Dravet Syndrome Foundation

Research Summary

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BOARD PRESIDENT/SCIENTIFIC DIRECTOR, DSF

ICARE MEETING 2019

DRAVET SYNDROME FOUNDATION

Raising hope & changing lives through research

Objectives

DSF as a funding source

- What is our role?
- What is our strategy?

DSF-Funded research

- Program design
- Funding breakdown
- Current/Exciting research
- Where do we go from here?

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What is our role?

ICARE 2014 portfolio analysis:
$150 Million spent in 2013
95% Public (NIH etc.)
<5% Private (DSF Incl.)

2019 NINDS Budget
$2,216,913,000

Dravet/*SCN1A*
= $12,064,027
(0.5%)

- 6.75% of US residents have a neurological disorder,
  ≈ 0.09% of those are Dravet

Utilizing 0.5% of the NINDS budget
~~is actually pretty impressive~~

~~***BUT IT***~~ ***IS NOT ENOUGH***

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www.ninds.nih.gov/Funding/About-Funding/NINDS-Funding-Strategy/NINDS-Funding-Strategy-FY-2019

What is our role?

Goals	≠	Roles
Improved treatments		~~Bring treatments to market ($650 million)~~
Minimize/eliminate comorbidities		Improve understanding of mechanisms of Dravet, comorbidities
Better quality of life		Arm researchers & clinicians with preliminary data or support needed to pursue further study
Cure (?)		Prepare community for research

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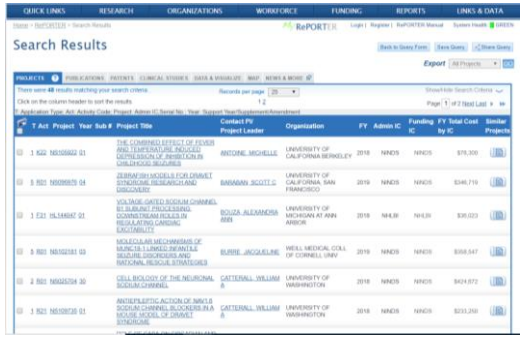
Prasad V, Mailankody S. Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval. JAMA Intern Med. 2017 Nov 1;177(11):1569-1575. doi: 10.1001/jamainternmed.2017.3601. Erratum in: JAMA Intern Med. 2017 Nov 1;177(11):1703

What is our strategy?

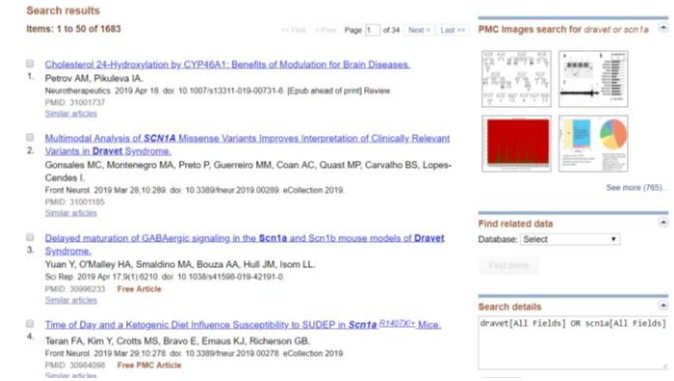
DSF Mission: "To aggressively raise research funds for Dravet syndrome, to… increase awareness, and to… provide support to families." Strategic Plan = 3 objectives: Cure, Treat, Learn

DSF's Strategy:

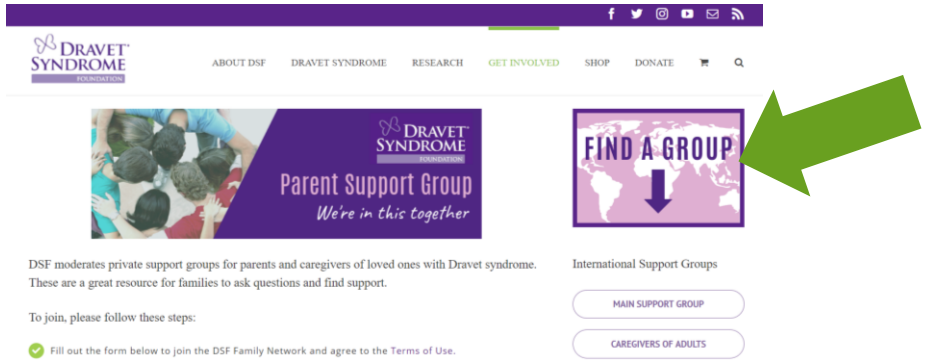
1) Increase the # of researchers studying Dravet



2) Support research that leads to larger (NIH) awards



3) Increase knowledge of disease/mechanisms/clinical care



4) Prepare the community for research!

