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

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 â€“ in real time. TRIUMFâ€™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 â€“ Canadaâ€™s national laboratory for particle and nuclear physics and accelerator-based science â€“ has unique capabilities in this area.</p>

<p>In his talk, Dr. Paul Schaffer, Associate Laboratory Director of TRIUMFâ€™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. Heâ€™ll share leading-edge developments and discuss the promise advanced medical isotopes hold for disease diagnostics and therapeutics, as well as talk about his teamâ€™s award-winning efforts to produce a secure supply of critical medical isotopes.</p>

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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

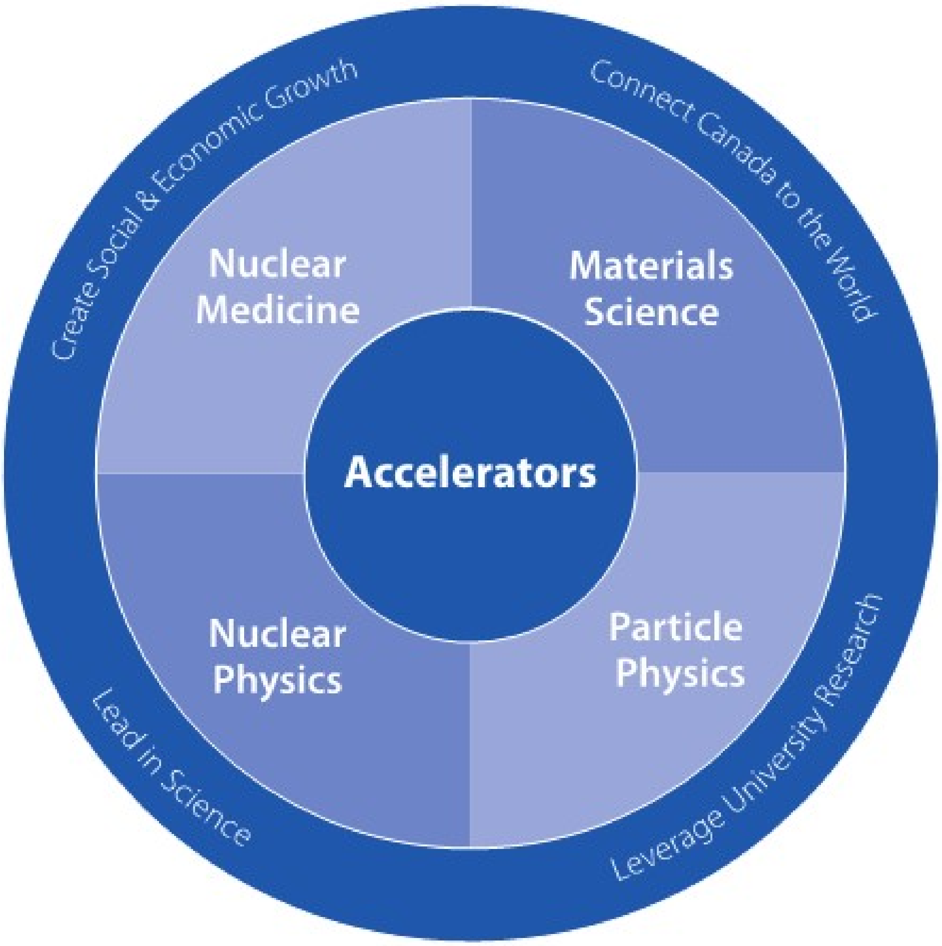
Paul Schaffer
Associate Laboratory Director – Life Sciences, TRIUMF

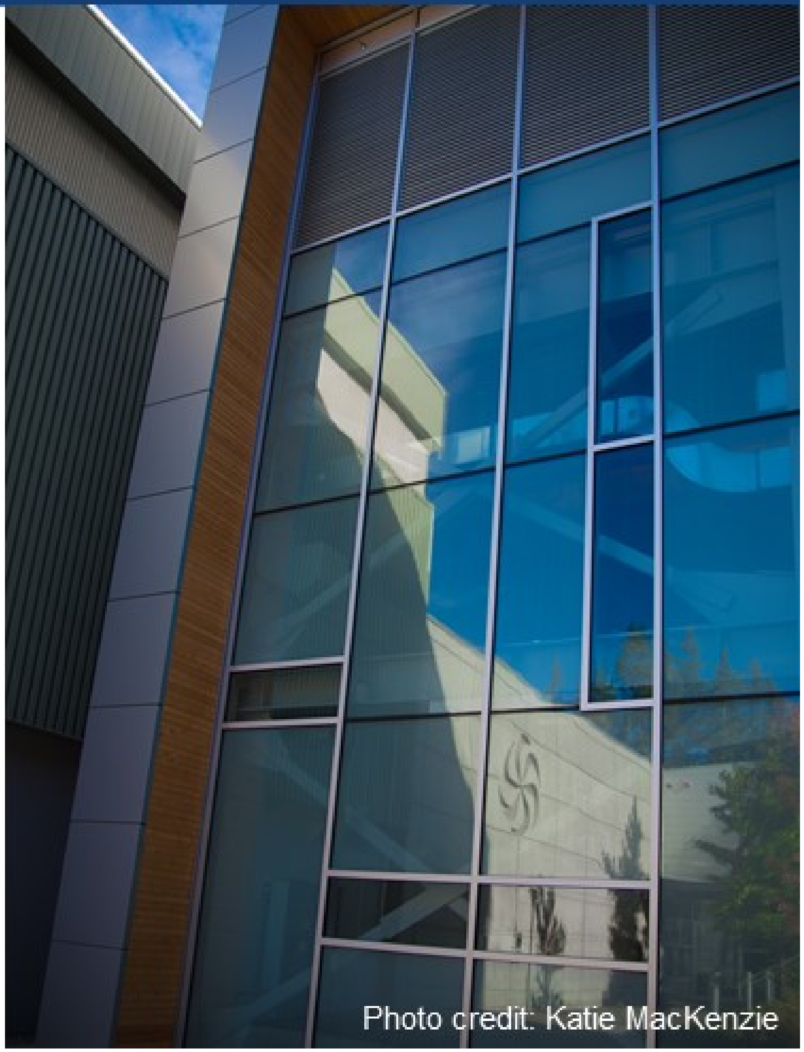
December 2, 2015

TRIUMF: A National Laboratory

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

TRIUMF: A National Resource





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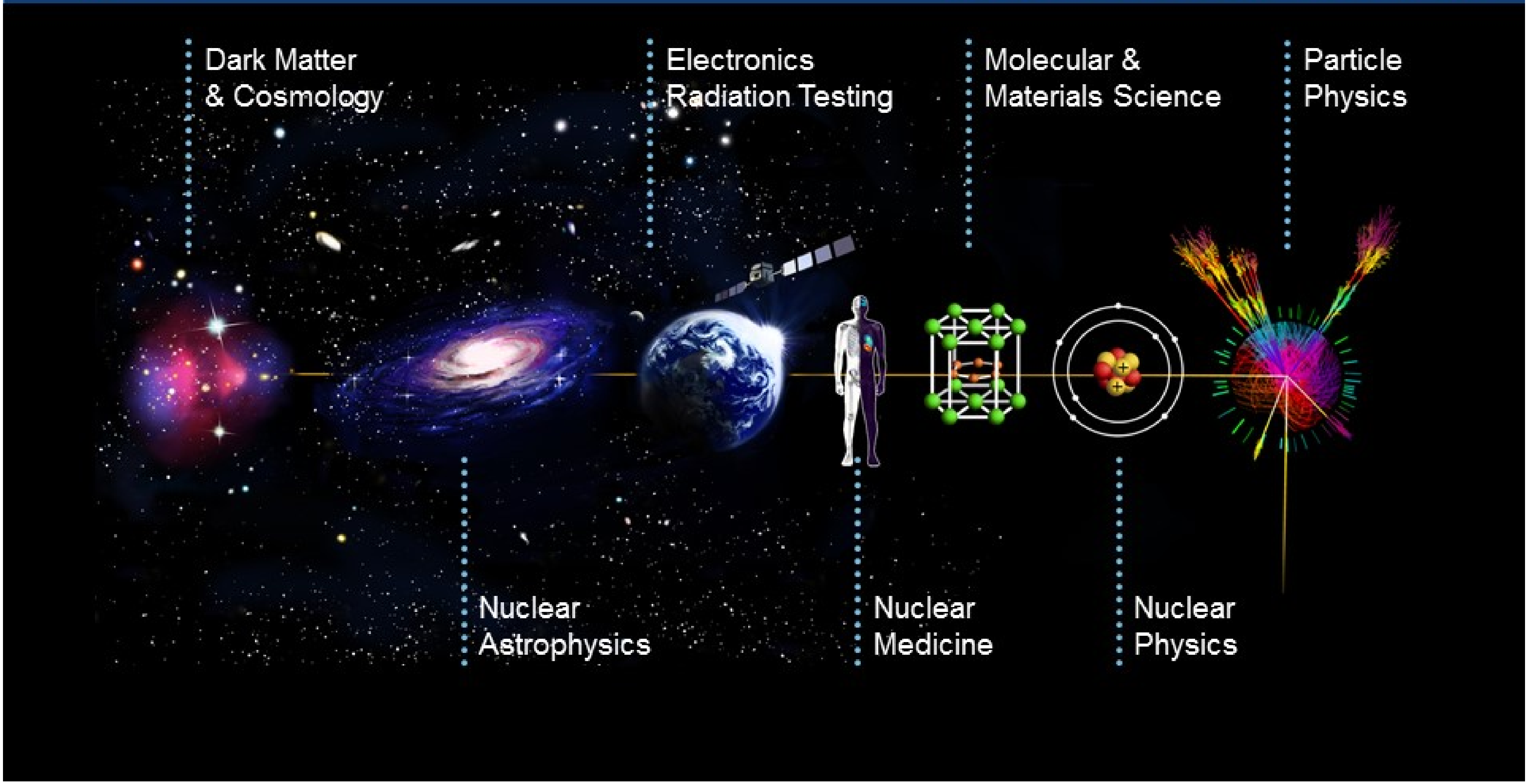
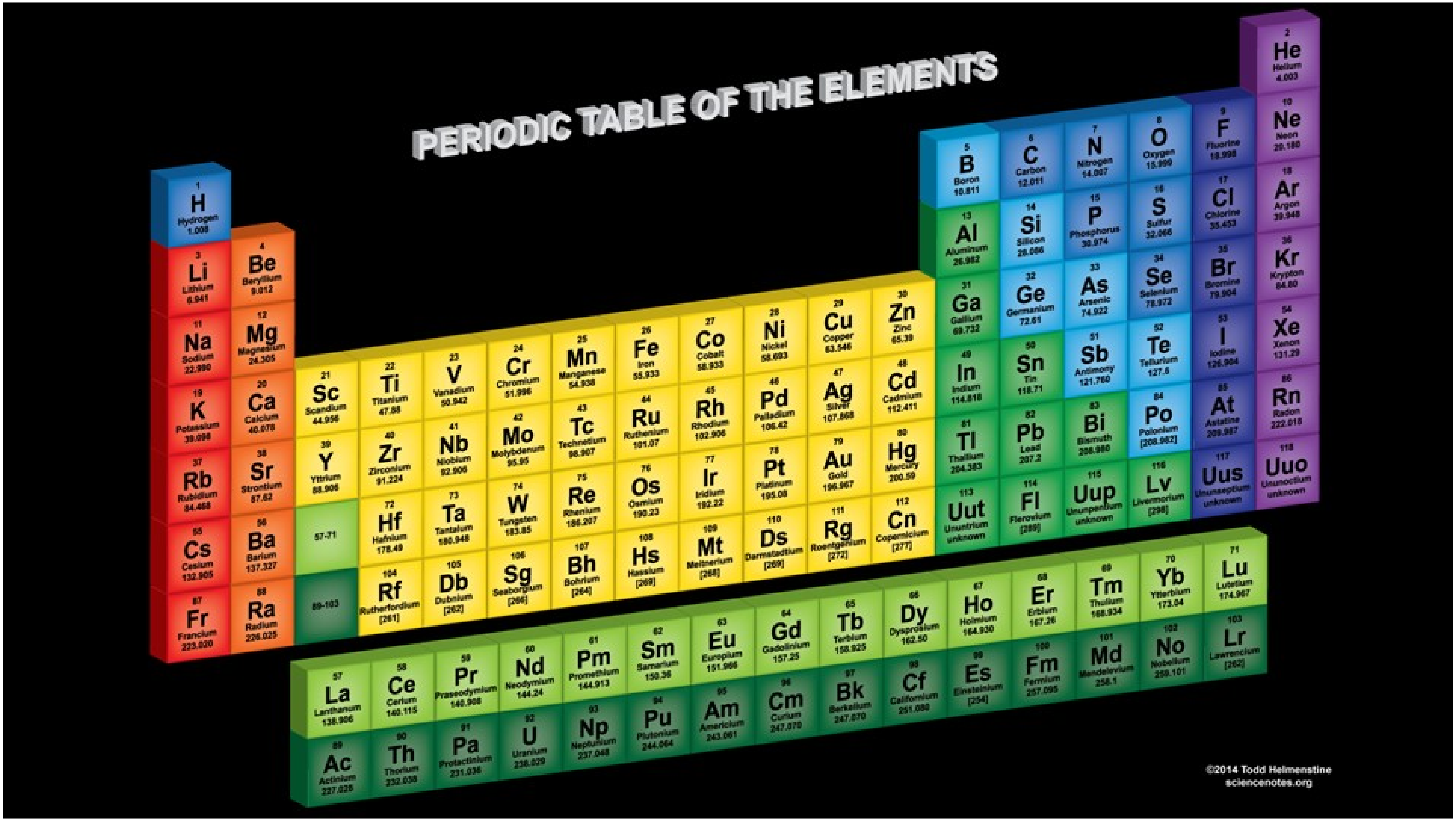
TRIUMF's Research Program




PERIODIC TABLE OF THE ELEMENTS
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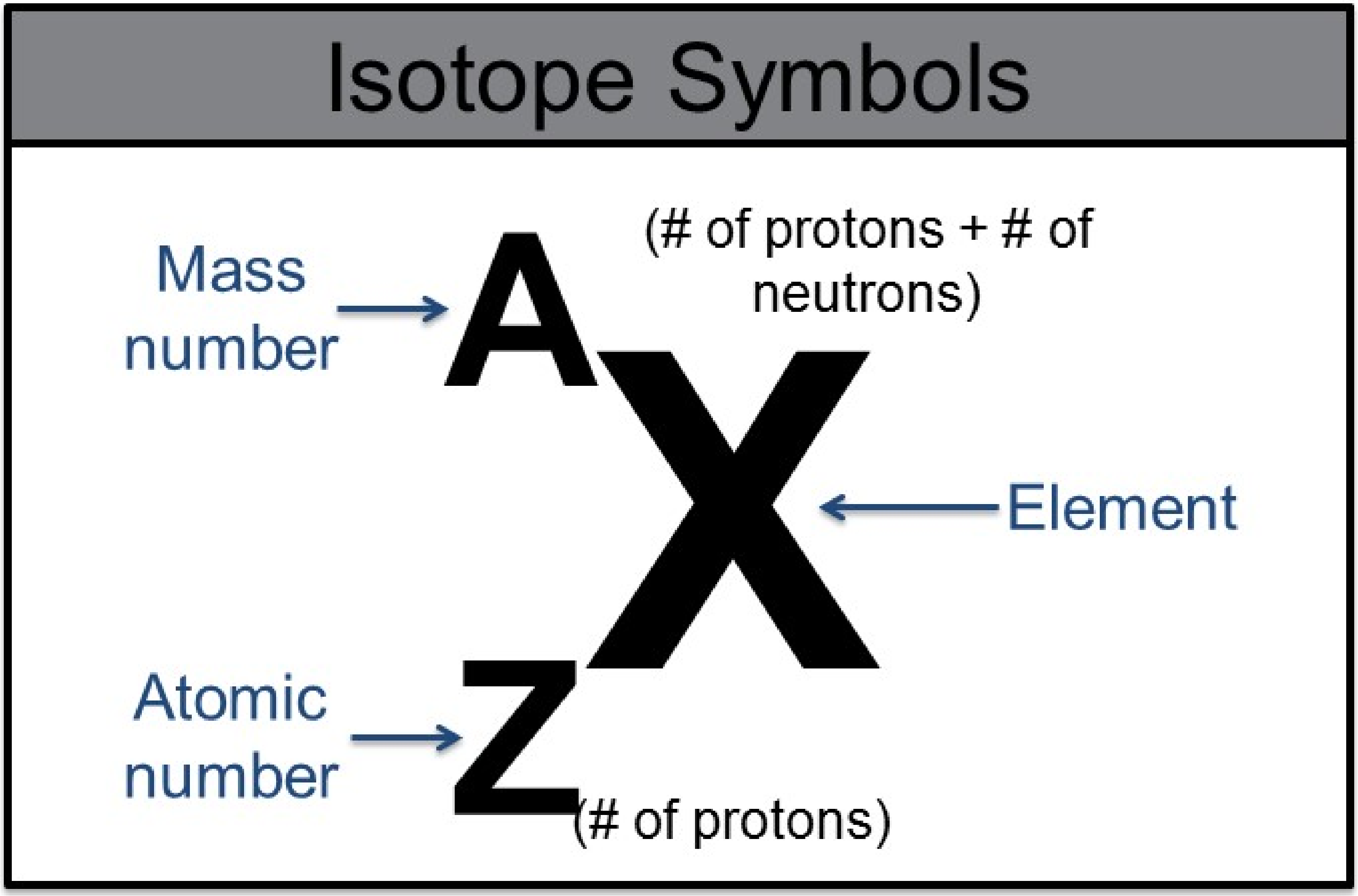
sciencenotes.org

