PUBLIC COMPETITION FOR ADMISSION TO THE PHD PROGRAMME OF NATIONAL INTEREST IN SYSTEMS MEDICINE – A. Y. 2025/2026 RESERVED FOR MEDICAL RESIDENTS 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. 2025/2026 RESERVED FOR MEDICAL RESIDENTS 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 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 19 October 2019, whereby the Ministry of 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

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to Directorial Decree (DD) no. 1288 of 2 December 2022, 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, Humanitas University of Milan and Fondazione "Scuola Superiore Europea di Medicina Molecolare" (SEMM — European School of Molecular Medicine), 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 2025/2026;
- Having regard to the note no. 8936 of 29 April 2025 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 15 and 29 April 2025, concerning the institution of the 41st doctoral cycle;
- Having regard to the letter sent by the AIRC Foundation for Cancer Research and Fondazione Cariplo to the University on 30 May 2025, whereby the two foundations declared their willingness to fund FC-AIRC scholarships for the PhD programme of national interest in Systems Medicine, as well as additional related costs;
- Having regard to the resolution adopted by the Board of Directors in the session of 24 June 2025, authorising the University of Milan to participate in a joint project with the AIRC Foundation for Cancer Research and Fondazione Cariplo for the training of physician-scientists

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HEREBY DECREES AS FOLLOWS:

Art. 1 - Institution

Subject to accreditation by the Ministry of University and Research (MUR), in compliance with the laws in force, the University of Milan (administrative headquarters), Fondazione "Scuola Superiore Europea di Medicina Molecolare" (SEMM — European School of Molecular Medicine), the University of Naples "Federico II", the University of Bari, the University of Turin, the University of Trento and Humanitas University of Milan hereby institute a highly innovative doctoral programme of national interest called "PhD in Systems Medicine" for the academic year 2025/2026 (41st cycle — starting on 1 November 2025), reserved for 10 medical residents in accordance with the provisions set forth in art. 7 and art. 8, paragraph 5 of Ministerial Decree 226/2021.

The idea to launch this PhD for medical residents was sparked by the AIRC Foundation for Cancer Research and Fondazione Cariplo, 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 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.

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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

10

Scholarships

10 scholarships funded by the AIRC Foundation for Cancer Research and Fondazione Cariplo

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 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 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 apply for admission to the doctoral research programme, applicants must hold a second-cycle degree (*Laurea magistrale*) belonging to the degree class LM-41 Medicine and surgery, an equivalent

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qualification, or a qualification equivalent to the level of studies (Master's degree) awarded by a foreign university. Moreover, they must be enrolled, for the a. y. 2024/2025, in the final year of a medical postgraduate school at an Italian University.

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**, by accessing the website http://www.semm.it. The application form is an online CV that applicants must complete on the 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:
  - Master's diploma (or equivalent qualification obtained abroad) with transcript of records, **or** Diploma Supplement. All documents must be in Italian, English, French, German or Spanish.
  - Self-certification of academic records (or similar certificate) regarding the medical postgraduate school in which the applicant is enrolled, issued by the corresponding University. The document

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must specify the name of the postgraduate school, the duration of the programme, and the academic years of enrolment.

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, 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 within 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.

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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.

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 20 October 2025**, 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. Such 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

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documents:

a) identity card;

b) passport;

c) (Italian) driving licence.

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

1. his/her previous educational track: max. 10 points;
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 **22 October 2025.**

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

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available places have been filled. Where applicants achieve the same score, preference will be given to the younger applicant, with the exception of the priority criterion for doctoral scholarships set forth in art. 12 of this call for applications. 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.
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 another university programme is subject to the provisions of Law no. 33 of 12 April 2022, entitled "Provisions on simultaneous enrolment in two higher education programmes".

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 Education Incentive Programme in the amount of €140.00, 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

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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.

Applicants with foreign qualifications

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

1. **original degree certificate** with an official translation into Italian (if the original document is not written in English, French, Spanish or German), along with a Statement of Comparability and a Statement of Verification issued by CIMEA (i.e. the Italian ENIC-NARIC centre) or other ENIC-NARIC centres

   OR

2. **original degree certificate legalised** by the competent authorities of the issuing country, with an official translation into Italian (if the original document is not written in English, French, Spanish or German), 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 (the list of required documents is available here) or another statement issued by other ENIC-NARIC centres and containing all information needed to assess the foreign qualification
   - Statement of Correspondence downloaded from ARDI (Automatic Recognition Database Italia), if the qualification was obtained in one of the signatory countries

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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.

Applicants with non-Italian citizenship

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

- Italian tax ID (*codice fiscale*);
- valid residence permit or application receipt of residence permit for study reasons (only for non-EU citizens);
- student visa for the a. y. 2025/2026 (only for non-EU citizens residing abroad).

Non-EU citizens residing abroad (with the exception of students from Norway, Iceland, Liechtenstein, Switzerland, Republic of San Marino and Vatican City) are required to submit an application for pre-enrolment on Universitaly in order to obtain their student visa. In the case of admission, and after the pre-enrolment application has been confirmed, applicants will be able to see the application receipt (Summary) on Universitaly. This receipt is necessary to request 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 28 November 2025**, 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 rejected 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.

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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 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

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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 (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 starting 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 starting 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 annual 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.

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In accordance with the agreement signed by and between the University of Milan, AIRC, Fondazione Cariplo and the European School of Molecular Medicine (SEMM), after the dual-enrolment period, PhD students 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. This is in line with an 80:20 work split, which is typical of training programmes for physician-scientists.

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 Fondazione SEMM.

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

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applicants. All data provided will be processed solely for purposes related and instrumental to the competition and to manage the applicant's relationship with the University, where necessary, in compliance with current laws. Fondazione SEMM 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 call for applications shall be regulated in accordance with the 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 call for applications is Ms Monica Delù (Head of the Post-Graduate Programmes and International Students Services Sector).

For further information or clarifications please use the InformaStudenti service, selecting the category: Postgraduate > Doctoral research (PhD).

Milan 29 July 2025

THE RECTOR OF THE UNIVERSITY OF MILAN

(Signed Marina Brambilla)

Filed as record no. 3385/2025 of 30 July 2025

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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	Amati Bruno
Hosting Institution	Istituto Europeo di Oncologia I.R.C.C.S. S.r.l. (European Institute of Oncology)
Proposal Title	Exploiting synthetic-lethality toward targeted therapeutic development against MYC/BCL2-driven B-cell lymphoma
Keywords	Mitochondria; Lymphomas; RNA binding proteins; bcl2 family; Myc
PhD Project Description	Our research seeks to identify synthetic-lethal interactions allowing the selective elimination of MYC-driven cancer cells by targeted drug interventions. The PhD candidate will be involved the discovery and characterization of such interactions, followed by development of novel targeted therapies against aggressive MYC-driven malignancies, with a focus on MYC/BCL2 "double-hit" B-cell lymphoma (DHL) [1, 2]. As exemplified in previous studies [3-6] select gene-drug and drug-drug interactions will be characterized at the phenotypic and molecular levels in cultured cells, followed by preclinical assessment of their therapeutic potential in animal models. An important outcome of this research lies in the discovery of new indications for existing drugs, paving the way for their combinatorial repurposing in oncology - as suggested for tigecycline and venetoclax for the treatment of DHL [5]. Important emphasis will be placed on the analysis of mechanisms-of-action, involving the use of advanced cellular and molecular biology tools, such as genomic engineering, -omic technologies, etc... For example, where applicable, short- and long-read RNA-seq technologies will be combined to address the consequences of MYC activation and drug treatment on mRNA processing and expression profiles. In turn, the mechanisms and pathways uncovered by these studies may provide new leads for targeted intervention, which may then be pursued and characterized on their own right. For example, alongside other studies, our work on mitochondrial inhibitors led to the identification of the integrated stress response (ISR) pathway as a common therapeutic effector [2, 4], a connection that we are now extending to other drugs and studying in detail in the laboratory. The PhD student may carry out his/her clinical duties in the Clinical Haemato-Oncology Division of the European Institute of Oncology, Directed by Dr. Enrico Derenzini. https://www.ieo.it/en/About-Us-old/Our-Organization/Clinical-Divisions/Clinical-Haemato-Oncology-EMADV/ https://www.ieo.it/it/CHI-SIAMO/Come-siamo-

