

Development of methods for testing lipase-drug interactions

Summary

The goal of the project is to develop biophysical methods that can be used for testing lipase-drug interactions. The main disadvantage of the current methods is that the studies are performed in environments that are very different from those where lipases act. Therefore, many drug development projects fail. To achieve better results, it is necessary to develop methods that allow testing drug candidates in a close-to-native conditions. This PhD project involves testing different biophysical techniques and approaches to find most suitable ones for testing lipase-acting drugs under physiological conditions.

Research field:	Chemistry and biotechnology
Supervisors:	Prof. Dr. Riina Aav Dr. Aivar Lõokene
Availability:	This position is available.
Offered by:	School of Science Department of Chemistry and Biotechnology
Application deadline:	Applications are accepted between June 01, 2022 00:00 and June 30, 2022 23:59 (Europe/Zurich)

Description

Lipases are important drug targets. These enzymes play crucial roles in lipid metabolism, transport and distribution. Deficiency of lipases or their dysregulation leads to various diseases, including atherosclerosis, pancreatitis and obesity. Our research is focused on gastro- intestinal lipases (gastric lipase, pancreatic lipase) and vascular lipases (lipoprotein lipase, hepatic lipase and endothelial lipase). The action of these lipases controls the level of triglycerides (fats) in the blood circulation. Although significant progress has been made in understanding the complex regulation system of the lipases of our interest, there are still several aspects that require further investigation. This is primarily because the main knowledge about their action is mostly based on experiments performed with purified proteins and synthetic lipid substrates in conventional buffer solutions. However, in vivo lipases act in complex environments at the surface of lipid particles. Many drug development projects on lipases have failed because the investigations were performed under artificial conditions. Our recent studies suggest that combined using of isothermal titration calorimetry, surface plasmon resonance, nuclear magnetic resonance and fluorescence techniques would provide promising results in testing drug candidates that affect the action of lipases.

The goal of this PhD project is to further develop experimental approaches for investigation lipase-drug interaction. The project also includes design and testing of drug candidates that increase the activity of lipoprotein lipase or decrease the activity of pancreatic or gastric lipase.

Supervisors

Main supervisor: Dr. Aivar Lõokene
Co-supervisor: Prof. Dr. Riina Aav

Responsibilities and (foreseen) tasks

- Compile a work plan for the 4-year PhD investigations (together with supervisors)
- Express and purify the desired recombinant proteins. Test various expression approaches: compare mammalian, yeast or bacterial systems
- Design of potential drug candidates that could affect lipases
- Perform experiments using isothermal titration calorimetry, surface plasmon resonance and fluorescence techniques
- Contribute to the organization of seminars where project findings are presented

Applicants should fulfil the following requirements:

- a master's degree in natural sciences
- a clear interest in biophysical techniques
- laboratory skills in chemistry or molecular biology
- good command of English
- strong and demonstrable writing and analytical skills
- capacity to work both as an independent researcher and as part of an international team

The following experience is beneficial:

- Working knowledge of protein chemistry and enzymology
- Working knowledge of chemical kinetics and statistics
- Working knowledge of organic chemistry

The candidate should submit a research plan for the topic, including the overall research and data collection strategy. The candidate can expand on the listed research questions and tasks, and propose theoretical lenses to be used.

We offer:

1. 4-year PhD position in a lab that is focused on drug-protein interaction studies.
2. The chance to be actively involved in drug development process
3. To learn modern biophysical techniques and approaches of protein science such as isothermal titration calorimetry, surface plasmon resonance and mass spectrometry
4. Opportunities for conference visits, research stays and networking with other research groups
5. The chance to continue research carrier in leading drug development labs

About the department

The Department of Chemistry and Biotechnology of Tallinn University of Technology is focused on research in biochemistry and organic chemistry, also in biotechnology and molecular biology. It is a center of Tallinn University of Technology that enables to perform interdisciplinary research for drug development. The department has major facilities and equipment needed to carry out for the proposed PhD project: a) Equipment for interaction and structural studies: fluorescence spectrophotometer Hitachi F-7000 (Hitachi High-Tech), isothermal titration calorimeters: nano ITC (TA Instruments) and MicroCal PEAQ-ITC (Malvern Instruments), surface plasmon resonance device BIAcore 3000 (GE Healthcare), ESI Q-TOF mass spectrometer (Agilent Technologies) b) Facilities for expression and purification of recombinant proteins: PCR and qPCR PCR-machines, three cell culture rooms for protein expression in *E. coli*, *P. pastoris* and the baculoviral expression systems, microscopes, incubators and shakers, steam sterilizers, water purification system, +4°C cold room, two -80°C freezers, and a protein purification system ÄKTA Purifier. NMR studies will be carried out in the National Institute of Chemical Physics and Biophysics. The institute will grant access to an 800 MHz Bruker Advance III spectrometer equipped with a cryogenically cooled QNP probe.

Additional information

For further information, please contact Dr. Aivar Lõokene aivar.lookene@taltech.ee



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