IITB-Monash Research Academy

Indian Institute of Technology Bombay | MONASH University

An Indian-Australian research partnership

Project Title:	**Investigating the link between anti-microbial activity and amyloid formation in frog peptides**	
Project Number	**IMURA0956**	
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Research Clusters:

Highlight which of the Academy's CLUSTERS this project will address? *(Please nominate JUST **one**. For more information, see www.iitbmonash.org)*	
1	*Material Science/Engineering (including Nano, Metallurgy)*
2	*Energy, Green Chem, Chemistry, Catalysis, Reaction Eng*
3	*Math, CFD, Modelling, Manufacturing*
4	*CSE, IT, Optimisation, Data, Sensors, Systems, Signal Processing, Control*
5	*Earth Sciences and Civil Engineering (Geo, Water, Climate)*
6	*Bio, Stem Cells, Bio Chem, Pharma, Food*
7	*Semi-Conductors, Optics, Photonics, Networks, Telecomm, Power Eng*
8	*HSS, Design, Management*

Research Themes:

Highlight which of the Academy's Theme(s) this project will address? *(Feel free to nominate more than one. For more information, see www.iitbmonash.org)*	
1	*Advanced computational engineering, simulation and manufacture*
2	*Infrastructure Engineering*
3	*Clean Energy*
4	*Water*
5	*Nanotechnology*
6	*Biotechnology and Stem Cell Research*
7	*Humanities and social sciences*
8	Design

The research problem

Several human diseases are characterised by aggregation of peptides or proteins.These include neurodegenerative diseases where protein aggregates, or amyloid, occur in the brain, such as, in Alzheimer's Disease. There is a high social and economic impact of these diseases hence an imperative to identify new targets for therapeutic intervention.Interestingly, recent studies have suggested possible functional, physiological roles for amyloid forming proteins and peptides which have been traditionally studied for pathological activity. Such candidates include certain anti-microbial peptides that also aggregate to form amyloid fibrils.

Amyloidogenesis is a type of polymerisation process in which soluble proteins misfold, initiating the formation of soluble aggregates and eventually insoluble, fibrillar amyloid. During an investigation of a number of peptides derived from the skin secretions of frogs we have identified an anti-microbial peptide that also aggregates to form amyloid. The aggregation process is influenced by several factors, such as, mutations in the peptide sequence, solvent composition and also proximity to a lipid bilayer. Multiple pathways consisting of nucleation and growth phases with sigmoidal kinetics are accessible during the process of amyloidogenesis; depending on the physiological conditions, protein sequence and the surrounding molecular environment. A systematic study of the aggregation behaviour of a family of peptides sequences next to a surface can provide important insights into the link between anti-microbial activity and the aggregation process. In this way, we are able to design drug targets and develop models to combat a number of amyloidogenic neurodegenerative diseases.

This project brings a strong and effective combination of biophysical techniques, molecular dynamics simulations and bioinformatics tools to investigate the fundamental molecular basis for the aggregation process using the frog peptides as a model system.

Peptides will be prepared that vary the amino acid sequences using D-amino acids, N- and C-terminal deletions. Examination of the effect of aggregation will be achieved using circular dichroism, transmission electron microscopy, atomic force microscopy and quartz crystal microbalance techniques. These methods will define the effect of these changes on the physical properties of the peptides addressing the amino acids that (i) initiate, (ii) contribute and (iii) extend the aggregation process leading to amyloid polymers. Complementary studies using molecular dynamics will provide a structural basis for the binding and aggregation propensity, explore early stage aggregation events that are difficult to probe with experimental tools, and examine peptide interactions with model surfaces. Since early stage events occur over very small time scales, such processes are ideally suited for investigation by molecular dynamics simulations. In addition, bioinformatics tools will also be used to align and cluster peptide conformations sourced from molecular dynamics data. Molecular dynamics simulations will be complemented with kinetic Monte Carlo simulations to simulate transitions during the aggregation phenomena.

Student Summary

Most animals have innate immune systems that comprise peptides, as a vital component with antimicrobial activity. We have studied the peptides secreted from the Australian tree frog and discovered that in addition to antimicrobial action there are also peptides that aggregate, to form insoluble amyloid fibrils. These aggregates are very similar to the deposits found in the brains of people that have Alzheimer's Disease. This research project will investigate the biophysical properties of the frog aggregating peptide using molecular dynamics simulations and bioanalytical tools to provide an understanding of the aggregation process hence enable the design of new therapeutic targets for Alzheimer's Disease. This project will combine theoretical and experimental experience and enablethe basic physical principles of aggregation and polymerisation to be applied to an important medical problem.

Project aims

The aims of the project are,

1. Examination of peptide aggregation using various biophysical techniques
2. Understanding the role of amino acid sequences on the physical properties of peptides
3. Identification of amino acids responsible for the initiation and extension of the aggregation process
4. Simulate the conformational dynamics of peptide clusters near model surfaces using molecular dynamics and kinetic Monte Carlo
5. Simulate peptide aggregation in presence of lipid bilayers using molecular dynamics simulations
6. Understanding the energetics of aggregation process near model surfaces using molecular dynamics

Expected outcomes

The following outcomes are expected,

1. Publications in high-impact journals
2. A PhD scholar with expertise in bioanalytical characterization tools, and multi-scale molecular simulations
3. Insight into the aggregation process of amyloidogenic peptides, derived from frogs

4. Design rules from simulations for guiding development of therapeutics

How will the project address the Goals of the above Themes?

The project involves high-performance computing as it deals with large-scale molecular dynamics simulations requiring parallelized computer architecture and specialized numerical methods for handling large data sets. In addition, the project also involves the use of bioinformatics and statistical data analysis tools. Consequently, the project is relevant to the theme of Advanced Computational Engineering, Simulation and Manufacture.

The phenomenon which is the subject of this study occurs at nanometer length scales, and several biophysical characterization tools are routinely used in nanotechnology. Hence, this project is relevant to the Nanotechnology theme.

The aggregation of peptides is directly relevant to development of therapeutics for several neuro-degenerative diseases, and hence relevant to the theme of Biotechnology and Stem Cell Research.

Capabilities and Degrees Required

The prerequisite skills needed in this project are a combination of mathematical modelling capabilities and knowledge of analytical/physical chemistry. Some experience with biology would be desirable but not essential.

Candidates with the following degrees are desirable,

1. B.Tech./M.Tech. in Chemical Engineering, Biochemical Engineering, Materials Engineering
2. M.Sc. in Chemistry (Physical Chemistry or Analytical Chemistry with Mathematics at the B.Sc. level)
3. M.Sc. in Physics (with interest in computations and biophysics)

Potential Collaborators

Please visit the IITB website www.iitb.ac.in OR Monash Website www.monash.edu to highlight some potential collaborators that would be best suited for the area of research you are intending to float.