Isotope Program
U.S. Department of Energy

Cu-67 DOE Isotope Program User Group Meeting

David A. Rotsch, Argonne National Laboratory

Argonne NATIONAL LABORATORY

NIDC | NATIONAL ISOTOPE DEVELOPMENT CENTER
MANAGED BY THE U.S. DEPARTMENT OF ENERGY ISOTOPE PROGRAM

U.S. DEPARTMENT OF ENERGY

Cu-67 AGENDA

AUGUST 24, 2021, 1 PM EDT

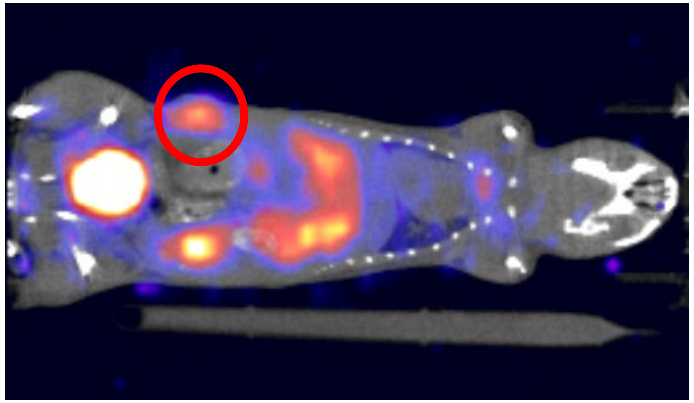
1:00 – 1:10 PM	**Dave Rotsch,** Argonne National Laboratory (Moderator) Introduction
1:10 – 1:25 PM	**Jack Shively,** City of Hope
1:25 – 1:40 PM	**Alan Packard,** Boston Children's Hospital
1:40 – 1:55 PM	**Brian Zeglis,** Hunter College
1:55 – 2:10 PM	**Jennifer Bartels,** University of Alabama at Birmingham
2:10– 2:25 PM	**Sheamus Gleason,** Clarity Pharmaceuticals
2:25 – 3:00 PM	Moderated Q&A Segment

Theranostic approach

Personalized medicine through diagnostic and therapeutic

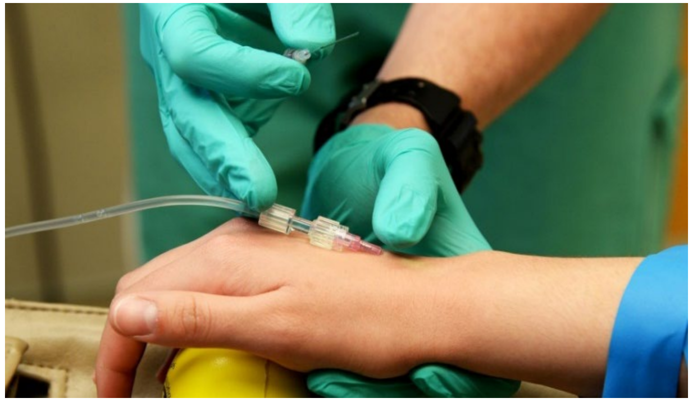
Diagnostic

- SPECT and PET
- ^{43,44}Sc, ^{64}Cu, ^{68}Ga, ^{82}Rb, ^{99m}Tc, ^{132}Ce



Therapeutic

- Alpha, Beta, Auger electrons
- ^{90}Y, ^{117m}Sn, ^{188,191,193,195m}Pt, ^{211}At, ^{212}Pb, $^{212/213}$Bi, ^{223}Ra, ^{225}Ac, ^{177}Lu



Both (Theranostic)

- Real-time monitoring of treatment
- ^{47}Sc, ^{67}Cu, ^{186,188,189}Re

Copper-67

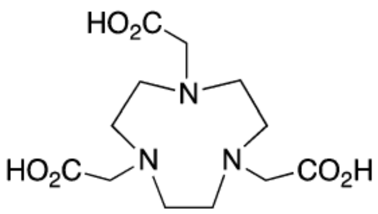
- **Theranostic**
  - $t_{1/2}$ = ~2.58 days
  - Average β^-: 141 keV
  - γ: 184.6 keV (49%)
  - Decays to stable Zn

