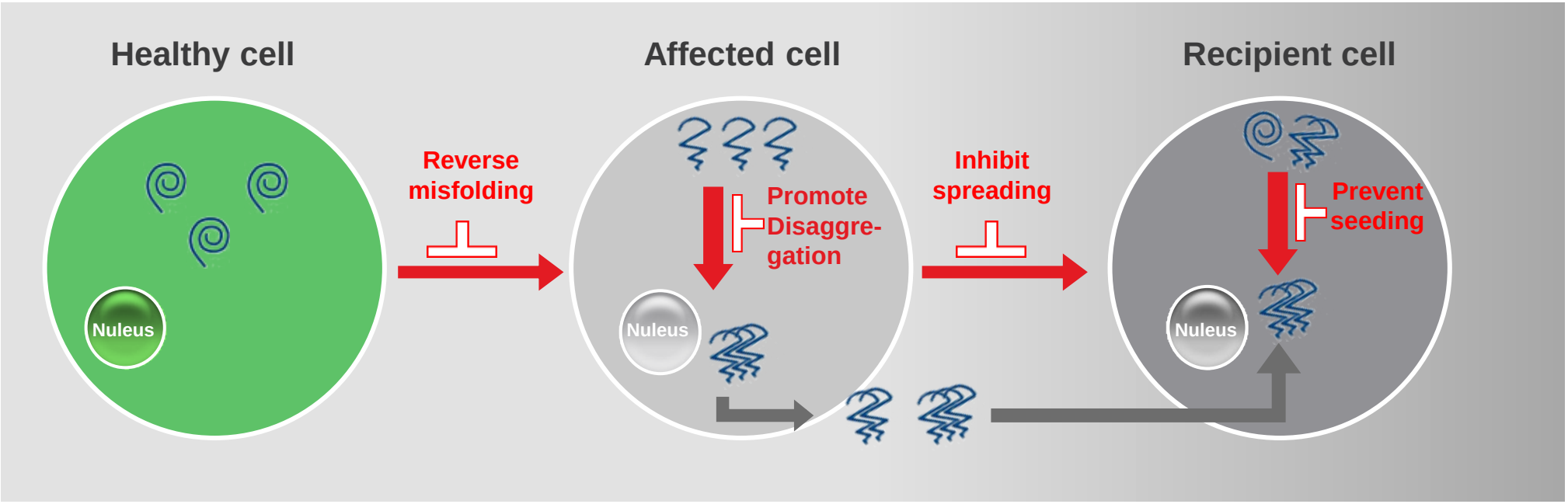
Anti-TAU APPROACHES

KOL Luncheon

AC Immune

AC Immune's Tau therapies intervene at key points in the disease pathway



Spread of Tau pathology is intimately linked to neurodegeneration

- Evidence for cell-to-cell spread across neuronal networks
- Proximate in time and place to symptom-localization and atrophy
- Unlike Amyloid, Tau burden correlates with cognition

Morphomer Tau

- ACI-35
- Anti-Tau antibody

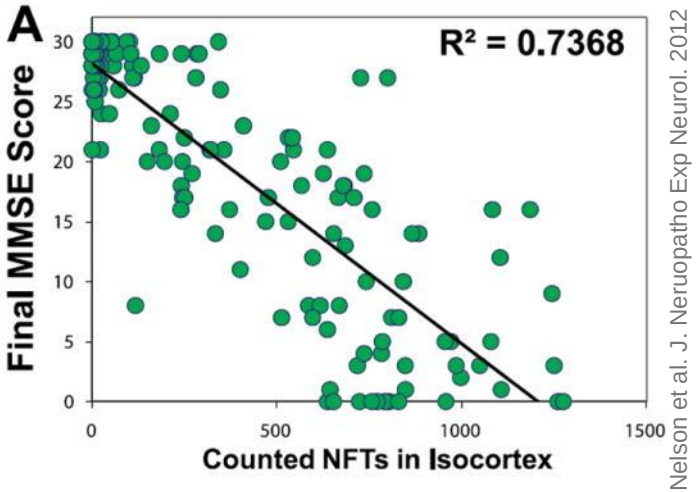
Morphomer Tau

Tau-PET imaging agent for companion diagnosis

ACI-35 - Rationale / Mode of Action

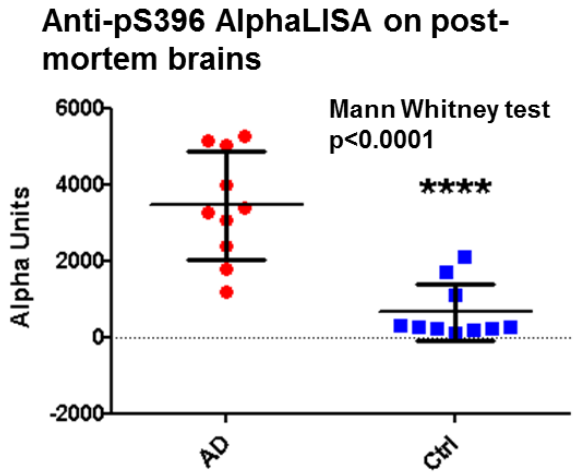
Tau tangles (NFT) and pTau (p396): validated targets for the treatment of AD

