Stoke Therapeutics

August 2020

Nasdaq: STOK

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This presentation contains "forward-looking" statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995, including, but not limited to: our year end results; our expectation about timing and execution of anticipated milestones, including our IND submission; the planned initiation of Part A of our Phase 1/2a Monarch clinical trial in Dravet syndrome, and our ability to use study data to advance the development of STK-001; the ability of STK-001 to treat the underlying causes of Dravet syndrome; Stoke's ability to precisely upregulate protein expression in OPA1 protein-deficient cells; Stoke's ability to treat the underlying cause of ADOA; and Stoke's ability to use preclinical data to advance the development of TANGO ASOs to treat ocular disease and the ability of TANGO to design medicines to increase protein production. These forward-looking statements may be accompanied by such words as "aim," "anticipate," "believe," "could," "estimate," "expect," "forecast," "goal," "intend," "may," "might," "plan," "potential," "possible," "will," "would," and other words and terms of similar meaning. These forward-looking statements involve risks and uncertainties, as well as assumptions, which, if they do not fully materialize or prove incorrect, could cause our results to differ materially from those expressed or implied by such forward-looking statements. These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements, including: our ability to develop, obtain regulatory approval for and commercialize STK-001 and future product candidates; the timing and results of preclinical studies and clinical trials; the risk that positive results in a clinical trial may not be replicated in subsequent trials or success in early stage clinical trials may not be predictive of results in later stage clinical trials; risks associated with clinical trials, including our ability to adequately manage clinical activities, unexpected concerns that may arise from additional data or analysis obtained during clinical trials, regulatory authorities may require additional information or further studies, or may fail to approve or may delay approval of our drug candidates; the occurrence of adverse safety events; failure to protect and enforce our intellectual property, and other proprietary rights; failure to successfully execute or realize the anticipated benefits of our strategic and growth initiatives; risks relating to technology failures or breaches; our dependence on collaborators and other third parties for the development, regulatory approval, and commercialization of products and other aspects of our business, which are outside of our full control; risks associated with current and potential delays, work stoppages, or supply chain disruptions caused by the coronavirus pandemic; risks associated with current and potential future healthcare reforms; risks relating to attracting and retaining key personnel; failure to comply with legal and regulatory requirements; risks relating to access to capital and credit markets; environmental risks; risks relating to the use of social media for our business; and the other risks and uncertainties that are described in the Risk Factors section of our most recent annual or quarterly report and in other reports we have filed with the U.S. Securities and Exchange Commission. These statements are based on our current beliefs and expectations and speak only as of the date of this presentation. We do not undertake any obligation to publicly update any forward-looking statements.

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STOKE THERAPEUTICS

Amplifying Science to Transform the Experience of Life

Stoke is making a new generation of RNA-based genetic medicines that upregulate protein expression to restore human health.

STOKE THERAPEUTICS

Foundational Elements of Stoke

Experienced Leaders in Innovation

Differentiated Platform with Broad Applicability

Focused Development Program

Strong Financial Position to Support Growth

TANGO Restores Protein Levels by Stoking Output From Healthy Genes

- Stoke's ASOs bind to specific stretches of pre-mRNA to **reduce non-productive mRNA and increase productive mRNA**
- The increased levels of productive mRNA from the functional copy of the gene result in **increased protein production**
- For **haploinsufficiences**, TANGO restores the target protein to near-normal levels

STOKE THERAPEUTICS

TANGO: An RNA-Based Genetic Medicine Platform for Protein Upregulation

Stoke uses RNA science to restore missing proteins by increasing – or stoking – protein output from healthy genes.

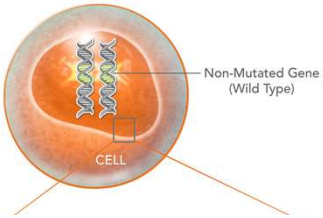
TANGO

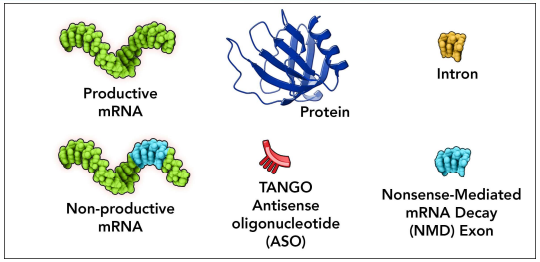
Targeted **A**ugmentation of **N**uclear **G**ene **O**utput

- Addresses underlying cause of disease
- Applicable to most loss-of-function mutations
- Applies equally to small or large gene targets
- Gene and tissue specific
- Controllable dose and duration
- Can address wide array of diseases
- Simple and scalable manufacturing

