RRMC – Santa Fe, NM

$^{203}Pb/^{212}Pb$ Theranostics for Cancer

Michael K Schultz PhD

Associate Professor, Radiology, Radiation Oncology, Pediatrics, Chemistry

The University of Iowa, Iowa City, Iowa USA

University of Iowa Holden Comprehensive Cancer Center
University of Iowa Health Care

University of Iowa Neuroendocrine Tumor Program

University of Iowa Stead Family Children's Hospital

SUPPORTED BY THE IOWA NEUROENDOCRINE TUMOR SPORE

Disclosures

Michael K Schultz PhD is Chief Science Officer, Viewpoint Molecular Targeting, Inc.

VIEWPOINT molecular targeting

No drugs presented are FDA approved.

Michael K Schultz has been selected as Best Dad Ever, 2018.

Selection Committee

$^{203}Pb/^{212}Pb$ Theranostics for Cancer

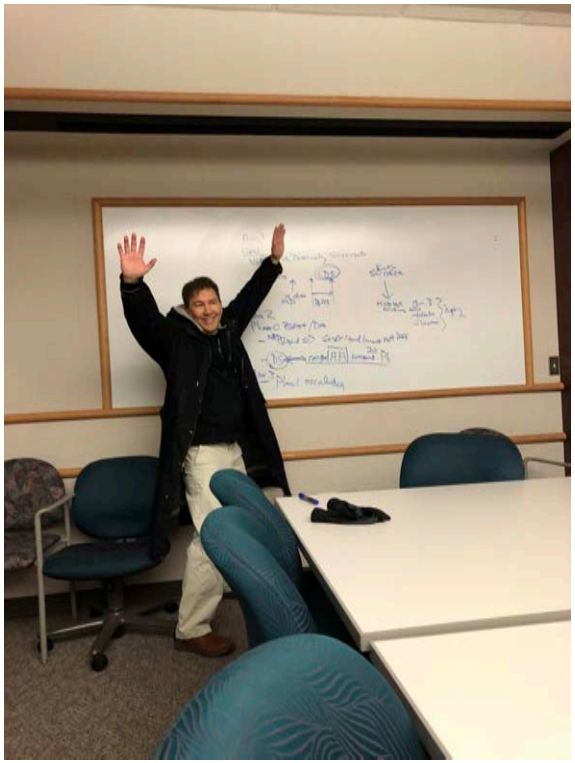
- Theranostics
- Rationale for α-particle therapy (*vs* β)
- Radionuclides for α-particle therapy
- $^{203}Pb/^{212}Pb$ based theranostics
- Preclinical imaging/therapy
- Production Chemistry
- Summary – promise and challenges

SUPPORTED BY THE IOWA NEUROENDOCRINE TUMOR SPORE

Theranostic Concepts

Combination of two words:

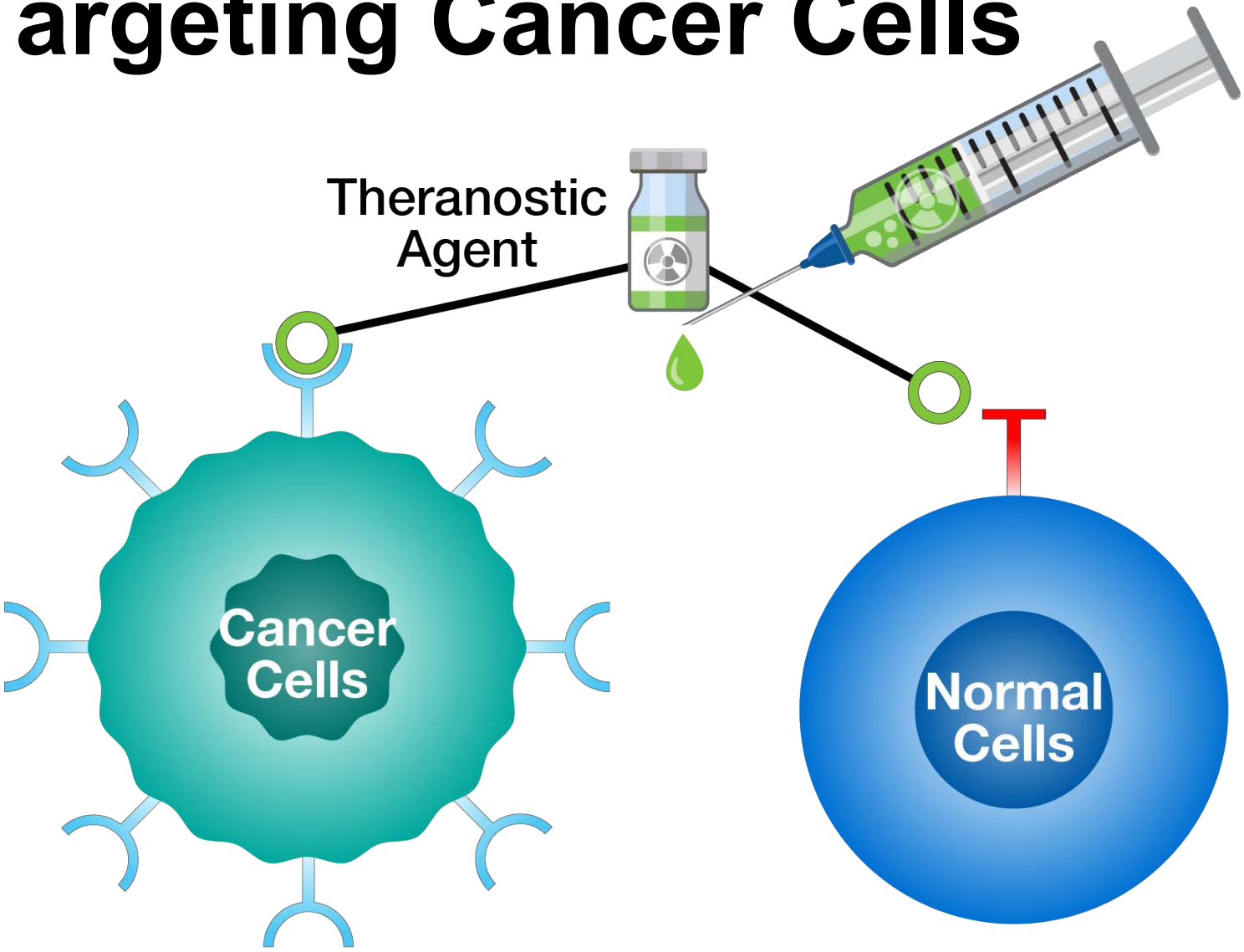
- **Thera**peutic + Diag**nostic**
- Sometimes referred to as Thera**g**nostics and *"Diapeutics."*
- Use of molecules that are labeled with radioactive atoms to identify cancer; and use the same molecule (or very closely related) to treat the cancer.



