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PROMISING NEW TREATMENTS FOR ALZHEIMER'S TARGET MULTIPLE DISEASE-RELATED PROTEINS, MAY HAVE BENEFITS FOR SEVERAL BRAIN DISEASES

Drugs Targeting Protein Misfolding May Be Useful Across Neurodegenerative Diseases According to New Results Reported at Alzheimer's Association International Conference 2015

WASHINGTON, DC, July 19, 2015 – Promising early results of new drugs that target common components of several brain diseases that cause dementia – including Alzheimer's disease, Parkinson's disease, and Lewy Body dementia – were reported today at the Alzheimer's Association International Conference® 2015 (AAIC® 2015) in Washington, D.C.

These diseases cause a range of debilitating symptoms, including memory loss, difficulty with language, visual hallucinations or problems with movement, but they all share the same hallmark – the death of brain cells. Many diseases that cause brain cell death and dementia share common characteristics. One is that a particular protein goes through a dramatic change in its shape; often it becomes toxic for nerve cells or the brain connections known as synapses.

Alzheimer's disease is a triple threat – with soaring prevalence, enormous costs and lack of effective treatment. Today, 47 million people are living with dementia worldwide, and that number is set to almost double by 2030 and more than triple by 2050, according to Alzheimer's Disease International.

When proteins misfold, they can start off a chain reaction of binding to other proteins. This process continues until large aggregates are formed. Two different misfolded proteins – amyloid beta and tau – have been shown to be toxic to brain cells. Their large aggregates – amyloid plaques and tau tangles – are the hallmark brain lesions of Alzheimer's disease. Treatments that target more than one Alzheimer's-related protein may be especially useful in managing the disease.

"Alzheimer's is very complex condition that has been extremely hard to address with the 'one target, one treatment' approach that's been successful in other diseases," said Maria Carrillo, PhD, Alzheimer's association Chief Science Officer. "Fortunately, we're beginning to see some very exciting early results at AAIC 2015 of a new treatment approach that targets common components of all the Alzheimer's proteins, which also are common to other diseases that cause dementia. If these results can be shown in people, this strategy could eventually have benefit not just in Alzheimer's but for other neurodegenerative diseases."

In February 2015, the Alzheimer's Association, Alzheimer's Research UK, and the Weston Brain Institute (Canada), launched a new global initiative called Mechanisms of Cellular Death in NeuroDegeneration, with a fund of $1.25 million for targeted research into brain diseases that cause dementia, such as Alzheimer's. The funding will support pioneering new projects to understand the causes of brain cell death across neurodegenerative diseases.

Effective treatments for Alzheimer's are desperately needed as it is a triple threat, with soaring prevalence, lack of treatment and enormous costs no one can afford. Alzheimer's disease is the sixth-leading cause of death in the United States, and the only top 10 cause of death without a way to prevent, cure, or slow its progression. It is the costliest disease to U.S. society.

New Drugs That Target Tau and Amyloid in Alzheimer's Also Recognize Proteins in Parkinson's and Lewy Body Dementia

It is generally agreed that the cause of several neurodegenerative diseases is related to the accumulation of proteins in aggregated (or oligomeric, where several proteins are bound together) forms. Disease-causing forms of these proteins can also change normal proteins into destructive forms, allowing toxic malformations to spread to different areas of the brain.

Fernando Goni, PhD, Adjunct Associate Professor, Department of Neurology, New York University School of Medicine, New York NY and colleagues announced new data at AAIC 2015 about a class of monoclonal antibodies that were shown to react to both amyloid and tau in Alzheimer's disease, and also to prion disease proteins. They report that the antibodies may also react to aggregated alpha-synuclein and other structures (known as Lewy Bodies) in the brain cells of people with Parkinson's disease, suggesting a potentially broad range of beneficial effects in neurological diseases.

