Session II: Considerations of delivery

Sarah DeVos / 04.23.19

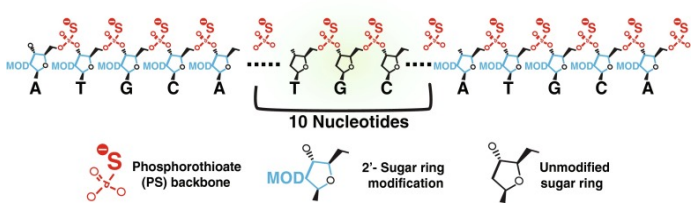
DISCLOSURE

THE IDEAS IN THIS PRESENTATION ARE MY OWN THOUGHTS AND OPINIONS AND DO NO REPRESENT THE DENALI THERAPEUTICS ORGANIZATION

CNS GENE THERAPY TECHNOLOGY ACROSS MULTIPLE MODALITIES

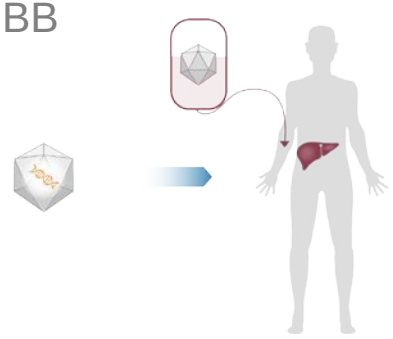
"Naked" Gene Therapy

- Those gene targeted therapies that do no use a viral capsid to modulate gene expression
- BBB penetration can be a major hurdle
- Often cell autonomous, though not always (ex. Alector's anti-sortillin approach)



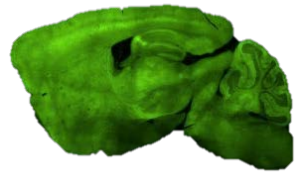
Peripheral AAV Gene Therapy

- Expressing your gene of interest in a peripheral setting using AAV
- BBB penetration still a hurdle – need to determine if your gene product can cross BBB
- Non-cell autonomous – generation of your protein in the periphery to impact those cells in the BBB



Central AAV Gene Therapy

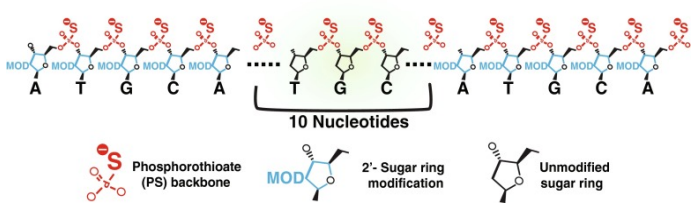
- Directed gene targeting to the CNS via direct injection into brain parenchyma, infusion into CSF, or IV delivery of BBB-crossing AAV
- BBB penetration for IV delivered AAV still an on-going hurdle, though actively pursued
- Can be cell autonomous or non-cell autonomous



CNS GENE THERAPY TECHNOLOGY ACROSS MULTIPLE MODALITIES

"Naked" Gene Therapy

- Those gene targeted therapies that do no use a viral capsid to modulate gene expression
- BBB penetration can be a major hurdle
- Often cell autonomous, though not always (ex. Alector's anti-sortillin approach)

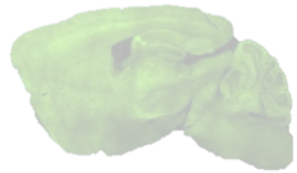


Peripheral AAV Gene Therapy

- Expressing your gene of interest in a peripheral setting using AAV
- BBB penetration still a hurdle – need to determine if your gene product can cross BBB
- Non-cell autonomous – generation of your protein in the periphery to impact those cells in the BBB

Central AAV Gene Therapy

- Directed gene targeting to the CNS via direct injection into brain parenchyma, infusion into CSF, or IV delivery of BBB-crossing AAV
- BBB penetration for IV delivered AAV still an on-going hurdle, though actively pursued
- Can be cell autonomous or non-cell autonomous



MAPT – MICROTUBULE ASSOCIATED PROTEIN TAU

- Tau was first described as a microtubule associated protein as it was found to bind to microtubules along the axons of neurons
  - This was further solidified when tau and beta-tubulin subunits were co-incubated in an in vitro system, long microtubules would form
- Was long thought that tau is required for neuronal function and axonal stability because of this first described function
- Duplication of 17q21.31 (location of MAPT) recently shown to cause prominent tau-related dementia with increased MAPT expression (Guennec et al, 2017)
- It may actually be the case that tau is sufficient for microtubule stability, but not necessary…

WHY TARGET TAU PRODUCTION VIA GENE TARGETED THERAPY?