Enthusiasm about α

SUPPORTED BY THE IOWA NEUROENDOCRINE TUMOR SPORE

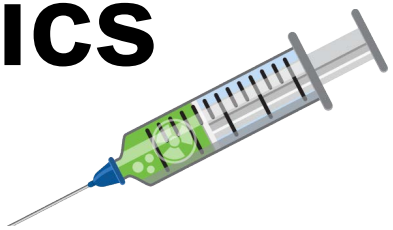
Targeting Cancer Cells



Selective Binding to Cancer Cells

No Binding to Normal Cells

Designing Theranostics



1. Target

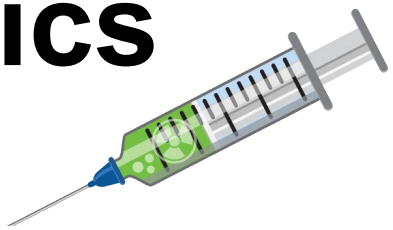
2. Ligand

Binding

3. Radiation Cage

Biochemistry | Chemistry | Radiochemistry

Designing Theranostics



Diagnostic atom

Target

Ligand

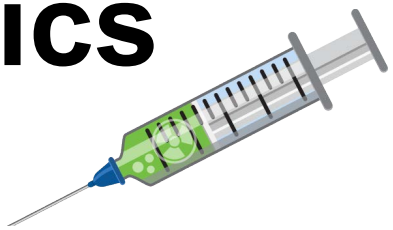
Binding

Gamma Rays

PET scans
SPECT scans

Biochemistry | Chemistry | Radiochemistry

Designing Theranostics



Therapeutic atom

Target

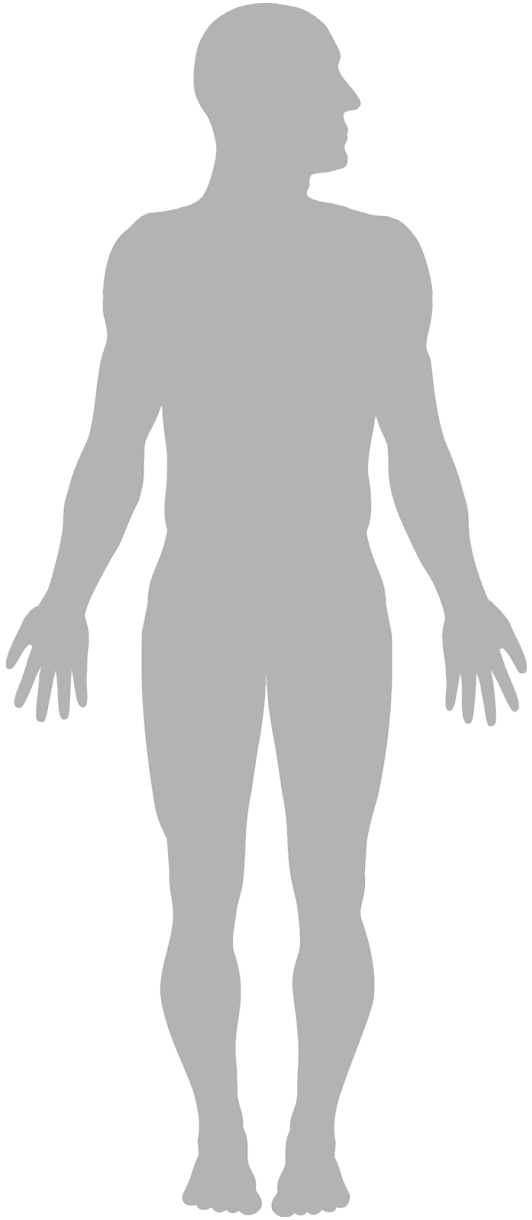
Ligand

Binding

Alpha-
Beta
particles

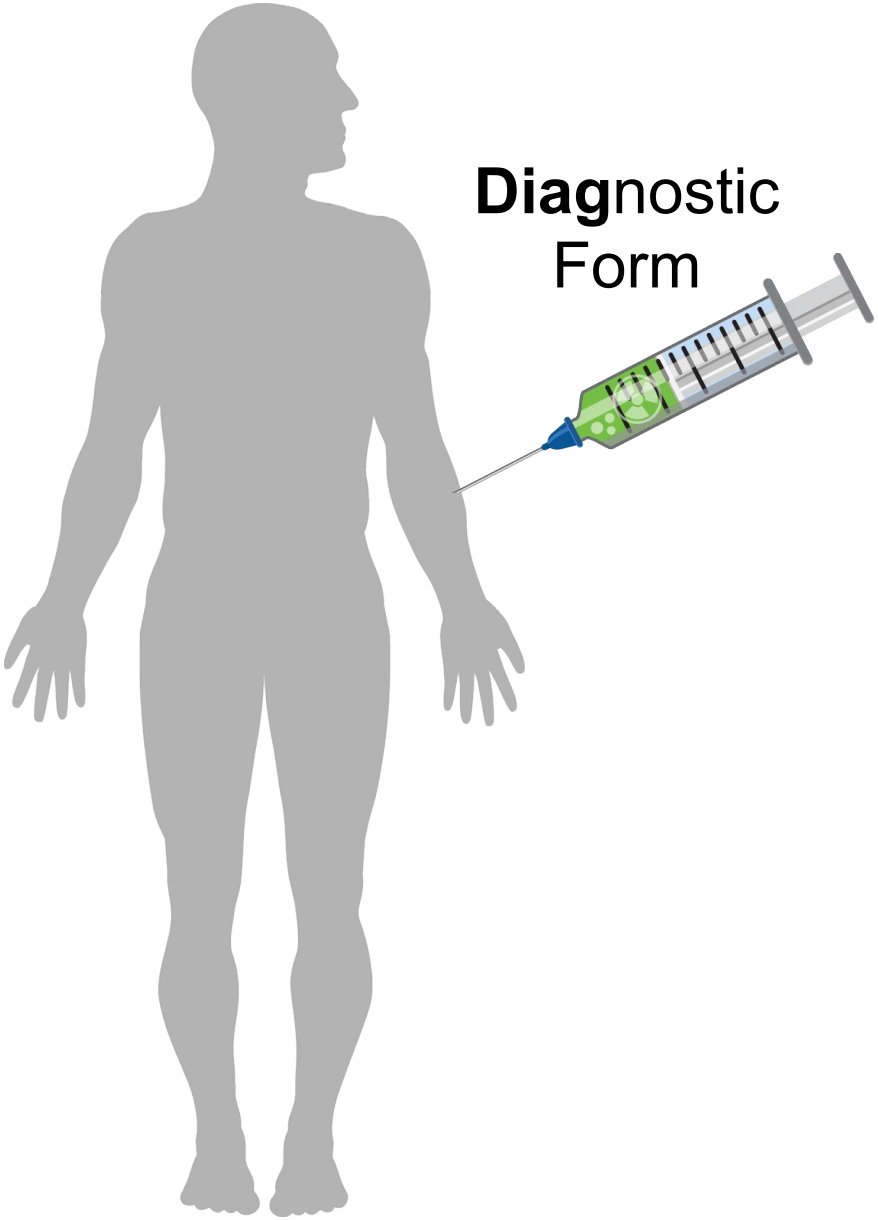
Biochemistry | Chemistry | Radiochemistry

Theranostics – Patient Care



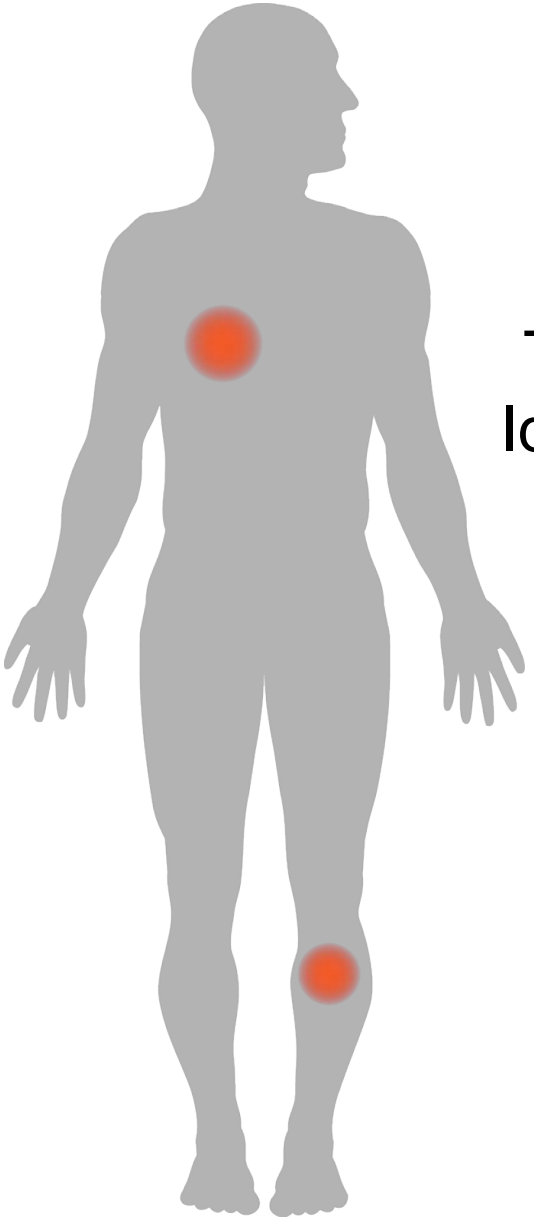
- Patient presents with symptoms or other tests that indicate a particular cancer.

Theranostics – Patient Care



- Patient presents with symptoms or other tests that indicate a particular cancer.
- Patient is injected with the diagnostic form.
- A medical scan is performed after a time for accumulation in the tumors.
- A dose plan is made by doctors.

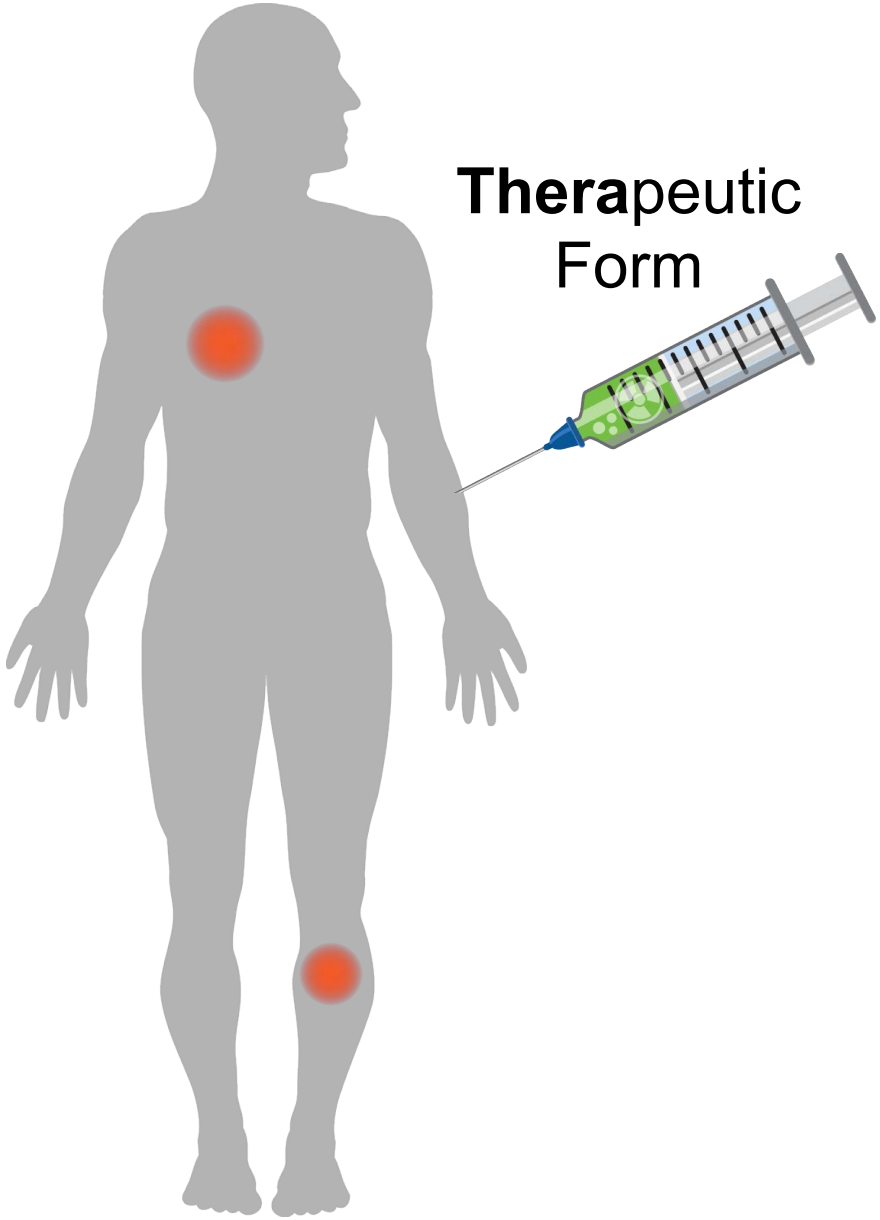
Theranostics – Patient Care



Tumors Identified

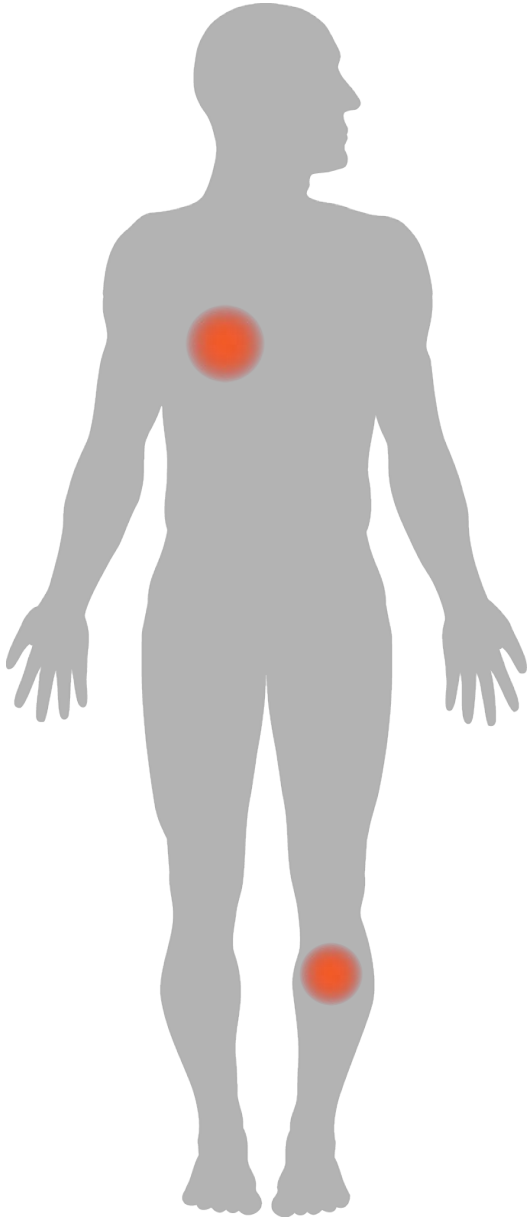
- Patient presents with symptoms or other tests that indicate a particular cancer.
- Patient is injected with the diagnostic form.
- A medical scan is performed after a time for accumulation in the tumors.
- A dose plan is made by doctors.

