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Novel cerebrospinal fluid and blood tau biomarkers in Alzheimer's disease and other neurodegenerative diseases

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet
Torgny Segerstedt (aulan), Universitetsplatsen 1, Vasaplatsen, fredagen den **8th April** 2022, klockan **13:00**
av **Juan Lantero Rodriguez**

Fakultetsopponent:
Diane P. Hanger, PhD, Prof.
King's College London, United Kingdom

Avhandlingen baseras på följande delarbeten

I. Thomas K. Karikari, Tharick A. Pascoal, Nicholas J. Ashton, Shorena Janelidze, Andréa Lessa Benedet, **Juan Lantero-Rodriguez**, Mira Chamoun, Melissa Savard , Min Su Kang, Joseph Therriault, Michael Schöll, Gassan Massarweh, Jean-Paul Soucy, Kina Höglund, Gunnar Brinkmalm, Niklas Mattsson, Sebastian Palmqvist, Serge Gauthier, Erik Stomrud, Henrik Zetterberg, Oskar Hansson, Pedro Rosa-Neto, Kaj Blennow. "*Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts*". The Lancet Neurology. 2020. 19(5):422-433.

II. **Juan Lantero-Rodriguez***, Thomas K. Karikari*, Marc Suárez-Calvet, Claire Troakes, Andrew King, Andreja Emersic, Dag Aarsland, Abdul Hye, Henrik Zetterberg, Kaj Blennow, Nicholas J. Ashton. "*Plasma p-tau181 accurately predicts Alzheimer's disease pathology at least 8 years prior to post-mortem and improves the clinical characterisation of cognitive decline*". Acta Neuropathologica. 2020. 140(3):267-278.

III. Nicholas J. Ashton, Tharick A. Pascoal, Thomas K. Karikari, Andréa L. Benedet, **Juan Lantero-Rodriguez**, Gunnar Brinkmalm, Anniina Snellman, Michael Schöll, Claire Troakes, Abdul Hye, Serge Gauthier, Eugeen Vanmechelen, Henrik Zetterberg, Pedro Rosa-Neto, Kaj Blennow. "*Plasma p-tau231: a new biomarker for incipient Alzheimer's disease pathology*". Acta Neuropathologica. 2021. 141(5):709-724.

IV. **Juan Lantero-Rodriguez***, Anniina Snellman*, Andrea L. Benedet, Marta Milà-Alomà, Elena Camporesi, Laia Montoliu-Gaya, Nicholas J. Ashton, Agathe Vrillon, Thomas K. Karikari, Juan Domingo Gispert, Gemma Salvadó, Mahnaz Shekari, Christina E. Toomey, Tammaryn .L Lashley, Henrik Zetterberg, Marc Suárez-Calvet, Gunnar Brinkmalm, Pedro Rosa-Neto and Kaj Blennow. "*P-tau235: a novel biomarker for staging preclinical Alzheimer's disease*". EMBO Molecular Medicine. 2021. 13(12):e15098

V. Anniina Snellman*, **Juan Lantero-Rodriguez***, Andreja Emeršič, Agathe Vrillon, Thomas K. Karikari, Nicholas J. Ashton, Milica Gregorič Kramberger, Saša Čučnik, Claire Paquet, Uroš Rot, Henrik Zetterberg and Kaj Blennow. "N-terminal and mid-region tau fragments as fluid biomarkers in neurological diseases". Brain (accepted)

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SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

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Novel cerebrospinal fluid and blood tau biomarkers in Alzheimer's disease and other neurodegenerative diseases

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Abstract

Tau is a protein predominantly expressed in neurons in the central nervous system (CNS), where it binds microtubules (MT), playing a major role regulating their dynamics and architecture. Under pathological conditions, tau detaches from MTs, leading to neuronal dysfunction and cell death. These events are the cornerstone of a group of diseases called tauopathies. In this context, Alzheimer's disease (AD) emerges as the most prevalent cause of dementia worldwide, accounting for 60 to 80% of all cases. Two common landmarks for all tauopathies are the abnormal phosphorylation and truncation of tau protein, which are highly relevant from a fluid biomarker perspective, as the resulting tau species leak from brain into cerebrospinal fluid (CSF) and blood, where they can be quantified as indicators of pathogenic processes in brain. At the time this PhD was started, only two fluid biomarker tau species were clinically validated for AD diagnosis: phosphorylated tau at threonine 181 (p-tau181) and total-tau (t-tau), both measured in CSF. While these biomarkers have consistently shown high performance assisting the clinical diagnosis of AD, their broad implementation worldwide has been severely hampered by the perceived invasiveness associated with lumbar puncture. Similarly, imaging biomarkers have failed to become a feasible alternative due to their lack of scalability and high costs. Thus, measuring tau biomarkers in blood has been a long-sought goal in the field of fluid biomarkers, as blood collection does provide the accessibility, cost-effectiveness and scalability required in clinical settings.

Our hypothesis was that the potential of tau protein as a fluid biomarker both in terms of disease staging and mechanistic understating was not yet fully uncovered. Therefore, the aim of this thesis was the identification and quantification of novel tau species (including different phosphorylated tau forms and fragments) in CSF and blood, generating clinically relevant tools that would improve our understanding of AD and other neurodegenerative diseases. First, we developed and validated two novel immunoassays capable of quantifying p-tau181 and p-tau231 in blood, demonstrating that both are highly specific biomarkers of AD (both during clinical and preclinical stages), capable of nearly perfect discrimination of neuropathology-confirmed AD from other neurodegenerative diseases, and showing high association with AD progression. Thus, this work has greatly contributed to the previously elusive goal of a worldwide implementation of fluid biomarkers through simple blood-testing. Another notable contribution of this thesis was the development of a biomarker capable of staging preclinical AD. While there are biomarkers capable of identifying incipient AD pathology during preclinical stages with high accuracy, they cannot determine whether AD cases are at the beginning or the end of the asymptomatic phase. In this context, the novel CSF biomarker p-tau235 was shown to stage preclinical AD on the basis of neuropathological findings found in post-mortem-confirmed AD brain. Our findings indicate that the combined measurement of CSF p-tau235 and p-tau231 can stratify preclinical AD into early and late cases. Finally, we investigated if tau fragments of different lengths provide meaningful advantages in terms of early detection of AD and availability in blood. Our results suggest that N-terminal t-tau forms increase early in the AD continuum, being more suitable for early detection, whereas mid-region t-tau assays provide a better diagnostic performance when discriminating AD dementia from non-AD dementia cases. Most notably, N-terminal assays appear to offer a superior diagnostic performance in blood, where we were able to demonstrate that they successfully identify AD cases.

In conclusion, the work included in this thesis demonstrates that tau protein as a fluid biomarker (both phosphorylated and non-phosphorylated), can reflect a much wider variety of subtle but meaningful aspects of brain pathology than previously understood, and that the uses of tau as a fluid biomarker expand not only from asymptomatic to symptomatic AD, but also to other tauopathies and acute neurological conditions.

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