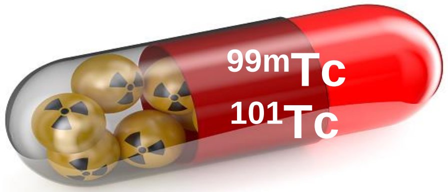
IAEA-CN301-129

Compact Accelerator Based Neutron Sources (CANS) Production of Technetium-99m and Technetium-101



Natalia Mayordomo,[1] Edward J. Mausolf,[2] Erik V. Johnstone,[2] David L. Williams,[3] Eugene Y. Z. Guan,[3] Charles K. Gary,[3] Jim Davis[4]

[1]Helmholtz-Zentrum Dresden – Rossendorf. Institute of Resource Ecology.

HZDR HELMHOLTZ ZENTRUM DRESDEN ROSSENDORF

[2]Innovative Fuel Solutions & AETMX.

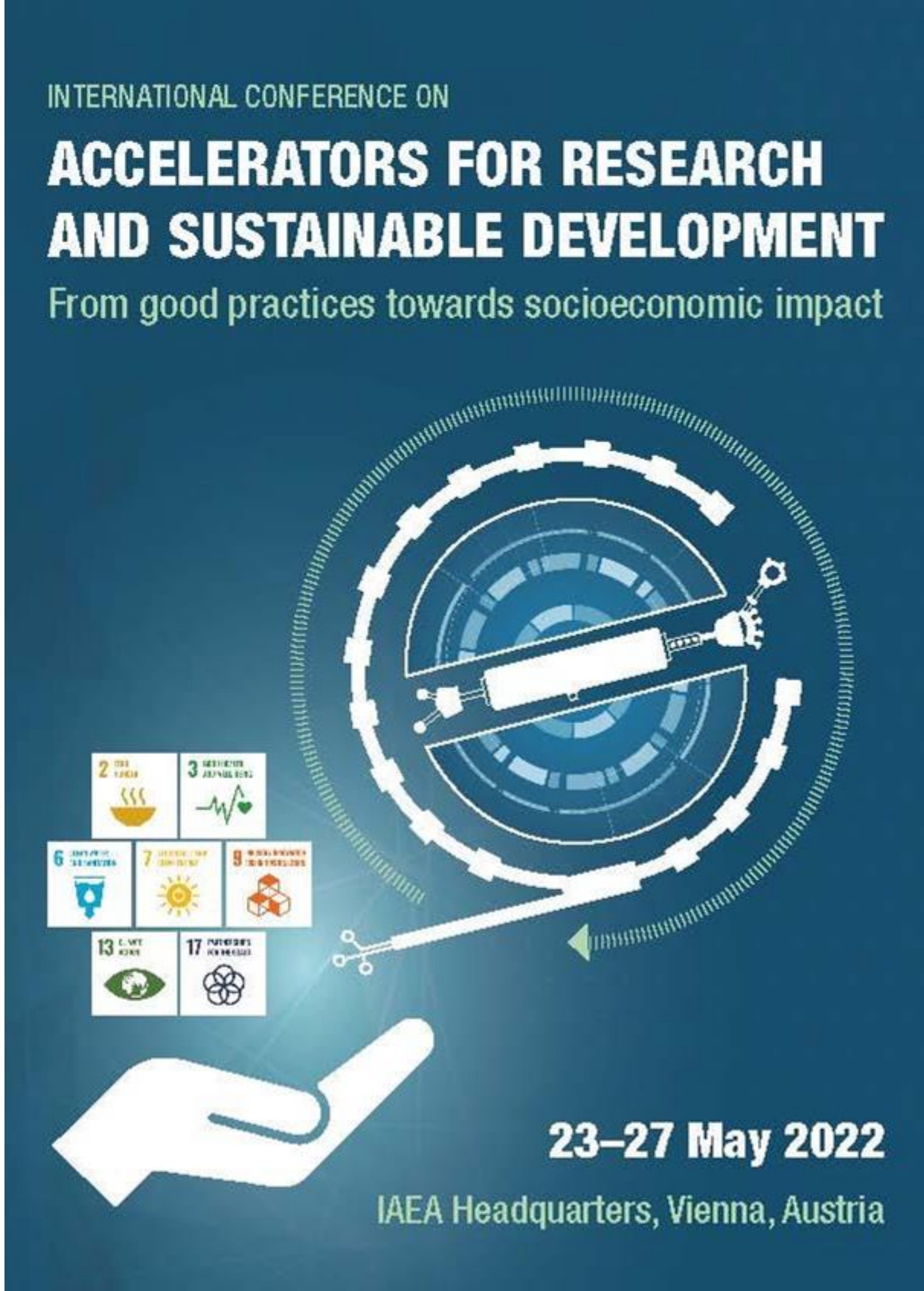
ÆTMX

[3]Adelphi Technology inc.