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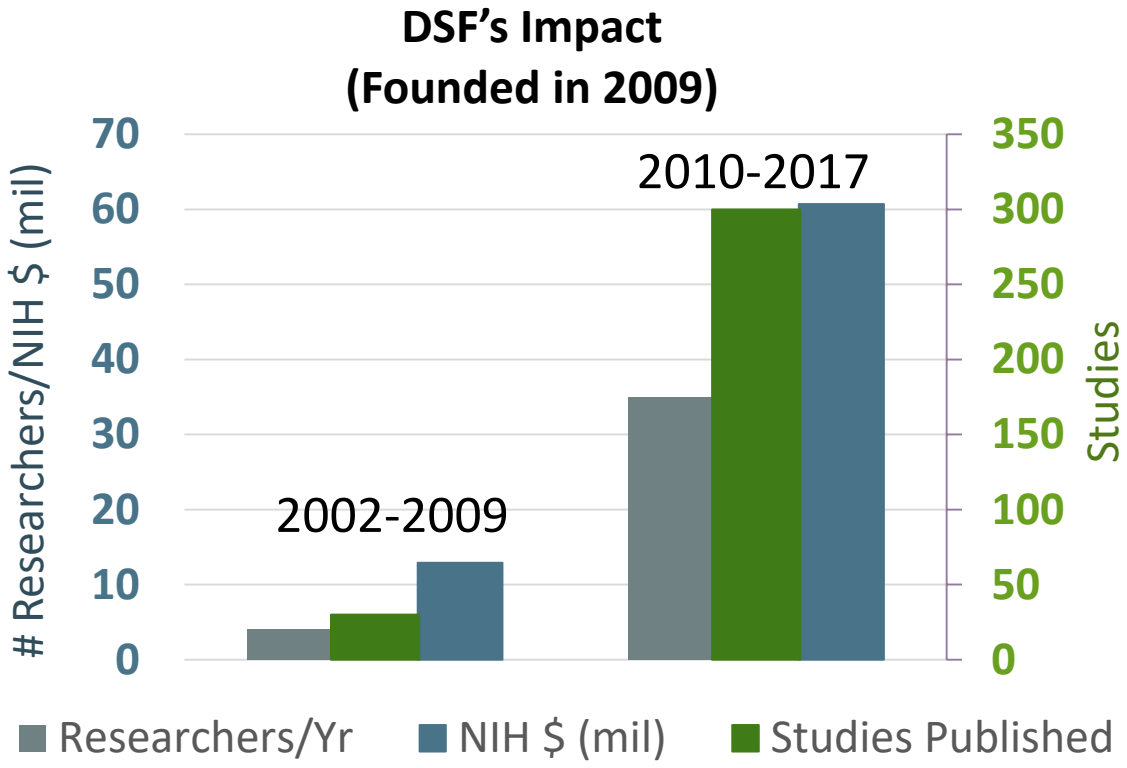
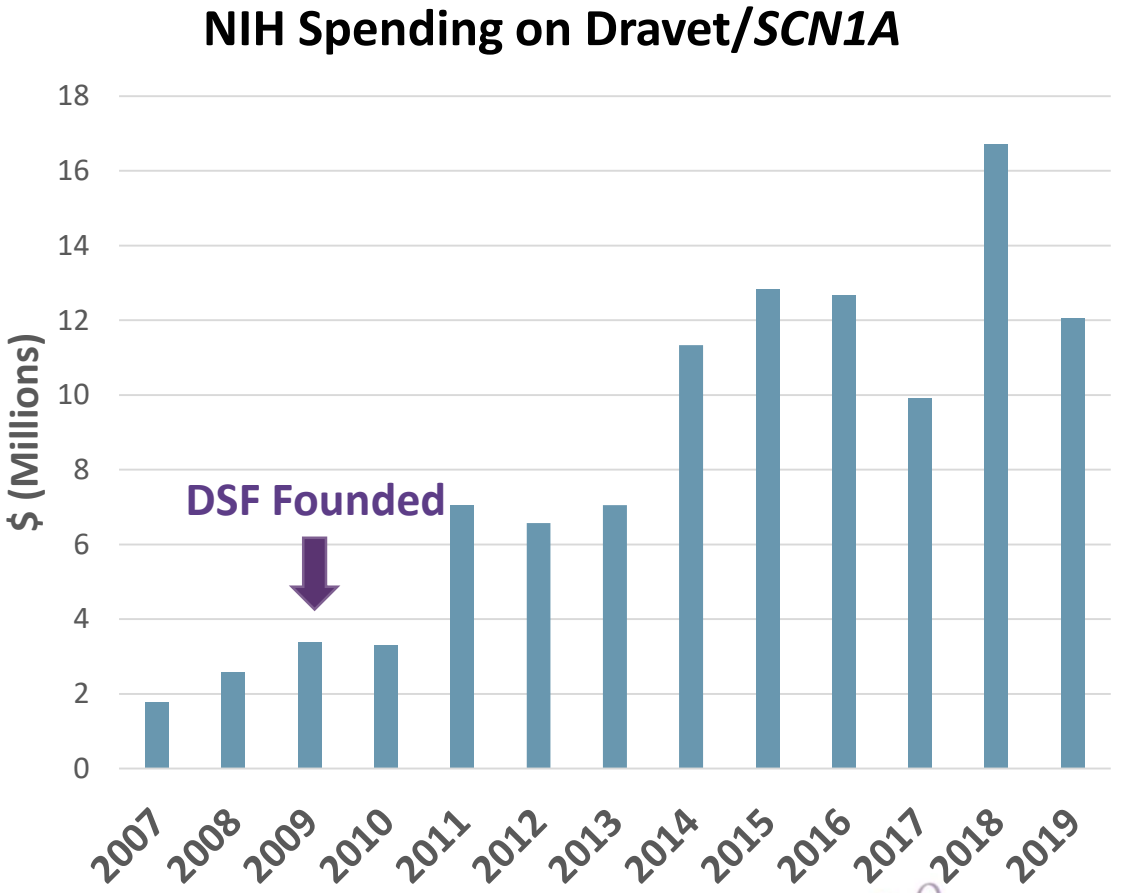
What is our strategy?





