TRIUMF

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

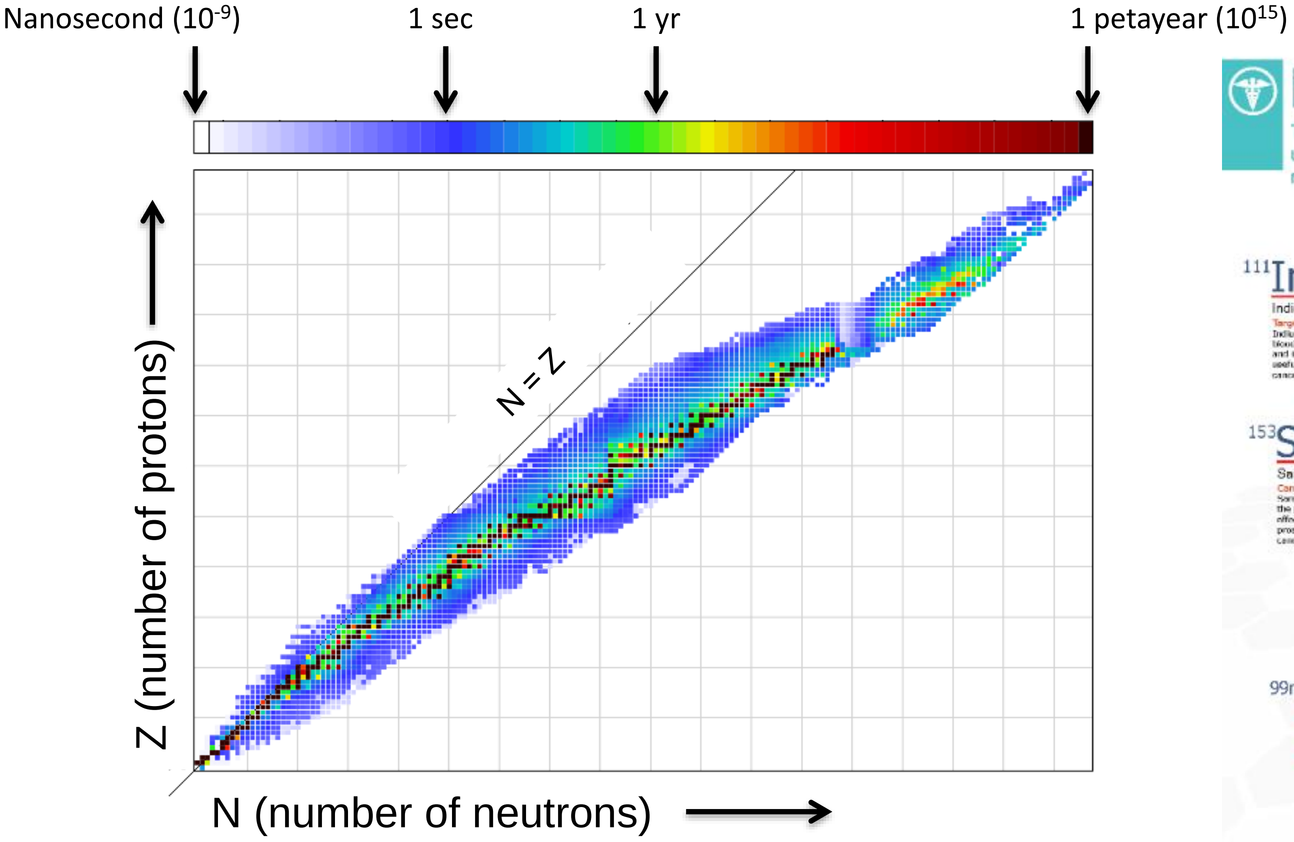
Medical Isotopes

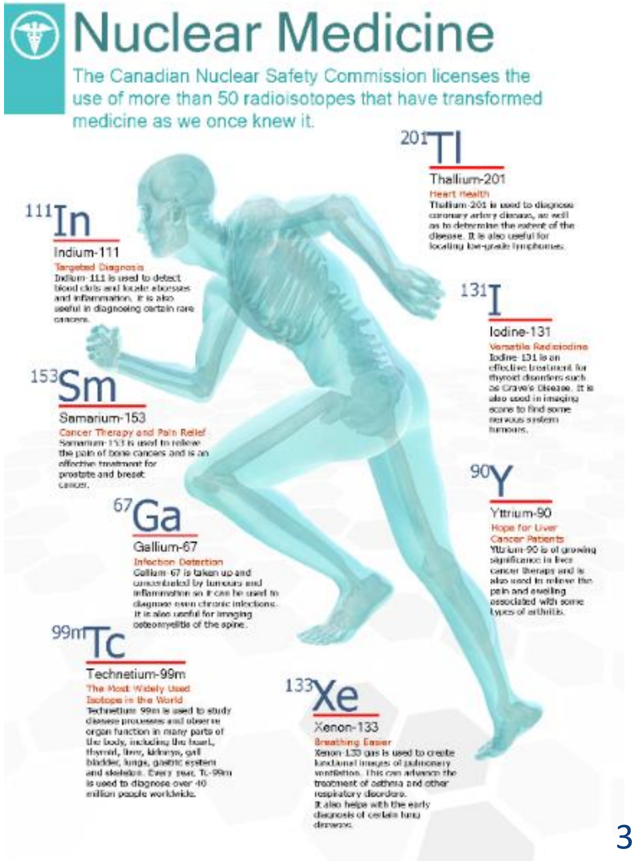
Paul Schaffer
Associate Laboratory Director – Life Sciences, TRIUMF

November 7, 2017

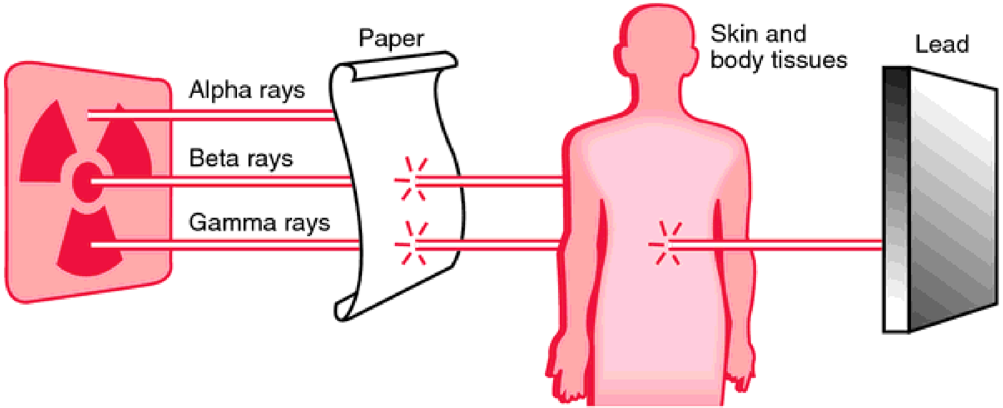
Disclosures

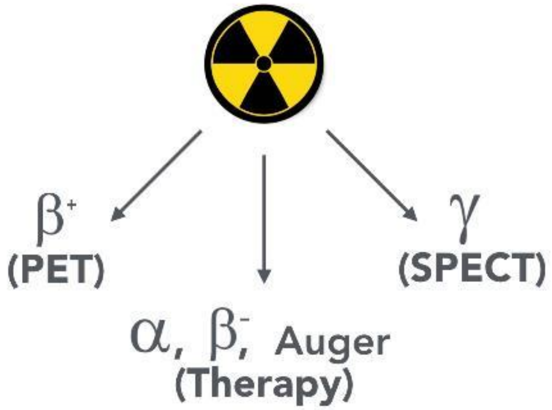
- I am a full-time employee of TRIUMF
- I hold an unpaid position (interim CEO), ARTMS Products, Inc.
- TRIUMF is part owner of ARTMS Products, Inc.
- I am a listed inventor on several patents in technology licensed to ARTMS





Taken from: http://www.cs.uml.edu/teams-academy/uploads/Physics4/nuclides.png





Considerations:
- Emission type/intended application
- Radiological properties: half-life, branching ratio(s)
- Chemical properties: compatibility with radiopharmaceutical process

1920s Biological experiments with natural radioactivity

(***Tracer principle***) G. deHevesy

Biological experiments with artificial radioactivity

1935 *Phosphorus metabolism in rats (^{32}P)*

O. Chievitz, G. deHevesy

1945 *Inhalation of ^{11}CO*

C.A. Tobias, J.H. Lawrence, F. Roughton

since 1946 Availability of many long-lived reactor-produced radionuclides

since 1960 Production of large number of short-lived radionuclides using cyclotrons for in-vivo studies

1980s Emergence of modern PET imaging

Current Status: Diagnostic vs Therapeutic Isotopes

Diagnostic Radionuclides

- **For SPECT**

  γ-emitters (100 – 250 keV)

  ^{99m}Tc, **(steady use)**

  ^{123}I **(increasing)**

  ^{201}Tl, ^{67}Ga **(declining)**

Therapeutic Radionuclides

- β^{-}-emitters (^{32}P, **^{90}Y**, ^{131}I, ^{153}Sm, **^{177}Lu**)
- α-emitter (^{211}At, **^{223}Ra, ^{225}Ac**)
- Auger electron emitters (^{111}In, ^{125}I, ^{119}Sb)
- X-ray emitter (^{103}Pd)

(increasing significance)

- **For PET**

  β^{+} emitters (511 keV photons)

  ^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{82}Sr (^{82}Rb), ^{64}Cu **(increasing use)**

  ^{68}Ge (^{68}Ga) **(rapidly increasing use)**

Making Isotopes

Reactor

Cyclotrons
(Accelerators)

Isotope Generators

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

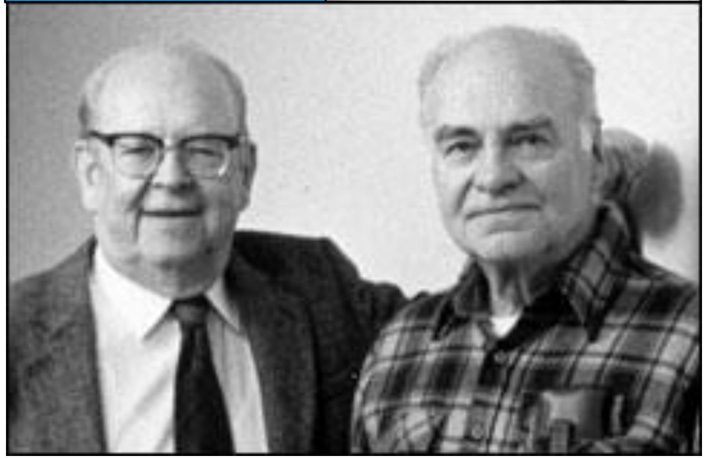
^{82}Sr/^{82}Rb
(25.4 d, 1.3 min)

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

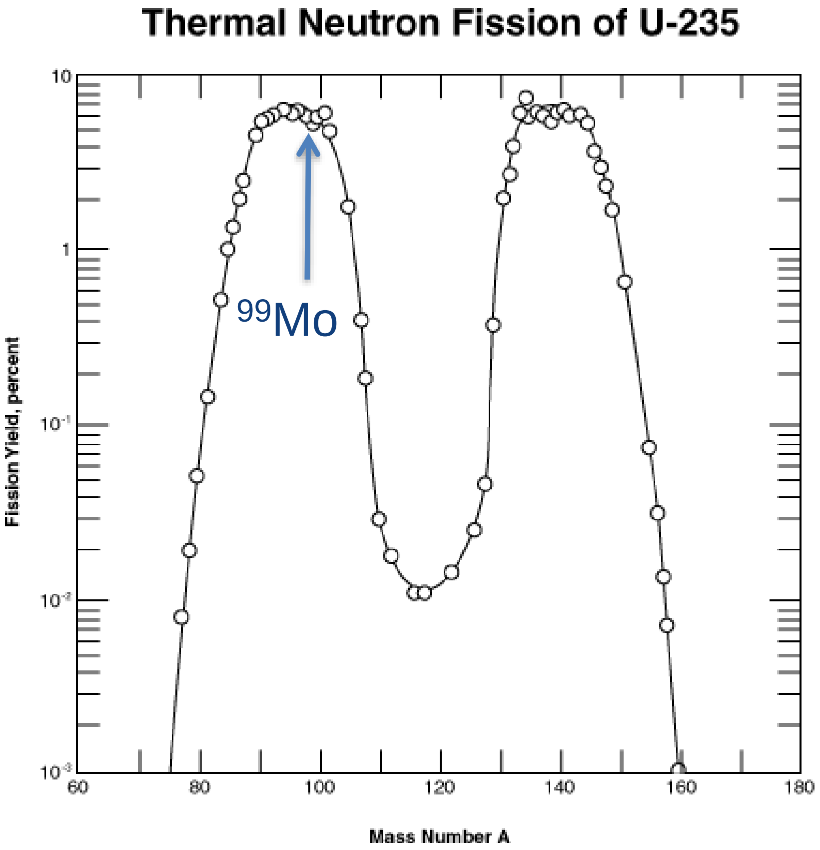
- Transportable, easy to use
- Some (^{68}Ga) experiencing wait times, difficult and expensive to purchase

Technetium

- BNL, 1950s: Walter Tucker and Margaret Green developed the first ^{99}Mo/^{99m}Tc generator (1957)
- 1958 patent application abandoned due to low market potential
- 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" (half-life = 6 hrs, 140 keV, ~100% IT)
- By 1966, BNL backed out of generator production in favour of commercial suppliers
- **Currently used in 30-40 million patients/yr**