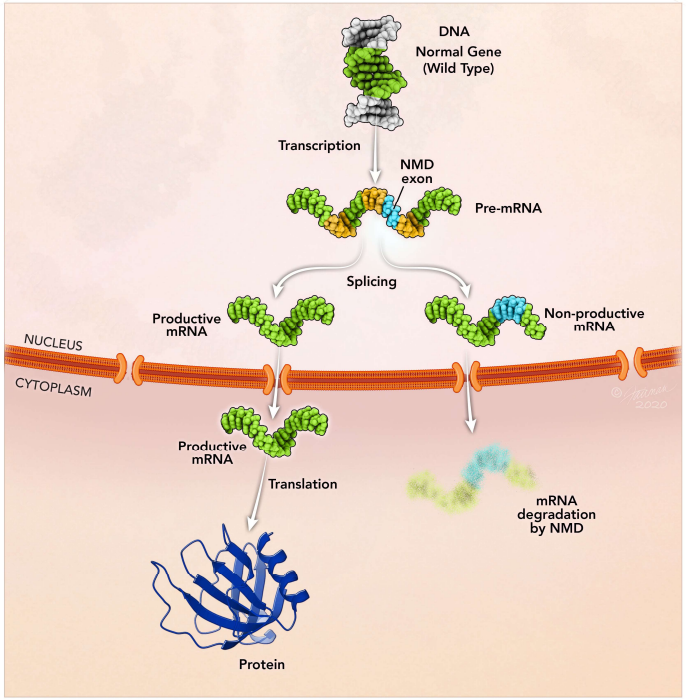
STOKE THERAPEUTICS

Transformative Potential of TANGO Technology for Gene Upregulation

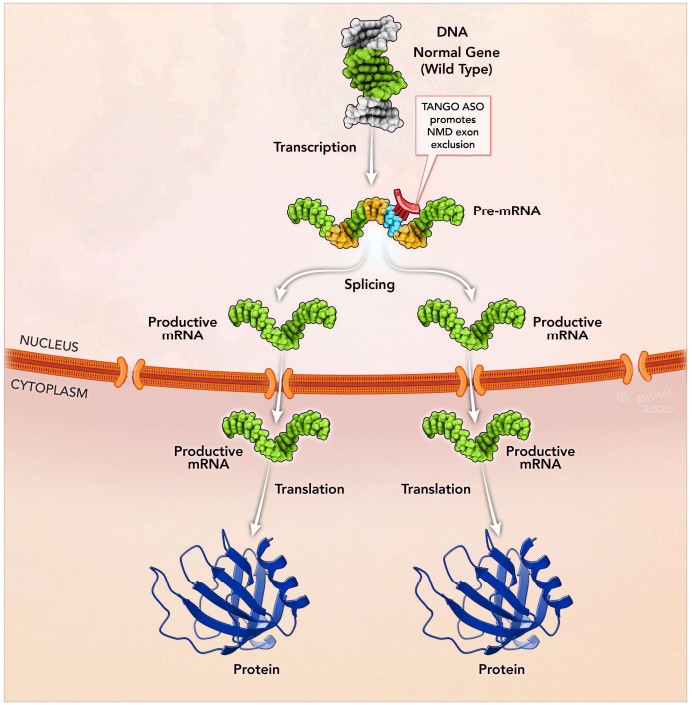




WITHOUT TANGO-ASO



WITH TANGO-ASO



nature COMMUNICATIONS

Source: Lim, K.H., Han, Z., Jeon, H.Y. *et al.* Antisense oligonucleotide modulation of non-productive alternative splicing upregulates gene expression. *Nat Commun* **11,** 3501 (2020).

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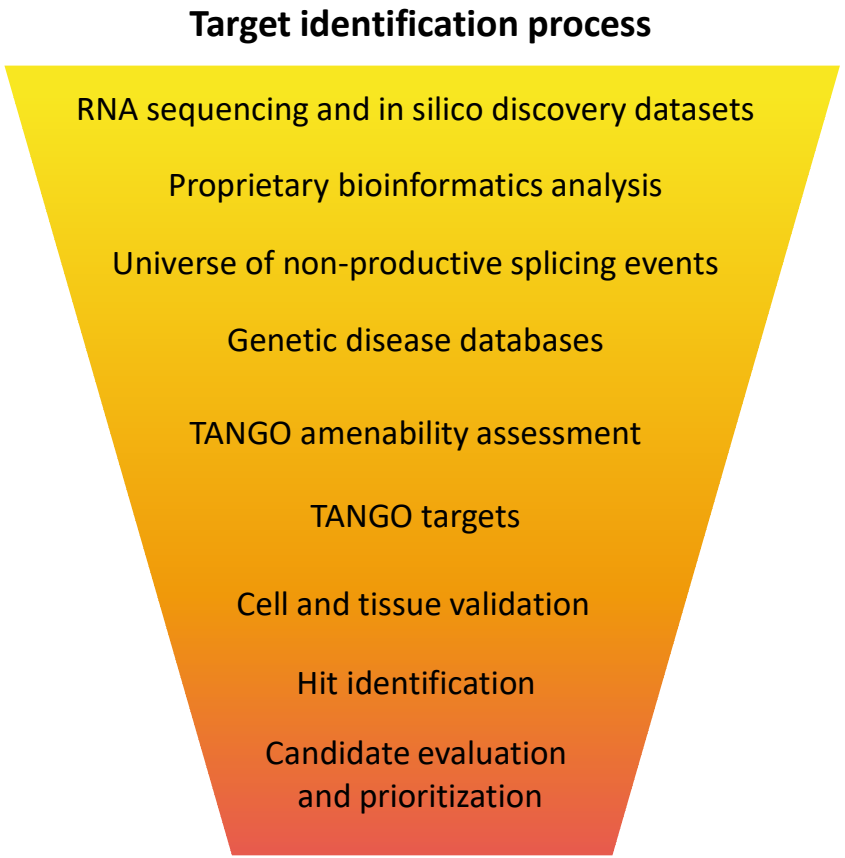
Robust Target Identification Process Utilizing Proprietary Bioinformatics



- Approximately 50% of human genes contain a TANGO signature
- Cross-referencing with genetic disease databases identifies approximately 2,900 monogenic diseases amenable to TANGO
- Enables rapid and systematic identification of clinically relevant targets

Source: Stoke data

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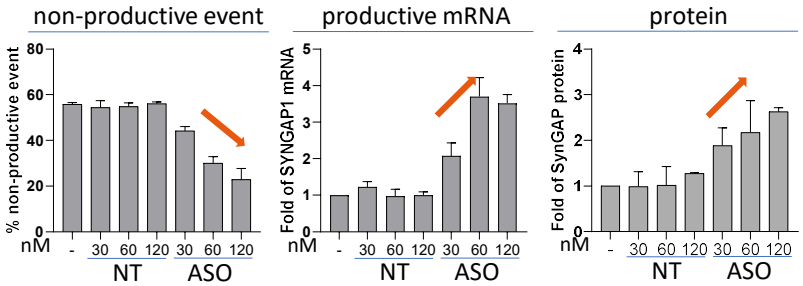
TANGO is Applicable to a Broad Range of Targets

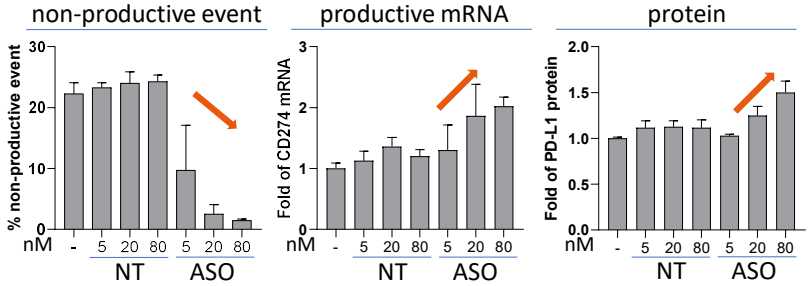
Genetic epilepsy – haploinsufficiency

SYNGAP1



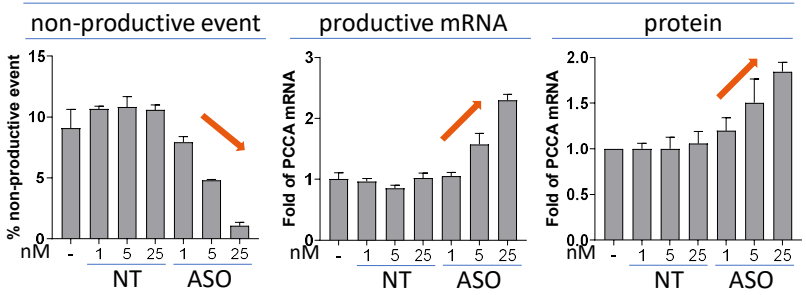
Pathway target – wild type

CD274 (PD-L1)

