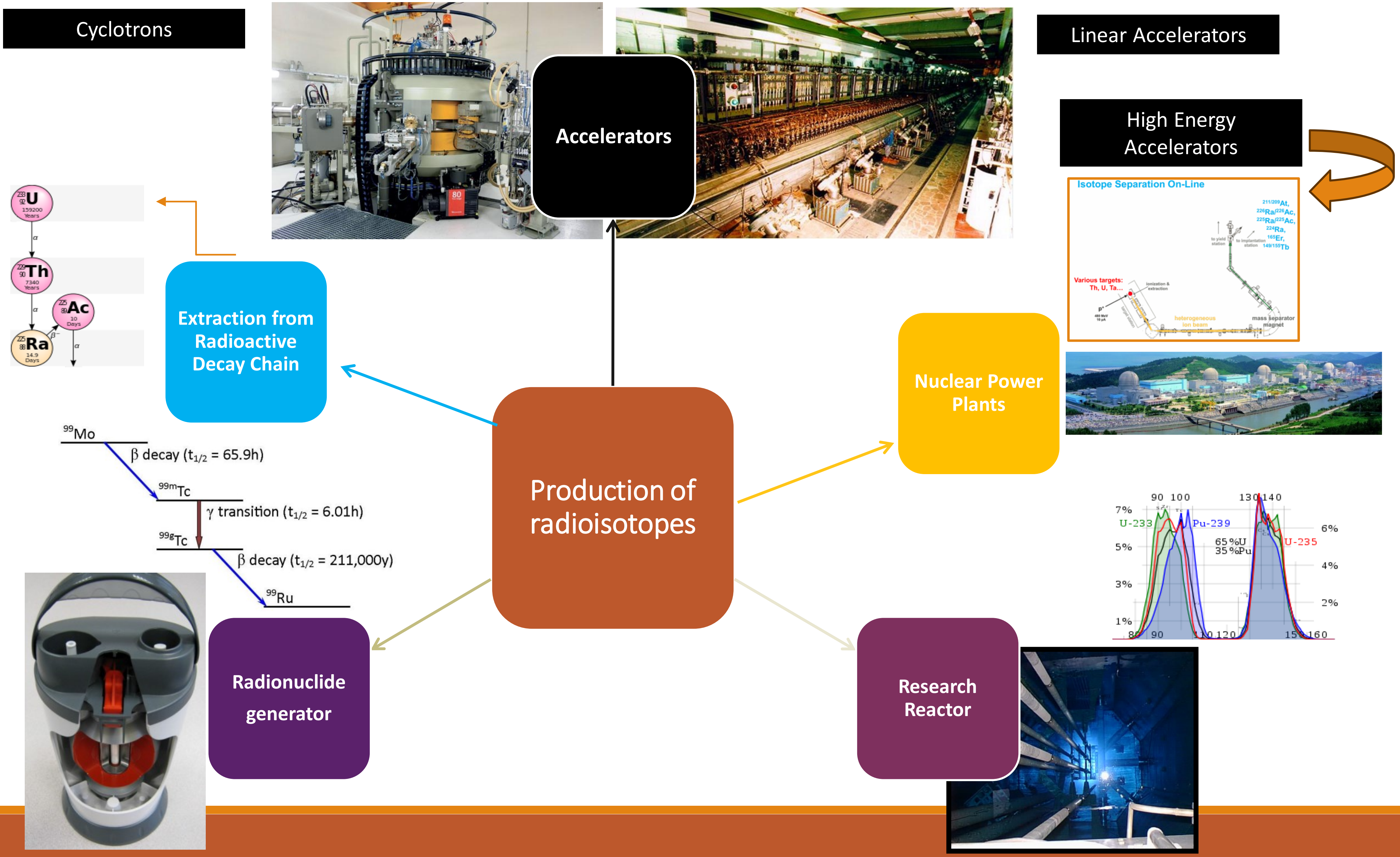
Produção de radionuclídeos: Status mundial no presente e expectativas para o futuro

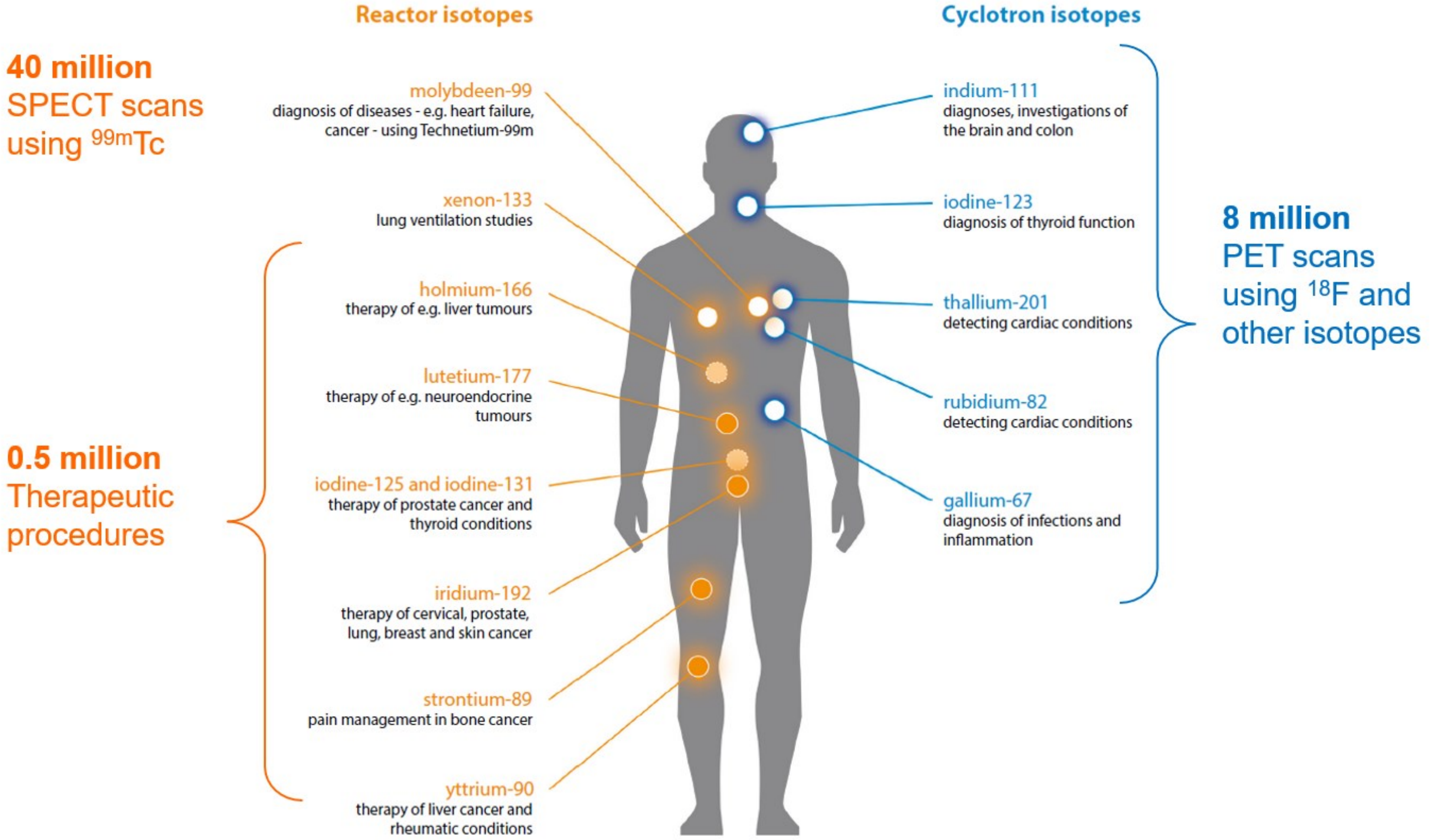
Round Table: New trends of Theranostic Radiopharmaceuticals applied in Nuclear Medicine

08/05/2024

João Alberto Osso Junior, PhD
jaossoj@yahoo.com.br
Former IPEN-CNEN/SP and IAEA


Cyclotrons
Accelerators
Linear Accelerators
High Energy Accelerators
Isotope Separation On-Line
Various targets: Th, U, Ta...
heterogeneous ion beam
mass separator magnet
Extraction from Radioactive Decay Chain
Production of radioisotopes
Nuclear Power Plants
Radionuclide generator
Research Reactor
U
Th
Ac
Ra
99Mo
β decay (t1/2 = 65.9h)
99mTc
γ transition (t1/2 = 6.01h)
99gTc
β decay (t1/2 = 211,000y)
99Ru
U-233
Pu-239
U-235
65 %U
35 %Pu
7%
5%
3%
1%
6%
4%
2%
90 100
130 140
90
120
160

Technetium-99m is most commonly used isotope worldwide



Source: MEDRaysintell 2017, Nuclear Netherlands, PALLAS

PALLAS

BWXT Medical Investor Presentation, September 2022

http://s2.q4cdn.com/477932843/files/doc_presentations/BWXT-Medical-September-2022-briefing-FINAL-v3-(1).pdf

Design work for Argentina's radioisotope production plant under way
23 April 2024
Share
Argentina's National Atomic Energy Commission (CNEA) and nuclear construction specialists INVAP have held a workshop focused on the design of the facility which will form part of the complex alongside the new RA-10 multipurpose reactor.

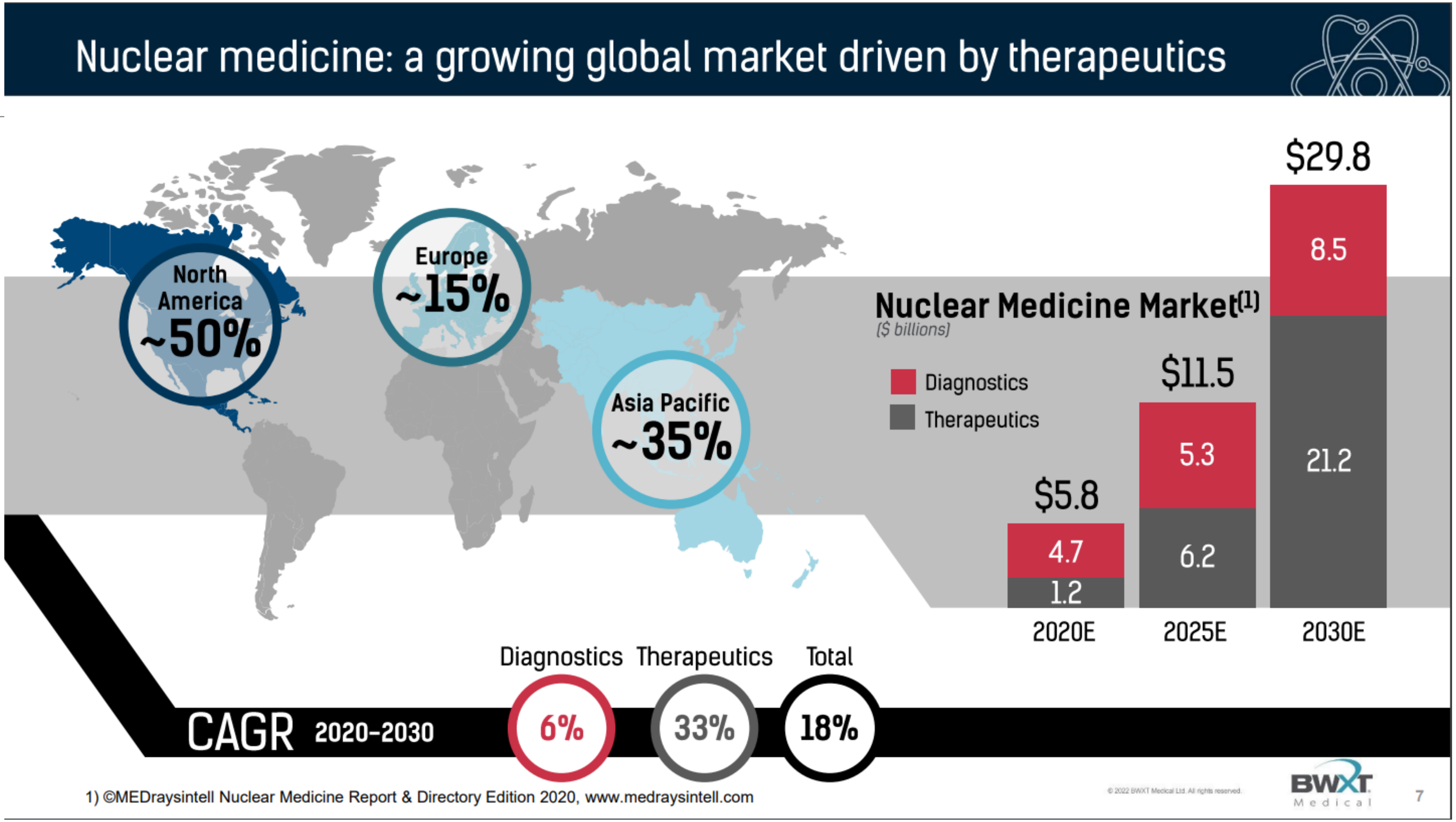
Construction starts for Russian medical isotopes plant
24 January 2023

AuntMinnie.com
Radiopharm, MD Anderson launch new theranostics company
By AuntMinnie.com staff writers
September 14, 2022 -- Radiopharm Theranostics and the University of Texas MD Anderson

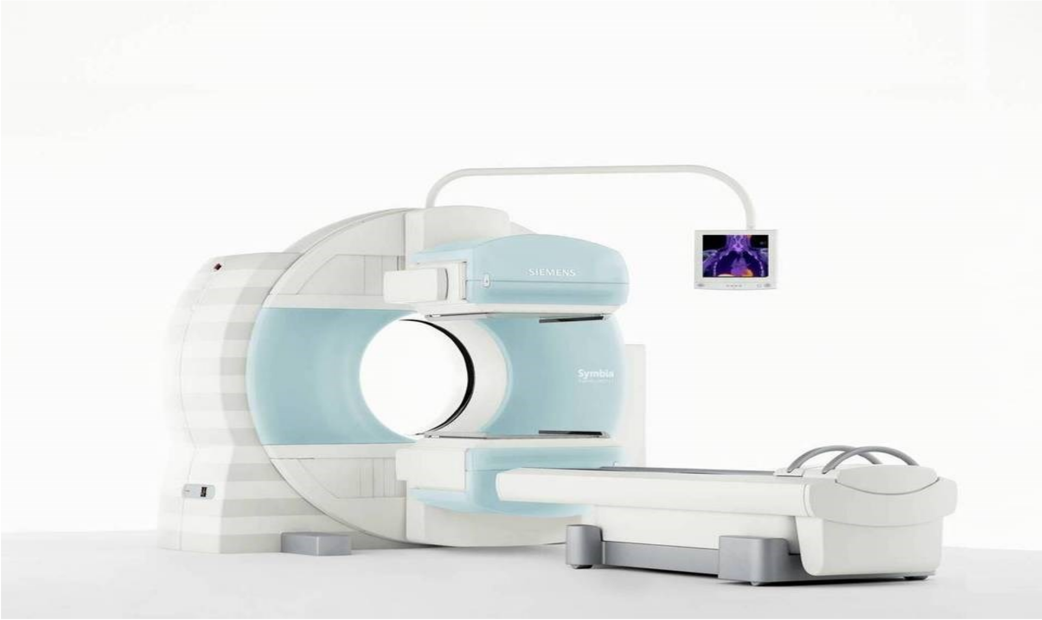
Monrol to open nuclear research reactor in Germany
By AuntMinnieEurope.com staff writers
September 30, 2022 -- Istanbul-based Eczacibasi-Monrol Nuclear Products

