TANGO for the Treatment of Genetic Diseases including Dravet Syndrome and Other Epilepsies

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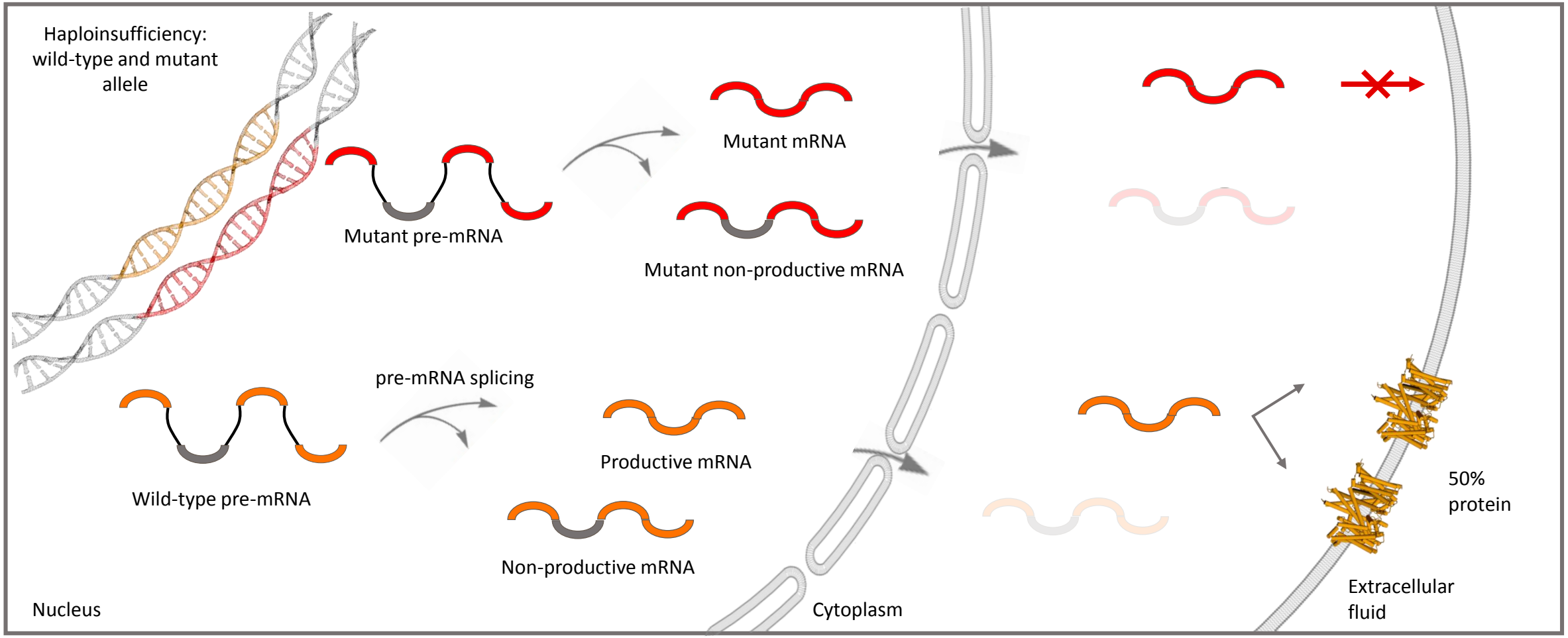
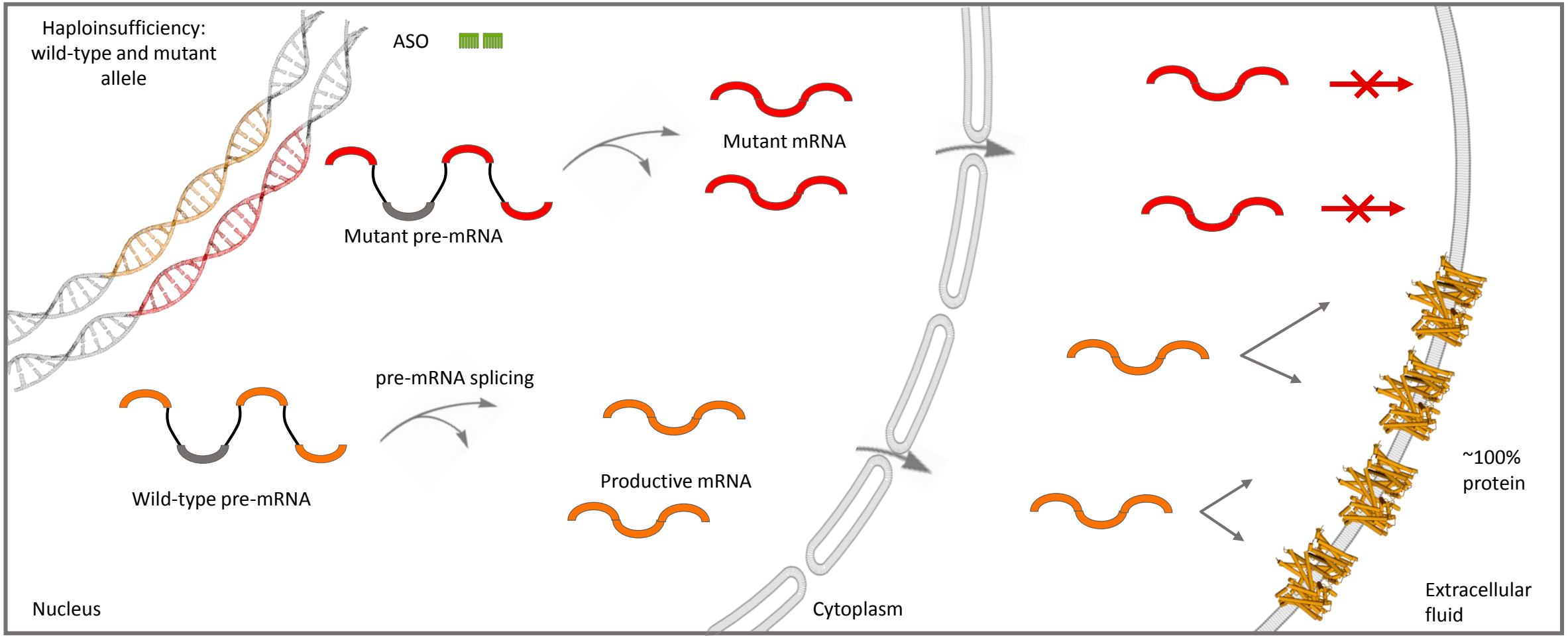
STOKE THERAPEUTICS