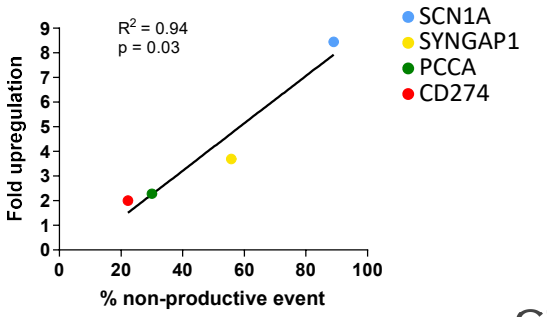


Liver target – autosomal recessive

PCCA

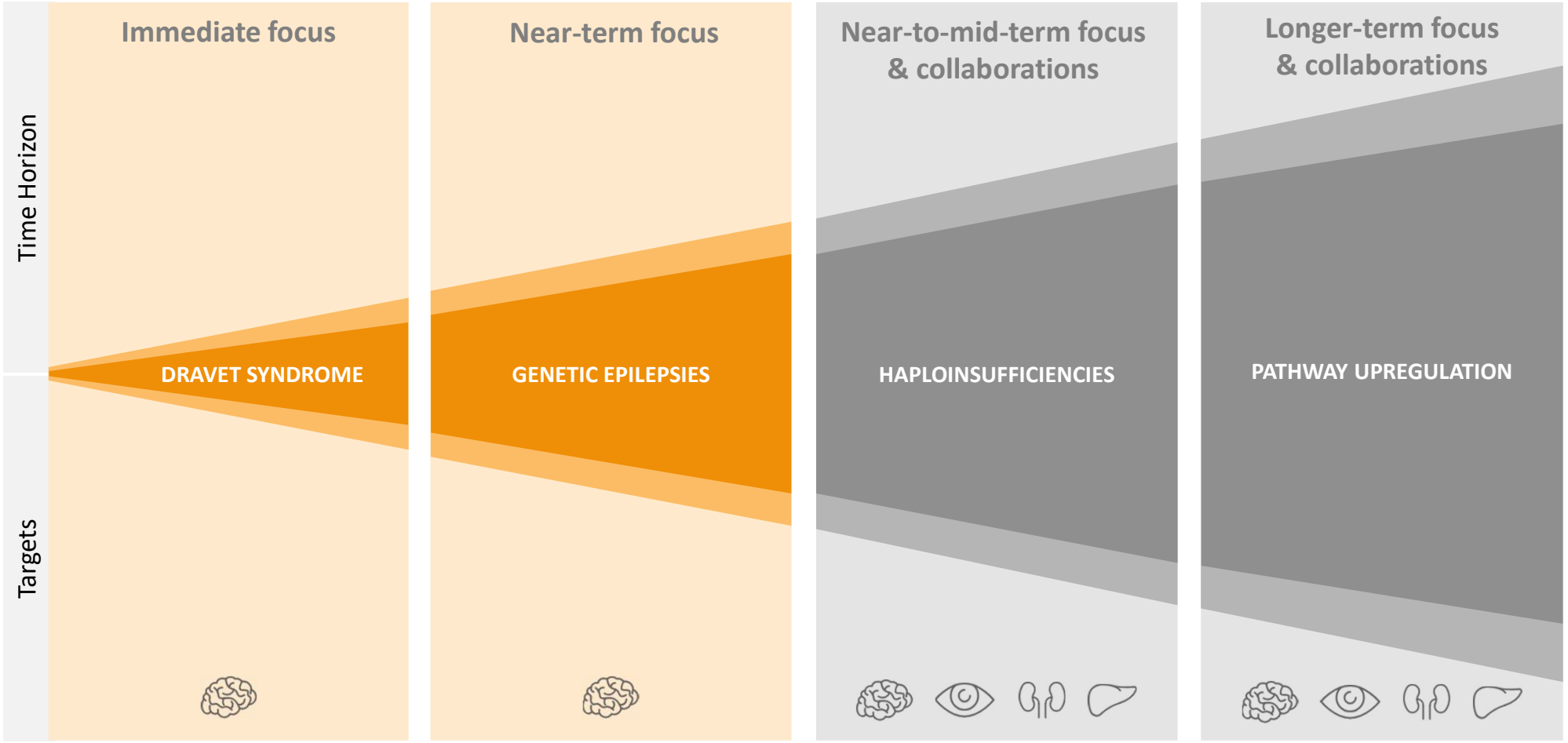


Correlation between event abundance (+CHX) & upregulation



NT: non-targeting ASO control, all experiments n = 3, *in vitro*

Stoke is Initially Focused on Dravet Syndrome and Other Genetic Epilepsies



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

Sources: 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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Dravet Syndrome: A Severe, Progressive Genetic Epilepsy

85% of cases caused by a haploinsufficiency of the *SCN1A gene* results in **50%** $Na_V1.1$ protein expression

Up to **20%** of children and adolescents with Dravet die before adulthood, due to SUDEP[1], prolonged seizures, seizure-related accidents or infections

1 out of **16,000** babies are born with Dravet syndrome

Seizures are not adequately controlled in **90%** of people with Dravet

~35,000 people affected in the U.S., Canada, Japan, Germany, France and the UK

Dravet syndrome is not concentrated in a particular geographic area or ethnic group.

