



This past week, the FamilieSCN2A Board of Directors participated in the 2018 American Epilepsy Society (AES) Annual Meeting in New Orleans, LA. This is the largest gathering on epilepsy in the world and engages epilepsy professionals in academia, clinical practice, industry, and advocacy. We had the opportunity to network with thousands of epilepsy specialists from all 50 states and nearly 70 countries.

The foundation and our community have been successful at getting SCN2A on the map and it showed this year at AES. Our board members and the booth itself were very busy as the name recognition and positive reputation of our organization has grown exponentially in the past 4 years we've attended.

**Our biggest takeaways from this year's AES Meeting:**

- Genetics was the most popular topic of childhood epilepsy presentations
- Shift from basic science, understanding of epilepsy and genetics to translation into therapeutics
- Compelling science paving the way towards precision medicine
- Increased interest from pharmaceutical and biotech companies in genetic epilepsies such as Ion Channels (Sodium, Calcium, and Potassium)
- Collaboration is crucial to moving towards a cure

The FamilieSCN2A Foundation hosted an in-person Scientific Advisory Board (SAB) meeting on November 30th where we worked together to devise a strategic plan for moving forward in supporting research in SCN2A.

Here are a few highlights from that meeting:

- A policy was created regarding how the foundation collaborates with Industry for-profit pharmaceutical and biotech companies and can be found on our website: <https://www.scn2a.org/research.html>
- A thorough review of the pipeline of research groups / projects the foundation currently supports
- The creation of a defined timeline for opening the FamilieSCN2A Foundation Request for Applications (RFA) which will fund new research projects and is set to launch February 1, 2019



**THE FOLLOWING ARE WORKING GROUPS AND RESEARCH PROJECT LISTS WHICH THE FAMILIESCN2A FOUNDATION IS CURRENTLY WORKING ON OR WITH.**

*This list is not all inclusive, but is here to provide you with details of what is in our pipeline and keep you up-to-date:*

## **Center Without Walls**

Northwestern has been awarded a \$12 million, five-year grant from the National Institutes of Health (NIH) to establish an interdisciplinary research center dedicated to advancing the genetic understanding of epilepsy.

The Channelopathy-Associated Epilepsy Research Center, led by Alfred George, Jr., MD, chair and Magerstadt Professor of Pharmacology, will focus on investigating sodium and potassium channel genes, the dominant class of genes responsible for early childhood-onset epilepsy. The center will be made up of a collaborative group of investigators at five academic medical centers, including Northwestern University, three free-standing research hospitals and two industry partners.

Here is the press release: [NINDS Launches New Epilepsy Center Without Walls | National Institute of Neurological Disorders and Stroke](#)

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## **Geoffrey Pitt, M.D., Ph.D., Weill Cornell Medicine**

Whole-exome sequencing studies of sporadic autism cases have identified SCN2A, which encodes the neuronal voltage-gated sodium channel NaV1.2, as one of the most commonly mutated genes associated with autism. How dysfunctional NaV1.2 affects neurons and consequent circuit function to produce behaviors associated with autism is not well understood.

Geoffrey Pitt and his colleagues at Duke University have recently characterized a familial autism mutation (R1902C) in SCN2A at the structural and biophysical level. This detailed understanding provides a platform upon which to generate a mouse knock-in model, offering a powerful tool for the research community to examine effects at any level — from the atomic (structural) level to behavioral phenotypes — of a monogenic autism mutation.

The researchers propose to generate a mouse bearing the R1902C knock-in mutation within SCN2A (using CRISPR/CAS9 technology) and to characterize the initial physiological and behavioral phenotypes. This mouse model, which will be shared with the research community after initial characterization, will then serve as a substrate for higher-level investigations into how a specific mutation in an autism susceptibility gene leads to the full spectrum of the disorder.

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### **The Bernier Lab**

The University of Washington continues to study the phenotype of individuals with Likely Gene Disruptive (LGD) Variants associated with Autism Spectrum Disorder, such as SCN2A. This research study works with families and individuals with these genetic events to try and better understand how these variants impact human development. We focus on the behavioral and medical profiles of individuals with these variants such as SCN2A, and use the same approach in individuals with other disruptive variants so that we can put our findings on SCN2A in context relative to other disruptive variants. We include electroencephalograms (EEG), eye-tracking, behavioral testing, a medical exam, blood draw, and parent testing in order to generate a more complete picture. Research activities can take place at the Bernier Lab at the University of Washington in Seattle, or in the home. We hope to gain a greater understanding of the clinical impact of disruptive variants so we can inform targeted precision treatment options and utilize appropriate outcome biomarkers.



