ION717: An Antisense Oligonucleotide Designed to Lower Prion Protein

Robert Pulido, Ph.D.

Ionis Pharmaceuticals

Presented at Prion 2025 Congress - November 3-7, 2025

Disclosures

- I am a full-time employee and shareholder of Ionis Pharmaceuticals

Today's Talk

What I will be talking about:



- Background on Ionis and antisense technology
- The drug development process and where we are today within that process
- Details about the PrProfile trial design to understand the types of insights it will generate
- What to potentially expect on the horizon

What I will not be talking about:



- Results from the ongoing PrProfile clinical trial
- Confidential details about the trial design

Background on Ionis and Antisense Technology

IONIS®

The Leading Innovator
in RNA-targeted therapeutics

Biotechnology Company
Founded 1989

Headquarters
Carlsbad, CA

A Passion to Innovate

Ionis is guided by world-class scientists and business leaders whose passion to innovate is matched only by their commitment to deliver transformational medicines to patients who need them.

Our Medicines - Treating the Untreatable

- With RNA as the basis of our discovery platform, we are able to bring therapeutic options to patients who would otherwise have limited or no options
- Ionis has discovered and developed marketed medicines for serious diseases, including breakthrough medicines for neurologic and cardiometabolic diseases

DAWNZERA™ (donidalorsen) 80 mg/0.8 mL injection

QALSODY® (tofersen) 100 mg/15 mL injection

Tryngolza® (olezarsen) 80 mg injection

WAINUA® (eplontersen) 45 mg injection for subcutaneous use

SPINRAZA® (nusinersen) injection 12 mg/5 mL

SPINRAZA and QALSODY are registered trademarks of Biogen. WAINUA is a registered trademark of AstraZeneca. TRYNGOLZA is a registered trademark and DAWNZERA is a trademark of Ionis Pharmaceuticals, Inc. All other trademarks are property of their respective owners.

Leading Neurology Franchise

3

Approved Medicines

11

Medicines in Clinical Development

6

Wholly Owned Medicines in Clinical Development[4]

SPINRAZA® (nusinersen) injection 12 mg/5 mL [1]

QALSODY® (tofersen) 100 mg/15 mL injection [2]

WAINUA™ (eplontersen) 45 mg injection for subcutaneous use [3]



Zilganersen*
Alexander disease
(GFAP)
Clinicaltrials.gov NCT04849741

ION582*
Angelman syndrome
(UBE3A-ATS)
Clinicaltrials.gov NCT06914609
Clinicaltrials.gov NCT05127226

ION464*
Multiple System Atrophy
(alpha-synuclein)
Clinicaltrials.gov NCT04165486

ION717*
Prion disease
(PRNP)
Clinicaltrials.gov NCT06153966

Ulefnersen*
FUS-ALS
(FUS)
Clinicaltrials.gov NCT04768972

Tofersen*
Presymptomatic SOD1-ALS
(SOD1)
Clinicaltrials.gov NCT04856982

IONIS-MAPT$_{Rx}$/BIIB080*
Alzheimer's disease
(Tau)
Clinicaltrials.gov NCT05399888

Tominersen*
Huntington's disease
(HTT)
Clinicaltrials.gov NCT05686551

Salanersen*
SMA (SMN2)
Clinicaltrials.gov NCT05575011

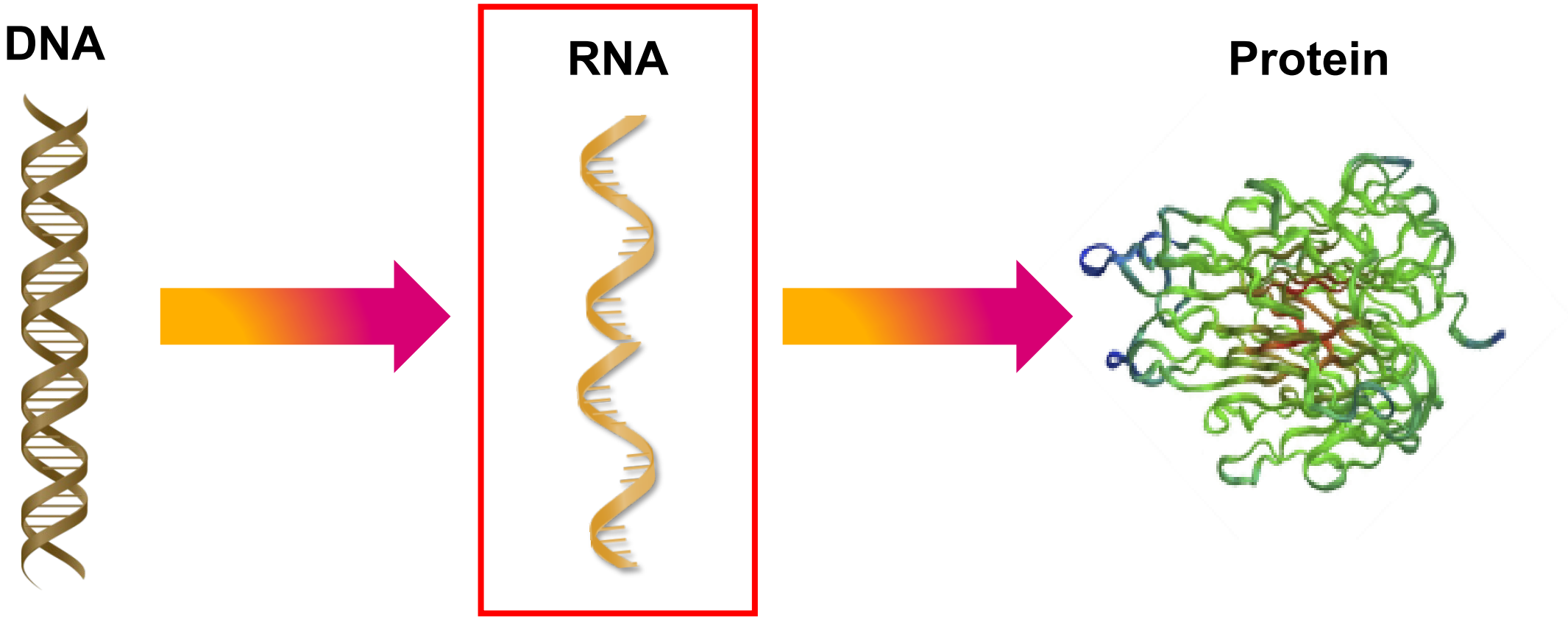
ION356*
Pelizaeus-Merzbacher
Disease (PLP1)
Clinicaltrials.gov NCT06150716

ION440*
MECP2 duplication
syndrome (MECP2)
Clinicaltrials.gov NCT06430385

***These investigational drugs are currently in clinical trials and have not been approved by any regulatory authority for marketing purposes in the populations being studied.**

