

Novel ^{99m}Tc -labeled Small Molecule Inhibitors of Prostate Specific Membrane Antigen (PSMA): Initial experience in healthy volunteers and men with metastatic prostate adenocarcinoma (PCa)

Shankar Vallabhajosula, Ph.D.

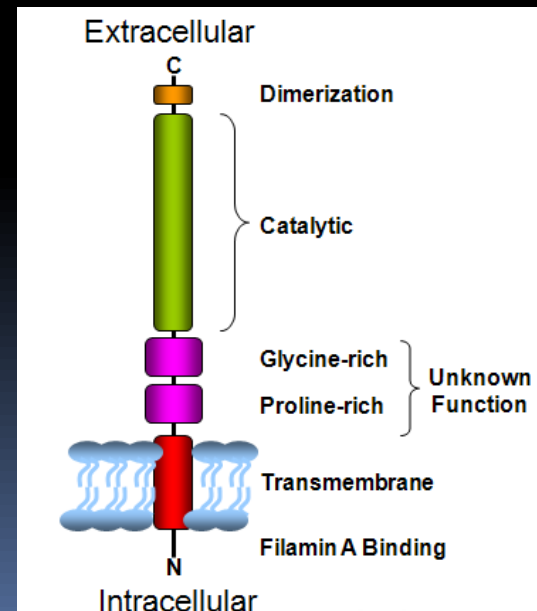
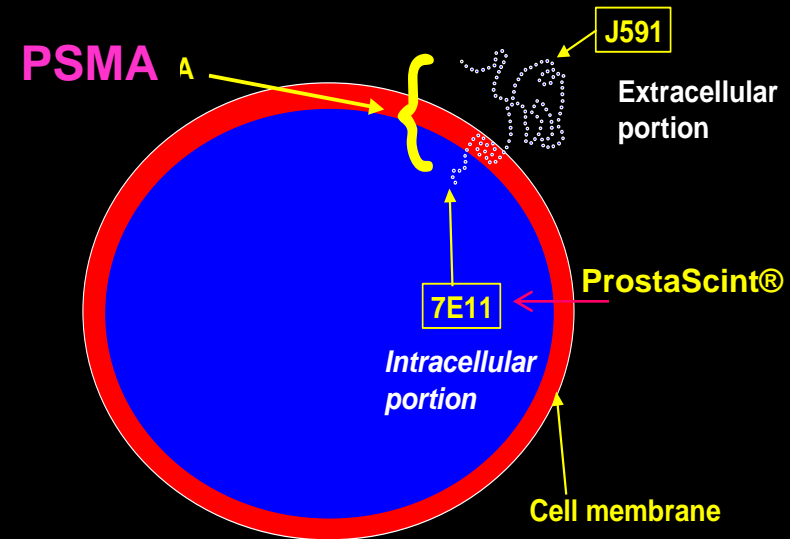
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Cambridge, MA, USA.**

Prostate Specific Membrane Antigen (PSMA)

- PSMA is a surface antigen expressed virtually on all prostate cancer cells
- PSMA expression increases progressively in:
 - Higher grade tumors
 - Metastatic disease
 - Hormone-refractory Prostate cancer
- PSMA is internalized
- PSMA is expressed also on the neo-vasculature of solid tumors but not on normal tissue



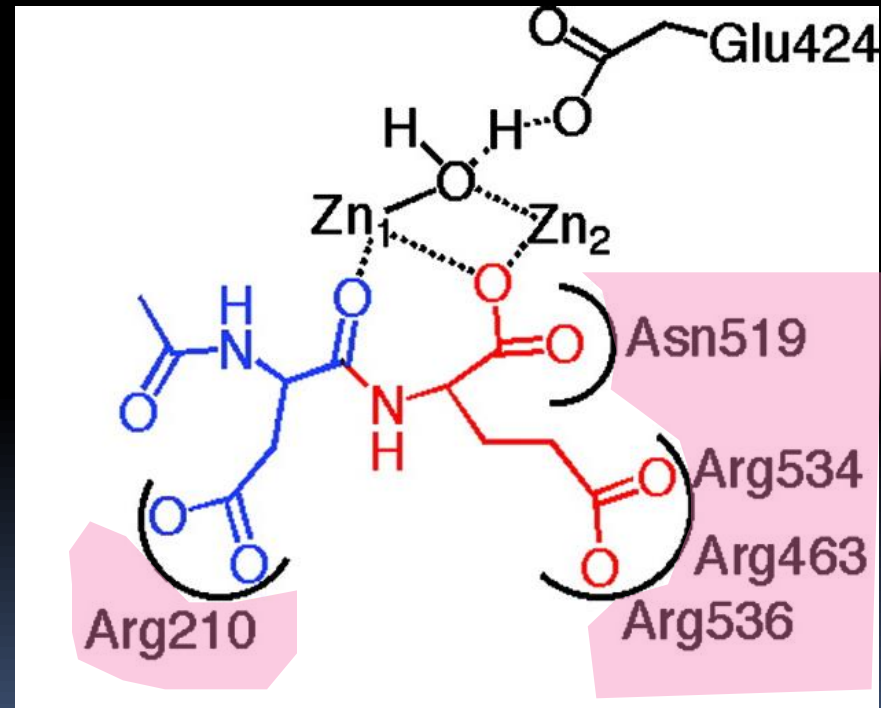
PSMA is a **glutamate carboxypeptidase**

NAALADASE (N-acetylated α -linked acidic Dipeptidase) and PSMA are Homologous)

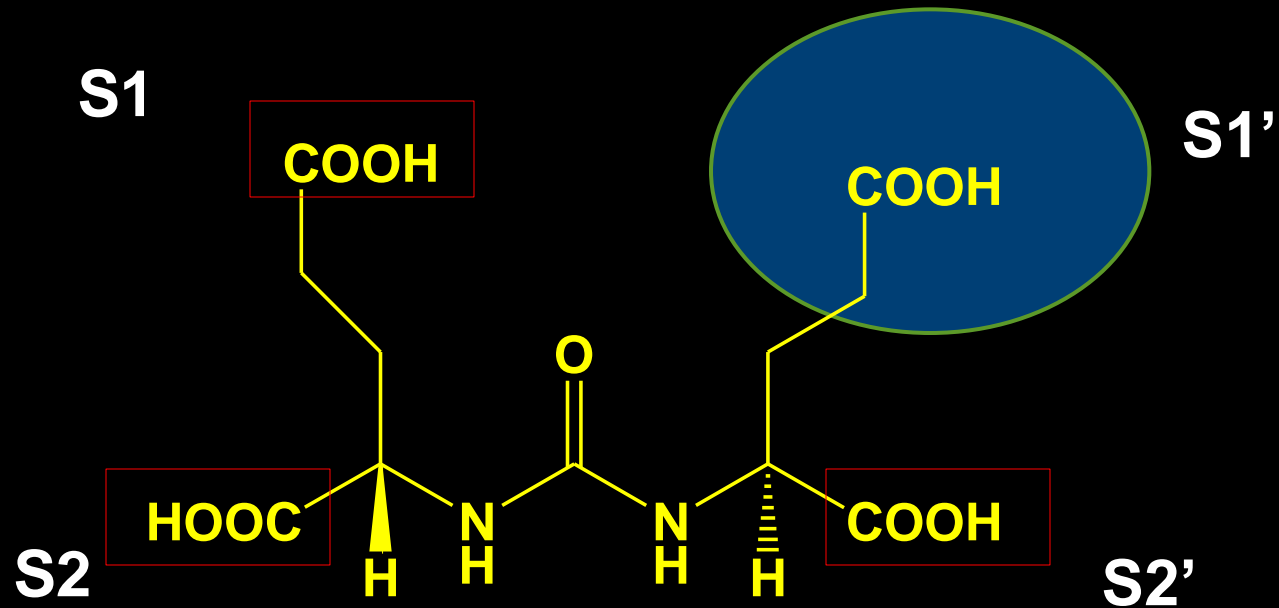
N-acetylaspartyl glutamate (NAAG) $\xrightarrow{\text{PSMA}}$ **NAA + Glutamate**

Enzymatic Site of PSMA is known:

N-acetylated α -linked acidic
Dipeptidase (NAALADASE)



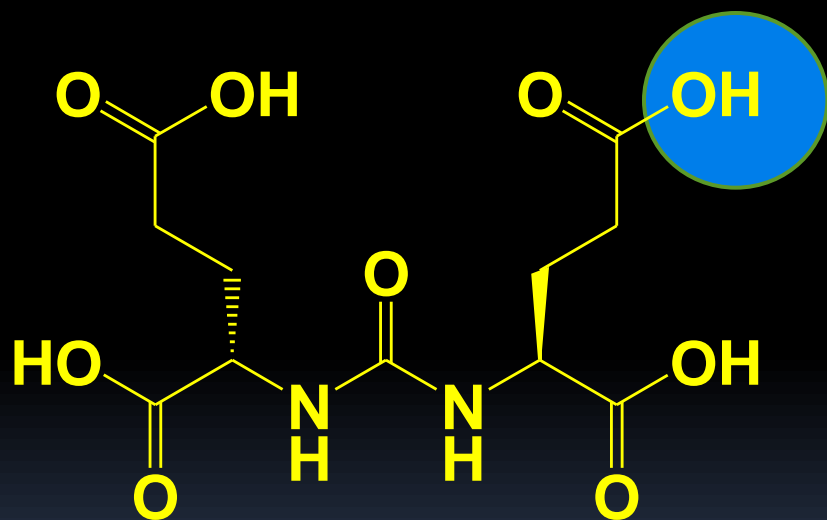
Design Approach: Glutamate Urea Amino Acid Heterodimers Radiolabeled at S1'



- It appears necessary to keep one glutamic acid unit intact
- S2 and S2' are intolerant to structural changes
- Assuming S1, S2 and S2' intact, S1' is tolerant to increase steric bulk

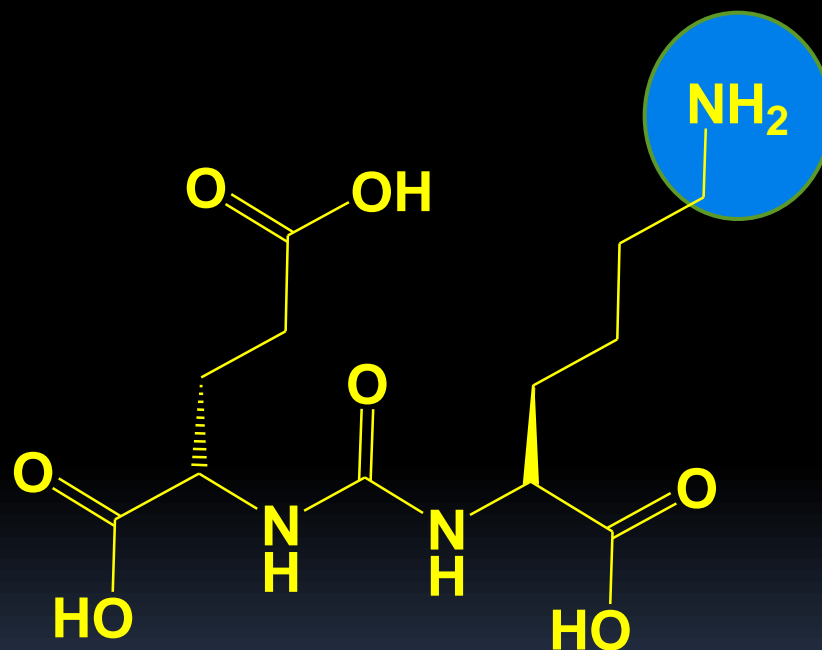
PSMA Binding: Glutamate Urea Heterodimers Radiolabeled at S1'

