Cu-67 ISOTOPE PRODUCTION *(overview)*

Based on the 2017' ST Review presentation by G. Kharashvili, July 2017

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Isotope Kick-off mtg, Aug 2018

^{67}Cu for Targeted Radiotherapy

- ***Theranostic*** radionuclide
  - 141 keV mean energy β^- for therapy (has the range in tissue of the order of a cell diameter)
  - 185 keV energy photons for SPECT imaging
  - Can be paired with ^{64}Cu for PET imaging
- Near-ideal half-life of 61.8 hours
  - Convenient for production, transportation, and delivery to patient
  - Same order as biological half-life of copper and zinc (^{67}Cu decays to stable ^{67}Zn)
- Favorable biochemistry – approved for human trials
  - Not a bone or an organ seeker
  - Not acutely toxic – both Cu and Zn are essential trace nutrients

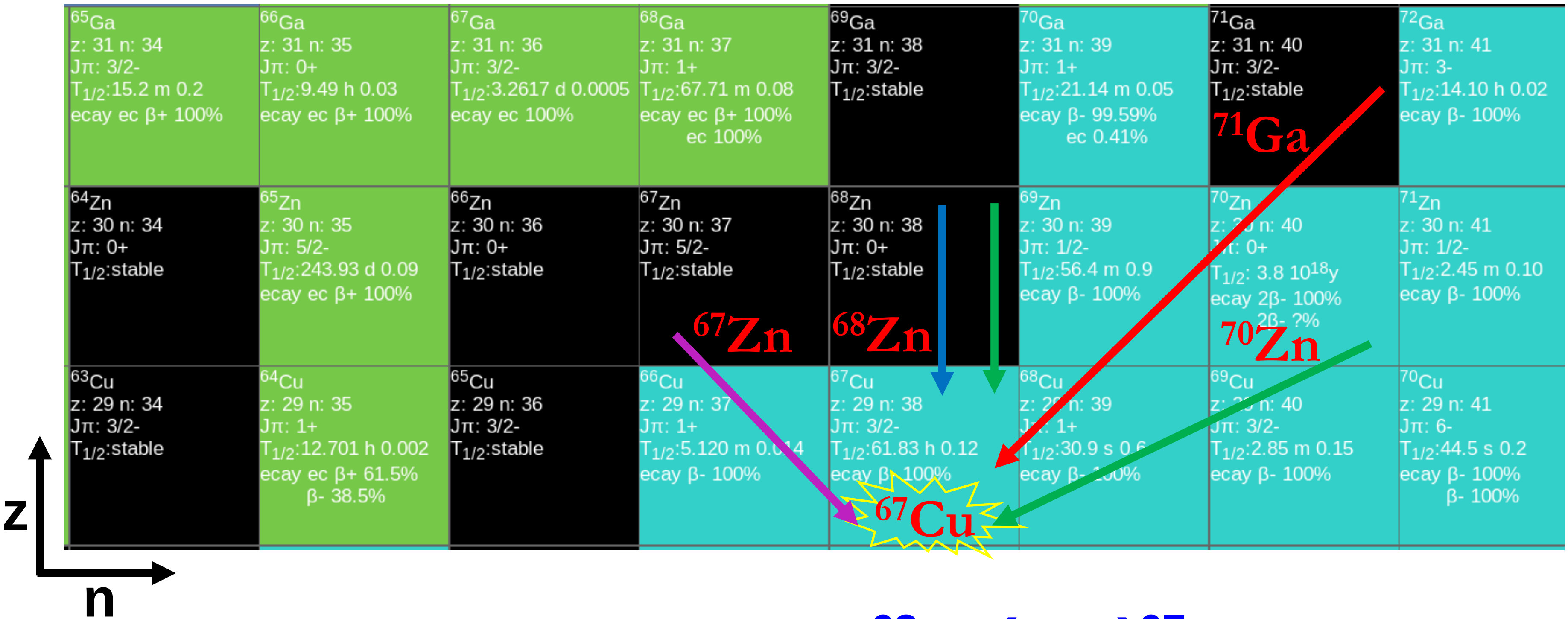
^{67}Cu Properties

- $T_{1/2}$ = 61.83 h
- Therapeutic:
  - β^- ranges in tissue are of the order of a cell diameter