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Program Design

DSF has awarded $4.1 million to research since 2009:

	Research Awards	Postdoctoral Fellowships	Clinician-Researcher Awards	Special RFA	Other
Award:					
Length:					
Projects Funded:					
Total $$ Awarded					
Publications From Research:					

For grant information, visit: www.dravetfoundation.org/dsf-funded-research/research-grant-program/

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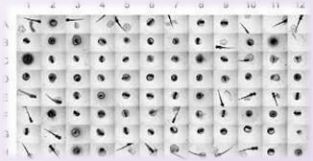
DSF Funding Breakdown

29% Clinical Research

$1.2 Million



71% Basic Science Research
(mice, iPSC, zebrafish)

$2.9 Million

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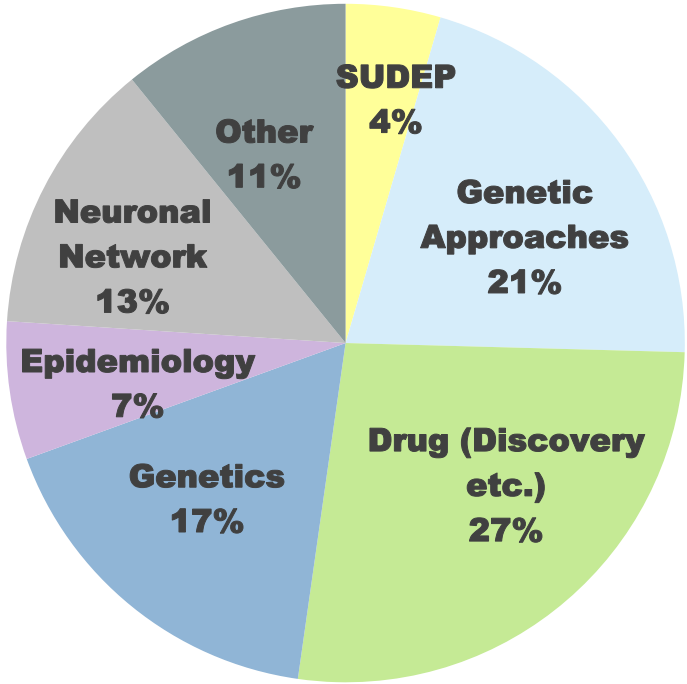
DSF Funding Breakdown

