Challenges in Getting Genome Editing Medicines into the Clinic

Phillip Ramsey

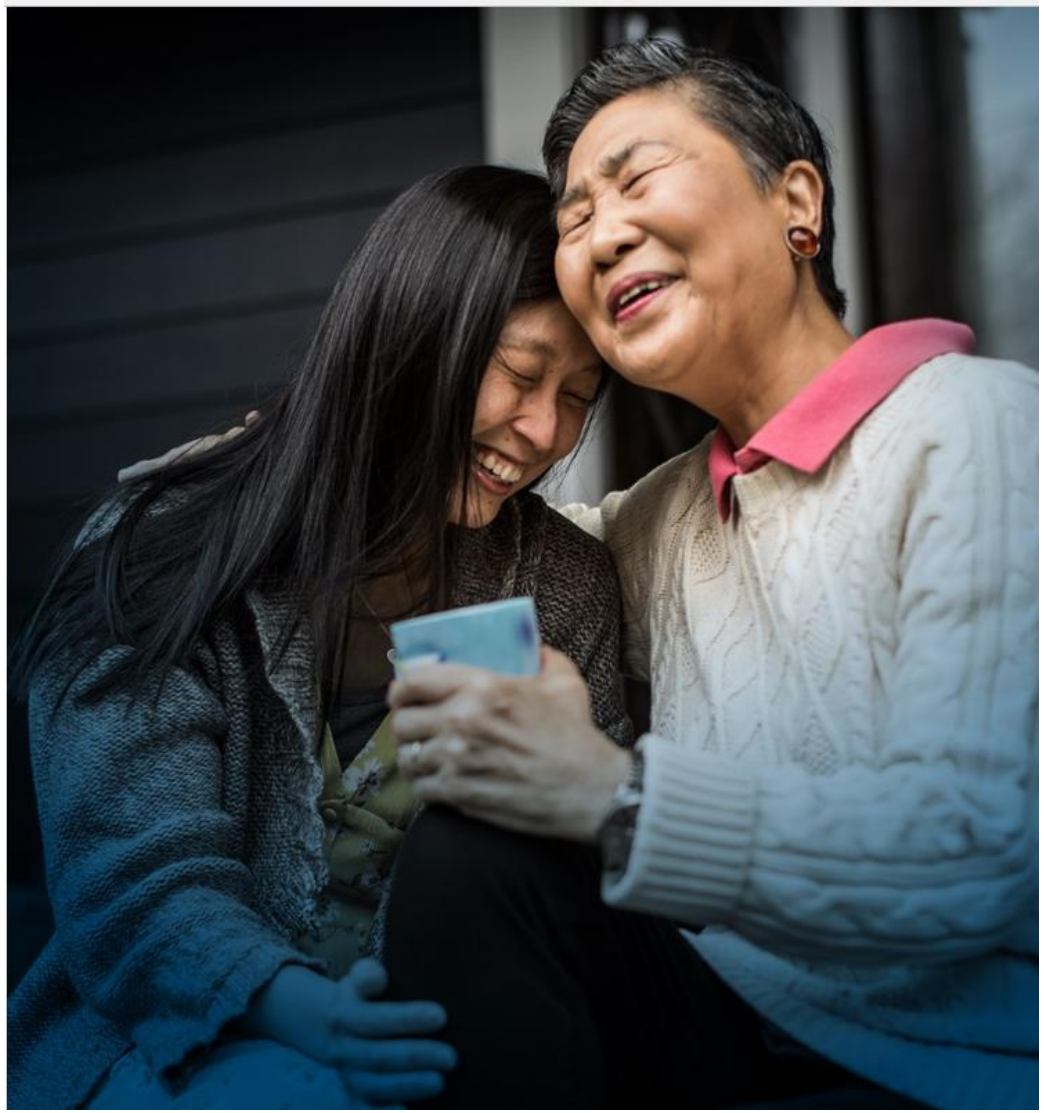
Sangamo Therapeutics Inc.

2025 CASSS CGTP June 10, 2025

Outline

- Overview of Sangamo
- Challenges in Moving Genome/Epigenetic Editing Tools into the Clinic
- Design Challenges: Case Study with Next Generation Gene Editing Tools
- Delivering Genome Editing Components: Case Study with Novel AAV Capsid Design
- How these First Two Challenges are Critical to Solving the Following Challenges:
  - Manufacturability
  - Safety
  - Regulatory Issues

Sangamo Overview



Sangamo is a differentiated genomic medicine company focused on treating debilitating neurological diseases

Sangamo THERAPEUTICS

Potent zinc finger epigenetic regulation technology, with neurology programs advancing towards the clinic

Industry-leading AAV capsid discovery platform has demonstrated non-invasive intrathecal and intravenous delivery to the brain

Powerful research platform **continually innovates in new modes of genome modulation** to support value creation opportunities for both wholly owned programs and potential partners

SHARP STRATEGIC FOCUS IN NEUROLOGY

Strong roster of current partners and a **clear regulatory pathway to Accelerated Approval agreed with U.S. FDA in Fabry disease, with partner negotiations ongoing**

OPTIMIZING ASSET VALUE

Company pipeline and business development opportunities

NEUROLOGY PIPELINE – WHOLLY OWNED

Indication	Preclinical	Phase 1/2	Pivotal	Partner	Commentary
Idiopathic Small Fiber Neuropathy *(ST-503)*				-	IND cleared, patient enrollment and dosing planned mid-2025.
Prion Disease				-	CTA submission anticipated in Q1 2026
Undisclosed neurology target(s)				-	

NEUROLOGY PIPELINE – PARTNERED

Partnered Indication	Preclinical	Phase 1/2	Pivotal	Partner	Commentary
Tauopathies				Genentech	**August 2024:** Announced epigenetic regulation and capsid delivery license agreement
Undisclosed neurology target				Genentech	
Undisclosed neurology target				astellas	**December 2024:** Announced capsid license agreement for up to five neurological diseases
Undisclosed CNS target				Lilly	**April 2025:** Announced capsid license agreement for up to five diseases of the CNS
ALS/FTD				Alexion	
Huntington's Disease				Takeda	

OTHER PROGRAMS

Indication	Preclinical	Phase 1/2	Pivotal	Partner	Commentary
Hemophilia A (Giroctogene fitelparvovec)				*	**July 2024:** Positive readout in Phase 3 AFFINE trial.
Fabry Disease (Isaralgagene civaparvovec)				-	BLA submission expected as early as 1Q 2026.

Sangamo THERAPEUTICS

Cargo Capsid

** Pfizer and Sangamo continue to work together to manage the transition of the collaboration which terminated on April 21, 2025*
IND: investigational new drug; CTA: clinical trial authorisation; CNS: central nervous system; BLA: biologics license application
Wholly owned programs subject to our ability to secure adequate additional funding

Why neurology genomic medicines?

- Widespread, debilitating diseases, largely unserved by current approaches
- Many neurology indications are single-gene or gene-associated
- Genomic medicines are well suited to neurology:
  - Targeting diseases at the DNA level reduces therapeutic complexity
  - Gene expression can be fine-tuned to the level needed for proper brain function
  - Potential for durable effect as most brain cells do not divide
- Addressing the issues of widespread brain delivery is critical to creating an effective neurology medicine

Sangamo THERAPEUTICS

Challenges

- Design
- Delivery
- Manufacturing
- Safety
- Regulatory

Sangamo THERAPEUTICS

Design

Design

Delivery

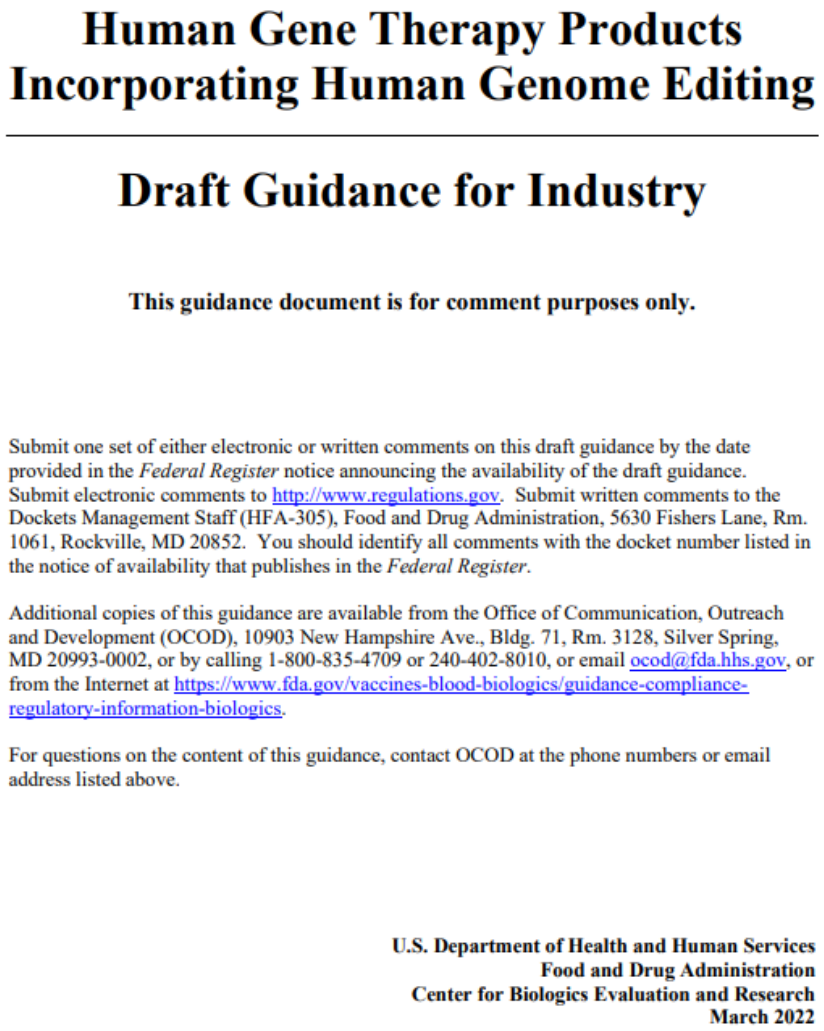
Manufacturing

Safety

Regulatory

FDA Guidance for Development of Human Gene Therapy Products Incorporating Genome Editing

- Key considerations:
  - While the potential benefit of genome editing (GE) products are clear, the potential risks are not as well understood
  - Some of the risks specific to GE products include unintended consequences of on- and off-target editing, and unknown long-term effects of on- and off-target editing
  - Recommendations are made for how to assess these potential risks as well as safety and quality



Human Gene Therapy Products Incorporating Human Genome Editing

Draft Guidance for Industry

This guidance document is for comment purposes only.

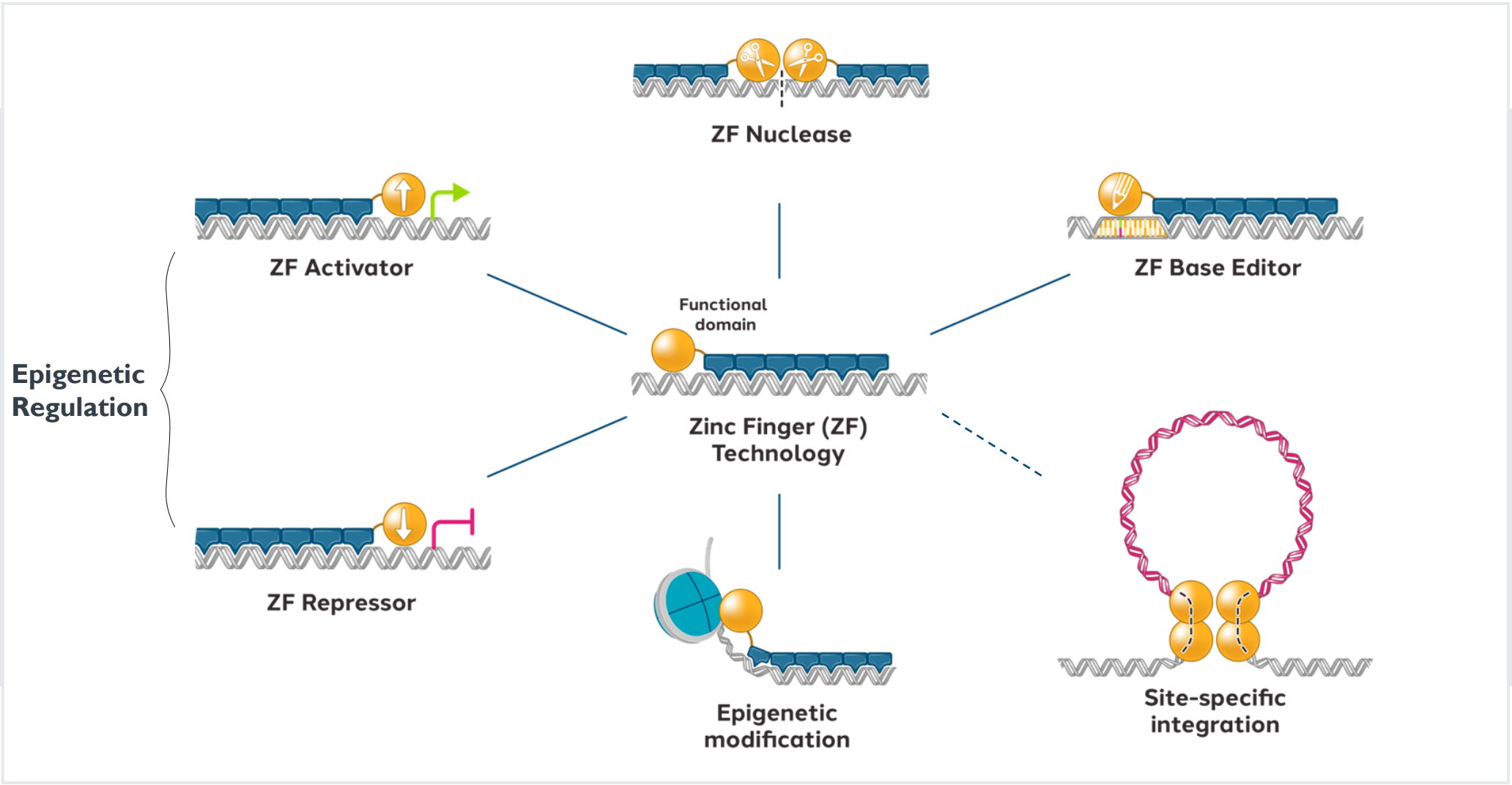
Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
March 2022

