Universitat Pompeu Fabra Barcelona | Master in Bioinformatics for Health Sciences

Master project 2024-2025

Personal Information

Supervisor	Enrique Marcos
Email	embcri@ibmb.csic.es
Institution	Molecular Biology Institute of Barcelona (IBMB), CSIC
Website	https://www.ibmb.csic.es/en/department-of-structural-and-molecular-biology/protein-design-and-modeling/
Group	Protein Design and Modeling

Project

Structural bioinformatics

Project Title:

De novo design of antibody-like proteins with expanded functionalities

Keywords:

protein design, protein structure prediction, beta-sheet proteins, ligand-binding, protein-protein interactions, allosteric regulation

Summary:

The de novo protein design revolution from the last decade has enabled the creation of a wide range of folds with hyperstability and structural accuracy, and customized for binding to target small-molecules or proteins, which opens the door to overcome the limitations of natural proteins in biotechnological and medical applications. To date, approaches to engineering antibodies rely on naturally occurring immunoglobulin backbone frameworks, and mainly focus on optimizing the antigen-binding loops and/or multimeric formats for improving targeting efficiency or biophysical properties. Despite their exponential advance as protein therapeutics, engineered antibodies have significant limitations in terms of stability, manufacturing, size and structure, among others. Additionally, there is considerable interest in regulating the activity of antibodies through endogenous or exogenous signals to achieve superior site-selectivity and minimize side effects, but this remains challenging to engineer due to the complexity and lack of structural control over natural antibody frameworks. Towards the de novo design of antibody-like proteins with superior properties and expanded functionalities, we have recently pioneered the de novo design of immunoglobulin frameworks by combining physics- and deep learning-based computational approaches, which were confirmed experimentally by combining biochemical methods and X-ray crystallography. Towards designing antibody-like proteins capable of binding any target of interest under the control of small molecule drugs or peptides, we will benchmark different computational pipelines to design ligand-binding loops in close proximity to ligand-binding pockets that could regulate the protein-binding activity. We will start from our in-house two-domain immunoglobulin frameworks, which can display pockets at the interface between the two domains, and tailor their structure to accommodate sites for ligands. We will then design and analyze the coupling between ligand- and protein-binding through a combination of deep learning-based structure prediction and design approaches (such as AlphaFold, RoseTTAFold, DiffDock, ProteinMPNN, among others) and molecular dynamics simulations. Beyond the scope of the master thesis, the most promising designs will be experimentally tested and characterized in our lab.

References:

Roel-Touris J, Carcelén L, Marcos E* (2024). “The structural landscape of the immunoglobulin fold by large-scale de novo design”. Protein Science, 33(4): e4936. Roel-Touris J, Nadal M, Marcos E* (2023). “Single-chain dimers from de novo immunoglobulins as robust scaffolds for multiple binding loops”. Nat. Commun., 14: 5939 Chidyausiku TM, Mendes S, Klima J, …, Gomis-Rüth FX*, Baker D*, Marcos E* (2022). “De novo design of immunoglobulin-like domains”. Nat. Commun., 13: 5661. DOI: 10.1038/s41467-022-33004-6. Posición: 14/14. Peñas-Utrilla D, Marcos E* (2022). “Identification of well-folded de novo proteins in the new era of accurate structure prediction”. Front. Bio. Mol. Sci., 9. DOI: 10.3389/fmolb.2022.991380 Marcos E*, Silva DA* (2018). “Essentials of de novo protein design: Methods and applications”. Wiley Interdiscip. Rev.-Comput. Mol. Sci, e1374. DOI: 10.1002/wcms.1374. Marcos E*, Chidyausiku TM, McShan A, .., Baker D* (2018). “De novo design of a non-local β-sheet protein with high stability and accuracy”. Nat. Struct. Mol. Biol., 25: 1028-1034. DOI: 10.1038/s41594-018-0141-6

Expected skills:

Knowledge on Linux and scripting languages (python), analytical thinking, curiosity, strong motivation and independence

Possibility of funding:

To be discussed

Possible continuity with PhD:

To be discussed