PUBLIC COMPETITION FOR ADMISSION TO THE PHD PROGRAMME OF NATIONAL INTEREST IN SYSTEMS MEDICINE – A. Y. 2026/2027, RESERVED FOR MEDICAL RESIDENTS AND SPECIALIST PHYSICIANS WHO HAVE COMPLETED THEIR RESIDENCY WITHIN THE LAST TWELVE MONTHS, WITH A DEGREE IN MEDICINE AND SURGERY (LM-41) AND AN INTEREST IN ONCOLOGY RESEARCH (PHYSICIAN-SCIENTISTS)

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PUBLIC COMPETITION FOR ADMISSION TO THE PHD PROGRAMME OF NATIONAL INTEREST IN SYSTEMS MEDICINE – A. Y. 2026/2027, RESERVED FOR MEDICAL RESIDENTS AND SPECIALIST PHYSICIANS WHO HAVE COMPLETED THEIR RESIDENCY WITHIN THE LAST TWELVE MONTHS, WITH A DEGREE IN MEDICINE AND SURGERY (LM-41) AND AN INTEREST IN ONCOLOGY RESEARCH (PHYSICIAN-SCIENTISTS)

THE RECTOR OF THE UNIVERSITY OF MILAN

- Having regard to Ministerial Decree no. 270, dated 22 October 2004, entitled "Amendments to Regulation no. 509 containing rules governing the educational autonomy of Universities, passed by a Decree of the Ministry for Universities and Scientific and Technological Research on 3 November 1999";
- Having regard to article 4 of Law no. 210 dated 3 July 1998, as amended by art. 19, paragraph 1, of Law no. 240 dated 30 December 2010;
- Having regard to Regional Law no. 33 dated 13 December 2004, entitled "Rules governing regional measures to ensure the right to study at university", which makes provisions for services in favour of students enrolled in doctoral programmes;
- Having regard to art. 6 of Regional Law no. 13 of 7 August 2025, entitled "Adjustment to the 2025-2027 budget, including modifications to regional laws";
- Having regard to Ministerial Decree no. 226 dated 14 December 2021, entitled "Regulations concerning the accreditation methods of doctoral locations and programmes and the criteria for the institution of doctoral programmes by accredited bodies", and in particular art. 7 and art. 8, paragraph 5;
- Having regard to Law no. 33 dated 12 April 2022, entitled "Provisions on simultaneous enrolment in two higher education programmes", and in particular art. 4, paragraph 1;
- Having regard to art. 1 of Ministerial Decree no. 930 dated 29 July 2022, which states that "starting from the academic year 2022/2023, Universities shall include in their academic regulations general provisions to facilitate the simultaneous enrolment of students";
- Having regard to Ministerial Decree no. 917 of 15 October 2019, whereby the Ministry of

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Education, University and Research (MIUR), pursuant to Ministerial Decree 45/2013, granted five-year accreditation to the doctoral research programmes proposed by the University of Milan, subject to ongoing compliance with the prescribed requirements, and having regard to Directorial Decree (DD) no. 877 of 28 October 2025, confirming accreditation for the doctoral programme in accordance with Ministerial Decree 226/2021;

- Having regard to the agreements stipulated by and between the University of Milan, the University of Naples "Federico II", the University of Bari, the University of Turin, the University of Trento, the Catholic University of the Sacred Heart in Rome, Humanitas University of Milan, IFOM ETS – AIRC Institute of Molecular Oncology, the European Institute of Oncology (IEO), the Human Technopole Foundation (HT), the National Institute of Molecular Genetics (INGM), the Italian Institute of Technology (IIT), the Italian Institute for Genomic Medicine (IIGM), CEINGE – Advanced Biotechnologies "Franco Salvatore", Telethon Foundation ETS and the European School of Molecular Medicine Foundation (SEMM), for the institution of the PhD programme of national interest in Systems Medicine;
- Considering that the afore-mentioned Universities intend to institute a new cycle of the doctoral programme for the academic year 2026/2027;
- Having regard to the note no. 2386 of 13 May 2026 of the Ministry of University and Research;
- Having regard to the resolutions adopted by the Academic Senate and the Board of Directors during their meetings of 17 and 31 March 2026, concerning the institution of the 42nd doctoral cycle;
- Having regard to the agreement concerning the launch and running of the AIRC-Cariplo joint project for the training of physician scientists within the PhD of national interest in Systems Medicine (41st, 42nd and 43rd cycles), with places reserved for medical residents and specialist physicians who have recently completed their residency

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HEREBY DECREES AS FOLLOWS:

Art. 1 - Institution

Subject to accreditation by the Ministry of University and Research (MUR) and in compliance with the laws in force, the University of Milan (administrative headquarters), the University of Naples "Federico II", the University of Bari, the University of Turin, the University of Trento, the Catholic University of the Sacred Heart in Rome, Humanitas University of Milan, IFOM ETS – AIRC Institute of Molecular Oncology, the European Institute of Oncology (IEO), the Human Technopole Foundation (HT), the National Institute of Molecular Genetics (INGM), the Italian Institute of Technology (IIT), the Italian Institute for Genomic Medicine (IIGM), CEINGE – Advanced Biotechnologies "Franco Salvatore", Telethon Foundation ETS and the European School of Molecular Medicine Foundation (SEMM) hereby open 12 PhD positions within the highly innovative doctoral programme of national interest called "PhD in Systems Medicine" for the academic year **2026/2027 (42nd cycle, starting on 1 November 2026**). These positions are reserved for medical residents and specialist physicians who have completed their medical residency in the last twelve months, and are governed by the provisions of article 7 and article 8, paragraph 5, of Ministerial Decree 226/2021.

The idea to launch this PhD for medical residents and newly qualified specialist physicians was sparked by the AIRC Foundation for Cancer Research and the Cariplo Foundation, who believe in the importance of enhancing training opportunities for future physician-scientists, in order to promote the profession within the Italian system.

The two foundations agree that advances in genetics and genomic sciences have triggered a revolution, transforming classical medicine into what is now known as precision medicine. This new approach is based on the acquisition and integration of vast amounts of quantitative molecular data, and their use for a personalised definition of disease and targeted therapy. These transformations highlight the importance of training medical specialists who are capable of translating the results of scientific research into clinical practice.

The contribution of physician-scientists is considered particularly crucial in the fight against cancer, which is one of the main causes of death worldwide and whose incidence – according to data published by the World Health Organisation (WHO) – is rising. In light of this situation, and of the

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substantial funds allocated to cancer research, there is a need to quickly harness research findings to the benefit of patients, developing customised approaches and precision-medicine practices.
The PhD in Systems Medicine aims to provide doctors with interdisciplinary theoretical and technological training in biomedical sciences to address the challenges of precision medicine. The goal is to train professionals capable of tackling highly complex technological and therapeutic strategies with multidisciplinary approaches.

The official language of the PhD in Systems Medicine is English.

Duration

4 years

Research topics

Applicants can view the proposed research topics for the programme — as identified by the Faculty of Instructors based on the programme's objectives and its research and educational focus — on the website of the University of Milan. Research topics are selected in the times and manner specified in art. 25 of the Regulation for PhD Programmes and Students of the University of Milan (administrative headquarters).

Places available

12

Out of these 12, a maximum of 6 places are reserved for specialist physicians who have completed their residency no more than 12 months before the start date of the programme.

Scholarships

12 scholarships funded by the AIRC Foundation for Cancer Research and the Cariplo Foundation
Out of these 12, a maximum of 6 scholarships are reserved for specialist physicians who have completed their residency no more than 12 months before the start date of the programme.

The number of scholarships may be increased, should external funding become available before the application deadline.

International applicants who are in receipt of scholarships issued by their country of origin may be

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admitted in excess of the enrolment quota, if they pass the admission exams set out in this decree.

PhD training activities may take place only at the organisations hosting the labs funded by AIRC, as listed in Annex A.

Coordinator

Prof. Diego Pasini, full professor in the scientific-disciplinary sector BIOS-08/A (phd@semm.it).

Admission is regulated by a public competition based on qualifications and exams, as provided for in the articles below.

Art. 2 - Admission requirements

To be eligible for admission, applicants must hold a second-cycle degree (*Laurea magistrale*) in Medicine and Surgery (LM-41) or an equivalent qualification (Master's degree) awarded by a foreign university. Moreover, they must either:

- be enrolled, for the a. y. 2025/2026, in the final year of a medical postgraduate school at an Italian university

  OR

- have completed their medical residency at an Italian or foreign university no more than 12 months before the start date of the programme (1 November 2026).

  For those who have completed their medical residency at a non-Italian university, the foreign residency diploma must be accompanied by a decree of the Italian Ministry of Health stating that the applicant is qualified to practise as a specialist physician in Italy. Instructions on how to obtain this document are available on the website of the Ministry of Health.

All documents must be in Italian, English, French, German or Spanish.

The validity of foreign qualifications is verified upon submission of the official documents.

Art. 3 – Application for admission

Applications must be submitted online by **10:00 on 16 September 2026**, by accessing the website http://www.semm.it. The application form is an online CV that applicants must complete on the

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website. Every application will be automatically assigned an ID number, which will be communicated to the applicant via e-mail as confirmation of the application being received. This number will be used to identify the applicant for any further communication posted on the website (admission to examination, final ranking, etc.).

Here below is a summary of the information to be provided in the application form:

- basic personal data;
- key elements of the applicant's educational track;
- exams passed, with the corresponding grades and credits;
- publications and work experiences, if any;
- personal scientific interests in relation to the topics of the programme;
- a description of the reasons why the applicant wishes to enrol in the programme;
- names of two referees (authors of the reference letters in support of the application);
- preferred research area and lab(s) for the PhD, among those listed in Annex A (please note that these preferences are not binding).
- Applicants must upload the following documents along with their application:
    1. Master's degree certificate (or equivalent foreign qualification) with transcript of records, **or** Diploma Supplement. All documents must be in Italian, English, French, German or Spanish.
    2. Self-certification of enrolment in a medical postgraduate school issued by the corresponding University, specifying the name and standard duration of the residency programme, the years of enrolment and the exams passed.

OR

Italian medical residency diploma (or equivalent foreign qualification, accompanied by the decree authorising the practice as a specialist physician issued by the Italian Ministry of Health), specifying the name and standard duration of the residency programme, the final mark and the exams passed. Self-certifications are accepted as and where provided for by the laws in force.

Furthermore, the Faculty of Instructors requires two reference letters to support the application. In an appropriate section of the application form, the applicant is asked to indicate the names,

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affiliations and email addresses of the two chosen referees. The referees will receive an automatic email with an invitation to submit their reference letters. It is the responsibility of the referees to submit their letters through the online system by the deadline. Referees must be academic professors, clinicians, hospital-based physicians or research project leaders.

Art. 4 - Applicants with disabilities

In order to ensure equal treatment of applicants, those holding a certificate of disability (*invalidità civile*) and/or handicap pursuant to Law 104/1992 may apply for accommodations by writing to COSP Disability Services (ausili.ammissioni@unimi.it) at least 15 days before the exam, attaching the certificate issued by the competent public health office. Applicants holding outdated certificates are required to apply for an updated certificate, to be submitted after enrolment for the purposes of using disability accommodations as offered by the University.

Art. 5 - Applicants with SLD

In order to ensure equal treatment of applicants, those holding a Specific Learning Disorders (SLD) certificate under Law 170/2010, issued by the National Health Service, a private affiliated centre, or a private specialist (with a compliance certificate from the competent health authority), may apply for accommodations by sending their certificate to COSP SLD Services (ausili.ammissioni@unimi.it) at least 15 days before the exam. If the SLD was diagnosed in childhood, and the certificate is over three years old, students should apply for an updated certificate, to be submitted after enrolment for the purposes of using SLD accommodations as offered by the University.

Art. 6 - Pre-selection

Once applications have been received, the Admission Committee will pre-select applicants.
The following are the pre-selection criteria used by the Admission Committee:

1. consistency between the degree(s) held by each applicant and the goals of the PhD programme: max. 10 points;
2. the applicant's previous educational track: max. 10 points;
3. publications and other qualifications: max. 10 points.

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The evaluation of the CV will take into account the applicant's entire university career, any publications, any professional experience and other qualifications held.
In scoring the CV, the Admission Committee will take into consideration the conditions and the amount of time taken by the applicant to obtain his/her qualifications.
The minimum score to pass the pre-selection stage is 18/30.

Pre-selected applicants will be invited to take the admission examination. The list of pre-selected applicants will be published on the website https://www.semm.it **on 24 September 2026**, and will serve as official notice.

Art. 7 – Admission examination

The examination schedule, specifying the date and time of the written test and oral exam for each applicant, will be published on the website http://www.semm.it. This publication will serve as official notice.
The admission examination will be in English and will include:

- an online multiple-choice test designed to assess applicants' knowledge of the topics covered by the PhD programme, as well as their reasoning skills;
- an online oral exam covering the following points: presentation of the applicant's degree thesis, or another research project in which the applicant took part during his/her career; discussion of a research project to be chosen from the ones proposed by the Committee, consistently with the research areas of the doctoral programme; the applicant's motivations, expectations and future career prospects.

To take both the test and the oral exam, applicants must present one of the following identity documents:

a) identity card;

b) passport;

c) (Italian) driving licence.

The Committee will assign a score to each applicant based on:

1. the applicant's previous educational track: max. 10 points;

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2. the written test: max. 30 points;
3. the oral exam: max. 60 points.

The outcome of the qualification assessment will be communicated to applicants before the examination dates.

The overall ranking will be calculated on the basis of the total number of points obtained by each applicant for their qualifications and exams, in compliance with the above-mentioned criteria.
The minimum pass score is 70/100. Following the test and oral exam, applicants will be invited to online informational interviews with the principal investigators of the available projects, as listed in Annex A. These interviews aim to give applicants an overview of the labs and organisations where they may be doing their PhD, but are not scored for the purposes of admission.

Art. 8 - Admission Committee

The Admission Committee is appointed by the Rector of the University of Milan, upon proposal of the Faculty of Instructors, by means of a decree issued in accordance with the applicable regulations.
The Committee must conclude its work by **20 October 2026.**

Art. 9 - Admission to the programme

After the examination, the Admission Committee will draw up the ranking list according to the scores obtained by each applicant. The ranking list will then be published on the SEMM website (http://www.semm.it).
Applicants are admitted to the programme according to their position in the ranking list, until all the available places have been filled. Where two or more applicants achieve the same score, preference is given to the younger applicant, without prejudice to the priority criterion for the allocation of doctoral scholarships set forth in article 12 of this decree. Scholarships are awarded based on the ranking order. Admitted applicants who do not enrol by the deadline lose their right to enrol in the programme.
Should any admitted applicant withdraw from the programme, applicants ranked as eligible but not admitted in the first instance may be invited to enrol in their stead, but no later than three months after the start of the programme.

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If the withdrawing student has already received any monthly scholarship payments, he/she will be required to return them.

Simultaneous enrolment in two academic programmes is allowed within the limitations provided for by current regulations, and must be assessed and approved by the competent bodies.

More specifically, simultaneous enrolment in a doctoral programme and a postgraduate medical school is subject to the provisions of Ministerial Decree no. 226 of 14 December 2021.

For information on how to apply for simultaneous enrolment in two study programmes, please visit the following link: Simultaneous enrolment in two higher education programmes | University of Milan (unimi.it).

Art. 10 – Enrolment

Admitted applicants must apply for enrolment in the PhD programme within 5 days of publication of the ranking list, by filling out the ad-hoc form prepared by the University of Milan.

Applicants are admitted conditionally and may be excluded from the programme if they are found not to meet the requirements.

Those enrolled in doctoral programmes must pay the annual regional tax for the right to higher education in the amount of €190.00, plus a €16.00 stamp duty and a €15.50 insurance premium.

Students with a disability at or above 66% and/or a recognised handicap pursuant to Law no. 104/92 will have the regional tax and insurance premium waived, provided that they submit an application for exemption; these students are only required to pay the €16.00 stamp duty.

Enrolment fees are non-refundable, even if a student withdraws from the doctoral programme.

Art. 11 - Enrolment of international applicants

International applicants are required to follow the same enrolment procedure as Italian applicants, but must also provide additional documents so that the University can check the suitability of their qualification, as well as the legitimacy of their stay in Italy.

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Applicants with foreign qualifications

Applicants with a foreign degree must upload the following documents when enrolling online:

1. **original Master's degree certificate** (with an official translation into Italian, if the original is not in English, French, Spanish or German), **legalised or apostilled** by the competent authorities of the issuing country — unless specific legal provisions allow for exemption from legalisation or apostille — plus **one** of the following documents:

    - Declaration of Value (*dichiarazione di valore in loco*) issued by the Italian Embassy in the country where the qualification was obtained;
    - CIMEA Statement of Comparability (see the list of required documents) or similar statements issued by other ENIC-NARIC centres, provided that they include all information necessary to assess the qualification;
    - Statement of Correspondence downloaded from ARDI, if the qualification was obtained in one of the signatory countries of the Lisbon Convention;
    - Diploma Supplement drafted using the European Commission's template and **legalised** by the competent authorities of the country where the qualification was obtained (unless specific legal provisions allow for exemption from legalisation or apostille).

OR

2. **original Master's degree certificate** (with an official translation into Italian, if the original is not in English, French, Spanish or German), accompanied by a Statement of Verification issued by CIMEA (the Italian ENIC-NARIC centre) or other ENIC-NARIC centres, and **one** of the following documents:

    - CIMEA Statement of Comparability (see the list of required documents) or similar statements issued by other ENIC-NARIC centres, provided that they include all information necessary to assess the qualification;
    - Statement of Correspondence downloaded from ARDI, if the qualification was obtained in one of the signatory countries of the Lisbon Convention;
    - Diploma Supplement drafted using the European Commission's template and **legalised** by the competent authorities of the country where the qualification was obtained (unless specific legal provisions allow for exemption from legalisation or apostille).

