Scientific Abstract

Pancreatic Cancer Collective Research Team:

"Molecularly Targeted Radionuclide Therapy via Integrin AlphaVBeta6 New Therapies Challenge"

[This abstract was provided by the scientists when their application was accepted.]

The integrin subtype avβ6 is an epithelial-specific cell surface receptor that is undetectable in healthy adult epithelium but is significantly up-regulated in a wide range of epithelial-derived cancers, including pancreatic ductal adenocarcinoma (PDAC). Almost all tumors demonstrate highly upregulated expression of avβ6. Furthermore, given the role of this receptor in the processes of invasion and metastasis, and preliminary data supporting further upregulation in metastatic sites, avβ6 is a very attractive target for targeted delivery of a therapeutic payload in PDAC.

We have developed an avβ6-directed molecular imaging agent, 18F-avβ6-targeting peptide (18F-avβ6-BP), a peptide that has high affinity (nM) and selectivity for the integrin avβ6 with favorable pharmacokinetics in tumor-bearing mice and non-human-primates and recently translated this imaging agent into a first-in-human study in patients with breast, colon, lung and pancreatic cancer. To date, 16 patients have undergone whole body imaging, with PET images demonstrating significant uptake of [18F] avβ6-BP in both the primary lesion and metastases. We now propose to advance this approach and develop a novel avβ6-targeted peptide based radionuclide therapy.

The overall goal of this project is to develop a novel avβ6-targeted peptide therapeutic. Successful PRTT requires: i) specific targeting of the peptide to deliver an effective radiation dose and ii) good *in vivo* stability and internalization of the peptide. Three specific aims are proposed:

Specific Aim 1: To synthesize and validate 68Ga-DOTA-peptide and 177Lu-DOTA peptide constructs. Binding, internalization and efficacy will be assessed in human pancreatic cancer cell lines.

Specific Aim 2: To perform and optimize dosimetry studies *in vivo* in orthotopic and metastatic mouse models of pancreatic cancer. Efficacy of the constructs will be assessed *in vivo* in mouse models. Positron emission tomography (PET) and bioluminescence imaging (BLI) will be used both to track *in vivo* biodistribution and quantify therapeutic efficacy of the PRRT.

Specific Aim 3: To prepare all necessary paperwork for filing IND to the FDA for a first-in-human study with the 177Lu-PRRT.