https://doi.org/10.1038/s41593-024-01641-3

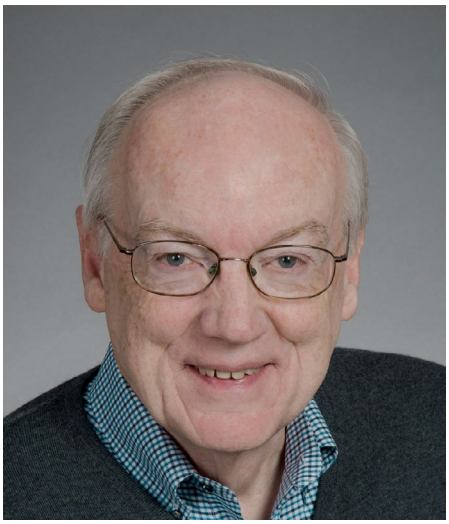
William Albert Catterall (1946–2024)

By Johannes W. Hell, Stefan Herlitze, Lori Isom, Amy Lee & Vladimir Yarov-Yarovoy

An icon left us on 28 February 2024. William Albert Catterall passed away at the age of 77 years while attending the Sixth International Calcium Channel Conference on Boracay in the Philippines. When snorkeling, he experienced cardiac arrest and could not be resuscitated. While there is never a good time and place to leave your loved ones, Bill had the privilege to do so amidst family, friends, and colleagues in a beautiful, scientific setting. He had just delivered another of his inspiring presentations on the regulation of the cardiac calcium channel that controls our heartbeat, a subject he studied for most of his life. Bill is survived by his daughter, Elizabeth, his son, Douglas, and his wife, Tina.

Bill Catterall was born in Providence, Rhode Island, on 12 October 1946. He received a BS in chemistry from Brown University in 1968 and a PhD in physiological chemistry from Johns Hopkins University in 1972. He started his work on sodium channels during his postdoctoral fellowship with Nobel laureate Marshall Nirenberg at the NIH from 1972 until 1974, when he was promoted to NIH staff scientist. In 1977, Bill was recruited by Edward Krebs to the Department of Pharmacology at the University of Washington in Seattle as an associate professor with tenure, where he swiftly rose through the ranks to become full professor in 1981, and department chair in 1984, a position he held for over 30 years until 2016. Bertil Hille, who made seminal contributions to our understanding of the workings of ion channels using cutting edge electrophysiological methods, was literally just around the corner from Bill's lab, providing an ideal collaborative environment for their early investigations into the ion channel field.

Bill was elected in 1989 to the National Academy of Sciences of the United States, in 2000 to the National Academy of Medicine, in 2000 as a Fellow of the American Academy of Arts and Sciences, in 2008 to the Royal Society London, in 2009 as a Fellow of the American Association for the Advancement of Science, and in 2019 as a Fellow of the American Society for Pharmacology and Experimental Therapeutics. His awards included the Robert R. Ruffolo Career Achievement Award in Pharmacology from the American Society of Pharmacology and Therapeutics and a Lifetime Achievement



Award from the International Union of Pharmacologists. In 2010, he received the prestigious Canada International Gairdner Award.

Bill entered the field of ion channel research at the dawn of modern electrophysiology, when Erwin Neher and Bert Sakmann were ringing in a new era with the patch clamp technique. Bill's pioneering spirit allowed him to define the exact mechanisms of the actions of these ion channel toxins and, later, clinically used ligands such as dihydropyridines, ultimately at atomistic levels. Before Bill's work, the functions of ion channels were well described by electrophysiological recordings, but their molecular nature was unknown. He was the first to isolate and identify sodium and calcium channels upon cross-linking with various channel-targeting toxins, demonstrate their complex subunit composition, and reconstitute their function from purified components. The next step was to proteolytically digest toxin-labeled channels, identify the labeled peptides by ground-breaking sequencing, and produce antibodies against synthetic peptides to further clarify and define binding sites for different channel ligands. His adroit use of antibody mapping, photoaffinity labeling, and site-directed mutagenesis defined the structural correlates of voltage sensors, inner pores, and inactivation gates of sodium channels. Parallel studies defined the receptor sites for toxins as well as pore-blocking drugs used in local anesthesia and to treat epilepsy and cardiovascular diseases.

Cloning of the first sodium and later calcium channel α-subunits by the late Shosaku Numa demonstrated that the pores of these channels are formed by four homologous domains, each consisting of six transmembrane segments. Guided by these maps, Bill proposed the 'sliding helix' or 'helical screw' model of S4 segment motion in sodium channel voltage sensors and showed that the loop between the putative membrane-spanning domains III and IV of the sodium channel formed the inactivation gate. Another important contribution from Bill's group was the use of voltage-clamp electrophysiology to map the binding sites of local anesthetic, antiarrhythmic, and anticonvulsant drugs, within the sodium channel inner pore. These seminal works were performed in collaboration with his long-term associate, Todd Scheuer, who would direct this line of research for several decades. Decades later, many of Bill's early hypotheses regarding voltage sensing, inactivation, and drug binding have been validated and refined using X-ray crystallography, cryo-electron microscopy, and computational modeling studies.