Glu-urea-Glu



403 nM

Glu-urea-Lys



497 nM

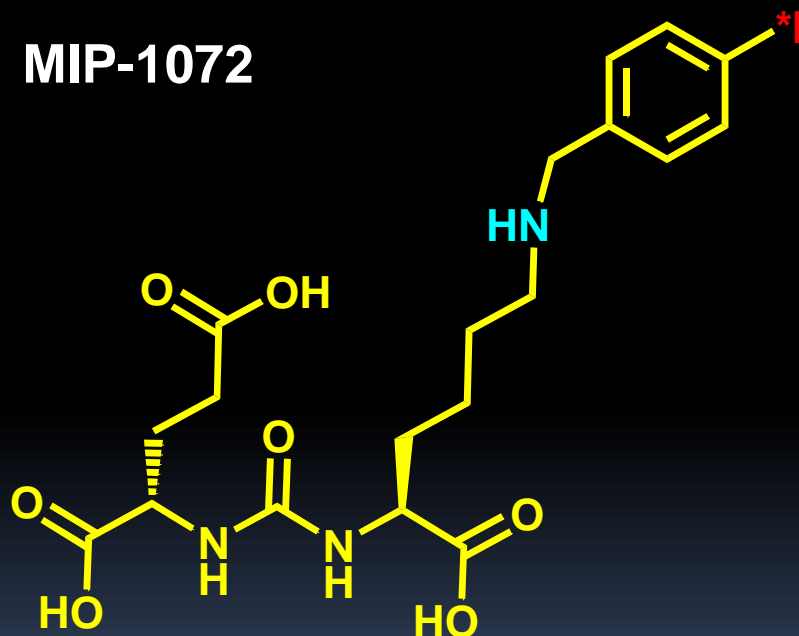
MIP-1072 and MIP-1095

NAALADase Inhibition (K_i)

MIP-1072 6 nM

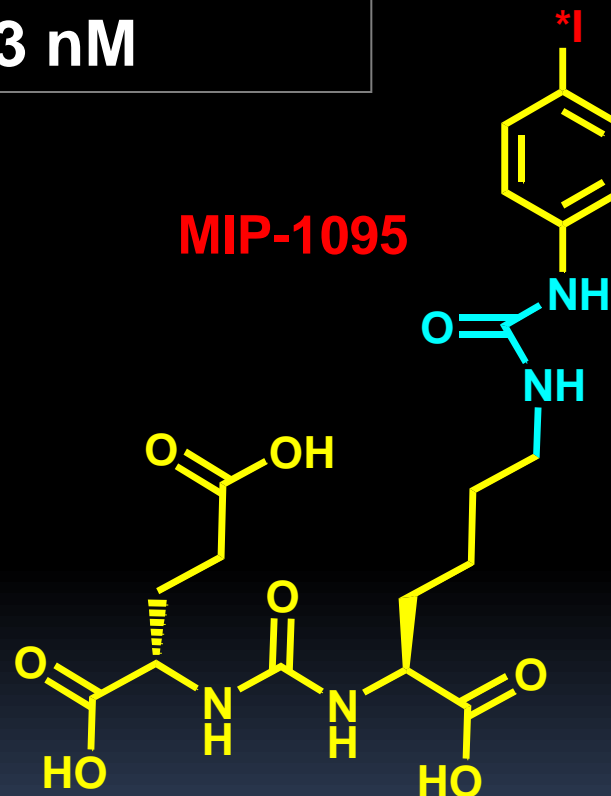
MIP-1095 0.3 nM

MIP-1072



2-(3-(1-carboxy-5-(4-iodo-benzylamino)-pentyl)-ureido)-pentanedioic acid

MIP-1095

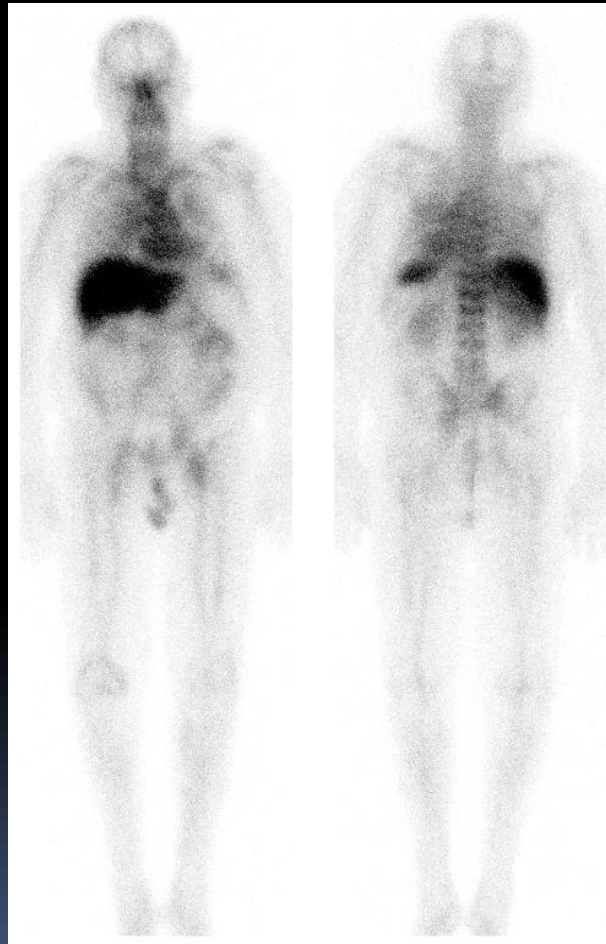


(S)-2-(3-(R)-1-carboxy-5-(3-(4-iodophenyl)ureido)pentyl)ureido)pentanedioic acid

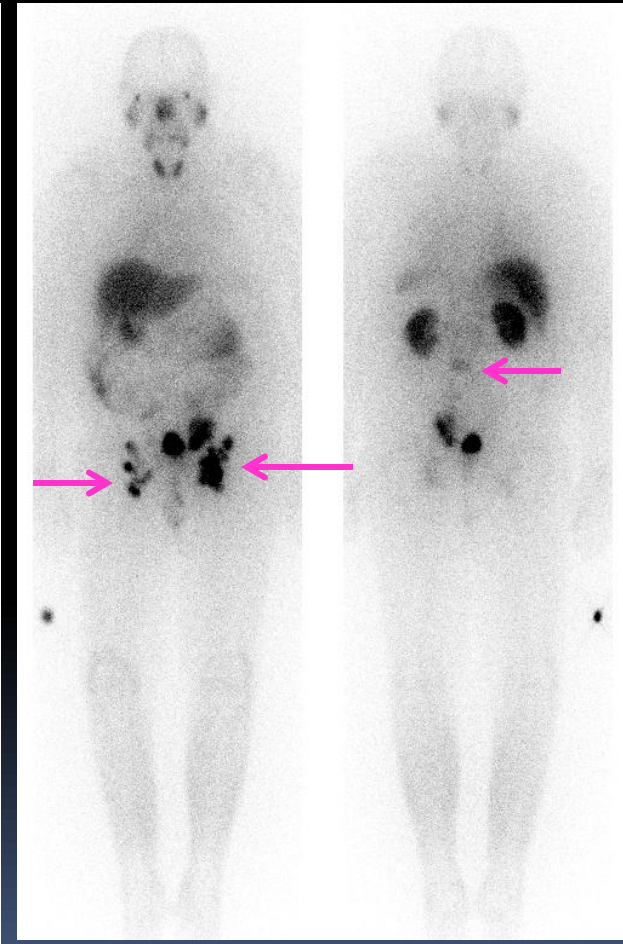
**^{99m}Tc -MDP
Bone Scan**



**^{111}In -ProstaScint
5 days**



**^{123}I -MIP-1072
4 Hours**



Development of ^{99m}Tc labeled anti-PSMA inhibitors based on Single Amino Acid Chelator (SAAC) Platform Technology

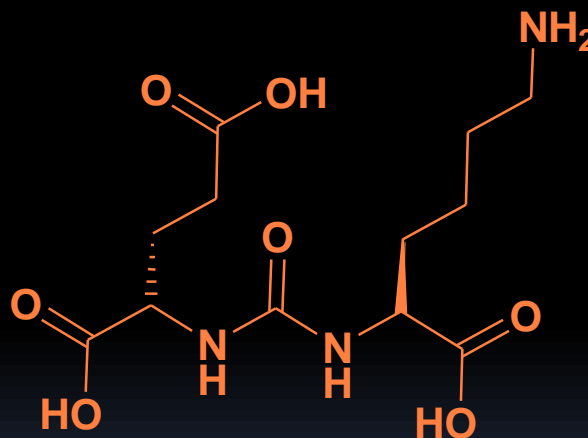
- *Exploit the inertness of the **Tc Tricarbonyl core** developed by Alberto and co-workers*
- **Ease of synthesis**
- **Readily incorporated into libraries of compounds**
- **Efficient radiolabeling, integral labeling moiety**
- **Chemical and radiochemical stability**
- **Biologically acceptable**

