Visualization of the in situ molecular architecture of tau pathology in the murine brain

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Background incl. aims
The accumulation of pathological tau protein aggregates is a hallmark of numerous neurodegenerative diseases, including Alzheimer's disease. The accumulation of misfolded tau in neurons is toxic, it disrupts cellular physiology, leading to neuronal death and the propagation of tau misfolding throughout the brain. Effects of tau pathology include disrupted axonal transport, mitochondrial and lysosomal dysfunction, and synapse degeneration. Despite advancements in understanding tau pathology, the relationships between initial tau misfolding, fibril formation, pathology propagation across connected neurons, and subsequent cytotoxicity on the level of individual neurons remain unclear. We aim to visualize the pathological changes in molecular architecture directly in the vitrified brain tissue of the murine model for tauopathy.

Methods
To visualize the native ultrastructure we use vitrified fresh brain without staining or fixation. We combine cryo-plasma-focused ion beam milling (FIB) and bio-contrast scanning electron microscopy (SEM) imaging with cryo-electron tomography (cryo-ET) on lamella. The cryo-plasma-FIB/SEM setup of the Helios Hydra V microscope allows imaging of non-stained vitrified hydrated biological samples with high biological contrast in nanometer resolution permitting volume imaging covering a much wider area than typical lamella used in cryo-ET.

Results
In this poster, we present our in situ visualization workflow and showcase preliminary bio-contrast cryo-plasma-FIB/SEM images and tomographs of murine brain tissue affected by tauopathy.

Conclusions
We showed that the novel bio-contrast cryo-plasma-FIB/SEM imaging workflow can be used for ultrastructural characterization of pathological tissues without chemical fixation and that the combination with lamella lift-out and in situ cryo-ET provides an excellent tool for uncovering the details of cellular mechanisms of neurodegeneration.

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Keywords:

in-situ cryo-ET, cryo-plasma-FIB/SEM, bio-contrast, tauopathy