

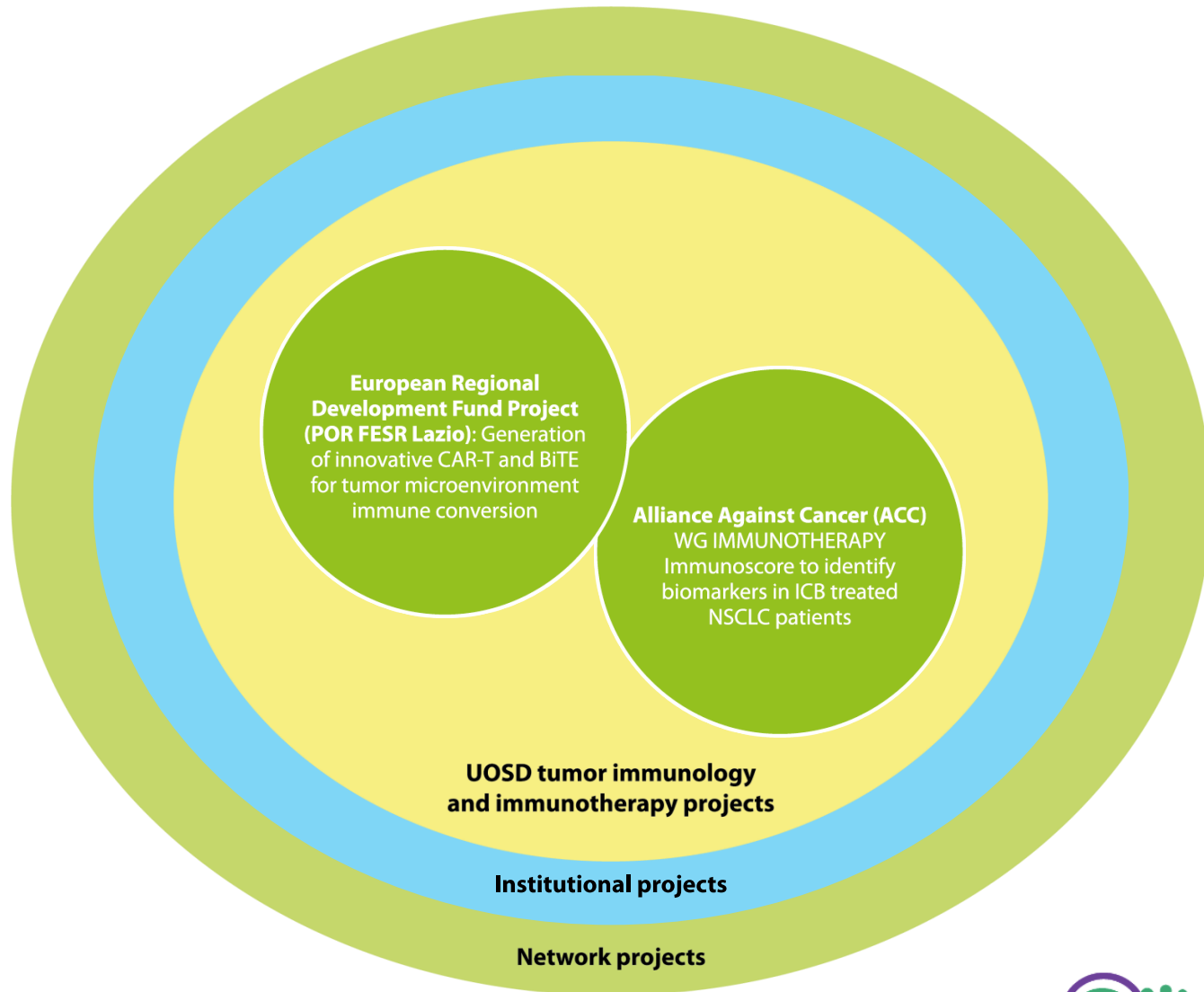


Discovery in Immuno-oncology

Paola Nisticò M.D.

UOSD Tumor Immunology and Immunotherapy

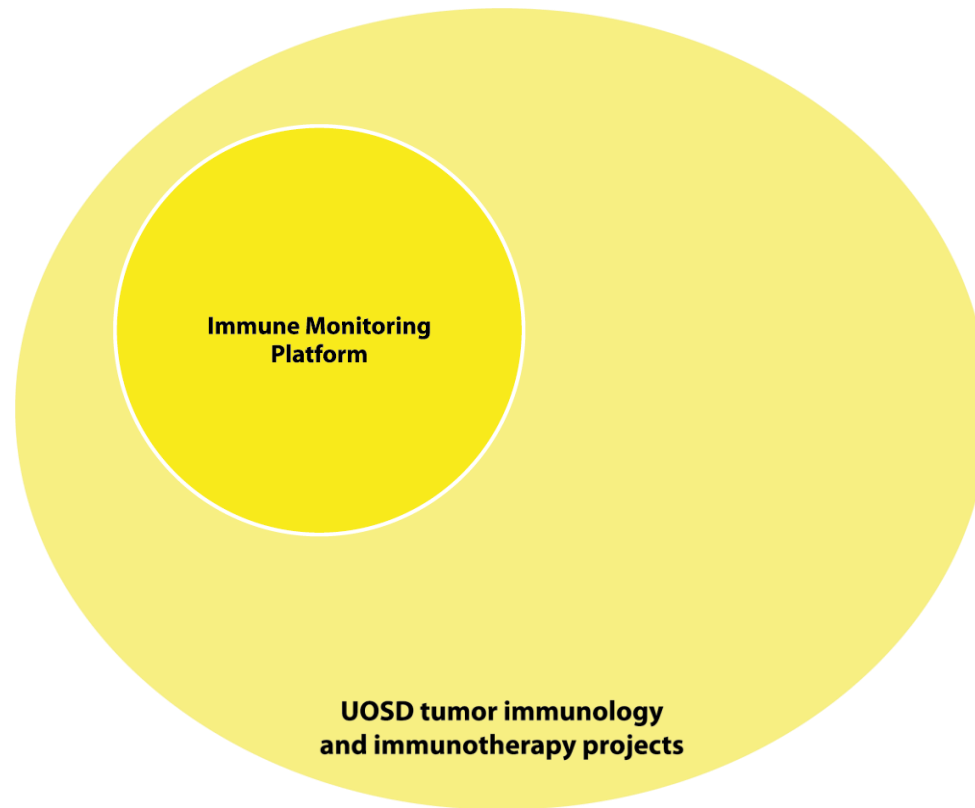
How to improve the efficacy and appropriateness of current immunotherapies?



