ST-506 – an Investigational Gene Therapy for Treatment of Prion Disease

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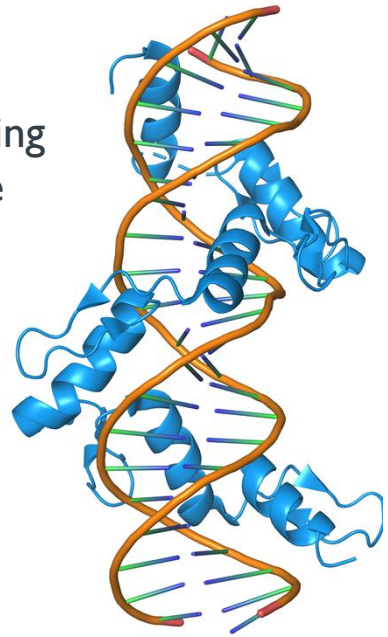
Sangamo combines the ability to control the functioning of specific genes with delivery technology to develop treatments for neurological diseases

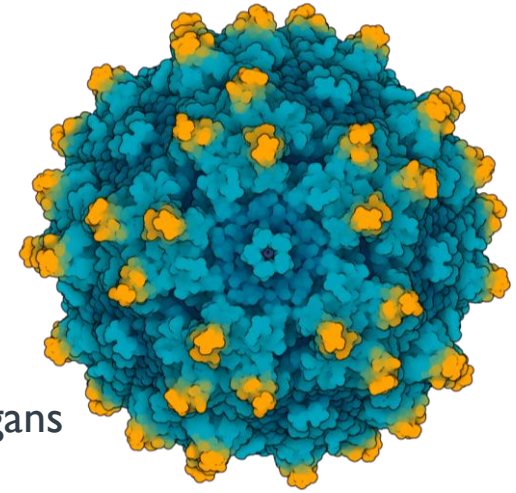
Therapeutic Cargo
Zinc finger proteins

- Most abundant DNA-binding proteins in human genome
- Tune gene expression up, down, or off
- Cell-type specific
- No permanent change to the genetic code



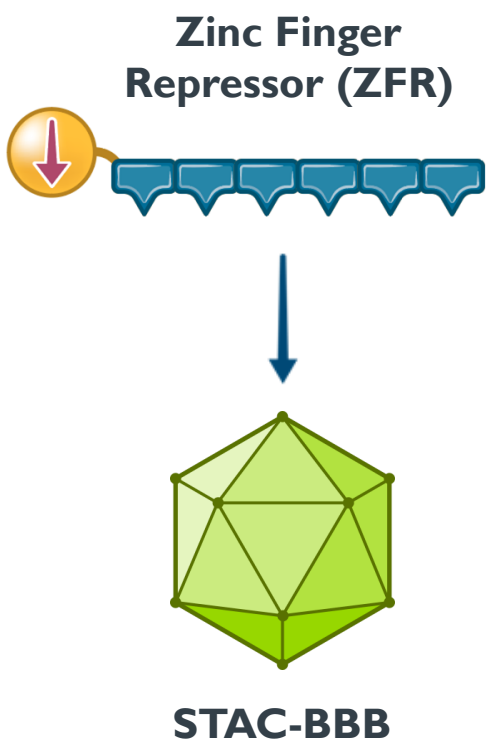
Capsid Delivery Technology
Delivery across the blood brain barrier (BBB)

- Intravenous (IV) delivery
- One-time dosing
- Capsid designed to target brain and de-target other organs including liver

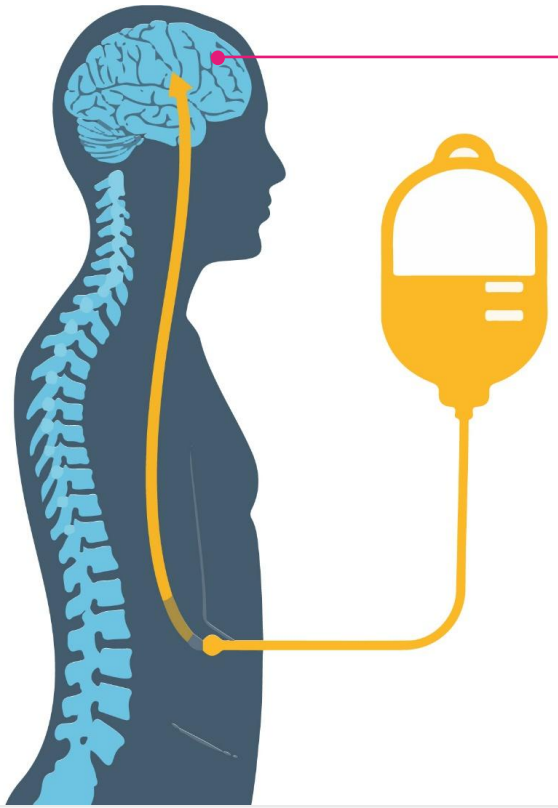


ST-506: A one-time IV-administered zinc finger repressor targeting the prion gene delivered by Sangamo's novel, neurotropic capsid, STAC-BBB

