IRE ISTITUTO NAZIONALE TUMORI REGINA ELENA ISG ISTITUTO DERMATOLOGICO SAN GALLICANO
ISTITUTI DI RICOVERO E CURA A CARATTERE SCIENTIFICO

DELIBERAZIONE N. **877** DEL **26/09/2025**

OGGETTO: PRESA D'ATTO DI AVVENUTA STIPULA DEL RESEARCH COLLABORATION AGREEMENT (RCA) TRA GOLGENIA S.R.L. e IFO-IRE ED ACCETTAZIONE DEL FINANZIAMENTO DI € 50.020,00 (INCLUSA IVA) PER LO SVOLGIMENTO DEL PROGETTO DI RICERCA DAL TITOLO: "INHIBITORS OF THE GOLPH3 ONCOGENE AS ANTICANCER DRUGS", DI CUI PI IL DOTT. PASQUALE ZIZZA.

Esercizi/o e conto 2025 - 401030401 Centri/o di costo 1101030 **- Importo presente Atto: € € 50.020,00** **- Importo esercizio corrente: € € 50.020,00** Budget **- Assegnato: € .** **- Utilizzato: € .** **- Residuo: € .** **Autorizzazione n°: -** Servizio Risorse Economiche: **Giovanna Evangelista**	STRUTTURA PROPONENTE **UOSD Servizio Amministrativo Ricerca** Il Dirigente Responsabile **Giovanna Evangelista** Responsabile del Procedimento **Emanuela Miceli** L'Estensore **Emanuela Miceli** Proposta n° DL-838-2025
PARERE DEL DIRETTORE SANITARIO Positivo Data 26/09/2025 IL DIRETTORE SANITARIO f.f. **Costanza Cavuto**	**PARERE DEL DIRETTORE AMMINISTRATIVO** Positivo Data 26/09/2025 IL DIRETTORE AMMINISTRATIVO f.f. **Giuseppe Zappalà**

Parere del Direttore Scientifico IRE f.f. **Giovanni Blandino** data 23/09/2025 Positivo

Parere del Direttore Scientifico ISG **Maria Concetta Fargnoli** data 25/09/2025 Positivo

La presente deliberazione si compone di n° 9 pagine e dei seguenti allegati che ne formano parte integrante e sostanziale:
Research Collaboration greement (RCA) Golgenia S.R.L. - IRE

Il Dirigente della UOSD Servizio Amministrativo Ricerca

Visto il decreto legislativo 30 dicembre 1992 n. 502 e successive modificazioni ed integrazioni;

Visto il decreto legislativo 16 ottobre 2003 n. 288 e il decreto legislativo 23 dicembre 2022 n. 200 di riordino della disciplina degli Istituti di Ricovero e Cura a Carattere Scientifico;

Vista la legge regionale 23 gennaio 2006, n. 2;

Vista Vista la deliberazione n. 814 del 03.09.2025 recante "Presa d'atto della deliberazione della Regione Lazio 7 agosto 2025 n.697 avente ad oggetto: "*Approvazione del Regolamento di Organizzazione e Funzionamento dell'IRCCS Istituti Fisioterapici Ospitalieri. Adozione del Regolamento di Organizzazione e Funzionamento degli IFO.*";

Visto il Decreto del Presidente della Regione Lazio n. T00015 del 12 febbraio 2025 avente ad oggetto "Nomina del Direttore Generale dell'IRCCS Istituti Fisioterapici Ospitalieri (Art. 8, comma 7 bis, della legge regionale 16 giugno 1994, n. 18 e s.m.i.)";

Vista la deliberazione n. 160 del 18.02.2025 di presa d'atto dell'insediamento del Direttore Generale dell'IRCCS Istituti Fisioterapici Ospitalieri Dott. Livio De Angelis;

Vista la deliberazione n.293 del 31.03.2025 con la quale il Dott. Massimo Armitari è stato nominato Direttore Amministrativo degli Istituti Fisioterapici Ospitalieri (IFO);

Vista la deliberazione n.367 del 23 aprile 2024 con la quale la Dott.ssa Costanza Cavuto è stata nominata Direttore Sanitario f.f. degli Istituti Fisioterapici Ospitalieri;

Visto il D.M. del Ministero della Salute del 20 giugno 2024 di conferma del riconoscimento del carattere scientifico dell'IRCCS di diritto pubblico a Istituti Fisioterapici Ospitalieri (IFO) relativamente alla disciplina di "oncologia" per l'Istituto

Nazionale Tumori Regina Elena (IRE) e alla disciplina di "dermatologia" per l'Istituto Santa Maria e San Gallicano (ISG);

Vista la deliberazione n.877 del 29.10.2024 avente ad oggetto: *"Nomina della Prof.ssa Maria Concetta Fargnoli quale Direttore Scientifico dell'Istituto Santa Maria e San Gallicano (ISG)"*;

Vista la deliberazione n.171 del 28.02.2025 avente ad oggetto: *"Nomina del Prof. Giovanni Blandino, Direttore della UOC Ricerca Traslazionale Oncologica, quale Direttore Scientifico IRE facente funzioni, a decorrere dal 01.03.2025.";*

Visto il decreto legislativo 10 febbraio 2005, n.30 recante il "Codice di Proprietà Industriale";

Vista la legge n. 102 del 24 luglio 2023 recante modifiche al "Codice della Proprietà Industriale";

Visti gli artt. 8 e 9 del decreto legislativo 16 ottobre 2003 n. 288, come da ultimo modificati dal D.lgs. 23 dicembre 2022, n. 200, che prevedono la possibilità per gli IRCCS di stipulare accordi e convenzioni, costituire e/o partecipare a consorzi e attuare misure di collegamento e sinergia con altre strutture di ricerca e assistenza sanitaria, pubbliche e private, nonché con le Università, per la realizzazione di comuni progetti di ricerca, in conformità all'art. 15 L. n. 241/1990;

Visti gli artt. 7 e 10 del suddetto decreto, che contemplano le diverse tipologie di ricavi degli IRCCS;

Visto l'art. 1, punto b) del Dlgs 288/2003 ai sensi del quale gli IRCCS sono tenuti a promuovere l'innovazione e il trasferimento tecnologico;

Vista la legge delega del 3 agosto 2022, n. 129, di riordino della disciplina degli IRCCS, che ha introdotto principi per favorire il trasferimento tecnologico, riconoscendo gli IRCCS come luoghi vocati alla ricerca traslazionale ed introducendo l'obbligo per queste strutture di dotarsi di Uffici di Trasferimento Tecnologico (UTT) per la valorizzazione dei risultati della ricerca e la collaborazione con le imprese al fine di facilitare il trasferimento tecnologico e l'innovazione, promuovendo le collabo-

razioni tra gli IRCCS e il settore industriale, nonché trasformare la ricerca scientifica in prodotti, servizi e tecnologie innovative;

Visto l'art. 8, comma 3 bis, del decreto legislativo 16 ottobre 2003 n. 288 ai sensi del quale le reti di ricerca degli IRCCS sono reti di eccellenza che perseguono finalità di ricerca prevalentemente traslazione, promuovendo il progresso delle conoscenze, sperimentando modelli di innovazione nei diversi settori dell'area tematica e che tali reti sono aperte alla collaborazione non solo con altri enti pubblici ma anche con partner scientifici e industriali nazionali e internazionali di natura privata;

Visto l'articolo 8 comma 5 sexies del decreto legislativo del 23 dicembre 2022, n. 200, ai sensi del quale gli IRCCS di diritto pubblico individuano il partner industriale in possesso di adeguate competenze tecnologiche e di ricerca per il trasferimento dei risultati della ricerca in ambito industriale anche mediante contratti di collaborazione industriale, di licenza, nonché attraverso la creazione di spin-off e start up e che a tal fine istituiscono e gestiscono l'albo dei partner industriali;

Premesso che l'IRCCS Istituto Nazionale Tumori Regina Elena (IRE), nello svolgimento delle proprie attività istituzionali, promuove azioni finalizzate alla valorizzazione dei risultati della ricerca scientifica attraverso collaborazioni con il settore industriale al fine di traslare la ricerca scientifica in nuovi trovati brevettabili, nonché in prodotti, servizi e tecnologie innovative;

Premesso che gli IFO adottano misure volte al trasferimento tecnologico, nonché a tutelare la Proprietà Intellettuale e Industriale delle proprie idee brevettuali, know-how, segreti commerciali, invenzioni industriali, modelli di utilità, topografie dei prodotti a semiconduttori, segreti commerciali e nuove varietà vegetali;

Premesso che, in virtù di quanto sopra, l'IRCCS IFO - IRE conduce diverse attività di ricerca al fine di testare una serie di inibitori dell'oncogene GOLPH3 in combinazione con farmaci chemioterapici tradizionali, su sferoidi tumorali, e modelli cellulari 3D derivati da linee tumorali selezionate per la presenza dell'oncogene GOLPH3;

Premesso che in questo settore l'IRCCS "IFO-IRE" sta realizzando progetti di ricerca e studi di fattibilità all'interno del laboratorio della UOC Translational Oncology Research;

Premesso che per gli scopi di cui sopra l'IRCCS "IFO-IRE" si avvale di numerose attività di collaborazione con partner industriali di comprovata esperienza e competenza tecnologica e di ricerca, tra i quali figura anche Golgenia S.r.l.;

Premesso Golgenia S.r.l., in qualità di startup innovativa impegnata nello sviluppo di know-how e di nuove tecnologie nell'ambito della biosintesi (o glicosilazione) dei glicani mediante l'apparato di Golgi, finalizzate sia alla generazione di nuovi approcci terapeutici sia alla creazione di glico-oncogeni (*Golgi Glyco-Oncogenes*) quale piattaforma di ricerca per lo sviluppo di farmaci antitumorali, ha richiesto in virtù delle collaborazioni scientifiche già in essere alla UOC di Ricerca Traslazionale Oncologica la disponibilità a effettuare test preclinici su una serie di inibitori dell'oncogene *GOLPH3*, in combinazione con farmaci chemioterapici convenzionali, utilizzando sferoidi tumorali derivati da linee cellulari selezionate per l'espressione del medesimo oncogene;

Considerato che l'attività di cui sopra è di grande interesse scientifico per gli scopi di ricerca istituzionali di IRCCS IFO-IRE e compatibile con le linee di ricerca degli Istituti;

Preso atto della nota del 18 marzo 2025 con la quale il Direttore dalla UOC Ricerca Traslazionale Oncologica, ha confermato la disponibilità a fornire le prestazioni richieste;

Dato atto che per gestire le attività richieste, ossia effettuare test preclinici su una serie di inibitori dell'oncogene GOLPH3, in combinazione con farmaci chemioterapici convenzionali, utilizzando sferoidi tumorali derivati da linee cellulari selezionate per l'espressione dell'oncogene GOLPH3, come indicato all'interno del piano di Ricerca (Research Plan) che, allegato al presente atto, ne costituisce parte integrante e sostanziale (All. RCA), nelle more dell'adozione dell'albo dei partner industriali, è stato necessario stipulare, in data 27 Giugno 2025, un *Research Collaboration Agreement (RCA)* tra Golgenia S.r.l. e IRCCS "IFO-IRE" dal titolo: "INHIBITORS OF THE GOLPH3 ONCOGENE AS ANTICANCER DRUGS";

Dato atto che le attività contemplate nel predetto RCA saranno svolte presso la UOC Ricerca Traslazionale Oncologica dell'IRCCS "IFO-IRE" sotto la responsabilità scientifica del Dr. Paquale Zizza;

Dato atto che il predetto RCA per lo svolgimento delle attività previste all'interno del piano di Ricerca (Allegato: *"Schedule 1 - Research Plan*) prevede un compenso omnicomprensivo in favore dell'IRCCS IFO – IRE pari ad € 50.020,00 (euro cinquantamila/20) comprensivo di IVA di legge e che tale somma verrà corrisposta in n. 3 rate da pagarsi rispettivamente:

- € 15.006,00 (euro quindicimilasei/00) comprensivo di IVA di legge, al momento dalla sottoscrizione del contratto;
- € 15.006,00 (euro quindicimilasei/00) comprensivo di IVA di legge, al sesto mese dalla firma dell'Accordo;
- € 20.008,00 (euro ventimilaotto/00) comprensivo di IVA di legge, al completamento di tutti i risultati ed all'elaborazione di un Report finale.

