3e CONGRÈS FRANCOPHONE MULTIDISCIPLINAIRE DE L'AMYLOSE

Progrès réalisés et à venir !

Jeudi 13 juin 2024

Fondation Biermans-Lapôtre ■PARIS

ISA 2024: actualités en Neurologie

Andoni Echaniz-Laguna

CRMR CERAMIC

CHU DE BICETRE

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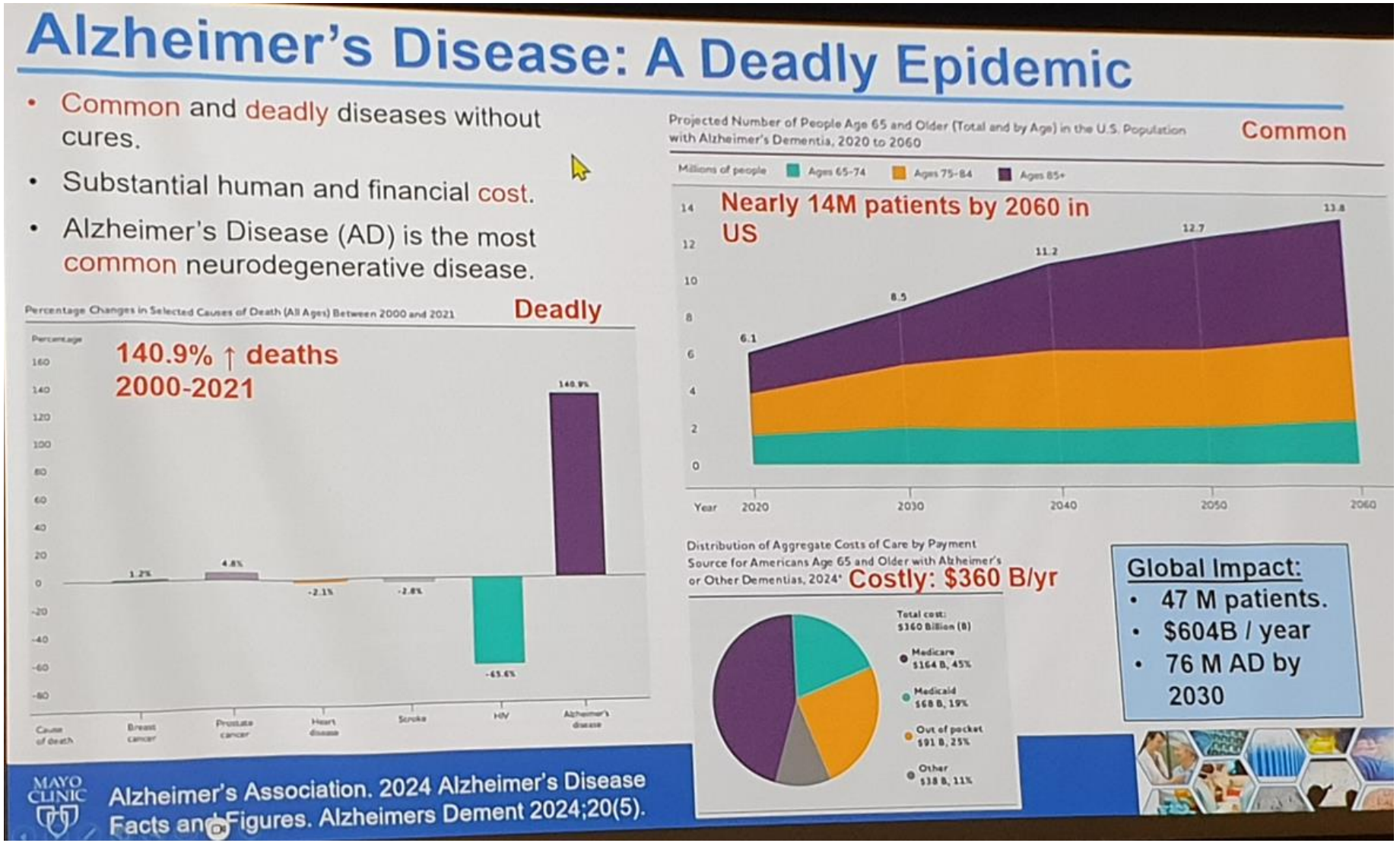
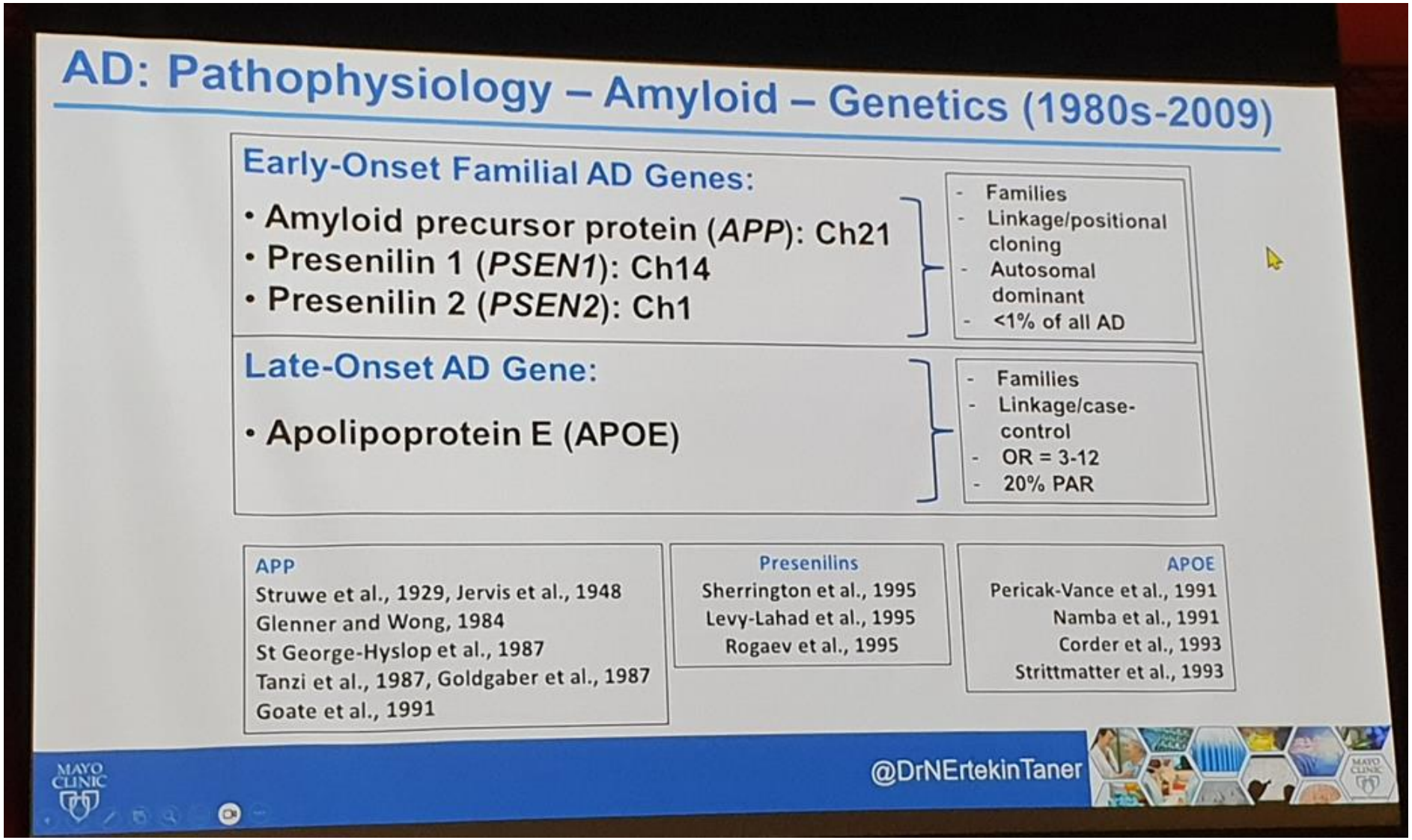
Centre de Référence Neuropathies Rares & Amyloïdes Île-de-France Caraïbes

