Additional Aspects of Dosimetry for Targeted Alpha Therapy

Brian W. Miller, PhD, DABR

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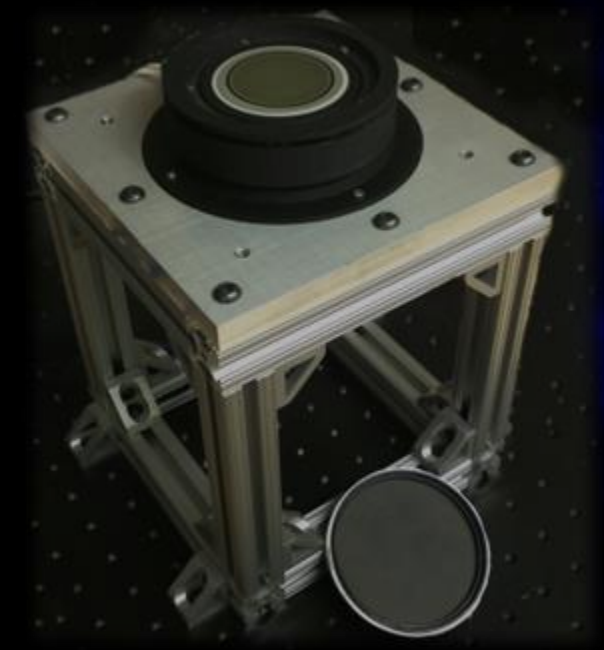
CCRI
CCRI-RTWG

Bureau International des Poids et Mesures



Workshop on Standards and Measurements for Alpha Emitting Nuclides in Therapeutic Nuclear Medicine
Paris, France
February 22-23, 2024

THE UNIVERSITY OF ARIZONA.

Center for Gamma-Ray Imaging

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Tucson

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Radiation Oncology

Relevant Disclosures

- QScint Imaging Solutions - Founder

QScint Imaging Solutions

AAPM Efforts in Radiopharmaceutical Therapy with Alpha emitters

AAPM Radiopharmaceutical Therapy Subcommittee (RPTSC)

1. Consolidate, disseminate and maintain available information concerning **RPT methodologies, dosimetry, science and practice**.
2. Establish structures needed for providing guidelines and Standard Operating Procedures (SOPs) for new and existing RPTs such as **Task Groups**, **Working Groups** or **MPPGs**.
3. Take an active role in the **education** of the AAPM and general radiation oncology community regarding **RPT methodologies** and **clinical practice**.
4. Coordinate with stakeholder groups within AAPM, advising them of overlaps and seeking mutual solutions where needed.
5. Coordinate with stakeholder groups outside of AAPM to develop uniform and effective approaches to common problems with regard to RPT. These may include SNMMI, EANM, ASTRO, ESTRO, ICRU, IAEA, ICRP, ABS, NIST, FDA, IROC, NRC, DOE.

Chair: Robert Hobbs

AMERICAN ASSOCIATION of PHYSICISTS IN MEDICINE

Working Group (Under Review): AAPM Radiopharmaceutical Therapy with Alpha Emitters (αRPT)

1. For **pre-clinical αRPT develop recommendations, strategies, and standardization methods for dose assessment.** This includes a **review of pre-clinical dose estimation techniques** and strategies **(micro to macro)** using quantitative digital autoradiography, micro-scale dosimetry, RBE estimates, and comparisons with histology.
2. For **clinical αRPT** and including α-emitting drugs and devices (e.g., creams and implantable devices) **develop recommendations, strategies and standardization methods.** This includes a **review of dose limits, RBE estimates, and imaging-based dose assessment techniques** such as **SPECT/PET imaging** with **direct or surrogate isotopes.**
3. For αRPT (including α-emitting drugs and devices) **review and develop recommendations and strategies for QA of radionuclide activities** and radiopharmaceutical purity, **QA for measurement instruments** and devices, and **patient release criteria**.
4. Promote highly impactful αRPT efforts at AAPM meetings. Provide instructive resources on αRPT dosimetry and imaging emerging concepts through symposia, refresher courses, and reports.

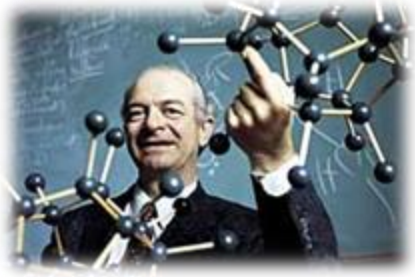
AMERICAN ASSOCIATION of PHYSICISTS IN MEDICINE

Chair: Brian Miller
Co-Chair: Denis Bergeron

Quantitative Digital Autoradiography and its Growing Role in Radiopharmaceutical Therapy with the iQID

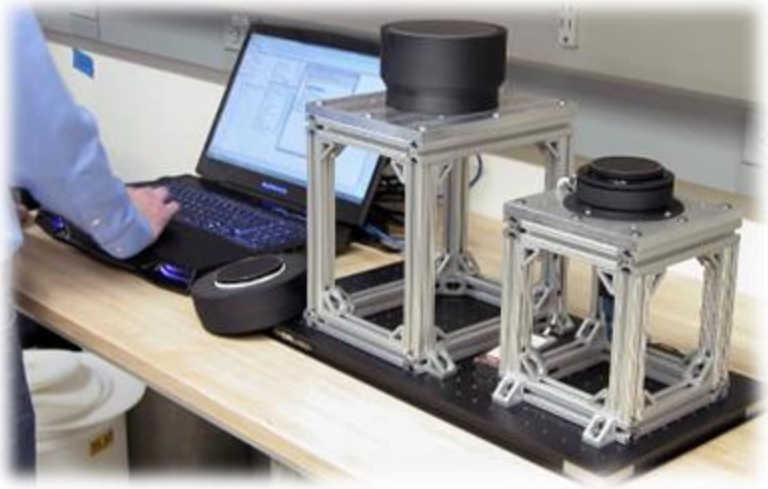
The iQID Camera

Linus Pauling Distinguished Postdoctoral Fellowship



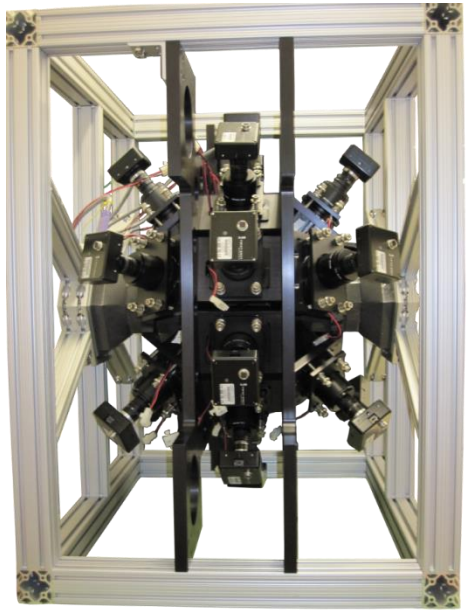
Pacific Northwest NATIONAL LABORATORY

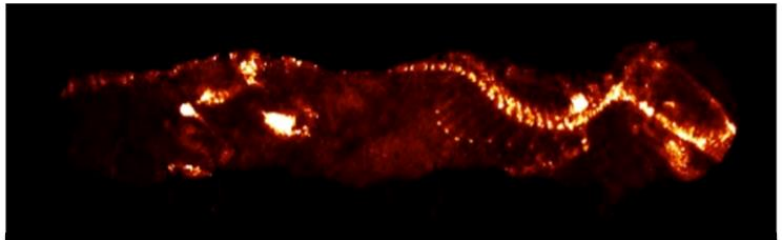
Proudly Operated by Battelle Since 1965

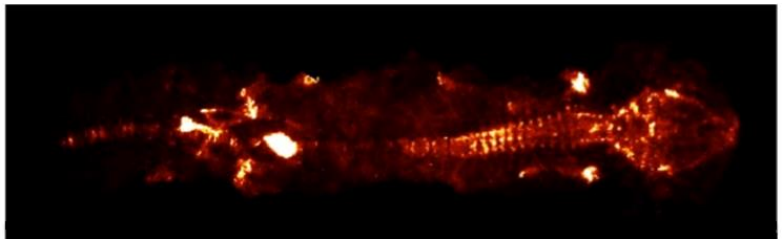


Ionizing-radiation sensitivity :

- Gamma/X-rays
- Alpha particles
- Betas
- Neutrons
- Fission fragments







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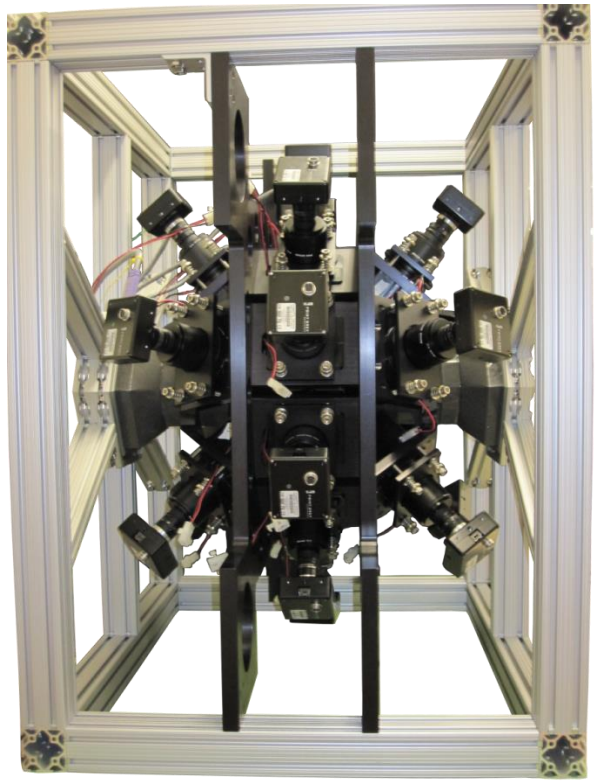
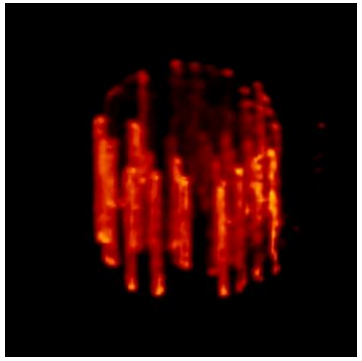
Center for Gamma-Ray Imaging

iQID: ionizing-radiation Quantum Imaging Detector

FastSPECT III

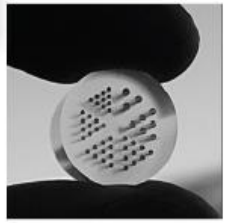


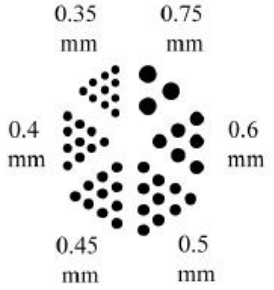


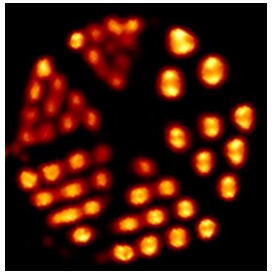
2009 IEEE Nuclear Science Symposium Conference Record M15-5

System Integration of FastSPECT III, a Dedicated SPECT Rodent-Brain Imager Based on BazookaSPECT Detector Technology

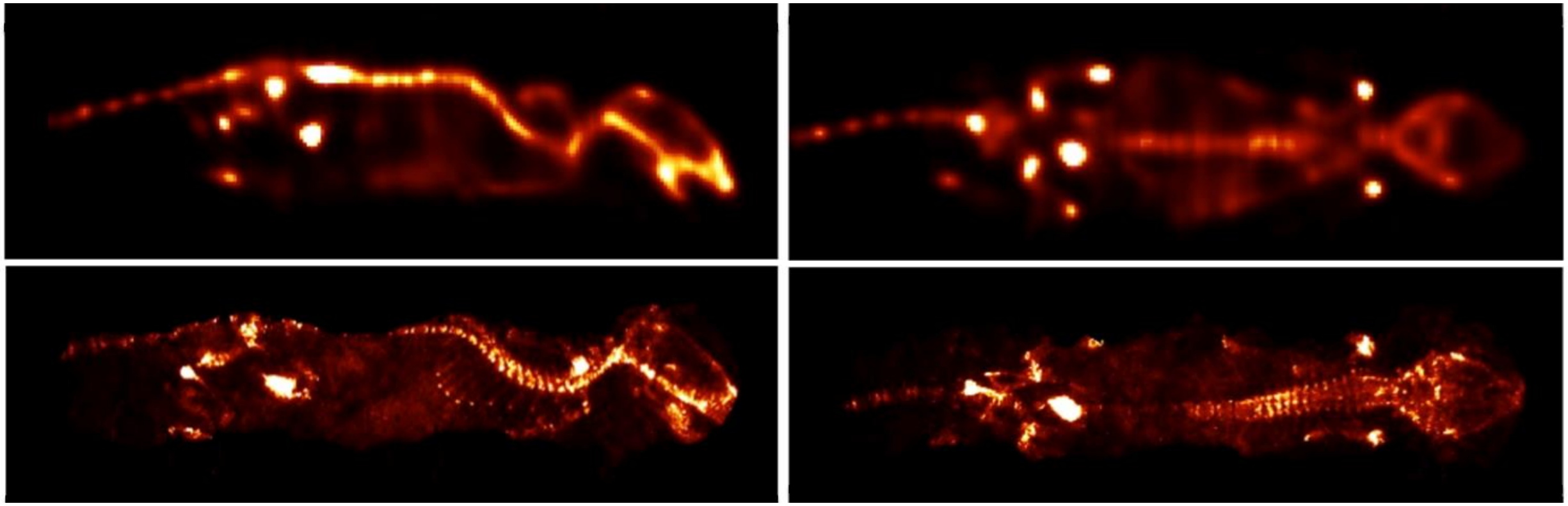
Brian W. Miller, *Member, IEEE*, Lars R. Furenlid, *Member, IEEE*, Stephen K. Moore, *Member, IEEE*, H. Bradford Barber, *Member, IEEE*, Vivek V. Nagarkar, and Harrison H. Barrett, *Fellow, IEEE*





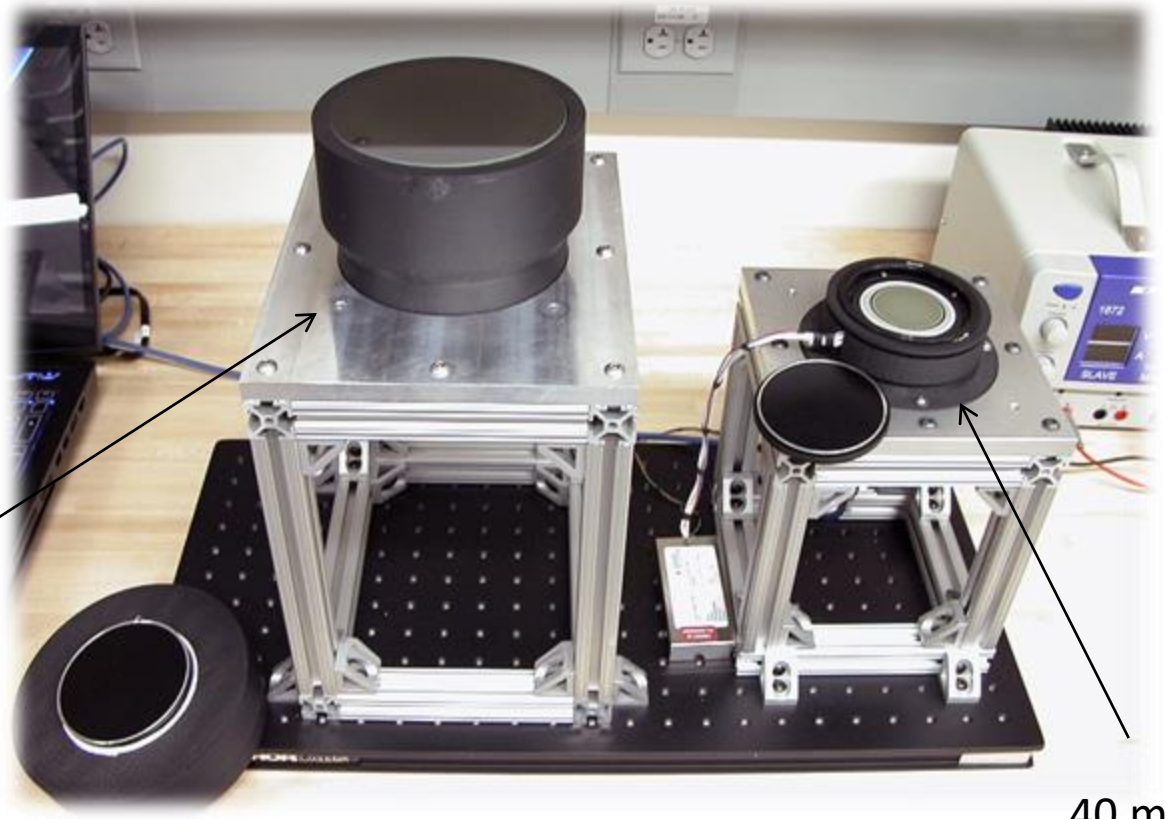


FastSPECT III



Ling Han, Luca Caucci, Brian Miller, Harrison Barrett, Jim Woolfenden, and Lars Furenlid, “System Calibration for FastSPECT III: An ultra-high Resolution CCD-Based Pinhole SPECT System

Large-Area iQID with Fiber-Optic Taper



115mm:40mm
fiber-optic taper

40 mm diameter
image intensifier

Nuclear Instruments and Methods in Physics Research A 767 (2014) 146–152

Contents lists available at ScienceDirect

Nuclear Instruments and Methods in Physics Research A

journal homepage: www.elsevier.com/locate/nima

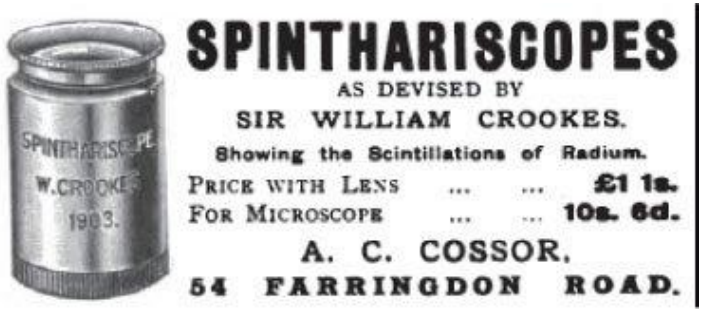
The iQID camera: An ionizing-radiation quantum imaging detector

Brian W. Miller [a,c,*], Stephanie J. Gregory [a], Erin S. Fuller [a], Harrison H. Barrett [b,c], H. Bradford Barber [b,c], Lars R. Furenlid [b,c]

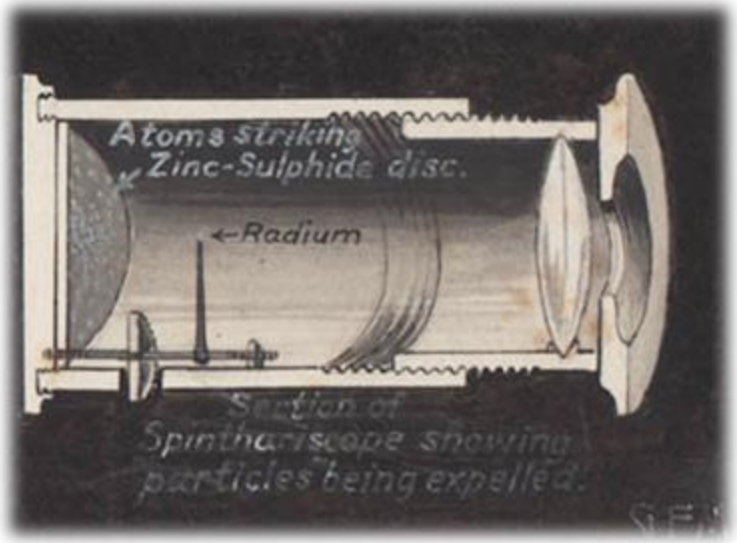
[a] Pacific Northwest National Laboratory, Richland, WA 99352, USA
[b] Center for Gamma-Ray Imaging, The University of Arizona, Tucson, AZ 85719, USA
[c] College of Optical Sciences, The University of Arizona, Tucson, AZ 85719, USA

Spinthariscope – Sir William Crookes

Sir William Crookes
17 June 1832 – 4 April 1919
British Chemist and Physicist

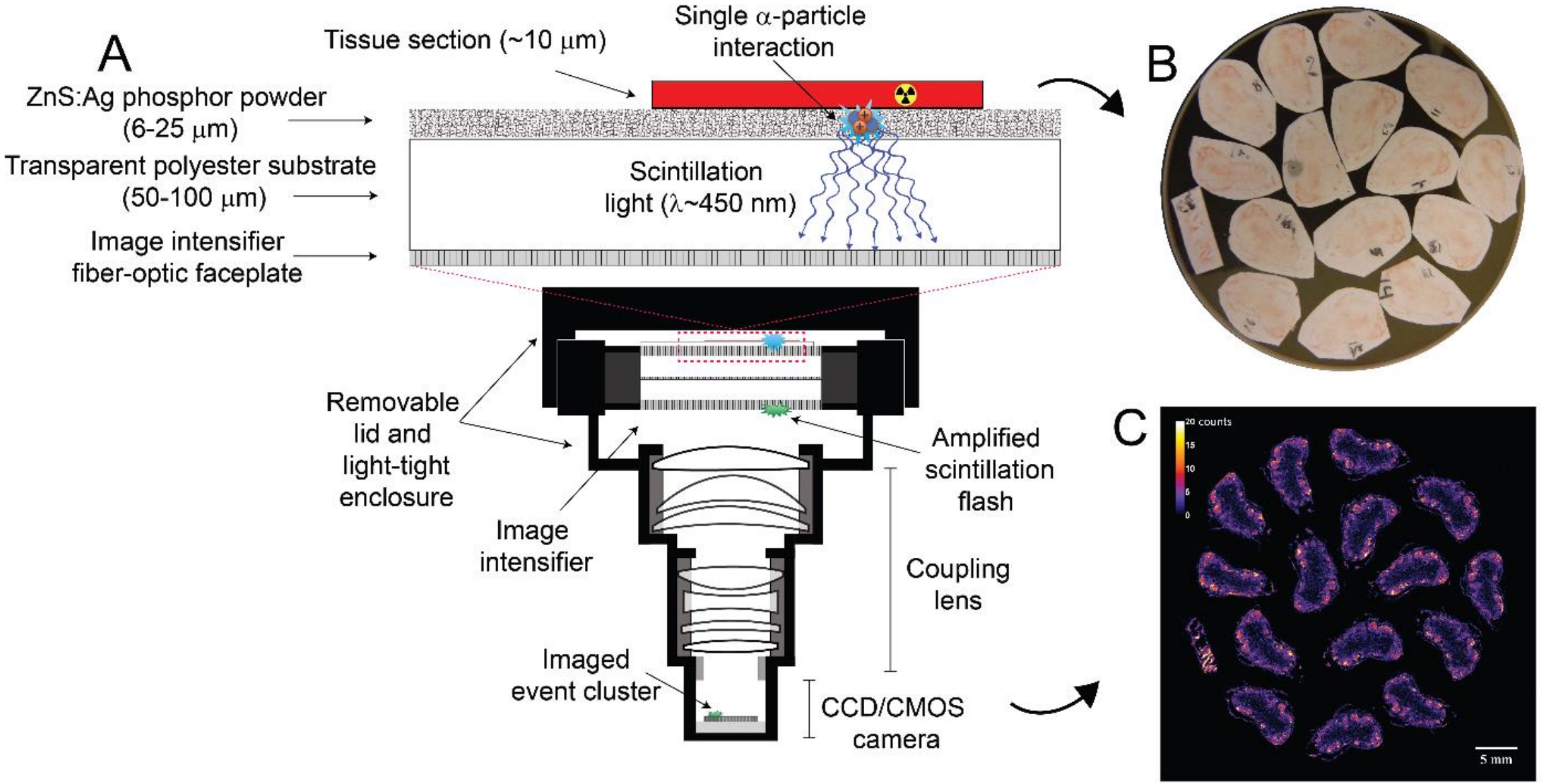


Source: http://periodictable.com

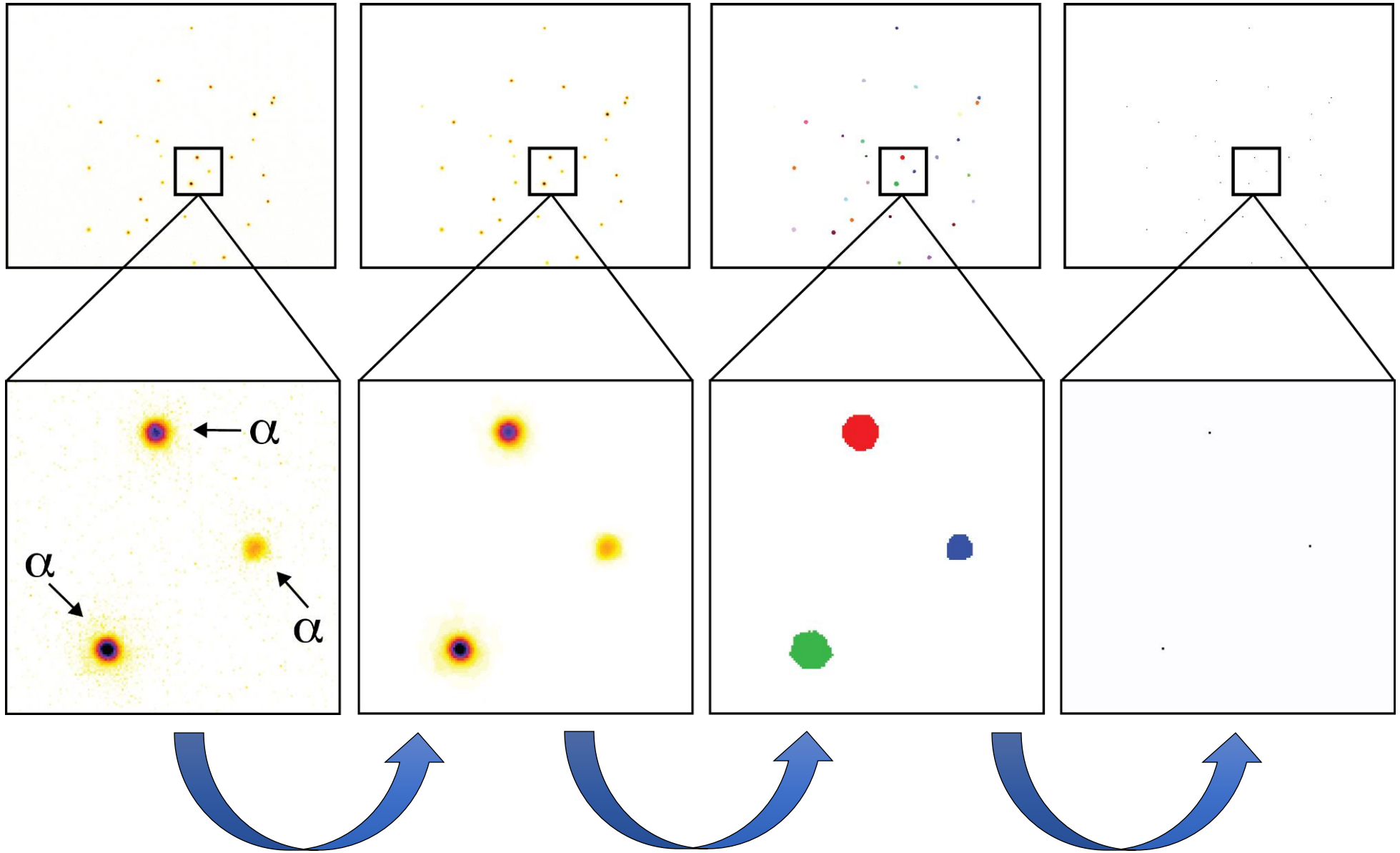


Source: George F. Morrell (1923)
http://www.georgeglazer.com/prints/science/morrellatom.html

