Use TRIUMF produced radionuclides for radiopharmaceutical development

Hua Yang

Research Scientist, Life Sciences Division, TRIUMF

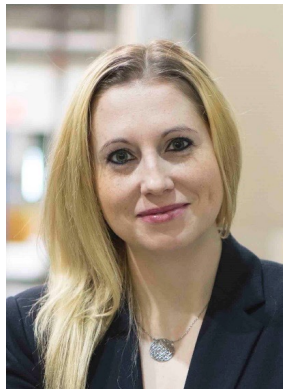
Adjunct Professor, Department of Chemistry, Simon Fraser University

2023-08-01

Life Sciences Division

Applied Ion Beams

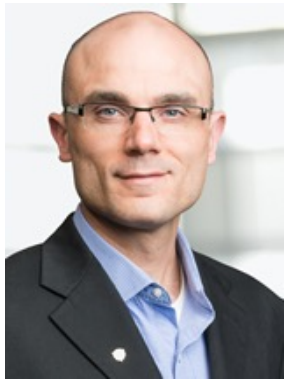
Cornelia Hoehr



Monika Stachura

Nuclear Chemistry

Valery Radchenko



Paul Schaffer

Applied Isotopes

Hua Yang

Caterina Ramogida

Nuclear Medicine

Theranostics

Imaging

PET (e^+): ^{18}F, ^{89}Zr, ^{68}Ga

SPECT (γ): ^{99m}Tc, ^{123}I

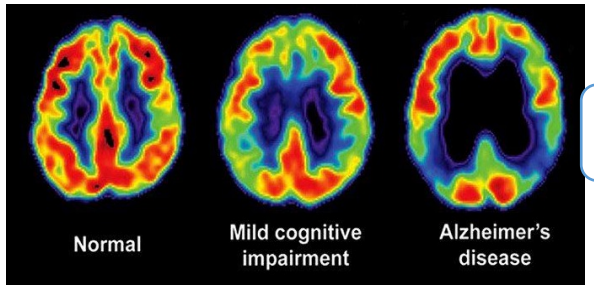
Radioisotopes

Therapy

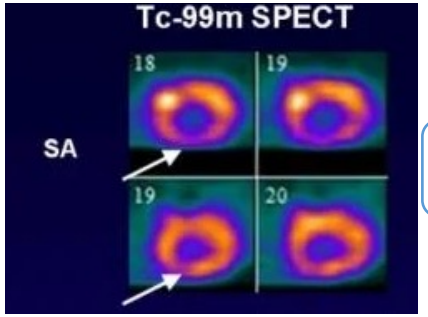
β: **^{90}Y, ^{177}Lu, ^{131}I,** ^{161}Tb

α: **^{225}Ac, ^{223}Ra,** ^{213}Bi, ^{227}Th

MAE: ^{111}In, ^{197}Hg, ^{165}Er

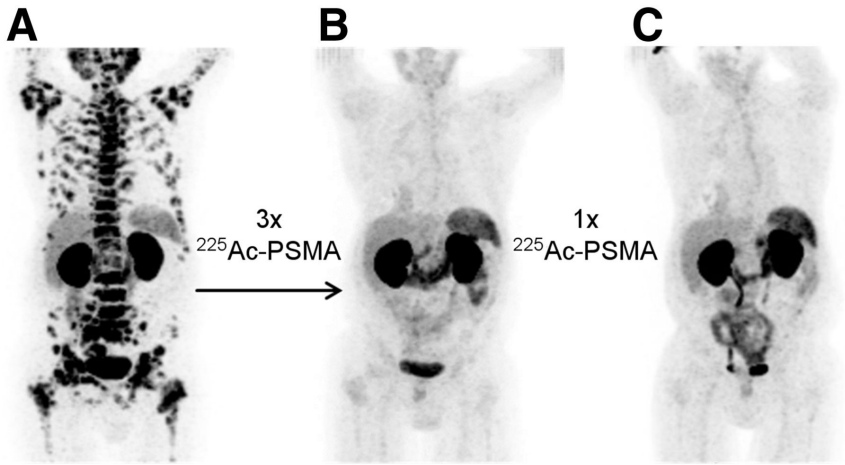


Brain



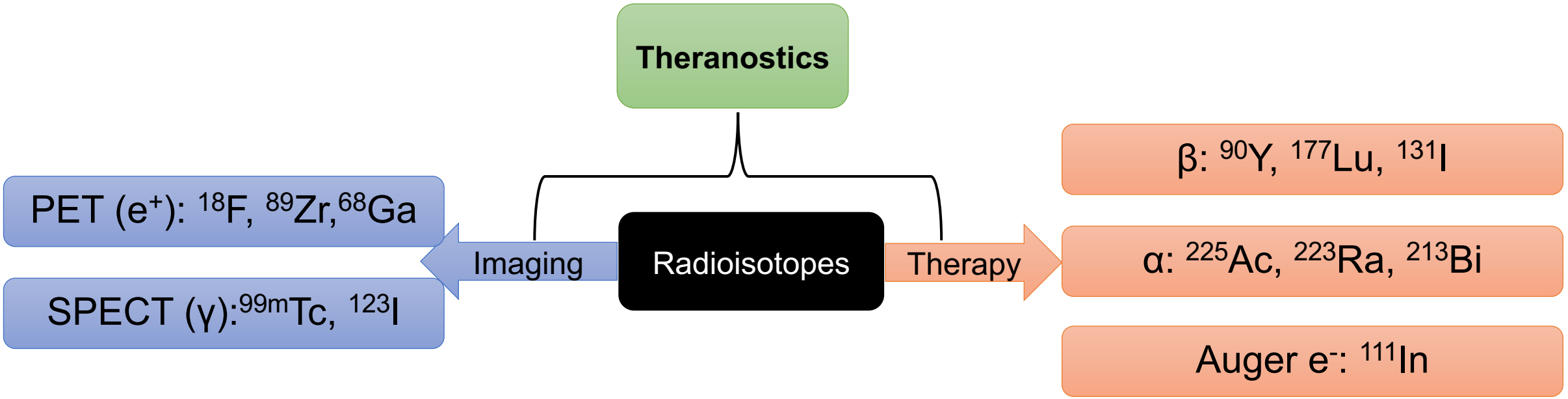
Heart

Whole body



Dicardiology.com
Everydayhealth.com
J. Nucl. Med. 2016

Nuclear Medicine



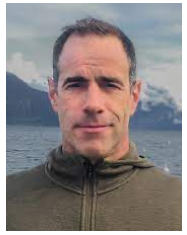
Our goals:

- Production of unconventional radionuclides
- **New chemistry** to incorporate radionuclides
- **Novel radiopharmaceuticals** for better cancer imaging or therapy

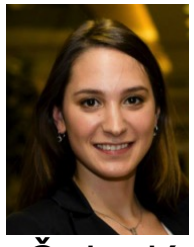
Dicardiology.com
Everydayhealth.com

Photocatalyzed fluorination – new method to make ^{18}F amino acids

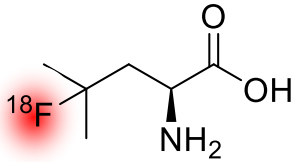

Britton

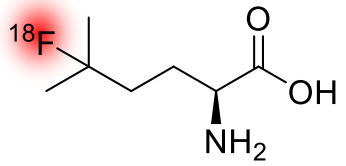

Nodwell

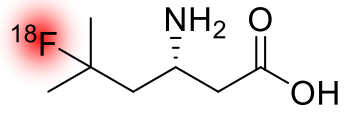

Schaffer

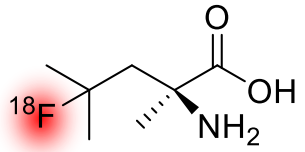

Čolović

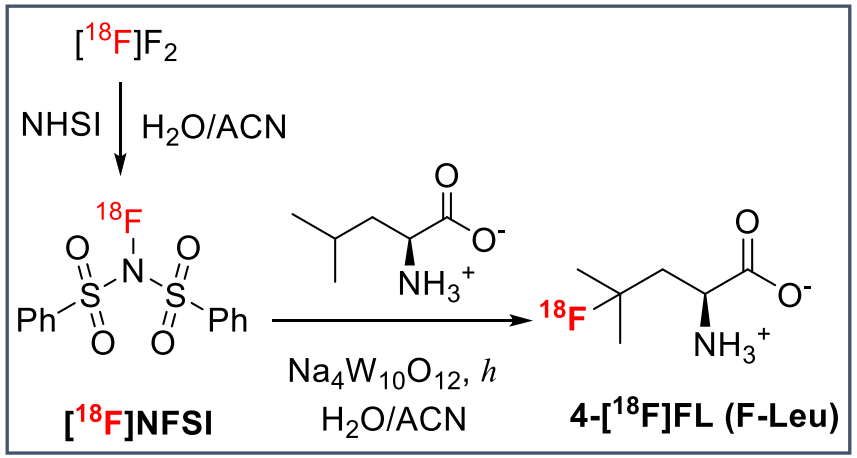
SFU: Robert Britton, Matthew Nodwell, Zheliang Yuan
TRIUMF: Paul Schaffer, Milena Čolović, Gokce Engudar, Hua Yang
BC Cancer: Francois Benard, Florian Kuchenbauer, Helen Merkens

