TEXAS A&M UNIVERSITY
Cyclotron Institute

Advancing Research in Texas through Experiments in Medical Isotope Science

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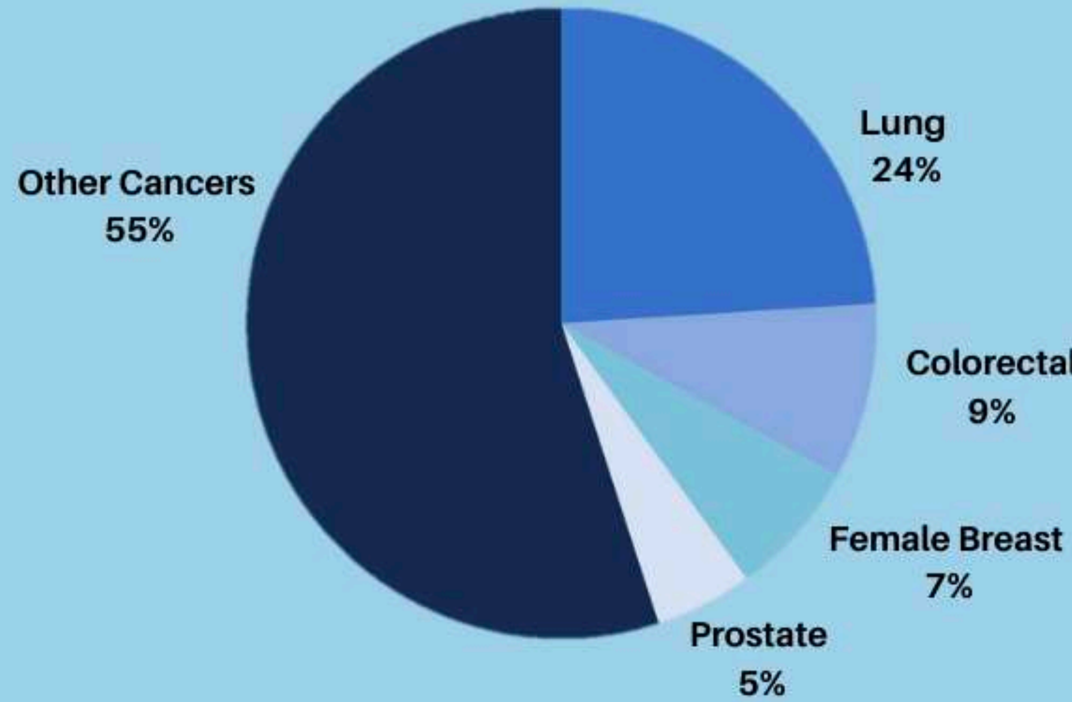
Texas A&M University

Texas A&M Cyclotron Institute and

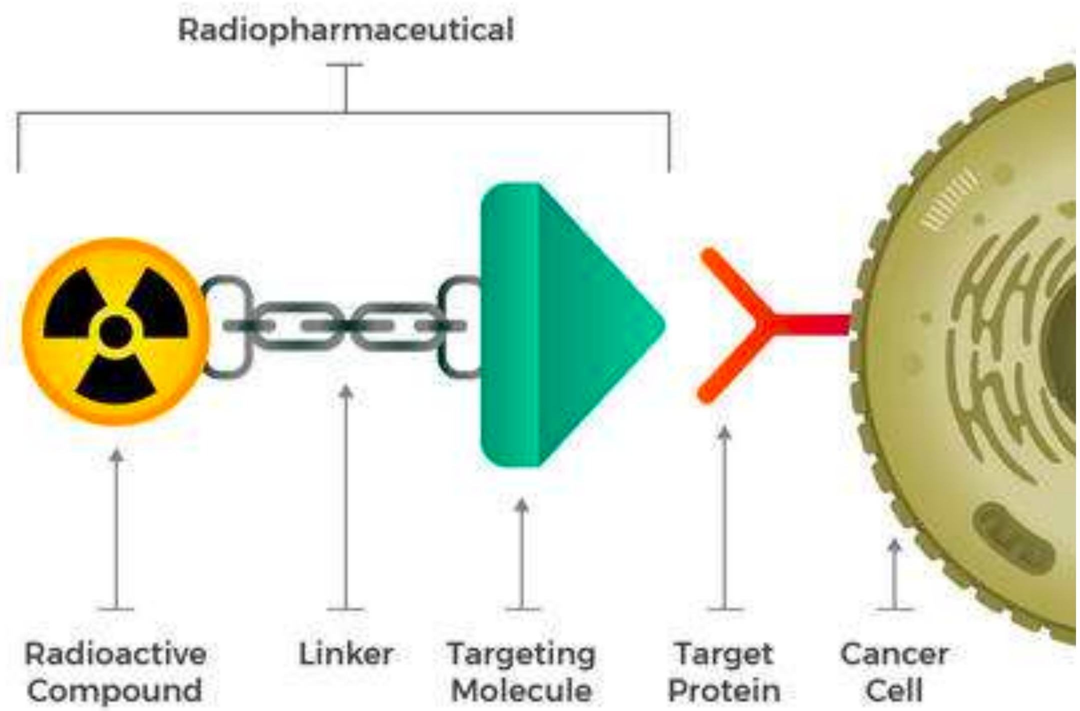
Nuclear Science and Engineering Center

Lung, prostate, female breast, and colorectal cancers accounted for almost half of all cancer deaths in 2017



Annual Report to the Nation 2020
seer.cancer.gov

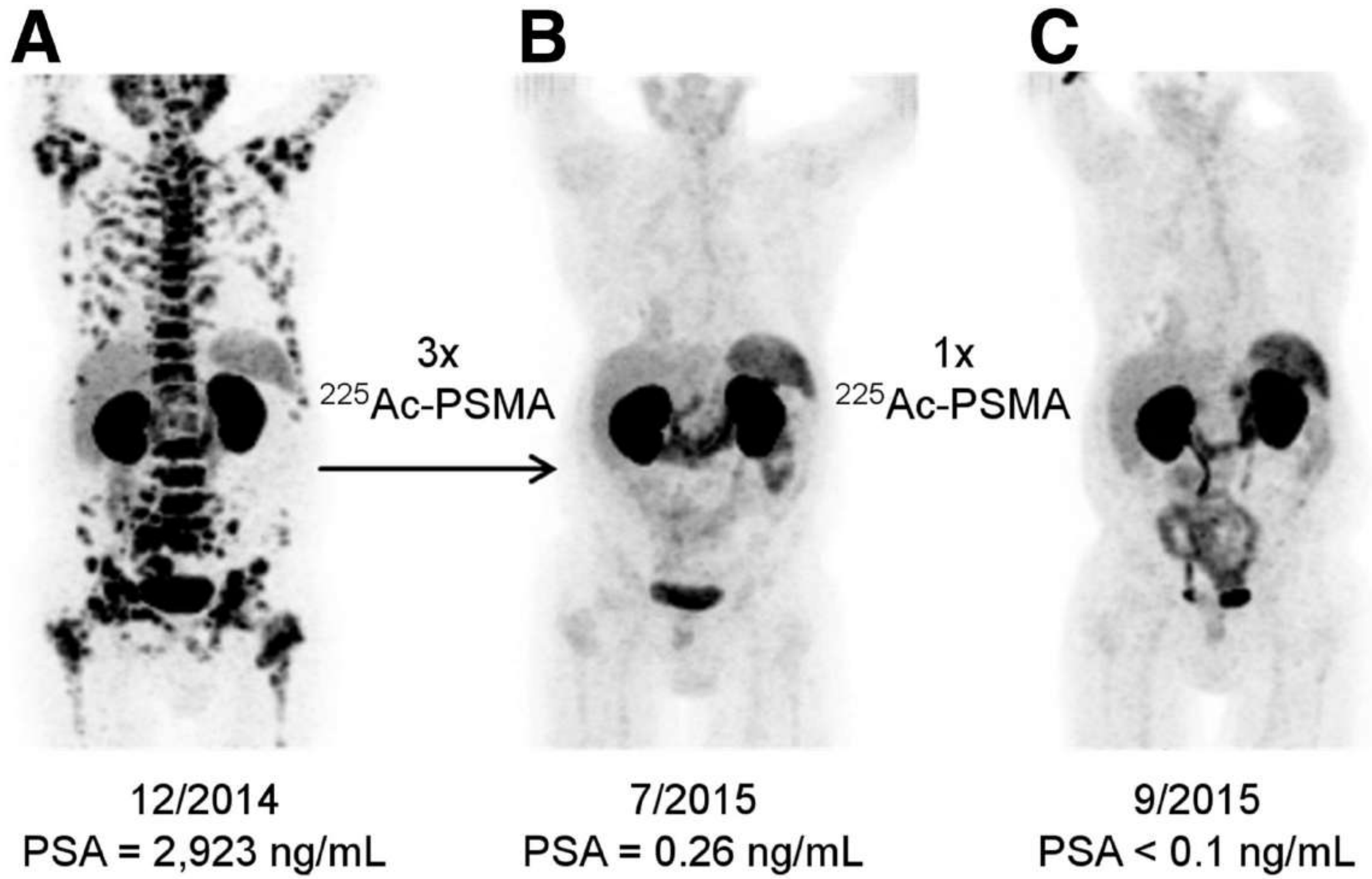
Radiation Drugs: emerging as cancer therapy



Radiopharmaceuticals consist of a radioactive molecule, a targeting molecule, and a linker that joins the two.