Note: [1] Sudden Unexpected Death in Epilepsy

Sources: *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

Non-Seizure Comorbidities of Dravet Syndrome Are Not Addressed by Current Therapies

Dravet is Not Limited to Seizures:

More than 90% of patients suffer from at least one non-seizure comorbidity, including

- Severe intellectual disabilities
- Severe developmental disabilities
- Motor impairment
- Speech impairment
- Autism
- Behavioral difficulties
- Sleep abnormalities

High Incidence of Premature Death:

Up to 20% of children and adolescents die before adulthood, due to:

- SUDEP
- Prolonged seizures
- Seizure-related accidents
- Infections

Sources: *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; Licheni et al, Developmental Medicine & Child Neurology 2018*

STOKE THERAPEUTICS

STK-001 Has Potential to Address the Genetic Cause of Dravet Syndrome

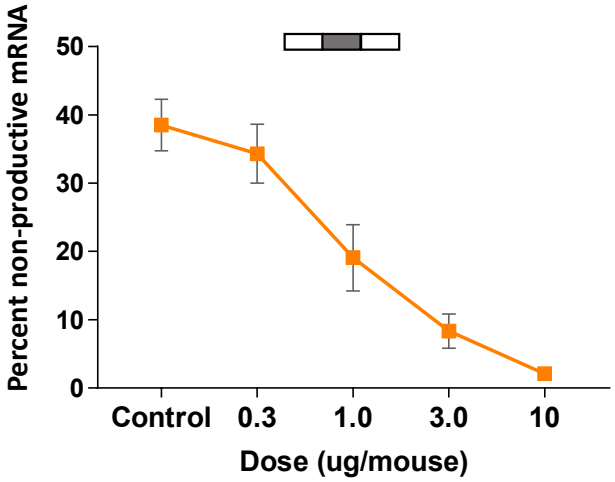
Preclinical data support the use of STK-001 in Dravet syndrome:

- Single dose restores $Na_V1.1$ from 50% to near normal levels for >3 months in Dravet syndrome mice
- Significantly reduces mortality and seizure frequency in Dravet syndrome mouse model
- Selective target engagement may limit potential off-target effects
- Broadly distributes in the brains of non-human primates with intrathecal delivery
- Well-tolerated at pharmacologically-active dose levels in non-human primates
- Able to dose titrate with wide therapeutic window