Tethered Glu-Urea-Lys-[X]-SAAC-1 Analogs



Glu-Urea-Lys

Linker — **SPACER** — **Chelate**
for ^{99m}Tc

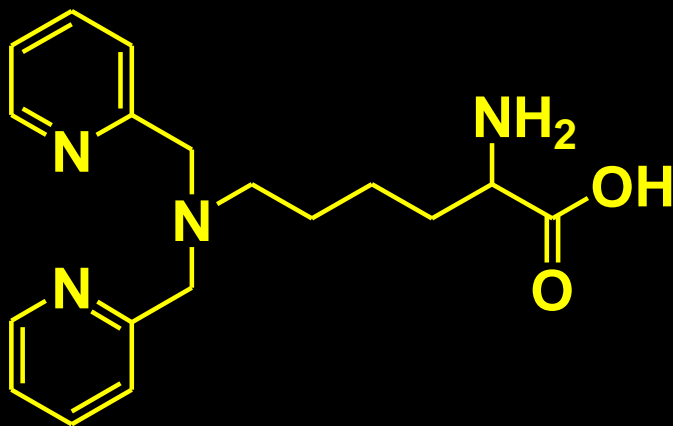


MIP-1033

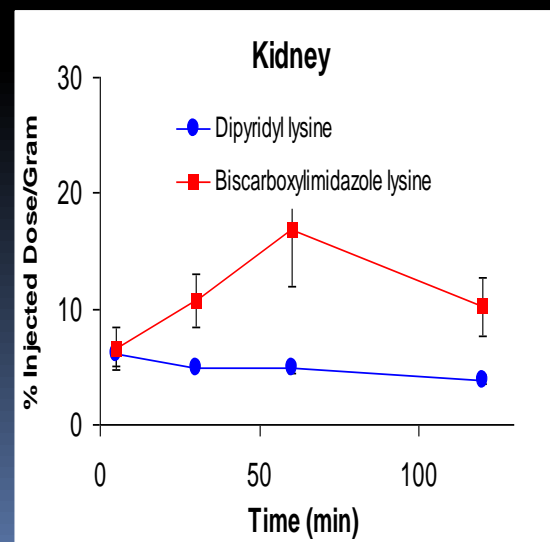
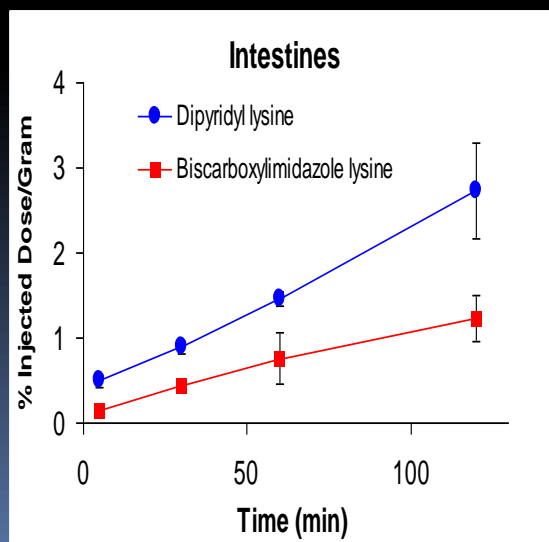
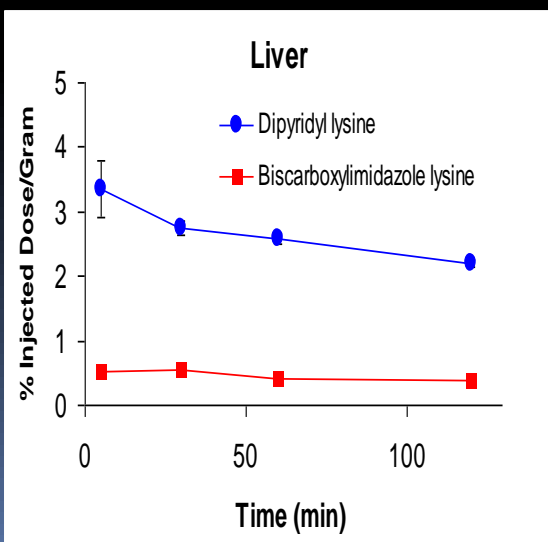
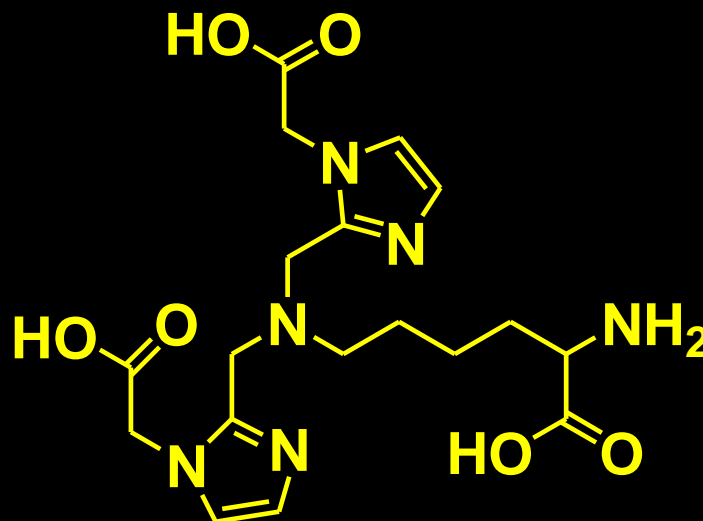
497 nM

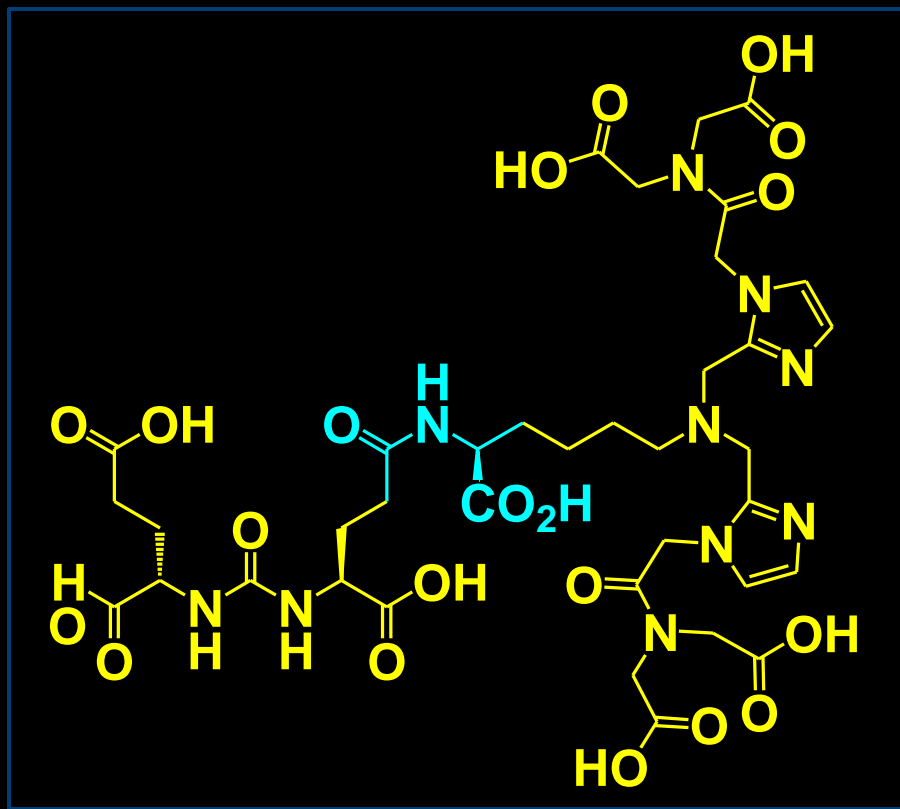
^{99m}Tc -Single Amino Acid Chelate (SAAC) Molecules Kinetics and Biodistribution in Rats

Dipyridyl Lysine



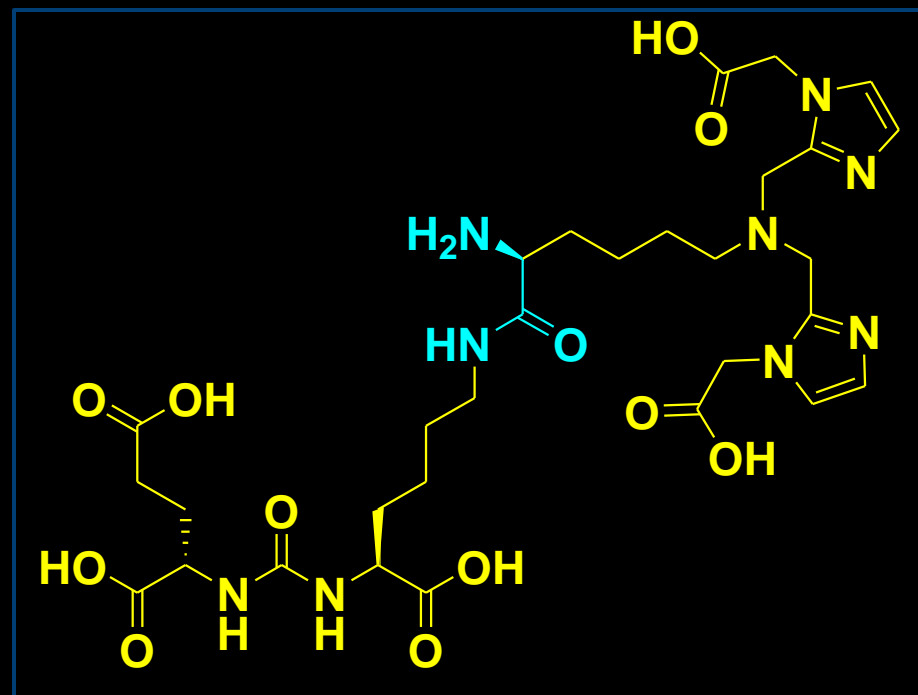
Bis-carboxymethyl-imidazole Lysine





MIP-1404 (104 nM)

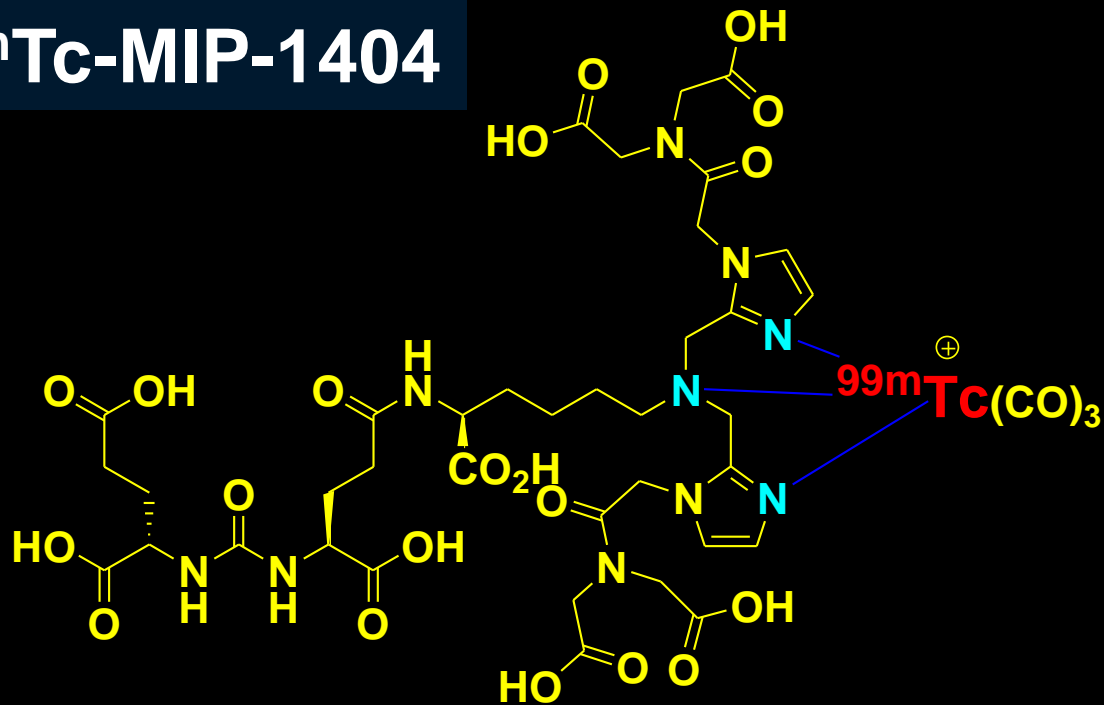
Re-MIP-1382 (2.0 nM)