Credit: National Cancer Institute

Curing Cancer from the Inside: The Promise of Targeted Alpha Therapy



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

JNM The Journal of NUCLEAR MEDICINE

The goal is kill more cancer cells than healthy cells

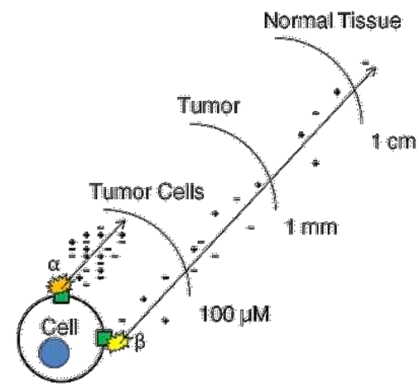
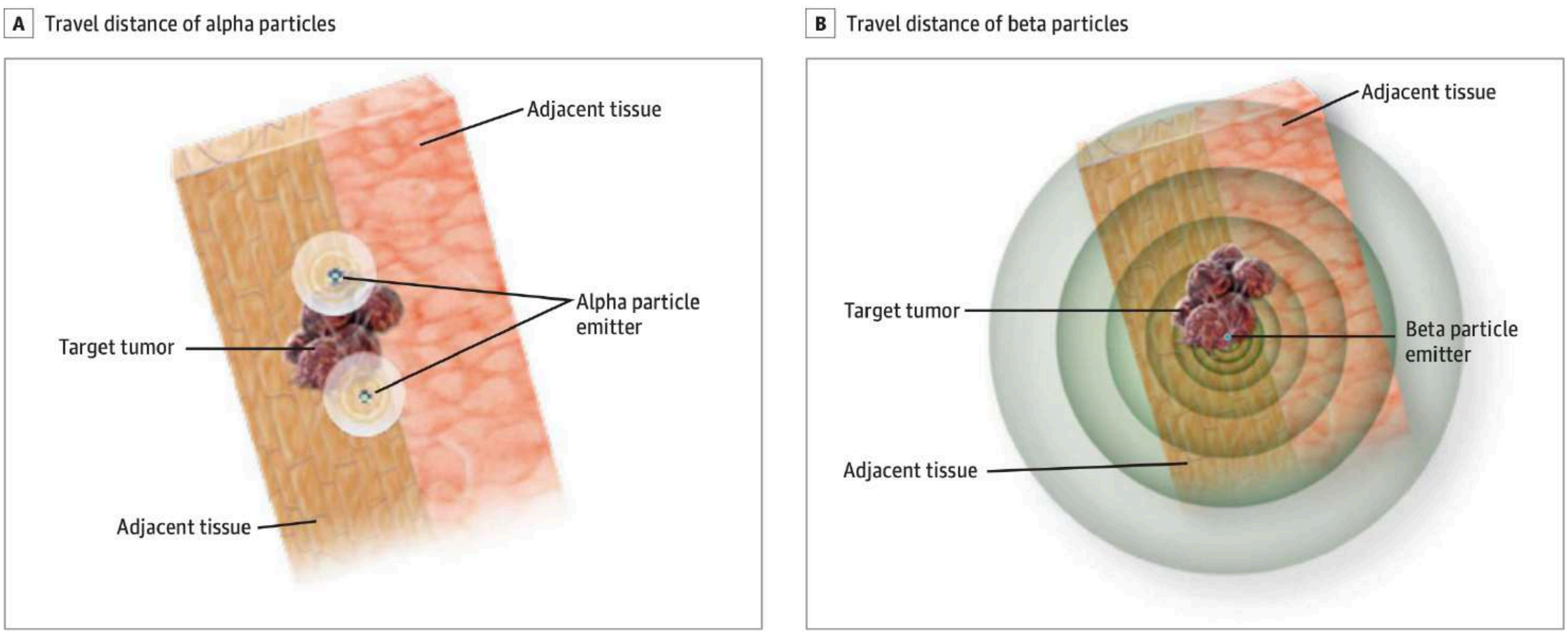


Figure 2. Relative Alpha Particle vs Beta Particle Emission Range in Tissue



JAMA Oncol. doi:10.1001/jamaoncol.2018.4044 Published online September 20, 2018

Alpha-Emitting Radionuclides Investigated for Targeted Alpha Therapy

- Tb-149; $t_{1/2}$ = 4.12 h; α = 4077 keV; β^+, γ = 352 keV
- At-211; $t_{1/2}$ = 7.21 h; α = 5867 keV; γ = 79 keV
- Bi-212; $t_{1/2}$ = 60.6 min; α = 8785 keV; γ = 727 keV
- Bi-213; $t_{1/2}$ = 45.7 min; α = 8378 keV; γ = 440 keV
- Ra-223; $t_{1/2}$ = 11.4 d; α_{avg} = 5348 keV; γ = 269 keV
- Ra-224; $t_{1/2}$ = 3.62 d; α_{avg} = 5094 keV; γ = 241 keV
- Ac-225; $t_{1/2}$ = 10.0 d; α_{avg} = 5450 keV; γ = 86 keV
- Th-226; $t_{1/2}$ = 30.9 min; α(75%) = 6338 keV; γ = 111 keV (3%)
- Th-227; $t_{1/2}$ = 18.7 d; α_{avg} = 5562 keV; γ = 236 keV (11.5%)
- Fm-255; $t_{1/2}$ = 20.1 h; α = 7022 keV; γ = 16 keV

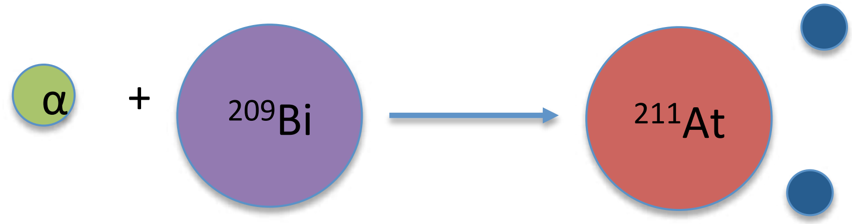
Review: D.S. Wilbur, *Current Radiopharmaceuticals 4*, 214-247, 2011

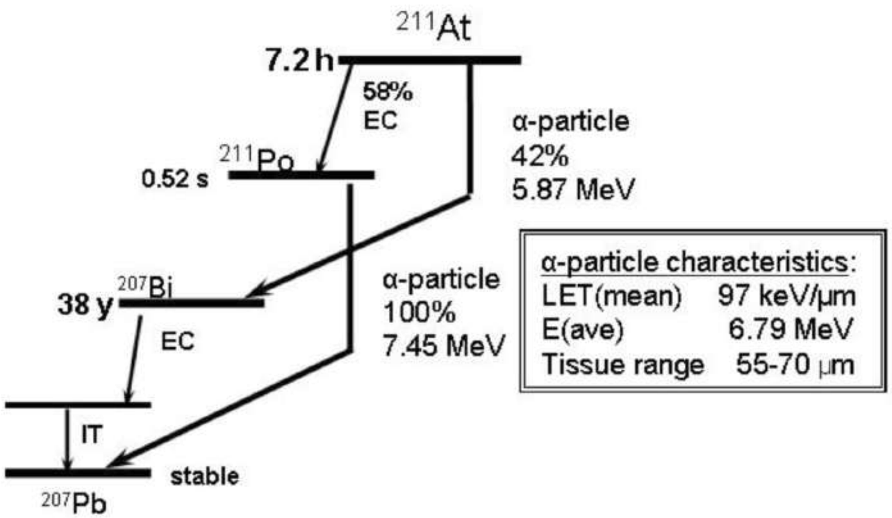
Astatine-211 (^{211}At)

7.2 h half-life

Alpha emission 100%

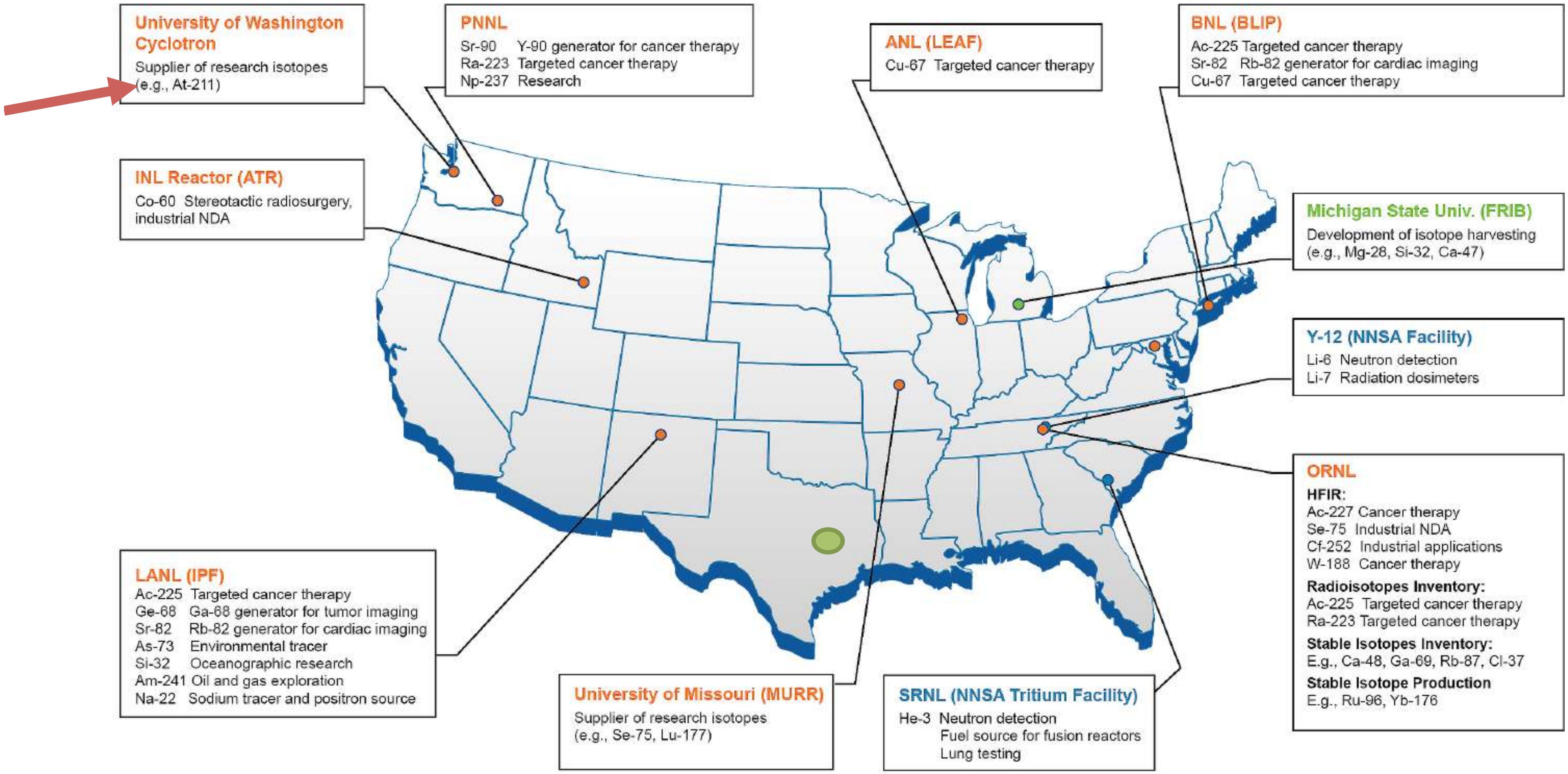
Gamma & X-ray emitter





M.R. Zalutsky, M. Paruszynski, *Curr. Radiopharm.*, 4(3), 117-185, 2020.