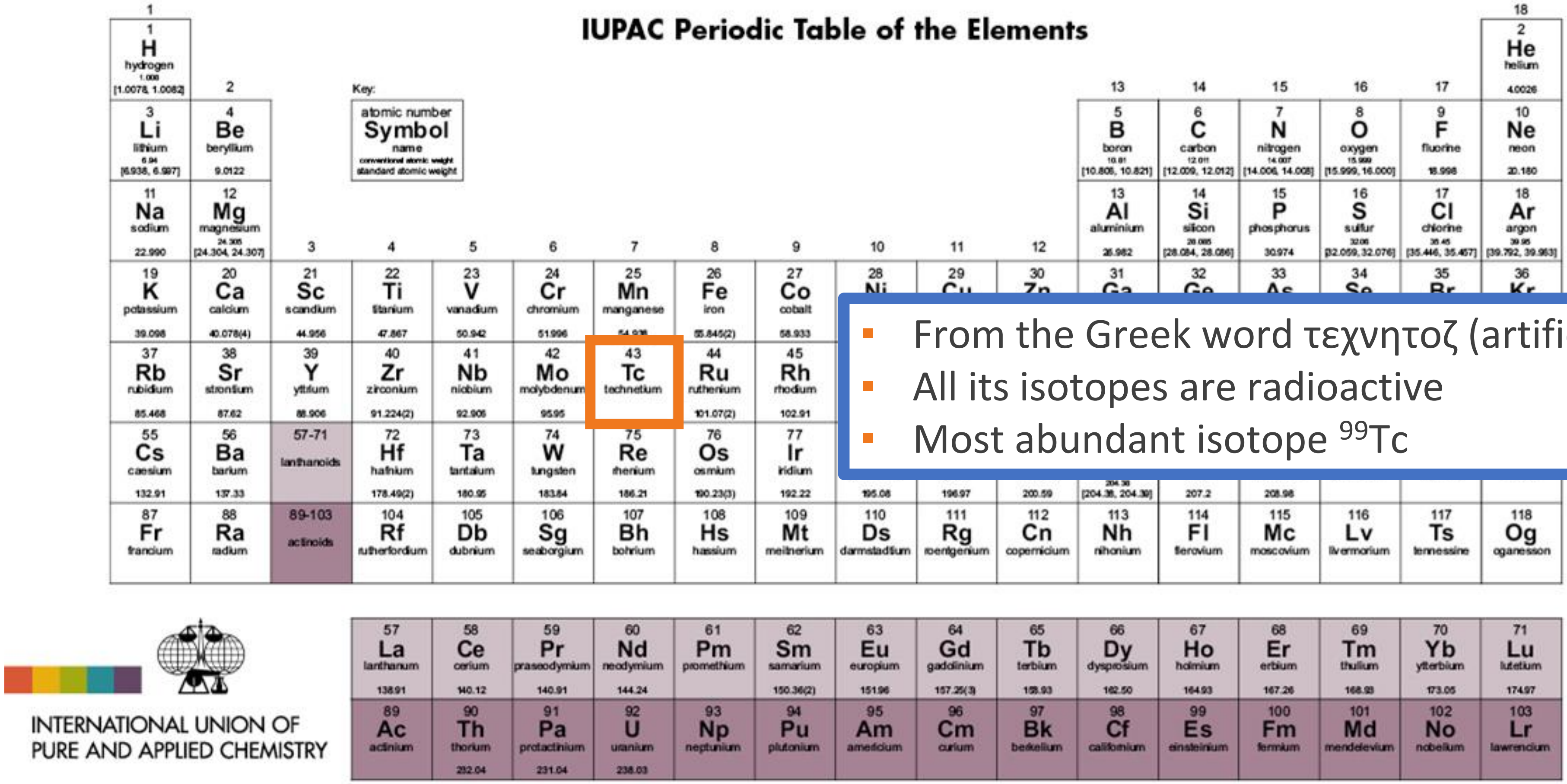
adelphi TECHNOLOGY, INC.

[4]Shertech Laboratories.

SHERTECH NUCLEAR



Technetium (Z = 43)



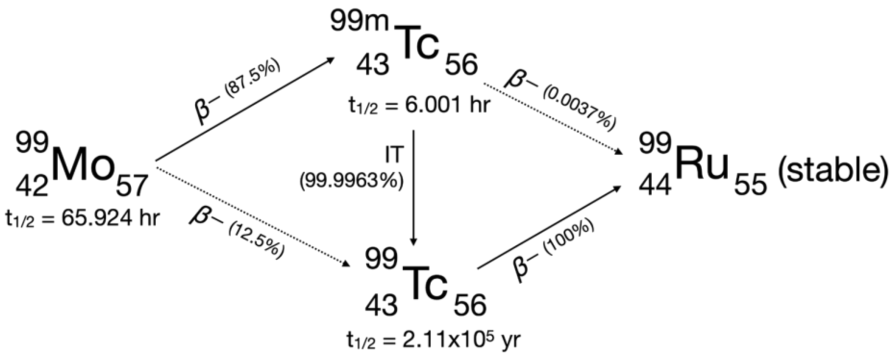
- From the Greek word τεχνητοζ (artificial)
- All its isotopes are radioactive
- Most abundant isotope ^{99}Tc

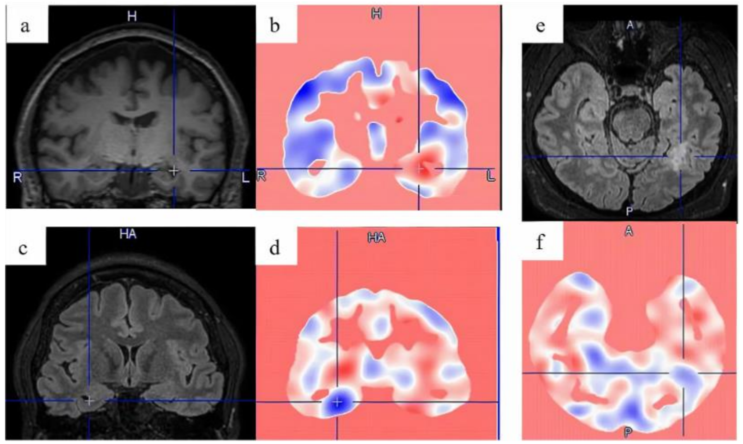
[1] https://iupac.org/what-we-do/periodic-table-of-elements/
[2] Johnstone, E. V. et al. (2017) *J. Chem. Ed.*.

