

Investigating Alzheimer's Disease Pathology using Operetta

Background

Alzheimer's disease is the most common of the age-related dementias. The memory loss and neuronal death observed in Alzheimer's disease is believed to be caused by an accumulation of amyloid beta peptide ($A\beta$) in the brain, particularly the neurotoxic, soluble, oligomeric form of $A\beta_{1-42}$. Evidence suggests that the pathologic effects of $A\beta_{1-42}$ oligomers are due to their impairment of glutamatergic signalling. In this study, researchers prepared physiopathologically relevant $A\beta_{1-42}$ oligomers and investigated different mechanisms of modulation of glutamatergic signalling. They also aimed to identify alternative targets for the treatment of Alzheimer's disease.

It is increasingly thought that the toxicity of $A\beta_{1-42}$ oligomers is due to their ability to bind to excitatory glutamatergic synapses. As part of this study, researchers investigated the binding of their pathophysiologically relevant $A\beta_{1-42}$ oligomers to hippocampal neurons (see figure). Primary hippocampal neurons (yellow) were incubated with $A\beta_{1-42}$ oligomers (red) from 1 nM - 500 nM, for 45 min at 37 °C, in 96-well plates.

How did Operetta and Harmony help them to achieve their research goals?

Plates were analyzed using the Operetta® High Content Imaging System and Harmony® Image Analysis Software. The red spots in panel A indicate the binding of $A\beta_{1-42}$ oligomers to hippocampal neuron synapses. Harmony was used to automatically detect and outline the neuronal cell bodies (panel B), and to define the dendritic projectory fields of individual neurons. The associated binding of $A\beta_{1-42}$ oligomers with neuronal dendritic fields was also automatically identified using Harmony, and marked with green spots (panel D).

The number of bound $A\beta_{1-42}$ oligomers (total spot count) was then plotted against $A\beta_{1-42}$ oligomer concentration (total $A\beta_{1-42}$) and a concentration-dependent (1 nM – 500 nM) increase in neuronal binding was observed.

How does this study contribute to scientific knowledge?

The researchers provide evidence that strongly supports the glutamatergic system as a target for the development of improved symptomatic and neuroprotective treatments for Alzheimer's disease.

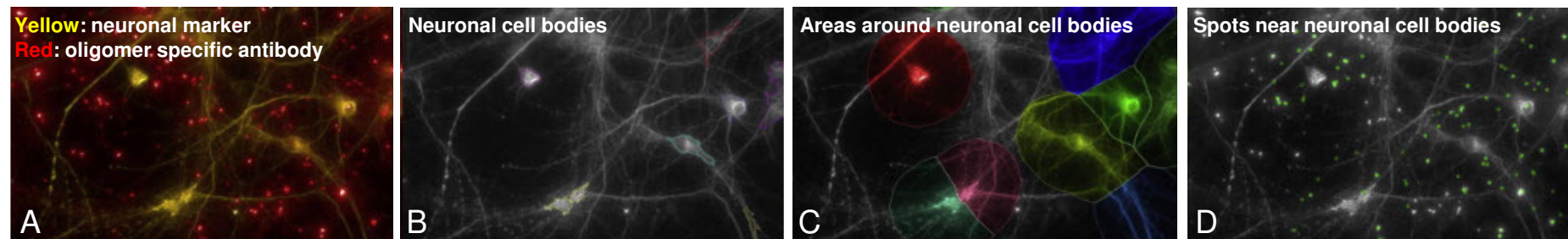


Figure: Harmony analysis of $A\beta_{1-42}$ oligomers binding to hippocampal neurons at low nM concentrations