Recognizing Isotopes



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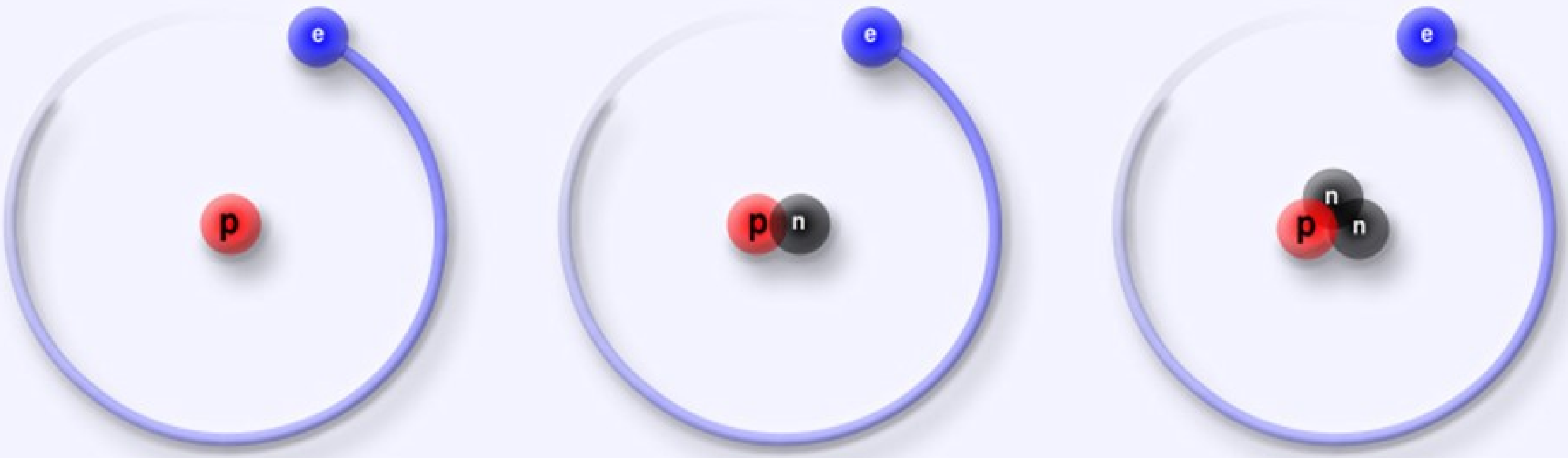
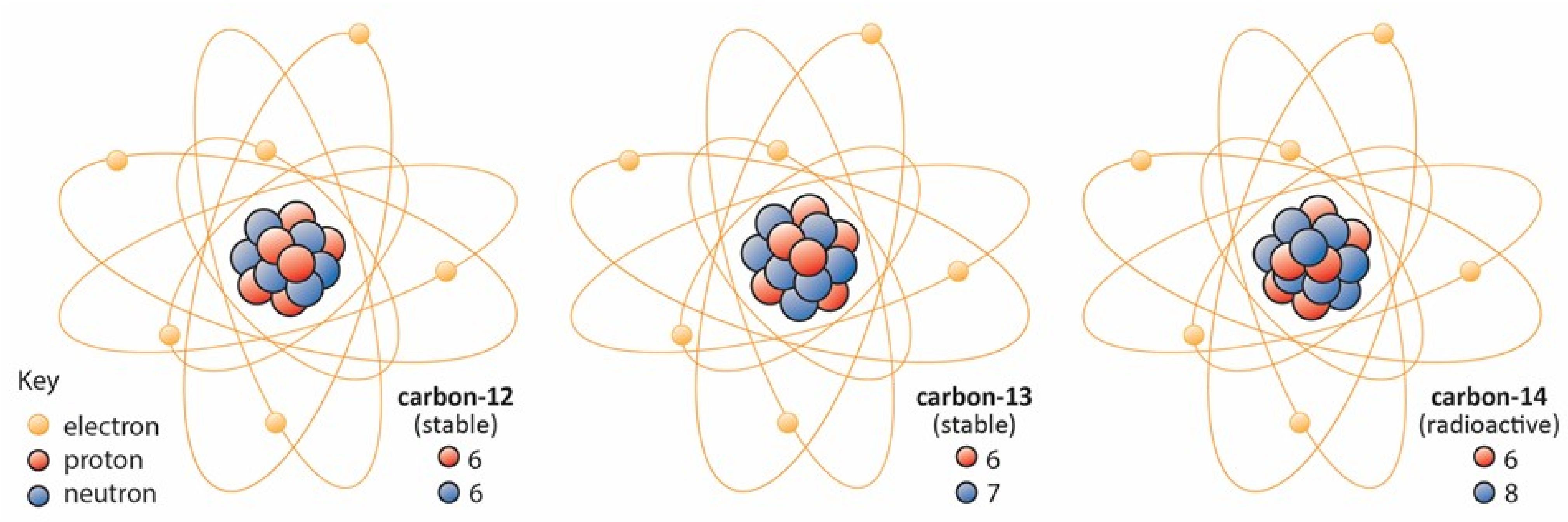
Isotopes Explained

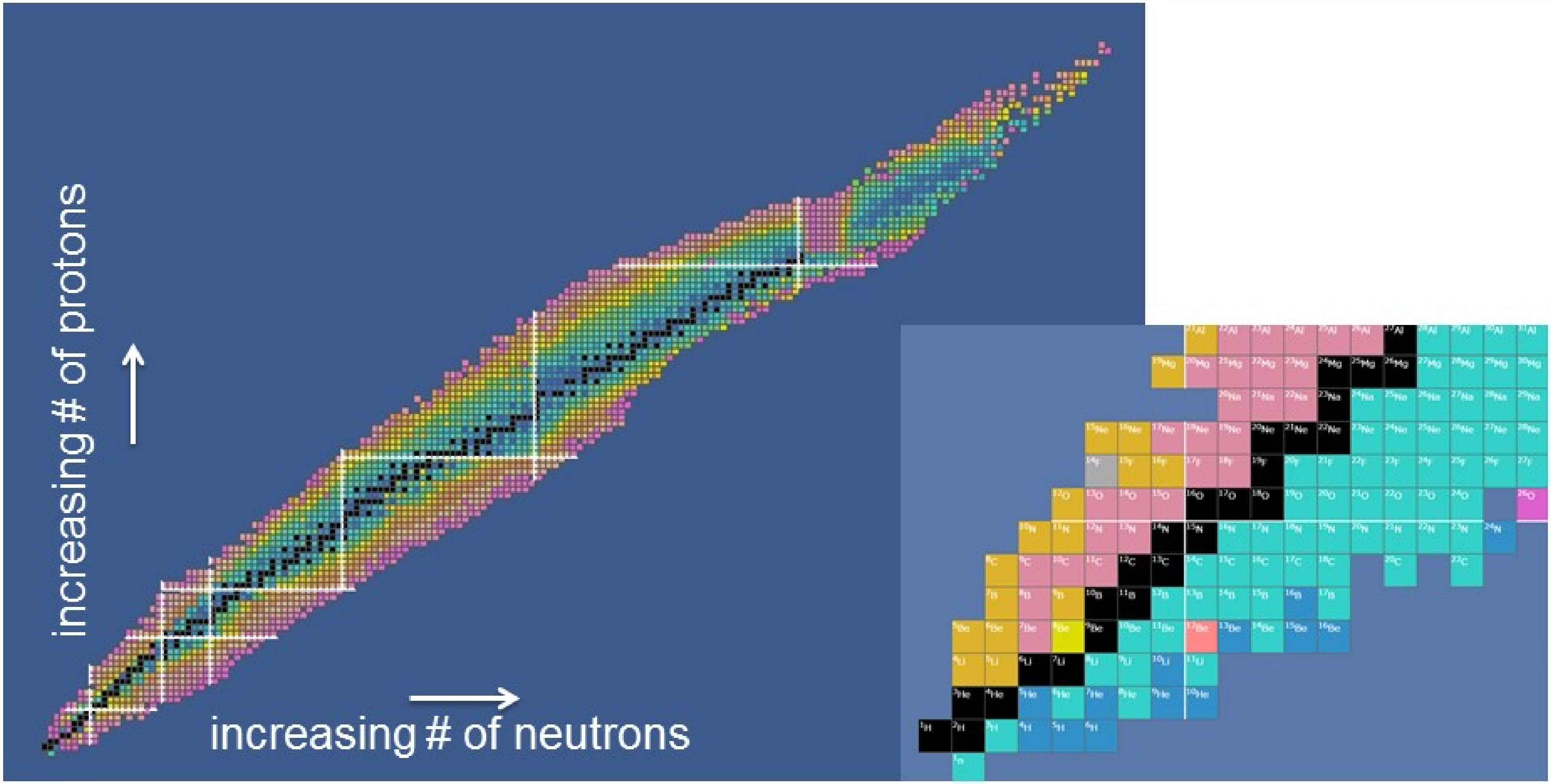


$^{1}_{1}H$	$^{2}_{1}H$	$^{3}_{1}H$
Protium	**Deuterium**	**Tritium**

Isotopes Explained

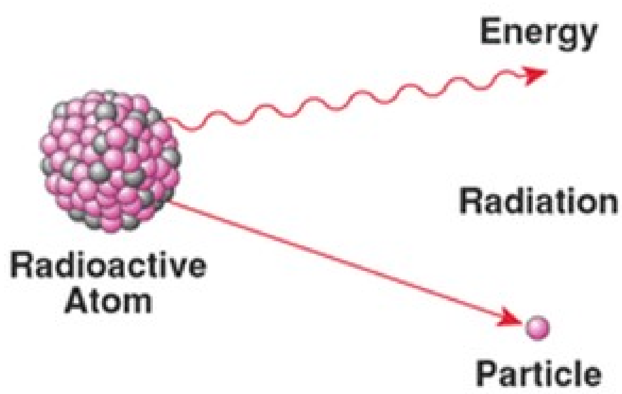


Charting our Universe (the Chart of Nuclides)



Radiation Defined

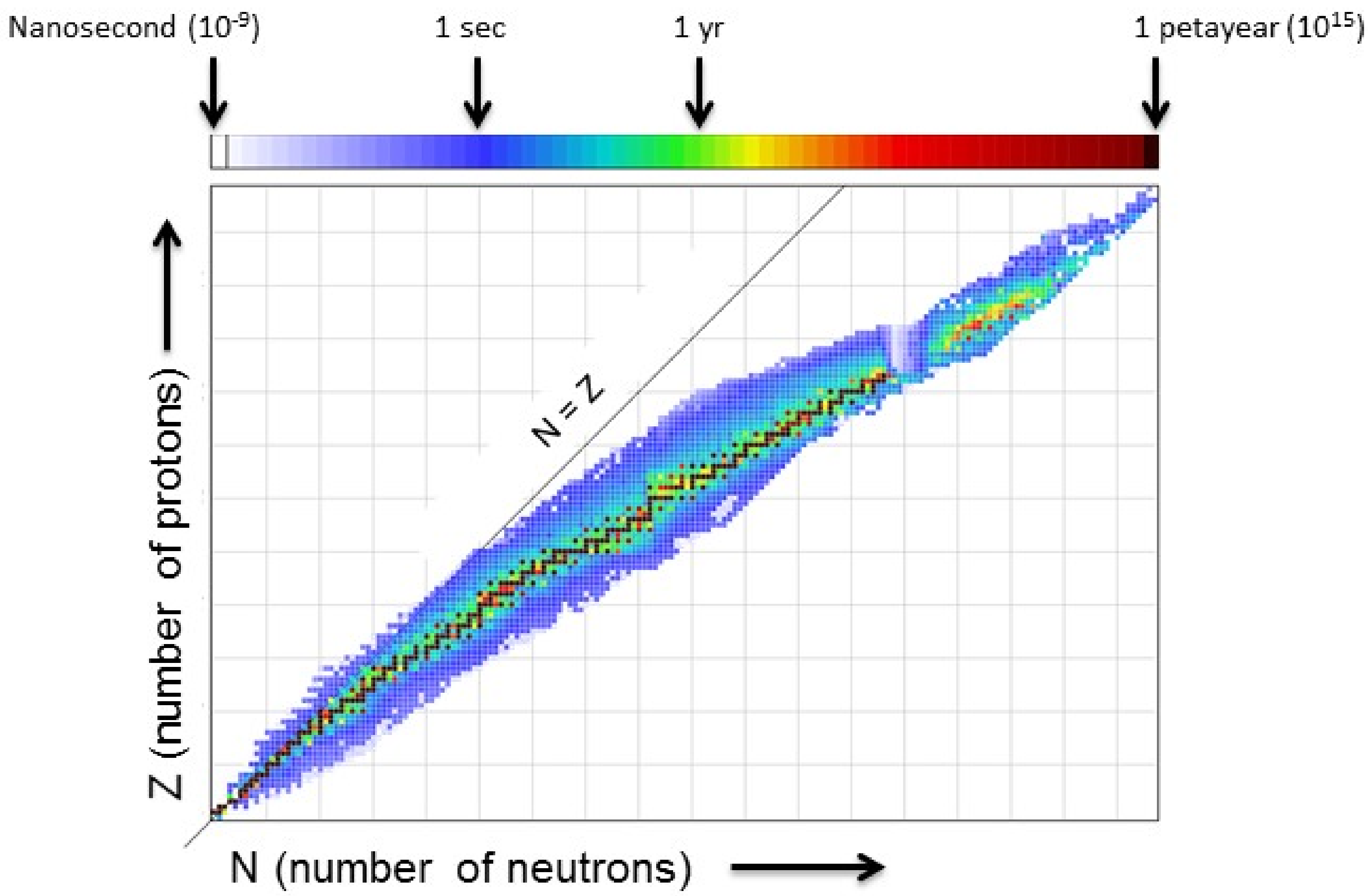
- Radiation: energy in motion through space
  - particulate vs. electromagnetic
- Particulate: have mass (charge) and velocity
  - (velocity proportional to energy)
  - examples: α, β, protons, neutrons
- Electromagnetic: no mass or charge, propagate as packets of energy (quanta or photons)



