TEXAS A&M UNIVERSITY

CYCLOTRON INSTITUTE

1967 - 2017 YEARS OF BEAM

exploring the nuclear frontier

A novel approach to medical radioisotope production using inverse kinematics

Márcia Regina Dias Rodrigues

HINP ΕΙΠΦ

HINPw6 – 14-16 May 2021

6th Workshop of the Hellenic Institute of Nuclear Physics

TEXAS A&M UNIVERSITY

CYCLOTRON INSTITUTE
1967 - 2017
50 YEARS OF BEAM
exploring the nuclear frontier

- Introduction
- Experimental set up
- Data and Analysis
- Results and Conclusions
- Next Steps

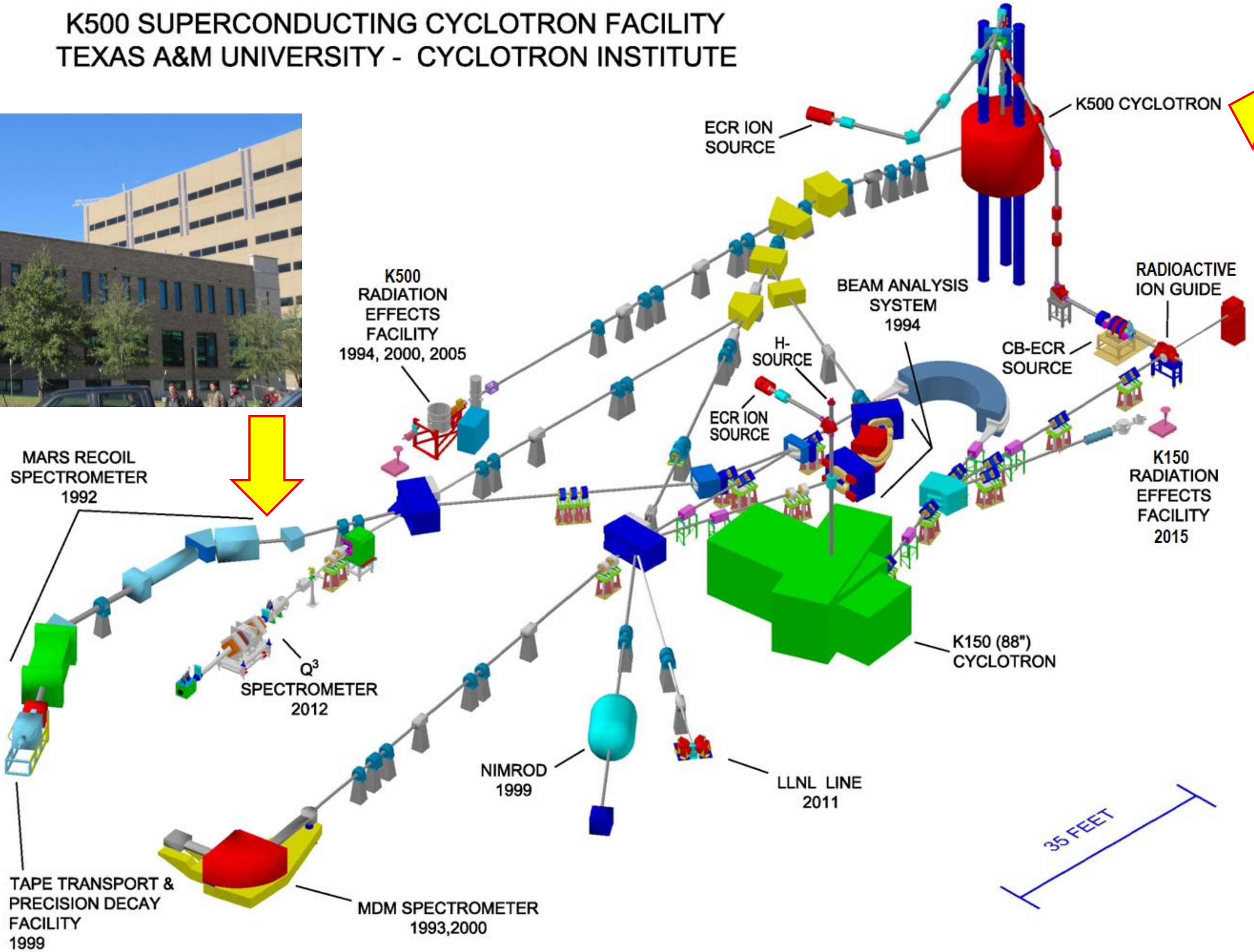
Introduction

Methodology → **Radioisotope production using inverse kinematics**

- heavy-ion beam
- light gas target (e.g., H, d, He)
- Products focused along with the beam direction
- Foil catcher
- quantity of the material is ~1,000 times less

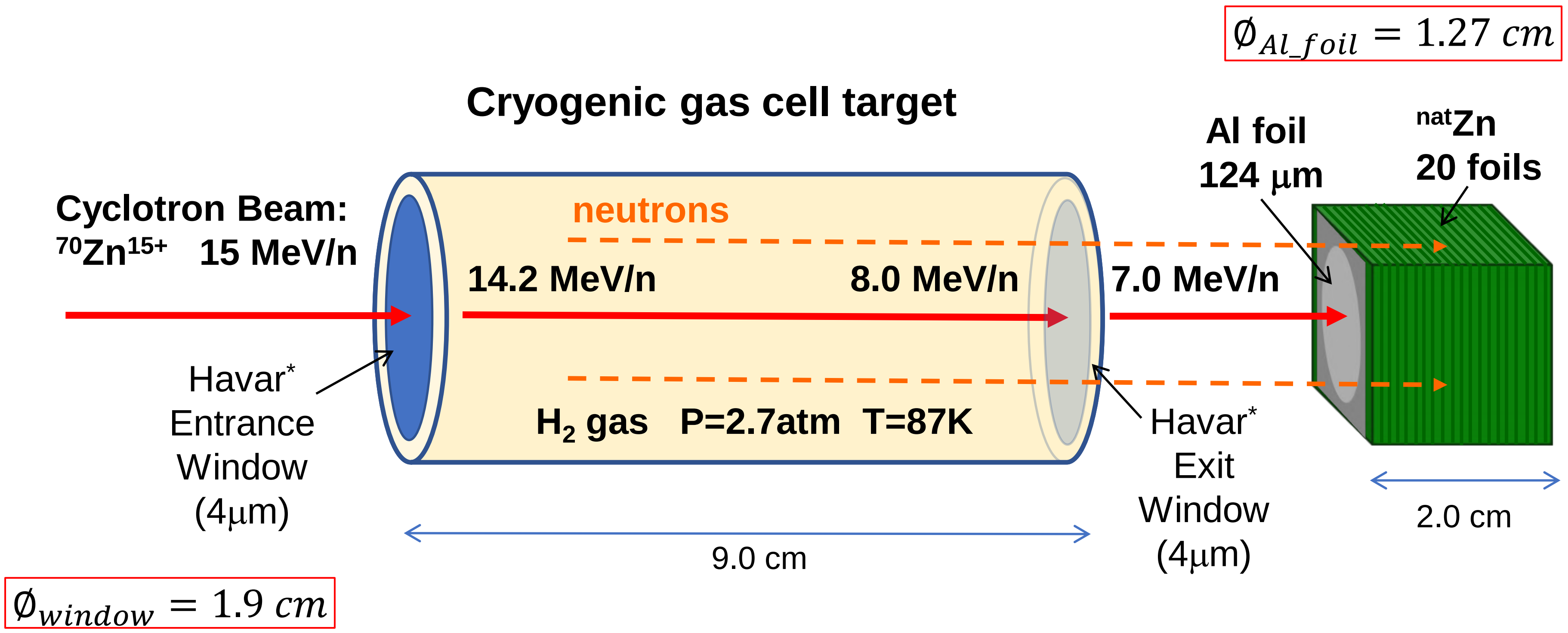
- Use of secondary emitted particles from the primary nuclear reaction to irradiate other targets