	organizzati/Le-divisioni/Oncoematologia/
Main Topics of the Lab	MYC-driven lymphoma; Synthetic-lethal gene-drug interactions; Transcription; RNA biology; Mitochondrial stress
Main Research Area	Molecular Therapy
Institutional Page Link	https://www.research.ieo.it
Lab Website Link	https://www.research.ieo.it/research-and-technology/principal-investigators/bruno-amati/

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Lab no. 2

Principal Investigator	Bardelli Alberto
Hosting Institution	Università degli Studi di Torino (University of Turin)
Proposal Title	Targeting Metastatic Prowess with Translational Oncology
Keywords	Genomics; Chemotherapy and/or chemotherapic drugs; Colorectal and/or Intestinal ca.; Clinical trials; Liquid biopsy
PhD Project Description	Candidates will join IFOM (The AIRC Institute of Molecular Oncology) and the Bardelli laboratory located in the heart of Milan, an internationally recognized hub for translational oncology. The lab offers long-standing expertise in genomics, translational medicine, computational biology and artificial Intelligence -applied to colorectal and other cancer types. The project will dissect the biological basis of intrinsic tumour aggressiveness through a novel "born to be bad" (BBB) versus "born to be good" (BBG) biological framework. BBB tumours are micrometastatic from the very beginning, persist as minimal residual disease (MRD) after surgery, and spread early. Conversely, BBG tumours remain localized and are cured by surgery alone. No clinical biomarker currently distinguishes these phenotypes, and patients are often treated the same way. This PhD aims to change that. The candidate will work across three integrated platforms: (i) clinical trials applying liquid biopsy to detect MRD in patients and classifying tumours as BBB or BBG; (ii) observational studies collecting human matched tissue, blood, and other samples; (iii) living biobanks of patient-derived organoids, xenografts and cell lines. Multi-omic technologies will span from genome sequencing to novel approaches like digital pathology ("pathomics"). According to candidate preferences, training will cover both wet-lab techniques (e.g., organoid manipulation, in vivo modelling) and/or dry-lab skills (bioinformatics, machine learning, AI-based image analysis) to foster a true physician-scientist profile. Projects can be tailored toward mechanistic experimentation (e.g. modelling BBB traits in vitro/in vivo) or broad vision development, for example building a pan-cancer MRD platform through a large network of clinical collaborations. One day/week of clinical activity at partner hospitals will be arranged in agreement with candidates and clinical directors. The PhD environment is international and multidisciplinary, bringing together physicians, molecular biologists, bioinformaticians, etc. Graduates will emerge with a competitive skill set poised for future

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	academic or industry leadership in precision oncology.
Main Topics of the Lab	Genomics of Cancer and Targeted Therapies
Main Research Area	Genomic Medicine
Institutional Page Link	https://www.mbc.unito.it/it/genomics-cancer-and-targeted-therapies
Lab Website Link	https://www.mbc.unito.it/it/genomics-cancer-and-targeted-therapies

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Lab no. 3

Principal Investigator	Bonecchi Raffaella
Hosting Institution	Università Humanitas (Humanitas University)
Proposal Title	Impact of IDH Mutation on immune dynamics in gliomas
Keywords	Glioma and/or glioblastoma; Hematopoiesis; Inflammation and/or inflammatory cytokines; Granulocytes; Chemokines
PhD Project Description	Mutations in isocitrate dehydrogenase (IDH) genes, particularly IDH1 and IDH2, have been identified in several tumor types, including gliomas. These mutations promote tumorigenesis by generating the oncometabolite 2-hydroxyglutarate, which disrupts cellular differentiation and reshapes the tumor microenvironment (TME). Routine screening for IDH mutations in glioma patients enables access to targeted therapies, expanding treatment options beyond first-line regimens. However, both primary and acquired resistance to these therapies remain common, and the mechanisms underlying off-target resistance are still poorly understood. Interestingly, despite arising from different tissues, IDH-mutant tumors share similar patterns of progression and survival, largely driven by IDH-associated mechanisms. For instance, lower-grade IDH-mutant gliomas typically exhibit a more favorable prognosis compared to their IDH-wild-type counterparts. Moreover, IDH mutations are associated with a modest but significant survival benefit and represent actionable targets for therapies that can moderately extend progression-free survival. This project aims to investigate the impact of IDH mutations in gliomas, with a focus on immune composition, cellular phenotypes, and their correlations with patient outcomes. The study will be structured around three main work packages: A comprehensive analysis of IDH-mutant and wild-type glioma samples using spatial transcriptomics and multiplex immune profiling; The development of novel, syngeneic, and clinically relevant mouse models of IDH-mutant and wild-type gliomas to enable in-depth characterization of the TME immune landscape; The evaluation of innovative therapeutic strategies using 3D spheroid systems for high-throughput drug screening. Through this integrated approach, the project seeks to identify immune-related therapeutic targets in IDH-mutant and wild-type gliomas and to deepen our understanding of TME dynamics and resistance mechanisms in this tumor type.

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Main Topics of the Lab	Inflammation and cancer
Main Research Area	Immunology
Institutional Page Link	https://www.humanitas-research.com/researchers/raffaella-bonecchi/

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Lab no. 4

Principal Investigator	Campaner Stefano
Hosting Institution	Università degli Studi di Padova (University of Padua)
Proposal Title	Targeting Transcription Replication Pathways in Tumors
Keywords	Transcription; Transcription factors; Genome wide screening/GWAS; Genomic/Genetic instability; Gene regulation
PhD Project Description	Activation of the oncogene c-Myc-through translocation, amplification or pathway-driven deregulation by Wnt, Notch, RTKs, Ras and others-occurs across many tumour types, making Myc a central hub of oncogenic signalling and a compelling pan-cancer target. Although unchecked Myc increases intrinsic replicative stress, tumour cells survive by engaging safeguard pathways that curb catastrophic genome instability. Our recent work pinpoints CDK12 as an essential protector in this setting, regulating early-S-phase transcription-replication conflicts that would otherwise trigger DNA double-strand breaks. We therefore hypothesise that dismantling CDK12-centred stress-mitigation circuits will expose actionable vulnerabilities in Myc-dependent cancers. To test this, we will map the upstream regulators and downstream effectors of CDK12 through a discovery campaign based on genome-wide CRISPR and RNAi screens to uncover genetic dependencies linked to CDK12 loss, paired to proteomic profiling to identify CDK12-binding partners. High-priority genes will be mechanistically characterised and evaluated for preclinical efficacy in eradicating Myc-driven lymphomas. We anticipate defining a regulatory network that prevents or resolves transcription-replication conflicts alongside CDK12, revealing synthetic-lethal targets and drugs capable of aggravating replicative stress-either alone or in combination with CDK12 inhibitors. Because CDK12 inhibitors are already entering clinical trials, our findings could rapidly inform combinatorial regimens against aggressive Myc-driven malignancies, and may also benefit prostate and ovarian cancers that harbour recurrent CDK12 loss-of-function mutations.
Main Topics of the Lab	Understanding the function of oncogenic transcription factors
Main Research Area	Cancer biology

