

Title: Paul Schaffer: Get a Half-Life: Isotopes as the unlikely Hero of Modern Medicine

Date: Dec 02, 2015 07:00 PM

URL: <http://pirsa.org/15120020>

Abstract: <p>Emerging techniques and technologies, drawn from many fields of science and medicine, are allowing us to peer inside the human body with unprecedented sensitivity and to probe the fundamental processes of life “ in real time. TRIUMF’s Life Sciences Division is making such studies possible with isotopes, short-lived elements that are harnessed and incorporated into next generation pharmaceuticals designed to provide incredible insight into the complex systems that make up life. With its specialized expertise and facilities in particle accelerator targets, isotope production, and radiochemistry, TRIUMF “ Canada’s national laboratory for particle and nuclear physics and accelerator-based science “ has unique capabilities in this area.</p>

<p>In his talk, Dr. Paul Schaffer, Associate Laboratory Director of TRIUMF’s Life Sciences Division, will explore how he and his team use accelerators to develop tools and techniques to advance the field of nuclear medicine. He’ll share leading-edge developments and discuss the promise advanced medical isotopes hold for disease diagnostics and therapeutics, as well as talk about his team’s award-winning efforts to produce a secure supply of critical medical isotopes.</p>



Canada's national laboratory
for particle and nuclear physics
and accelerator-based science

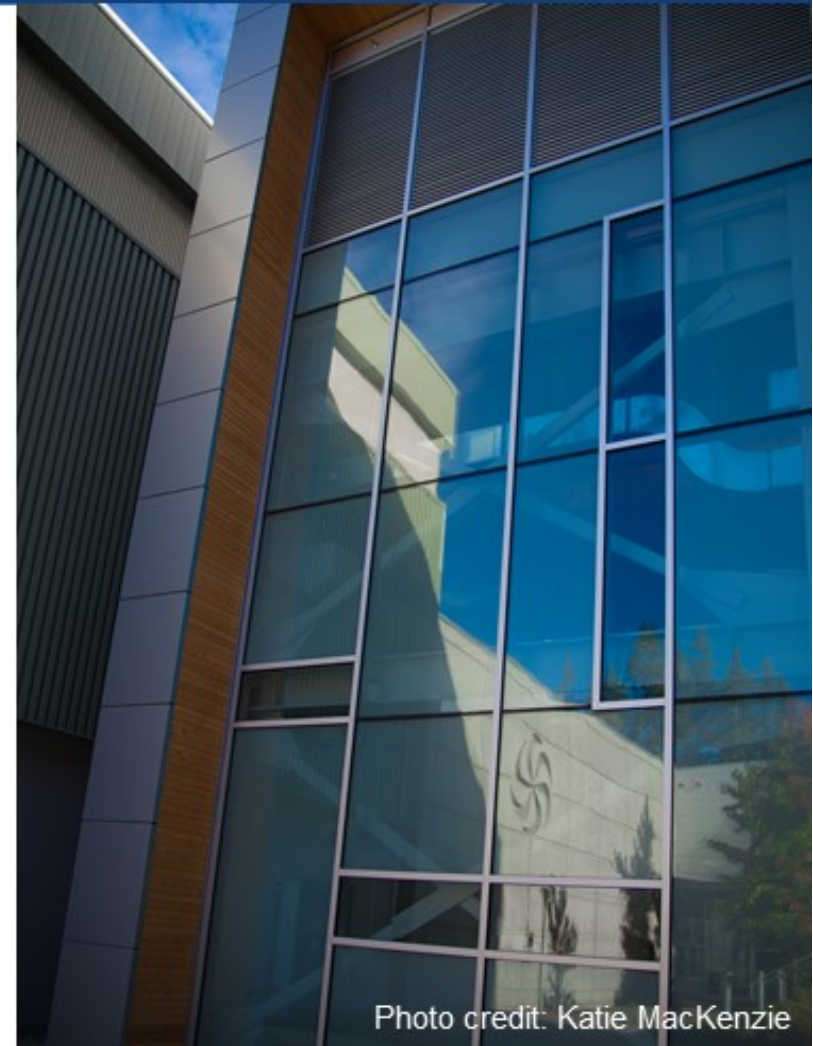
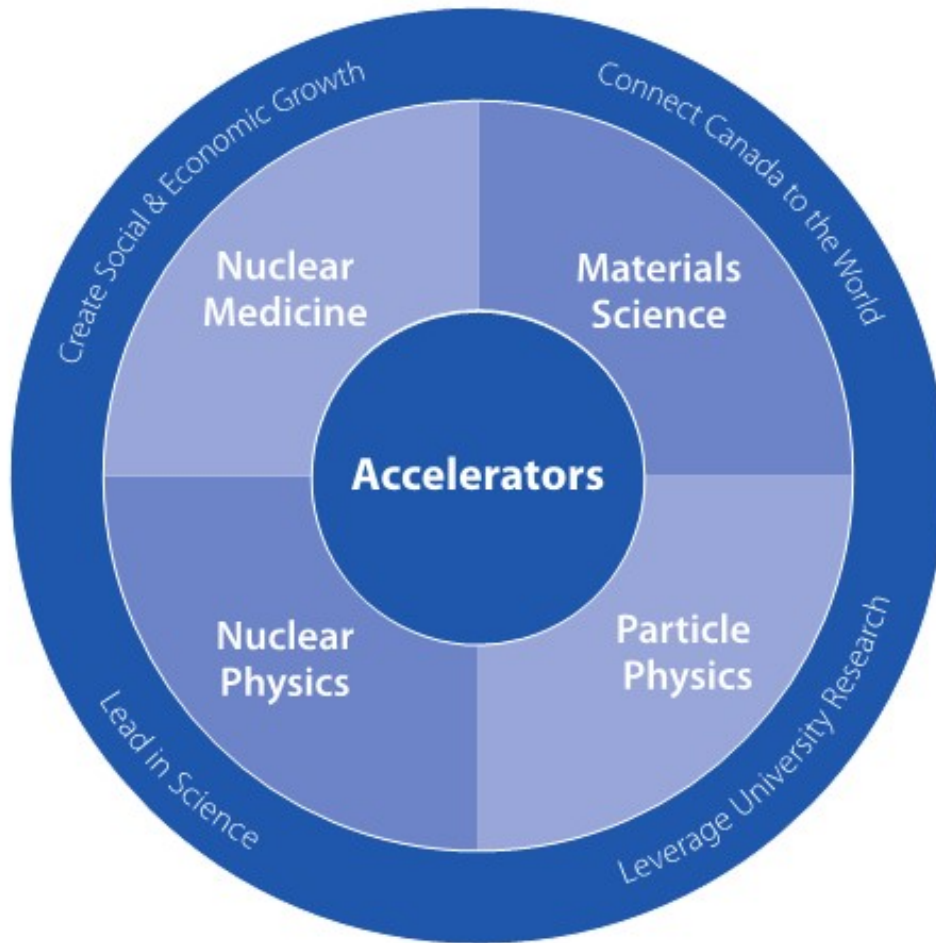
Get a Half-life: Isotopes as the Unlikely Hero of Modern Medicine

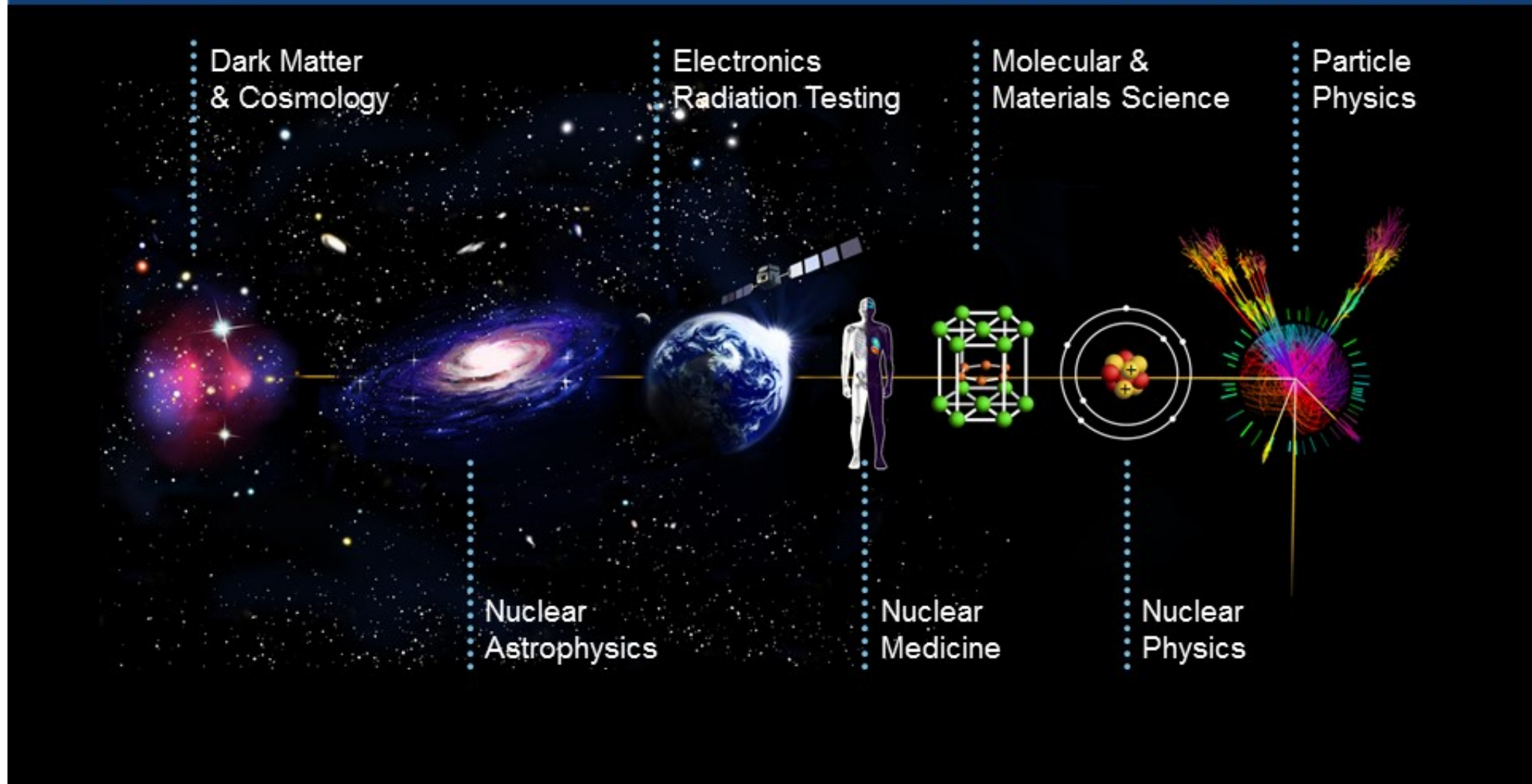
Paul Schaffer
Associate Laboratory Director – Life Sciences, TRIUMF

December 2, 2015



TRIUMF was founded in 1968 and has delivered nearly 50 years of science and innovation for Canada