Transformative Potential of TANGO Technology in Haploinsufficiency Diseases



Source: Stoke data

Transformative Potential of TANGO Technology in Haploinsufficiency Diseases



Source: Stoke data

Target Discovery Process Utilizing Proprietary Bioinformatics Capability

RNA sequencing and in silico discovery datasets

Bioinformatics analysis

Universe of non-productive splicing events

Genetic disease databases

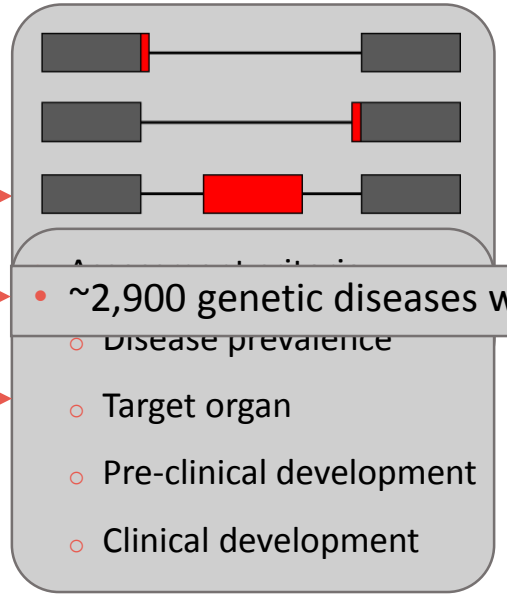
TANGO amenability assessment

TANGO targets

Cell and tissue validation

Hit identification

Candidate evaluation and prioritization



- Proprietary database of ~85,000 non-productive events in the human transcriptome
- ~2,900 genetic diseases with non-productive events
  - Disease prevalence
  - Target organ
  - Pre-clinical development
  - Clinical development

Source: Stoke data

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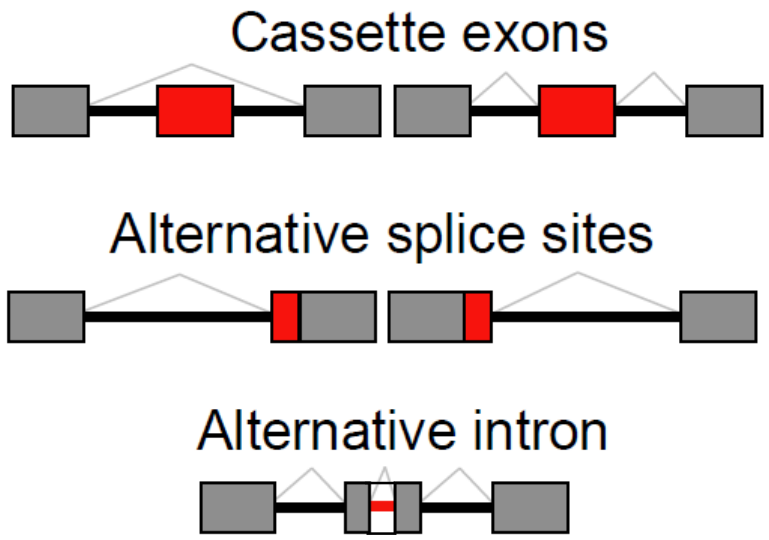
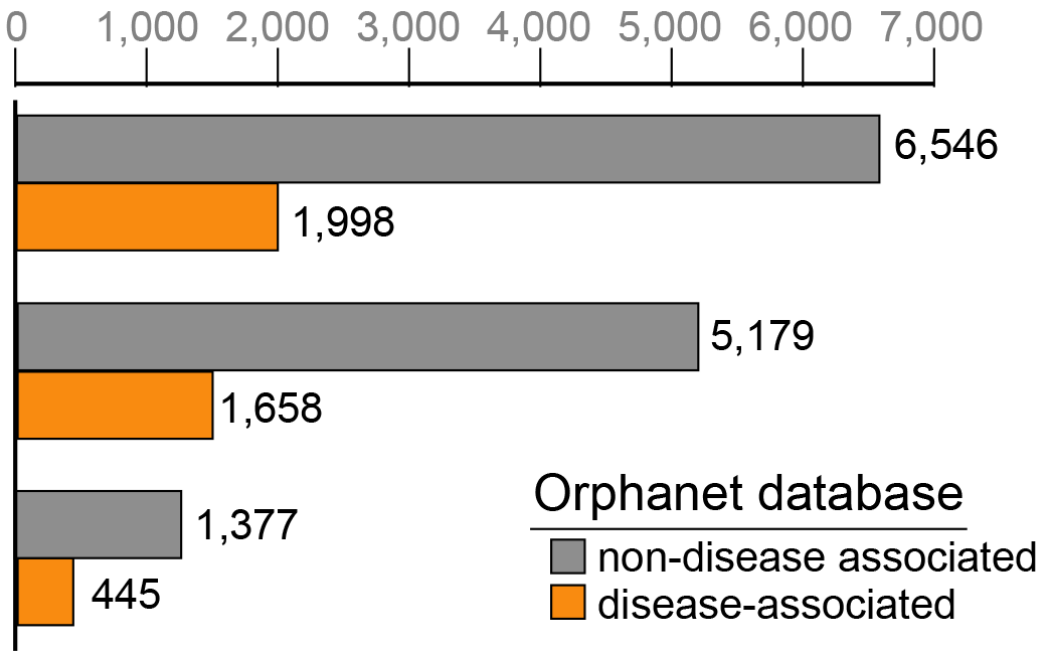
Identification of Naturally Occurring, NMD-Inducing Alternative Splicing Event Types

