Current and Possible New Methods for Accelerator-Based Production of Medical Isotopes

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Current and Possible New Methods for Accelerator-Based Production of Medical Isotopes

This talk will review current and possible new methods for accelerator-based production of medical isotopes. It will cover isotopes produced commercially, mostly by relatively low energy accelerators, and isotopes produced by government-operated facilities, usually by higher energy accelerators. Prospects for the production of traditionally reactor-produced isotopes such as ^{99}Mo via accelerator-driven methods will also be discussed. Also, the special case of accelerator production of alpha-emitting isotopes for radio-immunotherapy will be reviewed.

New report: Accelerators for America's Future

Accelerator-Based Production of Medical Isotopes

A MESSAGE FROM THE CHAIRS

In October 2009, the Department of Energy's Office of High Energy Physics sponsored a symposium and workshop, "Accelerators for America's Future." Its purpose was to elicit the views and opinions of a wide range of accelerator users on the challenges and opportunities for developing and deploying accelerators to meet national needs. Some 300 of them attended the one-day symposium and poster session. In the two-day workshop that followed, 120 users of accelerator technology, from small business owners to well-known researchers, formed five working groups in Energy and Environment, Industry, Medicine, National Security and Discovery Science. Their charge was to give us their perspective on needs, challenges and areas of greatest promise; and to provide guidance on bridging the gap between accelerator research and technology deployment. For two days, they discussed, disagreed, concurred, consulted, reconsidered—and eventually converged on results. The groups' reports varied in scope, approach and level of technical detail. Sometimes their findings conflicted. The workshop was designed as an inclusive, broad-spectrum effort to learn from stakeholders with boots on the ground in fields that depend on accelerator science and technology. This report captures what they told us. We present it as a resource for agencies as they develop their agendas and programs.

Walter Henning **Charles Shank**
"Accelerators for America" Symposium and Workshop Chairs
June 2010

www.acceleratorsamerica.org

Chapter on accelerator-produced medical isotopes

Contents

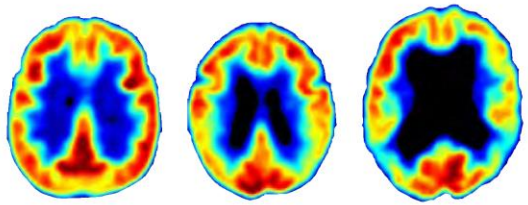
Radioisotopes

Radioisotopes have become vital components for scientific research and industry, with hundreds of applications in medicine, biology, physics, chemistry, agriculture, national security and environmental and materials science. Perhaps the most directly beneficial occur in medical diagnosis and therapy. Building on pioneering efforts at the DOE laboratories, isotopes have improved the diagnosis and treatment of disease and changed the quality of life for millions of patients.

The wide range of half-lives of radioisotopes and their differing radiation types allow optimization for specific applications. Isotopes emitting x-rays, gamma rays or positrons can serve as diagnostic probes, with instruments located outside the patient to image radiation distribution and thus the biological structures and fluid motion or constriction (blood flow, for example). Emitters of β rays (electrons) and α particles (helium nuclei) deposit most of their energy close to the site of the emitting nucleus and serve as therapeutic agents to destroy cancerous tissue.

The ability to attach a radionuclide to a pharmaceutical agent for transport of the isotope to the desired site is key to its effectiveness. Researchers have achieved considerable success in this area. For example, fluorodeoxyglucose, or FDG, serves as a carrier for the positron emitter ^{18}F to sites of high metabolic activity. Positron-emission tomography cameras, or PET scans, can produce detailed maps of active areas in the brain and other organs. Technecium-99m has now become the workhorse of diagnostic nuclear medicine, with over 50,000 procedures performed each day in the U.S. Therapeutic applications can also use radiopharmaceuticals as delivery agents (for α emitters such as ^{211}At), or can take the form of metallic "seeds" containing β-emitting isotopes such as ^{90}Sr, ^{103}Pd, ^{192}Ir, or others that are surgically implanted into a tumor, a procedure widely used now for prostate treatments.

The half-life of an isotope must be long enough to allow transport from production sites to end-use locations without excessive loss, and short enough to minimize the unwanted radiation dose to the patient after the procedure is complete. The use of "generators," such as ^{99}Mo/^{99m}Tc, involves a longer-lived parent (2.75-day ^{99}Mo) that decays to a shorter-lived daughter (6-hour ^{99m}Tc). Specialized reactors produce the ^{99}Mo as a fission fragment for transport to end-use sites, where clinicians "milk" the ^{99m}Tc daughter from the generator as needed for diagnostic procedures.



