Stoke Therapeutics

November 2019

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STOKE THERAPEUTICS

Stoke is pioneering a new way to treat the underlying causes of severe genetic diseases by precisely upregulating protein expression

.

We Believe Stoke's Approach is Highly Differentiated and Positioned for Success

Novel technology

Antisense oligonucleotides (ASOs) target pre-mRNA splicing to *restore target protein* to near normal levels

Disease-modifying therapies

ASOs are designed to *address the underlying cause* of severe genetic diseases, including autosomal dominant haploinsufficiencies

Efficient clinical program

Lead program for Dravet syndrome leverages *validated ASO chemistry*, a *well-defined patient population*, and *learnings from recently approved drugs*

Phase 1/2 trial expected to begin in 1H 2020; preliminary *efficacy data*, expected in 2021

Potential broad applications

Emerging pipeline spans severe genetic diseases of the *CNS, eye, liver and kidney*

Plan to *nominate second candidate* to treat an additional genetic disease for preclinical development by 1H 2020

STOKE THERAPEUTICS

Critical Components of the Stoke Strategy

- **Rapidly advance our lead program**, STK-001, to clinical proof-of-concept, approval and commercialization
- **Prioritize genetic epilepsies** for near-term development efforts
- **Expand our pipeline** into other disease areas to fully exploit the potential of our proprietary platform
- Continue to **strengthen and expand our IP portfolio**
- **Maintain broad commercial rights** to our product candidates
- **Opportunistically evaluate potential collaboration arrangements** with a pharmaceutical or biotechnology company

STOKE THERAPEUTICS

Executive Team with Proven Experience in Rare Disease Drug Development

Edward Kaye, M.D.
Chief Executive Officer and Director

Huw Nash, Ph.D.
Chief Operating Officer and Chief Business Officer

Barry Ticho, M.D., Ph.D.
Chief Medical Officer

Steve Tulipano, CPA
Chief Financial Officer

Gene Liau, Ph.D.
Executive Vice President, Head of Research and Preclinical Development

Robin Walker, J.D.
Senior Vice President, Chief Legal Officer

Precision Medicine Platform for Autosomal Dominant Haploinsufficiency Diseases

Autosomal Recessive	Autosomal Dominant Gain-of-function / Dominant Negative	Autosomal Dominant Haploinsufficiency
Disease examples: • Phenylketonuria • Lysosomal storage disorders • Beta-thalassemia • Cystic fibrosis	**Disease examples:** • Huntington's disease • Parkinson's disease • Spinocerebellar ataxia • Autosomal dominant hypocalcemia	**Disease examples:** • Dravet syndrome • Optic atrophy • Polycystic kidney disease • Tuberous sclerosis
Current / emerging approaches: • Gene therapy • Gene editing • Modified mRNA • Protein-based drugs • Small molecules	**Current / emerging approaches:** • Gene therapy • Gene editing • Protein-based drugs • Oligonucleotides • Small molecules	**Emerging approach:** • Stoke's TANGO technology

Existing precision medicine platforms are poorly suited to address haploinsufficiency diseases. Consequently, there has been little focus on drug development for these diseases despite a significant unmet medical need

Source: globalgenes.org; Mathura et al., *Science, 2019*; Lykken et al., *Journal of Neurodevelopmental Disorders*, 2018; Company websites

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

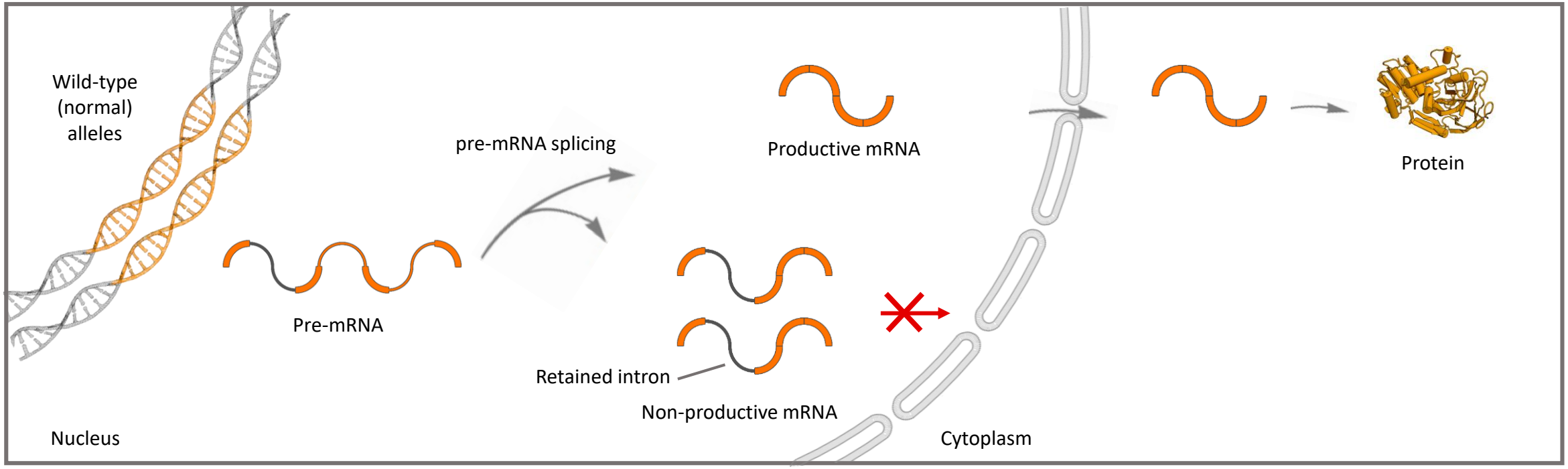
Ability to address underlying genetic cause of disease	TANGO exploits unique, patented mechanisms for antisense-mediated modulation of splicing to precisely upregulate protein expression, thereby addressing the underlying genetic cause of the disease rather than merely alleviating the symptoms of the 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.

STOKE THERAPEUTICS

Stoke's TANGO Technology Targets Retained Introns to Upregulate Protein Expression

TANGO mechanism for increasing protein synthesis: Retained Intron



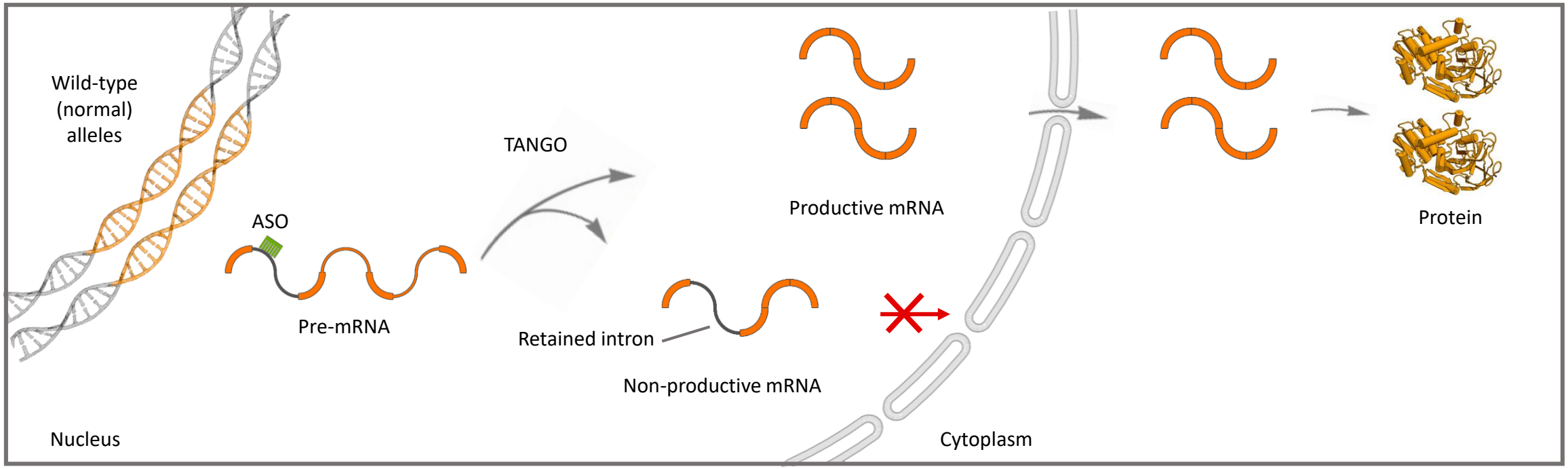
Retained introns are found in ~60% of gene transcripts and are part of the wild-type sequence of the gene. Non-productive mRNA remains in the nucleus and is not translated into protein

