Live-cell membrane protein semi-synthesis using protein trans-splicing

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Membrane proteins such as ion channels play crucial roles in human physiology and their dysfunction is associated with a variety of disease states, such as cardiac arrhythmias and stroke. Despite recent advances in our understanding of their structure and function, many aspects of their biology remain elusive. For example, their regulation by post-translational modifications (PTMs) or the effect of such PTMs on channel pharmacology is poorly understood. Here, I will present a protein trans-splicing-based approach that enables the incorporation of synthetic peptides carrying metabolically stable PTMs or non-canonical amino acids into ion channels using protein trans-splicing. Specifically, the presentation will cover our live-cell efforts to investigate the functional and pharmacological consequences of phosphorylation on cardiac sodium channels, both on WT and mutant channels carrying arrhythmia-causing patient mutations. Together, these studies highlight the potential of using semi-synthesis-based approaches to study the molecular function and pharmacology of membrane proteins.

[1] K.K. Khoo & I. Galleano et al, *Nature Communications*, **2020**, *11(1): 2284*.
[2] I. Galleano & H. Harms et al, *PNAS*, **2021**, *118(33): e2025320118*.