Research Summary

NICOLE VILLAS, M.ED

Objectives

State of research funding

- Public vs. Private
- What are academic scientists working on?
- How did DSF help us get here?

Current Projects

- Treatment vs. Cure
- Exciting Research (Public/Foundational, Private)

DRAVET SYNDROME FOUNDATION

Who funds research?

PUBLIC (Taxes)

National Science Foundation (NSF)

- Focused on basic science
- 10 centers – Biological Sciences (BIO) is most relevant to DS

National Institutes of Health (NIH)

- 27 Institutes – National Institute of Neurological Disorders and Stroke (NINDS) is most relevant to DS
- Projects performed at universities and academic centers
- Highly competitive
- Several types of awards
- $1.7 billion budget in 2017

PRIVATE

Foundations/Societies

- DSF
- CURE
- AES

Pharmaceutical Companies

- Greenwich Biosciences
- Zogenix
- Epygenix
- Ovid
- Others

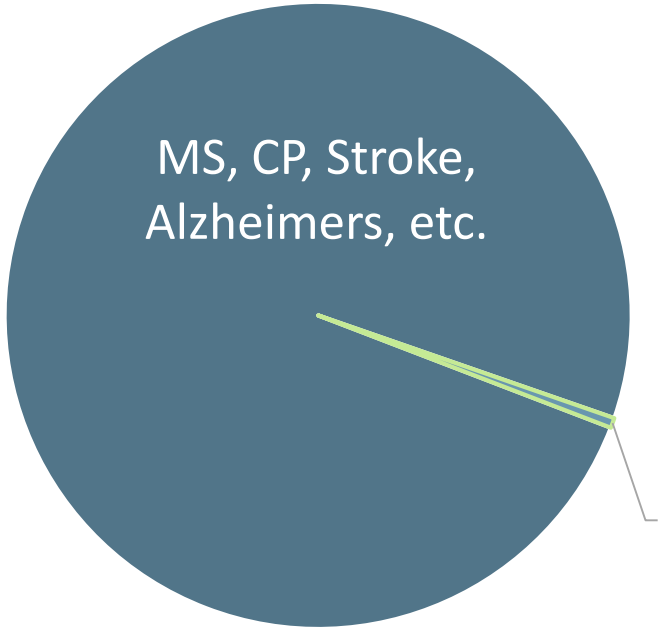
Biotech Companies

- Stoke Therapeutics
- Opko
- Others

DRAVET SYNDROME FOUNDATION

Public: NIH/NINDS Funding

2017 NINDS Budget
$1,695,000,000



Dravet/*SCN1A*
= $8.8 mil
(0.5%)

- 6.75% of US residents have a neurological disorder.

  ≈0.09% of those are Dravet syndrome (based on 1:15,700 incidence), ignoring age factors

Utilizing 0.5% of the NINDS budget is actually pretty impressive!
BUT IT IS NOT ENOUGH.

