynecological oncological evaluation; one to patients with abnormal pap and 1st and 2nd level colposcopy, one to HPV multidisciplinary office, one to hysteroscopy and one to follow-up of operated patients. The overall activity for 2013 accounts for over 4,000 out-patient visits.

In addition to their clinical and research activities, members of the Division also have university and institutional teaching responsibilities that mainly involve training residents and fellows, but they are also involved in Continuing Medical Education (CME) programs.

In the course of 2013, we started four important collaborations with National Institutes:

- Gynecologic Oncologic Unit, Catholic University of the Sacred Heart, Rome, Italy.
- Academic Department of Biomedicine and Prevention and Clinical – Section of Gynaecology - Tor Vergata University - Rome, Italy
- Department of Cell Biology and Neurosciences; Italian National Institute of Health; Rome, Italy.
- Faculty of Pharmacy and Medicine, Department of Anatomical, Histological, Forensic and Orthopaedic Sciences, Sapienza University of Rome, Rome, Italy.

Research activities

The clinical and surgical research will be directed towards three main fields of interest:

Robotic single site surgery of gynecologic tumors

Over the past 10 years, multiple studies have shown that minimally invasive surgery (MIS) for the treatment of gynecologic tumors reduce blood loss, length of hospital stay, the incidence and severity of surgical complications and better cosmesis compared with laparotomy. Robotically assisted laparoscopic surgery has been shown to provide benefits very similar to those of traditional laparoscopic surgery for hysterectomy in gynecologic tumors. An alternative to conventional laparoscopy or robotic surgery is the laparo-endoscopic single-port surgery (LESS), which further improves the cosmetic benefits of MIS while avoiding the potential morbidity associated with multiple incisions. In an attempt to solve the problems of single-incision techniques, recently, novel single-site instruments and accessories for the da Vinci Si System have been developed and tested in preliminary human studies. Our research in this field aims to test and develop the system of robotic single-site in gynecologic cancers.

Bank of ovarian tissue

Creation of a Fertility Preservation Unit for a centralized service that integrates a sophisticated network of oncologists, gynecologists, endocrinologists, psychologists and biologists, in order to provide procedures of cryopreservation of ovarian tissue to all patients in need. In addition the Unit aims to evaluate the efficiency and adequacy of clinical care of cryopreservation of ovarian tissue with the production of scientific protocols and guidelines. Another activity involvesingcreate a cryo-banking service of ovarian tissue through the close collaboration with the Gynecological and Oncological Units of Lazio. Moreover, it is committed to contributing to the training of gynecologists in extraction and transplantation of ovarian tissue, through practical courses and masters.

HPV-Unit

A multidisciplinary unit for the study, treatment and prevention of HPV disease has been formally established (HPV-UNIT). The Unit is divided into two main components: clinical (composed of professionals of gynecology, ENT, proctology, sexually transmitted diseases, dermatology) and laboratory (virologists, biologists, pathologists). Its main aim is to harmonize various clinical HPV-related disease approaches in order to provide medical services that are in line with and supported by scientific evidence. Secondly, another purpose of the HPV Unit is to create synergies for scientific projects. Lastly, the Unit aims to train and update the medical staff through providing training courses and to properly inform the users.

List of Publications 2012-2013

Origoni M, Cristoforoni P, Costa S, Mariani L, Scirpa P, Lorincz A, Sideri M. HPV-DNA testing for cervical cancer precursors: from evidence to clinical practice. Ecancermedicalscience. 2012;6:258. doi: 10.3332/ecancer.2012.258.

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Fagotti A, Corrado G, Fanfani F, Mancini M, Paglia A, Vizzielli G, Sindico S, Scambia G, Vizza E. Robotic single-site hysterectomy (RSS-H) vs. laparoendoscopic single-site hysterectomy (LESS-H) in early endometrial cancer: a double-institution case-control study. *Gynecol Oncol*. 2013 Jul;130(1):219-23.

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Ghezzi F, Cromi A, Ditto A, Vizza E, Malzoni M, Raspagliesi F, Uccella S, Corrado G, Cosentino F, Gotsch F, Martinelli F, Franchi M. Laparoscopic versus open radical hysterectomy for stage IB2-IIB cervical cancer in the setting of neoadjuvant chemotherapy: a multi-institutional cohort study. *Ann Surg Oncol*. 2013 Jun;20(6):2007-15.

Mariani L, Gadducci A, Vizza E, Tomao S, Vici P. Vaginal atrophy in breast cancer survivors: role of vaginal estrogen therapy. *Gynecol Endocrinol*. 2013 Jan;29(1):25-9.

Sperati F, Vici P, Maugeri-Saccà M, Stranges S, Santesso N, Mariani L, Giordano A, Sergi D, Pizzuti L, Di Lauro L, Montella M, Crispo A, Mottolese M, Barba M. Vitamin D supplementation and breast cancer prevention: a systematic review and meta-analysis of randomized clinical trials. *PLoS One.* 2013 Jul 22;8(7): e69269.

Mariani L, Sideri M, Costa S, Cristoforoni P, Origoni M, Preti M; Italian HPV Study Group. Human papillomavirus DNA and Pap tests: the need for cotesting in opportunistic setting during the transition time. *J Low Genit Tract Dis*. 2013 Jul;17(3):362-5.

HPV VVAP study group. Worldwide human papillomavirus genotype attribution in over 2000 cases of intraepithelial and invasive lesions of the vulva. *Eur J Cancer.* 2013 Nov;49(16):3450-61.

Suligoi B, Salfa MC, Mariani L, Corsini D, Timelli L, Fattorini G, Vittori G. A new surveillance gynecological network to assess the incidence and prevalence of genital warts in the Italian female population: lessons learned. *Minerva Ginecol*. 2013 Oct;65(5):577-85.

Lenzi A, Mirone V, Gentile V, Bartoletti R, Ficarra V, Foresta C, Mariani L, Mazzoli S, Parisi SG, Perino A, Picardo M, Zotti CM. Rome Consensus Conference - statement; human papilloma virus diseases in males. *BMC Public Health*. 2013 Feb 7;13:117.

Donà MG, Ronchetti L, Giuliani M, Carosi M, Rollo F, Congiu M, Mazza D, Pescarmona E, Vocaturo A, Benevolo M. Performance of the linear array HPV genotyping test on paired cytological and formalin-fixed, paraffin-embedded cervical samples. *J Mol Diagn.* 2013 May;15(3):373-9.

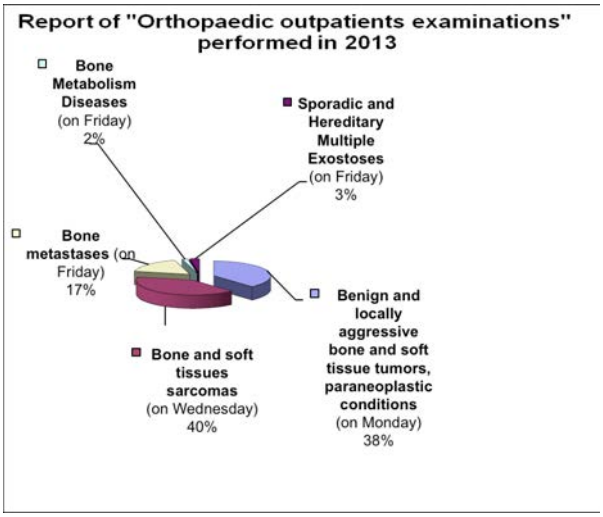
Department of Surgical Oncology

Unit of Oncological Orthopaedics

Roberto Biagini, MD

Director

STAFF Orthopedic Assistants: Leonardo Favale, Barbara Rossi, Nicola Salducca, Carmine Zoccali
Nurses: Grazia Amato, Paolo Asquini, Fabio Conti, Antonella Cutini, Rosario D'Angelo, Matteo Ferraro, Maria Teresa Imperi, Stefano Landi, Alessia Milotti.



Activities 2012-13

Clinical Activities

Beds: 12 regulars, 2 day surgery.
Outpatient clinics 3/week
Operative Theatres Regular: 7/month
Day Surgery: 1/month
Activeness: Programmed surgical operations 168, Day Surgery 42, Interventional Procedures 138, Outpatients accesses 2389, Admissions 175

The Oncological Orthopaedics Unit performs every kind of orthopedic oncological operation for primitive and metastatic muscular-skeletal tumors in adults and pediatric patients.
During 2013, the unit began using new technologies and new surgical techniques applied to tumors in computer-assisted navigated surgery.
The patients who have to undergo interventional procedures are hosted in the ward. The ward also has a fully furnished pediatric room containing videogames and a video-school (available for long-term stay pediatric patients).

Research Activities

Congress Speaker

Zoccali C, Prencipe U, Ferraresi V, Salducca N, Biagini R. "Subchondral bone reconstruction after curettage for benign bony lesions: the Regina Elena National Cancer Institute Experience". Milan 14-16 January 2013, 1st European congress "Defining a reconstruction ladder for the treatment of musculoskeletal conditions using regenerative approaches: a consensus conference".

Biagini R. "La chirurgia Dei sarcomi ossei". I Tumori Rari: aspetti patogenetici, nuovi farmaci e prospettive future. Bari, 13-14 giugno 2013.

Biagini R. "Riscostruzioni Vertebrali". Clinical Experience Exchange meeting. Roma, 28 Giugno 2013.

Zoccali C, Soriani A, Pinnarò P, Rossi B, Prencipe U, Salducca N, Favale L, Biagini R, Ferraresi V. The use of carbon fiber-reinforced peek orthopedic devices and implants in cancer patients who undergo radiotherapy. 17th General Meeting ISOLS Bologna, 11-13 Settembre 2013.

Biagini R. "Inquadramento clinico e problematiche chirurgiche dei tumori delle parti

molli". Diagnosi, Diagnosi differenziale e Radiologia Interventistica delle lesioni dell'osso e delle parti molli. L'Aquila, 5-7 Settembre 2013.

Zoccali C. "Problematiche chirurgiche al trattamento delle lesioni benigne". Diagnosi, Diagnosi differenziale e Radiologia Interventistica delle lesioni dell'osso e delle parti molli. L'Aquila, 5-7 Settembre 2013.

Sciuto R, Zoccali C, Ferraresi V, Covello R, Rossi B, Nuzzo C, Mazzone C, Romano L, Biagini R, Maini C L. 18f-FDG PET/CT role in the prediction of response to neoadjuvant chemotherapy in osteosarcoma: preliminary results. 17th General Meeting ISOLS Bologna, 11-13 Settembre 2013.

Rossi B. "*Trattamento delle metastasi ossee: stato dell'arte e prossimi passi*" ElettroChemioTerapia: Stato dell'arte e prospettive nel trattamento di melanoma, tumori cutanei, recidive e metastasi cutanee da carcinoma Mammario. Centro Congressi "R. Bastianelli" IFO Roma, 3 Ottobre 2013.

Biagini R. "Tumori delle parti Molli: trattamento chirurgico". 4° Corso GLOSMI. Roma 11-12 Ottobre 2013.

Zoccali C, Rossi B, Prencipe U, Marolda G, Salducca N, Favale L, Erba F, Biagini R. Plexur M™ in the reconstruction of subchondral bone: a new perspective in oncological orthopedics. Venice (Italy), October 12, 2013, 15th meeting of the Italian Orthopaedic Research Society (IORS).

Rossi B, Zoccali C, Prencipe U, Salducca N, Ferraresi V. "Carbone fiber-reinforced PEEK intramedullary nailing for the treatment of pathologic fractures due to metastases: short term results" Venice (Italy), October 12, 2013, 15th meeting of the Italian Orthopaedic Research Society (IORS).

Rossi B, Zoccali C, Prencipe U, Salducca N, Favale L, Erba F, Biagini R. "Percutaneous technique for incisional biopsy of soft tissue tumors: preliminary evaluation of an accurate alternative to open biopsy." Venice (Italy), October 12, 2013, 15th meeting of the Italian Orthopaedic Research Society (IORS).

Zoccali C, Rossi B, Prencipe U, Salducca N, Nuzzo C, Ferraresi V. "Il sarcoma di Ewing intradurale extramidollare: epidemiologia,presentazione clinica, approccio terapeutico, sopravvivenza." CIOSM, Congresso SIOT, Genova, 26-29 Ottobre 2013.

Rossi B, Zoccali C, Salducca N, Prencipe U, Giulio M, Fabi A, Ferraresi V, Biagini R. "Sintesi in carbonio in oncologia muscolo scheletrica". CIOSM, Congresso SIOT, Genova, 26-29 Ottobre 2013.

Rossi B, Zoccali C, Favale L, Prencipe U, Erba F, Ferraresi V, Biagini R. "Biopsia percutanea per i tumori delle parti molli: valutazione preliminare di una tecnica alternativa all'agobiopsia classica" CIOSM, Congresso SIOT, Genova, 26-29 Ottobre 2013.

R. Biagini. "Osteosintesi in carbonio in Oncologia: realtà o chimera". SIOT 2013, gruppo nazionale sulle metastasi ossee. Genova, 27 Ottobre 2013

Poster
Zoccali C, Rossi B, Prencipe U, Marolda G, Salducca N, Favale L, Erba F, Biagini R Engineered biomaterial bone Plexur m™ in reconstruction of subchondral bone after curettage of benign epiphyseal tumors. Bologna (Italy), September 11 - 13, 2013, ISOLS Congress.

Abstract book
Rossi B, Zoccali C, Prencipe U, Salducca N, Favale L, Erba F, Biagini R. Percutaneous technique for incisional biopsy of soft tissue tumors: preliminary evaluation of an accurate alternative to open biopsy. 15th Meeting I.O.R.S. P. 36.

Rossi B, Zoccali C, Prencipe U, Salducca N, Ferraresi V. Carbon fiber-reinforced PEEK intramedullary nailing for the treatment of pathologic fractures due to metastases: short term results. 15th Meeting I.O.R.S. P. 37.

Zoccali C, Rossi B, Prencipe U, Marolda G, Salducca N,L. Favale, F. Erba, R. Biagini. Plexur M™ in the reconstruction of subchondral bone: a new perspective in oncological orthopedics. Atti 15th Meeting I.O.R.S. p. 39.

Moderator
R. Biagini. 36° SICV & GIS. Sessione tumori vertebrali. Bologna, 16 – 18 Maggio 2013.

R. Biagini. Elettrochemioterapia: stato dell'arte e orispettive. IFO – Roma, 3 Ottobere 2013.

R. Biagini. Corso di Aggiornamento ALOTO: le fratture dell'anello Pelvico. Roma, 4 Ottobre 2013.

R. Biagini. La multidisciplinarietà in Osteoncologia. Roma, 10-11 Maggio 2013.

R. Biagini. Managemente delle ferite complesse con VAC e Vera Flow. Roma, 5 giugno 2013.

R. Biagini. CIOSM, Sessione III. SIOT 2013, Genova, 27 Ottobre 2013

Meeting organization
4° Corso GLOSMI. Roma 11-12 Ottobre 2013.

Publications 2012-2013

Rossi B, Ferraresi V, Appetecchia ML, Novello M, Zoccali C. Giant cell tumor of bone in a patient with diagnosis of primary hyperparathyroidism: a challenge in differential diagnosis with brown tumor. *Skeletal Radiol*. 2013 Nov 24.

Zoccali C, Marolda G, Di Francesco A, Favale L, Salducca N, Biagini R.; Pelvic sacral and hemi lumbar spine resection of low grade pelvic chodrosarcma: a multistage procedure involving vascular bypass, spine fixation and vascular exclusion. *Orthop Traumatol Surg Res*. 2013 Sep 25.

Zoccali C, Zoccali G, Bakaloudis G, Salducca N, Biagini R.: A new technique to perform pelvic osteotomy using Gigli saw. *J Surg Oncol*. 2013 Aug;108(2):136.

Department of Surgical Oncology

Unit of Plastic Reconstructive Surgery

Roy De Vita, MD

Director

STAFF MD Assistants: Alfredo Altieri, Maurizio Costantini, Stefano Feliciano, Pierpaolo Gullo, Massimo Panimolle, Marcello Pozzi, Antonio Varanese
Nurse, Vice Head: Iolanda Mantuano
Nurse: Attilio Santolamazza

Activities 2012-13

Plastic and Reconstructive Surgery is very important in the general management of oncologic patients of the Regina Elena National Cancer Institute and plays a seminal role in the therapeutic course of patients affected with breast cancer.
Our Unit has been actively involved in the definition and use of protocols for therapeutic methods. In particular, the expertise obtained has led to introducing several protocols and assistance programs for the purpose of cooperating with most representative national structures.

Breast reconstruction

In the past, the treatment of breast cancer had the sole purpose of survival of the patient, but more recently the problem of the breast reconstruction phase has become more prominent, even in relation to the evolution of its psychological aspects over time.
The loss and/or removal of the breast in women involves two sets of mental processes, respectively, one related to the cancer disease itself and the other the loss of identity following a mastectomy. Thus, the general surgeon carries out the removal of the tumour which is much less traumatic than undergoing radical breast surgery. The plastic surgeon in the other hand perfects the reconstructive techniques and gives indications on how to proceed with the breast reconstruction even in advanced stages of disease .
The behavioral changes arising after breast surgery are not so different in the order they occur (shock phase, reaction phase, phase equilibrium, phase of recovery or recovery) from those experienced by other cancer patients, but are much greater and more persistent over time. Patients experience feelings of physical mutilation, which consequently affects their ability to socialize in their personal relationships, inevitably inhibiting the perception of treating cancer.
This then provokes a spiral of anxiety-depressive illnesses often characterized by the refusal to live life as before and loss in sexual desire and activity.
Nonetheless, the main objective must remain for the woman to fully regain her body image, clearly understanding what can be expected in highly reconstructive surgery, such as fully restoring the breast removed.
Breast reconstruction does not interfere with complementary therapies. In fact, the efficacy of radiotherapy is in no way altered by the presence of breast implants as it has been shown that the tissues surrounding the prosthesis demonstrate dosimetric changes.
The only side effect emerging in the presence of breast implants during the course of radiotherapy treatment is the increased risk of capsular contracture.
Moreover, the presence of breast prosthetics has not been found to interfere with the efficacy of chemotherapy, however the side effects observed include an increase in tissue resistance and increased risk of infection. Lastly, breast reconstruction does not affect the timeliness of diagnosis of local recurrence and treatment.
Breast reconstructive surgery, both immediate and delayed, involves the use of implants or the use of pedicle flaps (latissimus dorsi muscle,

rectus abdominis) or microsurgical flaps (rectus) abdominal skin flap from the abdominal fat sparing muscle, and fatty skin flap from the region.
In collaboration with the Unit of General Surgery and Breast Cancer Unit, we began to perform mastectomies in selected breast cancer cases with highly conservative surgery involving the nipple-areola complex and immediate reconstruction using autologous tissue or prosthetics, a technique that is called nipple sparing mastectomy.
Nipple Sparing Mastectomy (NSM) initiated the evolution of breast conservative treatment for cancers located outside of the central area of the breast. It has been reported that this type of treatment has the best psychological impact in breast surgery. However, surgical indications of this type of treatment are varied.
Having reviewed the literature, it is evident that the NSM surgical procedure has been studied for many years by different authors, and is not associated with an increase of local recurrence than traditional surgery.
Our indications for NSM are patients with T0-T1, N0, M0 tumors, in small breasts. This type of conservative treatment does not have good cosmetic results in patients with T2, N0, M0 tumors, and in recurrence after conservative surgery.
All tumors must have a peripheral localization and multiple negative frozen sections of the subareola tissue.
We are now reviewing the patients data where the preliminary results have been judged excellent for the cosmetic management, the recurrence rate and for the psychological impact.
Until now, out of 504 patients observed, we only found 5 local recurrences, 7 total and 20 partial necrosis of the areola due to retroareolar dissection.
Considering the short term results (median follow up of 32 months), we did not observe any increase in local recurrence or any other complications when compared to data in literature.
According to our preliminary results the rate of patients eligible undergoing mastectomies were very high. Compared to traditional surgery, we noticed a lower number of recurrences, better cosmetic results and greater patient satisfaction.

Biological Mesh in implant-based breast reconstruction surgery

The expectations for improved results in postmastectomy reconstruction have risen in

the last decade. The use of surgical scaffolds in implant-based breast reconstruction provides pocket control, maximize coverage and a lower rate of capsular contracture. There is serveral data in literature reporting on acellular cadaveric dermis (AlloDerm® Tissue Matrix defined), while no data on in vivo human analyses of the histopatologic sequelae of biological matrices from animal sources such as Acellular Dermal Matrix (ADM) in implant-based breast reconstruction has not been reported yet.

Our aim is to investigate the histopathologic sequelae of the ADM SurgiMend®, a unique acellular collagen matrix derived from fetal bovine dermis. The study was designed to consider a two stage breast implant reconstructive surgery: at the first time, we collocated a SurgiMend® patch, in the second stage, real time clinical care of patients, we compared the tissue regenerated on the biological mesh with the native breast capsule by carrying out a histopathological examination.

Eventhough there is limited data available on capsular contracture in implant based breast reconstruction by using biological meshes, we can state that there are no differences in histopathologic changes on the capsula.

20 consecutive patients at our Institute were included in this study from January 2012 to June 2013. Age of patients was between 38-70 (mean 53.6). Surgical procedure involed the monolateral two stage postmastectomy breast reconstruction. Exclusion criteria included: smoking, hypertension, diabetes, history of prior implants, immunological diseases or radiotherapy. The average time to implant exchange at the second stage breast reconstruction was 6.4 months when biopsies for histopathological evaluation were performed: one on the integrated biologic mesh, the other on the native breast capsule. The frozen tissue sections will be analyze for granulation tissue, neoangiogenesis, chronic inflammatory, fibroblast cellularity, capsule fibrosis. The complication rate was scheduled as well.

The data obtained will be assessed according to a semiquantitative histopathologic score and then evaluated by Beherens-Fisher statistical analysis. The histopathological evaluation of the frozen sections found statistically significant differences between the bio-integrated patch and the native capsule. All levels of chronic inflammation were superimposable: granulation tissue: 1 vs 0.8; neoangiogenesis: 1.1 vs 1; chronic inflammation: 1.45 vs 1.33; fibroblast cellularity: 1.16 vs 1.16; capsular fibrosis: 1.8 versus 2.5. In our series, the complication rates were totally superimposable compared to the data reported in literature.

To our knowledge, this retrospective core study is the first histopathologic research study comparing biointegrated animal ADM (SurgiMend®) and native capsules in implant-based two stage breast reconstruction aiming to investigate a reduction in capsular contracture.

At second stage breast reconstruction, the patch appeared clinically and properly distinguished, and all patients showed a low clinical rate of capsular contracture. While there is clinical evidence showing a reduction in capsular contracture by using ADM in literature, similarly, this study demonstrates a similar histopathological pattern in native capsules and in the bio-integrated patches.

The exact cause and mechanism of capsular contracture in implant based breast reconstruction still remains to be elucidated . The low levels of all parameters of chronic inflammation in both samples may suggest a role played by the patch. A longer follow up of our series and further investigation is needed to confirm this.

Soft Tissue Sarcoma

The Plastic Surgery Unit deals with all types of skin cancers (epitheliomas, melanomas, other skin cancers locations) that focus especially on craniofacial locations that require complex reconstructions and together with the Dermatology Unit are dedicated on preventing skin cancer diseases. In collaboration with the General and Orthopedic Surgery Unit, the activities are aimed against sarcomas of the limbs through the morphofunctional microsurgical reconstruction of the structures involved.

Extravasation of anticancer drugs in Oncology: Prevention, treatment and outcomes

The incidence of extravasation of antineoplastic drugs reported in the literature, ranges from 3% to 6%. This percentage, however, is increasing for introducing new chemotherapeutic drugs such as Vinorelvina and Taxanes. While these drugs

certainly represent an important therapeutic alternative in the treatment of solid tumors, particularly breast cancer, local toxicity levels are higher in these drugs than those that preceded them.
We should therefore focus our attention even more on the prevention of extravasation and its treatment.
The project will include two phases: first, prevention, and educating and training the staff on the medicine used and patient treatment.

The second phase outlines the conditions of treating acute and chronic disease, functional impairment and the psychological aspects involved as well as possible surgical outcomes.
Preliminary results observed: less physical and psychological stress of patients, a reduction in hospital care costs. We observed a more aggressive vinorelvine of soft tissue significantly increasing the difficulty in treatment because the toxicity of this drug causes damage in a much shorter time than other chemotherapeutic drugs.

Department of Surgical Oncology

Unit of Thoracic Surgery

Francesco Facciolo, MD

Director

STAFF Surgeons: Sandro Carlini, Virna Cerasoli, Felicita Corzani, Enrico Melis, Gabriele Alessandrini, Daniele Forcella, Giovanni Leuzzi

Activities 2012-13

Clinical Activities

Our clinical activities mainly focused on surgery (curative intent / palliative / diagnostic) for:
Lung Cancer (particularly, Locally-Advanced NSCLC)
Tumors of the Chest Wall (Resective and Reconstructive surgery)
Tumors of the Mediastinum (particularly, Thymic Malignancies)
Tumors of the Esophagus
Tumors of the Thoracic Inlet
Malignant Pleural Mesothelioma (particularly, radical-intent surgery)
Metastatic disease of the lung (from other malignancies)
We apply multidisciplinary, integrated, dedicated protocols for the post-operative management of surgical patients (early extubation, peri-/post-operative intensive or sub-intensive care, pain control, early rehabilitation and mobilization). We perform minimally invasive diagnostic techniques (FiberBronchoscopy, EBUS, EUS).

Research Activities

Collection and banking of tumoral and healthy tissue from NSCLC, Thymomas and MPM for:
Study of tumoral microenvironment Isolation and culture of cancer stem cells Isolation of circulating markers with diagnostic/prognostic significance Molecular and genomic profiling of neoplastic cells Multicentric Clinical Trials (surgical outcomes for specific Neoplasms - NSCLC and MPM in particular).
Clinical impact of Extrapleural Pneumonectomy for MPM.
Feasibility of sublobar resections for early-stage NSCLC (Multicentric).
Analysis of the clinical impact of Mediastinal Lymphadenectomy.
Collaboration with Medical Oncologists in clinical studies.

Publications 2012-2013

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Department of Surgical Oncology

Unit of Urology

Michele Gallucci, MD

Director

STAFF MD Assistants: Ruggero Cantiani, Giuseppe Cusumano, Giovanni Mainiero, Surgeons: Salvatore Guaglianone, Luciano La Manna,Vincenzo Pompeo
Researchers: Rocco Papalia, Giuseppe Simone
Fellow: Mariaconsiglia Ferriero

Activities 2012-13

Clinical Activities

The clinical activities of our Unit of Urology mainly concerns minimally invasive surgery: robot-assisted and laparoscopic procedures. We have particularly expanded our expertise and gained experience in robotic radical cystectomy with total introcorporeal reconstruction of the neobladder and in minimally invasive partial nephrectomy without hilar clamping. Expanding the indications of minimally invasive surgery such as robot- assisted radical nephrectomy with caval trombectomy are still under investigation.

Research Activities

Clinical research on new minimal invasive surgical techniques, imaging advances in early cancer detection or imaging-guided surgery and oncologic outcomes after surgical treatments are our Unit's main research objectives. Basic research on molecular biomarkers, genetic assessments and stem cells in urological malignancy are additional research activities that our Unit carries out in cooperation with the dedicated departments of the Regina Elena National Cancer Institute and other international Institutes.
Since June 2012, the Unit of Urology has been a Site Coordinator of the observational study FE200486CS39 entitled "A prospective observational safety study in patients with advanced prostate cancer treated with firmagon® (degarelix) or a GNRH agonist".

In November 2013, AIFA carried out an inspection in the Unit of Urology for the above mentioned study.

Publications 2012-2013

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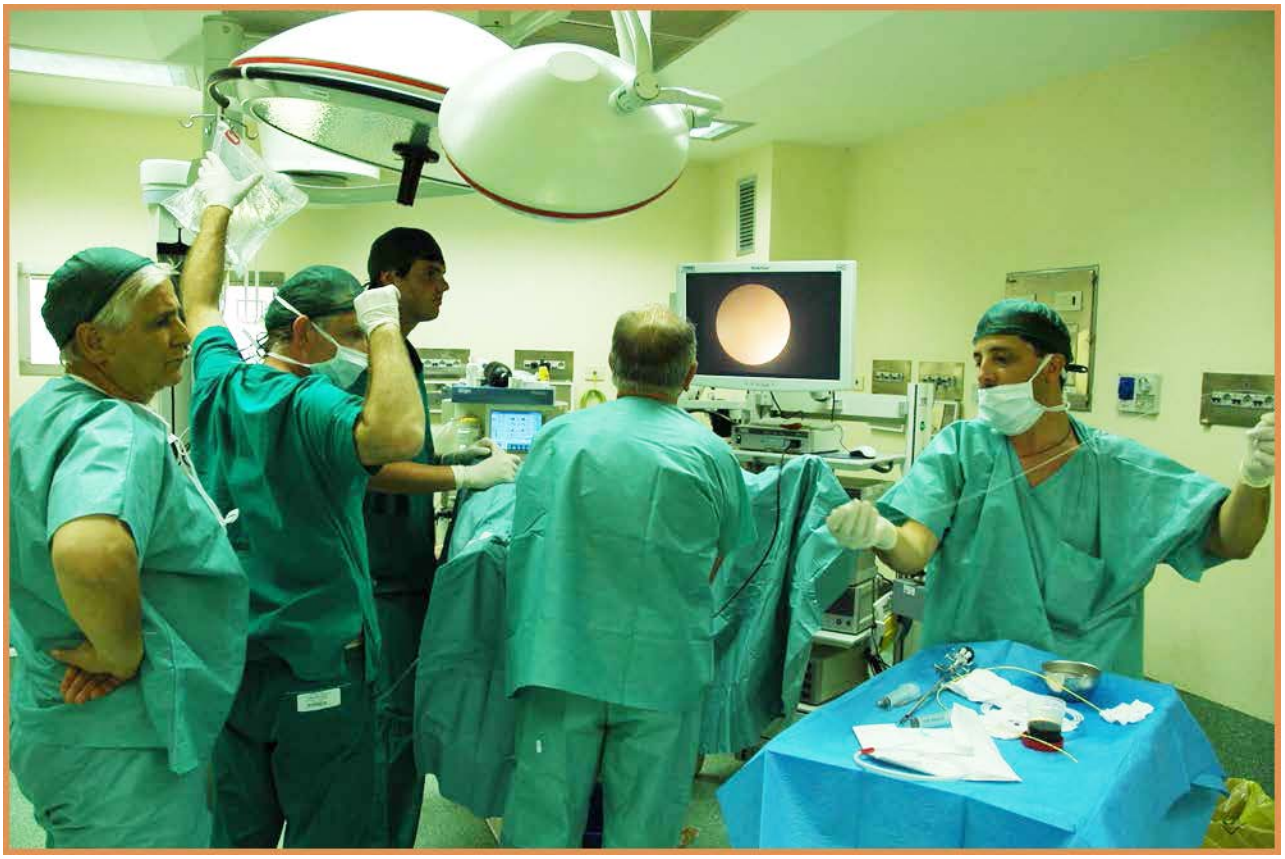

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Department of Medical Oncology

Unit of Haematology

Maria Concetta Petti, MD (until 31st October 2012)
Andrea Mengarelli, MD (from 1st November 2012)

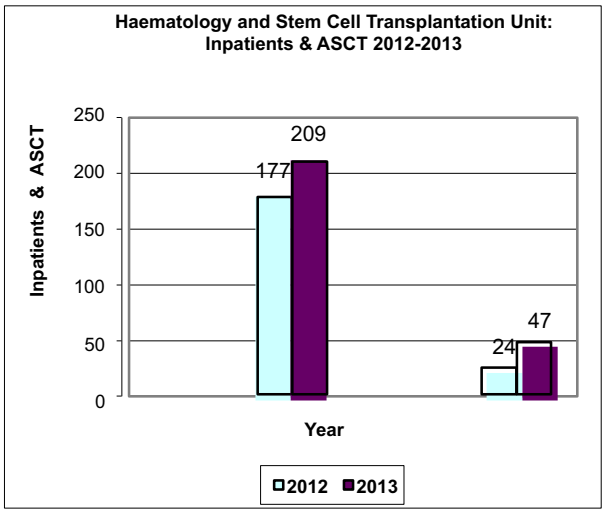
Director

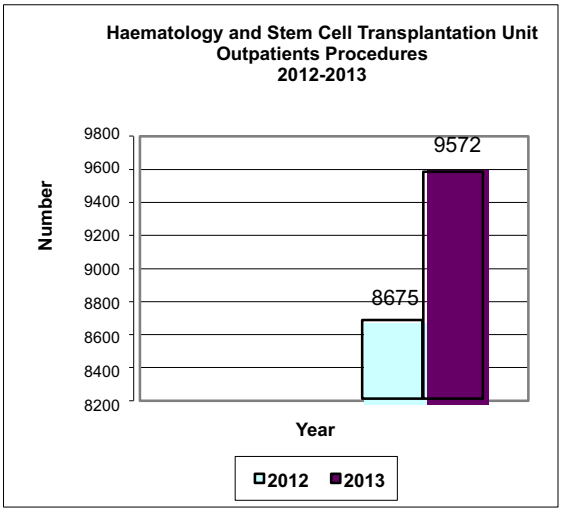
STAFF MD Assistants: Maria Laura Dessanti, Svitlana Gumenyuk, Francesco Marchesi, Francesca Palombi, Francesco Pisani, Atelda Romano, Antonio Spadea.
Nurses: Antonietta Pimpinella, Caterina Viggiani, Anna Attico, Paolo Bellucci, Giuseppina Cafarella, Tatiana Chierichetti, Gianluca Falzone, Nicoletta Hugeanu, Roberta Pascoletti, Alessandra Labella, Federica Pettine, Paola Presta, Fabrizio Pochettino, Raffaele Speranza, Anna Spinelli
Administrative Assistant: Cecilia Fagioli

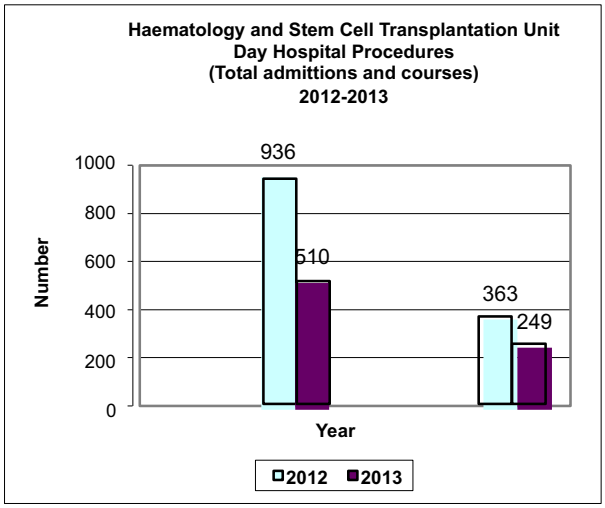
Activities 2012-13

Clinical Activities

The Haematology and Transplantation Unit specializes in the evaluation, treatment and care of patients with lymphoma, leukemia, multiple myeloma, myelodysplastic syndrome and myeloproliferative disorders. Although chemotherapy remains an integral component of the treatment for most haematologic malignancies, the development of disease-specific or targeted therapeutics represents the research goal of our Units' investigators.
Treatments are delivered according to the National and International clinical trials coordinated by cooperative groups (like GIMEMA, FIL, EORTC, IELSG) involved in the treatment of several onco-haematological diseases.
Stem cell transplantation is often indicated for the treatment of hematologic malignancies: U.O.C. Ematologia e Trapianti is one of the 6 Institutes located in Rome belonging to the Rome Transplant Network (RTN), a Metropolitan Hematopoietic Stem Cell Transplant Program for adult and paediatric patients established as a cooperative network. RTN is an innovative entity, which follows rules and standards established by The Joint Accreditation Committee ISCT-EBMT (JACIE) accreditation program: in June 2013 Policlinico "Tor Vergata" University Hospital, Regina Elena National Cancer Institute and Campus Biomedico University Hospital were found to meet the standards of the JACIE for Autologous & Allogeneic Transplantation in Adult Patients, as officially certified on 21.01.2014.
In 2012-2013, the RTN registered 338 Transplants (95 allogeneic and 243 autologous, 71 of them performed in our Unit).
The objectives of the RTN are: 1) to standardize transplant procedures; 2) to improve quality of transplant care; 3) to extend the potential of transplant activity over the metropolitan area; 4) to share expertise and professional education among healthcare providers; 5) to promote excellence of single transplant Centres; and 6) to rationalize cost-management of public health.
The tables summarize the activity of our Unit in 2012-2013 for inpatients (inward and day-hospital facilities) as well outpatients.







Research Activities

Over the last few years, the incorporation of novel agents into autologous stem cell transplantation (ASCT) has markedly improved the outcomes of younger patients with newly diagnosed multiple myeloma (MM). Superior results with experimental treatments vs previous standards of care have been reported after preliminary analysis and need to be confirmed with longer follow up. In a previous analysis performed by GIMEMA Italian Myeloma Network with a median follow-up of 36 months (mos), superior CR/nCR rates and extended Progression Free Survival (PFS) were demonstrated with bortezomib-thalidomide-dexamethasone after double ASCT. At the 2013 ASH Meeting, an updated analysis of the MM-BO2005 study (patients enrolled: 474, 6 of them by the U.O.C. Ematologia e Trapianti) was reported (unpublished data) demonstrating: 1) a persistent PFS benefit with VTD vs TD in the overall population, as well as in subgroups of patients with high risk and low risk MM; 2) the ability of VTD incorporated into double ASCT to overcome the adverse prognosis related to t(4;14); 3) the significant contribution of VTD consolidation to improve outcomes seen for patients randomized to the VTD arm; 4) the lack of more resistant relapses after exposure to VTD as induction and consolidation therapy compared to TD.

CMV reactivation is not uncommon in haematological malignancies after stem cell transplantation procedures and because of its well known impact on morbidity and mortality on this patient population, studies investigating possible correlations between previous treatments and CMV reactivation are warranted. Our Unit is involved in these studies, both regarding lymphoma and myeloma patients. In the latter category of patients, we already demonstrated that novel chemotherapeutics used in the induction phase, is the only factor significantly associ-

ated with the occurrence of post-transplant CMV infection after the first ASCT. At present, we are investigating the role of

immunomodulators on the risk of CMV reactivation after the second ASCT.

Primary central nervous system lymphoma (PCNSL) represents a huge challenge for clinicians and researchers, as the identification of prognostic biological factors and new therapeutic targets for more effective and less toxic treatment strategies are drastically needed. The U.O.C. Ematologia & Trapianti Unit, along with the Neurosurgery Unit and the Clinical Pathology Unit, are involved in this research area, investigating, in the clinical setting, innovative therapeutic approaches in the framework of IELSG clinical trials as well as studying, in the biological setting, the role of flow cytometry immunophenotyping in the diagnosis of this disease.

In recent years, Biosimilar Granulocyte Colony-Stimulating Factor (G-CSF) has been widely used both in neutrophilis recovery after myelosuppressive chemotherapy and in autologous peripheral stem cell mobilization. However, little is known about the safety and efficacy in comparison with traditionally used lenograstim and filgrastim. We performed two retrospective studies, evaluating either neutrophilis engraftment after ASCT or the autologous peripheral blood stem cell mobilization in adult patients with haematologic malignancies. The results of both studies were presented at the 2014 Annual European Bone Marrow Transplantation (EBMT) Meeting, held in Milan (Italy), 30.3-02.04 2014. To address these issues, further studies on a larger number of patients are needed where our Unit is actively taking part in it.

The research activities of the U.O.C. Ematologia & Trapianti Unit were aimed at carrying out clinical trials of primary relevance in different hematological malignancies working in cooperation with other haematological institutes. In particular, our

Unit is a member of the following cooperative group:
- Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA)
- European Organisation for Research and Treatment of Cancer (EORTC)
- Fondazione Italiana Linfomi (FIL)
- International Extranodal Lymphoma Study Group (IELSG)
- Gruppo Romano Mielodisplasie (GROM)
- Gruppo Laziale Sindromi Mieloproliferative Croniche Ph1 neg.
- Sorveglianza Epidemiologica Infezioni Fungine in Emopatie Maligne (SEIFEM)
- Dutch-Belgian Cooperative Trial Group for Hematology Oncology (HOVON)
- Gruppo Italiano Trapianto Midollo Osseo (GITMO)

During 2012-2013, 43 clinical research protocols proposed by the U.O.C. Ematologia & Trapianti were approved by the Regina Elena National Cancer Institute's (I.F.O.) Ethics Committee where 241 patients were enrolled.

Publications 2012-2013

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Activities 2012-13

The Division of Medical Oncology A has a long standing commitment in improving the detection and treatment of solid cancers. In 2012 and 2013, approximately 5000 new patients with solid cancers visited our Division, which has one of the largest referral programs for this disease. The Division's clinical activity guarantees the treatment and assistance for cancer patients requiring drug administration and clinical follow up. In particular, the Division is developing clinical research and new treatment strategies on solid tumors, especially gastrointestinal, lung, breast, gynaecologic tumors and melanomas, using either biological response modulators or drugs, molecularly aimed at specific biologic targets for different tumors, in addition to the classic antineoplastic drugs. The Division adopts regimens with optimal efficacy and with a low toxicity profile, such as the continuous infusion regimens which produce a lower burden of individual toxicity, offering patients an acceptable quality of life. Other fields of interest include the treatment of cancers which require a wide experience in medical oncology (e.g. gonadal or extragonadal germinal cell tumors and soft tissue and bone sarcomas).

Clinical activity is supported by an interdisciplinary Disease Management Team (DMT). Currently, DMT are operational for patients with tumors of the breast, lung, pancreas, biliary tract, gastrointestinal, liver, central nervous system, genito-urinary, head and neck, and sarcoma. In each DMT, a group of Physicians is dedicated to the treatment and follow up of patients according to guidelines or to approved experimental protocols. Team members provide state of the art diagnosis and treatment of patients with solid cancers, and are able to follow the patient by continually updating the database that tracks the patient.

The Division of Medical Oncology A consists of an in-patient unit including one with a total of 22 beds, an Ambulatory Service equipped with 14 visiting rooms for outpatient activities and a Day Hospital for delivering selected anticancer therapies. Approximately 20.000 visits and 15.000 medical antineoplastic treatments are performed every year.

The main research topic of the Division is the study of new drugs, their combinations and/or sequence and new strategies of integrated treatments.

The Division is committed to conducting clinical trials in collaboration with the pharmaceutical industry, and to designing

and carrying out investigator-driven clinical trials. Special emphasis is given to new drug developments and various collaborations with laboratory researchers to identify molecular prognostic or predictive biomarkers.

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Department of Medical Oncology

Unit of Medical Oncology B

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Technician: Anna Maria Edlisca

Activities 2012-13

Clinical Activities

The Division of Medical Oncology B seeks to gain insights that lead to cancer prevention and to improving diagnosis and treatment of adult patients with cancer. The Unit is composed of specialists in Medical Oncology who dedicate their time to the clinical management of over 600 new cancer patients/year.
The Unit is subdivided into small groups where each group is dedicated to a specific tumor (1-3 physicians). The physicians of each group are responsible for both clinically managing patients and applying the scientific strategies in their pertinent field.
The clinical activities of the Department are organized along the lines of an inpatient hospital service and solid tumor program outpatient clinics.

Clinics

The outpatient clinics are organized into solid tumor types with faculty dedicated to each solid tumor program caring for patients within specialty clinics. This type of service approach is especially useful during the first meeting with the patient, for routine clinical controls and for oncological screening activities, in order to diagnose neoplastic diseases at an early stage, therefore with a greater chance of a cure. First time visits, routine control visits and screening appointments are booked through the RECUP by calling the telephone number: 80.33.33. The waiting time for first time visits or oncological screenings does not exceed four days. Routine control visits are booked in agreement with the referring physician.

Hospitalization

All hospitalized medical oncology patients are admitted to a Medical Oncology B Ward Service consisting of an MD assistant and a MD fellow. Oncologists work from 8.00am to 8.00pm (Saturdays from 8.00am to 02.00pm and Sundays there is a doctor on duty) and are always available via mobile. Nursing staff are on duty 24 hours a day. Several activities are carried out: chemotherapy treatments, supporting therapies, advice from other specialists, diagnostic examinations, and psychological support. During their stay patients may receive visitors, participate in religious celebrations, go to the various cafeterias after being authorized by nurses. The waiting-time before being admitted to the Oncology Unit is of approximately ten days.

Day Hospital

Patient stay at the day hospital unit is carried out over several admission dates. Oncologists work from 8.00am to 2.30pm. Activities of the day hospital include: administering chemotherapy treatments and supporting therapies, receiving advice from other specialists, carrying out examinations, and providing psychological support. Once these daily activities are completed, patients return home and go back to the day hospital for their next admission. The waiting-time for a patients first-time visit/admission at the day hospital does not exceed seven days.

Due to the complexity of neoplastic pathology, a close collaboration among various specialists is required. Based on this principle the indication and choice of both diagnostic and therapeutic procedures used of each single patient are defined weekly during meetings termed "Disease Management Team" (DMT) under different residency specialist areas (oncologists, general surgeons, thoracic surgeons, ENT specialists, urologists, gynecologists, pathologists, radiologists and radiotherapists).
Further available resources consist of a data-management office, including one MD Assistant, four MD fellows and a research technician.

Research Activities

During 2012-2013, the Division of Medical Oncology B established and reinforced collaborations with several oncologic associations, universities, and pharmaceutical companies in common research areas. The clinical research activities focused on the evaluating new treatment strategies for solid tumours, specifically regarding innovative molecularly targeted drugs and their synergistic interactions with antiblastic chemotherapy or endocrine treatments. The research activities performed during 2012 and 2013 covered several fields in medical oncology, mainly breast cancer, gynaecologic cancers, and lung cancer.

Breast Cancer

The Division of Medical Oncology B acted as coordinator center in a variety of breast cancer clinical trials in neoadjuvant, adjuvant and advanced setting, in collaboration with other Italian cancer centers.

Neoadjuvant Setting

We designed a single centre prospective trial based on the use of trastuzumab in combination with docetaxel followed by epirubicin plus cyclophosphamide in patients with HER2-positive breast cancer (DECT trial). From December 2013, 43 patients entered the study, and 23/38 patients achieved a pathologic complete response. Enrolment is still ongoing. Preliminary data was discussed in a poster presentation at the ESMO and AIOM 2012 Conference.

Adjuvant Setting

In this setting, we coordinated and concluded a phase III multicenter randomized trial in order to test the efficacy of 4 cycles of

epirubicin/cyclophosphamide regimen versus the same regimen preceded by 4 cycles of docetaxel in node positive breast cancer patients. This is the first study testing the sequence taxanes→anthracyclines as adjuvant treatment in breast cancer patients. Accrual was completed in October 2005 with 750 patients enrolled in the study (147 in the Division of Medical Oncology B). The manuscript was published in Ann Oncol (2012).

In addition, our division significantly contributed to a significant cohort study assessing the predictive role of fasting glucose on treatment outcomes in nondiabetic patients with HER2 positive breast cancer. The study results were published in Ann Oncol 2012.

Moreover, another project, focused on the efficacy of the synergistic activity and the potential endocrine-resistance reversal of the metformin-fulvestrant (A multicentre phase ii randomized study of fulvestrant versus fulvestrant + metformin as first- and second-line endocrine treatment in nondiabetic postmenopausal women with hormone receptor positive, her-2 negative advanced breast cancer. THE META TRIAL) combination in advanced breast cancer was presented to the Ministry of Health within the 2011-12 call. This study further aimed to assess the predictive role of circulating, genomic and proteomic biomarkers on treatment outcomes.

Advanced breast cancer

During 2012-13, much effort was devoted to developing a new combination in molecularly targeted treatment, with a specific focus on multikinase inhibitors, mechanisms of resistance to endocrine treatment, cardiotoxicity risk, including testing some SNPs, and evaluating activity of hormonal agents in postmenopausal patients (Fides trial). Since 2011, various multicenter clinical trials have been designed and patient enrolment started, concerning new chemotherapic agents (eribulin) and hormonal treatment (FulFive).

In this setting, we participated in the study an open-label, multi-center, expanded access study for postmenopausal women with estrogen receptor positive locally advanced or metastatic breast cancer who have progressed following prior endocrine therapy, investigating the treatment of everolimus (RAD001) in combination with exemestane", sponsored by Novartis. 19 patients were enrolled in this trial.

Another project, focused on the efficacy of the synergistic activity and the potential endocrine-resistance reversal of the metformin-fulvestrant (A multicentre phase ii randomized study of fulvestrant versus fulvestrant + metformin as first- and second-line endocrine treatment in nondiabetic postmenopausal women with hormone receptor positive, her-2 negative advanced breast cancer. THE META TRIAL) combination in advanced breast cancer was presented to Minister of Health within the 2011-12 call. This study further aims to assess the predictive role of circulating, genomic and proteomic biomarkers on treatment outcomes.

Moreover, our Division was involved in another scientific, multicenter, clinical trial, concerning endocrine-resistance reversal in breast cancer (A phase III randomized, double blind, placebo controlled study of BKM120 with fulvestrant, in postmenopausal women with hormone receptor-positive HER2 negative AI treated, locally advanced or metastatic breast cancer who progressed on or after mTOR inhibitor based treatment- BELLE 3) sponsored by Novartis.

Our division also participated in two national, observational, retrospective trials called HERLAPAC and PROMHER.

In addition, during 2012-2013, the Division of Medical Oncology B collected data on tumor, patient characteristics and outcome, with subsequent publications in international scientific journals.

Other Tumors

The Division of MOB is also involved in several other trials in gastric cancer, gynaecological cancers, colorectal cancer, lung cancer, melanoma, and soft tissue sarcomas. Among the latter, gastrointestinal stromal tumors (GIST) have received particular attention through participating in trials evaluating targeted agents and in studies summarizing clinical and therapeutic aspects.

Two translational studies on cervical cancer are currently ongoing: a) the evaluation of ERCC1 expression in cervical cancer patients treated with neoadjuvant TIP regimen, correlate ERCC1 expression with pathological complete response; b) to evaluate HER-family (EGFR, HER2, HER3, HER4) expression and their modulation during neoplastic progression (from initial dysplasia

towards invasive carcinoma). Preliminary results were presented as poster at the 2012 International FIGO Congress.
In 2013, the Division of Medical Oncology B, designed an observational study with a prospective design aimed at testing the predictive role of a miR signature including miR-484, -642, and -217 in patients with relapsed, high grade serous (HGS) ovarian cancer re-challenged with platinum-based regimens ("Predictive role of a microRNA signature in relapsed, high-grade serous, ovarian cancer patients re-challenged with platinum based regimens").
Moreover, in 2012-2013, the Division of Medical Oncology B started/continued the enrollment in some multicenter prospective/retrospective clinical trials, which will continue in 2014.
In addition, during 2012-2013, the Division of Medical Oncology B collected data on tumor, patient characteristics and outcome, with subsequent publications in international scientific journals.

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Department of Oncology

Unit of Radiation Oncology

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Activities 2012-13

Clinical Activities

All our activities include treating tumors with external beam radiotherapy such as Intensity Modulated Radiotherapy (IMRT) and Rapid Arc (RA), Stereotactic Radiotherapy Surgery (SRS) of both brain and extracranic lesions, intraoperative radiotherapy (IORT) of breast, head and neck tumors as well sarcomas.

Research Activities

Our research focuses in hypofractionation for prostate cancer; IORT for breast cancer; Hypofractionation for breast cancer; Predicting response to (chemo) radiotherapy with MR for head and neck tumors; Early assessment and prediction of long term xerostomia according to both morphological (CT based) and functional (MR based) changes during (chemo) radiotherapy for head and neck cancer; Predicting response with MR during neoadjuvant chemoradiotherapy for rectal cancer.

Publications 2012-2013

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Activities 2012-13

Clinical Activities

The aim of the Clinical Pathology Unit is to provide accurate diagnosis and information of prognostic and therapeutic value to medical doctors, as well as to carry out research on cancer diagnosis, prognosis, and treatment. Much effort is made toward the identification and use of the most appropriate and innovative technologies in cancer diagnosis and treatment monitoring. This is supported by the close collaboration and interaction between physicians and preclinical investigators across different disciplines.

The Clinical Pathology Unit carries out laboratory biological tests using the most modern investigation techniques, that contribute to the clinical management of oncologic patients undergoing conventional and experimental therapies.

In 2013, more than 1,000,000 examinations were carried out, about 20% of the activity consists in high specialized diagnostic procedures.

	Examinations n°	Return euro
In-patients	508.120	1.769.994
Out-patients	531.562	3.524.377
Tot	1.039.682	5.294.371

The reliability of the results is guaranteed by high quality standards, constantly monitored by national and international External Quality Assessment (EQA). The Clinical Pathology Unit obtained a Certificate in Quality Management System under UNI EN ISO 9001:2000 since 09/26/2002. Following the renewal of the inspection carried out in July 2009, this Unit obtained the UNI EN ISO 9001:2008 certification for all diagnostic activities and clinical research in oncology (3-year certified n.IT253872 Bureau Veritas, exp. 03/03/2017). This certification allowed the Unit to participate in more than 30 different clinical trials enrolled at our Institute.

Medical laboratories are key partners in patient safety, where laboratory results influence 70% of medical diagnoses. Providing quality laboratory service is vital, directly affecting the quality of healthcare given. With this in mind, we prepared to meet the requirements in the International Standard ISO 15189, the first developed, particularly in the accreditation of medical laboratories. This accreditation emphasizes the laboratory-client interface and provides the best patient care promoting excellence.

Since the decree B1656 of April 2011 was sanctioned by the Lazio Region, the Unit has been a member of the Regional Network Laboratory. It was established for implementing and re-organizing the Medical Laboratory within the Lazio Region Hospital Network. The aims of the network include: organizing regional electronic

files for laboratory reagents, instrumentation and analytical methods for diagnostic procedures in Clinical Pathology, Microbiology, Pathology and Transfusion Medicine. A survey was conducted to support the Central Purchasing Office in preparing specific technical requirements for future regional competitions and for reviewing the facilities and skills of the local healthcare units. Moreover, at the moment the a number of laboratories are being selected for the highest specialized diagnostic procedure used.

Research Activities

The Unit significantly supports activities for clinical research trials conducted at the IRE and in several Italian and International Universities. It is also involved in the development of a institutional bio-bank adopted as a strategic link between clinical and research activities. The research program of the Unit focuses on the identification and validation of cancer-related molecular targets, the utilization of new technical approaches for tumour diagnosis, prognosis and monitoring in the context of innovative cancer therapy, the optimization of new drugs in experimental models by testing their delivery systems, for the best bench-to-bed-side clinical research application.

A new test, the 'Prostate Health Index (*phi*)" (Beckman Coulter, Inc.), based on a novel clipped form of the precursor form of PSA, called -2proPSA, has recently been introduced in our Lab. The -2proPSA is a component of a mixture of different forms of unbound PSA, called "free PSA". Its collective measurement was the basis of the last FDA approved diagnostic marker for prostate cancer after it was approved by the FDA in 1998. After more than a decade of research on the -2 pro PSA molecule by Dr. Slawin and others, using a blood test developed by Beckman Coulter, who exclusively licensed the technology from Dr. Slawin/Baylor College of Medicine, that could specifically measure it in the blood, the new "Prostate Health Index" (*phi*) was developed. It incorporated total PSA, free PSA and the new -2proPSA into a new mathematical ratio. The use of the *phi* reduced the risk of unnecessary biopsies due to "false positive" elevations, and was better at identifying high risk, potentially lethal prostate cancers, than the standard PSA test or the percent free PSA alone. Up to now, we have analyzed 107 samples, whose blood will be

analyzed to correlate different prostate cancer biomarkers.
The introduction of a new methodology that allows the identification of circulating TF microparticles is also in process. TF is an integral membrane protein, which is normally separated from the systemic blood circulation by the vascular endothelium. It forms a complex with Factor VIIa and plays a key role in initiating the blood coagulation cascade leading to thrombin generation and subsequent formation of fibrin clots.
TF is expressed by normal tissue and cells and after stimulation, by various cytokines, also by monocytes and macrophages. It is also known to be present in tumour cells, where its expression may support the metastatic potential of tumour cells. Moreover, TF is postulated to have a crucial role in the pathogenesis of cancer-associated VTE. Therefore, the investigation of TF for predicting VTE in cancer patients has attracted a lot of interest over the past few years. This approach should improve the identification and monitoring of the metastatic potential of cancer.
A bio-bank may be defined as the long-term storage of biological samples for research or clinical purposes. The future success of translational research is critically dependent on the availability of high-quality tissue specimens linked to accurate diagnostic and clinical information about the individual banked specimen. For optimal use, the banked human tissue needs to be appropriately consented, collected, classified and stored together with an accurate treatment and collection of outcome information from the patients who donated the tissue. The Institutional Biobank Group was established with the no. 180 on 14 March 2014, which includes a Steering Committee and an Operating Group. The Clinical Pathology Unit provides the collection and storage of peripheral blood biological samples such as serum and plasma, urine, spinal fluid, and tumour cells suspension as well as DNA and RNA for Institutional clinical trials and research projects. In order to meet the requirements of quality and traceability of biological samples, different protocols are utilized for the samples criopreservation, using tubes with two-dimensional codes and specific data base software for information storage and updates. An improvement of such relevant core facilities in terms of acquiring the most appropriate and innovative technologies for cancer cell and peripheral blood samples storage is one of the Unit's aims to guarantee the Regina Elena National Cancer Institute the best fluid tissue bank facility.
To ensure compliance with the laws and regulations concerning the conservation of biological samples, the Clinical Pathology Unit has also enhanced the monitoring of the temperature of the freezer with a reliable, valid alarm system.
In collaboration with the Pathology Unit, an informed consent was drawn up, submitted to the Ethics Committee, subsequently validated and added to the medical record.
The ongoing research projects focus on the role of coagulation disorders, angiogenesis and multi-parameter flow cytometry application for the diagnosis, prognostic stratification and treatment monitoring in cancer patients.

Coagulation disorder

Cancer is associated with pro-coagulant changes, angiogenesis and matrix remodeling. Pro-coagulant mechanisms are associated with tumor progression and metastasis. In paediatric patients, venous thrombosis (VT), although infrequent, is a severe cause of morbidity. In our Unit, we evaluated the prevalence of VT in children with solid tumours, demonstrating a significantly higher risk of VT in neuroblastoma (NB) stage 4 disease patients compared to other cancers ($P<0.05$). Our study highlights the relevant role of NB in the pathogenesis of thrombosis in patients with metastatic disease (Schiavetti A. et al J Pediatr Hematol Oncol. 2010).