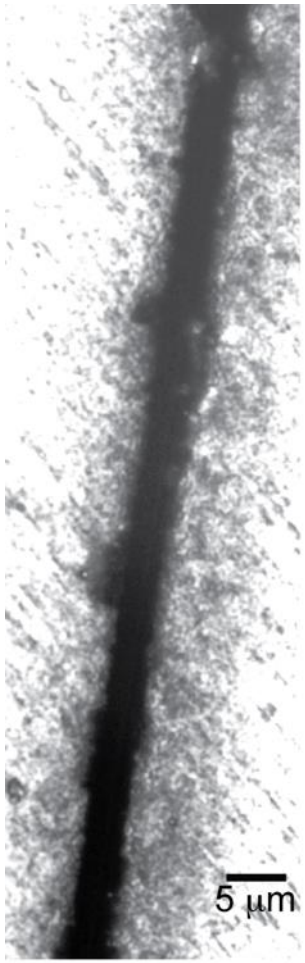
iQID Cross-Sectional View



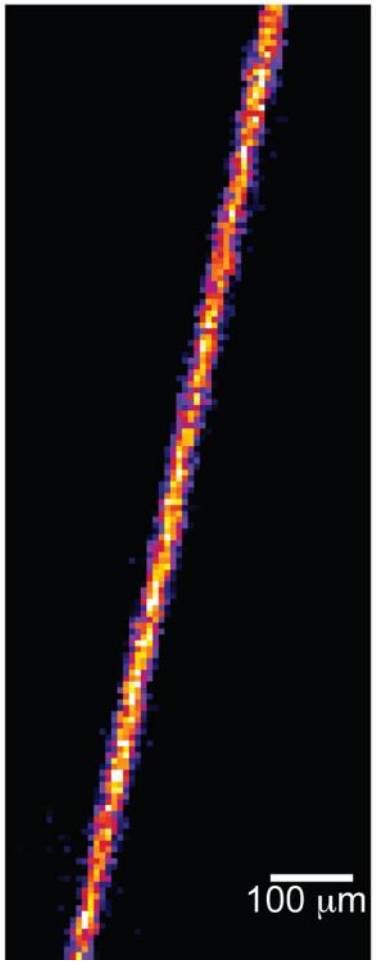
iQID Event Detection & High-Resolution Position Estimation



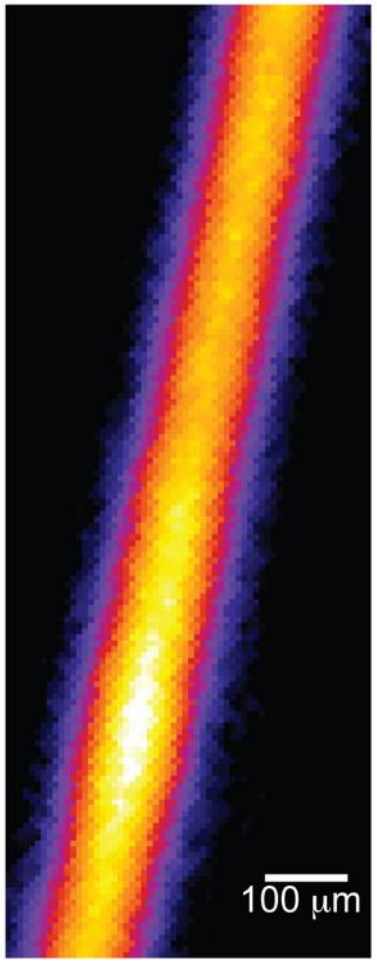
iQID Spatial Resolution – Alpha Particles



Tungsten foil with 5 μm slit

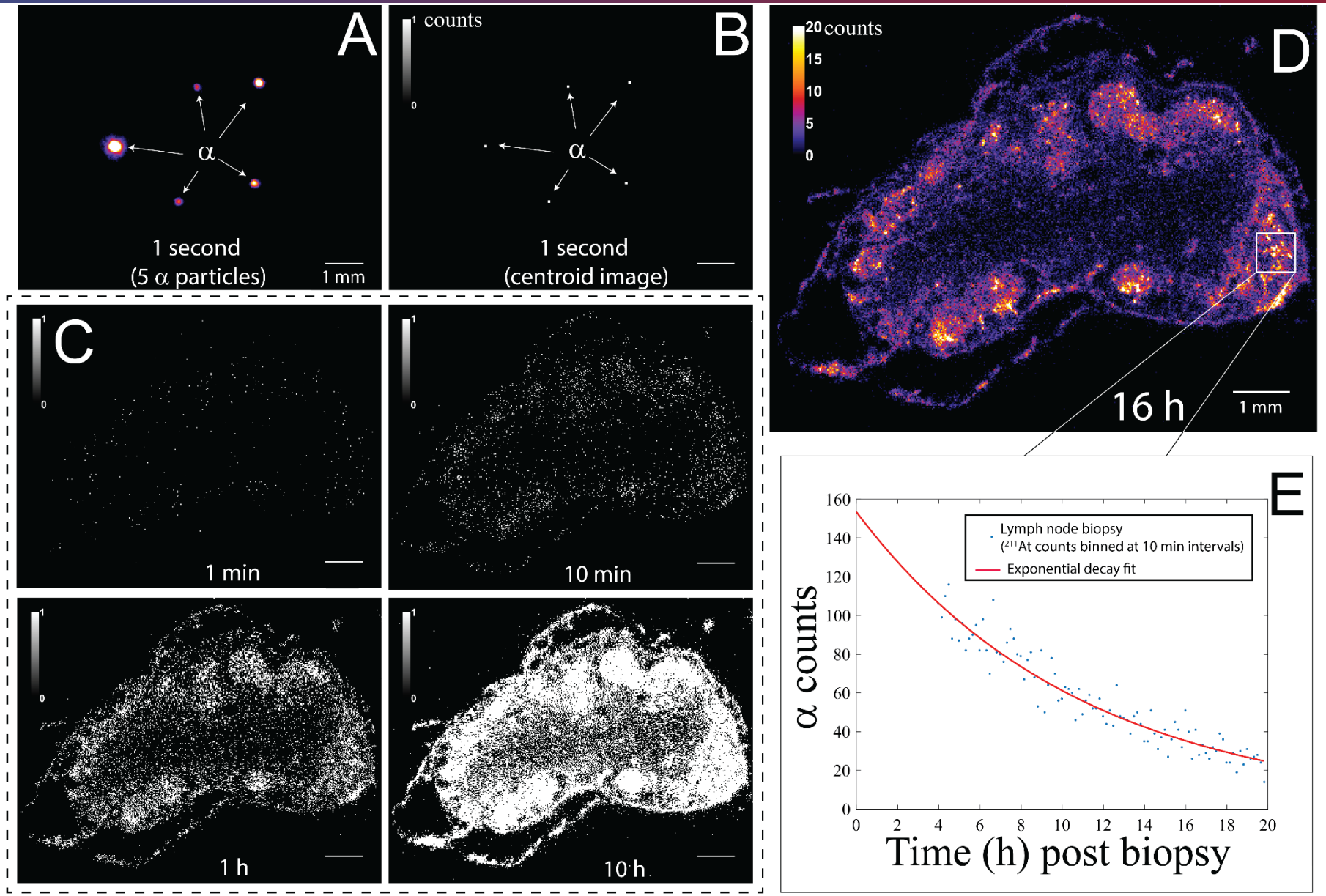


Single particle Imaging

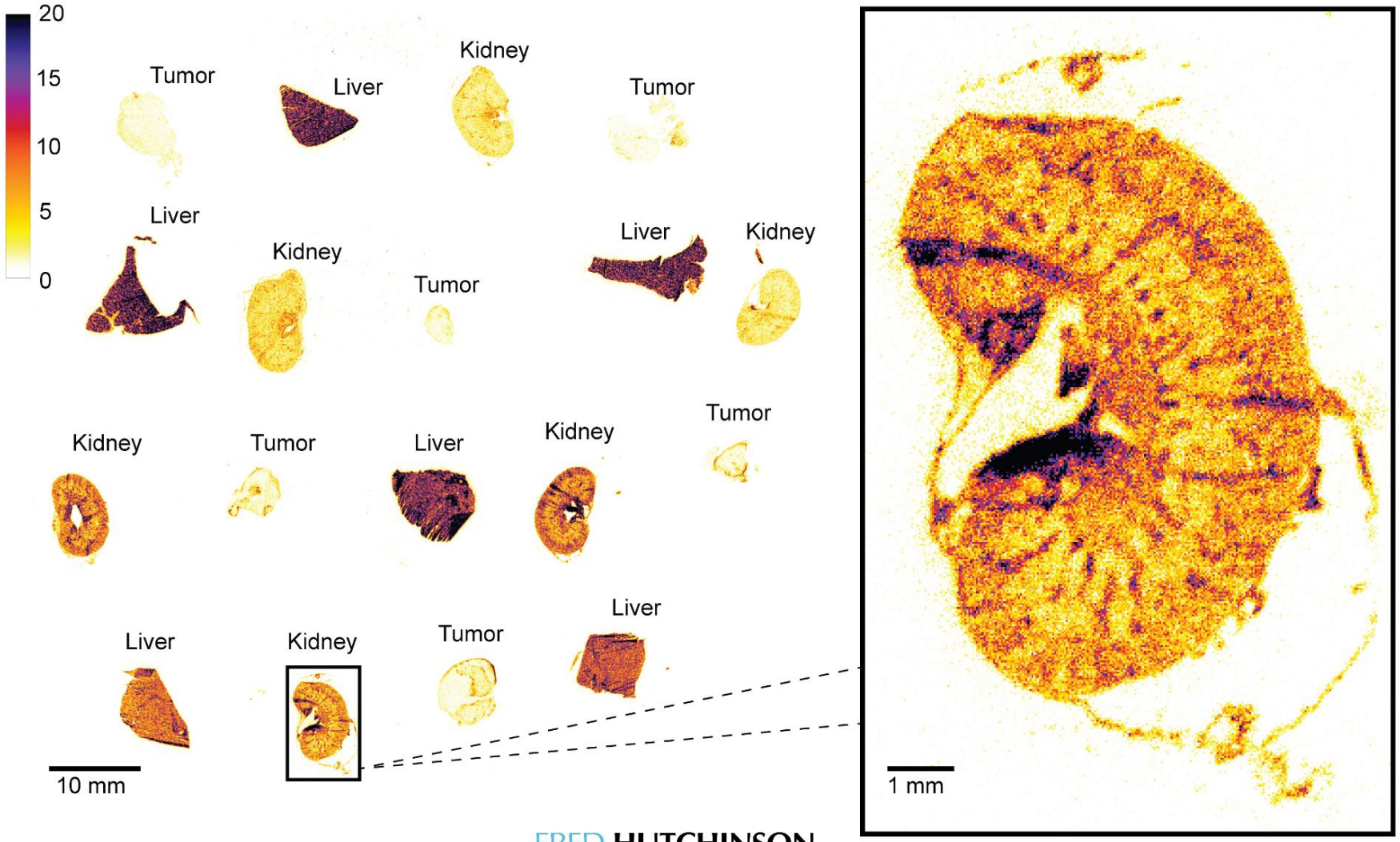


Traditional Integration Imaging

iQID Real-Time Digital Autoradiography (^{211}At)



iQID ^{211}At Imaging



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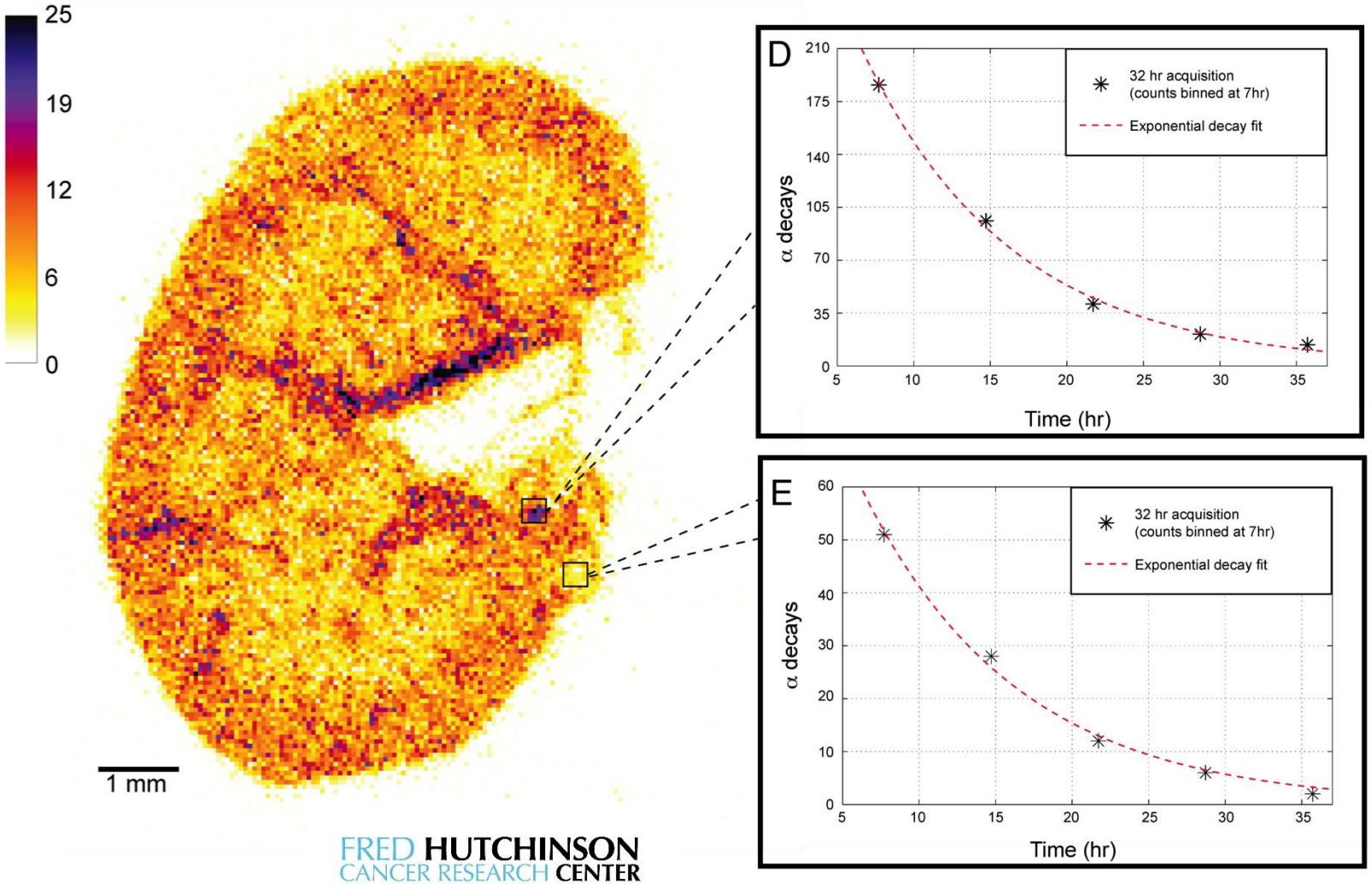
31.24 Bq @ 2h p.i.

iQID ^{211}At Imaging – Activity Estimation
4.81 Bq (130 pCi) at 20 hr p.i.



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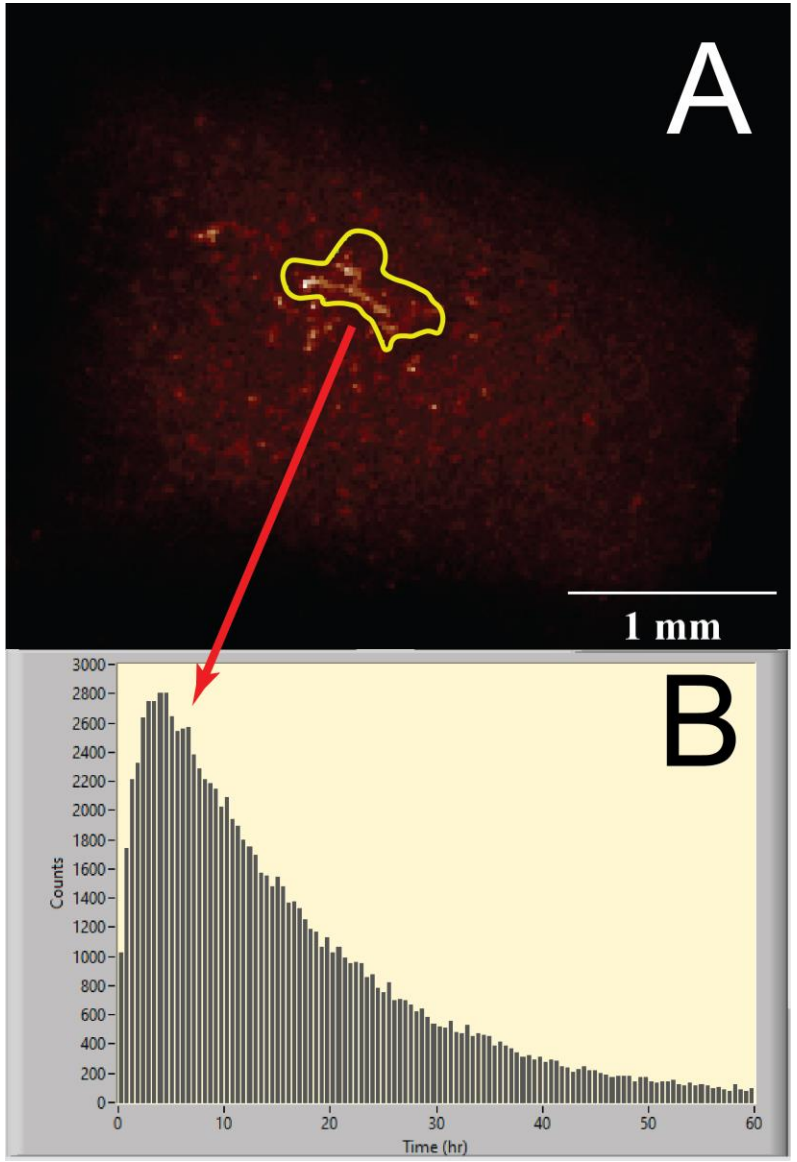
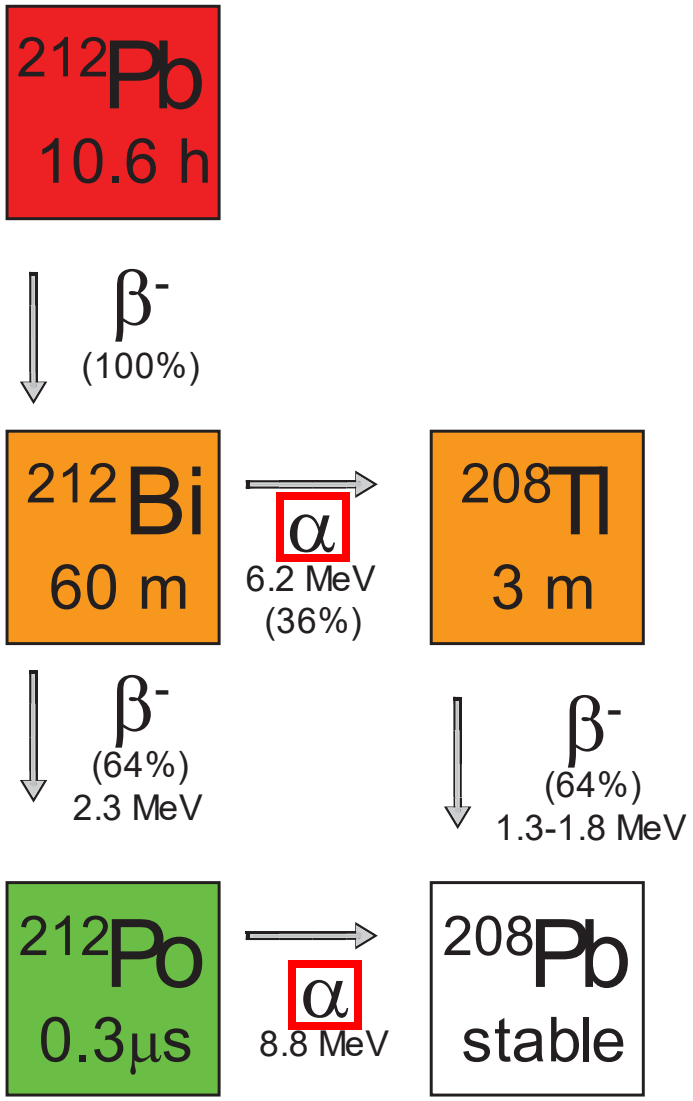
High ROI: 19.3 mBq (24.23 mBq/μg)
Low ROI: 4.4 mBq (5.52 mBq/μg)

Pb-212 Alpha Particle Imaging



MSKCC/Cornell (Sarah Cheal)



iQID ^{211}At Imaging:
Mean Activity Concentration 27.71 mBq/µg

27.71 mBq/µg @ 2hr post injection

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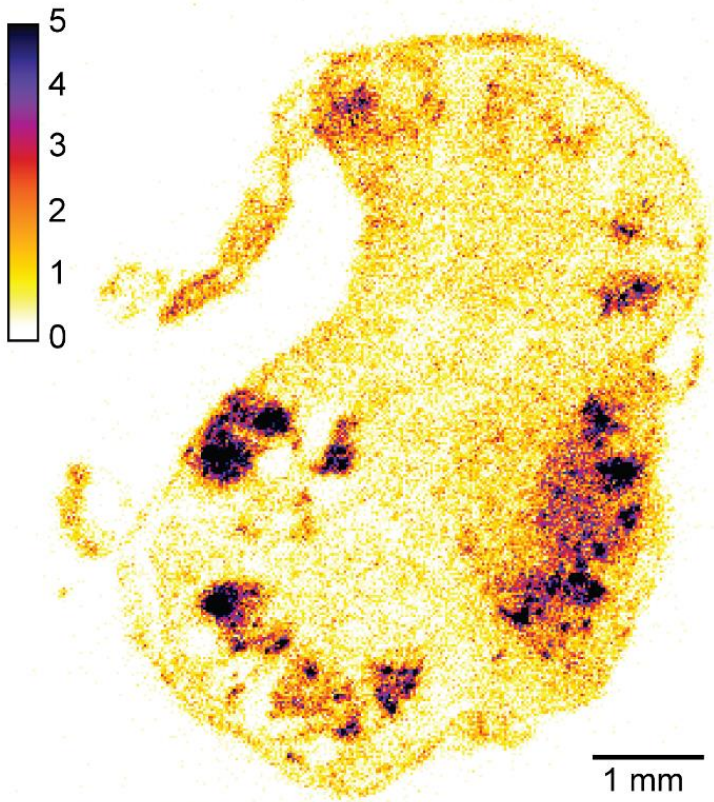
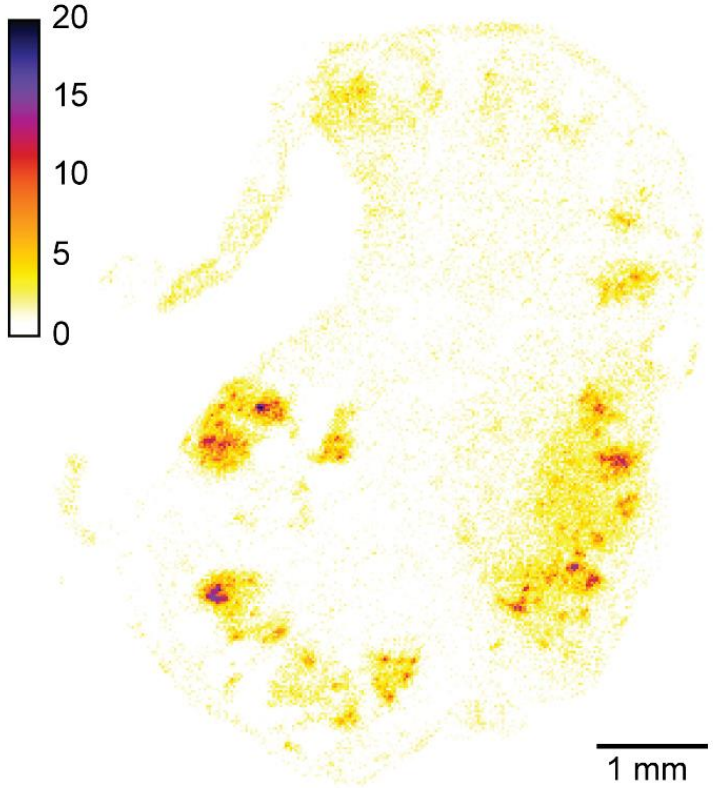
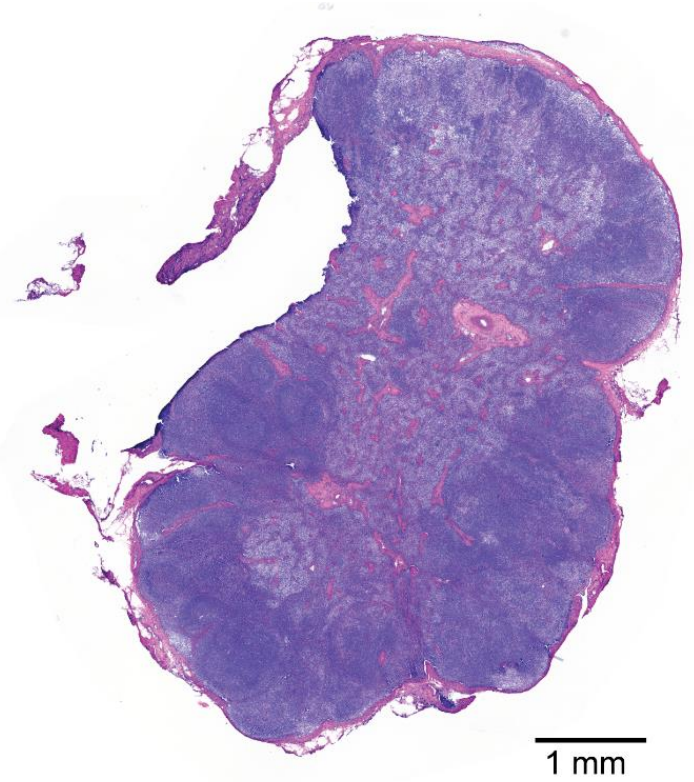






Medical Physics
The International Journal of Medical Physics Research and Practice

Quantitative single-particle digital autoradiography with *α*-particle emitters for targeted radionuclide therapy using the iQID camera

Brian W. Miller[1,a)], Sofia H. L. Frost[2], Shani L. Frayo[2], Aimee L. Kenoyer[2], Erlinda Santos[2], Jon C. Jones[2], Damian J. Green[3], Donald K. Hamlin[4], D. Scott Wilbur[4], Darrell R. Fisher[5], Johnnie J. Orozco[6], Oliver W. Press[7], John M. Pagel[7] and Brenda M. Sandmaier[7]

Med. Phys. **42**, 4094 (2015); http://dx.doi.org/10.1118/1.4921997

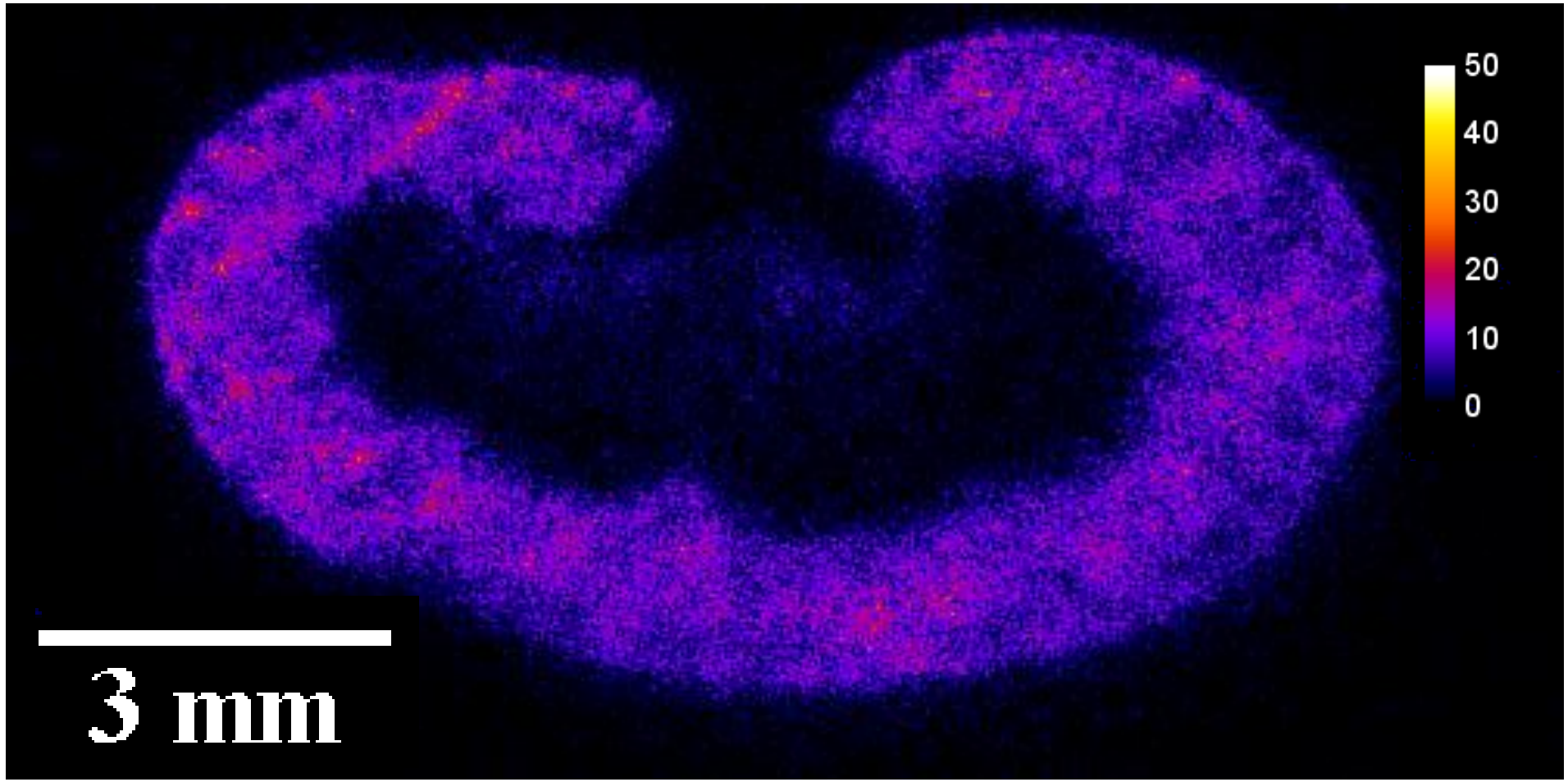
JNM
The Journal of Nuclear Medicine

J Nucl Med 2015 56:1766-1773.
doi: 10.2967/jnumed.115.162388

α-Imaging Confirmed Efficient Targeting of CD45-Positive Cells After ^{211}At-Radioimmunotherapy for Hematopoietic Cell Transplantation.

