saRNA Immunisation Accelerates Antibody Discovery Against Challenging GPCR Targets

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Background: Monoclonal antibodies (mAbs) have transformed treatment across many diseases because of their high specificity and affinity for cell-surface proteins. Despite this success, most approved mAb therapies target single-pass transmembrane proteins. In contrast, complex multi-transmembrane proteins (CMPs), including G protein-coupled receptors (GPCRs) and ion channels, remain among the most valuable yet challenging therapeutic targets. Progress in this area has been limited by the difficulty of expressing and purifying these proteins in stable, native-like forms. Recent advances in RNA-based immunisation offer a potential solution. mRNA vaccines have been shown to induce strong antibody responses in both mice and humans and enable rapid iteration of antigen design, helping accelerate the path from target selection to validation. Next-generation RNA platforms, such as self-amplifying RNA (saRNA), may further enhance immunogenicity while requiring lower doses. Method: Here, we evaluated RNA immunogen delivery within a hybridoma antibody discovery workflow and compared it with conventional protein-based immunisation using a complex 7-transmembrane GPCR target. We used a prime-boost strategy for RNA/LNP immunisation and multiple boosts for protein immunisation coupled with b-cell isolation and profiling. Results: The mRNA immunisation generated a threefold increase in isolated B cells relative to protein immunisation. The saRNA group produced more than tenfold higher responses overall while using the same streamlined mRNA dosing regimen. Subsequent antibody isolation and screening identified 122 unique binders to the target, including 14 cross-reactive binders recognizing both human and cynomolgus monkey receptors. Conclusion: These findings suggest that saRNA-based immunisation may provide a faster, more effective route for antibody generation against difficult membrane protein targets, with the potential to reduce timelines from target selection to immunisation and B-cell isolation by up to tenfold