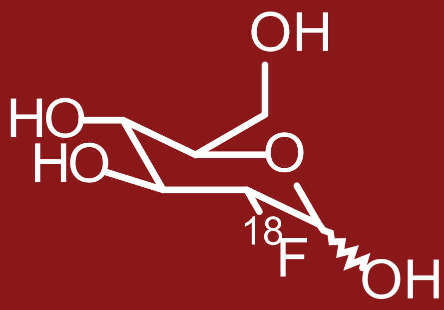
The Future of Nuclear Medicine

TRIUMF: Saturday Morning Lecture, Oct. 15th, 2011

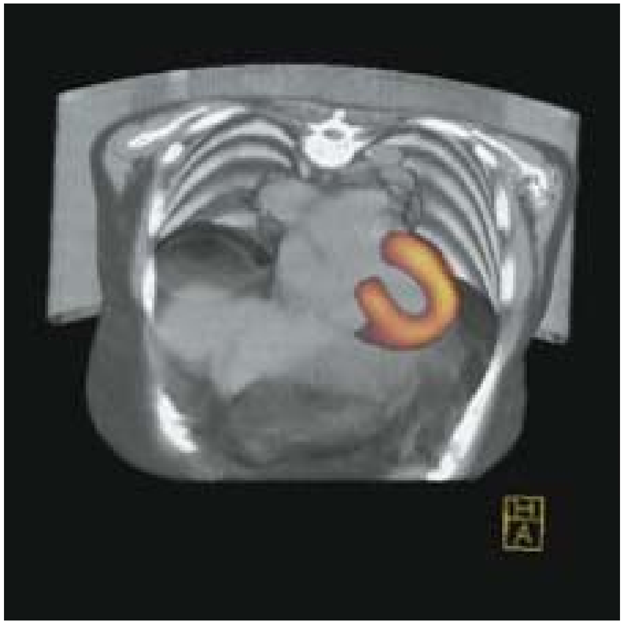
Paul Schaffer | Deputy Head, Nuclear Medicine | TRIUMF



Overview

- Introduction
- Brief History and Molecular Imaging Defined
- Nuclear Reactors and the ‘Case of the Missing Isotope’
- How (TRIUMF) accelerators will solve the isotope dilemma
- Nuclear Medicine: Today
- Nuclear Medicine: Looking Forward

Medical Imaging in Humans

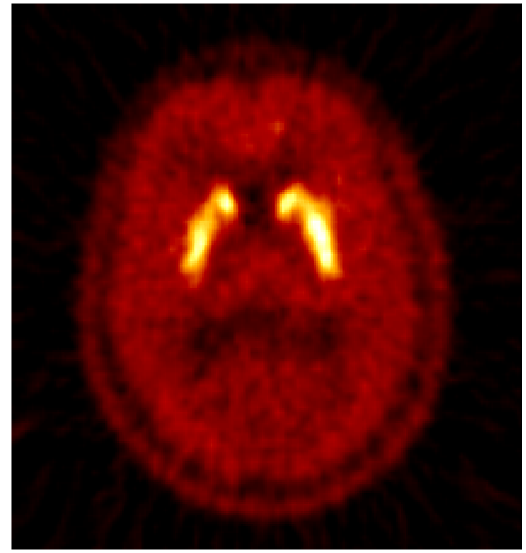


cardiology

Diagnostic and Invasive Cardiology website on November 9, 2006

Courtesy of R. Wassenaar, Ottawa Heart Institute

oncology



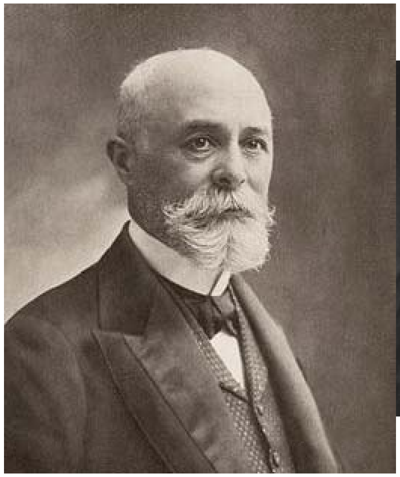
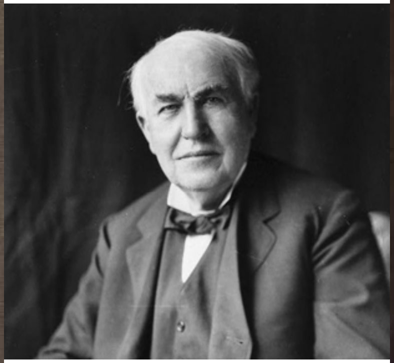
neurology

Courtesy of UBC Dept. of Neurology

A Brief History

- 1895 – Roentgen discovers X-rays
- 1896 – Edison created fluoroscope
  - Becquerel discovered radioactivity (shared Nobel Prize 1903)
- 1898 – M. Curie discovered radium, radioactivity is named
  - (shared Nobel Prize 1903)
- 1911 – George de Hevesy – first use of tracer, est. ‘Tracer Principle’ (Nobel Prize 1943 – recast in 1946 (?))



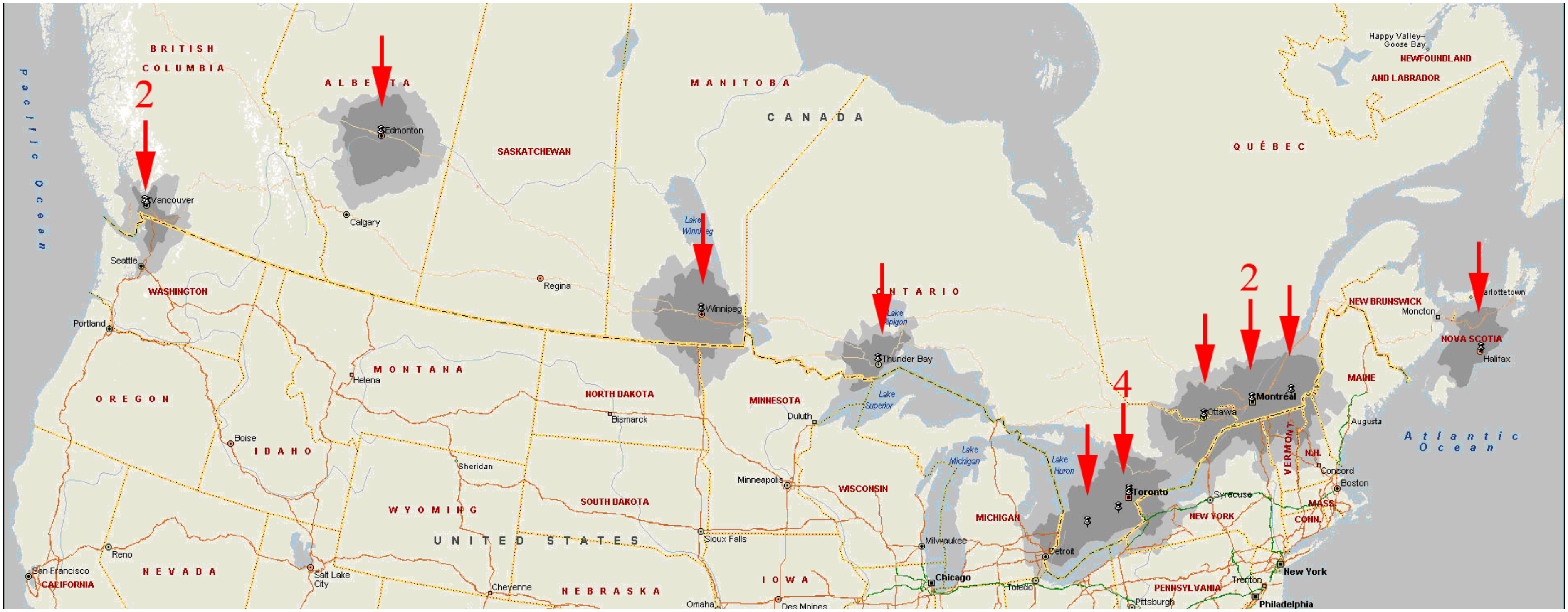
all images from wikipedia.org

A Brief History

- 1958 – Hal Anger – gamma camera
- 1973 – Phelps invents PET scanner
- 1980 – PET program starts at TRIUMF
- 1998 – [^{18}F]FDG gains regulatory approval for reimbursement in USA
- 2000 – PET/CT is Time's invention of the year
- 2003 – Health Canada introduces FDG into clinical trials

PET in Canada today

- Canada has a growing cyclotron infrastructure
- Disease focus: Oncology, Neurology and Cardiology



Molecular Imaging Defined

… the *in vivo* characterization and measurement of biological processes at the cellular and molecular level…to probe the molecular abnormalities that are the basis of disease rather than to image the end effects…[1]

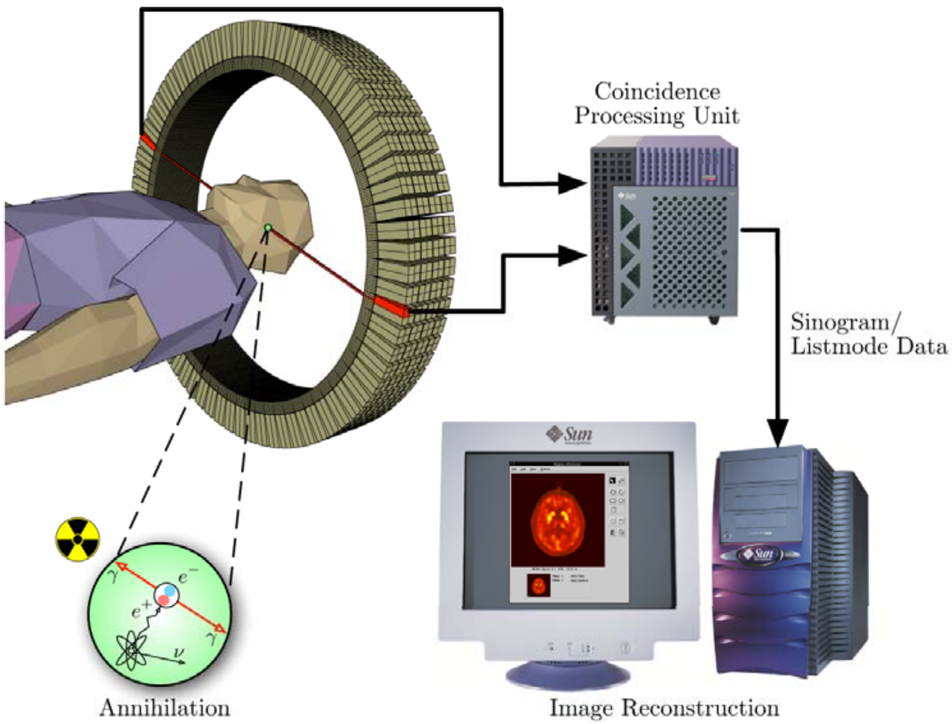
[1] R Weissleder and U Mahmood, Radiology 2001, 219, p316

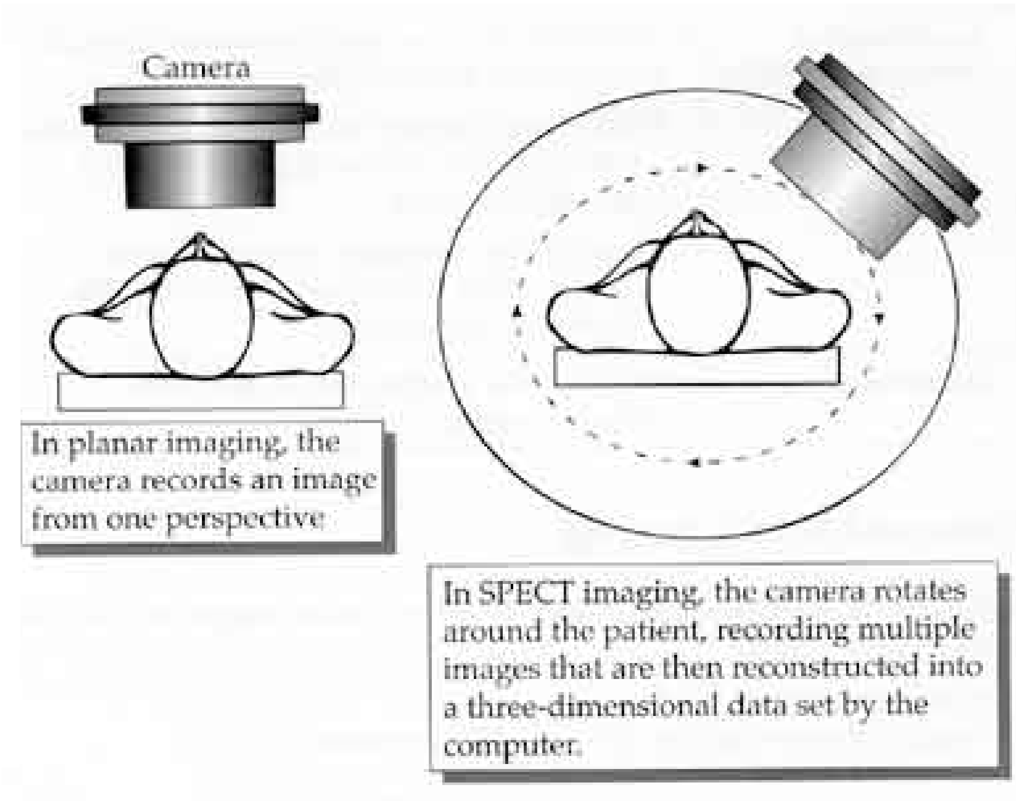
…directly or indirectly monitor and record the spatiotemporal distribution of molecular or cellular processes for biochemical, biologic, diagnostic, or therapeutic applications.[2,3]

[2] M Thakur and BC Lentle, Radiology 2005, 236, p753

[3] WC Eckelman, Nuclear Medicine and Biology 2006, 33, p1

SPECT vs. PET Imaging





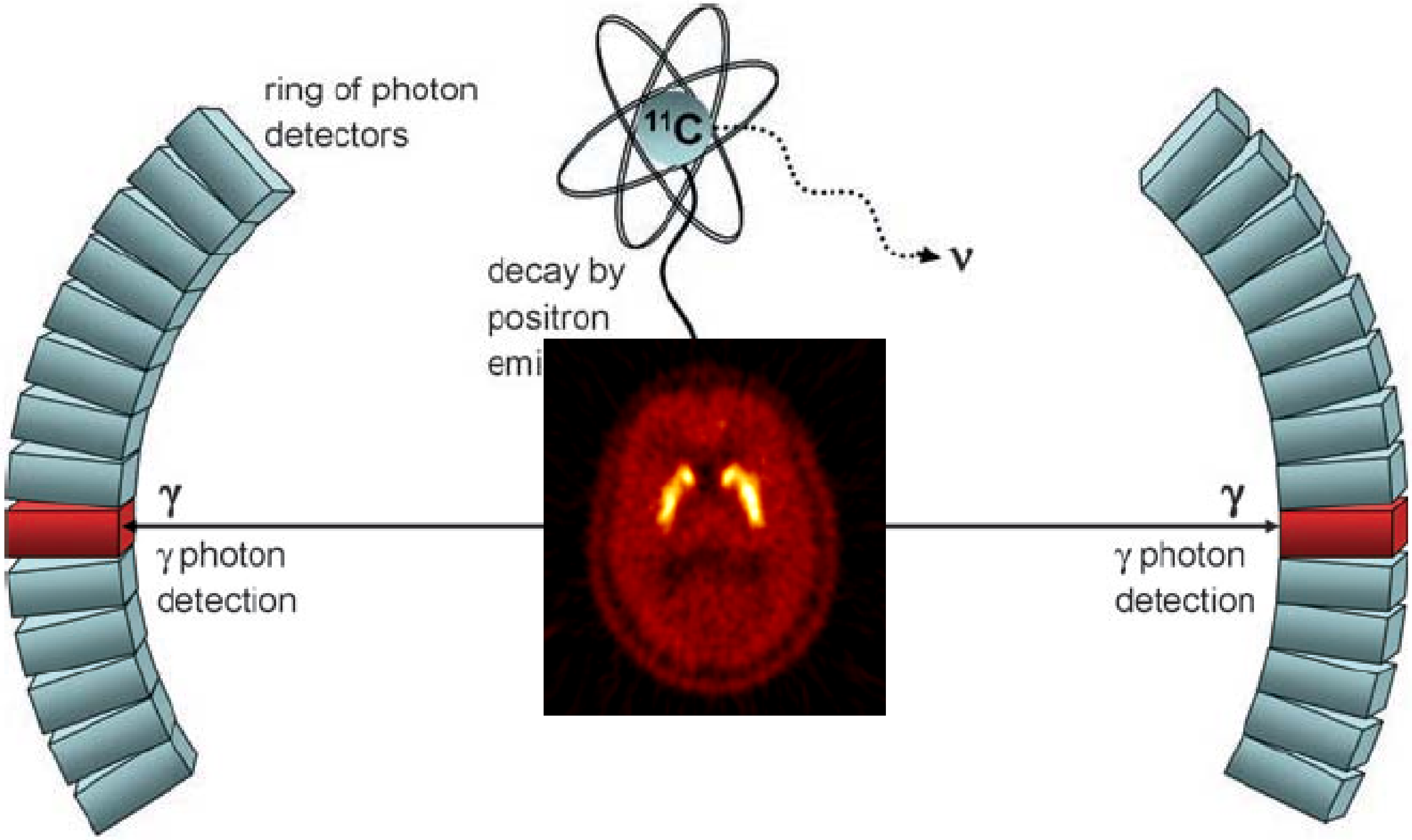
PET

Higher sensitivity, resolution

SPECT

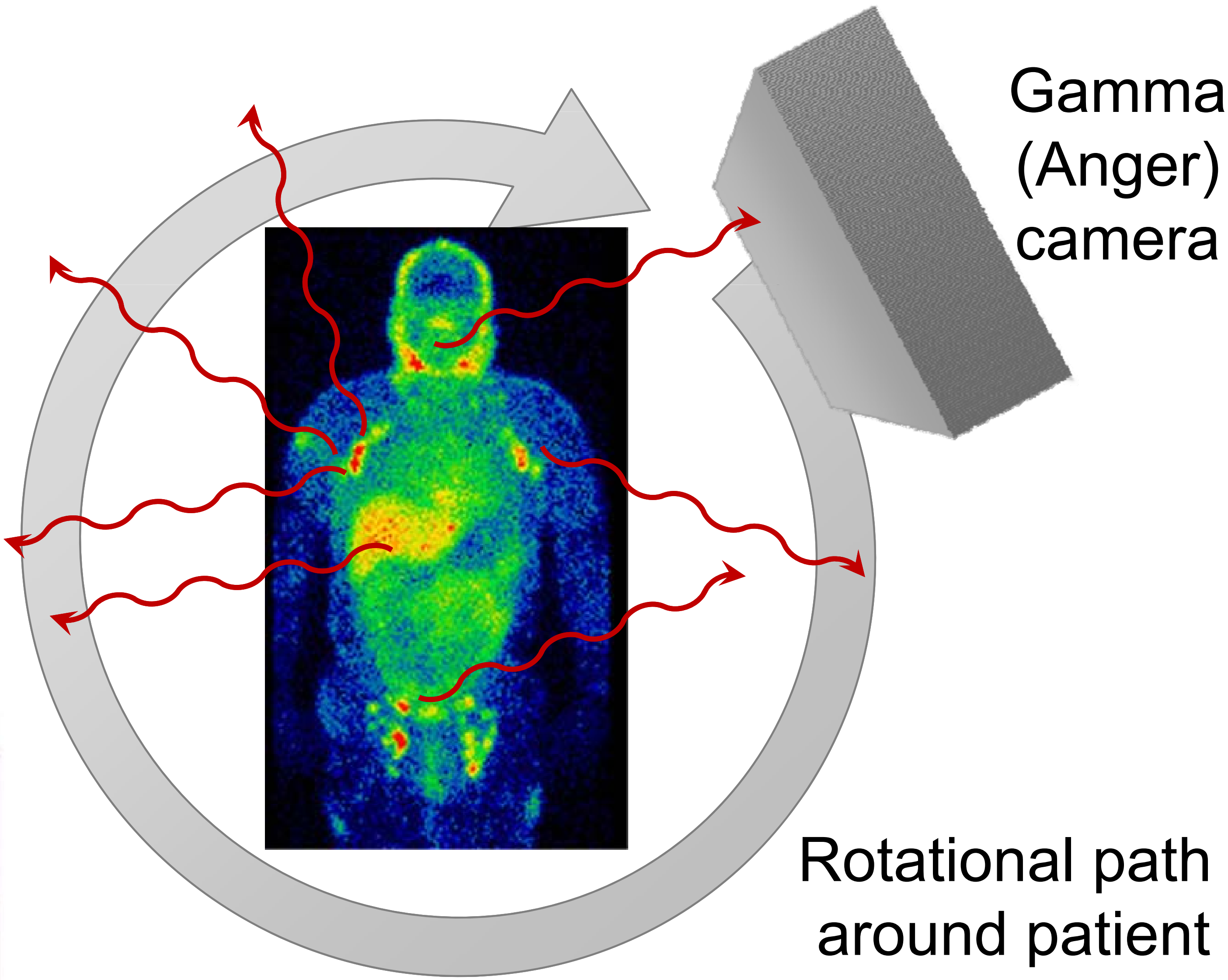
Inexpensive, widely avail.
Significant infrastructure