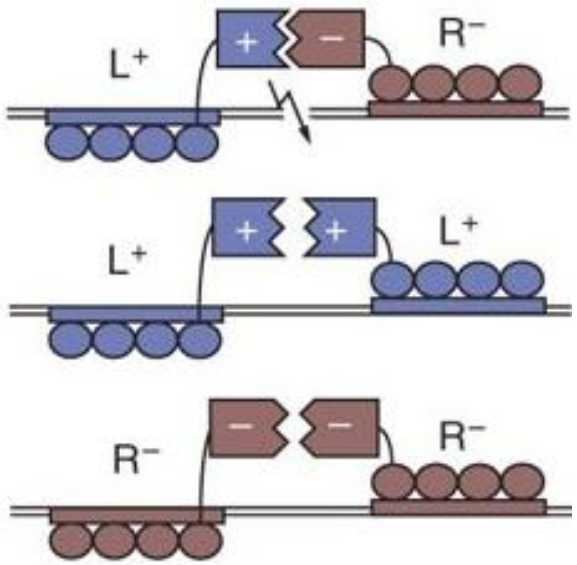
Sangamo's differentiated genomic engineering platform is flexible, creating specific tools for the needs of each target



Avoiding Off-Targets by Good Design Practices

Molecular safeguards - the FokI (+/-) heterodimer of Sangamo ZFNs

ZFNs



Miller, J.C., et al. *Nature Biotechnology* 25.7 (2007): 778-785.

Thoughtful molecular design of nucleases can universally minimize off-target activity

K. Meyer Applied Pharmaceutical Toxicology 2022

Nuclease-mediated genome engineering has limitations

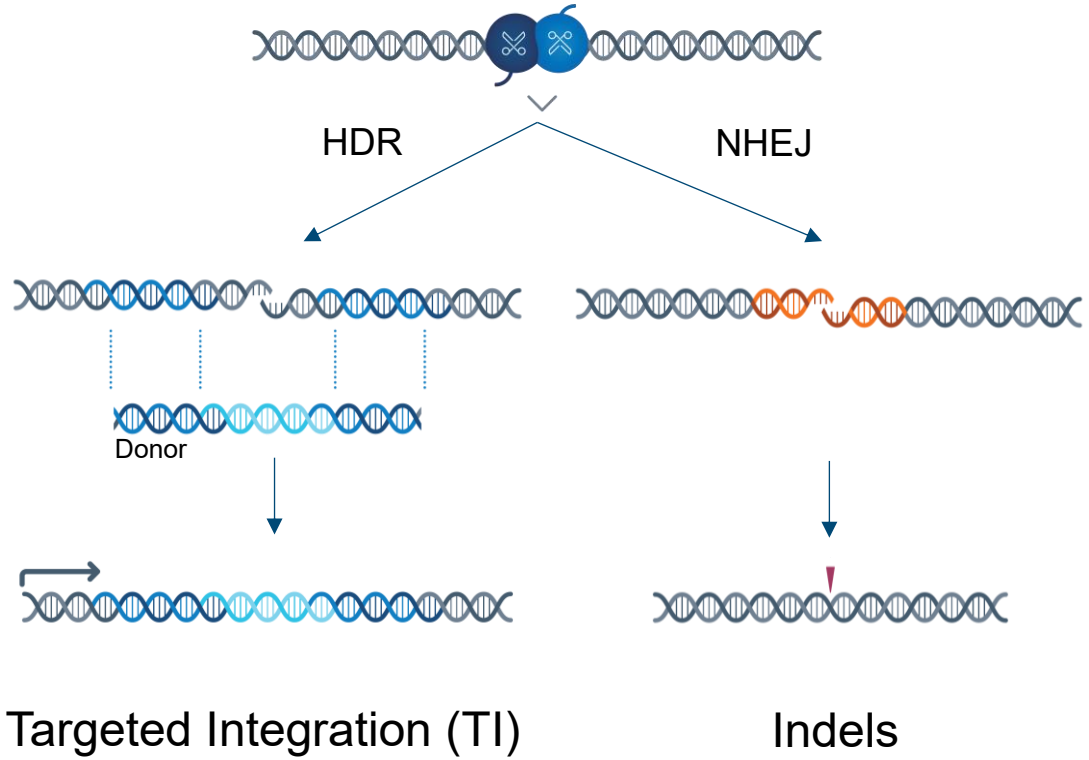
- ZFNs are very precise, efficient and specific but we have little control over what happens after they induce a DNA double-strand break (DSB)

- **Limitation #1: Nuclease applications depend on the DNA repair machinery of the host cells**

  → Multiple possible outcomes: NHEJ vs. HDR
  → Does the target cell type prefer NHEJ or HDR?

  - NHEJ → Indels: knock-out = loss-of-function
    - e.g. B2M and CIITA

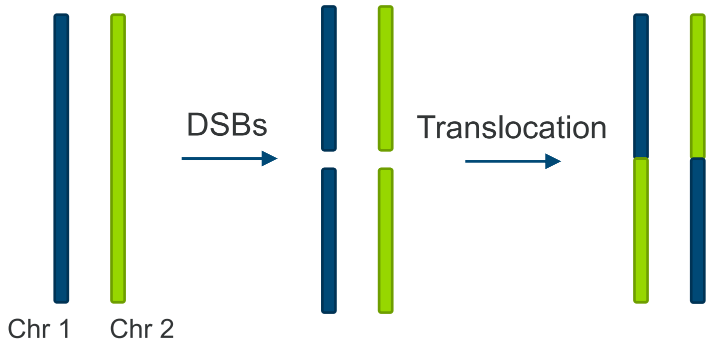
  - HDR → TI: knock-in = gain-of-function
    - e.g. CAR



NHEJ: Non-Homologous End Joining
HDR: Homology Directed Repair

Nuclease-mediated genome engineering has limitations

- **Limitation #2: (Multiplexed) nuclease applications can cause translocations between …**
  - On-target and off-targets
  - Off-target and off-targets
  - On-target or off-targets and natural occurring DSBs
  - On-target #1 and on-target #2 (multiplexing)



- **Limitation #3: Nucleases cannot correct all genetic mutations …**
  - Remove a disease-causing duplication event (e.g. CMT1A, Charcot-Marie-Tooth disease)
  - Reverse a disease-causing inversion event (e.g. Factor VIII, Hemophilia A)

- **Limitation #4: Nuclease-mediated KO results in low product purity**
  - NHEJ results in Indels of different lengths
  - A 3-bp Indel might not result in a knock-out phenotype
  - A very long deletion might also impact expression of neighboring genes

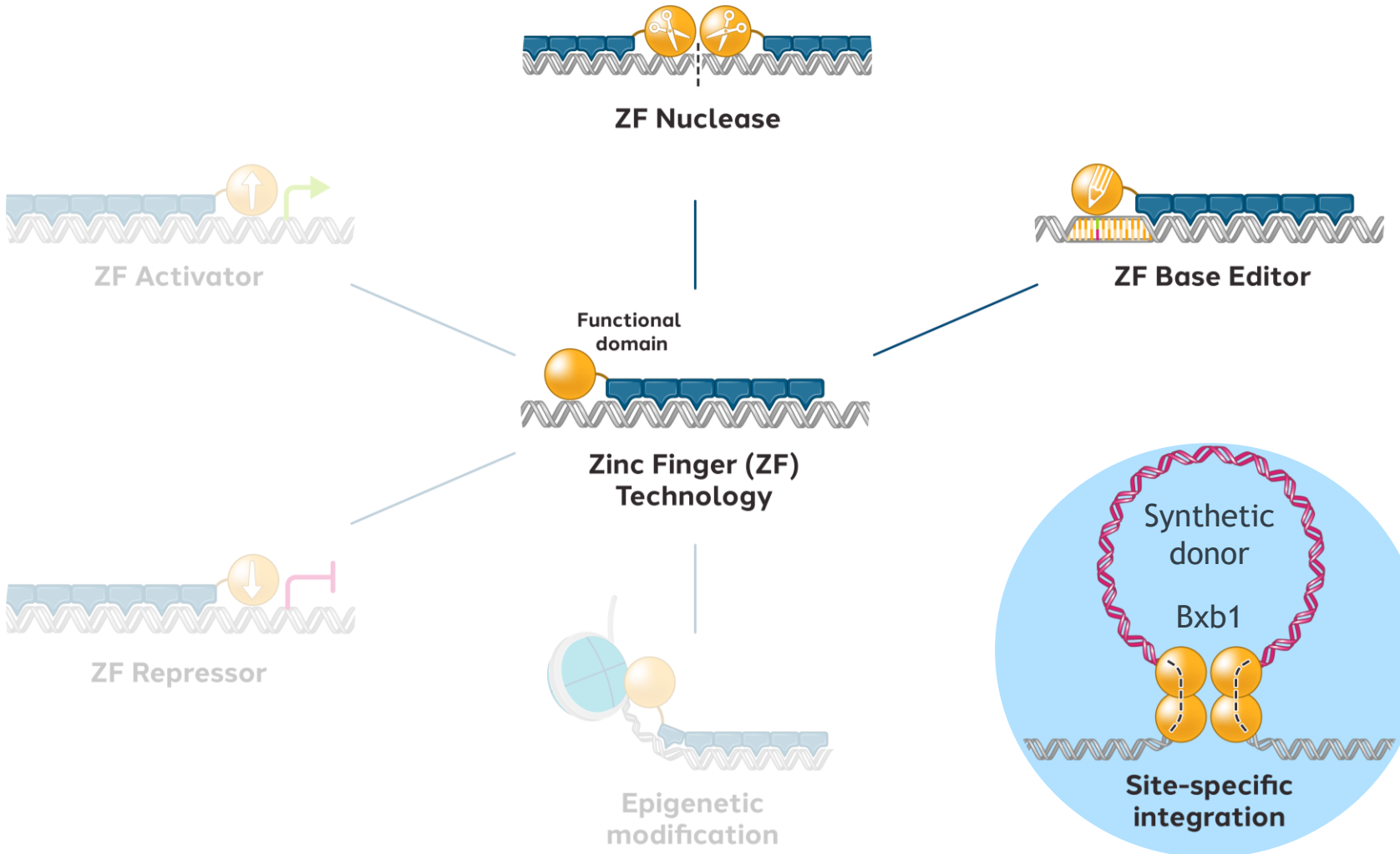
"Indel Christmas tree"

Comparison of Targeted Integration Platforms

Platform	Components	Challenge
CRISPR-associated transposases	CRISPR transposase and multiple bacterial co-factors + donor gene	Delivery of numerous components (including at least one that is toxic)
ZF/TALE/CRISPR-targeted recombinases or transposase	e.g. ZF/TALE/CRISPR-PiggyBac fusion + donor gene	No relevant platform revealed yet
Prime Editing + Serine Integrase	Prime Editor, two pegRNAs, cis or trans Serine Integrase + donor gene	Multistep process requiring delivery of many components, and editing outcome also depends on DNA repair pathways in target cell
Programmable Tyrosine Recombinase	Programmable recombinase + donor gene	Reversible, better suited for inversions/deletions, requires many rounds of evolution
Programmable Serine Integrase (Sangamo's MINT platform)	**Programmable integrase + donor gene**	**No one has demonstrated this yet**

Case Study: Advancing Next-Generation Genome Engineering

Sangamo's (Genome Editing) Technology Platforms

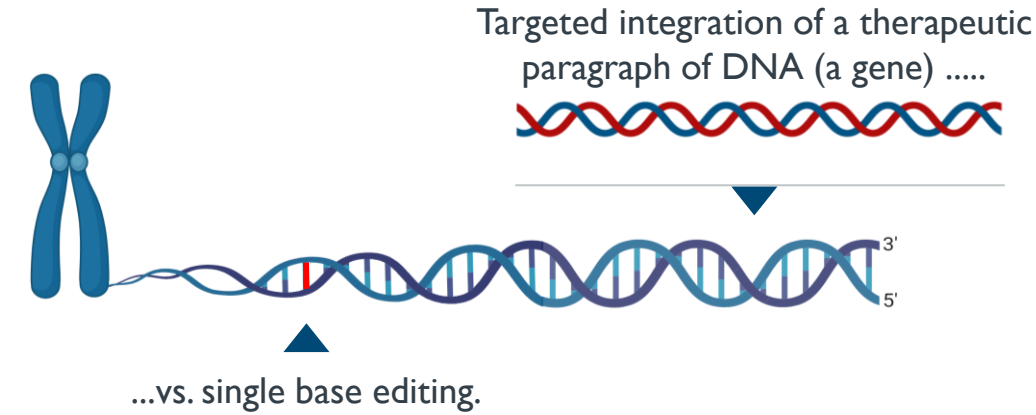


Modular Integrase (MINT) Platform

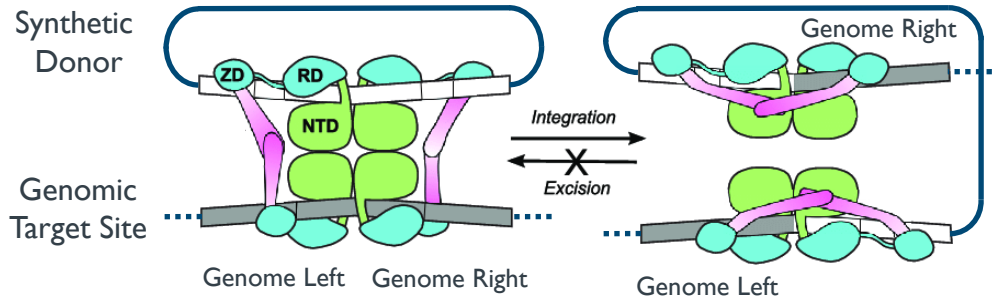
What is an integrase and why is it important?