Preso atto della deliberazione del Commissario Straordinario n. 801 del 26 ottobre 2015 con la quale è stato disposto di accantonare, dai finanziamenti acquisiti per la ricerca finalizzata provenienti da Enti erogatori pubblici e privati, una quota pari al 10% da suddividere come di seguito specificato:

5,75% Direzione Scientifica IRE;

4,25% Ente;

Acquisito il parere favorevole del Direttore Scientifico IRE f.f. Prof. Giovanni Blandino con nota protocollata del 15/07/2025;

Ritenuto opportuno prendere atto dell'avvenuta stipula, in data 27 Giugno 2025, del *Research Collaboration Agreement (RCA)* tra Golgenia S.r.l. e IRCCS "IFO-IRE" dal titolo: *"*INHIBITORS OF THE GOLPH3 ONCOGENE AS ANTICANCER DRUGS*"*;

opportuno accettare il finanziamento erogato da Golgenia S.r.l. in favore di IRCCS "IFO-IRE" per l'attività di ricerca commissionata, pari a € 50.020,00 (euro cinquantamila/20) comprensivo di IVA di legge, nelle seguenti modalità:

- € 15.006,00 (euro quindicimilasei/00) comprensivo di IVA di legge, al momento della sottoscrizione del contratto;

- € 15.006,00 (euro quindicimilasei/00) comprensivo di IVA di legge, al sesto mese dalla sottoscrizione del contratto;
- € 20.008,00 (euro ventimilaotto/00) comprensivo di IVA di legge, al completamento di tutti i risultati ed all'elaborazione di un Report finale.

Attestato che il presente provvedimento, a seguito dell'istruttoria effettuata, nella forma e nella sostanza è totalmente legittimo e utile per il servizio pubblico, ai sensi dell'art. 1 della legge 20/94 e successive modifiche, nonché alla stregua dei criteri di economicità e di efficacia di cui all'art. 1, primo comma, della legge 241/90, come modificata dalla legge 15/2005.

Propone

Per i motivi di cui in narrativa che si intendono integralmente confermati di:

- prendere atto dell'avvenuta stipula, in data 27 Giugno 2025, del *Research Collaboration Agreement* (*RCA*) tra Golgenia S.r.l. e l'IRCCS "IFO-IRE" dal titolo*: "*INHIBITORS OF THE GOLPH3 ONCOGENE AS ANTICANCER DRUGS*",* al fine effettuare test preclinici su una serie di inibitori dell'oncogene GOLPH3, in combinazione con farmaci chemioterapici convenzionali, utilizzando sferoidi tumorali derivati da linee cellulari selezionate per l'espressione dell'oncogene GOLPH3, come indicato all'interno del piano di Ricerca (Research Plan) che, allegato al presente atto, ne costituisce parte integrante e sostanziale (All. RCA);
- accettare il finanziamento erogato da Golgenia S.r.l. in favore di IRCCS "IFO-IRE" per le attività di indagine svolte pari a € 50.020,00 euro cinquantamila/20) comprensivo di IVA di legge, nelle seguenti modalità:
- € 15.006,00 (euro quindicimilasei/00) comprensivo di IVA di legge, al momento della sottoscrizione del contratto;
- € 15.006,00 (euro quindicimilasei/00) comprensivo di IVA di legge, al sesto mese dalla sottoscrizione del contratto;
- € 20.008,00 (euroventimilaotto/00 comprensivo di IVA di legge, al completamento di tutti i risultati ed all'elaborazione di un Report finale;
- dare esecuzione alla deliberazione del Commissario Straordinario n. 801 del 26 ottobre 2015, accantonare dal finanziamento la quota di 10% e redistribuirla come di seguito specificato:

- 5,75% Direzione Scientifica IRE;

- 4.25% Ente;

- dare mandato alla UOC Risorse economiche di iscrivere al piano dei conti n. 401030401 e al centro di costo n. 1101030 l'importo di € 50.020,00 (Comprensivo di IVA di legge);
- disporre che il Technology Transfer Office (TTO) curerà tutti gli adempimenti per l'esecuzione della presente deliberazione.

Il Dirigente della UOSD Servizio Amministrativo Ricerca

Giovanna Evangelista

Il Direttore Generale

Visto	il decreto legislativo 30 dicembre 1992, n. 502 e s.m.i.;
Vista	la legge regionale 23 gennaio 2006 n. 2;
Visto	il decreto legislativo 16 ottobre 2003 n. 288 e il decreto legislativo 23 dicembre 2022 n. 200 "Riordino della disciplina degli Istituti di ricovero e cura a carattere scientifico";
Vista	la deliberazione n. 814 del 03.09.2025 recante *"Presa d'atto della deliberazione della Regione Lazio 7 agosto 2025 n.697 avente ad oggetto: Approvazione del Regolamento di Organizzazione e Funzionamento dell'IRCCS Istituti Fisioterapici Ospitalieri. Adozione del Regolamento di Organizzazione e Funzionamento degli IFO.";*
Visto	l'art. 3 comma 6 del D.lgs. 502/92 e successive modificazioni ed integrazioni, nonché l'art. 8 comma 7 della L.R. del Lazio n. 18/94.
In virtù	dei poteri di cui alla delibera IFO n. 160 del 18 febbraio 2025 inerente l'insediamento del Direttore Generale Dott. Livio De Angelis;
Preso atto	che il Dirigente proponente il presente provvedimento, sottoscrivendolo, attesta che lo stesso a seguito dell'istruttoria effettuata, nella forma e nella sostanza è totalmente legittimo e utile per il servizio pubblico, ai sensi dell'art. 1 della legge 20/94 e s.m.i., nonché alla stregua dei criteri di economicità e di efficacia di cui all'art. 1, primo comma, della legge 241/90, come modificata dalla legge 15/2005.
Visto	il parere favorevole del Direttore Amministrativo e del Direttore Sanitario Aziendale;

ritenuto di dover procedere;

Delibera

di approvare la proposta così formulata concernente *"PRESA D'ATTO DI AVVENUTA STIPULA DEL RESEARCH COLLABORATION AGREEMENT (RCA) TRA GOLGENIA S.R.L. e IFO-IRE ED ACCETTAZIONE DEL FINANZIAMENTO DI € 50.020,00 (INCLUSA IVA) PER LO SVOLGIMENTO DEL PROGETTO DI RICERCA DAL TITOLO: "INHIBITORS OF THE GOLPH3 ONCOGENE AS ANTICANCER DRUGS", DI CUI PI IL DOTT. PASQUALE ZIZZA."* e di renderla disposta.

Il Direttore Generale

Dott. Livio De Angelis

Documento firmato digitalmente ai sensi del D.Lgs 82/2005 s.m.i. e norme collegate

Confidential
Subject to contract

RESEARCH COLLABORATION AGREEMENT

Between

IRCCS ISTITUTI FISIOTERAPICI OSPITALIERI-ISTITUTO NAZIONALE TUMORI REGINA ELENA

And

Golgenia S.r.l.

Dated as of [•] 2025[•]

TABLE OF CONTENTS

RESEARCH COLLABORATION AGREEMENT

This Research Collaboration Agreement (this "**Agreement**"), is effective as of July 1st, 2025 (the "**Effective Date**"), by and between:

(1) **IRCCS Istituti Fisioterapici Ospitalieri - Istituto Nazionale Tumori Regina Elena (IFO - IRE)**, with offices located at Via Elio Chianesi 53 -00144 Roma Tax Code 02153140583 and VAT no. 01033011006, represented by the Director Gneral Dr. Livio De Angelis, domiciled for the purpose at the IRCCS, as well as proper delegation to the Scientific Director f.f. Prof. Giovanni Blandino ("**Institution**").

and

(2) **Golgenia S.r.l.,** with offices located at Piazza Castello, 19, Milano (MI), 20121. Represented by CEO Dott. Khalid Islam and CSO Dott. Alberto Luini.(**"Golgenia S.r.l."**).

BACKGROUND

Institution and Golgenia S.rl.l wish to collaborate on scientific research related to evaluate "a series of inhibitors of this oncogene in combinations with traditional chemotherapeutics in tumor spheroids derived from tumor lines selected for the presence of the GOLPH3 oncogene." on and subject to the terms of this Agreement.

AGREEMENT

The Parties agree as follows:

1. DEFINITIONS

In this Agreement, the following terms shall have the following meanings:

1. "**Affiliate**" means, in relation to a Party, any person that Controls, is Controlled by or is under common Control with that Party. "Control" shall mean direct or indirect: (a) to possess the power to direct the management and policies of an entity or (b) ownership of more than fifty percent (50%) of the outstanding voting securities or other ownership interest of such Party.

2. "**Applicable Laws**" means all applicable laws and regulations, including any guidelines or other requirements of regulatory authorities that may be in effect from time to time. For clarity, Applicable Laws include GLP.

3. "**Authors**" has the meaning set out in Section 13.2.

4. "**Institution Materials**" means those materials to be provided by or on behalf of the Institution to Golgenia S.r.l. as set out in the Research Plan and: (a) any substance or structure that is a derivative, analogue, modification, replication, complex, or subunit of such materials; and (b) any other compositions made using such materials.

5. "**Institution Results**" means all Results that are: (a) related to the Institution Materials, their patents, or their uses or indications, whether as a single agent or in combination with other agents; or (b) created, generated or developed solely by or on behalf of Institution.

6. "**Background Intellectual Property**" has the meaning set out in Section 11.1.

7. "**Collaboration Compound**" means the Institution Material

8. "**Collaboration Partner**" means any person or entity with whom, as of the Effective Date, Golgenia S.r.l. has entered into an agreement for the development and/or commercialization of the Collaboration Compound or Product relating to the Research Activities, including the Affiliates of such person or entity.

9. "**Confidential Information**" means all information or material that, at any time before, on or after the Effective Date, has been or is provided or communicated to a Party or any of its Affiliates by or on behalf of the other Party or any of its Affiliates under or in connection with this Agreement or any related discussions or negotiations including any data, ideas, concepts or techniques embodied or contained in such information or materials. Confidential Information may be disclosed orally, visually, in writing, by delivery of materials containing Confidential Information or in any other form now known or hereafter invented. Notwithstanding the foregoing: (a) all Institution Results shall be the Confidential Information of Institution and Institution shall be deemed to be the Disclosing Party and Golgenia S.r.l. shall be deemed to be the Receiving Party with respect thereto; (b) all Golgenia S.r.l. Results shall be the Confidential Information of Golgenia S.r.l. and Golgenia S.r.l. shall be deemed to be the Disclosing Party and Institution shall be deemed to be the Receiving Party with respect thereto; and (c) the terms of this Agreement shall be deemed to be the Confidential Information of both Parties and both Parties shall be deemed to be the Receiving Party and the Disclosing Party with respect thereto.

