Research Reactor Production and Purification of ^{64}Cu and ^{67}Cu Using Enriched Zinc Target Materials

A. M. Johnsen,[1] B. J. Heidrich,[1] C. B. Durrant,[1,2] A. J. Bascom,[1,2] and K. Ünlü[1,2]

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Introduction

^{64}Cu and ^{67}Cu are short-lived, radioactive *theranostic* medical isotopes in high demand for use as *thera*peutic treatment agents for multiple types of cancer and in medical diag*nostics*. However, they have had a limited and inconsistent supply for several decades [1, 2]. To aid in their availability, we conducted preliminary development work for their production in a research reactor and their purification in our unique radioactive handling facilities, while also educating and training students in medical isotope production methods.

Background

^{64}Cu and ^{67}Cu have a number of radiological characteristics that make them valuable in medical settings (TABLE 1). ^{64}Cu has a unique combination of β^+, β^-, and gamma-ray decay modes. ^{64}Cu positron emissions allow for its use as a diagnostic agent via positron emission tomography (PET), and because its half-life is longer than those of more commonly used PET isotopes, it allows for up to 48 hours of imaging, enabling longer-term monitoring of slower biochemical reactions. ^{67}Cu also provides theranostic capabilities. Its low energy gamma-ray emissions allow for single photon emission computed tomography (SPECT) imaging and ^{67}Cu has been evaluated for treatments for non-Hodgkin's lymphoma and multiple types of cancer. Copper does not seek out bone tissue and has a moderate biological half-life of 13 to 33 days [3]. Neither copper nor the zinc decay products from ^{64}Cu and ^{67}Cu are toxic in therapeutic or diagnostic doses [2].

TABLE 1: Properties and uses of ^{64}Cu and ^{67}Cu [3]

	^{64}Cu	^{67}Cu
Half-life	12.700 ± 0.002 h	61.83 ± 0.12 h
Decay modes	β^+ ~278 keV (17.4%) EC (43.1%) β^- ~190 keV (39.0%)	β^- ~141 keV (100%) γ 184.6 keV (48.7%) 93.3 keV (16.1%) 91.3 keV (7.0%)
β^- tissue range	0.95 mm [4]	0.61 mm [4]
Medical uses	PET imaging Therapeutic treatments	SPECT imaging Therapeutic treatments

The ^{64}Cu and ^{67}Cu activity levels required by researchers and clinicians vary by application. Small mammal research requires between 0.1—0.4 mCi ^{64}Cu/subject and ~0.15—0.17 mCi ^{67}Cu/subject, while human diagnostic procedures require between 0.5—15 mCi $^{64/67}$Cu/subject. Human therapeutic activities require anywhere from 3—425 mCi ^{67}Cu/subject [3].

As of a 2008 report, there were only three ^{64}Cu suppliers and one ^{67}Cu supplier [1]. All current suppliers use charged particle based production methods, which are efficient, but have some limitations, including target cost and availability and the availability of high-energy accelerators for ^{67}Cu production.

Most research reactors cannot produce the ^{64}Cu and ^{67}Cu activities necessary for human diagnostic and treatment procedures, but can produce enough for small mammal research. If irradiation and purification protocols can be shared amongst many small research reactors, each reactor could provide ^{64}Cu and ^{67}Cu to nearby medical researchers, thus increasing the research-level supplies.

Reactor Production of ^{64}Cu and ^{67}Cu

Reactor-based ^{64}Cu and ^{67}Cu production rates are controlled by the energy dependent neutron cross-sections. ^{64}Zn has a fast neutron (≥2 MeV) (n,p) cross-section of ~0.3 barns and ^{67}Zn has a fast neutron (n,p) cross-section of ~0.01 barns, both of which are adequate to produce ^{64}Cu and ^{67}Cu in a reactor. However, there are additional isotopes created by irradiation of natural zinc targets, which are composed of multiple zinc isotopes, namely radioactive ^{65}Zn from thermal neutron activation of ^{64}Cu, radioactive ^{63}Ni from a fast neutron (n,α) activation of ^{66}Zn, stable ^{64}Ni from a fast neutron (n,α) activation of ^{67}Zn, and thermal activation of ^{68}Zn to radioactive ^{69m}Zn. Using zinc targets enriched in ^{64}Zn and ^{67}Zn and shielding the target from thermal neutrons can substantially reduce these undesired byproducts.

