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

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Peptide therapeutic discovery is experiencing a resurgence, particularly for challenging, historically “undruggable” targets. WuXi AppTec is leading the way in this field with innovative 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 15 amino acids long and inclusion of limited unnatural amino acids. 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 (6-9 amino acids) and innovative cyclization strategies, including the ‘click’ reaction. Conversely, we have also designed focused peptide-DEL libraries 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. In our poster we demonstrate the effectiveness of our technologies for discovering peptides including the discovery of i) a 9 nM cyclic inhibitor of the MDM2-p53 interaction, ii) potential tumor cell-specific peptide ligands that are being explored for targeted delivery of payloads via oligonucleotides or radioisotopes, iii) Significantly improved affinity from Display to DEL cyclic peptides.