Types of Radiation

- 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

Line of Stability



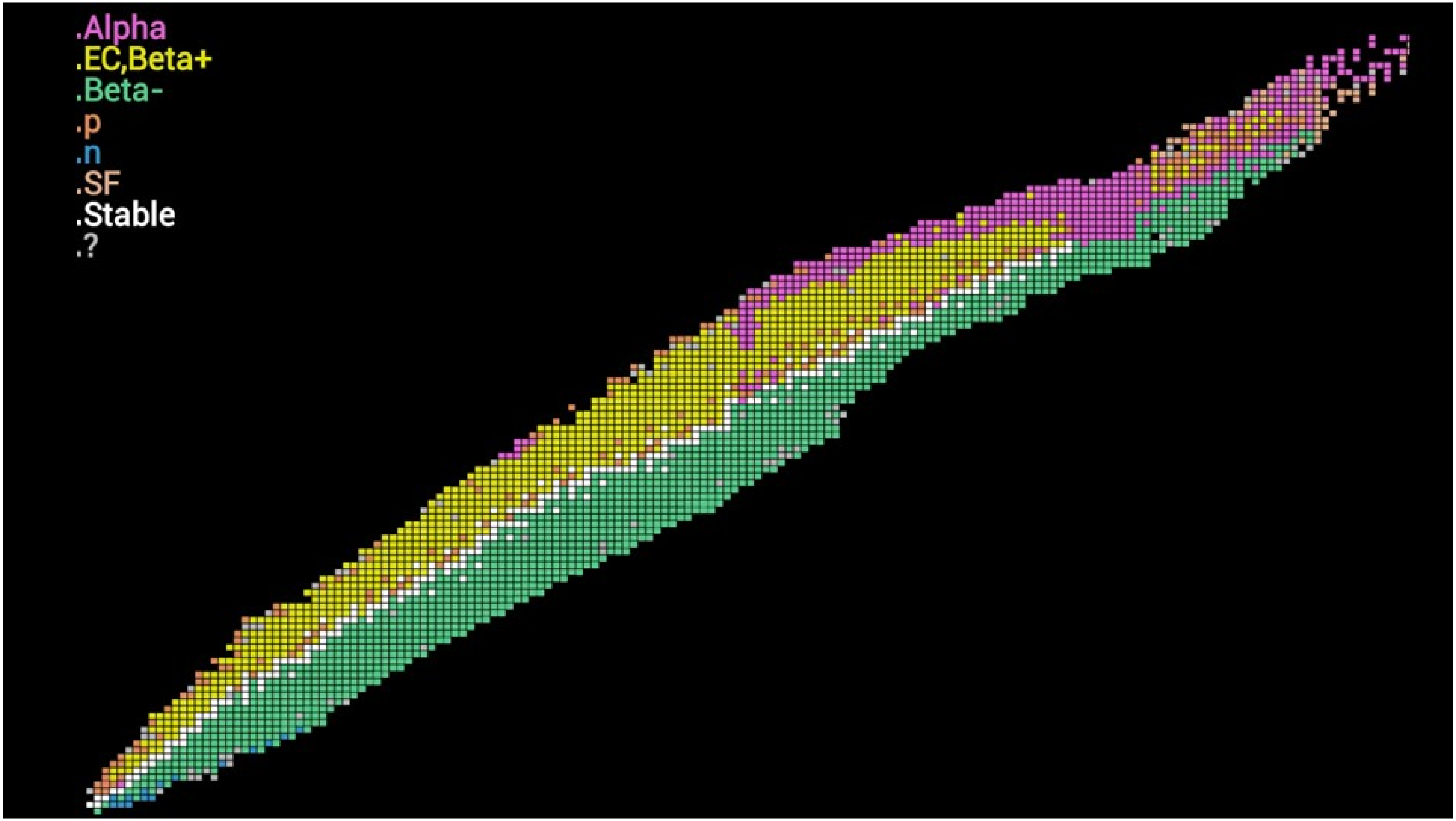
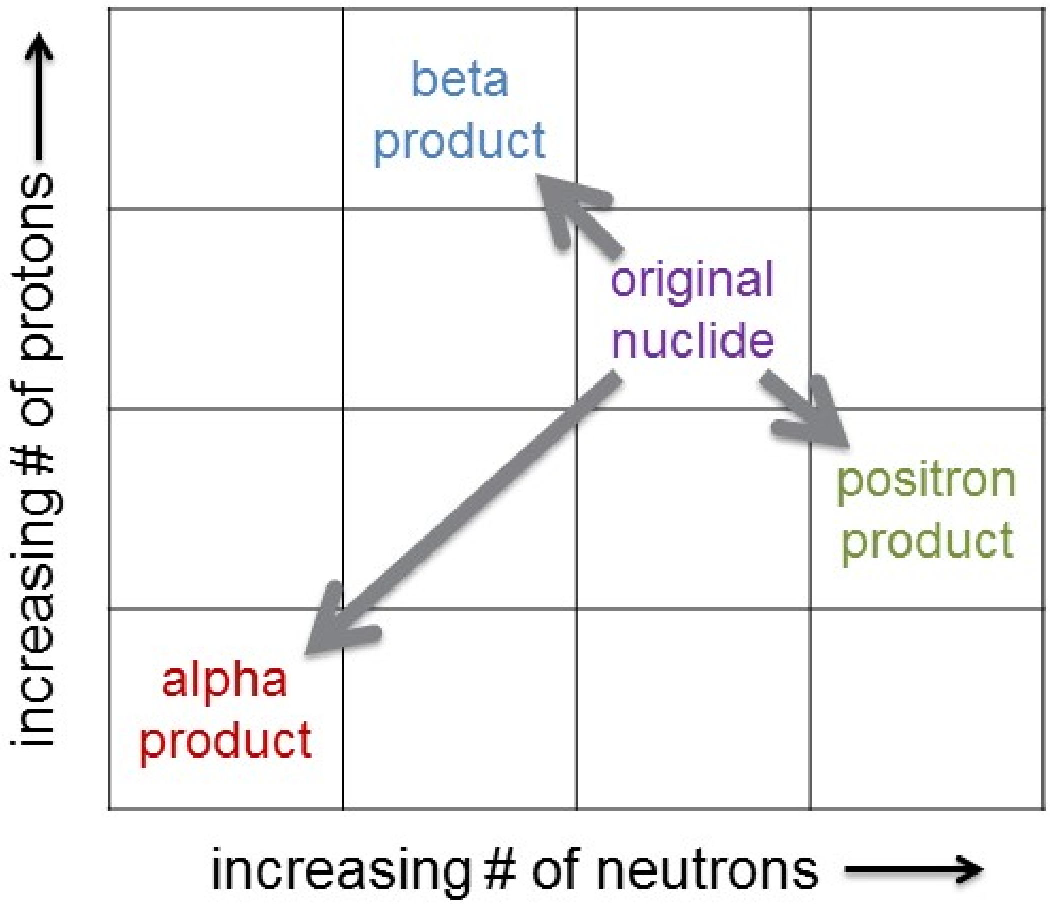

.Alpha
.EC,Beta+
.Beta-
.p
.n
.SF
.Stable
.?

Chart of Nuclides

- 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



Making Isotopes

Nuclear reactor

Cyclotron

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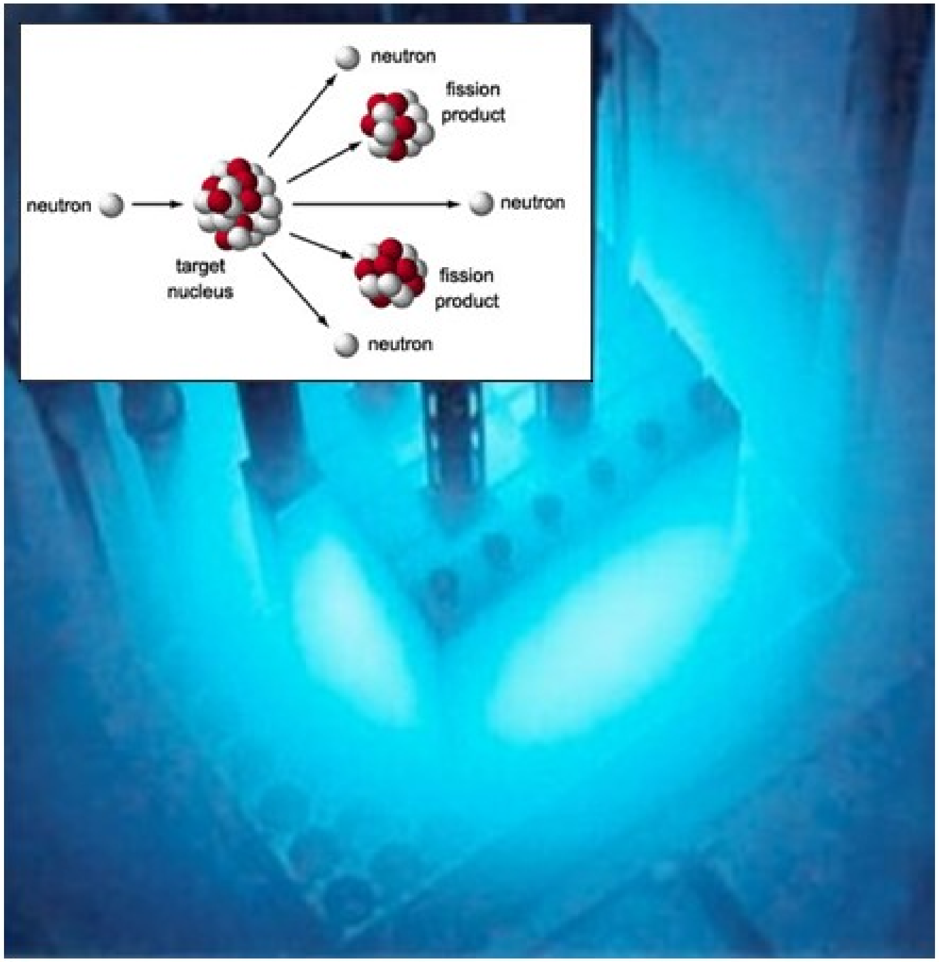
Making Isotopes: Reactors



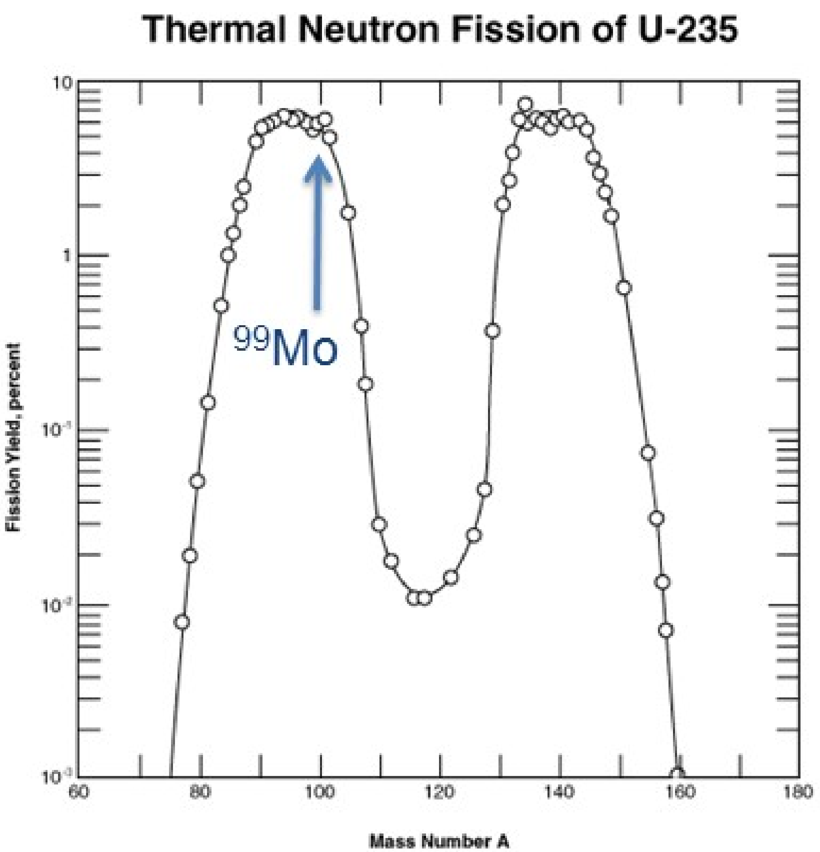
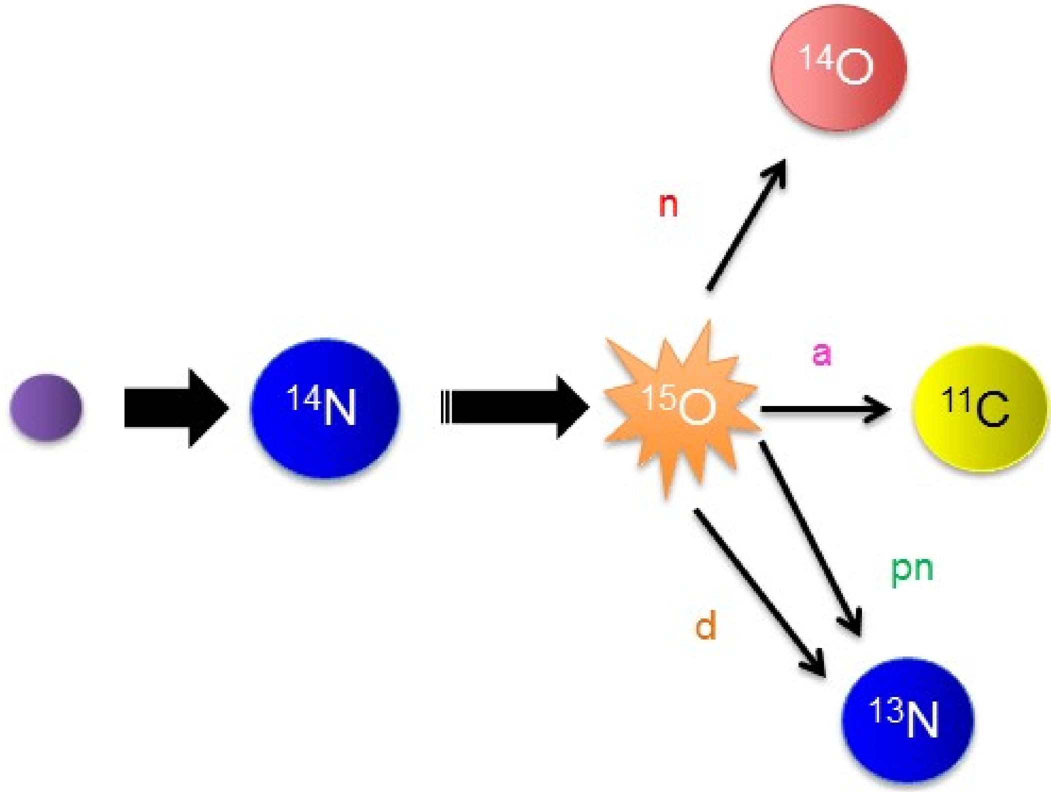
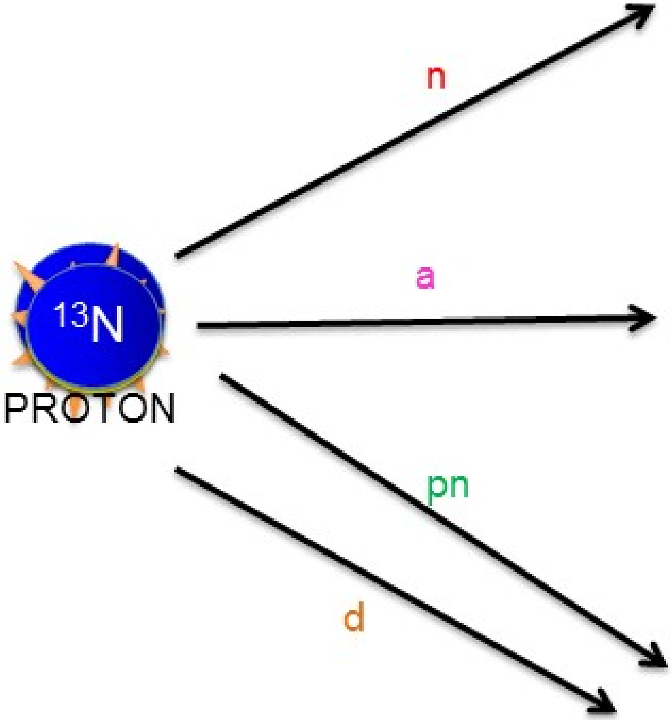


image from www.uwaterloo.ca

Making Isotopes: Accelerators (Cyclotrons)



Making Isotopes: Accelerators (Cyclotrons)