Positron Emission for PET

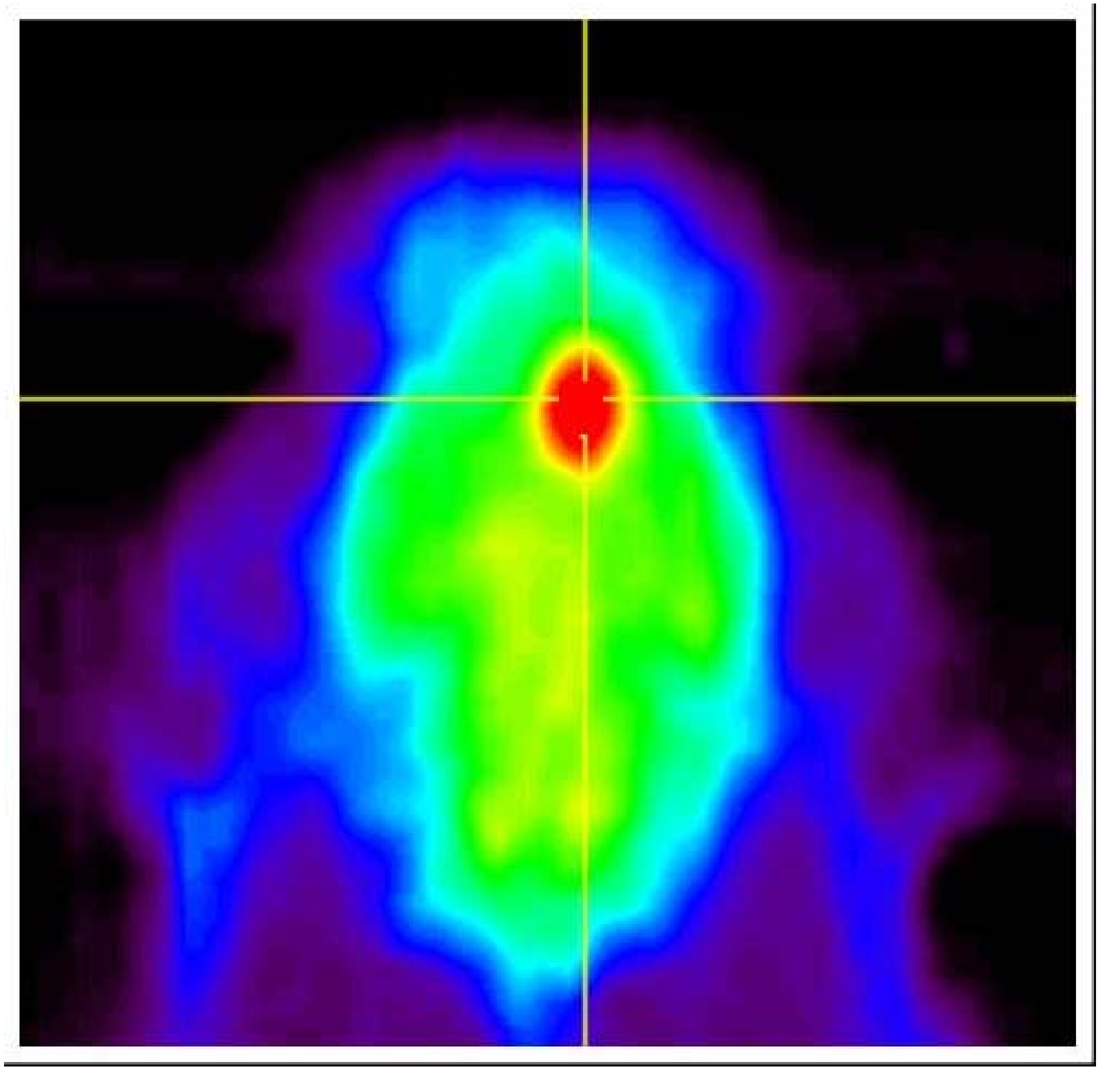


Angew. Chem. Int. Ed. 2008, 47, 8998 – 9033

Gamma (Single Photon) Emission for SPECT

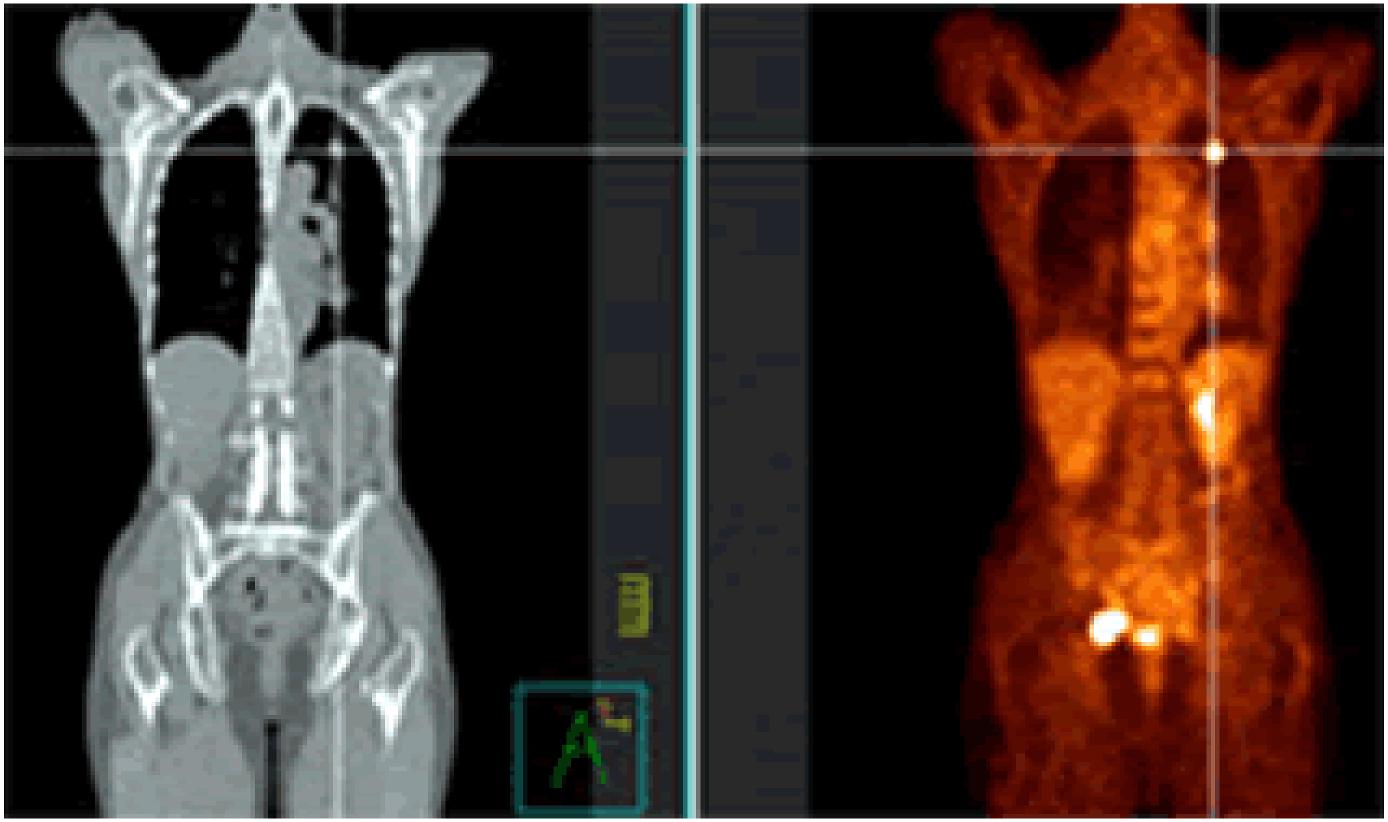


Functional Imaging is great, but…



What are we looking at, anyway?

Multimodal Imaging

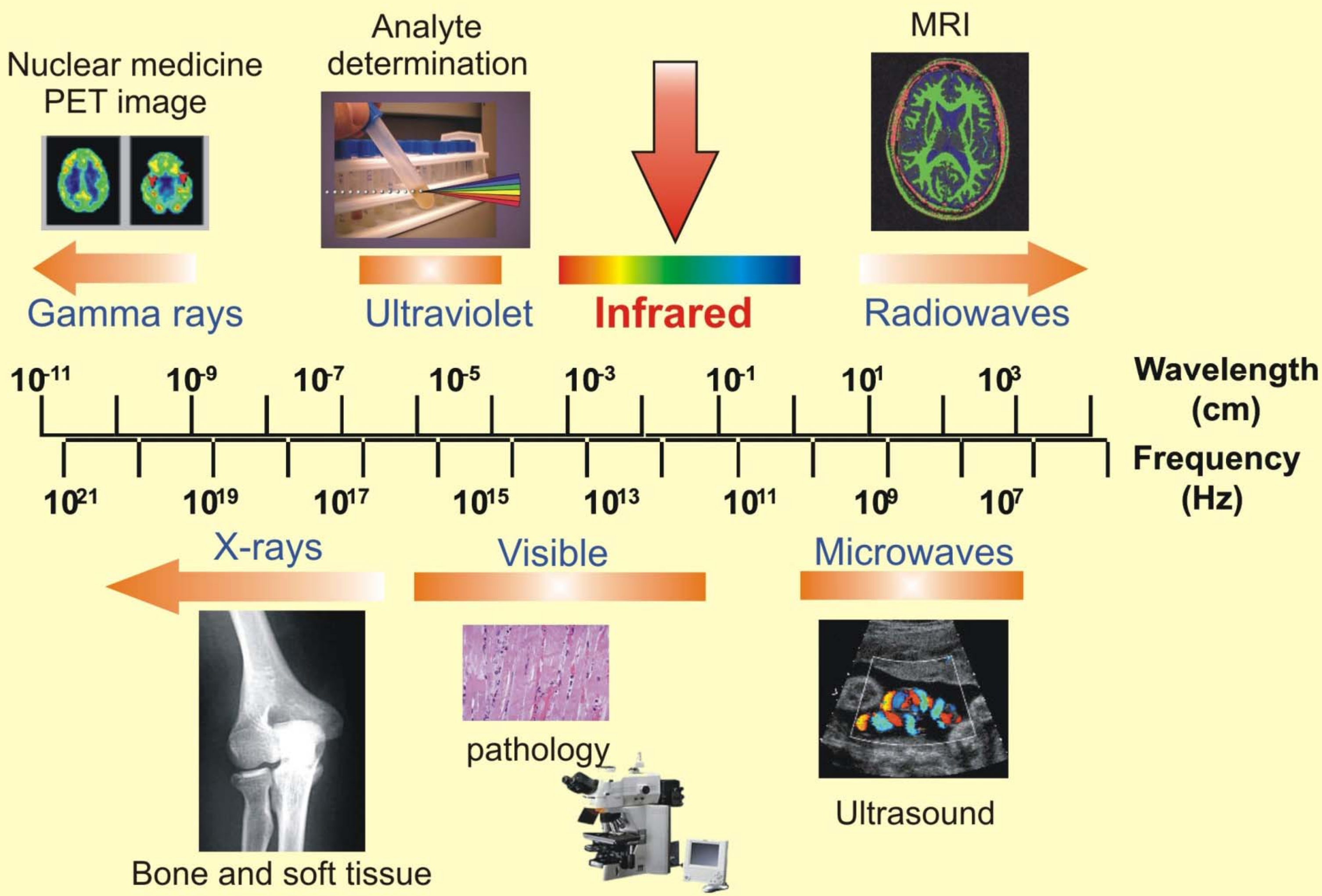


CT scan shows the anatomy.

PET scan shows increased cellular activity indicating cancer.

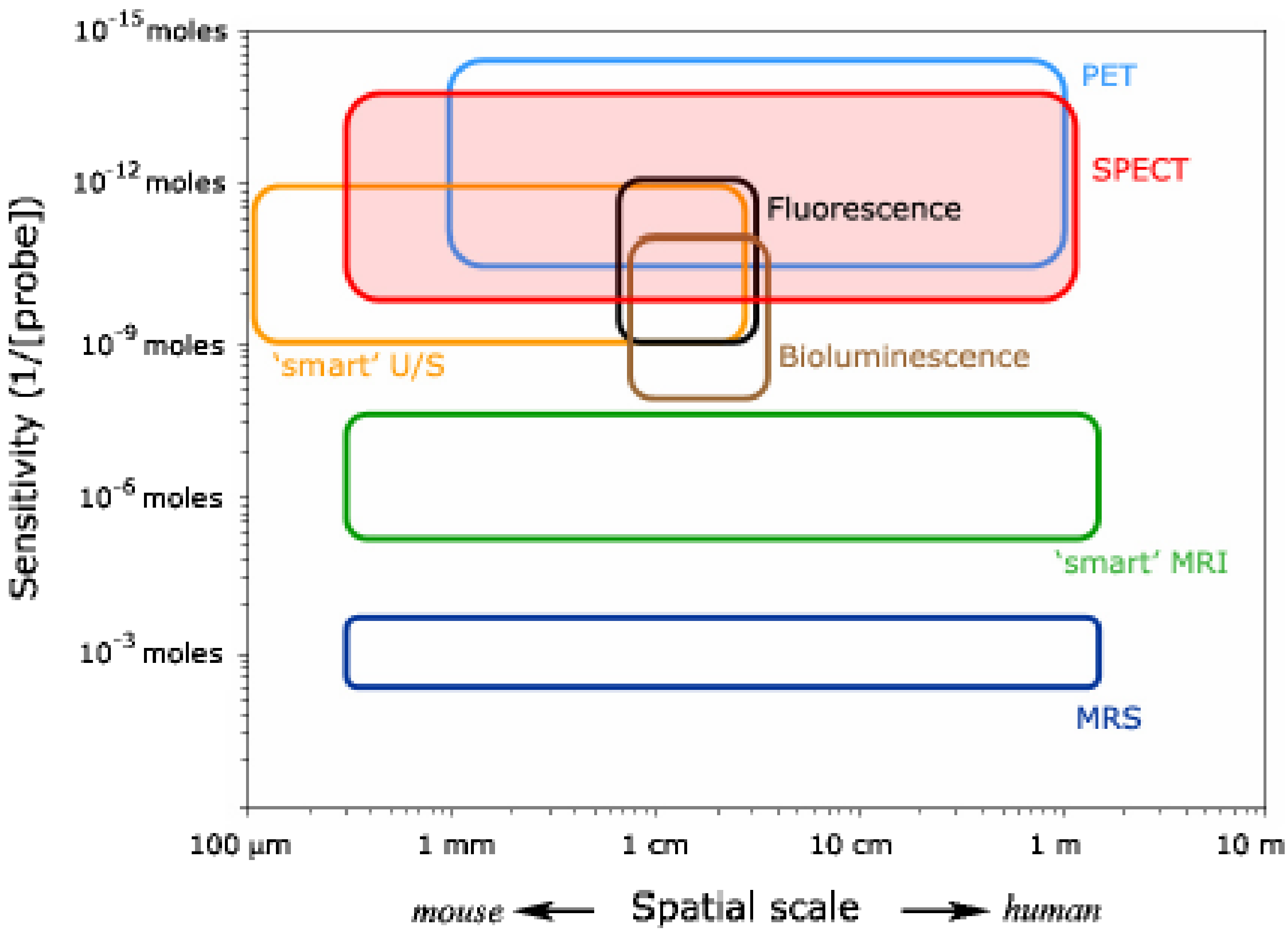
Combined, PET/CT pinpoints cancer anatomically.

Where the freq. is PET?



A Hynes et al. *BMC Molecular Imaging* ***2005, 5, 2***

Comparing Imaging Methods

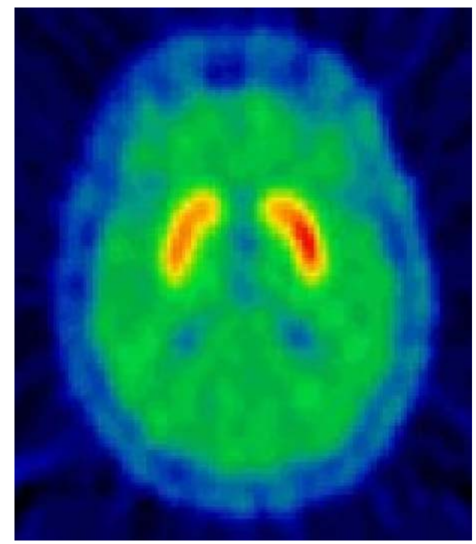


The Nuclear Medicine Process

Cyclotron Dev. → Target Dev. → Isotope Prod. → Tracer Prod. → (Pre)clinical Studies → Detector Dev.

