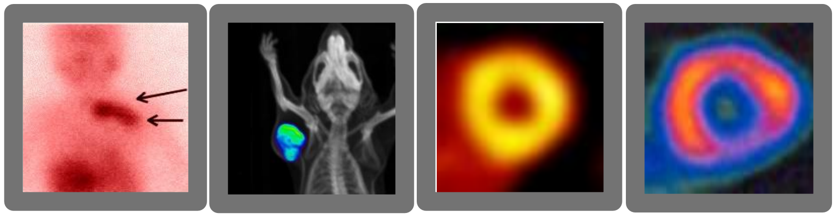
Evaluation of ^{99m}Tc-MIP-1407, an Octreotide Analog for Targeting Neuroendocrine Tumors

Abstract #482



John C. Marquis, Kevin P. Maresca, Genliang Lu, Shawn M. Hillier, Craig N. Zimmerman, Surajit Dhara, William C. Eckelman, Martin G. Pomper, John L. Joyal and John W. Babich

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PIONEERS IN MEDICINE. PARTNERS IN CARE.

June 8, 2010

Development of ^{99m}Tc-Labeled SSTR2 Peptides for Imaging Neuroendocrine Tumors

- Somatostatin Receptor 2 (SSTR2) is selectively upregulated in neuroendocrine cancer and other solid tumors, and radiolabeled peptides have validated SSTR2 as a molecular target
- Carcinoid and other neuroendocrine tumors are currently detected clinically by SPECT imaging with ^{111}In-Octreoscan (^{111}In-DTPA-octreotide)
- A ^{99m}Tc-labeled peptide would be preferable over ^{111}In-Octreoscan given the advantages in image quality, radiation dose, cost and availability
- Molecular Insight Pharmaceuticals has developed a series of lysine derived SAAC systems for the technetium tricarbonyl $\{^{99m}Tc(CO)_3\}^+$ core incorporating functionalized polar imidazole rings that show low hepatobiliary clearance and rapid clearance via the kidneys
- These SAAC chelators were incorporated into SSTR peptides, labeled with ^{99m}Tc and tested *in vitro* and *in vivo*

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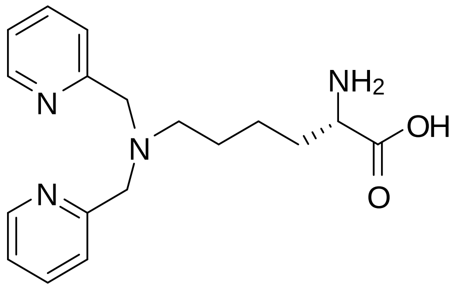
Single Amino Acid Chelator (SAAC) Platform Technology Evolution

- Development of a chelator system to readily incorporate ^{99m}Tc into peptide ligands
  - Easily synthesized and chemically stable
  - Successfully incorporated into peptide libraries
  - Robust radiolabeling
  - Stable to histidine/cysteine challenge

- Dipyridyl Lysine (DPK)
  - Met chemistry objectives outlined above
  - High hepatobiliary uptake due to intrinsic hydrophobicity



Dipyridyl Lysine

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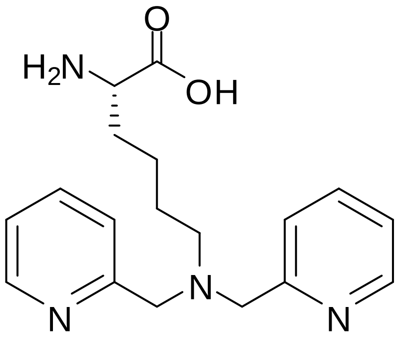
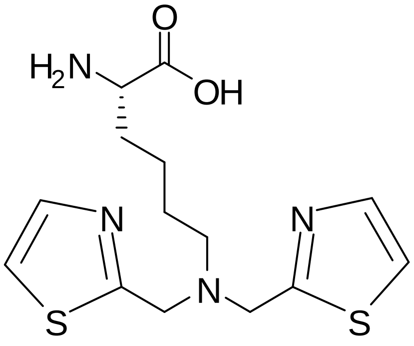
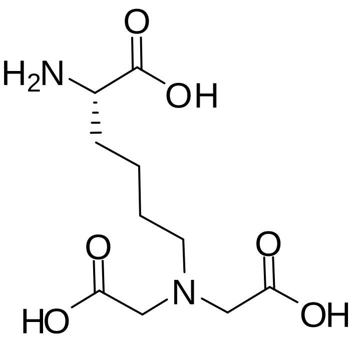
First Generation Lysine SAAC Chelators Incorporated into Tyr3-Octreotide Peptides



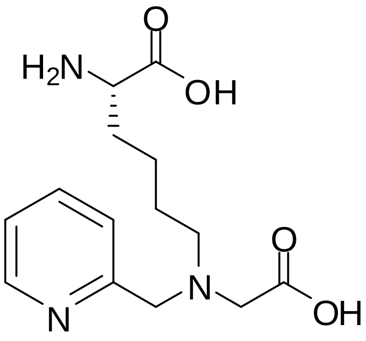
DPK (1)



