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 as a therapeutic modality. Herein we describe FXX489 (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. Importantly, FXX489 demonstrates BiC potential for anti-tumor efficacy in translationally relevant models (*e.g.*, PDAC, NSCLC) where FAP is expressed on CAFs, thus relying on the cross-fire mechanism. Multiple starting points were identified using mRNA display platform, co-crystallized with FAP and assessed for biodistribution *in vivo*. The series with the best tumor/kidney ratio was selected for further optimization. Optimization was enabled by the co-crystal structure and was focusing on maximizing compound affinity and proteolytic stability. FXX489 binds to both human and mouse FAP with the affinity < 10 pM; shows exquisite selectivity over other proteases (such as DPP4); is stable in blood and plasma.