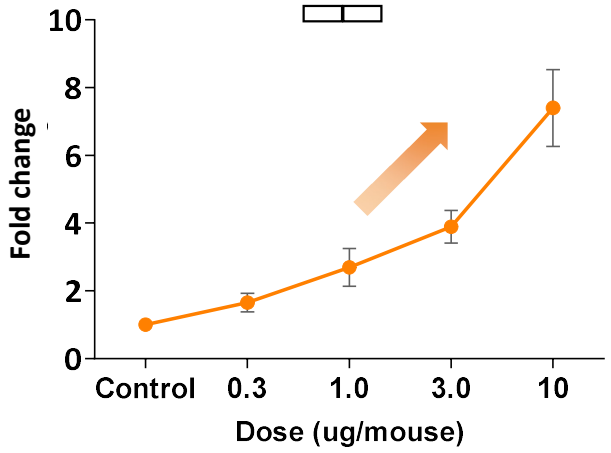
STOKE THERAPEUTICS

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

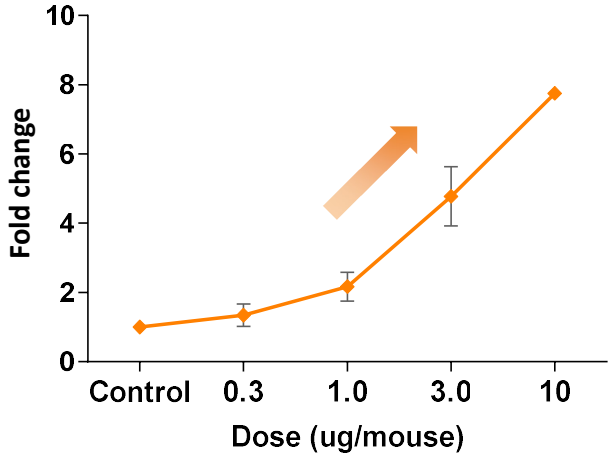
Decrease in non-productive *Scn1a* mRNA



Increase in productive *Scn1a* mRNA



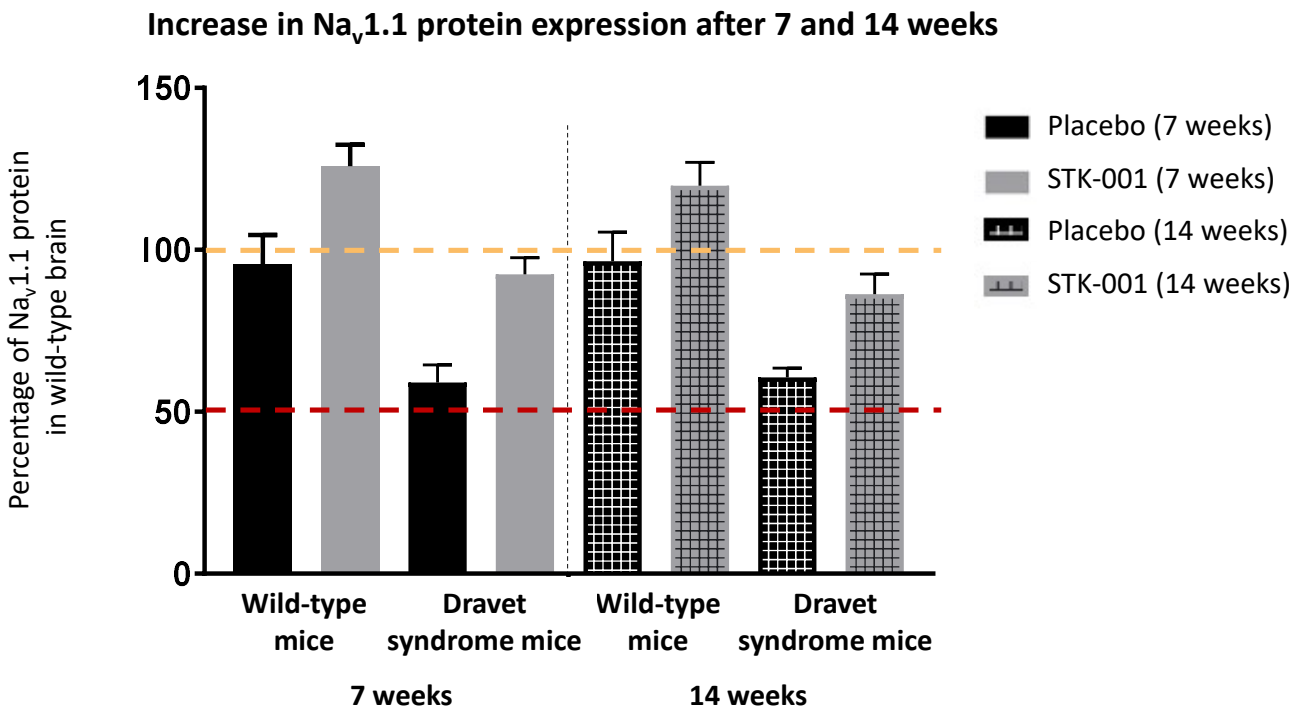
Increase of $Na_V1.1$ protein



Source: Stoke data

STOKE THERAPEUTICS

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



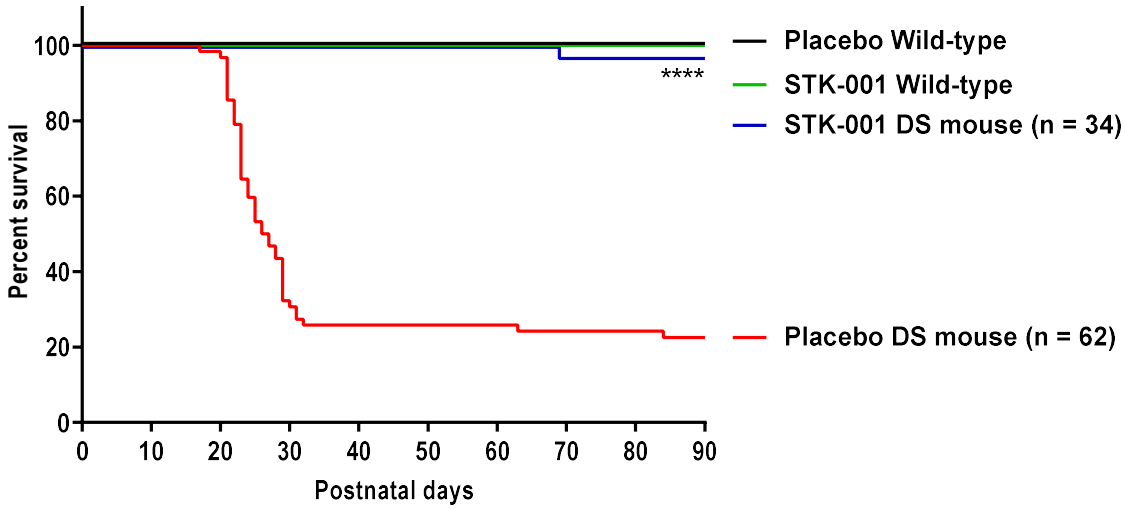
In preclinical studies, STK-001 exhibits long-lasting exposure, suggesting the potential for a favorable dosing regimen of as few as two to three administrations per year in humans

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

Significant improvements in survival among Dravet syndrome mice after STK-001 administration (20µg) at postnatal day 2

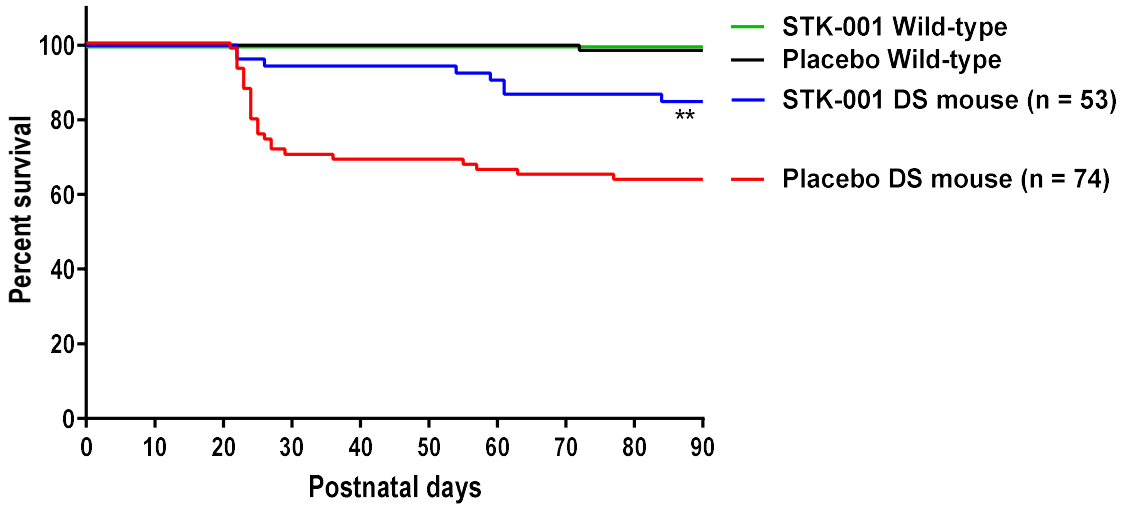


****p<0.0001

Source: Stoke data, presented at AES 2019

STK-001 Significantly Reduces Premature Mortality in Dravet Syndrome Mice

Significant improvements in survival among Dravet syndrome mice after STK-001 administration (60µg) at postnatal day 14

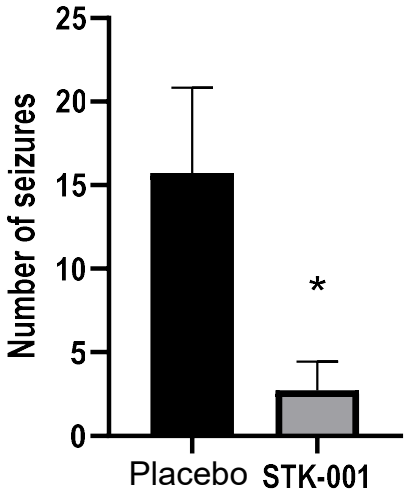


**p<0.005

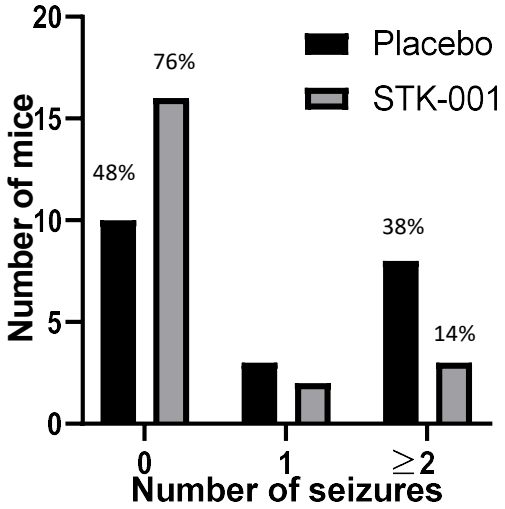
Source: Stoke data, presented at AES 2019