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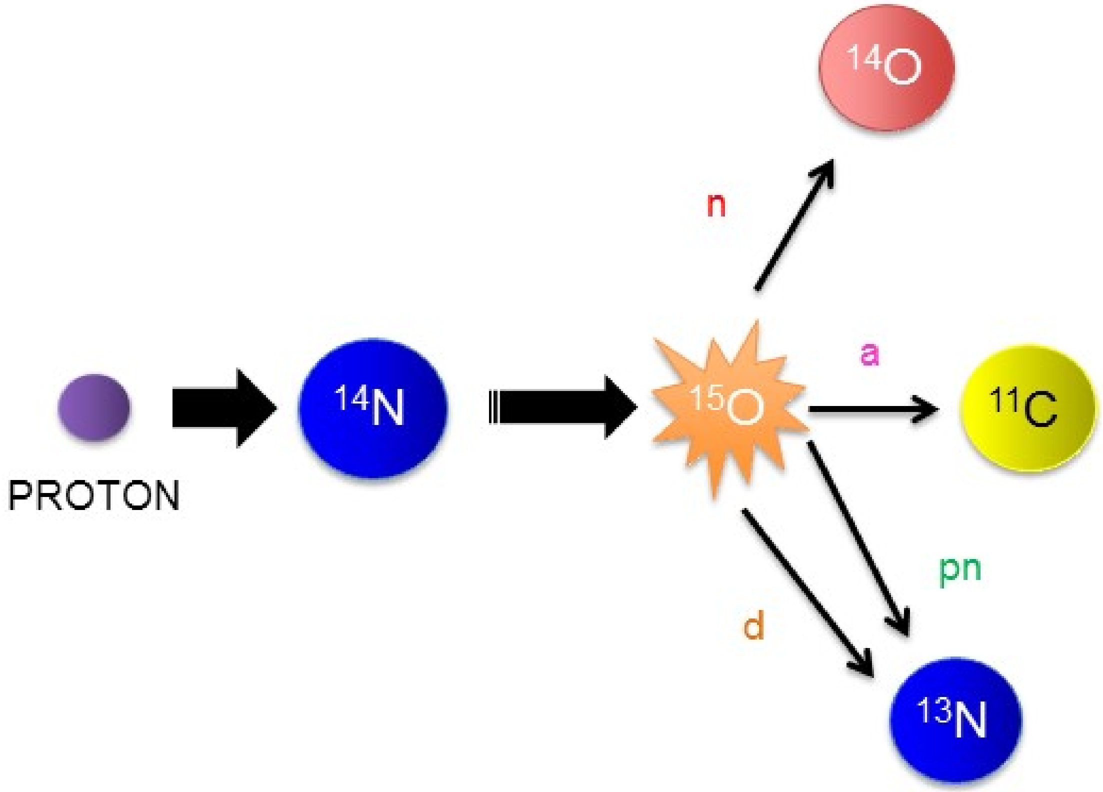
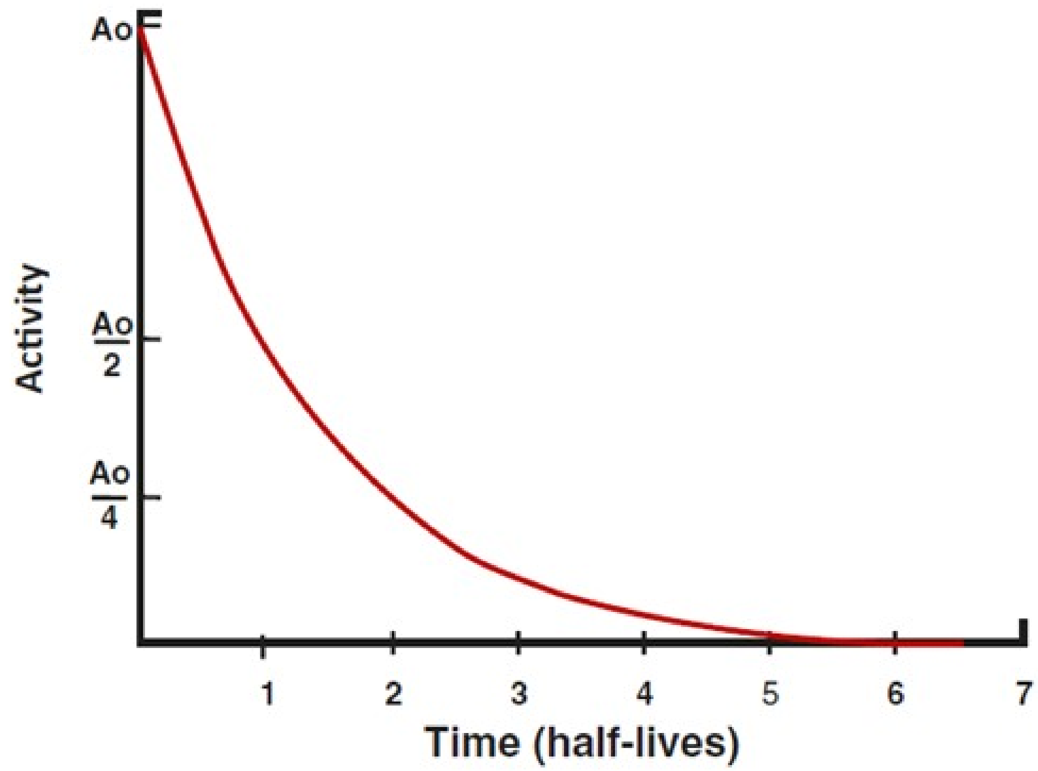
Making Isotopes: Accelerators (Cyclotrons)



Radioactive Decay

$$A = N\lambda$$

$$\lambda = \frac{ln2}{t_{1/2}}$$



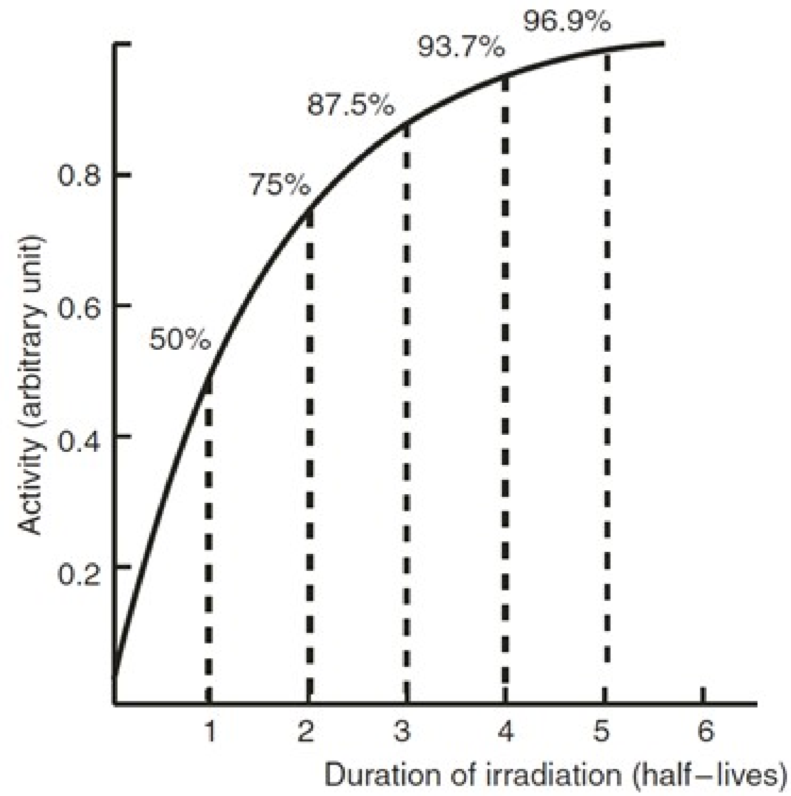
3 key cyclotron parameters

Beam intensity, beam energy, irradiation time

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

density, isotopic enrichment

2 key target parameters



Isotope Generators

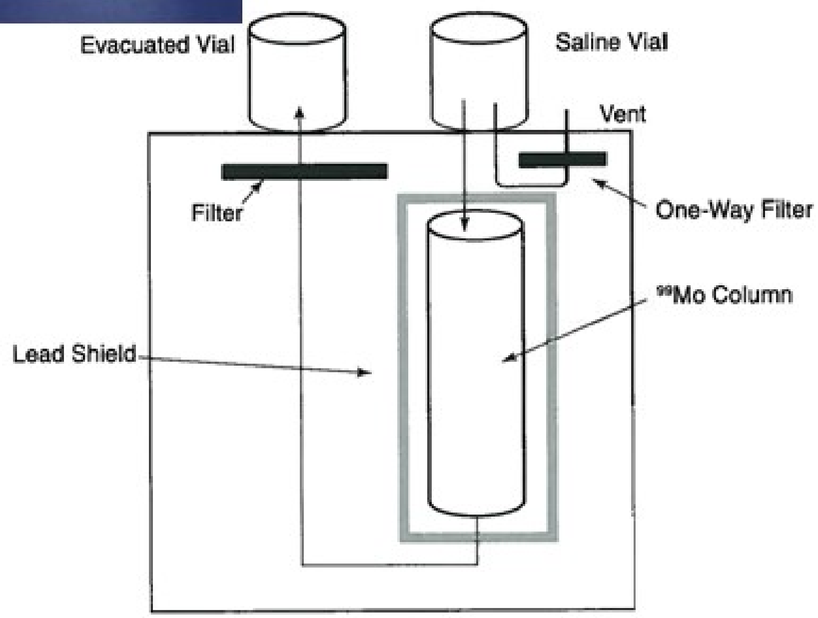
$^{68}Ge/^{68}Ga$
(271 d, 68 min)

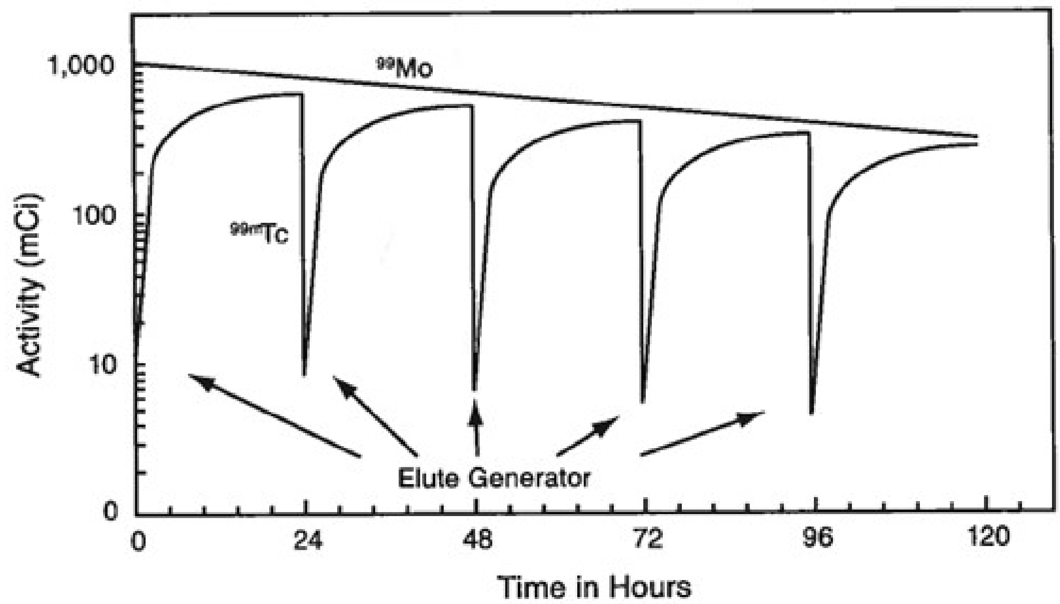
$^{82}Sr/^{82}Rb$
(25.4 d, 1.3 min)

- Transportable,
- Easy to use

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

How do generators work?





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

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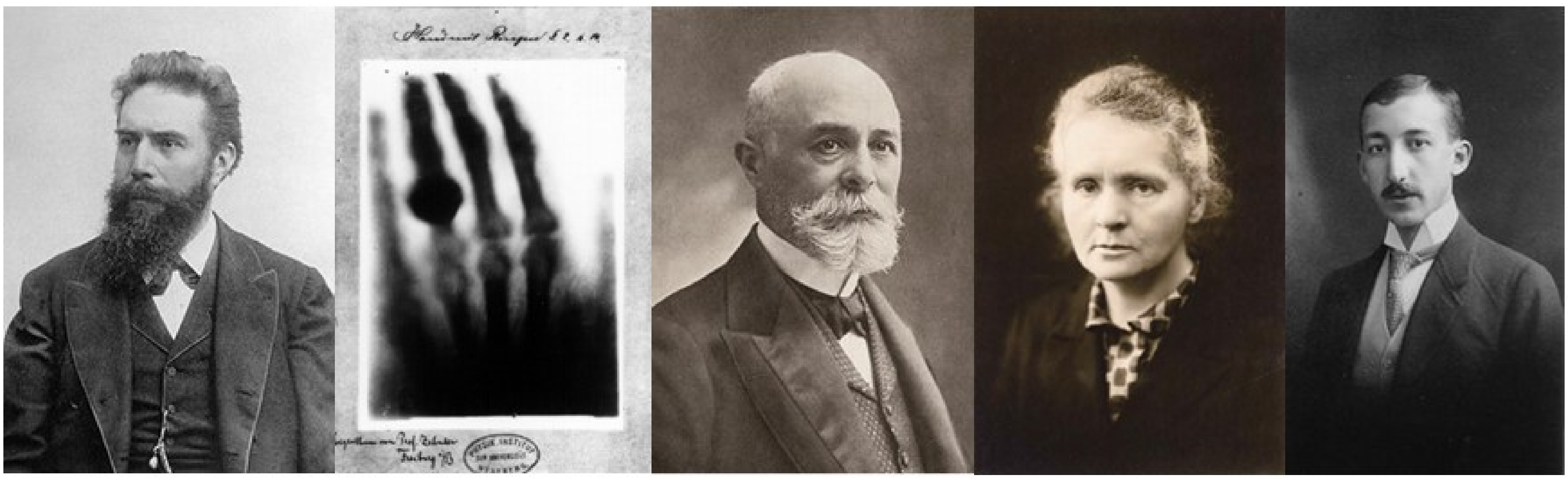
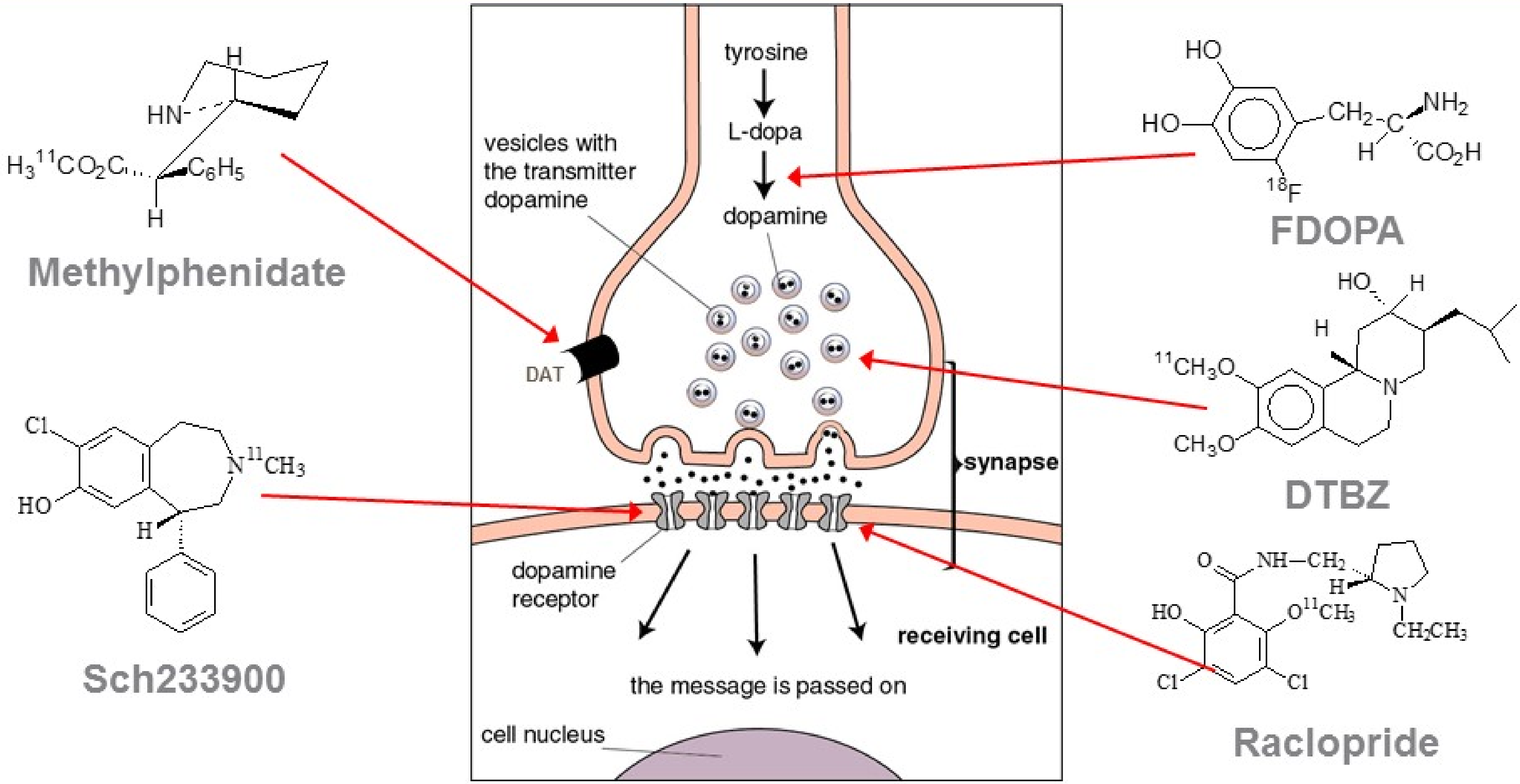
Isotopes (Radiation) Applied to Medicine: A Brief History

