Production of medical radionuclides at TRIUMF: current status and future perspectives.

Thomas J. Ruth, PhD
Emeritus – Life Sciences
TRIUMF
TRIUMF Accelerators

- 520 MeV, 350μA, H\(^+\) cyclotron
- ISAC 50kW ISOL facility
  - RFQ, 3 ≤ A/q < 30
  - DTL, A/q ≤ 7, 0.1-1.8 MeV/u
  - 40 MV Heavy Ion SC linac
- ARIEL e-linac (10mA, 30 MeV)
- 4+1 medical isotope cyclotrons (TR13, CP42, TR30-1, TR30-2; TR24 – coming 2021)

![Diagram of TRIUMF accelerators](image-url)
Routine production of $^{18}\text{F}$ and $^{11}\text{C}$ for clinical collaboration partners (UBC hospital, etc.)

Production of PET radiometals:
Liquid targets:
$^{68}\text{Ga}, ^{44}\text{Sc}, ^{86}\text{Y}, ^{89}\text{Zr}$

Easy to handle/transport
Significantly lower yield compare to solid targets

In progress: Solid target setup and expanding pallet of radiometals:
$^{68}\text{Ga}, ^{44}\text{Sc}, ^{45}\text{Ti}, ^{64}\text{Cu}, ^{86}\text{Y}, ^{90}\text{Nb}, ^{89}\text{Zr}$

TR-13 Operation team:
David Prevost
Linda Graham
Samuel Varah

Auger emitters for targeted therapy from solid target:
$^{119}\text{Sb}$ and $^{165}\text{Er}$
Production of medical radionuclides at TRIUMF:ISAC

ISAC
Production of small (pre-clinical) quantitates of imaging and therapeutic radionuclides

Isotope Production Facility (IPF), BL1A

ARIEL
Collection chamber
Proton and electron beamlines

IAMI
TR-24
Production in 6 cm diameter, 5 cm thick, 1.5 kg Th metal, [10 μA⁻¹ · s⁻¹]
ISAC production of medical radionuclides

ISAC Facilities for Rare-Isotope Beams

Uranium target

Ionization & extraction

\[ \text{480 MeV} \quad 10 \mu A \]

\[ \text{p}^+ \]

\[ \text{target station} \]

\[ \text{heterogeneous ion beam} \]

\[ \text{mass separator magnet} \]

\[ \text{225}^{\text{Ra}} \quad \text{&} \quad \text{225}^{\text{Ac}} \text{ion beam} \]

\[ \text{to yield station} \]

\[ \text{to implantation station} \]

\[ \text{SEM holder} \quad \text{(target)} \]

\[ \text{gate valve} \]

\[ \text{collimator} \]

Peter Kunz
ISOL $^{209}$At-based imaging to establish $^{211}$At α-therapy

**Imaging**

$^{209}$At

$\text{t}_{1/2} = 5.4 \text{ h}$

(γ-emitter)

**Therapy**

$^{211}$At

$\text{t}_{1/2} = 7.2 \text{ h}$

(α-emitter)
\(^{225}\text{Ac}/^{213}\text{Bi}\) promising system for TAT

- \(^{225}\text{Ac}\) (\(t_{1/2} = 9.92\) d) in combination with specific biomolecules (e.g., peptides) is a promising system for Targeted Alpha Therapy (TAT)

- \(^{225}\text{Ac}/^{213}\text{Bi}\) (\(t_{1/2} = 45.59\) min) generator system provides accelerator independent source of \(^{213}\text{Bi}\) for medical applications

- Ongoing clinical trials
  - \(^{225}\text{Ac}\) phase I
  - \(^{213}\text{Bi}\) phase III

*International Atomic Energy Agency. Technical Meeting Report “Alpha Emitting Radionuclides and Radiopharmaceuticals for Therapy” IAEA Headquarters Vienna, Austria. 24-28 June 2013*

Advanced Rare Isotope Laboratory (ARIEL)

- Represents ~$100 million investment by federal and provincial governments
- Supported by 21 university partners from across Canada
- To be completed in stages between 2019 – 2023