AD patients brain:
Inverse correlation of NFT with MMSE score

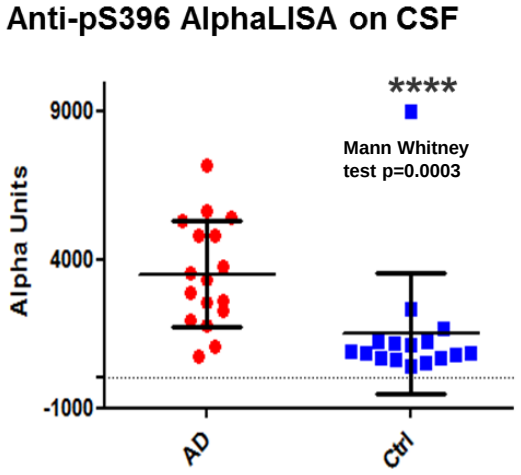


Nelson et al. J. Neruopatho Exp Neurol. 2012

Human brain soluble fraction:
Higher expression of pS396 in AD patients



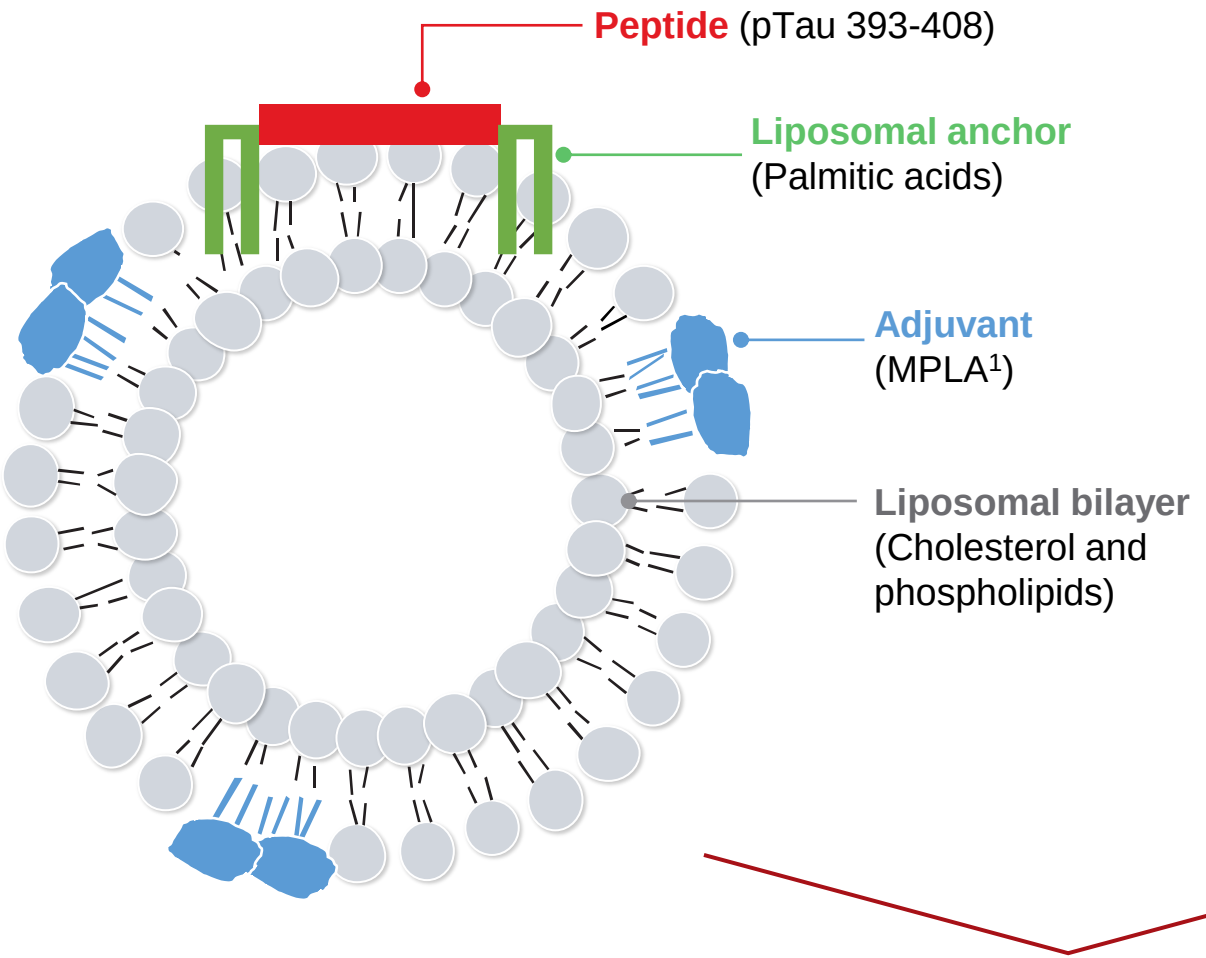
Human CSF:
Higher expression of pS396 in AD patients



- Correlation of NFT with cognitive decline
- Accumulation of pTau (S396) in AD brain and AD CSF suggests pTau as a promising target for immunotherapy

ACI-35

Anti-pTau liposomal therapeutic vaccine for AD



- Human phosphoTau 393-408 synthetic peptide as antigen
- 4 palmitoyl acid chains induce and stabilize induce and stabilize conformation
- Cholesterol, DMPC and DMPG liposomes to carry peptide and adjuvant
- MPLA to enhance immunogenicity

Key features

- Mimic pathological confirmation of phosporylated Tau
- T-cell independent immune response

(1) Monophospholipid A

ACI-35 - overview

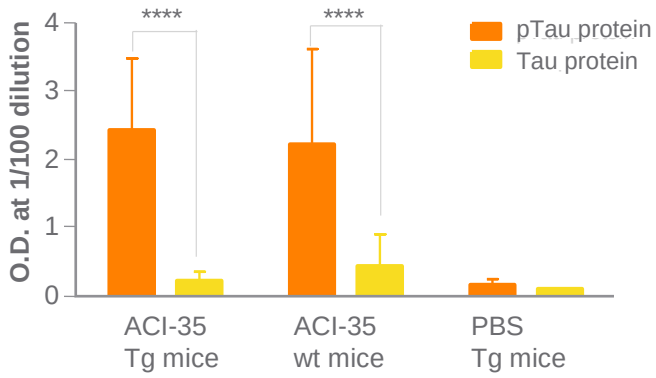
Anti-pTau therapeutic vaccine for AD – Phase 1b

Indication	Alzheimer's disease
Target	Aggregated pTau
Licensed to	janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson
Key results in pre-clinical studies	▪ High specific antibody response to pathogenic Tau ▪ Improvement of cognition, physical performance, behaviour and prolongation of survival ▪ Favorable safety profile with T-cell independent mode-of-action
Development status	Clinical phase 1b trial

Immune response highly specific to phosphorylated-

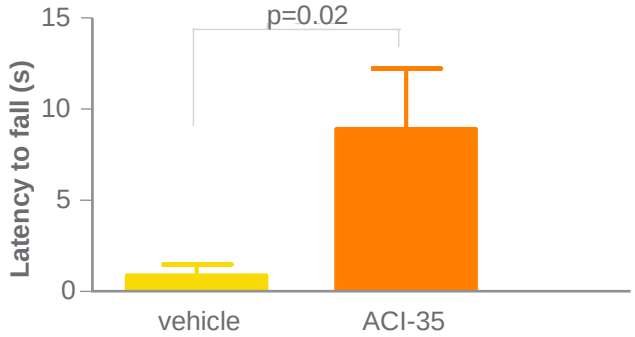
ACI-35 vaccinated mice

pTau vs. Tau protein after 5 immunizations



Highly significant improvement of behavior (P301S)

