Epilepsy Therapeutics for Genetic Epilepsies

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Therapies for Genetic Epilepsies

1: Need to diagnose a genetic epilepsy

- Some children underwent testing in past, Consider reanalysis or WES if panel was negative
- Adults with intellectual developmental disabilities often go undiagnosed

2: First do not harm

- Avoid Na-channel blockers if ? Dravet syndrome

3: Consider targeted anti-seizure medications (ASMs) or other medications

Precision Epilepsy Therapies: Conventional Therapies

- Ketogenic diet - GLUT 1 Deficiency (SLC2A1 gene)
- Sodium Channel blockers – SCN2A, SCN8A & KCNQ2
- Pyridoxine - ALDH7A1 (pyridoxine-dependent epilepsy)
- Pyridoxal 5’-phosphate – PNPO (pyridoxal 5’-phosphate-dependent epilepsy)
- MTOR Inhibitors (everloimus) in mTORopathies (TSC1 & TSC2)
  - ? GATOR 1 complex genes that downregulate mTOR (DEPDC5, NPRL2, NPRL3)
- Dravet syndrome (SCN1A) - fenfluramine, stiripentol, CBD

Approved Genetic Therapies

A ***In vivo*** **Gene Therapy Drugs**

Gendicine (Tp53)

Neovasculgen (VEGF)

Glybera (LPL^{S447X} gene)

Luxturna (hRPE65 gene)

Vitravene (ASO-CMV retinitis)

Spinraza (ASO-SMN2 pre-mRNA)

Onpattro (RNAi-transthyretin gene)

Kynamro (ASO - Apo lipoprotein B-100)

Imlygic (HSV-1oncolytic virus GM-CSF gene)

Eteplirsen (Morpholino Oligomer-Exon51 DMD)

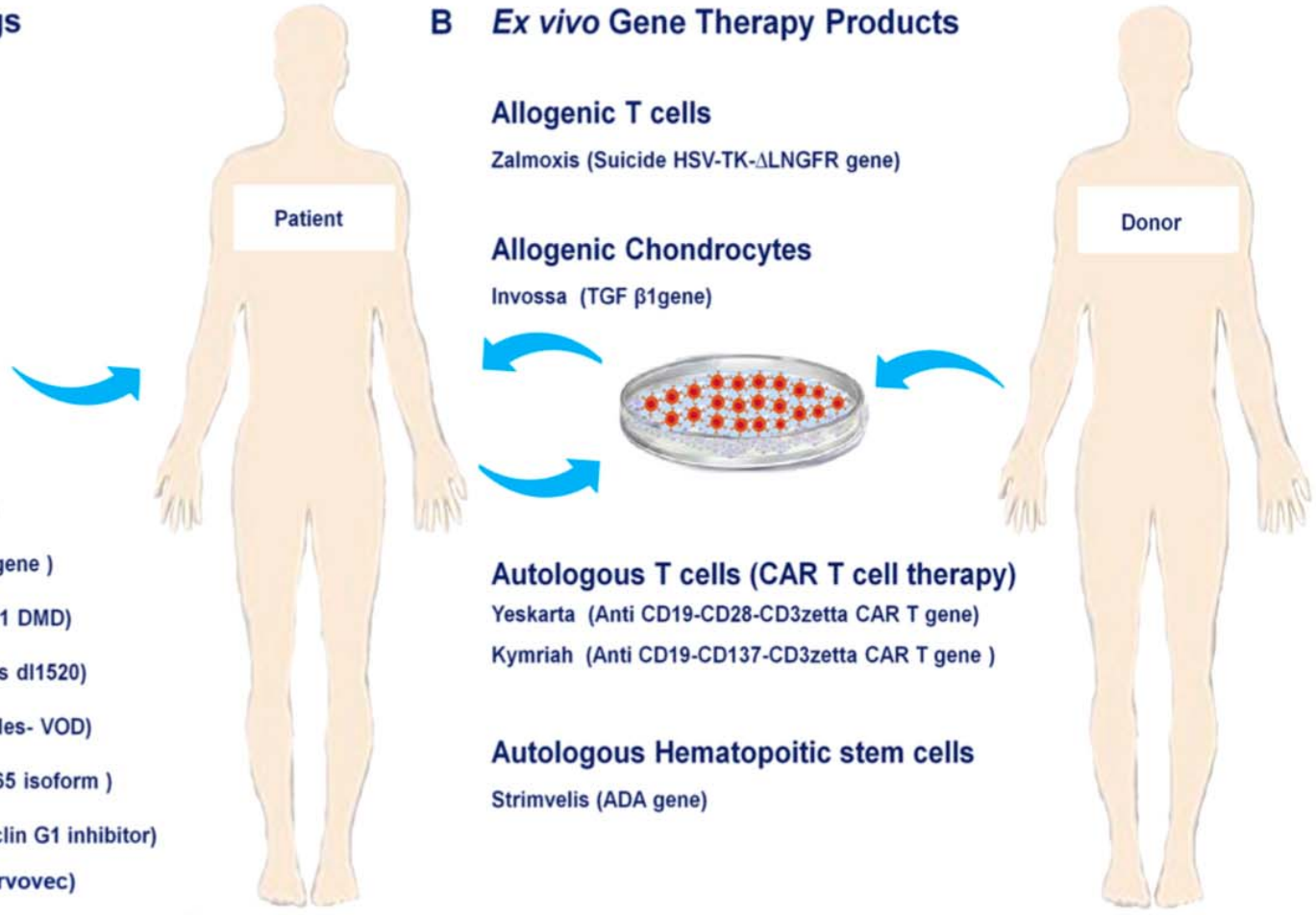
Oncorine (E1B 55kDa mutant adenovirus dl1520)

