# Stoke Therapeutics

NASDAQ: STOK

February 2021

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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: the ability of our TANGO platform to design medicines to increase protein production and the expected benefits thereof; the ability of STK-001 to treat the underlying causes of Dravet syndrome; the preclinical data and study results regarding OPA1; our preliminary cash, cash equivalents and restricted cash and shares outstanding as of December 31, 2020; our future operating results, financial position and liquidity; the direct and indirect impact of COVID-19 on our business, financial condition and operations, including on our expenses, supply chain, strategic partners, research and development costs, clinical trials and employees; our expectation about timing and execution of anticipated milestones, responses to regulatory authorities, expected nomination of future product candidates and timing thereof. 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 statements, including: our ability to develop, obtain regulatory approval for and commercialize STK-001, OPA1 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

## STOKE THERAPEUTICS

# Boldly Restoring Genetic Health

Addressing the underlying cause of severe diseases by up-regulating protein expression with RNA-based medicines.

# A Differentiated Platform for the Discovery and Development of Novel RNA-based Medicines

STOKE

**STOKE THERAPEUTICS HIGHLIGHTS**

**Proprietary RNA therapeutics platform**

Targets pre-mRNA splicing to restore target protein to near normal levels

**Broad therapeutic potential**

~1,200 monogenic disease genes and ~6,500 additional genes with RNA target signatures

**Disease-modifying approach**

Our compounds address the underlying cause of severe genetic diseases

**Clinical stage with emerging pipeline**

STK-001 is being evaluated in a Phase 1/2a study for Dravet syndrome (DS). OPA1 is a preclinical target for autosomal dominant optic atrophy (ADOA)

# Targeted Augmentation of Nuclear Gene Output

**Our compounds aim to restore protein levels by increasing protein production from the functional copy of a gene and:**

- Selectively boost expression only in tissues where the protein is normally expressed
- Offer one drug for diseases caused by many different mutations
- Apply to genes of diverse size: can be used to address small or large gene targets

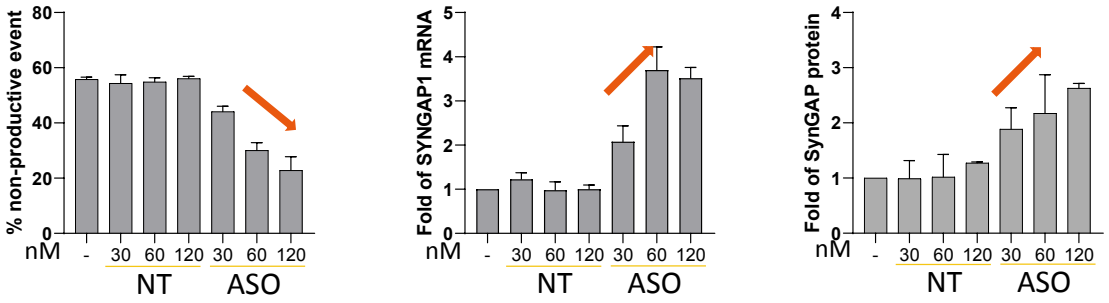
# TANGO ASOs Demonstrate Dose-Dependent Increases in Protein Expression Across Targets of Diverse Size, Type and Function

STOKE

## Genetic epilepsy – haploinsufficiency

### SYNGAP1

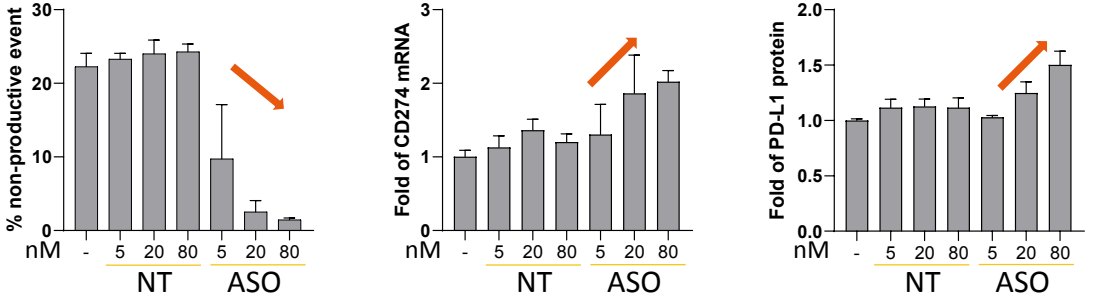
non-productive event | productive mRNA | protein




## Pathway target – wild-type

### CD274 (PD-L1)

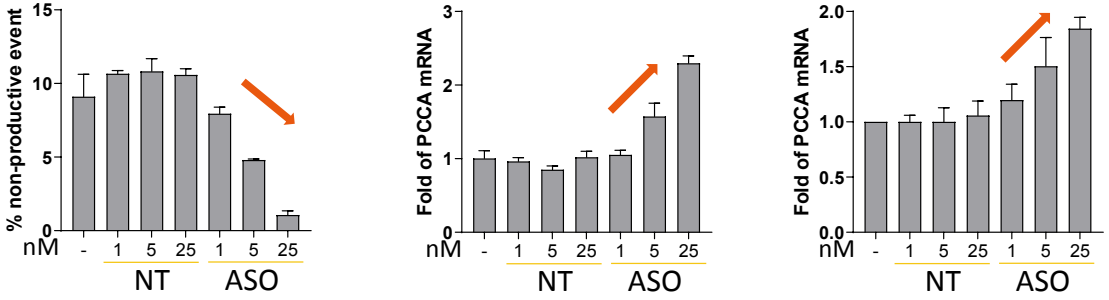
non-productive event | productive mRNA | protein