Theranostics – Patient Care

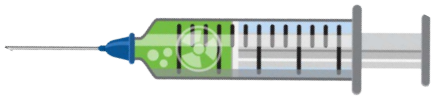


- Patient presents with symptoms or other tests that indicate a particular cancer.
- Patient is injected with the diagnostic form.
- A medical scan is performed after a time for accumulation in the tumors.
- A dose plan is made by doctors.
- Patient is treated with the therapeutic form.

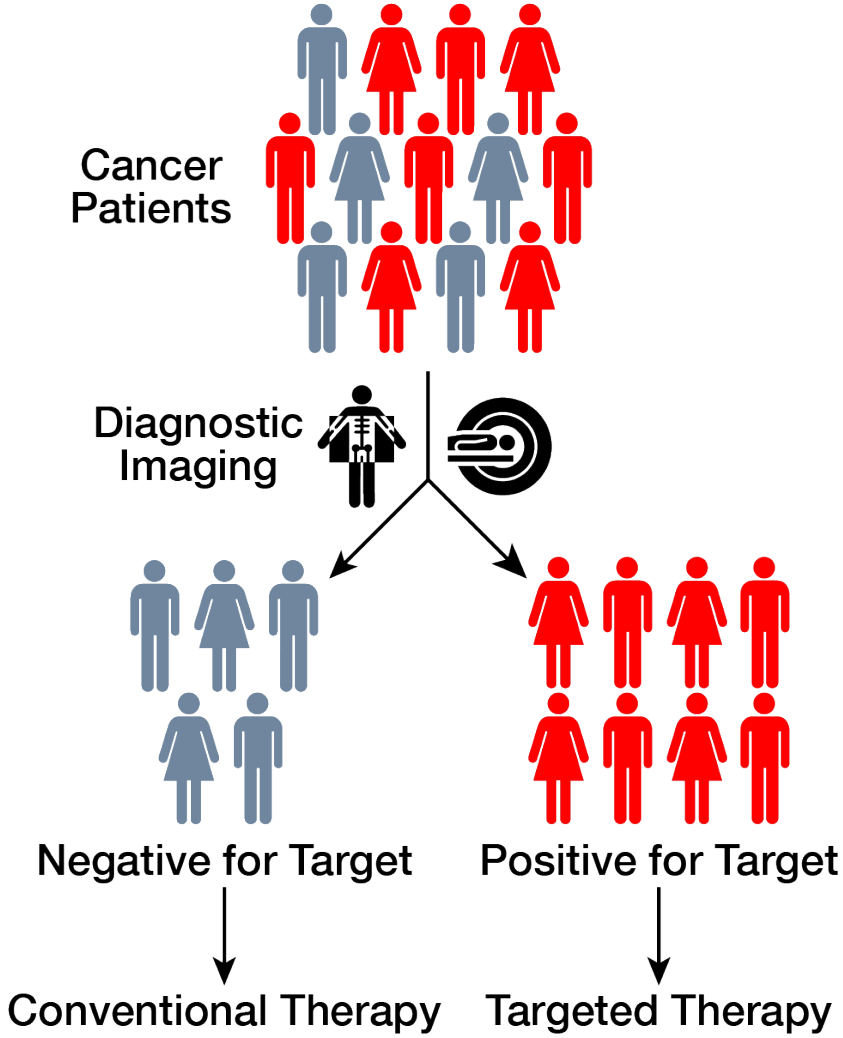
Theranostics – Patient Care



- Patient presents with symptoms or other tests that indicate a particular cancer.
- Patient is injected with the diagnostic form.
- A medical scan is performed after a time for accumulation in the tumors.
- A dose plan is made by doctors.
- Patient is treated with the therapeutic form.
- Response can be monitored with diagnostic form.



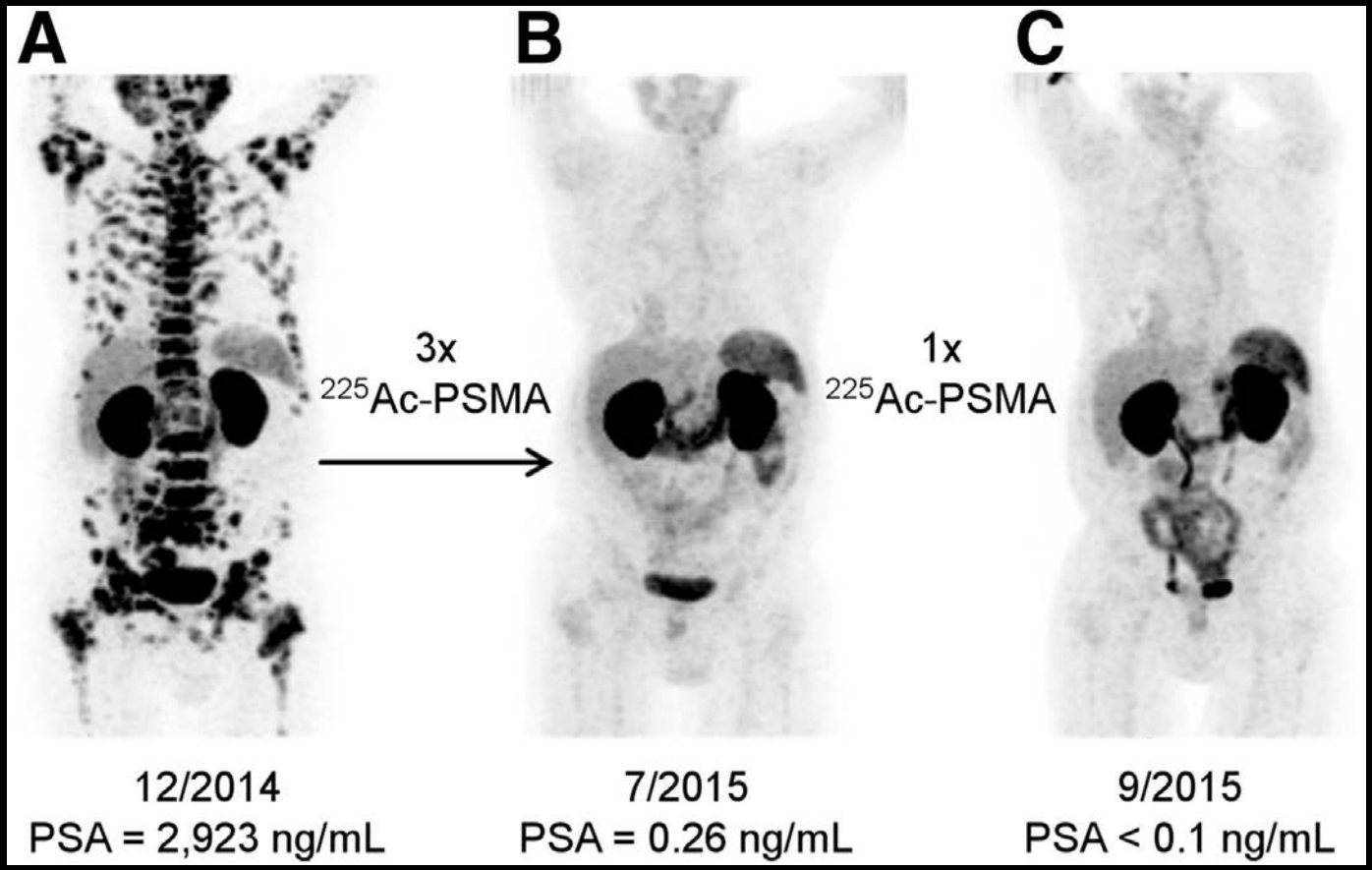
Value of Theranostics



- Diagnostic can be used to select patients for therapeutic clinical trials.
- Diagnostic can be used to develop a plan for the therapeutic dose.
- Particularly useful early in the clinical phase of development

SUPPORTED BY THE IOWA NEUROENDOCRINE TUMOR SPORE

Why pursue alpha particle *vs* beta particle therapy?



