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Editorial
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Translational Control of APP Expression for Alzheimer Disease Therapy

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Editorial

Alzheimer's disease (AD) is a chronic neurodegenerative disease, responsible for dementia in 5.5 million Americans [1]. Accumulation of β-amyloid (Aβ) in the brain is a driving force behind AD neurodegenerative cascade and it is considered a prime target for disease modulatory therapy. Given that Aβ accumulation precedes the onset of AD clinical symptoms by nearly two decades, therapeutics targeting Aβ buildup likely will need to be applied over an extended period of time what requires from them a reasonable safety profile. A-directed immunotherapy and inhibitors of amyloid precursor protein (APP) proteases: β-site cleaving enzyme 1 (BACE1) and γ-secretase complex (γ-SC), which sequential action yields Aβ, have been proposed as therapeutic approaches for AD. Unfortunately, thus far clinical trials of active Aβ immunotherapy, anti-Aβ monoclonal antibodies, and oral inhibitors of APP proteases conducted in AD subjects with mild and moderate dementia have encountered very limited success in improving cognitive metrics, while at the same time showed adverse effects specifically associated with each of these approaches [2-4]. Failure of these clinical trials has affected an attention shift toward exploring application of Aβcentered approaches in presymptomatic or prodromal AD subjects as well as fueled a search for better tolerated therapeutics. As Aβ production can be effectively suppressed by lowering the steady state level of its precursor protein, there has been growing evidence that targeting APP mRNA with an esoteric, small molecule compound can constitute a viable, alternative approach for AD disease modifying therapy.

APP is a transmembrane protein involved in brain development, synaptic plasticity and repair, and the rate of its proteolytic processing remains proportional to the degree of synaptic activity [5]. APP is at first processed on the cell membrane by enzymes with α-secretase activity or in the endosomal compartment by BACE1. This initial cleavage yields APP N-terminal fragments also known as soluble APP, which are released into the extracellular space and APPC-terminal fragments (CTFs), which are retained intracellularly. Soluble APP has synaptotrophic properties, while CTFs can be neurotoxic if allowed to accumulate [6]. Subsequent intracellular processing of CTFs by γ-SC generates APP intracellular domain and non-amyloidogenic P3 peptide from the α-CTF or Aβ from the β-CTF. Thus, targeting translation efficiency of APP mRNA into protein reduces levels of both toxic APP metabolites like CTFs and Aβ, but also is inherently associated with reduction in synaptotrophic soluble APP. The later concern is attenuated by the fact that the APP protein family also includes amyloid precursor like protein (APLP) 1 and 2, which serve as functional APP homologs [7,8]. Furthermore, the role of APP in modulating synaptic plasticity in the mature brain appears to be less essential than it is during brain development [9]. Thus, partial reduction in APP steady-state expression level in mature brain can be tolerated and offset by benefits of reduction in toxic APP metabolites.

Several known pharmaceuticals have been found to have off target effect on APP mRNA affecting its translational efficacy and in effect limiting Aβ secretion [10-12]. Specific examples include acetylcholinesterase inhibitor phenserine, a serotonin reuptake inhibitor paroxetine, macrolide antibiotics erythromycin and azithromycin, and iron chelator desferrioxamine. These findings have justified a search for compounds targeting APP mRNA in more potent and

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esoteric fashion. Identification of such compounds has occurred either through a small molecule screen or modification of already existing pharmaceuticals by eliminating their off target properties. Examples of esoteric translational APP translational modulators identified by small molecule compound screen include 4-(5-methyl-1Hbenzimidazol-2yl) aniline (JTR-009), which irreversibly binds to the iron response element of the APP mRNA 5' un translated region and constitutively represses APP translation[13]. Another example of a small molecule APP translational modulatoris 2-[(pyridin-2-ylmethyl)-amino]-phenol (2-PMAP; MW=200.2 Da), which selectively targets APP mRNA effectively reducing Aβ production already at the concentration of 0.1 μm, while imposes no significant changes on APLP-2 level upto the concentration of 25 μm. 2-PMAP is biostable and penetrates the blood-brain barrier well what allows for its testing in AD transgenic (Tg) mouse models. In $APP_{SW}/PS1_{dE9}$Tg mice 2-PMAP reduced brain levels of full length APP and its CTFs and chronic administration of 2-PMAP in the same Tg mouse model significantly reduced brain Aβ accumulation and protected the mice from developing memory deficit without evoking CNS and systemic toxicities[14]. Development of an APP translational modulator on the basis of already existing pharmaceuticals can be exemplified by posiphen, which is a chiral isomer of acetylcholinesterase inhibitor phenserine, with greatly reduced activity toward the acetylcholinesterase enzyme. Oral form of posiphen was tested in phase I clinical trial where it showed evidence for lowering the level of APP metabolites in the CSF, without noticeable toxicity, validating that an APP translational modulator can be safely used in humans [15]. These examples demonstrate that orally bioavailable APP translational modulators can serve as an alternative to BACE-1 inhibitors and γ-SC modulators whose development has been pursued. As both secretes have multiple client proteins, undesired off-target effects are a main drawback to implement their inhibitors in clinical practice [3,4] but such should not be a concern for APP translational modulators, which lower Aβ production through an utterly different mechanism of action.

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