Small molecule therapeutics for Alzheimers Disease

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Title of project or programme

Small molecule therapeutics for Alzheimers Disease

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1

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Research Abstract

SMALL MOLECULE THERAPEUTICS FOR ALZHEIMER’S DISEASE SUMMARY: Alzheimer’s disease (AD) is a progressive and fatal neurological disorder that affects approximately one-tenth of the population over the age of 65. There is currently no cure for the disease. The pathological hallmarks of the disease include the formation and accumulation in the brain of ß-

amyloid (Aß). Earlier therapeutic attempts at lowering total Aß by directly targeting the catalytic activities of ß- or ?-secretase were unsuccessful as the enzymes hydrolyze other substrates besides APP, many with critical cellular functions. Cenna has a novel technology that does not target the secretases, which has yielded two potential peptide drug candidates P8 and P4 from the amino terminal domain of Presenilin (PS-1), with the ability to inhibit the production of Aß in vitro and in a transgenic (Tg) mouse model of AD. We recently provided evidence (1) that peptides P4 and P8 give a strong, specific and biologically relevant binding with the purified ectodomain of APP 695. We further demonstrated that the reduction of Aß by the peptides does not affect the catalytic activities of ß- or ?-secretase, or the level of APP. These peptides and their derivatives offer new potential drug candidates for the treatment of AD. While P8 is being further developed as a peptide drug, P4 is too unstable. It is important to develop alternate back-up candidates besides P8. It would be advantageous to identify small molecule compounds that bind APP at the same sites as P4 and P8 and by so doing also reduce Aß. We have carried out molecular modeling studies to determine binding sites on the APP ectodomain for both P4 and P8. Having accomplished that, we virtually screened a library of e-compounds to identify those molecules that would be predicted to bind the same sites on APP as P4 and P8. Of the ~160,000 structures screened, a total of 249 suggested binding to APP at either the P4 or P8 binding site. These compound have been scored and grouped. In the current grant application our specific aims are: 1) To experimentally confirm by microarray analysis the binding to the APP ectodomain of the small molecule compounds identified by virtual screening. 2) To test the small molecule compounds that give positive hits for their ability to reduce A? production in vitro and 3) To test in vivo in APP Tg mice, selected compounds identified in vitro to reduce A? by similar amounts as P4 and P8. A successful completion of the project will provide us with small molecule candidates with the ability to reduce Aß in vitro and in vivo by the same mechanism as our peptide candidates. As with the peptides, the small molecule compounds would not be expected to affect the catalytic activities of the secretases. Furthermore, these compounds may be developed as oral drugs that can cross the blood brain barrier.

Further information available at:

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Investments < €500k

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United States of America

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N/A

Years:
2016

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N/A

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