Engineered M13-bacteriophages to target amyloid-β peptide in oligomeric/fibrillar form for Alzheimer’s Disease diagnosis

Ivone Martins 1, Ana Silva 1, Joana Azeredo 1, Helmut Kessels 2

1 Centre of Biological Engineering - University of Minho, Braga, Portugal
2 Center for NeuroSciences, Swammerdam Institute for Life Sciences - University of Amsterdam, Amsterdam, Netherlands

Alzheimer’s Disease (AD) is an age-dependent neurodegenerative disease with very high incidence worldwide and detrimental consequences. Manifests as a decline in cognitive functions and memory loss, characterized at molecular level by an increased deposition of amyloid-beta (AB) plaques. Nevertheless, it is AB in the still-soluble oligomeric/fibrillar form that impairs synaptic function and memory encoding [1]. Therefore, new tools that selectively target AB oligomers/fibrils in the brain hold great potential to halt AD at an early stage.

Specific amyloidogenic peptide motifs grafted into an antibody, were described to react with AB fibrils: AB30-39, and with fibrils and oligomers: AB33-42 [2]. However, the blood-brain-barrier, by sheltering the central nervous system from the systemic circulation, is a major bottleneck for peptide- and antibody-based applications. To overcome this limitation, bacteriophages and phage display can be applied [3,4].

We have successfully cloned peptides AB30-39 and AB33-42 into the M13 filamentous phage genome. The binding ability of AB-specific phages towards AB-oligomers was tested ex vivo and in vitro in mouse AD-tissue and AB42 peptide, respectively. Results showed that AB36-39 peptide selectively target AB-protofibrils, but not plaques, in brain slices from AD-model mice and not from wild-type (WT) littermate. In addition, control phage (carrying no AB-selective peptide), did not stain AD or WT tissue.

For future work, this system will be tested in AD-mouse models to assess the inhibition of the oligomeric AB-mediated synaptic loss and memory impairment.

The outcomes will allow the development of novel phage-based tools for the detection/treatment of early AD, with a direct impact on society and well-being, minimizing the economic burden due to late AD diagnosis and consequent medical treatments.