- Match pair with ^{64}Cu
  - PET

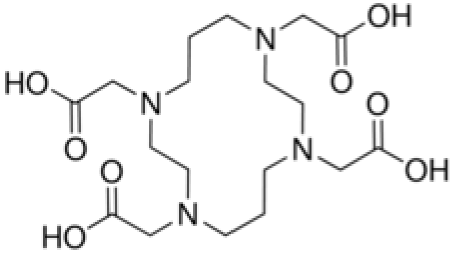
- Uses: treatment of non-Hodgkins lymphoma, neuroblastomas, and other cancers

- Chelation chemistry well-known due to ^{64}Cu PET-analogue

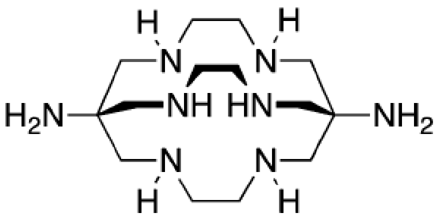
Multi-dentate Bifunctional Chelators



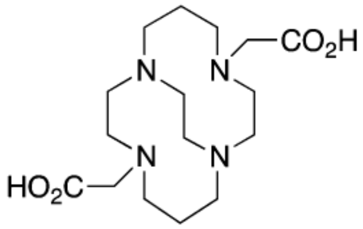
NOTA
1,4,7-triazacyclononane-1,4,7-tracetic acid



TETA
1,4,8,11-tetraazacyclotetradecane-,1,4,8-tetraacetic acid



Diamsar
3,6,10,13,16,19-hexaazbicyclo[6.6.]eicosane-1,8-diame



CB-TE2A
4,11-bis-(carboxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]-hexadecane

Copper-67 Production using p and n

- Production methods
  - $^{68}Zn(p,2p)^{67}Cu$, $^{70}Zn(p,a)^{67}Cu$, $^{67}Zn(n,p)^{67}Cu$, and heavy-ion fragmentation (FRIB Harvesting)

- Reported specific activities
  - 2-20 Ci/mg (74-740 GBq/mg)
  - <20 Ci/mg has demonstrated radiolabeling challenges

- ^{64}Cu is readily available, so why has ^{67}Cu been so difficult?
  - Production rates are relatively low compared to ^{64}Cu
  - Targetry is challenging
    - Zn melting point is low, ~420 ^{o}C ($Ni_{(m)}$ = 1,455 ^{o}C)
    - Zn wets and alloys with most metals (targetry considerations are difficult)
  - Cu is ubiquitous building/construction material

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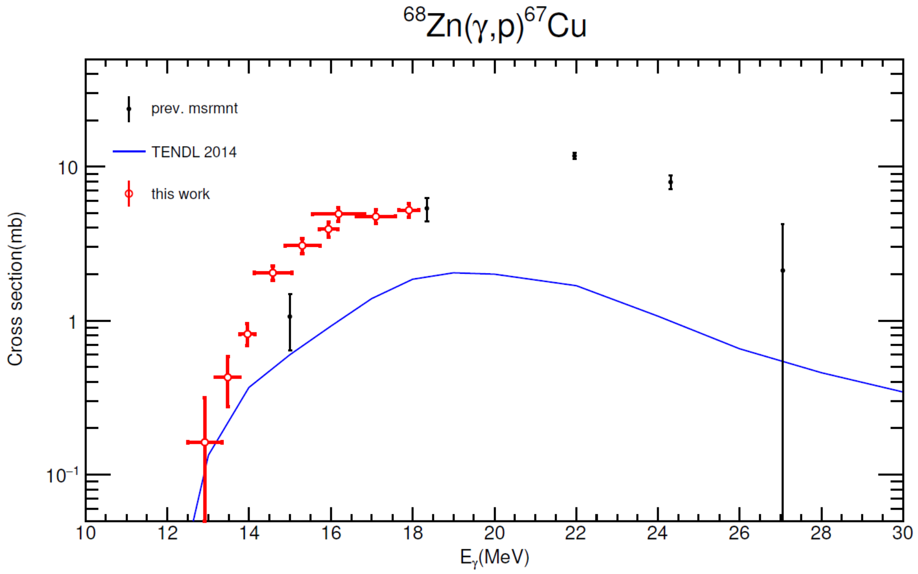
Photonuclear Production ^{67}Cu