University of California  
San Francisco

**The Bender Lab** is interested in understanding how loss of SCN2A affects nervous system function at the cellular, network, and behavioral level. Our recent focus has been to understand how SCN2A loss affects the function of neocortical networks in mouse models that either lack one Scn2a gene throughout life or are genetically engineered to delete one Scn2a gene in specific cell classes at specific developmental time points. We hope that these efforts will allow us to determine

where and when future therapeutics will have the most benefit.

**Sanders Lab** Post Doc, Dr Joon An is determining the nature and function of the SCN2A mutation in ASD; SCN2A is a gene that encodes a sodium channel that is critical for communication between brain cells, and has been shown to be important for both ASD and infantile seizures. This study will first use an animal model to examine how disruption of SCN2A function at different times in development affects other genes known to play a role in autism. Dr. An will also work with collaborators at UCSF to compare the behavioral and medical features of people with this mutation and autism compared to those without an autism diagnosis. This will help identify the more precise role of this mutation in autism. Eventually, this model could be used to test therapies that might improve symptoms in both people with the SCN2 mutation and those with other causes of ASD.

### **Nadav Ahituv, Ph.D.**

Exome sequencing studies for autism spectrum disorder (ASD) have identified variants in SCN2A as being among the most common risk factors for ASD<sup>1</sup>. SCN2A encodes the alpha subunit of the voltage-gated sodium channel Na<sub>v</sub>1.2, which plays a role in neuronal excitability, particularly during early development. Using Scn2a heterozygous mice, the laboratory of Kevin Bender at the University of California, San Francisco have unpublished findings that suggest that Scn2a haploinsufficiency leads to deficits in neuronal excitability during early development, as well as deficits in synaptic function that persist into adulthood.

The specific aims of this proposal are:

- **Optimize adeno-associated virus (AAV) CRISPRa conditions in mice.** In this proposal, Nadav Ahituv plans to use these mice as a tool to test a CRISPR activation (CRISPRa) therapeutic for this gene, upregulating the existing Scn2a functional copy in these mice and analyzing the phenotypic consequences of this upregulation. Preliminary results from Ahituv's laboratory suggest that CRISPRa can be used as a therapeutic tool to rescue deficits in Scn2a haploinsufficient mice in vivo.

Ahituv's laboratory will generate AAV vectors that target Scn2a in mice and optimize the titers, single guide RNA (sgRNA) targets and injection conditions (both location and developmental age) to achieve activation levels in Scn2a heterozygous mice similar to that of wild-type mice.

- **Assess the phenotypic consequences of Scn2a CRISPRa.** Using the optimized CRISPRa conditions, Ahituv's laboratory will rescue Scn2a levels in Scn2a heterozygous mice to wild-type levels and determine whether neuronal excitability and synaptic function is restored.

This work will provide insights into the possible therapeutic potential of CRISPRa gene therapy for the treatment of ASDs that are a result of SCN2A genetic mutations. In addition, this mouse model system will allow future testing, via targeted CRISPRa injections into Scn2a heterozygous mice, of the neural and

temporal specificity through which SCN2A haploinsufficiency can lead to ASD.



### **Broad:**

The Stanley Center is actively working on trying to develop compounds that can alter the function of Nav1.2 (SCN2A). The Therapeutics team is currently testing a large number of compounds using a novel technology they have co-developed with an external company to identify compounds that turn up or turn down the function of Nav1.2 to address the loss-of-function or gain-of-function patient populations respectively. The team has also recently characterized a loss-of-function SCN2A mouse model using EEG and are separately characterizing these mice looking at their behavior in collaboration with Harvard's Boston Children's Hospital. This past year Sumaiya Iqbal has created a program which automatically puts all known SCN2A variants onto its 3D structure. Recently Jen Pan and Dennis Lal have been awarded a grant with Al George and a number of other researchers where they will study a large number of SCN2A variants.

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### **Xenon**

#### **XEN901 info:**

Xenon is developing XEN901, a potent, highly selective Nav1.6 sodium channel inhibitor, for the treatment of epilepsy. A randomized, double-blind, placebo-controlled Phase 1 clinical trial to evaluate XEN901's safety, tolerability and pharmacokinetics is ongoing. Thus far, safety, tolerability and PK for XEN901 are supportive of further development. Xenon expects to test XEN901 in both adult focal epilepsy as well as in SCN8A (Nav1.6) gain-of-function epilepsy (EIEE13), based on feedback from regulatory agencies. Xenon expects to submit a regulatory package to propose development of XEN901 in EIEE13 by the end of 2018.

