Corso di dottorato in Scienze Biomolecolari
PhD in Biomolecular Sciences
Ciclo 42 / Cycle 42
A.Y. 2026-2027

Reserved scholarships C and D

La prestigiosa **Fondazione Pezcoller** finanzia n. 2 borse di dottorato per progetti in ambito "Ricerca sul Cancro".
Le posizioni sono contraddistinte a bando dalle lettere C e D.
I vincitori di tali borse potranno scegliere il laboratorio ed il progetto di ricerca del loro percorso di dottorato tra quelli elencati di seguito.

*Fellowships funded by the prestigious **Pezcoller Foundation** for cancer research projects (letters C and D)*
Winners can choose their host laboratory from the list agreed upon with the Foundation's scientific committee, available below.

Project nr.	Principal Investigator	Principal Investigator
1	Paola Bellosta Fabrizio Bianchi	Characterization of a Novel Therapeutic Axis Exploiting Nucleolar Stress Vulnerabilities in MYC-Dependent Lung Cancer
2	Emiliano Biasini Alberto Inga	Cryptic Co-translational Phosphorylation as a Driver of p53 Destabilization in Cancer
3	Alessandra Bisio Francesco Cordoni	GAP – (towards) Genomic Adjusted Particle-therapy
4	Marco Canossa, Luca Tiberi Beatrice Vignoli	Targeting the Stability of Tumor-Brain Interactions
5	Fulvio Chiacchiera	Decoding BAP1-Driven Oncogenesis using in vitro and in vivo approaches
6	Yari Ciribilli Graziano Lolli	Deciphering the ETV7 network and its pharmacological targeting in breast cancer
7	Emilio Cusanelli	Targeting telomeric transcripts and R-loops to impair telomere maintenance mechanisms and viability of cancer cells
8	Vito G. D'Agostino Michela A. Denti	Lost in Sorting: Exploiting EV-miRNA Dysregulation to Unmask Aberrant Protein Regulators in Prostate Cancer
9	Francesca Demichelis Francesca Lorenzin	Precision medicine approaches for novel prostate cancer treatments based on innovative genome editing strategies
10	Peter De Wulf	Identification of actionable protein drivers of CENP-A-fueled chromosomal instability for precision cancer therapy
11	Luca Fava	Epitranscriptomic editing for functional discovery of cancer-associated m6A sites
12	Luca Guglielmi	Human Brain Expansion and Medulloblastoma Susceptibility: An Evolutionary Trade-off?

13	Alessandro Provenzani	Elucidating the molecular mechanisms regulating TIGIT immunochekpoint in NK cells
14	Alessandro Romanel	Decoding the inherited blueprint of cancer evolution
15	Toma Tebaldi	Predictive modeling of m6A-regulated endogenous dsRNA formation and immunogenicity in splicing-mutant acute myeloid leukemia
16	Luca Tiberi	CAR-T Therapy for Glioblastoma
17	Alessio Zippo	Epigenetic mechanism in cancer dormancy

Si precisa che l'attivazione dei succitati progetti sarà condizionata al ricevimento delle autorizzazioni necessarie allo svolgimento dell'attività di ricerca.

Please note that the implementation of the above-mentioned projects will be subject to the receipt of the authorizations necessary for carrying out the research activity.

Project nr. 1

Characterization of a Novel Therapeutic Axis Exploiting Nucleolar Stress Vulnerabilities in MYC-Dependent Lung Cancer

Laboratory of Cellular Stress and Cancer Signaling

Principal Investigator: Paola Bellosta (Tutor), Dr. Fabrizio Bianchi (Co-tutor)

Synthetic description of the activity and expected research outcome
Cancer cells sustain rapid growth by increasing protein production, placing strong pressure on ribosome biogenesis in the nucleolus. While this process is essential for tumor survival, it also creates a potential vulnerability. Under these conditions, nucleolar stress activates p53, a key quality-control mechanism that eliminates cells unable to sustain proper protein synthesis. However, how cancer cells adapt to this stress, and how this safeguard can be exploited—remains poorly understood, particularly in aggressive lung cancers.
This project aims to uncover a novel vulnerability in MYC-driven lung cancer by investigating the CEBPZ–NOC3L nucleolar axis, a regulator of ribosome biogenesis that allows cancer cells to maintain protein synthesis under stress. We hypothesize that partial disruption of this pathway will reduce translational capacity and trigger nucleolar stress, leading to p53 activation and selective elimination of cancer cells. In MYC-driven tumors, where protein synthesis demand is particularly high, this mechanism may create a strong and exploitable vulnerability, especially in cancers where MYC itself is not directly targetable.
The project will address three main objectives: (i) define how MYC and p53 coordinate cellular responses to nucleolar stress; (ii) identify molecular signatures predicting sensitivity to ribosome biogenesis disruption; (iii) validate these vulnerabilities in clinically relevant lung cancer models.
The student will gain training in cutting-edge approaches, including functional genomics, RNA sequencing, and advanced 3D models such as patient-derived organoids. A distinctive aspect of the project is the integration of cross-species approaches, linking conserved mechanisms identified in Drosophila to human lung cancer.
The project is embedded in a highly collaborative and translational environment at CIBIO, with interactions with experts in lung cancer biology, pathology, and clinical oncology. This framework will allow the candidate to connect fundamental discoveries with clinically relevant questions, contributing to the development of new therapeutic strategies for aggressive lung cancers, particularly those driven by high MYC activity.
Collaborators:
Prof. Giovanni Bertalot – pathology and clinical specimens
Dr. Antonello Veccia – clinical oncology and patient stratification

Candidate's profile (skills and competencies)
We seek a motivated candidate with a Master's degree in Molecular Biology, Biotechnology, or a related field, and experience in basic molecular and cell biology techniques.
Interest in cancer biology and willingness to learn functional genomics and advanced models (e.g., organoids) are desirable. The candidate should be proactive, collaborative, and motivated to work in a interdisciplinary research environment

Project nr. 2

Cryptic Co-translational Phosphorylation as a Driver of p53 Destabilization in Cancer

Dulbecco Telethon Laboratory of Prions and Amyloids

Principal Investigator: Emiliano Biasini (Tutor), Alberto Inga (Co-tutor)

Synthetic description of the activity and expected research outcome
Scientific Background and Rationale
Protein folding is tightly regulated during translation, yet emerging evidence suggests that this process is vulnerable to regulatory perturbations. We recently identified a novel mechanism termed cryptic co-translational phosphorylation, whereby transiently exposed phosphosites within nascent polypeptides are modified before proper folding is achieved. These events may introduce destabilizing negative charges in hydrophobic regions, impairing folding trajectories and promoting degradation (Gasparotto et al. EMBO J. 2025). Tumor suppressors, particularly p53, appear especially susceptible to this mechanism. Computational analyses revealed multiple cancer-associated mutations mapping to cryptic phosphosites, including phosphomimetic substitutions that mimic constitutive cryptic phosphorylation. In p53, sites such as T155 and Y220 are of particular interest due to their known roles in stability and degradation pathways. We hypothesize that phosphomimetic mutations at cryptic phosphosites represent an underappreciated mechanism of tumor suppressor inactivation, contributing to cancer progression by promoting premature degradation of p53.