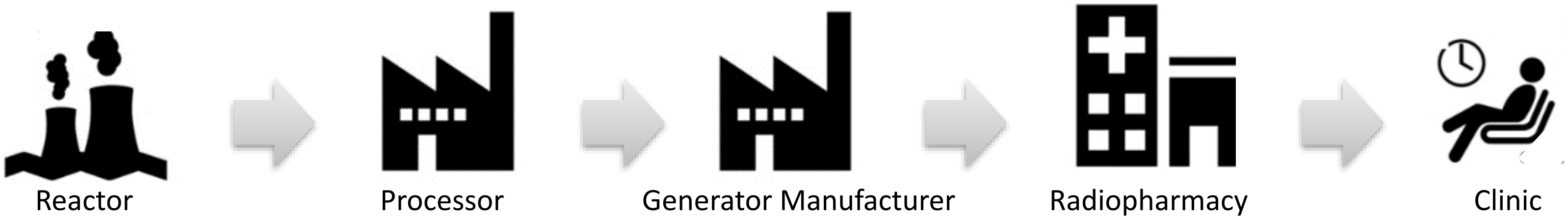
Making Isotopes: Reactors



http://www.toolboxpro.org/classrooms/template.cfm?ID=1730&P=113563

Reactor Supply Model

Issues:
- Economics/subsidies
- Politics/misuse
- Social/environmental
- Single point of failure



Reactor Supply: Focus on one isotope: $^{99}Mo/^{99m}Tc$

- Current ^{99}Mo demand: 9,000 6d Ci/wk
- Require 35% buffer capacity for supply stability
- No fewer than 9 producers, 6 processors currently on-line
  - 2 more produces, 1 additional processor expected on-line within 2 years
- Current ^{99}Mo production capacity: ~17,300 6d Ci/wk
  - Additional ~2500 6d Ci/wk capacity coming on-line <2 years
- Challenges continue:
  - Push for full-cost recovery
  - Anti-proliferation - conversion from HEU to LEU
  - 6 of 9 reactors scheduled to end operations within 10 years
  - Some products (^{60}Co, ^{192}Ir, ^{125}I…) not easily produced by other methods

- Production of ^{99}Mo via neutron bombardment of ^{98}Mo: $^{98}Mo(n,\gamma)^{99}Mo$

Current players: NorthStar

- Production of ^{99}Mo via fission of low enriched ^{235}U (with gas extraction):

Current players: nordion

In Pursuit of Alternative Production Methods for $^{99}Mo/^{99m}Tc$

- Production of ^{99}Mo via phototransmutation of ^{100}Mo: $^{100}Mo(\gamma,n)^{99}Mo$

  Current players: NorthStar; Canadian Isotope Innovations

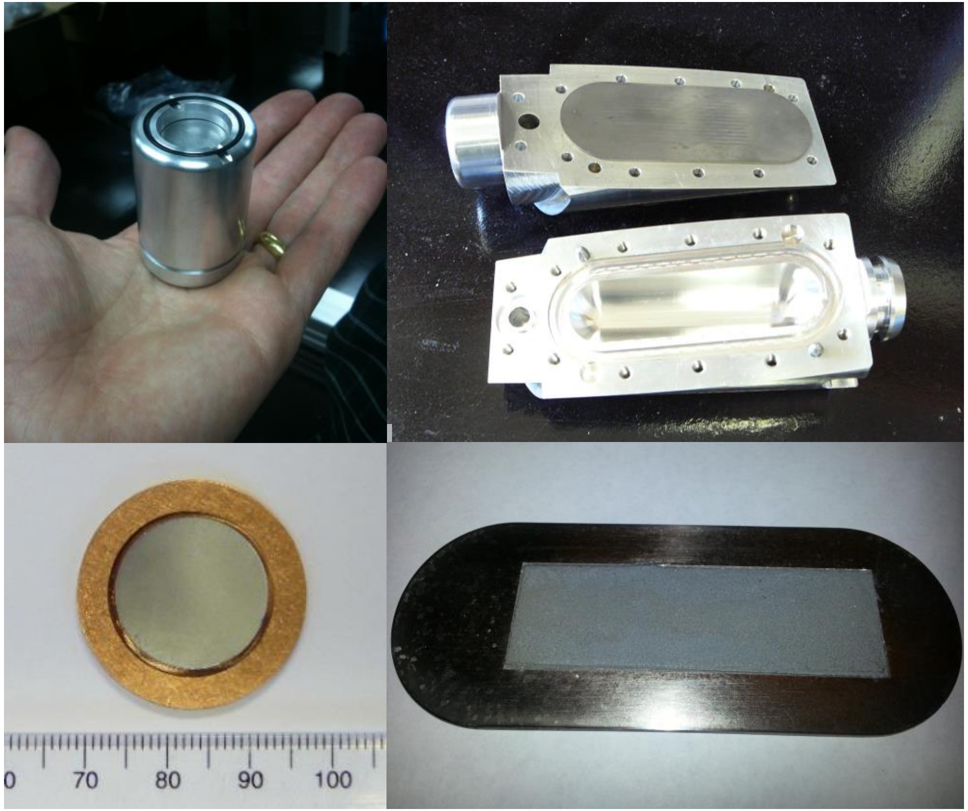
- Production of ^{99}Mo via subcritical fission of ^{235}U: $^{235}U(n,F)^{99}Mo$

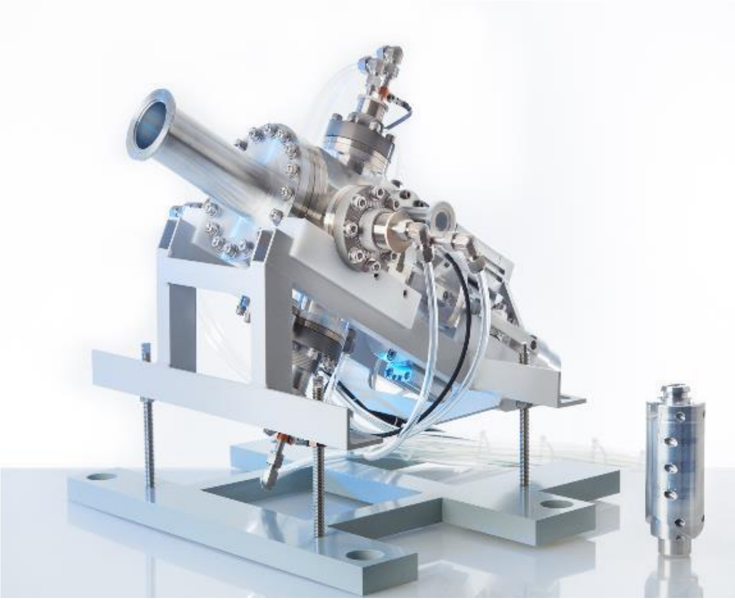
  Current players: SHINE Medical Technologies

- Direct production of ^{99m}Tc via proton irradiation of ^{100}Mo: $^{100}Mo(p,2n)^{99m}Tc$

  Current players: artms; Belgravia Tech, Inc.

Cyclotron-based production of ^{99m}Tc





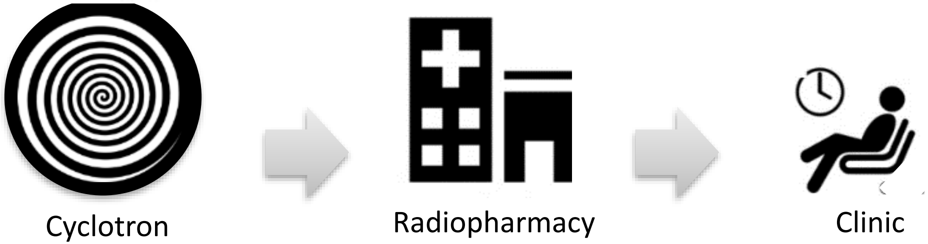
artms

ARTMS: Accomplishments to Date

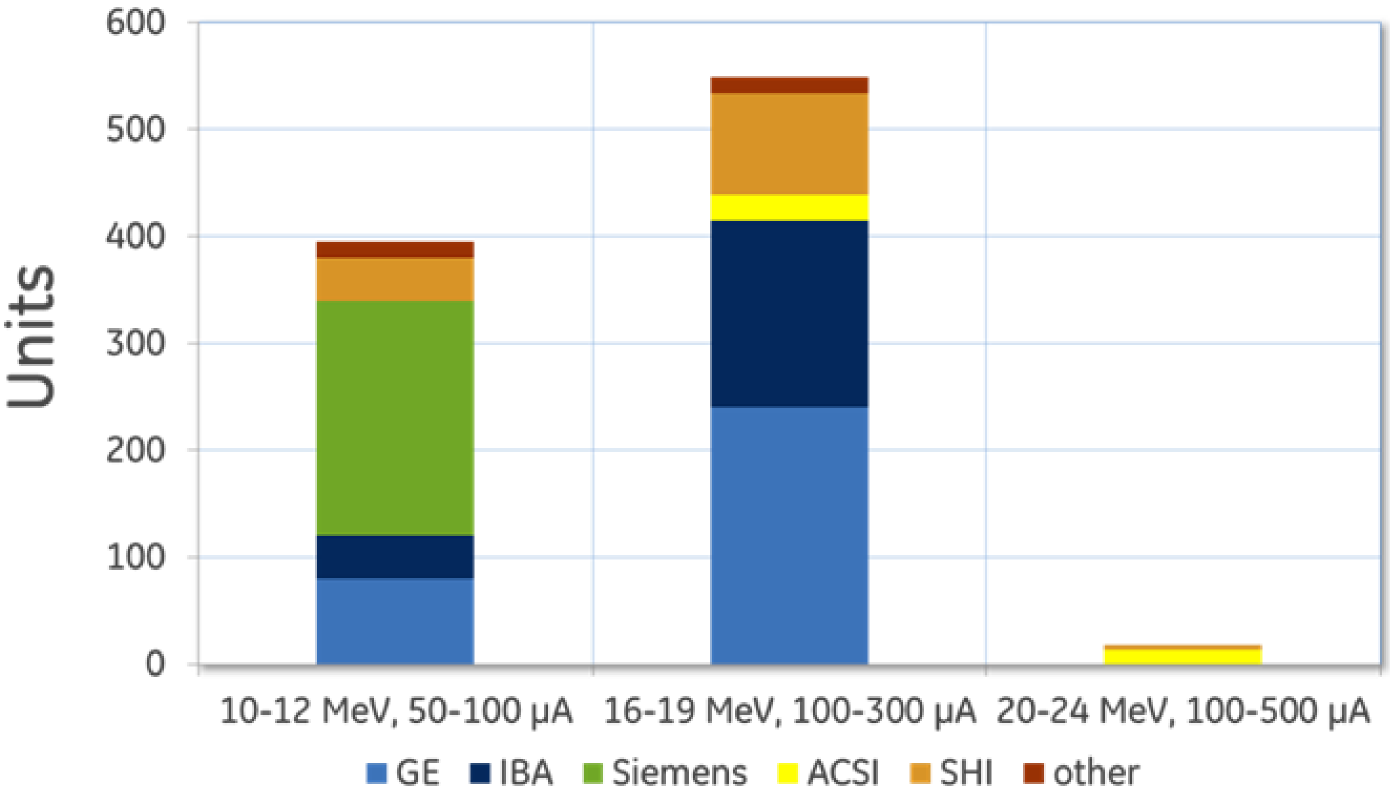
- Production yields of ^{99m}Tc
  - GE **PETTrace** (16.5 MeV, 130 μA): **4.7 Ci** in 6 hrs
  - ACSI **TR19** (18 MeV, 240 μA): **13.9 Ci** in 6 hrs
  - ACSI **TR30** (24 MeV, 450 μA): **~39** Ci in 6 hrs
- Concurrent ^{18}F production demonstrated successfully
- Purification efficiency: >**93%**
- ^{99}Mo recycling efficiency: **>95%**
- Clinical trial completed
- Regulatory filings for Canada, UK underway
- System installed in Denmark, scheduled for UK, Switzerland

Cyclotron Supply Model

Issues:
- Decentralized/regulatory
- Complex compared to generator
- Shorter-lived isotopes

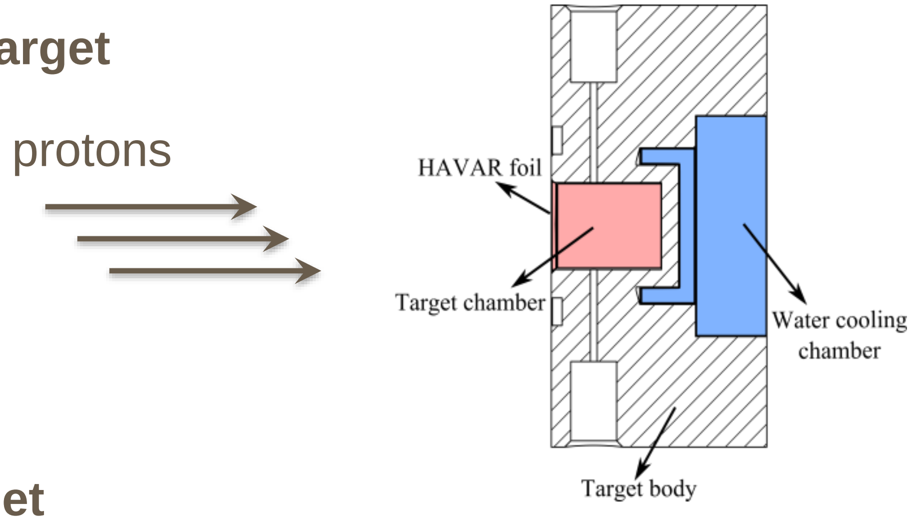


Global Cyclotron Count

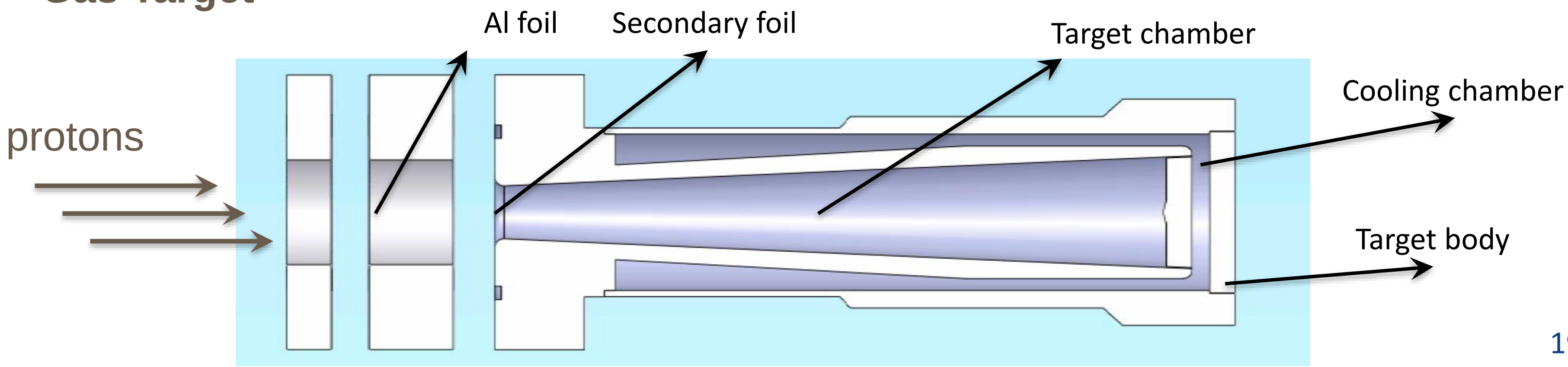


P Schaffer, F. Benard, A. Berstein et al. Phys Proc. 2015, 66, 383.

