Developing protein nanocages into a vaccine platform against Alzheimer's disease

Andrew Care[1]
[1]*University of Technology Sydney (UTS), Sydney, NSW, Australia*
andrew.care@uts.edu.au

Vaccines targeting Alzheimer's Disease (AD) aim to trigger the immune system to selectively clear causative forms of pathogenic proteins, such as hyperphosphorylated tau (pTau), from the brain and thus improve cognitive ability. However, these vaccines fail to translate into clinic due to a lack of therapeutic efficacy, caused in part by the low immunogenicity of antigens used. To overcome this, we are engineering encapsulin protein nanocages into a modular vaccine platform that enables the display and delivery of multiple pTau antigens to enhance its immunogenicity.

Encapsulins are self-assembling protein nanocages with outer and inner surfaces that can be readily engineered to display and/or package peptide/proteins, thus representing an adaptable scaffold for the rational design of modular vaccines[1-4]. Using the SpyCatcher-SpyTag protein coupling system, pTau antigens were coupled to the outer surface of encapsulins with a high conjugation efficiency. The pTau-displaying encapsulins exhibited robust stability after lyophilisation, eliminating cold-chain dependence. Upon administration of the pTau-displaying encapsulins, C57BL/6 mice generated a significantly higher number of antibodies against pTau compared to mice administered with the pTau antigen alone, and displayed no adverse effects, indicating the functionality and safety of the vaccine (**Fig 1**). Moreover, the pTau-specific antibodies generated in vaccinated mice bound to pathologic pTau in brain tissue isolated from AD-afflicted mice, without binding to brain tissue from healthy normal mice, indicating the specificity of the antibodies.

We are now evaluating the therapeutic efficacy of the vaccine by administering the pTau-displaying encapsulins into a clinically relevant AD mouse model (Tau58) and assessing clearance of pTau from the brain and cognitive behaviour changes.

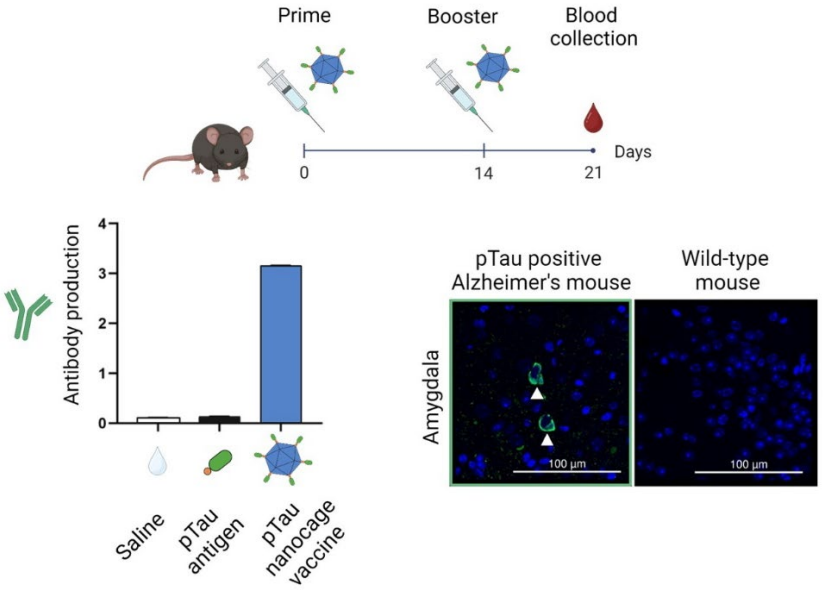

Fig 1: *Construction and administration of a pTau nanocage vaccine into mice led to enhanced generation of pTau-specific antibodies, which demonstrated selective binding to pathological pTau in brain section from AD mice.*

References:

[1]Sandra F., Khaliq NU., Sunna A., Care A. Nanomaterials. **2019** (9) 1329.
[2]Boyton I., Goodchild SC., Diaz D., … Care A. ACS Omega **2021**
[3]Diaz D., Vidal X., Sunna A., Care A. ACS Appl. Mater. Interfaces **2021** (13) 7977-7986.
[4]Rennie C., Sives C., Boyton I., … Care A. *Adv. Therap.* **2024**, 7, 2300360.