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Institutional Page Link	https://www.medicinamolecolare.unipd.it/
Lab Website Link	https://genomics.iit.it/cancer-biology

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Lab no. 5

Principal Investigator	Cea Michele
Hosting Institution	Università degli Studi di Genova (University of Genoa)
Proposal Title	Targeting Metabolic Reprogramming to Improve Therapeutic Outcomes in Multiple Myeloma
Keywords	Drug response and/or resistance; Epithelial mesenchyme transition (EMT); Biomarkers; Myeloma; Metabolism/Metabolomics
PhD Project Description	Multiple myeloma (MM) remains an incurable malignancy due to drug resistance and disease relapse. Increasing evidence indicates that metabolic reprogramming plays a crucial role in enabling MM cells to evade therapy and survive within the bone marrow microenvironment. This PhD project aims to investigate the clinical and therapeutic relevance of metabolic rewiring in MM, with the goal of identifying novel metabolic vulnerabilities that can be targeted to overcome resistance and improve patient outcomes. The student will integrate in vitro studies, patient-derived samples, and multi-omics approaches (metabolomics, transcriptomics) to define key metabolic pathways associated with resistance to both standard-of-care and emerging therapies. Focus will be given to the interaction between MM cells and the immune microenvironment under metabolic stress conditions, such as fasting or pharmacological NAD+ depletion. To identify actionable metabolic targets, the project will also incorporate a functional CRISPR-Cas9 knockout screen focused on metabolic and stress response genes. This approach will allow the discovery of genes essential for MM cell survival under therapeutic and nutrient-restricted conditions, providing mechanistic insights and guiding the development of combination strategies. In collaboration with clinical departments, the student will access longitudinal bone marrow and peripheral blood samples from MM patients undergoing therapy, including those enrolled in clinical trials investigating metabolic interventions. These samples will enable validation of laboratory findings and correlation with treatment response and minimal residual disease (MRD) status. The project offers a unique opportunity to work in a highly translational setting, fostering strong interaction between laboratory research and clinical practice. The student will be based at IRCCS Ospedale Policlinico San Martino-University of Genoa, within a multidisciplinary team of

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	hematologists, molecular biologists, and data scientists. Clinical duties, if applicable, may be carried out at the Clinic of Hematology and Bone Marrow Transplantation Unit, one of the leading centers for MM treatment in Europe.
Main Topics of the Lab	Our lab investigates metabolic and immune vulnerabilities in multiple myeloma to develop innovative, mechanism-based therapies that overcome drug resistance and improve patient outcomes.
Main Research Area	Cancer biology
Institutional Page Link	https://dimi.unige.it/

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Lab no. 6

Principal Investigator	Cosentino Lagomarsino Marco
Hosting Institution	IFOM - Istituto Fondazione di Oncologia Molecolare (Institute of Molecular Oncology)
Proposal Title	Characterization of persister cell population dynamics through high-content methods
Keywords	Cell cycle; Drug screening; Growth induction and/or growth arrest; Tolerance; Mathematical modeling
PhD Project Description	An obstacle in cancer treatment is the emergence of drug-tolerant "persister" cells, subpopulations capable of surviving therapy and driving relapse. For example, in colorectal cancer (CRC), persisters can survive anti-EGFR treatments, possibly contributing to minimal residual disease and recurrence. In our previous work (Russo et al., Nat. Genet. 2022), we quantitatively characterized the kinetics of persister formation and survival in CRC cell lines under drug pressure, and an ongoing high-content screening effort from our group is identifying promising drug combinations that synergize with EGFR blockade to target these persister cells more effectively. This PhD project will extend these findings, initially focused on a single cell line, to a broader panel of CRC cell lines and organoids. The project aims to explore how these combined treatments influence persister cell dynamics, including their formation, survival, and population-dynamics parameters, thus providing a predictive understanding of population-level responses. The position will be based at IFOM, a leading scientific institute in Milan dedicated to fundamental cancer research, as part of an AIRC-funded IG project on cancer persisters, as part of an AIRC-funded IG project on cancer persisters. We seek candidates with a strong motivation for interdisciplinary work and open to learning new techniques. The work will include (and potentially provide training for) cutting-edge experimental techniques, including high-content imaging at IFOM (Experimental Therapeutics, Mercurio Lab) and advanced cell culture in collaboration with the Russo Lab (U Turin) and the Bertotti Lab (IRCCS Candiolo). Furthermore, the candidate will work closely with the group's experts in mathematical modeling and quantitative data analysis to interpret experimental data and refine hypotheses. Finally, while CRC remains a central focus, we welcome the integration of the

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	candidate's clinical perspective, to transfer our quantitative approach to different cell line models and drug combinations relevant to specific tumor types within their medical field.
Main Topics of the Lab	Computational Biology
Main Research Area	Computational biology
Institutional Page Link	https://www.ifom.eu
Lab Website Link	http://spcg.unimi.it

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Lab no. 7

Principal Investigator	Costanzo Vincenzo
Hosting Institution	IFOM - Istituto Fondazione di Oncologia Molecolare (Institute of Molecular Oncology)
Proposal Title	Replication-stress-driven placental-like programme and immune escape in aggressive human cancers
Keywords	DNA repair; DNA damage; DNA replication
PhD Project Description	We have recently shown that abasic (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 placental proteins linked to immune tolerance and evasion. Starting from these results the proposed project will unravel the connection between AP formation, RS induction, placental mimicry and clinical aggressiveness, and test whether this axis represents a therapeutically exploitable weakness. The project will aim to characterize "born-to-bad" malignancies, prioritizing aggressive gastrointestinal, lung, breast, and gynaecological primaries and their metastases, 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 surgical and 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. Tumor samples will then undergo quantitative assessment of AP lesions and gaps, deep-proteome analysis with Orbitrap-DIA focused on placental peptides and spatial and single-cell mapping of the immune micro-environment. Statistical analysis will link these results with therapy response and survival. Patient-derived organoids will be established to test synthetic-lethal combinations with available drugs that target the pathways unraveled by the proteomic analysis. By combining these multiple approaches, the project aims to demonstrate that RS-driven placental-like reprogramming is a unifying,

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	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 oncology service, ensuring continuous feedback between bench discoveries and bedside application.
Main Topics of the Lab	DNA damage and repair, replication stress, cancer proteomics and basic tumour immune evasion mechanisms
Main Research Area	Cancer biology
Institutional Page Link	https://www.ifom.eu/it/ricerca-cancro/ricercatori/vincenzo-costanzo.php
Lab Website Link	https://www.ifom.eu/it/ricerca-cancro/ricercatori/vincenzo-costanzo.php

