BIOGRAPHICAL SKETCH

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NAME: **Paul M Riegelhaupt**

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POSITION TITLE: Assistant Professor of Anesthesiology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date	FIELD OF STUDY
Massachusetts Institute of Technology	BS	06/2001	Biology, Chemistry
Albert Einstein College of Medicine	PhD	10/2008	Laboratory of Dr. Myles Akabas, Physiology and Biophysics
Albert Einstein College of Medicine	MD	06/2010	Medicine
University of California San Francisco	Residency	07/2015	Anesthesia and Perioperative Care
University of California San Francisco	Post-doctoral Fellowship	07/2015	Laboratory of Dr. Daniel Minor, Biochemistry and Biophysics

A. Personal Statement

As an early-stage investigator in the process of defining the scope of my nascent laboratory, an overarching goal of mine has been to develop research projects that utilize basic biophysical studies of proteins toward translatable clinical applications. My early PhD work in Dr. Myles Akabas' laboratory introduced me to the $GABA_A$ receptor, an experience that ultimately inspired my decision to pursue anesthesiology as a clinical specialty and provided the foundation for my long-standing fascination with ion channels. While my PhD work eventually shifted to the study of malarial purine transporters as targets for novel anti-malarial drug development, the concept of studying basic biophysical properties of target proteins for a tangible clinical goal was integrated into my scientific perspective.

My interest in K2P potassium ion channels grew from their novel and poorly understood biophysical properties and the recognition of their importance in numerous diverse physiological systems, including anesthetic and pain biology, glucose homeostasis, ischemic preconditioning, arrhythmia, and regulation of smooth muscle cell tone. Despite their fundamental importance, attempts to dissect the roles of individual K2P channels in human physiology have often been hampered by a lack of specific and high affinity pharmacology. My initial studies of the TREK1 K2P channel, performed in Dr. Daniel Minor's laboratory during my anesthesiology residency at UCSF, helped elucidate some of the fundamental gating movements that underlie K2P channel modulation. However, the molecular biophysics governing the interactions between K2P channels and their surrounding lipid bilayer environment remained a lingering question and became a focus of my laboratory. Since my arrival as a faculty member at Weill Cornell, I have been developing expertise to address these questions. My lab now has expertise performing successful structural and functional studies of K2P channels in defined lipid environments, exploring how lipids modulate channel structure and function. My NIH funded laboratory (K08GM132781 and R01GM145918) is now turning our focus to the question of how conformation changes in the K2P channel pore region influence the selectivity filter, a major unanswered question in the field. The progress my lab has made over the last few years solving many structures of the TREK1 channel by cryo-EM has us uniquely positioned to answer this important question.

B. Positions, Scientific Appointments, and Honors

ACTIVITY/ OCCUPATION	START DATE (mm/yy)	END DATE (mm/yy)	FIELD	INSTITUTION/ COMPANY	SUPERVISOR/ EMPLOYER
Clinical Instructor	09/2015	08/2016	Anesthesiology	Weill Cornell Medicine	Weill Cornell Medicine
Assistant Professor	9/2016	present	Anesthesiology	Weill Cornell Medicine	Weill Cornell Medicine
Assistant Attending Anesthesiologist	09/2015	present	Anesthesiology	New York Presbyterian Hospital	New York Presbyterian Hospital
Residency Associate Program Director	2/2017	2/2021	Anesthesiology	Weill Cornell Medicine	Weill Cornell Medicine

Academic and Professional Honors

Howard Hughes Summer Research Fellowship, Krasnow Laboratory, Stanford University 2000
Fellowship, NIH/NIGMS T32GM008572 Molecular Biophysics Training Grant 2006-2008
Student Representative to Faculty Senate (elected), Albert Einstein College of Medicine 2006-2008
Anesthesia Resident Teaching Award, University of California, San Francisco 2011
Obtained State of California Medical License 2012
FAER oral presentation award (1st place), Western Anesthesia Resident Conference 2014
Resident Abstract Awards Finalist, International Anesthesia Research Society 2015
Obtained State of New York Medical License 2015
Association of University Anesthesiologists Junior Faculty Research Award 2016
Awarded a Foundation for Anesthesia Education and Research Mentored Research Training Grant 2016
Certified Diplomat of the American Board of Anesthesiologists 2017
Elected as Associate Member, Association of University Anesthesiologists 2017
Kosaka Best of Meeting Abstract Award, International Anesthesia Research Society 2018
William L. Young Neuroscience Research Award, Society for Neuroscience in Anesthesia and Crit Care 2021

Memberships in Professional Societies

1) Member, American Society of Anesthesiologists, 2011 - present
2) Member, California Society of Anesthesiologists, 2011 - 2016
3) Member, International Anesthesia Research Society, 2011 - present
4) Member, Biophysical Society, 2014 – present
5) Associate Member, Association of University Anesthesiologists 2017 – present
6) Society for Neuroscience in Anesthesia and Critical Care 2021 - present