Preliminary data
Our previous computational analysis identified hundreds of disease-related mutations at cryptic sites, including 11 phosphomimetic substitutions in hotspot loci of major tumor suppressors (pVHL, p53, PTEN). Experimentally, LC-MS/MS confirmed the presence of both cotranslational and cryptic phosphorylations on nascent chains. We also observed stability alterations related to the Y220 site when mutations at this site were introduced in the protein expressed in yeast. These findings on p53 align with previous evidence showing that phosphomimetic modification at T155 (T155E) drives Jab1-mediated nuclear export of p53, priming it for cytosolic degradation (Lee et al. BMB Rep. 2017).
Research Plan and Methodology
By uncovering how co-translational phosphorylation destabilizes p53, this work aligns strongly with the Pezcoller Foundation's mission to advance excellence in cancer research and may open new avenues for targeted cancer therapies. The project is expected to define a new layer of protein regulation in cancer biology. In addition, it will provide mechanistic insight into how cryptic phosphosites may contribute to tumor fitness. Finally, it will identify actionable vulnerabilities in tumor-associated, mutation-driven p53 inactivation that could be targeted therapeutically. These objectives will be pursued through three specific aims:
Aim 1: Identification and validation of cryptic phosphosites. Integrate existing datasets (COSMIC, PTMVar) with in-house phosphosite maps. Perform LC-MS/MS on ribosomeassociated nascent chains to detect co-translational phosphorylation events.
Aim 2: Functional characterization of phosphomimetic mutations. Generate p53 variants carrying phosphomimetic substitutions (e.g., T155E, Y200E). Measure protein half-life in mammalian cells via cycloheximide chase assays. Assess folding and stability using biochemical and biophysical assays. We will also carry out the mechanistic dissection of degradation pathways by investigating nuclear export and ubiquitin-proteasome involvement, as well as use imaging and subcellular fractionation to track p53 localization.
Aim 3: Therapeutic targeting of cryptic phosphosites. In order to capitalize on the new information regarding the cryptic phosphorylation of p53, we will screen small molecules predicted in silico to stabilize p53 folding and test pharmacological chaperones for their ability to rescue mutant p53 stability and function.
Training Value for the PhD Candidate
The PhD candidate will be immersed in an interdisciplinary research environment that integrates proteomics, molecular and cellular biology, and cancer research. Through hands-on experience with advanced techniques of analytical biochemistry and cell biology, they will develop strong expertise in studying protein folding and post-translational modifications in a physiologically relevant context. The project will also provide in-depth training in protein quality control mechanisms and their implications in tumor biology, with a particular focus on the regulation of p53 stability.
Beyond fundamental research, the candidate will be exposed to translational aspects of cancer biology, including early-stage drug discovery approaches aimed at restoring protein function through pharmacological chaperones. Working within the collaborative ecosystem of the Department, they will interact with researchers across different disciplines, gaining both technical and conceptual skills at the interface of protein folding, proteostasis, and cancer. This environment will foster scientific independence while providing strong mentorship and opportunities for career development.
Feasibility and Resources
The proposed project is highly feasible within the timeframe of a PhD, as it builds on strong preliminary data and established methodologies already available in the host laboratory. The lab has consolidated expertise in proteomics, protein folding, and cancer biology, ensuring a solid conceptual and technical foundation for the project. State-of-the-art infrastructure, including advanced mass spectrometry platforms and fully equipped molecular and cellular biology facilities, is readily accessible. Moreover, the experimental workflows required for this project, ranging from phosphosite mapping to functional assays of protein stability, are already well established in the labs of the tutor and the co-tutor. Together, these resources and expertise provide a robust framework that will enable the successful completion of the project within three years.

Candidate's profile (skills and competencies)
We are seeking a highly motivated and curious candidate with a strong interest in cancer biology, protein homeostasis, and molecular mechanisms of disease. The ideal applicant will hold (or be close to obtaining) a Master's degree in Biology, Biotechnology, Biochemistry, or a related field. Strong interest in cancer biology or protein folding/quality control pathways is mandatory. Previous background in molecular and cellular biology will be considered an advantage but not necessary, as the candidate will receive comprehensive training during the project. The candidate should demonstrate critical thinking, problem-solving skills, and the ability to work both independently and as part of a collaborative team. Given the interdisciplinary nature of the project, enthusiasm for integrating experimental approaches with computational analyses will be highly valued. Good communication skills in English, both written and spoken, are expected. Overall, we are looking for a proactive and committed student eager to contribute to innovative research at the interface of protein folding and cancer, and to develop into an independent scientist.

Project nr. 3

GAP – (towards) Genomic Adjusted Particle-therapy

Laboratory of Radiobiology

Principal Investigator: Alessandra Bisio (Tutor), Francesco Cordoni (Co-tutor)

Synthetic description of the activity and expected research outcome

Radiotherapy remains a cornerstone of cancer treatment; however, its efficacy is often limited by inter-patient variability in tumor radiosensitivity and the risk of damage to surrounding healthy tissues (1). Particle therapy with protons and carbon ions offers significant clinical advantages over conventional radiotherapy, thanks to superior dose distribution and enhanced biological effectiveness. Despite these advances, current treatment planning strategies remain largely based on physical dose and do not account for tumor molecular heterogeneity, limiting their potential for true personalization (2).

This limitation is particularly critical for two cancer types with major unmet clinical needs: lung cancer and pancreatic cancer. Both are increasingly recognized as targets for particle therapy, yet both are characterized by significant inter-patient genomic heterogeneity — driven in part by KRAS mutations — that profoundly modulates radiation response. Bridging this gap between genomics and particle therapy planning is not only scientifically compelling but also represents a concrete step toward truly personalized cancer treatment.

The proposed project, Genomic-Adjusted Particle Therapy (GAP), aims to overcome this limitation by integrating genomic information into particle therapy, with the goal of developing more precise and patient-specific cancer treatments (3). The central hypothesis is that different radiation qualities (protons versus carbon ions, at varying energies) induce distinct gene expression responses in tumor and normal tissues, and that these responses can be exploited to optimize therapeutic outcomes (4).

To address this, the project will combine advanced radiobiological experiments with computational modeling and data-driven approaches (5). Human cancer cell models representative of clinically relevant tumors (H460 lung cells and PANC-1 pancreatic cancer cells), together with matched non-tumorigenic fibroblasts (IMR90, HPF), will be irradiated with protons at the Trento Proton Therapy Center and with carbon ions at CNAO, Italy's national hadron therapy facility. Irradiations will cover a broad spectrum of radiation qualities, from clinically relevant low-LET protons to high-LET carbon ions, enabling systematic comparison with conventional X-ray irradiation. Experiments will include both conventional 2D systems and more physiologically relevant 3D tumor spheroids and co-culture models, enabling a better representation of the tumor microenvironment. Radiation-induced changes in gene expression and in key biological processes, such as cell survival, apoptosis, senescence, and extracellular vesicle release, will be characterized using next-generation sequencing and functional assays. A key objective is to identify genomic signatures associated with differential radiation response. These data will be integrated into advanced radiobiological models, extending current approaches by incorporating gene expression–dependent parameters. Machine learning methods will be used to identify the most relevant molecular predictors and to develop predictive models linking radiation quality, biological response, and treatment outcome.