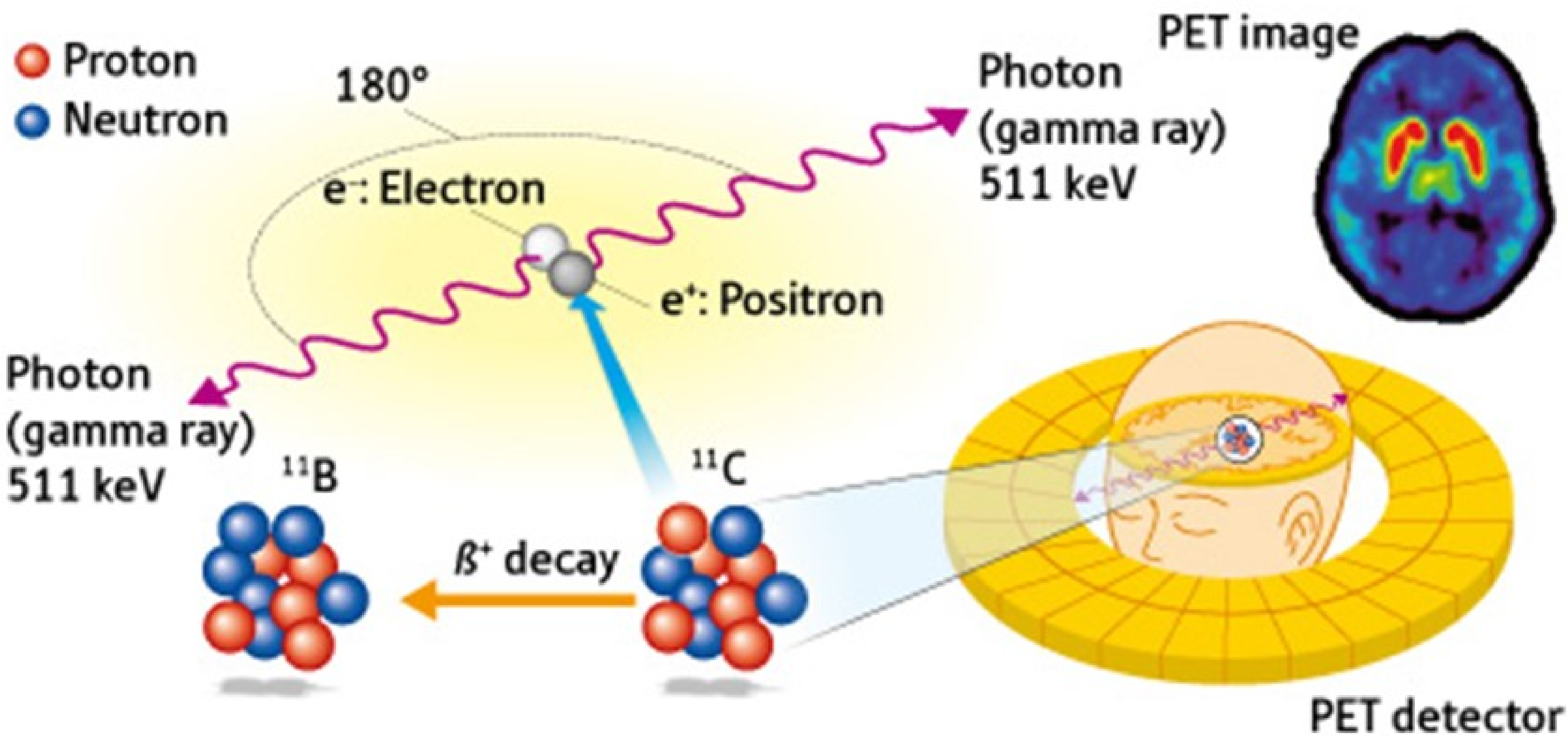
- 1895: Roentgen discovered ‘penetrating rays’’, aka X-rays (Nobel Prize 1901)
- 1896: Becquerel discovered radioactivity (shared Nobel Prize 1903)
- 1898: M. Curie discovered radium, radioactivity is named (Nobel Prize 1903)
- 1911: de Hevesy used isotopes as a tracer for the first time, established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



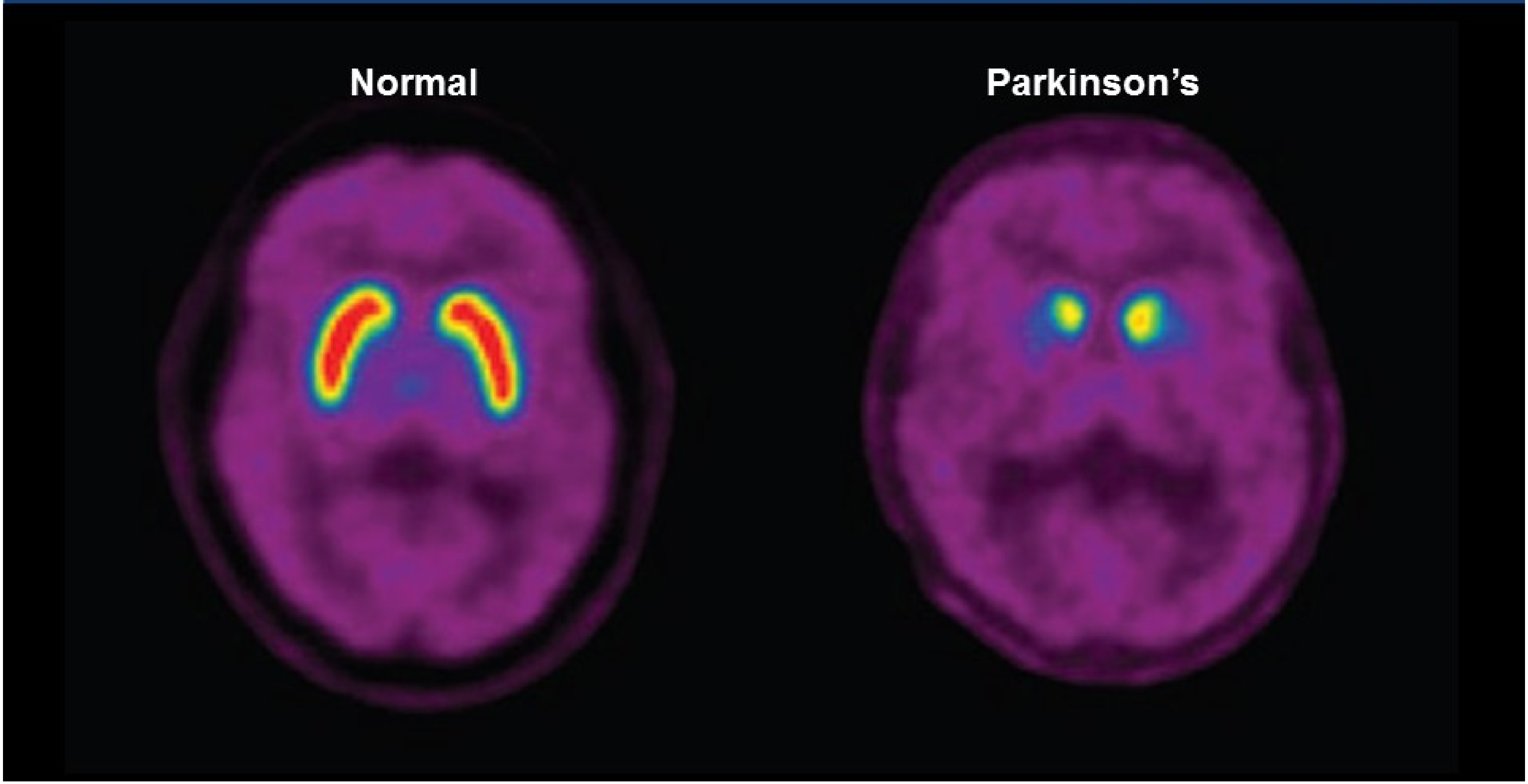
Radiotracers: Tools of the Trade



Positron Emission Tomography (PET)



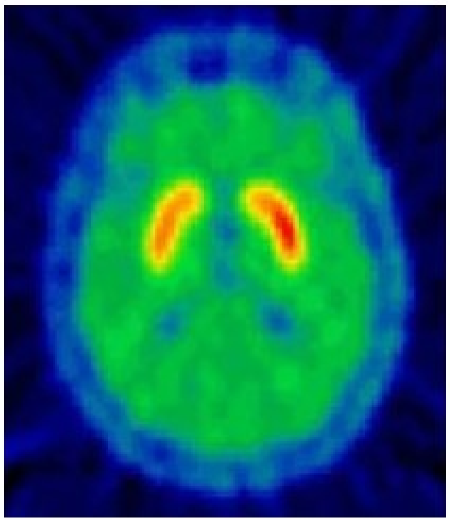
PET is Functional Imaging

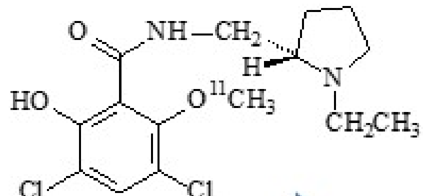



PET Advance NXi

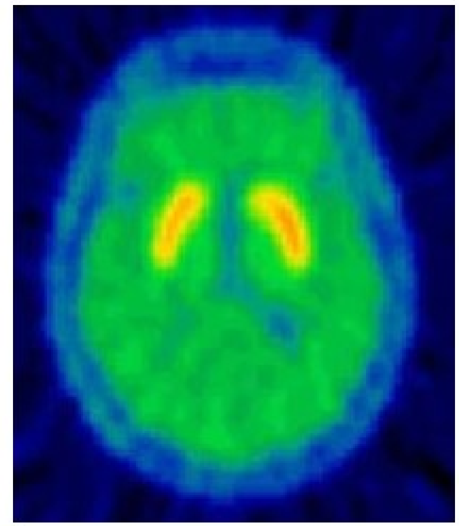
The Placebo Effect

"…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.

Tracer Principle

1 mole = 60,200,000,000,000,000,000,000,000 atoms/molecules
1 mole of water (H_2O) = 18 g (18 mL)
Typical radiopharmaceutical = dose 0.000000001 moles
Equivalent dose of water = 18 ng

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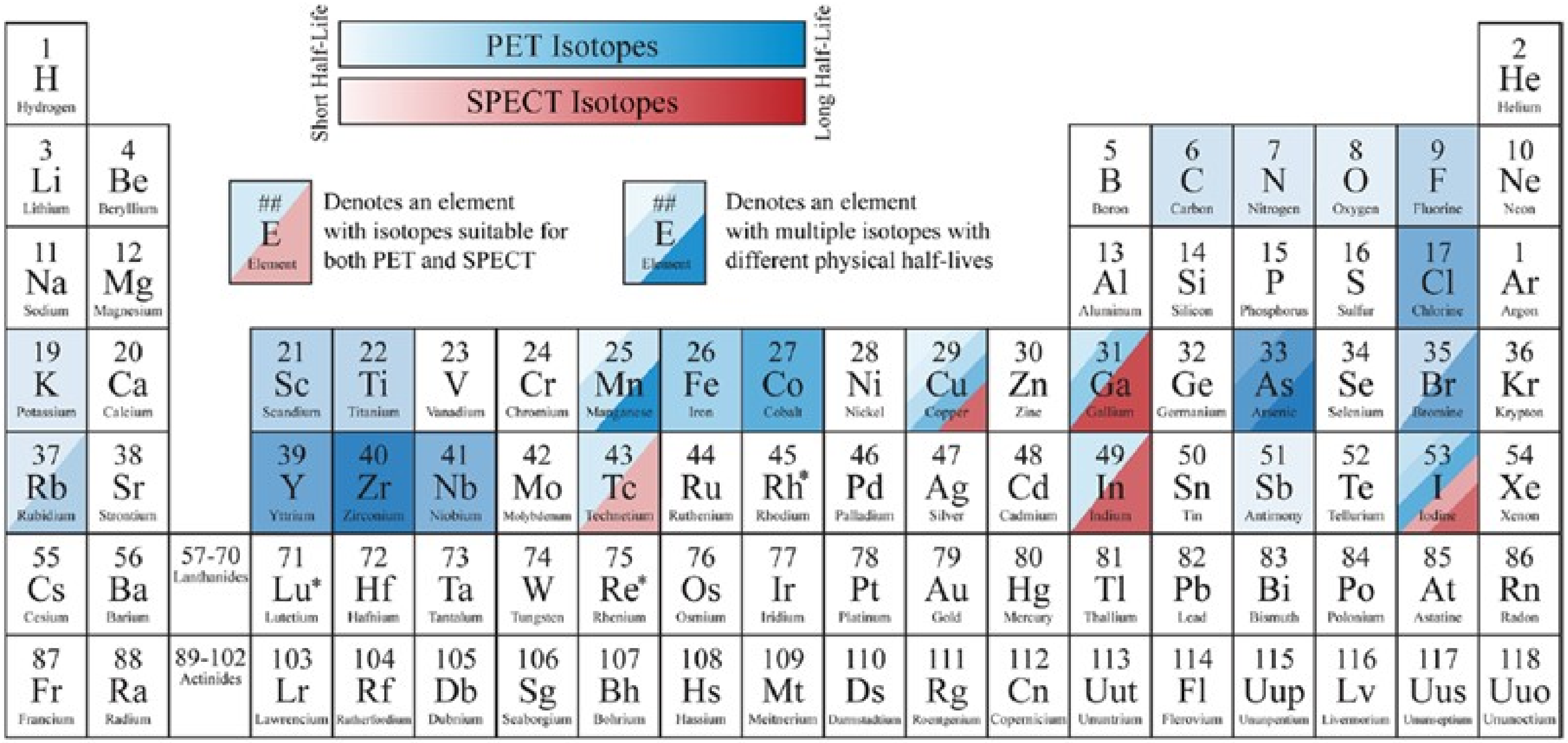
Isotopes for Medical Imaging

