European School of Molecular Medicine

RESEARCH ACTIVITY SHEET

2025 PhD selections

YOUR DETAILS

* Name & Surname: Stefano Casola

* Affiliation IFOM

PHD PROJECT DETAILS

* Title of the proposed project

When protection from autoimmunity causes aggressive B cell lymphomas: from molecular mechanisms to clinical implications

* Short description of the project (up to 300 words)

Self-reactive antibodies are responsible of several autoimmune disorders including rheumatoid arthritis and systemic lupus erythematosus. B cell autoimmunity results from faulty checkpoints preventing the maturation of B cell expressing autoreactive immunoglobulins. B cell receptor (BCR) editing (RE) is a rescue mechanism allowing newly formed autoreactive B cells to revise their B cell receptor specificity through secondary immunoglobulin light chain (IGL) rearrangements, overcoming initial self-reactivity. RE is catalyzed by the RAG1/2 recombinases. We recently reported that aggressive B cell lymphomas carrying MYC and BCl2 translocations (also called Double-hit lymphomas or DHL) express the RAG recombinases and undergo BCR editing. Notably, in these lymphomas, MYC translocations driving the aggressive phenotype results from aberrant secondary IGL chain rearrangements, juxtaposing the oncoprotein to IG regulatory sequences. These results establish a direct link between (faulty) BCR editing and lymphomagenesis.
Patients suffering from DHL recurrently report a previous history of Follicular lymphoma an indolent B cell malignancy driven by BCL2 rearrangements. We show that RAG1/2 expression can be already tracked in a subset of FL cells months/years prior to the onset of DHL. These results suggest that RAG1/2-positive cells in FL represent the precursors of DHL.
Why and how is receptor editing induced in FL/DHL precursor cells? Can we identify early biomarkers of FL evolution to DHL? What is the role of the B cell receptor in Fl to DHL evolution?
The candidate will be engaged in a research program addressing these questions. He/she will be involved in developing a new mouse model to recapitulate the steps linking receptor

editing to DHL ontogenesis. By exploiting single-cell (sc) and spatial sc transcriptomics of human FL specimens the student will try to capture the biology and topology of rare RAG1/2+ malignant cells to capture their identity, BCR specificity and cross-talk with local immune/stromal components.
The candidate is expected to have a good knowledge in (B cell) immunology and cancer genetics. Previous experience in working with mouse (lymphoma)n models will be highly considered. Previous experience in molecular biology, genetics and flow cytometry techniques will help the student to get rapidly acquainted with her/his project.

* Indicate the main research area for the project described above Cancer Biology

If needed indicate a second research area for the project described above Immunology

* Provide up to 3 key words for project:

B cell receptor, lymphoma, preclinical models

YOUR LABORATORY ACTIVITIES DETAILS

* Main topic/s of the lab

Molecular mechanisms controlling B cell differentiation, immunity and lymphomas

* Short description of the lab activity (up to 500 words)

Our lab focuses on studying mechanisms controlling B cell development, immunity and lymphomagenesis. We combine analyses of genetically engineered mouse models, primary human and mouse B lymphoma cultures and healthy and pathological lymphoid tissue specimens, including several types of B cell lymphomas. We apply in vivo conditional gene targeting methods to study gene function in a cell type and stage-specific manner. We employ CRISPR/cas9 gene editing to study gene function in 2D and (in the future) 3D human primary B cell cultures. We model human lymphomas engineering primary human germinal center B cells with combinations of tumor-promoting genes identified in human B cell malignancies. A major focus of the lab is to investigate in mouse models, primary human B cell cultures and human lymphoma tissue specimens the role of the B cell receptor in maintenance and immune surveillance of B cell lymphomas. The lab has established over the years a solid network of collaborations with internationally recognized pathologists, hemato-oncologists and B cell immunologists. The lab has a translational drive with the goal to transform basic knowledge in treatment options for lymphoma patients. The laboratory welcomes every year medical students from top national (i.e. Scuola Normale Sant'Anna, Pisa) and international (Kyoto University, Japan) universities with the goal to foster an interdisciplinary environment.

* Selected bibliography (max 5 references)

1. Sindaco P, Lonardi S, Varano G, Pietrini I, Morello G, Balzarini P, et al. B cell receptor silencing reveals the origin and dependence of high-grade B cell lymphomas with MYC and BCL2 rearrangements. 2025. doi: doi.org/10.1101/2024.07.13.603066; Blood Cancer Discovery, revised manuscript under final consideration).

2. Casola S, Perucho L, Tripodo C, Sindaco P, Ponzoni M, Facchetti F. The B cell receptor in control of tumor B cell fitness: biology and clinical relevance. Immunol. Rev. 2019.

3. Varano G, Raffel S, Sormani M, Zanardi F, Lonardi S, Zasada C, Perucho L,Petrocelli V, Haake A, Lee AK, Bugatti M, Paul U, Van Anken E, Pasqualucci L, Rabadan R, Siebert R, Kempa S, Ponzoni M, Facchetti F, Rajewsky K, Casola S. The B-cell receptor controls fitness of MYC-driven lymphoma cells via GSK3β inhibition. Nature. 2017 Jun 8;546(7657):302-306. doi: 10.1038/nature22353. PubMed PMID: 28562582.

* Group composition: total members, and roles distribution (PhD, postdoc, technician, etc.)

Our lab is currently composed of a post-doctoral fellow, a research technician, a senior staff researcher, two PhD students, one research fellow and one master thesis student.

Institutional page link

https://www.ifom.eu/en/cancer-research/research-labs/research-lab-casola.php
https://www.unimi.it/it/ugov/person/stefano-casola

Lab website link, if any

https://www.ifom.eu/en/cancer-research/research-labs/research-lab-casola.php

Social media links, if any

If you prepare a video to promote your lab/project, please include the link below