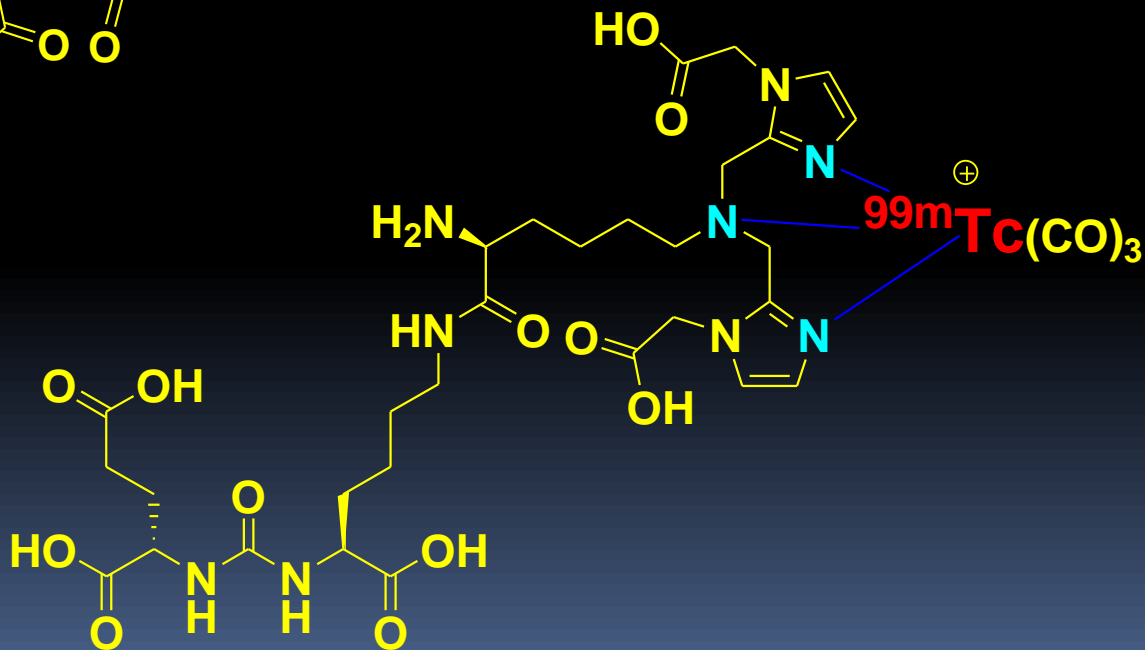
MIP-1405 (31 nM)

Re-MIP-1340 (20 nM)

^{99m}Tc -MIP-1404



^{99m}Tc -MIP-1405



Preparation of ^{99m}Tc -MIP-1404 or ^{99m}Tc -MIP-1405

$^{99m}\text{TcO}_4^-$ + Isolink Kit* + MIP-1404 or MIP-1405
3-7 – 7.4 GBq (0.1 – 0.2 Ci) (100 μg)

100° C, 60 min

* $^{99m}[\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3]^+$ forms in situ

^{99m}Tc -MIP-1404 or ^{99m}Tc -MIP-1405

C18 Sep-pack purification
0.22 μ Membrane filtration

Human dose: 0.74 GBq (20 mCi)

RCP > 90% (Based on HPLC)

Isolink™ (Covidien) Kit

- 2.85 mg sodium tetraborate decahydrate
- 8.50 mg sodium tartrate dihydrate
- 7.15 mg sodium carbonate
- 4.50 mg sodium-borano-carbonate

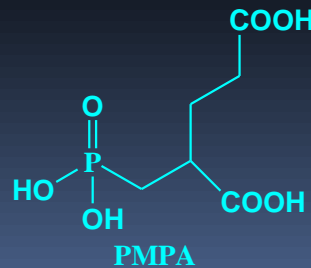
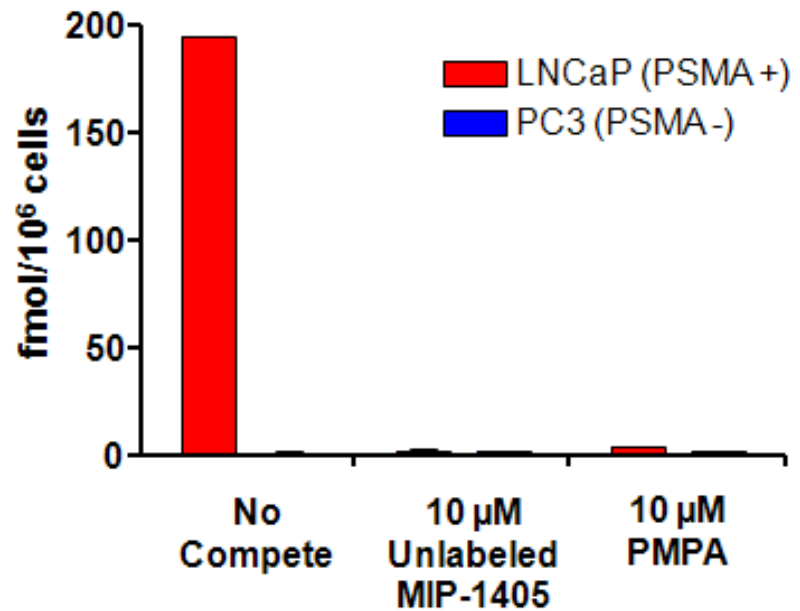
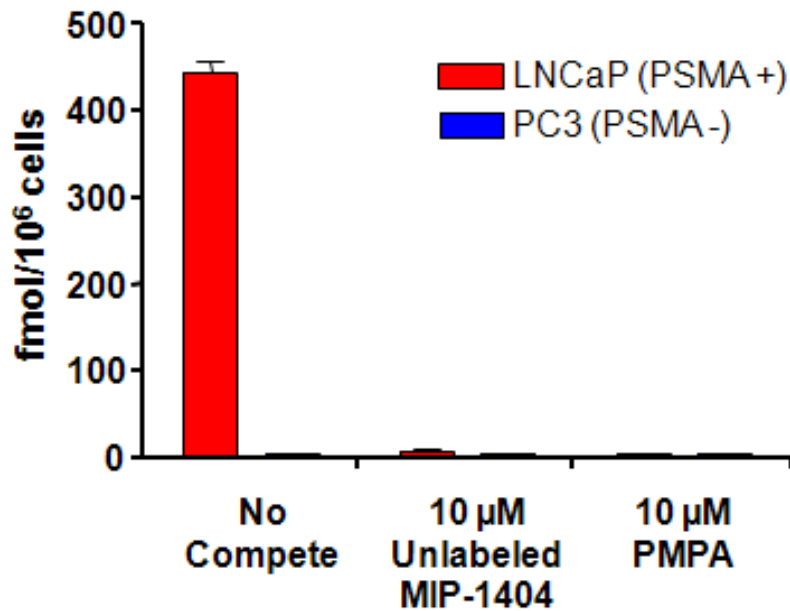
Sterile Lyophilized Formulation

Stable at 2-8 °C for 48 months

MIP-1404 and MIP-1405 Bind to PSMA+ LNCaP Cells with High Affinity and Specificity

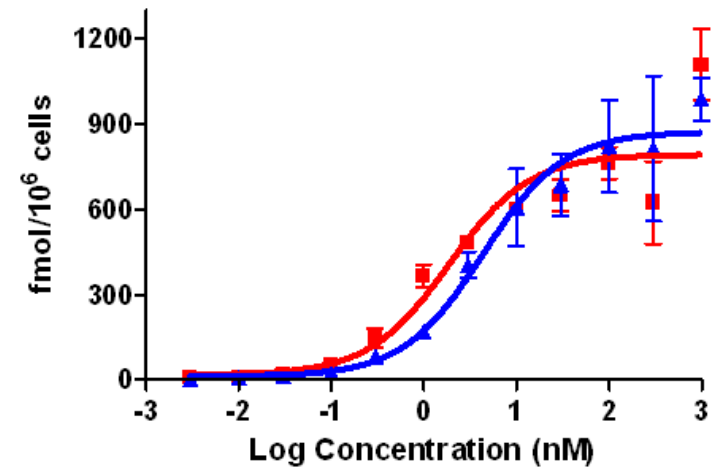
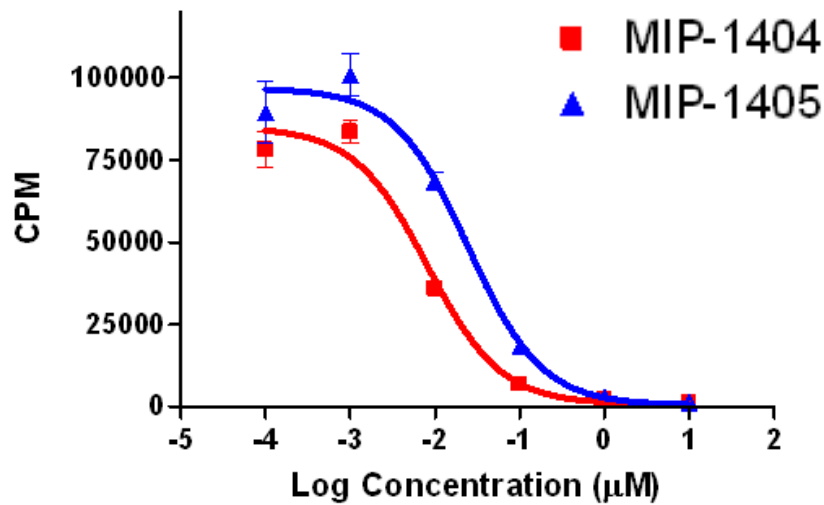
^{99m}Tc -MIP-1404

^{99m}Tc -MIP-1405



Competitive and Saturation Binding Assays with PSMA+ LNCaP cells

	IC_{50} (nM)	K_d (nM)	B_{max} (fmol/ 10^6 cells)
■ Re-MIP-1404	5.0	1.7	789
▲ Re-MIP-1405	22	4.1	871



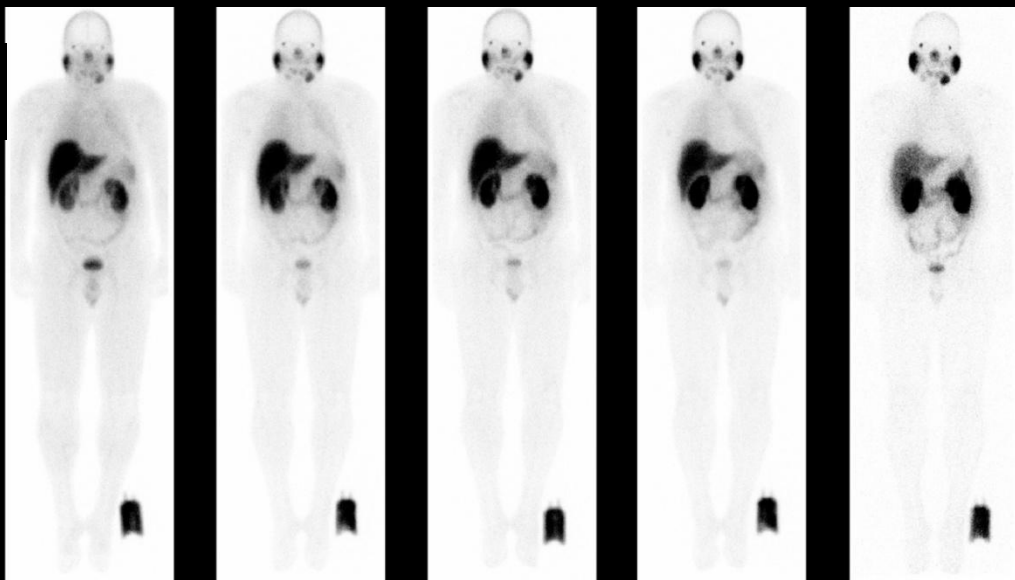
Novel ^{99m}Tc -labeled Small Molecule Inhibitors of PSMA: **First human studies in Patients with metastatic Prostate Cancer**