Types of AS-NMD events



Number of genes with AS-NMD events



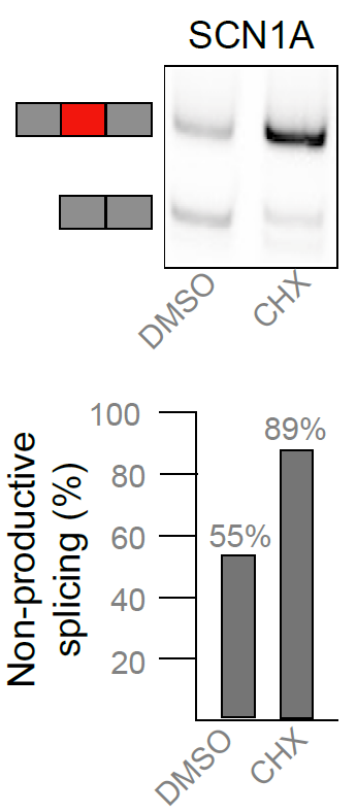
- AS-NMD events occur in approximately 10,771 protein-coding genes in human CNS, liver, and ocular samples
- Approximately 23% (2,482) of these genes are associated with genetic diseases

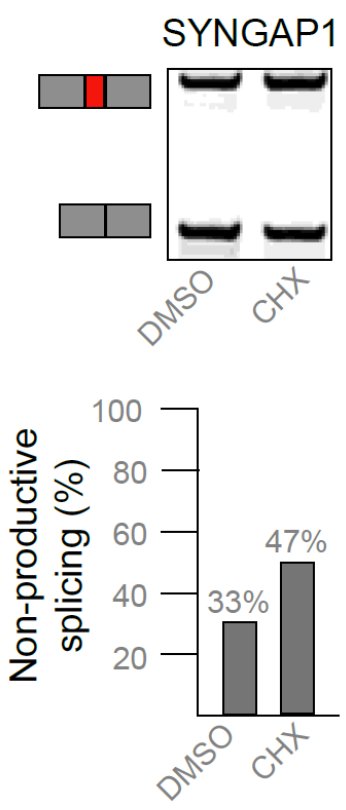
Source: Stoke data

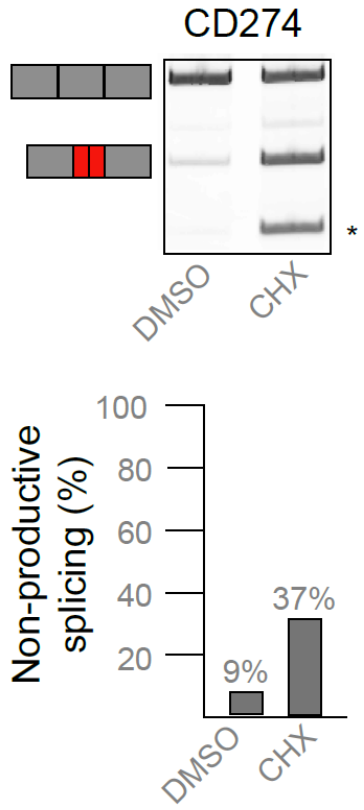
STOKE THERAPEUTICS

Validation of AS-NMD Events Using Cycloheximide (CHX)

Event type:	Cassette exon	Alternative splice site	Alternative intron (exitron)
Disease:	Dravet syndrome	Mental retardation 5	Pathway
Inheritance:	Autosomal dominant	Autosomal dominant	N/A
Organ:	CNS	CNS	EYE







Source: Stoke data

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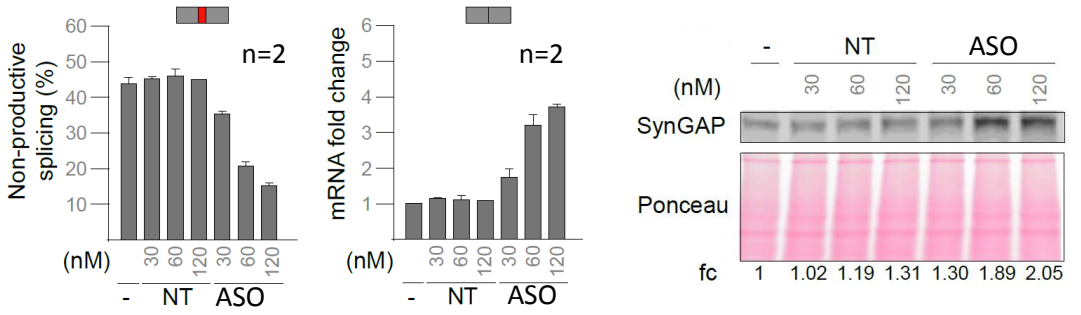
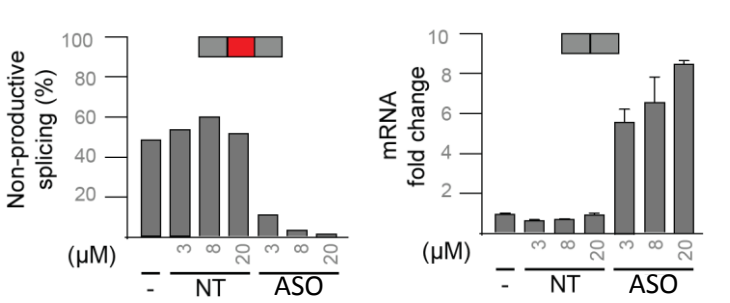
TANGO ASOs Targeting Various Types of NMD Events Increase mRNA & Protein *in Vitro*

SYNGAP1 (Alt 3’ splice site)



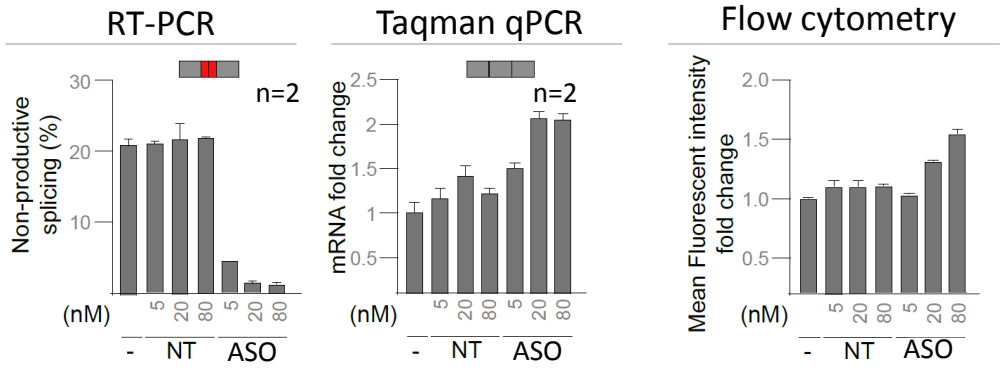
Transfection – Hek293 cells

SCN1A (cassette exon)