Source: Stoke data based on preclinical studies to date

STOKE THERAPEUTICS

Stoke's TANGO Technology Targets Retained Introns to Upregulate Protein Expression

TANGO mechanism for increasing protein synthesis: Retained Intron



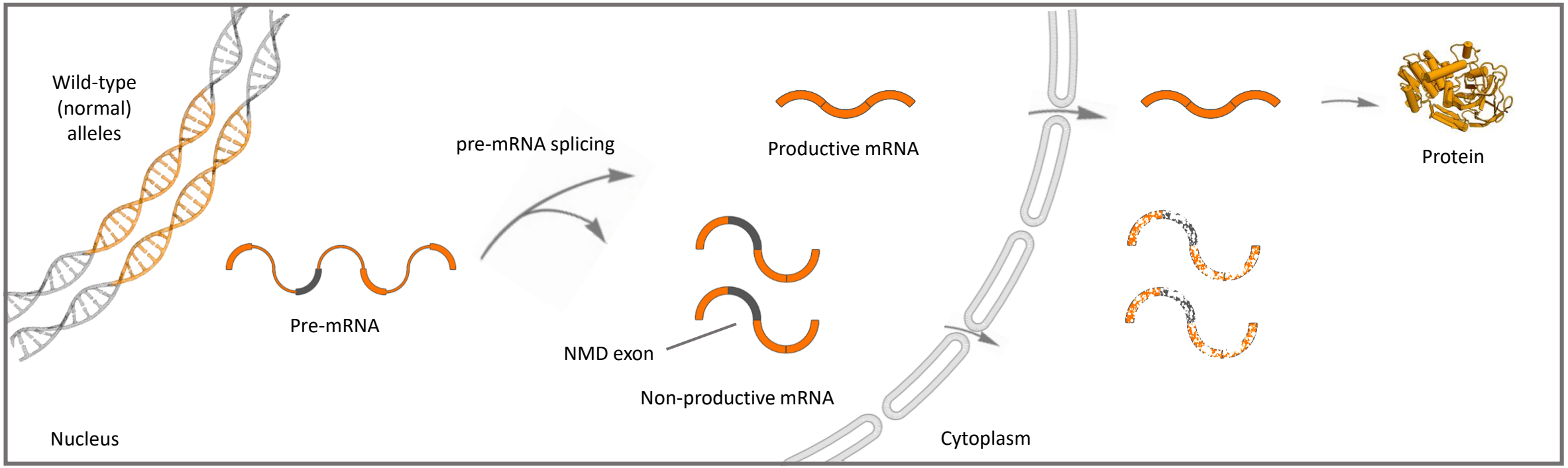
Stoke's ASOs bind to the pre-mRNA and redirect the splicing machinery to remove the retained intron. This splice-switching decreases non-productive mRNA and increase productive mRNA, which is translated into increased protein expression from the wild-type allele

Source: Stoke data based on preclinical studies to date

STOKE THERAPEUTICS

Stoke's TANGO Technology Targets NMD Exons to Upregulate Protein Expression

TANGO mechanism for increasing protein synthesis: Nonsense mediated decay (NMD) exon



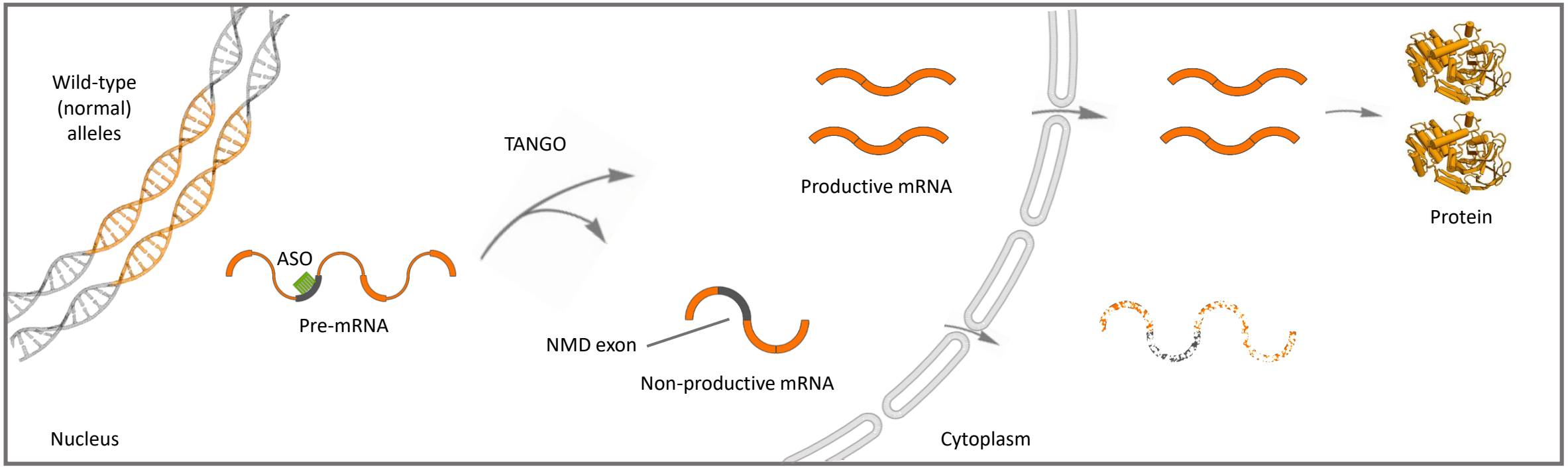
NMD exons are found in over 25% of gene transcripts and are part of the wild-type sequence of the gene. Non-productive mRNA is degraded in the cytoplasm by NMD and is not translated into protein

Note: NMD denotes nonsense-mediated mRNA decay
Source: Stoke data based on preclinical studies to date