The expected impact is strongly translational. By integrating genomic profiling into particle therapy planning, this project aims to move beyond a “one-size-fits-all” approach toward personalized radiotherapy. This could allow clinicians to tailor treatment to each patient's tumor molecular characteristics, improving tumor control while minimizing toxicity to healthy tissues. Ultimately, GAP has the potential to contribute to next-generation precision radiotherapy strategies, with relevance for aggressive cancers such as lung and pancreatic tumors, where innovative therapeutic approaches are urgently needed.

References

1. M. Durante and H. Paganetti, “Nuclear physics in particle therapy: a review,” Rep. Prog. Phys., 2016.
2. H. Paganetti, “Proton relative biological effectiveness–uncertainties and opportunities,” Int. J. Part. Ther., vol. 5, no. 1, pp. 2–14, 2018.
3. J. G. Scott et al., “A genome-based model for adjusting radiotherapy dose (GARD): a retrospective, cohort-based study,” Lancet Oncol., vol. 18, no. 2, pp. 202–211, 2017.
4. J. G. Scott et al., “Personalizing radiotherapy prescription dose using genomic markers of radiosensitivity and normal tissue toxicity in NSCLC,” J. Thorac. Oncol., vol. 16, no. 3, pp.428–438, 2021.
5. A. Attili, E. Scifoni, and F. Tommasino, “Modelling the HPRT-gene mutation induction of particle beams: systematic in vitro data collection, analysis and microdosimetric kinetic model implementation,” Phys. Med. Biol., vol. 67, no. 19, p. 195001, 2022.

Candidate’s profile (skills and competencies)

The candidate should be highly motivated and should have preferentially a background in molecular and cellular biology, like manipulation of mammalian cell lines in sterility, RNA, and protein analysis. Knowledge of radiobiology principles will be considered a plus. A fluent knowledge of the English language will be required.

Project nr. 4

Targeting the Stability of Tumor-Brain Interactions

Laboratory of Synaptic Plasticity

Principal Investigator: Marco Canossa (Tutor); Luca Tiberi (Tutor); Beatrice Vignoli (Co-tutor)

Synthetic description of the activity and expected research outcome

Gliomas are among the most aggressive and lethal cancers, largely due to their ability to integrate into and exploit the neural microenvironment. Neuronal activity promotes tumor growth, invasion, and therapy resistance, while gliomas increase neuronal excitability and remodel neural circuits, establishing a pathological neuron-tumor feedback loop (Monje, 2025). A central mediator of this interaction is BDNF-TrkB signaling, which enhances malignant synaptic plasticity by increasing AMPA receptor trafficking, synaptic strength, and neuron-to-glioma connectivity (Taylor et al., 2023). While this pathway is essential for tumor progression, current models focus on its activation and do not explain how it becomes persistent and self-sustaining over time. We propose that the missing mechanism lies in the tumor microenvironment. In physiological conditions, host astrocytes sustain TrkB signaling through Ca^{2+}-dependent release of BDNF, converting transient neuronal activity into persistent signaling required for long-term plasticity (Losi et al., 2025). We hypothesize that gliomas hijack this astrocyte-dependent mechanism to stabilize oncogenic signaling.

Central hypothesis: Host astrocytes sustain TrkB signaling in glioma cells, stabilizing the neuron-tumor feedback loop and promoting tumor progression.

Experimental Strategy: the project combines tumor-specific optogenetic control with astrocyte-selective manipulation: (i) tumor cells will be engineered ex vivo to express "optoTrkB", enabling precise temporal control of TrkB activation selectively in the malignant compartment via light stimulation; (ii) host astrocytes will be manipulated in vivo using validated astrocyte-specific genetic tools targeting Ca^{2+} signaling. Experiments will be performed both in in vivo glioma models and in patient-derived GBM organoids, to validate findings in a human-relevant 3D system.

Specific Aims: (1) Sufficiency of persistent TrkB signaling. Define how different temporal patterns of TrkB activation (transient vs sustained) affect tumor growth, synaptic plasticity, and neuronal hyperexcitability. (2) Requirement of host astrocytes. Test whether astrocyte Ca^{2+} signaling is necessary to sustain TrkB activation and tumor-supportive microenvironmental signaling; (3) Astrocyte-driven signaling. Implement a bioluminescent optogenetic strategy to directly couple astrocyte activity to TrkB activation in tumor cells, testing whether astrocytes are sufficient to drive persistent oncogenic signaling in vivo.

Conceptual and therapeutic implications: This project addresses a fundamental gap in cancer biology: how tumor-microenvironment interactions become stable over time. It introduces a new framework in which tumor progression depends not only on signaling pathways, but on the temporal mechanisms that sustain them. By identifying astrocytes as regulators of signaling persistence, this work may reveal novel therapeutic strategies aimed at disrupting the stability of tumor-brain interactions rather than their initiation.

Role of the Supervisors: The project integrates complementary expertise. Luca Tiberi: glioma biology, tumor models, and cellular states. Marco Canossa: synaptic plasticity and astrocyte-dependent signaling. This synergy enables a multiscale investigation of tumor-brain interactions, from molecular mechanisms to circuit function.

References:

Monje, M. (2025). The neuroscience of brain cancers. Neuron.
Taylor, K.R. et al. (2023). Glioma synapses recruit mechanisms of adaptive plasticity. Nature.
Losi, G. et al. (2025). Spontaneous activity of astrocytes is a stochastic functional signal for memory consolidation. PNAS.

Candidate's profile (skills and competencies)

The ideal candidate will hold a Master's degree in Neuroscience, Pharmaceutical science, Biology, Biotechnology or related disciplines, with a strong interest in research at the interface between neuroscience and cancer (Monje, M. The neuroscience of brain cancers. 2025 Neuron). The candidate should demonstrate strong motivation, enthusiasm, critical thinking, and the ability to work in a multidisciplinary environment. The ideal profile is a student eager to take full advantage of the complementary expertise provided by the two PIs, spanning glioma biology (Luca Tiberi) and synaptic plasticity (Marco Canossa), which together form the core scientific framework of the project. During the PhD, the candidate will be trained in advanced experimental approaches, including electrophysiology, optogenetics, in vivo tumor models, patient-derived GBM organoids, astrocyte-specific manipulation, and functional imaging, with the goal of integrating molecular and circuit-level analysis of tumor-brain interactions.

Project nr. 5

Decoding BAP1-Driven Oncogenesis using in vitro and in vivo approaches

Laboratory of Stem Cells and Cancer Genomics

Principal Investigator: Fulvio Chiacchiera

Synthetic description of the activity and expected research outcome

The loss of the tumor suppressor BAP1 represents a driver event in a broad spectrum of highly aggressive malignancies. Although BAP1 is functionally established as a deubiquitinating enzyme (DUB) involved cellular homeostasis and epigenetic regulation, the precise molecular mechanism linking its inactivation to tumorigenesis remains unknown. Our central hypothesis is that the oncogenic phenotype is triggered

by the aberrant hyperubiquitination of a specific target substrate (or a restricted network of targets) which, in the absence of BAP1 catalytic activity, escapes physiological control and acts as a molecular switch for malignant transformation.
This project aims to identify and characterize these targets and verify their involvement in tumour formation. To achieve this objective, we propose a cutting-edge, multimodal screening pipeline based on CRISPR/Cas9 libraries applied to in vitro isogenic systems and in vivo preclinical models. Through this large-scale genetic screening approach, we will compare the genetic dependency landscapes of BAP1-proficient and BAP1-deficient models, isolating the molecular nodes whose modulation affects tumour formation.
Uncovering the primary substrate responsible for tumour formation following BAP1 loss will not only rewrite the current mechanistic paradigm of this neoplastic syndrome but also unveil new, unexplored therapeutic vulnerabilities, paving the way for precision medicine strategies in tumours currently lacking effective targeted therapies.