Angiogenesis

In collaboration with the Paediatric Department of the University of Rome "La Sapienza", and the Department of Oncology in Liverpoool, we investigated the sVEGF-A level in patients with newly diagnosed RMS demonstrating a higher sVEGF-A level in high risk RMS patients compared to the low risk population. Larger prospective studies are currently ongoing to confirm the potential role of sVEGF-A for a better prognostic stratification of patients with RMS (Schiavetti A. et al. Pediatric Blood Cancer 2012).
Bevacizumab (BV), a monoclonal antibody against VEGF, is utilised in recurrent malignant glioma (MG), however the correlation between VEGF levels and response to BV has not been

investigated so far. In collaboration with the IRE Division of Neurology and the IRE Medical Oncology, we performed a prospective analysis on recurrent MG patients treated with BV alone or in combination with chemotherapy, evaluating the sVEGF, pVEGF and pro-coagulant factors such as Tissue Factor (TF) and Thrombin/Antithrombin Complex (TAT) plasma levels. From our study a significant difference between serum and plasma VEGF levels in responding patients compared to non responding patients has been found (p=0.003).

Multi-parameter flow cytometry

In collaboration with the Division of Neurosurgery within IRE, we characterized, by flow cytometry, the brain stereotactic biopsy of 16 consecutive patients with primary central nervous system lymphoma (PCNSL), providing evidence that a single brain stereotactic core biopsy is a reliable source for multiparameter flow cytometry characterization of brain lymphomas and tumour reactive side population, significantly supporting the histopatological diagnosis for a better classification and management of brain lesions (submitted for publication).

Cerebrospinal fluid (CSF) cytology is the gold standard for cancer neoplastic meningitis (NM) diagnosis. More recently, CSF flow cytometry has shown to significantly increase diagnostic accuracy in haematological NM. In collaboration with the Division of Haematology at IRE, we assessed the value of multi-parametric flow cytometry immunophenotype of CSF sample for the identification of acute leukaemia and non-Hodgkin lymphoma NM and compared the sensitivity of this innovative approach with conventional cytology. This confirmed the high sensibility and specificity of CSF flow cytometry on NM diagnosis as wells as demonstrating that flow cytometry sensitivity is several-fold higher than cytology for detection of minimal residual disease, particularly in CSF low cell counts (manuscript in preparation). In collaboration with the Division of Neurology and Medical Oncology at IRE, we have also characterized 15 cases of breast cancer in NM, identifying the immunophenotype of those cancer cells able to pass the Brain Blood Barrier, demonstrating that flow cytometry can significantly improve the diagnosis and monitoring of this severe complication, allowing an early identification of the disease.

The goal of treatment for multiple myeloma (MM) is to improve patients' long-term outcomes which are significantly associated to the quality of response to treatment. In our laboratory, we compared the free light chain assay and the bone marrow minimal residual disease (MRD) identification by flow cytometry in patients with multiple myeloma before and after autologous stem cell transplantation, treated at the Division of Haematology within IRE. Our preliminary results show that, since the flow cytometry is highly sensible in MRD monitoring, the serum free light chain determination can predict the relapse of the disease, illustrating it to be a powerful approach in identifying the appropriate timing for the bone marrow flow cytometry study.

In collaboration with the Clinical Dermatology of the IFO the S. Gallicano Institute**,** we characterized a large series of skin biopsies of patient with para-psoriasy and related disorders by flow cytometry, we then compared this approach with the histological, molecular, and clinical findings. The high specificity of flow cytometry suggests that it will be a useful adjunct to routine histology in the evaluation of skin biopsies. Moreover, immunophenotype seems able to identify those cases more likely to progress to more aggressive forms of skin disease like Mycosis Fungoide.

Innovative diagnostic marker

In collaboration with the IRE Urology Division, we investigated the prostate cancer gene 3 (PCA3), a non-coding mRNA specifically expressed in prostate tissue whose level increases by 60 to 100 times fold in patients with PCa. Urine PROGENSA PCA3 and serum free and total PSA (fPSA and tPSA respectively) tests were carried out on 1500 subjects with at least two risk factors for prostate cancer and a previous negative biopsy. Urine samples were collected after DRE. Up to now 231 men repeated a biopsy after PCA3 test, and its score was correlated to biopsy outcome, while its diagnostic accuracy was compared to those obtained from PSA expressed as tPSA and PSA ratio (fPSA/tPSA).

The urine PCA3 test, compared to the serum PSA test, showed its ability in predicting the presence of PCa with greater probability, thereby facilitating the rational selection of patients that

may benefit from repeating a prostatic biopsy when the risk for this pathology persists. Moreover, in our case, it seems to have a prognostic value too, as lower PCA3 score values are associated with a lower Gleason score and higher PCA3 score values are associated with a higher Grading. A conclusive definition of the threshold value is able to discriminate patients with prostate cancer from healthy individuals and to finally consolidate the prognostic value of PCA3 score where the clinical course of the enrolled subjects will be further monitored

Finally in collaboration with the Department of Medicine Surgery and Dentistry of University of Milan. we investigated in breast cancer the procoagulant changes, angiogenesis and matrix remodelling, mediated by the host and the tumour. Procoagulant responses are associated with tumor progression and metastasis, circulating physiologic anticoagulants are decreased in cancer patients, while the receptors thrombomodulin (TM) and endothelial protein C receptor (EPCR) are downregulated and/or shed from the endothelium due to inflammatory mediators and thrombin generation. Therefore, the soluble receptors sEPCR and sTM may be considered markers of endothelial activation by different mechanisms. Circulating sEPCR functions as a procoagulant, and has been shown to be associated with venous and arterial thrombosis. Circulating markers of coagulation, inflammation and angiogenesis in women with breast cancer were markedly increased compared to normal women, but did not correlate with breast cancer basic features (TNM), or with the women's age at presentation. The positive correlation between sEPCR and TAT levels confirm the procoagulant effect of sEPCR. Circulating markers of coagulation and inflammation possibly represent a general response of the host to the tumor. As in other cases, they might be more useful prospectively to identify thrombosis prone patients. Furthermore, only the follow up of this group of patients can be able to confirm whether these parameters predict a worse prognosis.

Ongoing research projects

Pilot Study of interference in vivo biological antineoplastic drugs by electrophoretic methods used in the diagnosis of plasma cell dyscrasias. PI G. Cigliana

The purpose of this study is to identify "in vivo" if the anti-neoplastic drugs considered "organic" in this protocol, caused alterations in the electrophoretic pattern allowed to reduce the false reports of CM by simply implementing a communication policy between the laboratory and medical applicants in reporting their activities of the patient in question. In vivo confirmation of the interference observed in vitro lead to drafting specific guidelines and the setting up computerized communication systems between clinicians and laboratory applicants in order to ensure the appropriateness of the prescriptive and analytical electrophoresis method.

Validating the use of PIVKA-II serum test in monitoring HCC development and stratifying patients with a greater risk for recurrence of HCC after liver transplant: a prospective study. PI G. Digiesi

Aims: To define the role of AFP and PIVKA-II, used alone or in combination, as markers in monitoring HCC pathological progression in monitored patients and characterize the ability of AFP and PIVKA-II, used alone or in combination, in predicting those with higher risk of recurrence among patients who underwent a liver transplant after HCC.

Diagnostic and prognostic value of blood dosage of Galectin-3 in prostate cancer. PI L. Tomao

This project aims to assess the clinical utility and diagnostic accuracy of the test serum of Galectin-3, alone or in combination with free and total PSA, by comparing a population of patients with PCa and BPH patients.

Calreticulin in early chronic lymphocytic leukemia. PI Antenucci A

Calreticulin (CRT) is an endoplasmic reticulum luminal Ca2+-binding chaperone protein. Recently, it was found that the soluble CRT (sCRT) level in lung cancer patients was significantly higher than healthy individuals. Information dealing with sCRT in patients with hematologic neoplasms are lacking. The purpose of this study is to evaluate serum level of CRT in a series of patients with early chronic lymphocytic leukemia, correlating with known prognostic variables and time to treatment.

Role of flow cytometry in minimal residual disease monitoring in Multiple Myeloma patients utilizing the new biological drugs. PI Masi S

In collaboration with the IRE Division of Haematology, we demonstrated a significant association between minimal residual disease, identified by flow cytometry, and disease free of survival in Multiple Myeloma patients after double autologous stem cell transplantation (manuscript in preparation). We are now adopting the same approach for the treatment response evaluation in MM patients using the new biological strategies. Our preliminary results show a faster and significant reduction of tumour plasma-cells compared to conventional approaches.

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Department of Oncological Prevention and Diagnosis

Unit of Digestive Endoscopy

Marcello Anti, MD

Director

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Nurse Coordinator: Guglielmo Irti
Nurses: Daniela Cannone, Paola Capra, Giuseppe Guastamacchia, Giuliana Panico, Susanna Pimpinella, Marina Santamaria,
Health Worker: Mario Di Stefano, Cinzia Torresi

Activities 2012-13

Clinical Activities

Cancer Prevention

Our research projects focused on Colorectal Cancer (CRC) screening in average-risk subjects.
Cancer Screening in high-risk individuals affected with breast cancer, early onset CRC with/without familial history, long-standing Inflammatory Bowel Diseases, Familiar Gastric Cancer.
-Family/Hereditary CRC Clinics – Molecular Diagnosis and Assessment of individual risk: individuals with diagnosis/suspicion of Hereditary CRC syndrome (HCCS) are referred to the dedicated outpatient clinics for genetic counselling and are selected for tissue molecular screening and mutational analysis of the suspected genes. Since 2005, the Gastroenterology and Digestive Endoscopy Unit has been recognized as the Familial Adenomatous Polyposis (FAP) Referral Centre of Lazio Region. The main activities of the Reference Centre are: to organize dedicated (reserved) routes for the clinical management of the affected individuals (diagnosis and follow-up), to organize Workshops, Educational training/courses and Congresses, and to produce information brochures on FAP.

Diagnostic-Operative Endoscopy

-Diagnosis of "early" cancerous lesions and precancerous lesions of the gastrointestinal tract by using advanced technologies (High Definition, Cromoendoscopy, Electronic Cromoendoscopy).
-Endoscopic treatment of neoplastic lesions (Difficult Polipectomy, Mucosectomy, Argon Plasma Coagulation).
-Diagnostic and Operative Endoscopy of bilio-pancreatic tract
-Diagnostic and operative Endoscopic Ultrasounds
-"Wireless Endoscopy" (videocapsule endoscopy for large and small bowels)
- Upper and lower Single Balloon Enteroscopy
- Palliation of advanced cancer of gastrointestinal tract ("stenting" and dilation)
-Emergency endoscopy for acute gastrointestinal bleeding and foreign body extraction
- Percutaneous Endoscopic Gastrostomy (PEG) for long term enteral nutrition

Outpatient Activities And Gi Consultations

- General Outpatient Gastroenterology
- Outpatient Hepatology
- Family Cancer Clinic
- Celiac Disease Referral Centre of Lazio Region
- Clinical Nutrition Outpatients Clinics
- GI consultations for inpatients and outpatients of all the Departments and Units of IFO
24-HOUR AVAILABILITY OF ENDOSCOPY

Research Activities

Our Unit's main research area is the field of colorectal cancer diagnosis and prevention, particularly, familial and hereditary colorectal cancer. Since 1983 the Unit has been involved in clinical, molecular and genetic studies on Familial and Hereditary Colorectal Cancer Syndromes, in the context of specific research projects. During

the last 30 years the expertise necessary for clinically managing these kinds of patients at the Family Cancer Clinics has been acquired and several scientific papers have been published on the issue.

A further field of interest is Celiac disease. Since 2003, a multidisciplinary clinical study in cooperation with IRE and ISG facilities has been carried out in patients with Celiac disease to assess dermatological and other autoimmune related diseases. Furthermore, in 2009 the Gastroenterology and Digestive Endoscopy Unit was officially recognized as the Celiac Disease Referral Centre of the Lazio Region.

In the last 3 years, the Unit carried out the following Research Projects:

- Hereditary colorectal cancer syndromes: novel strategies for appropriate patient selection, high-sensitivity/cost-effective genetic screening and tailored cancer surveillance programs. (NEW IDEA, current research funding).
- Collaborative Multicentric Study MOMA (Modifiers of Mismatch repair alleles), of CONSAMM (Consorzio per lo studio degli alleli del Mismatch Repair dei loro modificatori; coordinator of the study Dr. Malcolm Dunlop, Edinburgh University.
- "The TEF Project (Network nazionale italiano tumori eredo-Familiari)": to share the scientific knowledge, the technological resources and the clinical management of Hereditary Tumours syndromes, to optimize clinical guidelines and to improve the genetic-oncological counselling in the dedicated Centers. Furthermore, a major aim is to share and draft clinical and translational research projects. (funded by Alleanza Contro il Cancro)
- Multidisciplinary clinical study for Familial and Hereditary Colorectal Cancer syndromes .
- "Phase III study on celecoxib controlled with placebo in subjects genotype positive for familial Adenomatous polyposis", (funded by Pfizer).
- "Comparison of balloon assisted enteroscopy (BAE) and capsule endoscopy (VCE) on diagnostic and prognostic efficacy of Familial Polyposis affected individuals".
- Multidisciplinary Clinical Study for Celiac Disease and related autoimmune and dermatological diseases
- MAG Study: Metaplasia Atrophy and Gastritis. Multicentric observational study (sponsor : AIGO and SIED)
- EUS evaluation of gastric wall in gastric lymphoma affected individuals before and after chemotherapy.
- HPV anal rectal disease treatment in cooperation with HPV Unit

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Department of Oncological Prevention and Diagnosis

Unit of Endocrinology

Marialuisa Appettecchia, MD

Director

STAFF Endocrinologists: Roberto Baldelli, Agnese Barnabei
Healthcare Assistants: Aurora De Leo, Maristella Mereu
Attending Endocrinologists: Antonella Paoloni, Francesca Rota
PhD Students: Laura Rizza, 20 students from University La Sapienza for one-month training

Activities 2012-13

Clinical Activities

Thyroid carcinomas (Differentiated and Medullary)

Patients with thyroid nodules who under our care are appointed a diagnostic health-care path which provides diagnostic laboratory tests (thyroid hormones) and instrumental tools (i.e. echocolor doppler thyroid scan and FNAB) in order to diagnose the nature (benign/malignant) of the nodular lesion. In case of suspecting or overt malignancy, patients are sent to undergo surgery or other treatments as appropriate, depending on their individual evaluation.

Patients with a differentiated diagnosis of thyroid cancer are regularly included in the follow-up at the Endocrinology Unit where laboratory and instrumental tools are used to carry out routine checks.

For all patients with thyroid cancer the following services are available: routine medical checks (follow-up), physical examinations, evaluations through laboratory support in order to investigate the state of the disease. The optimal frequency of follow-up assessments are personalized, in accordance with the stage of the patient's illness.

Hereditary endocrine tumours

Currently, the Endocrinology Unit follows:

- Over 100 patients with medullary thyroid cancer and their families
- Approximately 5 families with multiple endocrine neoplasia type I or type II (MEN 1 and 2),
- 20 patients with pheochromocytoma syndrome or pheochromocytoma / paraganglioma and their
- families
  50 patients with familial polyposis and endocrine diseases

It is for these reasons that an outpatient clinic dedicated to studying genetic counseling and prevention of hereditary oncological diseases has been activated. The incidence of these types of cancers is estimated to be approximately 5-10% of all cancers. Thus, it provides the following:

Multidisciplinary assessments or patients with suspected familial endocrine neoplasia having medical appointments with endocrinologists, geneticists, psychologists; along with the involvement of other specialists (oncologists, surgeons, gynecologists, gastroenterologists, molecular biologists, pathologists, radiologists) at different stages of diagnosis and therapy. They will also be undergoing molecular analyses for detecting small or large mutations in the genes responsible for: RET, MEN-1, VHL, SDHB, SDHD, SDHC. The patient with familial endocrine neoplasia is followed right from the first clinical suspicion of disease to molecular diagnosis, studying the family history to organizing follow-up examinations and indications for surgical treatment, and subsequent radio and chemotherapy treatments through to newer biological approaches, all with the support and help of a team of psychologists.

Osteoporosis and bone metabolism disorders in cancer patients

In patients with oncological disease, most cases are long-term survivors who, as a result of therapeutic treatments, experience menopause at times early therefore, with frequent reoccurring problems related to bone metabolism, or due to demineralizing effects of some drugs (e.g.: steroids).

In these patients, treating metabolic bone disease becomes all the more necessary than in non-cancer patients, not only for the overall improvement of its compliance but also for the psychological implications.

It is also reported that some metabolic bone diseases tend to emulate clinically neoplastic diseases while others are true paraneoplastic disorders.

The Endocrinology Unit often sees cancer patients to set specific therapies for osteoporosis. Treating these patients need to be based on indicators other than those usually used in non-oncological patients with osteoporosis.

All the more reason why an outpatient clinic dedicated has been activated.

Familial adenomatous polyposis (FAP)

Patients with FAP have a higher risk in developing cancer of the thyroid than the general population; therefore a follow-up visit that includes annual and ultrasound of the thyroid is needed. The Unit of Gastroenterology and Digestive Endoscopy is a Reference Center in the Lazio Region for FAP which, being rare disease, patients should be ensured to receive comprehensive clinical management, with dedicated paths, providing diagnostic evaluations and follow-ups of target organs, including the thyroid.

Diagnostic and therapeutic healthcare paths in patients with FAP APC POS / unknown mutations include undergoing endocrine tests due to the increased incidence of endocrine disease in these patients such as thyroid tumours (Gene variants associated to malignant thyroid disease in familial adenomatous polyposis: a novel germline APC mutation. Martayan A, Sanchez-Destinations L, Baldelli R, Falvo E, Bernabei A, Conti L, Giacomini P Appetecchia M, Stigliano V J Endocrinol Invest. Oct 2010, 33 (9) :603-6.

As a result, the Endocrinology Unit has activated a dedicated clinical path for these patients.

Here, we present the Flowchart for the multidisciplinary assessment of FAP established at our Institute.

Doctor in charge of the reference centre: Vittoria Stigliano

Gastroenterology	Vittoria Stigliano, Lupe Sanchez Mete
Molecular diagnostic	Aline Martayan
Diagnostic imaging	Mauro Caterino, Marcello Greco
Surgery	Maurizio Cosimelli
Endocrinology	Maria Luisa Appetecchia, Roberto Baldelli, Agnese Barnabei
URP-Public Relations Office	Giovanna D'Antonio

At moment, we are following approximately 50 patients affected with FAP and endocrine diseases.

Other topics we are interested include: Neuroendocrine Tumours, Adrenal Tumours, Fertility disorders in cancer patients, Endocrine side-effects of anti-cancer therapies, Pituitary Tumours and Adults Growth Hormone Deficiency (GHD)

Research Activities

The research efforts of the Endocrinology Unit involve evaluating and developing novel clinical and laboratory tools useful in the diagnosis and monitoring of human endocrine cancers.

The Endocrinology Unit has long-standing commitment and care in improving the detection and treatment of endocrine cancers.

In particular, the Unit is involved with clinical research and new treatment strategies regarding thyroid and neuroendocrine tumours.

Other fields of interest include the endocrine effects of tumours or of related treatments, such as Growth Hormone Deficit (GHD) or hypopituitarism in brain neoplasms, hypogonadism and sexual dysfunctions due to gonadal tumours or consequences of surgery, chemotherapy or radiotherapy and their impact on the quality of life of the patients. Ongoing projects include topics regarding osteoporosis and bone metabolism disorders in cancer patients.

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Activities 2012-13

Clinical Activities

The clinical activities covered in 2012 and 2013 include: macroscopy and conventional histopathology on biopsy and surgical samples (surgical pathology), cytology on cytological samples (diagnostic cytology), and clinical necroscopy (autopsy). Furthermore, immunohistochemistry, FISH/SISH analyses, HPV detection a/o genotyping, gene mutational status analyses, and molecular evaluations (OSNA) of sentinel lymph nodes in breast cancer patients were also routinely performed. In 2012 and 2013, surgical or biopsy samples obtained from about 11.000-12.000 patients were studied, these included a whole spectrum of the most common human cancers (particularly, urogenital, lung, breast and colorectal cancers). All cases of malignant tumours were histologically typed and graded according to the most recent WHO classification, and were pathologically staged (pTNM) according to the latest TNM/UICC edition. Ancillay (histochemistry, immunohistochemistry and molecular) studies were performed whenever required. In 2012 and 2013, cytological samples from about 9.000-10.000 patients were studied, including FNAC, effusion, urine and, to a lesser extent, cervico-vaginal cytology. In 2012 and 2013 about 18.000-20.000 diagnostic immunohistochemistry tests were performed, including mainly tumour immunohistological typing and assessment of prognostic and/or predictive factors. In 2012 and 2013 about 600-650 FISH/SISH, 1000-1100 gene mutation, 900-1000 HPV molecular detection a/o genotyping, and 400-450 OSNA tests were carried out. FISH/SISH analyses were performed mainly in selected breast, gastric carcinoma (HER2) and lung adenocarcinoma cases (ALK). EGFr, K-RAS, B-RAF, C-KIT and PDGF-alpha gene mutational status analyses were routinely performed in lung adenocarcinoma (EGFr, K-RAS), in colorectal adenocarcinoma (K-RAS, B-RAF), in metastatic malignant melanoma (B-RAF), and Gastro-intestinal Stromal Tumours/GIST (C-KIT, PDGF-alpha). The One Step Nuclear acid Amplification (OSNA) method was performed for intra-operative quantitative molecular evaluation of the sentinel lymph node status in breast cancer patients. Furthermore, about 150 molecular tests for MGMT promoter gene mutilation status and IDH1-IDH2 gene mutation in primary CNS tumours, and MSI evaluation in colorectal cancer were carried out and have so every year.

Research Activities

Studies on breast, colorectal, lung and gastric cancer, HPV-related diseases, malignant melanoma, and thymic epithelial tumours have mostly been collaborative type studies conducted

with both internal and external research groups that aimed to identify novel biomarkers of prognostic and predictive potential. Molecular analyses, including immunohistochemistry, gene mutation and microRna expression, were performed using formalin fixed and, when available, frozen tissues collected in our institute's biobank.

Breast Cancer

In collaboration with the Translational Oncogenomic Laboratory of the Regina Elena National Cancer Institute, we showed, that microRNA-10b* is a master regulator of breast cancer (BC) cell proliferation, which is downregulated only in tumors. Three novel target mRNAs of miR-10b*, BUB1, PLK1 and CCNA2, whose high expression is associated with reduced disease-free survival, were validated by immunohistochemistry on a retrospective series of human breast carcinomas. In collaboration with the University ''G. D'Annunzio'' of Chieti, we studied the immunohistochemical expression of Phospholipase Cc1 (PLCc1) in human BC starting with evidence that the down-regulation of the stable and inducible form of this protein resulted in an almost complete inhibition of BC-derived experimental lung metastasis formation. Our study demonstrated, that the activated forms of the PLCc1 were associated with the incidence of distant metastases in a series of 292 (training set) and 122 (validation set) BC. We participated in a coordinated multi-centre large scale biomarker study, in collaboration with Prof V. Speirs, from St James's University Hospital, Leeds, UK, to define and compare hormone receptor profiles and survival between 251 male and 263 female invasive BC matched for grade, age, and lymph node status. Hierarchical clustering revealed common clusters between genders. In female breast cancer, Estrogen Receptor α (ERα) clustered with Progesterone Receptor and its isoforms; in male breast cancer, ERα clustered with ERβ isoforms and Androgen Receptor. These findings support the hypothesis that male and female breast cancer is biologically different. Focusing on biomarkers of predictive value, we analyzed EGFR protein and gene status in a series of 50 metastatic HER2-positive BC patients treated with Lapatinib, a dual HER2/EGFR tyrosine kinase inhibitor (TKI). We evidenced a statistically significant correlation between high EGFR gene copy number (GCN) value (> 3.36), HER2 score 3+ and response to the TKI lapatinib

(p = 0.01). Although further investigations are needed to confirm these findings, EGFR GCN could be a suitable screening test to identify the subset of breast cancer patients who are particularly responsive to the dual TKI lapatinib. We evaluated the performance of intraoperative one-step nucleic acid amplification (OSNA) assay in detecting sentinel lymph node (SLN) metastases compared to postoperative histology considering the BC molecular classification in a prospective series of 903 consecutive SLN. In our series, concordance between OSNA and histopathology was 95%, and logistic regression highlighted that positive axillary lymph node dissection was significantly associated with a higher cytokeratin 19 mRNA copy number (>5000; p< 0.0001), HER2 subtype (p=0.007) and lymphovascular invasion (p< 0.0001). Conversely, BC patients with cytokeratin 19 mRNA copy number <2000>250 mostly presented a luminal subtype and a negative axillary lymph node dissection suggesting that in this subset of BC patients omission of axillary lymph node dissection could be proposed. A correct HER2 status detection in BC patients plays a pivotal role in planning anti HER2 therapies. An External Quality Assessment (EQA) program was developed to investigate the state of the art of HER2 immunohistochemical determination in 16 Pathology Departments in the Lazio Region (Italy). Our findings highlight that in the whole HER2 evaluation process the two intermediate categories, scores 1+ and 2+, are less reproducible than scores 0 and 3+. These findings are relevant in clinical practice where the choice of treatment is based on HER2 positivity, suggesting the need to share evaluation procedures within laboratories and implement educational programs.

Colorectal Cancer

In a prospective multicenter phase II trial of radioembolization with yttrium-90 (90Y-RE) in chemorefractory liver-dominant metastatic colorectal cancer (mCRC), we showed that 48% of 50 patients achieved disease control. In this extension retrospective study, we evidenced a decrease of surviving, p53, Bcl-2 expression and of Ki-67 proliferation index on liver biopsies collected post-90Y-RE as compared to pre-90Y-RE. This biomarker modulation was accompanied by conventional morphological changes. Although our analysis was conducted in a very limited number cases, these changes appear strictly related to the response to 90Y-RE therapy and may deserve further investigation on a larger series of mCRC patients.

Gastric Cancer

In collaboration with the Translational Oncogenomic Laboratory, we analyzed 123 gastric cancers (GC) for the expression of 851 human miRs, using Agilent Platform. Among the eight miRs differentially expressed between tumoral and peritumoral sample, the downregulation of miR-204 emerged as a prognostic biomarker which correlates with increased immunostaining of Bcl-2 protein. Altogether, these findings suggest that modulation of aberrant expression of miR-204, which in turn releases oncogenic Bcl-2 protein activity, might hold promise for preventive and therapeutic strategies of GC.

Lung Cancer

In collaboration with Dr M. Milella (Dept of Medical Oncology A IRE) we participated in a prospective phase II study to evaluate the activity of EGFR-TKI in four different patient groups, according to the combination of molecular (*EGFR* gene mutations, *EGFR* gene copy number and protein expression, phosphorylated AKT (pAKT) expression and clinicopathological (histology and smoking habits) factors. Multivariate analysis confirmed the impact of sex, history of smoking, *EGFR/KRAS* mutation, and pAKT have on outcomes and allowed us to derive an efficient predictive model. Histology, *EGFR* mutations, and pAKT were independent predictors of response to first-line chemotherapy at retrospective analysis, whereas pAKT and HER2 overexpression were the only independent predictors of progression-free survival and overall survival.

HPV-related diseases

a) Uterine cervix: claspin immunoreactivity, analyzed in a series of cervical biopsies, significantly increased from the normal tissues to carcinomas. Moreover, a statistically significant correlation between claspin expression and HR-HPV infection was observed. Collaboration: ISPO, Firenze, Italy. HPV E6/E7 mRNA assay was evaluated as prognostic marker in a prospective series of HR-HPV DNA-positive women with negative colposcopy or histology. The absolute CIN2+ risk was 5-fold higher in mRNA-positive

than in -negative women. p16/ki67 immunostaining was investigated in liquid-based cervico-vaginal samples. A strong association between p16/Ki67 and HR-HPV infection was found. In addition, p16/Ki67 positivity rate significantly increased with the severity of the cyto/histologic abnormalities and resulted strongly associated with a CIN2+. b) Head and Neck: we participated in the International Epidemiologic Study of Worldwide Distribution of Type-Specific Human Papillomavirus (HPV) DNA in Invasive Cancers and Pre-Neoplastic Lesions of the Vulva and Head-Neck Tumors. Collaboration: Institut Català d'Oncologia, Spain. Evaluation of cytology and HPV testing on cytobrushing of oral/oropharyngeal lesions. Patients with abnormal cytology had a significantly higher risk of having an HNSCC. Moreover, HPV positivity in the oropharyngeal brushing was associated with a nearly 5-fold higher risk of having abnormal cytology and a histologically-proven cancer. Collaboration: UOC Otolaryngology Unit at IRE. Expression of TP53 mutation and miRNA expression profiling on a prospective series of HNSCC samples. TP53 mutations were significantly associated with a shorter recurrence-free survival. The expression of 49 miRNAs was significantly associated with TP53 status and 12 among them correlated with recurrence-free survival. miRNAs correlating with survival were independent prognostic factors. Collaboration: Translational Oncogenomics Unit IRE. c) Anal cancer: anal HPV infection in HIV-negative and HIV-positive men who have sex with men (MSM). Among HIV-infected and -uninfected MSM, we assessed prevalence and features of anal HPV infection, and prevalence of anal cytological abnormalities. A high prevalence of anal HPV infection and cytological abnormalities was evidenced in both populations, although higher in HIV-infected MSM. Moreover, among the HPV16 positive samples of HIV-uninfected MSM, we found that HPV integration was rarely evidenced. Collaborations: UOC Dermatologia Infettiva e Allergologica ISG, Virology Laboratory IRE.

Malignant melanoma

We reviewed over 100 selected papers on the use of gene expression profiling to establish melanoma molecular classes for prognosis, listing 10 reasons why melanoma molecular classes have not yet been implemented in the clinical diagnosis and prognosis. Collaboration: Immunology Laboratory at IRE.

Thymic epithelial tumours

Our department also significantly focuses on Thymic Epithelial Tumors (TET), although they are rare tumours, they often show unpredictable oncologic behaviour, recur locally several times and eventually metastasize at distant sites. Biomarker research by tissue based studies are in progress, based on immunohistochemistry, molecular genetic or molecular biology, in the framework of multicenter/multidisciplinary collaborative research projects on TET. Clinical and diagnostic reference activities on a nation-based scale is being pursued. Moreover, the Department of Pathology also participates in and promotes a multidisciplinary national network that deals with TET therapy. It also actively contributes to the TET Staging project of the International Thymic Malignancy Interest Group (ITMIG) (www.itmig.org), together with IASLC, for the upcoming 8th edition of the TNM staging manual of the UICC. In particular, accurate histological subtyping and molecular genetic profiling (cKIT mutational analysis) provided data on targeted TET therapy for an AIFA-granted Phase II monitored clinical trial for evaluating the treatment of patients with Thymic Epithelial Tumours (TET) or Histiocytosis X (LCH) with Imatinib Mesylate (FARM6HJ7CA). Furthermore, we participate in internationally established, web-based, biobanks actively participating in TET study (Virtual Thymic Tumor Bank, www.thymicbank.org) and contribute to the web-based, Retrospective and Prospective Databases of Thymic tumors established at HubZero (http://www.hubzero.org). The HubZero world web-based retrospective database collected more than 8000 TET cases from 77 centers across 16 countries. Retrospective data analysis has begun based on the main outcome indicators (stage according to Masaoka and Masaoka-Koga, overall survival, relapse free survival), followed by histotype and other evaluation parameters (in progress). The first paper describing the guiding principles in the development of a new Staging classification system has been published.

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Department of Oncological Prevention and Diagnosis

Nuclear Medicine Unit

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Activities 2012-13

Clinical Activities

The activities of the Nuclear Medicine Division focus on clinical research directed towards therapy and diagnostics in the main fields of oncology. In 2012-2013, over 30.000 therapeutic and diagnostic procedures were performed with approximately 870 cancer radionuclide treatments.

Therapy: Is the main field of our clinical activities. It includes radionuclide treatment of thyroid carcinoma, selective internal radiation therapy of liver tumors, and pain from bone metastases. Biological optimization of radiation dose studies have been performed using new algorithms and modified Montecarlo protocols to evaluate heterogeneous dose distribution in tumor lesions. Good clinical practice procedures on radiopharmaceuticals preparations have been drafted and implemented according to national guidelines and norms. Training on innovative treatments with new radiopharmaceuticals were performed and clinical protocols validated.

Diagnostics includes: PET/CT with FDG and non FDG tracer, sentinel node mapping, cardiac gated-SPET and all routine oncological studies. In addition, PET-CT protocols with 18F-Coline and 18F-Fluoride were elaborated and optimized: the Centre is leader in both these fields.

Quality improvement: Standard of diagnostic and therapy activities are guaranteed by ISO 9000; professional quality certification by AIMN-Bureau Veritas was also obtained in February 2013.

Thyroid cancer

The main clinical area of interest of the Nuclear Medicine Division, since 1992, has focused on thyroid cancer management and the role of radioiodine therapy. Over 450-500 in-patients/year have been treated with radioiodine therapy and over 7000 patients with DTC have been followed in our aftercare, which is one of the largest referral centres in Italy for this disease. This large accrual of patients with DTC, which have been treated homogeneously and on a long term basis, has produced a large series of data. This has made it possible to investigate some interesting topics according to EBM criteria

Clinical activities have been based on the analysis of clinical presentation of DTC in the last 15 years and on refocusing disease approaches both in therapy and in follow-up, considering the progressively increasing tumor incidence and the continual improvement of diagnostic modalities. In particular, there are two results which have a significant impact on DTC clinical management. Firstly, post-operative pTNM staging system understages DTC patients. This is particularly the case for low-risk T1 patients so that diagnostic and post-therapeutic ^{131}I whole-body scans are

necessary to avoid possible undertreatment. Secondly, radioiodine therapy improves recurrence rate and specific cancer mortality both in low-risk and in high risk patients. These results were previously published in Annals of Oncology. *(Ann Oncol. 2009 Oct;20(10):1728-35*)

Selective internal radiation therapy (sirt) in liver tumors

Selective Internal Radiation Therapy (SIRT) is a technique was developed in 1987 in Australia and has been administered to over 600 patients. SIRT consists of embolising radioactive SIR-Spheres® into the arterial supply of the liver following which the SIR-Spheres® preferentially lodged in the vasculature of the tumour. The spheres deliver high doses of ionising radiation to the tumour component while maintaining radiation to the normal liver at a tolerable level. The radiation half-life of yttrium-90 is 62 hours. High response rates have also been reported using SIR-Spheres® combined to chemotherapy in the regional treatment of liver metastases without any severe complications. Our Institute has gained extensive experience acquiring more than 500 treated patients leading to the technical and clinical optimization of the procedure both in liver metastases and in the hepatocarcinoma patients.

Skeletal metastases from solid tumors

Since 1992, we have carried out more than 500 treatments for bone metastases performed with the three available bone seeking radioisotopes (^{89}Sr; ^{186}Re; ^{153}Sm) using the same clearly defined criteria for enrolling in the treatment and response evaluation. This rigorous standardized and reproducible methodology has produced a vast wealth of comparable data leading to making extraordinary original contributions to this field. The results played a role in both clarifying clinical indications using standard procedures and exploring innovative strategies through a series of clinical trials. An original dosimetric model to validate the clinical choice of individual doses has also recently been implemented and published. Having established a leading role in this field resulted in a number of invited requests to conferences /scientific meetings. A systematic review is currently in progress in collaboration with the scientific association AIMN, AIRO, AIOM to develop a clinical consensus on national guidelines on bone pain management and preliminary results have also been recently published.

PET and Scintigraphy

- ^{18}F-Choline PET : IRE Nuclear Medicine Dpt. has the most extensive experience in the world in using F-Choline in prostate cancer adopting original dynamic protocols. The preliminary results of the Phase III study were presented at

the EANM congress in Birmingham in Oct 2011 and there is a paper in its final stages. One of the main, and original findings is the very high sensitivity at PSA low values (< 1 ng/ml) with concomitant high specificity.

- ^{18}F-FDG PET: The clinical evaluation on the efficacy of FDG PET in preoperative staging of bladder cancer and metabolic characterization of primitive bone tumors are still ongoing. The center has accrued a wide clinical experience with over 16.000 studies with double reading by two nuclear physicians.
- ^{99m}TC MAG 3 scintigraphy is used for evaluating renal function in controlled hypotension during urological surgery procedures

Research Activities

Thyroid Cancer

Clinical research has been based on the clinical presentation analysis of differentiated thyroid cancers in the last 15 years and on refocusing approaches to disease both in therapy and in follow-up, considering the progressively increasing tumor incidence and the continual improvement of diagnostic modalities. The main research areas in the last few years were:

– new therapeutic strategies using recombinant human TSH instead of hormone withdrawal which are currently ongoing to improve the quality of life of patients and minimize discomfort related to hypothyroidism. The vast gained experience in using recombinant human TSH for diagnostic purposes in over 1000 patients has led to optimization of the technical and health-economic impact of the procedure. A retrospective multicenter European study aimed at assessing the efficacy of radioiodine therapy in locally advanced tumors versus standard therapy with thyroid hormone withdrawal was recently published. *(High-Risk Patients with Differentiated Thyroid Cancer T4 Primary Tumors Achieve Remnant Ablation Equally Well Using rhTSH or Thyroid Hormone Withdrawal. Bartenstein P, Calabuig EC, Maini CL, Mazzarotto R, Muros de Fuentes MA, Petrich T, Rodrigues FJ, Vallejo Casas JA, Vianello F, Basso M, Balaguer MG, Haug A, Monari F, Vaňó RS, Sciuto R, Magner J.Thyroid. 2014 Jan 17)*. The primary endpoint was based on evaluating diagnostic radioiodine scan thyroid bed uptake more than six months after the ablation procedure, while stimulated serum Tg was a secondary endpoint. Safety was evaluated within 30 days after rhTSH or 131I. Data on 144 eligible patients with T4 tumors were collected and the following conclusions were drawn: use of rhTSH as preparation for thyroid remnant ablation in patients with T4 primary tumors achieved a rate of ablation success that was high and not inferior to the rate seen after THW, and rhTSH was well tolerated.

- The role of 124I PET/CT both for biological and dosimetric optimization in order to individualize radioiodine treatment in advanced thyroid carcinoma and for diagnostic use has been also investigated with preliminary results currently under evaluation.
- The role of ^{124}I PET/CT both for biological and dosimetric optimization to individualize radioiodine treatment in advanced thyroid carcinoma and for diagnostic use has also been investigated with preliminary results currently under evaluation.

Selective Internal Radiation Therapy (SIRT) in Liver tumors

We participated in multicenter studies involving 10 European Centers of excellence in the field who are also pioneers in the dosimetry and radiobiology of ^{90}Y-microspheres.

Clinical research over the last few years has focused on the identification of specific SIRT indications in the context of the standard HCC staging and treatment guidelines (BCLC staging system and EASL guidelines) and integration of radioembolisation into multimodal treatment of liver-dominant metastatic colorectal cancer.

^{18}F-Choline PET :

Preliminary results of Phase III study evidencing a very high sensitivity at PSA low values (< 1 ng/ml) with concomitant high specificity are currently in press.

Publications 2012-2013

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Department of Oncological Prevention and Diagnosis

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Activities 2012-13

Clinical activities

According to the current spending review by the Regione Lazio, the ratio between inpatients and outpatients has observed a small but progressive decrease at the Department of Radiology. During 2012, 45350 patients underwent diagnostic examination and out of these, 15000 were inpatients and 30350 outpatients. In 2013, 47500 patients underwent diagnostic examinations and of these 14000 of them were inpatients and 33500 outpatients.

Currently, all radiological imaging appointments at the Department of Radiology are made and managed by the CUP. Even though all appointments are scheduled on-site, except for urgent examinations or those related to clinical controlled trials, setting up appointments in accordance with the medical oncologists' demands still remains a challenge.

In fact, the response in matching (service) capacity to (patient) demand for diagnostic exams has reached critical level, despite efforts in attempting to insert extra sessions within the departments' opening hours for carrying out both CTs and MRIs trying to optimize service capacity, based on the long waiting lists as well as making

-timed use of all changes emerging during the month in relation to the requests for days off or sick leave.

The main critical issue emanating from the Radiology Department concerns requests regarding patient follow-up, for which services are guaranteed regardless placing urgent clinical requests in primary position before other standard requests scheduled by the Radiology and Diagnostic Imaging Department. An agenda called "Diagnosis" is a list of patients who have been newly diagnosed with malignancies in the territory of Lazio. This register facilitates first-time patients access to the Institute as waiting lists only contain those patients undergoing follow-up. There was an increase in the number of MRIs exams carried out as well as an improvement in organising MRI protocols which consequently significantly reduced MRI execution time. Experimental activities using the 3T further increased the number of patients undergoing MRI examinations. A rise in the demand of angiography exams was observed where also

-regional treatment of liver tumors and liver radioembolization with Yttrium 90 are performed. Percutaneous ablative procedures,

treatment for preoperative embolization of tumors of bone and muscles and elective percutaneous ablative treatments of osteoid osteoma with a steady increase in services provided primarily for inpatients are also performed. Progressively, the Unit increasingly observed a shift in appointments from the agendas distributed by the Cup, to which the General Directors Office accordingly implemented services for Pre-hospitalisation and Day Surgery and Day Service.
Exams and Assistance Services favouring other Units: As a result there was an increasing need and greater demand to hire healthcare technicians to work in the operating rooms who have experience with mobile C-arms for fluoroscopy. This was also the case for the Orthopedics Unit where a large number of long operations and particularly complex planned surgery are performed. Our Unit provides a full range of radiological exams supporting endoscopic procedures that are performed in the Radiology Gastroenterology Unit 2 sessions per week (Wednesday and Thursday) using computer-assisted technology and 1 technician for carrying out fluoroscopy exams. The Wednesday session takes place in the Angiography Unit as there is a short supply of rooms available due to an overwhelming demand of radiological requests, particularly in relation to the possible interventional radiological emergencies. In regards to hepatobiliary surgery, there was an increase in the number of ultrasounds requested, particularly in relation to MDC where there are radiologists dedicated CT and MRI diagnostic exams; an increase in the use of MRIs; ultrasounds performed in the department in the early postoperative days; and a higher rate of participation in multidisciplinary meetings (DMT).

Morning And Afternoon Shifts:
Opening hours from Monday to Friday:
- The morning sessions cover shifts that consist of 10 radiological diagnostic methods (1 Rx Traditional, 1 Remote controlled, Angiography 1, 2 Mammography, Ultrasound 1 2 CT, 2 MRI) and 1 in the operating room, on demand. (On Wednesdays 1 TC is only available for ISG, however on Wednesdays the Mammotome device is available in the Breast Unit.
- The afternoon sessions cover 3-4 radiological diagnostic methods (CT, MRI and / or ultrasound, X-ray Traditional) and 1 operating room, on request.
Saturday shifts include:
- The morning sessions perform 4 types of radiological diagnostic techniques (CT, MRI, Ultrasound / Mammography, traditional Rx) with 3 Radiologists available.
Emergency intervention is guaranteed every day, even in the hospital wards and operating theaters.

Activities in collaboration with nuclear medicine unit: The collaboration between the Radiology Unit and Nuclear Medicine Unit started 2013 with the use of contrast agents during PET-CT examinations.

Research activities

Throughout 2012-2013 experience with the 128-slice CT for both 3D techniques such as virtual colonoscopy to CT perfusion techniques applied to the evaluation of brain lesions and tumors of the bone was consolidated and intensified. We continued to obtain excellent results in using CTs in evaluating the response of drug therapy to radiation in the context of experimental clinical trials that use antiangiogenic agents and radiation treatments performed by adopting IMRT or stereotactic techniques.
The possibility of using 1.5 T MRI equipment and especially the 3T, reflects the significant advances made in neuroradiological research. In particular, we are carrying out functional studies that define the neoangiogenesis through perfusion and cellular and diffusion studies. At the moment, we are evaluating the effects of chemotherapy treatments with biopharmaceutical agents in short time.
The MRI 1.5 Tesla has already paved the way to using new MRI techniques in the clinical setting and in research in order to study its diffusion, perfusion, spectroscopy and tractography. Studies in collaboration with the Laboratory of Medical Physics have already begun on identifying the best post-processing techniques in acquiring and evaluating the most effective information for differentiating tissues within the tumor or tumor recurrence compared to tissues within the inflammatory type lesion or of another nature such as fibrosis post-surgical or post-radiotherapy. These assessments have also allowed to differentiate residual lymph nodes in

chemo-radiotherapy, which are not typeable through morphological imaging. Sequences such as those of diffusion, which allow you to get information on cellular activity by determining the movement of water molecules into the interstitial space, renders it possible to hypothesize the nature of the residual lymph node and distinguish those metabolically active from the fibrotic ones, and correlating the data with metabolic imaging such as PET-CT. At the moment, diffusion sequences are being used through adopting multi B values (technical IVIM) in order to obtain information on the degree of perfusion and cellular activity within tissue without using a contrast medium. With these sequences, it is possible to monitor response to treatment, either during or directly after completing both treatments with combined chemo-radiotherapy or chemo /or radiotherapy alone. This technique is now being used not only in assessing the response to chemo-radiotherapy in the treatment of head and neck cancer but even in liver metastases where preliminary results are currently under evaluation. Another objective of this study is related to the ability to define through the variation of the fraction of perfusion and changes in levels of apparent diffusion coefficient (ADC) or the so-called pure diffusion of patients responding to treatment to the non-responding ones. There are now active study protocols created for the MRI 3 tesla ranging from cancers of the breast, bone tumors, colorectal, gynecological and urological malignancies. Preliminary results are expected with foreseeable data to be published once obtained. In collaboration with the Division of Radiology at the “La Sapienza” University, a study protocol with 3 T MR tumors of the rectum with diffusion and perfusion weighted sequences is now underway.

The new Bio-imaging techniques of the prostate include: dynamic MRI using contrast medium through a detailed analysis of the kinetic data, a reliable tool that has been validated by clinical studies in evaluating both the density of micro vasculature (MVD) and tumor perfusion. These parameters are considered to be important prognostic factors in the treatment of patients with prostate cancer.

In regards to ultrasound imaging, there are still studies being carried out by the "Sarcoma Group" that uses ultrasound-guided biopsy techniques investigating endovascular MDC that is able to enhance signs of intratumoral microcirculation obtaining a lower number of false-negative results for sampling areas of necrosis. New channels were also activated to allow the use of contrast agents for assessing hepatic lesions.

With the introduction of MRI 1.5 and 3 Tesla, the Clinical Breast Unit started working together with the Surgical, Oncology and Radiation therapeutic Units to make scientific evaluations regarding the study on breast nodules, the effectiveness of neoadjuvant therapy and some radiation treatments. Another novel study is currently underway which investigates the use of iodinated contrast agents associated with mammography exams. The digital mammographies used have a software system installed that is capable of generating multiple mammographic images acquired after a bolus-infusion of MDC associated with subtraction and processing 3D techniques. Evaluation of this new technology will allow to test its validity consequently consolidating it as a valid and functional tool to be used in the diagnostic course of the patient. It is placed in an intermediate position between the second level mammography exam and mammo-MRI with obvious implications in relation to technical appropriateness and the issue of cost containment in carrying out these MRIs.

In regards to vascular and interventional radiology the Institute’s major fields of interest pertinent to oncology are:

- Applying radio-chemo-embolization techniques (with beads and Yttrium 90) in primary and metastatic tumors of the liver in a combined effort involving the SC Nuclear Medicine Unit.
- Performing the embolization of renal tumors in treatment using conservative urogenital laparoscopic techniques in a combined effort involving the Urology Unit.
- Carrying out the embolization of tumors in the skeletal region in a combined effort involving the Surgical Units.
- Applying percutaneous techniques (radiofrequency, other energies) in treating certain cancers of various organs or tissues (liver, bone, others)
- Applying biopsy techniques with computer-assisted imaging of the bone and deep organs.
- The application of a range of stents in the urinary and hepatobiliary areas.

In 2013, the III Congress on the Multidisciplinary Approach used in the Follow-up of the Head and Neck Neoplasms between Morphological

Imaging, Non-Morphological and Metabolic was held at Centro Bastianelli (Convention Centre) within the Institute. Other CME courses on brain tumors, evaluation of the response especially in the era of molecular targeted treatments are currently being offered.

Pubblications 2012-2013

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Department of Neurosciences and Head-Neck Pathology

Unit of Neurology

Andrea Pace, MD

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Psychologists: Sonia Ieraci, Lara Guariglia
Physioterapists: Stefano Di Felice, Cristiano Parisi, Maria Uzzeo
Neuro-psychologist: Chiara Zucchella
Sociologist: Laura Osnato
Data Manager: Silvia Focarelli
Research collaborations: Marzia Piccoli

Activities 2012-13

Clinical Activities

The clinical activities of the Neurology Unit include:
-Neurology clinic
-Neuro-oncology clinic
-Neuropathic Pain Clinic
-Neuropsychology and cognitive rehabilitation
-Neuro-oncologic Day Service for chemotherapy and supportive treatment of brain tumour patients
-Multiple Sclerosis Regional Center
-Neurophysiology lab (Electromyography, Electroencephalography, Evoked Potentials)
-Rehabilitation service specialized in cancer rehabilitation for in- and outpatients

Research Activity

The Research activities of the Neurology Unit cover several topics. These include:

Clinical neuro-oncology

The role of chemotherapy in recurrent malignant brain tumor was evaluated in phase II trials exploring the activity and toxicity of several anticancer agents including: temozolomide, fotemustine, bevacizumab, and carboplatin.
A prospective observational study on the association of bevacizumab plus fotemustine has been conducted in 23 patients with recurrent glioma. The response rate was 26% (all partial responses). Seven patients (30.4%) achieved disease stabilization. Median PFS and OS were 4 months (95% C.I.: 2.5-5.5) and 6 months (95% C.I.: 5.2-6.7), respectively. The combination of BV and FTM in RMGs revealed a good activity in pts previously treated with CT without relevant toxicity. The final results are in press on Biomed Research International

Response evaluation to antiangiogenic treatment

Response evaluation after antiangiogenetic treatment was evaluated by Perfusion Computed Tomography CT and MRI in order to evaluate if early perfusion changes during treatment may be predictive of response to antiangiogenic therapy in high grade gliomas. Results: Perfusion changes resulted in agreement with follow-up morphological MR imaging, anticipating, in the majority of cases, the post-gadolinium T1-weigthed and FLAIR volume modifications. Preliminary results have been presented in scientific meetings and recently published.

The possible predictive value of circulating VEGF, von Willebrand factor (vWF) and procoagulant factors in patients with recurrent GBM treated with antiangiogenic therapy. The role as possible biomarkers of outcome was investigated with serial evaluations of plasma VEGF levels, vWF antigen and procoagulant factors such as thrombin-antithrombin complex (TAT), prothrombin fragment F1+2 (F1+2), Factor VIII and D-Dimer. Baseline, and post-treatment samples were collected at each administration of BV. Preliminary data suggest that low vWF antigen levels might help predict response in recurrent MG patients treated with BV.

The activity of a low dose of temozolomide (50 mg/mq) administered for 1 week on and 1 week off for the treatment of newly diagnosed LGG required treatment for the presence of negative prognostic factors such as residual tumors after surgery or biopsy, age higher than 40 years, neurological deficits or uncontrolled epilepsy was evaluated in a phase II trial. The main objectives included evaluating the activity with an objective response rate, PFS at 12 and 24 years and toxicity. After 6 years of follow up continuous administration of a low dose of temozolomide shows interesting activity with objective responses (28%) and clinical benefit (38%), particularly in patients harboring IDH1 mutation and 1p/19q codeletion.

Role of PET f-dopa in low-grade glioma management

The diagnostic role of PET FDOPA in low grade gliomas (LGG) were evaluated in a prospective study. All patients affected by low grade glioma underwent FDOPA PET and MRI examination for the evaluation of anaplastic progression or assessment of response during chemotherapy. The PET images were interpreted as positive when the lesion definitely increased F-FDOPA accumulation taking into account the background and the controlateral site. We enrolled 56 (35 males and 21 females) patients affected by LGG. Quantitative measurement of metabolic activity of the tracer showed that a SUV max greater than 1.65 was the only independent predictor of disease progression (HR=4.59, 95% CIs from 0.99 to 21.31, p=0.054). This implies that a patient with a SUV max higher than 1.65 had an almost 5-fold increased risk of disease progression, regardless of its clinical and MRI characteristics. The study is still ongoing and preliminary results have been presented in national and international meetings.

Cognitive impairment assessment and rehabilitation

Cognitive impairment is one of the most common neurological disorders in neuro-oncological patients exerting a deep negative impact on quality of life interfering with familiar, social and career-related activities. The role of cognitive rehabilitation programs was investigated in different setting of care (in patients, outpatients, home care setting). Preliminary data showed beneficial effects of a computer-based cognitive rehabilitation programme and positive impact on Quality of Life in neuro-oncological patients both in the early phase after surgical resection and in outpatients during the course of disease. Two papers have been published in the Journal of Neuro-oncology.

Home-care for brain tumor patients

A pilot program of comprehensive palliative care for brain tumour patients started at the Regina Elena National Cancer Institute in Rome in October 2000, supported by the Lazio Regional Health System. The aim of this model of assistance was to meet patient's health care needs in all stages of disease, family support and reducing the re-hospitalization rate. The efficacy of the model of care was evaluated analyzing place of death, caregiver satisfaction, re-hospitalization rate and the impact on Health System costs. The results of this project have been presented in national and international scientific meetings and two papers are in press in Neuro-oncology Practice and in Review in Oncology.

Palliative neuro oncology and telemedicine

The lack of adequate continuity of care for patients affected by BTs in the last stage of disease results in frequent hospital readmission with increased health-care expenditures and compromised quality of care. Information-Communication Technology (ICT) resources, applied to innovative models of health-care (e-Care), are considered a powerful instrument in facilitating the clinical management and health and social service delivery.

We developed a health WEB site portal applied to Neuro-Oncology supportive and palliative care issues (www.portaleneuroncologia.it). The Web site is a tool used for promoting and diffusing guidelines and treatment recommendations.

Peripheral neurotoxicity of anticancer drugs

We are involved in an international study entitled "The Chemotherapy-Induced Peripheral Neuropathy Outcome Measures Standardization" (CIPerinoms) including 20 European and US oncology and neurology centres, specifically designed to compare the validity and reliability of different methods proposed for the assessment of chemotherapy-induced peripheral neuropathy in a formal way. The final aim of CIPerinoms is to propose a standardized set of measures for optimal assessment of chemotherapy-induced peripheral neuropathy in future clinical studies. The results of this study have been published on Annals of Oncology, European Journal of Cancer and Journal of Peripheral Nervous System.

Rehabilitation in Oncology

The Neurology Unit's research activity includes the clinical research and methodological assessment of rehabilitation strategies in oncology. We participated in the National Research Project of the Ministry of Health (On Rehab): *defining a model for rehabilitating cancer patients: multidisciplinary paths, traceability networks and innovative tools* which concluded in 2012.

Multiple Sclerosis Centre

The IRE Multiple Sclerosis Centre was founded in 1996 (approved by Regione Lazio). This centre provides comprehensive patient-care, comprising of a full range of services utilized to help patients in the diagnostic process, treatment choices and rehabilitation. The centre is affiliated with the "Associazione Italiana Sclerosi Multipla" (AISM).

It focuses on researching the causes, natural history and treatment of MS in collaboration with other national and international MS centers.

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Sociologist: Laura Osnato
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Data Manager: Silvia Focarelli, Marzia Piccoli

Activities 2012-13

Clinical Activities

The research activity of the Division of Neurosurgery focus on the study of new diagnostic and therapeutical approaches in the integrated treatment of primitive and secondary tumours of the nervous system. Research is oriented either on new, innovative, safer surgical techniques, or in clinical neuroncology. In these fields, since 2007, cooperative studies with national and international institutes were pursued, have been activated, or are in progress.
During this year, the accrual of patients affected with glioma of different grading was continued, considering both newly diagnosed tumours, and recurrences with clinical/radiological progression.
The patients have been followed through the efficient integration of the different structures within the Neuro-Oncological Disease Management Team which discusses weekly relevant clinical cases, and proposes new scientific studies and projects. Furthermore our centre is closely connected to other regional structures. The activity of our DMT has currently favoured the accrual of patients in clinical studies. In this way, interesting data were collected and evaluated for presentations in national and international meetings, and facilitate to prepare scientific papers.
New therapeutic protocols have been activated and considered after surgical procedures (biopsy and/or microsurgical removal), radiation treatment and chemotherapy with different therapeutic schedules, both as first line (mainly Temozolomide), and as second one (mainly with Fotemustine). In addition, the increasing efficacy of new therapeutic strategies (microsurgical resection, with second surgical look and intratumoural antiblastic treatment, conformal radiotherapy, with eventual focal boost, adjuvant and/or concomitant chemotherapy) allowed in selected patients the indication to second and, in selected cases, third line chemotherapy.
At present, we are trying to correlate the data regarding tumour bio-molecular characteristics with the clinical data of these patients. As a matter of fact, in this field the definition of predictive markers of potential efficacy of different therapeutic approaches stimulates prominent interest, and a more adequate knowledge in clinical, radiological, histological, immuno-histochemical and bio molecular areas which could contribute in defining more selective and efficient diagnostic-therapeutic strategies, as well as allowing a more clear cut stratification of patients accrued in new clinical trials.
In the literature, different authors (and our group too) described a series of prognostic markers, as expression of p53, amplification and over expression of EGFR, 10q LOH in astrocytic

gliomas, and, 1p and 19q LOH in oligodendrogliomas, methylation of methyltransferase, determining chemo resistance to methylating and alkylating agents. This research is a part of the Ministry of Health (Ministero della Salute), coordinator Prof. Felice Giangaspero – Neuromed (associated unit: resp. C.M. Carapella).
New protocols for combined treatment of malignant gliomas have been activated, including new modalities of drug delivery, mainly considering the direct infusion of new drugs and toxins into tumoural and peritumoral region, utilising techniques of convection enhanced delivery, that allow to overcome the limits linked to the presence of BBB.