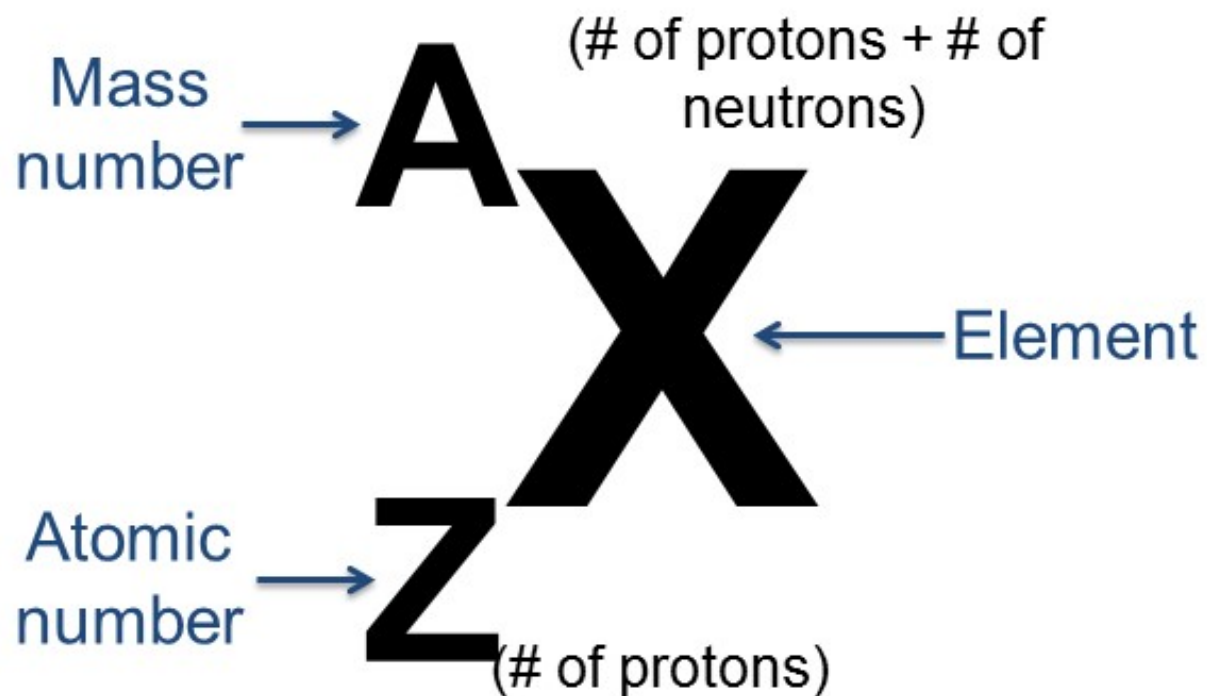


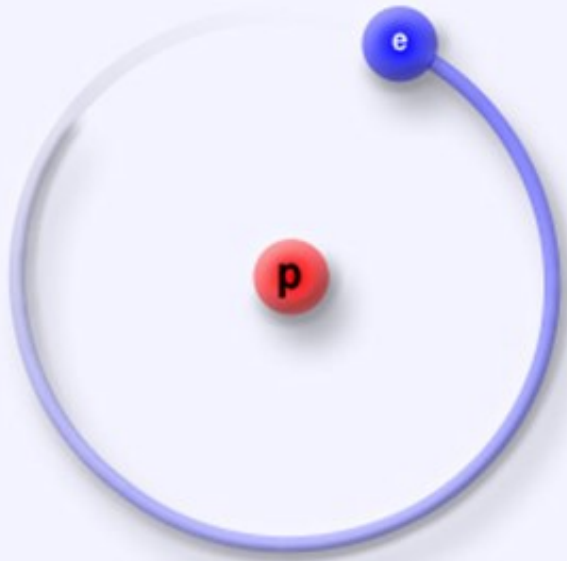
PERIODIC TABLE OF THE ELEMENTS

1 H Hydrogen 1.008																	2 He Helium 4.003
3 Li Lithium 6.941	4 Be Beryllium 9.012											5 B Boron 10.811	6 C Carbon 12.011	7 N Nitrogen 14.007	8 O Oxygen 15.999	9 F Fluorine 18.998	10 Ne Neon 20.180
11 Na Sodium 22.990	12 Mg Magnesium 24.305											13 Al Aluminum 26.982	14 Si Silicon 28.086	15 P Phosphorus 30.974	16 S Sulfur 32.066	17 Cl Chlorine 35.453	18 Ar Argon 39.948
19 K Potassium 39.098	20 Ca Calcium 40.078	21 Sc Scandium 44.956	22 Ti Titanium 47.88	23 V Vanadium 50.942	24 Cr Chromium 51.996	25 Mn Manganese 54.938	26 Fe Iron 55.933	27 Co Cobalt 58.933	28 Ni Nickel 58.693	29 Cu Copper 63.546	30 Zn Zinc 65.39	31 Ga Gallium 69.723	32 Ge Germanium 72.61	33 As Arsenic 74.922	34 Se Selenium 78.972	35 Br Bromine 79.904	36 Kr Krypton 84.80
37 Rb Rubidium 84.468	38 Sr Strontium 87.62	39 Y Yttrium 88.906	40 Zr Zirconium 91.224	41 Nb Niobium 92.906	42 Mo Molybdenum 95.95	43 Tc Technetium 98.907	44 Ru Ruthenium 101.07	45 Rh Rhodium 102.906	46 Pd Palladium 106.42	47 Ag Silver 107.868	48 Cd Cadmium 112.411	49 In Indium 114.818	50 Sn Tin 118.71	51 Sb Antimony 121.760	52 Te Tellurium 127.5	53 I Iodine 126.904	54 Xe Xenon 131.29
55 Cs Cesium 132.905	56 Ba Barium 137.327	57-71	72 Hf Hafnium 178.49	73 Ta Tantalum 180.948	74 W Tungsten 183.85	75 Re Rhenium 186.207	76 Os Osmium 190.23	77 Ir Iridium 192.22	78 Pt Platinum 195.08	79 Au Gold 196.967	80 Hg Mercury 200.59	81 Tl Thallium 204.383	82 Pb Lead 207.2	83 Bi Bismuth 208.980	84 Po Polonium [209]	85 At Astatine 208.987	86 Rn Radon 222.018
87 Fr Francium 223.020	88 Ra Radium 226.025	89-103	104 Rf Rutherfordium [261]	105 Db Dubnium [262]	106 Sg Seaborgium [266]	107 Bh Bohrium [264]	108 Hs Hassium [269]	109 Mt Meitnerium [268]	110 Ds Darmstadtium [269]	111 Rg Roentgenium [272]	112 Cn Copernicium [277]	113 Uut Ununtrium unknown	114 Fl Flerovium [289]	115 Uup Ununpentium unknown	116 Lv Livermorium [293]	117 Uus Ununseptium unknown	118 Uuo Ununoctium unknown
57 La Lanthanum 138.906	58 Ce Cerium 140.115	59 Pr Praseodymium 140.908	60 Nd Neodymium 144.24	61 Pm Promethium 144.913	62 Sm Samarium 150.36	63 Eu Europium 151.966	64 Gd Gadolinium 157.25	65 Tb Terbium 158.925	66 Dy Dysprosium 162.50	67 Ho Holmium 164.930	68 Er Erbium 167.26	69 Tm Thulium 168.934	70 Yb Ytterbium 173.04	71 Lu Lutetium 174.967			
89 Ac Actinium 227.028	90 Th Thorium 232.038	91 Pa Protactinium 231.036	92 U Uranium 238.029	93 Np Neptunium 237.048	94 Pu Plutonium 244.064	95 Am Americium 243.061	96 Cm Curium 247.070	97 Bk Berkelium 247.070	98 Cf Californium 251.080	99 Es Einsteinium [254]	100 Fm Fermium 257.095	101 Md Mendelevium 258.1	102 No Nobelium 259.101	103 Lr Lawrencium [262]			

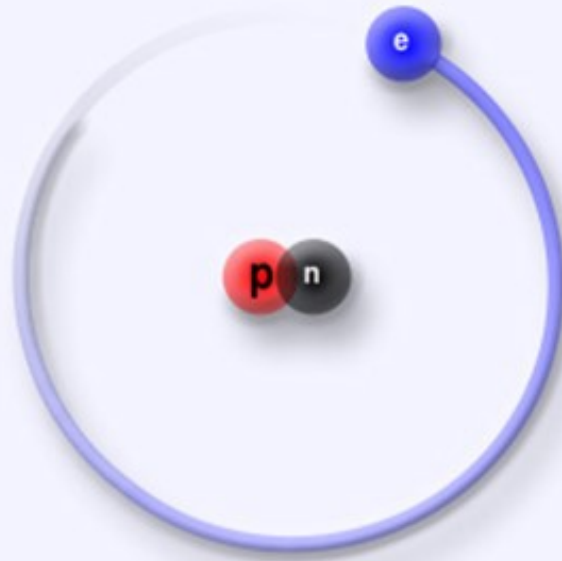
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Isotope Symbols