4thNov2020



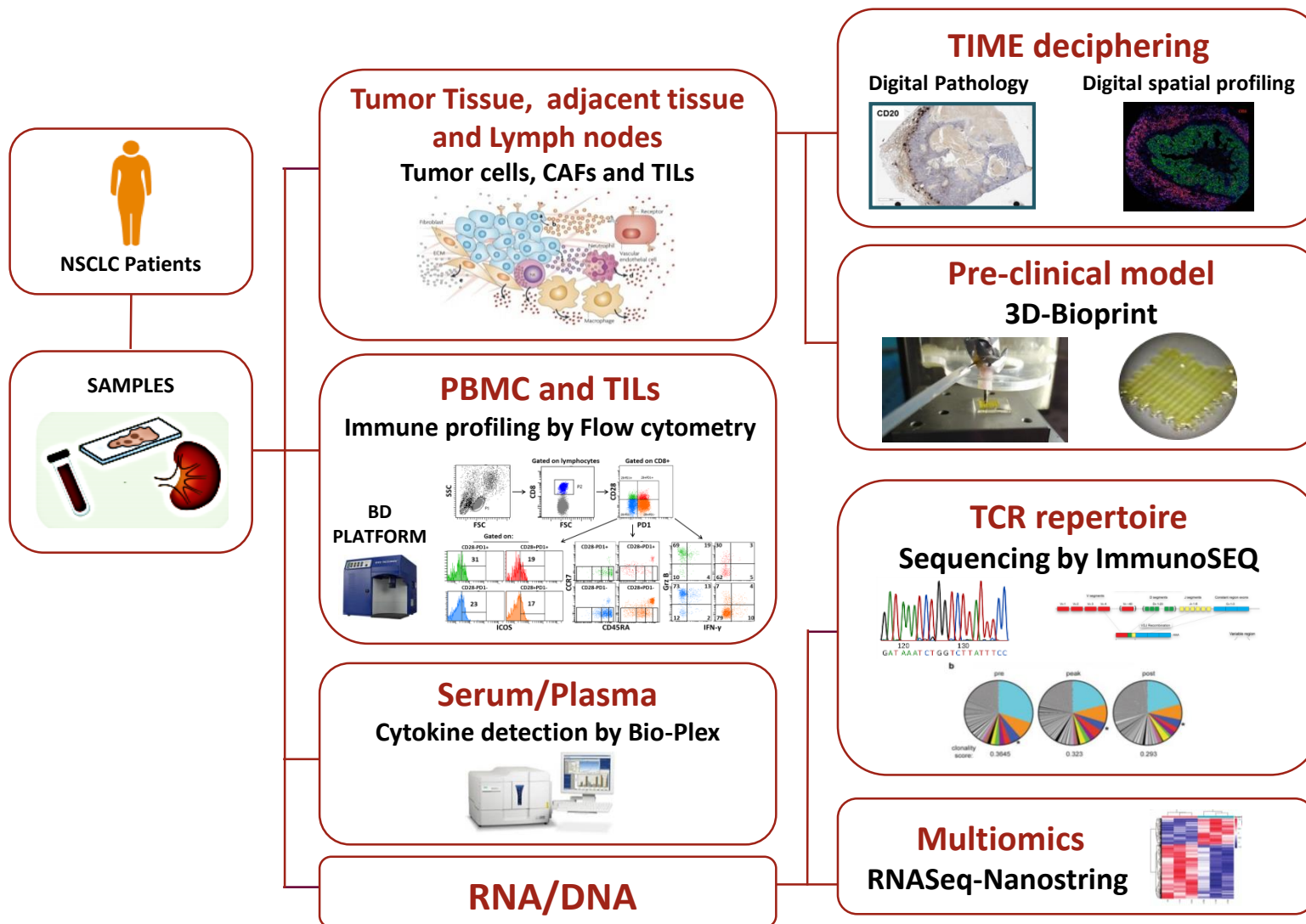
How to improve the efficacy and appropriateness of current immunotherapies?



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WORKFLOW



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How to improve the efficacy and appropriateness of current immunotherapies?

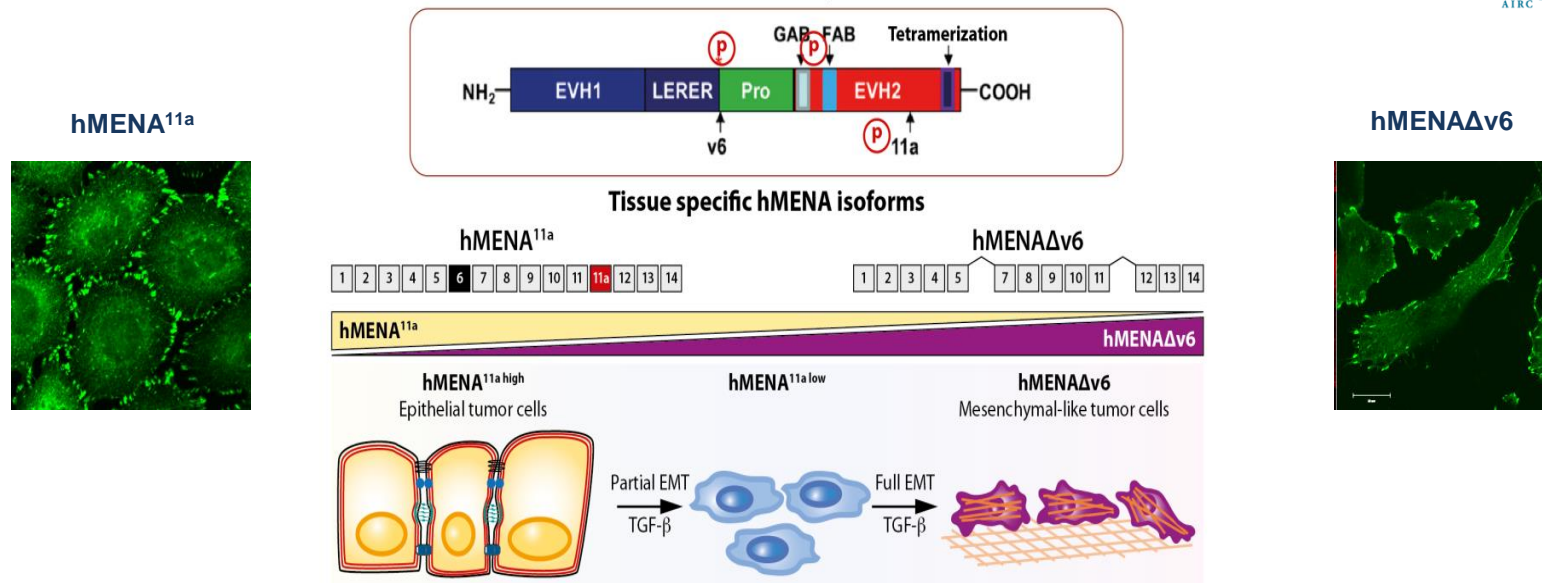
A platform to identify prognostic and theranostic biomarkers and druggable pathways: hMENA splicing as a crucial player in the communication among tumor, CAF, extracellular matrix and immune cells

UOSD tumor immunology and immunotherapy projects

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From the antibody response of a cancer patient a key regulator of actin cytoskeleton dynamics, hMENA and its tissue specific isoforms in cancer

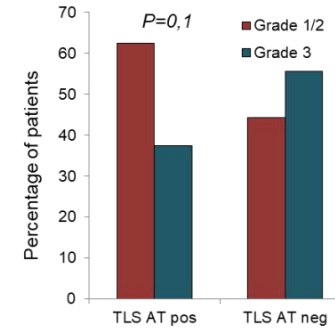
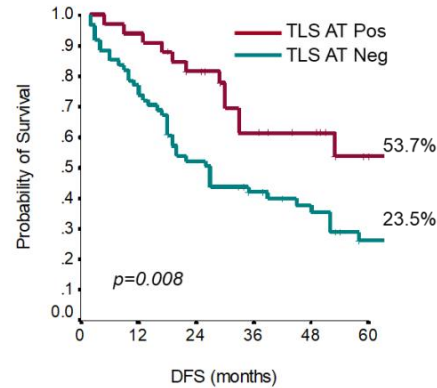
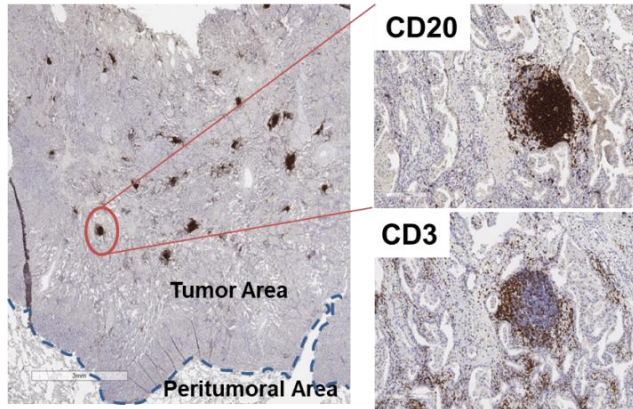