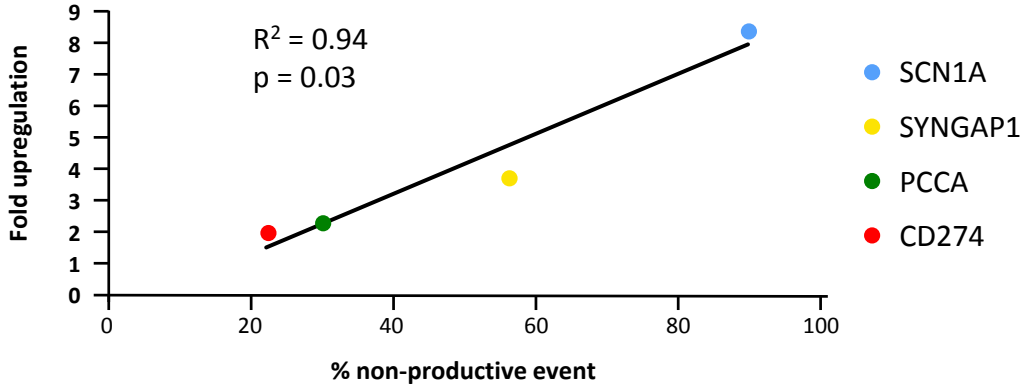

## Liver target – autosomal recessive

### PCCA

non-productive event | productive mRNA | protein




## Correlation between event abundance (+CHX) & upregulation




nature communications

Lim *et al.*, Nat Comm, 2020

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

# 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

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

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

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