Normal | Mild cognitive impairment | Alzheimer's disease

Positron emission tomography (PET) images showing reduced glucose metabolism in temporal and parietal regions of the brain in Alzheimer's disease and mild cognitive impairment *Image courtesy of S. Baker, W. Jagust and S. Landau*

Bone scans locating cancerous growth by indicating increased uptake of radioactive ^{99m}Tc *Image courtesy of the "Workshop on the Nation's Needs for Isotopes: Present and Future (2008)"*

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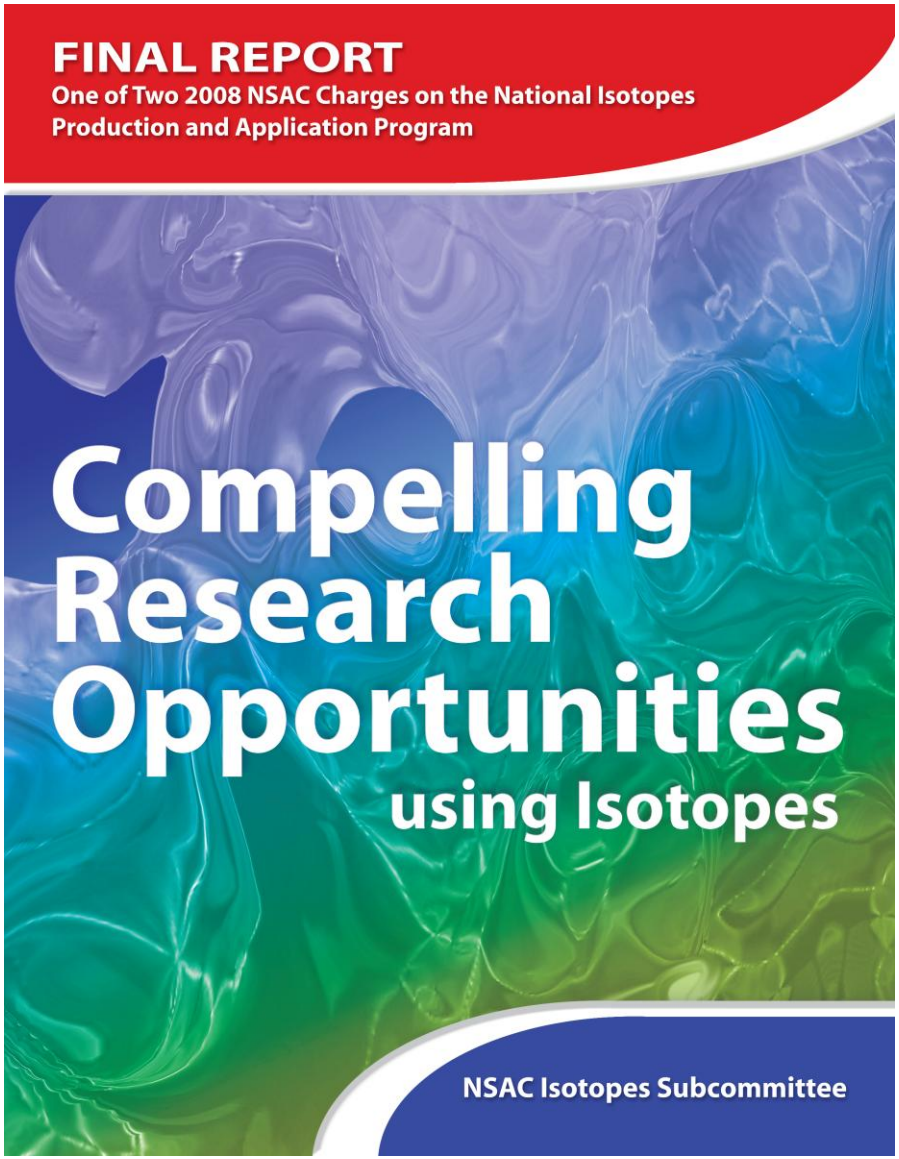
Current commercial production of medical isotopes by accelerators

