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Danna Alejandra Perlaza Meneses

ONE STEP CLOSER TOWARDS ALZHEIMER'S CURE

Universitat Autònoma de Barcelona

Full text

Bachelor's degree final thesis | Genetics (2018-2022)

Bibliografic Review

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that affects millions of people worldwide.

To date, there is no cure for AD and most of the drugs approved for treatment (donepezil, rivastigmine, galantamine and memantine) are intended to palliate its symptoms.

Consequently, new disease-modifying therapies (DMTs) that modulate the progression of the disease have been harvesting interest. DMTs target the two main pathological hallmarks of AD, deposition of amyloid beta (Aβ) plaques and neurofibrillary tangles of hyperphosphorylated tau protein (Fig. 1).

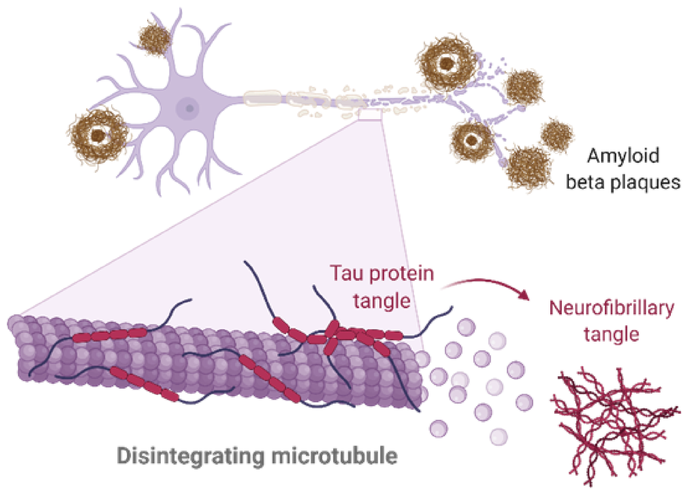


Figure 1. The two main hallmarks of Alzheimer's disease: extracellular amyloid plaques and intracellular neurofibrillary tangles (NFTs). Adapted from BioRender.com templates.

Methodology

Bibliographic research restricted by keywords and proper Boolean operators.

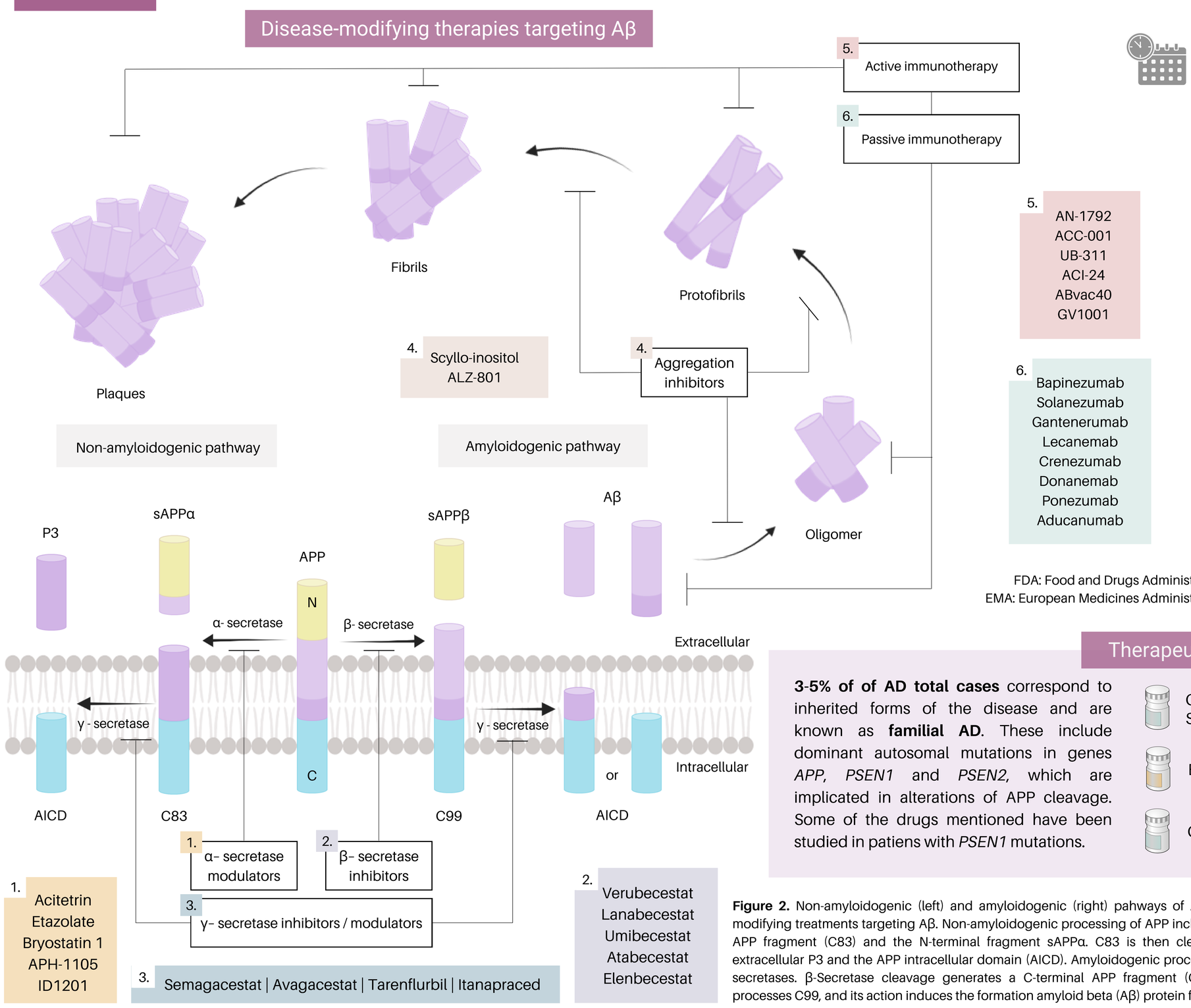
Clinical trials research restricted by those currently in phase II and III and that have beta-amyloid as target.