**~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*

[1] Sudden Unexpected Death in Epilepsy

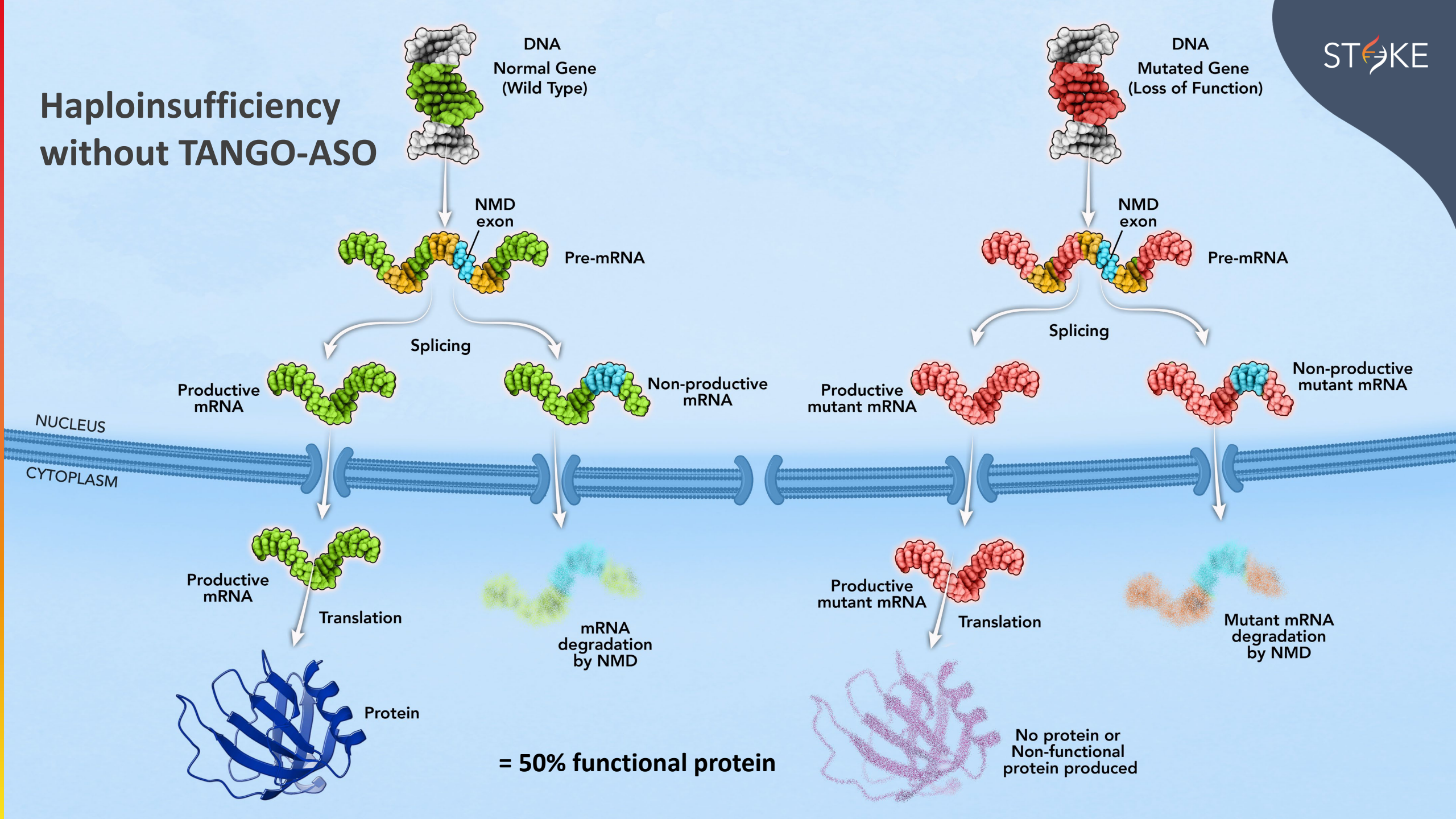
Sources: *2018 Health Advances Report*; Djémié et al., *Molecular Genetics & Genomic Medicine,* 2016; Lagae et al., *Developmental Medicine & Child Neurology,* 2017; Nabbout et al., *Orphanet Journal of Rare Diseases,* 2013

# No Approved Disease-Modifying Therapies for Dravet Syndrome

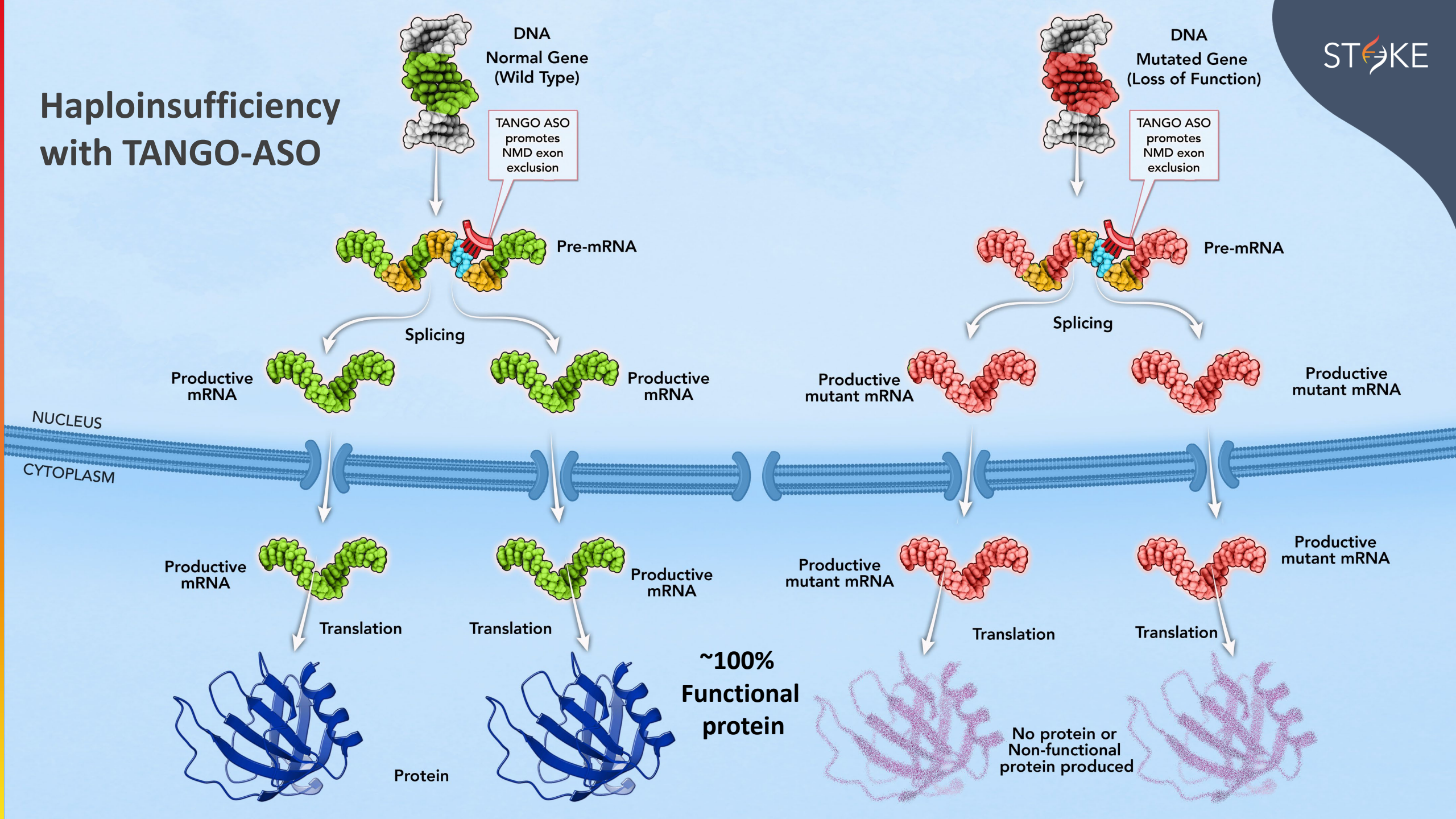
## Non-Seizure Comorbidities of Dravet Syndrome Are Not Addressed by Current Therapies