Isotope Production University Network



https://www.isotopes.gov/production-network

At-211 Program at Texas A&M

Production
$^{209}Bi(\alpha,2n)^{211}At$

↓

Dissolution of Target
8–12 M HNO_3

↓

Experimental Chemistry
Separations and Fundamental

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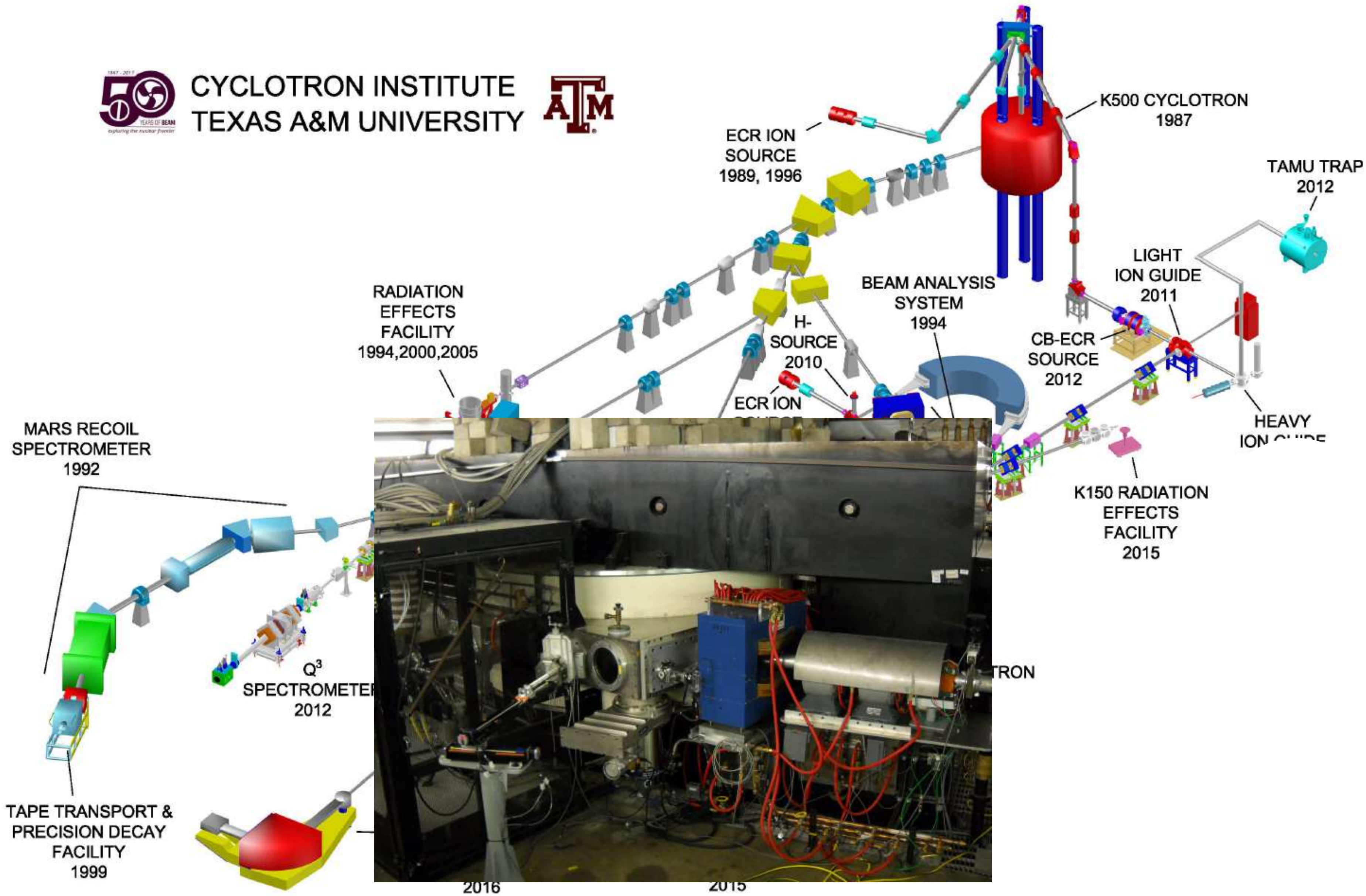
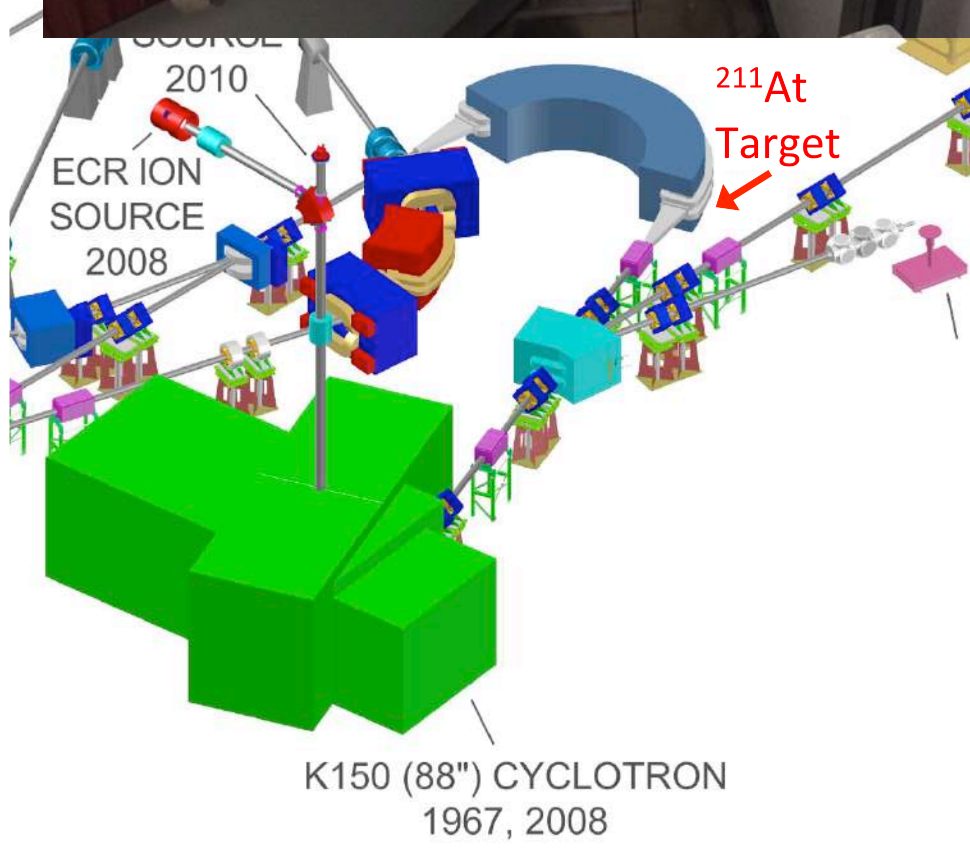