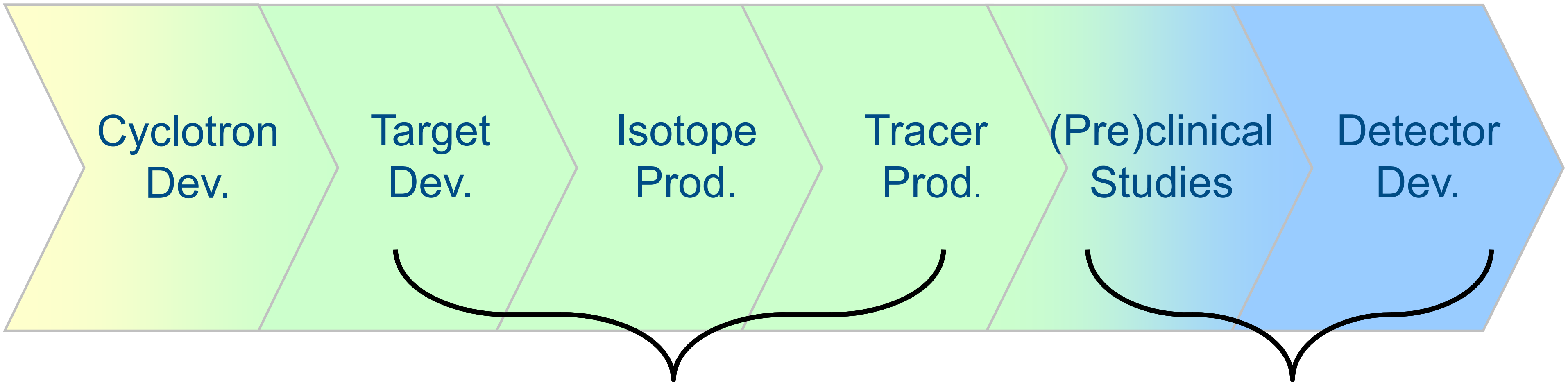
www.bccancerfoundation.com

www.wattcon.com



Courtesy of the PPRC

TRIUMF's Nuclear Medicine Expertise?

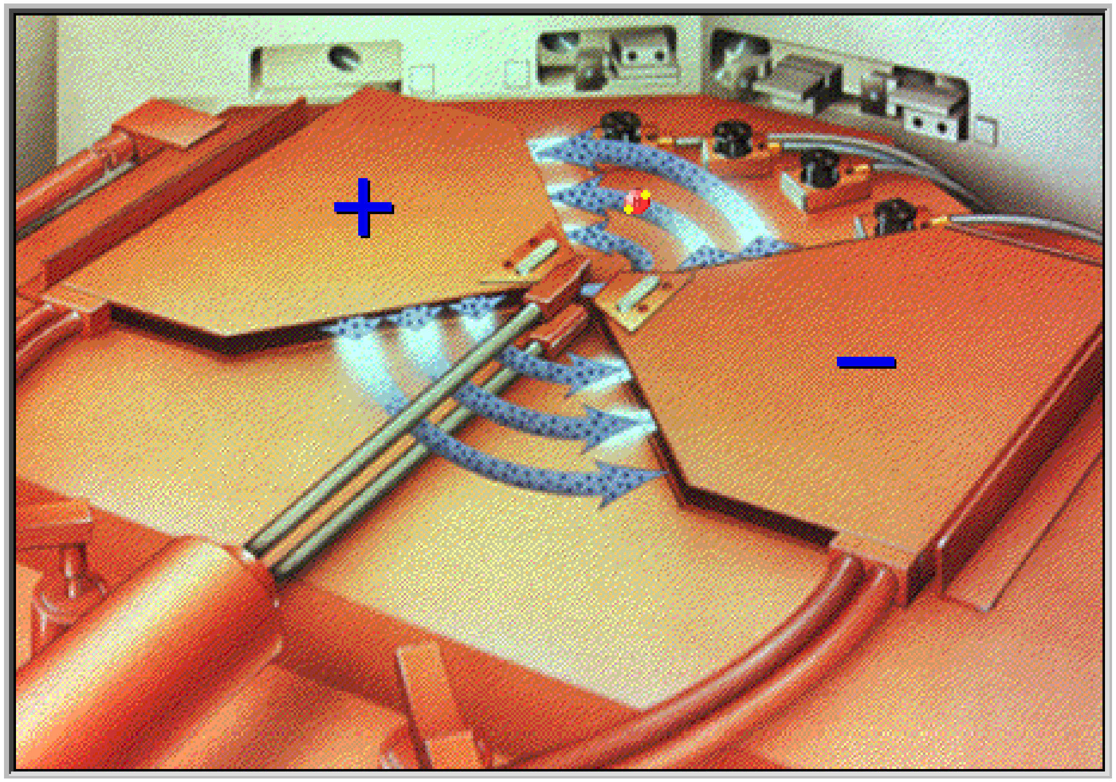


Historical and Core Capabilities

Driven by our Partners:
UBC/PPRC
BCCA
Nordion
GE

Isotope Production - Acceleration

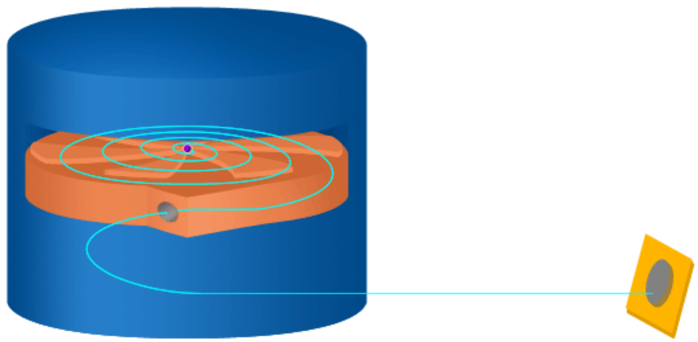
- Accelerator/Cyclotron Production



- Located near or in hospitals
- Produce short-lived isotopes on demand

Medical cyclotrons

- Medical cyclotrons are already running in Canada's major cities to produce PET isotopes



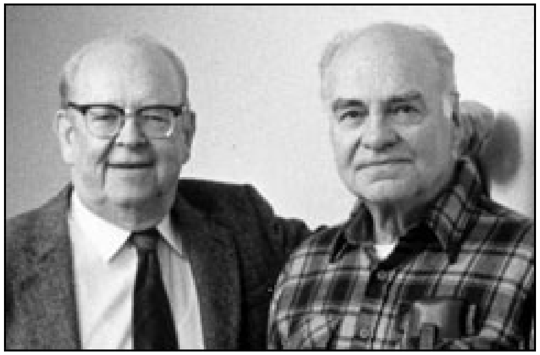
$$ {}^{1}_{1}H + {}^{18}_{8}O \longrightarrow {}^{18}_{9}F + {}^{1}_{0}n $$ $^{18}O(p,n)^{18}F$

$$ {}^{1}_{1}H + {}^{16}_{8}O \longrightarrow {}^{13}_{7}N + {}^{4}_{2}He $$ $^{16}O(p,\alpha)^{13}N$

$$ {}^{1}_{1}H + {}^{14}_{7}N \longrightarrow {}^{11}_{6}C + {}^{4}_{2}He $$ $^{14}N(p,\alpha)^{11}C$

A brief history of ^{99m}Tc

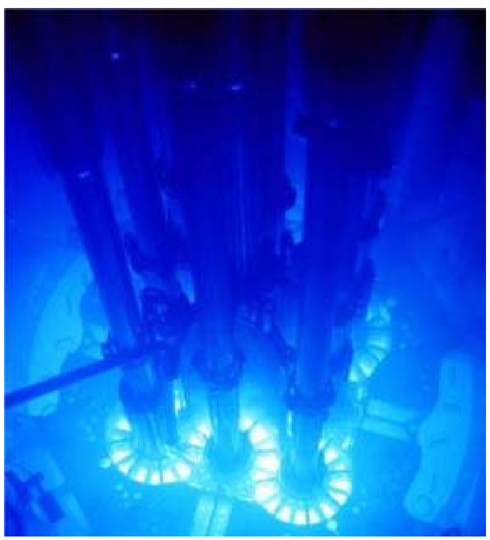
- BNL, 1950s: Walter Tucker and Margaret Green discovered Tc-99m as a ‘contaminant’ and developed the first ^{99}Mo/^{99m}Tc generator (1957)
- BNL, 1960: Powell Richards, newly in charge of isotope production, presented the first paper at the 7th International Electronic and Nuclear Symposium.
- Richards 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



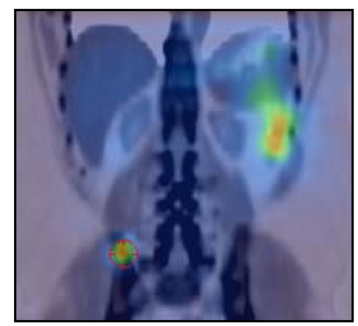
From http://www.bnl.gov/bnlweb/history/Tc-99m.asp

From U-235 to Tc-99m

Accelerator/ Reactor → Target Irrad. → Isotope Isolation → Tracer Prod. → Human Use

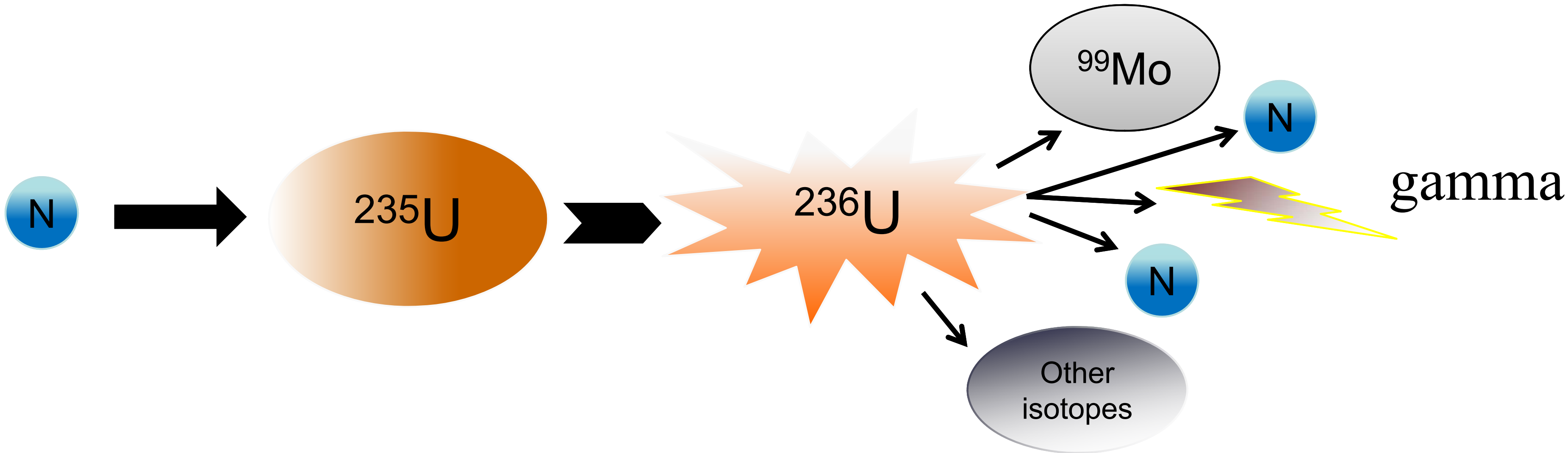


Imaging Technology News, June 2009



TRIUMF

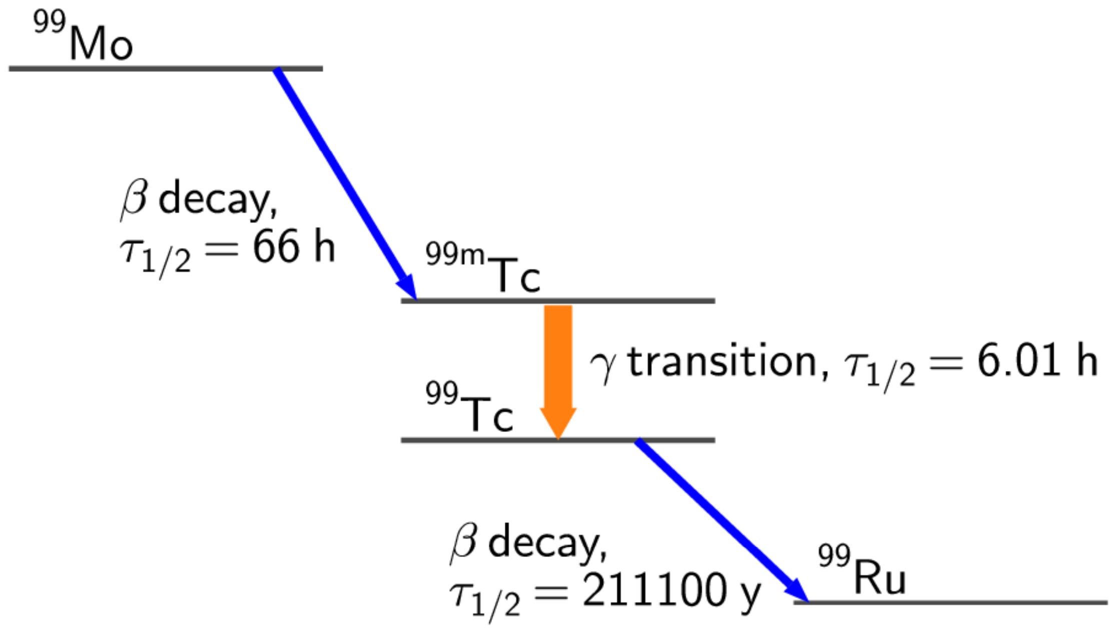
Making Mo-99 from U-235



Natural Uranium: ~ 0.8% U-235, 99.2% U-238
Low Enriched Uranium (LEU): <20% U-235
Highly Enriched Uranium (HEU): >85% U-235

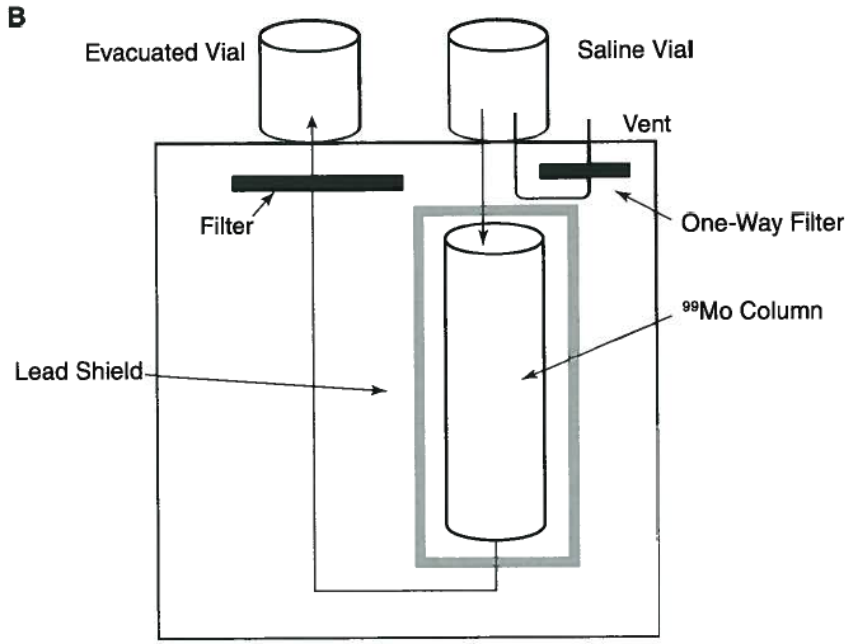
SPECT: Isotope Generators

Moly 'Cow'



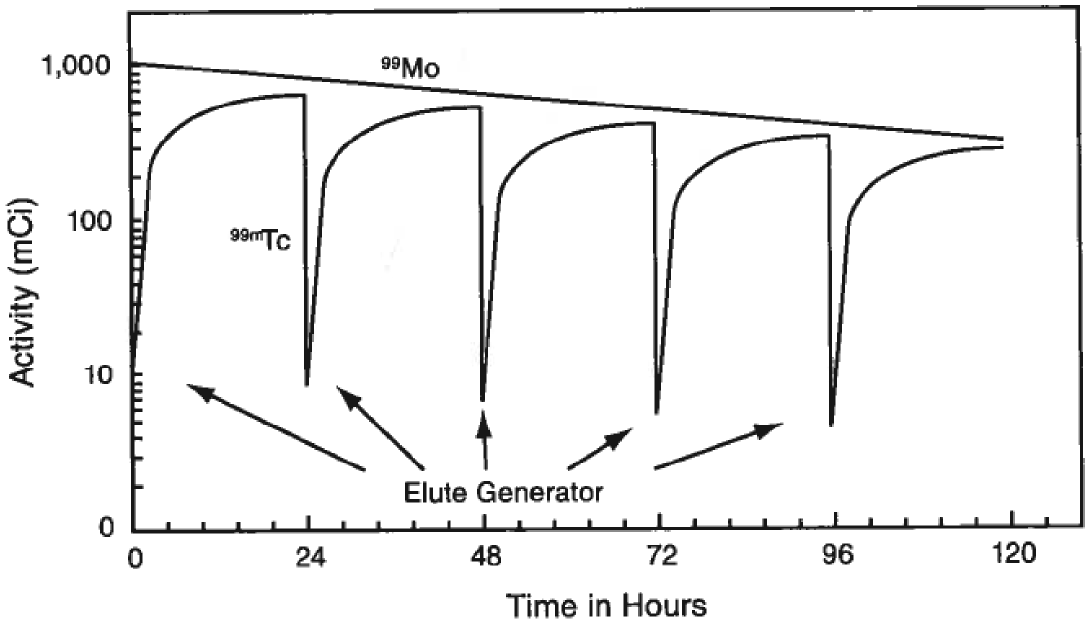
- Transportable
- Easy to use
- 'Recyclable'
- Tc-99m generator is SPECT enabler

Tc-99 Generators



- Transportable
- Easy to use
- 'Recyclable'

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



TRIUMF

Canada's Role in the Recent (Global) Isotope Crisis

- 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
- Future demands to increase

- **Recent NRU shutdown:** widespread shortages, cost/mCi escalating
- Adding suppliers faces technical and regulatory challenges

TRIUMF

The MAPLES

MAPLE: Multipurpose **A**pplied **P**hysics **L**attice **E**xperiment

- Two identical reactors
- Purpose: to succeed NRX (1992) and NRU (2016?)
- Construction started 1997, completed 2000
- Dedicated isotope production (^{99}Mo, ^{60}Co, ^{133}Xe, ^{131}I, ^{125}I)
- Capable of producing 200% of global ^{99}Mo/^{99m}Tc demand

