Misfolded Protein Structure in Alzheimer's Disease

Beamline: U10B

Technique: Infrared microspectroscopy

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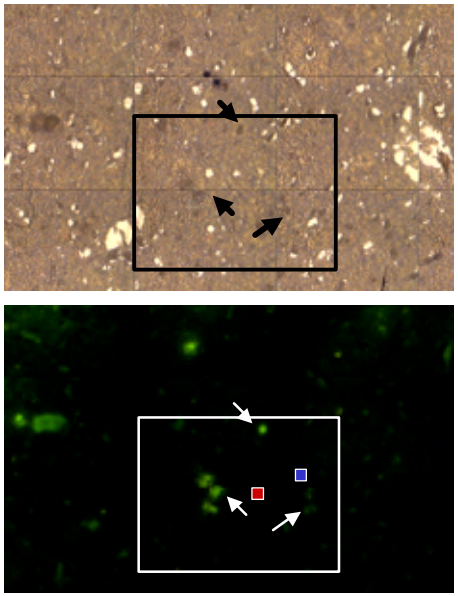
Motivation: Alzheimer's diseased brain is characterized by the presence of amyloid plaques that are thought to kill neurons in the brain. These plaques consist of aggregates of misfolded ß-amyloid protein. To date, the in situ structure of this misfolded protein is unclear and the mechanism by which the plaques form and damage surrounding nerve cells has yet to be elucidated. By combining fluorescence microscopy and synchrotron IRMS, the plaques can be identified in the tissue and the in situ structure of the misfolded ß-amyloid protein can be determined.



(Top left) Light microscope image of Alzheimer's diseased brain tissue. (Bottom left) Thioflavin-S stained brain tissue, indicating the presence of amyloid (green fluorescence). (Top right) Infrared spectra of normal tissue (blue) and amyloid plaque (red). (Bottom right) Infrared image of amyloid plaque distribution, calculated as a peak height ratio of 1630 / 1655 cm^{-1}.

Results: When comparing the Amide I spectral features of the amyloid versus normal brain tissue, dramatic differences are observed, indicating significant differences in protein structure. Specifically, the Amide I band of the normal tissue exhibits a single peak near 1650 cm^{-1}, representing an α-helical protein environment. In contrast, the Amide I band of the amyloid plaque contains two peaks, indicating a mixture of secondary structures in the plaque region. In addition to the α-helical component near 1650 cm^{-1}, an intense second peak is apparent near 1630 cm^{-1}, which is indicative of a β-sheet protein structure. Thus, the formation of β-amyloid plaque in the brain is associated with a change in protein secondary structure from α-helical to β-sheet, which likely leads to aggregation of the misfolded protein.