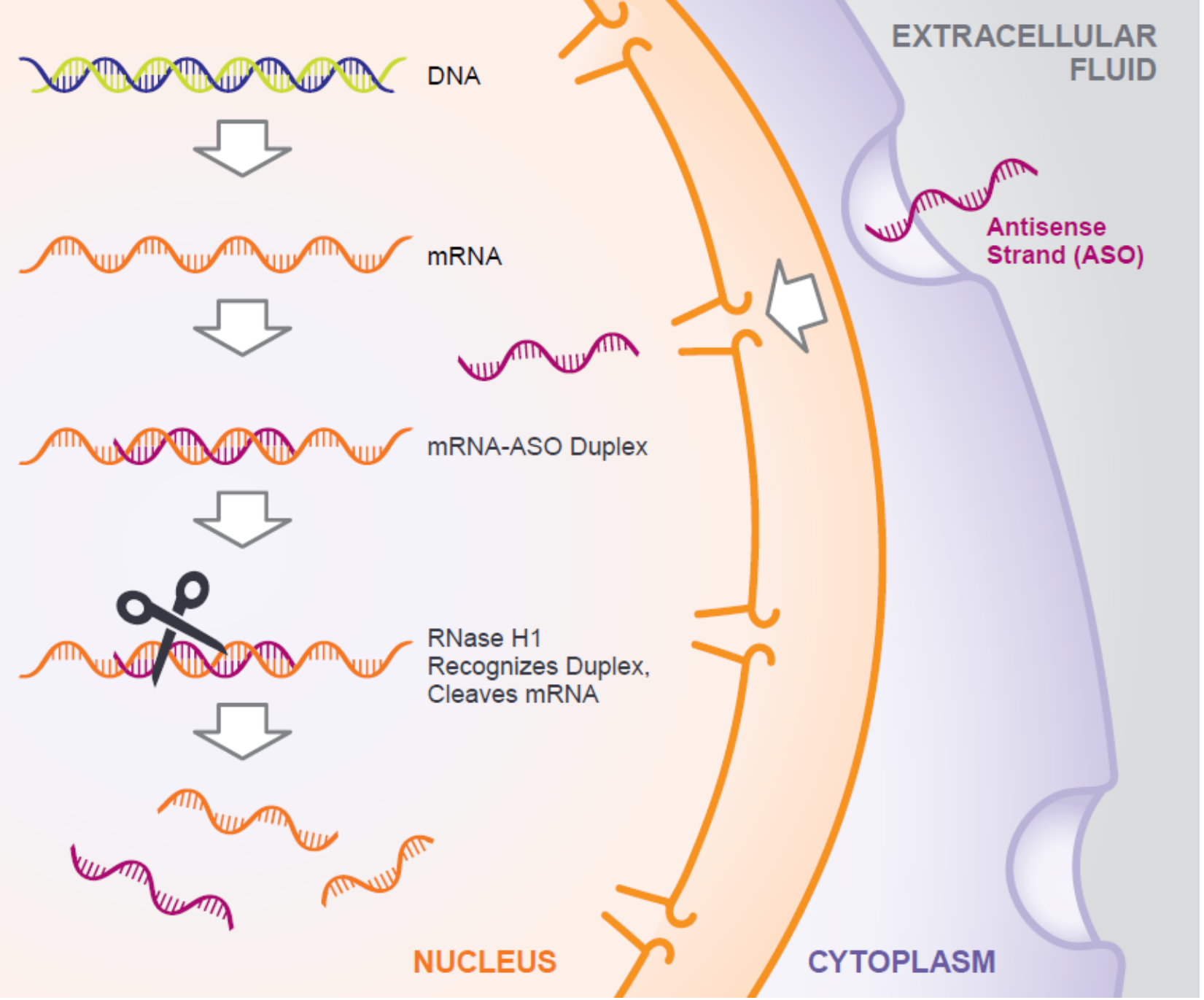
1. SPINRAZA: www.spinraza.com; 2. QALSODY: www.qalsody.com; Biogen is responsible for commercializing SPINRAZA and QALSODY; 3. WAINUA: www.wainua.com. Co-developing and commercializing WAINUA for ATTRv-PN and ATTR-CM in the U.S. with AstraZeneca. 4. Wholly owned programs include: zilganersen (Alexander disease), ION582 (Angelman syndrome), ION464 (MSA), ION717 (Prion disease), ION356 (PMD),and ION440 (MECP2 Duplication syndrome),

Central Dogma of Biology



The intermediate between DNA and protein

Less RNA = Less Protein



This image shows the RNase H1-mediated mechanism of action to lower protein production

Antisense Oligonucleotides (ASOs)