Productio

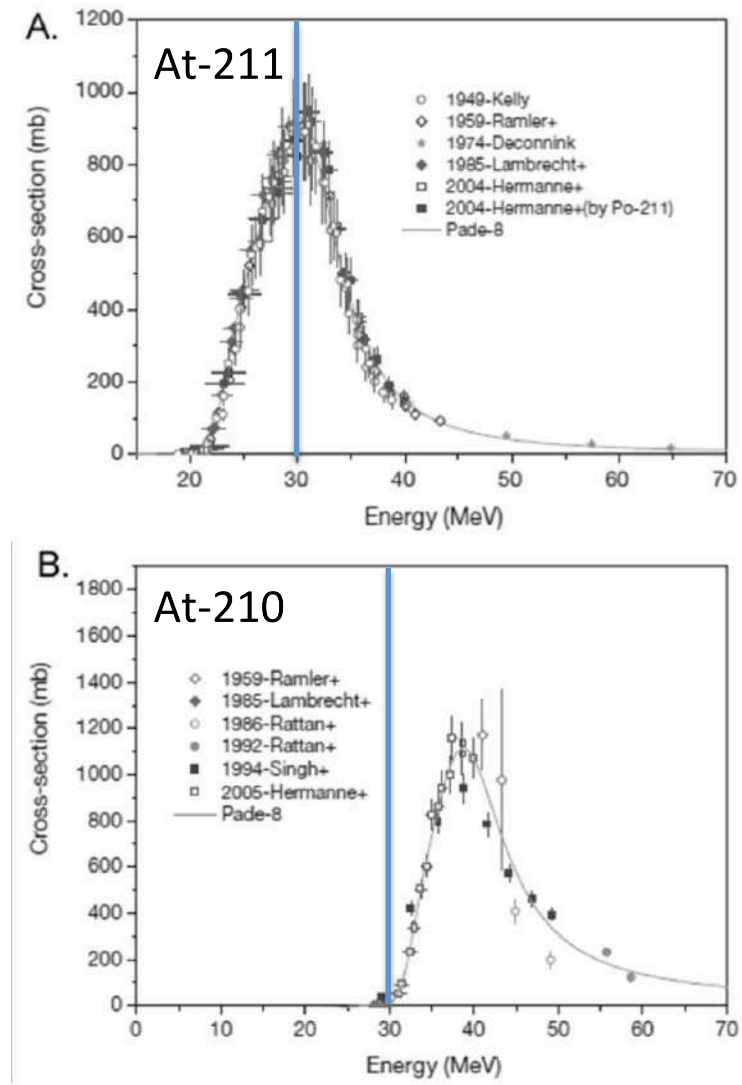
$^{209}Bi + \alpha \rightarrow$

- K150 Cyclotron
- Energy: 28.8 MeV



Alpha Beam

- 28.8 MeV, from K150
- Maximize At-211
- +1 charge state



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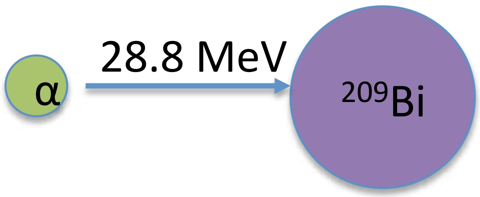
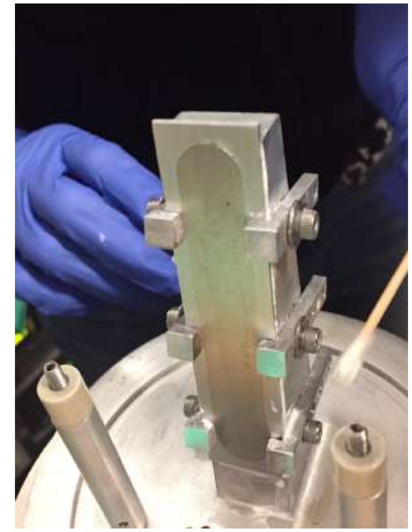
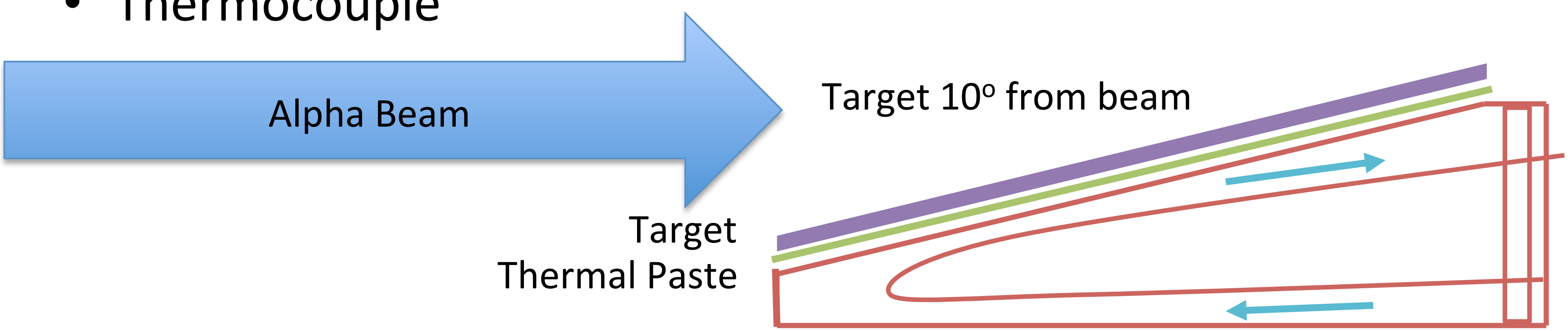


Original Target Mechanism

- Loosely based on UW Target Design
- Chilled water in cooling block (Bi mp: 271.4C)
- Thermal paste between frame and block
- Target 10º from beam
- Thermocouple



Flange

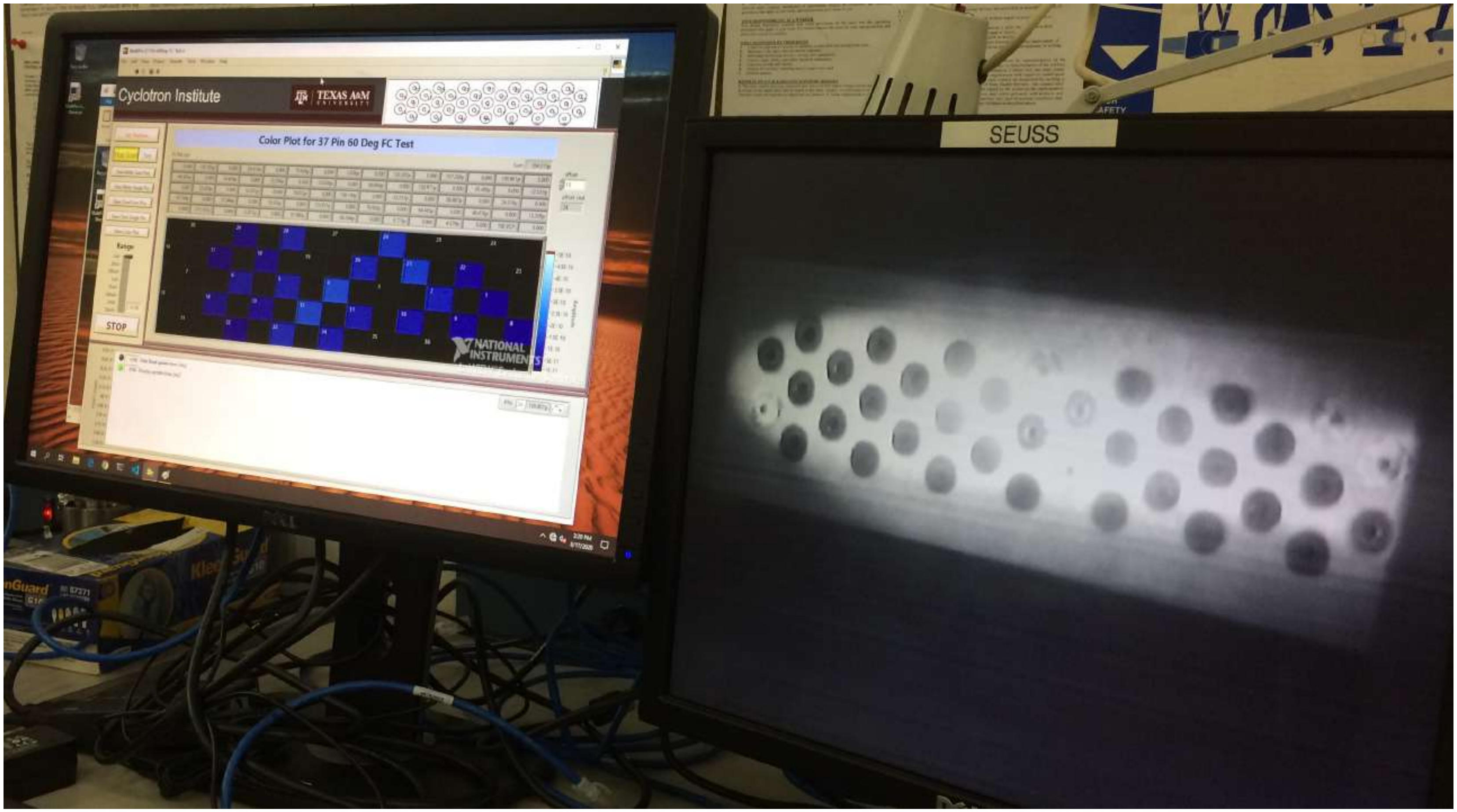


Schematic adapted from L. McCann

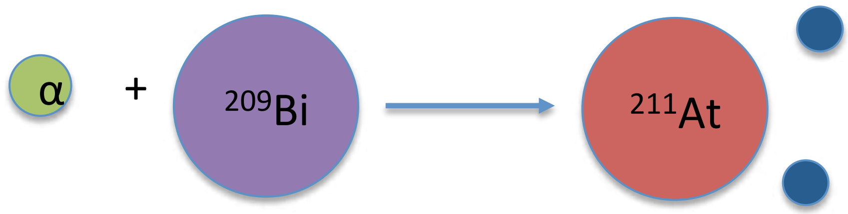
K. Gagnon *et al.*, *J. Label Compd. Radiopharm.*, **55**, 436-440, 2012.

