Production of Sr-82 for Rb-82 Generators

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Introduction

• Evaluation of cardiac viability by radionuclide imaging is one of the most powerful means available of determining response to a myocardial infarction, whether bypass surgery or medical management.

• A number of positron emitting radionuclides can be used for monitoring blood flow to cardiac tissue with high imaging resolution and less dose than Tc-99m or TI-201:
  – O-15, very short lived, cyclotron produced
  – N-13, very short lived, cyclotron produced
  – K-38, very short lived, cyclotron produced
  – Rb-82, very short lived, Sr-82 generator produced
Myocardial blood flow tracers with PET

<table>
<thead>
<tr>
<th>Tracer</th>
<th>$T_{1/2}$ (min)</th>
<th>$\beta^+$ (%)</th>
<th>$\beta^+$ range (mm)</th>
<th>Production routes</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_2^{15}O$</td>
<td>2.03</td>
<td>99.9</td>
<td>1.02</td>
<td>$^{14}N(d,n)$, $^{15}N(p,n)$</td>
</tr>
<tr>
<td>$^{13}NH_3$</td>
<td>9.97</td>
<td>99.8</td>
<td>0.57</td>
<td>$^{16}O(p,\alpha)$</td>
</tr>
<tr>
<td>$^{38}K$</td>
<td>7.6</td>
<td>98.7</td>
<td>2.60</td>
<td>$^{40}Ar(p,3n)$</td>
</tr>
<tr>
<td>$^{82}Rb$</td>
<td>1.27</td>
<td>95.2</td>
<td>2.60</td>
<td>$^{82}Sr$ decay</td>
</tr>
</tbody>
</table>
82Sr/82Rb generator

• The quick uptake of potassium analogue rubidium in cardiac muscle tissue and its availability from a generator has made 82Rb the agent of choice, especially for facilities without a cyclotron.

• The 82Sr half life of 25.36 d, with decay 100% by electron capture, is convenient for shipping and provides useful radioactivity in a generator for at least a month of frequent elutions.

• An FDA approved commercial generator, trade name CardioGen-82, has been available from Bracco Diagnostics Inc. for some years.
  – This generator is composed of a small plastic column (~4cmx0.5cm diam.) loaded with hydrous tin oxide. The distribution coefficient for Sr ions is about 21,000 and less than 3 for Rb ions when eluted with normal saline solution.
  – The generator is typically loaded with 100mCi (3.7GBq) of 82Sr, and infusions are microprocessor controlled.
  – Other vendors plan to bring other such systems to market soon.
Production of $^{82}\text{Sr}$

- $^{82}\text{Sr}$ is difficult and somewhat expensive to produce because it can only be effectively made with high energy proton reactions at relatively few large government owned accelerator facilities around the world.

- Irradiation scheduling is challenging since these facilities have other missions and do not operate continuously year round.
  - In response the Department of Energy coordinates a consortium of producers, called the Virtual Isotope Center.

- Timely transport of large quantities of radioactivity around the world also faces hurdles.
Production routes for $^{82}$Sr

<table>
<thead>
<tr>
<th>Nuclear Reaction</th>
<th>Target</th>
<th>Projectile Energy (MeV)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{89}$Y(p, spallation)</td>
<td>Yttrium oxide</td>
<td>60-240</td>
<td>Low radiopurity &amp; yield</td>
</tr>
<tr>
<td>natMo(p, spallation)</td>
<td>Mo metal</td>
<td>500-700</td>
<td>Low radiopurity, high cost</td>
</tr>
<tr>
<td>natRb(p,xn)</td>
<td>RbCl or Rb metal</td>
<td>40-90</td>
<td>Preferred</td>
</tr>
<tr>
<td>natKr(α,pxn)</td>
<td>Kr gas</td>
<td>20-120</td>
<td>Low radiopurity, low yield, little availability</td>
</tr>
<tr>
<td>natKr($^3$He,xn)</td>
<td>Kr gas</td>
<td>20-90</td>
<td>Low radiopurity, low yield, very little availability</td>
</tr>
</tbody>
</table>
One Target Stack Tuned for Simultaneous Production of $^{82}\text{Sr}$ and $^{68}\text{Ge}$