10. "**Data**" means any data or know-how to be shared by or on behalf of either Party with the other Party for use in the Research Activities, as described in the Research Plan.

11. "**Disclosing Party**" means, subject to the last sentence of the definition of Confidential Information, the Party disclosing, or whose Affiliates are disclosing, Confidential Information.

12. "**Final Report**" has the meaning set out in Section 5.2.2.

13. "**GLP**" means all then-current applicable laws, regulations and guidance of relevant regulatory authorities that constitute good laboratory practices.

14. "**HCO**" has the meaning set out in Section 10.3.1.

15. "**HCP**" has the meaning set out in Section 10.3.1.

16. "**Human Biological Samples**" or "**HBS**" means human biological samples being biological materials acquired or derived from living or deceased human beings which consist of or include human cells, and any derivatives or components thereof.

17. "**Institution Results**" means all Results, other than the Golgenia S.r.l. Results.

18. "**Negotiation Period**" has the meaning set out in Section 11.5.2.

19. "**Option**" has the meaning set out in Section 11.5.1.

20. "**Option Notice**" has the meaning set out in Section 11.5.2.

21. "**Option Period**" has the meaning set out in Section 11.5.2.

22. "**Parties**" means Institution and Golgenia S.r.l., and "**Party**" means either of Institution or Golgenia S.r.l..

23. "**Payment or Transfer of Value**" has the meaning set out in Section 10.3.2.

24. "**Principal Investigator**" means a senior scientist of the Institution appointed to supervise the Research Activities and identified in the Research Plan.

25. "**Product**" means any pharmaceutical product containing a Collaboration Compound, in any and all forms, presentations, doses and formulation.

26. **"Publication"** means the publication of an abstract, article or paper in a journal or an electronic repository, or an oral presentation at a conference or seminar, or other form of public disclosure in whatever form or medium, regarding any of the Research Activities carried out or Results generated under this Agreement.

27. **"Receiving Party"** means, subject to the last sentence of the definition of Confidential Information, the Party receiving (or whose Affiliates are receiving) Confidential Information.

28. **"Research Activities"** means all those tests, studies and other activities performed pursuant to the Research Plan or required to obtain the information set out in Research Plan.

29. **"Research Budget"** has the meaning set out in Section 4.1.

30. **"Research Documentation"** means all documents, records, accounts, books, notes, reports and other data relating to the Research Activities, in any form, created by or on behalf of the Institution.

31. "**Researchers"** has the meaning set out in Section 3.1.

32. **"Research Plan"** means a description of the research to be carried out by the Parties as set out in Schedule 1 (Research Plan), as amended from time to time by the Parties in writing.

33. **"Results"** means any ideas, inventions, discoveries, know-how, data (including raw data), documentation (including the Research Documentation), reports, materials, writings, designs, computer software, algorithms, predictive models, AI tools, processes, principles, methods, techniques and other information, recorded in any form, that are developed, discovered, conceived, reduced to practice or otherwise generated as a result of or in connection with the Research Activities, and any patent, trade secret, copyright, rights in know how or other intellectual property rights pertaining to any of the foregoing and the right to apply for any of such patent or other intellectual property rights. Results shall exclude the Institution Materials, HBS, Data and any other Background Intellectual Property of the Institution and of Golgenia S.r.l.

34. "**Term**" has the meaning set out in Section 18.1.

2. RESEARCH PROGRAM

1. **Research Activities and Research Plan**. Each Party shall carry out the Research Activities allocated to it in the Research Plan:

   1.1. with all due skill, care and diligence, allocating sufficient time, effort, equipment and suitably skilled personnel.

   1.2. in a good scientific manner, and in compliance with Applicable Laws; and

   1.3. in accordance with the Research Plan (including any timescales set out in it).

3. MANAGEMENT OF THE RESEARCH ACTIVITIES

1. **Principal Investigator**.

2. **Updates on Research Activities**.

4. RESEARCH FUNDING

1. **Research Budget**. In return for Institution's performance of the Research Activities, Golgenia S.r.l shall pay Institution the amounts specified in the research budget set out in Schedule 2 (the **"Research Budget"**) in accordance payment schedule set out in Schedule 2 (Research Budget).

The aggregate amount specified in the Research Budget is the maximum amount payable by Golgenia S.r.l under this Agreement for all Research Activities to be performed, expenses incurred, and rights granted, by Institution under this Agreement. The Parties acknowledge that the amounts to be paid by in accordance with the Research Budget are reasonable compensation, representing the fair market value for the work performed by Institution, and rights granted by Institution to Golgenia S.r.l under this Agreement, and that Institution has not received any other compensation or inducement in connection with this Agreement or its participation in the Research Activities.

2. **Payments**. Golgenia S.r.l. shall pay all invoices within sixty (60) days from receipt of a valid and undisputed invoice. All amounts payable by Golgenia S.r.l. under this Agreement are stated exclusive of any sales tax which Institution may be obliged to charge. If withholding tax applies, Golgenia S.r.l. shall be entitled to make deductions or withholdings as required by Applicable Laws.

3. **Invoices**. No payment will be made by Golgenia S.r.l. unless a purchase order/invoice request is issued by the Institution. Purchase orders and invoices shall be issued in accordance with Schedule 3 (Invoice Requirements), which may be updated from time to time upon written notice by Institution.

4. **Interest on Late Payments.** If either Party fails to pay any undisputed amount due under this Agreement within fourteen (14) days after payment is due, then the other Party may charge simple interest on the overdue amount on a daily basis at a rate equal to the lesser of: (a) the European Central Bank main refinancing rate plus two percent (2%); or (b) the maximum rate permitted under Applicable Laws.

5. **Books and Records**. Institution shall maintain complete and accurate books, records and accounts that, in reasonable detail, fairly reflect the use of the financial support provided by Golgenia S.r.l. under this Agreement. Golgenia S.r.l. may review and audit such books, records and accounts.

5. RECORDS, REPORTING AND INFORMATION EXCHANGE

1. **Record keeping**. Institution shall prepare and maintain complete, accurate, organised and legible records of all Research Documentation. Institution shall keep the Research Documentation secure and separate from other records and to a standard suitable for patent and regulatory purposes. Institution shall retain all Research Documentation until the seventh (7th) anniversary of the end of the Term (or longer if so required by Applicable Laws).Then (or earlier if so agreed by the Parties), Institution shall transfer the Research Documentation to Golgenia S.r.l. (or destroy it) at Golgenia S.r.l.'s request and expense.

2. **Reporting**.

   2.1. **Periodic Reports**. Institution shall submit written progress reports to Golgenia S.r.l. as and when specified in the Research Plan. Each such report shall include a detailed summary of all work done and all Results, including samples of any materials generated and all raw data and other information obtained, for the relevant period.

   2.2. **Final Report**. Institution shall submit a final written report to Golgenia S.r.l. within thirty (30) days after completion of the Research Activities (or, if earlier, the end of the Term). Such final report shall include a comprehensive summary of the Research Activities carried out and the Results (the "**Final Report**").

   2.3. **Sharing with Collaboration Partner**. Golgenia S.r.l. may share Confidential Information and Results and reports received from Institution with its Collaboration Partner. Any such disclosures between Golgenia S.r.l. and its Collabo\ration Partner made pursuant to this Section shall be made in confidence, in accordance with existing confidentiality obligations between Golgenia S.r.l. and its Collaboration Partner.

3. **Information Exchange**. Each Party shall provide Data, Research Documentation, Results and reports on the Research Activities to the other Party in a safe and secure manner, in the formats and in accordance with the methods for transferring such information (or otherwise making it accessible) to the other Party set out in the Research Plan or as otherwise agreed between the Parties. The provisions of this Section 5.3 are without prejudice to any other term of this Agreement (including those in relation to data privacy and cyber security), and in the event of any conflict, the most stringent measures for the exchange of information will prevail.

6. AUDIT AND INSPECTION

1. **Audits**. Golgenia S.r.l. or its representatives shall have the right, during regular working hours, to:

   1.1. monitor the conduct of the Research Activities and inspect Institution's premises where the Research Activities are, or will be, carried out;

   1.2. review and audit or inspect all Research Documentation, Golgenia S.r.l. Materials and HBS during the Term and during the period thereafter in which Institution is required to retain the same pursuant to the terms of this Agreement (or, if earlier, or if no such retention period is specified herein, until such time as the same have been transferred to Golgenia S.r.l. or destroyed in accordance with this Agreement); and

   1.3. interview the Principal Investigator and the Researchers.

   in each case to verify Institution's compliance with its obligations under this Agreement. Institution shall and shall cause the Principal Investigator, the Researchers and other Institution personnel to cooperate with any such activities.

2. **Regulatory Inspections**. Institution shall promptly inform Golgenia S.r.l. if any governmental or regulatory authority carries out (or states that it intends to carry out) an audit, inspection or other action connected with or potentially affecting the Research Activities or Research Documentation. Institution shall keep Golgenia S.r.l. reasonably updated on such action (including material correspondence related to it, and the findings and consequences of it).

7. SUPPLY OF INSTITUTION MATERIALS

1. **Institution Materials.** Institution shall supply Golgenia S.rl. the quantities of Institution Materials (at such times) that are specified in the Research Plan. As between the Parties, Institution owns and shall keep ownership of the Institution Materials. Golgenia S.rl.l shall keep the Institution Materials under its control and store them securely. Golgenia understands and acknowledges that the Research Activities relate to one or more Collaboration Compounds or Products and agrees that, with regard to the Research Activities, the rights and obligations regarding confidentiality and ownership of Results and Institution Materials shall apply to both Golgenia S.r.l. and its Collaboration Partner for the particular Collaboration Compound or Product.

2. **Use and Handling of the Institution Materials**. Golgenia S.r.l. acknowledges and agrees that the Institution Materials are experimental in nature. Golgenia S.r.l. use the Institution Materials only in connection with the performance of the Research Activities, and for no other purpose. In the event Golgenia S.r.l. uses the Institution Materials outside the scope of the Research Activities, any results arising from such a breach of the Agreement and related to the Materials or their uses shall be deemed to be Institution Results and shall be treated accordingly. Institution shall use, store and handle the Golgenia S.r.l. Materials in accordance with any instruction provided by Golgenia S.r.l. and Applicable Laws.
3. **Restrictions**. Golgenia S.r.l. shall not use the Institution Materials: (a) for the benefit of any third party, or transfer them to any person, without the prior written consent of Institution except for transfers to the Principal Investigator and the Researchers; (b) in research or testing involving human subjects; (c) for any commercial purpose, or (d) in combination with any other pharmaceutically active agent except as explicitly set out in the Research Plan.

4. **Prohibition on Structure Determination**. Golgenia S.r.l. shall not (and shall ensure that the Principal Investigator and the Researchers shall not) (and shall not attempt to) determine the structure of the Institution Materials (e.g.,) or otherwise characterize the Institution Materials without the prior written consent of Institution except as contemplated by the Research Plan.

5. **Return or Destruction of Golgenia S.r.l. Materials**. Golgenia S.r.l., at its cost and expense, either return to Institution, or at Institution's option destroy, all Golgenia S.r.l. Materials within forty-five (45) days following the end of the Term or Golgenia S.r.l.'s earlier request, unless the Parties agree otherwise in writing.

6. **Disclaimer**. Institution Materials are provided "AS IS" and to the maximum extent permitted by Applicable Law, Institution. hereby disclaims and excludes all representations, warranties, conditions or other terms, whether written or oral, expressed or implied, with respect to the Institution Materials, including any representation or warranty of quality, performance, merchantability or fitness for a particular use or purpose, or that the use of the Institution Materials does not infringe any intellectual property rights or other proprietary rights of a third party.