To establish the effect of their antibodies on various forms of alpha-synuclein, the researchers created single alpha-synuclein proteins, oligomeric alpha-synuclein proteins, and dense fibrillar forms known to accumulate in brain tissue. The researchers then tested their antibodies to see how they interacted with each form of alpha-synuclein. Three types of monoclonal antibodies from their laboratory were used, each of which binds to amyloid and tau and also reverses Alzheimer's-like damage to brain tissue in animals. They found that all three monoclonal antibodies bind to the oligomeric forms of alpha-synuclein but not to the monomeric forms. They subsequently confirmed the antibodies' affinity for alpha-synuclein related structures within neurons using samples of human brain tissue from individuals with Parkinson's disease.

"We have developed monoclonal antibodies that recognize the toxic oligomeric proteins from multiple diseases that cause brain cell death and dementia," said Goni. "This is very promising. We are now at a point where we can test them in other animal models as a precursor to clinical trials for human neurodegenerative diseases."

Discovery, Preclinical Development, and Clinical Trial Approach for NPT088

At AAIC 2015, Richard Fisher, PhD, of NeuroPhage Pharmaceuticals, Cambridge, MA and colleagues shared the results of tests with NPT088, a new type of therapeutic that includes the General Amyloid Interaction Motif (GAIM), a molecule that the company claims "blocks misfolded proteins from aggregating, protects cells from protein aggregate toxicity, and targets multiple types of aggregated proteins, including amyloid beta, tau and alpha-synuclein."

The researchers found that NPT088 was effective at preventing protein aggregation in laboratory-cultivated brain cells and helped brain cells survive after exposure to toxic aggregated proteins. NPT088 also had broad beneficial effects in transgenic mice with brain damage similar to that seen in Alzheimer's and Parkinson's disease, in most cases improving memory and cognition, and reducing the brain levels of amyloid beta, aggregated tau and alpha-synuclein. According to the researchers, NPT088 has successfully completed one-month exploratory monkey and rat safety studies, and is currently in the final stages of safety testing prior to the initiation of clinical trials.

"NPT088 effectively treats brain pathologies in mouse models of both Alzheimer's and Parkinson's disease, which we believe is unique for a drug candidate," Fisher said. "Pending regulatory approval, we plan to begin clinical testing in people with Alzheimer's in early 2016."

Stopping Protein Misfolding with Small Molecules Targeted to Amyloid and Tau

At AAIC 2015, Marcia Taylor, PhD, of Treventis Corporation, Toronto, ON, Canada presented data on TRV 101, a new drug designed to enter the brain and inhibit protein misfolding of beta-amyloid and tau.

Using computer modeling techniques, Taylor and colleagues identified an abnormal shape that enables a protein to misfold and become toxic. The researchers say the shape is "common to several proteins known to misfold and is implicated in many diseases." They screened more than 11 million compounds through the computer model and, based on the results, synthesized a library of compounds that may prevent toxic protein-protein interactions. A representative compound is TRV 101. In test tube models, TRV 101 demonstrated prevention of toxic oligomerization of both beta-amyloid and tau.

"Because both beta-amyloid and tau contribute to the pathology of Alzheimer's disease, having compounds which can inhibit the formation of oligomers of both proteins would be transformative for treatment," Taylor said. "We have created compounds, such as TRV 101, that are capable of preventing beta-amyloid, tau, or both from forming oligomers in a test tube. This could allow natural clearing mechanisms to remove existing protein aggregates and improve cognitive function. We are currently testing our compounds in animal models to verify if we can reduce the levels of oligomers in the brain."

About AAIC

The Alzheimer's Association International Conference (AAIC) is the world's largest gathering of leading researchers from around the world focused on Alzheimer's and other dementias. As a part of the Alzheimer's Association's research program, AAIC serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community.
AAIC 2015 home page: www.alz.org/aaic/
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About the Alzheimer's Association®

The Alzheimer's Association is the leading voluntary health organization in Alzheimer's care, support and research. Our mission is to eliminate Alzheimer's disease through the advancement of research, to provide and enhance care and support for all affected, and to reduce the risk of dementia through the promotion of brain health. Our vision is a world without Alzheimer's. Visit alz.org or call 800.272.3900.