α 28.8 MeV

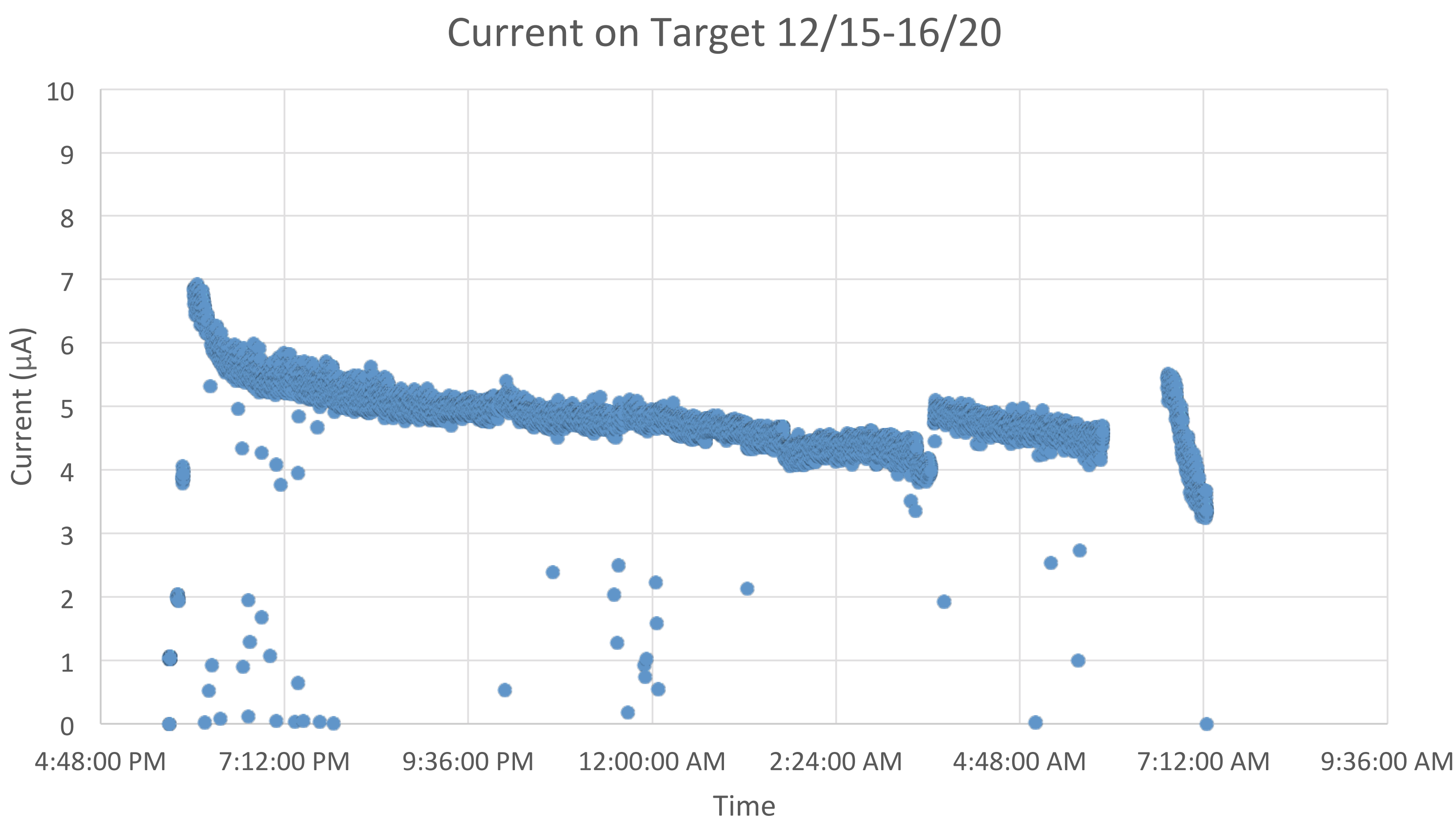
Beam Uniformity



- 37 Faraday Cups, 5 s read time



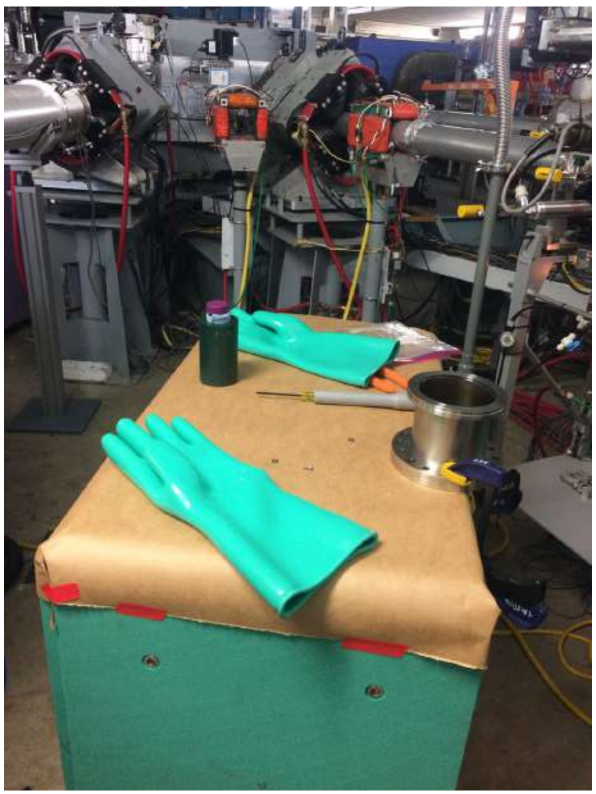
Overnight Bombardment

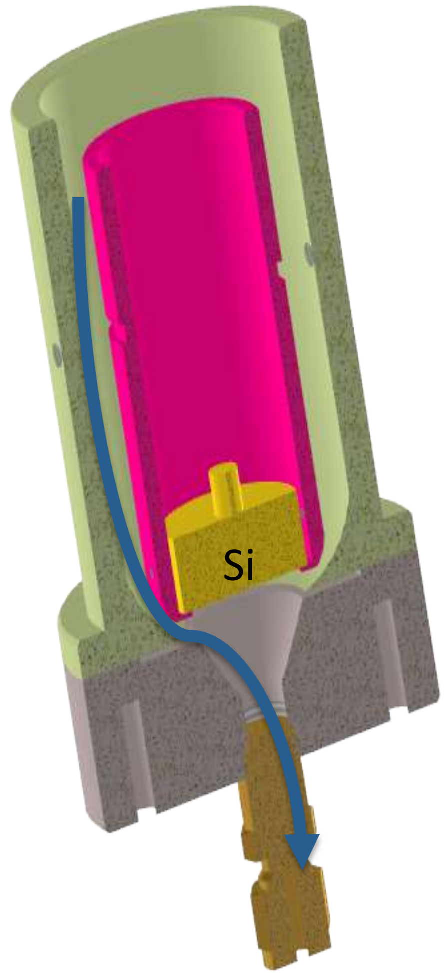


^{211}At

Target Extraction

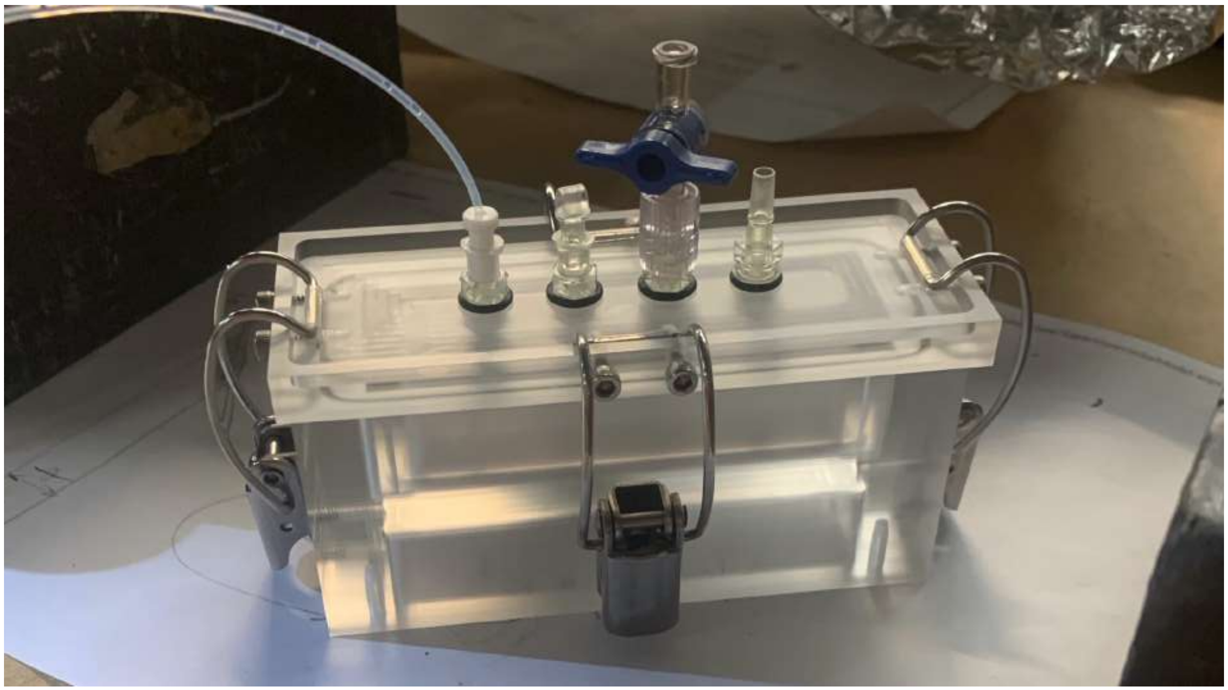
- ALARA
- Air Testing



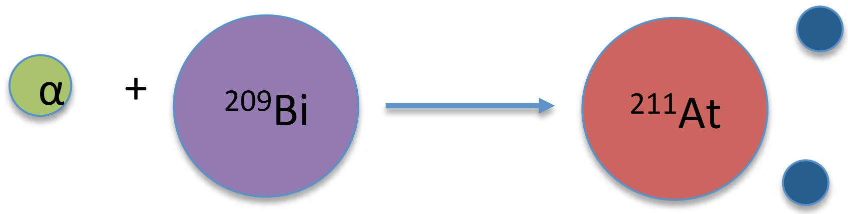


^{211}At

Dissolution, Separation, Chemistry



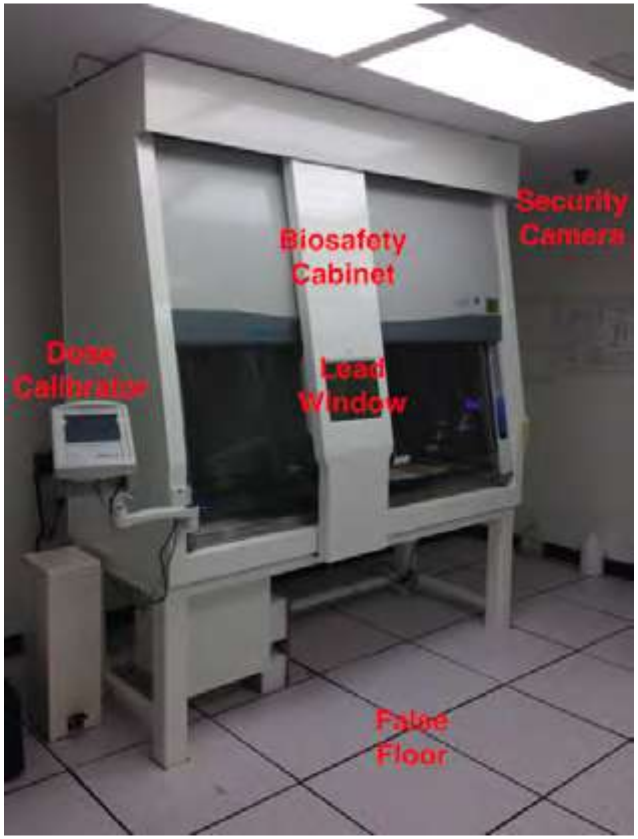
J.D. Burns, *et al.*, *Chem. Commun.*, **56**, 9004-9007, 2020.
J.D. Burns, *et al.*, *J. Sep. Pur.*, **256**, 117794, 2021.