- *Primary chemotherapy with temozolomide vs. Radiotherapy in patients with low grade gliomas after stratification for genetic 1p loss: a phase iii study (eortc 22033 study*): PI Carmine Carapella (approved by EC and activated; 4 patients have been registered and randomised – all in the RT arm; the accrual ended and the final results were presented in 2013).
- *Cilengitide in newly diagnosed glioblastoma multiforme and methylated mgmt gene promotor* – international multicenter randomised phase III study, in association with standard chemo-radiation treatment (CENTRIC study): PI Carmine Carapella (approved by EC and activated; 12 patients have been registered; 1 single case showed MGMT methylation has been accrued; the patient is still alive after more than 85 weeks and is in the follow up phase).
- *Bevacizumab, temozolomide and radiotherapy, in patients with newly diagnosed glioblastoma* – international randomized, double blind, placebo controlled, multicenter Phase III trial (AVAglio study): PI Carmine Carapella (approved by EC but never activated due to the MRI equipment issue; the study ended the accrual and the final results are in progress).
- *Cilengitide in newly diagnosed glioblastoma multiforme and unmethylated mgmt gene promoter* - international multicenter, open-label Phase II study (CORE study): PI Carmine Carapella (approved by EC and activated; 2 patients entered the study and were treated; the accrual at has now ended and further results are in progress).
- *EGFRviii peptide immunotherapy in newly diagnosed glioblastoma multiforme – phase I-II cooperative trial sponsored by ACC* – It Health Min: PI Gaetano Finocchiaro (Ist Neurol Besta – Milan) IRE Coordinator Carmine Carapella (the study has been activated and the peptide obtained; the clinical phase 0/I is in progress).
- The regional project *" Continuative home care for brain tumor patients"* started in 2000, October 1st. At present this Grant is sponsored by "Regione Lazio" until 2009 for 250.000 euro/year. It was renewed for 2012 and 2013. It is in cooperation with the neurological staff of the Institute. P.I. Andrea Pace and Alfredo Pompili.
More than 800 evaluable patients were enrolled over the years. An average of 45 patients/months are assisted.
- *A Prospective, Multi-center Trial of NovoTTF-100A Together With Temozolomide Compared to Temozolomide Alone in Patients with Newly Diagnosed GBM (Novocure EF-14)*: PI Carmine Carapella (approved by EC and activated; 2 patients have been registered; 1 patient is presently under treatment)
- As an active member of the EORTC Brain Tumour Group (C.M. Carapella) another randomized phase III study on post-operative residual benign meningiomas has been approved by our EC and activated: *Observation versus conventional- fractionated radiotherapy or radiosurgery after non-radical surgery for benign intracranial meningiomas.* This trial has been closed by EORTC due to the limited accrual.

A second relevant research activity is directed toward the evaluation of new surgical strategies in the treatment of spinal and vertebral tumors; of pituitary adenomas and tumors of the sellar region; in the treatment of infratentorial secondary tumors; mainly defining the role of new technologies and mini invasive approaches.
On the theme of brain metastases in 2012, a MD graduation thesis was carried out by the medical student Matteo Rasi with our material:
"Multidisciplinary treatment of brain metastases. A retrospective study on 117 patients" in cooperation with Rome University " La Sapienza"
On the theme of meningiomas, a MD graduation thesis was carried out in 2013 with our clinical

material: *"Biomolecular and immunihistochemical risk-factors in recurrent intracranial meningiomas",* student Alessandro Izzo, in cooperation with the Rome University "La Sapienza".
- *Assisted techniques* (190 patients enrolled 2004-2013) P.I. A.Pompili.
- *One stage vertebrectomy with reconstruction and stabilization for metastatic spinal tumors*. 52 enrolled (2004 - 2013). P.I. F.Caroli.
- *One stage removal and reconstrucion for primary spinal tumors*. 28 enrolled (2004-2013) P.I. F.Caroli
- *The use of new technologies in the removal of spinal tumors*. 89 enrolled (2004-2012). P.I. L.Raus. Study closed

Research Activities

In regards to what we call "Current Research", we have many lines that are still open for enrollment and evaluation:
Pituitary adenomas, brain metastases, mininvasive supraorbital approaches for sellar and parasellar tumors, spinal intradural tumors, somatectomy and vertebrectomy for spinal metastases and primary tumors, modern technologies in spinal surgery. For the number of patients enrolled please see your scores about "Clinical Trials 2012". We held both lectures and posters on these topics at national and international meetings and peer reviewed publications: Dr Telera published the clinical material on the supraorbital approach for anterior cranial base meningiomas in Neurosurgical Review, a paper on brain metastases and radionecrosis is in press in the Journal of Neuroncology, by Dr. Telera. Data regarding the intradural extramedullary tumors are ready to be submitted to "Neurosurgery".

Synthetically, our clinical research activity is divided into four different fields: advanced studies on integrated treatment of brain gliomas; microneurosurgical and endoscopy-assisted pituitary surgery; new surgical approaches with mini invasive techniques in the resection of brain and spinal tumours; surgical procedures of removal and reconstruction in the treatment of primary and secondary vertebral tumours.
Internet: the neurosurgical Division has an internet site called "Neurochirurgia-IRE.it" that uses simple language to explain our activities and the main features of neurosurgical pathologies, mainly tumors. The website has been active since August 2006 and since January 2007 it has appeared in the first page of either google and yahoo. Since 2009, the website has been available also in English and can be found on the first page of google and yahoo by searching mininvasive neurosurgery and/or neuronavigation - brain tumor.
Prospective ideas for 2014:

- Final Evaluation of our meningioma series 2001-2007 (more than 200 cases) to detect risk and prognostic factors for recurrences. We are going to manage the data collected by Alessandro Izzo for his graduation thesis
- Evaluation and publication of the data of patients with spinal locations of hematological malignancies .
- The new material VK100 for Kyphoplasty is at present under evaluation. Waiting for the ethical committee's approval.
- Testing new materials as dural sealants and for watertight closures either in brain or in spinal tumor patients.
- Studies of "Current Research"
- Studies in prospective international trials for brain tumors.

Publications 2012 -2013

Telera S, Carapella C.M.; Caroli F, CrispoF, Cristalli G, Raus L, Sperduti I, Pompili A. Supraorbital keyhole approach for removal of midline anterior cranial fossa meningiomas: A series of 20 consecutive cases. Neurosurg.Rev., 2012, 35, 1, 67-83

Maschio M, Dinapoli L, Sperati F, Pace A, Fabi A, Vidiri A, Pompili A, Carapella CM. Effect of pregabalin add-on treatment on seizure control, quality of life, and anxiety in patients with brain tumour-related epilepsy: a pilot study. *Epileptic Disord*. 2012, 14(4):388-97.

Pace A, Di Lorenzo C, A Capon, V Villani, D Benincasa, Guariglia L, M Salvati, C Brogna, V Mantini, Padovan A, Mastromattei, Pompili A: Quality of care and rehospitalization rate in the last stage of disease in malignant gliomas assisted at home: a cost effectiveness study *J Palliat Med*. 2012 Feb;15(2):225-7.

Vidiri A, Guerrisi A, Pinzi V, Fabi A, Mirri MA, Pompili A, Caporale N, Pace A, Crecco M, Marzi S. Perfusion Computed Tomography (PCT) adopting different perfusion metrics: recurrence of brain metastasis or radiation necrosis? *Eur J Radiol*. 2012 Jun;81(6):1246-52.

Telera S, Fabi A, Pace A, Vidiri A, Anelli V, Carapella CM, Marucci L, Crispo F, Sperduti I, Pompili A. Radionecrosis induced by stereotactic radiosurgery of brain metastases: results of surgery and outcome of disease. J Neurooncol. 2013 Mar 25.

Salmaggi A, Simonetti G, Trevisan E, Beecher D, Carapella CM, Dimeco F, Conti L, Pace A, Filippini G. Perioperative thromboprophylaxis in patients with craniotomy for brain tumours: a systematic review. J Neurooncol. 2013 113(2):293-303.

Pace A, Villani V, Di lorenzo C, Guariglia L, Maschio M, Pompili A, CarapellaCM. Epilepsy in the end-of-life phase in patients with high-grade gliomas. J. Neuro-oncol. 2013 111 (1) 83-6

Department of Neurosciences and Head-Neck Pathology

Head and Neck Surgery

Giuseppe Spriano, MD

Director

STAFF MD Assistants: Raul Pellini, Giovanni Cristalli, Giuseppe Mercante, Paolo Marchesi, Valentina Manciocco, Barbara Pichi

Activities 2012-13

Clinical Activities

Our Department is dedicted to ear, nose and throat and maxillofacial oncological surgery. We treat fairly common head and neck cancers to more complicated and difficult cases. Highly specialized surgical protocols and/or procedures are performed by the staff and every decision regarding the clinical cases is submitted to the Head and Neck Disease Management Team, which includes experts specialising in surgery, radiation oncology, medical oncology, endocrinology, radiology, pathology, speech therapy, plastic and reconstructive surgery, dental and maxillofacial prosthetics, nutrition, and pain management. The group meets weekly and works together to meet their patients' diverse needs.

Research Activities

- Local treatment of Head and Neck Disease with ECT. Evaluation of disease control and survival.
- Phase III study – Pre-surgical chemotherapy according TPF protocol for local advanced oral carcinoma in order to enhance the percentage of pathological complete reactions.

Publications 2012-2013

Marchese C, Cristalli G, Pichi B, Manciocco V, Mercante G, Pellini R, Marchesi P, Sperduti I, Ruscito P, Spriano G. Italian cross-cultural adaptation and validation of three different scales for the evaluation of shoulder pain and dysfunction after neck dissection: University of California - Los Angeles (UCLA) Shoulder Scale, Shoulder Pain and Disability Index (SPADI) and Simple Shoulder Test (SST). Acta Otorhinolaryngol Ital. 2012 Feb;32(1):12-7.

Cristalli G, Mercante G, Covello R, Sperduti I, Cristalli MP, Spriano G. Histopathological Assessment in Glossectomy: Harmonic Shears versus Monopolar Electrosurgery Pilot Study. Otolaryngol Head Neck Surg. 2012 Dec; 147(6):1076-1082.

Pellini R, Mercante G, Spriano G. Step-by-step mandibular reconstruction with free fibula flap modelling. Acta Otorhinolaryngol Ital. 2012 Dec;32(6):405-9.

Mercante G, Marchese C, Giannarelli D, Pellini R, Cristalli G, Manciocco V, Ruscito P, Pichi B, Marchesi P, Spriano G. Oncological outcome and prognostic factors in malignant parotid tumours. J Craniomaxillofac Surg. 2013 Mar 28.

Pellini R, Mercante G, Marchese C, Terenzi V, Sperduti I, Manciocco V, Ruscito P, Cristalli G, Marchesi P, Pichi B, Spriano G. Predictive factors for postoperative wound complications after neck dissection. Acta Otorhinolaryngol Ital. 2013 Feb;33(1):16-22.

Mercante G, Grammatica A, Battaglia P, Cristalli G, Pellini R, Spriano G. Supracricoid Partial Laryngectomy in the Management of T3 Laryngeal Cancer. Otolaryngol Head Neck Surg. 2013 Nov;149(5):714-20

Trimboli P, Giovanella L, Crescenzi A, Romanelli F, Valabrega S, Spriano G, Cremonini N, Guglielmi R, Papini E. Medullary thyroid cancer diagnosis: An appraisal. Head Neck. 2013 Aug 16.

Mercante G, Ruscito P, Pellini R, Cristalli G, Spriano G.Transoral robotic surgery (TORS) for tongue base tumours. Acta Otorhinolaryngol Ital. 2013 Aug;33(4):230-5.

Ganci F, Sacconi A, Bossel Ben-Moshe N, Manciocco V, Sperduti I, Strigari L, Covello R, Benevolo M, Pescarmona E, Domany E, Muti P, Strano S, Spriano G, Fontemaggi G, Blandino G. Expression of TP53 mutation-associated microRNAs predicts clinical outcome in head and neck squamous cell carcinoma patients.Ann Oncol. 2013 Dec;24(12):3082-8.

Pellini R, Mercante G, Ruscito P, Cristalli G, Spriano G. Ectopic lingual goiter treated by transoral robotic surgery. Acta Otorhinolaryngol Ital. 2013 Oct;33(5):343-6.

Mercante G, Battaglia P, Manciocco V, Cristalli G, Pellini R, Spriano G. Three-dimensional minimally invasive video-assisted thyroidectomy: preliminary report. J Exp Clin Cancer Res. 2013 Oct 18;32(1):78.

Critical Care Department

Unit of Anaesthesiology

Ester Forastiere, MD

Director

STAFF MD-Anaesthetists: Claudia Claroni, Cecilia Coccia, Luca Colantonio, Alessandra Costantino, Marco Covotta, Piera Di Angelo, Luana Fabrizi, Claudia Frigieri, Francesca Romana Giordano, Maria Grazia Giovanetti, Maria Elena Marcelli, Ilaria Monteferrante, Paolo Moricca, Federico Pierconti, Francesca Principi, Maria Sofra

Activities 2012-13

Clinical Activities

Preoperative assessment of surgical patients; Intraoperative anaestetic management. Perioperative assistance for patients after surgery.

Research Activities

Clinical protocols of Translational research approved by Ethical Committee: retrospective, observational randomized prospective studies.
Multicentric trials carried out in collaboration with the University of Udine and Università Cattolica Sacro Cuore of Rome.
Scientific events on issues correlated with the following:
- Perioperative Medicine, role of Anaesthetist (date: 28 of June 2014)
- Hot Topics in Thoracic Anaesthesia (date: 6 of December 2013)
- Clinical risk management in Critical Area (date: 29 of March 2014)
- Perioperative management for oncological patients. What's changed? (date: 27 of June 2014).

Ended Study Protocols with published or in press manuscripts:
- Immunomodulatory effects of total intravenous and balanced inhalation anesthesia in patients with bladder cancer undergoing elective Cystectomy preliminary results
- Prothrombotic factors and different anaesthetic techniques: Is thromboembolic prophylaxis required in prostate cancer patients undergoing laparoscopic and robotic radical prostatectomy?
- A prospective randomized trial of goal-oriented directed therapy vs. standard fluid therapy in cytoreductive surgery with hyperthermic intraperitoneal chemotherapy
- Evaluation of Renal function under controlled hypotension in zero ischemia robotic assisted partial nephrectomy for peripheral renal tumors

Studies in progress:
- Protective effect of Sevoflurane in ischemic damage - riperfusion for patients undergoing plastic surgery with microsurgical flap. Randomized controlled multicenter trial.
- Postoperative pain treatment in major orthopedic oncologic surgery: PCA in intermittent continuous bolus. Observational prospective trial.
- Pulmonary atelectasis prevention with enrolment operations during gynaecologic robotic surgery in obese patients.
- Continuous Infusion of naropine through perilesional catheter: evaluation of Wound Healing assessment.
- Double-Lumen Intubation: Glidescope video laryngoscope and standard MAC video laryngoscope evaluation.
- Awakening quality and impact on cognitive functions after reversal with sugammadex in radical robotic cystectomy. Prospective randomized study.

- Anaesthetic Management in robotic assisted laparoscopic cystectomy. Observational prospective study.

Pubblications 2012-2013

Papalia R, Simone G, Ferriero M, Costantini M, Guaglianone S, Forastiere E, Gallucci M. Laparoscopic and robotic partial nephrectomy with controlled hypotensive anesthesia to avoid hilar clamping: feasibility, safety and perioperative functional outcomes. *J Urol*. 2012 Apr;187(4):1190-4.

Sofra M, Fei PC, Fabrizi L, Marcelli ME, Claroni C, Gallucci M, Ensoli F, Forastiere E. Immunomodulatory effects of total intravenous and balanced inhalation anesthesia in patients with bladder cancer undergoing elective radical cystectomy: preliminary results. *J Exp Clin Cancer Res*. 2013 Feb 3;32:6. doi: 10.1186/1756-9966-32-6.

Della Rocca G, Coccia C. Acute lung injury in thoracic surgery. *Curr Opin Anaesthesiol*. 2013 Feb;26(1):40-6.

Vizza E, Corrado G, Mancini E, Baiocco E, Patrizi L, Fabrizi L, Colantonio L, Cimino M, Sindico S, Forastiere E. Robotic single-site hysterectomy in low risk endometrial cancer: a pilot study. *Ann Surg Oncol*. 2013 Aug;20(8):2759-64. doi: 10.1245/s10434-013-2922-9. Epub 2013 Mar 7.

Department of Critical Area

Unit of Cardiology

Francesco Rulli, MD

Director

STAFF MD Assistans: Salvatore Accogli, Armando Carpino, Fabio Maramao, Nicola Antonio Morace, Giuseppe Toglia MD

Activities 2012-13

Clinical Activities

The Unit of Cardiology provides clinical assistance and counseling to all patients at the Regina Elena National Cancer Institute and San Gallicano Dermatology Institute.

The outpatient clinic is dedicated to cancer patients involved in the Pre-hospitalisation, Day Hospital and Day Surgery Services at both institutes. It is also committed to all patients who need ongoing monitoring and evaluation of chemo-radiotherapy, in accordance with the follow-up treatment protocols.

The Unit of Cardiology mainly deals with the following areas:

- Providing surgical support in terms of assessing cardiovascular functional pre-operative management of emergencies, intra-operative and hospital wards.
- Assessing the state of the cardiac patient undergoing chemotherapy or radiation therapy, pre and / or post-surgery, in addition to clinical and instrumental monitoring, in accordance with the established protocols that are shared among oncologists and which are in line with the available guidelines.
- Managing emergencies or urgent care situations (of family, carers) in common locations for direct walk-in/immediate visits or by referral from the Manager of the First Aid Unit at the Institute.
- Managing emergencies or urgent care during the evening and public holidays and Medical Directors on Duty in accordance with the methods and number established by the current national labor contract.

In 2012, the Unit of Cardiology, with confirmation of ISO 9001-2008, achieved a 4% annual increase in the loyalty index, that is, in total healthcare assistance provided, no instances of "non-compliance" were recorded by an internal audit carried out, achieving 4/4 of the proposed objectives.

The budget objectives for 2012 and 2013 were accomplished with the abovementioned increase in healthcare assistance provided and costs reduced (bias - 18.81%).

After various meetings with anesthesiologists, a protocol was compiled as a tool to define shared for the operative risk assessment shared in cardiac patients undergoing oncologic surgery.

This past year the Unit of Cardiology was included as a reference unit for the two new GOI, the Breast Unit (Prof. Roy De Vita) and the Psoriasis Unit (Prof. Enzo Berardesca).

Research Activities

The main activities covered in recent years focused on:

- Establishing a database for collecting data on advanced echocardiographic imaging (Pulsed-wave Tissue Doppler) for evaluating preclinical cardiotoxicity from antineoplastic agents in groups of patients in relation to the type of treatment (indicator budget).
- Participating in Institutional research protocols such as:

1. "Study multicenter phase II MBVD in elderly patients and / or cardiac patients suffering from Hodgkin's lymphoma. HD0803" (Hematology).

2. "A prospective, multicentre, phase II non-randomized trial to evaluate the efficacy of ABVD dose dense as first-line therapy in patients with Hodgkin's lymphoma stage I, IIA and IIB non-bulky" cod. FIL-DDABVD (Hematology).
3. "ESAI. A multi-center, randomized, double-blind, placebo-controlled, phase 3 trial of E7080 in 131I-refractory differentiated thyroid cancer "(Endocrinology).
4. "Randomized phase II trial with the MEK inhibitor MSC1936369B or placebo in combination with gemcitabine in patients with metastatic carcinoma of the pancreas" (Medical Oncology A).
5. "RAD001 / Everolimus. Study open-label, multicenter, expanded access for women in post-menopausal breast cancer in estrogen receptor-positive locally advanced or metastatic who have progressed after prior endocrine therapy, to study treatment with everolimus (RAD001) in combination with exemestane "(Medical Oncology A).
6. "Study in open-label, randomized, phase II trial, designed to evaluate treatment concomitant use of MM-121 and paclitaxel compared to paclitaxel treatment only in patients with advanced stage ovarian cancer resistant / refractory to platinum "(Medical Oncology A).
7. "GSK MEK115306 (pathology: advanced melanoma)" (Medical Oncology A).
8. "A randomized, double-blind, placebo-controlled, Phase III, with BKM120 in combination with fulvestrant in postmenopausal patients with breast cancer hormone receptor-positive locally advanced or metastatic HER2 negative that has progressed during or after aromatase inhibitor therapy "(Medical Oncology A).
9. "A Phase III, double-blind, placebo-control towards Vemurafenib Vemurafenib + GDC-0973 in patients with previously untreated BRAF V6000 mutation-positive, unresectable or locally with metastatic melanoma" (Medical Oncology A).
10. "A randomized, multicenter, open-label, randomized, phase II inhibitor or MEK pimasertib decarbazina in patients not previously treated with N-Ras mutation in melanoma skin cancer (Medical Oncology A).
11. "Study 52-week, phase III, randomized trial. Comparing active and placebo-controlled". Study to evaluate the efficacy and safety / tolerability of subcutaneous administration of SCH 900222 / MK-322, in subjects with moderate-to-severe psoriasis (Dermatology Clinic).

12. A Phase I / II open-label to assess the safety, tolerability, pharmacokinetics and antitumor activity of escalating doses of AZD9291 in lung cancer patients with advanced non-small cell progressing after prior therapy with an agent inhibitor Tirochinasi of the receptor for epidermal growth factor (AURA), (Medical Oncology A).

Educational Activities

Training events at IFO: Have organized 5 events over the last three years, national events hosting external speakers. Events were aimed at general practitioners, cardiologists, oncologists, anesthesiologists with a 98% participation rate, exceeding our expectations, events completely free, an average of 5 ECM recognized (min. 3, max 6.5) and deemed "effective event" by the Educational Office at IFO.

Ongoing Medical Training: The Unit of Cardiology hosted three Erasmus students graduating in Medicine and Surgery from the University of Lublin (Warsaw, Poland) for a trimester. Following this trimester, students met their academic expectations in accordance with their University's requirements. As a result, we were invited by the Dean of the Polish University to hold a seminar regarding cardiology and oncology.

Publications 2012-2013

Doppler pulsato tissutale e cardiotossicità da farmaci antitumorali: cut-off della velocità sistolica e diagnosi precoce. (Maramao F, Conde Y, Sperduti I, Rulli F). Giornale Italiano di Cardiologia.

Early Diagnosis of cardiotoxicity by anticancer therapy with pulsed wave tissue doppler imaging (Maramao F, Conde Y, Sperduti I, Rulli F). Eur. J. Heart Failure.

Department of Critical Area

Unit of Intensive Care (ICU), Pain Therapy and Palliative Care

Lamberto Laurenzi, MD

Director

STAFF MD Assistants: Antonio Calamaro, Felice Centullo, Loriana Di Emidio, Gianfranco Fusco, Lorella Pelegalli, Francesco Rendina, Carmela Stigliano

Activities 2012-13

Clinical Activities

The clinical activities of the Unit handle Intensive care, pain therapy and vascular access implant and management.

ICU: 755 patients were hospitalized in 2012 and 745 during 2013. Patients undergoing orthopedic, abdominal, neurosurgical and thoracic major surgery were the most representative, hospitalized for complications or hemodynamic monitoring. Sepsis, septic shock, respiratory failure and renal failure were the most relevant complications.

Vital functions support such as mechanical ventilation, dialytic treatment and hemodynamic care were administered. Medical oncology patients were also hospitalized with febrile neutropenia, pneumonia, renal failure, cardiac failure.

Pain therapy: The activities of the Unit involve the diagnosis and treatment of cancer pain and chronic non-malignant pain. Medical therapy and invasive procedures were

performed. In 2012 and 2013, a total of 2643 patients were examined and 2266 invasive treatment, like epidural and subdural blocks, electrics and pharmacological central and peripheral nervous neuromodulation, were carried out.
Implant and management vascular access: In order to perform chemotherapy and support therapy, cancer patients need stable and safe long-term vascular access in a central vein.
In 2012 and 2013, an total of 1928 vascular accesses were implanted including port systems, Groshong catheters and peripherally inserted central catheters

Research Activities

Main topics:
- Hospitalized patient care in ICU. In this field our clinical research aimed to identify risk factors and prevention of hospital-associated infections. An observational study on the prevention of multi drug resistant ventilator associated pneumonia was carried out.

- Pain therapy and palliative care. Full compliance with the law 38/10 regarding processing medical records aimed at detecting and treating pain in outpatients and hospitalized patients.
Research: open label, multicenter, observational prospective study on post cancer pain in cancer survivor. Principal investigator: L. Di Emidio MD.

- Vascular access. Establishing a centralized team for carrying out vascular access implants, management and elaborating the database that keeps records on thrombotic and infectious complications due to central venous accesses.

Department of Critical Area

Unit of Pulmonary Physiopathology

Vincenzo Cilenti, MD (until September 2013)
Maria Papale, MD (from October 2013)

Director

STAFF MD Assistants: Eliuccia Mastropasqua, Giorgio Piperno
Physiotherapists: Marina Bonaccorsi, Daniela Fargnoli
Nurses: Sabrina Fraternali, Carmelina Pronesti
For the project "Hospital free of smoke": Dr. Antonio Scappaticci

Activities 2012-13

Clinical Activities

The Physiopathology Respiratory Unit has continued its long-established mission to address and program research activities aimed at the prevention, diagnosis, cure and rehabilitation of pulmonary diseases. The directives have been the following: primary and secondary prevention in the field of pneumology through education (above all concerning addiction to smoking) and clinical-functional diagnostics, respiratory therapy and rehabilitation for both inpatients and outpatients, participation in research programmes and internal and external work groups of the Institute, participation and organization of courses, conferences and congresses for scientific activity reports as well as professional development. During 2012-13 about 34.342 services (medical visits, consultations, instrumental tests and respiratory rehabilitation activity) were conducted on patients from various units within the Institute. Cooperation with the Surgical Departments, particularly with the Department of Thoracic and Abdominal Surgery, was particularly intense due to the need of more accurately identifying the surgical risks.

A total of 28.311 services (visits, instrumental tests and respiratory rehabilitation activity) were carried out on outpatients who came either for lung cancer treatment and other diseases or treatments for quitting smoking or patients in need of respiratory rehabilitation.

Respiratory rehabilitation is offered mainly to external patients who either have to undergo major thoracic or abdominal surgery, or who have already undergone pulmonary cancer resections or those suffering from COPD. The aim is to improve quality of life as well as increase our knowledge in the area of respiratory rehabilitation which requires further study. In 2012-13, about 5844 services of respiratory rehabilitation were performed on internal patients and 6582 on external patients.

About 147 individuals sought help from the Centre that provides treatments to quit smoking (referral Centre for the Observation of Smoking, Alcohol and Addiction of the I.S.S.). In collaboration with the Unit of Psychology of I.R.E. the aim in evaluating the validity of integrated pharmacologic treatment (substituted with nicotine or bupropione or with vareneclina) and behavioural treatment of addiction to smoking is pursued. Efforts regarding smoking prevention have mainly involved educational and didactic interventions for young people in schools.

Research Activities

The "Smoke Free Hospital" project has implemented didactic initiatives and monitoring activities

The Unit is also involved in a biennial project entitled "Primary or Secondary prevention in high risk subjects for development of lung cancer" in collaboration with the "Lega Italiana contro i Tumori".

The Unit has also participated in the following studies:

- Prot. REGIRE “Registro Epidemiologico denominato REGIRE, studio osservazionale trasversale per la valutazione dei dati epidemiologici di prevalenza ed incidenza dell’insufficienza respiratoria finalizzati alla corretta programmazione sanitaria ed all’ottimizzazione dell’impegno delle risorse economiche per il trattamento della malattia” (Promotore A.I.P.O.)
- Prot. TECLA “Studio multicentrico randomizzato controllato TECLA (Tobacco dependence treatment in smokers performing a spirometry and the Effect of telling tobacco Consumers the Age of their Lungs)” (Promotore AIPO)
- Patient accrual for the Study DB2113360 ended in January 2012
- Patient accrual for the observational Study “ OPTIMO” ended in 2012

Our Units’ future activities and objectives involve implementing respiratory rehabilitation activities, in particular investigating quality of life and the recovery of respiratory functionality through suitable tests.

The Unit (Dr. V. Cilenti) was part of a project by the "Agenzia di Sanità Pubblica-Lazio (ASP) " entitled “ Definizione e implementazione di un modello di assistenza domiciliare integrata per malati affetti da insufficienza respiratorio in ossigenoterapia a lungo termine o ventilazione meccanica domiciliare” which has been approved by the "Centro Nazionale per la prevenzione e il controllo delle malattie". The results were presented at the Congress Centre “Bastianelli” at IFO in October 2013.

The Unit (Dr. V. Cilenti) was a member of the working group “Fattori di qualità per le attività di riabilitazione in regime di postacuzie ospedaliera”, composed by ASP Lazio (2012)

The Unit also took part in the international Phase III multicentric study “A 52-week treatment, multi-center, randomized, double-blind, parallel-group, active controller study to

evaluate the effect of QVA149 (110/50 mg o.d. vs NVA237 (50mg o.d.) and open-label tiotropium (18 mg o.d.)) on COPD exacerbations in patients with severe to very severe chronic obstructive pulmonary disease (COPD)".

Publications 2012-13

Allegra L, Cremonesi G, Girbino G, Ingrassia E, Marsico S, Nicolini G, Terzano C; PRISMA (PRospectIve Study on asthMA control) Study Group. Real-life prospective study on asthma control in Italy: cross-sectional phase results. *Respir Med*. 2012 Feb;106(2):205-14.

Della Rocca G, Coccia C, Pierconti F, Badagliacca R, Vizza CD, Cilenti V, Papale M, Melis E, Facciolo F. Intersociety consensus statement of preoperative evaluation for elective lung resection surgery. Published on *SIAARTI site.*

Mattioni M, Chinzari P, Soddu S, Cilenti V e Mastropasqua E. Serum p53 antibody detection in patients with impaired lung function. *BMC Cancer* , 2013, 13:62.

Romano F, Scichilone F, Sestini P, Cilenti V, e al.: Aerosolterapia domiciliare con nebulizzatori in asma e BPCO: cosa sta cambiando in Italia?. *Rassegna di Patologia dell'Apparato Respiratorio* 2013; 28:36-41.

CLINICAL RESOURCES

Clinical Resourcers – Translational Group

TG Brain Tumors

PI: Carmine Maria Carapella, MD

Biomolecular characterization and advanced imaging modalities in the diagnosis of brain gliomas: validation of prognostic and predictive factors. BIG

Background: Malignant gliomas (GMs), mainly glioblastomas (GBMs), represent the most lethal of all primary brain tumors. They are associated with high morbidity, presenting unique challenges to therapy due to their location, aggressive biological behavior and diffuse, infiltrative growth. GMs can develop either de novo (primary GBMs), or through progression from low-grade tumors (secondary GBMs); although pathologically indistinguishable, primary and secondary GBMs exhibit distinct patterns of cancer gene alterations. Previous efforts in GM genome characterization have identified somatic changes in well-known GM genes (EGFR, PTEN, IDH1, TP53 and NF1, among others) and nominated putative cancer genes with somatic mutations. These so-called driver mutations enable the proliferation of certain clones of transformed cells within the tumor microenvironment while secondary mutations emerge from the clonal selection process during treatment. Next Generation Sequence (NGS) approach have several potential advantages over traditional methods and genotyping approaches, including the opportunity of fully sequencing a large number of genes in a single test and to detect known and novel mutations. Recently, a computational pipeline that computes copy number variations (CNVs) at any locus in the human genome with the somatic mutation rate for genes residing at that genomic location has identified somatic mutations in 18 new genes in GBMs. Among the driver mutations is the isocitrate dehydrogenase 1 gene (IDH1), that is somatically mutated predominantly in more than 70% of lower grade gliomas and secondary GBMs, but infrequently in primary GBMs (about 5%). Interestingly, IDH mutations result in the aberrant production of the potential oncometabolite d-2-hydroxyglutarate (2HG). Recent data suggest the possibility of detection of 2HG in IDH1-mutated tissue samples using magnetic resonance spectroscopy (MRS). Relative 2HG levels and mutant IDH1 cells yield relevant correlations with various pathological parameters including mitotic activity, tumor vascularization, relative tumor content, and increased cell density. These data provide a novel characterization of mutant IDH1 lesions, suggesting the potential diagnostic value of 2HG and related imaging parameters as markers of clinically relevant tumor characteristics. On this basis, precise in vivo detection of this oncometabolite by magnetic resonance spectroscopy (MRS) may provide a non-invasive diagnostic and prognostic tool for the improvement of clinical management in patients affected by brain tumors. This opportunity opens a wider scenario with respect to the past, not only in the non invasive accuracy of brain tumor grading before any selected therapeutic approach, but also in the prediction of outcome, and in the assessment of therapeutic response. Furthermore, the improvement of MR imaging modalities such as Perfusion or MRS techniques have been proposed useful in providing information on size, metabolic and physiological aspects of tumor tissues. Extensively, Perfusion MRI is a non-invasive quantitative method of investigating microvascular structure and function by tracking the pharmacokinetics of injected low-molecular weight contrast agents as they pass through the tumor vasculature. The technique is sensitive to alterations in vascular permeability, extracellular extravascular and vascular volumes, and in cerebral blood flow (rCBV). Several studies have demonstrated that rCBV measurements have clinical utility in glioma grading and recent studies showed that progression-free survival was significantly different according rCBV level (>/< 1.75) in malignant as well as in low grade gliomas.

MicroRNAs (miRNA) are small noncoding RNAs that play an important role in the regulation of various biological processes through their interaction with cellular messenger RNAs. They are frequently disregulated in cancer and have shown great potential as tissue-based markers for cancer classification and prognosis. MiRNAs are also present in extracellular human body fluids such as serum, plasma, saliva, and urine. Most of circulating miRNAs have been found in membrane-bound vesicles such as exosomes. Since miRNAs circulate in the bloodstream in a highly stable, extracellular form, they may be used as blood-based biomarkers for cancer and other diseases. So far few data are available for circulating as well as resident biomarkers used for diagnosis, response to therapy, and/or early detection of gliomas. However, a global serum miRNA signature in a large cohort of malignant glioma patients has been recently reported. In particular, seven serum miRNA (miR-15b*,miR-23a, miR-133a, miR-150*, miR-197, miR-497 and miR-548b-5p) whose concentrations were significantly decreased in the serum of malignant astrocytomas patients compared to normal controls have been identified. Interestingly, these identified serum miRNAs also exhibited a global decrease in tumor tissues relative to normal tissues and were markedly elevated after operation. The seven-serum miRNAs signature identified in this study show great potential as noninvasive biomarkers for malignant gliomas; nevertheless, further studies are necessary in serially acquired blood samples of a larger cohort of patients combined with long-term follow-up. Few tissue miRNAs profiles for this neoplasia has not yet been identified. However, several data have demonstrated a deregulated expression of tissue specific miRNAs among them miR-9/9*, miR10b, miR-21, miR-221, miR-101, miR-137, miR-330, miR17, miR20a, miR-222, miR-10a, miR26, miR27a, miR182, miR-519d, miR-7 miR-31, miR34a were observed to be aberrantly expressed. Based on the above considerations, we hypothesize that the identification of new imaging modalities and molecules as biomarkers will improve the glioma prognosis and therapeutic response.

Aims: The primary aim of our current project is to identify new molecular and imaging glioma biomarkers useful for diagnosis, prognosis and/or predictive of tumor therapeutic response. The secondary aim is to use the new identified biomarker as useful tools for gliomas classification. On these bases, we believe to eventually yield a significant improvement in managing these patients. To accomplish these aims, we will take advantage of retrospective as well as prospective case series collected at IRE.

1. Validation of driver mutation genes in gliomas by next generation sequencing (NGS).
2. Identification of glioma molecular biomarkers.
3. Identification of new molecular and imaging glioma biomarkers useful for diagnosis, prognosis and/or predictivity. At the end of these studies, we hypothesize to document the potential non-invasive diagnostic and prognostic role of MRI and MRS in the combined treatment of glioma patients, strictly correlated with biomolecular data and therapeutic response observed in the IRE cohort of patients enrolled between 2006-2013 as well as prospectively in new enrolled patients.

Clinical Resources – Translational Group

TG Colo-Rectal Tumors

PI: Marcella Mottolese, PhD

Exploiting next-generation sequencing and loss-of-function genetic screens for discovering novel molecular predictors and therapeutic targets in colorectal cancer

Background: The advent of -omics, the expanding complexity of colorectal cancer (CRC) taxonomy, and the first successes in the design of targeted therapy have spurred a wave of clinical investigation with pathway-targeted inhibitors. Nevertheless, it is estimated that approximately 95% of compounds with documented anticancer activity in the preclinical setting fail during clinical development. Multiple factors concur in determining this high attrition rate, such as the difficulty in co- developing novel anticancer agents and predictive biomarkers. By cataloguing genetic abnormalities in CRC, the Cancer Genome Atlas (TCGA) network revealed the existence of multiple molecular entities, each one characterized by specific molecular abnormalities, and by a different spectrum of activated/inactivated molecular networks. The identification of a set of 'driver' mutations modulating gene expression networks, the possibility to explore gene and pathway interactions with a considerable throughput, and a renewed pipeline of molecular targeted agents currently under clinical development call for more focused clinical and preclinical investigations aimed at identifying both novel biomarkers and 'actionable' alterations. Hypothesis: Whole-genome and exome DNA sequencing technologies together with transcriptomic and proteomic analysis allowed to capture the individual molecular make-up of each patient tumor. In CRC, the integration of data coming from exome sequencing with gene expression, DNA copy number variation, and epigenetic status provided a snapshot of molecular derangements coexisting in CRC. Overall, 32 recurrent somatic mutated genes were identified: 15 in the hypermutated and 17 in non-hypermutated cancers. The dissection of the genetic landscape of CRC and the evidence that multiple genetic changes, coexisting in CRC, deregulates a limited numbers of modules, represent a starting point for optimizing genotype-driven therapy. Deregulated gene networks are involved in key oncogenic activities, spanning from mitogenic growth signals and apoptotic pathways to DNA repair and cancer stem cell maintenance/enrichment. We hypothesized that the evaluation of 'driver' mutations in CRC samples will allow a series of hypothesis-driven, correlative analyses aimed at understanding the clinical role of pathways that harbor activated/inactivated mutations in key components. Considering that the majority of non-silent genetic alterations cannot be directly targeted with established and investigational targeted agents, as a parallel approach to complement clinical studies we will took advantage of high-throughput loss-of-function genetic screens in in vitro model systems in order to uncover alternative strategies for targeting undruggable mutations.

Aim 1: To develop a custom panel targeting mutations in genes implicated in CRC development and progression, focusing on the 32 genes whose alterations are defined as non-silent. Since the spectrum of mutations differs according with the microsatellite status, the methylation and mutation in Mismatch Repair genes will be evaluated. In more detail, the following 30 genes (2 overlapping genes between hypermutated and non-hypermutated cancers) whose mutation frequency spans form 3% to 81% will be analyzed: ACVR1B, ACVR2A, APC, BRAF, CASP8, CDC27, CTNNB1, EDNRB, FAM123B, FBXWT, FZD3, GPC6, KIAA1804, KRAS, MAP7, MIER3, MSH3, MSH6, MYO1B, NRAS, PIK3CA, PTPN12, SMAD2, SMAD4, SOX9, TCERG1, TCF7L2, TGFBR2, TP53, and TTN.

Aim 2: To explore the clinical potential of the wide CRC genotyping described above. As a first

analysis, we will focus on anti-EGFR therapy. The logic behind it is that KRAS is not an exact predictor, as not all KRAS wild-type CRC patients respond to anti-EGFR therapies, independently from existing abnormalities in functionally-related genes. Indeed, BRAF mutations possess a negative prognostic value, rather than predictive one. It has been recently demonstrated that patients KRAS-BRAF-NRAS wild type (triple negative) showed a very significant better clinical outcome in terms of overall survival than other subgroups, when treated with an anti-EGFR therapy as first line. Conversely, evidence supporting the usefulness of other genetic markers such as PIK3CA and PTEN are still lacking. Consistently, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group 10-11 found insufficient evidence to recommend for or against testing these genes in the same clinical scenario, and discourages the use of these tests in guiding anti-EGFR therapy. The analytic approach will be initially performed in 'positive and negative outliers' in order to evaluate the potential of wide genotyping on clinical outcomes of metastatic CRC (mCRC) patients treated with cetuximab plus chemotherapy. In more detail, to isolate predictive genetic signatures we will adopt a dichotomous model by comparing responders and non-responders (training set). Non-responders will be defined as patients who have experienced disease progression at the first post-therapy radiologic assessment, according to Response Evaluation Criteria In Solid Tumors (RECIST). Responders will be defined as patients who have experienced a complete or partial response and are free from disease progression at 1 year. This first analysis plans to increase our chances in isolating candidate predictive biomarkers by evaluating a highly selected patient population, representing ~30% of the cases in the clinical practice. Afterwards, a more comprehensive, confirmatory analysis will be carried out in a consecutive series of unselected mCRC patients treated with first-line FOLFIRI plus cetuximab to determine the predictive value of specific genetic changes stemming from the training set on the progression-free survival time (identification set), defined as the time elapsed between treatment initiation and tumor progression or death from any cause. To ensure reproducibility of our data, internal validation procedures will be applied with bootstrap analysis.

Aim 3: The comprehensive genomic characterization of CRC raised the need for investigating strategies for targeting undraggable oncogenic drivers. The development of high-throughput loss-of-function screens based on RNA interference technology in vitro model systems represents a powerful tool for identifying less intuitive genetic interactions whose abrogation impair cell fitness. Consistently, when these screens are conducted in different genetic backgrounds they might uncover molecular networks that can be exploited for targeting undruggable mutations via "synthetic lethal" interactions. Synthetic lethality is a therapeutic modality relying on the concept that cancer cells defective for a specific (mutated) pathway are exposed to the inhibition of a different, albeit partially overlapping, signaling avenue, and the combined abrogation of redundant pathways results in a significant impairment of cell fitness. When interactions in a given genetic background are searched, the use of isogenic cell line pairs that only differ for the genetic lesion of interest, obtained via homologous recombination gene targeting, represents the optimal case-control model for limiting false positive hits. We plan to conduct genetic screens in a panel of isogenic cell line pairs, exclusively differing from the mutational status of TGFRB2, SMAD4 and SOX9. This choice stemmed from the important biological functions governed by these genes, which are involved in key pathways/biological functions and for which no direct inhibitors are available (TGF-beta pathway and self-renewal pathways). Overall, the aim is to capture gene functions that, when abrogated, are lethal only in cell lines carrying mutations in the gene of interest, which intrinsically represents the predictive biomarker.

Aim 4: Complex mutational landscapes and individual mutations are both operationally inefficient at capturing the mutational complexity of individual cancers for clinical use. This will likely require robust, intermediate throughput approaches. Evidence has been provided that a multiplexed assessment of a few parallel oncogenic pathways is necessary and sufficient to predict with considerable accuracy whether or not a given target therapy will work in a specific patient. For instance, certain KRAS, NRAS and BRAF mutations, but not others, are predictive of

the outcome of anti EGFR treatment in colorectal carcinomas. Along the same line, each tumor lesion comprises hundreds of tumor cell clones undergoing branched evolution. Each carries common and private driver mutations. Under the pressure of targeted therapy, Darwinian selection results in the rapid onset of distinct secondary mutations. Thus, in the near future, primary lesions, local metastastic foci, and escape tumor variants will have to be quickly screened for small panels of cooperating mutations. Target therapy will have to be selected and/or adjusted to a changing mutational landscape, through disease stages and during progression. To shorten the timeline of precision medicine, we will interrogate a selected subset of the sequenced DNA biobank for model actionable markers (e.g., KRAS and BRAF mutations) using Nanoparticle-Enhanced Surface Plasmon Resonance Imaging (NE-SPRI). NE-SPRI is built around an innovative optofluidic biosensor bearing non-conventional hybridization probes (Peptide Nucleic Acids-PNA and PNA analogues). It detects analyte DNA in a PCR-free ultrasensitive format (less error-prone), and may be of interest as a cost-effective future clinical applications for the rapid (minutes) detection of pre- defined combinations of druggable drivers of transformation/progression. Skipping PCR and similar DNA amplification steps makes NE-SPRI less prone to sample cross-contamination. This is expected to greatly facilitate molecular diagnosis in a routine pathology lab handling hundreds of different DNA templates.

Clinical Resources – Translational Group

TG Lung Tumors

PI: Paolo Visca, MD

Identification of novel genomic alterations in smoking-related nsclc by analyzing tumor and stromal-associated cells

Background: Lung cancer is the leading cause of cancer death in males and the second in females worldwide, accounting for 1.6 new cases and 1.4 million deaths in 2008. In Italy, 38.000 new lung cancer cases, 30% of which occur in women, and 34.000 lung cancer-related deaths are expected in 2013, resulting in a lifetime probability of 1/10 in males dying from lung cancer (26% of all cancer deaths) and 1/44 in females (11% of all cancer deaths). More than 85% of lung cancer cases are attributed to cigarette smoking. Indeed, the observed variations in lung cancer rates and trends across countries or between males and females within each country largely reject the differences in the stage and degree of the tobacco epidemic. Following the trends observed in smoking habits, lung cancer incidence in Italy is decreasing slightly in males (- 2.0%/year), but with a striking increase in females (+2.5%/year between 1996 and 2010). Despite progress in this area, there is a poor 5-year survival rate for metastatic disease, 11% in Europe, and cure rates are highly dependent on tumor staging; as symptoms are not specific and have a late onset. This disease is usually diagnosed at an advanced stage, resulting in an overall 5-year survival rate of approximately 14% . These data suggest that screening as well as a deeper comprehension of biological mechanisms underlying this disease could lead to an earlier diagnosis, leading to more appropriate treatment strategies and a decrease in lung cancer mortality. As shown by recent advances in the medical treatment of lung cancer, use of biological drugs to consolidate a standard of treatment for selected patients, a more comprehensive understanding of genomic alterations in non-small lung cancer (NSCLC) is of paramount importance in this rapidly evolving scenario. In particular, detection of tumor-specific genomic profiles palys a critical role in clarifying possible mutational pathways in cancerogenesis. Although tumorigenesis has been considered for decades as a large process involving genetically transformed cancer cells, recently compelling evidence has revealed the importance of the microenvironment surrounding the tumor and the dynamic reciprocity between tumor cells and their microenvironment. Fibroblasts and immune cells are crucial components of the tumor microenvironment. The mutation of tumor suppressor genes in stromal fibroblasts induces epithelial cancer development, suggesting an important role of the stroma in epithelia homeostasis. Cancer-associated stromal cells (CAFs) produce a plethora of factors (secretome) also in response to tumor cell stimulation, sustaining tumor progression and immune suppression. De novo formation of tertiary lymphoid structures (TLS) has been described in lung cancers. The local density of tumor-infiltrating T cells influences the clinical outcome of the patients and more recently preclinical and clinical data has shown that an antibody blockade of immune checkpoints can significantly enhance antitumor immunity, also in lung cancer. Thus, it is mandatory to assess the genomic mutational landscape not only in tumor cells, but also in the relevant cell components of the surrounding microenvironment. As it has been extensively described, tobacco smoking is the major cause of lung cancer worldwide, due to numerous carcinogens as well as agents that cause inflammation, which play an important role in carcinogenesis. Thus, tobacco potentially targets multiple lung cellular populations. Tobacco smoking increases the risk of all major histological types of lung cancer, but appears more prevalent for squamous cell carcinoma, followed by small cell carcinoma and adenocarcinoma. The goal of this multidisciplinary project is to strengthen the lung translational group at our Institute and to provide

new insights on how mutational events in stromal cells may impact smoking-associated lung cancer progression. The final aim is to make a coordinated effort to analyze clinical tumor specimens for a panel of specific, actionable mutations, aimed at identifying potential therapeutic targets in smoking associated NSCLC to select lung cancer patients with a history of smoking for appropriately targeted clinical trials. Hypothesis: 1) By acting as both a direct carcinogen and a potent pro-inflammatory stimulus, tobacco smoking may induce qualitatively different genetic alterations in diverse lung compartments; 2) Compartment-specific mutations may differentially impact on lung cancer prognosis and response to treatment(s); 3) Within each 'compartment-specific' mutation profile, novel oncogenic drivers and potentially actionable therapeutic targets may emerge; 4) Some of the identified smoking related genomic alterations may correspond to macroscopic patterns which may be investigated by minimally/non-invasive techniques, such as functional imaging and perfusion CT, or circulating biomarkers.

Aim 1. To describe the mutation landscape of NSCLC that occurs in patients who smoke in four different tissue compartments: a) tumor; b) proximal uninvolved peritumoral tissues; c) distant 'normal' tissue; d) bronchial 'normal' epithelium.

Aim 2. To identify potentially novel oncogenic drivers in smoking-associated NSCLC, by studying stromal cells isolated from proximal peritumoral tissue in comparison to matched lung carcinoma.

Aim 3. To characterize the functional role of the identified candidate drivers in preclinical models *in vitro* and *in vivo*, focusing on sensitivity /resistance to standard cytotoxic and targeted therapy.

Aim 4. To correlate functional imaging with histopathological characteristics of the tumor, immune infiltrating cells and identified genomic mutations.

Aim 5. To explore the possibility of identifying surrogate biomarkers in the plasma of patients.

Aim 6. To validate the putative prognostic or predictive biomarkers in a retrospective/prospective series of NSCLC patients with a history of smoking.

Clinical Resources – Translational Group

TG Sarcomas

PI: Roberto Biagini, MD

Identification of prognostic factors and definition of predictive drug response elements in selected sarcoma patients.

Background: Sarcomas are a heterogeneous class of tumors whose sub-classification is named after the type of tissue they resemble or derive from. In most high-grade sarcomas, prognosis is often dismal and standard therapeutic approaches in metastatic disease are palliative. If compared to carcinomas, sarcomas are relatively rare, and their sub-classification further decreases the chances for a single institute to reach a statistically significant number of cases. In spite of this, these tumors represent an important nosologic category in our Institute. We will focus our interest on selected histotypes, due to specific clinical considerations and the number of evaluable cases.

Hypothesis: The relative low occurrence and heterogeneous morphological and clinical characteristics of sarcomas did not encourage accurate and significant studies of these pathologies at a molecular level. Nevertheless, the extremely successful therapeutic response in specific subtypes, e.g. gastro-intestinal stromal tumors (GIST) using molecular targeted therapeutic approaches (Imatinib and derivatives), strongly encourages the use of high-throughput molecular analysis in these pathologies. Taking also into account the clinical cases treated at our Institute, we will focus our attention on a) high-grade osteosarcomas, as models of chemosensitive tumors and identification of biological factors related to tumor necrosis; b) high-grade soft tissue sarcomas for their refractoriness to therapy, in particular liposarcoma. Most types of adipocytic neoplasms have distinctive karyotype aberrations which can be of considerable help in diagnosis and treatment.

Aims: The aim of this project is to investigate sarcoma patients and tumors using the state-of-art technologies available for molecular biology of nucleic acids and proteins, in order to pursue two main tasks: 1) identification and validation of predictive biomarkers; 2) establishment of new concepts for the personalized treatment of this disease. Before performing any molecular analyses, we must set the ground for a solid backbone for the management of patients data and biological samples. All these samples (tumor, normal tissue and plasma of patients) will be collected and stored in collaboration with the Pathology and Clinical Pathology divisions, and all the data will be filed in a dedicated database. Fresh specimens will be treated to obtain: a) fresh tumor fragments suitable for xenotransplantation in immunocompromised mice; b) dissociated (bulk) sarcoma cells. Primary cultures and tumor-propagating cells (cancer stem cells, CSCs) will be tentatively generated; c) frozen surgical specimens will also be collected. This will set the ground to proceed with the scientific aims concerning prognosis and therapy. In order to overcome the intrinsic variability of human tumor samples that could negatively affect the experimental results and their interpretation, we are planning to take advantage of *in vitro* and *in vivo* experimentation involving cells derived from fresh surgical sarcoma specimens. In the former case, we will set up bulk and primary culture cells as well as CSCs when possible. In the latter case, xenografting of human tumor tissue in immunodeficient mice will be employed due to its effectiveness in improving the predictive power to assess patient response to anticancer drugs also in sarcomas. We aim to develop patient-derived tumor xenografts by the implantation of fresh surgical tissue specimens collected from patients treated at our Institute. Due to the heterogeneity of these tumors and corresponding metastases, these tasks will be particularly relevant for performing reproducible experimental results.

Clinical Resources – Translational Group

TG Urologic Tumors 1

PI: Michele Gallucci, MD

New tools for individual risk assessment and treatment assignment in prostate cancer patients

Background: Prostate cancer is one of the leading causes of cancer death among the male population. Prostate specific antigen (PSA) assessment is currently the mainstay of prostate cancer screening. However, large clinical studies demonstrated the inadequacy of PSA-based test due to its inability to distinguish cancer from benign hypertrophy/inflammation. Besides the absence of a reliable diagnostic indicator, prostate cancer management is also impaired by the lack of tools to guide treatment assignment and evaluate therapy response. The availability of biomarkers that discriminate patients with indolent or aggressive tumors would allow on the one hand to avoid surgical over-treatment of patients with low-risk disease, on the other to appropriately treat early tumors doomed to become aggressive and metastatic. Likewise, effective biomarkers for patient stratification would allow to distinguish patients eligible for either surgery or active surveillance. Moreover, new molecular markers of therapy response will be essential in driving therapy decision-making of advanced tumors. Therefore, an overall improvement of prostate cancer management will need a comprehensive effort to devise new tools for cancer diagnosis, patient stratification and prediction of therapy response. Tumors have been demonstrated to release exosomes loaded with proteins and nucleic acids into the bloodstream that reflect the molecular setting of parental cancer cells. Exosomes also contain microRNAs (miRs), that are transferred to target cells where they can repress corresponding messenger RNAs. Recent studies from our and other laboratories have reported the role of miRs as potential biomarkers in cancer. In particular, we have previously demonstrated that miRs 15/16 are downregulated in advanced prostate cancer, and their functional reconstitution results in tumor regression in vivo. More recently, we have identified the perturbation of miR-21 and miRs 15/16 as a critical step in prostate cancer progression (Bonci D. et al, submitted), suggesting that levels of these miRs may represent a useful indicator of aggressive disease. Our preliminary data suggest that molecular profiles of exosomes released by prostate tumors represent innovative and powerful tools for diagnosis and therapy assessment. In this context, the possibility to collect tumor-released exosomes from plasma samples represents a unique opportunity to obtain tumor-derived material without the use of invasive procedures. Tumor-specific exosomes will then be used to extract miRs to be used for miR profiling and proteins that will be used for Reverse-Phase Protein Arrays (RPPA). The latter technique is particularly suitable to analyze the expression of total and phosphorylated proteins in small biological samples and has been adapted by the PI for exosome protein profiling (see Preliminary Results section). The analysis of miRs and proteins contained in tumor-derived exosomes will be then correlated with patient outcome in order to identify new biomarkers for the diagnosis and therapy of prostate cancer. HYPOTHESIS: We hypothesize that miR and protein profiles of PSA-Ex may provide an innovative and powerful tool for prostate cancer diagnosis and for identifying patients that have a high risk in developing an aggressive form of the disease. Since current diagnostic and prognostic methods are based on histological examination of multiple biopsies, the use of nanovesicles as non-invasive liquid biopsies could represent a major improvement in the clinical

management of prostate cancer. In addition, results of this project may provide new molecular tools for patient follow-up and for predicting therapy response.

Aim 1: To validate new tests based on exosome-expressed surface markers for prostate cancer diagnosis and prognosis. Aim 2: To identify new prognostic biomarkers through generating the molecular profiles of tumor-derived exosomes by RPPA and miR analysis and correlation with risk groups. Aim 3: To identify new potential biomarkers of therapy response in prostate cancer patients through analysing exosomes derived from treated patients with advanced cancer.

Clinical Resources – Translational Group

TG Urologic Tumors 2

PI: Michele Gallucci, MD

Evaluation of in vitro/in vivo-drug sensitivity and phosphoproteomic expression profiles in renal cancer patients: stem cells models and new molecular biomarkers for personalized therapy

Background: Renal Cell Carcinoma (RCC) represents 2-3% of all adult malignancies, and a significant percentage (30%) of patients present with an advanced disease at diagnosis. Surgical resection is the standard therapy for localized tumors, and for a niche of metastatic diseases. Median survival for patients with metastatic disease is extremely low, and may reflect the inadequate responsiveness to chemotherapy. Recently, new drugs entered the therapeutic arena, including several tyrosine kinase inhibitors (TKIs) and mTOR inhibitors, which significantly improved patient survival. Moreover, these agents are administered in unselected patient populations, due to the lack of predictive biomarkers, an approach that is expensive in a highly heterogeneous disease. Cancer Stem Cells (CSCs) are defined as a stem-like population endowed with self renewal and multi-lineage differentiation abilities. On the one hand, CSCs are thought to be responsible for tumor growth, heterogeneity, and resistant to current treatment protocols. On the other hand, the possibility to isolate, expand and indefinitely maintain CSCs in culture is offering the opportunity to test conventional and investigational anticancer agents against the actual population of tumor-propagating cells isolated from each individual patient tumor. The project herein proposed is designed to optimize medical treatment of RCC patients by taking advantage of a CSC-based drug sensitivity assay coupled with a deep molecular characterization. HYPOTHESIS: Personalized therapy is the new challenge for modern oncology. The administration of pathway-focused inhibitors in patients whose tumors harbour specific genetic defects is improving their therapeutic potential. Nevertheless, RCC remains an orphan disease due to the lack of molecular parameters able to drive the go/no go decision process. High-throughput technologies (gene sequencing and RPPM) provide a snapshot of deregulated oncogenic signals. Therefore, these technologies hold the potential for redefining the molecular taxonomy of RCC, by identifying multiple oncogene-addicted disease entities requiring specific therapeutic interventions. We hypothesize that the outcome observed *in vitro* (death rate) following the exposure of putative CSCs to standard first-line therapeutics correlates with the response of metastatic RCC patients to TKIs. Overall, integrating the large body of information coming from high-throughput approaches, with our CSC-based pharmacological assay might represent the ideal working model for redefining current criteria for treatment assignment in metastatic RCC patients.

Aim 1: To determine the accuracy of the *in vitro* and *in vivo* Stem Cell Sensitivity Assay (SCSA) in predicting the benefit of metastatic RCC patients to first-line TKI therapy (objective responses according to RECIST criteria).
Aim 2: To explore potential predictive biomarkers of activity/resistance to TKIs in tumor tissues. To do this, we propose an integrated, high-throughput approach designed to explore mutational events and deregulated pathway nodes through whole-exome sequencing and Reverse-Phase Phosphoprotein Microarray (RPPM).
Aim 3: To evaluate Progression Free Survival (PFS) and Overall Survival (OS) metastatic patients (follow-up 3 years) trying to associate a significant correlation with corresponding molecular signatures.

