

Alzheimer's Disease (AD)

Alzheimer's disease (AD) is a complex disease, which results from multiple molecular defects and, therefore, involves more than one key pathogenic target.

AD has two principal pathological characteristics:

- Amyloid or senile plaques composed of aggregated β -amyloid peptide; and
- Neurofibrillary tangles composed of hyperphosphorylated tau protein.

Current drugs for AD are simply symptomatic; they only alleviate symptoms by temporarily reducing the neurotransmitter degradation.

Multifunctional AD Modifying Compounds

The research group from the [University of Barcelona](#) led by [Diego Muñoz-Torrero](#) has developed a new family of multifunctional AD modifying agents hitting multiple biological targets involved up and down-stream the neurotoxic cascade.

The **multifunctional AD modifying compounds** inhibit BACE-1, $A\beta$ aggregation, AChE, and BChE in vitro. Bioavailability tests predict that these compounds successfully cross the blood-brain barrier. Additionally, an ex vivo AChE inhibitory activity study demonstrates that these compounds cross the blood-brain barrier in mouse as fast as donepezil (5 minutes).

The compounds could not only provide a symptomatic relief associated to the increased levels of neurotransmitter acetylcholine resulting from the inhibition of central cholinesterases but, more importantly, could directly interfere with the beginning of the AD neurotoxic cascade through their inhibitory effect on $A\beta$ formation and aggregation, thus delaying or slowing down the neurodegenerative process.

Multifunctional AD modifying compounds interact at 4 different levels of the neurotoxic cascade:

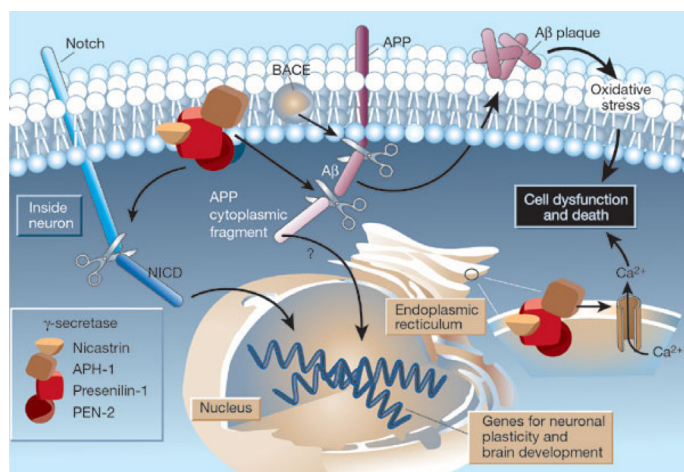
- **1st Action Mechanism:** block the β -amyloid peptide ($A\beta$) formation through inhibition of β -secretase (BACE-1).
- **2nd Action Mechanism:** show significant inhibitory effect on the acetylcholinesterase-induced and self-induced beta-amyloid aggregation.
- **3rd Action Mechanism:** high acetylcholinesterase inhibitory activity.
- **4th Action Mechanism:** significant inhibitory activity toward butyrylcholinesterase (BChE).

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Advantages

The new anti-Alzheimer agents hitting multiple biological targets involved up and down-stream the neurotoxic cascade are superior to donepezil, currently the best and most prescribed anti-Alzheimer drug.

- Two-fold more potent inhibitors of AChE-induced $A\beta$ aggregation;
- Up to 6-fold more potent inhibitors of self-induced $A\beta$ aggregation;
- Equipotent to donepezil as inhibitors of BACE-1;
- Up to 8-fold more potent inhibitors of human AChE;
- Up to 120-fold more potent inhibitors of human BChE;
- Brain penetration test in rodents: shown to be able to cross blood-brain barrier; and
- Straightforward synthesis, ready to scale up.

Partnering Opportunity

- Genoma España has signed a collaboration agreement between the Bosch i Gimpera Foundation and the research group. It includes support for the funding of proof-of-concept in animals, the optimisation of preclinical development as well as the commercialisation of the compound.
- The research group is looking for other collaboration and/or license agreements.

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