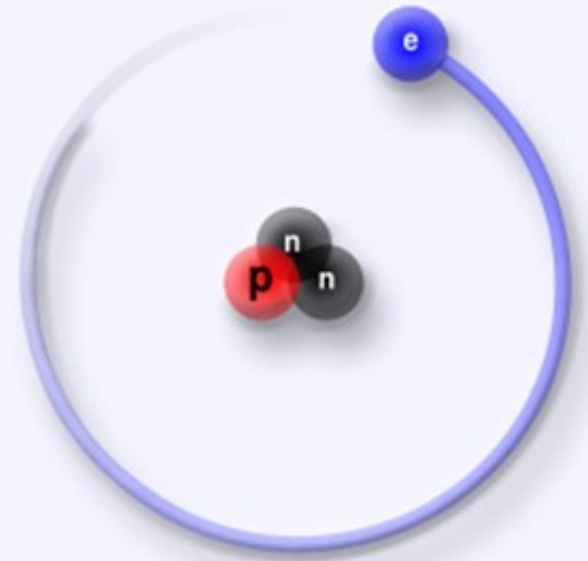




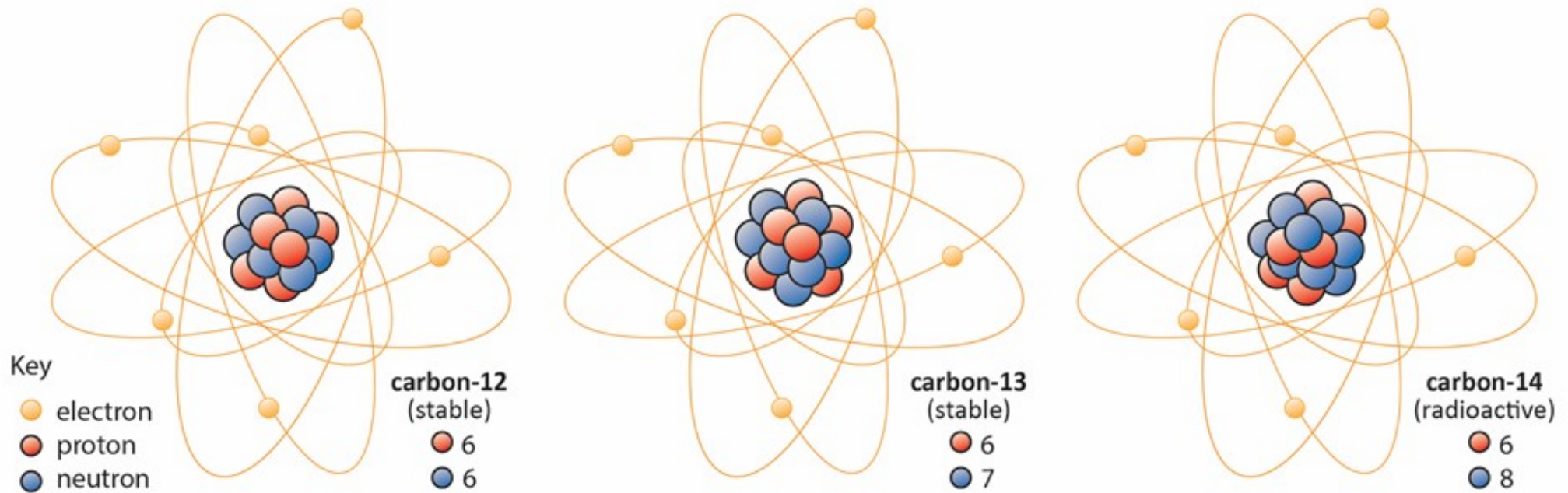
Protium

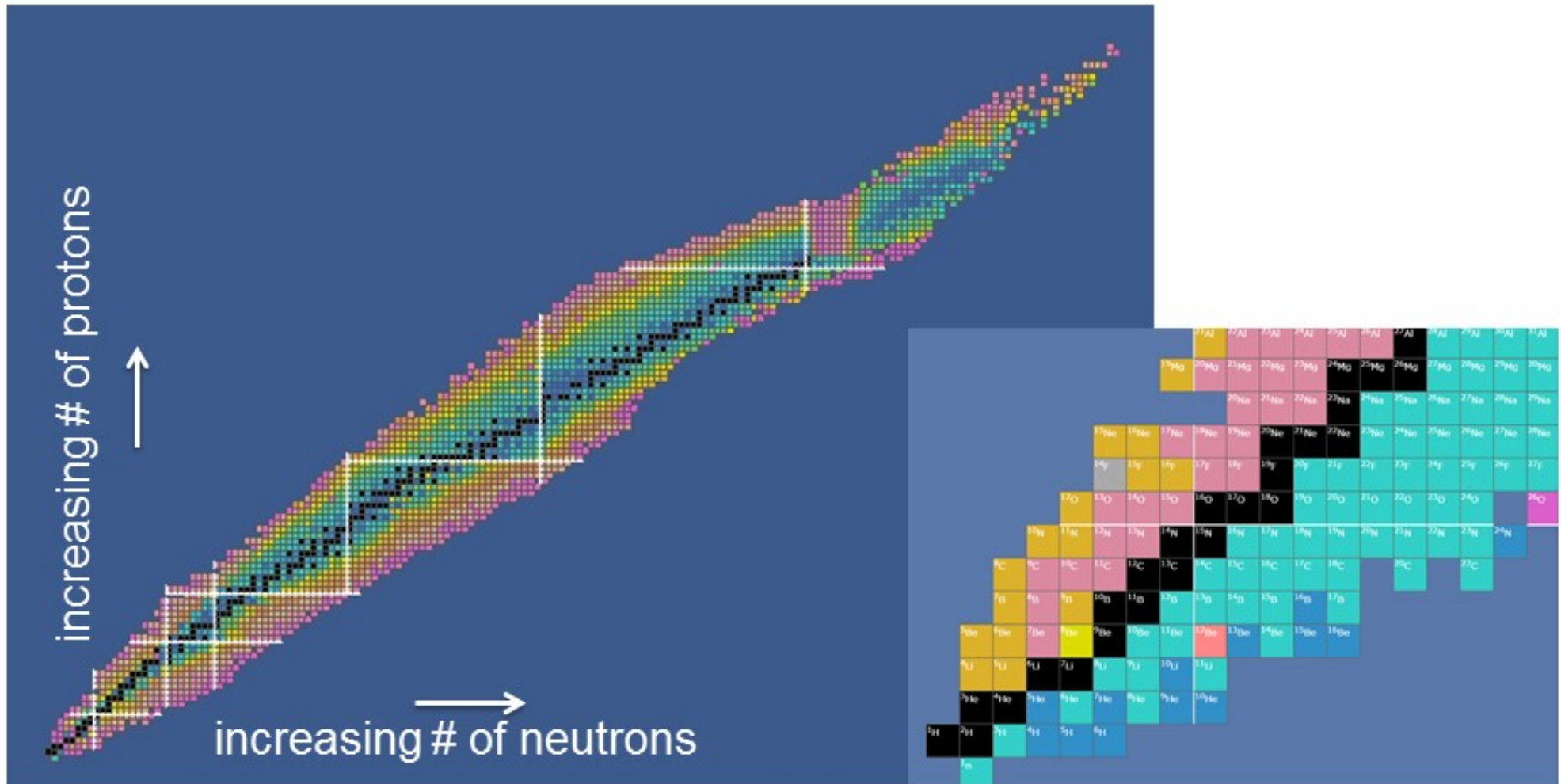


Deuterium

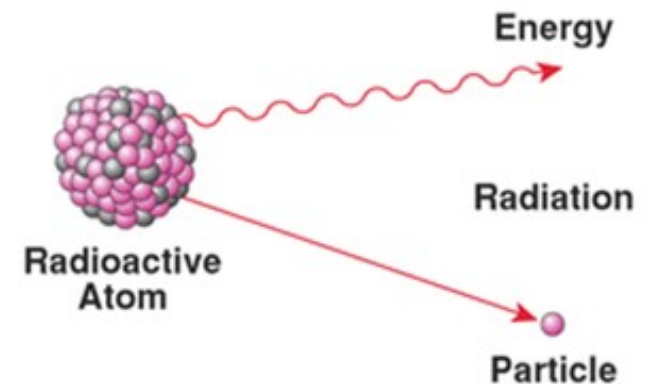


Tritium

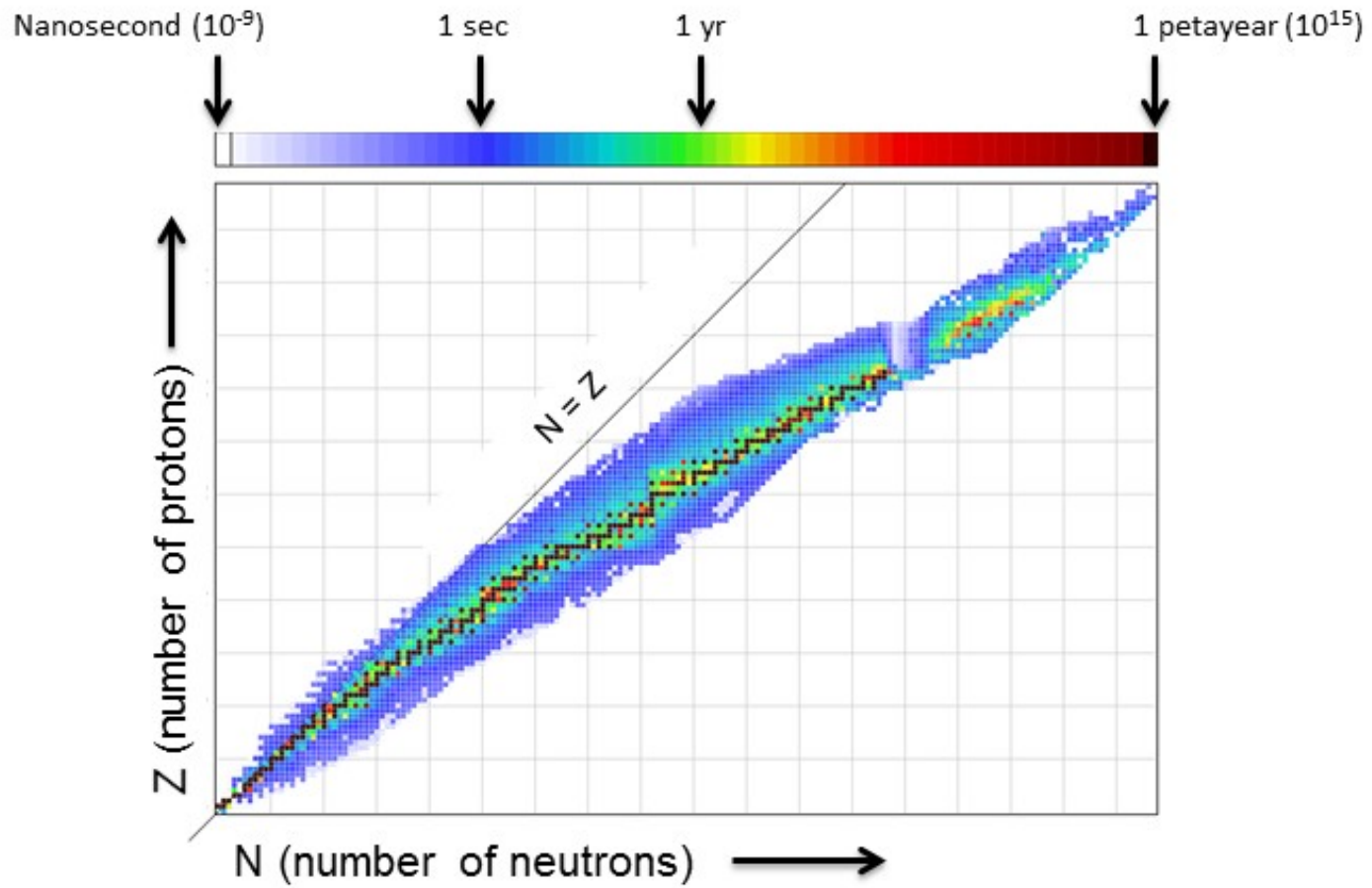




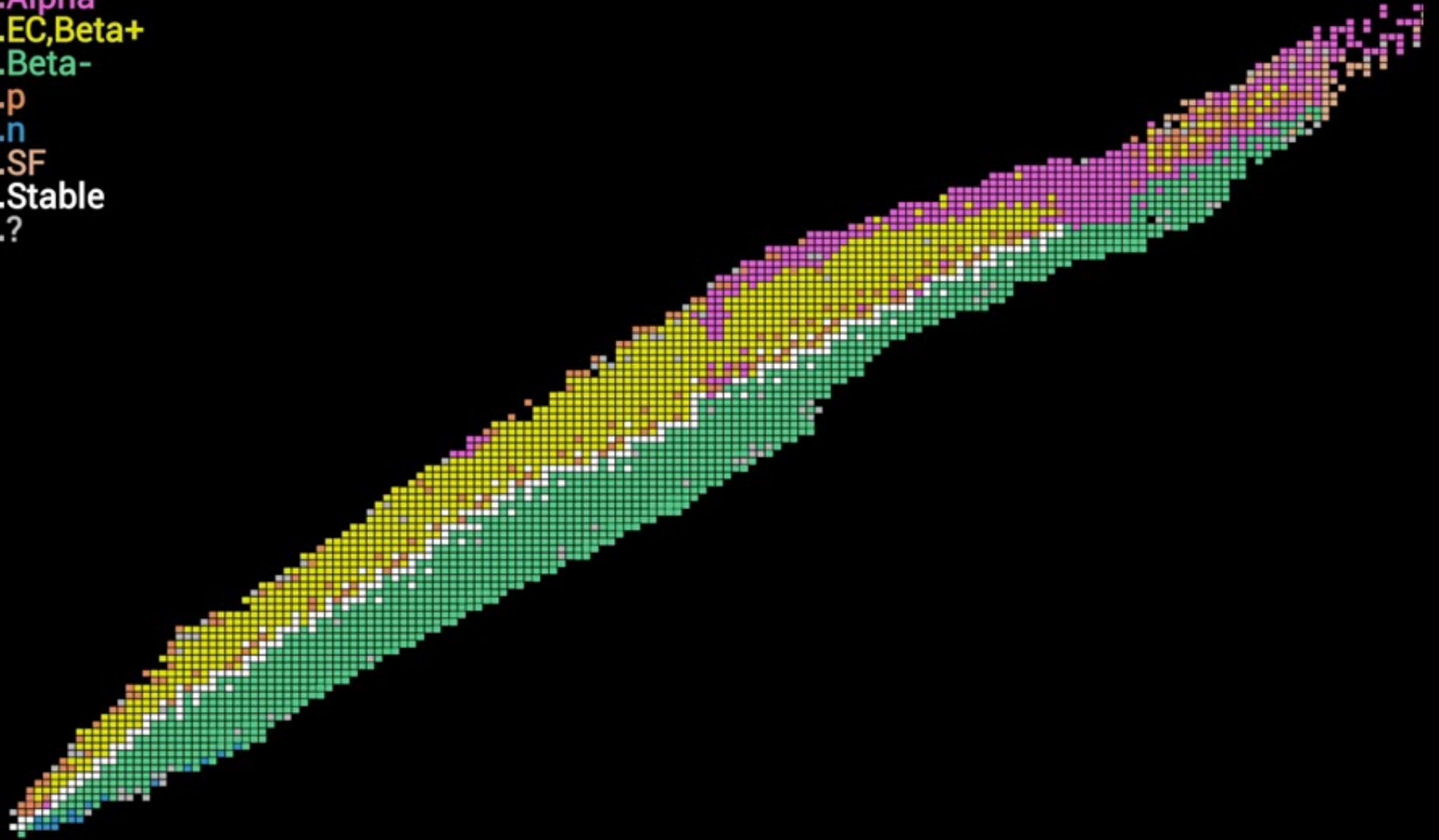
- Radiation: energy in motion through space
 - particulate vs. electromagnetic
- Particulate: have mass (charge) and velocity
 - (velocity proportional to energy)
 - examples: α , β , protons, neutrons
- Electromagnetic: no mass or charge, propagate as packets of energy (quanta or photons)



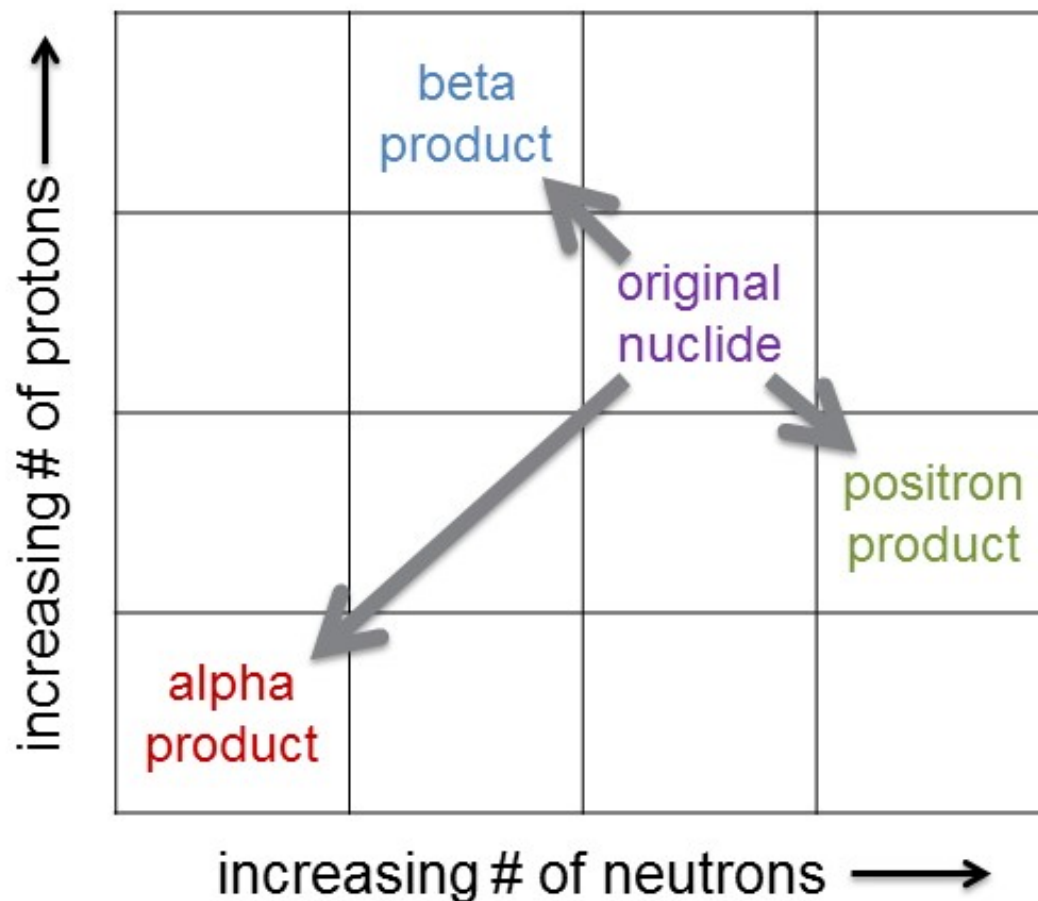
- Fission (F)
 - One heavy nucleus splits into two fragments plus 2-3 neutrons
- Isomeric Transition (IT)
 - Nuclear relaxation from an excited state to a ground state (^{99m}Tc to ^{99g}Tc)
 - Gamma-ray emission – EM emission based on ΔE
 - Internal conversion – electron ejection
- Alpha Decay (α)
 - Emission of a helium nucleus
- Beta Decay (β^- , β^+)
 - For $N/Z >$ stable nuclei: neutron converted to proton – electron is emitted
 - For $N/Z <$ stable nuclei: proton converted to neutron – positron is emitted
- Electron Capture (EC)
 - Orbital electron is captured by nucleus – proton converts to a neutron



.Alpha
.EC,Beta+
.Beta-
.p
.n
.SF
.Stable
.?



- The chart of nuclides can help you predict the outcome of nuclear reactions
- It is a map to understand the radioactive and/or nuclear behavior of nuclides

