Precision Strategies in Alzheimer's Disease: From Biomarkers to Combination Therapies

Larisa Reyderman

Eisai Inc

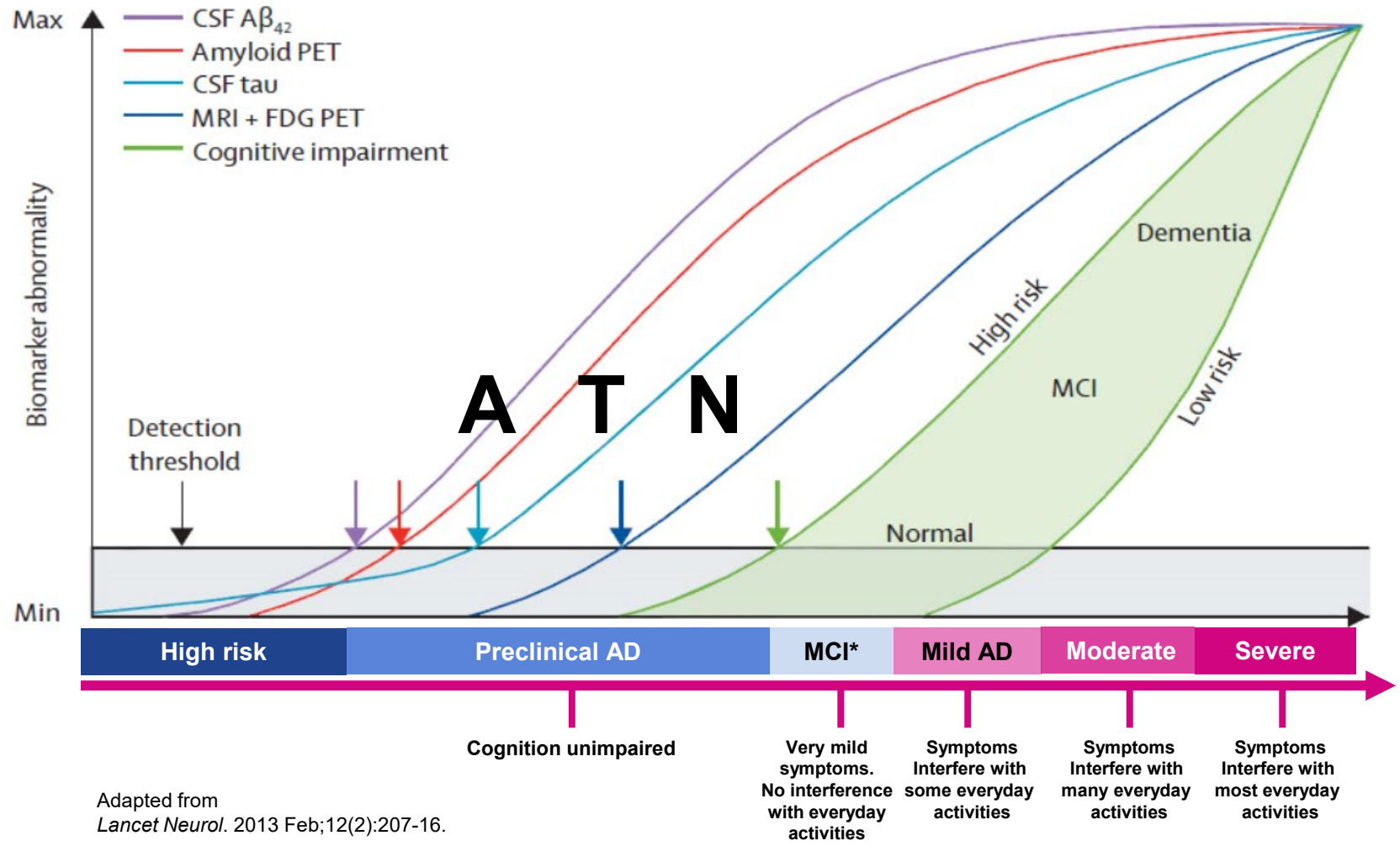
Alzheimer's Disease Continuum

A/T/N Framework

A — Amyloid
Measured by amyloid PET, CSF Aβ42, or plasma Aβ42/40

T — Tau
Measured by CSF p-tau, tau PET, or plasma p-tau

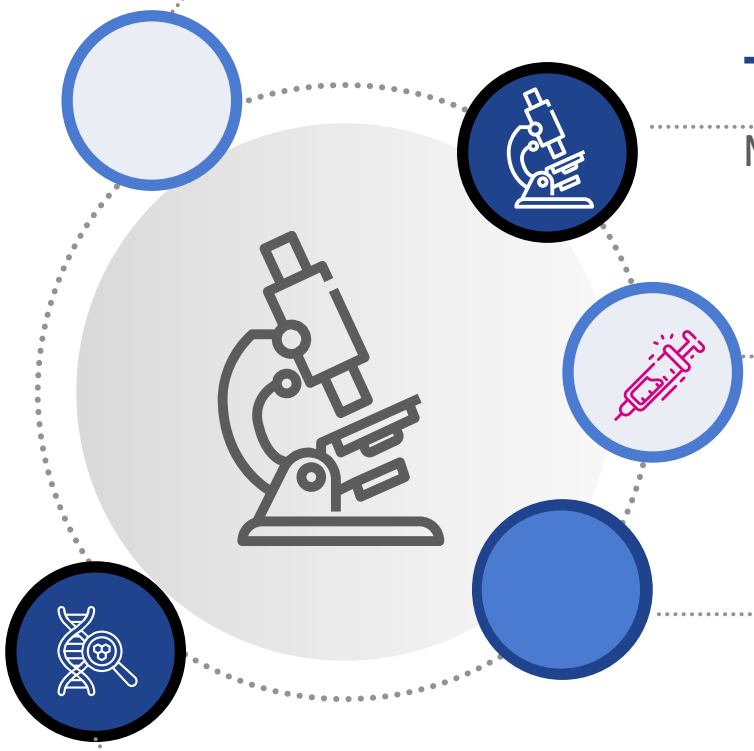
N — Neurodegeneration
Measured by MRI atrophy, FDG-PET, or NfL



Adapted from
Lancet Neurol. 2013 Feb;12(2):207-16.

*MCI due to AD.
Aβ, amyloid-beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography.