Clinical Resources – Translational Group

TG Ovarian Tumors

PI: Patrizia Vici MD, Maddalena Barba MD

Exploring biomarkers and pathways driving disease outcome in high grade serous ovarian carcinoma (HGS OCa)

Background: Ovarian cancer ranks first among the causes of death from gynecologic malignancies. The significant high frequency of advanced stages at diagnosis, along with the emergence of resistance to administered treatment, substantiate still unacceptable rates of recurrence and death from the disease, with 5 year survival of only 30% in women diagnosed with cancer spread out of the pelvic cavity and/or pelvine/para-aortal lymph node involvement. Conversely, at the time of diagnosis, disease is exclusively confined to the ovary or pelvis [International Federation of Gynecology and Obstetrics (FIGO) stage I and II, respectively] in about one third of women, with a 5-year survival of approximately 92% and 71%, respectively. Surgical debulking followed by platinum- and taxane-based chemotherapy represent the mainstay of treatment for all epithelial ovarian cancers. Despite the efforts from the cancer research community, overall survival for women with ovarian cancer has remained substantially unchanged over the past thirty years. In recent years, the compelling need for a comprehensive assessment of the mechanisms regulating disease development and progression has led the cancer genome atlas (TCGA) network to perform an integrated genomic analysis including 489 clinically annotated stage II-IV high grade serous ovarian carcinomas (HGS OCa). Mutations of TP53 resulted largely predominant (96%), while BRCA1/2 were mutated in 22% of tumors and further genes were significantly mutated in only 2-6% of the cases assessed. A hundred thirteen significant focal DNA copy number aberrations and epigenetic silencing of 168 genes were identified. Four ovarian cancer transcriptional subtypes, three micro RNA (miRNA) subtypes, four promoter methylation subtypes, and a transcriptional signature associated with survival duration were described. Most commonly altered pathways included Retinoblastoma (RB), Rat sarcoma (RAS)/Phosphoinositol 3 kinase (PI3K), Forkhead box M1 (FOXM1), NOTCH, and Homologous Repair (HR). This first large scale integrative view of the genetic and epigenetic aberrations of HGS OCa provides the prototype for further studies of biomarkers and pathways driving disease outcome in HGS OCa. Such studies are undoubtedly preliminary to the identification of increasingly specific and potentially 'actionable' targets in HGS OCa patients. Extensive studies have revealed that G protein-coupled receptors (GPCR) family members, such as endothelin A receptor (ETAR), Frizzled (FZD), that serve as receptors in the Wnt signaling pathway, chemokines, thrombin and lysophosphatidic acid receptors play a key role in epithelial ovarian cancer (EOC) progression. In this context, ETAR and its ligand endothelin-1 (ET-1) have been involved in the pathophysiology of a wide range of human tumors, including EOC. ET-1 and ETAR are expressed in 85% of EOC and their expression correlates with advanced stages. High-throughput screening analysis has allowed the characterization of molecular profiles associated with response to chemotherapy in EOC identifying ETAR as one of the genes differentially expressed between samples from patients exposed to platinum-based chemotherapy and samples from unexposed patients (i.e. collected prior to chemotherapy). Furthermore, the ET-1 signaling has been identified among the canonical pathways associated with platinum resistance. Immunohistochemical analysis of EOC human tissues revealed that ETAR is overexpressed in resistant tumors. A surprising finding from a recent unbiased approach to somatic mutations in cancer genome has led to the discovery that GPCRs are mutated in approximately 20% of all cancers, including EOC that commonly harbor somatic mutations in GPCR, such as ETAR and FDZ5. This raises the possibility that activating mutations in these receptors may be involved in

the onset of chemoresistance. On this basis, a detailed analysis revealing mutations or the presence of hotspot mutations in their coding sequences that may result in a gain expression in samples from platinum-resistant patients warrant further investigation. Angiogenesis has been consistently validated as a target in ovarian cancer. The approval of bevacizumab, an antivascular endothelial growth factor, in first-line treatment of advanced ovarian cancer has undoubtedly expanded the range of the viable therapeutic options. However, the ideal target population for bevacizumab remains largely unidentified, with treatment efficacy being potentially diluted by generalized administration. Studies of candidate microRNA biomarkers might drive bevacizumab administration towards well selected subgroups of EOC patients who are most likely to benefit from a bevacizumab-including regimen. When addressing angiogenesis, consideration of determinants of degradation of the vascular basement membrane and remodeling of the extra cellular matrix (ECM) is mandatory due to their role in developmental vascular patterning and pathological neovascularization. Matrix metalloproteinases, (MMPs) a group of zinc-dependent endopeptidases degrading ECM macromolecus, interact with VEGF and regulate tumour progression. Belotti and colleagues have provided evidence in support of a complex cross talk between VEGF and MMPs in ovarian cancer progression and invasion. Wang and coauthors have proposed a functionally significant role for VEGF in vasculogenic mimicry. Accordingly, the construction of a fluid-conducting, matrix-rich network critical for tumor blood supply is mediated by VEGF upregulation of EphA2 and final activation of MMPs. Accumulating evidence suggests that epigenetic deregulation may precede the genetic changes such as mutations in tumor suppressors or oncogenes. Therefore, the detection of DNA methylation could reflect the early development of cancers. Recently, evidence linking DNA methylation to platinum sensitivity in ovarian cancer has emerged. The analysis of miR-484 has revealed that the platinum sensitive phenotype is caused by a modulation of tumor vasculature through the regulation of the VEGFB and VEGFR2 pathways. On this basis, it is plausible to hypothesize that blockage of VEGF through the use of an anti-VEGFA antibody may not be sufficient to improve survival in ovarian cancer patients with active VEGFB signaling. In recent years, the body of evidence regarding the role played by metabolic determinants in the etiology of ovarian and, more in general, gynecological cancers has grown notably. In a pooled analysis of fifteen case-control studies carried out by Olsen and colleagues, obesity and overweight were associated with an overall increased risk of borderline and invasive ovarian cancers. However, in invasive cancers the association was restricted to the non-serous and low-grade subtypes, with the possible exception of pre-menopausal women. Obesity is associated with increased insulin levels, which lead to increases in the insulin-like growth factor 1 (IGF1). There is no clear relation between adiposity and IGF1. However, high levels of IGF1 have been associated with ovarian cancer in women aged 55 years or less. In addition, growing evidence supports a role of the IGF-1 receptor (IGF-R) pathway in gynecologic cancers and *in vivo* and *in vitro* studies have shown a significant impact of IGF-1R targeted therapies in these malignancies, mainly ovarian and endometrial cancers. Results from several epidemiologic studies including diabetic patients support the association between metabolic disorders and risk of ovarian cancer, whereas there is paucity of data on the potential role of metabolic determinants in the pathogenesis of ovarian cancers in non-diabetic patients. Moreover considerable evidence supports a mechanistic role of ET-1 in the pathophysiology of adiposity-related metabolic disorders. The link between higher ET-1 activity and obesity suggests a possible role of ET-1 as a surrogate biomarker for ovarian cancer. HYPOTHESIS: The proposed study is built on the following hypotheses: 1. The shift from a traditional, morphology-based approach to an innovative paradigm based on integrated analysis including genetic and epigenetic alterations, miRNA profiling and immunohistochemistry in tissue microarray (IHC-TMA) will provide solid ground for distinguishing between platinum resistant and platinum sensitive HGS OCa patients. The prediction of cancer behaviors and, ultimately, response to therapy in HGS OCa cases differing by platinum sensitivity will allow to take major steps towards personalized therapy and improved outcome. 2. Combining data generated by an integrated genomic analysis with measurements of anthropometric indicators and biomarkers of metabolic disorders might further enhance our ability to interpret platinum

sensitivity/resistance and better address individual patients' needs.

We will rely on a mixed study design with both a retrospective and a prospective component. These two sub-studies will be run in parallel during the first eighteen months of the intended study period, while conclusive analysis and study closure will occur over the last six months. The retrospective study will be based on an integrated analysis performed in Formalin-Fixed, Paraffin-Embedded (FFPE) tissues from the primary tumour of 200 women with clinically annotated stage II-IV HGS OCa. In these patients, platinum sensitivity/resistance as defined according to the criteria stated by Markman will be interpreted in light of the results of the integrated analysis previously mentioned and described in greater detail in the following pages. The findings from the retrospective study will provide the basis for defining the minimum sample required to conduct the prospective investigation (sample size calculation) that will pose the basis for ultimately translating our results into clinical practice.
Aim 1: In FFPE tissues obtained from the primary tumour of 200 women with clinically annotated stage II-IV HGS OCa, we will assess: a. genomic alterations by MiSeq Next Generation Sequencing (NGS). The high resolution characterization of custom-targeted genes from genomic DNA will include: TP53, BRCA1/2, Wnt/β-catenin, and ETAR. b. Signatures potentially explicative of platinum resistance including ET-1, VEGF, MMP-9 and MMP-14 and epigenetic alterations (e.g., miR-484). c. The activation state of key oncogenic pathways throughout IHC-TMA. The pathways of interest will include: 1. RB 2. RAS/PI3K 3. FOXM1 4. NOTCH 5. Wnt/beta-catenin 6. ET-1.
Aim 2: prostective study - In actively enrolled women, we will: a. Validate results from the integrated analysis described above in tissue and ascitic fluid samples collected in course of surgical procedures. b. Investigate signatures potentially explicative of platinum resistance including those related to ET-1, VEGF, MMPs (MMP-9 and MMP-14) and epigenetic alterations (e.g., miR-484). MiRNA profiling will be performed in fresh tissues from HGS Oca, in serum and, when applicable, ascitic fluid samples collected at repeated time points (i.e. on study entry and at disease progression/death/study exit (whichever comes first). Results will be also evaluated in light of serum CA125 and tumour features including stage and histological subtype. c. Evaluate the predictive role of the following biomarkers and anthropometric indicators on the existence and type of genomic alterations and different miRNA expression profiles: 1. Circulating levels of fasting glucose, insulin, and insulin like growth factor I (IGF-I), and ET-1 in serum samples collected at baseline and at repeated time points (as above specified) and in ascitic fluid samples, when applicable. 2. Anthropometric measures including height, weight, body mass index (BMI) and waist circumference as assessed at baseline and at different time points. d. Provide human biological specimens for developing and implementing biobanking at the Regina Elena National Cancer Institute. The proposed study will supply blood derivatives (i.e., plasma and serum samples) and tissue samples (i.e., fresh tissues, FFPE and, when available, correspondent frozen tissues) from HGS OCa patients. Sample collection, handling and storage will be performed according to preset, standardized operative procedures and the highest technological standards under the supervision and responsibility of the Pathology and Clinical Pathology Divisions for tissue samples and blood derivatives, respectively. Ethical approval and written informed consent are intended as mandatory requirements. Clinical and pathological records matched to the biological samples will converge into a linked-database including data on demographics (e.g., age at diagnosis, cancer family history, co-morbidities), anthropometrics (e.g., height, weight, waist circumference), cancer related features (e.g., primitive site, histological subtype, stage, grade), treatment and related outcomes (e.g., efficacy, toxicity), assessment of molecular aberrations (e.g., TP53, BRCA1, BRCA2). The development and implementation of such an integrated platform (i.e. biobank and linked-database) will provide solid ground for multidisciplinary collaborations focused on translational research in ovarian cancer within and outside the Regina Elena National Cancer Institute.

Clinical Resources

HPV Unit

Regina Elena National Cancer Institute and San Gallicano Dermatological Institute

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Activities 2012-13

Clinical Activities

HPV-UNIT for its multi-disciplinarily activity has involved, as expertise on HPV infection, the two contiguous areas of oncology (Regina Elena National Cancer Institute) and dermatology (San Gallicano Dermatologic Institute). The primary activity was focused on coordinating many diagnostic interventions by clinical interpretation of molecular data from assay test, advice in evaluation of clinical cases by clinical teams ,out patients counseling and advising in many preventive actions (such as individual screening or HPV vaccination) or enabling a direct path consulting with the users. This last activity was particularly important as in a few months (the inauguration of the HPV-UNIT was on January 2013) the number of contacts to the specific website for HPV-related consultation was increased by almost 40%. This is of particular significance since it did not result from a targeted information campaign, but rather was a consequence of proposing an

appropriate referral point to both physician and general population. Thus, this approach, which encompass all the aspects of HPV infection and related diseases (diagnosis, prevention, therapy), appears most appropriate in responding to the growing information needs of the male-female population.

We anticipate that those systems that successfully implement interdisciplinary collaboration will be ahead of the curve in providing high-quality care, with a most favourable cost/efficacy ratio for the Public Health Systems, improving health education and, in the mean time, providing the ground for the development of clinical and basic research in critical medical and social areas.

The same increased in number of analysed patients within the Unit was noticed. Indeed, the overall consultation and overall medical care for gynaecological needs related to HPV diseases increased, in respect to the historical data, by 45% after the first year of HPV-Unit activity (from 1280 to 1857). Furthermore, a vaccination program dedicated to adult female population (up to 45 years old) has been activated and was set the stage for male vaccination (operating in the next few weeks).

In the mean time has been also implemented the clinical consultation for ENT pathology (with 151 consultations) and Proctology (91 consultations or laser-therapy).

Research Activities

The mean scientific activities of HPV-UNIT were focused on translational researches of virus–associated cancers and on the development of permanent professional training facilities and information addressed to the citizens. This last point is one of the key points o f the HPV-UNIT.

Training of Wealth Care Workers-HCW and patients

The training activity is scheduled with courses for HCWs annually: medical specialists and general practitioners; nursing staff. It also provides for the establishment of a School of Preventive Oncology Gynecology, producing teaching materials and ad-hoc meetings. The activity of the user's information was carried out by telephone, by email and through open meetings specifically structured on two levels of questions: administrative queries (where / how / as for diagnostic and therapeutic pathways already known by the user) and information queries (What is HPV? What can I do? Where can I go?). Moreover, the training course for health care givers (gynecologist, dermatologist, pediatricians or general practitioners) also had an important role during the first year.

HPV-UNIT has organized the following meetings:

- Opening meeting of HPV-UNIT (Rome 18 January 2013). It was the occasion to present the beginning of the clinic-scientific activities of the Unit, by involving a multi-disciplinary set of specialists.
- Corso su HPV della Società Italiana di Oncologia Ginecologica (Roma 25 ottobre) It was a course organized together with the Italian Society of Gynecologic Oncology to give information to the Gynecology specialists about the last achievements in the HPV field.

- HPV: come comunicare col paziente (Rome 12 Dicembre 2013). The course was aimed at HCWs and was directed to various aspects of communication with the patient, in particular, the peculiarities of the communication of a sexually transmitted infectious disease and a malignant disease

With the same aims HPV-UNIT participated to national/international meetings and examples of such participations are reported in the following list:

1. Efficacia e sicurezza del vaccino nella prevenzione delle lesioni genitali esterne HPV-correlate (HPV e Patologie dei Genitali, Assisi, 30 gennaio 2013)
2. Epidemiologia delle lesioni preneoplastiche e neoplastiche della vulva (HPV e Patologie dei Genitali, Assisi, 30 gennaio 2013)
3. Vaccinazione HPV (Salute sessuale e salute riproduttiva: ruolo del territorio Abano, 28 febbraio 2013)
4. HPV: stato dell'arte (10° Congresso Nazionale FIMMG, Ferentino 22 marzo 2013)
5. Lights and shades on the immunotherapy of Human Papilloma Virus (HPV) infections, the aetiologic agent of cervical cancer (UniversitàdegliStudi di Milano Seminars, 22 Marzo 2013)
6. Vaccinazione HPV: nuovi scenari vaccinali (VI Corso Basso Tratto Genitale, Alassio, 23 maggio 2013)
7. Screening organizzato e individuale alla prova dei nuovi algoritmi di prevenzione secondaria:premesse e scenari (Congresso GISCI, Riva del Garda 22 maggio, 2013)
8. Vaccinazione HPV: attualità e prospettive future (88° Congresso Nazionale SIGO, Napoli 2013)
9. Genetic vaccines against HPV major oncogenes (Genetic Vaccination in Cancer Ascoli Piceno 9-11-ottobre, 2013)
10. New orthotopic mouse models of HPV-associated cancer for testing therapeutic vaccines (Genetic Vaccination in Cancer, Ascoli Piceno 9-11-ottobre 2013)
11. Recent advances in HPV-based immunotherapy of head and neck cancers with the help of green world (EUROGIN, Firenze 4 Novembre, 2013)
12. Low-grade findings in colposcopy (Inter FederationColposcopy, IFCPC, Milano 18 ottobre, 2013)
13. Anal HPV integration and identification of other DNA viruses in HIV-uninfected men who have sex with men (EUROGIN, Firenze 4 novembre 2013)
14. HPV male vaccination (EUROGIN, Firenze 4 novembre 2013)
15. Presentation of HPV-UNIT (EUROGIN, Firenze 5 novembre 2013)
16. High prevalence of genital warts among young women in Italy (IUSTI, Vienna 15 febbraio 2013)
17. Are cutaneous HPVs involved in oral cavity cavity cancer? (EUROGIN Firenze 3 novembre 2013)

TRANSLATIONAL RESEARCHES

HPV interaction with ErbB receptor family during carcinogenesis.

High risk HPV can interact with the transductional pathway of different growth factor receptors, mostly through E5 and E6 oncogenes. In particular the EGF receptor (EGFR) was already demonstrated to be up-regulated by HPV 16 E5. The EGFR belongs to the ErbB tyrosine kinase receptor family that is involved in the regulation of many cellular functions. In preliminary works we already demonstrated that in addition to EGFR other members of this receptor family can be regulated by the interaction with HPV 16 genes. This interaction was further analysed in vitro (W12 cell line) and in vivo (46 samples of low- and high-grade cervical lesions). ErbB receptor family expression was analysed in W12 cells at early (W12E) and late passages (W12G) because in this cell line all the phases (including integration and E2 regulation loss) of viral transformation can be reproduced. It is well known that increased EGFR expression can be detected in women during disease progression and in W12G we detected high levels of EGFR, indicating the perfect matching

between this W12 cellular model and patient's infection/progression. Interestingly, among the other members of ErbB family the highest differences in the expression was detected for the ErbB3, with a strong reduction in W12G. The analysis of clinical samples showed that when the HPV 16 is in eipsomal form, and thus is E2 expressing, high expression of ErbB3 can be detected whereas in samples with proved HPV 16 viral integration (loss of E2) the ErbB3 expression was very low, confirming the "in vitro" results in a clinical setting. In conclusion, the new discovered activity of HPV 16 E2 protein may affect the expression of ErbB receptor family with a clear inhibition of the ErbB 3 that could play a role during transformation in association with viral integration.

Molecular epidemiology of HPV types.

1- Genital tumours - The performance of different methods currently used for virological evaluation of cervical cytological sample has been assayed in a cohort of women. The final results indicate that discordant results are obtained with different HPV tests. The standardization of type-specific sensitivity and accuracy of genotyping methods are thus urgently needed in order to use genotyping assays in cervical cancer screening programs.

A clinical project is already started in evaluating the performance of new detection system Cobas (Roche) in the diagnosis of HPV infection, extending its application to samples from other anatomical region including anal and oral localization. Moreover, we are involved in a joint study with European Institute of Oncology (Milan) of comparative evaluation of different system of HPV detection.

In the same time,14 patients underwent cone biopsy, are enrolled in a program to the definition of the recurrence risk associate to the presence of a specifics HPV genotype (i.e. type 189). Indeed, preliminary results seem to indicate a different risk associated to different HPV types.

In all the samples already collected and stored within the HPV-UNIT an analysis of other HPV not detected by the commercial available test will be performed in order to ascertain the emerging evidence about the presence of beta and gamma HPV in mucosal localization.

2- Extra-genital tumors - Studies were performed in two main areas the oro-pharyngeal cavity and the skin. HPV associate H&N tumors are a subset of tumours that may have a well defined behavior and analyses were performed in order to define the types of HPV in the oro-pharyngeal localizations and the viral expression. Mucosal HPV types are associated with the presence of cancers. Conversely, cutaneous HPVs were associated with non-malignant lesions (p=0.007). Thus different types of HPVs infect the oral epithelium, but only the mucosal types, particularly HPV 16, are clearly associated with tumors.

Other studies are in progress in the attempt to define other markers of cancer progression in HPV-associated cancer and differences in the field cancerization between HPV+ and HPV- tumours.

Recent data show that cutaneous HPV are detected mostly in smokers and/or drinkers patients whereas mucosal HPV are mostly (with statistically significant differences p=0,03) evidenced in cancer of no drinkers/no smokers suggesting that only mucosal HPVs may be involved in this subgroup of patients. Finally, we are recruiting patients to start a project on the de-intensification of therapy in HPV+ oral cancer patient.

The oncogenic role of cutaneous HPV in skin cancer is still a controversial issue but a role of mucosal HPV is still to be defined. To date only few studies have addressed this question by investigating the integration (a key marker of cancer progression) of mucosal HPV in anal cancers. HPV physical status and the presence of other circular DNA viruses were performed in the anal region of MSM patients. Viral

Integration into chromosome 14 q was observed in one HPV16-positive sample (0.9%). In41.5% of patients the presence of circular DNA viruses was detected, corresponding to beta HPV, polyomaviruses) (MCPyV) and TTV. The significance of the presence of these other viruses needs to be assessed.

New therapies of HPV-associated cancers.

A totally new approach to the therapy of HPV-associated cancer was developed.

In the last decades, emerged the possibility of designing drugs based on antibodies against virtually any antigen of interest, whether tumor or not. Nevertheless, recombinant non-human antibodies, mainly obtained by Hybridoma technology, show some drawback due to the possible induction of an immune response and to the large size which hinders adequate exposure of solid tumors to drugs. Single-chain antibody fragments (scFvs), derived from the IgG repertoire by genetic engineering, represent the smallest molecules (27 KDa) able to specifically bind to an antigen, and find multiple applications in diagnosis and therapy. ScFvs can be easily tailored to modify pharmacokinetics, immunogenicity, specificity and effectors functions in a cost-effective-way, can be expressed and produced in *E. coli*, or delivered to cells as intracellular antibodies (intrabodies) to alter the function of specific targets, thus representing a powerful alternative to methods of gene inactivation. Previously data on two of the intrabodies produced the scFv43M2 and scFv51 were shown to exert a specific anti-proliferative activityin cervical cancer cells. Interestingly, the most efficacious intrabodies resulted to be 43M2SD (M2SD) and 51SD, both localized in ER.

We tested the M2SD intrabody for the antitumor activity in two mouse models for HPV tumors based respectively on TC-1 and C3 cells. In both models, a marked delay of tumor onset with respect to the controls was observed in all the treated mice and, importantly, a significant percentage of mice remained tumor-free permanently. In conclusion, this is the first report of the *in vivo* antitumor efficacy of an intrabody directed against an HPV oncoprotein, and suggests that such intrabody may be profitably employed in the therapy of HPV-associated early lesions, tumors and metastatic lesions, even in combination with the conventional chemotherapeutic agents currently in use for CC.

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EXPERIMENTAL ONCOLOGY

Experimental Oncology

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Activities 2012-13

Our research laboratory focused on studying the critical points where cancer becomes resistant to treatment, particularly in colon and epithelial ovarian carcinoma (EOC) and melanoma. The activation of signal transduction machinery is an escape mechanism that thwarts the inhibitory effects of drugs. Targeting these pathways represents an attractive option for overcoming drug resistance. Our research team led the study linking the endothelin (ET-1) axis to the development and the progression of cancer. Dr. Bagnato's research group belongs to the national and international ET-1 network consisting og outstanding researchers and pharma companies. Activation of autocrine and paracrine signalling by ET-1 binding to its receptors elicits pleiotropic effects on tumour cells and on the host microenvironment. This activation modulates cell proliferation, apoptosis, migration, epithelial-to-mesenchymal transition (EMT), chemoresistance and neovascularization, thus providing a strong rationale for targeting ET-1 receptors in cancer. Therefore, ET-1 receptor antagonists may inhibit tumour progression by blocking crucial signalling events in tumour cells and its microenvironment. Small-molecule antagonists for targeting ET-1 receptors have been evaluated in several recent clinical trials (Bagnato A. Curr. Pharm. Design. 2012; Rosanò L. et al. Nat Rev. Cancer 2014).

Our preclinical results provided a framework for targeting ET-1 receptors on the tumor cells and its microenvironment for designing combination therapy, such as the phase II multi-centre randomized international study, in which the specific ETAR antagonist zibotentan was evaluated versus placebo when given in addition to carboplatin and paclitaxel in patients with advanced EOC (Cognetti F. et al. Gynecol. Oncol.2012). Future improved clinical trials might incorporate predictive biomarkers focusing on subsets of patients who are most likely to respond, using other clinical settings or adopting rational combination therapy with chemotherapeutics or targeted agents. This ongoing research project will address acquired resistance, by evaluating the changes in ET-1-driven signaling pathways or microenvironment-mediated cross-talk.

Overcoming chemoresistance by targeting ETAR/Wnt signaling pathway connection

In search for key regulators responsible for chemoresistance in EOC, we define a novel bypass mechanism through which ETAR/β-arrestin-1 (ß-arr1) links Wnt signaling to acquire a chemoresistant and EMT phenotype and stemness features. We provide evidence

that β-arr-1 exerts this activity forming a nuclear complex with β-catenin resulting in histone acetylation leading to chromatin reorganization and enhanced transcription of genes, such as ET-1, responsible for regulating the rate limiting step of drug response. Macitentan, a small molecule dual ETAR/ETBR antagonist, prevented core complex formation, impairing the signaling network involved in cell survival, plasticity and invasiveness. *In vivo* macitentan, by interfering

with ETAR expressed on EOC cells and ETBR expressed on stromal cells, significantly inhibited tumor growth, neovascularization, intravasation, and peritoneal dissemination in chemoresistant EOC xenografts. Analysing human chemoresistant EOC tissues, provided further support for a direct association between β-arr1 and β-catenin at ET-1 gene promoter. In these tissues, ETARexpression is significantly associated with poor clinical outcome and chemoresistance, but not ETBR.

In summary, we provide novel mechanistic insights on how β-arr-1-β-catenin represents the initial scaffold on which transcriptional regulatory complexes could be built to regulate the transcription of specific target genes, orchestrating the network regulating the onset of chemoresistance. The present study is therefore of both biological and translational relevance in understanding the mechanisms underlying chemoresistance and the development of novel treatments for EOC,

which is still penalized by a high percentage of recurrences. (Rosanò L. et al. Cancer Res. 2014 in press)

ß-arrestin-1 is a critical adaptor of ET-1 signaling in cancer progression

Our recent findings demonstrate that β-arr1-mediated signalsomes are critical to ETAR-mediated signal transduction and consequent biological function of EOC. In these cells, the ETAR/ß-arr-1-mediated signalplex was crucial for NF-κB signalling (Cianfrocca R. et al. Life Sci. 2014), as well for tyrosin kinase receptor transactivation, such as EGFR (Cianfrocca R. et al. Life Sci. 2012). It is also important for nuclear compartmentalization of ETAR signaling, which mediates histone modification and gene transcription required in tumor progression (Rosanò L. et al. Oncogene 2013). Altogether these findings reveal a previously unrecognized pathway that depends on β-arr1 in sustaining response to ETAR activation in EOC. In this context, with the collaboration of Dr. Benigni from the Mario Negri Institute, Bergamo, we demonstrated that the signalplex ETAR/β-arr-1/Src is critical for EGFR transactivation, and podocite migration (Buelli S. et al. J Am Soc Nephrol. 2014). Given that aberrant signal transduction can be activated through β-arr1-mediated cross talk between receptors, we also reported the functional relationship between ETBR and the VEGFR system, which was accompanied by the recruitment of ß-arr-1 with c-Src, and how this cross talk might influence the aggressive behavior of melanoma cells (Spinella F. et al. J. Mol. Med. 2012).

Role of ET-1 in angiogenesis and lymphangiogenesis

In addition to tumour cells, ET-1 receptors are found in tumour-associated host cells, such as blood and lymphatic endothelial cells, fibroblasts and inflammatory cells, regulating the contribution of these cell types to cancer progression. We previously demonstrated that ET-1 through binding with ETBR, and expressed in lymphatic endothelial cells (LEC), induced cell growth and invasiveness. Hypoxia, as well as ET-1, induced an increase in VEGF-A/-C/-D expression. Moreover, hypoxia increased the formation of vascular-like structures and in combination with ET-1, this effect was markedly enhanced. These results demonstrated that ET-1 and hypoxia might cooperate in inducing the expression of important mediators critical for lymphatic differentiation (Garrafa E. et al. Life Sci. 2012), further supporting the role of ET-1 as potent lymphangiogenic factor. Moreover, we reveal a PHD2-mediated mechanism through which ET-1 stabilizes HIF-1α and HIF-2α pathway thereby regulating LEC behavior and lymphangiogenesis (Caprara V. et al. Life Sci. 2014). In this context, we demonstrate the ability of the ET-1 axis to affect the interplay between melanoma, blood and lymphatic cells in hypoxic microenvironment, sustaining the melanoma progression (Spinella F. et al. Carcinogenesis 2014). On the basis of our know-how in tumor neovascularization, we collaborated in describing the existence of G4 in the VEGFR-2promoter, whose expression and function can be markedly inhibited by G4 ligands, thereby revealing a new way to block VEGFR-2 (Salvati E. et al. Nucleic Acids Res 2014). Furthermore, in collaboration with Chieti University, we demonstrated that in breast cancer cells, lectin galactoside binding soluble 3 binding protein (LGALS3BP), induces VEGF expression and promotes angiogenesis (Piccolo E. et al. J. Mol. Med. 2012) and that the SP-2 anti-LGALS3BP antibody was able to block all these effects (Traini S. et al. Mol. Cancer Ther. 2014).

Endothelin axis in cancer-stem cells

The limited clinical response observed in many tumor patients may be related to the presence of chemoresistant stem cells (SC) that are regulated by different growth factors. All cell clones, isolated from patients with colorectal cancer (CRC) samples, significantly

expressed ET-1 and ETAR. The overexpression of ETAR in these CRC-SC is associated with the expression of the scaffold protein b-arr-1. ETAR blockade inhibits CRC-SC cell growth sustained by ET-1/ETAR autocrine loop. The expression profile of EMT markers was associated with high expression of ETAR, suggesting that ET-1/ETAR -induced EMT might represent an escape mechanism to a new adverse niche, in which acquisition of stemness ensures tumor progression. Macitentan inhibits CRC-SC growth, matrix metalloprotease expression and cell invasion and in CRC-SC xenografts inhibits tumor growth, indicating that this drug could block ETAR/b-arr1, representing a critical hub at the intersection of complementary pathways driving chemoresistance/stemness phenotype in CRC.

Objectives

Establishing EOC patient-derived xenografts (PDX) or EOC primary cultures, that mimic clinical resistance mechanisms.

Evaluation of the therapeutic efficacy of the new ET-1 receptor antagonist, macitentan, in monotherapy and in combination with chemotherapy and identification of predictive markers of clinical response.

Dissection of miRNA targeting ET-1 receptors.

Ch-IP Seq profiling of b-arrestin signalosomes in EOC sensitive and resistant to chemotherapy.

Validation of ETAR as new prognostic marker in EOC.

Characterization of the molecular mediators involved in tumor-microenvironment Interplay.

Analysis of ETAR targeting in CRC-SC-derived models.

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Experimental Oncology

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Activities 2012-13

Telomere maintenance is central to cell division control. In many organisms, the protective function of telomeres depend upon at least two pathways. The first relies on telomerase, which can compensate for replicative erosion; the second relies on a particular chromatin organization protecting chromosome ends from aberrant signalization and repair. It is now clear that by simply inhibiting telomerase does not presumably result in the anticancer effects that were originally hypothesized. While telomerase may not be the universal target for cancer therapy, telomere maintenance mechanisms are important in research aimed toward a successful strategy for curing cancer. Possible targets for the disruption of telomere maintenance are represented by specific DNA structure, such as G-quadruplex, that can form telomeric sequences.

The recent advances in the G-quadruplexes research field further support the crucial role played by these DNA motifs in living organisms, validating them as key targets in anticancer therapy.

However, none of the G4 ligands developed so far, have made it through the drug discovery pipeline due to poor drug-like properties and/or selectivity profile. This is strongly encouraging the researchers to put further effort in the identification of G4 binding agents as potential anticancer drugs. The application of structure-based VS succeeded in the identification of a novel chemotype as potent and selective binders of the human telomeric G4. Results of this inspection led to the identification of a set of potential G4 ligands for which the *in-vitro* binding was verified through fluorescence melting experiment and fluorescent intercalator displacement assay. Interestingly, among the three chemotypes identified as true hits, one of them displayed impressive G4 binding and stabilizing properties. A full physicochemical characterization allowed characterizing the binding profile of these ligands. The subsequent profiling of the biological properties of the selected compounds demonstrated that this compound is outstandingly potent in inducing selective DNA-damage at telomeres of cancer cells *vs* normal untransformed cells. In addition, this compound is endowed with efficient antiproliferative effect on several tumor cell lines at low micromolar concentrations.

Increasing knowledge in the telomere structure and the various proteins involved in telomere maintenance provides several targets for modulation.

The protection of human telomeres involves TRF2, a protein binding the duplex part of telomeric DNA and participating in t-loop formation. TRF2 is essential to protect

telomeres from being repaired by non-homologous end-joining and recognized as DNA damage by ATM. Accordingly, TRF2-depleted telomeres appear deprotected or uncapped and can undergo end-to-end fusions and subsequent chromosome

growth rate, viability, clonogenicity, senescence/apoptosis during their *in vitro* expansion before their injection in mice. Similarly, and at the same time unexpectedly, the antitumor effects of TRF2 inhibition cannot be attributed to the activation of DNA

abnormalities. Moreover, increased levels of TRF2, a key factor in telomere protection, have been observed in various human malignancies and contribute to oncogenesis. However, the mechanism by which TRF2 controls tumorigenesis is unknown.

Consistent with its oncogenic role in human cancers**,** an increased dosage of TRF2 in a variety of human and mouse tumor cells enhanced their tumorigenicity and aggressiveness, while TRF2 depletion by RNA interference or the expression of a dominant-negative form noticeably reduced tumor growth. The effect of TRF2 modulation on the tumorigenic potential of several cancer lines cannot be merely explained by variation in

damage response pathwaysince TRF2 knockdown in several of the cancer cells used in this study neither uncapped nor shortened telomeres nor increased the rate of telomere fusions or chromosome rearrangements. Taken together, these results show that the oncogenic properties of TRF2 can be uncoupled from a cell-autonomous pathway of telomere protection and growth control, raising the interesting possibility that TRF2 triggers cell-non autonomous functions. Interestingly, we found that a high level of TRF2 in tumor cells decreased their ability to recruit and activate natural killer (NK) cells. Conversely, a reduced dose of TRF2 enabled tumor cells to be more easily eliminated by NK

cells. Consistently with these results, a progressive upregulation of TRF2 correlated with decreased NK cell density during the early development of human colon cancer.
The key question remained the molecular mechanism by which TRF2 regulates NK cells. As we could neither explain the effect of TRF2 on NK cells by its canonical role in telomere protection against the DDR, nor by the identification of known modulators of NK cells regulated by TRF2, we hypothesized that TRF2 could directly regulate the expression of NK cell modulator genes. Therefore, we used TRF2 ChIP-seq data, previously obtained using BJ-HELTRas cells, to search for TRF2 direct target genes involved in NK cell function. Among the genes containing a high-affinity DNA-binding site for TRF2 either within an intron or <10 kb from the transcription start site, *HS3ST4* was the only one that encoded a protein involved in extracellular functions (sulfation of heparan sulfate proteoglycans) and whose expression (at both the mRNA and protein levels) was positively regulated by TRF2.
Finally, we addressed the relevance of these findings to human oncogenesis by analyzing samples of human colon for TRF2 expression and NK cell density. These data reveal a specific decline in NK cell number with a concomitant, progressive increase in TRF2 expression during the early stages of malignant transformation.
In summary, we propose a model in which a high TRF2 level in tumor cells contributes to early oncogenesis, not only by delaying replicative senescence but also by a non-cell autonomous mechanism preventing innate immune surveillance. In addition, the identification of the ITS-associated *HS3ST4* gene as a TRF2 target sheds new light on the mechanisms of NK cell recognition by tumor cells and provides a paradigm for studying ITS function. Our reserach presents the novel idea that NK cells can be controlled by changes of TRF2 dosage in tumor cells, which regulate the expression of ITS-associated genes rather than altering cell-intrinsic programs that lead to growth arrest. These findings suggest a sophisticated mechanism of coevolution between telomeres, ITSs, and the innate immune system to keep tissue integrity in check**.**
Given these interesting results and the close collaboration with the University of Naples "Federico II, we will move onto discovering small compounds targeting TRF2. Based on the crystal structure of TRF2, we have designed and synthesized a series of peptides through mutations and cyclization. Aided by computer simulation, we were able to identify the first TRF2 binders capable of inducing telomere damage. Further experimental studies will involve employing this pharmacological tool to study the role of TRF2 protein hub in shaping and safeguarding telomeres. The research will be achieved by fully characterizing the antiproliferative properties of the true hits along with confirming their mechanisms of action.

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Experimental Oncology

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Activities 2012-13

Genome-wide analyses of cancer specimens for the identification of new diagnostic/prognostic biomarkers.

The development of new genome-wide approaches and the completion of the human genome sequencing offer great opportunities to increase knowledge and progress in cancer research, and to tailor cancer diagnosis and treatment to individual patients. However, to gather a deeper understanding of the basic mechanisms that control and determine cancer transcriptome, descriptive (phenotypic) oncogenomics must evolve into a more functional genome-wide approach. To this end, we need to implement innovative technological approaches to identify new target molecules and define protein/DNA/RNA modifications that (a) alter gene expression control in cancer cell progenitors during transformation and tumor progression, (b) are responsible for cancer cells response to therapy.

For many cancers, patients with tumors of the same clinicopathological stage may not have the same disease progression, response to clinical treatments, rate of disease recurrence and survival. In these cases a deep molecular characterization could greatly improve treatment choice and potentially improve survival. In the last few years microRNAs (miRs) expression profile is emerging among the best markers for diagnosis, staging and treatment of cancer. To paint a molecular portrait of HNSCC, mesothelioma, breast, cholangiocarcinoma, gastric and colon cancers, which are characterized by the need of biomarkers able to stratify patients' subpopulations and predict clinical outcome, we performed microRNAs expression profiling using the Agilent platform. These genome-wide studies were performed in close collaboration with various surgical departments at IRE. These analyses lead to the identification of groups of microRNAs that are specifically altered in tumor tissues compared to autologous normal and/or adjacent peritumor tissues in each malignancy. Moreover, the expression levels of several microRNAs was correlated to specific clinicopathological features of patients and showed the ability to predict recurrence-free

and/or overall survival rates. The combination of data obtained from expression profiling with data from the ongoing mutational/methylation profiles will likely provide new relevant biomarkers to be used in the development of new targeted anticancer therapies.

The research group has been previously involved in studies concerning the *gain-of-function* (GOF) activity of mutant p53 proteins. In particular, the two aspects of mp53 GOF that are object of our interest include: **(a)** the transcriptional activity exerted by mp53 through the interaction with additional transcription factors, that leads to the modulation of genes involved in carcinogenesis, **(b)** the interaction of mp53 with other p53 family members (p63 and p73), that leads to the impairment of the transcriptional activity of the latter.

In regards to the transcriptional activity of mutant p53, we are currently involved in studies aimed at evaluating the ability of mutant p53 to modulate microRNAs expression. We indeed demonstrated that p53R175H, a hotspot of mutant p53, induces microRNA (miRNA)-128-2 expression in NSCLC cells (Donzelli et al., 2011). p53 mutations have profound effects on non-small-cell lung cancer (NSCLC) resistance to chemotherapeutic treatments. We observed that mutant p53 binds to the putative promoter of miR128-2 host gene, ARPP21, determining a concomitant induction of ARPP21 mRNA and miR-128-2. miR-128-2 expression in lung cancer cells inhibits apoptosis and confers increased resistance to cisplatin, doxorubicin and 5-Fluorouracyl treatments. This study emphasizes miRNA-128-2 role as a master regulator in NSCLC chemoresistance.

Aside from lung cancer, we are also investigating correlations existing between mutant p53 proteins and altered microRNA expression in head/neck squamous cell carcinomas. By sequencing *TP53* gene in HNSCC samples and integration of this information with that of microRNA profiling, we could assess that p53 mutations are

associated with differential expression of several microRNAs. Many of these altered rates. Current studies are functionally characterizing the activity of mp53 proteins in the altered expression of these miRNAs.
In relation to point **(b)**, we have recently shown that short peptides of 8 to 10 residues (named SIMPs) that resemble the DNA binding domain of p73 are capable of selectively disassembling protein complexes involving mutant p53 and p73. To evaluate the in vivo functional relevance of SIMPs, we generated tumor xenografts in BALB/c nude mice using breast and colon cancer cell lines carrying endogenous mutant p53. Intravenous injection of SIMPs alone or in combination with other anticancer agents highlighted SIMPs ability to efficiently inhibit tumor growth in vivo. Additional in vivo studies are currently evaluating the possible clinical application of these molecules for human cancer treatment.

Study of transcriptional co-factor YAP.
We originally showed that the transcriptional co-activator YAP interacts with long forms of TA-p73 and TA-p63 but not with wt-p53 and short isoforms of both p73 and p63. Furthermore, p73, YAP and PML proteins form an auto-regulatory feedback loop which becomes pro-apoptotic in response to anticancer DNA damaging agents. Ongoing research is devoted to further elucidating the molecular mechanisms underlying the involvement of YAP in transcriptional and functional axis in response to DNA damage.

Molecular Chemoprevention

Project Leader: Sabina Strano

Cancer is the final endpoint of different genomic and epigenomic events that occur inside the cell. Emerging evidence clearly suggests that novel therapeutic strategies must be developed for killing cancer cells that are the root cause of tumor recurrence.
Chemoprevention is an area of cancer research that aims to reduce the incidence microRNAs are interestingly associated with patients' survival and burden of cancer through developing agents to prevent, reverse or delay the carcinogenesis process. Successful implementation of chemoprevention depends on a mechanistic understanding of carcinogenesis at the molecular, cellular and tissue levels.
Identifying molecular mechanisms involved in carcinogenesis provides strong rationale for developing strategies for cancer treatment and prevention.
Therefore, focused research on elucidating the expanding role of chemopreventive agents not only for primary prevention of cancer, but also for the prevention of tumor recurrence, and further assessing the role of these natural agents for sensitization of cancer cells to conventional therapeutics is warranted.
The research group is currently facing the following research issues:

Chemoprevention activity of Metformin
Metformin isthe most widely prescribed anti-hyperglycemic agent used worldwide. Observational studies reported that metformin treatment reduces human breast cancer incidence and improves the prognosis of breast cancer. Although antidiabetic activities of metformin are well described, its biological and molecular activity against carcinogenesis is not well understood. In addition to its efficacy in lowering glucose levels, metformin is a pharmacological activator of AMPK. AMPK is a central cellular energy sensor which may be a crucial factor in the interaction between metabolism and cancer. Metformin modulates AMPK signaling in vitro and it has been shown to elicit growth suppression on breast cancer cells. Altered metabolism is a key feature of cancer cells. However, it has never been clearly established whether metformin affects cancer directly or indirectly by inhibiting the diabetic state. The aim of our studies is to demonstrate a close link between the metabolic activity of

metformin and its anticancer properties. We are studying the genomic and metabolomic effects of metformin on several breast cancer cell lines belonging to different histological and molecular sub-types. The effects that Metformin exerts in vitro on both bulk cells and cancer stem cell (CSC)- enriched cell subpopulations and, in vivo, on xeno-transplanted breast cancer cells are under evaluation. In addition, we are currently using a combined approach of 1H-NMR metabolomic foot-printing analysis and genomic profiling to deeply investigate how metformin can exert its anti-cancer effects. Our findings will highlight the potential use of reprogramming altered cancer metabolism to counteract breast cancer development.

Chemoprevention activity of Melatonin

Melatonin is a well known antioxidant that regulates the daily and seasonal circadian rhythms, it also plays an important role as an anti- inflammatory. Some studies have demonstrated a seasonal variation in melatonin synthesis in humans, with higher levels in Winter than in Summer. Altered patterns and levels of melatonin secretion has been reported to coincide with some tumors. Current evidence suggest that high levels of artificial light at night in industrialized societies may play a role in cancer risk; results from previous studies indicate that night-shift work, a surrogate for exposure to light at night, is associated with an increased risk of breast cancer . Women involved in various types of work during the night have consistently demonstrated an up to threefold increase in the relative risk of breast cancer.

Melatonin seems to exert its anticancer effects through diverse mechanisms. In terms of limiting the frequency of cancer initiation, one of the mechanisms may be the ability of melatonin to reduce severe DNA damage that is a consequence of unstable oxygen and nitrogen-based reactants. It may exert such action either by scavenging reactive oxygen species or their primary sources, or by stimulating the repair of oxidative damage in DNA. Since this type of DNA damage is reflected in oxidative base modifications that are primarily repaired by base-excision repair (BER), we are trying to investigate in our present work whether melatonin could influence this DNA-repair system.

Chemoprevention activity of short interfering peptides

To establish a critical role for the protein complex mutant p53/p73 in the response of tumor cells to conventional chemotherapy and to override its oncogenic effects, we have engineered short synthetic peptides capable to physically disassemble the protein complex mutp53/p73. Transduction of the short interfering peptides (SIMPs-Short Interfering Mutantp53 Peptides) in tumor cells bearing mutant p53 proteins enhances cisplatin and adriamycin-induced apoptotic response. SIMPs do not have any effects on both p53 null and wt-p53 expressing cells, thereby indicating that SIMPs activity is strictly connected to the presence of mutant p53 protein. We have originally reported that the formation of the protein complex mutantp53/p73 involves the core domain of mutantp53 and the DNA binding domain (DBD) of p73 and p63, respectively (Strano et al, 2000; Strano et al, 2002; Strano et al, 2003). We have recently shown that short interfering peptides (DiAgostino et al, 2008) that resemble the DNA binding domain of p73 are capable to selectively disassemble protein complexes involving mutantp53 and p73. Our findings clearly show that SIMP5 and SIMP6 disrupt selectively protein complexes involving mutant p53 His175 and p73, while SIMP1 disassembles those containing mutant p53 His273.

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Experimental Oncology

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Activities 2012-13

The studies carried out in 2012-2013 were mainly funded by AIRC (Grant no. IG11377 2011-2014, to Dr. G. D'Orazi, Title: Role of HIPK2 and zinc in modifying molecular pathways to restrain tumor growth) and mainly performed by Dr. Alessia Garufi (Borsista AIRC). In addition, we collaborated with several research groups both at Regina Elena National Cancer Institute (Dr. C. Leonetti, Dr. R. Falcioni), Sapienza University of Rome (Dr. M. Cirone, Dr. A. Faggioni), Tor Vergata University of Rome (Dr. G. Pistritto), Istituto Superiore di Sanita', Rome (Dr. G. Carpinelli), University of Calabria, Cosenza, Italy (Prof. D. Pucci), Weizmann Institute of Science, Rehovot, Israel (Prof. D. Givol), Cancer Research Center, Chaim Sheba Medical Center, Tel-Hashomer, Tel-Aviv, Israel (Prof. G. Rechavi, Prof. N. Amariglio), and Georgetown University of Washington, DC, USA (Prof. M.L. Avantaggiati).

In summary, the studies undertaken in 2012-2013 allowed us to demonstrate that a novel fluorescent curcumin-based Zn(II)-complex (Zn(II)-curc) is able to reactivate mutant p53 in cancer cells and directly induce its wild-type transactivation and oncosuppressor activities. Interestingly, the translational potential in cancer therapy, the Zn(II)-curc was able to cross the tumor-blood barrier in an ortothopic glioblastoma model *in vivo*. The translational potential was also assessed in experiments involving tumor-host interaction whereas zinc supplementation inhibited the production of immunosuppressive molecules such as prostaglandin E2 (PGE2) and reactivated the immune response seen as efficient maturation of dendritic cells (DCs). Tumor cell death was achieved by inducing immunogenic cell death following zinc-induced pre-apoptotic calreticulin (CRT) exposure on the membranes of tumor cells, a novel marker for immunogenic cell death.

In regards to the role of HIPK2 in restraining tumor growth, we observed, by starting with a microarray analysis, that HIPK2 downregulated vimentin expression (a mesenchymal marker of tumor invasion) in invasive, vimentin-positive breast cancer cells. At functional level, vimentin downregulation by HIPK2 overexpression correlated with inhibition of breast tumor cell invasion. Altogether, these data show that vimentin is a novel target for HIPK2 repressor function and that HIPK2-mediated vimentin downregulation can contribute to inhibit breast cancer invasion that may be applied in the clinical setting.

Another molecule that was inhibited by HIPK2 is cyclooxigenase-2 (COX-2) that induces PGE2 production, leading to an inflammatory, immunosuppressive tumor phenotype. The *in vivo* relationship between COX-2 and HIPK2 was performed in an *in-silico* co-expression analysis from the Oncomine integrated cancer database research tool. Analyses of datasets

obtained from specimens of normal tissues and primary colon adenocarcinomas revealed an inverse correlation between HIPK2 and COX-2 expression. We found that HIPK2 depletion in colon caner cells led to COX-2 upregulation, mostly depending on HIF-1 activity while HIPK2 overexpression drastically reduced COX-2 expression and PGE2 production. As HIPK2 may be inhibited in tumors by several mechanisms, and such inhibition induces tumor progression as observed in studies performed in knock-out mice. Our studies are in agreement with the role HIPK2 oncosuppressor plays through inhibiting molecules that are important for tumor progression and tumor-host interaction such as vimentin and COX-2.

In further studying the role of HIPK2 in retraining tumor growth, we found by linking metabolic (through H-NMR, H-nuclear magnetic resonance, studies) and biochemical studies, that HIPK2 depletion leads to increased colon cancer cell production of lactate and glycolytic metabolism. The increased glycolytic metabolism induced cancer cell resistance to glucose restriction, compared to HIPK2-carrying cancer cells that underwent apoptotic death. Zinc supplementation was able to counteract the glycolytic metabolism and restore the glucose restriction-induced cell death. These studies demonstrate that an intact HIPK2 function contributes to inhibit the cancer cell tolerance to metabolic stress that in many tumors is linked to tumor growth, resistance to therapy and inhibition of immune response.

The results of these studies were published in several scientific papers and presented in National and International meetings:

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Experimental Oncology

Donatella Del Bufalo, PhD

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Activities 2012-13

Two projects were carried out during 2012 and 2013: 1. to identify new inhibitors of acetyltransferase (HAT) and deacetylase (HDAC) with antitumoral activity, 2. to study the molecular mechanism through which bcl-2 cooperates with hypoxia to induce HIF-1/VEGF expression. Moreover, studies with external collaborators were performed. In particular, we demonstrated that:

- CPTH6, a thiazole derivative, induces histone hypoacetylation and apoptosis (1), and impairs autophagy in a panel of human cancer cell lines (6).
- tert-Butylcarbamate-containing histone deacetylase inhibitors induce apoptosis cytodifferentiation, and antiproliferative activities in cancer cells (8). Moreover, we reported hydroxamates [2] and 2-aminoanilides [3] as histone deacetylase inhibitors bearing the 1,3,4-oxadiazole ring. Among the selected compounds, 2t, 2x and 3i were the most potent against HDAC1 without affecting HDAC4. Compound 2t was also able to inhibit HDAC6 better than SAHA. In human leukemia cells, such compounds induced dose-dependent apoptosis with 2t being more potent than SAHA, and 3i displayed the highest cytodifferentiation with a potency similar to MS-275 (under review).
- BH4 domain of bcl-2 is involved in the regulation of hypoxia inducible factor-1-mediated vascular endothelial growth factor (VEGF) expression in hypoxic tumor cells (7), and deletion of BH4 domain decreases *in vivo* tumor growth through activation of autophagy (10).
- The mitogen-activated protein kinase cascade controls phosphatase and tensin homolog expression through multiple mechanisms (2), and inhibition of mitogen-activated extracellular signal-regulated protein kinase shows therapeutic potential in acute myelogenous leukemia (4). Collaboration with Dr M Milella, IRE.
- Down-regulation of the PTTG1 proto-oncogene contributes to the melanoma suppressive effects of the cyclin-dependent kinase inhibitor PHA-848125 (3). Collaboration with Dr S D'Atri, IDI.
- LMNA knock-down affects differentiation and progression of human neuroblastoma cells (5). Collaboration with Dr I D'Agnano, CNR.
- High expression of cox-2 and low expression of kai-1/cd82 are associated with increased tumour invasiveness of papillary carcinoma of the thyroid (9). Collaboration with Dr S Scarpino, Sapienza University.
- At least two promoters need to be considered for let-7c transcription: the distal host-gene and the proximal intronic promoter. While the host-gene promoter may control let-7c expression in acute myeloid leukemia, the intronic promoter contributes or

preferentially regulates let-7c transcription in solid tumors, such as prostate and lung adenocarcinoma (Pelosi A et al Mol Cancer Res. 2014). Collaboration with Dr MG Rizzo, IRE.

- In non-small cell lung cancer (NSCLC) lines, histone deacetylase (HDAC) inhibition by ITF2357, a pan-HDACi currently used in clinical trials as an anti-cancer agent, induced histone and tubulin acetylation and downregulated thymidylate synthase (TS) expression at the mRNA and protein level. In combination experiments *in vitro* ITF2357 and pemetrexed, a multi-target folate antagonist, demonstrated sequence-dependent synergistic growth-inhibitory effects, with the sequence pemetrexed followed by ITF2357 inducing a strikingly synergistic reduction in cell viability and induction of both apoptosis and autophagy in all cell line models tested, encompassing both adenocarcinoma and squamous cell carcinoma. Conversely, simultaneous administration of both drugs achieved clear antagonistic effects, while the sequence of ITF2357 followed by pemetrexed had slightly synergistic growth-inhibitory effects only in certain cell lines. Similarly, highly synergistic growth inhibition was also observed in patient-derived lung cancer stem cells (LCSC) exposed to pemetrexed followed by ITF2357. In terms of molecular mechanisms of interaction, the synergistic growth-inhibitory effects observed were only partially related to TS modulation by ITF2357, as genetic silencing of TS expression potentiated growth inhibition by either pemetrexed or ITF2357 and, to a lesser extent, by their sequential combination. Genetic and pharmacological approaches provided an interesting link between the autophagic and apoptotic pathways and showed that sequential pemetrexed/ITF2357 causes a toxic form of autophagy consequentlyng activating a caspase-dependent apoptotic program. *In vivo* experiments in NSCLC xenografts

confirmed that sequential pemetrexed/ITF2357 is feasible and results in increased inhibition of tumor growth and increased mice survival. Overall, these data provide a strong rationale for the clinical development of sequential schedules employing pemetrexed followed by HDACi in NSCLC (under review).

- Expression of a dominant negative of Highly Expressed in Cancer protein1, a constituent of the Ndc80 complex, a kinetochore component that plays a fundamental role in stable kinetochore-microtubule attachment, chromosome alignment and spindle checkpoint activation at mitosis, reduces *in vivo* growth of HeLa xenograft (under review). Collaboration with Dr F. Degrassi, CNR.

- The existence of a novel calcium-based cellular machinery specific for the receptor 2 subtype (VEGFR2) involving the calcium (Ca2+)-mobilizing messenger nicotinic acid adenine-dinucleotide phosphate (NAADP) and the specific engagement of the two-pore channels (TPC) 2 subtype resulting in Ca2+ release and angiogenic responses. The NAADP/TPC2/Ca2+signalling pathway activated by VEGF was targeted at different points, either using the NAADP antagonist, Ned-19, or genetically using transgenic mice with knocked out expression of Tpcn2, invariably resulting in the inhibition of angiogenesis *in vitro* and *in vivo*. In human umbilical vein endothelial cells, Ned-19 abolished VEGF-induced Ca2+ release, impairing phosphorylation of ERK1/2 MAPK, Akt, eNOS, JNK (but not p38 MAPK), cell proliferation, migration and capillary-like tube formation. More importantly, *in vivo*, Ned-19 was able to abolish VEGF-induced vessel formation in matrigel plugs in WT mice, result that was mimicked using Tpcn2-/- mice, but not in Tpcn1-/- animals. These results demonstrate that VEGFR2/NAADP/TPC2/Ca2+ signalling controls VEGF-induced angiogenesis *in vitro* and *in vivo* and hence represents a novel set of potential targets for therapeutic strategies. Given that VEGF can elicit both pro- and anti-angiogenic responses depending upon the balance of signal transduction pathways activated, VEGFR2-blocking strategies targeting specific downstream pathways could overturn this balance, potentially leading to finely tailored therapies (under review). Collaboration with Dr A Filippini, Sapienza University.

- Poly I:C, the synthetic dsRNA analogue able to activate the toll like receptor, while inducing considerable apoptosis in LNCaP PCa cells, does not kill normal prostate epithelial cells RWPE-1 and RWPE-1-derived tumorigenic RWPE-2. Among the poly I:C-activated pathways, interferon regulatory factor-3 (IRF-3) signaling was observed to play an essential role in TLR3-mediated apoptosis in LNCaP cells mainly through the activation of intrinsic apoptotic pathways since pharmacological and genetic inhibition of IRF3 significantly reduced poly I:C-induced apoptosis and the cleavage of Caspase 3. Nevertheless, surprisingly the siRNA for Noxa, well known proapoptotic IRF-3 target, resulted in increased poly I:C-induced apoptosis in LNCaP cells. Moreover, we demonstrated for the first time the direct anticancer effect of poly I:C as a single therapeutic agent in a well-established human androgen sensitive PCa xenograft model, showing that the tumor growth was greatly impaired in poly I:C treated immunodeficient mice. Immunohistochemical analysis of PCa xenografts highlighted the antitumor role of poly I:C *in vivo* both on cancer cells and, indirectly, on endothelial cells. Finally, we show the presence of TLR-3 and IRF-3 in both human normal and PCa clinical samples potentially envisaging poly I:C-based therapy for PCa (under review). Collaboration with Dr A Riccioli, Sapienza University.

Publications 2012-2013

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Experimental Oncology

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Activities 2012-13

Response to therapy in breast cancers

The phosphoinositide 3-kinases are heterodimers which consist of the catalytic subunit p110 and the regulatory subunit p85. The PI3K/Akt pathway is strongly deregulated in breast cancer representing one of the mechanisms of resistance to therapies. Therefore, the identification of inhibitors of PI3K components represents one of the main goals to produce therapeutic agents. We evaluated the efficacy of a phosphopeptide, P-1257, that when targeting p85 it strongly inhibits PI3K activity. We tested the effects of P-1257 administration *in vitro* and *in vivo* using breast cancer cells expressing different levels of ErbB-2 and resistant or responsive to Trastuzumab. We demonstrated that inhibition of p85 activity by P-1257 induces cell death and sensitizes resistant JIMT-1 and KPL-4 ErbB-2-overexpressing breast cancer cells to Trastuzumab treatment. It is worthy to note that P-1257 delivery *in vivo* by electroporation or liposomes significantly inhibits the proliferation of tumor cells engrafted at sub-cutaneous and visceral sites, respectively. Overall, our data indicate that the p85 subunit is a valid target for therapeutic approaches and suggest that the structure of the peptide used in our study could be utilized for developing novel drugs to apply in combination with therapies that fail to cure breast cancers with high PI3K activity. (Folgiero et al., 2012).

Regulation of molecular marker of invasiveness

α6β4 integrin is an adhesion molecule for laminin receptors involved in tumor progression. We studied a link between β4 integrin expression and miR-221/222 in the most prevalent human mammary tumor; luminal invasive carcinomas (Lum-ICs). Using human primary tumors that display different β4 integrin expression and grade, we showed that miR-221/222 expression inversely correlates with tumor proliferating index, Ki67. Interestingly, most high grade tumors express β4 integrin and low miR-221/222 levels. We ectopically transfected miR-221/222 into a human derived mammary tumor cell-line, that recapitulates the luminal subtype, to investigate whether miR-221/222 regulates β4 expression. We demonstrated that miR-221/222 over-expression results in β4 expression down-regulation, breast cancer cell proliferation and invasion inhibition. The role of miR-221/222 in driving β4 integrin expression is also confirmed via mutating the miR-221/222 seed sequence for β4 integrin 3'UTR. Furthermore, we showed that these two miRNAs are also key breast cancer cell proliferation and invasion regulators, via the post-transcriptional regulation of signal transducer and activator of transcription 5A (STAT5A) and of a disintegrin and metalloprotease-17 (ADAM-17). We further confirmed these data by silencing ADAM-17, using a dominant-negative or an activated STAT5A form. miR-221/222-driven β4 integrin, STAT5A and ADAM-17 did not occur in MCF-10A cells, denoted "normal" breast epithelial

cells, indicating that the mechanism is cancer cell specific. These results provided the first evidence of a post-transcriptional mechanism

that regulates β4 integrin, STAT5A and ADAM-17 expression, thus controlling breast cancer cell proliferation and invasion. Pre-miR-221/222 use in the aggressive luminal subtype may be a powerful therapeuticanti-cancer strategy. (Dentelli P et al., 2014).

