Adaptation of an Investigational β-Emitting NTSR1-Targeted Radiopharmaceutical into the Targeted Alpha Therapeutic [^{225}Ac]-FPI-2059

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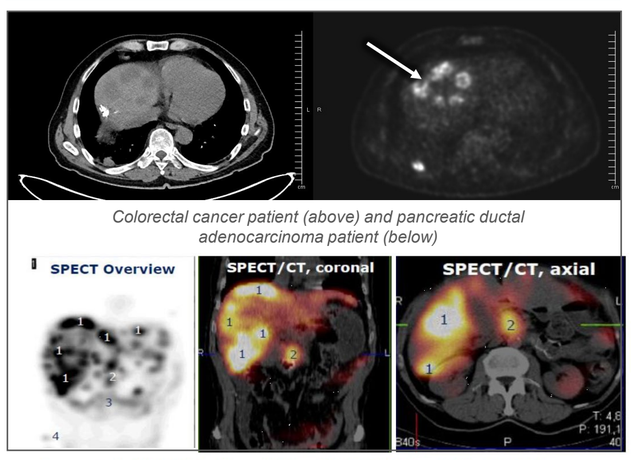
Introduction

Fusion Pharmaceuticals licensed [^{177}Lu]-IPN01087 (formerly [^{177}Lu]-3BP-227), a clinical phase small molecule antagonist radiopharmaceutical targeting the neurotensin receptor 1 (NTSR1), from Ipsen in April 2021. Phase 1 trials of [^{177}Lu]-IPN01087 in patients with colorectal, pancreatic, and gastric cancers demonstrated confirmed tumor uptake of the radiopharmaceutical in multiple patients as exemplified in the figure below.

Imaging Confirms Targeted Uptake in NTSR1^{+} Tumors



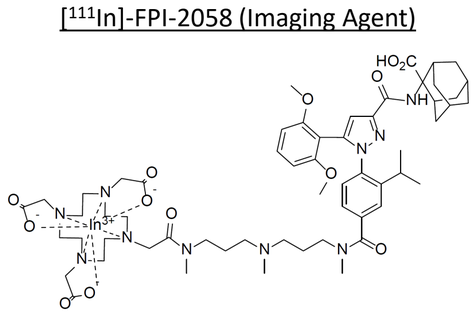
Colorectal cancer patient (above) and pancreatic ductal adenocarcinoma patient (below)

Tumor Indication	Relative Expression
Pancreatic Ductal Adenocarcinoma (PDAC)	+++
Colorectal Carcinoma (CRC)	++/+++
Ewing's Sarcoma	+++
Meningioma	+++
Prostate Cancer (NET)	++
Small Cell Lung Cancer	++
Breast Cancer	+

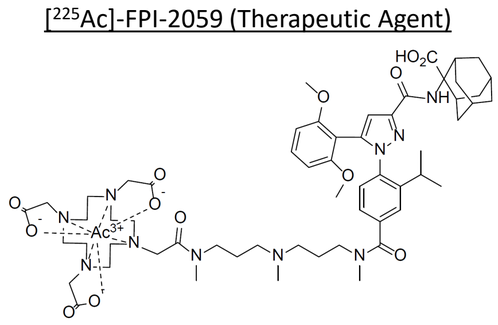
Baum et al., JNM, 2017 (also published JNM, 2018 May 59(5):809-814)

Fusion focuses on discovery and development of Targeted Alpha Therapies (TATs) and hypothesizes that the radiobiological properties of alpha-emitting isotopes such as ^{225}Ac (e.g. very high linear energy transfer for alpha particles) may lead to superior anti-tumor efficacy than beta-emitting isotopes such as ^{177}Lu. To test this hypothesis, Fusion has re-engineered [^{177}Lu]-IPN01087 into the theranostic pair [^{111}In]-FPI-2058 and [^{225}Ac]-FPI-2059 (depicted below) by changing the isotope chelated in the NTSR1-targeted small molecule but otherwise retaining the structure of the molecule.

[^{111}In]-FPI-2058 (Imaging Agent)