Defitelio (single-stranded oligonucleotides- VOD)

Macugen (RNA oligonucleotide- VEGF165 isoform)

Rexin-G (Retroviral vector encoding cyclin G1 inhibitor)

Zolgensma (Onasemnogene Abeparvovec)



B ***Ex vivo*** **Gene Therapy Products**

Allogenic T cells

Zalmoxis (Suicide HSV-TK-ΔLNGFR gene)

Allogenic Chondrocytes

Invossa (TGF β1gene)

Autologous T cells (CAR T cell therapy)

Yeskarta (Anti CD19-CD28-CD3zetta CAR T gene)

Kymriah (Anti CD19-CD137-CD3zetta CAR T gene)

Autologous Hematopoitic stem cells

Strimvelis (ADA gene)

Shahryari Frontiers in Genetics, 2019

NeuroGenetic Therapies in Trial

Product	Developer	Structure/MOA	Indication/Target
Lenti-D	Bluebird Bio	*Ex vivo:* CD34+ SCs via lentiviral vector with ABCD1 gene	Cerebral adrenoleukodystrophy (CALD), ABCD1 gene
NSR-REP1 (AAV2-hCHM)	Spark Rx's Nightstar Rx	*Ex vivo:* CD34+ SCs via lentiviral vector: ABCD1 AAV2 vector REP1 into eye	Retinal Gene Rx for choroideremia
Vocimagene amiretrorepvec	Tocagen, ApolloBio	Toca 511 retroviral vector expressing cytosine deaminase. Toca FC prodrug of 5-fluorouracil	Glioblastoma Multiforme And Anaplastic Astrocytoma

Shahryari Frontiers in Genetics, 2019

Genetic Epilepsy Therapies: Challenges

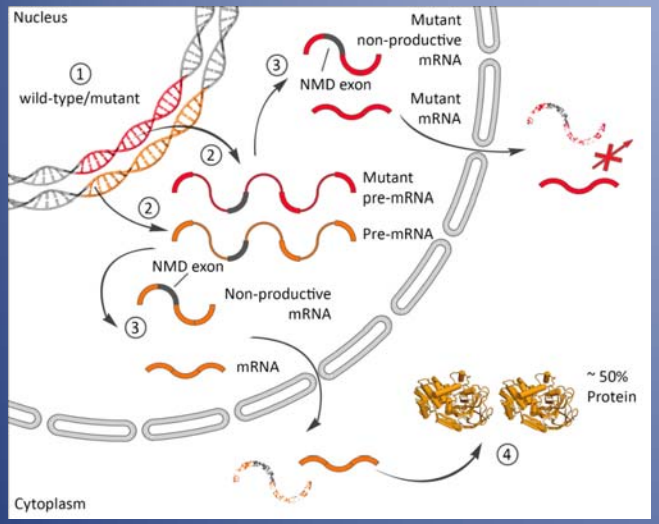
- Blood-brain barrier
- Size of genes to package in viral/other vector
- Immune response to vector
- Dosing – too little or too much?
- Off target effects on other genes or noncoding elements
- Duration of efficacy
- Counter-regulatory effects on gene networks