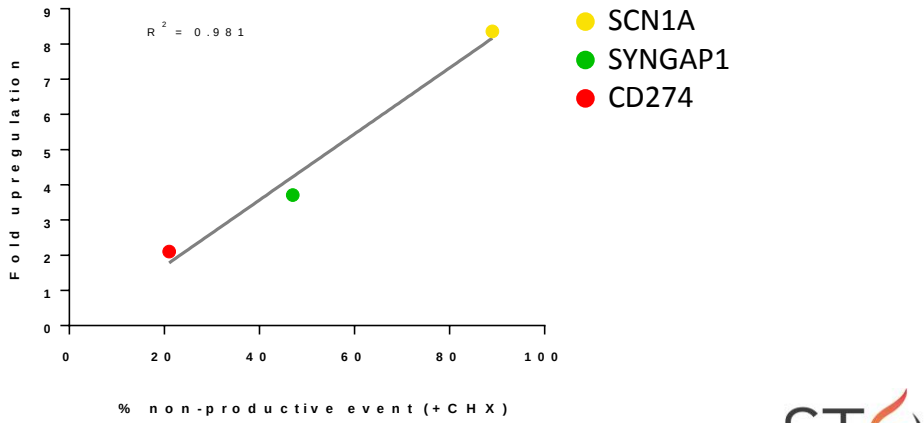
Free-uptake – RenCells VM

CD274 (Alt intron)



Transfection – Huh7 cells

Correlation between event abundance (+CHX) & upregulation



NT: non-targeting ASO control

Source: Stoke data

We Believe Stoke's TANGO Technology Offers Key Advantages Based on Preclinical Studies

Ability to address underlying genetic cause of disease	TANGO exploits unique, patented mechanisms for antisense-mediated modulation of splicing to precisely upregulate protein expression, thereby addressing the underlying genetic cause of the disease rather than merely alleviating the symptoms of the disease
Applicability to most loss-of-function mutations	ASOs upregulate expression of the wild-type allele, meaning the TANGO mechanism does not rely on targeting a specific mutation
Utility across small and large gene targets	ASOs upregulate protein expression regardless of gene size and are not constrained to smaller gene targets
No observed unwanted off-target effects	TANGO-mediated upregulation of protein expression only occurs where the gene is being naturally transcribed, limiting the likelihood of expression in non-native tissues
Ability to control dose level and duration	ASOs provide the ability for dose titration, thereby allowing for dose-dependent and reversible control of level and duration of protein expression. The ability to titrate dosage will enable us to deliver the right dose, at the right location, for each indication
Utility across a wide array of diseases and tissue types	ASO delivery to the CNS, eye, kidney and liver is well-established, enabling Stoke to address a broad range of genetic diseases. FDA-approved ASO (SPINRAZA) demonstrates ASO delivery to the CNS, and there are other ASOs in clinical development
Simple and scalable manufacturing	ASOs are synthesized by highly scalable, solid-phase chemical synthesis and leverage a well-established, global manufacturing base

Source: Stoke data based on preclinical studies to date. Our product candidate has not been approved by the FDA.

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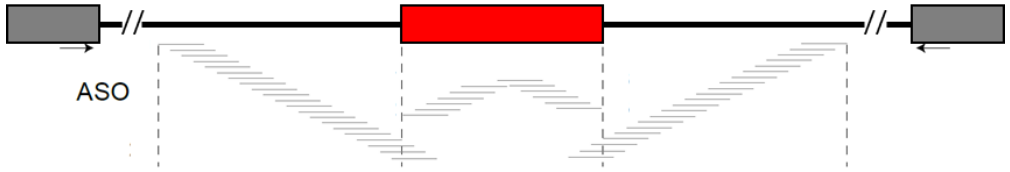
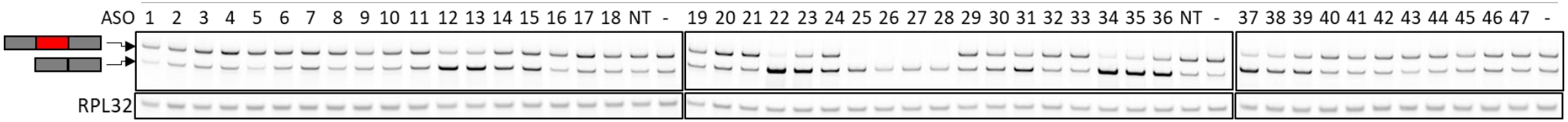
Example Screening Identifies ASOs that Prevent AS-NMD and Increase Productive mRNA

- Cells: human neural progenitor (RenCell VM)
- ASOs: 20 uM
- Delivery method: gymnotic (free) uptake
- Time course: 3 days