Experimental Set up



15.0 MeV/u beam of $^{70}Zn_{15+}$

Experimental Set up

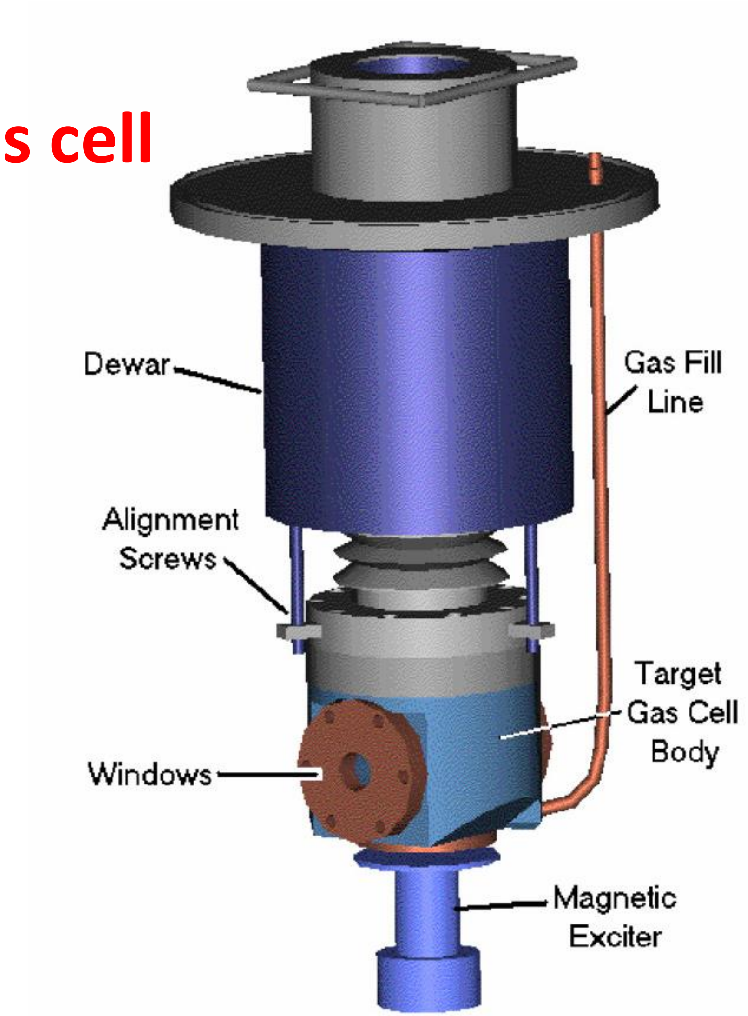


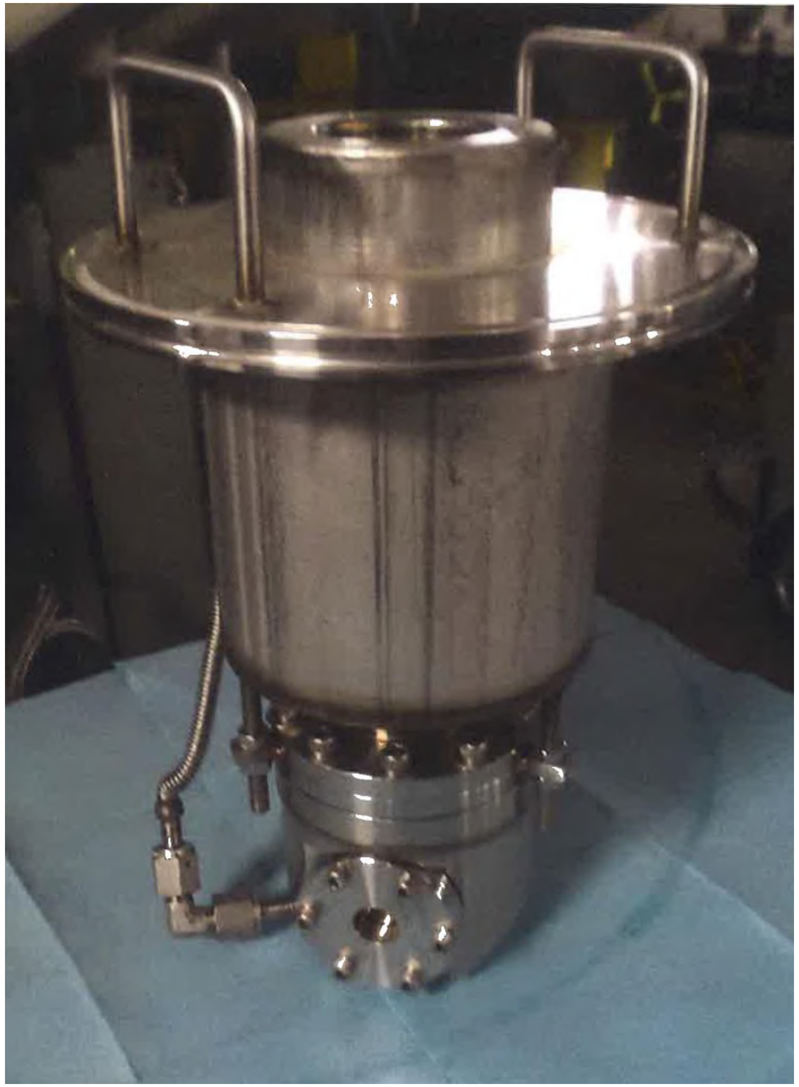
G.A. Souliotis, M.R.D. Rodrigues, K. Wang, V. Iacob, N. Nica, B. Roeder, G. Tabacaru, M. Yu, P. Zanotti-Fregonara, A. Bonasera, Applied Radiation and Isotopes 149, 89 (2019).

*HAVAR® - High strength non-magnetic alloy foil
Co 42.0% Mo 2.2% Cr 19.5% Mg 1.6% Ni 12.7% C 0.2% W 2.7% Fe Balance

Experimental Set up

Cryogenic gas cell





Introduction

^{67}Cu production

Radioimmunotheranostics - radioimmunotherapy (RIT) and diagnostic imaging

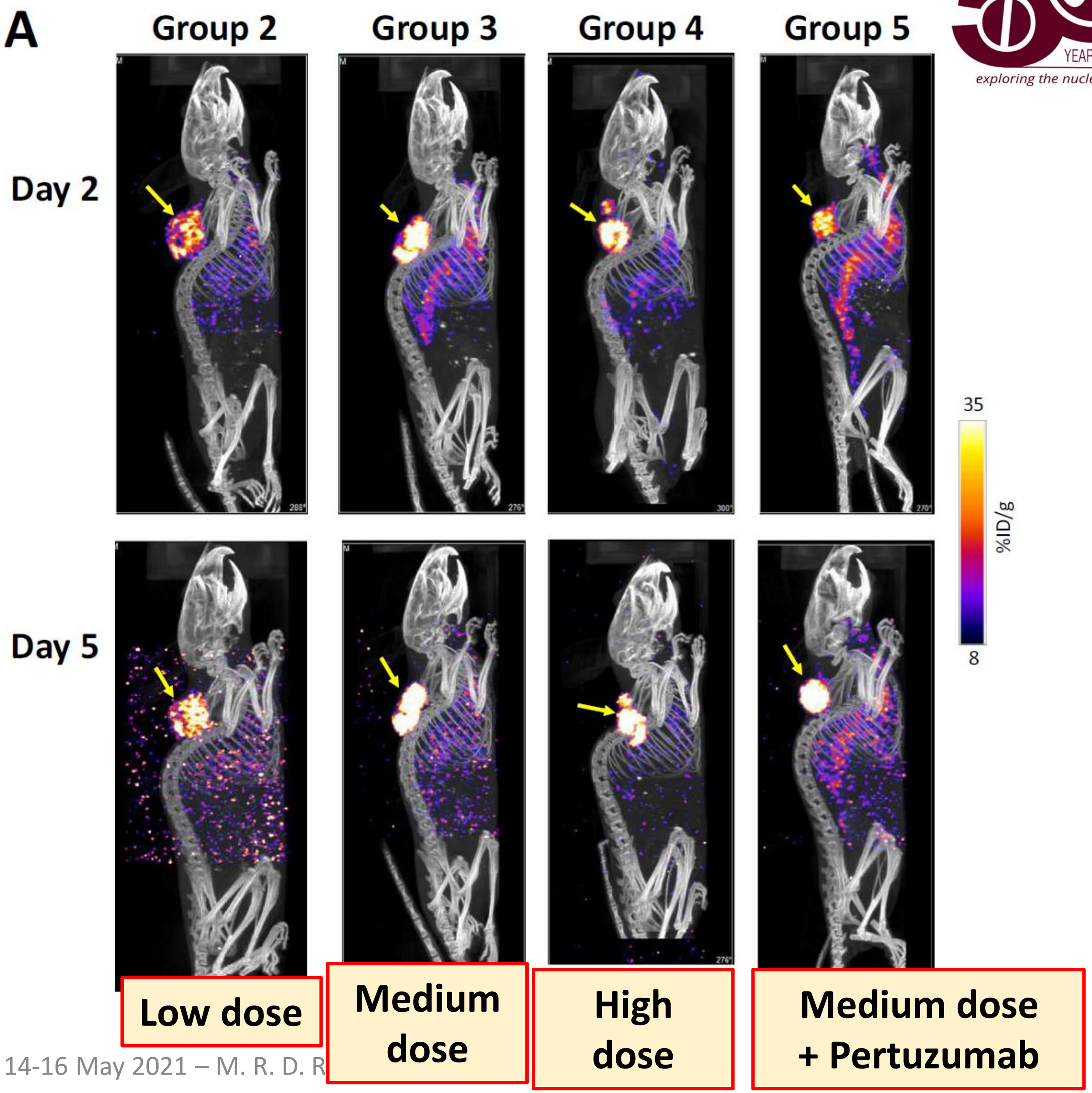
- RTI - injection of a radioisotope-labeled monoclonal antibody (mAb) to treat cancer
- $T_{1/2}$ = 61.9 h (longest-lived radioisotope of copper)
- β^- decay ($E_{e,max}$ = 577 keV)
- γ-radiation 91 keV (7%)
  93 keV (16%)
  184.6 keV (48.7%)
- imaging the radiotracer distribution by single-photon emission computed tomography (SPECT)
- combined with the same type of radiopharmaceuticals as ^{64}Cu ($T_{1/2}$=12.7 h) leading to efficient theranostic pairs
- Theranostic approach to pretargeted radioimmunotherapy (PRIT)
- Limited availability

Introduction

^{67}Cu radioimmunotheranostics

Hao, G., Mastren, T., Silvers, W. *et al.* Copper-67 radioimmunotheranostics for simultaneous immunotherapy and immuno-SPECT. *Sci Rep* **11,** 3622 (2021).

