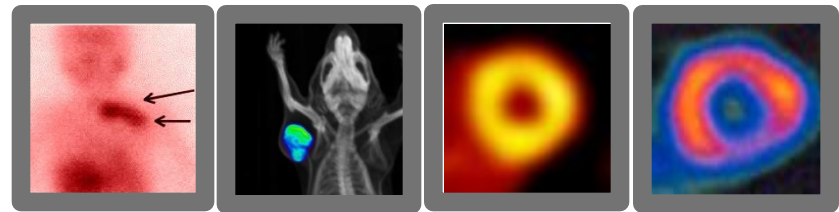


^{99m}Tc -MIP-1340, a Small Molecule Inhibitor of PSMA for Molecular Imaging of Prostate Cancer



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molecularinsight
pharmaceuticals

PIONEERS IN MEDICINE. PARTNERS IN CARE.

Prostate Cancer and PSMA

- Prostate cancer is the second leading cause of cancer-related deaths amongst men in the USA; ~200,000 men are diagnosed with prostate cancer each year, and ~30,000 will die from the disease
- Challenging to detect recurrent disease despite the availability of multiple imaging modalities including MRI, CT, bone scan, and several PET agents
- PSMA is a transmembrane protein expressed in normal prostate, and expression is increased in prostate cancer. Numerous reports demonstrate a correlation of PSMA expression with PSA level, tumor stage, disease recurrence, and time to progression
- Radiolabeled PSMA antibodies have met with limited success due primarily to the long plasma half-life and reduced tissue penetrability, and most likely the intracellular epitope in the case of Prostascint
- Molecular Insight Pharmaceuticals' [¹²³I]MIP-1072 (Trofex™) has validated targeting the catalytic domain of PSMA with small molecules in patients with metastatic prostate cancer

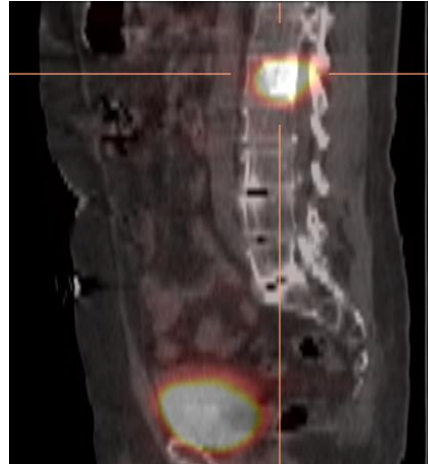
Detection of Bone and Soft Tissue Prostate Cancer Metastases with the PSMA Inhibitor [¹²³I]MIP-1072



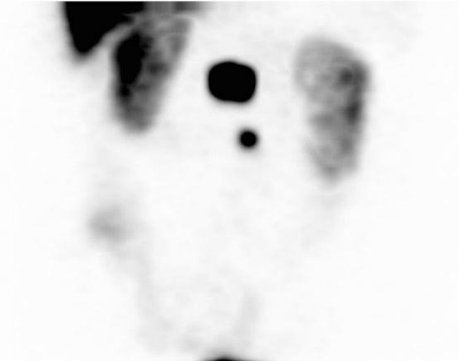
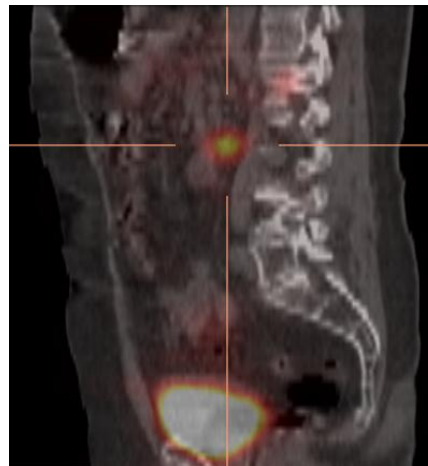
Anterior