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Applicants with non-Italian citizenship

Applicants with non-Italian citizenship must also attach the following:

- Italian tax ID (*codice fiscale*);
- valid residence permit, or the receipt issued to them upon applying for a residence permit for study purposes (only for non-EU citizens);
- student visa for the a. y. 2026/2027 (only for non-EU citizens residing abroad).

How to obtain a student visa:

Non-EU applicants residing abroad (with the exception of citizens from Norway, Iceland, Liechtenstein, Switzerland, Republic of San Marino and Vatican City) are required to submit an application for pre-enrolment via Universitaly in order to obtain a student visa.
Once they are admitted and their pre-enrolment application is validated, they will be able to download their pre-enrolment receipt (also known as Summary) from Universitaly and use it to apply for a student visa.

Applicants who are not in possession of one or more of the above-mentioned documents when enrolling online must produce the missing documents **by 30 November 2026**, via the Enrolment documents integration service.

The suitability of academic qualifications earned abroad is evaluated by the University in compliance with applicable laws and regulations.

The validity of foreign qualifications is verified upon submission of the official documents. Until then, applicants are admitted to the programme conditionally, and may be excluded from the programme if they are found not to meet the requirements. The University reserves the right to ask applicants to produce other documents in addition to those already submitted, in order to check their authenticity and suitability.

Art. 12 - Scholarships

Scholarships are awarded to applicants in accordance with the laws in force, based on the ranking order. The gross amount of the scholarship is **€34,480.00** per year. The scholarship is not subject to

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IRPEF (personal income tax) in accordance with art. 4 of Law no. 476 of 13 August 1984, and is subject to the social security provisions set forth in art. 2, paragraphs 26 et seq., of Law no. 335 of 8 August 1995, as subsequently amended.

Working students falling into the categories appearing in art. 26 of the University Regulation for PhD Programmes and Students will be eligible to apply, provided their working income does not exceed the scholarship amount. Income under the limitation is defined as gross earnings during the year to which the scholarship is principally allocated.

In the event of applicants ranked equally, scholarships are awarded by assessing the applicant's economic situation according to the ISEE (Equivalent Economic Situation Indicator).

Scholarships have a yearly duration and are renewed if the Faculty of Instructors promotes the student to the following year, after ascertaining that he/she has correctly and successfully completed the programme of activities in the previous year.

In addition to the scholarship, each PhD student is given a budget for research activity in Italy and abroad suited for the type of programme, and in any case amounting to no less than 20% of the amount of the scholarship itself.
During the dual-enrolment period, medical residents are not entitled to receive the scholarship. Being enrolled in a medical postgraduate school, they are subject in the first instance to the provisions of the contract for specialist physicians in training.

Art. 13 - Obligations of doctoral students

The rights and obligations of doctoral students are regulated by **articles 26 and 27 of the University Regulation for PhD Programmes and Students**. Please bear in mind the following:

- doctoral research programmes entail 1,500 hours of **training-education and research activities** per year. A full-time commitment is required of each student for the whole duration of the programme.
- in order to obtain their PhD, doctoral students **are required to demonstrate English proficiency at level B2 of the Common European Framework of Reference for Languages**

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(CEFR).

To meet the language proficiency requirement, doctoral students must submit an English certificate from one of the certifying bodies recognised by the University (https://www.unimi.it/en/study/language-proficiency/placement-tests-and-english-courses/accepted-language-certificates), at B2 level or above, by the end of the first programme year.

An exemption from submission of a language certificate is granted only to:

- those who, by the start date of the PhD programme, have earned a Master's degree featuring an English-language specialisation in one of the following Master's degree classes: LM-37 Modern American and European languages and literature, LM-38 Modern languages for communication and international cooperation, LM-39 Linguistics, LM-94 Interpreting and specialised translating, or equivalent Master's degree;
- those who, by the start date of the PhD programme, have earned a Master's degree in a programme taught entirely in English. No other exemptions will be granted;
- those who, during their prior study programme, have earned a B2 English language statement issued by SLAM – University of Milan Language Centre.

No other exemptions will be granted.

PhD students are required to regularly participate in the courses and to be fully committed to the programme, with regard to both individual and guided study and to their assigned research activities, as requested by the Faculty. Information on the nature and duration of courses can be found on the website http://www.semm.it.

With a view to the organisation of assessments, PhD students will be asked to submit a written report about their research activities, including findings and future prospects for the project. The report must be submitted by the deadline established by the Faculty of Instructors.

In accordance with the agreement signed by and between the University of Milan, AIRC, the Cariplo Foundation and the European School of Molecular Medicine (SEMM), after the dual-enrolment

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period, medical residents must complete all the activities of the PhD programme, up until the end of its standard duration.

Due to the peculiarity of this PhD and in light of the goals illustrated in the recitals, PhD students will be required to work in clinical practice for at least 20% of their time, within the framework of the assigned research project and in accordance with the international academic standards for physician-scientists training programmes.

Art. 14 - Civil servants

Pursuant to art. 12, paragraph 5, of Ministerial Decree 226/21, civil servants admitted to a doctoral programme may be granted a leave as contemplated by the applicable collective agreement, or, for those employed under public law, an extraordinary leave for study purposes, for the standard duration of the programme — provided that such leave does not conflict with the needs of the employing administration, as per art. 2 of Law no. 476 dated 13 August 1984 — but only if this is the first time that they enrol in a doctoral programme, independently of the programme subject area; the leave may be paid or unpaid, subject to the civil servant's right to explicitly forego the scholarship. This does not affect their right to receive a budget for research activities in Italy and abroad, as per art. 9, paragraph 4, of Ministerial Decree 226/21.

Art. 15 - Awarding of the degree

The degree of Doctor of Philosophy, abbreviated to "Dott. Ric." or "PhD", is awarded jointly by the Rectors of the University of Milan, the University of Naples "Federico II", the University of Bari, the University of Turin, the University of Trento and Humanitas University of Milan in compliance with Ministerial Decree no. 226 dated 14 December 2021. The qualification and certificate will explicitly mention the institutional and scientific role of the SEMM Foundation.

Art. 16 – Processing of personal data

Pursuant to Legislative Decree no. 196 of 30 June 2003, as amended by Legislative Decree no. 101 of 10 August 2018, as well as Regulation (EU) 2016/679 (General Data Protection Regulation, GDPR), the University undertakes to respect the confidential nature of the information provided by applicants. All data provided will be processed solely for purposes related and instrumental to the

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competition and to manage the applicant's relationship with the University, where necessary, in compliance with current laws. The SEMM Foundation and all other partner Universities shall be bound by the same provisions.

Art. 17 - Applicable laws and regulations

Any items for which no specific provision has been made in this competition notice shall be regulated in accordance with Italian laws and regulations governing doctoral programmes.

Art. 18 – Person in charge of the procedure and contact details

Pursuant to Law no. 241 of 7 August 1990, the person in charge of the procedure set forth in this competition notice is Ms Monica Delù (Head of the Postgraduate Programmes and International Students Services Sector).
For further information or clarifications please use the InformaStudenti service, selecting the category: Postgraduate > Doctoral research (PhD).

Milan, 21 July 2026

THE RECTOR OF THE UNIVERSITY OF MILAN
(Signed Marina Brambilla)

Filed as record no. 3121/2026 of 21 July 2026

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Annex A

PHYSICIAN SCIENTIST

LA MEDICINA INCONTRA LA RICERCA

promosso da: AIRC Fondazione CARIPLO | con il supporto di: SEMM European School of Molecular Medicine, UNIVERSITÀ DEGLI STUDI DI MILANO

Lab. No. 1

Principal Investigator	Altucci Lucia
Institute of Affiliation	Università degli Studi della Campania Luigi Vanvitelli
Title of the proposed project	Advancing Novel Epigenetic-Based Strategies to Target CRC
Short description of the project	Epigenetic dysregulation is increasingly recognized as a fundamental driver of cancer development and progression. Among epigenetic regulators, Chromobox protein homolog 2 (CBX2), a key component of the Polycomb Repressive Complex 1 (PRC1), has emerged as a critical epigenetic reader capable of reshaping chromatin organization and oncogenic gene expression programs. Deregulation of CBX2 has been associated with multiple cancer types and may profoundly alter cellular processes linked to tumorigenesis. However, the exact mechanisms underlying its oncogenic role remain largely unknown, particularly in colorectal cancer (CRC). This PhD project aims to elucidate the molecular and functional role of CBX2 in CRC and to explore its potential as a therapeutic target within precision oncology approaches. Aim 1 is to define the molecular mechanisms through which CBX2 contributes to colorectal tumorigenesis, with a particular focus on downstream signaling pathways, chromatin regulation, and cancer-associated cellular programs that represent actionable therapeutic vulnerabilities. Aim 2 is to investigate the upstream mechanisms responsible for CBX2 deregulation in CRC, determining their biological and clinical relevance through the comprehensive analysis of epigenetic and transcriptional regulatory networks. Aim 3 is to exploit these findings to evaluate innovative therapeutic strategies targeting CBX2 in CRC, identifying and characterizing promising compounds capable of modulating its activity and assessing their efficacy in preclinical models. By combining molecular biology, epigenomics, and translational cancer research approaches, this project will generate novel mechanistic insights into CBX2-driven oncogenesis and provide a robust rationale for the development of targeted therapeutic interventions aimed at improving outcomes for CRC patients.
Main research area for the project	Molecular Therapy
5 key words for the project	Target therapy, Drug discovery and/or development, Epigenetics, Carcinogenesis, Gene regulation
Lab Website Link	https://www.medicinadiprecisione.unicampania.it

Lab. No. 2

Principal Investigator	Ambrogio Chiara
Institute of Affiliation	Università degli Studi di Torino
Title of the proposed project	Decoding tumor evolution to optimize sequential RAS-targeted therapies
Short description of the project	The therapeutic landscape of RAS-driven cancers has rapidly evolved with the development of multiple classes of inhibitors, including allele-specific compounds, pan-RAS inhibitors and degraders. While these agents represent a major breakthrough, clinical benefit remains limited by heterogeneous responses and the rapid emergence of resistance. Importantly, there are currently no validated biomarkers to guide the optimal sequencing of these therapies, representing a major unmet need in precision oncology. This project aims to systematically address the complexity of RAS targeting by defining how different classes of RAS inhibitors shape tumor evolution and therapeutic response when used sequentially. We hypothesize that distinct mechanisms of action impose specific selective pressures on tumor cells, leading to predictable patterns of signaling adaptation and resistance that can be leveraged to rationalize treatment sequences. To test this, we will exploit a unique panel of genetically defined KRAS-mutant models developed in our laboratory, enabling direct comparison of multiple RAS-targeted therapies in a longitudinal setting. We will evaluate approved drugs as well as compounds in clinical development, including next-generation inhibitors and degraders, assessing their effects on RAS signaling output and pathway rewiring. Both in vitro systems and in vivo models will be employed to study the dynamic nature of treatment response. Using integrated multi-omics approaches, we will construct a robust "tumor evolution" framework that maps how cancer cells adapt overtime to different therapeutic sequences. This will allow us to identify molecular determinants of sensitivity and resistance and uncover vulnerabilities that emerge during treatment. A key strength of this project is the close integration between basic and clinical research, ensuring that experimental findings are aligned with real-world therapeutic challenges. By providing a mechanistic understanding of how tumors evolve under sequential RAS inhibition, this work has the potential to directly help clinical decision-making and optimize treatment strategies for patients with RAS-driven cancers.
Main research area for the project	Molecular Therapy
5 key words for the project	RAS/RAS inhibitors, Cell signaling, Animal models, Lung ca., Response and/or resistance to therapy
Lab Website Link	www.ambrogiolab.com, https://www.ifom.eu/en/cancer-research/researchers/chiara-ambrogio.php

Lab. No. 3

Principal Investigator	Bachi Angela
Institute of Affiliation	IFOM - Istituto Fondazione di Oncologia Molecolare, ETS
Title of the proposed project	Proteomic profiling of epitheliod sarcoma to identify diagnostic markers and clinically actionable pathways
Short description of the project	Epithelioid sarcoma (ES) is a rare soft tissue malignancy characterized by aggressive behavior, local recurrence, and distant metastasis. It accounts for less than 1% of all soft tissue sarcomas and predominantly affects young adults, causing significant morbidity and reduced quality of life. Current diagnostic approaches rely on histopathological criteria and loss of SMARCB1/INI1 expression, yet these markers lack sensitivity and specificity for early or equivocal cases. Therapeutic options remain limited and the molecular landscape driving ES progression is incompletely characterized, highlighting an urgent need for novel biomarker discovery. Membrane and global proteomic profiling was performed on patient-derived ES tumor tissues and matched healthy counterparts using state-of-the-art mass spectrometry. Analysis revealed distinct proteomic signatures discriminating neoplastic from non-neoplastic tissues, identifying differentially expressed proteins enriched at the cell surface - a compartment particularly relevant for diagnosis and therapeutic targeting. These findings motivate expanding the analytical framework to include metabolomic profiling for a more comprehensive molecular characterization. Building on these preliminary data, the project will develop along four interconnected tasks: 1. Biomarker identification. Candidate proteins from the proteomic discovery phase will be validated as diagnostic markers via immunohistochemistry on tissue microarrays and targeted mass spectrometry on an expanded patient cohort. 2. Bioinformatic analysis. Pathway enrichment, protein-protein interaction mapping, and integration with transcriptomic and metabolomic datasets will prioritize clinically relevant candidates and key dysregulated networks. 3.Orthogonal validation. Selected candidates will be confirmed using immunohistochemistry, targeted mass spectrometry, and flow cytometry, with attention to subcellular localization and surface accessibility. 4. Functional studies. Top candidates will be assessed through in vitro loss- and gain-of-function experiments, evaluating their role in proliferation, invasion, and pharmacological response. The student will gain hands-on competence across the full analytical pipeline, from sample preparation and data acquisition to statistical analysis and biological interpretation, with focus on proteomics and metabolomics.
Main research area for the project	Cancer Biology
5 key words for the project	Proteomics, Sarcoma, Biomarkers
Lab Website Link	https://www.ifom.eu/en/cancer-research/research-labs/research-lab-bachi.php

Lab. No. 4

Principal Investigator	Bardelli Alberto
Institute of Affiliation	Università degli Studi di Torino
Title of the proposed project	Targeting Metastatic Prowess with Translational Oncology
Short description of the project	The candidate will join IFOM (The AIRC Institute of Molecular Oncology) and the Bardelli laboratory in the heart of Milan, an internationally recognised hub for translational oncology, with long-standing expertise in genomics, patient-derived models, multiomics and artificial intelligence applied to colorectal (CRC) and other cancers. The project will dissect the biological basis of intrinsic tumour aggressiveness through the "born to be bad" (BBB) versus "born to be good" (BBG) framework. BBB tumours are micrometastatic from the outset, persist as minimal residual disease (MRD) after surgery and recur, whereas BBG tumours remain localised and are cured by surgery alone. No clinical biomarker currently distinguishes these phenotypes, and patients are often treated alike. The candidate will work across three integrated objectives: (i) liquid biopsy/ctDNA-guided clinical trials - building on studies such as PEGASUS, that tailor adjuvant therapy in resected colon cancer according to MRD status; (ii) functional drug screening on patient-derived "avatars" (2D lines, 3D organoids and xenopatients) to dissect mechanisms of primary and acquired resistance, including drug-tolerant persister cells, and to identify new and repurposed therapies; (iii) translation of laboratory programmes into early-phase clinical trials, with particular emphasis on DNA-repair vulnerabilities as therapeutically actionable determinants of tumour evolution and immune responsiveness. According to candidate preferences, training will combine wet-lab techniques (organoid manipulation, drug-screening assays, in vivo modelling) and dry-lab skills (bioinformatics, machine learning, AI-based "pathomics") to foster a true physician-scientist profile able to bridge laboratory research, clinical trials and new drug development. A defining feature will be weekly clinical activity in a high-level oncology setting, ensuring continuous communication between laboratory and hospital and a genuine bench-to-bedside loop. The PhD environment is international and multidisciplinary, bringing together physicians, molecular biologists and bioinformaticians, and prepares graduates for future leadership in precision oncology.
Main research area for the project	Genomic medicine
5 key words for the project	Genomics, Chemotherapy and/or chemotherapic drugs, Colorectal and/or intestinal ca., Clinical trials, Liquid biopsy
Lab Website Link	https://www.mbc.unito.it/it/genomics-cancer-and-targeted-therapies

Lab. No. 5

Principal Investigator	Bello Lorenzo
Institute of Affiliation	Università degli Studi di Milano
Title of the proposed project	Personalized Function-based resection for IDH-mutant glioma patients
Short description of the project	Surgical treatment of IDH-mutated gliomas is a therapeutic strategy capable of significantly altering the natural history of the disease; its goal, when feasible, is the removal of both the visible and invisible (infiltrative) portions of the tumor (so-called supratotal resection) and the preservation of the patient's functional integrity. This significantly delays recurrences, prolongs survival and maintains long-term quality of life. This is achievable through so-called brain mapping techniques, which allow for resection within functional boundaries. The ability to achieve this goal depends on the degree of functional reorganization achieved by the individual's brain-that is, how the interaction between the tumor and the brain circuits where the tumor develops has altered brain functionality, leading to the reorganization and deactivation of the infiltrated circuits. The aim of surgery, using personalized function-based resection techniques, is to identify the interface between infiltrative tumor cells and still functioning brain circuits. The identification of this interface (in terms of location and extension) determines the extent of the surgical resection (EOR), as well as its oncological and functional outcomes The project aims to determine in patients with IDH-mutated gliomas the degree of functional reorganization achieved through tumor-brain interaction in the individual patient's brain and to evaluate its impact on oncological end functional outcomes. The project consists of three phases: 1) preoperative: determination of the degree of functional reorganization at individual patient and population levels through the integration of rs-fMRI and neuropsychological and psycho-oncological assessments; 2) intraoperative: validation of the established degree of reorganization through individualized intraoperative functional mapping; definition of location, extension and functional reprogramming; correlation with pre-operative findings; 3) post-operative: functional (post-operative short and long-term neuropsychological assessment) and oncological (EOR) outcomes The project aligns with the objectives of the AIRC IG 27184 grant, which focuses on the reorganization of the motor system.
Main research area for the project	Neurobiology
5 key words for the project	Glioma and/or glioblastoma, Magnetic resonance imaging (MRI), Surgery, Clinical trials, Neoadjuvant therapy
Lab Website Link	https://www.unimi.it/it/ugov/person/lorenzo-bello