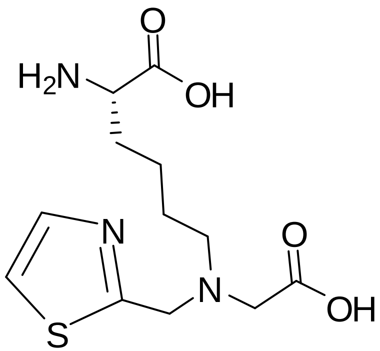
DTK (3)



Diacid-K (5)



PAMA-K (2)



MTMA-K (4)

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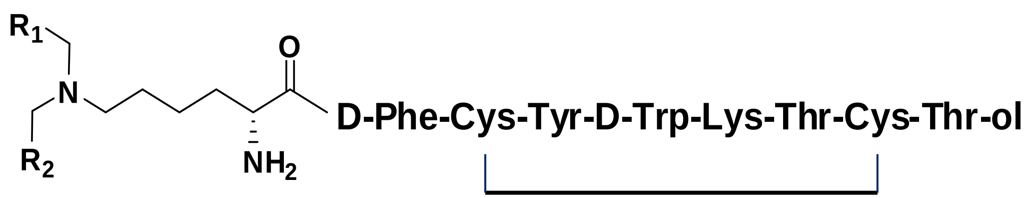
Tissue Distribution of SSTR Peptides in AR42J Xenograft Mice - Selected Tissues (% ID/g) 4h



	Blood		Liver		Intestines		Kidneys		Tumor	
^{111}In-DTPA-octreotide	**0.1**	± 0.00	**0.3**	± 0.03	**0.9**	± 0.21	**34.5**	± 6.54	**3.4**	± 1.10
^{111}In-DOTATOC	**0.1**	± 0.00	**0.4**	± 0.05	**1.0**	± 0.38	**17.2**	± 3.01	**7.8**	± 0.85
SAAC I										
DPK (1)-TOC	**0.9**	± 0.11	**18.1**	± 3.77	**7.9**	± 1.48	**38.0**	± 5.13	**17.6**	± 4.27
PAMA-K (2)-TOC	**0.8**	± 0.22	**6.8**	± 1.48	**10.3**	± 1.59	**12.7**	± 1.05	**7.5**	± 5.70
DTK (3)-TOC	**4.1**	± 1.51	**30.5**	± 2.81	**3.9**	± 0.22	**60.0**	± 3.11	**9.0**	± 3.71
MTMA-K (4)-TOC	**0.5**	± 0.05	**5.4**	± 0.95	**11.8**	± 2.39	**17.7**	± 3.63	**30.5**	± 7.79
Diacid-K (5)-TOC	**4.1**	± 0.34	**3.6**	± 0.61	**3.4**	± 1.10	**3.5**	± 0.62	**1.2**	± 0.21

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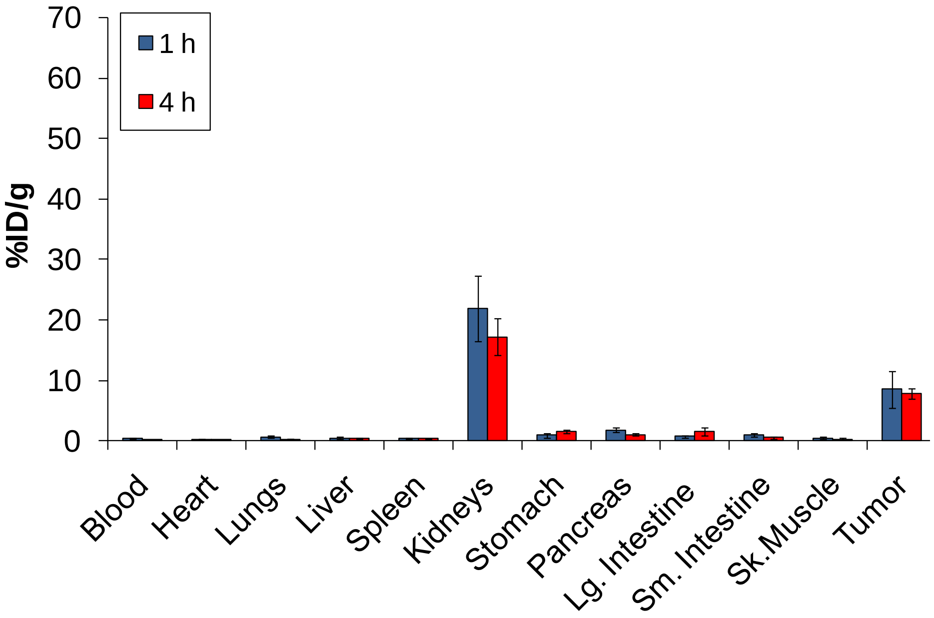
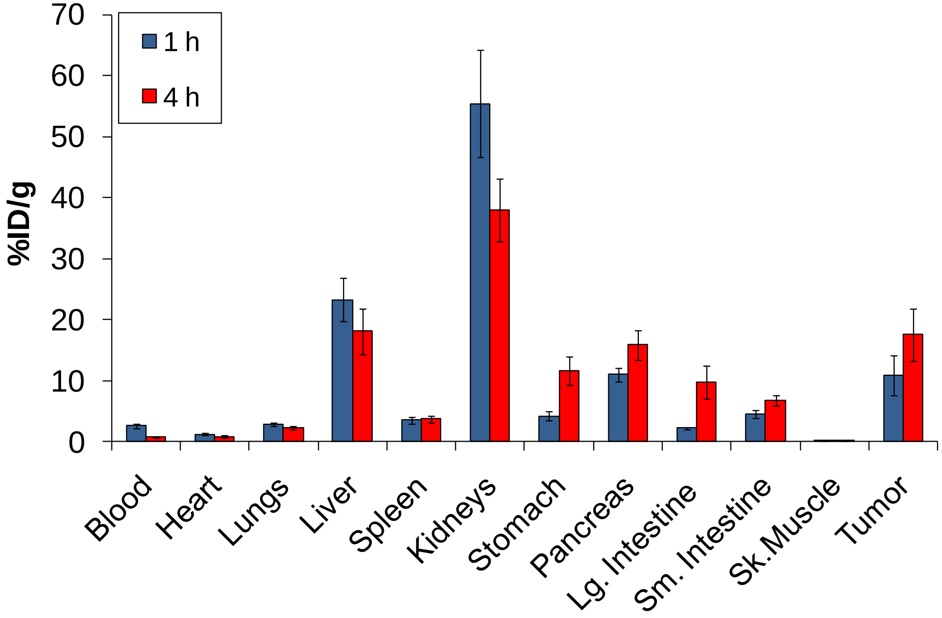
Tissue Distribution of SSTR Peptides in AR42J Xenograft Mice (% ID/g)