Act on RNA

Depending on design -

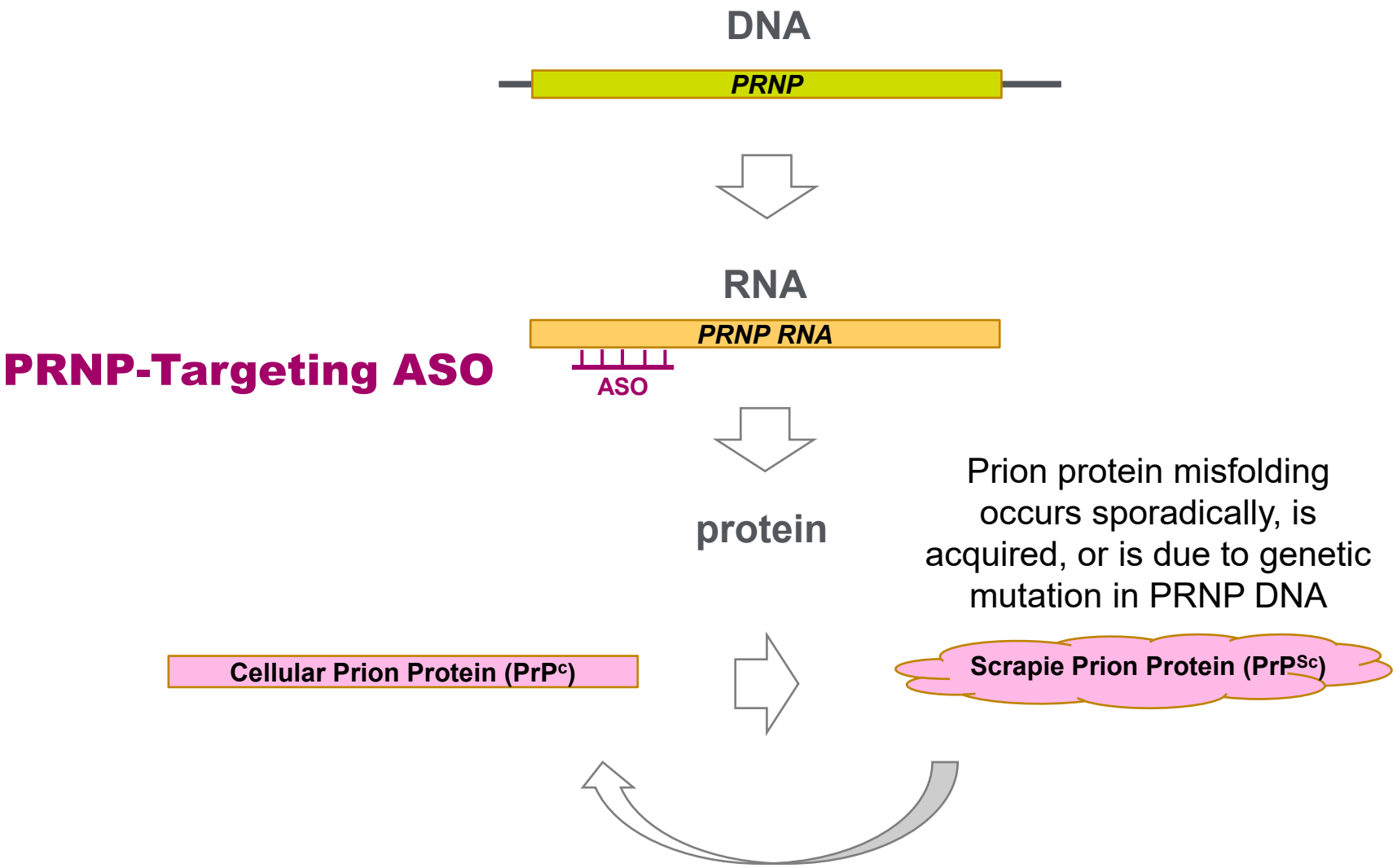
↑ or ↓ protein production

or change the protein that's produced

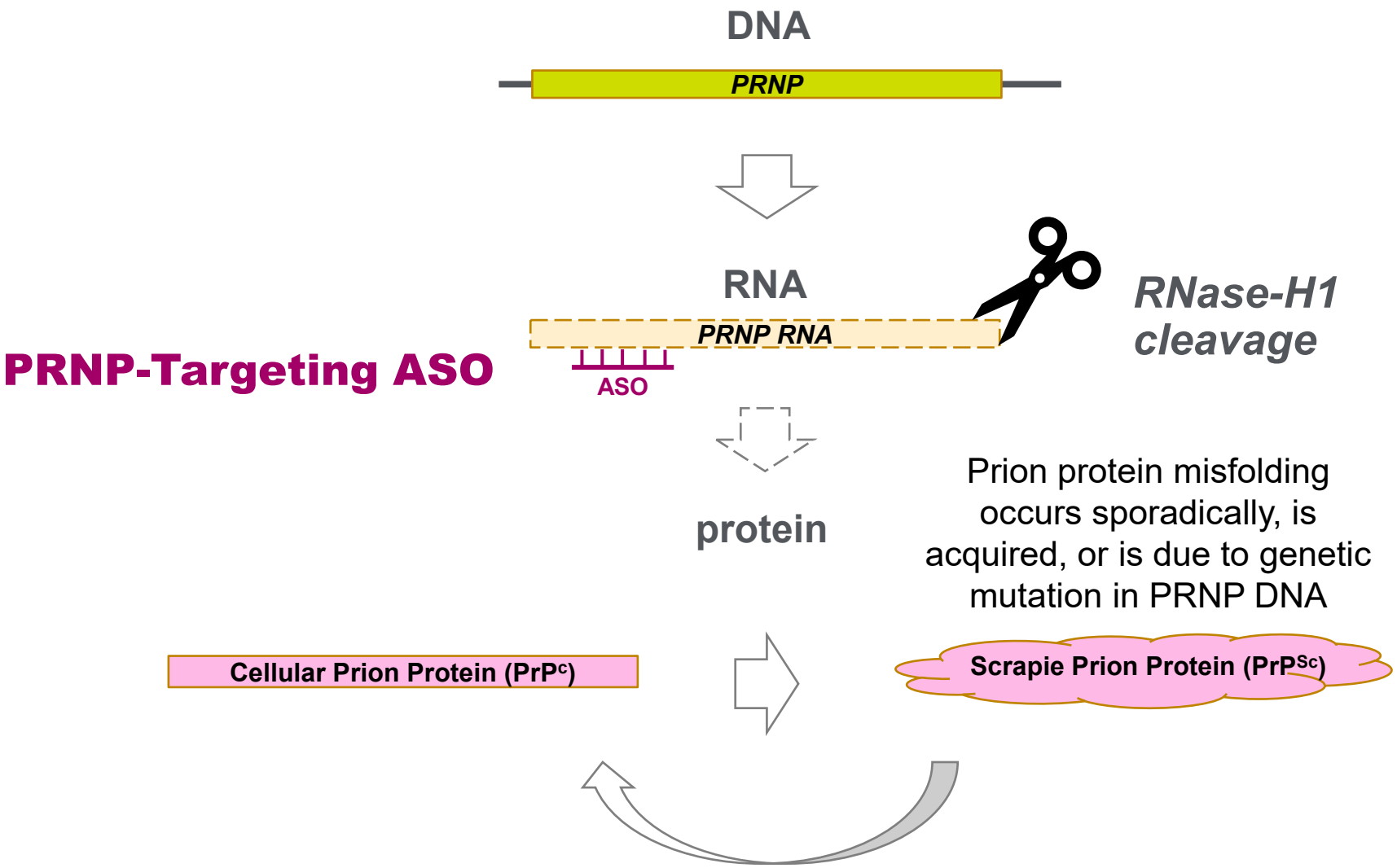
Highly specific & titratable

Treatments, not cures

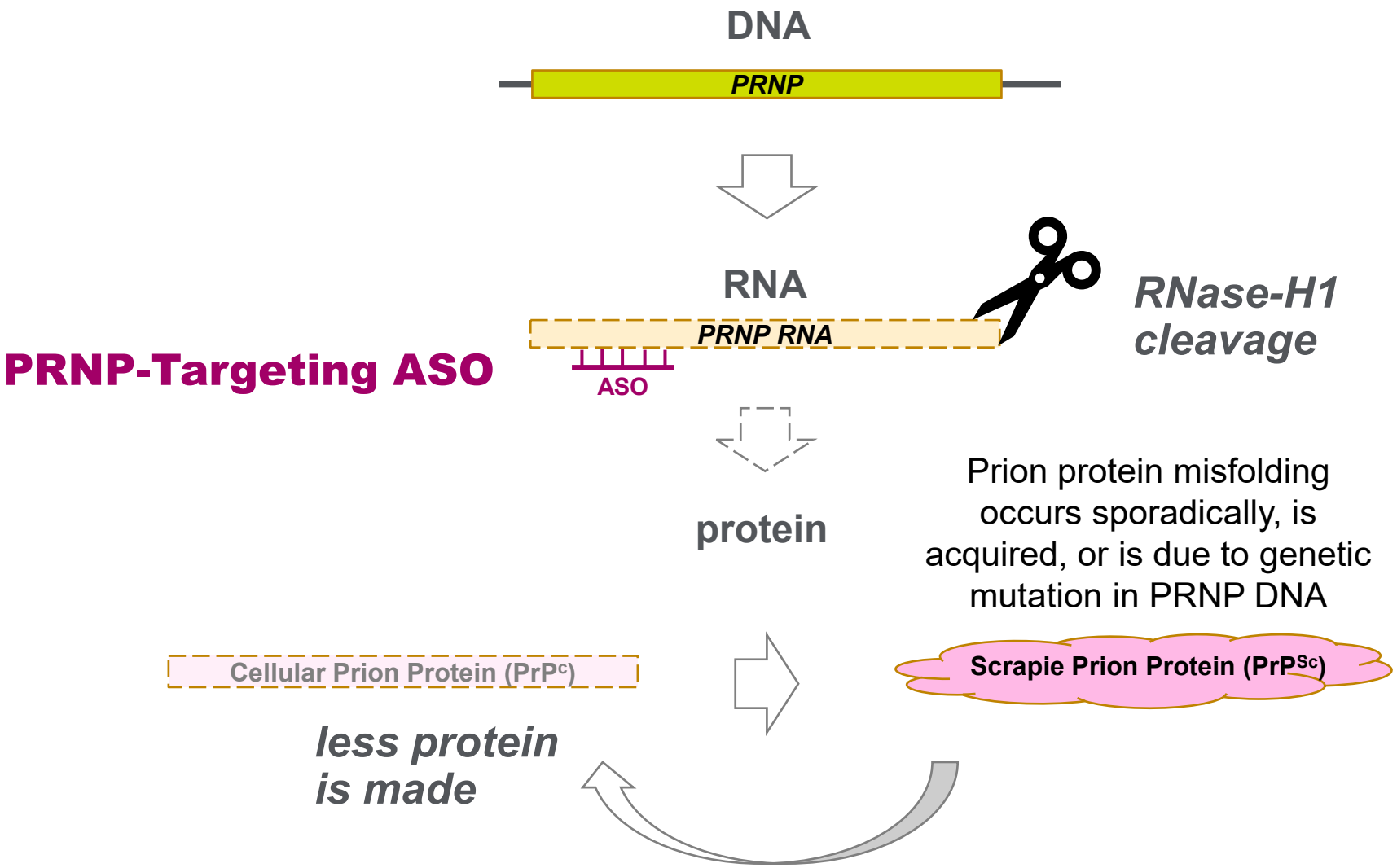
PRNP-targeting ASO
A Potential Therapeutic Approach to Treat Prion Disease