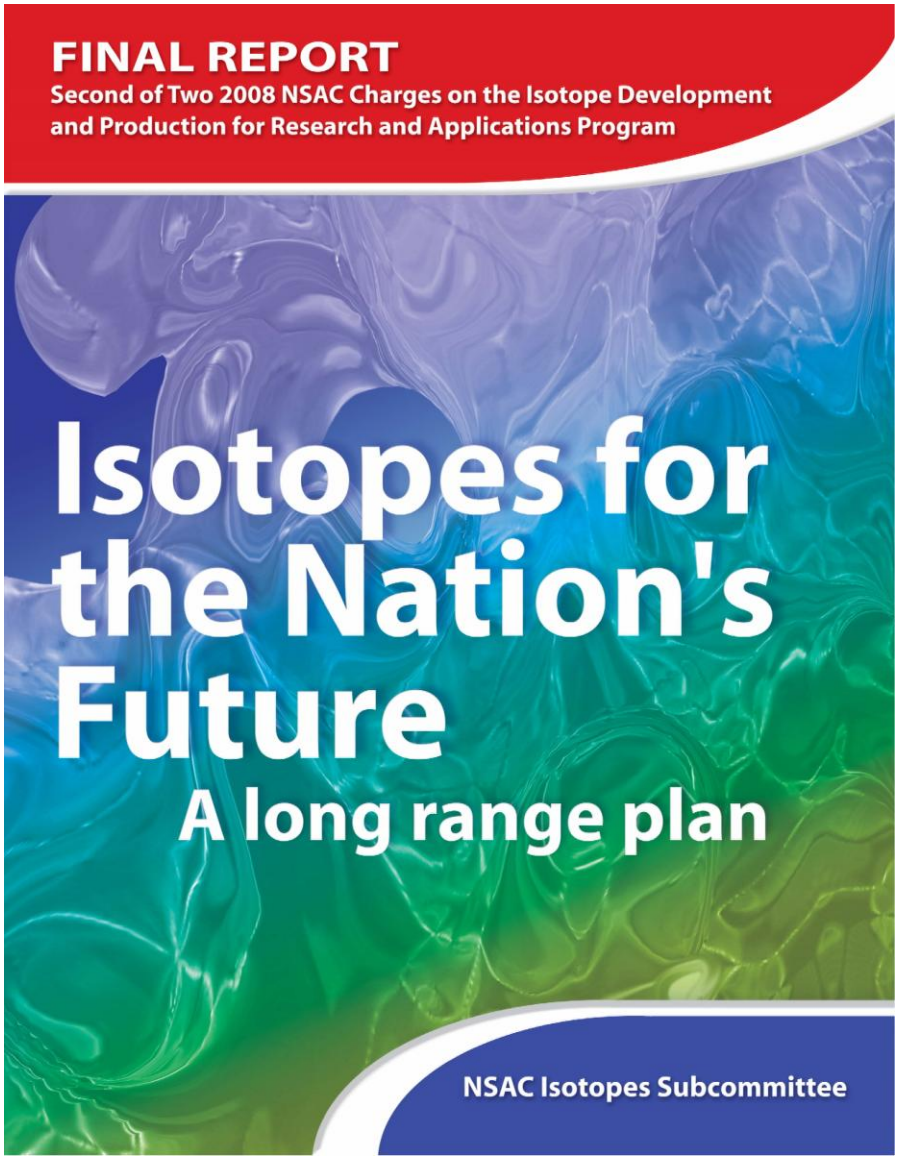
- PET isotopes – mostly ~10-MeV cyclotrons (world-wide)
  - Mostly 18F (2-hour half-life) produced and delivered regionally
- Isotopes produced by ~30-MeV cyclotrons
  - Nordion cyclotrons located on-site at TRIUMF
  - GE/Healthcare (former Amersham)
  - Isotopes include: 201Tl, 127I, 67Ga, 103Pd
- Isotopes produced by ~70-MeV cyclotrons
  - Arronax: a new 70-MeV cyclotron facility in Nantes, France
    - Goals ~750 microamps of protons and 35 microamps of alpha particles.
    - Isotopes include: 64Cu, 82Sr, 124I, 86Y, 68Ge, 211At (under development)
  - Nordion use of TRIUMF internal beam
    - 82Sr at ~70-MeV

Government operated accelerators

- DOE facilities in the US (managed by DOE/OS/ONP): “Research isotopes”
  - BLIP facility: 200-MeV p linac at BNL, 100 microamps, many isotopes
  - Isotope production facility at LANL; 100-MeV p facility at LANSCE linac, 250 microamps
  - Medical isotopes include: 68Ge, 82Sr, and 67Cu
- INR, Troitsk, Russia
  - Meson-factory facility; 160-MeV p at 140 microamps
  - Sales of 82Sr (collaboration with LANL)
  - 82Sr, 103Pd, 68Ge

US Nuclear Science Advisory Committee Isotopes Panel





Accelerator-Based Production of Medical Isotopes

First recommendation of the NSAC-I panel

There are compelling research opportunities using alpha-emitters in medicine. There is tremendous potential in developing far more effective treatments of cancers by the use of alpha-emitters in comparison to other radio-isotopes. Therefore, development and testing of therapies using alpha emitters are our highest priority for research isotope production for the medical field. This opportunity can be realized by a variety of alpha emitters with the highest priority given to ^{225}Ac. This priority is reinforced by the potential need for rapid action due to the 2012 deadline for downblending of current DOE stocks of ^{233}U, a procedure that would eliminate its value as a source of ^{225}Ac.