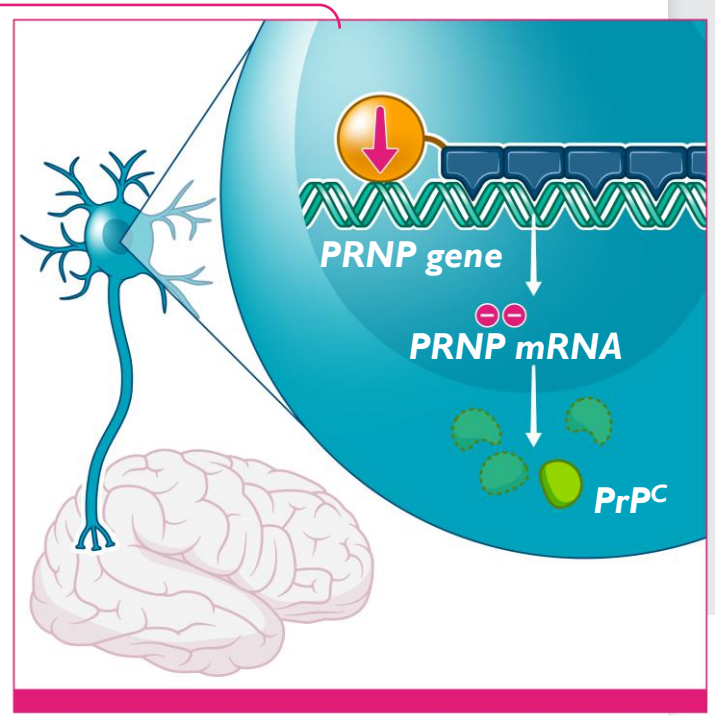
Neuron-targeted ZFR packaged into STAC-BBB AAV capsid



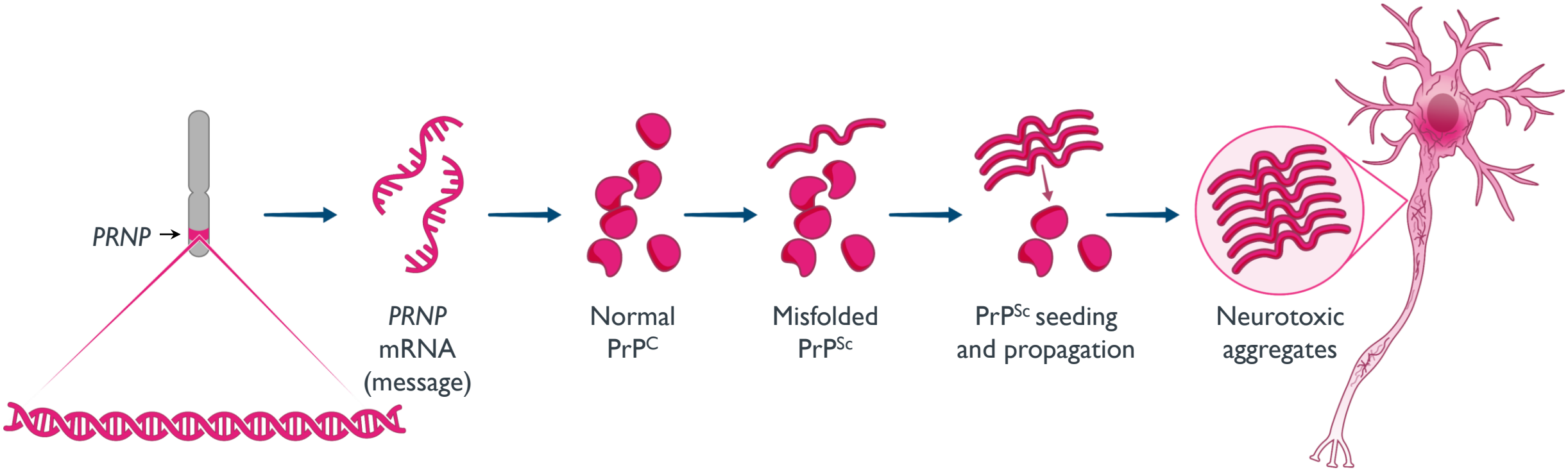
One-time IV administration



Stable PrP reduction in neurons in the brain



Lowering prion protein (PrP) can slow and prevent disease progression caused by misfolded, neurotoxic aggregates



