

Similarities and Differences Between Small Molecules and Biologics: Examples of Drugs for Alzheimer's Disease

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Abstract: Alzheimer's disease is a neurodegenerative disease with a hidden onset. Existing therapeutic drugs can only delay the progression of the disease and relieve symptoms. Small interfering RNAs show potential for the treatment of Alzheimer's disease by cleaving mRNA encoding target genes, but many challenges need to be overcome by stably delivering small interfering RNA to the lesions. This paper describes the pathological mechanism of Alzheimer's disease, existing drug targets, the advantages and challenges of small interfering RNA therapy, research progress in the transblood-brain barrier delivery system, new small interfering RNA delivery system and ongoing clinical trials of Alzheimer's disease drugs, etc., and strives to provide reference and reference for related research on small interfering RNA therapy for Alzheimer's disease.

Keywords: Biological small molecules; Drugs for Alzheimer's disease; Drug research and development

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1. Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disorder caused by nerve cell damage, affecting around 45 million people globally^[1]. Neuropathologically, AD develops in parallel with the accumulation of amyloid- β (A β) and phosphorylated tau protein (p-tau)^[2], accounting for the cognitive decline in affected individuals. Nowadays, medications used to treat AD include small molecules and biologics and could be classified as symptomatic treatment and disease-modifying therapy (DMT)^[3,4]. Small molecules are typically low molecular weight (MW) compounds that can be synthesized through chemical processes, while biologics are larger molecules derived from living organisms or cells^[5]. Currently, several monoclonal antibodies (mAbs) for AD have been approved by the United States Food and Drug Administration (FDA), providing new hope to AD patients^[6].

2. Drug design and mechanism of drug action

2.1. Small molecules

2.1.1. Cholinesterase inhibitors (ChEIs)

Acetylcholine (ACh) is a neurotransmitter related to brain functions, such as attention and memory. Acetylcholinesterase

(AChE) is a cholinesterase enzyme that hydrolyses the ACh and terminates the nerve impulses transmitted to cholinergic synapses conducted by ACh^[7]. It is believed that during AD development, cholinergic synapses experience a massive loss^[8], followed by the cholinergic deficit, resulting in memory dysfunction and ultimately dementia^[9]. Therefore, the usage of ChEIs to block the AChE and maintain the ACh level becomes a promising strategy for treating AD. Currently, donepezil, rivastigmine, and galantamine constitute the pivotal ChEIs that have been approved for AD treatment by the FDA in 1996, 2000, and 2001, respectively. Besides, the first ChEI once authorized in 1993 was tacrine, and was withdrawn due to hepatotoxicity in 2013^[10].

2.1.2. N-methyl-D-aspartate receptor (NMDAR) antagonists

Glutamate is the agonist of the NMDAR and an excitatory transmitter in the nervous system, which is considered a neurotoxin as well, accounting for several neurodegenerative disorders^[11]. This implies that inhibiting the NMDAR and the glutamate-mediated neurotoxicity may ameliorate the cognitive decrease in AD patients^[12]. Memantine approved in 2003 is applied to moderate the overactivation of NMDAR^[13]. In addition, Namzaric, a fixed-dose combination of donepezil and memantine, was approved in 2014 (**Figure 1**). However, these five medications are symptomatic treatments that only alleviate the symptoms instead of resolving the underlying cause to discontinue the long-term progression of AD; thus, the efficacy is temporary and fleeting^[14].

2.2. Biologics

Accumulation of A β and p-tau is thought to play an essential role in the development of AD^[15]. A β is a fragment of amyloid precursor protein (APP), which is similar to a cell surface receptor and could produce A β as soluble monomers^[16]. Apart from monomers, A β exists as dimers, oligomers, protofibrils, fibrils, and eventually forms plaques. Additionally, these A β forms can convert from each other (**Figure 2**)^[16].

In recent years, some biologics targeting A β have been approved. In 2021, aducanumab (Aduhelm), was approved via the accelerated approval (AA) pathway by the FDA. Aducanumab was a human mAb that targets the A β soluble oligomers and insoluble fibrils^[17], reducing the amyloid plaque in the brain^[18]. It was also the first approval of DMT for AD^[4,19]. However, since the follow-up studies failed to confirm the anticipated clinical benefit, aducanumab was withdrawn in 2024^[20,21]. Lecanemab (Leqembi) was another humanized mAb targeting A β soluble oligomers and protofibrils^[22], approved via the AA pathway in 2023 and converted to a traditional approval 6 months later. Furthermore, another A β -targeted mAb for AD called donanemab (Kisunla)^[23], received full FDA approval directly in 2024, which can target the pyroglutamate-modified A β and bind to the amyloid plaques selectively (**Table 1**).

