



UNIVERSITY
OF WARSAW



Doctoral School of
Exact and Natural
Sciences

CeNT CENTRE
OF NEW
TECHNOLOGIES

CeNT-27-2023

Competition notice

PRELUDIUM BIS

Project title: Biological membranes and macromolecular crowding in the function of the hepatitis C virus proteases

Research project manager: Joanna Trylska, Biomolecular Machines Laboratory, Centre of New Technologies

E-mail: joanna@cent.uw.edu.pl

Project description

Enzymes are biocatalysts that speed up chemical reactions. These reactions occur in cells, which form a crowded environment. Cells, apart from water and ions, contain many other molecules such as nucleic acids, proteins, ribosomes, lipids, and metabolites. In addition, the cellular environment is compartmentalized by phospholipid membranes. Membranes are used for cell protection, transport of compounds, and organizing cells' interior space. All in all, a specific biochemical reaction occurs with background macromolecules that may occupy 30% of the volume in mammalian cells. Apart from physically restricting the space for the enzyme of interest, the crowders and the membranes also nonspecifically interact with the enzyme and its substrates. The confinement and interactions may affect the reaction rates as compared to dilute water conditions. In addition, such conditions also affect the binding and effectiveness of enzyme inhibitors that are used as drugs.

However, for ease of interpreting the results, in a laboratory test tube, enzymes are often studied in dilute buffer solutions, which do not reflect the physiologic conditions and cell context. So, to understand what controls enzymatic activity and obtain realistic reaction rates or inhibitor efficiencies, we will perform enzymatic assays accounting for complex surroundings.

Proteases are an important class of enzymes that cleave peptide bonds and are involved in many biological functions. Also, viral genomes encode proteases that cleave the viral protein chain precursors after they are translated by the host cell machinery. Since these proteases are key to viral replication, they have been viable drug targets. Drugs inhibiting proteases of the human immunodeficiency virus and hepatitis C virus (HCV) have been used in antiviral combination therapies in humans.

We will investigate the reactions catalyzed by two enzymes encoded by the HCV genome. This virus causes liver inflammation which can lead to serious liver damage and cancer. One of the HCV enzymes that we will focus on is called the NS3/4A protease and is a known drug target with several drugs approved for clinical use in the last decade. The second one is the NS2 protease with no approved drugs as yet, but it is a possible target to consider. These two proteases work at the endoplasmic reticulum membranes of the host cell. Our goal is to determine how membrane environment and macromolecular crowding affect the

activity of these two hepatitis C virus proteases crucial for viral replication. We will also investigate how the membrane and crowded surroundings affect the efficiency of two drugs binding to NS3/4A. As membrane mimics we will use micelles, lipid vesicles and nanodiscs, which are nanoscale lipid bilayers. As crowder molecules, we will use synthetic polymers such as polyethylene glycol, polysucrose, polyglucose, and proteins. The efficiencies of the reactions will be monitored by various techniques such as fluorescence spectroscopy, electrophoresis, chromatography, and microcalorimetry.

Requirement

The call is open to all those who are not Ph.D. holders and are not students at the doctoral schools and:

- will hold an MSc degree in (bio)physics or a related discipline before Oct 1st, 2023, i.e., at the time of starting the Doctoral School,
- have a background in biophysics and biochemistry,
- are knowledgeable and interested in biophysics and biochemistry methods such as fluorescence and circular dichroism spectroscopy, and microcalorimetry,
- are interested in enzymatic reactions, biological membranes, and crowded milieu,
- will apply for and do a six-month internship abroad in the USA,
- will comply with the rules of the Preludium BIS projects found on the National Science Centre Poland webpage.

In addition:

- experience in laboratory work, especially with peptides and proteins, will be beneficial,
- very good command of spoken and written English is a must, as well as teamwork skills and critical thinking.

Discipline: physical sciences

Admission limit: 1

Recruitment schedule

- registration in the Internet Registration of Candidates, referred to as “IRK”, submitting an application to the IRK: from 10 May to 31 May 2023
 - qualification procedure: from 01 June to 07 June 2023
 - announcement of the ranking list: until 16 June 2023
 - accepting documents from qualified candidates: from 19 June to 21 September 2023 (2 p.m. Warsaw time)
 - announcement of the list of accepted candidates: until 30 September 2023
- Beginning of education – October 2023.

Recruitment fee

200 PLN

Form of the qualification proceedings

Qualification proceedings include the assessment of the following items:

- 1) the candidate's scientific activity, based on their CV or Resume, documented by the scans of materials attached to the application for admission to the School;
- 2) top ranked candidates may be invited for an interview (online interview is possible);
- 3) other achievements.