Identification of two novel molecular marker of invasiveness in BRAF^{V600E} melanoma

Genetic changes affecting *NRAS* and *BRAF* behave as driver mutations and occur in ~20% and ~70% of tumors, respectively. *BRAF^{V600E}-specific* and MEK-specific inhibitors have shown to have significant impact on progression-free and overall survival in advanced melanoma. However, primary and secondary resistance mechanisms restrict the efficacy of these target-specific drugs, suggesting that additional therapeutic targets need to be identified, firstly in highly frequent BRAF-mutant melanomas. In order to make a comparison, we selected a peculiar model based on melanoma clones, isolated from a single tumor characterized by a mutually exclusive expression of activated BRAF and activated NRAS in different cells. Real-time PCR, Western blot analysis on cell lines and immunohistochemistry on tissue sections from BRAF and NRAS-mutant tumors confirmed the preferential expression of SEMA6A and Mical-1 in BRAF-mutant melanomas. By having carried out specific RNA-interference experiments, we found that SEMA6A depletion causes cytoskeletal remodeling, loss of stress fibers, generation of actin-rich protrusion, and cell death by anoikis. On the contrary, the overexpression of Sema6A in NRAS mutant clones induces a strong invasiveness in revealing for the first time, the role of Sema6A in controlling metastatization of BRAF mutant melanoma. Mical-1 depletion restores MST-1-dependent NDR phosphorylation and promotes NDR-

dependent apoptosis. Overall, our data suggest that SEMA6A and Mical-1 are new potential therapeutic targets in BRAF-mutant melanomas.

Sema6A and Mical1 in metastatic $BRAF^{V600E}$ mutant melanomas: novel targets for therapy

Rossella Loria, et al., 2014 (*Manuscript in preparation*)

HER3 involvement in the mechanism of resistance to therapy in colon cancer stem cells

A recent understanding of the heterogeneous makeup of the cancer cells in a tumor has revealed the presence of colon cancer stem cells (CSCs), which exhibit self-renewing characteristics, and the ability to initiate tumors from a small number of cells that are highly chemo-resistant. Carcinoma recurrence is in part due to fact that conventional chemotherapy only targets the rapidly dividing cells that form the bulk of the tumor, but spares the CSCs that increase after conventional chemotherapy. The presence of chemotherapy resistant CSCs in the primary tumor may in part be responsible for the failure of completely eradicating tumor resulting in its recurrence at the primary and secondary sites. Development of novel therapeutic strategies, which specifically target CSCs is, therefore, warranted. In attempt to analyze the biological characteristic of CSCs, we found that CSCs express high level of b4 integrin subunit, whose expression correlates with tumor progression, and HER2 and HER3 receptors whose functions are strictly related to cell proliferation and survival. Moreover, in mammary cancer, we previously demonstrated that p73, in the absence of p53 function, induces the transcription of b4 integrin that in turn regulates HER-3 translation. These phenomena activate a positive feedback loop that constitutively activates PI3K activity in tumors. Based on our results, we investigated the role of p73 and HER3 in CSCs survival pathway. Our results indicated that p73 depletion in CSCs cells, by specific siRNA, induces a strong cell death by apoptosis and sensitize the CSCs to chemotherapy with Oxaliplatin and 5Fluorouracyl. Interestingly, depletion of p73 inhibits HER3 expression and Akt phosphorylation. In attempt to verify the role of HER3 as a possible target for therapy in these cells, we used a humanized monoclonal antibody direct to HER3 (U3-1287). Specifically, we found that this monoclonal antibody strongly inhibits the phosphorylation of HER3 and Akt in CSCs cells as well as in colon cancer cells and induces cell cycle arrest at the G0/G1 phase. Studies are in progress to verify in vivo the potentiality of U3-1287 as novel therapeutic alone or in combination with chemotherapy and/or MAPK inhibitors.

Collaborations

i) In collaboration with Dr. D'Orazi, we contributed in demonstrating that vimentin is a novel target for HIPK2 repressor function and that HIPK2-mediated vimentin down regulation can contribute to inhibition of breast cancer cell invasion that might be applied in clinical therapy. (Nodale C, et al., 2012).

ii) In collaboration with Prof. Varda Rotter, we were able to demonstrate that depending on the specific adipogenic differentiation program, p53 might exert a positive or a negative effect. More specifically, we found that p53 is required for brown adipogenic differentiation and has a protective role against diet-induced obesity (Molchadsky A et al., 2013).

Publications 2012-2013

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Experimental Oncology

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Activities 2012-13

Controlling transcription and chromatin remodelling in response to DNA damage are the main areas of interest for Dr. Fanciulli. In particular, this work-group focused on the functional characterization of the Che-1 protein.

Che-1 is a human RNA polymerase II binding protein highly conserved from yeast to man which is involved in the regulation of gene transcription. Notably, DNA damage by different genotoxic agents is associated with Che-1 phosphorylation and extended half-life. These post-translational modifications are induced by ATM and Chk2, which phosphorylate Che-1 on specific residues and are functionally linked to DNA damage-induced G2/M checkpoint. Based on the observations reported above, it can be hypothesized that Che-1 might be an important component of the DNA damage response (DDR) that protects cells from early progression of human cancer and for this reason it deserves a better characterization of the pathways involved. Thus, in the last year we have subdivided our efforts into different tasks each aimed at investigating different aspects of Che-1 function:

Characterization of the role of Che-1 in cell growth and in the transcription

One essential role of Che-1 is to promote cellular transcription as an adaptor or mediator that links specific transcription factors to general transcription apparatus. In performing siRNA experiments, we observed that Che-1 depletion produced a cell growth arrest and a strong reduction of total RNA. To functionally correlate Che-1 binding with gene expression, we generated ChIP-seq maps for H3K4me3, a peculiar modification observed in actively transcribed promoters and activated phospho-Ser5 RNA polymerase II. These maps were coupled with maps that were obtained from Che-1 depleted cells. Interestingly, we have found that Che-1 inhibition strongly affects general RNA polymerase II recruitment onto DNA, thus suggesting that this protein might play an important role in RNA polymerase II initiation. In agreement with these data, we observed a global decrease of H3K9Ac a histone modification associated to euchromatin and a concomitant increase of H3K27me3, a marker of repressive state of the chromatin. Notably, histone acetylase activity was found to be associated with Immunoprecipitated endogenous Che-1, thus confirming this protein's involvement in Chromatin remodelling processes. Next, we found that Che-1 expression is highly repressed in resting cells such as differentiated cells. During 2014, we plan to perform FAIRE (Formaldehyde-Assisted Isolation of Regulatory Elements) experiments in HCT116 cells with or without Che-1 inhibition and extend our analyses to Chromatin status. At the same time, we plan to produce BJ fibroblasts over expressing Che-1 in a tetracycline-regulated way (tet-on) to confirm the results obtained.

Analysis of the functional role played by Che-1 in the centrosome checkpoint

Since Che-1 has been associated with centrosomal proteins, we performed experiments to characterize a possible role of Che-1 in the centrosomal regulation in and Che-1 depletion in HCT116 cells induced abnormal centrosome number, resulting in the formation of multipolar spindles.

Analysis of cell cycle regulation of Che-1 localization allowed us to assess that the centrosomal localization of this protein is regulated during the cell cycle and is undetectable in mitotic cells. In addition, HCT116 cells were treated with different genotoxic stresses, confirming that in DDR Che-1 changes its intracellular localization and centrosome accumulation. At molecular level, response to genotoxic agents, and to determine whether these proteins are functionally relevant for the centrosome inactivation checkpoint. Our results showed centrosomal accumulation of endogenous Che-1 in response to DNA damage, we found that Che-1 depletion strongly affects Chk1 centrosomal accumulation, Notably, Che-1 inhibition abolished the ability of Chk1 to bind pericentrin and to localize at centrosomes, which, in its turn, deregulates the activation of centrosomal cyclin B-Cdk1 and anticipates entry into mitosis. Our results reinforce the notion that Che-1 plays an important role in DDR, and that its contribution seems to be relevant for the control of cell division.

Characterization of the physical interaction between Che-1 and the oncosuppressor p53

The p53 tumor suppressor, which is mutated or inactivated in the majority of human cancers, functions as a master regulator of the cell response to several types of stress including DNA damage and oncogenic stimuli. This year, we further characterized the direct interaction between Che-1 and p53. This interaction essentially occurs when cells are subjected to sub-lethal DNA damage and requires Che-1 phosphorylation by Checkpoint

kinases, whereas this binding is lost when cells undergo to apoptosis and p53 is modified by several factors such as Pin1. To characterize the functional relevance of the p53/Che-1 complex, we performed a chromatin immunoprecipitation experiment coupled with high-throughput sequencing (Chip-Seq). This analysis was performed using I.R. or Doxorubicin treated HCT116 cells, and anti-p53 antibody, demonstrating that Che-1 depletion strongly reduced the presence of p53 onto the promoter of genes involved in growth arrest, and inhibited their transcription, whereas this oncosuppressor increased its level onto the promoter of apoptosis genes. These results were valitated by performing Chip experiments and by analizing gene expression by quantitative real time PCR. In order to extend these findings *in vivo*, we treated it with I.R. wild type and Che-$1^{+/-}$ C57BL/6 mice. The thymocyte analyisis obtained from these animals showed that the reduction of Che-1 expression was associated with an increase in apotosis induction as well as Puma and Bax expression.

Characterization of the physiological role/s played by Che-1 in the regulation of mTOR pathway in response to different cellular stresses

Since Che-1 was found to be involved in cellular response to several stress conditions, an involvement of Che-1 in regulating mTOR signalling that controls cell growth, proliferation and survival can be hypothesized. Consistent with this hypothesis, Che-1 was found to be specifically phosphorylated by checkpoint kinases in response to hypoxic and metabolic stresses and was able to control mTOR activity.

Since Che-1 is a RNA Pol II-binding protein involved in gene transcription, we took advantage of a high-density Affimetrix microarray analysis performed in HCT116 cells conditionally depleting Che-1. Given that Che-1 is a RNA Pol II-binding protein involved in gene transcription, we took advantage of a high-density Affimetrix microarray analysis performed using HCT116 transiently transfected with control siRNA or Che-1 siRNA (GEO accession number GSE45009). Interestingly, among the downregulated genes in Che-1-depleted cells we identified Redd1, Redd2 and Deptor, important genes involved in mTOR regulation under stress condition. mTOR signaling pathway is a critical negative regulator of autophagy and several cellular stresses induce autophagy via inhibition of mTOR. Therefore, we evaluated whether Che-1 could be involved in autophagy induction. Che-1 depletion strongly reduced LC3-II accumulation in response to brefeldin A. These results were confirmed when treating HCT116 cells with Cloroquine (CQ), an inhibitor of autophagic degradation. Moreover, glucose deprivation, hypoxia and I.R. caused LC3-II accumulation in HCT116 cells, but in response to each treatment, Che-1 depletion strongly reduced autophagy induction.

Next, we evaluated Che-1 expression in human MM cells, a disease characterized by high levels of autophagy. Oncomine database analyses suggested that Che-1 mRNA expression correlates with MM progression. To further confirm these data, we analyzed Che-1 and Deptor expression in a cohort of 110 human primary MM samples. Western blot analysis of CD138 enriched plasma cells derived from monoclonal gammopathies of undetermined clinical significance (Mgus) and MM patients revealed almost undetectable Che-1 and Deptor protein expression in the plasma cells from 22 Mgus samples but their progressive and widespread expression in 8/25 (29%) of smoldering myeloma and 24/38 (63%) of symptomatic myeloma samples. Notably, autophagy levels in these samples strongly correlated with Che-1 and Deptor expression. To further confirm the correlation between Che-1 and MM, we analyzed Che-1 expression in bone marrow samples from Vk*MYC mice Immunohistochemical assay of these samples revealed high levels of Che-1 expression in MM cells, whereas other components of the bone marrow did not

exhibit Che-1 positivity. Next, we analyzed Che-1 levels in different MM cell lines and found that lines with high levels of Che-1 (Kms18 and Kms27) showed Deptor expression and induction of autophagy. Inactivation of Che-1 or Deptor in Kms18 and Kms27 cells produced similar effects, increasing mTORC1 activity and an inactivation of mTORC2 activity. To further confirm these findings, under more physiologically relevant conditions, we generated an *in vivo* conditional Che-1 shRNA model. When these cells were treated with Doxycycline (Dox), Kms27 ind-shChe-1 but not Kms27 ind-shControl cells exhibited a strong reduction of Che-1 levels. Therefore, to perform studies *in vivo*, either ind-shChe-1 or ind-shControl engineered cells were were implanted subcutaneously in nude immune-depleted mice. Results from these experiments showed that in comparison to animal control (ind-shControl +/-Dox and ind-shChe-1 –Dox) ablation of Che-1 had an impact on tumor growth, producing a strong reduction of formed tumor. To corroborate these results, we isolated $CD138^{+}$ MM cells from patients with symptomatic myeloma and co-cultured these cells with stromal cells from the same patient before infecting them with shChe-1 or shControl lentiviral vectors. shChe-1 transduction in Che-1 expressing cells produced, in addition to Che-1 depletion, a reduction of autophagy induction with a concomitant increase in cell death, whereas these effects were not observed in an MM sample where Che-1 was not expressed. Hence, taken together these findings strongly indicate that Che-1 maintains the viability of myeloma cells and suggest it as a possible therapeutic target in this disease.

Pubblication 2012-2013

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Experimental Oncology

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Activities 2012-13

Malignant mesotheliomas are aggressive lethal neoplasms arising from the mesothelial cell lining of the pleura, peritoneum, tunica vaginalis testis and pericardium. Human malignant pleural mesothelioma is the most common form of mesothelioma that grows aggressively, spreading throughout the pleural cavity, and is frequently associated with massive pleural effusion. Malignant pleural mesothelioma is considered to be closely associated with a history of prolonged exposure to asbestos fibres in patients, although several etiologic factors iron and simian virus 40 (SV40) are reported to be involved in the development of malignant pleural mesothelioma. The incidence of malignant pleural mesothelioma is expected to increase at an alarming rate over the next few years, despite the banning of asbestos. Disease incidence varies markedly within and between countries. Time from asbestos exposure to disease diagnosis is on average greater than 40 years. Non occupational asbestos exposures contribute an increasing proportion of disease. With the exception of the United States, incidence continues to be on the increase. In developed countries the peak incidence is expected to occur before 2030. Malignant pleural mesothelioma, sometimes takes 10 years or more for changes to appear which are indicative of pleural disease, and even longer for symptoms to manifest. Patients frequently present respiratory symptoms, including dyspnea, shortness of breath and chest pain, extremely limiting the quality of life of the patients with this disease. Following diagnosis, most cases of malignant mesothelioma have poor survival. The standard therapeutic modalities for malignant pleural mesothelioma, including surgery, chemotherapy and radiation, have yielded unsatisfactory outcomes. The combination of cisplatin and pemetrexed has become standard first-line therapy worldwide for patients who are not suitable for aggressive surgery, or in whom chemotherapy is recommended as part of a multimodality regimen with a mean survival of 12.1 months and 18.34. Therefore, in order to improve the clinical outcome in the pharmacological treatment of this refractory tumour, drugs aimed at targeting novel and/or characterized tumour-specific cellular targets are needed. We recently demonstrated the presence of aromatase, the key enzyme in the biosynthesis of estrogens, in malignant pleural mesothelioma cell lines and tumor tissue sections from patients with malignant pleural mesothelioma. Exemestane, an aromatase inhibitor, inhibits the proliferation of malignant pleural mesothelioma cells. *In vitro,* exemestane inhibited the proliferation of mesothelioma cells by acting on the cyclic adenosine monophosphate (cAMP) levels, response element-binding protein (CREB) activation and CD44 expression. Only a cell line was less sensitive to the drug. In an attempt to understand the mechanism underlying this different sensitivity to exemestane, we are studying the drug uptake, production of reactive oxygen species (ROS) and enzymes involved in detoxification processes.

In an *In vivo* model of immunosuppressed mice carrying malignant pleural mesothelioma, exemestane induced a significant reduction of the tumor mass and an increased survival compared to a group of control mice carriers of malignant pleural mesothelioma but without drug treatment. In the *in vivo* model the association between pemetrexed-exemestane was more effective than pemetrexed-cisplatin in significantly reducing the tumor mass with a complete regression of 78%. We clearly showed the increased efficacy of exemestane alone or in combination with pemetrexed versus the standard therapy pemetrexed-cisplatinum against malignant pleural mesothelioma in the xenograft implantation model. These findings are encouraging and possibly support further investigation of exemestane in the clinical malignant pleural mesothelioma context and highlight the
opportunity to test, in the experimental MPM model, new compounds active with the same mechanism of action. In light of this evidence a small library of both [2,3-h] and [3,2-f] novel pyrroloquinolines equipped with an azolylmethyl group designed and synthesized as nonsteroidal CYP19 aromatase inhibitors were tested in mesothelioma cell lines. These new *in vitro* compounds inhibited the proliferation of mesothelioma cell lines after 72h treatment, we are now starting to test them in an *in vivo* mesothelioma mouse model.

In addition to these agents, CELLFOOD™ (CF) a nutritional supplement is under investigation. Cancer chemoprevention using natural or synthetic compounds to prevent or suppress the development of cancer is an area of active investigation. Many compounds belonging to diverse chemical classes have been identified as potential chemopreventive agents, including dietary constituents, nutraceuticals, naturally occurring phytochemicals, and synthetic compounds. Because of their safety and the fact that they are not perceived as 'medicine', natural compounds have created high interest for their development as chemopreventive agents that may find widespread, long-term use in populations at normal risk.

It is known that cancer cells cannot grow in a high oxygen environment and that the prime cause of cancer is the replacement of the normal respiration of oxygen by an anaerobic cell respiration, focusing on the vital role of oxygen. Our body uses oxygen to metabolize food and to eliminate toxins and waste through oxidation. Cells undergo a variety of biological responses when placed in hypoxic conditions, including a switch in energy metabolism from oxidative phosphorylation to glycolysis and activation of signalling pathways that regulate proliferation, angiogenesis and death. Cancer cells have adapted these pathways, allowing tumours to survive and even grow under hypoxic conditions, and tumour hypoxia is associated with poor prognosis and resistance to therapy. In most solid tumours, the resistance to cell death is a consequence of the suppression of apoptosis (dependent on mitochondrial energy production). In this context, CF, the "physiological modulator" aimed to make available oxygen "on-demand", was investigated for apoptosis and cancer prevention. CF (also known as Deutrosulfazyme™), is a nutraceutical supplement whose constituents, including 78 trace elements and minerals, 34 enzymes, 17 amino acids, electrolytes and deuterium sulphate, are all naturally occurring substances which are essential to the body's biochemical functions. We tested the activity of CF on 12 different cell lines, 2 normal and 10 cancerous. Our results showed that CF reduced cell proliferation in a dose-dependent manner in all the cancer cell lines used. CF suppresses cell growth by apoptosis in mesotelioma (MSTO-211) and colon (HCT-116) cancer cell lines. In particular, we found that CF caused an increase of sub-G1 and a reduction of G1 in MSTO-211, and a cell cycle arrest in G1 in HCT116. We speculated that CF-induced proliferative block was irreversible due to the significant increase in population with a sub-G1 and G1 DNA content (that are indicative of apoptosis) observed in the treated cells as compared to the untreated ones. Moreover, increased expression levels of p53, p21, and p27, downregulation of c-myc and Bcl-2, and inhibition of Akt activation were also found in CF-treated MSTO-211 and HCT-116 cells. p53 is one of the most important tumour suppressor genes, and it is frequently inactivated in various cancers. p53 modulates various cellular functions, such as apoptosis and cell cycle arrest via transcriptional regulation. c-myc has an important function in cell proliferation and apoptosis induction. CF induced downregulation of c-myc and upregulation of p21 and p27 thus, the suppression of c-myc expression by the nutraceutical may render substantial therapeutic benefits in colorectal cancer and mesothelioma patients by inhibiting the driving activities of c-myc in cell proliferation and cell cycle progression. One mechanism by which Akt prevents apoptosis is considered to proceed through phosphorylation and inactivation of the pro-apoptotic protein and also induction of the antiapoptotic Bcl-2 protein expression. The pro-survival Bcl-2 family members are pivotal regulators of apoptotic cell death; therefore, they are considered as attractive targets for drug design. Interestingly, we found p-AKT and Bcl-2 downregulation in HCT-116 and MSTO-211 upon CF treatment, thus leading us to believe that CF can be used for the prevention of tumours and can possibly sensitize cancer cells to standard therapy. Consistent with this assumption, we are studying the effect of CF and radiation treatment in different cancer cell lines. Preliminary results showed a synergistic effect.

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Experimental Oncology

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Activities 2012-13

HLA-E and tumor immune response

Several collaborative studies were published in cooperation with the clinical Departments at our Institute. Prognostic methods were developed based on proprietary models and reagents. In collaboration with the Units of Dermatology, Pathology, Surgery and Biostatistics, early-passage melanoma cells were cDNA profiled and were compared to normal cutaneous melanocyte cultures. Remarkably, the latter were established from the adjacent, morphologically intact skin of the patients donating tumor cells, in a fully autologous setting. This unique model has led to the identification and validation of novel overexpression immune signatures at the protein level, including several T/NK cell ligands, particularly HLA-E. Immunohistochemistry with specific antibodies to HLA-E is used to predict the prognosis of melanoma and colorectal carcinoma.

Our group has been active in the areas of immuno-engineering and nanomedicine. We have generated genetically modified cells and molecular objects with therapeutic potential. Our aims were to contrast tumor and viral immune evasion, and develop new platforms and concepts to improve chemotherapy.

Tumor Immune Evasion

In collaboration with the Pediatric Hospital Bambino Gesù (Dr. Doriana Fruci), we knocked out genes in the antigen processing machinery and discovered hierarchically high transcription factors regulating tumor immunogenicity in neuroblastoma. Tumor immune phenotypes were induced that incite recognition by both T and NK cells, e.g. the two major cytotoxic effector lineages of the immune system. This concerted action conflicts in part with the missing self dogma. Missing self postulates that T and NK cells are two alternative arms of the anti-tumor immune response, but we have shown that combined recruitment and activation of T and NK cells is possible, and may result in the synergistic rejection of murine tumors. These studies provide new practical tools to enhance immunity against neuroblastoma and melanoma, and suggest a general strategy to address the long vexing question of how we can render tumors visible to the patient's immune system. To obtain further insight into this issue, a novel cell-on-chip device, named DEPArray (Dielectrophoresis Array) has been manufactured by the Universities of Bologna and Ferrara in collaboration with Silicon Biosystems. The DEPArray forms dielectrophoretic cages that entrap and levitate single cells acting as partners in heterotypic interactions (e.g., effectors and targets of immune lysis). Cages and their content may be moved to pre-determined positions in the Cartesian space, and the DEPArray monitors the outcome of lytic interactions between CTLs and NK cells on the one hand, and tumor cells on the other. We found that the DEPArray identifies highly lytic antiviral CTLs and tumor cells that are

particularly refractory to NK cell lysis, providing a clue to select optimal effector target pairs for immunotherapeutic exploitation.

Control of HIV Infection

In collaboration with the S. Raffaele Institute in Milan, the University of Verona, and St. George's University of London, we challenged the view that the Human Leukocyte Antigen C (HLA-C) might be a key element in protecting humans from HIV infection. This view is supported by genome-wide screens, but HLA-C expression has been assessed by antibodies that are poorly characterized. Considering the data in the public domain, and our own unpublished data demonstrating cross-reactivity between HLA-C and HLA-E, we hypothesize that HIV-1 is not controlled by an orthodox HLA-C-restricted T lymphocyte response, but by a non-conventional response involving both HLA-C and HLA-E. The mechanism remains to be investigated.

Nano-Oncology

Trastuzumab-emtansine (TDGM-1) has set new qualitative standards and opened new horizons for the clinical exploitation of chemotherapeutic agents and therapeutic antibodies. The so-called Antibody-Drug Conjugates (ADC), of which TDGM-1 is the prototype, promise to revolutionize cancer therapy, making it truly specific, but still suffer from considerable limitations: lack of site-specific drug-Ab conjugation, low cytotoxic payload, low Ab: drug stoichiometry (typically 1:4), variability in the product even on the industrial level, critical restrictions in drug selection, off-target drug leakage, and inherent complexity, which limits the number of leads to be pursued even in a hi-tech big Pharma setting. Novel antibody-driven nanomolecular objects may overcome at least

some of these limitations. Over the past two years, in collaboration with Dr. Pierpaolo Ceci (CNR, Rome Italy), we constructed and described the first nanoconjugate in which an antibody, a ferritin nanoparticle cage, directs the Chondroitin Sulphate ProteoGlycan 4 antigen (CSPG4) onto melanoma cells and xenotransplants entrapping 50 cisplatin molecules in its hollow core. Given that the antibody and the drug components of this novel ADC are separated, and drugs are contained in a dedicated cavity, the drug:Antibody conjugation process does not hinder antibody performance. High drug: antibody stoichiometry and unique manufacturing properties make this nano-object exquisitely modular, versatile, potent and specific. At the ADC summit which was held in Frankfurt in February 2014, an international committee placed our anti CSPG4 nanoparticle in a novel category, that of the so-called *X*DCs. The XDC family is being rapidly populated by novel antibody-based (and non-antibody-based) molecular therapy tools, the primary sequence of which is invariably packed with considerable amounts of information. XDCs, including CSPG4-XDC, are designed to incorporate polypeptide sequences that bear specific programs. They direct the step-wise targeting of tumor cells, prevent non-specific dispatch of naked drugs to healthy cells, and determine controlled activation and release of enhanced antitumor cargoes only at the tumor site, and only upon antibody engagement. Next-generation nano-chemotherapy will enable clinical oncologists to administer very high doses of very toxic drugs with minimal side effects and in many different clinical settings. For instance, our CSPG4-XDC nano-drugging melanoma system, although prototypic, has been shown to improve at least 25 times the therapeutic index of naked cisplatin in animal models.

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Experimental Oncology

Carlo Leonetti, PhD

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Activities 2012-13

Dr. Carlo Leonetti's research centres on the evaluation of antitumor efficacy of new targeted compounds in combination with standard chemoterapeutics in preclinical models of human cancer, and to identify effective therapies for translational application. He also focused on the development of new nanodevices able to change pharmacokinetic and distribution profile of antineoplastic compounds and improve their delivery to tumor sites.

In collaboration with IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST, Meldola), we identified two new small molecules as androgen receptor antagonists for the treatment of hormone-refractory prostate cancer (HRPC). In particular, we observed that the new compounds, (R)-9 and (S)-11, exhibited a higher cytotoxic effect than the reference compound ((R)-bicalutamide) in hormone-sensitive or resistant human prostate cancer cell lines. A significant reduction in PSA levels was observed after exposure to both molecules; moreover, (R)-9 and (S)-11 inhibited DNA synthesis by blocking the androgen-induced increase in cyclin D1 protein levels. *In vivo* studies on the toxicological profile of (R)-9 did not reveal the presence of adverse events. Furthermore, (R)-9 inhibited tumor growth in various *in vivo* models, especially LNCaP-Rbic xenografts, represent recurrent disease. In conclusion, the significant *in vitro* and *in vivo* antitumor activity shown by (R)-9 in prostate cancer models highlights its potential usefulness in advanced human disease, where current therapeutic options remain unsatisfactory.

We have previously reported that a new type of nanocarrier named self-assembly nanoparticles (NPs) are able to deliver the bisphosphonate zoledronic acid (ZOL) into tumors of different hystotypes including myeloma, prostate and breast cancer. These systems, compared with classic nanodevices such as liposomes, offer the possibility to be prepared before use, thus avoiding storage issues that are sometimes encountered with the development of liposome formulations. Recently, we developed new self-assembling nanoparticles (NPs) functionalized with transferrin (Tf) in order to improve the rate of internalization of ZOL into the cells. We found that Tf-NPs-ZOL were superior to the anticancer activity of free-ZOL and to NPs-ZOL and had greater cytotoxic activity on different glioblastoma cell lines than Temozolomide, a gold standard for clinical treatment of this tumor. The sequential therapy of Temolozomide and Tf-NPs-ZOL led to superior therapeutic activity compared to their single administration producing necrosis and autophagy on glioblastoma cells. On the other hand, Tf-NPs-ZOL showed higher antitumor efficacy when compared to the one caused by NPs-ZOL in immunosuppressed mice intramuscularly bearing U373MG-LUC glioblastoma xenografts, inducing a significant inhibition of tumor growth, with a complete

tumor regression in 1 out of six mice treated. The experiments performed on orthotopic models demonstrated that Tf-NPs-ZOL given i.v. were able to overcome the blood-brain barrier, produced the stabilization of the disease in 3 out of eight mice treated and, impressively, a complete tumor response was reported in one mouse. These effects were paralleled by an higher intratumour localization of fluorescently-labeled- Tf-NPs. In conclusion, our results demonstrate that the encapsulation of ZOL in Tf-NPs increases the antitumor efficacy of this drug in glioblastoma through acquiring the ability to cross the blood-brain barrier, thus suggesting the application of this strategy in the clinical setting.

This new NPs formulation invention has been internationally patented and the Regina Elena National Cancer Institute is one of the co-patentees, together with Second University and University "Federico II" of Naples.

Colorectal cancer is the second most common cause of cancer-related death in many industrialized countries. Even though adding oxaliplatin or topoisomerase I (Top1) inhibitor irinotecan to 5-fluorouracil (5-FU)/leucovorin regimen has greatly improved survival, treatment failure frequently occurs. Strategies to counteract resistance to Top1 poisons include their combination with poly(ADP-ribose) polymerase (PARP) inhibitors (PARPi). Germline mutations of mismatch repair (MMR) genes or epigenetic inactivation of the mismatch repair component MLH1 may be present in colorectal cancer and influence the response to antineplastic drugs and clinical behaviour. Based on a long-standing

collaboration with University "Tor Vergata" of Rome, we studied the impact of MLH1 expression on colon cancer cell chemosensitivity by using cell lines in which the defective gene product was restored by chromosome transfer or by transfection of the corresponding wild-type cDNA. The results demonstrated that MLH1-proficiency and low Top1 expression resulted in reduced sensitivity to irinotecan, but pharmacological inhibition of PARP activity or silencing of PARP-1 gene increased the susceptibility of colon cancer cells to the Top1 poison. Interestingly, cells with lower levels of PARP-1 protein could still be sensitized to irinotecan by PARPi. On the whole, these results indicate that MLH1, together with low levels of Top1, contributes to colon cancer resistance to Top1 poisons. Remarkably, inhibition of PARP-1 function always increases the antitumor activity of irinotecan even in the presence of low PARP-1 expression, thus strengthening the importance of this combination therapy for the clinical management of colorectal cancer.

Our studies on G-Quadruplex ligand compounds as potential anticancer agents led to the selection of new derivatives which maintain the same biological features of the leading compound RHPS4, however improving toxicological profile. Therefore, identifying suitable molecules for clinical development and offering new pharmacological strategies in cancer treatment. Moreover, a G-Quadruplex ligand of a different class, which is structurally and biologically similar on one side to coronene and on the other side to a bay-monosubstituted perylene, named EMICORON, was evaluated *in vitro*. The results demonstrated a preferential antiproliferative activity of this compound against tumor cells while normal cells were unaffected. Moreover, this compound exhibits a strong synergistic cytotoxic activity against colon cancer cells. Finally, EMICORON given orally in mice had a favourable pharmacological profile and was markedly active inhibiting more than a 50% growth of patient-derived xenografts (PDXs), obtained by s.c. injection of fresh tumor tissue from patients with pathologically confirmed colon cancer and unresponsive to chemotherapy. In conclusion, these results identify EMICORON as a new G-Quadruplex ligand with promising antitumor activity on relevant experimental models of human colon cancer thus warranting further studies of EMICORON-based combination treatments.

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Experimental Oncology

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Activities 2012-13

Tumor-stroma interaction and immune response

This research group is dedicated to studying the cross talk between tumor cells and the tumor microenvironment as well as to studying the role of the host immune response in carcinogenesis and tumor progression. By analysing the repertoire of antibodies specific for autologous tumor molecules in breast cancer, the group has identified hMENA, a cytoskeleton regulatory protein and two alternatively expressed isoforms. Research activity is now aimed at identifying the hMENA alternative splicing program as a central node in "druggable" signaling pathways activated by microenvironmental cues and as predictive biomarker of invasion, metastases and of therapeutic response in breast, lung and pancreatic cancers.

This group is a leader in the Italian Network for Immune monitoring which belongs to an international immune monitoring network system aimed at minimizing variability of T-cell assay results through assay harmonization establishing cellular immune response as a reproducible biomarker. We also investigated its relationship with clinical outcomes. The group is responsible for the immune monitoring of a phase II open-label, randomized ongoing clinical trial in order to prove the concept of effectiveness of combined chemo-immunotherapy strategy.

hMENA splicing program generates isoform with opposite functions in cancer: invasive and anti-invasive

Alternative splicing (AS) mechanisms generate from a single gene a variety of proteins, a key mechanism for increasing proteomic diversity and modulating gene expression. AS is frequently misregulated during tumorigenesis and participates in specific cellular programs i.e. apoptosis, cell growth, angiogenesis and Epithelial Mesenchymal Transition (EMT). Proteins with opposite functions may be generated and recently AS is emerging as a growing and promising field in basic and translational oncology. AS has been shown to influence tumor cell morphology and motility by controlling the activity of genes that mediate cytoskeletal function. hMENA along with VASP and EVL comprise the Ena/VASP family of actin regulatory proteins, which modulate cell adhesion and migration. This group has recently reported that hMENA splicing program generates two isoforms alternatively expressed with opposite functions in breast tumor progression. In collaboration with Mina J Bissell (Lawrence Berkeley Laboratory, Univ. of California, Berkeley, USA) in a 3D isogenic model of human breast cancer progression, hMENA[11a] is

expressed in premalignant cells, whereas hMENAΔv6 expression is restricted to invasive cancer cells. “Reversion” of the malignant phenotype by EGFR inhibitors leads to concurrent down-regulation of all hMENA isoforms. In breast cancer cell lines, hMENA^{11a} reduced the migratory and invasive ability of these cells, whereas the hMENAΔv6 increased it. hMENA^{11a} splicing is regulated by the epithelial regulator of splicing 1 (ESRP1). Transfection of ESRP1 in invasive mesenchymal breast cancer cells induced changes in the cytoskeletal architecture, re-expression of hMENA^{11a}, and reduction in cell invasion (Figure 1). Primary tumors hMENA^{11a}-negative are more frequently E-cadherin low in comparison with tumors expressing hMENA^{11a}, suggesting that isoform-specific hMENA detection may represent a novel biomarker characterizing a subgroup of tumors enriched for mesenchymal cell features and low proliferation activity,offering a useful signature for the diagnosis, prognosis of early stage breast cancer.

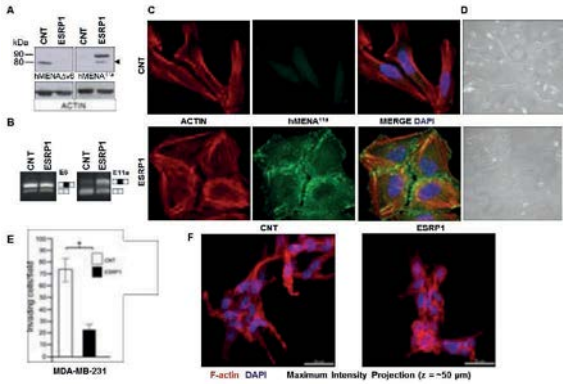

Figure 1. *ESRP1* transduction induces hMENA^{11a} expression in parallel with changes in cell shape and actin cytoskeleton architecture in MDA-MB-231 cells (from Di Modugno et al. PNAS 2012)

hMENA isoforms, signal checkpoints in *breast cancer proliferation and invasion*

***i)** Cross talk among hMENA isoforms and β1 Integrin (Co-leaders P. Nisticò-F. Di Modugno).*

To explore the mechanism underlying the opposite roles of hMENA^{11a} and hMENAΔv6 in the invasive behaviour of breast cancer cells, we investigated the link between hMENA isoforms and β1 Integrin, a big player in cell invasion and in the resistance of tumor cell to radiotherapy and targeted therapies. A correlation between the expression of the "invasive" hMENA□v6 isoform and high level of β1 Integrin has been found in breast cancer cell lines, whereas cell lines expressing the epithelial anti-invasive hMENA^{11a} show undetectable β1 Integrin expression. More importantly, the two hMENA isoforms differently affect β1 integrin and downstream molecules (i.e. FAK; SRC). The mechanism underlying the cross-talk between the different hMENA isoforms and β1 Integrin signaling and their role in cancer cell invasion are under investigation in collaboration with Dr. Martin Schwartz (Yale School of Medicine, USA).

ii) hMena splicing program as a node in ErbB signaling of breast cancer (Co-leaders P. Nisticò-F. Di Modugno)

In a previous paper, we have shown that hMena/hMena^{11a} knock-down reduced HER3, AKT and p44/42 MAPK phosphorylation and inhibited the EGF and NRG1-dependent HER2 phosphorylation and cell proliferation (Di Modugno et al. Plos One 2010). Of functional significance, hMena/hMena^{11a} knock-down reduced the mitogenic activity of EGF and NRG1. To study the signal networks influenced by the different hMena isoforms and linked to a proliferative or invasive behaviours of breast cancer cells, we are defining the activated signaling protein profile by reverse phase protein arrays (RPPA), in collaboration with the Tumor Stem Cells Biobank of ISS. The analysis was carried out through RPPA breast cancer cell lines transfected or silenced for the different hMena isoforms untreated, or Neuregulin treated. Activated signaling profiles obtained from RPPA have identified hMENA^{11a} as a relevant molecule in sustaining HER3 signalling pathway.

Identification of early markers of pancreatic cancer

EMT, a process related to inflammation and tumor progression, is an early event in pancreatic ductal adenocarcinoma (PDAC). We have shown that in pancreatic cancer cell lines hMENA^{11a} and hMENAΔv6 spliced isoforms correlate with an epithelial and a mesenchymal phenotype, respectively. We observed that hMENA^{11a} epithelial specific isoform is involved, as well as VASP (the other member of the family) in cell-cell adhesion. In addition, the interaction and function of these two proteins in normal and pancreatic cancer cell lines were studied. We found that the phosphorylation status of both the proteins is decisive for their functions (i.e. cell-cell adhesion) as demonstrated by gain and loss of function approaches.

TGFβ acts as a potent driver of cancer progression and induces EMT. To identify the role of hMENA isoforms in TGFβ mediated EMT, we performed experiments on freshly explanted and long term culture pancreatic cancer cell lines. Results clearly show that the expression of hMENA^{11a} sustains the expression of E-Cadherin, whereas the expression of hMENAΔv6 downregulates E-Cadherin and increases the vimentin expression. Moreover, the TGF□-mediated EMT is supported by hMENA splicing (Melchionna et al. manuscript in submission).

hMENA is not expressed in normal pancreatic ducts, but is overexpressed in 73% of PDAC analysed by immunohistochemistry with Pan-hMENA Ab. hMENA alternative splicing in pancreatic cancer leads to the frequent lack of the "epithelial" hMENA^{11a} isoform and the overexpression of the "mesenchymal" hMENAΔv6. We suggest that the lack of hMENA^{11a} isoform is an early event in pancreas tumorigenesis and may represent a

crucial step in pancreatic cancer progression (Iapicca et al. manuscript in submission).
PDAC, cancer cells are surrounded by a fortress of desmoplastic stroma composed of cancer-associated fibroblasts (CAFs) and inflammatory cells along with copious amounts of extracellular matrix components. CAFs are an established source of well-known tumor promoting growth factors (i.e. EGF, TGF-□, HGF), thus the identification of CAFs produced factors and of autocrine and paracrine factors able to modulate the cross-talk between tumor cells and stroma may help in the identification of novel targetable pathways in this incurable disease. CAFs from fresh biopsies of the main tumor, proximal peritumoral lesions and normal tissues were collected in collaboration with Hepatobiliary surgery. CAFs express hMENAΔv6 and hMENA but not express hMENA^{11a} isoform. Interestingly, hMENAΔv6 is up-regulated in CAFs when compared to normal fibroblast. In the same surgical specimen CAFs expressed hMENAΔv6 whereas autologous epithelial tumor cells express hMENA^{11a} at mRNA and protein level, again suggesting that the two isoforms are differently regulated in epithelial and mesenchymal tissues.

Anti-hMENA antibody response in pancreatic cancer patients

To evaluate whether anti-hMENA seroreactivity could represent an early marker of PDAC we set-up and standardized ELISA procedure, with the hMENA and hMENA^{11a} recombinant proteins. Sera from PADC patients and healthy donors were tested by ELISA for the reactivity against hMENA^{11a} and hMENA isoforms. Results indicate a significant higher seroreactivity in PDAC patients compared to healthy donors. Moreover, preliminary data suggest that PDAC patients may exert a different seroreactivity versus the two isoforms, that may be related to patient survival. We are currently analyzing a larger cohort of patients where we are going to correlate seroreactivity with hMENA isoform expression on autologous primary tumor when available. All these data were obtained in collaboration with the research group of Dr. Franco Novelli (University of Turin).

hMENA splicing program as a prognostic marker in lung cancer

The potential significance of alternative splicing as a target for lung cancer diagnosis or treatment has recently been highlighted. We analyzed the hMENA isoform expression by biochemical, functional and immunohistochemical methodologies. In lung cancer cell lines hMENA isoforms have antagonistic roles in cell invasion and migration. Of clinical relevance, in a training set of 248 patients, in collaboration with the Medical Oncology A and the Dept of Pathology of our Institute, we found that pan-hMENA and hMENA^{11a} expression, evaluated as continuous variables, were the only significant predictors of DFS, CSS, and OS at multivariate analysis. The model was externally validated in an independent dataset of 133 patients. These findings will potentially enable clinicians to incorporate all relevant prognostic features with a relatively simple and practical prognostic algorithm also possibly paving the way for novel therapeutic approaches based on hMENA splicing related pathways (paper submitted).

Predictive biomarkers of melanoma progression and of clinical response to chemo-immunotherapies

An improved understanding of immunomodulatory pathways and microenvironment changes occurring during melanoma progression has helped in the development of novel combined effective treatments for melanoma patients. Emerging evidence suggest that reprogramming antitumor immunity is essential in designing therapeutic strategies able to control and cure melanoma. We have recently reported that the combination of chemo-immunotherapy may give clinical benefits in disease-free HLA-

A2 positive melanoma patients. hemotherapy works in parallel on the tumor cells and on the tumor micro- and macroenvironment, often requiring the contribution of adaptive immunity to defeat cancer.
We monitored the antigen specific CD8+ T cell immune response of 35 patients and evaluated molecular and biochemical events occurring in Ag-specific T cells. We found that dacarbazine (DTIC) plus vaccination shapes the TCR repertoire and activates non-canonical (CD28-CD27 independent) AKT pathway affecting the quality of T cell response. This pathway is related to functional events such as the production of Th-1 cytokines i.e. IFNγ, TNFα and Granzyme B by CD8 T lymphocytes (manuscript submitted).
Quantitative and functional analysis of γδ T lymphocytes showed that the Vγ9Vδ2 T population is preferentially expanded in patients treated with the combination therapy. This subpopulation of cells has a high antitumor lytic activity.

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CN103282514 A - 04/09/2013

Experimental Oncology

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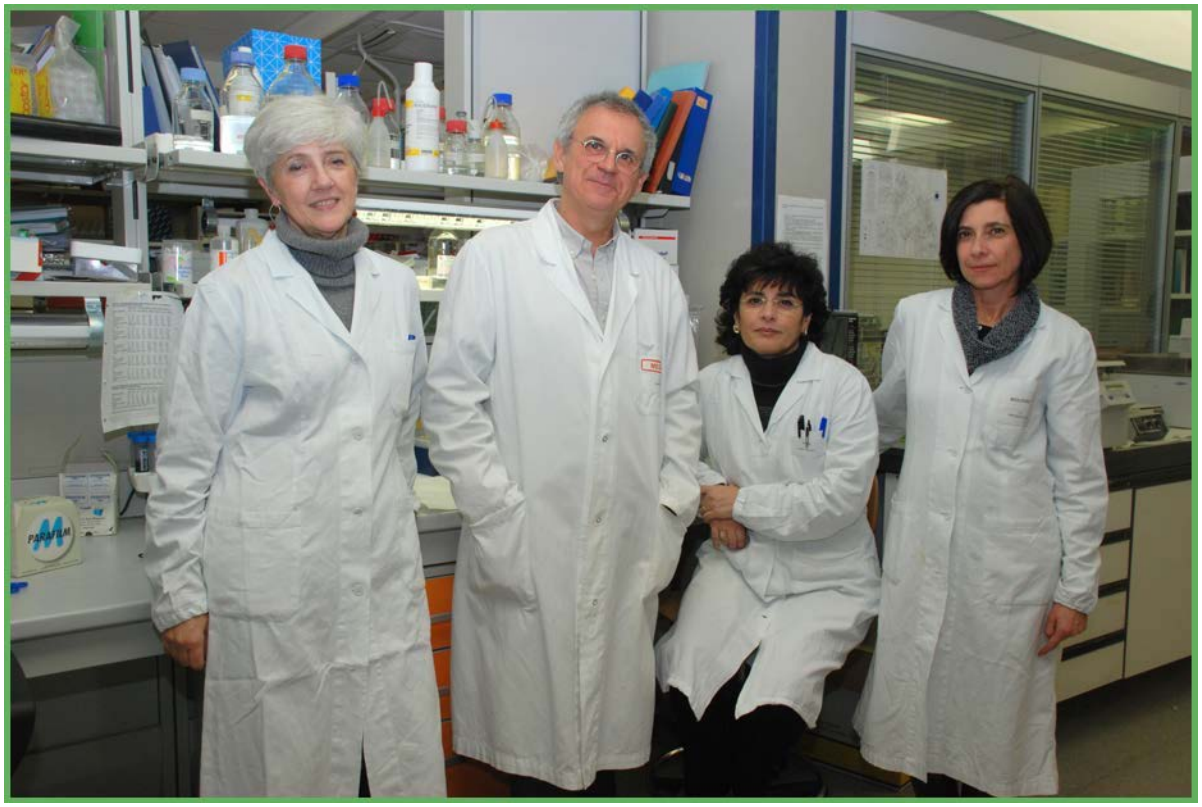
Activities 2012-13

Viral oncogenesis

A. The Human Papillomavirus-16 E7 oncoprotein exerts anti-apoptotic effects via its physical interaction with the actin-binding protein Gelsolin. The oncoprotein E7 from Human Papillomavirus 16 (HPV-16 E7) plays a pivotal role in HPV post-infective carcinogenesis and its physical interaction with host cell targets is essential to its activity. We identified a novel cellular partner for the viral oncoprotein: the actin-binding protein gelsolin (GSN), a key regulator of actin filament assembly and disassembly. In fact, biochemical analyses, generation of a 3D molecular interaction model and the use of specific HPV-16 E7 mutants provided clear cut evidence supporting the crucial role of HPV-16 E7 in affecting GSN integrity and function in human immortalized keratinocytes. Accordingly, functional analyses clearly suggested that stable HPV-16 E7 expression induced an imbalance between polymeric and monomeric actin in favor of the former. These events also lead to changes of cell cycle (increased S phase), to the inhibition of apoptosis and to the increase of cell survival. These results provide support to the hypotheses generated from the 3D molecular interaction model and encourage the design of small molecules hindering HPV-induced host cell reprogramming by specifically targeting HPV-16 E7-expressing cells.

B. Identification of pivotal cellular factors involved in HPV-induced dysplastic and neoplastic cervical pathologies. Cervical carcinoma represents the paradigm of virus-induced cancers, where virtually all cervical cancers come from previous "high-risk" HPV infection. The persistent expression of the HPV viral oncoproteins E6 and E7 is responsible for the reprogramming of fundamental cellular functions in the host cell, thus generating a noticeable, yet only partially explored, imbalance in protein molecular networks and cell signaling pathways. Eighty-eight cellular factors, identified as HPV direct or surrogate targets, were chosen and monitored in a retrospective analysis for their mRNA expression in HPV-induced cervical lesions, from dysplasia to cancer. Real-time quantitative PCR (qPCR) was performed by using formalin-fixed, paraffin embedded archival samples. Gene expression analysis identified 40 genes significantly modulated in LSIL, HSIL, and squamous cervical carcinoma. Interestingly, among these, the expression level of a panel of four genes, TOP2A, CTNNB1, PFKM, and GSN, was able to distinguish between normal tissues and cervical carcinomas. Immunohistochemistry was also done to assess protein expression of two genes among those up-regulated during the transition between dysplasia and carcinoma, namely E2F1 and CDC25A, and their correlation with clinical parameters.

Besides the possibility of significantly enhancing the use of some of these factors in diagnostic or prognostic procedures, these data clearly outline specific pathways, and thus key biological processes, altered in cervical dysplasia and carcinoma. Deeper insight on how these molecular mechanisms work may help widen the spectrum of novel innovative approaches to these virus-induced cell pathologies.



C. Understanding the targeting of the RB family proteins by viral oncoproteins to defeat their oncogenic machinery. The retinoblastoma (RB) family consists of three genes, RB1, RBL1, and RBL2, that code for the pRb, p107, and pRb2/p130 proteins, respectively. All these factors have pivotal roles in controlling fundamental cellular mechanisms such as cell cycle, differentiation and apoptosis. The founder and the most investigated RB family protein is pRb, which is considered to be the paradigm of tumor suppressors. However, p107 and pRb2/p130 clearly display a high degree of structural and functional homology with pRb. Interestingly, these factors were first identified as physical targets of the Adenovirus E1A oncoprotein. Indeed, RB family proteins are the most important and widely investigated targets of small DNA virus oncoproteins, such as Adenovirus E1A, human papillomavirus E7 and Simian virus 40 large T antigen. By interacting with pRb and with other RB family members, these oncoproteins neutralize their growth suppressive properties, thus stimulating proliferation of the infected cells, de-differentiation, and resistance to apoptosis. All these acquired features strongly favor the rise and selection of immortalized and mutation-prone cells, leading to a higher propensity in undergoing transformation. Our present work aims to illustrate and delve into these protein-protein interactions. Considering that these viral oncoproteins are dispensable for normal cellular functions, they can create "oncogene addiction" in the

infected/transformed cells. This makes the possibility to dismantle these extremely attractive interactions, thus promoting the development of highly specific smart molecules capable of targeting only the infected/transformed cells that express these viral factors

Signal transduction: Sgk1 kinase in cancer chemoresistance and its expression in NSCLC

A. Sgk1 enhances RANBP1 transcript levels and decreases taxol sensitivity in RKO colon carcinoma cells. The serum- and glucocorticoid-regulated kinase (Sgk1) is essential for hormonal regulation of epithelial sodium channel-mediated sodium transport and is involved in the transduction of growth factor-dependent cell survival and proliferation signals. Growing evidence now points to Sgk1 as a key element in the development and/or progression of human cancer. To gain insight into the mechanisms through which Sgk1 regulates cell proliferation, we adopted a proteomic approach to identify up- or downregulated proteins after Sgk1-specific RNA silencing. Among several proteins, the abundance of which was found to be up- or downregulated upon Sgk1 silencing, we focused our attention on RAN-binding protein 1 (RANBP1), a major effector of the GTPase RAN. We report that Sgk1-dependent regulation of RANBP1 has functional consequences on both mitotic microtubule activity and taxol sensitivity of cancer cells.

B. Determination of SGK1 mRNA in non-small cell lung cancer samples underlines high expression in squamous cell carcinomas. Lung cancer represents the most frequent cause of death for cancer. In non-small cell lung cancer (NSCLC), which accounts for the vast majority of this disease, only early detection and treatment, when possible, may significantly affect patient prognosis. An important role in NSCLC malignancy is attributed to the signal transduction pathways involving PI3Kinase, with consequent activation of the AKT family factors. The serum and glucocorticoid kinase (SGK) factors, which share high structural and functional homologies with the AKT factors, are a family of ubiquitously expressed serine/threonine kinases under the control of cellular stress and hormones. SGK1 is the most represented SGK member. By means of immunohistochemistry and quantitative real-time PCR, we determined SGK1 protein and mRNA expression in a cohort of 66 formalin-fixed, paraffin-embedded NSCLC surgical samples. All samples belonged to patients with a well-documented clinical history. mRNA expression was significantly higher in squamous cell carcinomas, and correlated with several clinical prognostic indicators, being elevated in high-grade tumors and in tumors with bigger size and worse clinical stage. No correlation was found between SGK1 protein expression and these clinical parameters. This explorative analysis of SGK1 expression in NSCLC samples highlights the potential role of this factor in NSCLC patient prognosis. Moreover, the higher expression in the squamous cell carcinoma subtype opens new therapeutic possibilities in this NSCLC subtype by designing specific kinase inhibitors.

Chemopreventive and antitumoral activities of artichoke polyphenols

Some nutraceuticals exhibit potent antitumoral properties and can modulate cell cycle, apoptosis and or differentiation, probably by virtue of their antioxidant functions. Among the dietary compounds, we focused on polyphenols derived from total purified artichoke extracts (AEs). We investigated AEs effect on human breast cancer cells and demonstrated a pronounced apoptotic activity on cancer cells and a low or no toxicity on normal cells. Furthermore cell motility and invasion capabilities were remarkably inhibited by AEs in highly invasive breast cancer cell lines. Since senescence is considered an anticancer progression process and therapy-induced senescence represents a novel functional target that may improve

cancer therapy, we focused on premature senescence mechanisms. Our data show that AEs induce senescence on breast cancer cells through epigenetic DNA alterations and increased ROS production. This study could lead to improve the understanding of the biological role of dietary polyphenols and to search for novel agents with potential chemopreventive properties in populations at normal risk and in higher risk subjects of developing breast cancer disease. Moreover, a promising cytostatic approach is a pro-senescence therapy which may provide a persistent growth inhibitory effect in both early and late stage cancers. The suppressive role of senescence in cancer progression has suggested that AEs-induced premature cell aging could be a complement to conventional anticancer treatments in the future.

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Experimental Oncology

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Activities 2012-13

Deciphering new molecular pathways through which the transcription factor NF-Y exerts its role on cell proliferation.

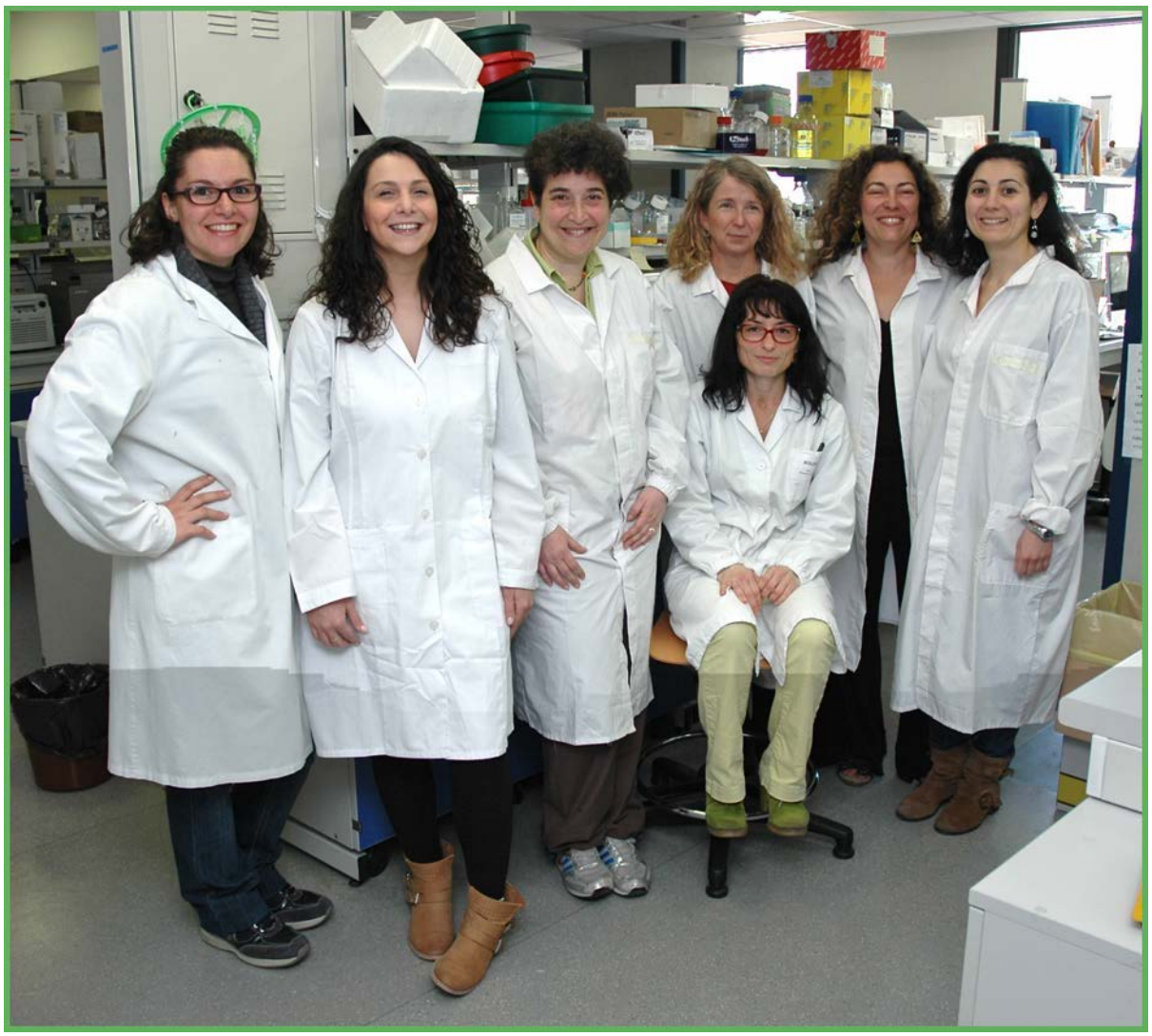
The CCAAT-binding complex NF-Y is a ubiquitous protein, composed of 3 subunits, NF-YA, -YB and –YC, whose genes are highly conserved from yeast to mammals, involved in cell proliferation and cancer. NF-YA is the regulatory subunit of the complex. Recently, by mass spectrometry, we identified LMNA as a novel NF-YA interactor in breast and colon cancer cell lines. To get clues on NF-YA and LMNA interaction, we generated the cytoplasmic, nucleoplasmic and the chromatin fractions. This analysis indicates that NF-YA/LMNA association occurs in the chromatin. fraction. To understand the functional role of the protein complex, we isolated eu- and heterochromatin fractions by mild MNase treatment. Our data show that NF-YA and LMNA co-localize in transcriptionally active regions. Moreover, evidence obtained by chromatin immunoprecipitation analysis and luciferase assays suggest a putative role of LMNA in the NF-Y transcriptional function.

