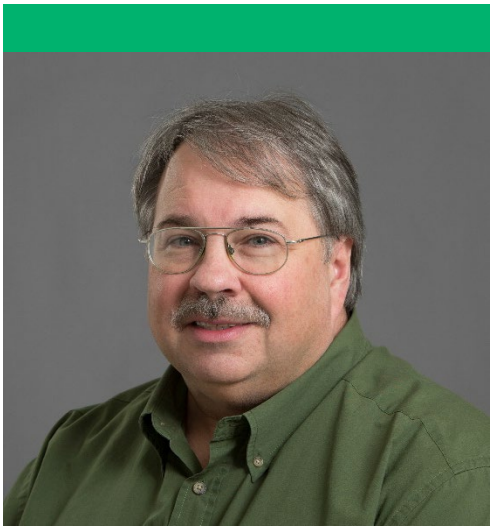
RUSH

Michael Fill, PhD

The Francis N. and Catherine O. Bard Professor of Physiology



Advancement of Medicine

In 2023, we advanced our ongoing exploration of control mechanisms that are fundamental to many cellular phenomena and are often sites of pathological failure and potential targets for therapeutic intervention. My lab is internationally recognized for our world-class experimental expertise investigating certain signals — called Ca signals — generated by the ryanodine receptor, or RyR, Ca release channel in excitable cells. RyRs are known to modulate a myriad of physiological functions. Our lab details clinically significant structure-function attributes of single RyR function in health and disease, including local RyR control by Ca, closely regulatory proteins and post-translational modifications. This provides a strong mechanistic foundation for our group's ongoing work toward developing new RyR-targeted drugs that will hopefully be applied to limit/treat diseases exacerbated or caused by hyperactive RyR Ca signaling. Our investigations, sponsored by the National Institutes of Health, or NIH, have received a myriad of awards over the years, and we present our research regularly at the most prestigious professional conferences and in professional journals.

Research

Funds from the Francis N. and Catherine O. Bard Endowment supported basic science preclinical research that is defining mechanisms governing acid-base balance, various cardiac arrhythmias and skeletal muscle myopathies as potential targets for future therapeutic innervations. This research is carried out by nine research faculty members in the Department of Physiology and Biophysics.

In 2023, we carried out our NIH RO1 study, "Collective Ryanodine Receptor Operations at Release Sites," which investigated why abnormal intracellular calcium release between heartbeats may

trigger arrhythmias that can lead to sudden death. This project defines why this abnormal calcium release occurs and explores therapeutic strategies to make it less likely to occur and thus advances our understanding of cardiac arrhythmia prevention and treatment.

Publication Highlights – Abbreviated

- "Isolated cardiac ryanodine receptor function varies between mammals," *Journal of Membrane Biology*, 2024.
- "Ligand sensitivity of type-1 inositol 1,4,5-trisphosphate receptor is enhanced by the D2594K mutation," *Archives of European Journal of Physiology*, 2023.
- "Distinct pathophysiological characteristics in developing muscle from patients susceptible to malignant hyperthermia," *British Journal of Anesthesiology*, 2023.
- "Muscle calcium stress cleaves junctophilin1, unleashing a gene regulatory program predicted to correct glucose dysregulation," *eLife*, 2023.
- "Unexpected expansion of the voltage-gated proton channel family," *FEBS Journal*, 2023.
- "Mimicking effects of cholesterol in lipid bilayer membranes by self-assembled amphiphilic block copolymers," *Soft Matter*, 2023.

The Year Ahead: 2024 and Beyond

Your generosity will continue to support basic preclinical research in the Department of Physiology and Biophysics.

With Gratitude

Thank you for your ongoing support, over many years now, of our basic research, which is identifying physiological mechanism(s) that fail in disease, thus fostering the discovery of novel potential therapeutic interventions that promise to save lives.