Targeted integration enables large-scale genome editing

- Capable of delivering large payloads - 10 kb+
- No copying required - low error rate
- Self sufficient - no dependence on cell DNA repair machinery
- No DNA breaks - reduced translocation risk



Bxb1 Integration Mechanism

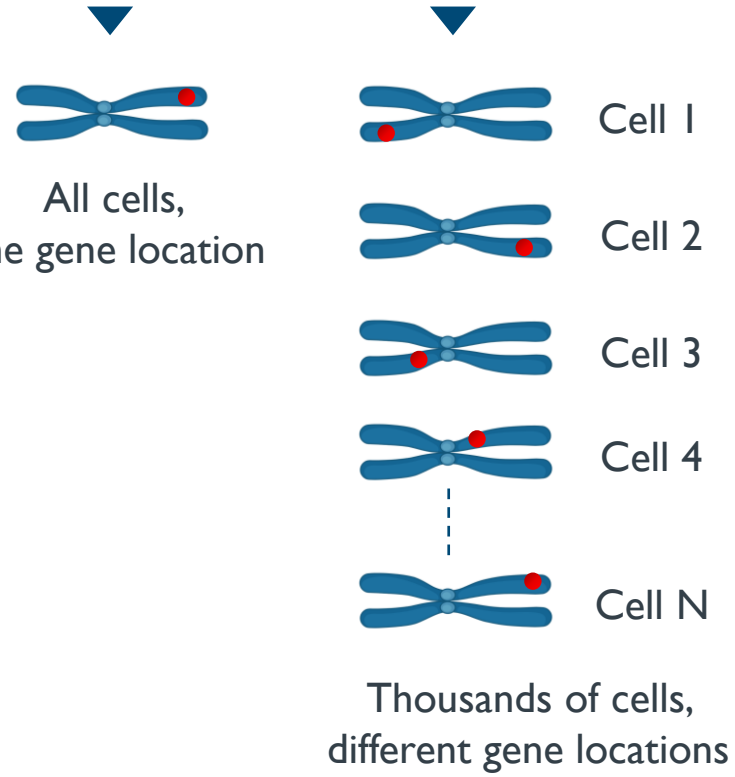


Adapted from Gupta et al., NAR (2017)
doi: 10.1093/nar/gkx474

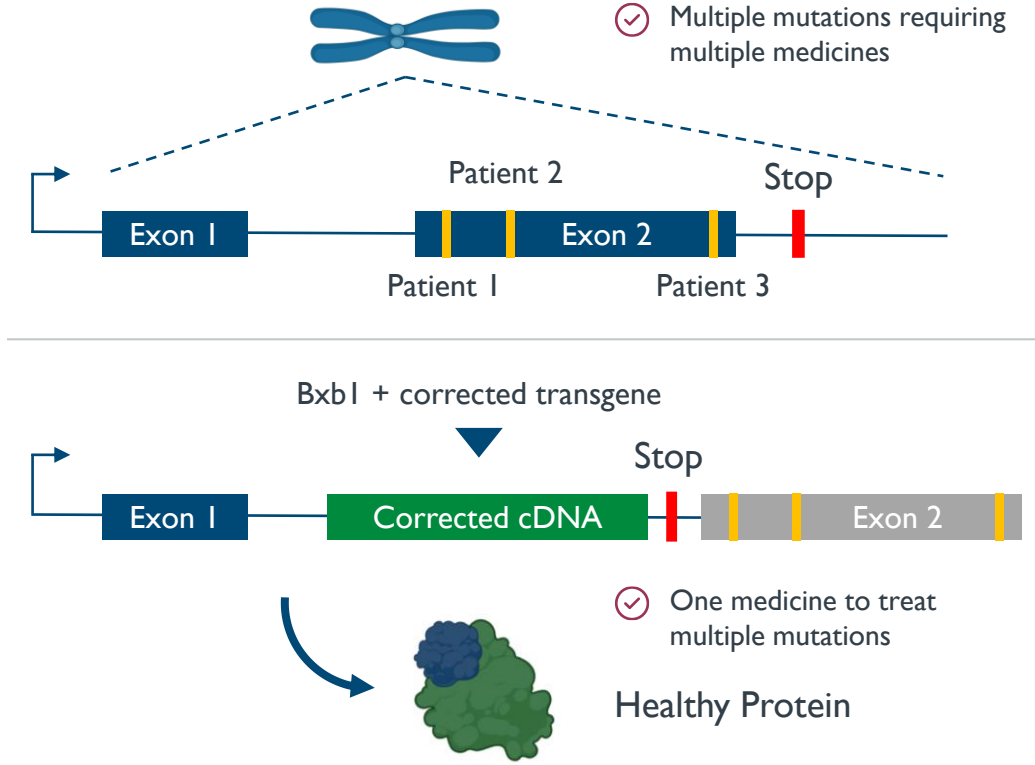
Sangamo THERAPEUTICS

Targeted integration improves existing therapies, and enables new therapies

Targeted vs. Random Integration

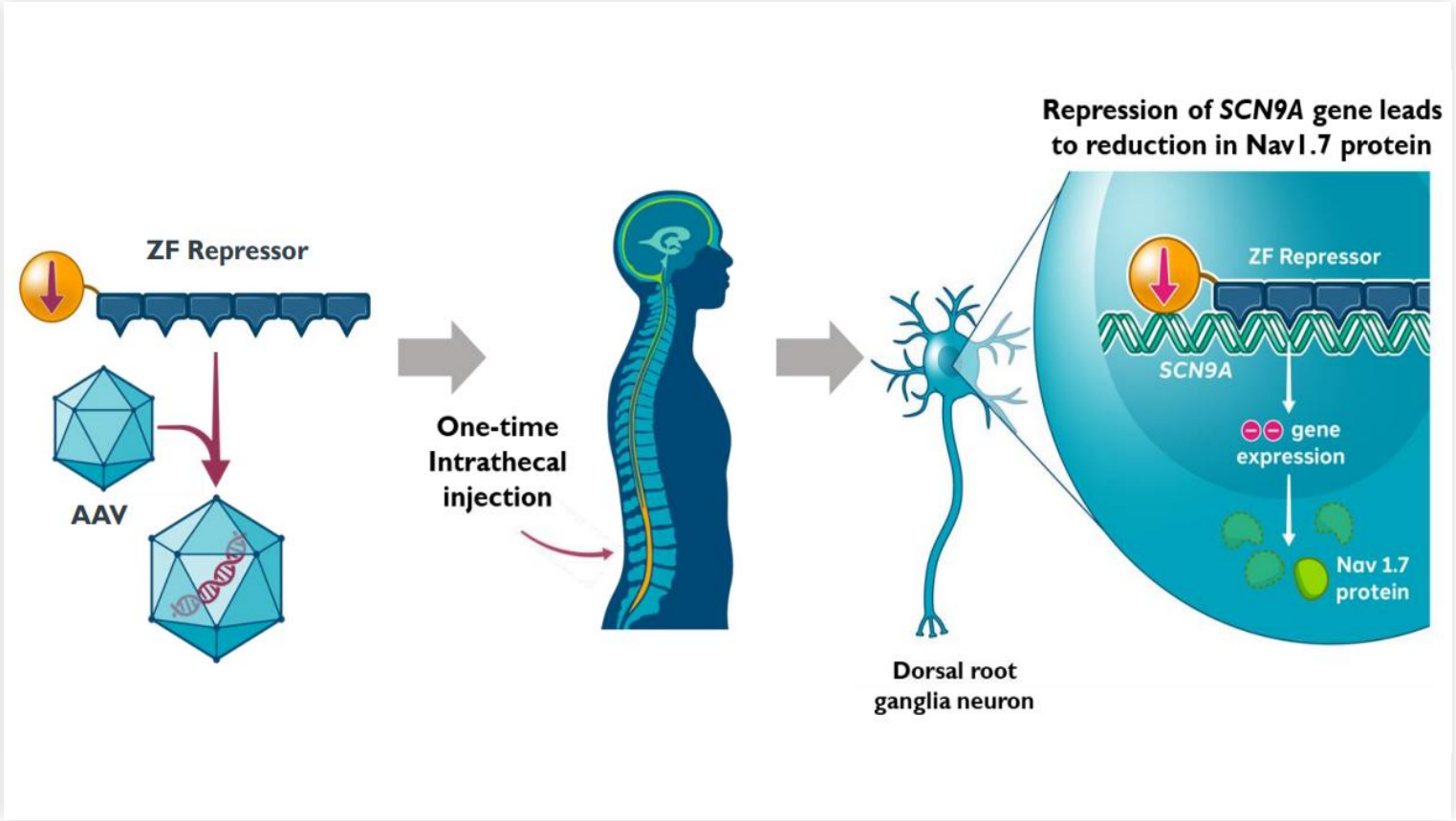


One medicine vs. multiple variants for each mutation

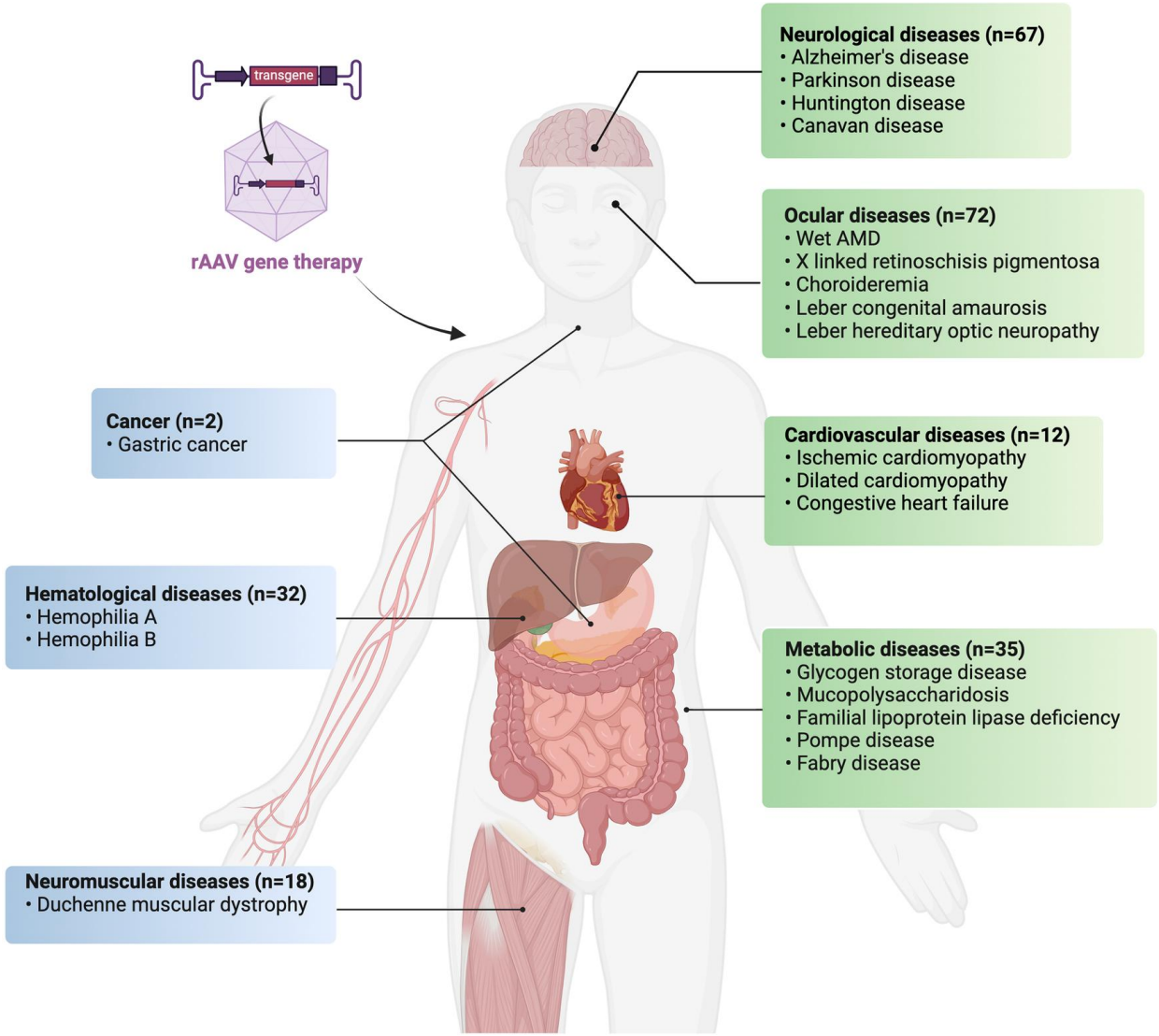


Images by Biorender

Delivery


Repression of SCN9A gene leads to reduction in Nav1.7 protein
ZF Repressor
AAV
One-time Intrathecal injection
Dorsal root ganglia neuron
ZF Repressor
SCN9A
gene expression
Nav 1.7 protein