^{111}In-DOTA-Tyr3-Octreotide (DOTATOC)



^{99m}Tc-DPK-Tyr3-Octreotide (DPK-TOC)



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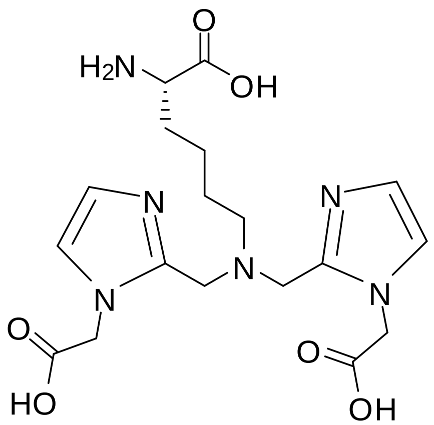
Second Generation SAAC Chelators

- Functionalized imidazoles - acetals, ketones, ethers, carboxylates, thiazoles, amines
  - Maintained chemistry objectives
  - Met biological objectives
    - Reduced hydrophobicity resulted in clearance predominantly through the kidney, and much less non-specific binding
  - Examples where successfully employed
    - SSTR2 (Abstract # 482)
    - PSMA (Abstract # 481)
    - CAIX   (Abstract # 1533)



Di-carboxymethylimidazole Lysine

(Maresca et al. *Bioconj. Chem.* 2010)

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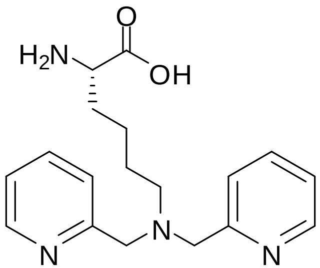
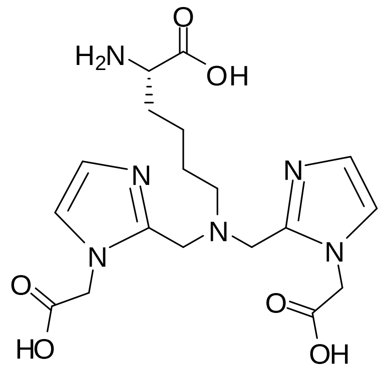
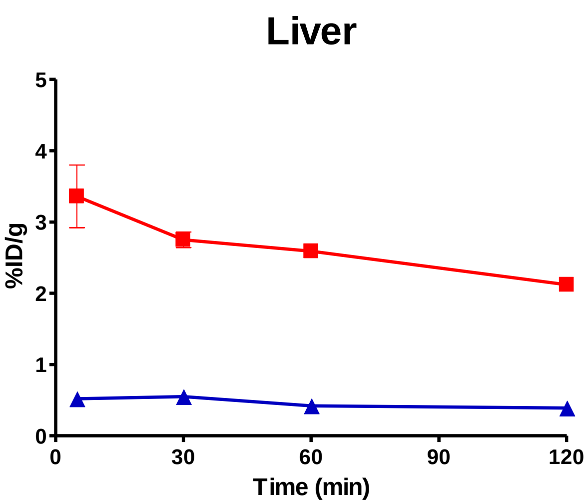
Clearance of First and Second Generation SAAC Molecules in Rats

