

Development of a Novel mRNA Vaccine for Alzheimer's Disease

Alicia K. Yong^{1,2,3}, Lauren Holz^{2,4}, Stewart Fabb⁵, Colin Pouton⁵, Kevin Barnham^{1,2}, Adam Wheatley^{2,4}, Rebecca Nisbet^{1,2,3}

1.The Florey Institute of Neuroscience and Mental Health, Melbourne, VIC, Australia 2.The University of Melbourne, Melbourne, VIC, Australia 3. National Health and Medical Research MIND-AD Centre of Research Excellence; Australia 4.The Peter Doherty Institute for Infection and Immunity, VIC, Australia 5.Monash Institute of Pharmaceutical Sciences, VIC, Australia

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Introduction

Early intervention targeting amyloid- β ($A\beta$) accumulation remains a promising strategy to slow or prevent Alzheimer's disease (AD) progression.¹ As one of the earliest pathological events in AD, $A\beta$ aggregation is thought to drive downstream neurodegenerative processes, making it an attractive target for disease-modifying therapies (Fig 1).² The clinical success of mRNA vaccines has accelerated interest in extending this technology beyond infectious diseases to chronic disorders, including AD, where active immunotherapy targeting $A\beta$ has the potential to modify disease progression. Here, we evaluate novel mRNA vaccine candidates targeting $A\beta$ for the prevention and treatment of AD to determine their capacity to elicit a robust anti- $A\beta$ immune response and inform the preclinical development of mRNA-based immunotherapies (Fig 2).

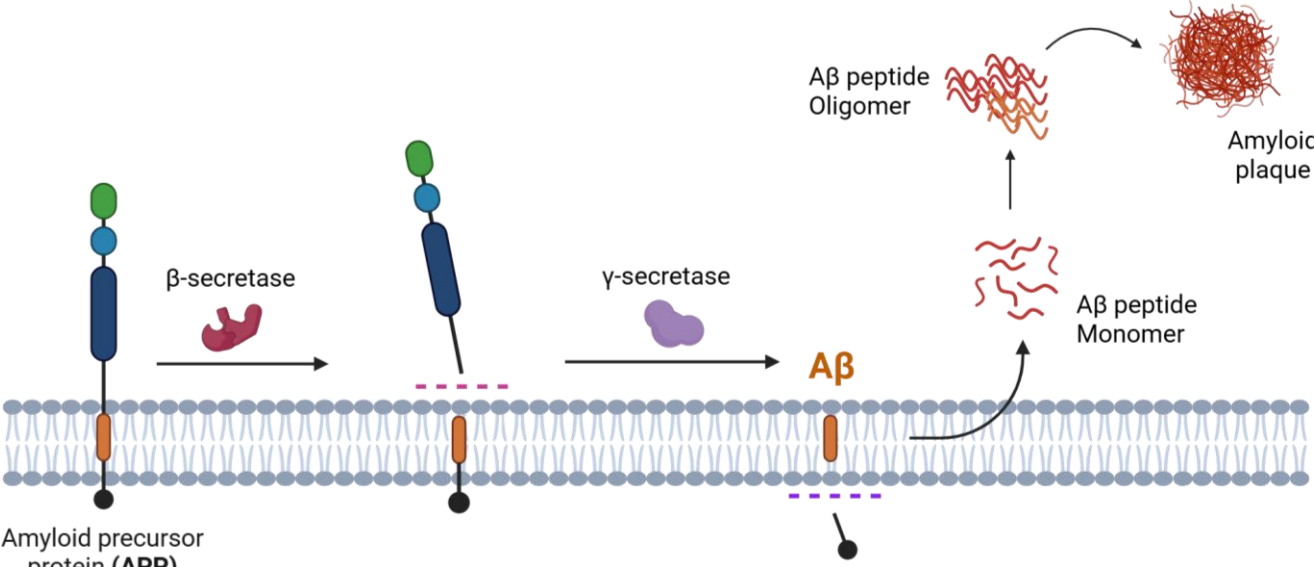


Figure 1. Schematic of the formation of $A\beta$ pathology. Pathology begins with the abnormal cleavage of amyloid precursor protein, which releases monomers that aggregate forming oligomers, and ultimately amyloid plaques. Image created by biorender.com