Adeno-associated virus as a delivery vector for gene therapy of human diseases



- Discovered in 1965
- 3 approvals:

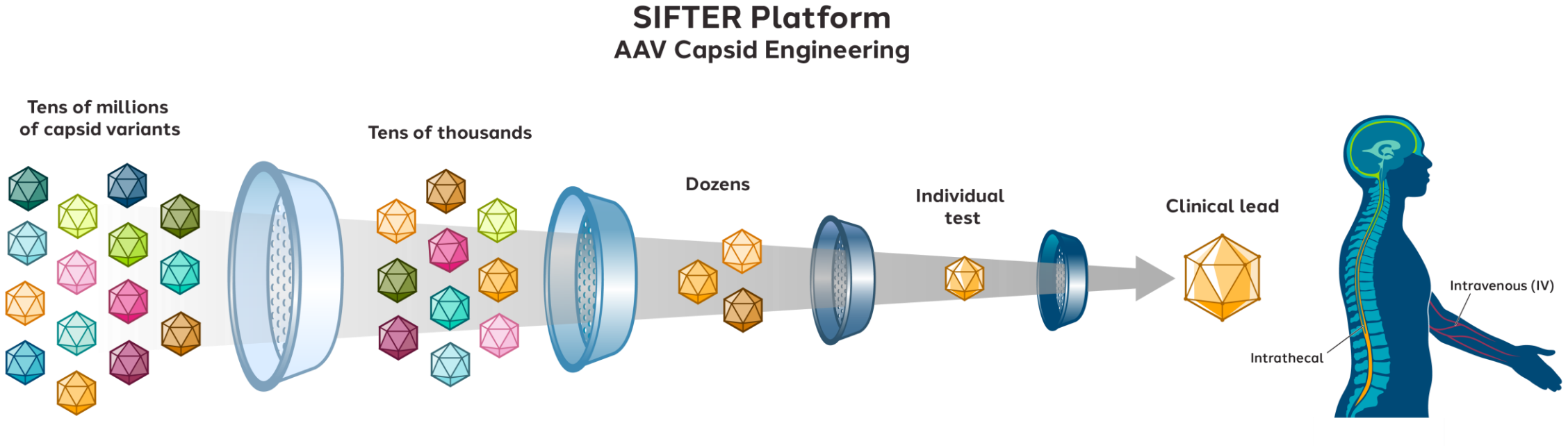
  Luxturna, Zolgensma and Hemophilia B
- 238 clinical trials
- Advantages of AAV
  - ✓ Safety profile
  - ✓ Immunogenicity
  - ✓ Tissue tropism
  - ✓ Long-lasting effects
  - ✓ Versatility
  - ✓ Established clinical Use
  - ✓ Low toxicity

Sangamo THERAPEUTICS

Jiang-Hui Wang *et al.* "Adeno-associated virus as a delivery vector for gene therapy of human diseases. Signal Transduction and Targeted Therapy (2024): ISSN 2059-3635

Case Study: Achieving Widespread Central Nervous System Delivery for Optimal Therapeutic Benefit

Widespread CNS delivery is challenging with conventional AAVs. Our SIFTER platform is designed to enable the selection of neurotropic AAV capsids to potentially advance our innovative preclinical programs to the clinic.

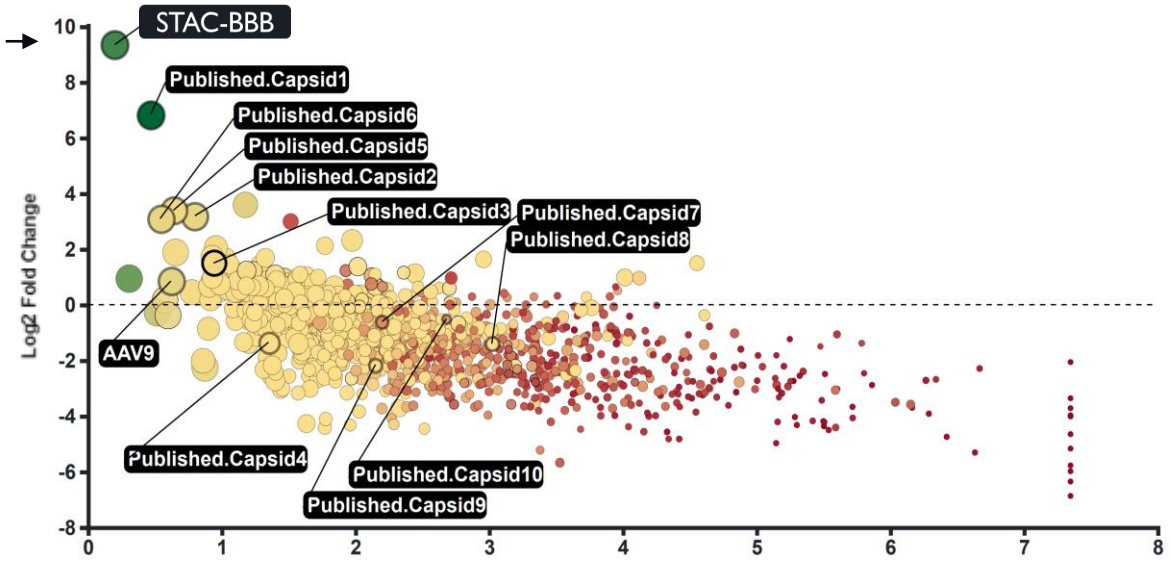


SIFTER: *Selecting In vivo For Transduction and Expression of RNA*

In vivo library evaluation in cynomolgus macaques identified STAC-BBB as the top performing BBB-penetrant capsid, with additional enhancements in progress

Capsid-mediated expression of cargo in neurons

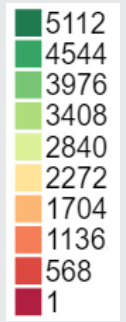
644-fold enrichment in brain →



Log_2 Fold Change (Y-axis): Enrichment score relative to the administered library **Larger value is better**

WHOLE BRAIN ASSESSMENT

Coefficient of Variation (X-axis): Variation in performance across tissue samples that were evaluated **Smaller value is better**

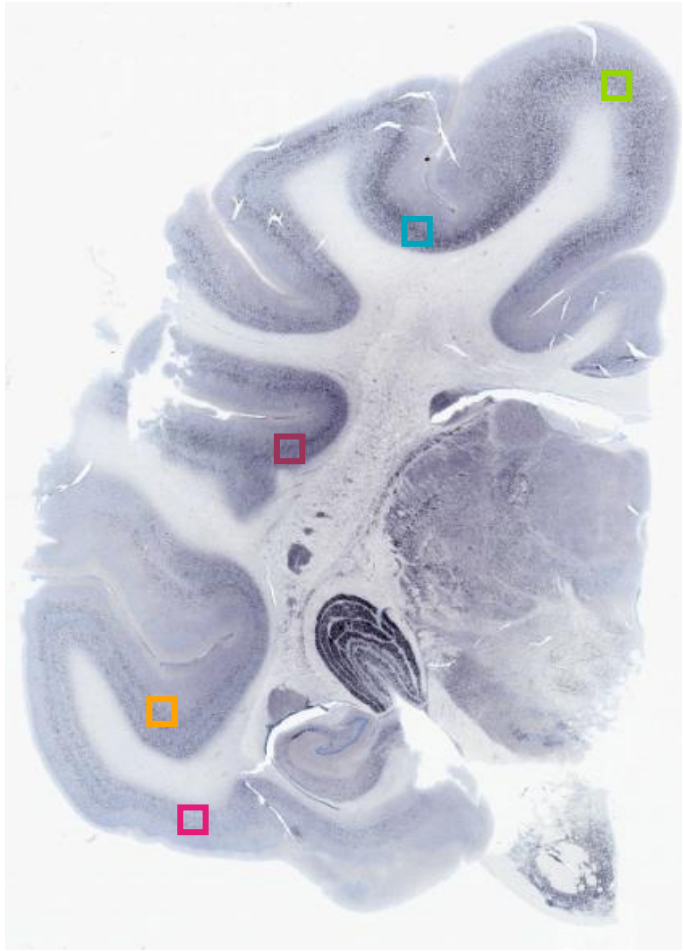


Unique Molecular Identifier count (Color): Informs number of unique AAV transduction events **Darker green is better**

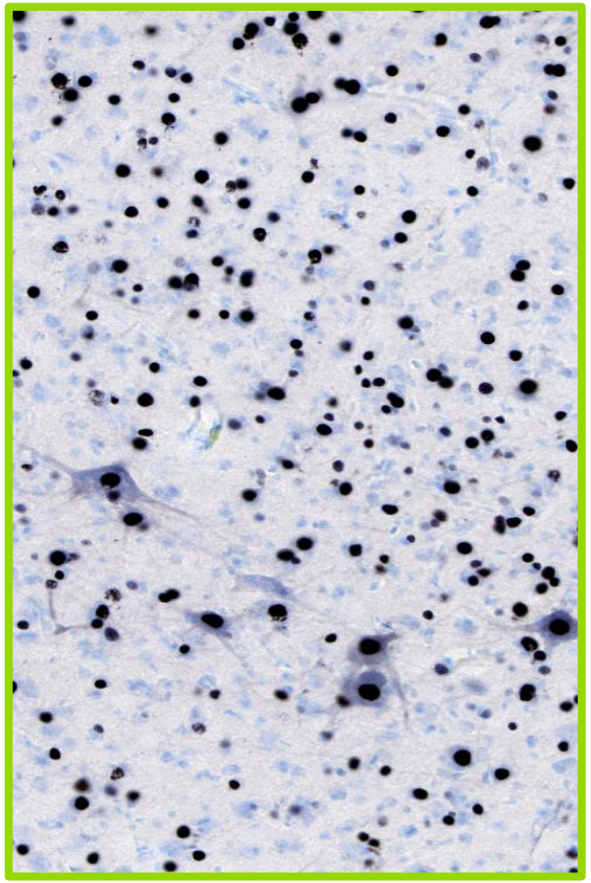
Fraction of replicates found (Bubble size): Informs consistency of replicate recovery **Larger circle is better**

Neuronal RNA expression (3-week study, hSyn1)

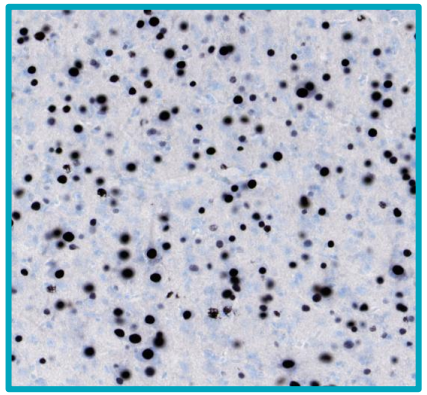
STAC-BBB showed widespread neuronal transduction across all cortical regions



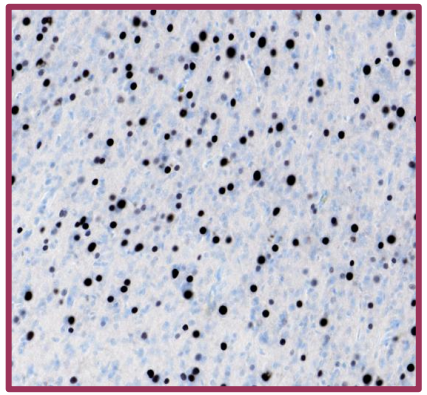
Precentral Gyrus (Motor Cortex)