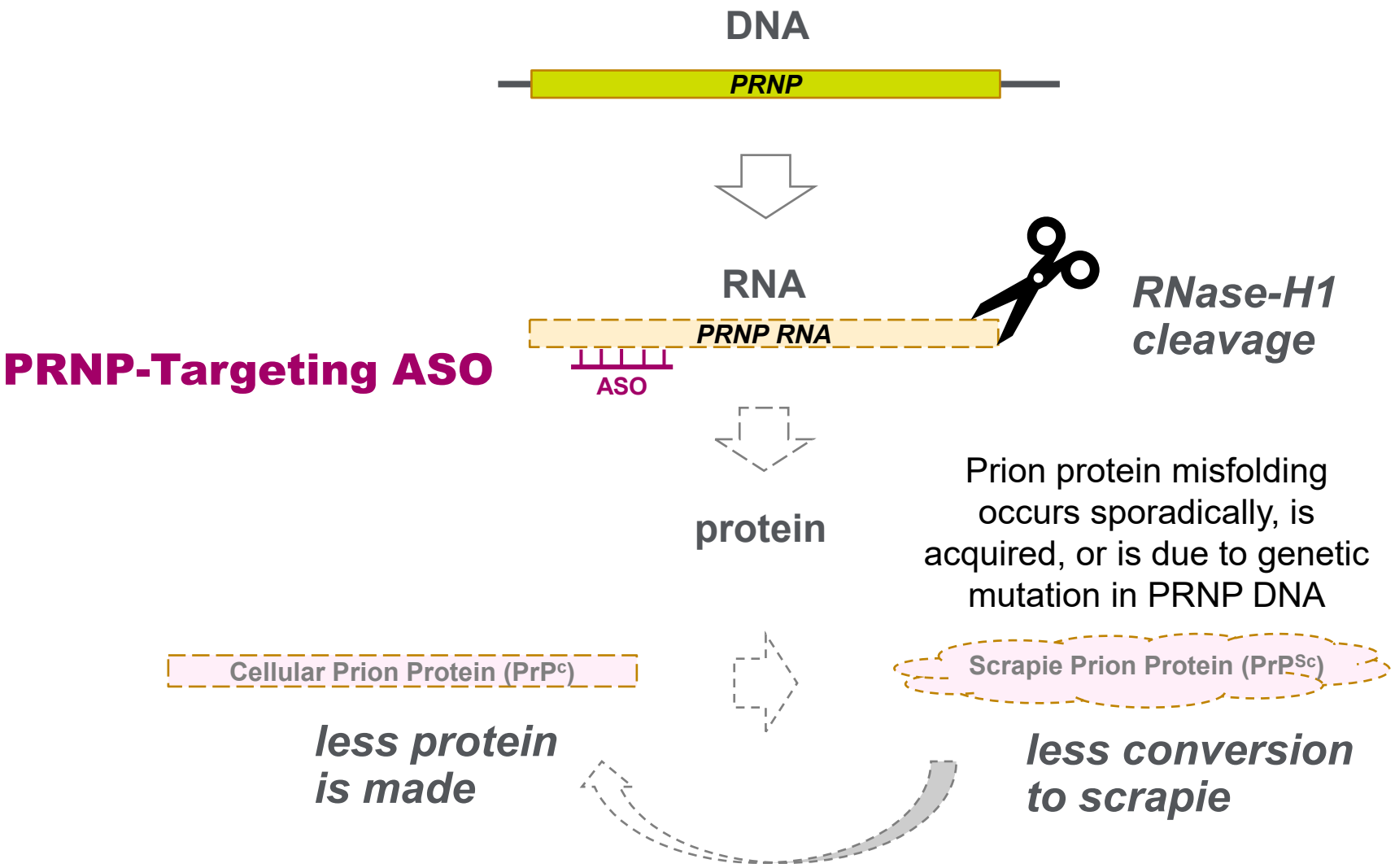
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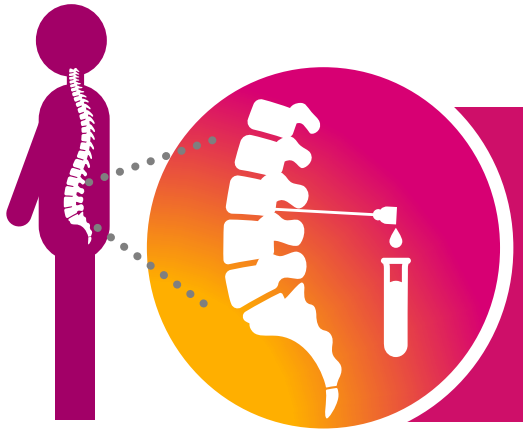
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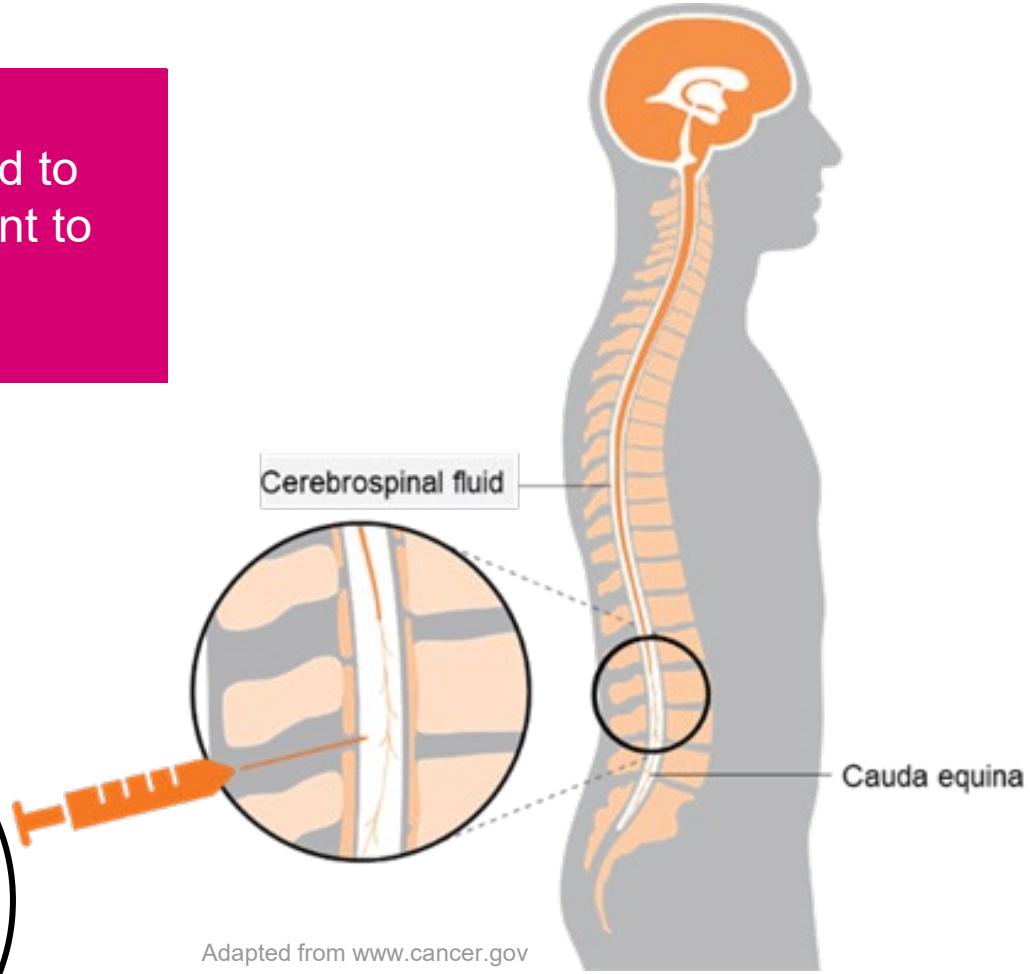
ASOs do not Cross the Blood-Brain Barrier and are Administered via Intrathecal (IT) Injection for Central Nervous System Targets



Cerebrospinal fluid (CSF) is collected to assess safety and biomarkers relevant to the disease of interest

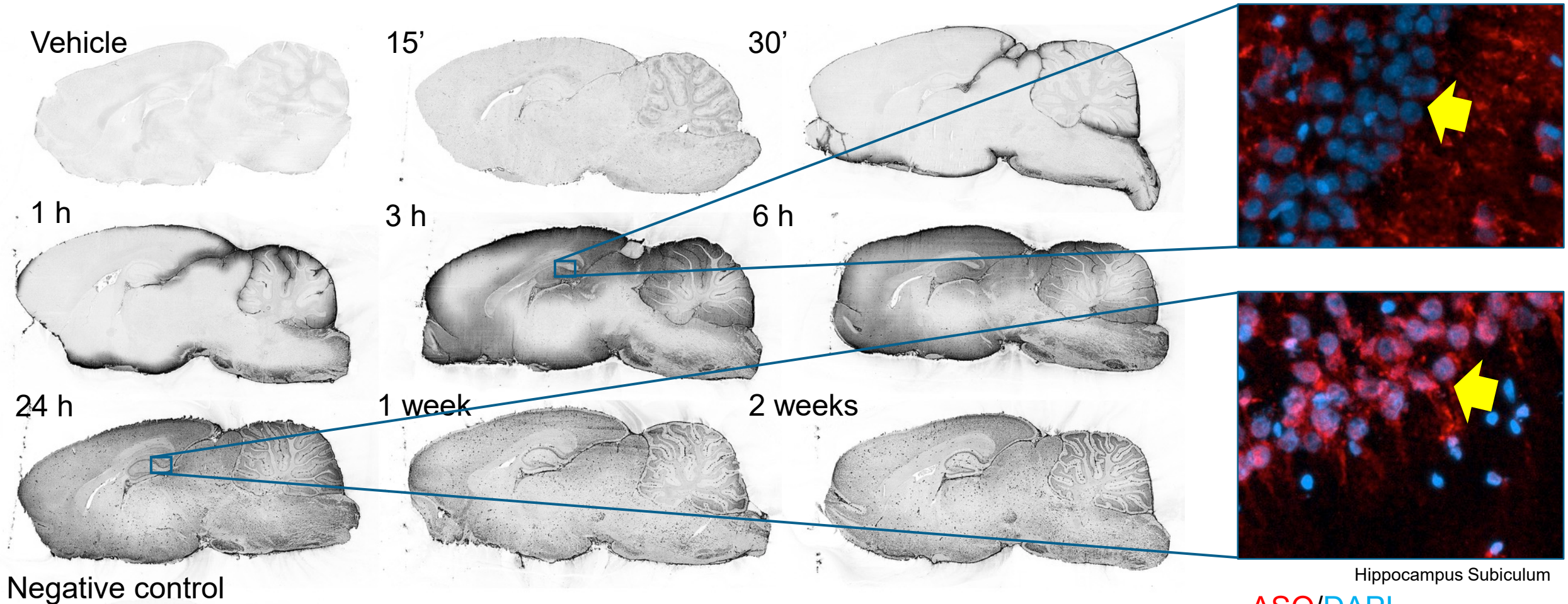
Study drug is administered intrathecally into the CSF via lumbar puncture