Posterior

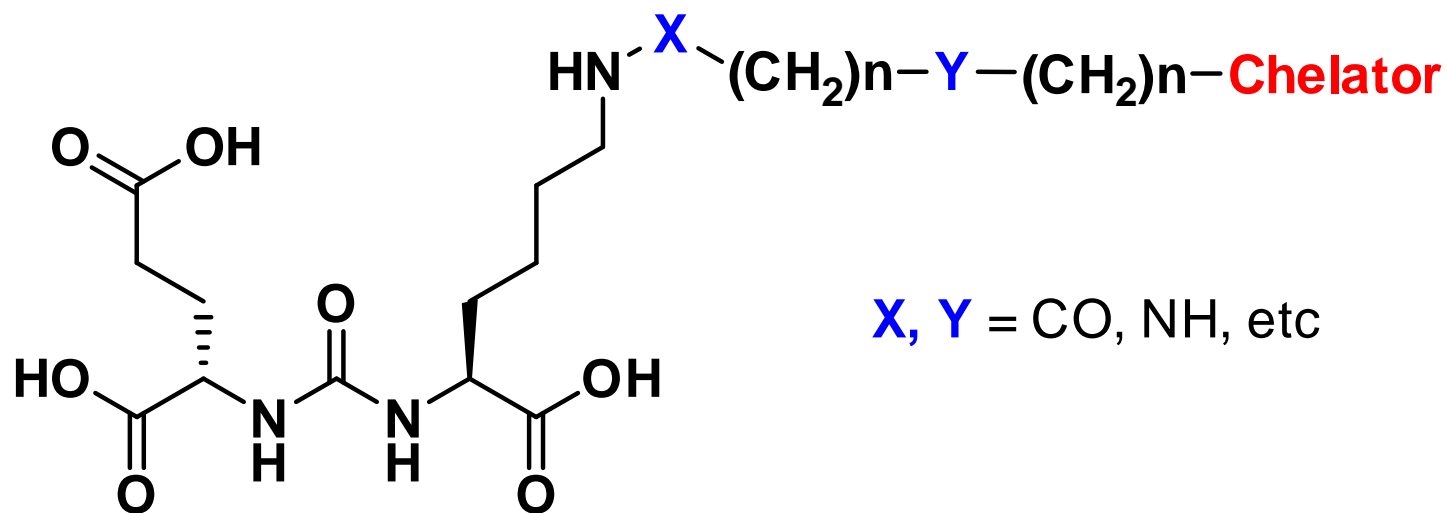


WL: 1383 WW: 3145



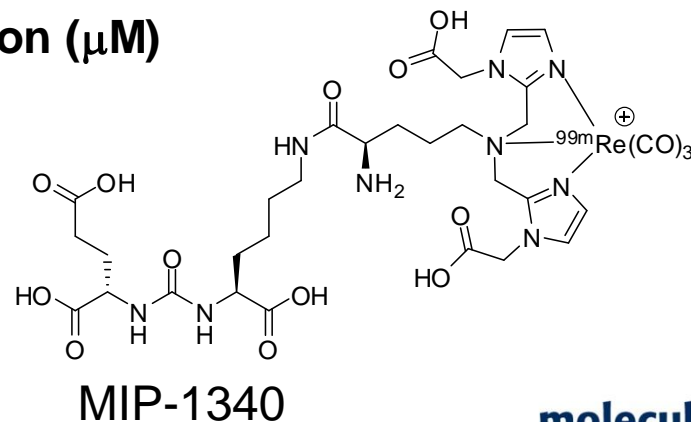
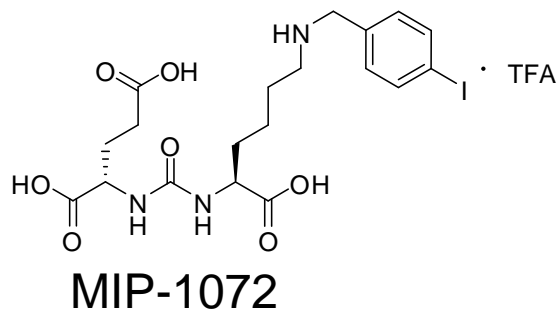
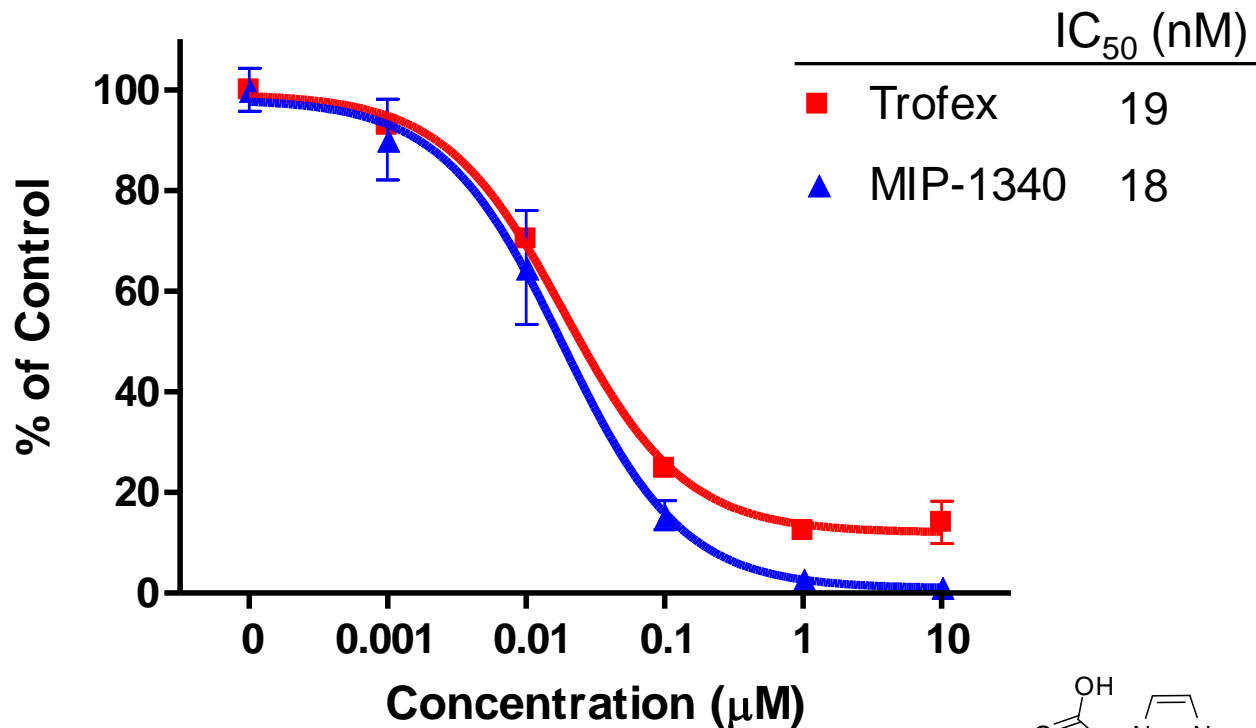
A