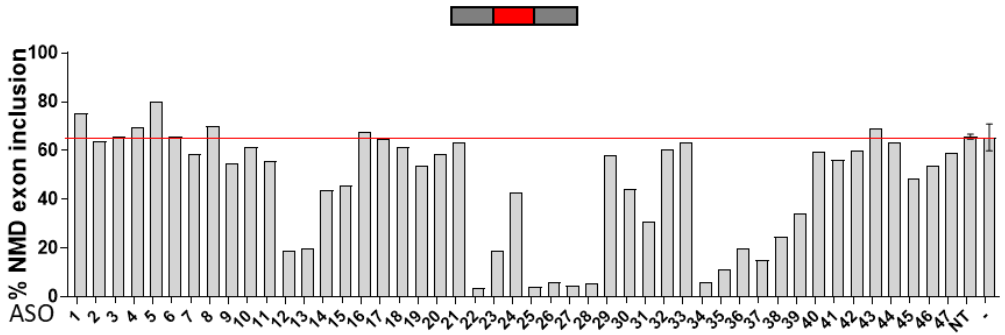
ASO walk design



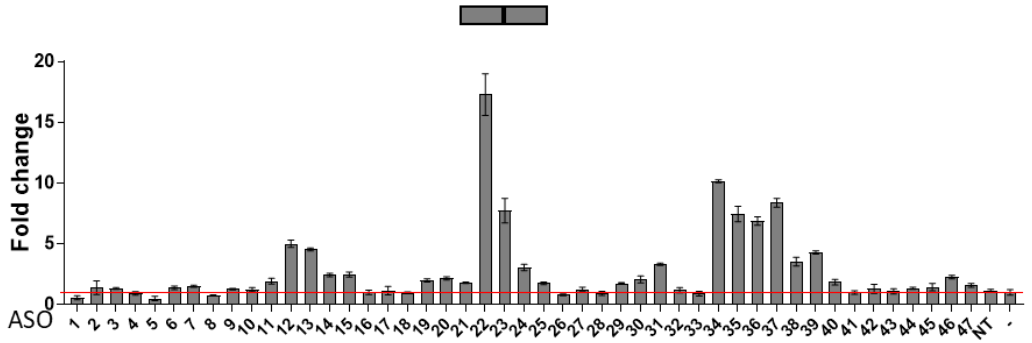
RT-PCR (SYBR-safe)



Decrease in NMD exon – RT-PCR (SYBR-safe)