Types of Potential Gene Therapies for Epilepsy

- Small molecules to read through premature stop codons (~15-20% of haploinsufficiencies)
- Antisense oligonucleotides
- Regulatory elements
- CRISPR gene editing – can correct missense and frameshifts
- tRNAs to read through or optimize codons

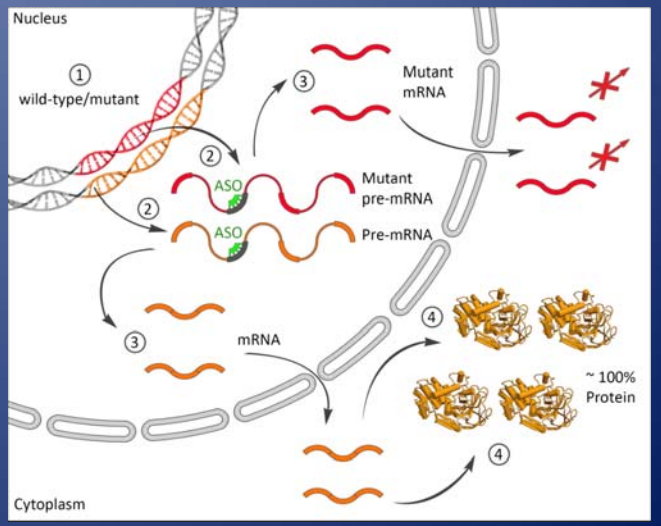
STOKE
THERAPEUTICS

TANGO: Targeted Augmentation of Nuclear Gene Output (Stoke's proprietary technology platform)



- RNA-based genetic medicine platform for protein upregulation
- Stoke's antisense oligonucleotides (ASOs) bind to specific stretches of pre-MRNA to reduce non-productive mRNA and increase productive mRNA, resulting in increased protein production

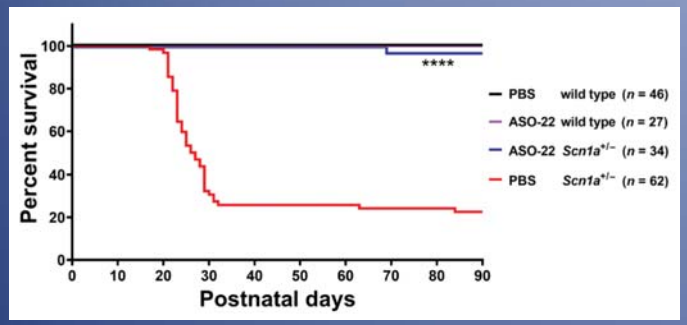
- For haploinsufficiencies, TANGO restores the protein to near normal levels

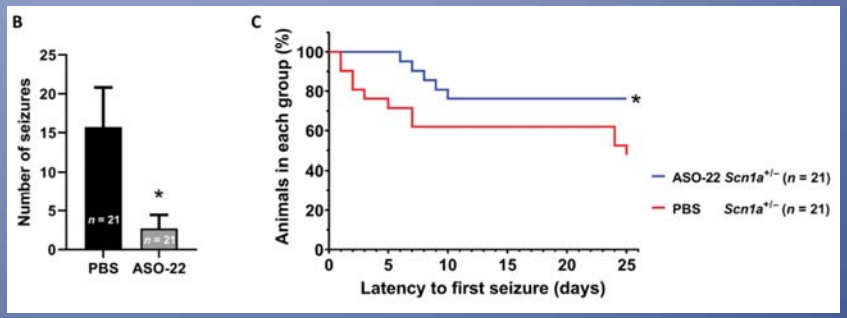


ASOs increase SCN1A expression and reduce seizures and SUDEP in Dravet Syndrome mice

A single ICV injection of 20 µg of ASO-22 at postnatal day 2 resulted in:

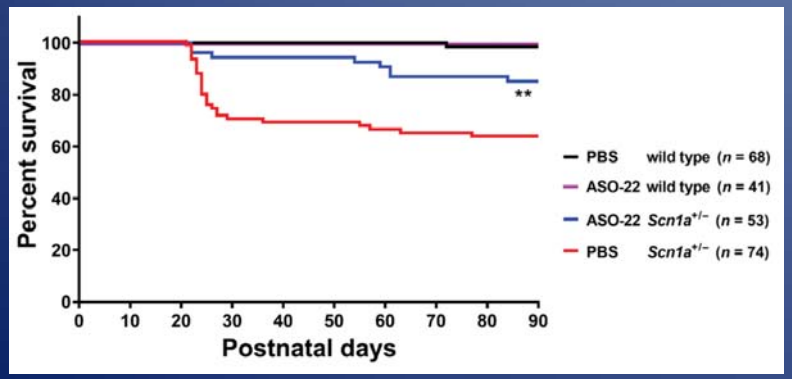
- ✓ reduced SUDEP incidence
- ✓ reduced seizures
- ✓ prolonged latency to first seizure





A single ICV injection of 60 µg of ASO-22 at postnatal day 14 resulted in:

- ✓ reduced SUDEP incidence



Han Science Translational Medicine, 2020

The BUTTERFLY Study

- Ongoing, two-year observational study of children and adolescents ages 2-18
- Aiming to enroll 36 participants
- Designed to collect information on:
  - Seizure frequency
  - Intellectual disabilities
  - Motor impairment
  - Speech impairment
  - Behavioral problems
  - Sleep abnormalities

BUTTERFLY
An observational study of Dravet syndrome patients

MONARCH Study

- An Open-Label Study to Investigate the Safety and Pharmacokinetics of Single Ascending Doses of Antisense Oligonucleotide STK-001 in Children and Adolescents with Dravet Syndrome (Protocol: STK-001-DS-101)

- Phase 1/2a
- Plan to enroll up to 48 patients at ~20 U.S. sites, with first patient dosed August 2020
- Duration of study for each patient is 7-9 months total

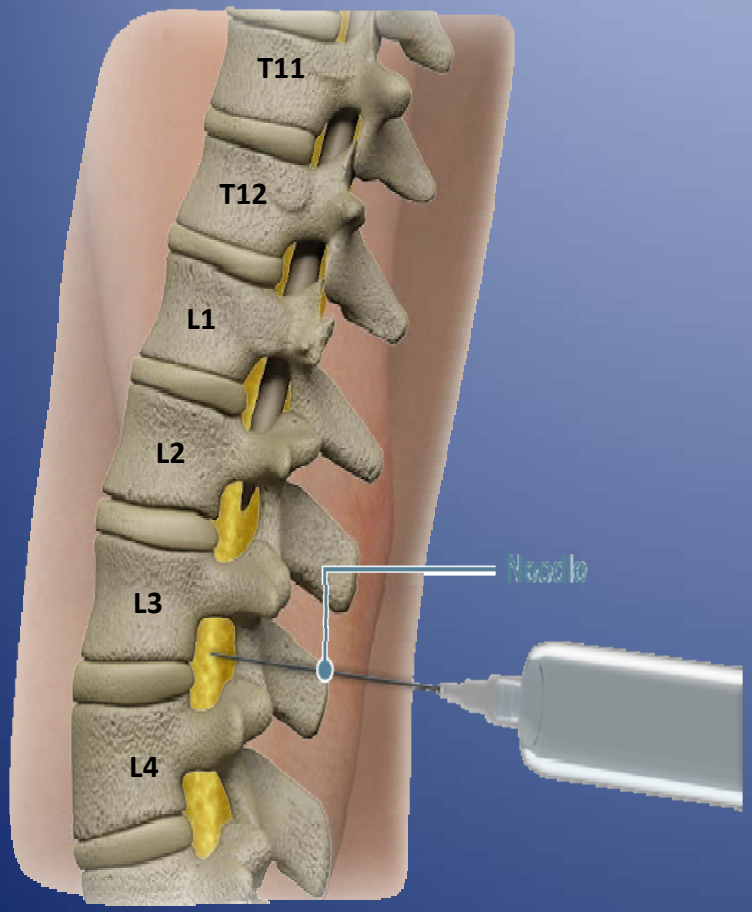
- Primary endpoints: safety and tolerability of a single-ascending dose, characterize human pharmacokinetics
- Secondary endpoints: change in seizure frequency over 12- weeks, quality of life