- Intellectual disability
- Developmental delays
- Movement and balance issues
- Language and speech disturbances
- Growth defects
- Sleep abnormalities
- Chronic infections
- Disruptions of the autonomic nervous system
- Mood disorders

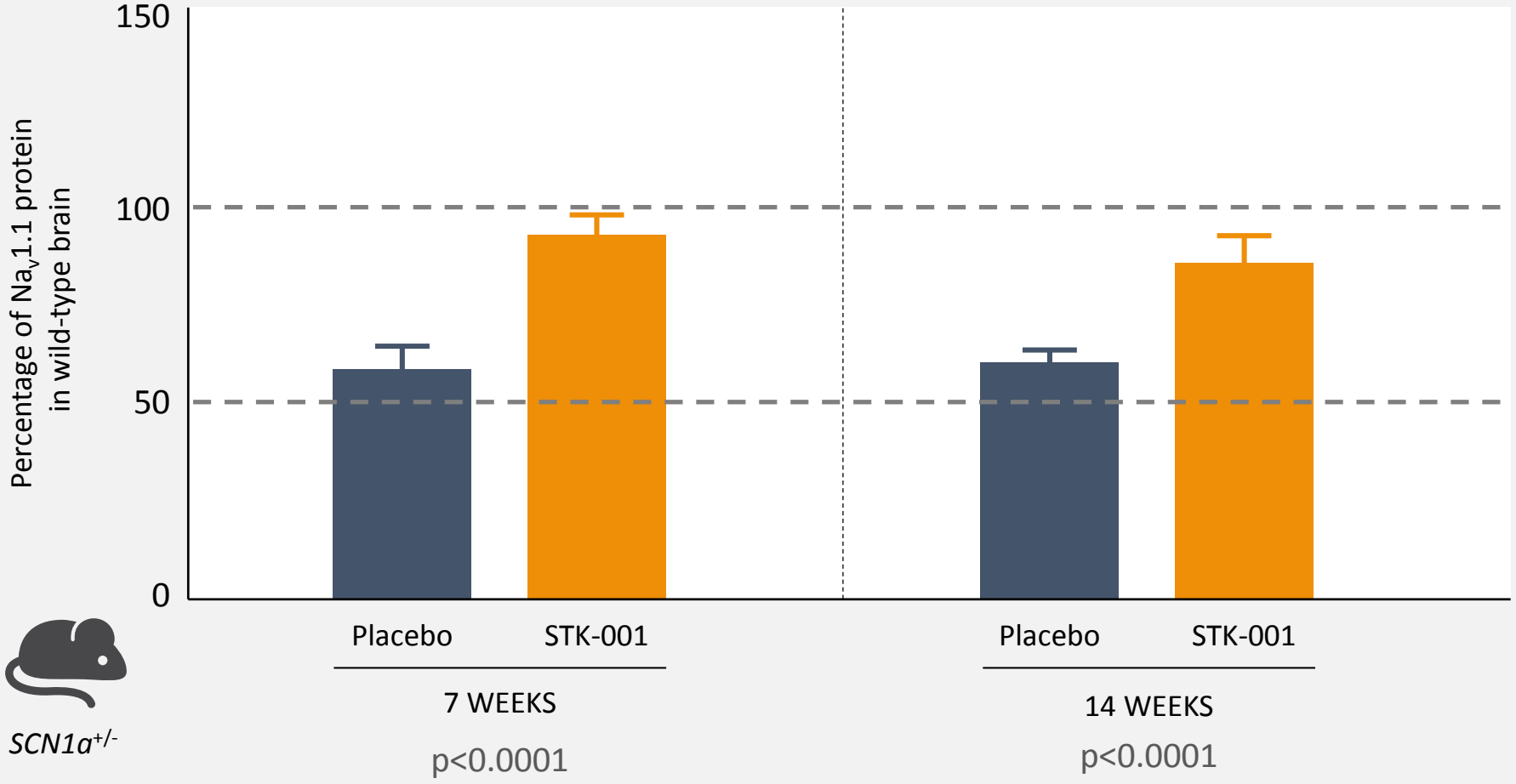
# Haploinsufficiency without TANGO-ASO



# Haploinsufficiency with TANGO-ASO



# STK-001 Restores $Na_V1.1$ to Near Normal Levels for >3 Months in Dravet Syndrome (DS) Mice after a Single Dose

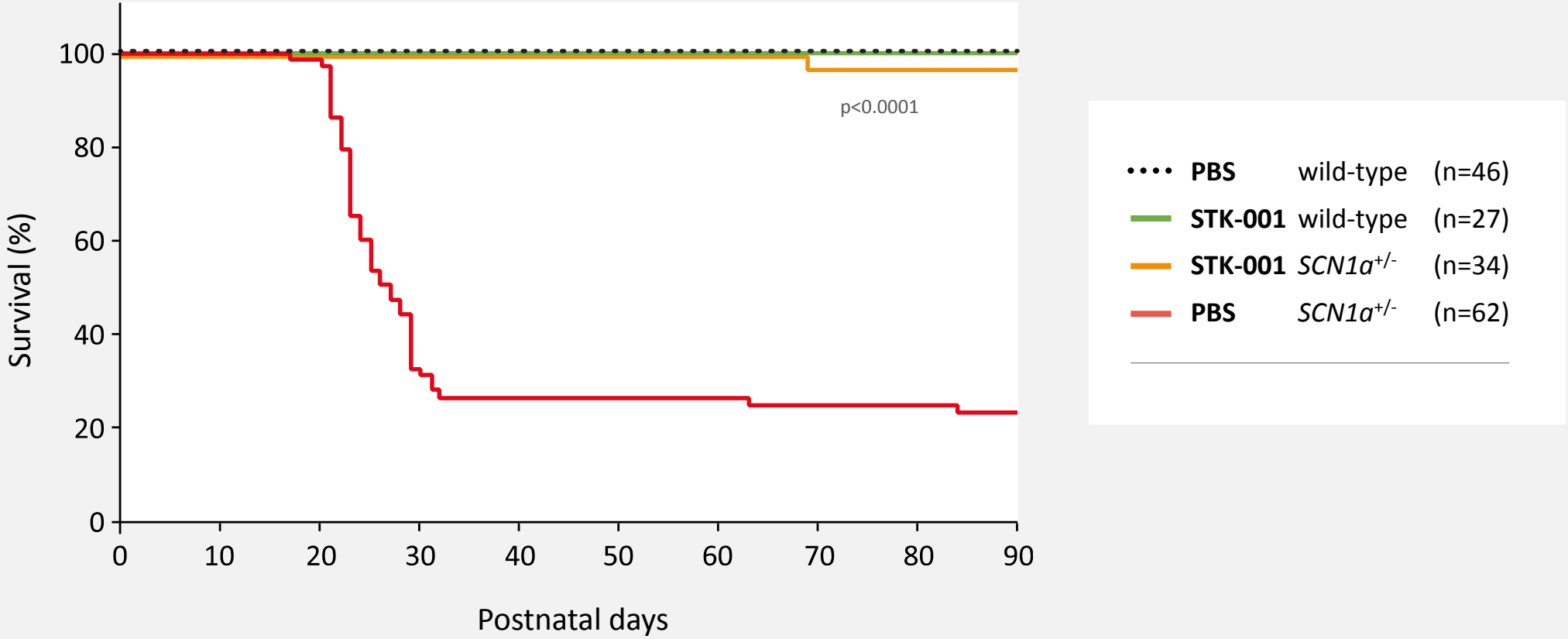



Science Translational Medicine AAAS

Sources: Han *et al.*, Science Trans Med, 2020

# STK-001 Significantly Reduces Premature Mortality in DS Mice After a Single Dose

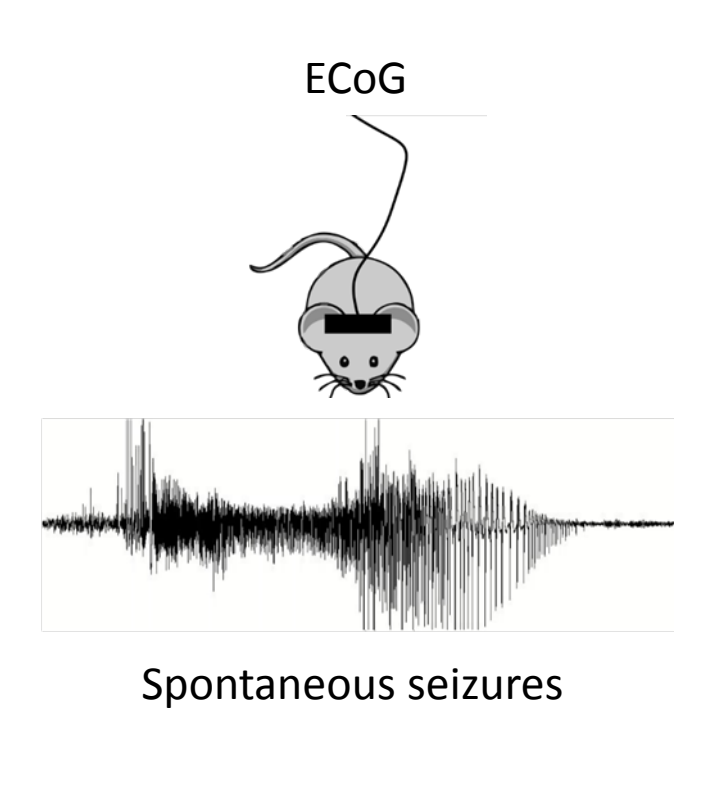
**Significant improvements in survival after STK-001 administration at postnatal day 2**