SCN1A mRNA increase – SYBR-green qPCR

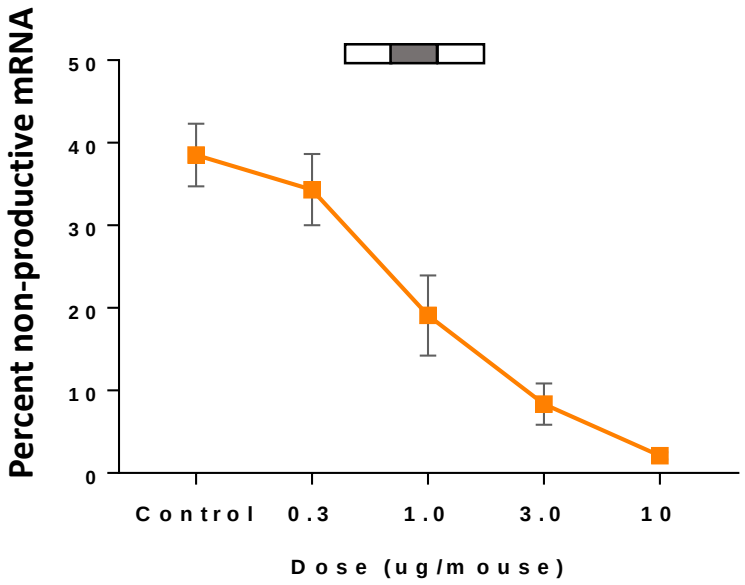


NT: non-targeting ASO control

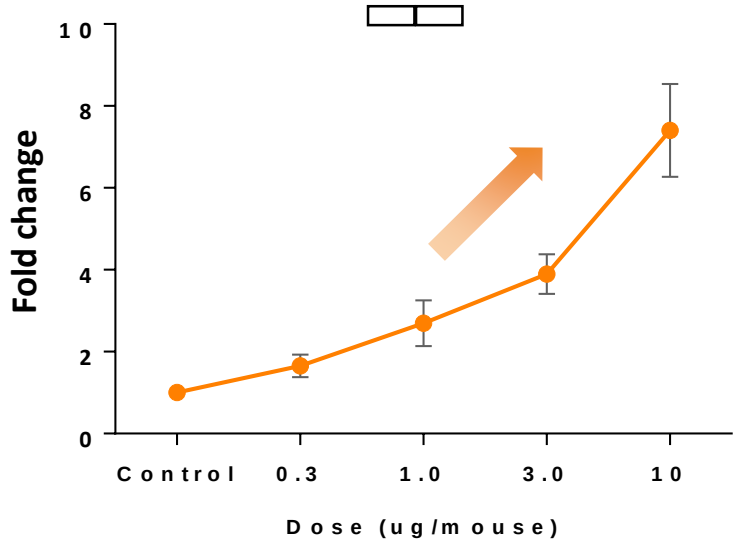
Source: Stoke data

STK-001 Increases *Scn1a* mRNA and $Na_V1.1$ Protein in Wild-type Mice

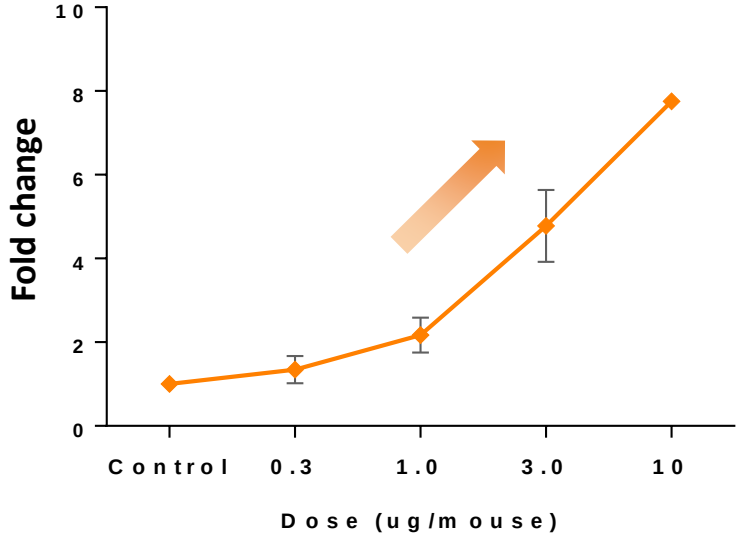
Decrease in non-productive *Scn1a* mRNA



Increase in productive *Scn1a* mRNA



Increase of $Na_V1.1$ protein



Source: Stoke data

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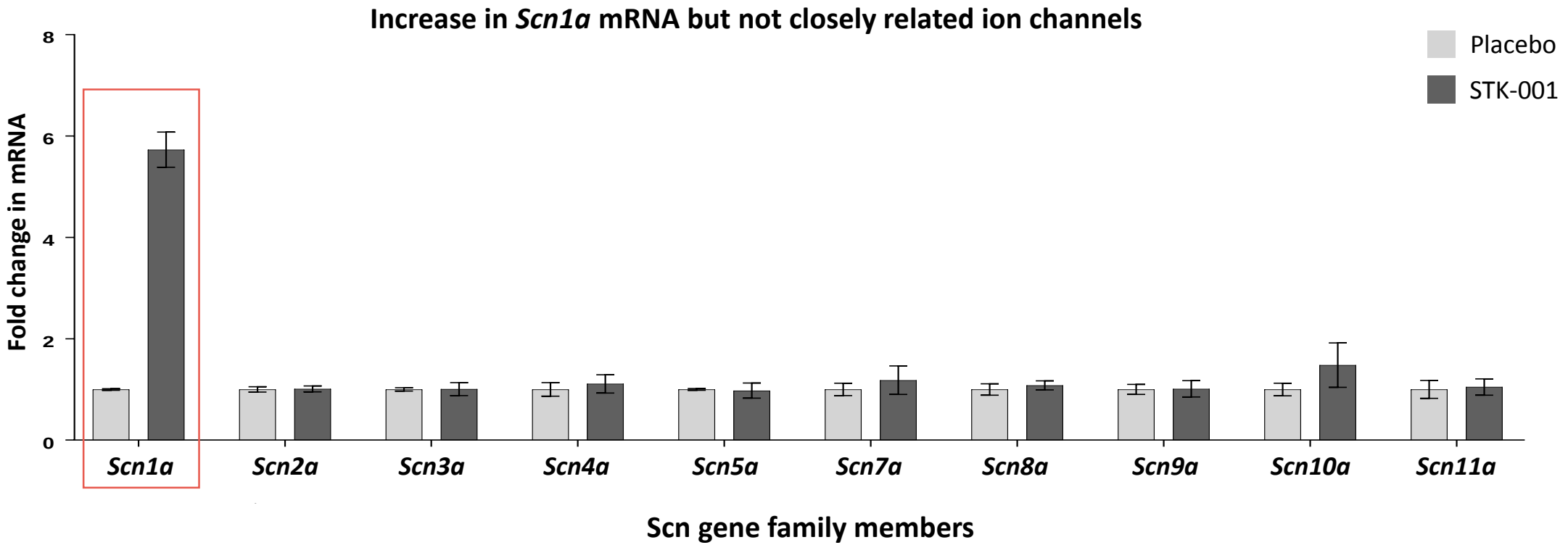
STK-001 Selectively Upregulates *Scn1a* Gene in Wild-type Mice



STK-001 is very specific for *Scn1a* among the highly homologous family of sodium channel genes, limiting the likelihood of off-target activities

Source: Stoke data

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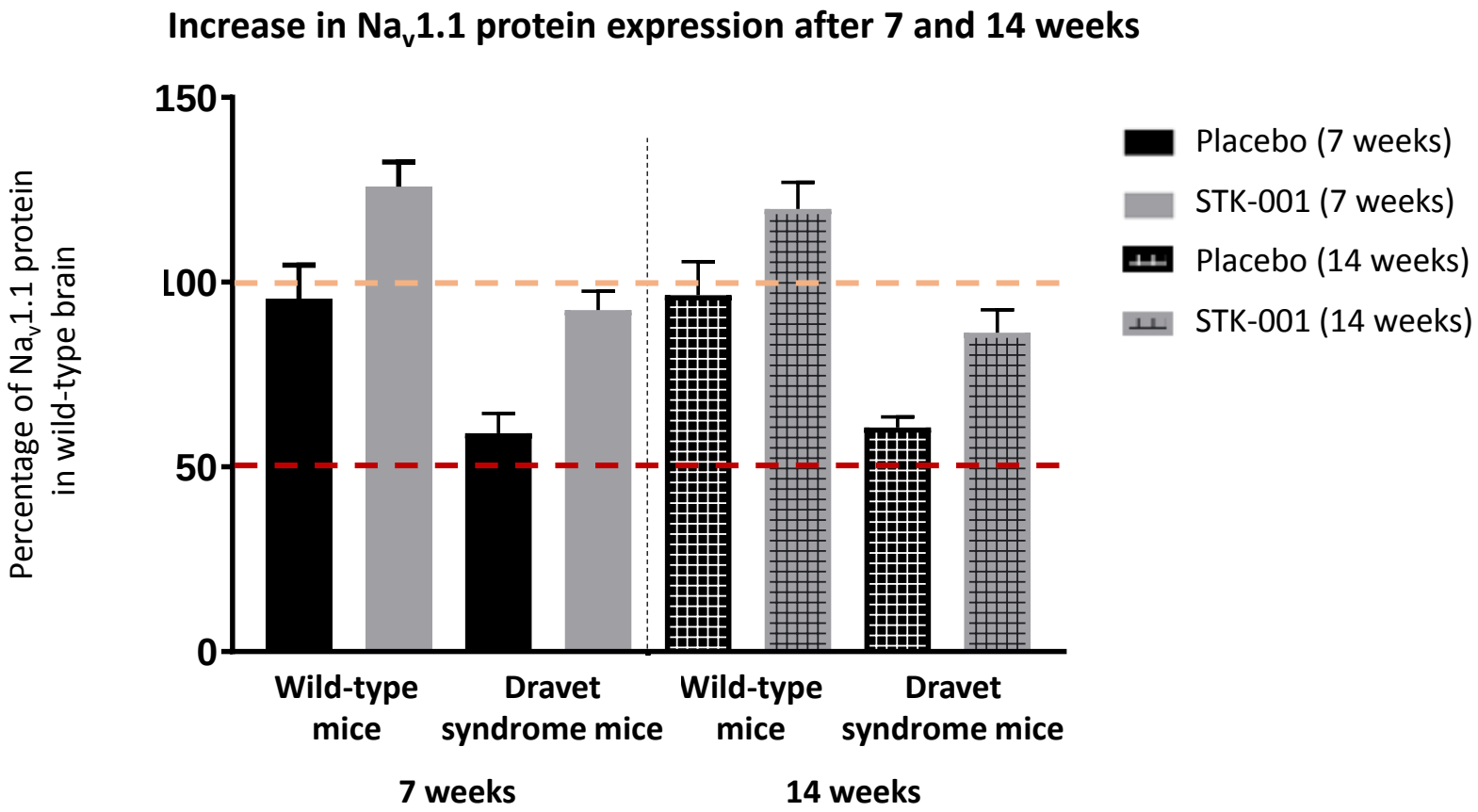
STK-001 Restores $Na_V1.1$ to Near Normal Levels for >3 Months in Dravet Syndrome Mice



