

# Correlative Chemical Imaging of Amyloid Plaque Pathology in Alzheimer's Disease

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligen försvaras i Hjärtats aula, Sahlgrenska universitetssjukhuset, Vita stråket 12, Göteborg, den **24 januari 2025**, kl. **9.00** av **Junyue Ge**

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## Avhandlingen baseras på följande delarbeten

- I. Wehrli, P. M, **Ge, J**, Michno, W, Koutarapu, S, Dreos, A, Jha, D, Zetterberg, H, Blennow, K, Hanrieder, J. Correlative Chemical Imaging and Spatial Chemometrics Delineate Alzheimer Plaque Heterogeneity at High Spatial Resolution, *JACS Au*, 2023, 3, 762-774.
  - II. **Ge, J**, Koutarapu, S, Jha, D, Dulewicz, M, Zetterberg, H, Blennow, K, Hanrieder, J. Tetramodal Chemical Imaging Delineates the Lipid-Amyloid Peptide Interplay at Single Plaques in Transgenic Alzheimer's Disease Models, *Anal Chem*, 2023, 95, 4692-4702.
  - III. **Ge, J\***, Dulewicz, M\*, Koutarapu, S, Jha, D, Zetterberg, H, Blennow, K, Hanrieder, J. Delineating A $\beta$  Plaque Associated Lipid Co-Aggregation Dynamics Using Pulse-Chase Spatial Multiomics. (Manuscript)
  - IV. **Ge J\***, Pagnon de la Vega M\*, Zampar S, Koutarapu, S, Giedraitis V, Lannfelt L, Syvänen S, Hanrieder J<sup>#</sup>, Ingelsson M, Sehlin D<sup>#</sup>. The *Uppsala APP* mutation promotes wildtype A $\beta$  aggregation and deposition *in vivo*. (Manuscript)
  - V. Koutarapu S, **Ge J**, Jha D, Blennow K, Zetterberg H, Lashley T, Michno W, Hanrieder J. Correlative chemical imaging identifies amyloid peptide signatures of neuritic plaques and dystrophy in human sporadic Alzheimer's disease, *Brain Connectivity*, 2022, 13, 297-306.
  - VI. Koutarapu S\*, **Ge J\***, Dulewicz, M\*, Srikrishna M, Szadziewska A, Wood J, Blennow K, Zetterberg H, Michno W, Natalie S Ryan, Lashley T, Savas J, Schöll M, Hanrieder J. Chemical imaging delineates A $\beta$  plaque polymorphism across the Alzheimer's disease spectrum. (Manuscript)
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# Correlative Chemical Imaging of Amyloid Plaque Pathology in Alzheimer's Disease

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## Abstract

The formation of beta-amyloid (A $\beta$ ) plaques and neurofibrillary tangles are key pathological hallmarks of Alzheimer's disease (AD), where amyloid has been identified to precede and even initiate other neurodegenerative processes including Tau. Consequently, studying beta-amyloid pathology has been a central focus in AD research yet the molecular mechanisms underlying plaque formation and its role in initiating AD remain poorly understood. A $\beta$  plaque pathology is characterized by significant heterogeneity in morphology, including variations between cored and diffuse plaques, as well as structural polymorphism in amyloid fibril formation. Moreover, A $\beta$  does not correlate with cognitive performance and is even observed in elderly, cognitively normal individuals. Recent evidence further suggests that neuronal lipids also play a crucial role in amyloid plaque formation and progressing plaque pathology. Together this poses a significant challenge and highlights the need for new, biochemical tools that allow to disentangle the complex molecular interactions associated with AD pathogenesis and plaque formation in particular.

To address this gap, we utilized advanced chemical imaging techniques to probe the molecular events associated with diverse plaque pathologies in AD.

In this thesis, we developed a tetra-modal chemical imaging approach that integrates matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI) with fluorescence imaging. This allowed for detailed mapping of lipid and amyloid peptide distributions in brain tissue of genetic AD mouse models. Through the application of novel, multivariate tools for multiblock analysis, we identified distinct lipid profiles linked to different stages of plaque formation, highlighting the correlation of GM1 ganglioside with both plaque seeding and growth. We further validated the relevance of lipid-amyloid co-aggregation by developing a dynamic imaging approach based on metabolic labeling of lipids and peptides with stable isotopes. This allowed to dissect plaque and lipid coaggregation dynamics and identified the sequence of ganglioside and amyloid deposition in precipitation plaque pathology in AD mouse model.

Furthermore, we examined the co-existence of different A $\beta$  peptides in novel transgenic models harboring the *Uppsala APP* mutation, revealing its significant impact on A $\beta$  aggregation dynamics. Finally, we applied these advanced imaging techniques to understand heterogeneous plaque pathology in the human brain. Here, we successfully identified specific amyloid plaque signatures for distinct plaque types, such as A $\beta$ 1-42(ox) and A $\beta$ 2-42 in neuritic plaques. Using a novel AI driven plaque segmentation scheme, we identified that A $\beta$ 1-40 was found to be associated with plaque maturation into cored deposits in AD patients. Further, A $\beta$  x-40 is present in cored, coarse grain plaques and vascular plaques (CAA) in both sAD and fAD.

Together these findings enhance our understanding of amyloid plaque heterogeneity as well as underscore the importance of lipid-amyloid interactions in AD pathology. This work lays the groundwork for future investigations aimed at elucidating the complex interactions between lipids and amyloid peptides in the context of AD.

**Keywords:** Alzheimer's disease, amyloid plaque pathology, lipid, correlative chemical imaging, MALDI-MSI, microscopy