Postdoctoral Research Position
Senior Fellow or Instructor Appointment Level
Structural Basis for Function and Pharmacology of Voltage Gated Sodium and Calcium Channels

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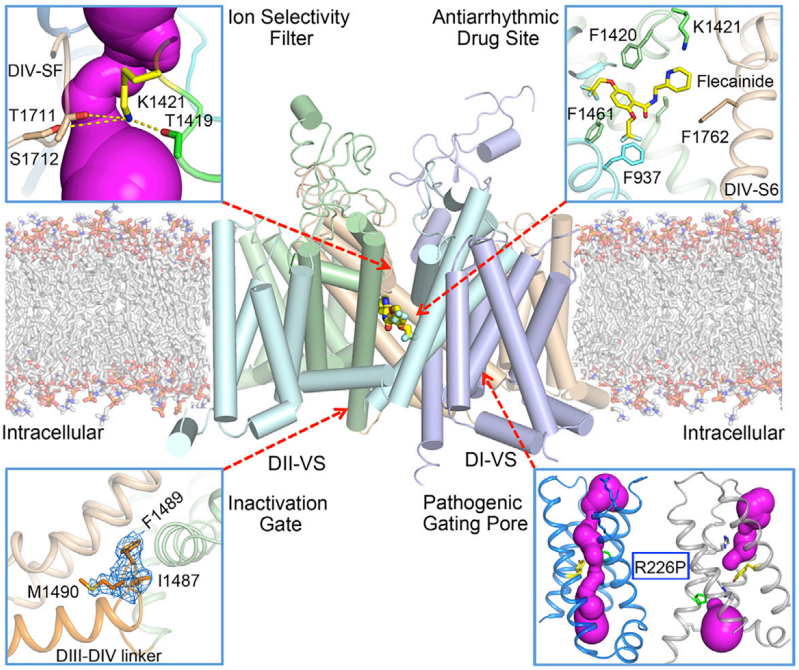
Voltage-gated sodium and calcium channels initiate electrical signaling, synaptic transmission, and muscle contraction. They are the molecular targets for drugs used in local anesthesia and in therapy of epilepsy, pain, and cardiac arrhythmia. Our research program aims to understand the function and pharmacology of sodium and calcium channels at the atomic level. Our studies involve x-ray crystallography, cryogenic electron microscopy (cryo-EM), and detailed membrane biophysics and patch-clamp electrophysiology. We have a two-pronged approach that emphasizes integrated structural and functional studies.

We use the ancestral sodium channel NavAb and the model calcium channel CavAb to study the basic structure-function relationships of these ion channels, including the molecular mechanisms of voltage-dependent gating, pore opening and closing, ion conductance and selectivity, and receptor sites for neurotoxins and drugs. Recent advances include determining the structures of these channels in closed/resting, activated/open, and slow inactivated states and analyzing the binding sites of potent neurotoxins and pore-blocking drugs.

We recently determined the structure of the mammalian cardiac sodium channel Nav1.5 by cryo-EM and imaged the binding of a pore-blocking antiarrhythmic drug in its receptor site. Looking ahead, we will analyze the unique aspects of cardiac sodium channels that allow them to initiate the heartbeat, generate cardiac arrhythmias, and serve as therapeutic targets. Planned studies include determining the structure of cardiac sodium channels in resting, open, and inactivated states, defining the mechanism of state-dependent binding of antiarrhythmic drugs to these channels, and probing the structural effects of mutations in Nav1.5 that cause life-threatening cardiac arrhythmias.

Structure of the Cardiac Sodium Channel Reveals Detailed Functional Insights



Graphical Abstract. Jiang D, Shi H, Tonggu L, Gamal El-Din TM, Lenaeus MJ, Zhao Y, Yoshioka C, Zheng N, Catterall WA. 2020. Structure of the cardiac sodium channel. *Cell* 180:122-134.

Relevant Publications

1: Jiang D, Banh R Gamal El-Din T, Tonggu L, Pomès R, Zheng N, Catterall WA. 2021.Open-sate structure and pore gating mechanism of the cardiac sodium channel. ***Cell Online*****,** 13Sep2021

2: Jiang D, Tonggu L, Gamal El-Din TM, Banh R, Pomès R, Zheng N, Catterall WA. 2021. Structural basis for voltage-sensor trapping of the cardiac sodium channel by a deathstalker scorpion toxin. ***Nature Comm*** 12(1):128.