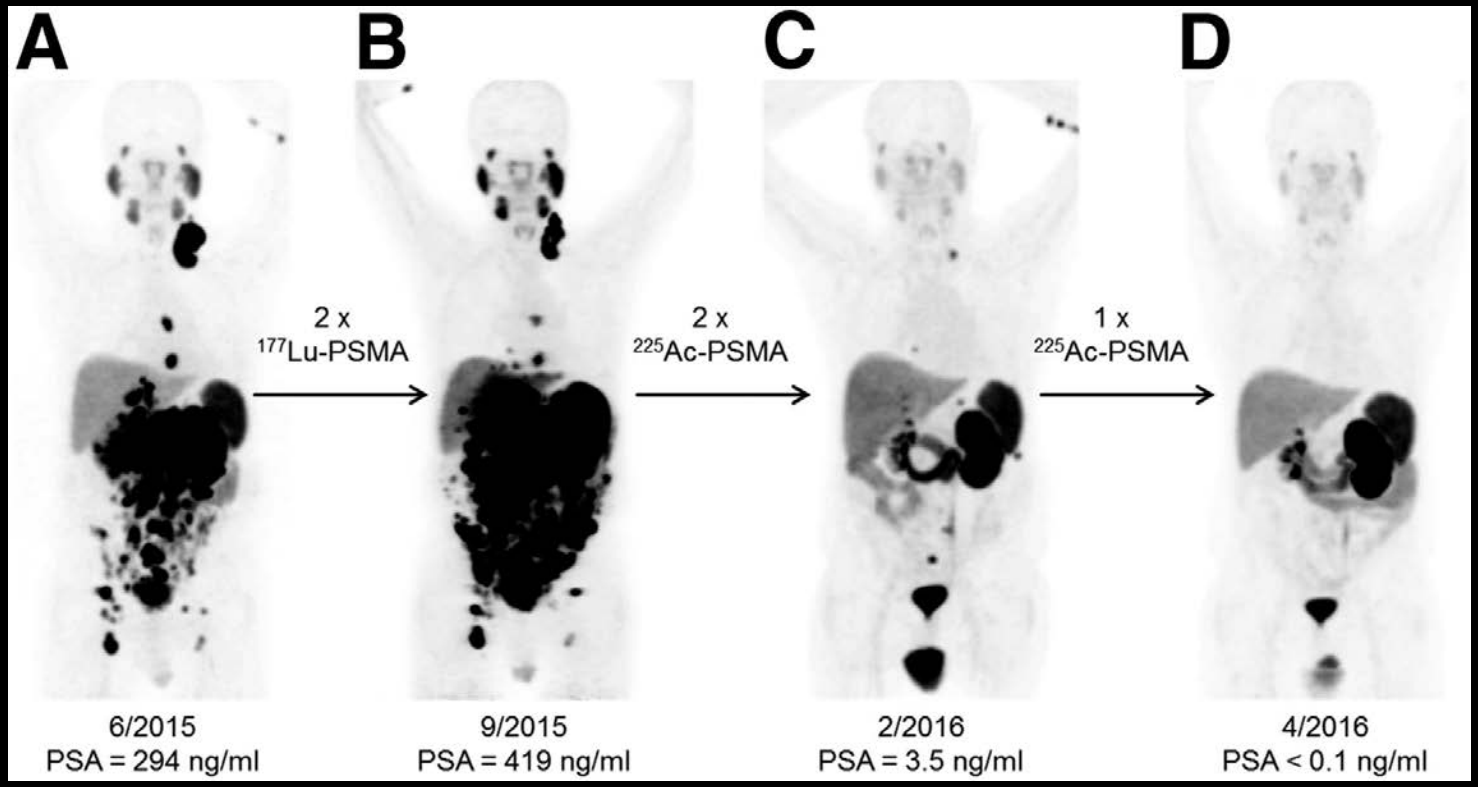
^{68}Ga-PSMA-11 PET/CT scans of patient A. Pretherapeutic tumor spread (A), restaging 2 mo after third cycle of ^{225}Ac-PSMA-617 (B), and restaging 2 mo after one additional consolidation therapy (C). Clemens Kratochwil *et al.* J Nucl Med 2016;57:1941-1944

SUPPORTED BY THE IOWA NEUROENDOCRINE TUMOR SPORE

Why pursue alpha particle therapy?

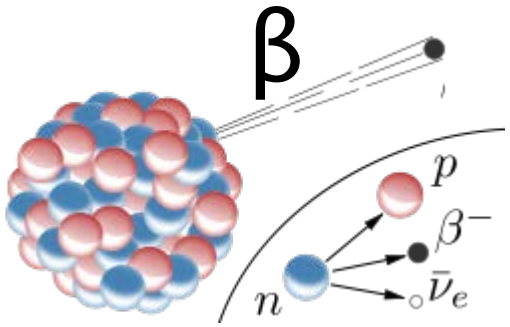
Progression after beta particle therapy.

Virtual complete response to alpha therapy.

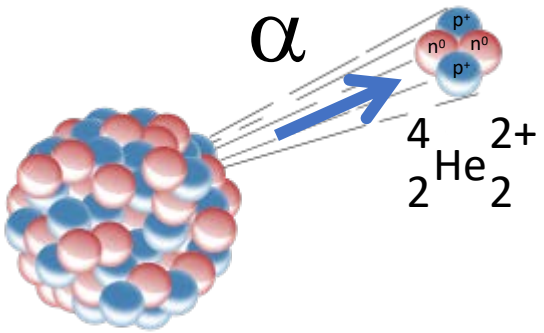


^{68}Ga-PSMA-11 PET/CT scans of patient B. In comparison to initial tumor spread (A), restaging after 2 cycles of β-emitting ^{177}Lu-PSMA-617 presented progression (B). Kratochwil *et al.* J Nucl Med 2016;57:1941-1944

α vs β particle properties



$m_\beta = 10^{-31}$ kg
<2 MeV



$m_\alpha = 10^{-27}$ kg
4-9 MeV

(1) Massive
(2) High Energy
(3) High LET
(3) DS DNA breaks

Falzone *et al.*, *Theranostics*, 2018

- Modeled RBE of ^{212}Pb vs ^{177}Lu
- ^{212}Pb may be more effective in short range

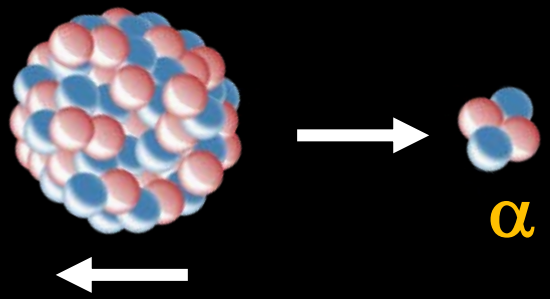
Lee *et al.*, *Radiation Research*, 2018

- Depth-dose distributions ^{212}Pb vs ^{225}Ac
- Internalization improves RBE

Promising α-Emitter "*Series*"

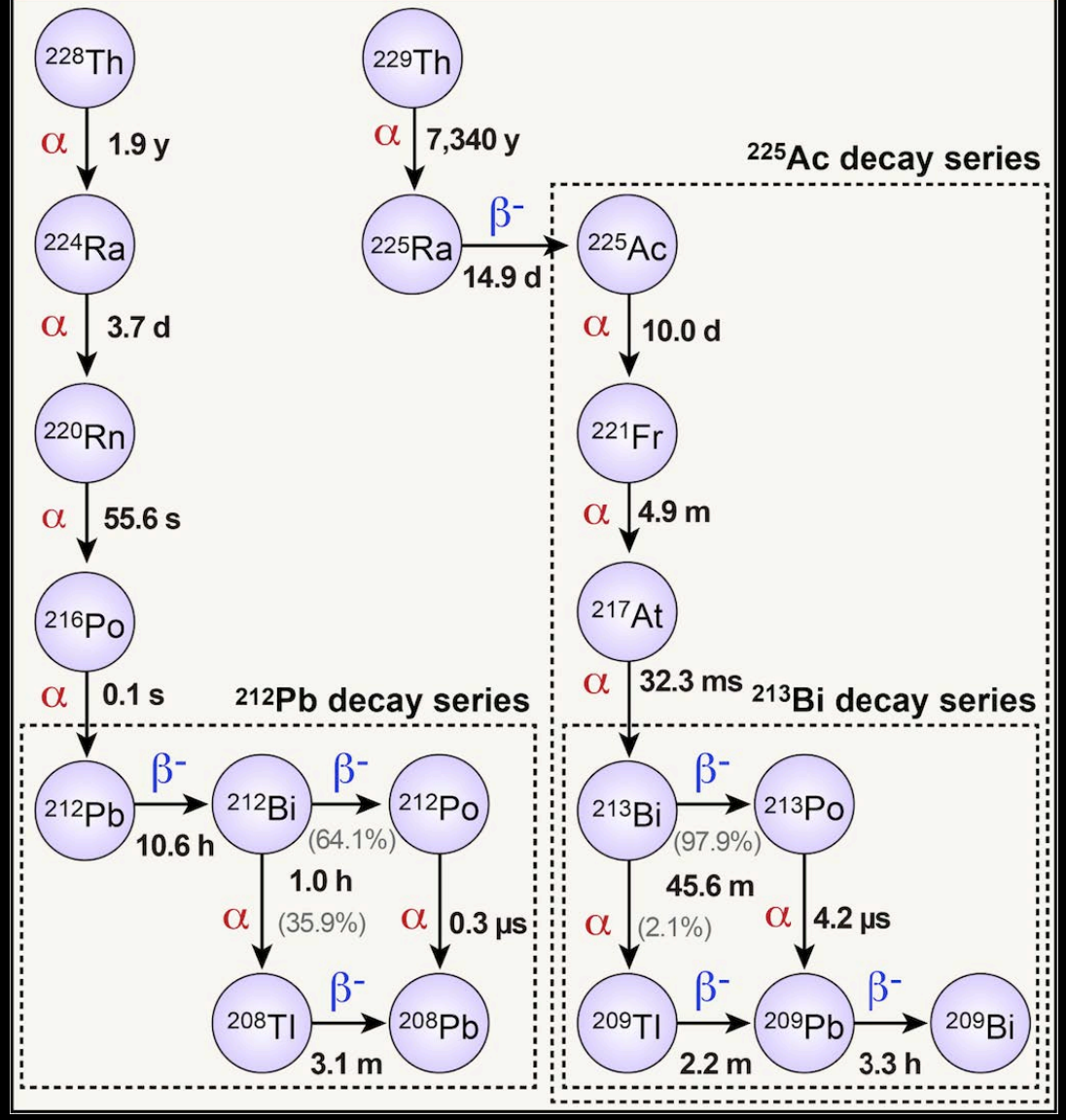
- **Actinium-225 (Ac-225, ^{225}Ac) 10 d**
- **Lead-212 (Pb-212, ^{212}Pb) 11 h**
- **Thorium-227 (Th-227, ^{227}Th) 18 d**
- **Radium-223 (Ra-223, ^{223}Ra) 11 d**
- **Astatine-211 (At-211, ^{211}At) 7 h**

$m_1v_1 = m_2v_2$



SUPPORTED BY THE IOWA NEUROENDOCRINE TUMOR SPORE

Lee *et al.*, *Rad. Res.*, 2018 *In Press*



Ac *vs* Pb

Actinium-225

- $T_{1/2}$ = 10 d (5 α's)
- Central prod./distr.
- Capacity? Impurity?
- Fast daughter ingrowth
- mAbs (biological $T_{1/2}$)
- "Stable" Bi endproduct
- No matching imaging isotope