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- Fernando Goni, PhD, et al. Monoclonal Antibodies That Recognize Oligomeric Tau and Aβ, Also Recognize Pathological Structures in Parkinson's Disease Human Brains. (Funders: U.S. National Institutes of Health, Alzheimer's Association, and Seix Dow Foundation)
- Richard Fisher, PhD, et al. Discovery, Preclinical Development, and Clinical Trial Approach for NPT088, a General Amyloid Interaction Motif (GAIM)-Immunoglobulin Fusion. (Funders: NeuroPhage Pharmaceuticals, The Michael J. Fox Foundation)
- Marcia Taylor, PhD, et al. Inhibition of Protein Misfolding By Optimization of Small Molecules Targeted to Both Beta-Amyloid and Tau Peptides. (Funders: Treventis Corporation, the Wellcome Trust)

Proposal ID: P4-174
Poster, Wednesday, July 22
Theme Selection: Therapeutics; Therapeutics: Preclinical

Monoclonal Antibodies That Recognize Oligomeric Tau and Aβ, Also Recognize Pathological Structures in Parkinson's Disease Human Brains

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Background: It has been increasingly recognized that the pathogenesis of many neurodegenerative diseases is related to the accumulation of diverse proteins in aggregated/oligomeric forms. The pathological conformers can spread to different areas of the brain via a "prion-like" conversion mechanism mediated by the mobile β-sheet oligomeric structure of each particular peptide or protein. Previously we have characterized conformational monoclonal antibodies that react to both oligomers of Aβ and tau in AD, as well as to prion disease proteins. We have now determined their binding specificity and capacity to be extended to synthetic oligomers of α-synuclein and to pathological intracellular structures present in Lewy body containing neurons of Parkinson's disease (PD) subjects.

Methods: Recombinant α-synuclein was produced and characterized in monomeric, oligomeric and fibrillar forms by electron microscopy and circular dichroism. Histological specimens of formalin fixed brains from human AD and PD confirmed cases were used for reaction with three anti-conformational mAbs IgM previously described. The mAbs that reacted to oligomeric Aβ and tau and showed high affinity, specific binding by surface plasmon resonance, and/or were shown to reverse AD pathology after infusion in old 3xTg AD animal models were used for immunohistochemical detection on human PD brain specimens and detection of different α-synuclein conformers.

Results: By SDS-PAGE the mAbs IgM showed specificity for oligomeric forms of polymerized α-synuclein but not to the monomeric forms. The mAbs showed specific intraneuronal reactivity around the Lewy bodies in human brains from confirmed cases of PD.

Conclusions: Conformational monoclonal antibodies that are well characterized to react against pathological conformers in AD human brains and that can produce amelioration of existing AD pathology in AD animal models can also recognize oligomeric forms of α-synuclein and intraneuronal structures associated with Lewy bodies. Monoclonal antibodies that are specific for pathology associated conformations are good candidates to be used as immunotherapeutical agents alone or in combination with other approaches in many neurodegenerative diseases including Parkinson's disease.

Proposal ID: O1-05-01
Oral session, Sunday, July 19, 2-3:30 pm, #146
Theme Selection: Therapeutics; Preclinical: Preclinical Abeta/Amyloid Therapeutics

Discovery, Preclinical Development, and Clinical Trial Approach for NPT088, a General Amyloid Interaction Motif (GAIM)-Immunoglobulin Fusion

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Background: The accumulation of combinations of aggregated amyloid-β, tau, and α-synuclein within a single disease, such as found in Alzheimer's disease (AD), evokes therapeutic strategies that generically target aggregates, independent of primary protein sequence. NPT088 is a human immunoglobulin (huIgG1Fc) fusion that displays two copies of the General Amyloid Interaction Motif (GAIM). We have shown that NPT088 has uniquely broad activities, both in vitro and in vivo, against multiple neuropathological aggregates, making it a novel candidate for treating AD.