15 rpm ACI-R-40 Rotarod 5M vehicle vs. ACI-35



AC Immune unpublished data

Note: Tg = Transgenic, wt = wild type

ACI-35 – Phase 1b study with Janssen Pharmaceuticals

Phase 1b

- Multicenter prospective placebo-controlled, double-blind and randomized study of ACI-35 versus placebo over 48 weeks, including 6 months safety follow-up
- 5 cohorts with 3 doses (300 µg, 900 µg and 1800 µg/injection) sequentially started in ascending dose order. 2 highest doses studied in 2 different schedules

Patient population

- Mild to moderate AD patients (MMSE: 18-28), with 60-85 years of age, males and females
- Involved countries : UK and Finland

Primary and secondary endpoints

Primary

- Preliminary assessment of safety and tolerability of ACI-35 and induction of anti-pTau IgG titer in serum

Secondary

- Explore induction of anti-Tau and anti-pTau IgG titers in serum and CSF and anti-Tau and anti-pTau IgM in serum
- Explore putative biomarkers including Tau proteins and Abeta levels in plasma and CSF and alpha-synuclein in cerebral spinal fluid; explore T-cell activation

ACI-35

Interim data of Phase 1b study and next steps

Interim analysis of Phase 1b

- Revealed acceptable safety and tolerability
- Showed dose-dependent and target-specific antibody response to pTau
- Final data analysis ongoing

Next steps

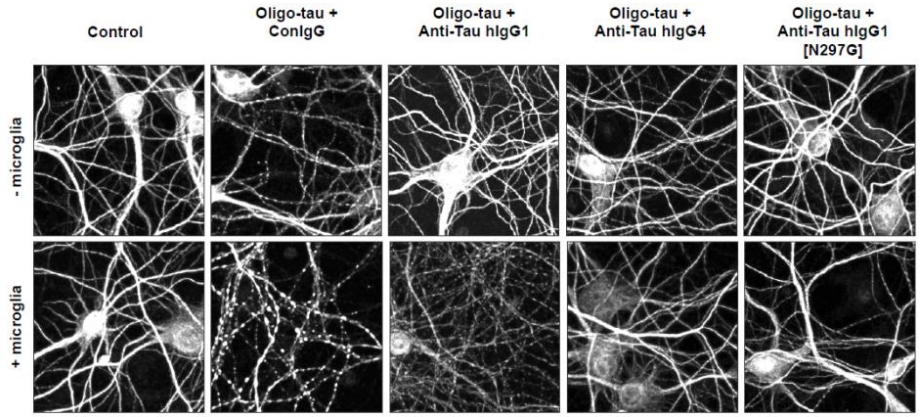
- AC Immune and Janssen Pharmaceuticals jointly decided to advance anti-Tau vaccine program
- Achieved scientific advisory meeting with regulatory agencies to support next phase of development

Anti-Tau antibody

Tau is a compelling target - passive anti-Tau immunotherapy shows efficacy

Protection against toxic oligomeric Tau

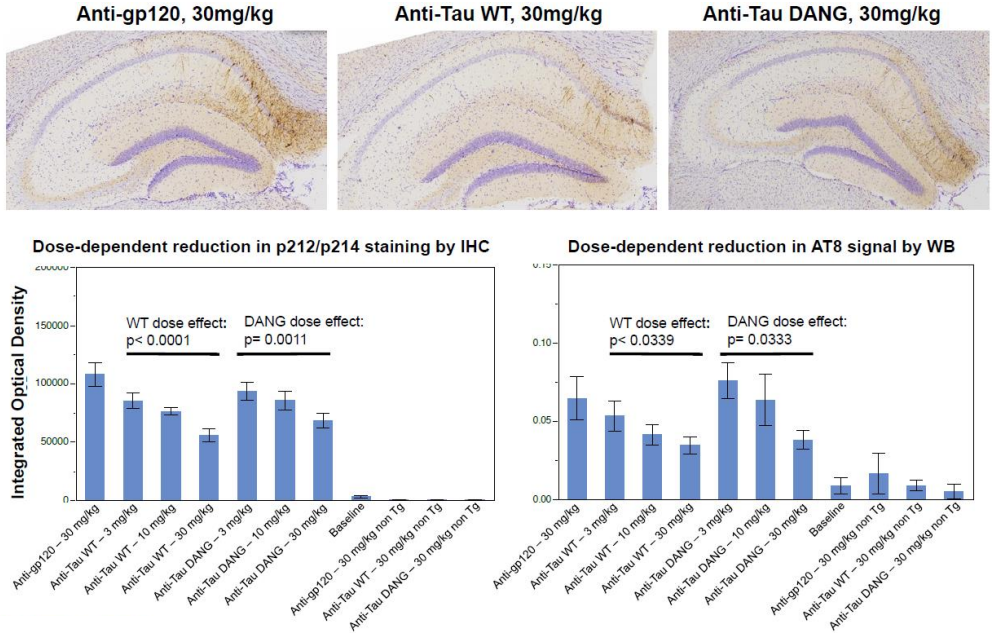
Reduced effector anti-tau is protective against Tau-mediated toxicity in the presence of microglia



Ref: Ayalon et al, AD/PD 2017 (Genentech oral presentation)

Dose-dependent inhibition of Tau spreading, independent of effector function

Dose-dependent efficacy shown for passive anti-Tau immunization, in the presence (WT) or absence (DANG) of IgG effector function



Ref: Brendza et al, AD/PD 2017 (Genentech poster)

Passive immunization with an anti-Tau antibody demonstrated dose-dependent efficacy, independent of antibody effector function, in support of the mechanism of action of targeting Tau spreading

Anti-Tau antibody (RO7105705)