In preclinical studies, STK-001 exhibits long-lasting exposure, suggesting the potential for a favorable dosing regimen of as few as two to three administrations per year in humans

Note: $Na_v1.1$ protein quantification based on standard curve obtained from untreated wild-type mouse brain as a reference control
Source: Stoke data; University of Michigan (in-life study)

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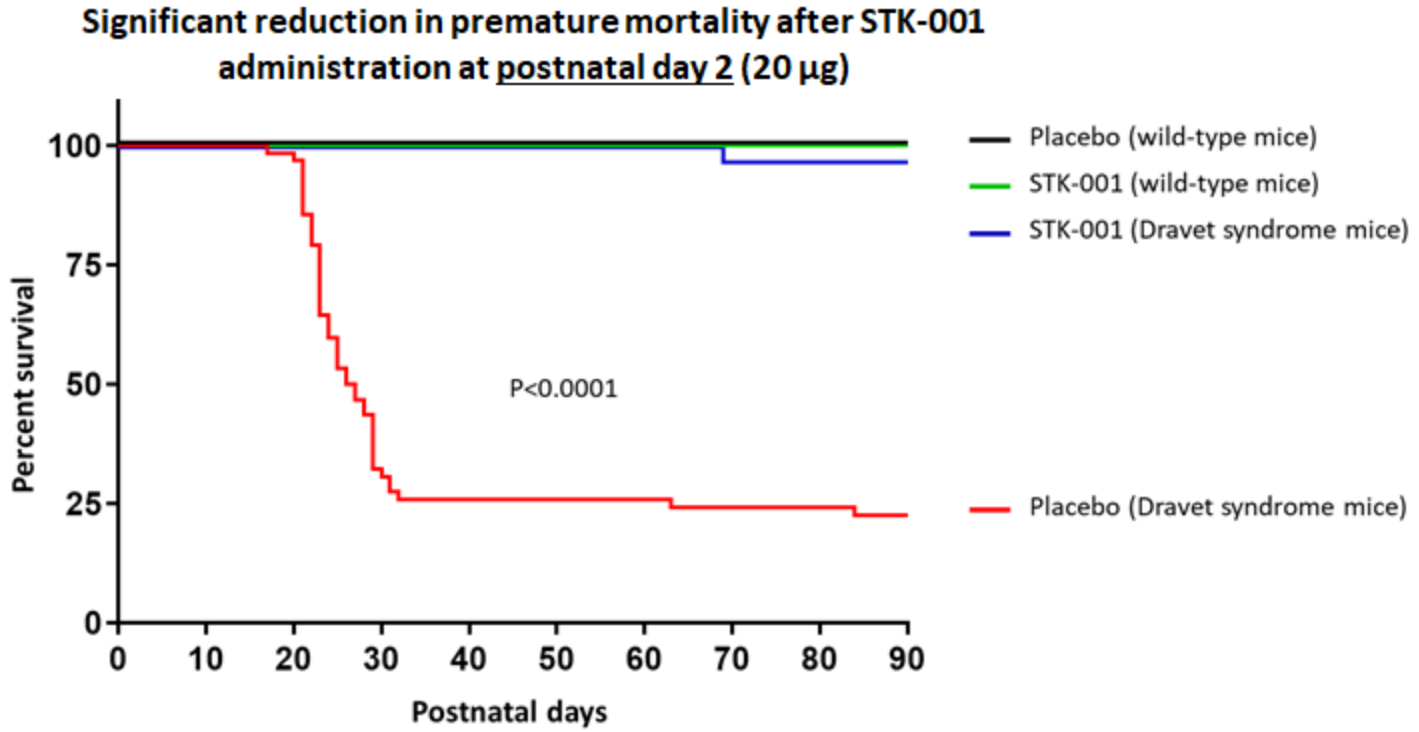
STK-001 Significantly Reduces Premature Mortality in Dravet Syndrome Mice



	Placebo wild-type	Placebo Dravet syndrome	STK-001 wild-type	STK-001 Dravet syndrome
Total n through 90 days	49	62	27	34
Number of deaths	0	48	0	1

Note: Neonate Dravet syndrome and wild-type mice were administered a single injection dose of either placebo (consisting of a phosphate-buffered solution) or 20 ug of STK-001 by intracerebroventricular injection (placebo: n=49 wild-type mice, n=62 Dravet syndrome mice; STK-001: n=27 wild-type mice, n=34 Dravet syndrome mice)
Source: Stoke data, University of Michigan

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Preclinical Studies Show STK-001 Well-Tolerated at a Pharmacologically-Active Dose in Non-Human Primates

Key safety measures	
No complement activation	✓
No decrease in platelet counts	✓
No change in hepatic function	✓
No clinical signs or symptoms over 28 day period after administration	✓
Normal histopathology in key organs	✓

Note: Company's final report pending
Source: Stoke data

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Strong Preclinical Dataset Supporting Use of STK-001 in Dravet Syndrome

- Increase in *Scn1a* mRNA expression and $Na_V1.1$. protein levels in wild-type mice
- Selective upregulation of *Scn1a*, and not closely related ion channels in wild-type mice
- Restoration of $Na_V1.1$ protein to near normal levels in Dravet syndrome mice
- Effects persisting for at least 14 weeks in Dravet syndrome mice
- Dramatic reduction in mortality in Dravet syndrome mice
- Well-tolerated at a pharmacologically-active dose level in non-human primates

Source: Stoke data, University of Michigan

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Stoke Presentations at AES 2019:

- Poster Session 1: Poster #1.116 Targeted Augmentation of Nuclear Gene Output (TANGO) of SCN1A Prevents SUDEP in a Mouse Model of Dravet Syndrome. Saturday, December 7, 2019, 12:00 PM – 6:00 PM ET (Lori Isom)
- Poster Session 2: Poster #2.195 TANGO Oligonucleotides for the Treatment of Dravet Syndrome: Safety, Biodistribution and Pharmacology in the Non-Human Primate. Sunday, December 8, 2019, 10:00 AM – 4:00 PM ET (Anne Christiansen)
- Investigators Workshop: Gene Therapy for Developmental Epileptic Encephalopathies. Sunday, December 8, 2019, 10:30 AM – 12:00 PM ET, Room 343-344 (Barry Ticho)
- Investigators Workshop: Poison Exons: From Development and Disease to Therapeutic Target. Sunday, December 8, 2019 1:30 PM – 3:00 PM ET, Room 337-338 (Lori Isom)
- Genetic Epilepsies – Updates in the Science and Diagnosis. Scientific Exhibit in Collaboration with BioMarin, Invitae, Xenon and Stoke: Sunday, December 8 8:00 AM – 5:00 PM ET, Convention Center, Room 318–319, Level 300

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Significant Unmet Need in Genetic Epilepsies

50 million people globally affected by epilepsy

>30% of patients are refractory to medical treatment, especially those with a genetic epilepsy

Up to **50%** of patients with epilepsy have significant cognitive problems

>50% of epilepsies have an identified genetic cause and many of these are haploinsufficiencies

Diagnostic work-up of epilepsy routinely includes genetic testing for more than **180** disease associated genes

While genetic mechanisms are often well understood …

0 genetically-targeted therapies for epilepsies are available

Source: WHO 2018 fact sheet; Sirven, Cold Spring Harbor Perspectives in Medicine 2015; Pal et al., *Nature Reviews Neurology* 2010; Chen et al., *JAMA Neurology* 2018; Lagae et al., *Developmental Medicine & Child Neurology* 2017; Vlaskamp et al., *Neurology* 2019; Reddy SD et al., J Pharmacol Exp Ther 2018; NIH Genetics Home Reference; Company websites

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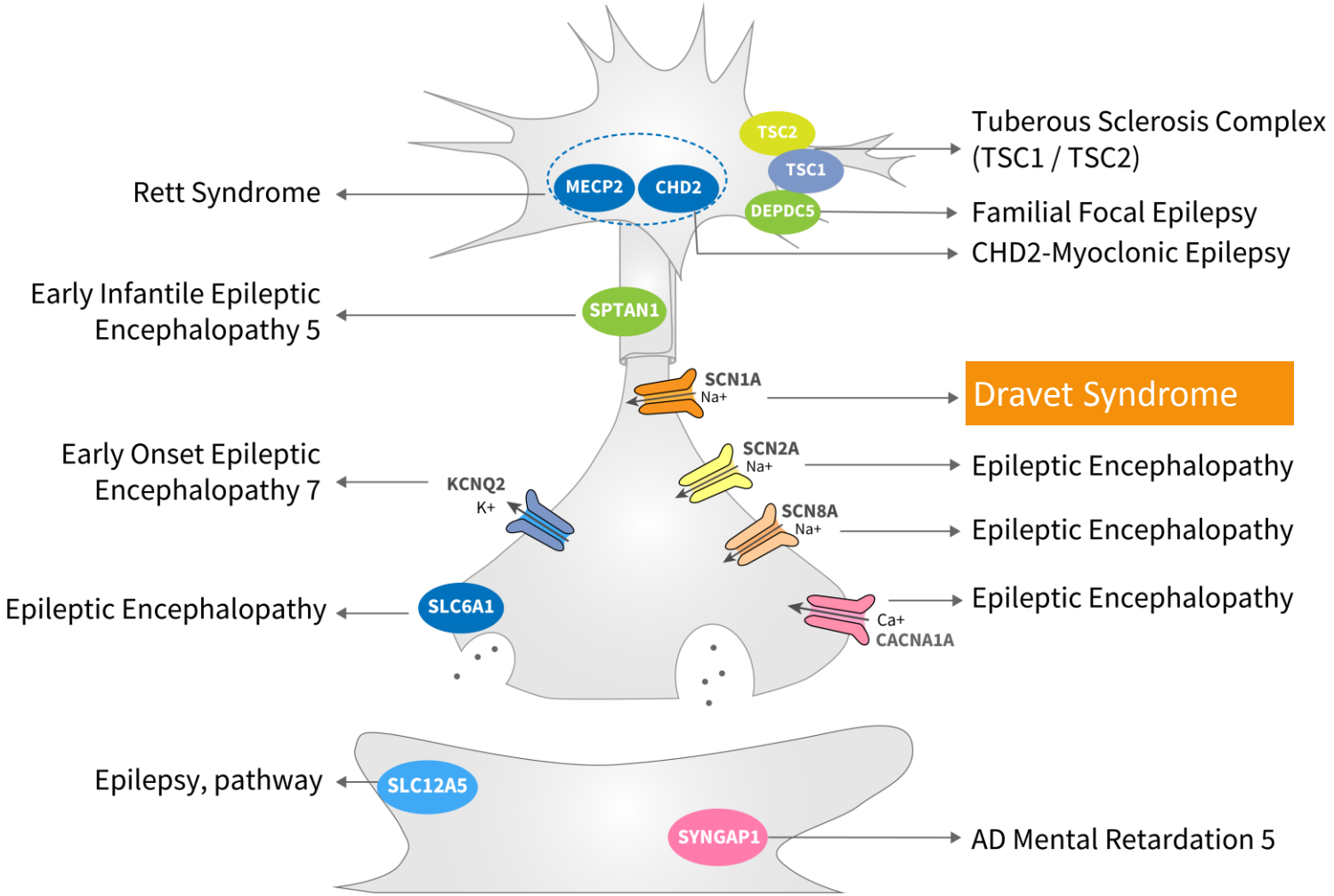
We Believe Many Genetic Epilepsies are Amenable to Stoke's TANGO Technology

Lead Program



Source: Modified from McTague et al., *Lancet* 2016; Stoke data

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The Stoke Team

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