<p>Expression</p> <ul style="list-style-type: none"> • Epithelial cells • Absent in invasive cells • Down-regulated by TGFβ1 during EMT 	<p>Function</p> <ul style="list-style-type: none"> • Promotes cell-cell adhesion • Sustains E-Cadherin expression • Anti-apoptotic • Pro-proliferative • Anti-invasive • Reduces ECM components (Fibronectin and MMPs) and MMP activity • Inhibits TGFβ1 signaling • Inhibits β1 integrin signaling
<p>Relationship to outcome</p> <p>hMENA-hMENA^{11a} → Favourable outcomes</p>	

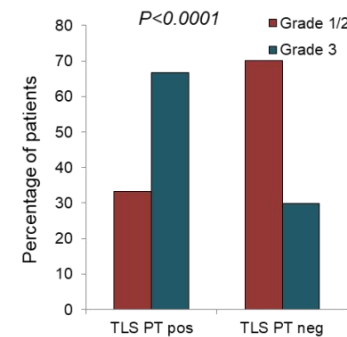
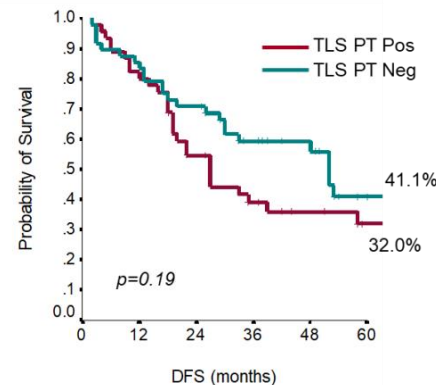
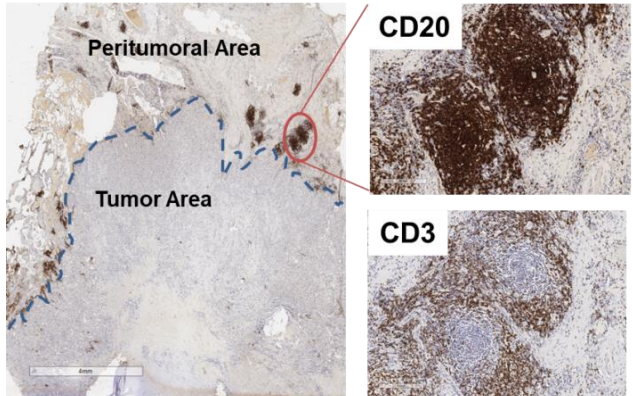
<p>Expression</p> <ul style="list-style-type: none"> • Mesenchymal "like" epithelial cells • Mesenchymal cells • Over-expressed by TGFβ1 during EMT • Up-regulated by TGFβ1, β-catenin, ET1 	<p>Function</p> <ul style="list-style-type: none"> • Sustains Vimentin expression • Increases cell invasiveness • Invadopodia formation and function • Promotes TGFβ1 induced EMT • Increases β1 integrin signaling • Increases ECM components
<p>Relationship to outcome</p> <p>hMENA-hMENAΔv6 → Poor outcomes</p>	

Tertiary lymphoid structures localized within the tumor core are predictive of survival in early N0 NSCLC patients

TLS in the Tumor Area (AT)



TLS in the Peritumoral Area (PT)

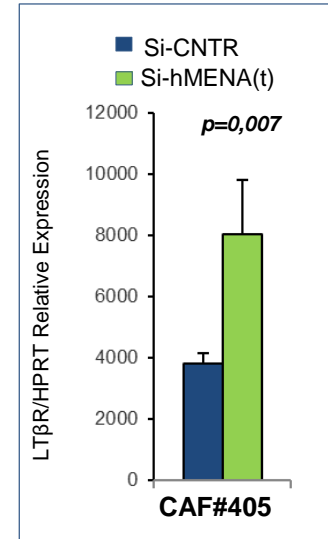
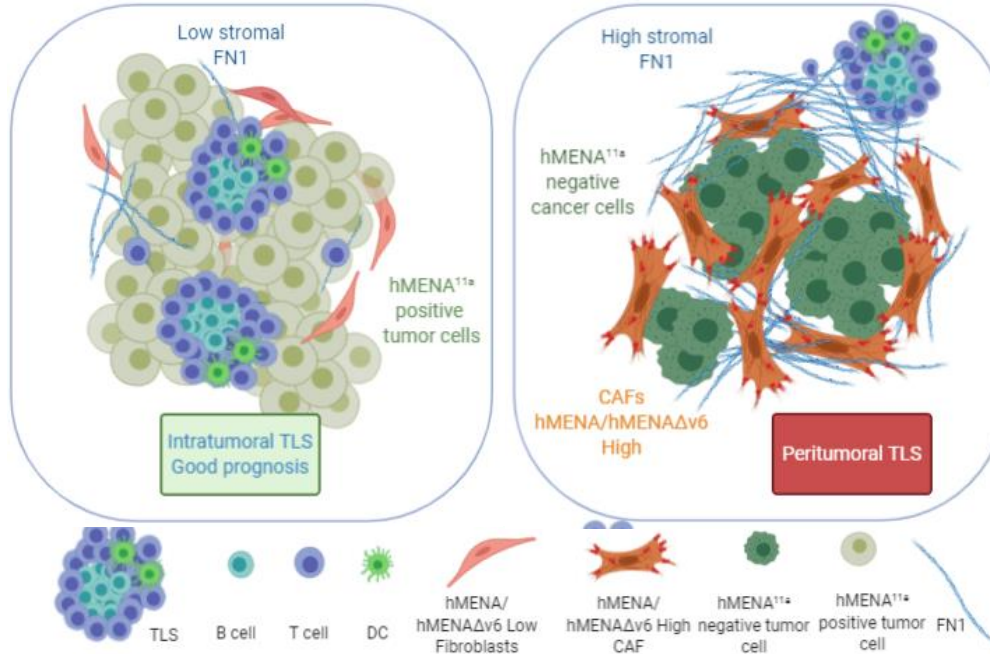
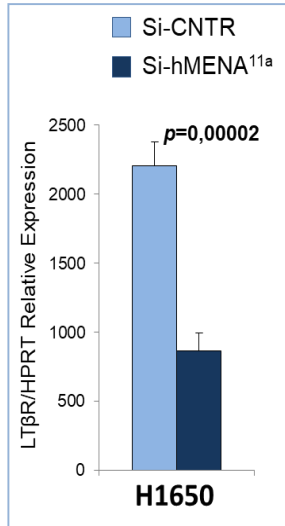


- [Tertiary lymphoid structures improve immunotherapy and survival in melanoma.](#) Cabrita R, et al. Nature. 2020
- [B cells and tertiary lymphoid structures promote immunotherapy response.](#) Helmink BA, et al. Nature. 2020
- [B cells are associated with survival and immunotherapy response in sarcoma.](#) Petitprez F, et al. Nature. 2020

Intratumoral tertiary lymphoid structure (TLS) localization is associated with hMENA^{11a} expression in tumor cells, low hMENA/hMENA Δ v6 expression in CAFs and low stromal Fibronectin in NO NSCLC