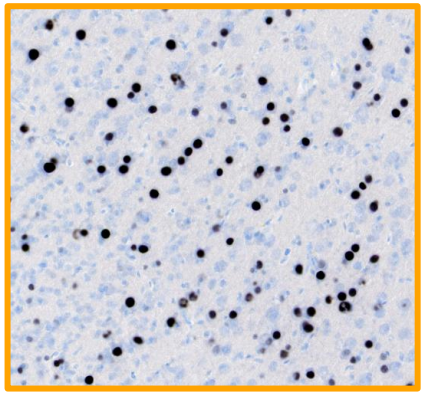
Postcentral Gyrus



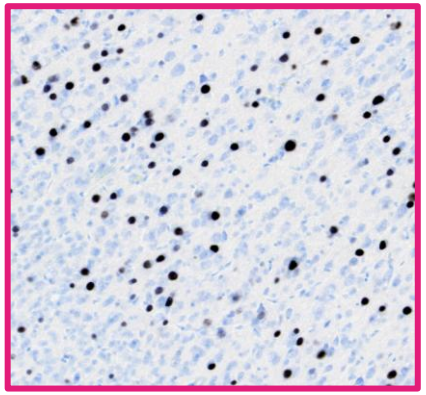
Superior Temporal Gyrus



Middle Temporal Gyrus

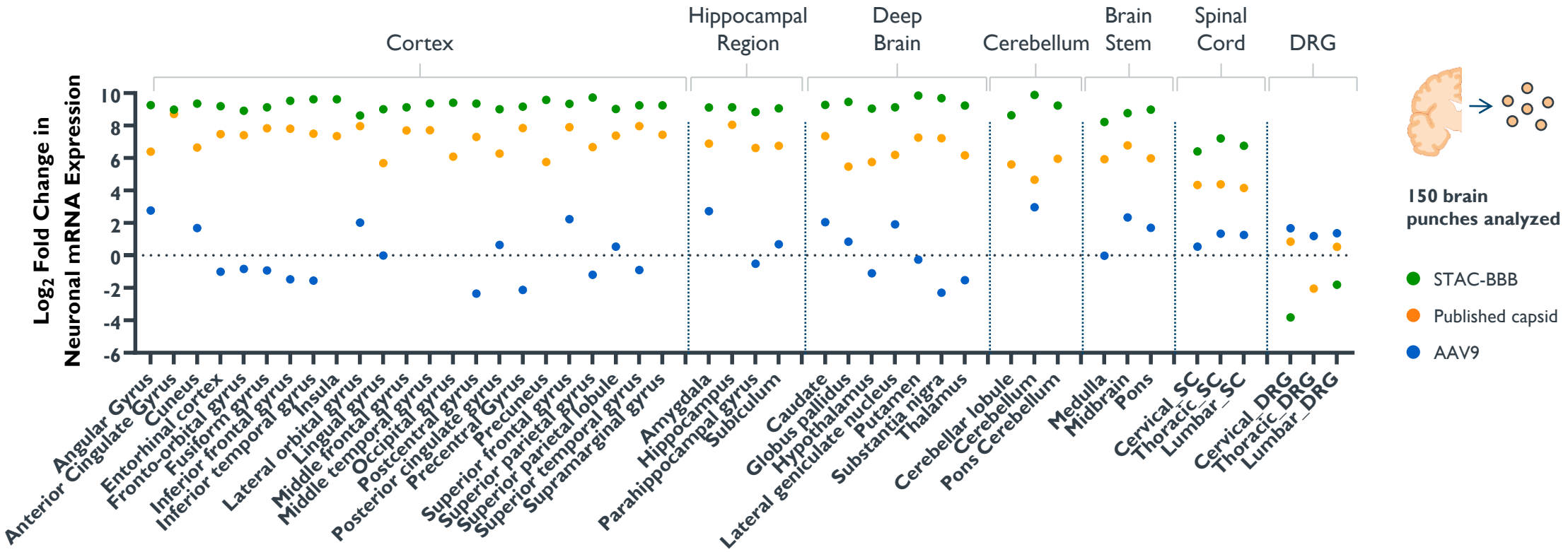


Inferior Temporal Gyrus



STAC-BBB was enriched in neuronal RNA expression in all CNS regions

Capsid-mediated expression of cargo in neurons

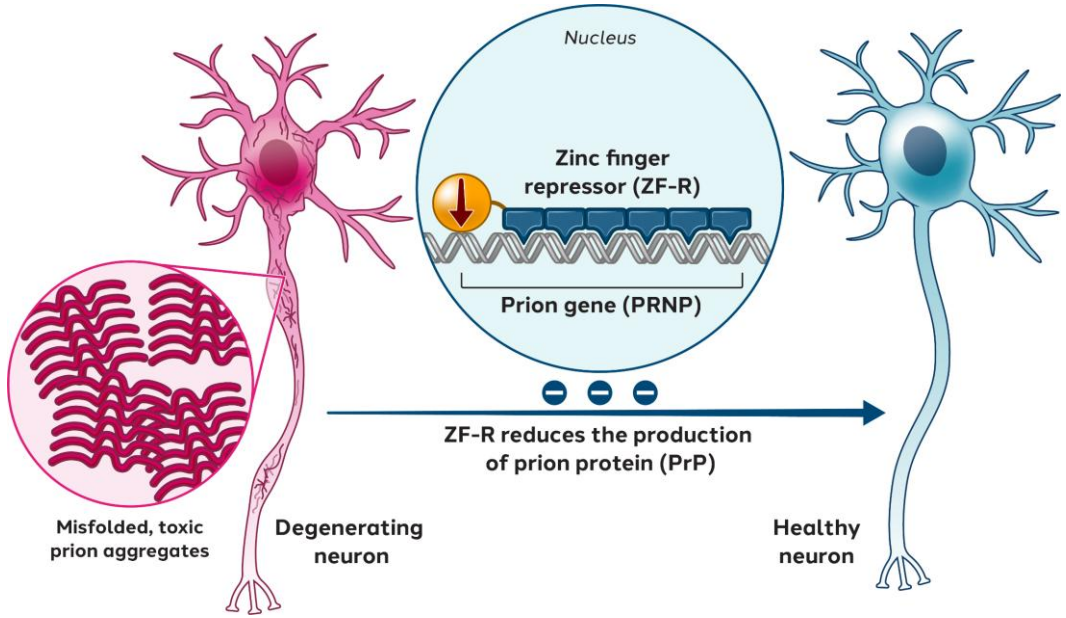


Neuronal RNA expression (3-week study, hSyn1)

Case Study: Epigenetic regulation to address prion disease, leveraging STAC-BBB

Prion disease is rapidly progressive and always fatal

Path to potential clinical validation in a devastating disease with no current approved treatment options



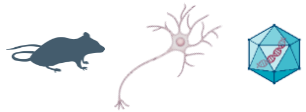
- Progressive condition, with **no disease modifying therapy**
- Caused by the misfolding of the prion protein (PrP) into toxic species, **leading to neurodegeneration and death**
- At least **1,300 new cases** each year in **U.S. and Europe***
- **Sporadic, inherited and acquired** forms
- **Well-defined** patient population
- **Excellent fit** for a zinc finger repression approach
  - Prion knockout animals do not get disease
  - Prion reduction can delay disease
- Repression of prion expression in the brain **should slow or halt disease progression and neurodegeneration**
- **First-in-human** trial of **STAC-BBB** capsid, which if successful, could validate broader wholly owned and partnered programs

Sangamo THERAPEUTICS

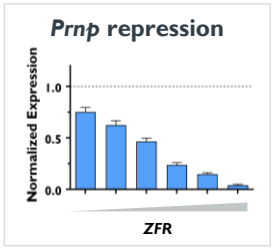
** US (per CDC) and Europe (https://www.eurocjd.ed.ac.uk/)*

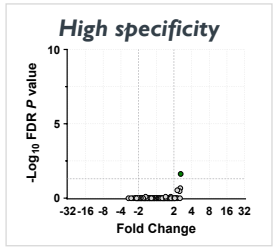
Zinc finger repressors extended survival in a mouse model of aggressive prion disease, even when administered post-symptomatically

Potent and specific repression



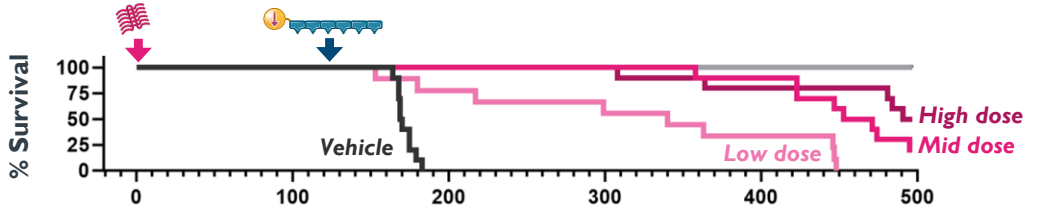
Primary neurons



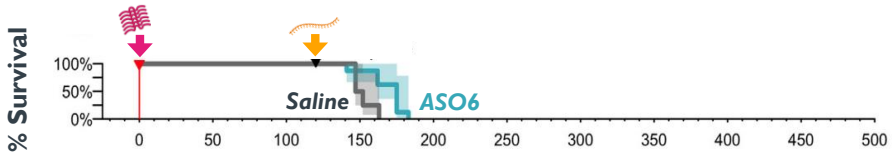


Mouse survival extended, even when administered post-symptomatically

ZFR **
119 dpi***

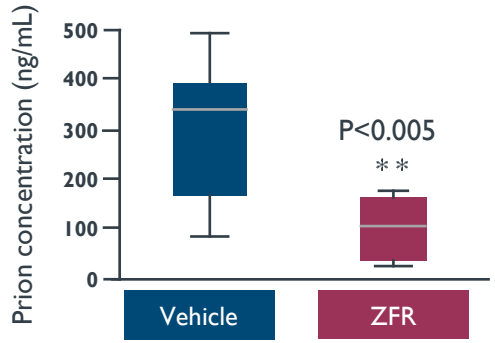


ASO*
120 dpi



Reduction of CSF biomarker

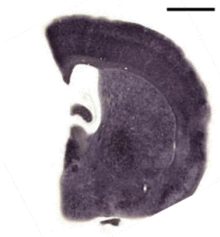
CSF



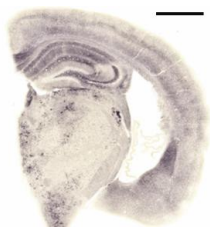
Sustained brain-wide PrP knockdown in prion disease mice

Black: PrP protein antibody labeling

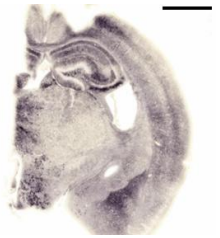
(scale bar = 1mm)



No treatment control
Assessment at 164 dpi



ZFR at 60dpi (pre-symptomatic)
Assessment at 500 dpi



ZFR at 122dpi (symptomatic)
Assessment at 500 dpi

Data presented at ASGCT 2023, Prion 2024

** Antisense oligonucleotide (ASO) data from Minikel et al 2020*
*** ZFR administered intravenously using PHPB capsid *** dpi: days post inoculation*

Sangamo THERAPEUTICS

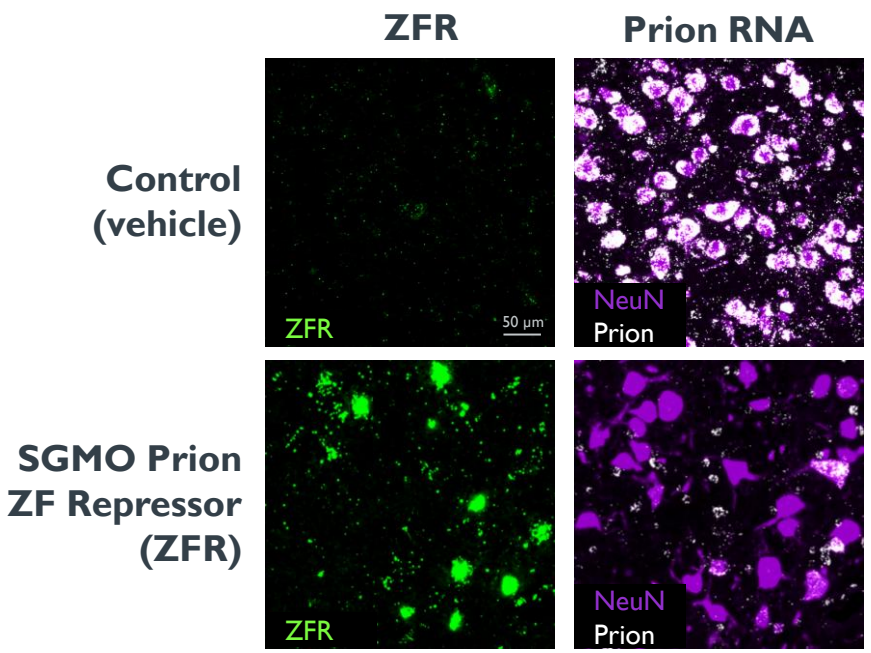
Sangamo pairs the epigenetic regulation *and* capsid delivery capabilities needed to create neurology genomic medicines