STOKE THERAPEUTICS

Stoke's TANGO Technology Targets NMD Exons to Upregulate Protein Expression

TANGO mechanism for increasing protein synthesis: NMD exon



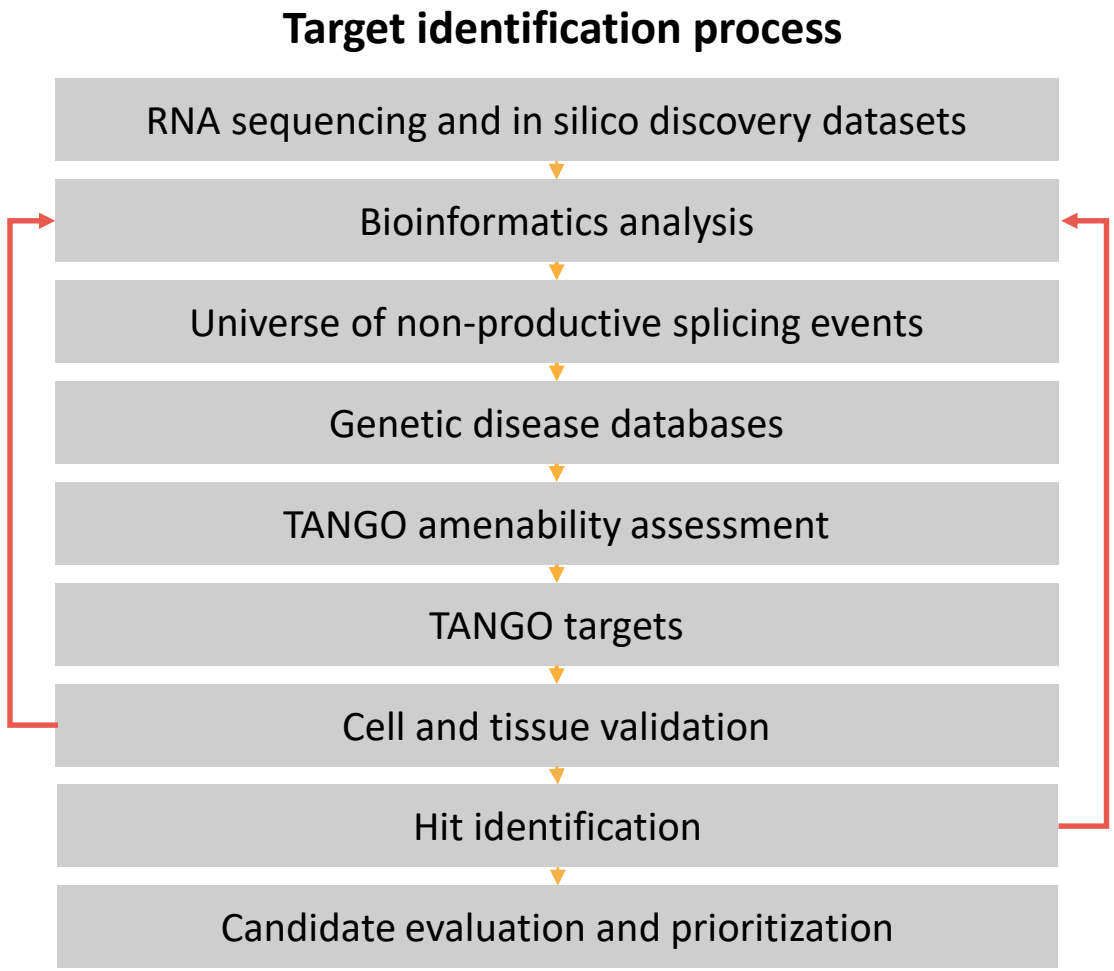
Stoke's ASOs bind to the pre-mRNA and redirect the splicing machinery to prevent inclusion of the NMD exon.

This splice-switching decreases non-productive mRNA and increase productive mRNA, which is translated into increased protein expression from the wild-type allele

Note: NMD denotes nonsense-mediated mRNA decay
Source: Stoke data based on preclinical studies to date

STOKE THERAPEUTICS

Robust Target Identification Process Utilizing Proprietary Bioinformatics



- Next generation RNA sequencing yields proprietary database of approximately 85,000 non-productive events in the human transcriptome
- Cross-referencing with genetic disease databases identifies approximately 2,900 monogenic diseases amenable to TANGO
- Approach is highly predictive and enables rapid and systematic identification of clinically relevant targets

Source: Stoke data

STOKE THERAPEUTICS

Intellectual Property Estate Including TANGO Mechanism and Top Targets

- Patents for TANGO technology exclusively licensed from University of Southampton and Cold Spring Harbor Laboratory
- Multi-national allowed and pending claims for the TANGO mechanisms, which cover the mechanisms independent of therapeutic strategy
- Multi-national pending claims for more than 140 genetic diseases amenable to TANGO
- Leveraging previously-validated ASO chemistries

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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 …

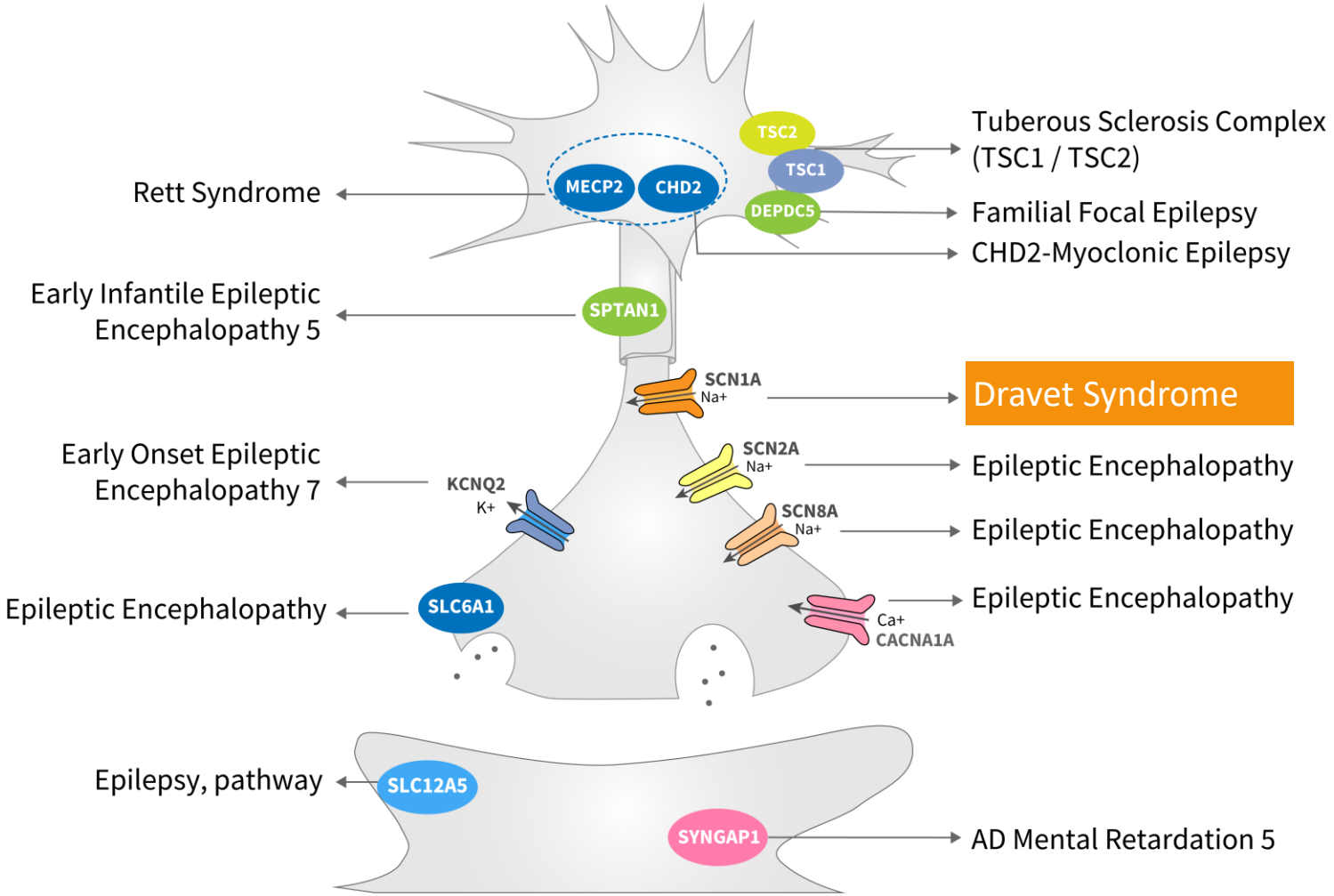
0 genetically-targeted therapies for epilepsies are available

