AMBASSADE DE FRANCE EN INDE
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CEFIPRA

INSTITUT FRANÇAIS India

Job offer – PhD in Biotechnology/ Biophysics

Research Project Short Title as Submitted to CEFIPRA: "Structural insight into the molecular mechanism of amyloid interactions with lipid membranes"
Principal Investigator contact: "Prof MANGENOT Stéphanie, stephanie.mangenot@u-paris.fr", Université Paris Cité
Reference Number of the Job Offer: IFI_CEF_24_09

Project description:

- **Keywords:** Biophysics, Membrane Mechanics, Lipo-protein interactions, Alzheimer's, In vitro system

- **Context:**

  Deposition of amyloid fibrils as plaques is a general feature in neurodegenerative diseases, and particularly in Alzheimer's Disease (AD). The amyloid beta (Aβ) protein is linked to AD through its abnormal aggregation (fibrillation process), which can spread in a prion-like manner. Aβ aggregates disrupt the cellular membranes causing homeostasis of the cells, further leading to the cascade of biochemical processes in AD progression. Understanding structural changes in lipid membranes upon binding of different assembly forms of Aβ is the key in understanding the cytotoxic mechanisms. At a microscopic level, these structural changes are manifested by membrane fluidity, lipid composition, local curvature, and charge density of lipid head groups. In this project, we propose to resolve the nanomechanics of amyloid interactions with membranes using an in vitro approach with a combination of optical and electron microscopy (with 3D reconstruction and cryo-tomography), Atomic Force microscopy, optical tweezers, and molecular dynamics simulation studies.

- **Abstract of the Research Project**:

  In this project, we propose to resolve the nanomechanics of amyloid interactions with membranes using a combination of spinning disk confocal microscopy, cryo-electron microscopy with 3D reconstruction, cryo-tomography, optical tweezers, and molecular dynamics simulation studies. Neuronal-membrane mimicking lipid bilayer with varying compositions (DOPC, DOPE, cholesterol, and sphingomyelin) will be reconstituted. Interaction of amyloid of different assembled forms with this bilayer and their cytotoxicity will be studied. The binding affinity of amyloid on lipid bilayer of different charge density and membrane composition will be investigated. Extent of amyloid penetration into the lipid bilayer and membrane remodeling characteristics of amyloid will be investigated by biomimetic in vitro assays using giant unilamellar vesicles (GUV). Further, binding affinity towards positive and negative bilayer curvature will be studied with the help of cryo-electron microscopy. To support the experimental results, all-atom and coarse-grained molecular dynamics simulations will be performed. These simulations are expected to reveal molecular-level processes that underpin amyloid-membrane interactions and membrane structural changes. The combined experimental and computer simulations studies not only further our understanding of molecular mechanics of amyloid-lipid interaction, but could also provide guiding principles for the development of therapeutic drugs for AD.

- **Scientific Objectives of the Project:**

  The project contains 3 mains objectives which are:

  i- To investigate amyloid binding affinity towards different lipid compositions and their conformational changes in real-time using confocal and OT
  ii- To elucidate the amyloid membrane reshaping and penetration mechanics using high-speed AFM, confocal, and cryo-electron microscopic technique

iii- To attain molecular insights into amyloid lipid interactions using MD simulation

The PhD candidate will mostly be recruited to work on the first two points with experimental approach. He/she will perform various in vitro lipidic system to study how the Aβ proteins will interact and deform the lipidic membrane. The different deformation and interaction will be studied at various scale with combined optical and electron microscopy.

- **Methodology and Timeline of the Project:**

The thesis, spanning a duration of 36 months, would be evenly distributed between the two proposed milestones. We will progress synergistically on each of the objectives. Following the purification and labeling of the proteins (first 4 months), they will be deposited onto supported lipid bilayers to investigate their binding affinity (12 months). Subsequently, the proteins will be applied to Giant Unilamellar Vesicles (GUV) to measure the mechanical effect on the membrane (12-18 months), considering the lipid composition. Concurrently, Atomic Force Microscopy (AFM) experiments will be conducted to correlate the mechanical effects observed on GUV with AFM measurements (18-24 months). Finally, the transition from monomer to fibril state of the proteins will be examined using electron microscopy (24-30 months). The final phase of the duration will be dedicated to writing the PhD manuscript and preparing for the PhD defenses. Additionally, we plan to submit scientific articles for publication throughout the duration of the PhD. Finally, the PhD student will attend French and international scientific conferences to present his/her results.