Objectives

- Under an exploratory IND, and cross over design compare the pk, biodistribution and tumor uptake of ^{99m}Tc -MIP-1404 and ^{99m}Tc -MIP-1405
- Each subject had both tracers, **2 wks apart**
- Patients (n=6) and normal cotrols (n=6)
- **Dose 20 mCi** (0.74 GBq); SA = 1-2 mCi/ μg
- Imaging studies: Planar: at 10 min, 1, 2, 4, 24 hrs
SPECT: at 4 and 24 hours
- Serial blood samples for 24 hours
- Total urine collection (0-2, 2-4 and 4-24 hours)
- Safety studies: Blood chemistry, EKG

Biodistribution in Normal Subjects

MIP-1404



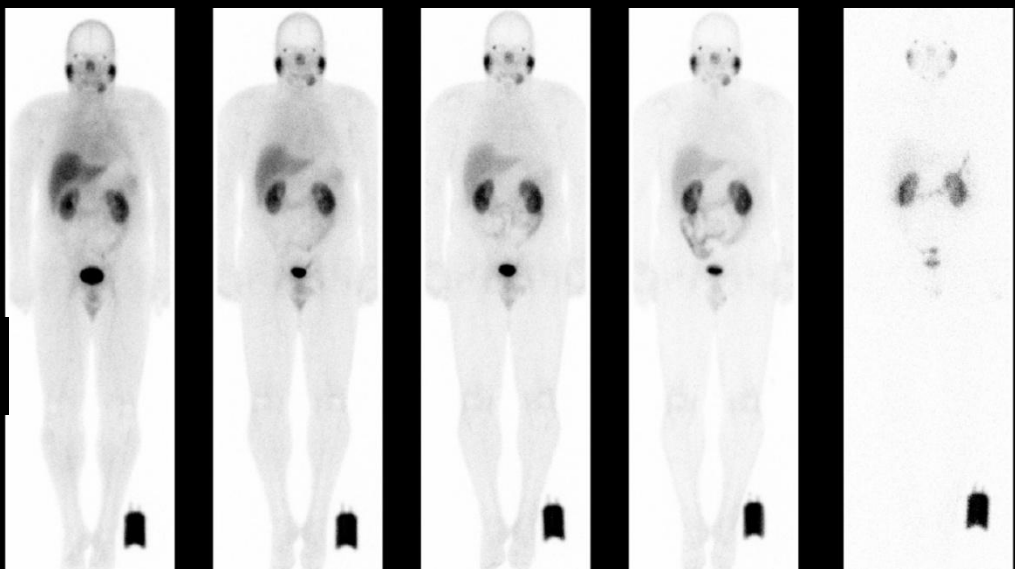
10 min

1 h

2 h

4 h

24 hours



MIP-1405

- Rapid blood clearance
- Liver and kidney uptake

MIP1404 > MIP 1405

- Urinary clearance

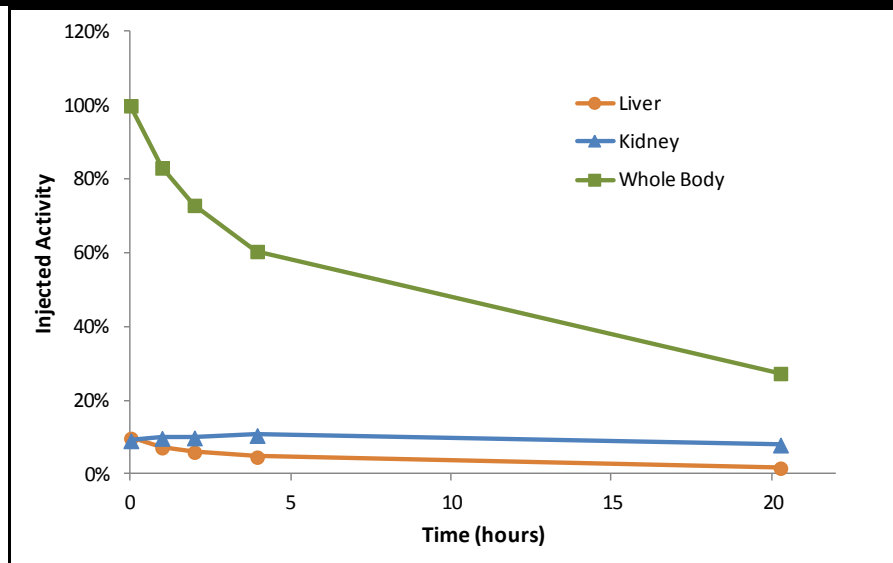
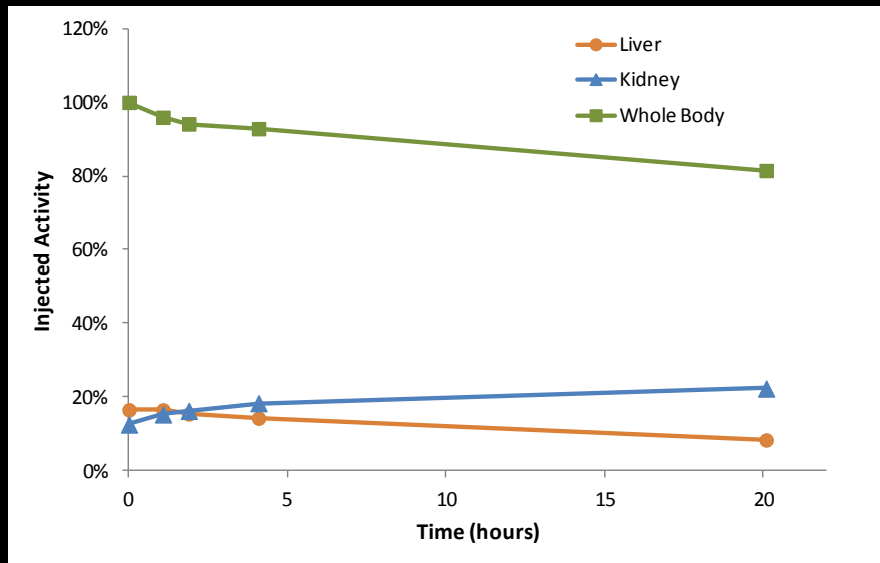
MIP1404 < MIP 1405

- Rapid and persistent uptake in the salivary, lacrimal and parotid glands.

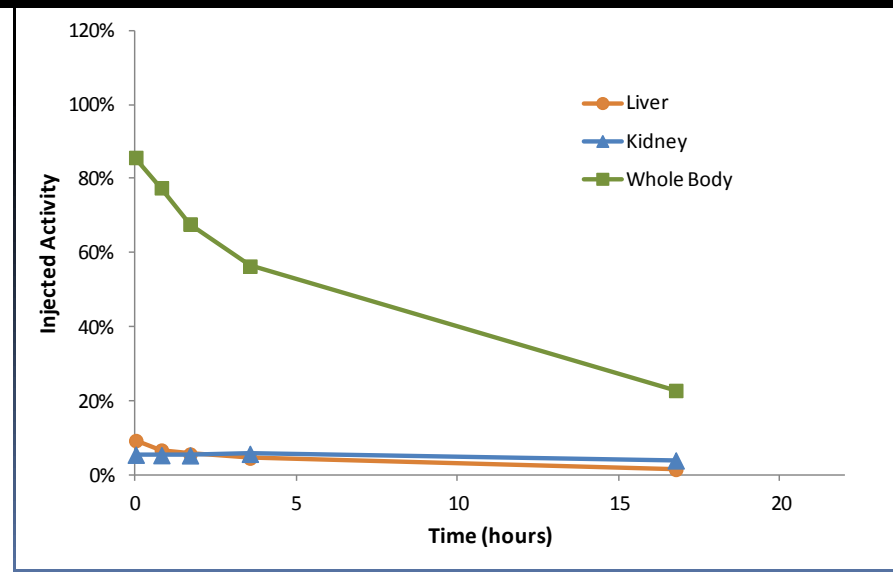
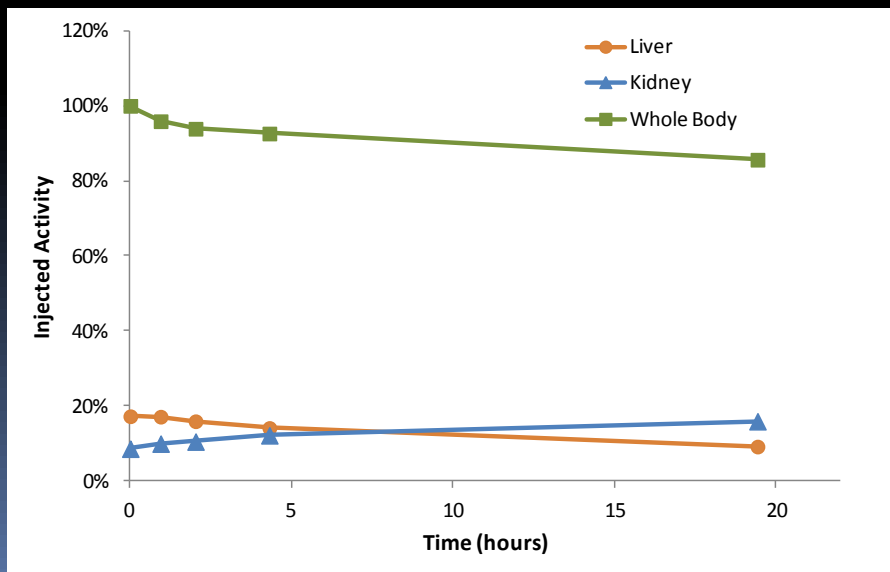
Biodistribution: Liver, Kidney and Whole body

