Medicinal Radiochemistry

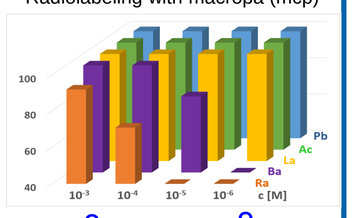
Institute of Radiopharmaceutical Cancer Research

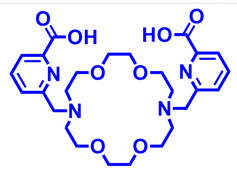
HELMHOLTZ ZENTRUM DRESDEN ROSSENDORF

Chelator design: synthesis, radiolabeling, stability test

Ac 225 10,0 d α: 5,830 γ: 0,100	**La 133** 3,91 h ε ; β⁺ 1,2 γ: 0,279; 0,302
Pb 212 10,64 h β⁻: 0,3; 0,6 γ: 0,239	**Pb 203** 51,9 h ε γ: 0,279
Bi 212 60,60 min α: 5,7162 β⁻: 2,3 γ: 0,269	**Bi 213** 45,59 min α: 5,87 β⁻: 1,4 γ: 0,440

Radiolabeling with macropa (mcp)

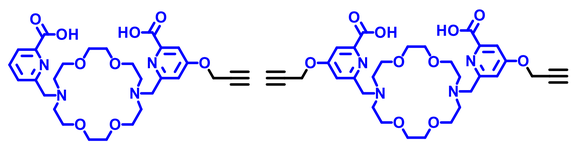




macropa (mcp)

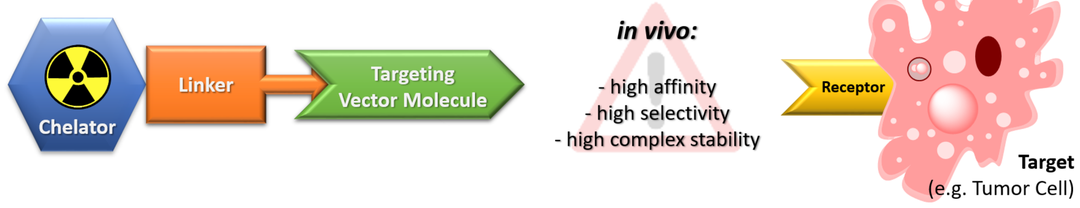
Chelator functionalization

Click-labeling with **small compounds/peptides**



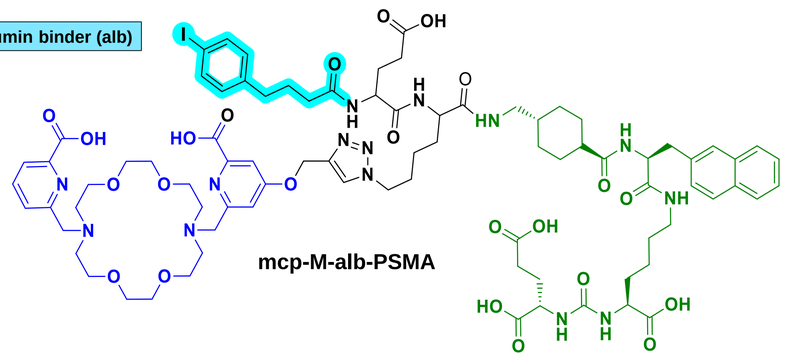
mcp-M-click mcp-D-click

General composition of radiometal-based radiopharmaceuticals



Isotopes for targeted alpha therapy

Albumin binder (alb)



mcp-M-alb-PSMA

PSMA = prostate specific membrane antigen

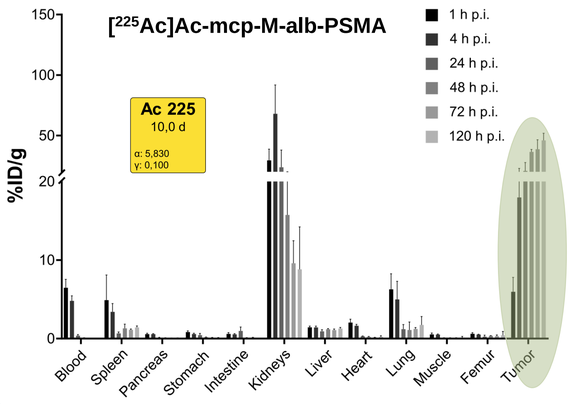
- enzyme located in cell membrane of prostate cancer cells