3. Pharmaceutical production process

3.1. Manufacturing process

The manufacturing processes for small molecules include the identification of drug targets and the active pharmaceutical ingredient (API) first. Then, the API was synthesized through the chemical synthetic pathways, including substitution, addition and elimination, oxidation and reduction reactions, and more. Lastly, these chemical synthesis pathways are scaled up. Moreover, the chemical synthetic processes of small molecules are standardized with manageable and scalable steps, which ensures a high batch consistency.

In contrast, advanced biotechnologies are conventionally utilized for the manufacturing process of most biologics, making the processes more complicated. Firstly, the target for drug action and a specific protein interacting with the target are identified, with a functional DNA sequence created based on the chosen protein and its genetic code. After that, the functional sequence is inserted into different host cells to screen for the cell line that could produce the chosen protein most effectively. Then, the cell line is cultured and grown in the bioreactors and undergoes the fermentation process to produce the target protein. Lastly, the target protein is separated by filtration, followed by purification, stabilization

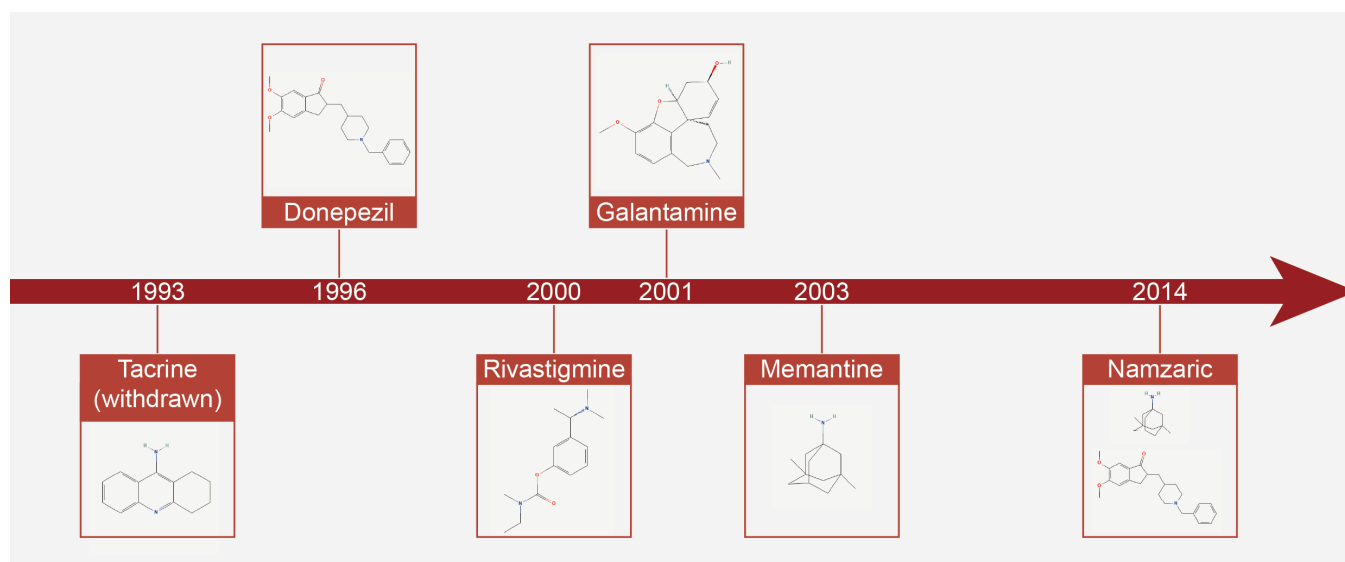


Figure 1. Development history of small molecules approved by FDA for AD and their structure.