Endpoint Energy (keV)	Yield (%)
183.5	1.1
392.4	57
483.7	22
577	20

- Diagnostic
  - 185 keV photon with 48.7% yield
  - 93.3 keV photon with 16.1% yield

How is ^{67}Cu Produced?



- ^{68}Zn(p, 2p)^{67}Cu
- ^{70}Zn(p, α)^{67}Cu
- ^{67}Zn(n, p)^{67}Cu
- ^{68}Zn(γ, p)^{67}Cu
- ^{71}Ga(γ, α)^{67}Cu
  – 2017 JSA Patent Submitted

Demand and Availability of ^{67}Cu

- Historical lack of an adequate and reliable supply has impeded the development of ^{67}Cu applications
- By some estimates (based on treating a half of all new Non-Hodgkin Lymphomas) there is a potential US demand of ~12000 Ci / year

  Smith, Bowers, Ehst, "The production, separation, and use of ^{67}Cu for radioimmunotherapy: A review", *Applied Radiation and Isotopes* 70 (2012) 2377–2383
- ^{67}Cu is currently produced:
  - Brookhaven National Laboratory: Proton irradiation of zinc, produced periodically, ~60% of activity upon delivery is composed of ^{64}Cu
  - Idaho Accelerator Center: Photoproduction in zinc up to 10s of mCi / week, not intended for human use
- **Higher specific activities and improved radiological purity are desired**

Photoproduction of ^{67}Cu in Gallium via ^{71}Ga(γ,α)^{67}Cu (1)

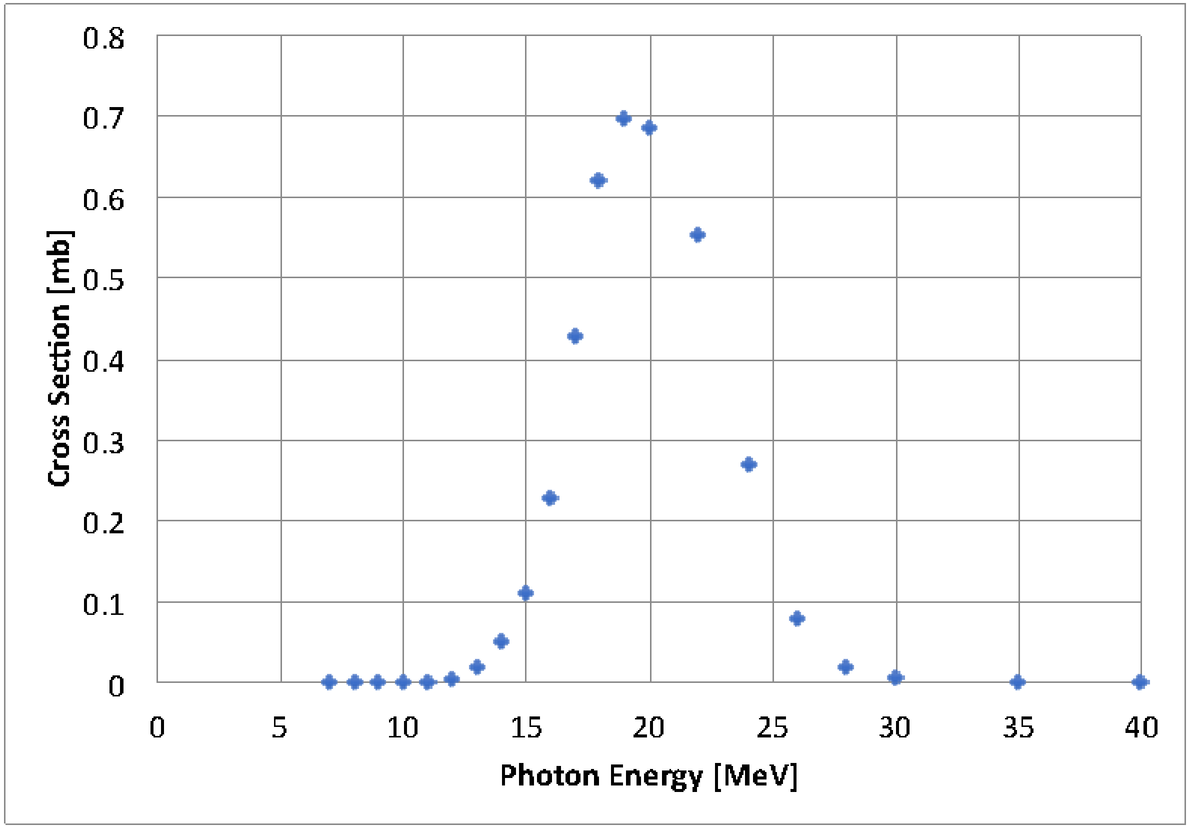
- Gallium has favorable properties for high power targets
  - ✓ Low melting point of 30 °C
  - ✓ High boiling point of 2204 °C
  - ✓ Low vapor pressure
  - ✗ Corrosive to metals except tungsten and tantalum

