

ISA 2024: actualités en Neurologie

Andoni Echaniz-Laguna

CRMR CERAMIC

CHU DE BICETRE

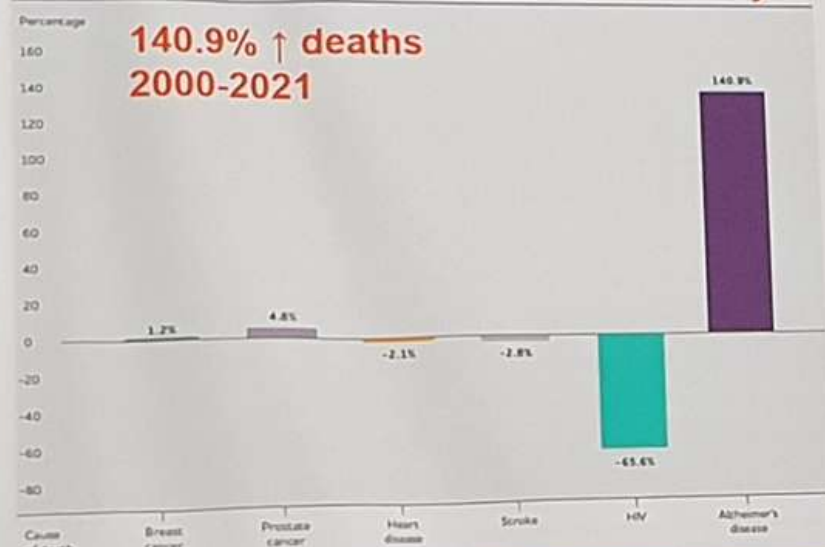


la maladie d'Alzheimer: la plus fréquente des amyloses

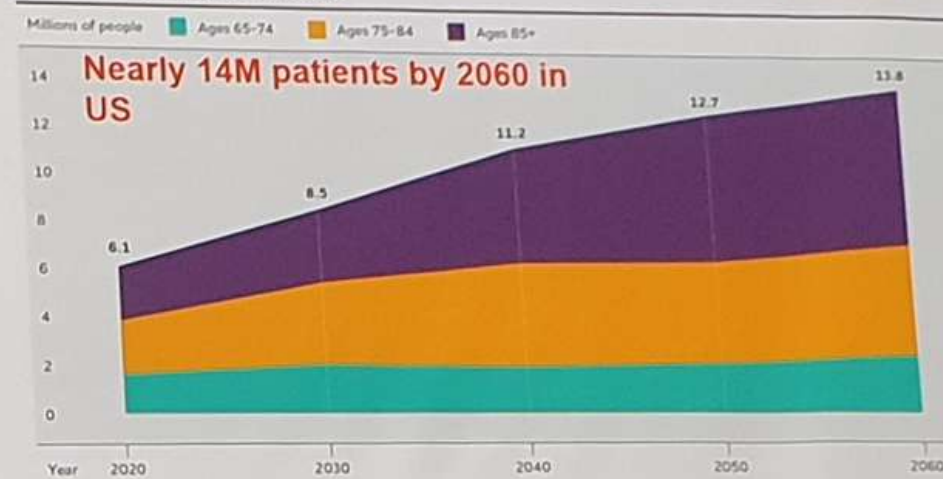
Alzheimer's Disease: A Deadly Epidemic

- Common and deadly diseases without cures.
- Substantial human and financial cost.
- Alzheimer's Disease (AD) is the most common neurodegenerative disease.

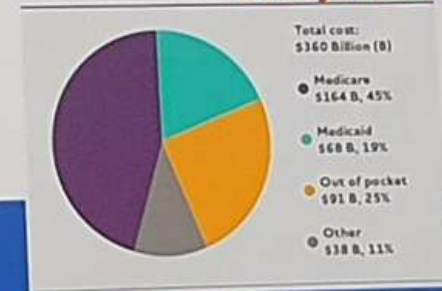
Percentage Changes in Selected Causes of Death (All Ages) Between 2000 and 2021



Projected Number of People Age 65 and Older (Total and by Age) in the U.S. Population with Alzheimer's Dementia, 2020 to 2060



Distribution of Aggregate Costs of Care by Payment Source for Americans Age 65 and Older with Alzheimer's or Other Dementias, 2024* **Costly: \$360 B/yr**



Global Impact:

- 47 M patients.
- \$604B / year
- 76 M AD by 2030

AD: Pathophysiology – Amyloid – Genetics (1980s-2009)

Early-Onset Familial AD Genes:

- Amyloid precursor protein (*APP*): Ch21
- Presenilin 1 (*PSEN1*): Ch14
- Presenilin 2 (*PSEN2*): Ch1

- Families
- Linkage/positional cloning
- Autosomal dominant
- <1% of all AD

Late-Onset AD Gene:

- Apolipoprotein E (*APOE*)

- Families
- Linkage/case-control
- OR = 3-12
- 20% PAR

APP

Struwe et al., 1929, Jervis et al., 1948
Glennner and Wong, 1984
St George-Hyslop et al., 1987
Tanzi et al., 1987, Goldgaber et al., 1987
Goate et al., 1991

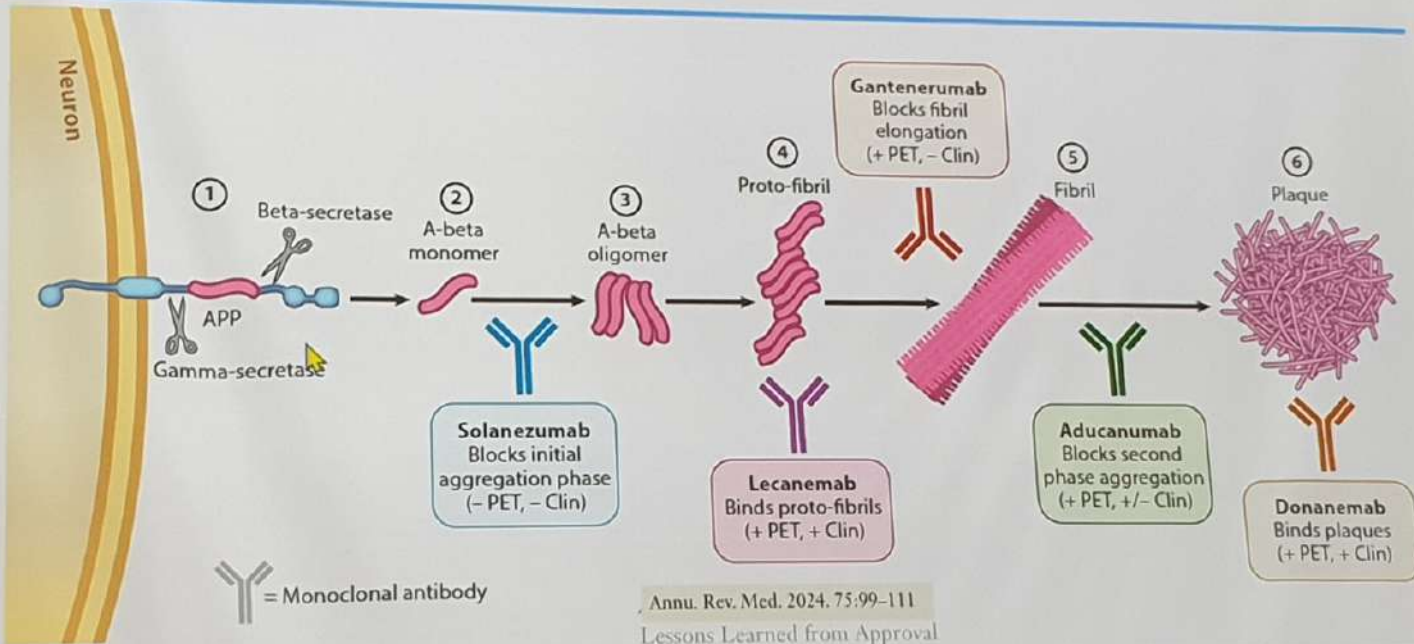
Presenilins

Sherrington et al., 1995
Levy-Lahad et al., 1995
Rogaev et al., 1995

APOE

Pericak-Vance et al., 1991
Namba et al., 1991
Corder et al., 1993
Strittmatter et al., 1993

Alzheimer's disease – Monoclonal Anti-Amyloid Antibody Therapies



Annu. Rev. Med. 2024. 75:99-111
Lessons Learned from Approval of Aducanumab for Alzheimer's Disease
Judith L. Heidebrink^{1,2} and Henry L. Paulson^{1,2,3}