la maladie d'Alzheimer: la plus fréquente des amyloses



Ertekin, ISA 2024



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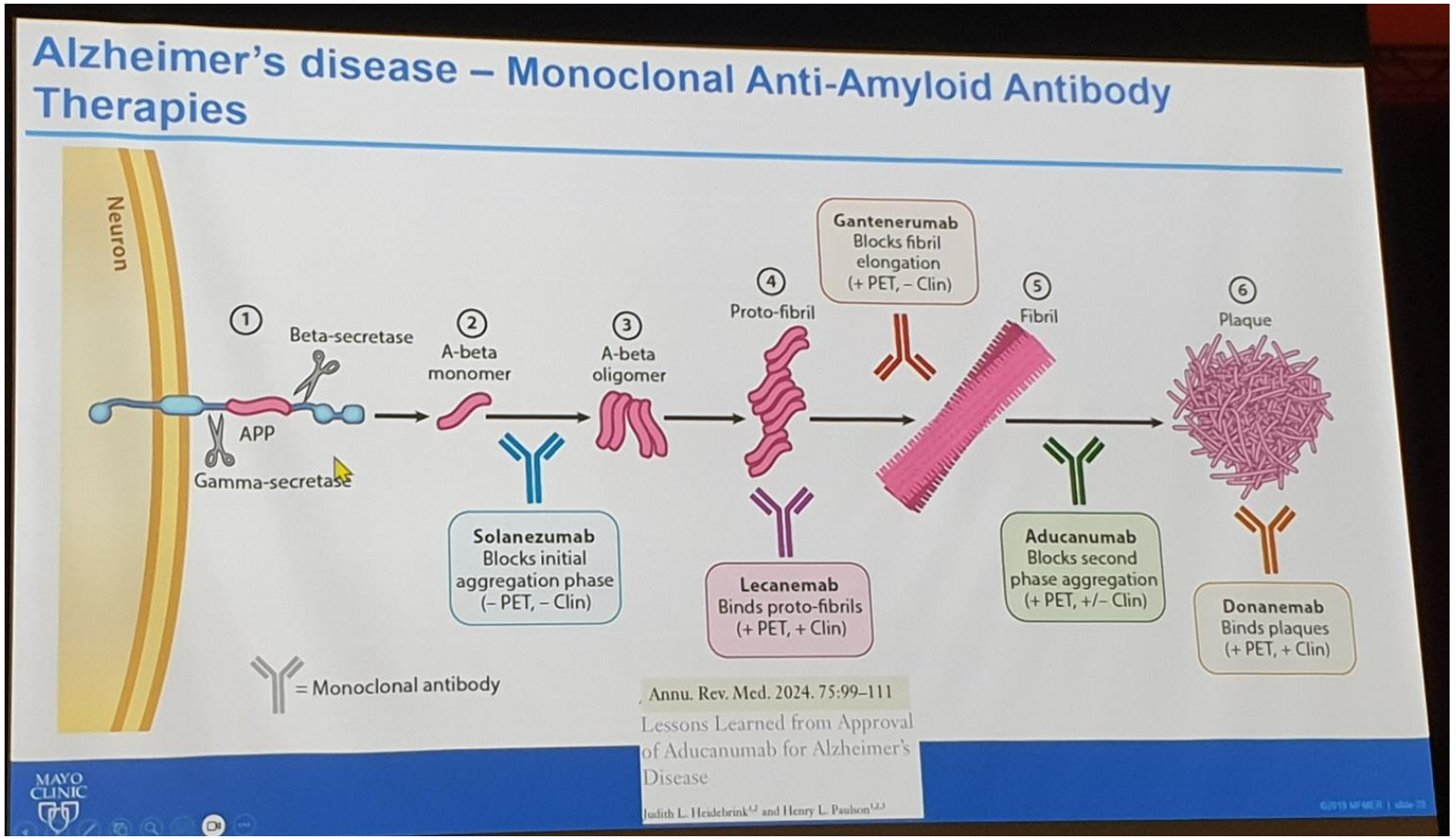


Two Phase 3 Trials of Gantenerumab in Early Alzheimer's Disease

R.J. Bateman, J. Smith, M.C. Donohue, P. Delmar, R. Abbas, S. Salloway, J. Wojtowicz, K. Blennow, T. Bittner, S.E. Black, G. Klein, M. Boada, T. Grimmer, A. Tamaoka, R.J. Perry, R.S. Turner, D. Watson, M. Woodward, A. Thanasopoulou, C. Lane, M. Baudler, N.C. Fox, J.L. Cummings, P. Fontoura, and R.S. Doody, for the GRADUATE I and II Investigators and the Gantenerumab Study Group*

What the Gantenerumab Trials Teach Us about Alzheimer's Treatment

Lon S. Schneider, M.D.