C. Contributions to Science

1) Establishment of *Plasmodium* Nucleoside Transporters as targets for anti-malarial drug development - Malaria continues to account for nearly 1 million deaths annually, largely due to parasite resistance to formerly effective anti-malarial drugs. There is an ongoing need for new antimalarial pharmacology and my PhD work helped to establish the purine uptake pathway as a viable drug target. Malarial parasites replicate their DNA extensively during each 48-hour lifecycle and are incapable of *de-novo* purine synthesis, suggesting that blockade of purine import could starve parasites of this important building block. When I entered this field, very few studies had characterized purine uptake transporters in malaria. My work established much of the basic understanding of the function of these transporters and suggested a means by which to design a high-throughput screen to search for nucleoside transport inhibitors with anti-malarial properties. Members of the Akabas laboratory continued to

work on this project after the completion of my PhD thesis and have discovered picomolar affinity small molecule inhibitors of the malarial nucleoside transporter that exhibit significant anti-malarial activity in-vivo. This work continues to be an area of active investigation in the laboratory of Dr. Myles Akabas.

a. Cassera MB, Hazleton KZ, **Riegelhaupt PM**, Merino EF, Luo M, Akabas MH, Schramm VL. Erythrocytic adenosine monophosphate as an alternative purine source in Plasmodium falciparum. The Journal of Biological Chemistry. 2008; 283(47):32889-99.
b. Nkrumah LJ, **Riegelhaupt PM**, Moura P, Johnson DJ, Patel J, Hayton K, Ferdig MT, Wellems TE, Akabas MH, Fidock DA. Probing the multifactorial basis of Plasmodium falciparum quinine resistance: evidence for a strain-specific contribution of the sodium-proton exchanger PfNHE. Mol Biochem Parasitol. 2009 Jun;165(2):122-31.
c. **Riegelhaupt PM**, Cassera MB, Fröhlich RF, Hazleton KZ, Hefter JJ, Schramm VL, Akabas MH. Transport of purines and purine salvage pathway inhibitors by the Plasmodium falciparum equilibrative nucleoside transporter PfENT1. Mol Biochem Parasitol. 2010; 169(1):40-9.
d. **Riegelhaupt PM**, Frame IJ, Akabas MH. Transmembrane segment 11 appears to line the purine permeation pathway of the Plasmodium falciparum equilibrative nucleoside transporter 1 (PfENT1). The Journal of Biological Chemistry. 2010; 285(22):17001-10.

2) Structural and functional characterization of K2P potassium channel gating transitions – My post-doctoral fellowship with Dr. Daniel Minor contributed to major advances in elucidating the molecular basis for the gating behavior of tandem pore (K2P) potassium channels. While K2P's contain a classical potassium selectivity filter signature sequence, these channels are otherwise quite distinct from previously characterized potassium channels. K2P's exhibit a unique structural architecture and are modulated by physical cues not known to affect most other K^+ channels (temperature, mechanical stretch). Through a combination of electrophysiological (by myself) and structural approaches (by others in the Minor lab), we identified the conformational movements that underlie channel activation and discovered previously unrecognized regions of the channel with functional importance. Our findings suggested a framework for interpreting the effects of many channel modulators on K2P channels. Since leaving the Minor lab, I have focused my attention on identifying the mechanism by which volatile anesthetics activate K2P channels. Through an ongoing collaboration with Dr. Roderick Eckenhoff's laboratory, I have identified a putative anesthetic binding site for the volatile anesthetic isoflurane in TREK1 K2P channels. The TREK1 anesthetic modulatory site sits at a region of the TREK1 protein that is highly dynamic during channel gating, suggesting a mechanistic link between volatile anesthetic binding and channel activation.

a. Lolicato M, **Riegelhaupt PM**, Arrigoni C, Clark KA, Minor DL Jr. Transmembrane helix straightening and buckling underlies activation of mechanosensitive and thermosensitive K(2P) channels. Neuron. 2014; 84(6):1198-212.
b. **Riegelhaupt PM**, Tibbs GR, Goldstein PA. HCN and K2P Channels in Anesthetic Mechanisms Research. Methods Enzymol. 2018;602:391-416.
c. Hemmings HC Jr, **Riegelhaupt PM**, Kelz MB, Solt K, Eckenhoff RG, Orser BA, Goldstein PA. Towards a Comprehensive Understanding of Anesthetic Mechanisms of Action: A Decade of Discovery. Trends Pharmacol Sci. 2019 Jul;40(7)
d. Wague A, Joseph TT, Woll KA, Bu W, Vaidya KA, Bhanu NV, Garcia BA, Nimigean CM, Eckenhoff RG, **Riegelhaupt PM**. Mechanistic insights into volatile anesthetic modulation of K2P channels. Elife. 2020 Dec 21;9

Complete List of Published Work:

https://www.ncbi.nlm.nih.gov/myncbi/paul.riegelhaupt.1/bibliography/public/