Genome-Targeting Cargo

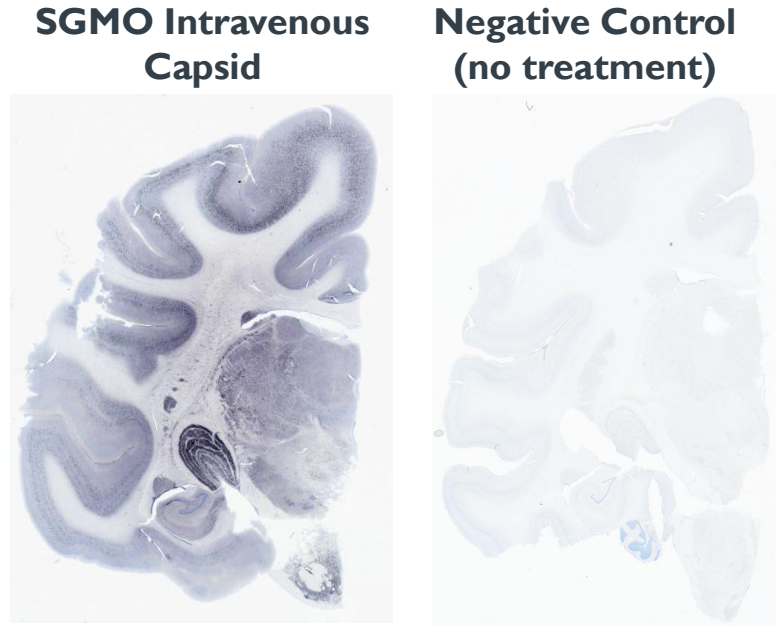
Epigenetic regulation platform

Capsid Delivery Engine

AAV capsid delivery platform via intravenous delivery



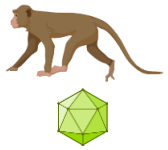
Nonhuman primate (NHP) pons



Nonhuman primate

Future of Neurology Genomic Medicines

Brain-wide PRNP repression seen in NHPs in the range of that associated with marked survival in mouse



STAC-BBB

STAC-BBB capsid with human-specific ZFR 2e13 vg/kg

PHP.B

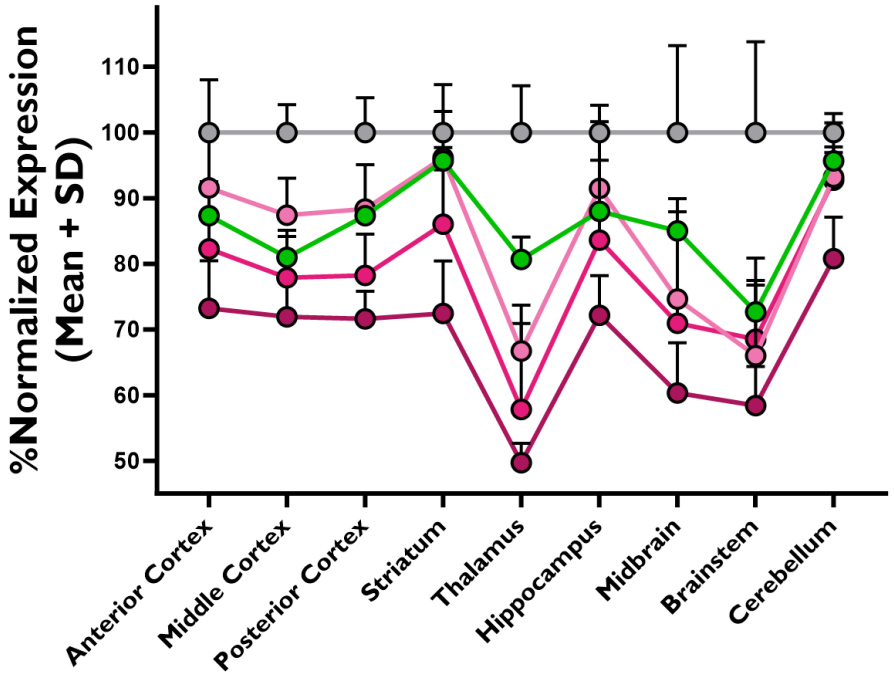
PHP.B capsid with mouse-specific ZFR

1e13 vg/kg
3e13 vg/kg
1e14 vg/kg
Vehicle

Higher doses in NHP are feasible and should provide higher repression of PRNP

***Prnp* mRNA repression seen across key brain regions:**

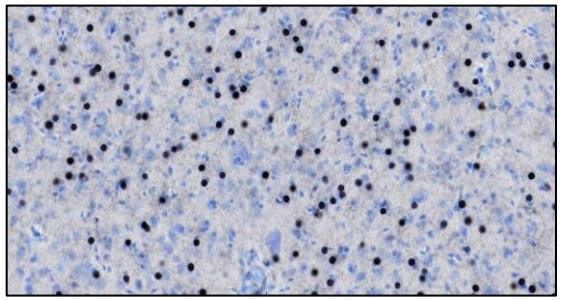
- **Pink:** repression in mouse survival study at three doses
- **Green:** repression in NHP study at 2e13 vg/kg dose
- Prion repression in NHP similar to mouse at comparable doses
- Anticipate greater repression with clinical manufacturing process and higher doses in NHP



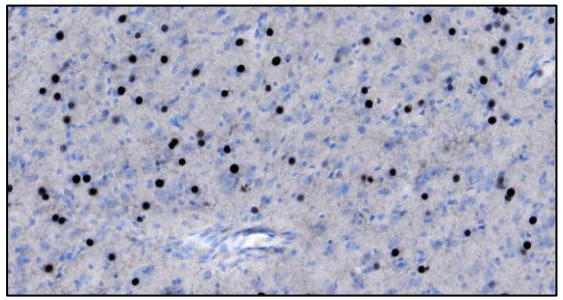
Data presented at ASGCT 2023, Prion 2024

STAC-BBB mediated widespread brain transduction

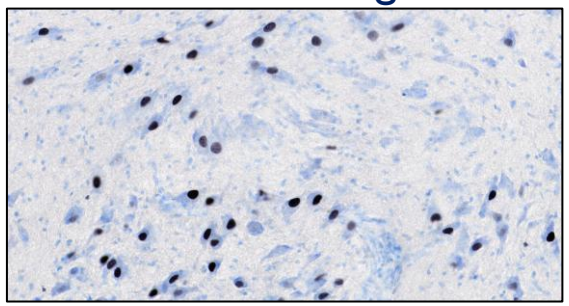
Putamen



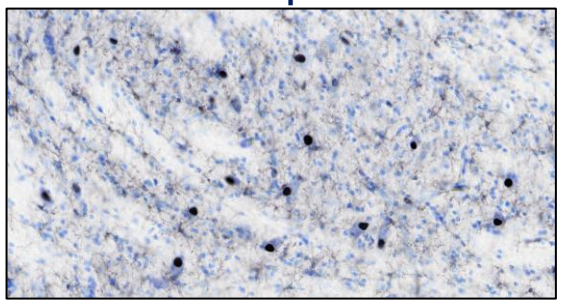
Caudate



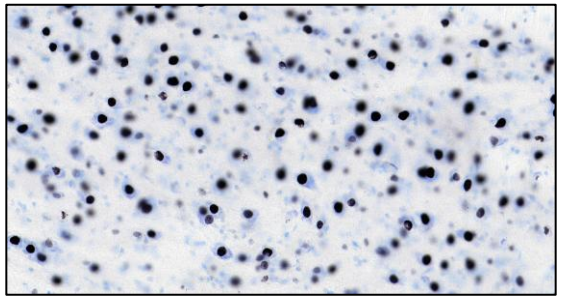
Substantia nigra



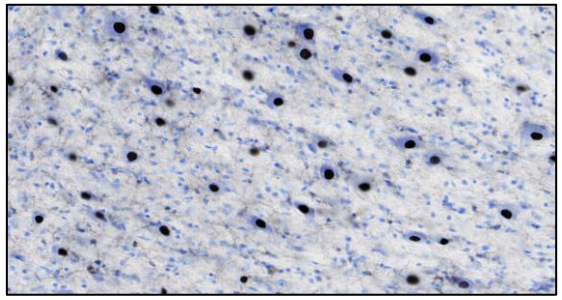
Globus pallidus



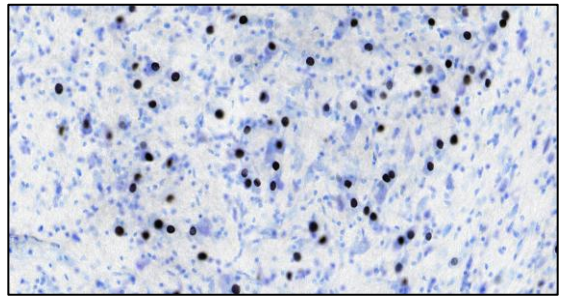
Pons



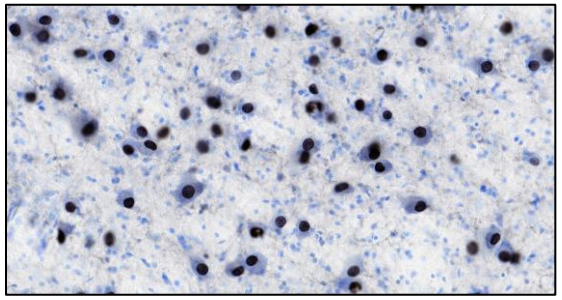
Dentate nucleus



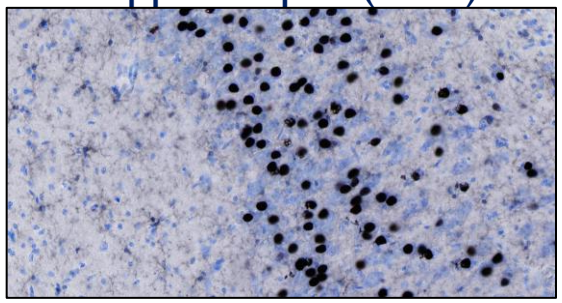
Cuneate nucleus



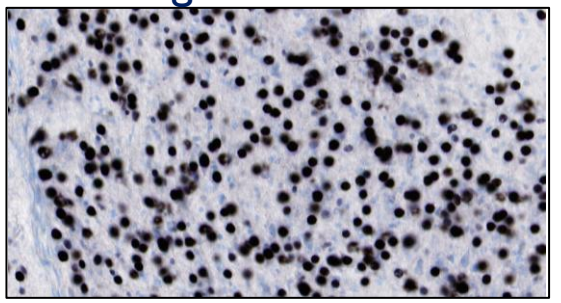
Thalamus



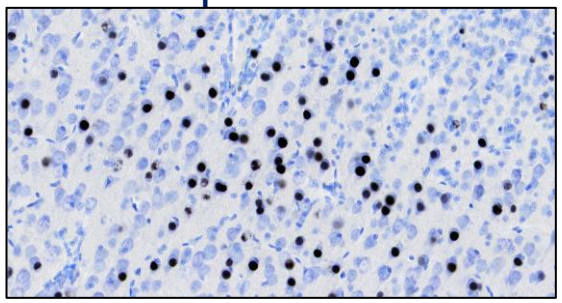
Hippocampus (CA2)



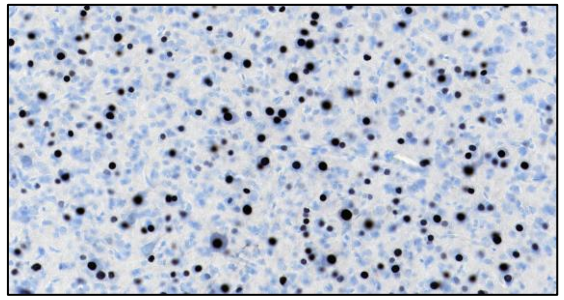
Lateral geniculate nucleus



Temporal cortex



Motor cortex



Sangamo THERAPEUTICS

2e13 vg/kg STAC-BBB, 19 days post administration

Manufacturing

Design

Delivery

Manufacturing

Safety

Regulatory

We believe ZFR-STAC-BBB is manufacturable at scale

- Capsid manufacturability is critical to create a successful potential commercial drug product for patients
- Key attributes:
  - Manufacturable at commercial scale using standard cell culture and purification processes
  - Soluble using known excipients
  - Can be characterized using available analytics
- We have successfully manufactured up to 50-liter scale, and further scale up to 500-liter is in progress

Safety

Design

Delivery

Manufacturing

Safety

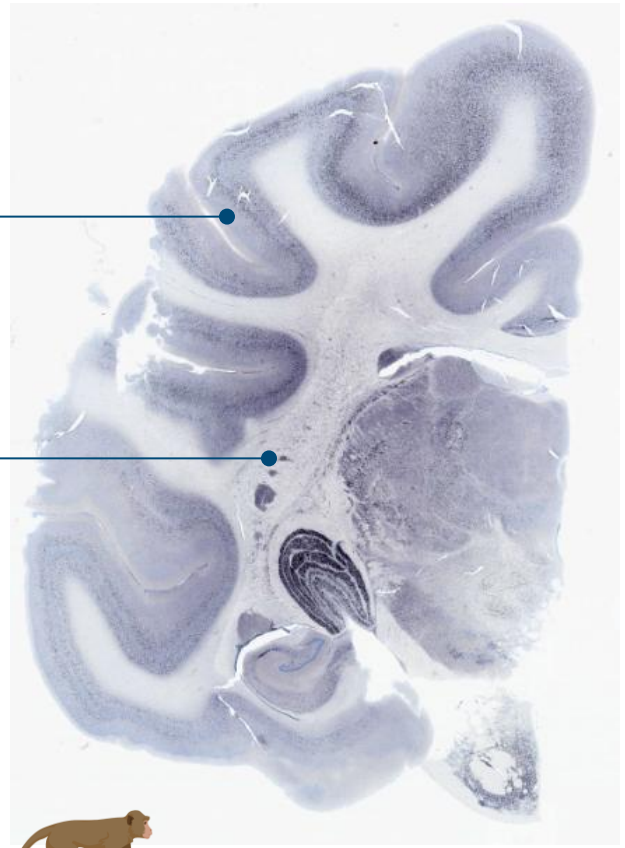
Regulatory

Similar *in vivo* performance of STAC-BBB is observed in NHP and mouse brains

Grey matter (cell bodies)

