Institut de Bioenginyeria de Catalunya

COLLABORATIVE IBEC INTERNATIONAL PhD PROGRAMME

Position

1. Project Title:
   AI-Driven Phenotypic Targeting: Molecular Engineering for Precision Medicine

2. Research project/ Research Group description

We propose to combine molecular engineering and machine learning (ML) to develop precision therapeutics that achieve phenotypic targeting at both receptor and cellular levels. Phenotypic targeting represents the next frontier in precision medicine, combining weak but highly selective interactions at single receptors with multi-receptor specificity at the cellular level. It eliminates off-target effects and creates unique interaction profiles based on the phenotypic signature of target cells. However, designing molecular systems capable of such specificity remains a significant challenge due to the complexity of biochemical and biophysical factors involved. The project will address this challenge by integrating molecular engineering and artificial intelligence advances. We will engineer drugs with well-defined supramolecular architectures, employing amphiphilic block copolymers and peptidic ligands to create assemblies such as micelles and vesicles with tailored properties. These architectures will maximise entropy-driven selectivity and optimise for specific phenotypes. Machine learning techniques, including generative models and predictive analytics, will explore and optimise design space, while experimental validation will iteratively refine the computational models.

The research will be conducted collaboratively between the Molecular Machine Learning group led by Prof. Francesca Grisoni (Eindhoven University of Technology) and the Molecular Bionics group led by Prof. Giuseppe Battaglia (IBEC). Prof. Grisoni's expertise in ML for drug discovery complements Prof. Battaglia's pioneering work in molecular engineering, offering the PhD candidate a unique opportunity to engage in cutting-edge research at the intersection of computation and experimentation. This project promises to deliver transformative methodologies and therapeutic candidates, advancing the fields of precision medicine, molecular engineering, and artificial intelligence.

3. Job position description

The PhD candidate will work on developing machine learning models to predict molecular properties linked to phenotypic outcomes, with a particular focus on entropy-driven selectivity and binding dynamics. This will include training predictive models, employing generative approaches such as variational autoencoders (VAEs) and generative adversarial networks (GANs) to design tailored molecular constructs, and implementing explainable AI to uncover key

drivers of selectivity. Building on previous work on **low-density lipoprotein receptor-related protein 1 (LRP1)** and its critical role in blood-brain barrier (BBB) crossing, the candidate will focus on designing supramolecular drug systems that exploit LRP1-mediated transport. Using available structural information about LRP1, including its quaternary structure, the candidate will collaborate on molecular engineering to create micelles decorated with optimised peptides. The optimisation process will combine **molecular docking simulations** to predict binding affinities and conformations with **biophysical techniques** such as **surface plasmon resonance (SPR)** and **quartz crystal microbalance (QCM)** for validation and refinement. These micelles will be synthesised and characterised using advanced methods, including **transmission electron microscopy (TEM)** and light or neutron scattering, to optimise their size, shape, and stability for phenotypic targeting. The candidate will also analyse interaction profiles at single-receptor and cellular levels to identify unique phenotypic signatures. This will lead to the design of super-selective molecular constructs by integrating weak interaction motifs with polymer stabilisation, size, and shape engineering. Expected outcomes include the development of AI tools capable of predicting and designing phenotypic targeting molecules, a library of experimentally validated drug candidates, and high-impact publications in molecular engineering, machine learning, and precision therapeutics.

Candidates will undergo advanced training in machine learning, computational chemistry, molecular design, and polymer science. They will also learn about the synthesis and characterisation of micelles or vesicles, along with advanced techniques such as TEM, SPR, and QCM. Essential programming skills include proficiency in Python or similar languages. We are looking for candidates with a physical sciences or engineering background who excel in teamwork and communication and are genuinely interested in interdisciplinary research. This project offers a rare opportunity to collaborate with leading experts, access state-of-the-art facilities at TU/e and IBEC, and engage in groundbreaking research at the intersection of molecular engineering, machine learning, and precision medicine.

Group Leader at IBEC

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Collaborator at ICMS

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