- A 50 kW irradiation of optimal Ga target will produce *
  - 100s mCi of ^{67}Cu per week in natural gallium
  - > 1 Ci/week in ^{71}Ga (40% of natural Ga)
  - Typical medical dose of ^{67}Cu – order of 10 mCi

  * Yields are calculated using FLUKA and scaled with data

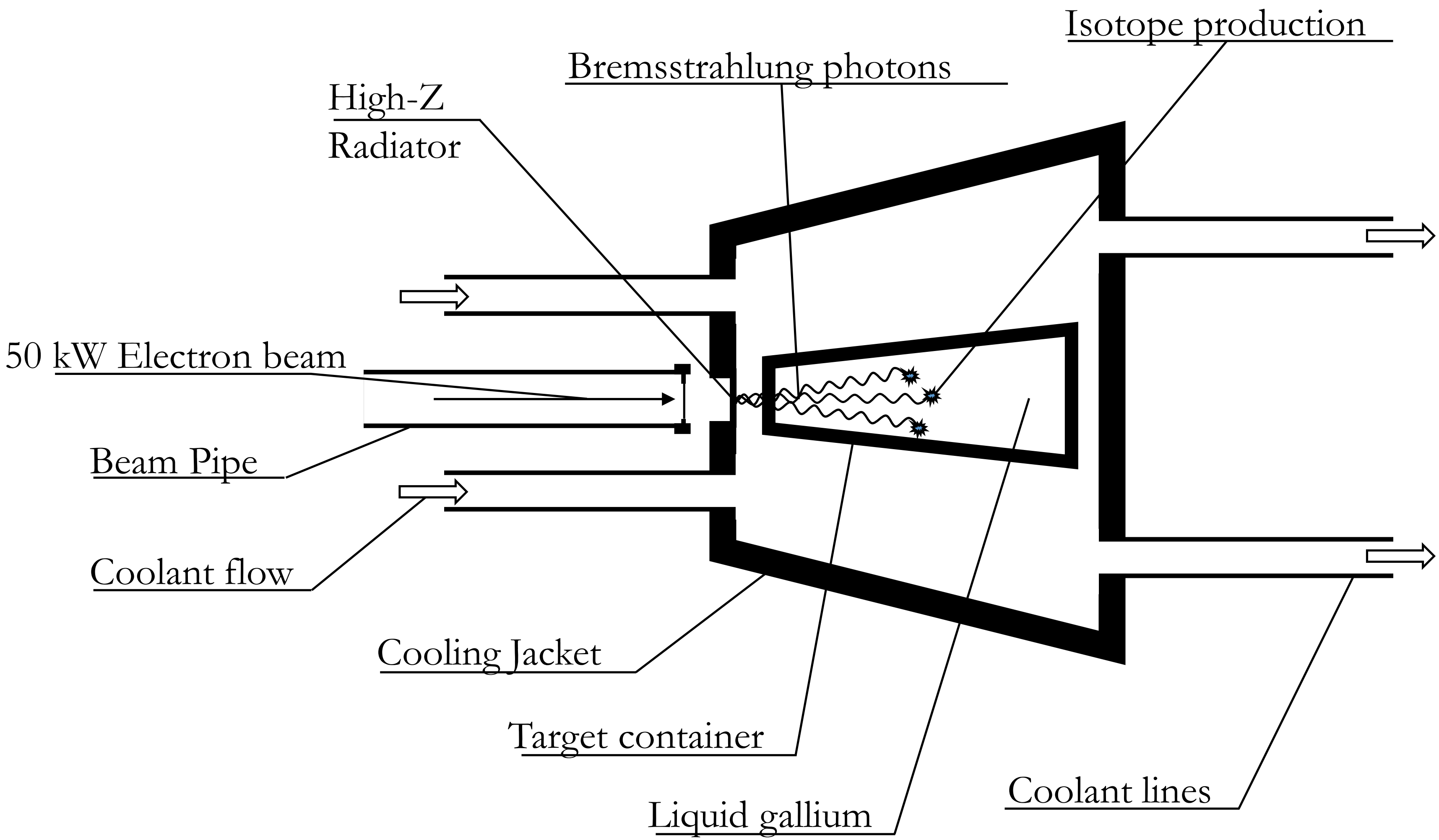
Photoproduction of ^{67}Cu in Gallium via ^{71}Ga(γ,α)^{67}Cu (2)