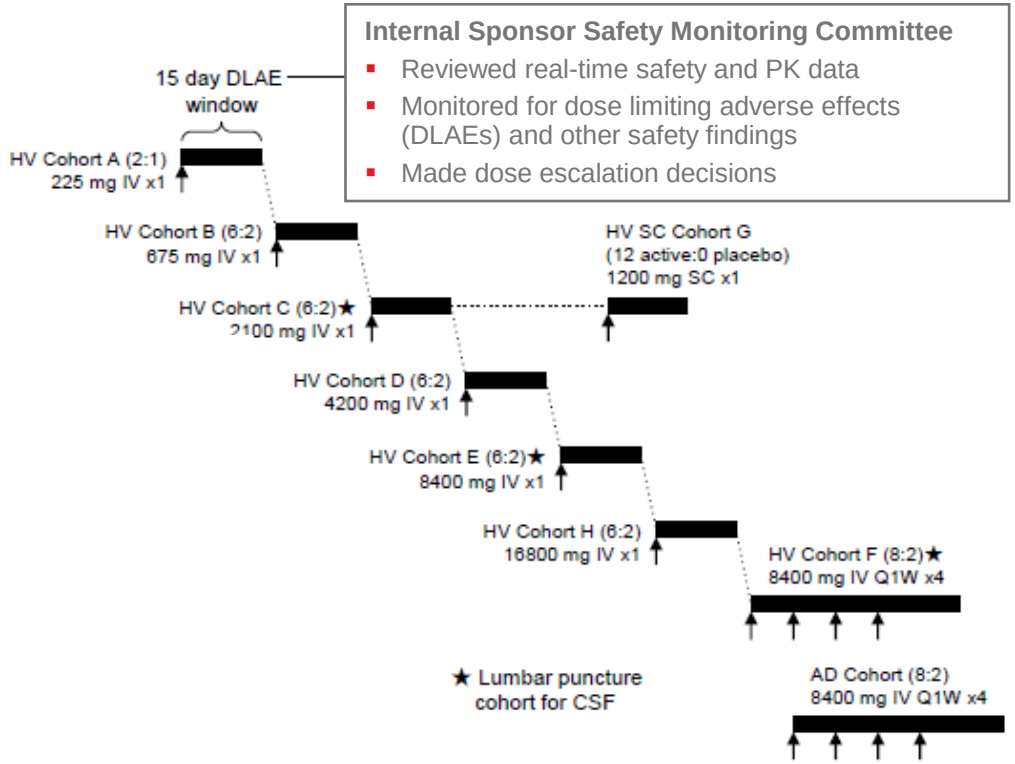
Phase 1 clinical trial design

RO7105705

- RO7105705 is an anti-Tau, humanized, monoclonal antibody in development for AD and other Tauopathies
- It is designed to bind and intercept Tau in the extracellular brain environment, blocking cell-to- cell spread of Tau pathology

Primary endpoints

- To evaluate the safety of single and multiple doses of RO7105705 compared with placebo
- **Secondary endpoints**
  - To characterize the pharmacokinetic profile following subcutaneous. or intravenous



Safety Monitoring

- AEs, labs, ECGs, vitals physical/neurological exams, C-SSRS
- 15-day DLAE window
- 16-week follow-up after last dose
- Structural MRI
  - In AD patients at baseline and end-of-study
  - In any participant upon any sign or symptom of an acute CNS disturbance

Ref: Kerchner et al, CTAD 2027 (Genentech oral presentation)

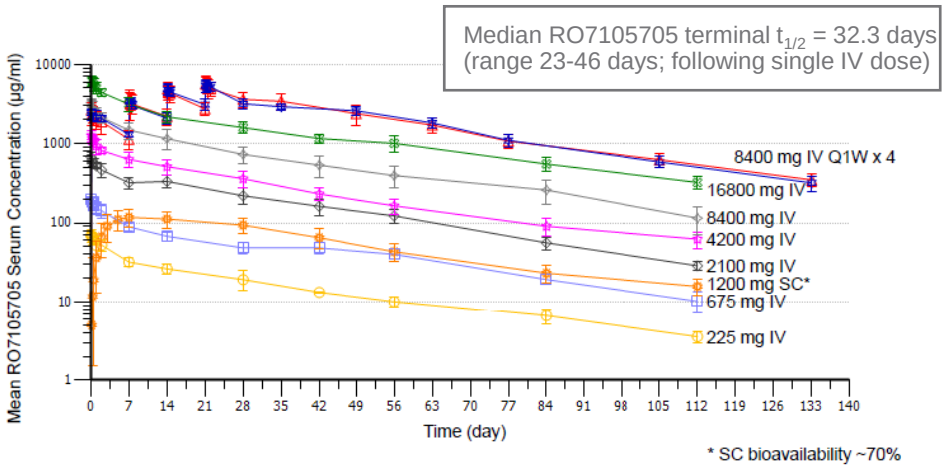
Anti-Tau antibody (RO7105705)

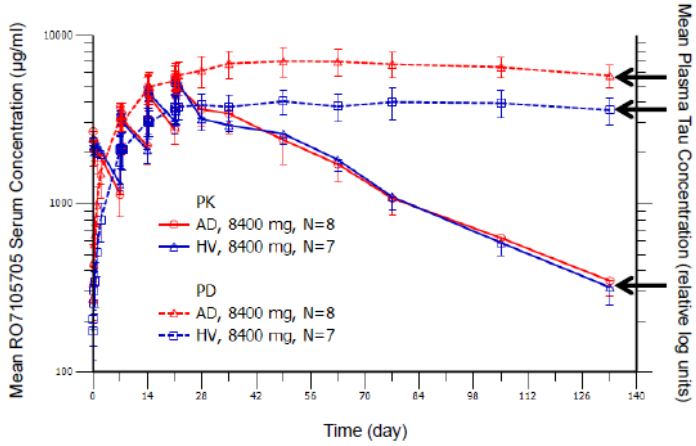
Phase 1 clinical trial results

Safety

- No dose-limiting toxicities up to high doses, no serious adverse events, no deaths, no discontinuations due to an adverse event, no treatment withdrawals/modifications/interruptions due to an adverse event were reported