DRAVET SYNDROME FOUNDATION

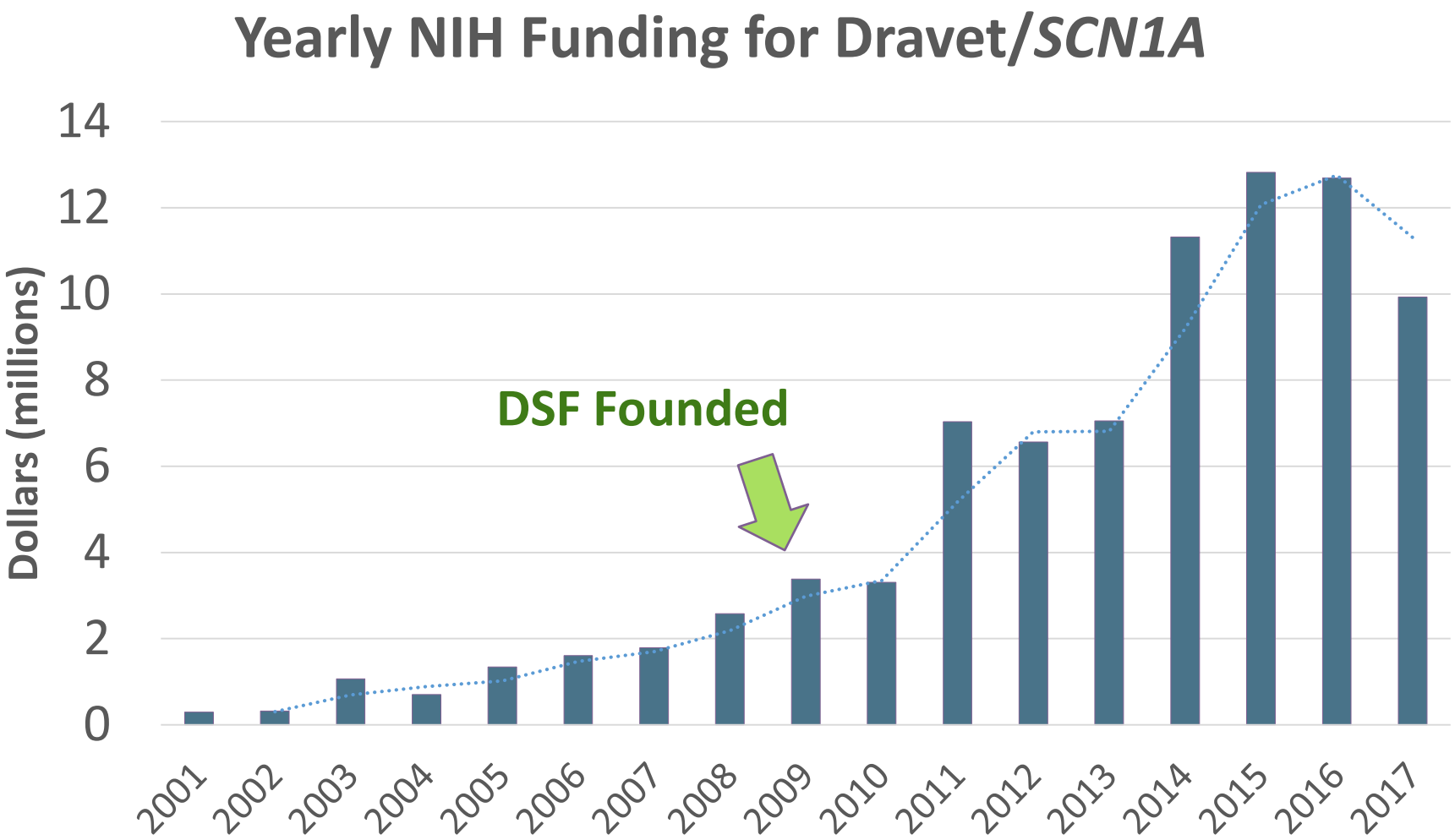
Public: Current NIH Projects

Number	Name	Institute	Subject
1	Antoine, Michelle	UC Berkeley	Effects of fever on seizure susceptibility
2	Baraban, Scott	UC San Francisco	Zebrafish models for DS - further characterization
3	Burre, Jacqueline	Cornell	STXBP1, SEC1 (Munc18-1) genes in epilepsy
4	Catterall, William	U. of WA	Cell biology of sodium channel, neuronal circuitry
5	De La Iglesia, Horacio	U. of WA	Circadian rhythm/sleep and DS
6	Escayg, Andrew	Emory	Loss of function SCN8A mutations alleviate DS symptoms, role in temporal lobe epilepsy
7	Escayg, Andrew	Emory	Huperzine A and DS
8	Escayg, Andrew	Emory	Understanding what affects scn1a transcription
9	Feng, Huajung	Mass General	5-HT, norepinephrine, and dopamine as preventatives for seizure-related sudden death
10	Goldman, Alica	Baylor	SUDEP Research Alliance (human patient sample analysis)
11	Goldman, Alica	Baylor	SUDEP Research Alliance (creating a clinical network core)
12	Isom, Lori	U. of MI	Role of SCN1B
13	Isom, Lori	U. of MI	IPSCs and mechanisms in DS
14	Jalife, Jose	U. of MI	NaV1.5 (cardiac sodium channel) and potassium channel interactions
15	Kang, Jing-Qiong	Vanderbilt	Synaptic mechanisms in DS, incl aggregation of mutant gamma2 subunits
16	Kearney, Jennifer	Northwestern	Identifying genetic modifiers of DS
17	Kollarik, Marian	Johns Hopkins	Ion channels in esophagus/heartburn, etc.
18	Maheshwari, Atul	Baylor	Drug response in DS may be predicted by interictal electrical signals on EEG
19	Martina, Marco	Northwestern	Nimodipine (a dihydropyridine) as a treatment in DS mice and prevention of febrile seizures, epilepsy
20	Mefford, Heather	U. of WA	Genetic studies on childhood epileptic encephalopathies (CEE)

Public: Current NIH Projects (cont.)