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

STOKE THERAPEUTICS

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

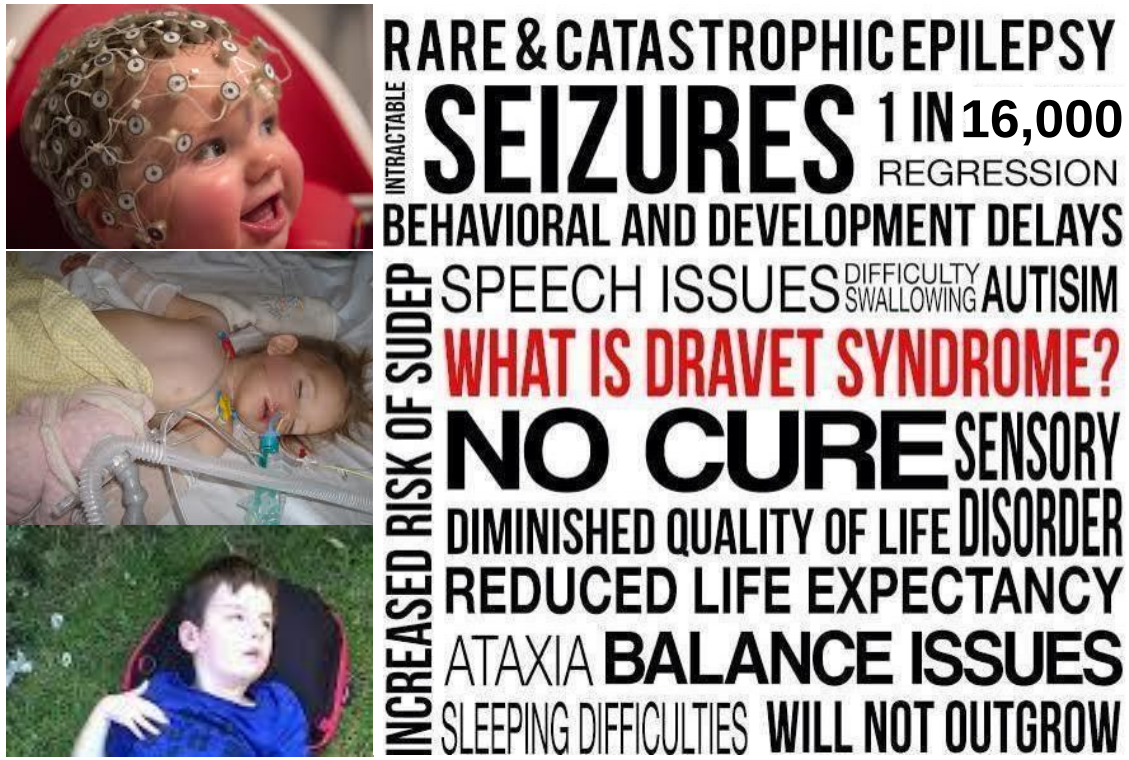
Lead Program



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

STOKE THERAPEUTICS

Dravet Syndrome: A Severe and Progressive Genetic Epilepsy



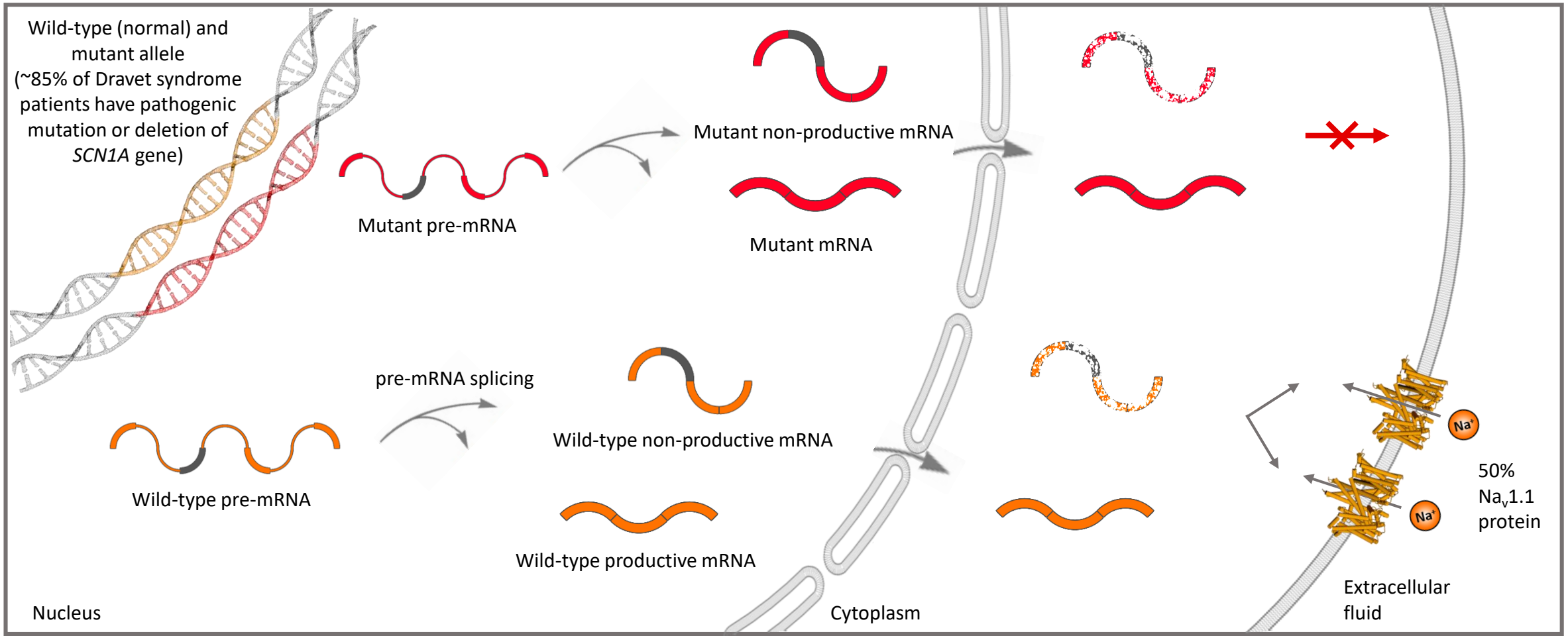
- Autosomal dominant condition caused by more than 1,250 *de novo* mutations in *SCN1A*, resulting in 50% $Na_V1.1$ protein expression
- Caused by pathogenic mutation or deletion of the SCN1A gene in ~85% of patients
- Existing antiepileptic drugs only address the occurrence of seizures, and more than 90% of Dravet syndrome patients still report suffering from incomplete seizure control
- No disease-modifying therapies in clinical development
- ~35,000 patients across U.S., Canada, Japan, Germany, France and the UK

Source: 2018 Health Advances Report; Djémié et al., *Molecular Genetics & Genomic Medicine* 2016; Lagae et al., *Developmental Medicine & Child Neurology* 2017; Nabbout et al., *Orphanet Journal of Rare Diseases* 2013

STOKE THERAPEUTICS

Transformative Potential of TANGO Technology in Dravet Syndrome

TANGO mechanism for increasing protein synthesis in a prospective patient with Dravet syndrome



Source: Escayg and Goldin, *Epilepsia* 2010; Stoke data based on preclinical studies to date