1. **Invest in new production approaches of alpha-emitters with highest priority for ^{225}Ac. Extraction of the thorium parent from ^{233}U is an interim solution that needs to be seriously considered for the short term until other production capacity can become available.**

Demand for isotopes for clinical trials for cancer therapy

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Cancer Therapy with Alpha-Emitters Labeled Peptides

Ekaterina Dadachova, PhD*,†

Actively targeted α-particles offer specific tumor cell killing action with less collateral damage to surrounding normal tissues than β-emitters. During the last decade, radiolabeled peptides that bind to different receptors on the tumors have been investigated as potential therapeutic agents both in the preclinical and clinical settings. Advantages of radiolabeled peptides over antibodies include relatively straightforward chemical synthesis, versatility, easier radiolabeling, rapid clearance from the circulation, faster penetration and more uniform distribution into tissues, and less immunogenicity. Rapid internalization of the radiolabeled peptides with equally rapid re-expression of the cell surface target is a highly desirable property that enhances the total delivery of these radionuclides into malignant sites. Peptides, such as octreotide, α-melanocyte-stimulating hormone analogues, arginine-glycine-aspartic acid-containing peptides, bombesin derivatives, and others may all be feasible for use with α-emitters. The on-going preclinical work has primarily concentrated on octreotide and octreotate analogues labeled with Bismuth-213 and Astatine-211. In addition, α-melanocyte-stimulating hormone analogue has been labeled with Lead-212/Bismuth-212 in vivo generator and demonstrated the encouraging therapeutic efficacy in treatment of experimental melanoma. Obstacles that continue to obstruct widespread acceptance of α-emitter–labeled peptides are primarily the supply of these radionuclides and concerns about potential kidney toxicity. New sources and methods for production of these medically valuable radionuclides and better understanding of mechanisms related to the peptide renal uptake and clearance should speed up the introduction of α-emitter–labeled peptides into the clinic.