PSMA expression in prostate cancer:

- in tumor tissue: 100-1000x higher (compared to normal tissue)

→ **ideal biomarker and therapeutic target**

Radioconjugates: *in vivo* evaluation



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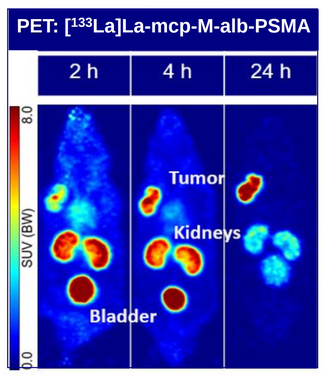
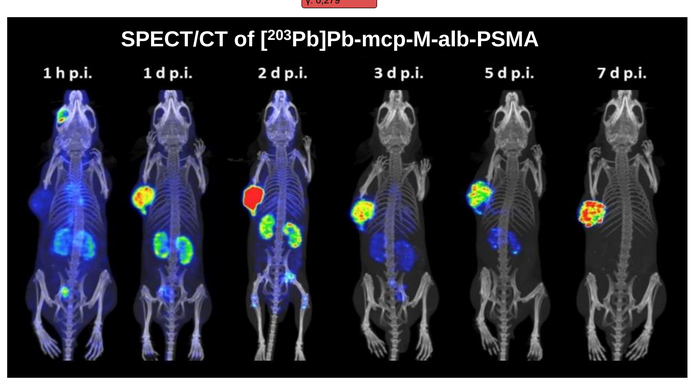


PET: LNCaP-tumor xenograft

Pb 203 51,9 h ε γ: 0,279



SPECT: LNCaP-tumor xenograft

Bachelor thesis ideas:

- **Design and synthesis of new chelators for barium/radium**
- **Functionalization of chelators**
- **Analytic testing of chelator and complexes (NMR, ITC, Eu-TRLFS, radiolabeling)**

References: Thiele NA et al. *J Am Chem Soc.* **2018,** *140,* 17071; Reissig F et al. *Theranostics* **2022**, *12*, 7203; Reissig F et al. *Cancers* **2021**, *13*, 1974; Blei MK, Waurick L et al. *Inorg Chem* **2023,** *62*, 20699.

Interested in Medicinal Radiochemistry?

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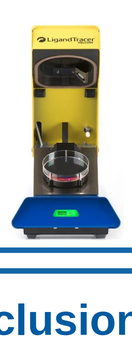
1. Synthetic strategy

- **Convergent** synthetic strategy towards **central aryl** building blocks
- **Water-soluble units** via reductive amination
- **Linker** and **chelator**

2. Properties and biological evaluation

- *In vitro*: log $D_{7.4}$, **stability**, **binding kinetics** and **affinity**
- *In vivo*: Xenograft mouse models with **PD-L1 positive** and **negative** tumors

In vitro binding kinetics using **real-time radioligand binding**

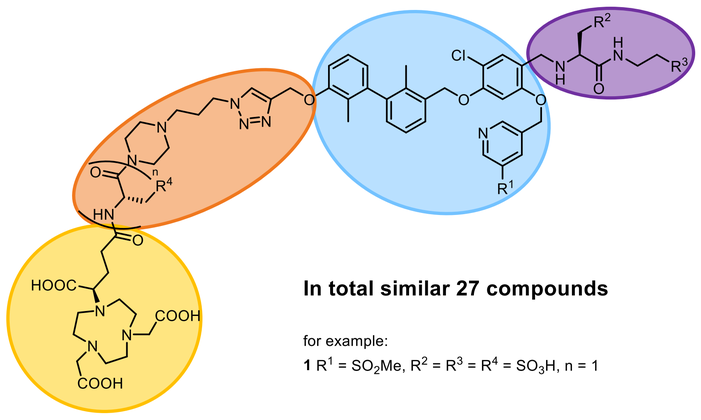


In vivo tumor uptake using **small-animal PET/CT**

Conclusions

- Multiple generations of PD-L1 small molecule ligands (>30 compounds) synthesized, radiolabeled and fully evaluated
- Next generation compounds can compete with antibodies and peptides AND would allow targeted radionuclide therapy

