

# DNA-Encoded Libraries and Display Technologies Empower Early Discovery of Peptide Drugs and Peptide-Based Delivery Tools

# WuXi Biology

Wanfa Yang<sup>1</sup>, Rhys Taylor<sup>2</sup>, Jin Li<sup>1</sup>, Hui Fang<sup>1</sup>, Qiaoqiao Zhu<sup>1</sup>, Wenjing Li<sup>1</sup>, Jing Wen<sup>1</sup>, Yan Ping<sup>1</sup>, Wen Luo<sup>1</sup>, Yage Liang<sup>1</sup>, Jason Deng<sup>2</sup>, Zhongyao Ma<sup>1</sup>, Weiren Cui<sup>1</sup>, Qi Zhang<sup>1</sup>, Alex Satz<sup>3</sup>, Letian Kuai<sup>1</sup>, Wenji Su<sup>1</sup>  
1. WuXi Biology, WuXi AppTec, Shanghai, China. 2. WuXi Biology, WuXi AppTec, Natick, MA, USA. 3. Crelux GmbH – A WuXi AppTec Company, Gräfelfing, Germany.

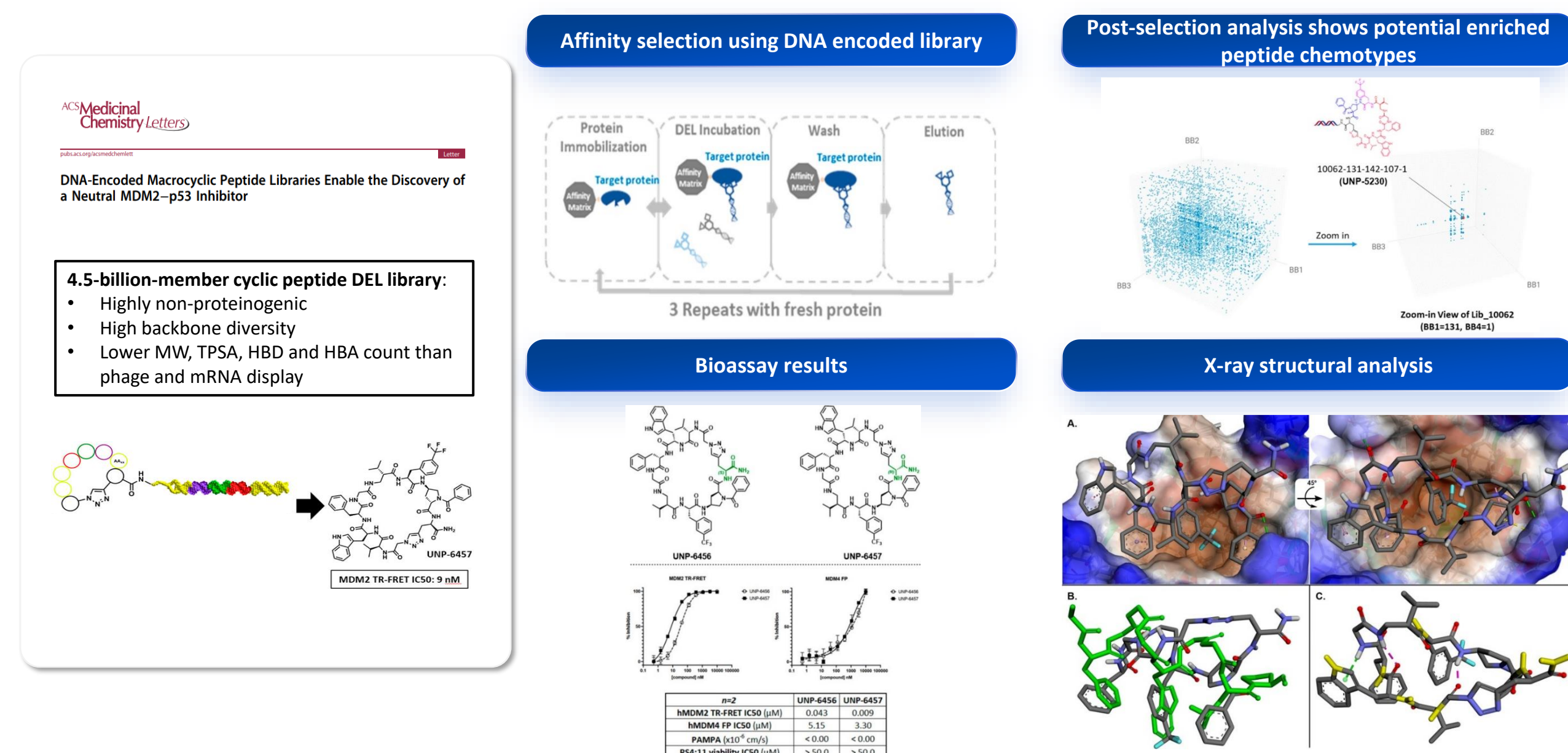
## Abstract

Peptide therapeutic discovery is experiencing a resurgence, particularly for challenging, historically “undruggable” targets. WuXi AppTec is leading the way in this field with cutting-edge technologies and platforms. Traditional phage display, while cost-effective and providing substantial library diversity, is limited by its reliance on only the 20 natural amino acids, resulting in restricted chemical diversity. In response, we have developed our mRNA display capabilities, which surpasses phage display in robustness with macrocycles up to 20 amino acids long. Currently, this service uses only natural amino acids, but we plan to incorporate unnatural amino acids starting in 2026.