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Lab no. 8

Principal Investigator	Damia Giovanna
Hosting Institution	Istituto di Ricerche Farmacologiche "Mario Negri" I.R.C.C.S. (Mario Negri Institute for Pharmacological Research)
Proposal Title	Overcoming poly-ADP-rybose-polymerase inhibitor resistance in ovarian carcinoma
Keywords	Pharmacology; DNA repair; Response and/or resistance to therapy; Ovarian ca.; Poly-ADP-ribose polymerase (PARP)
PhD Project Description	Poly(ADP-ribose) polymerase inhibitors (PARPis) have transformed the treatment options available for ovarian carcinoma, improving progression-free survival, particularly in patients with defects in homologous recombination repair. However, resistance to therapy eventually emerges and poses an obstacle to cure. Using different preclinical models, the project aims to: - dissect the molecular and cellular factors of olaparib resistance in vivo using complementary approaches; Identify biomarkers of response to olaparib, including validating the RAD51 foci score in a cohort of ovarian cancer patients; assess new combination strategies to delay and/or overcome olaparib resistance. State-of-the-art omics technologies will be employed to profile the genome and assess the expression of mRNA and miRNAs during the acquisition of olaparib resistance in the PDX preclinical models available in our laboratory. Studies of the tumour microenvironment in the olaparib-resistant syngeneic mouse model may reveal modifications that occur with the acquisition of resistance. The RAD51 foci score will be prospectively validated in a cohort of ovarian cancer patients enrolled in the Iolanthe study: a phase IIIb-IV trial aimed at confirming the efficacy of olaparib in combination with bevacizumab as a frontline maintenance treatment for HRD-positive ovarian tumours. Omics studies on the available PDXs and data generated in acquired olaparib-resistant models will reveal pathways involved in drug resistance, which will be validated and targeted in order to overcome or revert drug resistance, and which may lead to the identification of new predictive biomarkers of response. The development of novel and effective combinations of olaparib with other drugs to

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	overcome/delay olaparib resistance will be prioritized for clinical evaluation. This project is highly relevant from a medical perspective, as it focuses on PARPi resistance. With the introduction of these agents at an early stage in the treatment of ovarian cancer patients, this will represent an important medical need in the near future.
Main Topics of the Lab	Sensitivity and resistance to therapy in ovarian cancer
Main Research Area	Molecular Therapy
Institutional Page Link	https://www.marionegri.it/

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Lab no. 9

Principal Investigator	De Cecco Loris
Hosting Institution	Fondazione I.R.C.C.S. Istituto Nazionale dei Tumori – Milano
Proposal Title	Spatial Metagenomic and Tumor Microenvironment landscape in Head and Neck Cancer for AI-Driven Immunotherapy Prediction
Keywords	Immunotherapy; Genomics; Head and neck ca.; Clinical trials; Transcriptome/Transcriptomics
PhD Project Description	Immune checkpoint inhibitors are widely used for head and neck squamous cell carcinoma, but patient responses in clinical practice remain highly variable. This project, developed under the AIRC IG23573 grant (PI: Dr. De Cecco), aims to validate novel AI biomarkers and assess their predictive power in real-world settings. The intratumoral microbiota, the collection of microorganisms within a tumor, can significantly impact the effectiveness of immunotherapy by influencing the tumor microenvironment and modulating the host's immune response. The project integrates five key domains: clinical efficacy, resistance mechanisms, host/microbiota relationships, biomarker discovery, and personalized oncology strategies. Central to this effort is the use of spatial metatranscriptomics to decode the tumor microenvironment (TME), revealing immune-microbiota interactions and spatial gene expression gradients that may drive therapeutic outcomes and immune evasion. Hypothesis and Aims We hypothesize that spatial gene expression profiling will uncover actionable biomarkers and spatial immune-microbiota dynamics predictive of treatment response. Specific aims include: 1)Generating high-resolution spatial maps of TME architecture. 2)Identifying immune, stromal, and microbial gene expression signatures within intact tissues. 3)Comparing spatial features to reveal immune evasion mechanisms. 4)Integrating spatial and bulk/single-cell transcriptomics to build a multi-layered atlas for outcome stratification. Computational Framework A five-module pipeline will support the project: 1)High-resolution spatial transcriptomics using technologies like STOmics Stereo-seq and tools like Cell2location. 2)Multi-omics integration via VAEs, denoising autoencoders, and knowledge graphs. 3)Predictive modeling using deep

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	multi-task networks, XGBoost, and interpretable AI. 4)Generative modeling with VAEs and GANs to simulate synthetic cohorts and phenotypes. Clinical validation and deployment under TRIPOD and CONSORT-AI standards, supporting integration into clinical systems through FHIR, dashboards, and privacy-preserving data sharing. This project seeks to advance precision immunotherapy through robust, spatially informed biomarker discovery and clinically actionable predictive tools.
Main Topics of the Lab	• Integrated experimental and computational framework • Multi-omics profiling • Spatial transcriptomics • Advanced computational analytics • Biomarker discovery • Translational precision oncology
Main Research Area	Computational biology
Institutional Page Link	https://www.istitutotumori.mi.it/en/home

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Lab no. 10

Principal Investigator	Di Tommaso Luca
Hosting Institution	Università Humanitas (Humanitas University)
Proposal Title	Dissecting the transcriptomic profile of endothelial cells (EC) in VETC+ cancers pave the way to a true personalized med
Keywords	Tumor-stroma interaction; Endothelial cells; Hepatocellular carcinoma (HCC); Biomarkers; Liquid biopsy
PhD Project Description	The student will coordinate with clinical collaborators to prospectively collect fresh tumor and adjacent normal tissues from hepatocellular carcinoma (HCC), clear cell renal cell carcinoma (ccRCC) and thyroid cancer (TC) patients, to oversee ethical approvals, patient consent procedures, and sample biobanking. The student will optimize protocols for tissue dissociation and fluorescence-activated cell sorting (FACS) to isolate Endothelial Cell (EC) populations based on established surface markers. She/he will prepare single-cell suspensions, perform library construction with the 10x Genomics platform, and sequence samples on Illumina instruments. She/he will apply rigorous quality control pipelines, align reads, and generate cell-by-gene matrices. Employing bioinformatics tools such as Seurat and Scanpy, the student will identify distinct EC clusters, perform statistical differential expression analyses, and compare transcriptional signatures across cancer types. They will build pseudotime trajectories to infer lineage relationships and uncover cluster-specific markers. The student will validate the identified EC clusters and markers using image-based techniques including multiplex immunofluorescence, in situ hybridization, and immunohistochemistry. The student will also explore potential therapeutic targets by cross-referencing cluster-specific genes with drug databases and conducting preliminary functional assays in vitro. Throughout the PhD, the student will attend journal clubs, present findings at international conferences, and contribute to manuscript preparation. They will gain expertise in translational cancer biology, single-cell genomics and computational analysis, ultimately advancing our understanding of multi-tumor VETC-driven metastasis and identifying novel avenues for therapeutic intervention.