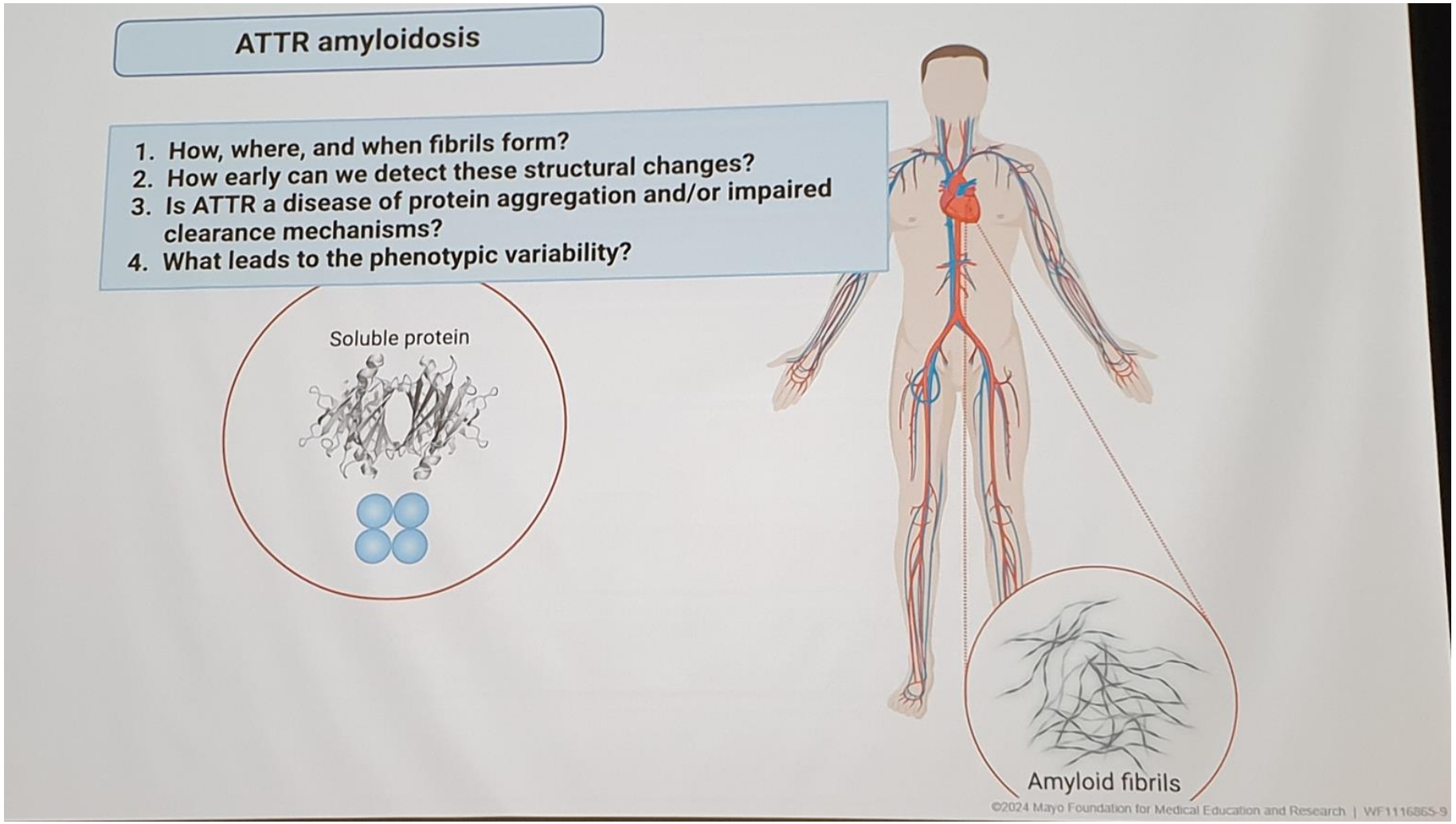
Lecanemab in Early Alzheimer's Disease

C.H. van Dyck, C.J. Swanson, P. Aisen, R.J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L.D. Kramer, and T. Iwatsubo

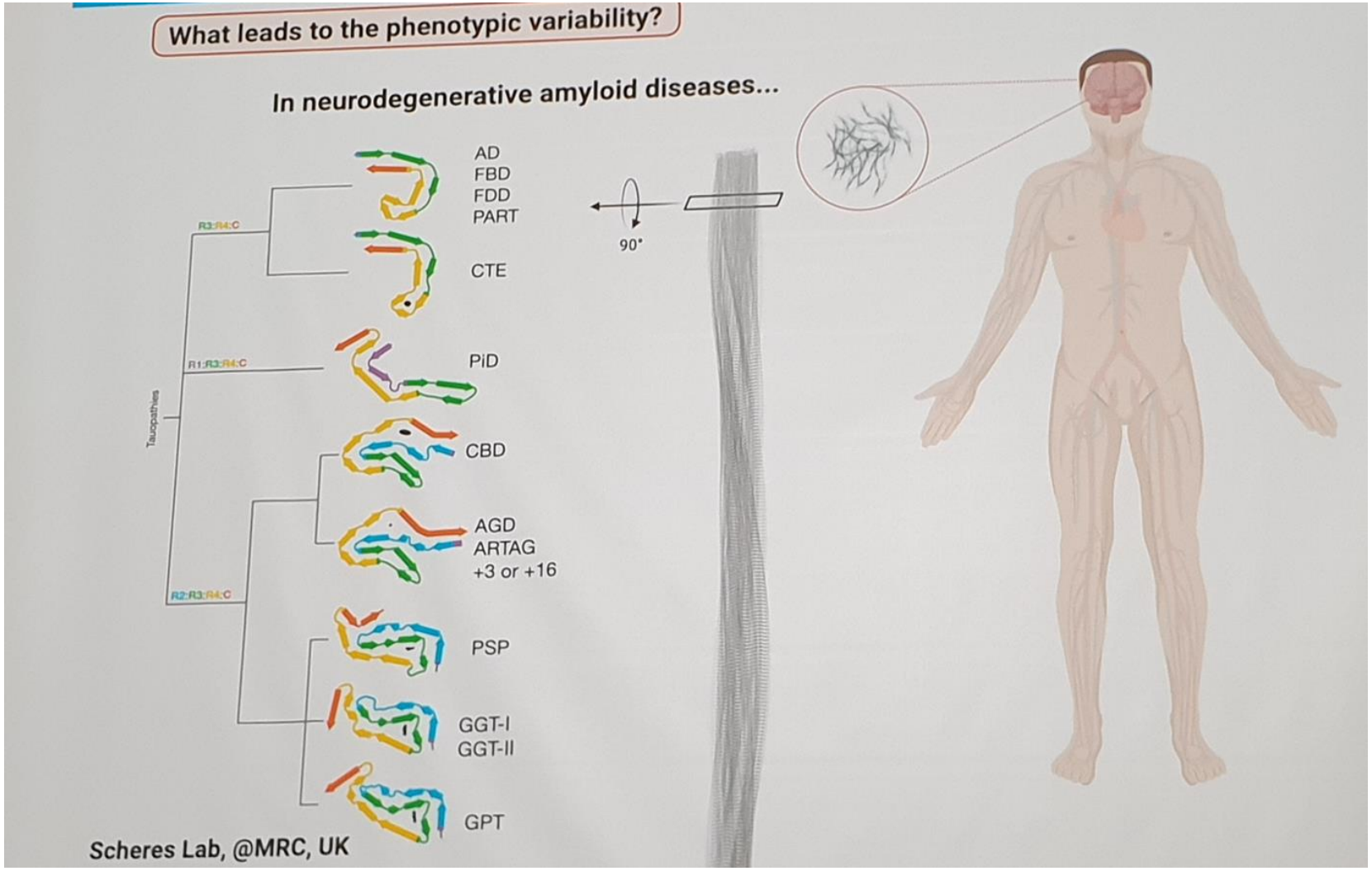
Lecanemab and *APOE* Genotyping in Clinical Practice—Navigating Uncharted Terrain