Technetium for Radiodiagnostics: Tc-99m

1. First ^{99m}Tc generator produced in 1957 by Tucker and Greene
2. Linchpin diagnostic radioisotope: ≈40 M procedures/year
3. Commercially produced for large-scale distribution using fission-based (HEU/LEU) targets in nuclear reactors via ^{99}Mo
   - Accelerator platforms (cyclotrons, LINACS, neutron generators, etc.) serve as potential alternatives for direct / indirect production
4. Multifaceted diagnostic agent: oncology, neurology, cardiology, pulmonology, nephrology, urology, orthopedics, etc.

Issues in supply-chain logistics and operation have led to recurring shortages in the market; LEU ^{99}Mo/^{99m}Tc deemed unsustainable





[3] Sukprakun, C. *et al.* (2022). *Brain imaging and behaviour*, *15*, 1-9.

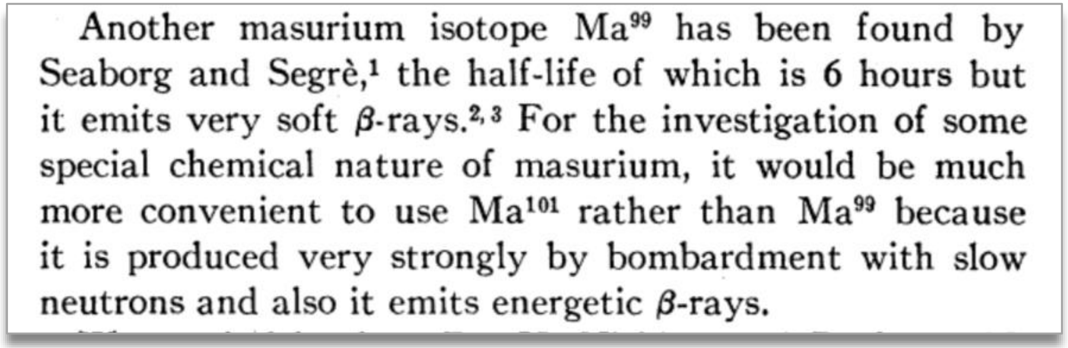
Natalia Mayordomo ErikVJohnstone@gmail.com

An Alternative Technetium Isotope: ^{101}Tc

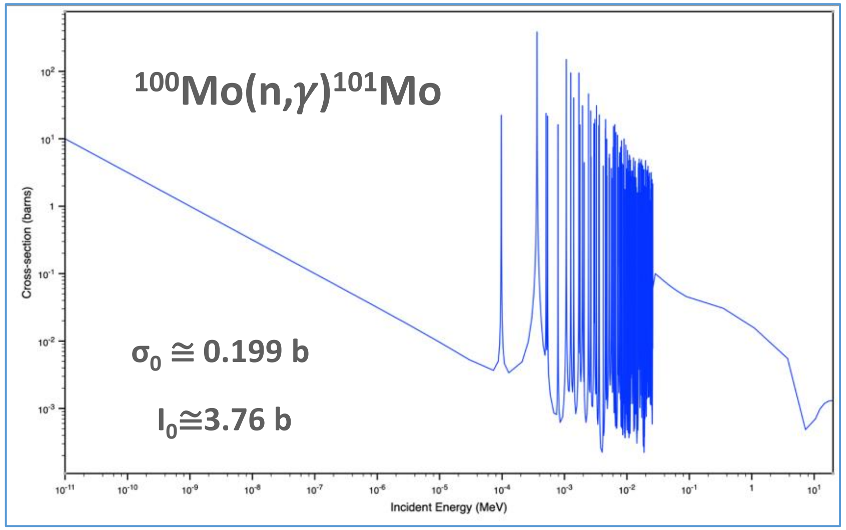
$$^{101}_{42}\mathrm{Mo}_{59} \xrightarrow[14.62\ \mathrm{m}]{\beta-} {}^{101}_{43}\mathrm{Tc}_{58} \xrightarrow[14.02\ \mathrm{m}]{\beta-} {}^{101}_{44}\mathrm{Ru}_{57}\ \text{(stable)}$$

1. First reported in 1940 by Sagane *et. al.*; confirmed by Hahn und Strassmann and Maurer and Rahm in 1941
2. Produced through a variety of nuclear transformations, either directly or indirectly via ^{101}Mo
3. Used for neutron activation analysis (NAA), tracking fission signatures, potential Tc isotope for nuclear medicine
4. Often reported as co-contaminant during ^{99m}Tc production (i.e., cyclotron, linac, reactor)

Ideal for theranostics: $E_{\beta max}$≅1320 keV with $E\gamma$ ≅306.8 keV (~89%)
→ similar nuclear decay properties to ^{32}P, ^{89}Sr, $^{188/186}$Re and ^{131}I


Another masurium isotope Ma^{99} has been found by Seaborg and Segrè,[1] the half-life of which is 6 hours but it emits very soft β-rays.[2,3] For the investigation of some special chemical nature of masurium, it would be much more convenient to use Ma^{101} rather than Ma^{99} because it is produced very strongly by bombardment with slow neutrons and also it emits energetic β-rays.