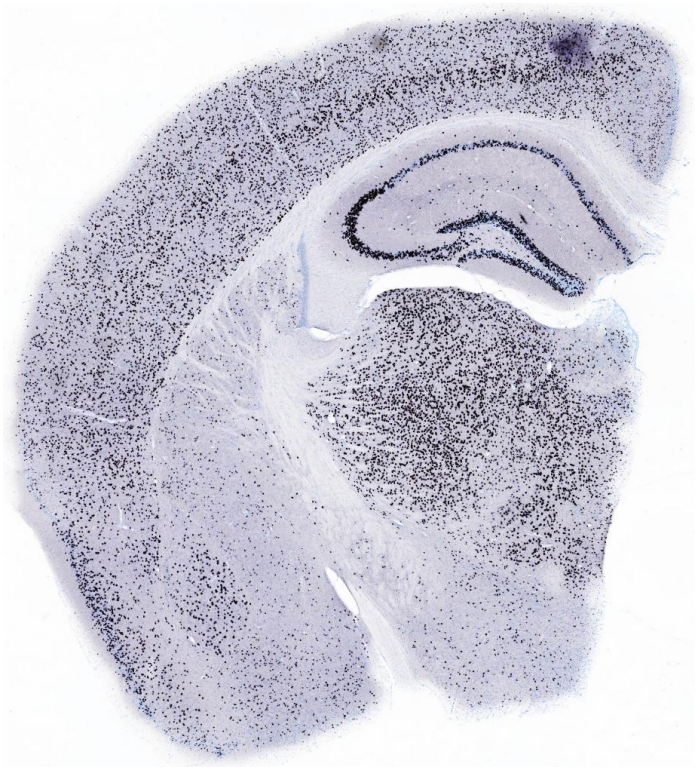
White matter (nerve fibers)

Nonhuman Primate



2e13 vg/kg STAC-BBB, 19 days post administration

Mouse



1e14 vg/kg STAC-BBB, 28 days post administration

Nissl staining (light blue):

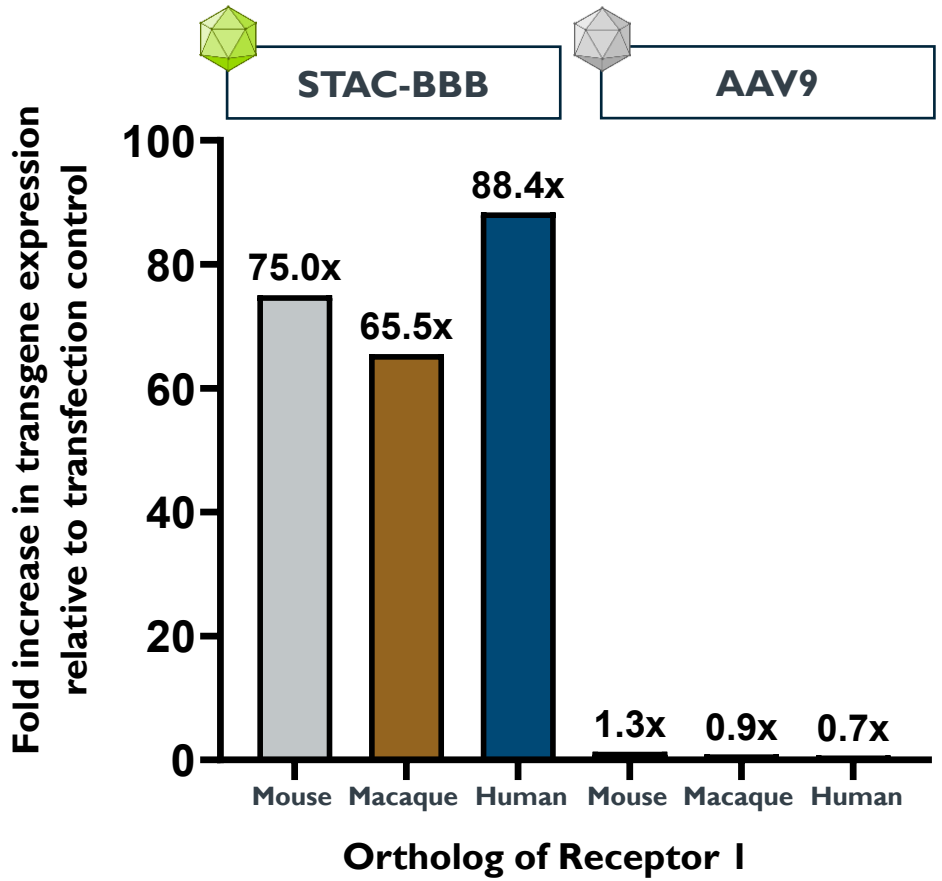
All cell nuclei

Antibody labeling for green florescent protein (GFP) expression (black):

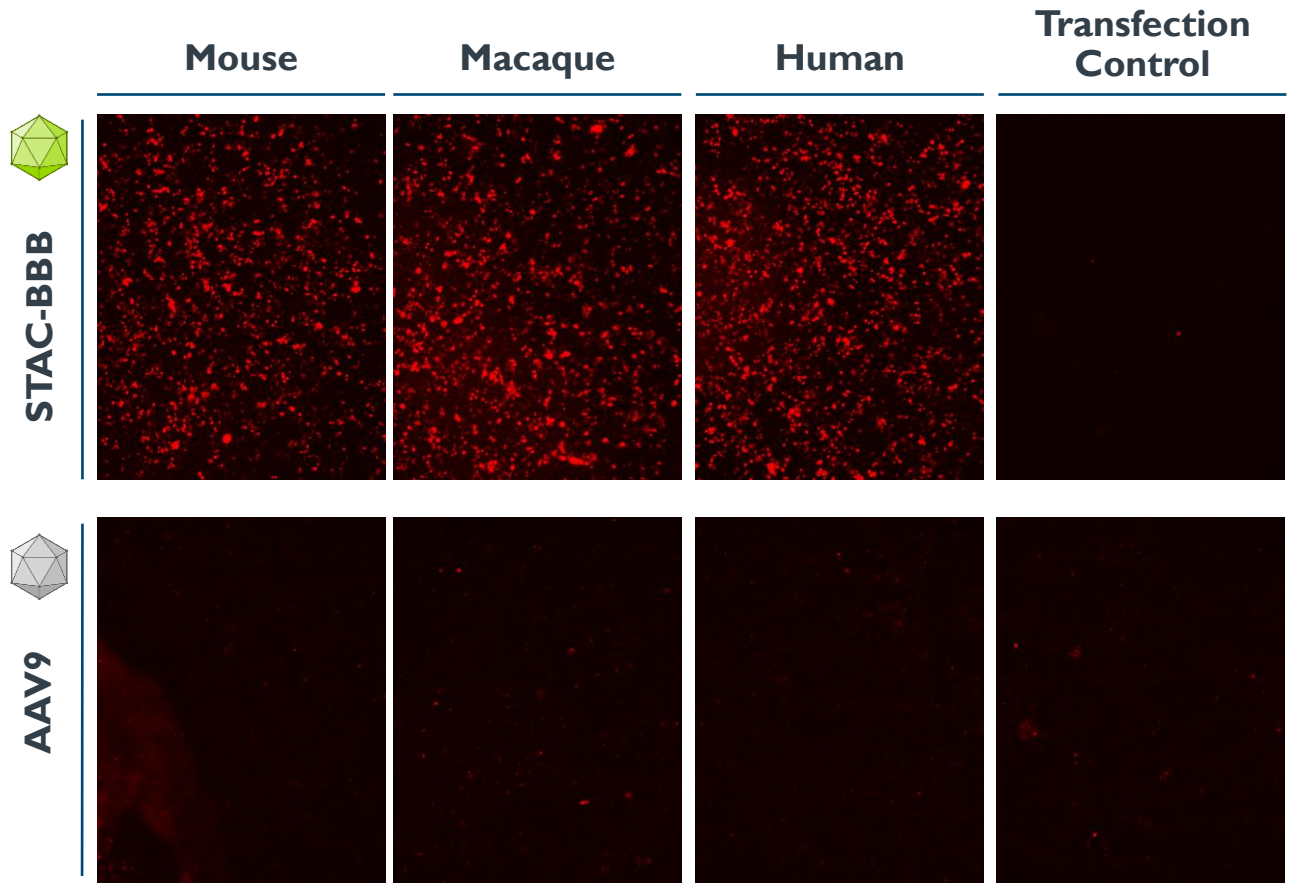
Cells transduced with STAC-BBB

Overexpression of mouse, macaque, and human Receptor 1 confers a gain-of-function for STAC-BBB transduction

Transgene expression – RT-qPCR



Detection of fluorescent reporter



Expression of a mCherry reporter was evaluated across a 1E3 to 1E5 MOI range in HEK293 cells. A nonlinear regression model was used to interpolate relative transgene expression values for each capsid-construct condition. These values were then scaled to a GFP transfection control value for each capsid.

Regulatory

Design

Delivery

Manufacturing

Safety

Regulatory

Epigenetic regulation to address chronic neuropathic pain

The urgent need for novel chronic neuropathic pain therapeutics

Epigenetic regulation
has the potential to fundamentally reshape the treatment of intractable pain

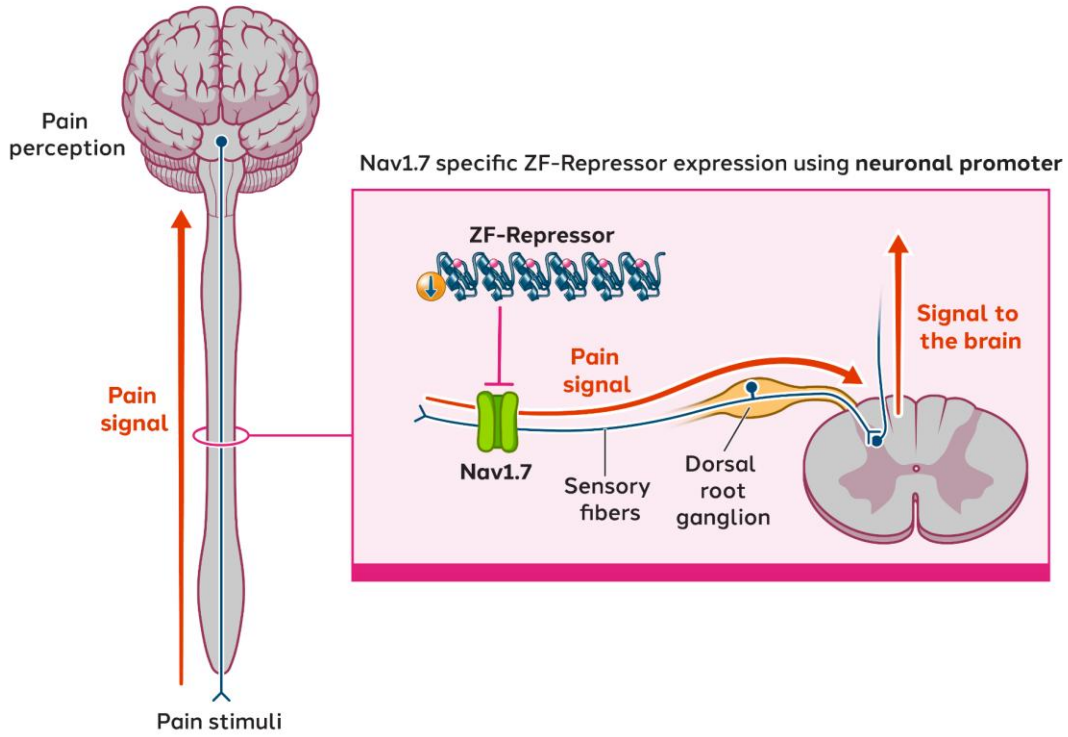
Past	Present	Future
Anti-inflammatories Analgesics Opioids	Pain signal inhibitors	**Epigenetic regulation**

- ST-503 is an **investigational epigenetic regulator** for the treatment of **intractable, chronic neuropathic pain**
- **Peripheral neuropathies** are estimated to affect **~40 million Americans**
- Our **first study** assesses ST-503 in **idiopathic small fiber neuropathy** (iSFN), a type of chronic neuropathic pain
- iSFN is a **chronic, highly debilitating** pain syndrome, with an estimated prevalence of at least **43,000 patients in the U.S**
- **High unmet medical need**, with insufficient current treatment options (anticonvulsants, opioids and topical therapies)
- **Short timescale** to expected clinical efficacy readout
- **Gateway indication:** if successful, ST-503 could be **broadened** to other types of **chronic neuropathic pain**

Sangamo THERAPEUTICS

Targeting the Nav1.7 pathway at the DNA level, we seek to succeed where others have failed

ST-503 targets a gene validated by human genetics and leverages an AAV delivery capsid already in the clinic