Ertekin, ISA 2024

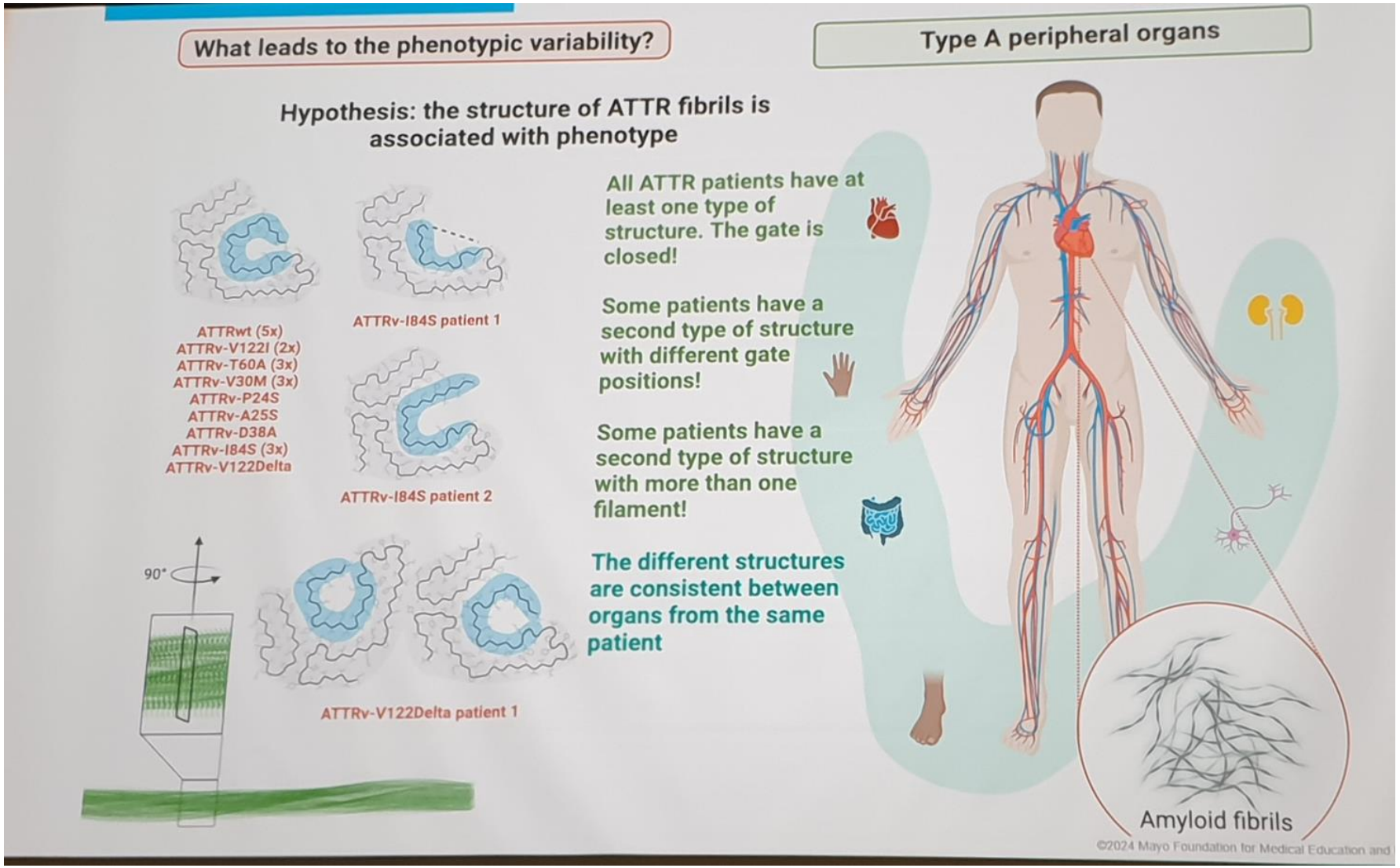
la maladie d'Alzheimer: un modèle pour l'amylose à transthyrétine?