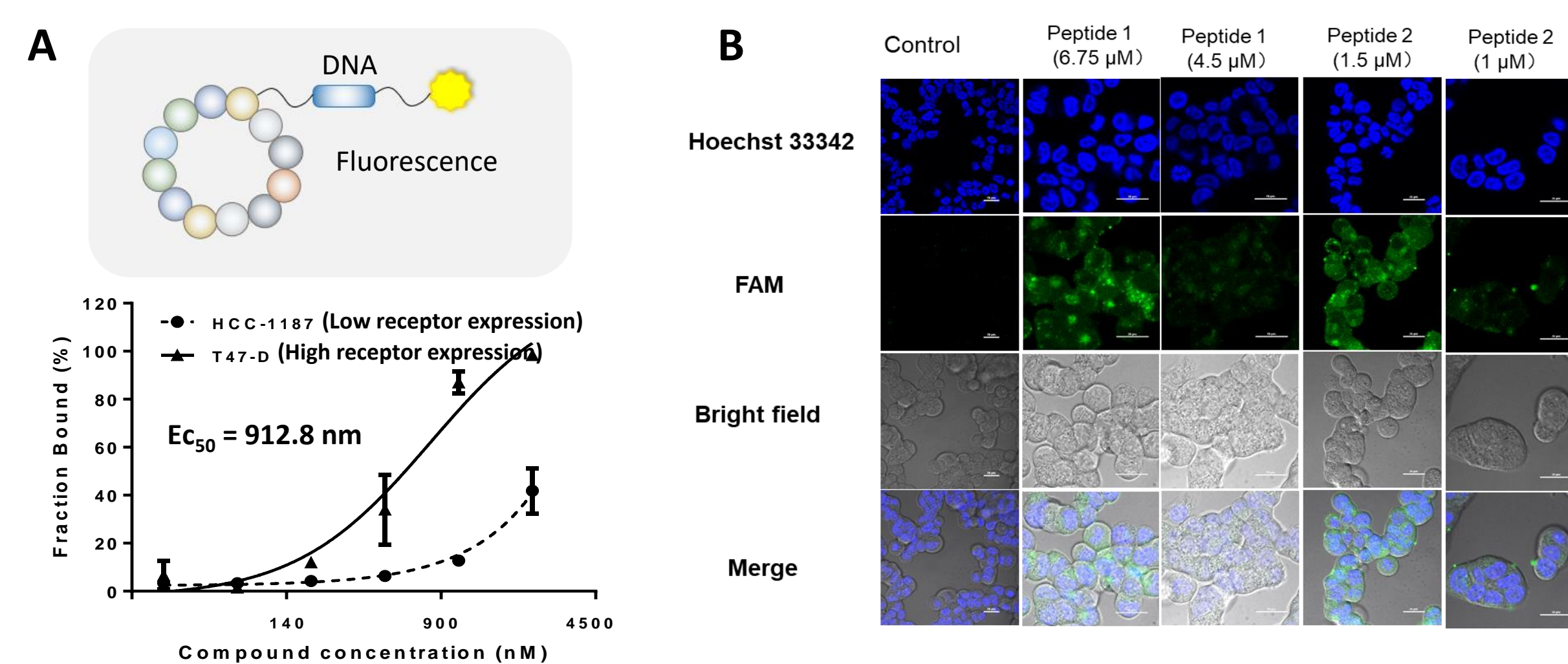
Additionally, our peptide DNA-encoded library (DEL) service provides an alternative approach, leveraging unnatural amino acids to generate hundreds of billions of linear and cyclic peptide-like molecules. These DEL macrocycles offer broader chemical diversity and improved physicochemical properties compared to traditional peptide libraries, with smaller ring sizes (4-12 amino acids) and innovative cyclization strategies, beyond disulfide and thiol-ether bonds, such as the ‘click’ reaction. Conversely, we can also design a focused peptide-DEL library based on an initial phage or mRNA-Display screen with up to 4 sites to include any of our 1400+ validated natural and unnatural amino acids, and diverse cyclization strategies can be used. In our poster, we demonstrate the effectiveness of our technologies for discovering peptides including 1) discovered both orthosteric and allosteric peptide binders with single-digit nM binding via mRNA display, 2) identified a 9 nM cyclic inhibitor of the MDM2-p53 interaction through peptide DEL, 3) discovered potential tumor cell-specific peptide ligands that are being explored for targeted delivery of payloads via oligonucleotides or radioisotopes, 4) Peptide DEL and mRNA display show a synergy both in peptide discovery and hit-to-lead optimization.