Experimental Methods

This project had four overarching research and development goals: (1) design of an irradiation fixture

[1] Radiation Science and Engineering Center, Pennsylvania State University, University Park, PA 16802
[2] Department of Mechanical and Nuclear Engineering, Pennsylvania State University, University Park, PA 16802

for the irradiation of ^{NAT}ZnO, ^{64}ZnO, and ^{67}ZnO targets that reduces the thermal neutron flux (and thus unwanted thermal irradiation products) while maintaining the fast neutron flux for ^{64}Cu and ^{67}Cu production and all necessary reactor safety requirements; (2) evaluate zinc-copper separation methods for the highest effectiveness, including copper yield, zinc separation factor, and simple, rapid use; (3) irradiation of ^{NAT}ZnO, ^{64}ZnO, and ^{67}ZnO targets to evaluate the performance of the irradiation fixture, purification methods, and production capacities; and (4) the education and training of graduate and undergraduate students in the concepts and skills relevant for isotope production.

To minimize the production of unwanted isotopes and allow for maximum ^{64}Cu and ^{67}Cu production, a new irradiation fixture was developed, using computer simulation to perform virtual prototyping prior to fixture construction. Several shielding materials were investigated to reduce the thermal to fast neutron ratio to the target: boron carbide (B_4C), enriched $^{10}B_4C$, boron nitride (BN), and cadmium. An MCNP [5] model of the PSBR Core Loading 54 (2012-2013) was generated using TRIGSIM-S, the RSEC's fuel management software. This model was modified to add the sample holder to the PSBR central thimble irradiation location, as well as to estimate the neutron flux within the target material using different shielding designs and materials. MCNP can also estimate the reactivity effect to the core and the heat production in the boron material from (n,α) reactions. These estimates were later confirmed via measurement.

Due to radiation safety issues, actual target irradiation used a modified sample holder in the PSBR dry tubes, which are air-filled tubes on the outer edges of the reactor core. However, the shielding material type and thickness were the same as those determined from the MCNP modeling, and only the outer aluminum encapsulation was modified. Future irradiations with larger targets can be handled in the PSBR Hot Cell Laboratory, mitigating this issue.

All irradiations were made with zinc oxides sealed in high-purity quartz ampoules (Heraeus Quarzglas). High purity, naturally isotopic ZnO (Alfa Aesar), 99.4% enriched ^{64}Zn, and 94.8% enriched ^{67}Zn (Trace Sciences International, Inc.) were used. Acids were Trace Metal grade (Fisher) and the AG1-X8 (100-200 mesh) ion exchange resin was from Bio-Rad.

Irradiations consisted of test targets of ^{NAT}ZnO (20 mg), ^{64}ZnO (40 mg), or ^{67}ZnO (20 mg) (see TABLE 2). To evaluate the neutron fluences in the sample holder, three flux wires were irradiated with each target. Two aluminum-gold wires, one bare and one encased in 1 mm thick cadmium tubing, measured the thermal and epithermal neutron fluxes. Titanium metal wire measured the fast neutron flux, as ^{46}Ti(n,p)^{46}Sc has a similar cross-section shape for fast neutron (n,p) reactions as ^{64}Zn(n,p)^{64}Cu and ^{67}Zn(n,p)^{67}Cu.

TABLE 2: Irradiation parameters for zinc oxide irradiations

	PSBR Core	Core Location	Reactor Power	Irradiation Time
^{NAT}ZnO	54	Dry tube	900 kW	2 h 14 m
^{64}ZnO	55	Dry tube	800 kW; D_2O tank	3 h 46 m
^{67}ZnO	55	Dry tube	800 kW; D_2O tank	3 h 46 m

After 3 to 7 days of decay time for the aluminum sample holder, the target was dissolved in 8 M HCl. The dissolved sample was measured with high-purity germanium (HPGe) gamma-ray spectroscopy to determine all measurable activation products. The dissolved sample then was heated to almost dryness.