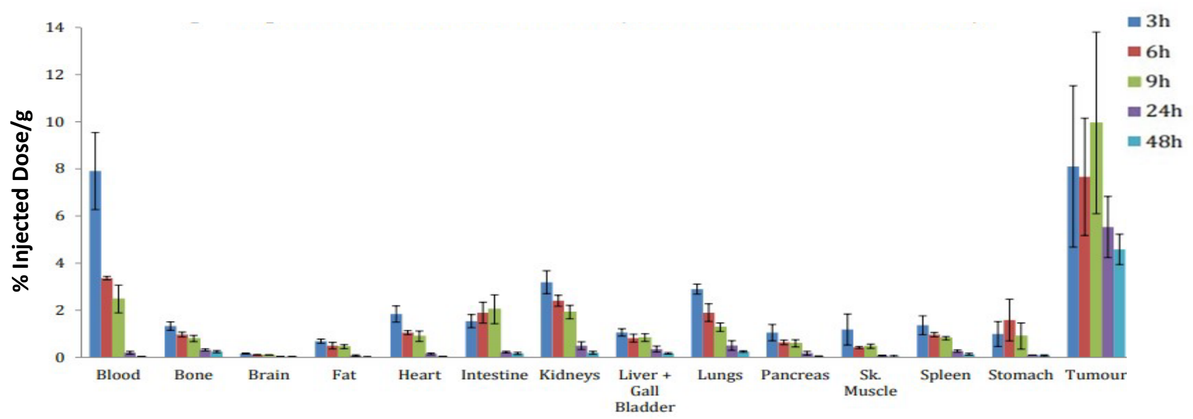


[^{225}Ac]-FPI-2059 (Therapeutic Agent)

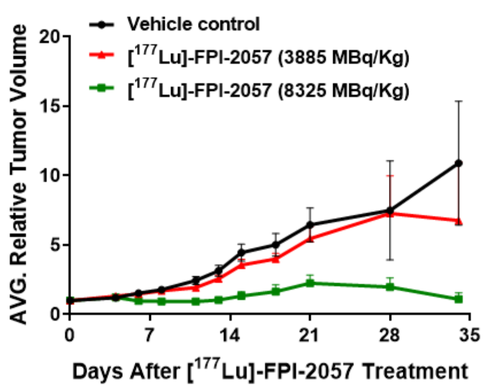


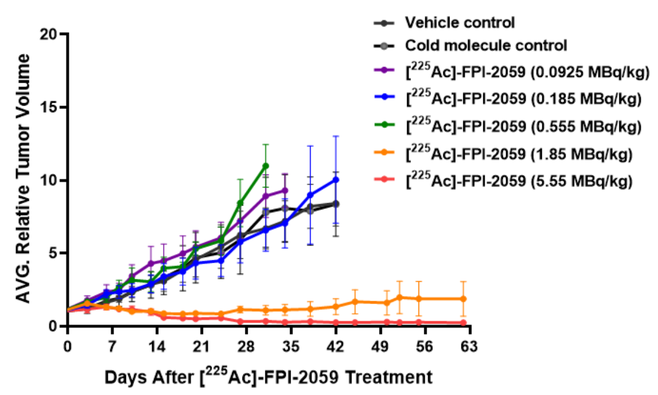
Preclinical Efficacy of [^{225}Ac]-FPI-2059 and Comparison to [^{177}Lu]-IPN01087

A ^{177}Lu surrogate of [^{225}Ac]-FPI-2059, [^{177}Lu]-FPI-2057, was utilized to evaluate the in vivo biodistribution of the radiopharmaceutical in mice bearing HT29 colorectal cancer xenograft tumors. The results are summarized in the figure below. [^{177}Lu]-FPI-2057 was cleared rapidly from the blood and normal organs with <1% injected dose/gram detectable at time points ≥ 24 hours. The tumor showed rapid uptake detectable at the earliest time point (3 hours), with gradual slow clearance from the tumor over several days post-dose.



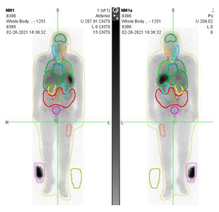
To test the hypothesis that a TAT would be more potent and effective at controlling tumor growth than a beta-emitter, Fusion conducted dose/response studies of intravenously administered [^{225}Ac]-FPI-2059 and [^{177}Lu]-FPI-2057 (previously [^{177}Lu]-IPN01087) in HT29 colorectal cancer xenograft tumor models. [^{177}Lu]-FPI-2057 was shown to be effective in controlling tumor growth as a single dose at 8325 MBq/kg but was ineffective at 3885 MBq/kg. In contrast, in the same mouse model [^{225}Ac]-FPI-2059 showed single dose efficacy at ≥1.85 MBq/kg, suggesting that the TAT form of the radiopharmaceutical is ~1500-fold more potent than the beta-emitter. Both compounds were well tolerated at all dose levels as determined by body weight.





Human Biodistribution and Dosimetry Projections

In a Phase 1 study of [^{177}Lu]-IPN01087, patients underwent planar and SPECT imaging following a 1 GBq imaging dose of [^{177}Lu]-IPN01087. These images were analyzed and the biodistribution and biokinetic data from N=11 patients administered [^{177}Lu]-IPN01087 were utilized to project the human dosimetry of [^{111}In]-FPI-2058 and [^{225}Ac]-FPI-2059.