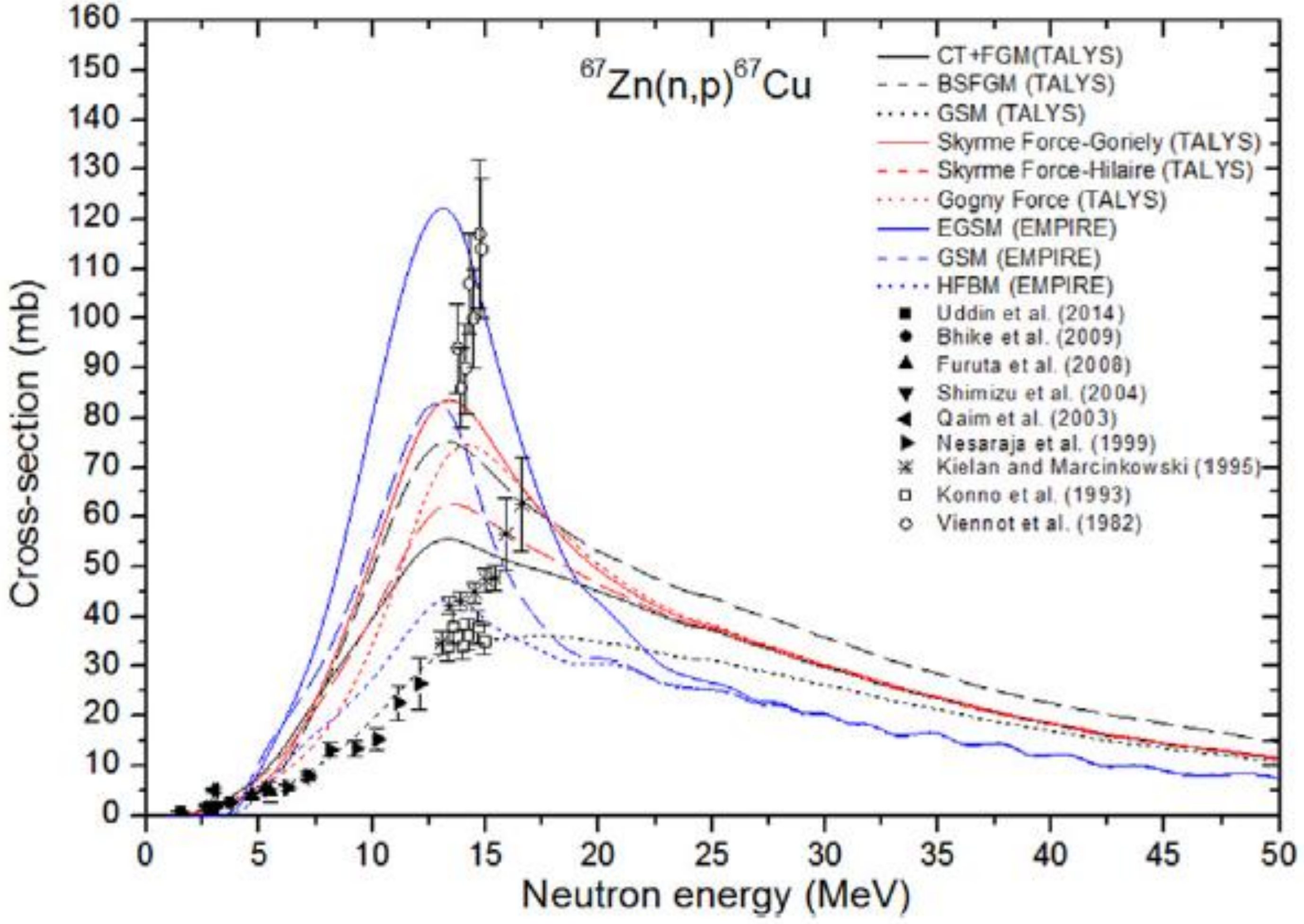
Representative maximum intensity projection (MIP) SPECT/CT images of HCC1954 HER2+ tumor-bearing mice injected with [67Cu]Cu-NOTA-Pertuzumab



Introduction

^{67}Cu production

^{67}Zn(n,p)^{67}Cu
^{68}Zn(p,2p)^{67}Cu
^{70}Zn(p,α)^{67}Cu
^{71}Ga(p,x)^{67}Cu
^{75}As(p,spall)^{67}Cu
^{70}Zn(d,x)^{67}Cu
^{68}Zn(d,x)^{67}Cu
^{67}Zn(d,2p)^{67}Cu
^{64}Ni(α,p)^{67}Cu
^{68}Zn(γ,p)^{67}Cu

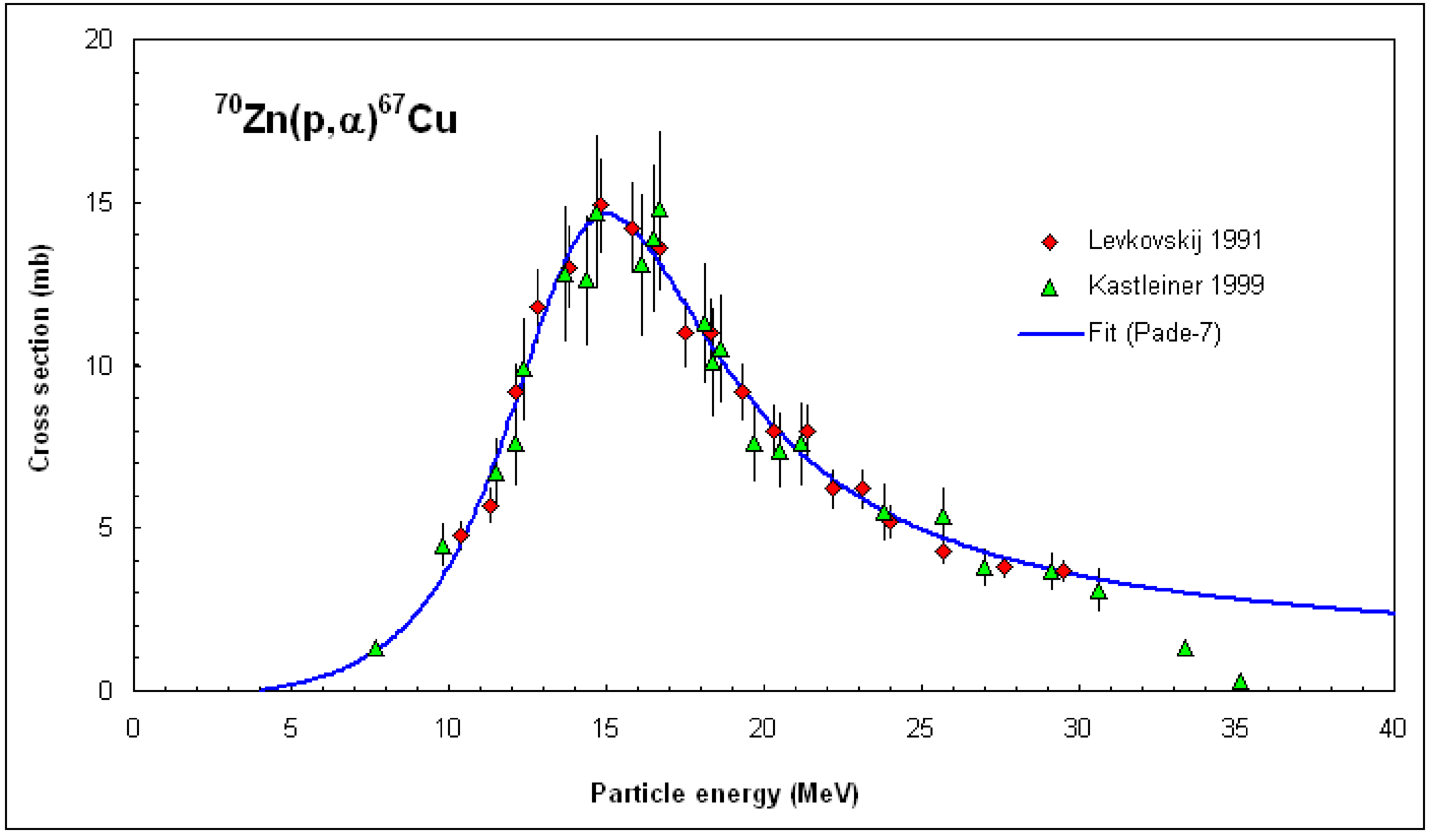


Applied Radiation and Isotopes 144 (2019) 64–79

Introduction

^{67}Cu production

$^{67}Zn(n,p)^{67}Cu$
$^{68}Zn(p,2p)^{67}Cu$
$^{70}Zn(p,\alpha)^{67}Cu$
$^{71}Ga(p,x)^{67}Cu$
$^{75}As(p,spall)^{67}Cu$
$^{70}Zn(d,x)^{67}Cu$
$^{68}Zn(d,x)^{67}Cu$
$^{67}Zn(d,2p)^{67}Cu$
$^{64}Ni(\alpha,p)^{67}Cu$
$^{68}Zn(\gamma,p)^{67}Cu$