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

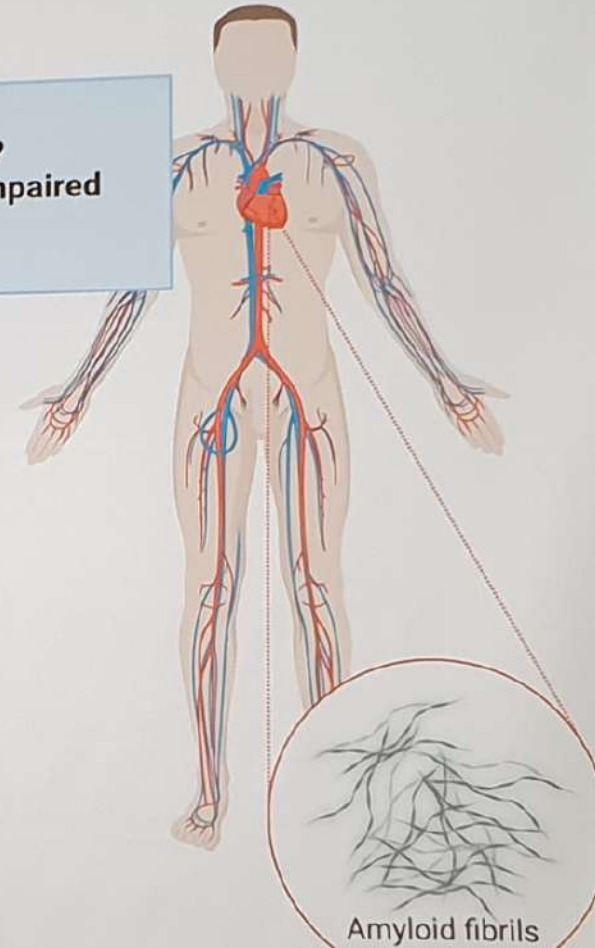
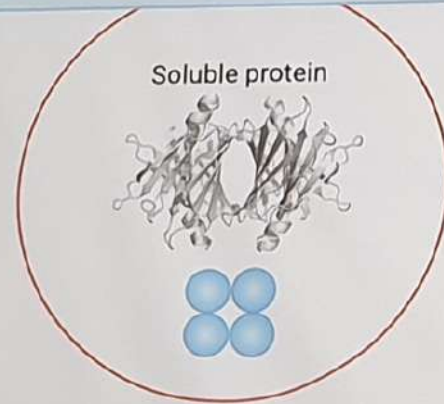
C.H. van Dyck, C.J. Swanson, P. Aisen, R.J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L.D. Kramer, and T. Iwatsubo