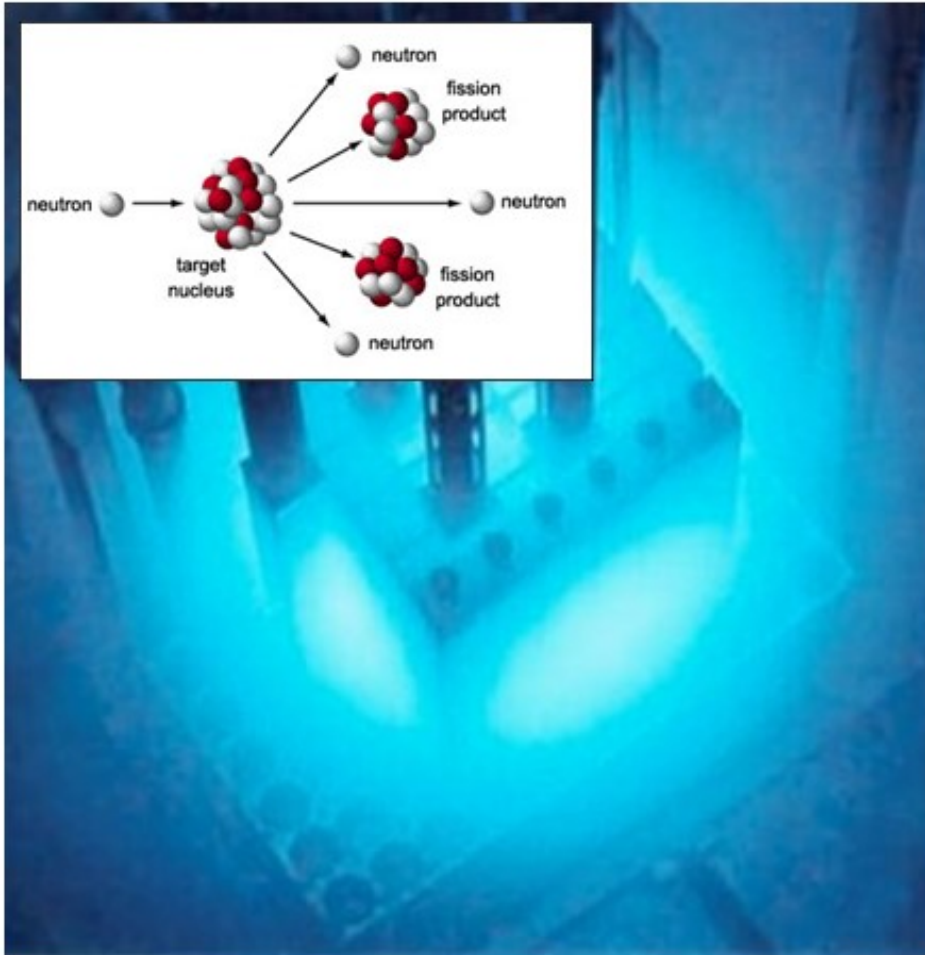




Nuclear reactor



Cyclotron



Thermal Neutron Fission of U-235

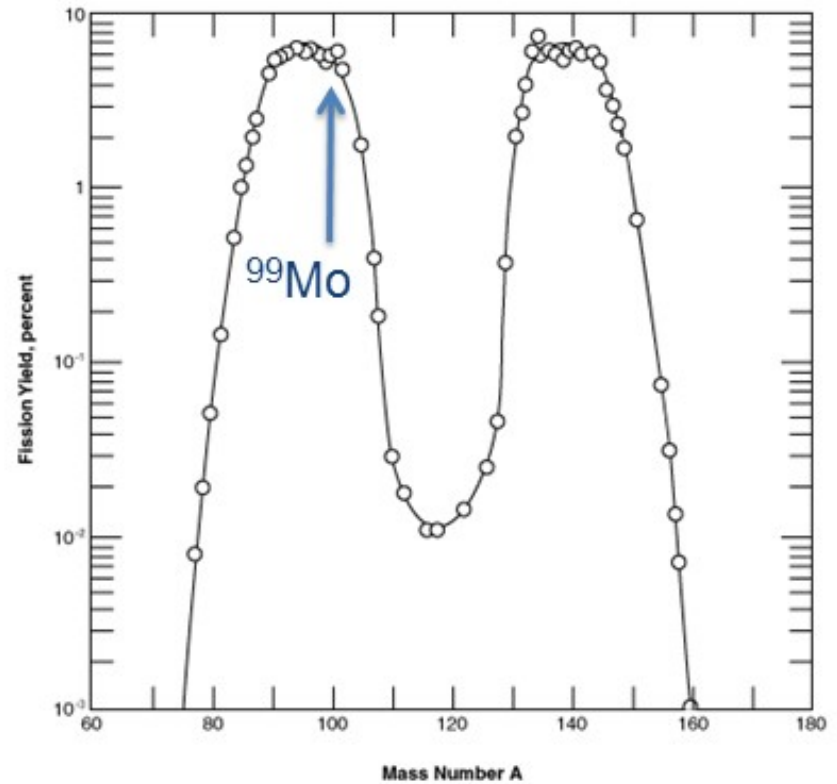
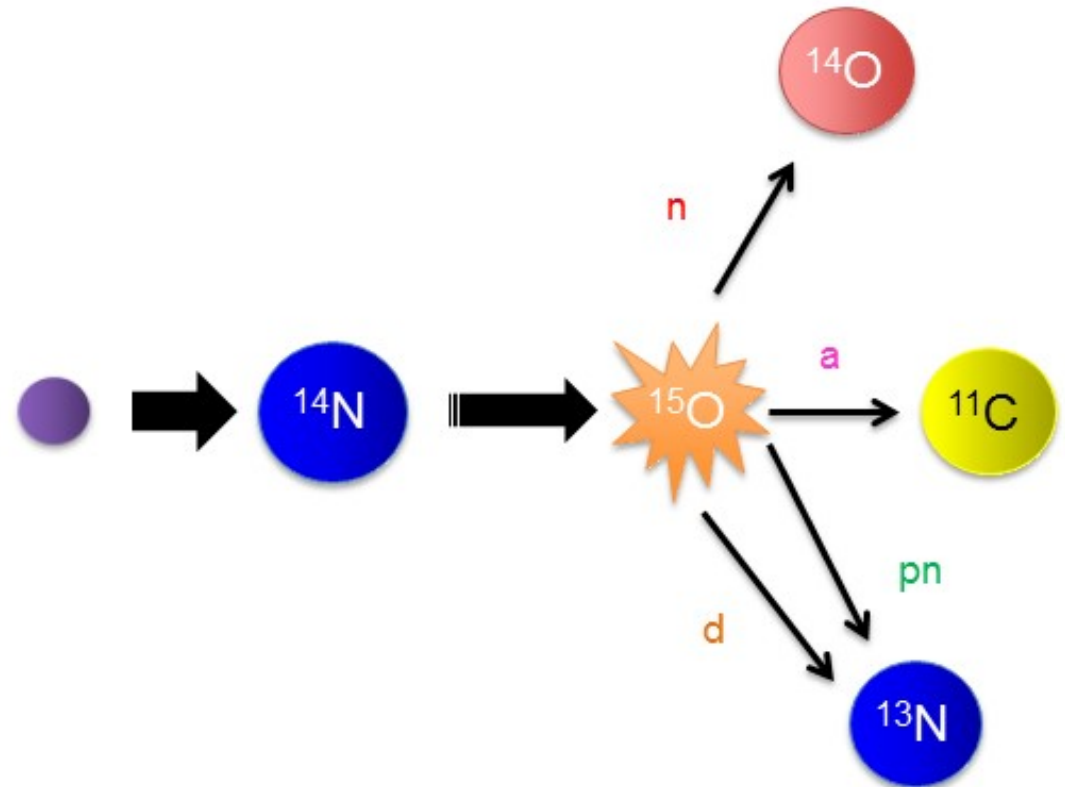
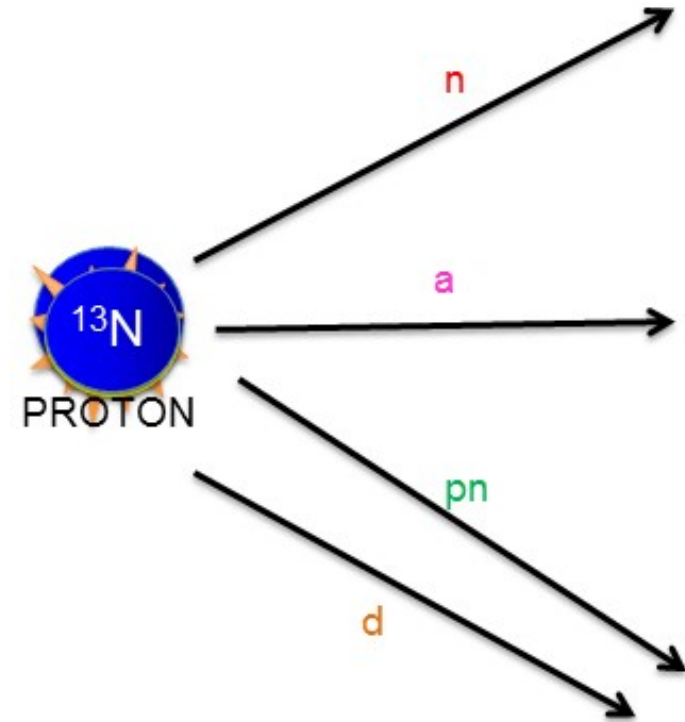
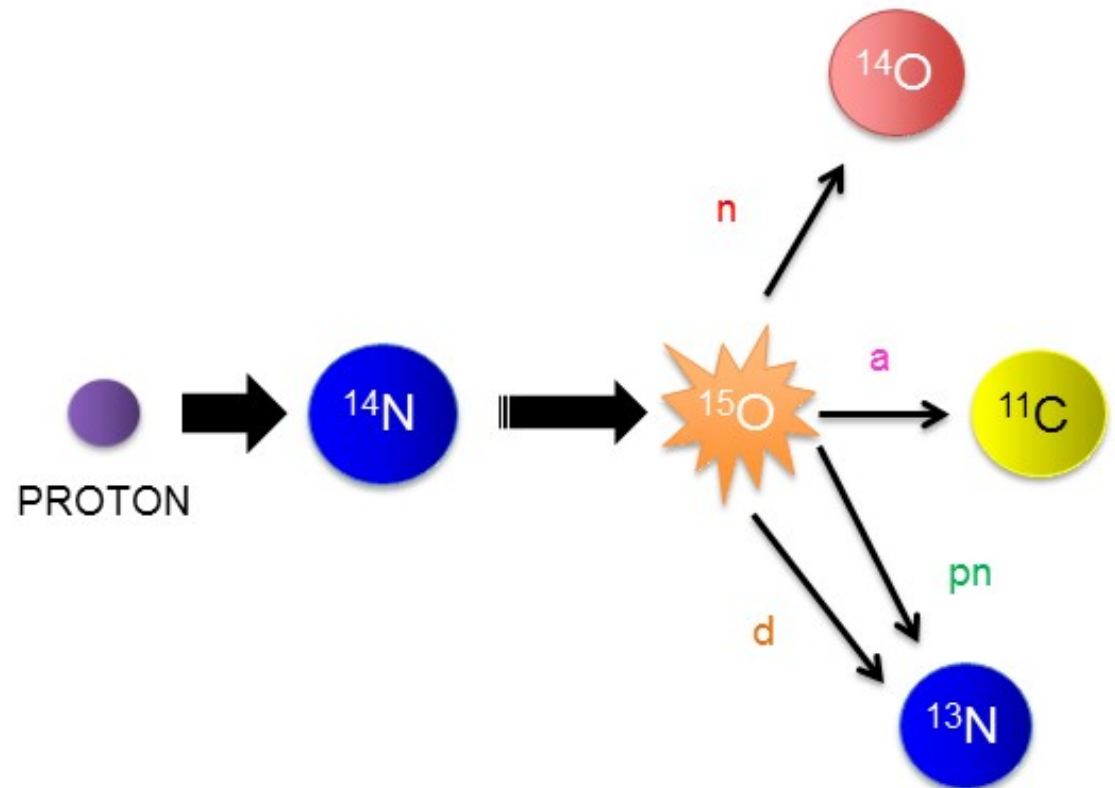


image from www.uwaterloo.ca

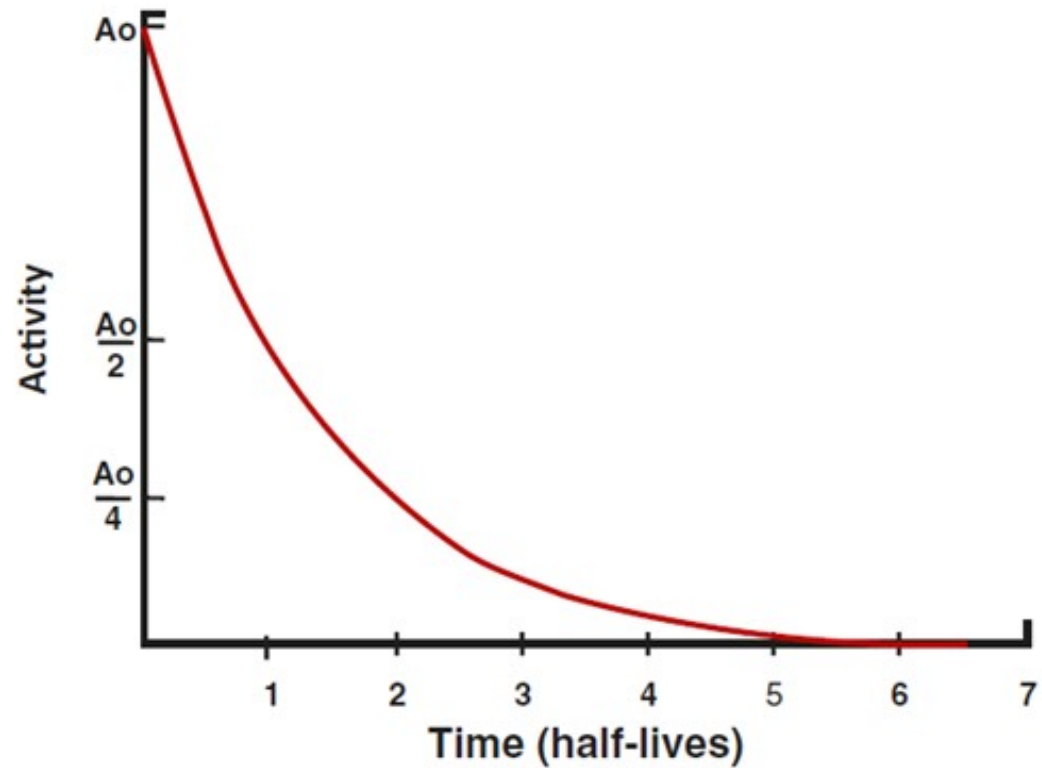






$$A = N\lambda$$

$$\lambda = \frac{\ln 2}{t_{1/2}}$$



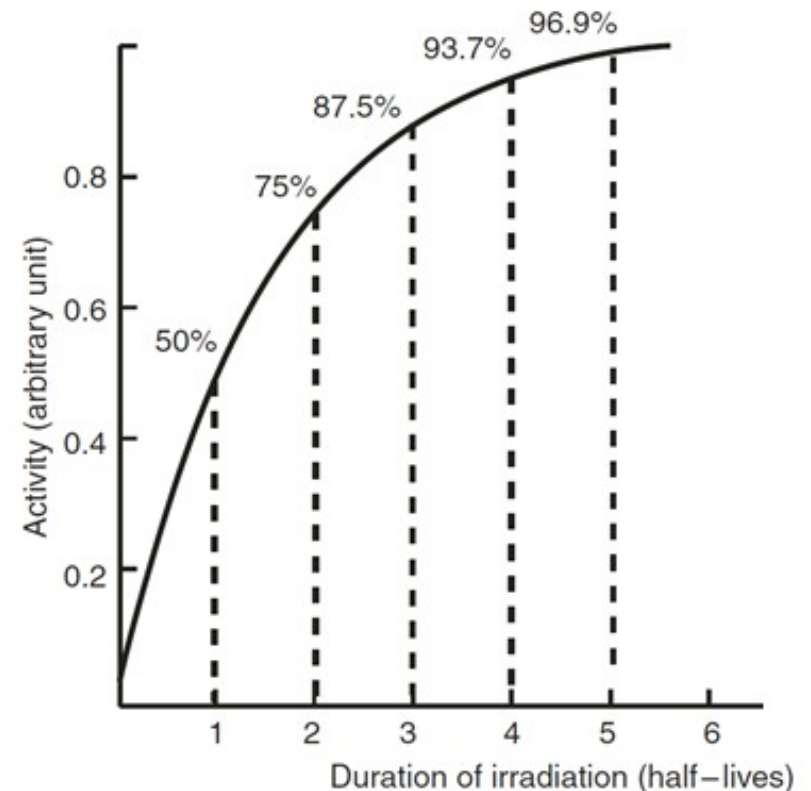
3 key cyclotron parameters

Beam intensity, beam energy, irradiation time

$$A = IN\sigma(1 - e^{-\lambda t})$$

density, isotopic enrichment

2 key target parameters





$^{68}\text{Ge}/^{68}\text{Ga}$
(271 d, 68 min)

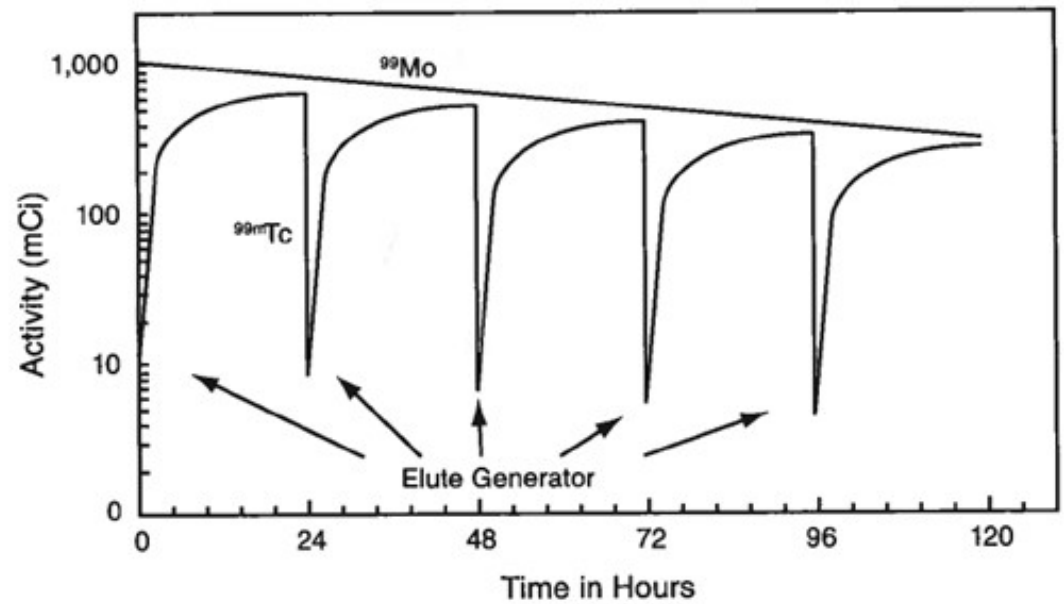
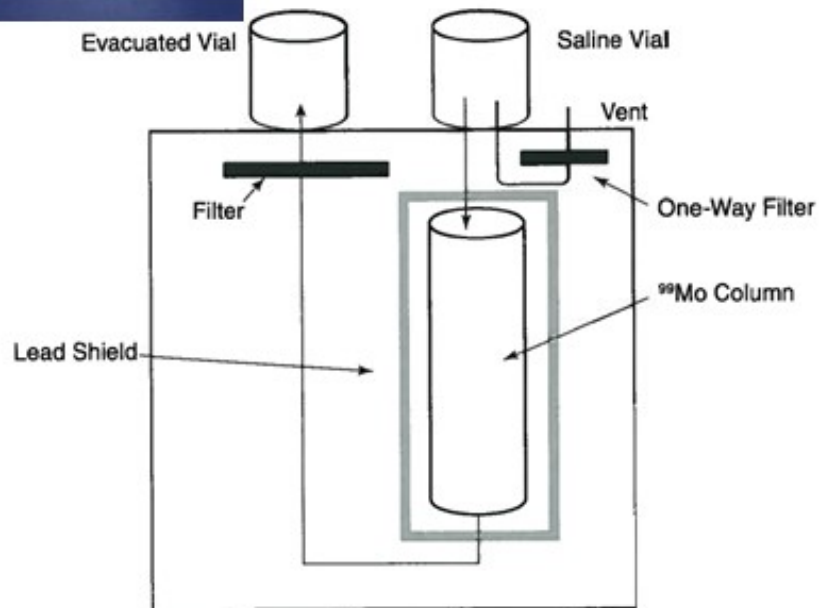


$^{82}\text{Sr}/^{82}\text{Rb}$
(25.4 d, 1.3 min)