What Precision Medicine Means in Alzheimer's Disease



Select the right patients

Those with the biology the drug targets

Test the Right Hypothesis

Mechanism-aligned and mapped to the Alzheimer's disease cascade

Select the Right Dose

Dose justified by biomarker evidence of target engagement and pathway modulation

Measure the right pharmacodynamic signals

To show target engagement and pathway modulation

Design rational combination therapies

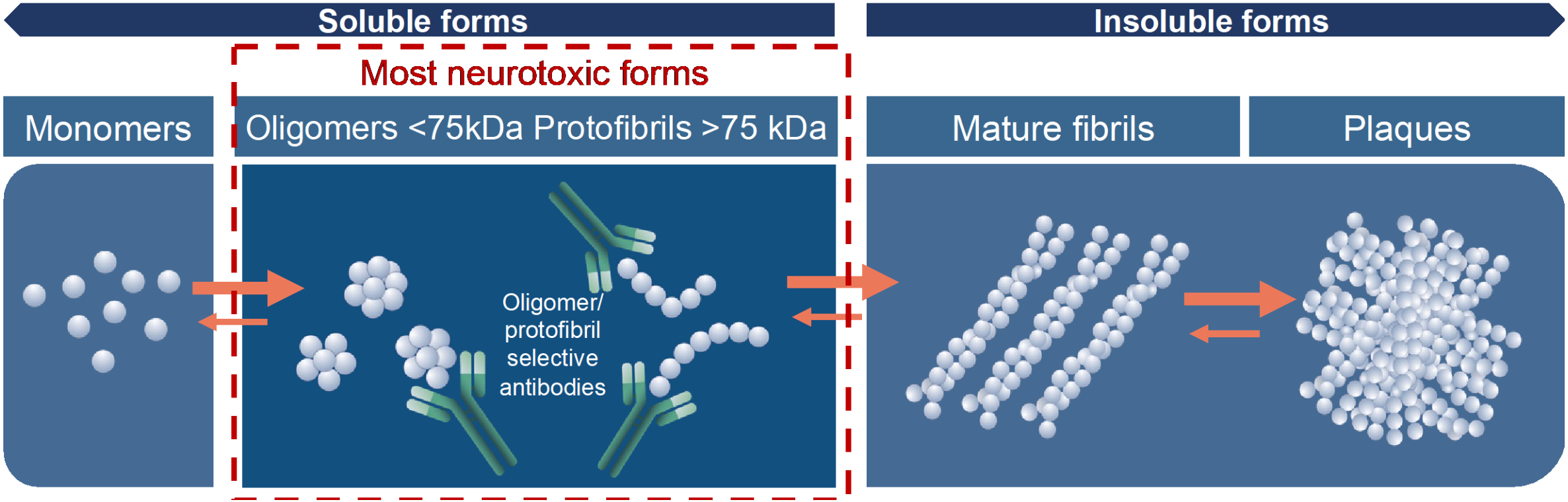
Based on where patient is on the biomarker trajectory