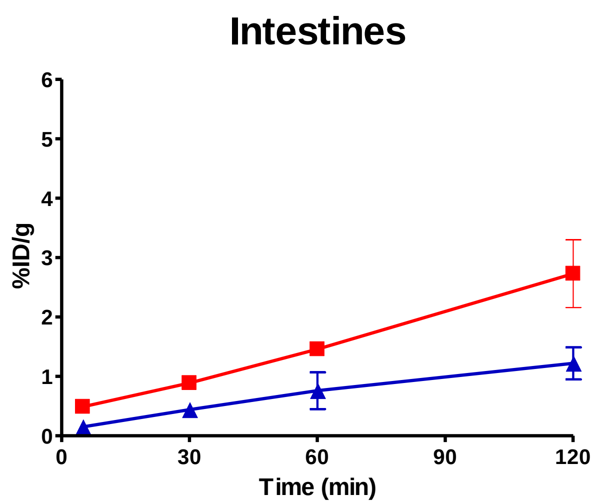


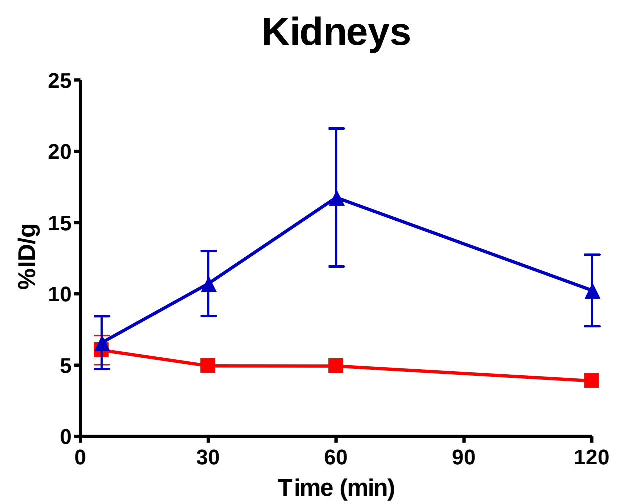
Dipyridyl Lysine (DPK)



Di-carboxymethylimidazole Lysine (CIM-K)







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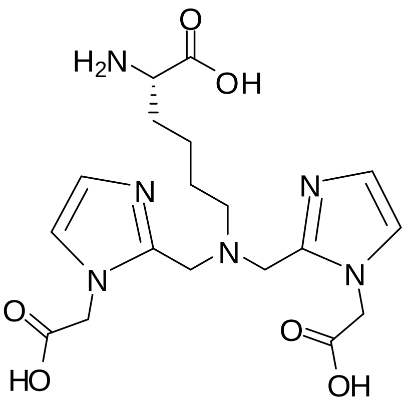
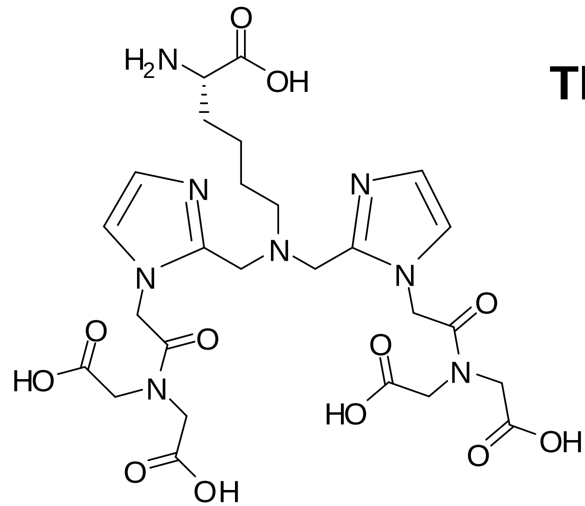
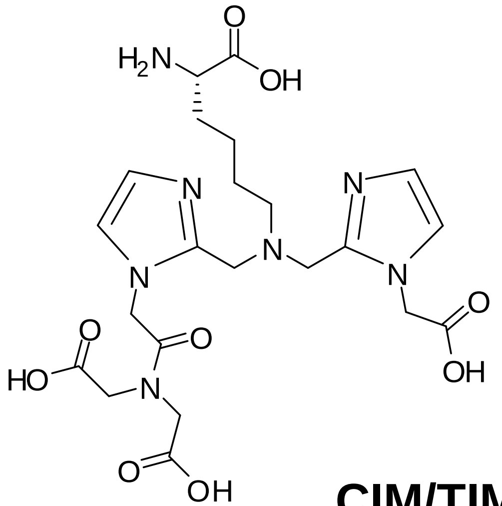
Second Generation SAAC Compounds Incorporated into Tyr3-Octreotide Peptides