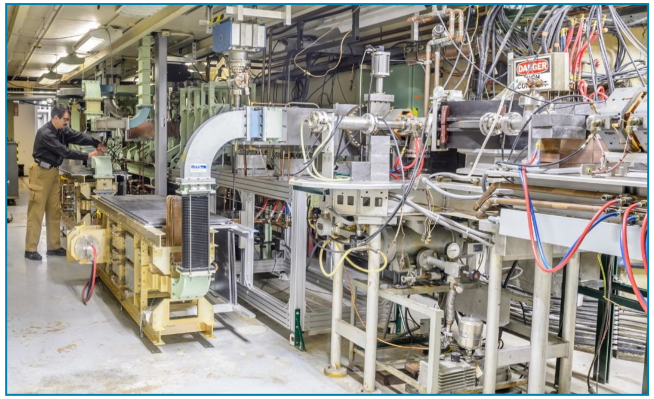
- Bremsstrahlung: ^{68}Zn(γ,p)^{67}Cu and ^{71}Zn(γ,a)^{67}Cu
  - ^{68}Zn(γ,p)^{67}Cu – 12 MeV threshold, peak at ~20 MeV, σ = 26 mb (~12 mb TENDL)
  - ^{71}Zn(γ,a)^{67}Cu – 15 MeV threshold, peak at 20 MeV, σ = 0.7 mb
- ^{68}Zn(γ,p)^{67}Cu
  - Enriched ^{68}Zn ingot
    - Enriched targets eliminates co-produced radioisotopes
      - ^{68}Zn – 18.45% abundant
    - Zn targetry considerations
      - No metal contact
      - Target temperature (melting point ~420 °C)