Anti-Amyloid Therapies: Lecanemab and Donanemab

Lecanemab Mechanism

Lecanemab Targets Protofibrils

Lecanemab Clears Plaques



Donanemab Mechanism

Donanemab targets a pyroglutamate-modified Aβ epitope found on deposited plaques

Modified from Abbott. *Nature*. 2022;603:216-219. Söderberg L, et al. *Neurotherapeutics*. 2022

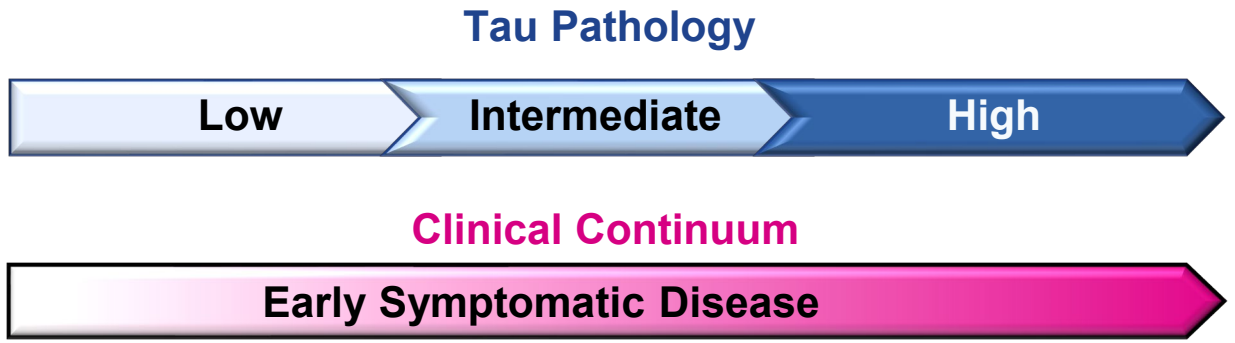
Patient Selection: Who to Treat

AMYLOID POSITIVITY
Required via amyloid PET, CSF, or plasma Aβ

CLINICAL STAGE
Restricted to early symptomatic disease