Issues (there are many)*:
- sticky shut-off safety system
- positive co-efficient of reactivity
- use of HEU
- operating license until 10/31/2011
- project terminated 5/16/2008

* Issues are the sole opinion of the presenter

Alternatives for Tc-99m production

- 1950's and 60's $^{235}U(n,F)^{99}Mo/^{99m}Tc$ generators gain widespread use. Continues today. *From http://www.bnl.gov/bnlweb/history/Tc-99m.asp*
- 2007 – Several prolonged shutdowns of major production reactors highlight ^{99}Mo supply vulnerability

- Alternatives are well known
- at various stages of commercial-scale production:

Neutron 'solution(s)':

LEU $^{235}U(n,F)^{99}Mo$

$^{98}Mo(n,\gamma)^{99}Mo$

Photon 'solution(s)':

$^{238}U(\gamma,F)^{99}Mo$

$^{100}Mo(\gamma,n)^{99}Mo$

Proton 'solution':

$^{100}Mo(p,2n)^{99m}Tc$

$^{100}Mo(p,2n)^{99m}Tc$

- 1971 – Beaver and Hupf* report $^{100}Mo(p,2n)^{99m}Tc$

PRODUCTION OF ^{99m}Tc ON A MEDICAL CYCLOTRON: A FEASIBILITY STUDY

J. E. Beaver and H. B. Hupf

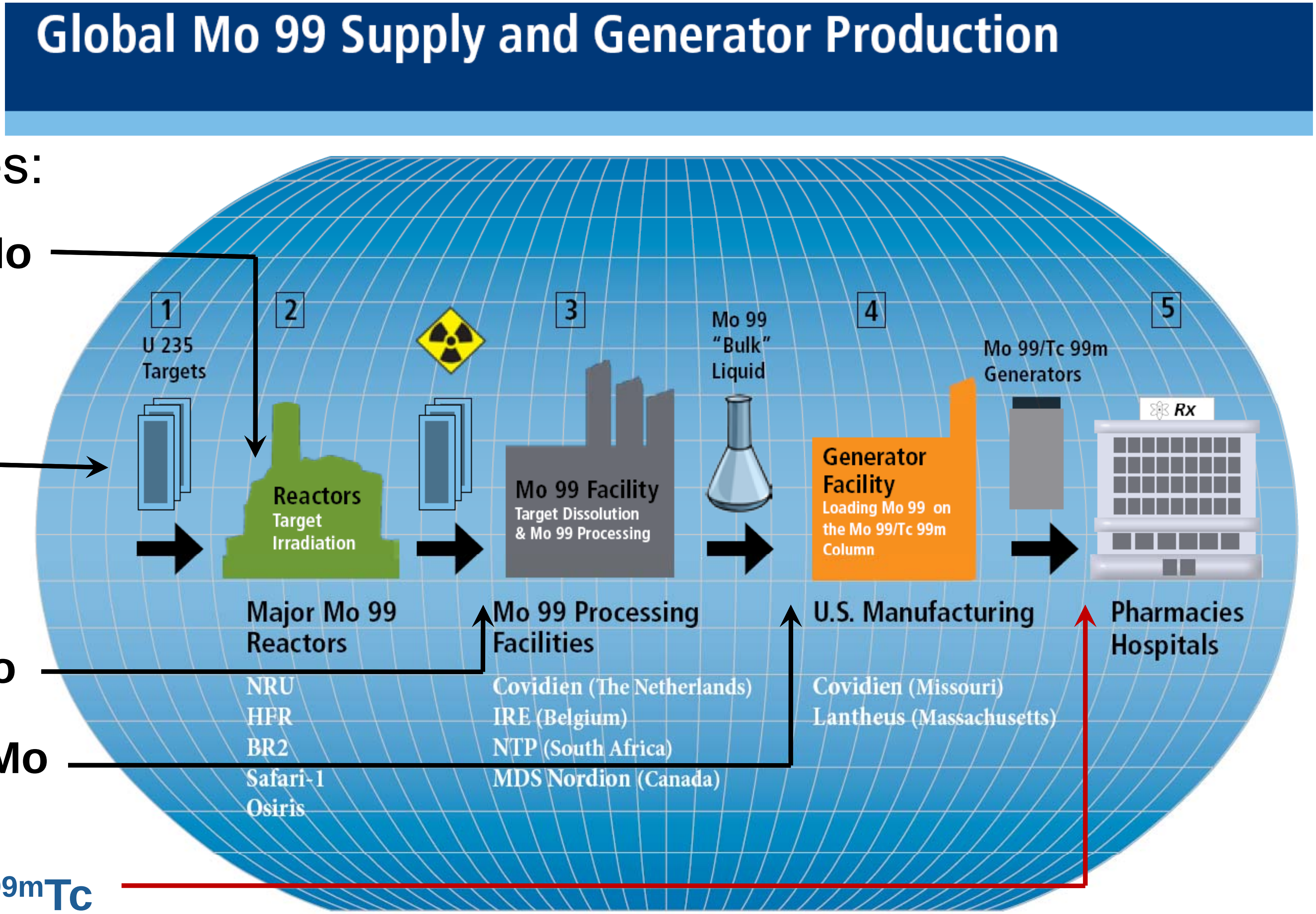
University of Miami School of Medicine, Mount Sinai Medical Center, Miami Beach, Florida

Experimental data indicate that yields of 15 Ci/hr of ^{99m}Tc and 500 mCi/hr of ^{99}Mo are possible with 22-MeV protons at a target power level of 10 kW

- 1999-2010 several reports on cross-sectional measurement
- 2011 – Gagnon et al.** re-measure ^{99m}Tc and determine ^{99g}Tc cross sections. Refined production yield to 9.6 Ci in 1hr with 99m/99g ratios of 25% (@22 MeV)

*J. Beaver, H. Hupf, J Nucl Med 1971;12:739-741
** K Gagnon et al. Nuc. Med. Biol. 2011, in press

Isotope Crisis Alternative: Cyclotrons



Alternatives:

$^{98}Mo(n,\gamma)^{99}Mo$

LEU

$^{238}U(\gamma,F)^{99}Mo$

$^{100}Mo(\gamma,n)^{99}Mo$

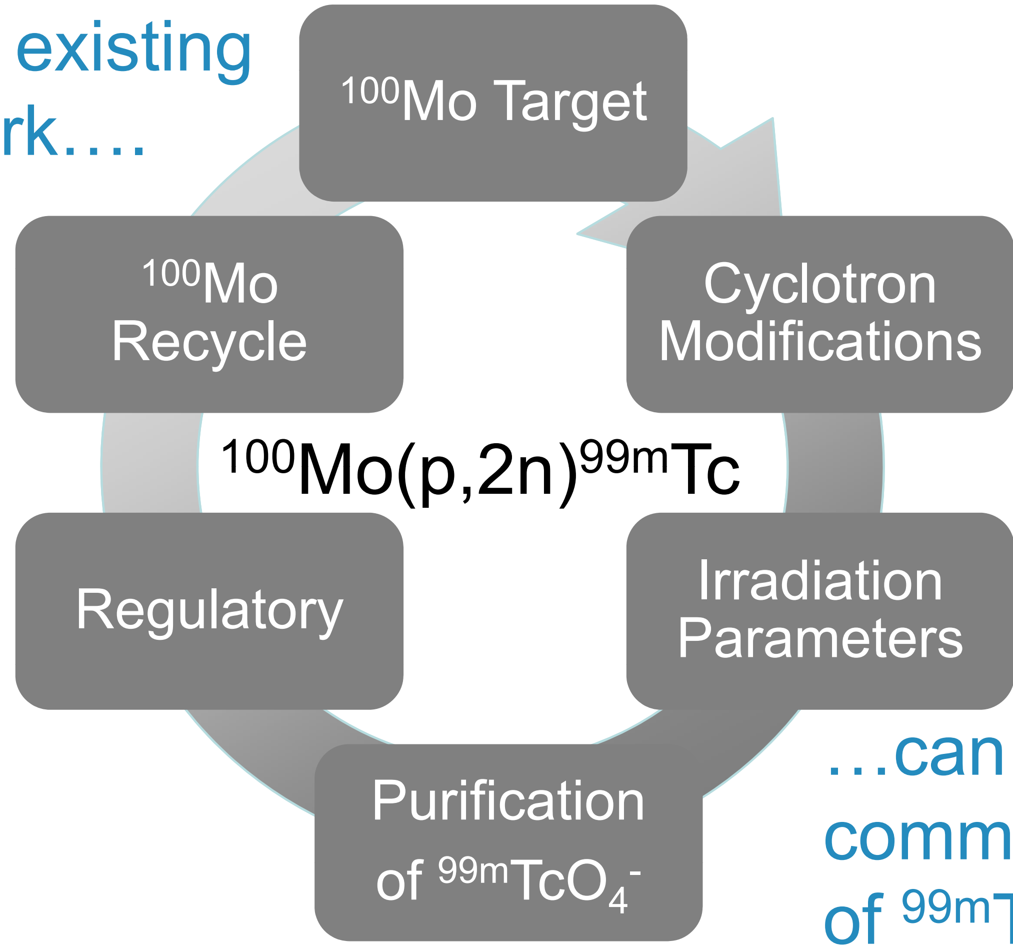
$^{100}Mo(p,2n)^{99m}Tc$

graphic from http://www.covidien.com/

TRIUMF

Direct Production of ^{99m}Tc

To demonstrate existing cyclotron network….

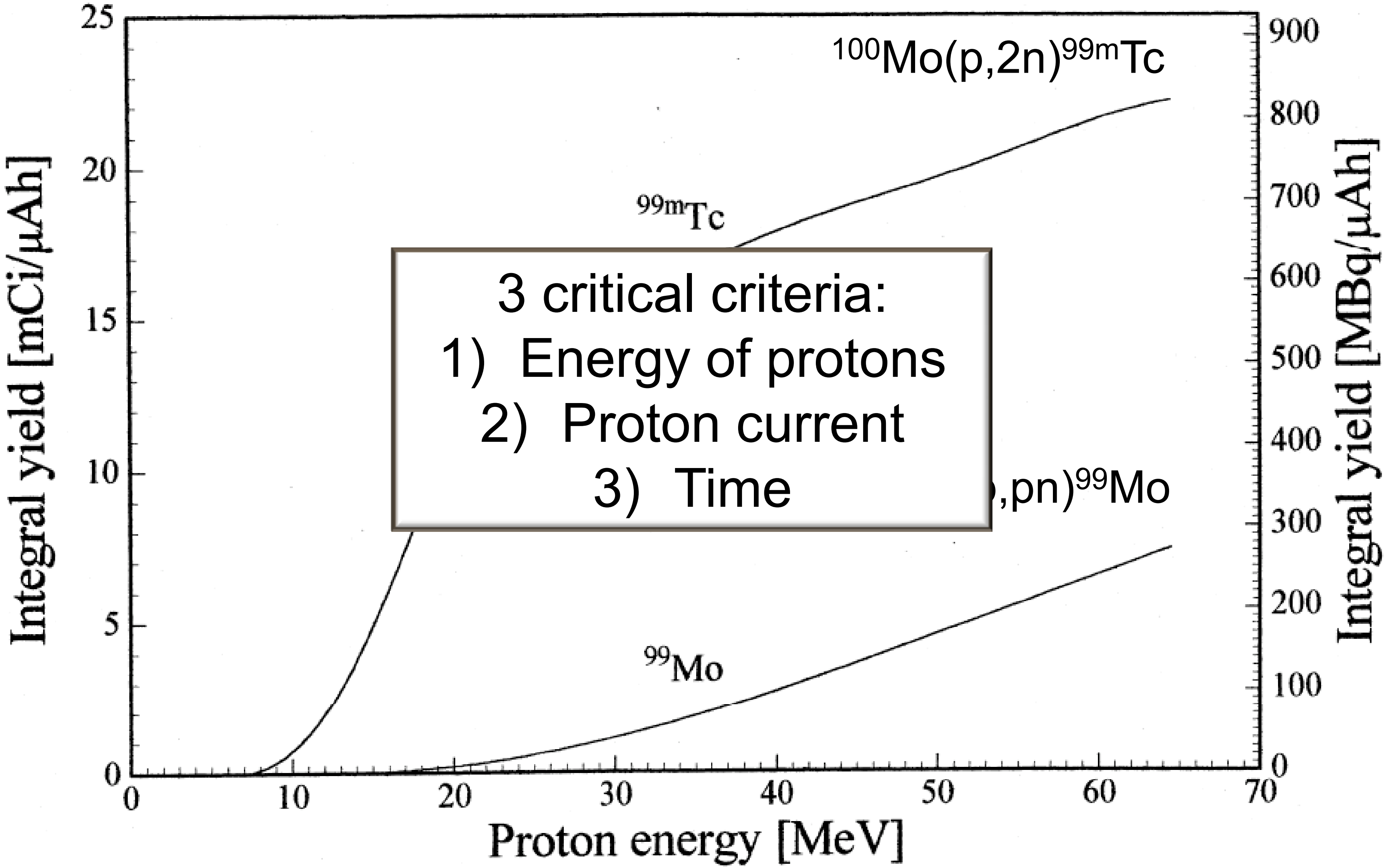


…can produce commercial quantities of ^{99m}Tc

Goal: To change the global thinking on ^{99m}Tc production

- Help formulate Government of Canada policy on $^{99}Mo/^{99m}Tc$ medical isotope production

Theoretical Yields



3 critical criteria:

1) Energy of protons
2) Proton current
3) Time

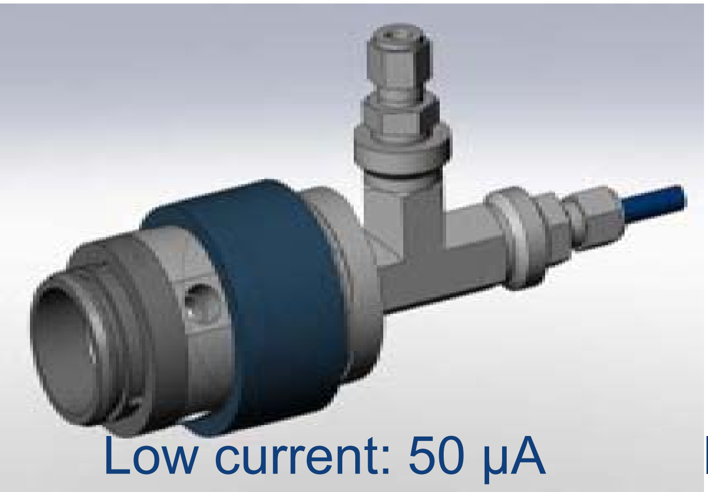
Projected Production Capabilities

Cyclotron	Energy (MeV)	Current (mA)	Irradiation Time (hours)	Theoretical Activity at EOB (Ci)
CP42	19	0.2	3	6.1
	19	0.2	6	10.4
	19	0.2	12	15.6
	24	0.2	3	8.6
	24	0.2	6	14.7
	24	0.2	12	22.1
TR19	19	0.2	3	6.1
	19	0.2	6	10.4
	19	0.2	12	15.6
	19	0.5	3	21.4
	19	0.5	6	36.7
	19	0.5	12	55.1
GE PETtrace	17.5	0.08	3	2
	17.5	0.08	6	3.4
	17.5	0.08	12	5.1
	17.5	0.16	3	4
	17.5	0.16	6	6.8
	17.5	0.16	12	10.2

YVR

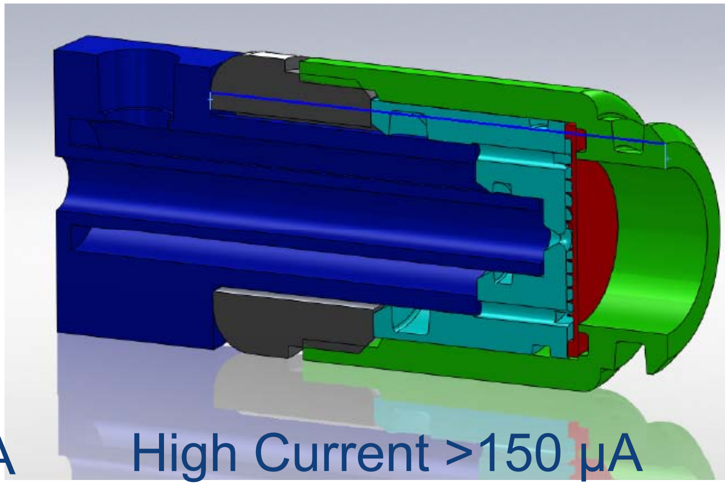
Target Housing

TRIUMF-design and manufacture

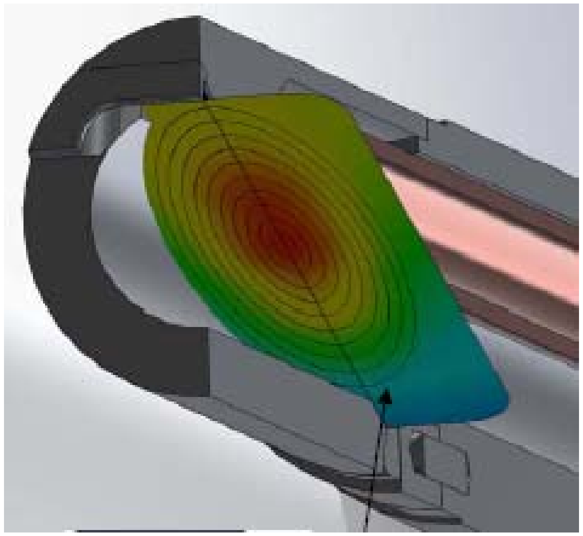


Low current: 50 μA

Intermediate current: <100 μA



High Current >150 μA



Questions to answer:

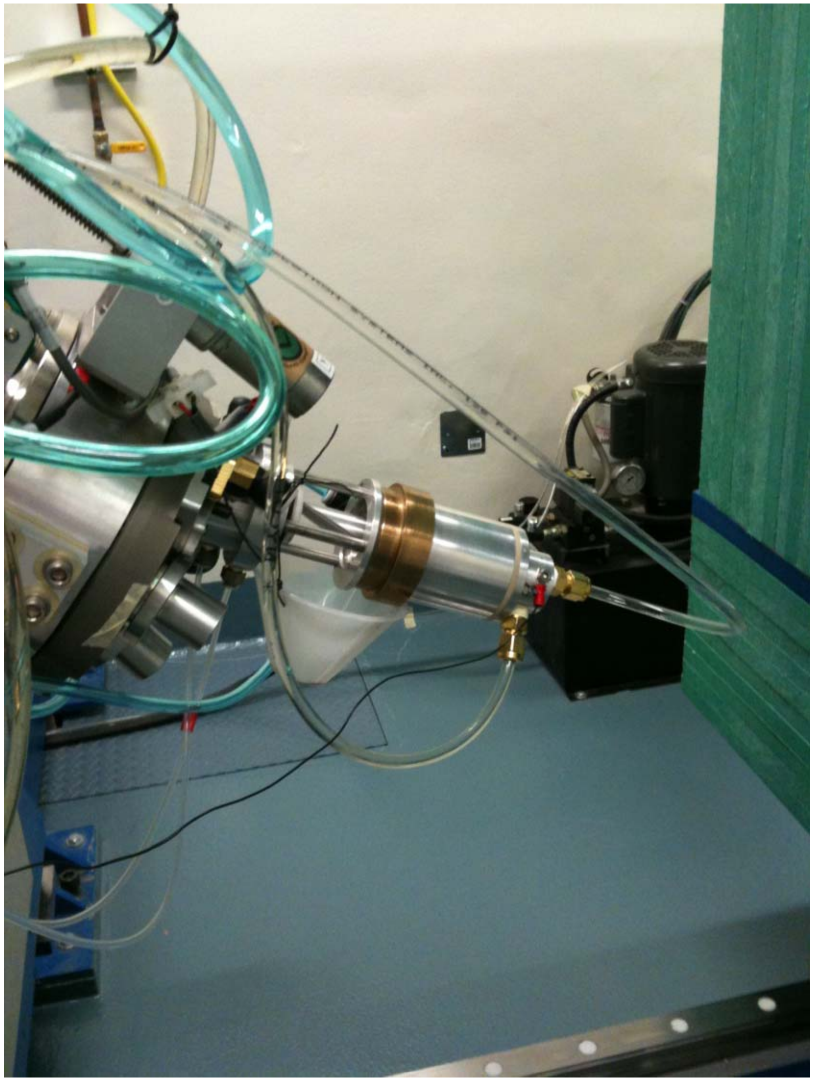
- Which proton energy are we using?
- What current are we using?
- How long are we irradiating?

