Alzheimer’s disease (AD) is characterised by misfolding and aggregation of two amyloid proteins, amyloid β (Aβ) and Tau. Tau aggregates have recently been found to propagate from cell to cell in a prion-like manner. Hyperphosphorylation leads to its detachment from microtubules, which deconstructs the cell skeleton and disrupts axonal transport. To study these processes in detail we constructed a microfluidic device that permits us to investigate different neuronal compartments in isolation, and in particular to study trans-synaptic transfer of Tau aggregation. The device can be used with any optical microscopy technique, including optical nanoscopy methods. Here we use a FRET sensor developed in our group to monitor aggregation reaction[1, 2, 3], and axonal transmission, of tau in live differentiated SH-SY5Y cells via TCSPC-FLIM. In the device neurons were incubated with soluble K18-Tau labelled with Alexa 488 (‘donor cells’) and the subsequent uptake and aggregation was observed in wild type receiver cells (‘acceptor cells’). Fluorescence lifetimes of K18-488 transmitted to the acceptor cells were found to be significantly lower than those in the donor cells, suggesting an acceleration of aggregation reactions on amyloid transmission, which may be significant in the context of disease.

Figure 1: Tau transfer is accompanied by a decrease in fluorescence lifetime. Lifetimes were found to be 3300 ps (donor cells), 3100 ps (axons situated in microgrooves), and 2900 ps (acceptor cells) indicative of progressive aggregation during transfer. (*: p<0.05; **: p<0.01; ****: p<0.0001; n.s. stands for no significance, all via two way ANOVA).

References