Design of Glutamate Urea Heterodimers

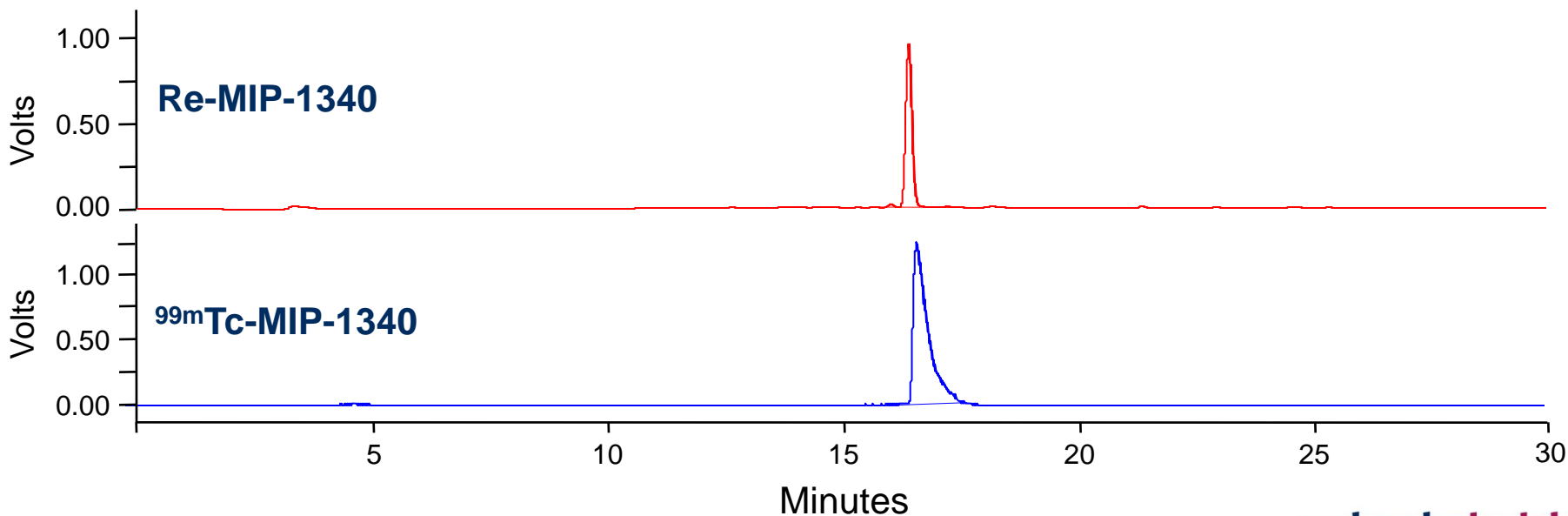
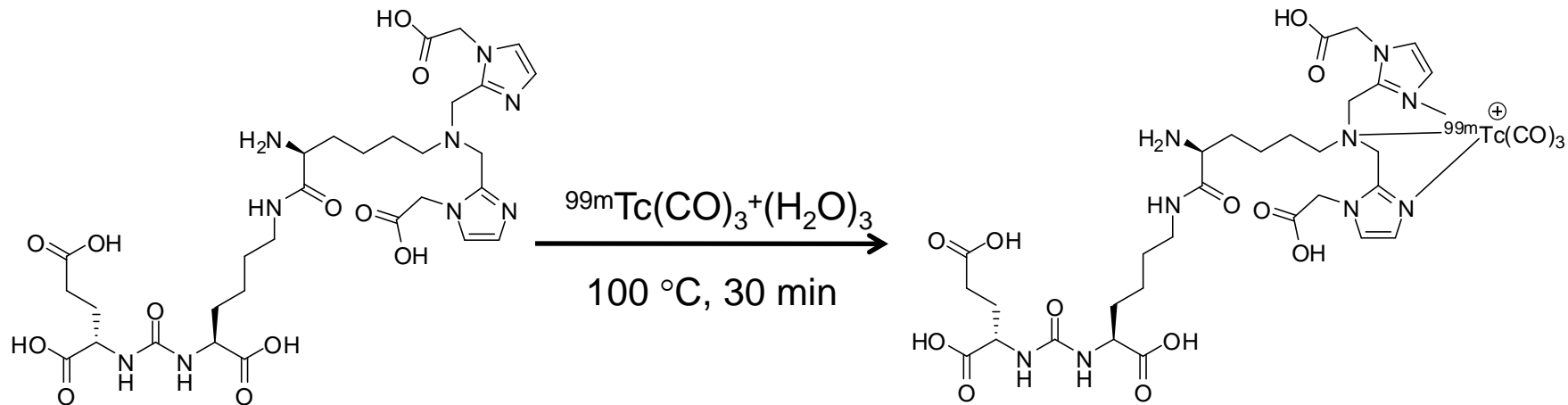