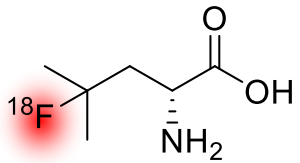

4-[^{18}F]FL

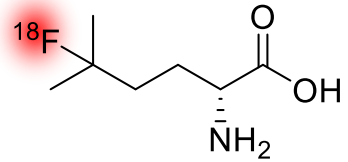

5-[^{18}F]FHL

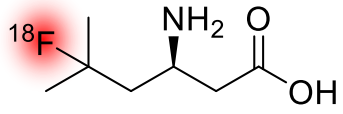

5-[^{18}F]FBAHL

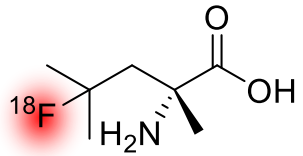

4-[^{18}F]F ML

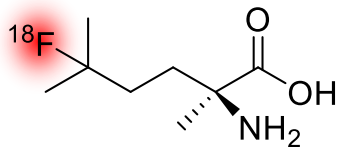


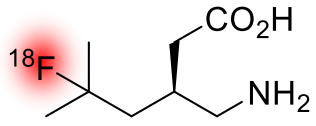

D-4-[^{18}F]FL

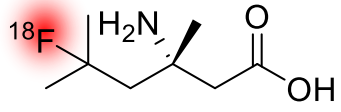

D-5-[^{18}F]FHL

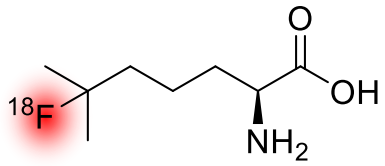

D-5-[^{18}F]FBAHL


D-4-[^{18}F]F ML

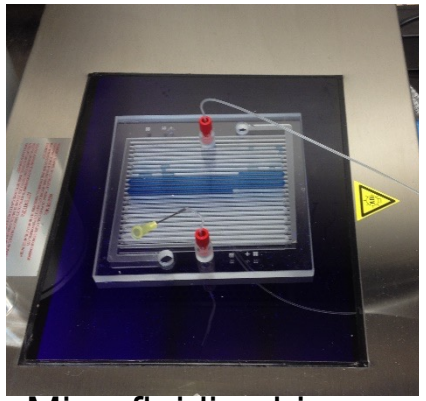

5-[^{18}F]F MHL


5-[^{18}F]FPregab

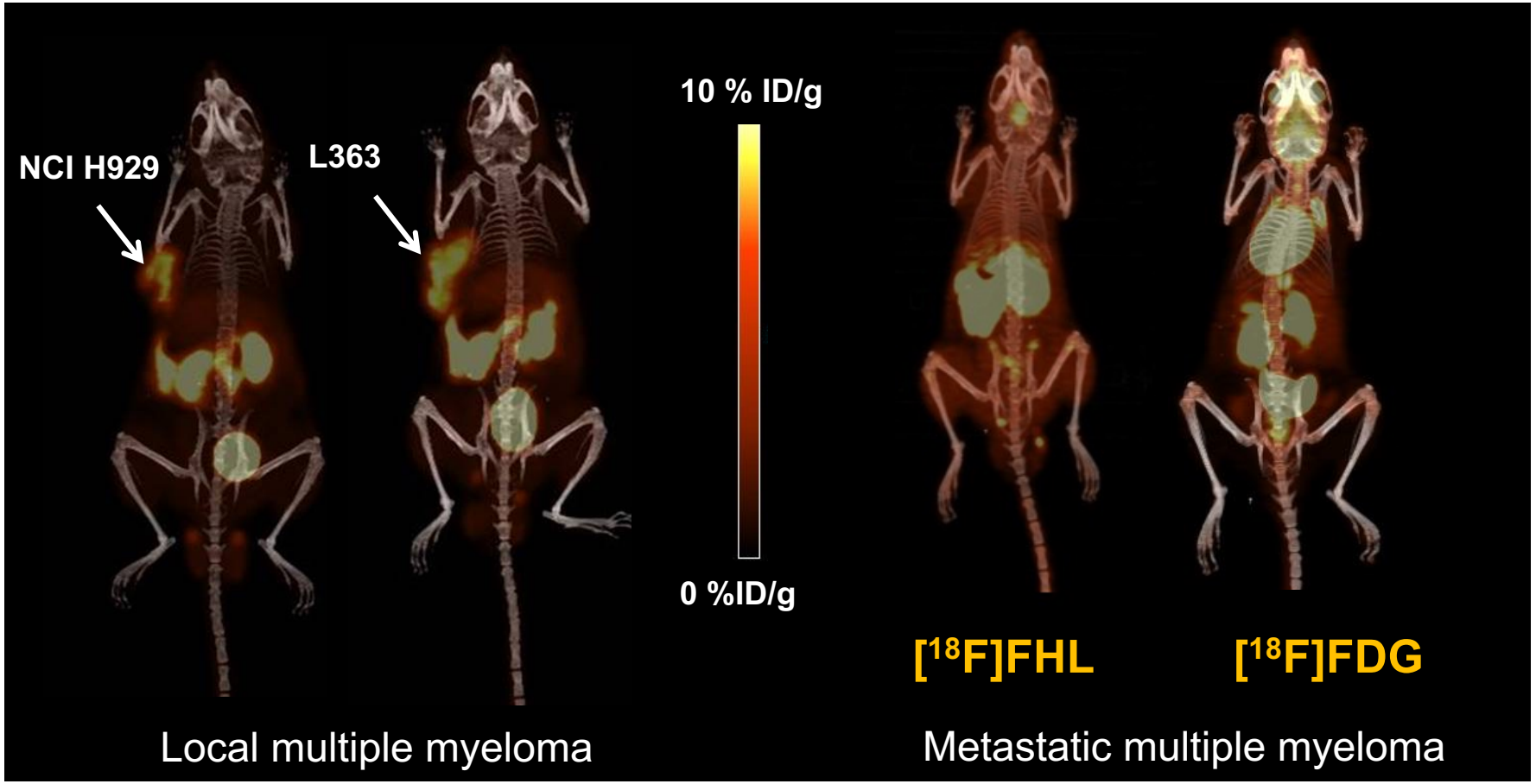

5-[^{18}F]FBABMHL

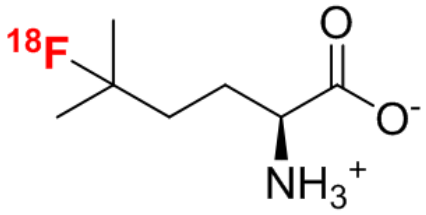

6-[^{18}F]FHHL

1-step fluorination from unmodified amino acid precursors


Microfluidic chip

Imaging multiple myeloma with L-5-[^{18}F]FHL



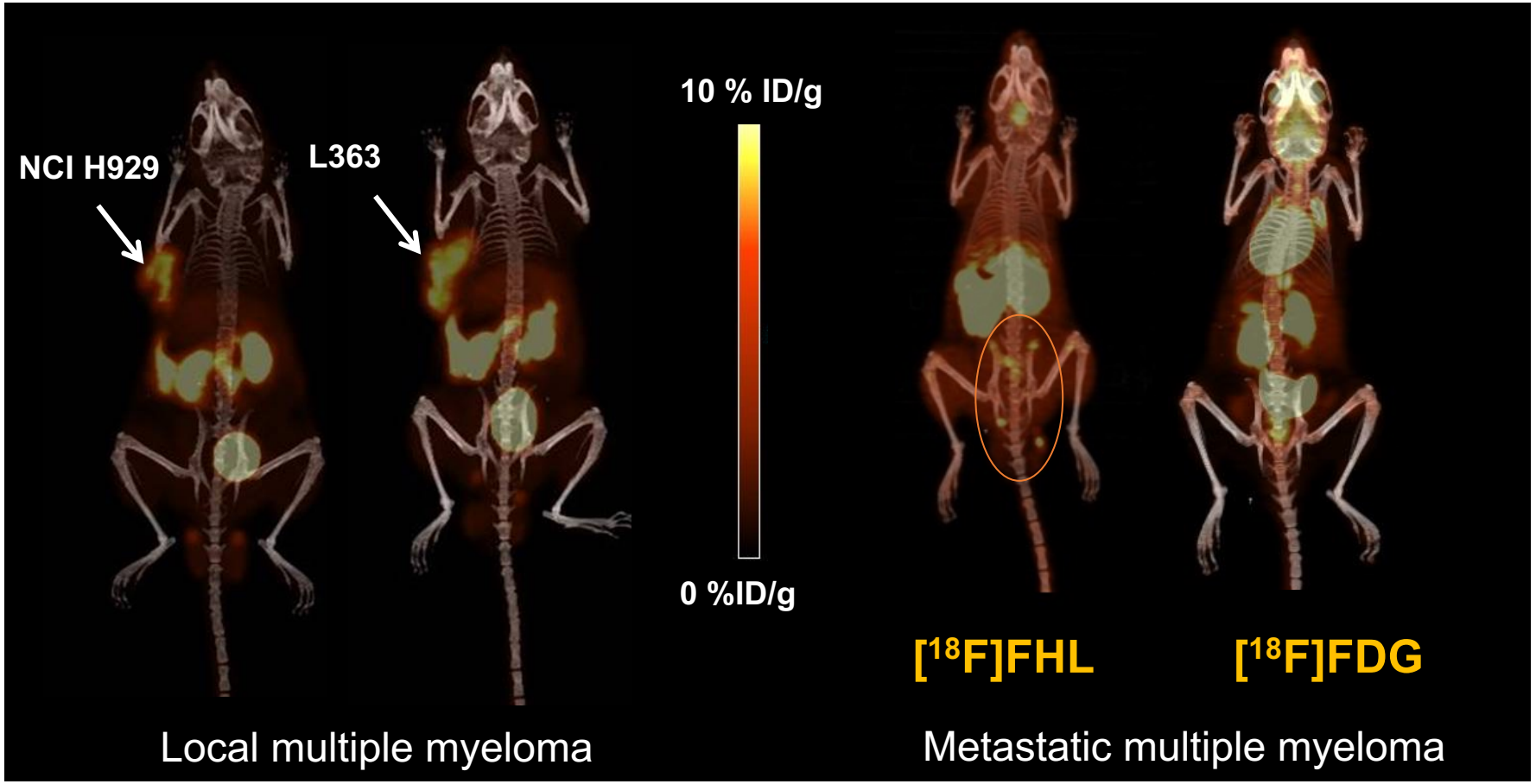