Language of the selection process, including the interview

The interview shall be carried out in Polish or English – in accordance with the candidate's preferences presented in IRK. If the Polish language is selected, the interview may include parts in English.

Required documents

The candidate shall submit a School admission application only through the IRK. The application shall include the following:

- 1) indication of the selected discipline in which the candidate plans to pursue education or in the case of applying for the Interdisciplinary Doctoral School – fields of science with the specification of the leading field (and where there is no leading field – at least two equivalent disciplines), PESEL number or passport number, nationality, contact information (residence address, e-mail address, telephone number), information whether the candidate agrees to receive administrative decisions by means of electronic communication, consent for processing of personal data for the purposes of the admissions procedure;
- 2) a scan of the graduation diploma of uniform master's degree or postgraduate studies or an equivalent diploma obtained under separate regulations or in the case of candidates pursuing education within the European Higher Education Area – a certificate of obtaining a Master's degree or a declaration that the diploma or certificate of obtaining a Master's degree shall be provided by 21.09.2023 – declaration form. In case the diploma was issued in a language other than Polish or English, the candidate shall attach its certified translation;
- 3) a resume or CV outlining the candidate's scientific activity, including scholarly interests and achievements during the five calendar years preceding the application (if a candidate became a parent during this time, as evidenced by a scan of the child's birth certificate attached to the application, this period shall be extended by two years for each child), including, but not limited to:
 - publications,
 - research and organizational work at student research groups,
 - participation in scientific conferences,
 - participation in research projects,
 - awards and honorable mentions,
 - research internships,
 - research skills training programs completed,
 - activities promoting science,
 - activity in science movement representative bodies,
 - average of their university grades,
 - professional career,
 - level of proficiency in foreign languages;
- 4) scans of materials evidencing scientific activity mentioned in their CV and/or resume;
- 5) a document confirming at least B2 proficiency level in English or a declaration of the level of proficiency in English allowing education at the School;

- 6) the scan of a declaration by the planned supervisor, confirming their agreement to undertake the duties of a supervisor and of the number of doctoral students, for whom they perform the duties a designated supervisor, in accordance with the template constituting Appendix no.4 to the Resolution no. 17 of the Senate of the University of Warsaw of 20th January 2021 on rules of admission to doctoral schools at the University of Warsaw (the University of Warsaw Monitor of 2021, item 142), the candidate may also attach a scan of their planned supervisor's opinion and opinions of other academics about the candidate and their scientific activity and/or proposed research project;
- 7) the photograph of a candidate's face that allows for their identification;
- 8) a declaration confirming whether the candidate was or is a doctoral student or a participant of doctoral studies or whether they have initiated a doctoral dissertation process or whether proceedings to award them a doctoral degree have been initiated – and if yes, the title of their doctoral dissertation or the research project prepared by a candidate, including the name and last name of the candidate's tutor or supervisor;
- 9) a declaration confirming that they have reviewed the Resolution no. 17 of the Senate of the University of Warsaw of 20th January 2021 on rules of admission to doctoral schools at the University of Warsaw (the University of Warsaw Monitor of 2021, item 142) and Articles 40 and 41 of the Code of Administrative Procedure;
- 10) scanned transcripts of records of the graduate and postgraduate studies or the uniform Master's degree studies, or equivalent documents (e.g. diploma supplement);
- 11) abstract of the master's thesis or master's project in English (up to 3,000 characters with spaces);

Evaluation criteria

- a) competencies to perform specific tasks in a research project (70% of the final score)
 - 3 points - very good
 - 2 points – good
 - 1 point – poor
 - 0 points - no competencies
- b) publication track record, including publications in renowned scientific papers / magazines (30% of the final score)
 - 4 points – prominent
 - 3 points - very good
 - 2 points – good
 - 1 point – poor
 - 0 points - no publication track record

Education program

The education lasts 4 years. It includes obligatory classes (no more than 300 hours in total during the whole period of education) and the implementation of an individual research program, carried out under the supervision of a supervisor. Beginning of education – October 1, 2023.

Scholarships

PRELUDIUM BIS doctoral scholarships shall amount to:

- PLN 4266.00 gross per month, until the month in which a PhD student's mid-term evaluation is performed at the doctoral school and
- PLN 5119.00 gross per month, after the month in which a PhD student's mid-term evaluation is performed at the doctoral school and

shall be awarded pursuant to the Act on Higher Education and Science of 20 July 2018.