- S1 and S1' permit structural modification to increase steric bulk
- S1' is tolerant to relatively large hydrophobic groups
- S2 and S2' are intolerant to structural changes
- It appears necessary to keep one glutamic acid unit intact

Competitive Binding to PSMA on LNCaP Cells with MIP-1340

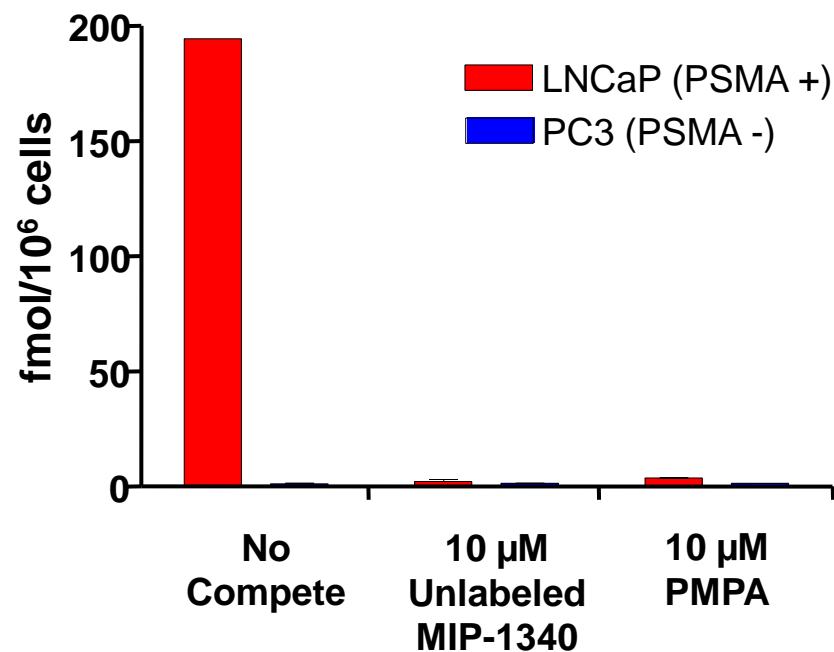
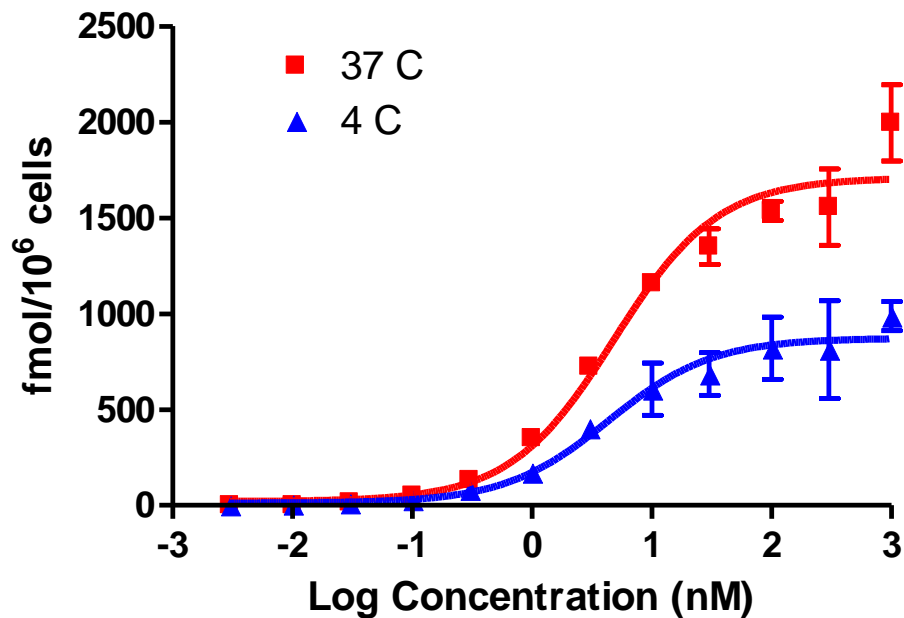