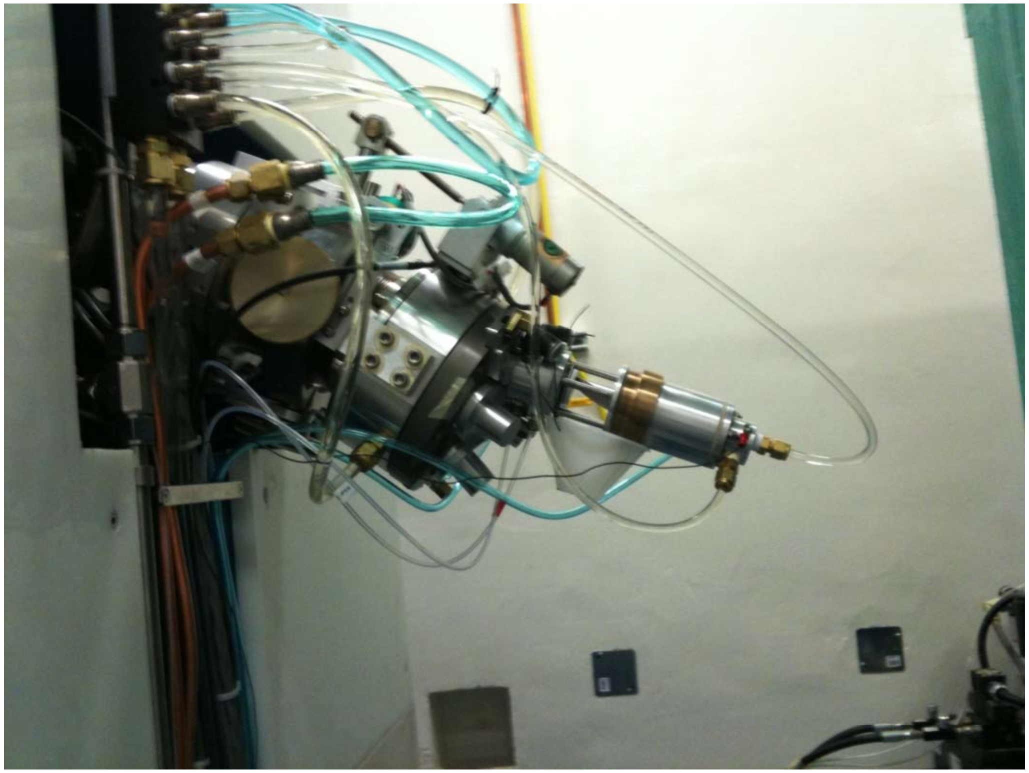
Also:

- How do we move material when done?
- Turnaround for next run

Goal: > 100 μA, 16.5 to 18 MeV, 3 - 6 hours

Target Housing Installation at BCCA



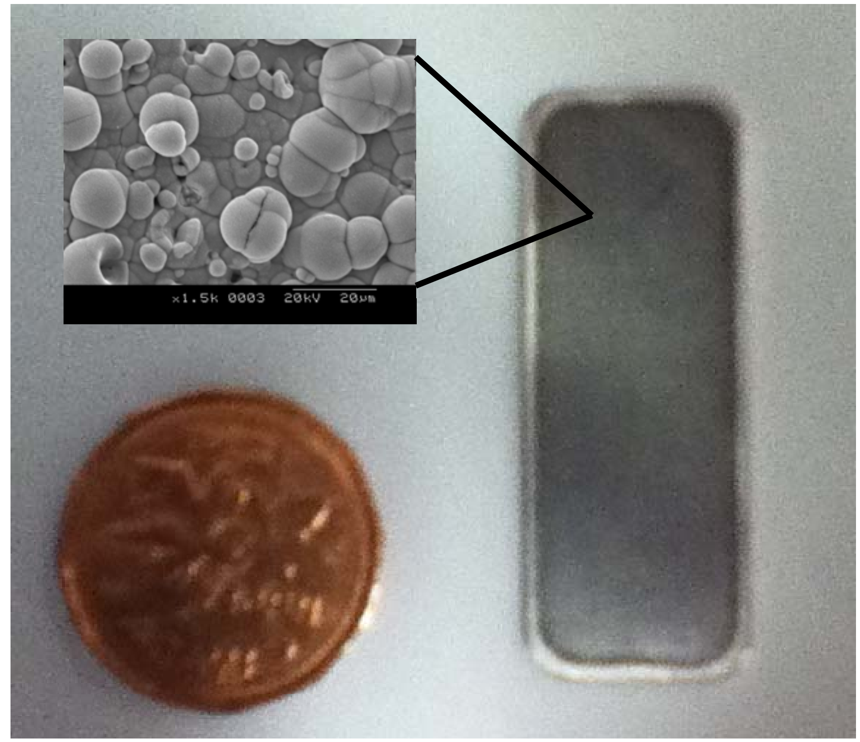


Target Plate Manufacture

Target Design and Function
-High risk!

- Fewer than 10 reports on aqueous deposition of Mo
  - Aqueous preferred (MoO_4^{2-})
  - All report <1 μm coatings

- Require T_{eff} > 300 μm



Three parallel efforts: electroplating, sintering and sputtering

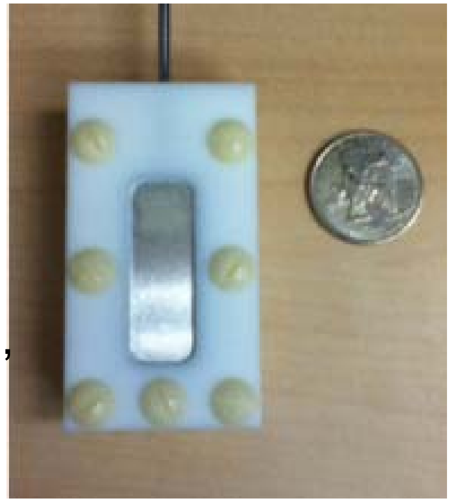
Energy (MeV)	Thickness ^{100}Mo (μm)	Mass ^{100}Mo (mg)
GE (16.5-10)	317	564-1003
ACSI (18.5-10)	408	320-818
CP42 (22-10)	673	1239

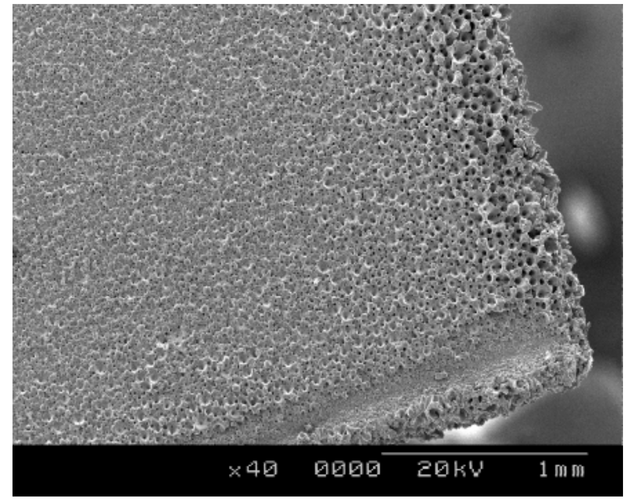
$$T_{eff} = \frac{T_{actual}}{\sin\theta}$$

Electroplating Results

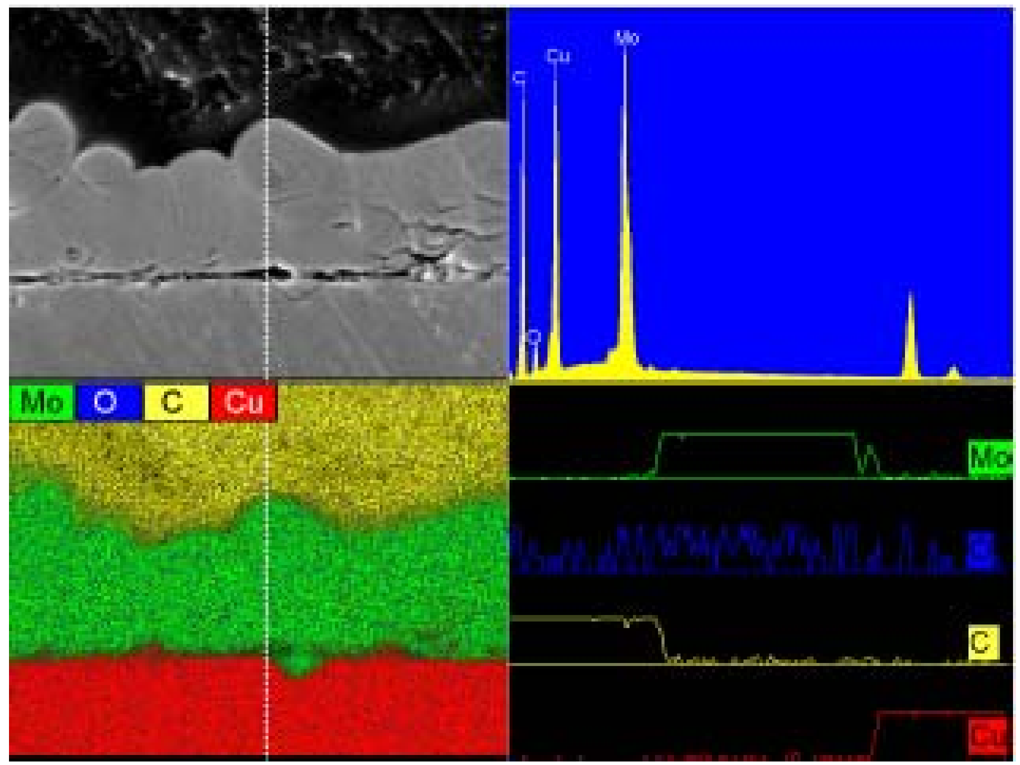
Early efforts - three outcomes;
1) No deposit
2) Black deposit MoOx
3) Metallic deposit (<1μm)

Possible variables:
Current, pH, Temperature, [MoO_4^{2-}], counterion, Agitation, Additives, Cell (anode, cathode) composition, Duration





Hints from literature:
Organic acid to stabilize intermediate Mo states
Sequester the available water
Use a saturated electrolyte with ligand salt

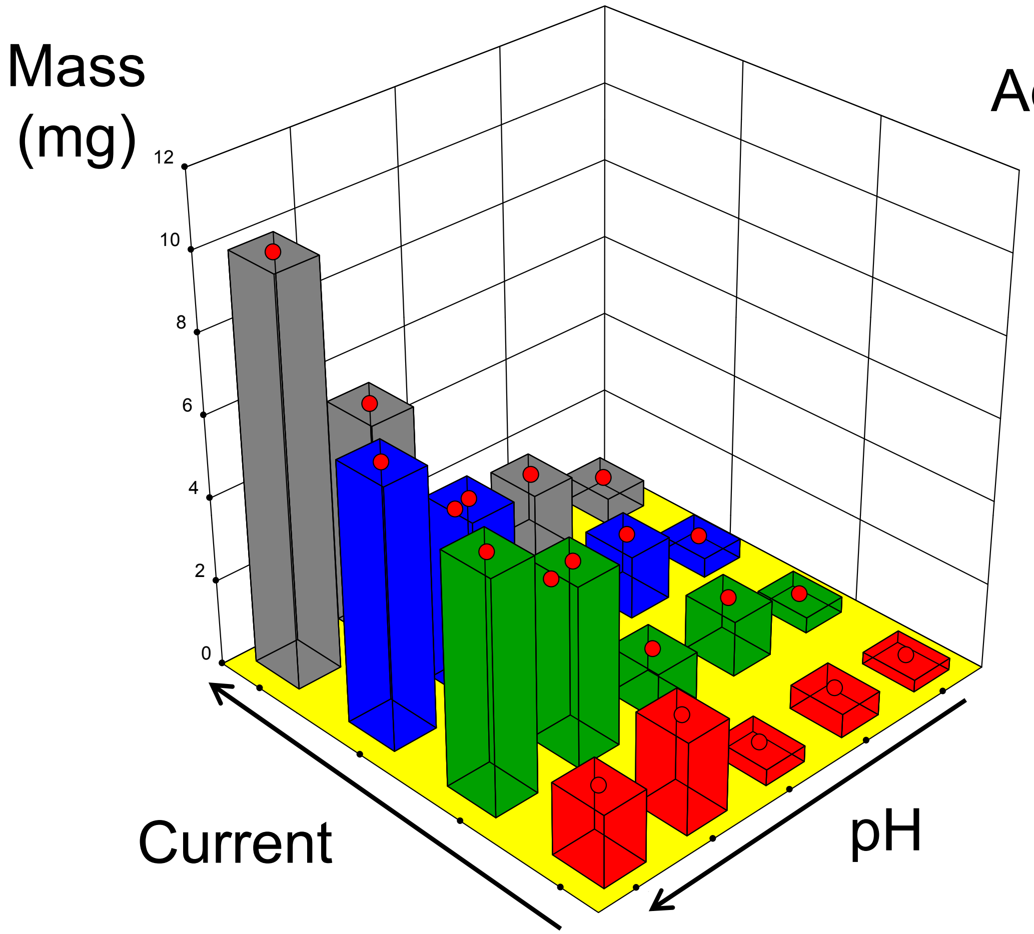


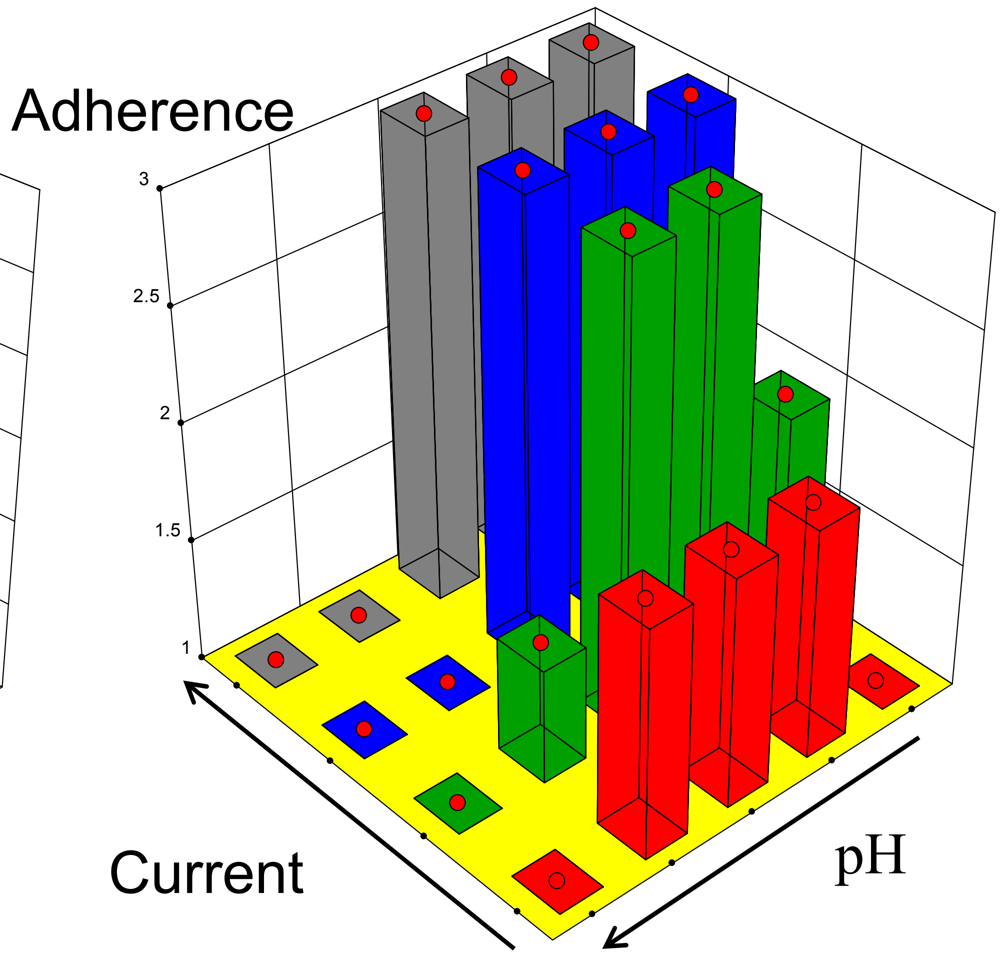
Result:
Metal (not oxide) deposit, up to ~30μm
Recall – need T_{eff} >300μm

Optimization continues:
Contingency plans to utilize sintered Mo

Quality Tools for Focused Research

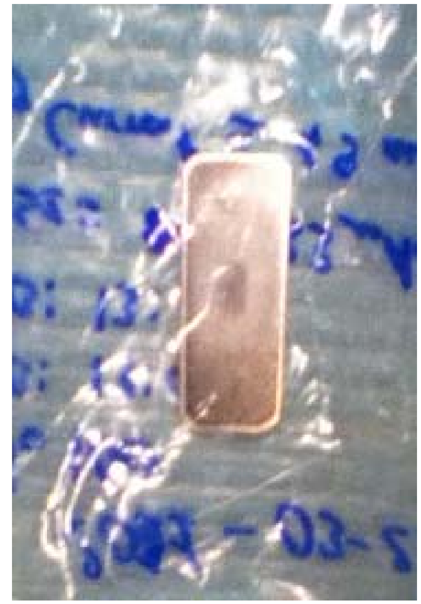
Screening Experiments:
pH, current, agitation, electrolyte volume, [MoO_4^{2-}]
Identified current and pH as most important





