**Announcing the Final Examination of Nabin Kandel for the degree of Doctor of Philosophy in Physics**

**Date:** July 5, 2019
**Time:** 8:00 a.m.
**Room:** PSB 160
**Dissertation title:** Molecular basis of membrane pore formation by amyloid beta peptide

**Abstract:**
Alzheimer's Disease (AD) is a neurodegenerative disorder that affects around 50 million people worldwide and causes cognitive decline, brain atrophy and death. Despite extensive basic and clinical studies and drug development efforts, currently no effective treatments are available for AD. The amyloid β (Aβ) peptide is neurotoxic and is tightly associated with AD pathology, but the molecular mechanism of its action remains poorly understood. There are various forms of Aβ in the brain, ranging from the full-length $A\beta_{1-42}$ to shorter peptides, such as a strongly toxic $A\beta_{25-35}$ fragment. The prototype Amyloid Cascade Hypothesis postulated that extracellular Aβ deposits cause the disease. More recently, the soluble Aβ oligomers came into the focus of research efforts as they proved to be the major neurotoxic entities. One of the mechanisms by which Aβ peptides, including $A\beta_{25-35}$, kill neurons is membrane perforation and disruption of cellular homeostasis. Although direct membrane interaction and pore formation by Aβ has been documented, the detailed structural aspects of membrane pores remain to be elucidated. Here, we quantitatively describe the structure of $A\beta_{25-35}$ in aqueous buffer and in lipid environment, its binding to membranes, pore formation, and the molecular details of membrane pores. We have shown that membrane binding of $A\beta_{25-35}$ is electrostatically driven. $A\beta_{25-35}$ forms β-barrel-like structures ranging from hexamers to octamers, which then assemble into supra-molecular structures forming calcium-conducting pores in the membrane with inner radius of 6-7 Å. The structural features of $A\beta_{25-35}$ pores, as identified by a variety of biophysical approaches, depend on the content of cholesterol in the membranes. Moreover, the aggregation and structural changes of a series of Aβ fragments have been analyzed to identify the segment(s) of highest propensity for fibrillogenesis that might serve as initiators of Aβ aggregation and conversion into toxic species. Finally, the structures of the full-length $A\beta_{1-42}$ and a hypertoxic version of Aβ, $pEA\beta_{3-42}$, in lipid environment have been analyzed by solid state nuclear magnetic resonance. Collectively, these studies will elucidate the structural details of membrane pores formed by Aβ peptides as targets for new anti-AD therapies.

**Outline of Studies:**
Major: Physics

**Educational Career:**
M. S. University of Texas, Brownsville, 2014
B. S. Tribhuvan University, Nepal, 2008

**Committee in Charge:**
Dr. Suren A Tatulian (Chair)
Dr. Bo Chen
Dr. Alfons Schulte
Dr. Kenneth Teter (External Committee Member)

Approved for distribution by Dr. Suren A. Tatulian, Committee Chair, on June 17, 2019.

The public is welcome to attend.