Targeting CA19.9 for Radioimmunotherapy and Therapeutic Monitoring in Pancreatic Cancer

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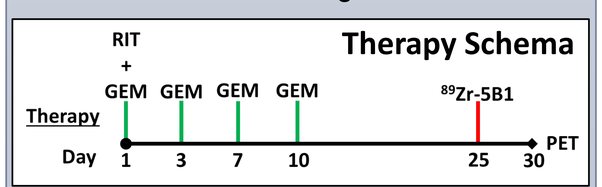
OBJECTIVE

Outcomes for locally advanced or metastatic pancreatic cancer (PCa) are dismal with survival measured in months. Treatment options are limited to systemic chemotherapy and radiation therapy, which only modestly improve survival. There is an unmet need for new therapies and diagnostic imaging modalities. We adapted 5B1, an anti-CA19.9 human antibody which showed exquisite tumor uptake in PET studies[1], to serve as a radioimmunotherapy (RIT) construct.

METHODS

- 5B1 antibody functionalized with DOTA or CHX-A"-DTPA and chelated to either ^{90}Y or ^{177}Lu.
- Immunoreactivity (IR) for each radioconjugate determined by a cell binding assay in CA19.9(+) human BxPC3 PCa cells.
- Biodistribution studies performed in nude mice bearing BxPC3 PCa ectopic xenografts.
- Radioimmunotherapy initiated in tumor bearing mice at a tumor volume of ~100mm^3.
- Preclinical RIT studies performed at different doses and in combination with gemcitabine.



- Tumor uptake of 5B1 measured at completion of RIT using ^{89}Zr-DFO-5B1 and positron emission tomography (PET).
- RIT performed in an orthotopic BxPC3-luciferase expressing murine PCa model with MRI anatomical imaging and bioluminescence signal measured to assess tumor response.

RESULTS

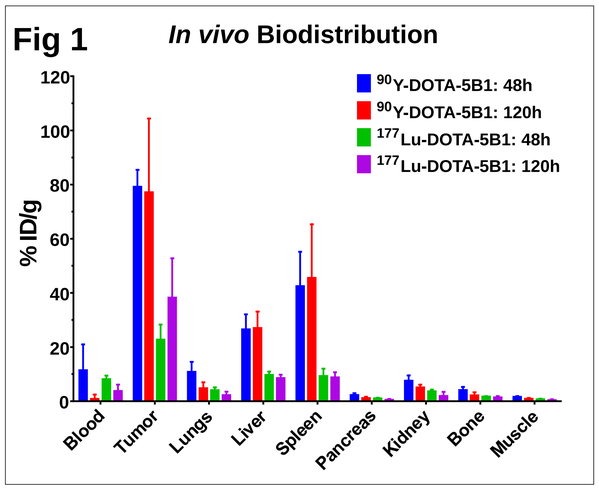
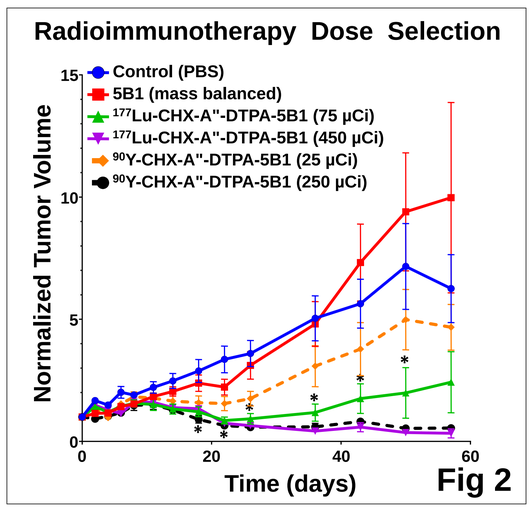
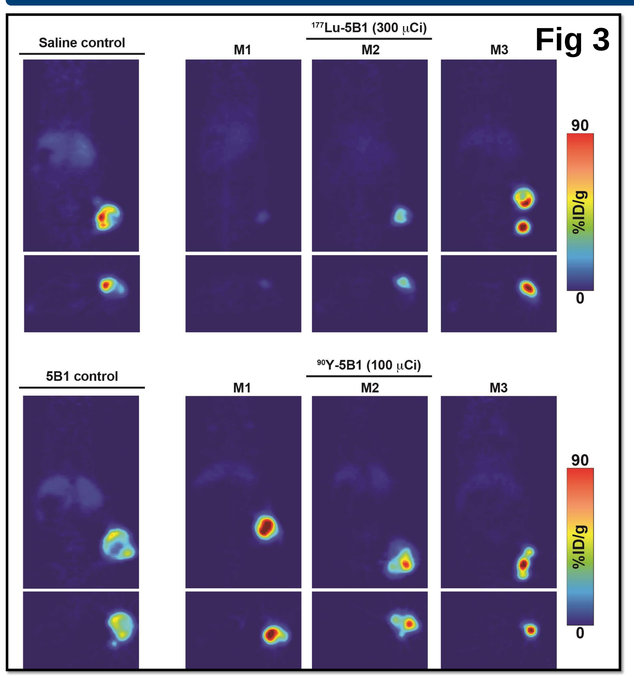


Fig 1: DOTA constructs - uptake for the ^{90}Y-DOTA-5B1 and ^{177}Lu-DOTA-5B1 were 79±6 & 77±27 and 23±6 & 38±14 %ID/g, respectively at 48 and 120h. N = 5 for each group

Fig 2: *In vivo* pre-clinical RIT at multiple doses matched for equivalent tumor absorbed dose between ^{90}Y and ^{177}Lu constructs. Treatments at all doses exhibited significant growth delay. N = 8 each group.