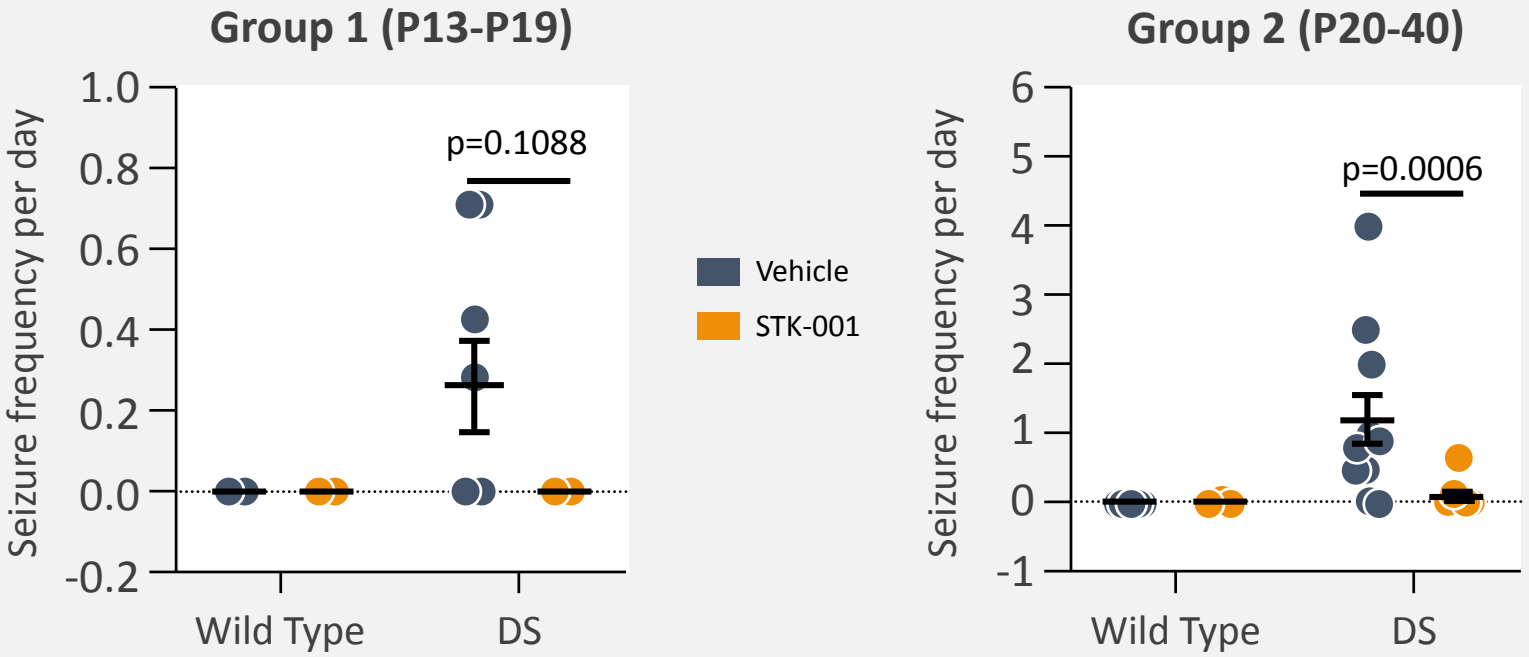

Science Translational Medicine AAAS

Sources: Han *et al.*, Science Trans Med, 2020

# STK-001 Administration Reduces Seizure Frequency in DS Mice



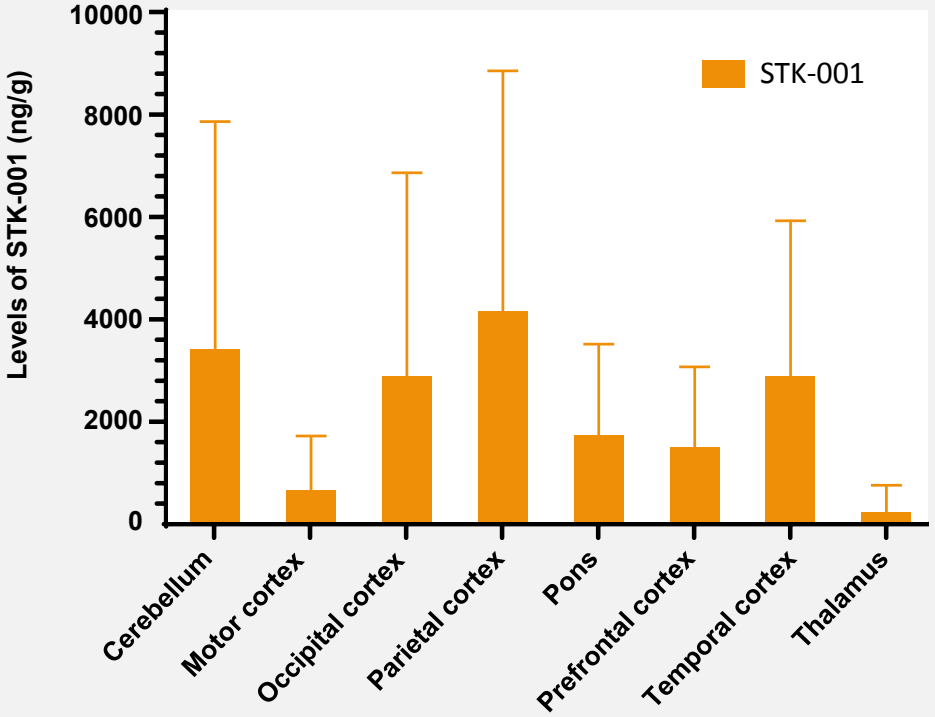

**A single dose of STK-001 completely stopped seizure events early (P13-19) and substantially reduced seizure frequency late (P20-40)**



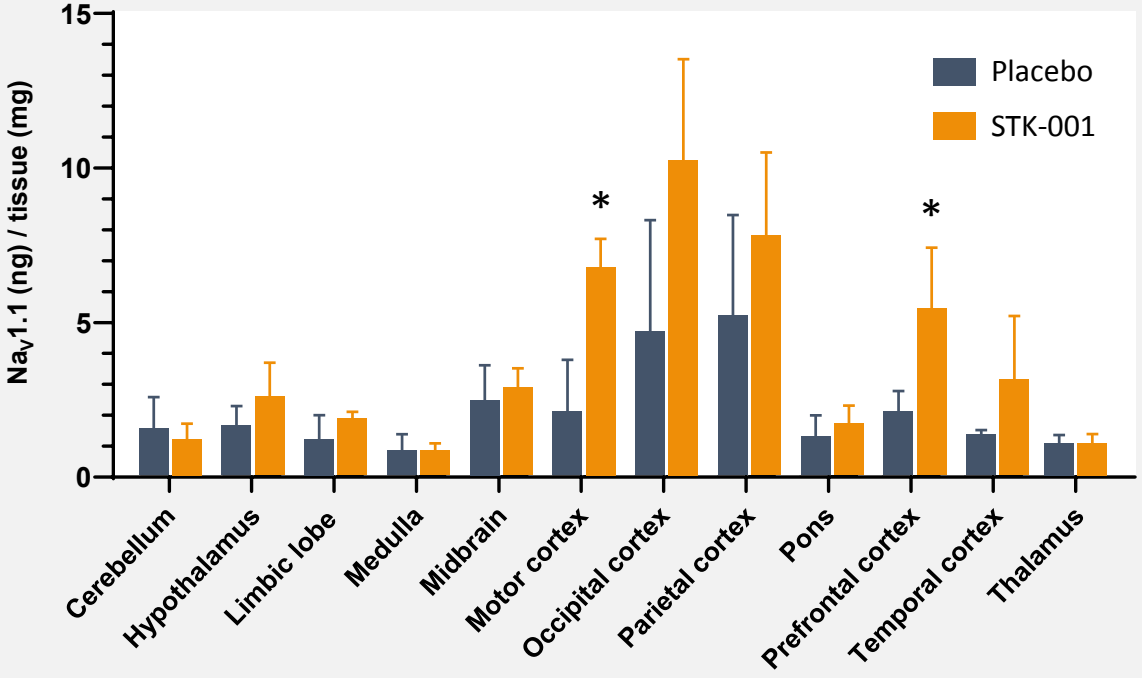

Source: Targeted Augmentation of Nuclear Gene Output (TANGO) of SCN1A reduces seizures and rescues parvalbumin positive interneuron firing frequency in a mouse model of Dravet syndrome (AES 2020)

# STK-001 Achieves Broad Distribution and Increases $Na_v1.1$ Protein Expression in NHPs

## Study 1: Exposure of STK-001 observed in all brain regions




## Study 2: $Na_v1.1$ protein levels increased up to 3-fold




* = p<0.05

NHP = Non-human primate
Source (left graph): Stoke data
Source (right graph) TANGO oligonucleotides for the treatment of Dravet Syndrome: Safety, biodistribution and pharmacology in the non-human primate (AES 2019)

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

## 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 ✓

*In non-GLP studies in NHPs, at levels above the NOAEL, hind limb paresis was observed; at extremely high dose levels, acute convulsions were observed.

Source: Stoke data

# STK-001 Has Potential to Address the Genetic Cause of Dravet Syndrome (DS)

- Single dose restores $Na_V1.1$ to near normal levels for >3 months in DS mice
- Significantly reduces mortality and seizure frequency in DS mice
- Achieves broad distribution and increases $Na_V1.1$ protein expression in NHPs
- Well-tolerated as shown in single and multiple-dose toxicology studies in NHPs