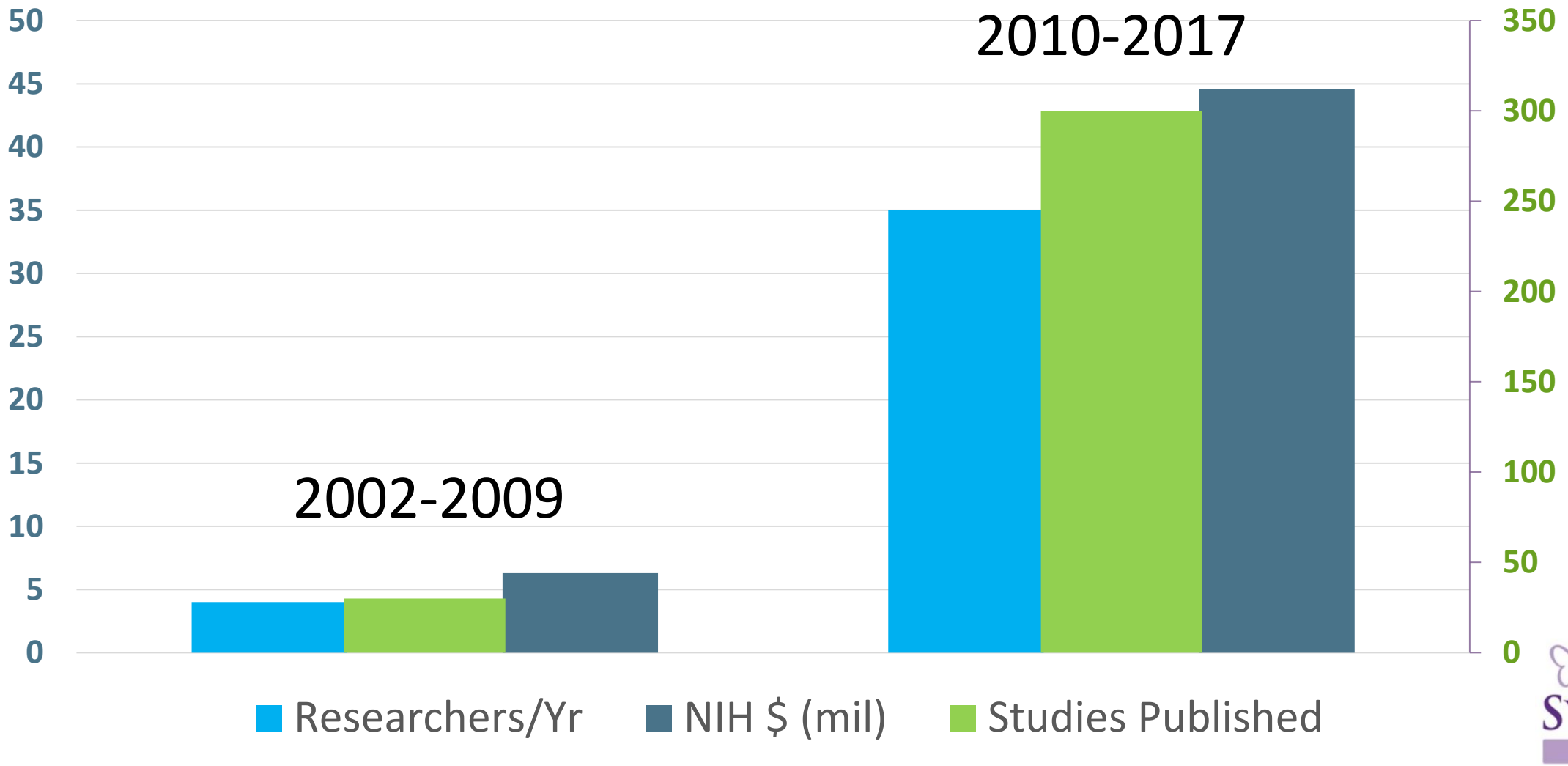
Number	Name	Institute	Subject
21	Meisler, Miriam	U. of MI	Further characterizing a conditional SCN8A mouse model
22	Mucke, Lennart	Gladstone Institutes	Tau reduction in ASD (previously showed tau reduction helped DS symptoms)
23	O'Dowd, Diane	UC Irvine	Fruit fly (drosophila) DS model and human IPSCs
24	Oakley, John C	U. of WA	Electrical patterns (SWR) and their relationship to scn1a expression, memory performance, and seizures
25	Parent, Jack	U. of MI	SUDEP Research Alliance (IPSC and mouse neurocardiac models)
26	Patel, Manisha	U. of CO, Denver	Ketoaldehydes and their role in epileptogenesis (mainly temporal lobe epilepsy)
27	Poolos, Nicholas	U. of WA	HCN1 channel dysfunction in development of epilepsy
28	Richerson, George	U. of IA	SUDEP Research Alliance (mechanisms/pathways of cardiorespiratory function in DS)
29	Richerson, George	U. of IA	SUDEP Research Alliance (brainstem, amygdala role cardiorespiratory function and arousal)
30	Rosenberg, Evan	NYU	LPI (lypophosphatidylinositol), CBD's efficacy, & seizure activity's upregulation of GPR55 membrane expression
31	Schaefer, Anne	Mount Sinai	Modulating miR-128 (a micro RNA that regulates neuronal signaling) in DS as a treatment, delivering miR-128 via AAV to specific neurons
32	Soltesz, Ivan	Stanford	Creating EEG algorithms that automatically identify mouse behavior to distinguish between non-epileptic SCN1B mice and their wild type controls.
33	Stella, Nephi	U. of WA	Effects of newly discovered enzyme, alpha/beta-hydrolase domain 6 (ABHD6), on mouse model of DS
34	Sunderam, Sridhar	Signal Solutions, LLC	Using non-invasive sensors to identify seizures in mice, instead of the highly invasive EEGs curently used.
35	Tallent, Melanie	Lifesplice Pharma, LLC	Preclinical testing of splice modulating oligonucleotides (SMOs) that create fewer functional copies of SCN8A to treat DS
36	Unavailable	National Heart, Lung, and Blood Institute	Sudden Death in Young (incl SIDS and SUDEP) - creating a registry and analyzing data
37	Wagnon, Jacy	U. of MI, Ann Arbor	CRISPR-Cas9 to create a DS mouse with a 3rd conditional copy of scn1a to study the reversibility of DS
38	Werley, Christopher	Q-State Biosciences , LLC	Developing an optical system to evaluate iPSC neuron response to medications in DS
39	Zhou, Chengwen	Vanderbilt	GABAergic receptor subunit mutations and their role in seizures

Public – How did we get here?