3: Wisedchaisri G, Tonggu L, Gamal El-Din TM, McCord E, Zheng N, Catterall WA. 2021. Structural basis for high-affinity trapping of the Nav1.7 channel in its resting state by tarantula toxin. ***Molecular Cell*** 81:38-48.

4: Catterall WA, Wisedchaisri G, Zheng N. 2020. The conformational cycle of a prototypical voltage-gated sodium channel. ***Nature Chemical Biology*** 16:1314-1320.

5: Jiang D, Shi H, Tonggu L, Gamal El-Din TM, Lenaeus MJ, Zhao Y, Yoshioka C, Zheng N, Catterall WA. 2020. Structure of the cardiac sodium channel. ***Cell*** 180:122-134.

6: Wisedchaisri G, Tonggu L, McCord E, Gamal El-Din TM, Wang L, Zheng N, Catterall WA. 2019. Resting-state structure and gating mechanism of a voltage-gated sodium channel. ***Cell*** 178:993-1003.

7: Gamal El-Din TM, Lenaeus MJ, Zheng N, Catterall WA. 2018. Fenestrations control resting-state block of a voltage-gated sodium channel. ***Proc Natl Acad Sci U S A.*** 115:13111-13116.

8: Jiang D, Gamal El-Din TM, Ing C, Lu P, Pomès R, Zheng N, Catterall WA. 2018. Structural basis for gating pore current in periodic paralysis. ***Nature*** 557:590-594.

9: Lenaeus MJ, Gamal El-Din TM, Ing C, Ramanadane K, Pomès R, Zheng N, Catterall WA. 2017. Structures of closed and open states of a voltage-gated sodium channel. ***Proc Natl Acad Sci U S A*** 114: E3051-E3060.

10: Tang L, Gamal El-Din TM, Swanson TM, Pryde DC, Scheuer T, Zheng N, Catterall WA. 2016. Structural basis for inhibition of a voltage-gated calcium channel by Ca^{2+} antagonist drugs. ***Nature*** 537:117-121.

11: Tang L, Gamal El-Din TM, Payandeh J, Martinez GQ, Heard TM, Scheuer T, Zheng N, Catterall WA. 2014. Structural basis for Ca^{2+} selectivity of a voltage-gated calcium channel. ***Nature*** 505: 56-61.

12: Chakrabarti N, Ing C, Payandeh J, Zheng N, Catterall WA, Pomès R. 2013. Catalysis of Na^{+} permeation in the bacterial sodium channel NavAb. ***Proc Natl Acad Sci U S A*** 110:11331-11336.

14: Payandeh J, Gamal El-Din TM, Scheuer T, Zheng N, Catterall WA. 2012. Crystal structure of a voltage-gated sodium channel in two potentially inactivated states. ***Nature*** 486:135-139.

15: Payandeh J, Scheuer T, Zheng N, Catterall WA. 2011. The crystal structure of a voltage-gated sodium channel. ***Nature*** 475:353-358.

UW and Catterall/Zheng Laboratory Facilities

UW Cryo-EM Facility: FEI Titan Krios 300 keV electron microscope with Gatan Summit K3 camera and GIF energy filter, Glacios 300 keV Cryo-TEM with Gatan Summit K2 camera, FEI Vitrobot, and SPT Chameleon.

Catterall/Zheng Laboratories:

Extensive equipment and technical support for molecular biology, protein expression, purification, and characterization, including fluorescent size exclusion chromatography.

Extensive electrophysiological equipment for whole-cell voltage clamp and single channel recording.

Two 8x GPU systems for handling, storage, and analysis of cryo-EM data.

Position Requirements

PhD or equivalent in biochemistry, biophysics, bioengineering, or structural biology.

Experience in molecular biology, cell culture, and protein expression, purification, and characterization.

Excellent communication skills and successful experience in a team research environment.

Two years experience with cryo-EM data collection, processing, and analysis.

Successful determination of a protein structure by cryo-EM.

Application Requirements

Curriculum Vitae

Names of three referees

University of Washington is an affirmative action, equal opportunity employer. All qualified applicants will receive consideration without regard to race, color, religion, sex, sexual orientation, gender identity, gender expression, national origin, age, protected veteran or disabled status, or genetic information.