

 <p>UniSR Università Vita-Salute San Raffaele</p>	<p>APPLICATION TO ACT AS SUPERVISOR AND RESEARCH PROJECT PROPOSAL</p>	<p>MO 20-5 ed. 02 of 16/01/2026 PO 20 Page 5 of 12</p>
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PROJECT

Supervisor: MASSIMO DEGANO

Title: DECODING B CELL RECEPTOR SIGNALLING IN CHRONIC LYMPHOCYTIC
LEUKEMIA

Curriculum: Molecular Medicine - Basic and Applied Immunology and Oncology

Link to the personal page of the University or relevant hospital website: <https://research.hsr.it/en/divisions/immunology-transplantation-and-infectious-diseases/biocrystallography.html>

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Chronic lymphocytic leukemia is characterized by the accumulation of mature B cells whose survival and expansion depend on signalling through the B cell receptor (BCR). In addition to antigen-driven activation, CLL cells can exhibit cell-autonomous signalling mediated by receptor-receptor interactions. However, the relative contribution and interplay of autonomous versus microenvironment-derived signals remain incompletely understood. Recent findings indicate that antigen engagement within the microenvironment also plays a significant role, raising key questions about how different modes of BCR engagement shape leukemic cell behaviour.

Rationale and hypothesis

We hypothesize that CLL BCRs integrate signals arising from distinct modes of engagement—including homotypic interactions and binding to self or non-self antigens—with different affinities and avidities, leading to qualitatively different signalling outputs and cellular programs. Understanding how these molecular interactions are encoded and translated into functional responses is essential to explain disease heterogeneity and may reveal new opportunities for targeted intervention.

Objectives and specific aims



The project aims to define the molecular and functional basis of BCR-mediated signalling in CLL. Specific aims are a) To characterize the molecular features of BCRs involved in autonomous and antigen-dependent signalling; b) To investigate how different modes of engagement (homotypic vs antigen-driven) and binding properties (affinity/avidity) influence receptor activation; c) To link distinct interaction modes to downstream signalling pathways and cellular responses in primary CLL cells and model systems; d) To explore the feasibility of designing BCR-binding polypeptides using AI-based approaches for potential therapeutic applications.

Expected outcomes

The project will provide a mechanistic framework linking modes of BCR engagement to signalling and functional outcomes in CLL. It is expected to clarify how autonomous and antigen-driven processes coexist and contribute to disease variability. In addition, the development of designed BCR-binding molecules may open new avenues for therapeutic strategies, including their potential use in engineered cellular therapies or bispecific formats.

Skills that the student should acquire (max. 600 characters including spaces):

The student will gain interdisciplinary training in molecular and cellular immunology, including the study of receptor interactions, signalling mechanisms, and functional responses. They will develop skills in experimental design, data analysis, and interpretation, with exposure to structural and computational approaches. The project fosters an integrative view linking molecular detail to cellular function.

References (max. 15)

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