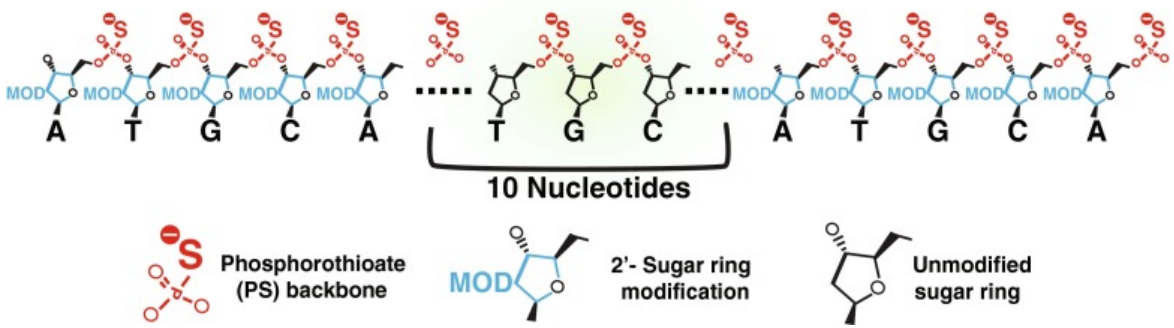
- There are several different mechanisms through which to target tau therapeutically:
  - Phosphorylation inhibition
  - Aggregation inhibitors
  - Microtubule stabilizers
  - Tau immunotherapy
  - Tau repression

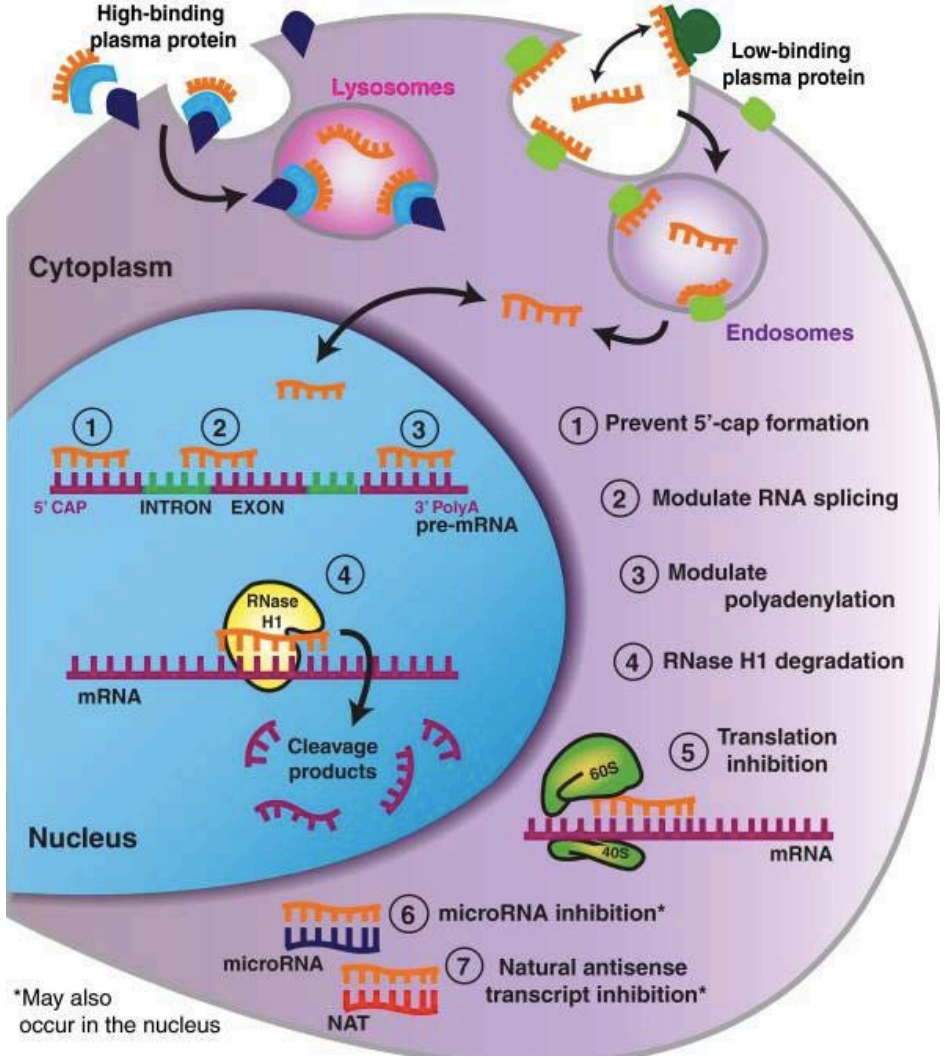
- **Rationale:**
  - Tau repression would directly and specifically target **all forms of tau intraneuronally**

HOW TO LOWER TOTAL TAU LEVELS WITH A NAKED GENE THERAPY?