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Main Topics of the Lab	Precision Medicine Lab
Main Research Area	Molecular Therapy
Institutional Page Link	https://www.humanitas-research.com/groups/piscuoglio-group/

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Lab no. 11

Principal Investigator	D'Incalci Maurizio
Hosting Institution	Humanitas Mirasole S.p.A.
Proposal Title	Analysis of DNA from cervical swabs for early detection of ovarian and p53-abnormal endometrial cancers
Keywords	Gene alteration/gain or loss; Diagnosis; Gynecological tumors; Retrospective studies
PhD Project Description	This project aims to validate and expand the EVA test, a novel molecular assay for early detection of ovarian cancer (OC) and p53-abnormal endometrial cancer (p53abn EC) through DNA analysis of cervical swabs. The test is based on the hypothesis that tumor DNA from ovarian surface, Fallopian tube, or endometrial tissues sheds into the cervical canal during early tumor progression, and could be detectable before blood biomarkers. Tumor DNA is identified by measuring genome-wide Copy Number Alterations (CNAs), indicative of chromosomal instability, using low-coverage whole genome sequencing. In a previous study (doi: 10.1126/scitranslmed.adi2556), we showed that Copy number Profile Abnormality (CPA) score, providing a quantitative determination of CNAs, can distinguish OC cases from controls with 75% sensitivity and 96% specificity, detecting tumor DNA up to 9 years before diagnosis. This project will validate the test's accuracy in high-grade serous OC and extend its evaluation to other OC histotypes and p53abn EC by examining archival cervical swabs from a large multicenter cohort, including age-matched healthy controls. It aims to optimize test cut-offs, explore clinical factors influencing accuracy, and assess test performance over time. Having already secured ethical approval and support from 23 Italian clinical centers, as well as a patient association, arranged for external management of the clinical study, and established a centralized database, the study now plans to select at least 320 OC cases, 200 p53abn EC cases, and 400 controls. This validation seeks to establish the EVA test as a sensitive, non-invasive screening tool for early diagnosis of gynecological cancers. The PhD Student will be based at Humanitas San Pio X Hospital, collaborating with the clinical team of the Gynaecological Oncology Unit for patient selection and sample collection, while performing molecular biology

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	analyses in our laboratory. The Student will also contribute to data analysis, interpretation, reporting, and scientific publication.
Main Topics of the Lab	Translational genomics and molecular pharmacology
Main Research Area	Genomic Medicine
Institutional Page Link	https://www.humanitas-research.com/
Lab Website Link	https://www.humanitas-research.com/groups/maurizio-dincalci-group/

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Lab no. 12

Principal Investigator	Elisei Rossella
Hosting Institution	Università di Pisa (University of Pisa)
Proposal Title	GENETIC HALLMARKS OF INVASIVE AND NON-INVASIVE MEDULLARY THYROID CANCER
Keywords	Genomic/Genetic instability; Thyroid ca.; Metastasis; RET; Circulating tumor DNA
PhD Project Description	The proposed PhD research project for the candidate is part of the bigger IG-2024 project that, at this moment, and hopefully for more 4 years, is now running at the Department of Clinical and Experimental Medicine of Pisa University under the supervision of . He/she will be involved in the IG-2024 project whose PI is Prof. Rossella Elisei. The global project is aimed at identifying genetic features involved in tumoral progression of medullary thyroid carcinoma (MTC). The proposed project for the candidate is regarding the evaluation of the role of ESR1 and ESR2 genes in the pathogenesis and aggressiveness of MTC. ESR1 and ESR2 genes encode for 2 estrogen receptors involved in cell survival and proliferation. Despite the well-known role of these 2 genes in breast cancer, a few data are available for MTC but it is already known that, when mutated, they can upregulate the wild-type RET activity that is the gene whose activation is responsible for 98% of hereditary MTC and 50% of sporadic MTC. Moreover, an ESR2 germline mutation was already reported in a case of hereditary MTC. The candidate will be involved in this part of the project and in particular he/she will identify MTC patients to be enrolled in the study and maintain the database with the clinical and pathological. The candidate will be also involved in the search for ESR1 and ESR2 mutations. ESR1 and ERS2 mutated cases will be then studied for the expression levels of RET transcript by droplet digital PCR and RET transcript levels detected in ESR1 or ESR2 mutated cases will be compared with RET transcript levels in a matched non mutated control group.
Main Topics of the Lab	Thyroid cancer studies
Main Research Area	Cancer biology
Institutional Page Link	https://endocrinologia.med.unipi.it/

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Lab no. 13

Principal Investigator	Ficara Francesca
Hosting Institution	Humanitas Mirasole S.p.A.
Proposal Title	Targeting PBX as a novel therapy for myeloproliferative neoplasm: effect on disease course through innovative assays
Keywords	Drug response and/or resistance; Hematopoiesis; Mouse models; Hematopoietic stem cells; Myeloproliferative neoplasms
PhD Project Description	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

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	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 Topics of the Lab	Myeloid neoplasms; Hematopoietic stem cells
Main Research Area	Cancer biology
Institutional Page Link	https://www.humanitas-research.com/
Lab Website Link	https://www.humanitas-research.com/researchers/francesca-ficara/

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Lab no. 14

Principal Investigator	Lugli Enrico
Hosting Institution	Humanitas Mirasole S.p.A.
Proposal Title	Biomarkers of anti-tumor response in solid tumors treated with combination immunotherapy targeting immunosuppression
Keywords	Immunotherapy; Treg cells; Biomarkers; Immunosuppression and/or suppressor cells; Tumor-Infiltrating Lymphocytes (TIL)
PhD Project Description	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 remain unexplored. At the Humanitas Research Hospital in Milan, we designed a 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. Multiomic 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 be optimized for improved efficacy. The successful MD candidate will have clinical expertise in solid tumor oncology and basic laboratory expertise

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	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 Topics of the Lab	Identifying molecular mechanisms of immune dysfunction and immunosuppression in solid tumors
Main Research Area	Immunology
Institutional Page Link	https://www.humanitas-research.com/
Lab Website Link	https://www.humanitas-research.com/groups/enrico-lugli-group/

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Lab no. 15

Principal Investigator	Marcenaro Emanuela
Hosting Institution	Università degli Studi di Genova (University of Genoa)
Proposal Title	Decoding Natural Killer Cell Function in the Tumor Microenvironment of Women's Cancers: from Bench to Bedside
Keywords	Breast ca.; Immunotherapy; NK and/or NKT cells; Combination therapy; Ovarian ca.
PhD Project Description	The proposed PhD project aims to dissect the phenotypic and functional diversity of Natural Killer (NK) cells in the tumor microenvironment (TME) of women's cancers, with a primary focus on breast and ovarian tumors. NK cells play a crucial role in immune surveillance, yet their activity is often impaired in solid tumors. Understanding the molecular and cellular mechanisms that shape NK cell dysfunction in the TME will support the identification of actionable immune targets. The candidate will integrate flow cytometry, in vitro functional assays, and next-generation sequencing approaches (bulk and/or single-cell RNA-seq) to characterize NK cells from tumor tissue, blood, and peritoneal fluids. Special attention will be given to receptor-ligand interactions, immune checkpoint expression, and the impact of tumor-derived signals on NK cell effector programs. In recent years, we have introduced transcriptomic analyses to complement our established immunophenotyping pipeline, and the PhD student will play a central role in this transition, contributing to the design and execution of multi-omics studies. The research will be hosted at the Molecular Immunology Lab, Department of Experimental Medicine (DIMES), University of Genoa, in close collaboration with IRCCS Ospedale Policlinico San Martino, where clinical samples will be collected. The candidate will be involved in two ongoing translational research projects focused on the immunobiology of high-grade serous ovarian carcinoma and breast cancers. Approximately 80% of the time will be dedicated to laboratory work; the remaining 20% will involve training and clinical observation in units such as Breast Surgery or Gynecologic Oncology, depending on the availability and agreement of the respective unit supervisors. The candidate will be directly supervised by the PI and supported in manuscript preparation, data dissemination, and participation in international grant