Abandoned for similar, but more effective approach

$^{99m}TcO_4$ Purification



Irradiations performed up to 30 μA, 15-18 MeV for 1 hour

Goal: > 100 μA, 16.5 to 18 MeV, 3 hours

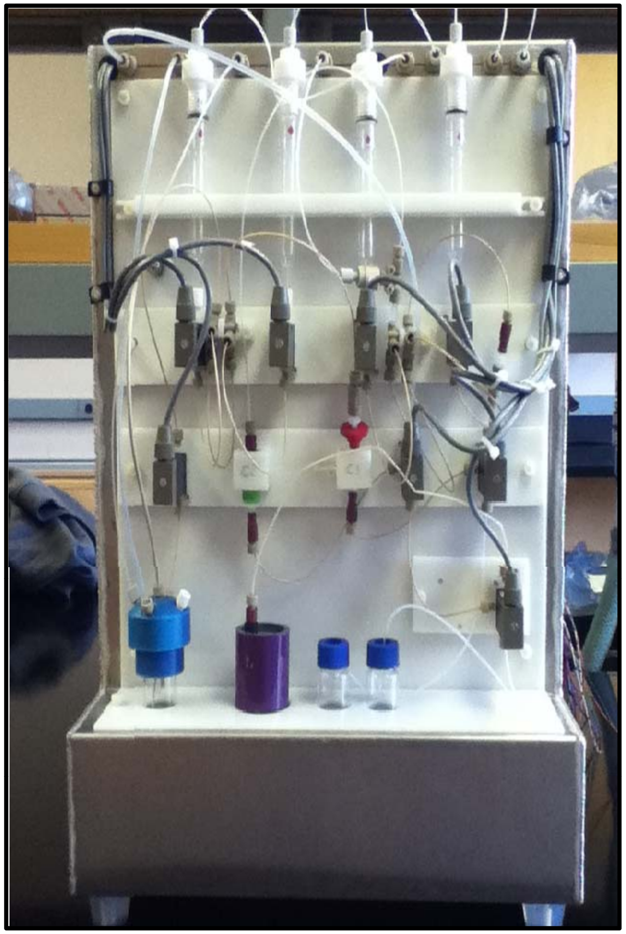
	Activity (mCi)		
Isotope	1μm target	5μm target	>400μm target*
Tc-99m	0.4	3.0	95
Mo-99	0.003	0.03	unknown

Tc-95/96/97 detected at the <10 kBq level

*produced using alternative method

Automated Isotope Purification

Remote separation system



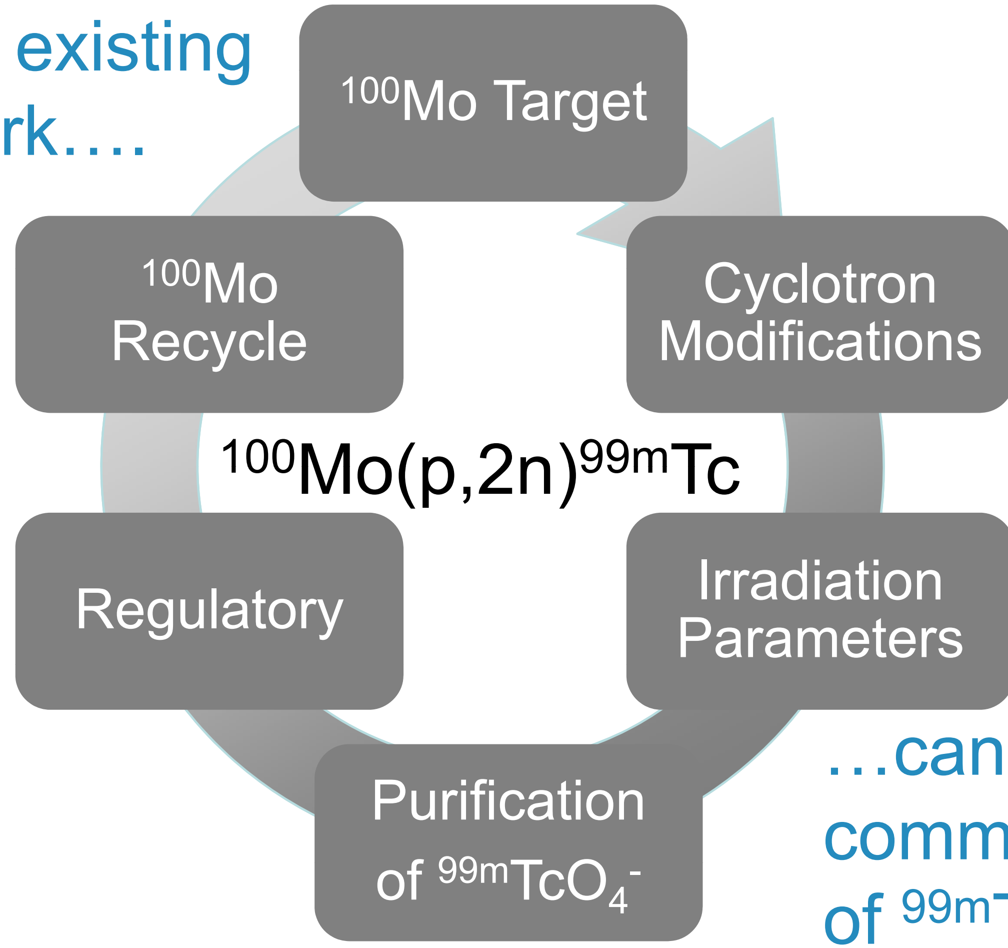
- **Dissolution:** rapid in H_2O_2
- **Ion exchange:** Dowex™ vs ABEC
  - Dowex is flow dependent
  - Capture @ <2mL/min, release @ <1 mL/min
- **Time:** complete in <30 min.
- **Efficiency:**
  - Dowex: 72% (35 min)
  - ABEC >90% (30 min)
- **Radiochemical Purity:** >99.99% TcO_4
- **Trace analysis:** <10 Bq Mo-99, <5 ppm Al^{3+}

- Other Tc isotopes detected: ^{97}Tc, ^{96}Tc, ^{95}Tc
- 97.39% enriched ^{100}Mo used
  - May require higher enrichement (99.1%)

McAlister and Horwitz, Appl.Radiat. Isotope 2009, 67, 1985 (two-column approach)
Chattopadhyay et al. Appl. Radiatl. Sotop. 2008, 66, 1814 (Dowex)
Bond et al. Ind. Eng. Chem. Res. 1999,38, 1683 (ABEC)

Direct Production of ^{99m}Tc

To demonstrate existing cyclotron network….



…can produce commercial quantities of ^{99m}Tc

Goal: To change the global thinking on ^{99m}Tc production

- Help formulate Government of Canada policy on $^{99}Mo/^{99m}Tc$ medical isotope production

TRIUMF

Nuclear Medicine: Moving Forward

Hypothesis: Nuclear pharmacies will shift to rely entirely on accelerators for production of medical isotopes within 10 years

- If accelerators can produce isotopes traditionally obtained from nuclear reactors at similar cost, quality, then production by reactor becomes obsolete
- Many other isotopes are produced using hospital-based accelerators (cyclotrons)
- Positron emitters comprise of growing list of isotopes used for imaging
- Many hospitals are developing in-house expertise to produce and study novel radiopharmaceuticals

Imaging Mechanisms

Three mechanisms for (targeted) tracer uptake

Non-targeted

1) Perfusion

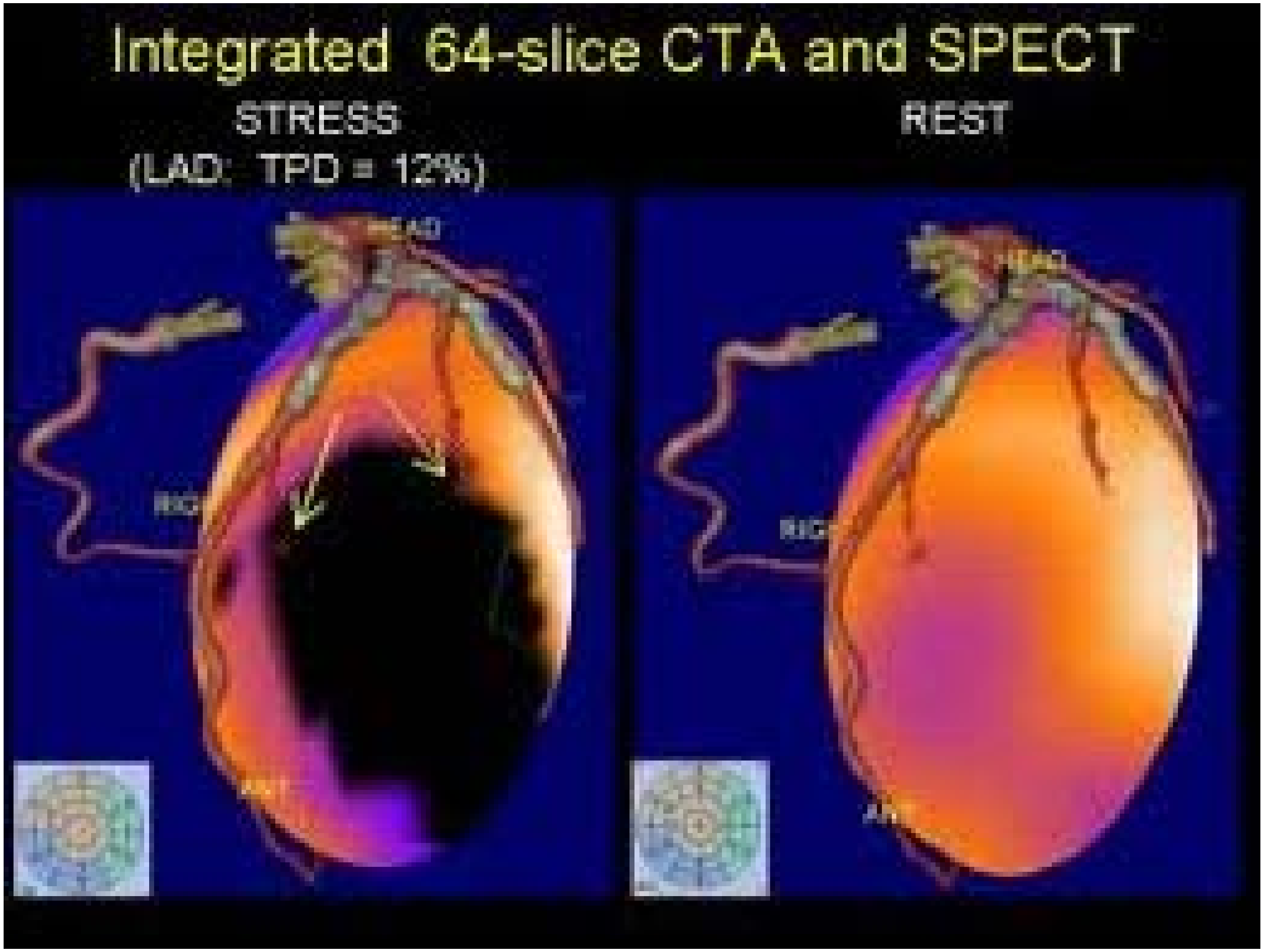
Targeted

1) Binding – cell surface markers

2) Accumulation – transport / metabolism

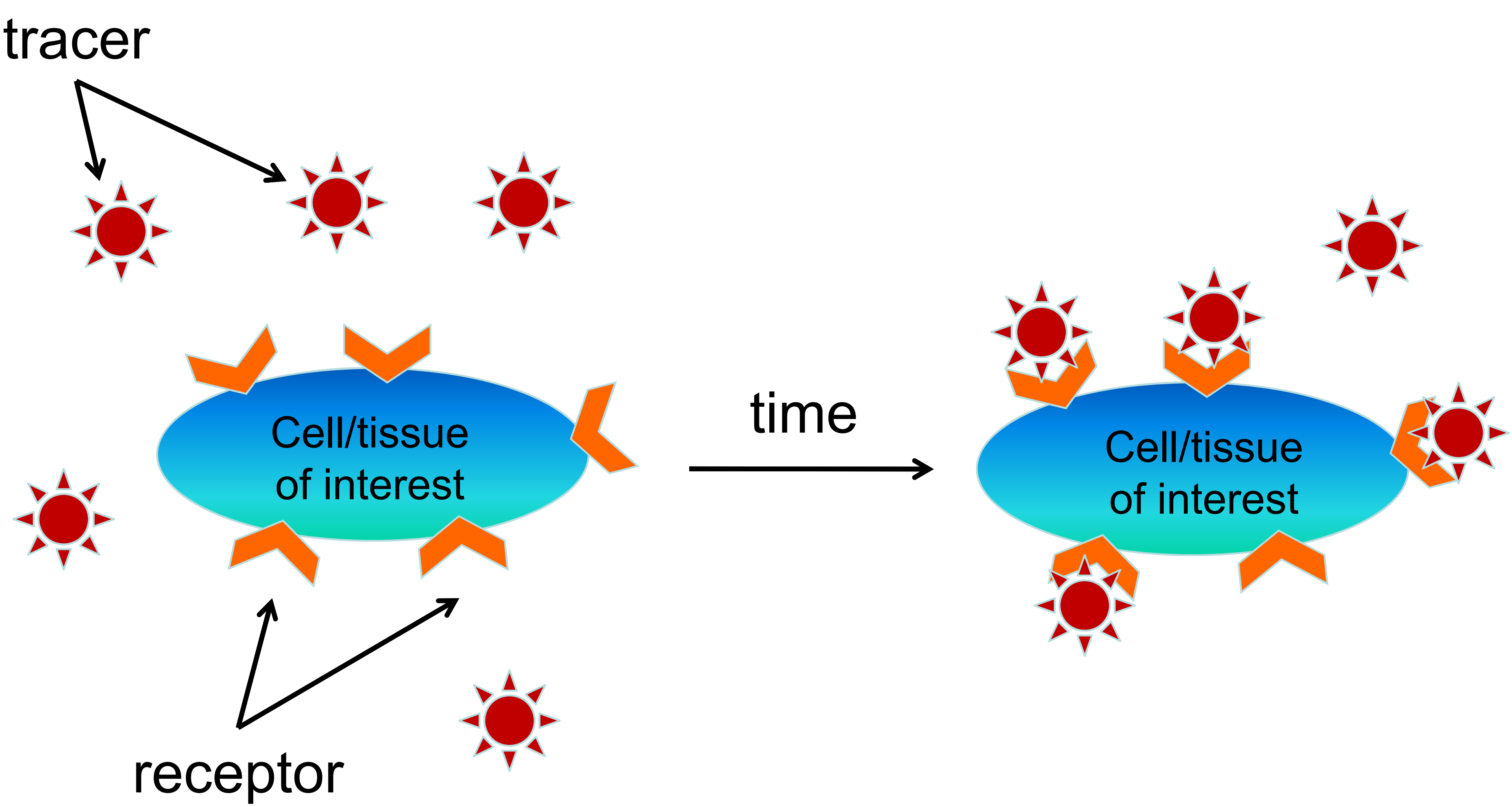
3) Conversion – activates probe (not for PET)