Antisense Oligonucleotides

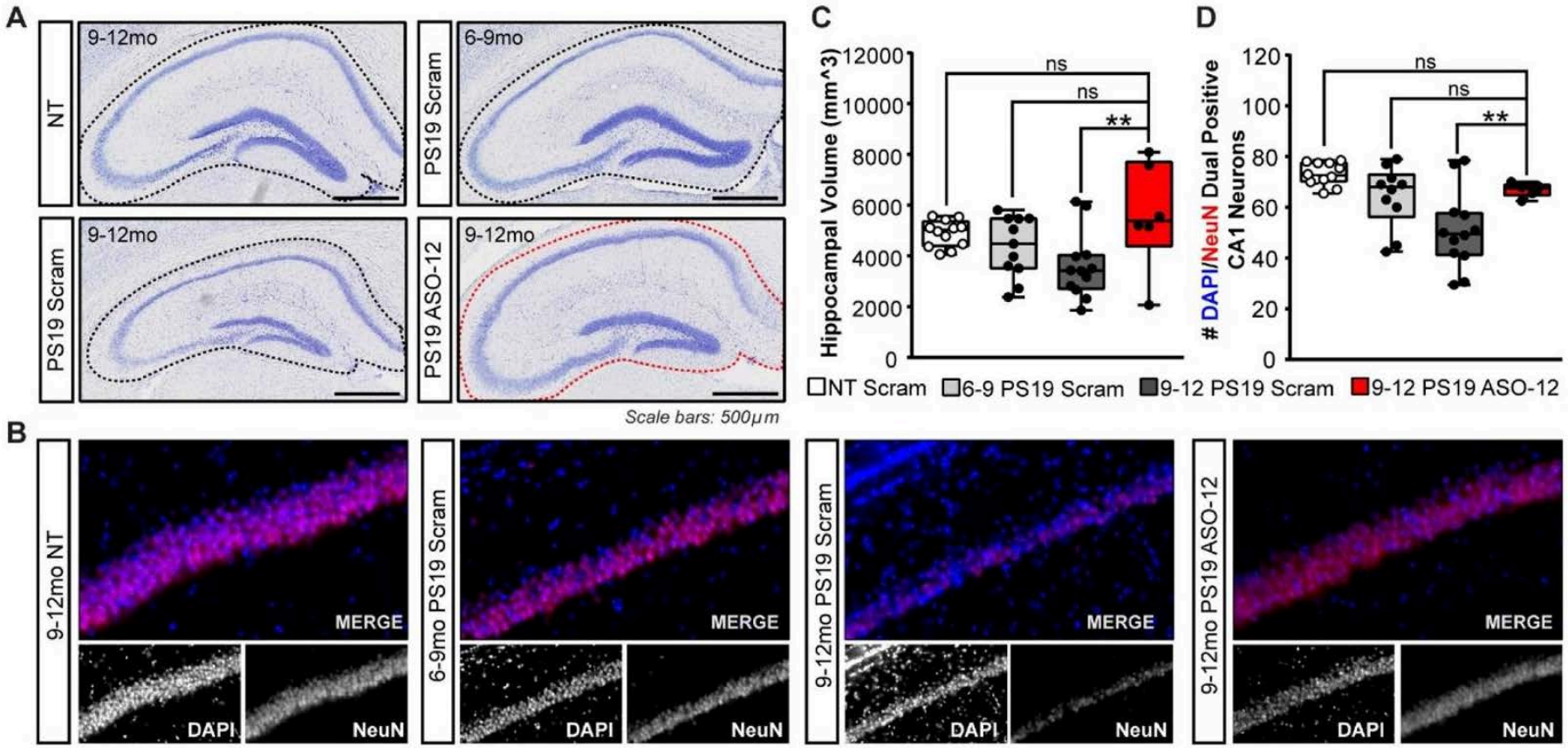
CAVEAT DOES NOT CROSS BBB





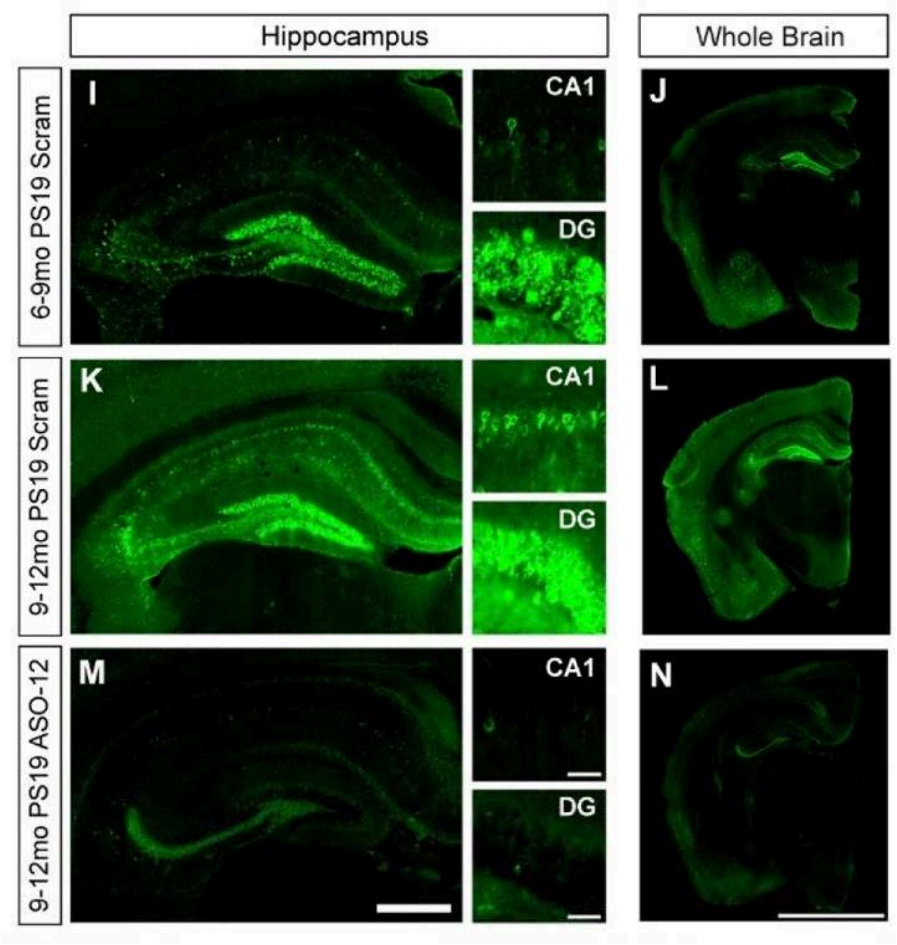
HUMAN TAU KNOCKDOWN IS PROTECTIVE IN FTD AND AD MOUSE MODELS

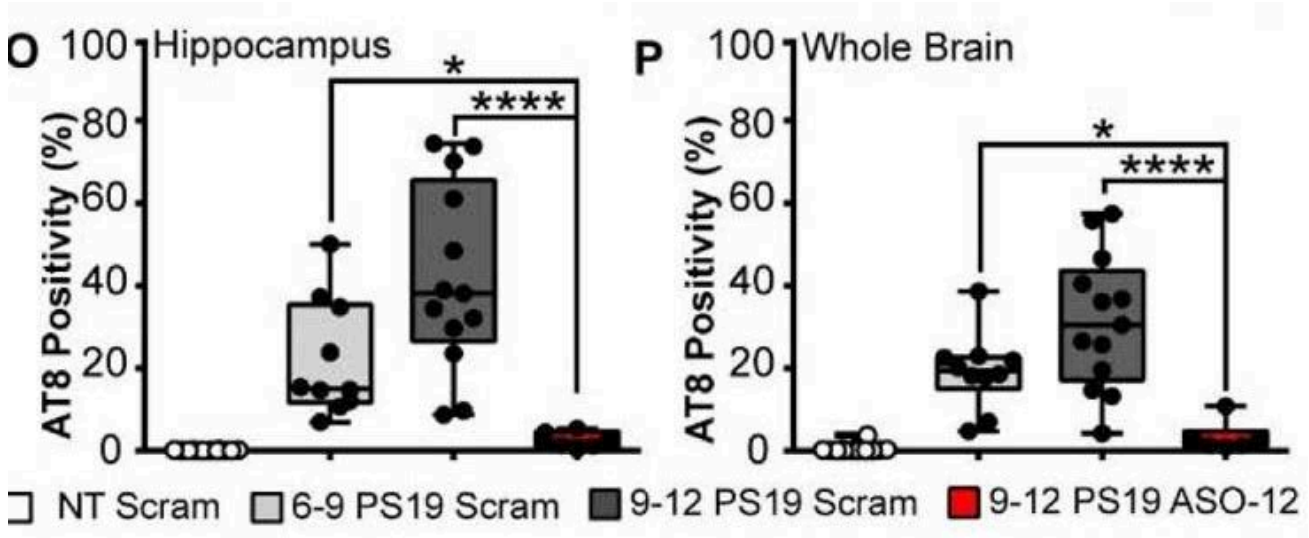
- Knocking down human tau with ASO protects PS19 mice from neuronal death and reverses tau pathology and seeding (DeVos et al, 2017)



HUMAN TAU KNOCKDOWN IS PROTECTIVE IN FTD AND AD MOUSE MODELS

- Knocking down human tau with ASO protects PS19 mice from neuronal death and reverses tau pathology and seeding (DeVos et al, 2017)





ENDOGENOUS TAU KNOCKDOWN IN HUMANS BIIB080 – SAFETY TBD

IONIS PHARMACEUTICALS

Biogen

OVERVIEW

Name: BIIB080
Synonyms: IONIS-MAPTRx, ISIS 814907
Therapy Type: RNA-based (timeline)
Target Type: Tau (timeline)

Condition(s): Alzheimer's Disease
U.S. FDA Status: Alzheimer's Disease (Phase 1)
Company: Biogen, IONIS Pharmaceuticals

BACKGROUND

This investigational therapeutic is the first antisense oligonucleotide (ASO) targeting tau expression to enter clinical trials. Developed by IONIS in collaboration with Timothy Miller at Washington University, St. Louis, ASOs that inhibit the translation of tau mRNAs into protein have been shown to reduce toxin-induced seizures, neuronal loss, and neurofibrillary pathology in adult tau-transgenic mouse models. They have also been shown to normalize behavioral phenotypes and lengthen survival in such mice. Infusion of tau ASO into the CSF of cynomolgus monkeys was shown to reduce tau mRNA across different brain regions, and CSF tau levels following ASO exposure have been correlated to hippocampal tau levels (Devos et al., 2013; DeVos et al., 2017).

Previous ASO therapies—developed against mutant SMA, SOD1, and huntingtin proteins—are delivered intrathecally to patients. The SMA, SOD1, and this tau-targeted ASO are partnered with Biogen; the ASO targeting huntingtin is partnered with Roche.

FINDINGS

In June 2017, Ionis started a 13-week, multiple-ascending-dose study of monthly intrathecal BIIB080 injections. Conducted at 10 sites in Canada and five European countries, this trial enrolls 44 people between age 50 and 74 whose mild AD is confirmed by CSF biomarkers. The primary outcome is adverse events; secondary outcomes include pharmacokinetic parameters such as trough and maximum concentrations reached in the CSF, time to maximal concentration and plasma elimination half-life, and concentration-time curves.