Pharmacodynamics



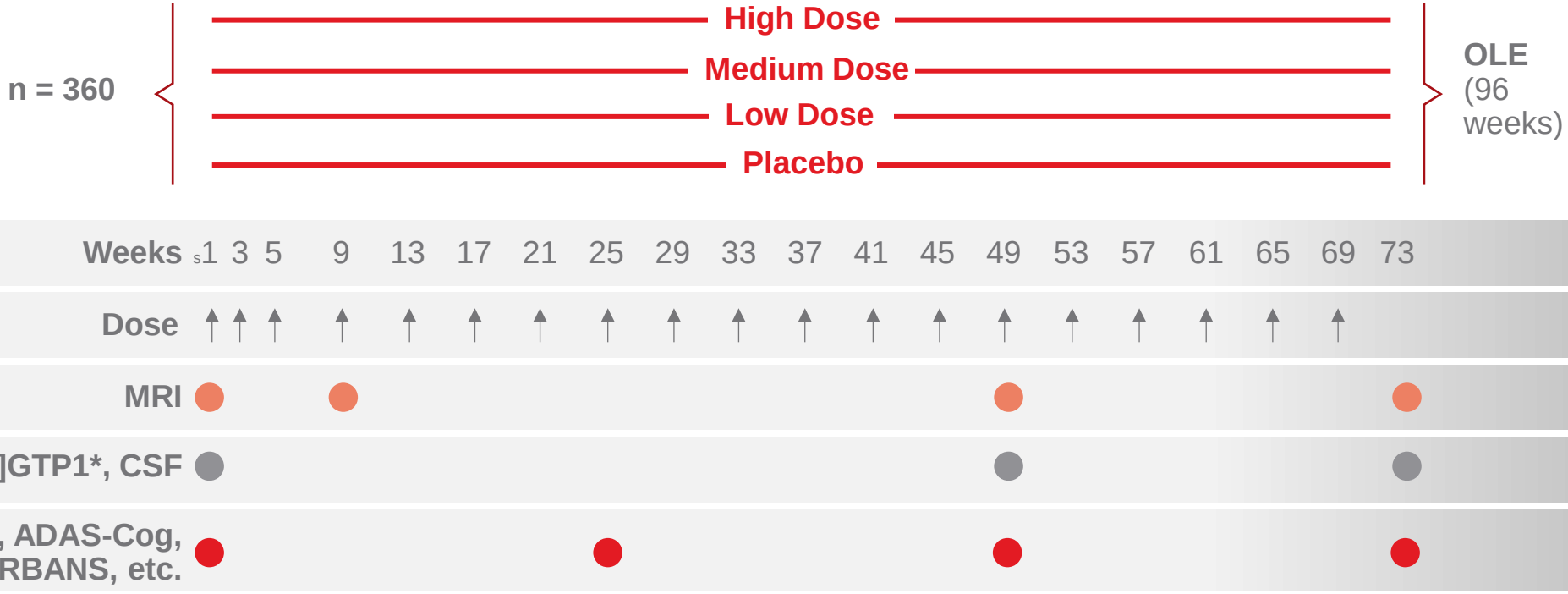


- No dose-limiting toxicities up to high doses
- Dose-proportional PK with median half-life of 32.3 days
- Detectable in CSF, indicating CNS exposure
- Pharmacodynamic response: 2x greater plasma Tau concentrations observed in patients with Alzheimer's disease than in healthy volunteers

Ref: Kerchner et al, CTAD 2027 (Genentech oral presentation)

Anti-Tau antibody (RO7105705)

Phase 2 clinical trial design

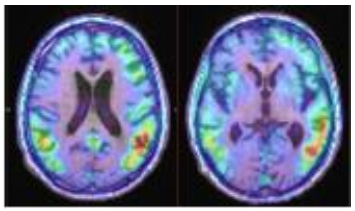


Population

- MMSE 20-30, CDR-GS 0.5 or1
- RBANS Delayed Recall ≤ 85
- Amyloid-PET positive; or CSF Aß-positive

*[18F]GTP1 Tau PET Imaging

- Selective tau PET tracer already in use in longitudinal clinical AD research



- 360 prodromal-to-mild AD patients (MMSE 20-30, CDR-GS 0.5 or 1)
- 3 active doses or placebo for 72 weeks, followed by 96 week open label study
- Primary endpoints: safety measures and CDR-SB

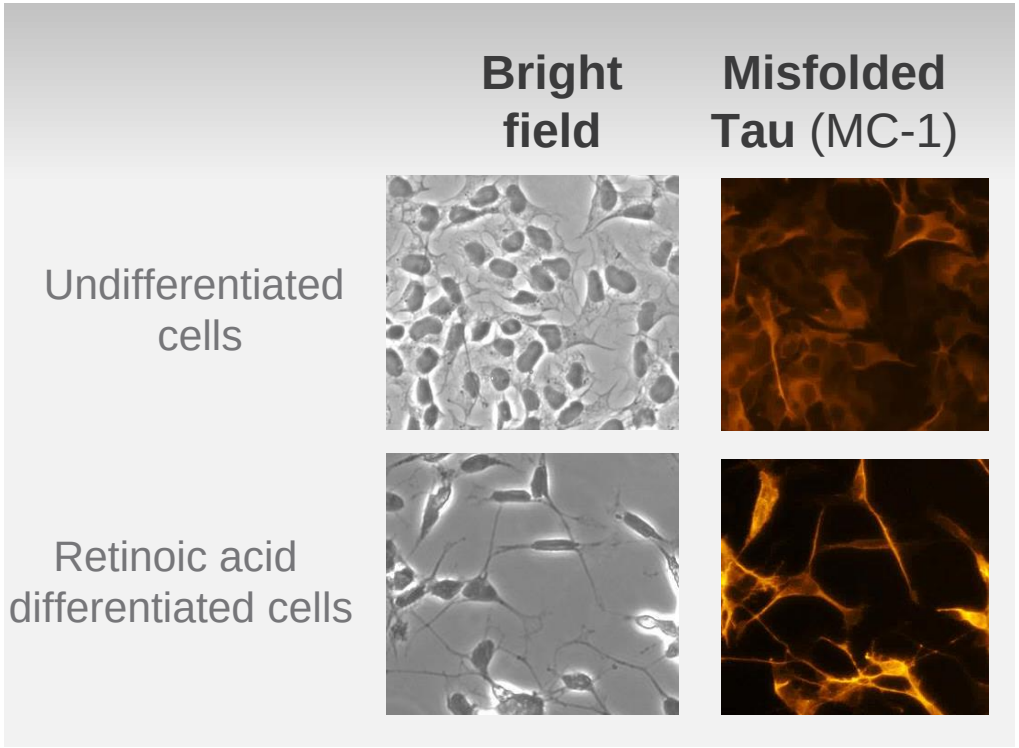
Ref: Kerchner et al, CTAD 2027 (Genentech oral presentation)