- A significant body of evidence implicates **sodium channels** in mediating the **pathophysiology of neuropathic pain**
- **Nav1.7** is a voltage gated sodium channel expressed in the Dorsal Root Ganglion (DRG)
- Blocking Nav1.7 in the DRG is expected to prevent the **transmission of nociceptive pain signals** to the brain
- This allows us to target multiple **neuropathic pain indications**, regardless of the cause of the pain
- Reducing pain by inhibiting Nav1.7 is not predicted to be associated with **any neurological side effects**
- Administered **intrathecally via AAV9**, a well-established, well-tolerated capsid

Zinc finger repressors potently reduced Nav1.7 in human neurons with high level of specificity

iPSC-derived neurons

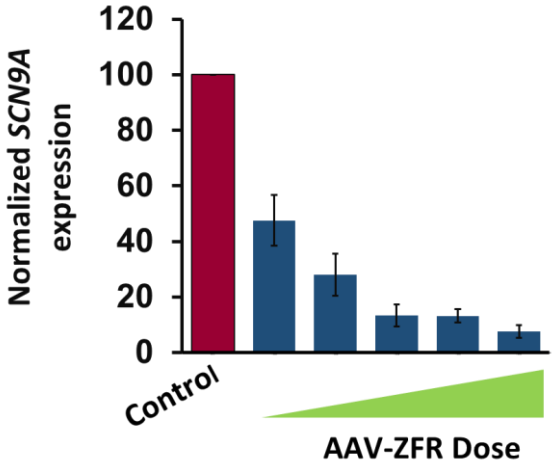
\+

AAV + ZFR

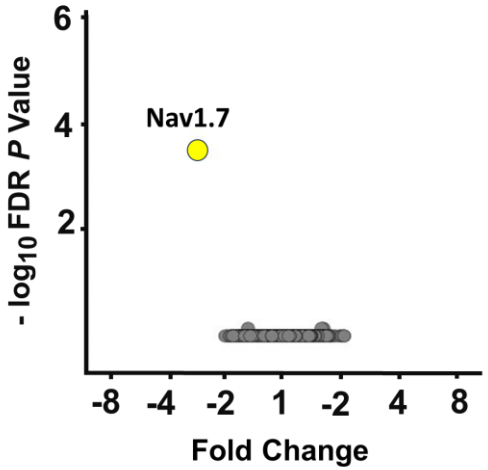
↓ 30d

Nav1.7 expression, Off-target assessment

Potent and dose-dependent repression of *SCN9A* gene, which encodes Nav1.7

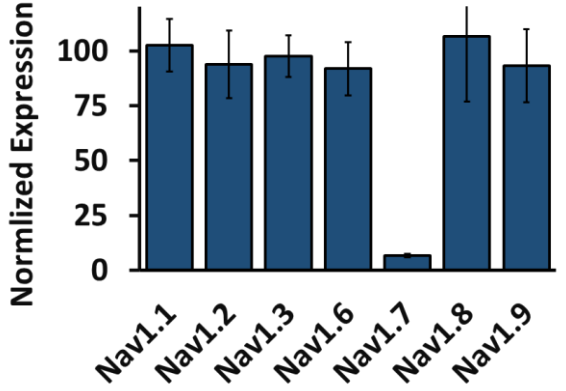


Selective repression of SNC9A as shown by global transcriptome analysis



Differential expression of 20,000 genes was evaluated

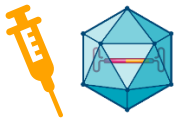
Specific repression of Nav1.7 without impacting other sodium channels



Data presented at ASGCT 2023

Nav1.7 repressor reversed neuropathic pain in preclinical mouse models

Intrathecal
lumbar injection

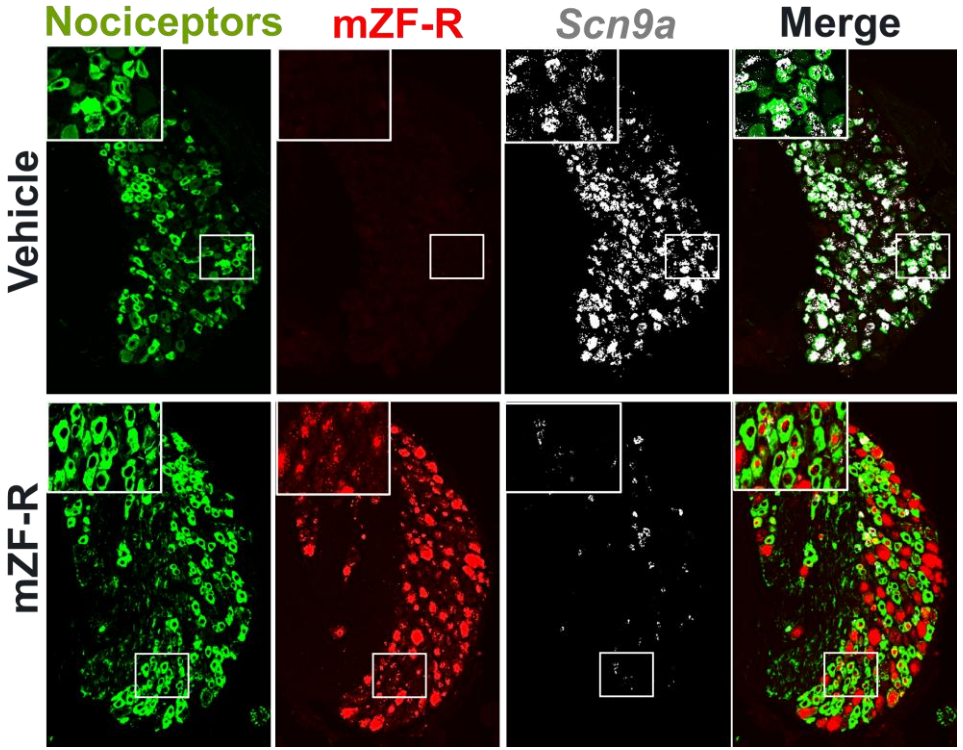


AAV-mZFR

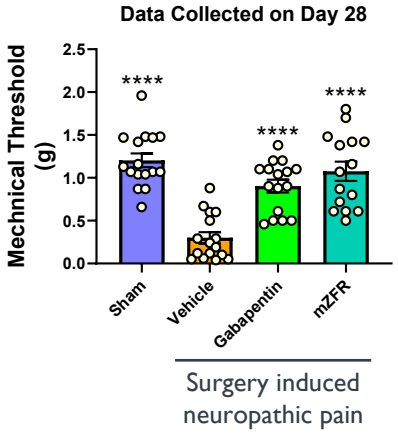
↓ **28d**

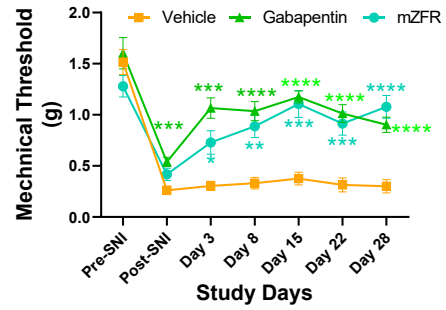
Nav1.7 expression,
Pain assessment

Potent *Scn9a* mRNA repression in mouse Lumbar DRG nociceptors



Full restoration of normal sensitivity to mechanical pain



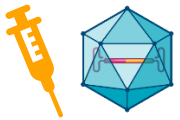


mZFR: mouse ZFR

Sangamo THERAPEUTICS

Potent and selective repression of *SCN9A* observed in NHPs, with no clinical signs of toxicity or adverse clinical pathology

Intrathecal lumbar injection

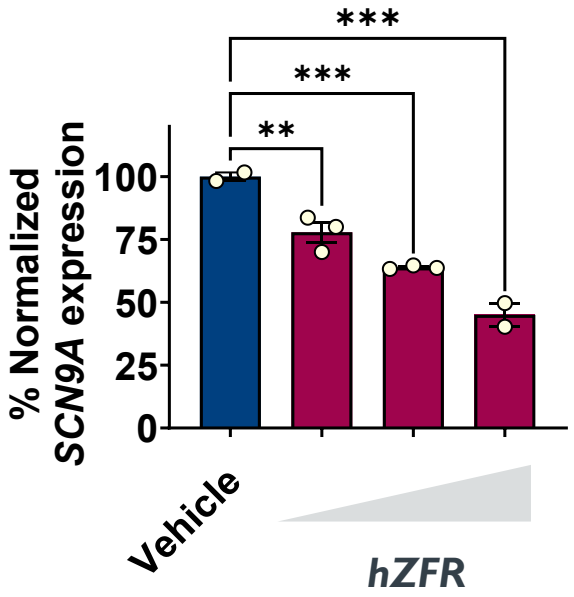


AAV-hZFR

↓ **28d**

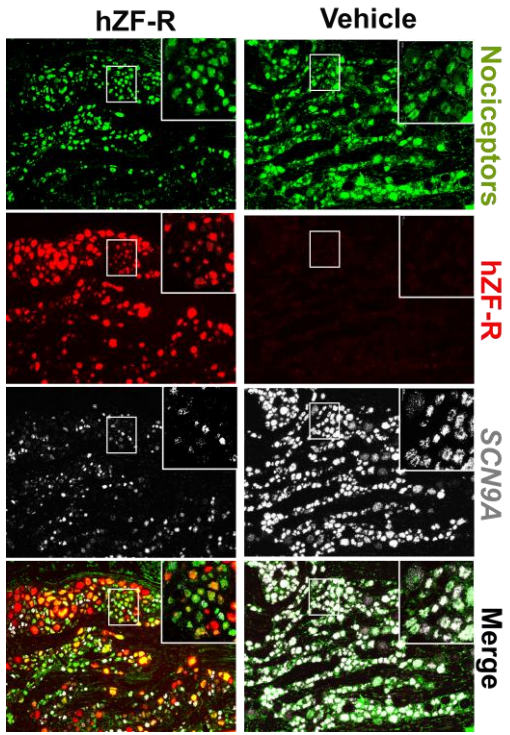
Nav1.7 expression

Potent and dose-dependent repression of *SCN9A* gene, which encodes Nav1.7

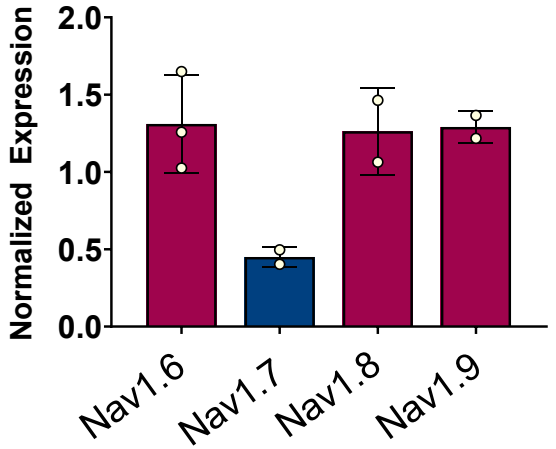


Comparable data were obtained in other DRG levels

Selective repression of *SNC9A* as shown by single cell analysis



Specific repression of Nav1.7 without impacting other sodium channels

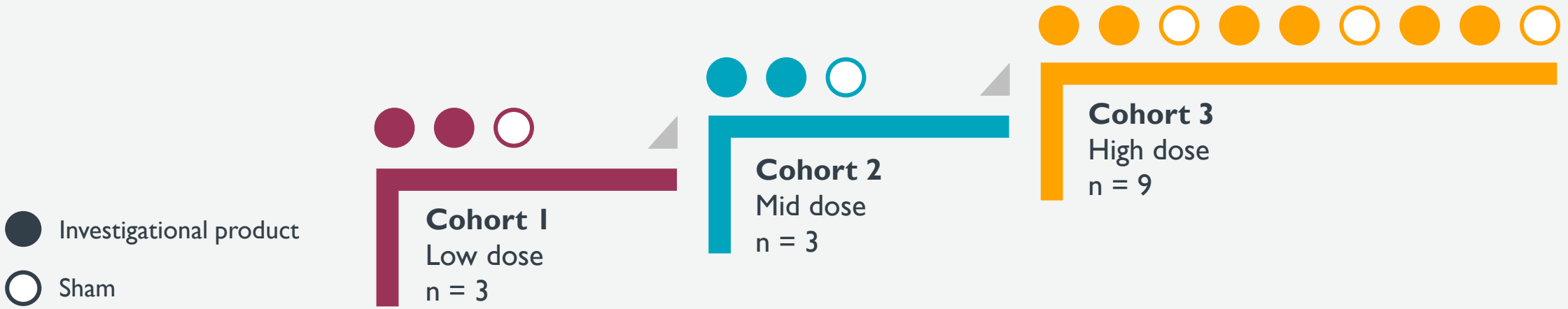


Comparable data were obtained in other DRG levels

hZFR: human ZFR

Sangamo THERAPEUTICS

Clinical study preparations are advancing, with preliminary proof of efficacy data anticipated in Q4 2026



- FDA **clearance of IND** received November 2024 to assess **ST-503 in iSFN patients**
- Preparing for **double-blind, randomized, sham-controlled dose escalation** study to determine safety and tolerability of single dose **intrathecal ST-503** gene therapy
- Dose escalation protocol with a **2:1 randomization** of investigational product to sham
- Plan to initiate patient enrollment and **dosing by mid-2025**
- Anticipate preliminary **proof of efficacy data in Q4 2026**

Sangamo THERAPEUTICS

Thank You

Acknowledgements:

- Technology Team
- CNS Research Team
- Capsid Engineering Group