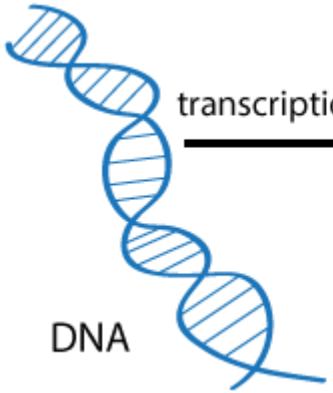
DRAVET SYNDROME FOUNDATION

DSF's Impact: Before/After founding



DRAVET SYNDROME FOUNDATION

Research: Cure vs. Treatment

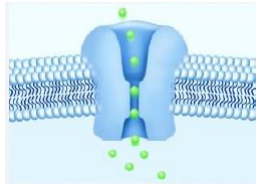


transcription

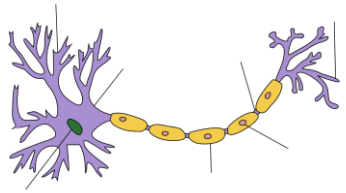
translation

folding

protein
(ion channel)



transport to membrane



neuron

neuronal network

seizures

other organ systems, comorbidities

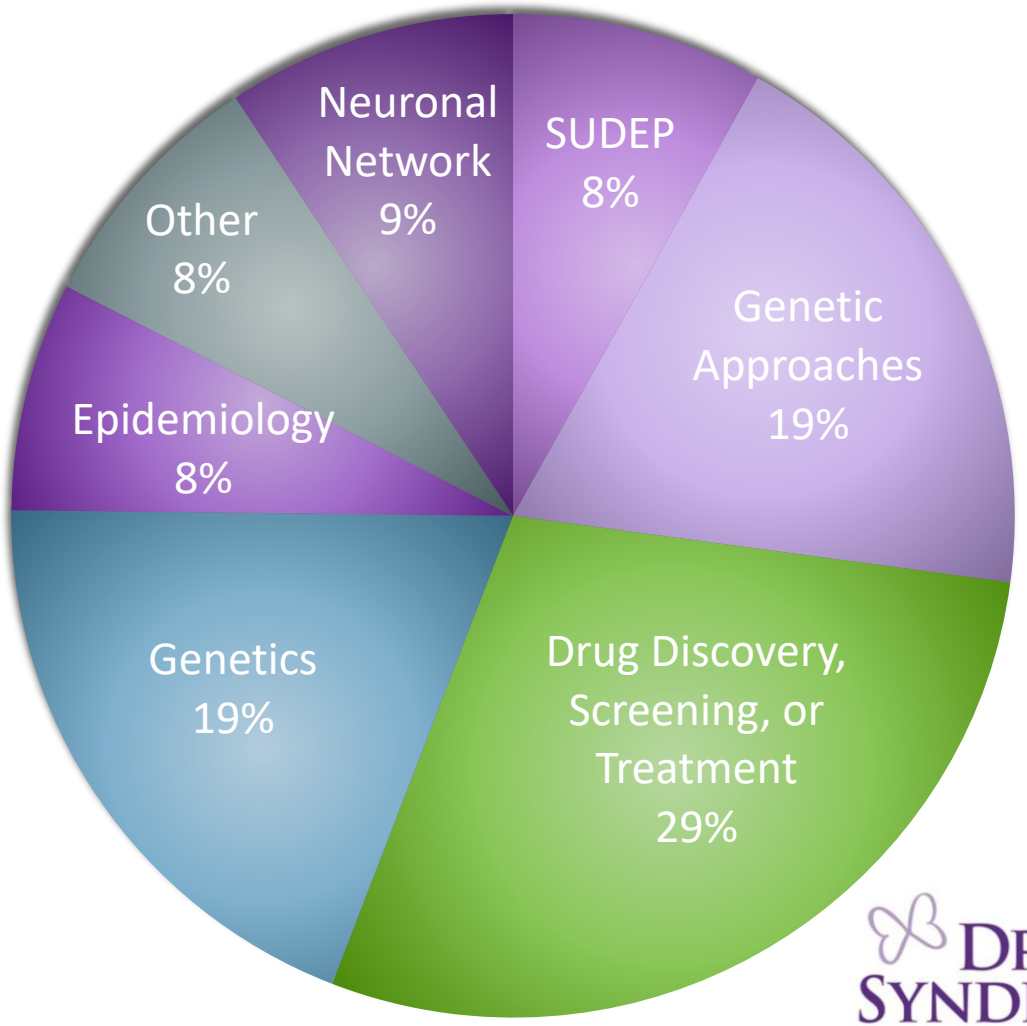
populations, epidemiology

DRAVET SYNDROME FOUNDATION

https://ayearofai.com/rohan-lenny-1-ne, http://biosocialmethods.isr.umich.edu/epigenetics-tutorial/epigenetics-tutorial-gene-expression-from-dna-to-protein/, https://www.csblab.or.kr/IonChannel, By Quasar Jarosz at English Wikipedia, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=7616130, ural-networks-the-backpropagation-algorithm-explained-abf4609d4f9d, *Getty,*

DSF Grant breakdown

Drug Discovery/Screening/ Treatment	$1,063,000
Genetics	$714,000
Genetic Approaches	$703,000
Neuronal Network	$345,000
SUDEP	$300,000
Other	$300,000
Epidemiology	$273,000
Total	$3,698,000



DRAVET SYNDROME FOUNDATION

Exciting Research (Public/Foundational Grants)

Genetic Approaches	Oakley, Wagnon	Creating a mouse model that can be turned off and on at different stages of life to determine how fixing the *SCN1A* problem affects development and seizures
	Hampson, Waddington, Karda, Rubinstein, others	Taking steps toward gene therapy – studying possible delivery vectors
	Mallamaci	RNA-based transcription/translation stimulation of healthy *SCN1A*
SUDEP Mechanisms	Goldman, Richerson, Mulkey, others	Investigating the cardiorespiratory failure in SUDEP and its relation to *SCN1A,* studying patient data in depth to elicit cause and effect
Cellular Models	Parent, Isom, Kiskinis, Dang, others	Creating iPSC models that can more quickly identify therapeutic approaches

