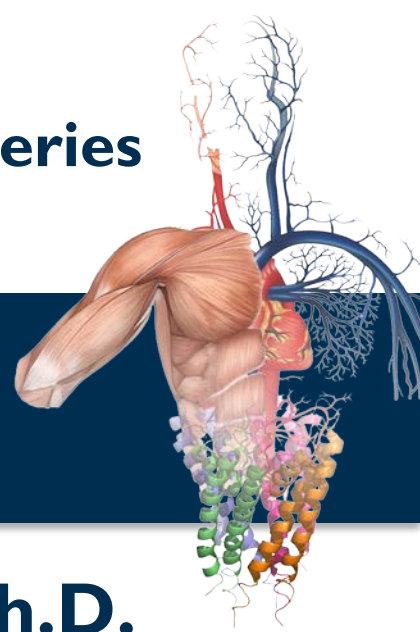


# Distinguished Lecture Series in Physiology

## Physiology and Membrane Biology

University of California, Davis



## Leslie A. Leinwand, Ph.D.

University of Colorado, Boulder  
Department of Molecular, Cellular, and Developmental Biology

### "Myosin Myopathies: Pathogenesis and Potential Therapeutics"

Over 300 mutations in 5 myosin heavy chain genes cause a variety of skeletal and cardiomyopathies. Most of these are missense mutations and they are inherited in an autosomal dominant manner. We have taken multiple approaches to understand how these mutations cause disease. First we have begun analyzing the impact of these mutations on many aspects of myosin motor function. These include in vitro motility, ATPase activity and kinetics of the cross-bridge cycle. We hypothesize that mutations in the rod contribute to pathogenesis in distinct ways from those in the motor domain. We have measured thermal stability and  $\alpha$  helical content for rod mutations and while we have seen defects, they are neither striking nor uniform in different mutations. Cellular approaches have revealed more defects for rod mutations than the biophysical measurements. One curiosity is that  $\beta$  myosin is expressed in both cardiac and skeletal muscle in humans and yet there are mutations that cause only cardiomyopathies and others that cause only skeletal myopathies. We are currently trying to understand this apparent paradox. We are taking a therapeutic approach to eliminating the autosomal dominant mutant protein by allele-specific silencing in the case of rod mutations and preliminary results suggest good progress. In other approaches we will be testing small molecule modulators of myosin function. Finally, we have uncovered unusual properties of an apparent sarcomeric motor in brain and ear.

Genome Auditorium  
Thursday, April 28, 2016  
11:00 a.m.

Contact: Keith Baar [kbaar@ucdavis.edu](mailto:kbaar@ucdavis.edu)