The trial uses a sentinel design, whereby the first two participants in each dose group are randomized 1:1 to placebo and at least one week must pass between dosing in these patients and any other patients. The design calls for four dose administrations and seven lumbar punctures (Lane et al., ANA 2017).

The trial is set to run until January 2020.

For all trials on this drug, see clinicaltrials.gov.

CLINICAL TRIAL TIMELINE

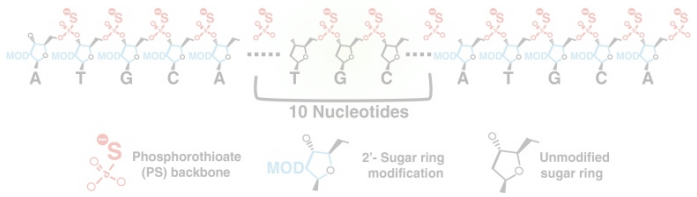
Phase 1/2 | Study completed / Planned end date | Planned end date unavailable | Study aborted

Sponsor	Clinical Trial	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027
IONIS Pharmaceuticals	NCT03186989			N=44										

CNS GENE THERAPY TECHNOLOGY ACROSS MULTIPLE MODALITIES

"Naked" Gene Therapy

- Those gene targeted therapies that do no use a viral capsid to modulate gene expression
- BBB penetration can be a major hurdle
- Often cell autonomous, though not always (ex. Alector's anti-sortillin approach)

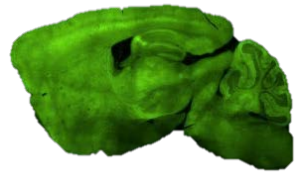


Peripheral AAV Gene Therapy

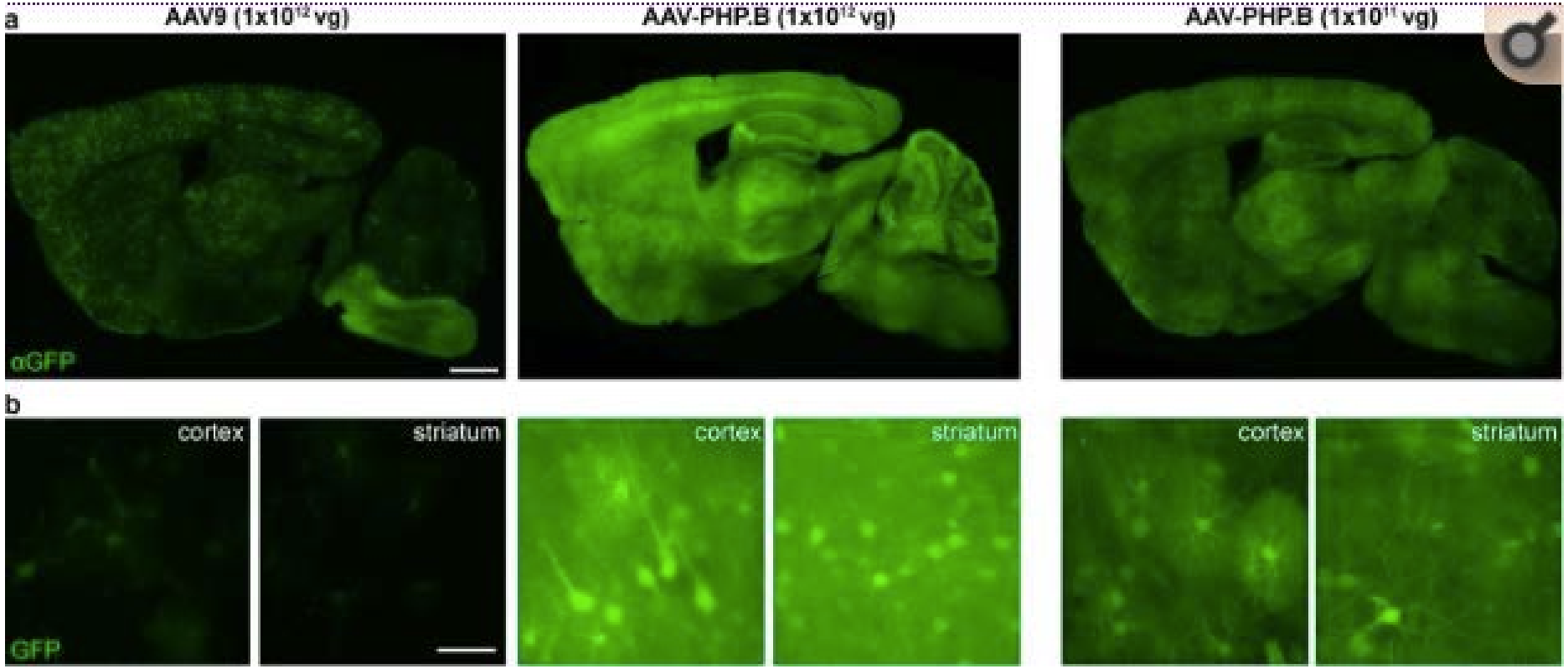
- Expressing your gene of interest in a peripheral setting using AAV
- BBB penetration still a hurdle – need to determine if your gene product can cross BBB
- Non-cell autonomous – generation of your protein in the periphery to impact those cells in the BBB