Liquid Target

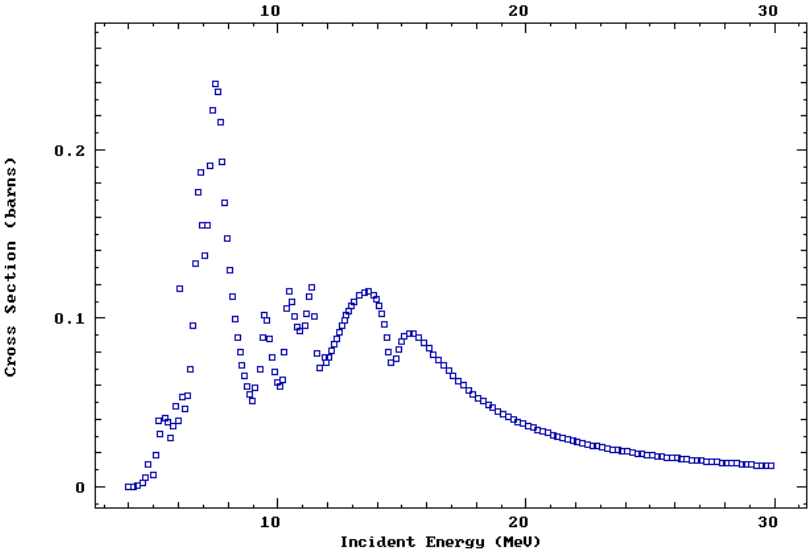


Gas Target

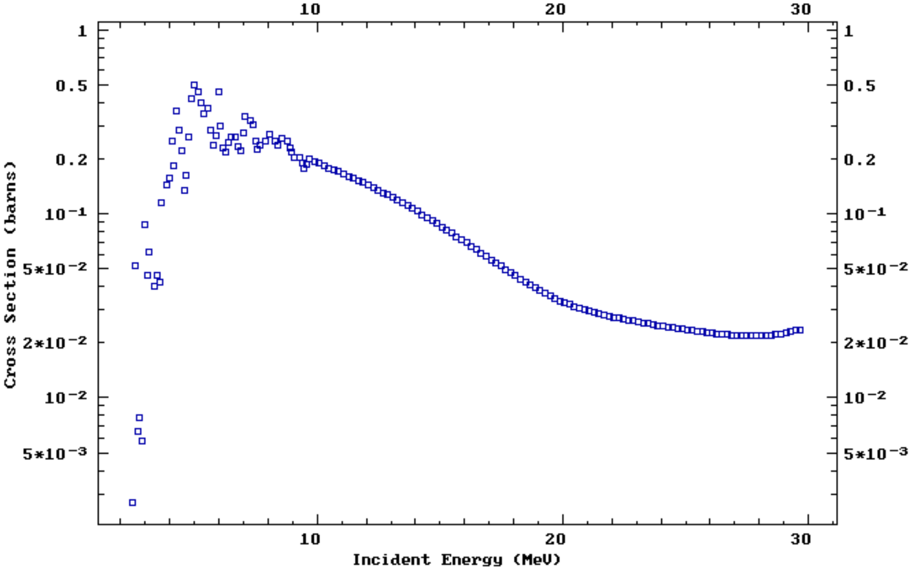


Cyclotron Production: F-18 and C-11

$^{14}N(p,\alpha)^{11}C$



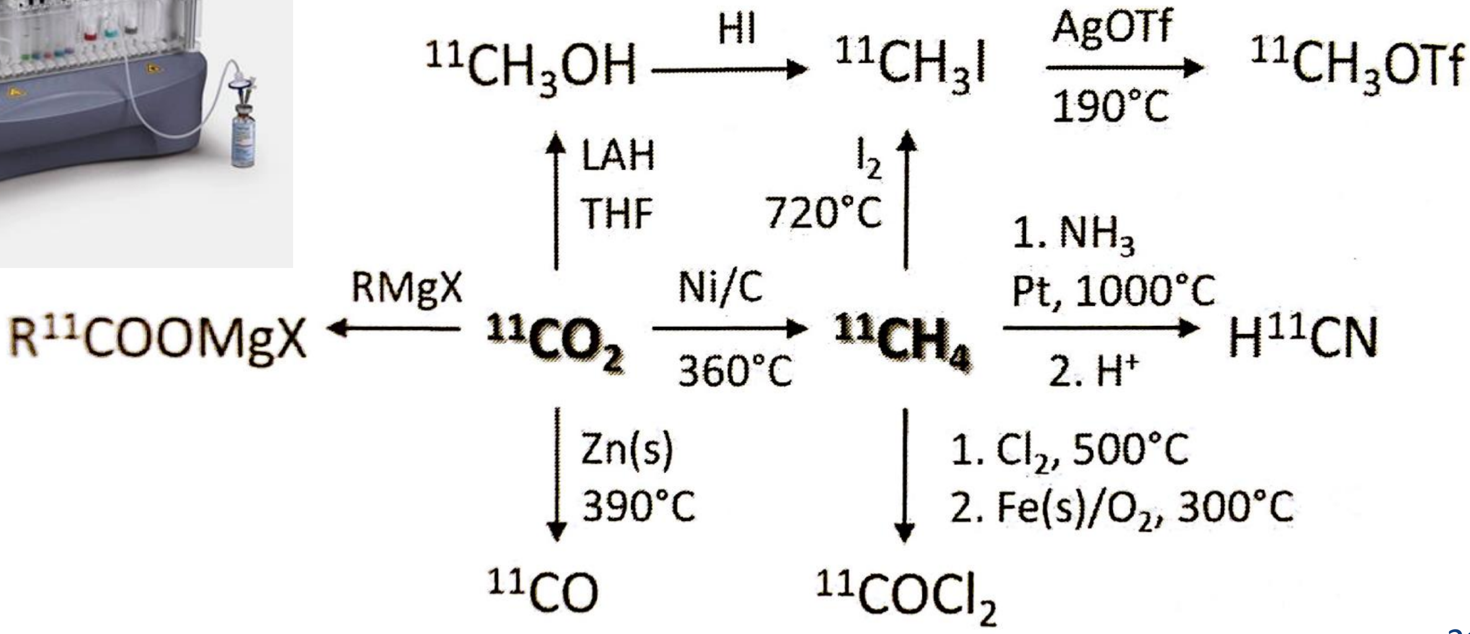
$^{18}O(p,n)^{18}F$

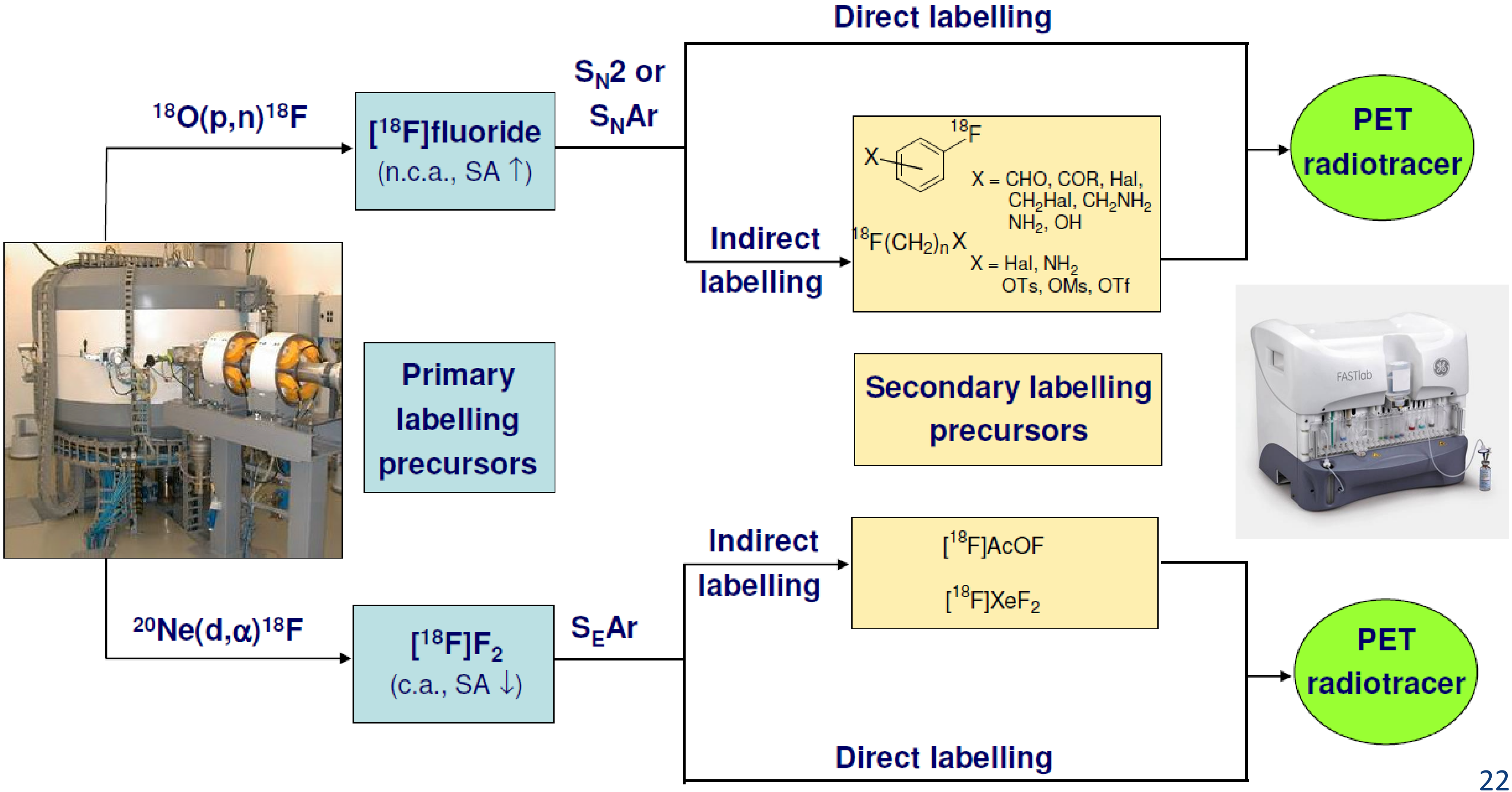


- Can be produced in gas ($^{11}CH_4$, $^{11}CO_2$, $^{18}F_2$) or liquid ($^{18}F^-$) form
- Easy to manipulate post irradiation
- Well established, automated chemistry

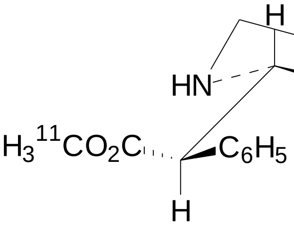
Plots obtained using EXFOR: Nucl. Data Sheets 2014, 120, 272; S. Takács JNIM/B 2003,211,169


FASTlab

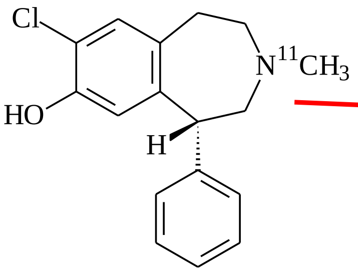

$^{11}CH_3OH$
HI
$^{11}CH_3I$
AgOTf
190°C
$^{11}CH_3OTf$
LAH
THF
I_2
720°C
1. NH_3
Pt, 1000°C
2. H^+
$H^{11}CN$
$R^{11}COOMgX$
RMgX
$^{11}CO_2$
Ni/C
360°C
$^{11}CH_4$
Zn(s)
390°C
^{11}CO
1. Cl_2, 500°C
2. Fe(s)/O_2, 300°C
$^{11}COCl_2$


Direct labelling
$^{18}O(p,n)^{18}F$
$[^{18}F]$fluoride
(n.c.a., SA ↑)
S_N2 or
S_NAr
^{18}F
X
X = CHO, COR, Hal, CH_2Hal, CH_2NH_2 NH_2, OH
Indirect labelling
$^{18}F(CH_2)_nX$
X = Hal, NH_2 OTs, OMs, OTf
PET radiotracer
Primary labelling precursors
Secondary labelling precursors
FASTlab
Indirect labelling
$[^{18}F]AcOF$
$[^{18}F]XeF_2$
$^{20}Ne(d,\alpha)^{18}F$
$[^{18}F]F_2$
(c.a., SA ↓)
S_EAr
PET radiotracer
Direct labelling

