**Allosteric BACE Inhibitors For Treatment Of Alzheimer’s Disease**

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**SUMMARY**

UCLA researchers from the Department of Neurology have discovered a new class of drug candidates for Alzheimer’s disease. These small molecule compounds can specifically inhibit target enzymes to prevent target protein cleavage through an allosteric mechanism, preventing off-target side effect.

**BACKGROUND**

Alzheimer's disease (AD) is the most prevalent dementia that is currently affecting 5.7 million patients in the US. Amyloid plaque, resulting from accumulation of amyloid-β (Aβ) in brain tissue, is the key characteristic of AD. Many currently approved therapeutics only provide temporary symptom relief. Nevertheless, several specific targeted therapeutics, such as aspartyl protease β-site amyloid precursor protein cleaving enzyme 1 (BACE1, BACE) inhibitors, have shown promising results. However, these BACE inhibitors lead to undesirable side effects due to inhibition of cleavage of proteins that are not amyloid precursor protein (APP). Another challenge of treating AD is making the targeted therapeutics cross the blood-brain barriers. Many proteins, macromolecules, and charged molecules cannot efficiently diffuse through the blood brain barrier. This challenge drives the discoveries of small molecule therapeutics that can specifically inhibit APP cleavage or prevent Aβ production.

**INNOVATION**

Allosteric BACE inhibitors were screened and tested for specific inhibition of APP cleavage. These inhibitors do not directly interact with the active/catalytic site of BACE, but rather a remote exosite far away from the catalytic site. This interaction changes the general shape of BACE, blocking it from binding to APP like substrates, but doesn’t prevent it from binding to other smaller substrates. A molecular model was generated to showcase that previously discovered small molecule peptides can effective interact with Loop F of BACE, changing its shape. A high-throughput screening assay was performed to identify small molecule BACE inhibitors that specifically inhibit APP like protein cleavage and sparing others through an allosteric binding mechanism. Several small molecule candidates were discovered that can bind to the previously defined exosites and change the shape of BACE that prevents specific cleavage of only APP like proteins. They are likely to be neutral in charge and can easily cross the blood-brain barrier. These promising drug candidates can prevent Aβ build-up while avoiding undesirable off-target side effects.

**APPLICATIONS**

- Alzheimer’s disease
- Mild cognitive impairment
- Cerebral amyloid angiopathy
- Ischemic stroke
- Amyotrophic lateral sclerosis
- Other diseases wherein BACE activity is pathologically upregulated

**ADVANTAGES**

- Specificity
- Minimal off-target effect
- Easy to cross blood-brain barrier

**PATENT STATUS**

Patent Pending

**ADDITIONAL TECHNOLOGIES BY THESE INVENTORS**

- New 3D-Exoquant Method For The Analysis Of Surface Molecules And Quantification Of Tissue-Specific Exosomes In Biological Fluids
- Pathway-Dependent Inhibition Of Proteopathic Seed Transmission
- Identification And Development Of Dual nSMase2-AChE Inhibitors For Neurodegenerative Disorders
- Exercise In A Pill: Compounds That Reproduce The Effects Of Exercise On Muscle Metabolism And Growth