Sofia H.L. Frost, Brian W. Miller, Tom A. Bäck, Erlinda B. Santos, Donald K. Hamlin, Sue E. Knoblaugh, Shani L. Frayo, Aimee L. Kenoyer, Rainer Storb, Oliver W. Press, D. Scott Wilbur, John M. Pagel, and Brenda M. Sandmaier

Bi-213

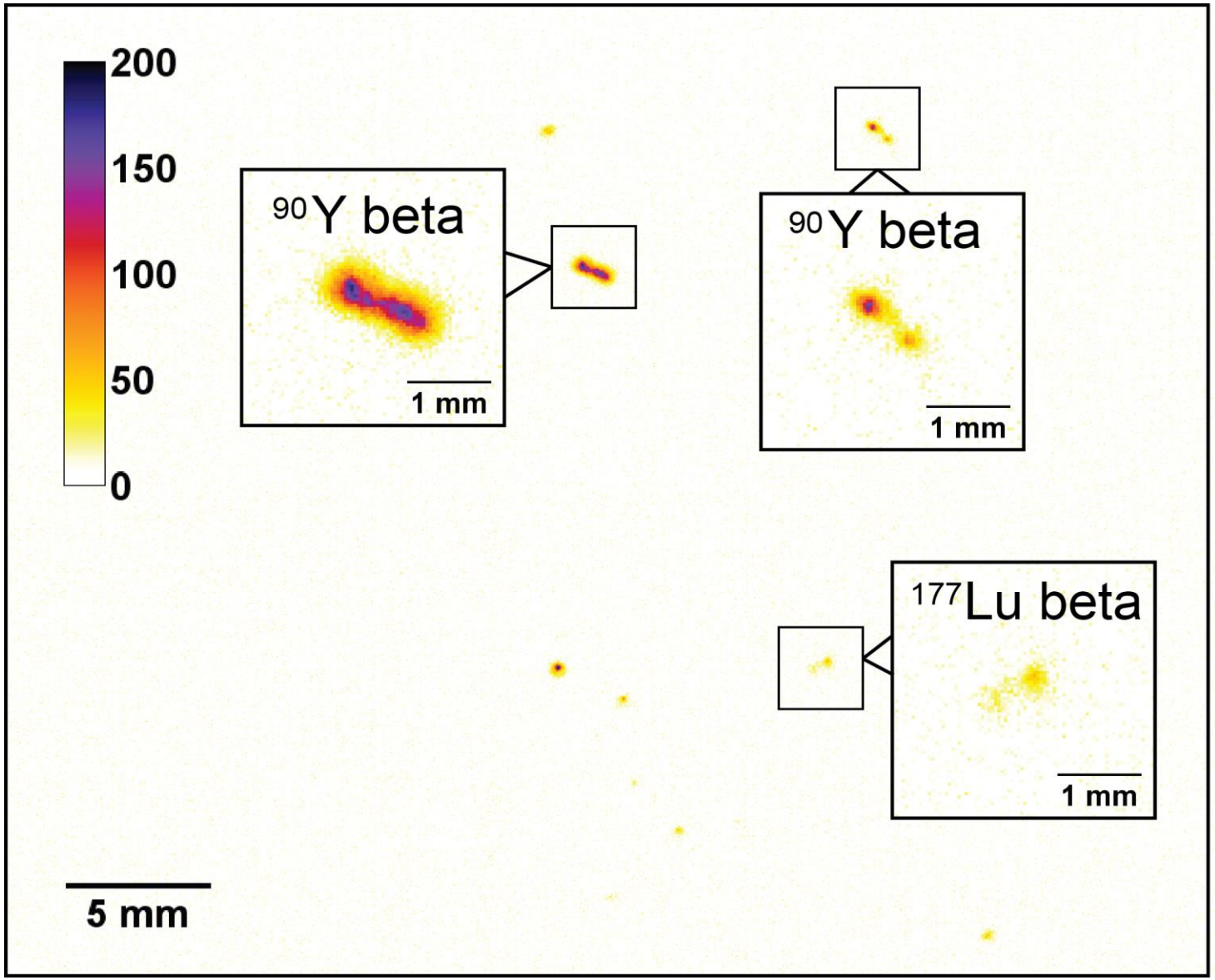


ACS Publications
Most Trusted. Most Cited. Most Read.

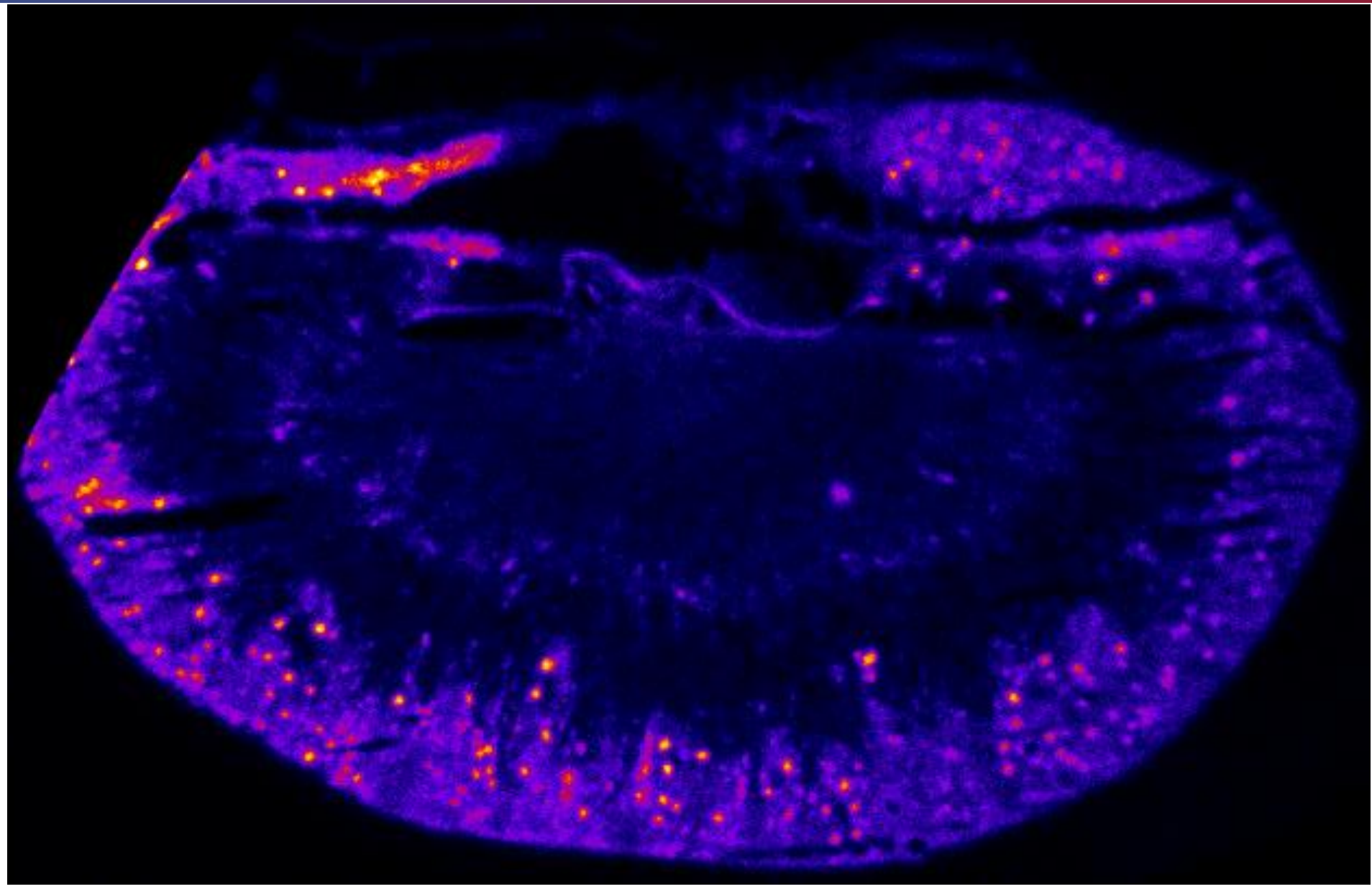
Therapeutic Efficacy of ^{213}Bi-labeled sdAbs in a Preclinical Model of Ovarian Cancer

Yana Dekempeneer*, Vicky Caveliers, Maarten Ooms, Dominic Maertens, Mireille Gysemans, Tony Lahoutte, Catarina Xavier, Quentin Lecocq, Ken Maes, Peter Covens, Brian W. Miller, Frank Bruchertseifer, Alfred Morgenstern, Thomas Cardinaels, and Matthias D'Huyvetter

Pretargeted radioimmunotherapy (PRIT) - ^{177}Lu, ^{90}Y



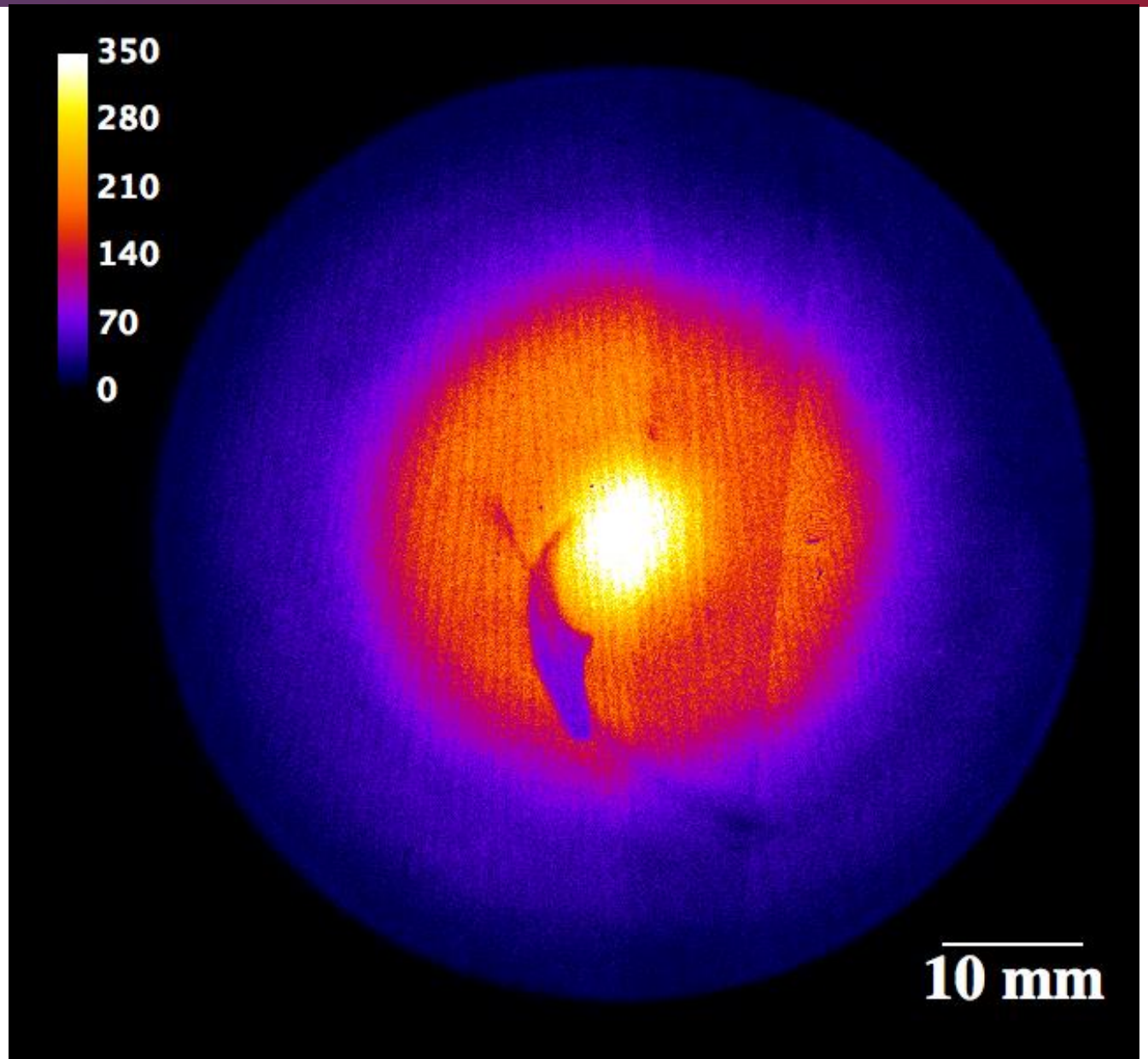
iQID Lu-177 (Unpublished MSKCC)



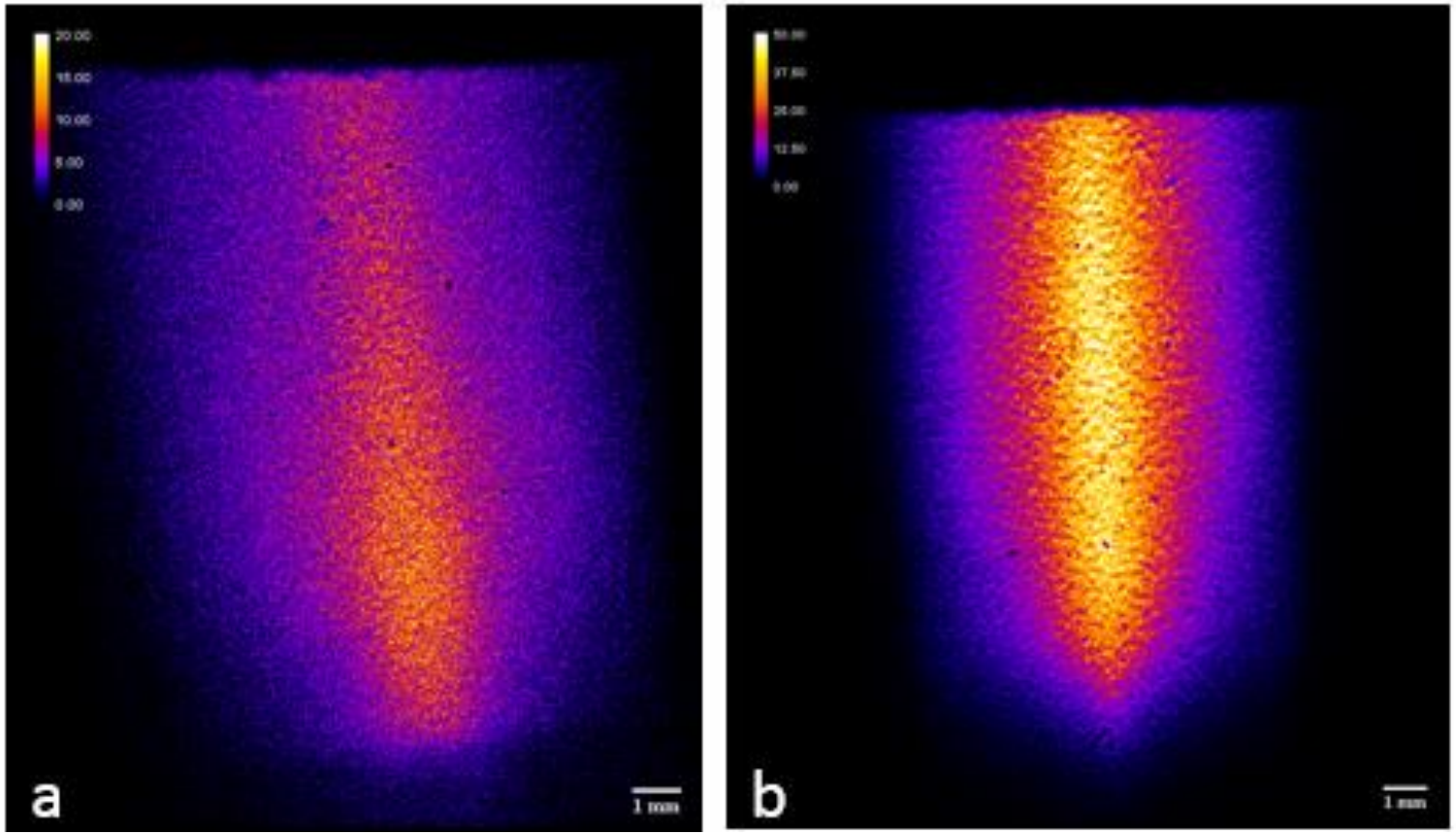
Source QA

Electro-Plated Disk Source

Radiation Toxicology Laboratory, France :
Stephanie Lamart, Nina Griffiths, Anne Van Der Meeren, Jaime F. Angulo



Po-210 Production within Bismith Target for At-211 Production



Acquired images of the 28.8 MeV (a) and the 29.8 MeV (b) target with the iQID-camera

ELSEVIER

Radiation Physics and Chemistry

Volume 212, November 2023, 111155

Optimized cyclotron production of ^{211}At: The challenge of ^{210}Po-characterization

Matthijs Bart C. Sevenois [a], Brian WM. Miller [b], Holger Jan Jensen [c], Matthias D'Huyvetter [a], Peter Covens [a]

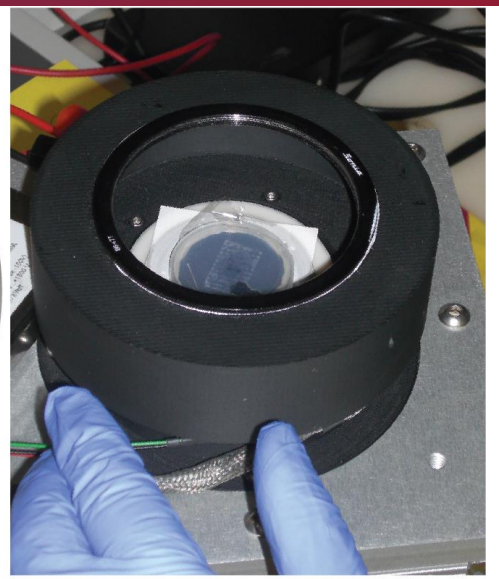
High Spatial Resolution with Alpha Collimators

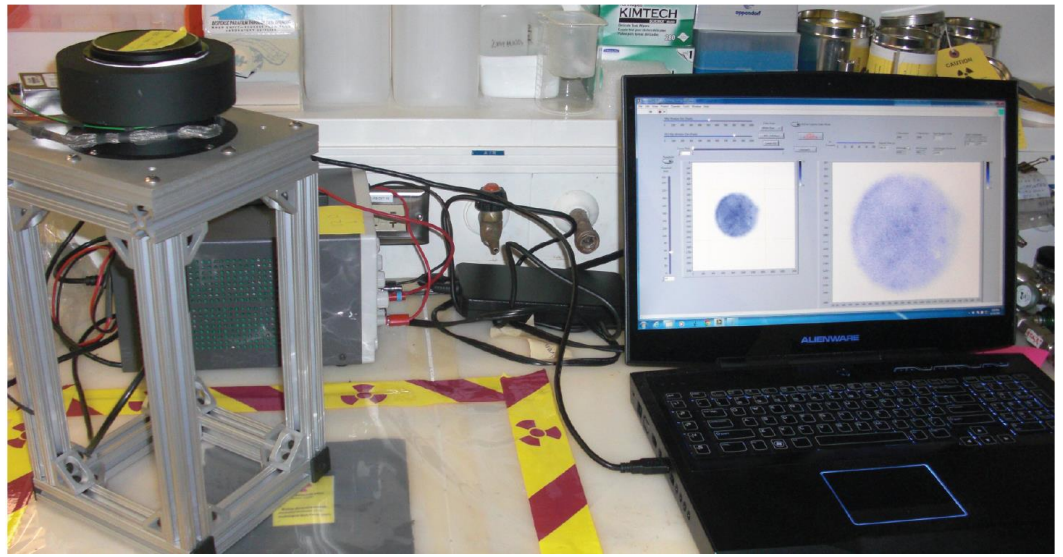
ELSEVIER

Applied Radiation and Isotopes
Volume 166, December 2020, 109348

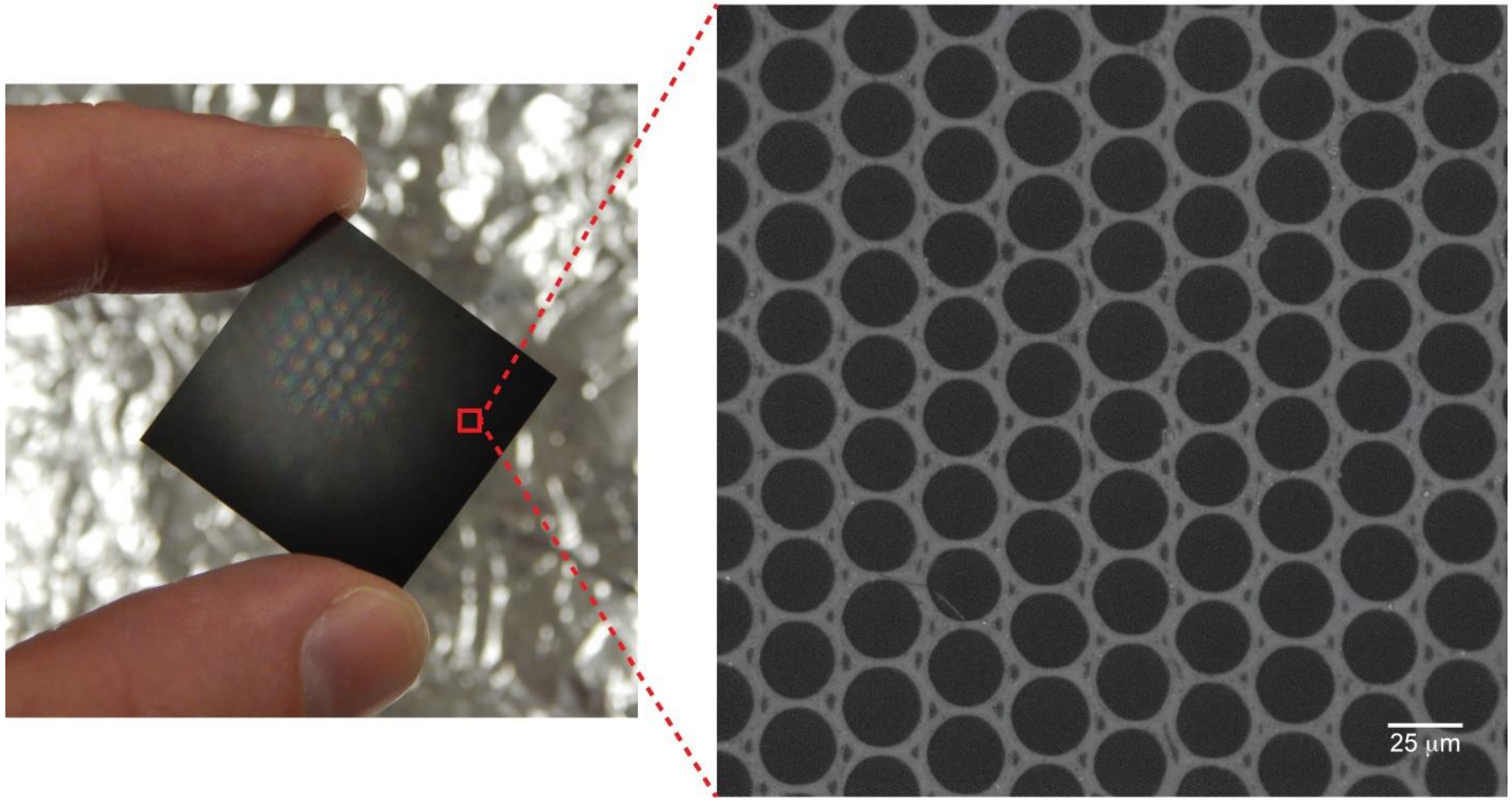
High-resolution, single-particle digital autoradiography of actinide sources using microcapillary array collimators and the iQID camera

Brian W. Miller [a b], James M. Bowen [c], Erin C. Morrison [c]