Saelices, ISA 2024

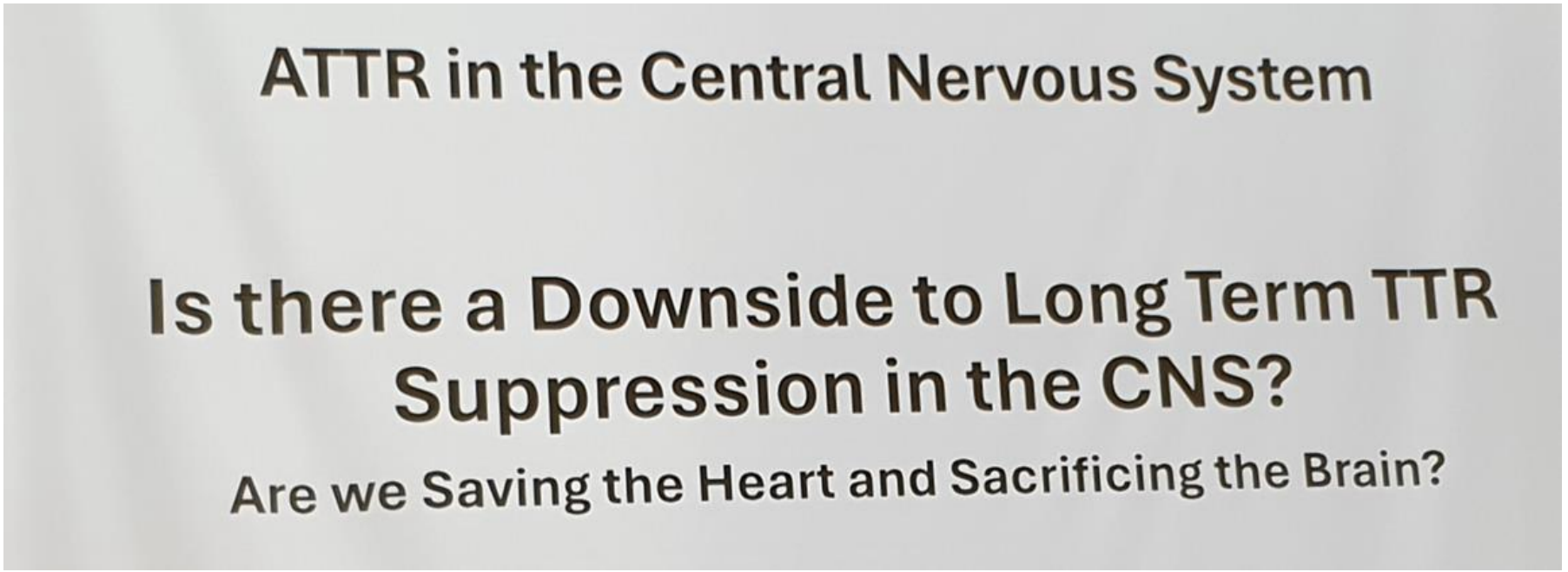


Saelices, ISA 2024



Saelices, ISA 2024

transthyrétine & cerveau: les liaisons dangereuses



Buxbaum, ISA 2024

Unmet Needs in ATTR therapy

- **CNS**: pV50M CNS not same as OLMA disease associated with other mutations with respect to age of onset, clinical symptoms, pathology, pathogenesis.
- **Ocular**: Most eye findings in ATTR pV50M are also seen with other mutations associated with systemic deposition.
- **Potential Solutions**:
  - Intraocular/intrathecal administration of current oligonucleotides
  - Systemic administration using, better tissue specific biological vectors, e.g. AAV's.
  - Better medicinal chemistry of small molecule stabilizers, to suppress or stabilize TTR in these previously inaccessible sites.
- Is there a downside to achieving these goals?

Buxbaum, ISA 2024

Ttr Null Mice

Normal lifespan and fecundity; normal thyroid function; normal vitamin A metabolism if diet sufficient.(Episkopou V et al. PNAS(USA) 90:23, 1993; Palha J et al. AM J Physiol 272:485, 1997).

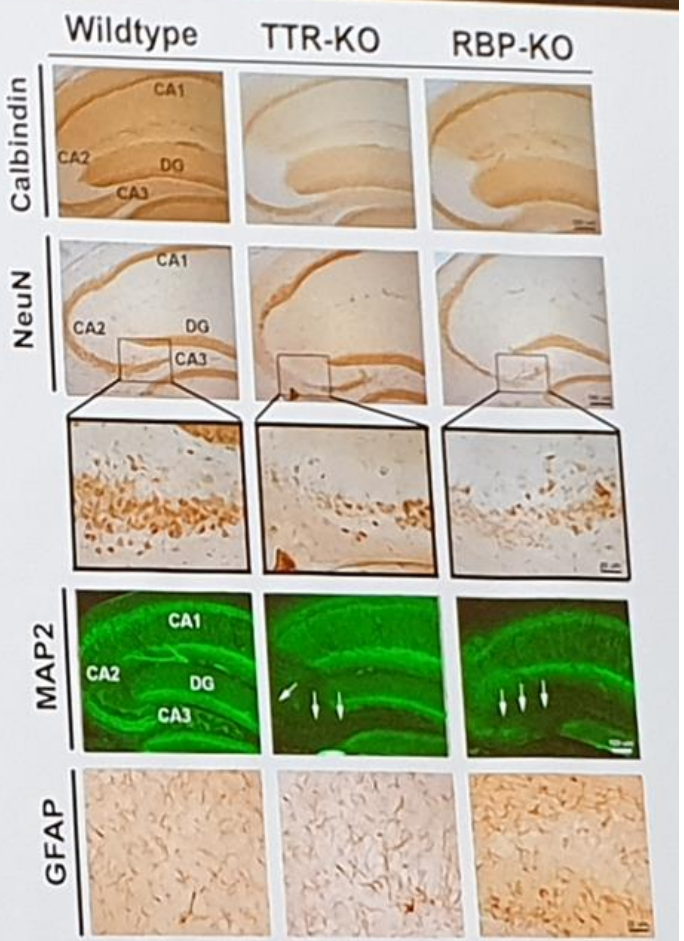
NPY phenotype; obesity hyperphagy (Nunez et al. FASEB J 20:166, 2006).

Behavioral Defect in spatial memory (Sousa JC et al. Neurobiol 88:381, 2007).

Differ from RBP knockouts in both function and pathology: Neuronal loss, astrogliosis in dentate gyrus; Apparent reduction in SGV neuroblasts (Buxbaum JN et al. Neuroscience 275:352 2014).

"Hyper-myelinated" oligodendrogliocytes in development (Alshehri B et al. Sci Rep 10:4189, 2020).

Enhanced susceptibility to effects of human AD transgenes. (Stein et al. JNS 24:7707, 2004 Choi et al. JNS 27:7006, 2007: Buxbaum et al. PNAS 105:2681, 2008).