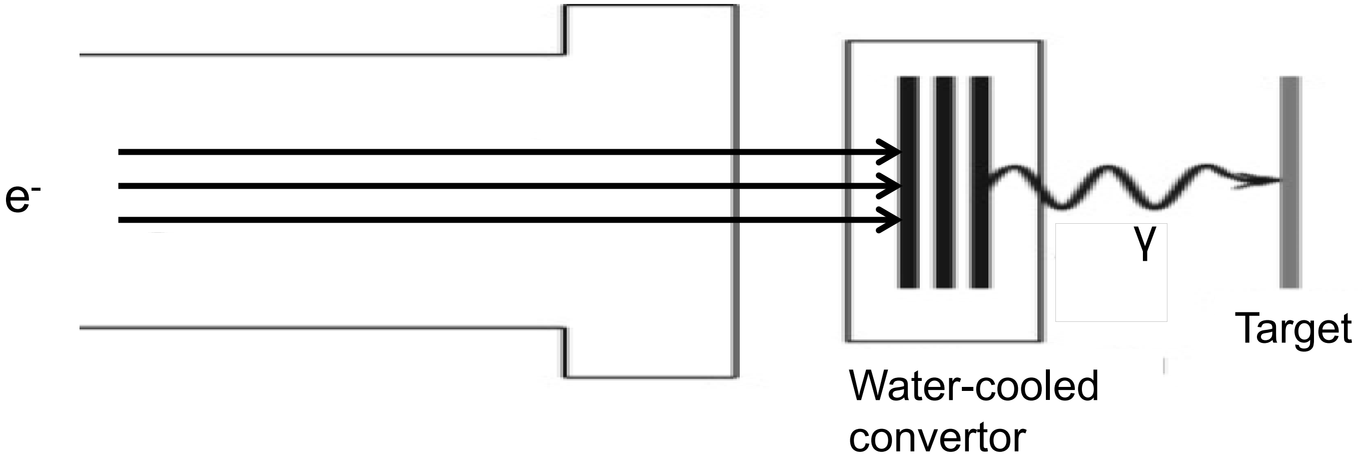


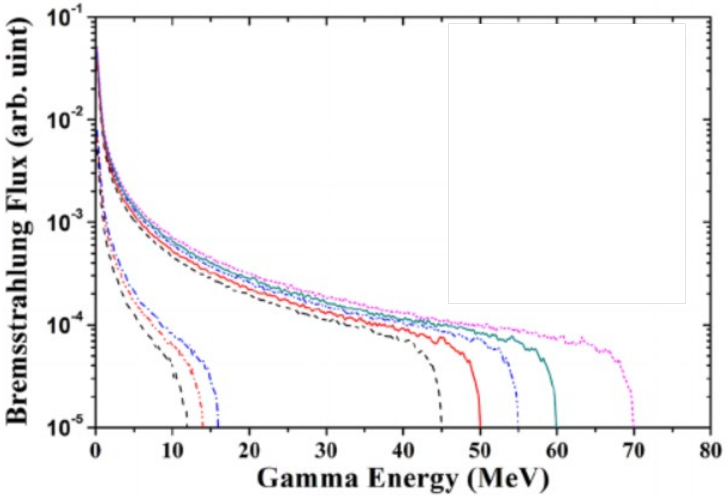
Koning, A.J., et al. *TENDL-2014: TALYS-based evaluated nuclear data library*. **2014**, Available from: ftp://ftp.nrg.eu/pub/www/talys/tendl2014/gamma_html/gamma.html

Low Energy Accelerator Facility (LEAF)

- High energy electrons are bombarded on convertor
- Electrons brake on the convertor and produce Bremsstrahlung photons
- Photons interact with the target primarily via (γ,n), (γ,p), and (γ,a)







Photonuclear Production of ^{67}Cu, $^{68}Zn(\gamma,p)^{67}Cu$

- Certificate of Analysis
  - 2 Ci at end of bombardment (EOB)
  - ~1.2 Ci at time of Shipping (806 available with NIDC 24-hr decay allowance)
  - Shipped as solid $CuCl_2$
  - Identified by 93 and 184 keV gamma emissions
  - ≥99% radionuclide purity
  - ≥50 Ci/mg (^{67}Cu/total Cu at EOB)

Batch	SA (Ci/mg @ EOB, ^{67}Cu mass corrected)	TETA (mCi/nmole @ time of labeling)	DOTA (mCi/nmole @ time of labeling)	MeCOSAR (mCi/nmole @ time of labeling)
Average	101.9	1.38	1.18	2.32

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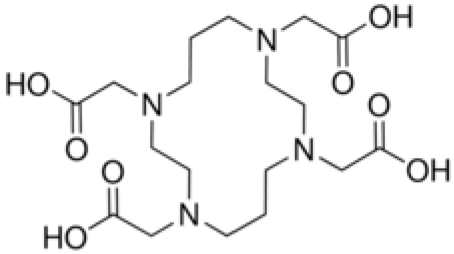
Radiolabeling

Apparent Molar Activity (AMA)

- Radiolabeling occurs ~1 half-life after EOB.

Conditions
- 0.5 M NH_4COOH (pH = 5.5)
- 40-90 °C
- 30 minutes
- EDTA added for MeCOSar after labeling



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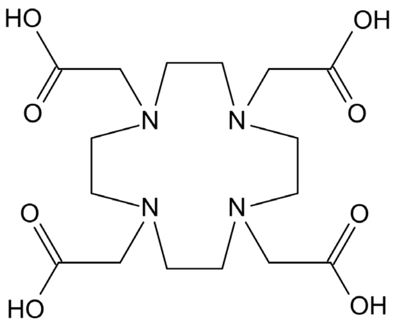
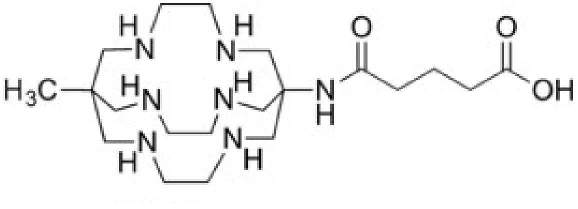


DOTA
1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid



MeCOSar
5-(8-methyl-3,6,10,13,16,19-hexaaza-bicyclo[6.6.6]icosan-1-ylamino)-5-oxopentanoic acid

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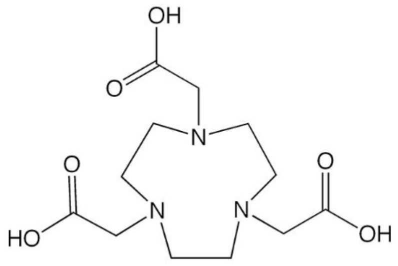
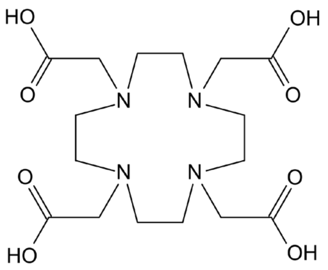
Independent quality evaluation



