NTSR1 Targeted Alpha Therapeutic $^{225}$Ac-FPI-2059 Induces Regression in Preclinical Colorectal Xenograft Model

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Fusion utilizes Targeted Alpha Therapy to deliver high energy alpha particle emitting isotopes (actinium 225) to the targeted tumor cells.

Fusion’s TAT platform and product candidates provide several potential advantages over currently available radiopharmaceuticals, including:

- Ability to use multiple classes of targeting molecules such as antibodies, peptides and small molecules
- Enhanced tumor-killing power with precision by using alpha particle radiation
- Broad applicability across multiple tumor types - effective against both dividing and nondividing tumor cells
- Ability to incite an immune response against tumor cells

We hypothesize that Targeted Alpha Therapies may lead to better therapeutic efficacy than beta therapies.
Neurotensin Receptor 1 (NTSR1) is a Promising Target for TAT Therapy

- NTSR1 is upregulated in multiple solid tumor types, including colorectal and pancreatic cancers
- FPI-2059 is a small molecule antagonist targeting NTSR1 and radiolabeled with actinium-225
  - Previously in Phase 1 clinical development as a lutetium-177-based radiopharmaceutical (as IPN-1087) for solid tumors expressing NTSR1
  - Imaging studies demonstrate tumor uptake in patients with gastrointestinal tumors including colorectal and pancreatic cancers (primary and metastatic sites)
- Fusion has acquired this molecule from Ipsen in order to create an alpha-emitting radiopharmaceutical, FPI-2059, to test our hypothesis that TATs are more potent and potentially more efficacious than beta therapies

### NTSR1 Expression

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal pancreatic adenocarcinoma</td>
<td>+++</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>++</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>++</td>
</tr>
<tr>
<td>Colorectal carcinoma</td>
<td>++/+++</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>+</td>
</tr>
<tr>
<td>Meningioma</td>
<td>+++</td>
</tr>
<tr>
<td>Ewing's Sarcoma</td>
<td>+++</td>
</tr>
</tbody>
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### Imaging Shows Targeted Uptake In: CRC and PDAC patients

Baum et al., JNM, 2017 (also published JNM, 2018 May 59(5):909-814)
Study Goal and Methods

**Goal:**
Perform therapeutic efficacy studies of NTSR1-targeting $^{225}\text{Ac}$-FPI-2059 and provide a comparison to $^{177}\text{Lu}$-FPI-2057 when tested in colorectal xenograft model

**Methods:**
- **Mouse strain:** CD1 nude
- **Tumor model:** HT29 colorectal xenograft tumor model
- **Radio-conjugates & doses:**
  - $^{177}\text{Lu}$-FPI-2057: **2.1-4.5 mCi [3885-8325 MBq/kg]**
  - $^{225}\text{Ac}$-FPI-2059: **1-3 μCi [1.85-5.55 MBq/kg]**
- **Number of doses:** Single dose once tumors reached $212 \pm 46 \text{ mm}^3$
  - Day of dosing is denoted as day “0”

![mRNA and Protein Analysis](image)

*Kim et al, 2017*  
*Saada et al, 2012*
Blood levels of $^{177}$Lu-FPI-2057 rapidly decrease from 8-10% to <1% between 3h to 24h post dosing.

5-10% [of %ID/g] of $^{177}$Lu-FPI-2057 was observed in tumors between 3h to 48h post dosing.
Durable tumor regression was observed with $^{225}\text{Ac}$-FPI-2059 therapy.

Body weight of the animals was similar in all the treatment groups (data not shown). No signs of toxicity was observed in any of the groups.
NTSR1 is a promising target for Targeted Alpha Therapy, specifically for colorectal and pancreatic cancers due to frequent overexpression in these indications.

Tumor regression with $^{225}\text{Ac}$-FPI-2059 is achieved at doses 1500x-lower than $^{177}\text{Lu}$-FPI-2057.

Our data support testing the hypothesis that Targeted Alpha Therapies may lead to better efficacy than beta therapies in patients with cancer.

Fusion intends to submit an IND application for FPI-2059 in the first half of 2022.