NF-Y/miRNA200 axis: unrevealing a role of the transcription factor NF-Y in EMT transition.

A widespread deregulation of miRNAs is commonly observed in human cancers and promotes cellular transformation and tumorigenesis. Recently, we catalogued, from literature, a set of common miRNAs deregulated in colon cancer. This search retrieved 118 deregulated miRNAs. Through a computational analysis on 5,5 kb around the TSS, we identified conserved NF-Y consensus motif in 39 (corresponding to 55 miRNAs) of the 118 miRNA's promoters, among them the two promoters of miR-200 family. The miR-200 family comprises five members: miR-200a, -200b,-200c, -141 and -429. Being potent inhibitors of epithelial-mesenchymal transition (EMT), the members of miR-200 family are down-regulated in aggressive human cancers. By ChIP experiments performed in human colon cancer cells we observed that NF-Y directly binds the CCAAT-box of miR-200 family promoters and this binding correlates with the appearance of open chromatin marks. Consistent with this, NF-Y silencing and overexpression experiments indicate that NF-Y sustains E-cadherin protein expression regulating miRNA-200 family expression at transcriptional level. Finally, through a computational analysis we identified NF-Y as putative target of miR-200 family members.

In vivo molecular imaging of cell proliferation during mammary tumor progression to identify new biomarkers useful for clinical applications.

We have recently developed a mouse model engineered to express the luciferase gene in



cells undergoing proliferation, MITO-Luc reporter mice. In these reporter mice, by using a unique multi technological approach based on non-invasive *in vivo* imaging, we have already identified early steps of mammary transformation. Indeed, in these mice we analysed, in a dynamic way, the development of breast cancer in chemical induced and genetic tumours. As well as our purpose of identifying clinical useful biomarkers for early diagnosis, our major aim is now to characterise the expression of a specific miRNA profile, in breast tissues and in serum, in the transformation process stages identified through *in vivo* imaging.

MicroRNAs regulated by mutated p53 oncoproteins in cancer

Project Leader: Aymone Gurtner

Human cancers are characterized by deregulated miRNA expression and defects in miRNA biogenesis promoting cellular transformation and tumorigenesis; still, the mechanisms through which miRNAs are regulated in cancer remain unclear. Tumor suppressor p53, mutated in approximately 50% of human cancers, can acquire GOF activities favoring tumor induction, maintenance, spreading. miRNAs can be regulated by wtp53 at transcriptional and post-transcriptional level but few data about mutp53-dependent miRNA expression are not yet available. Our preliminary results, acquired by a genome wide analysis, reveal 31 miRNAs up-regulated after interference of mutp53 in human colon adenocarcinoma cells. Validation of the microarray analysis for mature miRNAs and pri-miRNAs shows that mutp53 regulates 12 miRNAs at post-transcriptional level, playing a role in Drosha-complex inhibition. Moreover, we found that 4 of the post-

transcriptional regulated miRNAs show tumor suppressive properties (cell proliferation and migration inhibition). These data support the idea that mutp53 is one of the key factors leading to the decreased expression of miRNA in human cancers by interfering with miRNA processing.

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Activities 2012-13

The PI, Dr Maria Giulia Rizzo, is a group leader of a unit devoted to the study of the involvement of a specific microRNA (miRNA) signature in the pathogenesis of acute myeloid leukaemia (AML), in particular of acute promyelocitic leukemia (APL). She has a long record of studies on the mechanisms of tumor transformation and development. During the last years she and her group focus on topics relevant to AML inizially, investigating the role of p53 gene and the potential involvement of newly discovered p53 family member, p73 and its isoforms, then studying the role of differentiation-associated miRNAs in normal and pathological granulo-monocytopoiesis.

MiRNAs, small non-coding RNAs that regulate gene expression post-transcriptionally, are involved in many complex cellular processes. Several miRNAs are differentially expressed in hematopoietic tissues and play important roles in normal differentiation, but, when aberrantly regulated, contribute to the abnormal proliferation and differentiation of leukemic cells. Recently, we reported that a small subset of miRNAs is differentially expressed in APL blasts and is modulated by treatment with all-trans-retinoic acid (ATRA). In particular, PML/RAR□-positive blasts from APL patients display lower levels of miRNA let-7c, a member of the let-7 family, than normal promyelocytes and its expression increases after ATRA treatment. Moreover, we found that let-7c ectopic expression promotes granulocytic differentiation of AML cell lines and primary blasts. We, also, identified PBX2, a well-known homeodomain protein whose aberrant expression enhances HoxA9-dependent leukemogenesis, as a novel let-7c target that may contribute to the AML phenotype. These studies raise the possibility that perturbation of the let-7c-PBX2 pathway may have a therapeutic value in AML.

Let-7c is an intronic miRNA embedded in the long non-coding gene LINC00478**.** Previously, we found a coordinated regulation of let-7c expression with that of the host gene suggesting that its transcription was controlled by the host gene promoter whose canonical RARE elements are bound by PML/RARα in an ATRA-sensitive manner. Interestingly, we found that at least two promoters are functional in let-7c transcription: the distal host-gene promoter and a proximal intronic promoter not previously identified. Of note, we provided evidence that the host-gene promoter is responsive to ATRA and essentially the only one active in AML cells, whereas in solid tumors the intronic promoter too is regulating let-7c expression. These data led us to propose a model in which dual or alternative promoter usage could represent a regulatory mechanism of let-7c expression in different tissues. Thus let-7c could provide a useful resource for the study of both development and disease pathogenesis.

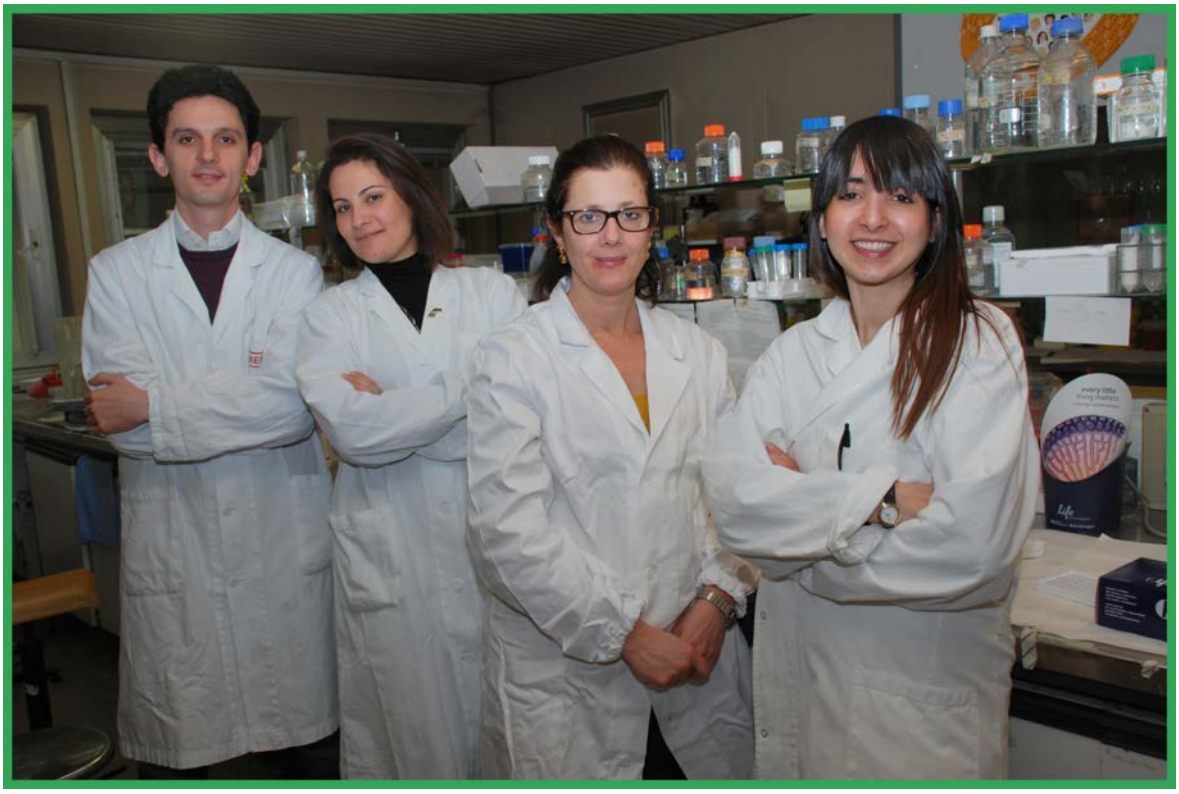
Based on the above data, these studies are exciting because increasing evidence also supports the important role of specific miRNA expression not only in the pathogenesis of human cancer, including hematological malignancies, but also as a tool for disease classification and outcome prediction. In

particular, it is very intriguing the concept that, in spite of distinct genetic abnormalities, different myeloid leukemias may express a common miRNA signature which can potentially lead to the development of novel therapies from which most AML patients could benefit. This hypothesis is consistent with the dismal prognosis of a large majority of AML patients regardless of the genetic background. In particular, we are encouraged to focus our studies on let-7c as potential marker of treatment outcome and prognosis in AML patients since we believe that the screening for let-7c expression in samples derived from AML patients belonging to different genetic subtypes before and after therapy could contribute to identify let-7c, or other miRNAs of a specific signature already identified, as new molecules implicated in therapeutic response and/or as prognostic markers in AML.

In summary the main expected results and impact of the Dr. Rizzo research will be: *i*) identification of novel predictors of response to treatment in AML; *ii*) correlation between changes in chromatin conformation of individual promoters and clinical outcome in leukemia; *iii*) transfer of this information to clinical setting for diagnostic, prognostic and (long term) therapeutic purposes.

The major scientific accomplishment of the PI contributed to seminal publications in the cancer field and invitation in National/International Cancer Conferences. They also contributed to significant teaching/mentoring activities for the fellows involved in the research that received fellowship from FIRC, or Fondazione Veronesi, as well as the Associazione Italiana Leucemie (AIL) and Boehringer Fellowships and selection of posters as oral presentation in National/International Cancer Meetings. In the past few years, the PI was responsible for tutoring excellent undergraduate students and was supervisor of Ph.D thesis for the PhD Program in Molecular Medicine at “Sapienza” University of Rome. Presently, she is responsible for tutoring undergraduate students from “ROMA TRE” and ”Sapienza” University.

Collaborators: Access to a large number of AML patient samples and potential for designing and conducting clinical trial is made possible through the collaboration



with the Italian Cooperative GIMEMA group (Prof Francesco Lo-Coco, Associate Professor of Hematology, University Tor Vergata-Rome and national coordinator of APL biological studies in the Italian GIMEMA group). Moreover, the PI has a long lasting collaboration with Dr. Bruno Calabretta, Professor of Pathology, Università degli Studi di Modena e Reggio Emilia and Professor of Cancer Biology, Thomas Jefferson University Medical School, Philadelphia, USA. Prof. Calabretta is an investigator at the forefront of leukemia research with a long track record of basic science discoveries and a continuous focus in translating these findings in potential therapeutic applications in leukemias.

Pubblications 2012-2013

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Experimental Oncology

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Activities 2012-13

Signalling by ErbB receptors can instruct the execution of key cellular programmes such as cell survival, proliferation and motility. However, excessive ErbB signalling may disrupt tissue homeostasis and lead to cellular transformation [1].

Cells oppose a threat inherent to excessive ErbB activity by elaborating negative signals capable of limiting the strength and duration of receptor activity. Some mechanisms of negative signalling target ErbB RTKs since the inception of their activation (e.g. dephosphorylation by phosphotyrosine phosphatases and endocytosis-mediated downregulation). This is integrated over time by the activity of de novo expressed feedback inhibitors. These transcriptionally induced feedback inhibitors include LRIG1, RALT (also known as MIG6 or ERRFI1), SOCS4 and SOCS5 [2].

Our laboratory focuses on understanding the role of RALT in negative regulation of ErbB signalling. Loss and gain of function experiments in cultured cells indicate that RALT is a powerful inhibitor of biological responses downstream to ErbB RTKs, including cell division and cell locomotion [3-7]. Genetic ablation of RALT in the mouse germline causes phenotypes due to excess EGFR-driven cell proliferation in several epithelia. Remarkably, hyperplastic epithelial lesions in RALT null mice may progress to full malignancy [8]. Collectively, these studies indicate that a) RALT has an essential role in the regulation of ErbB signalling; b) RALT has the properties of a tumour suppressor.

RALT inhibits ErbB catalytic function by docking onto the receptor kinase domain via its ErbB binding region (EBR) [9,10]. In addition, RALT-bound EGFR molecules undergo endocytosis-dependent degradation despite being catalytically inert. This has been linked to RALT acting as a platform for molecular interactions with endocytic proteins such as AP-2, Intersectins and Syntaxin 8. This allows RALT to instruct EGFR to undergo clathrin-dependent endocytosis and subsequent sorting into late endosomes [11,12]. The available data are consistent with a model in which RALT acts sequentially at the cell membrane to i) nullify ligand activation of EGFR via repression of its tyrosine kinase function; b) limit subsequent cellular responses to further EGFR stimulation by reducing EGFR expression [11]. The temporally dilated impact of RALT on EGFR activity is well suited to rationalize the proposed role of RALT as key controller of ErbB mitogenic signalling in G1 [4,8]. Because kinase suppression and receptor down-regulation are the very mechanisms of action of clinically approved drugs that target ErbB receptors, the above model can also account for the tumour suppressor activity of RALT unveiled by genetic studies in mice [8].

Our present work focusses on addressing novel issues pertaining to mechanistic and regulatory aspects of RALT function in ErbB regulation and tumour suppression. Using EGFR as prevalent model system, we are investigating whether tumour cells may

circumvent the RALT anti-tumour barrier by exploiting the function of molecules/pathways known to regulate ErbB signalling in a positive fashion. Specifically, we are focussing on a) the intersections between RALT and Cytohesins in the regulation of ErbB catalytic activation; b) the role of SRC in modulating the pro-endocytic function of RALT.

Cytohesins, a family of guanyl nucleotide exhange factors (GEF) for ARF GTPases, have been shown recently to act as intracellular enhancers of EGFR catalytic activation [13]. Cytohesins appear to influence the geometry and/or orientation of EGFR asymmetric kinase dimers [13], exerting an effect opposite to that of RALT [10]. We hypothesize that EGFR occupancy by Cytohesins precludes RALT binding and vice versa. Given that the apparent affinities of RALT and ARNO (i.e. Cytohesin 2) for the EGFR were shown to be similar [13], variations of Cytohesins abundance could have a considerable impact on EGFR:RALT complex formation. According to this model, high Cytohesin expression (as detected, for instance, in lung tumours showing high EGFR activation, see ref. 13) would enhance EGFR kinase activity not only directly, but also via the indirect effect due to their ability to outcompete RALT. We are therefore investigating whether a) RALT and cytohesins compete with each other for binding onto ErbB RTKs, b) increased ratios of Cytohesin: RALT expression are detected in NSCLC, are causally linked to EGFR oncogenic signalling and may be predictive of tumour addiction to oncogenic EGFR signalling.

SRC is a downstream effector of EGFR and ERBB2. Pharmacological inhibition of SRC accelerates RALT-driven EGFR degradation. Interestingly, the adaptor protein PDLIM4, which has been recently shown to promote SRC inactivation [14], interacts with RALT in the yeast two hybrid (Y2H) assay as well as in mammalian cells. Of note, the *PDLIM4* gene is frequently hyper-methylated in human tumours [14 and references therein], which is consistent with its biological function of cell growth suppressor and its biochemical function of SRC inhibitor. The RALT:PDLIM4 physical interaction raises the possibility that RALT modulates SRC activity via PDLIM4 during endocytic traffic of EGFR:RALT complexes. Thus, we are currently investigating the role of SRC and its inhibitor PDLIM4 in RALT-dependent endocytic traffic of the EGFR.

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Experimental Oncology

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Administrative Assistant: Daniela Bona.

Activities 2012-13

In the past decade, several DNA damage response (DDR) proteins have been shown to localize to mitosis- and cytokinesis-associated organelles such as the central spindle, midbody and centrosomes. Dysfunction of these organelles promotes aneuploidy, suggesting that along with DNA caretaker activities, particular DDR proteins might contribute to ploidy maintenance by organelle-specific, non-nuclear functions. Our group has significantly contributed to this topic by discovering a centrosome activity of the p53 tumor suppressor and a midbody-associated activity of the p53 activator HIPK2. Most of the work we carry out stem from these observations.

ATM heterozygosity as a tumor-susceptibility factor in the general population: from screening to therapy

Based on our previous molecular studies on p53 subcellular localization at the centrosomes, we have developed a simple, fast, minimally invasive, reliable, and inexpensive test to determine mutant ATM zygosity. In a preliminary study, our test confirmed ATM as a breast cancer-susceptibility gene. These data open the possibility of cost-effective, early diagnosis of A-T homozygotes and large-scale screenings for heterozygotes. In fact, we are currently carrying out these types of screening in patients with lung, colon, ovarian, or breast cancer. In addition, we are utilising our test to assess whether mono-allelic mutations of ATM predispose to familial breast and ovarian cancers that carry wild-type BRCA1 and BRCA2 genes.

Development of effective cancer therapies based on functional proteomics and cancer stem cell targeting

In the process of characterizing the DNA damage response in cancer stem cells explanted from colon cancer (colon CSCs), we observed very low and non-inducible levels of HIPK2, an evolutionarily conserved S/T kinase involved in the regulation of cell survival and proliferation during development and response to genotoxic damage or hypoxia. Through adopting several alternative approaches we are testing: *i*) whether and how this aberrant HIPK2 expression/behavior might contribute to CSC resistance to anti-neoplastic treatments, *ii*) the performance in deep molecular and functional characterization of HIPK2 role in CSCs, and *iii*) the development of strategies to overcome their detrimental effects.

MeCP2 phosphorylation and related kinases (HIPK2 and CDKL5) in the Rett Syndrome

Rett syndrome (RTT) is a neurodevelopmental disorder mainly caused by mutations in the transcriptional repressor MeCP2 or in the S/T kinase CDKL5. Recently, we have demonstrated that HIPK2 is also required for proper functioning of the central nervous system, and that binds and phosphorylates MeCP2. In 2012, we published that HIPK2 localizes at the midbody and regulates abscission, the final steps of cytokinesis. In addition, we observed that also MeCP2 and CDKL5 localize at this structure. Furthermore, we observed that CDKL5 and a phosphospecific isoform of MeCP2 linked to a variant form of RTT localize at the centrosomes in dividing cells and post-mitotic neurons. Importantly, the lack of MeCP2 in cycling cells affects microtubule nucleation, increases centrosome number, forms micronuclei and dramatically reduces cell proliferation. Altogether these data imply that MeCP2, CDKL5 and HIPK2 functions might converge at the centrosome/midbody suggesting the relevance of characterizing the biological implications of this localization for genomic integrity of cycling cells and for neuronal polarization, differentiation and migration. We are now characterizing the role and impact of MeCP2, CDKL5 and HIPK2 in centrosome and midbody physiology of cycling cells and post-mitotic neurons.

Role of the putative oncosuppressor HIPK2 in cytokinesis and induction of chromosomal instability

Project Leader: Cinzia Rinaldo

After discovering the HIPK2 localization at the midbody as a senior post-doc in the PI group, Dr. Rinaldo started her own research group at the CNR and in affiliation with IRE. The aim of her study is to characterize the role played by HIPK2 in cytokinesis and its impact on cancer formation and progression. Cytokinesis

progresses through a series of temporally and spatially tightly controlled events, ultimately leading to cleavage furrow ingression, intercellular bridge formation and physical separation of the two daughter cells by abscission. Failure of cytokinesis may give rise to genetically unstable states, such as tetraploidization and multinucleation. These events can contribute to chromosomal instability and are considered early critical steps in tumor formation/progression. The goal of the study is to gain clues on the molecular mechanisms of cytokinesis and how its deregulation may impact cancer.

Serum p53 Ab detection and prognostic value in patients with impaired lung function or lung cancer

Project Leader: Manlio Mattioni

Mutations in the *TP53* gene can lead to expression of dysfunctional, overexpressed proteins and production of circulating anti-p53 antibodies (p53Abs). We assessed the possible role of p53Abs as early and/or prognostic markers in patients with impaired lung function or with lung cancer. To investigate p53Abs as early markers of the onset of lung cancer, we carried out a large prospective study (675 subjects) enrolling non-smokers, ex-smokers, and smokers with or without impairment of lung function. The levels of serum p53Abs were evaluated by ELISA and correlated with smoking habits, impairment of lung function, development of lung or other cancers. Although significant levels of serum p53Abs were detected only in a few subjects (5.2%), a strong correlation was observed with the number of cigarettes smoked per day and packs per year and with the worst lung function impairment. No difference was observed in the presence of p53Abs with regard to age and gender. At this time, no evidence of cancer was found in the fifteen p53Ab-positive subjects that joined the follow-up. In a second study, we evaluated the presence and prognostic role of p53Abs in lung cancer patients and studied whether their presence is related to mutant p53 expression in tumor tissues. A total of 201 lung cancer patients and 54 patients with non-malignant disorders were studied. Serum p53Abs were measured by ELISA and compared with data from the relative tumor samples, *i.e.*, p53 expression by immunohistochemistry (IHC) and the *TP53* gene status by direct sequencing. Serum p53Abs were found in 20.4% of lung cancer patients and correlated with p53 overexpression detected by IHC. In patients with non-small cell lung cancer, p53Abs were significantly associated with poorly differentiated tumors and their survival time was significantly shorter compared to patients without any detectable levels of p53Abs. At present, Dr Mattioni is involved in the project regarding ATM-heterozygosity (see above).

Role of hypoxia and inflammation in tumor progression of malignant mesothelioma

Project Leader: Alessandra Verdina

Malignant mesothelioma (MM) is an aggressive tumor highly resistant to radio and chemotherapy and with a very poor prognosis. MM occurs in the contest of chronic inflammation and is characterized by hypoxic areas. However, their contribution to MM progression is still largely unknown. By studying the MM cell response to hypoxic stimuli, Dr. Verdina has shown an early activation of HIF-1 alpha and NF-kB, the master regulators of hypoxia and inflammation, and the modulation of different inflammation-related genes. Silencing of HIF-1 alpha and treatment with the NF-kB inhibitor parthenolide showed that the observed modulations depend both on HIF-1 alpha and NF-kB transcriptional activity. In addition, a late induction of HIF-3 alpha, a less-characterized hypoxia responsive factor was observed. Importantly, IHC analysis of human MM samples showed, for the first time, an increased expression of HIF-3 in tumors compared to healthy tissue, and a significant correlation among high expression of HIF-3

alpha and CXCR4, a cytokine receptor associated with increased proliferation, invasion and migration, and poor survival. At present, Dr. Verdina is involved in the project on cancer stem cell targeting (see above).

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Experimental Oncology

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Activities 2012-13

Clinical Activities

The clinical activity basically focuses on a second level diagnosis of HPV and other cancer-associated viruses. In particular, the diagnosis was performed in clinical samples for the diagnosis of beta-HPV infection that are not detected by commercially available tests and for determining viral expression as well as for analysising uncommon or unconventional tissue specimen. Other cancer-associated DNA viruses were also analyzed, particularly, the diagnosis focused on polyomaviruses that are emerging as new infectious agents in cancer development.
More than 200 samples (such as Finalized Research grants and Corporate tariffs) were analyzed. The majority of samples consisted of biopsies from skin, oral cavity, and genital/perianal areas. In addition, a new clinical activity was programmed for the HPV vaccination in males.
All the staff members were also involved in the activity of HPH-UNIT. Within the activity of the HPV-UNIT, a multidisciplinary unit gathered professionals from the dermatology and oncology units. The staff provided their expertise in viral typing in uncommon or unconventional tissue specimen, clinical interpretation of molecular data from assay test, advice in evaluating clinical cases by clinical teams ,out patient counseling and advice.

Research Activities

The scientific activities of the S.C. Virology Unit were focused on basic and translational research regarding virus–associated cancers and on other degenerative non neoplastic diseases.

Molecular mechanisms in HPV Carcinogenesis.

Animal models

New orthotopic mouse models for HPV-associated tumours in the cervix and in oropharynx are under development. We succeeded in creating an orthotopic mouse model for HPV-related oral tumors, a subset of HN tumors for which no models have been generated before. The model was obtained by inducing the stable expression of the HPV16 E7 protein into the mouse oral squamous cell carcinoma (OSCC) AT-84 (AT-84 E7). The AT-84 E7 cells were injected into the mouth pavement of C3H mice via an extra-oral route to obtain orthotopic tumors. The model turned out to mimic the natural history of the human HPV oral cancer. From AT-84 E7, through to engineering and expressing luciferase, the bioluminescent AT-84 E7-Luc cells were obtained for a fast and easy monitoring via imaging. The proposed tumor model is easy to handle and reproduce and it is effective in monitoring immunotherapy. Furthermore, it is expected to be more predictive of clinical outcome of therapeutic vaccines than non-orthotopic models that are currently used. Finally, imaging offers unique opportunities to predict formulation efficacy through measuring tumor growth *in vivo.*

New function of HPV-16 E2 protein in carcinogenesis: interaction with ErbB receptor family

HPV and cellular ErbB family expression was compared in early (episomal HPV) and late passages (integrated HPV) of W12 cells. ErbB-3 receptor expression was strongly reduced in late passages. Since E2 and E5 viral genes are lost by integration, reconstitution experiments were performed showing that only the E2 gene can restore the ErbB-3 expression. HPV 16 E2 can modulate ErbB-3 by interacting with the ubiquitin ligase Nrdp-1 that is involved in the regulation of this receptor.

The link between HPV16 and oxidative stress

A study was carried out to produce data on the possible relevance of oxidative stress in the HPV16 carcinogenesis. In comparing the proteomic and redox proteomic pattern of HPV16 positive tissues in cervical high grade dysplastic lesions with one neoplastic lesion, a number of observations were reported. The proteins ERp57 and GST both involved in unfolding /refolding proteins (a repairing mechanism for oxidatively misfolded proteins) were sharply elevated in dysplastic and neoplastic tissues. The Thioredoxin reductase 2 (TrxR2) peaked in dysplastic samples

while iNOS was progressively reduced in dysplastic and neoplastic samples. By using the redox proteomic approach, five proteins were found to have increasing levels of carbonyls in dysplastic samples compared to controls namely: cytokeratin 6, actin, cornulin, retinal dehydrogenase and GAPDH. In carcinoma samples, the peptidyl-prolyl cis-trans isomerase A, ERp57, serpin B3, Annexin 2 and GAPDH were found less oxidized than in dysplastic tissues. Overall, these results suggest that HPV16 neoplastic progression is associated with an endocellular environment with increased oxidizing potentials contributing to a conducive environment for neoplastic progression. Conversely, full neoplastic tissues seem to attain an improved control over oxidative damage as shown by the selective, comparative reduction of carbonyl adducts on key detoxifying/prosurvival proteins which makes them decidedly suitable with the highly oxidative, uncomfortable metabolic environment.

Molecular epidemiology of HPV types.

Genital tumours

The performance of different methods currently used for virological evaluation of cervical cytological sample has been assayed in a cohort of 281 women. The final results indicate that discordant results are obtained with different HPV tests. The standardization of type-specific sensitivity and accuracy of genotyping methods are thus urgently needed in order to use genotyping assays in cervical cancer screening programs.

For unknown reasons, HPV58 accounts for a significant proportion of cervical cancers in East Asia and parts of Latin America, but it is uncommon elsewhere. Through an international collaborative study, E6 and E7 genes obtained from HPV58 samples from around the world were examined. The HPV58 variant containing T20I and G63S substitutions in E7 had a greater risk of developing cancer. This variant was also more prevalent in Asia than in other regions, and may therefore help to explain the higher disease burden observed in this region.

Extra-genital tumors

Studies were performed in two main areas the oro-pharyngeal cavity and the skin. HPV associated Head/Neck (H/N) tumors are a subset of tumours that may have a well defined behavior and analyses were performed in order to define the types of HPV in the oro-pharyngeal localizations and the viral expression. To determine the HPV type specific prevalence in different samples collected from the oral cavity of three groups of patients: (A) healthy; (B) non-malignant lesions; and (C) cancers. Mucosal HPV types were associated with the presence of cancers. This trend was statistically significant if the analysis was performed for HPV 16 ($p=0.04$), which is the most prevalent type detected in oropharyngeal cancers. Conversely, cutaneous HPVs were associated with non-malignant lesions ($p=0.007$). The multiple correspondence analysis confirmed these data. Viral transcripts of only mucosal HPVs were detected in non-malignant lesions and cancers. In conclusion, different types of HPVs infect the oral epithelium, but only the mucosal types, particularly HPV 16, are clearly associated with tumors. The discovery that cutaneous HPVs are associated with potential malignant oral disorders brings other data to understand the significance of their presence in the oral cavity.

The oncogenic role of cutaneous HPV in skin cancer is still a controversial issue. In a large study investigating basal skin carcinoma (BSC), we demonstrated that p16INK4a and pAkt are over-expressed in BCC and that the high expression of p16INK4a and of Akt2 isoform is often associated with the presence HPV 15 suggesting that the beta-HPV species 2 may exert a role in the BCC carcinogenesis as well as in other, still undefined, biological property of these tumors. If this particular type of BCC reflects a different biology, it will remain undisclosed until further studies. To date, there have been only a few studies that investigated integration (a key marker of cancer progression) of anal Human Papillomavirus (HPV). We aimed to investigate HPV physical status in HIV-negative men who have sex with men (MSM) with a detectable anal HPV infection, irrespective of the presence of lesions. We also sought to explore the presence of other circular DNA viruses in the anal region. Integration was observed only in one HPV16-positive sample (0.9%), in which integrate-derived viral transcripts were detected. Integration occurred in chromosome 14 q. In 22 of the 53 (41.5%) mucosal HPV-negative samples, RCA restriction results would seem to indicate the presence of circular DNA viruses. Indeed, cutaneous HPV (4 samples), MCPyV (5 samples)

and TTV (4 samples) were detected. The significance of this last occurrence needs to be assessed.

Immunotherapy of HPV-associated cancers.

In a search of innovative methodologies for the production of therapeutic vaccines against HPV associated pre-neoplasia and cancer the production of the E7-based therapeutic vaccine was achieved in Chlamydomonas reinhardtii, an organism easy to grow and transform and fully amenable to GMP guidelines.

The E7 antigen was mostly soluble and reached 0.12% of total soluble proteins and was able to induce specific anti-E7 IgGs and E7-specific T-cell proliferation suggesting that the C reinhardtii chloroplast is a suitable expression system for the production of the E7GGG protein, in a soluble, immunogenic form. The production in contained and sterile conditions highlights the potential of microalgae as alternative platforms for the production of vaccines for human uses.

In another study, heterologous prime-boost schedule was utilized to improve efficacy of genetic vaccines. In this study, DNA or Fowlpox (FP) virus recombinants expressing the harmless variant E7GGG of the HPV-16 E7 oncoprotein [DNA(E7GGG) and FP(E7GGG)] were generated. The results obtained established a preliminary indication for therapy of HPV-related tumors by the combined use of DNA and avipox recombinants, which might represent safer immunogens than vaccinia-based vaccines. Finally a totally new approach to the immunotherapy of HPV-associated cancer was developed by using specific antibodies in a single-chain format expressed as intracellular antibodies (intrabodies). We tested the M2SD intrabody for the antitumor activity in two mouse models for HPV tumors based respectively on TC-1 and C3 tumor cells. In both models, a marked delay of tumor onset with respect to the controls was observed in all the treated mice and, importantly, a significant percentage of mice remained tumor-free permanently. This is the first in vivo demonstration of the antitumor activity of an intrabody directed towards an HPV oncoprotein.

Non neoplastic degenerative diseases. A reverse model for cancer research.

A number of collaborative research studies were carried out on non-neoplastic degenerative metabolic and neurological disorders including Multiple Sclerosis (MS). This is an autoimmune progressively invalidating disorder whose pathogenesis is strongly associated with Oxidative Stress damage. Surprisingly, MS is statistically linked with an association to solid tumours. Consistently, a MS Regional Reference Unit is located within this Institute. Thanks to the collaboration of this MS Unit a Redox protomic evaluation of sera form MS patients was done. The results indicate that a number of oxidized proteins found in MS correlated with some aspects of the clinical course of the pathology. Interestingly, remission phases seemed to be associated with a ‘‘healthy-like’’ condition where apparently almost no significant accumulation of oxidative damage occurs. Thus, it was hypothesized that during remission OS occurs at an inadequate level for immediate toxic effect. Nonetheless, it is still able to initiate a cascade of reactions progressively impairing several proteins that eventually ignite the relapse outburst. Other collaborative research studies also focused on the factors driving stem cells homing in wound repair and cancer metastasis and on the risk of re-stenosis in artificial stent positioning.

Publications 2012-2013

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SERVICES DEPARTMENT

Services Department

Laboratory of Medical Physics and Expert Systems

Lidia Strigari, MP

Director

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Engineer: Chiara Forina
Researchers: Gianluca Bossi PhD, Silvia Baldari PhD, Valentina Ubertini PhD,
Trainees: Silvia Minosse, Sara Ungania
Technicians: Giampiero Carlino, Sandro Carpino, Stefano Luppino, Sandro Nocentini, Massimo Pedrini

Activities 2012-13

Clinical Activities

The Laboratory of Medical Physics and Expert Systems (in the following named Lab) supports different Departments using ionizing and non-ionizing radiation. In particular, it supports the Radiotherapy Department developing personalized treatment plans for treated patients. Clinical treatments included: conventional External Beam Radiation Therapy (EBRT); intra-operative RT (IORT) on head and neck, breast cancer, prostate cancer and sarcoma; intensity modulated RT (IMRT/VMAT); mono and or/ multi-institutional hypofractionated studies (on breast cancer, prostate cancer and primary or metastatic lung tumour).
The Lab verifies the administered treatments by daily monitoring devices, with patient-specific dosimetric verification using both commercial and self-developed software.
When appropriate, RT treatments are based on image fusion studies in order to combine multimodality images and radiobiological models to assess the dose-effect relationship, as reported in the following paragraphs.
The Lab provides support to the Nuclear Medicine Department concerning patient-specific dosimetry aiming to optimise the dose administration activity in order to improve tumour control, sparing normal tissue (red marrow, liver, kidneys, etc.).
The Lab cooperates with the Radiology Department regarding image analysis and determination of quantitative predictors useful in daily clinical practice. In particular, the Lab uses specific software to determine quantitative data from imaging, to perform image fusion and to improve the predictive capability of imaging, by introducing quantitative methods for diagnostic imaging. The Lab is currently developing software dedicated to specifically improve the diagnostic ability of medical imaging based on the full DICOM information.
The Lab carries out measurements directed at reducing unjustified doses to patients and third parties (family members and population).
The Lab is also involved in the radioprotection of patients and workers, which is ensured by quality assurance programs and by the management of radioprotection from physical agents.
In particular, the Lab supervises the use of devices producing ionizing and non ionizing radiations which could be potentially dangerous for workers. The main aim of this activity is to reduce the risks maintaining a level of safety in accordance with the standard request by technical regulation, checking/estimating the absorbed doses, planning and acting appropriate procedures and methods.

Research Activities

The Lab is involved in preparing protocols to conduct clinical trials and perform data analyses of clinical and dosimetric results, such as:

- the impact of adaptive radiotherapy in the treatment of pelvic disease;
- the implementation of strategies for accumulated dose calculation in radiotherapy of head and neck cancer;
- the assessment of dosimetric predictors of radiation-induced side effects or tumor control in breast, head and neck or prostate cancer patients treated with accelerated or hypofractionated or SBRT radiotherapy;
- the use of functional imaging, molecular markers and/or radiobiological modelling to predict the response to radiotherapy in head and neck or brain cancer;
- the impact of single nucleotide polymorphisms (SNP) in discriminating patients with/without toxicity after partial breast irradiation;
- the impact of prognostic gene on tumor control and survival;
- the use of miRNA in prostate cancer to assess the tumor control;
- the abscopal effect in radiotherapy;
- the impact on tumor control of tumor re-oxygenation during SBRT.

The Lab. has studied the effect of tissue heterogeneity in dose calculation, and has developed a tool for automatic calculation of biologically equivalent fractionation schedules in radiotherapy using modulated treatments with a simultaneous integrated boost technique.

The Lab is involving in optimising the RT approaches by comparing different methodologies for dose assessment in high dose/fraction RT. The Lab cooperates with ENEA and ISS in the evaluation of unflattened beams effect in terms of response of measurement devices to delivered dose at different dose-rate, response of out-of-field tissues. It is also involved in preclinical studies to identify novel molecular markers with prognostic significance.

The Lab supports Nuclear Medicine Department for developing innovative dosimetric methods to optimise the dose administration activity or estimate doses to tumour and normal tissues (red marrow, liver, kidneys, etc.). Dr. Strigari is involved in the development of the European guidelines on nuclear medicine dosimetry and she is currently a member of Dosimetry Committee of EANM.

Moreover, the Lab performs Monte Carlo simulations to calculate 3D-dose distributions, and it investigates predictive radiobiological

models for radiotherapy and nuclear medicine. Novel models have also been recently published.
The Lab supports the Radiology Department for image comparison and determination of quantitative predictors useful in daily clinical practice. Quantitative methods have been applied to the sonographic-based elastography under real-time (RTE) conditions, which has proven to be able to measure and evidence the alteration in tissue elasticity (due to the increase of cell density of breast tumours compared to the surrounding normal tissues). Patient images have been exported and analysed with dedicated software developed within the Lab, to delineate the regions of interest and to quantify some parameters. A significant correlation has been found between the diagnosis given by RTE and the biopsy. A study on functional imaging (CT perfusion) in cerebral lesions has been conducted. Studies on the role of combined imaging modalities in tumour staging are still on going to improve therapy in extra cerebral district. The Lab also co-operates in the optimisation of inter-departmental computer networks.
In order to achieve high quality standards in the use of devices based on ionising radiation, the Lab co-operates with other Departments in the maintenance and realisation of quality assurance programmes on equipment using ionising and non-ionising radiation.
The Lab is involved in a project regarding proton therapy with ENEA and ISS; and in the development of a hybrid device for IORT.

The wtp53 roles in Radiation-therapy induced abscopal effects

The indirect anticancer abscopal effects (AE) of radiation-therapy (RT) have been clinically observed in areas separated from the irradiated (IR) tissue in many human malignancies since 1952. Moreover, recent studies demonstrated for the first time in vivo that wtp53 is required to induce antitumor AE. At present, however, the molecular mechanisms behind AE are unknown. During 2012, we identified and characterized an experimental model of RT induced AE. We generated wtp53 or p53-null HCT116 xenograft tumors in both flanks of nude mice, and a dose of 10 or 20Gy (IR groups) was delivered to a tumour established in one side flank, leaving the other non-irradiated (NIR groups). Irradiation was performed, under strict dose monitoring, with a dedicated mobile accelerator designed for intra-Operative-RT (IORT). We found that along with reduced growth of directly-irradiated tumours, a significant effect was found in NIR wtp53 tumours in the 20Gy-irradiation group, with a moderate effect also evident after 10Gy-irradiation. On the contrary, no significant difference was observed in the NIR p53-null tumours independently from delivered doses. Results suggested that the interplay between delivered dose and p53 status might help to sterilize out-of-field tumour cells.
Future aims.

- Explore RT induced AE in more suitable disease for RT treatments as prostate cancer
- Identify the RT induced AE
- Identify molecular and cellular mediators involved RT induced oncosuppressive AE

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Department of Services

Unit of Psychiatry

Tonino Cantelmi, Psychiatrist

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Nurse: Rosa Parlagreco
Administration Staff: Pietro Capogna, Maria Maiorano
Scientific editor: Lesley Pritikin

Activities 2012-2013

Clinical Activities

- Specialist psychiatric consultations
- Cognitive-Interpersonal psychotherapy
- EMDR psychotherapy
- Psycho-neuro-oncology (EEG, neurological examination, memory and executive functions testing, training for cognitive disorders, evoked potentials, Electromyography) and Centre for the therapy of Tumor-related Epilepsy (Clinical performances, Instrumental analysis, Rehabilitation Training)

- Group therapy for clients, employees and volunteers (social dreaming)
- Psychiatric consultations in healthcare
- Support humanization activities
- Occupational medicine psychiatric support
- Support activities to the Regional Center for Transplants
- Support activities for Bank Ovarian Tissue - IRE
- Support activities for Musculoskeletal Tissue Bank
- Support activities and volunteer training
- Spiritual coping
- Epilepsy and Quality of life Support

Research Activities

- Psoriasis and depression (Research Protocol*:* Evaluation through High-resolution Magnetic resonance imaging (RMN 3 tesla) of the Morpho-functional alterations of the brain specific areas in psoriatic patients, with or without Major Depression (MMD). A pilot study)
- Quality of life and tumor-related epilepsy

Agreements for apprenticeships

- Training in Cognitive-Interpersonal Psychotherapy - SCINT (MIUR)
- Training in Cognitive-Behavioral Psychotherapy Scuola di Specializzazione in Psicoterapia Cognitivo- Comportamentale – Skinner (MIUR)

Publications 2013

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Services Department

Unit of Psychology

Patrizia Pugliese, Psychologist

Director

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Activities 2012-13

Clinical Activities

The clinical objectives of the Unit of Psychology are focused on prevention, treatment and rehabilitation of psychological distress and on quality of life in all the phases of the disease.

The main clinical approach used to achieve these objectives is through combining psychological and medical care plans (i.e. permanent presence of psychologists in epatobiliopancreatic, breast, prostate, orthopedic, oncoematologic and head and neck disease management team – DMT, and in the departments of oncology and dermatology) aimed to decrease both psychological suffering and direct and indirect costs. The team of psychologists belonging to this Unit also uses more traditional interventions such as individual, group, couple and family psychotherapy sessions tailoring to the needs of the patient and/or family members. In addition, the clinical activities include the intervention of a psychologist in the doctor-patient relationship, the psychologist is present in the event of a crisis as well as providing telephone support.

Other activities pursued by the Unit of Psychology combine treatment with support from psychologists and other professionals involved in the health-care setting (nurses and volunteers), creating a network of psychologists in the Lazio Region, that work in various hospitals and local health care centres.

This Service Unit also makes use of personnel trained to the psycho-oncological issues under the supervision of the director.

This Unit's scientific productivity is in line with the budget negotiation for the biennium 2012/2013.

In accordance with the humanization project pursued by the Institute the Unit also seeks customer satisfaction, where it has achieved 99% in patient satisfaction.

Research Activities

The main research activities conducted during 2012-2013 were based primarily on psychological distress, quality of life, information and translational studies.

Quality of life study

"Miglioramento della qualità dell'assistenza nella pratica clinica quotidiana – percorsi psicologici diagnostico-terapeutici"

Neoplastic diseases can have a significant impact on the emotional, social, sexual functioning and mental health of patients (35% - 40%) and their family (20% - 71%).

Unmet psychological needs in patients are associated with a worse quality of life (QoL), a greater risk of psychological distress in the family, lower adherence to therapy, a worse doctor-patient relationship, an increase in recovery, rehabilitation and hospitalization times, lower biological effectiveness of oncological therapy, shorter survival and an increased risk of disease recurrence.

The aim of the project is to enhance quality of care through experimenting psychological paths in daily clinical practice that focus on improving distress and the QoL of patients and their relatives.
The psychological paths are centered on the following: routine psychological distress assessments, psychological therapy within the medical care plan, improving information and doctor-patient communication, and responding to the needs of patients and their family with advanced disease.
Investigating psychological distress with the Distress Thermometer (DT 0-10) was performed on 294 patients enrolled at the Breast Surgery and Breast Medical Oncology Department, Epatobiliopancreatic Surgery Department and Department of Orthopedics.
The results showed levels of distress >4 (cut-off) in 153 patients. 70% of these risk patients received early psychological treatment with an 67% improvement level of distress.
For improving doctor-patient communication a checklist of questions was validated in a pilot study of 20 patients and 15 health professionals.
An educational workshop for professionals specializing in hepatobiliary surgery was developed.

"Valutazione e miglioramento della qualità dell'assistenza in pazienti da sottoporre a trattamenti di terapia radiometabolica".
The project is part of a institutional long-term process carried out in collaboration between the Unit of Psychology and the Unit of Nuclear Medicine in patients with thyroid cancer undergoing isolation and radionuclide therapy.
The aims of the project are:
- to assess the psychological variables (such as the experiences, behaviors, coping style and

situational anxiety aroused by isolation and cancer treatment)
- improving quality of care through communication interventions aimed at
- reducing psychological distress and through psychological support for risk patients.
To date, 40 patients have been enrolled.

Translational study

"Epigenetic control of breast cancer progression: animal and clinical studies"
The project was carried out in collaboration with Medical Oncology Department of Regina Elena National Cancer Institute and ISS (Istituto Superiore di Sanità).
Initial and progressive stages of carcinogenesis are affected by both genetic and environmental factors. Stress in particular is known to unleash a cascade of events with multiple effects on both central and peripheral targets, leading to cancer. Critical changes in cell genome, such as silencing of tumor-suppressor genes, activation of oncogenes and defects in DNA repair, are caused not only by mutagenetic but also by epigenomic mechanisms influenced by environmental stimuli. Epidemiological studies have revealed that lack of social support increases the risk of death associated with several chronic diseases.
Often an underestimated factor is that the tumor itself can induce depressive symptoms through producing humoral factors, such as cytokines, affecting brain function, and worsening prognosis. Despite clear evidence for a potential physiological connection among social environment/phychological factors, neuroendocrine stress response, tumor gene expression and phenotype, the precise molecular consequences of a stressful environment have not been defined.
The main aim of the project is to elucidate the molecular mechanisms involved in the effects of stress on breast cancer progression by investigating its role in animal models of breast cancer and in breast cancer patients, characterized by a high risk for relapse.
Since July 2012, the clinical study has enrolled 65 women (mean age = 50.5). At follow-up, 28 women were reassessed.
At baseline, 32% of women showed moderate-severe levels of depression, high state anxiety, 34.4% a post-traumatic stress disorder, 50% a positive coping strategy and 78% support from a life-partner/spouse. After undergoing chemotherapy, women showed an increase in depression levels, a decrease in anxiety levels and in post-traumatic stress disorder, a stable positive coping strategy and vital emotional support.
From a physiological point of view, a significant change in cortisol levels after 6 months from surgery was found in all subjects, with increased levels of cortisol throughout the day suggesting a state of chronic stress. After six months of chemotherapy, we found an increased level of the chemokine MIP-1b LFA-IV which has been suggested not to only have tumor-promoting roles but also to be directly related with a poor prognosis. Moreover, in some patients, an interesting increment of G-CSF involved in differentiation and function of neutrophil precursors, was found. By contrast, after treatment, breast cancer patients showed decreased levels of the pro-inflammatory cytokine IL-17.
The activities planned for 2014 include: a control group of women waiting to perform the mammotome biopsy system for detecting breast cancer.
The study "Stile di vita come fattore di rischio nella progressione del tumore al seno: indagine sui biomarcatori neuroendocrini e molecolari dello stress" (Ricerca finalizzata 2012 Fondazione Umberto Veronesi) proposes the same aims of the previous study and funding are used to perform a follow-up on the breast cancer patients already enrolled at the IRE in order to detect relapses.

Informational study

The study "Strategie sinergiche per la salvaguardia della fertilità nei pazienti oncologici: approccio integrato tra medicina della riproduzione e istituzioni", coordinated

by Centro di PMA (Procreazione Medicalmente Assistita) dell'Ospedale San Raffaele – Milano in collaboration with Istituto Superiore di Sanità (ISS), Associazione Italiana Malati di Cancro (AIMaC) and Psychology Unit, ended in May 2013. The project encompassed both an experimental and epidemiological aims. The first investigated the optimal methods of cryopreservation in female gametes and their clinical application in cancer patients. The second concerned the level of information received from patients regarding the possibility in preserving fertility before applying antineoplastic treatments. For this latter aim, the Psychology Unit submitted 52 questionnaires to breast cancer patients emphasizing the low level of information received.

Publications 2013

Grassi L, Johansen C, Annunziata MA, Capovilla E, Costantini A, Gritti P, Torta R, Bellani M; Italian Society of Psycho-Oncology Distress Thermometer Study Group. Screening for distress in cancer patients: a multicenter, nationwide study in Italy. Cancer. 2013 May 1;119(9):1714-21.

EDUCATIONAL PROGRAMS

Educational Programs

Unit of Education and Training

Anita Caruso, Psychologist

Director

STAFF Psychologist: Antonia Tramontana
Administrative Assistant: Massimo Bisozzi, Sabrina Del Pesco, Lucia Migliaccio
Nurse: Emilia Marsala

Activities 2012-13

Clinical Activities

Ongoing professional development/training is one of the strategic tools or resources used for encouraging and supporting the improvement of health care assistance offered to citizens. The aim of this continued training is to meet the needs of the organizational culture and to deepen, develop and update specific professional skills and knowledge of operational processes, as well as to promote the continuous training in medical education (CME). The professional approach adopted must be able to welcome and cope with the rapid and continuous development of medicine alongside managerial, technological and organizational innovations.

Continued medical education guarantees individual physicians to meet and match their types of training needs to the needs of the organization within the context of the specific healthcare profession.

The development of continued training involves and encourages opportunities for health care professionals to share experiences and participate in discussions favouring and shaping the healthcare workers' attitude and behavior, as well as medical procedures and healthcare pathways all aimed at reaching excellence in health care.

Training healthcare personnel provides support to the Hospital Medical Offices who are in charge of improving the technical, managerial and behavioral skills of the healthcare professionals in addition to enhancing innovative management, organizational and technological skills.

Hospital Physiotherapy Institutes (IFO) received accreditation as a sole health provider on 16 May, 2011.

The accreditation of a provider means that an institute is recognized as an active and qualified body in the field of medical education, that is authorised to carry out training activities recognized for Continuing Medical Education (CME), assigning credit points directly to participants.

The actual body of IFO is made up of the Regina Elena National Cancer Institute and San Gallicano Dermatological Institute that deal with educational activities through accreditation events offered to internal and external healthcare personnel.

The IFO Institute aims to promote education & training and updating activities tailored to developing the skills of healthcare professionals in order to guarantee quality performance in individual-centered healthcare service.

The corporate training strategies aim to:

- Shift from an exclusively theoretical training approach to a more practical approach where the methodology of "continued professional development" is put into practice, representing a real opportunity for health professionals to implement their skills in their real workplace environment.
- Transform the acquired CME credits from simply a matter of numbers to actual quality opportunities;
- Build the ECM system through the development of credit points earned.

Internal and external healthcare professionals and administrative support health care staff of the Institute are the direct recipients of the CME training courses.
The training activities consist of info-training

actions and tools carried out through residential training methods. These also include the use of interactive classroom techniques and/or practical work (role-play, group work, and exercises.

The educational objectives of the Institute met the aims AGENAS established for 2012 - 2013 which were:

1. Accreditation of healthcare Organisations and professionals. Building a culture of quality.
2. Applying the principles and procedures of evidence-based medicine in daily practice (EBM - ebn - ebp).
3. Social aspects (internal and external communication with patients) and the humanization of healthcare.
4. Technical and vocational content (knowledge and skills) specific to each profession, specialization and super-specialistic activity
5. An integrated inter-professional and multi-professional, inter-institutional education.
6. Patient safety
7. Guidelines - protocols - procedures - clinical documentation
8. Healthcare Management. Managing innovative and experimental organizational and management models
9. Clinical healthcare courses/diagnostic/ rehabilitation, assistance profile and healthcare treatment profiles.
10. Food safety and/or related conditions
11. Environmental Safety and Safety in the workplace and/or related conditions.

Educational activities targeting healthcare professionals involve:

Doctors, dentists, pharmacists, biologists, chemists, psychologists, physicists, health-

assistants, dietitians, physical therapists, professional educators, nurses, pediatric nurses, speech therapists, orthoptists, Midwives/or pathophysiology technicians of cardiovascular and cardiovascular perfusion, biomedical laboratory sanitary technicians, radiology technicians, audiometry technicians, audiology technicians, neurophysiology technicians, orthopedic technicians, psychiatric rehabilitation technicians, technicians for environmental and workplace prevention, technicians for neurodevelopmental and psychomotor skills in infants, and veterinarians. IFO contains a Congress Center "Raffaele Bastianelli" which hosts cultural, scientific and educational activities. It is located within the IFO Institute. It has three conference rooms and is equipped with audiovisual d computer technology.
In addition, several educational activities take place within the rooms located in the Library and in the Operating theatres within the Institute.

The data relating to training activities carried out in the years 2012 - 2013 are shown in the tables below:

Year 2012

Number of events produced	70
Number of hours for learning activities	887
Total number of credits assigned to participants	19,924
Total number of participants with award credits	1,020
Total number of participants without assigning credits	402
Total number of credits allocated to teachers	1,700
Total number of teachers with assignment credits	200
Total number of teachers without assigning credits	125

The number of participants and teachers was calculated by applying the tax code only.

Total number of credits assigned to participants and teachers	21.624

Year 2013

Number of events produced	63
Number of hours for learning activities	793
Total number of credits assigned to participants	18068.6
Total number of participants with award credits	768
Total number of participants without assigning credits	234
Total number of credits allocated to teachers	2.957
Total number of teachers with assignment credits	197
Total number of teachers without assigning credits	52

The number of participants and teachers was calculated by applying the tax code only.

Total number of credits assigned to participants and faculty	21025.6

Pubblications 2012

Caruso A., Vigna C. Aspetti psicologici del counseling genetico per i tumori ereditari della mammella e dell'ovaio: a pratica clinica e la ricerca scientifica in Italia. Link, 2012,(1):12-18

Caruso A., Vigna C. Bigazzi V., Sperduti I., Bongiorno L., Allocca A. Burnout among physicians and nurses working in oncology. Il burnout di medici e infermieri che lavorano in ambito oncologico Medicina del lavoro. 2012,103,(2):96-105

Caruso A., Bigazzi V., Tramontana A., Bonaventura S. Burnout and Psychological Training for Clinical Staff in Oncology. Neuropathological Diseases 2012, 2 (1): 131-144

Caruso A. "Communication skills training programme for physicians in reducing patients' distress" Abstract Book XXX International Congress of Psychology, 2012 July 22–27, 457- 458

ISTITUTIONAL COURSES CLINICAL TRIALS AND PUBLICATIONS

Istitutional Courses 2012

In 2012 IRE organized 62 training events, up to a total of: 1029,5 ECM credits, 1821 attending people, 133 training days.