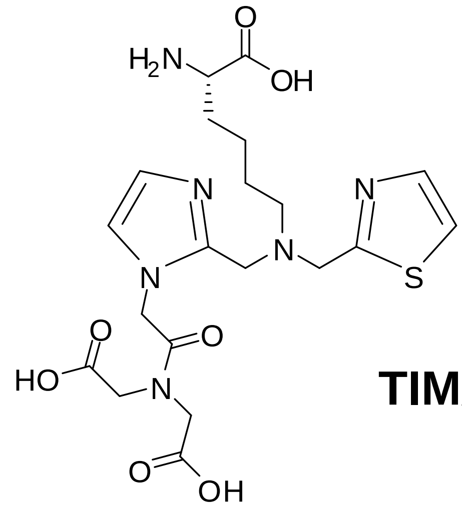
CIM-K (6)



TIM-K (7)



CIM/TIM-K (8)



TIM/Thiazol-K (9)

Tissue Distribution of SSTR Peptides in AR42J Xenograft Mice - Selected Tissues (% ID/g) 4h

	Blood	Liver	Intestines	Kidneys	Tumor
^{111}In-DTPA-octreotide	**0.1** ± 0.00	**0.3** ± 0.03	**0.9** ± 0.21	**34.5** ± 6.54	**3.4** ± 1.10
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SAAC I					
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DTK (3)-TOC	**4.1** ± 1.51	**30.5** ± 2.81	**3.9** ± 0.22	**60.0** ± 3.11	**9.0** ± 3.71
MTMA-K (4)-TOC	**0.5** ± 0.05	**5.4** ± 0.95	**11.8** ± 2.39	**17.7** ± 3.63	**30.5** ± 7.79
Diacid-K (5)-TOC	**4.1** ± 0.34	**3.6** ± 0.61	**3.4** ± 1.10	**3.5** ± 0.62	**1.2** ± 0.21
SAAC II					
CIM-K (6)-TOC	**0.2** ± 0.05	**1.7** ± 0.37	**2.6** ± 0.47	**14.7** ± 2.84	**19.2** ± 5.57
TIM-K (7)-TOC	**0.2** ± 0.02	**0.6** ± 0.03	**0.7** ± 0.17	**25.8** ± 2.29	**5.5** ± 1.71
CIM/TIM-K (8)-TOC	**0.1** ± 0.03	**0.5** ± 0.09	**1.2** ± 0.24	**16.8** ± 1.99	**8.7** ± 1.83
TIM/Thiazol-K (9)-TOC	**0.3** ± 0.04	**3.1** ± 0.43	**3.1** ± 0.54	**21.7** ± 2.61	**6.6** ± 1.60

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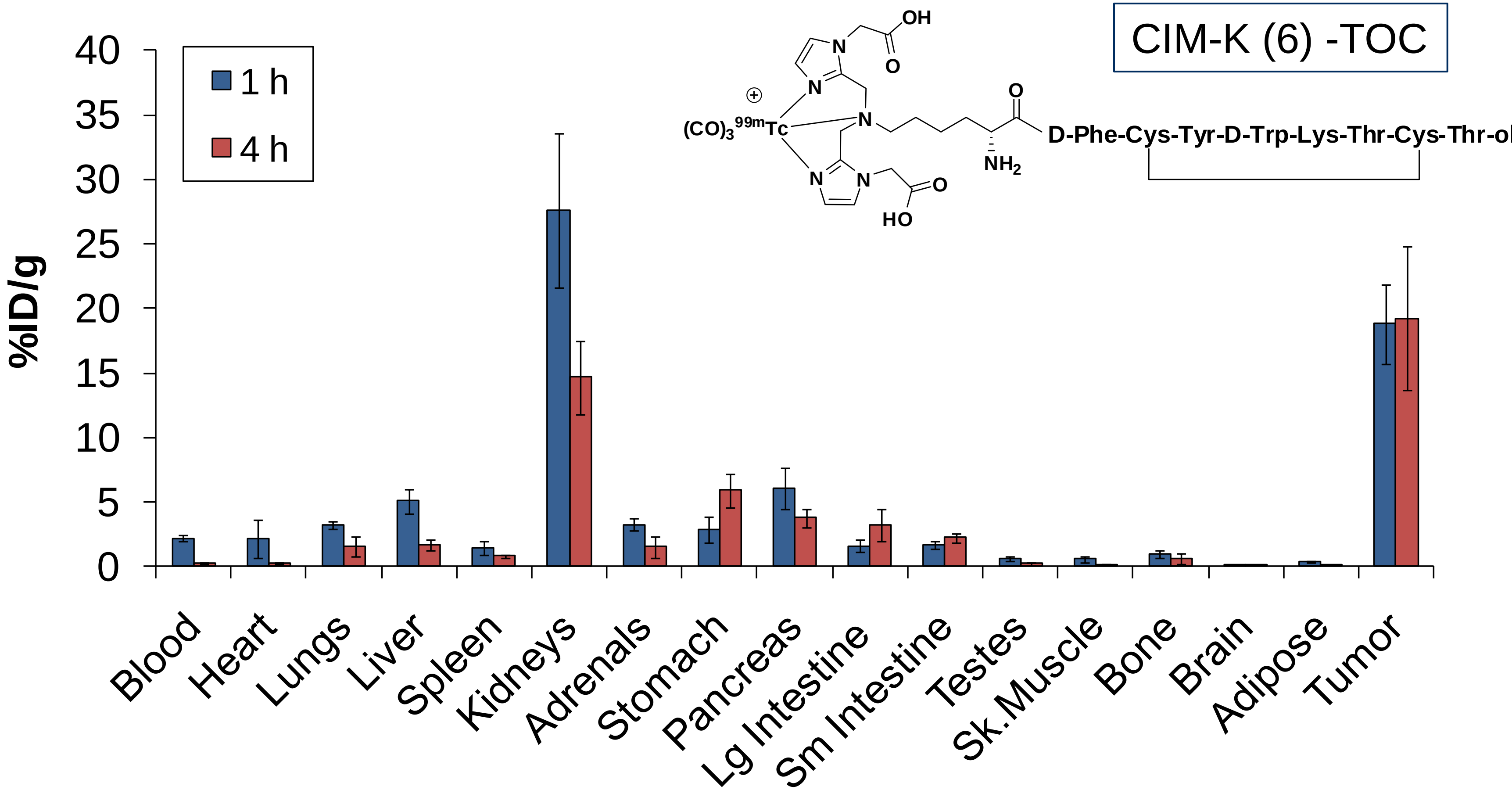
Tissue Distribution of ^{99m}Tc-MIP-1407 in AR42J Xenograft Mice