Transformative Potential of TANGO Technology in Dravet Syndrome

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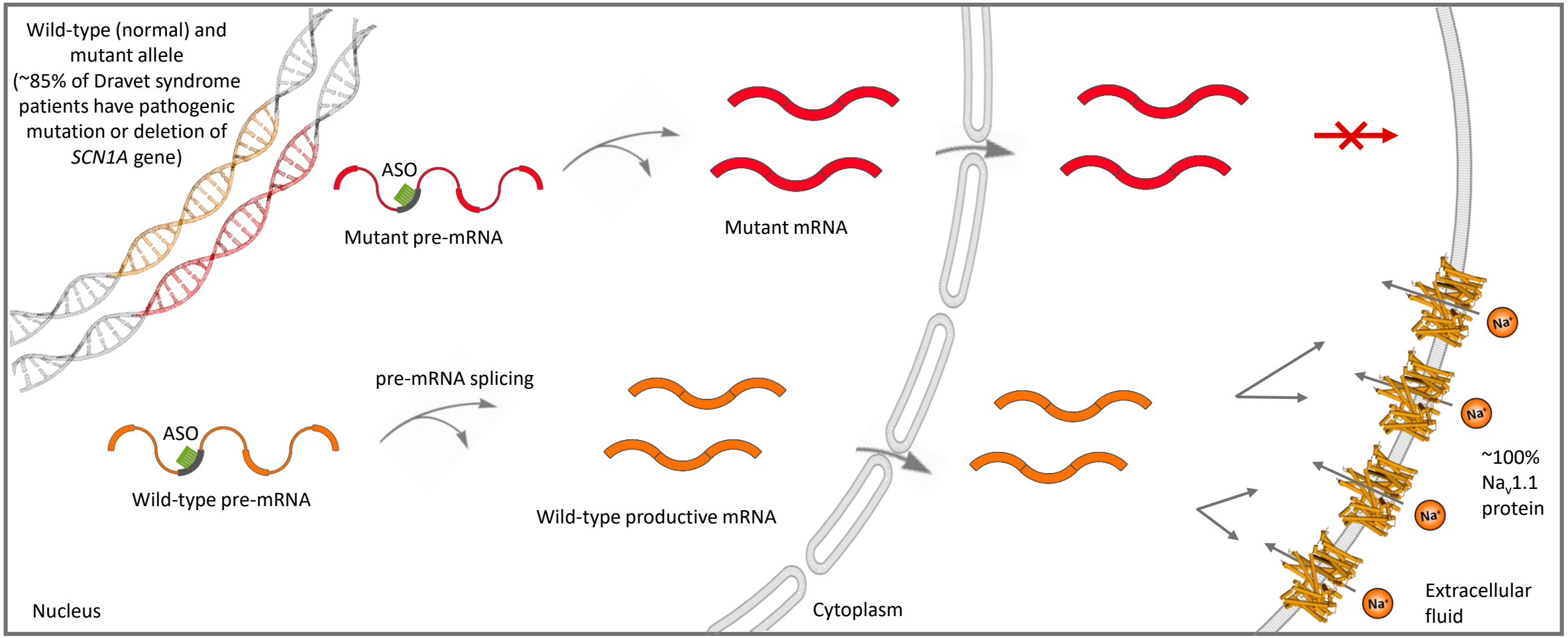
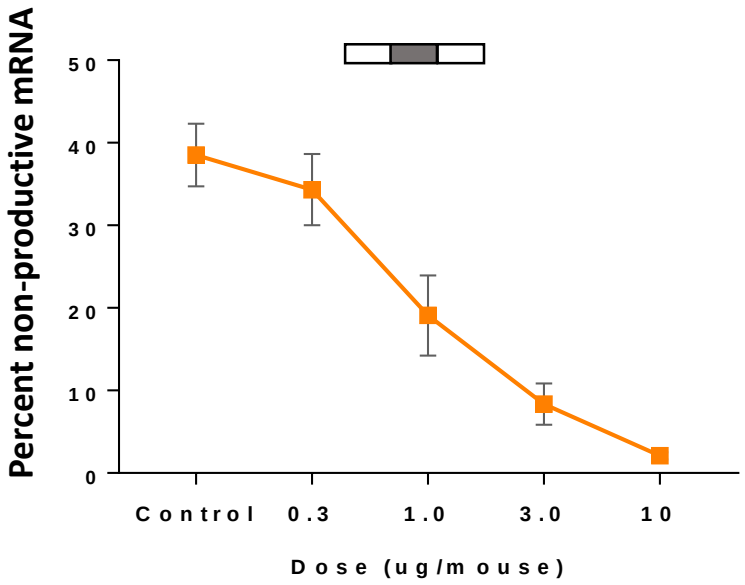


Source: Escayg and Goldin, *Epilepsia* 2010; Stoke data based on preclinical studies to date