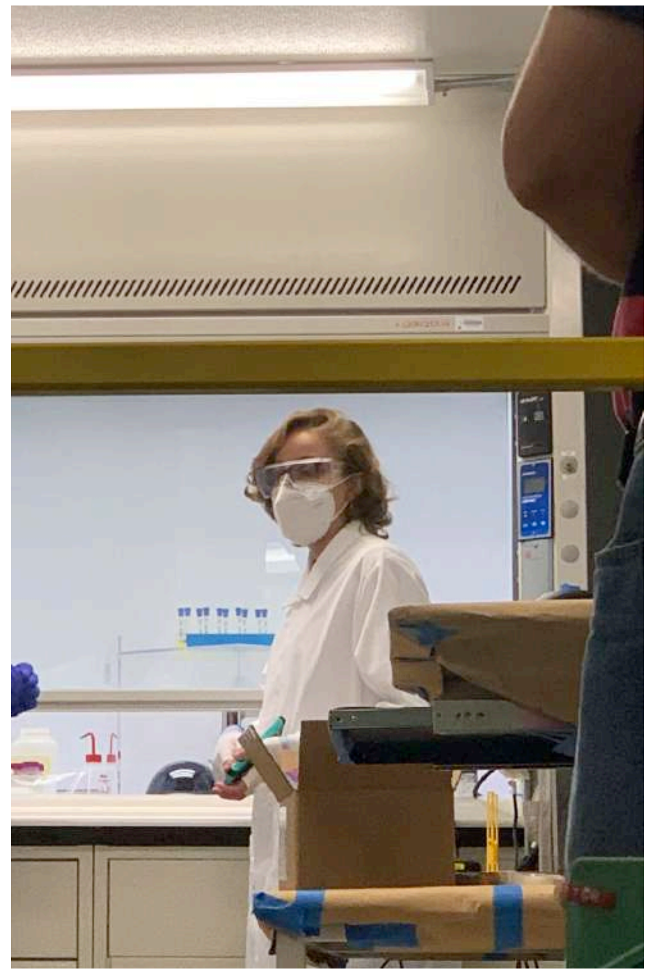


Bombardments

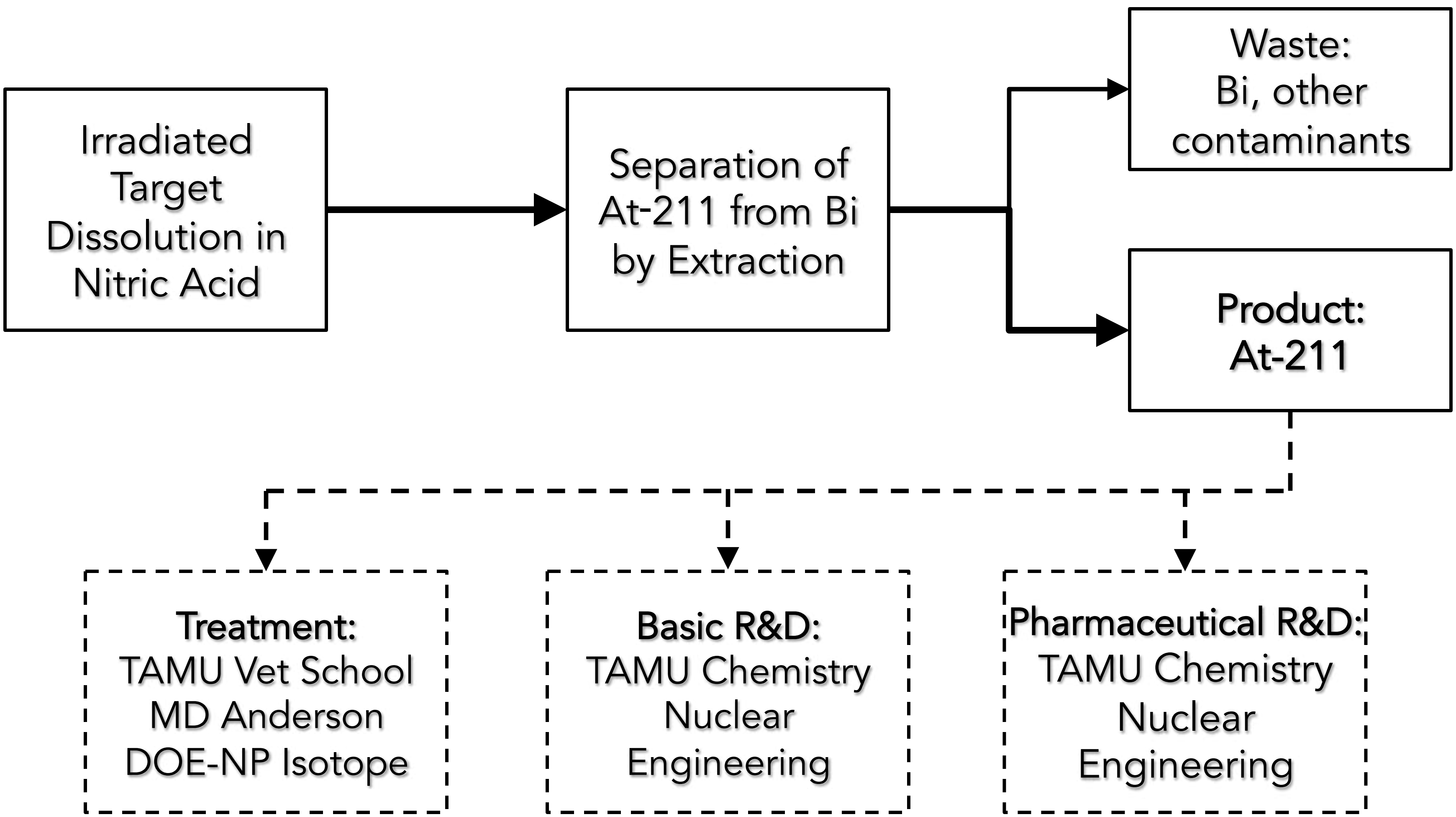
Irradiations	Highest Instantaneous Beam Current (pμA)	Average Beam Current (pμA)	Irradiation Length (h)	At-211 Activity at EoB (mCi)
December 2019	4.4	3	8	24 ± 2
March 2020	3.5	3	9	41 ± 3
June 2020	4.5	2 (Unstable)	9	8.0 ± 1.3
August 2020	2.6	2	9	21 ± 2
September 2020	7.4	5	7	22 ± 2
October 2020	5	4	8	12 ± 1
November 2020	7.2	4	10	24 ± 2
December 2020	6.8	45	14	47 ± 5
April 2021	7.8	6	13	17 ± 2