Lab. No.6

Principal Investigator	Benelli Matteo
Institute of Affiliation	Università degli Studi di Firenze
Title of the proposed project	Tracking non-tumor-derived cfDNA in longitudinal liquid biopsies to monitor treatment response in metastatic cancer
Short description of the project	This translational and computational PhD project is designed for a physician-scientist seeking to specialize in cancer multi-omics and translational oncology. While liquid biopsy studies in metastatic cancer predominantly focus on tumor-derived alterations, particularly circulating tumor DNA (ctDNA), this project will investigate the non-tumor component of cell-free DNA (cfDNA), including immune-cell and tissue-derived signals, as a dynamic readout of systemic host response during anticancer therapy. The specific research objectives are: - To profile the longitudinal dynamics of non-tumor cfDNA in patients undergoing systemic therapy for metastatic breast and colorectal cancers. - To characterize early therapy-induced modulation of host-derived cfDNA methylation signals, including immune-cell and tissue-of-origin contributions, across serial treatment time points, and assess whether these dynamics are associated with treatment response and early disease progression. The candidate will have access to existing longitudinal plasma datasets profiled by genome-wide DNA-methylation sequencing, integrated with project-specific data generated during the PhD. These molecular profiles are paired with clinically curated information on treatments, outcomes, and, for a subset of patients, matched imaging data. A key clinical component will involve defining clinically meaningful study populations and curating longitudinal clinical datasets, including treatment lines, baseline disease features and key outcomes. The methodological core involves applying state-of-the-art computational methods for signal deconvolution and, where needed, developing AI-based approaches based on informative DNA methylation patterns. These pipelines will refine estimation of cell-type and tissue-of-origin contributions to cfDNA and track their modulation from baseline through early on-treatment time points. A specific clinical placement has not yet been identified; potential host institutions include the Careggi University Hospital and the Azienda USL Toscana Centro, although other options could also be considered.
Main research area for the project	Computational Biology
5 key words for the project	Breast ca., Bioinformatics, Epigenetics, Liquid biopsy, Artificial Intelligence
Lab Website Link	https://www.sbsc.unifi.it/vp-410-gruppo-benelli.html

Lab. No. 7

Principal Investigator	Bianchi Fabrizio
Institute of Affiliation	Fondazione Casa Sollievo della Sofferenza - I.R.C.C.S.
Title of the proposed project	The Role of Non-coding RNA in Lung Cancer Progression and Chemo-Immunotherapy Response
Short description of the project	Lung cancer remains the leading cause of cancer-related mortality worldwide, largely due to disease progression and variable responses to systemic therapies. In recent years, chemo-immunotherapy has become a standard of care for many patients with locally-advanced and advanced non-small cell lung cancer (NSCLC); however, primary and acquired resistance remain major clinical challenges. Emerging evidence indicates that non-coding RNAs (ncRNAs), including microRNAs, play a central role in regulating tumor cell plasticity, immune evasion, and therapeutic response. This work explores the contribution of ncRNAs to lung cancer progression and response to chemo-immunotherapy through their dynamic interaction with the lung cancer transcriptome and the tumor immune microenvironment. We highlight how ncRNAs modulate key oncogenic and immune-related pathways, including interferon signaling, antigen presentation, immune checkpoint regulation, and cancer cell plasticity. In particular, ncRNA-mediated regulation of immune checkpoint molecules such as PD-L1 and interferon-γ-responsive programs emerges as a critical determinant of immunotherapy sensitivity. By integrating bulk and single-cell transcriptomics, spatial profiling, and functional validation, this study aims to identify ncRNA-driven regulatory networks that underlie tumor evolution and therapy resistance. Understanding these mechanisms will provide a framework for the development of ncRNA-based biomarkers to predict response to chemo-immunotherapy and may uncover novel therapeutic vulnerabilities to improve clinical outcomes for patients with lung cancer. All research activities will be carried out at the Unit of Cancer Biomarkers, Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy.
Main research area for the project	Cancer biology
5 key words for the project	Immunotherapy, Lung ca., microRNA, Response and/or resistance to therapy, Functional genomics
Lab Website Link	https://www.cancerbiolab.com/

Lab. No. 8

Principal Investigator	Bodega Beatrice
Institute of Affiliation	Fondazione "Istituto Nazionale Genetica Molecolare - INGM"
Title of the proposed project	Translational development of LINE1-targeting RNA therapeutics to restore anti-tumor T-cell function
Short description of the project	T-cell dysfunction is a major barrier to effective anti-cancer immunity and limits the clinical benefit of immunotherapy in many patients. Our laboratory recently identified a new RNA-based regulatory mechanism controlling human T-cell states: LINE1-derived transcripts accumulate at chromatin in dysfunctional T cells and contribute to the repression of activation and effector programs. In Marasca et al., Nature Genetics, we showed that targeting LINE1-containing transcripts with antisense oligonucleotides (ASOs) can restore effector functions in exhausted tumor-infiltrating lymphocytes, supporting LINE1-derived RNAs as a new class of actionable immune-regulatory molecules. Building on this published work and on our ongoing AIRC Investigator Grant, this PhD project will develop LINE1-targeting RNA therapeutics for translational immuno-oncology. We have already generated solid single-cell RNA-sequencing datasets from CD3+ T cells infiltrating non-small-cell lung cancer and colorectal cancer, allowing us to characterize dysfunctional T-cell states and identify recurrent, TIL-associated LINE1 transcripts suitable for therapeutic targeting. The project will pursue three integrated objectives. First, the candidate will prioritize recurrent LINE1-containing transcripts associated with exhausted T-cell states across NSCLC and CRC samples and use this information to design transcript-informed ASOs. Second, selected ASOs will be tested in clinically relevant models of T-cell dysfunction, including in vitro exhausted T cells, ex vivo patient-derived TILs and tumor-T-cell co-culture systems, measuring target engagement, exhaustion markers, cytokine production, cytotoxicity and tumor-cell killing. Third, the project will explore T-cell-directed delivery strategies, including targeted lipid nanoparticles and antibody-guided approaches, to improve therapeutic selectivity and translational feasibility. This project is designed for a physician scientist interested in cancer immunology, RNA therapeutics and translational oncology. It will provide training in patient-derived immune profiling, RNA-targeting drug development, functional immunological assays and clinically oriented therapeutic validation, with the long-term goal of developing new strategies to overcome T-cell dysfunction and resistance to immunotherapy.
Main research area for the project	Molecular biology
5 key words for the project	Immunotherapy, Bioinformatics, Immunosuppression and/or suppressor cells, Tumor-Infiltrating Lymphocytes (TIL), Transcriptome/Transcriptomics
Lab Website Link	https://bodegalab.org

Lab. No. 9

Principal Investigator	Bossi Paolo
Institute of Affiliation	Humanitas Mirasole S.p.A.
Title of the proposed project	Translational and clinical activities related to trials for oral cancer prevention and treatment
Short description of the project	Oral squamous cell carcinoma (OSCC) has a poor prognosis, often diagnosed late. Oral potentially malignant disorders (OPMD) carry a risk of malignant transformation. Non-invasive monitoring via oral brushing and immuno-interception strategies, like CD40 agonists, show promise in preventing cancerization. In advanced OSCC, combining chemotherapy and immunotherapy may improve outcomes, optimizing treatment selection to enhance efficacy while minimizing unnecessary toxicity. The project is expected to enhance oral cancer prevention and early detection, by using non-invasive tools like oral brushing to identify high-risk individuals and lesions needing treatment, reducing reliance on invasive biopsies. The project also will evaluate how intralesional CD40 agonist injections in premalignant lesions may boost immune response while minimizing systemic toxicity. Translational research will clarify the mechanism of activity of the drug and identify responsive patients. Moreover, the project will look for predictive biomarkers for neoadjuvant chemo-immunotherapy so as to optimize patient selection and treatment monitoring, addressing emerging challenges in neoadjuvant immunotherapy. The impact on cancer will be at the following levels: a. Development of a prognostic model that integrates clinical, pathological, and molecular data to improve risk stratification in OPMD. b. Immunological, microbiota, and LOH analysis in OPMD patients treated with CD40 agonist to enhance patient selection and uncover resistance mechanisms. c. Identifying circulating or tissue biomarkers for neoadjuvant chemo-immunotherapy response to optimize OSCC patient treatment. The project will be carried on in Humanitas Mirasole (Milan) for what concerns the clinical part and in Humanitas University Laboratories for what concerns the translational activities.
Main research area for the project	Cancer biology
5 key words for the project	Head and neck ca., Precancerous lesions, Prevention and/or chemoprevention, Chemoimmunotherapy, Transcriptome/Transcriptomics
Lab Website Link	www.hunimed.eu

Lab. No. 10

Principal Investigator	Brancolini Claudio
Institute of Affiliation	Università degli Studi di Udine
Title of the proposed project	Targeting Epigenetic and 3D Genome Vulnerabilities in Uterine Leiomyosarcoma
Short description of the project	Uterine leiomyosarcoma (uLMS) is a rare and highly aggressive uterine cancer characterized by poor prognosis, high rates of metastasis, and limited therapeutic options. Although recurrent genetic alterations have been identified, these alone do not fully explain the disease's aggressive behavior or resistance to treatment. This project hypothesizes that uLMS progression is driven by extensive remodeling of enhancer networks and three-dimensional chromatin architecture, which establish oncogenic gene expression programs that promote tumor growth, metastasis, and therapy resistance. To investigate this hypothesis, the project in collaboration with the Dipartimento Mamma-Bambino (Azienda Ospedaliera Universitaria Friuli Centrale), will integrate patient-derived models with advanced multi-omics approaches and CRISPR-based epigenome engineering. First, a biobank of normal myometrium, uterine leiomyoma, and uLMS tissues, together with primary cell cultures and patient-derived organoids, will be established to provide robust experimental models. Second, the epigenetic and three-dimensional chromatin landscape of uLMS will be characterized using whole-genome sequencing, RNA sequencing (scRNA-seq), ChIP-seq (H3K27ac), and HiChIP. These complementary techniques will identify active enhancers, super-enhancers, chromatin interactions, and regulatory networks that are uniquely altered in malignant tissues. The final phase of the project will functionally validate candidate oncogenic distal regulatory elements using CRISPR interference (dCas9-KRAB) to silence selected enhancers. The effects on cell proliferation, invasion, apoptosis, drug sensitivity, and gene expression will determine whether these regulatory elements are essential for maintaining the malignant phenotype and therefore represent potential therapeutic targets. The expected outcome is the first comprehensive atlas of enhancer activity and chromatin organization in uLMS, providing new insights into the epigenetic mechanisms underlying tumor development and progression. Beyond advancing the understanding of uLMS biology, the project will generate valuable patient-derived resources, identify novel biomarkers for diagnosis and prognosis, and uncover enhancer-dependent molecular vulnerabilities that could support the development of innovative epigenetic therapies and precision medicine strategies for this devastating disease.
Main research area for the project	Cancer biology
5 key words for the project	Histone modifications, Gene expression and/or profile, Epigenetics, Soft tissue tumors, CRISPR/Cas9
Lab Website Link	https://people.uniud.it/page/claudio.brancolini

Lab. No. 11

Principal Investigator	Caretti Giuseppina
Institute of Affiliation	Università degli Studi di Milano
Title of the proposed project	The methylate SMYD3 Links Chromosomal Instability to the Cytosolic DNA Sensing in Breast Cancer
Short description of the project	Chromosomal instability (CIN) is a hallmark of breast cancer, present in approximately 89% of invasive cases. It plays a critical role in tumor development, disease progression, treatment response, and prognosis. In triple-negative breast cancer (TNBC)-an aggressive subtype lacking classical therapeutic targets-CIN is particularly prevalent and is strongly associated with errors in chromosome segregation during cell division. In triple-negative breast cancer CIN can chronically and pathologically activate pathways that sustain enhanced survival and growth of cancer cells through different signaling pathways, such as STAT3 and non-canonical NF-κB. SMYD3 is an epigenetic factor that adds methyl groups to histone and non-histone proteins. Importantly, it is overexpressed in various cancers, including breast cancer, and contributes to cellular proliferation through the regulation of signaling pathways such as Ras and through control of cell cycle progression. More recently, our group uncovered SMYD3 role in regulating the epithelial-to-mesenchymal transition (EMT)-a process tightly linked to invasiveness and metastasis-as well as its involvement in breast cancer stemness (manuscript submitted). SMYD3 role in multiple cancer-related mechanisms has driven the development of selective inhibitors of its activity, including BCI-121, EPZ031686, and the irreversible inhibitor EM127. These compounds have enabled new preclinical studies with key translational relevance, opening novel avenues to therapeutic strategies targeting SMYD3 in breast cancer. In this PhD project, the candidate will use recently developed inhibitors, advanced imaging techniques, next-generation sequencing, and both in vivo and in vitro approaches to investigate SMYD3 role in chromosomal instability and cancer development. This project offers the candidate the opportunity to gain expertise in epigenetics, cancer biology and next generation sequencing, with direct relevance to the development of new therapeutic approaches for triple-negative breast cancer.
Main research area for the project	Molecular biology
5 key words for the project	Genomic/Genetic instability, Epigenetics, Triple negative breast ca., Aneuploidy, Mitosis
Lab Website Link	https://www.unimi.it/it/ugov/person/giuseppina-caretti

Lab. No. 12

Principal Investigator	Cavallaro Ugo
Institute of Affiliation	Istituto Europeo di Oncologia I.R.C.C.S. S.r.l.
Title of the proposed project	Unraveling the ovarian cancer immune microenvironment and its response to immunotherapy through patient-derived models
Short description of the project	High-grade serous ovarian carcinoma (HGSOC) is a highly lethal tumor type, mainly due to the frequency of tumor relapse and acquired chemoresistance. As its prognosis has changed negligibly in the last thirty years, there is an acute need to identify new therapeutic targets and prognostic biomarkers that can improve HGSOC management. In this context, immunotherapy approaches based on immune checkpoint blockade have improved significantly the outcome of different tumor types. However, the response of HGSOC to such treatments remains unsatisfactory, and a deeper understanding of tumor biology is mandatory to design better immunotherapy strategies. HGSOC progression is driven by a subpopulation of ovarian cancer stem cell (OCSC, also defined as tumor-initiating cells) which, due to their intrinsic biological features, are able to overcome the chemotherapy cytotoxicity and to fuel peritoneal dissemination and tumor relapse, thus emerging as an ideal target for OC eradication. We have recently uncovered a molecular axis whereby the cancer-associated vasculature modulates the OCSC pathophysiology and, in particular, confers them with an immune-modulatory phenotype. The PhD project will capitalize on a platform of patient-derived experimental models, consisting of tissue explant cultures that preserve the original tumor microenvironment, including the immune compartment. This will enable the PhD student to: 1. Dissect the molecular basis of OCSC-driven rewiring of tumor immunity. 2. Identify molecular/cellular features of the vasculature/OCSC/immune axis in patient-derived models and investigate their potential role as clinically relevant biomarkers. 3. Explore the involvement of OCSC-dependent rewiring of tumor immunity in immunotherapy response, possibly unveiling actionable vulnerabilities to sensitize the tumor. This project is, therefore, poised to provide novel insights into HGSOC biology and to pave the way to innovative treatments to improve the outcome of such a devastating disease. The clinical duties of the PhD student will be carried out at the Istituto Europeo di Oncologia, Milano.
Main research area for the project	Cancer biology
5 key words for the project	Tumor-stroma interaction, Immunotherapy, Cancer stem cells, Ovarian ca., Immune escape
Lab Website Link	https://www.research.ieo.it/research-and-technology/principal-investigators/unit-of-gynecological-oncology-research/

Lab. No. 13

Principal Investigator	Cazzaniga Giovanni
Institute of Affiliation	Fondazione M. Tettamanti M. De Marchi Onlus
Title of the proposed project	Predisposition to childhood acute lymphoblastic leukemia: from genes to families and back
Short description of the project	Childhood acute lymphoblastic leukemia (ALL) is the most common pediatric cancer. Although cure rates are exceeding 90%, the causes of the disease remain largely unknown, many children with clinical features suggestive of cancer predisposition still lack molecular diagnosis, and the biological significance of many rare germline variants remains unresolved. The granted IG project aims to elucidate the genetic and biological basis of predisposition to childhood ALL through integrated approaches. Within this context, the PhD candidate will: 1) investigate large national cohorts of pediatric ALL by integrating germline sequencing and somatic data to identify novel susceptibility genes, characterize rare pathogenic variants, and define genotype-phenotype correlations, with particular attention to variants of uncertain significance in DNA repair, cohesin genes and other regulators of hematopoietic development. 2) Selected variants will undergo functional validation using cellular models, genome editing, transcriptomic analyses and assays of genome stability. 3) A major objective for the MD-PhD candidate is the translation of research findings into clinical practice. Starting from the questionnaire collected from 1500 patients, the candidate will actively contribute to the multidisciplinary Childhood Leukemia Predisposition Clinic, participating in patient recruitment, genetic counselling and implementation of standardized workflows for germline testing, variant interpretation and surveillance of individuals at increased cancer risk. The project will ultimately contribute to improving diagnosis, patient management and family counselling while laying the foundations for future strategies of early detection and leukemia prevention. Through close interaction between laboratory research and clinical activity, the candidate will acquire multidisciplinary expertise in pediatric hematology-oncology, human genetics, functional genomics and translational medicine, preparing for an independent career as a physician-scientist in pediatric cancer predisposition. Clinical duties for the MD-PhD (ideally a Pediatrician) can be carried out at the Pediatric Hematology-Oncology Unit of Fondazione IRCCS San Gerardo dei Tintori, Monza.
Main research area for the project	Cancer biology
5 key words for the project	Pediatric tumors, Hereditary tumors, Acute Lymphoblastic Leukemia (ALL), Precancerous lesions, Prevention and/or chemoprevention
Lab Website Link	https://fondazionetettamanti.it/centro-di-ricerca/