- Transportable,
- Easy to use

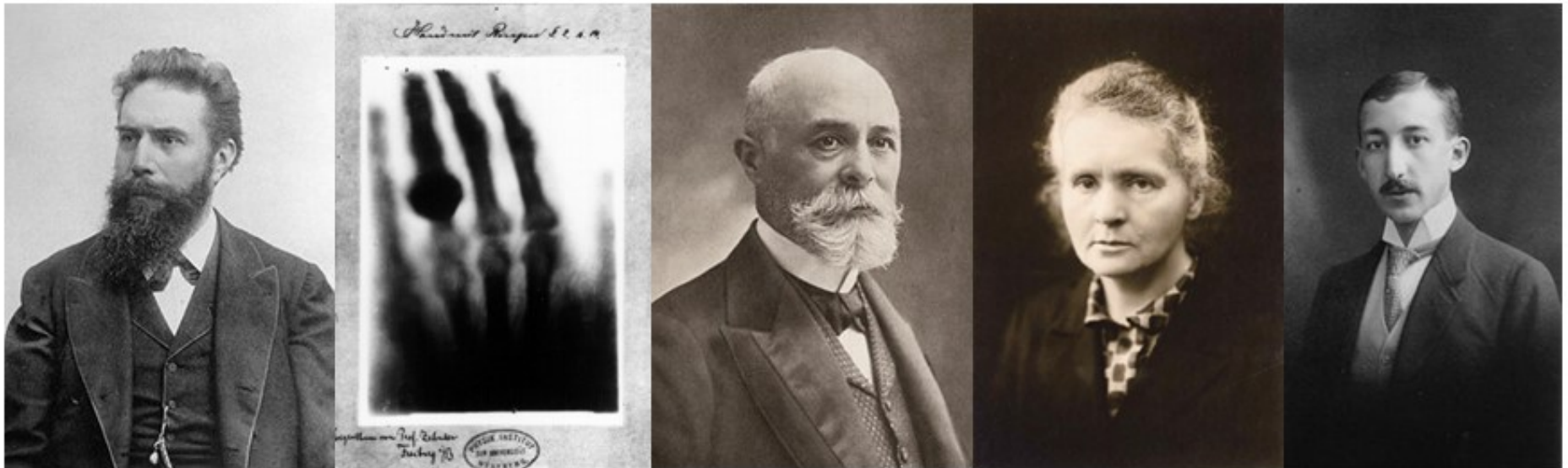


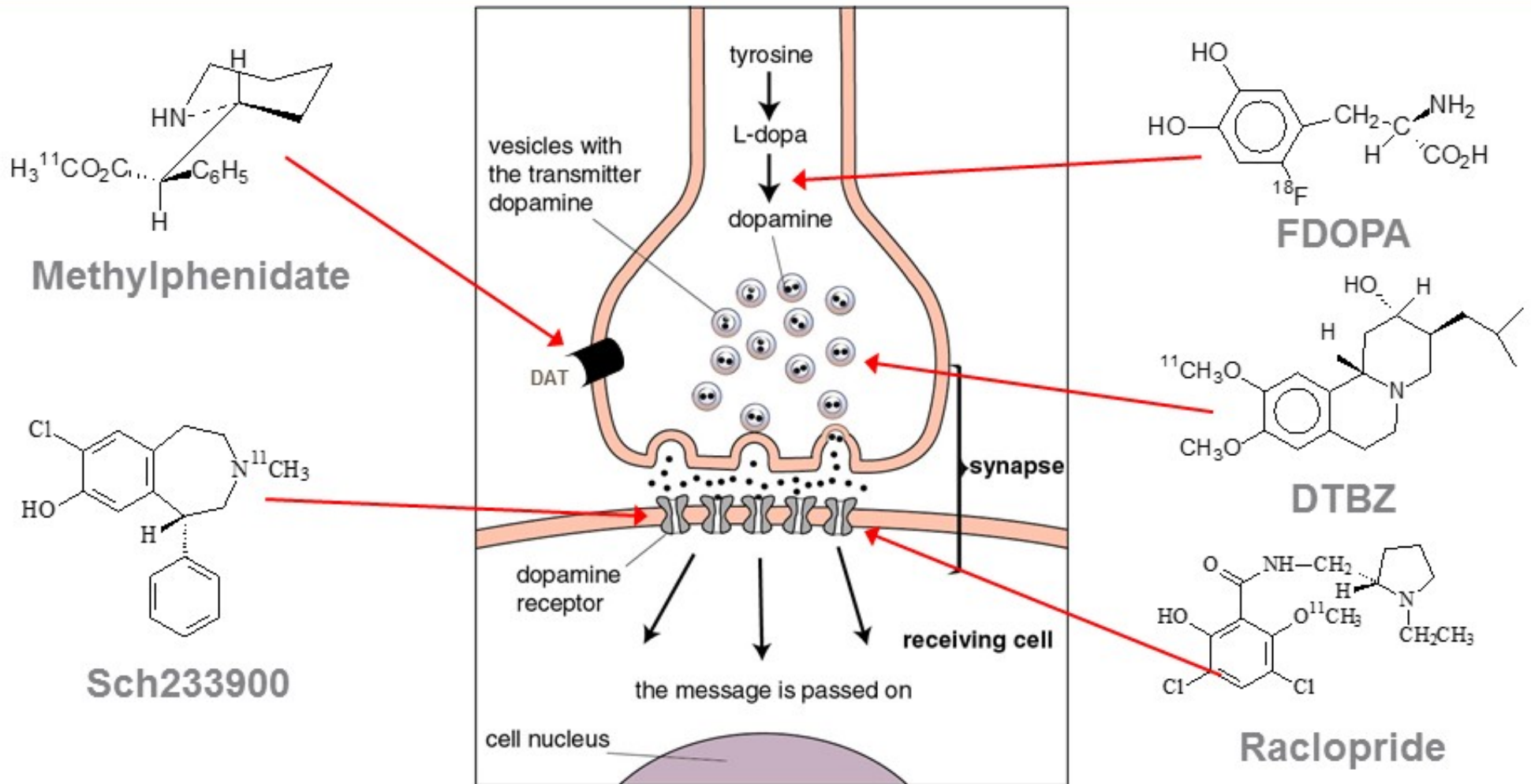
$^{99}\text{Mo}/^{99\text{m}}\text{Tc}$
(66 hr, 6 hr)

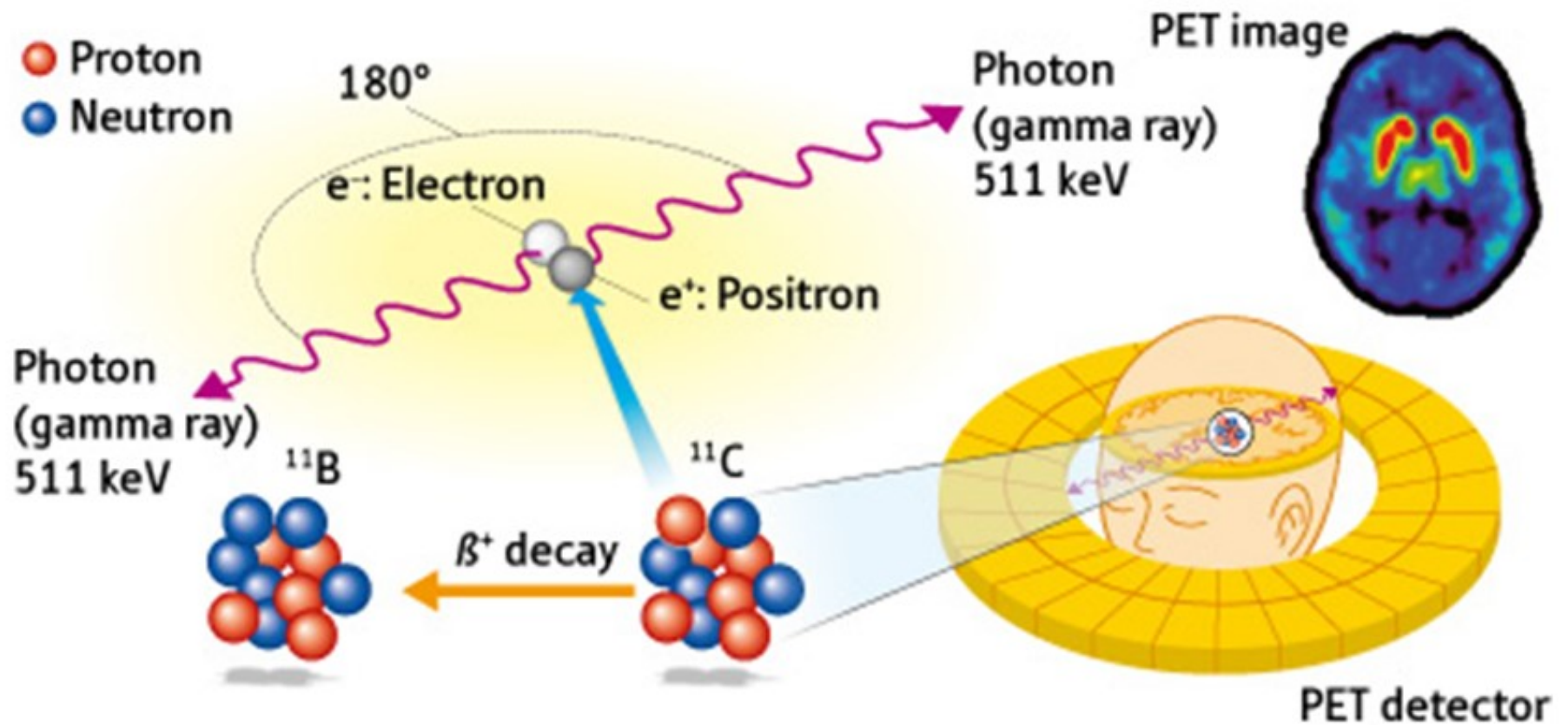


- Tc-99m is “milked” from the generator
- Tc-99m is tagged to tracers and then injected into the patient

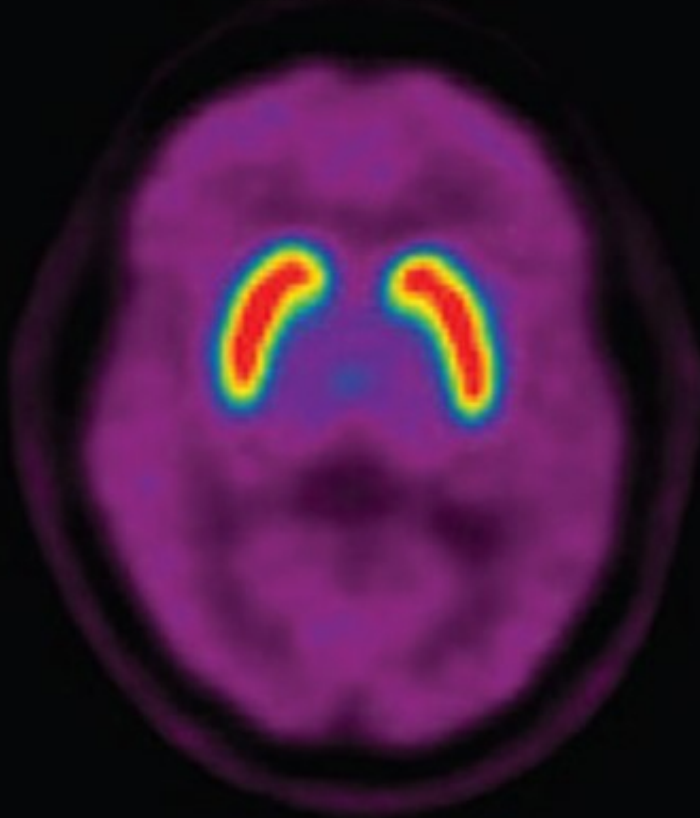
- 1895: Roentgen discovered 'penetrating rays", aka X-rays (Nobel Prize 1901)
- 1896: Becquerel discovered radioactivity (shared Nobel Prize 1903)
- 1898: M. Curie discovered radium, radioactivity is named (Nobel Prize 1903)
- 1911: de Hevesy used isotopes as a tracer for the first time, established 'Tracer Principle' (Nobel Prize 1943)







Normal

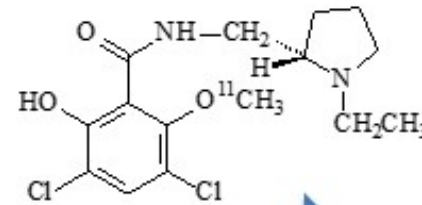
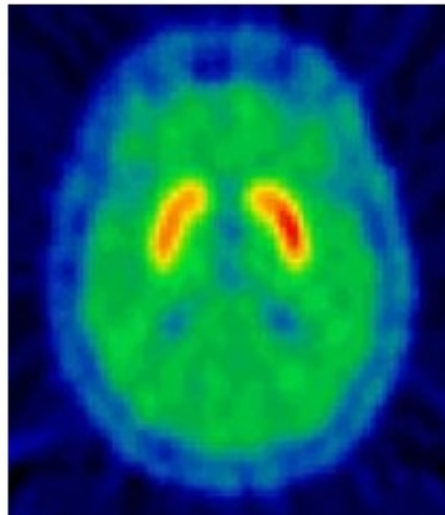


Parkinson's

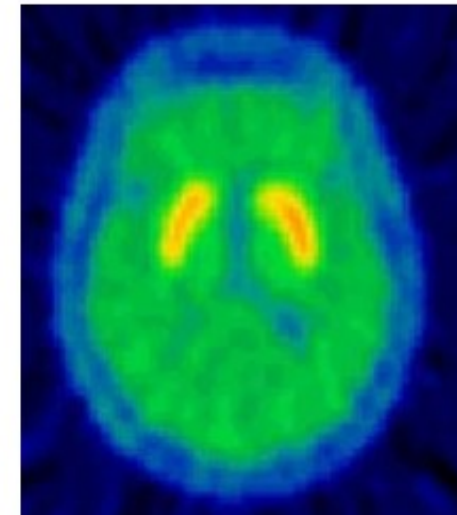




“...the act of receiving any treatment may, in itself, be efficacious because of expectation of benefit.”