Lecanemab and APOE Genotyping in Clinical Practice—Navigating Uncharted Terrain

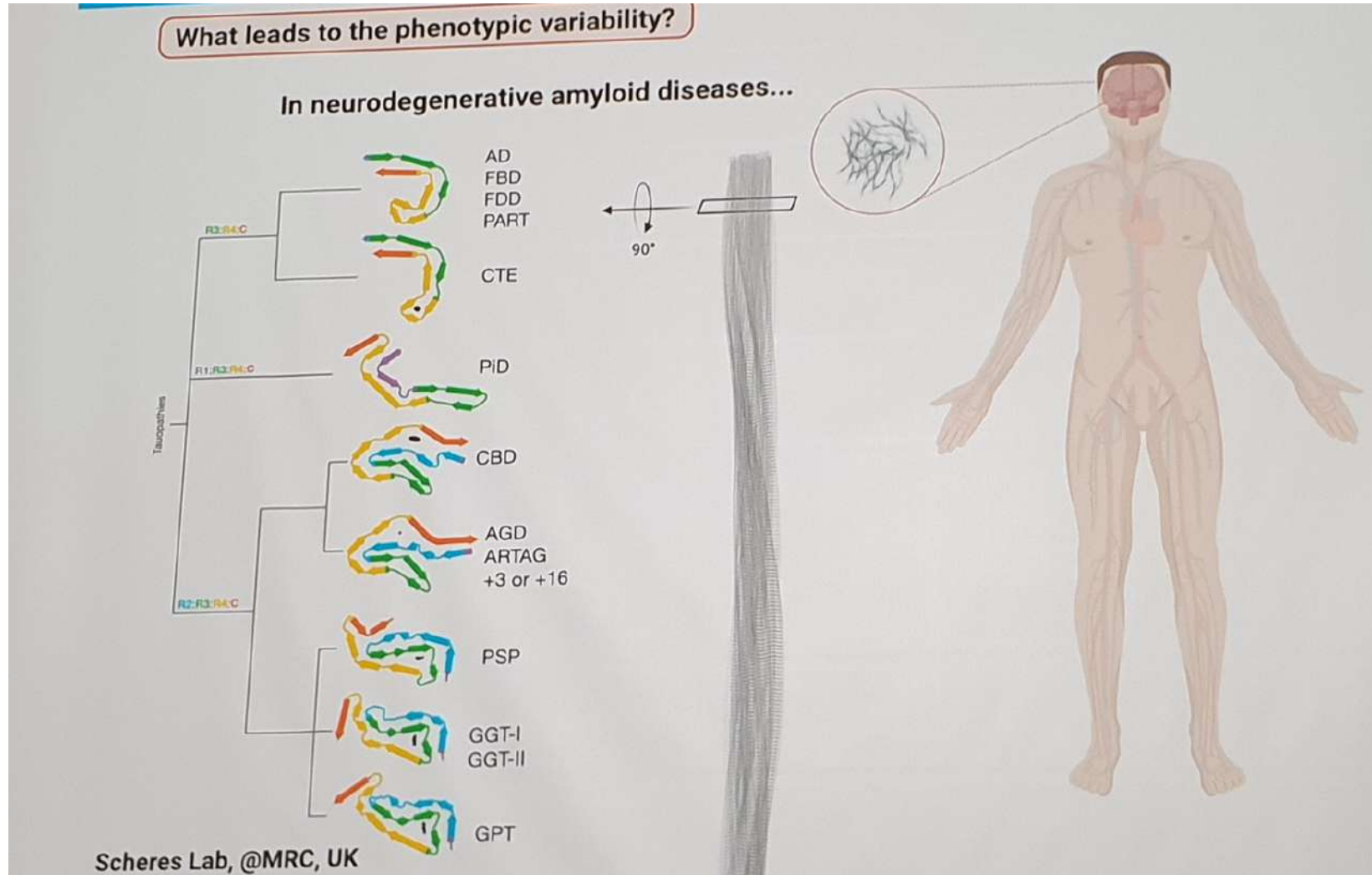
la maladie d'Alzheimer:
un modèle pour l'amylose à transthyrétine?

ATTR amyloidosis

1. How, where, and when fibrils form?
2. How early can we detect these structural changes?
3. Is ATTR a disease of protein aggregation and/or impaired clearance mechanisms?
4. What leads to the phenotypic variability?

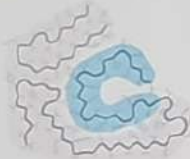


Amyloid fibrils

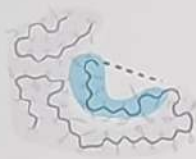


What leads to the phenotypic variability?

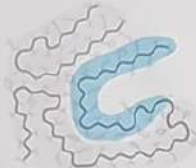
Hypothesis: the structure of ATTR fibrils is associated with phenotype



ATTRwt (5x)
ATTRv-V122I (2x)
ATTRv-T60A (3x)
ATTRv-V30M (3x)
ATTRv-P24S
ATTRv-A25S
ATTRv-D38A
ATTRv-I84S (3x)
ATTRv-V122Delta

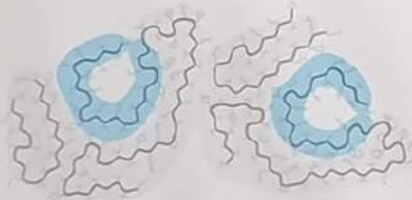


ATTRv-I84S patient 1



ATTRv-I84S patient 2

90°



ATTRv-V122Delta patient 1



Type A peripheral organs

All ATTR patients have at least one type of structure. The gate is closed!

Some patients have a second type of structure with different gate positions!

Some patients have a second type of structure with more than one filament!

The different structures are consistent between organs from the same patient



Amyloid fibrils

transthyrétine & cerveau: les liaisons dangereuses

ATTR in the Central Nervous System

Is there a Downside to Long Term TTR Suppression in the CNS?

Are we Saving the Heart and Sacrificing the Brain?

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?

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" oligodendrogliaocytes 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).