NOTA

2.3 mCi/nmol

pH 5.5, NaOAc buffer
Reaction time: 30min@25°C



DOTA

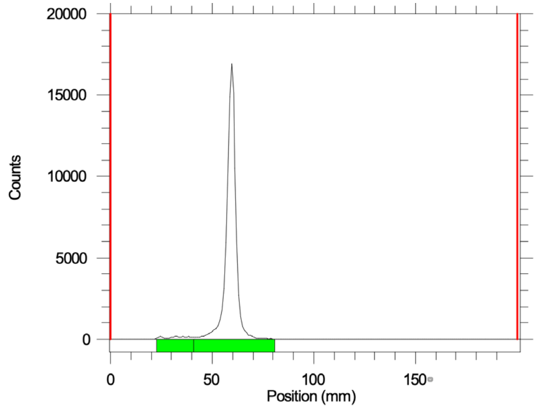
3.6 mCi/nmol

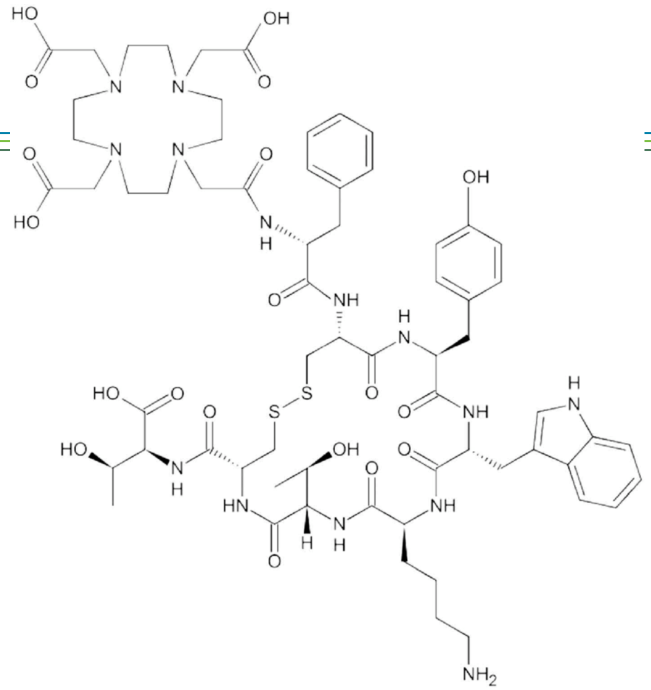
pH 5.5, NaOAc buffer
Reaction time: 30min@90°C

WISCONSIN
UNIVERSITY OF WISCONSIN–MADISON

Work Performed by:
Ed Sarduy
Christopher Kutyreff
Jonathan Engle

- ^{67}Cu-DOTATATE





THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Work performed by:
Dr. Jen Bartels
Dr. Suzy Lapi

Temperature	Target SA (µCi/µg)	DOTATATE (µg)	^{67}Cu (µCi)	Labeling efficiency (%)
37°C	100	5	544	19
65°C	100	5	545	72
90°C	100	5	550	94
90°C	10	5	54	97.3
90°C	50	5	260	97.5
90°C	100	5	549	98.4

