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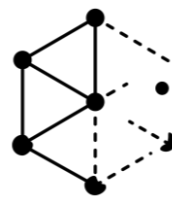
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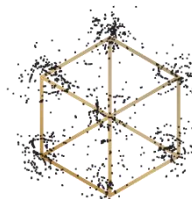
香港中文大學



NTNU



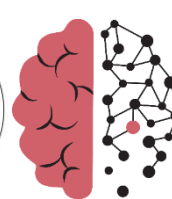
K.G. Jebsen Centre for
Alzheimer's Disease



Kavli Institute for
Systems Neuroscience



NO-Age



NO-AD



MIT-AD

The NO-Age and NO-AD Seminar Series 024

14:00-16:30 (CET), Monday, 19th April 2021

14:00-15:15: 'Amyloid and tau pathology in Alzheimer's disease: Neuropathology in symptomatic and presymptomatic cases' by Prof. **Dietmar Thal**, Katholieke Universiteit Leuven, Belgium

15:15-16:30: 'Selective mitochondrial autophagy in health, aging, and neurodegeneration' by Prof. **Wolfdieter Springer**, Mayo Clinic, Florida, USA

Register in advance for this webinar:

https://uio.zoom.us/webinar/register/WN_bYm0QgKYTrKePgI7I64GBg

Organizers:

Evandro F. Fang (UiO), Martin Vyhnálek (CBAS), Menno P. Witter (NTNU), Jon Storm-Mathisen (UiO), Lene Juel Rasmussen (KU), W.Y. Chan (CUHK)

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Previous recorded talks are available here: <https://noad100.com/videos-previous-events/>



Name: Dietmar Thal

Institute: Katholieke Universiteit Leuven

Email: dietmar.thal@kuleuven.be

Photo: provided by the speaker

Speaker: Dietmar Thal

Title: Amyloid and tau pathology in AD: Neuropathology in symptomatic and presymptomatic cases

Abstract:

Alzheimer's disease (AD) is the most frequent cause of dementia in elderly individuals. Its neuropathological hallmark lesions are senile plaques consisting of aggregates of the amyloid β protein ($A\beta$) and neurofibrillary tangles (NFTs) representing fibrillar aggregates of abnormal phosphorylated τ -protein ($p\text{-}\tau$). $A\beta$ plaques and NFTs do not only occur in symptomatic AD patients. They can also be seen in brains of non-demented individuals. Based upon topographical staging systems describing the distribution of $A\beta$ plaques and NFTs in the human brain it became evident that non-symptomatic cases with $A\beta$ and NFT pathology show early stages of the pattern observed in symptomatic AD cases. In those brain regions that become involved into $A\beta$ or $p\text{-}\tau$ pathology in symptomatic AD cases $A\beta$ plaques and NFTs show a similar sequence of aggregate maturation as in other regions already developing pathology in asymptomatic cases. I.e. plaques first contain only $A\beta$ lacking pyroglutamate formation or phosphorylation before $A\beta N3pE$ can be found. $A\beta pSer8$ is restricted to only a few cases, usually symptomatic AD cases. $p\text{-}\tau$ phosphorylated at specific sites of the τ -protein accumulates first as IC-(initial cytoplasmic pT231- τ) and IN-tau (initial neuropil pS396/pS404- τ) before pretangles are formed exhibiting multiple phosphoepitopes of τ incl. pS202/pT205 and later develop into argyrophilic NFTs. These steps in the development of NFTs are observed in the entorhinal region before the respective cases are become demented whereas a similar maturation of τ pathology in the primary cortex and the cerebellum is observed in symptomatic AD. Thus, there is a propagation $A\beta$ and $p\text{-}\tau$ pathology in the development of AD starting a similar maturation process in all regions once a given region becomes affected. To clarify which $A\beta$ and $p\text{-}\tau$ species are involved in this process we tested distinct types of human brain tissue-derived brain lysates to induce $A\beta$ and $p\text{-}\tau$ pathology in APP and TAU transgenic mouse models. We will show the seeding characteristics of different $A\beta$ and $p\text{-}\tau$ preparations received from brain lysates. The results indicate that multiple types of $A\beta$ aggregates can induce $A\beta$ seeding while sarkosyl-insoluble $p\text{-}\tau$ showed superior seeding effects compared to more soluble forms of brain-lysate derived $p\text{-}\tau$ confirming previous results from other groups.