- Modest cross-section of ^{71}Ga(γ,α)^{67}Cu reaction can be compensated by high beam power and a thick target



Koning *et al.* "TENDL-2015: TALYS-based evaluated nuclear data library" https://tendl.web.psi.ch/tendl_2015/tendl2015.html

Photoproduction of ^{67}Cu in Gallium via $^{71}Ga(\gamma,\alpha)^{67}Cu$ (3)



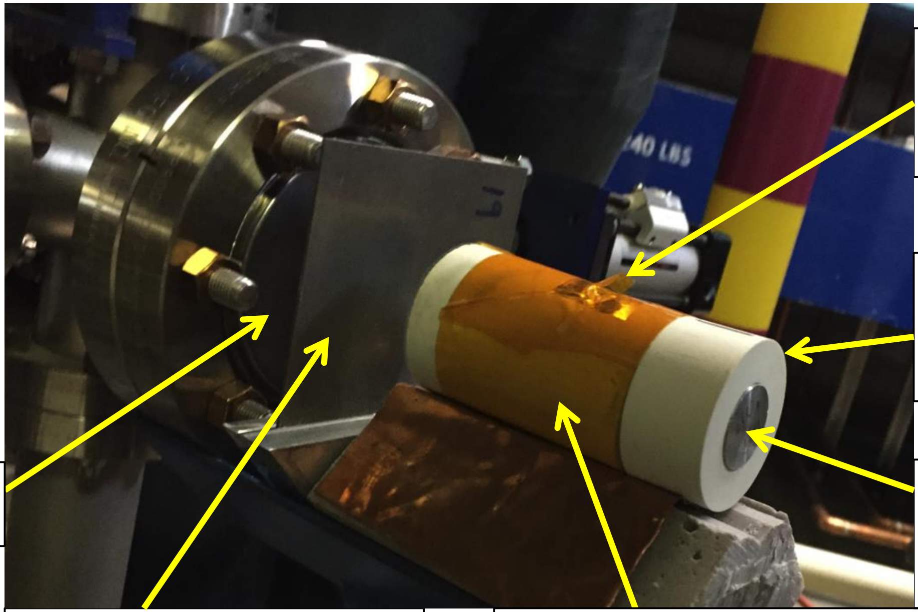
Overall Objectives and First Steps

- The overall objective is to integrate
  - Production
  - Chemical Separation
  - Delivery

