Sodium Channel Coalition Workshop
July 18-19, 2018

The Dravet Syndrome Foundation (DSF), FamilieSCN2A Foundation, and Wishes for Elliott were pleased to host a 1.5-day Sodium Channel Coalition (SCC) workshop at Children's Hospital Colorado in July 2018. This workshop, made possible by a Patient-Centered Outcomes Research Institute (PCORI) Eugene Washington Engagement Award to the Dravet Syndrome Foundation (7881-DSF), brought the top researchers studying sodium channels together to collaborate, brainstorm, and learn about PCOR in the hopes of advancing research toward better treatment for the sodium channelopathies *SCN1A, SCN2A,* and *SCN8A.*

Six dedicated researchers planned and chaired the workshop, inviting 26 of their colleagues to participate in 6 sessions focused on different aspects of sodium channel research:

Session	Focus	Chair
1	Sodium Channels: History, Present, & Future Treatment	Michael Hammer, PhD University of Arizona
2	Molecular Mechanisms of Pathogenesis	Alfred George, Jr., MD Northwestern University
3	Cellular Mechanisms of Pathogenesis	Lori Isom, PhD University of Michigan
4	*In vivo* Models of Sodium Channelopathies	Miriam Meisler, PhD University of Michigan
5	Small Molecule Therapeutics	Manoj Patel, PhD University of Virginia
6	Funding Mechanisms for Collaborative Programs	Jack Parent, MD University of Michigan

The patient assistance groups compiled information for the participants on patient-centered outcomes research (PCOR), their families' priorities and concerns regarding research, and opportunities for engagement with patients in research design, implementation, dissemination, and funding. These materials were distributed to each participant at the start of the meeting. To expand on the concept that patients should be critical components in determining research objectives and design, the participants were invited to stay for the 3rd biennial Dravet Syndrome Foundation Family and Professional Conference, held at the same venues, from July 19-22, 2018. This provided an opportunity for researchers to connect with patients and caregivers to fully understand how the disorders they study

in the laboratory affect real families beyond the traditional research measures of seizures and electroencephalographic discharges.

The recurring theme of the workshop was: "It's the network!" In each session, researchers presented their work on specific aspects of sodium channels but always returned to the theme, noting that the complexity of their findings suggest the background signaling, network, and even variation in other genes beyond *SCN1A, 2A, or 8A* contribute to the overall clinical picture of the channelopathies.

In a brief history of sodium channels, Dr. Meisler reminded us of the similarities among *SCN1A*, *SCN2A,* and *SCN8A:* All are essential genes, since knock-out of each of them in the mouse is lethal; all have a similar 4-domain structure; and all are highly conserved through evolution and within the human population, with only 1/10 the expected number of loss-of-function variants in a database of 60,000 healthy individuals.

The types of patient mutations in the different sodium channels vary. *SCN1A* mutations associated with Dravet syndrome usually result in loss of function (LOF). Dravet syndrome is characterized by frequent, prolonged seizures, speech impairment, developmental delay, and other comorbidities. Because of the effect of this LOF in inhibitory interneurons, there is an excess of excitation in the brain. *SCN8A* mutations that cause epilepsy often result in gain of function (GOF), creating an environment of hyperexcitability, while LOF *SCN8A* mutations are more likely to cause intellectual disability without seizures. *SCN8A*- related epilepsy differs in presentation from Dravet syndrome by the absence of febrile seizures and presence of obvious movement disorders. Both LOF and GOF mutations of *SCN2A* are observed in patients, associated with a wide clinical spectrum from benign familial neonatal infantile seizures (BFNIS) to generalized epilepsy to Autism Spectrum Disorder (ASD).

As genetic disorders, each of the channelopathies begs for gene therapy. Difficulties associated with the large size of the genes, the need for delivery to the specific neurons affected, and/or transport across the blood-brain barrier have excluded the sodium channelopathies from current gene therapy approaches. During the workshop, a gene therapy expert noted that other CNS conditions such as lysosomal storage disorders have relied on the concept of "cross-correction," in which gene therapy is delivered to a small subset of cells that can then excrete the necessary products to surrounding cells, making it unnecessary to deliver the therapy to every cell. Although this is not likely to be a solution for the transmembrane sodium channels, the concept reminded researchers to circle back to the theme of the workshop: It's the network! Successful treatment may involve manipulating the neuronal network or other factors to effectively compensate for the genetic defect, rather than direct correction of the sodium channel mutation.

Researchers have attempted to model the neuronal network by studying mutations with known clinical presentations through various cellular, molecular, animal, and computer simulated techniques. What emerges from nearly every study is that a specific mutation can result in different electrophysiological features, depending on factors such as genetic background or environment (in animals and iPSCs), development of the neuronal network, or the computer model in which the effects are tested.

Experts on new compounds undergoing preliminary studies underscored how basic science research can translate quickly to human patients, presenting molecules that effectively target a specific component of the neuronal network, ameliorating symptoms downstream of the target. Compounds such as XEN901,

GS967/PRAX330, and other proprietary molecules are reaching human patients faster than previously anticipated, and researchers are feverishly studying their effects on the entire network.

Overall, the discussion-based format of the meeting was highly effective. The committee chairs chose to focus on short presentations with equal time for discussion, encouraging participants to think beyond their own areas of expertise and brainstorm ways to attack the complex network. The presence of the patient advocacy groups kept the meeting focused on patients and finding treatments that will improve their quality of life. The Dravet Syndrome Foundation, FamilieSCN2A Foundation, and Wishes for Elliott extend our deepest gratitude to the planning committee, session chairs, and researchers who took the time to attend this critical workshop.