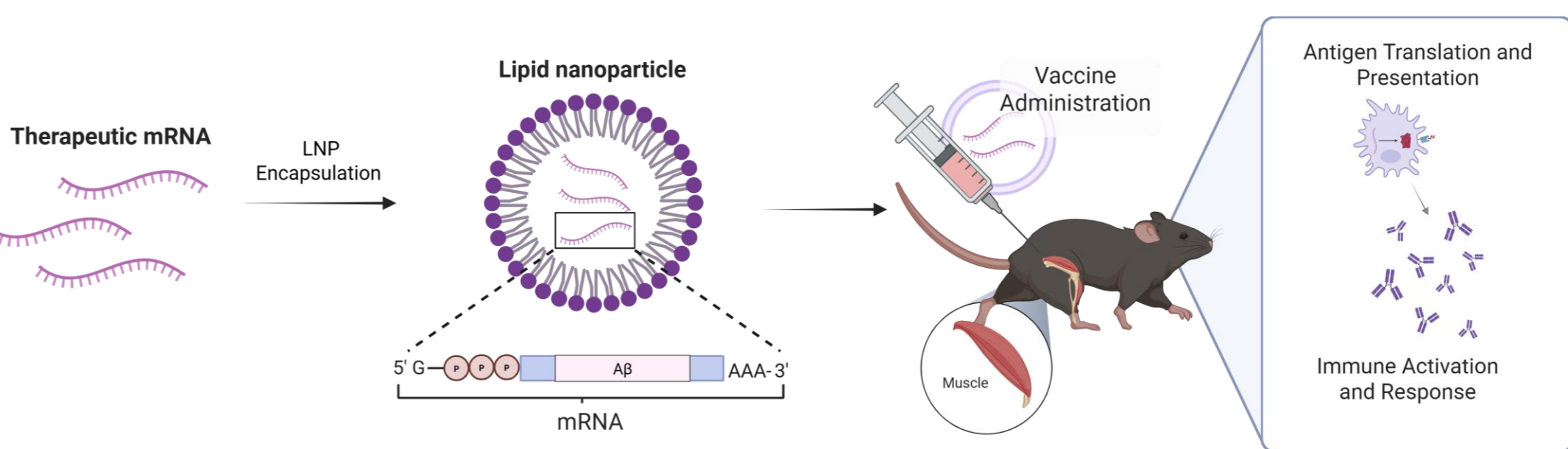


Figure 2. Schematic of synthesis and administration of mRNA vaccine candidates. Graphical diagram depicting mRNA vaccine synthesis, encapsulation and delivery. Therapeutic mRNA is encapsulated into a lipid nanoparticle (LNP) to enhance stability and cellular delivery. Following intramuscular administration (I.M.), the mRNA is translated in vivo, and the antigen is presented to the immune system, eliciting a protective immune response. Image created by biorender.com

1. mRNA vaccination in wild-type mice elicit safe and strong anti- $A\beta$ antibody responses.