TAU LEVELS
Help refine the population

Lecanemab focuses on early AD without tau restriction

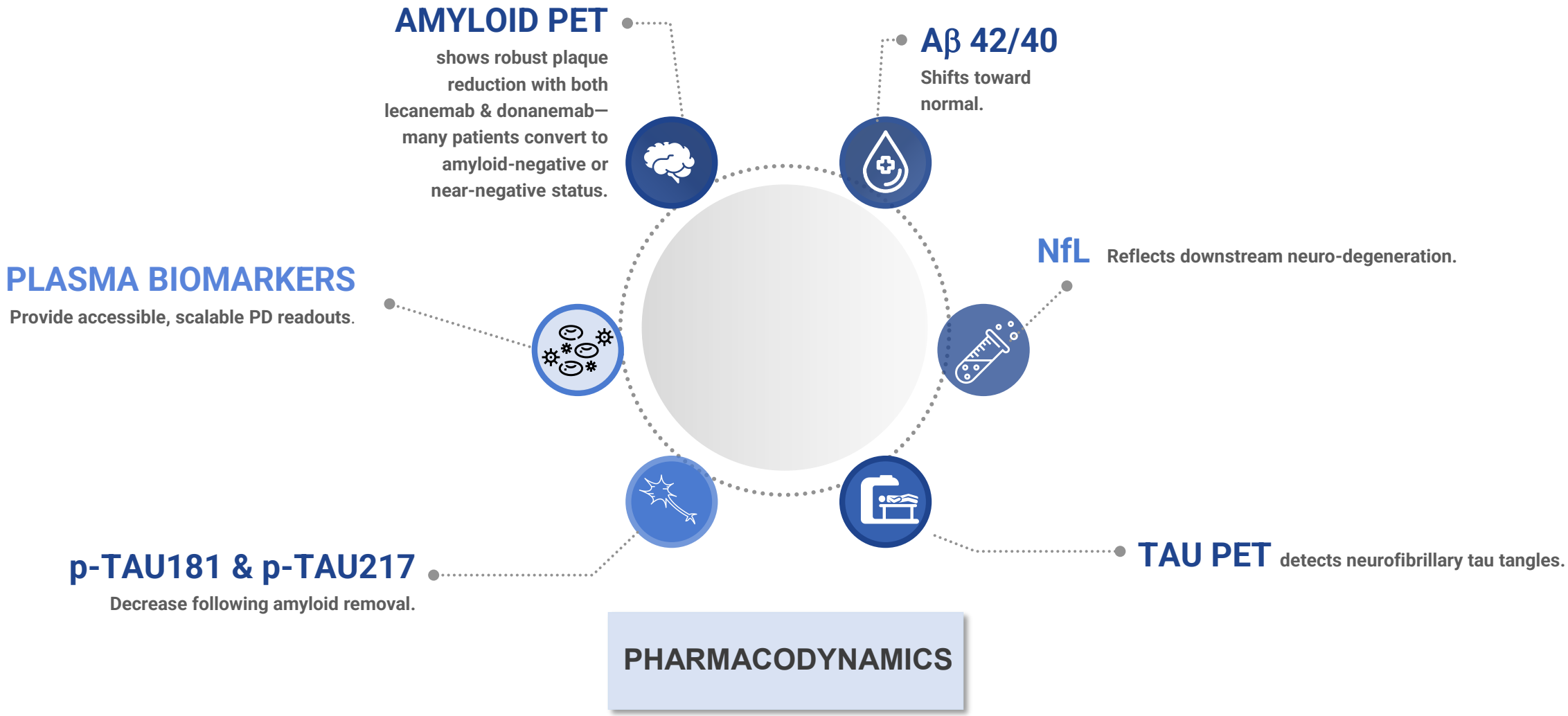


Donanemab pivotal trials focus on intermediate tau

This ensures we enroll patients who truly have AD biology, who are early enough to benefit, and who will show measurable progression in a clinical trial timeframe

Measuring Pharmacodynamic Response for Lecanemab

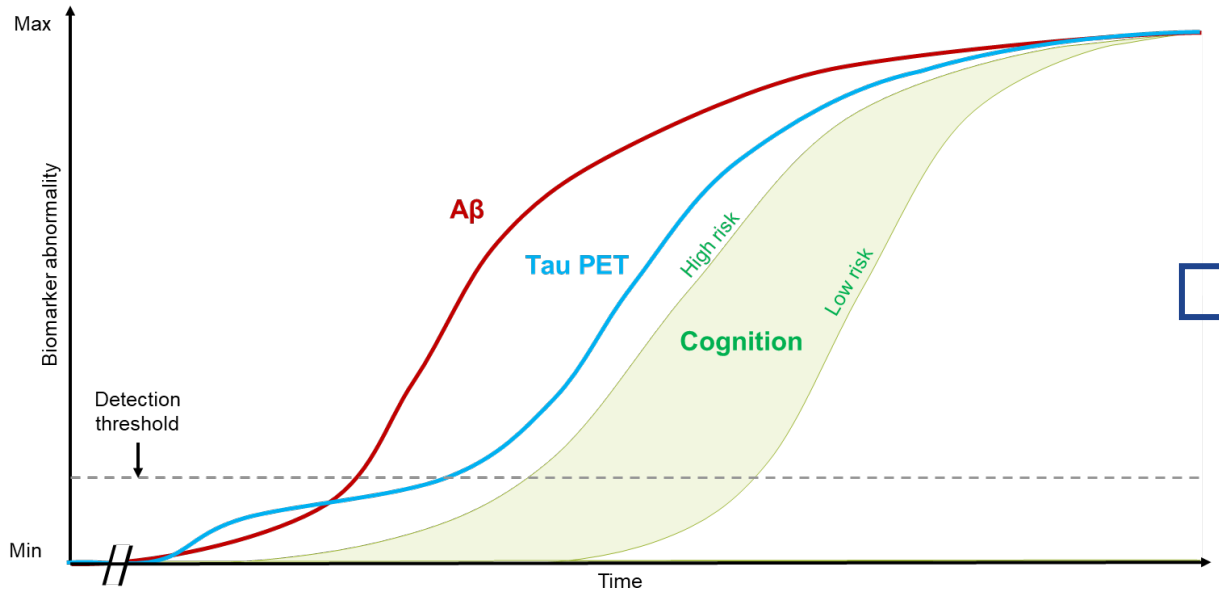
A Panel That Maps onto the A/T/N Framework