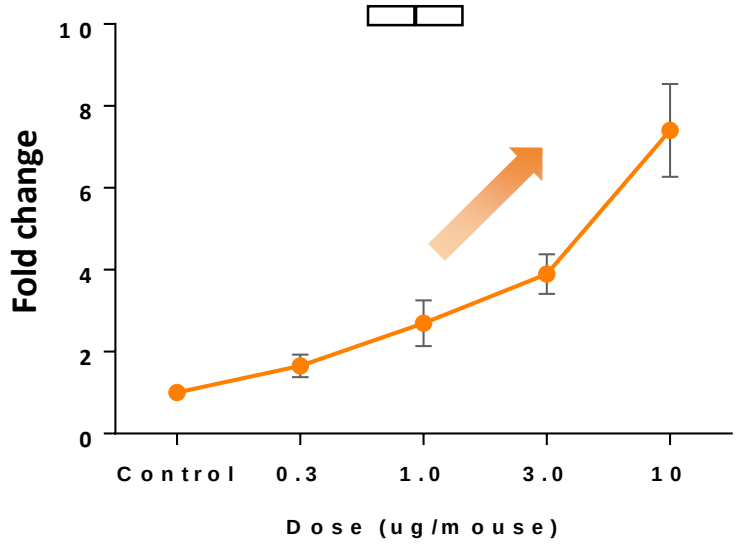
STOKE THERAPEUTICS

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

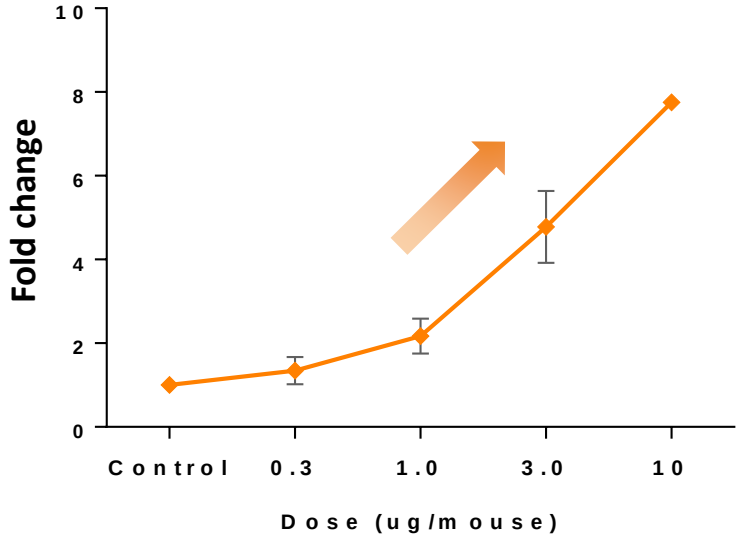
Decrease in non-productive *Scn1a* mRNA



Increase in productive *Scn1a* mRNA

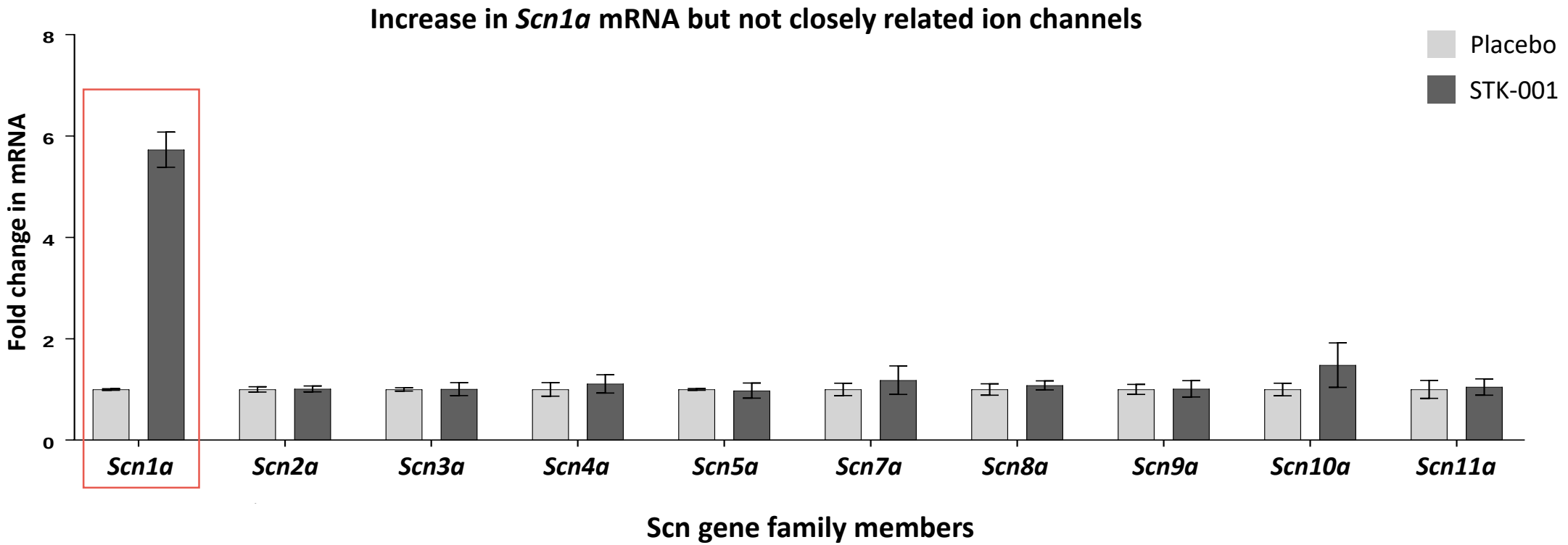


Increase of $Na_V1.1$ protein



Source: Stoke data

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

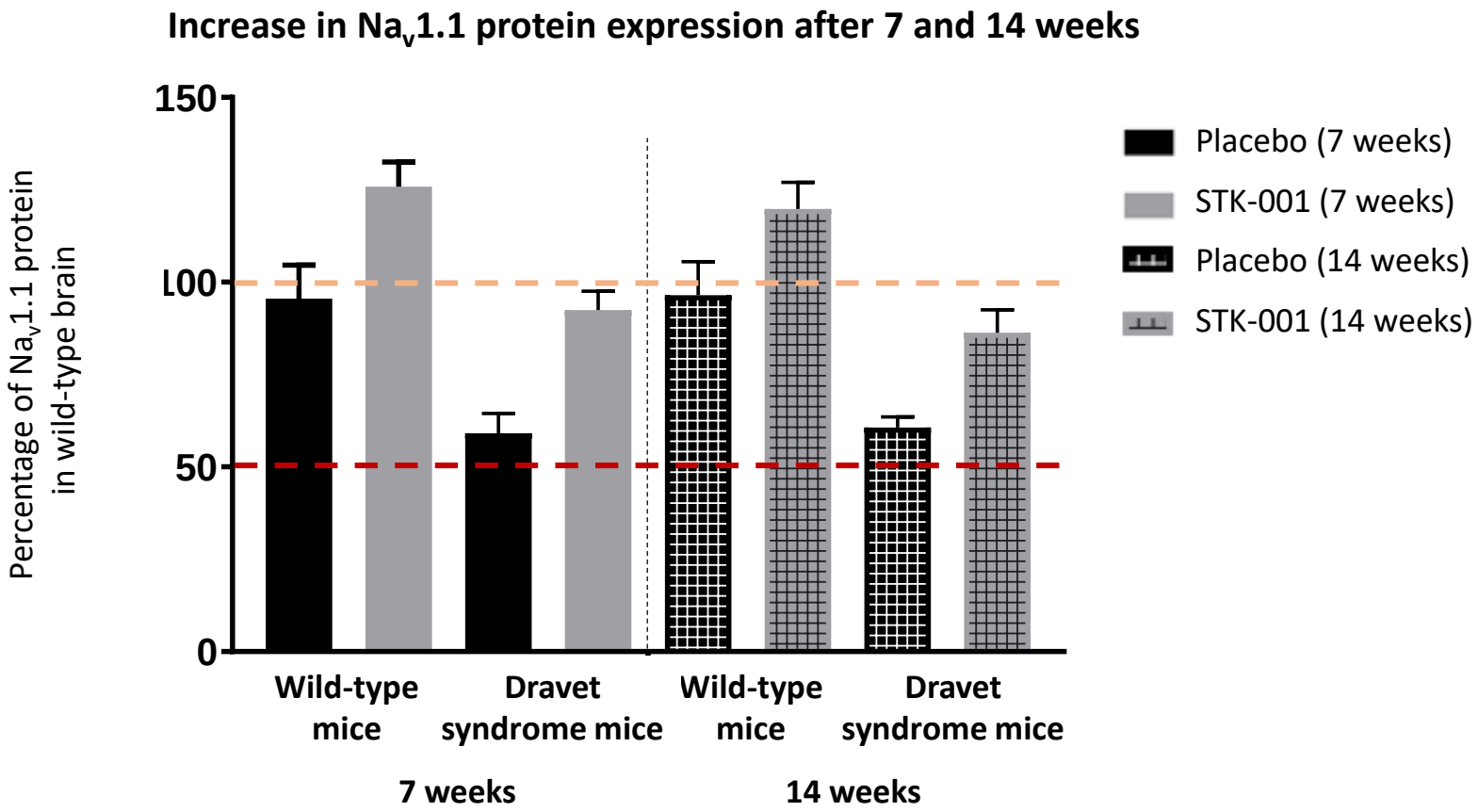


STK-001 is very specific for *Scn1a* among the highly homologous family of sodium channel genes, limiting the likelihood of off-target activities