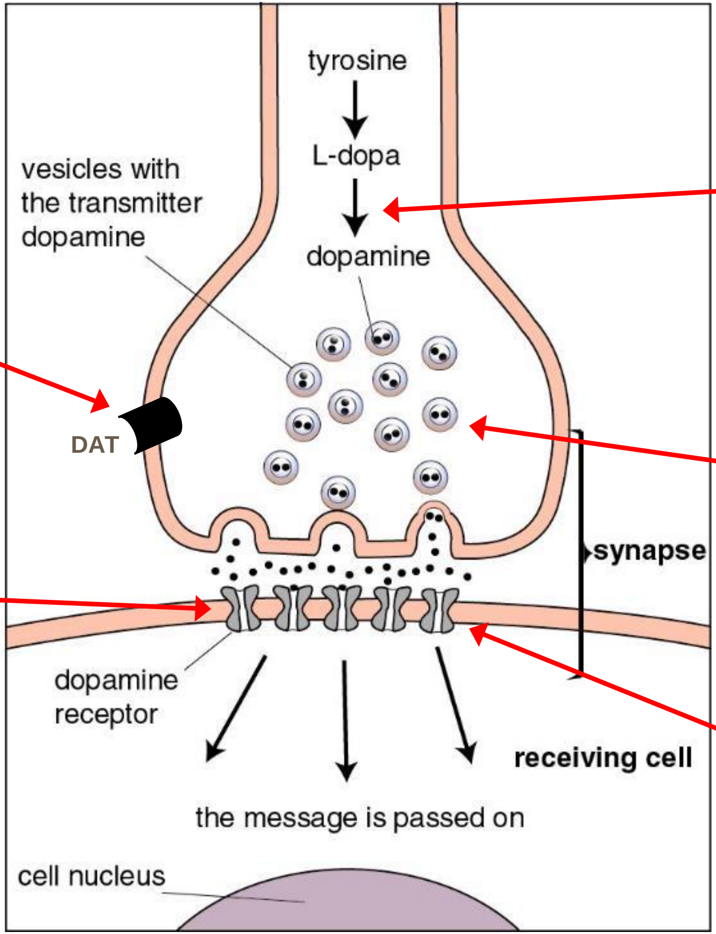
Example: Neurology

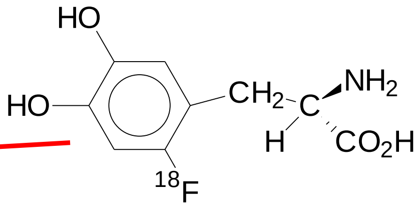


Methylphenidate

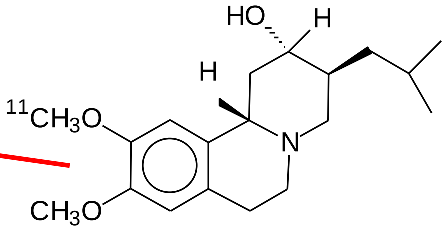


Sch233900

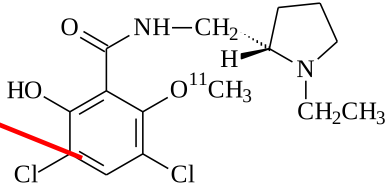




FDOPA

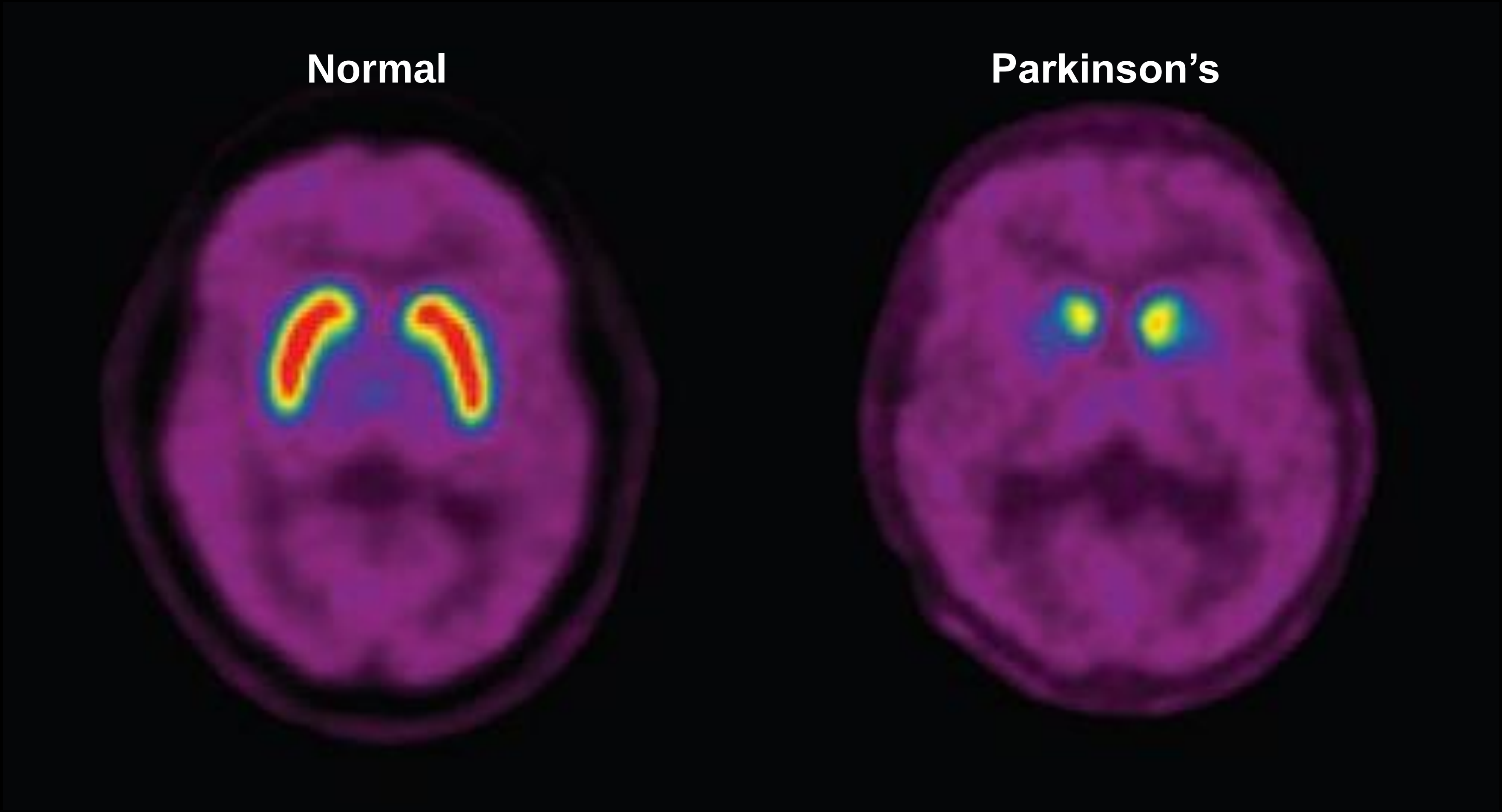


DTBZ



Raclopride

PET is Functional Imaging



Radiotracers: Tools of the Trade

Generation 1: Simple: salts, diffusion-based, non-specific imaging

$^{99m}TcO_4$, ^{99m}TcMDP, $^{18}F^-$ (bone), colloid (liver)

Generation 2: Targeted, small molecule, metabolic

^{99m}TcMIBI (heart), ^{99m}Tc-exametazime/ECD (brain), ^{18}FDG (tumors)

Generation 3: Targeted, larger molecular weight (peptides, antibodies), binders

radiolabeled (^{111}In, ^{68}Ga) octreotide, octreotate, ^{99m}Tc TRODAT, PSMA

Generation 4(?): Theranostic, simultaneous or iso-pharmaceutical imaging/therapy

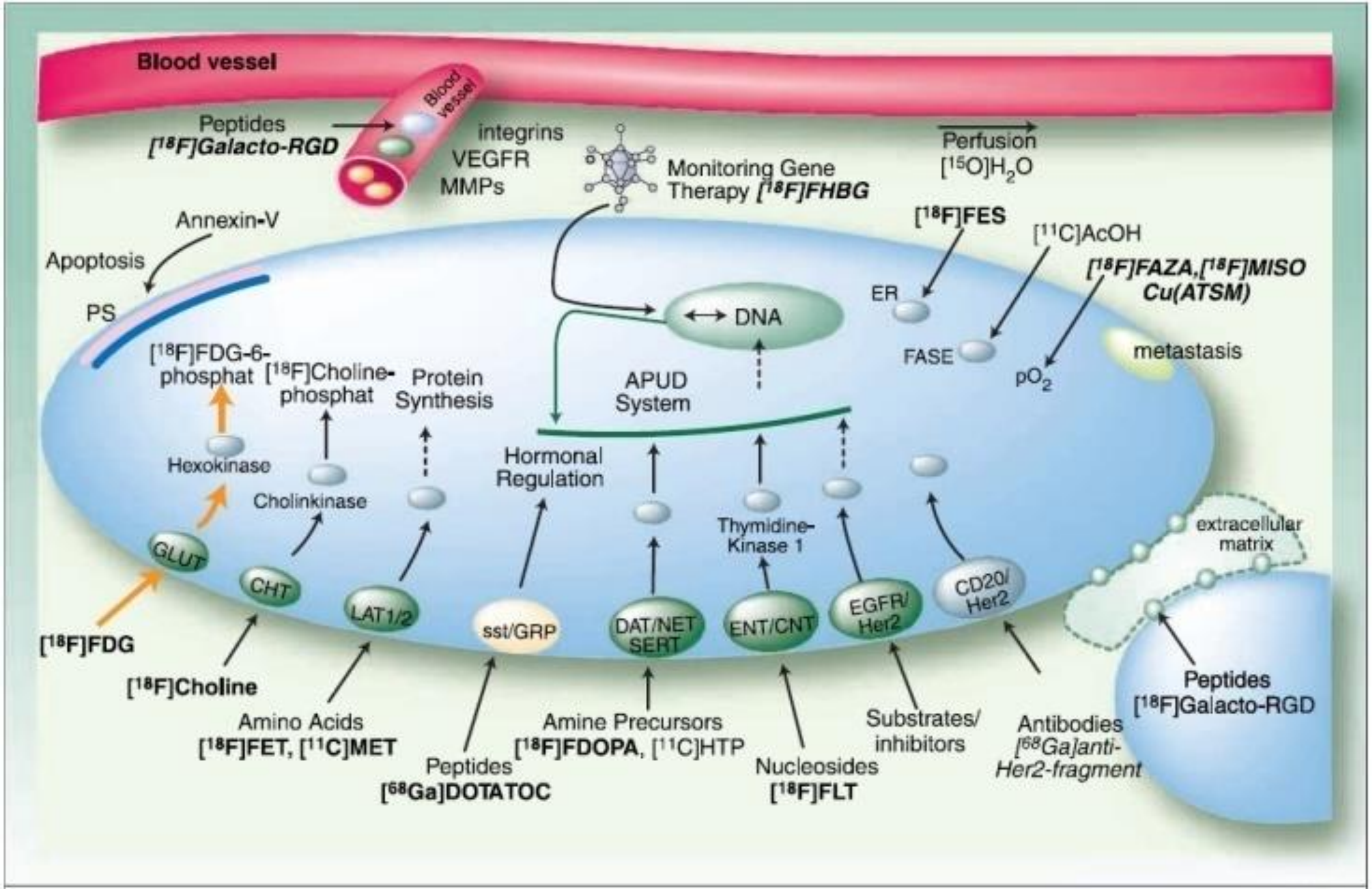
[^{223}Ra]$RaCl_2$ (Xofigo), ^{153}Sm, ^{89}Sr, ^{131}I, [^{131}I]Bexxar, [^{90}Y]Zevalin

^{225}Ac, ^{212}Pb, ^{213}Bi, ^{212}Bi, ^{211}At…targeted using Gen 3 vectors

2013 tracer count*:	PET (all) = 622; (humans) = 122
	SPECT (all) = 430; (humans) = 65

* MICAD Database – final year of online catalogue update

Cellular/Metabolic Targets



Drivers of Radiotracer Development

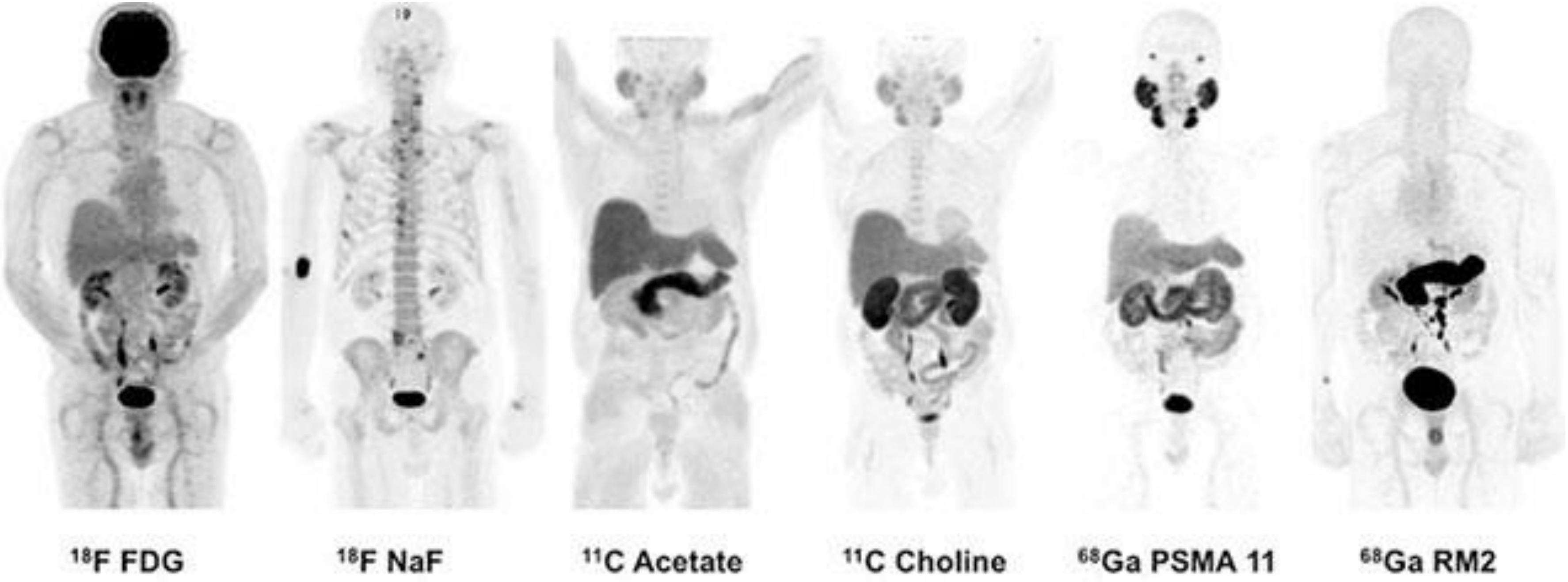
R&D into the ‘Big 4’: cardiovascular, neurological, oncology, metabolic research