# Non-Seizure Comorbidities of DS are Progressive and Measurable

STOKE

## Enrollment completed (n=36, 2-18 year-olds). Study ongoing.

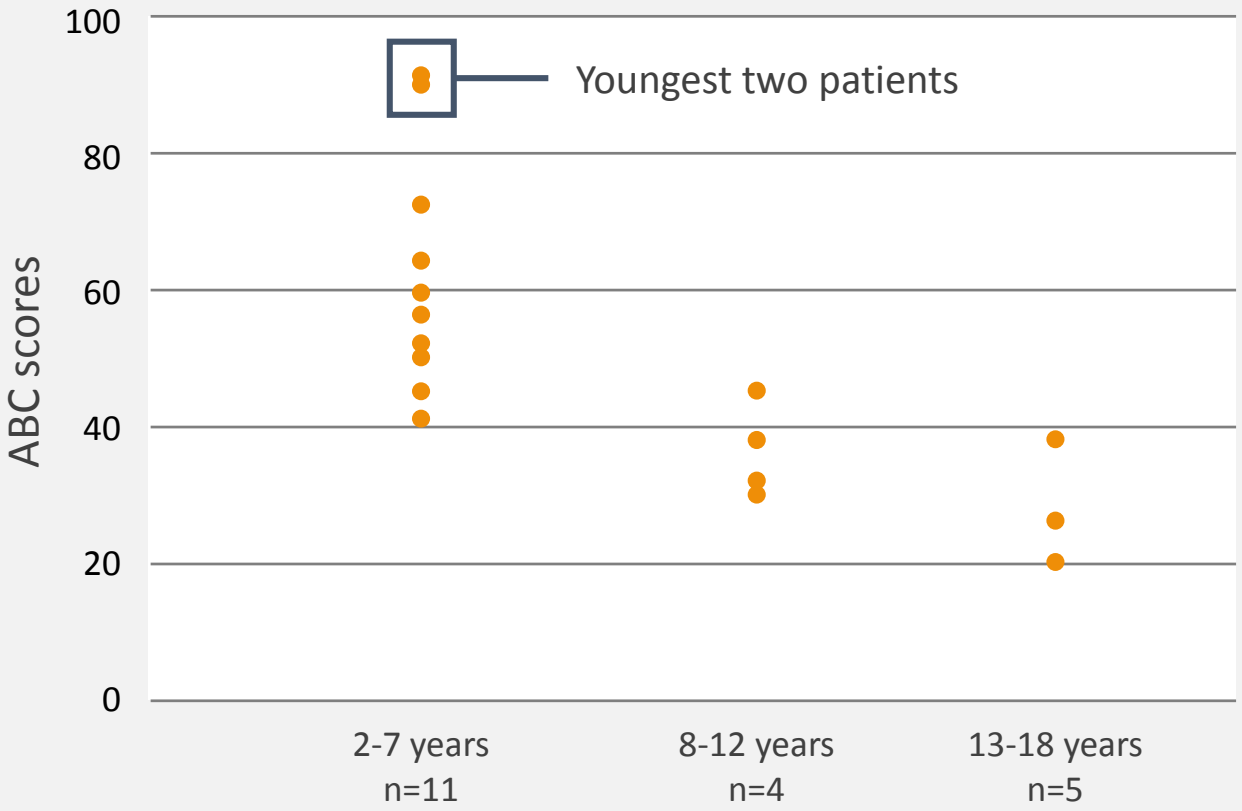
BUTTERFLY

An observational study of Dravet Syndrome patients

**Initial findings showed:**

- Validation of standard cognitive measures for use in DS patients
- Substantially decreased neurocognitive abilities despite the use of multiple anti-epileptic therapies
- Apparent widening from normal levels in overall intellectual development that increases with age
- A gap in adaptive functioning

**Baseline VABS-III Adaptive Behavior Composite (ABC)***




* VABS = Vineland Adaptive Behavior Scales
* ABC score based on Communication, Daily Living, and Socialization domains and expressed relative to normative mean of 100
Source: Observational Study to Investigate Cognition and Quality of Life in Children and Adolescents with Dravet Syndrome: Baseline Analysis of the BUTTERFLY Study (AES 2020)

# Enrollment and Dosing in MONARCH Phase 1/2a Trial is Ongoing

| | |
|---|---|
| **Design** | Open-label evaluation of single and multiple ascending doses of STK-001 (up to 30mg)<br>• SAD: Currently enrolling<br>• MAD: Planned initiation 2H 2021<br>*Doses >30mg remain on FDA partial clinical hold* |
| **Target Enrollment** | ~48 children and adolescents ages 2-18 years old with Dravet syndrome and confirmed *SCN1a* variant |
| **Primary Endpoint** | Safety and tolerability of single and multiple ascending dose levels; characterize human pharmacokinetics (PK) |
| **Secondary Endpoint** | Change in seizure frequency over 12-weeks, quality of life |
| **Preliminary Data** | Initial safety and PK data anticipated in 2021 |
| **Open-Label Extension** | Currently enrolling |

monarch
A DRAVET SYNDROME STUDY

swallowtail
A DRAVET SYNDROME EXTENSION STUDY

Source: Safety and Pharmacokinetics of Antisense Oligonucleotide STK-001 in Children and Adolescents with Dravet Syndrome: Single and Multiple Ascending Dose Design for the Open-Label Phase 1/2a MONARCH Study (AES 2020)

# Autosomal Dominant Optic Atrophy (ADOA): A Severe, Progressive Optic Nerve Disorder

**65-90%**

of cases caused by a **HAPLOINSUFFICIENCY** in the *OPA1* gene

RESULTS IN

**50%**

OPA1 protein expression and disease manifestation

**1 out of 30,000**

people are affected globally with a higher incidence of ~1 out of 10,000 in Denmark due to a founder effect

**>400**

Different *OPA1* mutations reported in ADOA patients

**Up to 46%**

of patients are registered legally blind

**80%**

of patients are symptomatic by age 10

**~18,000**

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

Sources: Yu-Wai-Man P et al. *Ophthalmology*, 2010; Yu-Wai-Man P, Chinnery PF. *Ophthalmology*, 2013; P. Amati-Bonneau P et al. *The International Journal of Biochemistry & Cell Biology*, 2009; Lenaers G, Hamel C, Delettre C, et al. *Orphanet J Rare Dis*, 2012; Chun BY and Rizzo JF III. *Curr Opin Ophthalmol,* 2016; Le Roux B, Lenaers G, Zanlonghi X et al. *Orphanet J Rare Dis*, 2019; "What is ADOA?" Autosomal Dominant Optic Atrophy Association. Accessed May 6, 2020, from https://www.adoaa.org/what-is-adoa;

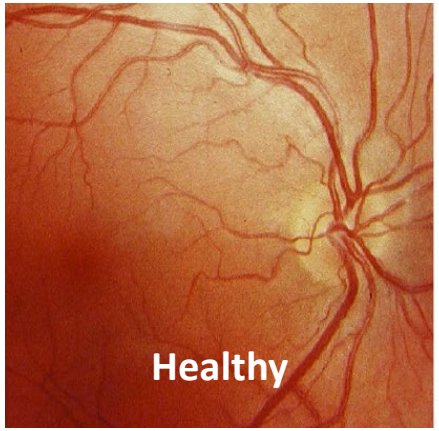
# No Approved Disease-Modifying Therapies for ADOA

STOKE

**Healthy Vision**

**Simulation of Optic Neuropathy**

- Most common inherited optic nerve disorder
- Leads to central field defects and reduced color vision in both eyes
- Severity can vary; rate of vision loss difficult to predict
- Supportive services and low-vision aids are offered for patients