38 Projects

Drug Discovery/Screening/ Treatment	$1,113,000
Genetics	$714,000
Genetic Approaches	$868,000
Neuronal Network	$545,000
SUDEP	$187,500
Epidemiology	$273,000
Other	$450,000
Total	**$4,150,500**

DSF Funded Research



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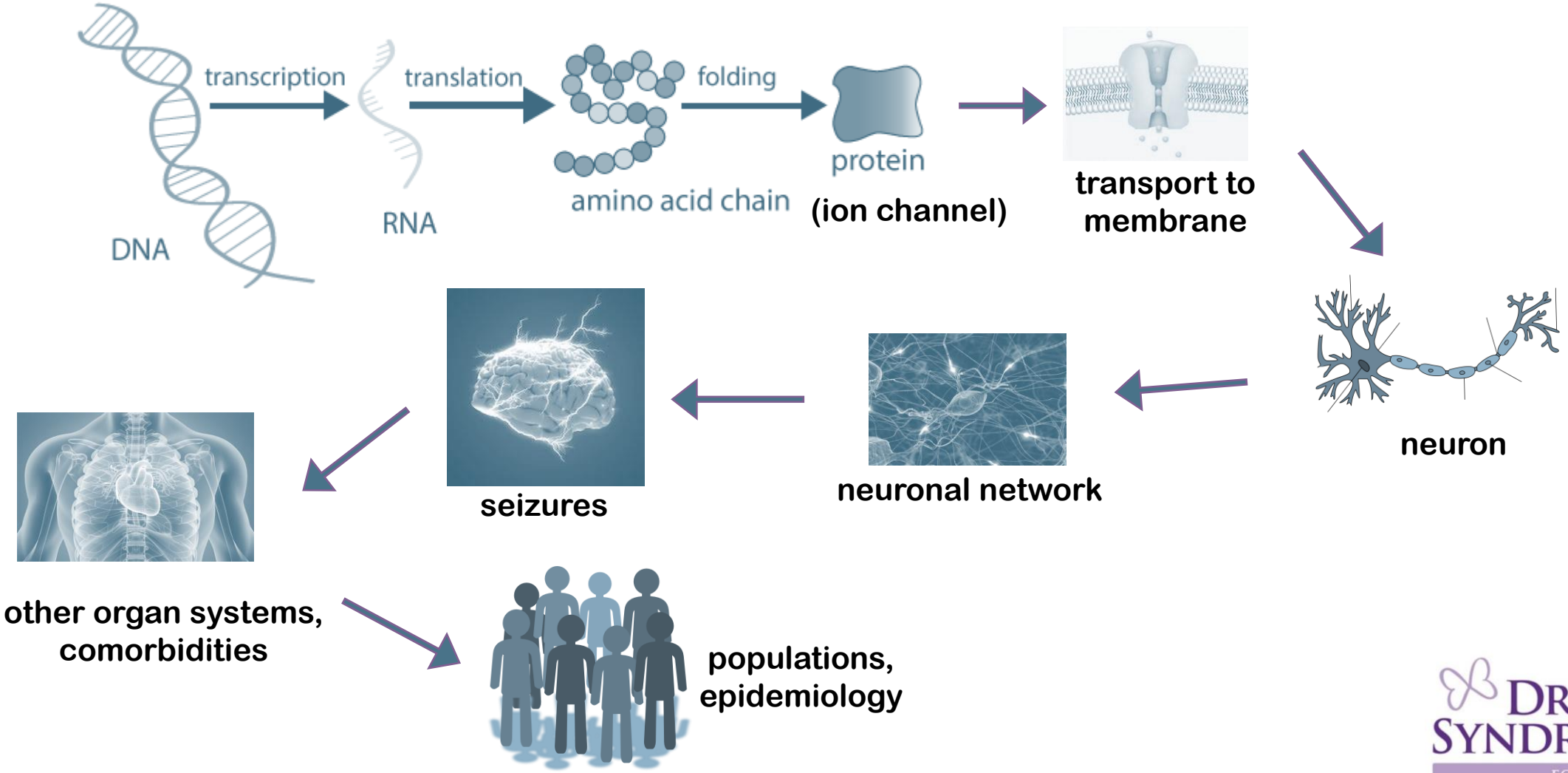
DSF Funding Breakdown



