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# Antibody Discovery for Non-Small Cell Lung Cancer Using Distinct Phage Display Strategies

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Lung cancer remains the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of cases. Although antibody-based therapies targeting tumour-associated antigens (TAAs) or immune checkpoints have improved clinical outcomes, tumour heterogeneity and off-target toxicity continue to limit the development of selective therapeutic agents. This study investigated distinct phage display strategies for the discovery of canine single-chain variable fragment (scFv) antibodies with potential relevance to NSCLC, using both target-directed selection against recombinant TAAs and target-agnostic whole-cell biopanning.

In the target-directed approach, scFv antibodies binding recombinant TAAs were isolated and validated by enzyme-linked immunosorbent assay (ELISA), and their sequences were characterised by Sanger sequencing. A lead candidate was subsequently expressed in multiple full-length antibody formats for further evaluation. While the selected antibodies bound the recombinant antigen used during biopanning, flow cytometric analysis demonstrated no detectable binding to cell lines expressing the corresponding native cell-surface antigen. These findings demonstrate that binding to a recombinant antigen does not necessarily predict recognition of the corresponding native cell-surface antigen and emphasise the importance of validation in physiologically relevant cellular systems.

Separately, subtractive whole-cell biopanning was performed using human alveolar epithelial cells (huAECs) for negative selection and H460 NSCLC cells for positive selection. Flow cytometry demonstrated enrichment of phage pools and individual scFv clones that bound H460 cells while showing no detectable binding to huAECs, indicating preferential reactivity towards NSCLC cells following selection.

Collectively, these findings demonstrate the strengths and limitations of distinct phage display strategies for NSCLC antibody discovery. Selection against recombinant antigens identified antibodies that did not recognise the corresponding native cell-surface target, whereas whole-cell biopanning enriched for clones with preferential binding to NSCLC cells. These results highlight the importance of validating antibody candidates in native cellular systems and support whole-cell selection for identifying physiologically relevant binders.