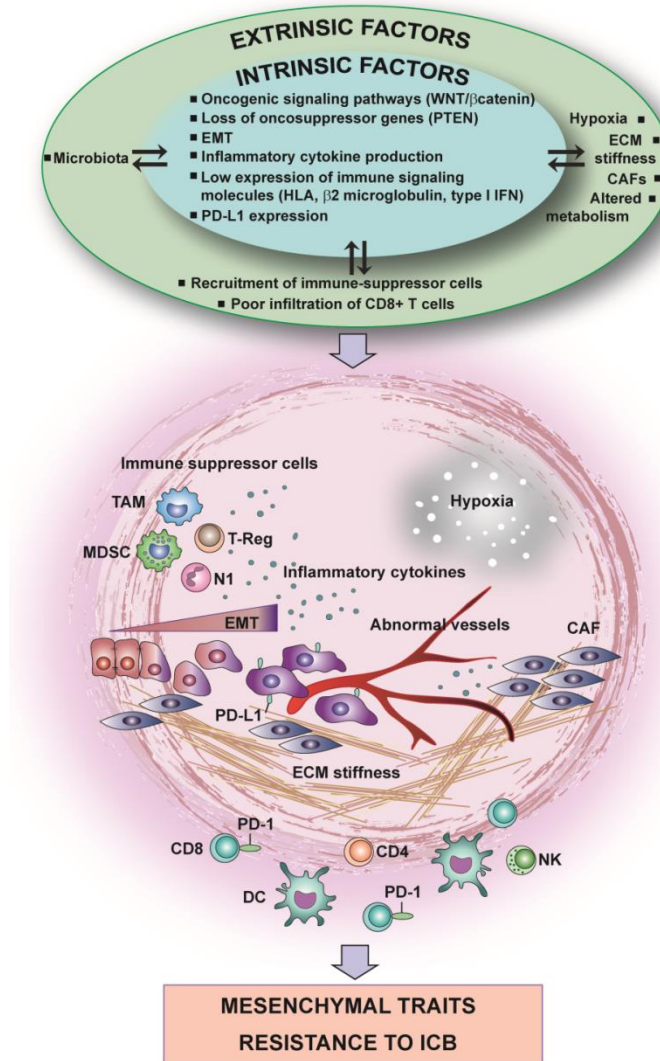
Francesca Di Modugno Anna Di Carlo



- RNA-SEQ analysis of NSCLC cell lines revealed that depletion of hMENA^{11a} in NSCLC cell lines increased the expression of Fibronectin and reduced the Lymphotoxin beta receptor (LTβR), a crucial molecule in lymphoid tissue organogenesis and maintenance. The depletion of hMENA/hMENA Δ v6 in CAFs induces the expression of LTβR, indicating that the pattern of hMENA isoform may contribute to TLS organization and localization

Studies are ongoing to evaluate hMENA isoform expression and TLS localization in tumor tissues of ICB-treated NSCLC patients

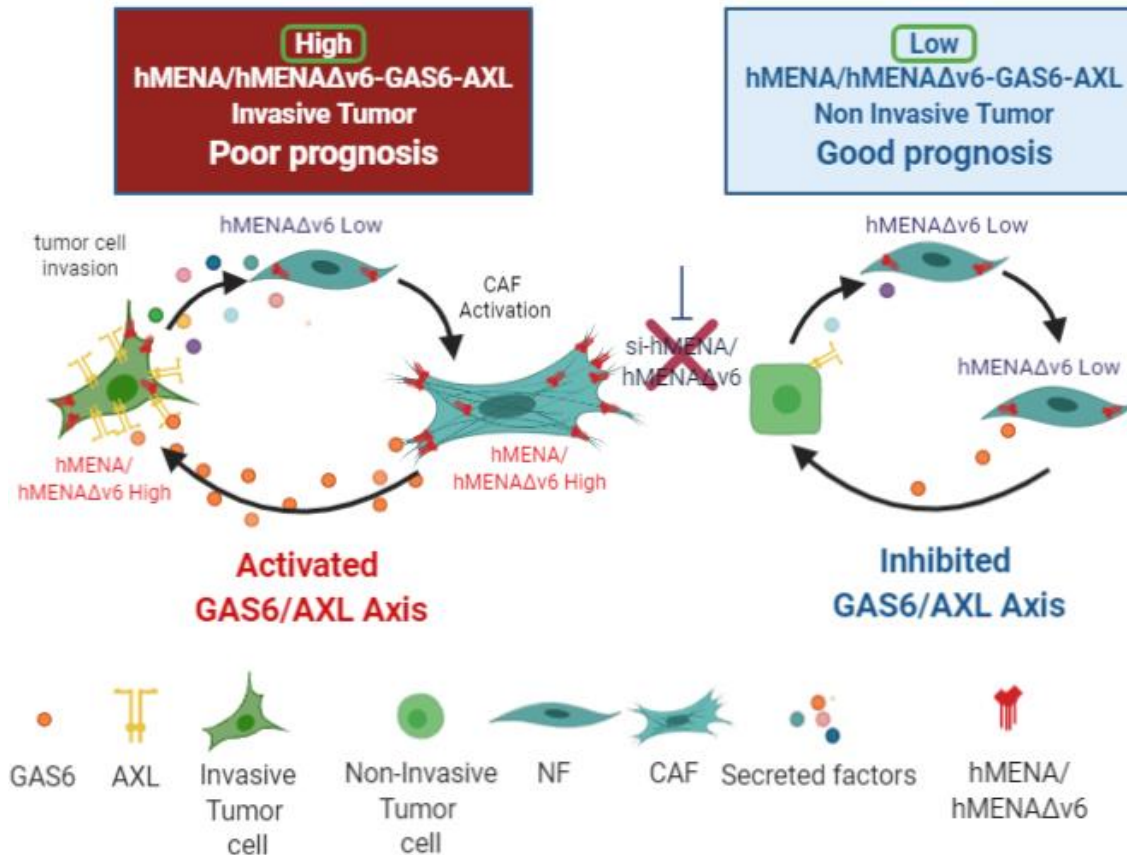
Mesenchymal traits resulting from tumor intrinsic and extrinsic factors influence T-cell trafficking and function determining resistance to ICB and CAR-T treatment in solid tumors



The actin modulator hMENA regulates GAS6-AXL axis and pro-tumor cancer/stromal cell cooperation



Roberta Melchionna



- CAFs with a pro-tumor activated state express higher levels of hMENA/hMENA Δ v6 compared to normal fibroblasts.
- CAFs over-expressing hMENA Δ v6 secrete GAS6 and favor the invasiveness of AXL-expressing PDAC and NSCLC cells.
- Reciprocally in tumor cells hMENA/hMENA Δ v6 regulate AXL expression, and sustain GAS6-AXL paracrine axis.
- A high hMENA/GAS6/AXL gene expression signature identifies PDAC and NSCLC patients with a poor prognosis.

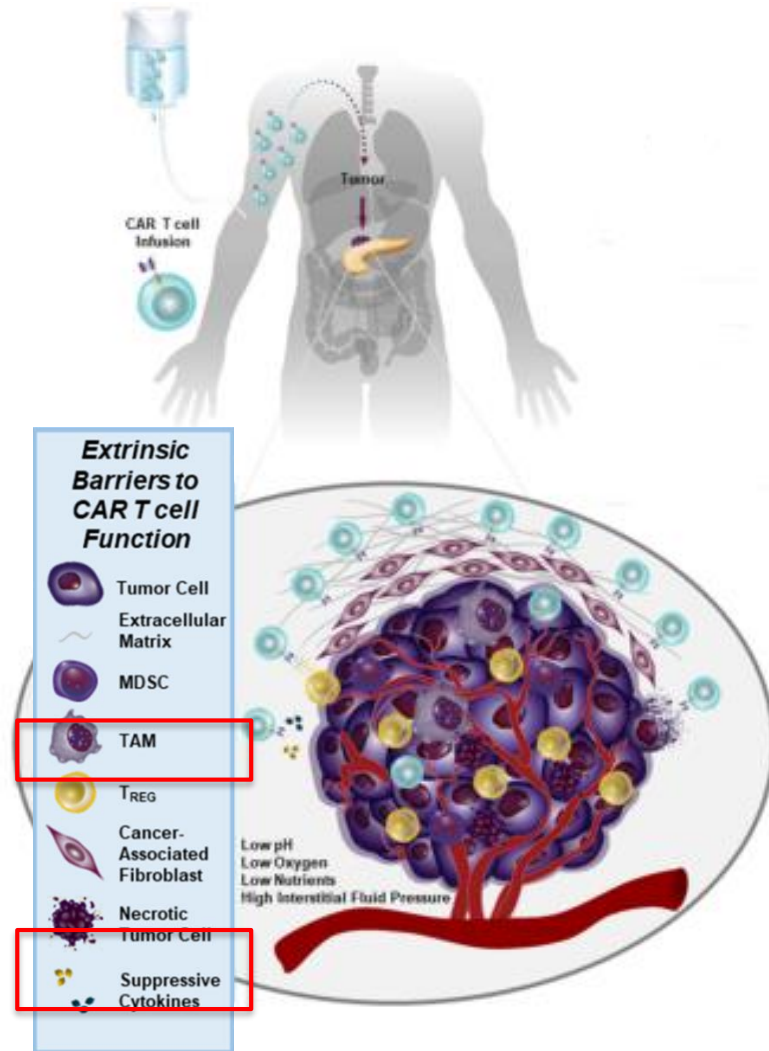
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Identification of novel TME-derived targets suitable for CAR T cell therapy