Adapted from www.cancer.gov

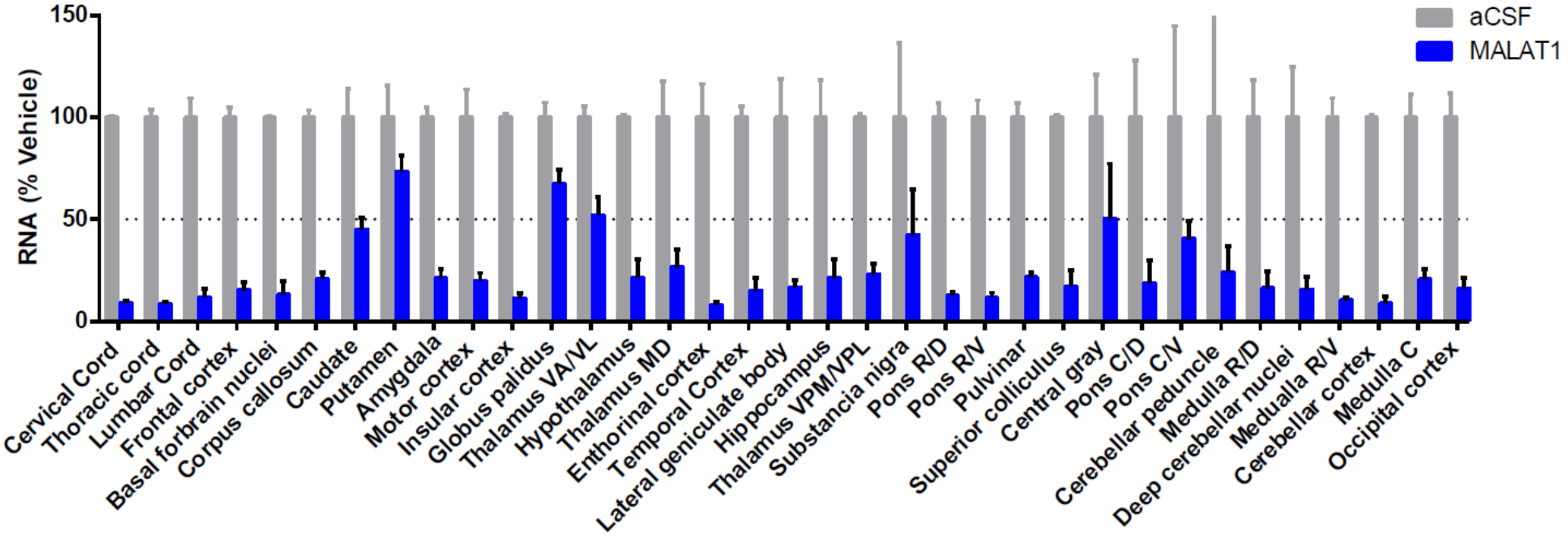
Early Time Course of ASO Uptake after Intrathecal dosing



ASO distributes to soma of neurons within 24 hours after dosing

Mazur et al. (2019) *JCI Insight*

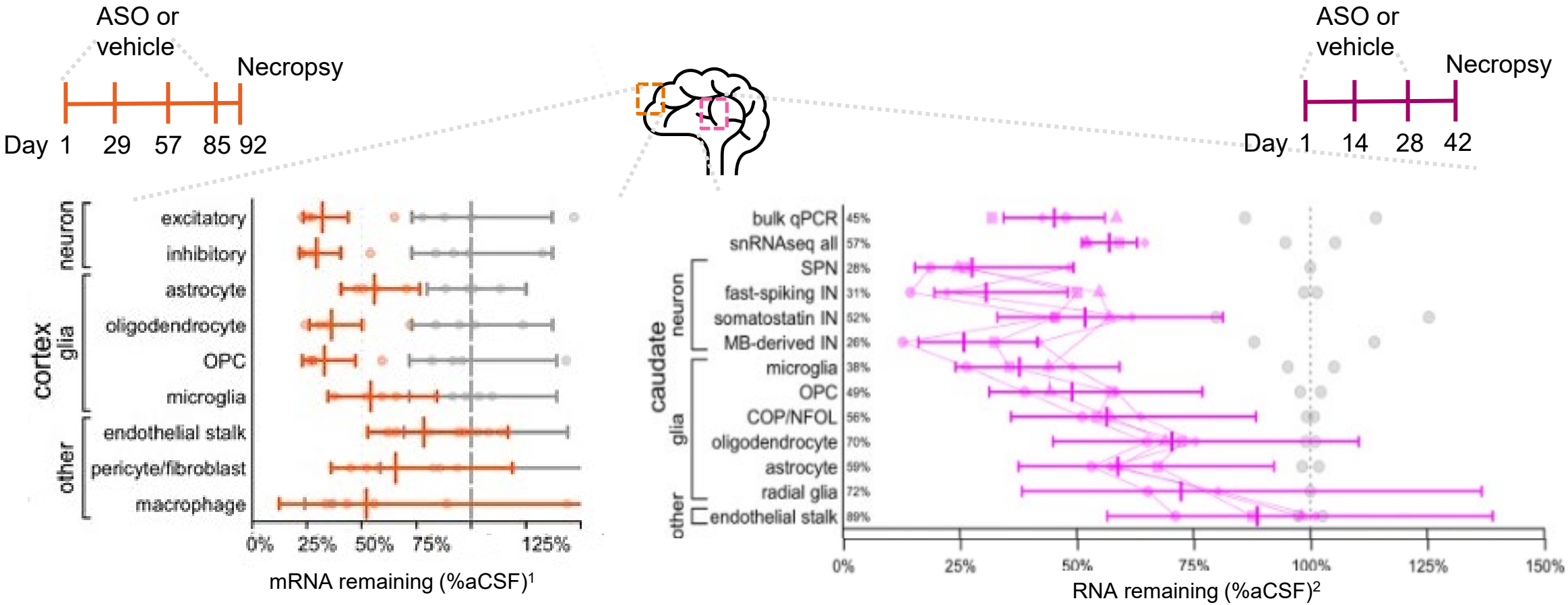
ASO Activity Observed Throughout Nonhuman Primate CNS Following Intrathecal Dosing



Jafar-nejad et al. (2021) *NAR*

ASO Activity Observed Across Cell Types in the CNS Following Intrathecal Dosing in Nonhuman Primate

- Single nuclei RNASeq of NHP brain treated with ASO
- Target knockdown observed in all CNS populations[1-2], albeit to different extent



1. Mortberg et al., NAR 2023 PMID: 27188501, 2. Frei et al., NAR 2025 PMID: 40857674

The Drug Development Process: Where are we today?