Source: Stoke data

STOKE THERAPEUTICS

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

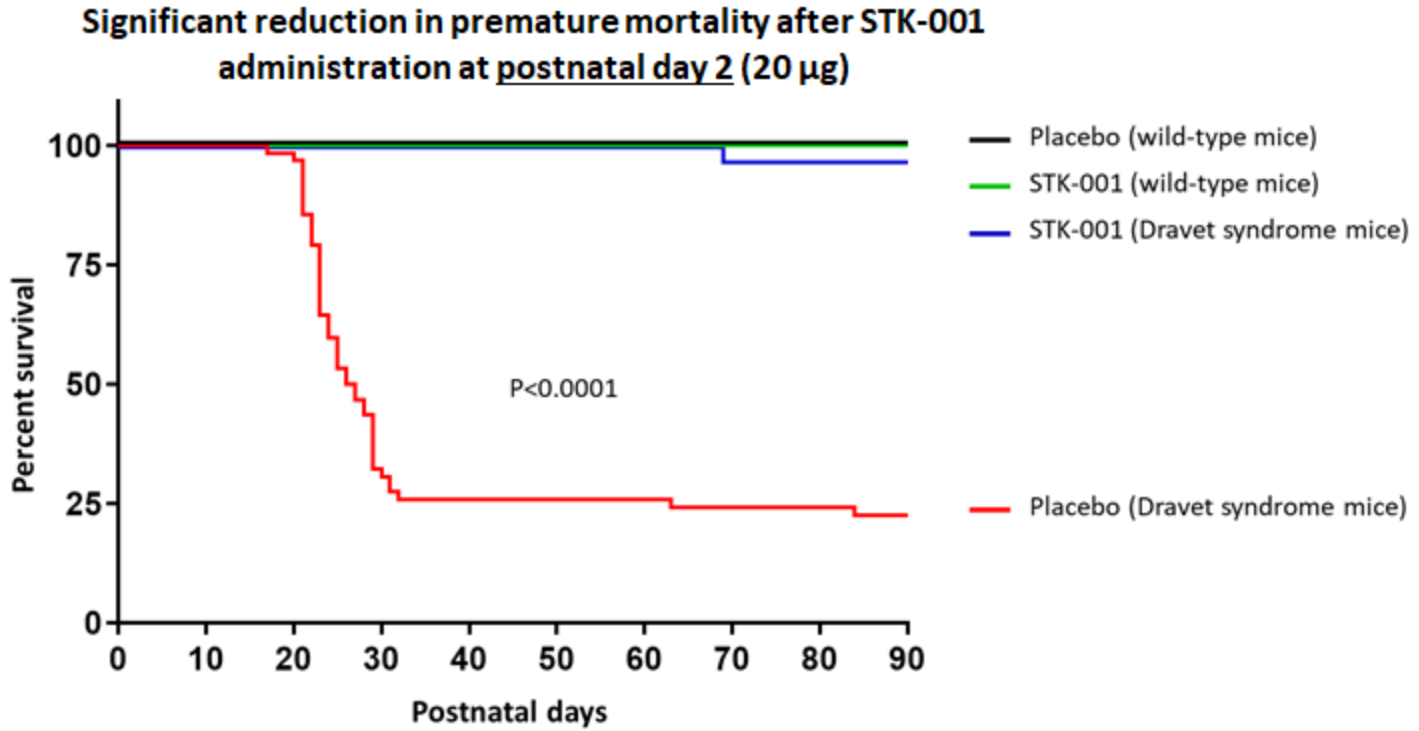


In preclinical studies, STK-001 exhibits long-lasting exposure, suggesting the potential for a favorable dosing regimen of as few as two to three administrations per year in humans

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)

STOKE THERAPEUTICS

STK-001 Significantly Reduces Premature Mortality in Dravet Syndrome Mice



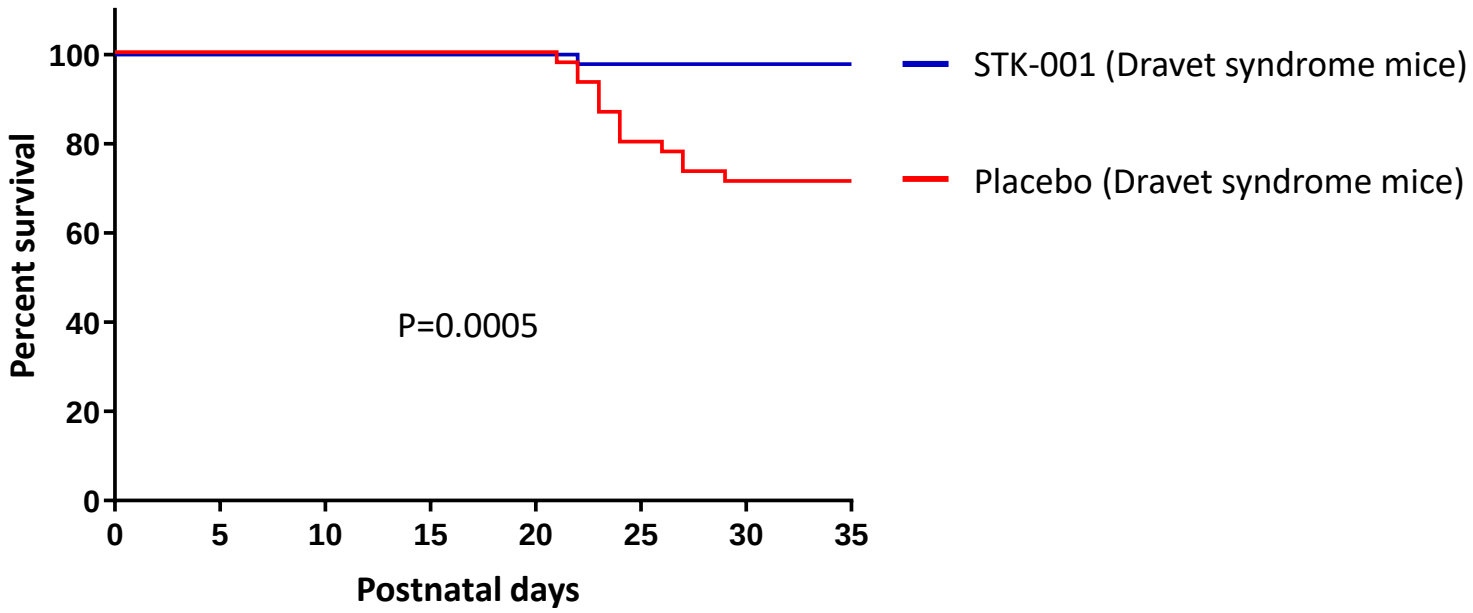
	Placebo wild-type	Placebo Dravet syndrome	STK-001 wild-type	STK-001 Dravet syndrome
Total n through 90 days	49	62	27	34
Number of deaths	0	48	0	1

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

STOKE THERAPEUTICS

STK-001 Therapeutic Dosing also Significantly Reduces Premature Mortality

Significant reduction in premature mortality after STK-001 administration at postnatal day 14 (60 µg)



	Placebo wild-type	Placebo Dravet syndrome	STK-001 wild-type	STK-001 Dravet syndrome
Total n through 35 days	68	45	41	46
Number of deaths	0	13	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 60 ug of STK-001 by intracerebroventricular injection (placebo: n=68 wild-type mice, n= 45 Dravet syndrome mice; STK-001: n= 41 wild-type mice, n=46 Dravet syndrome mice). Data is preliminary
Source: Stoke data, University of Michigan

STOKE THERAPEUTICS

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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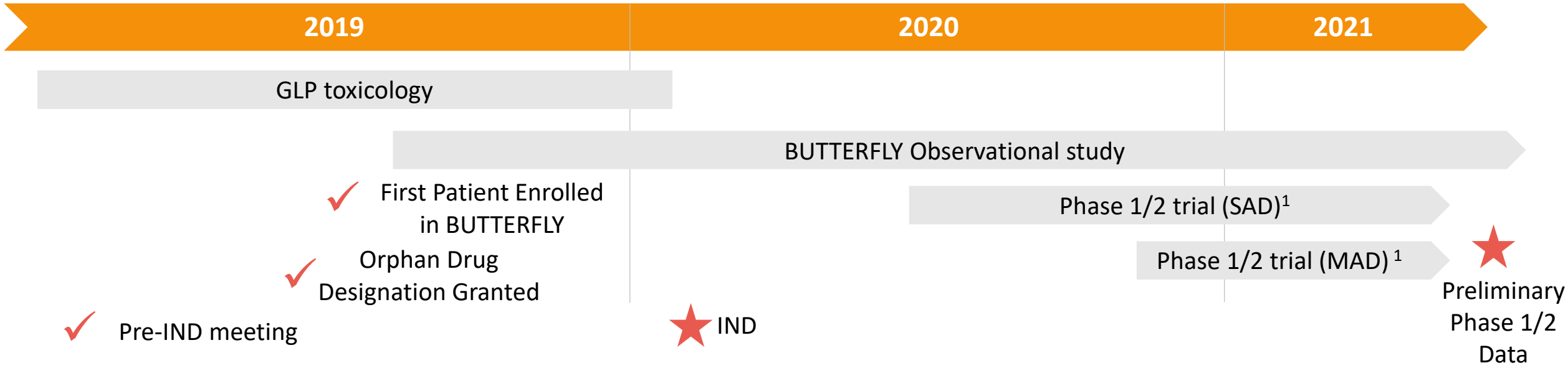
Efficient Clinical Program for STK-001 in Dravet Syndrome