Lead-212

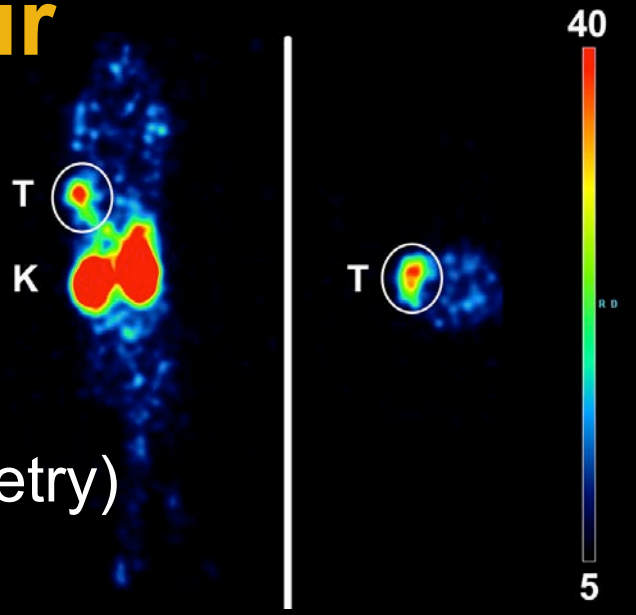
- $T_{1/2}$ = 11 h (2 α's)
- ^{224}Ra Generator ($T_{1/2}$ = 3.7 d)
- Slower daughter ingrowth
- Peptides, small molecules
- ^{212}Bi generator possible
- Stable Pb endproduct
- ^{203}Pb elementally matched

SUPPORTED BY THE IOWA NEUROENDOCRINE TUMOR SPORE

^{203}Pb/^{212}Pb Theranostic Pair

- **^{203}Pb – diagnostic**

  ^{203}Pb -> ^{203}Tl (EC; stable)
  279 keV gamma (SPECT; I = 81%)
  $T_{1/2}$ = 52 h (patient selection and dosimetry)



- **^{212}Pb – therapeutic**

  ^{212}Pb -> ^{212}Bi (β; I = 100%)
  Two α's in "*series*" (^{212}Bi and ^{212}Po)
  $T_{1/2}$ = 11 h (peptides, small molecules, faB's, RNA aptamers)

Energy (keV)	End-point energy (keV)	Intensity (%)
41.1 *6*	154.6 *19*	5.08 % *9*
93.5 *7*	331.3 *19*	83.1 % *16*
171.7 *7*	569.9 *19*	11.9 % *16*

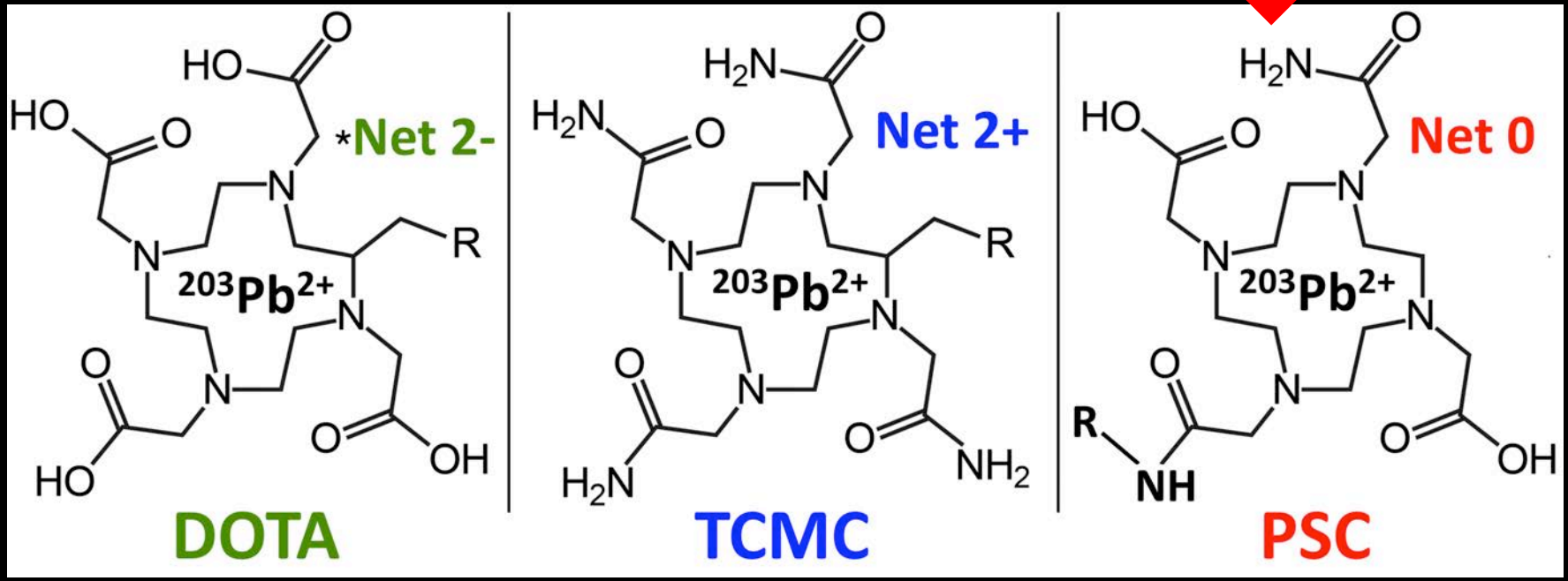
Li et al., 2017 *Appl. Rad. Isot.*

Identical chemistry

SUPPORTED BY THE IOWA NEUROENDOCRINE TUMOR SPORE

$^{212/203}$Pb Chelators

Iowa

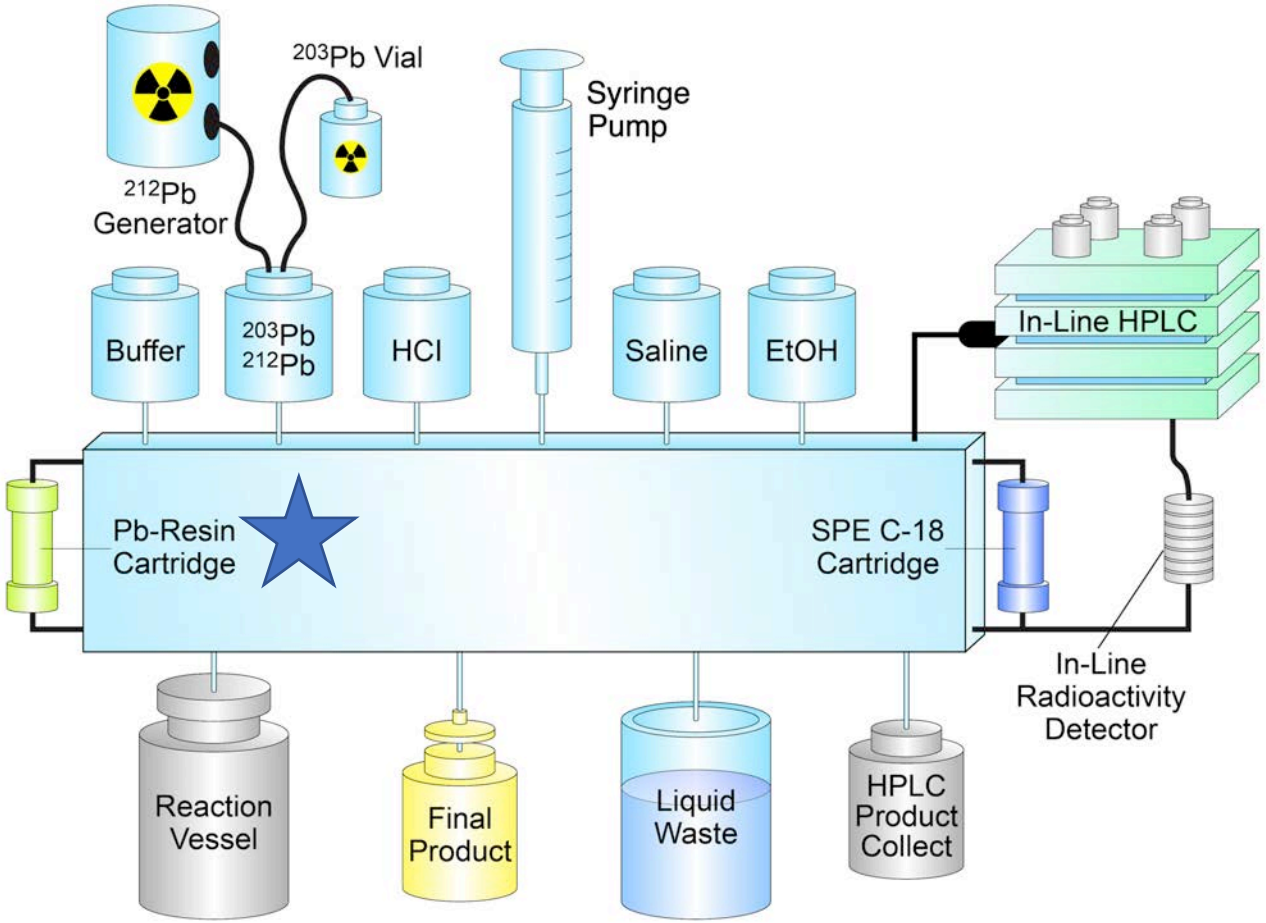


Commercially Available

CheMatech
macrocycle design technologies

SUPPORTED BY THE IOWA NEUROENDOCRINE TUMOR SPORE

$^{203/212}$Pb Radiopharmaceutical Production



Specifications

1. Full Automated
2. Single use cassettes
3. Sterile
4. Pyrogen free
5. Radiochemical Purity
6. Radionuclidic Purity
7. Rapid
8. Reproducible
9. ^{203}Pb and ^{212}Pb

MLPT System

Li *et al.*, 2017 ARI

SUPPORTED BY THE IOWA NEUROENDOCRINE TUMOR SPORE

^{203}Pb Cyclotron Production/Purification

- **^{203}Pb – Production/Impurities**

25 MeV

^{205}Tl (p, 3n) ^{203}Pb

^{203}Tl (p, 3n) ^{201}Pb ($T_{1/2}$ = 9.33 hours; 90 h hold)