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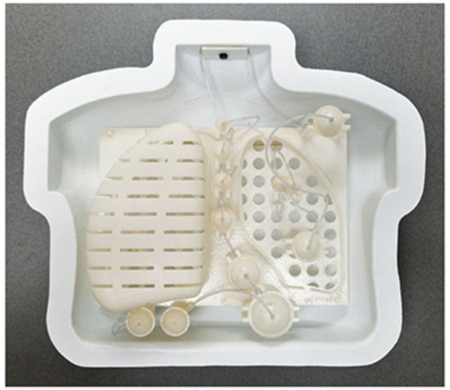
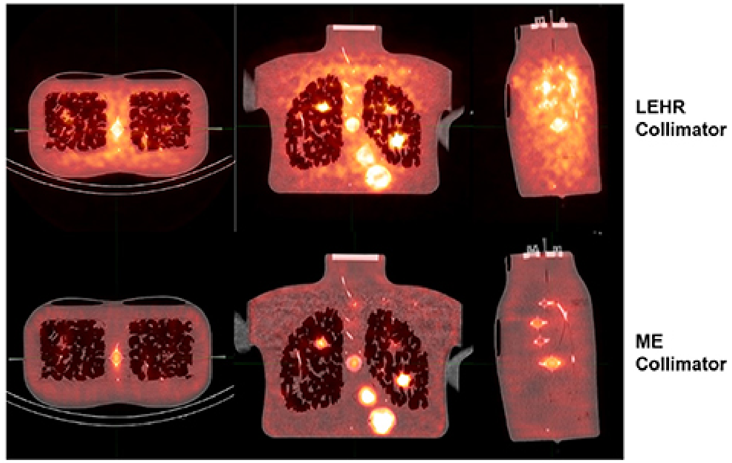
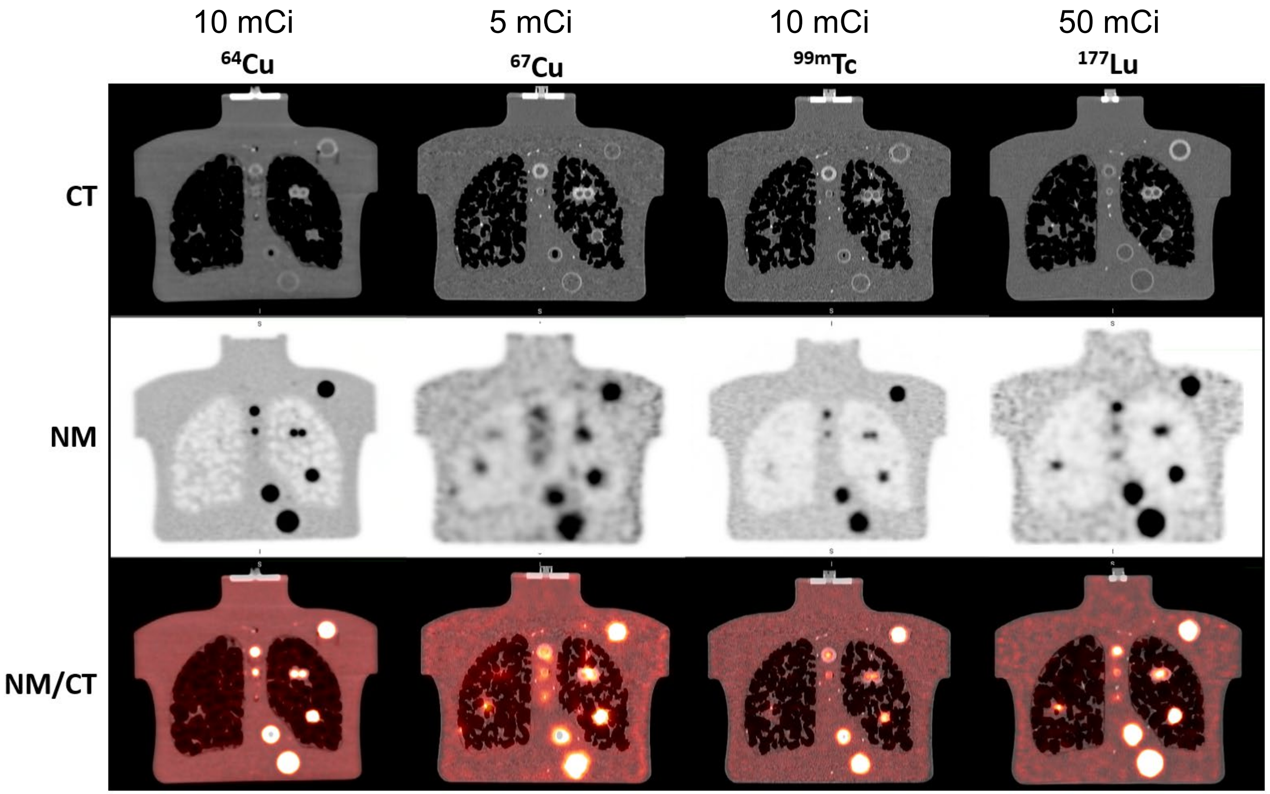
^{67}Cu as a Theranostic



Society for Nuclear Medicine and Molecular Imaging (SNMMI) Clinical Trials Network (CTN) anthropomorphic chest phantom.