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	applications. This project offers a unique opportunity to gain expertise at the interface of tumor immunology, genomics, and translational oncology.
Main Topics of the Lab	Our research aims to dissect NK-mediated immune regulatory mechanisms, identify novel immunotherapeutic targets, and translate findings into clinical applications.
Main Research Area	Immunology
Institutional Page Link	https://dimes.unige.it/

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Lab no. 16

Principal Investigator	Mavilio Domenico
Hosting Institution	Università degli Studi di Milano (University of Milan)
Proposal Title	Targeting tumor immune-evasion mechanisms to limit the metastatic progression of human colorectal cancer to liver.
Keywords	Innate immunity; Liver development and/or regeneration; Microenvironment; Colorectal and/or Intestinal ca.; Metastasis
PhD Project Description	Colorectal cancer (CRC) poses a significant health challenge, with approximately 50% of patients developing colorectal liver metastases (CRLM), a primary cause of CRC-related mortality. Within six months of an initial CRC diagnosis, 25% of patients are found to have CRLM, underscoring the urgency of effective intervention strategies. Moreover, even after initial treatment, a significant percentage of patients experience liver recurrence, further complicating disease management. Current treatments, including curative resection and chemotherapy, offer limited 5-year survival rates of 20-50%. Hence, there is an imperative need to discover new: i) therapeutic approaches; ii) diagnostic markers for detecting liver recurrence; iii) prognostic indicators of treatment outcomes. Our group already identified several immune-mechanisms conferring protective effects against both primary CRC and metastatic liver tumors. Using scRNA-seq technology and multi-parametric spectral flow cytometry, we characterized distinct subsets of unconventional gamma-delta T cells and tumor-reactive cytotoxic Natural Killer cells associated with favorable clinical outcomes. However, the molecular and cellular modalities that either promote or suppress immune recruitment and infiltration in CRLM are unclear. In particular, significant gaps persist in our understanding of how the spatial organization of the CRLM TME influence disease progression and therapeutic responses. This study aims to implement novel therapeutic and prognostic strategies by integrating analyses of immune and tumor cell-state regulators, tumor genetic variations and spatial biology within the CRLM tumor microenvironment (TME). The specific objectives are: a) Spatiomolecular profiling of the CRLM TME; b) Identification of malignant cell states and genetic factors predicting immune

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	susceptibility and evasion; c) Development of predictive models for CRLM outcome and recurrence risk. By combining our expertise in clinical CRLM and immuno-oncology, access to an extensive patient cohort with detailed clinical data, cutting-edge single-cell spatial transcriptomic, computational analysis, and machine learning approach, this project will identify key immunoregulatory mechanisms to develop novel therapies for CRLM.
Main Topics of the Lab	Impact of Innate immune responses in Cancer and viral infections
Main Research Area	Immunology
Institutional Page Link	https://www.unimi.it/en
Lab Website Link	https://www.labmavilio.it

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Lab no. 17

Principal Investigator	Mazzucchelli Serena
Hosting Institution	Università degli Studi di Milano (University of Milan)
Proposal Title	Exploitation of Indocyanine green loaded engineered protein nanocages for photodynamic therapy of Breast Cancer
Keywords	Breast ca.; Nanotechnology/Nanoparticles; In vivo imaging; Photodynamic therapy and photodetection; Fluorescence imaging system
PhD Project Description	Photodynamic therapy (PDT) has emerged as a minimally invasive cancer treatment that combines localized irradiation of photothermal agents with the generation of heat and reactive oxygen species (ROS) to induce immunogenic cell death and recruit T lymphocytes. This dual action makes PDT especially attractive for tumors unresponsive to standard therapies, such as triple-negative breast cancer (TNBC), and for converting "cold" tumors into immunologically active sites. Indocyanine green (ICG), a fluorescent dye long used in diagnostics, has recently shown promise as a photothermal agent, but its rapid degradation and poor tumor selectivity limit its clinical potential. To overcome these hurdles, here we propose to encapsulated ICG within human H-ferritin nanocages (HFn-ICG), leveraging HFn's high affinity for the transferrin receptor 1 (TfR1), which is ubiquitously overexpressed on cancer cells. In breast cancer cell lines, HFn-ICG demonstrated significantly enhanced PDT efficacy compared with free ICG, and in vivo studies confirmed rapid, tumor-specific accumulation of the nanoconstruct. Building on these preliminary successes, during this PhD project the candidate will engineer HFn's outer surface to extend circulation time and further sharpen tumor targeting. Three objectives will be achieved: (i) optimize production of engineered HFn (HP) and efficient ICG loading (HP-ICG); (ii) assess HP-ICG's targeting ability, tissue penetration, PDT effectiveness, and immunostimulatory impact in breast cancer cell monolayers and patient-derived organoids; and (iii) characterize HP-ICG's biodistribution and tumor tropism in an in vivo TNBC model. By unveiling HP's tumor-homing capacity and validating HP-ICG's boosted immunogenic PDT in highly translational, patient-derived systems, this project paves the way for broad application across diverse cancer types.

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Main Topics of the Lab	Development of nanodelivery systems for cancer application
Main Research Area	Molecular Therapy
Institutional Page Link	https://dibic.unimi.it/it/ricerca/gruppi-e-risorse-della-ricerca/gruppi-di-ricerca/laboratorio-di-nanomedicina

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Lab no. 18

Principal Investigator	Morandi Andrea
Hosting Institution	Università degli Studi di Firenze (University of Florence)
Proposal Title	Investigating the role of peroxisomes in modulating radiotherapy response in breast cancer
Keywords	Breast ca.; Drug response and/or resistance; Estrogens and/or receptors; Response and/or resistance to therapy; Metabolism/Metabolomics
PhD Project Description	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

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	findings could pave the way for integrating peroxisome-targeting agents with RT to enhance efficacy and delay recurrence in ER+ breast cancer patients.
Main Topics of the Lab	Therapy resistance and cancer metabolism
Main Research Area	Cancer biology
Institutional Page Link	https://www.sbsc.unifi.it/
Lab Website Link	https://www.sbsc.unifi.it/vp-326-gruppo-morandi.html

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Lab no. 19

Principal Investigator	Pelicci Pier Giuseppe
Hosting Institution	Istituto Europeo di Oncologia I.R.C.C.S. S.r.l. (European Institute of Oncology)
Proposal Title	Dissecting and Targeting IFI6-Driven Chemoresistance in Acute Myeloid Leukemia (AML)
Keywords	Target therapy; Response and/or resistance to therapy; Chemotherapy and/or chemotherapic drugs; Acute Myeloid Leukemia (AML); DNA methylation
PhD Project Description	The project will be carried out at IEO, enabling the candidate to carry out both research (at the experimental oncology department) and clinical activities (in the IEO onco-hematology division). The project stems from an ongoing AIRC grant investigating AML chemoresistance mechanisms. Using patient-derived xenograft (PDX) models recapitulating primary and secondary resistance, we identified a transcriptional interferon (IFN) response signature in chemotherapy-persistent blasts. Silencing of the most upregulated gene of this signature restores chemosensitivity leading to complete leukemia eradication in vivo. Mechanistic studies suggest that the molecular mechanism involves apoptosis induced by STING pathway inhibition. However, pharmacological STING activation only partially restores chemosensitivity, suggesting that STING is either suboptimally activated by the tested compound or additional mechanisms are involved. The project aims at: 1) Biomarker Development - To evaluate the IFN-response signature as predictive biomarkers of chemoresistant relapse in AML. We will perform single-cell RNAseq on peripheral blood or bone marrow samples collected at the end of induction chemotherapy in newly diagnosed AMLs. If a predictive correlation is observed, we will adapt the assay to clinically applicable formats such as bulk RNA-seq or digital-PCR. 2) Preclinical Therapeutic Modeling - To determine whether combining chemotherapy with STING agonists prevents chemoresistant relapse in AML PDXs. We preliminarily tested one STING agonist in combination with chemotherapy, using a 5-day schedule aligned with chemotherapy but at doses established for chronic administration. We will evaluate multiple STING agonists and optimize both dosing and scheduling specifically for concurrent use with