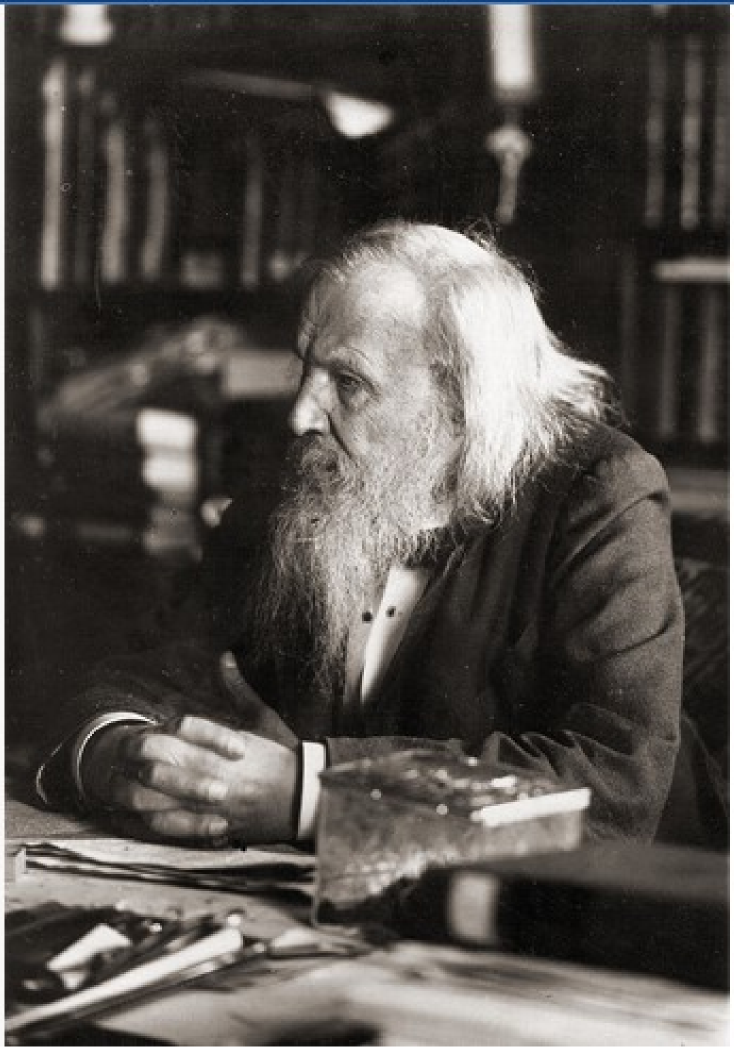


BM Zeglis et al. Inorg. Chem. 2014, 53, 1880

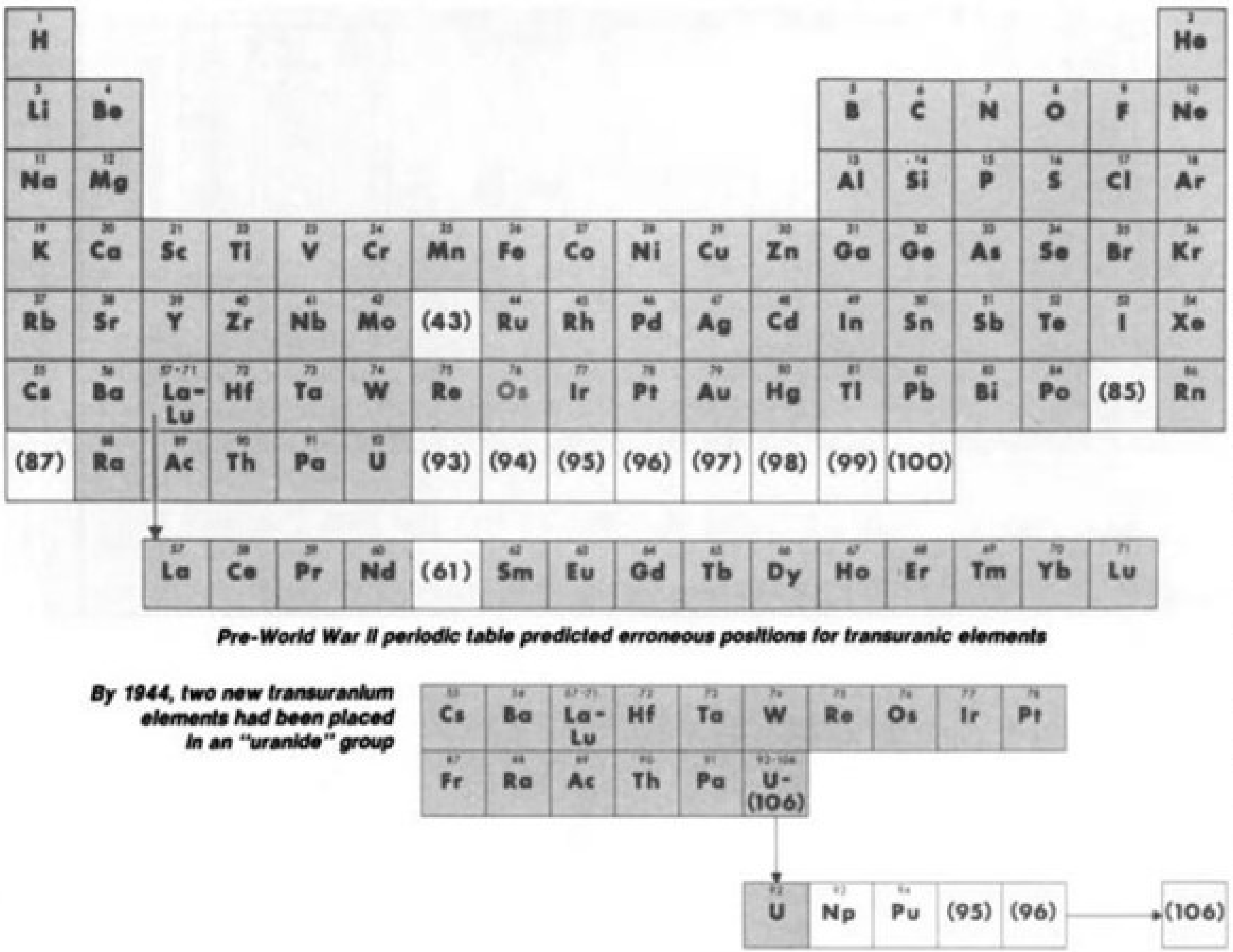
Mendeleev's Periodic Table of 1871

Mendeleev's Periodic Table of 1871[1]

	I --- R_2O	II --- RO	III --- R_2O_3	IV RH_4 RO_2	V RH_3 R_2O_3	VI RH_2 RO_3	VII RH R_2O_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	? 44	Ti 48	V 51	Cr 52	Mn 55	Fe, Co, Ni,Cu 56, 59, 59, 63
5	Cu 63	Zn 65	? 68	? 72	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	?	



Seaborg's Periodic Table



Ida Noddack

- 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)

Ida Noddack

- 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

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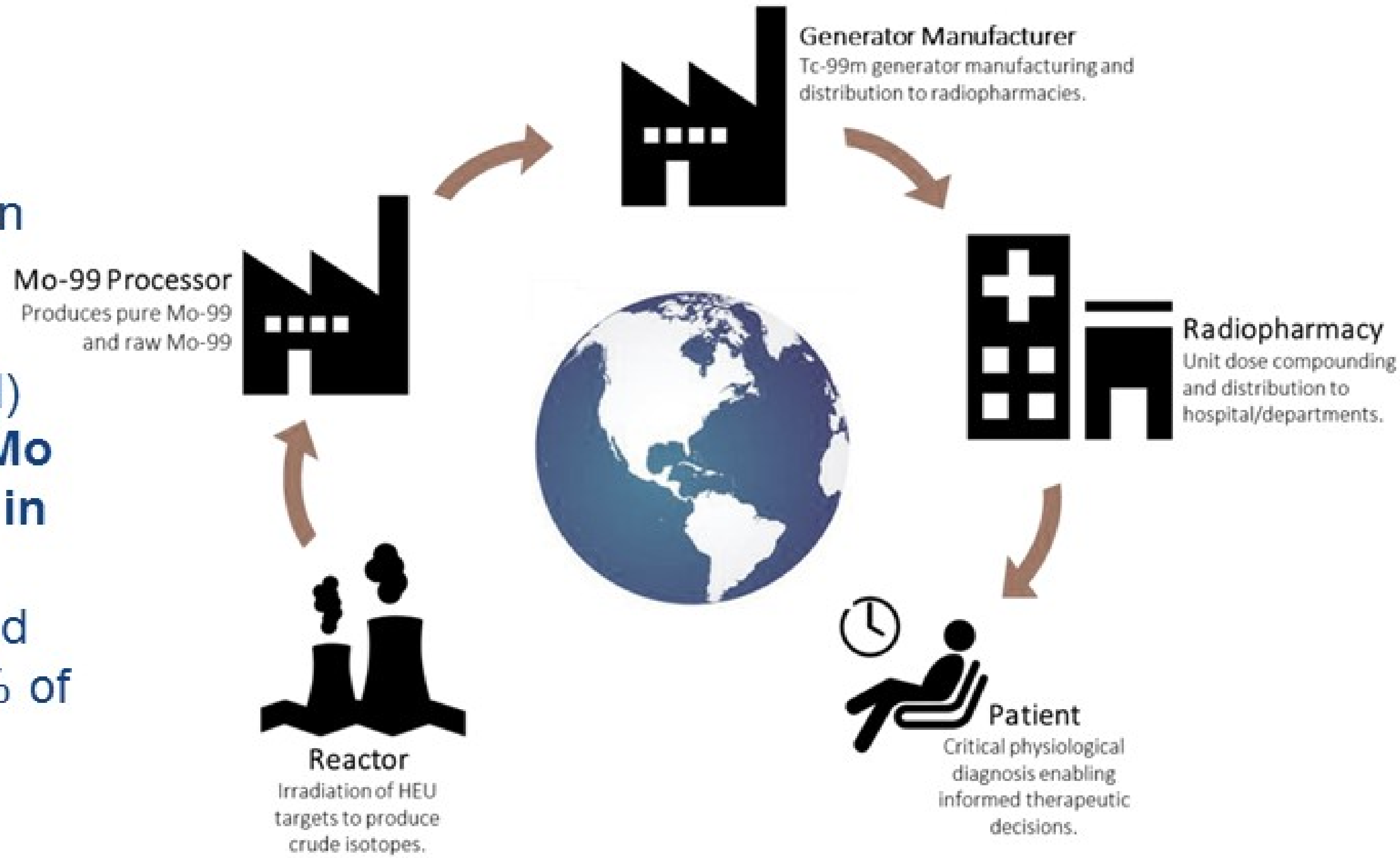
Technetium

- BNL, 1950s: Walter Tucker and Margaret Green discovered ^{99m}Tc as a ‘contaminant’ and developed the first $^{99}Mo/^{99m}Tc$ 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

- Single point of failure supply chain; aging infrastructure

- Global demand for $^{99}Mo/^{99m}Tc$ ~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



Global Medical Isotope Reactors

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

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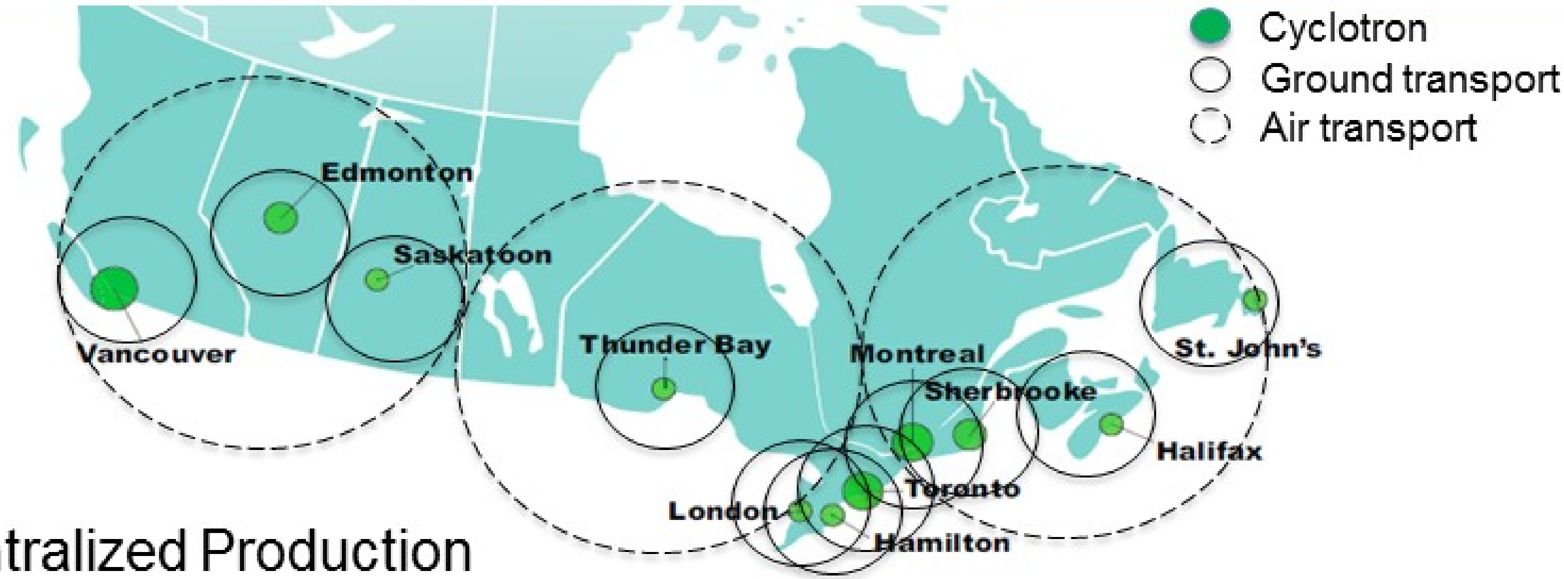
Proposed Solution



- 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

^{99m}Tc and Cyclotrons Go Way Back

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

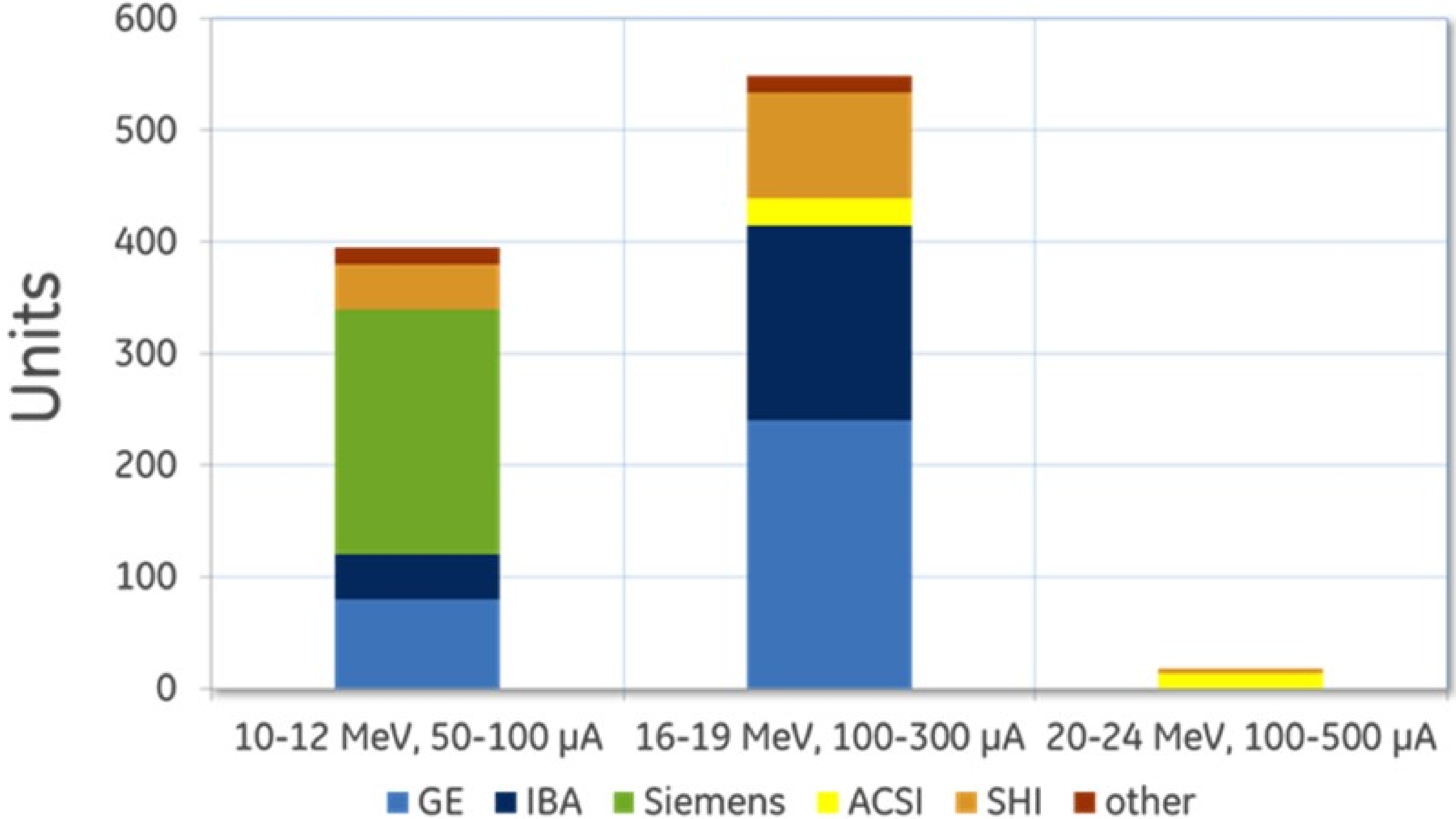
Radiation Laboratory,
Department of Physics (E.S.),
Department of Chemistry (G.T.S.),
University of California,
Berkeley, California,
October 14, 1938.