$^{99m}\text{Tc}(\text{CO})_3\text{-MIP-1340}$ is Synthesized in High Radiochemical Yield and Purity

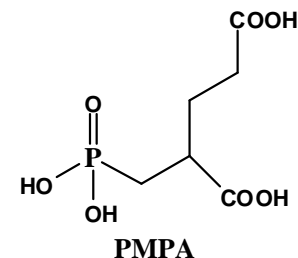


RCY = 90%, RCP = 97%, SA >20,000 mCi/ μmol (based on LOD)

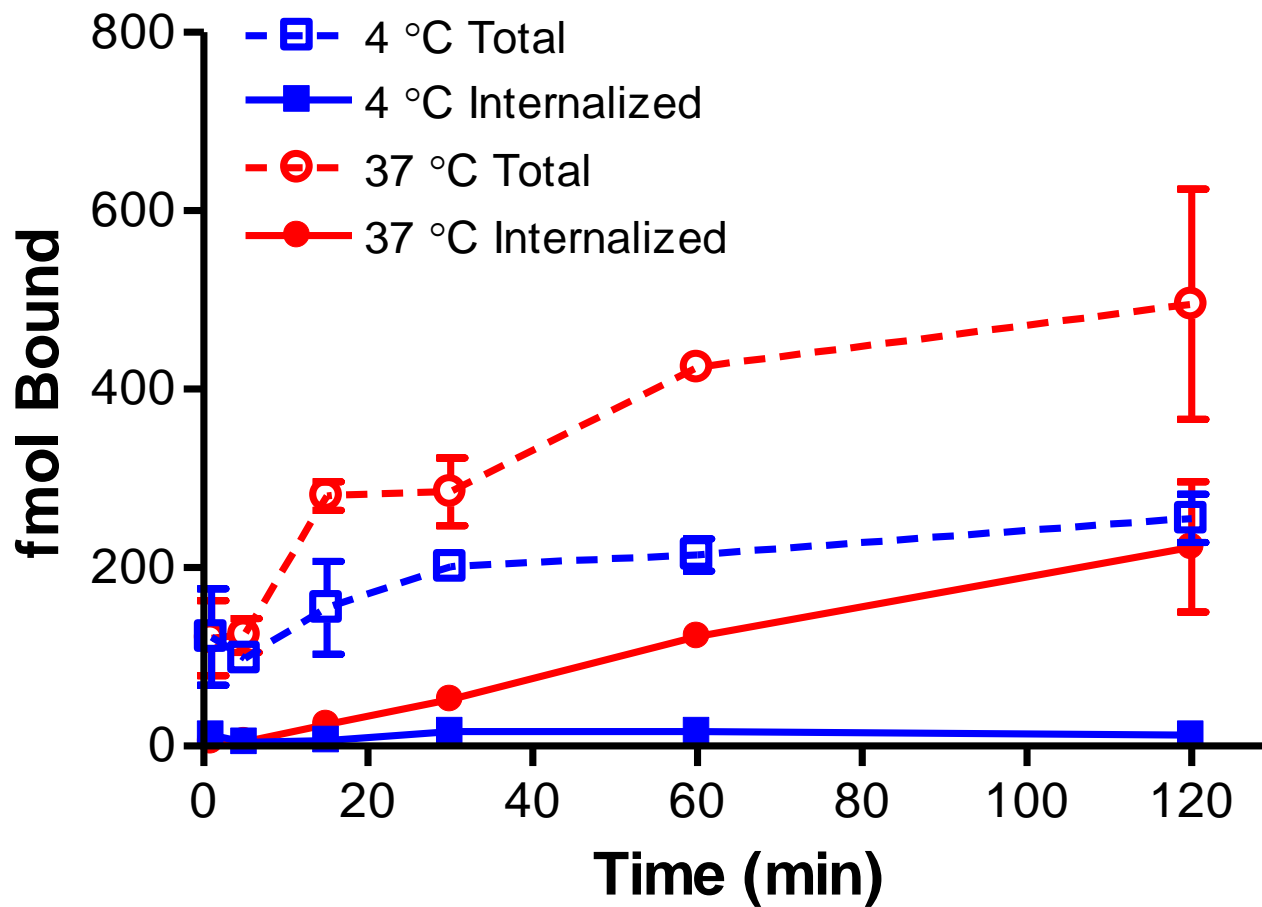
^{99m}Tc -MIP-1340 Exhibits High Affinity Binding Specific to PSMA Expression