Clinic: cardiovascular, oncology, neurology

- emergence of personalized healthcare
- basic treatment response – surgery, chemo, radiation
- move to use imaging to improve/avoid unnecessary treatment
    - molecular identification (breast, neuroendocrine), specific cellular antigens
- result: high cost of development to benefit few patients
- recent push into more general tracers, but with complementary utility to FDG
    - alternative metabolics (amino acids)

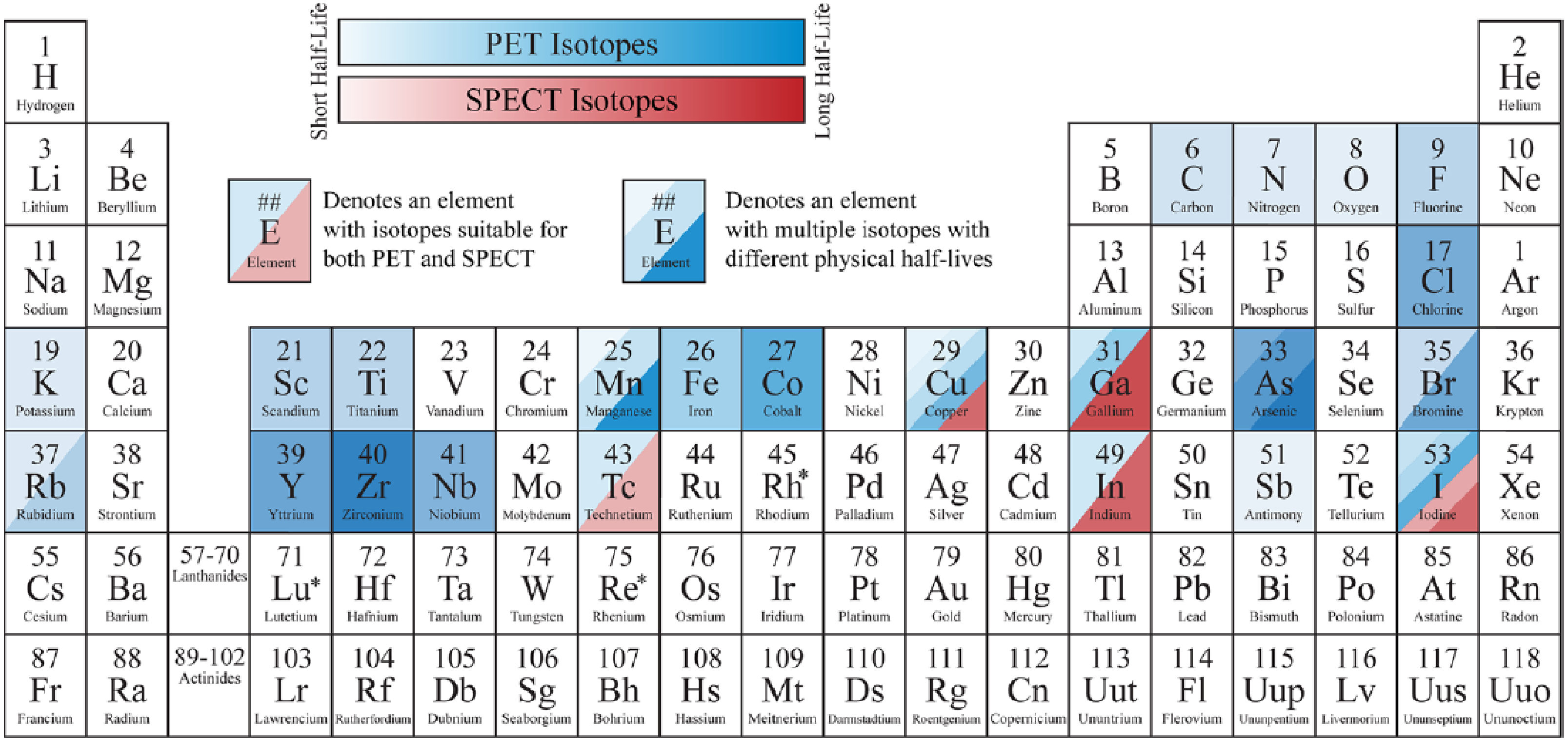
- Not all fields ready
    - Neurology – challenges with treatment, unable to treat even if one knew
    - i.e. Parkinson’s, Alzheimers

83-year-old man with biochemically recurrent prostate cancer



A. Iagaru, et al. J. Nucl. Med. 2016;57(4):557-62

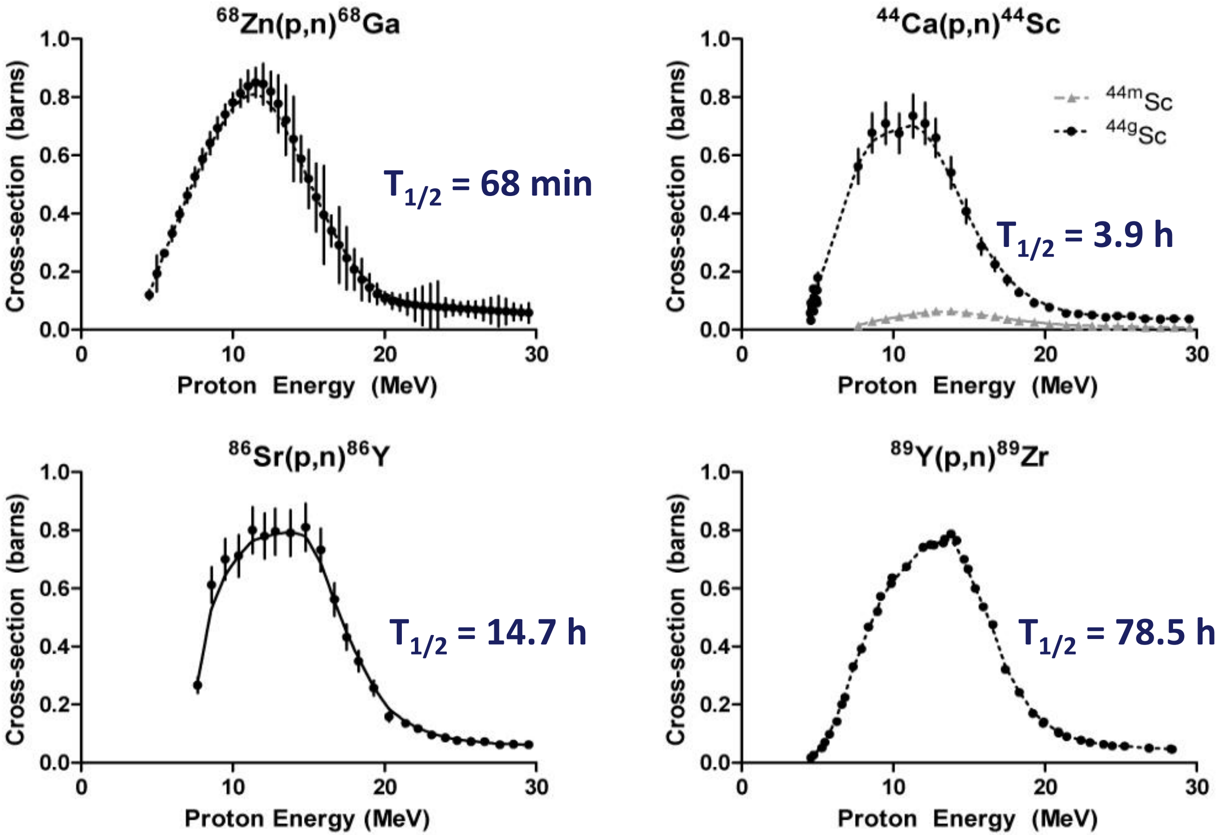
Metallic Radioisotopes Offer Many Options



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

TRIUMF

Radiometals: Excitation Functions



Production routes:

1) Solid Target
2) ‘Salt’ Target

“Toolbox” for Radiometals

^{64}Cu $t_{1/2}$ 12.7 h

^{86}Y $t_{1/2}$ 14.7 h

^{99m}Tc $t_{1/2}$ 6.01 h

^{213}Bi $t_{1/2}$ 0.76 h

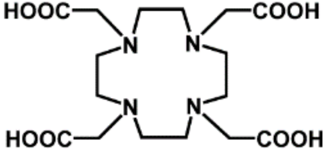
^{68}Ga $t_{1/2}$ 1.13 h

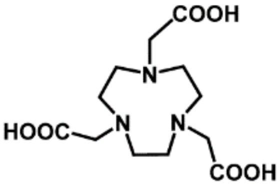
^{44}Sc $t_{1/2}$ 3.97 h

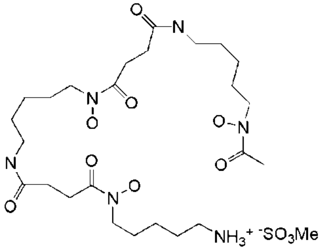
^{90}Nb $t_{1/2}$ 14.6 h

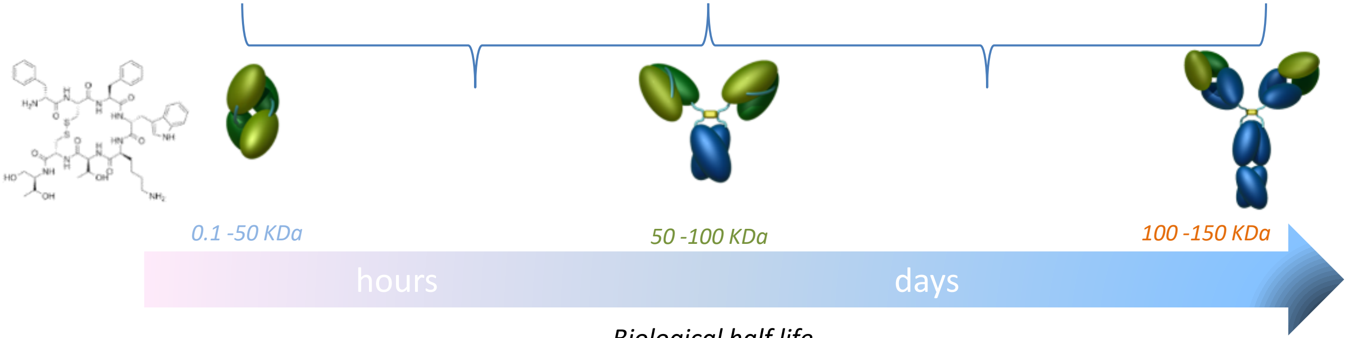
^{89}Zr $t_{1/2}$ 78.4 h

^{225}Ac $t_{1/2}$ 238.1 h



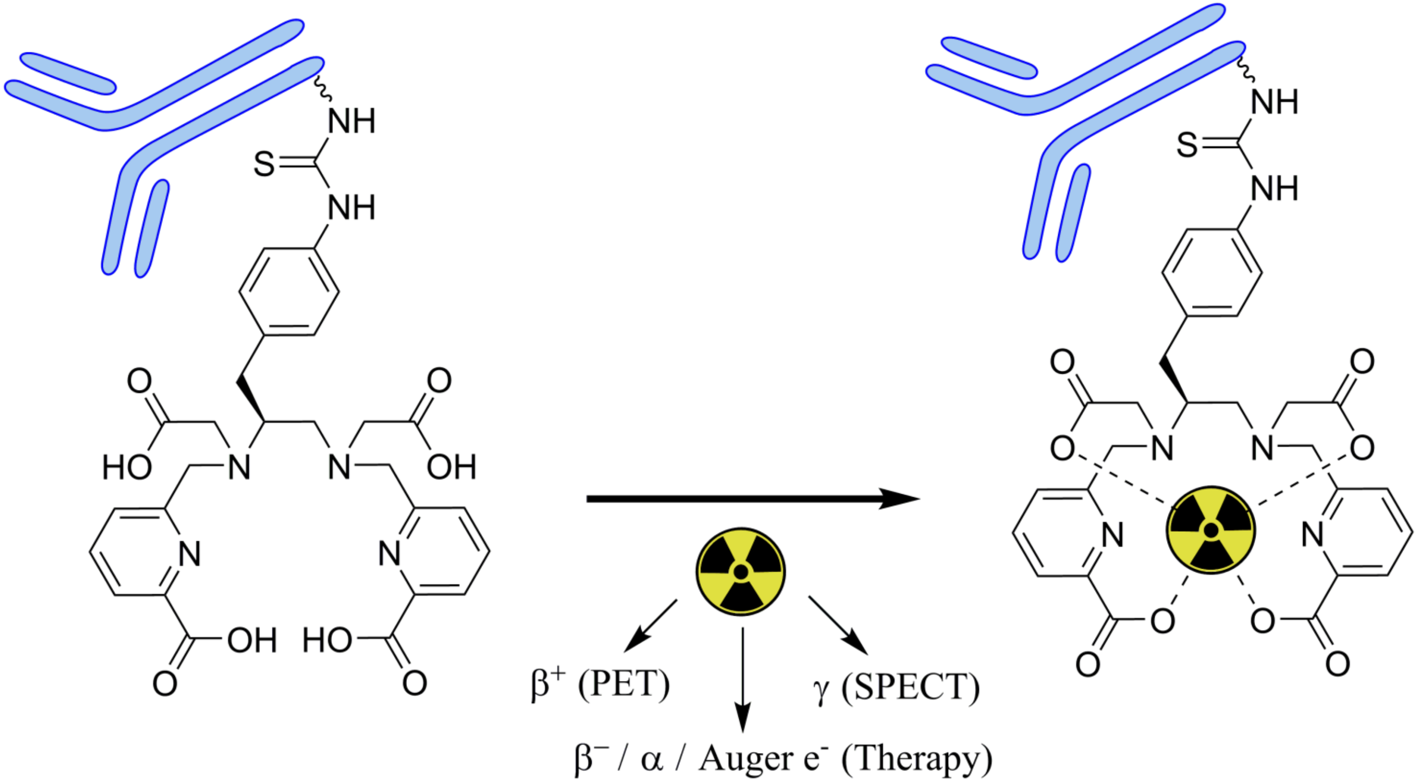






Biological half life

Therapeutic/Theranostic Radiopharmaceutical Development



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

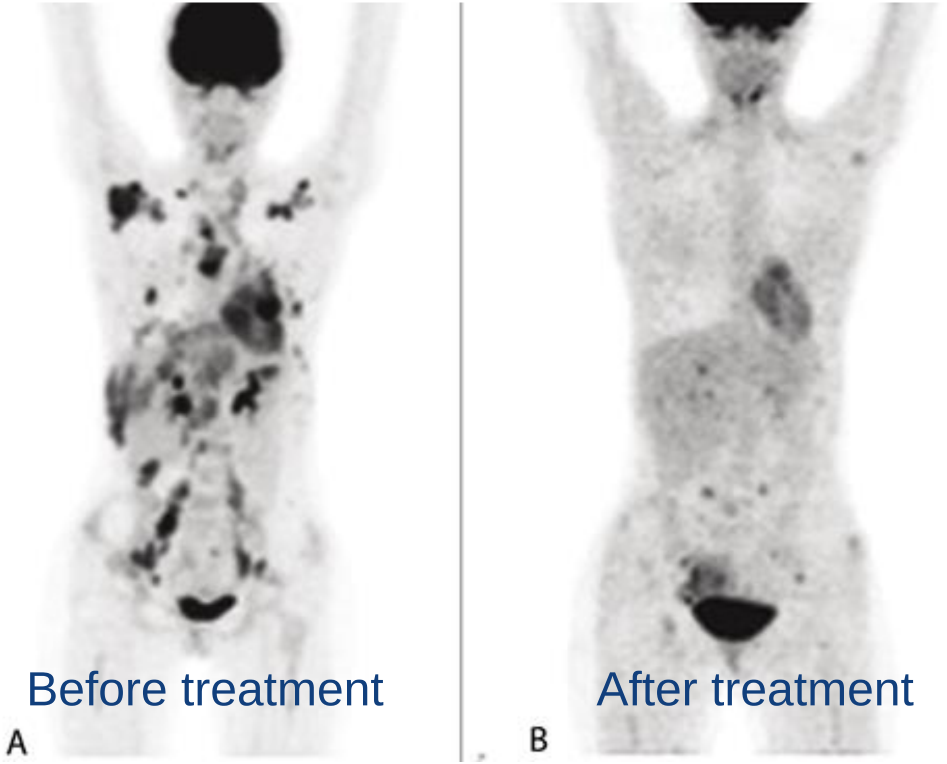
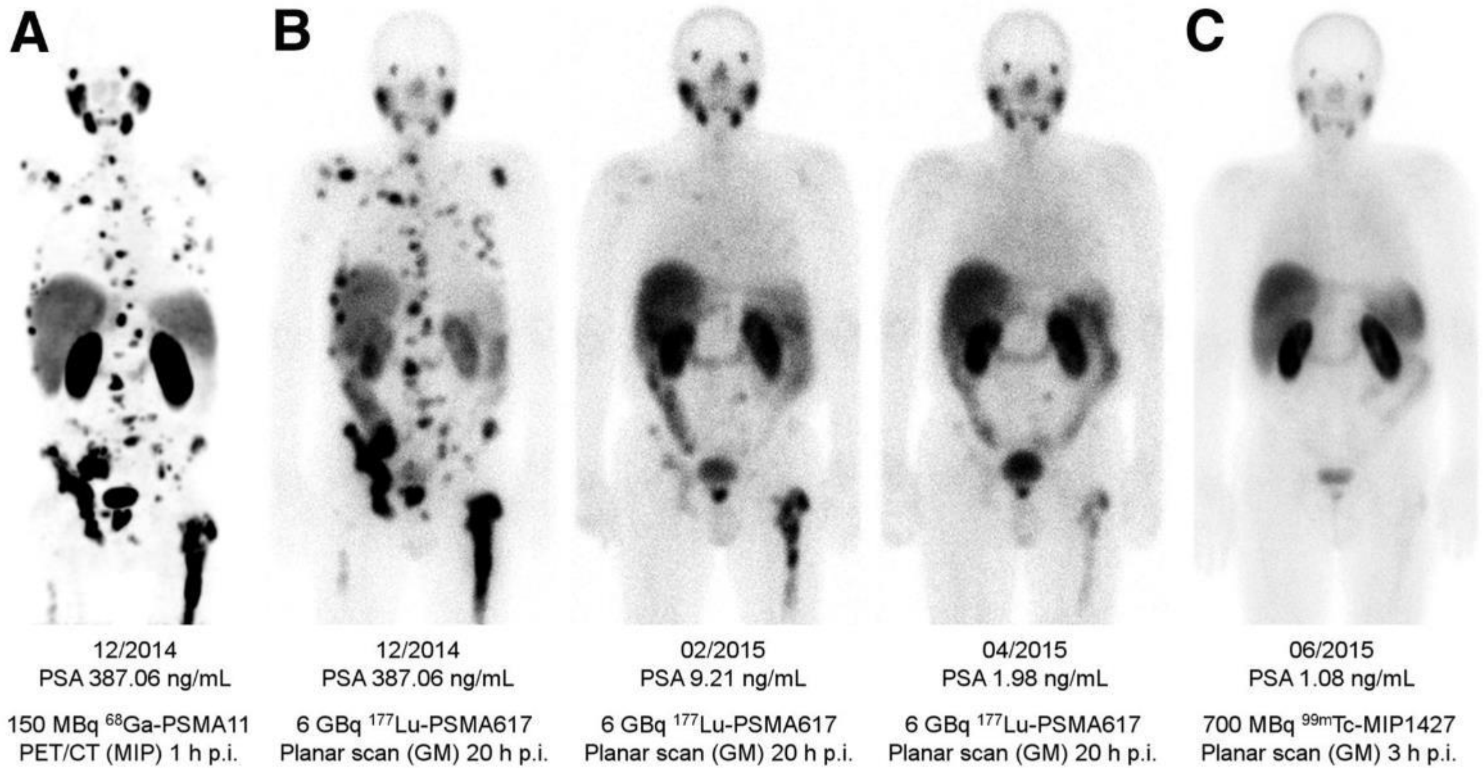


Image taken from:
CME Aug 2013 Vol. 31 (8), 292

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

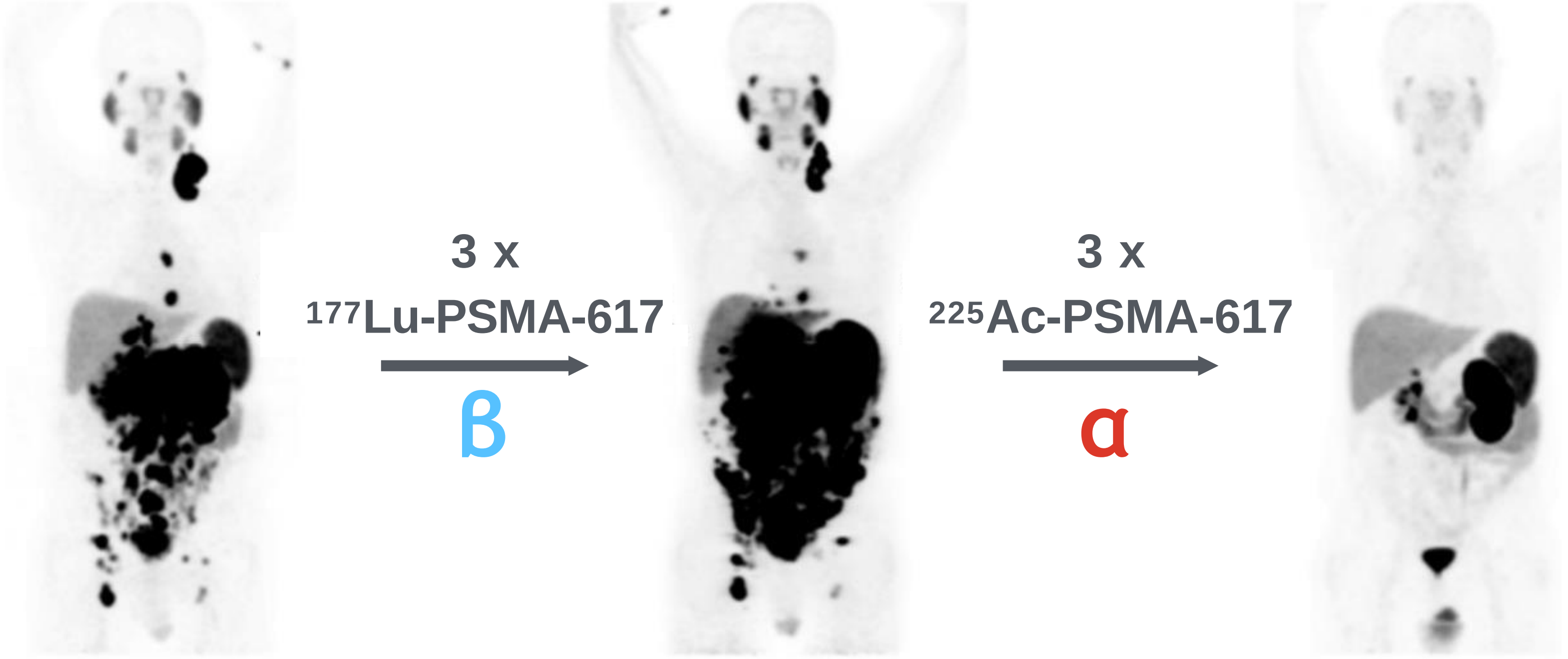
Radionuclide Therapy



(A) PSMA PET/CT delivers highest resolution. C. Kratochwil et al. J Nucl Med 2016, 57, 1170

JNM The Journal of NUCLEAR MEDICINE

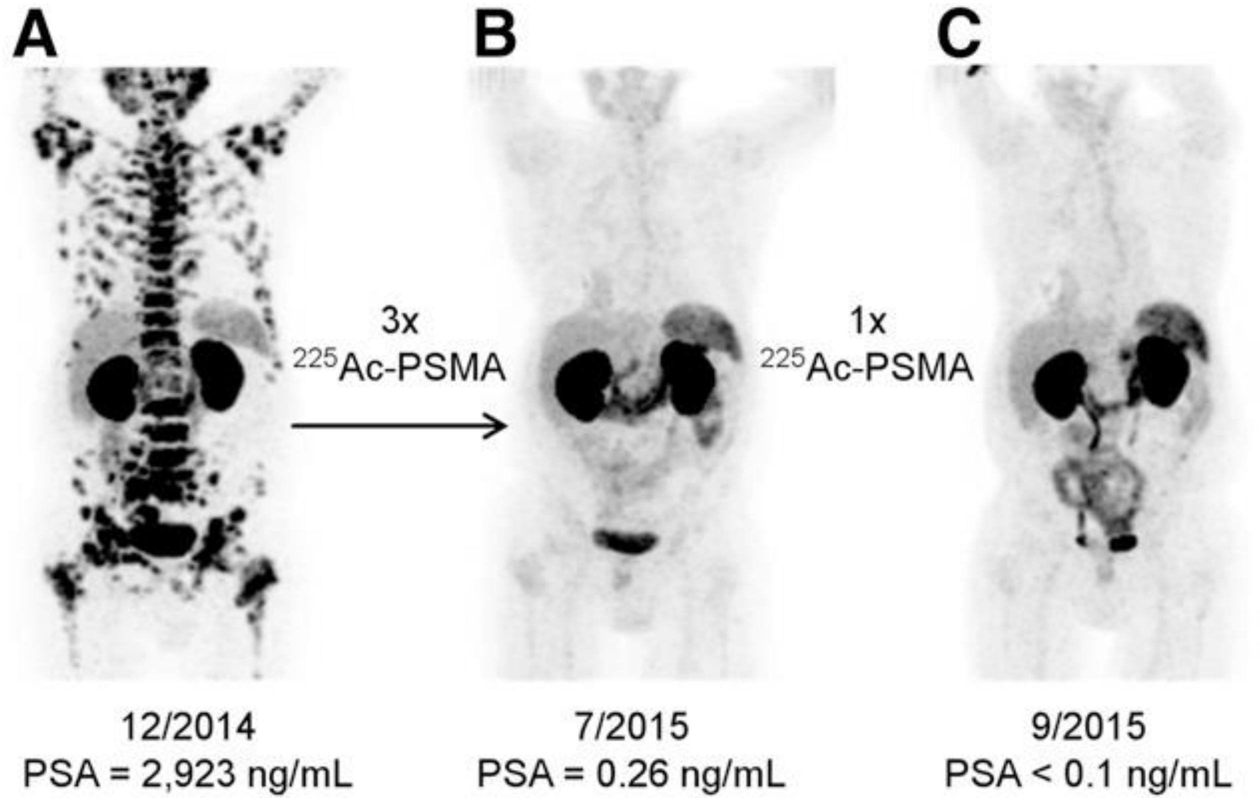
When betas fail....



Kratochwil et al., 2017.

...there are always alphas!