https://www-nds.iaea.org/medical/zn067cu0.html

Introduction

^{67}Cu production

$$^{70}Zn + {}^{1}H \longrightarrow {}^{67}Cu + \alpha$$

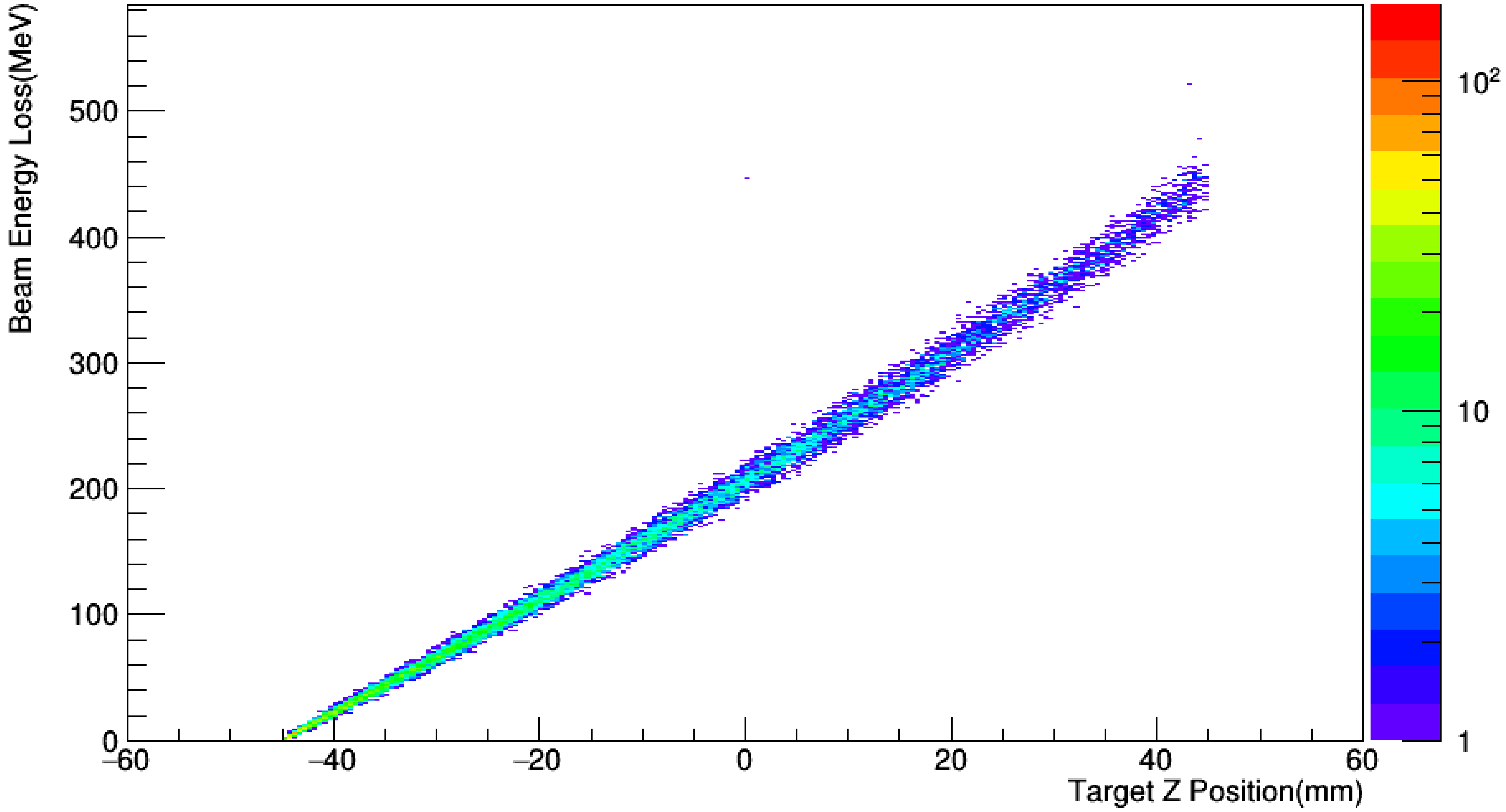
Primary reaction

$$n + {}^{67}Zn \longrightarrow {}^{67}Cu + p$$

Secondary reaction

Data and Analysis

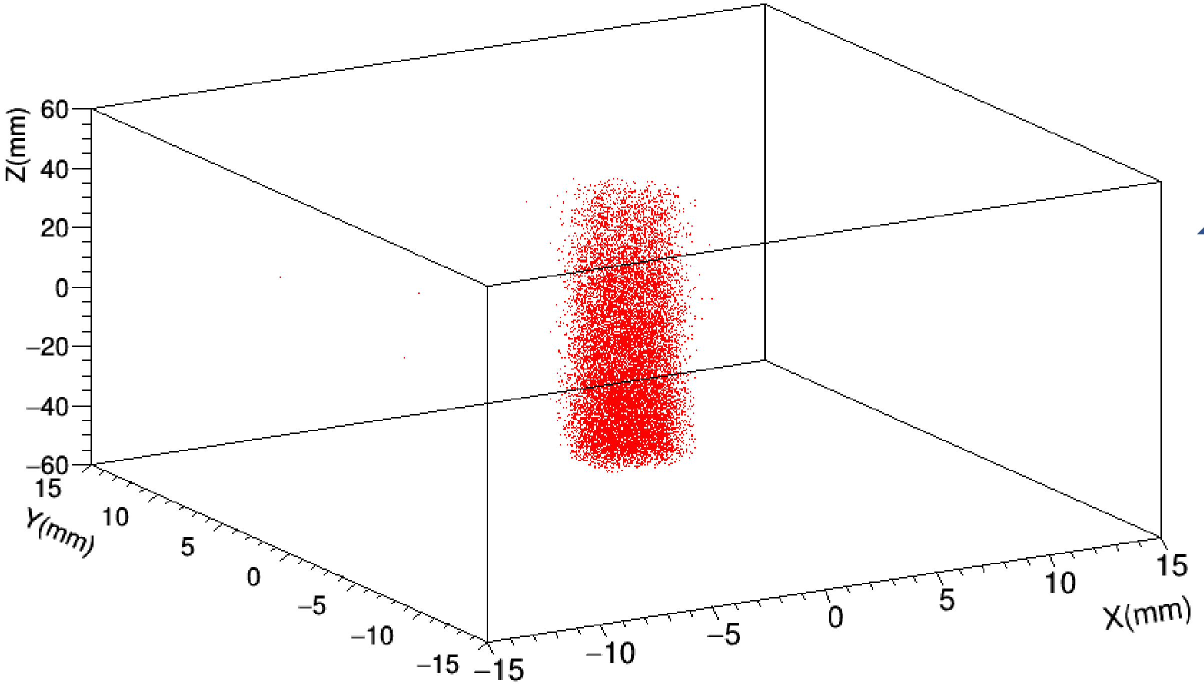
Geant4 Simulation



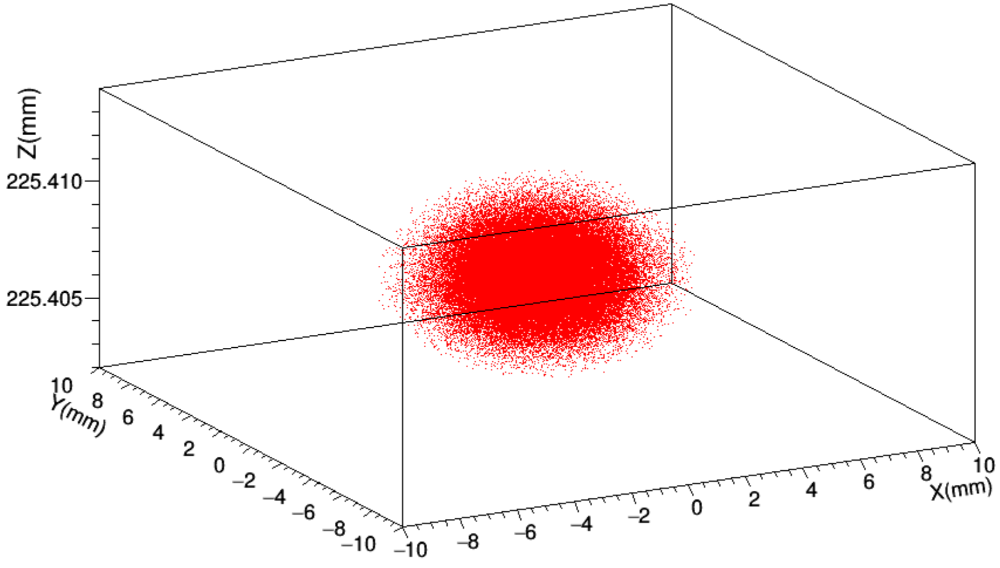
Data and Analysis

Geant4 Simulation

Gas Target Reaction Position



Al foil beam range



5.3 % of ^{67}Cu do not hit Al foil

$$\langle \sigma \rangle = 8.7 \text{ mb}$$

$$R_{Al} = 5.3\ kBq$$

Data and Analysis

Irradiation

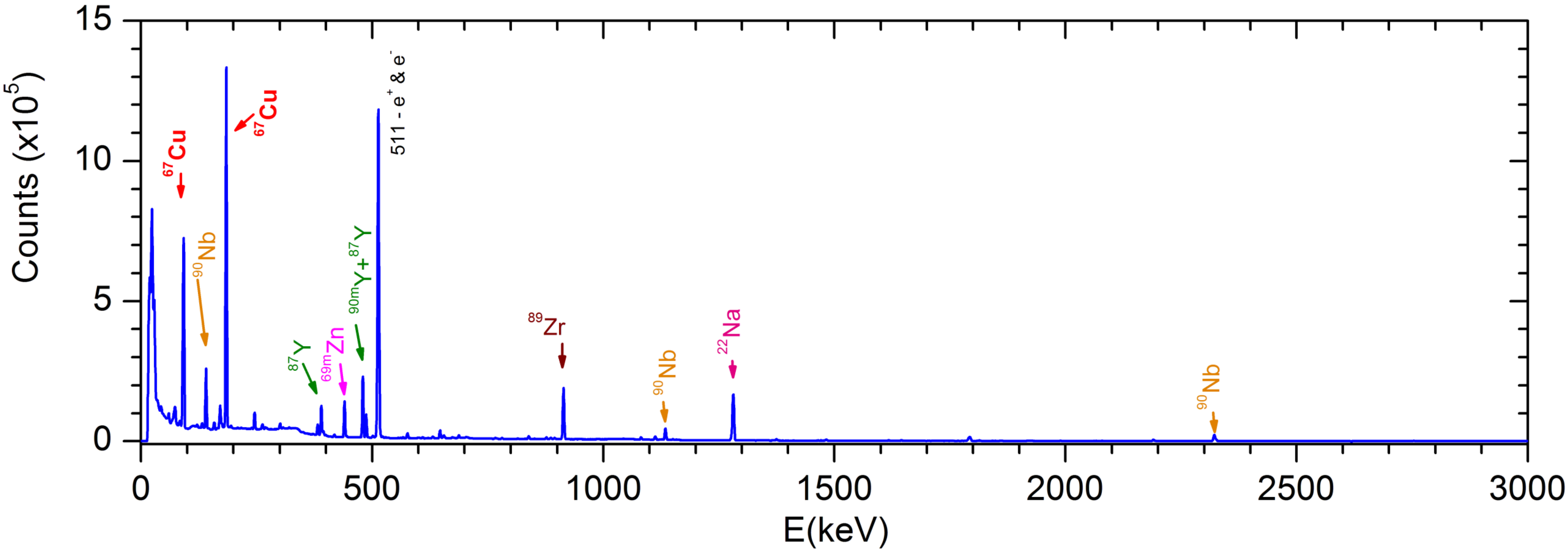
- Beam current of 0.31 pnA (particle nA) (2.0×10^9 particles s^{-1})
- 8.0 nA of ^{70}Zn (7.0 MeV/nucleon) at an average charge state of 26^+
- Beam current was periodically monitored and was nearly constant (within 15 %)
- 6.5 h irradiation

Off-line γ-ray analysis

- Ge detector
- Al foil d = 17.2(10) mm
- dead time 2-3%
- Energy resolution 2.5–4.0 keV (FWHM)
- Cool time: 36h34min
- Measurement time: 6h34min

G.A. Souliotis, M.R.D. Rodrigues, K. Wang, V. Iacob, N. Nica, B. Roeder, G. Tabacaru, M. Yu, P. Zanotti-Fregonara, A. Bonasera, Applied Radiation and Isotopes 149, 89 (2019).

Data and Analysis



Data and Analysis

Averaged Observed Activity →

$$\langle R \rangle = \frac{C}{\varepsilon \Delta t_L I_\gamma}$$

