CD46 targeted theranostics for imaging and treatment of prostate cancer

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Background: Molecular imaging and radiopharmaceutical therapy utilizing agents targeting prostate specific membrane antigen (PSMA) has transformed the standard of care in prostate cancer. However, as with all cancer imaging agents and therapies, there are notable limitations including heterogeneous or low target expression in some patients. This challenge has spurred great interest in studying new targets in prostate cancer with differential expression profile, with many demonstrating promise.

Methods and Results: We have recently identified CD46 as a targetable antigen in prostate cancer, with particularly high expression in aggressive disease including metastatic adenocarcinoma and neuroendocrine cancer phenotypes (Figure 1A, B). The YS5 antibody was developed which targets a cancer specific epitope present on tumor associated CD46, but not normal tissue antigen [1]. We have utilized this antibody to develop antibody drug conjugate (ADC), ^{89}Zr-labeled immunoPET [2], and ^{225}Ac labeled radiopharmaceutical agents [3], which have demonstrated great promise in preclinical studies (Fig 1A-C, E). More recently, the antibody drug conjugate and immunoPET agents have been translated into the clinic, with promising initial PET images observed in men with mCRPC (Fig 1D).

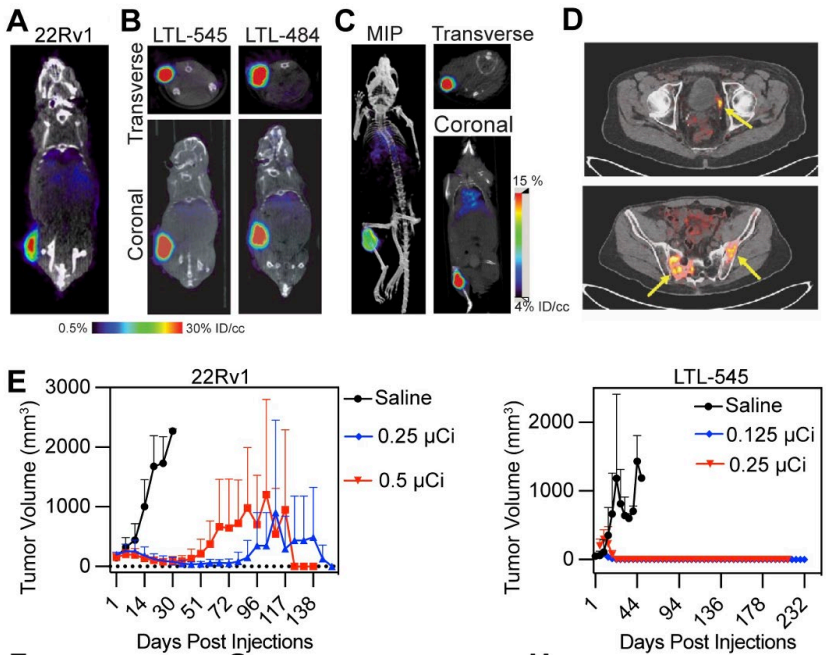

Figure. Efficacy of CD46 directed PET imaging and radiopharmaceutical therapy in prostate cancer. PET imaging following administration of 89Zr-DFO-YS5 in prostate cancer models including A) 22Rv1 xenograft subcutaneous tumors, B) LTL-545 neuroendocrine prostate cancer and LTL-484 adenocarcinoma prostate cancer subcutaneous xenografts, and C) 22Rv1 orthotopic metastatic bone tumor models. D) PET/CT imaging of ^{89}Zr-DFO-YS5 in osseous and lymph node metastases in human prostate cancer. E) Therapeutic efficacy study of ^{225}Ac-DOTA YS5 in 22Rv1 subcutaneous cell line derived xenografts and LTL-545 neuroendocrine prostate cancer xenografts.

Conclusions: These results demonstrate promise for both PET imaging and radioligand therapy of prostate cancer targeting CD46.

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Conflicts of interest: The clinical study of 89Zr-DFO-YS5 is supported in part by Fortis and Fibrogen.

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