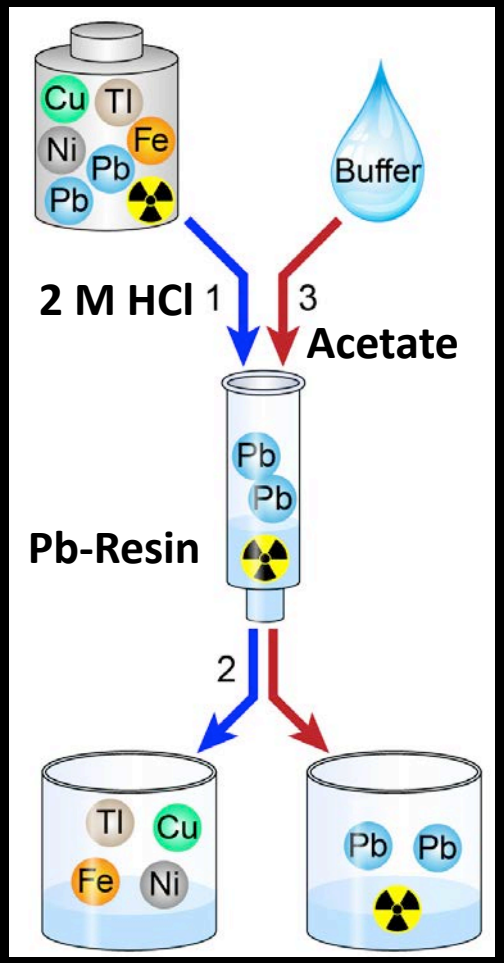
^{205}Tl (p, 2n) ^{204m}Pb ($T_{1/2}$ = 1.12 hours)

^{203}Pb ($T_{1/2}$ = 51.92 hours) → ^{203}Tl Stable

^{201}Pb ($T_{1/2}$ = 9.33 hours) → ^{201}Tl ($T_{1/2}$ = 72.91 hours)

^{204m}Pb ($T_{1/2}$ = 1.12 hours) → ^{204}Pb Stable

(small, optimizing)



Lantheus Medical Imaging

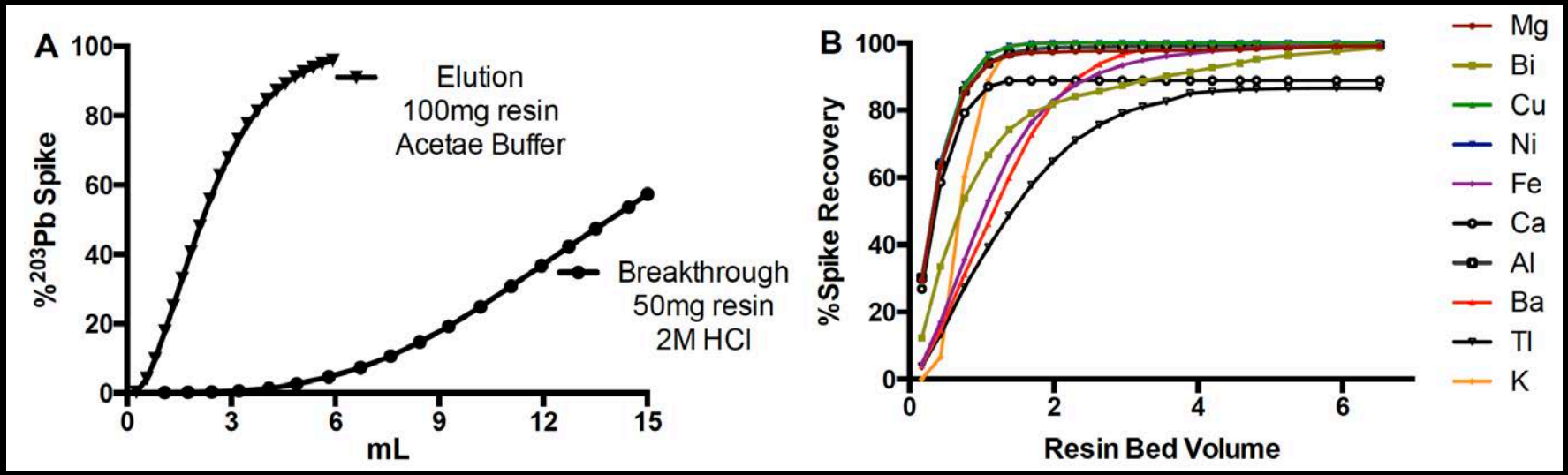
Li *et al*., 2017 *Appl. Rad. Isot.*

SUPPORTED BY THE IOWA NEUROENDOCRINE TUMOR SPORE

$^{203/212}$Pb Purification

Rapid Elution

Removal of impurities



Manageable Pb breakthrough

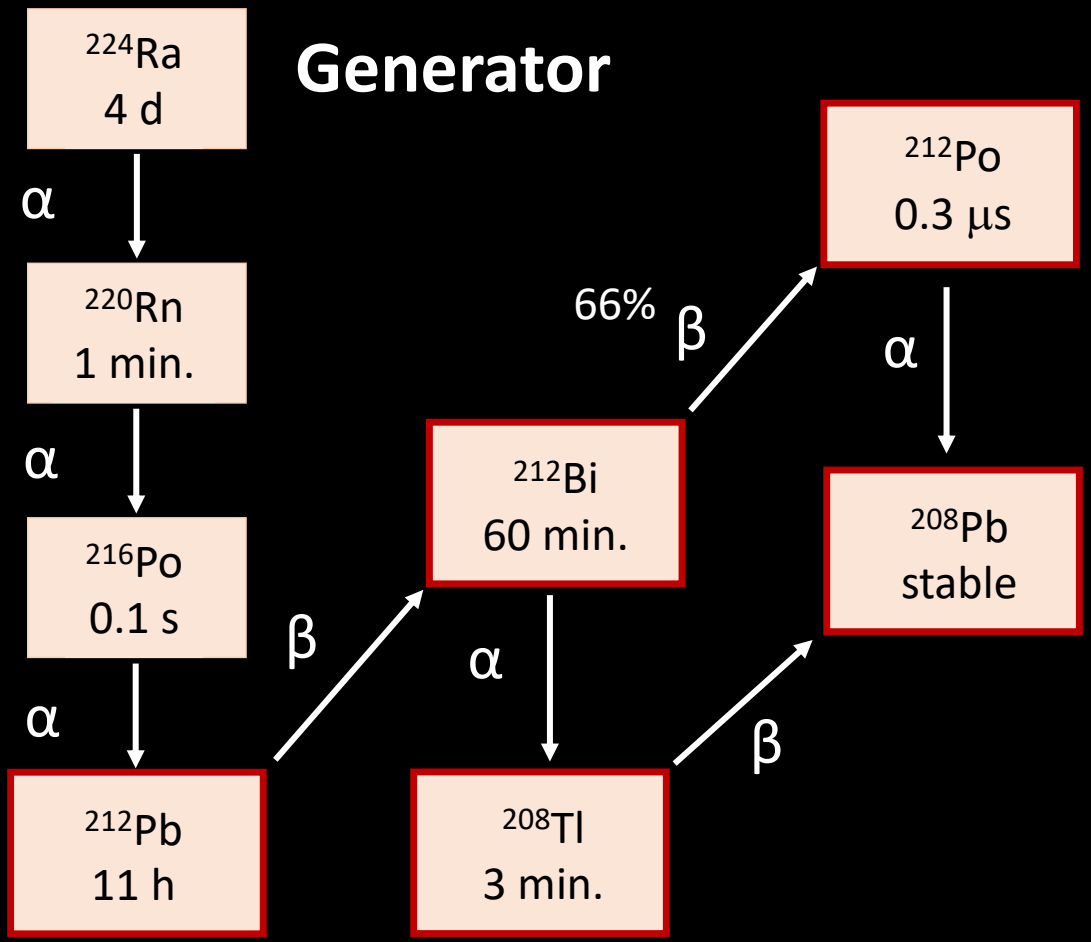
Li *et al.*, ARI 2017

SUPPORTED BY THE IOWA NEUROENDOCRINE TUMOR SPORE

^{212}Pb Production/Decay

^{228}Th
2 y

Generator



^{212}Pb Decay Series
Injected drug.

Process Basics

1. Ra-224 Generator Shipped.
2. Pb-212 Eluted from Generator.
3. Pb-212 Chelated to Ligand.
4. Pb-212 labeled ligand injected.

Potential: 2 α + 3 β

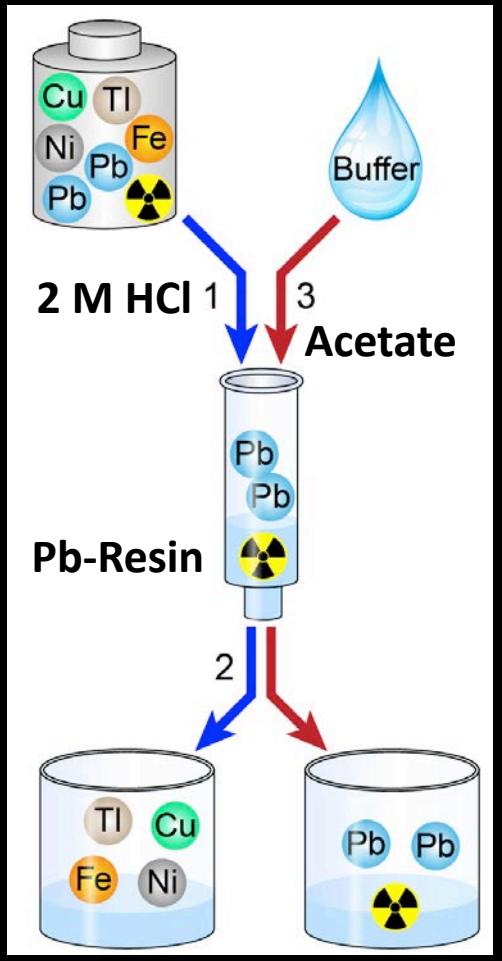
Li *et al*., 2017 *Appl. Rad. Isot.*

^{212}Pb Production/Purification

- **Generators (ORNL; Orano Med)**

Impurities

- Metals (**Fe**, Ni, Cu, Tl, Ba, **Pb**)
  - ✓ Purification Pb-resin (Eichrom Technologies)
- Radionuclides
  - ✓ Th-228/232, Ra-224, U-232, actinides α-spec. (<MDA)
  - ✓ Ra-224 breakthrough (<MDA)