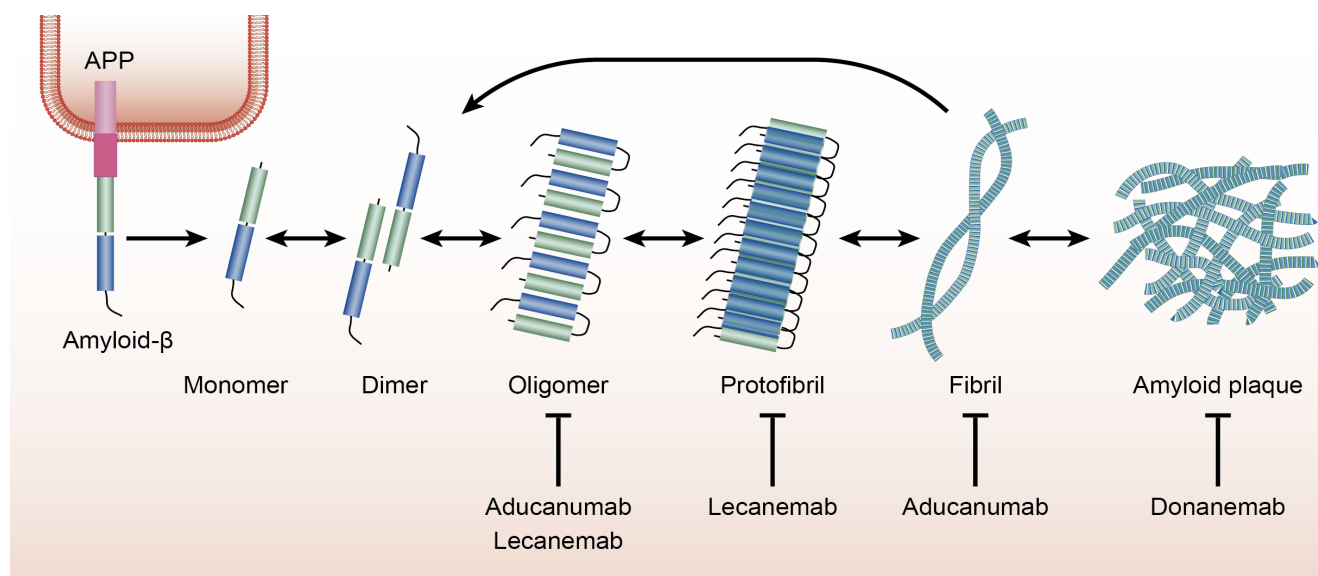


Figure 2. Aβ cycle and its aggregation species, and different targets of mAbs approved by the FDA.

Table 1. Details of the three mAbs targeting Aβ, once approved by the FDA

Drug	Target	Approval pathway	Approval status
Aducanumab	Aβ soluble oligomers and insoluble fibrils	AA pathway (2021)	Withdrawn (2024)
Lecanemab	Aβ soluble oligomers and protofibrils	AA pathway (2023)	Traditional approval (2023)
Donanemab	Pyroglutamate-modified Aβ and amyloid plaques	Traditional approval (2024)	Traditional approval (2024)

and then processed into a medicine. Consequently, due to the complex manufacturing process, there could be a longer manufacturing time and a wider variation between batches for biologics compared to small molecules.

3.2. Dosage forms

Small molecule drugs are readily formulated in various dosage forms due to their stable physical and chemical properties, such as tablets, capsules, granules and solutions for oral administration; liquid preparations and lyophilized powder for injection; semisolid dosage forms, transdermal preparations and inhaled powder for topical administration, and more. Different dosage forms demonstrate the capacity to satisfy various purposes, such as higher bioavailability and effectiveness, lower required dose or administration frequency, and fewer adverse events (AEs). Compared to small molecules, the dosage forms of biologics are more monotonous. Since biologics are mostly proteins that cannot preserve activity in the acidic environment of the stomach, biologics are generally formulated as liquid injections (**Table 2**).

Table 2. Information about FDA-approved dosage forms of AD medications

Type	Drug	Brand-name	Dosage form	Market Status
Small molecules	Donepezil	Aricept	Tablet	Prescription
			Solution	Discontinued
		Aricept ODT	Disintegrating tablet	Discontinued
		Adlarity	Transdermal preparation	Prescription
	Rivastigmine	Exelon	Capsule, solution	Discontinued
			Transdermal preparation	Prescription
	Galantamine	Razadyne	Tablet, solution	Discontinued
		Razadyne ER	Extended-release capsule	Discontinued
		Zunveyl	Delayed-release tablet	Prescription
	Memantine	Namenda	Tablet	Prescription
			Solution	Discontinued
		Namenda XR	Extended-release capsule	Discontinued
	Donepezil and memantine	Namzaric	Extended-release capsule	Prescription
Biologics	Lecanemab	Leqembi	Injection	Prescription
	Donanemab	Kisunla	Injection	Prescription

3.3. Quality control (QC)

It is indispensable to conduct quality tests for drug development, regulatory acceptance, and batch consistency, as well as to ensure safety and efficacy. Commonly utilized analytical technologies in QC for API of small molecules include high-performance liquid chromatography (HPLC), ultra-performance liquid chromatography (UPLC), liquid chromatography-mass spectrometry (LC-MS) and gas chromatography-mass spectrometry (GC-MS) for the purity examination; X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR), Raman spectroscopy for the structural characterization; dynamic light scattering (DLS), differential scanning calorimetry (DSC), potentiometric titration for the physical properties analysis^[24].