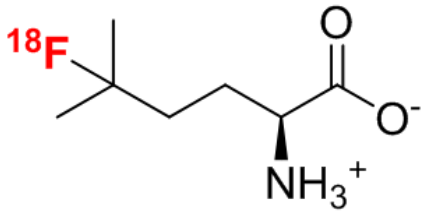
L-[^{18}F]FHL (F-homoleu)

- [^{18}F]FHL uptake via LAT1 transporter
- Metastases evident on PET/CT scans with [^{18}F]FHL and [^{18}F]FDG, **Many more metastases could be identified with [^{18}F]FHL PET**
- Higher basal uptake of [^{18}F]FDG overall
- Liver metastasis evident on [^{18}F]FDG scan which would have likely been missed on the [^{18}F]FHL scan

- Radiochemical process allows synthesis of large number of radiotracers
- High impact, award winning publications, multiple grants
- *Pending clinical translation*

Imaging multiple myeloma with L-5-[^{18}F]FHL





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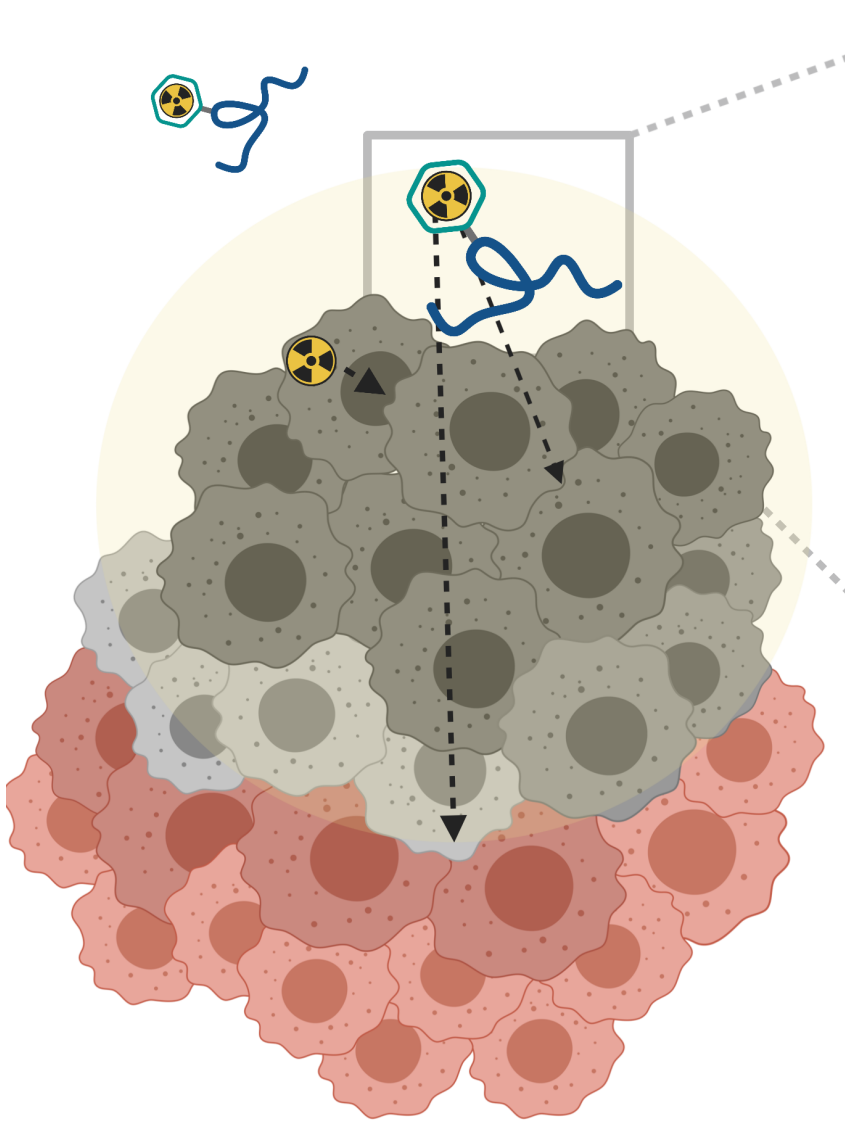
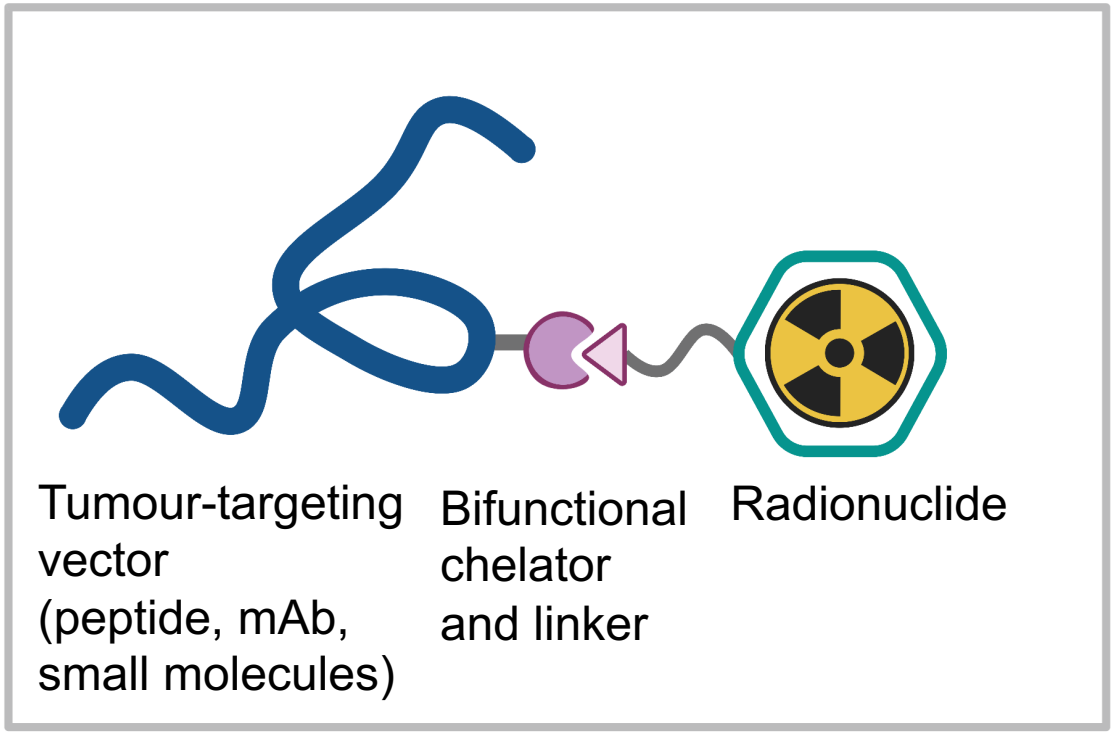
New chemistry for Targeted Radionuclide Therapy (TRT)