Radioimmunotherapy Response by ^{89}Zr-5B1 PET

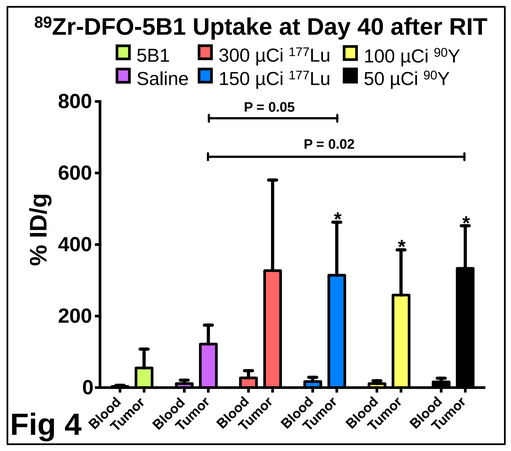
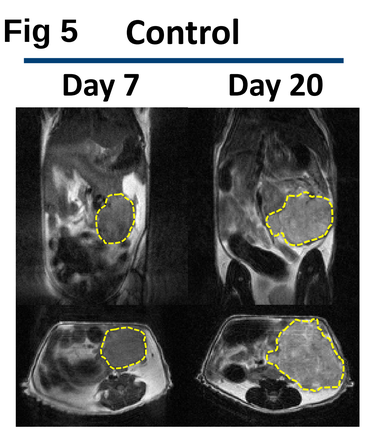
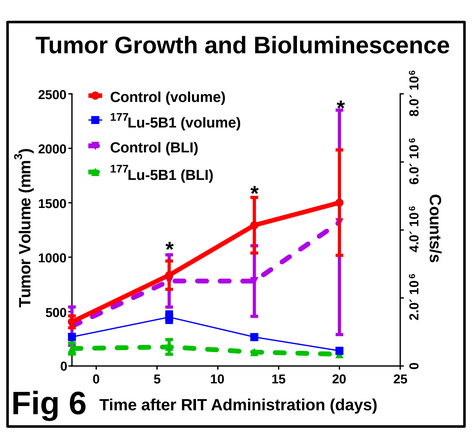


Fig 3 & 4: ^{89}Zr-DFO-5B1 PET imaging on day 60 post-therapy – uptake in treated and control tumors. Post-PET necropsy - ↑ tumor uptake for all the treated mice versus the controls. N = 4 each group.

Radioimmunotherapy in Orthotopic Pancreatic Cancer

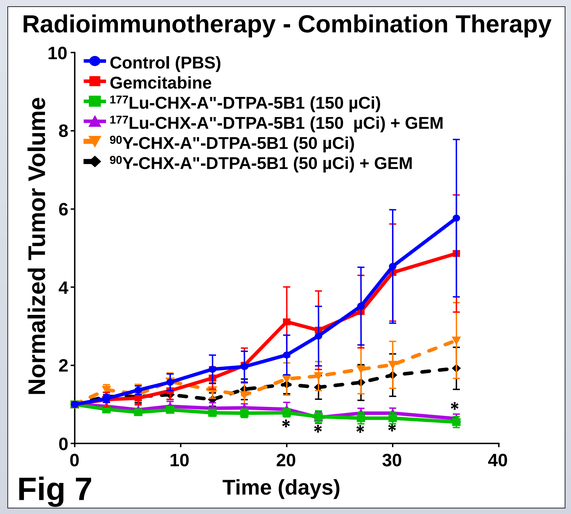
Fig 5 & 6: ^{177}Lu-CHX-A"-5B1 radioimmunotherapy (300 µCi) in mice bearing BxPC3-luciferase tumors. T2-weighted MRI demonstrated significant growth delay with RIT. Bioluminescence also significantly decreased. Post-therapy necropsy in treated mice showed minimal residual tumor. N = 8 (RIT) and N = 6 (control). * - significantly different.





RESULTS (continued)

- Radiochemical conjugate yields >65% and after column purification >95%
- CHX-A"-DPTA-5B1 constructs demonstrated significantly better IR than the DOTA-5B1 constructs (95.3% vs 85.6%, P<0.001).
- DTPA-5B1 constructs showed excellent tumor localization at 48 and 120 hours post-injection.
- Combined therapy with RIT and gemcitabine did not show significant synergism at select doses (**Fig 7**).



CONCLUSIONS

- Radioimmunotherapy scaffolds targeting CA19.9 in preclinical models demonstrate significant tumor cytotoxicity with either ^{90}Y or ^{177}Lu
- Tumor selectivity of 5B1 constructs remained elevated over controls at the completion of therapy
- Radiolabeled constructs targeted to CA19.9 prove versatile in both delivering and monitoring therapy

REFERENCES

1. Viola-Villegas NT *et al*. Applying PET to broaden the diagnostic utility of the clinically validated CA19.9 serum biomarker for oncology. J Nucl Med. **54**:1876-82 (2013).

CONTACT / FUNDING

For questions or comments, please contact Ryan Lanning at lanningr@mskcc.org, or Jason Lewis at lewisj2@mskcc.org

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