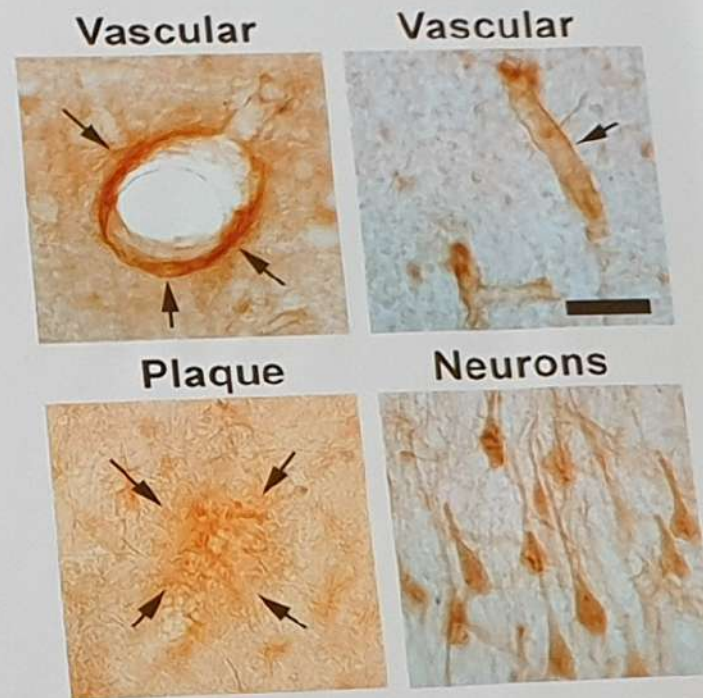


Human AD Brains Stain with Anti-TTR antibody

(Masliah and Buxbaum unpublished)

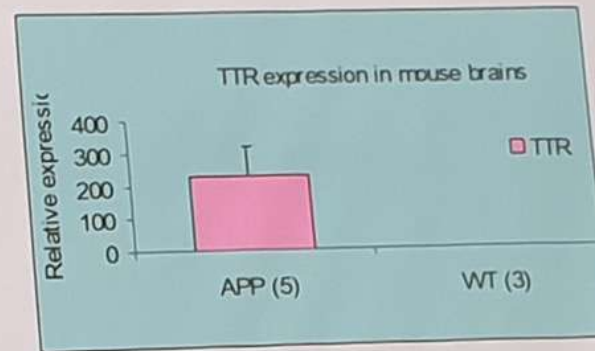
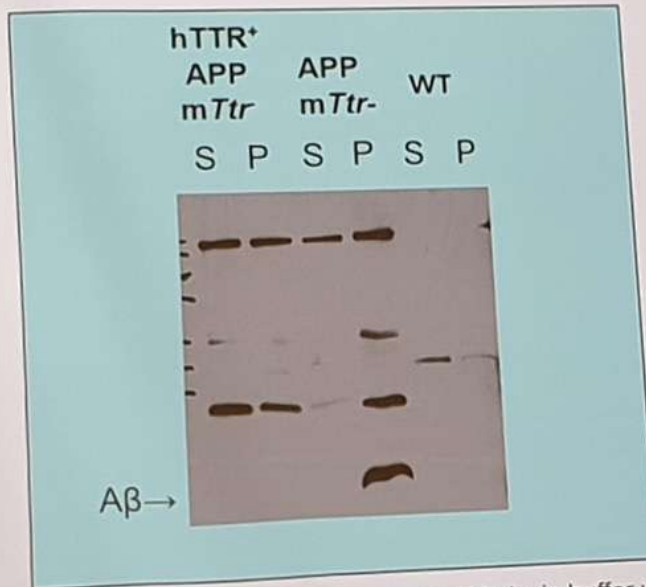
Senile Cerebral Amyloid Prealbumin as a Common Constituent in the Neuritic Plaque, in the Neurofibrillary Tangle, and in the Microangiopathic Lesion Shirahama, Skinner, Westermarck, Rubinow, Cohen, Brun and Kemper, *J Pathol* **1982**, 107:41-50

Good data are good data even 30 years later.