- C → Net area of the peak
- ε → Efficiency
- Δt_L → Measurement time
- I_γ → Branching Ratio

Activity after Irradiation →

$$R_{AI} = \langle R \rangle\, e^{\lambda t_{dk}} \frac{\lambda \Delta t_R}{\left(1 - e^{-\lambda \Delta t_R}\right)} \frac{\lambda t_{irr}}{\left(1 - e^{-\lambda t_{irr}}\right)}$$

- t_{dk} → Cool time
- Δt_R → Real time
- λ → Decay Constant
- t_{irr} → Beam time

Correction for activity drop during Cool time	Correction for decay during measurement	Correction for decay during irradiation
1.507	1.436	1.037

$$H_{AI} = \frac{R_{AI}}{I_{beam} t_{irr}}$$

Data and Analysis

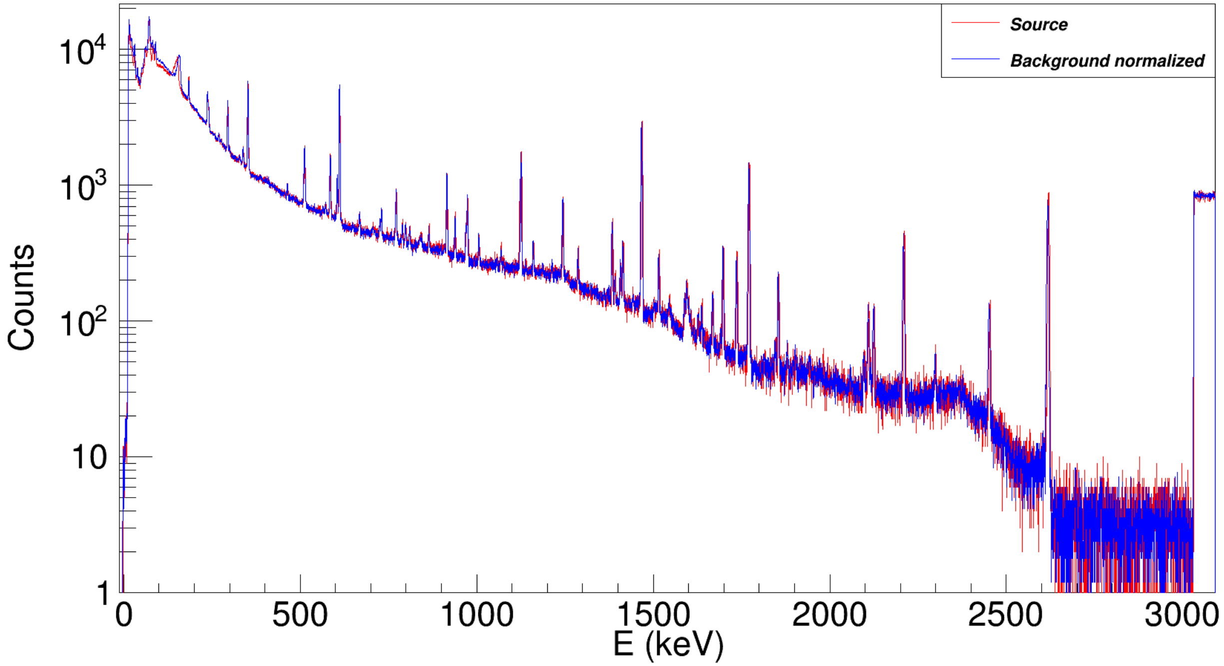
Element	E_γ (keV)	Iγ (%)	Half Life	R_M (Bq)	R_{AI} (Bq)	H_{AI} (kBq/pnA.h)
^{67}Cu (Al foil)	91.266 + 93.311 184.577	7 + 16.1 48.7	61.83h	1214	2518	1.164
^{67}Cu (frame)	91.266 + 93.311 184.577	7 + 16.1 48.7	61.83h	101	145	0.067

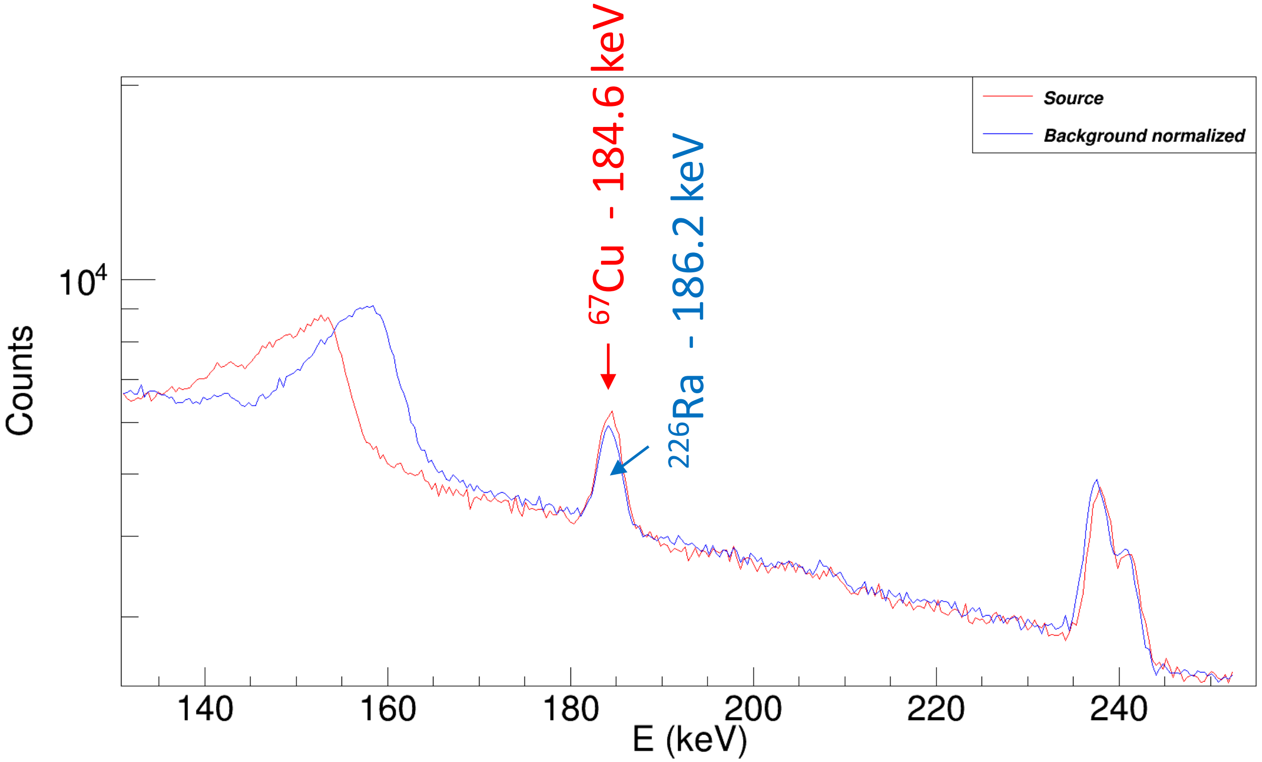
Corrections
Solid angle 5.3 % not detected
Dead time 0.97 %
Uncertainties
Beam current 20%
Efficiency at low energy 20%

$$H_{AI} = 1.2(4)\left(\frac{kBq}{pnA.h}\right)$$

Data and Analysis

Secondary reaction $^{67}Zn(n,p)^{67}Cu$





Data and Analysis

Secondary reaction $^{67}Zn(n,p)^{67}Cu$

Element	E_γ (keV)	I_γ (%)	Half Life	R_M (Bq)	R_{AI} (Bq)
^{67}Cu (^{nat}Zn target)	184.577	48.7	61.83h	0.72	6.2

