Development of ^{177}Lu-FL-091 for the treatment of NTSR1-positive cancers

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Introduction

Neurotensin receptor 1 (NTSR1) belongs to the family of neurotensin receptors (NTSRs), which modulate the effects of the neuropeptide hormone neurotensin in the gastrointestinal system[1]. NTSR1 is the primary mediator of neurotensin signaling due to its sub-nanomolar affinity to its natural ligand[2]. Overexpression of NTSR1 has been associated with disease progression of multiple types of cancers, including colorectal, breast, pancreatic, and head and neck cancers[3-5], making it a promising target for diagnostic imaging and radioligand therapy. In this study, we investigated the preclinical characteristics of a novel NTSR1-targeted radioligand, ^{177}Lu-FL-091, which demonstrated favorable biodistribution profiles and encouraging anti-tumor activities.

Methods and Materials

- Binding affinity and cellular function of FL-091 were determined by competitive binding assay in HT-29 cells and FLIPR assay in NTSR1 overexpression cells.
- *In vivo* biodistribution was assessed by SPECT/CT and *ex vivo* cut-and-count of ^{177}Lu-labeled FL-091 on AsPC1 xenograft model at different time points.
- *In vivo* efficacy was determined with ^{177}Lu-FL-091 in comparison with ^{177}Lu-3BP-227 in PC-3 and AsPC-1 tumor-bearing nude mice.
- NTSR1 expression in tumors was evaluated by immunohistology staining in tissue microarrays of different types of tumors.

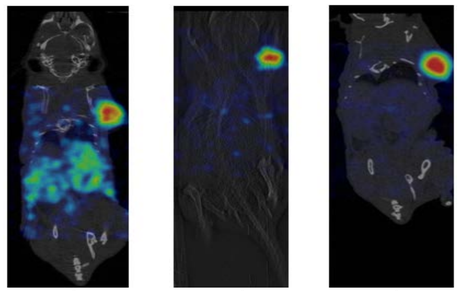
Results

Table 1. *In vitro* characterizations of FL-091

Compound	IC_{50} (nM) of ^{177}Lu ligand competitive binding assay[1]	IC_{50} (nM) of FLIPR antagonist assay[2]
FL-091	0.21	11.70
3BP-227	4.46	45.41

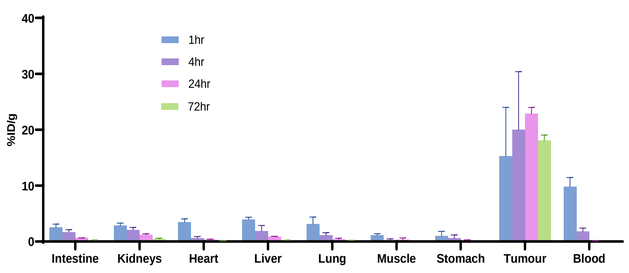
- [1]N=4 and [2]N=2.
- Less than 50% inhibition of binding or activity was observed by FL-091 at 10 μM against 86 targets including receptors, ion channels, enzymes, and transporters.

Figure 1. *In vivo* SPECT/CT Imaging with ^{177}Lu-FL-091 in AsPC-1 model



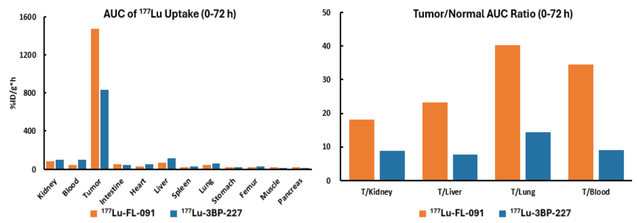
- Representative SPECT/CT image (maximum intensity projection) after ^{177}Lu-FL-091 administration in AsPC1 model at 4 h, 48 h and 72 h.

Figure 2. Biodistribution of ^{177}Lu-FL-091 in AsPC-1 model



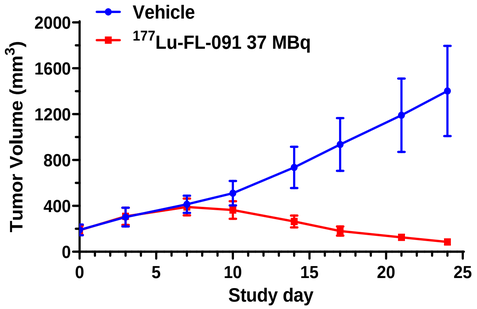
- Biodistribution data in major organs at different time points post dose of ^{177}Lu-FL-091 in AsPC1 model. Data are represented as mean±SD (N=3).

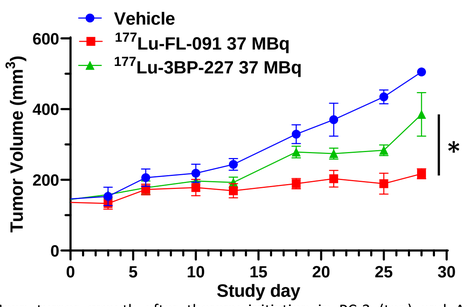
Figure 3. Biodistribution comparison in AsPC-1 model



- Accumulative uptake in major organs post dose of ^{177}Lu-FL-091 or ^{177}Lu-3BP-227 in AsPC1 model.

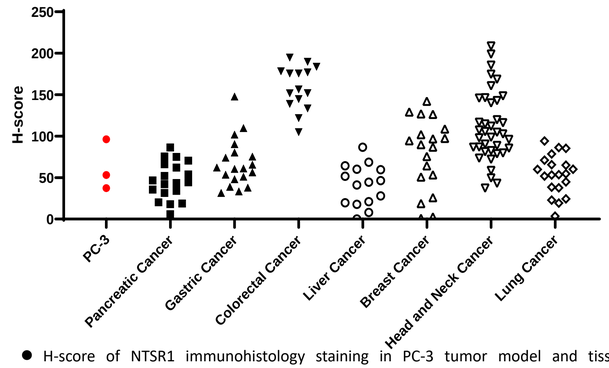
Figure 4. *In vivo* efficacy of ^{177}Lu-FL-091 in different xenograft models





- Mean tumor growth after therapy initiation in PC-3 (top) and AsPC-1 (bottom) xenograft models. Statistical analysis on tumor volume was conducted by one-way ANOVA with Tukey's multiple comparison test. *p<0.05.

Figure 5. Evaluation of NTSR1 expression in tissue microarrays



- H-score of NTSR1 immunohistology staining in PC-3 tumor model and tissue microarrays.

Conclusion

- FL-091 displayed enhanced binding affinity to NTST1 and antagonist activity compared to 3BP-227.
- ^{177}Lu-FL-091 demonstrated improved in vivo biodistribution profile vs. ^{177}Lu-3BP-227 with increased tumor uptake and faster normal tissue clearance.
- ^{177}Lu-FL-091 showed promising in vivo efficacy in different xenograft models, with more favorable anti-tumor activity against ^{177}Lu-3BP-227 at the same dose level.
- NTSR1 was highly expressed across multiple types of cancers, especially in head and neck and colorectal cancers.
- Taken together, these results collectively demonstrate that ^{177}Lu-FL-091 is a promising NTSR1-targeting radioligand therapy candidate. Studies to investigate FL-091 conjugated to the radionuclide Actinium-225 are in progress.

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References

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