Tumour-targeting vector (peptide, mAb, small molecules)

Bifunctional chelator and linker

Radionuclide

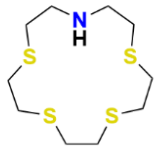
Expression level
Off-target uptake
Stability
Pharmacokinetics

Labeling efficiency
Labeling conditions
Stability
Impact on uptake

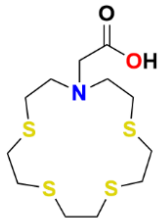
Decay characteristics
Tissue penetration
Availability

Therapeutic radiation dose is selectively delivered to malignant tissue using tumor-targeting vector

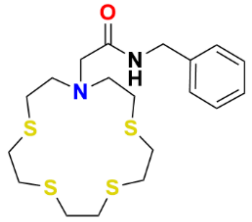
Capturing the Exotic Meitner-Auger Emitter $^{197m/g}$Hg with Sulfur-rich Macrocycles



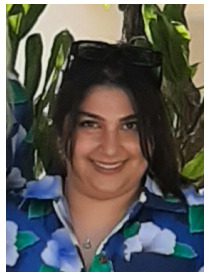
NS_4



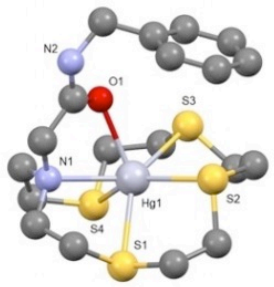
NS_4-CA



NS_4-BA

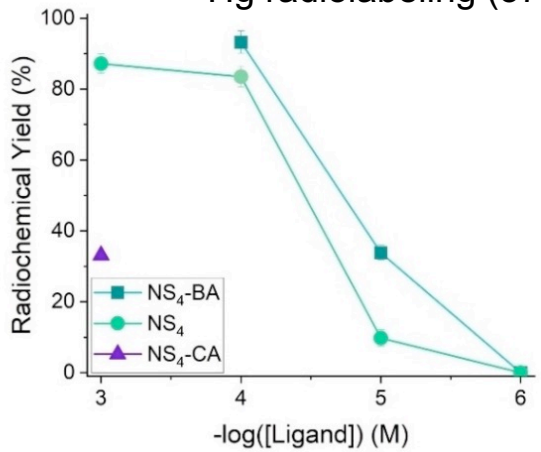


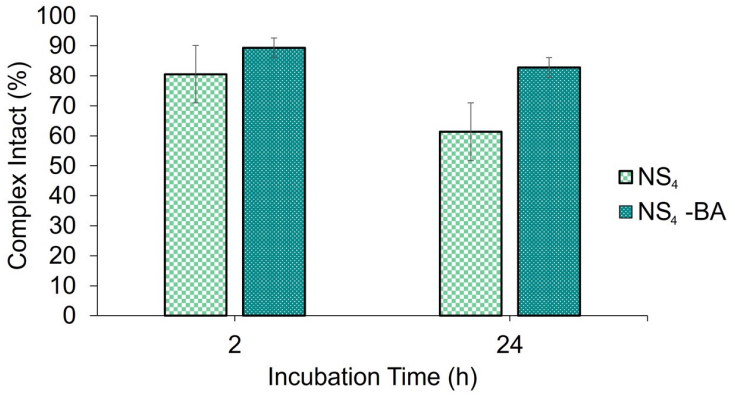
Parmissa Randhawa
PhD Candidate



DFT of $[Hg(NS_4\text{-}BA)]^{2+}$
(lowest energy configuration)

$^{197m/g}$Hg radiolabeling (37°C)



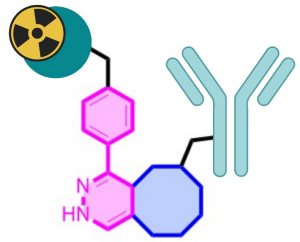


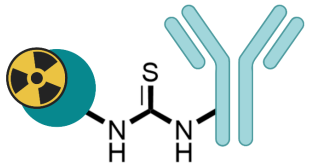
Radiometal-complex stability in human serum

Therapy + SPECT imaging

Therapy

Preparation of immunoconjugates currently underway for targeted in vitro/in vivo studies





CIHR IRSC

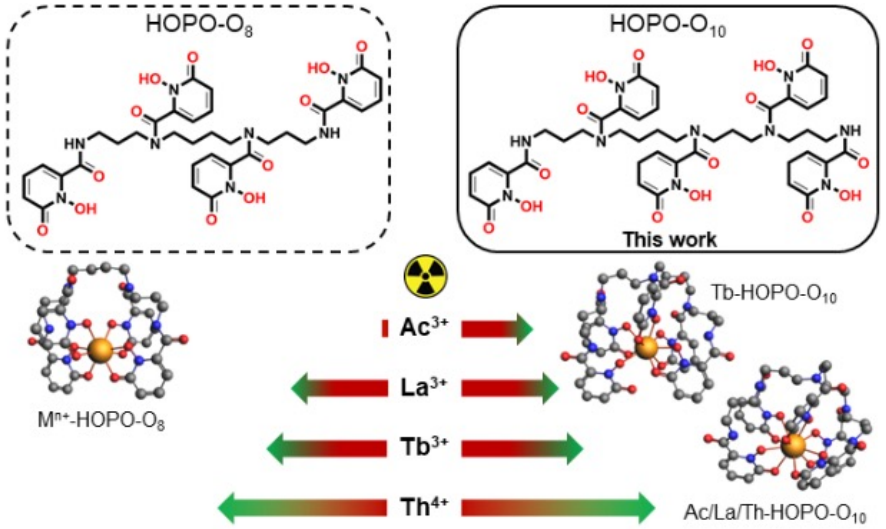
UNIVERSITY OF TORONTO

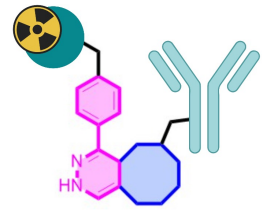
Reilly Lab

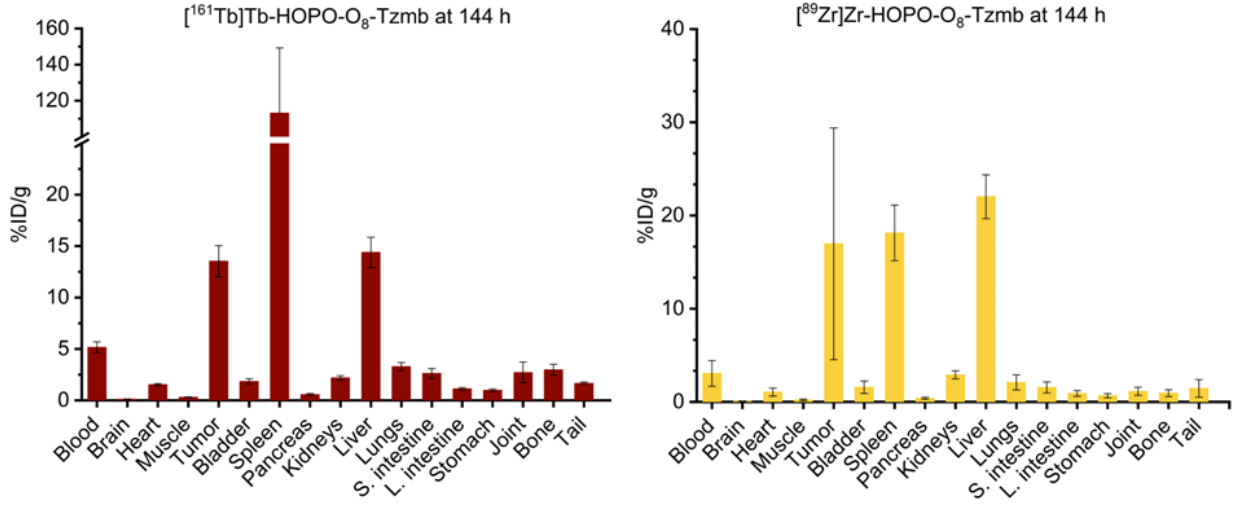
Randhawa, P., *et al. Chem. – A Eur. J.* **2023,** 29, e202203815.
https://doi.org/10.1002/chem.202203815

