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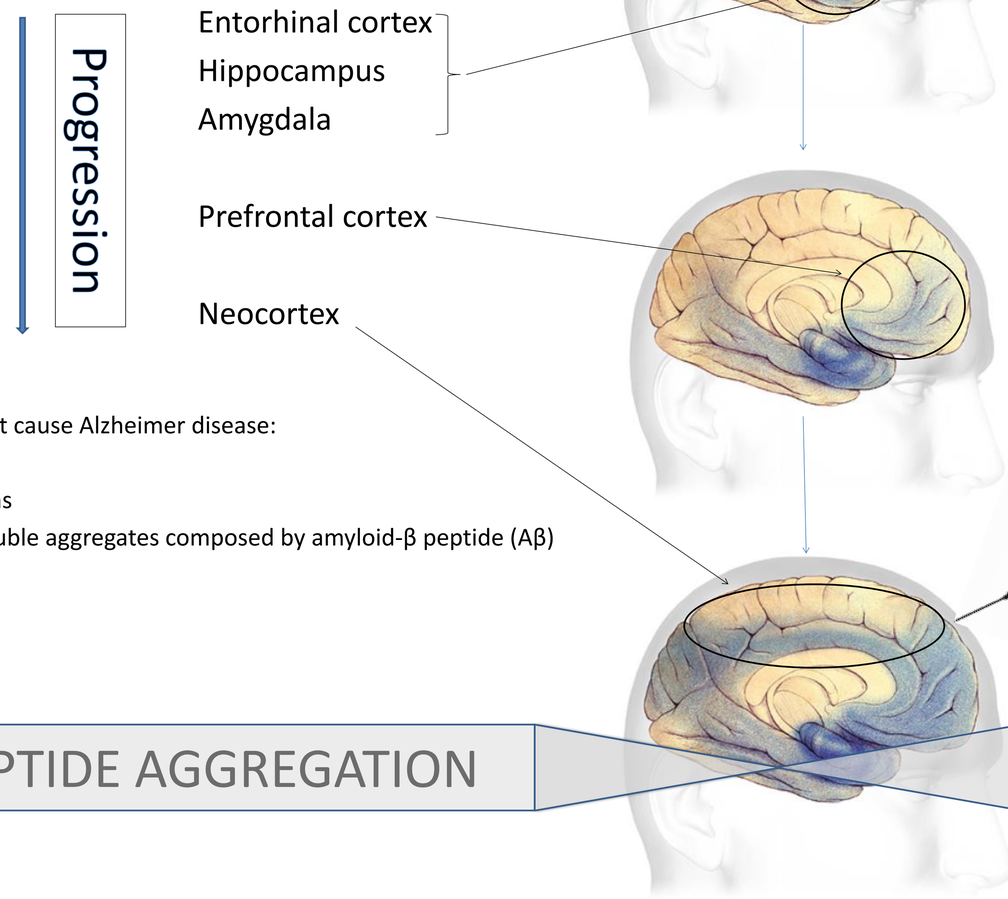
Gene therapy strategies for Alzheimer Disease

Universitat Autònoma de Barcelona

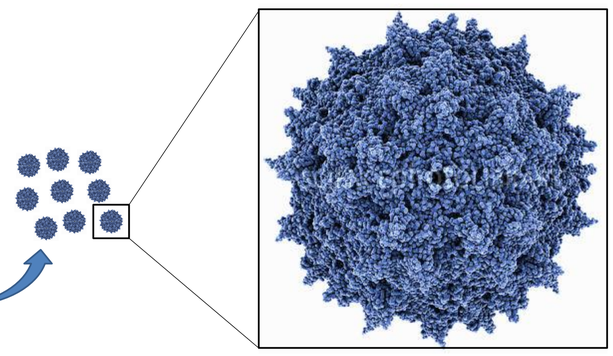
INTRODUCTION

Alzheimer Disease is the neurodegenerative disorder with the highest prevalence, mostly present in elders. The neuronal degeneration and loss of synapses progresses over time spreading through the brain.



There are **TWO main pathways** that cause Alzheimer disease:

Degeneration of cholinergic neurons
Accumulation of extracellular insoluble aggregates composed by amyloid-β peptide (Aβ)



AMYLOID-β PEPTIDE AGGREGATION

Its production originates from the **amyloid precursor protein (APP)** through γ-secretase **processing** (Fig. 2).
Amyloid-β oligomers increase the neurons glutamate, leading to toxicity and posterior **denervation** (Fig. 1).

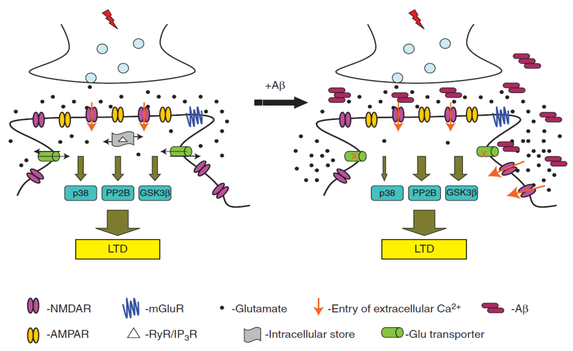


Fig. 1. Main pathways implicated in LTD facilitated by soluble Ab oligomers

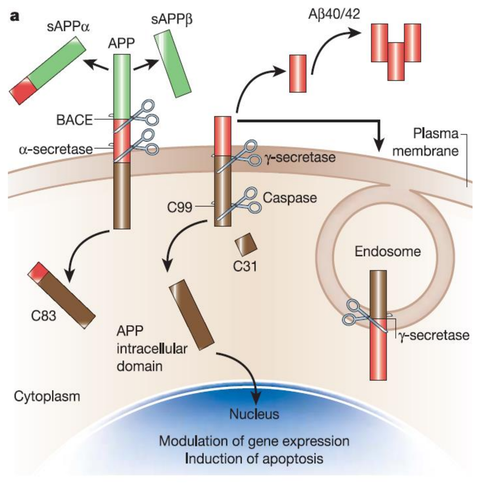


Fig.2. APP cleavege processing signalling

GENE THERAPY

This technique consists in the **delivery of nucleic acid polymers** in the patient's cell to either **express** a protein **or interfere** with a protein expression.