Lab. No. 14

Principal Investigator	Chiarle Roberto
Institute of Affiliation	Università degli Studi di Torino
Title of the proposed project	In vivo transduction of engineered TCRs for next-generation lung cancer therapy
Short description of the project	ALK-positive non-small cell lung cancer (ALK+ NSCLC) is a molecular subtype of lung cancer driven by oncogenic ALK fusion proteins that promote tumor growth and survival. Although ALK tyrosine kinase inhibitors (TKIs) have dramatically improved outcomes, most patients with advanced disease eventually develop resistance and experience relapse. As a result, ALK+ NSCLC remains largely incurable, highlighting the need for therapeutic strategies capable of eradicating residual disease and achieving durable remission. This project aims to develop ALK-directed T-cell receptor (TCR) immunotherapy delivered directly in vivo. Building on the identification of human and murine TCRs that specifically recognize ALK-derived antigens, we will evaluate approaches to engineer endogenous T cells through targeted delivery of ALK-specific TCR constructs using viral vectors or lipid nanoparticle (LNP)-based platforms. This strategy has the potential to overcome the complexity, cost, and manufacturing challenges associated with conventional ex vivo T-cell therapies while enabling scalable generation of ALK-reactive T cells within the patient. The anti-tumor activity of these in vivo-engineered ALK.TCR T cells will be assessed in preclinical models of ALK+ NSCLC, including models that mimic minimal residual disease and acquired resistance following ALK inhibitor therapy. We will also investigate how engineered T cells interact with the tumor microenvironment and host immune system to identify mechanisms that enhance therapeutic efficacy. Importantly, these studies will be conducted in parallel with a first-in-human clinical trial of ALK.TCR T-cell therapy for patients with ALK+ NSCLC, planned to open at the Dana-Farber Cancer Institute (DFCI) in summer 2027. This integrated translational effort will enable rapid bidirectional exchange between laboratory and clinical investigations, accelerating the development of a novel, scalable, and potentially curative immunotherapeutic strategy for patients with ALK+ NSCLC and other ALK-driven malignancies.
Main research area for the project	Molecular Therapy
5 key words for the project	Tyrosine kinase receptors (TKR) and/or inhibitors, Gene therapy, Neuroblastoma, CAR engineered cells
Lab Website Link	https://chiarlelab.com

Lab. No. 15

Principal Investigator	Condorelli Gerolama
Institute of Affiliation	Università degli Studi di Napoli “Federico II”
Title of the proposed project	Aptamer-based liquid biospy on EVs from breast cancer
Short description of the project	Breast cancer progression and therapeutic resistance are strongly influenced by interactions between tumor cells and the surrounding microenvironment. Extracellular vesicles (EVs) are emerging as key mediators of this communication, carrying proteins, nucleic acids, and signaling molecules that promote stromal activation, angiogenesis, immune modulation, and metastatic dissemination. At the same time, EVs released by cancer cells can be detected in body fluids, making them attractive candidates for liquid biopsy applications. This PhD project aims to investigate the biological role of EV-mediated communication in breast cancer and to develop innovative aptamer-based approaches for their detection and therapeutic targeting. The candidate will characterize tumor-derived EVs from breast cancer cell lines and patient samples, identify molecular determinants involved in tumor-stroma crosstalk, and evaluate their functional impact on fibroblasts, endothelial cells, and other components of the tumor microenvironment. A major translational focus of the project will be the development of liquid biopsy strategies based on RNA aptamers capable of selectively recognizing breast cancer-derived EVs in blood samples. By integrating aptamer technology with advanced biosensing platforms, the project aims to establish minimally invasive tools for early cancer detection, molecular stratification of patients, monitoring of treatment response, and identification of disease recurrence. The performance of aptamer-based EV detection will be evaluated in relation to clinical and pathological features and compared with established circulating biomarkers. The project will combine molecular biology, extracellular vesicle profiling, transcriptomic analyses, organoid models, and patient-derived samples to bridge fundamental cancer biology and translational medicine. The expected outcome is the identification of novel EV-associated biomarkers and the development of innovative diagnostic and therapeutic strategies for precision oncology.
Main research area for the project	Cancer biology
5 key words for the project	Tumor-stroma interaction, Breast ca., Exosomes and/or endogenous microvescicles, Cancer-associated fibroblasts
Lab Website Link	https://www.mmbm.unina.it/

Lab. No. 16

Principal Investigator	Costanzo Vincenzo
Institute of Affiliation	IFOM - Istituto Fondazione di Oncologia Molecolare, ETS
Title of the proposed project	Replication-stress-driven re-programming and immune escape in aggressive human cancers
Short description of the project	We have recently shown that a basic (AP) sites, among the most frequent DNA insults, induce replication stress (RS) by promoting single-stranded DNA gap formation in cancer cells (Hanthi, Mol Cell-2024). We have also demonstrated that RS in stem cells activates trophoblast-placental-like programs that support immune escape and tissue invasion (Atashpaz, Elife-2020). In agreement with these findings, preliminary analyses of aggressive tumors revealed high AP sites and gap densities that track with RS markers and expression of embryonic proteins linked to immune tolerance and evasion (Mauri, Santorelli et al Research Square 2025). Starting from these results the proposed project will unravel the connection between AP formation, RS induction and clinical aggressiveness, and test whether this axis represents a therapeutically exploitable weakness. The project will aim to characterize aggressive tumors and their metastases, including solid malignancies and advanced hematological cancers depending on availability and agreements with the clinical partner. During the first year the physician-scientist will secure ethical approval for a prospective biobanking protocol, collect pathology samples and implement case-report forms capturing treatment outcomes. These activities will confer Good Clinical Practice competence, embedding laboratory effort in a clinical framework. Samples will then undergo quantitative assessment of AP lesions and gaps, deep-proteome analysis, RNA- and DNA-seq profiling, and single-cell mapping. Statistical analysis will link these results with therapy response and survival. Patient-derived cells and organoids will be established to test synthetic-lethal combinations with available drugs that target the pathways unraveled by the multi-omics analyses. By combining these diverse approaches, the project aims to demonstrate that RS-driven reprogramming is a unifying, targetable vulnerability across diverse aggressive cancers. Majority of fellow's effort will be devoted to laboratory work at IFOM, with the remaining time embedded in the partnering service, ensuring continuous feedback between bench discoveries and bedside application.
Main research area for the project	Cancer biology
5 key words for the project	DNA repair, DNA damage, DNA replication
Lab Website Link	https://www.ifom.eu/it/ricerca-cancro/ricercatori/vincenzo-costanzo.php

Lab. No. 17

Principal Investigator	Costi Maria Paola
Institute of Affiliation	Università degli Studi di Modena e Reggio Emilia
Title of the proposed project	Multi-Omics studies of the Mechanism and Toxicity of a Novel Anticancer Drug in Colorectal Cancer
Short description of the project	This research program aims to advance a first-in-class thymidylate synthase (TS) dimer disruptor (DDi) as a novel strategy to exploit nucleotide metabolic vulnerabilities in drug-resistant colorectal cancer (CRC). Unlike conventional TS inhibitors such as 5-fluorouracil (5-FU), which inhibit the catalytic site while stabilizing the active TS homodimer and frequently promote TS accumulation and drug resistance, our allosteric inhibitors (Patent: 102025000013885) destabilize the TS homodimer, inducing rapid proteasomal degradation and sustained TS depletion. This fundamentally distinct mechanism converts nucleotide dependency into replication stress, exposing previously unrecognized therapeutic vulnerabilities. Our lead compounds have demonstrated strong translational potential: Pharmacokinetics: Favorable in vivo pharmacokinetic properties, with a half-life of 10-14 hours following intraperitoneal administration and prolonged exposure after oral dosing. Preclinical efficacy: Robust antitumor activity in colorectal cancer xenografts, ovarian cancer xenografts, and orthotopic pancreatic ductal adenocarcinoma (PDAC) mouse models, demonstrating efficacy comparable or superior to 5-FU across multiple tumor settings. Mechanistic activity: TS dimer destabilization induces rapid TS degradation, nucleotide imbalance, replication stress, DNA damage, ATR-CHK1 checkpoint activation, G2/M arrest, and apoptotic cell death, identifying TS as a critical metabolic vulnerability. Cancer stem cell targeting: DDis efficiently eradicate colorectal cancer spheroid cells (CR-CSphCs), maintaining activity independently of basal TS expression and targeting clinically relevant models of tumor heterogeneity and therapeutic resistance. The proposed research will integrate state-of-the-art non-animal methodologies (NAMs) with a comprehensive systems biology approach, combining quantitative proteomics, metabolomics, transcriptomics, advanced bioinformatics, and Oxford Nanopore DNA sequencing performed at the Human Technopole National Facility for Genomics. This allows to reach specific objectives related to understanding the mechanism of action at a deeper level, bioinformatic analyses will identify patterns of genomic instability, structural DNA alterations, and DNA damage-associated signatures linked to nucleotide depletion and replication stress. Then a verification process to integrate the different results will be performed.
Main research area for the project	Molecular Therapy
5 key words for the project	Pharmacology, Proteomics, Drug response and/or resistance, Drug discovery and/or development, DNA damage
Lab Website Link	https://www.mariapaolacosti.com

Lab. No. 18

Principal Investigator	Della Porta Matteo Giovanni
Institute of Affiliation	Università Humanitas
Title of the proposed project	Functional validation of clonal evolution patterns in myelodysplastic syndromes using bone marrow organoids
Short description of the project	Myelodysplastic syndromes (MDS) are clonal hematopoietic stem cell neoplasms characterized by ineffective hematopoiesis, peripheral cytopenias, and a variable risk of progression to acute myeloid leukemia (AML). These hematologic malignancies represent a unique in vivo model for studying the multistep process of neoplastic transformation of hematopoietic stem cells. In our previous work, we performed longitudinal single-cell multi-omics analyses to define trajectories of clonal evolution from MDS to AML, as well as patterns of treatment response and relapse. While these studies identified distinct evolutionary trajectories of malignant stem and progenitor cells, such observational approaches cannot establish direct causal relationships or fully elucidate how microenvironmental and immune factors drive clonal selection and disease progression. This PhD project aims to functionally validate clonal evolution patterns, treatment responses, and relapse mechanisms using human induced pluripotent stem cell (iPSC)-derived three-dimensional (3D) bone marrow organoids as a controlled experimental platform. The selected candidate will isolate patient-derived clonal hematopoietic cells and engraft them into 3D organoid systems designed to recapitulate the key structural and functional components of the bone marrow niche. Key research responsibilities will include: - Analyzing the functional expansion, persistence, and survival dynamics of malignant stem and progenitor cells within the 3D organoid environment. - Evaluating how specific microenvironmental conditions, including inflammatory and immunoregulatory states, selectively influence clonal trajectories over time. - Testing functional responses to clinically relevant pharmacological treatments to investigate mechanisms of drug resistance and disease relapse. - Integrating functional experimental readouts with single-cell molecular profiles to establish a robust link between descriptive patient-derived data and mechanistic functional validation. The PhD student will carry out his/her clinical and research activities at Humanitas University.
Main research area for the project	Cancer biology
5 key words for the project	Response and/or resistance to therapy, Prognosis, Immune escape, Organoids, Myelodisplastic syndromes (MDS)
Lab Website Link	https://www.humanitas-research.com/groups/matteo-della-porta-group/

Lab. No. 19

Principal Investigator	Demichelis Francesca
Institute of Affiliation	Università degli Studi di Trento
Title of the proposed project	Functional and Liquid Biopsy Genomics to Characterize PARP Inhibitor Responses in Prostate Cancer
Short description of the project	Poly (ADP-ribose) polymerase inhibitors (PARPi) have received regulatory approval for the treatment of several malignancies, including prostate cancer (PCa), a leading cause of cancer-related death among men. Although PARPi demonstrated remarkable therapeutic potential for PCa, important limitations have emerged - including a response rate of about 50% in patients with BRCA1/2 alterations and a heterogenous sensitivity to PARPi among patients with defects in DNA Damage Response and Repair genes (DDR)-underscoring the need for a better understanding of the molecular features of PARPi-responders and non-responders and for refined patient selection strategies. Building on yet unexplored dependencies nominated by in house CRISPR/Cas9 screens, which recently identified LIG1 as potential biomarker for PARPi response (Fracassi et al 2025), the project will investigate novel genetic dependencies that modulate PARPi treatment efficacy. In parallel, plasma samples from PARPi-treated PCa patients collected within the COROS observational multi-institutional trial (NCT06783127; access through the IG29370 to F.D.) will be analyzed to delineate the molecular underpinnings of treatment response and resistance. Through an iterative framework, candidate genes from functional genomic screens will be investigated in patient-derived molecular data and clinically informed findings will be integrated with screening results and validated and characterized in vitro. The activities related to the project include engineering of PCa cell lines using CRISPR/Cas and RNA interference, assessment of cell viability and cell death with metabolic assays and flow cytometry, isolation and sequencing of cell free DNA, interrogation of extracellular vesicle cargo (RNA and selected proteins), and integration of molecular findings with clinical variables.
Main research area for the project	Genomic medicine
5 key words for the project	Prostate ca., BRCA, Response and/or resistance to therapy, Liquid biopsy
Lab Website Link	https://www.cibio.unitn.it/83/laboratory-of-computational-and-functional-oncology

Lab. No. 20

Principal Investigator	Facciotti Federica
Institute of Affiliation	Università degli Studi di Milano – Bicocca
Title of the proposed project	Spatial Multi-Omics Mapping of the Intestinal Microenvironment in Colitis-Associated Cancer
Short description of the project	Background and Rationale Patients with longstanding Inflammatory Bowel Disease (IBD) face a two-fold increased risk of developing colitis-associated colorectal cancer (CAC) compared to the general population. Despite advances in endoscopic surveillance, the cellular and molecular events driving the transition from chronic inflammation to malignant transformation remain poorly understood. Interleukin-22 (IL-22), produced by tissue-resident immune cells including conventional T and unconventional T cells, plays a dual role: sustaining mucosal healing in IBD while potentially promoting epithelial proliferation and tumorigenesis. The gut microbiome produces AhR ligands capable of polarizing T cells towards an IL-22-secreting phenotype. However, the spatial architecture of this microbiome-immune-epithelium circuit in pre-cancerous and cancerous intestinal tissues has never been systematically characterized. Overall Aim This PhD project aims to spatially resolve the IL-22-dependent cellular and molecular programs mediating CAC development by integrating state-of-the-art spatial multi-omics technologies at the single-cell level. Experimental Plan The project will unfold across four years. In Year 1, spatial transcriptomics (10X Genomics Xenium, 5,000-gene panel) will be performed on FFPE tissue sections from CAC, pre-CAC, IBD, and sporadic CRC patients (n≥55), mapping IL-22-producing cell populations and their transcriptional neighborhoods. In Year 2, spatial proteomics via multiplex iterative immunofluorescence (MACSIMA Miltenyi, up to 50 markers/slide) will phenotypically and functionally characterize immune, epithelial, and stromal compartments, including conventional and unconventional T cell subsets. In Year 3, MALDI-Mass Spectrometry Imaging will spatially localize microbial-derived metabolites and (iNK)T-stimulatory lipids within the same tissue specimens. In Year 4, multi-modal data integration using cloud-based bioinformatic pipelines (Squidpy, Scanpy, Seurat, Novae) will reconstruct cellular niches and temporal dynamics of IL-22-mediated microenvironment remodeling across disease stages. Expected Outcomes This project will generate the first spatially resolved, multi-omic atlas of the CAC microenvironment, identifying actionable cellular and molecular targets for CAC prevention in IBD patients.
Main research area for the project	Immunology
5 key words for the project	NK and/or NKT cells, Cytokines/Interleukins, Mouse models, Colorectal and/or Intestinal ca., Microbiome
Lab Website Link	https://www.unimib.it/federica-facciotti

Lab. No. 21

Principal Investigator	Fazio Grazia
Institute of Affiliation	Fondazione M. Tettamanti M. De Marchi Onlus
Title of the proposed project	Advanced proteomic characterization of relapse and immunotherapy resistance in PAX5-rearranged pediatric B-cell Leukemia
Short description of the project	Pediatric B-cell precursor acute lymphoblastic leukemia (BCP-ALL) harboring alterations of the PAX5 gene represents a biologically distinct subgroup associated with poor clinical outcomes, yet its molecular mechanisms remain poorly characterized. PAX5 is a key regulator of B-cell differentiation and directly controls the transcription of genes involved in B-cell identity, including CD19. Alterations affecting PAX5 may therefore contribute not only to leukemogenesis but also to immune escape mechanisms associated with CD19 loss after treatment with Blinatumomab or CD19-directed CAR-T cells, an issue of increasing clinical relevance with the progressive introduction of immunotherapy into frontline treatment protocols. Within the AIEOP-BFM ALL protocols, PAX5r cases have been identified and Whole Transcriptome Sequencing (RNA-seq) performed by our group on diagnostic samples from pediatric BCP-ALL patients enrolled across Italian centers, identifying a specific transcriptional signature in PAX5-rearranged cases. The aim of this project is to extend the analysis to sequential relapse samples in order to investigate mechanisms of clonal evolution, treatment adaptation, and relapse occurrence, even after immunotherapy. Particular attention will be devoted to understanding whether PAX5 alterations contribute to CD19 downregulation and resistance to immunotherapy. Transcriptomic analyses will be integrated with high-dimensional single-cell proteomic profiling using Cytometry by Time-Of-Flight (CyTOF). Customized metal-conjugated antibody panels will be developed to characterize signaling pathways, cellular heterogeneity, and leukemic subpopulations at the single-cell level, as well as to identify novel predictive biomarkers and potential therapeutic targets. The integration of transcriptomic and proteomic data is expected to provide novel insights into the biology of PAX5-altered BCP-ALL, identify biomarkers predictive of adverse outcomes, and uncover potential therapeutic vulnerabilities. The PhD candidate will carry out clinical activity at Tettamanti Center, located within the Pediatric Hematology Unit of IRCCS Fondazione San Gerardo dei Tintori, a leading center in pediatric hematologic malignancies and translational leukemia research.
Main research area for the project	Cancer biology
5 key words for the project	Pediatric tumors, Acute Lymphoblastic Leukemia (ALL), Fusion genes, Preclinical studies, Next generation sequencing
Lab Website Link	https://fondazionetettamanti.it/centro-di-ricerca/