STK-001 Significantly Reduces Spontaneous Seizures in Dravet Syndrome Mice

80% reduction in the average number of spontaneous seizures compared to placebo (p<0.05)



76% of mice treated with STK-001 were seizure-free compared to 48% of placebo-treated mice



As measured between postnatal days (PND) 22 and 46 in Dravet syndrome mice after a single 20 µg injection of STK-001 at PND 2

Source: Stoke data, presented at AES 2019

STOKE THERAPEUTICS

Pivotal Preclinical Single and Multiple-Dose Toxicology Studies in NHPs Showed STK-001 Well-Tolerated

The no observed adverse effect level (NOAEL) in the GLP studies in NHPs exceeds the highest human equivalent dose that we plan to administer in our Phase 1/2a clinical study

Key safety findings from GLP studies

No observed adverse events at highest dose tested	✓
No change in platelet counts or renal/hepatic function	✓
No adverse histopathology in brain, spinal cord, liver and kidney	✓

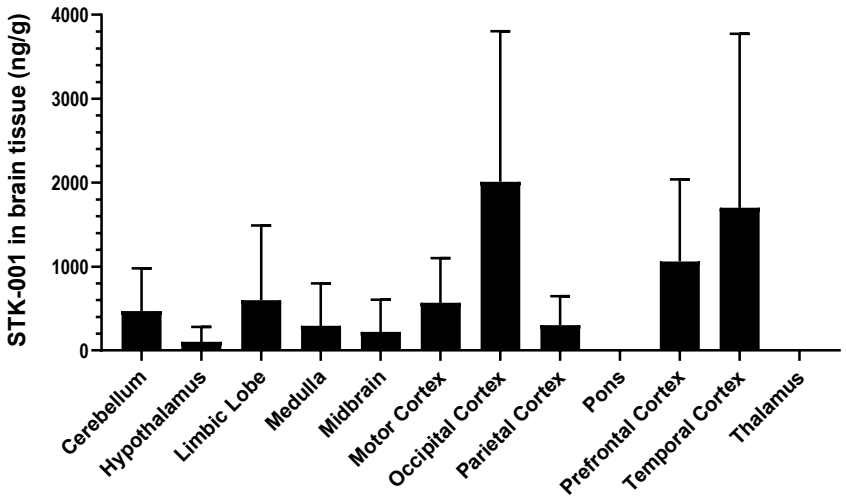
IT=Intrathecal, NHP= non-human primate

Source: Stoke data

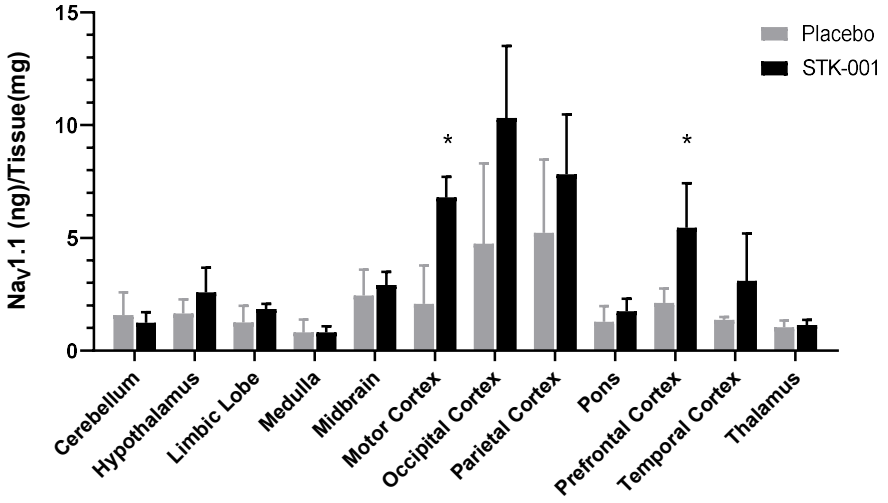
STOKE THERAPEUTICS

STK-001 Achieves Broad Distribution and Increases $Na_v1.1$ Protein Expression in NHPs (n=3)

Exposure of STK-001 observed in all brain regions except pons and thalamus



$Na_v1.1$ protein levels increased up to 3-fold



Source: Stoke data, presented at AES 2019

STOKE THERAPEUTICS

BUTTERFLY Observational Study Ongoing

BUTTERFLY

An observational study of Dravet syndrome patients

- Two-year observational study of children and adolescents ages 2-18
- Designed to evaluate seizure frequency and non-seizure comorbidities associated with Dravet syndrome, including:
  - Intellectual disabilities
  - Developmental disabilities
  - Motor impairment
  - Speech impairment
  - Behavioral problems
  - Sleep abnormalities

STOKE THERAPEUTICS

MONARCH Phase 1/2a Trial Now Enrolling and Dosing Patients

- Open-label study of children and adolescents ages 2-18 with Dravet syndrome
  - Plan to enroll ~40 patients at ~20 sites in the U.S.
  - **Primary endpoints**: safety and tolerability of a single-ascending dose, characterize human pharmacokinetics
  - **Secondary endpoints:** change in seizure frequency over 12-weeks, quality of life
- Two-part trial design:
  - **Part A** will evaluate two dose cohorts; first patient dosed August 2020
  - **Part B** will evaluate higher doses and is on partial clinical hold, pending data to more fully characterize STK-001's safety profile at doses higher than the current no observed adverse effect level (NOAEL). We have completed the single-dose toxicology study and are in the process of preparing our complete response to the FDA in order to facilitate the removal of the partial clinical hold.
  - For each dose level, sentinel group ages 13-18, followed by group ages 2-12
- Preliminary data expected in 2021