[4] Sagane, et. al.. *Phys. Rev.* **1940**, *57*, 70



[5] ENDF/B-VIII database

Our Motivation

pharmaceuticals

MDPI

Article

Fusion-Based Neutron Generator Production of Tc-99m and Tc-101: A Prospective Avenue to Technetium Theranostics

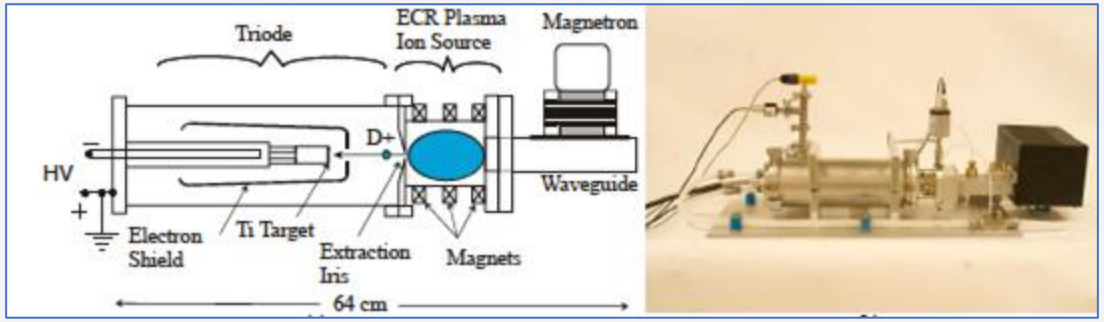
Edward J. Mausolf [1], Erik V. Johnstone [1,*], Natalia Mayordomo [2], David L. Williams [3], Eugene Yao Z. Guan [3] and Charles K. Gary [3]

Pharmaceuticals ***2021****, 14, 875.***

1. Provide alternatives for ^{99m}Tc production that promote sustainability, i.e., environmental, economic, and security perspectives
2. Neutron irradiations using low-cost, high-yield neutron sources
3. Demonstrate small-scale production and isolation of ^{99m}Tc and ^{101}Tc via low specific activity (LSA) ^{99}Mo and ^{101}Mo

****Mausolf, E.; Johnstone, E. Patent Pending, (2018).**

Compact Accelerator Neutron Sources (CANS)



[6] https://www.adelphitech.com/products/dd109m-dd110m.html

Neutron Generator (Adelphi DD110)

- Deuterium-deuterium: $d(d,n)^3$He
  - Acceleration voltage 160 kV
  - Magnetron and ECR ionization source; D^+-current ≈30 mA
- Neutron flux: 2×10^{10} n/s to 5×10^{10} n/s
- E_n = 2.45 MeV
- Isotropic emission from Ti-Cu target
- Cost: ~$0.1M to $1.0M
- Power: 10 kW

Pharmaceuticals ***2021****, 14, 875.*

Cyclotron (PETtrace 800 series)

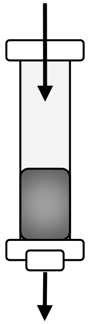
- $^{18}O(p,n)^{18}F$ reaction and other (p,n) reactions
  - Accelerating voltage 16.5 MeV
  - H^--current ≈75 to 85 μA; up to 100 μA per target; dual target irradiations possible
  - Internal beam; external beam available
- Neutron flux: 5.2×10^{11} to 1.0×10^{12} n/s
- E_n = 0.1 to 10 MeV neutrons
- Anisotropic to incoming H-beam
- Cost: ~$1.0M to $10M
- Power 75 kW

[7] Asp,et. al. *Med Phys*,. 2019.

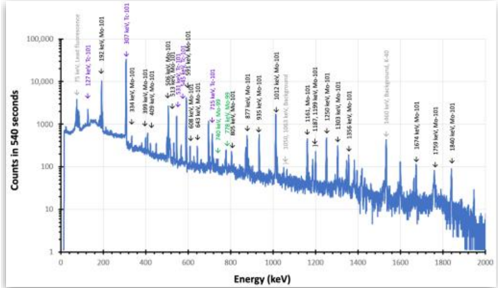
CANS Generation of ^{99m}Tc and ^{101}Tc: Experimentation

1. **Target Preparation**
   Nat. Mo ~10 to 30 g as the metal or an aqueous, acidic solution of $(NH_4)_6Mo_7O_{24}$ (AHM)
2. **CANS Irradiation of Mo Target**
   DD generator or hybrdized PET cyclotron neutron irradiations of Mo targets; t_{irrad} from minutes to hours
3. **Production / Isolation of ^{99m}Tc and ^{101}Tc**
   Activated carbon substrate used for removal of Tc isotopes from dissolved LSA Mo target
4. **Characterization**
   Gamma spectroscopy with HPGe or NaI(Tl) detectors; characteristic γ-ray and half-life