Lab. No. 22

Principal Investigator	Ficara Francesca
Institute of Affiliation	Humanitas Mirasole S.p.A.
Title of the proposed project	Targeting PBX as a novel therapy for myeloproliferative neoplasm: effect on disease course through innovative assays.
Short description of the project	Myeloproliferative neoplasms (MPN) are heterogeneous blood malignancies associated with increased risk of leukemic transformation and of inflammation-related thrombotic events. MPN are initiated by somatic mutations occurring in hematopoietic stem and progenitor cells (HSPC) that result in unregulated activation of the JAK/STAT pathway. By exploiting an MPN mouse model, we uncovered a role for the transcription factor PBX1 in driving tumor progression; upon PBX1 genetic inactivation, typical MPN features did not develop or resolved over time, with reversion of the aberrant HSPC transcriptome including downregulation of inflammation-related genes. We are currently exploiting PBX1 as a therapeutic target, taking advantage of the recently developed small molecule T417 that inhibits PBX1 binding to DNA. Preliminary data obtained in our mouse model of MPN indicate that the administration of T417 rescues the thrombocytosis typical of the disease. The aim of the PhD project is to study the effect of T417 on patient's cells through novel xenotransplantation assays and in vitro 3D models that recapitulate the bone marrow microenvironment. Through these tools the candidate will assess if targeting PBX1 dampens the malignant clone, reverts MPN features, and/or resolves inflammation. This research will establish if PBX1 inhibition, compared to or in combination with other treatment modalities, could serve as a novel and more targeted therapy in MPN. While current therapies reduce the risk of adverse events and improve quality of life, they are not curative, leaving unmet clinical needs. This study will provide a proof of principle for using approaches acting at the HSPC level. The project will be carried out at the Humanitas Research Hospital and will take advantage of the local Biobank; the PI is part of the CALR (Center for Accelerating Leukemia/Lymphoma Research) consortium led by Prof. Matteo Della Porta and benefits from daily interactions with the hematologists of the Humanitas Cancer Center.
Main research area for the project	Cancer biology
5 key words for the project	Drug response and/or resistance, Hematopoiesis, Mouse models, Hematopoietic stem cells, Myeloproliferative neoplasms
Lab Website Link	https://www.humanitas-research.com/researchers/francesca-ficara/

Lab. No. 23

Principal Investigator	Fiermonte Giuseppe
Institute of Affiliation	Università degli Studi di Bari Aldo Moro
Title of the proposed project	Human Genetically Defined PDAC Organoids to Identify Early Diagnostic Biomarkers
Short description of the project	Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies, largely due to late diagnosis and the lack of effective early detection strategies. PDAC development is driven by the progressive accumulation of genetic alterations, most commonly involving KRAS, TP53, CDKN2A, and SMAD4. However, the molecular and metabolic events associated with the sequential acquisition of these alterations remain poorly understood. Our laboratory has established human induced pluripotent stem cell (iPSC)-derived pancreatic organoid models carrying inducible oncogenic KRAS alone or in combination with mutant TP53, providing a unique platform to study early stages of pancreatic tumorigenesis. Building on these preliminary models, the PhD candidate will generate and characterize additional organoid lines with CDKN2A and SMAD4 downregulation, creating a genetically defined series that recapitulates the stepwise evolution of PDAC. The project will investigate how the progressive accumulation of these driver events reshapes cellular identity, signaling pathways, and metabolic programs during malignant transformation. To achieve this, the candidate will apply integrated multi-omics approaches, including transcriptomic profiling by RNA sequencing and characterization of the secretome through extracellular vesicle analysis, small RNA sequencing, and metabolomic profiling. A major objective of the project will be the identification of molecular and metabolic biomarkers associated with early PDAC development. Candidate biomarkers will be prioritized through integrative computational analyses and validated using publicly available patient datasets to assess their clinical relevance. This interdisciplinary project combines stem cell biology, cancer genetics, organoid technology, and multi-omics approaches to address fundamental questions in pancreatic cancer initiation. The resulting models are expected to provide novel insights into the earliest stages of PDAC development, reveal candidate biomarkers for early detection, and establish a versatile platform for future mechanistic and therapeutic studies.
Main research area for the project	Cancer biology
5 key words for the project	Mitochondria, Oxidative stress and/or Reactive Oxygen Species (ROS), Metabolism/Metabolomics, Glucose metabolism and/or Warburg effect, Cell metabolism
Lab Website Link	https://www.uniba.it/en/

Lab. No. 24

Principal Investigator	Gargliardi Paolo Armando
Institute of Affiliation	Università degli Studi di Torino
Title of the proposed project	Multiplexed single-cell measurements of ERK/JNK/p38 dynamics to predict colorectal cancer response to chemotherapy
Short description of the project	Even genetically identical cancer cells can show heterogeneous responses to therapy. Some cells die rapidly, others die only after prolonged treatment, while others enter drug-tolerant states and survive despite therapy. An intriguing possibility is that intrinsic cellular variability and microenvironmental cues place cancer cells in distinct dynamic signaling states that ultimately shape therapeutic response. However, signal transduction is highly dynamic and remarkably variable at the single-cell level. For example, epithelial mammary cells display pulsatile MAPK/ERK activity when monitored by live microscopy using fluorescent biosensors, and the frequency of ERK pulses correlates with cell survival or death upon treatment with doxorubicin. The field of fluorescent biosensors is rapidly expanding and now includes reporters for stress-response pathways such as JNK and p38-MAPK, both of which are critically involved in cancer cell responses to drug-induced stress. We hypothesize that multiplexed live-cell biosensor measurements can reveal dynamic signaling states that predict therapeutic response in colorectal cancer. We will combine fluorescent reporters for MAPK/ERK, JNK and p38-MAPK in colorectal cancer models ranging from established cell lines to cancer organoids treated with clinically relevant chemotherapeutic agents, including 5-FU, irinotecan, oxaliplatin and combination regimens such as FOLFIRI. This approach will generate single-cell temporal measurements from thousands of cells, linking pathway dynamics to cell fate decisions such as mitosis, apoptosis, arrest, and survival. Computational analysis will be used to extract temporal and spatial features of signaling across the three pathways and identify dynamic fingerprints associated with sensitivity, delayed response, or drug tolerance. Finally, pharmacological and genetic perturbations of critical pathway nodes will test whether these signaling states can be shifted to enhance chemotherapy-induced cell death or prevent the emergence of tolerant cells. The long-term goal is to identify rational combinations of colorectal cancer chemotherapeutic agents with modulators of MAPK, JNK, or p38 signaling to improve therapeutic efficacy.
Main research area for the project	Cancer biology
5 key words for the project	Cell signaling, Chemotherapy and/or chemotherapic drugs, MAP Kinases, In vitro imaging and/or live cell imaging, Fluorescence imaging system
Lab Website Link	https://sites.google.com/view/cancer-cell-dynamics-lab

Lab. No. 25

Principal Investigator	Geginat Jens Albrecht
Institute of Affiliation	Fondazione "Istituto Nazionale Genetica Molecolare - INGM"
Title of the proposed project	Dissecting the IL-10/IL10R axis in human Melanoma: Spatial immunophenotyping to predict immunotherapy response.
Short description of the project	Background: Cytotoxic T cells (CTL) mediate anti-tumor responses and are mainly CD8+, but CD4+ T-cells can also differentiate to CTL and exert complementary functions. CD4+ regulatory T cells (Treg) are in contrast immunosuppressive and impair effective CTL responses, thus playing a pro-tumorigenic role. There are at least two subsets of Tregs, i.e. FOXP3+Tregs and EOMES+ type 1 regulatory T cells (Tr1) that are enriched in tumors and possess IL-10 producing capacities. The identity of cells that actually produce IL-10 in human tumours and their targets are however unknown. We demonstrated previously that EOMES^{+}Tr1-like cells accumulate in melanomas, were associated with poor survival but also with response to ICB. Moreover, unpublished data suggests that IL-10 produced by Tr1-cells inhibits CD8+T-cell responses, promotes tumor growth and is required for the therapeutic effect of ICB in melanoma-bearing mice. Aims: The proposal will identify IL-10 producing immune cells and their targets in primary melanomas with different responses to ICB. Experimental Design: We will use imaging mass spectrometry and/or the multiparametric MACSIMA immaging platform on FFPE human melanoma sections to characterize tumor-infiltrating lymphocytes. We will assess the relevance of IL-10-associated immune phenotypes for immunotherapy responsiveness by analyzing tumor sections from melanoma patients who received ICB with documented positive or negative clinical outcomes. Moreover, FRET-based imaging with the Abberior Stedycon super-resolution system will be used to identify IL-10/IL-10R interactions. Impact on cancer: This project combines innovative technologies with clinically relevant human samples to achieve a mechanistic understanding with high translational potential. Indeed, unraveling the cellular and molecular mechanisms that cause resistance to Immune checkpoint blockade (ICB) in melanoma is crucial to improve treatment efficacy and stratify patients. By establishing the identity of IL-10-producing cells and their targets within the tumor microenvironment, we might also provide a rationale to block IL-10 to treat melanoma.
Main research area for the project	Immunology
5 key words for the project	Melanoma, Immunotherapy, Treg Cells, Cytokines/Interleukins, T cells/TCR
Lab Website Link	https://ingm.org/en/geginat_lab_eng/

Lab. No. 26

Principal Investigator	Giacomini Arianna
Institute of Affiliation	Università degli Studi di Brescia
Title of the proposed project	Novel small molecule FGF traps as drug candidates for cancer therapy: from biophysical screening to in vivo validation
Short description of the project	The fibroblast growth factor (FGF)/FGF receptor (FGFR) signalling pathway is a key driver of tumor progression, promoting cancer cell proliferation, survival, angiogenesis, and resistance to therapy. Aberrant activation of this pathway is frequently observed across multiple cancer types and represents a major mechanism of escape from anti-angiogenic treatments. Although FGFR tyrosine kinase inhibitors have shown clinical efficacy, their use is often limited by systemic toxicity, on-target/off-tumor effects, and acquired resistance. To overcome these limitations, our research focuses on an innovative therapeutic strategy based on small-molecule FGF traps. We previously identified NSC12, the first orally available pan-FGF trap capable of inhibiting tumor growth and angiogenesis in several preclinical cancer models (Ronca and Giacomini et al., Cancer Cell, 2015). Despite these promising results, NSC12 displays suboptimal pharmacological properties that prevent its further development. In collaboration with Prof. Mor's laboratory at the University of Parma, we recently generated a novel series of non-steroidal NSC12 derivatives with improved chemical and pharmacological properties. Preliminary structure-activity relationship studies identified molecular determinants regulating FGF binding and selectivity, providing a framework for the rational optimization of next-generation compounds. The aim of this project is to develop highly selective small-molecule FGF traps with enhanced affinity, drug-like properties, and anti-tumor activity. We will integrate computational drug design, medicinal chemistry, biophysical characterization of ligand-FGF interactions, and functional validation in FGF-dependent biological systems by using in vitro, ex vivo and in vivo models. Lead compounds will be evaluated for (i) anti-angiogenic activity, (ii) anti-tumor activity in relevant human models, including aggressive non-Hodgkin lymphomas, and (iii) toxicity. By targeting extracellular FGF ligands rather than intracellular FGFR kinase activity, this project proposes a first-in-class therapeutic strategy expected to overcome the limitations of current FGFR inhibitors. Successful completion will provide novel drug candidates and establish a broadly applicable platform for treating FGF-driven malignancies.
Main research area for the project	Cancer biology
5 key words for the project	Lymphomas, Target therapy, FGF and/or receptor, Small molecule inhibitors
Lab Website Link	https://www.unibs.it/it

Lab. No. 27

Principal Investigator	Iannacone Matteo
Institute of Affiliation	Università Vita-Salute San Raffaele
Title of the proposed project	Restoring Immune Surveillance in Liver Tumors through Endothelial Reprogramming
Short description of the project	The liver is a frequent site of primary and secondary malignancies, including hepatocellular carcinoma, cholangiocarcinoma, and metastases from colorectal and other cancers. Despite major advances in cancer immunotherapy, many liver tumors remain poorly responsive to immune-based treatments. Emerging evidence suggests that alterations in the tumor vasculature may represent a previously underappreciated mechanism of immune escape. This PhD project will investigate how endothelial cells regulate immune surveillance across different liver tumors and how vascular remodeling influences the ability of cytotoxic lymphocytes to detect and eliminate malignant cells. The candidate will combine analyses of human tumor specimens with advanced mouse models, intravital microscopy, spatial transcriptomics, single-cell genomics, and functional immunological approaches to define the molecular pathways controlling endothelial plasticity during tumor progression. The project will focus on three objectives: (i) identifying endothelial programs associated with immune-permissive and immune-resistant tumor states; (ii) determining how vascular remodeling alters communication between tumor cells and immune cells within the liver microenvironment; and (iii) developing strategies to reprogram the tumor vasculature and restore effective anti-tumor immunity. Particular emphasis will be placed on understanding whether common vascular mechanisms operate across different liver tumor types and can be therapeutically targeted. The candidate will receive multidisciplinary training in cancer immunology, vascular biology, imaging, genomics, and translational oncology within a highly interactive research environment. The project offers extensive opportunities for interaction with clinicians, surgeons, pathologists, and computational biologists, with the ultimate goal of developing innovative therapeutic approaches for patients with liver cancer. Clinical duties (20% effort) can be carried out at IRCCS Ospedale San Raffaele, Milan, within the candidate's specialty program or through affiliated clinical units, subject to agreement with the relevant specialty school.
Main research area for the project	Immunology
5 keywords for the project	Innate immunity, Immunotherapy, Endothelial cells, Hepatocellular carcinoma (HCC), Metastasis
Lab Website Link	www.iannaconelab.com

Lab. No. 28

Principal Investigator	Lugli Enrico
Institute of Affiliation	Humanitas Mirasole S.p.A.
Title of the proposed project	Biomarkers of anti-tumor response in solid tumors treated with combination immunotherapy targeting immunosuppression
Short description of the project	Immune checkpoint blockade revolutionized cancer therapy but a number of patients fail to respond because of primary or secondary mechanisms of resistance, in many cases involving a suppressive architecture of the tumor microenvironment. Our lab has previously identified intratumoral and systemic T-cell characteristics associated with improved progression and enhanced response to cancer immunotherapy. Immunosuppressive T cell populations, particularly those with effector characteristics, play a critical role in blocking anti-tumor immune responses and are associated with poor prognosis across multiple solid tumor types. Preclinical data suggest that combining immunosuppressive T-cell depletion with anti-PD-1/PD-L1 immunotherapy enhances anti-tumor activity, yet its immunodynamic effects in humans are still unknown. At the Humanitas Research Hospital in Milan, we designed an innovative clinical trial targeting immunosuppressive T cell populations in combination with immune checkpoint blockade immunotherapy in metastatic solid tumor patients, with a major focus on translational endpoints and biomarker discovery. Serial multi-tissue biopsies and blood samples will be collected pre- and post-treatment to capture immune changes. Multiomics cellular, molecular and spatial technologies will profile circulating immune subsets, the spatial architecture of tumors and systemic changes to identify biomarkers undergoing modulation with, and predicting response to combination immunotherapy. Following results from this trial, we anticipate to conduct follow-up clinical and laboratory studies where the cohort of most sensitive tumors will be expanded and the combined immunotherapy optimized for improved efficacy. The successful MD candidate will have clinical expertise in solid tumor oncology and basic laboratory expertise in cellular immunology, molecular biology, biochemistry or related fields. Access to Humanitas facilities (flow cytometry, genomics, histology, microscopy, metabolomics and advanced bioinformatics) will be granted.
Main research area for the project	Immunology
5 keywords for the project	Cytotoxic T Lymphocytes (CTL), Treg cells, Combination therapy, Clinical trials, Tumor-Infiltrating Lymphocytes (TIL)
Lab Website Link	https://www.humanitas-research.com/groups/enrico-lugli-group/

