PhD Offer - Biophysics/Immuno-Oncology - France

Adhesion and Inflammation Lab (LAI) Web: https://labadhesioninflammation.org/
Aix Marseille University – CNRS – Inserm – Luminy Campus, Marseilles, FRANCE

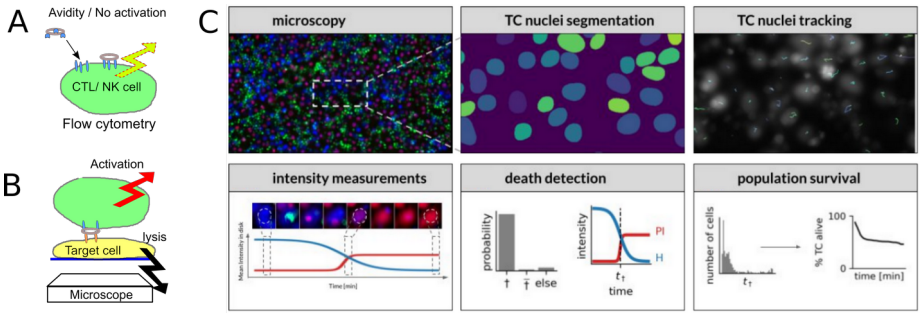
Mechanisms of action of new molecular agents at immune cell surfaces

The function of immune cells is finely controlled by specific biomolecular recognition and signaling at cell-cell contacts. While the genetics and biochemistry of these phenomena have been extensively studied, the emergent roles of biophysical factors like geometry, multivalency and mechanical forces intervening at this interface are still poorly understood. The multiscale structures from single ligand-receptor bonds to supramolecular assemblies, as well as the entanglement of biochemical and physical mechanisms at the nanoscale render functional studies and mechanistic descriptions very complex. While this interface constitutes a target of choice for immunotherapy strategies, the above limitations render haphazard the design of new therapeutic agents. We propose to combine rigid or flexible DNA scaffolds which provide extraordinary structural programmability with the exquisite protein recognition properties and small size of single domain antibodies (or Nanobodies). These new agents, DNAnobodies, will be co-developed for precise biophysical / biological applications and tested by experts within our interdisciplinary consortium, funded by ANR (French National Research Agency).

Project

The intrinsic multispecificity of DNAnobodies makes them natural cross-linkers of cell-surface receptors, which leads to signaling by receptor clustering and recruitment phenomena in both cis and trans configurations. The aim of the PhD project is to build on consortium results to design and test bridging multispecific DNAbs capable of recruiting effector immune cells on target cells and mediate a cytotoxic effector response. Ideally, the properties of the bridging agent would combine:

i) bind to target cells from solution with high selectivity
ii) bind to immune effector cell from solution without causing cell activation
iii) activate immune cell upon cell-cell binding, possibly via force-mediated action
iv) be efficient at low concentration



A. Selected DNAbs will be incubated with immune or target cells to test for avidity and activation properties. B. They will be further co-incubated with target and effector cells for mediating cell cytotoxicity in a high throughput AI-based microscopy assay developed in LAI and detailed in C.

The strategy will consist in four steps: a) based on previous packages results, define some candidate DNA scaffolds and Nb functionalizations to achieve the required properties b) perform high content information assays to test the interactions of selected DNAbs separately on effector and target cells, and c) in

co-cultures of targets and effectors. d) correlate recruitment and force mapping with cytotoxicity efficiency in order to refine the choice of DNAb properties.

Keywords
Bispecific therapeutic antibodies, Single molecule and single cell techniques, High-content microscopy, Surface optical microscopy, Deep-learning, Modeling.

Interdisciplinarity and environment

This project is part of an interdisciplinary consortium coordinated by L. Limozin and gathering for teams from antibody engineering, single molecules studies, nanosciences and biophysics. The candidate will work in close collaboration with a Biology PhD student in charge of the synthesis of DNAnobodies (Centre de Recherche en Cancérologie de Marseille, Team Chames) as well as a postdoctoral physicist in charge of testing DNAnanobodies on artificial surfaces (Centre Interdisciplinaire de Nanosciences de Marseille, Team Sengupta) both members of the consortium.

Profile of the candidate

The candidate should have an academic background in physics/biophysics or in biology (eg. Immunology, biochemistry or molecular biology) with previous experience of in biophysics and quantitative approaches. Previous experience in microscopy and biophysics will be highly considered. We look for strongly motivated candidates willing to work at the interface of physics and biology, in young and interdisciplinary laboratories, gathering physicists, biologists and medical doctors.

Recruitment Procedure

The proposed PhD is funded through a project coordinated by Laurent Limozin. Candidate should send by email, their CV with excellent academic records, a letter of motivation and provide the name of two references. Position is available immediately.

Contact: Laurent Limozin (LAI), laurent.limozin@inserm.fr,
Tel : +33491828855, Web: https://laurentlimozin.wordpress.com/