Phase 1/2 trial

- Analogous trial design and endpoints to recently approved antiepileptic drugs for Dravet syndrome
- Change in seizure frequency over 12-week treatment period, cognitive function, and quality of life will be included as secondary endpoints
- Preliminary clinical data for primary and secondary endpoints of Phase 1/2 SAD study expected in 2021

Note: Timelines are estimates and subject to change; [1] 'SAD' denotes Single Ascending Dose; 'MAD' denotes Multiple Ascending Dose

STOKE THERAPEUTICS

Strong Momentum Going into 2020

- ✓ Nominated lead target
- ✓ Demonstrated *in vivo* proof of concept in mouse model for Dravet syndrome
- ✓ Completed pre-IND meeting for Dravet syndrome
- ✓ Completed Series B financing

2018

2019 – 2020

- ✓ Completed Initial Public Offering
- ✓ Received FDA orphan drug designation for STK-001
- ✓ Enrolled first patient in BUTTERFLY, observational study for Dravet syndrome
- ❑ Complete GLP toxicology studies to support STK-001 IND application for Dravet syndrome in early 2020
- ❑ Initiate Phase 1/2 clinical trial for Dravet syndrome in 1H 2020
- ❑ Nominate second candidate to treat an additional genetic disease for preclinical development by 1H 2020
- ❑ Opportunistically secure first pharma partnership as early as 2019

Stoke's TANGO Technology may also be Well Suited for Treatment of Eye Diseases

Benefits of focusing on the eye for ASOs

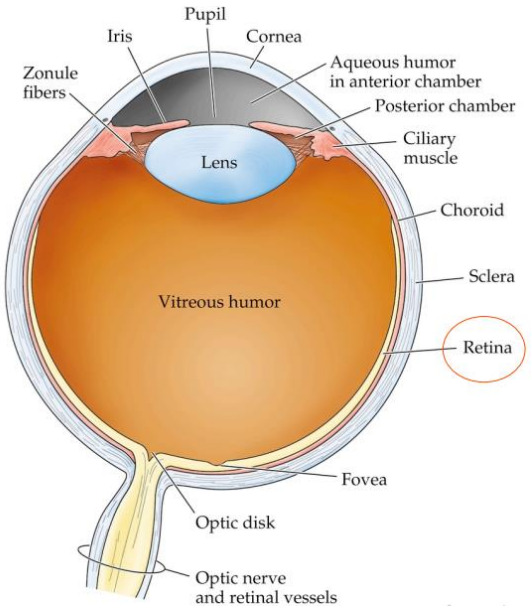
- Localized delivery
- Immune privileged and small treatment space (0.05% of total body weight)
- Contralateral control for clinical trials
- Availability of non-invasive measurements that reflect functional outcome e.g. OCT

Advantages of TANGO for the eye

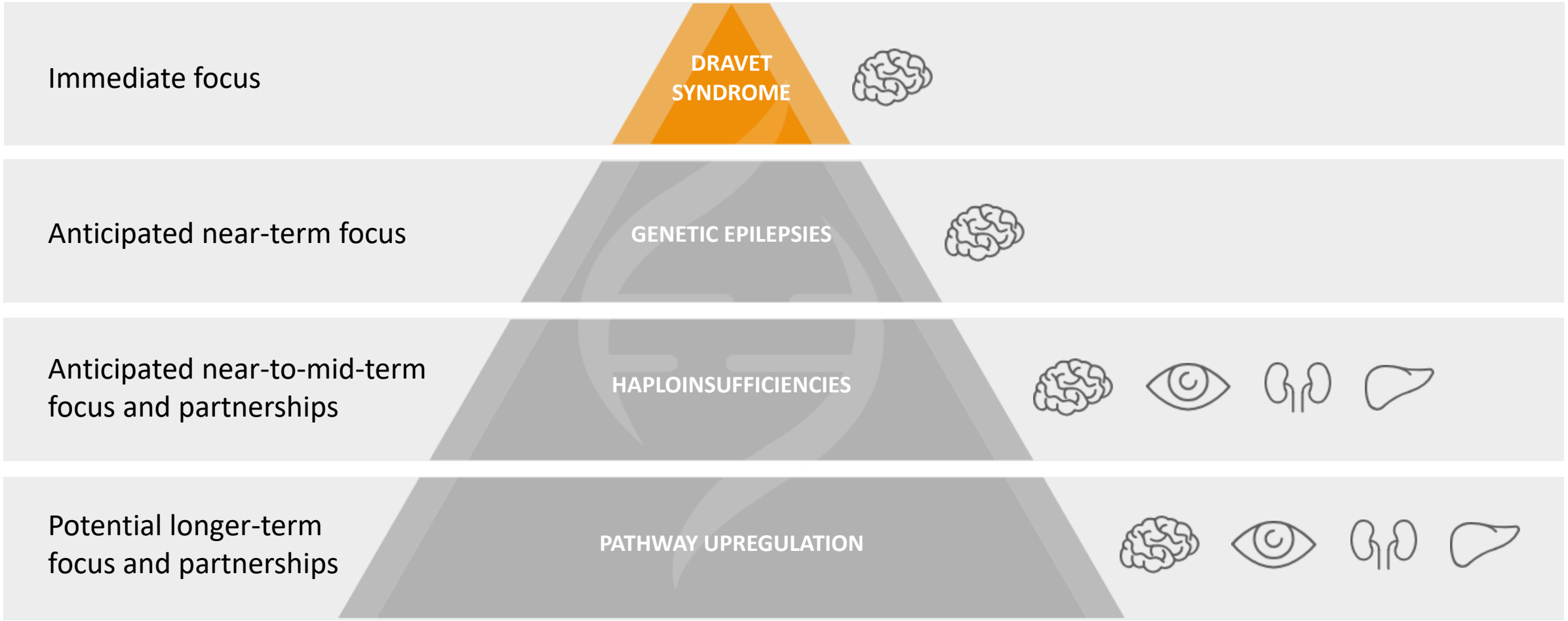
- Intravitreal delivery has safety & patient acceptance advantage over subretinal delivery
- Stoke preclinical data demonstrates long-term effects of up to 12 months
- Tunable and reversible control of level and specificity of protein expression
- No formulation or viral vector requirement
- Approved product precedence (Vitravene for cytomegalovirus retinitis)
- Potential to target large genes

Example TANGO targets

- *CD274* (PD-L1) for autoimmune uveitis
- *OPA1* for autosomal dominant optic atrophy



Stoke is Building a Pipeline of Precision Medicines



STOKE THERAPEUTICS

Cash Expected to be Sufficient to Fund Operations into 2023

Cash, Cash Equivalents and Restricted Cash *as of 09/30/2019*	$233.2 million
Common Shares Outstanding *as of 09/30/2019*	32,724,153

Raised $151.9 million in net proceeds in June 2019 initial public offering

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