Candidate profile

- Indian candidates or candidates with a research experience in India are eligible; French candidates are not eligible
- Applicants for PhD must have a master's degree (or be in the process of obtaining one) or have a University degree equivalent to a European Master's (5-year duration) to be eligible at the time of the deadline of the call
- Applicants for post-doctorate must have a PhD degree (or be in the process of obtaining one) ;
- No competences in French language is required
- Candidate competences: Trained as physicists, candidates should have a pronounced interest in working at the interface of biology and physics. Candidates must possess a strong background in physics, along with proficiency in optical microscopy and electron microscopy. Basic understanding of biophysics is advantageous but not mandatory. The candidate must be able to design and conduct experiments rigorously, following experimental protocols and ensuring data quality.
- Candidate know-how:
  - Strong background in physics, with an advanced understanding of fundamental principles of physics.
  - Hands-on experience in laboratory techniques, including handling state-of-the-art equipment such as optical and electron microscopes.
  - In-depth knowledge of data analysis methods used in biophysics, such as imaging, spectroscopy, and image analysis.
  - Ability to work independently and solve problems creatively, focusing on resolving experimental challenges.
  - Programming and computer skills for data analysis, modeling, and simulation, preferably with commonly used software in biophysics such as MATLAB or Python.
  - Effective communication skills, both written and verbal, to present and discuss research findings with colleagues and supervisors.
  - Ability to work collaboratively in an interdisciplinary research environment, collaborating with researchers from different disciplines to solve complex problems in biophysics.
- Expected starting date: **Between 01-09-2024 and 01-01-2025**

How to candidate ?

Documents to be provided :

i. A cover letter (reasons for the candidature, professional project …) max 2 pages
ii. A copy of the master's degree or a proof of the program followed (and expected date of end) OR A copy of the PhD degree or a proof of the PhD program followed (and expected date of defense) max 1 page
iii. A copy of results for previous scholarship (max 3 pages)
iv. International curriculum vitae (max 2 pages)
v. Two letters of recommendation: one from any Indian institution and one from the French institution planned to host the candidate –mandatory- (max 2 pages)
vi. All should be submitted within 1 pdf file of no more than 10 pages.

Applications should be submitted to the following email address: msi@ifindia.in mentioning the reference number of the Job offer clearly.

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Candidates are requested to contact the French scientific principal investigator of the project before submission. A recommendation letter from the scientific principal investigator is mandatory.

Benefits:

- Monthly allowance of 1710 euros for PhD
- Travel allowance
- University fee
- Carte de séjour fee
- Campus France management fee
- Registration to the French social security scheme

Selection process:

Selection is made by a dedicated selection committee of at least 4 persons. Decisions will be transmitted by the Embassy of France to CEFIPRA. **No consideration will be given for candidates with no recommendation letter from the French institution.**

Criteria for applicants' selection:

Academic excellence

- Excellence of the Academic background, Academic records, Honors, Letters of support, Participation to international research projects, exchange programmes and conferences.

Motivation and qualities

- Academic maturity: appropriation of the thesis project (stakes and contexts) • Quality of the presentation (oral expression, skills for synthesis, English level) • Maturity of the professional project: capacity to project her/himself within five years in terms of career development.

About CEFIPRA:
Indo-French Center for the Promotion of Advanced Research (CEFIPRA/IFCPAR) is an Indian body which promotes scientific cooperation between France and India in advanced fields of Science and Technology. It is supported by the Department of Science and Technology, Government of India and the Ministry of Europe and Foreign Affairs of the French government