Göteborg, 2025

P-tau212: a novel biomarker for tau pathology in specific neurodegenerative diseases

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i R-Aulan, Länsmansgatan 28, Mölndal, fredagen den 16 maj 2025, klockan 13.00

av Przemysław R. Kac

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Avhandlingen baseras på följande delarbeten

I. **Przemysław R. Kac**, Fernando González-Ortiz, Andreja Emeršič, Maciej Dulewicz, Srinivas Koutarapu, Michael Turton, Yang An, Denis Smirnov, Agnieszka Kulczyńska-Przybik, Vijay R. Varma, Nicholas J. Ashton, Laia Montoliu-Gaya, Elena Camporesi, Izabela Winkel, Bogusław Paradowski, Abhay Moghekar, Juan C. Troncoso, Tammaryn Lashley, Gunnar Brinkmalm, Susan M. Resnick, Barbara Mroczko, Hlin Kvartsberg, Milica Gregorič Kramberger, Jörg Hanrieder, Saša Čučnik, Peter Harrison, Henrik Zetterberg, Piotr Lewczuk, Madhav Thambisetty, Uroš Rot, Douglas Galasko, Kaj Blennow & Thomas K. Karikari; *Plasma p-tau212 antemortem diagnostic performance and prediction of autopsy verification of Alzheimer's disease neuropathology*. Nat Commun 15, 2615 (2024).

II. **Przemysław R. Kac***, Daniel Alcolea*, Laia Montoliu-Gaya, Susana Fernández, Juan Lantero Rodriguez, Lucía Maure, Fernando González-Ortiz, Bessy Benejam, Michael Turton, Isabel Barroeta, Peter Harrison, Laura Videla, Nicholas J. Ashton, Alberto Lleó, Henrik Zetterberg, María Carmona-Iragui, Thomas K. Karikari, Juan Fortea, and Kaj Blennow; *Plasma p-tau212 as a biomarker of sporadic and Down Syndrome Alzheimer's disease.* Alzheimer's Dement 2025: Accepted

III. **Przemysław R. Kac***, Katheryn A.Q. Cousins*, Leslie M. Shaw, Thomas K. Karikari, Michael Turton, Vivianna van Deerlin, Peter Harrison, Hlin Kvartsberg, Jörg Hanrieder, Henrik Zetterberg, David A. Wolk, Corey T. McMillan, Edward B. Lee, David J. Irwin, and Kaj Blennow; *MTBR-tau368 improves p-tau diagnostic accuracy for FTLD-tau from FTLD-TDP.* Manuscript

IV. **Przemysław R. Kac***, Armand González-Escalante*, Marta Milà-Alomà, Nicholas J. Ashton, Mahnaz Shekari, Paula Ortiz-Romero, Michael Turton, Peter Harrison, Henrik Zetterberg, Juan Domingo Gispert, Thomas K. Karikari, Marc Suárez-Calvet, Kaj Blennow; *Plasma p-tau212 accurately identifies cognitively unimpaired individuals with emerging amyloid-beta pathology*. Manuscript

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SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

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P-tau212: a novel biomarker for tau pathology in specific neurodegenerative diseases

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Abstract

Tau protein is involved in multiple physiological processes in the central nervous system, one of which is microtubule stabilization. Post-translational modifications of tau, such as phosphorylation strictly regulate this process. Dysregulation leads to pathological tau lesions, including mislocalization, propagation, and aggregation. In consequence, tau aggregation is a hallmark of the neurodegenerative diseases group called tauopathies. The most prevalent tauopathy is Alzheimer's Disease (AD) – a leading cause of dementia. AD develops much earlier in people with Down Syndrome (DS), reaching a lifetime risk of over 90% in the seventh decade of life. Other pathologically and clinically defined tauopathies belong to the frontotemporal lobar degeneration (FTLD) tau type. Definitive diagnosis of tauopathies can be achieved only post-mortem, and commonly, there is an overlap between clinical manifestations. Therefore, reliable, robust, and accessible ante-mortem biomarkers to differentiate tauopathies are urgently needed. Currently, nothing like that exists for FTLD, however, we experience rapid development of blood-based biomarkers for AD, i.e. phosphorylated tau (p-tau) species. Yet, they differ in their diagnostic performance, which may be linked to various biological mechanisms underlying their formation.

The principal objective of this thesis was to assess the utility of some understudied p-tau epitopes as biomarkers for neurodegenerative diseases, one such example being p-tau212, which is located in the rich region of tau that makes it susceptible to multiple kinases. One of those is dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A). The gene for this kinase is located at chromosome 21 in the DS critical region. Additionally, p-tau212 was linked to neurodegeneration, aggregation, and microtubule assembly impairment.

Following the optimization and validation of plasma and CSF p-tau212 immunoassays, their diagnostic performance was evaluated in AD biomarker-positive and negative cohorts, sporadic AD cohorts, AD Down Syndrome cohorts, post-mortem AD cohorts, and preclinical AD cohorts. Additionally, the utility of CSF p-tau212 was assessed in the post-mortem validated FTLD cohort. Results were compared with other existing biomarkers. We show that plasma p-tau212 has high diagnostic accuracy to differentiate AD from control groups, and in few cases, the performance is significantly better than currently existing biomarkers. Plasma p-tau212 is increased in preclinical, sporadic, prodromal, and DSAD. Plasma p-tau212 increased approximately 15 years before the onset of AD in DS and before established positron emission tomography cutoff points. In addition, we have found elevated levels and high diagnostic accuracy of CSF p-tau212 to differentiate clinical FTLD cases with different proteinopathies underlying the manifestations.

In conclusion, the result of this thesis is developed and validated a new fluid biomarker for AD and FTLD. Its diagnostic performance challenges currently available methods, and the robustness of the assays makes it cost-effective and easy to implement biomarkers for diagnosis of ongoing AD and FTLD-tau pathophysiological processes, clinical trial recruitment purposes, therapy monitoring, target engagement for anti-amyloid drugs and DYRK1A modulators, and theragnostic.

Keywords: Alzheimer's Disease, p-tau212, plasma biomarkers, tauopathies

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