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, $p=0.07$

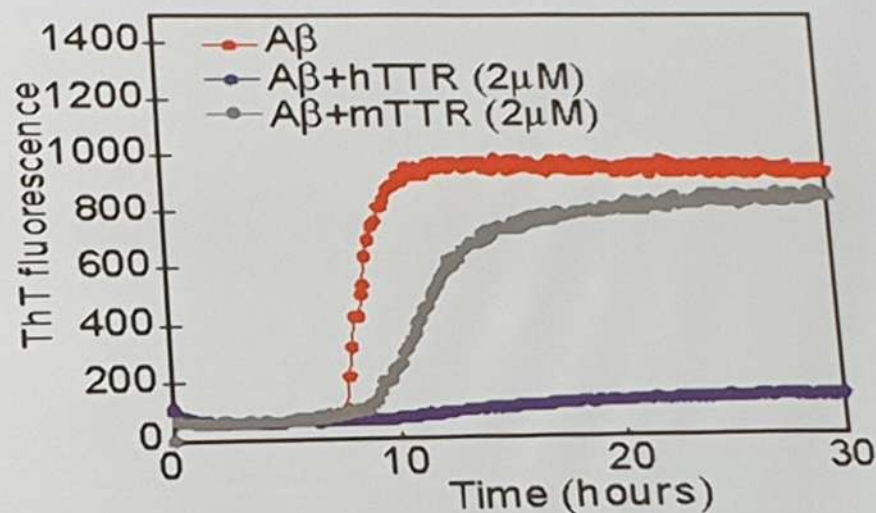
Cortex pieces were homogenized in lysis buffer with proteinase inhibitor and centrifuged at 10,000g for 10min at 4C, then pellet resuspended and sample boiled 10 min. Probed with 6E10 antibody (anti-Aβ)

How Does
Increased
Human TTR
reduce A β
neurotoxicity?

TTR binding to A β 1-40

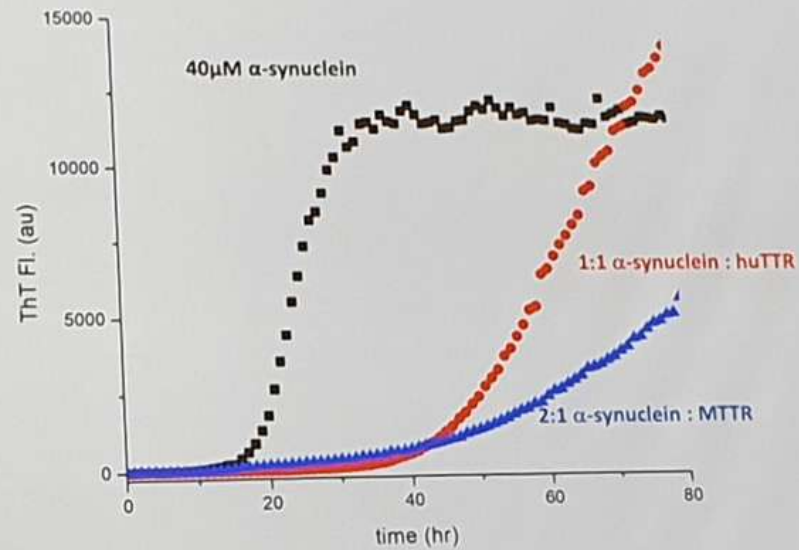
huTTR KD $24 \pm 12 \mu\text{M}$
muTTRKD $16 \pm 7 \mu\text{M}$

TTR inhibits A β aggregation
in vitro



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

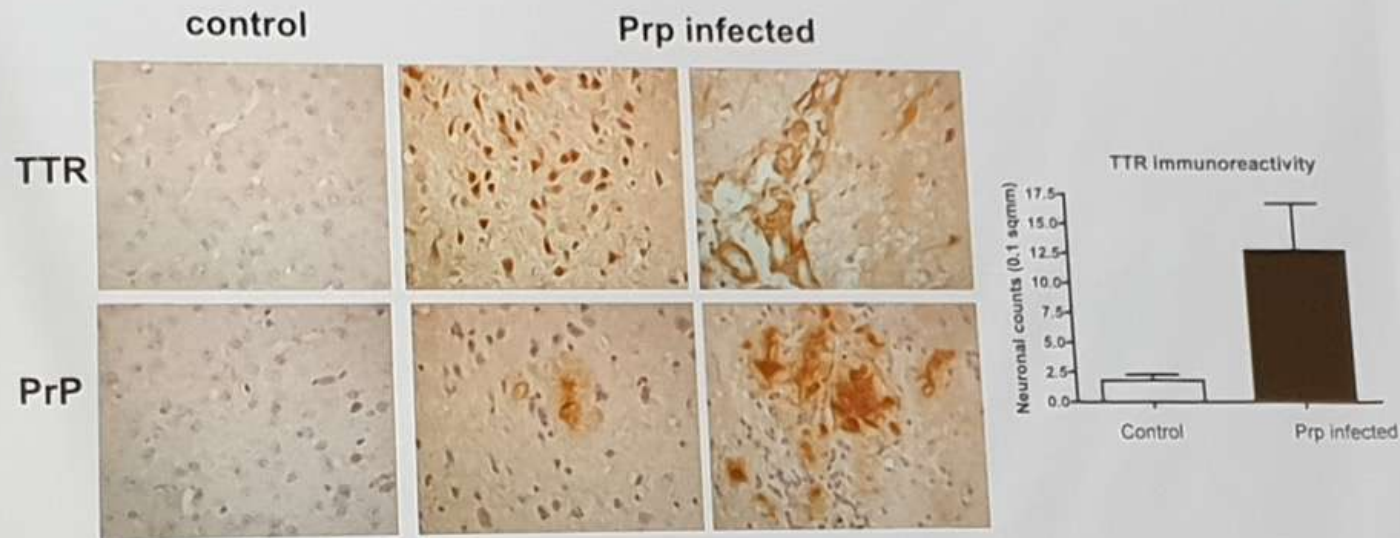
Transthyretin inhibits α -synuclein fibrillogenesis *in vitro*