7. **No Liability**. To the fullest extent permitted by Applicable Laws, Institution shall not be liable to Golgenia S.r.l. its subcontractors, or any of its employees or agents (including the Principal Investigator and the Researchers) whether for breach of contract, negligence or otherwise, regarding the supply of the Institution Materials to, or the use or possession thereof by Golgenia S.r.l. its subcontractors or any of its employees or agents (including the Principal Investigator and the Researchers).

8. HBS

1. With respect to any and all Human Biological Samples to be used by or on behalf of the Institution in the Research Activities, Institution shall ensure that all HBS are and have been sourced, stored, handled, retained, used, transferred, transported, packaged, labelled and disposed of in accordance with Applicable Laws. Without prejudice to the foregoing, Institution represents, warrants and undertakes that:

   1.1. it has adequate facilities to collect and store the HBS for research purposes;

   1.2. it has relevant licences, permissions and ethical approvals for: (a) the collection of the HBS; and (b) the storage and use of the HBS for research purposes (including DNA or RNA analysis, if any);

   1.3. to the extent required by Applicable Law, it has obtained, or will obtain, explicit informed consent to use such HBS for research purposes (including DNA or RNA analysis, if any) from (or on behalf of) donors from whom the HBS were obtained or (subject to explicitly informing Golgenia S.r.l. that this is the case) it has obtained authorised research ethics committee approval for such research purposes; and

   1.4. The proposed storage and use of the HBS in the Research Activities (in collaboration with Golgenia S.r.l.) shall fall, if necessary, within the scope of such consent or research ethics committee approval (as applicable).

2. If Institution obtains HBS from a third party, Institution shall ensure that such third party: (a) grants Institution the right to freely use such HBS in carrying out the Research Activities; and (b) satisfies the requirements set out in Section 8.1 in respect of such HBS (including in respect of having obtained informed consents or research ethics committee approvals for the storage and use of the HBS, as applicable).

3. To the extent any HBS and any Data relating to any donor of HBS are delivered to Golgenia S.r.l. pursuant to this Agreement shall be delivered in such a format so that Golgenia S.r.l. does not know the identity of the donor. Golgenia S.r.l. acknowledges the importance of data privacy of donors and it commits not to: (a) attempt to locate or re-identify any donor: (b) combine such Data with other sources of data that could lead to the identification of any donor or other individual; or (c) reverse engineer, reverse assemble or decompile such Data. Despite the fact such Data is not to include any information from which the donor's identity could be known by Golgenia S.r.l., to the extent such Data constitutes Personal Data, Section 9 shall apply.

9. DATA AND PERSONAL DATA

1. Each Party shall provide to the other Party the Data that are specified in the Research Plan (at such times as are specified in the Research Plan), in accordance with Section 5.3. For clarity, the other Party's use of such Data shall be subject to the terms of this Agreement, including those set out in Section 11 and Section 12.

2. For the purpose of carrying out the Research Plan, **Personal Data** will not be collected, and any data that is collected will always be treated in a strictly confidential manner, in such a way as to guarantee its confidentiality, protection, and security, in compliance with **Applicable Laws**.

3. The Parties undertake to ensure that, should Personal Data be collected, it will be processed in compliance with data protection laws in accordance with EU Regulation 2016/679 (GDPR) and the Privacy Code (Legislative Decree 196/2003 and subsequent amendments), and that the legal basis for processing the Personal Data will lie in the consent expressed by the data subject pursuant to Articles 6, paragraph 1, letter a) and 9, paragraph 2, letter a) of the GDPR. The processing of the Data must therefore take place in a lawful, fair, and transparent manner in relation to the data subject pursuant to Article 5 of the GDPR (General Data Protection Regulation). Personal Data will be processed within the limits of the purposes to be defined, or for other similar or compatible purposes with the reasons for the collection of the Personal Data.

4. The Parties undertake to adopt all appropriate technical and organizational security measures pursuant to Art. 32 of the GDPR during the collection, use, and transmission phases of the Data. The Parties also undertake to ensure a level of security, including IT security, appropriate to the risk, taking into account the nature, scope, context, and purposes of the processing, as well as the risks of varying probability and severity for the rights and freedoms of the data subjects.

5. In the case of processing Personal Data, the Parties will guarantee the adoption of the principle of minimization in the use of Personal Data, meaning that only data that is adequate, relevant, and limited to what is necessary to achieve the purposes of this Agreement will be processed. The Parties undertake to adopt all appropriate technical and organizational security measures required by Applicable Laws both during the collection of Personal Data and use and transmission phases of the same.

6. The Parties shall comply with Applicable Laws in relation to the transfer, acquisition or other processing of Personal Data. Each Party shall ensure that any Personal Data shared with the other Party in connection with the Research Activities and in this agreement is delivered in such a format so that Golgenia S.r.l. does not know the identity of the donor, patient or other individual to whom the Data relates.

7. For the purpose of this Section 9, "**Personal Data**" means any information relating to an identified or identifiable natural person who can be identified directly or indirectly and in particular includes but is not limited to the following information about a living individual: first and last name, age, date of birth, gender, address, contact information, government-issued identifiers (such as passport and social security numbers), location data, an online identifier or any specific physical, health related, physiological, genetic, mental, economic, cultural or social information about that natural person.

8. The Institute will act characterized as the Data Controller and will process the Data only with IT and/or paper methods, tools and procedures strictly necessary for the purposes envisaged in the

Project and by means of operations indicated in the art. 4 of the GDPR (Legislative Decree 2016/679).

9. Both Parties must promptly notify each other in writing of any act, omission or other fact of which either of them becomes aware which could have a negative effect on the security of the IT systems used by them for the purposes of this Agreement. With reference to future activities to be carried out under this agreement, the Data Controller undertakes to keep and correctly update the Registers of processing activities pursuant to art. 30 of the GDPR.

The Parties have appointed their own Data Protection Officer (D.P.O.), respectively identified:

•For the Institution: Scudo Privacy Srl, in the person of Dr. Carlo Villanacci, reachable at the following email address: c.villanacci@scudoprivacysrl.com

•For the Golgenia S.r.l.: in the person of Dr. Gianni Luini, reachable at the following email address: gianni.luini@golgenia.it

10. TRANSPARENCY REQUIREMENTS

1. Golgenia recognises Institution commitment to compliance with Applicable Laws and transparency principles and shall cooperate with Institution to meet such commitments. To that end, and to the extent required by Applicable Law or any applicable industry code of practice, Institution may disclose on websites controlled Institution or any of its Affiliates (or on websites controlled by relevant industry bodies) and report to government entities and other third parties, the payments made to Institution by or on behalf of Golgenia S.r.l. pursuant to this Agreement.

2. Golgenia shall not contract with or make any Payment or Transfer of Value to an HCP or HCO in connection with the Research Activities or this Agreement or on behalf of Institution without Institution's prior written approval. Any payments to an HCP or HCO will be made according to rates agreed with Institution Such rates must be based on relevant local fair market value rates (rates may differ between countries). Golgenia S.r.l. acknowledges and agrees that any request for payment of, or reimbursement for, a Payment or Transfer of Value to an HCP or HCO will require that Golgenia S.r.l. provide Institution detailed expenditure information either through a template and/or system access, or as a file extract out of Institution's own system including all the required data fields as outlined by Institution If applicable, Institution and Golgenia S.r.l. will annually discuss the data collection process to confirm Golgenia S.r.l. understanding of Institution requirements. Golgenia S.r.l. shall provide such expenditure reporting to Institution by the end of the month after the month in which such Payment or Transfer of Value to an HCP or HCO is made. Documentation concerning Payments or Transfers of Value to an HCP or HCO must be maintained by Institution and Golgenia S.r.l. for five (5) years.

3. In this Section 10:

   3.1. A healthcare professional (**"HCP"**) includes a member of the medical, dental, pharmacy, and nursing professions, related administrative staff, and governmental officials who may prescribe, purchase, recommend, supply or administer medicines. A healthcare organisation (**"HCO"**) includes any legal entity that is a healthcare, medical or scientific association, organisation or learned society; or through which one or more HCPs provide services.

   3.2. A **"Payment or Transfer of Value"** is any payment or transfer of value from Golgenia S.r.l., or from Institution at the direction or request of Institution, to an HCP or HCO, and may include: compensation, matters or products that are provided free of charge or on a subsidised basis (such as free medicines or equipment), reimbursement for expenses, meals, travel, medical journal reprints, study supplies and medical writing and publications assistance.

11. INTELLECTUAL PROPERTY

1. **Background Intellectual Property**. All intellectual property, data and know-how owned or controlled by a Party or any of its Affiliates which is: (a) existing as of the Effective Date, or (b) developed, acquired or generated outside the scope of this Agreement ("**Background Intellectual Property**") shall remain the property of the owning or controlling Party. Nothing in this Agreement shall transfer any rights in such Background Intellectual Property to the other Party.

1.1. Each Party (and in the case of Golgenia S.r.l., its Affiliates) and their respective permitted subcontractors shall be permitted to use the Data (and, if applicable, other Background Property) of the other Party solely if and to the extent necessary to perform the Research Activities; and

1.2. If a license to certain Background Intellectual Property owned or controlled by the Institution is necessary for Golgenia S.r.l. to develop or commercially exploit the Results, and if the Institution is able to grant Golgenia S.r.l. rights to such Background Intellectual Property, then, upon Golgenia S.r.l.'s request, the Institution shall use reasonable efforts to grant Golgenia S.r.l. a paid license on commercially reasonable terms for such Background Intellectual Property which will not exceed a 1% of the value of the sale of the background Intellectual Property or of Golgenia S.r.l. up to a maximum value of 1 millions euros.

1.3. Any industrial and commercial exploitation of the Results arising from the Research Plan, as well as the associated licensing and royalty regime, shall be agreed upon in advance between the Parties, taking into account the level of commercial exploitation (such as, by way of example, quantity, units, territorial scope, etc.) and, if applicable, involving Collaboration Partners and/or third parties.

1.4. The Parties undertake to negotiate separately the licensing regime and any contractual extensions, which shall be agreed upon in advance between the Parties, both in terms of experimental development and in relation to the economic value derived therefrom.

11.2 Ownership of Results; Cooperation

11.2.1 **Golgenia S.r.l. Results.** Golgenia S.r.l. shall own free-of-charge all right, title and interest in and to all Golgenia S.r.l. Results.

11.2.2 **Institution Results.** Institution shall own all right, title and interest in and to all Institution Results.

11.2.3 **Cooperation**. At the request and expense of Institution, Golgenia S.r.l. shall, and shall cause the Principal Investigator and the Researchers to, execute and deliver any and all documents or instruments and perform all such acts as Institution may reasonably require to give effect to this Section 11 and to enable Institution (or its designee) to apply for, procure, maintain and enforce intellectual property rights in Institution. Results anywhere in the world as Institution (or its designee) may in its sole discretion determine. In no event shall Golgenia S.r.l. file any patent relating to the Institution Results.

11.2.4. **Costs.** Each Party shall be responsible for all costs associated with applying for, prosecuting, maintaining and enforcing intellectual property rights in Results owned by such Party pursuant to Section 11.2.1 or Section 11.2.2.

11.3 **Consultation on Patent Filings**. For patent applications covering Institution Results that Golgenia S.r.l. has exclusively licensed under Section 11.5, Institution shall consult with and cooperate with Golgenia S.r.l. prior to and during the preparation, filing, prosecution and maintenance of

such patent applications (and resulting patents) and take Golgenia S.r.l.'s reasonable comments into account.