Lab. No. 29

Principal Investigator	Marcenaro Emanuela
Institute of Affiliation	Università degli Studi di Genova
Title of the proposed project	Reprogramming NK cell dysfunction in breast and ovarian cancers to enhance immunotherapy efficacy
Short description of the project	The proposed PhD project aims to define the phenotypic, functional, and spatial heterogeneity of Natural Killer (NK) cells within the tumor microenvironment (TME) of women's cancers, focusing on breast and ovarian malignancies. Despite being key effectors of anti-tumor immunity, NK cells are frequently functionally impaired in solid tumors, where tumor-immune interactions and immune checkpoint pathways drive immune escape and heterogeneous responses to immunotherapy. Building on ongoing work in tumor immunology and NK-cell biology, including previous characterization of NK-cell receptor repertoires in breast and gynecological cancers, this project will integrate multi-omics (transcriptomics and proteomics) and functional approaches to define NK-cell states associated with immune dysfunction and clinical outcome. The candidate will combine multiparametric flow cytometry, in vitro functional assays, bulk and single-cell RNA sequencing, and spatial transcriptomics to generate a spatially resolved map of NK-cell biology across tumor tissue, blood, and clinically relevant compartments. A central goal is to decode receptor-ligand networks, immune checkpoint landscapes, and NK-cell spatial organization within tumor and stromal niches, to identify functionally relevant subsets and predictive biomarkers of response or resistance to immunotherapy. Mechanistic insights will be validated in vivo using tumor models to interrogate NK-tumor cell interactions in a physiologically relevant context and to test strategies aimed at restoring NK-cell function, including blocking monoclonal antibodies targeting immune checkpoints such as PD-1 and NKG2A. The project will be conducted at the Molecular Immunology Laboratory (DIMES), University of Genoa, in close collaboration with IRCCS AOU San Martino Hospital, where clinical samples will be collected. The candidate will be involved in translational research and may participate in clinical observation within breast and gynecological oncology units. This program will train a physician-scientist at the interface of tumor immunology, multi-omics, and translational oncology, aiming to develop more precise NK-cell-based immunotherapeutic strategies for women's cancers.
Main research area for the project	Immunology
5 keywords for the project	Breast ca., Immunotherapy, NK and/or NKT cells, Cervix or endometrial ca., Ovarian ca.
Lab Website Link	https://rubrica.unige.it/personale/UkNHWlJh

Lab. No. 30

Principal Investigator	Mazzanti Chiara Maria
Institute of Affiliation	Fondazione Pisana per la Scienza Onlus
Title of the proposed project	Beyond Pathology: Integrating FLIM and MALDI Imaging for Hidden Ultrastructural Insights in Glioblastoma
Short description of the project	Glioblastoma (GBM) is a highly heterogeneous malignancy where conventional histopathology lacks spatial-functional resolution. This project introduces an innovative translational approach by integrating standard diagnostics with advanced imaging and multi-omics to resolve hidden metabolic and ultrastructural profiles. The research relies on an established pipeline of GBM models (paraffin sections, organotypic slices, tumoroids, cell lines) and an ongoing repository that currently includes over 200 patient-derived vital tumor tissues, which are progressively undergoing comprehensive genomic, transcriptomic, and methylomic characterization. Multimodal imaging will be performed on identical tissue coordinates: mapping spatial metabolism via endogenous NADH lifetime, evaluating chromatin compaction through DAPI lifetime analysis, and acquiring lipidomic profiles via MALDI-imaging. These advanced datasets will be co-registered and overlapped with gold-standard Hematoxylin and Eosin (H&E) staining. This multimodal strategy allows the identification of deeper layers of information invisible to standard methodologies; by integrating these parameters with existing oncological data, it is possible to enrich the insights extracted from a single tissue section, which fundamentally represents a spatial snapshot of the tumor during its temporal progression. Within this framework, since the omics profiling is currently ongoing, the PhD candidate will actively participate in and learn these high-throughput technologies, gaining comprehensive research experience spanning genomics, biophotonics, MALDI imaging, and machine learning. Concurrently, the student's background in brain tumor anatomy will be highly complementary to the laboratory's workflows, specifically aiding in the evaluation and structural recognition of patient-derived vital tissues. The candidate will guide data integration by annotating histopathological features on H&E slides, ensuring that physical, metabolic, and lipidomic readouts are correctly mapped onto classical microscopic structures and tumor niches. This approach holds significant potential to refine conventional pathology and identify novel approaches for patient stratification. The ideal candidate is a medical doctor trained in Neuropathology or Anatomical Pathology eager to embrace digital pathology, genomics, biophotonics, and machine learning.
Main research area for the project	Cancer biology
5 keywords for the project	Glioma and/or glioblastoma – Genomics - Patient risk stratification - Fluorescence imaging system - Machine learning
Lab Website Link	https://www.fpscience.it/

Lab. No. 31

Principal Investigator	Morandi Andrea
Institute of Affiliation	Università degli Studi di Firenze
Title of the proposed project	Investigating the role of peroxisomes in modulating radiotherapy response in breast cancer
Short description of the project	Radiation therapy (RT) remains a cornerstone of breast cancer treatment, especially in early-stage disease and as a postoperative modality. While the molecular mechanisms underpinning resistance to systemic therapies in estrogen receptor-positive (ER+) breast cancer have been extensively investigated, far less is known about cellular processes that contribute to radio-resistance in this subset. Emerging data implicate peroxisomes, key regulators of redox homeostasis, lipid metabolism, and innate immune signaling, as crucial players in therapy adaptation. Given their role in managing oxidative stress, peroxisomes may influence how tumor cells respond to ionizing radiation. This PhD project aims to explore the contribution of peroxisomes to the cellular response and adaptation to RT in ER+ BC. Specifically, the project will: (a) define how peroxisome abundance and activity change upon radiation exposure in ER+ breast cancer models; (b) elucidate how peroxisomes influence redox dynamics, DNA damage response, lipid metabolism and immune signaling; (c) investigate whether modulating peroxisome function (genetically or pharmacologically) alters radiosensitivity and survival post-radiation; (d) identify potential peroxisome-related biomarkers predictive of radio-resistance using patient-derived samples and transcriptomic data. The project will leverage a multidisciplinary approach combining cell line models, 3D organoids, and patient-derived xenografts-organoids (PDXO), complemented by multi-omic profiling (transcriptomics, metabolomics, and redox flux analysis). CRISPR-based perturbation and small-molecule inhibitors will be used to modulate peroxisome function. Radiation response will be assessed through clonogenic survival, DNA damage assays, and immune signaling profiling. This research will uncover novel insights into peroxisome-mediated mechanisms of radio-response and resistance in ER+ breast cancer, potentially revealing therapeutic vulnerabilities and informing precision RT strategies. The findings could pave the way for integrating peroxisome-targeting agents with RT to enhance efficacy and delay recurrence in ER+ breast cancer patients.
Main research area for the project	Cancer biology
5 keywords for the project	Breast ca. - Drug response and/or resistance - Estrogens and/or receptors - Response and/or resistance to therapy - Metabolism/Metabolomics
Lab Website Link	https://www.sbsc.unifi.it/vp-326-gruppo-morandi.html

Lab. No. 32

Principal Investigator	Morotti Alessandro
Institute of Affiliation	Università degli Studi di Torino
Title of the proposed project	Platelet function evaluation in patient with lung cancer
Short description of the project	Solid cancers, and in particular Lung cancer, are associated with a markedly increased risk of arterial and venous thromboembolic events, which substantially contribute to morbidity and mortality. Emerging evidence indicates that platelets actively participate not only in thrombosis but also in tumor progression, immune evasion, and metastasis. However, the functional characteristics of platelets in patients with lung cancer remain poorly understood, and reliable biomarkers for thrombotic risk stratification are currently lacking. This PhD project aims to investigate platelet function in patients with non-small cell and small cell lung cancer, evaluating its relationship with tumor molecular profile, disease stage, metastatic burden, and clinical outcomes. The study will combine prospective and retrospective patient cohorts to characterize platelet reactivity using state-of-the-art functional assays, including platelet aggregation testing, flow cytometry, intracellular signalling analysis, ELISA-based inflammatory pathway assessment, and platelet metabolomics. Functional findings will be integrated with clinical, laboratory, and molecular data to identify biomarkers associated with thrombotic complications and disease progression. The project is expected to improve the understanding of the mechanisms linking cancer biology and platelet activation, identify patient subgroups at particularly high thrombotic risk, and provide the basis for personalized strategies for thromboprophylaxis and antithrombotic treatment. In addition, the identification of platelet-related biomarkers may offer novel prognostic indicators and contribute to the development of precision medicine approaches in thoracic oncology. The research will be conducted at the TRECIM Laboratory (dept. of Clinical and Biological Sciences, Orbassano, University of Turin), where advanced expertise in platelet biology, translational thrombosis research, and biomarker discovery provides an ideal environment for multidisciplinary investigation and the translation of laboratory findings into clinical practice.
Main research area for the project	Cancer biology
5 keywords for the project	Tumor-stroma interaction – Microenvironment - Cell migration, motility and/or invasion – Metastasis - Hemostasis and thrombosis
Lab Website Link	https://www.dscb.unito.it/do/home.pl?_nfls=false

Lab. No. 33

Principal Investigator	Muzi Falconi Marco
Institute of Affiliation	Università degli Studi di Milano
Title of the proposed project	A novel gene modulating genomic instability in cancer cells: mechanisms and functions in chromatin regulation
Short description of the project	Transcription-replication conflicts and genome instability are major vulnerabilities of cancer cells. Non-canonical nucleic acid structures, including R-loops and G-quadruplexes, are important sources of these conflicts because they can obstruct DNA replication and repair. They impair replication fork progression, promote DNA damage, and contribute to mutations and chromosomal rearrangements. G-quadruplexes are enriched in regulatory regions, oncogenes, repetitive sequences, and telomeres, where they can induce replication stress and genome fragility. We recently identified in human cells a putative orthologue of Saccharomyces cerevisiae Vid22, a G4-binding protein. Both proteins contain conserved BED and RNase H-like domains, suggesting an evolutionarily conserved role in nucleic acid metabolism. Mass spectrometry analysis of proteins interactors identified several crucial chromatin regulators. Loss of the Vid22 orthologue leads to micronuclei formation, increased MYC and KRAS expression, deregulation of inflammatory pathways, and altered expression of histone genes, supporting its role in genome and chromatin homeostasis. This project will test the hypothesis that the human orthologue of Vid22 protects cancer-relevant genomic regions from G4- and R-loop-associated instability by coordinating chromatin remodeling, transcription, replication, DNA repair, and checkpoint signaling. We will define how it functionally interacts with chromatin remodellers to control replication stress responses and transcription-replication conflicts. By combining molecular, genomic, and cellular approaches, the PhD student will determine whether this novel human gene acts as a guardian of difficult-to-replicate genomic regions and will clarify how its dysfunction contributes to cancer-associated genome instability. The proposed work links mechanistic cancer biology to clinically relevant questions on genome maintenance, oncogene activation, inflammatory signaling, and potential therapeutic vulnerabilities. The Department of Biosciences, University of Milano, offers access to all the relevant facilities and an international and scientifically stimulating environment. The PhD student will be supported by a senior lab member and will be trained in state of the art molecular biology and genomics approaches.
Main research area for the project	Molecular biology
5 keywords for the project	DNA damage - Genomic/Genetic instability - Chromatin remodeling - Translesion synthesis - DNA replication
Lab Website Link	https://www.unimi.it/en/ugov/person/marco-muzifalconi

Lab. No. 34

Principal Investigator	Necchi Andrea
Institute of Affiliation	Università Vita-Salute San Raffaele
Title of the proposed project	Single-cell predictors biomarkers of sacituzumab govitecan (SG) or SG + pembrolizumab in muscle-invasive bladder cancer
Short description of the project	Sacituzumab govitecan (SG) is an antibody-drug conjugate (ADC) targeting TROP2 and delivering the topoisomerase-I inhibitor SN-38. SG has demonstrated significant clinical activity in advanced and metastatic urothelial carcinoma and is now being explored in earlier disease settings, including muscle-invasive bladder cancer (MIBC). The SURE-01 and SURE-02 phase II trials, led by Andrea Necchi and colleagues at IRCCS San Raffaele Hospital, investigated perioperative SG-based strategies in cisplatin-ineligible patients with MIBC. SURE-01 evaluates neoadjuvant SG monotherapy prior to radical cystectomy, while SURE-02 investigates the combination of SG with pembrolizumab in a bladder-preserving strategy. Interim analyses from these trials have reported encouraging pathological and clinical complete response rates, supporting the therapeutic potential of anti-TROP2 approaches alone or combined with immune checkpoint inhibition. Importantly, exploratory translational analyses based on bulk transcriptomic profiling have suggested that molecular subtype may influence treatment sensitivity, with luminal tumors appearing particularly responsive to SG ± pembrolizumab. Additional transcriptomic correlates of response and resistance have also begun to emerge, including TOP1 expression (SURE-01)1 or stromal signature (SURE-02). Despite these advances, the biological determinants of response to SG-based therapy remain incompletely understood. Bulk transcriptomic analyses average signals across all cells within a tumor specimen and therefore cannot distinguish tumor-intrinsic programs from microenvironmental features that may critically influence ADC sensitivity and response to immunotherapy. Moreover, bulk approaches cannot resolve intratumor heterogeneity, which may play a major role in treatment resistance through the coexistence of distinct tumor cell states with variable TROP2 and TOP1 expression, proliferative capacity, DNA damage response programs, or immune interactions. Understanding how tumor cells and the tumor microenvironment jointly shape response to SG and SG + pembrolizumab is therefore essential to optimize patient selection, identify biomarkers of resistance, and rationally design future combination strategies.
Main research area for the project	Cancer biology
5 keywords for the project	Immunotherapy - Antibody/mAb therapy - Bladder tumor – Chemoimmunotherapy - Neoadjuvant therapy
Lab Website Link	www.hsr.it

Lab. No. 35

Principal Investigator	Orso Francesca
Institute of Affiliation	Università degli Studi del Piemonte Orientale "Amedeo Avogadro"
Title of the proposed project	DEMO-BRCA: Deciphering the Epigenetic and Microenvironmental Modifiers of BRCA1/2-Driven Tumor Onset
Short description of the project	Germline mutations in BRCA1/2 significantly elevate the lifetime risk of developing a spectrum of aggressive malignancies. While BRCA1/2 mutations are notoriously tied to breast and ovarian cancers, they also elevate risks for pancreatic and prostate malignancies. The striking variation in age of onset and tissue specificity among carriers indicates that secondary microenvironmental and epigenetic modifiers govern penetrance. Defective DNA repair in these carriers drives a premature aging phenotype-marked by systemic chronic inflammation, cellular senescence, and immune exhaustion-while tissue-specific triggers, such as local microbial dysbiosis act as critical oncogenic catalyst. MicroRNAs (miRNAs) serve as critical epigenetic rheostats; however, how the alteration of specific miRNA networks interacts with underlying BRCA1/2 deficiencies to drive cellular transformation remains poorly understood. We hypothesize that BRCA1/2 mutations establish a baseline state of accelerated tissue aging, which disrupts host miRNA expression profiles. This altered non-coding RNA landscape interacts synergistically with local microbial dysbiosis to epigenetically reprogram pre-malignant cells, ultimately dictating tissue-specific tumor onset and explaining incomplete penetrance. In collaboration with the Gynecology Division, University of Torino, Ospedale Mauriziano, Italy, we plan to: • Perform small RNA-sequencing alongside single-cell RNA-seq/ATAC-seq on pre-malignant tissues from young mutation carriers and controls to identify dysregulated miRNA signatures associated with accelerated cellular senescence, epithelial identity shifts, and immune exhaustion. • Utilize patient-derived organoid models to determine how microbial dysbiosis, bacterial genotoxins, and microbial-derived estrogen metabolites modulate host miRNA networks, and evaluate how these non- coding RNAs drive localized genomic instability. • Analyze longitudinal blood/plasma samples from mutation carriers to correlate shifts in circulating miRNAs with the onset of cellular senescence and early-stage tumorigenesis across different organs. The project will elucidate how miRNAs translate tissue-specific microbial stress and premature aging into oncogenic signals, aiming to uncover non-invasive, miRNA-based predictive biomarkers for multi-organ tumor onset and identify targeted RNA-based prevention strategies for high-risk carriers.
Main research area for the project	Cancer biology
5 keywords for the project	Breast ca. - Aging and cancer – microRNA – Organoids - Cell metabolism
Lab Website Link	https://upobook.uniupo.it/francesca.orso

Lab. No. 36

Principal Investigator	Ottini Laura
Institute of Affiliation	Università degli Studi di Roma "La Sapienza"
Title of the proposed project	Dissecting Male Breast Cancer: Inherited Risk, Tumor Biology and Multi-Omics Integration for Clinical Translation
Short description of the project	Male breast cancer is a rare, biologically and clinically under-characterized disease. Despite its rarity, it represents an important unmet clinical need as outcomes are often poorer than in female breast cancer, and clinical management is still largely extrapolated from female disease, highlighting the need for more appropriate male-specific strategies. This PhD project will use integrative multi-omics approaches to identify inherited risk factors and tumor molecular features associated with susceptibility, heterogeneity and clinical outcome. The project builds on the first Italian multicenter study on male breast cancer, coordinated by our group, providing a unique national framework and well-characterized clinical-biological resources for the proposed analyses. The candidate will combine germline genetic analyses with tumor profiling, including genomic, transcriptomic, epigenomic/methylomic and spatial omics data, integrated with clinical-pathological and epidemiological information. Particular focus will be on BRCA1/2 and other cancer-predisposition genes, sex-related differences in cancer risk, and the relationship between inherited predisposition and tumor biology. The PhD student will contribute to sample and data collection, molecular analyses, bioinformatic processing, statistical modeling, multi-omics integration and validation of candidate biomarkers. The project is innovative, competitive and feasible within four years, offering training in both wet-lab and dry-lab approaches. By focusing on a rare cancer with unmet biological and clinical questions, the project aims to generate new knowledge and support the development of sex-specific strategies for risk prediction, prevention, early diagnosis, precision oncology and tailored clinical management in breast cancer. Research activities will be carried out at the Department of Molecular Medicine, Sapienza University of Rome. The Department, recognized as a "Dipartimento Universitario di Eccellenza 2023-2027", provides all the necessary training resources and expertise in both experimental and computational aspects of translational cancer research. Clinical and translational research-related activities, where applicable and subject to appropriate agreement, may be carried out at Sapienza-associated clinical facilities.
Main research area for the project	Genomic Medicine
5 keywords for the project	Breast ca. – BRCA – Biomarkers - Next generation sequencing - Patient risk stratification
Lab Website Link	https://sites.google.com/uniroma1.it/labottini