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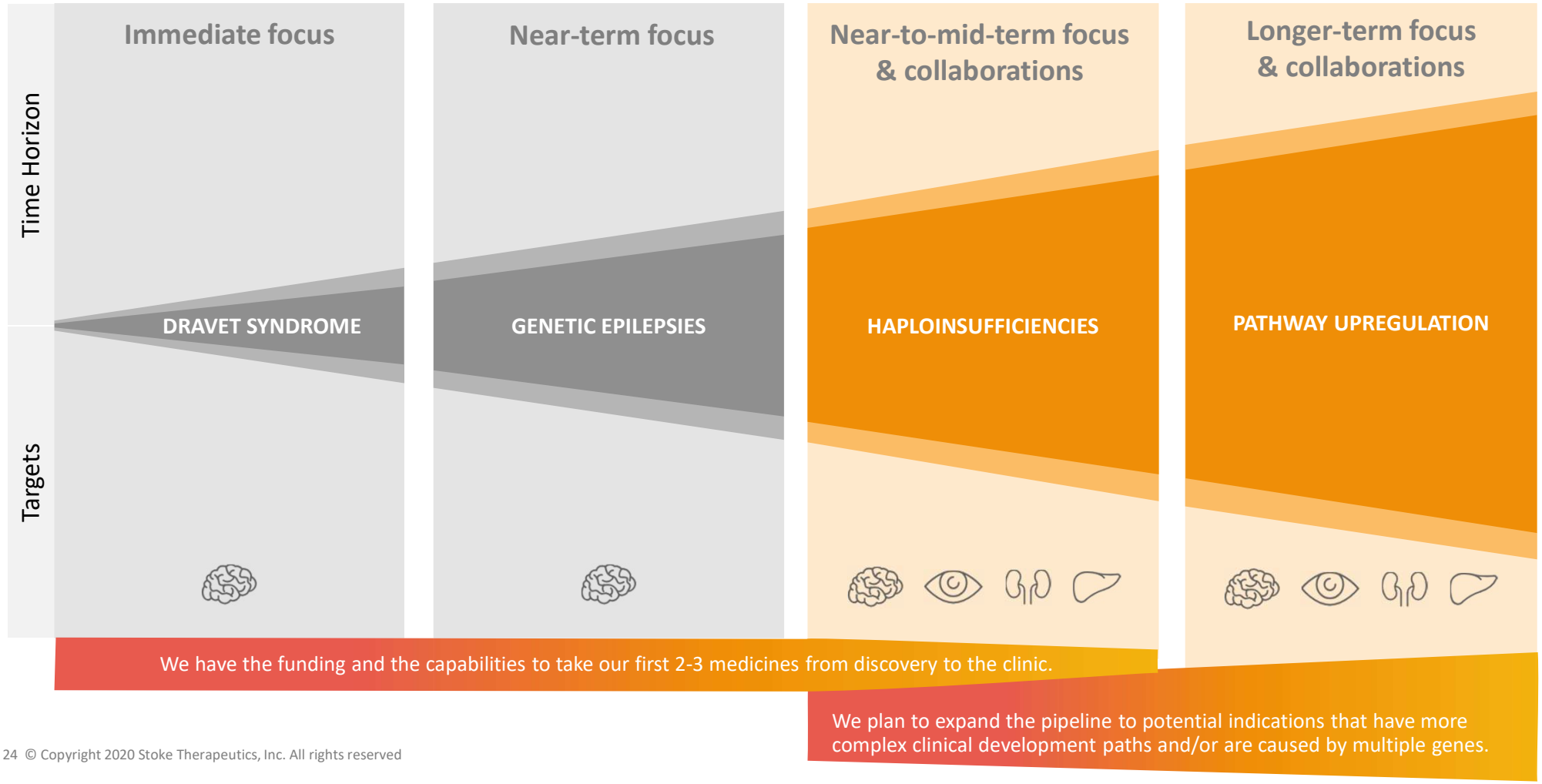
Expanding the Pipeline Using Stoke's Proprietary Bioinformatics and TANGO



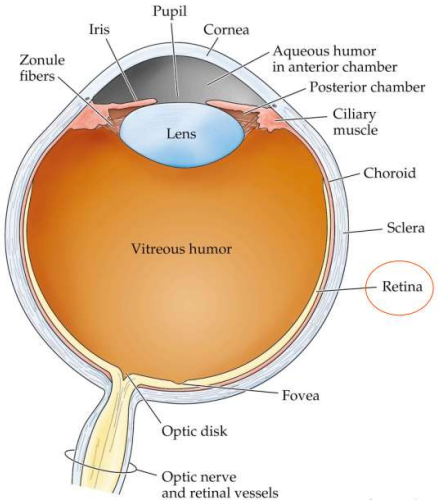
TANGO May Also be Well Suited for Treatment of Eye Diseases

Benefits of focusing on the eye for ASOs

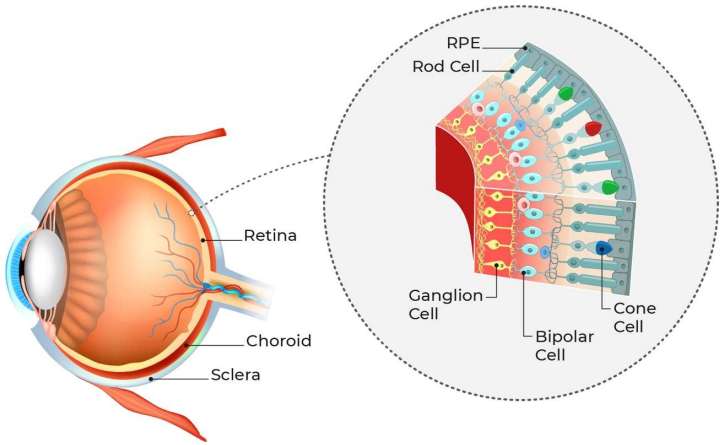
- Localized delivery
- Immune privileged and small treatment space (0.05% of total body weight)
- Contralateral control for clinical trials
- Availability of non-invasive measurements that reflect functional outcome (e.g. OCT)

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



OPA1 Protein Deficiency is One of Several Eye Disease Targets Under Consideration



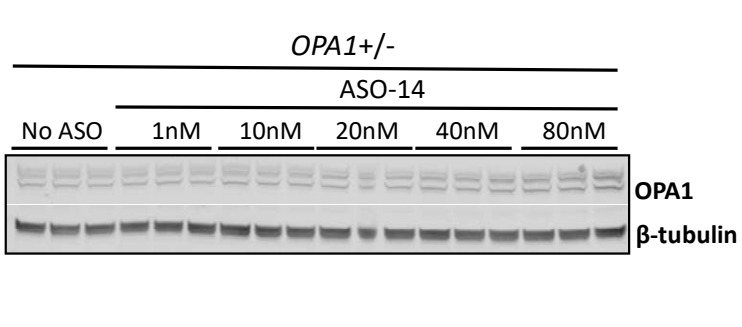
- Autosomal dominant optic atrophy (ADOA) is the most common inherited optic nerve disorder seen in clinical practice
- ADOA causes progressive and irreversible vision loss in both eyes starting in the first decade of life. Many children progress to blindness
- The disease affects 1/30,000 people globally with a higher incidence of ~ 1/10,000 in Denmark due to a founder effect
- 65%-90% of ADOA is caused by mutations in one allele of the *OPA1* gene which leads to haploinsufficiency and disease manifestation
- More than 400 different OPA1 mutations have been reported in people diagnosed with ADOA
- Stoke's TANGO ASO targets a non-productive splicing event in the *OPA1* gene to increase productive mRNA in the retinal ganglion cells