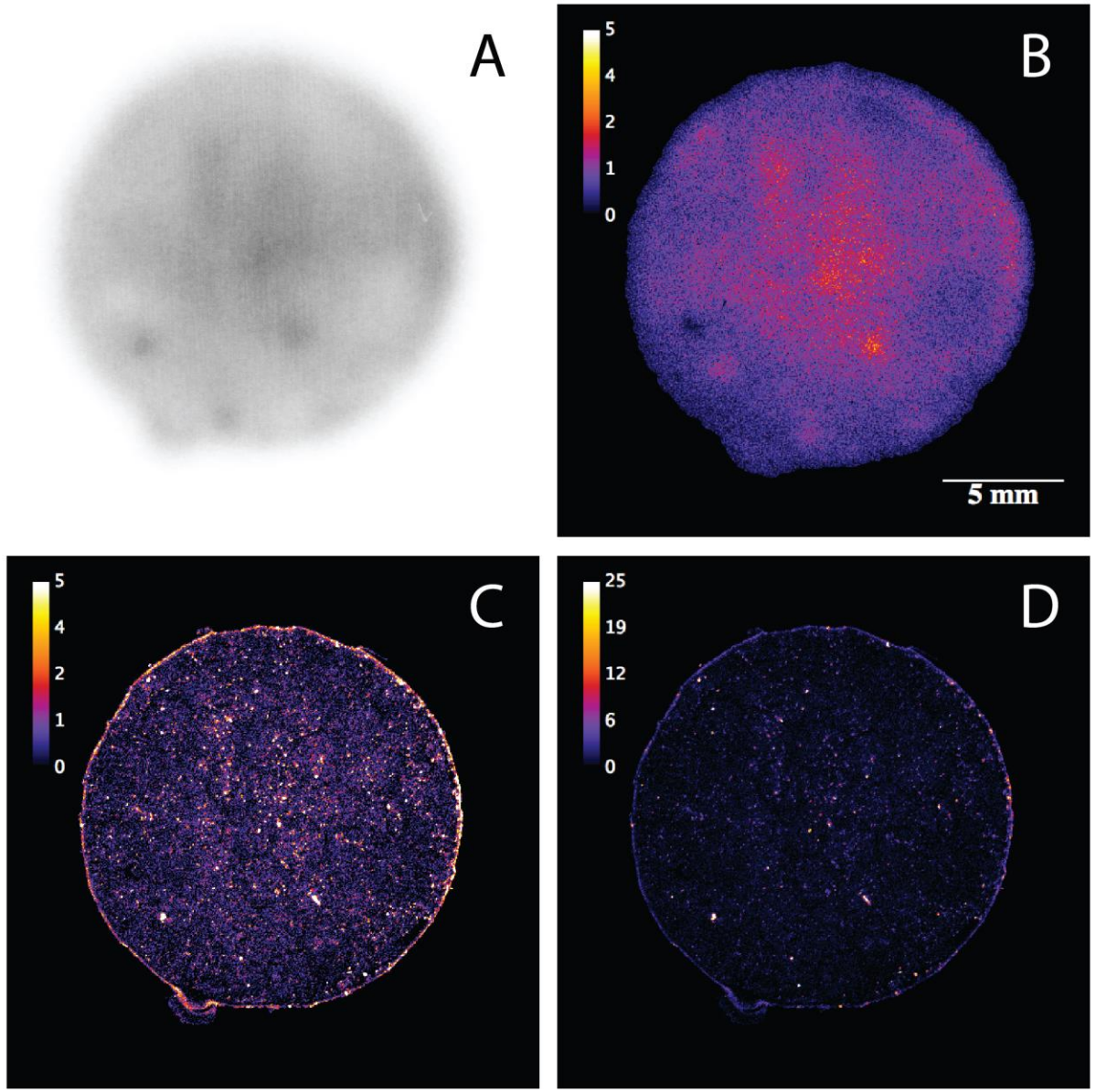




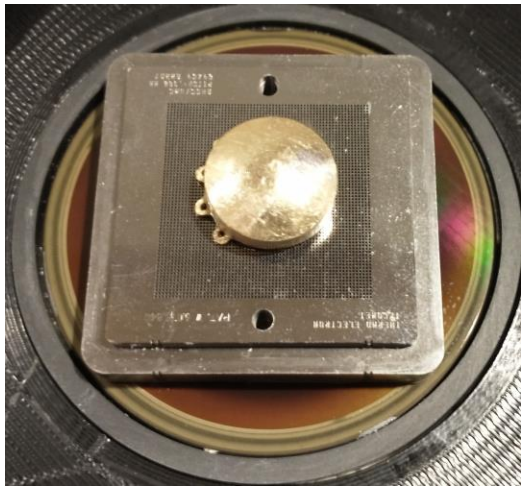
Microcollimator Alpha Imaging

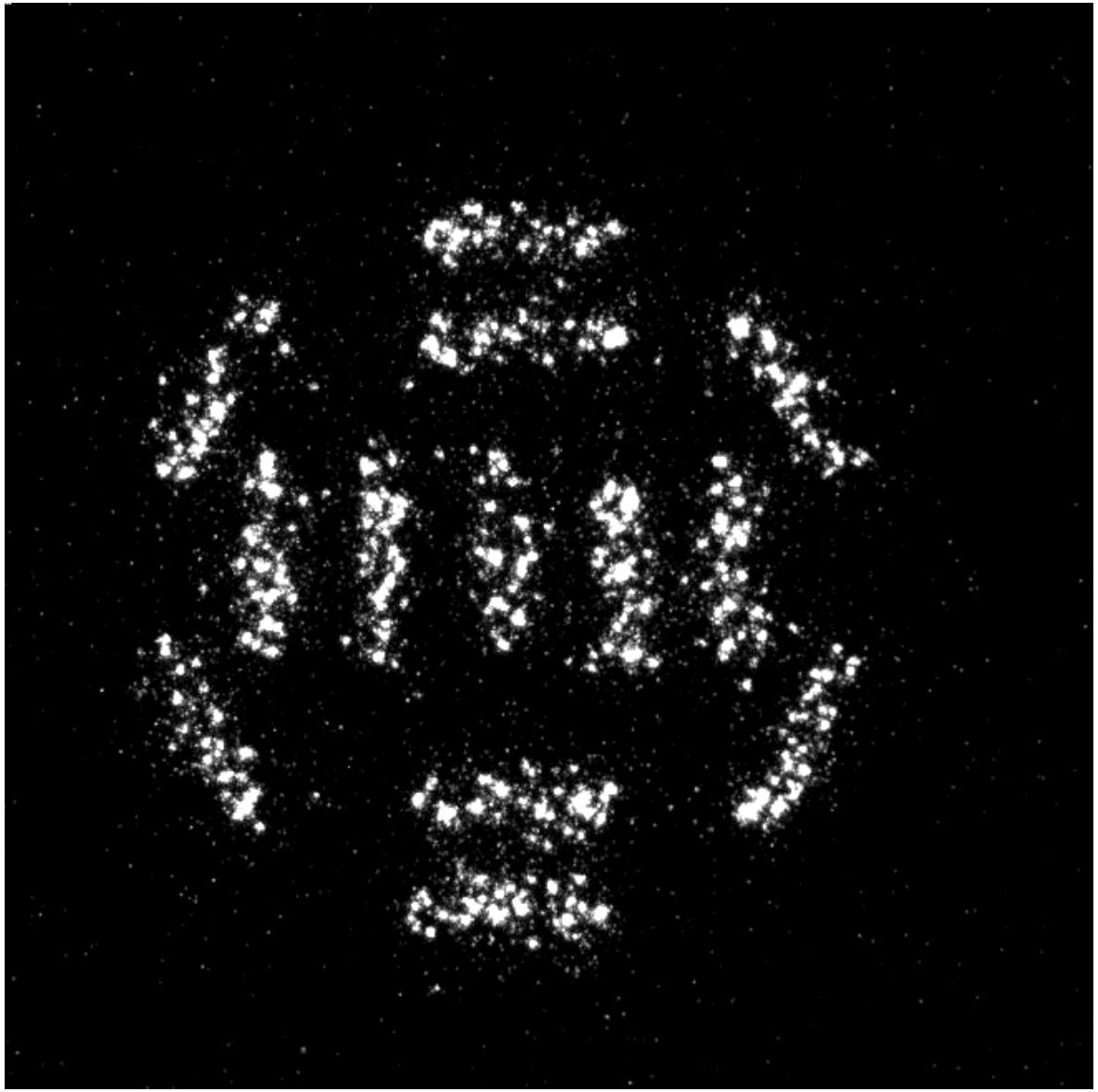


Source Evaulation



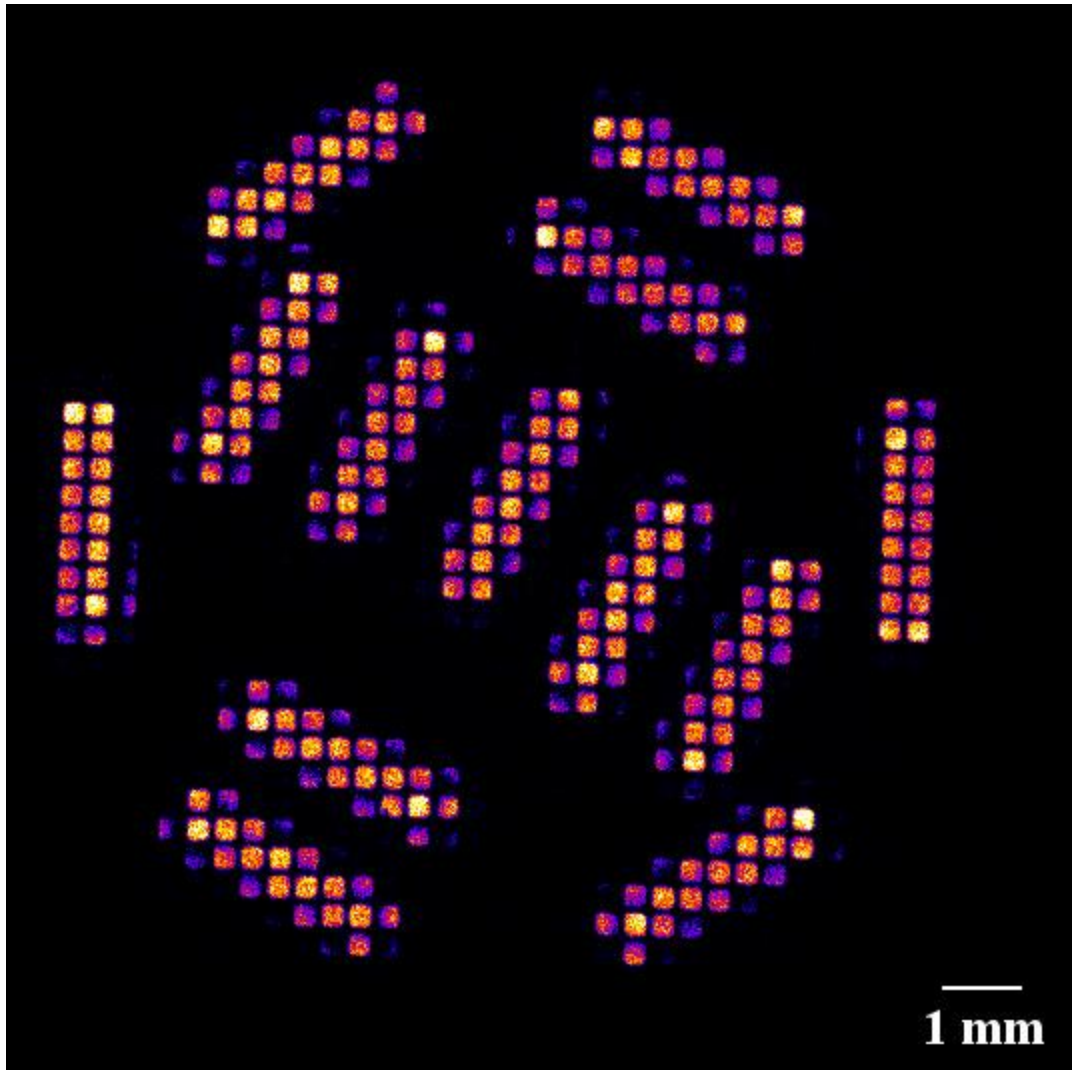
iQID Scintigraphy with eye plaques (unpublished)

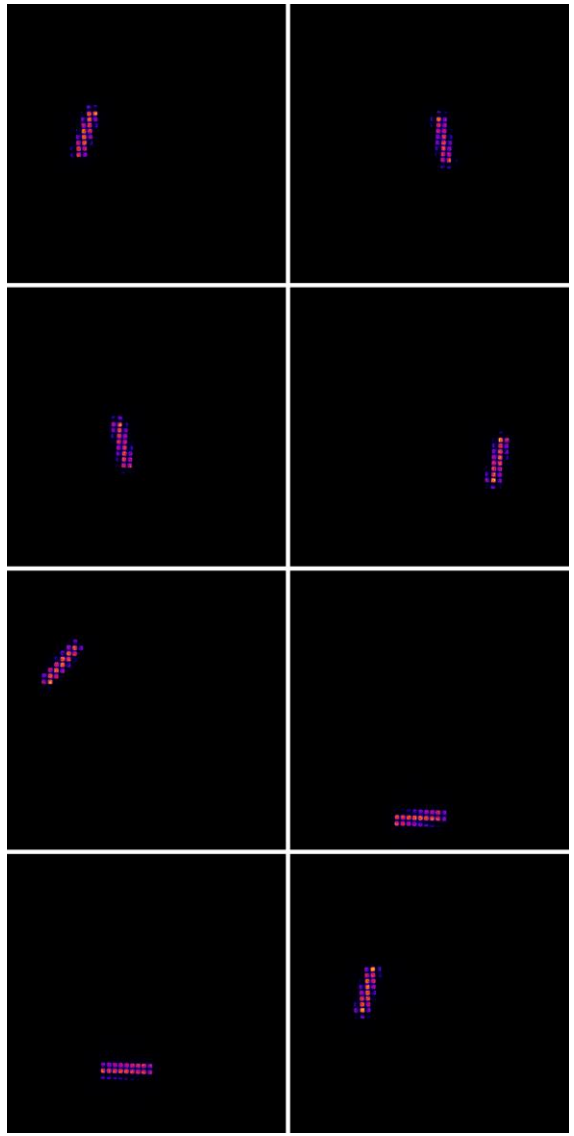




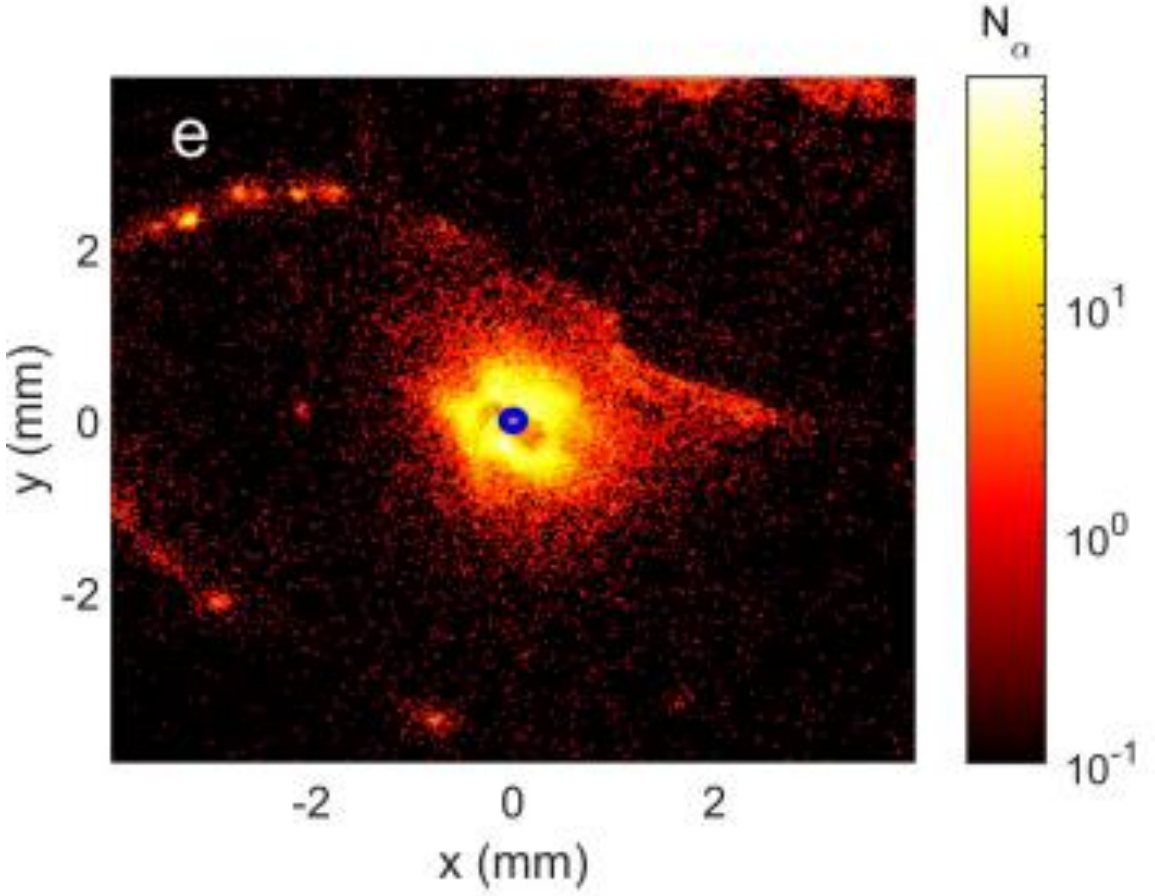
iQID Scintigraphy with eye plaques (unpublished)

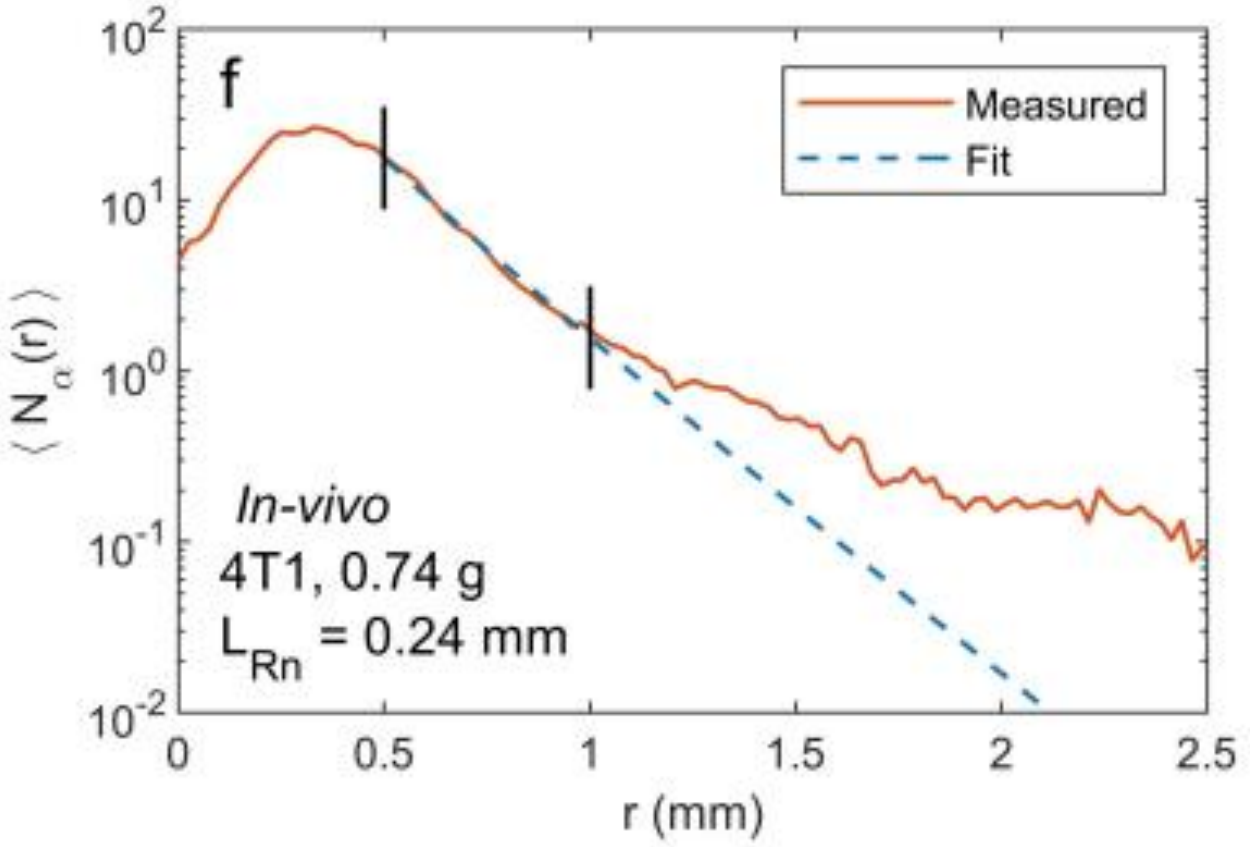
- 5 min Counting Acquisition

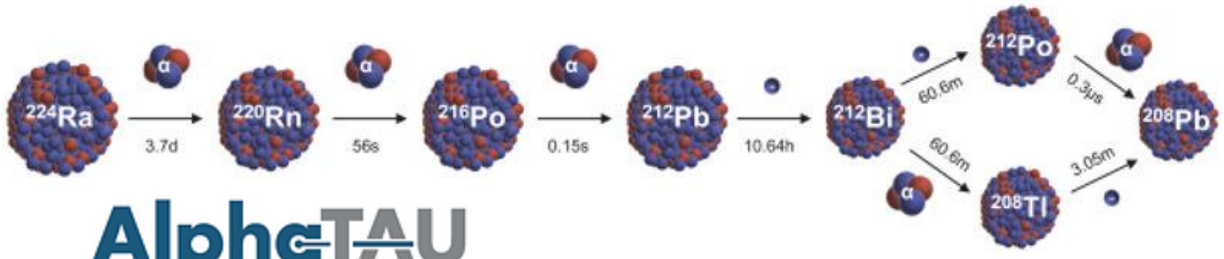




AlphaTAU, AlphaDaRT – Radium-224 Diffusion Study







AlphaTAU

First measurements of radon-220 diffusion in mice tumors, towards treatment planning in diffusing alpha-emitters radiation therapy

Guy Heger[1,*], Mirta Dumančić[1,*,†], Ishai Luz[2], Maayan Vatarescu[2], Noam Weizman[1,3], Brian W. Miller[4], Tomer Cooks[2,‡], Lior Arazi[1,‡]

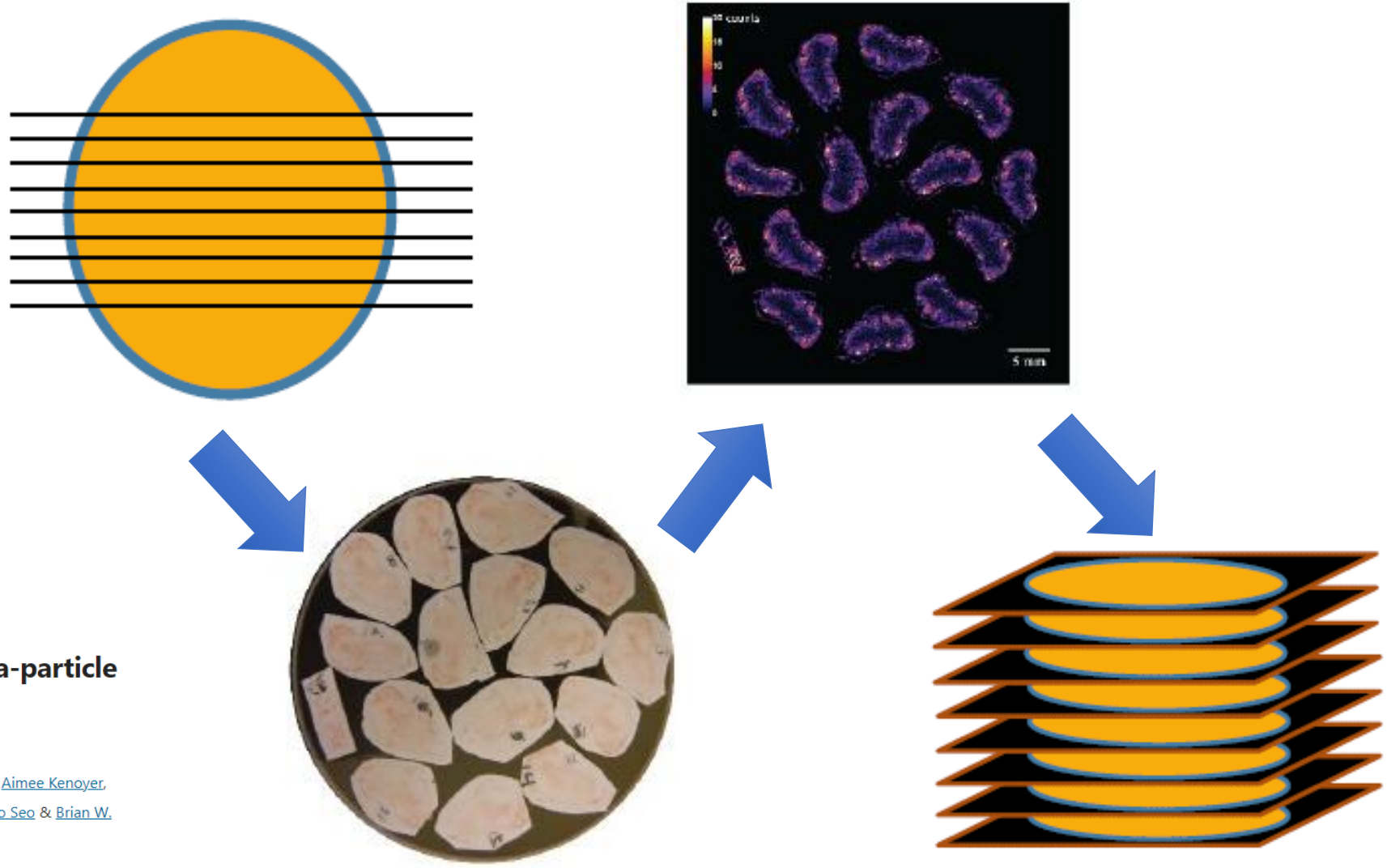
iQID Micro-Scale Dosimetry

Dosimetry Process & Challenges

- Collect **pharmacokinetic** and **biodistribution** data at appropriate scales
  - Scale at which calculations must be performed to arrive at absorbed dose estimates that are more likely to predict biological effects
  - Isotope Specific dose estimates from Macro-Micro
    - Whole organ
    - **Sub organ**
- (In Development) Standardize dosimetry methods so they can be implemented in clinical trials, initially to collect dose-response data and later treatment planning

Sgouros, George. "**Dosimetry, radiobiology and synthetic lethality: radiopharmaceutical therapy (RPT) with alpha-particle-emitters.**" *Seminars in nuclear medicine*. Vol. 50. No. 2. WB Saunders, 2020.

iQID Small-Scale Dosimetry



scientific reports

Small-scale (sub-organ and cellular level) alpha-particle dosimetry methods using an iQID digital autoradiography imaging system

Robin Peter ✉, Brenda M. Sandmaier, Michael P. Dion, Sofia H. L. Frost, Erlinda B. Santos, Aimee Kenoyer, Donald K. Hamlin, D. Scott Wilbur, Robert D. Stewart, Darrell R. Fisher, Kai Vetter, Youngho Seo & Brian W. Miller

Scientific Reports **12**, Article number: 17934 (2022) | Cite this article

iQID ^{211}At Voxel-Based Dosimetry CD-45 in Lymph Node @ 20hr p.i.

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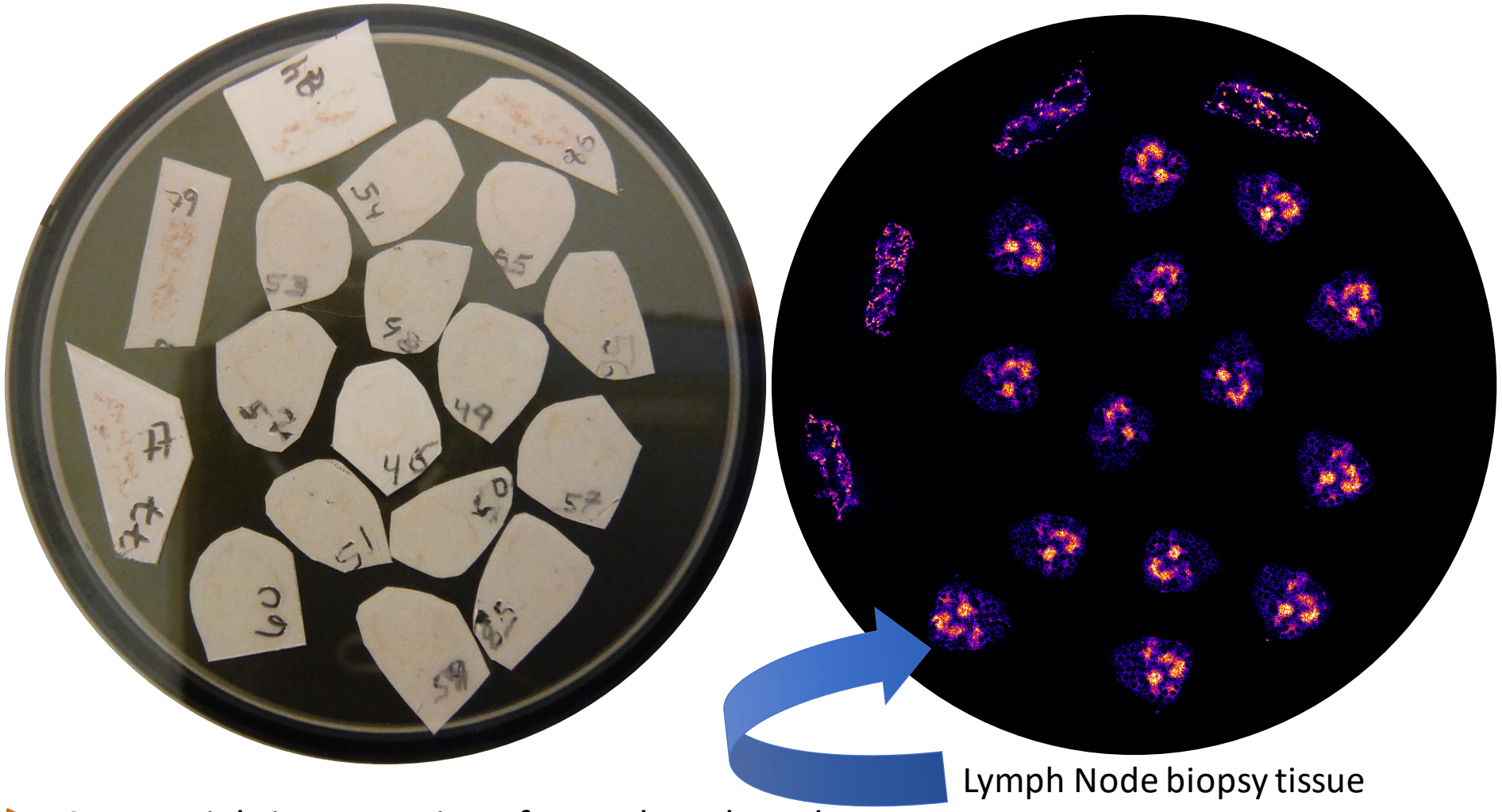
A LIFE OF SCIENCE



Lymph Node biopsy tissue

- Sequential tissue sections from a lymph node biopsy. Each approximately 12 microns thick that span the range of At-211 alpha particles

iQID ^{211}At Voxel-Based Dosimetry
CD-45 in Lymph Node @ 20hr p.i.