Candidate's profile (skills and competencies)
We are looking for passionate and curious open-minded candidates able to take risks and willing to fail. A mental attitude tuned towards problem solving and to collaborative work is required. He/she should hold a master's degree in biology, biotechnology, medicine, or related fields. Experience in topics such as genomic and epigenomics, mouse genetics, or histology, is preferred but is not mandatory. Willingness to work in vivo and strong ethical values are mandatory.

Project nr. 6

Deciphering the ETV7 network and its pharmacological targeting in breast cancer

Laboratory of Molecular Cancer Genetics (LMCG)

Principal Investigator: Yari Ciribilli, Graziano Lolli

Synthetic description of the activity and expected research outcome
ETV7/TEL2 is a poorly characterized transcriptional repressor member of the large ETS family of transcription factors, up-regulated in many types of cancer, including breast cancer (BC). We demonstrated that ETV7 is up-regulated upon the treatment with various DNA-damaging agents, and this increased expression led to the development of drug resistance (1). Moreover, we determined that ETV7 over-expression is associated with a remarkable increase in cancer stem cell-like population (2) and showed that ETV7 can reduce inflammatory responses (3). All these data suggest that ETV7 is an important regulator of cancer aggressiveness. Given that ETV7 is a relatively understudied protein, a better comprehension of its network and the mechanism behind its repressive functions is needed. To this aim, different genome-wide analyses such as ChIP-seq, chromatin accessibility profiling via Assay for Transposase-Accessible Chromatin (ATAC)-seq and DNA methylation on CpGs at a global scale, will be employed. Additionally, in order to identify the network of ETV7 co-factors, we will decipher the ETV7 interactome through Mass Spectrometry upon immunoprecipitation of ETV7 from breast cancer cells over-expressing ETV7 with and without treatment with chemotherapy.
In parallel, we have produced preliminary data in different BC cells demonstrating that siRNAs targeting ETV7 showed an induction of massive apoptosis, a phenotype that can be exploited therapeutically. Indeed, we have recently determined by X-ray crystallography at 1.6 Ang the crystal structure of the pointed (PNT) domain of human ETV7 protein with the crucial collaboration with the Laboratory of Protein Crystallography and Structure-Based Drug Design led by Prof. G. Lolli here at Dept. ETV7 PNT domain was aligned to the one from the closet relative in the ETS family, ETV6, revealing similar but significantly different structural features. For this reason and given that the PNT domain is essential for ETV7 protein-protein interactions, we are exploiting the targeting of this domain to design pharmacological inhibitors of ETV7. Indeed, based on this structure, we have identified a pocket region within the PNT domain to design ligands able to bind and potentially disrupt its oligomerization ability. The first 60 compounds have been already tested for binding via Surface Plasmon Resonance and nano- Differential Scanning Fluorimetry (DSF). Three small molecules showed partial binding to ETV7 PNT domain. Those structures will be the starting point for a ligand optimization campaign. Analogs of the most promising ligands will be computationally designed and tested by molecular docking by the group led by Prof. E. Biasini (Dept. CIBIO) and, again, top hits will be obtained commercially and tested by SPR/BLI. For this second round of measurements, we will exploit the Creoptix SPR-GCI system now available at CIBIO Dept. The best hits will be used to treat a) breast cancer cells stably over-expressing ETV7 and b) patient-derived BC organoid models (a biobank of 23 organoids derived from TNBC patients is available from Dr. Scheele, an established collaborator) alone or in combination with standardof-care chemotherapy.
Interestingly, we determined two different structures of the ETV7 PNT domain. They actually differ in a single region with, however, a relevant functional impact. In particular, in one of the structures, K114 and C88 form a N-O-S bond, with an oxygen covalently linking the two amino acids. In the other conformation, the link is not present. Strikingly, a few years ago the formation of these bridges has been discovered for the first time as a way proteins use to sense redox perturbations leading to a switch in protein conformation (4). Given that ETV7 is stimulated by exposure to DNA-damaging agents (producing ROS) and elevated ETV7 levels are associated with reduced sensitivity to these drugs, we will verify whether N-O-S bonds may play a role in ETV7-mediated resistance to chemotherapy. In the last part of the project, with the help of the already established collaboration (3) with the Unit of Pathologic Anatomy at Santa Chiara Hospital in Trento (Drs. Barbareschi

and Bertalot, two experienced pathologists), we will analyze by immunohistochemistry the correlation between ETV7 protein levels with specific clinical characteristics and the levels of selected newly identified ETV7 targets in a selected local cohort of breast cancer patients (a large collection with > 10 years of follow-up, Trentino Biobank). Overall, this project will shed light on the functions of ETV7 an oncoprotein commonly up-regulated in cancer but still poorly described, which is beneficial for a better understanding of breast cancer progression. Noteworthy, the results of this project will also propose new therapeutic strategies for aggressive BC.

References

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2. Pezzè, L. et al. Cell Death Dis. 2021 Jul 27;12(8):742. doi: 10.1038/s41419-021-04005-y.
3. Meskyte, E. M., et al. Cell Death Dis. 2023 Apr 12;14(4):263. doi: 10.1038/s41419-023-05718-y.
4. Wensien M, et al. Nature 2021 May;593(7859):460-464. doi: 10.1038/s41586-021-03513-3.

Collaborators:

Prof. Emiliano Biasini
Prof. Alberto Inga

Candidate's profile (skills and competencies)

The candidate should be highly motivated and have a strong background in molecular and cellular biology, like the manipulation of mammalian cell lines in sterility, RNA and protein analysis, and qPCR measurements. Working in a group and personal skills are welcomed. A fluent knowledge of the English language will be required, as the host institution is mainly international.

Project nr. 7

Targeting telomeric transcripts and R-loops to impair telomere maintenance mechanisms and viability of cancer cells

Laboratory of Cell Biology and Molecular Genetics

Principal Investigator: Emilio Cusanelli

The unlimited proliferative capacity of cancer cells depends on their ability to maintain telomere maintenance mechanisms (TMMs). Most human tumors achieve this endeavor by expressing the enzyme telomerase, a reverse transcriptase that adds telomeric DNA to the extremities of chromosomes. A minority of cancers activate mechanisms of alternative lengthening of telomeres (ALT) that rely on homologous recombination. Telomerase inhibition leads to telomere shortening and cancer cell death. Similarly, ALT deregulation compromises genome stability, ultimately impairing cancer cell viability. Thus, as TMMs are not active in most human somatic cells, they represent promising cancer therapeutic targets. For this reason, understanding the molecular mechanisms regulating TMMs may pave the way for the development of novel cancer therapeutic strategies.