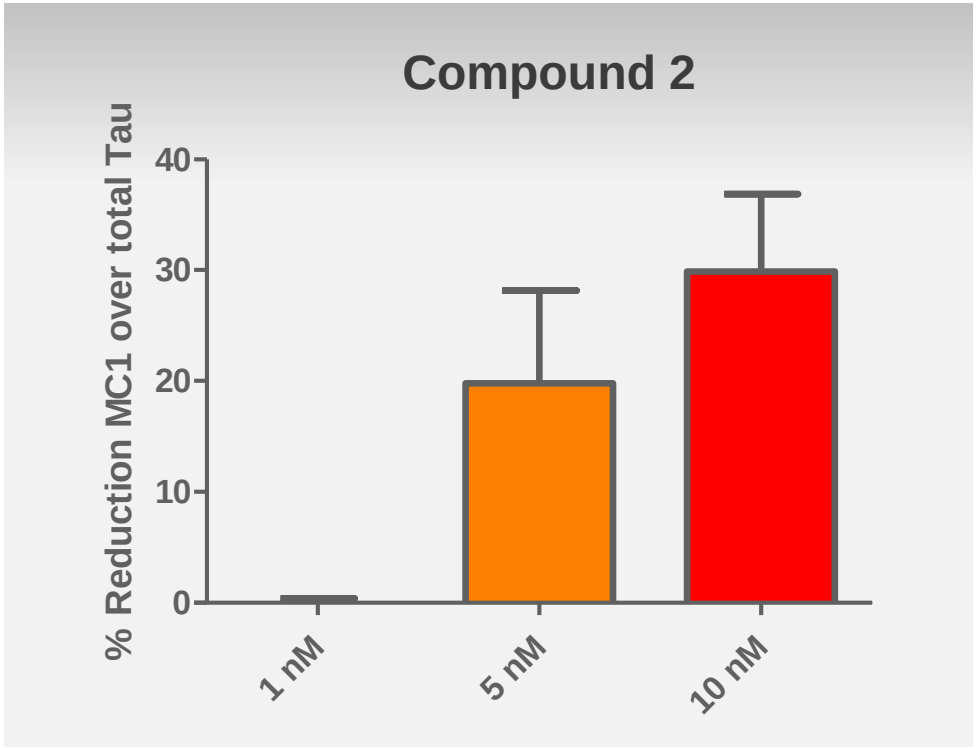
Morphomer Tau – Pharmacology

Cell-based assays – Compounds used in the nanomolar range

Reduction of intracellular Tau misfolding *in vitro* -differentiated SH5Y-SY TauP301L cells

Immuno-cytochemistry assay measures effects on spontaneous Tau misfolding in retinoic acid differentiated SH5Y-SY Tau P301L cells





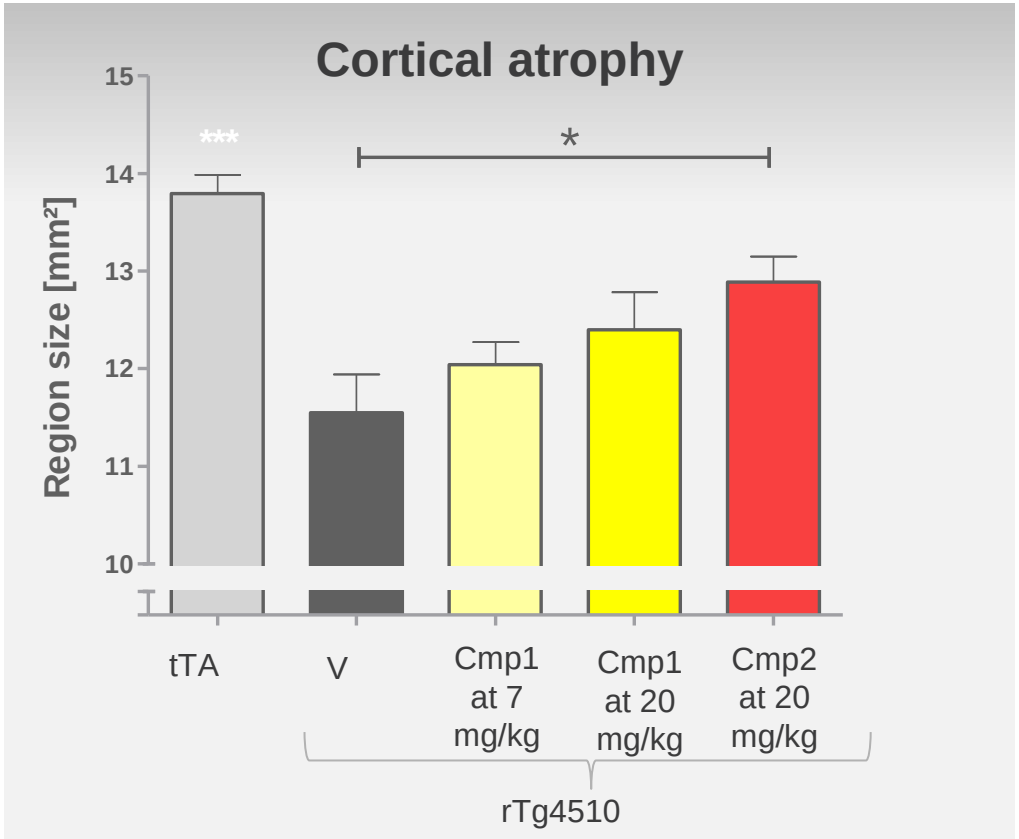
In *in vitro* differentiated SH5YSH TauP301L cells, that acquire neuronal morphology with high level of misfolded Tau expression, treatment with Compound 2 led to a dose-dependent decrease of misfolded Tau in low nM range

