Design of Peptide Therapeutics against Global Diseases

Dr. Krishna Kumar[a,b,c]

[a]***Department of Chemistry, Tufts University, Medford, MA 02155 USA,*** [b]***Department of Biomedical Engineering, Tufts University, Medford, MA 02155 USA, Cancer Center,*** [c]***Tufts Medical Center, Boston, MA 02110 USA***

<krishna.kumar@tufts.edu>

The gut-derived incretin hormone, glucagon-like peptide 1 (GLP-1), plays an important physiological role in attenuating postprandial blood glucose excursions in part by amplifying pancreatic insulin secretion. Native GLP-1 is rapidly degraded by the serine protease, dipeptidyl peptidase-4 (DPP4); however, enzyme-resistant analogs of this 30-amino acid peptide provide an effective therapy of type 2 diabetes (T2D) and can curb obesity via complementary functions in the brain. In addition to its medical relevance, the incretin system provides a fertile arena for exploring how to better separate agonist function at cognate receptors versus susceptibility of peptides to DPP4-induced degradation. We have discovered that novel chemical decorations can make GLP-1 and its analogs completely DPP4 resistant while fully preserving GLP-1 receptor activity. These constructs have better physicochemical profiles both *in vitro* and *in vivo* (mouse and rat models) than the top two T2D compounds in the clinic, lirgalutide and exenatide and teduglutide for short bowel syndrome. The universe of the derivatives possible is in the tens of thousands. All secretin family peptide ligands are amenable to modification in this manner. The translational potential of such compounds is immense and we report here 50+ derivatives acting on five different receptors that have potential to reduce the footprint of global diseases such as T2D, obesity, Alzheimer's and Parkinson's diseases, and fatty liver disease (NASH).