Sources: Yu-Wai-Man P et al. The Prevalence and Natural History of Dominant Optic Atrophy Due to OPA1 Mutations. Ophthalmology. 2010 August; 117(8): 1538-1546; Yu-Wai-Man P, Chinnery PF. Dominant Optic Atrophy: Novel OPA1 Mutations and Revised Prevalence Estimates. Ophthalmology. Vol. 120, Number 8, August 2013: 1712-1712; 3. P. Amati-Bonneau P et al. OPA1-associated disorders: phenotypes and pathophysiology. The International Journal of Biochemistry & Cell Biology 41, 1855-1865 (2009); "What is ADOA?" Autosomal Dominant Optic Atrophy Association. Accessed May 6, 2020, from https://www.adoaa.org/what-is-adoa; Lenaers G, Hamel C, Delettre C, et al. Dominant optic atrophy. Orphanet J Rare Dis 7, 46 (2012); Chun BY and Rizzo JF III. Dominant optic atrophy: updates on the pathophysiology and clinical manifestations of optic atrophy 1 mutation. Curr Opin Ophthalmol 2016; 27:475-480; Le Roux B, Lenaers G, Zanlonghi X et al. OPA1: 516 unique variants and 831 patients registered in an updated centralized Variome database. Orphanet J Rare Dis 14, 214 (2019).

STOKE THERAPEUTICS

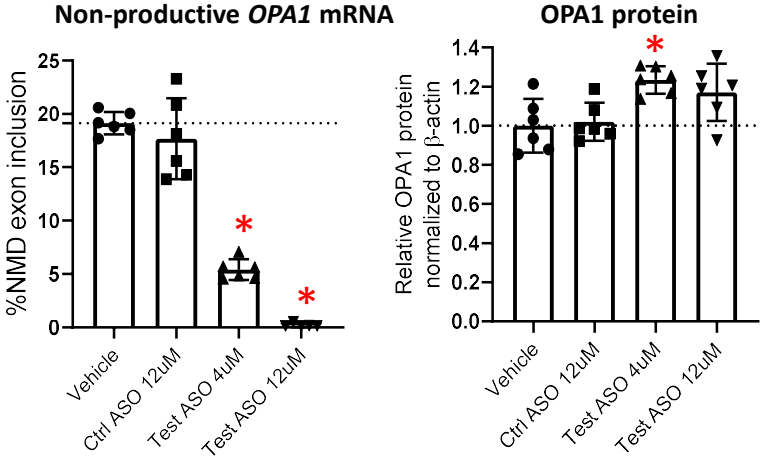
TANGO ASOs Demonstrated *In Vitro* and *In Vivo* Target Engagement & Protein Upregulation in OPA1 Protein Deficiency

ASO increases OPA1 expression in an OPA1 haploinsufficient (OPA1+/-) cell line



ASO increases OPA1 protein levels in *OPA1* $^{+/-}$ HEK293 cells by 50%, which translates to 75% of wild-type levels.

Rabbit ASO decreases non-productive splicing & increases OPA1 expression in wild-type rabbit retinae



ASO was administered by intravitreal injection and was well tolerated for up to 15 days after IVT injection.

Source: Stoke Data. Antisense oligonucleotide mediated increase of OPA1 expression using TANGO technology for treatment of autosomal dominant optic atrophy. ASGCT, May 2020

STOKE THERAPEUTICS

Rapidly Scaling Stoke to Support Growth as a Clinical-Stage Company

2018

Stoke is Launched

- Closed $40M Series A financing
- Nominated Dravet syndrome as lead program; generated *in-vivo* proof of concept
- Completed FDA pre-IND meeting
- Closed $90M Series B financing
- Built robust intellectual property estate

2019

Stoke is Poised to Enter the Clinic

- Completed $163.3M Initial Public Offering
- Received FDA orphan drug designation for STK-001, a potential disease modifying medicine for Dravet syndrome
- Enrolled first patient in the BUTTERFLY observational study
- Presented preclinical data supporting efficacy of STK-001
- Submitted IND for STK-001 to the U.S. FDA

2020

Stoke Becomes a Clinical-Stage Company

- ✓ Early 2020: FDA communicated that Part A of MONARCH may proceed with dosing
- ✓ 2H 2020: Began enrollment and dosing of patients in MONARCH in Aug. 2020
- ❑ 2H 2020: Nominate new candidate for preclinical development in an additional genetic disease
- ❑ Continuously evaluate potential collaborations to expand the pipeline
- ❑ Build the organization and capabilities to scale as a clinical-stage company

STOKE THERAPEUTICS

Current Financials Anticipated to Fund Operations into 2023

Cash, Cash Equivalents and Restricted Cash *as of 06/30/2020*	**$202.1 million**
Common Shares Outstanding *as of 06/30/2020*	**33,212,544**

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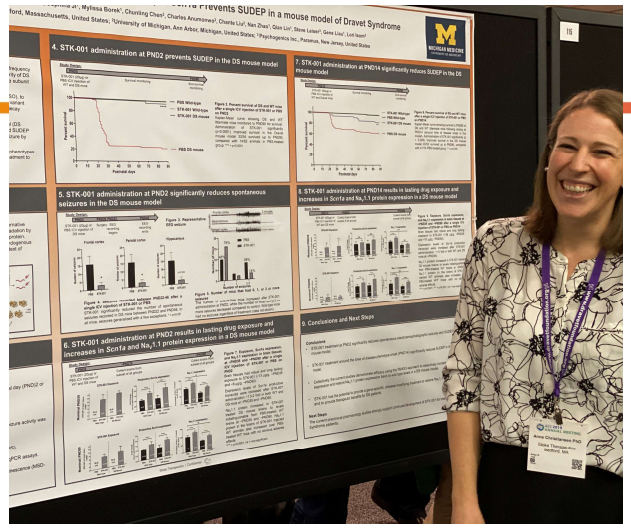

The Commitment that Drives Stoke

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