Central AAV Gene Therapy

- Directed gene targeting to the CNS via direct injection into brain parenchyma, infusion into CSF, or IV delivery of BBB-crossing AAV
- BBB penetration for IV delivered AAV still an on-going hurdle, though actively pursued
- Can be cell autonomous or non-cell autonomous

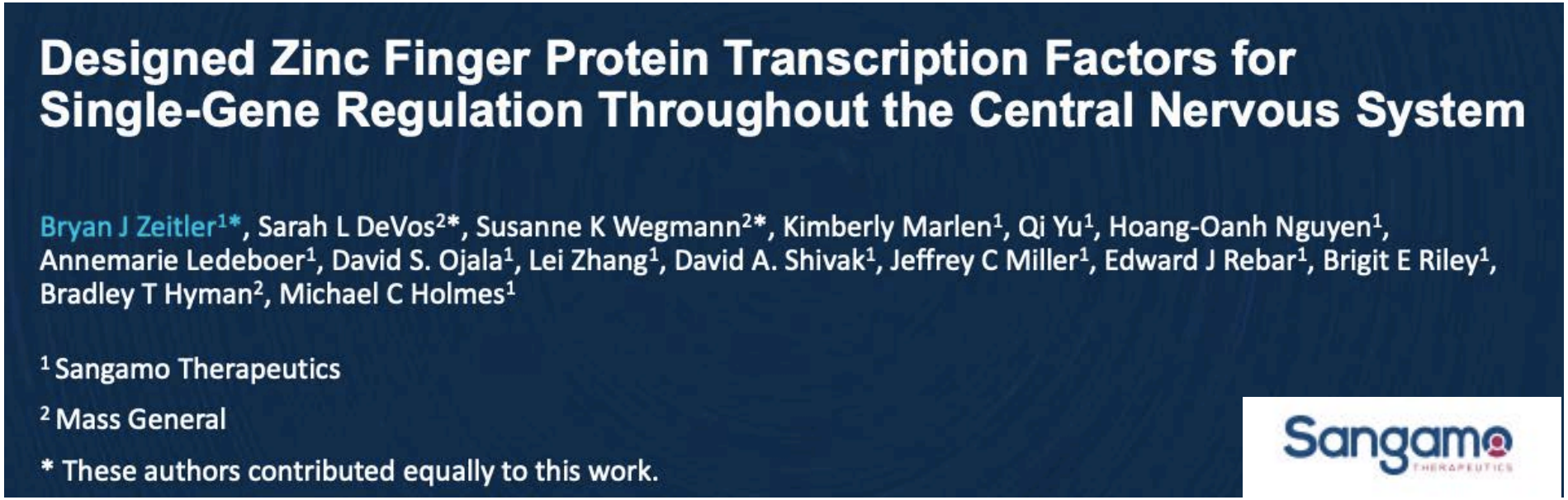


CENTRAL AAV GENE THERAPY AS A LONGER LASTING APPROACH



Deverman et al, 2016

CENTRAL AAV GENE THERAPY AS A LONGER LASTING APPROACH - MAPT



Designed Zinc Finger Protein Transcription Factors for Single-Gene Regulation Throughout the Central Nervous System

Bryan J Zeitler[1]*, Sarah L DeVos[2]*, Susanne K Wegmann[2]*, Kimberly Marlen[1], Qi Yu[1], Hoang-Oanh Nguyen[1], Annemarie Ledeboer[1], David S. Ojala[1], Lei Zhang[1], David A. Shivak[1], Jeffrey C Miller[1], Edward J Rebar[1], Brigit E Riley[1], Bradley T Hyman[2], Michael C Holmes[1]

