Paul F. Cranefield Award to Frank T. Horrigan

The late Paul F. Cranefield, M.D., Ph.D., was the Editor of the *Journal of General Physiology* for 30 years, from 1966 to 1995. During this time, he worked incessantly to further the mission of the Journal: to promote and publish studies at the interface between biology, chemistry, and physics in order to obtain insights into fundamental mechanisms that underlie biological function at all levels.

When Dr. Cranefield stepped down as Editor, the Council of the Society of General Physiologists discussed how best to acknowledge his numerous contributions to the Journal and thus to the Society. In the end, it was decided to institute a Paul F. Cranefield Award, which should go to a young investigator who in the preceding year had published an article of exceptional quality in the Journal. The award would be given at the Annual Meeting and Symposium of the Society, which takes place in Woods Hole, MA. It also was decided that the criteria for selecting the awardee should be so stringent that the award might not be given every year.

Despite these high standards, there were many outstanding candidates. One stood out, namely Frank T. Horrigan from the Department of Physiology at the University of Pennsylvania School of Medicine, who has made many important contributions toward understanding the regulation of BK-type voltage- and Ca^{2+}-activated K^+ channels. Dr. Horrigan accepted the award at the September, 2007, meeting of the Society.

Dr. Horrigan received his Ph.D. from Stanford University, where he worked in the laboratory of William F. Gilly and studied potassium channel function. He received post-doctoral training with Richard J. Bookman at the University of Miami where he studied exocytosis in adrenal chromaffin cells. He then pursued additional training with Richard W. Aldrich at Stanford University, where he began his studies on BK channels. Dr. Horrigan focused initially on voltage-dependent regulation, demonstrating that BK channels can open in the absence of voltage sensor activation and that the interaction between voltage sensor and activation gate is best described by an allosteric mechanism. He then turned his attention to Ca^{2+}-dependent regulation, building on previous work by J. Cui and D.H. Cox in the Aldrich laboratory and other investigators, to propose a dual-allosteric model of voltage- and Ca^{2+}-dependent activation (Horrigan, F.T., and R.W. Aldrich. *J. Gen. Physiol.* 2002. 120:267–305) in which voltage and Ca^{2+} sensors act almost independently to promote channel opening. In the course of this work Dr. Horrigan pioneered methods of studying BK channel ionic and gating currents over extreme ranges of voltage, $[Ca^{2+}]$, and open probability to isolate interactions among voltage sensor activation, Ca^{2+} binding, and channel opening. This rigorous experimental approach, together with the dual-allosteric model has served as a framework for analysis of BK channel regulation in the laboratories of Dr. Horrigan and many others.

Since this seminal work, Dr. Horrigan has sought to understand the molecular bases of allosteric interactions in BK channels and the mechanism of action of regulatory ligands. Work from his laboratory and in collaboration with those of J. Cui and T. Hoshi indicates that the action of intracellular Mg^{2+}, heme, and extracellular metal ions, unlike Ca^{2+}, depends on voltage sensor activation. Thus a detailed understanding of voltage sensor function has become critical to understanding many aspects of BK channel regulation. Although BK channels share many conserved charged residues in the S1–S4 voltage sensor domain with well-studied voltage-dependent K (K_v) channels, BK channels exhibit only one fifth the voltage sensitivity of K_v channels, raising several questions: Why are BK channels so weakly voltage dependent? Do BK and K_v channels undergo the same conformational changes? Do the same residues sense voltage? If not, why are they conserved? These questions were resolved in large part by a study in Dr. Horrigan's laboratory, published in the March 2006 issue of the Journal (with Z. Ma and X.J. Lou, 127:309–328). Systematic mutation of charged residues in the S1–S4 segments of *mSlo1* BK channels revealed that only one of three conserved arginines in S4 contributes to gating charge. This pattern of voltage sensing residues and the small contribution of individual residues to gating charge suggests that S4 movement in BK channel is restricted relative to K_v channels, reducing its voltage sensitivity. Contributions to the gating charge from positively and negatively charged residues in S2 and S3 provided additional clues about voltage sensor movement. Finally, two arginines in S4 that do not contribute to gating charge strongly influenced voltage sensor stability and the allosteric coupling of voltage sensor and gate, accounting for their conservation in *Slo1* channels. This study, together with Dr. Horrigan's previous work on BK channel regulation, confirms his role as a leader in the field.

J. Gen. Physiol. © The Rockefeller University Press $30.00
Volume 131 Number 2 February 2008 103
http://www.jgp.org/cgi/doi/10.1085/jgp.200709922