Bill was able to translate this basic research into important preclinical findings, contributing to the discovery that ion channels are the targets of genetic variants that contribute to a broad range of diseases. Bill and colleagues were the first to demonstrate that mice haploinsufficient for *Scn1a*, encoding Nav1.1, exhibited spontaneous seizures and sudden unexpected death in epilepsy (SUDEP), the first vertebrate animal model of Dravet syndrome, a devastating developmental and epileptic encephalopathy. Bill's lab also investigated the regulation of these channels in heart and brain using biochemical and electrophysiological methods. One project focused on heart rate stimulation by protein kinase A (PKA), downstream of norepinephrinergic signaling in response to stress, and identified phosphorylation sites on the cardiac Ca^{2+} channel that they showed to be part of this mechanism. It was this line of research he presented during his last talk at the Calcium Channel Conference.

In a fruitful collaboration with Terry Snutch at UBC and Ruth Westenbroek, another long-term associate at UW, Bill developed antibodies to define the subcellular localization of and biochemically identified the

two neuronal L-type calcium channels, Cav1.2 and Cav1.3, which were shown later to control neuronal excitability and gene expression, as well as the two presynaptic N- and P/Q-type calcium channels, which regulate neurotransmitter release. This work opened yet another new field for Bill to explore – the role of G proteins in the regulation of presynaptic channels. An important question at this time was how various G-protein-coupled receptors modulate presynaptic Ca^{2+} channels. Bill showed, in collaboration with Bertil Hille's lab, that this modulation is mediated via Gβγ rather than the initially suspected Gα subunit of the respective trimeric G proteins that act downstream of these receptors. They also demonstrated that the interaction involves specific intracellular sequences of the P/Q- and N-type channels, which overlap with the interaction sites for Ca^{2+} channel β-subunits and were later further implicated in channel inactivation.

In the mid-1990s, Bill's lab identified a synaptic protein interaction site ('synprint') on the cytoplasmic loop between domains II and III of the Cav2.2 N-type calcium channel, and, in collaboration with Sumiko Mochida, demonstrated a critical role for the synprint motif in regulating neurotransmitter release. Bill's team also discovered a calmodulin binding site in the C-terminal domain of the Cav2.1 P/Q-type channel and established that calmodulin (CaM) binding promotes an initial facilitation, followed by inactivation during repetitive stimuli, Ca^{2+}-dependent inactivation and facilitation (CDI and CDF, respectively).

In the final chapter of Bill's relentless pursuit of channel structure, function, and modulation, he set up channel crystallization with Ning Zheng's laboratory in 2008. Together, they solved the first structure of a bacterial sodium channel and determined the structural basis of the calcium channel selectivity filter. They solved cryo-electron microscopy structures of the bacterial sodium channel in a resting state, which further supported the sliding helix model of the S4 segment motion in sodium channel voltage sensors proposed by Bill in 1986. They went on to solve cryo-electron microscopy structures of the mammalian cardiac sodium channel, which provided atomic-level insights into molecular mechanisms underlying action potential generation, drug block, and fast inactivation.

Bill balanced his professional work with his passion for the outdoors. He was an avid skier in winter and a skillful skipper in summer. He would periodically invite his lab onto his boat. We remember one afternoon when he tested his new sailboat with us in strong winds on Lake Washington, not far from our lab in the medical school. Bill cheered when we reached a speed of 8 knots, which he rarely was able to achieve with his previous boat. He would also join his lab crew of 20 people on annual backpacking trips, some of which lasted for 4 days, to the nearby mountains and coastlines. Our annual ski outings were equally popular, even for beginners – Bill would always suggest a plan and location that offered something for everybody, Snoqualmie Pass and Steven's Pass being perhaps his favorites for these outings. And then, of course, there were the weekly gatherings on Friday afternoons at Big Time Brewery for happy hour, where discussions of projects were interwoven with the newest reports of some outdoor adventures and many other occasions. These events helped to build camaraderie amongst his trainees and lab staff and provided venues for scientific discussions beyond our interactions in the lab.

Bill loved to savor good foods, especially salmon in season, with a good bottle of wine, watching the spectacular sunsets over Puget Sound. He loved to travel to explore cultures and wildlife around the world, ideally in combination with providing seminar presentations at different universities or participating in scientific conferences and symposia.

We would like to invite the reader to take a minute of silence to contemplate our loss.

Rest in peace, Bill

Johannes W. Hell [1] ✉, **Stefan Herlitze** [2] ✉, **Lori Isom** [3] ✉, **Amy Lee** [4] ✉ & **Vladimir Yarov-Yarovoy** [5] ✉

[1]Department of Pharmacology, University of California, Davis, Davis, CA, USA. [2]Department of Zoology and Neurobiology, Ruhr-University Bochum, Bochum, Germany. [3]Department of Pharmacology, University of Michigan, Ann Arbor, Ann Arbor, MI, USA. [4]Department of Neuroscience, University of Texas at Austin, Austin, TX, USA. [5]Department of Physiology and Membrane Biology, University of California, Davis, Davis, CA, USA.
✉e-mail: jwhell@ucdavis.edu; sxh106@googlemail.com; lisom@umich.edu; amy.lee1@austin.utexas.edu; yarovoy@ucdavis.edu

Published online: 30 April 2024