Disulfide-Rich Peptides Phage Display for the Accelerated Discovery of Multicyclic Peptides with Antibody-like Affinity

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Recent success of oral PPI inhibitors: MK-0616 (MSD) and JNJ-2113 (J&J and Protagonist) in the clinic has validated the potential of peptides as an alternative drug modality to antibodies. In addition, multiple pharmaceutical and biotech companies are developing a variety of peptide drug conjugates (PDCs) at an accelerated pace to replace traditional ADCs for the treatment of cancer. One of the key properties required of these peptide therapeutics is antibody-like affinity (sub-nM to pM) to the protein target, which is achieved by a time- and resource-intensive hit-to-lead optimization efforts.

Peptide hit discovery platforms like mRNA Display (PeptiDream) and Phage Display (Bicycle Tx) have been extremely successful, however, the hits generated are typically in the single- to double-digit nM affinities and require several months to a few years of med-chem effort to make them antibody-like lead molecules. At PepLib, we have developed Disulfide-Rich Peptides Phage Display (DRP-PD) platform to discover novel multicyclic peptide hits as PPI inhibitors or leads for PDC development with antibody-like affinity (sub-nM to pM) and enhanced serum stability (several hours to days). These potent and stable lead-like molecules are discovered only under six months with no med-chem directly from the platform. In addition, the platform can enable the discovery of bi-functional PDC leads, where multiple loops of a peptide hit have been tuned to bind to two different receptor targets.

During this presentation, we will highlight the design and execution of the DRP-PD platform as well as showcase three case-studies described below:

TSLP/TSLPR Inhibition: Tezepelumab is an FDA-approved mAb that inhibits TSLP/TSLPR interaction and is used for the treatment of medium to severe asthma. Using the DRP-PD platform, we discovered a 30-mer multicyclic peptide hit with ~ 17 pM binding affinity in SPR and ELISA PPI inhibition activity (IC_{50} ~ 1 nM) like Tezepelumab directly from the platform. In the cellular assay, the hit demonstrated only 3- to 5-fold weaker activity (IC_{50} ~ 130 nM vs 45 nM) . Hit-to-lead optimization is underway to improve the cellular activity.

PRC against FAP: FAP-2286, discovered by 3B Pharma and licensed to Novartis, is being investigated as a peptide-targeted radionuclide therapy in phase 1/2. The DRP-PD platform afforded a novel bicyclic peptide with better binding affinity to FAP expressed on cells and 5x enhanced endocytosis than the clinical candidate FAP-2286. Like FAP-2286, our PRC shows T-1/2 > 24 hours in mouse and human serums. The PRC originating from the DRP hit is under investigation in tumour mice model.

Bi-functional PDC-lead against Nectin-4 & Trop-2: Nectin-4 and Trop-2 are being targeted by multiple drug conjugates (ADCs and PDCs) in the clinic to treat a variety of cancers. However, it is known that multiple cancer-types co-overexpress Nectin-4 and Trop-2. We believed that multicyclic DRP-PD platform could evolve a bi-functional hit to bind both Nectin-4 and Trop-2. Here, we will showcase the discovery of a multicyclic 30-mer peptide with sub-nanomolar affinity to both Nectin-4 and Trop-2 in SPR and direct binding to Nectin-4 and Trop-2 expressed on cells. This, in our knowledge, is the first example of a bifunctional peptide hit against Nectin-4 and Trop-2.