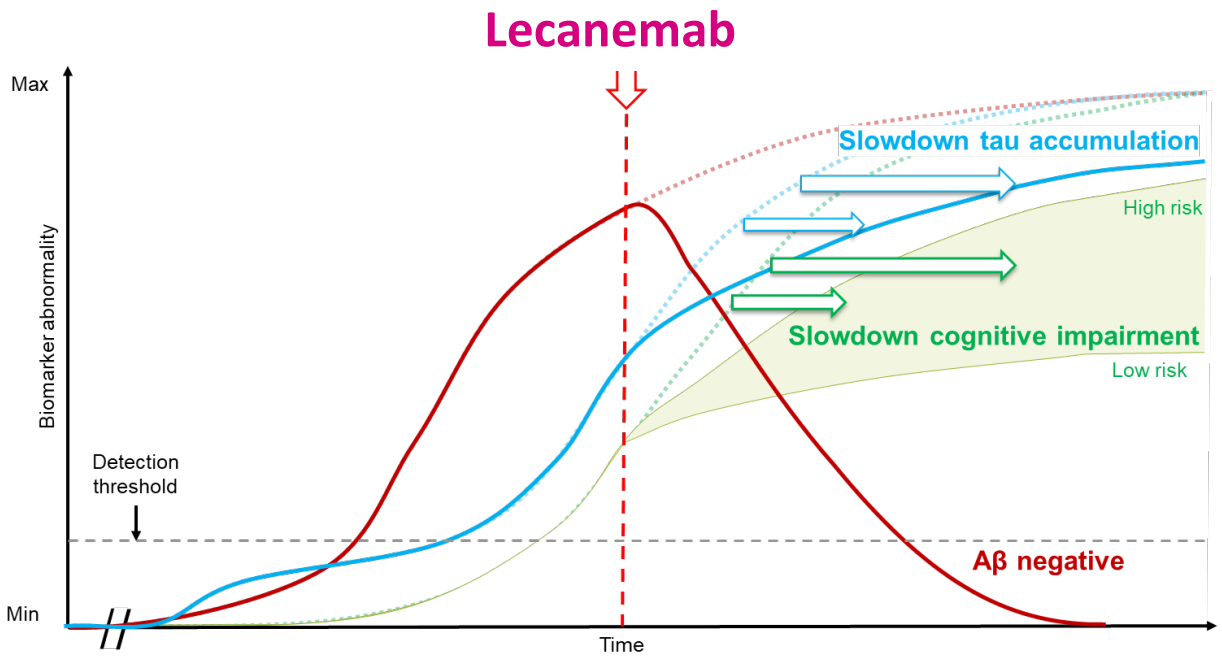
How Amyloid Removal Changes AD Continuum

Amyloid-removal therapies don't just clear plaque.
They alter the shape of the Alzheimer's disease trajectory

Original "Jack Curve" (natural disease progression)