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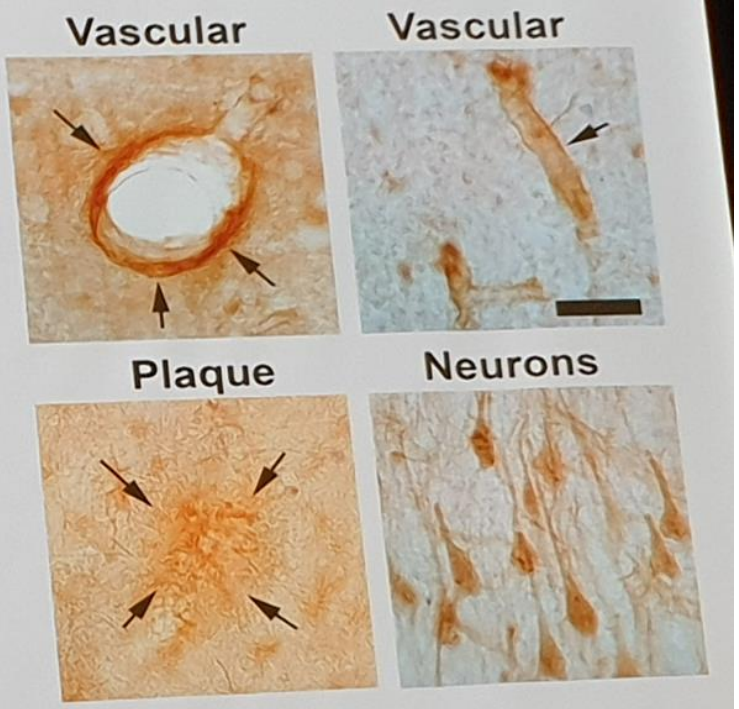
Human AD Brains Stain with Anti-TTR antibody

(Masliah and Buxbaum unpublished)



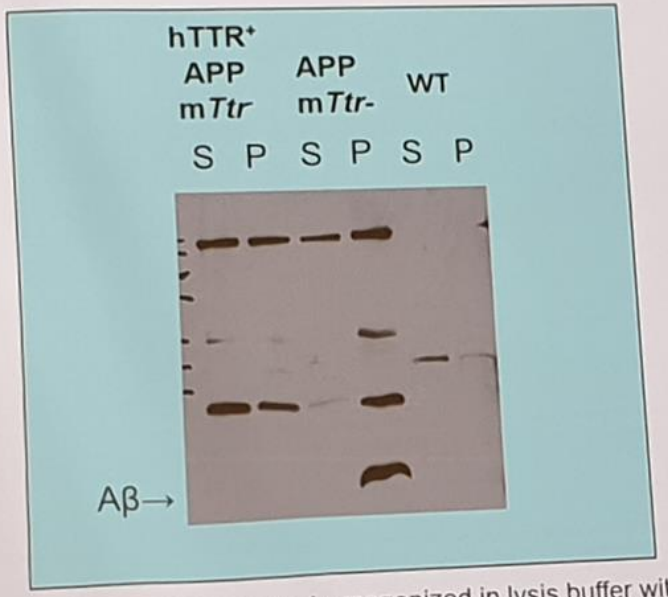
Senile Cerebral Amyloid Prealbumin as a Common Constituent in the Neuritic Plaque, in the Neurofibrillary Tangle, and in the Microangiopathic Lesion Shirahama, Skinner, Westermark, Rubinow, Cohen, Brun and Kemper, J Pathol **1982**, 107:41-50

Good data are good data even 30 years later.

Buxbaum, ISA 2024

TTR is up-regulated in brains of APP mice and hTTR transgene reduces Abeta species

- In brains of hTTR+/APP mice, Abeta species were reduced compared to those of APP mice
- In brains of APP mice, TTR transcription was upregulated compared to those of WT mice.



qRT-PCR APP23 (*mTtr*+/+)
Two sample t-test, p=0.07

Cortex pieces were homogenized in lysis buffer with proteinase inhibitor and centrifuged at 10,000g for 10min at 4C, then pellet resuspended and sample boiled 10 min. Probed with 6E10 antibody (anti-Aβ)

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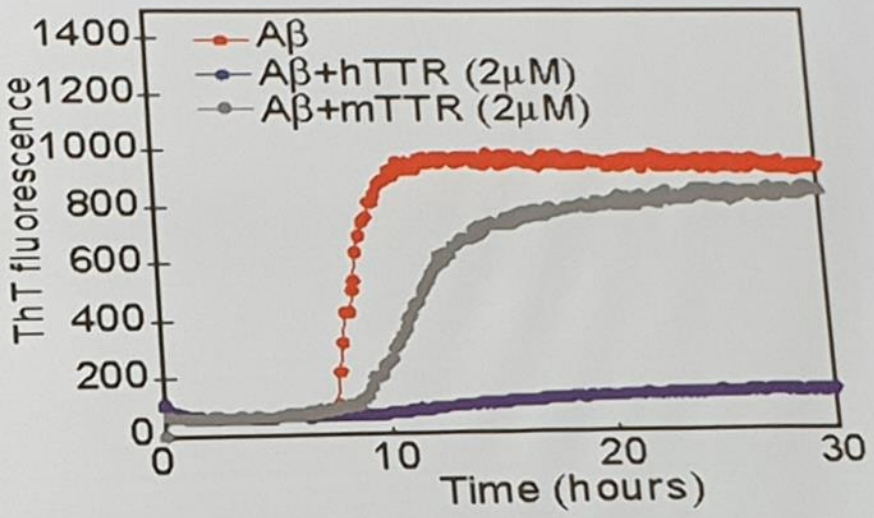
How Does Increased Human TTR reduce Aβ neurotoxicity?

TTR binding to Aβ1-40

huTTR KD 24±12 μM
muTTRKD 16±7 μM

TTR inhibits Aβ aggregation *in vitro*



Li X, et al. J Neurosci 31:12483-90, 2011

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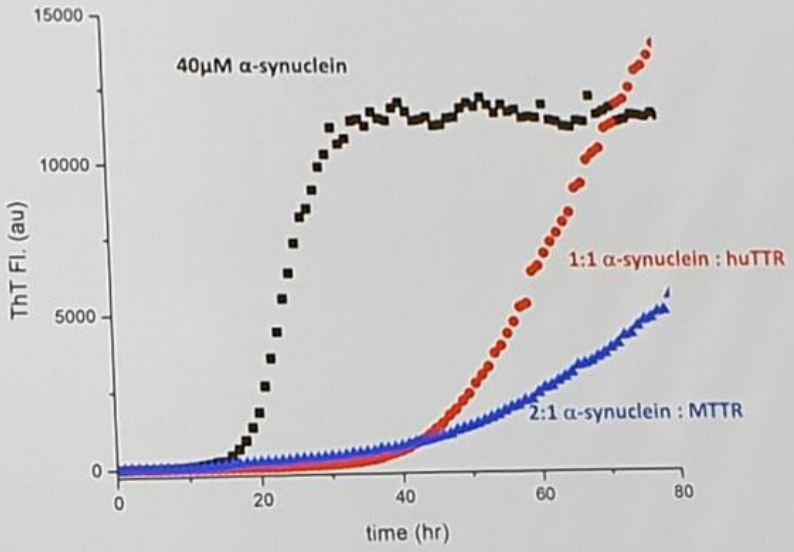
Transthyretin inhibits α-synuclein fibrillogenesis *in vitro*