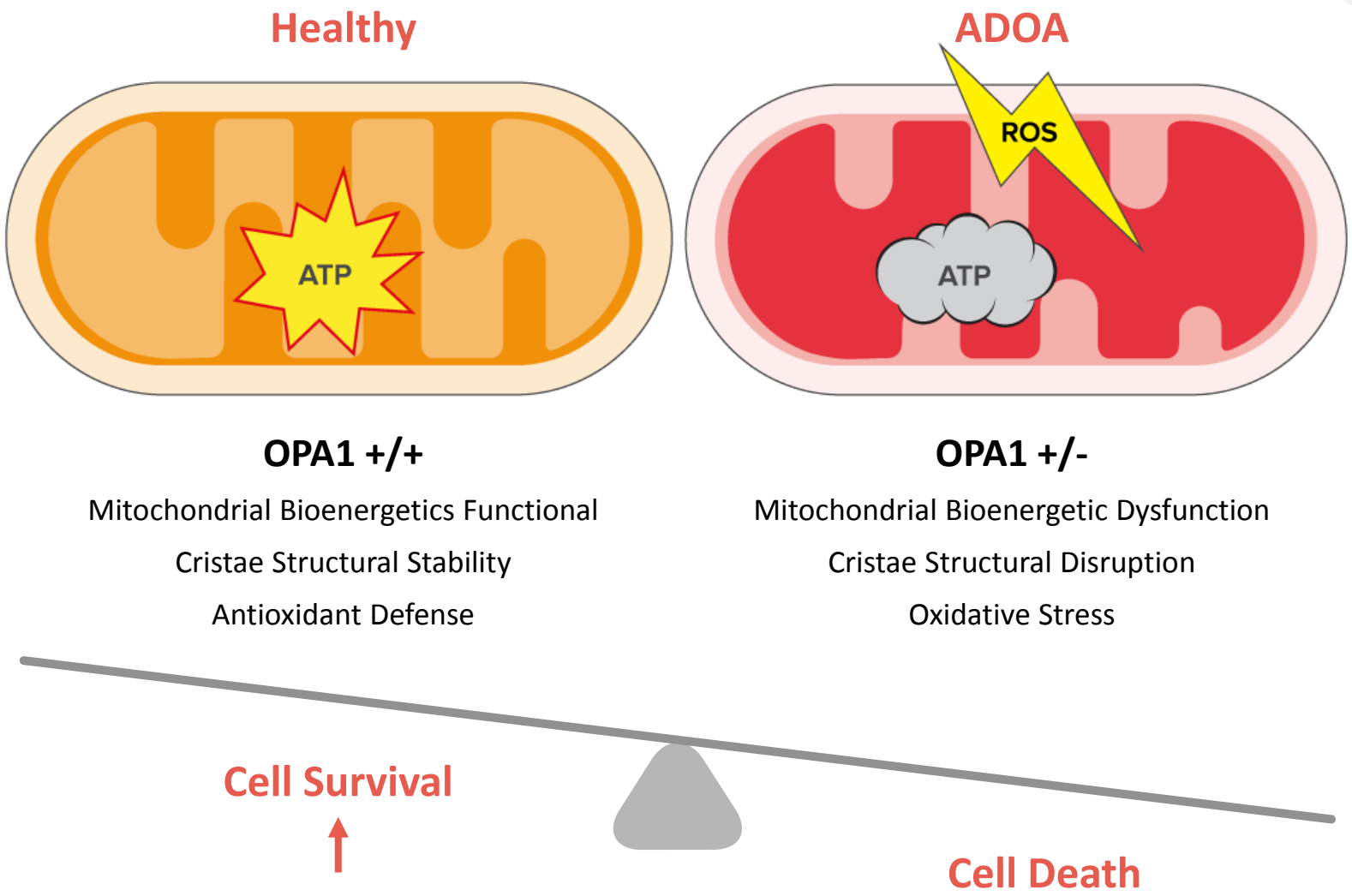




Sources: Yu-Wai-Man P et al. *Ophthalmology*, 2010; Yu-Wai-Man P, Chinnery PF. *Ophthalmology*, 2013;
Lenaers G, Hamel C, Delettre C, et al. *Orphanet J Rare Dis*, 2012; Chun BY and Rizzo JF III. *Curr Opin Ophthalmol,* 2016
Image of child sourced from ICR, Ophthalmology Center Barcelona. Accessed Jan. 8, 2021 from https://icrcat.com/en/eye-conditions/leber-hereditary-optic-neuropathy/ Credit: Lhon Eye Society Sweden. Image shown depicts Leber Hereditary Optic Neuropathy, which presents visual effects similar to ADOA.

# OPA1 is Critical for Normal Mitochondrial Function and Cellular Metabolism

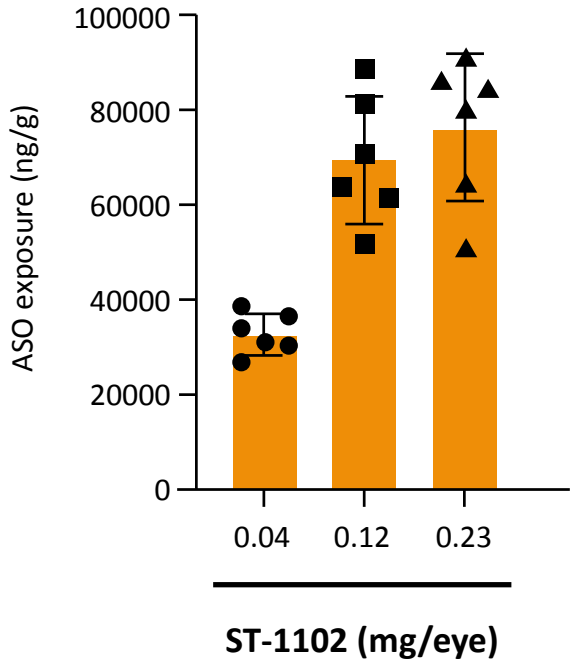
- Retinal ganglion cells have very high energy (ATP) requirements
- Impaired mitochondrial function leads to cell death
- OPA1 is critical for mitochondrial function and energy production