## Case Studies for Peptide DEL

### I. Protein-protein interaction: MDM2-p53 inhibitor

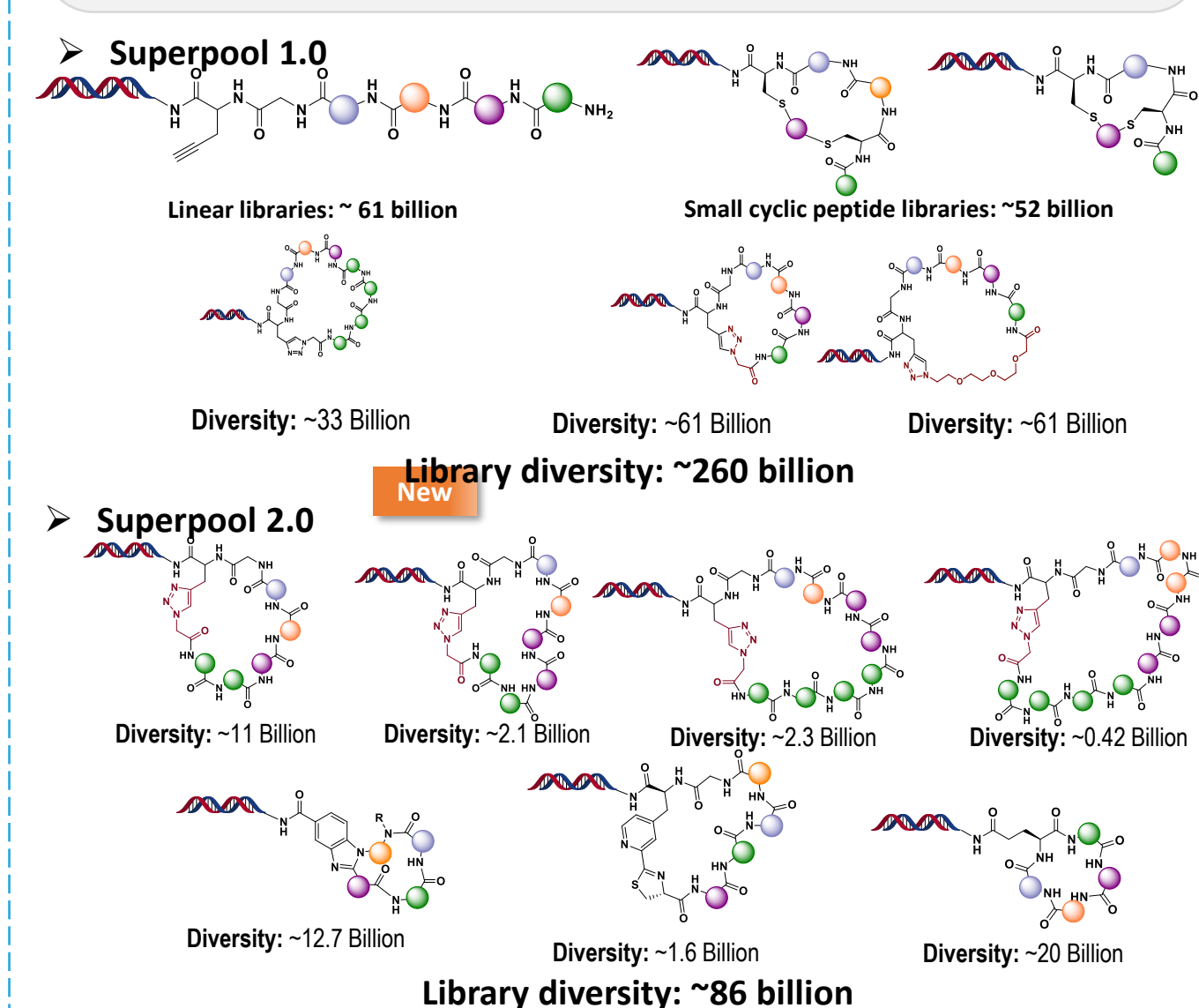


### II. Discovery of tumor cell-specific peptide ligands

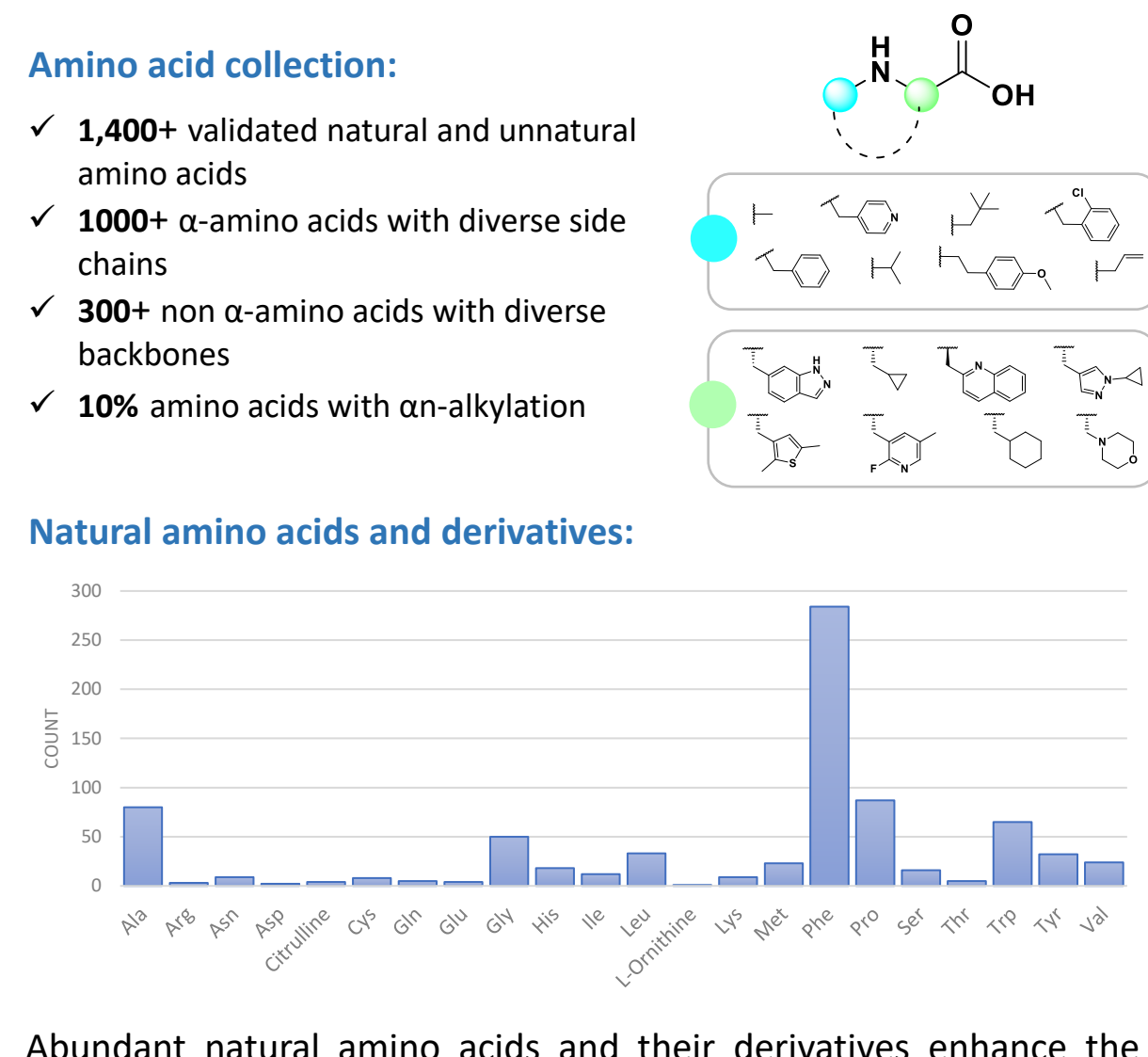