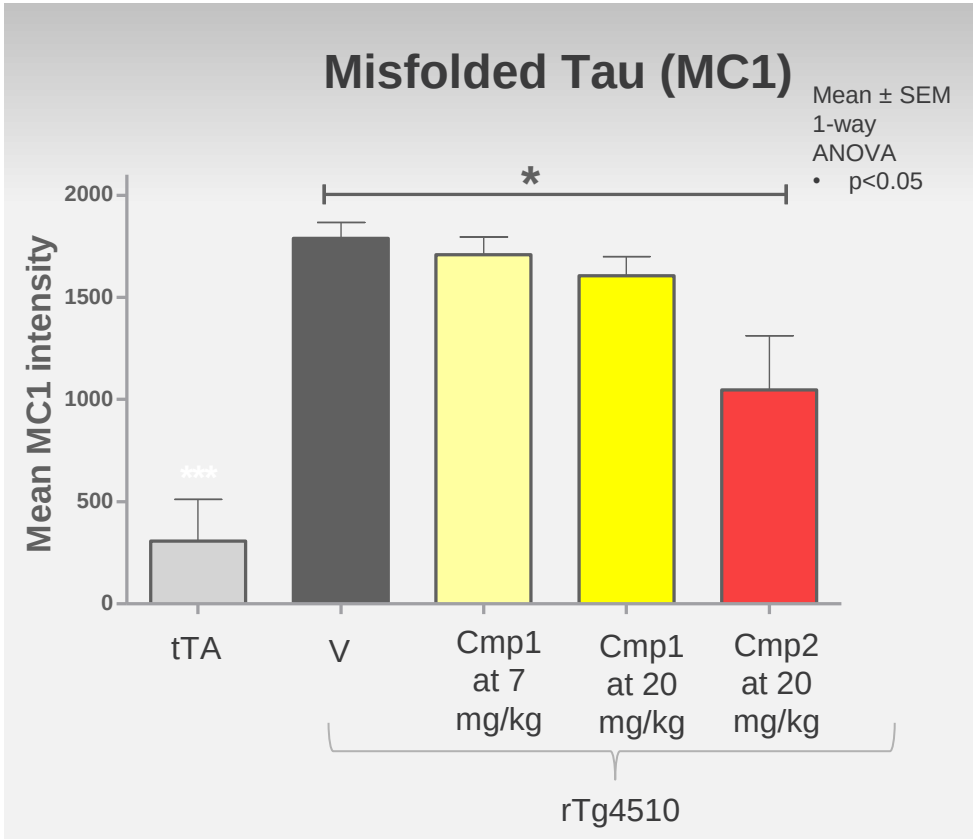
Ref.: AC Immune unpublished data

Morphomer Tau – in vivo efficacy

Assessment of compound efficacy in an aggressive Tauopathy model

Histology: Analysis of brain atrophy and misfolded Tau





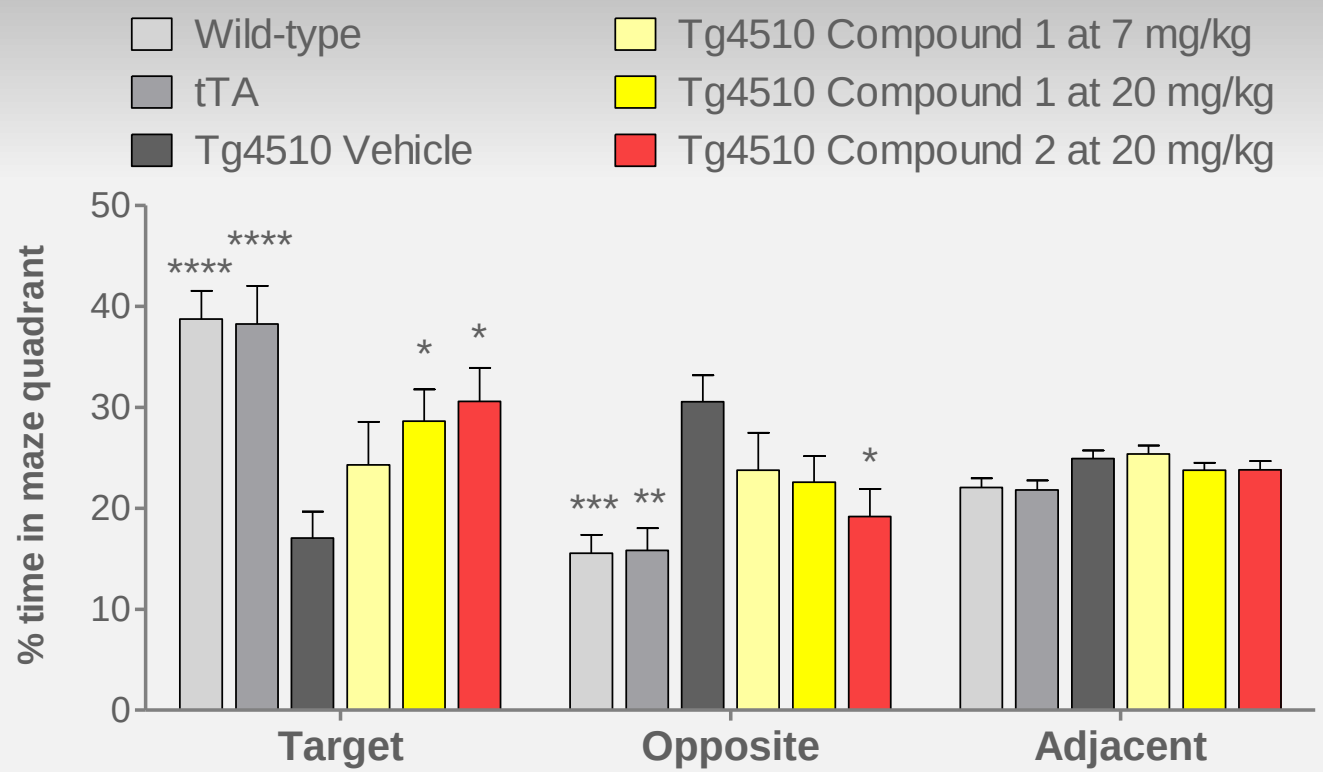
Treatment with Compound 1 resulted in a tendency for dose-dependent rescue of brain atrophy. Treatment with Compound 2 exhibited a significant effect on brain atrophy rescue as well as reduction of misfolded Tau

Ref: Adolfssen et al, SFN 2015

In vivo efficacy study

Assessment of compound efficacy in an aggressive Tauopathy model

Behavioral test: Morris Water Maze memory test



Mean ± SEM
2-way ANOVA
• p<0.05
** p< 0.01
*** p<0.001
**** p<0.0001

- Potent Morphomer demonstrated dose-dependent effects on memory performance
- Rationally designed small molecules targeting misfolded and aggregated Tau are a promising strategy to reduce Tau pathology