Lab. No. 37

Principal Investigator	Pagani Massimiliano
Institute of Affiliation	IFOM - Istituto Fondazione di Oncologia Molecolare, ETS
Title of the proposed project	Mapping the Spatial Microenvironment and Cellular Plasticity in Metastatic Colo-rectal cancer
Short description of the project	Solid tumors represent complex entities shaped by diverse interactions occurring between malignant and stromal cells in a highly structured and heterogeneous ecosystem known as the tumor microenvironment (TME). Rather than acting as mere bystanders, non-tumoral tissue-resident cells critically shape tumor pathogenesis and therapeutic outcomes. Crucially, the cellular composition of the TME depends on the organ of origin and individual patient characteristics, shifting our perception of cancer from a purely genetic disease to a dynamic landscape of malignant and normal cell interactions. Among the most heterogeneous cancer types reside colon adenocarcinomas (CRC). Initially considered as a condition driven solely by a streamlined sequence of genetic alterations occurring in epithelial cells of the colon mucosa, recent findings have uncovered the prominent role of nongenetic cellular plasticity as a mean to promote metastasis and immune evasion in CRC. Several molecular studies have employed RNA sequencing at single-cell resolution to show an enrichment in proportions for specific TME cell phenotypes with putative function in the establishment of a pro-metastatic environment including specific pro-inflammatory cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), and immunosuppressive regulatory T cells (Tregs) that correlate with worse prognosis. However, the exact spatial relationships, co-existence patterns, and ranges of interaction between these immune and cancer cells remain poorly understood. This doctoral project utilizes high-throughput technologies capable of retaining spatial resolution in situ to explore cancer cell plasticity. The study aims to identify key cellular states in primary CRC that initiate metastasis and link their functionality to the surrounding TME niche. By bridging phenotypic information with the original spatial architecture, the project will chart the spatial relationships between tumor, stromal, and immune cells (with particular emphasis on Tregs and TAMs). Ultimately, this research will highlight biologically meaningful and therapeutically actionable communication axes that elicit invasive phenotypes, providing ideal translational training for a physician-scientist.
Main research area for the project	Cancer Biology
5 keywords for the project	Treg cells – Microenvironment - Colorectal and/or Intestinal ca. – Metastasis - Transcriptome/Transcriptomics
Lab Website Link	https://www.ifom.eu/it/ricerca-cancro/ricerca-lab/ricerca-lab-pagani.php

Lab. No. 38

Principal Investigator	Pasini Diego
Institute of Affiliation	Istituto Europeo di Oncologia I.R.C.C.S. S.r.l.
Title of the proposed project	Uncovering Therapeutic Vulnerabilities in EZH2-Mutant Germinal Center Lymphomas
Short description of the project	The Polycomb Repressive Complex 2 (PRC2) is a major epigenetic regulator of cellular identity, and its deregulation is a recurrent driver of cancer. Germinal center lymphomas provide a paradigmatic example, as 25-30% of cases harbor heterozygous gain-of-function mutations in EZH2, the catalytic subunit of PRC2. These mutations increase H3K27 trimethylation, resulting in widespread transcriptional repression and altered cell fate programs. Although their oncogenic role has been firmly established, the molecular dependencies that sustain EZH2-mutant lymphoma cells remain poorly defined. The development of tazemetostat (Tazverik), the first FDA-approved EZH2 inhibitor, validated mutant EZH2 as a therapeutic target and demonstrated the clinical potential of epigenetic therapy. However, its recent withdrawal following the emergence of secondary hematologic malignancies highlights the need for alternative therapeutic strategies that selectively target the vulnerabilities created by EZH2 mutations. This PhD project aims to identify the molecular dependencies of EZH2-mutant germinal center lymphomas using advanced functional genomic approaches. Together with the Hematoncology Division of the European Institute of Oncology (IEO), directed by Prof. Derenzini and in direct collaboration with his research group, the student will establish and apply pooled genetic screening platforms coupled with advanced phenotypic readouts, including high-content imaging, transcriptomic profiling, and single-cell approaches such as Perturb-seq. These complementary strategies will enable the identification of genes and pathways required for the identity and maintenance of EZH2-mutant lymphoma cells. Candidate vulnerabilities will be validated using genomic and epigenomic approaches and assessed on clinically annotated patient samples. The project combines innovative functional genomics with access to patient-derived resources, providing a strong translational framework. By uncovering novel therapeutic vulnerabilities associated with oncogenic EZH2 mutations, it aims to uncover effective treatment strategies, potentially safer, for germinal center lymphomas. The student will receive advanced training in functional genomics, epigenomics, and translational cancer research, complemented by clinical exposure within the IEO Hematoncology Division.
Main research area for the project	Cancer Biology
5 keywords for the project	Lymphomas - Histone modifications - Drug screening – Epigenetics - Functional genomics
Lab Website Link	https://www.research.ieo.it/research-and-technology/principal-investigators/diego-pasini/

Lab. No. 39

Principal Investigator	Pelicci Pier Giuseppe
Institute of Affiliation	Istituto Europeo di Oncologia I.R.C.C.S. S.r.l.
Title of the proposed project	Targeting metabolic vulnerabilities of circulating tumor cells to prevent metastatic relapse.
Short description of the project	Metastatic relapse remains the leading cause of cancer-related mortality despite major advances in surgery, systemic therapies, and (neo)adjuvant treatment strategies. Circulating tumor cells (CTCs), the obligate intermediates of metastatic dissemination, represent an attractive therapeutic target. However, the biology of viable CTCs remains poorly understood because their isolation and functional characterization are technically challenging, and no therapies targeting CTC-specific vulnerabilities are currently available. We developed a clinically relevant platform enabling large-scale isolation and functional interrogation of viable metastasis-derived CTCs (mCTCs) from patient-derived xenograft models. Using integrated clonal tracking, transcriptomic, metabolomic, and functional analyses, we identified a previously unrecognized adaptive state that enables CTC survival during hematogenous dissemination. This state is characterized by metabolic rewiring, suppression of mitochondrial activity, and activation of antioxidant programs. Importantly, disruption of this adaptive mechanism using a repurposed clinically available drug selectively impairs CTC fitness, reduces metastatic colonization, and markedly suppresses metastatic relapse in preclinical models (in preparation). The PhD project will investigate whether this metabolic vulnerability represents a general and therapeutically exploitable feature of metastatic dissemination. The candidate will: (i) determine the conservation of this adaptive program across multiple tumor types: breast cancer, melanoma, and lung cancer; (ii) evaluate the efficacy of CTC-targeting strategies alone and combined with chemotherapy and immune checkpoint blockade in models of minimal residual disease and metastatic cancer; and (iii) translate these findings to patients by developing microfluidic and imaging-based assays for functional characterization and pharmacological interrogation of human CTCs. This project integrates cancer biology, metastasis research, functional genomics, translational medicine, and early drug development. Clinical activities (20% of the training program) may be carried out at the Division of New Drugs for Innovative Therapies at IEO, directed by Prof. Giuseppe Curigliano. The project is embedded within a translational collaboration between the two laboratories, providing exposure to preclinical and clinical drug development.
Main research area for the project	Cancer Biology
5 keywords for the project	Oxidative stress and/or Reactive Oxygen Species (ROS) – Genomics - Circulating tumor cells – Metastasis - Metabolism/Metabolomics

Lab Website Link	https://www.research.ieo.it/research-and-technology/principal-investigators/pier-giuseppe-pelicci/

Lab. No. 40

Principal Investigator	Pellegata Natalia Simona
Institute of Affiliation	Università degli Studi di Pavia
Title of the proposed project	Dissecting the molecular underpinnings of clinically relevant NET cell states to improve patients' outcome
Short description of the project	The AIRC-funded project explores the molecular basis of cancer cell plasticity in neuroendocrine tumors (NETs), especially in paragangliomas (PPGLs). It investigates how cells transition between pseudohypoxic and dedifferentiated states, processes linked to aggressive disease and poor prognosis. By decoding these dynamics, the project aims to reveal state-specific vulnerabilities and therapeutic opportunities, addressing a critical unmet clinical need. The candidate will combine experimental and computational approaches to dissect cell state transitions using the well-established PC12 model (PPGL). Guided by a bioinformatician, the physician scientist will analyze RNA-seq datasets to identify transcriptional programs driving the pseudohypoxic-to-dedifferentiated switch, applying differential expression and pathway analyses. Findings will be validated with qRT-PCR and extended to additional aggressive NETs (SCLC). The physician scientist will conduct CRISPR-based genome editing to modulate the expression of candidate transcription factors (TFs) driving cell plasticity such as ASCL1 and YAP1, along with novel TFs emerging from the RNASeq analyses, and will assess the impact of these factors on cell identity, differentiation, epithelial-mesenchymal traits, proliferation, migration, invasion, and metabolism across engineered cell lines. Advanced co-culture systems (primary tumor cells-cells from the tumor microenvironment) will be used to investigate inter-cellular interactions, elucidating how cellular heterogeneity and plasticity contribute to tumor progression and therapeutic vulnerability. These studies will enable the physician scientist to integrate multi-layered datasets spanning genomics, functional assays, and phenotypic analyses, to link molecular alterations to biological outcomes. This interdisciplinary training in molecular biology, genomics, bioinformatics, and translational cancer research will provide the candidate with a strong and versatile scientific skill set. In parallel, he/she will develop key competencies in experimental design, data interpretation, and scientific communication, necessary for careers in clinical or translational research, while empowering them to tackle complex biomedical challenges and contribute to the development of innovative precision medicine strategies aimed at improving outcomes for patients with aggressive NETs.
Main research area for the project	Cancer Biology
5 keywords for the project	Animal models - Drug response and/or resistance - Epithelial mesenchyme transition (EMT) – Metastasis - Neuroendocrine cancers
Lab Website Link	https://geneticslabunipv.wixsite.com/tcglab

Lab. No. 41

Principal Investigator	Piazza Rocco
Institute of Affiliation	Università degli Studi di Milano – Bicocca
Title of the proposed project	Towards new therapeutic approaches for the treatment of SETBP1-driven leukemias
Short description of the project	Here is a plain-text draft of approximately 275 words. Towards new therapeutic approaches for the treatment of SETBP1-driven leukemias SETBP1 mutations and deregulated SETBP1 expression are recurrent events in aggressive myeloid malignancies, including myelodysplastic/myeloproliferative neoplasms and acute myeloid leukemia, and are associated with poor clinical outcome. However, the cellular mechanisms through which SETBP1 drives leukemic transformation and therapeutic resistance remain incompletely understood. This PhD project aims to dissect SETBP1-driven leukemogenesis at single-cell resolution and to identify new therapeutic vulnerabilities that could be translated into innovative treatment strategies. The project will combine advanced single-cell technologies, functional genomics and in vivo disease modeling. The PhD student will analyze single-cell transcriptomic and multiomic datasets from human leukemia samples and experimental models to define the cellular states, differentiation blocks and transcriptional programs associated with SETBP1 activation. Particular attention will be given to leukemic stem and progenitor compartments, clonal evolution, inflammatory signaling, epigenetic regulation and interactions with the bone marrow microenvironment. Candidate pathways emerging from computational analyses will be experimentally validated using cellular models, perturbation approaches and molecular assays. A central component of the project will be the development and characterization of mouse models of SETBP1-driven leukemia. These models will be used to investigate disease initiation and progression in vivo, to validate candidate therapeutic targets and to test novel treatment approaches alone or in rational combinations. Integration of mouse model data with human single-cell datasets will allow the identification of conserved disease mechanisms and clinically relevant biomarkers. The candidate will acquire multidisciplinary expertise in leukemia biology, single-cell and spatial technologies, bioinformatic data analysis, and preclinical modeling. Clinical duties, where applicable, could be carried out at the Hematology Unit of the San Gerardo Hospital, Monza, in close connection with the University of Milano-Bicocca.
Main research area for the project	Cancer Biology
5 keywords for the project	Target therapy - Mutation (somatic and/or germline) - Signal transduction inhibitors - Myelodisplastic syndromes (MDS) - Myeloproliferative neoplasms
Lab Website Link	https://www.medicina.unimib.it/it

Lab. No. 42

Principal Investigator	Salvatore Domenico
Institute of Affiliation	Università degli Studi di Napoli "Federico II"
Title of the proposed project	Targeting thyroid hormone signaling to overcome cancer-related fatigue driven by tyrosine-kinase inhibitors
Short description of the project	Cancer-related fatigue (CRF) affects up to 95% of cancer patients and represents one of the main causes of reduced treatment adherence, dose intensity, quality of life, and survival. CRF is common in patients receiving tyrosine kinase inhibitors (TKIs). Despite its clinical relevance, the biological mechanisms underlying TKI-induced CRF remain poorly understood and preventive strategies are lacking. Our hypothesis is that TKI-induced CRF is driven, at least in part, by impaired thyroid hormone (TH) signaling within the brain. We and others have demonstrated that several clinically relevant TKIs inhibit type 2 deiodinase (D2), responsible for converting thyroxine (T4) into the active hormone triiodothyronine (T3). Since brain T3 availability largely depends on D2 activity, TKI-induced D2 inhibition may reduce local T3 levels and disrupt neural pathways involved in cognition, memory, behavior, and neuronal plasticity, all processes implicated in CRF. Preliminary studies from our Endocrinology Lab at Federico II University showed that TKIs inhibit D2 activity. Furthermore, RNA sequencing of mouse brain cortex after lenvatinib treatment revealed extensive transcriptional alterations affecting pathways related to cognition, synaptic plasticity, and neuronal function. Similar abnormalities have been described in models of defective D2 activity and can be improved by T3 supplementation. The project combines transcriptomic analyses, cellular models, animal studies, and a pilot clinical trial to determine whether impaired TH signaling contributes to TKI-induced CRF and whether restoration of T3 availability can reverse these alterations. Specifically, we will identify TKI-induced brain molecular signatures, evaluate rescue strategies in neuronal models, test thyroid hormone supplementation in vivo, and assess the impact of LT3 supplementation on fatigue and quality of life in patients receiving TKIs. This translational research may identify novel biomarkers and therapeutic approaches for CRF, ultimately improving treatment tolerance, quality of life, and clinical outcomes in cancer patients.
Main research area for the project	Cancer Biology
5 keywords for the project	Thyroid hormone – Endocrinology - Thyroid ca.
Lab Website Link	www.ceinge.unina.it

Lab. No. 43

Principal Investigator	Santaguida Stefano
Institute of Affiliation	Istituto Europeo di Oncologia I.R.C.C.S. S.r.l.
Title of the proposed project	Molecular and clinical characterization of micronuclei in chromosomally-unstable tumors
Short description of the project	Background Chromosomal instability (CIN) generates micronuclei (MNi), promoting genomic instability and metastasis via micronuclear envelope collapse. In our recent publication (Martin et al., Science 2024), we identified the autophagic receptor p62/SQSTM1 as a key regulator of micronuclear stability. Hypothesis Given the strong correlation between p62 levels, micronuclear rupture, and chromothripsis, we hypothesize that p62 might serve as a prognostic marker in chromosomally-unstable tumors, such as breast and ovarian cancers. Furthermore, the identification of the molecular mechanisms regulating p62's micronuclear localization can potentially lead to the identification of therapeutic targets that could prevent micronuclear envelope rupture and thus inhibit tumorigenesis. Experimental design We will analyze p62 protein levels in breast and ovarian cancer samples and will identify proteins regulating p62's micronuclear localization. This will be achieved at the European Institute of Oncology (IEO, Milano) through cutting edge techniques, such as genome editing, mass-spectrometry, super resolution microscopy. Expected results This research will be the first to assess p62 levels in breast and ovarian cancers, testing the hypothesis that high p62 levels correlate with poor prognosis in CIN-high tumors. We will also identify key regulators of p62 activity to enable the development of novel inhibitors. Impact on cancer diseases This research will assess p62 as a prognostic marker in CIN-high tumors, such as breast and ovarian cancers, potentially improving risk stratification, guiding treatment decisions, and survival. It will also identify novel therapeutic targets for these malignancies, contributing to earlier and more effective interventions, thus improving patient outcomes and survival rates.
Main research area for the project	Cancer Biology
5 keywords for the project	Cell cycle - Genomic/Genetic instability – Aneuploidy - Mitosis
Lab Website Link	https://www.santaguidalab.org

Lab. No. 44

Principal Investigator	Serafini Marta
Institute of Affiliation	Fondazione M. Tettamanti M. De Marchi Onlus
Title of the proposed project	Multifunctional CARs for enhanced leukemic stem cell targeting and bone marrow homing
Short description of the project	Therapeutic resistance and relapse in AML are largely driven by leukemic stem cells (LSCs), which persist within the protective bone marrow (BM) niche after standard therapies. To address these barriers, we aim to develop multifunctional next-generation CAR T cells that combine LSC-directed dual-antigen targeting with enhanced BM homing to achieve more effective elimination of LSCs within their niche. We have previously engineered dual-targeting CARs using the IF-BETTER strategy to simultaneously recognize CD33 and the LSC-associated marker TIM-3, by pairing a second-generation CAR with a cytokine-costimulatory receptor (CCR). These constructs showed potent, antigen-restricted cytotoxicity against AML cell lines and primary blasts, including LSCs, while sparing normal immune and hematopoietic cells (doi10.64898/2026.04.22.719217). In parallel, forced CXCR4 expression in conventional CD33CARs improved BM homing, eradication of BM-resident leukemia, and survival in AML xenografts (doi10.1182/blood.2022018330). This project will integrate these features into tricistronic TIM-3/CD33CAR-CXCR4 constructs and evaluate them in vitro and in vivo. We will use Cytokine-Induced Killer (CIK) cells (doi:10.1182/blood-2011-02-336321) non-virally engineered with Sleeping Beauty (SB) transposon system to express multifunctional CARs. These effector cells and the gene transfer platform have been already tested clinically by our group in relapsed ALL after HSCT with CD19.CAR-redirected CIK cells, demonstrating the safety and efficacy of this strategy (doi:10.1172/JCI138473). TIM-3/CD33CAR-CXCR4 CIK cells will be evaluated in vitro for antigen specificity, cytotoxicity, cytokine production, proliferation, exhaustion marker expression, and CXCR4-dependent chemotaxis. In vivo efficacy will be tested in established AML cell line and patient-derived xenograft (PDX) models using dual-luciferase tracking and multiparametric flow cytometry. Residual LSCs will be quantified by flow cytometry and by limiting-dilution secondary/tertiary transplantation into NSG recipients. Finally, a humanised ossicle model will be used to assess TIM-3/CD33CAR-CXCR4 CIK cell infiltration and LSC clearance within a physiologically relevant human stromal BM microenvironment (doi10.1016/j.scr.2014.01.006).
Main research area for the project	Cancer Biology
5 keywords for the project	Cancer stem cells - Acute Myeloid Leukemia (AML) – Microenvironment - CAR engineered cells
Lab Website Link	https://fondazionetettamanti.it/centro-di-ricerca