Radiochemistry Facilities

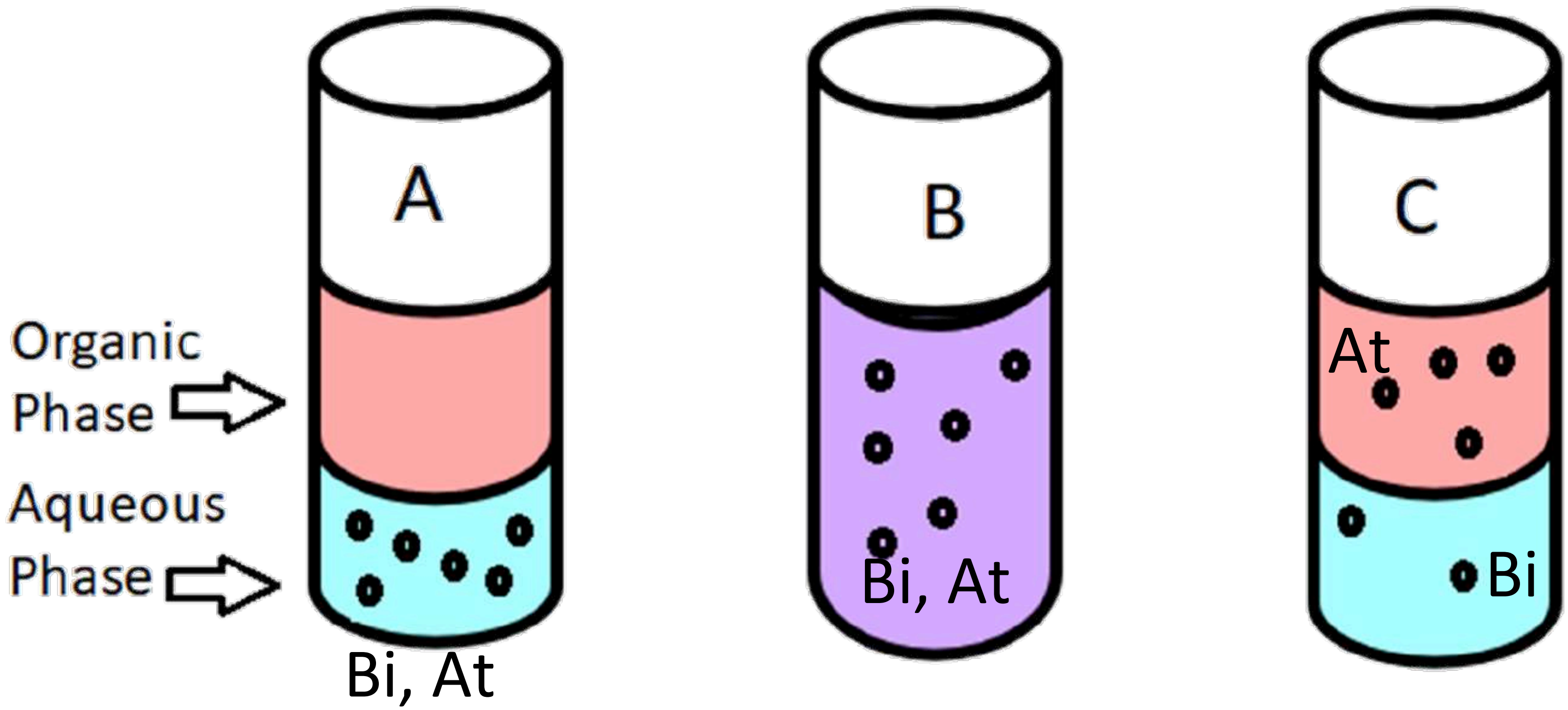




At-211 Recovery and Purification



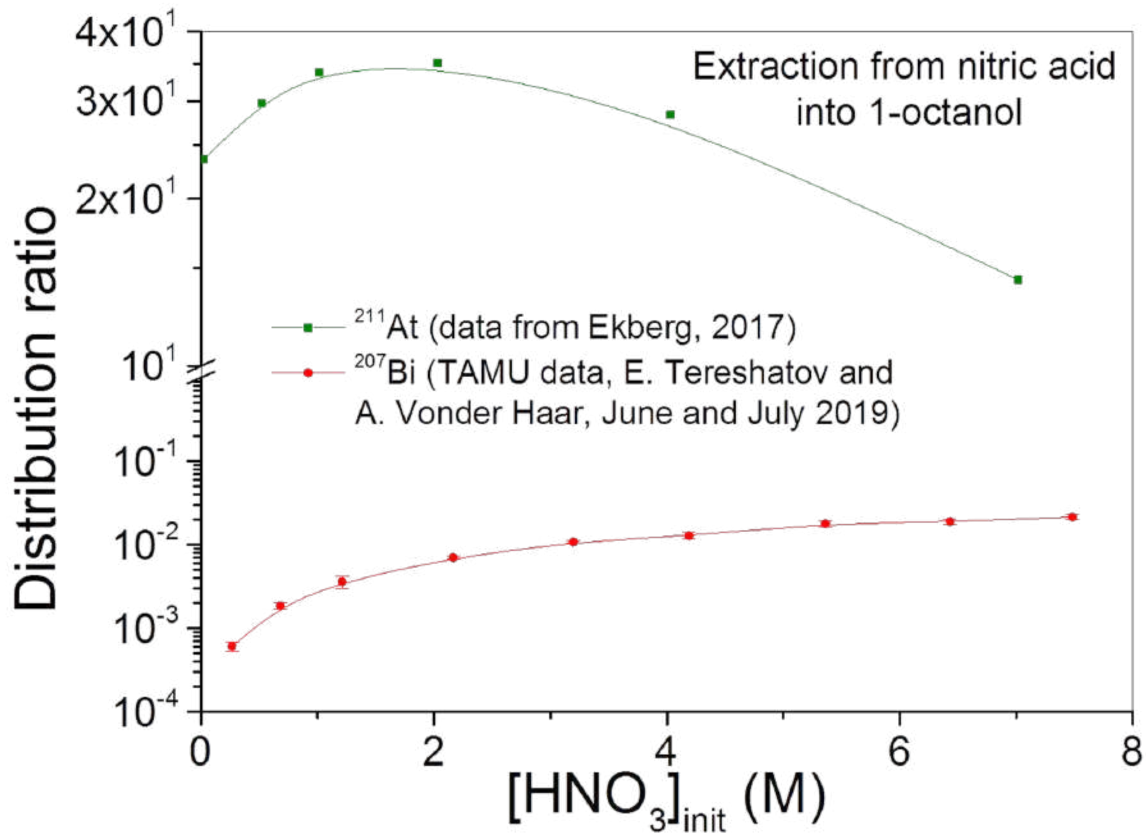
Liquid-Liquid Extraction Experimental Methods



E. E. Tereshatov, *et. al.*, *Green Chem.*, **18**, 4616 (2016).
E. E. Tereshatov *et. al.*, *J. Phys. Chem. B*, **120**, 9, 2311 (2016).

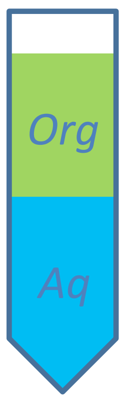
Extraction of bismuth from nitric acid media using 1-octanol

(Amy L. Vonder Haar)



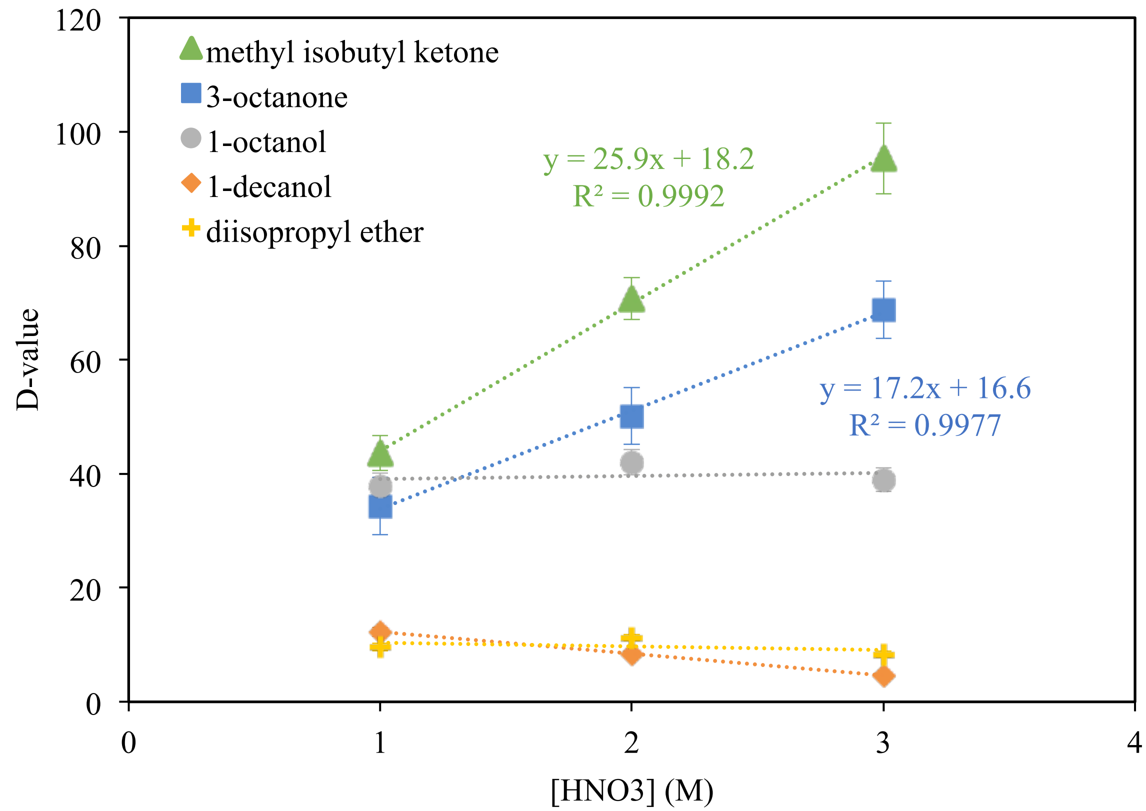
C. Ekberg, H. Jensen, S. P. Mezyk, B. J. Mincher, and G. Skarnemark, J. Radioanal. Nucl. Chem., 314, 235 (2017).

At-211 Separations



$D=C_{org}/C_{aq}$

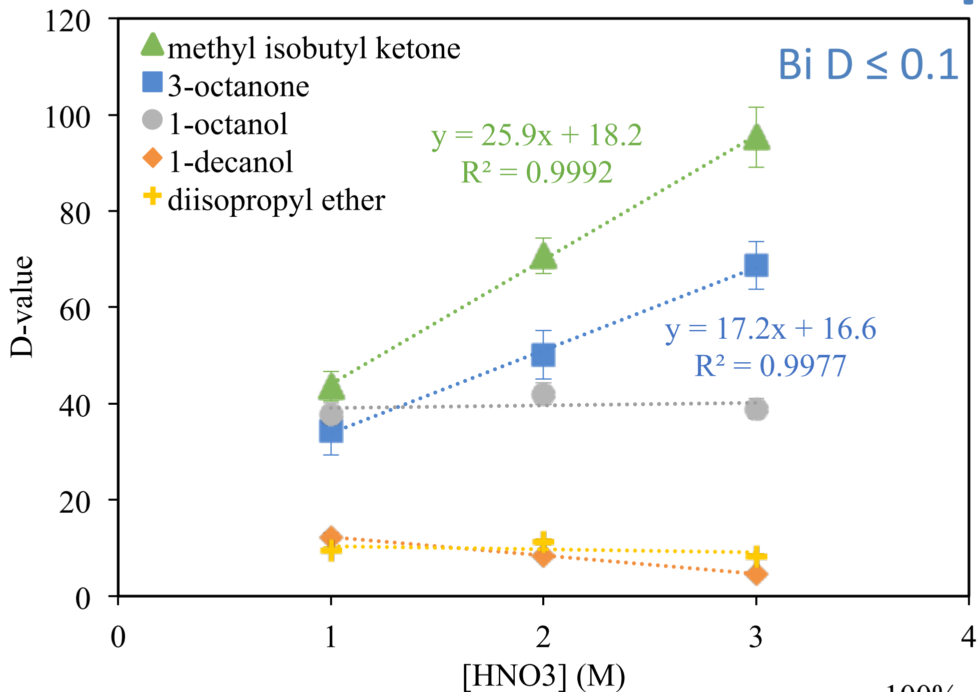
Bi $D \leq 0.1$



Solvent	Dielectric Constant
methyl isobutyl ketone	13.11
3-octanone	10.5
1-octanol	10.3
1-decanol	7.93
Diisopropyl ether	3.81

Burns et al, *Chemical Communications, 2020*

At-211 Separations



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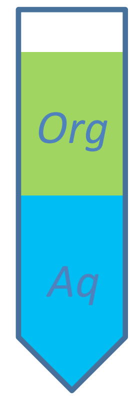