- First (opportunistic) steps
  - Confirm ^{67}Cu production in gallium
  - Chemically separate ^{67}Cu from gallium
  - Investigate ^{67}Cu delivery mechanisms

First Opportunistic Irradiation Test

- Irradiation of Ga and Zn targets during beam studies in CEBAF injector:
  - 18.5 MeV (to avoid interference from ^{67}Ga), 2.5 μA, 1 h
  - ~ 0.1 μCi ^{67}Cu detected in each



Natural Ga target

Boron Nitride crucible

Natural Zn target

Be window

1mm Tungsten radiator

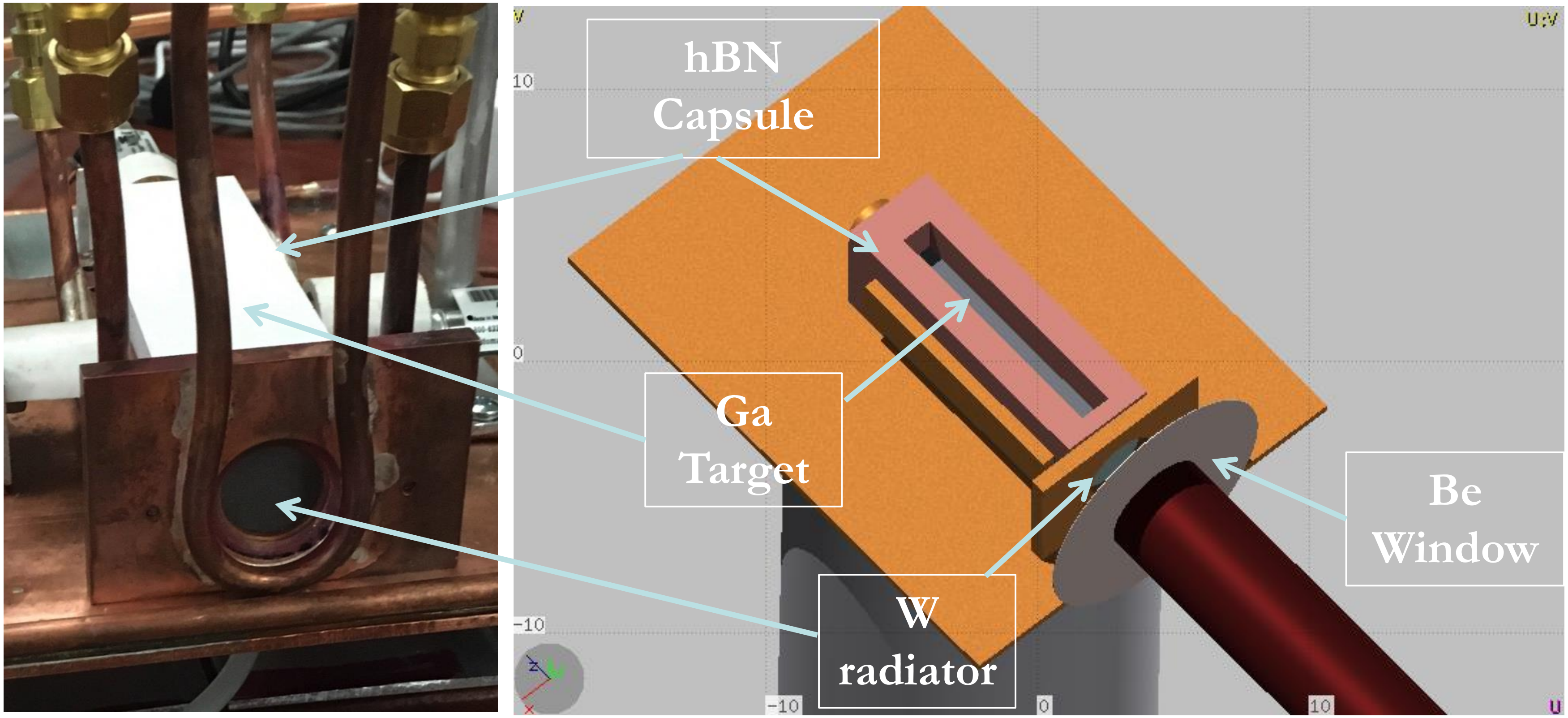
Kapton tape to prevent Ga spills

Chemical Separation Test

- Chemical separation test at Virginia Commonwealth University (VCU)
  - 1 mCi of ^{67}Cu was obtained from the National Isotope Development Center, shipped from BNL to VCU
  - The sample was dissolved in HCl and added to Gallium Chloride in solution
  - Separation by liquid-liquid extraction and column chromatography recovered ~95% of the radioactive copper after a single pass

Second Opportunistic Irradiation Test (1)

- During 2017 beam studies of 4K operation in CEBAF injector a parasitic isotope irradiation opportunity was realized
- 85 g gallium target irradiated for several hours at ~1 kW (18.65 MeV, 50 µA) with the intent to chemically separate ^{67}Cu



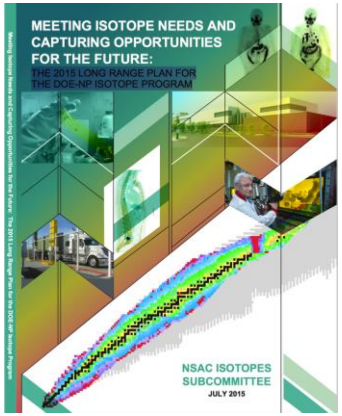
Second Opportunistic Irradiation Test (2)

- Due to failure of monitoring instrumentation, run was terminated earlier than anticipated
- ~130 µCi ^{67}Cu was produced, ~70 µCi was available at the time of sample retrieval (expected to produce ~500 µCi)