High dentate HOPO chelator for radioactinides/lanthanides

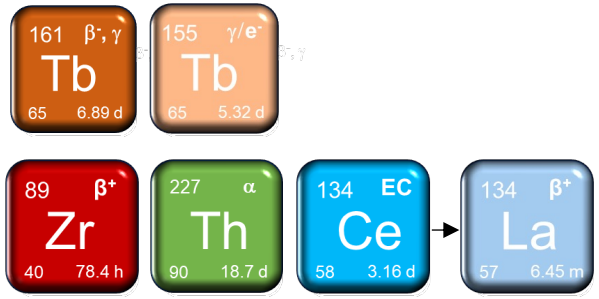
$^{89}Zr/^{161}Tb/^{227}Th/^{134}Ce$-HOPO-$O_8$-Tz immunoconjugates for (pre-)targeting



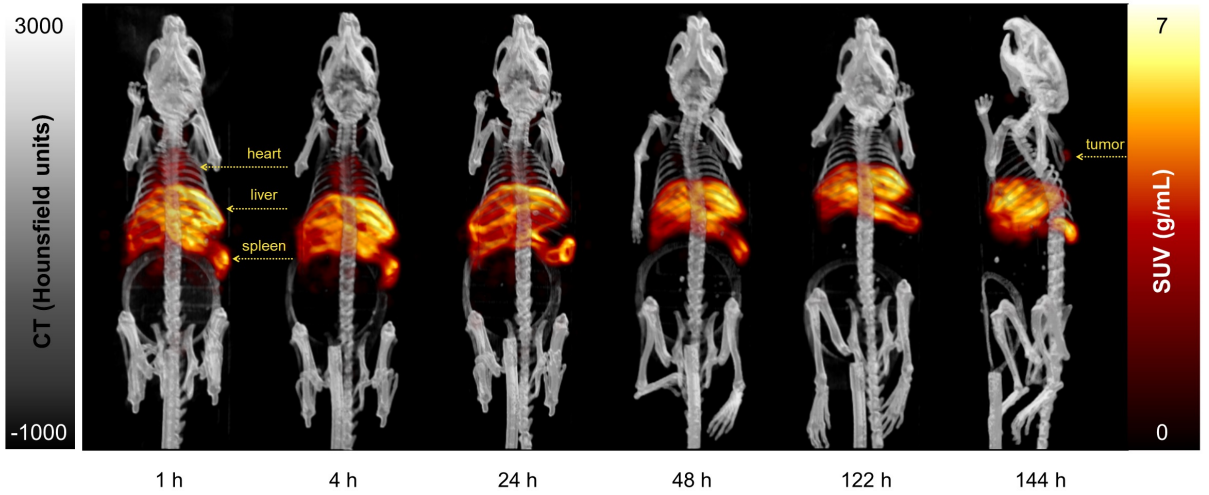




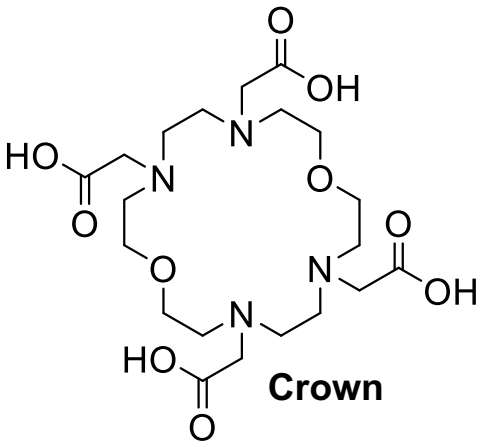
Carbo-Bague, I., *Inorg. Chem.* **2023**, asap.
https://pubs.acs.org/doi/10.1021/acs.inorgchem.2c03671



Imma Carbo-Bague
PhD Candidate



New chelators for therapeutical isotopes: crown

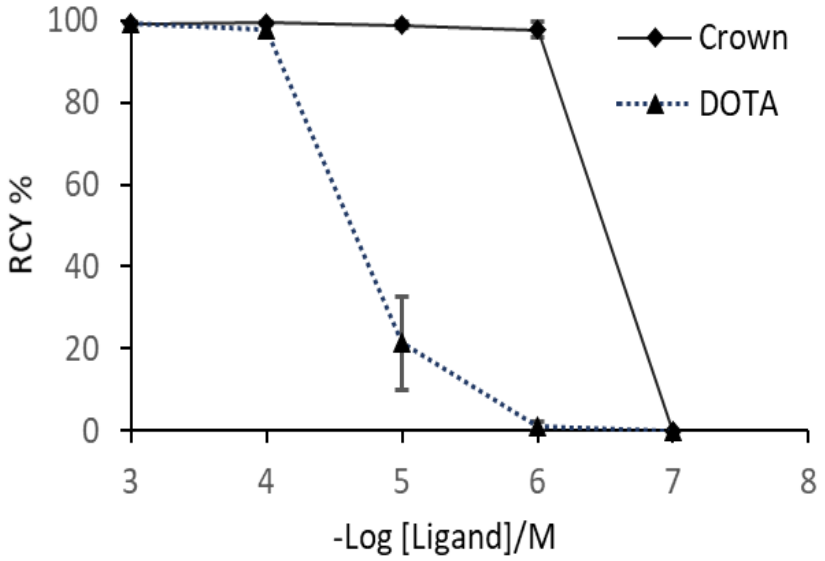


Crown

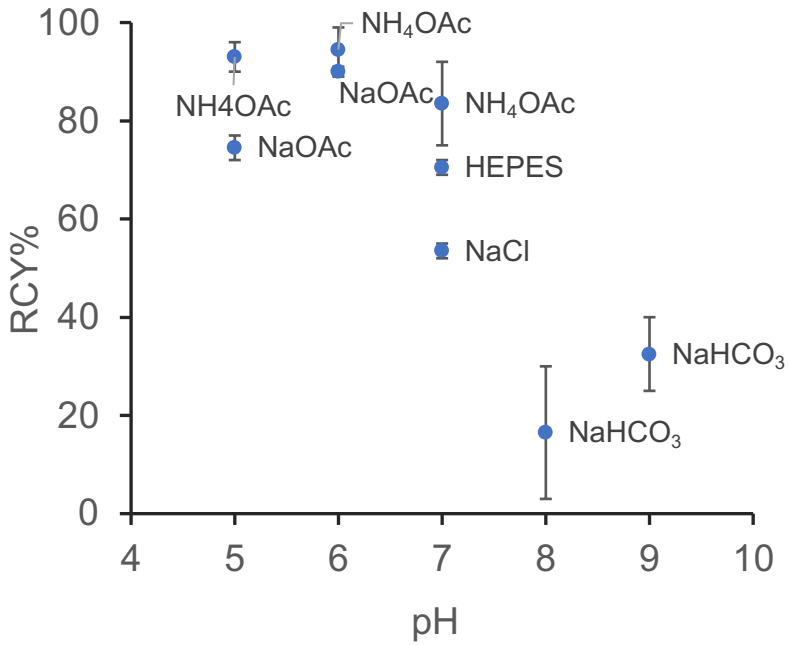
- Crown: a new generation chelate for therapeutic isotopes: Ac^{3+}, Bi^{3+}, Lu^{3+}, Tb^{3+}
- Labeling: quantitative, fast, ambient temperature, physiological pH

TRIUMF proprietary chelator

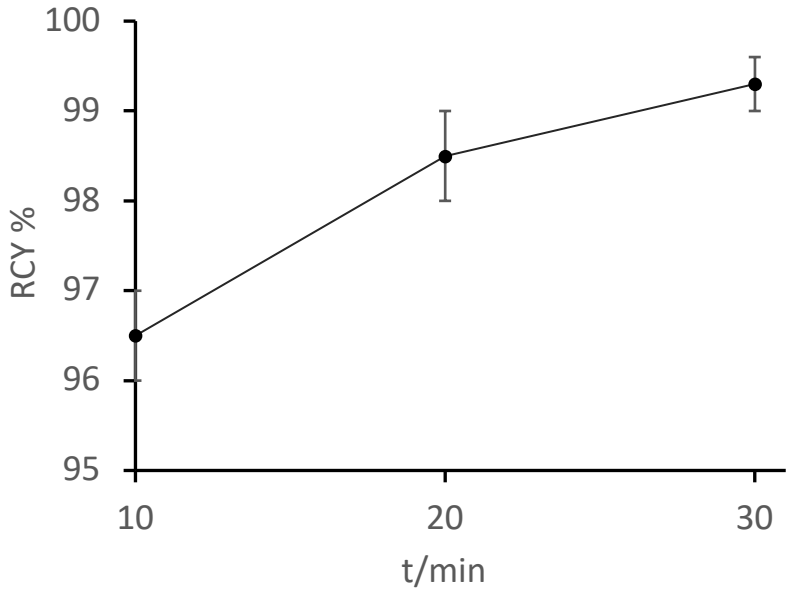
^{225}Ac labeling at various ligand concentration
Crown: r.t.; DOTA: 85°C, 15 min