Objectives

1. To explore current phase II and III clinical trials of DMTs targeting Aβ
2. To discuss the controversy generated surrounding aducanumab's approval
3. To search applications of anti-Aβ DMTs to inherited forms of AD.

Results

Disease-modifying therapies targeting Aβ



Aducanumab

2 phase III clinical trials abandoned due to no clinical efficacy

October 2019
Biogen claims that EMERGE (NCT02484547) did show significant results

Access to the accelerated approval pathway

June 2021
Aducanumab is approved by the FDA

December 2021
The EMA rejects aducanumab's approval because of its controversial results

May 2022
Beginning of phase IV clinical trial to prove clinical benefits

FDA: Food and Drugs Administration
EMA: European Medicines Administration

Therapeutic approaches for familial AD

3-5% of of AD total cases correspond to inherited forms of the disease and are known as **familial AD**. These include dominant autosomal mutations in genes *APP*, *PSEN1* and *PSEN2*, which are implicated in alterations of APP cleavage. Some of the drugs mentioned have been studied in patiens with *PSEN1* mutations.

Gantenerumab Solanezumab	Current phase II clinical trial expected to finish by the end of 2022
Bryostatin I	Compasionate trial that lasted 8 weeks
Crenezumab	Phase II/III clinical trial showed no clinical benefits

Figure 2. Non-amyloidogenic (left) and amyloidogenic (right) pahways of APP clevage and mechanism of action of the disease-modifying treatments targeting Aβ. Non-amyloidogenic processing of APP includes cleavage by α-secretase, which leaves a C-terminal APP fragment (C83) and the N-terminal fragment sAPPα. C83 is then cleaved by the γ-secretase, resulting in two mollecules: extracellular P3 and the APP intracellular domain (AICD). Amyloidogenic processing of APP includes the sequential action of β- and γ-secretases. β-Secretase cleavage generates a C-terminal APP fragment (C99) and N-terminal sAPPβ. γ-secretase subsequently processes C99, and its action induces the formation amyloid beta (Aβ) protein fragments and AICD. Adapted from Vaz, M., *et al.* (2020)

Conclusions

- Several trials targeting Aβ have failed, probably due to inappropriate drug doses, testing at late stages of the disease, wrong target engagement, and an incomplete understanding of the pathophysiology of AD[4].
- This failure has brought interest in anti-tau treatments but there are few phase III clinical trials because of the recent emergence of this field.
- Aducanumab's approval by the FDA has opened the door to novel trials of AD immunotherapies, although its clinical benefits are yet to be confirmed.
- There are few drugs tested for familial AD and further research is needed.

Relevant references

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