- Preliminary data expected in 2021

Key Inclusion/Exclusion Criteria

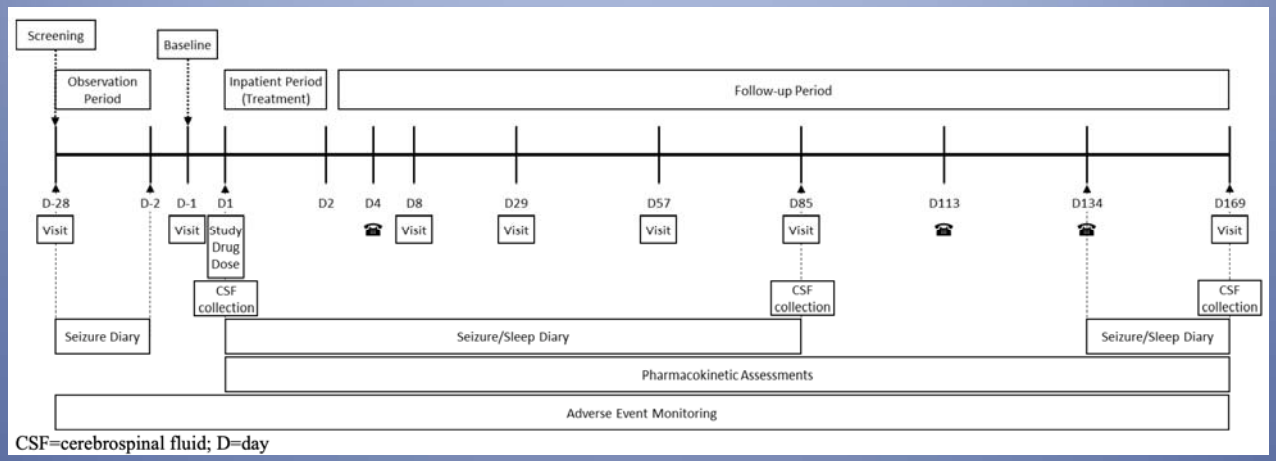
- 2 to 18 years
- Dravet syndrome clinical features and SCN1A variant
- MRI - unremarkable
- Failed ≥2 AEDs
- Currently on ≥1 AED at stable
- ≥ 4 convulsive seizures 28 day Observations Period.

