Research Project

29.06.2024

Development of Inhibitors Targeting the Complement System: An Integrative Approach Using Computational Chemistry and Empirical Methods

The Complement system, a vital component of our immune response, is a key target for therapeutic intervention. Researching serine proteases as therapeutic targets has gained significant interest in recent years. Manipulating this system by designing effective inhibitors can revolutionize treatments for various health conditions. This project bridges the gap between computational biophysics and bioassays to identify and validate potential inhibitors. Notably, the first hits already exist, providing a solid foundation for further development.

Upon successful completion, this project aims to produce a set of potential inhibitors with validated activity against the complement system. This can pave the way for further in-depth studies and eventual therapeutic applications.

We invite enthusiastic and dedicated students to be a part of this project. We offer the opportunity to work in an emerging research branch of the immune system and to learn various computational as well as molecular biological assays.

Aims

To design, validate, and optimize small molecule inhibitors that effectively block the complement system. This endeavor combines computational and lab-based methods. The chemical synthesis itself is performed by a senior chemist in the lab. In addition, the student will determine the selectivity profile of the compounds to other serine proteases from the complement and coagulation system.

Requirements

- Students of pharmacy, Drug Science and open to external students.
- Strong motivation to perform both computational tasks and biological assays.
- A keen interest in proteins, biophysics and chemistry.
- A willingness to learn the basics of programming, which will be fundamental for some computational methods applied in the project.

Methods used

Wet Lab Techniques:

- These will include enzymatic assays to test the activity of proposed inhibitors on specific complement system enzymes.
- Enzymatic assays: Competitive inhibition assays with fluorscent and chromogenic reporters.
- ELISA (Enzyme-Linked Immunosorbent Assay): For quantitative detection of complement system inhibition.
- Optional: Biophysical binding assays: MST, SPR, ..

Computational Techniques:

- Molecular Docking: To predict the binding orientation of the inhibitor to the protein targets, which can predict the strength and nature of the interaction.
- Molecular Dynamics: For simulating the physical movements of atoms and molecules, enabling the study of the dynamics between the proposed inhibitor and the target.
- Rational Design: Systematic approaches will be used to optimize inhibitor design based on feedback from both computational predictions and lab results.

Software and Programming:

- Maestro Schrödinger: For molecular modeling, simulation, and analysis.
- PyMol: A tool for visualizing molecular structures and understanding protein-ligand interactions.
- Python: Basic programming skills in Python will be required for certain simulations and data analysis tasks.

Duration

The research can be tailored to two formats:

- A comprehensive Master's thesis spanning several months.
- A more concise research project for a shorter duration, focusing on specific aspects of the research objective.

Potential start dates: 01.08.2024 - 01.03.2025

Contact

The project will be supervised by:

- Rüthemann Peter, PhD, Molecular & Computational Pharmacy (peter.ruethemann@unibas.ch)
- Prof. Martin Smieško, Computational Pharmacy

Please apply with a CV and a motivation letter to Rüthemann Peter.