Pallas construction permit granted
15 February 2023

Welsh plan for new nuclear medicine laboratory
10 January 2023



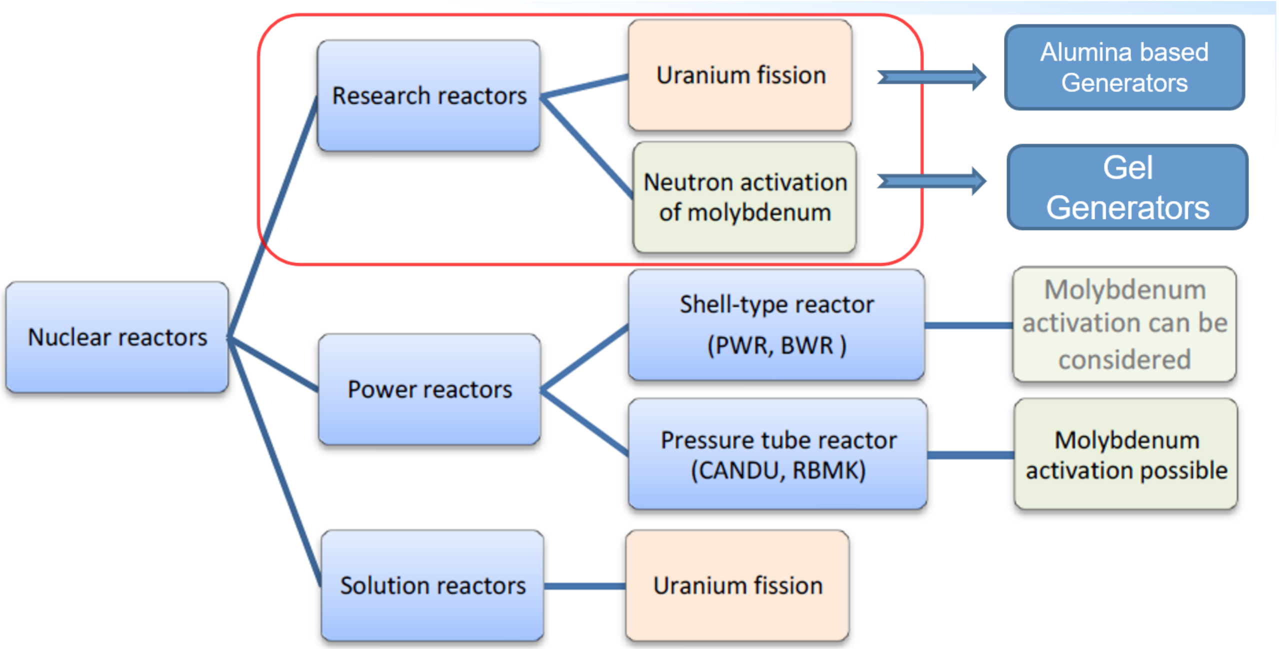
DIAGNOSTIC-SPECT



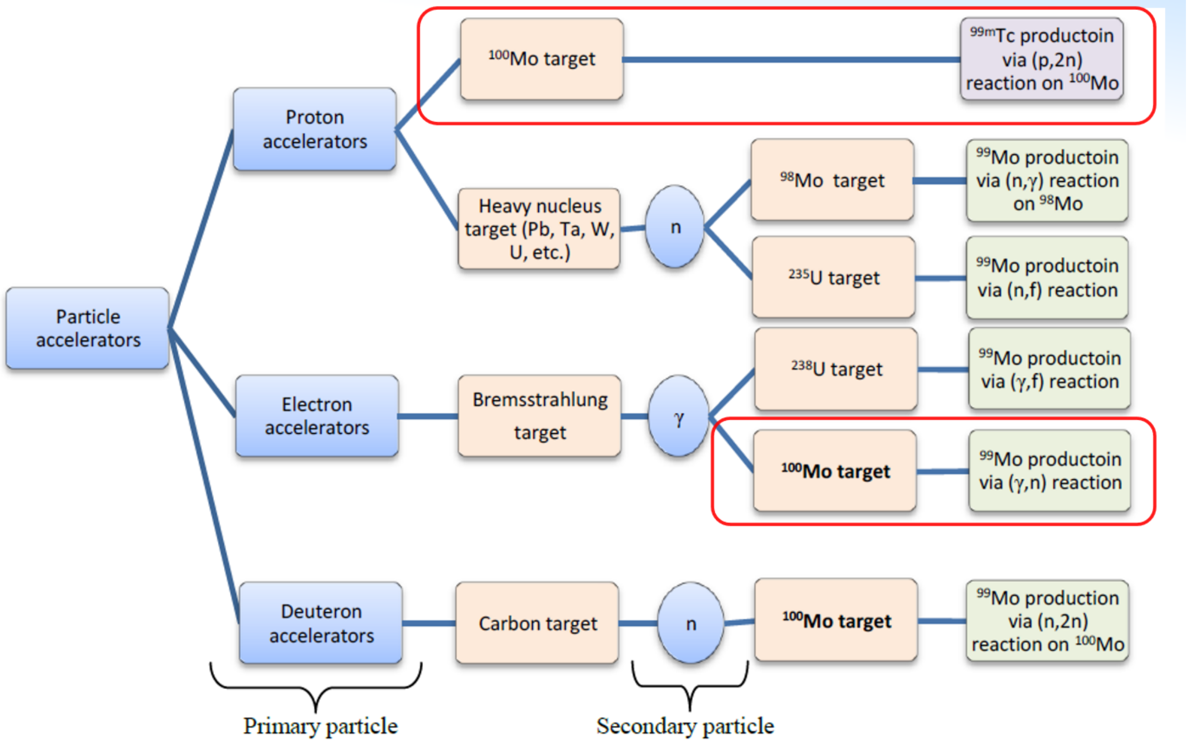
Isotope	^{67}Ga	^{99m}Tc	^{111}In	^{123}I	^{201}Tl
Half-life	78.3 h	6 h	67.2 h	13 h	73 h
Production	$^{68}Zn(p,2n)^{67}Ga$ enriched	Generator (^{99}Mo-^{99m}Tc)	$^{112}Cd(p,2n)^{111}In$ enriched	$^{124}Xe(p,2n)^{123}Cs$ $^{123}Cs \rightarrow {}^{123}Xe \rightarrow {}^{123}I$ enriched	$^{203}Tl(p,3n)^{201}Pb$ $^{201}Pb \rightarrow {}^{201}Tl$ enriched

Mo-99 Production Routes

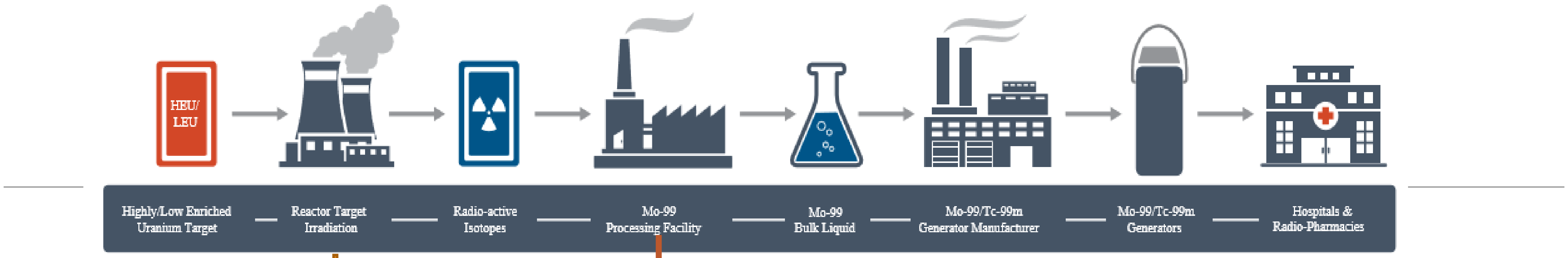
Reatores Nucleares



Aceleradores

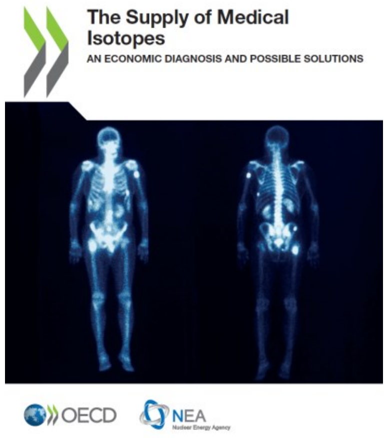


Source: modified from "The supply of medical radioisotopes-Review of potential Molybdenum-99/Technetium-99m production technologies". Nuclear Energy Agency-OECD November 2010



Reactor	Country	Maximum Capacity (6 day Ci)	World Share capacity
OPAL	Australia	3500	16%
CNEA (RA-3)	Argentina	400	2%
MARIA	Poland	2200	9%
SAFARI-1	South Africa	3000	14%
HFR	Netherlands	6200	26%
LVR-15	Czech RPB	3000	10%
RIAR & KARPOV	Russia	890	5%
BR-2	Belgium	6500	15%
MURR	USA	750	4%

Name	Country	Maximum Capacity (6 day Ci)	World Share capacity
ANM (G)	Australia	3500	18%
CNEA (G)	Argentina	400	2%
Curium ©	Netherlands	5000	32%
IRE (SG)/©	Belgium	3500	22%
NTP (SG)	South Africa	3000	16%
NorthStar©	USA	750	5%
Rosatom (SG)	Russia	890	5%



OECD: Demand and supply of medical radioisotopes

The NEA welcomed more than 200 international experts to take part in the International Workshop on Medical Radioisotopes Supply on 30-31 October 2023, including over 70 in-person participants in Paris.

Day 1, Session 1: Assessing the security of supply of ^{99}Mo and ^{131}I
Session 2: The current situation and challenges to supply of ^{177}Lu
Session 3: Current developments in new production: ^{99}Mo (SHINE and BWXT) and new RRs
Day 2, Session 1 will discuss trends in innovative radioisotopes, while Session 2 will focus on three of these radioisotopes: ^{68}Ge and its daughter nuclide ^{68}Ga, α-emitting ^{225}Ac and ^{211}At.
Programmes and sustainable financing models; Pharmaceutical regulatory considerations for medical radioisotopes and radiopharmaceuticals; Stakeholders panel discussion; Specialists in medical field and private sector panel discussion

OECD Reports: Demand and supply of Mo-99

OECD-NEA: https://www.oecd-nea.org/jcms/pl_87477/the-security-of-supply-of-medical-radioisotopes-demand-and-capacity-projections-for-99mo/99mtc-for-the-2023-2027-period?details=true

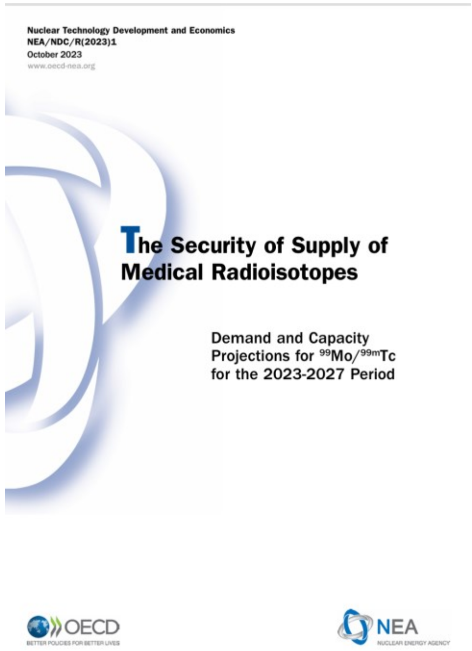
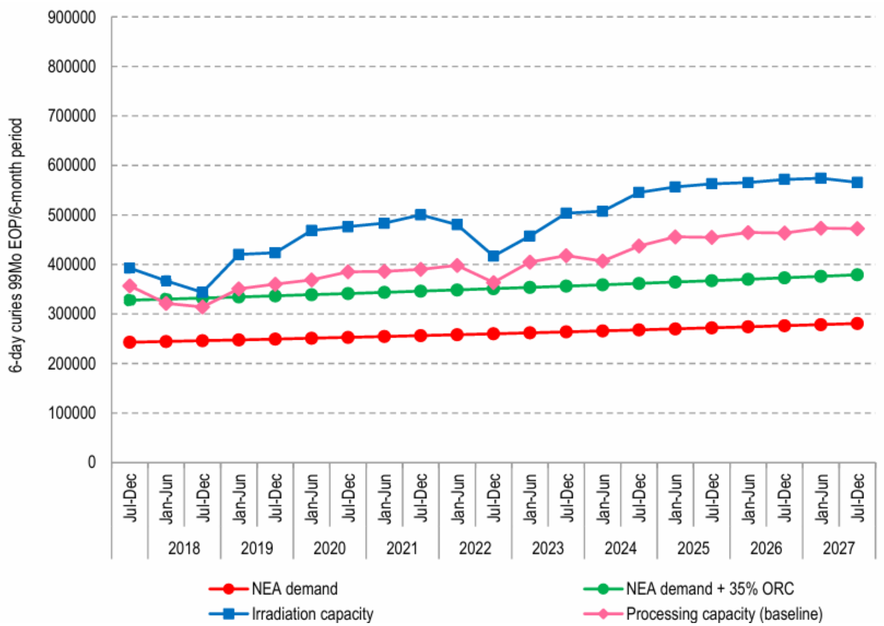


Figure 4.1: NEA demand and NEA demand +35% ORC vs. irradiation and processing capacity (2017-2027)



Conclusions

- Global demand up to 10,000 6-day Ci
- Positive: HEU to LEU conversion (90%)
- Delays in alternative technologies (2027)
- Continuous service during COVID
- Shortages: NTP (before 2020) and late 2022
- Current irradiators and processors, if well maintained and scheduled, should be able to manage limited periods of unplanned outage.

Building Resilience into the Nation's Medical Product Supply Chains (2022)

Communication from NMEU to EU Observatory for the Supply of Medical Radioisotopes

Global Mo-99 and I-131 Production Impacted by delay of BR2 Reactor Restarting from Scheduled Maintenance

Brussels, 28 October 2022

HFR Reactor Restart Delayed; Some Disruption to Mo-99 Supply Expected

April 9, 2024

The Nuclear Research and Consultancy Group (NRG) communicated that a deviation had been found in the cooling system of the Petten High Flux Reactor (HFR) in Petten, Netherlands, which delayed the restart of HFR for its next cycle.

The HFR team made good progress with the required technical modification, allowing HFR to restart on April 7.

Nuclear Medicine Europe (NMEU) anticipates some disruptions to Mo-99 supply this week, but I-131 supplies are expected to be stable.

See the latest communication from NMEU **here**.

Table 1. Current irradiators

Reactor (Fuel)	Current targets[6]	Normal operating days/year	Anticipated ^{99}Mo production weeks/year	Expected available capacity per week (6-day Ci ^{99}Mo)	Expected available capacity per year (6-day Ci ^{99}Mo) by 2027	Estimated end of operation
BR-2 (HEU)[1]	LEU	203	29	8 600	249 400	2036
HFR (LEU)	LEU	265	38	6 200	235 600	2030
LVR-15 (LEU)	LEU	210	30	3 000	90 000	2028
MARIA (LEU)	LEU	200	36	2 200	79 200	2040
MURR (HEU)[2]	EnMo in CRR	339	52	3 000	156 000	2037
OPAL (LEU)[3]	LEU	308	44	3 200	140 800	2057
RA-3/RA-10 (LEU)[4]	LEU	230	46	500	23 000	2027 or earlier based on RA-10 introduction
SAFARI-1 (LEU)	LEU	305	44	3 000	130 700	2030
RIAR[5] (HEU)	HEU	350	50	540	27 000	At least until 2025
KARPOV[5] (HEU)	HEU	336	48	350	16 800	At least until 2025

Notes: 1). BR-2 total capacity substantially increased since 2019 report with increased weekly capacity and additional operating days; 2). MURR capacity is limited by NorthStar processing capacity, capacity is planned to increase progressively until 2024 reaching the level shown in this table; 3). OPAL capacity is restricted by ANM processing capacity, capacity is planned to increase progressively from 2022 until reaching the 2027 level shown in this table; 4). RA-10 will be providing the irradiation for the 23 000 6-day Ci ^{99}Mo per year by 2027; 5). RIAR and KARPOV capacity remains reported at the 2019 report level, 6). EnMo = Enriched Mo^{98} target, HEU >20% enriched Uranium, LEU <20% enriched Uranium.

Table 2. Current processors

Processor	Targets[6]	Anticipated ^{99}Mo production weeks/year	Available capacity per week (6-d Ci ^{99}Mo)	Expected available capacity per year (6-d Ci ^{99}Mo) by 2027	Expected year of full conversion to LEU targets[7]	Estimated end of production[7]
ANSTO Nuclear Medicine (ANM)[1]	LEU	44	3 200	140 800	LEU	2057
CNEA[2]	LEU	46	500	23 000	LEU	2027 or earlier based on RA-10 introduction
Curium	LEU	52	5 000	260 000	LEU	NK
IRE[3]	LEU	52	3 500	182 000	LEU	At least until 2032
MURR/NorthStar[4]	EnMo	52	3 000	156 000	NA	At least until 2037
NTP	LEU	44	3 000	130 700	LEU	At least until 2030
RIAR[5]	HEU	50	540	27 000	NK	At least until 2025
KARPOV Institute[5]	HEU	48	350	16 800	NK	At least until 2025

Notes: 1). ANM processing capacity is planned to increase progressively from 2022 until reaching the 2027 level shown in this table; 2). CNEA will be processing 23 000 6-day Ci 99Mo per year by 2027 from RA10; 3). The IRE started LEU target conversion in 2020 with full conversion achieved in March 2023; 4). MURR/NorthStar processing capacity is in a scale-up phase with maximum capacity planned by 2025; 5). RIAR and KARPOV capacity remains reported at the 2019 report level; 6). EnMo = Enriched Mo98 target, HEU >20% enriched Uranium, LEU <20% enriched Uranium, NA = Not Applicable, NK = Not Known.