42
Mo
Molybdenum
95.94

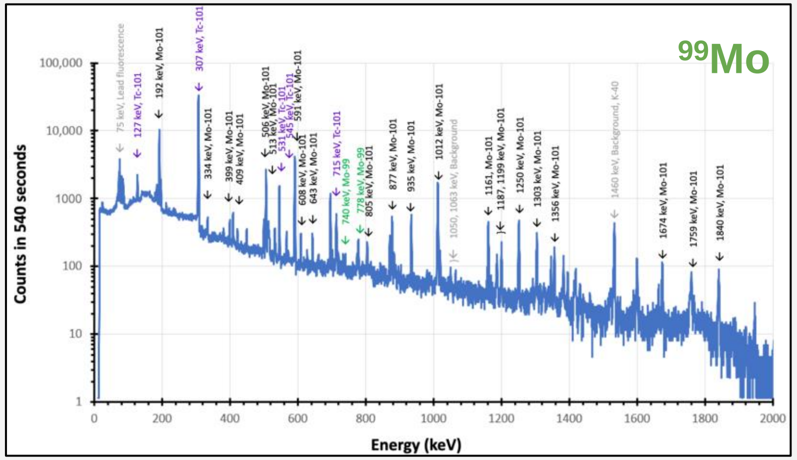


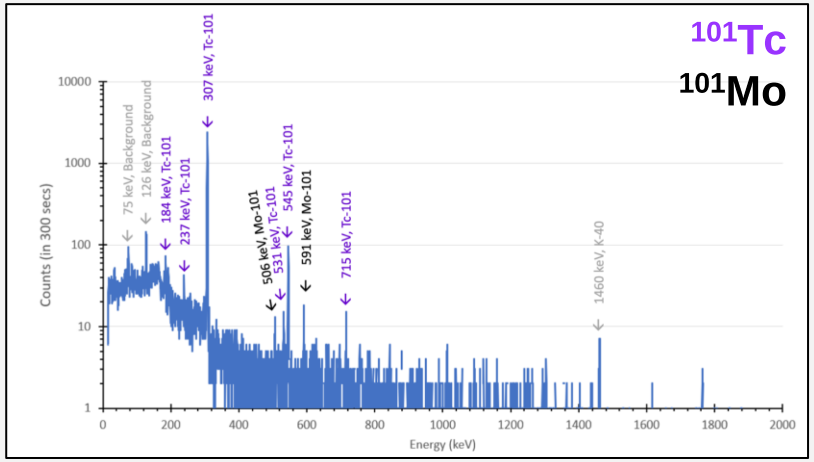
Activated Carbon

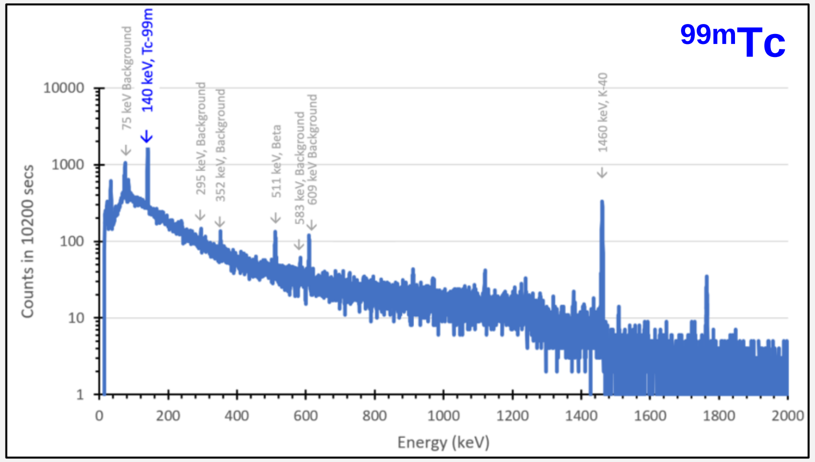


Pharmaceuticals ***2021***, *14*, *875.*

Neutron Generator Production and Isolation of ^{101}Tc and ^{99m}Tc



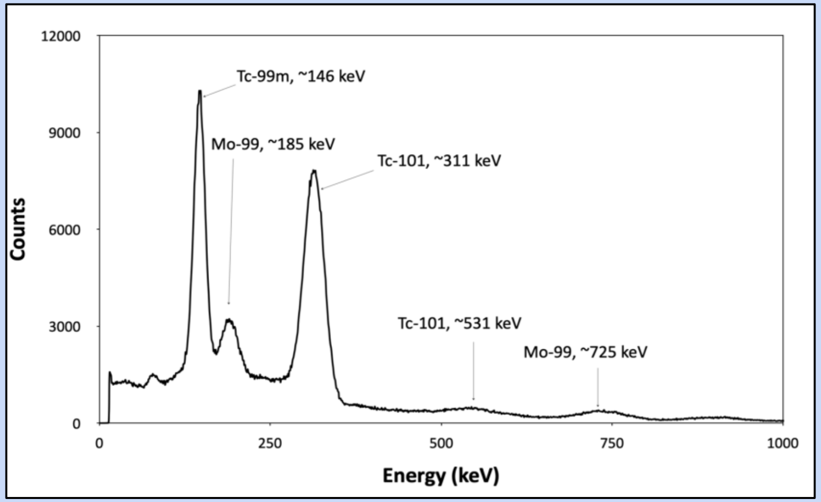


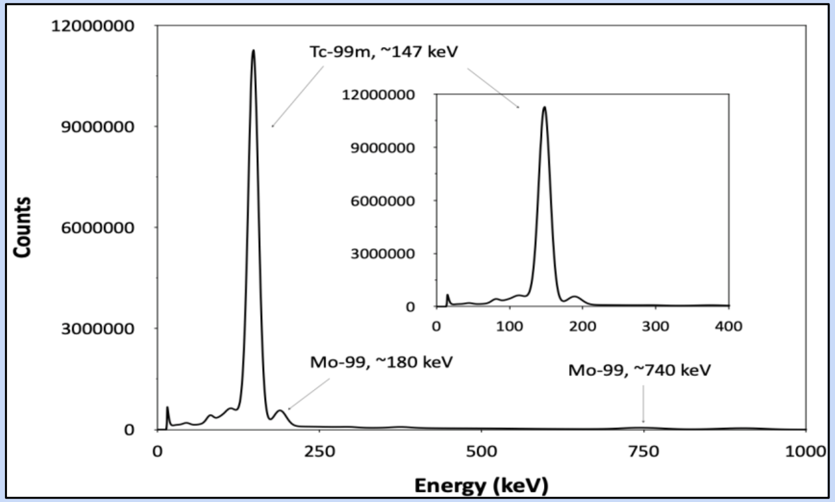


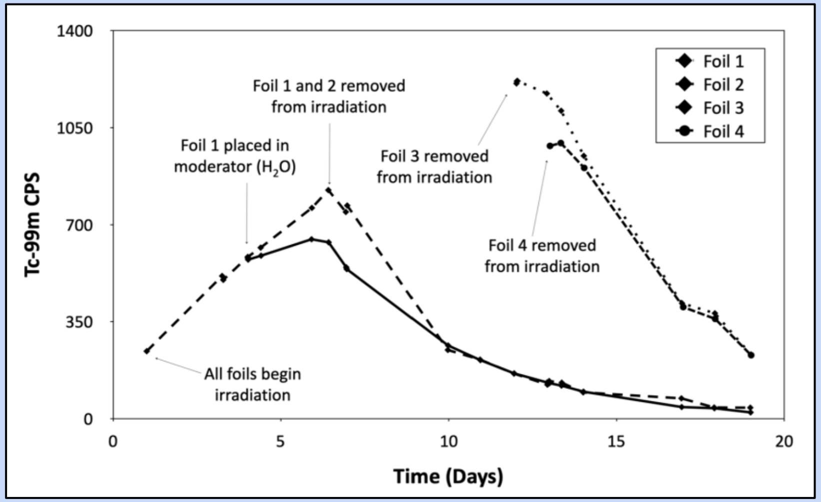
- Irradiation for ~15 min; separation performed directly after EOB and measured
- EOB activities ^{99}Mo = 52±3 Bq (1.3±0.1 nCi); ^{101}Mo = 1.2±0.1 kBq (32.7±3.5 nCi); ^{101}Tc = 4.6±0.5 kBq (124.1±13.2 nCi); no detectable ^{99m}Tc at EOB
- ^{101}Tc rapidly isolated on AC; only one prior report in literature of ^{101}Tc recovery with column chromatography
- Extraction proven viable at ultra-low concentrations of ^{101}Mo/^{101}Tc and ^{99}Mo/^{99m}Tc

Pharmaceuticals ***2021***, *14*, *875.*

Hybridized PET Cyclotron Production of ^{101}Tc and ^{99m}Tc







- Irradiations for a total of ~5 hr; between multiple [^{18}F]FDG runs daily
- ^{99}Mo yield per day ~13 kBq (3.5 µCi); higher neutron outputs trend to higher production
- ^{101}Tc observable x6 $t_{1/2}$ (~14.22 min); no ^{101}Mo observed
- Long(er) $t_{irrad.}$ allows for ^{99m}Tc/^{101}Tc co-production, while longer decay yields for pure ^{99}Mo/^{99m}Tc
