

# Nanoparticles at the interface of blood-brain barrier

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# Nature's toolbox





# Targeted nanoplatform for medical diagnosis and therapeutics





# Anatomy of brain vasculature



The dense vascular network throughout the human brain includes large-diameter arterioles wrapped in vascular smooth muscle cells, which branch into the microvasculature (neurovascular unit) and then converge to venules.

# Unsuccessful investigational drugs for Alzheimer's disease











### Diverse pathogenesis vs Low clinical efficacy



Nat. Rev. Drug Discov. (2015)



### **NEEDS & CHALLENGES**



"A high dose is crucial. You must dose high enough for an amyloid β antibody that is 150,000 Da and crosses the blood-brain barrier very inefficietly, with levels 0.1 to 0.3% of blood levels reaching the nervous system." *Dennis J. Selkoe (Havard Medical School)* 

## **NEEDS & CHALLENGES**



Aducanumab reduces buildup of beta amyloid (shown in a positron emission tomography scan above) in the brains of people with Alzheimer's, but experts aren't convinced it slows cognitive decline. SEVIGNY ET AL., NATURE, 537, 50 (2016)

### Biogen's Alzheimer's drug candidate takes a beating from FDA advisers



If the U.S. Food and Drug Administration (FDA) wants to approve the first new drug for Alzheimer's disease in 17 years, it will have to do so against the overwhelming recommendation of the experts it turned to for advice on the matter. An independent advisory panel convened by the agency today to review data on the antibody drug candidate, called aducanumab, concluded that even the strongest available clinical trial data don't support its effectiveness.

FDA, which is expected to decide about aducanumab by March 2021, doesn't have to follow the advice of its advisory committees, but it typically does. If approved, aducanumab would be the first Alzheimer's drug prescribed to slow cognitive decline and would likely bring in tens of billions of dollars in sales for its developer, Biogen. It might also vindicate the battered theory that clearing the brain of the sticky protein called beta amyloid can effectively treat the disease.



The U.S. Food and Drug Administration approved aducanumab based on evidence that it reduced buildup of beta amyloid (shown in a positron emission tomography scan) in the brains of people with Alzheimer's disease. SEVIGNY ET AL., NATURE, 537, 50 (2016)

# Alzheimer's drug approved despite doubts about effectiveness

By Kelly Servick Jun. 7, 2021 , 3:00 PM

The antibody aducanumab today became the first new Alzheimer's disease drug approved in the United States since 2003. In a controversial decision that shocked some experts, the U.S. Food and Drug Administration (FDA) overruled a group of advisers to conclude that the drug, developed by Biogen, deserved market approval. The decision came despite thin and conflicting evidence from two large clinical trials about the drug's ability to slow patients' cognitive decline.

In **announcing the decision**, FDA acknowledged those studies of patients with early stage disease "left residual uncertainties regarding clinical benefit." But it opted to approve aducanumab, marketed as Aduhelm, based on strong evidence that it clears a toxic form of the protein beta amyloid, which accumulates in the brains of people with Alzheimer's and is thought to drive neuronal damage. Reduction of these plaques is "reasonably likely to predict important benefits to

# **Brain delivery strategies**



# **Crossing BBB for brain delivery: MPS-based peptide screening**

0.18

0.06

2 3



Choi et al., ACS Nano, online (2024).

UCIIS'C

In collaboration with Prof. T. E. Park (UNIST)

#### Rank Sequence Name YPAAYHTLTREP Tw1 1 ASLPKSDLGGNS Tw2 2 Chip Rank Sequence Name OMGFMTSPKHSV C1 1 2 DHAQRYGAGHSG C2

Transwell



# **Replacing in vivo screening?**



Choi et al., ACS Nano, online (2024).



Rank

1

# **Crossing BBB for brain delivery: MPS-based SELEX**

#### SELEX via BBB on a chip



Choi et al., ACS Nano, 17, 8153-8166 (2023).

#### In collaboration with Prof. T. E. Park (UNIST)

transport

influx

Ratio of i

\*\*\*\*

hBSOT





# **Cellular transcytosis penetrating BBB**

#### In collaboration with Prof. T. E. Park (UNIST)



Choi et al., ACS Nano, 17, 8153-8166 (2023).



# In vivo brain intake



Choi et al., ACS Nano, 17, 8153-8166 (2023).



10 µm 0.0

# Importance of curing AD is growing with aging of society



Created from data from the National Center for Health Statistics.<sup>330</sup>

In preparation



## Importance of curing AD is growing with aging of society



In preparation



# Nanoparticles for BBB penetration and brain delivery



One of the most compelling advantages of nanoparticle drug delivery systems is their ability to provide targeted and controlled release of therapeutic agents.

- Functionalizing nanoparticles with specific ligands enables them to bind selectively to receptors on the surface of BBB or neurons.
- The targeted approach ensures that drugs are delivered to the exact location of pathology, reducing the required dosage and potentially decreasing adverse effects.
- While challenges remain, the potential of nanoparticle-based drug delivery systems to transform brain therapeutics is immense and moves closer to fight against neurological diseases.

Nat. Rev. Drug Discov. (2021)

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