Table 3. Potential irradiators entering in period 2023 to 2027

Irradiation source (Fuel)[2]	Targets/technology[2]	Expected operating days/year	Anticipated Mo-99 production weeks/year	Expected available capacity per week (6-d Ci ^{99}Mo) by 2027	Potential maximum capacity per year (6-day Ci ^{99}Mo) by 2027	Expected first full year of production	Project status (end March 2023)
NorthStar (non-U)	Non-fissile/Electron accelerators	339	52	2 541	132 132	2024	Operating/Preparing FDA submission
SHINE USA (non-U)	LEU in solution	350	50	4 000	200 000	2024	Under construction
Ontario Power Generation (NU)	NMo in PR	365	52	2 722	141 544	2025	Equipment Factory Acceptance Test complete
FRM II (HEU)	LEU in CRR	240	32	2 100	67 200	2026	Irradiation facility under construction
RA-10 (LEU)[1]	LEU in CRR	315	48	+2 000	+96 000	2026	Finish building mid-2023
Niowave (non-U)	NU and LEU/Electron Linac	336	48	1 550	74 400	2026	Pre-licencing phase
SHINE Europe (non-U)	LEU in solution	350	50	4 000	200 000	2027	Pre-licensing phase

Notes: 1). MU Notes: 1). The RA-10 +96 000 6-day Ci ^{99}Mo irradiation capacity by 2027 is additive to the activity shown in Table 1; 2). CRR = Conventional Research Reactor, HEU >20% enriched Uranium, LEU <20% enriched Uranium, NMo = Natural Molybdenum, NU = Natural Uranium, non-U = a non-Uranium fuel, PR = Power Reactor.

Table 4. Potential processors entering in period 2023 to 2027

Processor	Targets[2]	Anticipated Mo-99 production weeks/year	Expected available capacity per week (6-day C ^{99}Moi) by 2027	Potential maximum capacity per year (6-day Ci ^{99}Mo) by 2027	Estimated first full year of production	Project status (end March 2023)
NorthStar	Non-fissile	52	2 541	132 132	2024	In production scale up
SHINE USA	LEU in solution	50	4 000	200 000	2024	Under construction
BWXT Medical	NMo	52	2 722	141 544	2025	Cold-run commissioning complete
CNEA[1]	LEU	48	+2 000	+96 000	2026	Building start by beginning 2024
Niowave	NU and LEU	48	1 550	74 400	2026	Pre-licencing phase
SHINE Europe	LEU in solution	50	4 000	200 000	2027	Pre-licensing phase

Notes: 1). MURR Notes: 1). The CNEA +96 000 6-day Ci ^{99}Mo irradiation capacity by 2027 is additive to the activity shown in Table 2; 2). LEU <20% enriched Uranium, NMo = Natural Molybdenum, NU =Natural Uranium

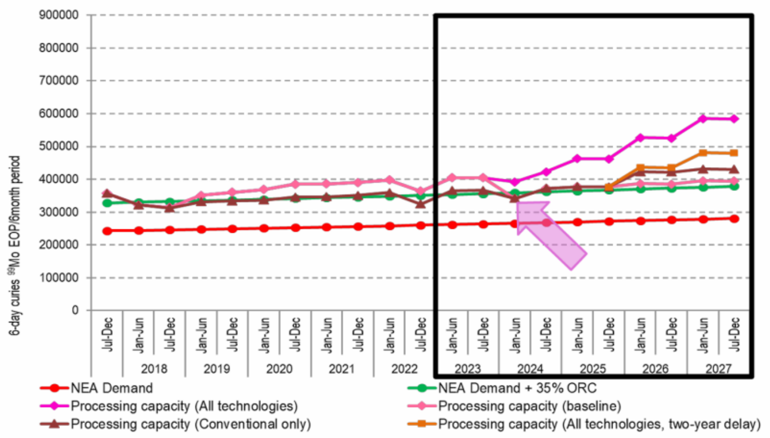
OECD Reports: Demand and supply of Mo-99

OECD-NEA: https://www.oecd-nea.org/jcms/pl_87477/the-security-of-supply-of-medical-radioisotopes-demand-and-capacity-projections-for-99mo/99mtc-for-the-2023-2027-period?details=true

2023 NEA Report: Recent Development - NorthStar Closure

- On 5 October 2023, NorthStar Medical Radioisotopes, LLC announced that it would "suspend manufacturing and commercialization of molybdenum-99"
  - o Reduces capacity available in large US market
  - o Increases risks for security of global supply when unplanned events occur
  - o Removes projected additional capacity from all Scenarios
- NorthStar indicates that economics are an underlying problem

Scenario C+: "2-year delay to projected capacity additions and no NorthStar" – Total and conventional processing capacity



2023 NEA Report: Conclusions Adapted to New Developments

- NorthStar development indicates that economics are underlying problem as Full Cost Recovery (FCR) remains elusive
- Delays and losses in both conventional and alternative technology projects are thus of serious concern
- With ORC even lower, co-ordination even more essential
- "Reference" scenario A has no longer improved since 2019 report
- Capacity to manage adverse events very limited in 2023-25 and further project delays would increase vulnerability

Mo-99: New producers

NorthStar USA

NorthStar to end production of Mo-99

NorthStar Medical Radioisotopes will shut down its molybdenum-99 (Mo-99) production facilities in Beloit, WI, by the end of 2023.

By — Will Morton

Oct 9th, 2023

IBA Rhodotron® TT300-HE
40 MeV Electron accelerator installed at Beloit, Wisconsin facility of NorthStar

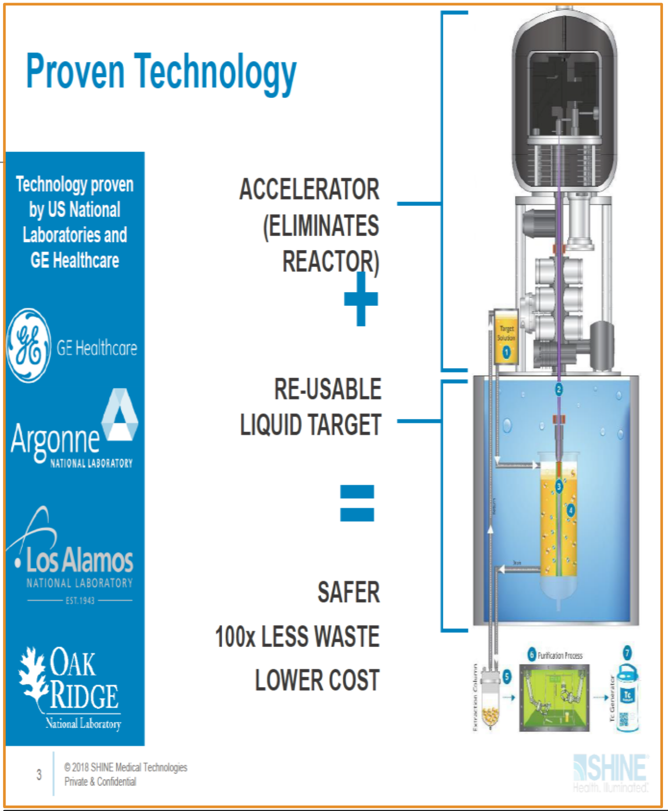
NorthStar Medical Radioisotopes' facility in Beloit, Wisconsin, has been built with financial and technical support from the US Department of Energy's National Nuclear Security Administration (NNSA). It will produce molybdenum-99 (Mo-99) without using highly enriched uranium.

NorthStar produces first Mo-99 batch at new facility

By AuntMinnie.com staff writers

January 11, 2023 -- NorthStar Medical Isotopes has produced the first batch

Shine Medical Technologies, USA



SHINE's final SER for Wisconsin facility issued by NRC

Wed, Mar 1, 2023, 3:00PM | Nuclear News

Mo-99: New Producers

Nuclear Power Plants, Canada

Darlington ready to produce medical radioisotope

02 February 2023

Ontario Power Generation (OPG), its subsidiary Laurentis Energy Partners (Laurentis), BWXT ITG Canada Inc. and its affiliates (BWXT) are making significant progress toward the production of molybdenum-99 (Mo-99) at OPG's Darlington Nuclear Generating Station

BWXT Canada Ltd. Isotopes Nuclear Energy Canada Press Release

Canadian nuclear power station on track to begin Mo-99 production

February 07, 2023
by John R. Fischer, Senior Reporter

Ontario Power Generation's Darlington Nuclear Generating Station in Canada is now capable of producing Molybdenum-99 (Mo-99) isotopes, bringing it one step closer to producing a stable domestic supply for North American healthcare providers.

AuntMinnie.com

BWXT Medical seeks FDA approval for Tc-99m generator
By AuntMinnie.com staff writers

September 14, 2022 -- BWXT Medical has submitted a new drug application to the U.S. Food and

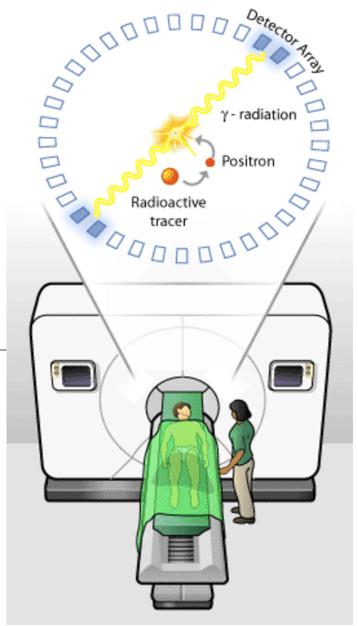
IMV: PET scan volumes continue to grow

The total volume of PET scans increased 10.2% year over year in 2023, according to the newly published IMV 2024 PET Market Summary Report.

By — Davin Korstjens

Mar 7th, 2024

DIAGNOSTIC- PET



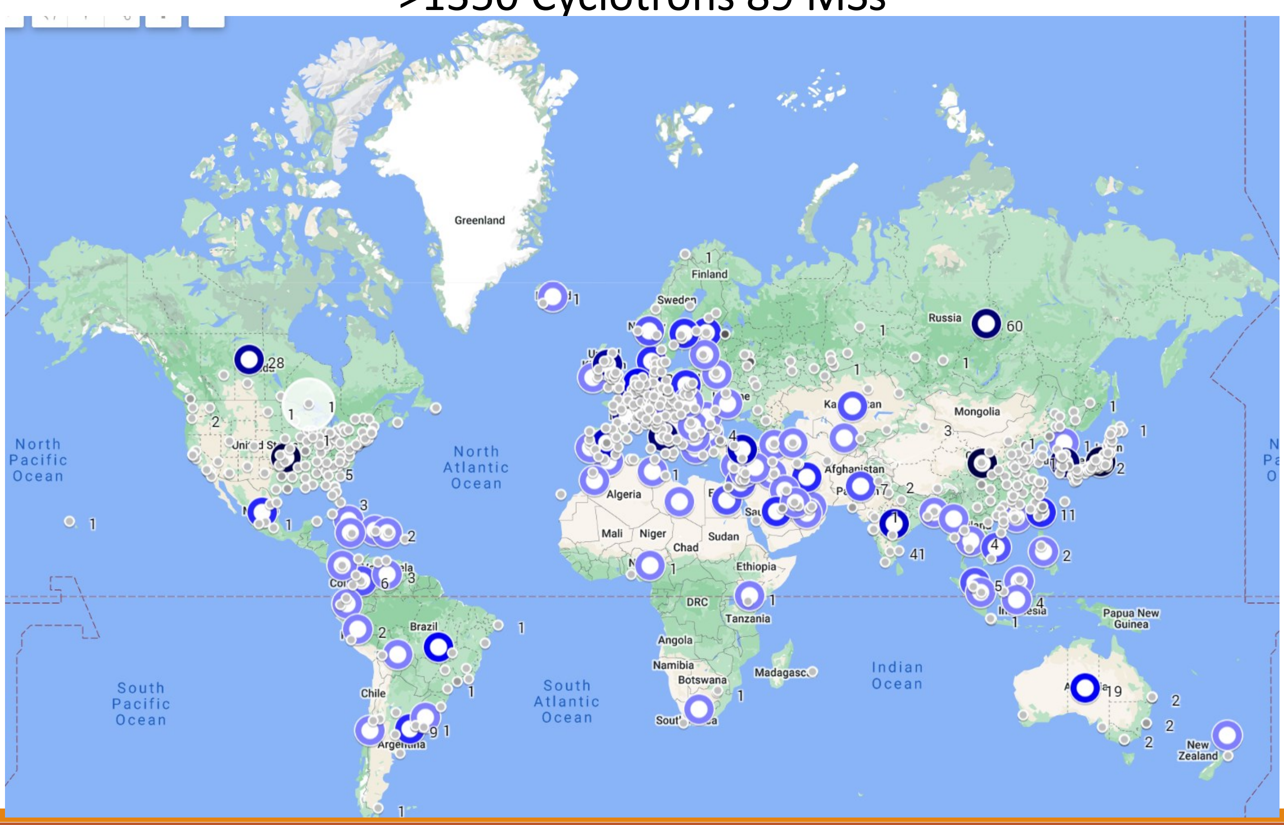
Isotope	^{11}C	^{13}N	^{15}O	^{18}F
Half-life	20 min	10 min	2 min	110 min
Production	$^{14}N(p,\alpha)^{11}C$	$^{16}O(p,\alpha)^{13}N$	$^{15}N(p,n)^{15}O$	$^{18}O(p,n)^{18}F$ enriched

Isotope	^{64}Cu	^{68}Ga	^{82}Rb	^{89}Zr
Half-life	12.7 h	68 min	1.25 min	78.4 h
Production	$^{64}Ni(p,n)^{64}Cu$ enriched	Generator (^{68}Ge-^{68}Ga) $^{nat}Ga(p,xn)^{68}Ge$ High energy Cyclotron	Generator (^{82}Sr-^{82}Rb) $^{85}Rb(p,4n)^{82}Sr$ High energy Cyclotron	$^{89}Y(p,n)^{89}Zr$

For radiopharmaceutical usage in 2023, the report found the following:

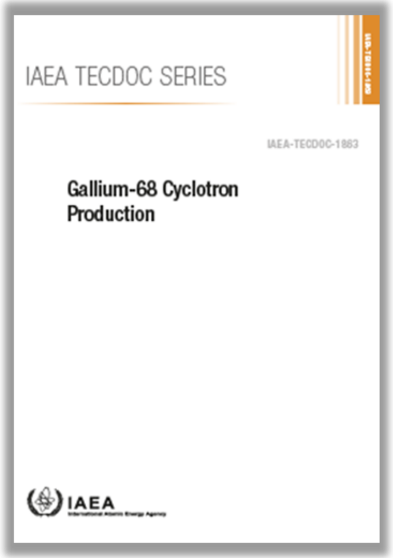
- 74% of PET scans use F-18 FDG-PET (F-18 fluoro-2-deoxy-D-glucose),
- 9% use Pylarify (F-18 DCFPyL),
- 6% use rubidium-82 (Rb-82),
- 3% use gallium-68 (Ga-68) prostate-specific membrane antigen (PSMA)-11,
- 3% use Ga-68 DOTATATE,
- 2% use copper-64 (Cu-64),
- 1% use F-18 sodium fluoride (NaF),
- 1% use Amyvid (florbetapir), and
- 1% use Axumin (fluciclovine F-18).