- Ingrowth of ^{99m}Tc tracked in irradiated Mo foils over a week of production

 Natalia Mayordomo ErikVJohnstone@gmail.com

CANS for the Production of ^{99m}Tc and ^{101}Tc

SPECT Model

Neutron-driven production of Tc-99m; exploit ^{99}Mo for production

+

PET Model

Distributed, redundant supply-chain located near the end-user with manageable waste streams and economics

→

CANS ^{99m}Tc / ^{101}Tc Model

Distributed, redundancy neutron-driven production of Tc-99m / Tc-101 located near the end-user with manageable waste streams using low(er)-cost CANS devices, targetry, and separation platform

Neutron outputs and costs:

Type	Estimate of Beam Energy (MeV)	Approximate Yield Range (n/s)	Approximate System Cost, Order of Magnitude ($M)
Reactor *	Not applicable	$>10^{17}$	~1000
Electron Accelerator † with Photoneutron Converter	30–40	5×10^{13} to 1×10^{14}	10
Cyclotron ‡	10–18.0	5.7×10^{12} to 2.1×10^{14}	1–10
RFQ Linac §	1.5–3.0	1×10^{11} to 1.3×10^{12}	1
D-D Neutron Generator	0.1–0.2	1×10^{8} to 1×10^{11}	0.1–1

* TRIGA reactor $270,000 in 1972 [33], adjusting for inflation is $1.72B in 2021 [34]. † Financial figures based on 35 MeV, 100 kW electron accelerator described in Ref. [35]. ‡ Financial figures based on Ref. [36]. § Financial figures based on Ref. [37].