Telomeres are transcribed by RNA polII giving rise to telomeric repeat-containing RNAs called TERRA. TERRA molecules play a central role in telomere biology and they regulate TMMs. Indeed, TERRA transcripts sustain ALT through formation of R-loop structures that promote homologous recombination. However, whether TERRA molecules act as trigger of ALT remains to be defined. Furthermore, recent evidence from our laboratory indicates that TERRA molecules impede telomerase recruitment at telomeres. Accordingly, TERRA depletion through antisense oligonucleotides (ASO) increased telomerase association to chromosome ends in cancer cells (Bettin et al., 2024). Therefore, modulating TERRA levels directly impacts telomerase recruitment and activity at telomeres.

Preliminary data in our lab indicates that inhibition of telomerase recruitment to telomeres is mediated by formation of R-loop structures at chromosome ends by TERRA molecules. Intriguingly, we also observed that ALT activation is dependent on R-loop formation at telomeres (manuscript under revision). Thus, telomeric R-loops play a pivotal role in TMMs.

Building from these observations, this project will investigate the role of telomeric R-loops in telomerase regulation and in ALT induction. We will use different methodologies to impair telomeric R-loop formation, such as TERRA ASO encapsulated in LNPs, RNaseH1 inducible expression, and pharmacological inhibition of Rad51, known to be involved in telomeric R-loop formation, and ATR, that our data indicates as regulator of telomeric R-loop formation. We will also employ approaches to increase R-loop at telomeres, such as transfection of RNaseH1- or SFPQ-targeting siRNAs. We plan to perform these experiments in telomerase positive and ALT cancer cell lines, as well as upon ALT induction from telomerase positive cancer cell lines, to study early stages of ALT. We will study the impact of R-loop deregulation on telomerase recruitment to telomeres, telomere function and the ALT mechanism, using multiple approaches, including cytologic methodologies, such as RNA FISH, IF, and DNA FISH. The consequences of telomeric R-loop deregulation on cancer cell viability will be assessed by biochemical assays and high content imaging equipment.

These experiments will enable us to characterize the function of TERRA and telomeric R-loops in telomerase regulation and ALT activation. Understanding the mechanisms regulating telomerase activity and ALT initiation will help identify novel therapeutic strategies to prevent TMM activation during tumor development.

Candidate's profile (skills and competencies)

The candidate should have demonstrated ability to work effectively in a team and to collaborate with colleagues, and previous experience in cell cultures and molecular biology and cell biology techniques, such as RT-qPCR and RNA FISH. The candidate should be able to work independently in the lab, at least at technical level. The ideal candidate will have previous laboratory experience in the study of telomere biology and/or cancer research.

Project nr. 8

Lost in Sorting: Exploiting EV-miRNA Dysregulation to Unmask Aberrant Protein Regulators in Prostate Cancer

Laboratory of Biotechnology and nanomedicine
Laboratory of RNA Biology and Biotechnology

Principal Investigator: Vito G. D'Agostino & Michela A. Denti

Synthetic description of the activity and expected research outcome
Prostate cancer (PCa) diagnosed at advanced stages has rising morbidity and mortality, highlighting the urgent need for novel predictive biomarkers and therapeutic targets. Extracellular vesicles (EVs) are being studied as a new source of biomarkers and, at the same time, as vehicles for RNA molecules that can shape interactions with immune cells. Taking advantage of an established collaboration with urologists at the Istituto Oncologico Bari, we characterized the RNA cargo of EVs in urine samples from patients with benign hyperplasia and with low/intermediate/high-grade PCa, stratified by progressive Gleason scores. From RNA-seq and Nanostring-based RNA profiling in independent patient cohorts, we identified a few dozen miRNAs that distinguished PCa cases and were coherently secreted or depleted with disease severity. By exploiting computational tools, these targets will be studied to identify common protein regulators, direct, such as RNA-binding proteins (RBPs), and indirect, such as altered RNA-RNA interactions and coding efficiency. By learning and integrating the expertise of two laboratories, the candidate will use prostate cancer and other solid tumor cell lines to study the biomarker profile of RBPs governing post-transcriptional miRNA distribution, and perform functional tests to uncover RNA-driven regulatory dependencies that could be further exploited for PCa treatment. Ultimately, this work seeks to establish EV-RNA as a novel entry point for the discovery of clinically relevant targets in prostate cancer.

Candidate's profile (skills and competencies)
The ideal candidate holds a solid background in molecular biology, biotechnology, or a related field, with a good understanding of post-transcriptional RNA regulation, particularly involving miRNAs and RNA-binding proteins (RBPs). Hands-on experience in molecular biology techniques (e.g., RNA extraction, qPCR, gene expression analysis), cell culture, and, preferably, extracellular vesicle research is highly desirable.
Familiarity with transcriptomic profiling technologies (such as RNA-seq, Nanostring, or similar platforms) and basic bioinformatics tools represents a strong advantage. The candidate should be able to integrate experimental and computational data to identify regulatory networks and interpret complex datasets.
Additional desirable qualities include the ability to work within interdisciplinary teams, strong organizational and communication skills, and a clear motivation for translational cancer research. Proficiency in scientific English, both written and spoken, is essential.

Project nr. 9

Precision medicine approaches for novel prostate cancer treatments based on innovative genome editing strategies

Laboratory of Computational and Functional Oncology

Principal Investigator: Francesca Demichelis (Tutor) and Francesca Lorenzin (Co-Tutor)

Synthetic description of the activity and expected research outcome
Prostate cancer (PCa) remains a leading cause of death among men, responsible for 4.1% of all cancer deaths. PCa is traditionally managed as a hormone-driven disease through androgen receptor (AR) targeting. Over the past decade, the integrated analysis of PCa genomics, transcriptomics, and histopathology associated with clinical outcomes nominated PCa molecular subtypes, supporting patient stratification for targeted therapies (e.g., ARSI, PARPi, AKTi, CDK4/6i). Nevertheless, treatment resistance ultimately emerges, and many oncogenic alterations remain 'undruggable', highlighting the need for alternative therapeutic modalities.
The project will investigate whether PCa somatic genomic alterations can be further exploited to develop novel therapeutic strategies tailored to individual patient genomic profiles. The clustered regularly interspaced short palindromic repeats (CRISPR)/Cas system represents the state of the art in genome engineering and has been recently used in preclinical studies to eliminate tumor cells. The PhD candidate will join

an interdisciplinary team, including computational and molecular biologists, to identify actionable genomic alterations and to design ad hoc CRISPR/Cas9 intervention strategies for in vitro testing in several models recapitulating different disease stages. These approaches will also be evaluated in combination with current PCa treatments, with the goal of enhancing therapeutic efficacy.