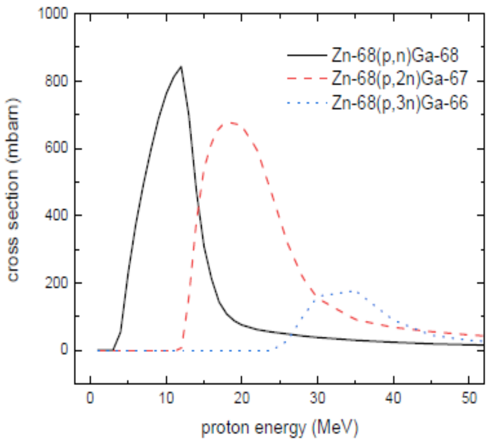
IAEA
https://nucleus.iaea.org/sites/accelerators/Pages/Cyclotron.aspx
>1350 Cyclotrons 89 MSs

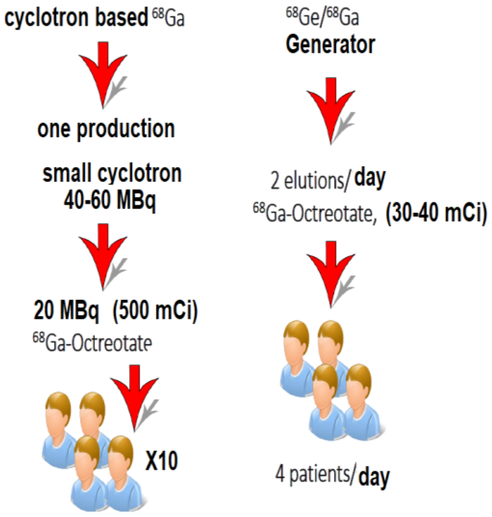


Ga-68

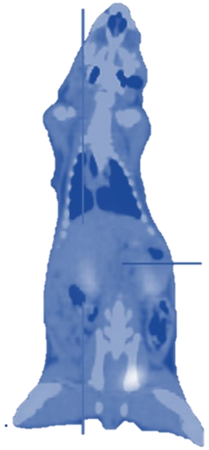
- Two production routes:
  - Direct: $^{68}Zn(p,n)^{68}Ga$
  - Indirect: Generator ^{68}Ge-^{68}Ga
    - $^{69}Ga(p,2n)^{68}Ge$





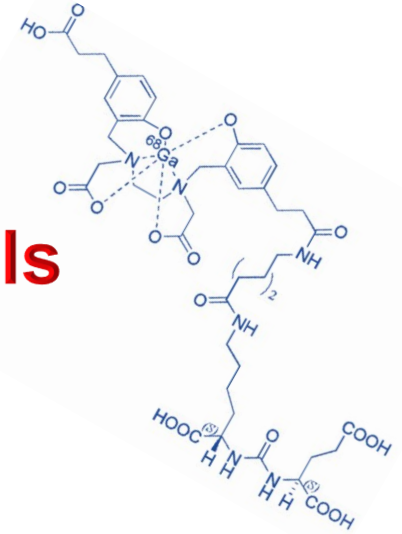


Source: Curium Oct 2023



Please join the IAEA webinar on:

Production and Quality Control of Cyclotron Based Ga-68 Radiopharmaceuticals



Wednesday, 29th May 2024

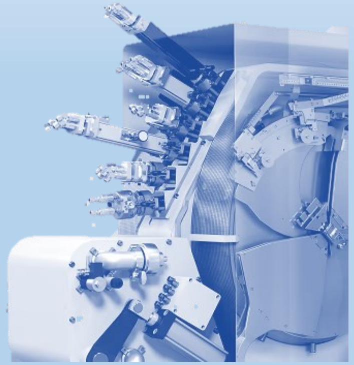
14:00 –16:00 CET

Opening

Ms. Melissa Denecke, Director, Division of Physical and Chemical Sciences, IAEA
Ms. Celina Horak, Section Head, RCRT, IAEA
Mr. Amir Jalilian, Scientific Secretary, RCRT, IAEA

Speakers

Mr. David Dick, USA
Mr. Miguel Avila-Rodriguez, Mexico
Mr. Robin Ippisch, USA
Ms. Brigitte Guérin, Canada
Ms. Katie Gagnon, Sweden
Ms. Cristiana Gameiro, Belgium
Mr. Antero Abrunhosa, Portugal
Ms. Ellen Pel, Strasbourg, France



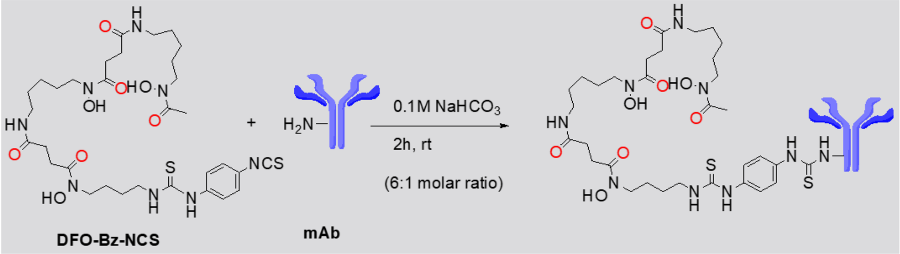
Please register freely at:
https://iaea.webex.com/weblink/register/r6e7526606c81b68d2a8886b87513fcab

Zirconium-89 $^{89}Y(p,n)^{89}Zr$

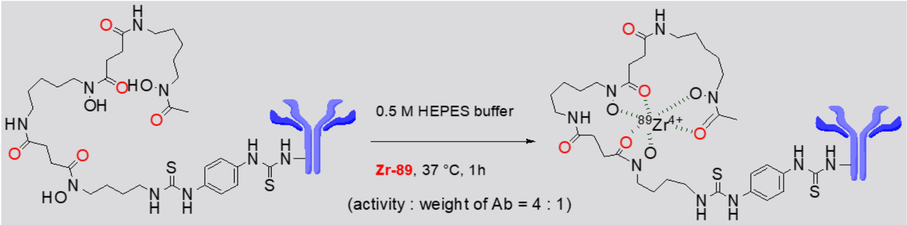
Half-life of 3.27 d – well suited for study of pharmacokinetics of antibodies (achieve optimal biodistribution ~4-5 d)

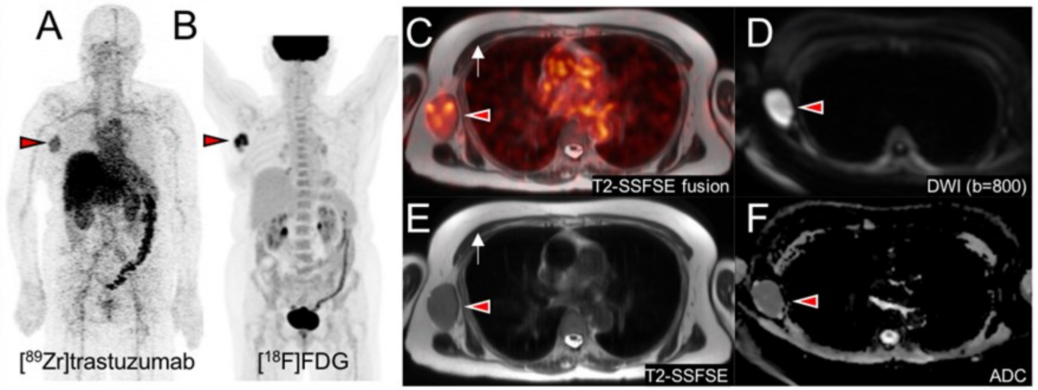
^{89}Zr: Conjugation and Labeling

(a) mAb conjugation to DFO-Bz-NCS



(b) Radiolabeling of DFO-Bz-NCS-Trastuzumab





[^{89}Zr]trastuzumab-PET/MRI
Breast cancer therapy response

First patient dosed with TLX250-CDx for ccRCC in Australia

April 29, 2024
Hannah Clarke

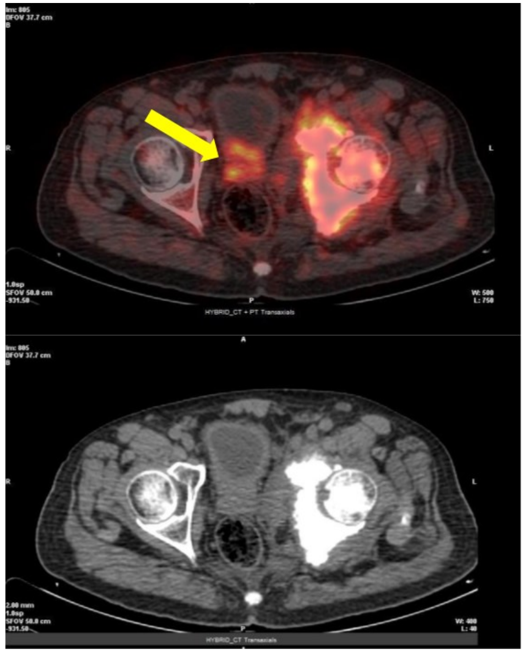
News Article

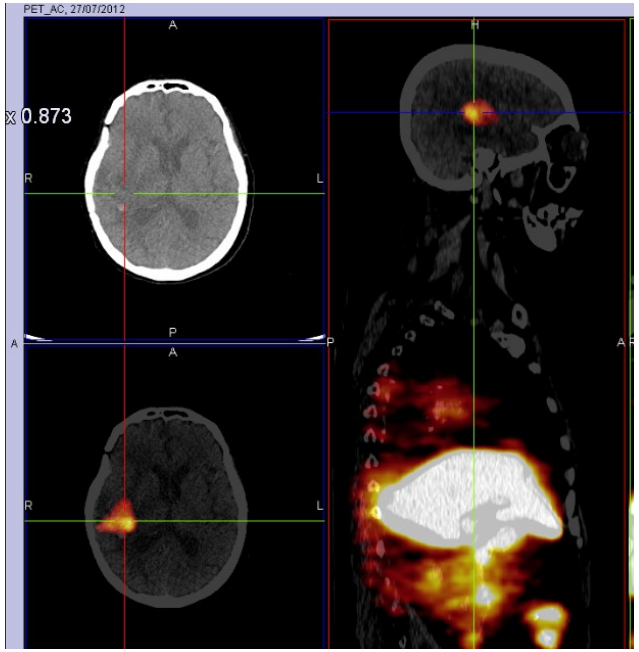
The first patient was treated with TLX250-CDx at the Olivia Newton-John Cancer Wellness Centre at Austin Health in Melbourne, Australia,

The first patient has been dosed in a Special Access Scheme (SAS) in Australia for TLX250-CDx (89Zr-DFO-girentuximab, Zircaix), PET/CT imaging in patients with clear cell renal cell carcinoma (ccRCC), according to a news release from Telix, the developer of the agent.[1]

Cu-64: $^{64}Ni(p,n)^{64}Cu$

- Potential use in diagnostic and therapy
- β^- , β^+ e CE emitter
- Radiopharmaceutical: ionic $CuCl_2$





Studies launch of copper Cu 64 PSMA I&T PET/CT in prostate cancer

April 24, 2024

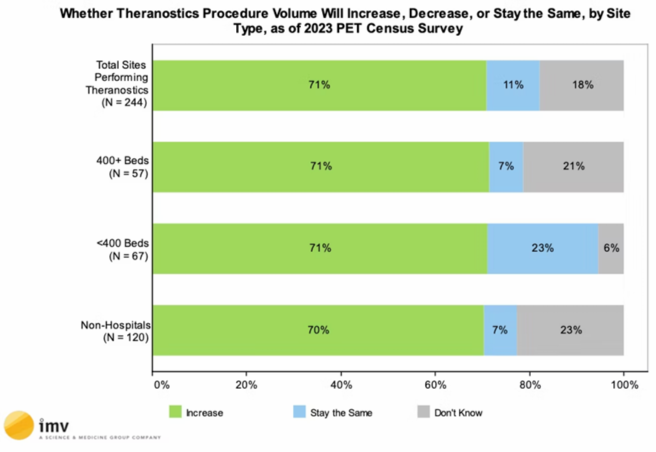
Hannah Clarke

News Article

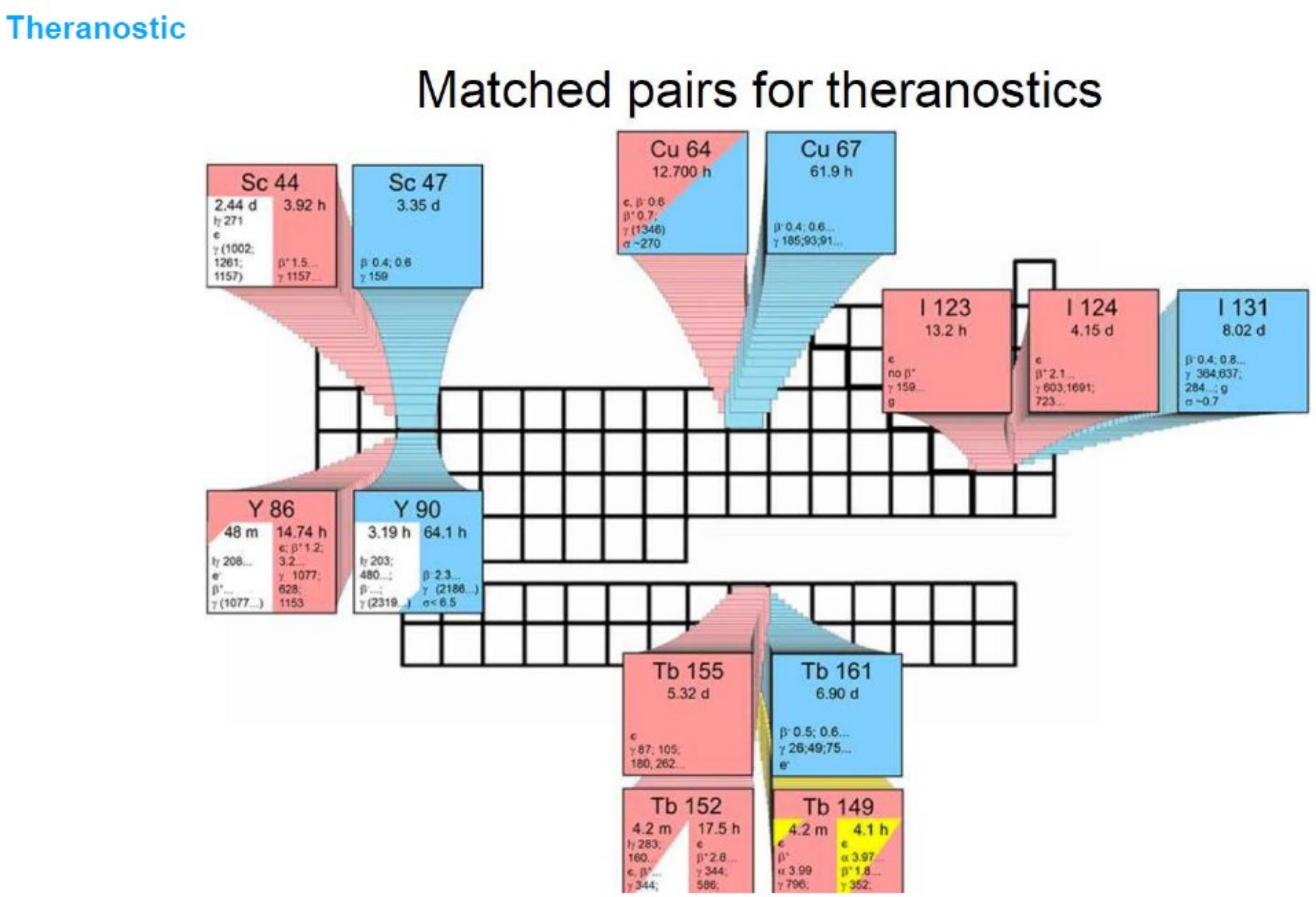
Both the SOLAR-STAGE and SOLAR-RECUR trials are currently enrolling patients with prostate cancer in the US, with additional sites expected to open in Europe later this year.