Ionis Prion Disease Drug Development Program



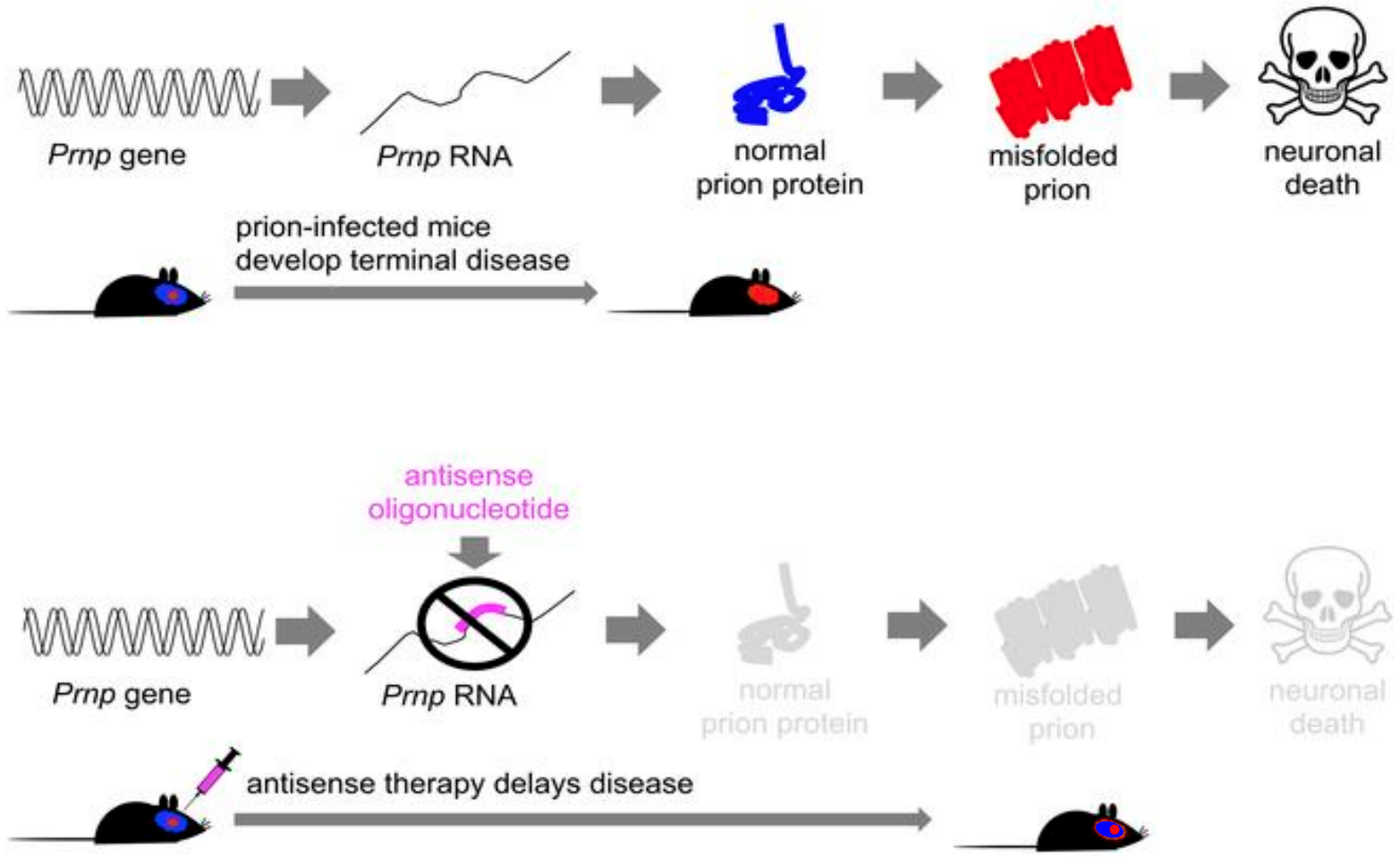
Prion disease program
began in 2006 with designing the first PRNP ASOs

Leveraging 30 years
of knowledge & experience with ASOs

Screened thousands of ASOs
for potency and tolerability

Identified ASOs
to trigger degradation of *PRNP* RNA

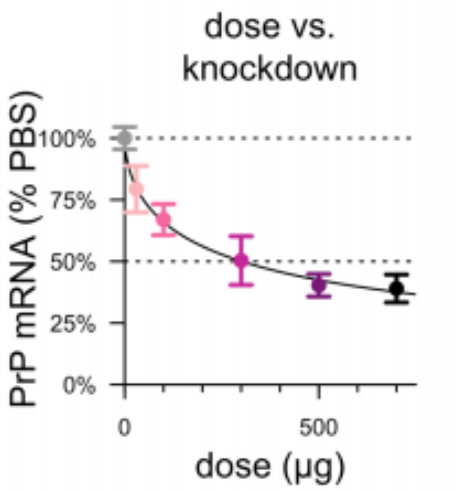
ASO-mediated PrP suppression is a disease modifying therapy in rodents with prion disease

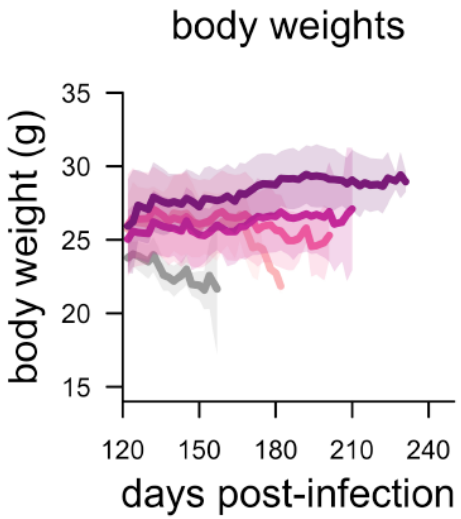


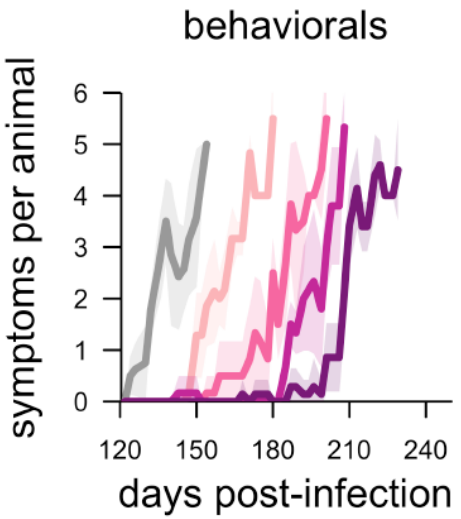
Raymond et al., JCI, 2019

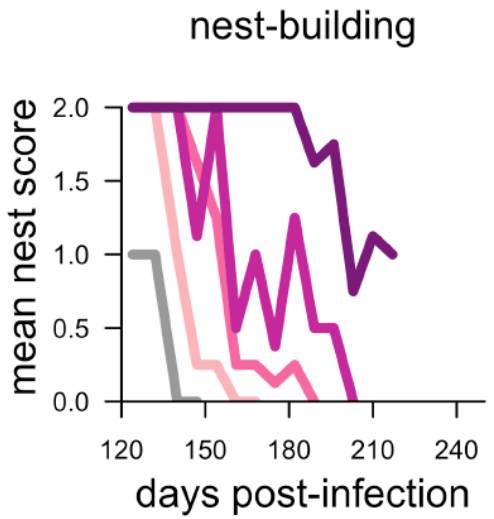
Prnp-Targeting ASO Activity and Efficacy are Dose-Responsive