Immunosuppressive barriers present in the solid tumor microenvironment that can hamper the efficacy of CAR T cell therapy

- Lack of CAR-T cell trafficking in the tumor site
- Presence of CAF and a dense extracellular matrix
- An immunosuppressive TME inhibiting T-cell migration, proliferation and functionality
- Heterogeneous expression of tumor-associated antigens

Hypothesis-driven bioinformatics analyses

CAF activation and low presence of CTL in tumor tissues



Lorenzo D'Ambrosio Eleonora Sperandio

Ecm-myCAF immuno-suppressive signature

ASPN, COL3A1, THY1, SFRP2, COL10A1, COL6A3, LRRC17, CILP, GRP, ITGBL1, COL8A1, COL14A1, ADAM12, OLFML2B, ELN, PLPP4, CREB3L1, FBN1, LOXL1, MATN3, LRRC15, COMP, ISLR, P3H1, COL11A1, SEPT11, NBL1, SPON1, SULF1, FNDC1, CNN1, MIAT, MMP23B, CPXM1, FIBIN, P4HA3, GXYLT2, CILP2, P3H4, CCDC80

+

CTL signature

CD8A, CD8B, GZMA, GZMB, PRF1

CANCER DISCOVERY

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Research Articles

Single-Cell Analysis Reveals Fibroblast Clusters Linked to Immunotherapy Resistance in Cancer

Yann Kieffer, Hocine R. Hocine, Géraldine Gentric, Floriane Pelon, Charles Bernard, Brigitte Bourachot, Sonia Lameiras, Luca Albergante, Claire Bonneau, Alice Guyard, Karim Tarte, Andrei Zinovyev, Sylvain Baulande, Gerard Zalcman, Anne Vincent-Salomon, and Fatima Mechta-Grigoriou

DOI: 10.1158/2159-8290.CD-19-1384 Published September 2020



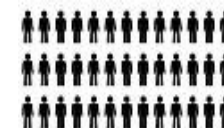
Quartile division and intersection



LUAD



LUSC

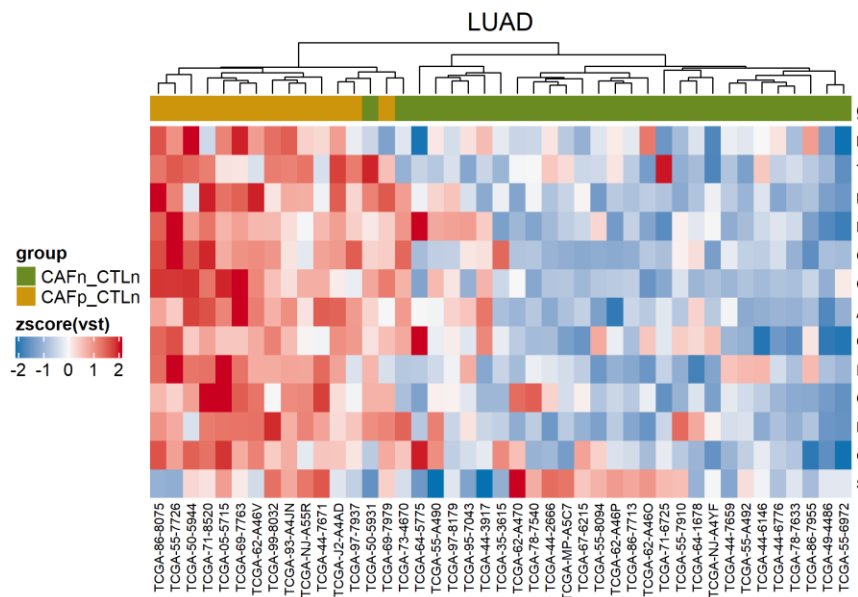


GO Biological Processes

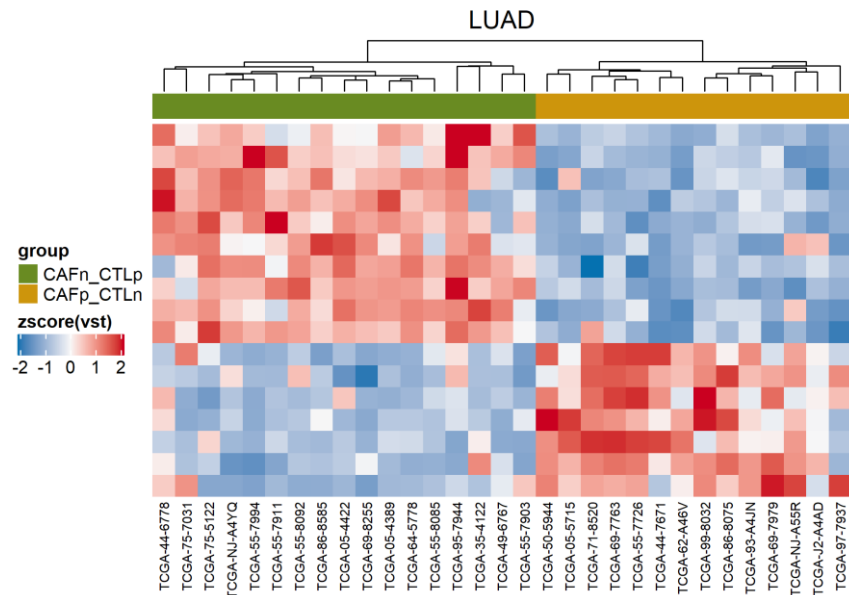
Extra cellular matrix organization

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Supervised Machine Learning



14 CAFpositive CTLnegative (CAFp_CTLn)
 versus
 29 CAFnegative CTLnegative (CAFn_CTLn)



14 CAFpositive CTLnegative (CAFp_CTLn)
 versus
 17 CAFnegative CTLpositive (CAFn_CTLp)

Preclinical Models

Analysis of immune cell infiltration in the HNSCC murine model and development of oncolytic vectors to be used in combination with the CAR- T treatment.



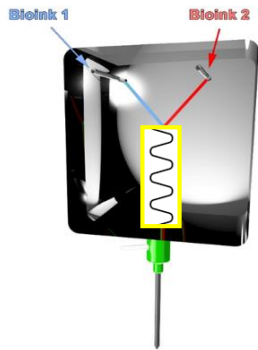
Francesca Paolini



Aldo Venuti

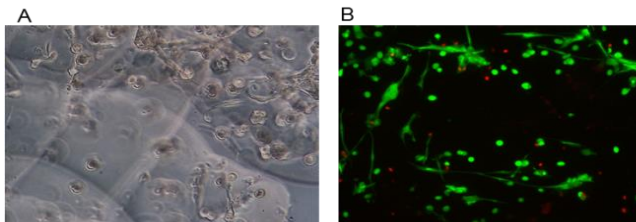
Preclinical Models 3D bioprint and microfluidic

Printing gradient of stiffness



Harnessing microfluidic channels to precisely control cells and biomaterial deposition, to guide patterning of cells, biomaterials or/and compounds