[1] Sangamo Therapeutics

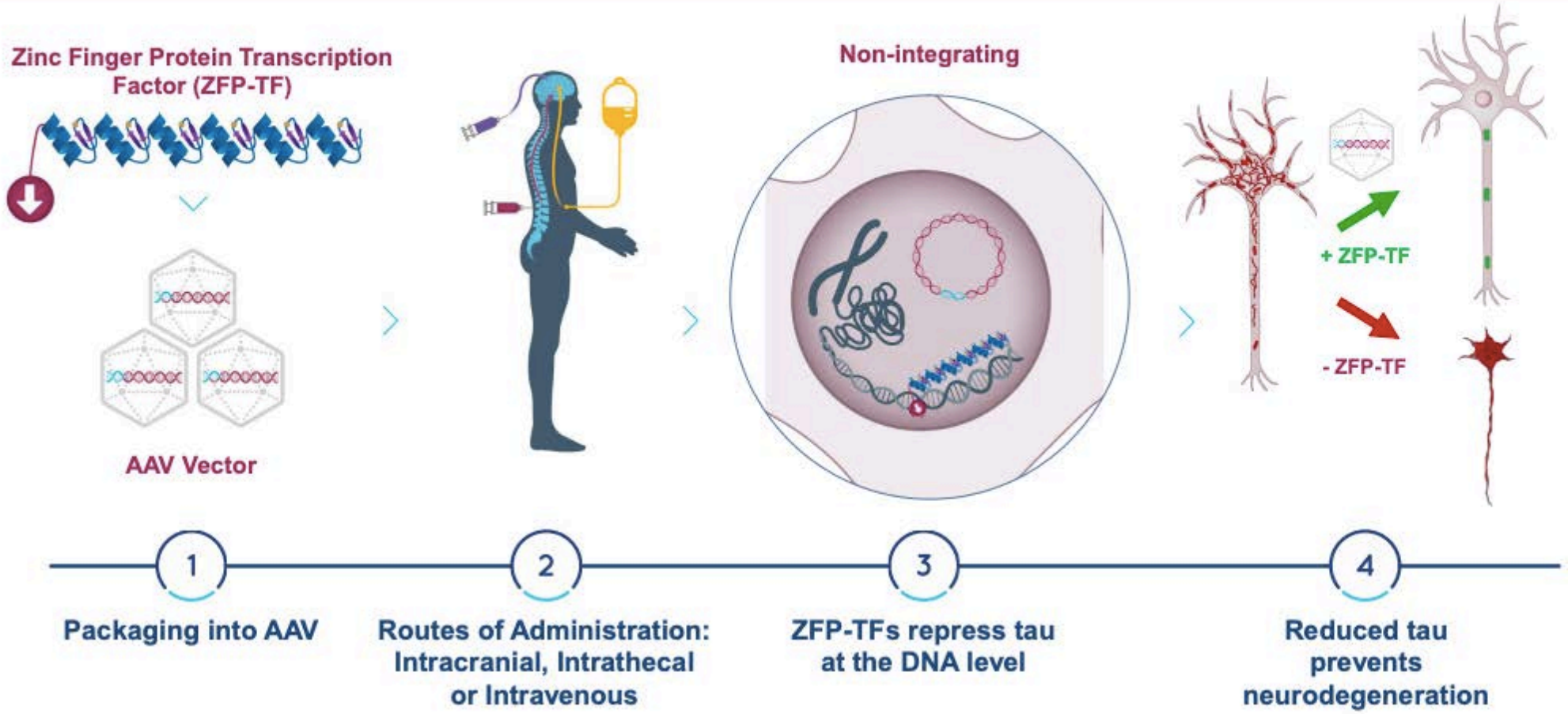
[2] Mass General

* These authors contributed equally to this work.

Sangamo THERAPEUTICS

CENTRAL AAV GENE THERAPY AS A LONGER LASTING APPROACH - MAPT

Single-administration AAV-ZFP-TF to lower all tau forms at DNA level



CENTRAL AAV GENE THERAPY AS A LONGER LASTING APPROACH - MAPT

Single-administration AAV-ZFP-TF to lower all tau forms at DNA level

Activity

- Potent tau reduction in mouse and human neurons
- Tau repression persists for at least 11 months in the hippocampus
- ZFP-TFs can reduce tau by up to 80% across the brain

Specificity

- ZFPs with no off-targets can be efficiently engineered
- Single-gene specific tau reduction in the hippocampus following IV delivery

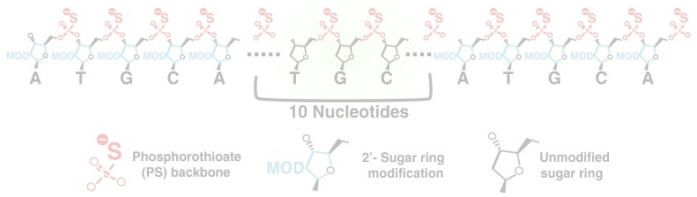
Efficacy

- ZFP-treatment reduced APP/PS1 neuritic dystrophies by 50% across the cortex

CNS GENE THERAPY TECHNOLOGY ACROSS MULTIPLE MODALITIES

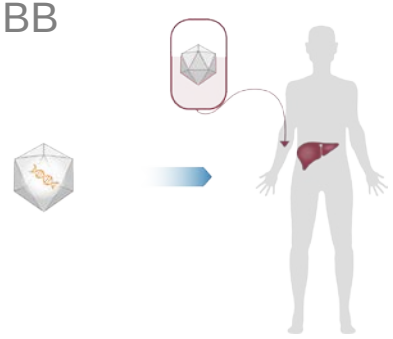
"Naked" Gene Therapy

- Those gene targeted therapies that do no use a viral capsid to modulate gene expression
- BBB penetration can be a major hurdle
- Often cell autonomous, though not always (ex. Alector's anti-sortillin approach)



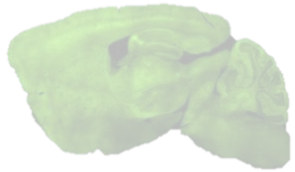
Peripheral AAV Gene Therapy

- Expressing your gene of interest in a peripheral setting using AAV
- BBB penetration still a hurdle – need to determine if your gene product can cross BBB
- Non-cell autonomous – generation of your protein in the periphery to impact those cells in the BBB



