SPEAKER SPOTLIGHT:

Treatment Strategies in Alzheimer's Disease

Identification of new therapeutic targets is urgently needed for the development of effective treatment strategies for Alzheimer's Disease. With critical advancements in novel biomarker technologies and diagnostic testing, the industry is poised to see more success in clinical trials for neurodegenerative disease. Christiane Volbracht has 17 years of experience in neuroscience drug discovery, and joined us to shed light on the key innovations occurring in Alzheimer's research. Christiane will discuss her work further at our Neuroscience Drug Discovery Congress taking place in Berlin, Germany, where she is speaking on "Tau Antibodies Targeting Seeding Competent Tau As Treatment Strategy In Alzheimer's Disease".

What is the current focus of your research in developing treatment strategies for Alzheimer's disease?

Alzheimer's disease (AD) is the most common form of dementia in the elderly. Dementia is characterized by progressive impairment of cognition, function and behavior. AD is a progressive degenerative disease of the brain defined by atrophy, extracellular amyloid plaques of beta-amyloid peptides (Aβ) and intraneuronal tau-containing neurofibrillary tangles (NFT) and neuropil threads (NT). Genetic data strongly implicate Aβ in AD pathogenesis. The appearance of NFT in different brain regions is classified in Braak stages and defines the neuropathological severity of AD. NFT burden in the neocortex has a stronger correlation than Aβ plaques with ante-mortem cognitive status. NFT and NT composed of aggregated hyperphosphorylated tau are thought to be the primary drivers of neurodegeneration. However, mechanisms underlying the pathogenic processes and the exact relationships of Aβ to tau pathology remain unclear. Evidence strongly suggests that pathological tau propagates or spreads between cells and that neuroinflammation triggered by microglial activation and astrogliosis contributes to tau-associated pathogenesis. The development of tau pathology is a complex multifactorial process, presenting multiple points where tau targeted therapeutic intervention is possible to prevent tau production, aggregation, or spread at the level of transcription, phosphorylation, depolymerization, and transport. One of our area of interests is to develop anti tau antibodies targeting spreading of tau pathology to halt disease progression in AD.

What are the advantages of developing tau antibodies for the treatment of Alzheimer's?

At present most tau-targeting therapies in Alzheimer's disease (AD) clinical trials are immunotherapies including active tau vaccines and therapeutic monoclonal antibodies. There are several advantages of therapeutic antibodies (passive immunotherapy). Passive immunotherapy does not require the immune system to generate an immune response, which is generally reduced in older individuals. In terms of pharmacology definition, therapeutic antibodies are precisely characterized by affinity, avidity, target specificity, half-life, concentration, and single isotype. Passive immunization offers therefore greater specificity for the epitope that is being targeted. Tau therapeutic antibodies could target, neutralize and eliminate monomeric, aggregated, phospho-specific, or conformationally altered forms of tau protein. During AD progression the pathological tau profile could change, and therapeutic antibodies could be tailored to the individual patient according to the disease stage. In terms of safety, patients are not developing an own immune response by passive immunization, effects of therapeutic antibodies are transient, and the risk of immunological adverse effects is reduced. However, therapeutic antibodies require chronic administration which generally bears a risk of formation of anti-antibodies, which could result in neutralization and/or have other unwanted immunological side effects, and this can be monitored.

CHRISTIANE VOLBRACHT

Principal Scientist, Neurobiologist, H. Lundbeck

Christiane Volbracht has a PhD in biology and for the past 17 years worked in neuroscience drug-discovery, focusing on neurodegeneration and particularly on Alzheimer's disease. Christiane is working as Principal Scientist at H. Lundbeck A/S in Copenhagen Denmark and has contributed to the development of a comprehensive pipeline of both possible disease-modifying and novel symptomatic treatments for Alzheimer's disease. Recently, she co-developed an anti-tau antibody that specifically targets hyper-phosphorylated pathological tau which is currently being evaluated in the clinic.

Describe the main priorities for the neuroscience industry in Alzheimer's over the next year. Will further research into alternative strategies to Amyloid-β and tau play a large role?

Today, only symptomatic treatments are approved for AD. The challenges for drug development are complex as trial populations have expanded and include preclinical and prodromal AD. These early AD trial populations require appropriate biomarkers for selection, staging and tracking. Most disease-modifying therapies under clinical investigation are aimed at preventing, slowing or ameliorating the production, oligomerization, aggregation and deposition of β-amyloid peptides (Aβ) and recently also of tau protein. Based on data from February 2019, improved symptomatic treatments are tested by 25% of agents in AD clinical trials targeting cognitive enhancement or intended to treat neuropsychiatric and behavioral symptoms in AD. 73% of agents in AD clinical trials aim for disease modification with 40% having Aβ as primary target, 18% being anti-tau agents and 15% targeting neuroprotection, inflammation, or metabolism. This distribution of disease-modifying treatments under clinical investigation reflects the former Aβ centered approach and recent tau focus in AD research as anti-tau therapies are beginning to populate AD clinical trials, mostly in Phase 1 and 2.

In your opinion, what key advancement with neuroscience has the potential to revolutionize Alzheimer's research?

Alzheimer's disease (AD) research will be revolutionized by identifying the cause of the disease and effective treatment strategies targeting the underlying pathogenic processes. On this journey advancement in the development of novel biomarkers and diagnostic tests will boost AD research. Neuropathologic examination is the standard for defining AD by Aβ plaques and neurofibrillary tangles (NFT). Validated, widely used biomarkers exist that are proxies for these AD neuropathologic changes. Biomarkers for Aβ plaques are cortical amyloid positron emission tomography (PET) ligand binding and low cerebral spinal fluid (CSF) Aβ42; for fibrillar tau are elevated CSF phosphorylated tau and cortical tau PET ligand binding; and for neurodegeneration are CSF total tau, fluorodeoxyglucose (FDG) PET hypometabolism, and atrophy on magnetic resonance imaging (MRI). Existing biomarkers are vital in characterizing and staging AD, for enrichment of subjects, and target engagement in clinical trials. But PET scans are expensive and lumbar punctures to obtain CSF are invasive procedures. Most AD patients have comorbid pathology contributing to the clinical symptoms including different protein inclusions in addition to Aβ plaques and NFT, underlining the need for biomarkers that can indicate the presence of multiple pathologies in AD patients. Inexpensive, simple to measure, reliable, and minimally invasive biomarkers for AD are in high demand, which may include retina- and blood-based assays. Development of novel fluid biomarkers such as neurofilament light and neurogranin is desirable which could then be integrated into clinical trials and more broadly characterize underlying pathogenic mechanisms, including neurodegeneration, neuroinflammation, and synaptic dysfunction.

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