3D bioprinting and measure of matrix rigidity by Brillouin microscopy

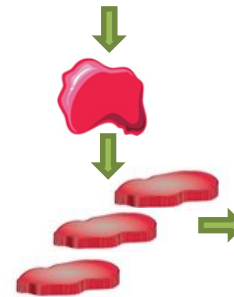


Collaboration with IIT Rome

1. Orthotopic Administration of AT-84 luc cells

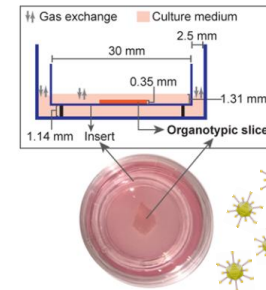


2. Tumor growth and explant




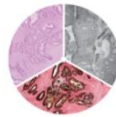
3. Tumor slicing

4. Organotypic culture



5. Oncolytic virus exposure

6. Possible Readouts

- Immunohistochemistry 
- Conditioned medium analysis (ELISA)
- Immuno cell profiling
- RNA sequencing
- RNAscope 
- Digital Spatial Profiling

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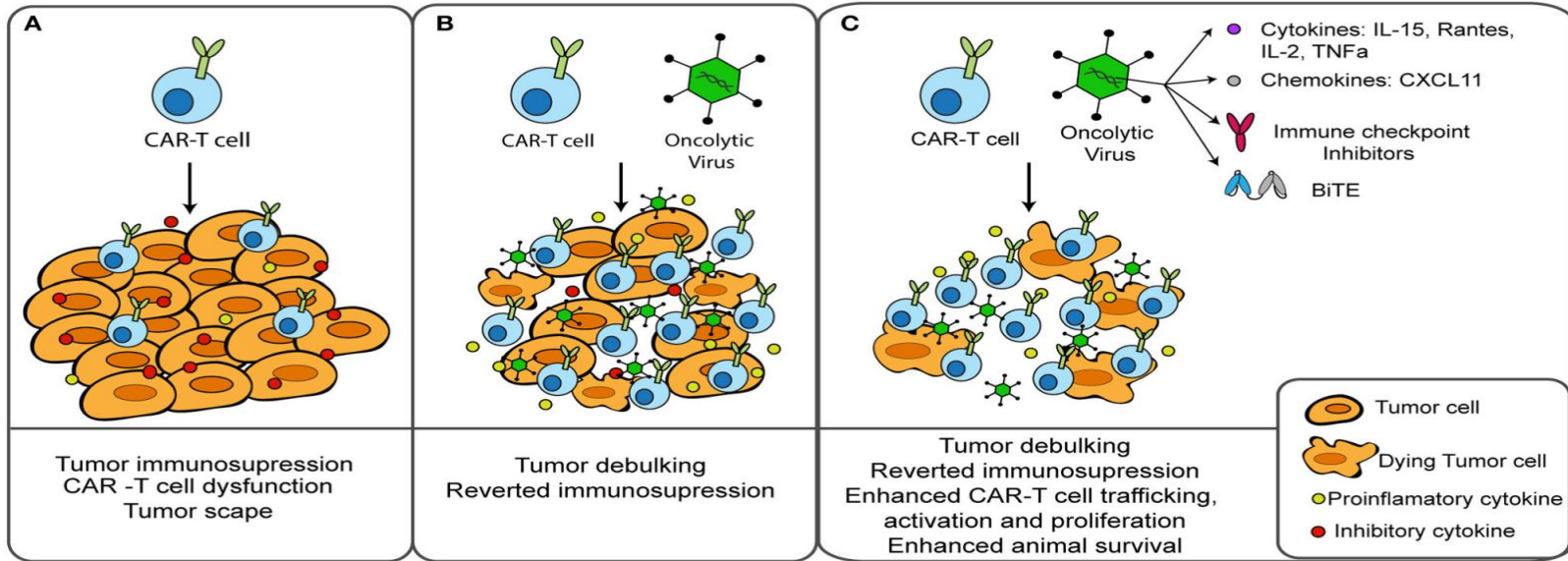
Combinatorial therapy for CAR-T therapy of solid tumors: CAR-T and oncovirotherapy



Silvia Baldari



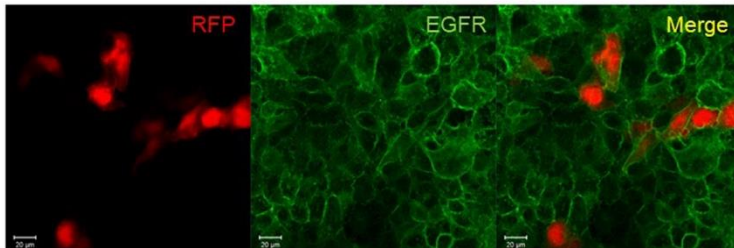
Gabriele Toietta



Frontiers in Immunology | October 2018 | Volume 9 | Article 2460

Oncolytic vectors

Onco Ad5-D24 (24pb deletion in E1A); Onco Ad5-D24-RFP (24pb deletion in E1A, Red Fluorescent Protein); Onco Ad5/3-D24 (24pb deletion, Ad3 knob); Onco Ad5-D24-CpG (24pb deletion CpG islands on backbone); Onco Ad5/3-D24-STING (24pb deletion, Ad3 knob, Stimulator of Interferon Genes)



IHC assessment of the expression of the EGFR as putative target for CAR-T therapy in combination with oncolytic virotherapy in HNSCC

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How to improve the efficacy and appropriateness of current immunotherapies?

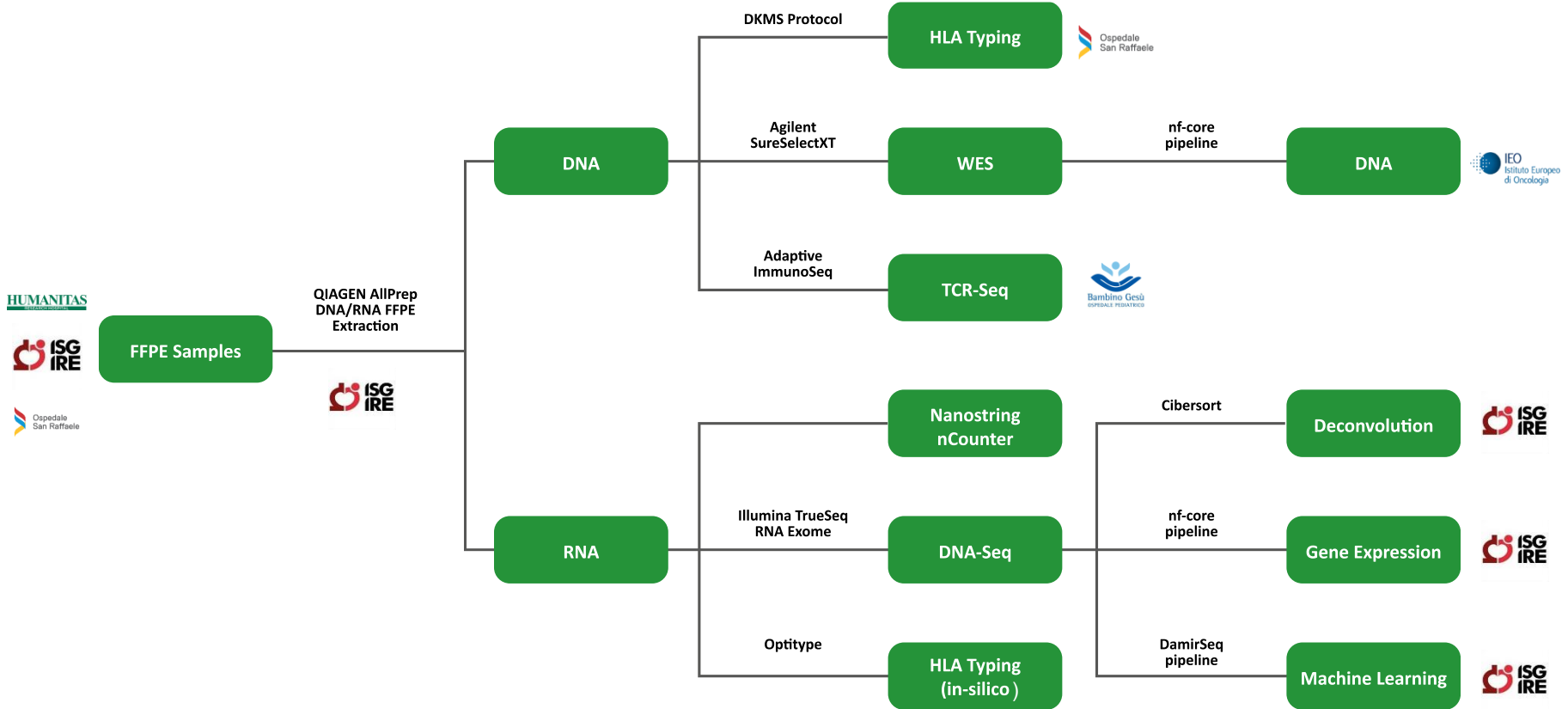
Alliance Against Cancer (ACC)
WG IMMUNOTHERAPY
Immunoscore to identify
biomarkers in ICB treated
NSCLC patients