FRED HUTCHINSON CANCER RESEARCH CENTER
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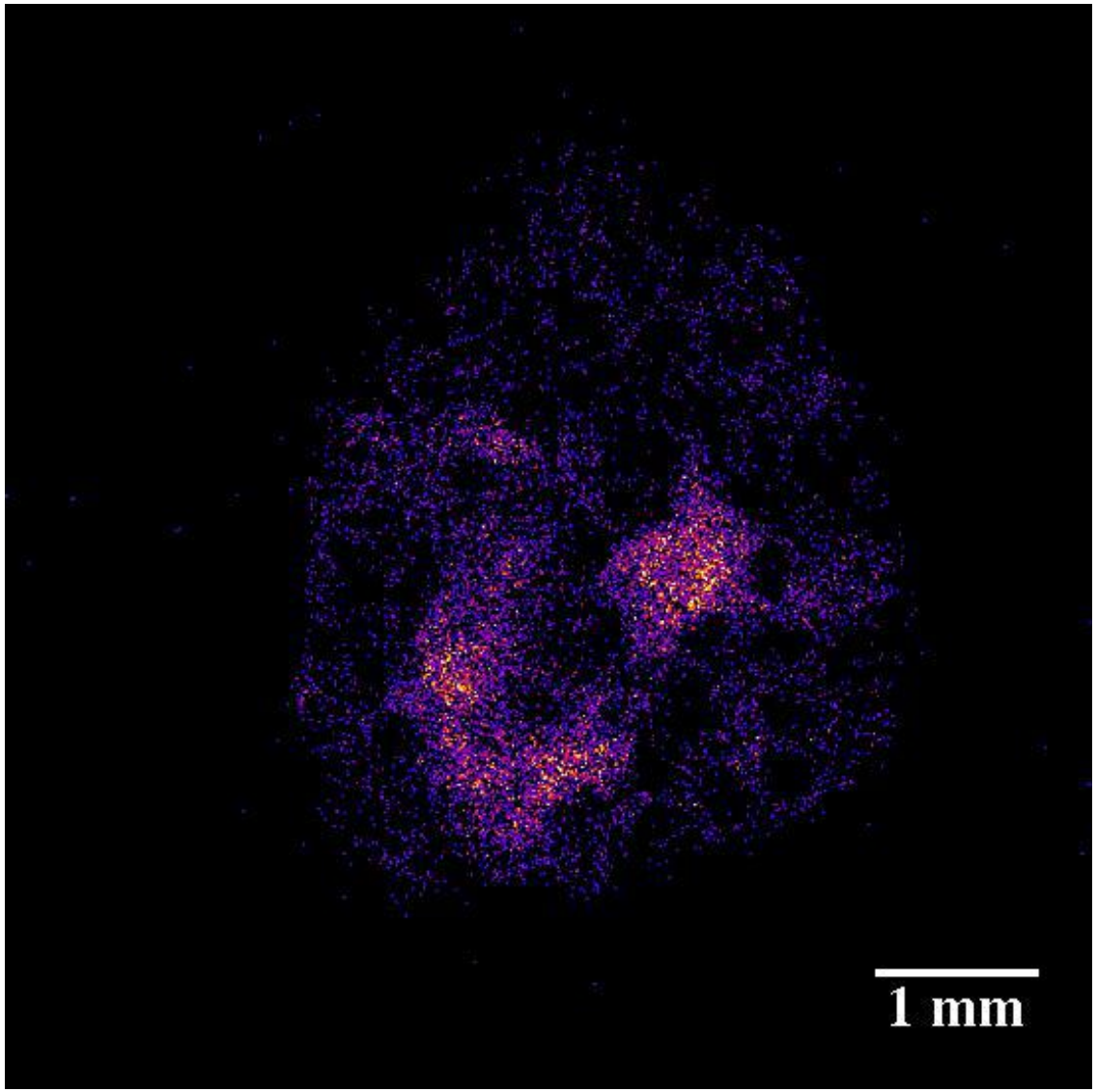
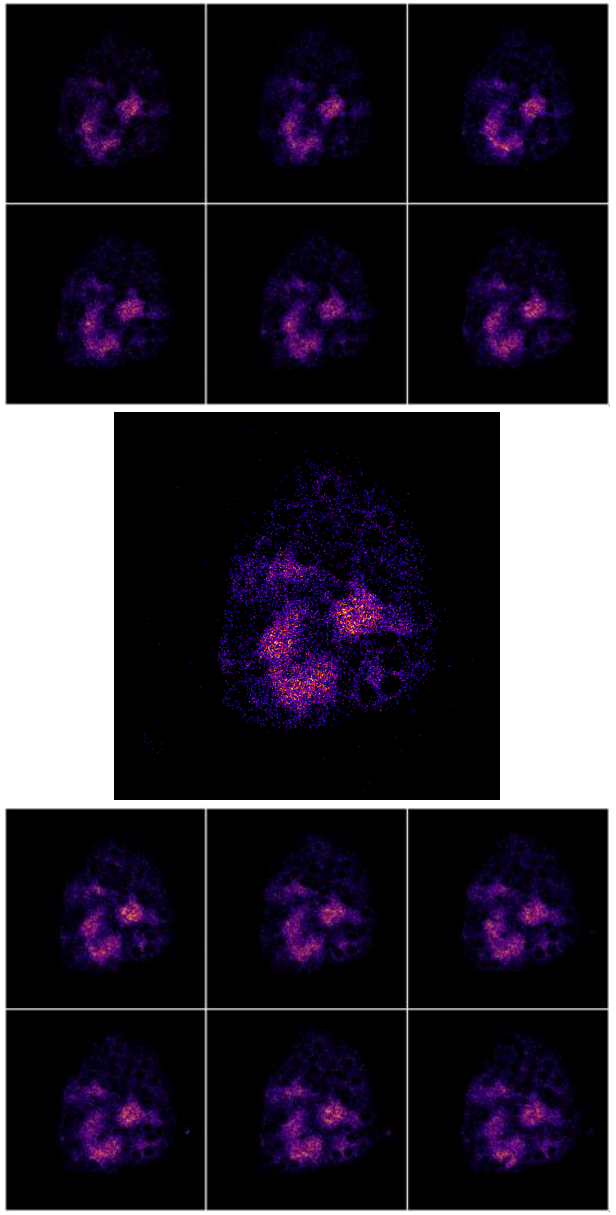
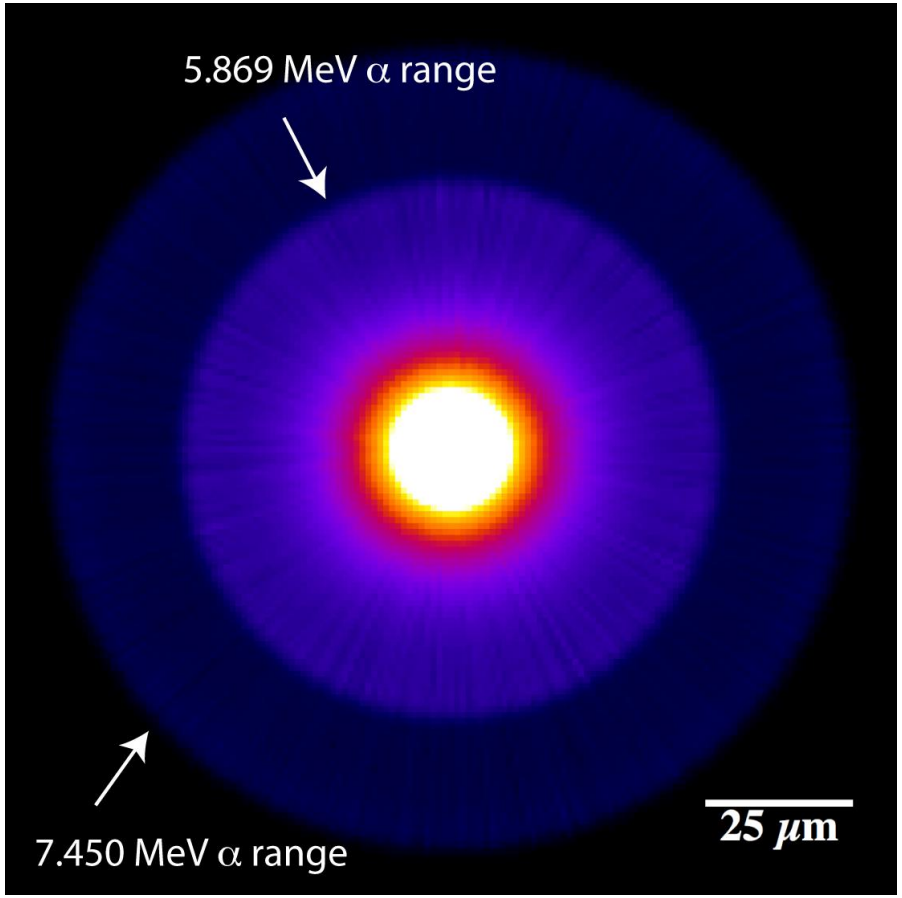
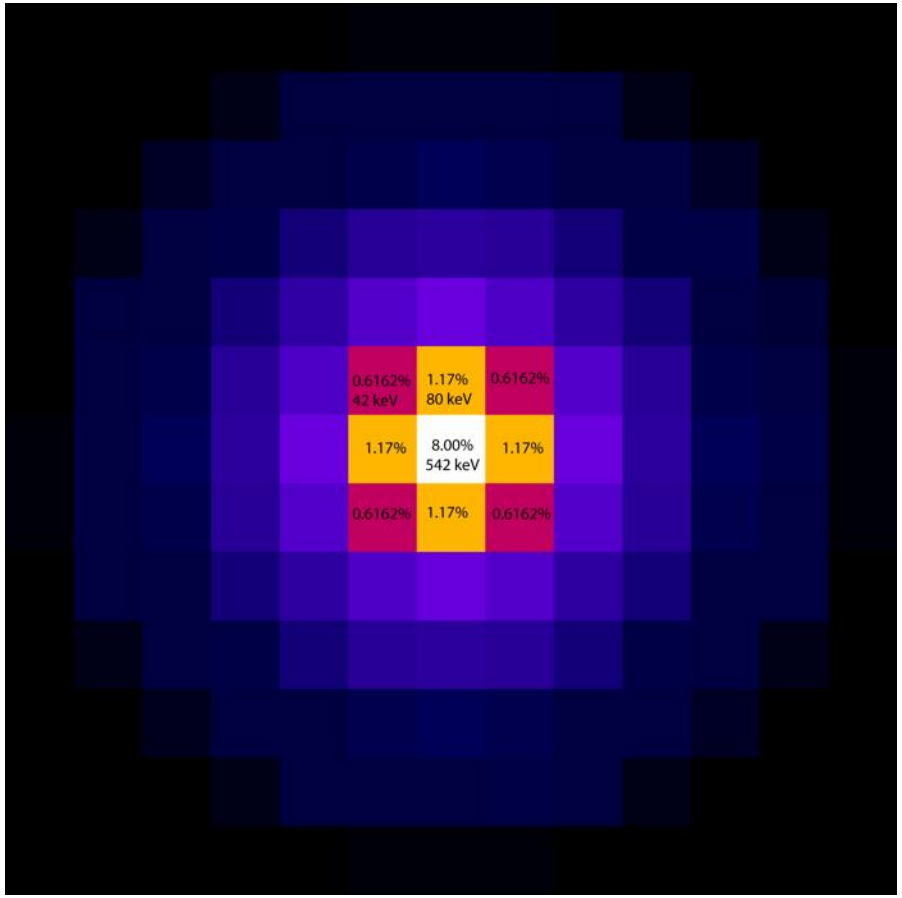


Center slice: 1.351 Bq @ 20h p.i.



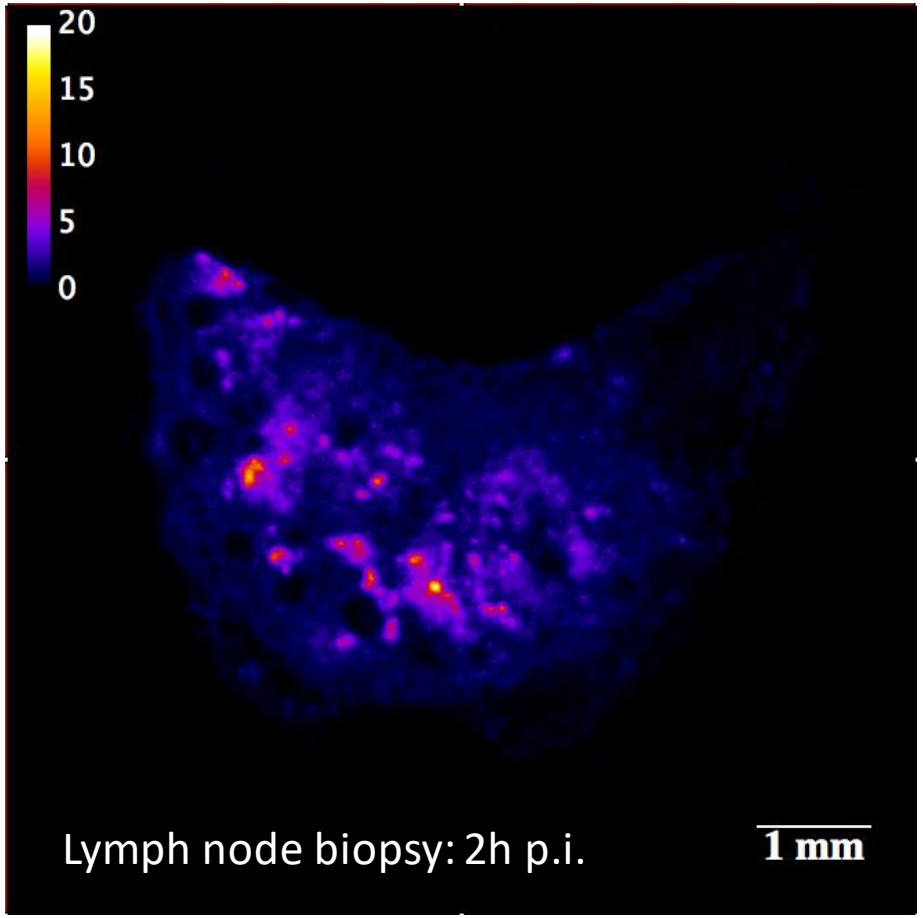
iQID ^{211}At Voxelized Dose Kernel



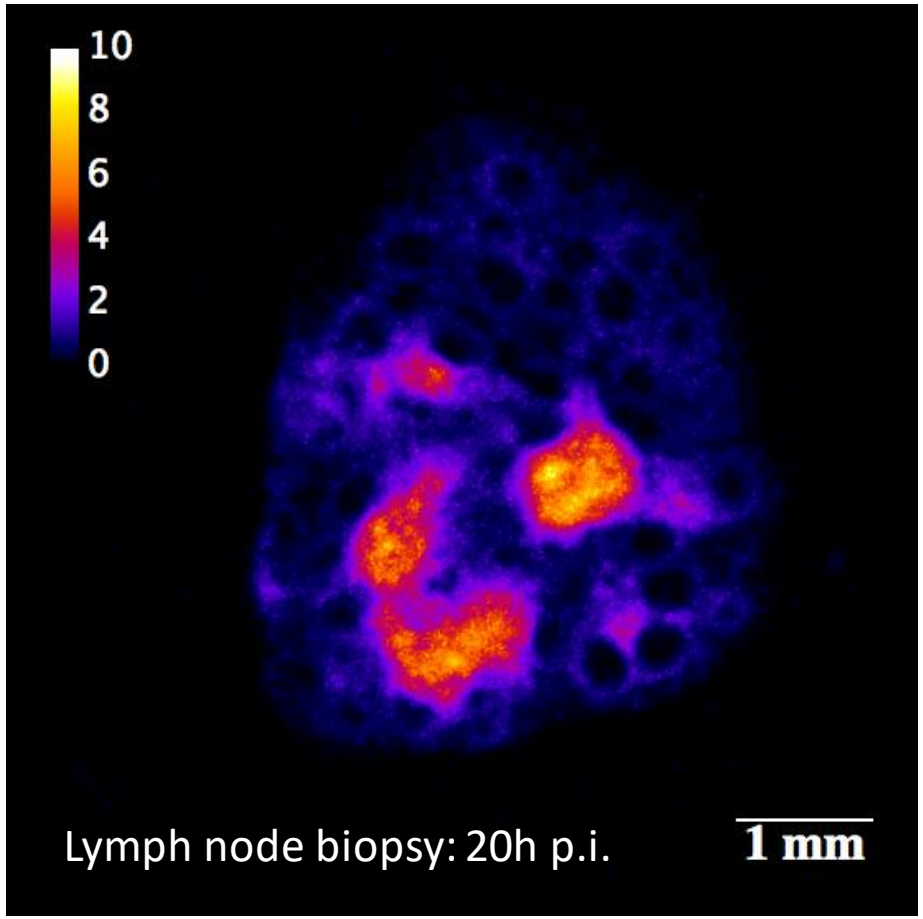


Central slice ^{211}At dose-point kernel: 1μm voxels, 151x151x151 voxels, 10^7 decays. Generated using Geant4. Visible are the ranges of the primary 5.869 MeV alpha from ^{211}At and the 7.450 MeV alpha from ^{211}Po daughter. *Michael Dion (ORNL)*

iQID ^{211}At Voxel-Based Dosimetry

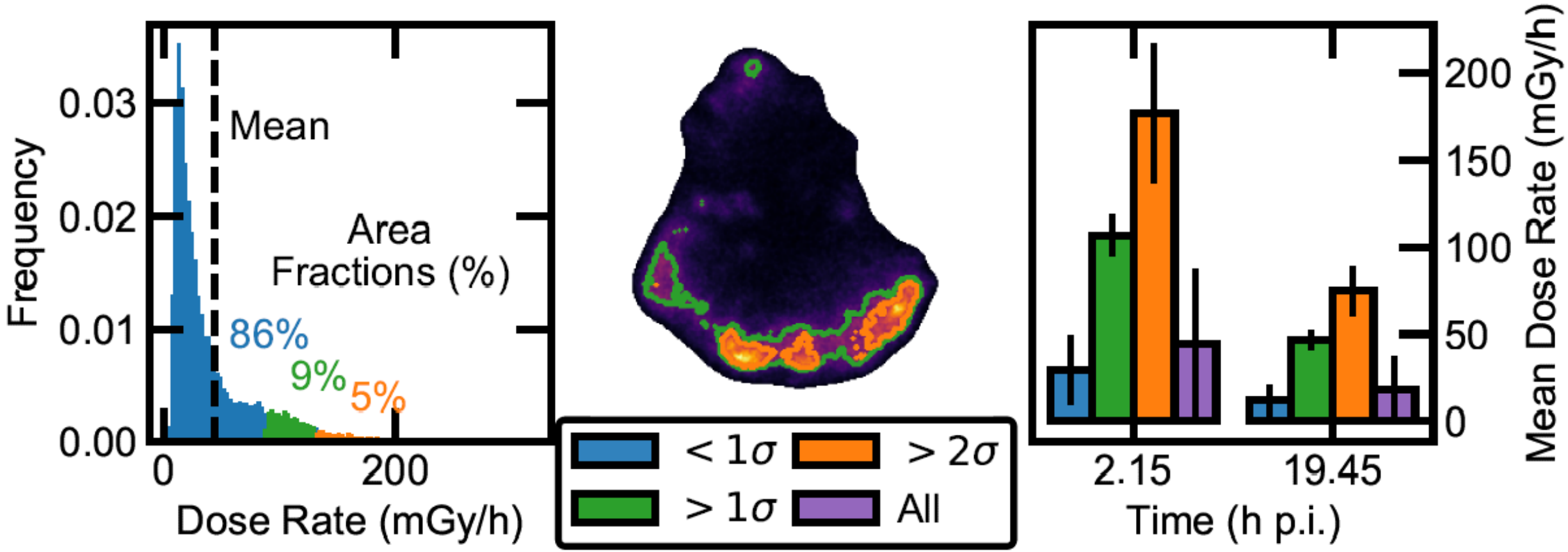


- Voxel size: 12 μm
- Mean dose rate: 8.183 μGy/s
- Mean total dose rate in section: 1.147 Gy/s



- Voxel size: 12 μm
- Mean dose rate: 7.6 μGy/s
- Mean total dose rate in section: 0.841 Gy/s

iQID ^{211}At Voxel-Based Dosimetry



scientific reports

Small-scale (sub-organ and cellular level) alpha-particle dosimetry methods using an iQID digital autoradiography imaging system

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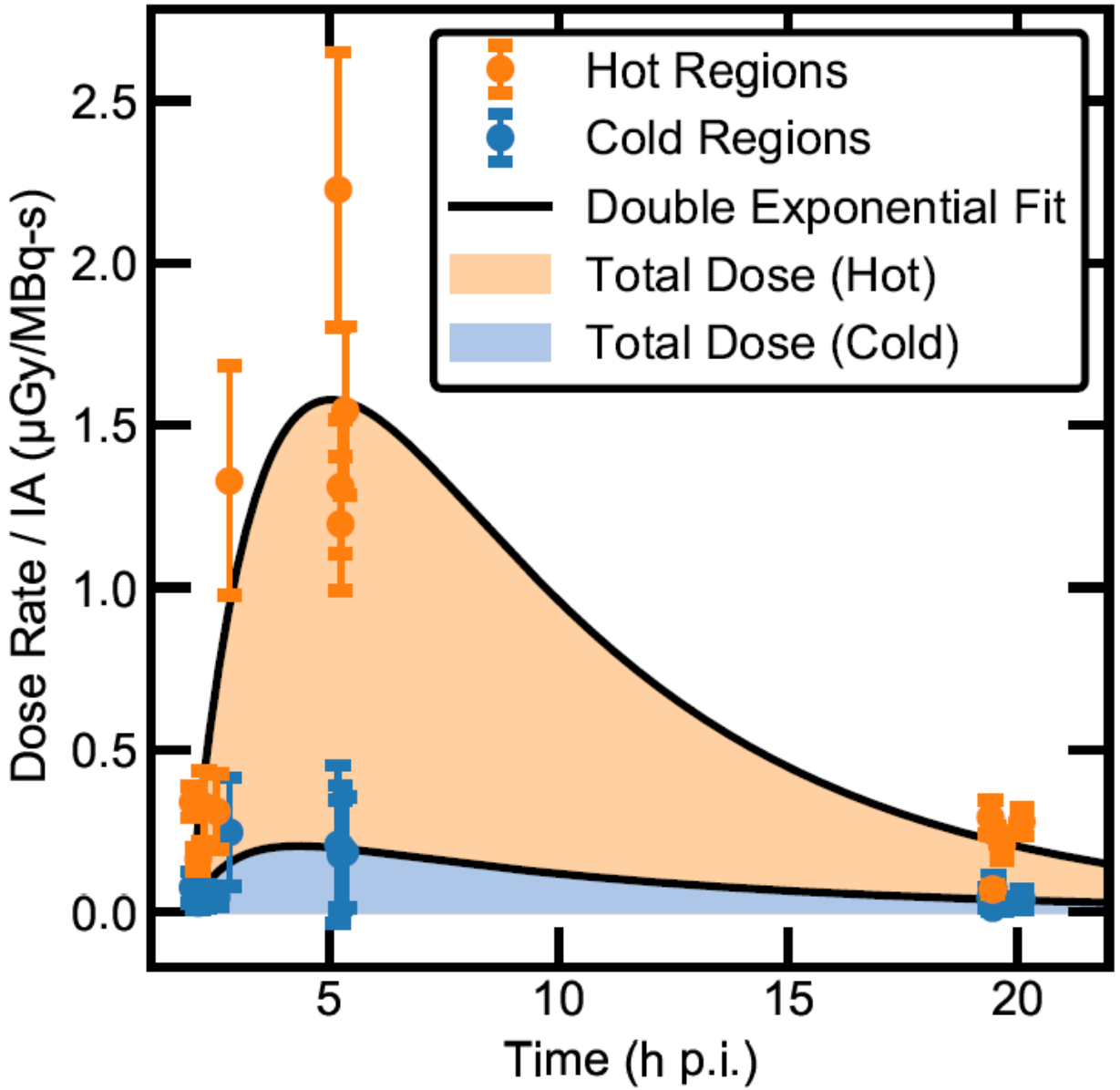
iQID ^{211}At Voxel-Based Dosimetry



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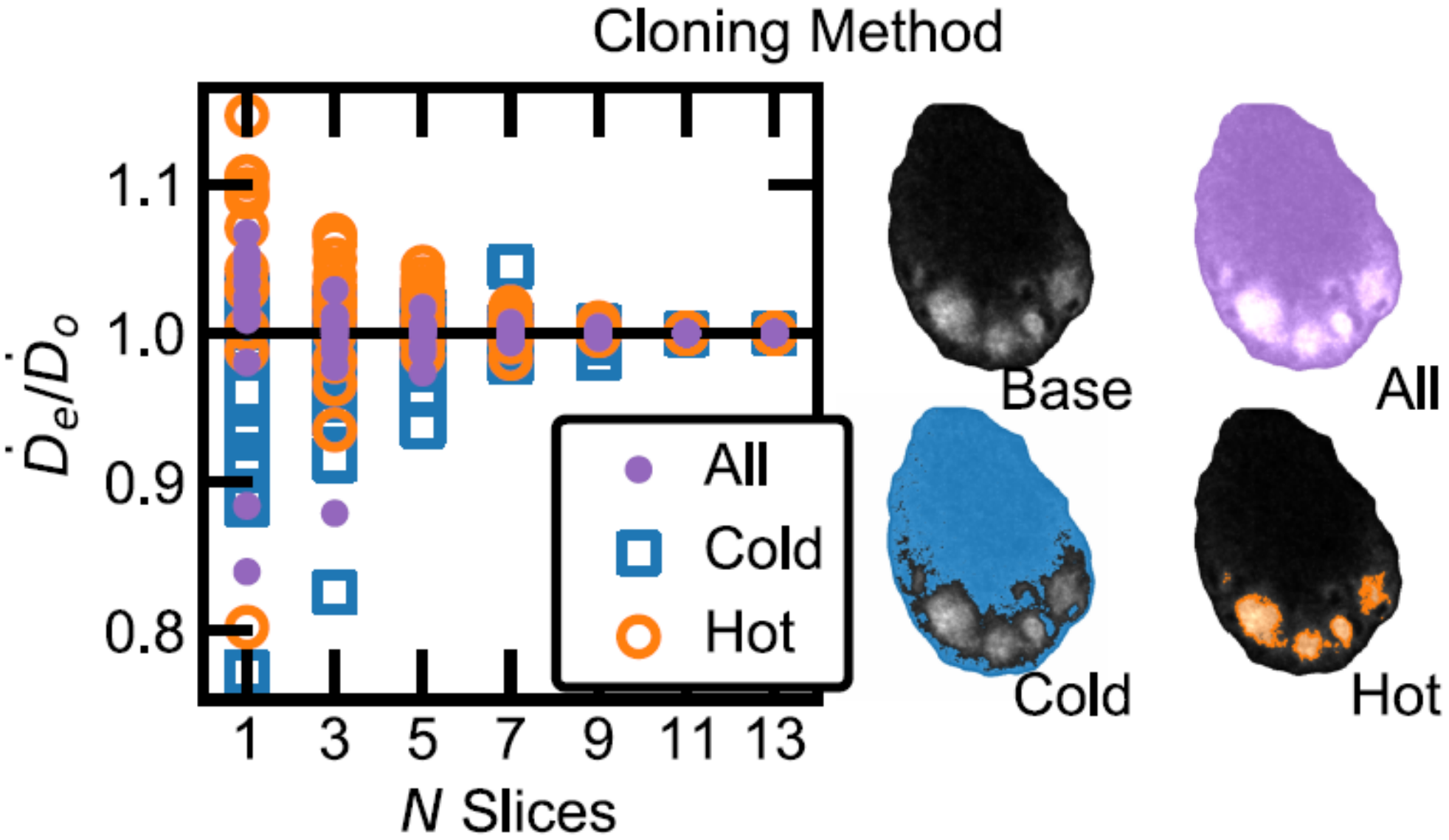
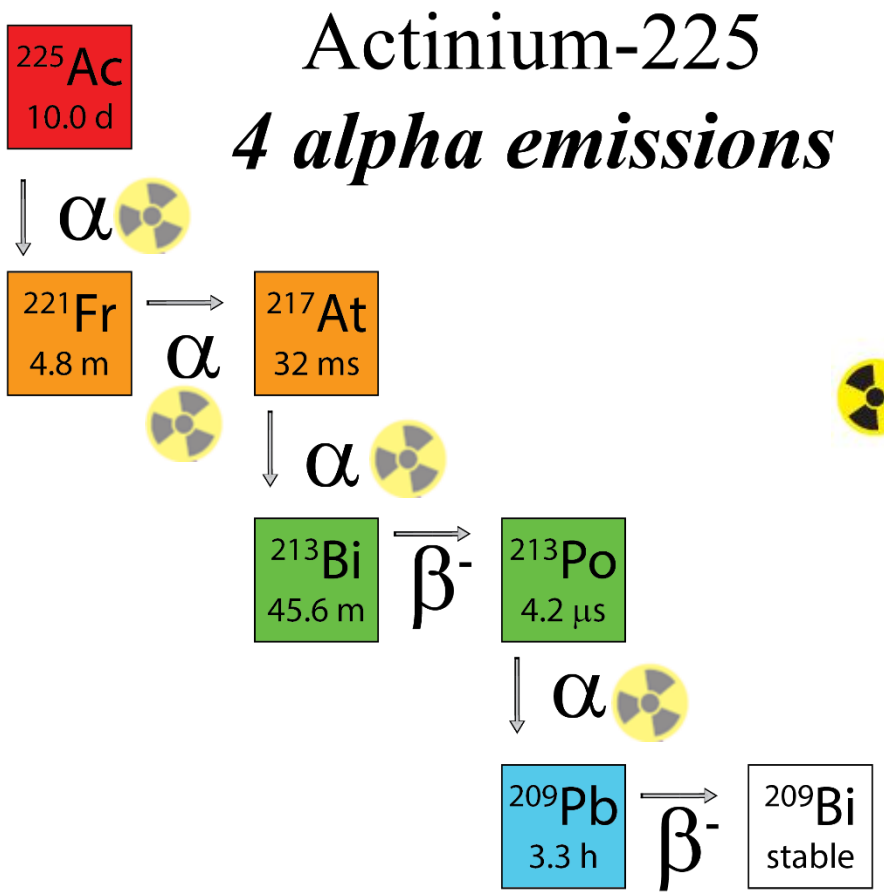
UCSF
University of California
San Francisco

