Peptide Information Compression Technology (PICT) for GPCR Drug Discovery using Cell-Based Functional High-Throughput Screening Assays

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Peptides have proven to be excellent drugs against GPCRs, specially to treat diabetes and obesity, due to their high potency and selectivity. However, nearly 60% GPCRs are yet to be explored as drug targets and recently, 87 orphan GPCRs were identified in the human genome. Furthermore, most peptide GPCR drugs have been developed from endogenous peptide ligands and function as agonists. High-throughput screening technologies using a one-well one-peptide library in conjunction with cell-based functional assays have the potential to discover both novel peptide agonists and antagonists and greatly accelerate the drug discovery efforts against the unexplored GPCR target space.

We have developed a unique peptide discovery platform capable of discovering functionally active peptide hits directly from a screen. Based on the proprietary Peptide Information Compression Technology (PICT), a library of cyclic peptides containing half a billion unique sequences has been designed and synthesized. Each member is individually expressed, head-to-tail cyclized, and purified in a genetic tag-free manner to build a one-well one-peptide library. The capabilities of the PepLib discovery platform extend beyond just binding assays to cell-based functional assays making it suitable for novel peptide drug discovery against GPCRs.

The PICT platform has been successful in novel ligand discovery against two GPCR targets. 1) **Human melanocortin receptor 3 (MC3R) antagonists**: a recent study from Prof. Roger Cone's lab demonstrated that co-administration of Liraglutide, a human glucagon-like peptide-1 (GLP-1) agonist [1] and a mouse MC3R antagonist [2] enhanced the acute anorexic and weight loss effects of liraglutide in mice.[3] However, discovery of selective human MC3R antagonists has been challenging so far. Using the PICT platform, we discovered several small cyclic peptide antagonists (10- to 14-mers) against human MC3R, where a 14-mer cyclic peptide (IC_{50} = 40 nM) demonstrated 1500-fold selectivity over hMC4R. 2) **The Apelin receptor (APJ) agonists** [4]: in addition to the antagonist discovery study, we will report the discovery of a novel linear 12-mer (EC_{50} = 0.45 nM) and a novel cyclic 15-mer (EC_{50} = 40 nM) peptide agonist against the Apelin receptor (APJ).

[1] Macêdo et al., *Obesities* **2022**, 2(3), 285-291
[2] Singh et al., *J. Med. Chem*. **2013**, 56, 7, 2747–2763
[3] Sweeny et al., *Sci. Transl. Med.* **2021**, 13 (590), eabd6434
[4] de Oliveira et al. *Peptides* **2022**, 147, 170697