^{225}Ac labeling yield with various buffer and pH



^{225}Ac labeling yield over time



Labels ^{225}Ac 100 x more efficient than DOTA

Hua Yang

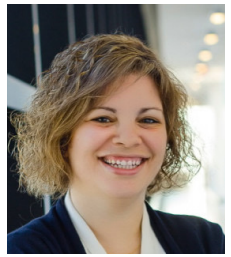
Yang, et. al. *Chem. Eur. J.* **2020**, 26, 11435
Wharton, et. al, Molecules, **2023**, 28, 3155

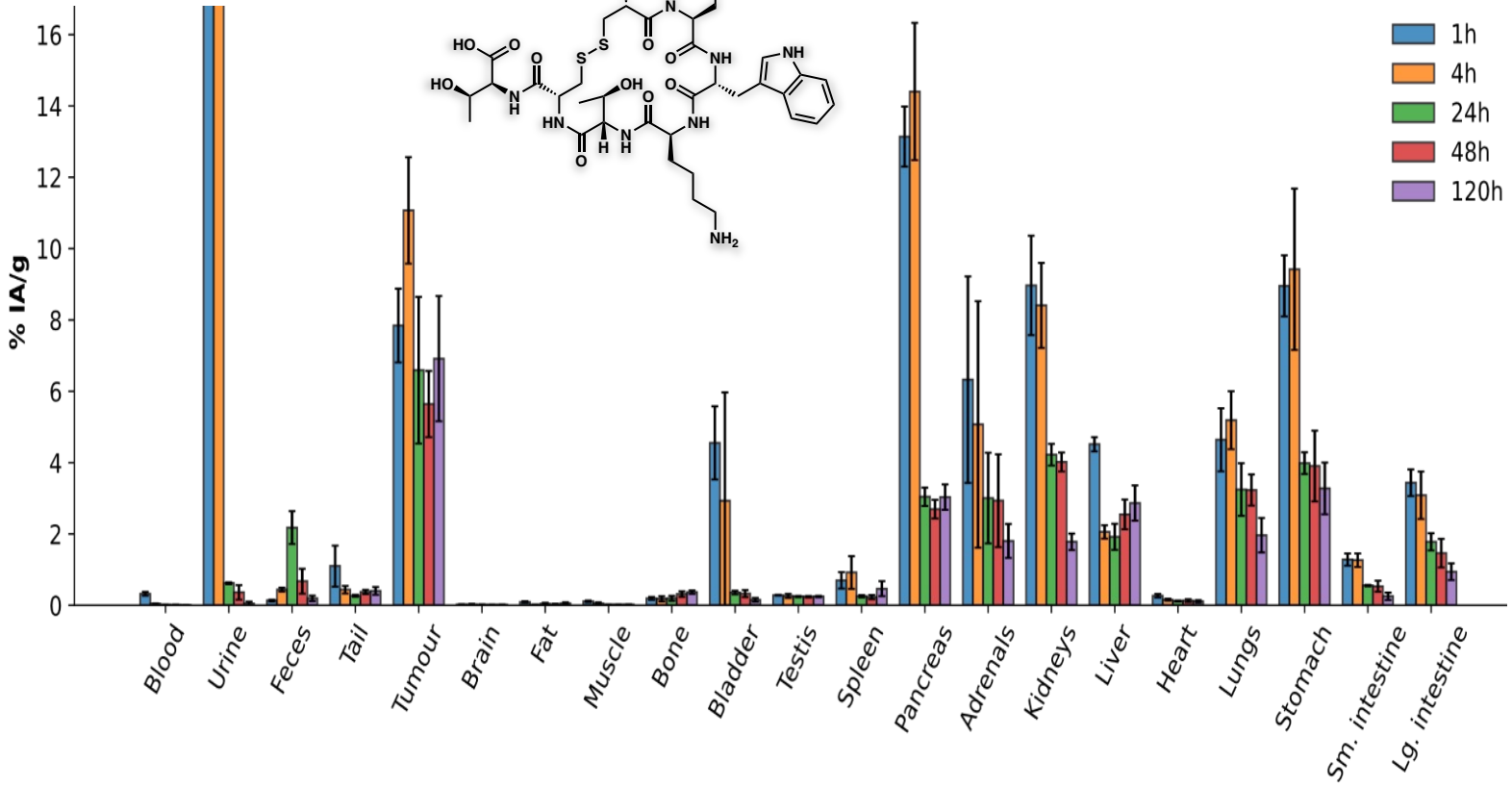
[^{225}Ac]Ac-crown-TATE animal studies

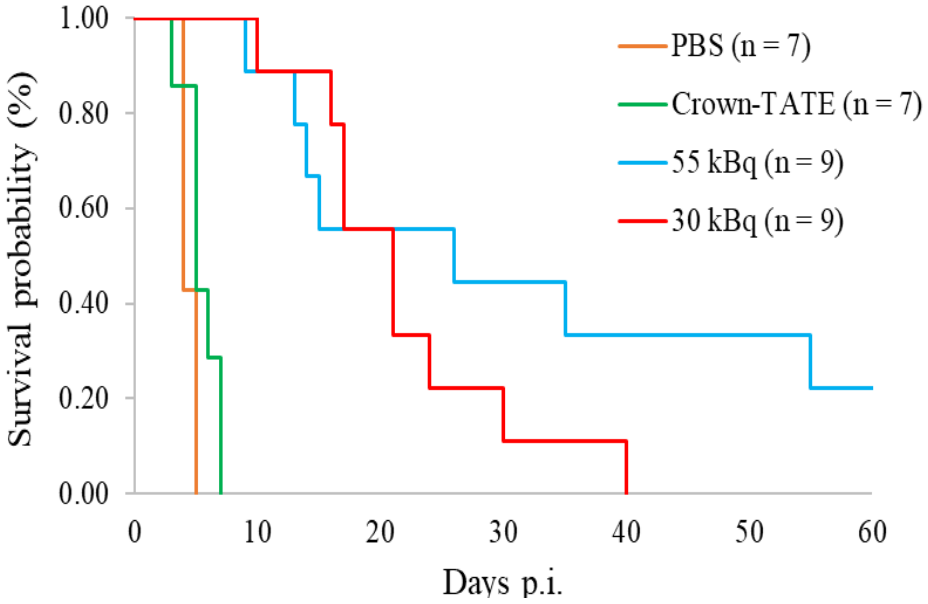

Ingham


Wharton


Merkens (BCC)


Rodriguez-Rodriguez (UBC)