#### **Nav1.6/1.2 dual inhibitors:**

Xenon is also developing additional compounds that are potent, selective blockers of both the Nav1.6 and Nav1.2 sodium channels, also for the treatment of epilepsy. These molecules are at the preclinical stages of development and if supported by the preclinical data, a Phase 1 clinical trial could be initiated in the next few years followed by efficacy studies potentially in SCN2A (Nav1.2) gain-of-function epilepsy (EIEE11) patients. Xenon

will continue to provide updates as these molecules advance into and through clinical development.

# Early Recognition of Genetic Epilepsy in Neonates

## **ERGENT**

Patients with disabilities from SCN2A related illness have been found to fall into two groups--those with seizures and encephalopathy beginning very early after birth, and those who do better early on but later in infancy or childhood have learning difficulties and/or autism. The early-onset group have features that are very similar to patients with KCNQ2 related illness. This makes some sense, since KCNQ2 is a gene for a potassium channel that functions with SCN2A to shape the brain's electrical signals.

FamilieSCN2A is collaborating with two KCNQ2 family-led foundations, the Jack Pribaz Foundation and KCNQ2 Cure Alliance, to support a research study called Early Recognition of Genetic Epilepsy in Neonates, or ERGENT. The goal of ERGENT is to help doctors learn when to suspect a genetic epilepsy and select those patients for rapid testing and diagnosis. ERGENT began recruiting in early August, and has received 8 applications as of Nov 30.



## **SFARI Meeting**

We wanted to let you know that the Simons Foundation Autism Research Initiative (SFARI) had a meeting of funded SFARI investigators recently where leading SCN2A researchers made up one of the featured panels. The talks were given by Raphe Bernier, PhD (University of Washington), Dr. Stephan Sanders, BMBS, PhD (UCSF), Kevin Bender, PhD (UCSF), and Dr. Alfred George, MD (Northwestern University). Each of these scientists gave fascinating updates on their ...innovative work in studying the SCN2A gene and its variants. From creating our children's variants in cell lines, to studying them in animal models, to recording biomarkers and better understand the function - it all leads towards a deeper understanding of SCN2A, new treatments and ultimately a cure.

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## **SCN2A International OT Database: A Database to Connect Therapists:**

By establishing an international database of OTs working with SCN2A children, we can begin to define parameters of best practices to ultimately measure effectiveness of therapy and determine multiple ways of supporting children diagnosed with SCN2A. With the scope of data available through therapy sessions, OTs also have the capacity to inform lab research, and to make a real difference not only in the research but in the lives of children and families living with the daily reality of SCN2A.

If your child is working with or has worked with an OT, please enter your email and download the form. Have the therapist fill it out and return it as indicated. If you have worked with an OT in the past but are no longer in contact, please complete the form with the therapist's name and any prior contact information you have, and we may be able to locate them.

To have your child's occupational therapist participate and register with the SCN2A International OT Database, please visit <https://www.otc-frederick.com/scn2a/>

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## ***Mark Your Calendars! The 3rd Family & Professional SCN2A Conference***



The banner features a scenic view of the Seattle skyline at sunset, with the Space Needle and Mount Rainier in the background. Below the image is a white banner with the text "SAVE THE DATE FOR 2019" in green, flanked by colorful circles. The main text is on a dark blue background: "AUGUST 1 - 3, 2019" in white, followed by "SCN2A FAMILY & PROFESSIONAL CONFERENCE" in large white letters. Below that is "Seattle, Washington | Graduate Hotel 4507 Brooklyn Avenue N.E." and "BROUGHT TO YOU BY:". At the bottom are logos for the FamilieSCN2A Foundation, Bernier Lab at the University of Washington, and the Center on Human Development and Disability.

**SAVE THE DATE FOR 2019**

**AUGUST 1 - 3, 2019**

**SCN2A FAMILY &  
PROFESSIONAL CONFERENCE**

Seattle, Washington | Graduate Hotel 4507 Brooklyn Avenue N.E.

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**FAMILIESCN2A**  
FOUNDATION

**Bernier Lab**  
University of Washington

**Center on Human Development  
and Disability**



We are excited to announce the dates of our 3rd SCN2A Family & Professional Conference which we be held next summer in Seattle, Washington!

This conference is brought to you by The FamilieSCN2A Foundation along with Bernier Lab, University of Washington and Center on Human Development and Disability (CHDD), UW Medical Center.

**Dates: August 1 - 3, 2019**

Location: Graduate Hotel: 4507 Brooklyn Ave N.E., Seattle, Washington

There will be more details to come on our website: [www.scn2a.org](http://www.scn2a.org)



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P.O. Box 82 East Longmeadow, MA 01028

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