Methods: NPT088 measured for amyloid (Aβ, tau, alpha-synuclein) binding and binding specificity using ELISA and SPR formats. Aggregation inhibition monitored by ThT. Oligomer-induced cytotoxicity, measured on N2a cells using adenylate kinase release assay. Aβ aggregate-NPT088 co-precipitation assays used aged Tg2576 brain homogenates. NPT088 administered to Tg AD and PD model mice weekly i.p., 14 weeks: Tg2576, 18 m.o.; rTg4510, 3.6 m.o.; mThy1-Hα-synuclein,3.2 m.o. Cognition assessed by spontaneous alternation (Y-maze) and novel object recognition. Brain biochemistry performed using Western or ELISA on soluble and insoluble fractions from homogenates or CSF. Neuropathology utilized 40μm fixed sections.

Results: NPT088 specifically and potently binds amyloid fibers of Abeta, tau and alpha-synuclein (Kds =5-46 nM), but does not bind monomers or natively aggregated proteins. NPT088 binds Abeta oligomers, blocks oligomer-induced cytotoxicity (IC50<5nM), and prevents Abeta and tau aggregation. NPT088 recognizes brain homogenate Abeta aggregates from aged Tg2576 mice. NPT088 effectively treats Tg AD and PD mouse models. In the Tg2576 hAPP model, NPT088 significantly: improves cognition; reduces brain Abeta(1-42) and Abeta plaque; and reduces Abeta in CSF. In rTg4510 tau mice, NPT088 significantly improves cognition, reduces levels of phospho-tau associated with neuropathology and lowers CSF tau. In mThy1-H alpha-synuclein mice, NPT088 significantly reduces proteinase-KRα-synuclein and increases tyrosine hydroxylase levels. NPT088 has successfully completed a 1-month exploratory monkey safety study.

Conclusions: These results demonstrate that NPT088 is a first-in-class therapeutic candidate for AD, which targets misfolded proteins generically, including aggregates of both Abeta and tau. Following IND filing in 4Q2015, NPT088 will be tested for proof of activity in AD by measuring reduction of PET amyloid markers.

Proposal ID: P1-307
Poster, Sunday, July 19
Theme Selection: Therapeutics; Therapeutics: Preclinical

Inhibition of Protein Misfolding By Optimization of Small Molecules Targeted to Both Beta-Amyloid and Tau Peptides

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Background: Protein misfolding followed by aberrant protein oligomerization and subsequent aggregation of both beta-amyloid and tau is often implicated in the development of AD. The clinical presentation of AD is heterogeneous (e.g. extrapyramidal symptoms in some people with AD and dementia symptoms in some people with PD). The clinical overlap amongst neurodegenerative disorders implies that AD is more of a syndrome than a disease and that the suppression of other aberrantly misfolded protein may afford additional therapeutic benefits. Accordingly, we are seeking to design and develop brain-penetrable small molecule new chemical entities targeting protein misfolding in general and both beta-amyloid and tau specifically. Based upon extensive in silico modelling a family of novel compounds has been identified. A representative compound is TRV 101.

Methods: Efficacy of TRV 101 in prevention of oligomerization was measured in vitro using biotin- beta-amyloid and biotin- tau assays. TRV 101 binding to beta-amyloid and tau 4NR2 was measured by Surface Plasmon Resonance (SPR). In vitro ADMET data along with mouse pharmacokinetics/ bioavailability (plasma and brain) was collected.

Results: TRV 101 demonstrated prevention of oligomerization activity against both beta-amyloid and tau. TRV 101 showed selective binding of the target protein by surface plasmon resonance (SPR). TRV 101 has optimum drug like properties, demonstrating favourable in vitro ADMET, high brain penetrance and oral bioavailability, and is benign in a 44-receptor panel test.

Conclusions: We have designed and developed a new class of compounds capable of inhibiting oligomerization of both beta-amyloid and tau proteins. Our small molecules have appropriate pharmacokinetic profiles and are able to reach the target tissue. Our compounds are currently being tested in several animal models of both beta-amyloid and tau pathologies.

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