UC San Diego
JACOBS SCHOOL OF ENGINEERING
NanoEngineering

# UC SAN DIEGO NANOENGINEERING

**Tuesday, February 21, 2017**
**Seminar Presentation: 11:00am – 12:00pm**
**Fung Auditorium**

## The role of physical forces in biology: Understanding the molecular basis of cardiomyopathy

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### Abstract:

From cardiac muscle contraction to cancer cell migration, physical forces play an essential role in biological form and function. My principal research interests lie in applying the laws of physics to answer biological questions. During my graduate work, I developed assays to measure how physical forces can alter proteolysis of extracellular matrix proteins at a single molecule level, an essential process during cancer metastasis and wound healing. I also developed FRET-based molecular force sensors to measure forces exerted on single integrin molecules by cells, and assays to measure how cells generate traction forces in three-dimensional soft matrices.

During my postdoctoral fellowship, I have been investigating how hypertrophic cardiomyopathy (HCM) mutations alter the biomechanics of human beta-cardiac myosin. HCM is a disease that affects 1 in 500 people and is characterized by thickening of the ventricular walls. It is the leading cause of sudden death among young athletes and has no known treatment. It is caused by missense mutations in the sarcomeric proteins (proteins responsible for cardiac muscle contraction) with ~30% mutations found in beta-cardiac myosin. Due to the disruption of the contractile machinery of the heart, the biomechanics of the system are severely affected.

Even though we have significant knowledge of the genetics of HCM, we know very little about the molecular basis of this disease. Studies using mouse models have shown variable results. To address this issue, I have been using recombinant human beta-cardiac myosin to study how early onset HCM mutations alter myosin function. Biomechanical measurements, such as force, velocity, and activity have revealed that these mutations lead to a significant gain in function for myosin, consistent with the clinical phenotype.

Currently, I am examining how HCM mutations alter interactions between different domains of myosin and lead to hyper-contractility. Preliminary data suggests that interactions that sequester myosin in an “off” state are disrupted, thereby increasing myosin activity and leading to hypertrophy. Based on this evidence we are now beginning to understand how these mutations can affect myosin biomechanics. However, our knowledge is still in its infancy and there are still several open questions. For example, how do these mutations alter the ensemble force-velocity relationship of myosin, and moreover, what effect do they have on cardiomyocyte function? These questions provide a unique opportunity to engineer solutions for addressing a biological issue, and these solutions will overcome an important obstacle in finding treatments for this disease.

### Biosketch:

Arjun Adhikari attended the Polytechnic Institute of New York University, where he graduated Summa Cum Laude in Chemical and Biological Engineering. Upon the completion of his Bachelor’s, he pursued his doctoral degree in Chemical Engineering at Stanford University and earned his Ph.D. under the guidance of Dr. Alexander Dunn. He was awarded a Stanford Graduate Fellowship to support this graduate work. His thesis project involved designing single molecule assays to understand the effect of mechanical tension on extracellular matrix proteolysis, and making tension sensitive FRET based probes which can measure forces in the range of pN. His work has been published in journals like JACS and Nano Letters. Currently, he is an American Heart Associate postdoctoral fellow in the lab of Dr. James Spudich, in the department of Biochemistry at Stanford University School of Medicine. Here he is investigating how hypertrophic cardiomyopathy mutations can alter the biomechanics of human beta cardiac myosin at the molecular level. His work on early onset HCM mutations was recently published in Cell Reports, and he is presently investigating how these mutations alter the power output of cardiomyocytes.