11. 4 If the use of the Institution's Material leads to improvements, discoveries, or inventions (whether patentable or not) related to the Material (an "invention," in the case of biological material, includes any progeny or derivative, or modifications of the material), Golgenia S.r.l. shall promptly inform the Institution of such invention, in order to discuss the possibility of filing one or more patent applications for inventions conceived by one or more collaborators who, through the use of the material, will be able to file for a patent.

11.5 Neither Party shall file a patent application claiming that inventions arise through the use of the Material without notifying the other Party involved in the Research Plan and without a written agreement and consent from the other Party. The Parties may agree on co-ownership of all related Intellectual Property Rights (IPR) and may negotiate in good faith, through a separate Agreement, all terms and conditions for the protection and commercialization of any jointly developed IPR.

11.6 **Licence to Institution Results**. By this Agreement, the Institution grants Golgenia S.r.l. a non-exclusive, royalty-free, fully paid-up license, as provided in the Budget Plan, for the use of the Research Plan Results for scientific research purposes, as outlined in this Agreement. Any Results derived from the Research Plan will be subject to prior discussion between the Parties, and the application of paid licenses on such Results will be governed by separate agreements to be negotiated and entered into by the Parties.

11.5 **Option to an Exclusive Licence to inventions within Institution Results**

11.5.1 Institution hereby grants to Golgenia S.r.l. an exclusive option (the "Option") to take an exclusive, worldwide, perpetual licence on commercially reasonable terms (the "License") to any inventions within the Institution Results. The License will allow Institution to use any such Institution Results for the sole purpose of academic research and teaching purposes, other than activities for or on behalf of, or funded by, or with, any third party other than a non-profit or governmental organisation.

11.5.2 Golgenia S.r.l. may exercise the Option at any time until the date twelve (12) months after the date of provision of the Final Report (the "Option Period") by giving Institution written notice ("Option Notice"). Following Institution's receipt of an Option Notice, Institution shall enter into and diligently pursue exclusive good faith negotiations for a period for up to twelve (12) months (the "Negotiation Period") with Golgenia S.r.l. or its designated Affiliate with the aim of granting Golgenia S.r.l. or such Affiliate the License.

11.5.4 If Golgenia S.r.l. does not give Institution an Option Notice during the Option Period, or if Institution and Golgenia S.r.l. or its Affiliate fail to reach agreement on the terms of a license agreement within the Negotiation Period, then Institution shall be free to negotiate with third parties with respect to the Institution Results and commercialise or license out the Institution Results (subject to Golgenia S.r.l.'s non-exclusive license rights under Section 11.6). Golgenia S.r.l. will have at any time during the negotiation by Institution with a Third Party the right to match the Licensing conditions offered to the Third Party to secure the Exclusive Licence .

11.5.5 Institution shall obtain from the Principal Investigator and the Researchers rights to all Results generated by or on behalf of the Institution, such that Golgenia S.r.l. or its designee shall receive from Institution, and Institution shall be in a position to grant, without payments beyond those required by Section 4, the assignments, licenses and other rights granted hereunder to Golgenia S.r.l. or its designee.

12. CONFIDENTIALITY

1. **Property of the Disclosing Party**. Except as otherwise provided in this Agreement, any Confidential Information disclosed by or on behalf of one Party or any of its Affiliates to the other

Party or any of its Affiliates in connection with this Agreement shall remain the property of the Disclosing Party.

2. **Confidentiality Obligations**. During the Term and for five (5) years after the expiration or termination of this Agreement, the Receiving Party undertakes and shall cause, its officers, directors and other employees and agents (including the Principal Investigator and the Researchers if Institution is the Receiving Party) to keep confidential and not publish or otherwise disclose and not use, directly or indirectly, for any purpose, any Confidential Information of the Disclosing Party, except to the extent such disclosure or use is expressly permitted by the terms of this Agreement.

3. **Exceptions**. The provisions of Section 12.2 shall not apply to any Confidential Information which the Receiving Party can demonstrate to the reasonable satisfaction of the Disclosing Party:

   3.1. was already in the possession of the Receiving Party and at the Receiving Party's free use and disposal or in the public domain prior to its disclosure by the Disclosing Party under this Agreement;

   3.2. was, prior to disclosure to it pursuant to this Agreement, legally acquired by the Receiving Party from a third party having good title thereto and the right to disclose the same;

   3.3. comes into the public domain, otherwise than through the fault of, or breach of this Agreement, by the Receiving Party or any of its Affiliates; or

   3.4. is independently generated by the Receiving Party or any of its Affiliates without any recourse or reference to the Confidential Information disclosed by the Disclosing Party.

   3.5. Permitted Disclosure for Granted Rights. Notwithstanding Section 12.2, Golgenia S.r.l. may disclose Confidential Information of Institution to any third party and allow such third party, subject to confidentiality and use obligations no less onerous than as set out herein, to use such Confidential Information to the extent required for the purposes of exploiting the Golgenia S.r.l. Results and the Institution Results in accordance with the licences and rights granted under this Agreement.

4. **Disclosures Required by Law**. Nothing in Section 12.2 shall preclude disclosure of any Confidential Information required by any governmental, quasi-governmental or regulatory agency or authority or court entitled by law to receive the Confidential Information, or which is required by law to be disclosed (including freedom of information requests), provided that the Receiving Party, subject to Applicable Laws, promptly notifies the Disclosing Party when such requirement to disclose has arisen, to enable the Disclosing Party to seek an appropriate protective order, to inform the relevant agency, authority or court the proprietary nature of the Confidential Information, and to make any applicable claim of confidentiality. The Receiving Party agrees to co-operate in any appropriate action that the Disclosing Party may decide to take. If the Receiving Party is advised to make a disclosure in accordance with this section, it shall only make a disclosure to the extent to which it is obliged.

5. **Press Releases and Use of Name**. Except as expressly permitted by this Agreement, neither Party shall make any press release or other public announcement relating to this Agreement or otherwise use the name, insignia, symbol, trademark, trade name or logotype of the other Party or its Affiliates in any publication, press release, promotional material or other form of publicity without the prior written approval of the other Party. The restrictions imposed by this Section 12.6 shall not prohibit either Party from making any disclosure that is required by Applicable Laws.

13. PUBLICATION OF RESULTS

1. Each Party recognises that collaborating with respect to Publications may be beneficial to both Parties. The intention of the Parties is jointly to make such Publications, where reasonably possible.

2. **Rights and Procedures**. Subject to the provisions of this Section 13, the Institution, the Principal Investigator, the Researchers, and any additional authorized authors (collectively, "Authors") shall have the right to publish the Results in scientific or other journals, or to present the Results at professional conferences or other meetings in accordance with academic standards, provided that any such Publication, whether joint or independent, shall be subject to review in accordance with this Section 13.2. At least forty-five (45) days prior to submission of any material for inclusion in a Publication (including materials for educational purposes), the Parties shall provide such material for review. Each Party shall have forty-five (45) days to respond with any comments. Upon written request, the Parties shall ensure that the Authors: (a) withhold the material from submission for publication or presentation for an additional ninety (90) days from the date of the request, to allow for the filing of a patent application or the taking of other measures deemed appropriate by either Party to establish and preserve their proprietary rights or those of their Collaboration Partner in the information contained in the material; (b) give reasonable consideration to any request by either Party to modify the publication; and (c) remove any information that, at the exclusive discretion of either Party, is deemed Confidential.

3. **Timing of Publications**. The Parties acknowledge that scientific lead-time is a key element of the value of the Research Activities and agree that premature publication of any Results before all Research Activities are completed and the data is collected and analyzed could be misleading. Therefore, the Institution and Golgenia S.r.l. commit to ensuring that the Authors agree not to publish or present the outcomes of the Research Activities or any Results until the completion of all Research Activities, and, if such Research Activities are part of a broader research project conducted at multiple study sites, until all data has been collected from all study sites.

4. **Golgenia S.r.l. Rights.** Golgenia S.r.l. and its Affiliates shall also have the right to publish or present independently the Results provided that due acknowledgement is made for the intellectual contribution made by Institution in accordance with standard scientific practice. However, Golgenia S.r.l. shall obtain the prior written consent of Institution to publish or present independently the Results before the earlier of: (a) the first joint publication, or publication or presentation by the Principal Investigator, of any Results; and (b) twelve (12) months after completion of the Research Activities.

5. **Responsibilities of Authors**. Institution shall ensure that Authors comply with the International Committee of Medical Journal Editors criteria regarding authorship and recommendations regarding disclosure of potential conflicts of interest, as well as all requirements with respect to disclosure required by any medical or scientific institution, medical committee or other medical or scientific organisation with which they are affiliated.

14. EXPECTATIONS OF THIRD PARTIES AND ANTI-BRIBERY

1. **Institution Expectations**. Institution recognises Golgenia S.r.l.'s commitment to work only with partners who embrace the standards of ethical behavior.

2. **Compliance.** Institution represents and will ensure that it: (a) will perform this Agreement and operate its business in compliance with all Applicable Law; (b) will perform this Agreement and operate its business to ethical standards; (c) will not take any action that will cause Golgenia S.r.l. or any Golgenia S.r.l. Affiliate to be in breach of any Applicable Law for the prevention of fraud, bribery and corruption, racketeering, money laundering, terrorism, product security or product safety, including the National Anti-Corruption Plan and the Italian anti-corruption legislation; ; and (d) will use its reasonable endeavours to cause its Affiliate, suppliers and subcontractors performing any Research Activities (where applicable) to operate their business in compliance with all Applicable Law.

3. **Anti-bribery.** Institution shall not and shall ensure that Principal Investigator and the Researchers shall not offer, pay, request or accept any bribe, inducement, kickback or facilitation payment, and will not make or cause another to make any offer or payment to any individual or entity for the purposes of influencing a decision for the benefit of Golgenia S.r.l. or any of its Affiliates (and Institution represents and warrants that it has not and Principal Investigator has not done any of the foregoing as at the Effective Date).

15. CYBER SECURITY REQUIREMENTS

1. **Cyber Security Measures.** In performing its obligations and exercising its rights under this Agreement, Institution warrants and represents that it will maintain adequate administrative, technical, and physical measures, controls, tools, systems, policies and procedures in accordance with good cyber security industry practice.

16. **Security Incidents.** Institution will notify Golgenia S.r.l., in writing, about any security incident affecting or which may affect any IT infrastructure or data or facilities owned, leased or used by and/or provided for use by Institution, which may affect the fulfilment of Institution's obligations under this Agreement, without undue delay and in any event within twenty four (24) hours after Institution becomes aware of or suspects that a security incident has occurred. Such notification will be, in the first instance, sent by e-mail to the following e-mail address: Gianni.luini@golgenia.it.

1. **Responsibilities.** Each Party shall be solely responsible and liable for: (a) its use or other exploitation of the Results; and (b) the collection, storage, use, handling, processing and disposal of any Institution Materials, HBS, and Data pursuant to this Agreement by it or on its behalf. The other Party accepts no liability or responsibility for, or in connection, with any of the foregoing except to the extent that such liability arises out of a breach of an express obligation, or such responsibility has been expressly assumed, by such other Party as set out in this Agreement.

2. **Limitation of Liability**. Subject to Section 16.3, neither Party shall be liable to the other Party for any lost profits, damages for lost opportunities or for any special, indirect, incidental punitive or consequential damages, whether in contract, warranty, negligence, tort, strict liability or otherwise, arising out of or in connection with this Agreement.

