1186 ENGINEERING BISPECIFIC DUAL-ANTAGONIST ANTIBODIES FOR NOVEL CANCER THERAPIES

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Background Bispecific antibodies have the potential to unlock novel biology and elicit unique functionalities. There is still an unmet need for effective and selective therapeutics for the cancer treatment. Here, we present the discovery of diverse panels of lead-quality antibodies against two cancer targets and reformatting them into bispecifics for the development of dual antagonist therapeutic antibody.

Methods Binders derived from immunizing AlivaMab® Mouse were engineered as bispecific antibodies with Fab and scFv as substrates using standard knob-into-hole heterodimerization approach. The antibodies were characterized by ELISA and FACS assays for target binding and blocking. Target dependent inhibition of cell proliferation was also investigated. Developability assessment for expression, purity, thermal stability, polyspecificity, and accelerated stability was performed.

Results We demonstrated that dual-antagonist bispecific antibodies are capable of blocking both targets, resulting in inhibition of cell proliferation when bound to two target antigens and showed superior activity to clinical comparators. Selected lead antibodies also met the developability acceptance criteria and showed good stability in serum and accelerated stability studies.

Conclusions A broad panel of molecularly diverse and highly potent target specific antagonist binders were discovered that can bind to the target in both cell surface and soluble forms. Function-first screening of the bispecific antibody matrix delivered quality leads as validated by cell-based assays. Early developability profiling showed that antibody format, scFv domain order and scFv sequence matter for the product quality, leads with high expression titer, purity, stability, and potency were selected to move forward.

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