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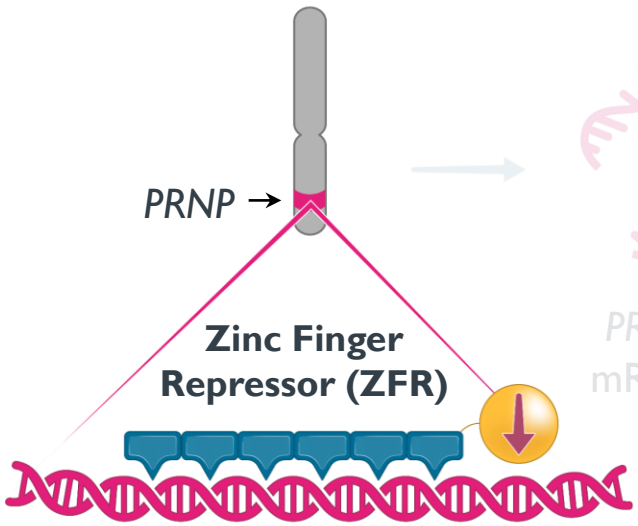
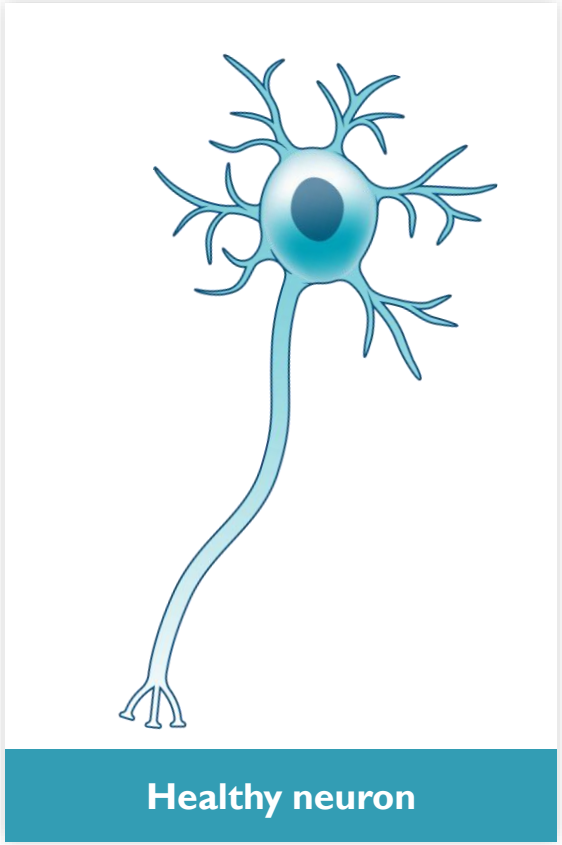