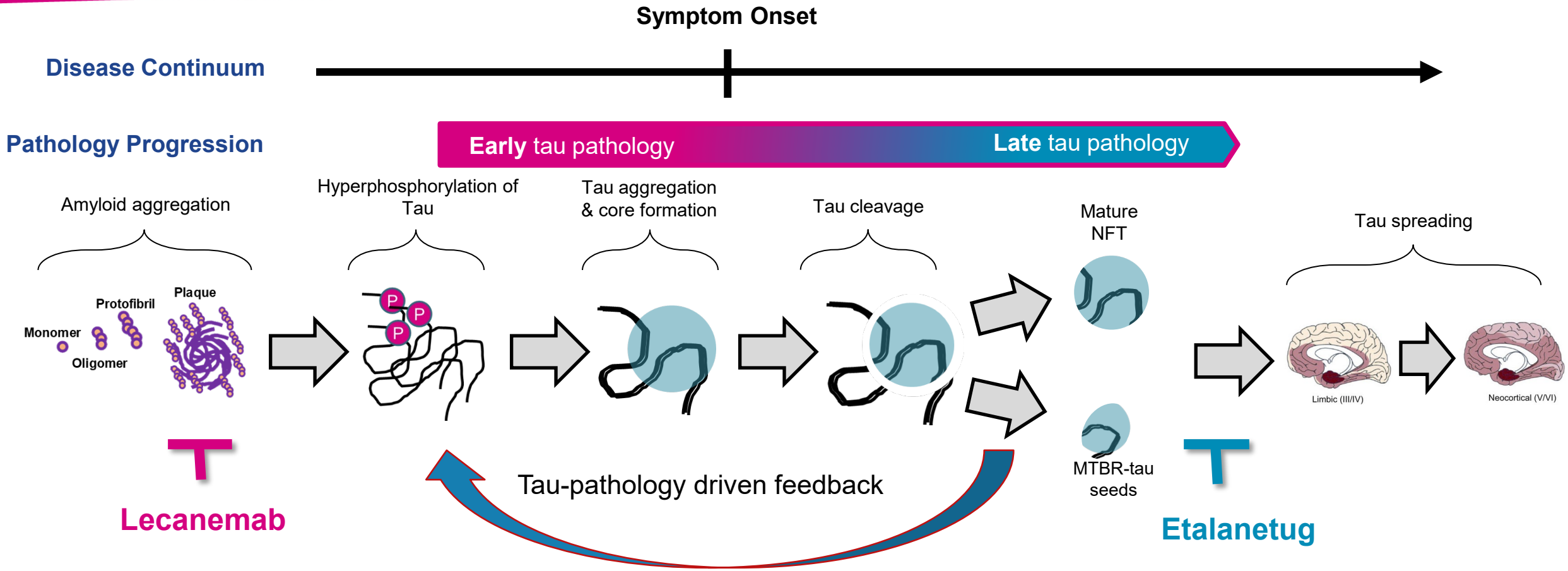


Anti-amyloid Therapy Modified "Jack Curve"



Modified from Jack CR, et al. *Lancet Neurol*. 2013.

Why Combination Therapy?



Lecanemab slows amyloid-induced tau pathology

Etalanetug (E2814) aims to block seeding and spreading of MTBR-induced tau pathology

Doherty T, et al. ADPD 2025

Dose Range Finding Study for Lecanemab + Etalanetug (E2814)

Study population is defined with precision:

- **Early symptomatic AD**
- **Amyloid positive and tau PET indicative of tau propagation**

Biomarker endpoints include:

- **CSF MTBR-tau243 as the primary PD marker**
- **Tau PET & p-tau217 as sensitive indicators of tau dynamics**
- **Amyloid PET to confirm that lecanemab is controlling the amyloid pathology**

This is precision medicine in action: Amyloid positive patients enriched for tau levels predicted to progress over clinical trial timeframe (18-24 month)

Biomarker Strategy

Demonstrating the Contribution of Each Individual Drug in the Combination

Biomarkers Hierarchy	Purpose	Hypothesis
Patient Selection	➢ Confirm diagnosis in early Alzheimer's disease (AD) ➢ Stage disease	• Treatment of early AD prior to significant irreversible neurodegeneration • Tailoring combination to appropriate patient
Target Engagement	➢ Activity against drug target	• Each drug in combination appropriately engages respective target • Dose selection
Pharmacodynamic	➢ Activity against pathophysiologic process relevant to the target	• Each drug in combination exhibits biological activity
Pathophysiological and Clinically Predictive	➢ Predict clinical benefit for accelerated approval ➢ Activity against downstream process in AD (disease modification)	• Additive or synergistic delay in progression of AD pathophysiological biomarkers
Clinical Consequence	➢ Confirm efficacy	• Additive or synergistic slowing of cognitive and functional decline

Clinical Trial Design Considerations in the Setting of Approved Anti-Amyloid Therapies

Whether or Not to Allow Amyloid Therapies

Choice of Amyloid Therapies

- Normal clinical care
- Standardizing to the same amyloid therapeutic
  - Titration
  - Safety (including ARIA)
  - Rate of amyloid clearance
- Standardizing to same level of amyloid clearance or other biomarker

Study Population

- Preclinical or symptomatic
- Biomarker defined (including genetic)

