Radioligand Therapy tales: from Discovery to Development

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FAP (Fibroblast Activation Protein) is expressed on cancer-associated fibroblasts (CAFs) and is a highly attractive target in Radioligand Therapy (RLT) due to its pan-cancer potential. The penetrating nature of β-radiation is hypothesized to drive a 'cross-fire effect' from CAFs to tumor cells resulting in DNA damage and tumor cell death. Known FAP-targeting ligands show excellent and selective tumor uptake in the clinic but suffer from short tumor retention which limits their application beyond imaging. Herein we describe [^{177}Lu]Lu-NNS309 (FAP targeting ligand) which improves tumor retention and is currently undergoing clinical evaluation in Phase 1 (NCT06562192) in patients with PDAC, NSCLC, Breast Cancer, and CRC. Multiple starting points were identified via an mRNA display platform, then co-crystallized with FAP and assessed for bio-distribution in vivo. The series with the best tumor/kidney ratio was selected for further optimization to maximize affinity and proteolytic stability. [^{177}Lu]Lu-NNS309 binds to both human and mouse FAP with affinity Kd < 10 pM, shows exquisite selectivity over other proteases (such as DPP4) and is stable in blood and plasma.

We will outline the discovery of [^{177}Lu]Lu-NNS309 followed by an overview of peptide-based radioligands, focusing on risk assessment illustrated by examples of epimerization in known examples of peptide radioligands.