## Off-The-Shelf & Highly Customizable Peptide Libraries

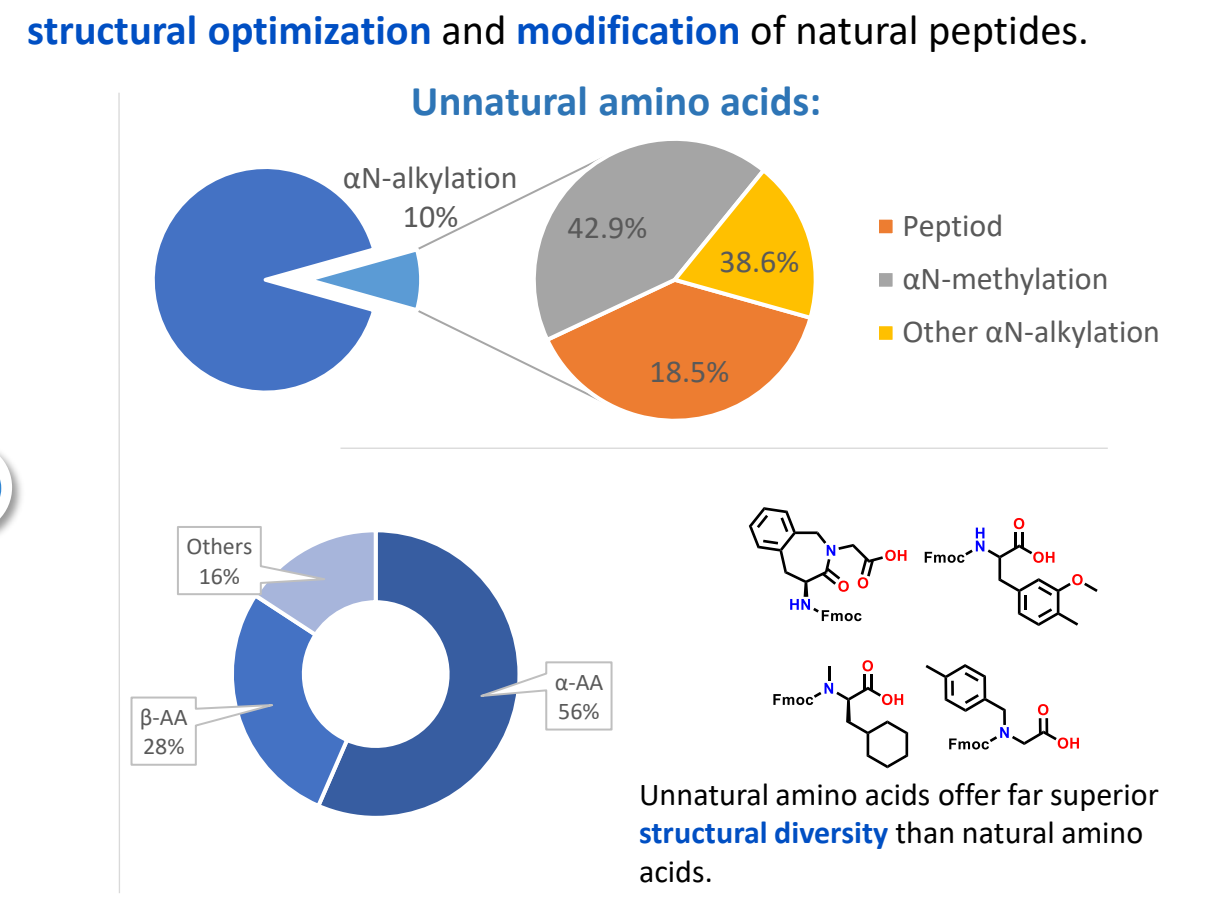
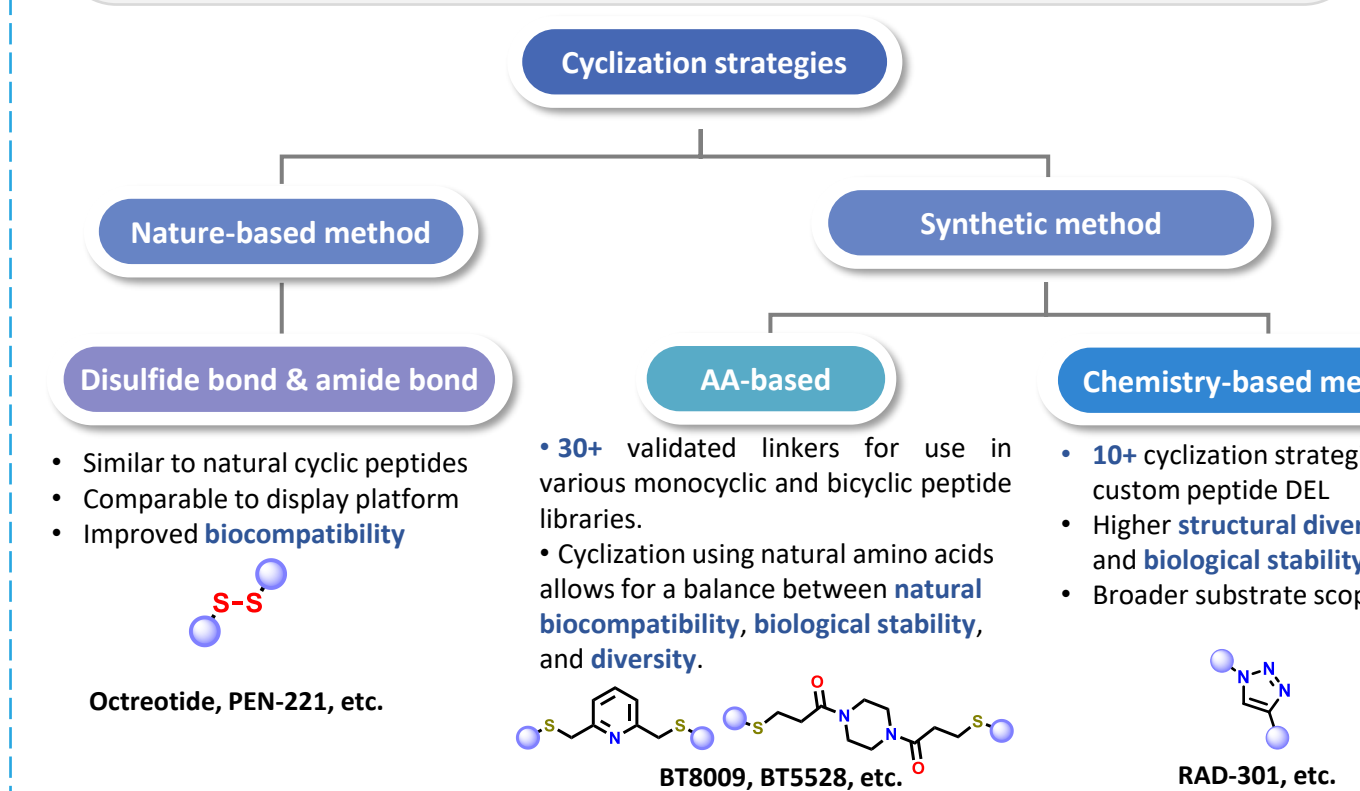
### Off-the-shelf peptide DEL (PeptideDEL 2.0)