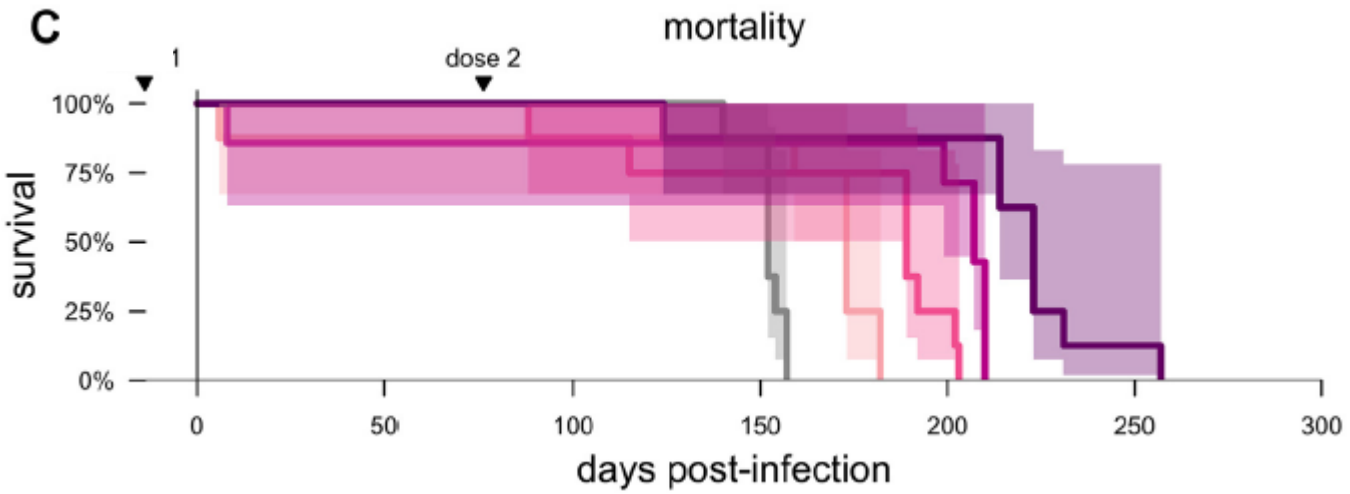






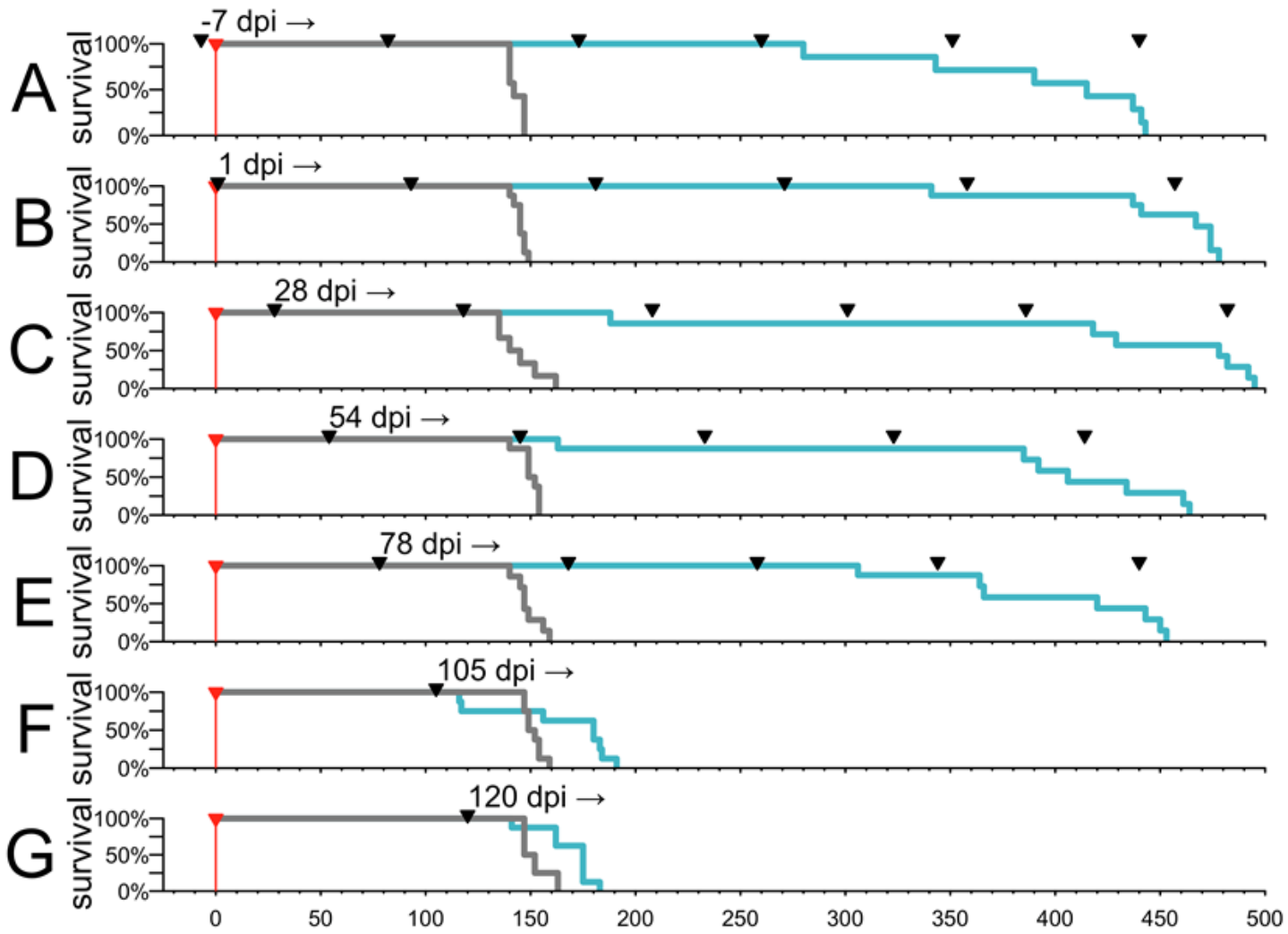






Minikel et al., NAR, 2020

Magnitude of efficacy in mice depends on timing of ASO treatment initiation



A PRNP-targeting ASO is a rational therapeutic approach to:

1. Prevent or delay onset of prion disease (at-risk mutation carriers)
2. Treat symptomatic prion disease (any etiology)

Panels A-G each represent survival plots in ASO-treated (blue) versus vehicle-treated (gray) prion-infected mice after initiating treatment after the number of days post-infection (dpi) denoted.

Minikel et al., NAR, 2020

Ionis Prion Disease Drug Development Program



Prion disease program

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Leveraging 30 years

of knowledge & experience with ASOs

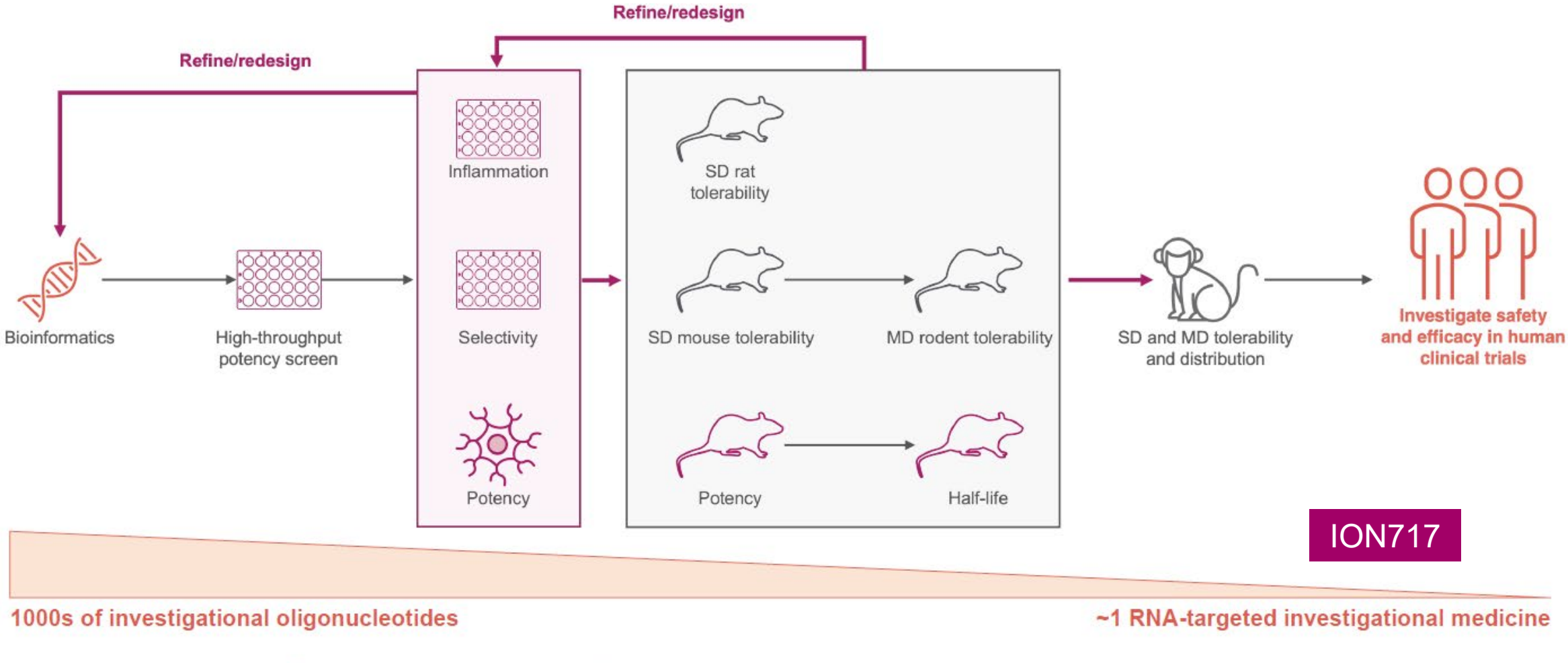
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Ionis is Continually Advancing the Design, Screening, and Development of its Investigational RNA-Targeted Medicines for Neurological Diseases



SD = single dose

MD = multiple dose

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Work with **clinicians, caregivers, advocacy groups, regulators** and **payers** to design optimal clinical trials to efficiently understand whether a drug is safe and effective

- Are we targeting the **right patient population**?
- Are we including the **right assessments**?
- Are we considering the **right operational factors**?