When told they had a **possibility** of being given drug of benefit



Parkinson's patient brain scan showing

^{11}C -raclopride accumulation

First demonstration of neurochemical effect of placebo

R. de la Fuente-Fernandez et al. Science 2001, 293, 1164.



1 mole = 60,200,000,000,000,000,000,000 atoms/molecules

1 mole of water (H_2O) = 18 g (18 mL)

Typical radiopharmaceutical = dose 0.000000001 moles

Equivalent dose of water = 18 ng

PET Isotopes
SPECT Isotopes

E
Element Denotes an element with isotopes suitable for both PET and SPECT

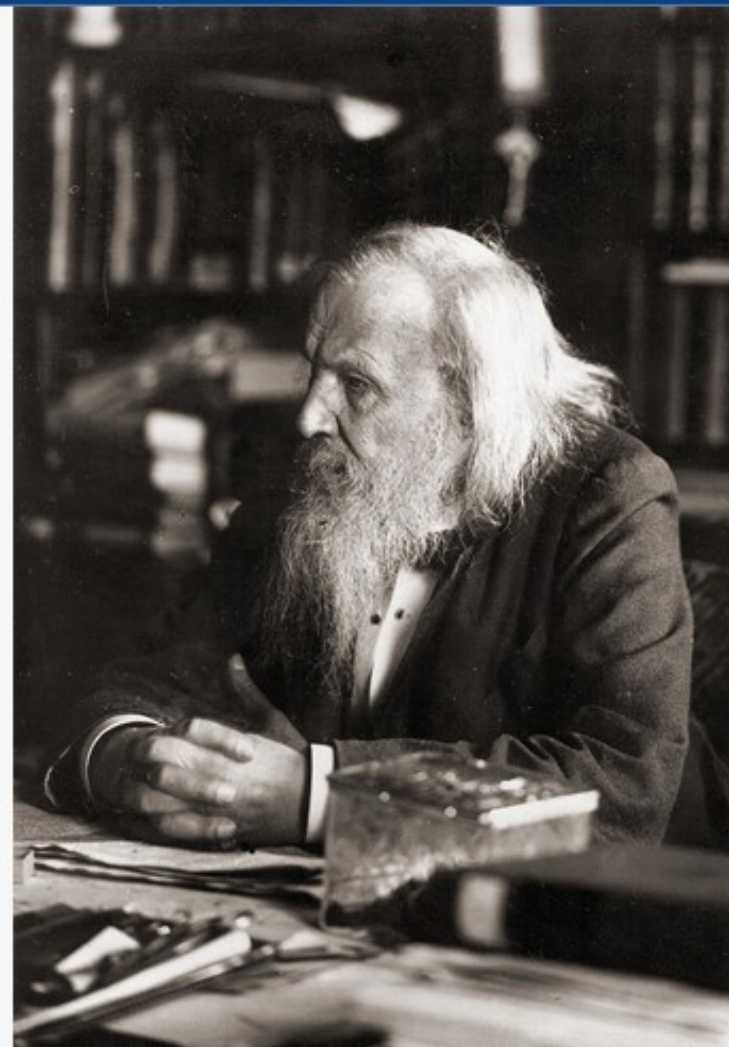
E
Element Denotes an element with multiple isotopes with different physical half-lives

1 H <small>Hydrogen</small>																	2 He <small>Helium</small>						
3 Li <small>Lithium</small>	4 Be <small>Beryllium</small>																	5 B <small>Boron</small>	6 C <small>Carbon</small>	7 N <small>Nitrogen</small>	8 O <small>Oxygen</small>	9 F <small>Fluorine</small>	10 Ne <small>Neon</small>
11 Na <small>Sodium</small>	12 Mg <small>Magnesium</small>																	13 Al <small>Aluminum</small>	14 Si <small>Silicon</small>	15 P <small>Phosphorus</small>	16 S <small>Sulfur</small>	17 Cl <small>Chlorine</small>	18 Ar <small>Argon</small>
19 K <small>Potassium</small>	20 Ca <small>Calcium</small>	21 Sc <small>Scandium</small>	22 Ti <small>Titanium</small>	23 V <small>Vanadium</small>	24 Cr <small>Chromium</small>	25 Mn <small>Manganese</small>	26 Fe <small>Iron</small>	27 Co <small>Cobalt</small>	28 Ni <small>Nickel</small>	29 Cu <small>Copper</small>	30 Zn <small>Zinc</small>	31 Ga <small>Gallium</small>	32 Ge <small>Germanium</small>	33 As <small>Arsenic</small>	34 Se <small>Selenium</small>	35 Br <small>Bromine</small>	36 Kr <small>Krypton</small>						
37 Rb <small>Rubidium</small>	38 Sr <small>Strontium</small>	39 Y <small>Yttrium</small>	40 Zr <small>Zirconium</small>	41 Nb <small>Niobium</small>	42 Mo <small>Molybdenum</small>	43 Tc <small>Technetium</small>	44 Ru <small>Ruthenium</small>	45 Rh <small>Rhodium</small>	46 Pd <small>Palladium</small>	47 Ag <small>Silver</small>	48 Cd <small>Cadmium</small>	49 In <small>Indium</small>	50 Sn <small>Tin</small>	51 Sb <small>Antimony</small>	52 Te <small>Tellurium</small>	53 I <small>Iodine</small>	54 Xe <small>Xenon</small>						
55 Cs <small>Cesium</small>	56 Ba <small>Barium</small>	57-70 Lanthanides	71 Lu* <small>Lutetium</small>	72 Hf <small>Hafnium</small>	73 Ta <small>Tantalum</small>	74 W <small>Tungsten</small>	75 Re* <small>Rhenium</small>	76 Os <small>Osmium</small>	77 Ir <small>Iridium</small>	78 Pt <small>Platinum</small>	79 Au <small>Gold</small>	80 Hg <small>Mercury</small>	81 Tl <small>Thallium</small>	82 Pb <small>Lead</small>	83 Bi <small>Bismuth</small>	84 Po <small>Polonium</small>	85 At <small>Astatine</small>	86 Rn <small>Radon</small>					
87 Fr <small>Francium</small>	88 Ra <small>Radium</small>	89-102 Actinides	103 Lr <small>Lawrencium</small>	104 Rf <small>Rutherfordium</small>	105 Db <small>Dubnium</small>	106 Sg <small>Seaborgium</small>	107 Bh <small>Bohrium</small>	108 Hs <small>Hassium</small>	109 Mt <small>Mendelevium</small>	110 Ds <small>Darmstadtium</small>	111 Rg <small>Roentgenium</small>	112 Cn <small>Copernicium</small>	113 Uut <small>Ununtrium</small>	114 Fl <small>Flerovium</small>	115 Uup <small>Ununpentium</small>	116 Lv <small>Livermorium</small>	117 Uus <small>Ununseptium</small>	118 Uuo <small>Ununoctium</small>					

BM Zeglis et al. Inorg. Chem. 2014, 53, 1880

Mendeleev's Periodic Table of 1871¹

	I --- R ₂ O	II --- RO	III --- R ₂ O ₃	IV RH ₄ RO ₂	V RH ₃ R ₂ O ₃	VI RH ₂ RO ₃	VII RH R ₂ O ₇	VIII --- RO ₄
1	H 1							
2	Li 7	Be 9.4	B 11	C 12	N 14	O 16	F 19	
3	Na 23	Mg 24	Al 27.3	Si 28	P 31	S 32	Cl 35.5	
4	K 39	Ca 40	?	Ti 48	V 51	Cr 52	Mn 55	Fe, Co, Ni, Cu 56, 59, 59, 63
5	Cu 63	Zn 65	?	?	As 75	Se 78	Br 80	
6	Rb 85	Sr 87	? Yt 88	Zr 90	Nb 94	Mo 96	? 100	Ru, Rh, Pd, Ag 104, 104, 106, 108
7	Ag 108	Cd 112	In 113	Sn 118	Sb 122	Te 125	I 127	
8	Cs 133	Ba 137	? Di 138	? Ce 140	?	?	?	?, ?, ?, ?
9	?	?	?	?	?	?	?	
10	?	?	? Er 178	?? La 180	Ta 182	W 184	?	Os, Ir, Pt, Au 195, 197, 198, 199
11	Au 199	Hg 200	Tl 204	Pb 207	Bi 208	?	?	
12	?	?	?	Th 231	?	U 240	?	



1 H																	2 He
3 Li	4 Be											5 B	6 C	7 N	8 O	9 F	10 Ne
11 Na	12 Mg											13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	(43)	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
55 Cs	56 Ba	57-71 La-Lu	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	(85)	86 Rn
(87)	88 Ra	89 Ac	90 Th	91 Pa	92 U	(93)	(94)	(95)	(96)	(97)	(98)	(99)	(100)				

57 La	58 Ce	59 Pr	60 Nd	(61)	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb	71 Lu
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Pre-World War II periodic table predicted erroneous positions for transuranic elements

By 1944, two new transuranium elements had been placed in an "uranide" group

55 Cs	56 Ba	57-71 La-Lu	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	
87 Fr	88 Ra	89 Ac	90 Th	91 Pa	92-104 U-(106)					
					92 U	93 Np	94 Pu	(95)	(96)	(106)





- One of the first women in Germany to study chemistry
- PhD 1921: positions were largely unpaid
- 1925: published a paper claiming discovery of elements 75 (Rhenium) and 43 (Technetium, aka Masurium)



- 1934: challenged Enrico Fermi's (Nobel Prize 1938) assertion of discovering element 93
 - Published her hypothesis that *"it is conceivable that the nucleus breaks up into several large fragments, which would of course be isotopes of known elements but would not be neighbors of the irradiated element"*
- In other words, she correctly identified nuclear fission years before its official 'discovery' in 1938
- Nominated for Nobel Prize 3 times
 - she never won

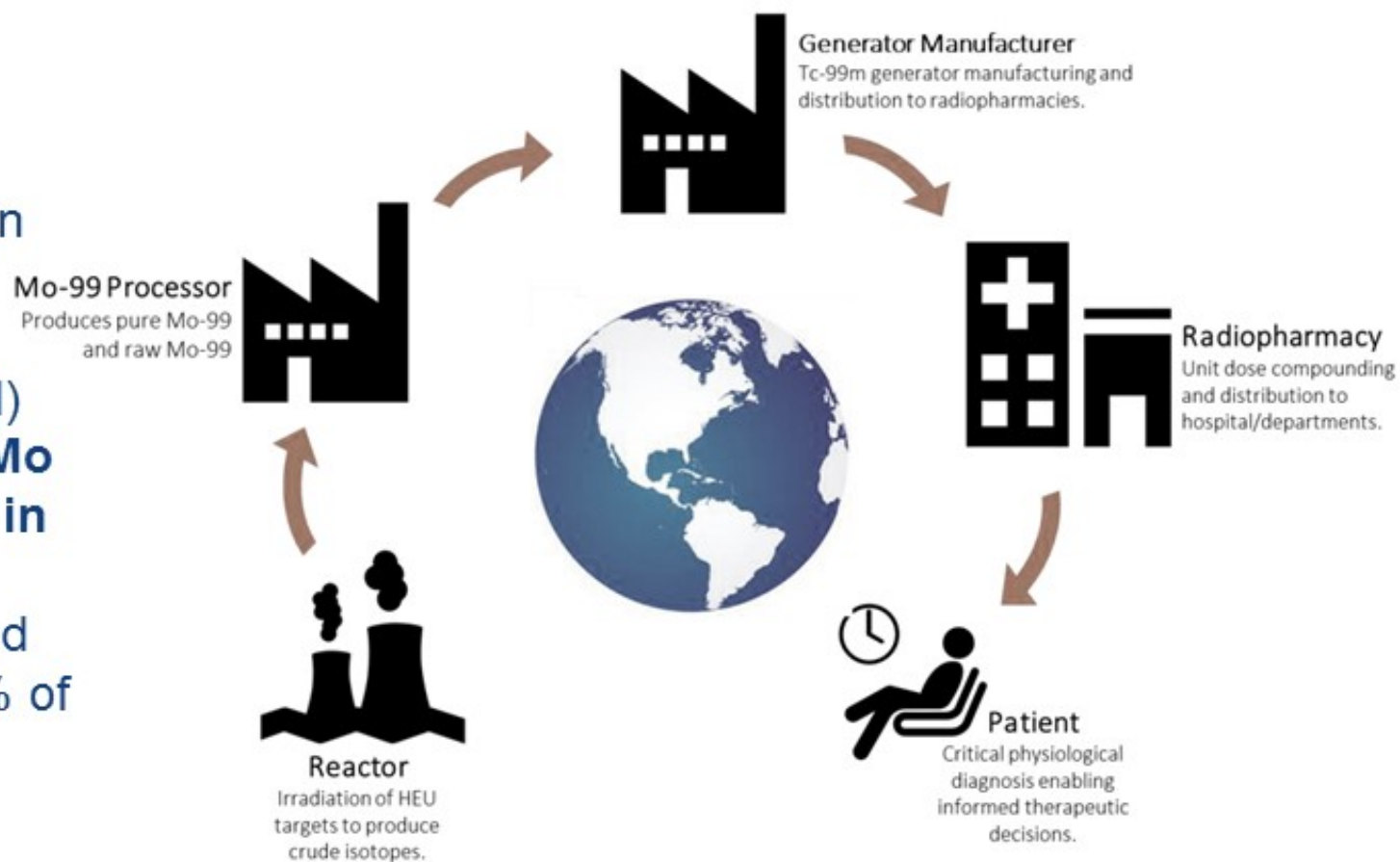


- BNL, 1950s: Walter Tucker and Margaret Green discovered ^{99m}Tc as a 'contaminant' and developed the first $^{99}\text{Mo}/^{99m}\text{Tc}$ generator (1957)
- BNL, 1960: Powell Richards, newly in charge of isotope production, presented the 1st paper at the 7th International Electronic and Nuclear Symposium
- Richards met with Paul Harper on the flight to Rome and spent the flight "extolling the merits of ^{99m}Tc "
- By 1966, BNL backed out of generator production in favour of commercial suppliers

<p>43 (97.9072)</p> <p>Tc</p> <p>Technetium</p> <p>$[\text{Kr}]4d^55s^2$</p>	
	

- Single point of failure supply chain; aging infrastructure

- Global demand for $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ ~40 million doses/yr
- 76,000 scans/day
 - (>1 scan/second)
- **30-40% of global ^{99}Mo obtained from NRU in Canada**
- Overall, 5 gov't owned reactors supply >95% of global demand



Reactor	Location	Target	Operating Days	Weekly Capacity (6-day Ci)	Year of Commissioning
BR-2	Belgium	HEU	140	7,800	1961
HFR	Netherlands	HEU	280	4,680	1961
LVR-15	Czech Republic	HEU	210	2,800	1957
MARIA	Poland	HEU	210	2,200	1974
NRU	Canada	HEU	280	4,680	1957
OPAL	Australia	LEU	300	1,000	2007
OSIRIS	France	HEU	182	2,400	1966
RA-3	Argentina	LEU	336	400	1967
SAFARI-1	South Africa	LEU	305	3,000	1965



- Decentralized Production

- ^{99m}Tc locally produced, locally used, competitively priced
- Redundant supply to avoid widespread shortages
- Fits with existing radiopharmacy distribution model
- Complementary to:
 - other medical isotopes produced by cyclotrons (^{18}F)
 - other sources of ^{99m}Tc

Some Chemical Properties of Element 43

C. PERRIER AND E. SEGRÈ,
Royal University, Palermo, Italy

(Received June 30, 1937)

1. INTRODUCTION

PROFESSOR E. O. LAWRENCE gave us a piece of molybdenum plate which had been bombarded for some months by a strong deuteron beam in the Berkeley cyclotron. The molyb-

J Chem Phys 1937; 5: 712



Nuclear Isomerism in Element 43

We wish to report briefly an interesting case of isomerism which has appeared during an investigation of the short-lived radioactive isotopes of element 43. The irradiation of molybdenum with deuterons or slow neutrons produces a radioactive molybdenum isotope with a half-life of 65 hours which emits electrons with an upper energy limit of approximately 1 Mev. (This molybdenum activity has also been reported recently by Sagane, Kojima, Miyamoto and Ikawa.)¹ This molybdenum decays into a second activity which has a half-life of 6 hours and which emits only a line spectrum of electrons. Since the molybdenum emits electrons, the daughter activity must be ascribed to element 43;

E. SEGRÈ
G. T. SEABORG

Radiation Laboratory,
Department of Physics (E.S.),
Department of Chemistry (G.T.S.),
University of California,
Berkeley, California,
October 14, 1938.