Adeno-associated virus (AAV) are the best vector selection in Alzheimer disease due to its **intrinsic safety** characterization when utilized in the nervous system.

Family	Parvoviridae
Group	ssDNA
Capacity	4,8 kb
Infectivity	Needs helper virus

CHOLINERGIC NEURONS DEGENERATION

The cholinergic neurons are **nerve growth factor (NGF)** dependent, establishing its **survival and synapsis** formation through axonal stimulation.

There is a **correlation** between the **aging** and the **reduction** in the concentration of **NGF** and the efficiency of its signalling pathway.

There is a loss of synapsis present in the ascendant cholinergic projections from the nucleus basalis of Meynert to the hippocampus and neocortex.

This is followed by the loss of NGF producer neurons, and a **decrease in the neuronal activity**.

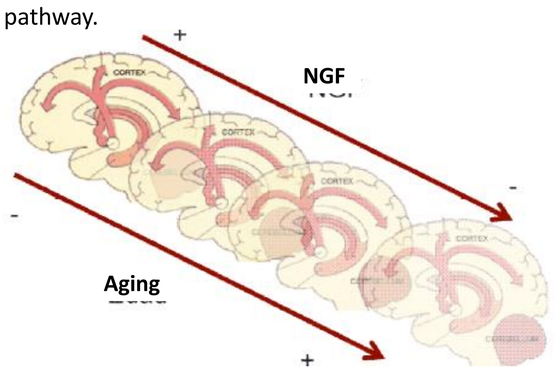


Fig.3. NGF correlation with aging

siRNA AND NEPRILYSIN GENE THERAPY

The delivery of **siRNA against APP mRNA** forms a silencing complex that induces its cleavage. However, it might effect on the physiological role of APP.

Neprilysin on the other hand, is an **endopeptidase** that cleaves peptides of 4-5 kDa, including the amyloid-β peptide.

Both experiments expressing neprilysin and siRNA against APP confirmed that recombinant gene therapy vectors successfully **decreased the levels of amyloid-β peptide** in vitro and in vivo conditions.

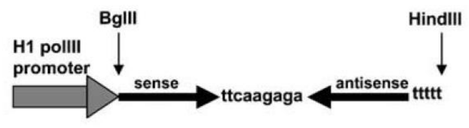


Fig. 4. schematic illustration of APP-RNAi construct

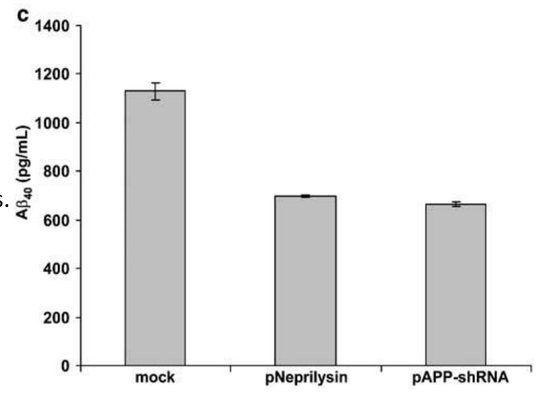


Fig. 5. Herpes simplex virus RNAi and neprilysin gene

NGF GENE THERAPY

After the treatment, the patients showed a median **reduction in the decline** of the score in both tests, MMSE and ADAS-Cog.

Interestingly, some subjects not only stopped the degeneration in the early stages after treatment, but also showed an **improvement**.

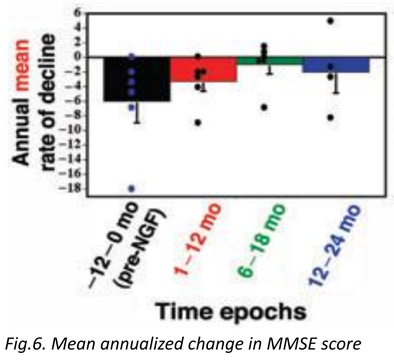


Fig.6. Mean annualized change in MMSE score

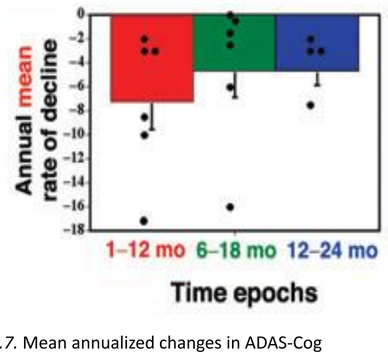


Fig.7. Mean annualized changes in ADAS-Cog

CONCLUSION

However, none of the gene therapy techniques successfully showed a fully recovery and functional restoration of the impaired brain areas, the cease in the deterioration of cholinergic neurons as well as β-amyloid plaques elimination could bring symptomatic mitigation and also stop the development of Alzheimer disease.

Further studies are needed to clear the remaining uncertain molecular pathways involved in Alzheimer's in order to enable the development of innovative gene based therapies.

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Fig. 6 and 7 Tuszynski MH, Thal L, Pay M, Salmon DP, U HS, Bakay R, et al. A phase 1 clinical trial of nerve growth factor gene therapy for Alzheimer disease. Nat Med. 2005;11(5):551–5