[1] Sagane, Kojima, Mijamoto 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)

Global Cyclotron Count



Problem Solvers

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LAWSON
HEALTH RESEARCH INSTITUTE

cpdc

BC Cancer Agency
CARE + RESEARCH
An agency of the Provincial Health Services Authority

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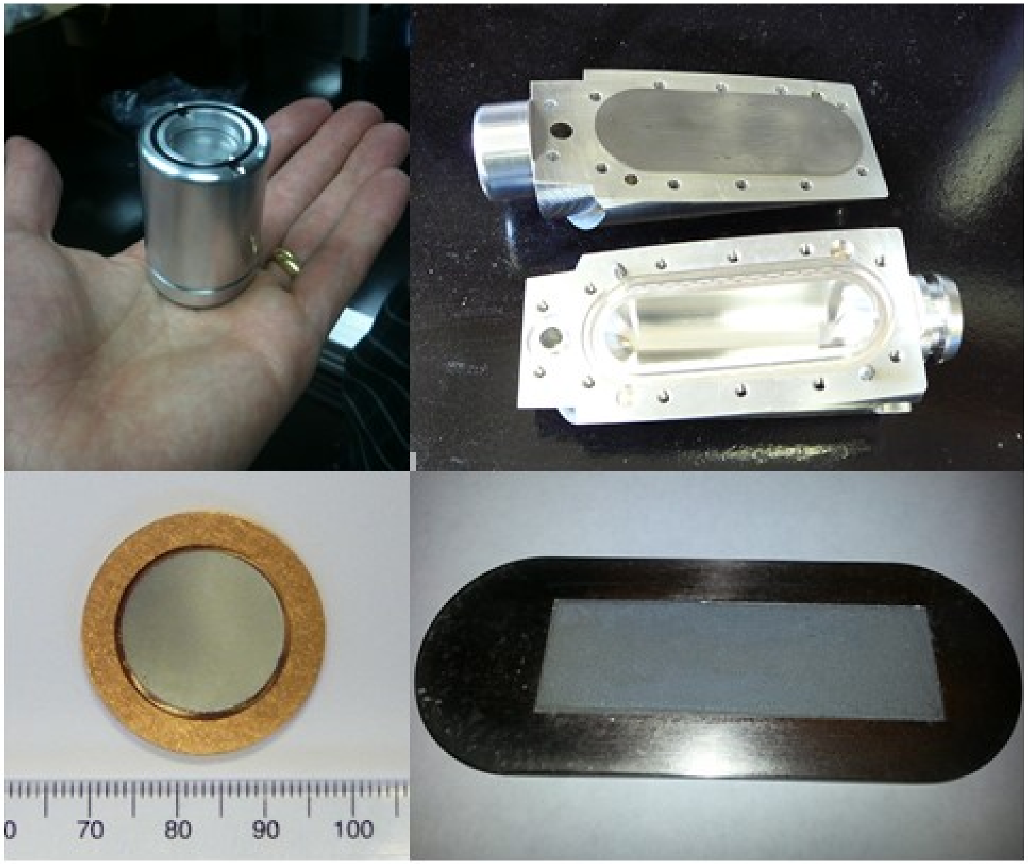
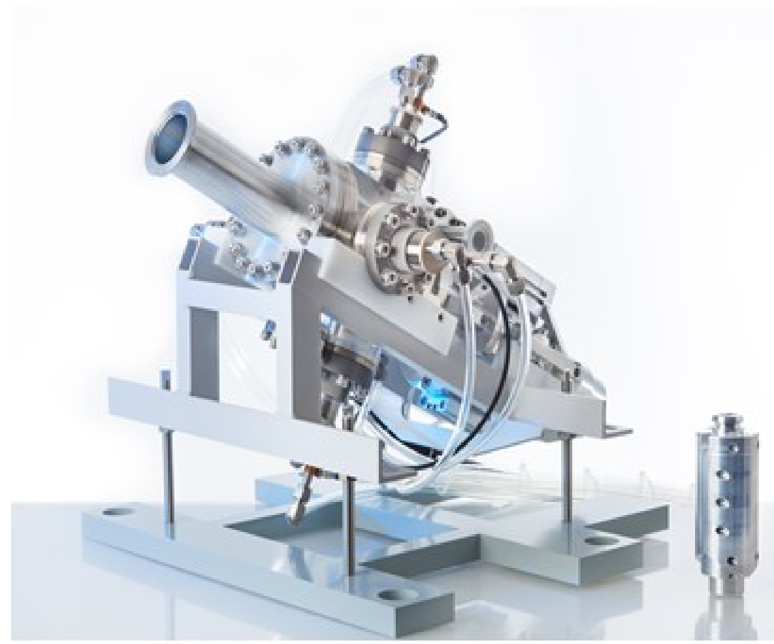
Made in Canada Technology





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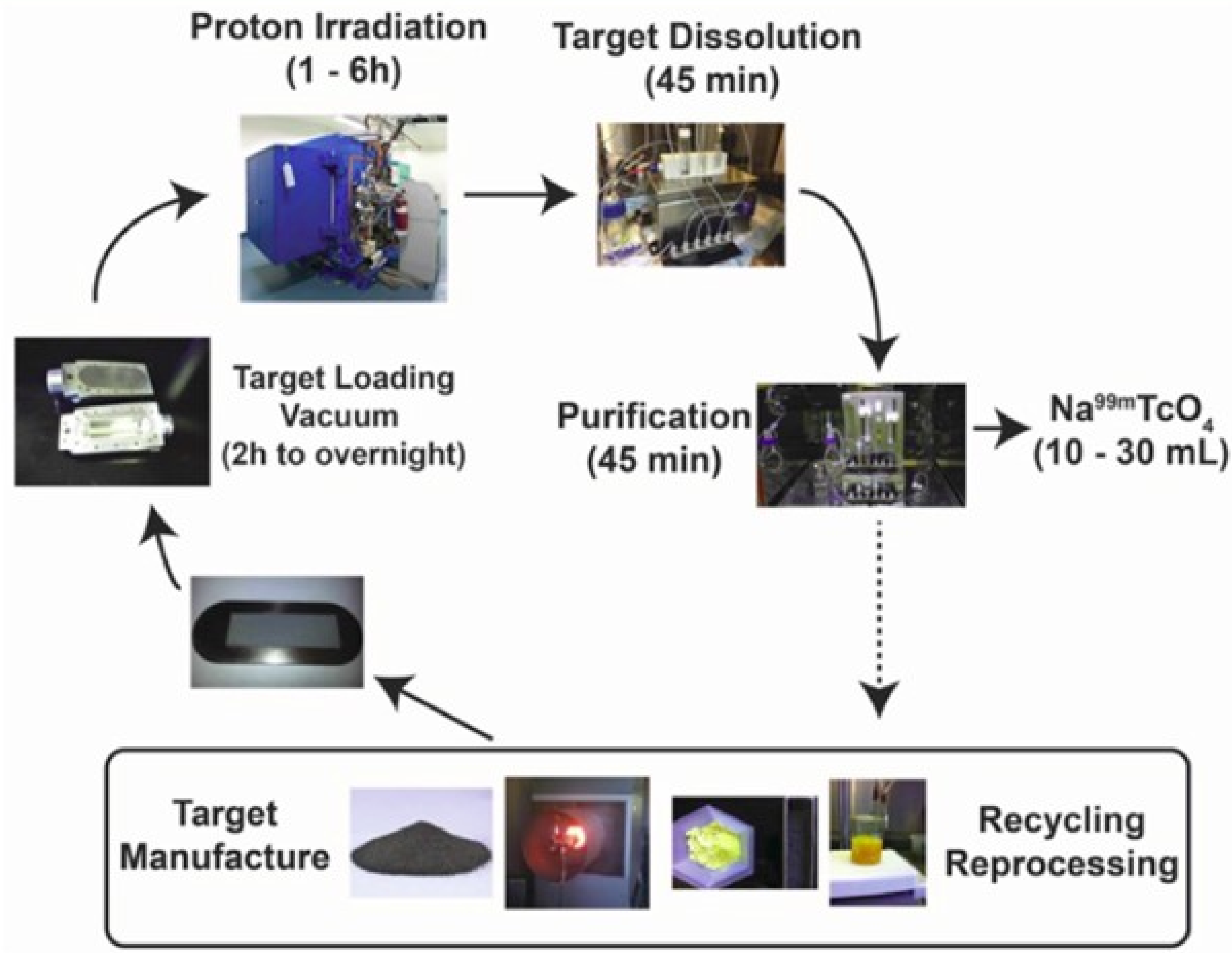
World Record Holder for Cyclotron Produced ^{99m}Tc

The Process


Proton Irradiation
(1 - 6h)
Target Dissolution
(45 min)
Target Loading
Vacuum
(2h to overnight)
Purification
(45 min)
Na99mTcO4
(10 - 30 mL)
Target
Manufacture
Recycling
Reprocessing

Accomplishments to Date

- 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**

Collaboration is Key

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

NSERC
CRSNG

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Future Direction: Therapeutic Isotopes

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

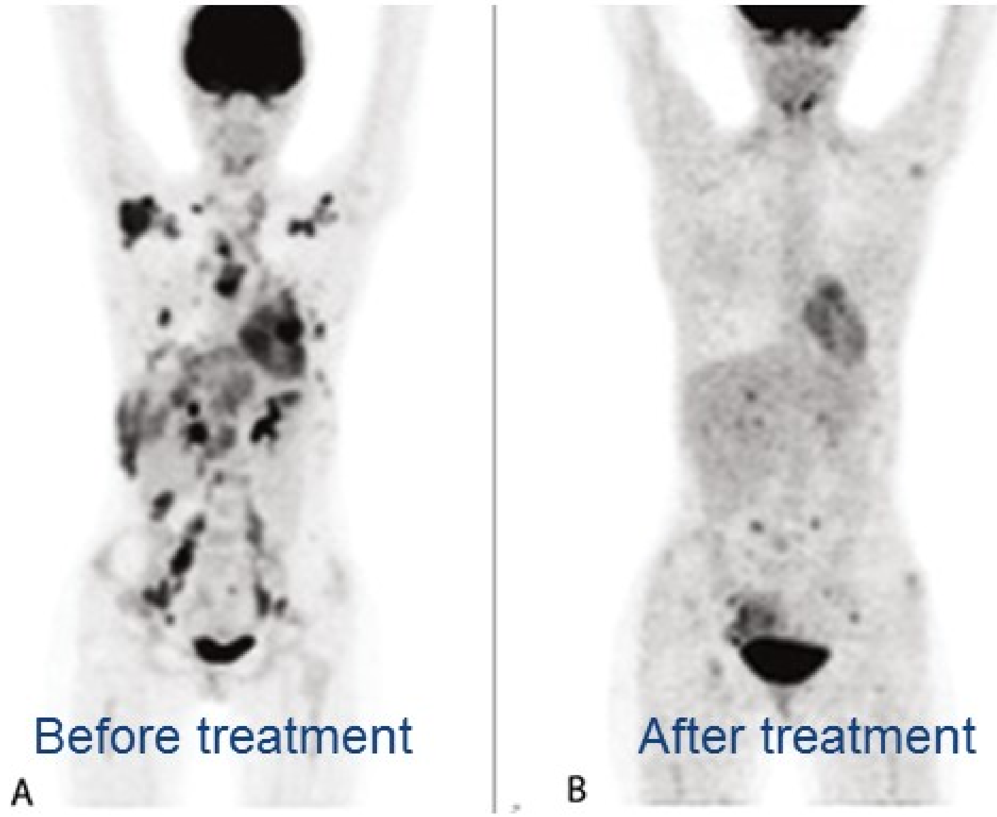
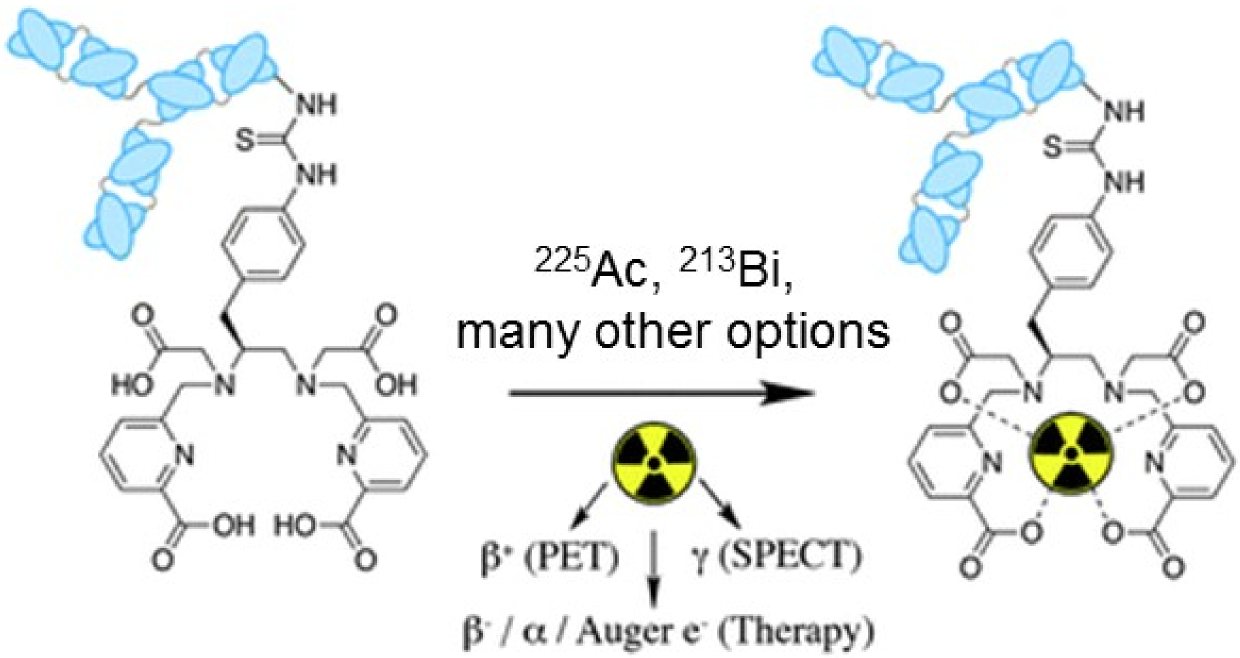


Image taken from:
CME Aug 2013 Vol. 31 (8), 292

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

Future Direction: Therapeutic Isotopes



Promising α-emitters:

^{211}At

^{225}Ac

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

^{212}Pb

^{223}Ra

^{227}Th

^{149}Tb

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

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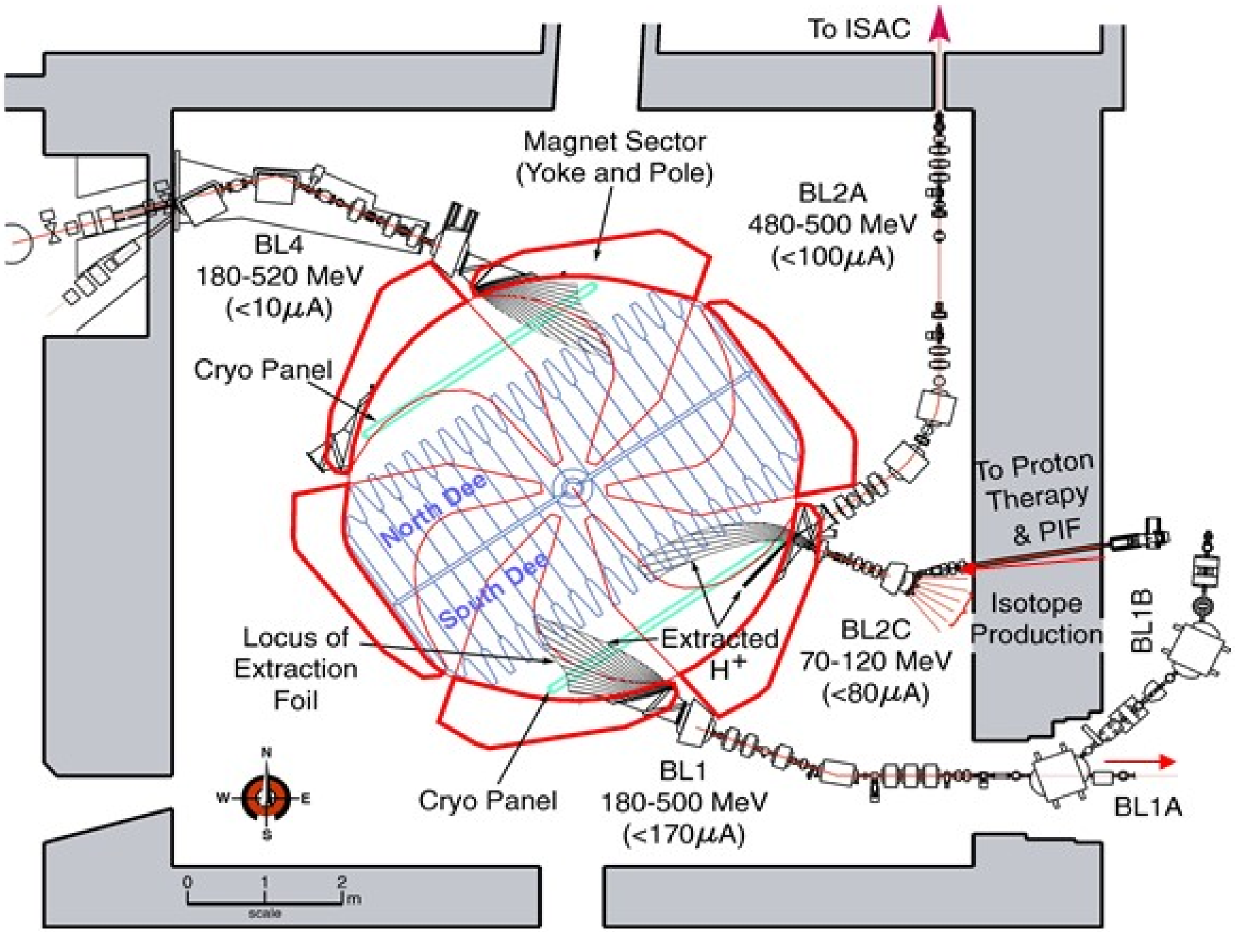
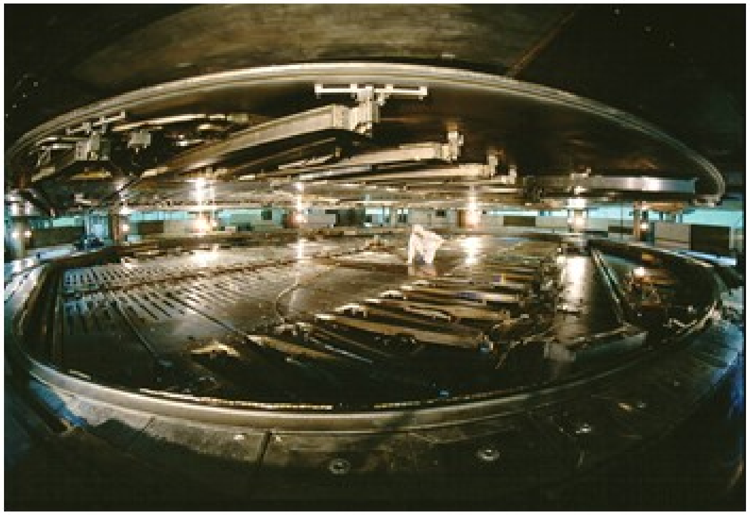
How Does Radionuclide Therapy Work?