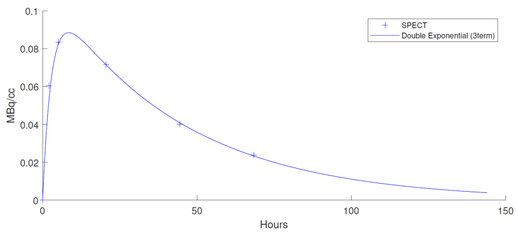
x5 Time Points
0.5, 3, 20, 44, 84 hr

Target Organ	Mean (Gy/MBq)	Mean (rad/mCi)	Coefficient of Variation (%)
Adrenals			
Brain			
Breasts			
Gallbladder wall			
LLI Wall			
Small intestine wall			

[^{225}Ac]-FPI-2059 and [^{111}In]-FPI-2058 dosimetry projections

AUC for ^{225}Ac/^{111}In by applying decay constants ratio as input for OLINDA

^{177}Lu $T_{1/2}$: 6.6 d
^{225}Ac $T_{1/2}$: 9.9 d
^{111}In $T_{1/2}$: 2.8 d



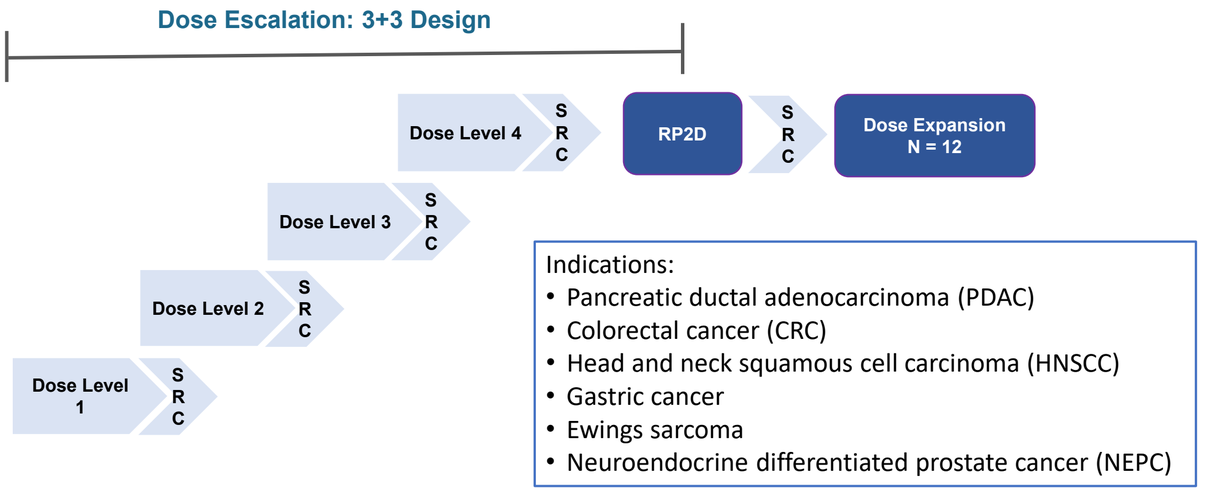
Time-activity curve fitting
^{177}Lu data for each organ

AUC for each organ (^{177}Lu)

$$\tilde{A}_h = \int_0^\infty A_h(t)dt = \sum_j A_j/(\lambda + \lambda_j) = 1.443 \sum_j A_j(T_j)_e,$$

First-In-Human Clinical Trial Design

Fusion is currently enrolling a first-in-human Phase 1 clinical trial (NCT05605522) designed to investigate the safety, tolerability, pharmacokinetics, and biodistribution of [^{225}Ac]-FPI-2059 and [^{111}In]-FPI-2058 in participants with NTSR1-expressing solid tumors.



Patients will be imaged by SPECT/CT following administration of the theranostic imaging agent [^{111}In]-FPI-2058 and must show positive tumor uptake of [^{111}In]-FPI-2058 to be eligible to receive [^{225}Ac]-FPI-2059. Eligible patients will receive up to 4 cycles of [^{225}Ac]-FPI-2059 at 8 week intervals between cycles.

Summary and Conclusions

- [^{225}Ac]-FPI-2059 is a novel TAT under development as part of Fusion's robust radiopharmaceutical pipeline that includes biologics, small molecules, peptides, and combination therapies
- The ^{177}Lu analog of [^{225}Ac]-FPI-2059 has been shown to target NTSR1+ tumors in human trials and preliminary efficacy and safety data support further development of the radiopharmaceutical as a TAT
- Preclinical xenograft mouse studies suggest that the targeting NTSR1 with a ^{225}Ac-based TAT offers superior efficacy relative to a beta-emitting NTSR1 radiopharmaceutical
- Fusion is leveraging the human safety and biodistribution data from [^{177}Lu]-IPN01087 to support the dosimetry projection and clinical dose justification for [^{225}Ac]-FPI-2059
  - Knowledge of human biodistribution/dosimetry and safety profile derived from the beta-emitter helps to guide dose escalation of the TAT
- The first-in-human Phase 1 trial of [^{225}Ac]-FPI-2059 and [^{111}In]-FPI-2058 (NCT05605522) is currently active and enrolling patients