- Due to transportation and communication issues did not proceed with chemical separation
- The two low energy irradiation tests showed reasonable agreement with the model predictions
  - FLUKA (our primary tool for activation calculations) appears to overestimate ^{67}Cu yields in Ga by approximately a factor of 2 at 18.5 MeV maximum bremsstrahlung energy

Summary and Proposed Future Work

- ^{67}Cu production via the $^{71}Ga(\gamma,\alpha)^{67}Cu$ reaction at LERF: Production of **high specific activity theranostic** isotope using **high power electron accelerator**
  - ✓ Measured photoproduction of ^{67}Cu at low energies (< 20 MeV) with no ^{64}Cu content
  - ✓ Chemically separated ^{67}Cu from Ga (obtained from BNL, then dissolved in Ga)
  - – Proposed future work
    - Complete smooth integration of photoproduction and chemical separation
    - Produce ^{67}Cu in Ga target at optimal electron beam energies (> 30 MeV)
    - Develop high power target system

NSAC Isotopes Recommendations on Isotope R&D



- *"Continue support for R&D on the production of **alpha-emitting** radioisotopes"*
- *"Support R&D into the production of **high specific activity theranostic** radioisotopes"*
- *"Continue support for R&D on the **use of electron accelerators** for isotope production"*
- *"Support R&D on the development of **irradiation materials for targets** that will be exposed to **extreme environments** to take full advantage of the current suite of accelerator and reactor irradiation facilities"*