Distinct from small molecules, in the purity examination, technologies utilized mainly include sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), size exclusion chromatography (SEC) and DLS. Mass spectrometry (MS), liquid chromatography-tandem mass spectrometry (LC-MS/MS), time of flight mass spectrometer

(TOF-MS), and circular dichroism (CD) are applied for structural characterization. Capillary isoelectric focusing (CIEF), DSC and SDS-PAGE are used for physical properties analysis. Additionally, bioactivity assay for biologics includes enzyme-linked immunosorbent assay (ELISA), antibody-dependent cell-mediated cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC) assays (**Table 3**).

Table 3. Some analytical technologies applied in QC for API

Test items	Analytical technologies	
	Small molecules	Biologics
Purity	HPLC, UPLC, LC-MS, GC-MS	SDS-PAGE, SEC, DLS
Structure	XRD, FTIR, Raman spectroscopy	MS, LC-MS/MS, TOF-MS, CD
Physical property	DLS, DSC, potentiometric titration	CIEF, DSC, SDS-PAGE
Bioactivity	/	ELISA, ADCC, CDC

4. Regulatory issues

4.1. Brand-name small molecules and biologics

Newly discovered candidate drugs and synthesized biological products are applied via the new drug application (NDA)^[25] and biologics license application (BLA)^[26], respectively. It is necessary for novel drugs applied via NDA or BLA pathways to undergo clinical trials, which would cost a great amount of resources, capital and time, leading to the high price of the brand-name drugs and the high failure rate of the application^[27]. After approval, they are also called brand-name small molecules and biologics. In addition, the period of market monopoly for small molecules and biologics is determined by the patents and regulatory exclusivity, providing market protection for new drugs^[28].

4.2. Generic small molecules and biosimilars

Both generic small molecule drugs and biosimilars refer to the generic products of reference-listed drug (RLD) products, providing alternatives to brand-name drugs. Generic drugs are approved via the abbreviated NDA (ANDA) and are strictly required to be identical to the corresponding RLD products in the dosage form, safety, effectiveness, administration strategy, and more^[29]. No additional clinical studies and only the bioavailability and bioequivalence data are required for a generic drug application^[30], thus less resource is required. Differently, biosimilars only need to illustrate highly similar properties to RLD products in purity, safety and potency^[31] but need additional clinical trials to demonstrate the therapeutic equivalence to RLD products and get approval via the BLA pathway^[32], causing a higher price in comparison with generic small molecules.

5. Discussion

It is generally accepted that both small molecules and biologics play an inevitable role in disease treatment and public health. It could be argued that biologics could have a more promising prospect for AD treatment from an industrial perspective. Firstly, biologics are more selective with higher safety and efficacy than small molecules. As mentioned before, ChEIs and NMDAR antagonists could only delay the progression of symptoms rather than address the underlying causes, while biologics for DMTs provide the possibility of curing AD. Secondly, from the factual perspective, since the approval of memantine in 2003, no completely novel small molecules have been approved. With the advances in biotechnology and the pathology of AD, more potential targets and pathways leading to the disease have been identified and validated, facilitating the new generation of biologics development^[33].

In addition, in terms of commercial prospects, on one hand, the biologics price tends to be more expensive^[34], and

a report ^[5] indicated that in the USA, although only 2% of prescriptions are taken up by biologics, spending on biologics accounts for around half of the total drug spending, illustrating an increasing market value of biologics. On the other hand, according to the Biologics Price Competition and Innovation Act (BPCIA), brand-name biologics have regulatory exclusivity for 12 years, which is longer than 5 years for small molecules, thus ensuring a longer period of market monopoly protection from biosimilar competition. Furthermore, since the requirement of additional clinical trials for approval of biosimilars, the price of biosimilars could be relatively higher than that of generic small molecules, thus it may reasonably be concluded that the approval of biosimilars will have less impact on the price of brand-name biologics, compared with that of approved generic small molecules on the price of brand-name small molecules, guaranteeing adequate returns on investment.

Last but not least, patient compliance is also an essential component to consider. Due to the longer half-life of biologics compared to small molecules, the frequency of administration for biologics is lower. For example, twice a day. Admittedly, it takes longer, about half an hour, to receive each intravenous infusion, but the possibility of missing a dose or overdosing is reduced. Moreover, the metabolism of small molecules in the liver can readily be affected by food or other medications, increasing the risk of AEs. Collectively, biologics may be more worthy of investment, with higher safety and efficacy, fewer side effects, rapid advancements in biotechnology, better business prospects, and regulatory support, as well as higher patient compliance.

Disclosure statement

The author declares no conflict of interest.

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