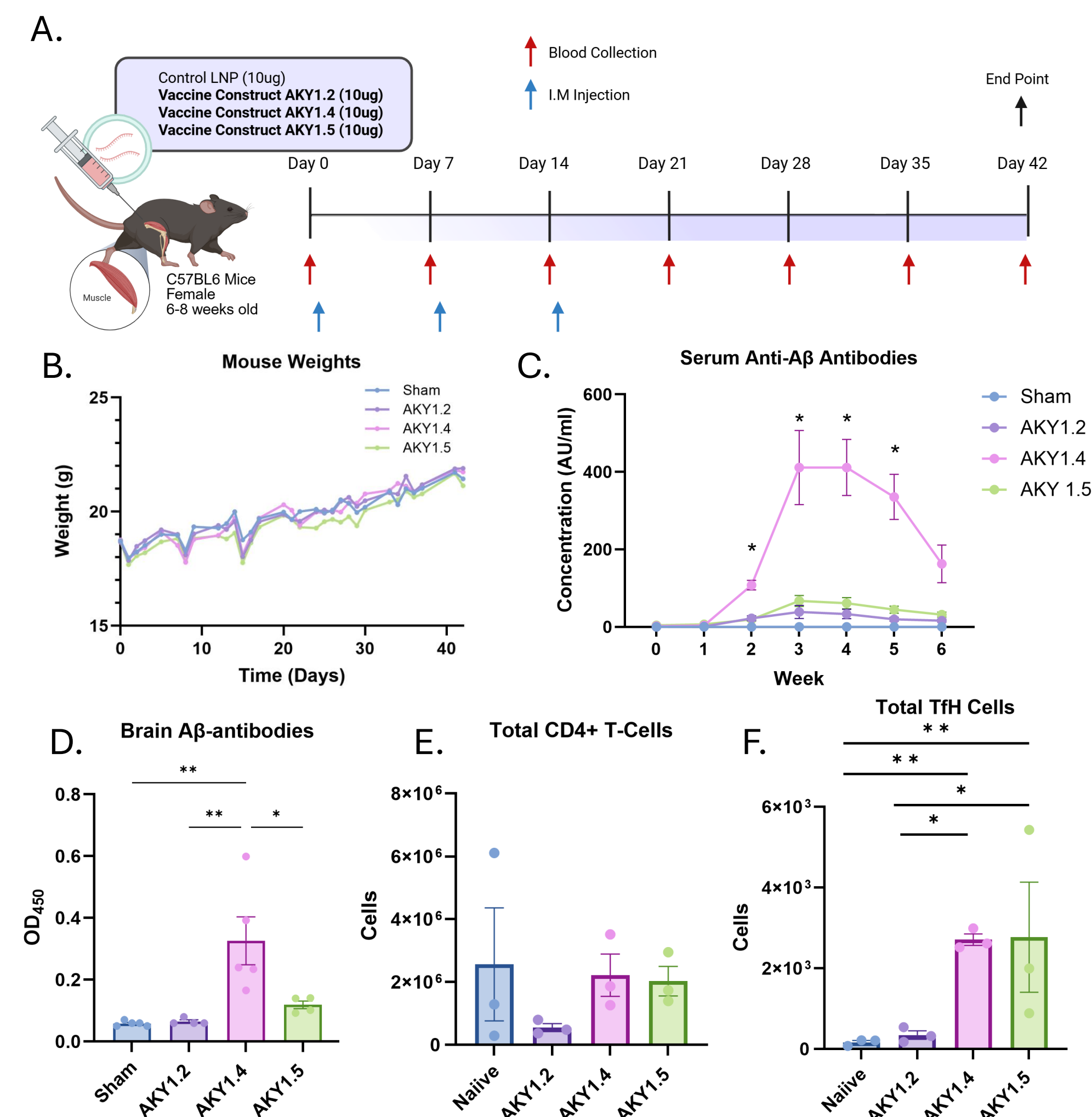


Figure 3. In vivo validation and immunogenicity of AKY constructs in wild-type mice. (A) Treatment schedule to evaluate immune response against AKY vaccine constructs. C57BL/6 female mice (6–8 weeks old) were I.M. vaccinated with 10 μ g mRNA-LNP according to their treatment group (Control/Sham, AKY1.2, AKY1.4, and AKY1.5) ($n = 5$). Mice received three vaccinations, administered once weekly (blue arrows) and were bled weekly (red arrow). (B) Daily monitoring of body weight in vaccinated mice indicated good overall tolerability. (C) Sera collected weekly were analysed to identify the peak antibody response during the vaccination regimen, which occurred at 3–4 weeks. (D) Anti- $A\beta$ antibodies induced by AKY1.4 and AKY1.5 were detected in the brain, demonstrating their capacity for brain penetration. (E) Total CD4+ T cells 7-days post single vaccination showed no significant difference between groups. (F) Total T follicular helper (Tfh) cell numbers 7-days after a single vaccination, showed increased Tfh cell numbers in AKY1.4 and AKY1.5 groups. Mean $\pm$ SEM, analysed with one-way ANOVA. (* $P < 0.05$) (** $P < 0.01$).

2. Anti- $A\beta$ antibodies from serum of vaccinated wild-type mice bind to $A\beta$ aggregates in APP/PS1 brain tissue.