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A Phase 1/2a Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of ION717

NCT06153966

Ph1/2a Study Objectives

Primary — *Safety & Tolerability*

- Adverse events
- Other safety parameters

Secondary — *Pharmacokinetics & Pharmacodynamics*

- ION717 levels in CSF, blood and urine
- PrP levels in CSF

Exploratory — *Efficacy*

- Clinician-, patient- and caregiver-reported outcome measures
- CSF and plasma biomarkers

Inform next steps (e.g., dose selection for subsequent research)

Study Periods and Evaluations

PrPROFILE

Screen → **Double-Blind Treatment Period** → **Open-Label Treatment Period** → **Untreated Follow-Up Period**

In-clinic **evaluation of eligibility** for study participation

Key **Inclusion Criteria** include:

- Adults with early-stage disease
- Willing to meet all study requirements

Key **Exclusion Criteria** include:

- Condition that could interfere with the lumbar puncture process, CSF circulation, or safety assessments
- Condition that could interfere with study participation

In-clinic and remote visits for **Study Drug (ION717 or placebo) administration & evaluations** of safety, PK, and exploratory PD & efficacy assessments

In-clinic and remote visits for **ION717 administration & evaluations** of safety, PK, and exploratory PD & efficacy assessments

In-clinic and remote visits for **evaluations** of safety, PK, and exploratory PD & efficacy assessments

Evaluations include:

- Adverse events
- Blood tests (drug, chemistry, hematology)
- Urine tests (drug, standard urinalysis)
- CSF tests (drug, safety, PrP, disease biomarkers)
- Vital signs
- ECG
- MRI
- Physical & neurological exams
- Columbia Suicide Severity Rating Scale (C-SSRS)
- MRC Prion Disease Rating Scale
- Motor Function Scale
- Telephone Interview for Cognitive Status (TICS)
- Neuropsychiatric Inventory Questionnaire (NPI-Q)
- Modified Rankin Scale
- Global Impression Measures

Double-Blind Treatment Period Analysis Plan

PrPROFILE

Screen → **Double-Blind Treatment Period** → **Open-Label Treatment Period** → **Untreated Follow-Up Period**

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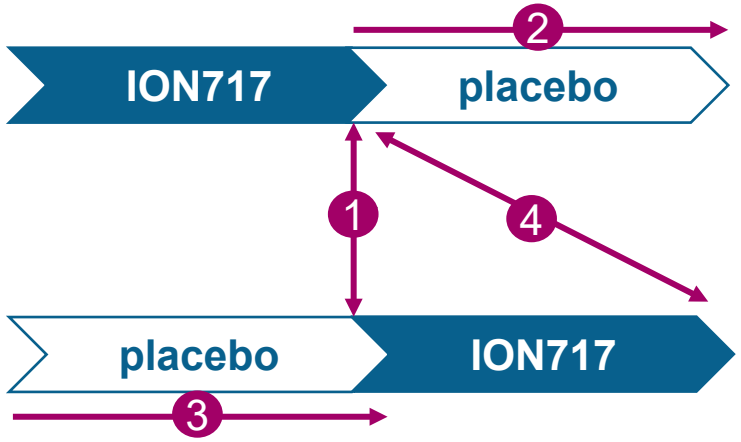
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Study Drug administration during the Double-Blind Treatment Period:

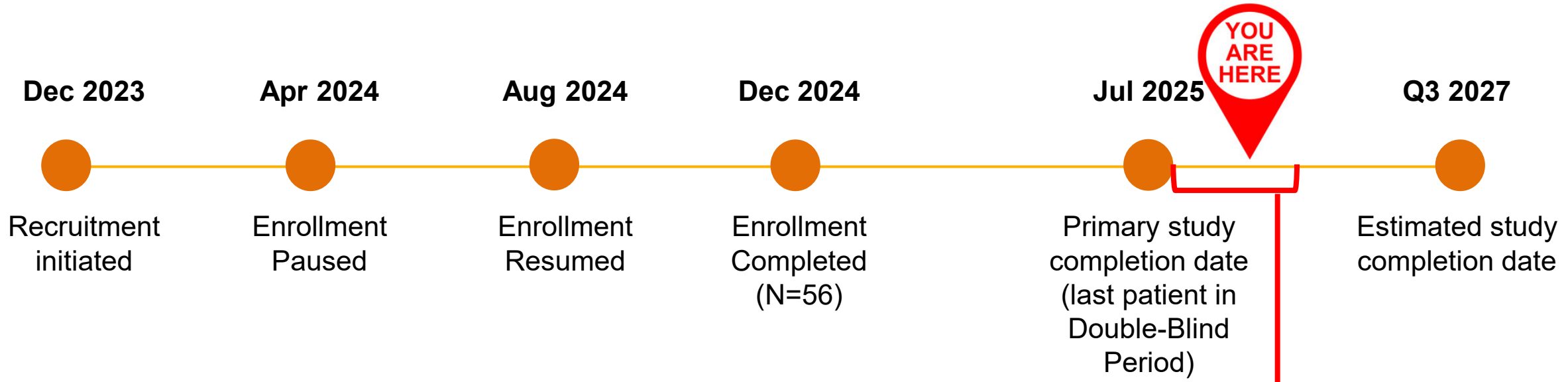


Analyses include:

1. ION717 effects vs. placebo
2. Durability of ION717 effects
3. Changes over time due to disease (natural history for this study population)
4. Impact of delayed initiation of ION717, i.e., ION717 effects when initiated “early” vs. “late”

What comes next?

Timeline of the PrProfile Study



- Study sites visited, data verified as complete and valid
- Database is locked (i.e., data can no longer be altered)
- Biostatisticians conducting preplanned analyses
- Data will be interpreted
- Plan to share initial results with community in 2026

Thank you!

- Phenomenal commitment from patients and caregivers to participate in clinical research
- CJD Foundation and CJDISA
- Dr. Alberto Bizzi for imaging expertise
- Ionis Prion Team
- PrProfile Study Vendors
- Other collaborators/advisors (too many to name!)

IONIS®

PrPROFILE

- PrProfile Investigators and Site Staff
  - Brian Appleby, University Hospitals Cleveland Medical Center
  - Inga Zerr & Peter Hermann, University Medical Center Göttingen
  - Steven Arnold, Massachusetts General Hospital
  - Nurit Omer & Noa Bregman, Tel Aviv Sourasky Medical Center
  - Jean-Philippe Brandel, Hôpital Universitaire Pitié Salpêtrière
  - Raquel Sánchez-Valle, Hospital Clinic De Barcelona
  - Hidehiro Mizusawa, National Center of Neurology and Psychiatry
  - Takashi Kanda, Neuromuscular Center Yoshimizu Hospital
  - Ban Mihara, Mihara Memorial Hospital
  - Giuseppe Di Fede, Fondazione I.R.C.C.S. Istituto Neurologico Carlo Besta
  - Massimo Pandolfo, McGill University Health Centre
  - Thomas Wisniewski, NYU Langone Health
  - Dennis Velakoulis, Royal Melbourne Hospital
  - Susan Perlman, UCLA Neurology Clinic
  - Valerie Sim, University of Alberta
  - Patrick Bosque, University of Colorado Hospital