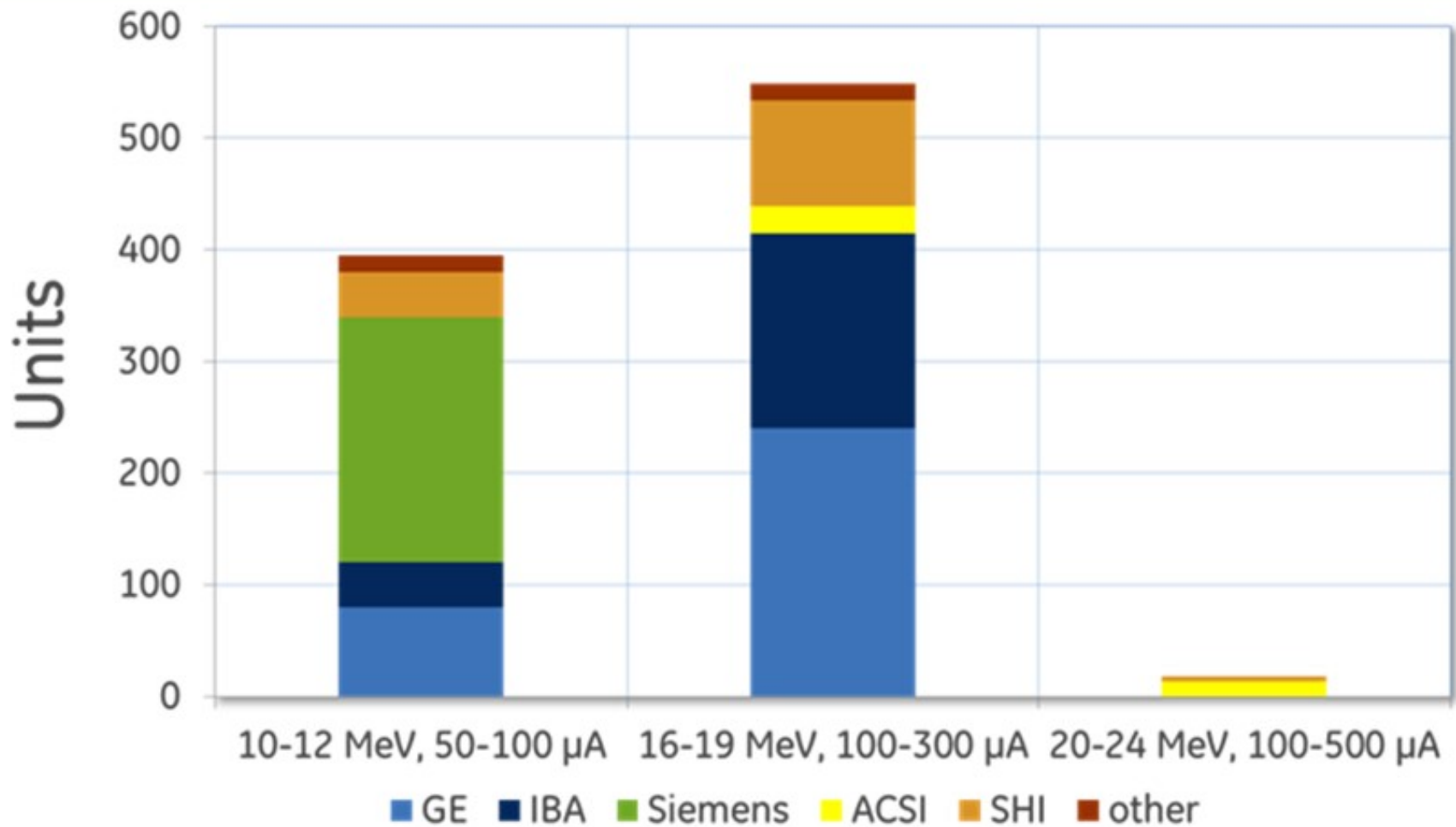
¹ Sagane, Kojima, Miyamoto and Ikawa, *Phys. Rev.* **54**, 542 (1938).

² Kalbfell, *Phys. Rev.* **54**, 543 (1938).

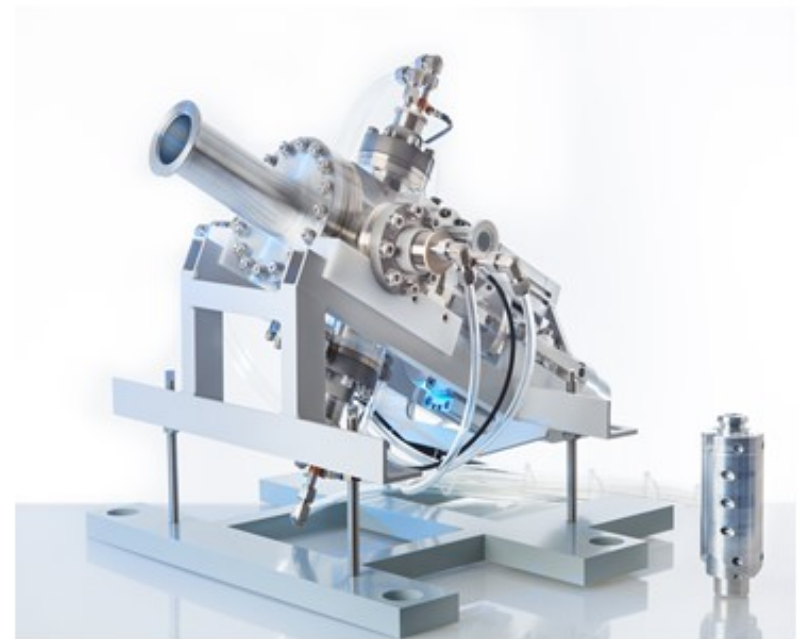
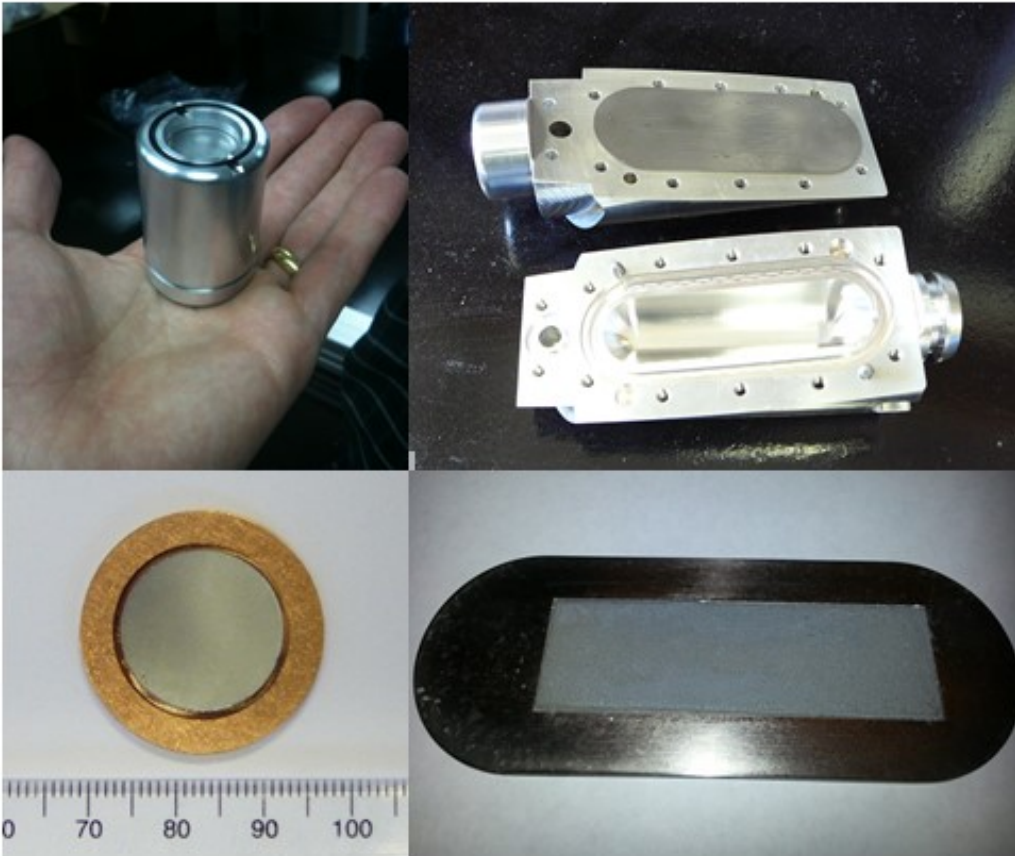
³ Pontecorvo, *Phys. Rev.* **54**, 542 (1938).

Phys Rev 1938; 772

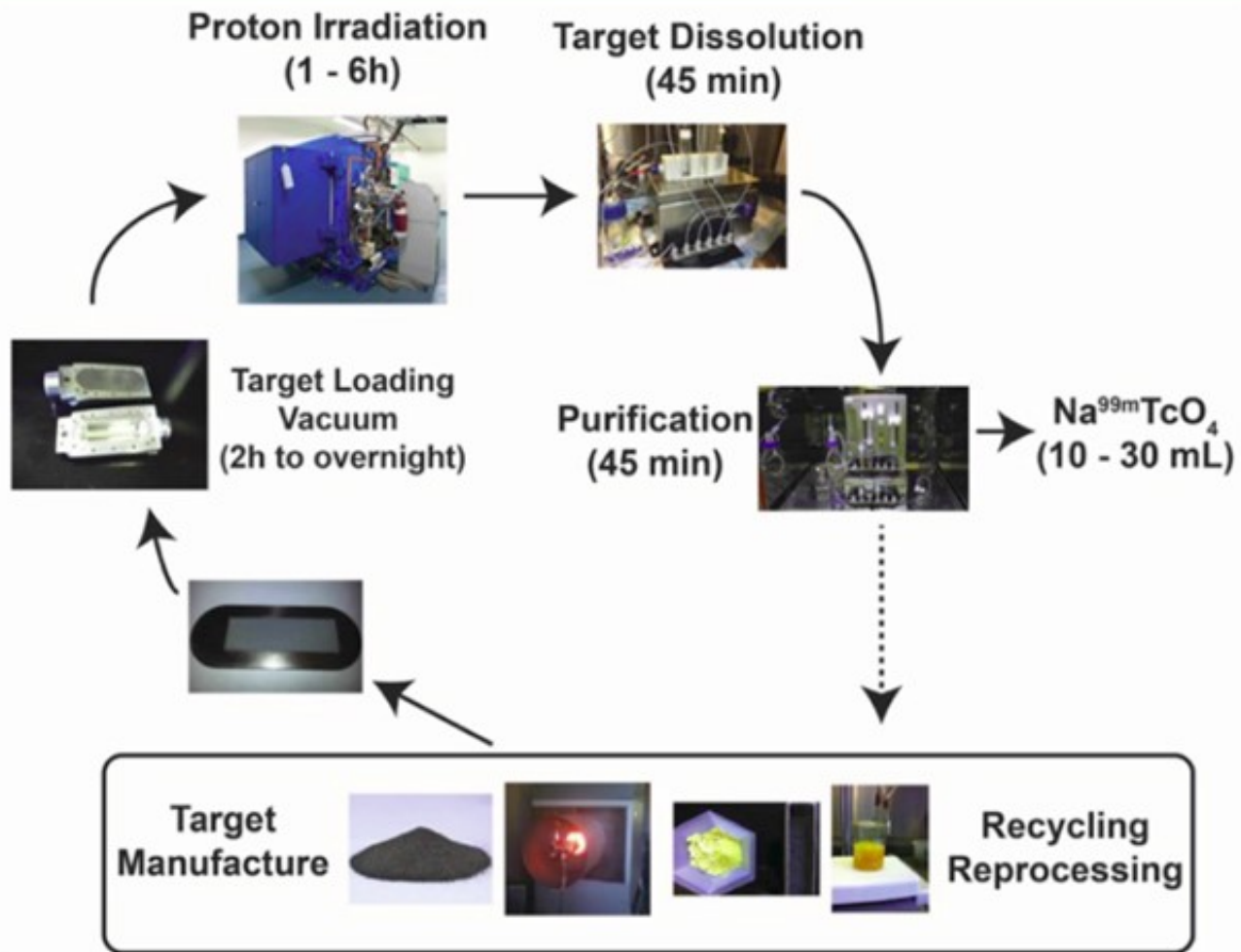
J Beaver, H Hupf – Miami, 1971 (*J. Nucl. Med.* 1971, 12, 739-741)











- Production yields of ^{99m}Tc
 - GE **PETTrace** (16.5 MeV, 130 μA): **4.7 Ci** in 6 hrs
 - ACSI **TR19** (18 MeV, 240 μA): **13.9 Ci** in 6 hrs
 - ACSI **TR30** (24 MeV, 450 μA): **~32 Ci** in 6 hrs
- Concurrent ^{18}F production demonstrated successfully
- Purification efficiency: **93%**
- ^{99}Mo recycling efficiency: **>95%**
- **Clinical trials currently underway**

- 2015: Awarded the Brockhouse Canada Prize for Interdisciplinary Research in Science and Engineering



Use of alpha- and beta-emitting nuclides to treat micro- and/or metastatic disease

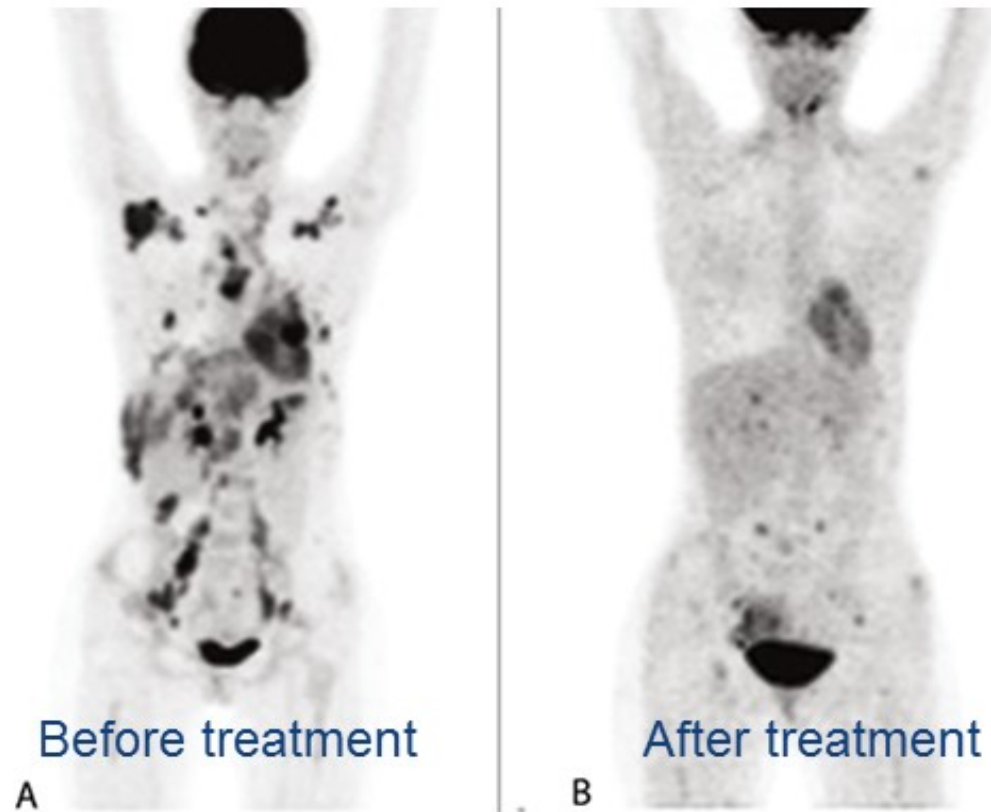
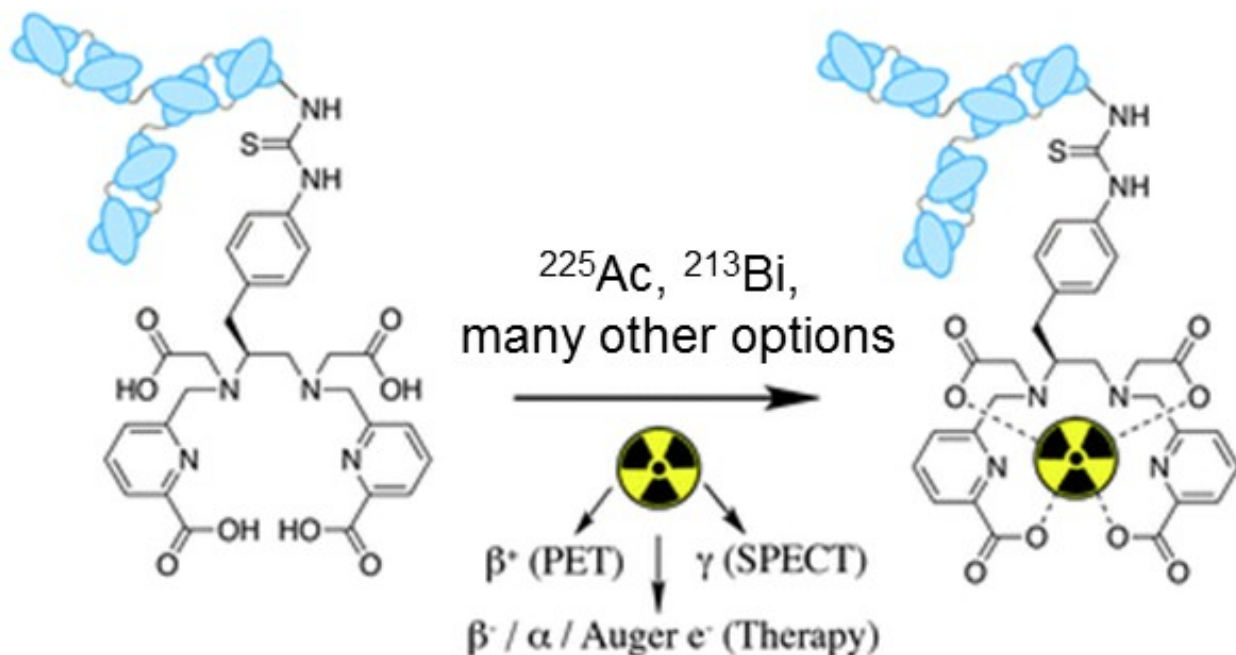