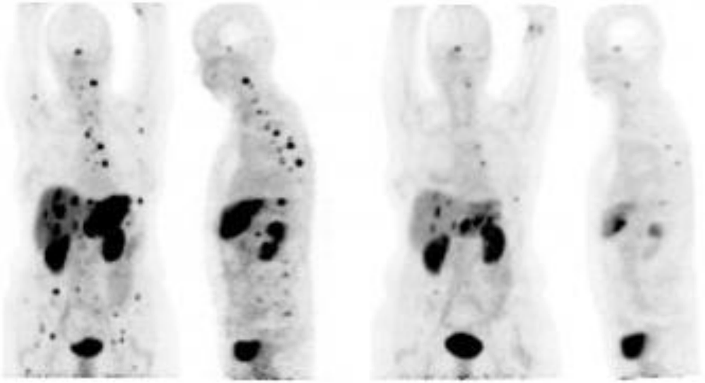
JNM The Journal of NUCLEAR MEDICINE



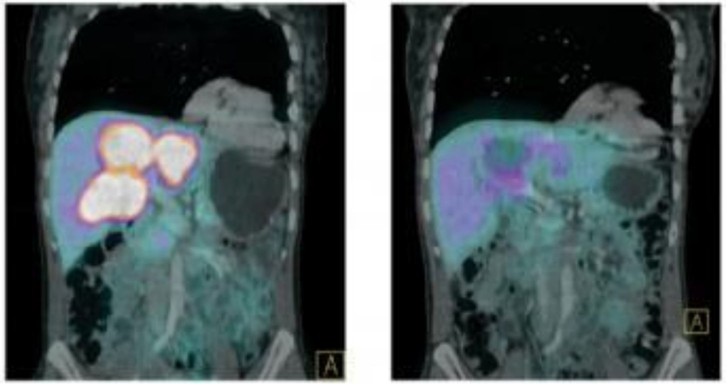
JNM The Journal of NUCLEAR MEDICINE

Kratochwil et al., J. Nuc. Med. July 2016.

Remarkable responses to Bi-213-DOTATOC observed in tumors resistant to previous therapy with Y-90/Lu-177-DOTATOC

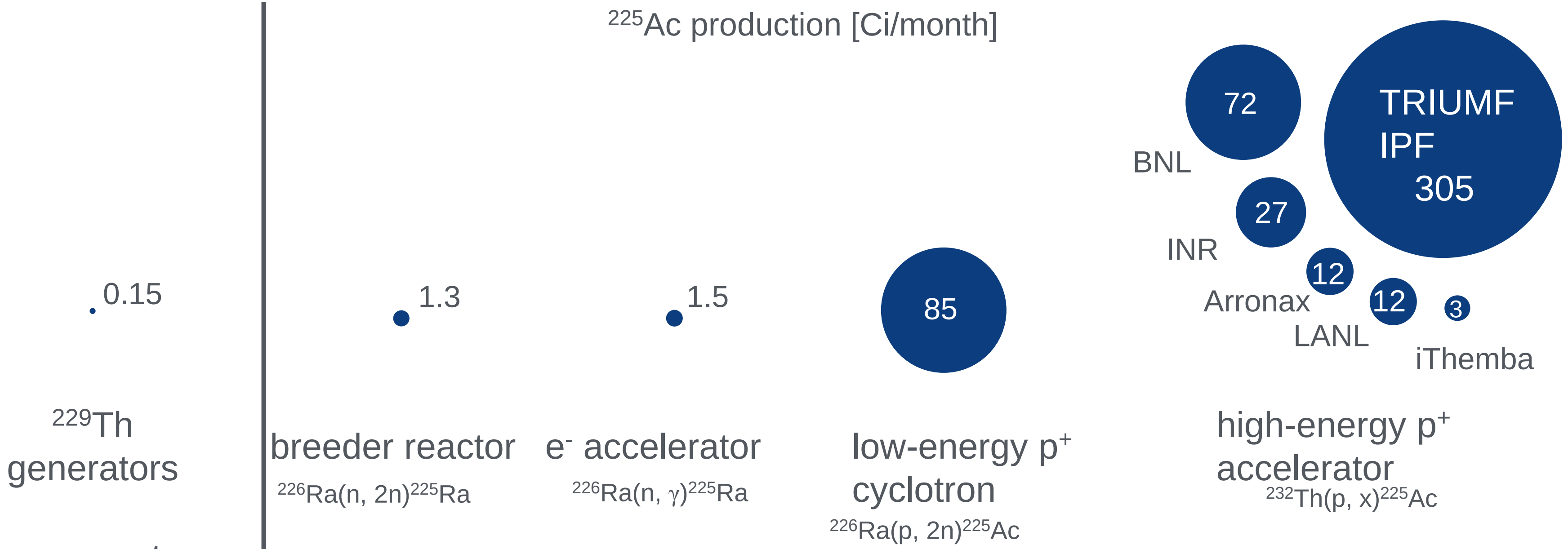


Case I: Shrinkage of liver lesions and bone metastases after i.a. therapy with 11 GBq Bi-213-DOTATOC



Case II: Response of multiple liver lesions after i.a. therapy with 14 GBq Bi-213-DOTATOC

Comparison of ^{225}Ac Production Methods



current production
(worldwide)

potential future production

(theoretical maximum ^{225}Ac monthly production [Ci] for a single facility)

slide courtesy of A. Robertson

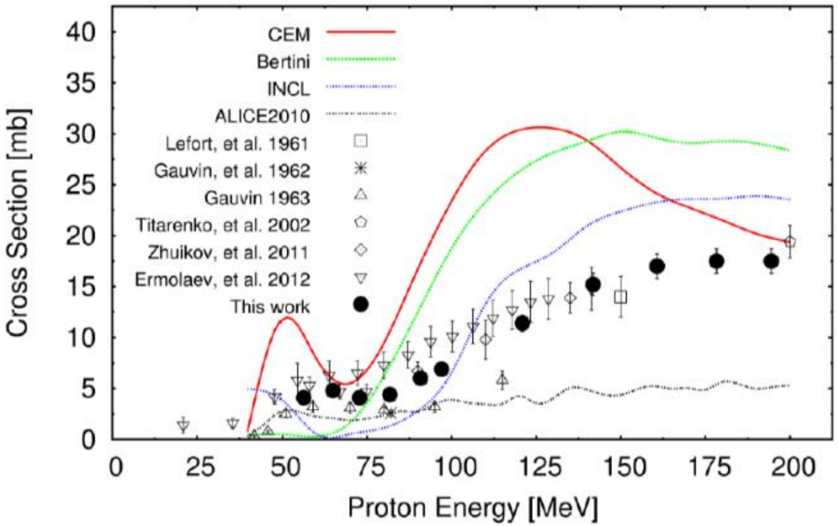
Current ^{225}Ac Production

Primary ^{225}Ac sources:

- ^{229}Th/^{225}Ac generator ($t_{1/2}$ ~ 7880 y) sourced via legacy stockpile, ORNL, ITU
- DOE Tri-Lab efforts: ^{232}Th(p,x) spallation
- Alternatives sought: ^{226}Ra irradiation

Global production is ~1-2 Ci per year (<5000 patients)

- Promising early clinical trial results
- Supply vs demand is out of balance, but market needs to be nurtured, and supply needs to increase and be reliable
- Efforts underway at TRIUMF to establish feasibility of producing bulk quantities of ^{225}Ac

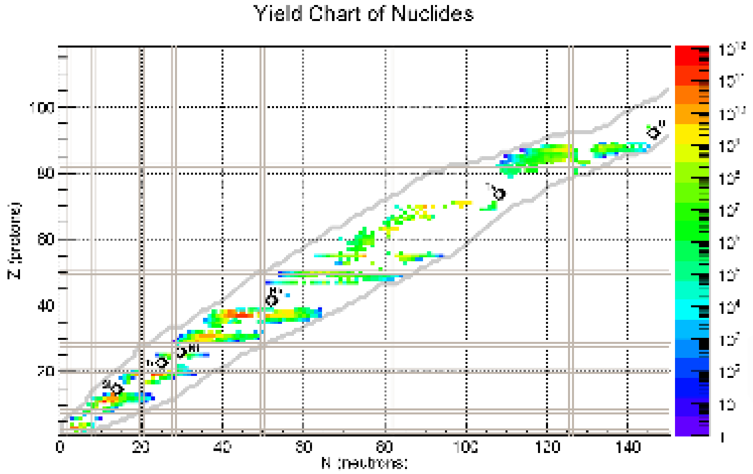


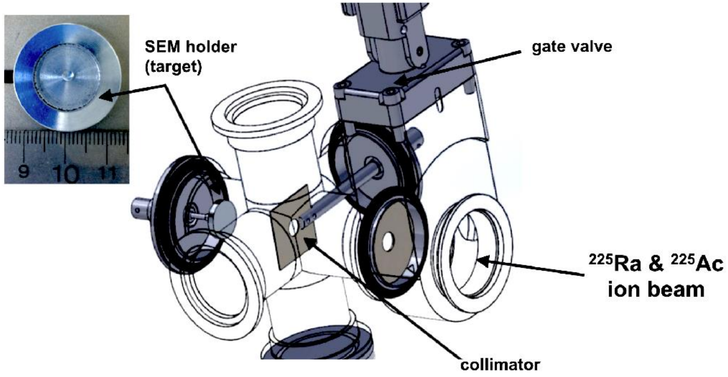
J.W. Weidner et al. Appl. Radiat. Isotop. 2012, 70, 2602

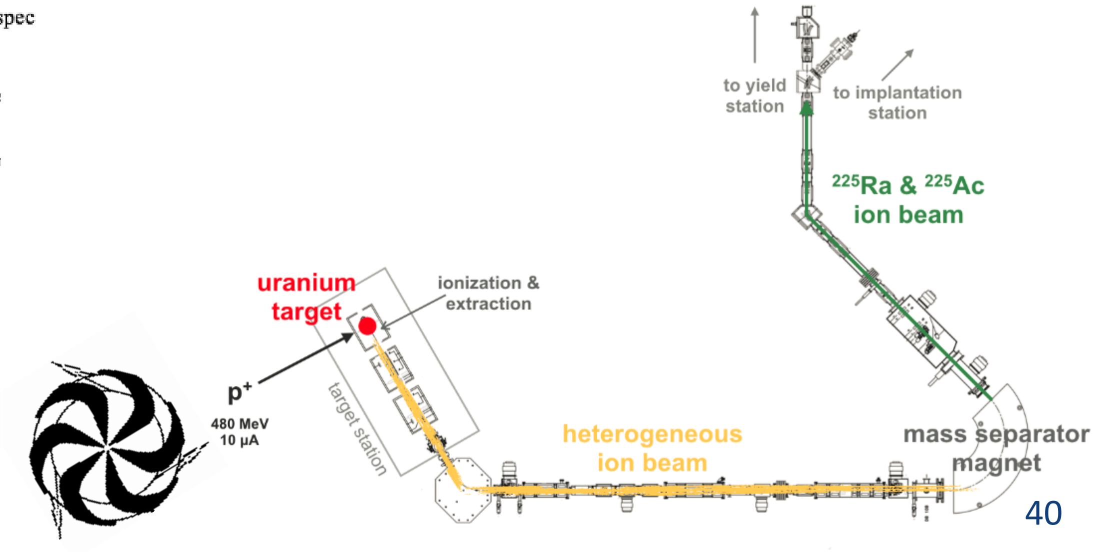
Tools for Discovery: ISOL for ^{211,209}At, ^{225}Ra/^{225}Ac

Run		Implantation		RIB Yields [ions/s]		Activity Produced [MBq][c]	
#	Date	Duration [h]	LIS[b]	^{225}Ra	^{225}Ac	^{225}Ra	^{225}Ac
1	Dec '15	13.3	X	3.2×10^7	3.8×10^6	0.19	0.16
2	Apr '16	44.8	On	4.0×10^6	1.0×10^7	0.99	1.40
3	May '16	48.9				1.13	1.35
4	Aug '16	21.6	On	1.6×10^8	5.7×10^7	7.1	10.5
5	Dec '16	45.0	On	9.3×10^7	1.3×10^8	6.8	18.0
6	Apr '17	80.7	X	9.0×10^7	2.8×10^6	7.5	1.7

[a]EE = extraction electrode; [b]Inisation source; [c]quantified by HPGe γ-spec







Tools for Discovery: ISOLDE-MEDICIS

85m-Y
86-Y
87-Y
88-Y
134-Ce
134-La
141-Ce
143-Pr
138-Nd
138-Pr
140-Nd
140-Pr
147-Nd
142-Sm
142-Pm
153-Sm
147-Eu

149-Gd
149-Tb
152-Tb
161-Tb
157-Dy
166-Dy
165-Er
167-Tm
169-Yb
172-Lu
177-Lu

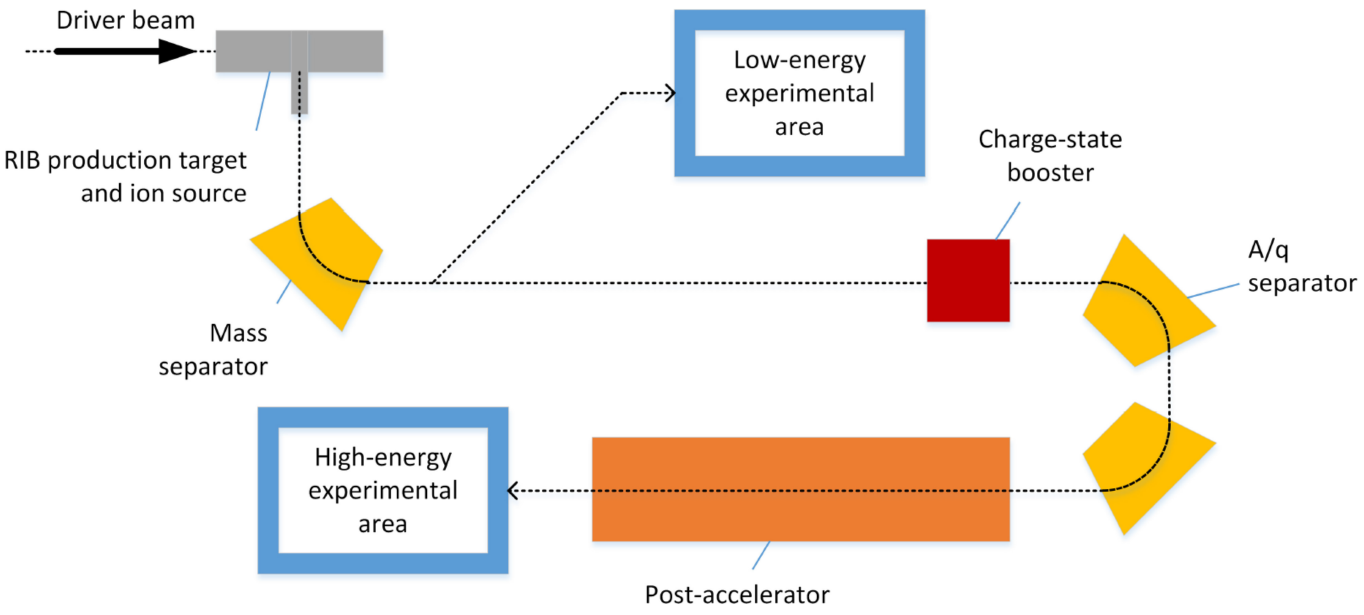
Selected radionuclides in the rare earth region available at the CERN ISOLDE facility having a potential in the field of biomedical research and nuclear medical application. Among those are single photon emitters suitable for SPECT, β^--emitters with different energies for therapy, positron emitters suitable for PET and the α-emitting ^{149}Tb suitable for cell targeting. The main nuclear physical parameters are indicated as well as alternative production routes based on reactors or small and medium size cyclotrons. (W-SI = Tungsten-surface ionization).