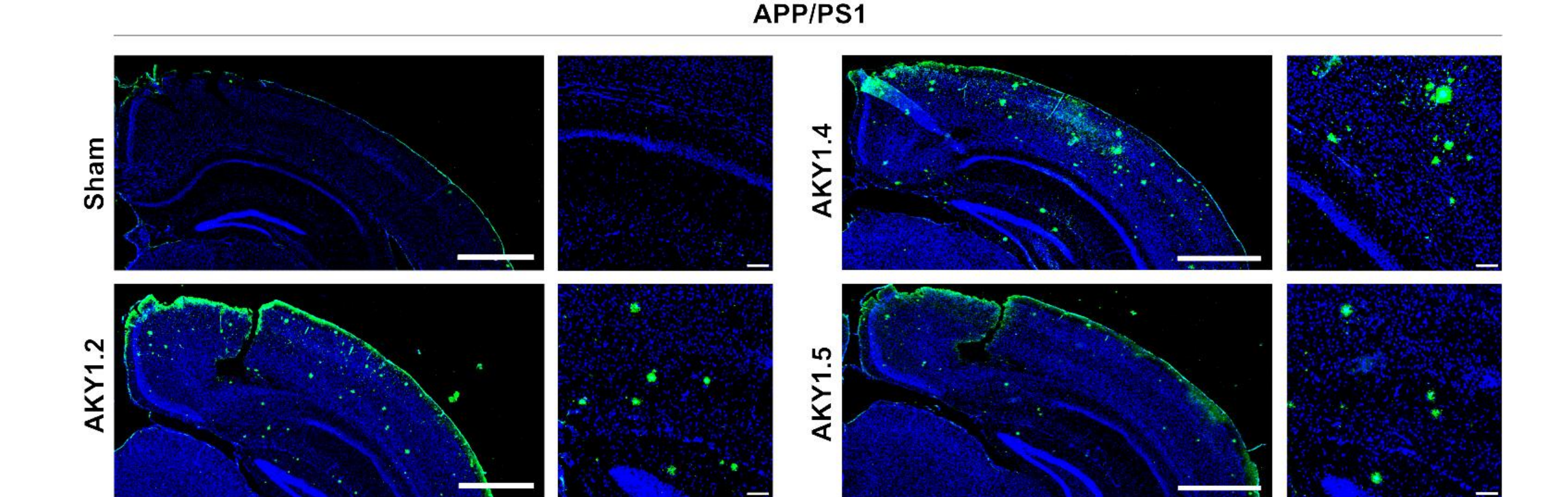


Figure 4. AKY mRNA vaccinated mice elicit anti- $A\beta$ antibodies that bind to $A\beta$ aggregates in 6-month-old APP/PS1 mice brains. 6-month-old APP/PS1 mice brain tissue was collected and probed with serum from vaccinated wild-type mice. This demonstrated successful detection of $A\beta$ aggregates (green). DAPI (blue) represent cell nuclei. AKY1.2 and AKY1.4 demonstrated stronger aggregate binding. Scale bars: 1000 μ m, 100 μ m.