Production energy windows utilized at IPF

$^{\text{nat}}\text{Ga}(p,\text{xn})^{33}\text{Ge}$

$^{\text{nat}}\text{Rb}(p,\text{xn})^{82}\text{Sr}$

Proton Energy (MeV)
Control of product radiopurity

- Rb-83,84,86 and Br-77,80m and P-32 are all coproduced and can be chemically separated from Sr-82
- Sr-83 (T_{1/2}=1.35d), and Sr-85 (T_{1/2}=64.8d) are coproduced with Sr-82 and cannot be chemically separated
  - Both are minimized by controlling the proton exit energy since the reaction cross section for them rises sharply at energies less than 41 MeV.
  - At EOB the $^{83}\text{Sr}/^{82}\text{Sr}$ and $^{85}\text{Sr}/^{82}\text{Sr}$ ratios are typically 4 & 0.4 respectively.
  - $^{83}\text{Sr}$ content is especially problematic since it decays into $^{83}\text{Rb}$. Therefore a decay period of 8 days post EOB is typical before start of chemical processing to allow the $^{83}\text{Sr}$ content to decay to less than specification. If chemistry is started earlier residual $^{83}\text{Sr}$ will grow into an unacceptable amount of $^{83}\text{Rb}$ in the final product.
# The “Virtual” Isotope Center

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Target type</th>
<th>Irradiation conditions</th>
<th>Typical batch yield at EOB (GBq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLIP @ Brookhaven National Lab (BNL), NY USA</td>
<td>RbCl pressed pellet in inconel</td>
<td>2 targets, 93-70 &amp; 64-41 MeV</td>
<td>220-300 (5.9-8.1Ci)</td>
</tr>
<tr>
<td>IPF @ Los Alamos National Lab (LANL), NM USA</td>
<td>RbCl cast puck in inconel</td>
<td>2 targets, 97-71 &amp; 65-45 MeV</td>
<td>300-450</td>
</tr>
<tr>
<td>Institute for Nuclear Research (INR), Troitsk</td>
<td>Rb metal in stainless steel</td>
<td>100-40 MeV</td>
<td>120-220</td>
</tr>
<tr>
<td>Russia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>iThemba Labs, Faure S. Africa</td>
<td>Rb metal in stainless steel</td>
<td>66-44 MeV</td>
<td>100</td>
</tr>
<tr>
<td>Arronax, Nantes France</td>
<td>RbCl pressed pellet in stainless steel</td>
<td>8 thin targets, 69-44 MeV</td>
<td>80-90</td>
</tr>
<tr>
<td>Nordion/TRIUMF, Vancouver Canada</td>
<td>Rb metal in stainless</td>
<td>60-48 MeV</td>
<td>60-100</td>
</tr>
</tbody>
</table>
Target Issues - RbCl

- **Advantages**
  - It is available in high purity, is easy to dissolve in water, can be pressed into a pellet at near theoretical density, or melted and cast into a capsule. The Rb atom density is higher than that of pure Rb metal, so the presence of Cl atom does not decrease yield compared to the pure metal. It is much less corrosive than Rb metal.

- **Disadvantages**
  - It is hygroscopic and must be carefully dried before use. Possible traces of RbCO$_3$ must be destroyed before target fabrication. The thermal conductivity is poor (7.6 Wm$^{-1}$K$^{-1}$) so survival at high beam current requires careful target design and limits target thickness. There can be a large difference in temperature from target interior and the cooled target surface. Indeed the salt can melt (MP 718°C) in the beam strike area. It then expands by 19% and pushes away from the central hot spot leading to a thinning of the target and resultant lower and erratic yield. A uniform beam intensity profile (raster scan) can overcome this problem and has been implemented at LANL, and is planned at BLIP.
Temperature profile in RbCl target with fixed Gaussian beam spot

- RbCl Target inconel body
- .012" inconel window
- Standard array
- 0.10" water gaps
- T=4.95 sec
- Current Gaussian
- Central melting (green zone)
Temperature profile in RbCl target with dual radius (19.5 & 6.5mm) circular raster at 5kHz

RbCl Target inconel body
.012” inconel window
Standard array
.10” water gaps
T=15.9 sec
Concentric Raster
Target Issues – Rb metal

• Advantages - high thermal conductivity (58.2 Wm$^{-1}$K$^{-1}$) permits the use of very thick targets in order to increase batch quantity.