Li *et al*., 2017 *Appl. Rad. Isot.*

Image-guided therapy for cancer

- Metastatic melanoma

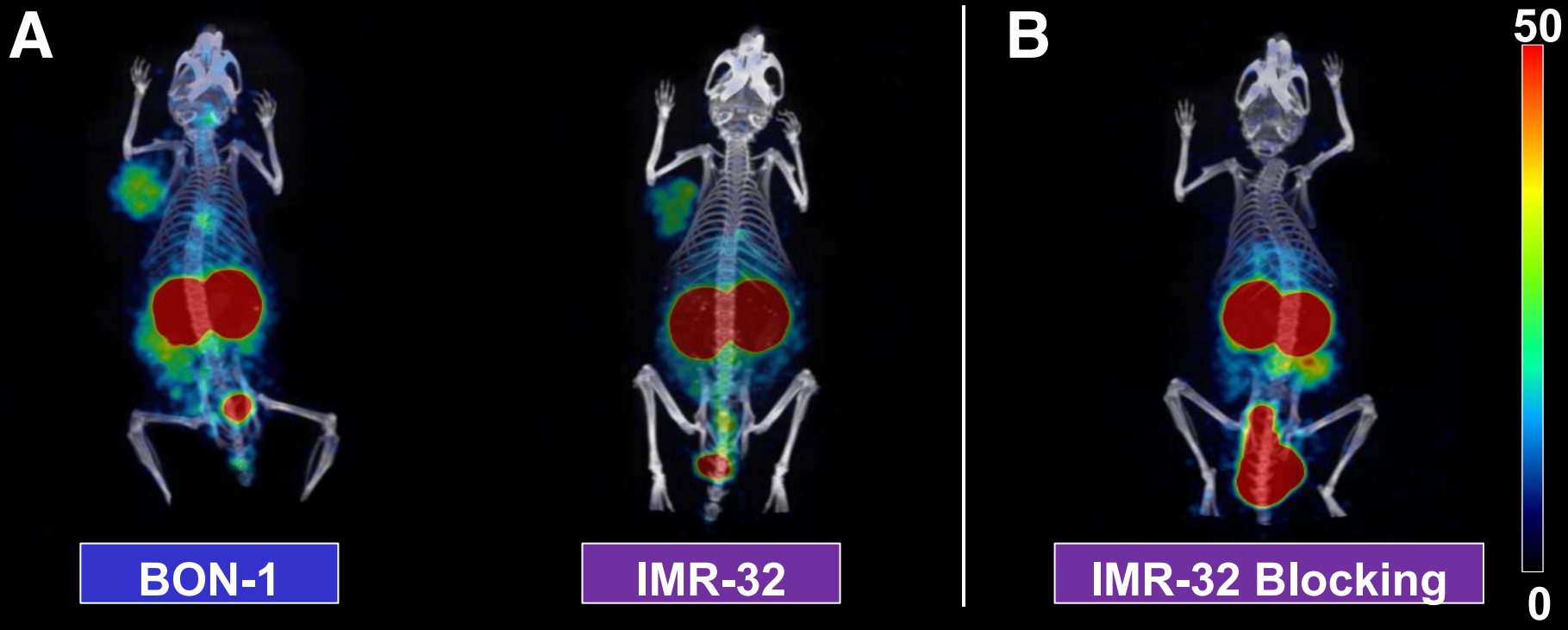
  Cancer of the skin
  Melanoma is fastest growing cancer incidence in the US
  Most diagnosed cancer in young adults under 30 years
  Very poor prognosis for metastatic disease
  Target: Melanocortin subtype 1 receptor (MC1R)

- Neuroendocrine tumors

  Enigmatic cancer of the endocrine system
  Poor prognosis
  Current therapies are largely palliative
  Target: somatostatin subtype 2 receptor (SST2R)

^{203}Pb SPECT/CT (SST2R+ models)

[^{203}Pb]DOTATOC SPECT

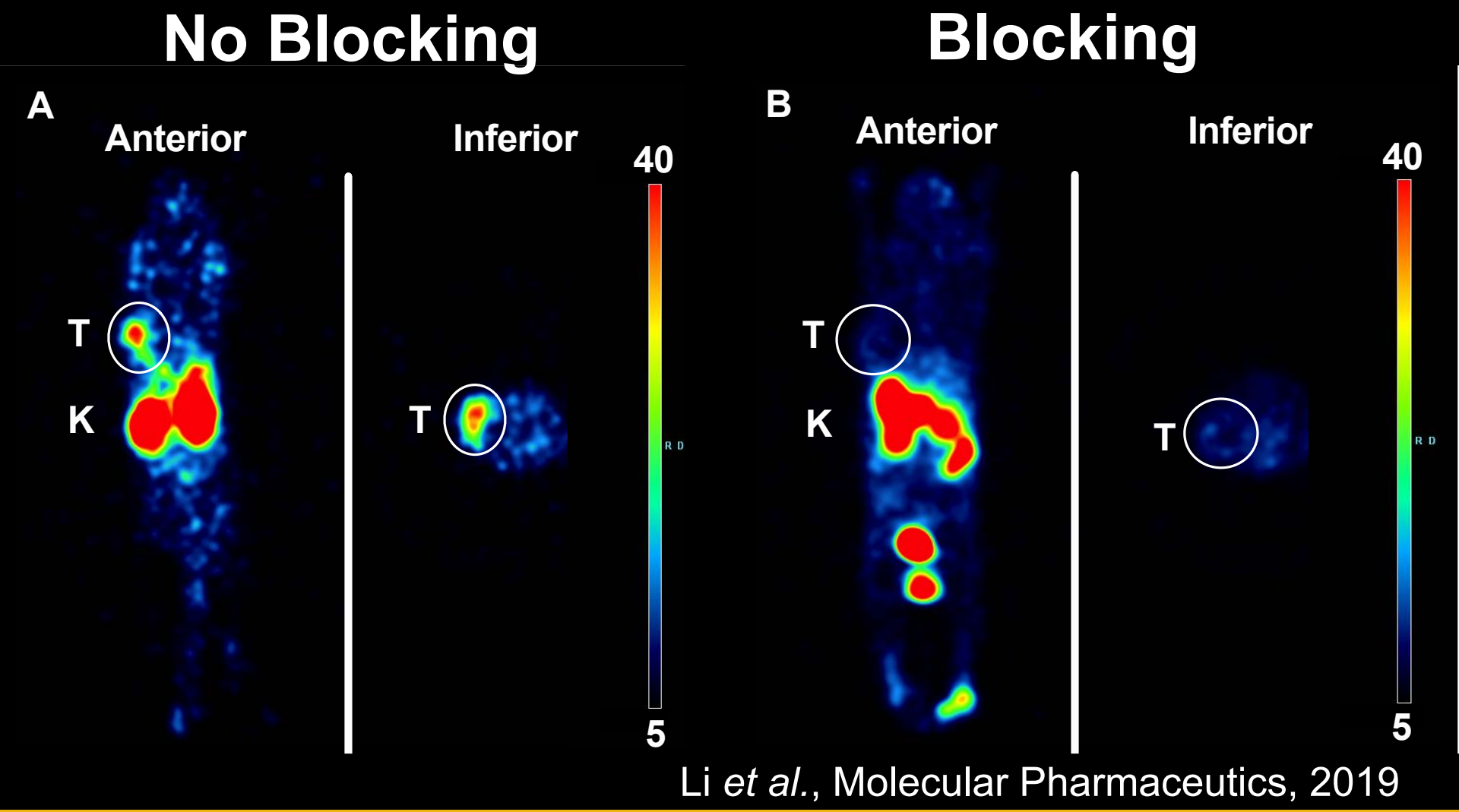


NET/Carcinoid **Neuroblastoma**

Lee *et al.*, In Prep

University of Iowa Holden Comprehensive Cancer Center
University of Iowa Health Care
University of Iowa Neuroendocrine Tumor Program
University of Iowa Stead Family Children's Hospital
SUPPORTED BY THE IOWA NEUROENDOCRINE TUMOR SPORE

^{203}Pb SPECT (MC1R+ model)

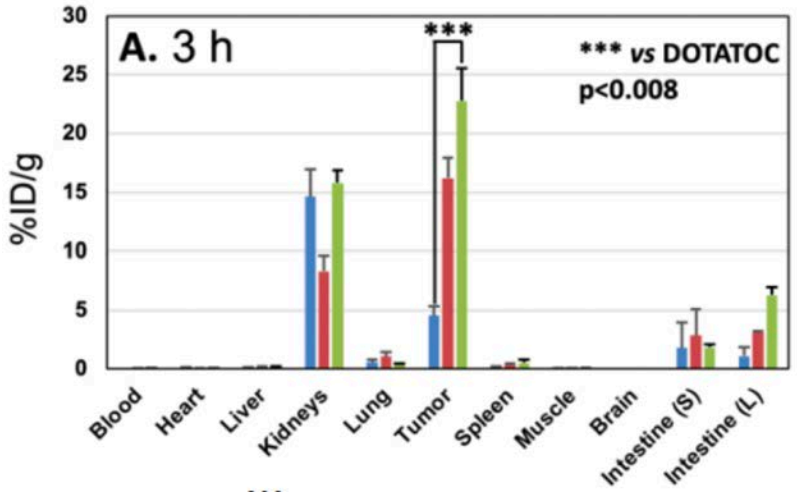


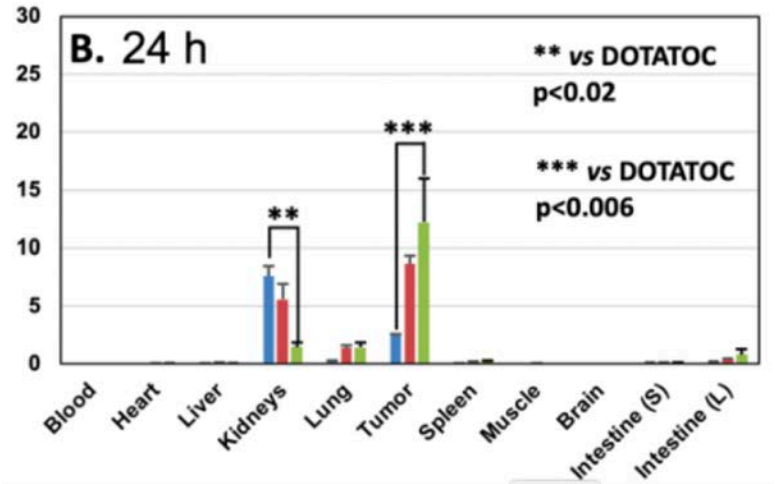
Li *et al.*, Molecular Pharmaceutics, 2019