3. Published Data



In total similar 27 compounds

for example:
1 $R^1 = SO_2Me$, $R^2 = R^3 = R^4 = SO_3H$, n = 1

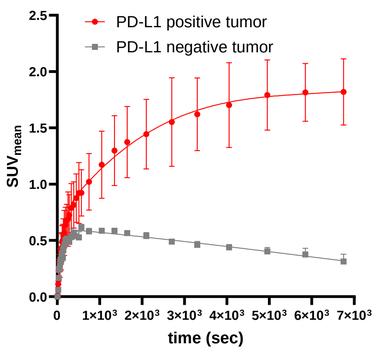
In vitro (A):

- Substantially **lowered log *D*$_{7.4}$** over lead structure
- Reduced albumin affinity compared to known structures
- **Affinities**: 1.8 - 1182 nM

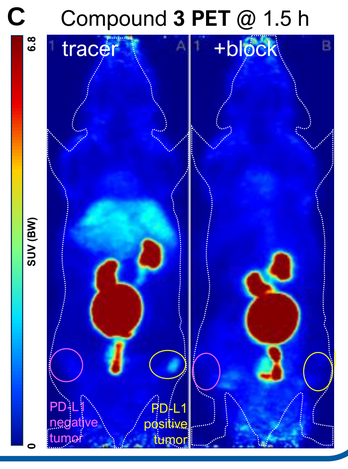
In vivo (B/C):

- **Substantially improved pharmacokinetics**
- **Faster & increased PD-L1** tumor uptake (SUV_{max} ~3.5)
- Primarily **renal** clearance

B Tumor uptake of compound **3**



C Compound **3** **PET** @ 1.5 h



4. Ongoing Research

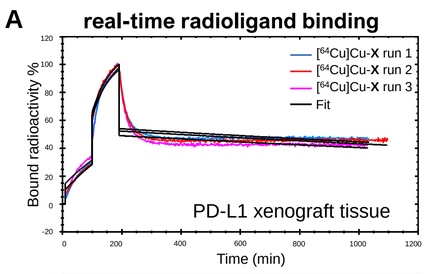
In vitro (A):

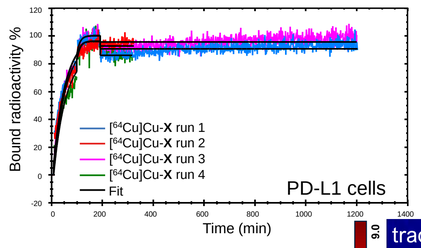
- Substantially **increased affinity** (app K_D ~ 30 pM)
- **Internalization** observed for the first time

In vivo (B):

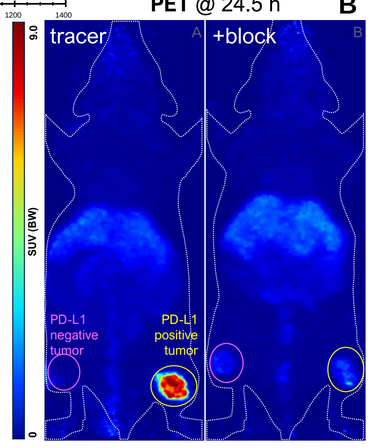
- **Drastically** improved **PD-L1** tumor uptake (SUV_{max} ~13.8)
- **Excellent contrast** over negative tumor
- Retained **renal** clearance

A





PET @ 24.5 h B



References: F. Krutzek *et al*. *Pharmaceuticals* **2022,** *15***,** 747; F. Krutzek *et al*. *Cancers* **2023**, *15*, 2638; F. Krutzek *et al*. *J. Med. Chem.* **2023**, *66*, 15894; F. Krutzek *et* al. *Int. J. Mol. Sci.* **2023**, *24*, 15088; F. Krutzek *et al*. *EJNMMI Radiopharm. Chem.* **2024**, *9,* 14.

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