• Disadvantages – Availability of very high purity material is difficult. There are serious safety issues in handling metallic Rb. It is VERY reactive and releases hydrogen in contact with water. It can ignite or explode upon exposure to air or moisture. All target fabrication, target opening after irradiation, and target dissolution must be done within an inert atmosphere (eg. dry argon). Initial target dissolution must be done with an anhydrous higher alcohol, typically propan-2-ol. Since all targets must be water cooled during irradiation, a puncture with contact with water could be catastrophic. Also hot Rb metal is quite corrosive, so there is substantial Fe arising from the target cladding that requires additional chemical steps to remove.
Facilities
iThemba Labs solid target station
ARRONAX, a high energy and high intensity cyclotron for nuclear medicine.

F. Haddad
Halls A1, A2, P2 and P3: radionuclide production.

Hall P1: R&D on highly intense beam
Cross section of the Irradiation station

Salle P2, P3, A1 et A2

Évacuation

shuttle

Collimator diam 10mm
shuttle 15°, Astate
Group of RbCl target

8 identicals targets
Isotope Production Facility (IPF) and LANSCE: A Powerful Combination for Production R&D

Photograph courtesy of Dr. Meiring Nortier, LANL
IPF Overview
Brookhaven LINAC Isotope Producer (BLIP)

The LINAC supplies polarized protons to the Booster for nuclear physics and NASA space radiobiology program. Excess high intensity unpolarized proton pulses (~92%) are diverted to BLIP. Energy to BLIP is variable from 66-202 MeV in ~23 MeV steps at integrated intensity up to 120µA.
Layout of BLIP Beam Line
BLIP SCHEMATIC

HOT CELL

LEAD

18' POLYETHYLENE BEADS

18' STEEL SHOT

12 3/4' O.D. STEEL INSPECTION PORT

CONCRETE SHIELD PLUG

18' O.D. STEEL SHAFT (SAND CONTAINMENT)

SAND

16' O.D. STAINLESS STEEL CONTAINMENT SHAFT (FILLED WITH WATER)

EXISTING BLIP TANK
8' 0" DIA. x 30' 4" LONG

SHIELD (SAND) SUPPORT STRUCTURE

TARGETS

LINAC BEAM

TUNNEL FLOOR

EXISTING FOOTING

U.S. DEPARTMENT OF
ENERGY

Office of Science

BROOKHAVEN NATIONAL LABORATORY
BLIP target array

- Targets are fully immersed in water and cooled by rapid flow across the faces. Soluble materials must be encapsulated but most other type of contents must also be isolated from contaminants in cooling water.
- Each target design has to be compatible (both energy and space) with simultaneous irradiation of other radionuclides.
Sr-82 process flow chart

- Separate Sr from bulk RbCl on Chelex-100 column

- Separate Sr from residual Rb, Se, Be on cation exchange column AG50W-X8

- Separate Sr from residual stable Fe on anion exchange column AG1-X8
Sr-82 product specifications

- **Radionuclidic Purity** determined by gamma ray spectroscopy
  - \(^{85}\text{Sr}/^{82}\text{Sr} \leq 5\) mCi per mCi \(^{82}\text{Sr}\) at calibration date (typically 18 d post EOB).
  - \(^{83}\text{Sr}/^{82}\text{Sr} \leq 0.0015\) mCi per mCi \(^{82}\text{Sr}\) at calibration date.
  - \(^{83}\text{Rb}/^{82}\text{Sr} \leq 0.0015\) mCi/mCi \(^{82}\text{Sr}\) at calibration date.
  - \(^{84}\text{Rb}/^{82}\text{Sr} \leq 0.0015\) mCi/mCi \(^{82}\text{Sr}\) at calibration date.
  - All other radionuclides \(\leq 0.01\) of the \(^{82}\text{Sr}\) activity at calibration date.

- **Specific Activity** determined by ICP-OES or ICP-MS
  - \(> 25\) mCi/mg

- **Activity Concentration**
  - \(> 50\) mCi \(^{82}\text{Sr}/\text{mL solution of 0.1 N HCl}\)

- **Stable elements** determined by ICP-OES or ICP-MS
  - Assay SOP checks 19 elements; primary concern are Rb, Ca, Ba, Fe, Ni, Cu as possible contaminants from target material, cladding or environment