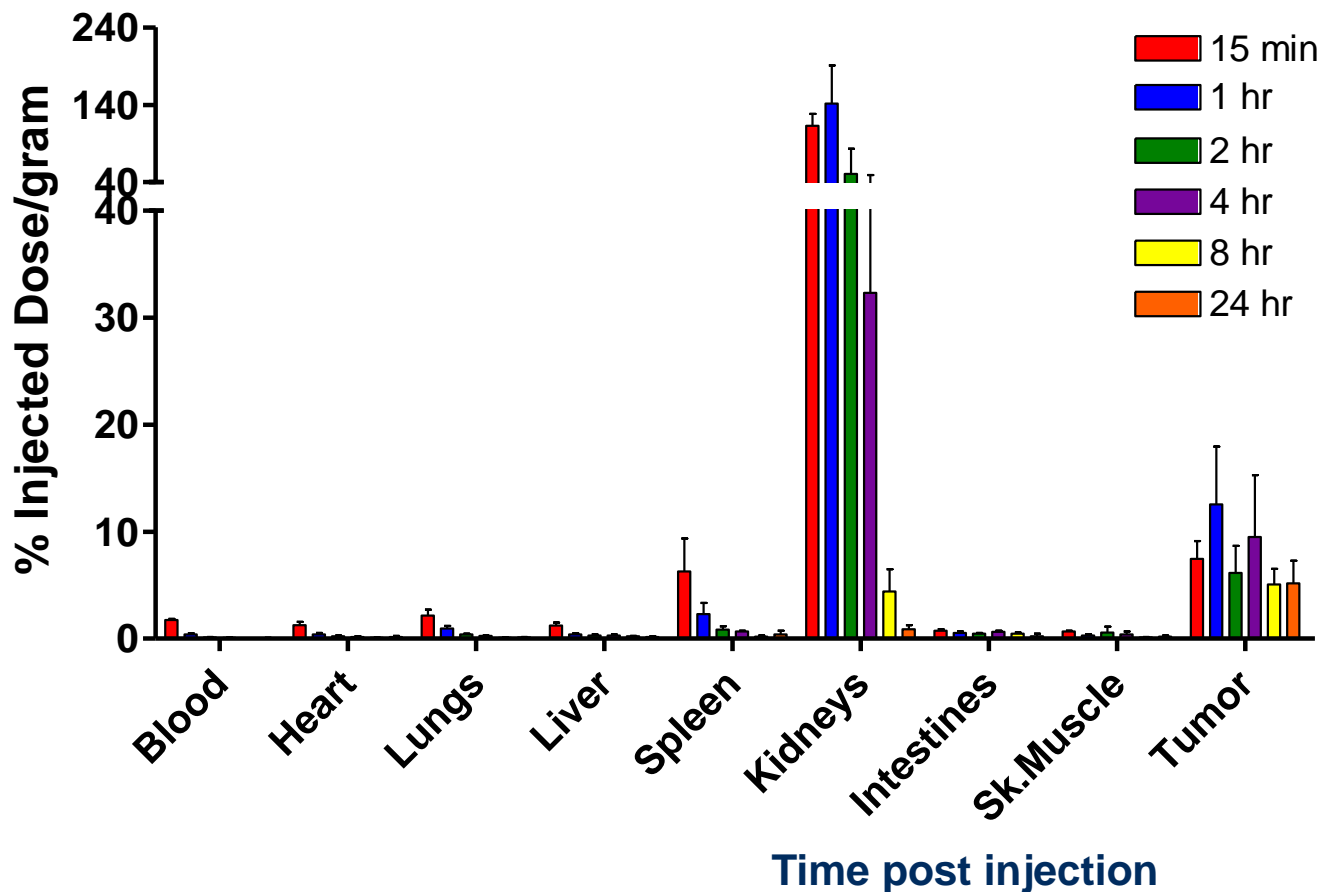
	4 °C	37 °C
Kd (nM)	4.1	4.6
Bmax (fmol/10 ⁶ cells)	870	1706