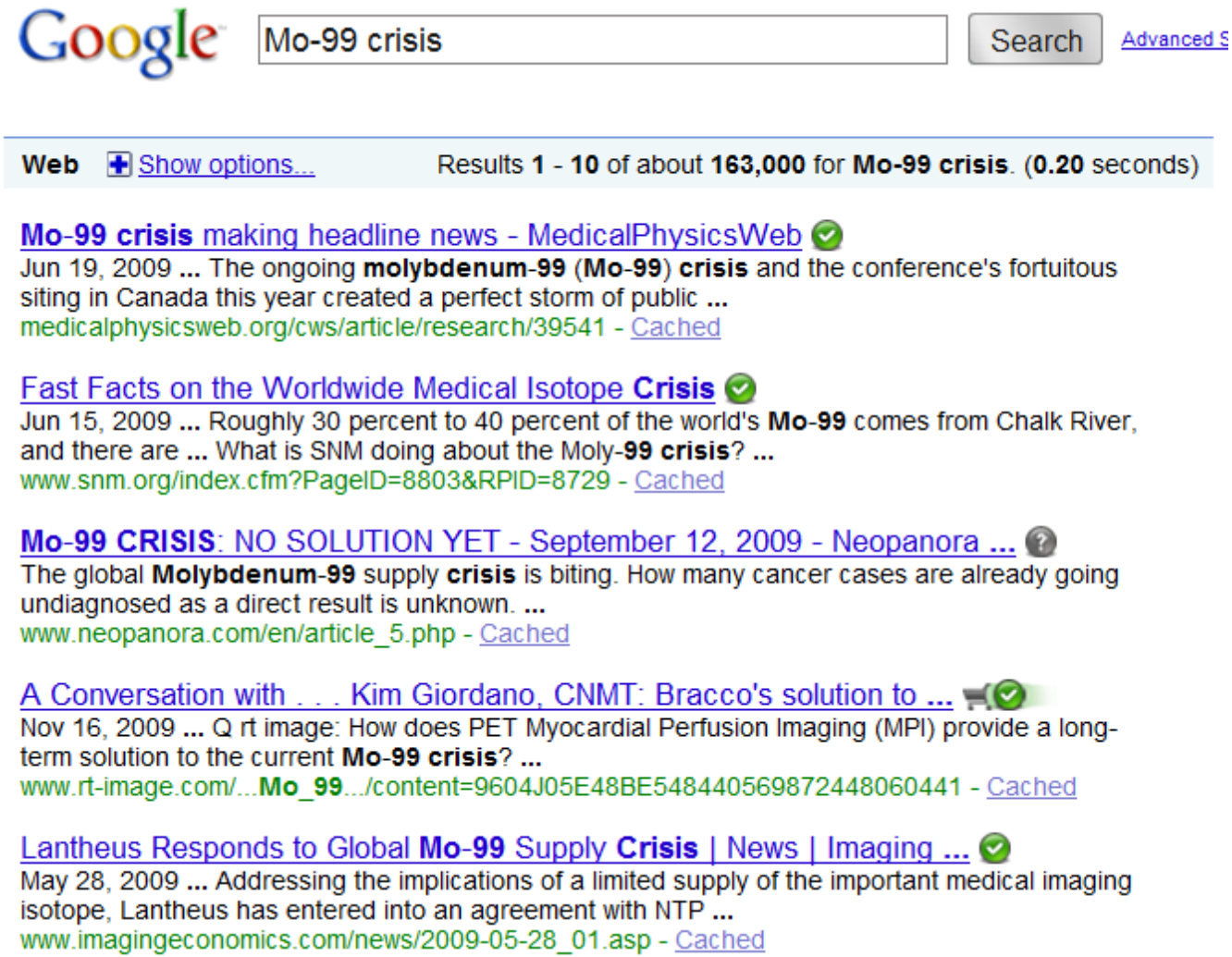
Semin Nucl Med 40:204-208

Yeshiva U., New York, 2010

Solution to the shortage identified by the NSAC-I panel: production of alpha-emitting isotopes for cancer therapy by accelerators

- Case 1: production of 225Ac/213Bi generator by proton spallation of thorium
  - Proposed by Argonne and ICGomes, Inc.
  - Large yield predicted for protons at any energy above 100 MeV
  - DOE funded for validation
    - Collaboration of Argonne, FermiLab, ICGomes, Inc., and NorthStar Medical Isotopes
    - Production test with FermiLab 8-GeV beam scheduled for late 2010
    - Separation and purification chemistry to be carried out at Argonne Chemistry Division
- Case 2: production of 211At at low energy
  - Reaction 209Bi(alpha,2n) at alpha beam energy below 30 MeV to avoid 210Po impurity
  - High power targetry being developed at Argonne and Arronax (France)

“99Mo Crisis” 163,000 Google hits



Why ^{99}Mo and what is the crisis?

- ^{99}Mo/^{99m}Tc "generators" are the basis of a wide variety of medical diagnostic procedures
- This one isotope is used in ~75% of all medical isotope procedures world-wide, about 16,000,000 annually in the U.S.
- The "crisis" is a severe shortage of this isotope due to problems with the >40-year old reactors that are its source
- Furthermore, these reactors presently use HEU (93% ^{235}U) targets for production of ^{99}Mo (~45 kg of ^{235}U annually)

COUNTRY	CITY/PROVINCE	FACILITY NAME	REACTOR AGE	% WORLD SUPPLY	MEGAWATTS
Canada	Rolphton, Ontario	NRU Chalk River	52 years old	31%	135
The Netherlands	Zijpe	HFR-Petten	47 years old	33%	45
Belgium	Mol	BR2	47 years old	10%	100
France	Saclay	OSIRIS	42 years old	8%	70
South Africa	Pelindaba	SAFARI	43 years old	3%	20
Australia	Sydney	OPAL	2 years old	NA	20

Are there alternatives to the ageing reactors?

