# Chemical Probes for the Discovery and Development of Peptide Therapeutics

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Peptide therapeutics have emerged as important modality in today's drug discovery efforts. Over the last decade significant progress has been made in the design of therapeutic peptides tailoring their pharmacokinetic and pharmacological properties. Chemical probes can help to better understand those novel peptide therapeutics, to identify novel candidates with superior properties and guide even their clinical development. For example, unimolecular dual agonists for the GLP-1 and glucagon receptor have emerged as promising approach for the treatment of diabetes and obesity. As of today there are no suitable direct biomarkers that reliably demonstrate glucagon receptor target engagement as the established readouts are affected also by GLP-1 pharmacology. To address this challenge, we have developed a specific, first in class PET tracer for the glucagon receptor, [68Ga]Ga-DO3A-S01-GCG. As glucagon itself suffers from poor physicochemical properties and is metabolized rapidly in vivo, careful optimization of the peptide was necessary to identify a suitable peptide tracer precursor, suitable for radiolabeling. After in-vitro and in-vivo characterization the novel glucagon tracer together with an already known GLP-1 PET tracer was used in preclinical animal studies (non-human primates) to assess and even quantify target engagement of various dual GLP-1 / glucagon receptor agonists. Correlation with corresponding pharmacodynamic results helped to better understand underlying mechanisms and potentially therapeutic windows.

In a second example, we have designed specific probes addressing different binding sites in human albumin. Reversible albumin binding has emerged as successful technology to prolong the half-life of peptides. With the recently established chemical probes, albumin binders can be better characterized and optimized or even newly discovered.