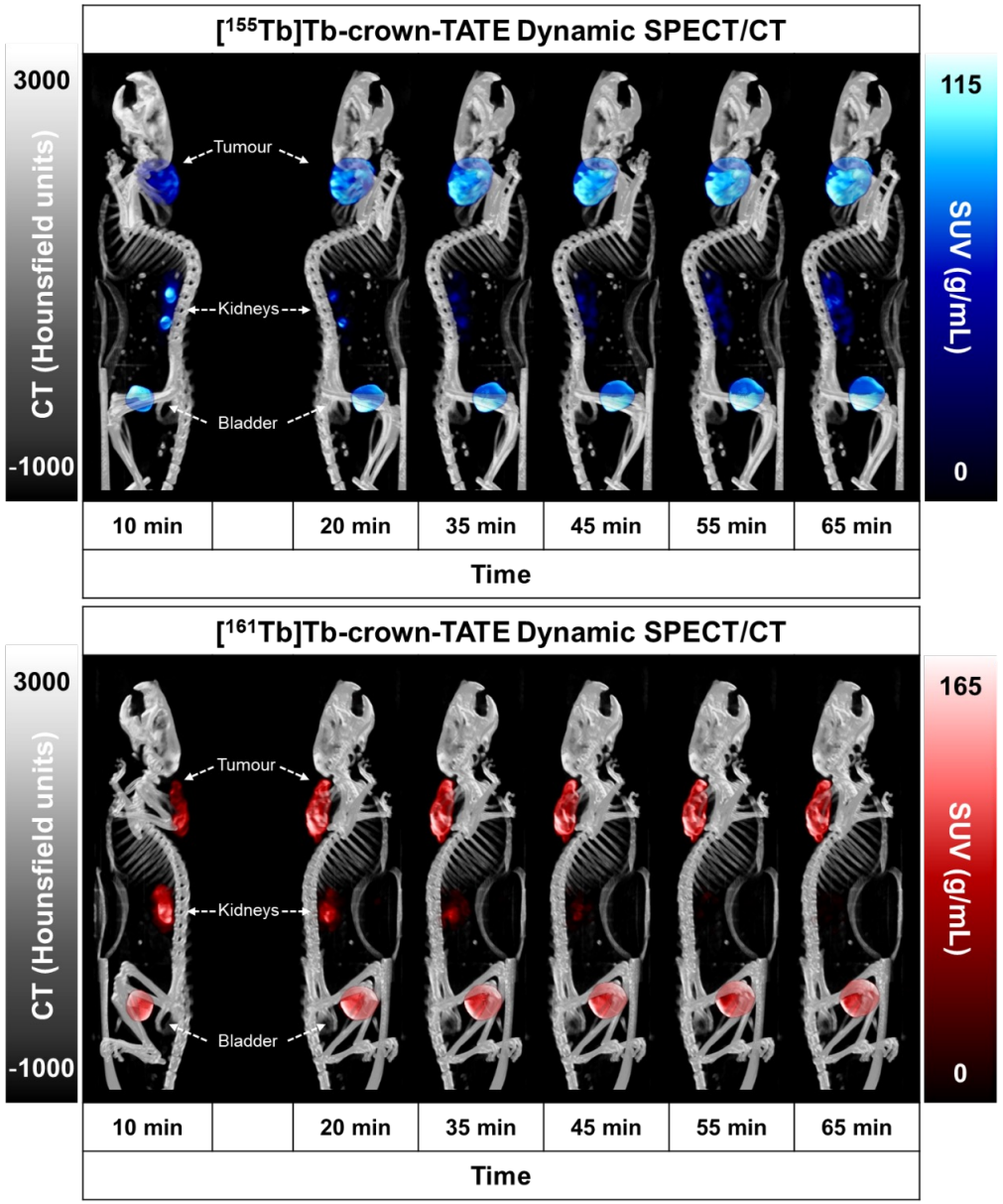




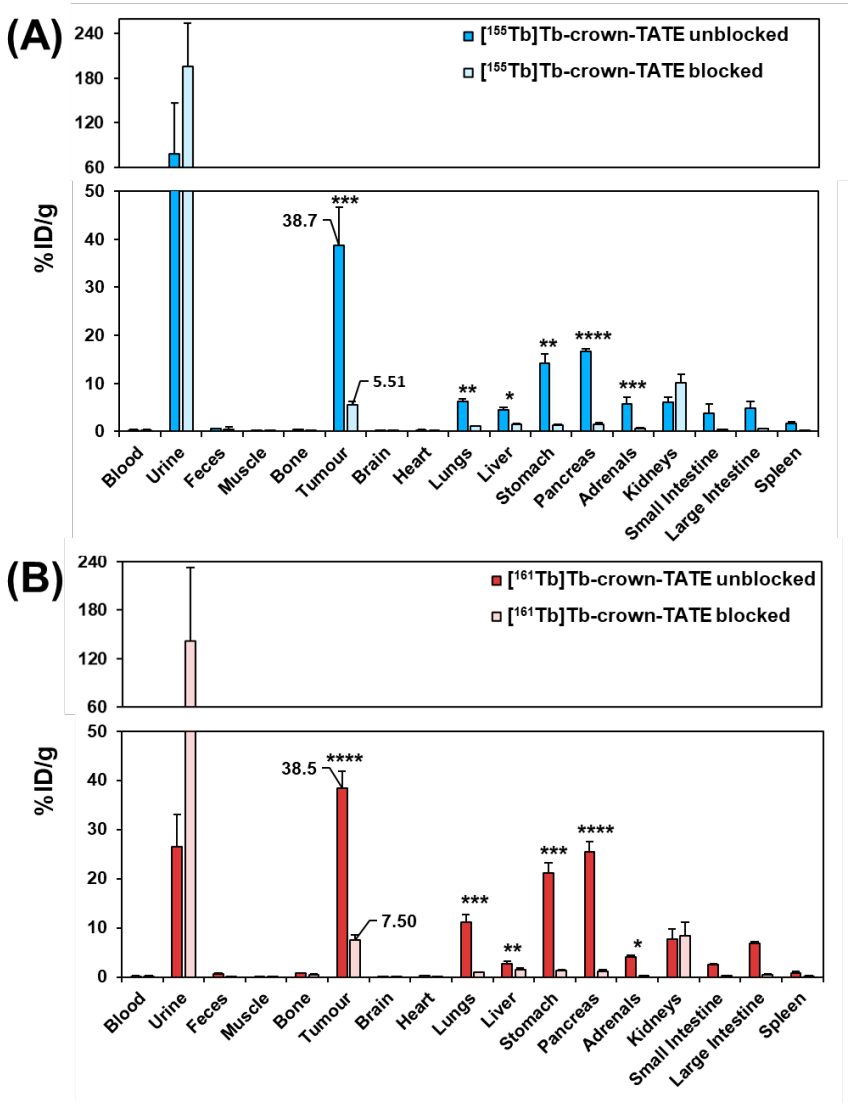
Biodistribution of [^{225}Ac]Ac-crown-TATE in AR42J tumour mice shows high tumor retention (%ID/g > 5) over 5 days (n=4)

- TRIUMF in-house developed radiopharmaceutical
- First animal study using our Th spallation produced ^{225}Ac