- The current world-wide usage of ^{99}Mo is ~100,000 end-of irradiation Curies per week (~12,000 “6-day Curies”)
- Accelerator people world-wide have been “brainstorming”
- Most alternatives being considered cannot economically supply a large fraction of this need
- A concept for an energy-efficient, accelerator-driven sub-critical target capable of supplying this entire need using LEU (<20% ^{235}U) targets – developed at Argonne

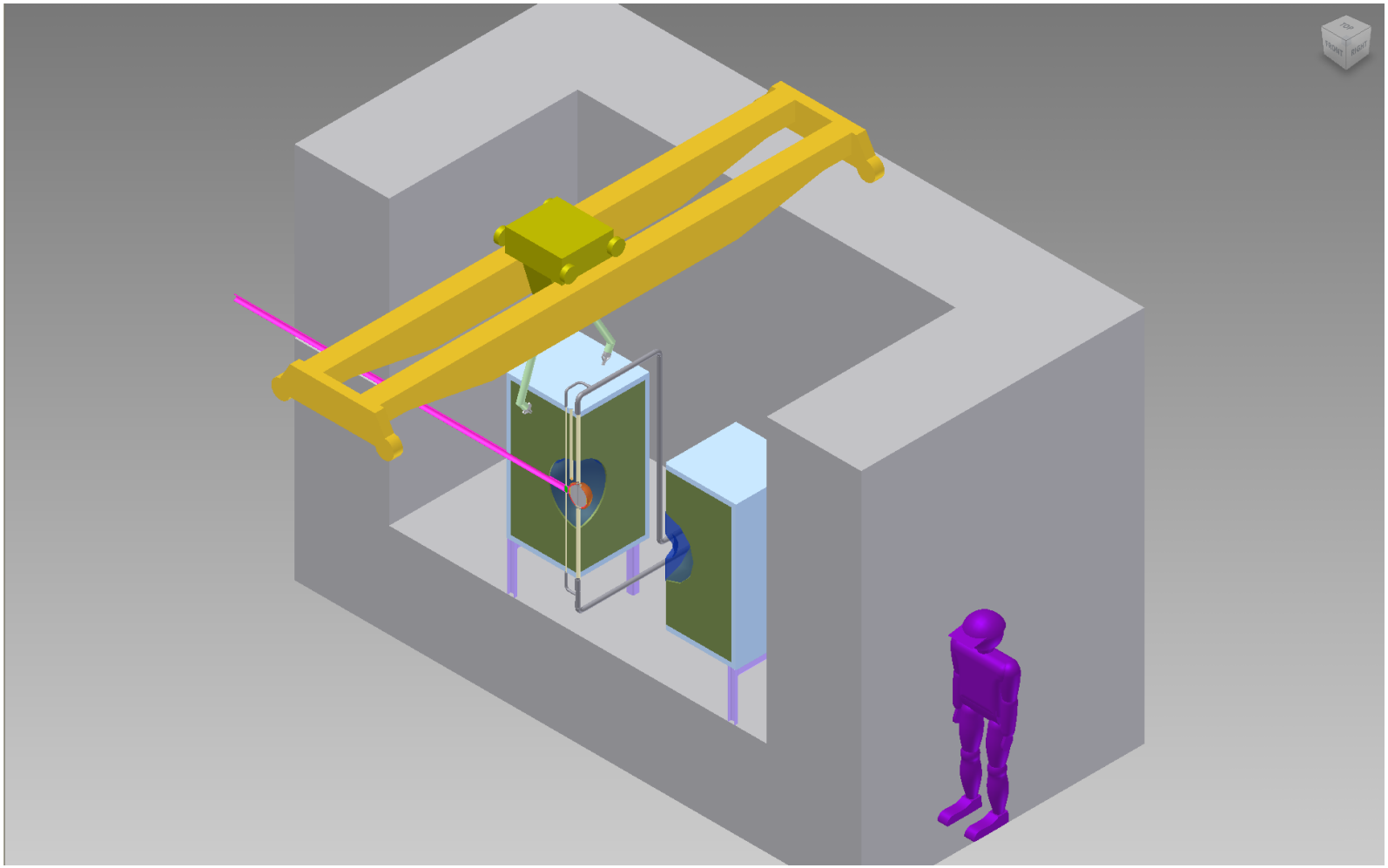
Methods for small-scale production by accelerators

- Methods that produce **high specific activity** (uranium fission)
  - Photo-fission of 238U by ~50-MeV electrons
    - < 1% of world need per MW of beam power
    - Pursued at TRIUMF for Canadian market
    - Pursued at RIKEN for Japanese market
    - ~500-kW, 50-MeV CW, SC electron linac being developed at TRIUMF as demo facility
- Methods that produce **low specific activity** (reactions on Mo targets)
  - Photo-nuclear reaction: 100Mo(gamma,n)99Mo using ~50-MeV electron linac
    - ~5% of world need per MW of beam power using separated 100Mo (10% natural)
    - Evaluation tests underway at Argonne low-power RT linac
    - Requires recycling of expensive 100Mo generators from hospitals
  - "Direct-Tech" – 100Mo(p,2n)99mTc (must be distributed in ~6 hours)
    - Being developed in Canada and at MIT – needs ~20-MeV protons
  - 100Mo(n,2n)99Mo using 14-MeV n from low energy d-t generator
    - Being pursued in Japan
  - 98Mo(d,p) using 40-MeV d beam from SC linac
    - Being considered at SARAF facility for Israel
    - < 1% of world need at 80-kW if run continuously using natural Mo target

