Towards Phase 2 of AXON's disease modifying tau immunotherapy: first-in-man, first-in-class

This symposium will provide a view on the results of the Phase 1 study and design of the Phase 2 trial of the first-in-man tau active vaccine AADvac1 in Alzheimer’s disease patients.
Program

- **Prof. Bengt Winblad, MD**
  Clinical Development and Current Status of Clinical Trials in AD

- **Prof. Khalid Iqbal, PhD**
  Tau As a Target For Disease Modifying Treatment of AD

- **Prof. Michal Novak, PhD**
  Preclinical Efficacy of Axon’s Active and Passive Vaccine

- **Prof. Reinhold Schmidt, MD**
  Safety and Tolerability of AADVac1 / Results from Phase1 of First in Man, First in Kind of Active Immunotherapy Against Diseased Tau Protein in AD

- **Matej Ondrus, MD**
  Design of Phase2 Clinical Studies of AADvac1 in AD

- **Prof. Markus Otto, MD**
  Possibilities in Treatment of Orphan Tauopathies
In 2010, the number of people affected by dementia worldwide was estimated to 36 million, with an estimated cost of approx. 600 billion USD. The prevalence of dementia is expected to reach 115 million in 2050, with an equivalent cost increase. The progressive nature of dementia influences the whole life situation for families during several years-decades and so far, no cure or highly significant symptom relieving treatment is available. Increased understanding of the pathophysiology of Alzheimer disease (AD) has given us new therapeutic targets, and by using new biomarkers possibilities to diagnose patients earlier.

Many clinical and experimental studies are ongoing, mainly based on anti-amyloid-β (Aβ) strategies, but the exact role played by Aβ in AD pathogenesis is not yet clear. During the last years we see an increased number of studies in AD targeting the tau-protein. Preclinical research is constantly providing us with new information of the complex AD puzzle, and an analysis of this information might reveal patterns of pharmacological interactions instead of single potential drug targets.

The last drug for AD entered the market place in 2002. Since then, many products in different development phases have failed. Why? Wrong molecules, inappropriate animal models, insufficient proof-of-concept studies, heterogeneous patient groups, too advanced disease, non-relevant outcome measures, inter-center variability in increasingly globalised multi-centre trials?

Our hope for the future is not only to give the patient an early symptomatic relief but that new therapies could potentially slow or even halt the progression of the disease. Increased global collaboration between academia, industry and regulatory authorities is a vital step for a successful drug development.

We have good hope that until 2025, ongoing studies directed towards beta-amyloid and/or tau metabolism have proven effective and are on the market.
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**Tau as a Target for Disease Modifying Treatment of AD**

Tau pathology, seen as intraneuronal neurofibrillary tangles, neuropil threads and as dystrophic neurites surrounding the amyloid beta cores of neuritic (senile) plaques in the brain, is a histopathological hallmark and the density of these lesions directly correlates with the severity of dementia in Alzheimer’s disease (AD). The presence of disease-causing mutations in tau in frontolobar tauopathies has unambiguously shown that dysfunctional tau can be a primary cause of neurodegeneration. Independent of the etiopathogenic mechanisms involved in AD and different tauopathies, tau pathology is made up of abnormally hyperphosphorylated protein. The hyperphosphorylated tau appears to cause the spread of pathology and neurodegeneration by sequestering functional tau and disrupting microtubules. A cause of neurofibrillary pathology is a decrease in the activity of protein phosphatase-2A (PP2A) which is the major regulator of phosphorylation of tau. Both dephosphorylation and clearance by passive immunization can ameliorate tau pathology. Reduction of tau pathology by treatment with monoclonal antibody 43D to the amino terminal region (amino acid 6-18) of tau both reduces tau pathology and rescues cognitive impairment in a 3xTg-AD transgenic mouse model of AD. In conclusion, tau is one of the most rational and promising therapeutic targets for the treatment of AD and related tauopathies.

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Preclinical Efficacy of Axon’s Active and Passive Vaccine

This year marks 100 years since the death of Alois Alzheimer, the man who first described “a peculiar disease” of the brain characterized by the presence of neurofibrillary tangles. It had taken almost a century to identify the nature of this pathological entity of Alzheimer’s disease. Today, tau protein – the main constituent of the neurofibrillary tangles, represents a targetable substrate for disease modifying treatment of AD.

Nowadays, tau immunotherapy is attracting increasing attention as a viable therapeutic option for AD. Growing body of evidence suggests that active and passive tau vaccines eliminate pathological tau from the brain and thus improve the behavioural phenotypes of animal models for human tauopathies.