STK-001 – Investigational Product

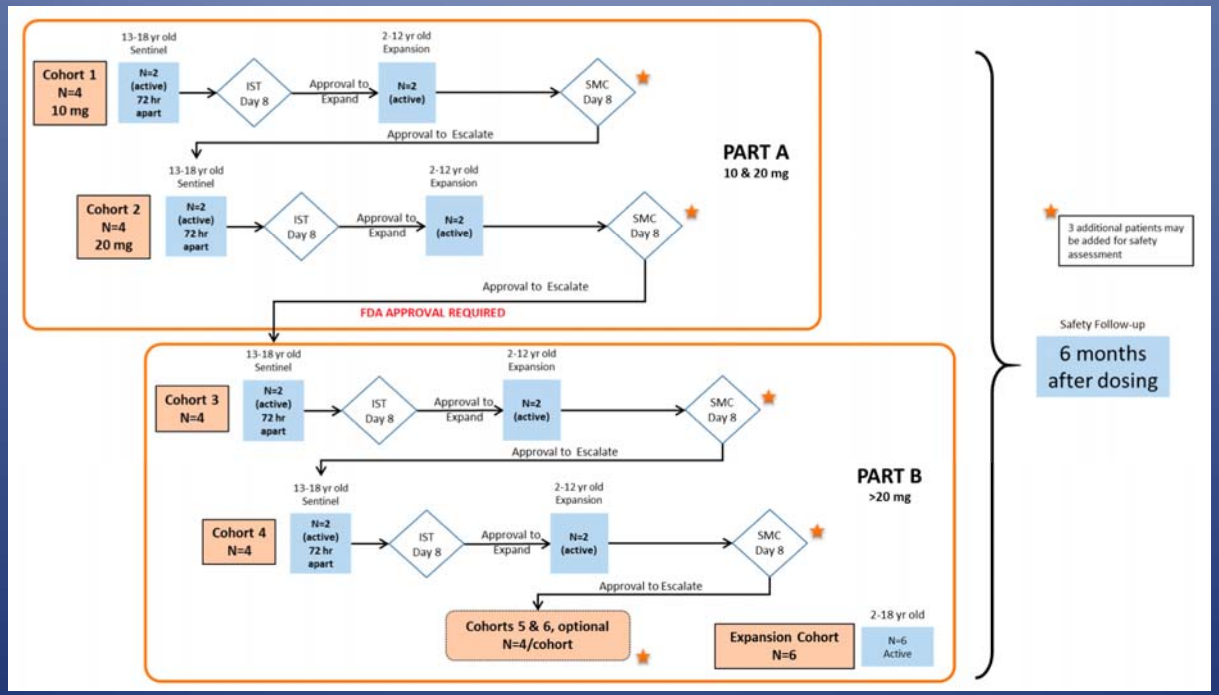


- STK-001 ID is a sterile, isotonic, phosphate-buffered (pH 6.6 – 7.6) solution (at 33 mg/mL in one use vials) intended for dilution with artificial cerebral spinal fluid (aCSF) solution followed by intrathecal administration.
- Clear, colorless liquid
- Diluted STK-001 administered IT as a 1-3 minute bolus
- Effects last 4-6 months