CIM-K (6) -TOC



	1 hr	4 hr
Tumor:Blood	**9**	**83**
Tumor:Skeletal Muscle	**31**	**210**

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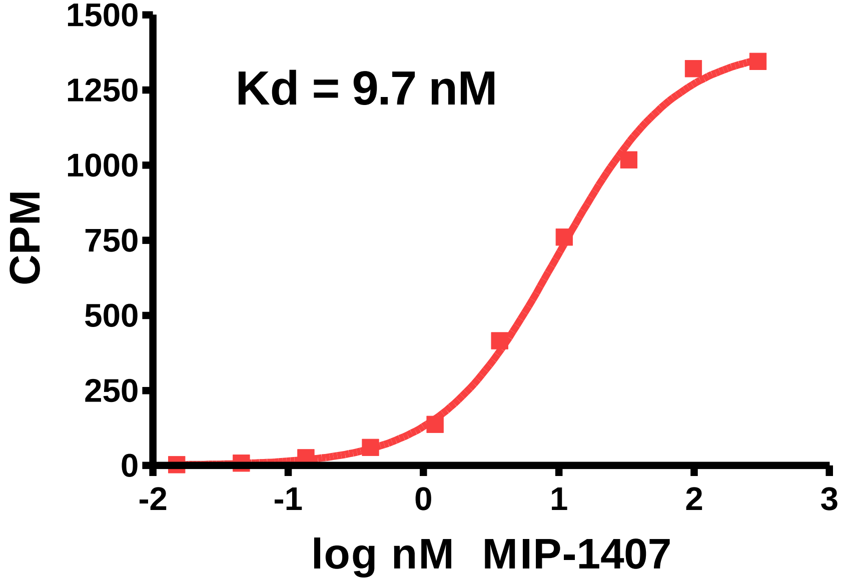
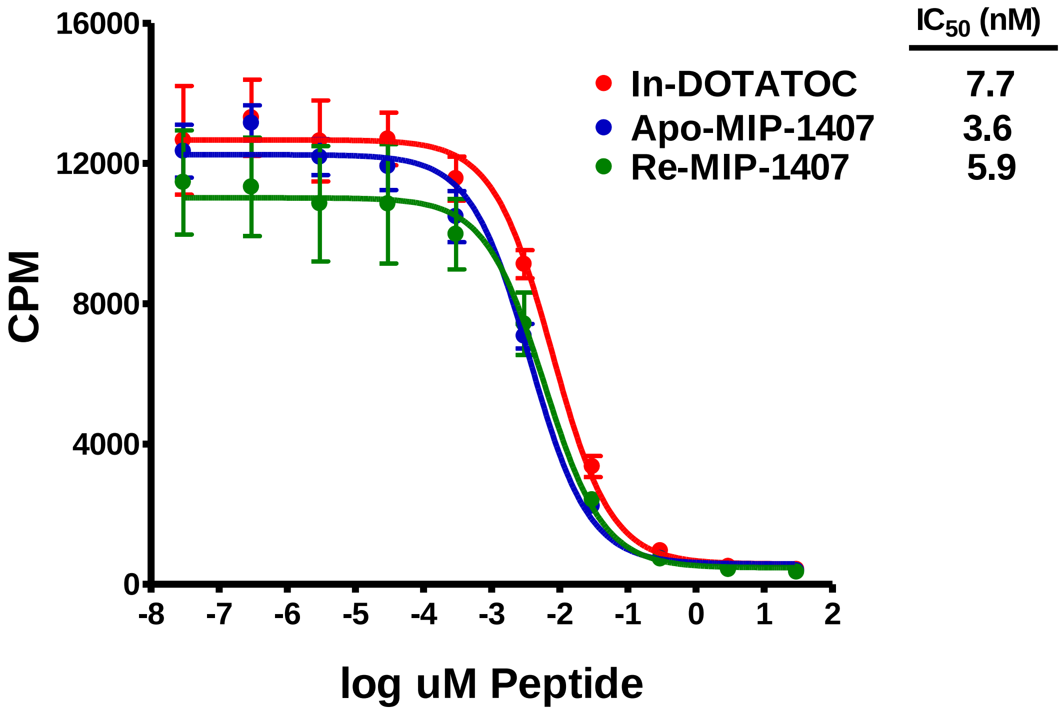
^{99m}Tc-MIP-1407 Exhibits High Affinity for SSTR-Expressing AR42J Cells