Network projects

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Multi-omics platform to identify biomarkers in ICB-treated NSCLC patients



Retrospective study in ICB-treated NSCLC patients

Tissue samples (n=24) analyzed by the multi-omics platform

Patient ID	Response	Istitution	Year	Sex
Patient_C	GR	IRE	2018	M
Patient_H	GR	IRE	2018	M
ACC_IMM_IRE_GR06_Q	GR	IRE	2019	M
ACCIMMUNO-01	GR	IRE	2019	M
ACCIMMUNO-03	GR	IRE	2019	F
IRE-GR09	GR	IRE	2019	M
ACCIMMUNO-10	GR	IRE	2019	M
Patient_2	GR	ISR	2019	F
Patient_3	GR	ISR	2019	F
Patient_9	GR	ISR	2019	M
HUM-ICH10	GR	HUM	2020	F
HUM-ICH05	GR	HUM	2020	F
HUM-ICH03	GR	HUM	2020	M

Patient ID	Response	Istitution	Year	Sex
Patient_D	FP	IRE	2018	F
Patient_F	FP	IRE	2018	F
Patient_B	FP	IRE	2018	F
ACCIMMUNO-02	FP	IRE	2019	M
ACC_IMM_IRE_FP07_Q	FP	IRE	2019	F
Patient_4	FP	ISR	2019	F
Patient_5	FP	ISR	2019	M
Patient_6	FP	ISR	2019	M
Patient_7	FP	ISR	2019	F
Patient_8	FP	ISR	2019	F
Patient_10	FP	ISR	2019	M

GR Good Responder at 10 months (n=13)

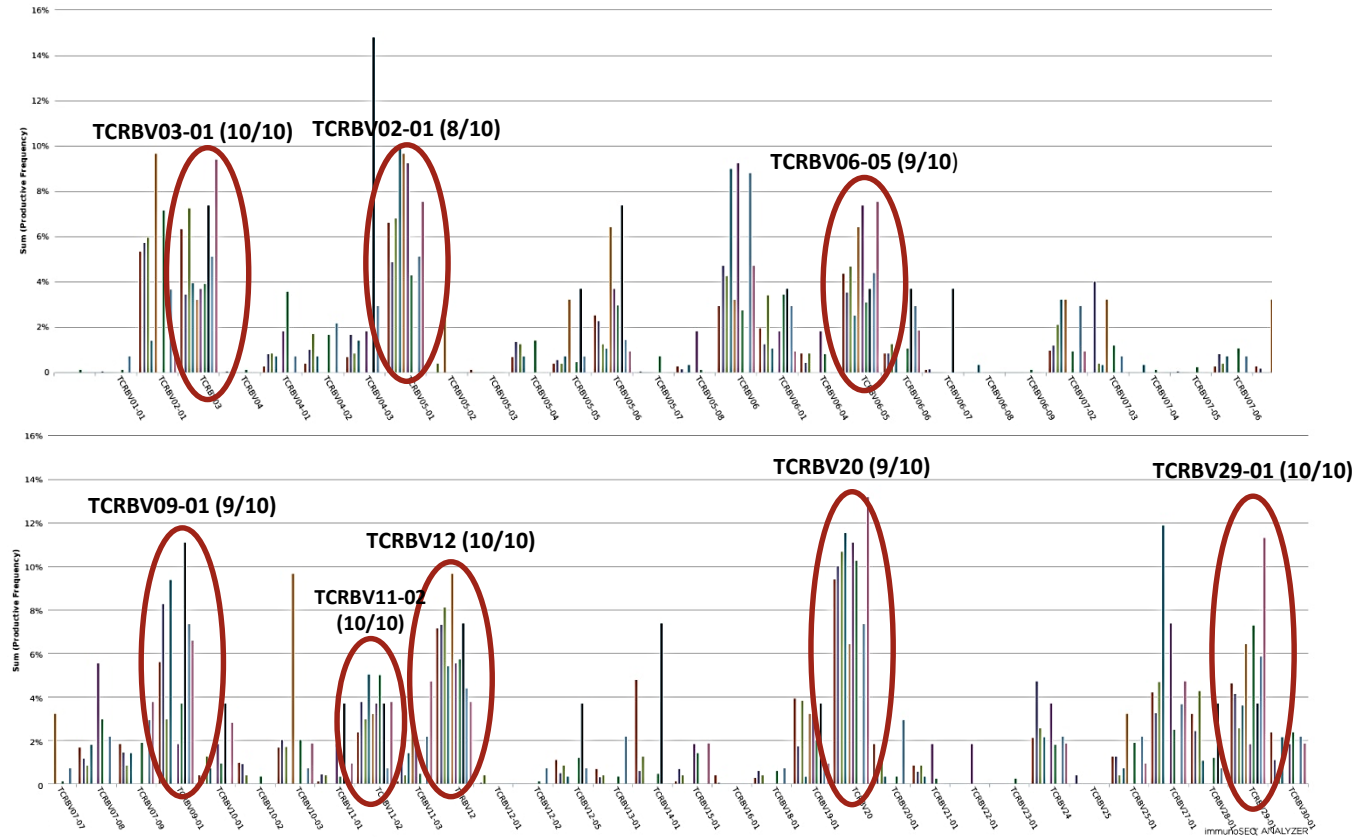
FP Fast Progressor at 3 months (n=11)

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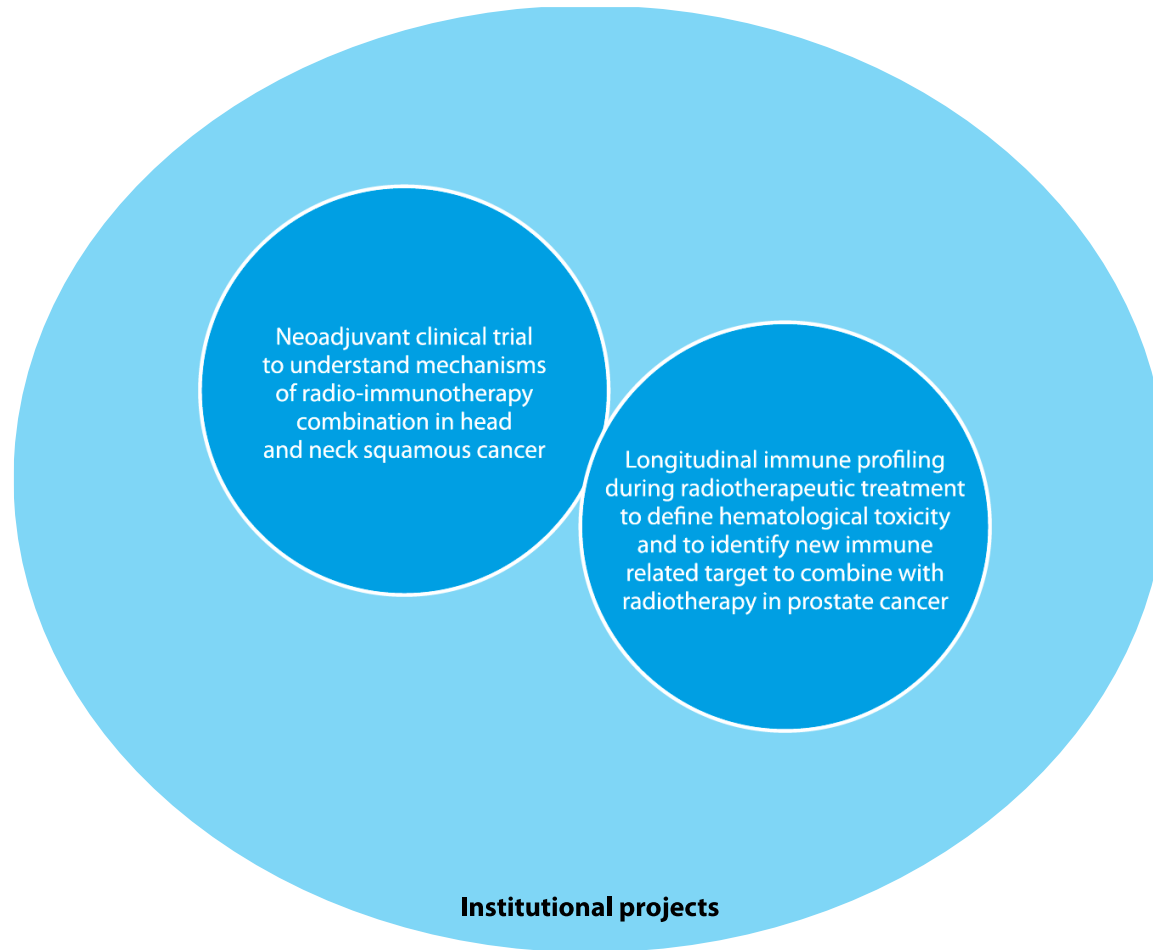
TCR Sequencing Analysis