### Amino acid selection for custom peptide DEL

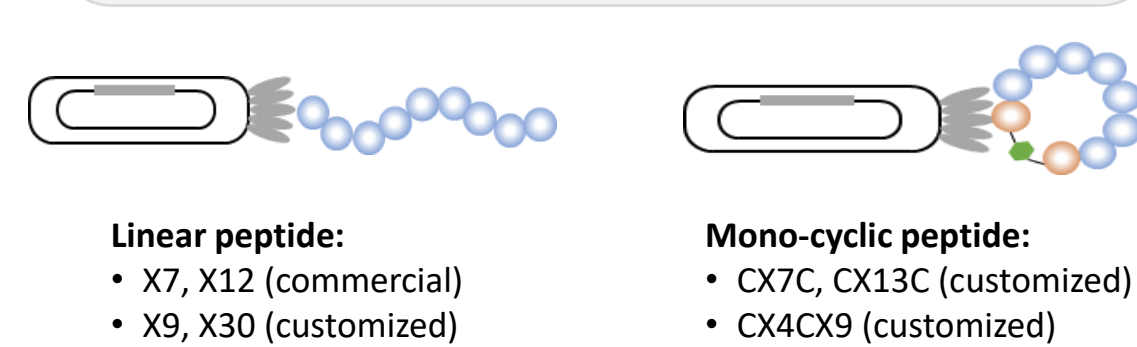


### Cyclization strategies for custom peptide DEL

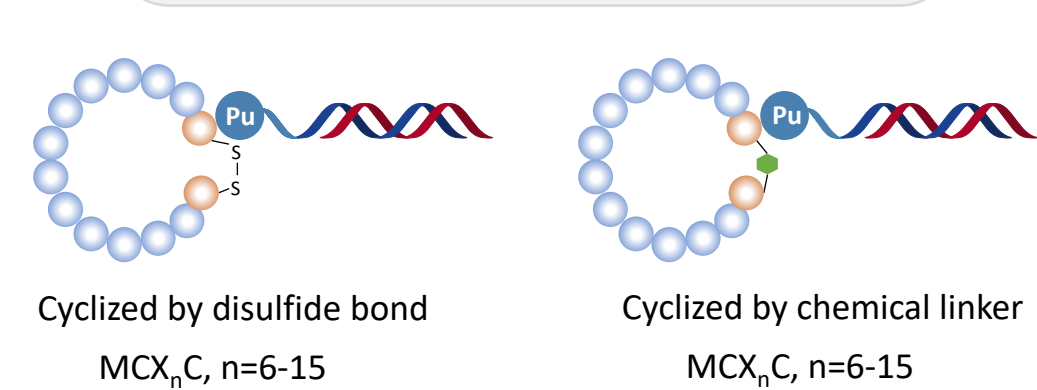


## Off-The-Shelf Libraries for Phage Display & mRNA Display