Central AAV Gene Therapy

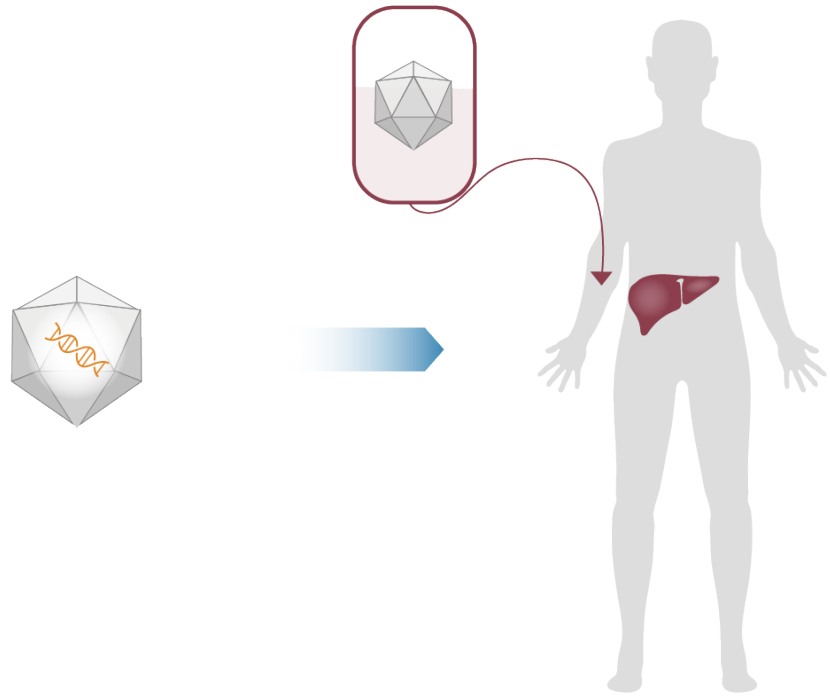
- Directed gene targeting to the CNS via direct injection into brain parenchyma, infusion into CSF, or IV delivery of BBB-crossing AAV
- BBB penetration for IV delivered AAV still an on-going hurdle, though actively pursued
- Can be cell autonomous or non-cell autonomous



RECENT DEALS/CLINICAL UPDATES ON AAV-DIRECTED LIVER EXPRESSION

2019 AAV Deals and News

- Roche – Spark:
  - $ 4.2B, liver focus
- Pfizer – Vivet:
  - $636M, liver focus
- Thermo Fisher – Brammer Bio
  - $1.7B, manufacturing
- Catalent – Paragon BioServices
  - $1.2B, manufacturing



- Clinical updates for Peripheral AAV approaches (all liver):
  - Sangamo (4/2019, $361M increase in stock price (AAV6 liver)
  - Uniqure (11/2018, 48% increase in stock price (AAV5 liver)
  - Biomarin (2/2019, accelerated filing planned for valoctocogene roxaparvovec (AAV5 liver)
  - Spark (12/2018, update on mid-dose LK03 liver)
  - AskBio (1/2019), Pompe FPI, AAV2/8 liver)

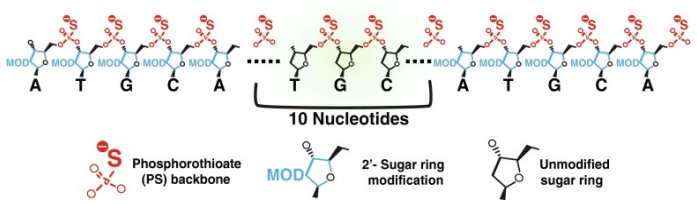
RECENT DEALS AND CLINICAL UPDATES FOCUSED ON AAV-DIRECTED LIVER EXPRESSION

Company	Preclinical	Phase I	Phase I/II	Phase III	Capsid	Dose
BIOMARIN					AAV5	high
uniQure					AAV5	high
Spark THERAPEUTICS					SPK-100	low
					LK03	medium
St. Jude Children's Research Hospital / UCL					AAV8	medium
Sangamo THERAPEUTICS					AAV6	high
ultragenyx pharmaceutical					AAV8	high
FREELINE THERAPEUTICS					AAVS3	low

CNS GENE THERAPY TECHNOLOGY ACROSS MULTIPLE MODALITIES

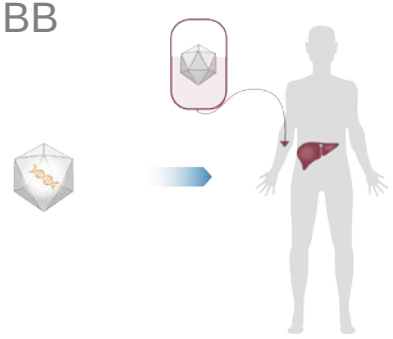
"Naked" Gene Therapy

- Those gene targeted therapies that do no use a viral capsid to modulate gene expression
- BBB penetration can be a major hurdle
- Often cell autonomous, though not always (ex. Alector's anti-sortillin approach)



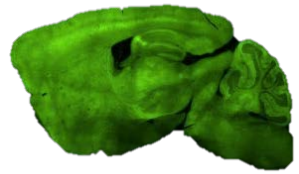
Peripheral AAV Gene Therapy

- Expressing your gene of interest in a peripheral setting using AAV
- BBB penetration still a hurdle – need to determine if your gene product can cross BBB
- Non-cell autonomous – generation of your protein in the periphery to impact those cells in the BBB



Central AAV Gene Therapy

- Directed gene targeting to the CNS via direct injection into brain parenchyma, infusion into CSF, or IV delivery of BBB-crossing AAV
- BBB penetration for IV delivered AAV still an on-going hurdle, though actively pursued
- Can be cell autonomous or non-cell autonomous




THANK YOU