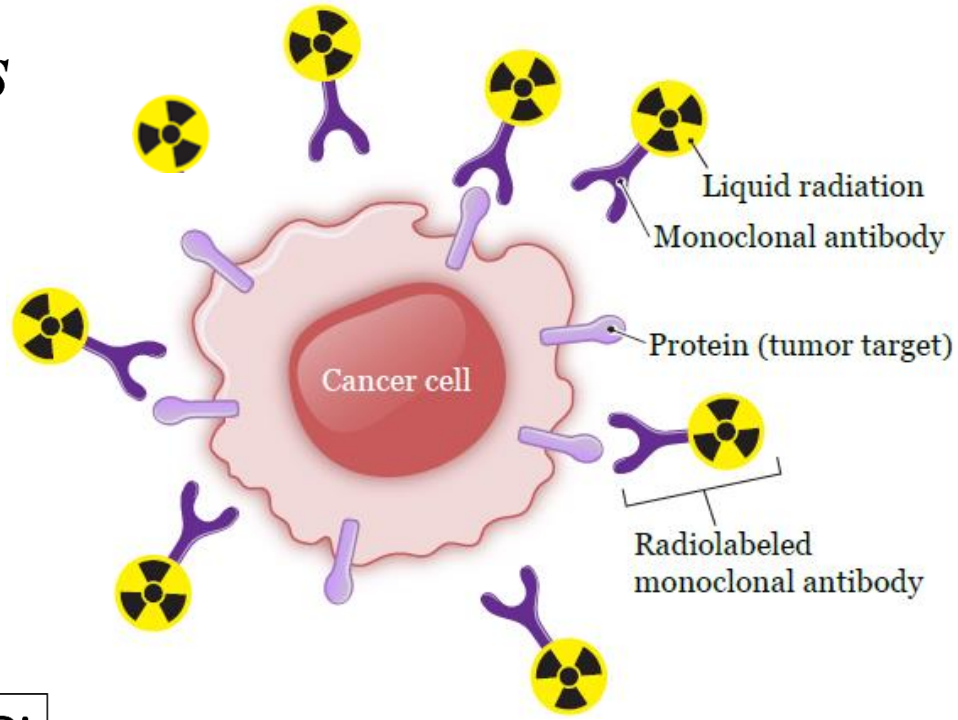
iQID ^{211}At Voxel-Based Dosimetry



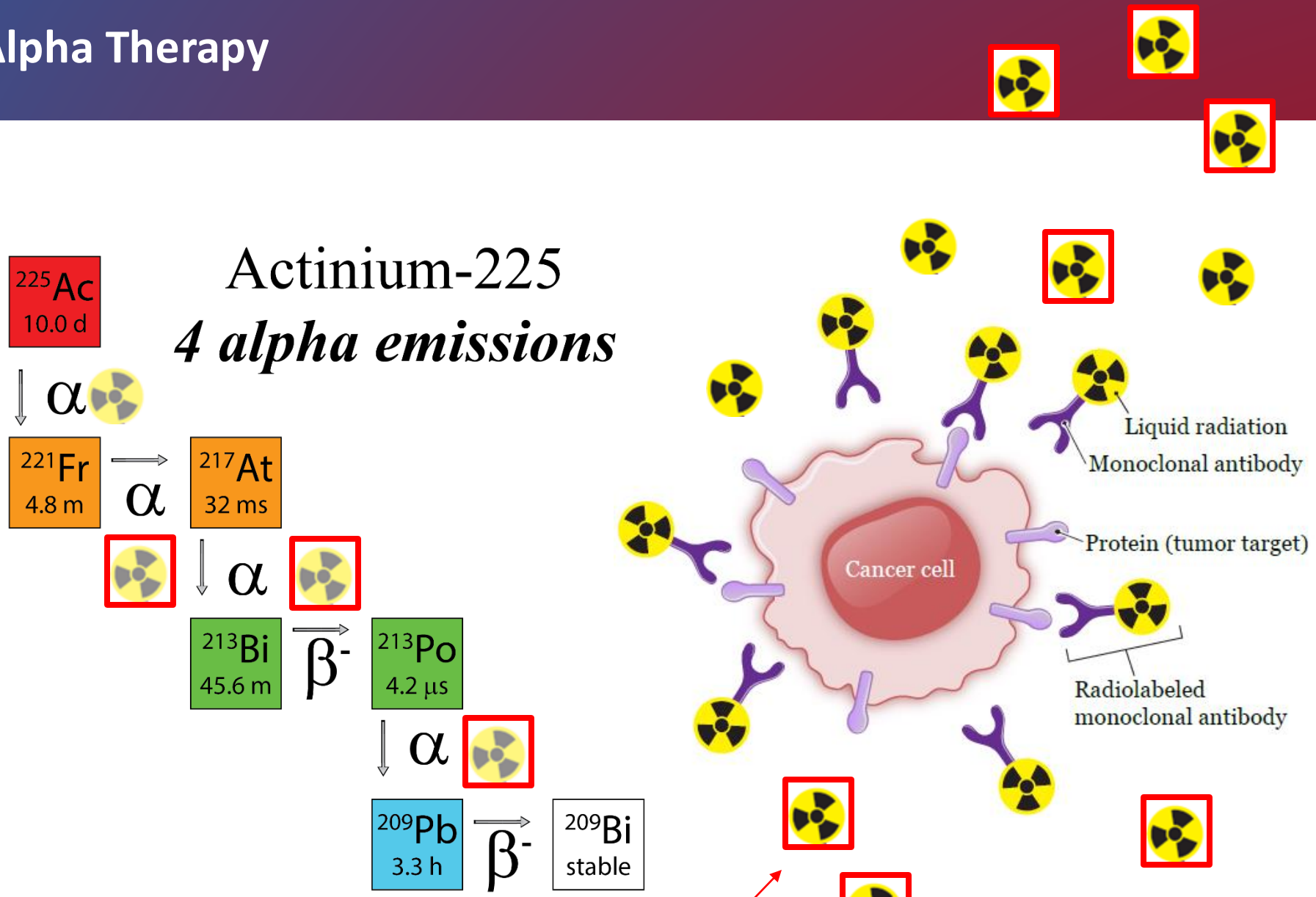
Parent/Daughter Isotope Imaging & Quantification

Targeted Alpha Therapy



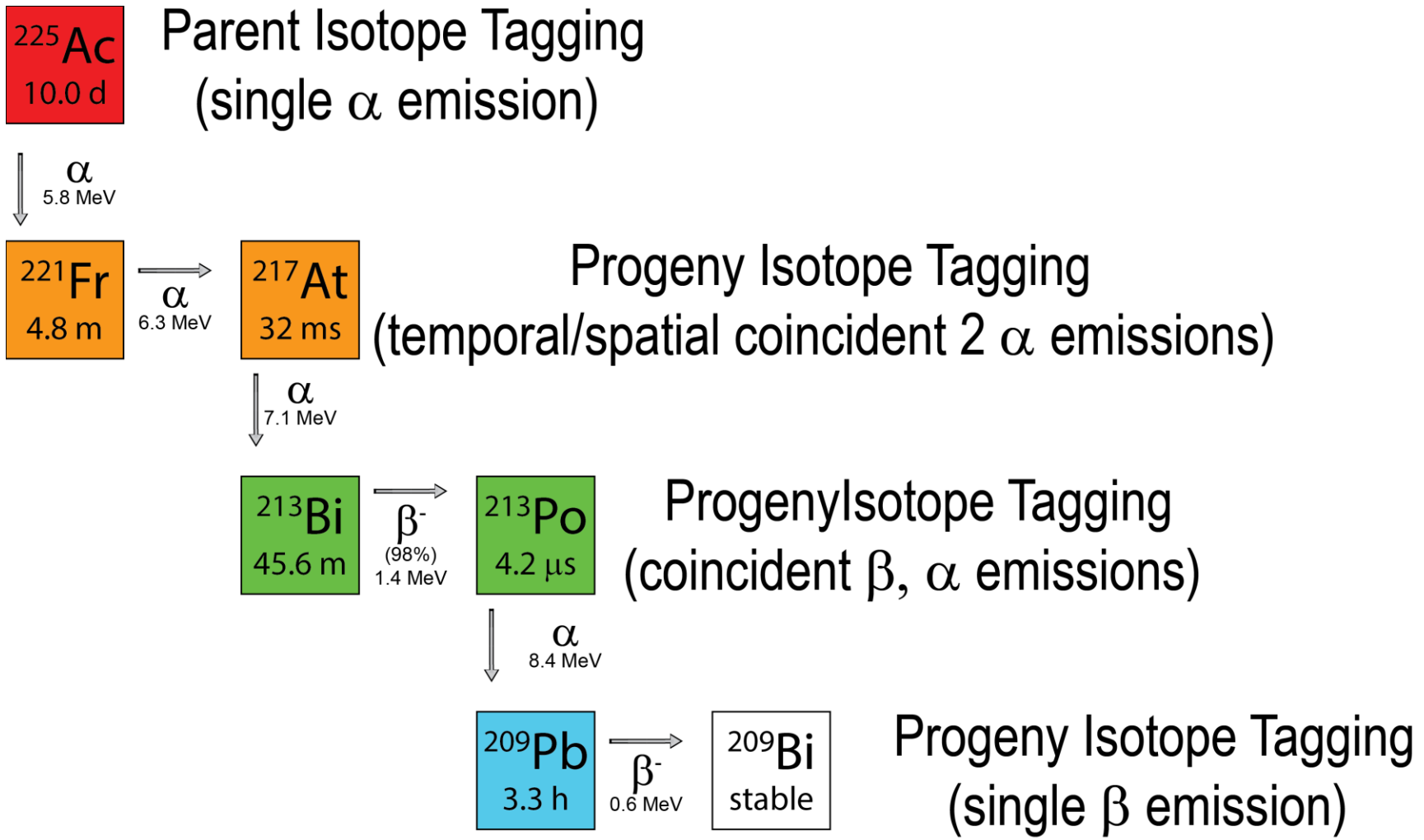


Targeted Alpha Therapy



Toxicity Concerns: Unbound parent and daughter isotopes that can relocate to normal organs

Ac-225 Decay Scheme



Quantitative SPECT/CT with Ac-225

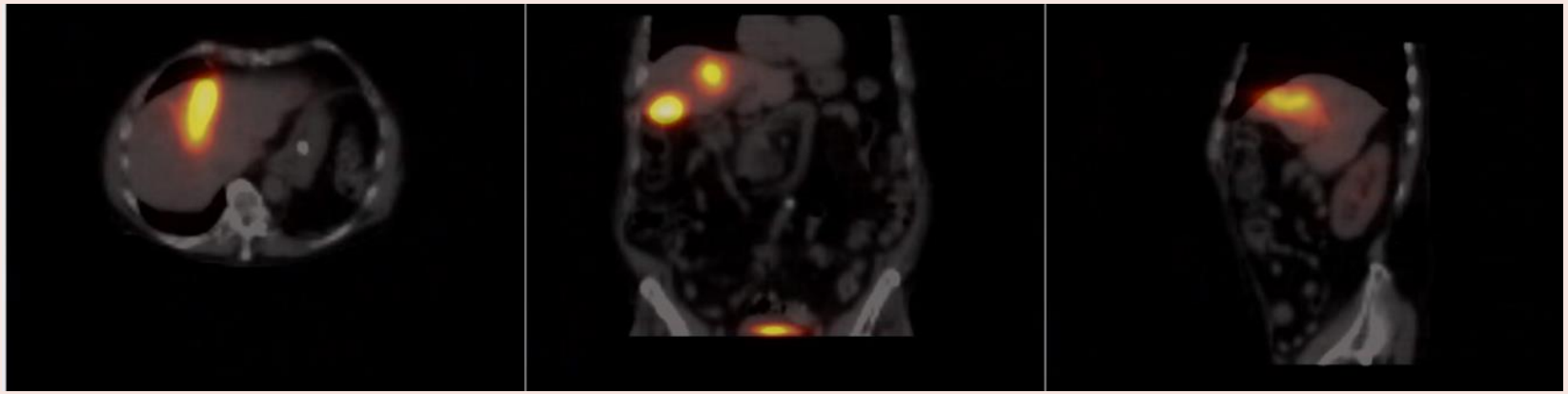
ACTION-1 dosimetry sub-study – Preliminary results *(Cycle 1, 4hrs)*

Rapid

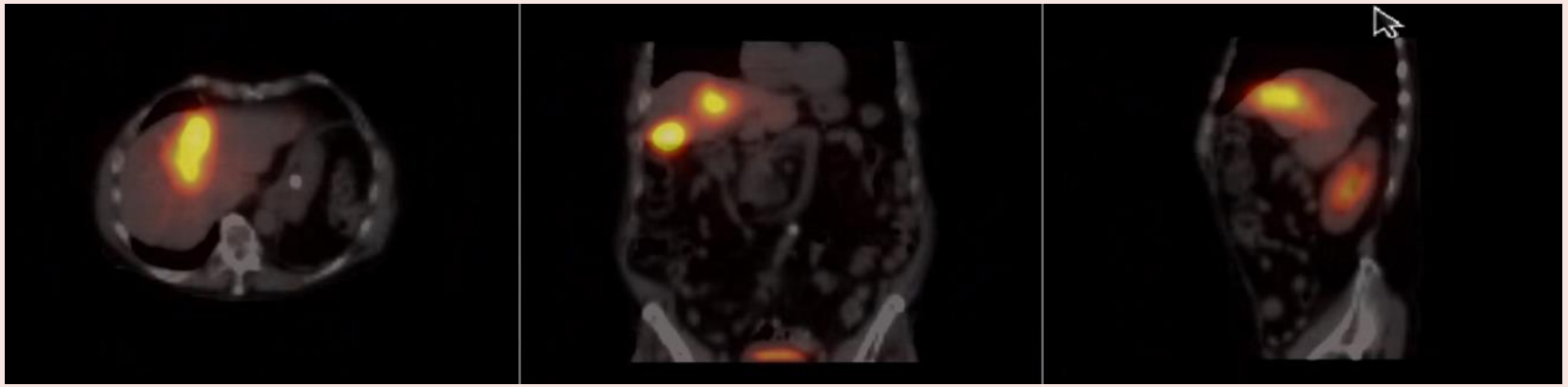
RayzeBio

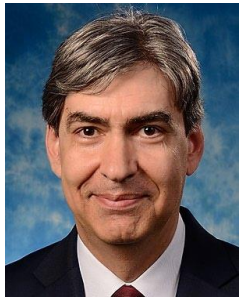
Cycle 1 – 4 hours post-infusion (Scale: max ~6 kBq/cc)

^{221}Fr



^{213}Bi





George Sgouros

Eric Frey

Presented at SNMMI 2023

ACTION-1 dosimetry sub-study – Preliminary results *(Cycle 1, 23hrs)*

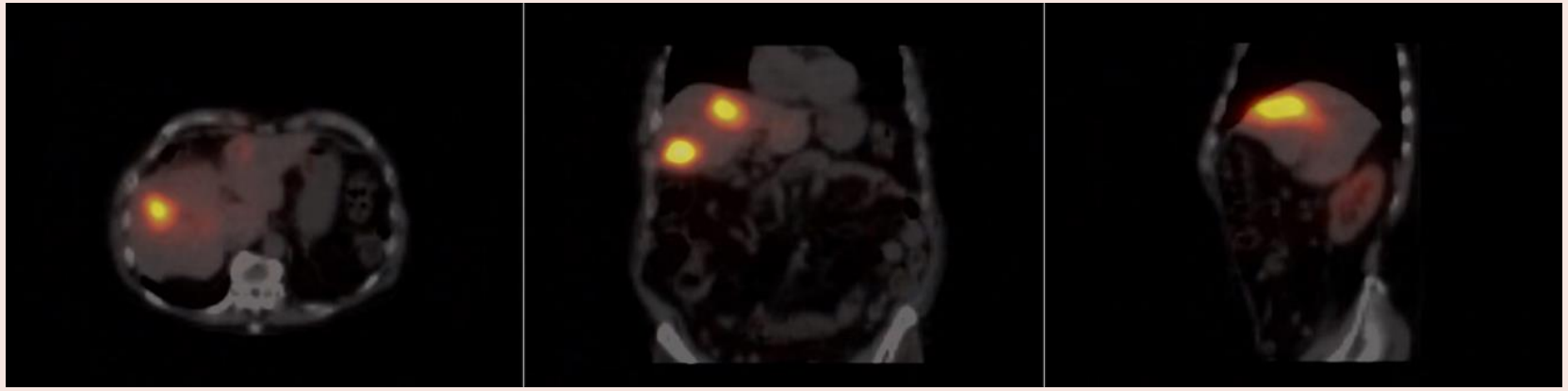
Rapid

RayzeBio

Cycle 1 – 23 hours post-infusion (Scale: max ~6 kBq/cc)

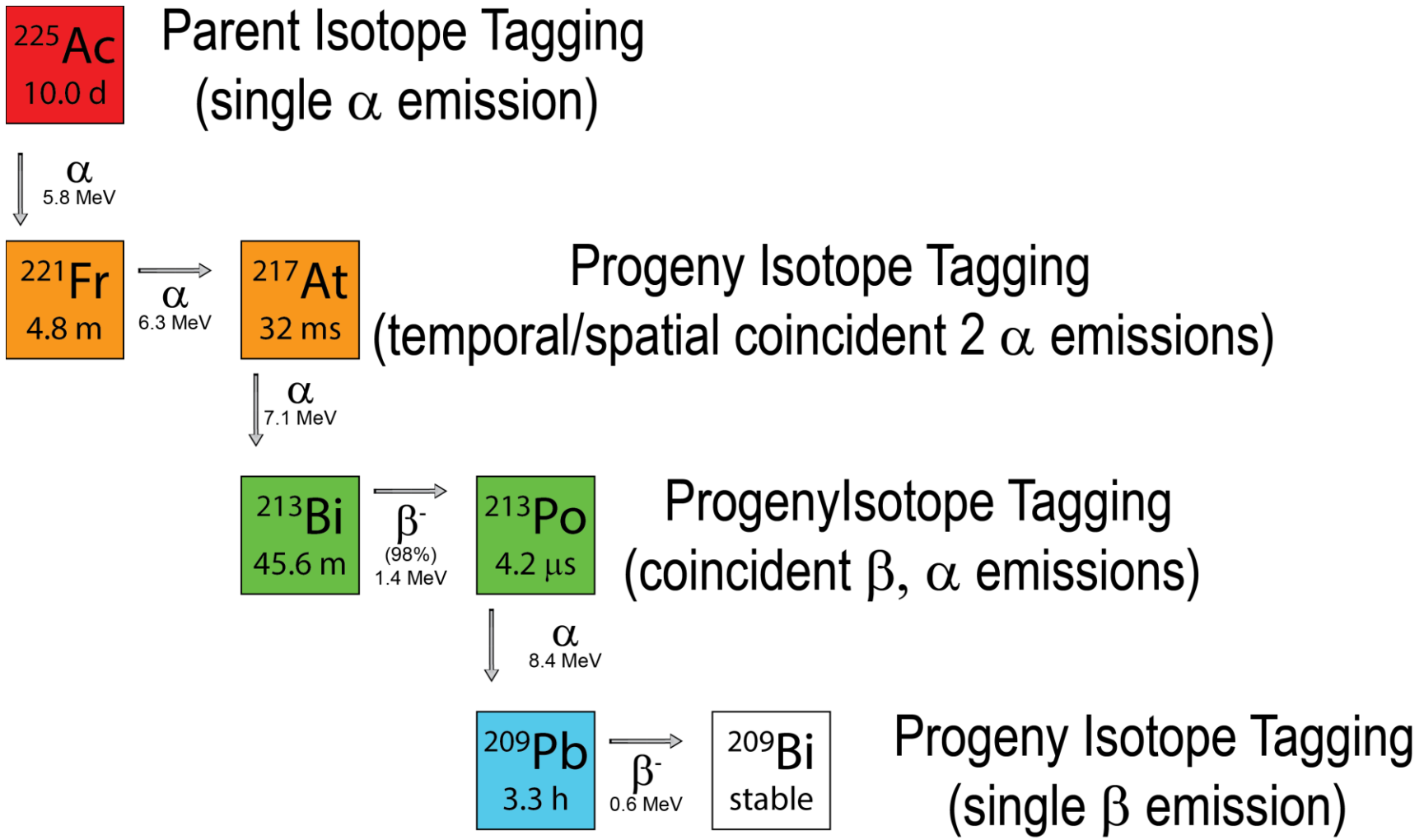
^{221}Fr

^{213}Bi

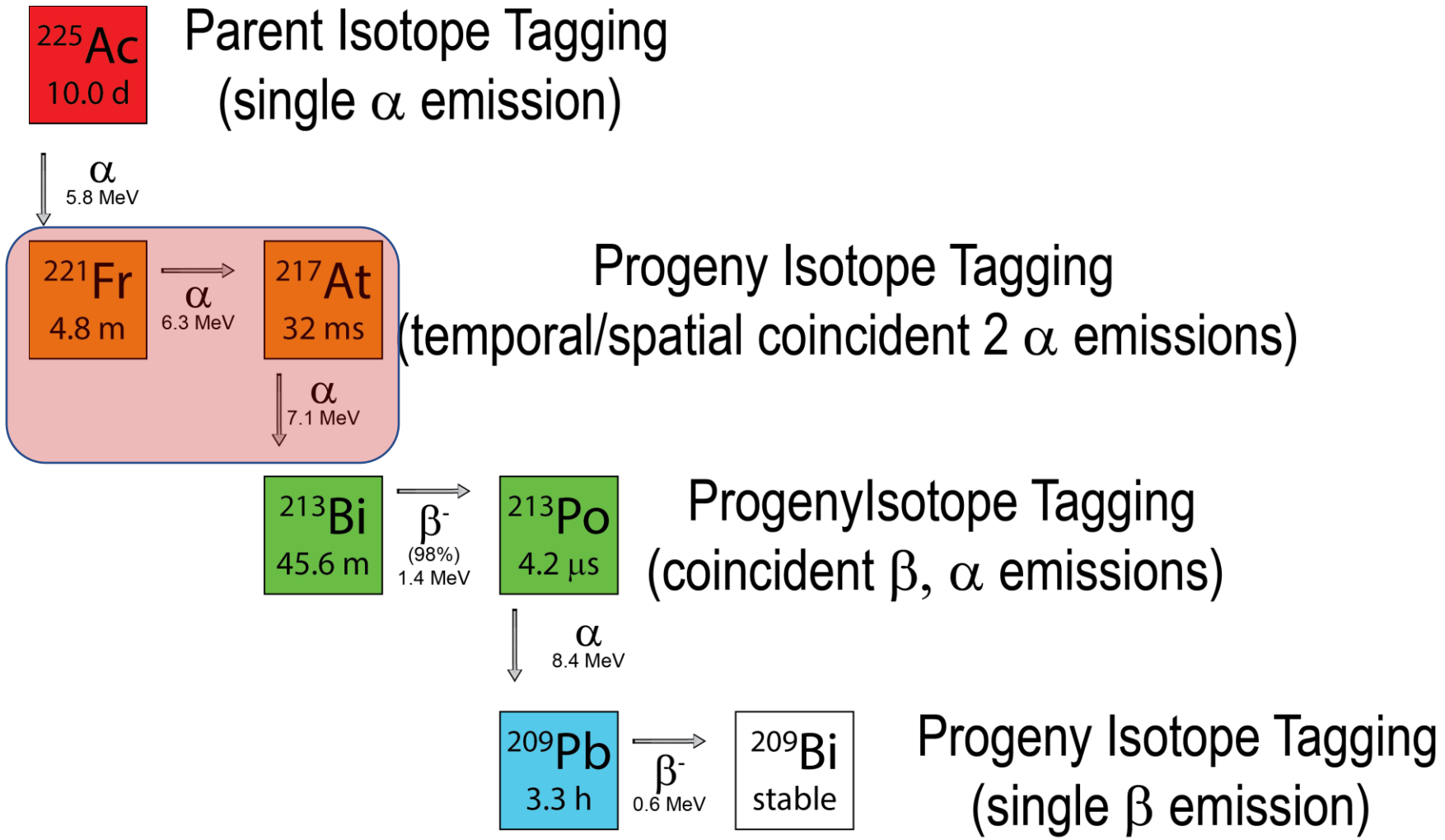


Presented at SNMMI 2023

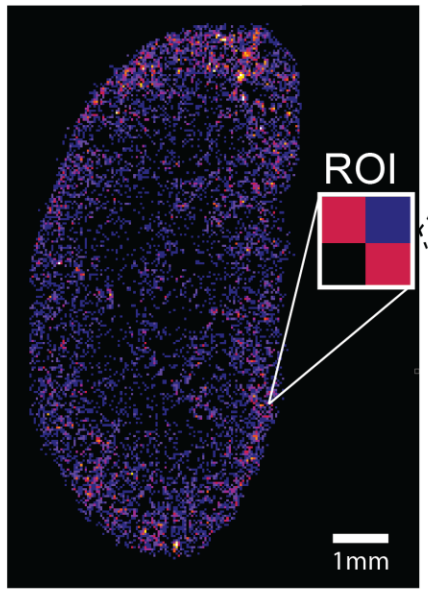
Ac-225 Decay Scheme



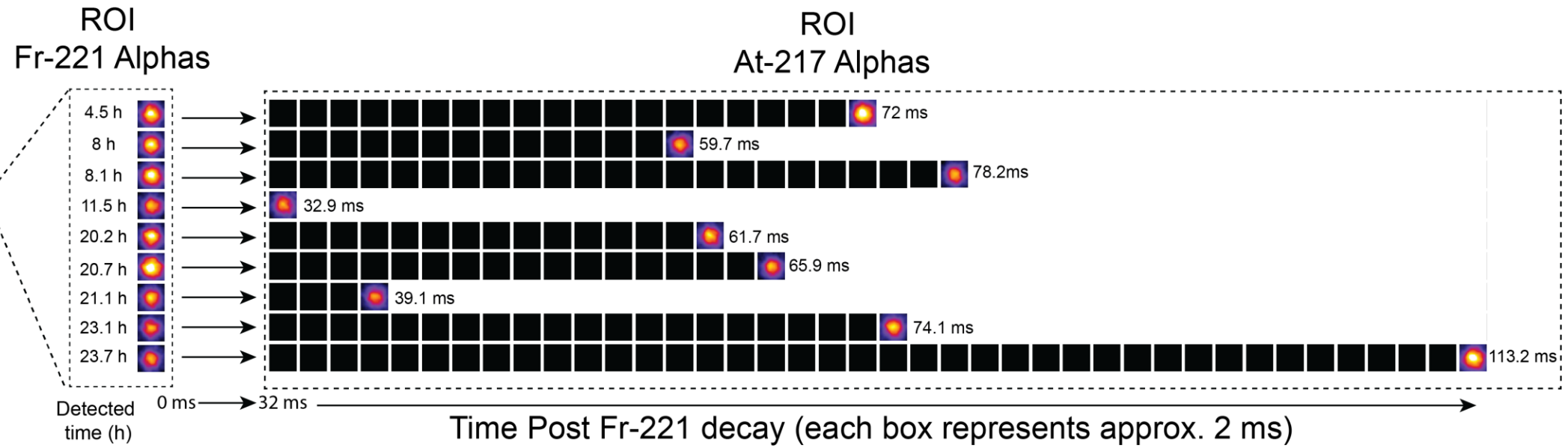
Ac-225 Decay Scheme

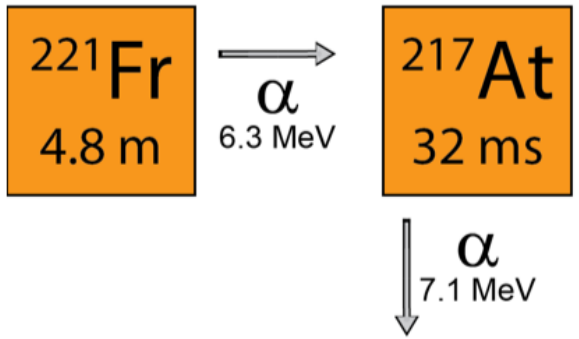


Ac-225 Parent/Daughter Discrimination [Unpublished]