IAEA contribution to the development of 64Cu radiopharmaceuticals for theranostic applications
Amir R. JALILIAN, et al. The Quarterly Journal of Nuclear Medicine and Molecular Imaging 2020 December;64(4):338-45. DOI: 10.23736/S1824-4785.20.03302-6

Theranostic



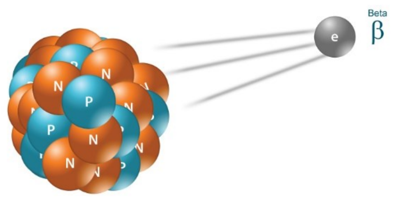
(Source: 2024 IMV PET Market Summary Report)



Ga-68 PSMA: Diagnosis
Lu-177 PSMA: Therapy beta
Ac-225 PSMA: Therapy alfa

Radiopharm Theranostics has Terbium-161 radiotherapeutics validated by pilot study in prostate cancer

Last updated: 01:35 28 Feb 2024 GMT, First published: 01:27 28 Feb 2024 GMT

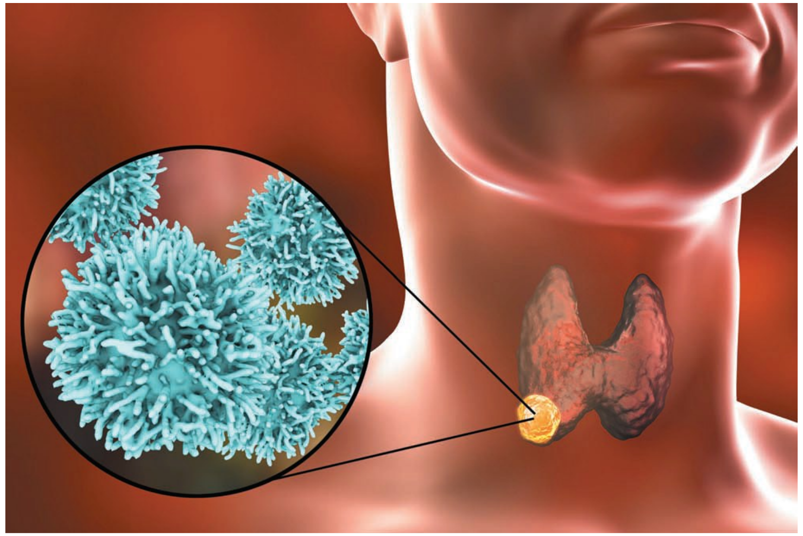


THERAPY- β^-

Isotope	^{32}P	^{90}Y	^{153}Sm	^{131}I	^{177}Lu
Half-life	14.3 d	2.7 d	46.3 h	8 d	6.7 d
Production	$^{32}S(n,p)^{32}P$	Generator (^{90}Sr-^{90}Y) $^{89}Y(n,\gamma)^{90}Y$ Fission product	$^{152}Sm(n,\gamma)^{153}Sm$ enriched	$^{130}Te(n,\gamma)^{131}Te$ $^{131}Te \rightarrow {}^{131}I$ Fission product	$^{176}Lu(n,\gamma)^{177}Lu$ $^{176}Yb(n,\gamma)^{177}Yb$ $^{177}Yb \rightarrow {}^{177}Lu$ enriched

Iodine -131

- Isolated & supplied by Mo-99 producers as a fission product
  - Shortage of supply follow Mo-99
- Produced locally by countries having RR facilities (neutron capture on Te-130)



Diagnostic radioiodine scan (I-131)

$$^{235}U\ (n,f)\ ^{131}I$$

$$^{130}Te(n,\gamma)\ ^{131}Te \xrightarrow{\beta^-} {}^{131}I$$

- 1st patient treated March 1941(mixture of I-130 and I-131 produced by cyclotron)
- No other radionuclide achieved (yet...) same success and acceptance that « RAI » had for treatment of thyroid diseases
- Best example of Theranostics !
- Not substituable in its current indication in most of the case

Suppliers

- NTP
- IRE
- Polatom
- MURR
- Others

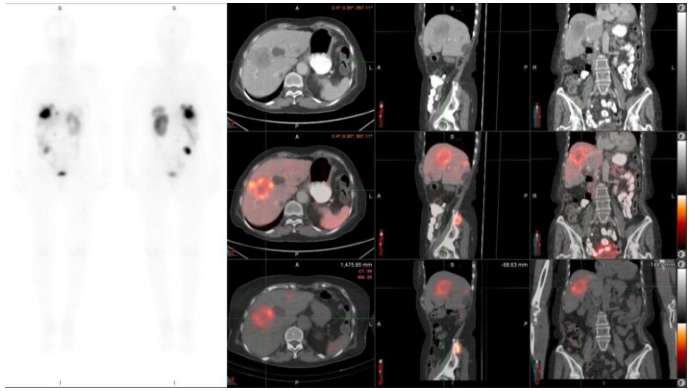
- 2 Mo-99 producers do not extract I-131
- The very low selling price is not worth the complexity and risk of the extraction process
- If total or even part of this volume would be extracted, global demand would be likely covered for the next decade

Lu-177

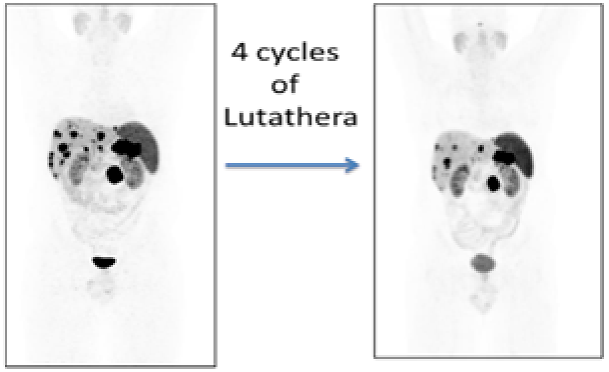
Currently the highest potential therapeutic radionuclide: ^{177}Lu-DOTATATE, ^{177}Lu-PSMA

Production: Two routes

- ^{176}Lu(n, γ) ^{177}Lu : ^{176}Lu can be natural or enriched (Limitation of specific activity)
- ^{176}Yb(n, γ) ^{177}Yb$\rightarrow$^{177}Lu (High specific activity no carrier added)
- Use of Research Reactors, Nuclear Power Plants and fission induced by accelerators
- Issues: availability and price of enriched target materials



Local production & distribution as well as commercial manufacturers supply pharmaceutical grade $^{177}LuCl_3$ suitable API for radiopharmaceutical preparation as well as radiopharmaceuticals



Current Lu-177 Production

Producer	Processing	Reactor(s)	nca/carrier
Eckert & Ziegler	Germany	BR-2 HFR	Yes/No
Isotopia	Israel Canada (AtomVie/CPDC)	BR-2 HFR	Yes/Yes
ITM-ITG (EndolucinBeta®)	Germany Australia - ANSTO	BR-2 OPAL HFR SAFARI FRM-2 ILL (FR)	Yes/No
Isogen/ITM-ITG	Germany	Bruce NPP (Canada)	Yes/No
JSC Isotope	Russia	RIAR, other (Russia)	Yes/Yes
McMasters University	Canada	McMasters RR	No/Yes
Monrol (LuMagic®)	Turkey	BR-2 HFR	Yes/Yes
MURR	USA	MURR	Yes/Yes
Novartis - AAA/IDB	Netherlands Indiana USA (2023?)	HFR INM? (RU)	Yes/Yes
POLATOM (LutaPol)	Poland	Maria	No/Yes
SHINE (IOCB Prague license)	USA	MURR	Yes/No

Additional small-scale production a BRIT (India), PARS (Iran), CMR (Russia), Perkin-Elmer (U.S.) and other locations

Lu-177 Production Projects

Planned Producer	Partner	Location	Announced
BWXT	Isogen	Canada	7/20/2020
Curium	Monrol (licensee)	Netherlands	1/28/2022
Eckert & Ziegler ($10M)	Point (supply)	Massachusetts, USA	9/25/2023
IRE/SCK		Belgium Fleurus, Mol/BR-2	2/13/2020 3/4/2022
Isotopia	Seibersdorf Labor	Austria	10/8/2021
Global Morpho Pharma (Framatome minority)	?	?	7/29/2022
Monrol (E35M expansion/new)		Turkey (Gebze)	9/11/2023
Point Biopharma (2023) (Lilly acquisition 10/3/2023)	IRE/SCK (licensee)	Indiana, USA	11/24/2021
SHINE (new facility end 2023)	IOCB Prague	Wisconsin, USA	6/22/2023

Source: Lantheus Oct 2023

3/9/23, 1:58 PM Pluvicto Supply Shortage Update: What SNMMI Is Doing - SNMMI

Pluvicto Supply Shortage Update: What SNMMI Is Doing

Curium confirms no supply challenges for Eclipse trial

By AuntMinnie.com staff writers

March 16, 2023 -- Nuclear medicine company Curium confirmed in a recent statement that it doesn't expect supply challenges of its lutetium-177 (Lu-177) prostate-specific membrane antigen (PSMA) with 3-iodo-D-tyrosine (I&T) for the company's Eclipse phase III clinical trial.

Shortage of Last-Ditch Drug for Advanced Prostate Cancer Worries Doctors

Novartis seeks to ramp up Pluvicto production to ease supply issues

Novartis said it is prioritizing the Pluvicto supply for patients who have already started the regimen.
PHOTO: ARND WIEGMANN/REUTERS

By Jennifer Calfas Follow *and Melanie Evans* Follow
March 16, 2023 5:30 am ET

Novartis struggles to meet Lu-177 demand

By AuntMinnie.com staff writers

March 15, 2023 -- Novartis said it is experiencing supply (
177) prostate-specific membrane antigen (PSMA)-617 rad
cancer patients.

Lu-177

FDA approves Lu-177 PSMA-617 for prostate cancer treatment
By Will Morton, AuntMinnie.com staff writer

March 24, 2022 -- The U.S. Food and Drug Administration (FDA) has approved lu
177) prostate-specific membrane antigen radioligand therapy (Pluvicto, Novartis)

Novartis receives approval for Pluvicto
By AuntMinnie.com staff writers

December 13, 2022 -- Novartis has secured approval from the European Commission for its Pluvicto lutetium-177 (Lu-177) prostate-specific membrane antigen (PSMA) radioligand therapy.

CLINICAL NEWS | MOLECULAR IMAGING | NUCLEAR MEDICINE

FDA approves Lutathera for some pediatric patients

The FDA has approved a new indication for Novartis' Lutathera.

By — AuntMinnie.com staff writers

May 1st, 2024

Bruce 7 starts producing innovative therapeutic isotope

26 October 2022

Share

The commercial production of lutetium-177 (Lu-177) has begun using a new isotope production system (IPS) that was installed in unit 7 of the Bruce plant in Ontario, Canada, during a planned maintenance outage earlier this year.

ITM begins Lu-177 production
By AuntMinnie.com staff writers

October 24, 2022 -- ITM Isotope Technologies Munich
therapeutic radioisotope lutetium-177 (Lu-177) in colla

ITM, Alpha-9 enter supply agreement for Lu-177

ITM and Alpha-9 Oncology are entering a supply agreement to support the latter's radiopharmaceutical therapy pipeline development.

By — AuntMinnie.com staff writers

Jan 30th, 2024

Framatome, KHNP to cooperate on medical isotope production

18 April 2024

Share

Framatome and Korea Hydro & Nuclear Power (KHNP) are to assess the feasibility of producing medical isotope lutetium-177 in the Candu pressurised heavy water reactors at the Wolsong nuclear power plant in South Korea.

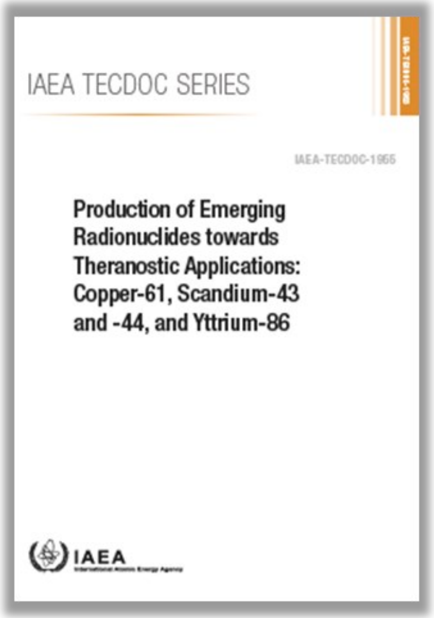
Shine reaches supply agreement with Nucleus RadioPharma

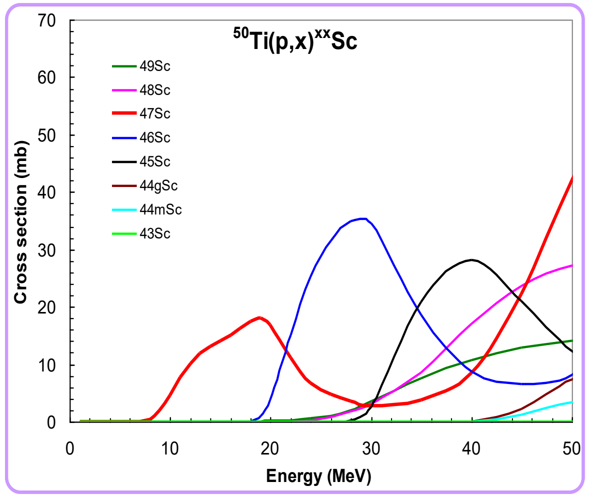
Shine Technologies has reached a long-term supply agreement with Nucleus RadioPharma for lutetium-177.

By — AuntMinnie.com staff writers

Nov 17th, 2023

^{67}Cu, ^{186}Re, ^{47}Sc





	Half-life	Emissions Image	Emissions therapy	Production methods	Decay product
^{47}Sc	3.3492 d	γ 159.38 keV (68.3 % 4)	β^- (100 %) $E_{\beta max}$ = 440.9 keV (68.4 % 6) $E_{\beta max}$ = 600.3 keV (31.6 % 6) $E_{\beta mean}$ = 162.0 keV	^{48}Ti(p,2p) ^{49}Ti(p,^{3}He) ^{50}Ti(p,α) ^{47}Ti(n,p)	^{47}Ti (stable)
^{67}Cu	61.83 h	γ 93.31 keV (16.1 % 2) γ 184.58 keV (48.7 % 3)	β^- (100 %) $E_{\beta max}$ = 377.1 keV (57 % 6) $E_{\beta max}$ = 468.4 keV (22.0 % 22) $E_{\beta max}$ = 561.7 keV (20.0 % 20) $E_{\beta mean}$ = 141 keV	^{68}Zn(p,2p) ^{70}Zn(p,α) ^{67}Zn(n,p) ^{68}Zn(γ,p) ^{68}Zn(n,x)	^{67}Zn (stable)
^{186}Re	3.7183 d	γ 137.16 keV (9.47 % 3)	β^- (92.53 % 10) $E_{\beta max}$ = 932.3 keV (21.54 % 14) $E_{\beta max}$ = 1 069.5 keV (70.99 % 14)	^{186}W(p,n) ^{186}W(d,2n) ^{192}Os(p,α3n)	^{186}Os (stable) ^{186}W (stable)


Multi-dose treatment with 67Cu-SAR-bisPSMA in mCRPC shows promise

Urology Times

News Article

"This was a very special moment, delivering the news to this patient that his cancer is now undetectable following the treatment with 2 doses of 8 GBq of 67Cu-SAR-bisPSMA," says Luke Nordquist, MD, FACP.

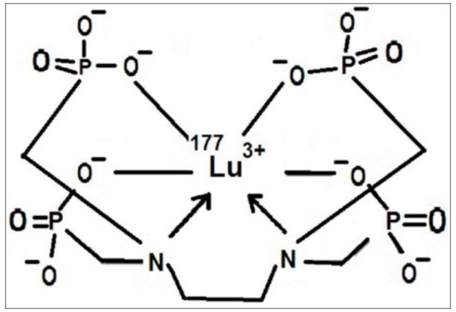
NorthStar MEDICAL RADIOISOTOPES, LLC

First Participant Treated Using NorthStar Medical Radioisotopes' Electron Accelerator-produced Copper-67 (Cu-67) in Clarity Pharmaceuticals' Phase I/IIa Theranostic Clinical Trial Investigating Cu-67 SARTATE for Treatment of Neuroblastoma

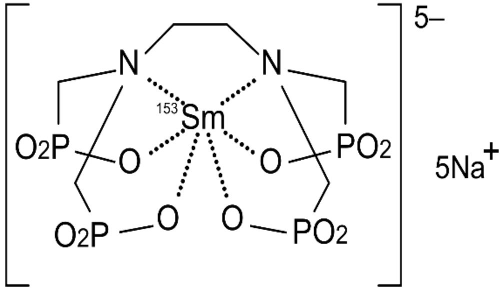
Bone pain palliation

Beta Emiters

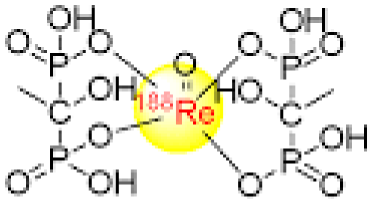
Lu-177 EDTMP



Sm-153 EDTMP



Re-188 HEDP



Alpha Emiters

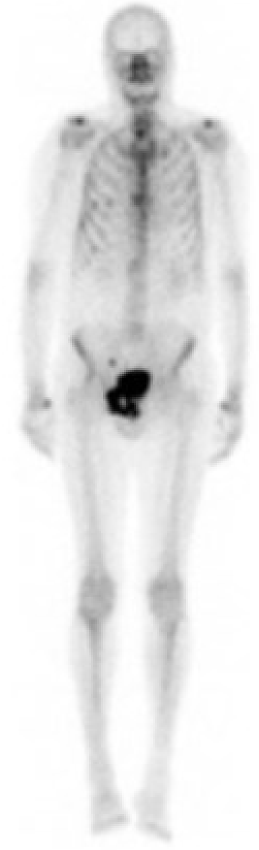
Ra-223 chloride

Ra^{2+}

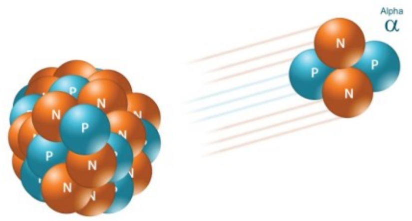
Cl^- Cl^-

Ra-223 Production

- Ac-227 decay (chain)
- Th-227 decay (direct)
- Ra-226(n,γ)Ac-227



Therapy - α



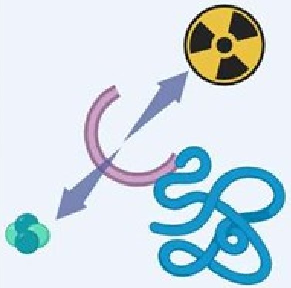
Matched pairs and a stable isotope

- ^{159}Tb — Stable
- ^{149}Tb — 4.1 h, α/PET
- ^{152}Tb — 17.5 h, PET
- ^{155}Tb — 5.23 d, SPECT
- ^{161}Tb — 6.96 d, β-/auger