SUPPORTED BY THE IOWA NEUROENDOCRINE TUMOR SPORE

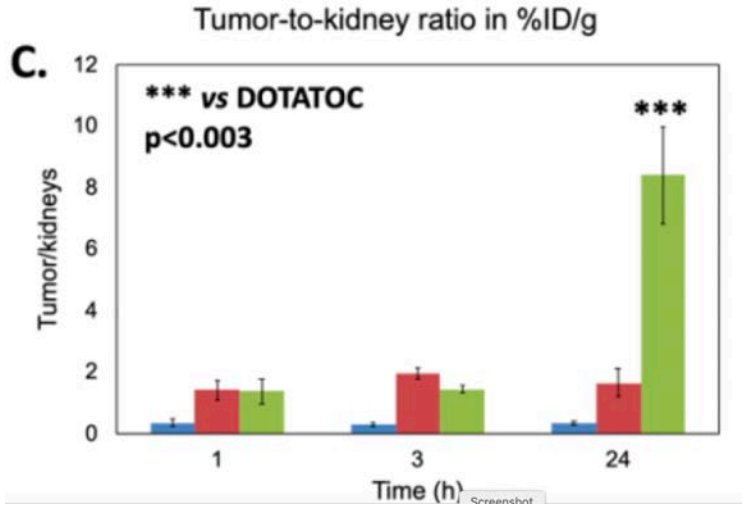
VMT-α-NET Preclinical Development

■ [^{203}Pb]DOTATOC ■ [^{203}Pb]PSC-TOC ■ [^{203}Pb]PSC-PEG2-TOC **(VMT-α-NET)**



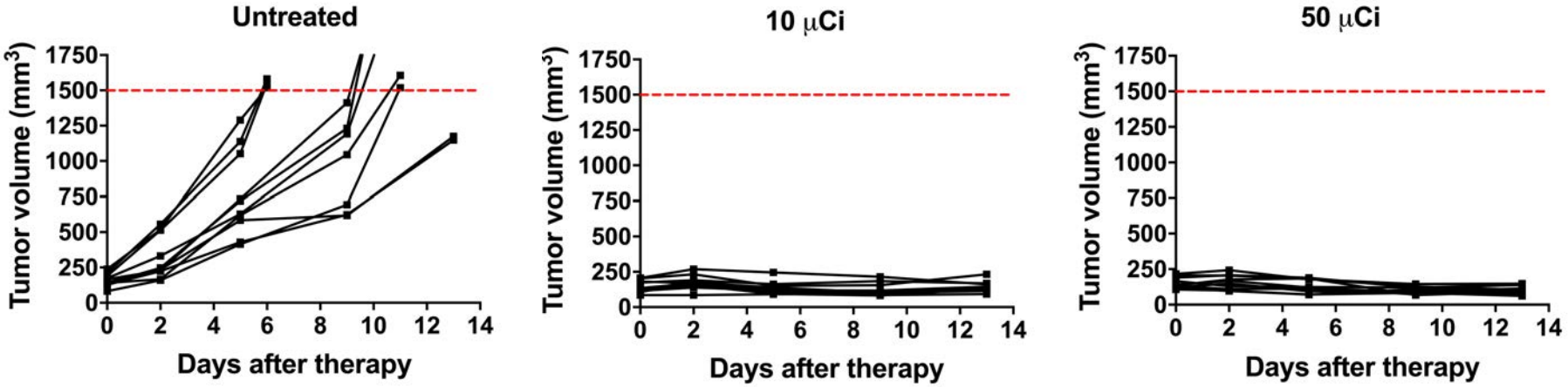


VMT-α-NET improved tumor:kidney 8-fold vs DOTATOC



VMT-α-NET Preclinical Development

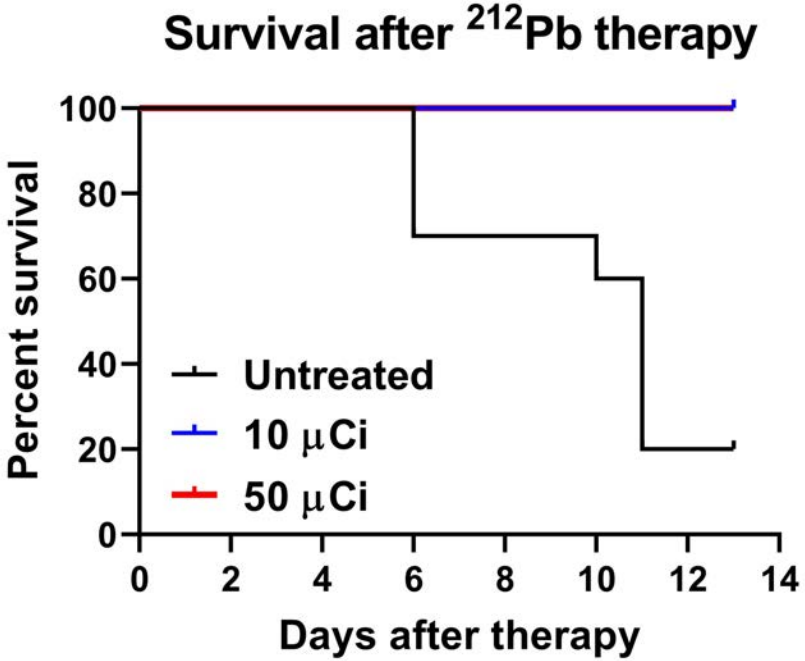
VMT-α-NET – 100% tumor response rate

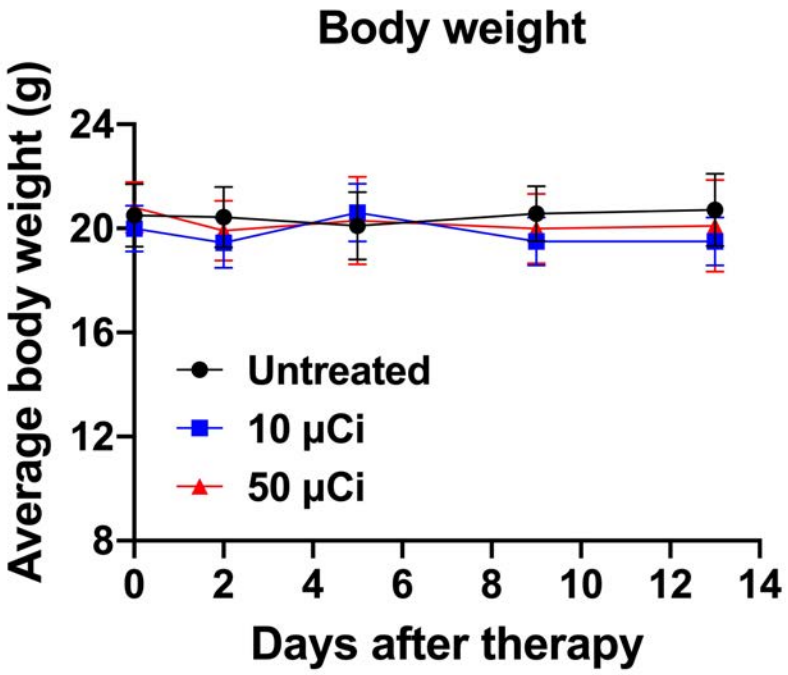


[^{212}Pb]VMT-α-NET therapy. 5.0x10^{6} AR42J rat pancreatic acinar cells were implanted on the left shoulder of athymic nu/nu female mice. After 1 week, when the average tumor size became around 150 mm^3, 274 MBq (7.4 mCi) ^{212}Pb were reacted with 30 nmol VMT-α-NET (9.1 MBq/nmol) in the presence of ascorbic acid (1 mg/ml) for 20 min at 85 °C. After reaction, the radio-peptide were purified by C-18 and resuspended with saline ascorbic acid (1 mg/ml). 0.37 MBq (10 μCi) and 1.85 (50 μCi) of ^{212}Pb- VMT-α-NET were injected via tail vein. DL-lysine (400mg/kg) was co-injected to block the kidney uptake of the radiotherapeutic.

VMT-α-NET Preclinical Development

VMT-α-NET survival benefit and tolerability





Promising Summary

- **^{203}Pb/^{212}Pb a promising *theranostic* pair**
  $T_{1/2}$'s – peptides, small molecules, aptamers, fAb's
- **α-particle therapy has potential advantages(*vs* β)**
  High LET
- **Production/impurities (purifications) suitable to advance to clinical radipharmaceuticals**
  Automated production (Li *et al.*, Appl Rad Isot., 2017)
- **Improved chelator for Pb^{2+} is promising –** modeling could explain improved labeling observed.
- Initial ^{203}Pb NIST standardization completed

SUPPORTED BY THE IOWA NEUROENDOCRINE TUMOR SPORE

Thank you! Questions?

Acknowledgements

Schultz Lab
Mengshi Li PhD
Major Dongyoul Lee
Somya Kapoor PhD
Dustin May

Viewpoint Lab
Frances Johnson
Brenna Marks
Edwin Sagastume
Jessica Miller

Pigge Lab
Chris Pigge PhD
Moustafa Gabr PhD

O'Dorisio Lab
Sue O'Dorisio MD PhD
Dijie Liu PhD

SNMMI
Bonnie Clarke
Ruth Lim MD PhD

Clinical Trials Network
John Sunderland PhD
Michael Graham MD PhD
Jon Maconathy PhD

Lantheus Medical Imaging
Chematech
Eichrom Technologies

Funding
US NIH 1P50CA174521
US NIH K25CA172218
US NIH 1R01CA167632
US NIH SBIR Phase II HHSN2612017000-36C
US NIH R01EB017279
US NIH I-CORPS NIH HHSN261201500069C
US NIH SBIR Phase I 1R43CA203430
US NIH HHSN261201500069C
US NIH SBIR Phase I 1R43CA195925
US NRC (NRC-HQ-12-G-38-0041)
US DHS/DNDO (SCUREF – 040112-15)
US DOE (INL/Battelle – 00131031)
INVICRO, Inc
Takeda Pharmaceuticals
Eichrom Technologies, Inc.
ICTS, University of Iowa
Holden Comprehensive Cancer Center
Iowa Department of Public Health
Iowa Economic Development Authority
Iowa Bio
Iowa Innovation Corporation
UI Melanoma Mog Mo Milhem MD

University of Iowa Holden Comprehensive Cancer Center
University of Iowa Health Care

University of Iowa Neuroendocrine Tumor Program

University of Iowa Stead Family Children's Hospital

SUPPORTED BY THE IOWA NEUROENDOCRINE TUMOR SPORE