Candidate's profile (skills and competencies)
Specific requirements:
• Master's degree in biology or biotechnology;
• Experience in cellular and molecular biology techniques (e.g., DNA isolation, cloning, cell line handling, functional assays);
• Teamwork attitude;
• Excellent knowledge of the English language

Project nr. 10

Identification of actionable protein drivers of CENP-A-fueled chromosomal instability for precision cancer therapy

Laboratory of Chromosome Segregation Biology

Principal Investigator: Peter De Wulf

Synthetic description of the activity and expected research outcome
During cell division, the histone H3 variant CENP-A is specifically incorporated at centromeres to epigenetically mark these loci for kinetochores recruitment. Kinetochores are large multi-protein complexes composed of >100 subunits that attach the sister chromatids (the replicated, and paired chromosomes) to the mitotic spindle, to then manage their accurate segregation between the mother and daughter cells. This tightly controlled process ensures that the newly formed cells receive a correct number of chromosomes, ascertain "chromosomal stability".
One third of all cancer cells suffer from CENP-A overexpression, which results in CENP-A becoming deposited not only at centromeres but also along the chromosomes. This mislocalization promotes the formation of pseudo-kinetochores and titrates kinetochore components away from bona fide centromeres, thereby impairing kinetochore assembly and function. As a consequence, sister chromatids missegregate, resulting in "chromosomal instability" (CIN). CIN is a key driver of tumorigenesis, contributes to cancer cell heterogeneity, therapy resistance, and poor patient prognosis. Despite its prevalence and clinical significance, the cellular mechanisms that counteract CENP-A overaccumulation and misincorporation remain poorly understood.
Recent work from our lab has identified a conserved surveillance-and-response pathway that restricts the misincorporation of CENP-A beyond centromeres. Using the yeast Saccharomyces cerevisiae as the model species, we demonstrated that the atypical kinase Rio1 (RioK1 in humans) suppresses CIN by phospho-activing the E3 ubiquitin ligase Psh1, thereby promoting the proteasomal degradation of excess CENP-A (CENP-A is named Cse4 in yeast). Loss of Rio1 activity leads not only to Cse4 stabilization and accumulation but also to its sequestration into an intranuclear condensate, which is visible under the microscope as a nuclear membrane-associated fluorescent Cse4-GFP "dot". This condensate acts as a protective sink that limits the ectopic incorporation of Cse4 across the genome. Importantly, we found that this pathway is conserved in human cells, where depletion of RioK1 similarly induces the formation of a CENP-A condensate. We hypothesize that the regulated sequestration of excess CENP-A safeguards centromere identity and genome stability, and that dysregulation of this pathway in cancer contributes to CIN.
To define this pathway at the molecular level in human cells, we will first perform a genome-wide yeast genetic screen (see figure below) using the Cse4-GFP condensate phenotype as a quantitative and visual readout (e.g., changes in condensate size, intensity, or formation (presence/absence)). This work will be carried out in collaboration with the laboratory of Prof. Brenda Andrews (University of Toronto, Canada), a leader in high-throughput yeast genetics. Candidate regulators identified in yeast will be mapped to conserved human orthologues and functionally validated in both normal and cancer cell lines (see figure below). Using RNA interference, we will assess their roles in CENP-A homeostasis under conditions of both RioK1 depletion and CENP-A overexpression. Readouts will include live-cell imaging of CENP-A-GFP localization (supported by ChIP-qPCR), immunofluorescence-based analysis of kinetochore integrity, and real-time 4D tracking of chromosome dynamics. Druggable components of this pathway will be prioritized and tested pharmacologically for their ability to restore CENP-A homeostasis.
This Ph.D. project thus integrates yeast genetics with human cell biology, combining high-throughput screening, quantitative imaging, and myriad molecular biological and biochemical approaches. By elucidating a conserved buffering mechanism that controls Cse4/CENP-A levels and activity, this work will advance our understanding of centromere identity and uncover new therapeutic vulnerabilities in cancers characterized by CENP-A overexpression. Ultimately, these findings promise to mitigate CIN and therapy resistance, with the potential of significantly improving patient survival.

Candidate's profile (skills and competencies)

Project nr. 11

Epitranscriptomic editing for functional discovery of cancer-associated m6A sites
Armenise-Harvard Laboratory of Cell Division
Principal Investigator: Luca Fava
Synthetic description of the activity and expected research outcome N6-methyladenosine (m6A) RNA methylation has emerged as a critical oncogenic regulatory mechanism in multiple cancers, particularly those sustained by poorly differentiated and stem-like cellular states. Recent CRISPR-based epitranscriptomic editors enabled site-specific interrogation of m6A function, but their limited catalytic efficiency likely restricts the identification of functional cancer-associated m6A sites. Using an in vitro evolution approach, we generated a hyperactive METTL3 variant with enhanced methyltransferase activity. We hypothesize that fusion of this hyperactive METTL3 to dCasRx will improve programmable m6A deposition and increase the sensitivity of functional epitranscriptomic screening in cancer cells. The project will: (1) develop and validate a next-generation hyperactive dCasRx–METTL3 editor; (2) perform focused epitranscriptomic screening of cancer-relevant oncogenes and tumor suppressors; (3) characterize the molecular and phenotypic consequences of top candidate m6A regulatory sites. This work will provide novel insight into RNA-based regulation of tumorigenesis and establish improved tools for functional cancer epitranscriptomics.
Candidate's profile (skills and competencies) Candidate with training in molecular and cancer biology and strong interest in RNA epitranscriptomics, functional genomics and CRISPR-based technologies. The project will provide interdisciplinary training in cancer research, including epitranscriptomic editing, massively parallel functional screening and mechanistic characterization of oncogenic RNA regulatory pathways.

Project nr. 12

Human Brain Expansion and Medulloblastoma Susceptibility: An Evolutionary Trade-off?
Laboratory of Human Brain Morphogenomics
Principal Investigator: Luca Guglielmi
Synthetic description of the activity and expected research outcome The human cerebellum has undergone striking evolutionary expansion compared with other species. This increase in size, likely driven by the protracted nature of human neural development, have contributed to the emergence of advanced motor and cognitive abilities. However, this evolutionary advantage may have come at the cost of increased disease susceptibility. Humans are particularly vulnerable to neurodevelopmental tumours of the cerebellum, such as medulloblastoma (MB), suggesting a potential link between human brain expansion and cancer risk. This relationship is exemplified by Sonic hedgehog (SHH) medulloblastoma, in which mutations in SUFU, a negative regulator of SHH signalling, predispose humans to MB but do not produce equivalent tumours in mouse models. Given that SHH is a key morphogen controlling cerebellar growth and neuronal proliferation during gestation and beyond, we hypothesize that species-specific differences in SHH signalling regulation may underlie differences in oncogenic potential. To test this, we will genetically and pharmacologically titrate SHH pathway activity in human and mouse cerebellar organoids and compare their responses to equivalent perturbations. We will use single cell transcriptomics and neuronal morphometrics to assess changes in cell states, growth dynamics, tissue morphology, and signalling regulation to uncover species-specific mechanisms that influence tumour susceptibility. Overall, this project aims to understand why some species are protected from tumorigenesis, with the goal of leveraging these protective mechanisms to inform new therapeutic strategies for human disease.
Candidate's profile (skills and competencies) 1 A master's degree in conformity with the institutional regulations: An Italian "Laurea magistrale" instituted in conformity with Italian Ministerial Decree 270/2004, or a university degree of the previous regulations (Italian "Laurea specialistica " or "Diploma di Laurea"), or an equivalent degree obtained abroad (Master's degree) and recognized as equivalent to the Italian "Laurea magistrale" by the Admissions Committee for the sole purposes of admission to the Doctoral programme, also within the framework of international agreements.)