Compact Accelerator-Driven Multiplier for Isotopes: CAMI

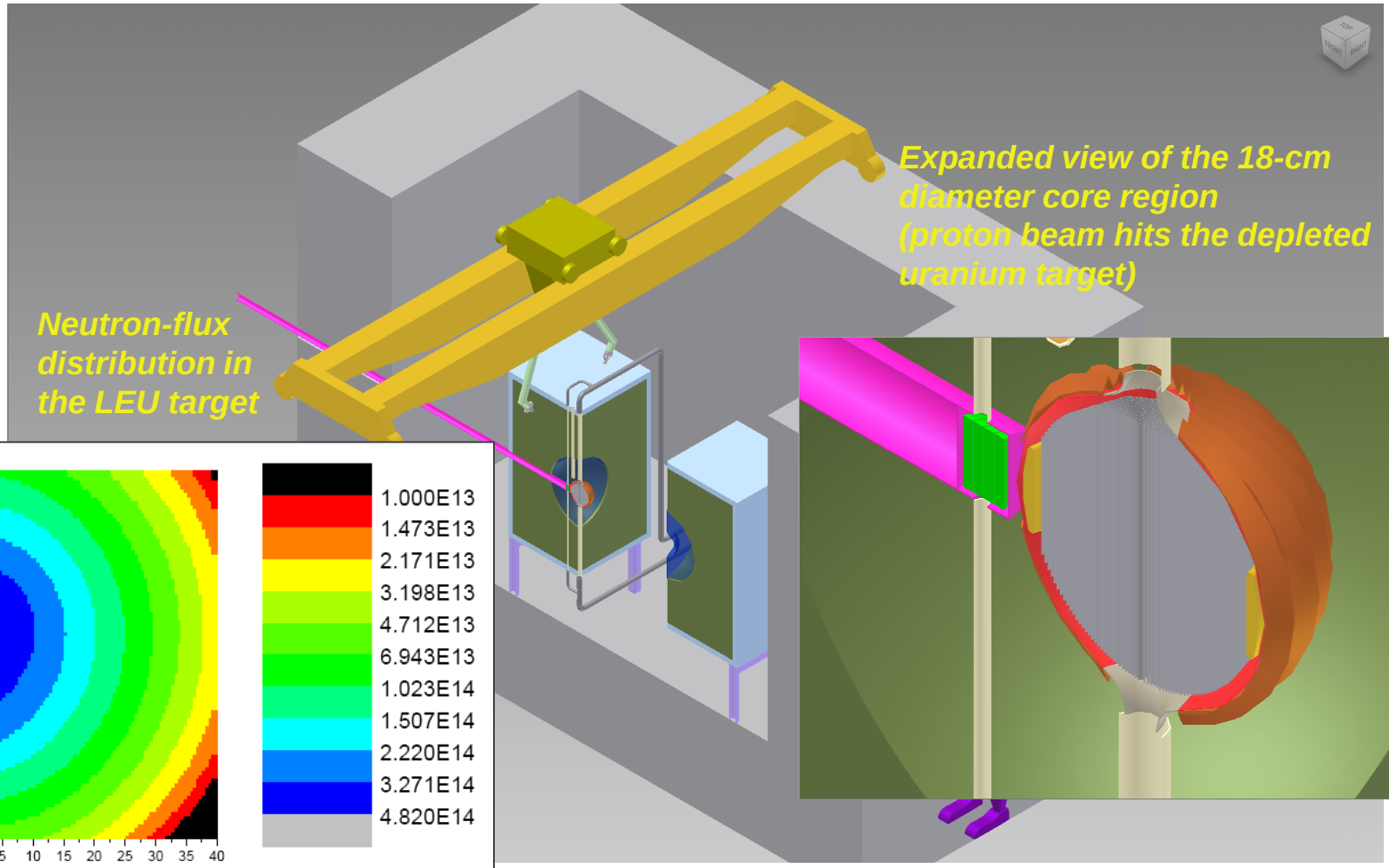
- The target consists of a sub-critical array of LEU foils cooled and moderated by light water (300 grams of ^{235}U in 1.5 kg LEU)
- The LEU foils developed at Argonne (Chemistry and Nuclear Engineering Divisions)
- The array is 18-cm in diameter surrounded by a beryllium and graphite reflector with a criticality of 0.95
- A primary target of depleted uranium is irradiated with protons
- With 200-MeV protons there are 12 fissions per proton for an energy gain of 12
- The beam power required for 6000 6-day Curies in a 5.5 day irradiation is 100 kW with 200-MeV protons or 200 kW at 100 MeV
- High specific activity is achieved via neutron flux of 3-5E14 n/cm^2-s