Study Design



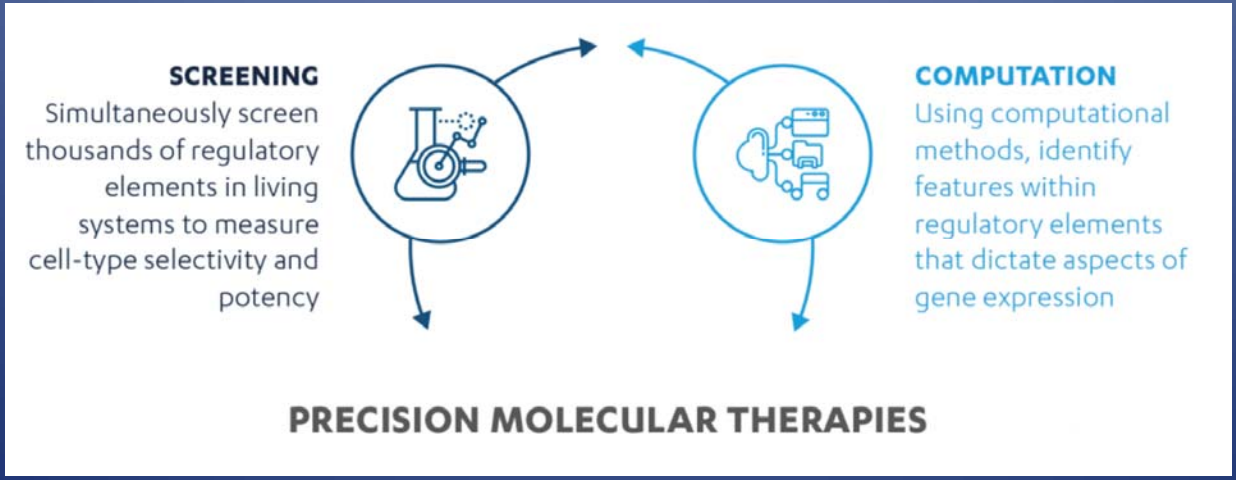
CSF=cerebrospinal fluid; D=day



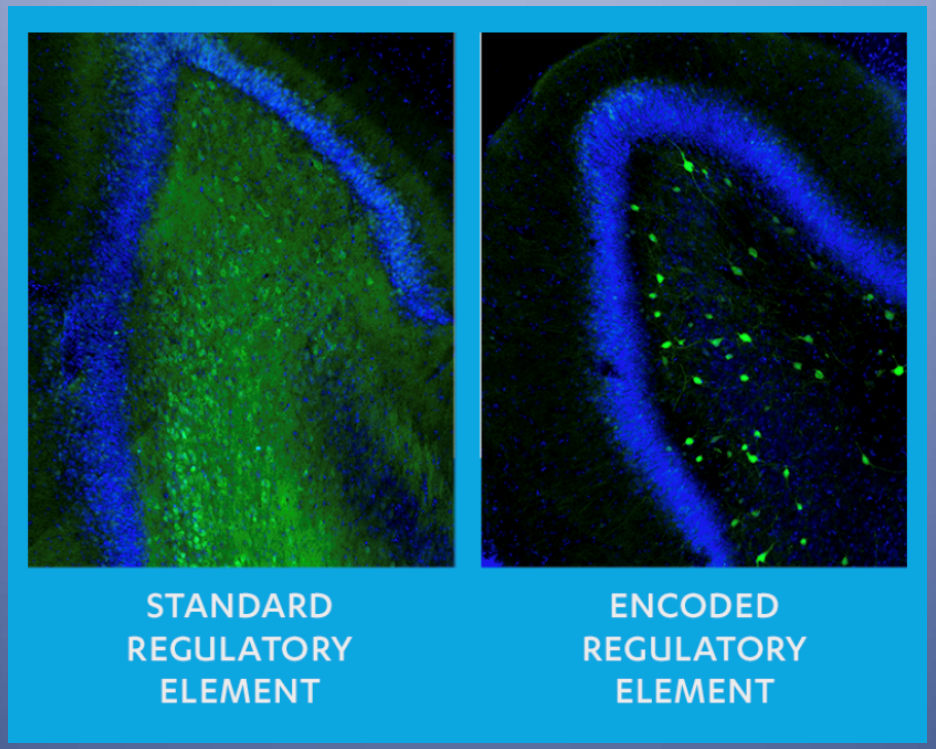
Encoded THERAPEUTICS

Regulatory Elements

- Encoded - characterized millions of regulatory elements: DNA sequences controlling gene expression
- Encoded platform identifies & optimizes REs
- Potent & selective gene therapies
- Adeno-associated (AAV) vectors – lasts over 10 years in non-dividing cells with a 4.5 kb capacity

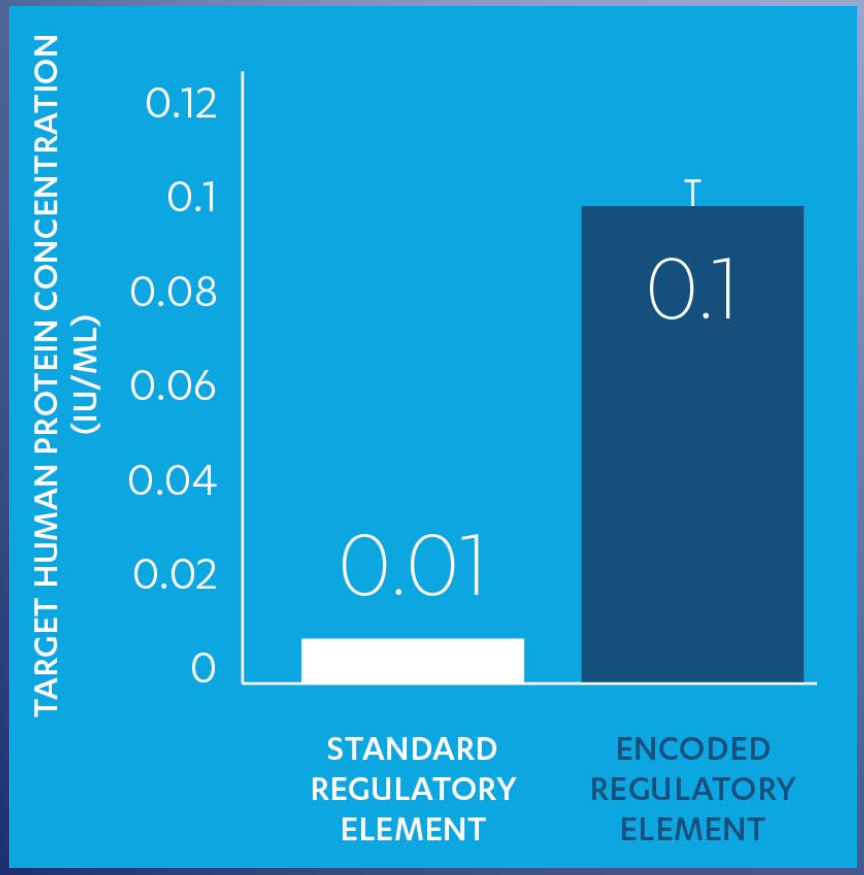


Cell-Type Selectivity



Cell-type selective regulatory elements for precise expression, resulting in efficacy and improved safety

