

BCH 251/252 Seminar Series



Yun Lyna Luo, Associate Professor, Department of Biotechnology and Pharmaceutical Sciences, Western University of Health Sciences

Seminar Title: "Unlocking Mechanosensitive Channel Gating for Drug Design"

Abstract: The rapid conversion of mechanical forces into biological signals in vertebrates is commonly achieved by two mechanosensitive ion channels, PIEZO1 and PIEZO2. Over the past six years, my group has been developing computational approaches to understand how PIEZO channels sense mechanical forces and how to design PIEZO modulators. Using all-atom and a newly developed hybrid-resolution molecular dynamics, we simulated PIEZO1&2 gating motion in response to changes in membrane curvature and lateral tension [1]. Based on these models, we identified a potential binding site of a small molecule PIEZO1 activator, Yoda1, at the transmembrane mechanosensing domain [2]. This binding site, validated through three computational binding assays and experimental disulfide bridges, led us to discover two Yoda1 analogs and two novel activators with improved efficacy or potency [3]. In addition, we developed a super coarse-grained model to simulate the spontaneous clustering of ion channels in a submicron membrane patch. This model will help us answer whether PIEZO channels may undergo cooperative gating.

1. Jiang, et. al., Crowding-induced opening of the mechanosensitive Piezo1 channel in silico. *Commun. Biol.* 2021
2. Botello-Smith, et al., A molecular Mechanism for the Chemical Activation of the Mechanosensitive Piezo1 Channel, *Nat. Commun.*, 2019
3. Jiang, et. al., Structural and thermodynamic framework for PIEZO1 modulation by small molecules, *PNAS*, 2023

Tuesday, April 8, 2025 12:00 p.m. - 12:50 p.m. PST

In-Person: Genomics Auditorium 1102A

Host: Dr. Chia-en Chang