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	chemotherapy. If therapeutic eradication is not achieved, we will test the involvement of additional pathways. To this end, we will reconstruct protein complexes containing the most upregulated gene of the chemotherapy-persistent blast signature, before and after chemotherapy, to identify new actionable effectors. By bridging biomarker discovery with therapeutic modeling, the project is ideally suited for physician-scientist training.
Main Topics of the Lab	identification of molecular determinants of therapy resistance in leukemia and breast cancer
Main Research Area	Cancer biology
Institutional Page Link	https://www.research.ieo.it/
Lab Website Link	https://www.research.ieo.it/research-and-technology/principal-investigators/pier-giuseppe-pelicci/

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Lab no. 20

Principal Investigator	Polo Simona
Hosting Institution	IFOM - Istituto Fondazione di Oncologia Molecolare (Institute of Molecular Oncology)
Proposal Title	Decoding Early Metastasis in Colorectal Cancer: The Hidden Role of Alternative Splicing
Keywords	Wnt/beta-catenin pathway; Cell signaling; Colorectal and/or Intestinal ca.; Metastasis; RNA splicing
PhD Project Description	Despite progress in screening, diagnosis, and treatment, colorectal cancer (CRC) remains the second leading cause of cancer-related mortality worldwide. Originating from stem cells in the colonic crypt, CRC arises through genetic and epigenetic changes that lead to neoplastic transformation. Mutations in tumor suppressors (e.g., APC, TP53, SMAD4) and oncogenes (e.g., KRAS) drive its progression. The most lethal phase involves tumor invasion and spread. Although metastasis accounts for most CRC deaths, no consistent metastasis-specific driver mutations have been identified, leaving its molecular basis unclear and limiting targeted therapeutic development. The traditional model of stepwise progression has been challenged by the identification of "born to be bad" (BBB) CRCs, which exhibit early dissemination of metastasis-competent cells, as opposed to "born to be good" (BBG) tumors that are micrometastatis-negative as defined by the absence of circulating cell-free tumor DNA. Recognizing CRCs with early metastatic potential is crucial for risk stratification and therapeutic intervention. Our laboratory has uncovered a novel cancer-intrinsic mechanism contributing to early metastasis: alternative splicing (AS) reprogramming driven by nuclear ß-catenin. AS generates multiple protein isoforms from a single gene. We have found that activated ß-catenin suppresses a key splicing factor, promoting cancer-specific isoforms associated with invasion and metastasis across multiple CRC subtypes. We hypothesize that AS acts as a regulatory layer enhancing tumor adaptability and plasticity in early metastatic CRCs. Using CRC organoids and unbiased RNA sequencing, we are profiling AS signatures that distinguish BBB from BBG tumors. Our goal is to link specific alternatively spliced isoforms to early metastatic behavior, thereby identifying novel

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	biomarkers and therapeutic targets. This project will equip a physician-scientist with critical expertise in molecular and cancer biology, transcriptomics and reverse genetic engineering approaches. The candidate will join a multidisciplinary, collaborative and friendly lab where continuous training is pursued at all levels.
Main Topics of the Lab	Ubiquitin signaling pathways and alternative splicing programs in physiology and cancer
Main Research Area	Cancer biology
Institutional Page Link	https://www.ifom.eu/en/cancer-research/programs/molecular-machines-signalling-pathways.php

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Lab no. 21

Principal Investigator	Roti Giovanni
Hosting Institution	Università degli Studi di Parma (University of Parma)
Proposal Title	Dissecting ETP-ALL Vulnerabilities Via Single-Cell Genomics and Ex Vivo Drug Response Profiling
Keywords	Acute Lymphoblastic Leukemia (ALL); Kinase/Kinome; Small molecule inhibitors; Signal transduction inhibitors; Artificial intelligence
PhD Project Description	Early T-cell precursor acute lymphoblastic leukemia (ETP-ALL) is a high-risk subtype of T-ALL marked by stem-like properties, multilineage transcriptional programs, and resistance to conventional chemotherapy. ETP-ALL cells co-express lymphoid and myeloid gene signatures and lack definitive immunophenotypic markers, making them challenging to classify and treat using standard genomic-guided approaches. As such, there is an urgent need to identify new therapeutic vulnerabilities, particularly in the relapsed/refractory setting. This project aims to define actionable treatment strategies for ETP-ALL through the integration of ex vivo drug response profiling (DRP) with single-cell multi-omic characterization. We have assembled a unique cohort of 30 primary ETP-ALL patient samples, for which we have generated high-resolution single-cell RNA-seq and ATAC-seq data, along with comprehensive ex vivo drug sensitivity profiles across nearly 200 targeted and investigational compounds. By integrating these datasets, we aim to map drug sensitivities to specific transcriptional states, chromatin accessibility patterns, and leukemic subpopulations. This approach will allow us to uncover functional dependencies and pharmacologic vulnerabilities that are not evident from bulk genomics alone. Our preliminary data suggest that ETP-ALL cells are selectively sensitive to BCL-2 and MCL-1 inhibition. Through this platform, we will validate and expand these observations in a patient-specific and mechanistically informed manner. In parallel, ongoing DRP profiling linked to national clinical studies at the Hematology and BMT Unit of the University of Parma enables rapid clinical translation. This includes the implementation of individualized, N-of-1 therapeutic strategies based on ex vivo responses. Ultimately, we aim to construct predictive models that link chromatin states, gene expression programs, and drug sensitivities to support a dynamic, systems-level precision medicine framework. Our goal is to improve therapeutic outcomes

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	for patients with ETP-ALL by enabling biology-driven treatment decisions, particularly in genomically uninformative or treatment-resistant cases.
Main Topics of the Lab	Genomics of Acute Leukemia | High throughput screening| Target discovery
Main Research Area	Genomic Medicine
Institutional Page Link	https://www.ao.pr.it/curarsi/reparti-e-servizi-sanitari/ematologia-e-centro-trapianti-midollo-osseo/
Lab Website Link	https://mc.unipr.it/laboratorio-di-ematologia-traslazionale-e-chemogenomica