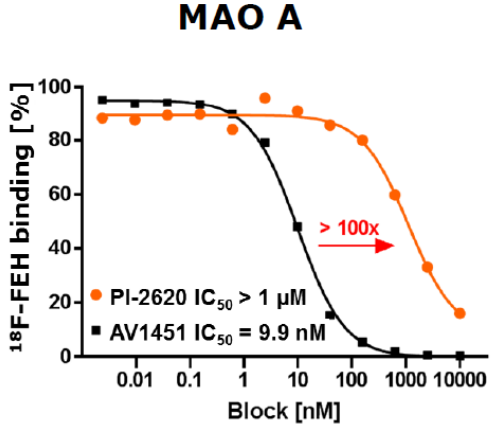
Ref: Adolfssen et al, SFN 2015

Tau-PET imaging – Phase 1 in AD and PSP

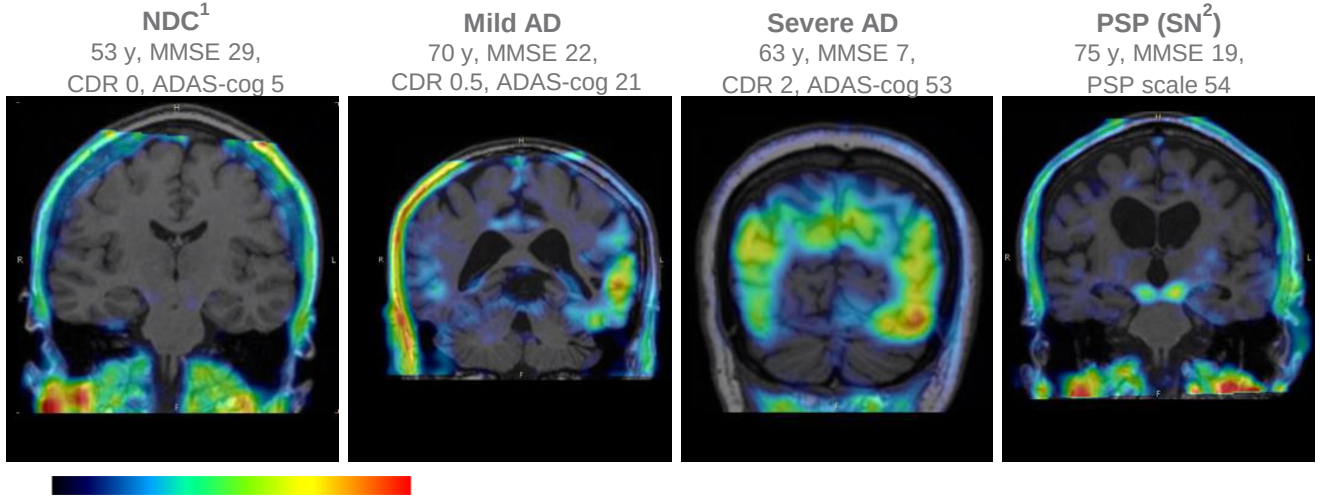
Morphomer Tau PI-2620

Target	Misfolded Tau (4R and 3R)
Licensed to	Piramal Imaging
Key results	▪ High specificity for pathological forms of human Tau in AD and other tauopathies ▪ Outstanding PET tracer-profile – excellent brain penetration and high selectivity even in early disease stage

Pre-clinic: High selectivity and absence of off-target binding



Phase 1 clinical study: distinct, specific Tau distribution pattern in AD and PSP



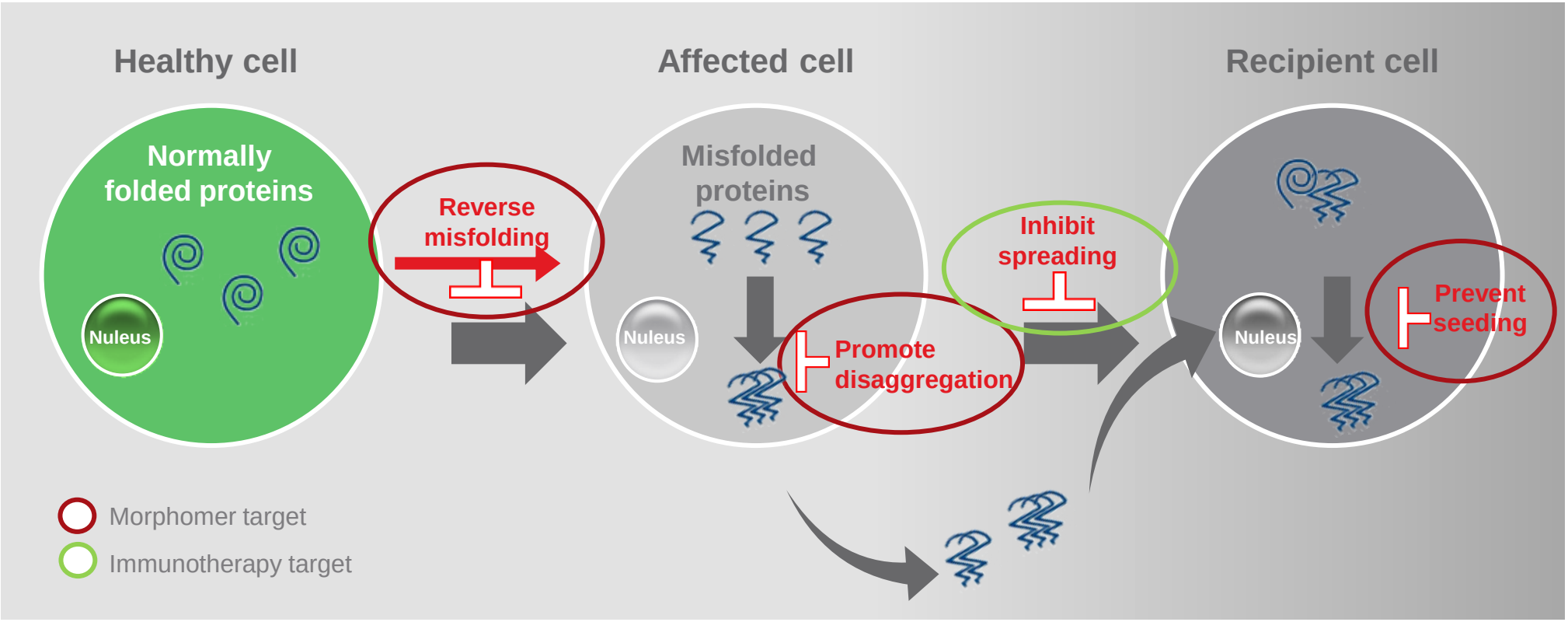
Stephens, AD/PD conference, Vienna, April 2017

Development status	Clinical Phase with interim data ▪ Fast kinetics with robust brain uptake, fast wash-out in non-target regions and low off-target uptake ▪ Distinct and specific Tau distribution pattern in AD and PSP subjects ▪ Good reproducibility of PET-scans confirmed by test-retest study

(1) NDC = non-demented control; (2) SN = substantia nigra

AC Immune's targets in spreading hypothesis of misfolded tau in neuro-degenerative diseases

AC Immune's therapies intervene at key points in the disease pathway



- Targeting both, intracellular seeds and extracellular spreading by combination therapy of Morphomers and immunotherapy enables fully control Tau pathology progression
- High selective Tau imaging diagnostic enables more precised patient characterization and potentially more presized AD progression prediction