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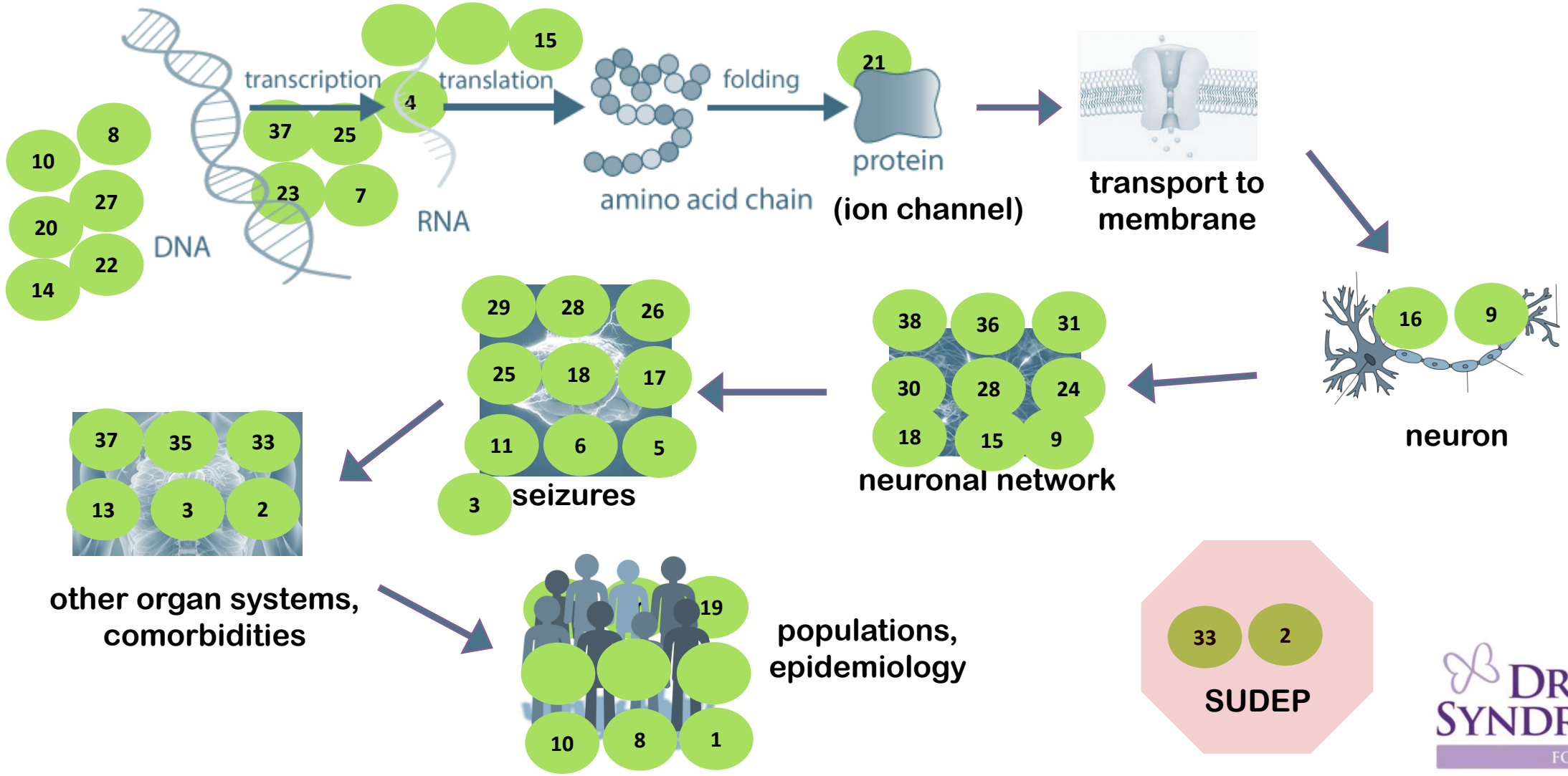
DSF Funding Breakdown



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DSF-Funded Research Highlights

- Zebrafish are a good model for efficient drug discovery (3 drugs in development as a result) and mechanistic studies (Baraban et al. 2013; Grone et al. 2016)
- Dravet is nearly 2x more prevalent than previously thought (Wu 2015)
- Postictal EEG suppression could be a factor in SUDEP (Kim et al. 2015)
- Expert consensus on diagnosis and treatment incl. 1st and 2nd line agents (Wirrell et al. 2017)
- Regulatory elements may play a key role in *Scn1a* expression and may account for the 10-15% of *SCN1A*-negative patients (Nord, AES poster 2016)

