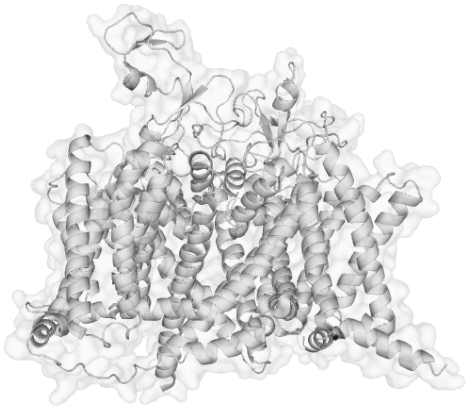
Understanding the mechanism behind disease-causing variants of the cardiac Nav1.5 channel.



Background:

Voltage-gated sodium channels (Nav) are membrane-embedded proteins that allow the passage of sodium through cellular membranes in response to voltage changes. Among them, the Nav1.5 isoform is found in cardiomyocytes, where it initiates the cardiac action potential. Many mutations result in impaired Nav1.5 function in humans, leading to often life-threatening arrhythmias. Nav1.5 is thus the target of many anti-arrhythmic drugs that are widely used in the clinic, but with often unpredictable outcomes depending on the genetic background of the patient.

Recent work by the Pless lab has led to the implementation of a protein engineering approach that allows to selectively incorporate new chemical functionalities into Nav1.5 channels[1], such as post-translational modifications and fluorescent sensors. The resulting fluorescent signals can reveal molecular mechanisms underlying the function of both wild-type and mutant Nav1.5.

Project aim:

The project aims at characterizing disease-causing variants of Nav1.5 containing fluorescent sensors and their behavior upon application of clinically used drugs.

Methodology and approach:

Molecular biology, electrophysiology, fluorescence measurements, pharmacology

Literature:

[1.] Galleano, I. et al. Functional cross-talk between phosphorylation and disease-causing mutations in the cardiac sodium channel Nav1.5. Proc. Natl. Acad. Sci. U.S.A. 118, e2025320118 (2021).