^{99m}Tc -MIP-1340 Internalizes in LNCaP Cells



Favorable Non-Target Tissue Pharmacokinetics and Tumor Uptake of ^{99m}Tc -MIP-1340 in LNCaP Xenograft Mice



	15 min	1 hr	2 hr	4 hr	8 hr	24 hr
Tumor:Blood	4	32	46	117	286	110
Tumor:Skeletal Muscle	11	41	10	23	46	26

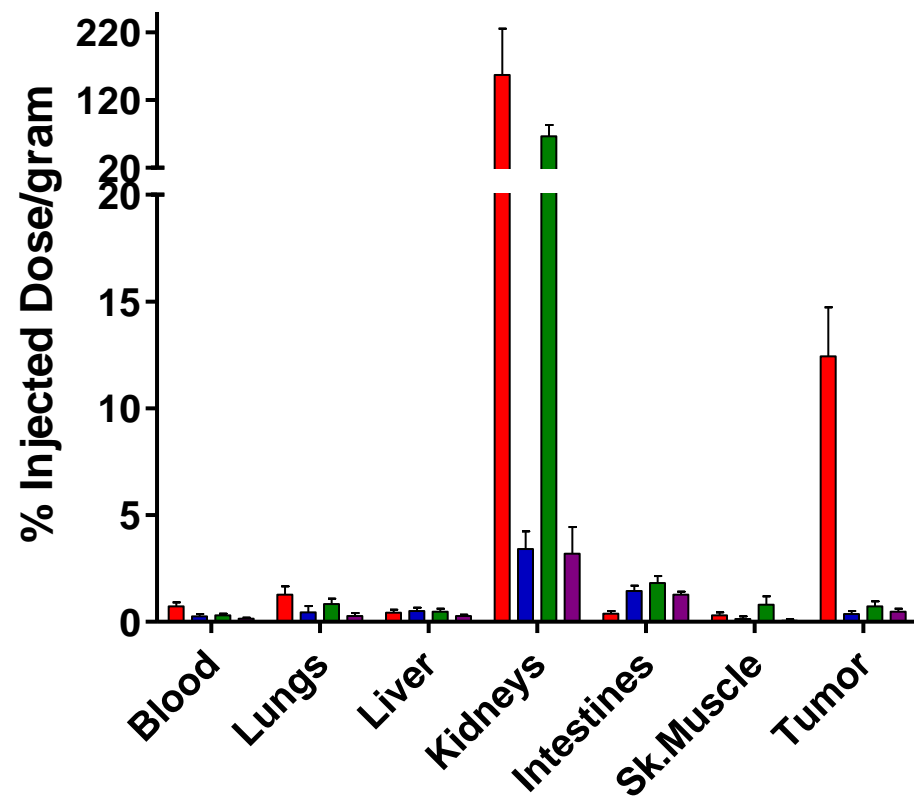
Specific Binding to PSMA is Demonstrated by PMPA and Cold MIP-1340 Blocking *in Vivo*

