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Engineering Cellular Interactions in Ligand Discovery and Cancer Immunotherapy

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66-110

Abstract: Engineered protein ligands have had profound impacts in the clinical setting. These molecular targeting agents greatly benefit patients through enhanced detection of a variety of diseases and by providing diverse therapeutic options for cancer, autoimmune diseases, infectious diseases, and endocrine disorders. Advances in genomic and proteomic discovery methods continue to grow the repertoire of clinically relevant targets, increasing the demand for new engineered ligands. High-throughput screening strategies, such as yeast surface display selections, can meet these challenges through their proven effectiveness in rapid discovery and evolution of ligands against a variety of target molecules. These targeted biomarkers are often transmembrane proteins, which are difficult to work with in an aqueous environment due to their hydrophobic transmembrane domains. Thus, ligand selections are often carried out against the recombinant soluble extracellular domains of these biomarkers. These molecules can be poor models for their respective full length proteins for a variety of reasons, leading to the generation of ligands that bind these soluble domains strongly and specifically, but have diminished or abolished activity when exposed to the cellular form of the biomarker. Improved molecular engineering techniques are clearly needed.

The work presented here aims to provide a new toolkit for ligand selection that overcomes this hurdle and advances the understanding of cell-cell interactions through developing a suite of techniques for yeast surface display selections directly against mammalian cell monolayers. Approaches for binder enrichment, non-specific binder depletion, and affinity-based selection are rigorously explored and optimized. Applications of these techniques result in generation of ligands against B7-H3 (CD276) for molecular ultrasound imaging of tumor vasculature and EpCAM for tumor targeting of multivalent nanorings. Lessons learned in engineering cellular interactions are applied to affinity modulation of chimeric antigen receptors, enlightening the impacts of the affinity-avidity interplay in treatment of hematologic malignancy with engineered T cells. Taken together, this work demonstrates the power of protein engineering to both engineer functional molecules to meet a variety of clinical challenges and further our fundamental understanding of cell-cell interactions and their impact on resulting biological processes.