One alpha emission

- ^{211}At — 7.2 h
- ^{149}Tb — 4.1 h
- ^{212}Pb — 10.6 hr

Stable chemistry



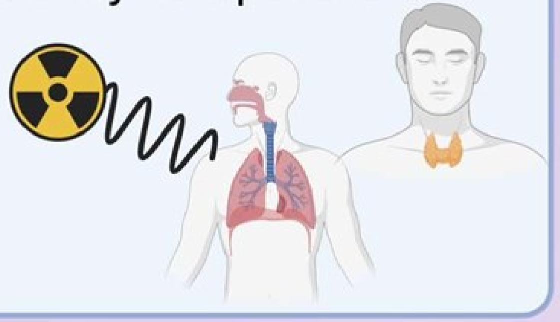
Upscaleable Production

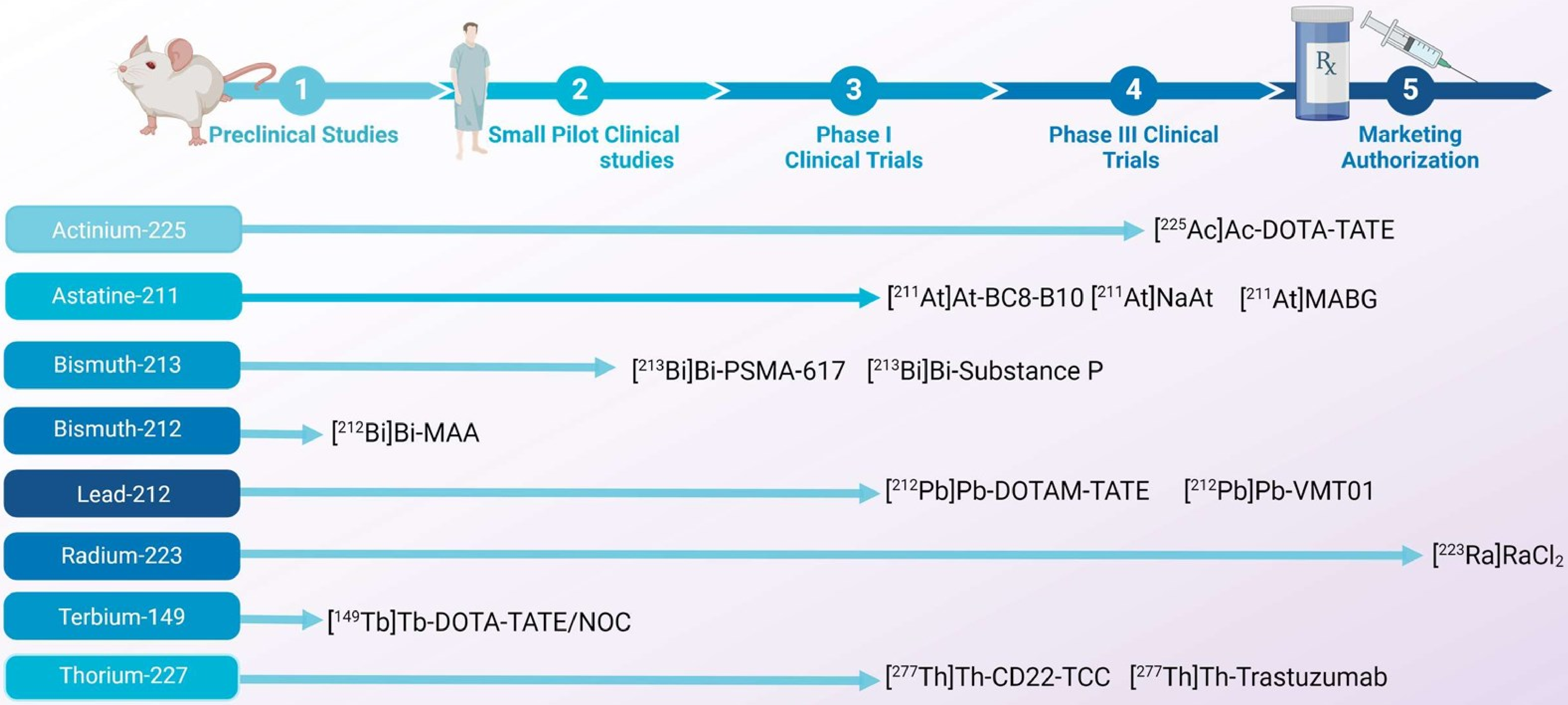
- ^{225}Ac — 10 days
- ^{212}Pb — 10.6 hr

Directly quantifiable

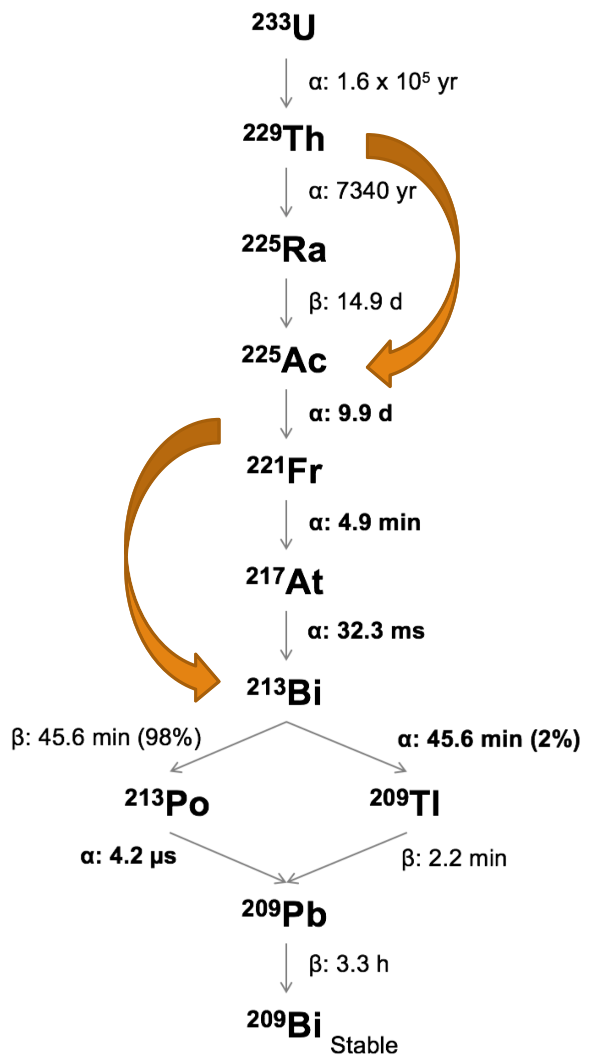
- ^{211}At — 7.2 h
- ^{149}Tb — 4.1 h, α/PET
- ^{212}Pb — 10.6 hr
- ^{213}Bi — 45 min

Safety to operators




1
Preclinical Studies
2
Small Pilot Clinical studies
3
Phase I Clinical Trials
4
Phase III Clinical Trials
5
Marketing Authorization
Rx
Actinium-225
[^{225}Ac]Ac-DOTA-TATE
Astatine-211
[^{211}At]At-BC8-B10
[^{211}At]NaAt
[^{211}At]MABG
Bismuth-213
[^{213}Bi]Bi-PSMA-617
[^{213}Bi]Bi-Substance P
Bismuth-212
[^{212}Bi]Bi-MAA
Lead-212
[^{212}Pb]Pb-DOTAM-TATE
[^{212}Pb]Pb-VMT01
Radium-223
[^{223}Ra]$RaCl_2$
Terbium-149
[^{149}Tb]Tb-DOTA-TATE/NOC
Thorium-227
[^{277}Th]Th-CD22-TCC
[^{277}Th]Th-Trastuzumab

Ac-225



Decay scheme of ^{225}Ac

RESEARCH & APPLICATIONS

PanTera to supply Ac-225 to Bayer

Tue, Feb 13, 2024, 6:00PM | Nuclear News

PanTera, a Belgian joint venture created by Ion Beam Applications (IBA) and SCK CEN, has signed a capacity reservation agreement with pharmaceutical giant Bayer for the supply of actinium-225 starting in the second half of 2024. An alpha-emitting radioisotope with a half-life of 10 days, Ac-225 has shown potential for treating various types of cancer through targeted alpha therapy.

Kleynhans *et al.*
EJNMMI Radiopharmacy and Chemistry (2022) 7:23
https://doi.org/10.1186/s41181-022-00175-y
EJNMMI Radiopharmacy and Chemistry

LETTER TO THE EDITOR Open Access

The determination of the radiochemical purity of Actinium-225 radiopharmaceuticals: a conundrum

Janke Kleynhans[1] and Adriano Duatti[2*]

NorthStar installs accelerator at its new Wisc. facility

By AuntMinnie.com staff writers

March 8, 2023 -- NorthStar Medical Radioisotopes has installed an electron beam a the commercial production of Actinium-225 (Ac-225) at its new facility in Beloit, WI.

TerraPower distributes first shipments of Ac-225

TerraPower Isotopes has shipped its first samples of Actinium-225 (Ac-225) to two pharmaceutical companies to develop targeted cancer treatments in drug trials.

By — AuntMinnie.com staff writers

Jan 24th, 2024

NorthStar and Bayer reach Ac-225 supply deal

By AuntMinnie.com staff writers

July 19, 2023 -- NorthStar Medical Isotopes will supply Bayer with the medical radioisotope actinium-225 (Ac-225).

BWXT to supply Ac-225 generation to Fusion Pharmaceuticals

Mon, Nov 20, 2023, 10:00AM | Nuclear News

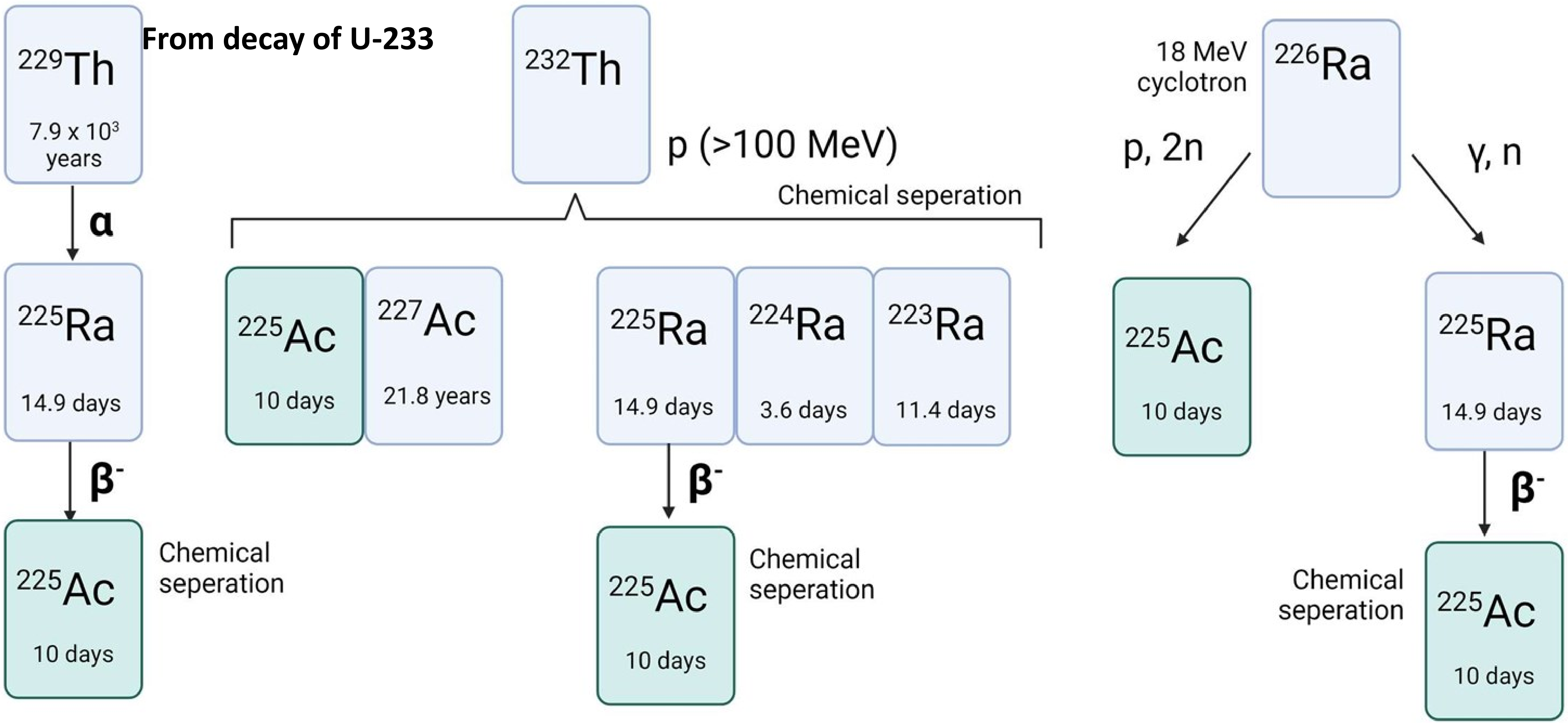
SpectronRx's New Medical Isotope Production Facility Produces Actinium-225

Radiopharmaceutical developer and manufacturer completes construction of new facility, installs two cyclotrons and produces low amounts of Ac-225.

03.09.23
SpectronRx, a radiopharmaceutical contract development and manufacturing organization (rCDMO), announced that initial construction of its Bunker Hill, IN, medical isotope production facility has been completed and two new cyclotrons have been installed.

Actinium-225

Research Reactor: Irradiation of Radium-226 for production of Th-229: **Ra-226 (3n,γ)Ra-229 → Ac-229 → Th-229**



Astatine-211

21 - 40 MeV cyclotron

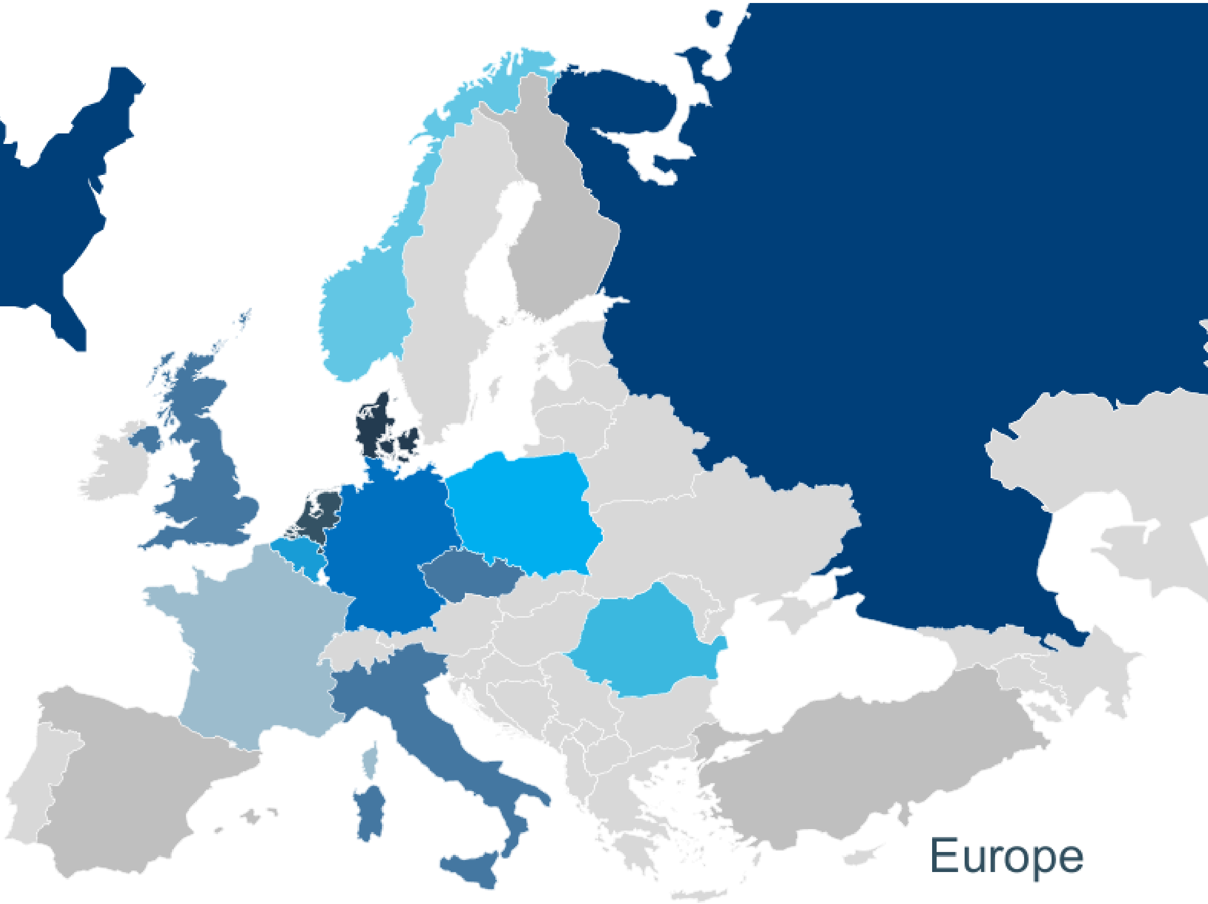
^{209}Bi

α, 2n

^{211}At

8.1 hour

Optimize irradiation conditions to keep $^{210}At/^{211}At$ acceptable

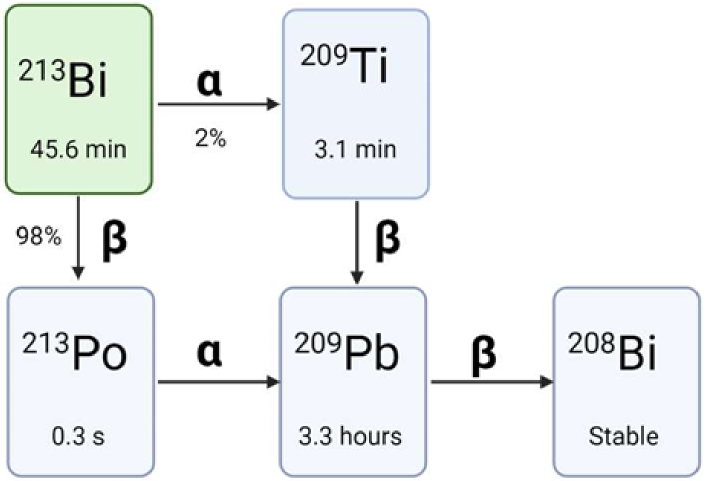


13/37 Cyclotrons identified produce astatine-211 regularly
About 30?