2. Preferred are students with experience in cancer biology and/or imaging and/or molecular biology and/or neurobiology university degree of the previous regulations (Italian "Laurea specialistica " or "Diploma di Laurea"), or an equivalent degree obtained abroad (Master's degree) and recognized as equivalent to the Italian "Laurea magistrale" by the Admissions Committee for the sole purposes of admission to the Doctoral programme, also within the framework of international agreements.).

Project nr. 13

Elucidating the molecular mechanisms regulating TIGIT immunochekpoint in NK cells

Laboratory of Genomic Screening

Principal Investigator: Alessandro Provenzani

Synthetic description of the activity and expected research outcome
Immunotherapy has been a constantly evolving field in recent years. The discovery of PD-1/PD-L1 and CTLA-4 immune checkpoint blockade as effective therapies has revolutionized cancer treatment. As the field moves forward, new important immune checkpoints are emerging, and it's crucial to further characterize the biology behind their upregulation and expression in the immune-cancer setting. The immune checkpoint TIGIT is an inhibitory molecule found overexpressed in immune cells in the tumor microenvironment. In particular, it inhibits the Natural Killer response when interacting with its ligand, CD155. The mechanisms behind its expression in Natural Killer cells are still not completely understood. We have identified two novel mechanisms for TIGIT upregulation in Natural Killer cells. By using a pooled CRISPR library targeting 1,078 different RNA Binding Proteins (RBPs), we have identified novel positive and negative RBP regulating TIGIT in the cell line NK-92. In addition, we have discovered that TIGIT mRNA expression and protein levels are mediated by factors in the cell culture media. Fresh cell culture medium results in immediate downregulation of TIGIT mRNA and protein, whereas media exhaustion leads to subsequent upregulation of TIGIT mRNA and protein. The project's aim is to further characterize the biological mechanisms behind these two novel regulation mechanisms, in order to exploit TIGIT regulation in immune-cancer coculture settings to improve NK cytotoxicity against cancer cells.
External collaborators:
Prof. Monika Walkers, Amsterdam institute for Immunology and Infectious diseases
Dott. Paola Vacca, Ospedale Pediatrico Bambino Gesù.

Candidate's profile (skills and competencies)
Degree in Biology, Biotechnology or Pharmaceutical Chemistry.
Preferred expertise: previous experience with CRISPR/Cas9 screening and genetic manipulation of NK cells, and previous work in the field of immunotherapy.
Mandatory expertise: basic techniques of molecular biology (PCR, gene cloning and western blotting) and of cell biology (cell culturing, phenotypic assays).

Project nr. 14

Decoding the inherited blueprint of cancer evolution

Laboratory of Bioinformatics and Computational Genomics

Principal Investigator: Alessandro Romanel

Synthetic description of the activity and expected research outcome
Cancer evolution is shaped by the interaction between inherited germline variation and somatic alterations acquired during tumor initiation and progression. Recent work from our laboratory (Dalfovo et al. 2024 npj Precision Oncology) showed that common germline variants can associate with somatic aberrations in oncogenic signaling pathways, and that polygenic scores can stratify patients according to pathway disruption, tumor subtype, survival and aggressive phenotypes. In parallel, our AIRC project investigates how common coding haplotypes modulate protein function and the effect of co-occurring germline and/or somatic mutations (Mazza et al 2025 Journal of Chemical Information and Modeling, Mazza et al 2026 Nucleic Acids Research).
This PhD project will extend this framework from coding haplotypes to a broader omnigenic model of germline-somatic interactions in cancer. The central hypothesis is that inherited cancer liability is mediated by both direct coding effects on protein function and diffuse non-coding regulatory effects acting through enhancers, promoters, transcription-factor binding, eQTLs, chromatin context and network-proximal genes. In this view, germline variants may collectively shape cellular states that favor the acquisition or selection of specific somatic alterations.

The project will pursue three objectives. First, it will build a pan-cancer catalogue of coding and non-coding germline variants potentially involved in the predisposition to somatic pathway aberrations, integrating TCGA, PCAWG/ICGC, UK Biobank, GTEx, ENCODE and CCLE data. Coding variants and haplotypes will be annotated using protein functional scores generated within the AIRC project, while non-coding variants will be prioritized through regulatory annotations, eQTL/sQTL links, transcription-factor motif disruption, co-expression and pathway/network proximity.
Second, the project will evaluate genome language models and sequence-to-function models to score the functional impact of non-coding regulatory variants. Reference and alternative genomic sequences will be compared to estimate perturbations in regulatory grammar, enhancer activity, promoter function and predicted gene regulation. These scores will be integrated with protein language model scores for coding haplotypes, generating a unified representation of germline functional impact across coding and non-coding regions.
Third, the project will develop network-informed Omnigenic Somatic Scores to predict somatic pathway alterations, mutational processes, tumor subtypes and aggressive clinical phenotypes. These models will combine coding protein-level effects, non-coding regulatory effects and network propagation across gene-regulatory, co-expression and protein-protein interaction networks. Their performance will be compared with classical polygenic somatic scores and validated in independent pan-cancer and cancer-specific datasets, with particular attention to prostate cancer, breast cancer and major oncogenic pathways such as TP53, MYC, PI3K, RTK-RAS, NRF2 and WNT.
The expected outcome is a computational framework to identify interpretable germline biomarkers of somatic cancer evolution. The project will generate testable mechanistic hypotheses on how inherited variation contributes to tumor subtype, pathway disruption and aggressiveness.

Candidate's profile (skills and competencies)
The ideal candidate should have a background in computational biology, bioinformatics, genomics, data science, computer science, biotechnology or related fields. Good programming skills in Python and/or R are required, together with interest in large-scale genomic data analysis.
Experience with next-generation sequencing data, cancer genomics, statistical genetics, GWAS or polygenic score methods, machine learning, biological networks or deep learning models for biological sequences will be considered an advantage. Previous knowledge of cancer biology, gene regulation, human genetics or molecular evolution is useful but not mandatory.
The candidate should be motivated to work at the interface of cancer genomics, molecular biology and artificial intelligence, with interest in developing interpretable computational methods with translational relevance for oncology.

Project nr. 15

Predictive modeling of m6A-regulated endogenous dsRNA formation and immunogenicity in splicing-mutant acute myeloid leukemia

Laboratory of RNA and Disease Data Science

Principal Investigator: Toma Tebaldi

Synthetic description of the activity and expected research outcome
RNA splicing alterations and RNA modifications are central regulators of gene expression in acute myeloid leukemia (AML). Mutations in splicing factors such as U2AF1 and SRSF2 generate aberrant transcripts, while the m6A pathway, mediated by METTL3, regulates RNA structure, RNA–protein interactions, and innate immune activation. Loss or inhibition of METTL3 can promote endogenous double-stranded RNA (dsRNA) accumulation, but the rules determining which dsRNAs become immunogenic remain poorly understood.
This PhD project will develop a computational framework to predict m6A-regulated immunogenic dsRNA regions in AML. The candidate will integrate RNA structure prediction, A to I editing, m6A-related features, RNA–protein interactions, splicing alterations, and single-cell transcriptomic data. The project will build on tools developed in the RDDS laboratory, including RNAEventProfiler, FoldARE, and the Cell Marker Accordion, and will apply quantitative and machine learning approaches to identify dsRNA vulnerabilities at nucleotide and cellular resolution.
The project will benefit from collaborations with Prof. Stephanie Halene at Yale University, providing AML models and innate immune systems, and Dr. Giulia Biancon at Policlinico di Milano, providing splicing-factor mutant systems and expertise in stress granule biology.