* Ed = Edition, § PI = Principal Investigator

N.	Ed*	Title	Dates	Credits	PI§
1	1	Percorsi riabilitativi in oncologia:la risposta interdisciplinare ai bisogni dei pazienti	12/01/2012 14/01/2012	18	Patrizia Pugliese
2	1	Malattia dolore nel paziente oncologico	16/01/2012 16/01/2012	9	Lamberto Laurenzi
3	1	Il mobbing in ambito sanitario:fenomeno psicosociale	30/01/2012 30/01/2012	11	Anita Caruso
4	1	Chirurgia tiroidea	7/02/2012 9/02/2012	39,3	Giuseppe Spriano
5	2	Malattia dolore nel paziente oncologico	16/02/2012 16/02/2012	9	Lamberto Laurenzi
6	1	Guida all'inserimento del tslb neoassunto e dello studente in formazione	24/02/2012 24/02/2012	12	Marco Zucchiatti
7	1	Il tutor clinico:guida all'inserimento del neoassunto e dello studente in formazione	05/03/2012 06/03/2012	19	Albina Paterniani
8	1	Prendersi cura. Risonanze emotive dell'operatore di fronte alla persona malata – i livello	07/03/2012 28/03/2012	33,5	Anita Caruso
9	1	Mediatore professionista integrato col modulo "il conflitto tr a operatori di struttura sanitaria e pazienti, con particolare attenzione alla responsabilita' medica"	08/03/2012 19/03/2012	50	Alessandra Chianesi
10	1	Il centro di sterilizzazione: la tracciabilita'del processo di sterilizzazione come indicatore di qualita' e sicurezza	10/03/2012 10/03/2012	10,3	Gabriella Angeloni
11	3	Malattia dolore nel paziente oncologico	15/03/2012 15/03/2012	9	Lamberto Laurenzi
12	2	Nursing degli accessi venosi	27/03/2012	12	Silvia

		centrali e sistemi midline	27/03/2012		Lolli
13	2	Guida all'inserimento del tslb neoassunto e dello studente in formazione	30/03/2012 30/03/2012	12	Marco Zucchiatti
14	1	La terapia medica dei tumori e la cardiotossicita':diagnostica convenzionale avanzata, possibili applicazioni	12/04/2011 12/04/2011	4	Francesco Rulli
15	1	Principi fisici e tecnici della formazione dell'imaging in rm	13/04/2012 14/04/2012	13,3	Elisa Tommasini
16	1	Nursing degli accessi venosi centrali e sistemi midline	17/04/2012 17/04/2012	12	Silvia Lolli
17	1	Abilita' comunicative e gestione del reclamo	19/04/2012 19/04/2012	11	Anita Caruso
18	4	Malattia dolore nel paziente oncologico	20/04/2012 20/04/2012	9	Lamberto Laurenzi
19	3	Guida all'inserimento del tslb neoassunto e dello studente in formazione	27/04/2012 27/04/2012	12	Marco Zucchiatti
20	2	Principi fisici e tecnici della formazione dell'imaging in rm	04/05/2012 05/05/2012	13,3	Elisa Tommasini
21	1	Corso base sulla metodologia della ricerca	07/05/2012 21/05/2012	20,5	Laura Iacorossi
22	1	Aspetti biologici e aspetti relazionali:dal curare al prendersi cura	07/05/2012 09/05/2012	32,7	Anita Caruso
23	1	Innovation on minimally invasive surgery in ginecology. Up to date	07/05/2012 08/05/2012	26	Enrico Vizza
24	1	Corso di formazione radioprotezione di operatori e pazienti in radiologia interventistica	09/05/2012 09/05/2012	6,5	Lidia Strigari
25	1	Corso di informazione in materia di radioprotezione	10/05/2012 10/05/2012	5	Lidia Strigari
26	3	Nursing degli accessi venosi centrali e sistemi midline	10/05/2012 10/05/2012	12	Silvia Lolli

27	1	Il contesto familiare e le dinamiche emotive degli operatori in ambito oncologico	14/05/2012 16/05/2012	33	Anita Caruso
28	1	Corso di formazione radioprotezione di operatori e pazienti in radioterapia	15/05/2012 15/05/2012	6,5	Lidia Strigari
29	1	Monitorizzzazione emodinamica del paziente chirurgico. Pro e contro	15/05/2012 15/05/2012	6,2	Ester Maria Alba Forestiere
30	1	Corso di formazione radioprotezione di operatori e pazienti in medicina nucleare	17/05/2012 17/05/2012	6,5	Lidia Strigari
31	2	Corso di informazione in materia di radioprotezione	22/05/2012 22/05/2012	5	Lidia Strigari
32	5	Malattia dolore nel paziente oncologico	22/05/2012 22/05/2012	9	Lamberto Laurenzi
33	1	Corso di formazione radioprotezione di operatori e pazienti in sala operatoria	24/05/2012 24/05/2012	6,5	Lidia Strigari
34	4	Guida all'inserimento del tslb neoassunto e dello studente in formazione	25/05/2012 25/05/2012	12	Marco Zucchiatti
35	1	Abuso Cronico Di Alcol:Rischio Per La Sicurezza, l'incolumita' E La Salute Di Terzi. La Sorveglianza Sanitaria Negli Operatori Sanitari	28/05/2012 28/05/2012	3,5	Alessandro Cataldo
36	2	Corso di formazione radioprotezione di operatori e pazienti in radioterapia	29/05/2012 29/05/2012	6,5	Lidia Strigari
37	2	Corso di formazione radioprotezione di operatori e pazienti in radiologia interventistica	30/05/2012 30/05/2012	6,5	Lidia Strigari
38	1	La comunicazione di cattive notizie	07/06/2012 07/06/2012	11,3	Anita Caruso
39	1	Valutazione del rischio da agenti chimici pericolosi e valutazione dell'esposizione da agenti cancerogeni e/o mutageni ai sensi del d.lgs 81-09/04/2008	11/06/2012 12/06/2012	15,2	Annalucia Cinquina

40	2	Corso di formazione radioprotezione di operatori e pazienti in sala operatoria	13/06/2012 13/06/2012	6,5	Lidia Strigari
41	2	Corso di formazione radioprotezione di operatori e pazienti in medicina nucleare	14/06/2012 14/06/2012	6,5	Lidia Strigari
42	1	Chirurgia parotidea	19/06/2012 21/06/2012	43,3	Giuseppe Spriano
43	1	La Qualita' Delle Relazioni Degli Operatori Per l'umanizzazione Delle Cure	19/06/2012 26/06/2012	22	Anita Caruso
44	1	La norma iso 9001-2008 nelle strutture sanitaria	20/06/2012 21/06/2012	15,7	Amalia Allocca
45	1	Giornata di aggiornamento in epilessia e tumori cerebrali	25/06/2012 25/06/2012	8,8	Marta Maschio
46	1	Seminari intramurali ire	05/09/2012 19/09/2012	50	Ruggero De Maria Marchiano
47	1	La comunicazione in ambito oncologico	10/09/2012 12/09/2012	32,8	Anita Caruso
48	1	The p53 family in stem cells, cancer and metastasis	13/09/2012 13/09/2012	8,6	Giovanni Blandino
49	1	Carcinoma del colon-retto metastatico. Una possibilita' di cura	14/09/2012 14/09/2012	6	Carlo Garufi
50	1	Il Bambino, l'adolescente E La Malattia Oncologica	17/09/2012 19/09/2012	33	Anita Caruso
51	1	Prendersi cura:risonanze emotive dell'operatore di fronte alla persona malata- ii livello	20/09/2012 13/12/2012	31,5	Anita Caruso
52	1	La prevenzione della malattia tubercolare negli operatori sanitari	02/10/2012 02/10/2012	7,1	Alessandro Cataldo
53	1	Chirurgia ricostruttiva	10/10/2012 12/10/2012	43,3	Giuseppe Spriano
54	1	Partial nephrectomy and new technology	18/10/2012 19/10/2012	5,5	Michele Gallucci
55	1	Il lavoro in euqipe : dalla multidisciplinarita' all'interdisciplinarieta'	24/10/2012 07/11/2012	33	Anita Caruso

56	1	Modelli assistenziali innovativi nella regione lazio	25/10/2012 25/10/2012	4	Andrea Pace
57	1	Diagnosi precoce di cardiotossicita' da terapia antineoplastica, gli strumenti: tecniche avanzate di imaging, markers biochimici, integr. Col territorio	26/10/2012 26/10/2012	9	Fabio Maramao
58	1	Svuotamenti del collo	20/11/2012 22/11/2012	43,8	Giuseppe Spriano
59	1	Corso avanzato sulla metodologia della ricerca	20/11/2012 11/12/2012	50	Laura Iacorossi
60	1	Malattia dolore nel paziente oncologico. Nozioni di fisiopatologia e terapia	26/11/2012 26/11/2012	7	Loriana Di Emidio
61	1	Biomarcatori in oncologia: ruolo del laboratorio e guida all'uso clinico	30/11/2012 30/11/2012	6	Laura Conti
62	2	Malattia dolore nel paziente oncologico. Nozioni di fisiopatologia e terapia	10/12/2012 10/12/2012	7	Loriana Di Emidio

Istitutional Courses 2013

In 2013 IRE organized 63 training events, up to a total of: 1019,6 ECM credits, 1941 attending people, 165 training days.

* Ed = Edition, § PI = Principal Investigator

N.	Ed*	Title	Dates	Credits	PI§
1	1	Corso teorico-pratico: utilizzo del separatore cellulare in sala operatoria, recupero sangue intraoperatorio	12/01/2013 16/01/2013	12,20	Romano Augieri
2	1	Banche dati e sistemi per l'informazione e la valutazione della ricerca	28/01/2013 29/01/2013	20,50	Gaetana Cognetti
3	1	Qualità della vita e delle relazioni degli operatori in ambito sanitario per l'efficacia delle prestazioni	22/01/2013 22/01/2013	11	Anita Caruso
4	1	I Modulo Seminari Isg	22/01/2013 26/02/2013	4,50	Di Carlo Aldo
5	1	Corso pratico di Project Management applicato all'analisi dei processi	24/01/2013 28/11/2013	28,30	Silvia Giovannetti
6	1	Tutor clinico: guida nell'inserimento del neoassunto e dello studente in formazione	11/02/2013 12/02/2013	18.50	Albina Paterniani
7	1	Abilità comunicative e gestione del reclamo	21/02/2013 21/02/2013	11	Anita Caruso
8	1	La qualità delle relazioni degli operatori per l'umanizzazione delle cure	12/02/2013 19/02/2013	22	Anita Caruso
9	1	Corso avanzato di formazione teorico-pratico per infermieri: posizionamento e gestione dei CVC ad inserimento	11/03/2013 22/03/2013	50	Lamberto Laurenzi

		periferico PICC			
10	1	Prendersi cura. Risonanze emotive nell'operatore di fronte alla persona malata - I livello	07/03/2013 21/03/2013	33	Anita Caruso
11	1	Il TSRM nel PDT del tumore della mammella	22/03/2013 23/03/2013	17,20	Maurizio Ballarotto
12	1	B.L.S.D. Medici	06/03/2013 06/03/2013	11	Francesca Principi
13	2	B.L.S.D. Medici	26/03/2013 26/03/2013	11	Francesca Principi
14	1	Corso base: l'approccio quantitativo nella ricerca infermieristica	04/03/2013 18/03/2013	19,50	Laura Iacorossi
15	2	II Modulo Seminari Isg	05/03/2013 16/04/2013	4,50	Aldo Di Carlo
16	3	B.L.S.D. Medici	16/04/2013 16/04/2013	11	Francesca Principi
17	1	Basi embriologiche della tecnica chirurgica	09/04/2013 10/04/2013	12,80	Enrico Vizza
18	1	Rassegne sistematiche metanalisi linee guida.	11/04/2013 12/04/2013	20,40	Gaetana Cognetti
19	3	III Modulo Seminari Isg	23/04/2013 28/05/2013	4,50	Aldo Di Carlo
20	4	B.L.S.D. Medici	07/05/2013 07/05/2013	11	Francesca Principi
21	1	B.L.S.D. Infermieri	29/05/2013 29/05/2013	11	Francesca Principi
22	1	Il ruolo del tecnico sanitario di laboratorio biomedico nel processo trasfusionale	10/05/2013 10/05/2013	10	Mara Maria Anna Battista
23	1	Il microbiota intestinale: questo sconosciuto	11/05/2013 11/05/2013	7	Lucio Capurso

24	1	Percorsi clinici e nuove realtà terapeutiche nel paziente ischemico ed aritmico in attesa di chirurgia oncologica	23/05/2013 23/05/2013	8,6	Francesco Rulli
25	1	Videoterminali: aspetti ergonomici, posturali, sorveglianza sanitaria e ginnastica preventiva	14/05/2013 14/05/2013	9,8	Alessandro Cataldo
26	1	La gestione dei farmaci antiblastici: misure di saefty care per pazienti ed operatori sanitari	16/05/2013 17/05/2013	16	Gabriella Angeloni
27	1	Aspetti biologici e aspetti relazionali nella malattia oncologica: dal curare al prendersi cura	13/05/2013 15/05/2013	33	Anita Caruso
28	1	Il contesto familiare e le dinamiche emotive degli operatori in ambito oncologico	20/05/2013 22/05/2013	33	Anita Caruso
29	2	B.L.S.D. Infermieri	11/06/2013 11/06/2013	11	Francesca Principi
30	5	B.L.S.D. Medici	25/06/2013 25/06/2013	11	Francesca Principi
31	1	Ricerca dell'informazione infermieristica sugli archivi elettronici	13/06/2013 14/06/2013	20,4	Gaetana Cognetti
32	1	Chirurgia Parotidea	18/06/2013 20/06/2013	43,5	Giuseppe Spriano
33	1	Sintesi e controllo di qualità dei radio farmaci	21/06/2013 25/06/2013	11	Carlo Ludovico Maini
34	1	Medicina perioperatoria. Ruolo dell'anestesista	28/06/2013 28/06/2013	5,5	
35	2	Il TSRM nel PDT del tumore della mammella	19/06/2013 20/06/2013	17,20	Maurizio Ballarotto

36	1	Incontri formativi di ricerca traslazionale – metabolomica della cute e degenerazione cellulare I Modulo	08/07/2013 14/10/2013	7,8	Mauro Picardo
37	2	Corso avanzato di formazione teorico-pratico per infermieri: posizionamento e gestione dei CVC ad inserimento periferico PICC	30/09/2013 11/10/2013	50	Lamberto Laurenzi
38	7	B.L.S.D. Medici	29/10/2013 29/10/2013	11	Francesca Principi
39	4	IV Modulo Seminari Isg	04/06/2013 10/09/2013	4,50	Aldo Di Carlo
40	1	La comunicazione in ambito oncologico	09/09/2013 11/09/2013	33	Anita Caruso
41	1	PSO Forum gestione multidisciplinare della psoriasi	12/09/2013 12/09/2013	8,2	Enzo Berardesca
42	1	La responsabilità professionale del tecnico di laboratorio biomedico	20/09/2013 20/09/2013	8,8	Marco Zucchiatti
43	1	Prendersi cura risonanze emotive nell'operatore di fronte alla persona malata – II livello	19/09/2013 20/12/2013	29,3	Anita Caruso
44	1	Il bambino, l'adolescente e la malattia oncologica	23/09/2013 25/09/2013	33	Anita Caruso
45	1	I segreti di Pubmed: metodologia della ricerca dell'informazione	23/09/2013 23/09/2013	20,4	Gaetana Cognetti
46	1	Chirurgia Ricostruttiva	24/09/2013 26/09/2013	43,50	Giuseppe Spriano
47	5	V Modulo Seminari Isg	17/09/2013 29/10/2013	4,50	Aldo Di Carlo

48	2	Incontri formativi di ricerca traslazionale – metabolomica della cute e degenerazione cellulare II Modulo	28/10/2013 16/12/2013	7,8	Mauro Picardo
49	1	Cardio-oncologia 2013: "Il management cardiologico e i sistemi integrati nel paziente oncologico"	24/10/2013 24/10/2013	7	Fabio Maramao
50	1	Elettrochemioterapia stato dell'arte e prospettive nel trattamento di melanoma, tumori cutanei, recidive e metastasi cutanee da carcinoma	03/10/2013 03/10/2013	6	Stefania Bucher
51	6	VI Modulo Seminari Isg	05/11/2013 17/12/2013	4,50	Aldo Di Carlo
52	1	Metodiche diagnostiche non invasive e management del melanoma cutaneo	22/11/2013 22/11/2013	8,1	Vitaliano Silipo
53	8	B.L.S.D. Medici	26/11/2013 26/11/2013	11	Francesca Principi
54	1	Incontri formativi di ricerca traslazionale – controllo della pigmentazione e dei processi di invecchiamento cellulare I Modulo	25/11/2013 29/11/2013	10	Mauro Picardo
55	1	Rome Transplant Network: la cultura del lavorare insieme	29/11/2013 29/11/2013	8	Adriana Pignatelli
56	1	La prevenzione e la gestione della caduta del paziente nelle strutture sanitarie	28/11/2013 28/11/2013	8,8	Gabriella Angeloni
57	1	Svuotamenti del collo	19/11/2013	43,50	Giuseppe Spriano

			21/11/2013		
58	9	B.L.S.D. Medici	10/12/2013 10/12/2013	11	Francesca Principi
59	2	Incontri formativi di ricerca traslazionale – controllo della pigmentazione e dei processi di invecchiamento cellulare II Modulo	09/12/2013 13/12/2013	10	Mauro Picardo
60	1	Web 2.0: Applicativi in medicina	09/12/2013 10/12/2013	20,4	Gaetana Cognetti
61	1	Hot topics in anestesia toracica	06/12/2013 06/12/2013	6	Ester Forastiere
62	1	HPV: come comunicare col paziente	12/12/2013 12/12/2013	7,1	Luciano Mariani
63	1	Il lavoro in èquipe: dalla multidisciplinarietà all'interdisciplinarietà	03/12/2013 17/12/2013	33	Anita Caruso

Clinical Trials active in 2012

BRAIN				
Status	**TITLE**	**DIVISION**	Principal Investigator	**Patients (total IRE)**
O	A Prospective, Multi-center Trial of NovoTTF-100A Together With Temozolomide Compared to Temozolomide Alone in Patients with Newly Diagnosed GBM	Neurosurgery	Carapella	**3**
O	Brain metastases: traditional surgery, innovative approaches, utilisation of novel technologies in the operating theatre	Neurosurgery	Pompili	**208**
C	Cilengitide for Subjects With Newly Diagnosed Glioblastoma and Methylated MGMT Gene Promoter - A Multicenter, Open-label, Controlled Phase III Study, Testing Cilengitide in Combination With Standard Treatment (Temozolomide With Concomitant Radiation Therapy, Followed by Temozolomide Maintenance Therapy) Versus Standard Treatment Alone (CENTRIC)	Neurosurgery	Carapella	**12**
C	Cilengitide in Subjects With Newly Diagnosed Glioblastoma and Unmethylated MGMT Gene Promoter - a Multicenter, Open-label Phase II Study, Investigating Two Cilengitide Regimens in Combination With Standard Treatment (Temozolomide With Concomitant Radiation Therapy, Followed by Temozolomide Maintenance Therapy)	Neurosurgery	Carapella	**4**
O	Economic analysis of the social and healthcare costs of epilepsy secondary to brain tumors	Neurology	Maschio	**0**
O	Evaluation of brain tumors by means of CT-Perfusion during diagnosis and follow-up. Observational study	Radiology and Diagnostic Imaging	Vidiri	**43**
O	Evaluation of seizure control and quality of life in patients with brain tumor related epilepsy treated with Lacosamide as add-on therapy: a prospective explorative study with a historical control group	Neurology	Maschio	**0**
O	Evaluation of seizure control, quality of life in patients with brain tumor-related epilepsy treated with zonisamide as add-on therapy: a osservational pilot study	Neurology	Maschio	**0**
O	Multi-centre, No-Profit Observational trial to evaluate the efficacy of Gliadel® Wafer (GW) plus concomitant temozolomide in patients with newly-diagnosed high grade glioma	Neurosurgery	Carapella	**1**
O	Observational study for the evaluation of the cognitive impairment in patients with brain tumors	Neurology	Pace	**147**
C	Primary treatment with temozolomide versus radiotherapy in low-grade glioma patients subdivided according to the presence of the gene 1p deletion: phase III study	Neurosurgery	Carapella/Pace	**4**
O	Project for continuing, integrated assistance and domiciliary neurorehabilitation for patients with brain tumors	Neurology	Pace	**693**

O	Randomized Non Comparative Phase II Trial With Bevacizumab and Fotemustine in the Treatment of Recurrent Glioblastoma	Medical Oncology "A"	Fabi	**9**
O	Tissue characterization of glial tumors with 3 Tesla diffusion, perfusion and spectroscopy MR. Correlation with morphologic MR and histopatholgic findings	Radiology and Diagnostic Imaging	Vidiri	**0**
O	Translational-observational study: prognostic value of some genetic alterations (1p, 19q, 10q) in low-grade gliomas	Neurology	Pace/Cianciulli	**99**
BREAST				
O	A multicenter randomized phase II study to compare the combination trastuzumab and capecitabine, with or without pertuzumab, in patients with HER2-positive metastatic breast cancer that have progressed after one line of trastuzumab-based therapy in the metastatic setting (PHEREXA)	Medical Oncology "A"	Cognetti	**1**
C	A multicenter, open label study to assess the effect of trastuzumab + whole brain radiotherapy (WBRT) on brain metastases from HER-2 positive breast cancer	Medical Oncology "A"	Fabi	**2**
C	A Phase 2 Randomized Open Label Study of Neratinib versus Lapatinib plus Capecitabine for the Treatment of ErbB-2 Positive Locally Advanced or Metastatic Breast Cancer	Medical Oncology "A"	Cognetti	**1**
O	A phase III prospective, two-cohort non-randomized, multi-centre, multinational, open label study to assess the safety of assisted- and self-administered subcutaneous trastuzumab as adjuvant therapy in patients with operableHER2-positive early breast cancer	Medical Oncology "A"	Cognetti	**4**
O	A Phase III randomized study evaluating the efficacy and safety of continued and re-induced bevacizumab in combination with chemotherapy for patients with locally recurrent or metastatic breast cancer after first-line chemotherapy and bevacizumab treatment	Medical Oncology "A"	Fabi	**6**
O	A phase III randomized, double blind placebo controlled study of BKM120 with fulvestrant, in postmenopausal women with hormone receptor-positive HER2-negative locally advanced or metastatic breast cancer who progressed on or after aromatase inhibitor treatment	Medical Oncology "A"	Cognetti	**0**
C	A phase III study comparing anastrozole, letrozole and exemestane, upfront (for 5 years) or sequentially (for 3 years after 2 years of tamoxifen), as adjuvant treatment of postmenopausal patients with endocrine-responsive breast cancer	Medical Oncology "A"	Cognetti	**109**
O	A Randomised, Double-blind, Parallel-group, Multicentre, Phase III Study to Compare the Efficacy and Tolerability of Fulvestrant (FASLODEXTM) 500 mg with Anastrozole (ARIMIDEXTM) 1 mg as Hormonal Treatment for Postmenopausal Women with Hormone Receptor-Positive Locally Advanced or Metastatic Breast Cancer Who Have Not Previously Been Treated With Any Hormonal Therapy (FALCON)	Medical Oncology "A"	Papaldo	**0**

C	A Randomized Double-blind Placebo-Controlled Trial of Neratinib (HKI-272) After Trastuzumab in Women With Early-Stage HER-2/neu Overexpressed/Amplified Breast Cancer	Medical Oncology "A"	Cognetti	**1**
C	A randomized phase III, double-blind, placebo-controlled multicenter trial of Everolimus in combination with Trastuzumab and Paclitaxel, as first line therapy in women with HER2 positive locally advanced or metastatic breast cancer	Medical Oncology "A"	Cognetti	**2**
O	A Randomized Trial with factorial Design comparing Fulvestrant ± Lapatinib ± Aromatase Inhibitor in metastatic breast cancer progressing after Aromatase Inhibitor therapy	Medical Oncology "A"	Cognetti	**8**
C	A randomized, multicenter, phase III open-label study of the efficacy and safety of trastuzumab-MCC-DM1 vs. capecitabine+lapatinib in patients with HER2-positive locally advanced or metastatic breast cancer who have received prior trastuzumab-based therapy	Medical Oncology "A"	Cognetti	**6**
C	A Randomized, Multicentre, Open-Label, Phase III Study of Lapatinib plus Capecitabine versus Trastuzumab plus Capecitabine in Patients with Anthracycline- or Taxane-Exposed ErbB2-positive Metastatic Breast Cancer	Medical Oncology "A"	Fabi	**9**
O	An open-label, multi-center, expanded access study for postmenopausal women with estrogen receptor positive locally advanced or metastatic breast cancer who have progressed following prior endocrine therapy, investigating the treatment of everolimus (RAD001) in combination with exemestane	Medical Oncology "B"	Vici	**5**
O	An open-label, multi-center, expanded access study for postmenopausal women with estrogen receptor positive locally advanced or metastatic breast cancer who have progressed following prior endocrine therapy, investigating the treatment of everolimus (RAD001) in combination with exemestane	Medical Oncology "A"	Cognetti	**5**
O	Elaboration of a new nomogram based on quantitative measurement of Cytokeratin 19 mRNA by One Step Nucleic Acid Amplification (OSNA) to predict non-sentinel lymph status in breast cancer patients with a positive sentinel node. European multicenter study	Breast Unit	Di Filippo	**200**
C	Electrochemotherapy /ECT) for the inductive treatment in operable, unifocal mammary carcinoma (<3 cm)	Breast Unit	Botti	**3**
O	Epigenetic control of the progression of mammary cancer: clinical studies and studies in animal models	Psychology	Pugliese	**32**
C	Feasibility study of dose-dense FEC wiith G-CSF support followed by dose-dense Ixabepilone wiith G-CSF support as neoadjuvant chemotherapy in ER-negative breast cancer	Medical Oncology "A"	Cognetti	**1**
O	Feasibility study of hypofractionated radiotherapy in patients that have undergone conservative surgery for breast cancer	Radiotherapy	Pinnarò	**180**
O	Fertility in young females affected by mammary cancer	Medical Oncology "B"	Vici	**0**
O	Fulvestrant 500 mg: evaluation of the clinical benefit in patients with hormone-responsive, metastatic mammary carcinoma: prospective,	Medical Oncology "B"	Vici	**10**

	observational cohort study			
O	Global burden of disease in patients with advanced breast cancer receiving oral versus intravenous (IV) vinorelbine and their caregivers in Europe	Medical Oncology "A"	Cognetti	**0**
O	Hormonal adjuvant therapy and bone health in male mammary carcinoma	Medical Oncology "A"	Fabi	**0**
O	Intraoperative diagnosis of the sentinel lymph node in mammary carcinoma with the RT-PCR methodology using the One Step Nucleic Acid Amplification (OSNA) procedure	Histology and Cytopathology	Marandino	**305**
O	Localisation of the surgical bed by means of fusion of images from 3 Tesla MR and computerized axial tomography for the design of radiotherapy treatment in patients with mammary tumor that have undergone conservative surgery	Radiology and Diagnostic Imaging	Ferranti	**0**
O	Long-term Anastrozole vs. Tamoxifen Treatment Effects (LATTE)	Medical Oncology "A"	Papaldo	**0**
C	Multicenter observational pilot study on the adherence and persisence to adjuvant hormone therapy in mammary carcinoma	Medical Oncology "B"	Vici	**57**
O	Observational multi-center study on the monitoring of the tolerability and quality of life in patients with metastatic mammary cancer under treatment with Eribulin (Halaven)	Medical Oncology "B"	Vici	**2**
O	Observational study on the evluation of the cognitive impairment in mammary carcinoma patients	Neurology	Pace	**23**
C	Phase I/II trial and pharmacokinetics of continuous low-dose, oral vinorelbine in patients with advanced mammary tumors	Medical Oncology "A"	Papaldo	**25**
O	Phase II trial of primary chemotherapy with trastuzumab in combination with docetaxel followed by epirubicin-cyclophosphamide in patients with HER-2-overexpressing operable breast cancer	Medical Oncology "B"	Vici	**34**
O	Prevalence of vertebral fractures in women with mammary carcinoma undergoing hormonal adjuvant therapy with aromatase inhibitors	Medical Oncology "A"	Fabi	**0**
O	Prevention programs in yound women with mutations of the BRCA1 and/or BRCA2 genes: evluation of the impact of a specialistic, psychological intervention on the quality of life	Psychology	Caruso	**0**
O	Prospective randomized study comparing quadrantectomy followed by external complementary radiotherapy with quadrantectomy associated with intraoperative radiotherapy or with partial external irradiation of the breast in a single fraction in patients with mammary carcinoma of small dimensions and >48 years in post menopause	Radiotherapy	Pinnarò	**134**
O	Protocols for test validation: cancer-specific distress and risk perception in hereditary-familial mammary tumors	Psychology	Caruso	**116**
O	Risk of relpase in mammary tumors of small dimensions with negative lymph nodes. Retrospective, multicenter analysis	Medical Oncology "B"	Vici	**166**

C	Role of Aprepitant in the prevention of delayed vomiting from moderately emetic drugs (cyclophosphamide + antracyclines) in patients with mammary carcinoma: controlled double-blind study	Medical Oncology "A"	Fabi	**96**
C	SHORT-HER: multicentric randomised phase III trial of adjuvant chemotherapy plus 3 vs 12 months of trastuzumab in breast cancer patients with her2 positive disease	Medical Oncology "A"	Cognetti	**1**
O	The BEACON Study (BrEAst Cancer Outcomes with NKTR-102): A Phase 3 Open-Label, Randomized, Multicenter Study of NKTR-102 versus Treatment of Physician's Choice (TPC) in Patients with Locally Recurrent or Metastatic Breast Cancer Previously Treated with an Anthracycline, a Taxane, and Capecitabine	Medical Oncology "A"	Cognetti	**1**
O	The Effect of Metformin, an insulin-sensitizing drug, on Breast Cancer Primary Prevention: The Plotina Breast Cancer Prevention Randomized, Placebo Controlled Trial	Experimental oncology	Blandino	**59**
ENDOCRINE				
O	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of E7080 in 131I-Refractory Differentiated Thyroid Cancer	Endocrinology	Appetecchia	**1**
C	A Retrospective, Non-interventional Study of Patients with T4 Tumours Comparing the Thyroid Remnant Ablation Success Following Thyrogen and 131I Administration Versus Thyroid Hormone Withdrawal and 131I Administration	Nuclear Medicine	Maini	**6**
O	Acrostudy – a multicenter, post marketing surveillance study of somavert therapy in patients with acromegaly in the us and europe	Endocrinology	Appetecchia	**6**
O	An international, non interventional, cross sectional study to assess neuroendocrine tumor (NET) patients currently treated by somatuline autogel for history of carcinoid syndrome associated with episodes of diarrhea	Endocrinology	Baldelli	**4**
O	An International, Randomised, Double-Blind, Two-Arm Study to Evaluate the Safety and Efficacy of Vandetanib 150 and 300 mg/day in Patients with Unresectable Locally Advanced or Metastatic Medullary Thyroid Carcinoma with Progressive or Symptomatic Disease	Endocrinology	Appetecchia	**0**
C	An open-label, multi-center, expanded access study of everolimus in patients with advanced neuroendocrine tumors	Medical Oncology "A"	Milella	**1**
O	Effect of the control of GH and IGF-1 secretion on blood pressure and cardiac rythm in patients with active acromegaly	Endocrinology	Appetecchia	**0**
O	Efficacy of adjuvant Mitotane treatment in prolonging recurrance-free survival in patients with adrenocortical carcinoma that have undergone radical surgery	Endocrinology	Appetecchia	**0**
O	Epidemiology of the anaplastic carcinoma of the thyroid: comparison between the decades 1990-2000 and 2001-2010	Endocrinology	Appetecchia	**0**

O	Natural history, geographic distribution and biological characterization of patients with neuroendocrine tumors (NET). Multicenter, clinical-biological I.T.M.O. study	Medical Oncology "A"	Cognetti	**0**
O	NET Management Project: Epidemiologic-retrospective protocol of neuroendocrine tumors of the chest and gastro-entero-pancreatic tract. Epidemiologic, retrospective protocol of non-functioning, neuroendocrine tumors	Endocrinology	Appetecchia	**39**
GASTROINTESTINAL				
O	A Phase II Multicentre Study of Systemic Chemotherapy versus Systemic Chemotherapy plus Selective Internal Radiotherapy (SIRT) in KRAS mutant colorectal liver metastases (IFO-SITILO 2)	Digestive Endoscopy	Cosimelli	**0**
O	A Phase III Placebo-Controlled Trial Of Celecoxib In Genotype Positive Subjects With Familial Adenomatous Polyposis	Digestive Endoscopy	Stigliano	**8**
C	A r andomised, multicentre, phase IIi, parallel-group trial of vandetanib monotherapy or vandetanib in combination with gemcitabine versus gemcitabine plus vandetanib matching placebo in subjects with advanced biliary tract cancer (gallbladder cancer, cancer of the extrahepatic bile duct, intrahepatic cholangiocarcinoma and ampullary carcinoma)	Medical Oncology "A"	Milella	**7**
O	A Randomised Open-Label Phase IIa Study to Assess the Efficacy and Safety of AZD4547 Monotherapy versus Paclitaxel in Patients with Advanced Gastric or Gastro-oesophageal Junction Cancer with FGFR2 Polysomy or Gene Amplification (Shine study)	Medical Oncology "A"	Garufi	**8**
O	A Randomized Phase II Trial of Second Line Therapy in Advanced Biliary Tract Cancer: Capecitabine or Capecitabine Plus Mitomycin C	Medical Oncology "A"	Milella	**0**
C	A Randomized Phase III Study of Weekly ABI-007 plus Gemcitabine versus Gemcitabine Alone in Patients with Metastatic Adenocarcinoma of the Pancreas	Medical Oncology "A"	Milella	**3**
C	A Randomized Phase III, Double-blind, Placebo-controlled, Multi-center Study to Evaluate the Efficacy and Safety of Everolimus (RAD001) in Adult Patients With Advanced Hepatocellular Carcinoma After Failure of Sorafenib Treatment - The EVOLVE-1 Study	Medical Oncology "A"	Cognetti	**2**
O	Diffusion MR of the liver: optimisation of the IVIM technique for the characterisation of focal liver lesions	Radiology and Diagnostic Imaging	Caterino	**0**
O	Genetic, gastroenterological consulting for familial, hereditary tumors of the colon	Digestive Endoscopy	Stigliano	**523**
O	HER2 early/advanced gastric epidemiology study; an assessment of HER2 status in tumor tissue samples of gastric & gastro-esophageal (GE) junction cancer	Histology and Cytopathology	Pescarmona	**23**
O	Isolation and characterization of tumor stem cells in intra- and extra-hepatic cholangiocarcinoma	General Surgery Epatobiliopancreatic	Grazi	**5**
O	Isolation and functional and molecular characterization of stem cells from gastric tumors for the development of novel therapeutic strategies	Experimental oncology	Blandino/Garofalo	**48**

C	MAG (Metaplasia, Atrophy and Gastritis)	Digestive Endoscopy	Anti	**12**
O	Molecular Biomarkers for Colorectal Liver Metastases Resectability after Chemotherapy plus Cetuximaab	Medical Oncology "A"	Garufi	**3**
C	Optimal control of liver metastases with intravenous cetuximab and hepatic artery infusion of three-drug chemotherapy in patients with liver-only metastases from colorectal cancer.	Medical Oncology "A"	Garufi	**0**
O	Phase II randomized trial of MEK inhibitor MSC1936369B or placebo combined with gemcitabine in metastatic pancreas cancer subjects	Medical Oncology "A"	Milella	**2**
O	Radical D2 gastrectomy and intraoperative chemohyperthermia in patients with gastric carcinoma at high risk for periotneal recurrence	Digestive Endoscopy	Garofalo	**0**
O	Study of the mutations of genes K-RAS, BRAF and PIK3CA as factors of prognostic and predictive relevance of the response to therapy of metastatic, colorectal tumors	Histology and Cytopathology	Mottolese	**598**
GYNAECOLOGICAL				
O	A Phase 3 Randomized, Double-blind, Placebo-controlled, Multicenter Study of AMG 386 With Paclitaxel and Carboplatin as First-line Treatment of Subjects With FIGO Stage III-IV Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancers	Medical Oncology "A"	Savarese	**0**
O	A Phase 3, Randomized, Double-Blind Trial of Pegylated Liposomal Doxorubicin (PLD) Plus AMG 386 or Placebo in Women With Recurrent Partially Platinum Sensitive or Resistant Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	Medical Oncology "A"	Savarese	**0**
O	A Phase II Randomized Open Label Study of MM-121 in combination with Paclitaxel versus Paclitaxel alone in patients with Platinum Resistant/ Refractory Advanced Ovarian Cancers	Medical Oncology "A"	Savarese	**1**
O	A randomized phase II study of carboplatin and paclitaxel +/- cetuximab, in advanced and/or recurrent cervical cancer	Medical Oncology "A"	Savarese	**1**
O	A Randomized Phase II Trial of Carboplatin-Paclitaxel compared to Carboplatin-Paclitaxel-Bevacizumab in advanced (stage III-IV) or metastatic endometrial cancer	Medical Oncology "A"	Savarese	**0**
C	Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial	Medical Oncology "A"	Savarese	**5**
O	Development of a therapeutic vacine based on the use of exosomes for the treatment of precancerous and cancerous lesions caused by type 16 human papillomavirus. New immunogens generated from exosomes engineered to carry protein antigens	Ginecology	Mariani	**0**
O	Double p16/ki67 staining as a marker in cytological cervical-vaginal samples: correlations with cytologic and histologic diagnosis, presence of papillomavirus (HPV) and HPV genotyping	Histology and Cytopathology	Vocaturo	**140**
O	Evaluation of efficiency indices of diagnostic tests in populations at risk for endometrial carcinoma	Ginecology	Vocaturo	**390**

O	Evaluation of the preformance of an assay for the genotyping of HPV (Linear Array) on histologic samples of cervical lesions	Histology and Cytopathology	Vocaturo/Benevolo	**39**
C	Learning curve of a laparoscopic score for the pediction of optimal cytoreduction in patients with advanced ovarian cacinoma at first surgery	Ginecology	Vizza	**5**
O	Multicenter, randomized, controlled clinical trial comparing two follow-up regimen at different frequencies of examinations in patients treated for endometrial cancer	Ginecology	Vizza	**6**
O	Randomized clinical trial comparing different mini-inasive surgical procedures in the treatment of early-stage endometrial cancer	Ginecology	Vizza	**2**
C	Stealth liposomal doxorubicin vs carboplatin/paclitaxel in recurrent ovarian cancer patients after a platinum-free interval of 6-12 months: a randomized, multicentre study	Medical Oncology "A"	Savarese	**0**
O	Use of new molecular assays for the diagnosis and treatment follow-up of precancerous lesions	Ginecology	Mariani	**8**
HAEMATOLOGICAL				
O	"Geriatric Assessment Adapted" Therapy for Ph- ALL Elderly Patients	Haematology Oncology	Spadea	**0**
O	A Multicenter Total Therapy Strategy for De Novo Adult Philadelphia Chromosome Positive (Ph+) Acute Lymphoblastic Leukemia (ALL)	Haematology Oncology	Spadea	**0**
O	A non-interventional observational post authorisation safety study of subjects treated with lenalidomide	Haematology Oncology	Mengarelli	**10**
C	A open label, phase 2, non randomized, multicentre trial to assess the feasibility of induction treatment with 5-azacitidine (5-AZA) followed by allogeneic stem cell transplantation (allo-SCT) or continued 5-AZA treatment in patients without a suitable -sibling or unrelated- stem cell donor with IPSS Int-2/High risk myelodysplastic syndromes (MDS)	Haematology Oncology	Spadea	**0**
O	A Phase 2, Randomized Study of Bortezomib/dexamethasone With or Without Elotuzumab in Subjects with Relapsed/Refractory Multiple Myeloma	Haematology Oncology	Pisani	**0**
C	A Phase II Multi-centre Study of MBVD in Elderly and/or Cardiopathic Patients Affected by Hodgkin's Lymphoma (HL)	Haematology Oncology	Pisani	**1**
O	A phase II study of R-CHOP with intensive CNS prophylaxis and scrotal irradiation in patients with primary testicular diffuse large B-cell lymphoma	Haematology Oncology	Pisani	**1**
O	A phase III, intergroup multicentre, randomized, controlled 3 arm parallel group study to determine the efficacy and safety of lenalidomide in combination with dexamethasone (RD) versus melphalan, prednisone and lenalidomide (MPR) versus cyclophosphamide, prednisone and lenalidomide (CPR) in newly diagnosed multiple myeloma elderly subjects	Haematology Oncology	Pisani	**1**

O	A randomized phase III study to compare Bortezomib, Melphalan, Prednisone (VMP) with High Dose Melphalan followed by Bortezomib, Lenalidomide, Dexamethasone (VRD) consolidation and Lenalidomide maintenance in patients with newly diagnosed multiple myeloma	Haematology Oncology	Pisani	**4**
C	A Randomized Pilot Study on Central Nervous System (CNS) Prophylaxiswith Liposome-Encapsulated Cytarabine (DepoCyte) in a Population of Adult Patientswith Acute Lymphoblastic Leukemia (ALL) Treated with an Updated and Lineage-TargetedMinimal Residual Disease (MRD)-Oriented Postremission Strategy	Haematology Oncology	Spadea	**0**
O	A randomized, open-label, multicentre, two-arm phase III comparative study assessing the role of mediastinal radiotherapy after Rituximab-containing chemotherapy regimens to patients with newly diagnosed Primary Mediastinal Large B-Cell Lymphoma (PMLBCL)	Haematology Oncology	Pisani	**0**
C	A Single-Arm Multi-Center Trial of Bendamustine Given With Ofatumumab (BendOfa) in Patients With Refractory or Relapsed Chronic Lymphocytic Leukemia (CLL)	Haematology Oncology	Romano	**0**
O	An open-label, multicenter, expanded access study of INC424 for patients with primary myelofibrosis (PMF) or post polycythemia myelofibrosis (PPV MF) or post-essential thrombocythemia myelofibrosis (PET-MF)	Haematology Oncology	Petti	**3**
O	Ancillary, observational study on the characterization of peripheral blood biomarkers in patients with Hodgkin lymphoma treated according protocols that foresee a PET-guided strategy	Haematology Oncology	Romano	**0**
O	Bendamustine, lenalidomide and rituximab (R2-B) combination as a second-line therapy for first relapsed-refractory mantle cell lymphomas: a phase ii study	Haematology Oncology	Palombi	**0**
C	Development of a personalized vaccine based on autologous dendritic cells for B-cell non-Hodgkin lymphoma	Haematology Oncology	Petti	**0**
O	Dose-dense ABVD as first line therapy in early stage unfavorable Hodgkin's Lymphoma: a phase II, prospective, multi-center study	Haematology Oncology	Petti	**5**
O	Early salvage with high-dose chemotherapy and stem cell transplantation in advanced stage Hodgkin's lymphoma patients with positive positron emission tomography after two courses of ABVD (PET-2 positive) and comparison of radiotherapy versus no radiotherapy in PET-2 negative patients	Haematology Oncology	Romano	**10**
O	Eltrombopag for the treatment of thrombocytopenia due to low- and intermediate risk myelodysplastic syndromes. (EQoI-MDS)	Haematology Oncology	Romano	**0**
O	Gemtuzumab Ozogamicin (GO) Monotherapy Versus Standard Supportive Care for Previously Untreated **AML** in Elderly Patients Who Are Not Eligible for Intensive Chemotherapy: A Randomized Phase II/III Trial (**AML-19**) of the EORTC-LG and GIMEMA-ALWP	Haematology Oncology	Romano	**0**
C	Multicenter observational study for the retrospective collection of data on the off-label use of lenalidomide (Revlimid®) in non-Hodgkin lymphoma patients	Haematology Oncology	Spadea	**1**

O	Multicenter, prospective, non-interventional register for monitoring the incidence and diagnostic and therapeutic behavior in the management of infections in patients with acute lymphatic leukemia	Haematology Oncology	Spadea	**0**
O	Multicenter, prospective, non-interventional registry for the monitoring of therapy-related, acute leukemias/myelodisplastic syndromes. Molecular characterization and evaluation of individual susceptibility	Haematology Oncology	Spadea	**4**
O	Observational study in patients with adult T-cell lymphoblastic lymphoma undergoing intensive chemo/radiotherapy or intensive chemotherapy followed by transplantation. Evaluation of clinical, pathological and biological parameters	Haematology Oncology	Spadea	**0**
C	Observational study on the treatment of multiple myeloma in routine clinical practice	Haematology Oncology	Petti	**6**
O	Phase II multicentric study to evaluate the efficacy and the safety of Bendamustine in adjunct to Etoposide, Aracytabin and Melphalan (BeEAM) as a preparative regimen for autologous stem cell transplantation in refractory/relapsed aggressive B-cell non-Hodgkin lymphoma patients	Haematology Oncology	Mengarelli	**1**
C	Phase III, Randomized, Open-label, 3-arm Study to Determine the Efficacy and Safety of Lenalidomide(REVLIMID) Plus Low-dose Dexamethasone When Given Until Progressive Disease or for 18 Four-week Cycles Versus the Combination of Melphalan, Prednisone, and Thalidomide Given for 12 Six-week Cycles in Patients With Previously Untreated Multiple Myeloma Who Are Either 65 Years of Age or Older or Not Candidates for Stem Cell Transplantation	Haematology Oncology	Pisani	**4**
C	Prognostic role of PET in patients with follicular lymphoma treated in the study FOLLO5	Haematology Oncology	Palombi	**5**
O	Prospective collection of data of possible prognostic relevance in patients with indolent non-follicular b-cell lymphomas	Haematology Oncology	Palombi	**0**
O	Prospective survey on severe infections during a multicenter study of risk-adapted, MRD-directed therapy for young adults with newly diagnosed acute myeloid leukemia	Haematology Oncology	Spadea	**0**
O	Randomized phase II trial on primary chemotherapy with high-dose methotrexate and high-dose cytarabine with or without thiotepa, and with or without rituximab, followed by brain irradiation vs. brain irradiation associated with high-dose BCNU and thiotepa chemotehrapy followed by autologous stem cells transplantation in immunocompetent patients with newly diagnosed primary CNS lymphoma	Haematology Oncology	Pisani	**3**
O	Risk-adapted, MRD-directed Therapy for Young Adults With Newly Diagnosed Acute Myeloid Leukemia	Haematology Oncology	Mengarelli	**4**
O	Rituximab plus Bendamustine as front line treatment in frail elderly (>70 years) patients with diffuse large B-cell non-Hodgkin's lymphoma: a phase II multicenter study of the Fondazione Italiana Linfomi (FIL)	Haematology Oncology	Palombi	**0**

C	SEIFEM 2010: Epidemiological Survey on Possible Pre-Hospital Risk Factors for Developing Invasive Fungal Infections in Patients Affected by Acute Myeloid Leukemia	Haematology Oncology	Spadea	**15**
O	SEIFEM 2012: impact of invasive fungal infections in patients with acute myeloid leukemia at diagnosis on the outcome of the basic pathology	Haematology Oncology	Petti	**0**
HEAD AND NECK				
O	Diffusion MR with IVIM technique in head and neck tumors (rhinopharynx, oral cavity, oropharynx, hypopharynx) for the predictive evaluation of the response to radiochemotherapy treatments with 3 Tesla MR	Radiology and Diagnostic Imaging	Vidiri	**0**
C	Evaluation of histochemical, biomolecular and radiologic parameters as markers of the biological behavior of head and neck carcinomas	Otorinolaringology	Spriano	**25**
O	Feasibility study of the integrated use of salvage surgery, intraoperative radiotherapy (IORT) and external beam radiotherapy (EBRT) in tumors of tumors of the cervical-encephalic district after radiotherapy	Radiotherapy	Pinnarò	**30**
C	Observational study on the role of morpho-functional imaging in the planning of planned neck dissection after radiochemotherapy treatment of carcinomas of the pharyngeal district	Otorinolaringology	Pellini	**58**
C	Observational study on the use of photodynamic therapy with temoporfin (Foscan®) for the palliative treatmnet of recurring head and neck tumors in patients not susceptible to other standard treatments	Otorinolaringology	Spriano	**9**
O	Pilot feasibility study on the use of intraoperative radiotherapy (IORT) as an "anticipated boost" in locally advanced tumors of the cervical-encephalic district	Radiotherapy	Marucci	**38**
O	Pilot study of the reiki technique applied to patients with head and neck cancer undergoing radiotherapy in order to control side effects	Radiotherapy	Bigiarini	**14**
O	Prospective randomized double-blind study on the treatment of oral mucositis (with a phytotherapeutic products versus placebo) in head and neck tumor patients undergoing radio-chemotherapy (RT-CT)	Radiotherapy	Giardina	**82**
O	Study of the expression profile of microRNAs in squamous carcinomas of the head and neck and in autologous, peritumoral or distant tissues	Experimental oncology	Blandino	**124**
LUNG				
O	A Phase III Randomised, Double blind, Placebo controlled, Parallel, Multicentre Study to Assess the Efficacy and Safety of continuing IRESSATM 250 mg in addition to Chemotherapy versus Chemotherapy alone in Patients who have Epidermal Growth Factor Receptor (EGFR) Mutation Positive Locally advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) and have progressed on First Line IRESSA™	Medical Oncology "A"	Cognetti	**0**

C	A randomized phase II trial of erlotinib (TARCEVA) or intermittent dosing of erlotinib and docetaxel in male former smokers with locally advanced or metastatic squamous nonsmall cell lung cancer (NSCLC) in second-line setting after failure on chemotherapy	Medical Oncology "A"	Ceribelli	**2**
O	An exploratory Phase 2 study of Pemetrexed and Cisplatin as Preoperative chemotherapy in the treatment of Stage IIIAN2 nonsquamous non-Small cell lung cancer	Medical Oncology "A"	Cognetti	**1**
O	Analysis of the transcriptional expression profile and microRNAs in stem cell subpopulations from tumor tissues of patients with pleural mesothelioma	Experimental oncology	Blandino/Facciolo	**15**
O	Clinical immunotherapy study using IL-2 administered by bronchoinstillation in the treatment of pulmonary and/or mediastinal metastases from melanoma and renal cell cancer. Phase II study	Thoracic Surgery	Filippetti	**2**
C	Multicenter phase III randomized study of cisplatin and etoposide with or without bevacizumab as first-line treatment in extensive stage (ED) small cell lung cancer (SCLC)	Medical Oncology "B"	Rinaldi	**0**
C	Multicenter phase III randomized study of cisplatin and etoposide with or without bevacizumab as first-line treatment in extensive stage (ED) small cell lung cancer (SCLC)	Medical Oncology "A"	Milella	**0**
C	Non-Small Cell Lung Cancer (NSCLC) management In patients progressing after First line of treatment	Medical Oncology "A"	Milella	**12**
C	Pharmacologic prevention with Varenicline in heavy smokers undergoing early detection lung cancer screening	Medical Oncology "A"	Cognetti	**35**
O	Phase 3, randomized, open-label study of the efficacy and safety of crizotinib versus pemetrexed/cisplatin or pemetrexed/carboplatin in previously untreated patients with non-squamous carcinoma of the lung harboring a translocation or inversion event involving the anaplastic lymphoma kinase (ALK) gene locus	Medical Oncology "A"	Cognetti	**0**
O	Phase I/II studyl on the use of hyper-fractionated, conformed radiotherapy in patients with primary or small-dimension secondary lung tumors	Radiotherapy	Pinnarò	**56**
C	Phase II study of cetuximab in combination with cisplatin-docetaxel in the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC): a biomarker-based assessment of activity	Medical Oncology "A"	Ceribelli	**0**
C	Phase II, open-label study of erlotinib (Tarceva) treatment In patients with locally advanced or metastatic non-small-cell lung cancer who present activating mutations in the tyrosine kinase domain of the epidermal growth factor receptor (EGFR)	Medical Oncology "A"	Milella	**0**
O	Phase III Multicenter Randomized Trial Comparing Adjuvant Pharmacogenomic-Driven Chemotherapy versus Standard Adjuvant Chemotherapy in Completely Resected Stage II-IIIA Non-Small Cell Lung Cancer	Medical Oncology "A"	Cognetti	**25**

O	Phase III study of first-line maintenance Tarceva vs Tarceva at the time of disease progression in patients with advanced non-small cell lung cancer (NSCLC) who have not progressed following 4 cycles of platinum-based chemotherapy	Medical Oncology "A"	Cognetti	**0**
O	Randomized Phase III Multicenter Trial of Customized Chemotherapy versus Standard of Care for 1st Line Treatment of Elderly Patients with Advanced Non-Small-Cell Lung Cancer	Medical Oncology "A"	Cognetti	**0**
O	Randomized, Double-Blind, Phase 3 Study of Docetaxel and Ramucirumab versus Docetaxel and Placebo in the Treatment of Stage IV Non-Small Cell Lung Cancer Following Disease Progression after One Prior Platinum-Based Therapy	Medical Oncology "B"	Rinaldi	**0**
C	Tailor (Tarceva Italian Lung Optimization tRial) Optimization of erlotinib for the treatment of patients with advanced non small cell lung cancer: an Italian randomised trial	Medical Oncology "A"	Ceribelli	**0**
MELANOMA				
O	A multicentre, open label, randomized Phase II trial of the MEK inhibitor pimasertib or dacarbazine in previously untreated subjects with N-Ras mutated, locally advanced or metastatic malignant cutaneous melanoma	Medical Oncology "A"	Ferraresi	**0**
O	A double-blind, randomized, placebo-controlled Phase III study to assess the efficacy of recMAGE-A3 + AS15 ASCI as adjuvant therapy in patients with MAGE-A3 positive resected stage III melanoma	Breast Unit	Di Filippo	**4**
C	A Phase III, randomized, double-blinded study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to dabrafenib and placebo as first-line therapy in subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma	Medical Oncology "A"	Ferraresi	**6**
C	A Randomized Double-Blind Phase III Study of Ipilimumab Administered at 3 mg/kg vs at 10 mg/kg in Subjects with Previously Treated or Untreated Unresectable or Metastatic Melanoma	Medical Oncology "A"	Ferraresi	**10**
C	An open-label, multicenter expanded access study of RO5185426 in patients with metastatic melanoma	Medical Oncology "A"	Ferraresi	**21**
O	Analysis of the genetic polymorphisms and soluble isoform of CTLA-4 as prognostic and predictive factors in melanoma	Medical Oncology "A"	Ferraresi	**0**
O	Constitution of a Clinical National Melanoma Registry (CNMR)	Breast Unit	Di Filippo	**16**
O	Peptide–based vaccine in combination or not with chemotherapy in melanoma patients: a phase II randomized clinical study	Medical Oncology "A"	Ferraresi	**34**
O	Selection of specific markers for the development of the molecular diagnosis of sentinel lymph nodes in melanoma patients	Breast Unit	Di Filippo	**39**

C	The TEAM Trial (Tasigna Efficacy in Advanced Melanoma): A randomized, phase III, open label, multicenter,two-arm study to compare the efficacy of Tasigna versus dacarbazine (DTIC) in the treatment of patients with metastatic and/or inoperable melanoma harboring a c-Kit mutation	Medical Oncology "A"	Cognetti	**0**
SARCOMA				
O	A European treatment protocol for bone-sarcoma in patients older than 40 years	Medical Oncology "A"	Ferraresi	**6**
O	A phase II, open label, non-randomized study of second or third line treatment with the combination of sorafenib and everolimus in patients affected by relapsed and non-resectable high-grade osteosarcoma.	Medical Oncology "A"	Ferraresi	**3**
O	A Randomized Phase 3, Multicenter, Open-Label Study Comparing TH-302 in Combination with Doxorubicin vs. Doxorubicin Alone in Subjects with Locally Advanced Unresectable or Metastatic Soft Tissue Sarcoma	Medical Oncology "A"	Ferraresi	**0**
O	Expression of the ABCB1/P-glycoprotein as a factor for the biological stratification of non-metastatic osteosarcoma of the limbs: prospective study	Medical Oncology "A"	Ferraresi	**0**
C	High-dose ifosfamide for continuous and prolonged administration using a portable infusion device in soft-tissue sarcomas of adults in advanced phase in second- or higher line chemotherapy	Medical Oncology "A"	Ferraresi	**7**
O	Localized high-risk soft tissue sarcomas of the extremities and trunk in adults: an integrated approach comprising standard vs histotype-oriented neoadjuvant chemotherapy (ISG-STS 10-01)	Medical Oncology "A"	Ferraresi	**2**
C	Observational clinical study for the treatment of non-metastatic osteosarcoma of the limbs	Medical Oncology "A"	Ferraresi	**8**
O	Open-label trial of Imatinib in patients with Desmoid Tumor and Chondrosarcoma	Medical Oncology "A"	Ferraresi	**3**
O	Open-label trial of Imatinib in patients with Desmoid Tumor and Chondrosarcoma	Medical Oncology "B"	Lopez	**3**
O	Phase II trial on the neoadjuvant treatment of high-risk soft-tissue sarcomas of the limbs and trunk	Medical Oncology "B"	Lopez	**4**
O	Phase III trial on the efficacy of dose intensification in patients with non-metastatic Ewing sarcoma	Medical Oncology "A"	Ferraresi	**3**
O	Y-IMAGE: a non-interventional multicenter, prospective study to evaluate treatment outcome as assessed in routine clinical practice on patients with advanced soft tissue sarcoma treated with trabectedin according to the Summary of Product Characteristics (SmPC)	Medical Oncology "A"	Ferraresi	**0**
UROLOGICAL				
C	A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety. Study of Oral MDV3100 in Chemotherapy-Na[illegible]ve Patients with Progressive Metastatic Prostate Cancer Who have failed Androgen Deprivation Therapy	Urology	Gallucci	**0**

O	A Prospective Observational Safety Study in Patients with Advanced ProstateCancer Treated with Firmagon® (Degarelix) or a GnRH Agonist	Urology	Gallucci	**14**
O	A Prospective Observational Study of Real World Treatment Patterns and Treatment Outcomes in Patients with Advanced or Metastatic Renal Cell Carcinoma Receiving Pazopanib	Medical Oncology "A"	Milella	**1**
O	A randomized, double-blind, placebo-controlled phase III study to evaluate the efficacy and safety of pazopanib as adjuvant therapy for subjects with localized or locally advanced RCC following nephrectomy	Medical Oncology "A"	Mlella	**3**
C	An Open Label Study of Abiraterone Acetate in Subjects with Metastatic Castration-Resistant Prostate Cancer Who Have Progressed After Taxane-Based Chemotherapy	Medical Oncology "A"	Cognetti	**18**
C	Androgen deprivation therapy withdrawal versus maintenance and intermittent docetaxel therapy versus continuous administration in patients with prostate cancer resistant to chemical castration	Medical Oncology "A"	Carlini	**0**
C	Medical optimization of TORisel (MoTOR): multicenter, phase II evaluation of torisel as ii-line treatment for metastatic RCC patients progressing after cytokine therapy, tyrosine kinase, or angiogenesis inhibitors	Medical Oncology "A"	Cognetti	**15**
C	Modification of the coagulation parameters in the oncology patient undergoing anesthesia for prostatectomy: pilot, observational and prospective study	Anaesthesiology	Forastiere	**100**
O	Multicenter, randomized phase III trial: radical prostatectomy only versus radical prostatectomy and intraoperative radiotherapy (IORT) in prostatic adenocacinoma patients at high risk for recurrence	Radiotherapy	Saracino	**2**
O	Observational study for the evaluation of the predictive value of in vitro pharmacosensitivity on cancer stem cells and the phosphoproteomic profiles in patients with advanced renal cell cancer that are candidates for therapy with multi-angiokinase and mTOR inhibitors	Scientific Directorate/Urology	De Maria/Gallucci	**29**
C	Observational study on the therapeutic attitude in prostate carcinoma patients	Radiotherapy	Pinnarò	**40**
O	Pilot feasibility study on the dose increase with intensity modulation radiotherapy (IMRT) in prostate carcinoma with intermediate prognosis	Radiotherapy	Petrongari	**39**
O	Randomized phase II study comparing hypofractionated and conventional radiotherapy in prostate cancer of intermediate or unfavorable prognosis, in association with hormone therapy	Radiotherapy	Saracino	**1**
O	Randomized, Open Label, Multi-Center Study Comparing Cabazitaxel at 25 mg/m2 and at 20 mg/m² in Combination With Prednisone Every 3 Weeks to Docetaxel in Combination With Prednisone in Patients With Metastatic Castration Resistant Prostate Cancer Not Pretreated With Chemotherapy	Medical Oncology "A"	Carlini	**6**
O	Register of treatment patterns in patients with metastatic castration-resistant prostate cancer (MCRPCc) with progression during or after docetaxel-based regimen	Medical Oncology "A"	Carlini	**6**

C	Retrospective study inmetastatic RCC patients treated with Sorafenib as first or seconf line target therapy. Three years of experience in Italy	Medical Oncology "A"	Milella	**14**
O	Sunitinib either before or after cytoreductive nephrectomy a phase II trial in patients with metastatic renal cell carcinoma	Medical Oncology "A"	Cognetti	**14**
MISCELLANEA				
O	A 12 months, prospective, observational study evaluating impact of DMT treatment on the emotional burden in recently diagnosed Multiple Sclerosis patients	Neurology	Koudriavtseva	**2**
C	A large-scale trial testing the intensity of CYTOreductive therapy to prevent cardiovascular events In patients with Polycythemia Vera (PV) – CYTO-PV	Haematology Oncology	Spadea	**2**
C	A multinational, multicenter, randomized, parallel-group study performed in subjects with Relapsing-Remitting Multiple Sclerosis (RRMS) to assess the efficacy, safety and tolerability of Glatiramer Acetate (GA) injection 40 mg administered three times a week compared to placebo in a double-blind design	Neurology	Koudriavtseva	**1**
O	Analysis of the transcriptional expression profile and microRNAs in brain metastases from primary tumors of various origin	Experimental oncology	Blandino/Telera	**49**
C	Anesthesia and modifications of the immune response	Anaesthesiology	Forastiere	**28**
C	BEACON - Prospective study on adhesion to treatment, way of addressing difficulties and nursing support in patients treated with Betaferon	Neurology	Koudriavtseva	**6**
C	DB2113360: A multicenter trial comparing the efficacy and safety of GSK573719/GW642444 with GW642444 and with tiotropium over 24 weeks in subjects with COPD	Pulmonary Phisiopathology	Cilenti	**2**
O	Development of effective cancer therapies based on functional proteomics and cancer stem cell targeting	Scientific Directorate	De Maria	**289**
O	Effect of intraoperative fluidotherapy on postoperative morbidity and mortality in major oncological surgery in high-risk patients: prospective, randomized comparison of three different fluidotherapy regimen (RFG, LFG, GDTFG)	Anaesthesiology	Forastiere	**140**
O	Electrochemotherapy for the treatment of bone metastases from solid tumors	Orthopaedics	Biagini	**1**
O	Epidemiologic registry named REGIRE, transversal observational study for the evaluation of epidemiologic data of prevalence and incidence of respiratory failure aimed at an appropriate health planning and optimal employ of economic resources in the treatment of the disease	Pulmonary Phisiopathology	Cilenti	**12**
C	Evaluation of the impact of a direct specific information to patients and risk-reduction precedure in the detection of toxicity, incidents and compliance in oral oncologic therapies	Pharmacy	Musicco	**154**