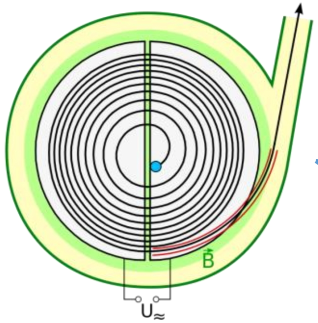
Pharmaceuticals ***2021***, *14, 875.*

Generator Flux	2×10^{10} n/s				2×10^{12} n/s			
Tc Isotope Produced	^{99m}Tc		^{101}Tc		^{99m}Tc		^{101}Tc	
Mo Target	Nat. Mo	^{98}Mo	Nat. Mo	^{100}Mo	Nat. Mo	^{98}Mo	Nat. Mo	^{100}Mo
Doses Generated per day	5	22	53	220	534	2200	5344	22,000
Generators Required	21,918	4981	2068	298	205	50	21	5

Maximize neutron economy and production, while minimizing processing and transportation times for maximizing system output

Technetium-101: an alternative approach to radiotheranostics

Most therapeutic radionuclides require a nuclear reactor, fissionable material, or high-energy accelerators for production



Isotope	Half-Life	E_{gamma} (keV)	E_{beta} (keV)	Tissue Penetration Range (mm)	Uses
^{89}Sr	50.5 d	N/A	587.10 (99.9%)	8	TRT [1]-osseous metastases
^{90}Y	64.00 h	N/A	933.7 (99.9%)	12	TRT-hepatic malignancies, lymphoma
^{131}I	8.02 d	284.3 (6.1%), 364.48 (81.5%), 636.98 (7.2%)	191.58 (89.6%), 96.62 (7.2%)	2.4	Diagnostic imaging (SPECT); TRT: thyroid ablation, neuroendocrine tumors, prostate seeds
^{177}Lu	6.647 d	208.36 (10.4%)	149.35 (79.4%), 47.66 (11.6%)	2.2	Diagnostic imaging (SPECT); TRT: PRRT [2], bone pain palliation, synovectomy, neuroendocrine, metastatic prostate, etc.
^{186}Re	3.72 d	137.16 (9.5%)	359.2 (71.0%), 306.1 (21.5%)	4.5	Bone pain palliation, synovectomy, endovascular irrad.
^{188}Re	17.01 h	155.04 (15.5%)	795.41 (70.7%), 728.88 (25.8%)	11	Bone pain palliation, synovectomy, endovascular irrad.
^{223}Ra *	11.43 d	~82.0 (<2.0%)	492.5 (99.7%), 471.3 (91.3%), 172.9 (0.3%)	-	Bone metastasises
^{225}Ac *	9.920 d	218.0 (11.4%), 440.45 (25.9%), 1567.1 (99.7%)	660.34 (97.4%), 492.2 (65.9%), 197.4 (100%), 93.4 (68.8%)	-	Metastatic castration-resistant prostate cancer
^{101}Tc	14.22 min	306.8 (89%), 545 (5.9%)	487 (90%), 385 (6%), 127.2 (2.64%)	N/A	N/A

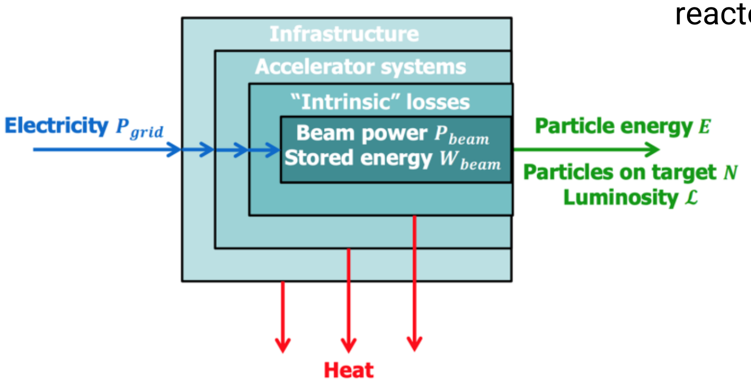
[1] TRT = targeted radionuclide therapy; [2] PRRT = peptide receptor radionuclide therapy. * Primarily α-decay, yet exhibit multiple decay modes, i.e., β, and γ, and daughter products; for comparison only β and γ reported from decay chain

Pharmaceuticals ***2021***, *14*, *875.*

Sustainability

Energy Consumption

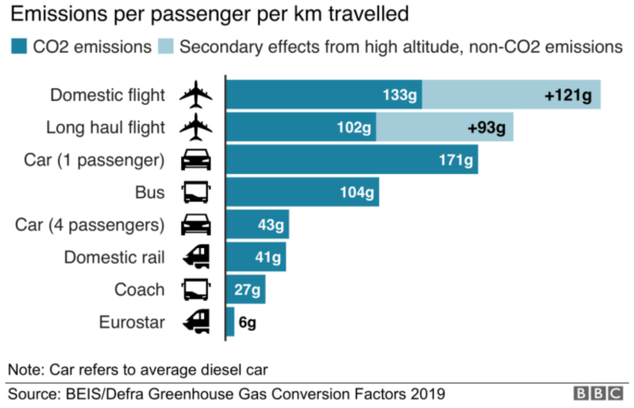
Accelerator input energy required and efficiency; neutron economy; research reactors generate zero electricity