Jain, Chapman, Buxbaum unpublished

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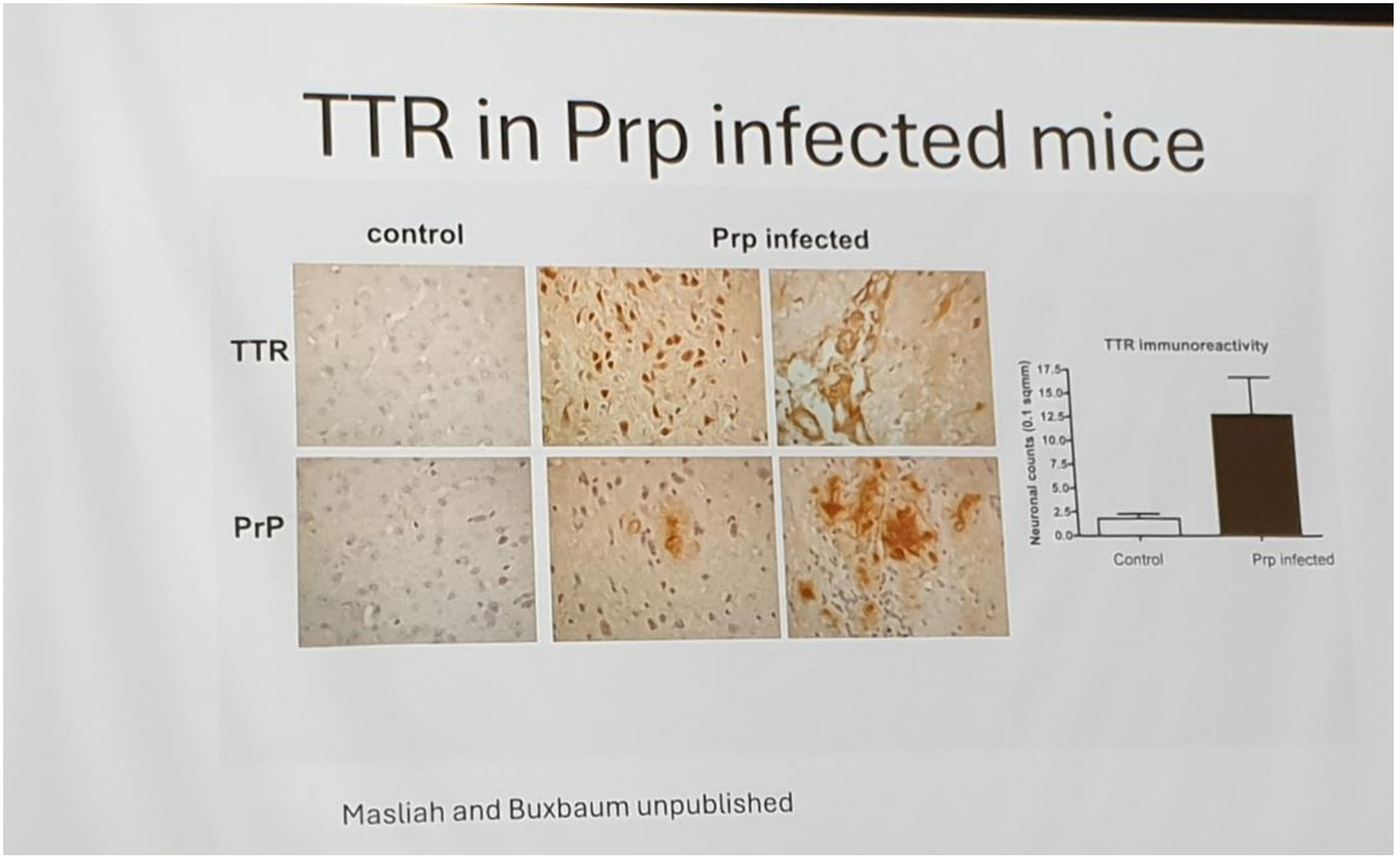

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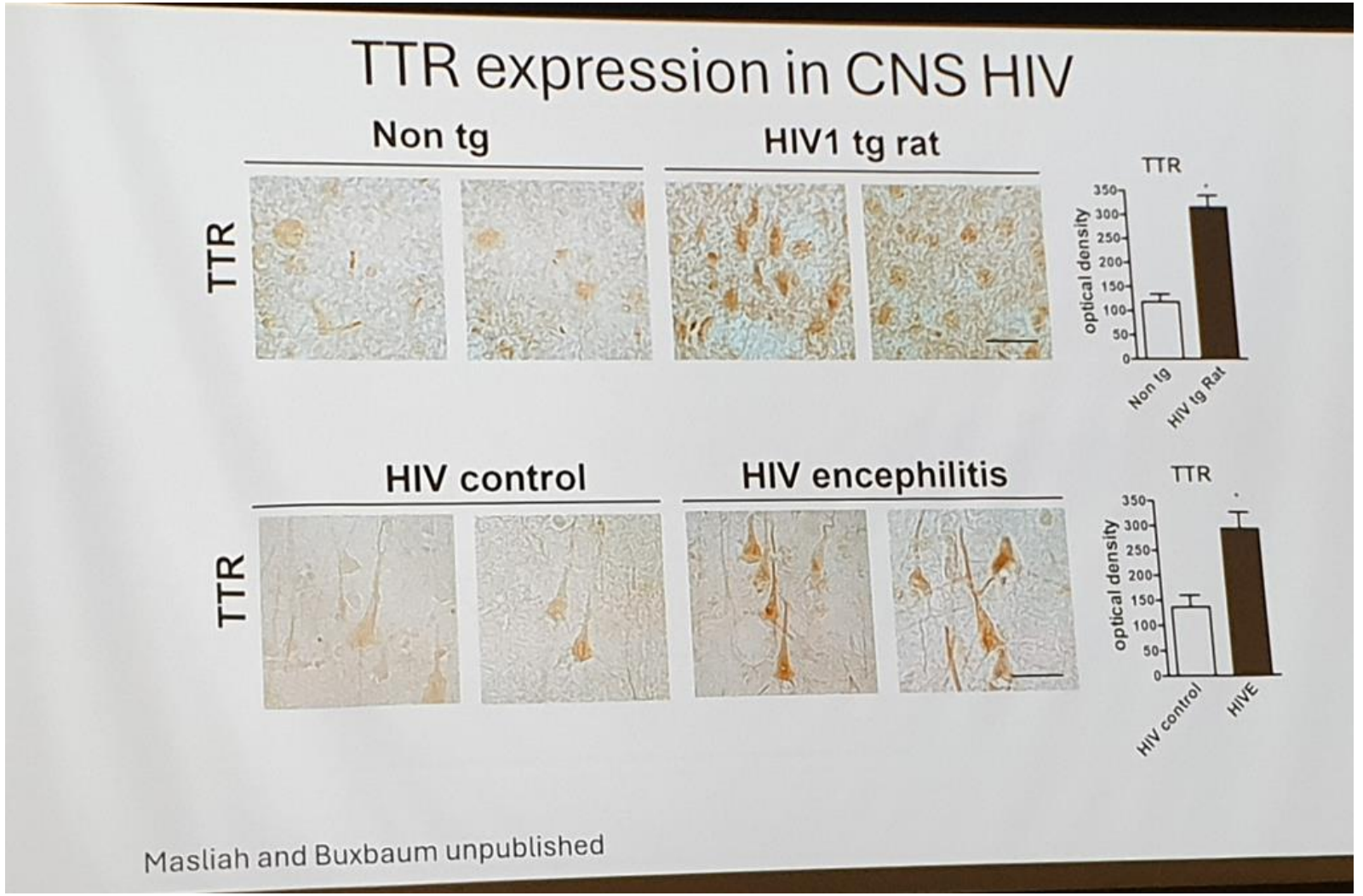