- Uses state-of-the-art, made-in-Canada superconducting RF accelerator technology
- Will add two new production targets
- Will provide three independent radioactive-ion beams for experiments
- Employs cutting-edge target and target station technology for electron and proton beams.
- Designed for beam power up to 300 kW; initial design will operate at 100 kW.
ARIEL – superconducting electron-Linac

- E-gun delivers max. 10 mA at 300 keV beam
- The injector cryomodule accelerates to 5-10 MeV
- The accelerator cryomodule is equipped with two cavities and reaches max. 30 MeV.
Possible relevant photonuclear reactions for medicine:

- $^{120}\text{Te}(\gamma, n)^{119}\text{Te} \rightarrow ^{119}\text{Sb}$ (auger therapy)
- $^{48}\text{Ti}(\gamma, p)^{47}\text{Sc}$ (beta therapy)
- $^{68}\text{Zn} (\gamma, p)^{67}\text{Cu}$ (beta therapy)
- $^{226}\text{Ra} (\gamma, n)^{225}\text{Ra} \rightarrow ^{225}\text{Ac}$ (alpha therapy)

- Using the 30 MeV electron beam from TRIUMF’s e-linac to produce isotopes for medical research
- Adding pneumatic distribution leg to planned symbiotic target transfer system
- Leveraging hot cell, transfer, shipping, shielding infrastructure
Previous studies by others*:
• Production of 2.44 MBq (66 µCi) of $^{225}$Ac after a 1 hr irradiation by 18 MV x-rays of a 20 mg $^{226}$Ra source located 12.5 cm from the tungsten converter and with an incident electron beam of 26 µA average current
• scales to a potential 48 GBq (1.3 Ci) of $^{225}$Ac per month (3 x 10 d irradiation) for a 1 g $^{226}$Ra source, further optimization possible
• ARIEL could theoretically produce up to 74 TBq (2000 Ci) of $^{225}$Ac/month from a 1 g $^{226}$Ra target

Advantages:
- Clean Ac isotope production
- Co-production of $^{224}$Ra occurs for photons above 12 MeV, no impact on desired $^{225}$Ra/$^{225}$Ac generator as $^{224}$Ra ($t_{1/2} = 3.7$ d) decays to inert $^{220}$Rn and does not result in the production of any Ac isotopes

Challenges:
- Many facilities are purposed for patient care, not for large-scale isotope production
- Large $^{226}$Ra mass requirements, cost, handling
- ARIEL: Target power capacity

CANREB: CANadian Rare isotope facility with Electron Beam ion source

CANREB implantation station:
- Will allow more time for medical isotopes collection

More robust/advanced implantation chamber
- More appropriate collection environment (liquid, ice, salts, etc.)
- Larger activities can be collected
- Broader isotopes varieties

\[ ^{225}\text{Ra} / ^{225}\text{Ac} / ^{213}\text{Bi}, \quad ^{211}\text{At}, \quad ^{224}\text{Ra} / ^{212}\text{Pb} / ^{212}\text{Bi}, \quad 149,152, 155\text{ Tb}, \quad 166\text{ Ho} \]
Elinac-based production of $^{225}$Ac via $^{226}$Ra(γ,n) has potential to produce significant (GBq – TBq) quantities.

TRIUMF ARIEL facility potentially capable of large-scale production; will come online in 2021+

Several, significant challenges remain for this approach (i.e. $^{226}$Ra procurement, handling, irradiation)
Isotope production using TRIUMF’s 500 MeV infrastructure

ISAC I production of $^{225}$Ra/$^{225}$Ac

Several times/year, high purity
Small amount (KBq-MBq/run)

Beam line BL1A ~480 MeV, ~110 µA
Proton irradiation of $^{232}$Th
2016-2017
Medium-Large amount (MBq-GBq)

ARIEL proton beam ~480 MeV, ~110 µA,
Proton irradiation of $^{232}$Th
2022-2025
Large amount (GBq)
Symbiotic Therapeutic Isotope Production 2021+

TRIUMF 500 MeV Cyclotron
ARIEL Symbiotic Target
Target Irradiation
Isotope Production

Target Processor
Isotope Harvesting

Generator Manufacturer
$^{225}\text{Ra}/^{225}\text{Ac}$
$^{225}\text{Ac}/^{213}\text{Bi}$
$^{224}\text{Ra}/^{212}\text{Pb}$
$^{212}\text{Pb}/^{212}\text{Bi}$