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Current DSF-Funded Research

2017 Awards (Currently in Year 2):

Daniel Mulkey, PhD – University of Connecticut
$150,000 – Research Grant (2 year project)
Disordered breathing contributes to SUDEP in a mouse model of Dravet syndrome

David R. Hampson, PhD – University of Toronto
$143,000 – Research Grant (2 year project)
Exploring gene therapy to treat sudden unexpected death and other pathological features of Dravet syndrome

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Current DSF-Funded Research

2018 Awards (Currently in Year 1):

Gemma Carvill, PhD – Northwestern University, *$165,000 (2 year project)*
Pathogenic splicing mechanisms of an SCN1A poison exon in Dravet syndrome

John M Schreiber, MD – Children's National / Children's Research Institute, *$150,000 (2 year project)*
Subclinical myocardial damage in Dravet syndrome, other refractory convulsive epilepsy, and convulsive status epilepticus

Sharon Swanger, PhD – Virginia Polytech Institute and State University, *$150,000 (2 year project)*
Balancing thalamic excitation and inhibition in a Dravet syndrome mouse model

Rajeswari Banerji, PhD – University of Colorado Denver, *$50,000 – 1 year postdoctoral fellowship*
Identifying a novel metabolic target for improving disease outcomes in Dravet syndrome

Jessica Chancey, PhD – University of Texas at Austin, *$50,000 – 1 year postdoctoral fellowship*
Mechanisms of altered neuronal excitability and synaptic integration in a mouse model of Dravet syndrome

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Other Exciting Research

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
	Stoke Therapeutics	Using ASO to increase the efficiency of mRNA processing in SCN1A's favor
	DSF Grant Recipient(s)	Genetic Approaches spring RFA recipient(s) to be announced in mid May 2019
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
Other	Industry	Preclinical work going on in several exciting areas

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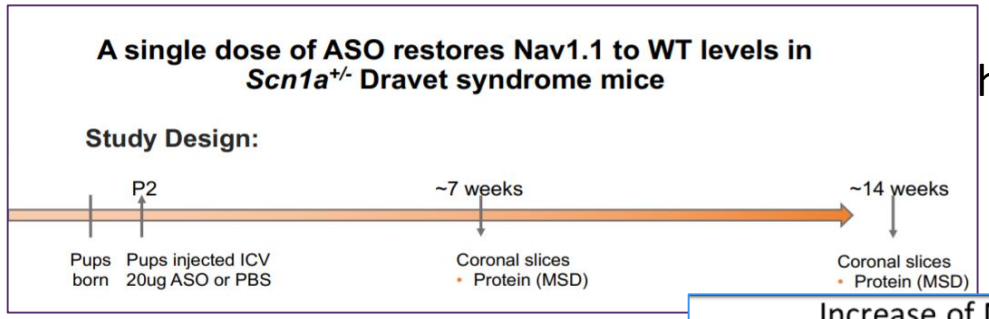
Other Exciting Research (Stoke)

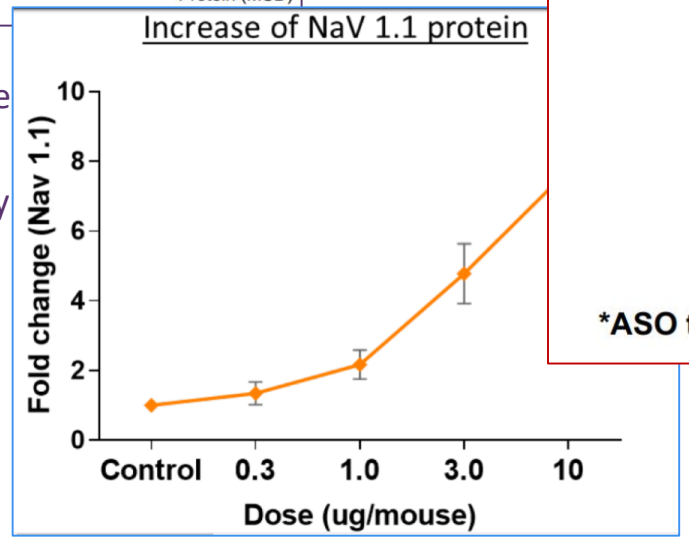
Stoke (TANGO) – Targeted Augmentation of Nuclear Gene Output