Normal Controls **MIP-1404**

MIP-1405

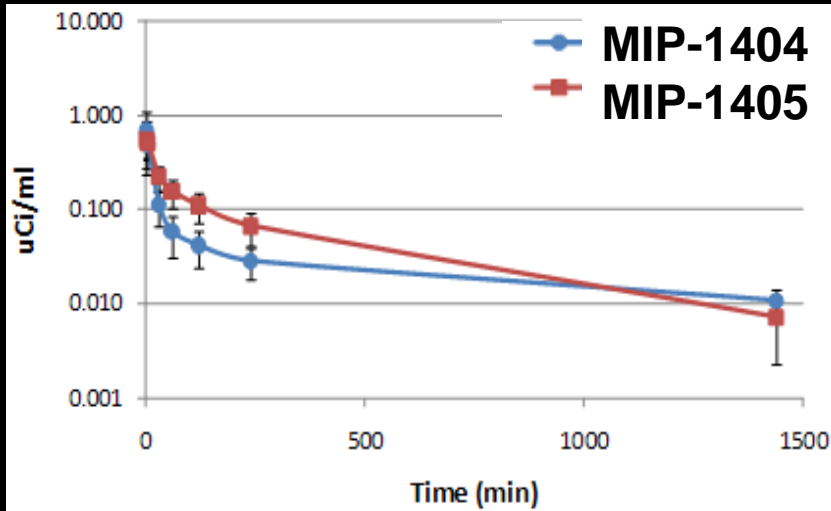


Patients with Prostate cancer

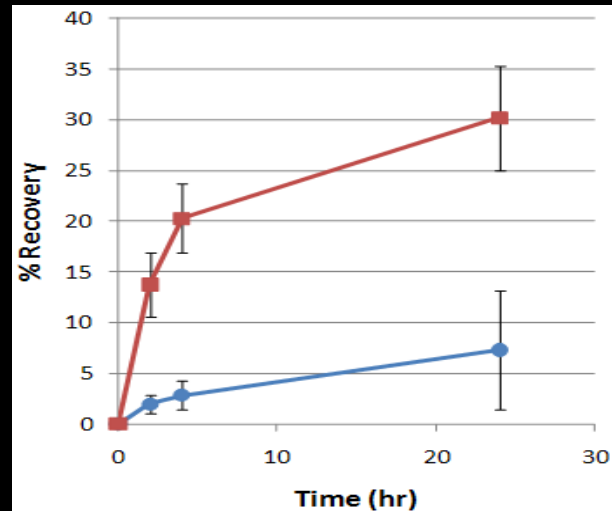


^{99m}Tc -MIP-1404 Vs. ^{99m}Tc -MIP-1405

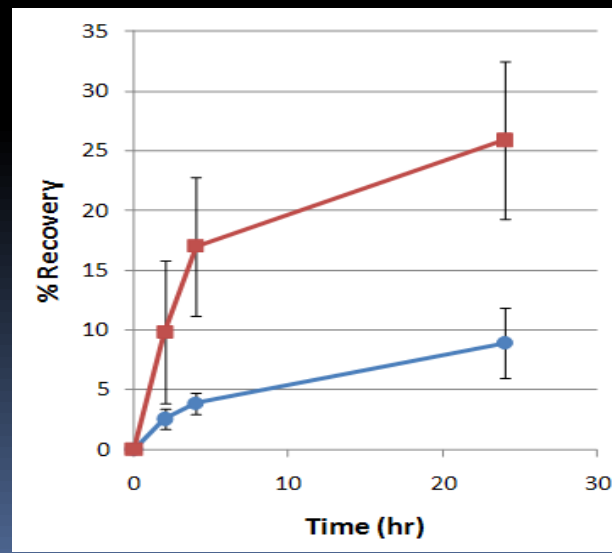
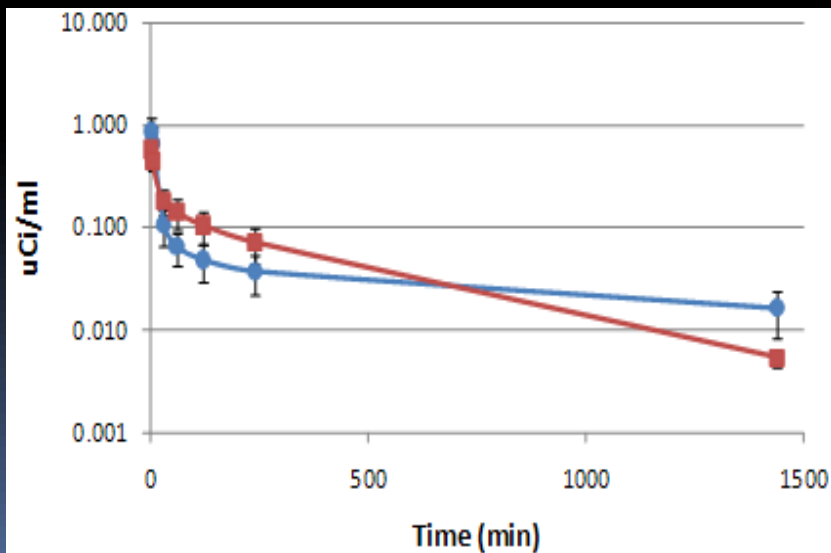
Blood Clearance



% Recovery in Urine



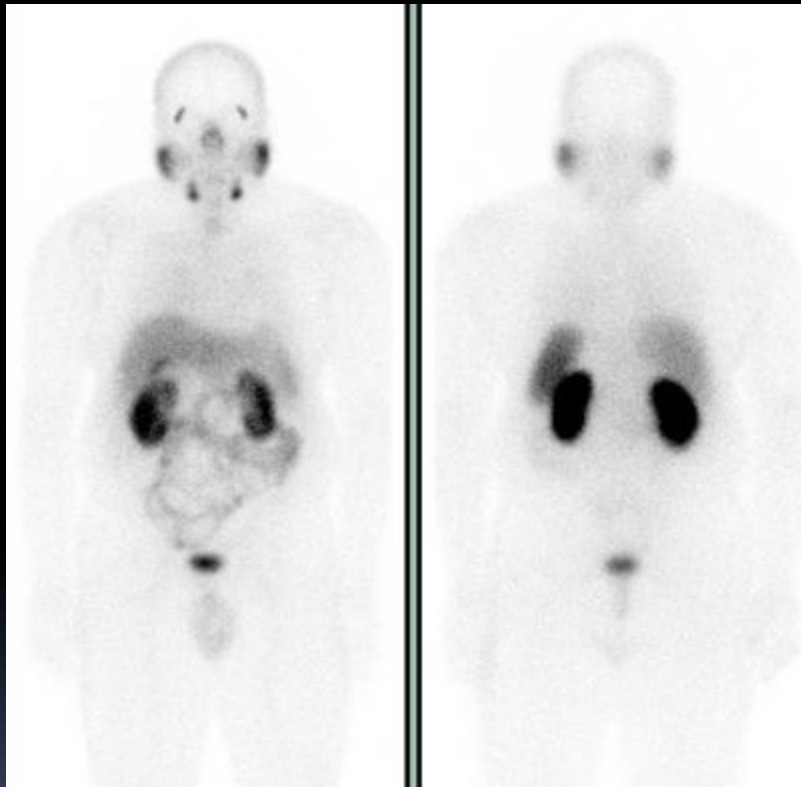
Normals



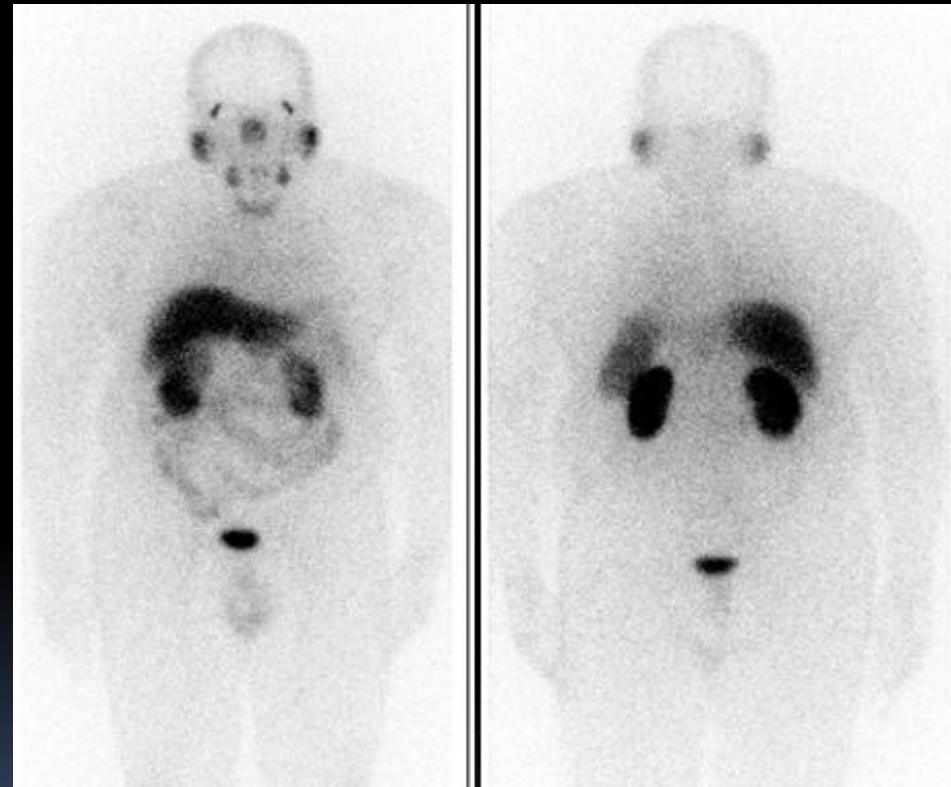
Patients

**Comparison of ^{99m}Tc -MIP-1405 vs. ^{123}I -MIP-1072
in the same normal control subject (at 4 hr post injection)**

^{99m}Tc -MIP-1405



^{123}I -MIP-1072



^{99m}Tc -MIP-1404 and ^{99m}Tc -MIP-1405 (at 4 hours)