Initial, non-radioactive experimental testing of copper-zinc ion exchange separation methods evaluated three procedures from the literature: a classic Type 1 anion exchange, a Chelex-100 acetic acid method, and a low acid/organic method. The Type 1 anion exchange method proved the most efficient [3]. The dried sample was reconstituted in 1.5 mL of 8 M HCl and loaded on a column containing 2.5 g AG1-X8 resin and rinsed with five 2.5 mL portions of 2 M HCl to elute copper, 2.5 mL of DI H_2O, and 6 2.5 mL portions of 2 M HNO_3 to elute zinc. All collected samples were measured for activity.

Results

The MCNP model demonstrated that $^{10}B_4C$ shields thermal neutrons most effectively; however, B_4C and BN provide more than adequate shielding at a much lower cost. The model also considered the presence or absence of a BN top; as expected, the top greatly improved the thermal neutron suppression (Figure 1). Cadmium metal also was modeled (not shown) and effectively shields thermal neutrons, but was abandoned because epithermal neutrons still reach the target chamber and because cadmium produces radioactive activation products, creating mixed waste. BN was selected as the sample holder material because it shields efficiently, is low cost, and is simple to manufacture.

The MCNP model also calculated the ^{64}Zn(n,γ)^{65}Zn and ^{64}Zn(n,p)^{64}Cu reaction rates within the target material. The ratio of the two rates was used to compare shielding effectiveness as the sample holder radius was decreased by 1/16-inch increments; the ratio remained between three and four for all sample holders outer radii between 1.00 to 0.75 inches, while reactivity and heating decreased dramatically. The final fast flux sample holder parameters are shown in TABLE 3. The holder and top were machined from a BN rod (hexagonal BN grade, Alfa Aesar).

The data from the irradiated gold and titanium neutron flux wires were analyzed using ASTM Standard Test Methods [6] and are shown in TABLE 4. The thermal neutron flux decreased from ~10^{13} n/cm^2/s (the typical neutron flux in a PSBR dry tube) by two to three orders of magnitude, enough to reach the limit of this

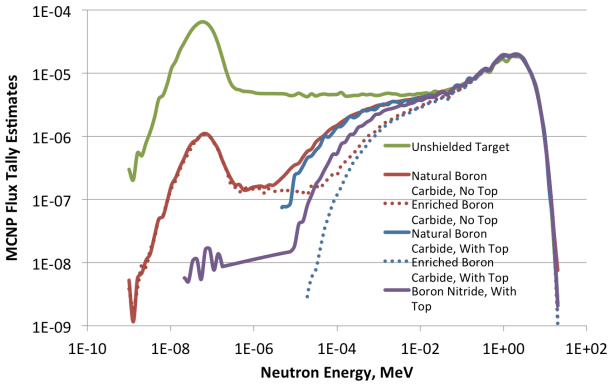

Figure 1: MCNP estimates of the neutron flux spectrum in the modeled sample irradiation fixture

TABLE 3: Final shielded sample irradiation fixture specifications

Total mass	58 g
Outer diameter	0.75 in
Shielding thickness	0.16 in
Sample chamber length	1.25 in
Overall shielded length	1.81 in
Boron nitride density	3.48 g/cm^3
Measured reactivity worth	-$0.80

measurement technique. The resonance neutron flux is reduced by an order of magnitude. The maximum fast neutron flux in the PSBR dry tubes is ~3×10^{12} to ~5×10^{12} n/cm^{2}s; a similar flux level was found in the BN-shielded sample holder, preserving fast neutrons for ^{64}Cu and ^{67}Cu production.

TABLE 4: Flux values calculated from aluminum-gold wires, aluminum-gold wires covered with cadmium, and titanium wires irradiated with each zinc oxide target sample [3]

Target	PSBR Core	Thermal Flux ×10^{-10} (n/cm^2/s)	Epithermal Flux ×10^{-10} (n/cm^2/s)	Fast Flux ×10^{-12} (n/cm^2/s)
^{NAT}ZnO	54*	-20.4 ± 0.3	8.4 ± 0.4	5.3 ± 0.4
^{64}ZnO	55	0.8 ± 1.8	5.5 ± 0.3	3.0 ± 0.3
^{67}ZnO	55	3.2 ± 2.1	5.9 ± 0.3	3.2 ± 0.3

*PSBR core 54 had an increased dry tube neutron flux than is typical.