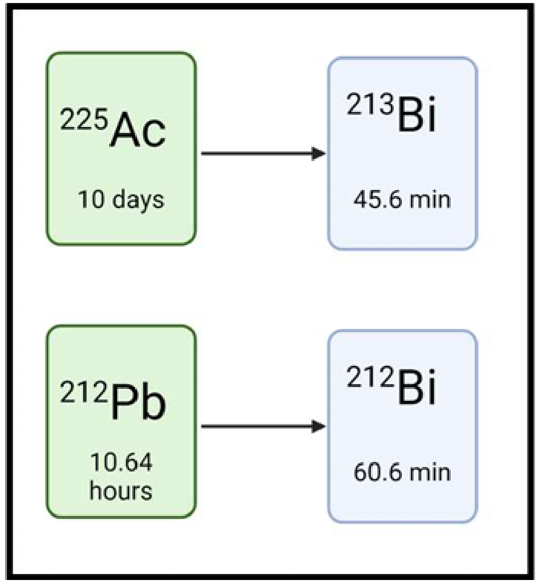
Source: NOAR Oct 2023

Bismuth-213

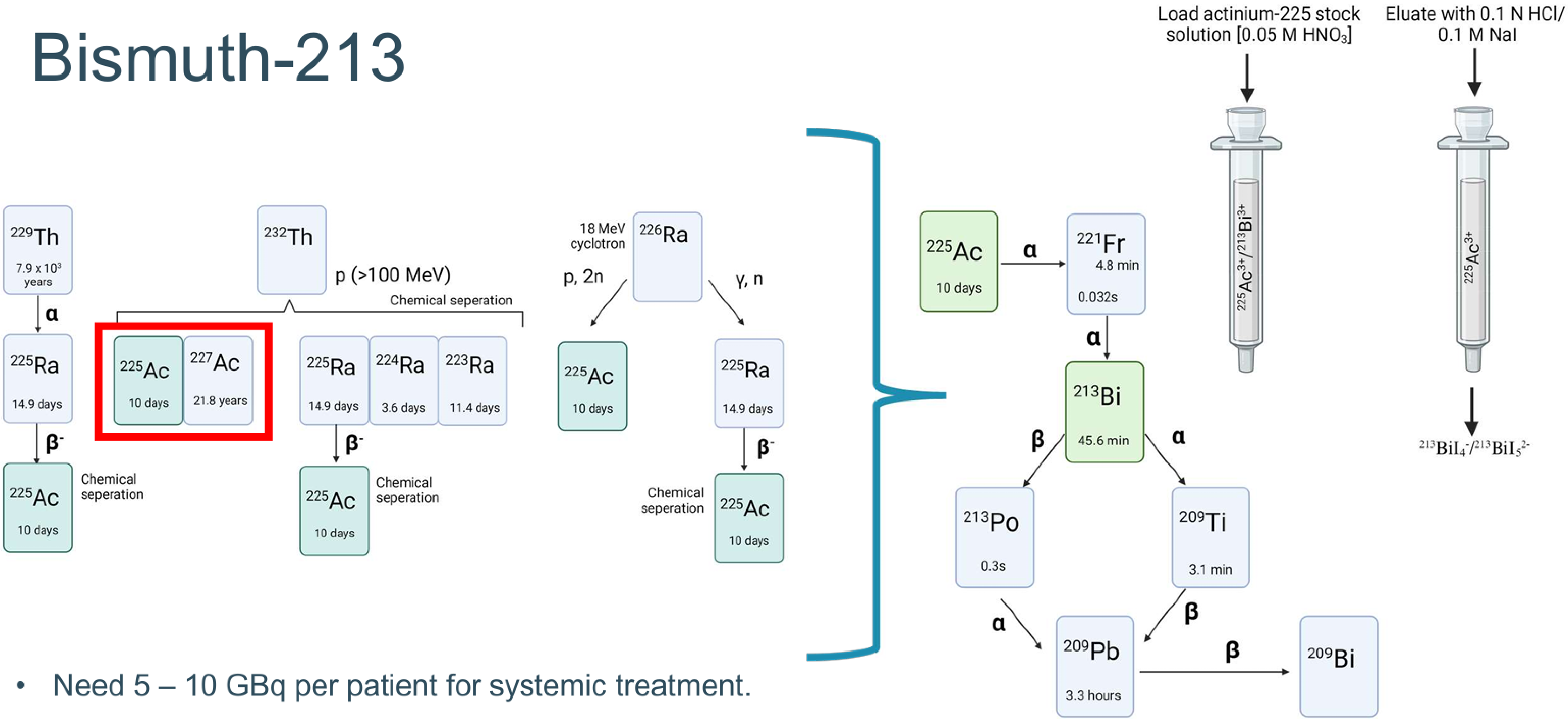
- Short t ½ of 45.6 minutes
- 440 keV-photon
- Bi (III) most prevalent oxidation state.
- Production dependent on the availability of actinium-225



In vivo generators preferred due to centralized production options.



Bismuth-213

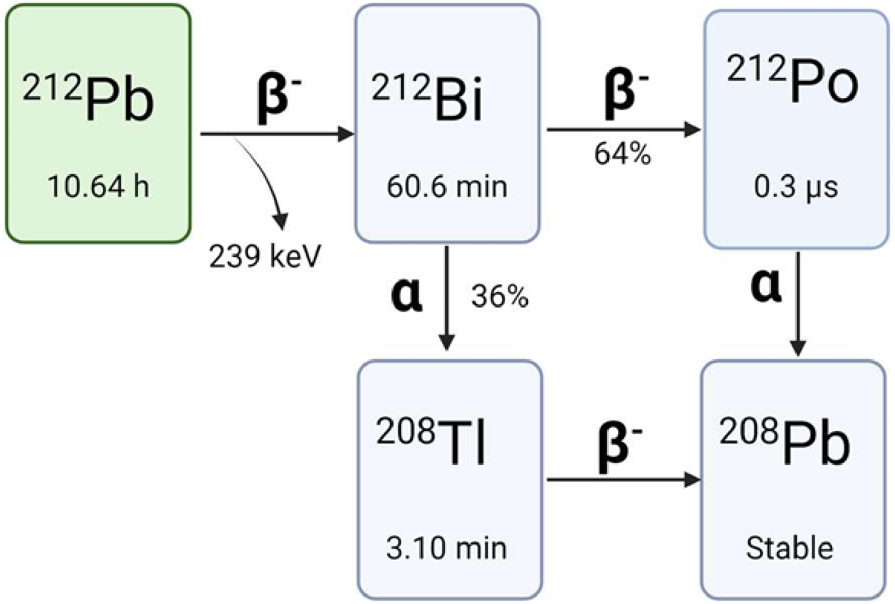


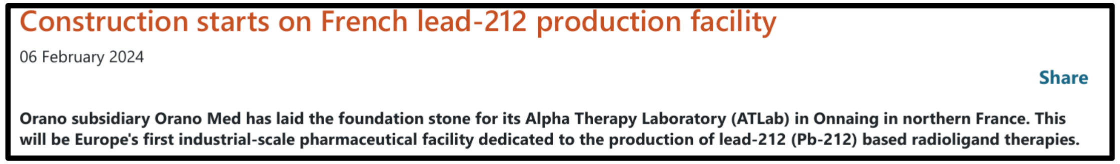
- Need 5 – 10 GBq per patient for systemic treatment.

Actinium-225 generators reported to have up to 80% yields of bismuth-213.

Lead-212

- Has a stable isotope
- Lead-203 theranostic pair for SPECT imaging
- *In vivo* generator for bismuth-212.
- Daughter thallium-208 provide high-energy γ-emission
- More than 15 companies working on offering lead-212 to the market.





Construction starts on French lead-212 production facility

06 February 2024

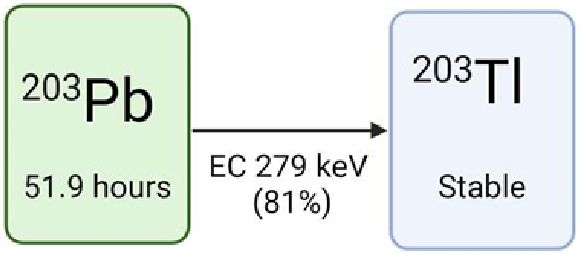
Share

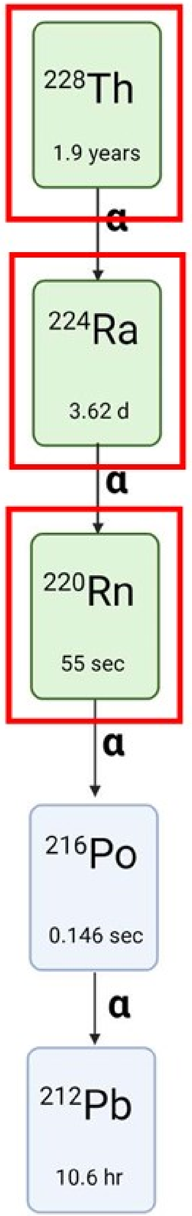
Orano subsidiary Orano Med has laid the foundation stone for its Alpha Therapy Laboratory (ATLab) in Onnaing in northern France. This will be Europe's first industrial-scale pharmaceutical facility dedicated to the production of lead-212 (Pb-212) based radioligand therapies.