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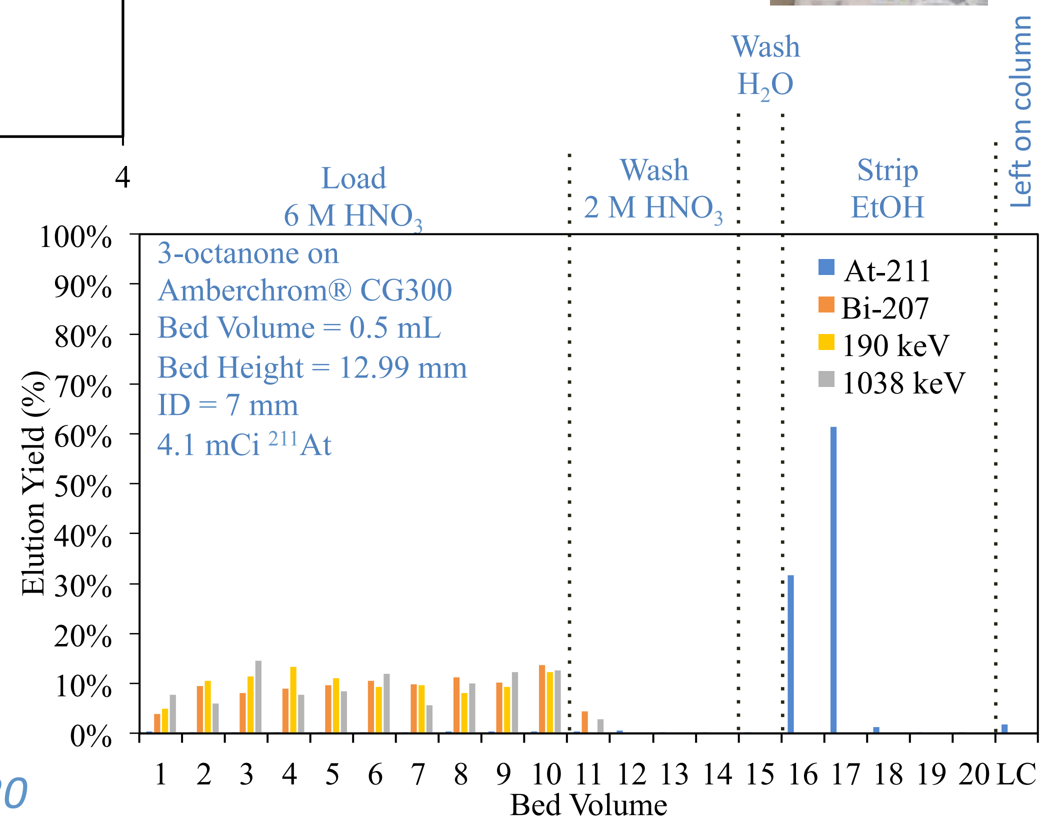


Burns et al, *Chemical Communications, 2020*

Hydrophobic Liquid Binary Mixtures

- Green chemistry: non-volatile, reduced toxicity, biodegradable
- A new form of organic solvent – never before used with Bi or At

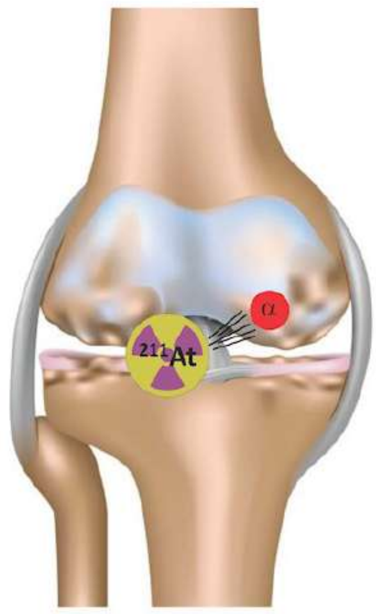
J. M. Edgecomb, *et. al.*, *Green Chem.*, **22**, 7047 (2020).

Current Chemistry in Progress

- Exploration of ^{211}At oxidation state (extracting with oxidizing, reducing agents)
- Continuing to probe organic solvents
- Beginning investigation with liquid binary mixtures as extraction solvent (ibuprofen, lidocaine, methyl anthranilate)

- Work in preliminary stages

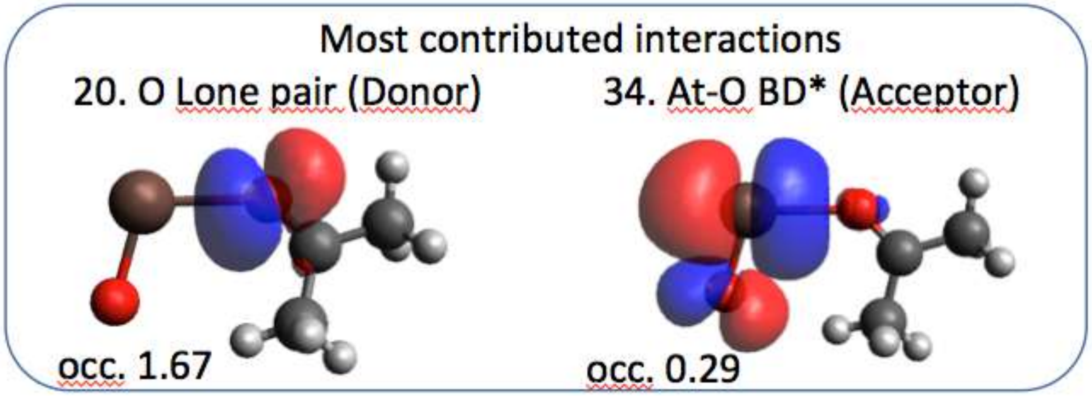
Developing At-211 For Treatment Osteoarthritis



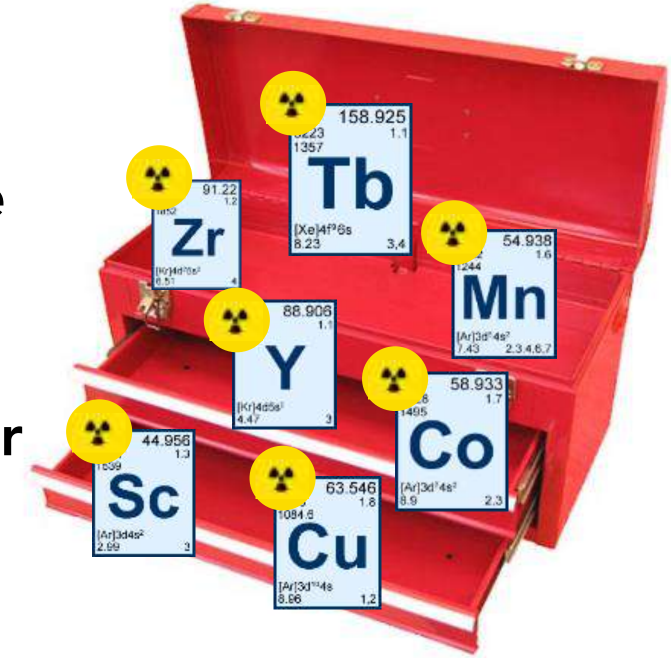
Osteoarthritis

Ligand Exchange Experiments

DFT Calculations to understand the interactions

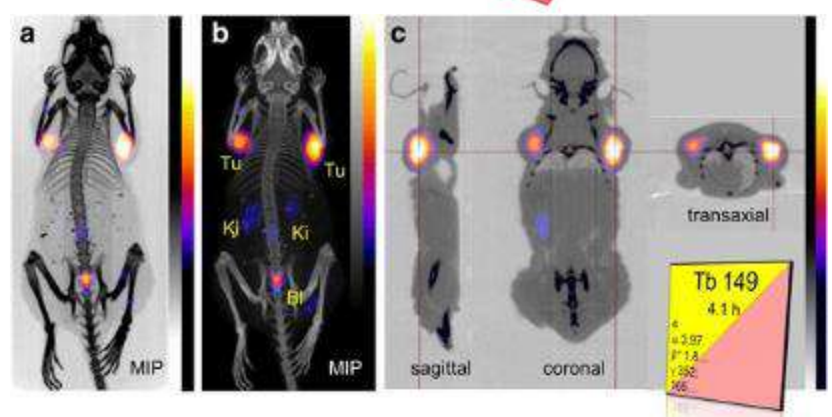


Expanding the Toolbox of Medical Radioisotopes



- Theranostic Isotopes – label the same drug with an isotope for therapy and diagnostic imaging – “see and treat” approach
- Terbium - β^+/α : Matched isotopes for PET imaging and therapy
  1) ^{149}Tb ($t_{1/2}$ = 4.12 h) decays by positron emission and α-decay
  2) $^{151/152}$Tb – longer

Stable chelation chemistry and initial studies using Tb from spallation are promising



EJNMMI Radiopharm Chem. 2017; 1(1): 5.

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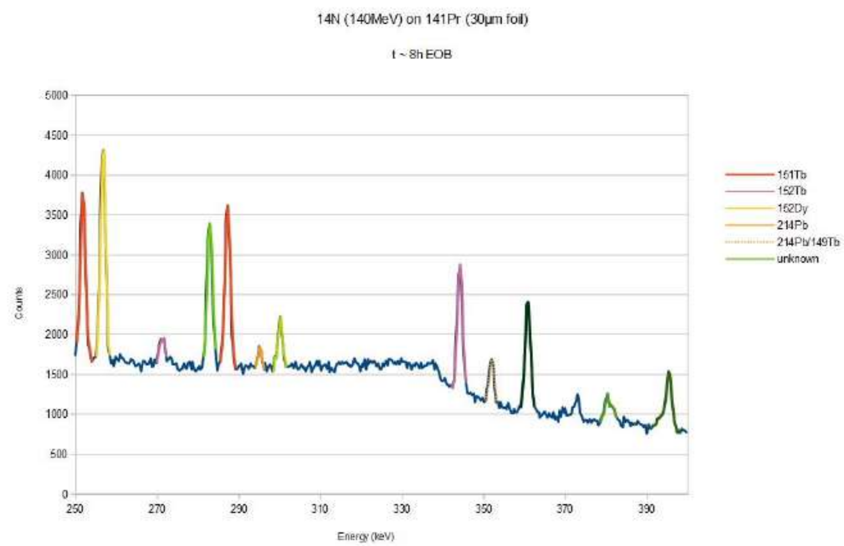
Terbium-149

- 140 MeV ^{14}N + Pr_6O_{11}, CeO_2 → Lots of ^{149m}Tb
- 258 MeV ^{63}Cu + ^{89}Y



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Advancing Research in Texas through Experiments in Medical Isotope Science (ARTEMIS)

- Starting with astatine for therapy by release of alpha particle (28.8 MeV α-beam, K150)

- ^{209}Bi(α, 2n)^{211}At
- ^{211}At half life: 7.2 h
- Metallic Bi target ⇨ Dissolve irradiated target in HNO_3
- Analyze samples using high-purity germanium detector (HPGe)
- Challenges: producing enough ^{211}At, efficient chemistry, isolating ^{211}At from bismuth target (extraction/separation)
- Investigating reactions of other possible interesting isotopes

Jon Burns, Lauren McIntosh, Evgeny Tereshatov, Gabi Tabacaru, Amy Vonder Haar, Laura McCann, Kylie Loftin, Steve Schultz, Dan Menchaca, M.B. Hall, X. Yang

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  3: University of Notre Dame

TEXAS A&M UNIVERSITY Cyclotron Institute

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- T3 Grant from TAMU
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Isotope Program U.S. Department of Energy

Question?