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Lab no. 22

Principal Investigator	Ruggeri Loredana
Hosting Institution	Azienda Ospedaliera di Perugia (Perugia Hospital Authority)
Proposal Title	How to reduce the incidence of acute GvHD and leukemia relapse after HSCT with Treg/Tcon adoptive immunotherapy.
Keywords	Immunotherapy; Treg cells; T cells/TCR; GVHD and/or Graft versus Tumor; Hematopoietic stem cell transplantation (HSCT)
PhD Project Description	Our Center demonstrated extensively T cell-depleted haploidentical (haplo) hematopoietic stem cells transplants (HSCT) may cure high risk leukemia patients across the HLA barrier without GvHD. T cell depletion without the need of post-transplant immune suppression gave the opportunity to discover the beneficial role of donor vs recipient natural killer (NK) cell alloreactivity which reduced the risk of GvHD and leukemia relapse. T cell-depleted transplant platform was also the best setting to explore donor immunotherapy. Recently, we showed infusion of donor regulatory T cells (Tregs) followed by conventional T cells (Tcons) at the time of transplant prevented GvHD while favouring GvL effect. In our clinical trials we observed low incidence of posttransplant leukemia relapse in high-risk acute leukemia patients. Even though we further decreased leukemia relapse and non-relapse mortality (NRM), we still observe 30% aGvHD in the absence of cGvHD, 10% relapse and 20% NRM in the haplo transplant setting. In Clinical Immunology Laboratory at Hematology section at Perugia University and General Hospital we are developing a project to further reduce GvHD and infection-mortality and relapse. Within such studies we propose a PhD research that aim to reduce incidence of GvHD: 1) by the use of citokine priming of Tregs in order to potentiate their inhibitory function, 2) by the use of drugs in Treg preparation that are able to preserve Tregs while eliminating Tcon contamination that could be responsible of GvHD. Moreover such project aims to design new donor or third party antileukemic car cells to eliminate residual leukemic cells.
Main Topics of the Lab	Clinical immunology in blood cancer, HSCT and immunotherapy

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Main Research Area	Immunology
Institutional Page Link	https://www.ospedale.perugia.it/strutture/ematologia

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Lab no. 23

Principal Investigator	Santaguida Stefano
Hosting Institution	Istituto Europeo di Oncologia I.R.C.C.S. S.r.l. (European Institute of Oncology)
Proposal Title	Molecular and clinical characterization of micronuclei in chromosomally-unstable tumors
Keywords	Cell cycle; Genomic/Genetic instability; Aneuploidy; Mitosis
PhD Project Description	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 build upon our recent publication (Martin et al., Science 2024) and we will analyze p62 protein levels in breast and ovarian cancer samples as well as identify proteins regulating p62's micronuclear localization. This will be achieved 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 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 Topics of the Lab	Genome Integrity

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Main Research Area	Cancer biology
Institutional Page Link	https://www.research.ieo.it/research-and-technology/principal-investigators/stefano-santaguida/
Lab Website Link	https://www.santaguidalab.org

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Lab no. 24

Principal Investigator	Tamagnone Luca
Hosting Institution	Università Cattolica del Sacro Cuore (Catholic University of the Sacred Heart)
Proposal Title	Novel molecular mechanisms controlling metastatic ovarian cancer cells
Keywords	Cell signaling; Ovarian ca.; Metastasis; Spheroids/3D cultures; Liquid biopsy
PhD Project Description	High-Grade Serous Ovarian Carcinoma (HGSOC) is the most lethal malignancy in women. Current therapeutic options are limited, due to lack of specific molecular targets. Moreover, biomarkers predicting drug response are missing or unsatisfactory. There is a need for primary HGSOC models, enabling more reliable and significant studies on the mechanisms sustaining cancer cell renewal, invasiveness and metastatic dissemination, as well as drug-responsiveness. Liquid biopsies of the ascitic fluid of HGSOC patients could provide valuable information by enabling genomic and transcriptomic analyses of patient-derived disseminated cancer cells, tumor-associated inflammatory cells and extracellular vesicles. Furthermore, the host lab has established a protocol for isolating and propagating in culture self-renewing patient-derived HGSOC cells that can provide new significant experimental models to study molecular mechanisms controlling cancer cell behavior, therapeutic response, peritoneal nesting/invasion, and metastatic dissemination in murine preclinical models. A Physician Scientist aiming to accomplish her/his PhD in our labs at the Università Cattolica/Policlinico Gemelli-IRCCS in Rome will be deeply involved in this project at the crossroads between patients and molecular research. We are currently applying Next Generation Sequencing (NGS) to study the genomic and transcriptomic profile of cancer cells, as well as extracellular vesicles, retrieved from a growing collection of (over 100) ascitic fluid biopsies from advanced HGSOC patients with annotated clinical follow-up. We will furthermore perform single-cell analysis of a subset of these samples, to investigate cellular heterogeneity and potentially identify molecular subtypes of HGSOC cells (or peculiar inflammatory cell profiles). The prospective PhD candidate will be involved in these analyses, and in the functional validation of promising novel candidate therapeutic targets and biomarkers predicting drug responsiveness. To this end,

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	the new lab member will be allowed to exploit patient-derived HGSOC 3D-models in culture and avatar xenografts in vivo.
Main Topics of the Lab	Molecular mechanisms controlling cancer progression and metastasis
Main Research Area	Cancer biology
Institutional Page Link	https://docenti.unicatt.it/ppd2/it/docenti/59412/luca-tamagnone/profilo

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Lab no. 25

Principal Investigator	Zucali Paolo Andrea
Hosting Institution	Humanitas Mirasole S.p.A.
Proposal Title	Targeting pathogenesis and therapies of Thymic Epithelial Tumors at crossroad between cancer immunology and autoimmunity
Keywords	Microenvironment; Autoimmunity/Autoantibodies; Immune escape; Computational biology; Thymoma
PhD Project Description	Hypothesis Our preliminary data revealed that, other than ab and gd T cells, the tumor micro-environment (TME) of TETs is also home of other infiltrating immune cells such as Natural Killer (NK) and B lymphocytes as well as of Dendritic Cells (DCs). While all these immune cells have been described to play a major role in the pathogenesis of many solid cancers and in the onset of several ADs, a deep characterization of tumor-infiltrating and circulating immune cells of TETs could allow us to a better understanding of the cellular and molecular immunologic mechanisms associated with TETs and autoimmunity. Aims The main aim of this research proposal is to investigate the phenotypes and functional relevance of tumor-infiltrating and peripheral blood immune cells from TETs' patients either showing or not co-morbidities with ADs. Experimental Design This project is sub-divided in 3 main tasks: 1) Patient recruitment and sample collection. 2) Characterization of tumor-infiltrating and circulating immune cells as follow: a. Phenotypic and Functional Characterization of DCs, T and NK cells b. B cells, autoimmunity c. Transcriptomic profiles 3) Characterization of tumor infiltrating immune cells by tissue imaging Expected Results Enroll and collect samples of at least 100 adult patients diagnosed with TET (at least 50 with and 50 without ADs) and 10 patients affected by thymic hyperplasia as controls. Characterize tumor-infiltrating and circulating immune cells to disclose the pathogenic mechanisms of tumor escape from the immune-surveillance exerted by DCs, T-, B- and NK-cells. Reveal the precise contribution and mechanisms of T-, B- and NK-cells in the co-morbidity of ADs with TET. Identify tissue biomarkers and cellular infiltrates possibly predicting TETs' disease progression and survival and/or correlation with ADs by imaging mass cytometry.

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Main Topics of the Lab	Characterization of tumour-infiltrating and circulating immune cells
Main Research Area	Cancer biology
Institutional Page Link	https://www.humanitas.it/

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