Using antibody imprinting technology, AXON Neuroscience identified the most vulnerable areas on tau protein that play a key role in pathological tau-tau interaction. Structural mapping of these domains allowed us to create the 3D structure of the target and design active and passive vaccines. This approach represents the first structure-based drug design for tau immunotherapy in Alzheimer’s disease drug research.

The lecture will provide a detailed look at the 10-year preclinical development of the first-in-man tau vaccine AADvac1 and look deeper into the process of current AD drug development.
Safety and Tolerability of AADVac1

Results from Phase 1 of First in Man, First in Kind of Active Immunotherapy Against Diseased Tau Protein in AD

The active vaccine against pathological tau protein AADvac1 has been assessed for safety and tolerability in the first-in-man study Axon CO18700, completed in March 2015. Enrolled were patients suffering from mild-to-moderate Alzheimer’s disease (MMSE 15-26) diagnosed according to the NINCDS/ADRDA criteria. The subjects were randomly assigned to one of the two treatment groups, either AADvac1 (n=24) or placebo (n=6). The study consisted of a 3-month double-blind period, followed by a 3-month open label period. Placebo subjects crossed over to AADvac1 treatment in the open label period. The primary objective of the study was to assess safety and tolerability of AADvac1.

The clinical study was performed in Austria at four investigational sites. Of the 30 patients enrolled into the study, 28 completed the planned 6-month investigation period. All but one patient developed an immune response to AADvac1, in most of the cases the immune response was robust. No safety signals have arisen from this study based on the assessments of adverse events, MRI results, laboratory tests, vital signs, and ECG. No worsening in cognition was observed over the course of the study, supporting the overall positive safety and tolerability results. The results indicate that tau targeted immunotherapy of AD can avoid the safety issues commonly observed in other clinical trials of vaccines against AD.

AADvac1 has maintained a positive risk benefit estimate, supporting the enrolment of larger, more informative patient sample in upcoming Phase II studies and the expansion of the AADvac1 development program to non-AD tauopathies.
Based on the promising safety, tolerability and immunogenicity results of the first-in-man phase-1 study, the active vaccine against tau protein pathology “AADvac1” is entering the next phase of its clinical development. The company is starting a phase II clinical study in Alzheimer’s disease (AD), and is preparing a dose finding study in AD.

AC-AD-003 will be a randomized, placebo-controlled, parallel group, double-blind, multi-center, phase II study to assess safety and efficacy of AADvac1 in patients with mild Alzheimer’s disease. The study participants will be randomly assigned to either AADvac1 or placebo treatment and will be investigated for 24 months. While the primary study objective will explore the safety and tolerability of AADvac1, the secondary and exploratory objectives will address immunogenicity and the impact of treatment on cognition, functioning, brain atrophy and blood and CSF biomarkers. Concomitantly and in a similar study population, AXON Neuroscience plans to conduct an open-label study, exploring the impact of different doses and vaccination regimens of AADvac1 on immunogenicity. Safety, tolerability, efficacy and biomarkers will simultaneously be evaluated as secondary and exploratory objectives.

The phase II program consisting of these two parallel studies will drive the selection of primary and secondary endpoints and guide the choice of the dose to be used in confirmatory Phase III studies, as well as furthering the understanding of mechanism of tau targeted immunotherapy in Alzheimer’s disease.
Possibilities in Treatment of Orphan Tauopathies

Frontotemporal lobar degeneration (FTLD) covers a whole spectrum of neurodegenerative disorders which principally affect the frontal and temporal lobes of the brain. Currently, the following disorders are grouped together under the overall title of FTLD: frontotemporal dementia as behavioural variant (bvFTD), non-fluent variant of primary progressive aphasia (nfvPPa), the semantic variant PPA (svPPA), amyotrophic lateral sclerosis with FTD, corticobasal syndrom (CBS) and progressive supranuclear palsy (PSP).

A major challenge for clinical trials in FTLD is the overlap of clinical syndromes, the change of symptoms during disease progression and the limited data available on possible robust clinical endpoints. Since 2011 the FTLD-trace study has been trying to overcome these challenges and to achieve a trial readiness for these disorders. Patients with nfvPPa, tau-mutation carriers and PSP patients are especially suitable for therapeutic intervention with tau modulating drugs, as an underlying tau-pathology can be assumed on clinical grounds.

During the talk the overall concept of the pilot trials for nfvPPA and tau-mutation carriers will be presented.
This symposium is held in conjunction with Alzheimer’s Association International Conference® 2015