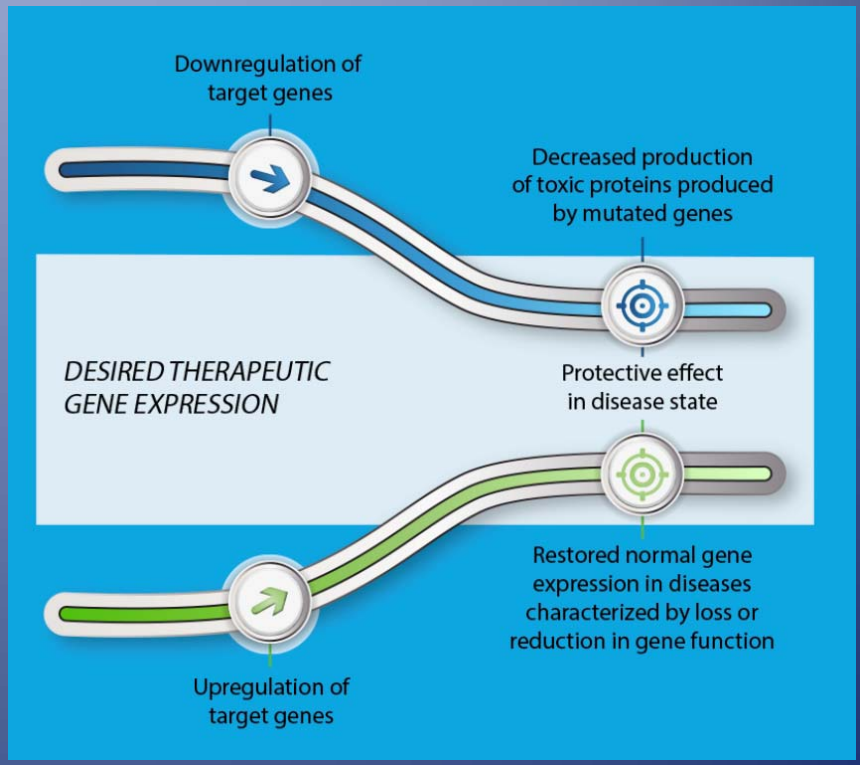
Potency

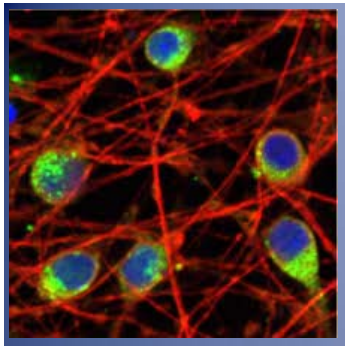


Encoded REs drive robust gene expression to increase viral gene therapy potency, creating opportunities to treat disorders that require high levels of therapeutic gene expression.

Endogenous Gene Control

Ability to upregulate or downregulate endogenous genes using clinically-validated viral delivery systems.





Pre-Clinical Data

- ICV AAV9 vector expressed only in GABAergic interneurons.
- AAV-ETX engineered transcription factor: potently & specifically up-regulates SCN1A upstream of the gene.
  - Selective up-regulation of SCN1A in human iPSC-derived GABA neurons, mouse & NHP CNS
  - Infuse P1 SCN1A +/- mice → ↑ SCN1A mRNA & Nav1.1 expression widely in hippocampal and cortex,
  - SCN1A +/- mice ↓ hyperthermic seizures & ↓ frequency & severity of spontaneous seizures
- Develop single Rx disease-modifying therapy: restore Nav 1.1 function in GABA neurons and ↓ Dravet symptoms

Natural History Study

- Natural History Study of Infants/Children with SCN1A Dravet Syndrome
- Two-year, observational study for children 6 - 60 months with SCN1A mutations 15 sites worldwide

- Rationale: further define seizure, neurodevelopmental, and behavioral features; explore disease impact on parents/caregivers

- Data will serve as external control to a clinical trial examining investigational gene therapy to improve the seizure burden and neurodevelopmental outcomes Subjects enrolled in this study may be rolled over into the future interventional study of a gene therapy investigational drug

- Phase 1/2 clinical trial to start in H1 2021