The radioisotope production from the irradiated zinc targets is shown in TABLE 5. The ^{NAT}ZnO sample had measureable amounts of ^{67}Cu, ^{65}Zn, and ^{76}As, clearly showing ^{67}Cu production and some ^{75}As from ^{74}As contamination in the target. ^{64}Cu and ^{69m}Zn were also detected, but enough time had passed between irradiation and measurement that the counting statistics could not be quantified.

The ^{64}ZnO target produced 460 µCi (1.21×10^{-10} g) of ^{64}Cu and 2 µCi (2.52×10^{-10} g) of ^{65}Zn. An unshielded sample in the PSBR core would be expected to produce

TABLE 5: Activity at the end of irradiation for ^{NAT}ZnO, ^{64}ZnO, and ^{67}ZnO oxide targets irradiated in the boron nitride sample holder in the PSBR dry tubes [3]

	Activity, mCi/g ZnO		
	^{NAT}ZnO (20 mg) ×10^3	^{64}ZnO (40 mg) ×10^2	^{67}ZnO (20 mg) ×10^4
^{64}Cu	†	11.5 ± 0.40	†
^{67}Cu	4.92 ± 0.12		0.80 ± 0.02
^{65}Zn	43.3 ± 0.9	5.05 ± 0.01	54.5 ± 1.0
^{69m}Zn	†	(0.39 ± 0.05)	1.35± 0.02
^{58}Co			0.21 ± 0.006
^{67}Ga			201 ± 6
^{72}Ga		1.13 ± 0.14	
^{76}As	0.48 ± 0.05		
^{182}Ta			7.20 ± 0.25

†Detected, but the counting statistics were too poor to be quantified at the time of sample analysis

~200 times as many ^{65}Zn atoms as ^{64}Cu atoms, but our fast flux sample holder reduced that ratio by two orders of magnitude. The ^{72}Ga in the target, which has a half-life slightly longer than ^{64}Cu, will have to be removed using an additional purification step.

The ^{67}ZnO target produced 16 µCi (2.03×10^{-11} g) of ^{67}Cu and 0.1 µCi (1.80×10^{-12} g) of ^{65}Zn. An unshielded sample in the PSBR core would be expected to produce ~6 times more ^{65}Zn atoms than ^{67}Cu atoms, but our fast flux sample holder allowed for ~11 times more ^{67}Cu than ^{65}Zn, reducing the ^{65}Zn production in ^{67}Zn targets by a factor of 66. The ^{58}Co in the sample is produced via ^{58}Ni(n,p)^{58}Co on nickel contaminants in the target material (100 ppm, as noted by the manufacturer). The target also contains ^{67}Ga, as well as ^{182}Ta, which is produced from thermal neutron capture on ^{181}Ta (99.988% natural abundance). The manufacturer did not specify this contaminant, but ^{182}Ta was clearly evident in the gamma-ray spectrum of this sample.

FIGURE 2 shows the ion exchange separation of the ^{64}Cu and ^{67}Cu products from the bulk zinc targets. The ^{NAT}ZnO sample yielded 87.8% copper recovery (fourth and fifth fractions) and a separation factor of 2400; the ^{76}As contaminant was too dilute to characterize in the individual fractions. The ^{64}ZnO target yielded 95.1% copper recovery (second through sixth fractions), and a separation factor of 2000. The ^{72}Ga was tracked through the separation, most of which eluted with the ^{64}Cu. The ^{67}ZnO target produced a copper yield of 94.8% (fourth and fifth fractions). Because the ^{67}ZnO target had very little ^{64}Zn, not enough ^{65}Zn was produced in the target to track the zinc content. Thus, a minimum detectable activity of 1 Bq of ^{65}Zn was used to determine a separation factor of 3500. Most of the ^{58}Co eluted prior to the copper, but the ^{67}Ga followed the copper elution almost exactly. The ^{182}Ta was too dilute to track through the separation. The removal of these radioactive contaminants will be addressed via additional ion exchange procedures in future work.