PRNP mRNA

Normal PrP^{C}

Misfolded PrP^{Sc}

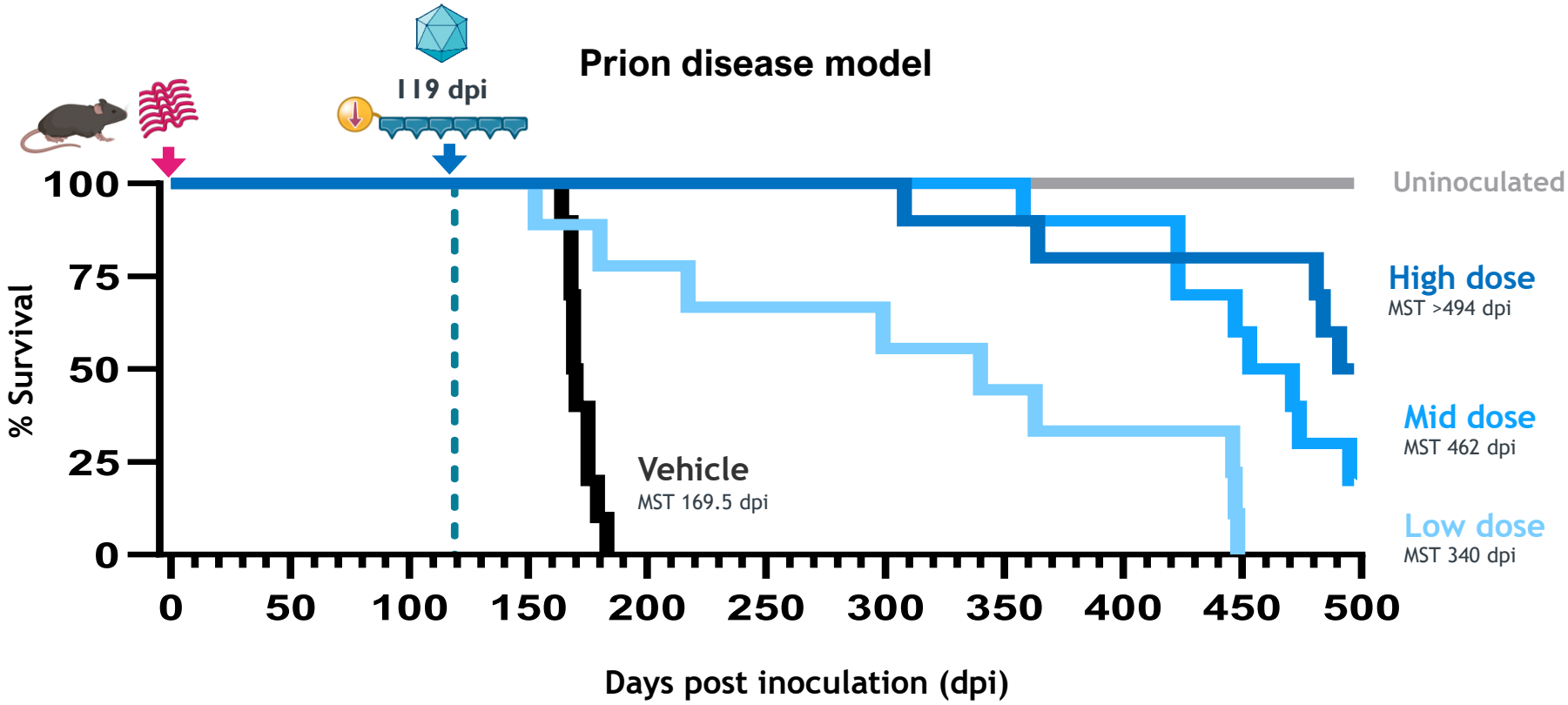
PrP^{Sc} seeding and propagation



Healthy neuron

Prusiner 1982; Bueler et al., 1992, 1993, 1994; Sailer et al., 1994; Brandner et al., 1996; Mallucci et al., 2003; Richt et al., 2007; Yu et al., 2009; Benestad et al., 2012; Raymond et al., 2019; Salvesen et al., 2020; Minikel et al., 2020; Vallabh et al., 2020; Lakkaraju et al., 2022; Gentile et al., 2024; An et al., 2025

Prolonged survival has been observed in a prion-disease model in mouse when dosed post-symptoms



Prion knockdown measured in brain regions in mouse and nonhuman primate studies (using ST-506 clinical candidate), is similar to repression in mouse survival study

3-month Good Laboratory Practice (GLP) toxicology study in nonhuman primates ongoing

ST-506
GLP Study

Capsid ZFR

IV administration

Low Dose
Mid Dose
High Dose

3 months

Cynomolgus Monkey

In-life evaluations

- Mortality/morbidity
- Clinical signs, including behavior assessment
- Food consumption and body weight
- Clinical pathology: hematology, clinical chemistry, coagulation
- Electrocardiography, heart rate, blood pressure, neurological assessment and ophthalmic exam

No ST-506-related in-life adverse findings

Terminal evaluations

- Pharmacology (brain regions for ZFR & PRNP mRNA, brain & CSF prion protein)
- Toxicokinetics
- Organ weights, gross pathology – **No ST-506-related adverse macroscopic findings**
- Histopathology of 38 FDA-recommended tissues – **No ST-506-related adverse microscopic findings**
- Biodistribution (brain regions and FDA recommended tissues)
- Shedding (saliva, urine, feces)
- Antibody assessment

No ST-506 related adverse findings in 3-month GLP toxicology study. ST-506 nonclinical program supports Clinical Trial Application filing

Sangamo THERAPEUTICS

In Summary

- Sangamo's nonclinical program is nearing completion. Key analyses for the Good Laboratory Practice (GLP) toxicity study required for clinical trial approval has been completed and shown no adverse effects in 2 species (mouse and nonhuman primate)
- Based on our strong nonclinical data, our hope is that ST-506 will be a meaningful treatment option for prion patients in the future
- Completion of final analyses of the nonclinical toxicity study and manufacturing of ST-506 needs to be completed prior to submission for regulatory approval of the clinical trial

What is next?

- Sangamo has started a legal process in the US called Chapter 11, which allows the company to restructure while continuing operations
- As part of this process, Sangamo has agreed to sell some of its programs, including the prion project, with Eli Lilly identified as a potential buyer. The final ownership will be decided through a formal sale process
- It is expected that a new owner will continue developing the prion program and work towards starting clinical studies
- Sangamo is working to complete the GLP toxicology study before the program is transferred to a new owner
- The new owner would take responsibility for producing the investigational treatment (ST-506) for use in a future clinical trial
- Sangamo team members are expected to support a smooth handover of the project to ensure continuity

What this means for patients and carers:

- The prion research program is expected to continue, although there may be some delays during the transition to a new owner
- The goal remains to progress this potential treatment into clinical trials