### Phage display

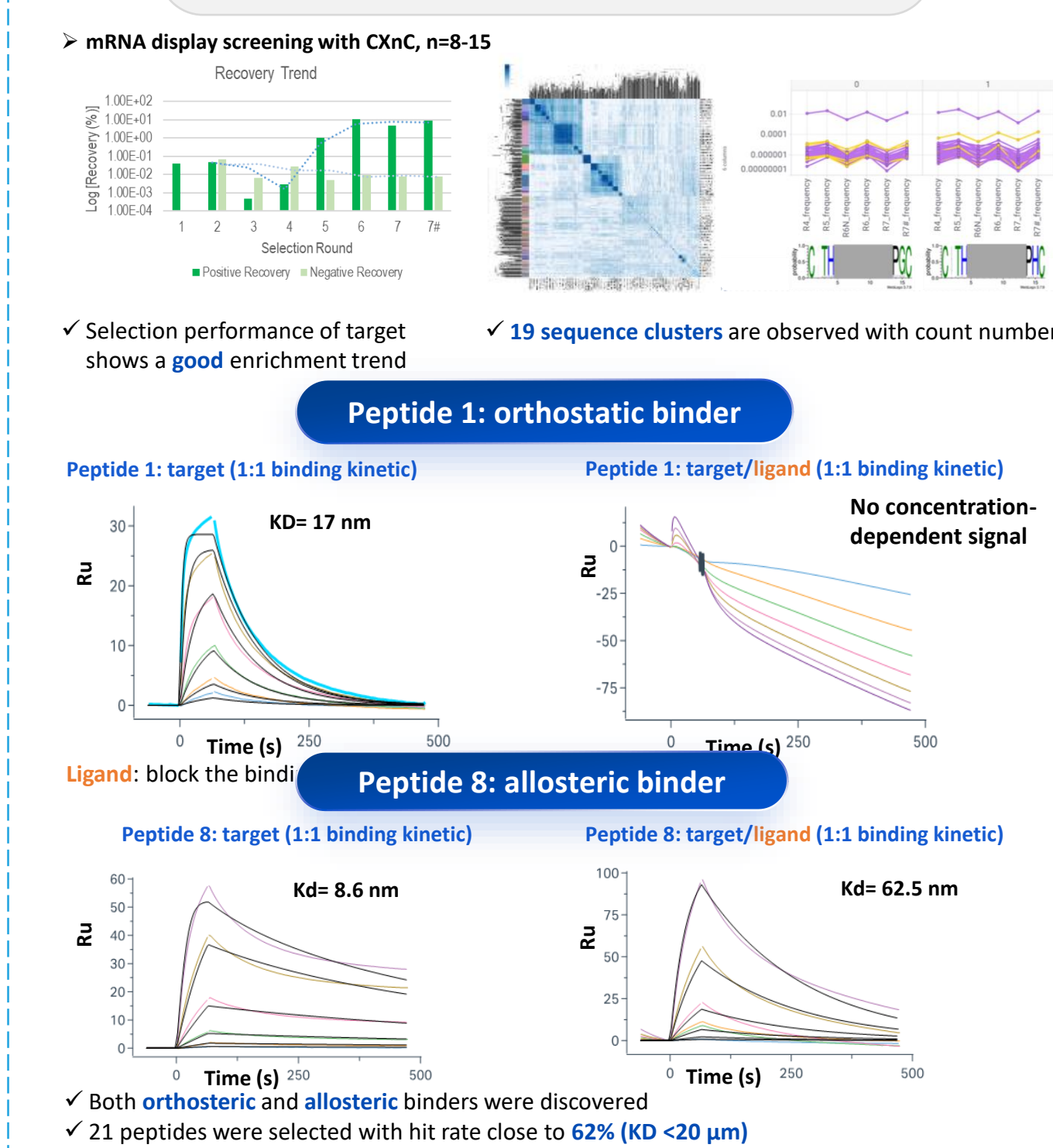


### mRNA display

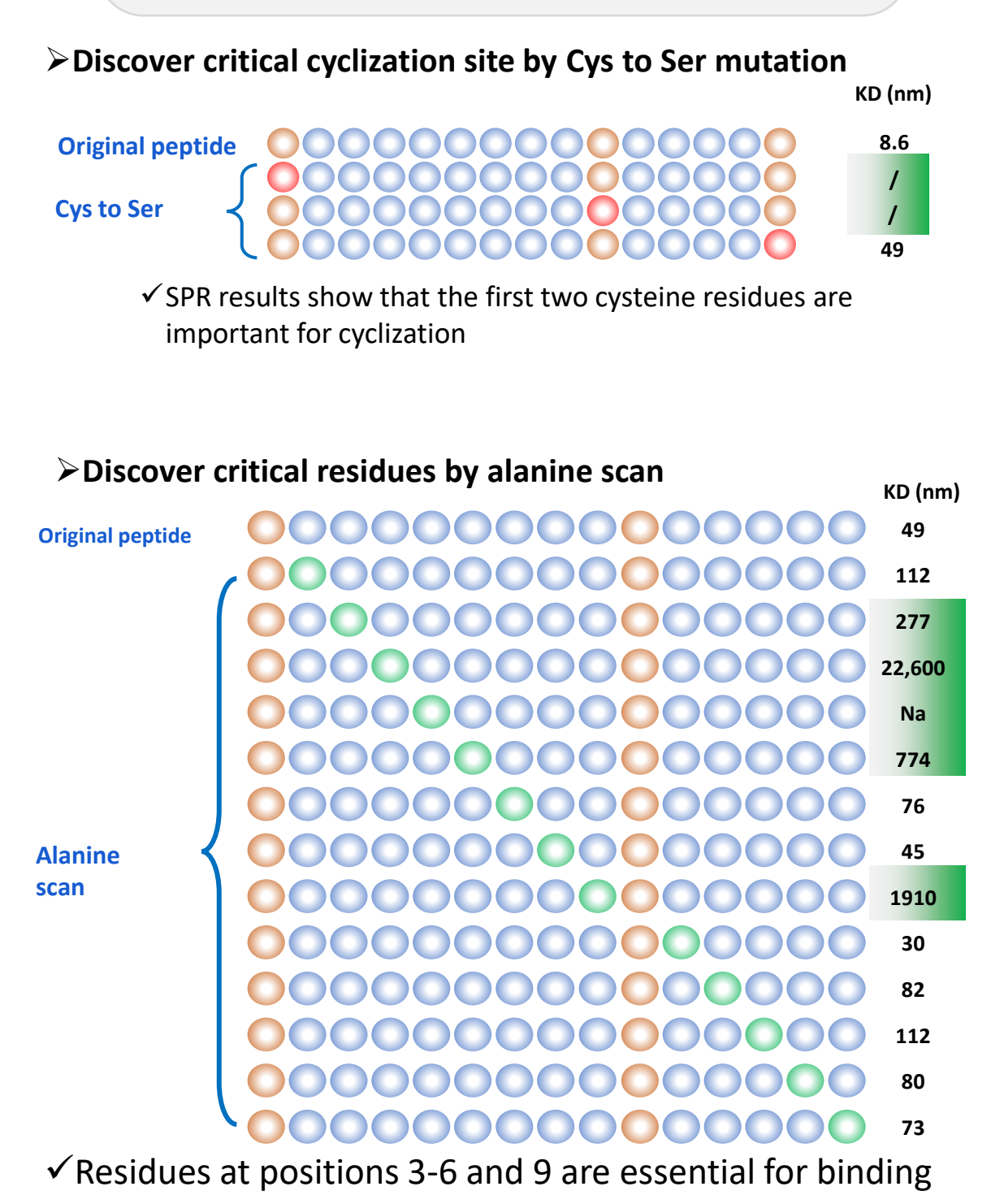


## Case Studies for mRNA Display

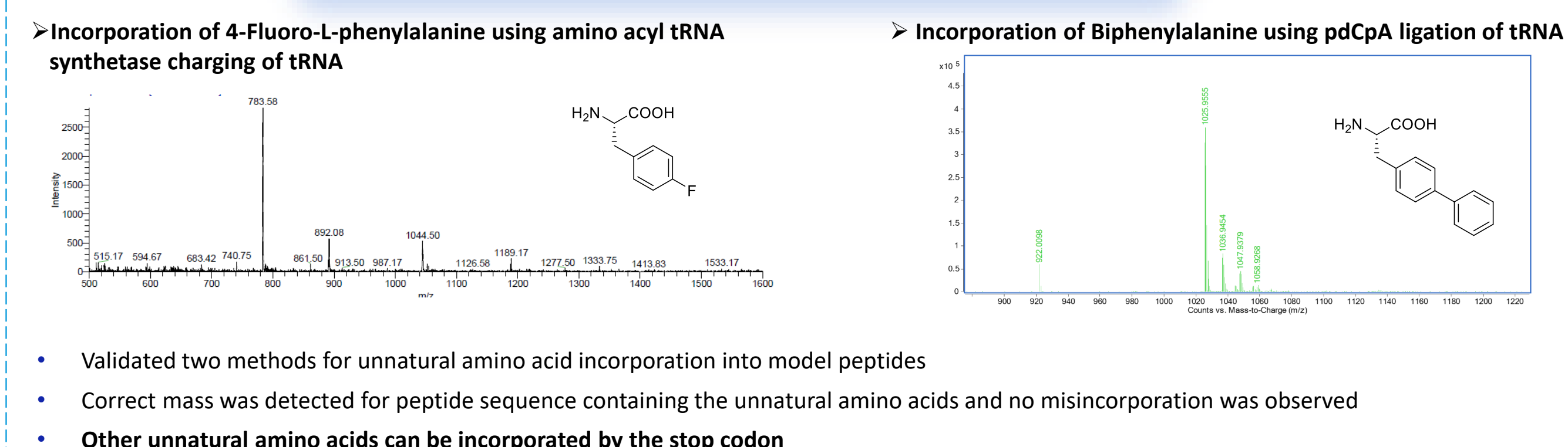
### Peptide discovery using mRNA display