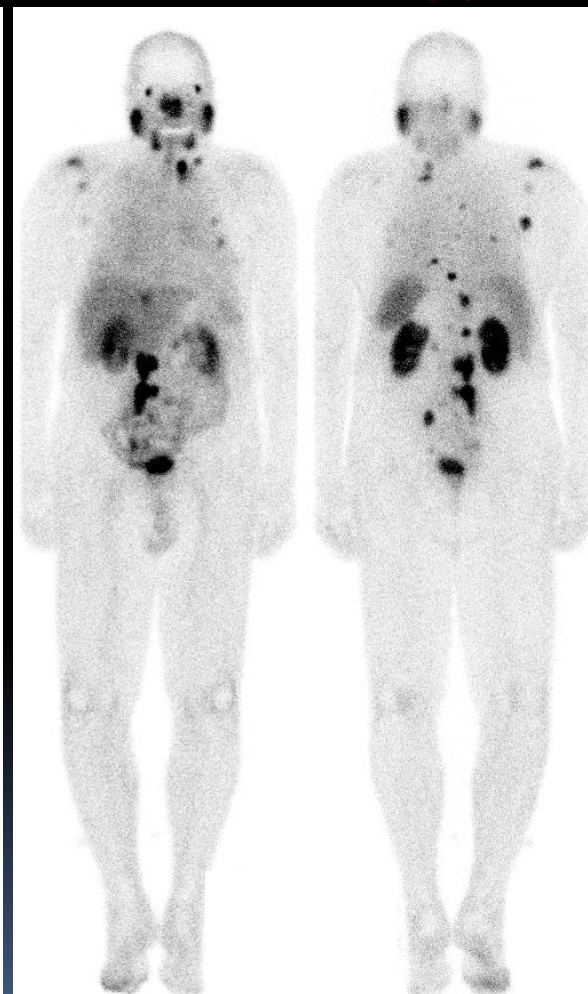
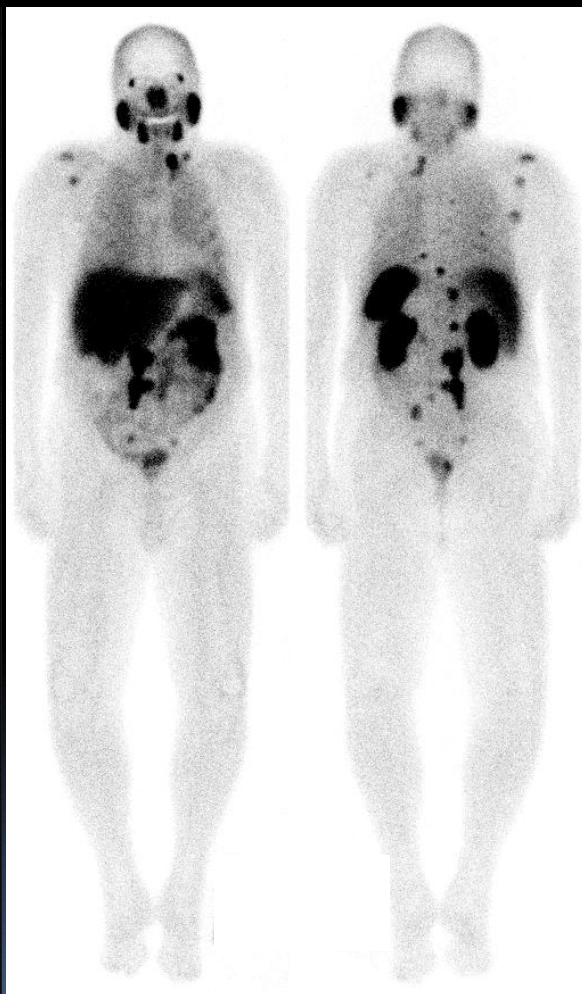
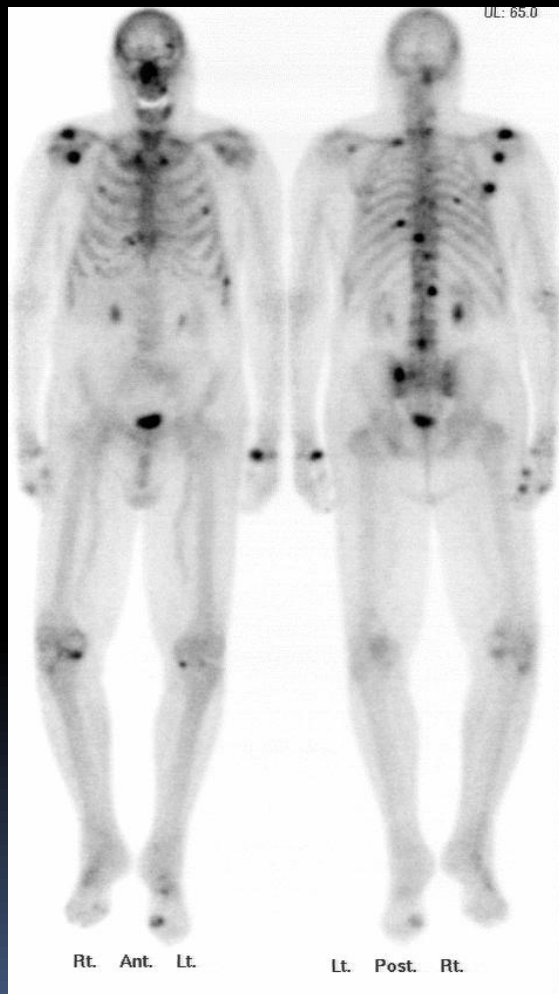
in a Patient with Prostate Cancer

