**Fibrillation-resistant peptide drugs**

Glucagon is a peptide hormone. In the body, glucagon is secreted by the pancreas to increase blood glucose levels, opposing the action of insulin. Glucagon is also used as an emergency treatment for hypoglycemia in diabetic patients, a condition that can lead to coma or even death if left untreated. Current glucagon products contain a vial of powdered glucagon and a syringe filled with an acidic solution. The powder must be dissolved and drawn back into the syringe before it can be administered to the patient. This form of the drug is necessary because glucagon is highly unstable in solution, rapidly forming amyloid fibrils. The fibrils have structures similar to those in the brains of patients with Alzheimer’s or Parkinson’s disease. In glucagon, they make the drug ineffective and more likely to cause side effects.

PI Liz Topp and her group have developed phosphate ester derivatives of glucagon that inhibit its fibrillation. Charge repulsion by the negatively charged phosphate group prevents molecules of glucagon from coming together to form fibrils. The phosphate group also increases the solubility of the drug at neutral pH. In the body, enzymes called phosphatases rapidly cleave the phosphate group, releasing the native form of glucagon. These patented ‘phosphoglucagons’ have been optioned by Monon Bioventures, a small business in Indianapolis, Indiana. The phosphoglucagons are now in preclinical development at Monon, with support from a Fast Track Small Business Grant (SBIR) from the U.S. National Institutes of Health (NIH).

In March, Dr. Topp and her group filed a provisional U.S. patent on phosphate ester derivatives of human calcitonin. Like glucagon, human calcitonin is a peptide hormone that rapidly forms fibrils. Clinically, calcitonins have been used to treat osteoporosis, Paget’s disease and other diseases of bone. Because human calcitonin is unstable, the more stable form found in salmon has been used in commercial drug products. The effectiveness of salmon calcitonin has been questioned, however, and there are some indications of increased cancer risk in patients who receive it. Dr. Topp and her group hope that their novel phosphorylated human calcitonins will provide safer and more effective treatments for patients with bone disease.