Lab. No. 45

Principal Investigator	Tamagnone Luca
Institute of Affiliation	Università Cattolica del Sacro Cuore
Title of the proposed project	Extracellular Vesicle-Mediated Tumor Evolution and Adaptive Resistance in Advanced High-Grade Serous Ovarian Cancer
Short description of the project	High-Grade Serous Ovarian Carcinoma (HGSOC) remains the deadliest gynecological malignancy, mainly due to extensive peritoneal dissemination, intra-tumoral heterogeneity, and the frequent developing of platinum-based chemotherapy resistance (PMID 37220750). Despite therapeutic advances, biomarkers able to predict aggressive disease behavior, therapy adaptation, and early relapse are still lacking. Increasing evidence suggests that chemoresistance is not primarily driven by genomic alterations, but is instead shaped predominantly by dynamic programs of cellular plasticity and tumor microenvironment (TME)-mediated signalling (PMID 37474499). Extracellular vesicles (EVs) from patient-derived biological fluids are emerging as promising tools to longitudinally capture adaptive resistant mechanism (PMID 41904344). We hypothesize that platinum-based chemotherapy reshapes EV-mediated communication within the peritoneal tumor ecosystem, promoting cellular states associated with disease progression and treatment failure. By comparing matched chemo-naive and post-treatment ascitic fluid samples, we aim to identify EV-associated molecular signatures of tumor adaptation and uncover therapeutic vulnerabilities. This project aims to investigate the role of EVs in HGSOC evolution (FIGO 2014 stage III-IV) through a unique translational platform established at Università Cattolica/Policlinico Gemelli IRCCS. The hosting lab has collected over 270 ascitic fluid samples from advanced HGSOC patients since 2023 (NCT05067283) and is currently expanding a longitudinal cohort of matched chemo-naïve and post-treatment samples. These resources provide an exceptional opportunity to characterize dynamic changes associated with platinum exposure. The PhD candidate will contribute to the molecular characterization of EVs isolated from ascitic fluid, through integrated proteomic, transcriptomic, and single-cell/single-vesicle approaches, with the aim of identifying EV-associated signatures linked to therapy adaptation, metastatic progression, and unfavorable clinical outcomes. Patient-derived HGSOC cells and 3D-culture models will provide a complementary platform to support the biological interpretation of EV-associated molecular signatures (PMID 41731502; 41520487). This project aims to identify clinically relevant biomarkers and actionable mechanisms to improve risk stratification and identify novel therapeutic opportunities for patients with aggressive HGSOC.
Main research area for the project	Cancer Biology

5 keywords for the project	Response and/or resistance to therapy - Ovarian ca. - Spheroids/3D cultures - Exosomes and/or endogenous microvescicles - Liquid biopsy
Lab Website Link	https://docenti.unicatt.it/ppd2/it/docenti/59412/luca-tamagnone/profilo

Lab. No. 46

Principal Investigator	Tiberi Luca
Institute of Affiliation	Università degli Studi di Trento
Title of the proposed project	CAR-T Therapy for Glioblastoma
Short description of the project	Background & Hypothesis Glioblastoma (GBM) is a highly aggressive adult brain cancer with a median survival of just 15 months. Current treatments offer limited efficacy. While CAR-T cell therapy shows promise, traditional preclinical mouse models fail to accurately replicate human tumor heterogeneity and immunosuppression. Patient-derived organoids (PDOs) serve as faithful 3D human tissue models. We hypothesize that implementing CAR-T therapy in GBM PDOs will significantly accelerate the development of effective clinical treatments. Core Aims Test Efficacy & Identify Antigens: Evaluate CAR-T cell therapy on deeply characterized GBM organoids to discover novel tumor antigens. Analyze the Microenvironment: Use a co-culture system and spatial transcriptomics to track CAR-T and tumor interactions over multiple timepoints, uncovering why certain immune cells become inactivated or "switched off." Bridge the Translational Gap: Create a more effective immunotherapeutic framework to successfully transition preclinical success into clinical applications for adult glioblastoma. Impact on Cancer With a 5-year survival rate under 5%, GBM urgently requires innovative intervention. Combining immunotherapy with PDOs allows researchers to address complex inter- and intra-tumoral heterogeneity in a human-recapitulating asset. Ultimately, this project is a pivotal step toward advancing personalized cancer medicine.
Main research area for the project	Cancer Biology
5 keywords for the project	Drug screening - Mouse models – Medulloblastoma – Oncogenes - Organoids
Lab Website Link	https://armeniseharvard.org/scientists/luca-tiberi/

Lab. No. 47

Principal Investigator	Tonon Giovanni
Institute of Affiliation	Università Vita-Salute San Raffaele
Title of the proposed project	Targeting mitochondria to prevent cancer tolerance and persistency
Short description of the project	Minutes after exposure to antibiotics, bacteria mount an intense response, named tolerance, to withstand even exceedingly high doses of antibiotics. In the clinic, tolerance is responsible for antibiotic treatment failures and bacterial infection relapses. We recently demonstrated that tolerance is present also in cancer cells, interfering with cancer treatment (Punzi et al., Nature Communications). As in bacteria, this tolerant response evolves towards persistence, whereby only a subpopulation survives treatment. As for the mechanism driving the transition from tolerance to persistency, we identified a defining feature of persister cells, that is, a prominent increase in mitophagy, the process where mitochondria are degraded and recycled. Importantly, blocking mitophagy erased tolerant cells. Of note, patients presenting an activated mitophagy signature present a markedly poor survival. Therefore, interfering with mitophagy is a promising avenue to tackle one of the most pressing clinical needs, eliminate dormant, residual cancer cells. In this project, we will leverage a microfluidic platform that we have devised, that allow the screening of hundreds of patient-derived organoids (PDOs), miniature, 3D multicellular tissue cultures grown in the lab from a patient's own biological samples. In the last decade, the use of PDOs has become a central tool for therapeutic screening and precision medicine, since PDOs closely mimic the heterogeneity at single cell level of a tumour tissue and match patient response to therapy. We will focus on metastatic colon cancer to the liver, one of the most intractable cancers. We will generate and validate reporter systems, where GFP will be placed under the control of the promoter of genes activated during mitophagy. We will then screen drug libraries, seeking to identify compounds able to quench mitophagy. The most promising candidates will be then validated into orthotopic mouse models, where PDOs will be injected in the mouse liver.
Main research area for the project	Molecular Therapy
5 keywords for the project	Drug response and/or resistance - Chromatin remodeling – Autophagy – Metastasis - Organ-on-chip
Lab Website Link	https://research.hsr.it/en/divisions/experimental-oncology/functional-genomics-of-cancer/giovanni-tonon.html

Lab. No. 48

Principal Investigator	Tripodo Claudio
Institute of Affiliation	IFOM - Istituto Fondazione di Oncologia Molecolare, ETS
Title of the proposed project	Perturbed hematopoiesis as a systemic driver of cancer evolution
Short description of the project	The PhD project will investigate how perturbed hematopoiesis shapes cancer evolution by modifying the host environment in which malignant clones expand, compete and adapt. The working hypothesis is that inherited or acquired alterations of hematopoiesis, including beta-globin defects, stress/extramedullary hematopoiesis and clonal hematopoiesis driven by lesions such as Dnmt3a or Tet2, generate systemic selective pressures that influence tumor growth, immune escape, tissue invasion, metastatic competence and treatment response. The project will use experimental cancer models in hematopoietically normal and perturbed hosts, with priority given to solid tumors but with the possibility of extending selected concepts to hematological malignancies when biologically appropriate. Tumor evolution will be assessed through longitudinal sampling, quantitative pathology, flow or mass cytometry, molecular profiling, single-cell and spatial transcriptomics, multiplex imaging and, where feasible, clonal tracking strategies. Particular attention will be given to how altered erythroid, myeloid and lymphoid output reshapes dendritic-cell function, T-cell priming, inflammatory set points, stromal organization and vascular or invasive-front niches. A specific exploratory axis will address whether iron availability, erythroid stress programs and macrophage iron-handling states contribute to tumor adaptation, and whether targeting iron metabolism, inflammatory myeloid circuits or hematopoiesis-derived immune suppression can modify tumor evolutionary trajectories. Host-conditioned tissue states will be integrated with tumor-intrinsic programs of proliferation, plasticity, DNA-damage response and immune evasion. The expected outcome is a spatially and mechanistically resolved framework linking abnormal hematopoiesis to cancer evolution, with candidate biomarkers and therapeutic vulnerabilities relevant to risk stratification, prevention of progression and precision treatment.
Main research area for the project	Cancer biology
5 keywords for the project	Hematopoiesis – Microenvironment - Transgenic mice - T cells/TCR – Ferroptosis
Lab Website Link	https://www.ifom.eu/it/ricerca-cancro/ricerca-lab/ricerca-lab-tripodo.php

Lab. No. 49

Principal Investigator	Trivellin Giampaolo
Institute of Affiliation	Università Humanitas
Title of the proposed project	Modeling PAM variants in ACTH-secreting pituitary tumors using human organoids
Short description of the project	Pituitary neuroendocrine tumors (PitNETs), although usually benign, can cause substantial morbidity through hormone hypersecretion and local mass effects. ACTH-secreting PitNETs lead to Cushing's disease (CD), a severe endocrine disorder with substantial unmet clinical need. Our lab identified loss-of-function variants in PAM, a multifunctional secretory-granule protein, in functioning PitNETs, including pediatric CD. Preliminary data support the hypothesis that altered PAM function contributes to pituitary hypersecretion and tumorigenesis. The aim of this PhD project is to develop a human induced pluripotent stem cell (hiPSC)-derived hypothalamic-pituitary organoid model to investigate five PAM variants associated with CD and located in distinct functional regions: c.-133T>C (5'UTR), p.Tyr200Ter and p.Val244Ala (PHM domain), p.His778fs (PAL domain), and p.Leu856Pro (transmembrane domain). Each variant will be introduced by CRISPR-Cas9 into two well-characterized iPSC lines, one male and one female, generating isogenic mutant and wild-type controls. Edited lines will be molecularly and cytogenetycally validated, differentiated into hypothalamic-pituitary organoids, and followed at multiple time points from early pituitary commitment (d40) to endocrine cell maturation (d100/200). Since corticotrophs represent the default differentiation pathway for pituitary progenitors in this system, the model is particularly well suited to assess their development, ACTH secretion, and tumorigenic potential. The organoid system preserves the hypothalamic-pituitary interaction regulating hormone secretion and allows evaluation of both pituitary and hypothalamic effects of PAM dysfunction. Readouts will include single-cell RNA sequencing, immunofluorescence for pituitary and hypothalamic markers, ELISA for basal and stimulated hormone secretion, and assessment of proliferation/progenitor signatures. Results will be integrated with ongoing AtT-20 cell line analyses and PamPomc-cKO mouse studies, providing a human, sex-specific platform to define how PAM variants perturb corticotroph physiology and predispose to corticotroph PitNETs. The student will spend 20% of the PhD on clinical duties, potentially within the Endocrinology and Metabolism Disease Specialty Program of the Humanitas Research Hospital, subject to the required agreement.
Main research area for the project	Genomic Medicine
5 keywords for the project	Normal stem cells – Hormones - Neuroendocrine cancers – Organoids - Transcriptome/Transcriptomics
Lab Website Link	https://www.hunimed.eu/member/giampaolo-trivellin/

Lab. No. 50

Principal Investigator	Ugel Stefano
Institute of Affiliation	Università degli Studi di Verona
Title of the proposed project	Tumor-Hijacked Monocytes as Drivers of Cancer Progression, Metastasis and Response to Immunotherapy
Short description of the project	This PhD project aims to investigate the role of tumor-hijacked monocytes in cancer progression, metastatic dissemination, and response to therapy. Emerging evidence suggests that tumors can reprogram circulating monocytes, converting them into immune cells that support disease progression and suppress effective anti-tumor immunity. Understanding the biology of these tumor-educated myeloid cells may provide novel opportunities for cancer diagnosis, patient stratification, and therapeutic intervention. The candidate will study the molecular and functional features of tumor-hijacked monocytes in patients with solid tumors by combining translational and clinical research approaches. The project will integrate high-dimensional single-cell technologies, multiparametric flow cytometry, transcriptomic profiling, bioinformatic analyses, and functional immunological assays to characterize immune cell heterogeneity and identify mechanisms linking systemic immunity to metastatic evolution. A major goal of the project will be to develop innovative strategies for monitoring tumor-hijacked monocytes in peripheral blood and to evaluate their potential as biomarkers of disease progression and response to immunotherapy. The student will work with patient-derived samples and clinically annotated cohorts, while also gaining experience with advanced experimental models and immune-monitoring platforms. The project offers multidisciplinary training at the interface of immunology, oncology, and precision medicine, within a highly collaborative environment involving basic scientists, clinicians, pathologists, and bioinformaticians. Research activities will be carried out at the Immunology Section, Department of Medicine, University of Verona. Clinical duties may be performed at the University Hospital of Verona (Azienda Ospedaliera Universitaria Integrata di Verona), in collaboration with the oncology and related clinical units involved in the project.
Main research area for the project	Immunology
5 keywords for the project	Innate immunity - Immune escape – Metastasis - Immuno-editing - Tumor dormancy
Lab Website Link	https://www.dm.univr.it/?ent=sezione&id=17

Lab. No. 51

Principal Investigator	Vago Luca Aldo Edoardo
Institute of Affiliation	Università Vita-Salute San Raffaele
Title of the proposed project	Genetic and Epigenetic Trajectories of Immune Escape in Post-Transplant AML Relapse
Short description of the project	Relapse of acute myeloid leukemia (AML) after allogeneic hematopoietic cell transplantation (allo-HCT) remains the principal cause of treatment failure and is largely driven by immune escape from donor-derived immunity. While genetic mechanisms such as HLA loss have been partially elucidated (Vago, NEJM, 2009; Fleischhauer, JCO, 2026; Toffalori, under submission), non-genetic epigenetic routes of immune evasion-including downregulation of HLA class II molecules and upregulation of inhibitory ligands-remain poorly characterized (Toffalori, Nat Med, 2019), particularly regarding their evolutionary origin and clinical determinants. This project aims to define the temporal and mechanistic basis of immune-resistant leukemia variants through integration of clinical metadata, multi-omic profiling, computational modeling, and experimental validation. We hypothesize that distinct relapse modalities arise from specific evolutionary trajectories shaped by intrinsic tumor features and post-transplant exposures, and that epigenetic immune escape frequently emerges de novo under selective pressure. We will analyze AML patients relapsing after allo-HCT using paired longitudinal samples collected at diagnosis and relapse. High-depth whole genome sequencing (WGS), combined with single-cell chromatin accessibility profiling (scATAC-seq), will reconstruct genetic and epigenetic clonal architecture. Building on frameworks developed with Prof. Giulio Caravagna, we will define "epiclones," integrating mutational and chromatin states, and infer their phylogenetic relationships. Coalescent-based modeling will estimate the timing of relapse-initiating clones, distinguishing pre-existing from post-transplant variants. Hierarchical non-negative matrix factorization will identify signatures linked to clinical exposures, which will be validated in vitro using AML cell lines exposed to stimuli that recapitulate clinically relevant conditions.Overall, this project will reconstruct AML relapse evolution and identify molecular signatures enabling risk stratification and personalized relapse prevention strategies.
Main research area for the project	Cancer biology
5 keywords for the project	Leukaemia – Epigenetics - Immune escape - Metabolism/Metabolomics - Hematopoietic stem cell transplantation (HSCT)
Lab Website Link	https://research.hsr.it/en/divisions/immunology-transplantation-and-infectious-diseases/immunogenetics-leukemia-genomics-immunobiology/luca-vago.html

Lab. No. 52

Principal Investigator	Vannucchi Alessandro
Institute of Affiliation	Università degli Studi di Firenze
Title of the proposed project	Addressing complexity of leukemia genome by chromatin 3D structure analysis
Short description of the project	The project aims to address the 3D chromatin structure as a new avenue of investigation in selected forms of acute myeloid leukemia (FLT3 and NPM1 mutated) to identify aberrations that might contribute to define and predict response to therapy and perspectively identify new targets. The applicant should be involved in developing techniques for 3D analysis and develop bioinformatics skills to interpret 3D organization. Furthermore development of cellular models to interpret such abnormalities will be presumably required at a certain time point along project development.
Main research area for the project	Genomic Medicine
5 keywords for the project	Drug screening – Genomics - Acute Myeloid Leukemia (AML) – Biomarkers - Chromatin remodeling
Lab Website Link	https://www.aou-careggi.toscana.it/internet/diagnosi-e-cura/strutture-cliniche/centri-di-innovazione-e-ricerca/centro-di-ricerca-e-innovazione-per-le-malattie-mieloproliferative-crimm-1/