[$^{161/155}$Tb]Tb-crown-TATE: in vivo SPECT imaging and biodistribution



SPECT imaging in AR42J tumour mice



Biodistribution at 2h in AR42J tumour mice with and without blocking reagent

Wharton

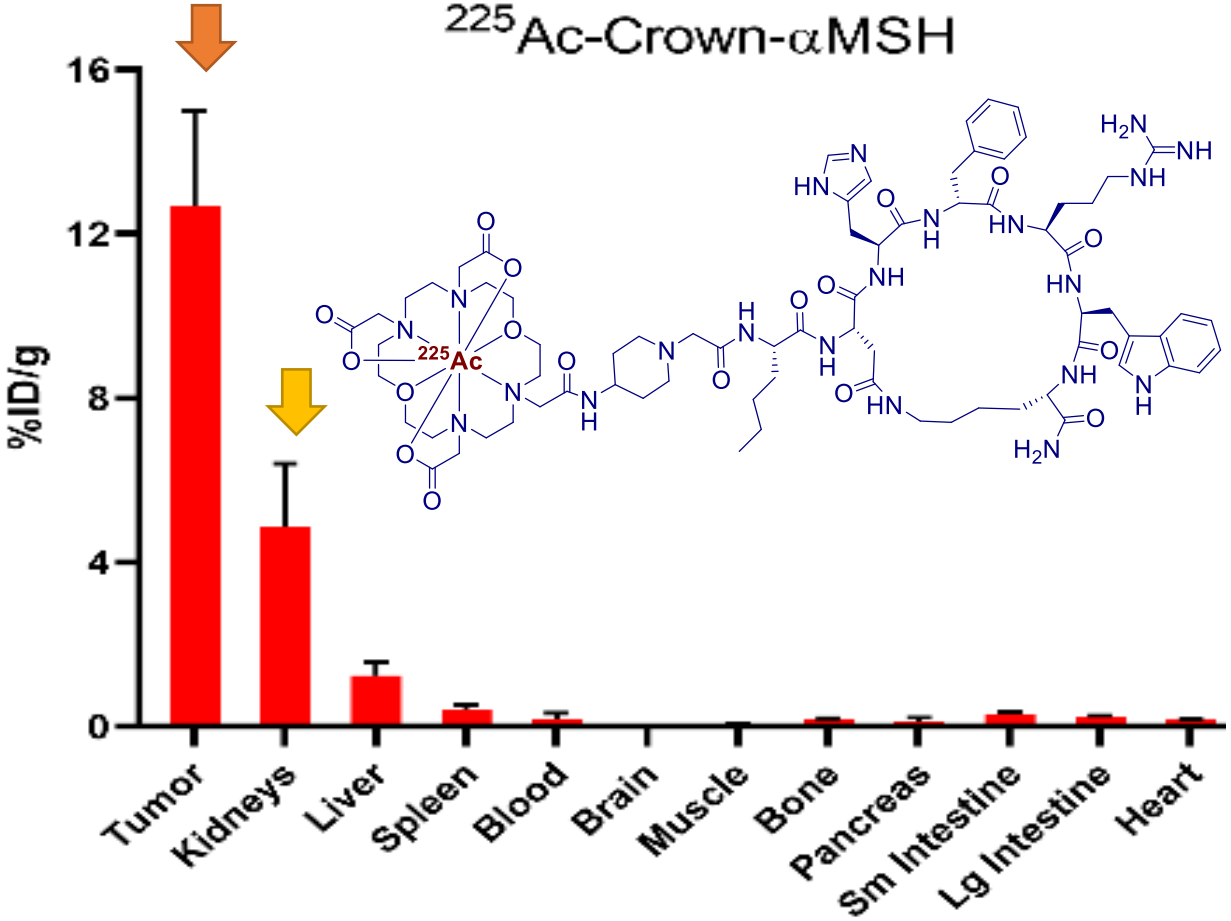
Kunz

S. McNeil

Radchenko

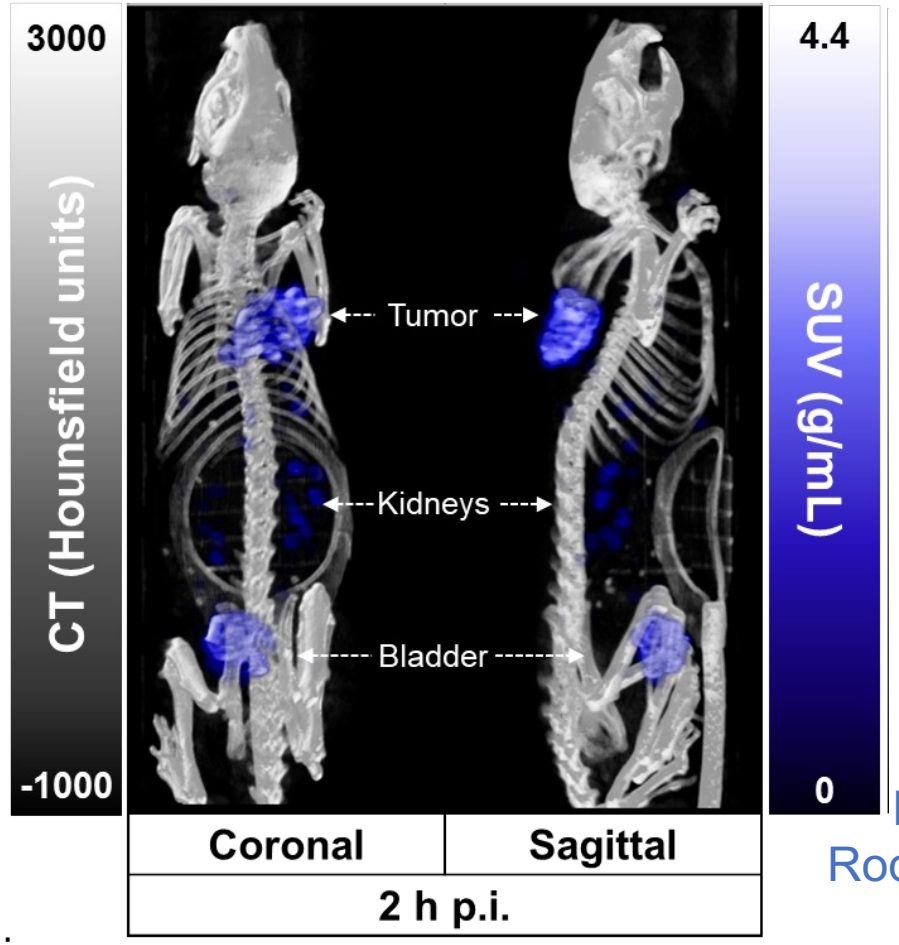
- ISAC produced ^{155}Tb
- SCK CEN gifted ^{161}Tb
- ^{155}Tb/^{161}Tb theranostic pair
- ^{155}Tb serves as imaging partners for ^{225}Ac for patient screening and dosimetry

Radiopharmaceutical development



^{155}Tb from ISAC mass separator

[^{155}Tb]Tb-crown-αMSH

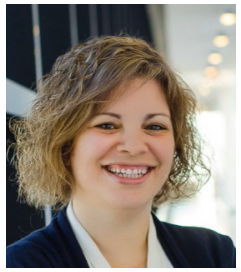


BioD in B16F10 (melanoma tumor bearing mice) at 2-hour post injection

- Late-stage melanoma: low long-term survival, no curable option
- MSH derivatives targeting MC1R are highly promising for therapy and imaging
- Because of low receptor density, highly effective chelator required to get enough radioactive payload on target
- ^{225}Ac-crown-aMSH showed high tumor accumulation and low uptake in healthy organs and tissues (low toxicity)
- Imaging partner with ^{155}Tb for patient screening, dosimetry and monitoring

Wharton

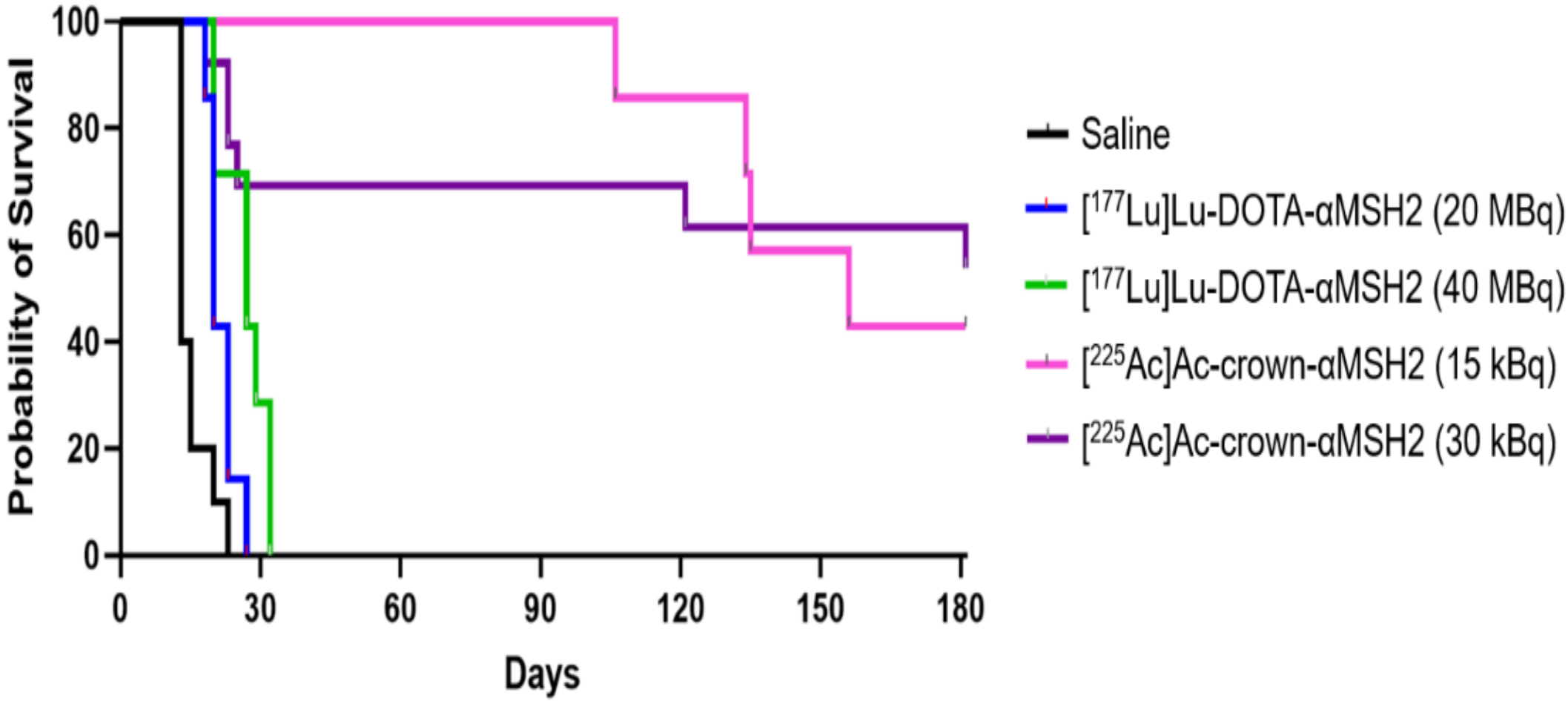
Zhang (BCC)



Rodriguez-Rodriguez (UBC)

Kunz

Therapy study with [^{225}Ac]Ac-crown-αMSH2



- Human melanoma model
- Significantly improve the survival of the tumour bearing mice
- Much better treatment efficacy compared to ^{177}Lu
- Clinical translation hopeful

Summary:

- Production of unconventional radionuclides: alpha-emitters and MAE emitters
  ^{225}Ac, ^{213}Bi, ^{227}Th, $^{212/203}$Pb, $^{197/m}$Hg, ^{119}Sb, ^{13x}La, ^{165}Er etc.
- **New chemistry** to incorporate unconventional radionuclides:
  - new fluorination method
  - new and better chelators for $^{197/m}$Hg, ^{225}Ac, $^{155/161}$Tb, and ^{227}Th
- **Novel radiopharmaceuticals** for improved cancer imaging or therapy
  - Targeting multiple myeloma, breast cancers, neuroendocrine tumours, and melanoma

Future directions:

Wed 5 Year Plan session: Paul Schaffer & Caterina Ramogida

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Thank you
Merci

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