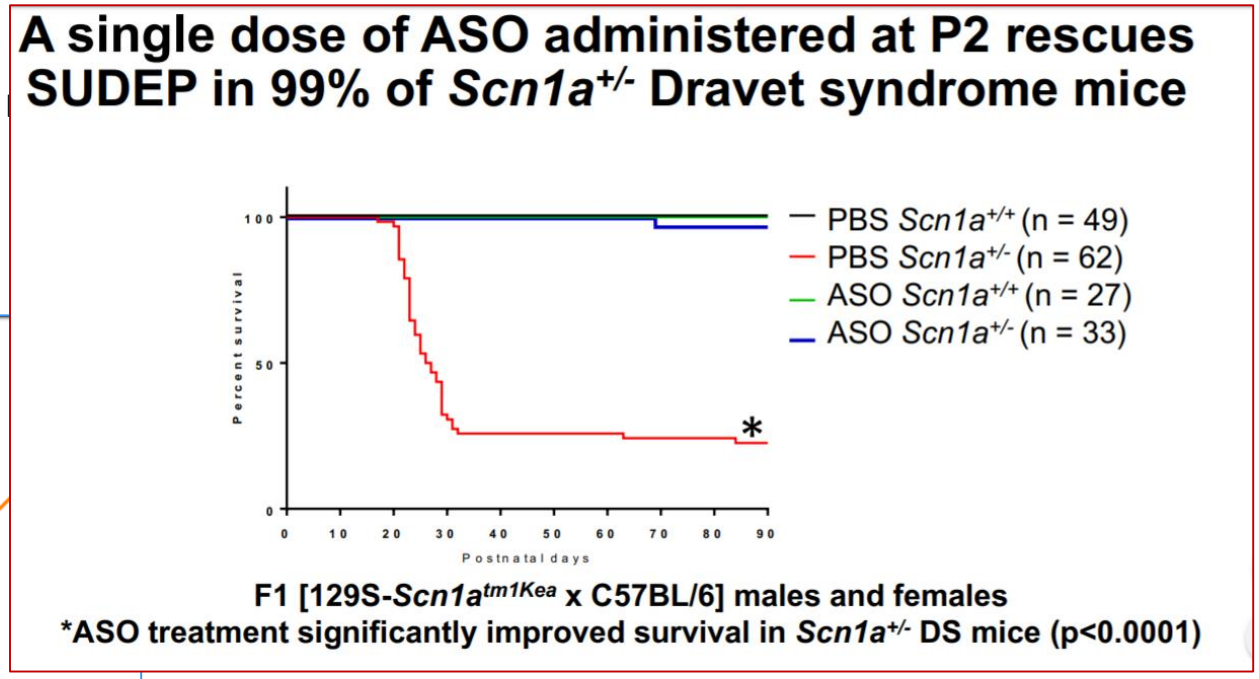
human iPSC

Increased sodium channels in Dravet mice when given 2 days after birth

- Increased sodium channels in healthy mice with no adverse effects



Increased sodium channels in Dravet mice was dose dependent



Prevented generalized seizures and SUDEP in 99% of animals

- When given at Day 14 instead, it still prevented seizures and SUDEP

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Poster presented at AES Dec 2018, https://www.stoketherapeutics.com/wp-content/uploads/Stoke-Poster-Dec-1.pdf

Where do we go from here?

1. Understanding is not complete:

- ✓ Collaborations between experts in research fields is required
- ✓ Address the root cause of the problem
- ✓ Determine effects on other organ systems
  - -How to measure those effects

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Where do we go from here?

2. Moving from understanding to action requires patient participation:

- ✓ Support natural history studies
- ✓ Define, measure, analyze outcomes/endpoints beyond seizures
- ✓ Prepare patient community for research
  - -Input on different trial designs, understanding of each design's limitations
  - -Address caregiver burn-out in trials

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Where do we go from here?

3. Moving from understanding to action requires more clinicians:

- ✓ Experts tapped out. Encourage clinician-researchers
- ✓ Expand network of experts
- ✓ Engage adult neurologists in studies, from characterization to clinical trials

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Nord, Alex, poster presentation at 2016 AES: www.aesnet.org/meetings_events/annual_meeting_abstracts/view/198665

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Thank you!

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