### Peptide optimization services

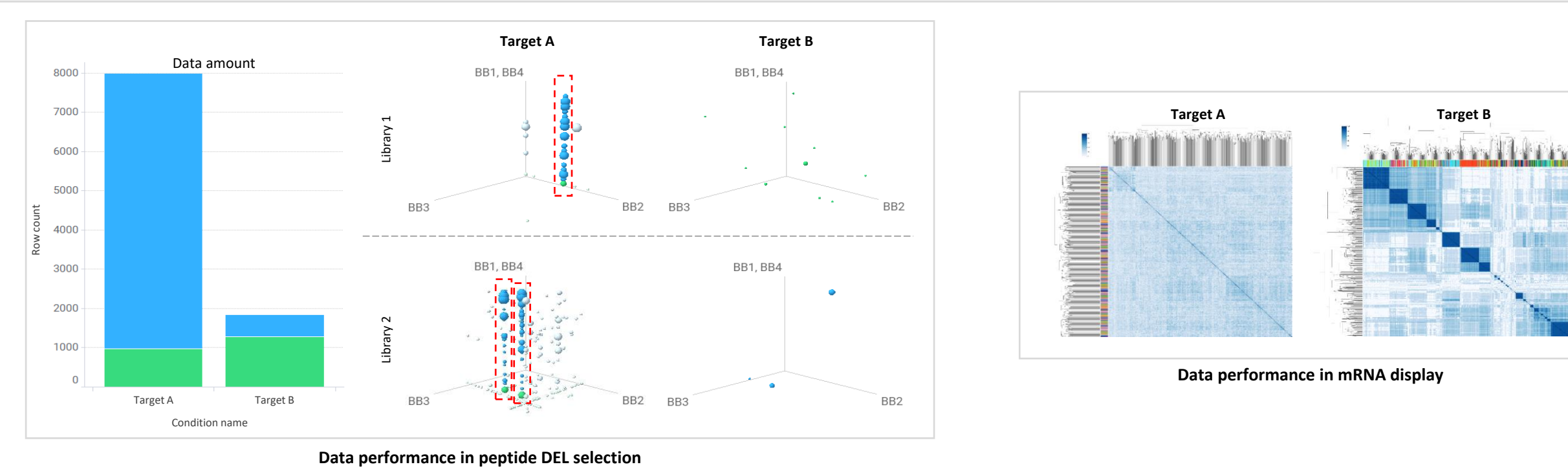


### Incorporation of unnatural amino acids by reprogramming

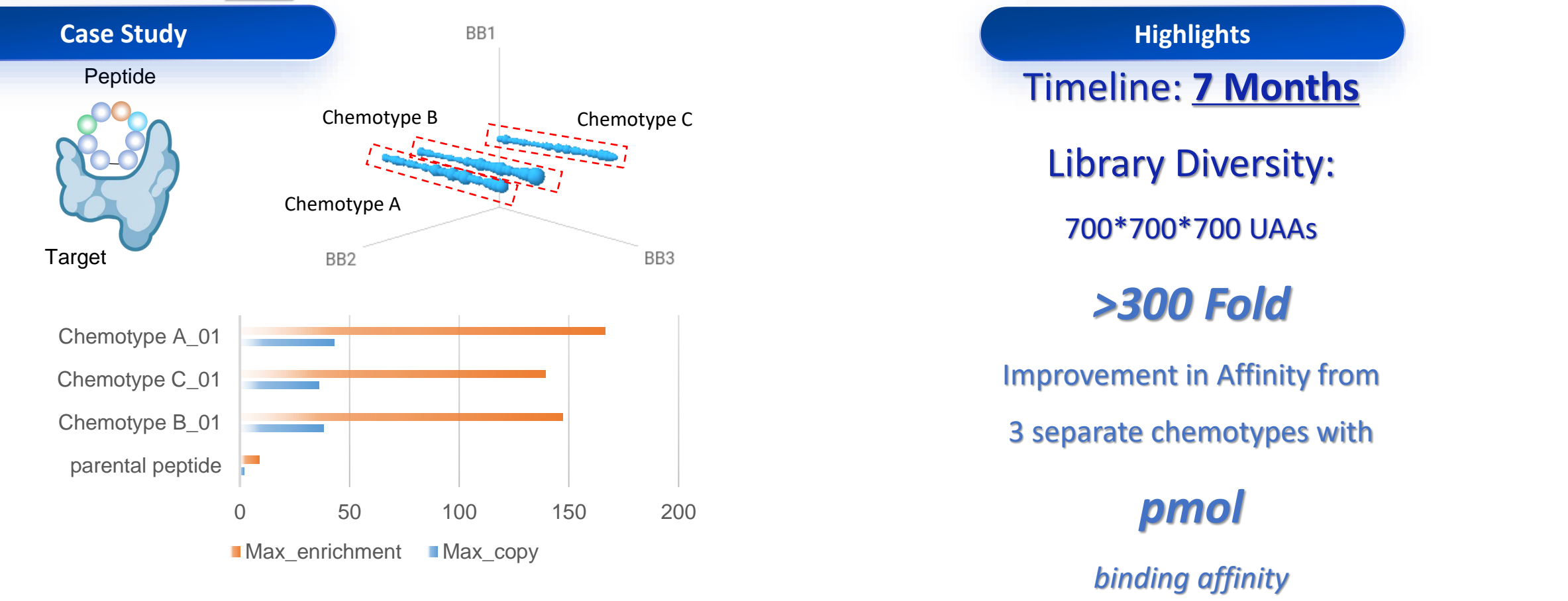
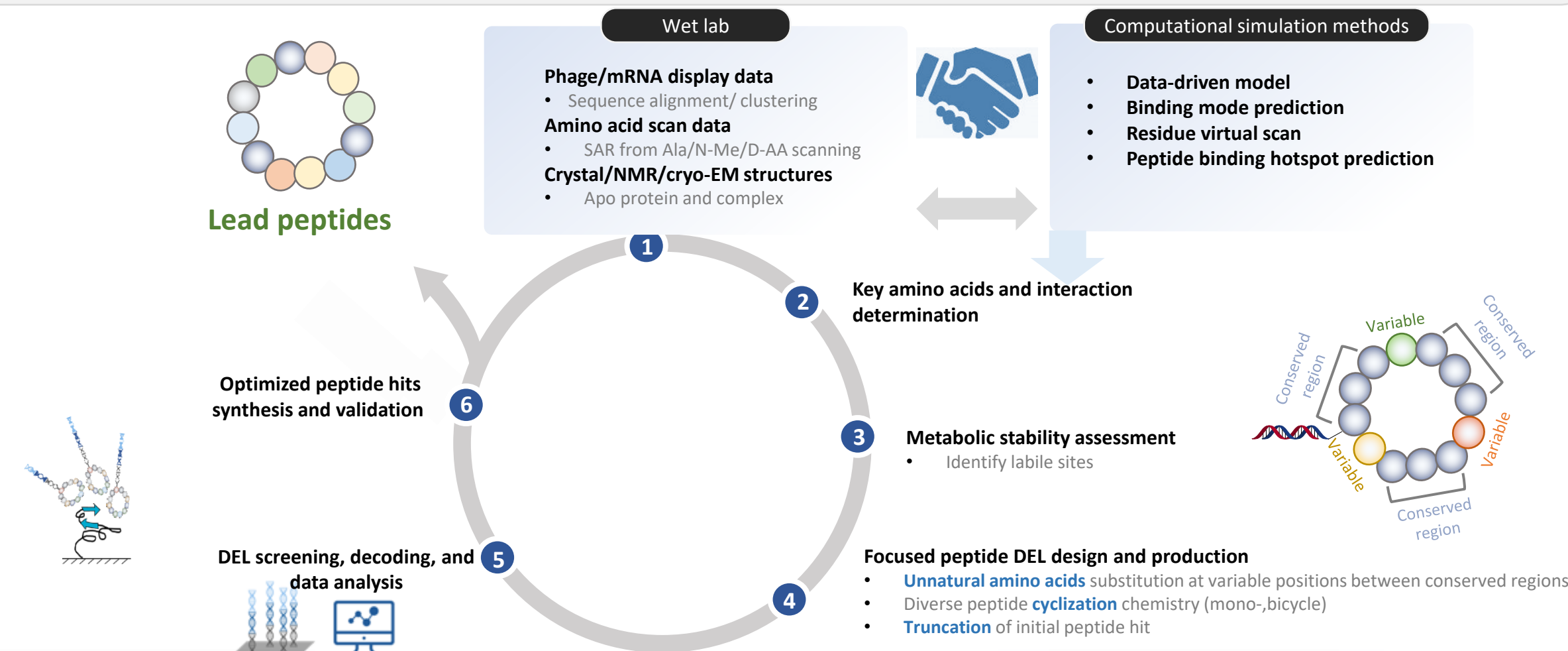


## Integrated Approaches in Peptide Discovery

### I. Complementary synergy of peptide DEL and mRNA display for hit peptide discovery



### II. Display to peptide DEL for hit-to-lead optimization



## Summary

- WuXi AppTec integrated peptide platform offers customized solutions, from *de novo* screening using DEL, phage display, and mRNA display, to optimization supported by expertise in peptide-specific CADD, medicinal chemistry, and assay capabilities.
- Newly designed libraries and validated cyclization strategies enable flexible choice for peptide hit discovery and library customization.
- mRNA display platform aided in allosteric binder peptide discovery with single-digit nM binding affinity and key binding residues were confirmed from alanine scan experiment.
- Peptides identified through peptide DEL screening have been successfully validated across multiple assays, demonstrating the robustness and effectiveness of the platform in generating high-quality peptide hits.
- Peptide DEL and mRNA display show a synergy both in peptide discovery for high success rate and hit-to-lead optimization with better physicochemical properties.

## Reference

- Silvestri, A. P., Zhang, Q., Ping, Y., Muir, E. W., Zhao, J., Chakka, S. K., Wang, G., Bray, W. M., Chen, W., Fribourgh, J. L., Tripathi, S., He, Y., Rubin, S. M., Satz, A. L., Pye, C. R., Kuai, L., Su, W., & Schwochert, J. A. (2023). DNA-encoded macrocyclic peptide libraries enable the discovery of a neutral MDM2-p53 inhibitor. *ACS medicinal chemistry letters*, 14(6), 820–826.