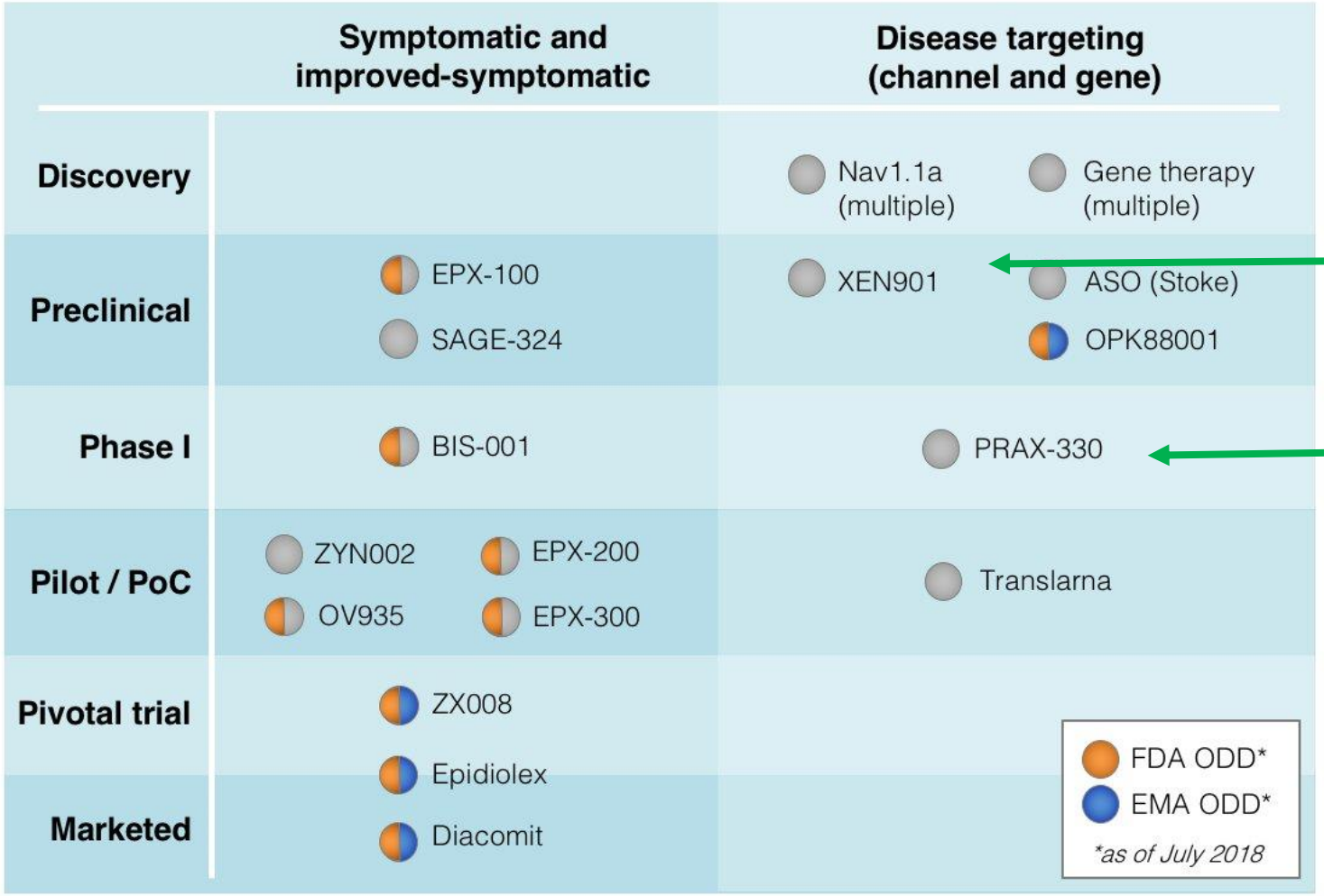
DRAVET SYNDROME FOUNDATION

Genetic Approaches (Private Companies)

Stoke Therapeutics	Using ASO to increase the efficiency of mRNA processing in *SCN1A's* favor	Preclinical research underway, successful approach in Spinal Muscular Atrophy (SMA) (Spinraza/nusinersen)
Others		Unpublished, preclinical studies
PTC Therapeutics	Reading through stop codons to increase *SCN1A* expression (ataluren/Translarna)	One small clinical trial in DS in progress (8 patients), questionable results in other diseases
OPKO	Upregulating *SCN1A* expression via AntagoNAT (OPK88001)	Has been in the works for several years. One study published, orphan drug designation, but no trials have started. Slow progress, few updates

DRAVET SYNDROME FOUNDATION

Exciting Research – Medication Pipeline



Targets Nav1.6 (SCN8A)

GS967, likely via SCN8A reduction

DRAVET SYNDROME FOUNDATION

Questions?

Jack Parent, MD

Univ. of Michigan, Ann Arbor

Lori Isom, PhD

Univ. of Michigan, Ann Arbor

Scott Baraban, PhD

Univ. of California, San Francisco

Thank you!


OUR SUPERHEROES
NEED A CURE
DRAVET SYNDROME
FOUNDATION
INCREASE AWARENESS
RAISE FUNDS
SAVE LIVES
LEARN MORE AT DRAVETFOUNDATION.ORG