3. **Exceptions to Limits.** Nothing in this Agreement shall limit or exclude either Party's liability arising out of or in connection with this Agreement for: (a) death or personal injury caused by negligence; (b) fraud or fraudulent misrepresentation; (c) willful misconduct; (d) breach of any of such Party's confidentiality or nondisclosure obligations or use restrictions in relation to Confidential Information, or any of its obligations under Section 8 (HBS), Section 9 (Personal Data) or Section 15 (Cyber Security Requirements); (e) its liability under Section 16.1; or (f) any acts or omissions in respect of which the governing law of this Agreement prohibits the exclusion or limitation of liability.

4. **Indemnification of Collaboration Partner**. Institution agrees to defend, indemnify and hold harmless the Collaboration Partner, its affiliates, and their respective officers and employees from and against any and all liabilities, claims, actions, suits, settlements, judgments and expenses, including reasonable attorney's fees, arising out of the use of the Collaboration Compound or Product or their modifications.

5. **Insurance**. Each Party will maintain adequate and appropriate insurance or self-insurance with respect to its activities in connection with the conduct of Research Activities. Each Party may request copies of documentation evidencing the existence of such insurance. Such insurance or self-insurance will be in such amounts and subject to such deductions as are required under Applicable Laws and internal risk management practice of a similar nature engaging in similar activities in the applicable jurisdictions.

17. REPRESENTATIONS, WARRANTIES AND COVENANTS

1. Each Party represents, warrants and covenants to the other Party that:

   1.1. it has the full power and authority under its constitution, and has taken all necessary actions, to execute and perform its obligations under this Agreement;

   1.2. entering into this Agreement, performing its obligations hereunder and granting rights to the other Party as set out in this Agreement does not conflict with any other agreement to which it is a party; and

1.3. it has the title and authority to and is entitled to assign to the other Party, the Institution Results (in case of Institution) and the Golgenia S.r.l. Results (in case of Golgenia S.r.l.), to grant the License and to grant all other rights and licenses granted to Golgenia S.r.l. in accordance with the terms of this Agreement.

2. Institution, on behalf of itself and the Principal Investigator (as applicable), represents, warrants and undertakes to Golgenia S.r.l. as follows:

2.1. all necessary consents, approvals and authorisations of all regulatory authorities and other persons required to be obtained by it in connection with this Agreement have been obtained;

2.2. none of Institution, the Principal Investigator or Researchers have, or will during the Term have: (a) any financial or other conflict of interest in the outcome of the Research Activities; or (b) entered into any contract that creates a conflict of interest;

2.3. entering into this Agreement and performing the Research Activities does not cause Institution, the Principal Investigator or any Researcher to be non-compliant with any policy or procedure of any institution or entity that it or they are affiliated with;

2.4. the Principal Investigator is permitted to perform and agree to be bound by the relevant terms of this Agreement and that this Agreement is consistent with the Principal Investigator's obligations to Institution;

2.5. shall not (and shall ensure that the Principal Investigator shall not) use any funding provided by any governmental authority to conduct any of the Research Activities if such funding would impair the ability of Institution or the Principal Investigator to perform any of the Research Activities or to own, assign and license any intellectual property rights consistent with the terms of this Agreement;

2.6. during the Term and within two (2) years of the termination of this Agreement ensure that: (a) if Principal Investigator is a member of a committee that sets formularies or develops clinical guidelines, the Principal Investigator will disclose to such committee the existence and nature of this Agreement and will follow the procedures required by the committee; and (b) if the Principal Investigator writes or speaks in public about a matter that is the subject of this Agreement or any other matter relating to Golgenia S.r.l. , they declare the fact that they are working in collaboration with Golgenia S.r.l. . Institution further agrees to ensure that the Principal Investigator fully complies with all applicable disclosure obligations relating to Principal Investigator's relationship with Golgenia S.r.l. that may be externally imposed on Principal Investigator based on the requirements of any institution, medical committee or other medical or scientific organisation with which Principal Investigator is affiliated.

2.7. **Warranty Disclaimer Regarding Results.** All Results provided to a Party are provided "AS IS" and to the maximum extent permitted by Applicable Laws and, save as expressly set out in this Agreement, each Party hereby disclaims and excludes all representations, warranties, conditions or other terms, whether written or oral, expressed or implied, with respect to the Results, including any representation or warranty of quality, performance, merchantability or fitness for a particular use or purpose, that the Results do not infringe the intellectual property rights or other proprietary rights of a third party.

18. TERM AND TERMINATION

1. **Term**. This Agreement shall commence on the Effective Date and continue until the later to occur of: (a) one (1) year after the Effective Date; or (b) the completion of the Research Activities and Golgenia S.r.l.'s receipt of the Final Report, unless this Agreement is earlier terminated in accordance with this Section 18 (the "**Term**").

2. **Termination for Material Breach by Either Party**. If a Party is in material breach of this Agreement, and such breach remains uncured for thirty (30) days after receipt of a notice of such

breach from the other Party, then the other Party shall have the right to immediately terminate this Agreement by giving written notice of termination to the breaching Party.

3. **Termination by Golgenia S.r.l.**. Golgenia S.r.l. has the right in its sole discretion to terminate this Agreement for any reason or no reason by giving thirty (30) days' written notice to Institution.

4. **Termination in absence of Principal Investigator**. If Institution is unable to secure a substitute Principal Investigator reasonably acceptable to Golgenia S.r.l. in accordance with Section 3.1 within ninety (90) days of notifying Golgenia S.r.l. that the Principal Investigator has become unavailable, then either Party shall have the right to terminate this Agreement by giving thirty (30) days' written notice to the other Party.

5. **Consequences of Expiry or Termination**. Upon expiration or earlier termination of this Agreement:

   5.1. each Party shall, subject to Section 5.1 return to the other Party or at the other Party's option, destroy all Confidential Information of the other Party (except for one copy of such Confidential Information may be retained for archival purposes, and further provided that such Party shall be permitted to retain such Confidential Information: (a) to the extent necessary to comply with Applicable Laws; or (b) for the purposes of exercising any ongoing licence or rights pursuant to this Agreement);

   5.2. Institution shall deliver to Golgenia S.r.l. the Final Report;

   5.3. Institution shall, in addition to any other remedy that may be available to Golgenia S.r.l. , promptly reimburse Golgenia S.r.l. for any excess amounts or unused funding paid to Institution pursuant to Section 4;

   5.4. in cases of termination of this Agreement by Institution pursuant to Section 18.2 or by Golgenia S.r.l. pursuant to Section 18.3 or by either Party pursuant to Section 18.4, Golgenia S.r.l. shall reimburse Institution for all documented non-cancellable costs reasonably committed before receipt of the notice of termination, provided that Institution provides Golgenia S.r.l. with satisfactory proof that such expenses cannot be cancelled or recovered and in no event shall such expense exceed the aggregate amount budgeted in the Research Budget; and

   5.5. at Institution' s option, Golgenia S.r.l. shall either destroy or return to Institution all of the Institution Materials, provided that in the case of the destruction of such Institution Materials, Golgenia S.r.l. shall certify in writing to Institution that such Institution Materials have been destroyed.

6. **Survival**. Termination or expiry of this Agreement shall not affect any rights and obligations of the Parties that accrued prior to termination or expiry. All provisions of this Agreement which, in accordance with their terms, are intended to have effect after termination or expiration of this Agreement shall survive indefinitely the termination or expiration of this Agreement.

19. MISCELLANEOUS

1. **Force Majeure**. Neither Party shall be held liable to the other Party or be deemed to have breached this Agreement for failure or delay in performing any term of this Agreement when such failure or delay is caused by or results from events beyond the reasonable control of the non-performing Party, including fires, floods, earthquakes, hurricanes, embargoes, shortages, epidemics, pandemics, quarantines, war, acts of war (whether war be declared or not), terrorist acts, insurrections, riots, civil commotion, strikes, lockouts or other labour disturbances (whether involving the workforce of the non-performing Party or of any other Person), acts of God or acts, omissions or delays in acting by any governmental authority (except to the extent such delay results from the breach by the non-performing Party or any of its Affiliates of any term of this Agreement). The non-performing Party shall notify the other Party of such force majeure within thirty (30) days after such occurrence by giving written notice to the other Party stating the nature of the event, its anticipated duration and any action being taken to avoid or minimise its effect.

The suspension of performance shall be of no greater scope and no longer duration than is necessary and the non-performing Party shall use commercially reasonable efforts to remedy its inability to perform.

2. **Assignment**. This Agreement may not be assigned by either Party in whole or in part without the prior written consent of the other Party, except that Golgenia S.r.l. without such consent may assign this Agreement and its rights and obligations hereunder to any of its Affiliates or any successor in interest to all or substantially all of the business to which this Agreement relates. Golgenia S.r.l. shall always have the right to perform any or all of its obligations and exercise any or all of its rights under this Agreement through any of its Affiliates. Each Party will remain fully liable for any acts or omissions of any of its Affiliates in breach of this Agreement as if they were its own.

3. **Governing Law**

The interpretation and construction of this Agreement shall be governed by the laws of Italy, with exclusive jurisdiction of the judicial authority based in Rome, excluding any conflicts or choice of law rule or principle that might otherwise refer construction or interpretation of this Agreement to the substantive law of another jurisdiction

4. **Escalation and Jurisdiction**

If a dispute arises between the Parties in connection with or relating to this Agreement, then either Party shall have the right to refer such dispute to officers within each of their respective organisations with the authority to make decisions for attempted resolution by good faith negotiations during a period of thirty (30) business days. If the Parties are unable to resolve any such dispute within such thirty (30) business day period, either Party shall be free to institute litigation in accordance with this Section. The Parties hereby consent to the exclusive jurisdiction of the courts of Italy for any action, suit or proceeding arising out of or relating to this Agreement that is not resolved in accordance with the above and, subject to Section 19.9, agree not to commence any action, suit or proceeding related thereto except in such courts.

5. **Notices**. Any notice or other communication required or permitted to be given by either Party under this Agreement shall be in writing and shall be deemed given as of: (a) the date delivered if delivered by hand, or reputable courier service; (b) the second (2nd) business day (at the place of delivery) after deposit with an internationally recognised overnight delivery service; or (c) the fifth (5th) business day after mailing if mailed by registered or certified mail, postage prepaid and return receipt requested, in each case addressed to the other Party at the addresses specified below, to such other addresses of which notice shall have been given in accordance with this Section. This Section 19.6 is not intended to govern the day-to-day business communications necessary between the Parties in performing their obligations under the terms of this Agreement.

Address for Notices

Institution	To: Via Elio Chianesi 53, 00144 – Rome, Italy. Attention:Scientific Director, Head of Translational Oncology Research Unit, Technology Transfer Office	With a copy to: dirscire@ifo.it Attention: Scientific Director Prof. Giovanni Blandino pasquale.zizza@ifo.it:: Head of Translational Oncology Research Unit technologytransfer@ifo.it Attention: Technology Transfer Office (TTO)

Golgenia S.r.l.	To: Golgenia S.r.l., Piazza Castello, 19, Milano (MI), 20121. Attention: CEO, CSO	With a copy to (which shall not constitute effective notice): info@pec.golgenia.it Attention: CEO, Khalid Islam alberto.luini@golgenia.it Attention : CSO, Dr. Alberto Luini

7. **Relationship of the Parties**. The status of a Party under this Agreement shall be that of an independent contractor. Nothing contained in this Agreement shall be construed as creating a partnership, joint venture or agency relationship between the Parties or, except as otherwise expressly provided in this Agreement, as granting either Party the authority to bind or contract any obligation in the name of or on the account of the other Party or to make any statements, representations, warranties or commitments on behalf of the other Party. All persons employed by a Party shall be employees of such Party and all costs and obligations incurred by reason of any such employment shall be for the account and expense of such Party.