Cool time: 7d 12h

Measurement time: 40 h

Corrections

Self absorption 50%

Dead time 0.97 %

Solid angle 2% of neutrons produced

Isotopic abundance ^{67}Zn (4.04%)

Uncertainties

Beam current 20%

Efficiency at low energy 20%

$$R_{AI} = 15.510\ Bq$$

$$H_{AI} = 8(2)\left(\frac{kBq}{pnA.h}\right)$$

Results and Conclusions

- ✓ The main radionuclide produced was the ^{67}Cu over ten times more intense.
- ✓ The only radioimpurity produced from ^{70}Zn + p reaction was ^{69m}Zn ($T_{1/2}$ = 13.8 h) and it can be reduced by further radio-cooling
- ✓ Low radioimpurity produced from beam interaction with Havar windows and Al catcher foil.
- ✓ Production of ^{67}Cu with secondary reaction.

Next steps

- Activities for preclinical studies → development of high-intensity heavy-ion primary beams.
- Pursuing the investigation of an alternative production method in inverse kinematics for important isotopes for nuclear medicine in high demand worldwide, where the production in reactors is not enough to supply the demand.
- The well-known ^{99}Mo/^{99m}Tc generator system – next talk Dr. Justin Mabiala

Colaboration

Cyclotron Institute, Texas A&M University, USA

Dr. Aldo Bonasera
Dr. Marcia R. D. Rodrigues
Dr. Victor E. Iacob
Dr. Ninel Nica
Dr. Brian Roeder
Dr. Gabriel C. Tabacaru
K. Wang
J. Romo

University of Athens, Greece

Dr. George Souliotis

HMRI, Houston Methodist Hospital, USA

Dr. Max Yu

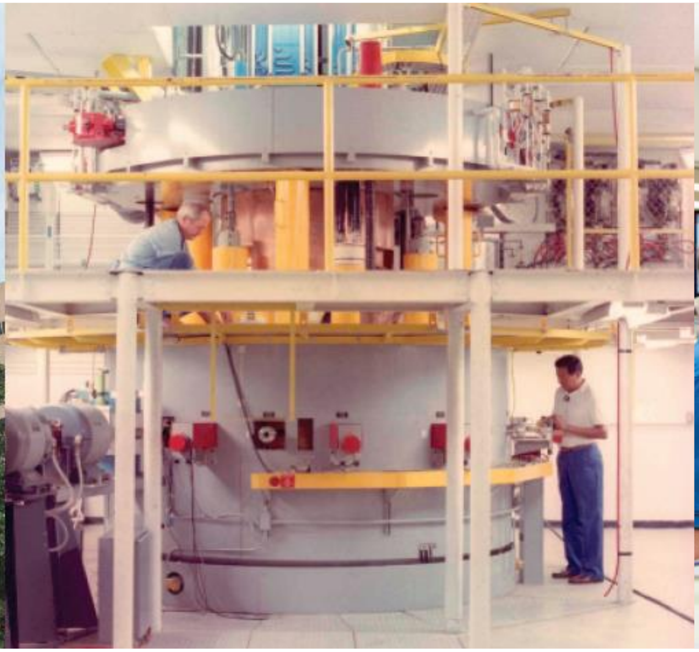
Dr. P. Zanotti-Fregonara

Praire View A&M University, USA

Dr. Justin Mabiala

TEXAS A&M UNIVERSITY

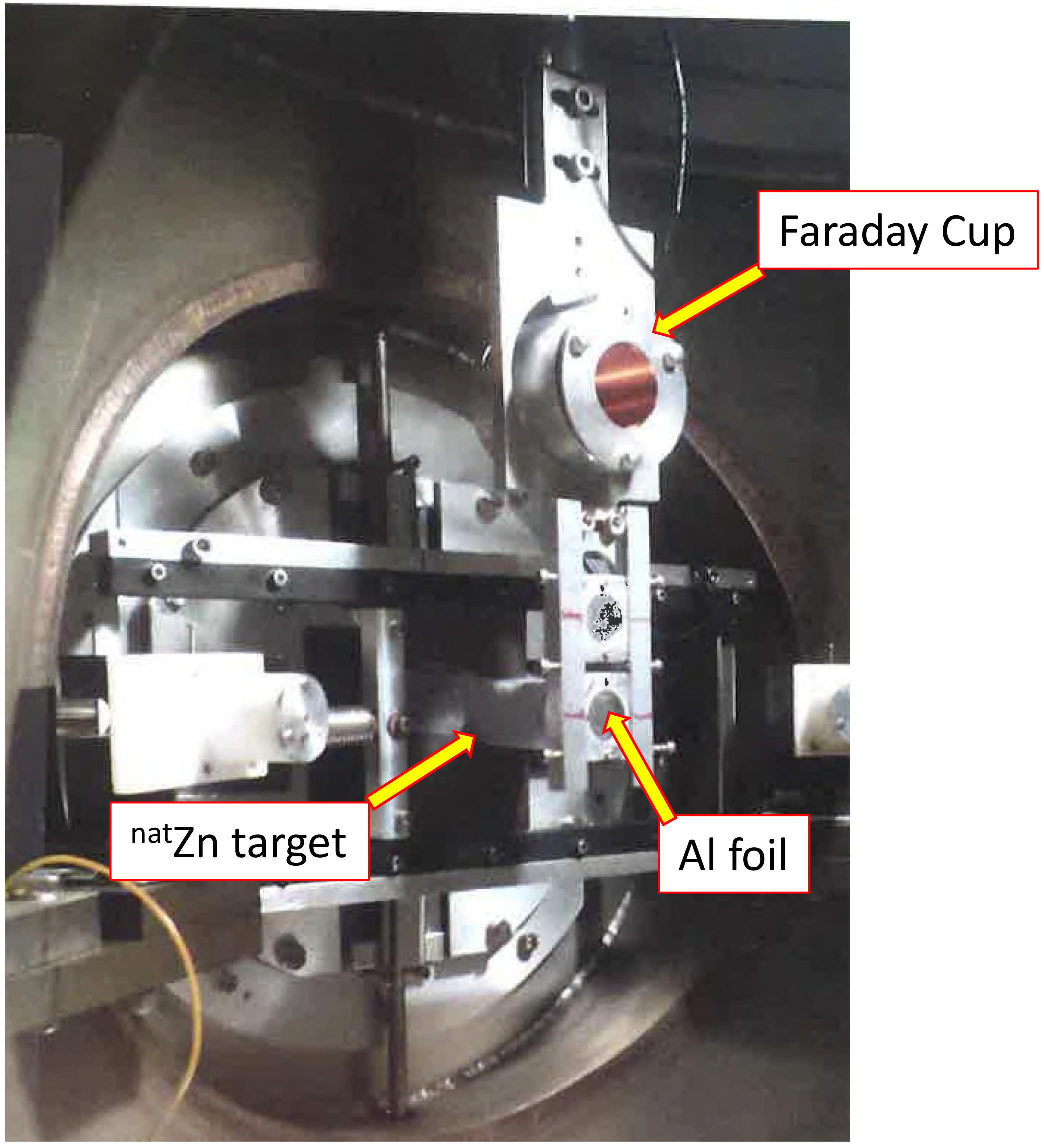
CYCLOTRON INSTITUTE
1967 - 2017
50 YEARS OF BEAM
exploring the nuclear frontier




Thank you

Back up slides

Experimental Set up



^{67}Cu radioimmunotheranostics

Harnessing ^{64}Cu/^{67}Cu for a theranostic approach to pretargeted radioimmunotherapy

Outi Keinänen[a,b], Kimberly Fung[a,c], James M. Brennan[a], Nicholas Zia[d], Matt Harris[e], Ellen van Dam[e], Colin Biggin[e], Amos Hedt[e], Jon Stoner[f], Paul S. Donnelly[d], Jason S. Lewis[b,g,h], and Brian M. Zeglis[a,b,c,g,1]