Combination Study Design

- Factorial
- Adjunctive to amyloid treatment
- Dosing sequence (initiating prior to, concurrent with, or after other therapy)
- Modalities and routes of administration (small molecule, mAb, ASO, etc.)
- Dose ranging studies

Outcomes

- Demonstrating contribution of each molecule in combination (additive, synergistic)
- Biomarker/Clinical
- Safety

Neuro-Dynamic Quantitative Systems Pharmacology Model

A predictive modeling/simulation engine for Alzheimer's drug development

Data

LEC DATA

- Amyloid PET
- Tau PET
- Plasma p-tau181
- Plasma Aβ42/40
- CDR-SB
- ADAS-Cog

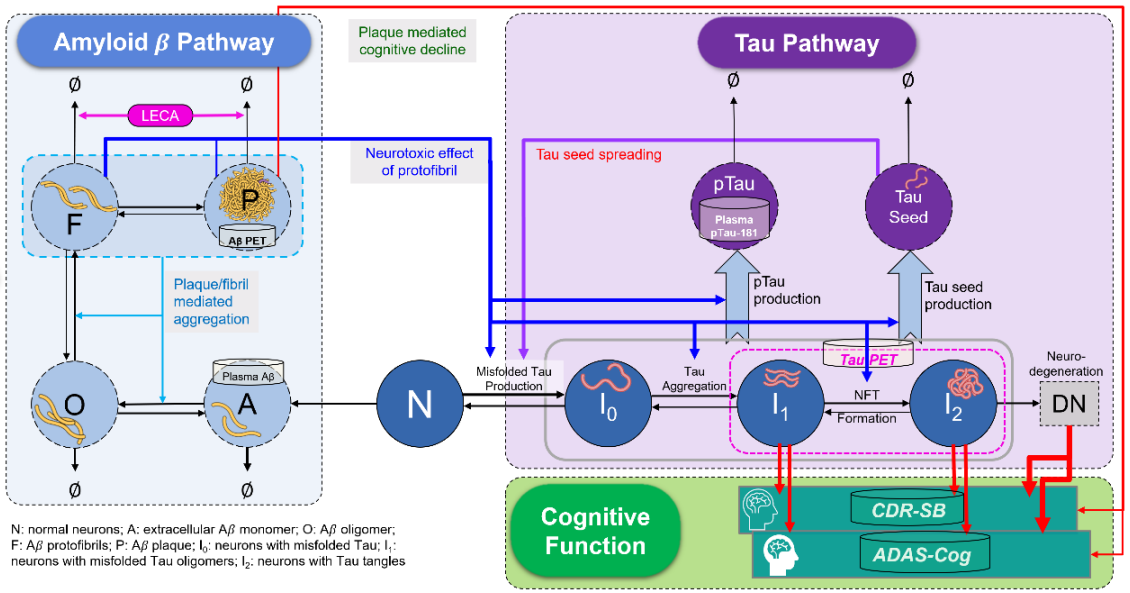
ADNI DATA

- Amyloid PET
- CDR-SB
- ADAS-Cog

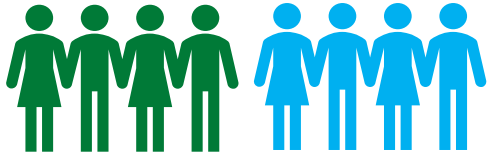
Literature

Mechanisms,
Rates, Kinetics,
Binding affinities

Neuro-Dynamic QSP Model



Virtual Patient Populations (represents diverse target population)



Model Validation & Clinical Outcome Prediction

Accurately predicted 8 endpoints:

- CDR-SB, ADAS-Cog
- Amyloid PET, Tau PET
- CSF Aβ42, p-tau181
- Plasma Aβ42/40 ratio, p-tau181

Clinical Trial Simulations

Predict and generate insights for:
Right mechanism of action,
Right patient population,
Right dose regimen,
Right time

Inform Decisions

Cao Y, et al. *npj Systems Biology and Applications*. In press.

Conclusion

- AD is now understood as a biomarker-defined continuum
- Anti-amyloid therapies bend Aβ trajectory and delay cognitive decline
- Precision medicine guides patient selection, target engagement and pharmacodynamic strategy
- Combination therapy, such as anti-amyloid and anti-tau, offer the potential for additive or synergistic disease modification
- Quantitative systems pharmacology modeling will enable individualized, stage-specific treatment strategies