Digital Autoradiograph (counts)



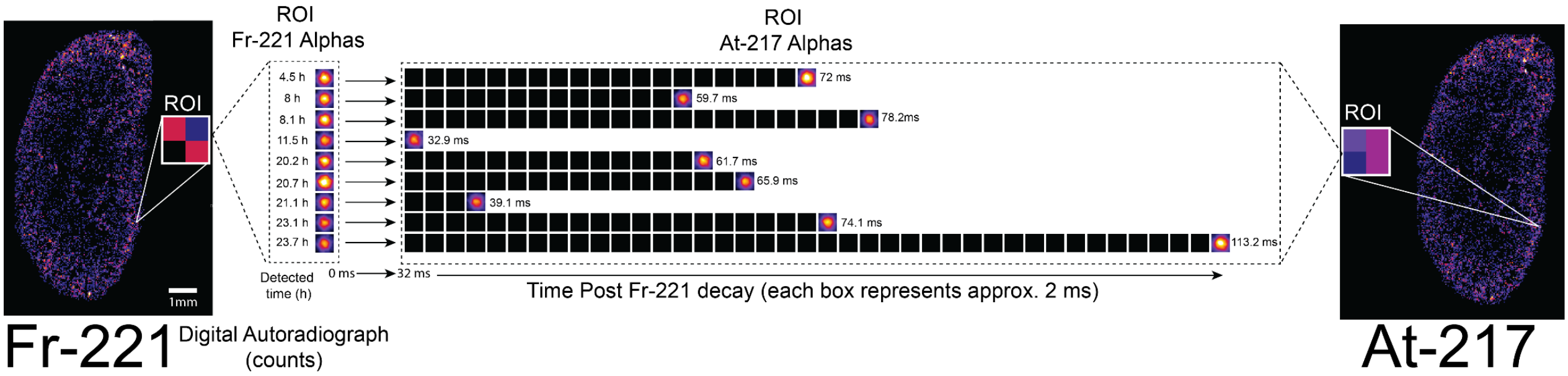


Weill Cornell Medicine

Memorial Sloan Kettering Cancer Center

In Collaboration with Sarah Cheal, PhD (Cornell), Sara Rinne, PhD (Cornell), Nicole Aguirre, MD (MSKCC)

Ac-225 Parent/Daughter Discrimination [Unpublished]



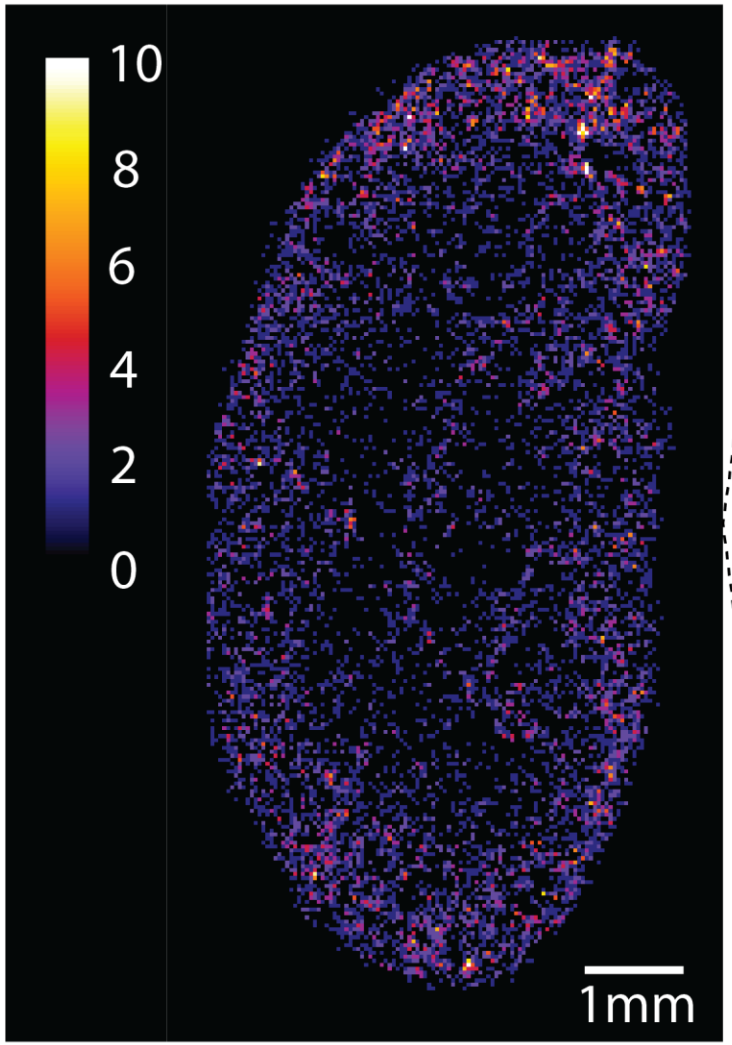
Weill Cornell Medicine

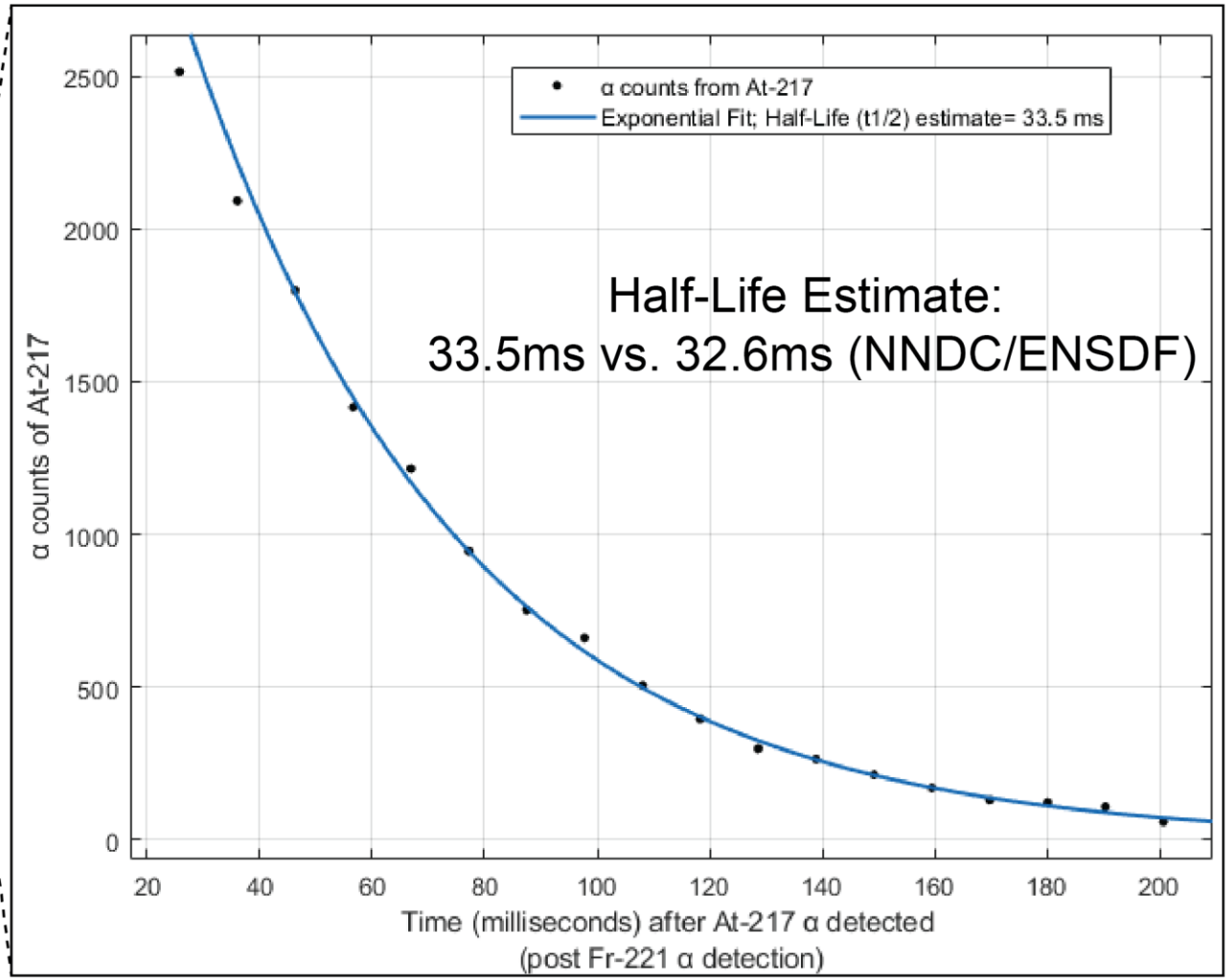
Memorial Sloan Kettering Cancer Center

In Collaboration with Sarah Cheal, PhD (Cornell), Sara Rinne, PhD (Cornell), Nicole Aguirre, MD (MSKCC)

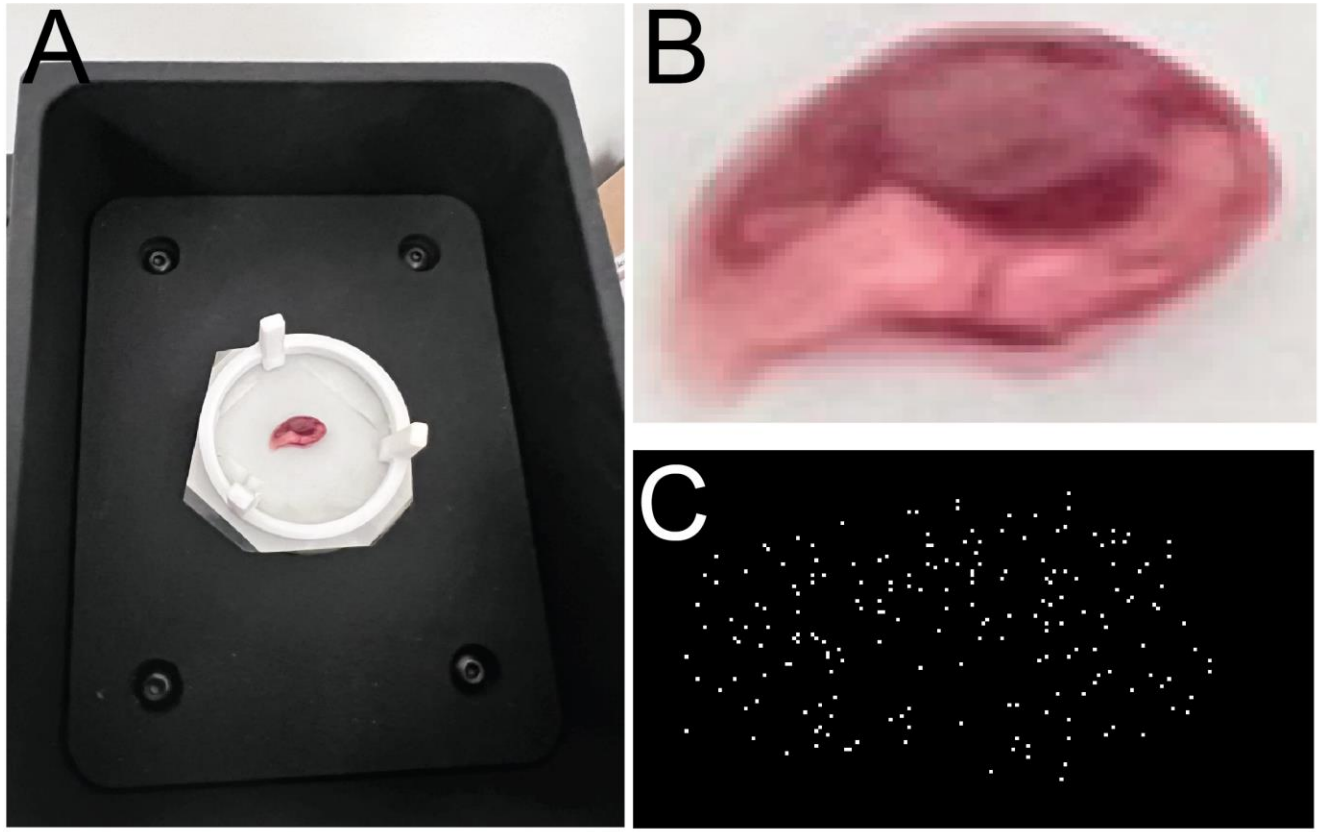
Ac-225 Parent/Daughter Discrimination [Unpublished]

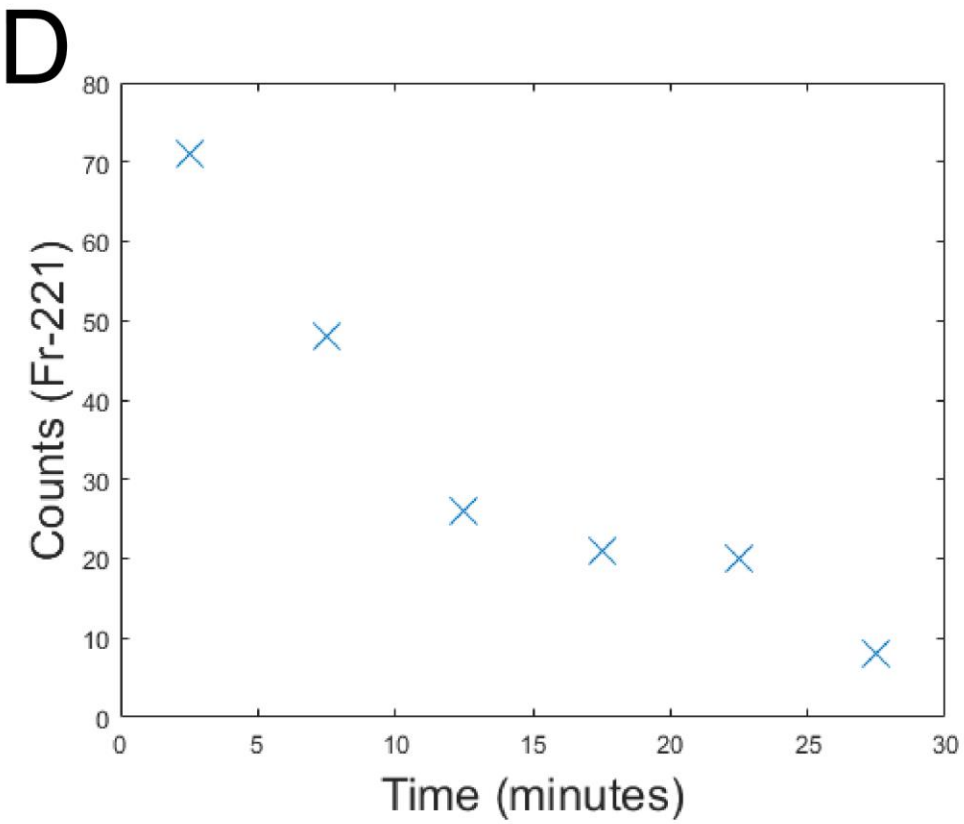
At-217 Digital Autoradiograph (counts)





Ac-225 Parent/Daughter Discrimination [Unpublished]





UPMC | HILLMAN CANCER CENTER

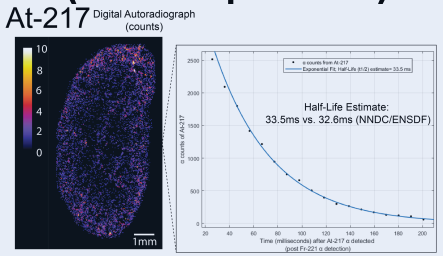
University of Pittsburgh

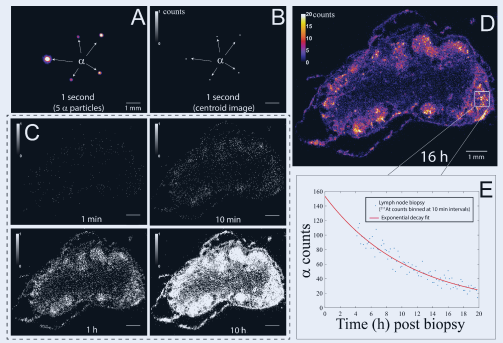
In collaboration with Anders Josefsson, Ph.D. & Jessie Nedrow, Ph.D

Summary/Big Picture

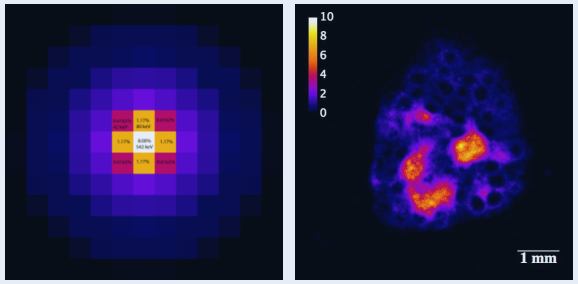
Quantitative Digital Autoradiography

Generate Parent/Daughter Autoradiographs (as required)

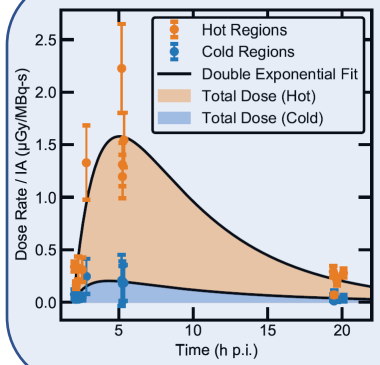




Decay Correct and Convert Autoradiograph to Activity Concentration (Bq/g)

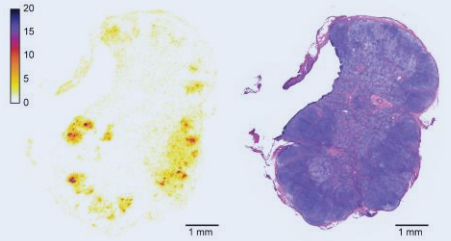


Generate Dose-Rate Images



Repeat for Multiple Timepoints and Parent/Daughter Isotopes (as required)

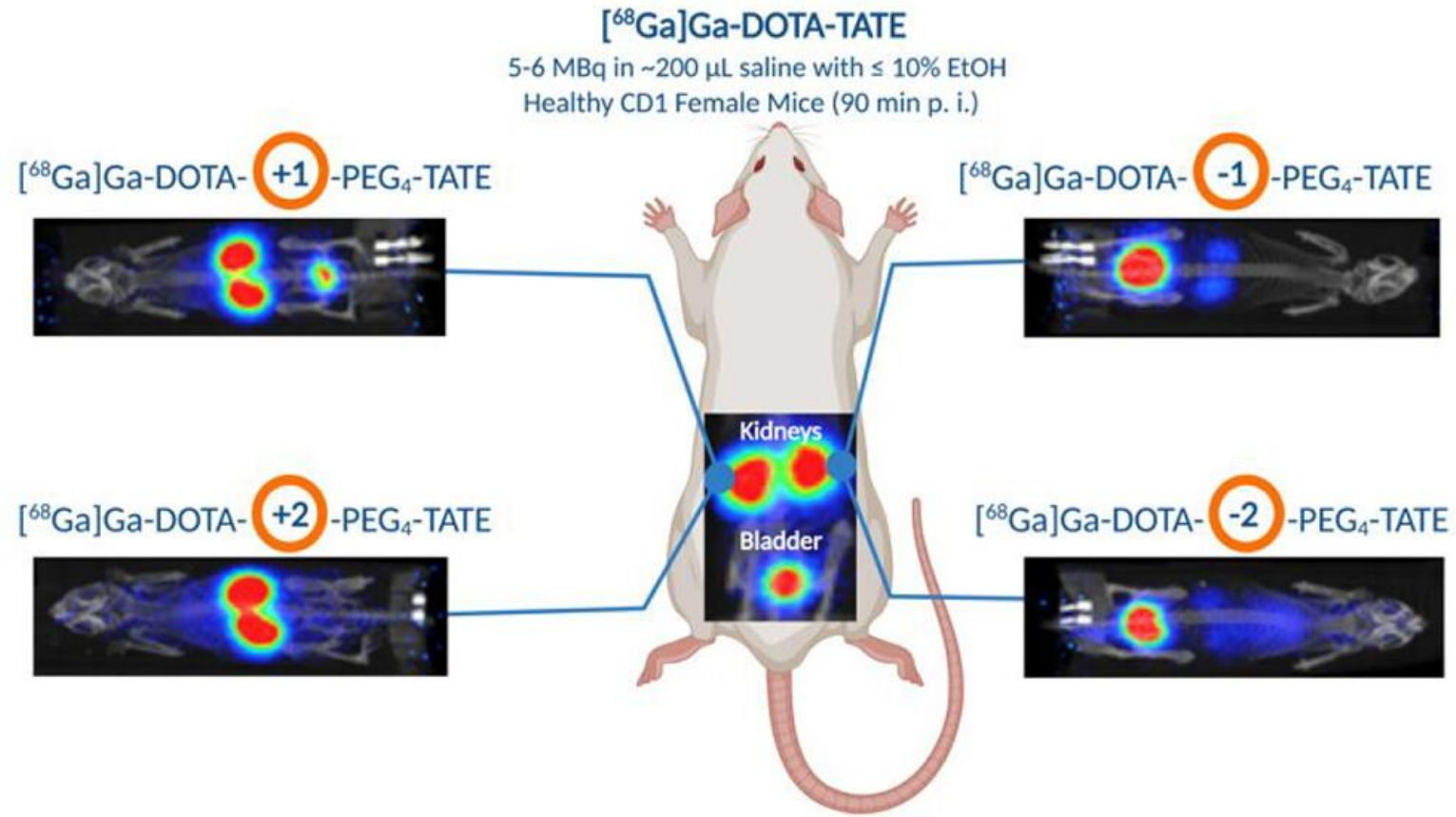
Combine With Histology, Other Modalities



Assessing Co-Injection of Alpha and Beta Emitters

DOTA-TATE and a series of derivatives with different net charges (+2, +1, 0, −1, −2)

- Negatively charged peptides had substantially decreased kidney uptake, but in this instantiation the tumor uptake was also impaired.



A Systematic Investigation into the Influence of Net Charge on the Biological Distribution of Radiometalated Peptides Using [^{68}Ga]Ga-DOTA-TATE Derivatives

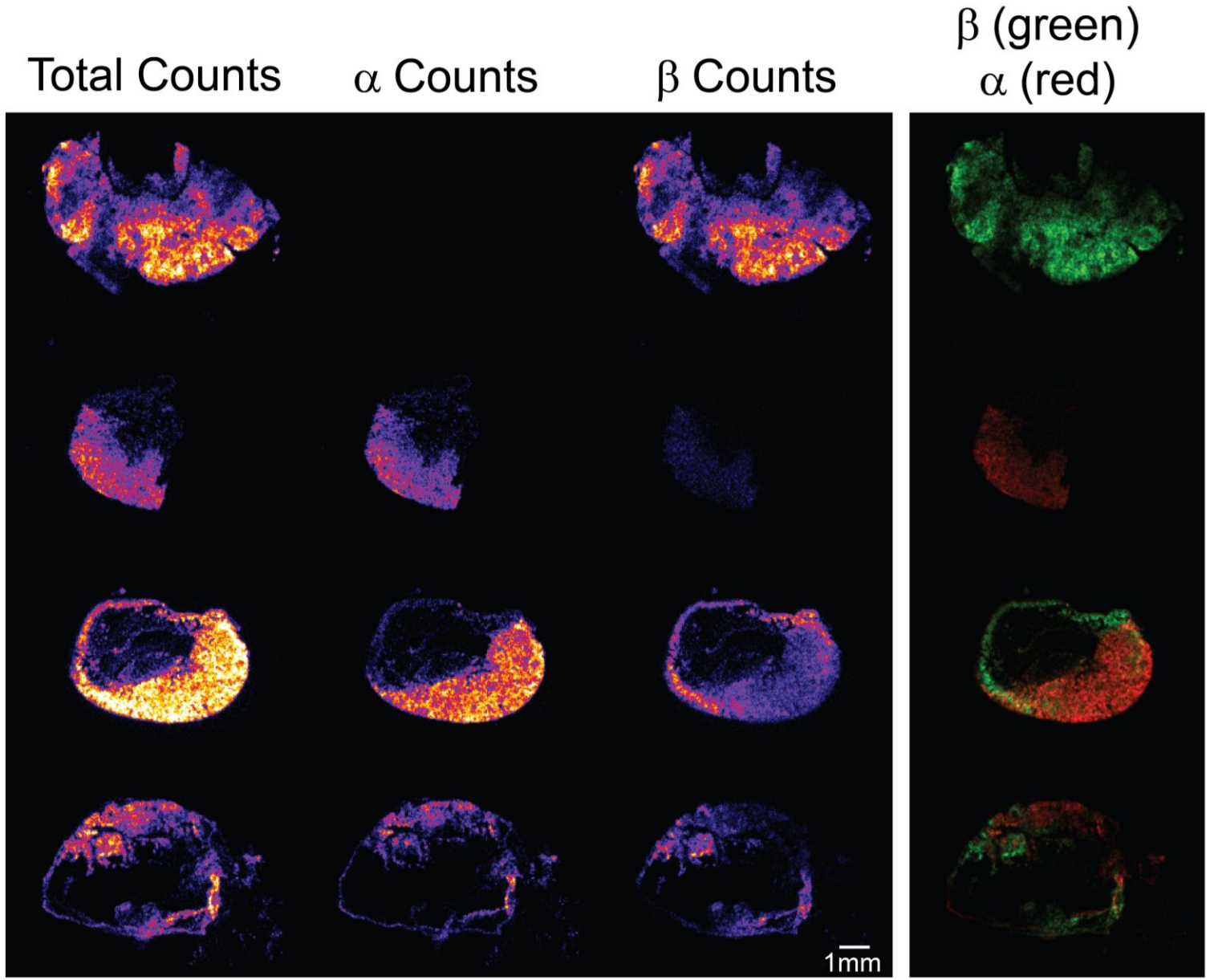
Shvan J. Raheem, Akam K. Salih, Moralba Dominguez Garcia, Jessica C. Sharpe, Behzad M. Toosi, and Eric W. Price*

https://doi.org/10.1021/acs.bioconjchem.3c00007

Combination α & β Radiopharmaceutical Therapy

Alpha Emitter	Companion Beta-Emitting Therapeutic
Ac-225	Lu-177

Co-Injection of Ac-225 and Lu-177 [Unpublished]



Injected activities:

- 50 μCi (1.85 MBq) Lu-177
- 1 μCi (37 kBq) Ac-225

Weill Cornell Medicine
Radiology

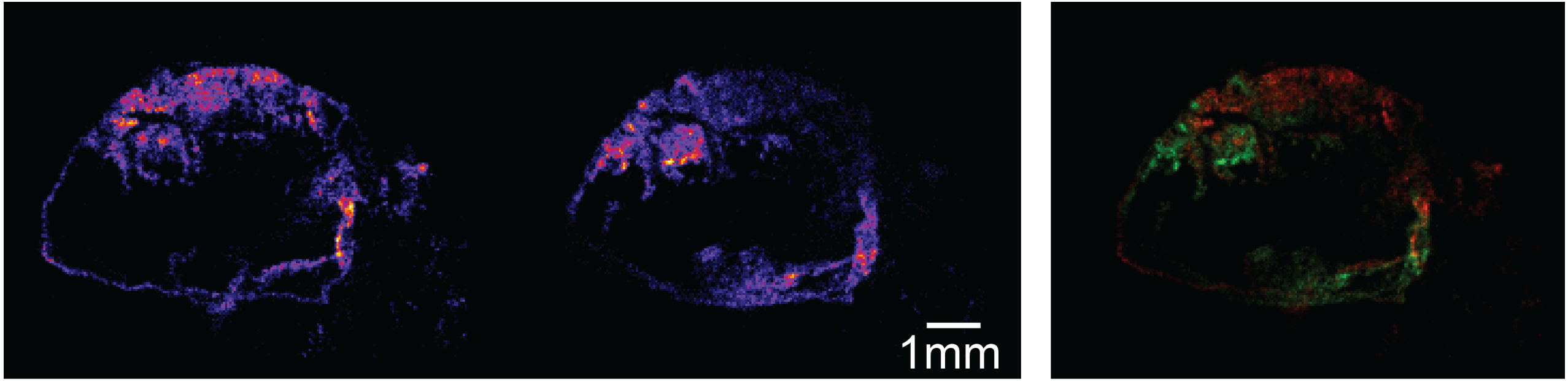
Sarah M. Cheal Laboratory: Sara Rinne, Nicole Aguirre, Brett Vaughn, Darren Veach, Hong-fen Guo, and Hong Xu, and Sarah M Cheal

Co-Injection of Ac-225 and Lu-177 [Unpublished]

α Counts

β Counts

β (green)
α (red)

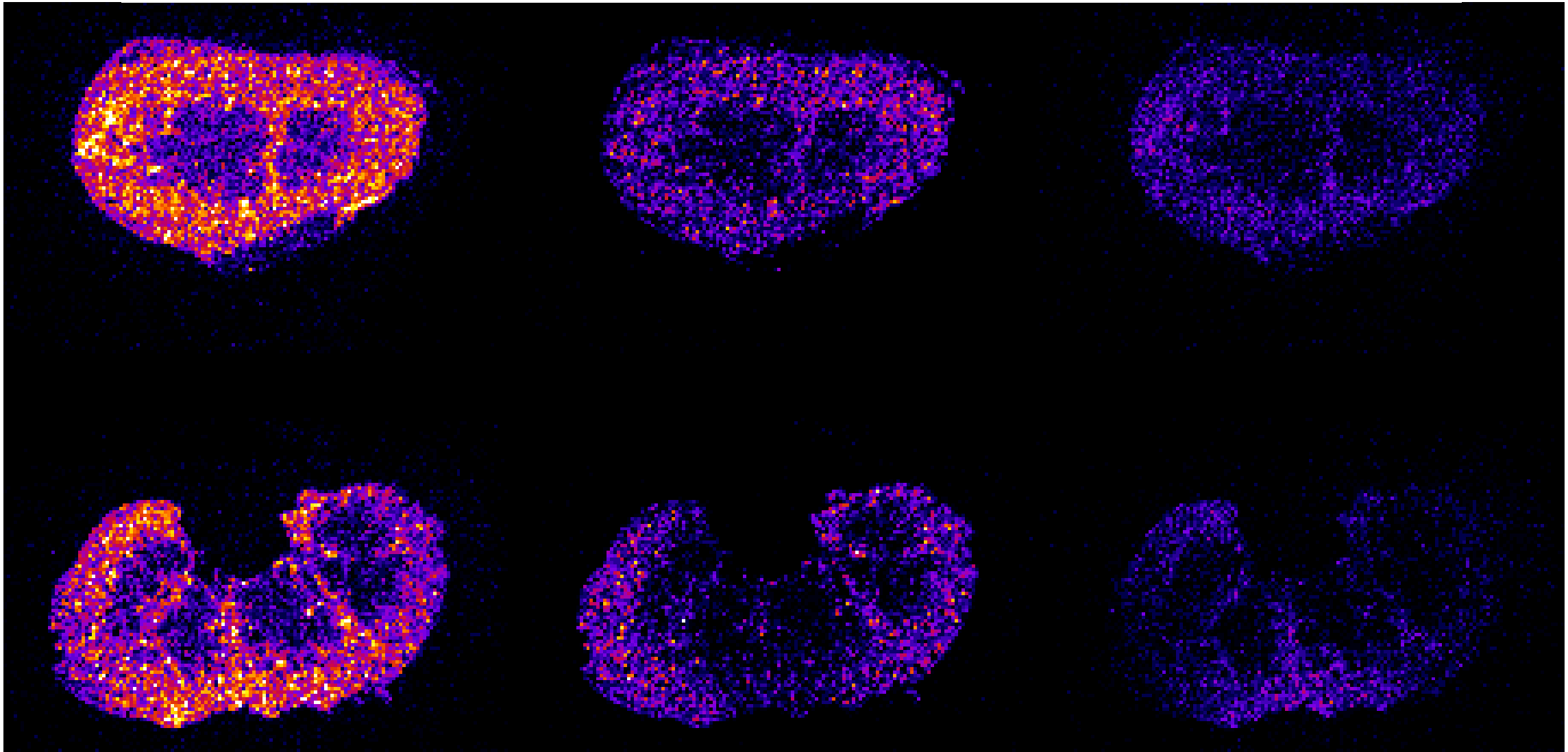


Weill Cornell Medicine
Radiology

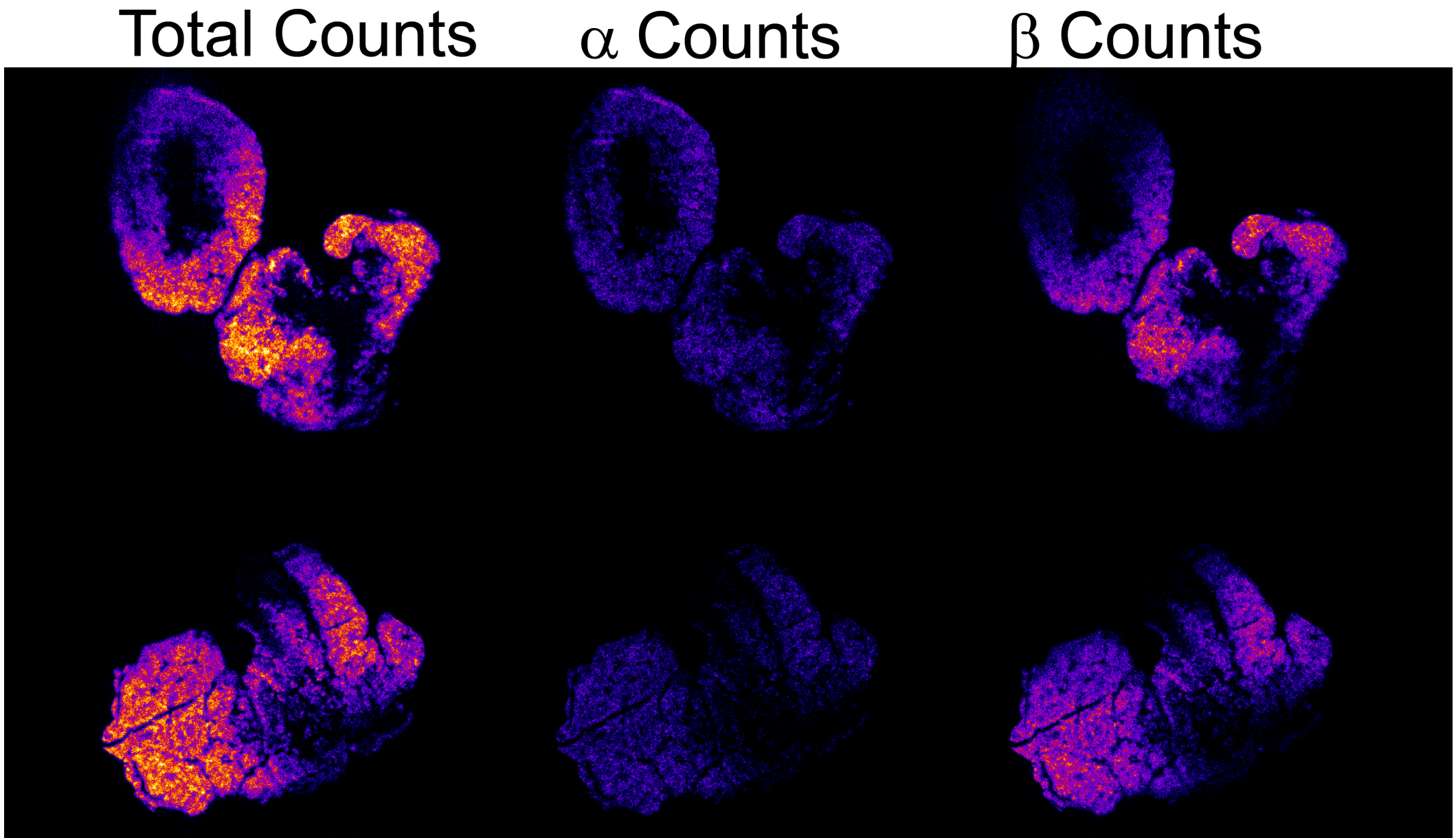
Sarah M. Cheal Laboratory: Sara Rinne, Nicole Aguirre, Brett Vaughn, Darren Veach, Hong-fen Guo, and Hong Xu, and Sarah M Cheal

Co-Injection of Ac-225 and Lu-177 [Unpublished]

Total Counts α Counts β Counts

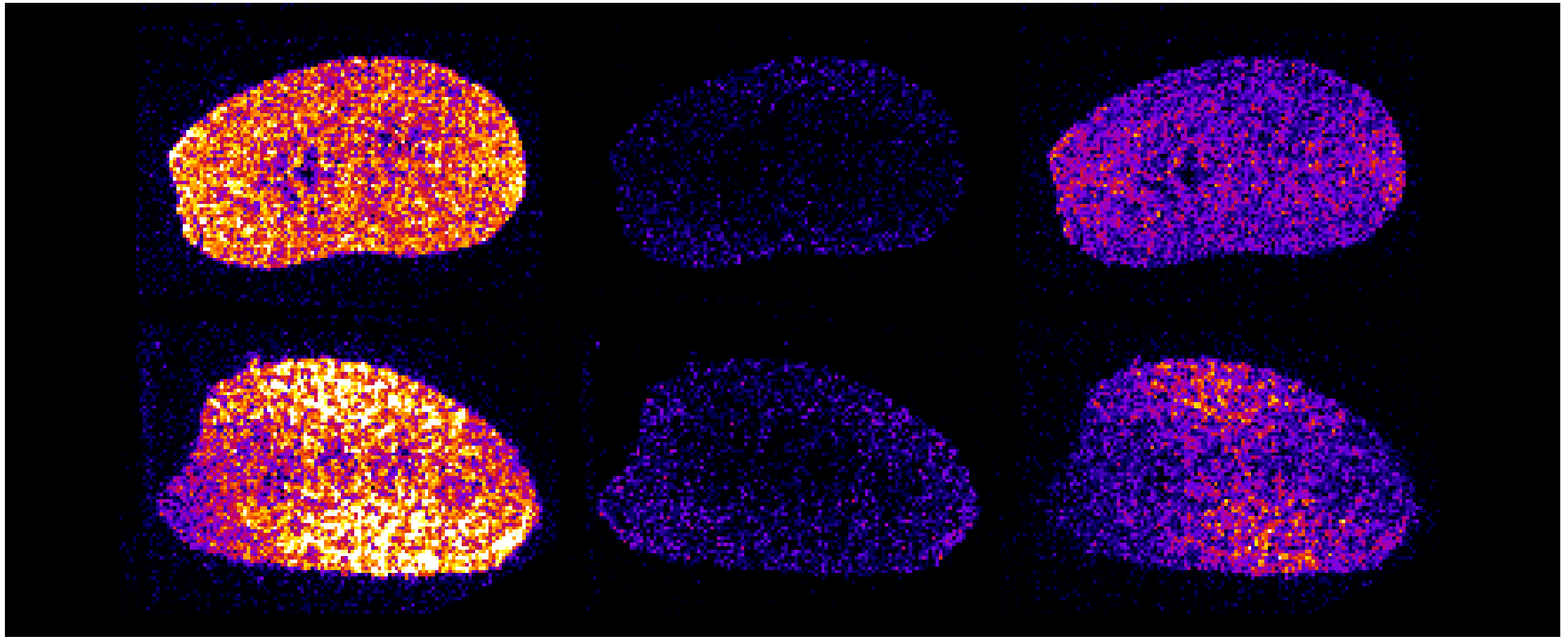


Co-Injection of Ac-225 and Lu-177 [Unpublished]



Co-Injection of Ac-225 and Lu-177 [Unpublished]

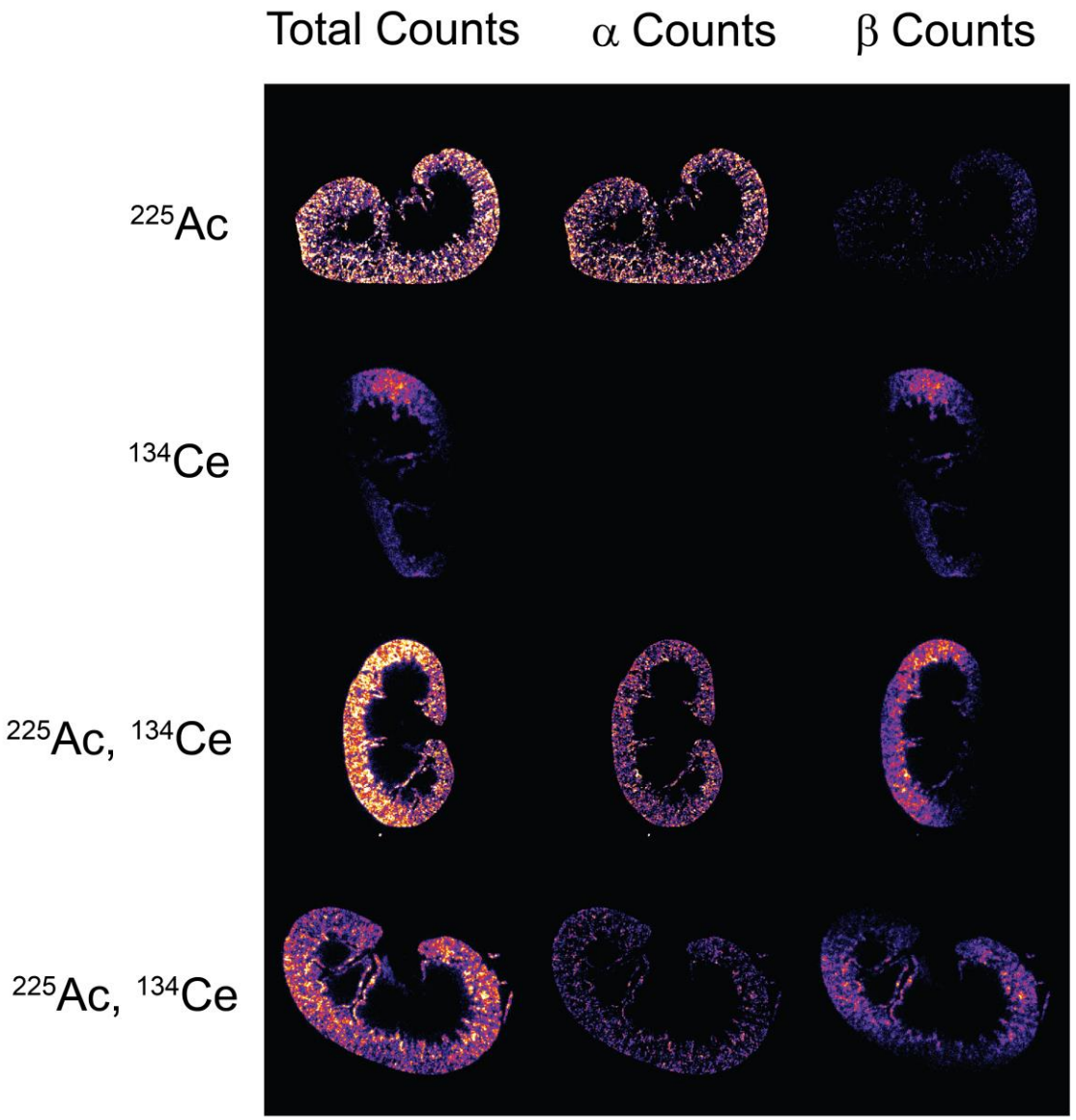
Total Counts α Counts β Counts



Companion SPECT, PET Isotopes

Alpha Emitter	Companion PET or SPECT Diagnostic Isotope
Ac-225	Ce-134 (La-134), In-111
Th-227	Ce-134 (La-134)
At-211	I-124, I-123
Pb-212 (Bi-212 α)	Pb-203

Co-Injection of Ac-225 and Ce-134 [Unpublished]



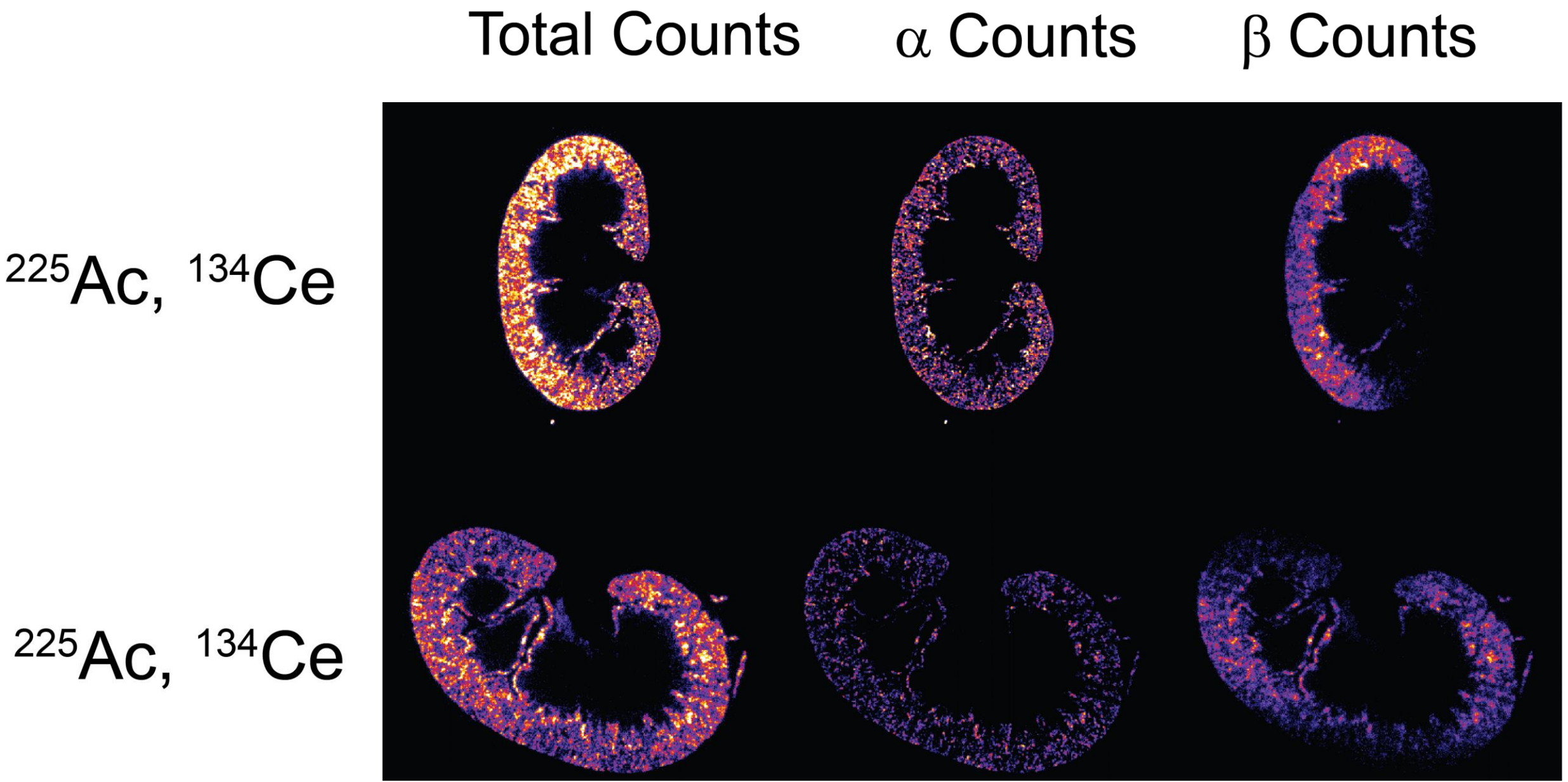
Injected activities:

- 50 μCi (1.85 MBq) Ce-134
- 1 μCi (37 kBq) Ac-225
- 6h post injection

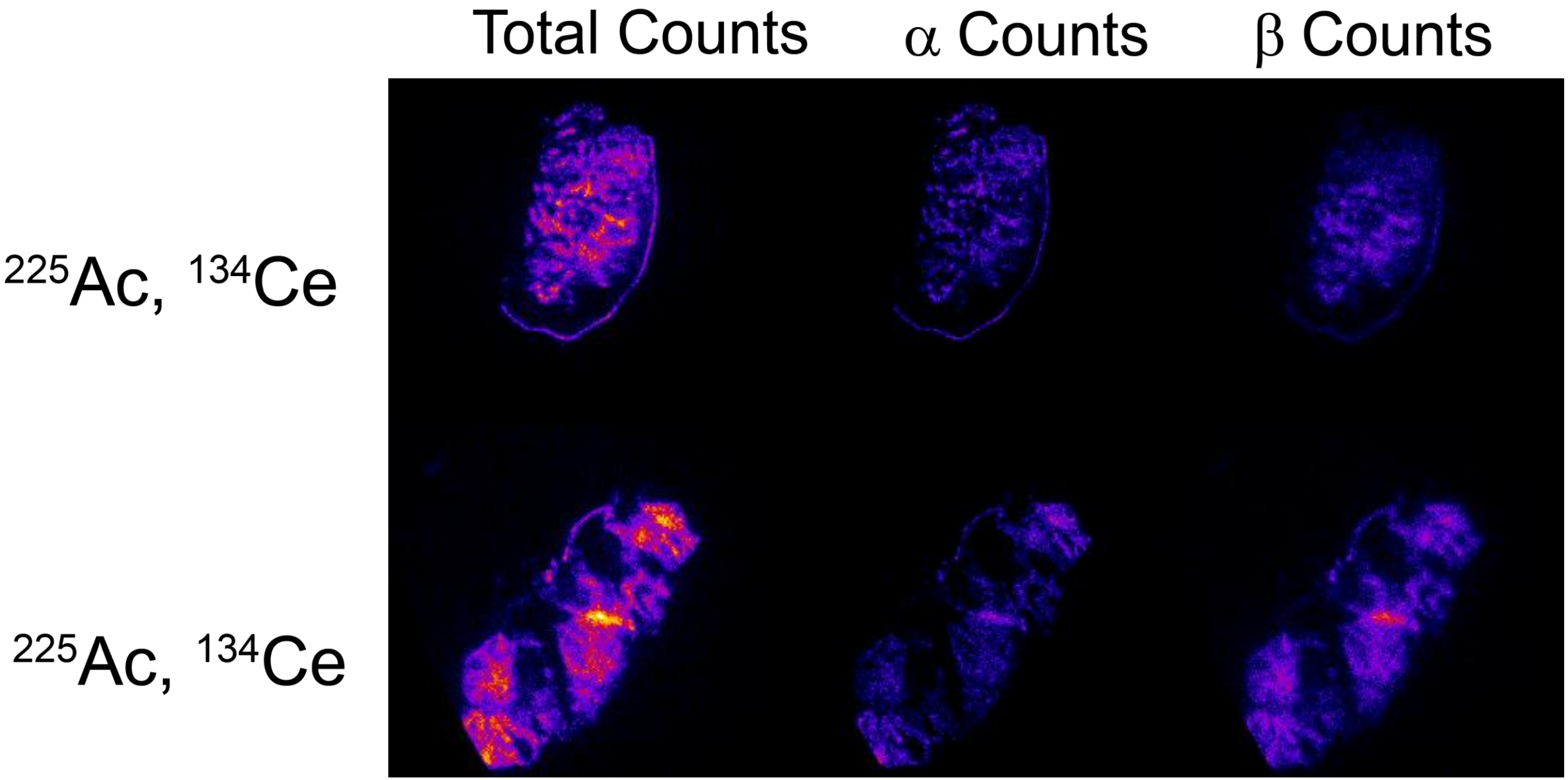
Weill Cornell Medicine
Radiology

James Kelly Laboratory: Anja Wacker, Sara Rinne, Alejandro Amor-Coarasa (Ratio Therapeutics), Sara Cheal, and James Kelly

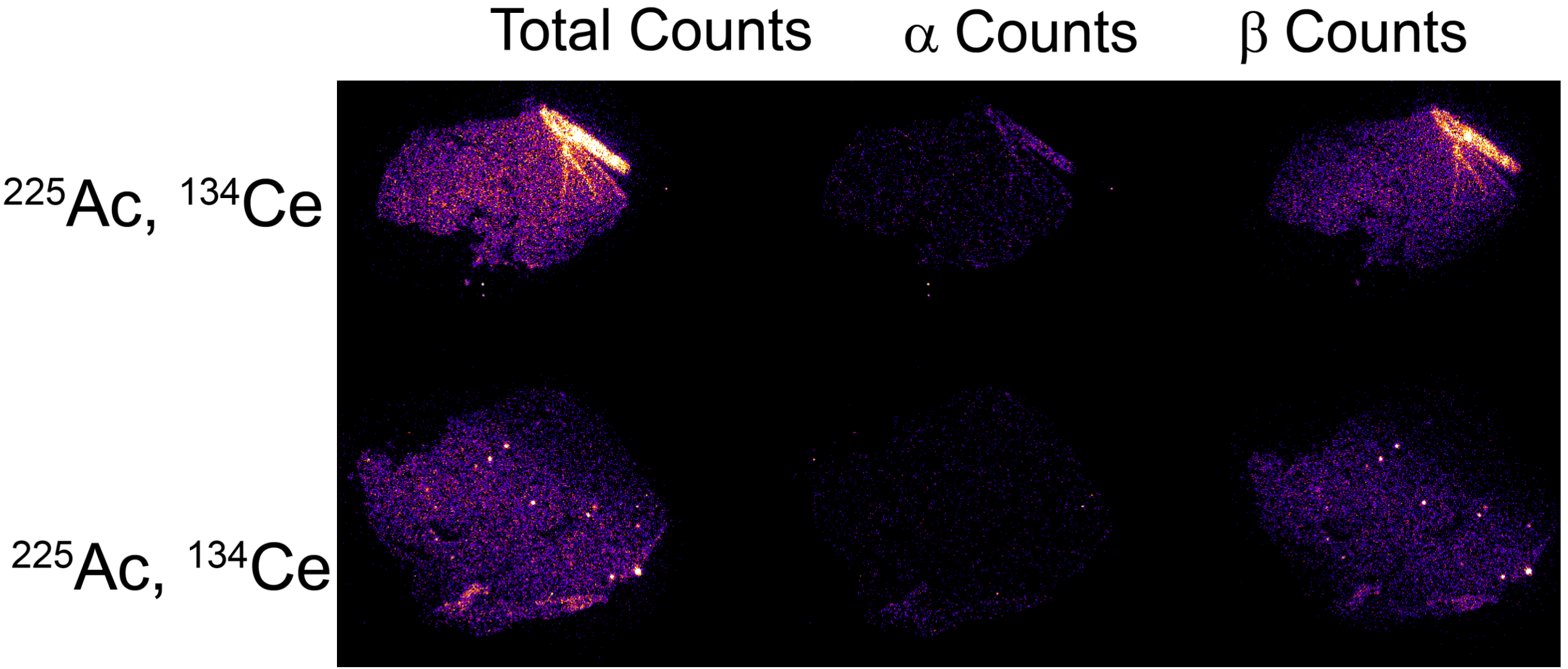
Co-Injection of Ac-225 and Ce-134 [Unpublished]



Co-Injection of Ac-225 and Ce-134 [Unpublished]



Co-Injection of Ac-225 and Ce-134 [Unpublished]



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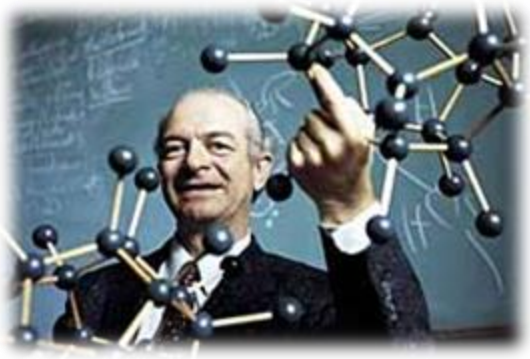

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