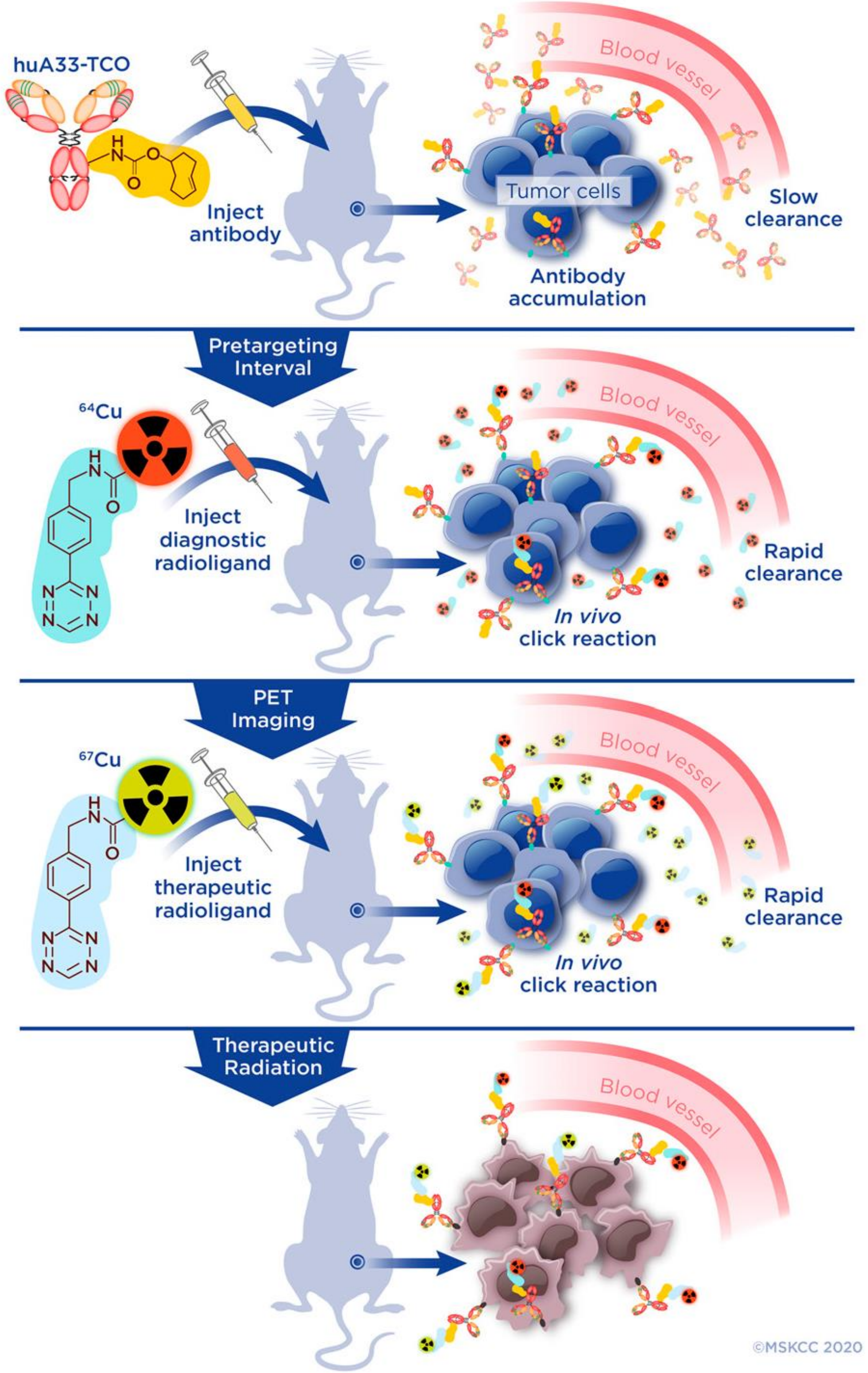
[a]Department of Chemistry, Hunter College, The City University of New York, New York, NY 10021; [b]Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY 10065; [c]PhD Program in Chemistry, Graduate Center of the City University of New York, New York, NY 10016; [d]School of Chemistry and Bio21 Molecular Science Institute, University of Melbourne, Melbourne, VIC 3010, Australia; [e]Clarity Pharmaceuticals, Sydney, NSW 2042, Australia; [f]Idaho Accelerator Center, Idaho State University, Pocatello, ID 83201; [g]Department of Radiology, Weill Cornell Medical College, New York, NY 10021; and [h]Program in Molecular Pharmacology, Memorial Sloan Kettering Cancer Center, New York, NY 10065

Edited by Jacqueline K. Barton, California Institute of Technology, Pasadena, CA, and approved September 24, 2020 (received for review May 18, 2020)

Over the past decade, theranostic imaging has emerged as a powerful clinical tool in oncology for identifying patients likely to respond to targeted therapies and for monitoring the response of patients to treatment. Herein, we report a theranostic approach to pretargeted radioimmunotherapy (PRIT) based on a pair of

Lu-DOTA-TATE (LUTATHERA) (17, 18). Similarly, [^{18}F]F- and [^{68}Ga]Ga-labeled probes that target prostate-specific membrane antigen (PSMA) have been used as companion imaging agents in patients undergoing treatment with the PSMA-targeted radiotherapeutics [^{177}Lu]Lu-PSMA-617 and [^{225}Ac]

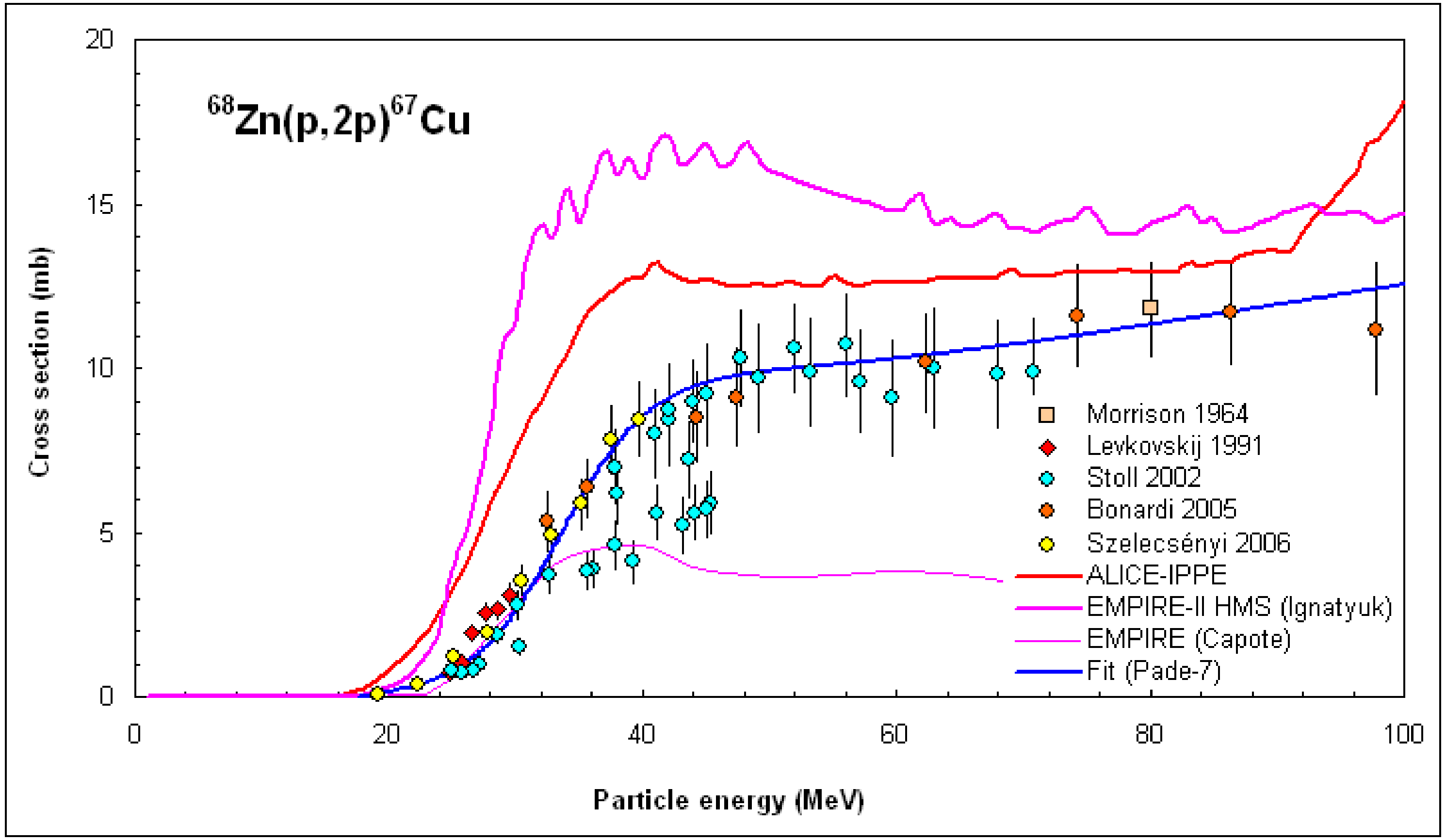
PNAS November 10, 2020 117 (45) 28316-28327