Perfusion Imaging

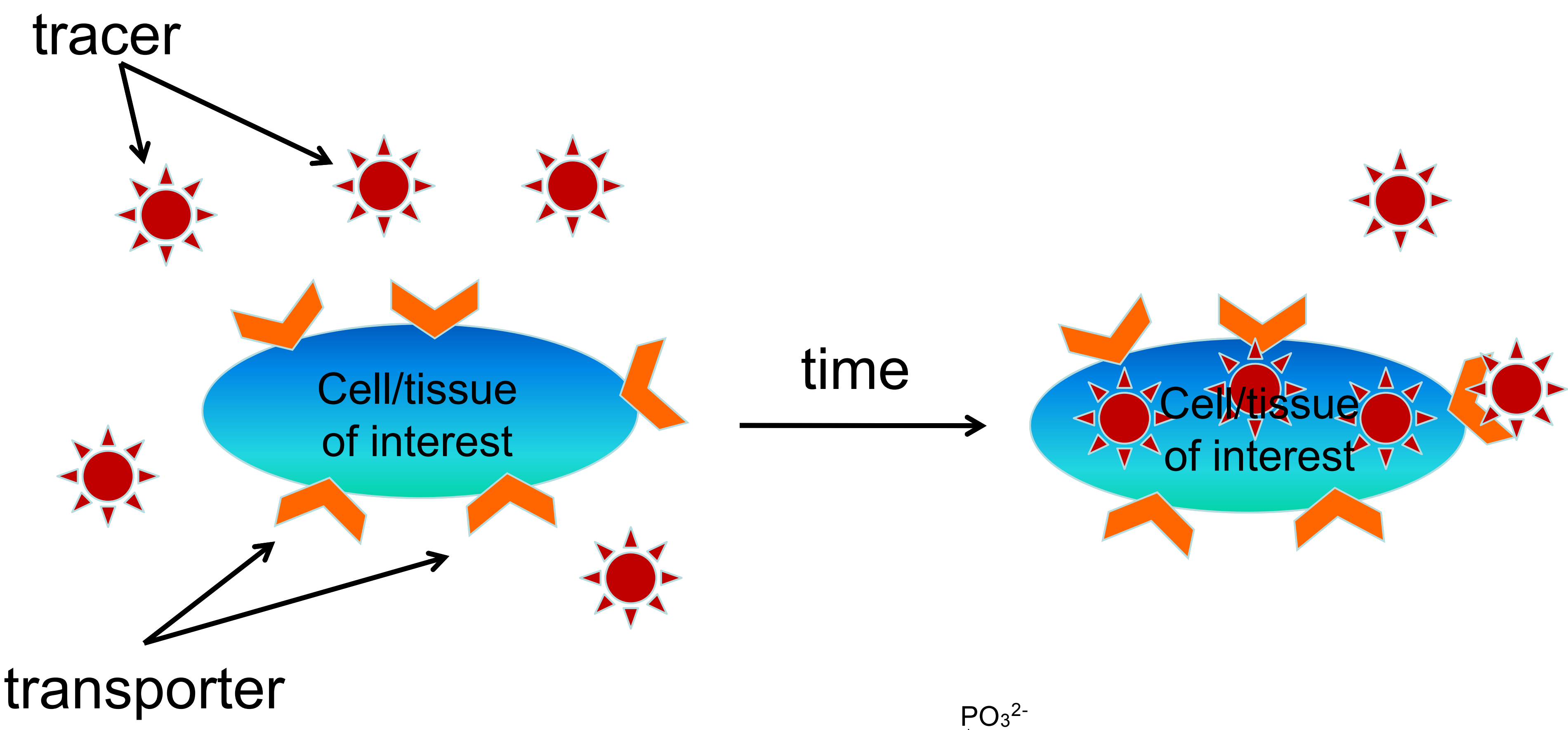


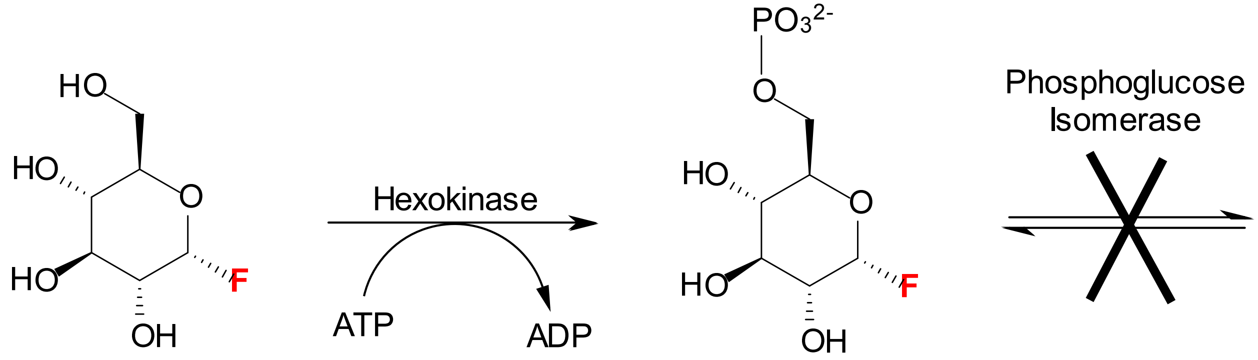
www.medicexchange.com

Targeted Imaging: Mechanism of Action - Binding

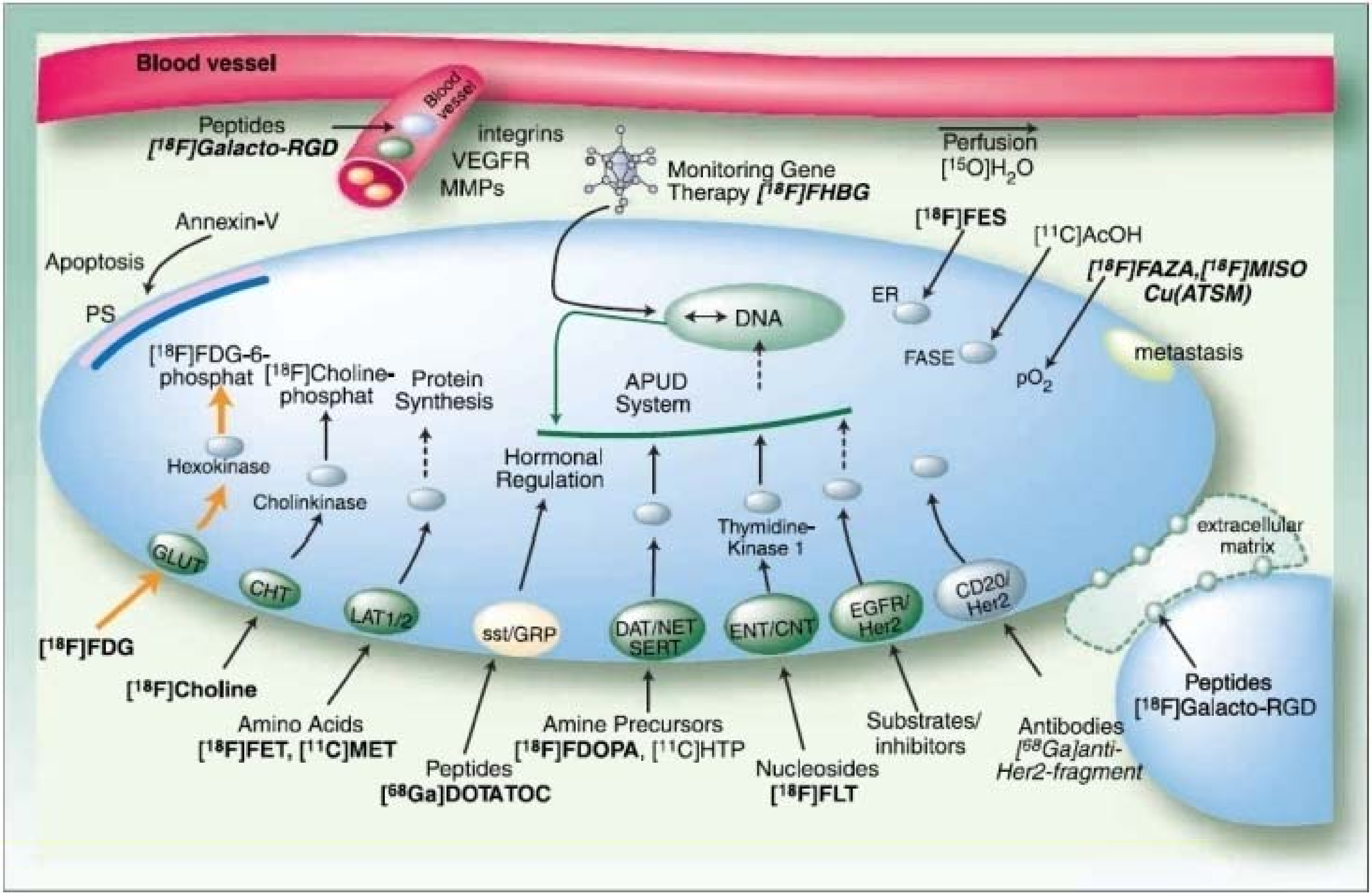


Targeted Imaging: Mechanism of Action - Accumulation



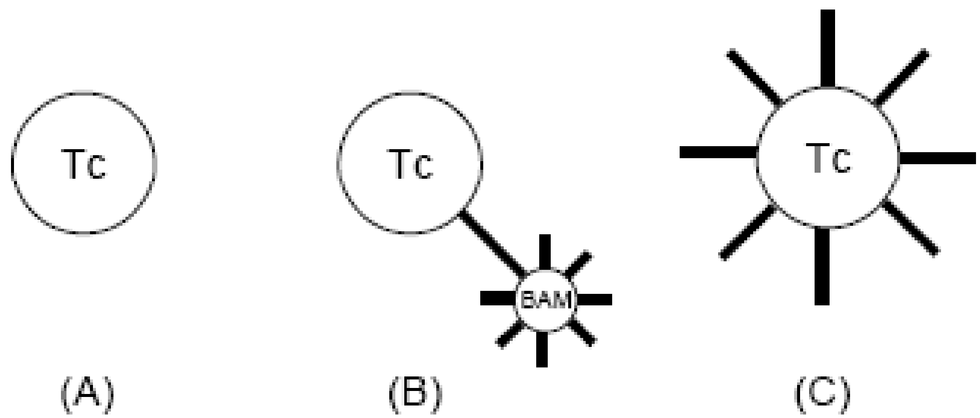


What Types of MI agents use PET?



Labeling Approaches

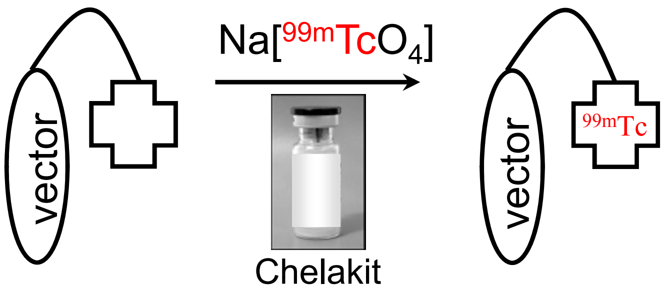
- Integrated
- Direct, non-regiospecific
- Direct, regiospecific,
- Indirect, regiospecific
- Indirect non-regiospecific



Chemical Society Reviews, 1998, 27, 43

The Paradigms of Nuclear Medicine

SPECT

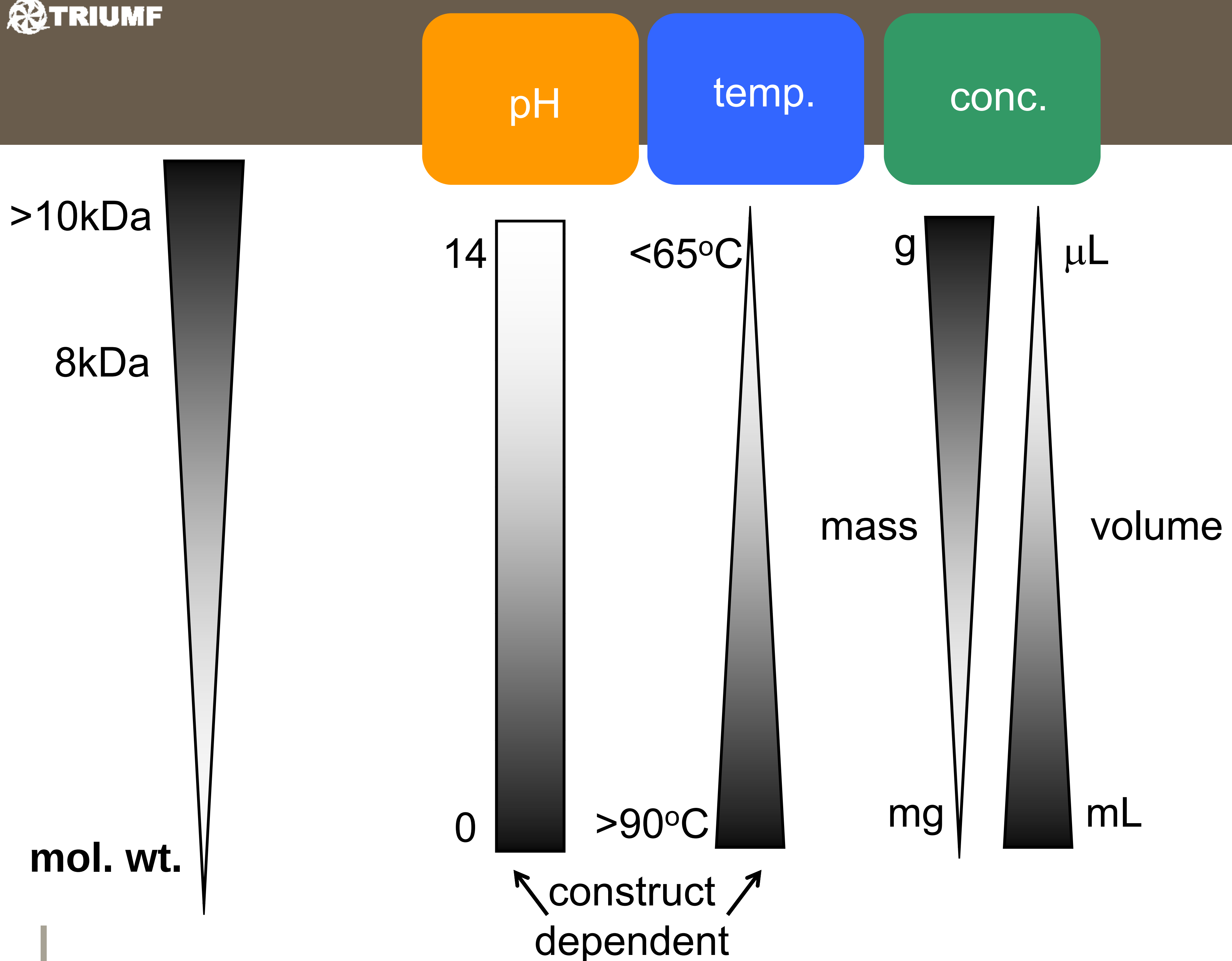


‘Shake and Shoot’

	halflife	keV
Tc-99m	6 hrs	140
I-123	13 hrs	159
In-111	2.8 d	171 / 245
Ga-67	3.3 d	93/184/300

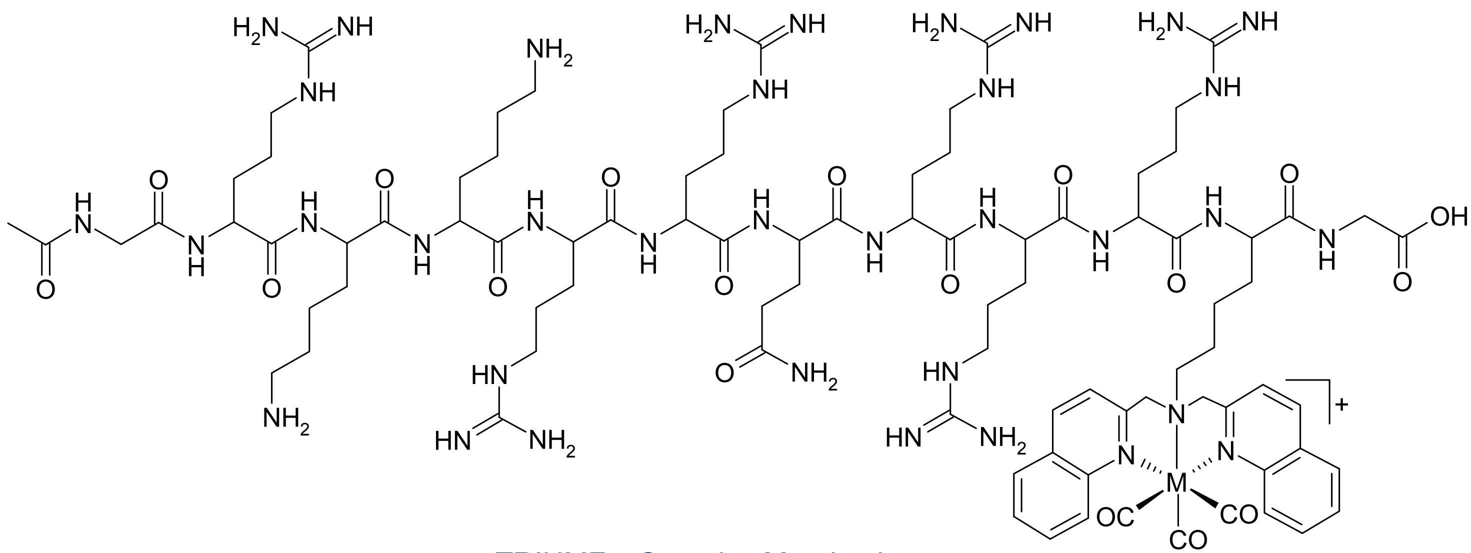
PET

	halflife	MeV
F-18	110 min	0.64
C-11	~20 min	0.96
N-13	~10 min	1.2
O-15	~2min	1.73
Ga-68	68 min	1.9
Cu-64	~13 hrs	0.65


pH
temp.
conc.
>10kDa
8kDa
mol. wt.
14
0
<65°C
>90°C
construct
dependent
g
mg
mass
µL
mL
volume

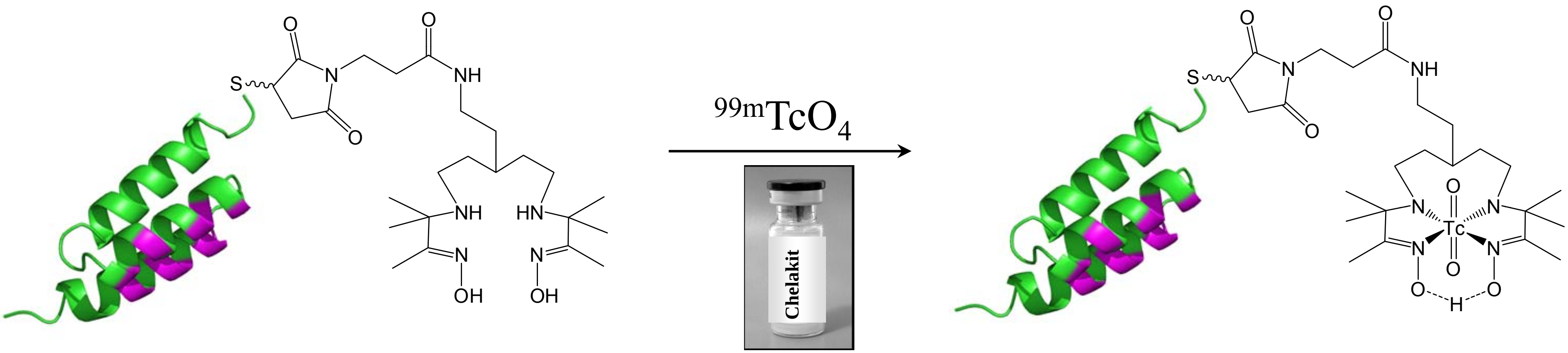
Attributes of Large Mol. Wt. Vectors

– peptides easily diffuse into tissue (better than proteins)
– tunable specificity
– good clearance profiles from non-target tissue (good signal-to-noise)
– low toxicity/immunogenicity

