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

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XXV International Linac Conference
September 17, 2010

This work was supported by the U.S. Department of Energy,
Office of Nuclear Physics, under Contract No. DE-AC02-06CH11357.
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

Accelerators for America’s Future

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 360 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

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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 DSE 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 a 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 18F 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 radioisotopes as delivery agents (for emitters such as 131I), or can take the form of metallic “seeds” containing β-emitting isotopes such as 103Pd, 125I, 192Ir; 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 99Mo/99mTc, involves a longer-lived parent (2.1-day 99Mo) that decays to a shorter-lived daughter (6-hour 99mTc). Specialized reactors produce the 99Mo as a fission fragment for transport to end-use sites, where clinicians “milk” the 99mTc daughter from the generator as needed for diagnostic procedures.
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

FINAL REPORT
One of Two 2008 NSAC Charges on the National Isotopes Production and Application Program

Compelling Research Opportunities using Isotopes

NSAC Isotopes Subcommittee

FINAL REPORT
Second of Two 2008 NSAC Charges on the Isotope Development and Production for Research and Applications Program

Isotopes for the Nation's Future
A long range plan

NSAC Isotopes Subcommittee

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

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 © 2010 Elsevier Inc. All rights reserved.
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(α,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)

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>CITY/PROVINCE</th>
<th>FACILITY NAME</th>
<th>REACTOR AGE</th>
<th>% WORLD SUPPLY</th>
<th>MEGAWATTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>Rolphoton, Ontario</td>
<td>NRU Chalk River</td>
<td>52 years old</td>
<td>31%</td>
<td>135</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Zijpe</td>
<td>HFR-Petten</td>
<td>47 years old</td>
<td>33%</td>
<td>45</td>
</tr>
<tr>
<td>Belgium</td>
<td>Mol</td>
<td>BR2</td>
<td>47 years old</td>
<td>10%</td>
<td>100</td>
</tr>
<tr>
<td>France</td>
<td>Saclay</td>
<td>OSIRIS</td>
<td>42 years old</td>
<td>8%</td>
<td>70</td>
</tr>
<tr>
<td>South Africa</td>
<td>Pelindaba</td>
<td>SAFARI</td>
<td>43 years old</td>
<td>3%</td>
<td>20</td>
</tr>
<tr>
<td>Australia</td>
<td>Sydney</td>
<td>OPAL</td>
<td>2 years old</td>
<td>NA</td>
<td>20</td>
</tr>
</tbody>
</table>
Are there alternatives to the ageing reactors?

- The current world-wide usage of $^{99}\text{Mo}$ is $\sim 100,000$ end-of-irradiation Curies per week ($\sim 12,000$ “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 ($<20\% \ ^{235}\text{U}$) 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

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Accelerator-Based Production of Medical Isotopes
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

Expanded view of the 18-cm diameter core region (proton beam hits the depleted uranium target)

Neutron-flux distribution in the LEU target

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 $\sim$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

Production linac

Radioisotopes for basic nuclear physics

“Reactor” isotopes

“Accelerator” isotopes

“Physics” isotopes

Accelerator-Based Production of Medical 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