gamma-secretase activating protein is a therapeutic target for alzheimer's disease: a path-breaking discovery finally paving way towards therapeutic intervention

Alzheimer's disease (AD) is the most common form of dementia. It is a terminal, progressive brain disorder which has no known cure. It leads to memory loss, confusion, impaired judgment, personality changes, disorientation and the inability to communicate. According to World Health Organization it is estimated that currently about 18 million individuals have Alzheimer's disease and by 2025, as the world population ages, this number could increase to 34 million leading to emotional and financial costs of which are enormous.

Two main pathological changes occur in the brain in Alzheimer's disease: one is the development of senile plaques between neurons, and the other one is development of neurofibrillary tangles within neurons.¹ These changes are thought to be intricately related to the cause, development, and severity of the disease. Researchers have demonstrated that inflammation around plaques destroys neighboring neurons. Plaques, which are composed of Amyloid- β Peptide (A β P), form as a result of its overproduction from its precursor protein (APP). A combination of genetic predisposition and environmental influence is believed to be responsible for the onset of the disease.

Many potential treatments for Alzheimer's disease are being investigated including the administration of drugs that could remove plaques, immunotherapy with A β amyloid antibodies, non-steroidal anti-inflammatory drugs (NSAIDs) and statins. The protective effects of estrogen, antioxidants (Vitamins A, C and E), *ginkgo biloba* and omega-3 fatty acids (found mainly in fish such as tuna and salmon) are also being tested in trials. However, none of them appear to have proved optimal for treating AD.

The central problem in AD is the accumulation of A β P which weakens and kills the nerve cells. Hence, inhibition of A β P production, by blocking gamma-secretase activity, is at present one of the most promising therapeutic strategies anticipated to slow the progression of Alzheimer's disease pathology. Thus, majority of the new drugs focus on gamma secretase

that snips a major protein, Amyloid Precursor Protein (APP), in order to produce A β P. The gamma secretase has crucial roles in the body in addition to making A β P. It removes stubs of proteins left behind on the surface of nerve cells and is needed to make other proteins, like *Notch*, an essential protein for body's function, therefore complete blocking may be problematic. Ablation of the PS1 and PS2 genes, therefore, results in a phenotype indistinguishable from that caused by a *Notch* knockout and completely blocks production of A β P and NICD (*Notch* IntraCellular Domain) production.² Moreover, mutagenesis of the critical aspartates also blocks the function of human PS in *Notch* signalling. Therefore, inhibition of PS activity not only blocks A β production, but also interferes with NICD generation and the *Notch* pathway. *Notch* plays a pivotal role in the development of blood-forming organs and the immune system.

Semagacestat, a γ -secretase inhibitor introduced by Eli Lilly, for example, worked like a sledgehammer to stop gamma secretase on its tracks and halt all of its functions impairing patient's ability to perform daily activities. Other experimental drugs may also affect the enzyme's other targets. Moreover, a dozen potential products designed to slow clumps of protein from forming in the brain, a condition linked to the disease since 1906, have failed in mid- to late-stage testing since 2003. New research from the laboratory of Nobel Laureate Dr. Paul Greengard from Rockefeller University, New York, however, suggests that treatments with the anticancer drug Gleevec or its analogue could be the solution.³

Earlier research by Greengard's lab showed that Gleevec successfully inhibited the ability of gamma secretase to form A β P without affecting the *Notch* pathway.⁴ A recent study led by him has added a new twist to the mode of action of Gleevec for treating AD. They have shown that Gamma Secretase Activating Protein (GSAP) modulates γ -secretase specifically to stimulate production of A β P in cell lines therefore its inhibition by

Gleevec inhibited A β P generation (Fig. 1). The researchers also looked at GSAP's action in a mouse model of Alzheimer's disease. They knocked down the gene that codes for GSAP using RNA interference, and found that levels of beta-amyloid as well as plaque development decreased. Biochemical studies showed that Gleevec reduces beta-amyloid production by binding to GSAP and preventing its activation of gamma-secretase activity.

Hence, the approach taken by Greengard and his team is revolutionary. Their aim is not to deactivate the enzyme itself, but targeting the protein that guides the enzyme to snip APP and to produce A β P. Deactivating the newly discovered gamma secretase activating protein will not affect the other functions of gamma secretase and only inhibit the production of A β P in the brain. Unfortunately, the Gleevec molecule does not cross the blood-brain barrier, that prevents some substances in the blood from entering the brain. Greengard, however, believes that it will be possible to design drugs that target GSAP but do not have this limitation.

"Anti-amyloid therapeutic drugs represent a valid approach to treating Alzheimer's disease, but their inability to accumulate in the brain has limited their usefulness," says Greengard. Another problem with Gleevec is that it does not stay in the brain long enough and is pumped out before it can act upon the required proteins. However, according to several medical experts, these are highly promising discoveries in the field of Alzheimer's treatment and very soon, using Gleevec as the 'lead molecule', a chemical can be synthesized that reaches and stays in the brain and blocks the appearance of the A β P.

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Gleevec

Fig. 1: γ -secretase inhibitor, Gleevec, inhibits Amyloid β -formation without affecting Notch cleavage. **(A)** Ternary complex of GSAP, APP and γ -secretase is associated with elevated γ -cleavage leading to increased A β production. **(B)** Gamma secretase inhibitor (GSI) leads to inhibition of γ -cleavage as well as that of NICD leading to decreased biological functions. **(C)** In the presence of Gleevec, GSAP interaction with the complex of APP and γ -secretase is inhibited leading to no γ -cleavage as well as decreased A β production without affecting Notch cleavage (NECD: Notch ExtraCellular Domain, NICD: Notch IntraCellular Domain).

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