8. **Construction**. Except where the context requires otherwise, whenever used the singular includes the plural, the plural includes the singular and the word "or" has the inclusive meaning represented by the phrase "and/or." The headings of this Agreement are for convenience only and do not define, describe, extend or limit the scope or intent of this Agreement or any of its provisions. The term "including" or "includes" as used in this Agreement means including, without limiting the generality of any description preceding such term. References to legislation shall be construed as a reference to that legislation as amended, re-enacted or replaced whether in whole or in part, and to any legislation implementing the foregoing. The wording of this Agreement shall be deemed to be the wording mutually chosen by the Parties and no rule of strict construction shall be applied against any Party.

9. **Equitable Relief**. The Parties recognise that any threatened breach or breach of Sections 11 (Intellectual Property), 12 (Confidentiality) or 13 (Publication of Results) may cause irreparable harm that is inadequately compensable in damages and that, in addition to other remedies that may be available at law or equity, the non-breaching Party is entitled to seek injunctive relief for such threatened or actual breach in any court of competent jurisdiction.

10. **Amendment; Waiver**. No amendment, modification or waiver of any of the terms of this Agreement shall be deemed valid unless made in writing and duly executed by authorised representatives of both Parties. Each Party shall have the right to enforce the Agreement in strict accordance with its terms. The failure of either Party to enforce its rights strictly in accordance with terms shall not be construed as having in any way modified or waived the same.

11. **Severability**. If any provision of this Agreement is held to be invalid, illegal or unenforceable in any respect, then to the fullest extent permitted by Applicable Laws: (a) such provision will be given no effect by the Parties and shall not form part of this Agreement; and (b) all other provisions of this Agreement shall remain in full force and effect.

12. **No Third Party Rights**. A person who is not a Party to this Agreement shall not have any rights to enforce any of its terms. The Parties may amend, renew, terminate or otherwise vary all or any of the provisions of this Agreement without the consent of any other person.

13. **Entire Agreement**. This Agreement and all Schedules constitute the entire agreement and understanding between the Parties with respect to the subject matter hereof and supersede all prior oral and written agreements, understandings, promises and representations with respect thereto. In the event of any inconsistency between any such Schedules and this Agreement, the terms of this Agreement shall govern.

14. **Counterparts**. This Agreement may be executed in two or more counterparts, each of which shall be deemed an original and all of which shall together be deemed to constitute one agreement. The Parties agree that execution of this Agreement by industry standard electronic signature software or by exchanging PDF signatures shall have the same legal force and effect as the exchange of original signatures, and that in any proceeding arising under or relating to this Agreement, each Party hereby waives any right to raise any defence or waiver based upon execution of this Agreement by means of such electronic signatures or maintenance of the executed agreement electronically.

[*Remainder of page intentionally left blank. Signatures follow.*]

Execution

THIS AGREEMENT IS EXECUTED by the authorised representatives of the Parties as of the Effective Date.

SIGNED for and on behalf of **Golgenia S.r.l.**		**SIGNED for and on behalf of** **IRCCS Istituti Fisioterapici Ospitalieri - Istituto Nazionale Tumori Regina Elena**	
Signature:		Signature:	.....
Name:	Khalid Islam	Name:	Prof. Giovanni Blandino
Title:	CEO	Title:	Scientific Director f.f.
Name:	Alberto Luini		
Title:	CSO		
Name:	Gianni Luini		
Title:	Amministratore delegato		

The Principal Investigator acknowledges that he/she has read this Agreement and understands the obligations Institution has undertaken on his/her behalf.

Acknowledged and Agreed to:

By: _____

Name: Dr. Paquale Zizza

Title: Principal Investigator

Date: 26/06/25

WORKPLAN 1

RESEARCH PLAN

INHIBITORS OF THE GOLPH3 ONCOGENE AS ANTICANCER DRUGS

Principal Investigator:

Dr. Pasquale Zizza pasquale.zizza@ifo.it

Translational Oncology Research Unit, Department of Research, Advanced Diagnostics, and Technological Innovation, Translational Research Area, IRCCS Regina Elena National Cancer Institute, Rome, Italy.

Scientific Lead (Golgenia S.r.l.):
Dr. Alberto Luini, alberto.luini@golgenia.it

Golgenia S.r.l., Milano (MI), Italy

SYNOPSIS

INTRODUCTION TO THE AGREEMENT WITH DR. ZIZZA ABOUT A RESEARCH PROGRAM ON INHIBITORS OF THE GOLPH3 ONCOGENE AS ANTICANCER DRUGS

GOLPH3 ONCOGENE

GOLPH3 is an oncogene amplified in the p13 region of chromosome 5 (5p13) and over-expressed in an important fraction of solid tumors (e.g. in 60% of squamous lung cancer, 50% of lung adenocarcinoma, 50% of breast cancer according to TCGA). It is generally associated with the development of chemoresistance and a poor prognosis.

The GOLPH3 protein localizes in the Golgi complex. Its biological properties have only been partially understood. It is however clear that the GOLPH3 works primarily in the Golgi as an adapter in two different roles:

a) In complex with MYO18, it transports growth-promoting proteins such as receptor tyrosine kinase from the Golgi to the plasma membrane. b) In complex with other partners, it carries out the retrograde transport of a group of glycoenzymes of glycosphingolipid metabolism (GSL) between the cisterns of the Golgi complex, in the context of the more general mechanism of maturation of the reservoirs defined as 'mosaic'.

Finally, GOLPH3 induces activation of various intracellular signaling pathways, particularly the PI3K-AKT-mTOR pathway, possibly through the mechanisms outlined above.

ONCOGENIC MECHANISM OF GOLPH3

The oncogenic mechanism of GOLPH3 has been studied intensively over the past 12 years and various models have been proposed. Our analysis is based on the role of GOLPH3 as an adapter in the Golgi and is shown in the diagram in Figure 1:

GOLPH3 acts in the transport of a group of Golgi glycoenzymes (GOLPH3 clients) that control, starting from the ceramide precursor, the synthesis, of glycophingolipids known to have pro-survival and pro-tumor functions. It binds to the cytosolic tails of these enzymes and activates their retrograde recycling (mosaic Golgi maturation), retaining them within the Golgi complex and preventing their arrival in lysosomes. In this way, it inhibits the lysosomal degradation of these enzymes and thus increases their levels (Figure 1).

The result is the accelerated conversion of ceramide, a lipid that has a potent proapoptotic effect, to metabolites such as globo- and gangliosides, which are known to activate mitogenic signaling pathways, predominantly via the PI3K-AKT-mTOR and WNT systems.

What role does GOLPH3 play in this context? GOLPH3 has an important functional significance not so much and not only for cell growth in quiescent conditions, but above all for cell survival under stress conditions such as chemotherapy-induced DNA damage. The reason for this is that during genotoxic stress from drugs, the cell produces large amounts of ceramide which would induce cancer cell death if GOLPH3 did not intervene by converting ceramide into globo- and gangliosides.

Further development of this study showed that globoside production in the Golgi activates an SRC and JNK-based signaling pathway that modifies the morphology of the Golgi and its ability to selectively secrete different classes of cargo proteins. The result is increased secretion on the plasma membrane of growth receptors such as MET, EGFR and others (Figure 2), which enhance cell growth and survival.

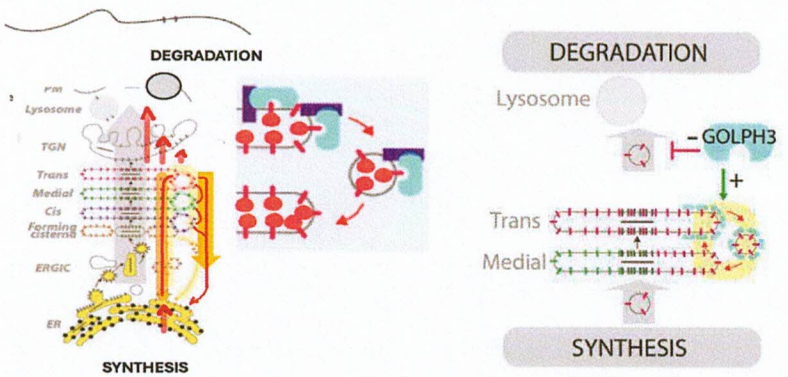


FIGURE 1. A. Golph3 (blue) binds to the cytosolic tails of a group of enzymes operating in the metabolism of GSL (red) and activates their retrograde recycling (maturation of mosaic cisterns). B. Thus Golph3 retains enzymes within the Golgi complex and prevents their arrival in lysosomes. In this way, it inhibits lysosomal degradation and increases the levels of these enzymes.

In summary, GOLPH3 has a complex and powerful mechanism to counteract chemoresistance based on the consumption of the tumor suppressor ceramide in favor of the production of gangliosides that lead to an increased secretion of growth receptors with a pro-survival effect. These two combined effects are the cause of GOLPH3's property of inducing chemoresistance and inducing-enhancing tumor transformation.

GOLPH3 INHIBITORS

In recent years, we have developed GOLPH3 inhibitor drugs. While direct inhibitors do not exist, it is possible to inhibit the action of GOLPH3 by blocking the metabolism of GSL (glycosphingolipids) at its inception, i.e. by blocking the UGCG enzyme that transforms ceramide into glucosylceramide. This means that GOLPH3 cannot exert its accelerating effect on the conversion from Ceramide to globo- and gangliosides, and thus indirectly inhibits the oncogenic action of GOLPH3. UGCG inhibitors have been developed for some time and are already in clinical use for the therapy of genetic lysosomal storage diseases such as Gaucher disease. The best known are eliglustat, miglustat and venglustat.

This makes it possible to reduce the development time of GOLPH3 inhibitor drugs using a repositioning strategy. In vitro experiments confirm that this group of drugs can markedly reduce resistance to chemotherapy and that the effect is selective for tumors that express the GOLPH3 oncogene, i.e. that show genomic amplification and overexpression of GOLPH3. In these tumors, the role of GSL metabolism in chemoresistance is predominant and its inhibition leads to the ablation of resistance to chemotherapy. Tumors that do not overexpress GOLPH3 and that have a slow GSL metabolism are not very sensitive to inhibition with eliglustat. It is therefore possible to select tumors that respond to UGCG inhibitors with reduction of resistance to chemotherapy by detecting of genomic amplification and overexpression of GOLPH3 in the target tumor.

