**Pharmacokinetic Investigations of Ghrelin(1-8) Analogues Towards Development of PET Imaging Probes for Prostate Cancer**

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The growth hormone secretagogue receptor 1a (GHSR), known as the ghrelin receptor, is differentially expressed in various diseases and cancer types, including pancreatic, breast, and prostate.[1] A ghrelin-based analogue was previously discovered with exceptional receptor affinity, however, *in vivo* evaluation revealed an unfavourable pharmacokinetics with rapid clearance and accumulation in the liver and intestines.[2] Stability investigations revealed a metabolic soft spot between amino acids Leu$^5$ and Ser$^6$.[3] Subsequently, a library of analogues were synthesized and evaluated for their *in vitro* stability, revealing two analogues with improved metabolic stability with retained receptor affinity. In this investigation, three analogues are being radiolabelled with a fluorine-18 6-fluoro-2-naphtyl (6-FN) prosthetic group and evaluated *in vivo* to assess their pharmacokinetic profiles. Peptides were synthesized using Fmoc solid-phase peptide synthesis, purified by preparative HPLC, and characterized by high-resolution mass spectrometry. An iodonium ylide precursor was synthesized and radiolabelled with fluorine-18 to yield the $^{18}$F-prosthetic group, which was then conjugated to the peptides. The probes are being evaluated in a prostate cancer xenograft model to assess varying pharmacokinetic profiles. This study demonstrates the intricate radiopharmaceutical optimization pathway, accounting for affinity, stability and biodistribution, towards the development of a peptide-based ghrelin-targeted PET probe for prostate cancer imaging.

**References**
(1) Lin, T.-C.; Hsiao, M. *Biochim Biophys Acta* **2017**, *1868*, 51–57.
(2) Childs, M. D.; Yu, L.; Kovacs, M. S.; Luyt, L. G. *Org. Biomol. Chem* **2021**, *19*, 8812.
(3) Childs, M. D.; Chandrabalan, A.; Hodgson, D.; Ramachandran, R.; Luyt, L. G. *ACS Pharmacol Transl Sci* **2023**, *6*, 1075–1086.