^{99m}Tc-MIP-1407 Saturation Binding on AR42J Cells



^{99m}Tc-MIP-1407 Competition Binding on AR42J Cells



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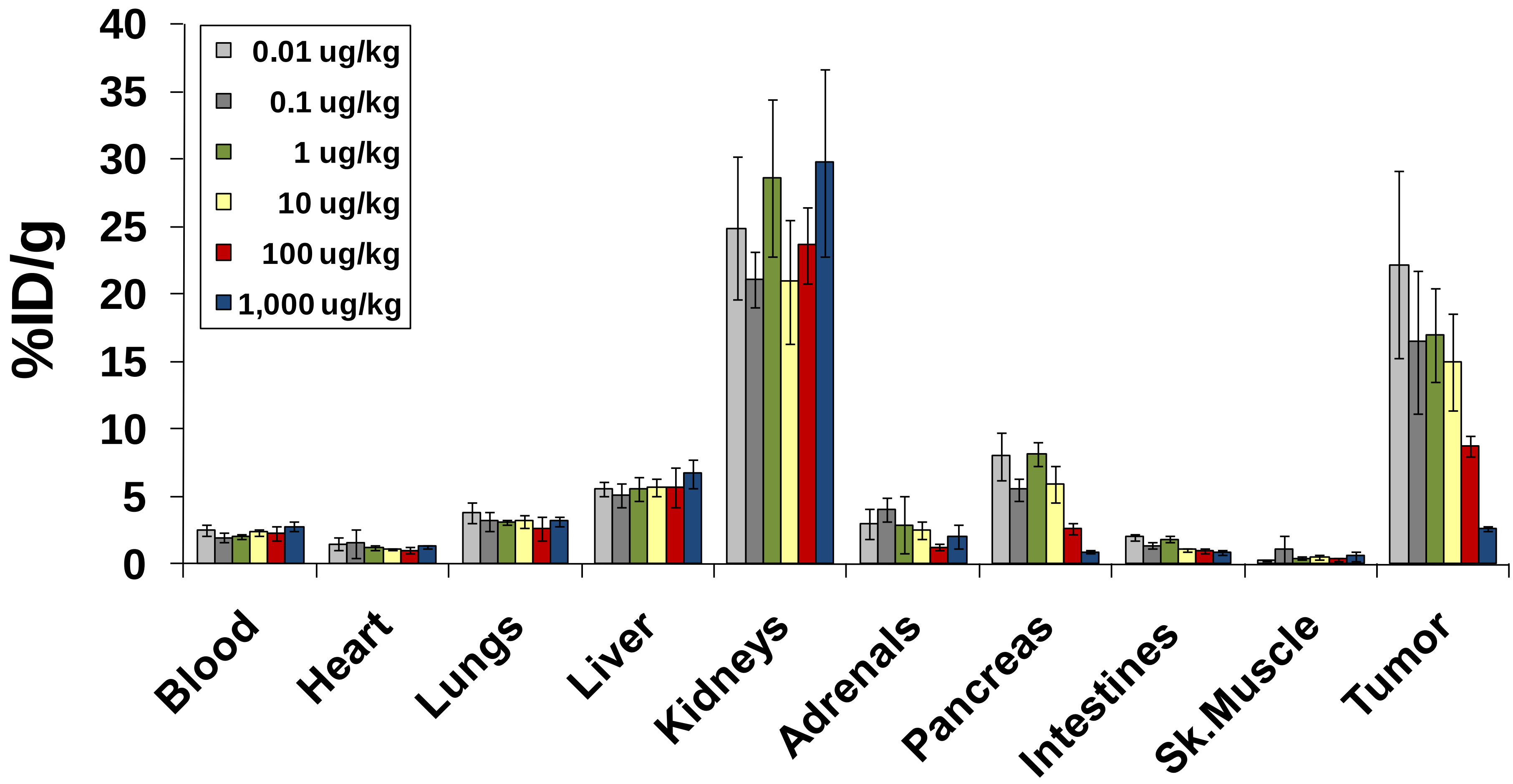
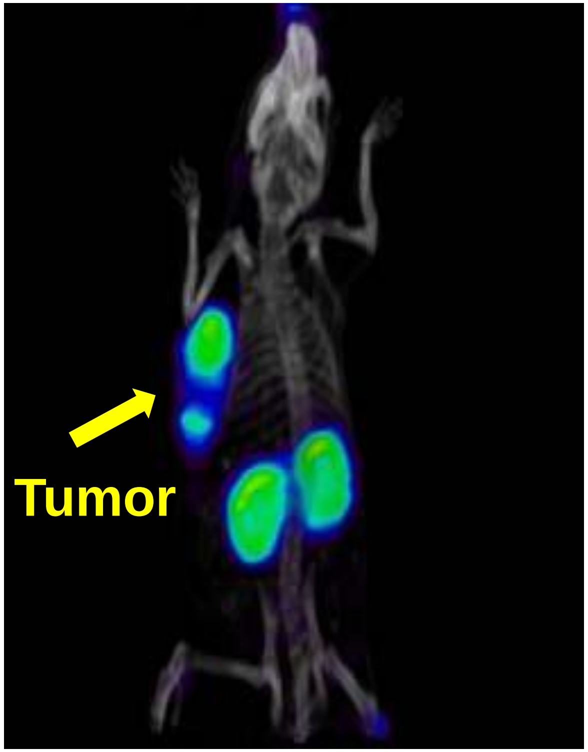
^{99m}Tc-MIP-1407 *In Vivo* Competition in AR42J Xenograft Mice