Comparison of ^{67}Cu SPECT/CT images acquired using the low-energy high-resolution (LEHR) collimator and the medium energy (ME) collimator.



MJ Merrick, et. al, "*Imaging and Dosimetric Characteristics of ^{67}Cu*" *Phys. Med. Biol.* **2021**, *66* 035002, https://doi.org/10.1088/1361-6560/abca52

The University of Iowa

Work performed by:
S. Graves
M. Merrick

Thank You!

For more information: **https://isotopes.gov/**

^{67}Cu test batch recipient responses

- 51.23 Ci/mg (^{67}Cu/total Cu, @ EOB)
- *"Very nice product! We're looking forward to doing more studies with Cu-67. Please keep us posted on the next time you are producing material, and we'll plan a larger mouse study."*
- *"In summary, we were very happy with our experience, and are pleased to see that high quality Cu-67 may soon be more widely available…"*
- *"The Cu-67 labeled beautifully… very interested in planning animal experiments with Cu-67."*

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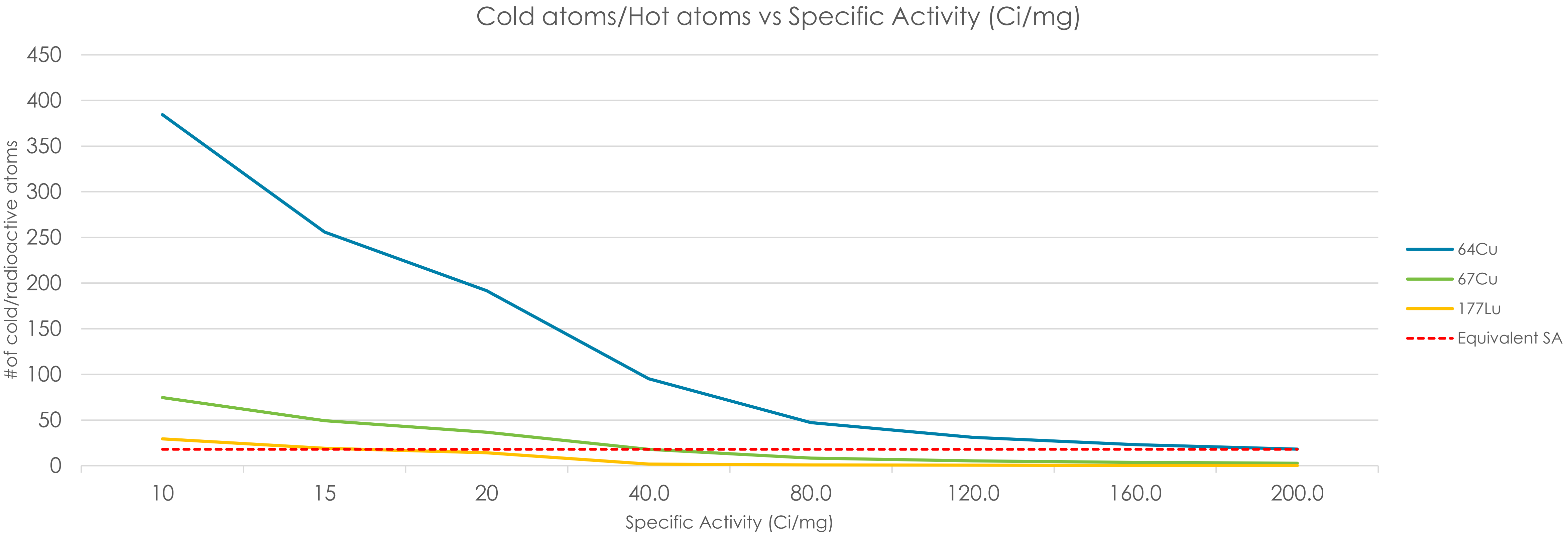
Impurity ratio vs specific activity

- ~200 Ci/mg ^{64}Cu = ~40 Ci/mg ^{67}Cu = ~18 Ci/mg ^{177}Lu



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