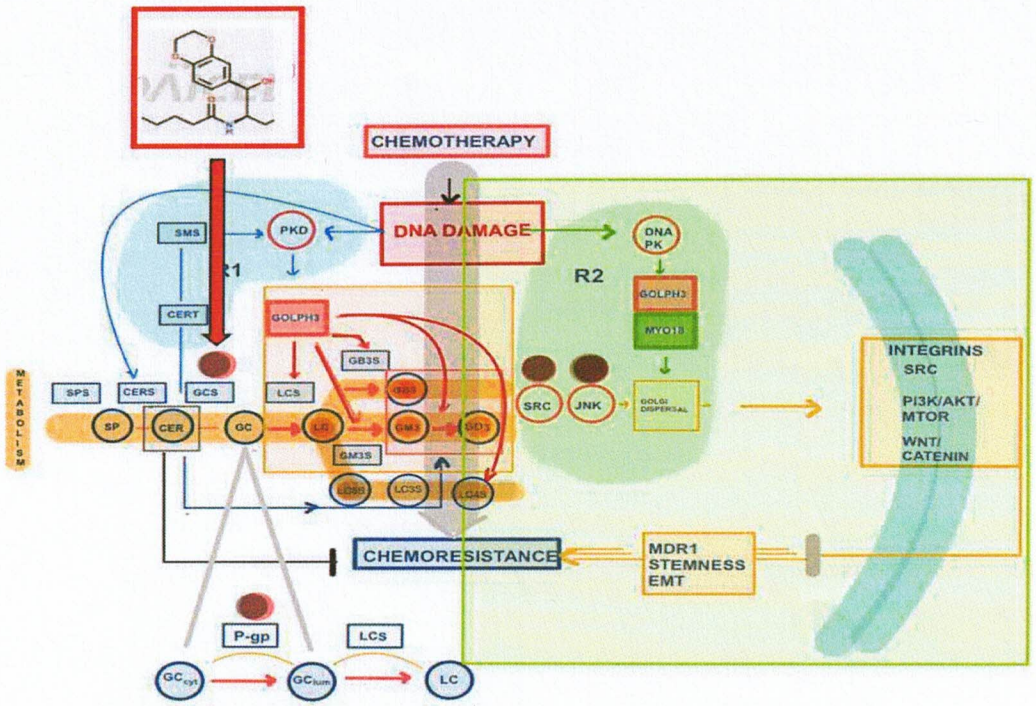


FIGURE 2. Increased enzymes for GSL metabolism (see figure 1) accelerate the conversion of ceramide, a lipid that has a potent proapoptotic effect, to metabolites such as globo- and gangliosides, which are known to activate mitogenic signaling pathways, predominantly via the PI3K-AKT-mTOR and WNT systems. The main steps of GSL metabolism are highlighted in orange. GOLPH3 (red box) acts on some main enzymes of this metabolism by increasing their levels (red arrows). During genotoxic stress, the cell produces large amounts of ceramide which would induce cancer cell death if GOLPH3 did not intervene by rapidly converting ceramide into globo- and gangliosides thus inducing chemoresistance (blue box). Further development of this study showed that globoside production in the Golgi activates a signaling pathway based on the GOLPH3/MYOSINA18 complex (red/green box), which activates SRC and JNK. This changes the morphology of the Golgi enables the cell to secrete different classes of cargo proteins. The result is the increased secretion on the plasma membrane of growth receptors such as MET, EGFR and others (orange on blue BOX).

The project proposed to Dr. Zizza is aimed at testing a series of inhibitors of this oncogene in combinations with traditional chemotherapeutic drugs in tumor spheroids derived from tumor lines selected for the presence of GOLPH3 oncogene.

EXPERIMENTAL PROCEDURES

1 – Cells selection.

Total n.10 Cancer cell lines selected for the different levels of GOLPH3 expression will be used for spheroids generation and subsequent evaluation of the sensitivity of these 3D structures to therapy with GCS inhibitors, combined or not with chemotherapeutic agents for a total of n.4 different Drugs.

2 – Spheroids set up.

Before starting the analyses, each cell line will be subjected to pilot experiments to define the optimal number of cells for a proper spheroids' formation. The experiments will be performed by seeding a growing number of cells (ideally 500, 1000, 2000, 5000, 10,000) and evaluating spheroids formation and growth over time. These experiments will allow, on the one hand, to define the effective capability of a specific cell line to generate spheres rather than simple cell aggregates, and, on the other hand, they will provide information concerning the shape of the spheres, their consistency, and also handleability for future processing and analyses.

3 – Spheroids generation: multi-well plates method.

The cells normally maintained in 2D growth conditions will be detached from their solid support, resuspended in the complete growth medium, seeded within 96-well U bottom ultra-low attachment plates, and centrifuged for 5 minutes at 300 x g to increase cell precipitation and interaction in the bottom of the well. For each of the evaluated cell lines, the optimal number of cells needed for proper spheroid formation will be defined in pilot experiments (see the "spheroids setup" section).

Upon cell seeding, plates will be incubated in the Incucyte, and the growth of the formed spheroids will be monitored. The image of each sphere will be taken (4x magnification) at intervals of 24 h. Upon complete sphere formation (ideally 48/72h), the cells will be subjected to treatment with selected GCS inhibitors (Eliglustat or Zosuquidar) and/or chemotherapeutic agents (see the "setting treatment conditions" section), and the spheroids growth will be monitored over time (ideally up to 10/12 days).

4 – Setting treatment conditions.

To optimize the treatment conditions, spheroids from each of the investigated cell lines will be treated with growing concentrations of drugs (chemotherapeutic drugs or GCS inhibitors), and sphere growth (and their eventual side diffusion) will be monitored over the days.

The drugs (or specific drug concentrations) promoting slight or no effects as single agents will be tested in combinatorial experiments to define any eventual additive/synergistic effect.

All drug concentrations will be defined on a literature basis and then experimentally validated.

5 – Data quality.

To guarantee data robustness, each experimental condition will be tested at least in triplicate (biological replicates), and each experiment will be performed at least three times

(experimental replicates). Final results will be derived from the average of the different experiments, and statistical relevance will be calculated by PRISM software.

6 – Preliminary pre-clinical analyses

To define the preclinical value of the obtained results, the role of GOLPH3, alone or in combination with selected oncogenes, as a prognostic and/or therapeutic marker in large cohorts of cancer patients from different datasets available online (e.g., ATCC) will be evaluated. Subsequently, the same analyses will be extended to samples from a bank of anonymized patients' organoids already established in the laboratory of Dr. Giovanni Blandino at the Translational Oncology Research Unit. Based on the results of the bioinformatic analyses, selected organoids will be experimentally tested for their response to therapy with GCS inhibitors in combination with chemotherapeutic agents.

Gantt chart

Months	1	2	3	4	5	6	7	8	9	10	11	12
Preliminary Data in Spheroid Models												
Data Validation and Model Generalization to Different Tumor Histotypes												
Pre-clinical data												

Reporting:

Reports to be provided every six (6) months, or as otherwise agreed between the Parties.

Time frame of the project:

Six (12) months

SCHEDULE 2

RESEARCH BUDGET

Total Research Budget:

	VAT	Details
1 Staff Salary		**0,00**
2 Researchers contracts		**0,00**
3 Equipment		**0,00**
4a Supplies		
Cell media, plasticwares and consumables Experimental kits and Reagents (e.g. antibodies, drugs, dyes)		**15000** **26000**
Subtotal Supplies		**41.000**
	22%	**9.020**
TOT Supplies (VAT included)		**50.020**
4b Model costs		**0,00**
4c Subcontracts		**0,00**
4d Patient costs		**0,00**
5 IT services and data bases		**0,00**
6 Pubblication costs		**0,00**
7 Dissemination – Congress		**0,00**
8 Travels		**0,00**
9 Overheads		**0,00**
10 Coordination costs		**0,00**
TOT.		**€ 50.020**

Payment Schedule:

30% of total Research Budget upon execution of the Agreement.
30% of the total Research Budget in the sixth month of signing the Agreement.
40% of total Research Budget upon completion of all deliverables and Golgenia S.r.l.'s receipt of the Final Report.;
Institution shall invoice Golgenia S.r.l. for each instalment of the Research Budget on, or promptly after, the achievement of the relevant deliverables or the relevant date(s) set out above (as applicable).

SCHEDULE 3

INVOICE REQUIREMENTS

Transmission of Purchase Orders. Institution agrees to participate in the electronic transaction program for Purchases Orders. will indicate the electronic transaction program applicable to Institution for each Purchase Order, details: gianni.luini@golgenia.it__or info@pec.golgenia.it. Participation in the electronic transaction program includes the preparation and regular maintenance of electronic catalogues to support a high-quality ordering process and accepting the electronic transmission of Purchase Orders from Golgenia S.r.l.. Institution agrees to provide the required data and to designate a representative to assist in ensuring implementation and maintenance of the electronic transaction program.

Invoices and Credit Notes. Institution agrees to submit all invoices and any corresponding credit notes to Golgenia S.r.l. electronically through the electronic transaction program designated. Golgenia S.r.l. will indicate the electronic transaction program applicable to Institution for each invoice. Institution should only submit invoices through the electronic transaction program and only valid invoices, or credit notes submitted through the electronic transaction program will be considered received by Golgenia S.r.l.. The electronic transaction program will allow Institution to either (i) transmit invoices and credit notes electronically or (ii) create those invoices or credit notes within the electronic transaction program. Golgenia S.r.l. may reasonably reject any invoice or credit note that does not meet at least the following relevant standards.

The relevant standard for an invoice is one that:

1. complies with local law, the European standard and any of the syntaxes published in Commission Implementing Decision (EU) 2017/1870.

2. documents the different goods and services within the invoice.

3. does not duplicate a pre-existing invoice or credit note for the goods or services.

4. contains the full details of the Golgenia S.r.l. party, including legal name, address and when applicable the Indirect Tax ID number; and

5. is raised by Institution, in all circumstances, unless Golgenia S.r.l. and Institution mutually agree in writing a self-invoicing scheme.

Credit notes should be used to amend incorrect invoices and should inform of the error being corrected and the invoices affected.

Accordo di Co-Development tra **IFO** e **Golgenia S.r.l.**

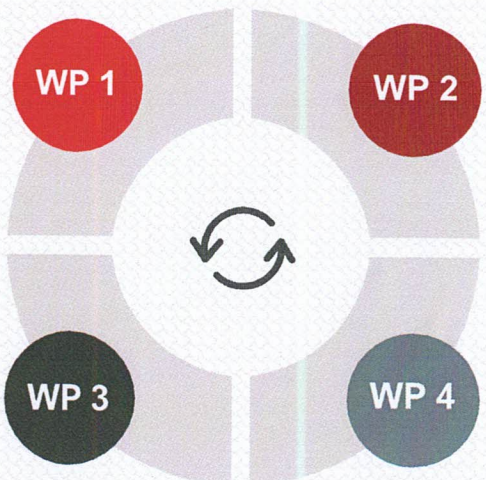
Preso in considerazione dal MdS (Ministero della Salute)
nell'ambito delle valutazioni relative alla Ricerca Corrente

PROGETTUALITÀ IN CORSO

Analisi della risposta al trattamento di n. 10 sferoidi da linee tumorali ed eventuali estensioni accessorie

SVILUPPO FASE IN VIVO

- Sviluppo di una fase in vivo in modello murino
- Fase Pre-Clinica con la Dr.ssa Soddu



ANALISI SU ORAGNOIDI DERIVATI DA PAZIENTI

- Selezione pazienti sulla base dei Dati clinici:
  - Visione Dati sensibili tramite tecniche di anonimizzazione
  - Visione Dati non anonimizzati (pseudo – anonimizzazione) - notifica al CE (Comitato Etico) e gestione degli aspetti Regolatori/Privacy
- Analisi della risposta ai farmaci da parte di organoidi derivati da pazienti (Dr. Giovanni Blandino)

SVILUPPO STUDIO CINICO CONGIUNTO

Potrà richiedere tempistiche più lunghe per:

- Scrittura e stesura dello studio;
- Gestione degli aspetti nel rispetto del GDPR e Codice Privacy (anonimizzazione, pseudonimizzazione, ruoli nel trattamento dei Dati (Titolare e/o Responsabile del trattamento dei Dati), modalità di trasmissione;
- Approvazione da parte del CE (Comitato Etico).

IRE Regina Elena ISG San Gallicano