The integrin subtype αvβ6 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 αvβ6. Furthermore, given the role of this receptor in the processes of invasion and metastasis, and preliminary data supporting further upregulation in metastatic sites, αvβ6 is a very attractive target for targeted delivery of a therapeutic payload in PDAC.

We have developed an αvβ6-directed molecular imaging agent, 18F-αvβ6-targeting peptide (18F-αvβ6-BP), a peptide that has high affinity (nM) and selectivity for the integrin αvβ6 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] αvβ6-BP in both the primary lesion and metastases. We now propose to advance this approach and develop a novel αvβ6-targeted peptide based radionuclide therapy.

The overall goal of this project is to develop a novel αvβ6-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.