Introduction

^{67}Cu production

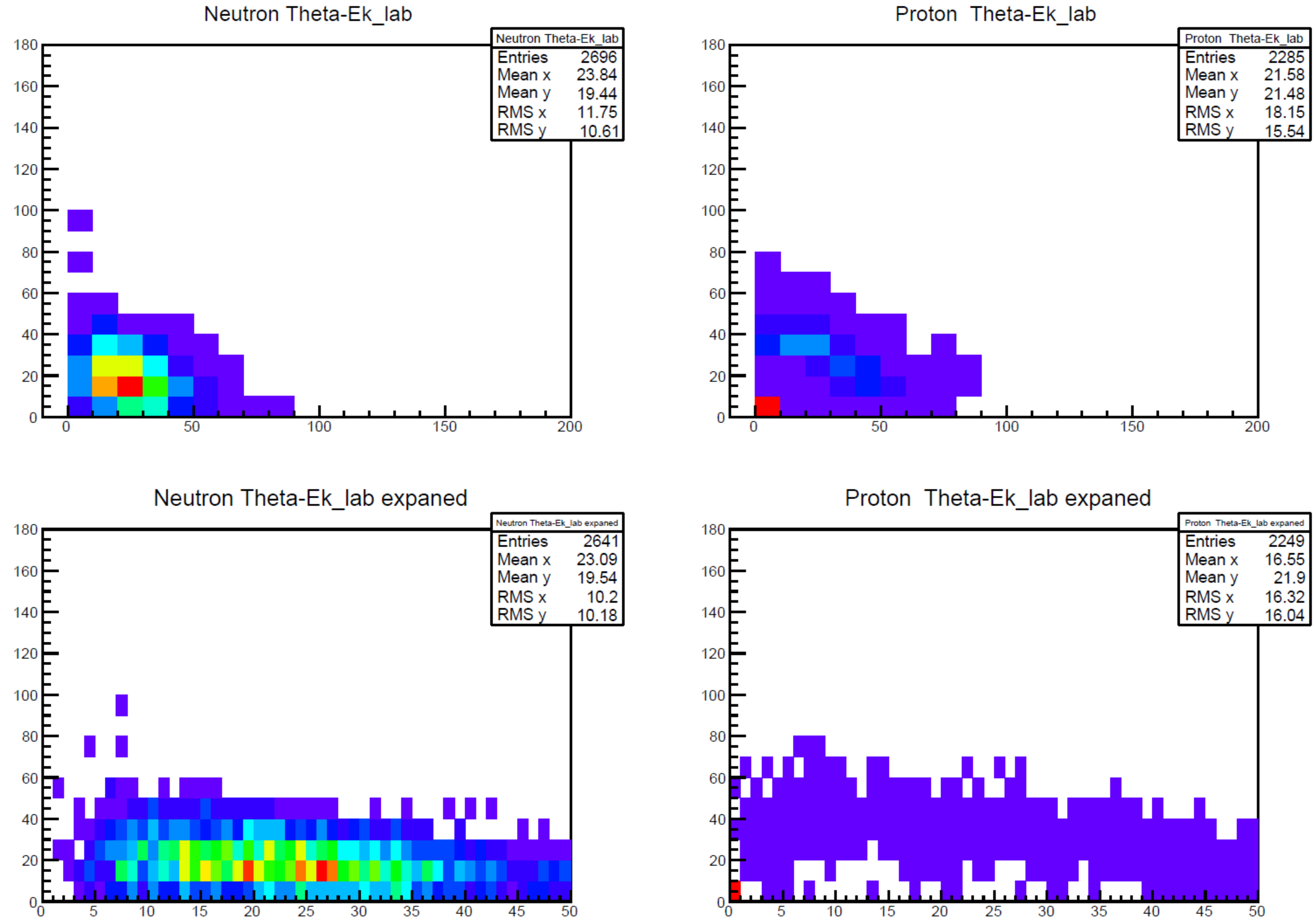
$^{67}Zn(n,p)^{67}Cu$
$^{68}Zn(p,2p)^{67}Cu$
$^{70}Zn(p,\alpha)^{67}Cu$
$^{71}Ga(p,x)^{67}Cu$
$^{75}As(p,spall)^{67}Cu$
$^{70}Zn(d,x)^{67}Cu$
$^{68}Zn(d,x)^{67}Cu$
$^{67}Zn(d,2p)^{67}Cu$
$^{64}Ni(\alpha,p)^{67}Cu$
$^{68}Zn(\gamma,p)^{67}Cu$



https://www-nds.iaea.org/medical/zn867cu0.html

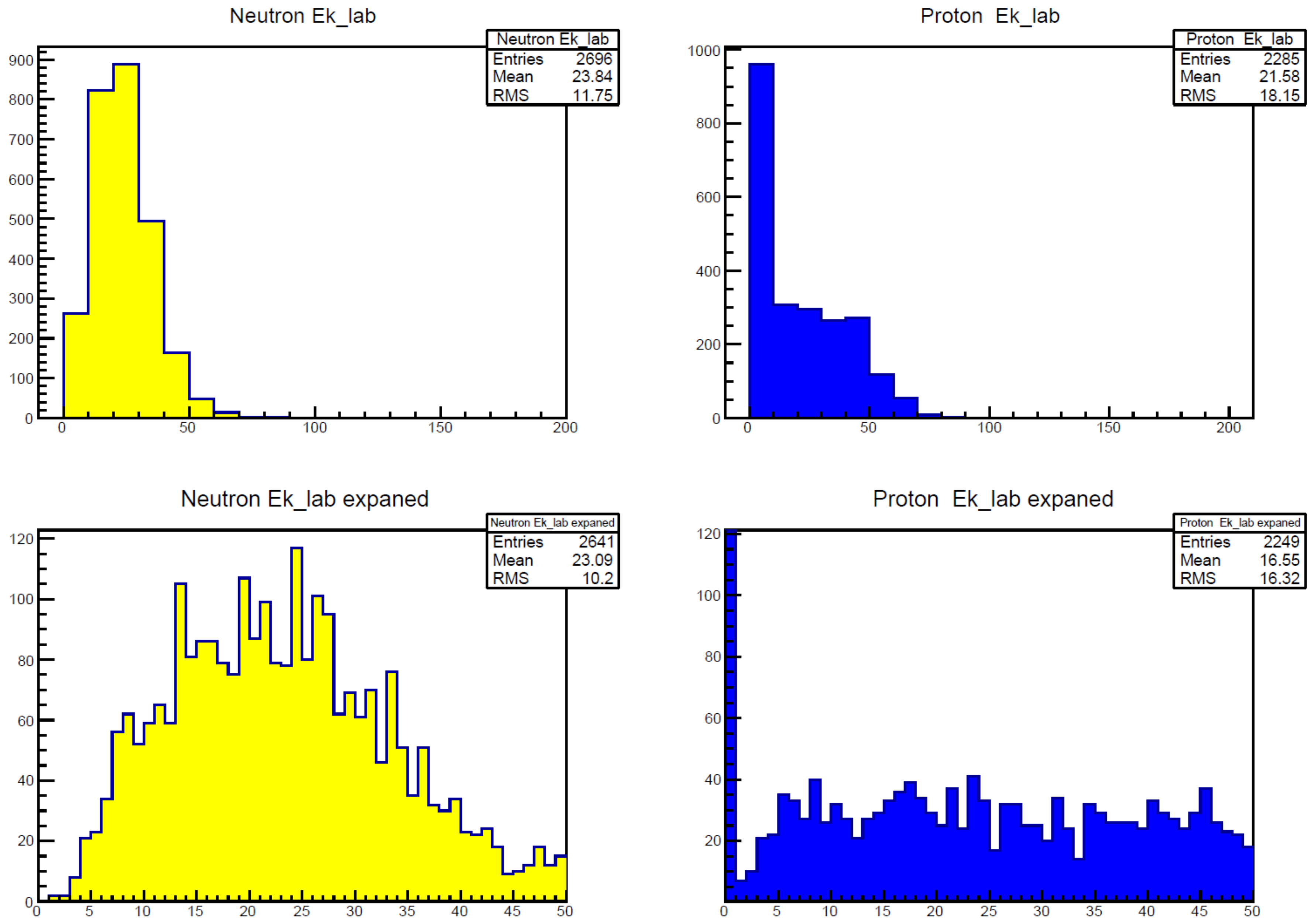
Neutron and proton production from ^{70}Zn + p reaction COMD

comd_20zn070pp_np_lab_c3



Neutron and proton production from ^{70}Zn + p reaction COMD

comd_20zn070pp_np_lab_c1



TEXAS A&M UNIVERSITY

CYCLOTRON INSTITUTE
1967 - 2017
YEARS OF BEAM
exploring the nuclear frontier

Data and Analysis

Table 1
Copper radionuclides produced via neutron irradiation of ^{nat}ZnO target.

Isotope of ^{nat}Zn with abundance	Reaction	Half-life of products	Decay mode	Cross section
^{64}Zn (49.17%)	^{64}Zn(n,p)^{64}Cu	12.7 h	ε^+, β^+, β^-	31 ± 2.3 mb
^{66}Zn (27.73%)	^{66}Zn(n,p)^{66}Cu	5.12 m	β^-	480 ± 80 μb
^{67}Zn (4.04%)	^{67}Zn(n,p)^{67}Cu	2.576 d	β^-	0.9 mb
^{68}Zn (18.45%)	^{68}Zn(n,p)^{68m}Cu $\xrightarrow{IT}$ ^{68}Cu	$t_{1/2}$ (^{68m}Cu) = 30.9 s $t_{1/2}$ (^{68}Cu) = 3.75 m	IT, β^-	15.6 ± 2.5 μb
^{70}Zn (0.61%)	^{70}Zn(n,p)^{70m}Cu $\xrightarrow{IT}$ ^{70}Cu	$t_{1/2}$ (^{70m}Cu) = 44.5 s $t_{1/2}$ (^{70}Cu) = 6.6 s	β^-	3 μb
	^{70}Zn(n,α)^{67}Ni $\xrightarrow{\beta^-}$ ^{67}Cu	21 s	β^-	12 μb

Annals of Nuclear Energy 133, November 2019, Pages 665-668