Docket #: S24-434

A Cell-based Peptide Display Platform for Discovering Potent Modulators of Peptide-activated Mammalian Receptors

New publication! Read the inventors' newly published *Cell Genomics* article for this technology (2025): "A peptide display system identifies a potent mutant β-melanocyte-stimulating hormone agonist of melanocortin-4 receptor."

Stanford scientists have developed a high-throughput cell-based peptide display platform for screening peptide variants that modulate G protein-coupled receptors (GPCRs). This system links GPCR activation to specific peptides within a single cell, overcoming the limitations of traditional resource-intensive methods. The platform's effectiveness was demonstrated by screening β-melanocyte-stimulating hormone (β-MSH) variants, identifying mutations with significantly enhanced melanocortin-4 receptor (MC4R) activation potential compared to native peptides.

G protein-coupled receptors (GPCRs) regulate numerous biological functions and account for over 34% of FDA-approved drugs. While most targeted GPCRs respond to small molecules, interest in peptide-activated receptors is growing due to their critical roles in human physiology. For example, MC4R regulates energy balance and appetite when activated by β-MSH, with mutations in this pathway causing monogenic obesity in humans. Despite their importance, existing methods for studying GPCR-peptide interactions remain limited - phage display often identifies non-functional binders, while traditional cell-based assays are constrained by scale and cost. These limitations have hampered systematic investigation of peptide-receptor interactions and the discovery of optimized peptide modulators for therapeutic applications.

Using this peptide display platform, a comprehensive screen of β-MSH peptide variants was successfully conducted, identifying several peptides that significantly impact MC4R activation. Most importantly, a novel mutant peptide was discovered that substantially enhances MC4R activation compared to the wild-type β-MSH, representing a potential breakthrough for therapeutic development. The platform efficiently integrates oligonucleotide library synthesis with a cell-surface peptide display system and an intracellular reporter, enabling direct functional readout of GPCR activation within a single cell. It successfully yielded optimized peptide variants with improved receptor activation properties, advancing drug discovery and offering promising therapeutic avenues for conditions like obesity. Consequently, this innovative approach enables higher throughput screening while minimizing workload for hit identification.

Stage of Development:
Preclinical – *in-vitro* data
Continued research – Improvement of the screen platform and testing it with other GPCRs

Applications

- High-throughput screening of peptide libraries for activation of various receptors
- Identification of novel peptide modulators with enhanced receptor activation potential
- Development of optimized peptide variants for therapeutic applications
- Clinical application of enhanced peptide variants for treating MC4R-related conditions

Advantages

- Platform enables direct functional readout of receptor activation within a single cell
- System provides significantly higher throughput than traditional peptide screening methods
- Platform minimizes false positives by directly linking peptides to functional outcomes

- Approach reduces time and resource requirements for peptide drug discovery
- Technology flexibly adapts to different receptor-peptide interaction studies

Publications

- Lin et al., A peptide display system identifies a potent mutant β-melanocyte-stimulating hormone agonist of melanocortin-4 receptor, *Cell Genomics* (2025). DOI: 10.1016/j.xgen.2025.100988

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