- Most frequent TCRBV usage in 10 NSCLC tissues



- An Italian repository for a more effective Immune-Checkpoint treatment
- Creation of a multicentric repository / web portal comprehensive of clinical, biological and lifestyle data of 2000 ICB-treated patients in accordance with current guidelines
- ACC network could represent an Italian Task Force and become an excellence reference in the international immunotherapy landscape

How to improve the efficacy and appropriateness of current immunotherapies?



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Longitudinal immune profiling during radiotherapeutic treatment to define hematological toxicity and to identify new immune related targets to combine with radiotherapy in prostate cancer



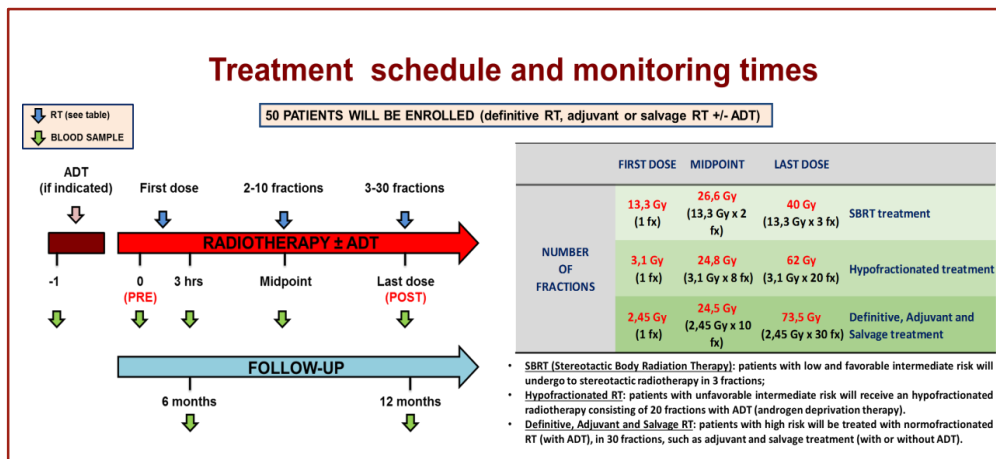
Belinda Palermo



Mariangela Panetta



Giulia Campo



Radiotherapeutic treatment and collected blood samples of 21 enrolled prostatic patients

Enrolled pts	21
Analyzed pts	20
Schedule of treatment	
SBRT	5 5 fx
Salvage RT	6 30 fx
Adjuvant RT	3 30 fx
Curative RT	7 20 fx
Androgen Deprivation Therapy (ADT)	
Yes	7
No	14
Treatment machine	
CYBERKNIFE	6
CLINAC	15
Number of blood samples	
N. of pts with pre-ADT blood sample	6 6
N. of pts with blood sample during treatment (4 TIMING)	21 84
N. of pts with 6 months post-treatment blood samples	20 20
N. of pts with 12 months post-treatment blood samples	12 12

Multiparametric flow cytometry of inhibitory receptors, differentiation and functional markers in B, NK cells and T lymphocytes

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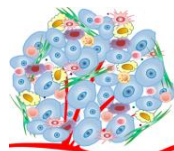
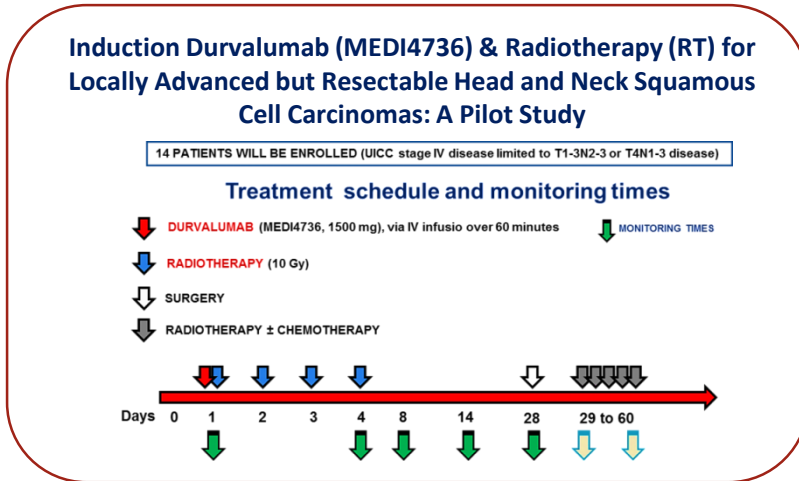
Neoadjuvant clinical trial to understand mechanisms involved in effectiveness of radio-immunotherapy combination in head and neck squamous cancer



Belinda Palermo



Mariangela Panetta



IN THE TUMOR:

Tumor biopsies before treatment

Tumor tissues after treatment at surgery

Lymph nodes (omo and controlateral)

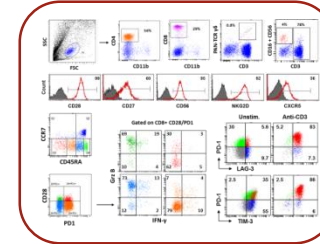
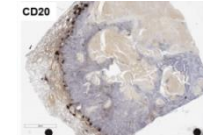
IN THE PERIPHERAL BLOOD:



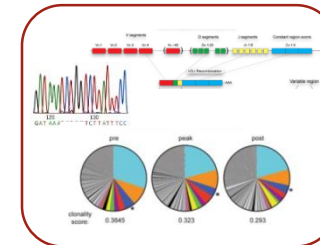
PBMC collection

Serum/plasma collection

Digital Pathology



Flow cytometry



TCR sequencing



Bio-Plex System

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ACKNOWLEDGMENTS

Tumor Immunology and Immunotherapy Unit

Francesca Di Modugno, Roberta Melchionna, Paola Trono, Anna Di Carlo, Belinda Palermo, Mariangela Panetta, Giulia Campo, Annalisa Tocci, Vittoria Balzano, Giuliana Falasca, Maria Vincenza Sarcone, Gabriele Toietta, Silvia Baldari, Annalisa Antonini, Anna Maria Mileo, Francesca Paolini, Aldo Venuti

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IRE Biobank

Simona Di Martino

Valentina Laquintana

Regina Elena National Cancer Institute, Rome, Italy

ACC WG Immunotherapy



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