Candidate's profile (skills and competencies)
We are seeking a motivated candidate interested in computational biology, RNA biology, cancer biology, or data-driven biomedical research. Applicants may come from biology, biotechnology, bioinformatics, computational biology, mathematics, physics, engineering, or related fields. Prior experience with programming, RNA-seq, machine learning, or single-cell analysis is welcome but not required, as these skills can be developed during the PhD in the RDDS laboratory.

Project nr. 16

CAR-T Therapy for Glioblastoma

Armenise-Harvard Laboratory of Brain Disorders and Cancer

Principal Investigator: Luca Tiberi

Synthetic description of the activity and expected research outcome

Background

Glioblastoma (GBM) is one of the most frequent and aggressive forms of brain cancer (Thakkar et al., 2014). The median length of survival of GBM patients is 15 months, and despite great progresses in surgery, chemotherapy, and radiotherapy, it has not been significantly improved (Wu et al., 2021). Current standard treatments for GBM comprise maximum safe surgical resection of the tumor in combination with radiotherapy and Temozolomide-based chemotherapy. Each of these procedures present limitations related to safety or efficacy. Research in immunotherapy against GBM is thriving, and emerging data show promising results, especially for Chimeric Antigen Receptor – T (CAR-T) cells therapy (Brown et al., 2024; Choi et al., 2024). The current state of the art in pre-clinical trials testing CAR-T cells approaches on GBM relies primarily on mouse models orthotopically injected with GBM cancer cell lines. Among the main factors influencing the failure of numerous immunotherapy-based preclinical and clinical trials against GBM, there is an absence of proper human-recapitulating genetical and cellular assets to rely on, molecular inter- and intra-tumoral heterogeneity, as well as local and systemic immunosuppression (Kirschenbaum et al., 2024). In this context, patient-derived organoids (PDOs) emerged as novel and reliable preclinical 3D models, given their faithfulness in recapitulating tissues' in vivo functionality, genetic features, molecular characteristics, and cellular structures (Lago et al., 2023). Based on this evidence, we suppose that PDOs might be an appropriate model to both test existing CAR-T cells therapies and to potentially search for new GBM antigens.

Hypothesis

Given the information from the literature, we believe that implementing CAR-T cells therapy in a model of patient-derived GBM organoids will increase the chances to establish more effective therapies with the ultimate goal of bringing them to clinic.

Aims

The primary aim is to implement and test CAR-T cell therapy on deeply characterized glioblastoma organoids to evaluate therapeutic efficacy and identify novel GBM antigens. By utilizing a co-culture system and spatial transcriptomics, the experimental design will analyze the interactions between CAR-T cells and the tumor microenvironment at multiple timepoints to determine why certain immune cells are "switched off" or inactivated. Ultimately, this project seeks to establish a more effective immunotherapeutic framework to bridge the gap between preclinical success and clinical application for adult glioblastoma

Impact On Cancer

Glioblastoma is the most common primary brain tumor in adults, and it is associated with poor prognosis, in fact less than 5% of patients survive 5 years post diagnosis. We strongly believe that immunotherapy is the most innovative and promising strategy that must be implemented for solid tumors. Moreover, patient-derived organoids unlock the possibility to exploit it considering inter- and intra-tumoral heterogeneity in proper human-recapitulating cellular and genetical assets. This project is pivotal in initiating the against-cancer personalized medicine era.

References

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Wu, W. et al. Glioblastoma multiforme (GBM): An overview of current therapies and mechanisms of resistance. Pharmacol. Res. 171, 105780 (2021).

Brown, C. E. et al. Locoregional delivery of IL-13Rα2-targeting CAR-T cells in recurrent high-grade glioma: a phase 1 trial. Nat. Med. 30, 1001–1012 (2024).

Choi, B. D. et al. Intraventricular CARv3-TEAM-E T Cells in Recurrent Glioblastoma. N. Engl. J. Med. 390, 1290–1298 (2024).

Kirschenbaum, D. et al. Time-resolved single-cell transcriptomics defines immune trajectories in glioblastoma. Cell 187, 149-165.e23 (2024).

Lago, C. et al. Patient- and xenograft-derived organoids recapitulate pediatric brain tumor features and patient treatments. EMBO Mol. Med. 15, e18199 (2023).

Candidate's profile (skills and competencies)

The ideal candidate will hold a Master's degree in Neuroscience, Molecular Biology, Biotechnology, or related disciplines, with a strong interest in cancer research. Previous experience in cell culture, molecular biology, or imaging is desirable but not required. The candidate should demonstrate motivation, critical thinking, and the ability to work in a multidisciplinary environment. During the PhD, the candidate will be trained in advanced approaches including organoid technology, immunology, and functional imaging.

Project nr. 17

Epigenetic mechanism in cancer dormancy

Laboratory of Chromatin Biology & Epigenetics

Principal Investigator: Alessio Zippo

Synthetic description of the activity and expected research outcome
Despite current clinical advancements, metastatic diseases remain the leading cause of cancer-associated deaths. After dissemination from the primary tumor, disseminated tumor cells (DTCs) encounter hostile conditions at distant sites, including immune surveillance and growth-restrictive cues from the microenvironment. DTCs can enter a reversible dormant state, enabling them to withstand these challenges for extended periods before reactivating to form overt metastases. We have recently shown that this ability to persist in a non-proliferative state relies on active, adaptive mechanisms, including transcriptional memory, a process by which past environmental signals are epigenetically encoded to shape future gene expression responses. Despite its relevance, the epigenetic regulators underlying transcriptional memory and their role in dormancy remain largely unexplored, representing both a critical knowledge gap and a potential therapeutic window to prevent relapse. With this project, the PhD student will characterize the epigenetic state of quiescent DTCs and identify chromatin factors that support transcriptional memory and enhances their fitness under stress. This project aims to: (i) identify epigenetic changes supporting transcriptional memory in quiescent DTCs; (ii) determine whether a primed chromatin landscape facilitates dormancy entry and maintenance;
(iii) characterize the chromatin factors that preserve dormancy and contribute to metastatic reawakening.
To tackle these questions, the PhD candidate will combine epigenetic profiling with CRISPR-based functional screening, targeting quiescent cancer cells. This interdisciplinary approach will integrate wet-lab techniques and computational analysis, offering a comprehensive training in quantitative cancer biology. Overall, this project offers a unique opportunity to advance our understanding of metastatic dormancy and inform future therapeutic strategies.

Candidate's profile (skills and competencies)
We are seeking highly motivated and enthusiastic candidates willing to challenge an innovative project by adopting a pro-active attitude and an analytical approach. The candidate should have a vivid interest in epigenome profiling and CRISPR-based functional screening to address chromatin changes in pro-metastatic cancer cells. The successful candidate will be involved in an interdisciplinary project with research at the crossroads between cancer biology, chromatin biology, and cell biology. The candidate should have a strong interest in multidisciplinary collaboration. Given the international framework, the candidate should also have excellent communication skills and a team-oriented working attitude.