Jain, Chapman, Buxbaum unpublished

Buxbaum, ISA 2024

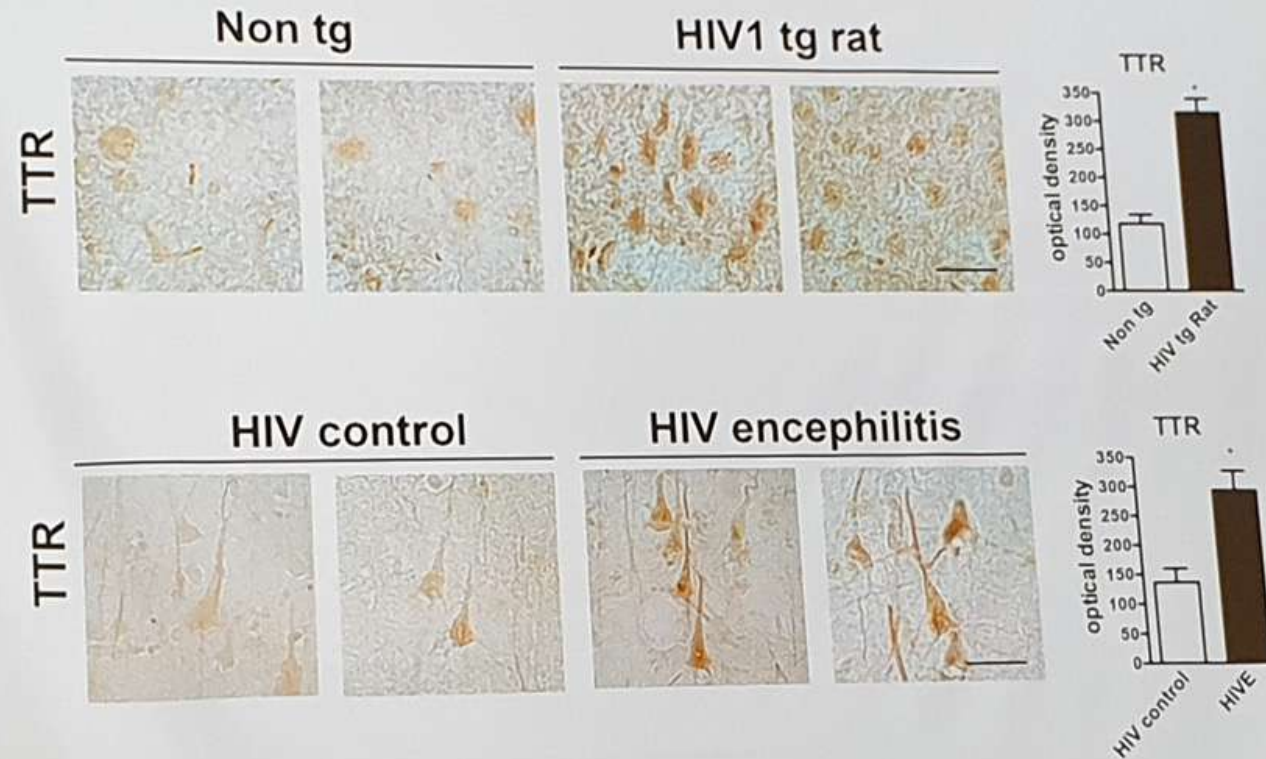
TTR in Prp infected mice



Masliah and Buxbaum unpublished

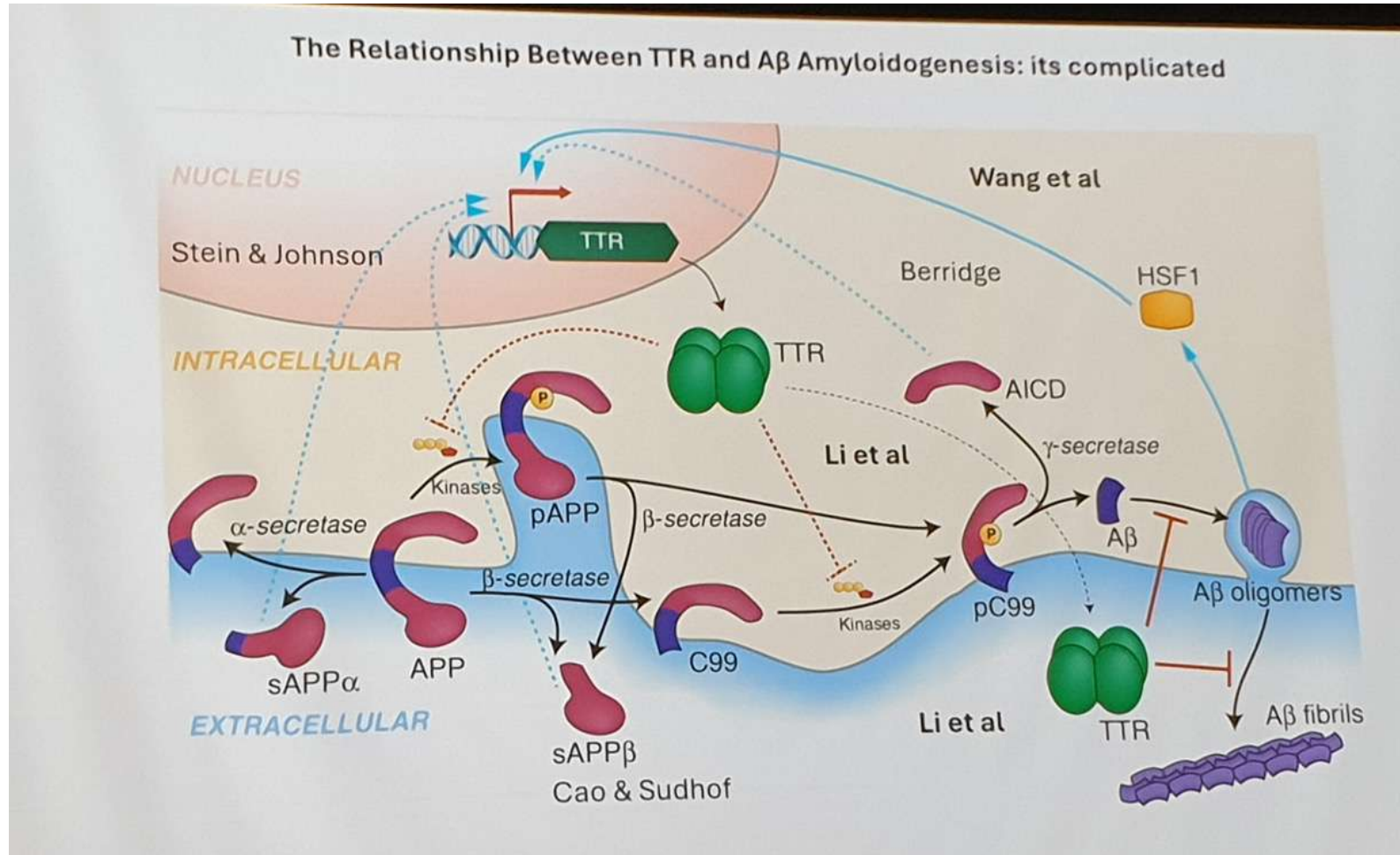
Buxbaum, ISA 2024

TTR expression in CNS HIV



Masliah and Buxbaum unpublished

Buxbaum, ISA 2024



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.

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!