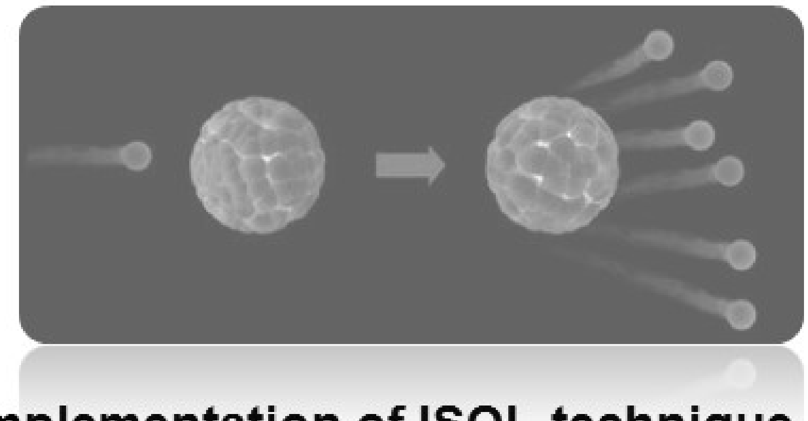
TRIUMF: 500 MeV Cyclotron Capabilities





TRIUMF: Isotope Accelerator Program (ISAC)

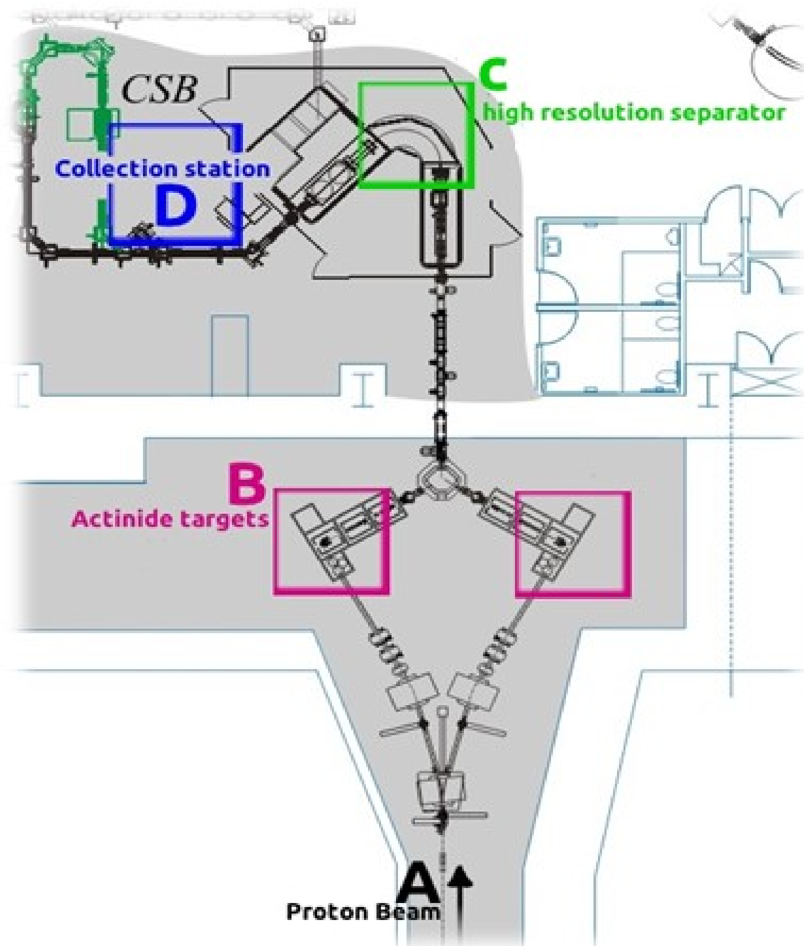
Isotope production via spallation of uranium, thorium:



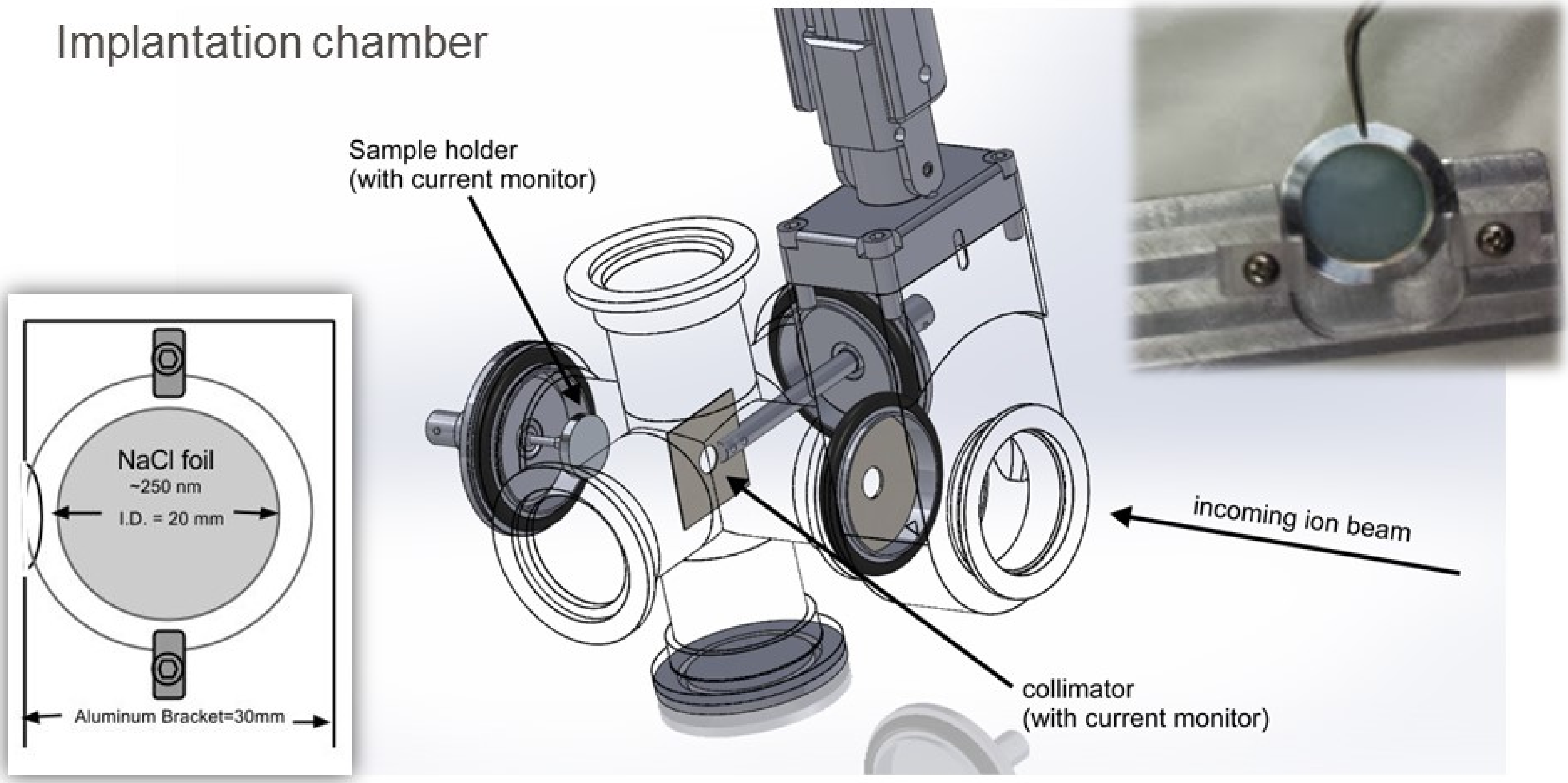
Implementation of ISOL technique

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

* using ^{238}U – non-enriched



Implantation chamber



ARIEL: The Future of TRIUMF

The **A**dvanced **R**are **I**sotop**E** **L**aboratory 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

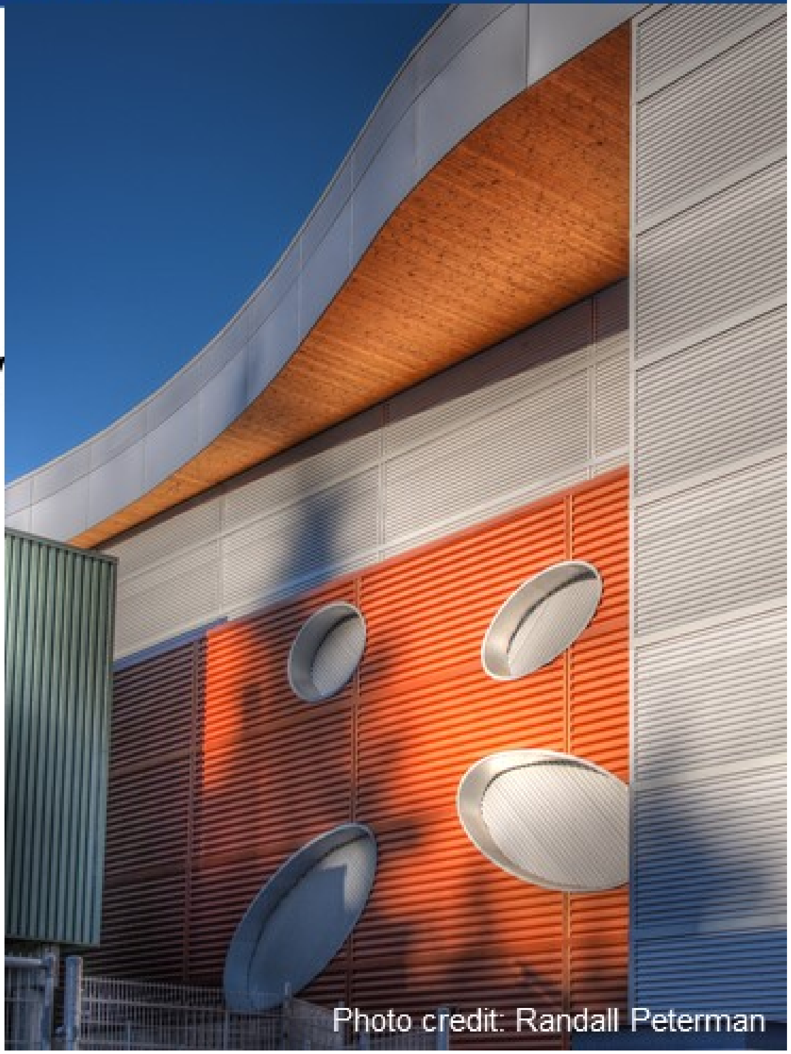


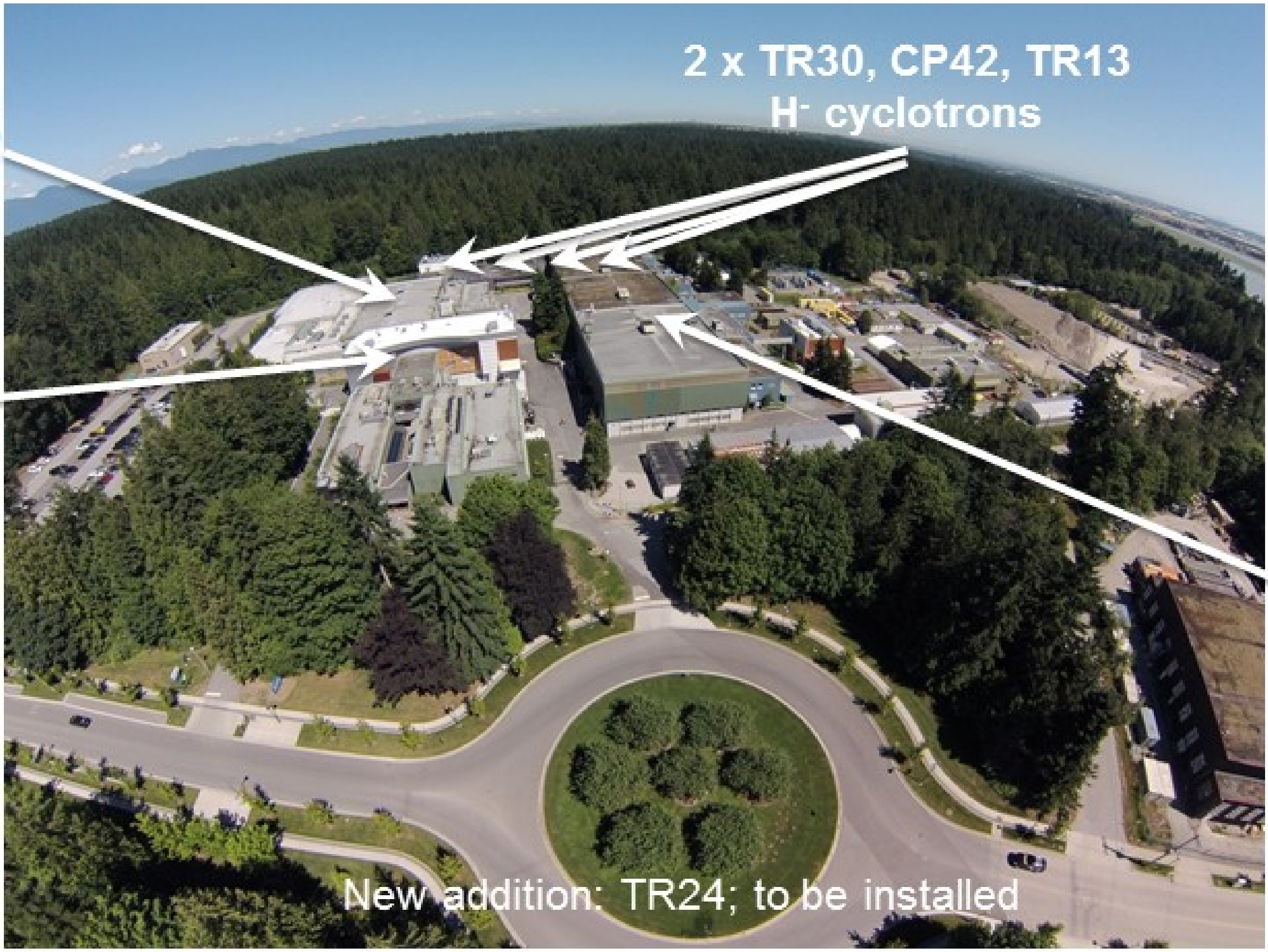
Photo credit: Randall Peterman

TRIUMF Accelerators: From Basic to Applied Research

TRIUMF

ISAC (RIB linac)

ARIEL
(50 MeV
electron linac)



500MeV
H^- cyclotron

TRIUMF

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