Radiopharmaceutical Development:
UBC
BCCA
U of Alberta
U of Toronto
Western

Melanoma
Prostate
Pancreatic (neuroendocrine)
Summary for $^{225}\text{Ac}$

- The development of $^{225}\text{Ac}$ production via proton spallation of thorium is the fastest way to reliably meet the current global demand for $^{225}\text{Ac}$ and support the widespread clinical use of any future therapies.
- TRIUMF is working towards the development of routine, GBq-level $^{225}\text{Ac}$ production via the irradiation of thorium metal targets on its primary beamline (BL1A)
- Low level (<100 mCi/3.7GBq, quarterly) processing will be performed on-site; high level processing will be accomplished via strategic partnerships
Cyclotron Production: $^{100}\text{Mo}(p,2n)^{99}\text{Tc}$

Method
- Proton irradiation of isotopically enriched Mo-100 at 16–24 MeV
- Automated Mo-100 dissolution with $\text{H}_2\text{O}_2$
- Automated Tc-99m purification
- Final Tc-99m form: Injectable Sodium pertechnetate

(t$_{1/2} = 6.02$ hours)
ARTMS Products

Venture Capital

$3 Million

Founding Institutions

Strategic Partners
What if?

Global demand for isotopes could be met without relying on a single-point-of-failure supply chain?
Solution:
Develop a method to produce Tc-99m, Ga-68 (and other isotopes) using hospital-based medical cyclotrons
QUANTM Irradiation System™

Target Capsules

Cyclotron Target Station

2-way Target Transfer

Automated Dissolution and Purification

Targets

Q4 2018
68Ga (t_{1/2} = 68 min)

99mTc (t_{1/2} = 6.02 hours)

64Cu (t_{1/2} = 12.7 hours)

89Zr (t_{1/2} = 3.3 days)
Global Installations of QIS™

**Vancouver, BC**
TR19, TR24 (pending)
Tc-99m, Ga-68, others

**Madison, WI**
GE PETtrace
various

**London, ON**
GE PETtrace
Tc-99m, Ga-68, others

**Birmingham, AL**
TR24 (targets only)
Y-89

**Hamilton, ON**
GE PETtrace

**Pending**
iba, ACSI, GE

**Dinnington, UK (2019)**
TR24 (Tc-99m)

**Zurich, CH**
GE PETtrace
(Ga-68, others)

**Odense, DE**
GE PETtrace
(Cu-64, others)
Tc-99m Installations – TRIUMF (IAMM)
IAMi will unite interdisciplinary partners to create a world-class centre for advanced isotope research, development, and production for the life sciences.

TR-24: Proton Energy 24 MeV, 500 µA will enable (p,2n) along with (p, n) reactions

Examples of p,2n reactions for production of medical radionuclides:

\[ ^{45}\text{Sc}(p,2n)^{44}\text{Ti} \]
\[ ^{69}\text{Ga}(p,2n)^{68}\text{Ge} \]
<table>
<thead>
<tr>
<th>Element</th>
<th>Isotope</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>$^{11}$C</td>
<td>PET</td>
</tr>
<tr>
<td>F</td>
<td>$^{18}$F</td>
<td>PET</td>
</tr>
<tr>
<td>Sc</td>
<td>$^{44}$Sc</td>
<td>PET/ $^{47}$Sc β- therapy</td>
</tr>
<tr>
<td>Ti</td>
<td>$^{45}$Ti</td>
<td>PET</td>
</tr>
<tr>
<td>Mn</td>
<td>$^{52,54}$Mn</td>
<td>PET</td>
</tr>
<tr>
<td>Co</td>
<td>$^{55}$Co</td>
<td>PET</td>
</tr>
<tr>
<td>Cu</td>
<td>$^{64}$Cu</td>
<td>PET/ $^{67}$Cu β+ therapy</td>
</tr>
<tr>
<td>Ga</td>
<td>$^{68}$Ga</td>
<td>PET/ $^{67}$Ga Auger therapy</td>
</tr>
<tr>
<td>Y</td>
<td>$^{86}$Y</td>
<td>PET/ $^{90}$Y β- therapy</td>
</tr>
<tr>
<td>Zr</td>
<td>$^{90}$Zr</td>
<td>PET</td>
</tr>
<tr>
<td>Nb</td>
<td>$^{90}$Nb</td>
<td>PET</td>
</tr>
<tr>
<td>Tc</td>
<td>$^{99m}$Tc</td>
<td>SPECT/ $^{94m}$Tc PET</td>
</tr>
<tr>
<td>Rh</td>
<td>$^{103m}$Rh</td>
<td>Auger therapy</td>
</tr>
<tr>
<td>In</td>
<td>$^{111}$In</td>
<td>SPECT</td>
</tr>
<tr>
<td>Sb</td>
<td>$^{119}$Sb</td>
<td>Auger/ $^{118}$Sb PET/ $^{117}$Sb Sf</td>
</tr>
<tr>
<td>I</td>
<td>$^{124}$I</td>
<td>PET/ $^{125}$I Auger therapy</td>
</tr>
<tr>
<td>Tb</td>
<td>$^{149}$Tb</td>
<td>Alpha therapy/ $^{161}$Tb β- th</td>
</tr>
<tr>
<td>Er</td>
<td>$^{165}$Er</td>
<td>Auger therapy</td>
</tr>
<tr>
<td>Lu</td>
<td>$^{177}$Lu</td>
<td>β- therapy</td>
</tr>
<tr>
<td>Pb</td>
<td>$^{203}$Pb</td>
<td>Alpha therapy</td>
</tr>
<tr>
<td>Bi</td>
<td>$^{213}$Bi</td>
<td>Alpha therapy</td>
</tr>
<tr>
<td>Ra</td>
<td>$^{223,224}$Ra</td>
<td>Alpha therapy</td>
</tr>
<tr>
<td>Ac</td>
<td>$^{225}$Ac</td>
<td>Alpha therapy</td>
</tr>
<tr>
<td>Th</td>
<td>$^{227,228}$Th</td>
<td>Alpha therapy</td>
</tr>
</tbody>
</table>

ISAC and Th spallation provides endless possibility for production of many other medical isotopes.

Slide courtesy of V Radchenko
## Acknowledgements

### TRIUMF Team
- M Adam,
- K Buckley,
- M Dodd,
- A Gottberg
- L Graham,
- V Hanemaayer,
- C Hoehr,
- J Huser,
- J Klug,
- P Kunz
- N Malik
- S McDiarmid,
- Q Miao,
- D Prevost,
- V Radchenko,
- C Ramogida,
- TJ Ruth,
- M Stachura,
- S. Varah,
- H Yang,
- Z. Yuan
- S Zeisler

### TRIUMF Team (cont’d)
- B Badesso
- M Colovic
- H Chen
- S Ferguson
- A Fong
- J Hanlon
- K Hayashi
- A Lam
- C Lee
- K Li
- A Limoges
- P Martini
- K McDuffie
- N McLean
- T Morley
- E Oehlke
- F Pau
- A Roberston
- P Tsao
- N Unick
- K Young
- N Zacchia

### BC Cancer Agency
- F Bénard,
- H Corbett
- G Dias,
- W English,
- K Frantzen
- KS Lin
- G Langlois
- J Song
- J Schlosser
- M Vuckovic,

### ARTMS
- K Wilson – CEO
- M Cross – COO
- J Kumlin
- B Hook
- R Coffey
- S Borjian
- A Kassaian

### Collaborators
- F Prato (Lawson)
- M Kovacs (Lawson)
- S Foster (Lawson)
- J Corsault (Lawson)
- N Cockburn (Lawson)
- J Valliant (CPDC)
- M Cross (CPDC)
- T Besanger (CPDC)
- F Gleeson (CPDC)
- J McEwan (CPDC)
- P Ruddock (CPDC)
- A Goodbody (CPDC)
- J McCann (CPDC)
- R Harper (CPDC)
- C Economou (CPDC)
- S. Britton (SFU)
- M. Nodwell (SFU)
- M Martinez (UBC),
- C Orvig (UBC),
- E Price (UBC, now U Sask),
- A Celler (UBC),
- J Tanguay (UBC),
- X Hou (UBC)
- J Wilson (Cornell)
- J Babich (Cornell)
Thank you
Merci