3. Successful immune response in APP/PS1 transgenic mice following vaccination with AKY mRNA vaccine constructs.

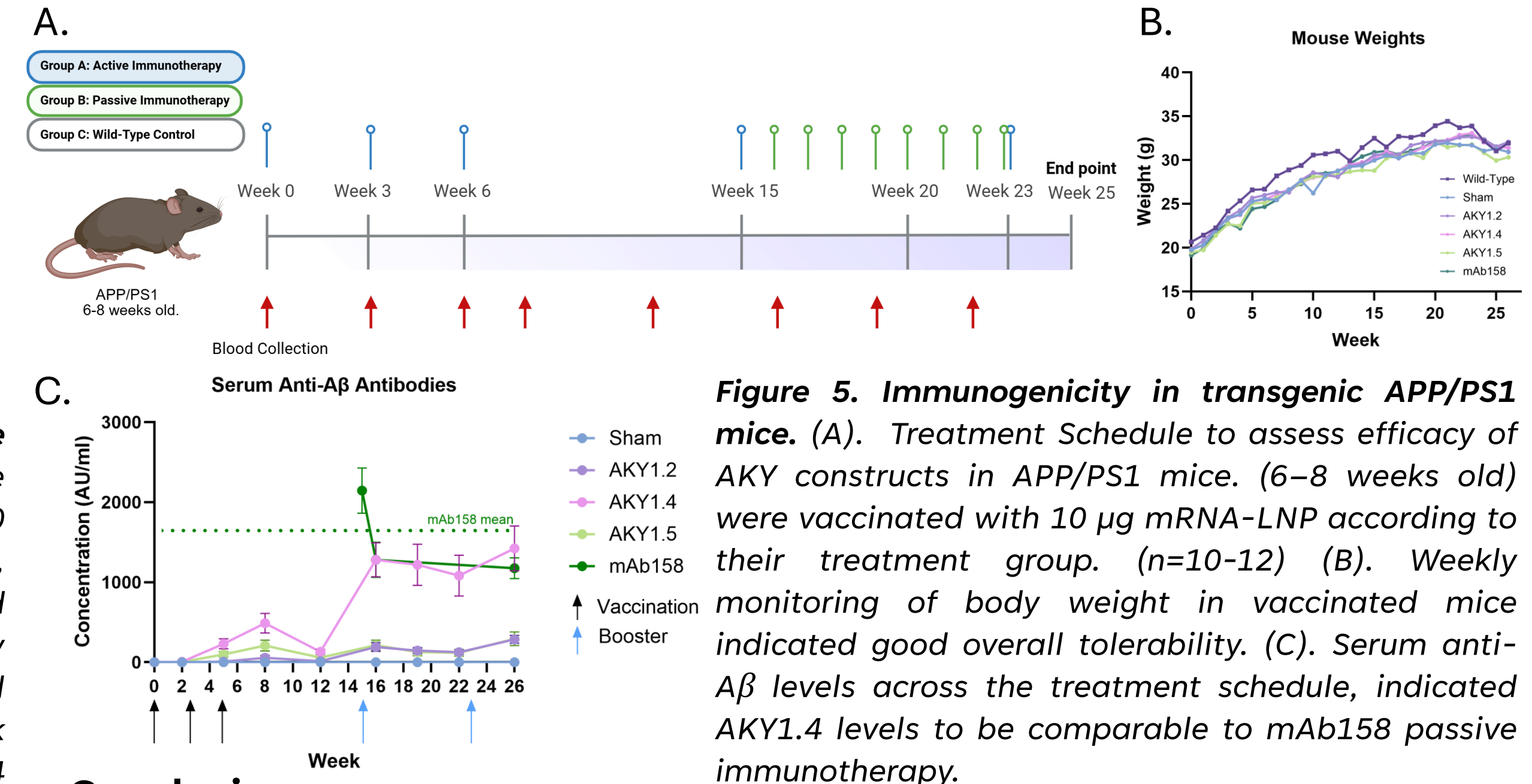


Figure 5. Immunogenicity in transgenic APP/PS1 mice. (A). Treatment Schedule to assess efficacy of AKY constructs in APP/PS1 mice. (6–8 weeks old) were vaccinated with 10 μ g mRNA-LNP according to their treatment group. ($n=10-12$) (B). Weekly monitoring of body weight in vaccinated mice indicated good overall tolerability. (C). Serum anti- $A\beta$ levels across the treatment schedule, indicated AKY1.4 levels to be comparable to mAb158 passive immunotherapy.

Conclusion

Here, we successfully synthesized mRNA vaccine constructs and demonstrated that all candidates elicited a measurable immune response. Among them, AKY1.4 induced the strongest antibody production, while both AKY1.4 and AKY1.5 generated antibodies capable of penetrating the brain, highlighting their relevance for neurodegenerative targets. Collectively, these results underscore the potential of mRNA vaccines as a strategy for the treatment and prevention of AD and other proteinopathies. By providing a foundation for further preclinical evaluation, this study advances the development of a safe and effective vaccine with the potential to transform AD therapeutics.



Alicia Yong
✉ alicia.yong@florey.edu.au
🌐 linkedin.com/in/aliciakyong



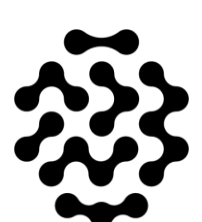
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