O	Isotonic contrast (iodixanol) administration vs. low osmolar contrast (iopromide) use: evaluating risk of contrast-induced nephropathy in cancer patients at very low risk	Radiology and Diagnostic Imaging	Canitano	**344**
O	Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy	Neurology	Koudriavtseva	**0**
O	Microneurosurgical, endoscopy-assisted removal of pituitary adenomas by transphenoidal route. Observational study and early evaluation of the results by MR	Neurosurgery	Pompili	**174**
O	Miniinvasive supraorbitary approach for the removal of tumors in the saddle region	Neurosurgery	Pompili	**39**
O	Miniinvasive unilateral approach for the removal of intradural spinal tumors. Observational study	Neurosurgery	Pompili	**130**
O	Modification of the gene and microRNA expression profile in vivo during chemo hyperthermia in patients undergoing peritectomy for carcinosis of any origin except mesothelioma: pilot study	Digestive Endoscopy	Valle	**9**
O	Multicenter prospective and observational study to evaluate the impact of an electronic device for self-injection on the psycho-social parameters in patients with Recurring Multiple Sclerosis	Neurology	Koudriatsveva	**9**
O	Multicenter, open label and observational Italian study performed in Centers for Pain Medicine on long-term surviving persons, not patients, with previous cancer diagnosis, in a disease-free state, that suffer from algias and fatigue linked to cancer and cancer therapies	Intensive Care, Pain Therapy	Di Emidio	**30**
O	Multicenter, retrospective observational study on the use of clinical data for scientific goals in patients with myelodisplastic syndromes that are followed in the department of hematology	Haematology Oncology	Petti	**41**
O	Observational clinical study on the hypercoagulability and efficacy of short-term or long-term antithrombotic prophylaxis with low molecular weight heparins in cancer patients carrying a permanent central venous catether	Intensive Care, Pain Therapy	Laurenzi	**76**
O	Observational study for the monitoring of chronic, Ph negative myelodisplastic syndromes (SMPC-Ph neg) in adults	Haematology Oncology	Spadea	**0**
O	Observational study of patients undergoing somatectomy and vertebrectomy performed at the same time, for the ablation and reconstruction, with stabilization, of vertebral metastases	Neurosurgery	Caroli	**48**
O	Observational study of the surgical treatment for the ablation and reconstruction with stabilization, of primary vertebral tumors	Neurosurgery	Caroli	**25**
C	Observational study on the therapeutic suitability of patients with moderate BPCO	Pulmonary Phisiopathology	Piperno	**15**
C	Observational study on the use of micafungin as therapy for systemic fungal infections	Infectivology	Toma	**5**
O	Observational study on the use of the most advanced surgical techniques and technologies in the domain of spinal tumors	Neurosurgery	Raus	**89**

O	Phase II clinical trial of high dose proton pump inhibitors (Lansoprazole) in patients with advanced and unresponsive thyroid, prostate and breast cancer	Endocrinology	Appetecchia	**3**
C	Phase II study of nilotinib efficacy in Pigmented Villo-Nodular Synovitis / Tenosynovial Giant Cell Tumor (PVNS / TGCT)	Medical Oncology "A"	Ferraresi	**3**
O	Preliminary study on the engineering of bone and muscle tissue	Orthopaedics	Biagini	**4**
O	Prevention of pulmonary atelectasias with manoeuvers of recruitment during robotic, gynecologic surgery in obese patients	Anaesthesiology	Fabrizi	**15**
O	Prospective evaluation of plasma posaconazole levels in patients with hematologic diseases under treatment with the anifungal drug posaconazole	Haematology Oncology	Spadea	**11**
O	Prospective evaluation of plasma voriconazole levels in patients with hematologic diseases under treatment with the anifungal drug voriconazole	Haematology Oncology	Spadea	**1**
O	Prospective, randomized comparison between different techniques of post-thoracotomic analgesia: evaluation of the quality of the analgesia and complications after thoracic surgery	Anaesthesiology	Forastiere	**32**
O	Ranolazine to treat early cardiotoxicity induced by antitumor drugs	Medical Oncology "A"	Fabi	**13**
C	Role of Aprepitant in the prevention of cisplatin-induced delayed vomiting: controlled double-blind study	Medical Oncology "A"	Fabi	**5**
O	Role of beta-arrestin as multifunctional adapter of the cell motility controlled by G-protein coupled receptors	Experimental oncology	Rosanò	**0**
O	Role of oxidative stress in multiple sclerosis. Proteomic analysis and red-ox proteomics	Neurology	Koudriavtseva	**101**
C	Serum and phosphoproteomics for the identification of specific tumor markers for the early diagnosis and targeted therapy of solid tumors - Italy-USA Project	Experimental oncology	Fanciulli	**4501**
O	Sicoa Patient Atrial Fibrillation - ISPAF Investigation	Cardiology	Morace	**56**
O	Study of the polymorhic profiles in patients undergoing peritonectomty and hyperthermic antiblastic inraperitoneal perfusion with cisplatin and doxorubicin or mitomycin	Digestive Endoscopy	Valle	**6**
O	TOP-TYSABRI Observational Program	Neurology	Koudriavtseva	**18**

Clinical Trials active in 2013

BRAIN				
Status	**TITLE**	**DIVISION**	Principal Investigator	**Patients (total IRE)**
O	A double-blind, placebo-controlled, randomized, Phase IIIb trial evaluating the efficacy and safety of standard of care (SOC) +/-continuous bevacizumab treatment following progression of disease (PD) in patients with glioblastoma (GBM) after first (1st)-line treatment with radiotherapy, temozolomide and bevacizumab	Medical Oncology "A"	Fabi	0
O	A Prospective, Multi-center Trial of NovoTTF-100A Together With Temozolomide Compared to Temozolomide Alone in Patients with Newly Diagnosed GBM	Neurosurgery	Carapella	4
O	Brain metastases: traditional surgery, innovative approaches, utilisation of novel technologies in the operating theatre	Neurosurgery	Pompili	222
O	Economic analysis of the social and healthcare costs of epilepsy secondary to brain tumors	Psichiatric Department	Maschio	0
O	Evaluation of seizure control and quality of life in patients with brain tumor related epilepsy treated with Lacosamide as add-on therapy: a prospective explorative study with a historical control group	Psichiatric Department	Maschio	0
O	Evaluation of seizure control, quality of life in patients with brain tumor-related epilepsy treated with zonisamide as add-on therapy: a osservational pilot study	Psichiatric Department	Maschio	10
O	Multicenter, randomized, non-comparative, open-label phase II trial on the efficacy of Ortataxel and Fotemustine in recurrent glioblastoma	Neurology	Pace	1
O	Multi-centre, No-Profit Observational trial to evaluate the efficacy of Gliadel® Wafer (GW) plus concomitant temozolomide in patients with newly-diagnosed high grade glioma	Neurosurgery	Carapella	3
O	Observational study on the evaluation of the cognitive impairment in brain tumor patients	Neurology	Pace	207

O	Project for continuing, integrated assistance and neurorehabilitation at home for patients with brain tumors	Neurology	Pace	823
O	Randomized Non Comparative Phase II Trial With Bevacizumab and Fotemustine in the Treatment of Recurrent Glioblastoma	Medical Oncology "A"	Fabi	9
O	Tissue characterization of glial tumors with diffusion, perfusion and 3Tesla MR. Correlation with morphologic MR and histopathological findings.	Radiology and Diagnostic Imaging	Vidiri	16
C	Translational-observational study: prognostic value of some genetic alteration (1p, 19q, 10q) in low-grade gliomas	Neurology	Pace	104
O	Weekly carboplatin in the treatment of recurring high-grade gliomas: observational study	Medical Oncology "A"	Fabi	0
BREAST				
O	A multicenter randomized phase II study to compare the combination trastuzumab and capecitabine, with or without pertuzumab, in patients with HER2-positive metastatic breast cancer that have progressed after one line of trastuzumab-based therapy in the metastatic setting (PHEREXA)	Medical Oncology "A"	Cognetti	1
O	A Phase 2 Randomized, Double-Blind, Placebo-Controlled, 2-Arm, Multi-Center Study Comparing Tivozanib Hydrochloride In Combination With Paclitaxel Versus Placebo In Combination With Paclitaxel in the Treatment of Subjects With Locally Recurrent and/or Metastatic Triple Negative Breast Cancer	Medical Oncology "A"	Cognetti	0
O	A Phase 2, Single-Arm, Open-Label, Multicenter Study of the Clinical Activity and Safety of Enzalutamide in Patients With Advanced, Androgen Receptor-Positive, Triple-Negative Breast Cancer	Medical Oncology "A"	Cognetti	0
O	A Phase III prospective, two-cohort non-randomized, multi-centre, multinational, open label study to assess the safety of assisted- and self-administered subcutaneous trastuzumab as adjuvant therapy in patients with operable her2-positive early breast cancer	Medical Oncology "A"	Cognetti	4
C	A Phase III randomized study evaluating the efficacy and safety of continued and re-induced bevacizumab in combination with chemotherapy for patients with locally recurrent or metastatic breast cancer after first-line chemotherapy and bevacizumab treatment	Medical Oncology "A"	Fabi	9

O	A phase III randomized, double blind placebo controlled study of BKM120 with fulvestrant, in postmenopausal women with hormone receptor-positive HER2-negative locally advanced or metastatic breast cancer which progressed on or after aromatase inhibitor treatment	Medical Oncology "A"	Cognetti	2
O	A Phase III Randomized, Double Blind, Placebo Controlled Study of BKM120 With Fulvestrant, in Postmenopausal Women With Hormone Receptor-positive HER2-negative AI Treated, Locally Advanced or Metastatic Breast Cancer Who Progressed on or After mTOR Inhibitor Based Treatment	Medical Oncology "B"	Vici	0
O	A Randomised, Double-blind, Parallel-group, Multicentre, Phase III Study to Compare the Efficacy and Tolerability of Fulvestrant (FASLODEXTM) 500 mg with Anastrozole (ARIMIDEXTM) 1 mg as Hormonal Treatment for Postmenopausal Women with Hormone Receptor-Positive Locally Advanced or Metastatic Breast Cancer Who Have Not Previously Been Treated With Any Hormonal Therapy (FALCON)	Medical Oncology "A"	Papaldo	1
O	A Randomized Trial with factorial Design comparing Fulvestrant ± Lapatinib ± Aromatase Inhibitor in metastatic breast cancer progressing after Aromatase Inhibitor therapy	Medical Oncology "A"	Cognetti	8
O	An open-label, multi-center, expanded access study for postmenopausal women with estrogen receptor positive locally advanced or metastatic breast cancer who have progressed following prior endocrine therapy, investigating the treatment of everolimus (RAD001) in combination with exemestane	Medical Oncology "A"	Cognetti	14
O	An open-label, multi-center, expanded access study for postmenopausal women with estrogen receptor positive locally advanced or metastatic breast cancer who have progressed following prior endocrine therapy, investigating the treatment of everolimus (RAD001) in combination with exemestane	Medical Oncology "B"	Vici	19
O	Assessment of Fracture Risk associated to aromatase Inihibitors by QUS	Endocrinology	Appetecchia	0
O	Burden of disease in patients with advanced breast cancer receiving oral versus intravenous (IV) vinorelbine and their caregivers in Europe	Medical Oncology "A"	Cognetti	6
O	Collection of retrospective data on the use of non-PEGylated liposomal doxorubicin and cyclophosfamide in sequential protocols with taxane in the neoadjuvant setting in patients with HER2-negative mammary carcinoma and contraindication for antrcycline use	Medical Oncology "B"	Vici	30
O	Diagnostic Accuracy of Contrast-Enhanced, Spectral Mammography (CESM) and 3 Tesla Magnetic Resonance Compared with Full Field Digital Mammography plus Ultrasound in breast lesion detection and characterization: results from a (pilot), open-label, single-centre prospective study	Radiology and Diagnostic Imaging	Ferranti	0

O	Elaboration of a new nomogram based on quantitative measurement of Cytokeratin 19 mRNA by One Step Nucleic Acid Amplification (OSNA) to predict non-sentinel lymph status in breast cancer patients with a positive sentinel lymph node. European multicenter study	Breast Unit	Di Filippo	393
O	Epigenetic control of the progression of mammary cancer: clinical studies and studies in animal models	Psichology	Pugliese	65
O	Evaluation of the response to neoadjuvant chemotherapy in mammary cancer with dynamic imaging and 3 Tesla diffusion MRI	Radiology and Diagnostic Imaging	Marsella	15
O	Fertility in young females affected by mammary cancer	Medical Oncology "B"	Vici	0
O	Fulvestrant 500 mg: evaluation of the clinical benefit in patients with hormone-responsive, metastatic mammary carcinoma: prospective, observational cohort study	Medical Oncology "B"	Vici	22
O	HERLAPAC. Observational, retrospective study in HER2+ metastatic mammary carcinoma treated with lapatinib and capecitabine	Medical Oncology "A"	Fabi	0
O	Hormonal adjuvant therapy and bone health in male mammary carcinoma	Medical Oncology "A"	Fabi	0
O	Intraoperative diagnosis of the sentinel lymph node in mammary carcinoma with the RT-PCR methodology using the One Step Nucleic Acid Amplification (OSNA) procedure	Histology and Cytopathology	Marandino	655
O	Introducing flexibility in targeted tumor therapy: ErbB2 antibodies and immunoconjugates	Experimental Oncology	Giacomini	0
O	Localisation of the surgical bed by means of fusion of images from 3 Tesla MR and computerized axial tomography for the design of radiotherapy treatment in patients with mammary tumor that have undergone conservative surgery	Radiology and Diagnostic Imaging	Ferranti	12
O	Neoadjuvant chemotherapy in mammary carcinoma patients: retrospective evaluation of efficacy and tolerability	Medical Oncology "B"	Vici	392

O	Observational multi-center study on the monitoring of the tolerability and quality of life in patients with metastatic mammary cancer under treatment with Eribulin (Halaven?)	Medical Oncology "B"	Vici	13
O	Observational study of the treatment of small cell tumors of the female genitals	Medical Oncology "B"	Vici	4
C	Observational study on the evluation of the cognitive impairment in mammary carcinoma patients	Neurology	Pace	23
O	Phase I/II trial and pharmacokinetics of continuous low-dose, oral vinorelbine in patients with advanced mammary tumors	Medical Oncology "A"	Papaldo	25
O	Phase II trial of primary chemotherapy with trastuzumab in combination with docetaxel followed by epirubicin-cyclophosphamide in patients with HER-2-overexpressing operable breast cancer	Medical Oncology "B"	Vici	43
O	Prevalence of vertebral fractures in women with mammary carcinoma undergoing hormonal adjuvant therapy with aromatase inhibitors	Medical Oncology "A"	Fabi	0
O	Prospective randomized study comparing quadrantectomy followed by external complementary radiotherapy with quadrantectomy associated with intraoperative radiotherapy or with partial external irradiation of the breast in a single fraction in patients with mammary carcinoma of small dimensions and >48 years in post menopause	Radiotherapy	Pinnarò	135
O	Randomized, multicenter, double-blind phase 3 study of PD-0332991 (oral CDK 4/6 inhibitor) plus letrozole versus placebo plus letrozole for the treatment of postmenopausal women with ER (+), HER2 (-) breast cancer who have not received any prior systemic anti-cancer treatment for advanced disease	Medical Oncology "A"	Cognetti	0
O	Retrospective evaluation of the efficacy of complete androgenic blockade (anti-androgen+LH-RH analogues) in metastasizing male mammary carcinoma	Medical Oncology "B"	Di Lauro	24
O	Retrospective evaluation of the efficacy of letrozole ± LH-RH analogues in metastasizing male mammary carcinoma	Medical Oncology "B"	Di Lauro	11
O	Retrospective observational study of HER2+, PT1A-B PN0 M0 mammary carcinoma	Medical Oncology "A"	Fabi	0

O	Retrospective observational study of HER2+, PT1A-B PN0 M0 mammary carcinoma	Medical Oncology "B"	Vici	10
O	Risk of recurrence in HER2+ mammary tumors. Retrospective, multicenter study	Medical Oncology "B"	Vici	255
O	Risk of relpase in mammary tumors of small dimensions with negative lymph nodes. Retrospective, multicenter analysis	Medical Oncology "B"	Vici	166
O	SentiMag-CIE: camparative evaluation for the implementation of the SentiMag/Sienna+ system in clinical routine	Breast Unit	Di Filippo	59
O	Study on the feasibility of a hypofractionated radiotherapy regime in patients undergoing conservative surgery for mammary cancer	Radiotherapy	Pinnarò	230
O	The BEACON Study (BrEAst Cancer Outcomes with NKTR-102): A Phase 3 Open-Label, Randomized, Multicenter Study of NKTR-102 versus Treatment of Physician's Choice (TPC) in Patients with Locally Recurrent or Metastatic Breast Cancer Previously Treated with an Anthracycline, a Taxane, and Capecitabine	Medical Oncology "A"	Cognetti	1
O	The Effect of Metformin, an insulin-sensitizing drug, on Breast Cancer Primary Prevention: The Plotina Breast Cancer Prevention Randomized, Placebo Controlled Trial	Experimental Oncology	Blandino	59
O	Tissue characterization of mammary lesions with 3 Tesla MR through diffusion and spectroscopy. Correlation with morphologic and dynamic MR data and histopathological confirmation	Radiology and Diagnostic Imaging	Saracca	20
ENDOCRINE				
O	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of E7080 in 131I-Refractory Differentiated Thyroid Cancer	Endocrinology	Appetecchia	2
O	A randomized, double-blind, multicenter, Phase III study of everolimus (RAD001) plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced NET of GI or lung origin - RADIANT-4	Medical Oncology "A"	Milella	0
O	Accuracy and clinical impact of 68-Ga-labeled octreotide analogues PET in diagnosis and staging of duodeno-pancreatic neuroendocrine tumors; proposal of a multicenter, prospective clinical trial	Endocrinology	Baldelli	5

C	An international, non interventional, cross sectional study to assess neuroendocrine tumor (NET) patients currently treated by somatuline autogel for history of carcinoid syndrome associated with episodes of diarrhea	Endocrinology	Baldelli	4
O	An International, Randomised, Double-Blind, Two-Arm Study to Evaluate the Safety and Efficacy of Vandetanib 150 and 300 mg/day in Patients with Unresectable Locally Advanced or Metastatic Medullary Thyroid Carcinoma with Progressive or Symptomatic Disease	Endocrinology	Appetecchia	0
O	Efficacy of adjuvant Mitotane therapy in prolonging recurrence-free survival in patients with adrenocortical carcinoma that have undergone radical surgery	Endocrinology	Appetecchia	0
C	Epidemiology of the anaplastic carcinoma of the thyroid: comparison between the decades 1990-2000 and 2001-2010	Endocrinology	Appetecchia	12
O	Multicenter 3-arm Trial to Evaluate the Efficacy and Safety of Pasireotide LAR or Everolimus Alone or in Combination in Patients With Well Differentiated Neuroendocrine Carcinoma of the Lung and Thymus - LUNA Trial	Medical Oncology "A"	Milella	0
O	Natural history, geographic distribution and biological characterization of patients with neuroendocrine tumor (NET). Multicenter, clinical-biological I.T.M.O. study	Medical Oncology "A"	Cognetti	0
C	NET Management Project: Epidemiologic-retrospective protocol of neuroendocrine tumors of the chest and gastro-entero-pancreatic tract. Epidemiologic, retrospective protocol of non-functioning, neuroendocrine tumors	Endocrinology	Appetecchia	39
O	Retrospective molecular study in patients with simultaneous occurrence of medullaary and papillary microcarcinoma of the thyroid	Experimental Oncology	Blandino/Appetecchia	0
O	Saftey of the treatment with high-dose lanreotide in neuroendocrine patients that are low responders to somatostatine analogues at standard doses	Endocrinology	Appetecchia	2
GASTROINTESTINAL				
O	A Phase II Multicentre Study of Systemic Chemotherapy versus Systemic Chemotherapy plus Selective Internal Radiotherapy (SIRT) in KRAS mutant colorectal liver metastases (IFO-SITILO 2)	Digestive Unit	Cosimelli	1

C	A Phase III Placebo-Controlled Trial Of Celecoxib In Genotype-Positive Subjects With Familial Adenomatous Polyposis	Digestive Endoscopy	Stigliano	8
O	A Randomised Open-Label Phase IIa Study to Assess the Efficacy and Safety of AZD4547 Monotherapy versus Paclitaxel in Patients with Advanced Gastric or Gastro-oesophageal Junction Cancer with FGFR2 Polysomy or Gene Amplification (Shine study)	Medical Oncology "A"	Garufi	8
O	A Randomized Phase II Trial of Second Line Therapy in Advanced Biliary Tract Cancer: Capecitabine or Capecitabine Plus Mitomycin C	Medical Oncology "A"	Milella	8
O	Analysis of microRNA expression for the identification of new serum/plasma biomarkers in colorectal cancer patients	Clinical Patology	Conti	0
O	Evaluation of 3 Tesla MRI in primary and secondary hepatic tumors undergoing selective hepatic 90Y radioembolization. Correlation of morphologic MRI and clinical outcome	Radiology and Diagnostic Imaging	Vallati	1
O	Genetic, gastroenterological consulting for familial, hereditary tumors of the colon	Digestive Endoscopy	Stigliano	631
C	HER2 early/advanced gastric epidemiology study; an assessment of HER2 status in tumor tissue samples of gastric & gastro-esophageal (GE) junction cancer	Histology and Cytopathology	Pescarmona	23
O	Isolation and characterization of tumor stem cells in intra- and extra-hepatic cholangiocarcinoma	General Surgery Epatobiliopancreatic	Grazi	16
O	Isolation and functional and molecular characterization of stem cells from gastric tumors for the development of novel therapeutic strategies	Experimental Oncology	Blandino/Garofalo	63
O	Molecular Biomarkers for Colorectal Liver Metastases Resectability after Chemotherapy plus Cetuximaab	Medical Oncology "A"	Garufi	12
O	MR diffusion of the liver: optimisation of the IVIM technique for the characterisation of focal liver lesions	Radiology and Diagnostic Imaging	Caterino	0

O	Multicenter observational study on the treatment with nab-paciltaxel in patients with metastatic pancreatic cancer	Medical Oncology "A"	Milella	0
O	Phase II randomized trial of MEK inhibitor MSC1936369B or placebo combined with gemcitabine in metastatic pancreas cancer subjects	Medical Oncology "A"	Milella	4
O	Phase II single-arm trial of Tivantinib (ARQ197) in combination with cetuximab in patients with locally advanced or metastatic colorectal cancers that are KRAS wild-type, resistant to EGFR inhibitors, and overexpressing MET in IHC (MET high)	Medical Oncology "A"	Garufi	0
O	Retrospective analysis of the efficacy of first-line treatment of docetaxel-containing regimen in patients with advanced-stage gastric adenocarcinoma	Medical Oncology "B"	Di lauro	15
O	Retrospective analysis of the efficacy of second-line treatment in patients with advanced-stage biliary tract cancer after gemcitabine chemotherapy	Medical Oncology "B"	Di Lauro	50
O	Study of the mutations of genes K-RAS, BRAF and PIK3CA as factors of prognostic and predictive relevance in the response to therapy of metastatic, colorectal tumors	Histology and Cytopathology	Mottolese	898
O	Systematic collection of hepatocarcinoma, intrahepatic cholangiocarcinoma and cholangiocarcinoma of the hilus that have undergone hepatic resection in the context of the Italian chapter IT-IHPBA	General Surgery Epatobiliopancreatic	Grazi	0
GYNAECOLOGICAL				
O	A multicenter study in patients with stage III-IV epithelial ovarian cancer treated with carboplatin/paclitaxel with bevacizumab: clinical and biological prognostic factors	Medical Oncology "A"	Savarese	1
O	A Phase 3 Randomized, Double-blind, Placebo-controlled, Multicenter Study of AMG 386 With Paclitaxel and Carboplatin as First-line Treatment of Subjects With FIGO Stage III-IV Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancers	Medical Oncology "A"	Savarese	0
O	A Phase 3, Randomized, Double-Blind Trial of Pegylated Liposomal Doxorubicin (PLD) Plus AMG 386 or Placebo in Women With Recurrent Partially Platinum Sensitive or Resistant Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	Medical Oncology "A"	Savarese	2

O	A Phase II Randomized Open Label Study of MM-121 in combination with Paclitaxel versus Paclitaxel alone in patients with Platinum Resistant/ Refractory Advanced Ovarian Cancers	Medical Oncology "A"	Savarese	2
O	A Phase III Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed BRCA Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy	Medical Oncology "A"	Cognetti	0
O	A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Patients with BRCA Mutated Advanced (FIGO Stage III-IV) Ovarian Cancer following First Line Platinum Based Chemotherapy	Medical Oncology "A"	Cognetti	0
O	A randomized phase II study of carboplatin and paclitaxel +/- cetuximab, in advanced and/or recurrent cervical cancer	Medical Oncology "A"	Savarese	1
O	A Randomized Phase II Trial of Carboplatin-Paclitaxel compared to Carboplatin-Paclitaxel-Bevacizumab in advanced (stage III-IV) or recurrent endometrial cancer	Medical Oncology "A"	Savarese	0
O	A Randomized Phase II Trial of Carboplatin-Paclitaxel compared to Carboplatin-Paclitaxel-Bevacizumab in advanced (stage III-IV) or recurrent endometrial cancer	Medical Oncology "B"	Vici	1
O	A two-part, randomized phase iii, double-blind, multicenter trial assessing the efficacy and safety of pertuzumab in combination with standard chemotherapy vs. placebo plus standard chemotherapy in women with recurrent platinum resistant epithelial ovarian cancer and low HER3 mRNA expression	Medical Oncology "A"	Savarese	0
O	Double p16/ki67 staining as a marker in cytological cervical-vaginal samples: correlations with cytologic and histologic diagnosis, presence of papillomavirus (HPV) and HPV genotyping	Histology and Cytopathology	Vocaturo	140
O	Evaluation of efficiency indices of diagnostic tests in populations at risk for endometrial carcinoma	Ginecology	Vocaturo	414
C	Evaluation of the preformance of an assay for the genotyping of HPV (Linear Array) on histologic samples of cervical lesions	Histology and Cytopathology	Vocaturo/Benevolo	39
O	Functional imaging with diffusion 3 Tesla MR in the early evaluation of the response to radiochemotherapy in cervical cancer	Radiology and Diagnostic Imaging	Marsella	20

O	HPV vaccination in women candiates for undergoing conservative theapy for HPV-correlated dysplastic pathology of the uterine cervix or ano-genital condyloma	Ginecology	Mariani	37
O	Multicenter, randomized, controlled, clinical trial comparing two follow-up regimen at different frequencies of examinations in patients treated for endometrial cancer	Ginecology	Vizza	6
O	Observational study of the treatment of borderline ovarian tumors	Ginecology	Vizza	0
O	Observational study of the treatment of borderline ovarian tumors	Medical Oncology "B"	Vici	6
O	Randomized clinical trial comparing different mini-inasive surgical procedures in the treatment of early-stage endometrial cancer	Ginecology	Vizza	44
O	Retrospective evaluation of the eficacy of the GEMOX scheme in patients with heavily protracted ovarian carcinoma	Medical Oncology "B"	Vici	41
O	Targeting endothelin-1 signalling to circumvent chemoresistance in epithelial ovarian cancer	Experimental Oncology	Bagnato	0
O	Use of new molecular assays in the diagnosis and post-treatment follow-up of pre-cancerous lesions	Ginecology	Mariani	16
HAEMATOLOGICAL				
O	"Geriatric Assessment Adapted" Therapy for Ph- ALL Elderly Patients	Haematology oncology	Spadea	2
C	A Multicenter Total Therapy Strategy for De Novo Adult Philadelphia Chromosome Positive (Ph+) Acute Lymphoblastic Leukemia (ALL)	Haematology oncology	Spadea	0

O	A non-interventional observational post authorisation safety study of subjects treated with lenalidomide	Haematology oncology	Mengarelli	13
C	A open label, phase 2, non randomized, multicentre trial to assess the feasibility of induction treatment with 5-azacitidine (5-AZA) followed by allogeneic stem cell transplantation (allo-SCT) or continued 5-AZA treatment in patients without a suitable -sibling or unrelated- stem cell donor with IPSS Int-2/High risk myelodysplastic syndromes (MDS)	Haematology oncology	Spadea	0
C	A Phase II Multi-centre Study of MBVD in Elderly and/or Cardiopathic Patients Affected by Hodgkin's Lymphoma (HL)	Haematology oncology	Pisani	1
O	A phase II study of R-CHOP with intensive CNS prophylaxis and scrotal irradiation in patients with primary testicular diffuse large B-cell lymphoma	Haematology oncology	Pisani	1
O	A phase II, multi-center, open label study of cyclophosphamide in multiple myeloma patients with biochemical progression during lenalidomide-dexamethasone treatment for relapsed/refractory multiple myeloma	Haematology oncology	Mengarelli	4
C	A phase III, intergroup multicentre, randomized, controlled 3 arm parallel group study to determine the efficacy and safety of lenalidomide in combination with dexamethasone (RD) versus melphalan, prednisone and lenalidomide (MPR) versus cyclophosphamide, prednisone and lenalidomide (CPR) in newly diagnosed multiple myeloma elderly subjects	Haematology oncology	Pisani	2
O	A randomized phase III study to compare Bortezomib, Melphalan, Prednisone (VMP) with High Dose Melphalan followed by Bortezomib, Lenalidomide, Dexamethasone (VRD) consolidation and Lenalidomide maintenance in patients with newly diagnosed multiple myeloma	Haematology oncology	Pisani	6
O	A randomized, open-label, multicentre, two-arm phase III comparative study assessing the role of mediastinal radiotherapy after Rituximab containing chemotherapy regimens to patients with newly diagnosed Primary Mediastinal Large B-Cell Lymphoma (PMLBCL)	Haematology oncology	Pisani	2
O	A Randomized, Open-label, Phase 3 Trial of A+AVD Versus ABVD as Frontline Therapy in Patients With Advanced Classical Hodgkin Lymphoma	Haematology oncology	Mengarelli	1
O	A single arm, multicentre, phase IIIb study to evaluate safety, efficacy and pharmacokinetics (PK) of subcutaneous (SC) rituximab administered during induction phase or maintenance in previously untreated patients with CD20+ diffuse large B cell lymphoma (DLBCL) or follicular lymphoma (FL)	Haematology oncology	Mengarelli	6
O	An open-label, multicenter, expanded access study of INC424 for patients with primary myelofibrosis (PMF) or post polycythemia myelofibrosis (PPV MF) or postessential thrombocythemia myelofibrosis (PET-MF)	Haematology oncology	Petti	4

C	Ancillary, observational study on the characterization of peripheral blood biomarkers in patients with Hodgkin lymphoma treated according protocols that foresee a PET-guided strategy	Haematology oncology	Romano	0
C	Bendamustine, lenalidomide and rituximab (R2-B) combination as a second-line therapy for first relapsed-refractory mantle cell lymphomas: a phase ii study	Haematology oncology	Palombi	0
O	Clinical-therapeutic profile of chronic lymphocytic leukemia patients treated with bendamustine and rituximab combination in the current clinical practice according to the indications authorized in Italy: observational study	Haematology oncology	Pisani	0
O	Dose-dense ABVD as first line therapy in early stage unfavorable Hodgkin's Lymphoma: a phase II, prospective, multi-center study	Haematology oncology	Petti	5
O	Early salvage with high-dose chemotherapy and stem cell transplantation in advanced stage Hodgkin's lymphoma patients with positive positron emission tomography after two courses of ABVD (PET-2 positive) and comparison of radiotherapy versus no radiotherapy in PET-2 negative patients	Haematology oncology	Romano	12
O	Eltrombopag for the treatment of thrombocytopenia due to low- and intermediate risk myelodysplastic syndromes.	Haematology oncology	Romano	0
O	Front-line nilotinib treatment of BCR-ABL+ Chronic Myeloid Leukemia in chronic phase. An observational multicenter study of the GIMEMA CML Working Party	Haematology oncology	Romano	0
O	Front-line treatment of BCR-ABL+ Chronic Myeloid Leukemia (CML) with dasatinib. An observational multicentric study	Haematology oncology	Romano	0
C	Gemtuzumab Ozogamicin (GO) Monotherapy Versus Standard Supportive Care for Previously Untreated **AML** in Elderly Patients Who Are Not Eligible for Intensive Chemotherapy: A Randomized Phase II/III Trial (**AML-19**) of the EORTC-LG and GIMEMA-ALWP	Haematology oncology	Romano	0
O	Multicenter, prospective, non-interventional register for monitoring the incidence and diagnostic and therapeutic behavior in the management of infections in patients with acute lymphatic leukemia	Haematology oncology	Spadea	10
O	Multicenter, prospective, non-interventional register for the monitoring of therapy-related, acute leukemias/myelodisplastic syndromes. Molecular characterization and evaluation of individual susceptibility	Haematology oncology	Spadea	4

O	Observational prospective multicenter study on lymphomas and chronic lymphoproliferative diseases in adult patients in the Lazio region	Haematology oncology	Pisani	0
O	Observational study in patients with adult T-cell lymphoblastic lymphoma undergoing intensive chemo/radiotherapy or intensive chemotherapy followed by transplantation. Evaluation of clinical, pathological and biological parameters	Haematology oncology	Spadea	0
O	Observational study of conception/pregnancy in adult patients with chronic myeloid leukemia (CML) treated with tyrosine kinase inhibitors	Haematology oncology	Romano	0
O	Phase II multicenter study to evaluate the efficacy and safety of Bendamustine in adjunct to Etoposide, Aracytabin and Melphalan (BeEAM) as a preparative regimen for autologous stem cell transplantation in refractory/relapsed aggressive B-cell non-Hodgkin lymphoma patients	Haematology oncology	Mengarelli	2
O	Prospective collection of data of possible prognostic relevance in patients with indolent non-follicular b-cell lymphomas	Haematology oncology	Palombi	0
O	Prospective survey on severe infections during a multicenter study of risk-adapted, MRD-directed therapy for young adults with newly diagnosed acute myeloid leukemia	Haematology oncology	Spadea	1
O	Radiotherapy in the initial stages of Hodgkin lymphoma: evaluation of the impact of the use of PET-TC performed in correspondence of the treatment site on the target delineation. Observational study	Radiotherapy	Petrongari	0
O	Randomized phase II trial on primary chemotherapy with high-dose methotrexate and high-dose cytarabine with or without thiotepa, and with or without rituximab, followed by brain irradiation vs. brain irradiation associated with high-dose BCNU and thiotepa chemotehrapy followed by autologous stem cells transplantation in immunocompetent patients with newly diagnosed primary CNS lymphoma	Haematology oncology	Pisani	3
O	Retrospective study aimed at validating the GITMO criteria for the identification of Poor Mobilizer (PM) patients in the serring of multiple myeloma and lymphomas	Haematology oncology	Mengarelli	70
C	Risk-adapted, MRD-directed Therapy for Young Adults With Newly Diagnosed Acute Myeloid Leukemia	Haematology oncology	Mengarelli	5
O	Rituximab plus Bendamustine as front line treatment in frail elderly (>70 years) patients with diffuse large B-cell non-Hodgkin's lymphoma: a phase II multicenter study of the Fondazione Italiana Linfomi (FIL)	Haematology oncology	Palombi	0

C	SEIFEM 2012: impact of invasive fungal infections in patients with acute myeloid leukemia at diagnosis on the outcome of the basic pathology	Haematology oncology	Petti	0
O	Staging and evaluation of the response to anti-angiogenic therapies in myelomas with 3 Tesla diffusion MR	Radiology and Diagnostic Imaging	Kayal	6
HEAD AND NECK				
O	Application of ECT for the local treatment of head and neck cancer. Analysis of the efficacy of the procedure for tumor control and survival	Otorinolaringoiogy	Spriano	12
O	Diffusion MR with IVIM technique in head and neck tumors (rhinopharynx, oral cavity, oropharynx, hypopharynx) for the predictive evaluation of the response to radiochemotherapy treatments with 3 Tesla MR	Radiology and Diagnostic Imaging	Vidiri	10
C	Evaluation of parameters of diffusion MR in patients with head and neck tumors: comparison between different modalities of quantitiative analysis of the images	Radiology and Diagnostic Imaging	Marzi	37
O	Feasibility study of the integrated use of salvage surgery, intraoperative radiotherapy (IORT) and external beam radiotherapy (EBRT) in tumors of tumors of the cervical-encephalic district after radiotherapy	Radiotherapy	Pinnarò	30
O	Identification of novel coding and non-coding transcriptional targets of gain-of-function mutant p53 proteins	Experimental Oncology	Blandino	20
O	Phase II study of preoperative TPF chemotherapy in locally advanced oral cavity scarcinoma in order to improve the rate of pathological complete response	Otorinolaringology	Spriano	0
O	Pilot feasibility study on the use of intraoperative radiotherapy (IORT) as an "anticipated boost" in locally advanced tumors of the cervical-encephalic district	Radiotherapy	Marucci	38
C	Pilot study of the reiki technique applied to patients with head and neck cancer undergoing radiotherapy in order to control side effects	Radiotherapy	Bigiarini	20

O	Prospective randomized double-blind study on the treatment of oral mucositis (with a phytotherapeutic products versus placebo) in head and neck tumor patients undergoing radio-chemotherapy (RT-CT)	Radiotherapy	Giardina	102
O	Study of the correlation between the expression profile of microRNAs and clinical evolution in patients with squamous carcinomas of head and neck	Experimental Oncology	Blandino	9
O	Study on the expression profile of microRNAs in squamous carcinomas of the head and neck and in autologous, peritumoral or distant tissues	Experimental Oncology	Blandino	149
LUNG				
O	A diagnostic Study of European and Japanese advanced NSCLC patients to evaluate suitable sample types for EGFR testing: The ASSESS Study	Medical Oncology "A"	Milella	10
O	A factorial study comparing pemetrexed with gemcitabine and testing the efficacy of the addition of cisplatin in elderly patients with non squamous advanced, metastatic or recurrent NS	Medical Oncology "A"	Ceribelli	0
O	A Phase III Randomised, Double blind, Placebo controlled, Parallel, Multicentre Study to Assess the Efficacy and Safety of continuing IRESSATM 250 mg in addition to Chemotherapy versus Chemotherapy alone in Patients who have Epidermal Growth Factor Receptor (EGFR) Mutation Positive Locally advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) and have progressed on First Line IRESSATM	Medical Oncology "A"	Cognetti	2
O	A Phase III, Double-Blind, Randomised, Placebo-Controlled Study to Assess the Efficacy and Safety of Selumetinib (AZD6244; ARRY-142886) (Hyd-Sulfate) in Combination with Docetaxel, in Patients receiving second line treatment for KRAS Mutation-Positive Locally Advanced or Metastatic Non Small Cell Lung Cancer (Stage IIIB – IV) (SELECT-1)	Medical Oncology "A"	Milella	0
O	A Randomized, Double-Blind, Phase 3 Study of Docetaxel and Ramucirumab versus Docetaxel and Placebo in the Treatment of Stage IV Non-Small Cell Lung Cancer Following Disease Progression after One Prior Platinum-Based Therapy	Medical Oncology "B"	Rinaldi	0
C	An Exploratory Phase 2 Study of Pemetrexed and Cisplatin as Preoperative Chemotherapy in the Treatment of Stage IIIAN2 Nonsquamous Non-Small Cell Lung Cancer	Medical Oncology "A"	Cognetti	3
O	An open label trial of afatinib in treatment-naive (1st line) or chemotherapy pre-treated patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s)	Medical Oncology "A"	Cognetti	1

O	An open-label, non-randomized, multicenter phase I/II trial of RO5424802 given orally to non - small cell lung cancer patients who have ALK mutation and failed crizotinib treatment	Medical Oncology "A"	Ceribelli	1
O	Analysis of the transcriptional expression profile and microRNAs in stem cell subpopulations from tumor tissues of patients with pleural mesothelioma	Experimental Oncology	Blandino/Facciolo	16
O	Clinical immunotherapy study using IL-2 administered by bronchoinstillation in the treatment of pulmonary and/or mediastinal metastases from melanoma and renal cell cancer. Phase II study	Thoracic Surgery	Filippetti	2
O	Multicenter randomized controlled TECLA study (Tobacco dependence treatment in smokers performing a spirometry and the Effect of telling tobacco Consumers of their Lung Age)	Pulmonary Phisiopathology	Cilenti	1
O	Phase I/II clinical trial on the use of hyper-fractionated, conformed radiotherapy in patients with primary or small-dimension secondary lung tumors	Radiotherapy	Pinnarò	56
O	Phase III Multicenter Randomized Trial Comparing Adjuvant Pharmacogenomic-Driven Chemotherapy versus Standard Adjuvant Chemotherapy in Completely Resected Stage II-IIIA Non-Small Cell Lung Cancer	Medical Oncology "A"	Cognetti	39
O	Phase III randomized study of standard lobectomy versus sublobar resection in patients with small, stage ia non-small cell lung cancer	Thoracic Surgery	Facciolo	0
O	Phase III randomized, open-label study of the efficacy and safety of crizotinib versus pemetrexed/cisplatin or pemetrexed/carboplatin in previously untreated patients with non-squamous carcinoma of the lung harboring translocation or inversion events involving the anaplastic lymphoma kinase (ALK) gene locus	Medical Oncology "A"	Cognetti	1
O	Randomized Phase III Multicenter Trial of Customized Chemotherapy versus Standard of Care for 1st Line Treatment of Elderly Patients with metastatic Non-Small-Cell Lung Cancer	Medical Oncology "A"	Cognetti	0
O	Randomized, double-blind, placebo-controlled phase III study of first-line maintenance Tarceva vs Tarceva at the time of disease progression in patients with advanced non-small cell lung cancer (NSCLC) who have not progressed following 4 cycles of platinum-based chemotherapy.	Medical Oncology "A"	Cognetti	1
MELANOMA				
O	A multicentre, open label, randomized Phase II trial of the MEK inhibitor pimasertib or dacarbazine in previously untreated subjects with N-Ras mutated locally advanced or metastatic malignant cutaneous melanoma	Medical Oncology "A"	Ferraresi	2

A	A Phase 3, Randomized, Double- Blind Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab Versus Ipilimumab Monotherapy in Subjects with Previously Untreated, Unresectable or Metastatic Melanoma	Medical Oncology "A"	Cognetti	5
O	A Phase 3, Randomized, Double-Blind Study of BMS-936558 vs Dacarbazine in Subjects with Previously Untreated Unresectable or Metastatic Melanoma	Medical Oncology "A"	Cognetti	6
O	A phase III, double-blind, placebo-controlled study of vemurafenib versus vemurafenib plus GDC-0973 (cobimetinib) in previously untreated BRAFV600-mutation positive patients with unresectable locally advanced or metastatic melanoma	Medical Oncology "A"	Ferraresi	15
O	A phase III, randomized, double-blind, placebo-controlled study of vemurafenib (RO5185426) adjuvant therapy in patients with surgically resected, cutaneous BRAF-mutant melanoma at high risk for recurrence	Medical Oncology "A"	Cognetti	2
O	A Randomized, Open-Label, Multicenter Phase II Study of Ipilimumab Retreatment versus Chemotherapy for Subjects with Advanced Melanoma who Progressed after Initially Achieving Disease Control with Ipilimumab Therapy	Medical Oncology "A"	Cognetti	2
O	A randomized, Phase III study of Fotemustine versus the Combination of Fotemustine and Ipilimumab in Patients with Metastatic Melanoma with brain metastasis	Medical Oncology "A"	Ferraresi	0
O	Analysis of the genetic polymorphisms and soluble isoform of CTLA-4 as prognostic and predictive factors in melanoma	Medical Oncology "A"	Ferraresi	0
O	Constitution of a Clinical National Melanoma Registry (CNMR)	Breast Unit	Di Filippo	22
O	Peptide–based vaccine in combination with chemotherapy in melanoma patients: a phase II randomized clinical study	Medical Oncology "A"	Ferraresi	34
A	Randomized Open-Label Phase III Trial of BMS-936558 versus Investigator's Choice in Advanced (Unresectable or Metastatic) Melanoma Patients Progressing after Anti-CTLA-4 Therapy	Medical Oncology "A"	Ferraresi	1

O	Selection of specific markers for the development of the molecular diagnosis of sentinel lymph nodes in melanoma patients	Breast Unit	Di Filippo	39
O	The NEMO trial (NRAS melanoma and MEK inhibitor): A randomized Phase III, open label, multicenter, two-arm study comparing MEK162 versus dacarbazine in patients with advanced unresectable or metastatic NRAS mutation-positive melanoma	Medical Oncology "A"	Ferraresi	0
O	ZeSS: A Prospective Observational Safety Study of Patients with BRAFV600 Mutation-positive Unresectable or Metastatic Melanoma Treated with Vemurafenib (Zelboraf®)	Medical Oncology "A"	Cognetti	0
SARCOMA				
O	A European treatment protocol for bone-sarcoma in patients older than 40 years	Medical Oncology "A"	Ferraresi	6
O	A phase II, open label, non-randomized study of second or third line treatment with the combination of sorafenib and everolimus in patients with relapsed and non-resectable high-grade osteosarcoma.	Medical Oncology "A"	Ferraresi	5
O	A Randomized Phase 3, Multicenter, Open-Label Study Comparing TH-302 in Combination with Doxorubicin vs. Doxorubicin Alone in Subjects with Locally Advanced Unresectable or Metastatic Soft Tissue Sarcoma	Medical Oncology "A"	Ferraresi	0
O	Expression of the ABCB1/P-glycoprotein as a factor for the biological stratification of non-metastatic osteosarcoma of the limbs: prospective study	Medical Oncology "A"	Ferraresi	6
O	Localized high-risk soft tissue sarcomas of the extremities and trunk in adults: an integrated approach comprising standard vs histotype-oriented neoadjuvant chemotherapy (ISG-STS 10-01)	Medical Oncology "A"	Ferraresi	10
O	Multicenter, prospective, randomized clinical trial for the treatment of patients with recurring osteosarcoma	Medical Oncology "A"	Ferraresi	0
O	Observational, noninterventional surveillance study of patients with high-grade osteosarcoma who are candidates for liposomal mifamurtide treatment	Medical Oncology "A"	Ferraresi	0

O	Open-label trial of Imatinib in patients with Desmoid Tumor and Chondrosarcoma	Medical Oncology "A"	Ferraresi	3
O	Open-label trial of Imatinib in patients with Desmoid Tumor and Chondrosarcoma	Medical Oncology "B"	Lopez	0
O	Phase II trial on the neoadjuvant treatment of high-risk soft-tissue sarcomas of the limbs and trunk	Medical Oncology "B"	Lopez	4
O	Phase III trial on the efficacy of dose intensification in patients with non-metastatic Ewing sarcoma	Medical Oncology "A"	Ferraresi	3
O	Y-IMAGE: a non-interventional multicenter, prospective study to evaluate treatment outcome as assessed in routine clinical practice on patients with advanced soft tissue sarcoma treated with trabectedin according to the Summary of Product Characteristics (SmPC)	Medical Oncology "A"	Ferraresi	0
UROLOGICAL				
O	A Prospective Observational Study of Real World Treatment Patterns and Treatment Outcomes in Patients with Advanced or Metastatic Renal Cell Carcinoma Receiving Pazopanib	Medical Oncology "A"	Milella	1
O	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Study of ARN-509 in Men with Non-Metastatic (M0) Castration-Resistant Prostate Cancer	Urology	Gallucci	0
C	A Prospective Observational Safety Study in Patients with Advanced Prostate Cancer Treated with Firmagon® (Degarelix) or a GnRH Agonist	Urology	Gallucci	20
O	A randomized, double-blind, placebo-controlled phase III study to evaluate the efficacy and safety of pazopanib as adjuvant therapy for subjects with localized or locally advanced RCC following nephrectomy	Medical Oncology "A"	Mlella	3
O	A randomized, open label, multicenter phase 2 study, to evaluate the efficacy of Sorafenib in patients with advanced Renal Cell Carcinoma (RCC) after a radical resection of the metastases	Medical Oncology "A"	Cognetti	0

O	A Randomized, Open-Label, Phase III Study of BMS-936558 vs. Everolimus in Subjects with Advanced or Metastatic Clear-Cell Renal Cell Carcinoma Who Have Received Prior Anti-Angiogenic Therapy	Medical Oncology "A"	Cognetti	0
O	Control of prostatic cancer progression by microRNAs 15 and 16	Scientific Directorate/Urology	De Maria/Gallucci	75
O	Evaluation of the tumor aggressiveness with 3 Tesla multiparametric MR. Correlation with morphologic MR and histopahologic data	Radiology and Diagnostic Imaging	Canitano	19
O	Multicenter observational study on the treatment of patients with high-risk metastatic renal cancer	Medical Oncology "A"	Milella	0
O	Multicenter, randomized phase III trial: radical prostatectomy only versus radical prostatectomy and intraoperative radiotherapy (IORT) in prostatic adenocacinoma patients at high risk for recurrence	Radiotherapy	Saracino	2
O	Observational study for the evaluation of the predictive value of in vitro pharmacosensitivity on cancer stem cells and the phosphoproteomic profiles in patients with advanced renal cell cancer that are candidates for therapy witho multi-angiokinase and mTOR inhibitors	Scientific Directorate/Urology	De Maria/Gallucci	71
O	Pilot feasibility study on the dose increase with intensity modulation radiotherapy (IMRT) in prostate carcinoma with intermediate prognosis	Radiotherapy	Petrongari	39
O	Randomized phase II study comparing hypofractionated and conventional radiotherapy in prostate cancer of intermediate and unfavorable prognosis, in association with hormone therapy	Radiotherapy	Saracino	6
O	Randomized, Open Label, Multi-Center Study Comparing Cabazitaxel at 25 mg/m2 and at 20 mg/m² in Combination With Prednisone Every 3 Weeks to Docetaxel in Combination With Prednisone in Patients With Metastatic Castration Resistant Prostate Cancer Not Pretreated With Chemotherapy	Medical Oncology "A"	Carlini	6
O	Register of treatment patterns in patients with metastatic castration-resistant prostate cancer (MCRPCc) with progression during or after docetaxel-based regimen	Medical Oncology "A"	Carlini	6
A	Sunitinib either before or after cytoreductive nephrectomy a phase II trial in patients with metastatic renal cell carcinoma	Medical Oncology "A"	Cognetti	14

O	Use of 3 Tesla diffusion MR for the evaluation of the response to radiotherapy in prostate cancer	Radiology and Diagnostic Imaging	Marsella	0
MISCELLANEA				
O	A 12 months, prospective, observational study evaluating impact of DMT treatment on the emotional burden in recently diagnosed Multiple Sclerosis patients	Neurology	Koudriavtseva	6
O	A Phase 1B Open-Label Three-Arm Multi-Center Study To Assess The Safety And Tolerability Of PF-05212384 (PI3K/MTor Inhibitor) In Combination With Other Anti-Tumor Agents	Medical Oncology "A"	Milella	0
O	A randomised, double-blind, placebo-controlled study to evaluate the efficacy of two different dose levels of orvepitant (10 and 30 mg) compared with placebo on EGFRi-induced intense pruritus in oncology subjects (The “RELIEVE 1” Study)	Medical Oncology "A"	Cognetti	0
O	Acrostudy – a multicenter, post marketing surveillance study of somavert therapy in patients with acromegaly in the us and europe	Endocrinology	Appetecchia	6
O	Analysis of the transcriptional expression profile and microRNAs in brain metastases from primary tumors of various origin	Experimental Oncology	Blandino/Telera	81
A	BRISMA Bendamustine and Rituximab for the treatment of Splenic Marginal Zone Lymphoma. The IELSG-36 phase II prospective study	Haematology oncology	Palombi	1
C	Cerbral vein thrombosis in myeloproliferative neoplasms (CVT-MPN Study)	Haematology oncology	Spadea	1
O	Comparison between balloon-assisted enteroscopy (BAE) and VideoCapsule enteroscopy (VCE) in diagnostic and prognostic capacity of patients affected by familial polyposis	Digestive Endoscopy	Stigliano	8
O	Comparison between morphologic and functional MR (perfusion MR, diffusion MR and spectroscopy MR) in the preliminary evaluation and follow-up of muscle-skeletal neoplasias with 3Tesla high-field MRI. Observational study	Radiology and Diagnostic Imaging	Anelli	39

O	Development of effective cancer therapies based on functional proteomics and cancer stem cell targeting	Scientific Directorate	De Maria	761
O	Effect of intraoperative fluidotherapy on postoperative morbidity and mortality in major oncological surgery in high-risk patients: prospective, randomized comparison of three different fluidotherapy regimen (RFG, LFG, GDTFG)	Anaesthesiology	Forastiere	170
O	Electrochemotherapy for the treatment of bone metastases from solid tumors	Orthopaedics	Biagini	6
O	Epidemiologic register named REGIRE, transversal observational study for the evaluation of epidemilogic data of prevalence and incidence of respiratory failure aimed at an appropriate health planning and optimal employ of economic resources in the treatment of the disease	Pulmonary Phisiopathology	Cilenti	12
O	Evaluation and improvement of the quality of assistance in patients undergoing radiometabolic therapies	Psichology/Nuclear Medicine	Pugliese	40
O	Evaluation of early indicators of the tumor response after treatment with anti-angiogenic drugs in patients with primary or metastatic non-small cell lung colorectal or renal cancer, using a 3 Tesla MR apparatus	Radiology and Diagnostic Imaging	Caterino	0
O	Evaluation of the eficacy, tolerability, quality of life and compliance of tapentadol in cancer patients with neuropathic pain due to chemotherapy, other antitumor therapies or the tumor itself	Neurology	Galiè	3
O	Global, clinical-pathological and molecular characterization of thymic epithelial tumors	Histology and Cytopathology	Marino	5
O	Intubation with double-lumen tubes: comparison between the videolaringoscope Gildescope and a standard laringoscope (McIntosh)	Anaesthesiology	Coccia	90
O	Isotonic contrast (iodixanol) administration vs. low osmolar contrast (iopromide) use: evaluating risk of contrast-induced nephropathy in cancer patients at very low risk	Radiology and Diagnostic Imaging	Canitano	423
O	Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy	Neurology	Koudriavtseva	8

O	Management of the airways in thoracic surgery	Anaesthesiology	Forastiere	86
O	Microneurosurgical, endoscopy-assisted removal of pituitary adenomas by transphenoidal route. Observational study and early evaluation of the results by MR.	Neurosurgery	Pompili	190
O	Miniinvasive supraorbitary approach for the removal of tumors in the saddle region	Neurosurgery	Pompili	43
O	Miniinvasive, unilateral approach for the removal of intradural spinal tumors. Observational study	Neurosurgery	Pompili	141
O	Multicenter, open label and observational Italian study performed in Centers for Pain Medicine on long-term surviving persons, not patients, with previous cancer diagnosis, in a disease-free state, that suffer from algias and fatigue linked to cancer and cancer therapies	Intensive Care, Pain Therapy and Palliative Care	Di Emidio	32
C	Multicenter, retrospective observational study on the use of clinical data for scientific goals in patients with myelodisplastic syndromes that are followed in the department of hematology	Haematology oncology	Petti	41
O	Multidisciplinary approach to biomarkers of the ERBB family, mechanisms of EGFR regulatory activity and characterization of microRNAs in thymic epithelial tumors (TET)	Histology and Cytopathology	Marino	60
O	Neurophysiological and clinical incidence and typing of chemoinduced neuropathies and evaluation of the associated neuropathic pain, if present	Neurology	Galiè	40
O	Observational clinical study on the hypercoagulability and efficacy of short-term or long-term antithrombotic prophylaxis with low molecular weight heparins in cancer patients carrying a permanent central venous catether	Intensive Care, Pain Therapy and Palliative Care	Laurenzi	76
O	Observational study for the monitoring of chronic, Ph negative myelodisplastic syndromes (SMPC-Ph neg) in adults	Haematology oncology	Spadea	67
O	Observational study of patients undergoing somatectomy and vertebrectomy performed at the same time, for the ablation and reconstruction, with stabilization, of vertebral metastases	Neurosurgery	Caroli	52

O	Observational study of the surgical treatment for the ablation and reconstruction with stabilization, of primary vertebral tumors	Neurosurgery	Caroli	26
C	Observational study on the use of the most advanced surgical techniques and technologies in the domain of spinal tumors	Neurosurgery	Raus	89
O	Oral antitumor drugs: nursing interventions in order to improve the management of the therapies and the safety of the patient	Medical Oncology "A"	Cognetti	0
O	Perfusion imaging with 3 Tesla MR in the early evaluation of the response to antiangiogenic treatment in patients with recurrring, high-grade malignant glioma	Radiology and Diagnostic Imaging	Vidiri	20
O	Phase II clinical trial on high dose proton pump inhibitors (Lansoprazole) in patients with advanced and unresponsive thyroid, prostate and breast cancer	Endocrinology	Appetecchia	3
O	Preliminary study on the engineering of bone and muscle tissues	Orthopaedics	Biagini	8
O	Prevention of pulmonary atelectasias with manoeuvers of recruitment during robotic, gynecologic surgery in obese patients	Anaesthesiology	Fabrizi	20
C	Prospective evaluation of plasma posaconazole levels in patients with hematologic diseases under treatment with the anifungal drug posaconazole	Haematology oncology	Spadea	11
C	Prospective evaluation of plasma voriconazole levels in patients with hematologic diseases under treatment with the anifungal drug voriconazole	Haematology oncology	Spadea	3
O	Prospective study for the monitoring of myelodysplastic syndromes in adult patients	Haematology oncology	Petti	20
O	Prospective, randomized comparison between different techniques of post-thoracotomic analgesia: evaluation of the quality of the analgesia and complications after thoracic surgery	Anaesthesiology	Forastiere	32

O	Protective effect of Sevoflurane in ischemia-reperfusion injury in patients undergoing reconstructive plastic surgery with microsurgical strip. Controlled, randomized, multicenter trial	Anaesthesiology	Forastiere	12
C	Ranolazine to treat early cardiotoxicity induced by antitumor drugs	Medical Oncology "A"	Fabi	24
O	Role of BCL-2 family proteins in cancer-stroma interplay: implication of BCL-2 homology domains	Experimental Oncology	Del Bufalo	0
O	Role of oxidative stress in multiple sclerosis. Proteomic and redox proteomic analysis	Neurology	Koudriavtseva	111
O	TOP-TYSABRI Observational Program	Neurology	Koudriavtseva	20
O	Treatment of post-operative pain in major oncologic oprthopedic surgery: PCA at intermittent continuous boli. Prospective observational study	Anaesthesiology	Monteferrante	10

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