Preclinical optimization of anti-CA19.9 immunoPET in the context of shed antigen

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Introduction

Background

- ^{89}Zr-DFO-5B1 is an anti-CA19.9 antibody with great potential for immunoPET imaging of pancreatic cancer (1)
- CA19.9 is shed into circulation, confounding the use of ^{89}Zr-DFO-5B1 for immunoPET
  - ^{89}Zr-DFO-5B1 may bind circulating CA19.9 prior to reaching target tissue
  - Lower image contrast and increased radiation exposure in healthy tissues

Hypothesis

- Injecting unmodified 5B1 prior to ^{89}Zr-DFO-5B1 would lead to improved PET images
  - "Soak up" circulating CA19.9 allowing more ^{89}Zr-DFO-5B1 to reach its target
  - Increased PET contrast and lower radiation exposure to healthy tissues

Goals

- Determine optimal conditions for improving PET contrast by preinjection of 5B1
  - Time prior to tracer injection; mass of unmodified 5B1 to inject

Methods

Radiotracer

- ^{89}Zr-DFO-5B1 was prepared as previously described (1) using typical labeling methods
  - Specific activity = 5.2 mCi/mg; Immunoreactivity >98%

Animal model

- Subcutaneous and orthotopic Capan-2 xenografts
  - Capan-2: human PDAC cell line; sheds clinically relevant amounts of CA19.9

Experimental design

- Inject unmodified 5B1, allow for "lag" time before injecting ^{89}Zr-DFO-5B1
  - Vary the "lag" time before radiotracer injection
  - Vary the amount of unmodified 5B1 at best time point
- Acute biodistribution and PET imaging studies
  - Determine optimal "lag" time and mass of unmodified 5B1
- Assess optimized strategy in orthotopic model of PDAC

Results

Determination of optimal *time* for 5B1 preinjection

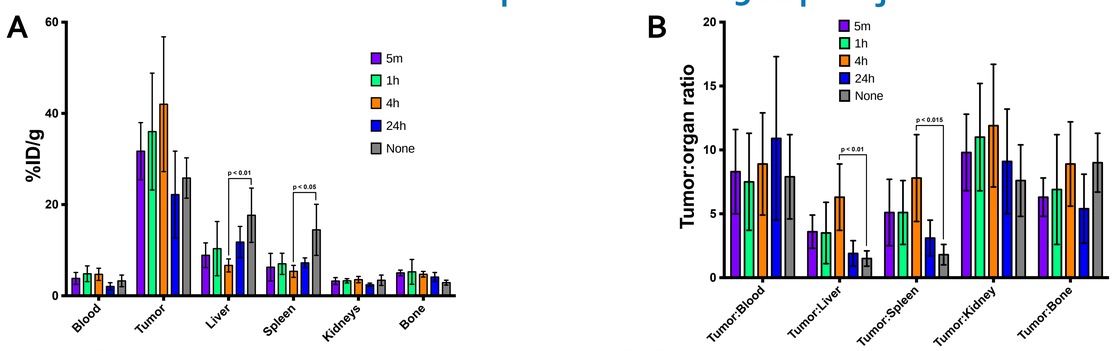

Figure 1: Overall uptake (**A**) and tumor to tissue ratios (**B**) from an acute biodistribution study of mice with subcutaneous Capan-2 xenografts that were injected with 5B1 (100 µg) at various times (5m, 1h, 4h, and 24h) prior to injection of the radiotracer. Biodistribution data was acquired 120h post injection of ^{89}Zr-DFO-5B1.

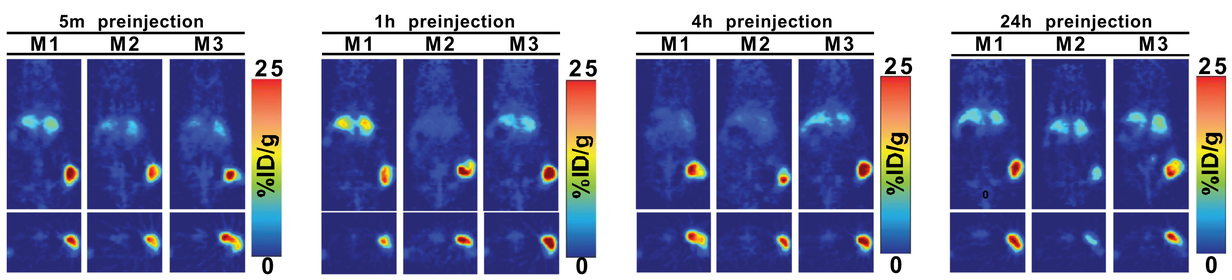

Figure 2: Small animal PET imaging of select mice with subcutaneous Capan-2 xenografts that were injected with 5B1 at various times (5m, 1h, 4h, and 24h) prior to injection of the radiotracer. Images were acquired 120h post injection of ^{89}Zr-DFO-5B1.