PSA = 48 ng/mL

^{99m}Tc -MDP

^{99m}Tc -MIP-1404

^{99m}Tc -MIP-1405



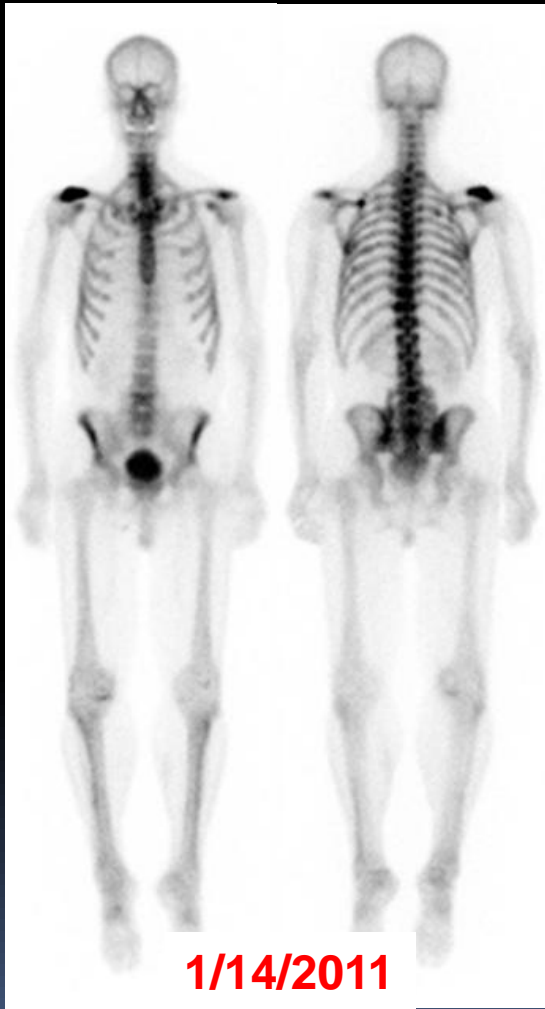
No Prostatectomy

2010 Radiation therapy, 66 Gy

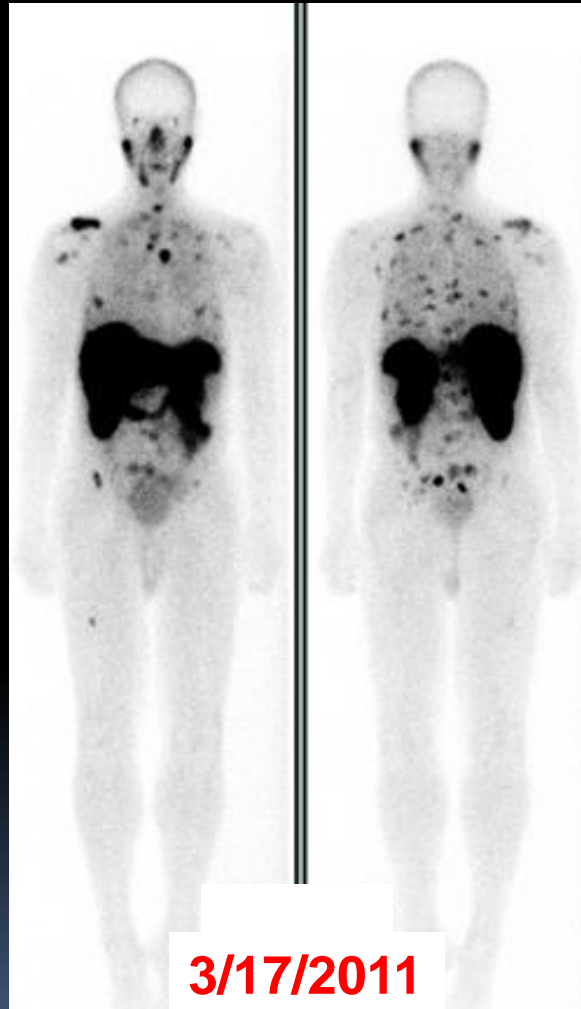
71 yr old male with rapidly rising PSA

11/2010 = 1.37 ng/mL
01/2011 = 2.48 ng/mL
03/2011 = **8.90** ng/mL

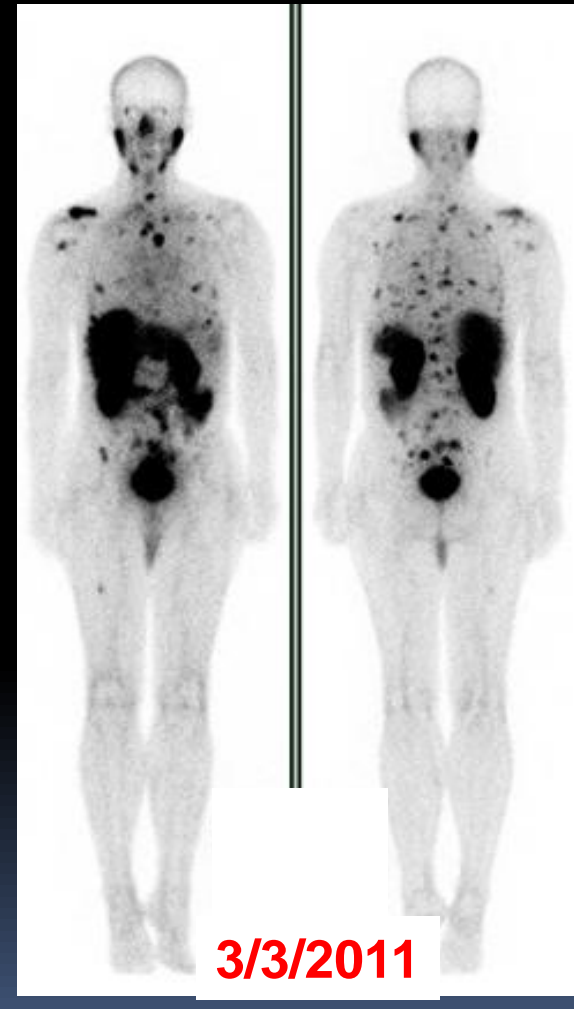
^{99m}Tc-MDP



^{99m}Tc-MIP-1404



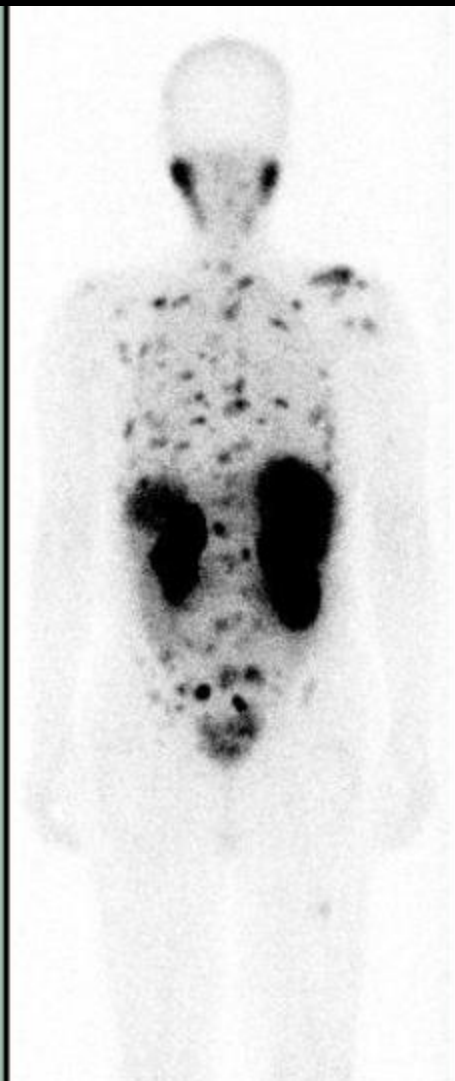
^{99m}Tc-MIP-1405



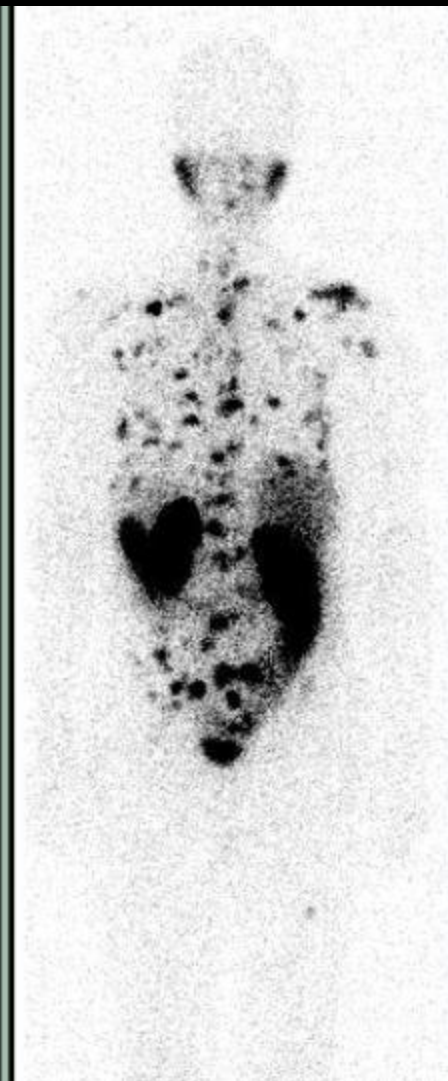
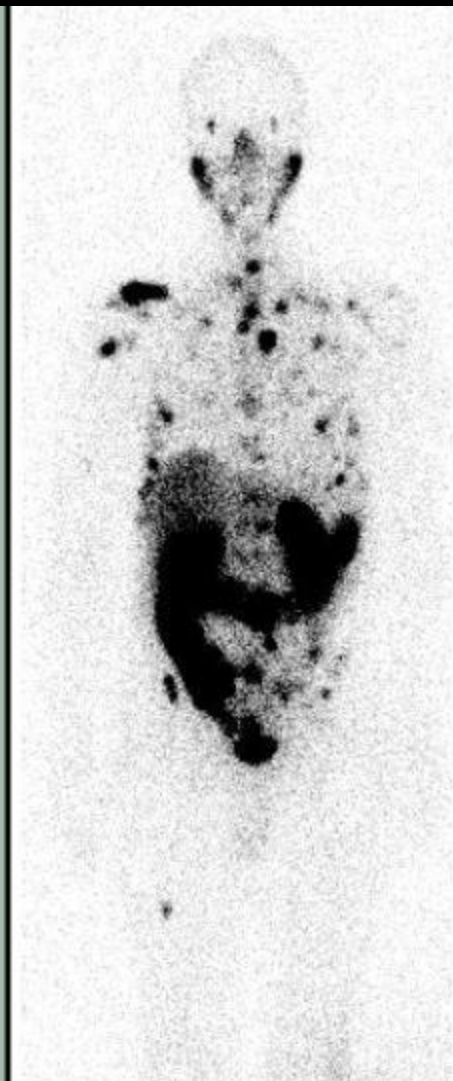
2008: Prostatectomy 2009: Radiation therapy, 70 Gy

^{99m}Tc -MIP-1404 and ^{99m}Tc -MIP-1405 (at 24 hours)
in a Patient with Prostate Cancer

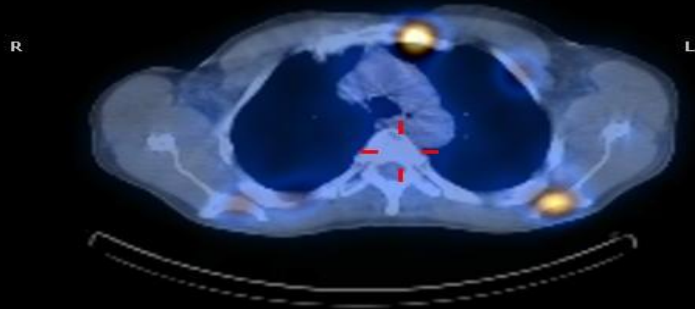
^{99m}Tc -MIP-1404



^{99m}Tc -MIP-1405



^{99m}Tc -MIP-1405: SPECT at 3-4 hours.



1249.68

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Fused Transaxials

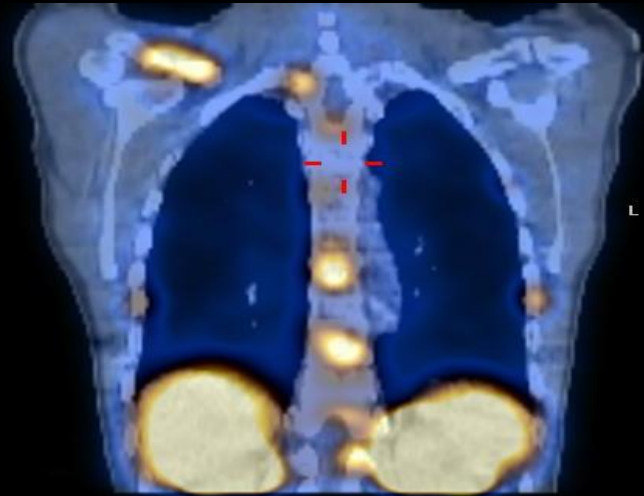
S

$\times 1.24$



25.40

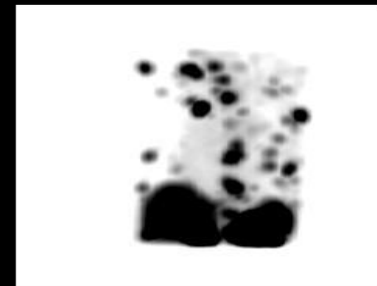
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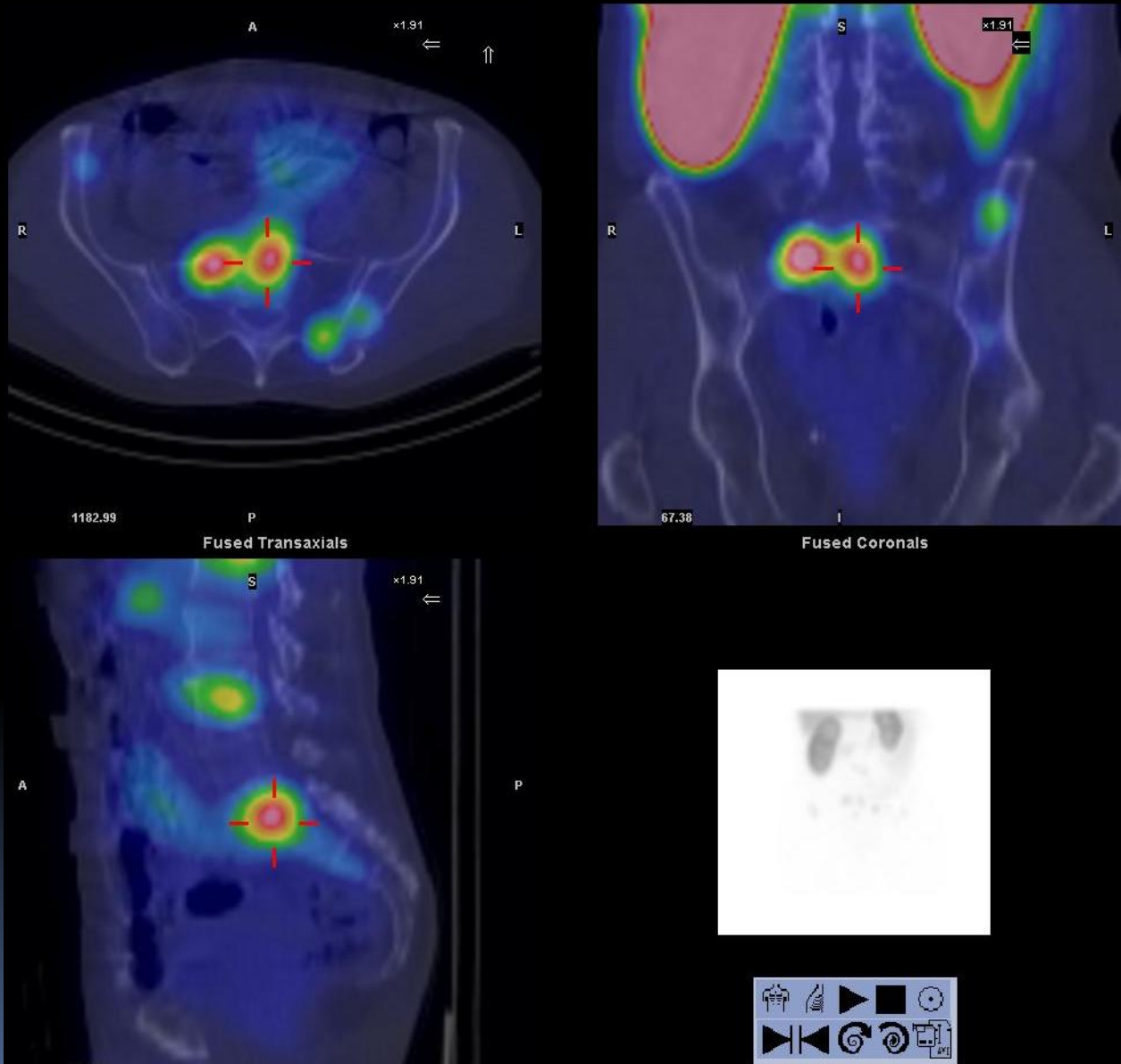
56.33

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Fused Coronals



^{99m}Tc -MIP-1404: SPECT at 3-4 hours.



Disease progression identified by anti-PSMA ^{99m}Tc agents earlier than bone scan

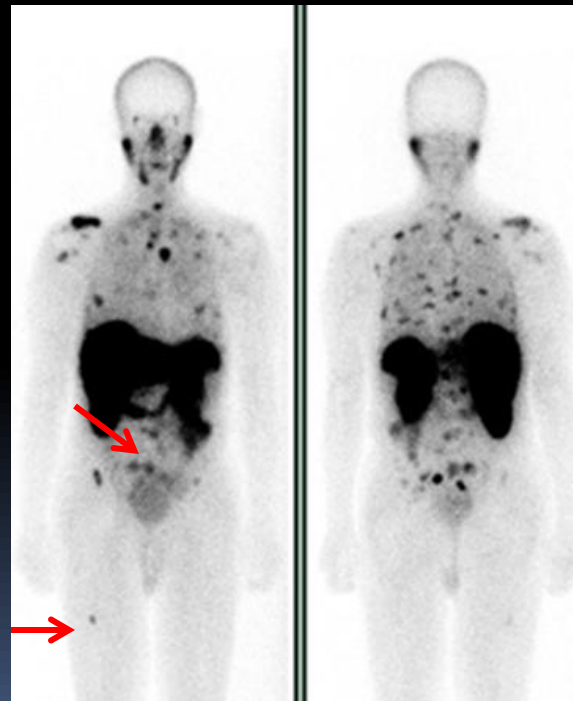
January 2011

^{99m}Tc -MDP



March 2011

^{99m}Tc -MIP-1404



June 2011

^{99m}Tc -MDP



Conclusions

- ^{99m}Tc labeled MIP-1404 and MIP-1405 bind to PSMA+ PC cells with **high affinity** and **specificity**.
- Both agents clear rapidly from blood.
- % Recovery in 24 hr urine is less with MIP-1404 compared to that with MIP-1405 (**7% vs 30%**).
- Liver uptake is higher with MIP-1404 compared to that with MIP-1405.
- Both agents rapidly localized in bone and lymph node lesions as early as 1 hr post injection.
- Both agents identified a greater number of lesions than bone scans and rapidly detected soft tissue PC lesions including sub-cm lymph nodes.

Thank You