LNCaP (PSMA +) Tumor

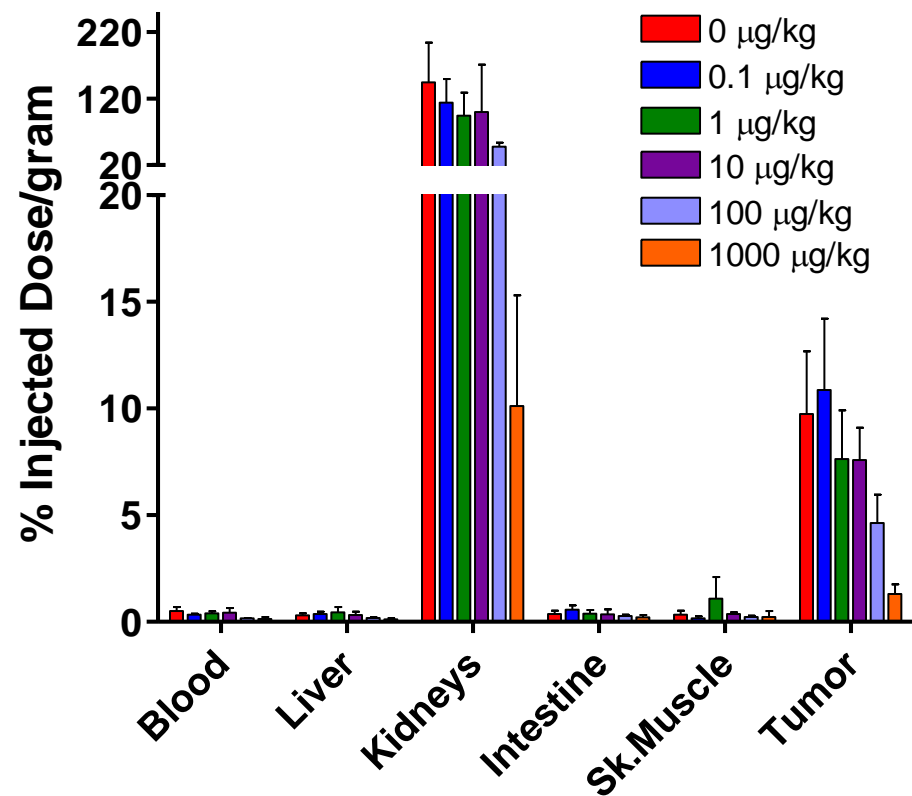
PC3 (PSMA -) Tumor

■ Unblocked
■ 50 mg/kg PMPA Blocked

■ Unblocked
■ 50 mg/kg PMPA Blocked

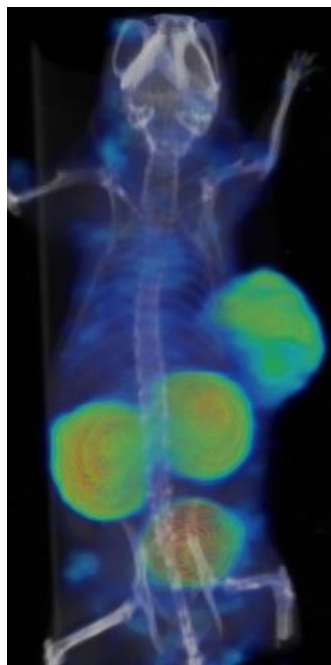


Tissue Distribution of ^{99m}Tc-MIP-1340 with Cold Competition



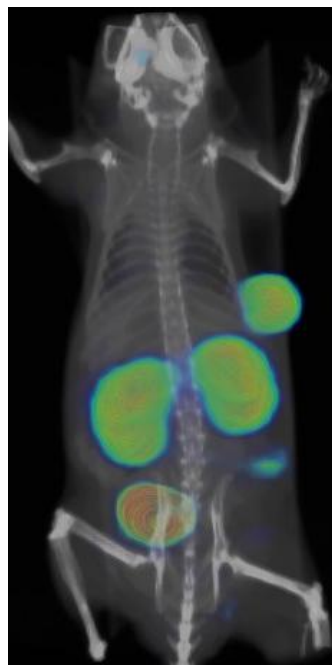
SPECT/CT Imaging of ^{99m}Tc -MIP-1340 in LNCaP Xenograft Mice

Mouse 1



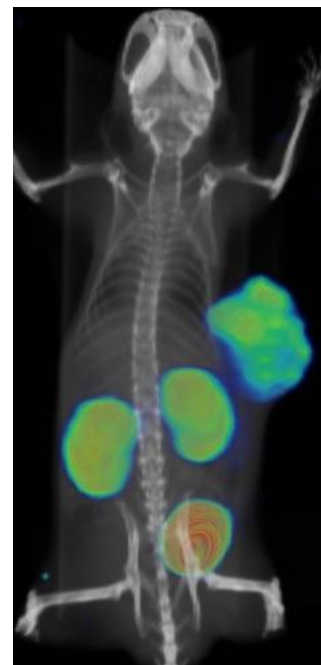
5-45 min

Mouse 2



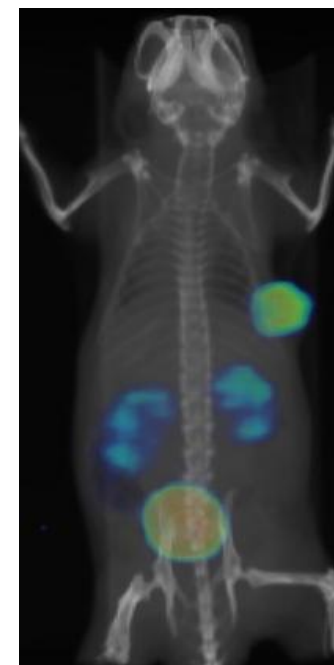
60-105 min

Mouse 1



120-165 min

Mouse 2



240-285 min

Conclusions

- A novel ^{99m}Tc -derived PSMA inhibitor based on glutamate-urea-lysine was designed, synthesized, and radiolabeled
- ^{99m}Tc -MIP-1340 binds to PSMA with high affinity and specificity *in vitro* and *in vivo*
- ^{99m}Tc -MIP-1340 selectively accumulates in PSMA positive human prostate cancer xenografts and clears rapidly from non-target tissues
- ^{99m}Tc -MIP-1340 shall be evaluated in prostate cancer patients under an exploratory IND
- ^{99m}Tc -MIP-1340 may permit the more accurate diagnosis and staging of prostate cancer, and enable the monitoring of therapy

Contributors

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