Biography:

Prof. Thal is neuropathologist and professor for Neuropathology at KU-Leuven (Belgium) with his main research focus on AD. His major interest is the expansion and maturation of protein aggregates in AD. He was able to discover phases describing the expansion of amyloid plaque pathology in the human brain. These phases are currently included in the diagnostic criteria for the neuropathological assessment of Alzheimer's disease (known as Thal-Phases).

Prof. Thal could show that the current amyloid PET-methods are usually restricted to the detection of moderate - advanced phases of amyloid plaques pathology distribution and in so doing represent a valuable tool for diagnosing the symptomatic disease and advanced stages of preclinical AD but not for picking up very early stages of the disease. When including the caudate nucleus SUVRs he was able to estimate the amyloid (Thal) phases with phase 3 being the earliest.

In addition, his group able to show that not only the anatomical expansion of amyloid plaque aggregates plays a role in the pathogenesis of AD but also the maturation of the aggregates, meaning that the composition of amyloid plaque/soluble and dispersible amyloid aggregates changes over time with specific proteins becoming detectable only in the symptomatic cases. Recently, his group found that the interaction of $A\beta$ with cellular prion proteins appeared to accelerate the spreading of τ -pathology in AD.

The major goals of his further research are: 1) To improve the preclinical detection of AD and other neurodegenerative disease to allow treatment before significant neuron loss has started; and 2) to identify critical steps in the cascade of protein aggregate maturation and its link the neuron loss in AD that can be tackled for therapeutic purposes.



Speaker: Wolfdieter Springer, Ph.D., Associate Professor of Neuroscience

Title: Selective mitochondrial autophagy in health, aging, and neurodegeneration.

Abstract:

The ubiquitin (Ub) kinase PINK1 and the E3 Ub ligase PRKN selectively recognize, label, and target damaged mitochondria to the autophagy-lysosome system for elimination (mitophagy). Loss of function mutations in either gene invariably lead to recessive early-onset Parkinson's disease (PD) and it is thought that the failure to identify and clear damaged mitochondria eventually results in neuronal death. In line with broad neuroprotective functions, reduced enzymatic activities or altered mitophagic flux may also contribute to risk, onset, and progression of later onset PD as well as other age-related, neurodegenerative conditions including Alzheimer's disease (AD). These mitophagy dysfunctions can occur at different steps of a dynamic process and may be mitochondrial, autophagic, and/or lysosomal in nature, and thus are difficult to track. Phosphorylated Ub (pS65-Ub) is the joint product of PINK1 and PRKN, and due to an enzymatic feedforward mechanism can be used to determine both Ub kinase and ligase activities. Besides its functions as an allosteric activator and receptor for PRKN, pS65-Ub also serves as the 'mitophagy tag', and, while transient, can be used as specific and quantitative marker of mitochondrial damage. We have recently developed means to assess and follow pS65-Ub in cells and tissues as well as in blood samples from animal models and patients. This has further underscored the importance of mitophagy under endogenous conditions and its relevance to aging and neurodegenerative disease. Additional efforts are underway to determine the suitability of pS65-Ub as a potential disease or pharmacodynamics marker.

Biography:

Dr. Wolfdieter Springer is a Consultant and Associate Professor in the Department of Neuroscience at Mayo Clinic in Florida, and his main research focus is on the molecular and cellular mechanisms underlying the pathogenesis of age-related, neurodegenerative disorders. He received his MSc in Biology from the University of Regensburg and his PhD in Biochemistry from the Ludwig-Maximilian-University in Munich, Germany. He then did postdoctoral training at the German Center for Neurodegenerative Diseases and the Hertie-Institute for Clinical Brain Research in Tuebingen, Germany. After the seminal discovery of the PINK1-PRKN mitophagy pathway, Dr. Springer joined Mayo Clinic in late 2011. With a focus on disease relevance, his laboratory continues to study both enzymes on a structural, molecular, cellular, and organismal level. Current projects aim at dissecting the genetic architecture of mitophagy and understanding of the consequences of impairments at individual steps of a dynamic process as well as the development of biomarkers and future therapeutics for diseases where mitochondrial, autophagic, and/or lysosomal dysfunctions emerge as a common theme.

For more information, please visit <https://www.mayo.edu/research/labs/translational-cell-biology-parkinsons-disease/overview> .