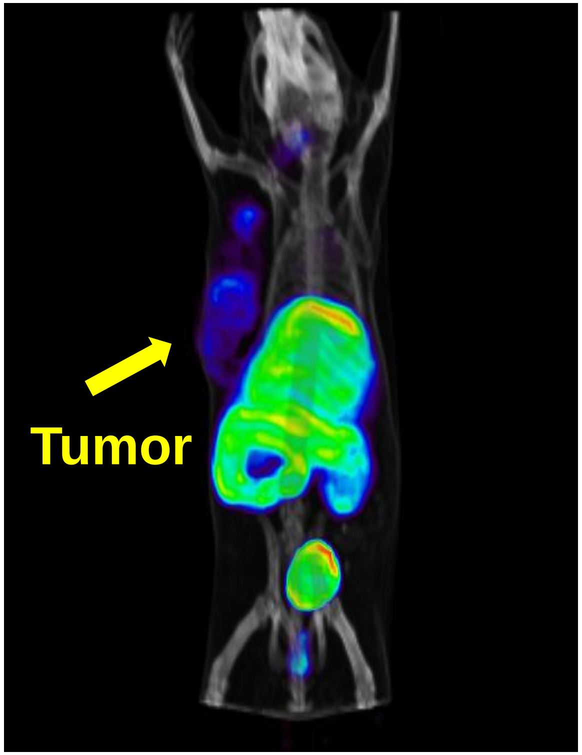


Selective Targeting of SSTR In AR42J Xenografts with ^{99m}Tc-SAAC Analogues

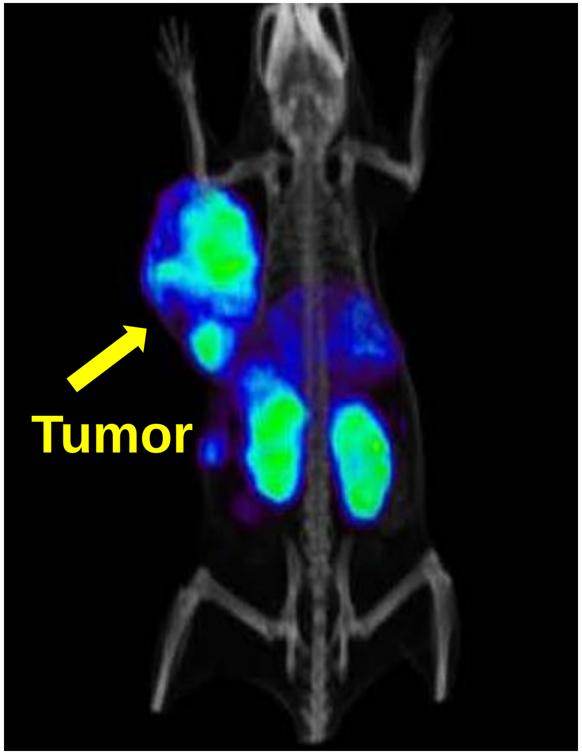
^{111}In-DOTATOC



1st Generation SAAC
^{99m}Tc-DPK-TOC



2nd Generation SAAC
^{99m}Tc-CIM-K-TOC



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Conclusions

- Incorporated novel polar SAAC chelators into high affinity SSTR peptides using solid phase synthesis
- Demonstrated specific binding to AR42J tumor cells
- Demonstrated specific uptake in AR42J tumor xenografts
- The high tumor uptake, excellent pharmacokinetics, and clearance predominantly through the kidneys make ^{99m}Tc-MIP-1407 an attractive candidate for clinical evaluation in patients with neuroendocrine tumors

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Acknowledgements

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