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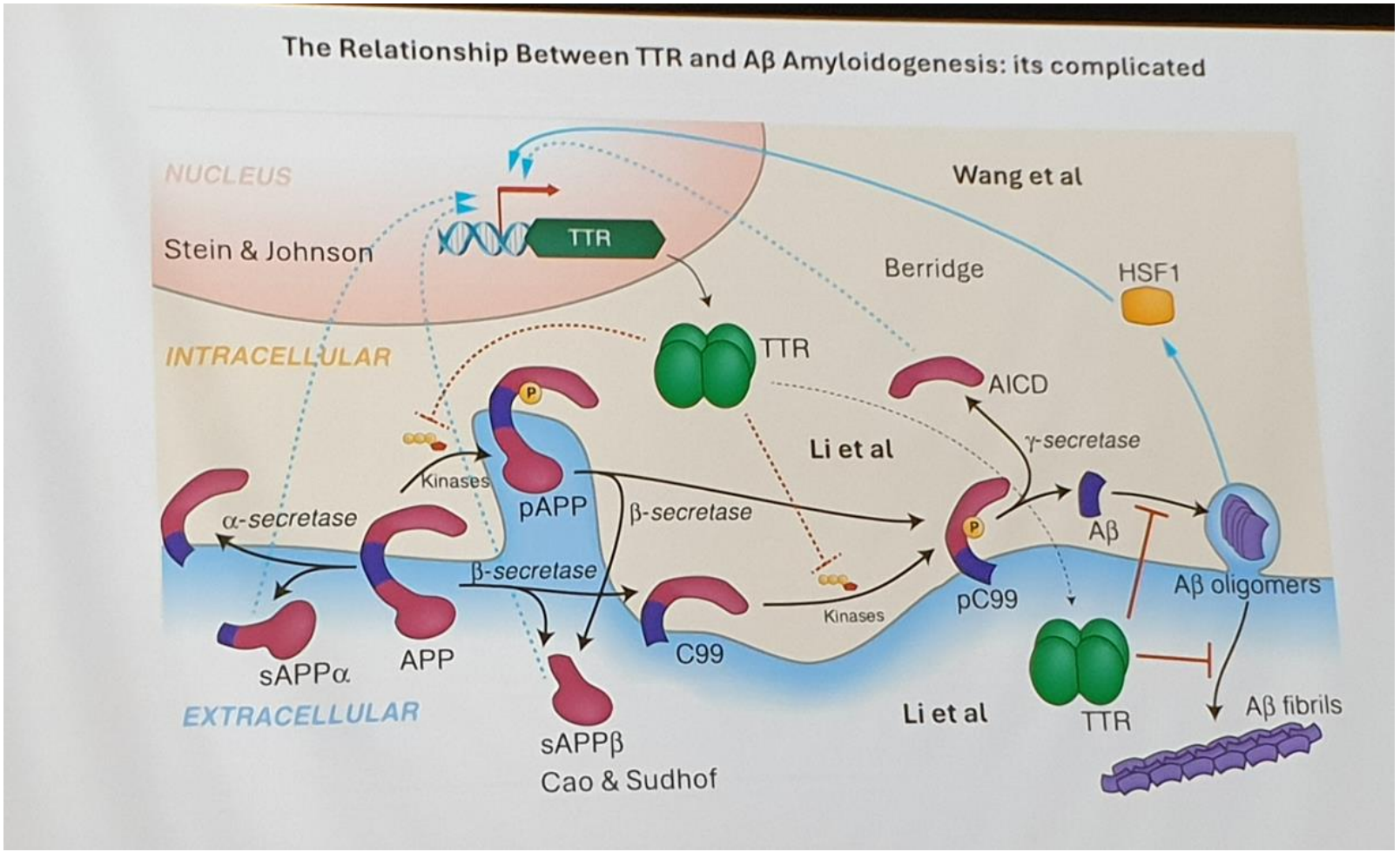

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Questions and Answers

- **Are we saving the heart and sacrificing the brain?**
  - Enhanced survival allows increased manifestations of CNS phenotypes.
  - These are present in some carriers early in ATTR pV50M primarily as cognitive dysfunction (symptomatic>asymptomatic; early>late; males>females.
  - Current systemic treatment is unsatisfactory because of inadequate CNS/ocular access.
  - Effective therapy is likely to be achieved by either systemic delivery of stabilizers or TTR synthesis suppressors that attain sustained therapeutic concentrations in the eye and brain or new modes of delivery (physical or biologic).
- **Is there a downside to long term TTR suppression?**
  - We may not yet recognize all the physiologic roles of TTR in the CNS.
  - Potential hazards of CNS targeted agents, particularly those that suppress TTR synthesis, could involve interfering with the apparent "chaperone" like function of TTR in the context of neuronal stress, particularly but not exclusively, those related to aging associated neurodegenerative diseases like AD and PD.

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conclusion

- la maladie d'Alzheimer –un modèle pour l'amylose à TTR?

- comprendre le rôle de TTR dans le système nerveux central - un préalable indispensable avant de cibler TTR dans le cerveau!