Determination of optimal *mass* of 5B1 for preinjection

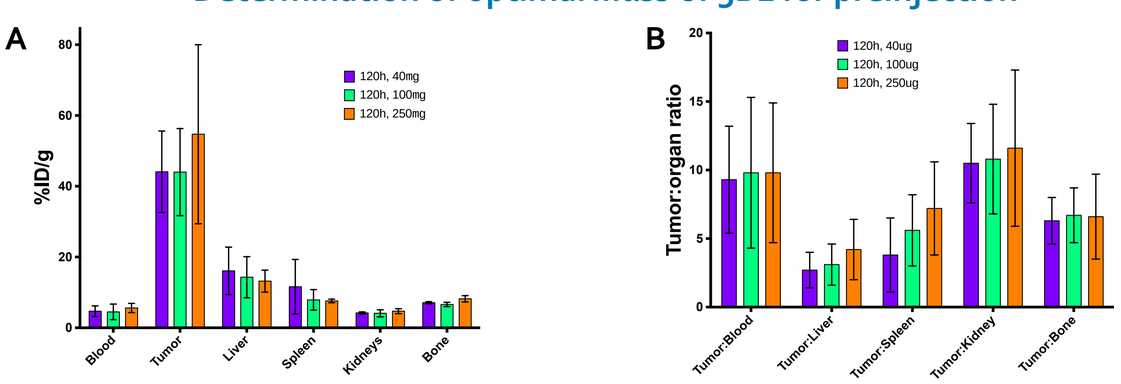

Figure 3: Overall uptake (**A**) and tumor to tissue ratios (**B**) from acute biodistribution study of mice with subcutaneous Capan-2 xenografts that were injected with unmodified 5B1 (40µg, 100µg, or 250µg) 4h prior to injection of ^{89}Zr-DFO-5B1. Biodistribution was performed at 120h post injection of the radiotracer.

Evaluation of optimized PET imaging protocol

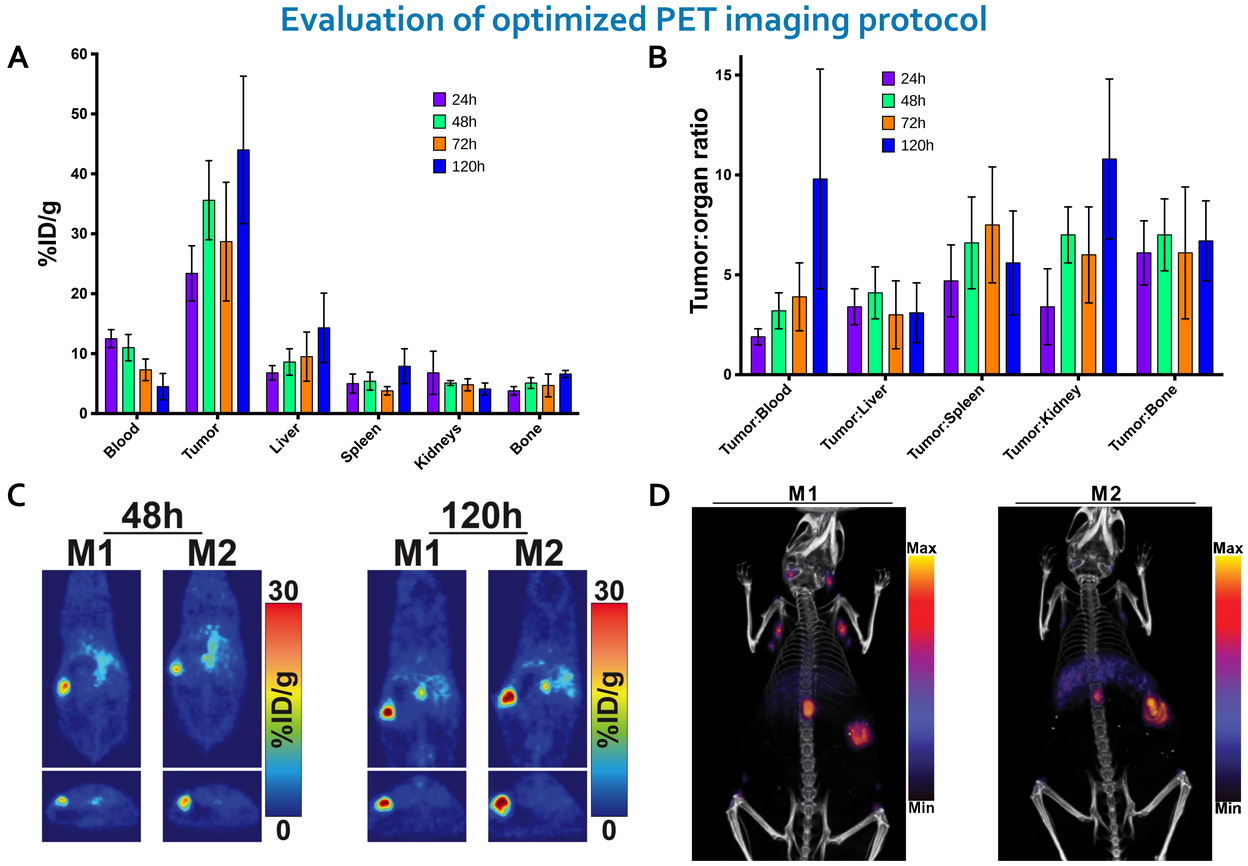

Figure 4: Serial biodistribution (**A**) and resultant tumor to tissue ratios (**B**) in mice with subcutaneous Capan-2 xenografts that were injected with unmodified 5B1 (100µg) 4h prior to injection of ^{89}Zr-DFO-5B1 are shown. Also shown are PET images acquired at 48h and 120h (**C**) along with corresponding PET/CT images acquired at 144h (**D**) of mice with orthotopic Capan-2 xenografts that underwent the optimized imaging.

Conclusions and Future Directions

- Injection of unmodified 5B1 prior to ^{89}Zr-DFO-5B1 improves PET contrast
  - Injection of 100µg at 4h before radiotracer was best in murine model
  - Variation in "lag" time was the more important variable
- This data will inform the design of upcoming first-in-human trials of to ^{89}Zr-DFO-5B1
- Further studies to correlate improvement in contrast to CA19.9 serum levels prior to preinjection of 5B1 using this approach are currently underway

Acknowledgements and References

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References: **(1)** Viola-Villegas, NT et al. J Nucl Med. 2013. 54(11):1876-82.