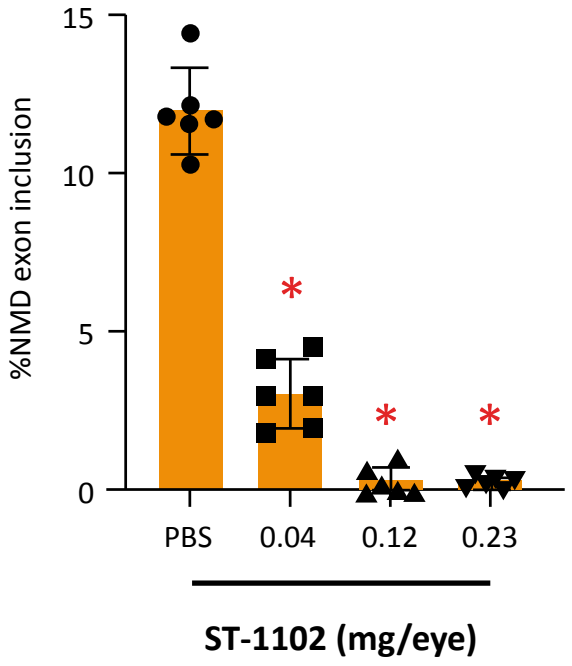

* ROS = Reactive Oxygen Species

# TANGO ASO Demonstrates Dose-Dependent OPA1 Protein Increases in Rabbit Retina

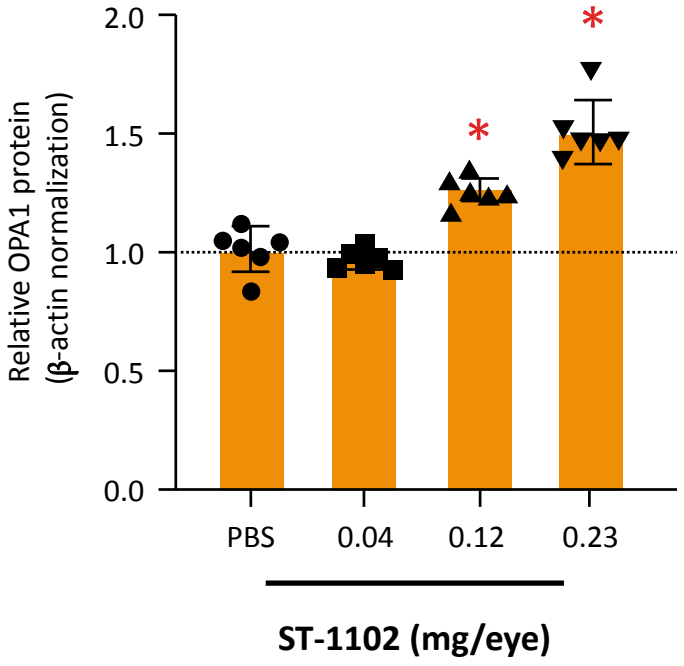
**ASO exposure in retina**
**Day 29**




**Target engagement**
**Day 29**




**OPA1 protein**
**Day 29**

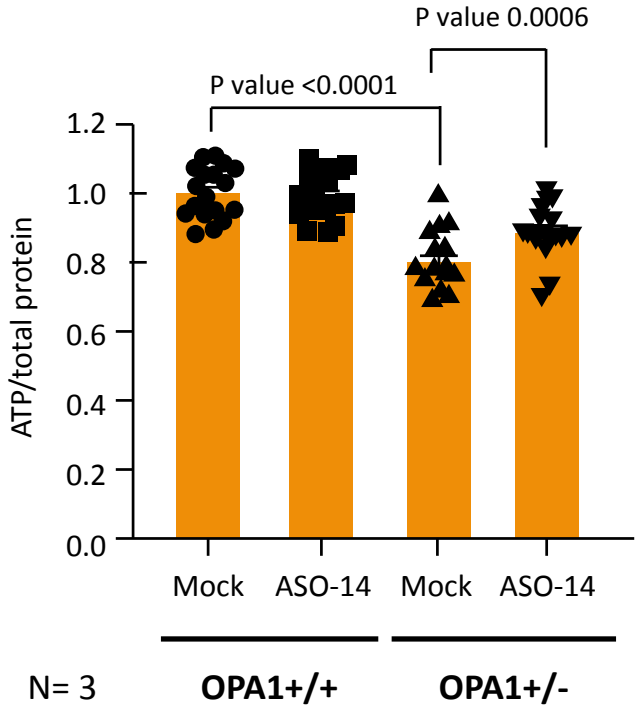



***P*<0.0005 by one-way ANOVA compared to PBS group**

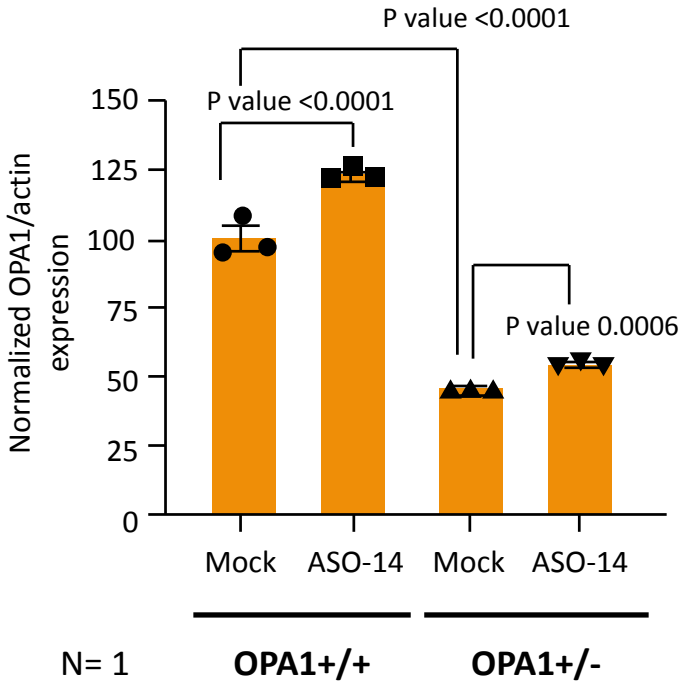
NMD = nonsense mediated decay
Source: TANGO oligonucleotides for the treatment of Dravet Syndrome: Safety, biodistribution and pharmacology in the non-human primate (AES 2019)

# TANGO ASO Partially Restores ATP and Protein Levels in Human OPA1 +/- Cells

**ASO treatment increased ATP levels in OPA1 deficient cells**




**ASO treatment increased OPA1 protein levels**




*one-way ANOVA
# t-test

Source: Stoke data

# TANGO ASOs Have the Potential to Address the Genetic Cause of ADOA

- Dose-dependent increases in OPA1 protein expression in rabbit retina ✓
- Increases ATP and protein levels in human OPA1 +/- cells ✓
- Well tolerated for up to 29 days after intravitreal injection in rabbit ✓

**Lead optimization is underway to potentially identify a clinical candidate in 2021**

# Broad Therapeutic Potential for TANGO

Stoke identified a variety of non-productive alternative-splicing events that lead to mRNA degradation and limit protein production.

**10K+**

Genetic diseases are caused by mutations in a single gene

**5%**

Of these diseases are addressed by current therapeutic approaches

**~1,200**

Monogenic disease genes containing at least one NMD-inducing non-productive event

**~6,500**

Additional unique genes found by Stoke that contained at least one NMD-inducing non-productive event

nature communications

Lim *et al.*, Nat Comm, 2020

# 2021 Milestones

| | |
|---|---|
| **1H2021** | Initiate Swallowtail Open Label Extension (OLE) study of STK-001 |
| **2H2021** | Initiate multiple ascending dose (MAD) study of STK-001 |
| **2H2021** | Preliminary safety and PK data from Phase 1/2a MONARCH study of STK-001 |
| **2H2021** | Initiate ADOA natural history data collection |
| **YE2021** | Complete lead optimization for OPA1 compounds |
| **YE2021** | Demonstrate *in vivo* proof of mechanism and safety for a third program |

# Current Financials Anticipated to Fund Operations into 2024

**$287.6M**

**Cash, Cash Equivalents & Restricted Cash**

*as of 12/31/2020*

**36.6M**

**Common Shares Outstanding**

*as of 12/31/2020*

# We Are Stoke

United in our mission to address the underlying cause of severe diseases by up-regulating protein expression with RNA-based medicines.