Image taken from:
CME Aug 2013 Vol. 31 (8), 292

Figure: [^{18}F]FDG scan of NHL patient A) before treatment B) after 2 treatments with ^{90}Y -Zevalin



Promising α -emitters:

^{211}At

^{225}Ac

$^{212-213}\text{Bi}$

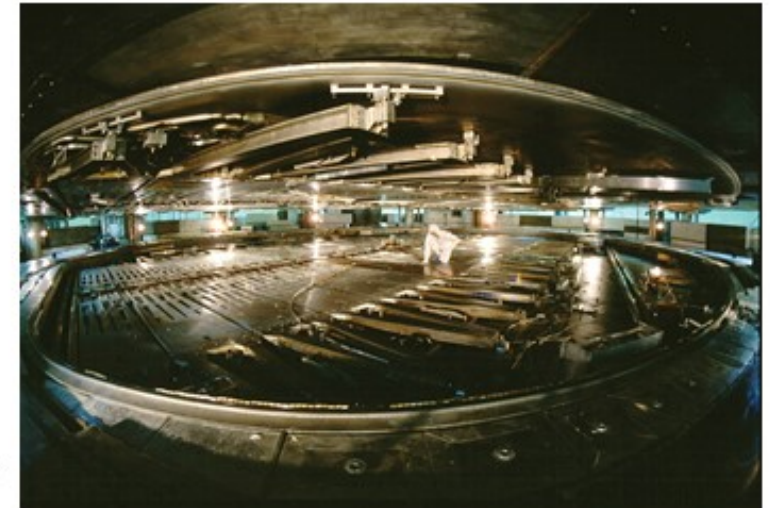
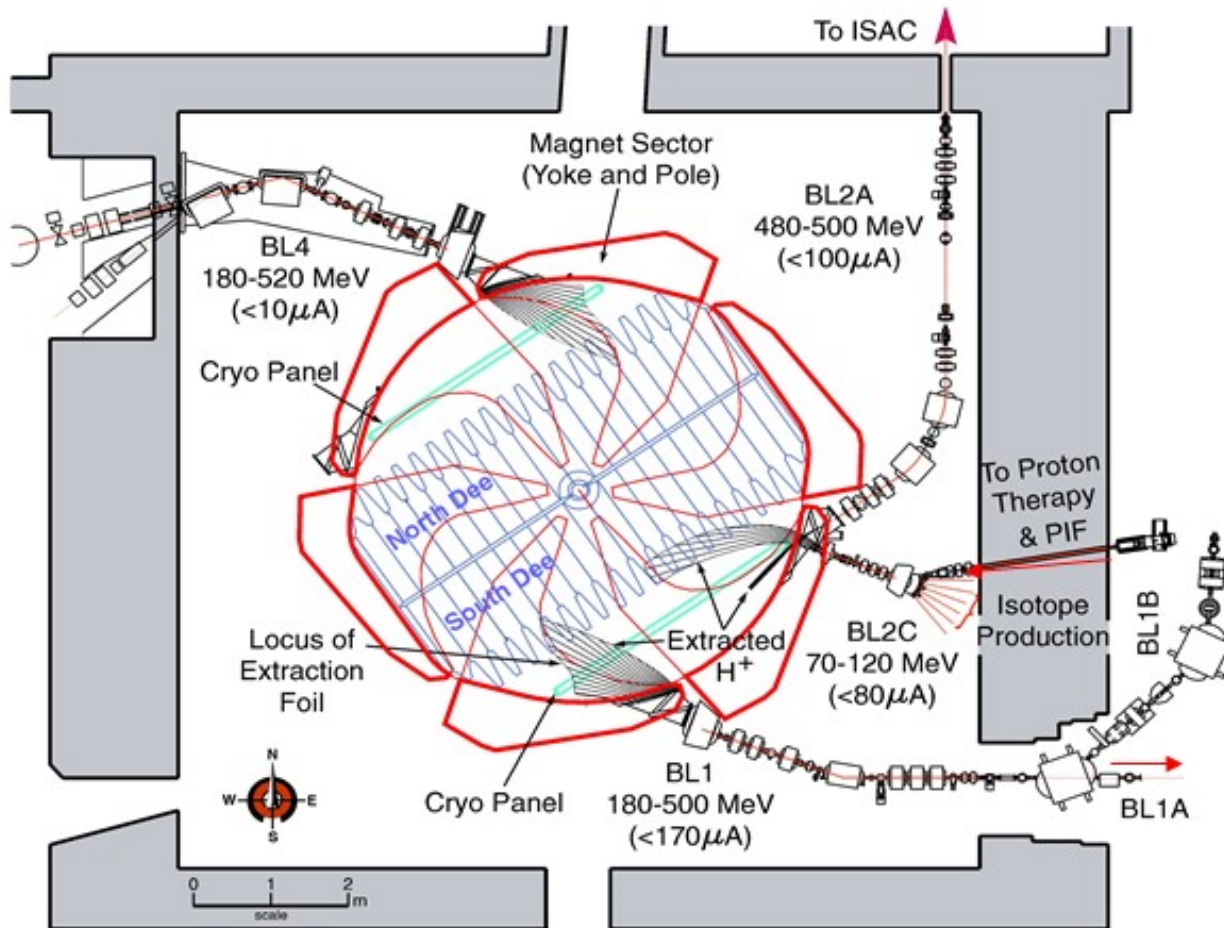
^{212}Pb

^{223}Ra

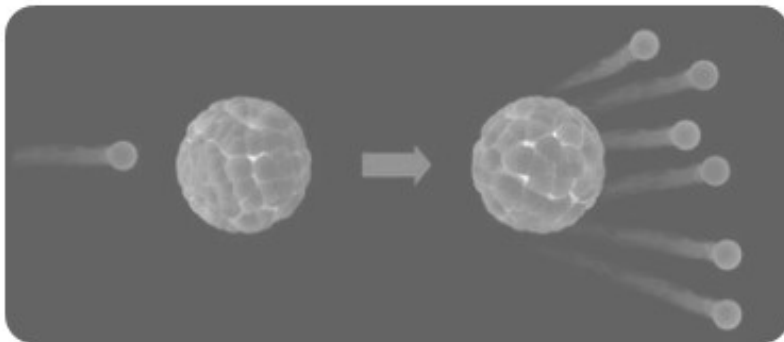
^{227}Th

^{149}Tb

Image taken from: E Price, C Orvig, *Chem. Soc. Rev.*, 2014,43, 260-290



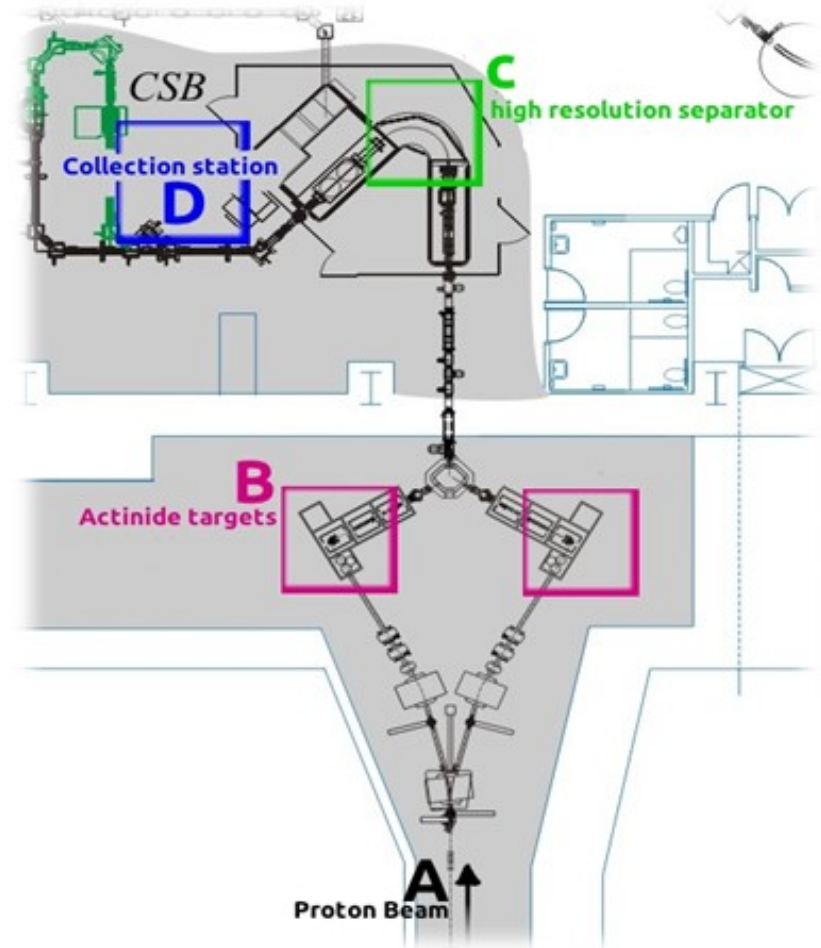
Isotope production via spallation of uranium, thorium:



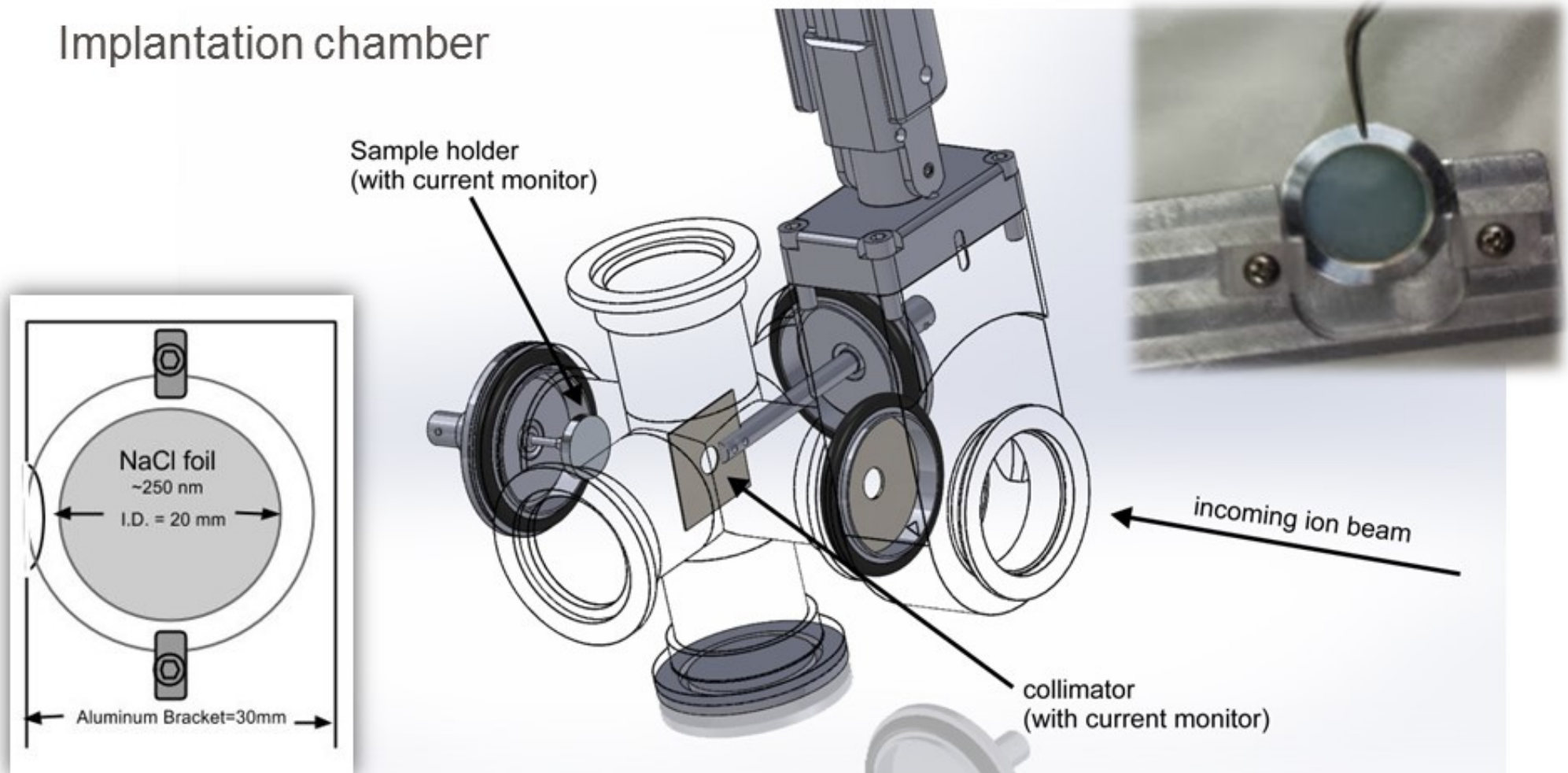
Implementation of ISOL technique

- ISOL = Isotope Separation On-Line
- Separate spallation products from uranium* carbide, thorium oxide, others

* using ^{238}U – non-enriched



Implantation chamber



The **A**dvanced **R**are **I**sotop**E** Laboratory will triple TRIUMF's isotope beam capacity

- Uses state-of-the-art, made-in-Canada super-conducting RF accelerator technology targets are designed to allow medical isotopes to be extracted alongside the experimental program
- Represents ~\$100 million investment (over 10 years) by federal and provincial governments; supported by 19 university partners from across Canada



ISAC (RIB linac)

ARIEL
(50 MeV
electron linac)

2 x TR30, CP42, TR13
H⁻ cyclotrons

500MeV
H⁻ cyclotron

New addition: TR24; to be installed





Canada's national laboratory
for particle and nuclear physics
and accelerator-based science

TRIUMF: Alberta | British Columbia | Calgary |
Carleton | Guelph | Manitoba | McGill | McMaster |
Montréal | Northern British Columbia | Queen's |
Regina | Saint Mary's | Simon Fraser | Toronto |
Victoria | Western | Winnipeg | York

The background of the right half of the slide is a dark blue image of a particle detector, showing a grid of vertical tubes and a central structure, all rendered in a lighter blue tone.

Thank you!
Merci!

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