Nucleus, Artbio sign manufacturing, supply deal

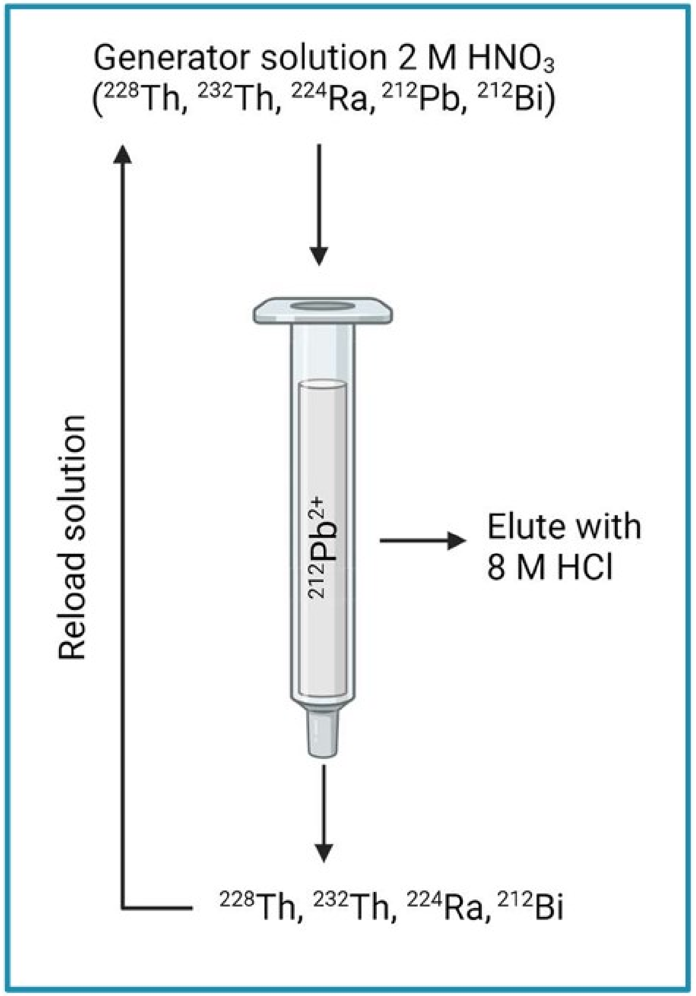
AuntMinnie.com staff writers

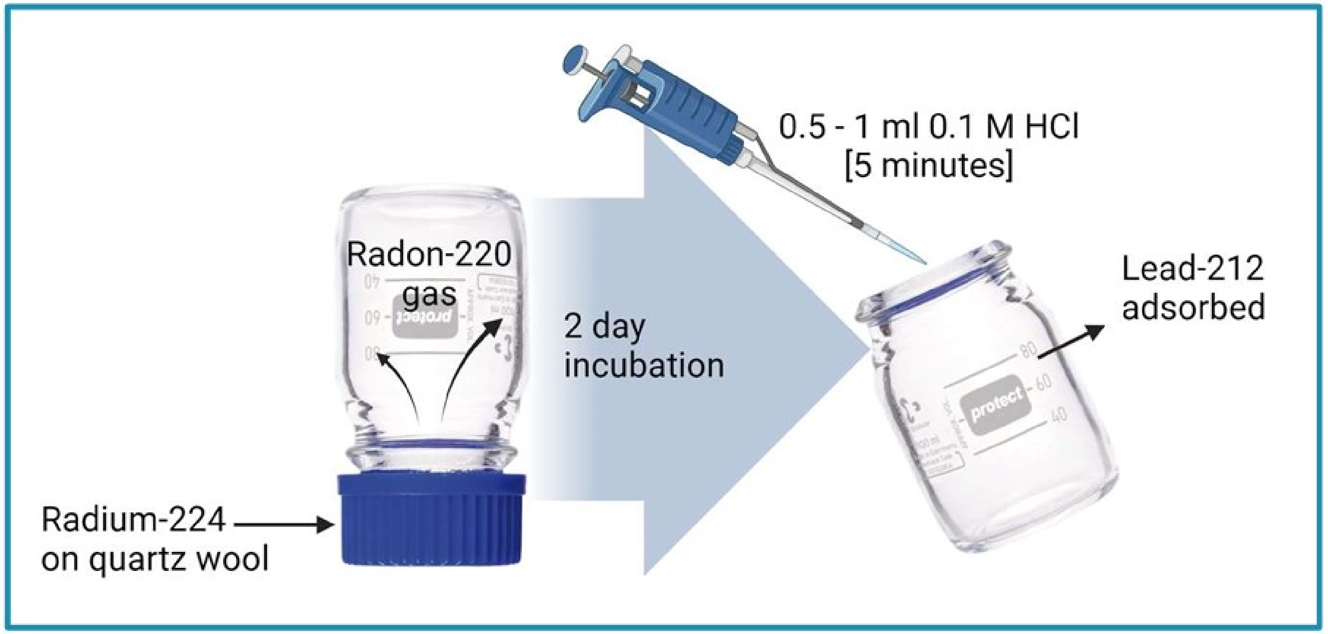
May 7, 2024





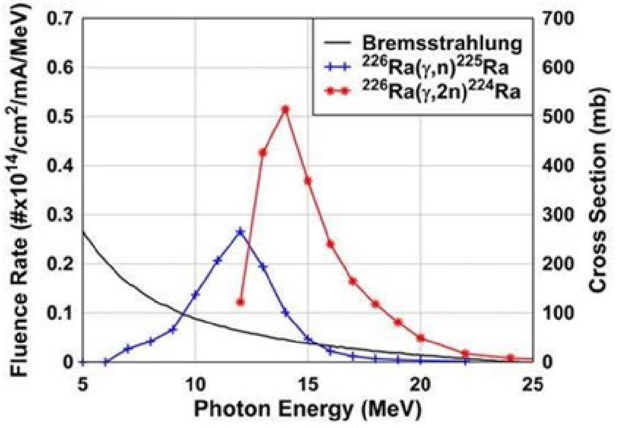
Lead-212





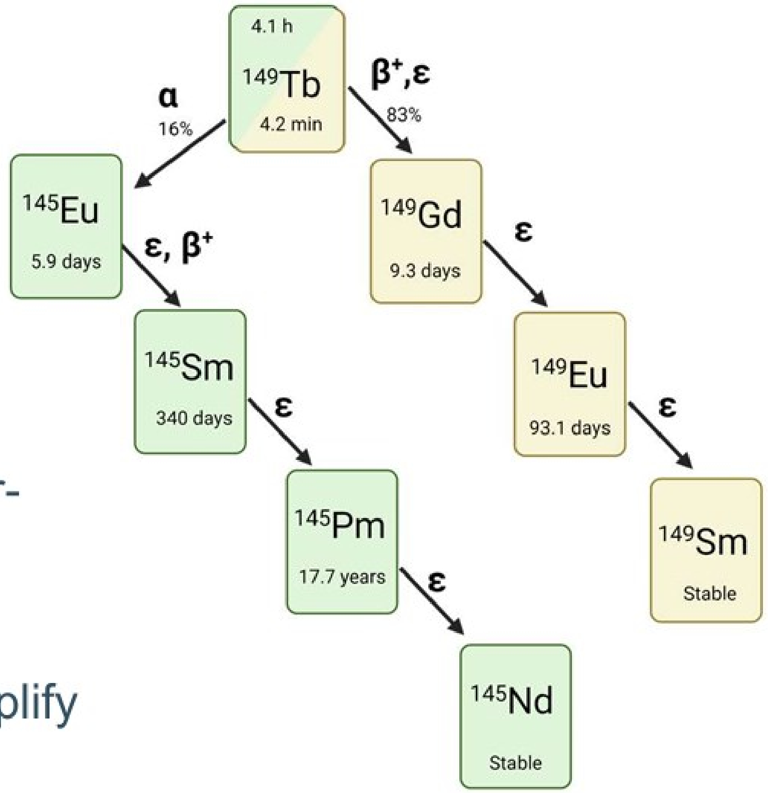
Production through photoconversion

$^{226}Ra(\gamma,2n)^{224}Ra \rightarrow ^{212}Pb$

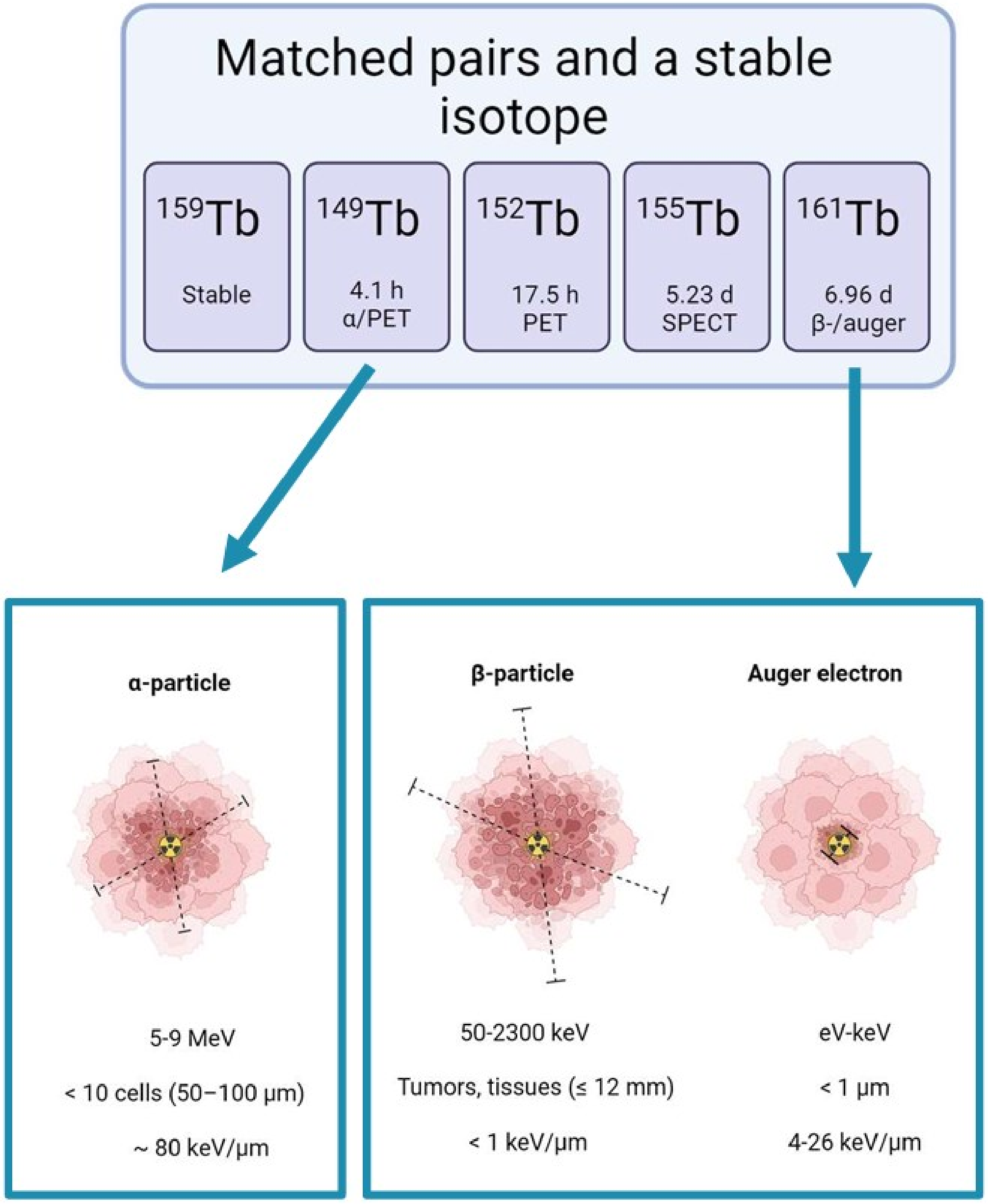


Li et al., 2023. J Nucl Med, 64: 173-176. DOI: 10.2967/jnumed.122.264009.
Diamond & Ross 2021. J Applied Phys, 129: 104901. DOI: 10.1063/5.0043509.

Terbium-149



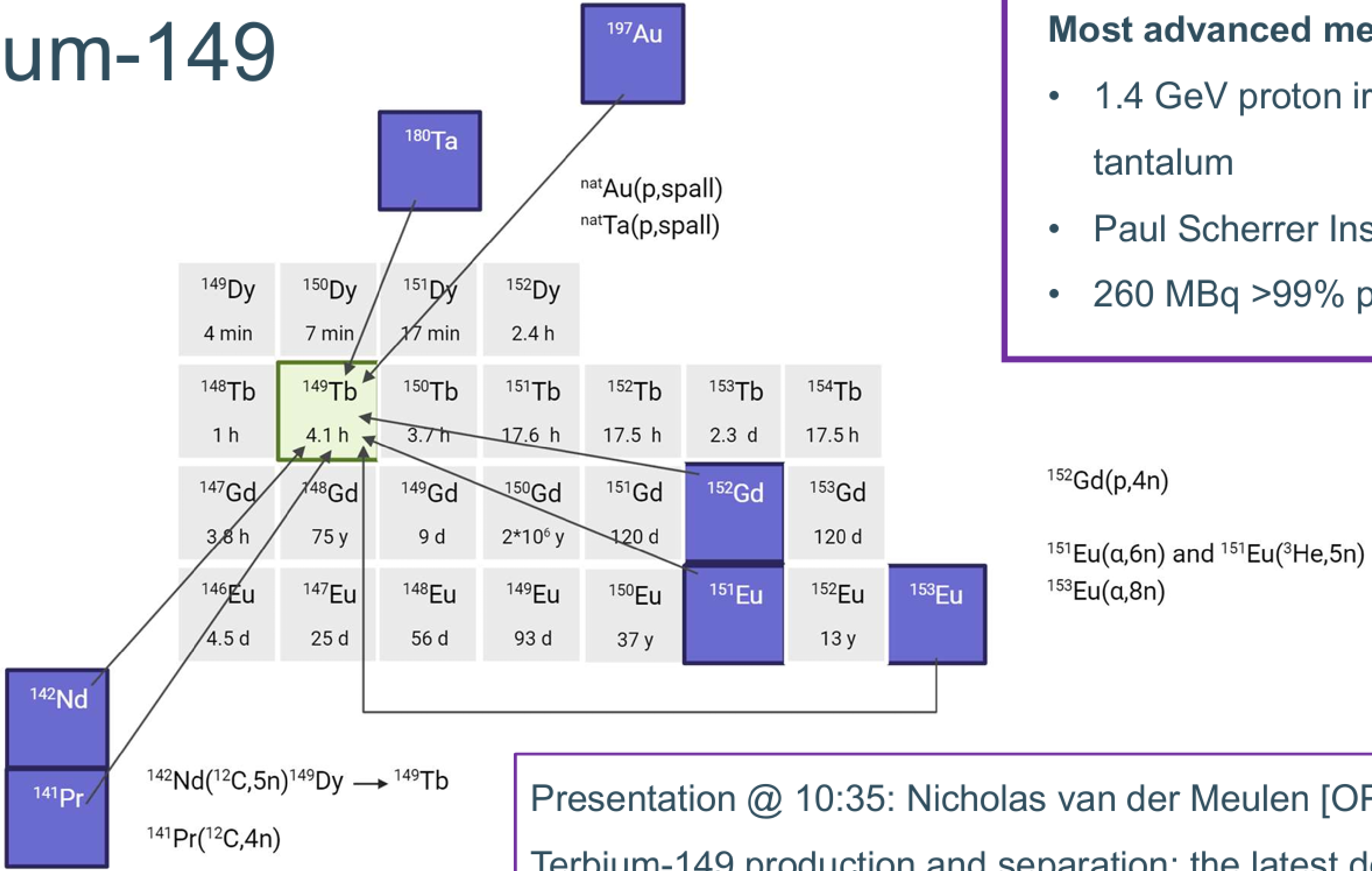
- Absence of alpha-emitting daughters
- Waste management of longer-lived daughter radionuclides to be considered
- Co-emission of positrons simplify post-treatment dosimetry
- Production of terbium-149 extremely challenging



Favaretto et al., 2024. Scientific Reports: 3284.
Van Laere et al., 2024. Theranostics 14(4): 1720-1743.

KU LEUVEN

Terbium-149



Most advanced method:

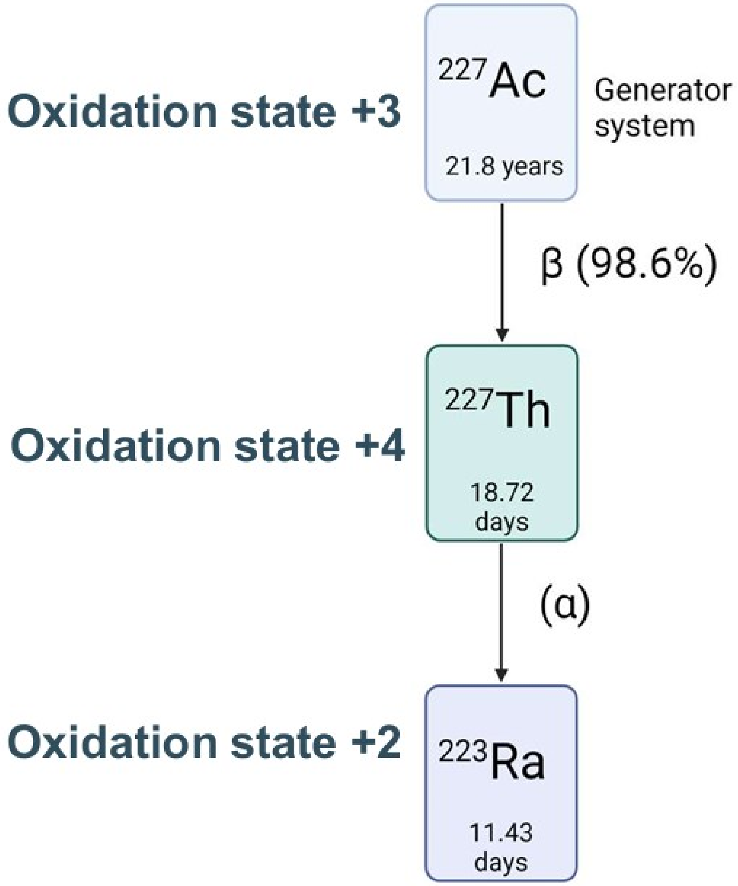
- 1.4 GeV proton irradiation of tantalum
- Paul Scherrer Institute
- 260 MBq >99% purity

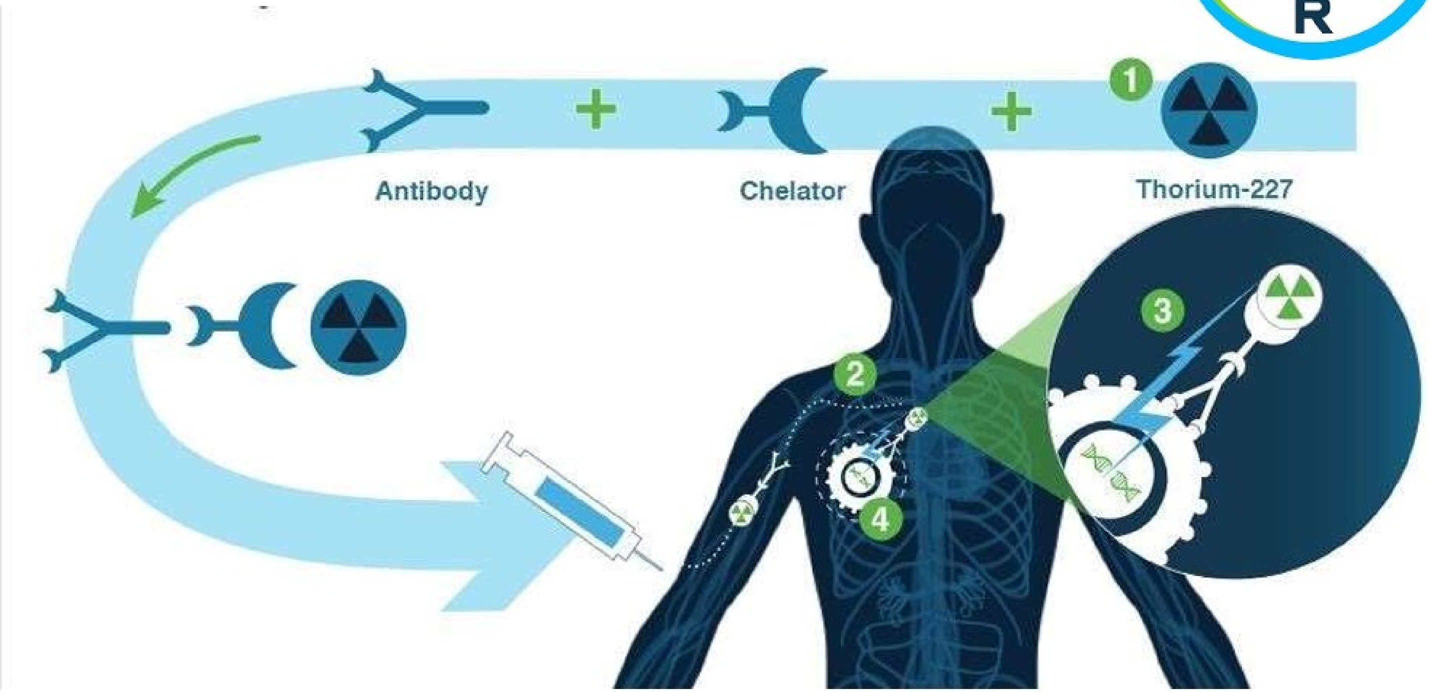
Presentation @ 10:35: Nicholas van der Meulen [OP31]

Terbium-149 production and separation: the latest development update.

Thorium-227

- Generator system, remove also daughter radium-223
- Radium-223 should be removed again if eluate is aged





Therapy – Auger emitters

Radionuclide	Half-life	Energy* γ(X)+e⁻, keV	Energy* γ(X), keV	Energy* e⁻, keV	Number of electrons		
					0.1 - 1.5 keV	1.5 - 5 keV	> 5 keV
^{111}In	2.8 d	440	405	35	1.91	1.02	0.31
^{103m}Rh	56.1 min	39.8	1.8	38	1.49	0.79	0.99
^{119}Sb	38.5 h	48.8	23.1	25.7	2.77	1.47	0.96
^{125}I	59.4 d	61.4	42	19.4	2.99	2.40	0.33
^{67}Ga	78.3 h	193	158	35	1.69	-	0.95
^{197m}Hg	23.8 h	308	94	214	?	1.90	2.40
^{197}Hg	64.1 h	136.3	69.9	66.4	?	2.07	1.70

Brazil–IAEA Nuclear Energy Management School
Rio de Janeiro, Brazil
23 June to 4 July 2025

OBRIGADO!

Thank You!

Gracias!