Cut-away of the multiplier target concept



Design concept by J.Nolen and I.C.Gomes

Cut-away of the multiplier target concept



Design concept by J.Nolen and I.C.Gomes

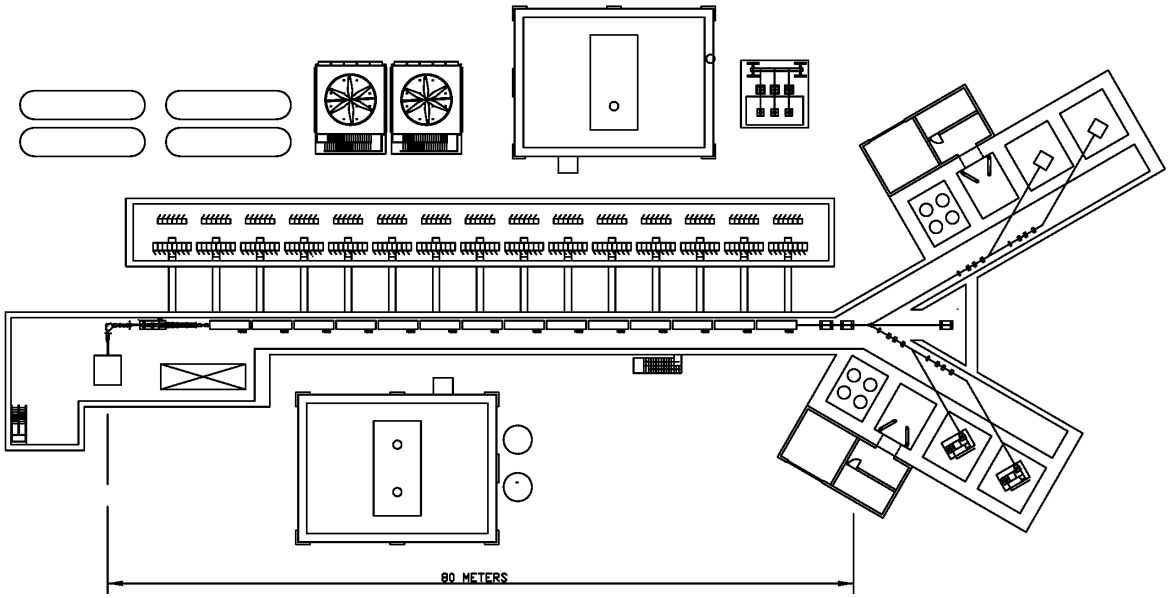
A possible facility configuration using recently developed superconducting linac technology

- The proton driver beam can be produced with a high-power superconducting linac using technology developed for RIA/FRIB (P.N. Ostroumov and colleagues at Argonne)
  - Two options: 100 MV acceleration with 1 MW beam power, or 200 MV, 2 MW
- Beam output power can be continuously shared between medical isotope production and nuclear physics programs
  - The beam power is delivered to multiple production stations
- Both “reactor-type” and “accelerator-type” isotopes can be produced simultaneously
  - E.g. ^{99}Mo, ^{131}I, and ^{133}Xe, plus radio therapeutic alpha emitters such as ^{225}Ac/^{213}Bi, ^{227}Ac, and ^{211}Pb
- Estimate of the 100-MV accelerator facility cost is ~$75M w/ 30% contingency

SC linac technology - status

- Based on ATLAS upgrade cryomodule recently commissioned at Argonne

Facility for isotopes and science (200 MV linac)



Radioisotopes for medicine

“Reactor” isotopes

“Accelerator” isotopes

Production linac

Radioisotopes for basic nuclear physics

“Physics” isotopes

Summary

- Accelerators play an ever increasing role world-wide to produce isotopes for medical diagnostics and therapy
- Most existing commercial suppliers of medical isotopes use 10-70 MeV cyclotrons
- RT linacs at government labs mostly provide “research isotopes”
- SC linacs are poised to play an increasing role in the near future
- Development of less costly SC linacs (and cyclotrons) for ~200-MeV protons at ~1-mA is required for commercial viability