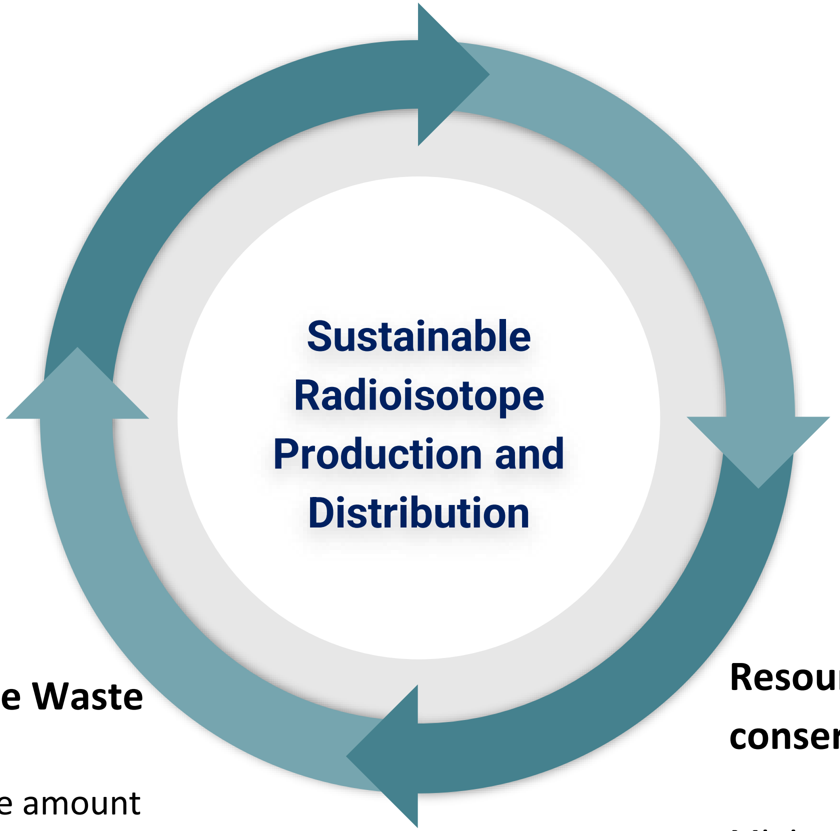


[10] Lebrun, Workshop on Magnet Design, 2014.

Fossil Fuel Consumption

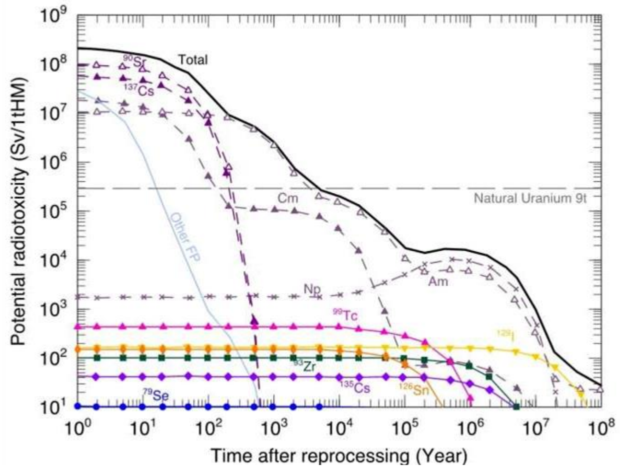
Centralized vs Decentralized production modes; which and how many different modes are utilized





Radioactive Waste

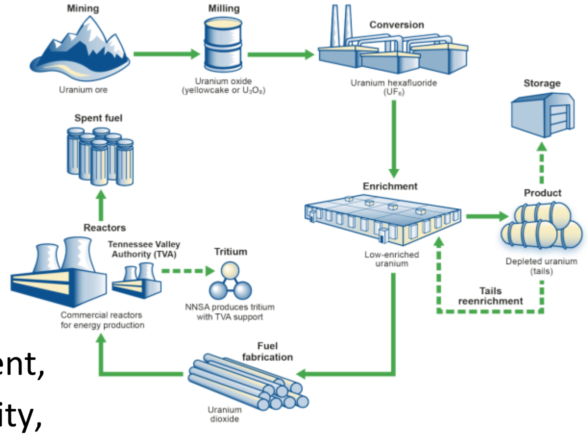
Reducing the amount of hazardous and long-lived radioactive waste; NORM / NARM vs HLW and GTCC



[11] Satoshi et. al.,*Scientific Reports*, 2017.

Resource use and conservation

Mining, target enrichment, consumables, recyclability, existing infrastructure



[12] GAO Report GAO-21-28, 2020.

Conclusions and Outlook

- An efficient method to obtain and isolate ^{99m}Tc and ^{101}Tc was demonstrated
- We envision the use of this methodology to help in providing a reliable and sustainable supply of ^{99m}Tc
- This work opens the door to further explore the use of ^{101}Tc for therapeutic/theranostic applications
- Development of a commercial production unit / separation platform
- Further investigate sustainable avenues for maximizing neutron production / economy while lowering costs, resource consumption, and waste production for new and known radioisotopes

Pharmaceuticals ***2021***, *14*, *875.*

Thank you

Any question?

Write us in:
ErikVJohnstone@gmail.com

ÆTMX
HZDR HELMHOLTZ ZENTRUM DRESDEN ROSSENDORF
adelphi TECHNOLOGY, INC.
SHERTECH NUCLEAR