Nuclid	$T_{1/2}$	Decay mode	$E_{\beta\,max}$ (MeV)	β^+ (%)	E_γ (MeV)	E_γ (%)	Production routes ISOLDE	Production routes others
85m-Y	4.9 h	β^+, γ	2.3	70	231	33.6	Nb-foil target, W-SI	86-Sr (p, 2n)
								84-Sr (d, n)
86-Y	14.7 h	β^+, γ	1.2	34	637	32.6	Nb-foil target, W-SI	86-Sr (p, n)
					1077	82.5		
87-Y	80.3 h	EC, γ		100	485	96	Nb-foil target, W-SI	85-Rb (α, 2n)
					388	83		88-Sr (p, 2n)
88-Y	106.6 d	EC, γ			898	94.0	Nb-foil target, W-SI	Mo, Nb (p, spall)
					1836	99.4		88-Sr (p, n)
134-Ce	75.9 h	EC		100	no gamma		Ta-foil target,	W-SI 132-Ba (α, 2n)
134-La	6.7 m	β^+, γ	2.7	64	605	7.6		134-Ce-generator
141-Ce	32.5 d	β^-, γ	0.6	70	145	49.3	U-carbide-target, W-SI	Fission products,
143-Pr	13.6 d							
138-Nd	5.2 h							
138-Pr	1.5 m							
140-Nd	3.4 d							
140-Pr	3.4 m							
147-Nd	11.1 d							
142-Sm	72.4 m							
142-Pm	40.5 s							
153-Sm	46.7 h							
147-Eu	24.6 d							

Nuclid	$T_{1/2}$	Decay mode	$E_{\beta\,max}$ (MeV)	β^+ (%)	E_γ (MeV)	E_γ (%)	Production routes ISOLDE	Production routes others
149-Gd	9.5 d	EC, γ			149	55	Ta-foil target, W-SI	147-Sm (α, 2n)
					293	26		
149-Tb	4.15 h	α, β^+, γ	1.8	4	165	26.9	Ta-foil target, W-SI	141-Pr (12-C, 4n)
					352	30.1		
152-Tb	17.5 h	β^+, γ	2.8	12			Ta-foil target, W-SI	141-Pr (12-C, n)
161-Tb	6.9 d	β^-, γ	1.7		74.6	14.0	(Ta-foil target, W-SI)	160-Gd (n, γ) 161-Gd (β^-)
157-Dy	8.1 h	EC, γ		100	326	94.5	Ta-foil target, W-SI	156-Sm (n, γ)
166-Dy	81.4 h	β^-	0.5		82.5	12	Ta-foil target, W-SI	164-Dy (2n, γ)
165-Er	10.3 h	EC, Auger		100	X-ray only		Ta-foil target, W-SI	166-Er (p, 2n) 165-Tm (EC)
								164-Er(n, γ)
167-Tm	9.25 d	EC, γ		100	207.8	42.0	Ta-foil target, W-SI	Ta (p, Spallation),
								165-Ho (α, 2n)
169-Yb	32.0 d	EC, γ		100	63.5	45	Ta-foil target, W-SI	168-Yb (n, γ)
					198	40		
172-Lu	6.7 d	EC, γ			181	20.5	Ta-foil target, W-SI	172-Hf generator
					1093	62.5		
177-Lu	6.7 d	β^-	0.5		208	11	(Ta-foil target, W-SI)	176-Yb(n, γ) 177-Yb (β^-)

G.J. Beyer. Hyperfine Interactions 2000, 129, 529
R.M. dos Santos Augusto. Appl. Sci. 2014, 4, 265

Concluding Remarks: High(er) Energy Isotope Production

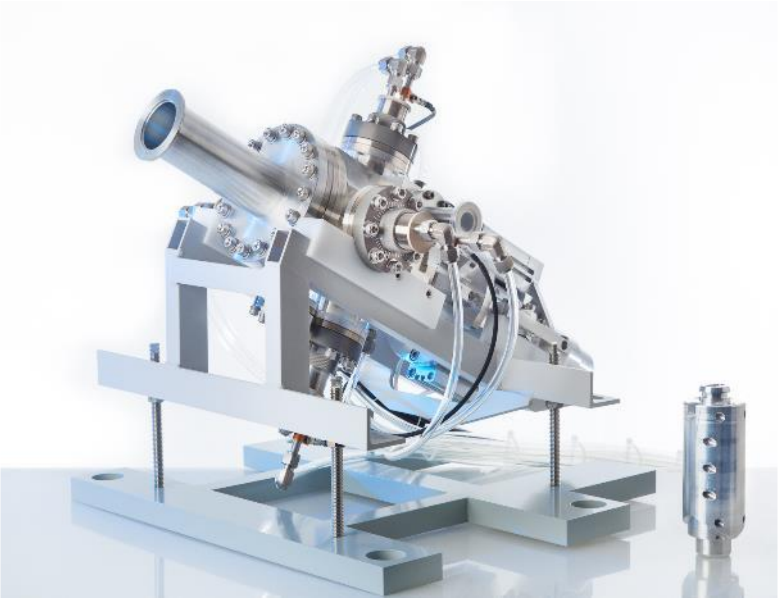


- ISOL is a powerful tool to help explore new isotopes
- Continued improvements in target/converter technology, separation efficiency, yields, chemistry
- Elinac production

R. Laxdal et al., RAST 2013,6,37

TRIUMF

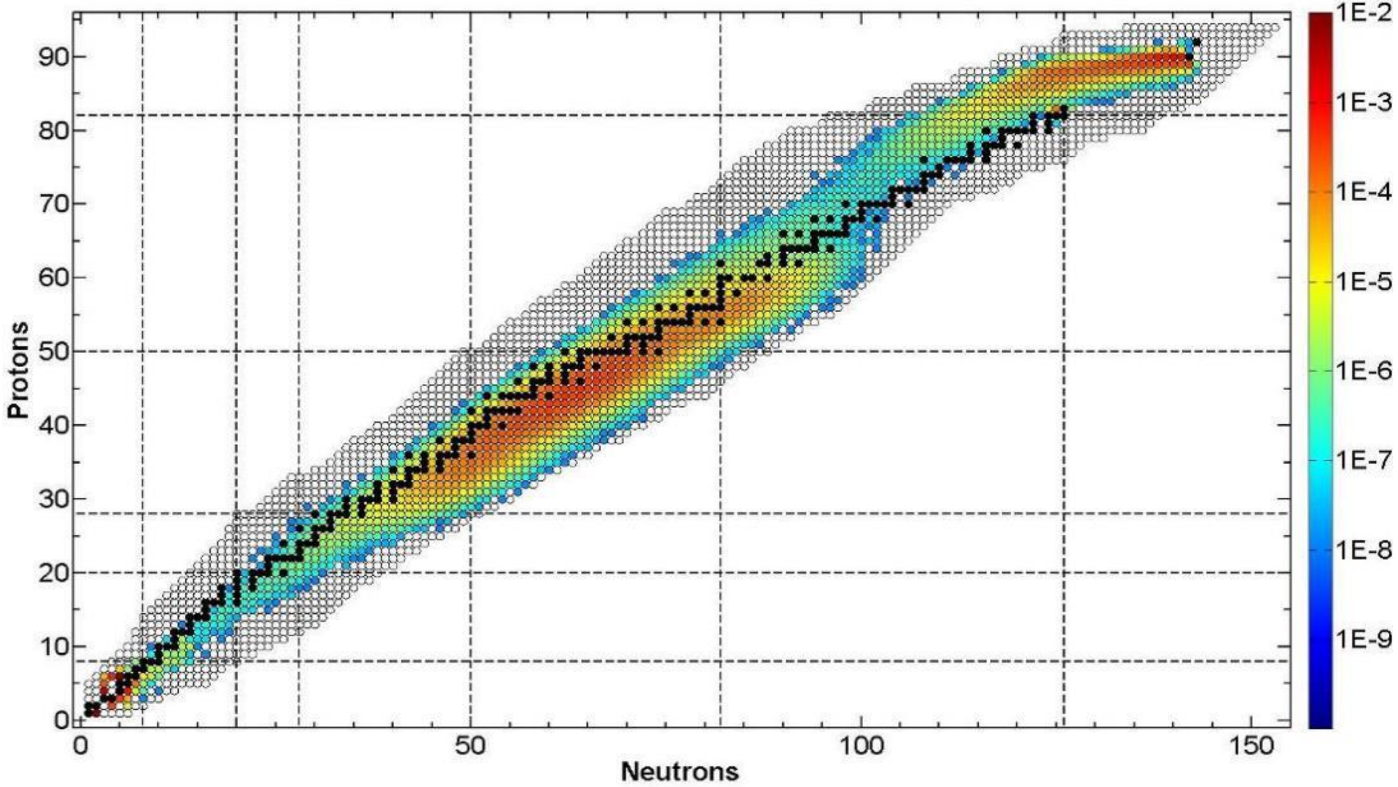
Concluding Remarks: Small Cyclotron Isotope Production



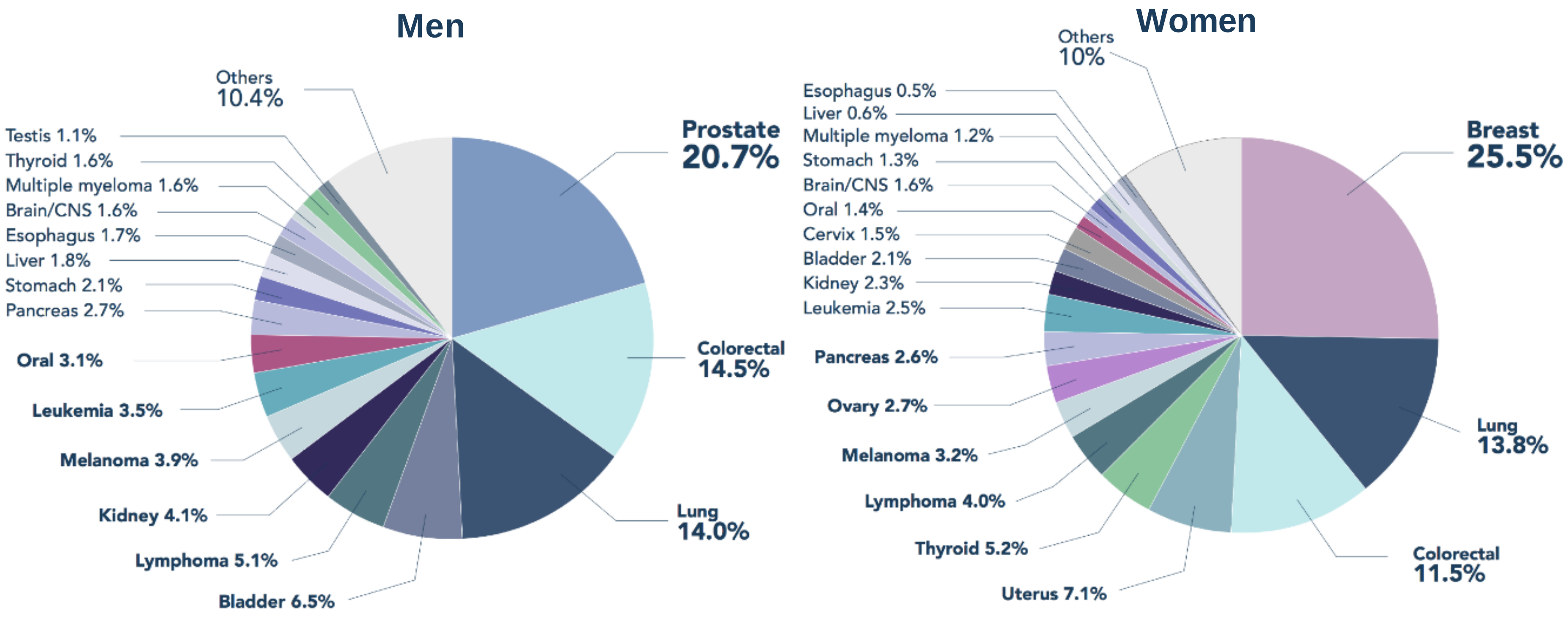
- Global shift to higher-energy cyclotrons
  - yesterday: low E (<16 MeV), low current (<100 uA)
  - today: higher E (16 – 24 MeV), higher current (>100 to 1000 uA)
  - Higher specific activity
- New approaches (i.e. salt target)
- Emerging solid target technologies enabling high power (E + µA) irradiation
- Improved handling and processing

- But…some isotopes can not be efficiently made by accelerator (^{60}Co, ^{192}Ir, ^{125}I…)

Concluding Remarks: High(er) Energy Medical Isotope Production



Going forward, where should we focus our efforts?



- multiple cancer subtypes (ex. 6 different breast cancers)
- different grades and stages of cancer

Canadian Cancer Society 2017 statistics

TRIUMF

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

Thank you!
Merci!

Follow us at TRIUMFLab

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