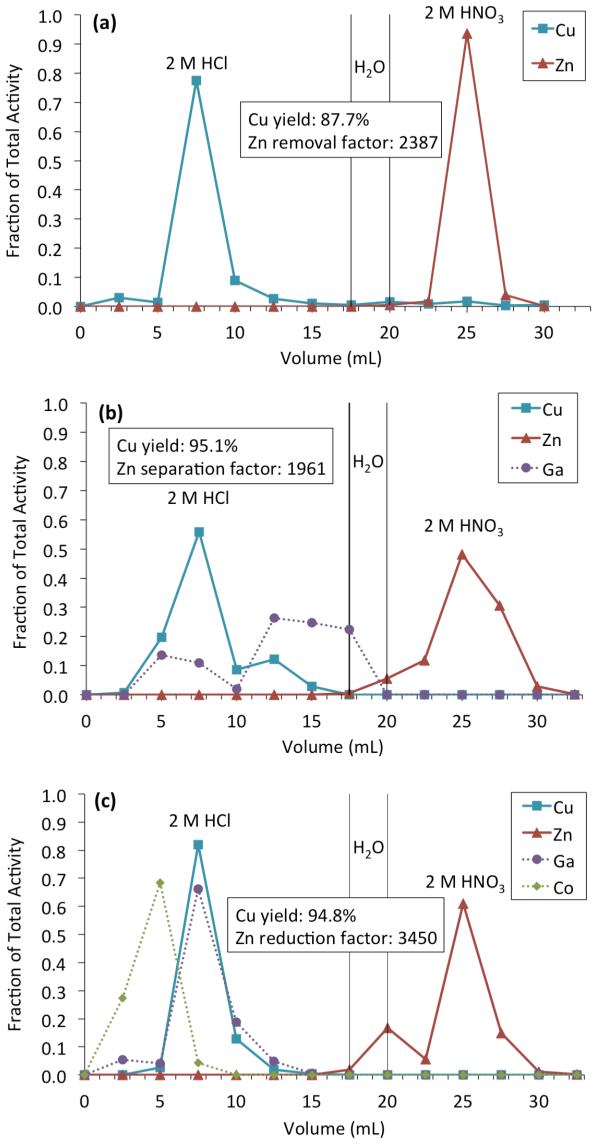

FIGURE 2: Separation of copper isotopes from (a) ^{NAT}ZnO, (b) ^{64}ZnO, and (c) ^{67}ZnO target materials and accompanying irradiation products [3].

Conclusions and Future Work

The production and initial purification of 460 µCi (11.5 mCi ^{64}Cu/g ^{64}ZnO) and 16 µCi (0.80 mCi ^{67}Cu/g ^{67}ZnO) in this work indicates that our irradiation process using enriched isotopes in the PSBR is comparable to other similar efforts (see [3]), and demonstrated the efficacy of the boron-shielded target chamber in reducing the production of unwanted radioactive byproducts by up to two orders of magnitude. Separations processes provided ~95% copper yields and one-pass ion exchange separations factors greater than 10^3.

Fortunately, we could produce enough ^{64,67}Cu for medical research with further development efforts. Several options to increase production include: (1) relocating the target to the PSBR central thimble (CT), which has a higher fast to thermal neutron ratio (0.5) than the PSBR dry tubes (0.33); (2) converting the water-filled CT to an air-filled CT to further increase the fast to thermal neutron flux ratio; (3) increasing the irradiation time; (4) increasing the reactor power from 800 kW to 1 MW; and (5) irradiating a larger sample mass. Increasing the irradiation time is particularly helpful. These trial irradiations acheived less than 20% of the ^{64}Cu saturation activity and less than 5% of the ^{67}Cu saturation activity. days Eight hours of irradiation for five days (the maximum weekly PSBR schedule) would yield ~85% of the ^{64}Cu saturation activity and five weeks of irradiation would yield over 90% of the ^{67}Cu saturation activity. We estimate that these improvements would allow the production of ~80 mCi ^{64}Cu/g ^{64}ZnO and ~20 mCi ^{67}Cu /g ^{67}ZnO, which would provide enough copper activity for several dozen small mammal research subjects at a time. Additional chemical purification steps to increase radiochemical purity, as well as the automation of the purification processes, will allow us to provide a highly pure sample with as much preserved activity as possible to medical researchers, providing an additional source for these isotopes to the medical research community.

Acknowledgements

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Publications

1. A. M. Johnsen, B. J. Heidrich, C. B. Durrant, A. J. Bascom, and K. Ünlü, "Reactor Production of ^{64}Cu and ^{67}Cu Using Enriched Zinc Target Material," *J. Radioanal. Nucl. Chem.*, **305**, 61–71 (2015).
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