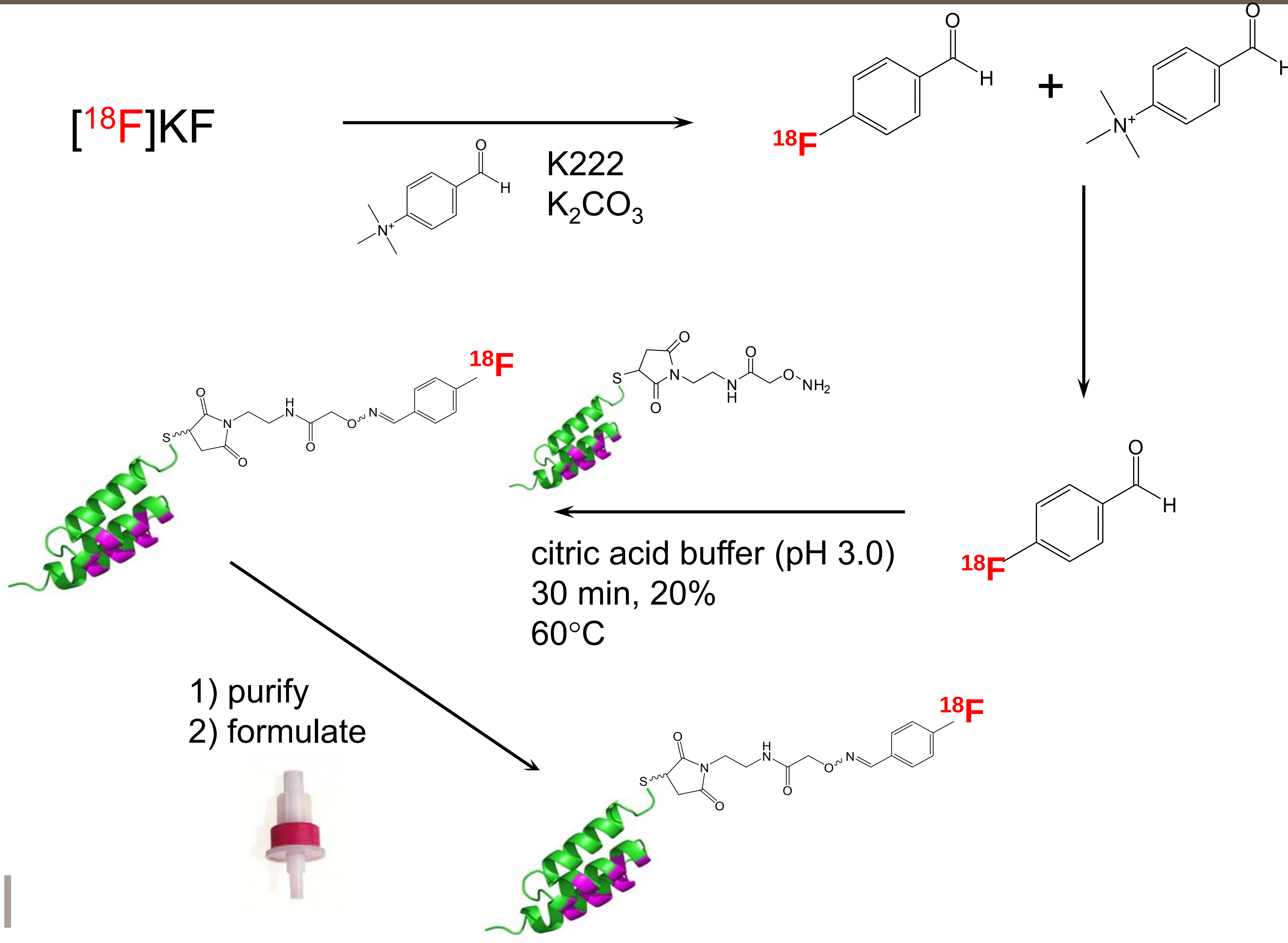


M = ^{99m}Tc, Re

Tc-99m Chemistry: Example

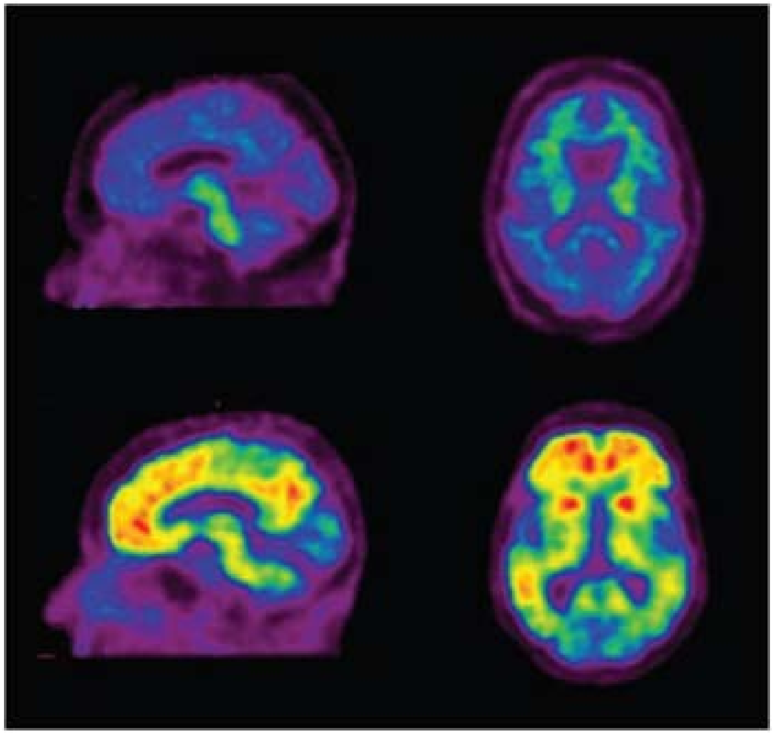


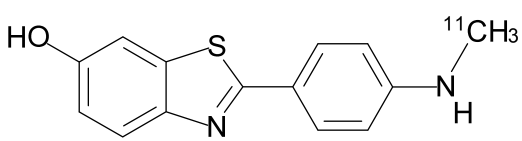
F-18 Chemistry for Large Mol. Wt.



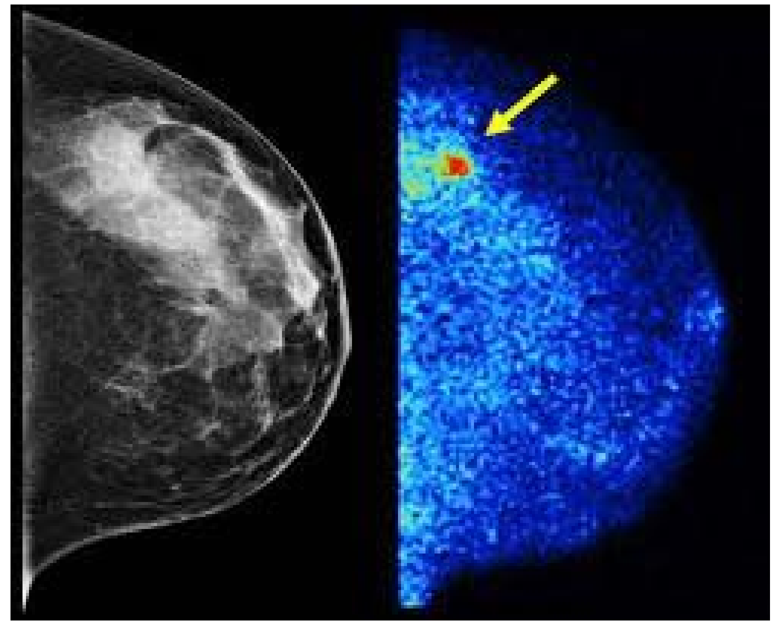
Medical Imaging in Humans - future

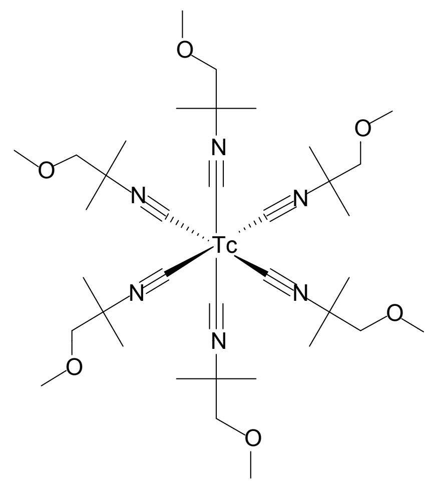
Alzheimer's



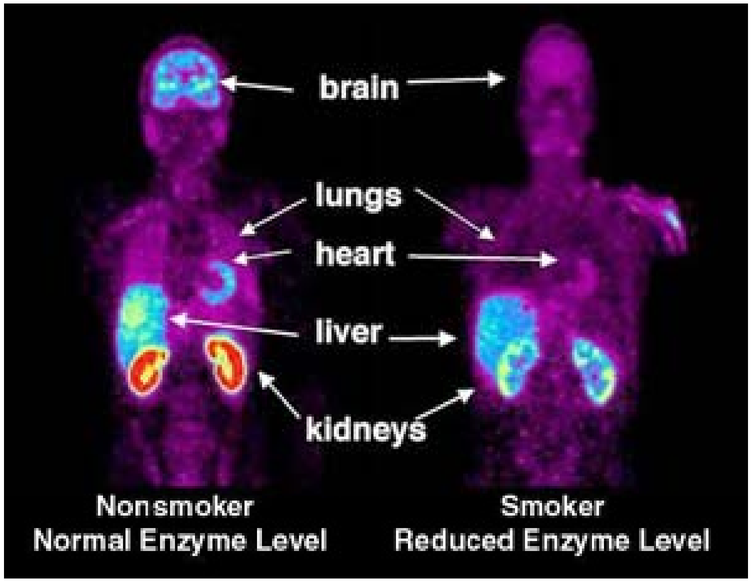


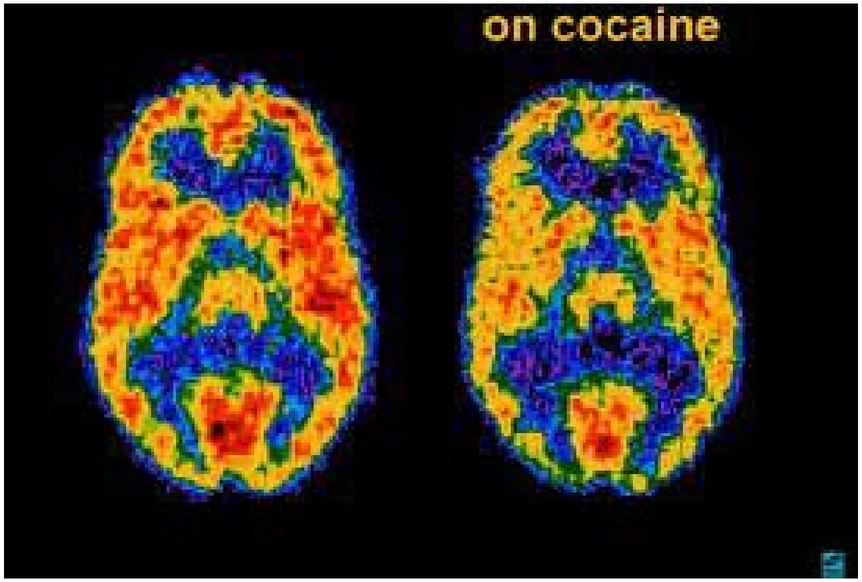
Breast Cancer

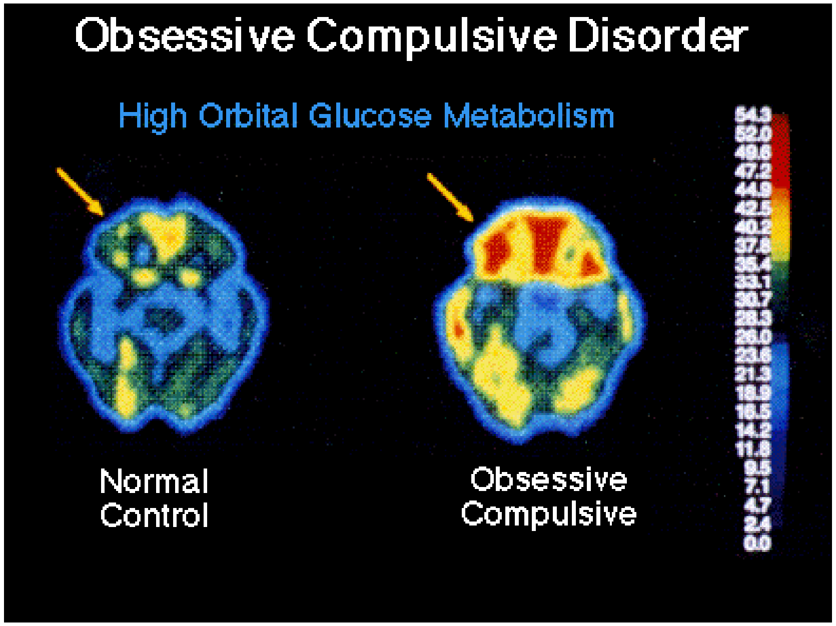




…and other conditions







TRIUMF

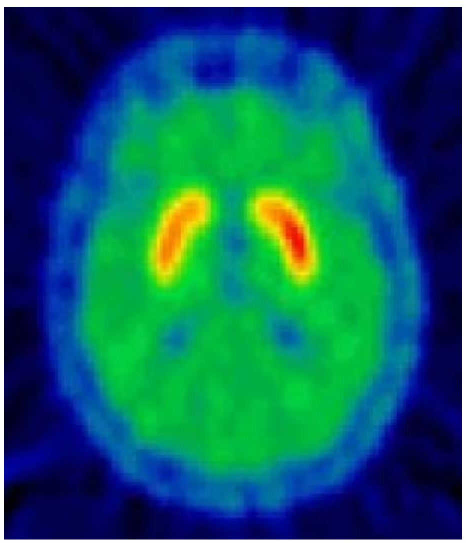
Positron Emission Tomography Imaging at THE UNIVERSITY OF BRITISH COLUMBIA

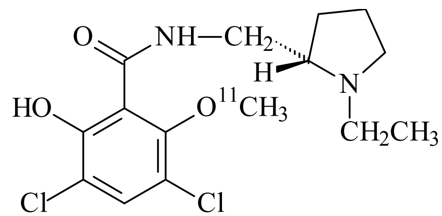
PPRC

Observing the Placebo Effect…

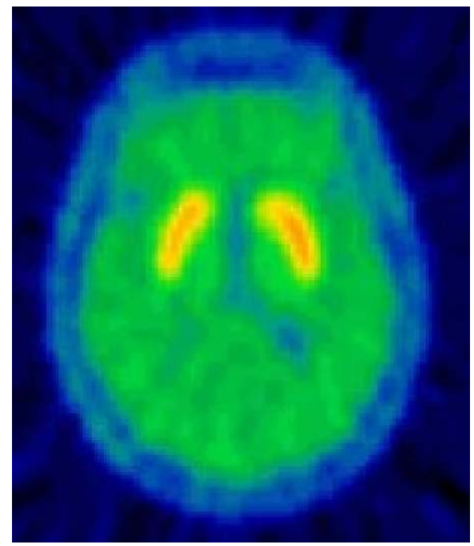
"…the act of receiving any treatment may, in itself, be efficacious because of expectation of benefit."

Parkinson's patient brain scan showing ^{11}C-raclopride accumulation





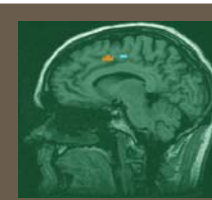
When told they had a **possibility** of being given drug of benefit



First demonstration of neurochemical effect of placebo

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

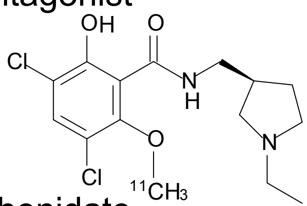
Core Program at TRIUMF



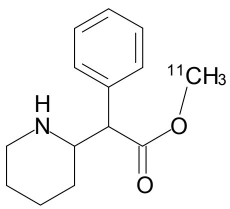
PPRC

^{11}C containing tracers

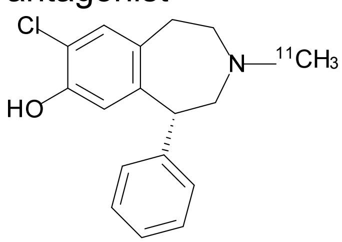
Raclopride
- Parkinsons
- D2 antagonist



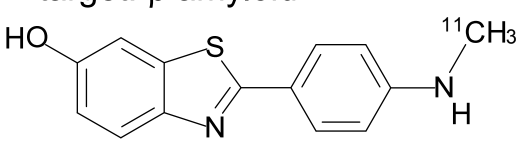
Methylphenidate
- Parkinsons
- DAT binder



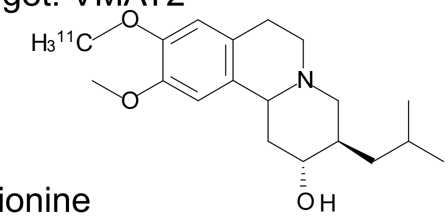
Sch233900
- Parkinsons
- D1 antagonist



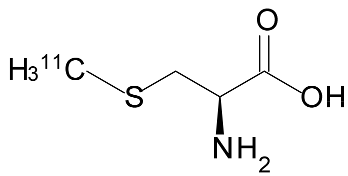
PIB
- Alzheimer's
- target: β amyloid



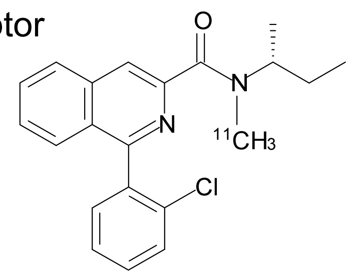
DTBZ
- Parkinsons/Diabetes
- target: VMAT2



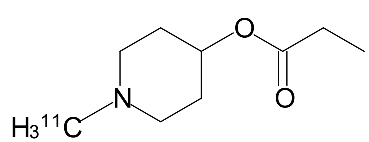
Methionine
- Oncology (brain, lung, breast)
- target: AA transport



PK11195
- Brain injury/inflammation
- PBR receptor

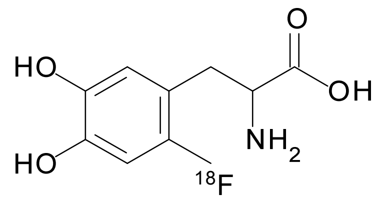


PMP
- Alzheimer's, Parkinsons, epilepsy
- AChE activity

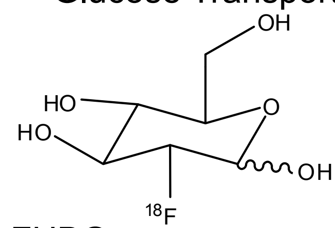


^{18}F containing tracers

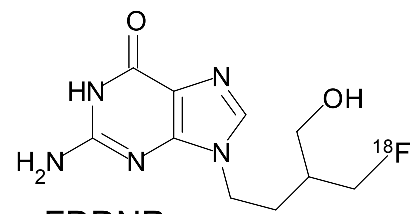
F-DOPA
- Parkinsons
- Dopamine metabolism



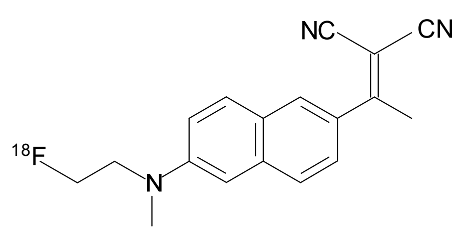
FDG
- Oncology/Neurology
- Glucose Transport



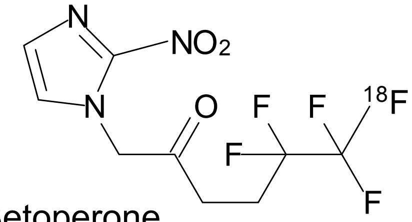
FHBG



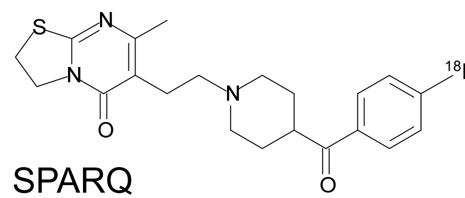
FDDNP
- Alzheimer's
- target: β amyloid



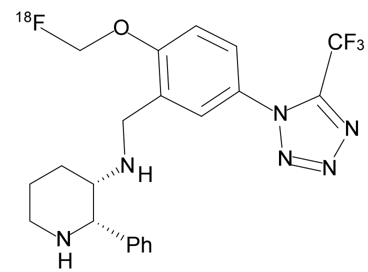
EF5
- Hypoxia



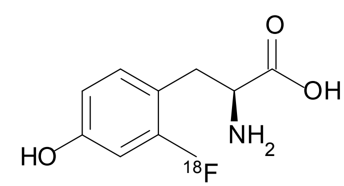
Setoperone



SPARQ
- Neurology
- Neurokinin

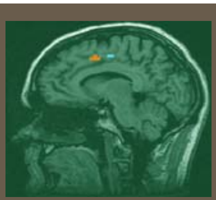


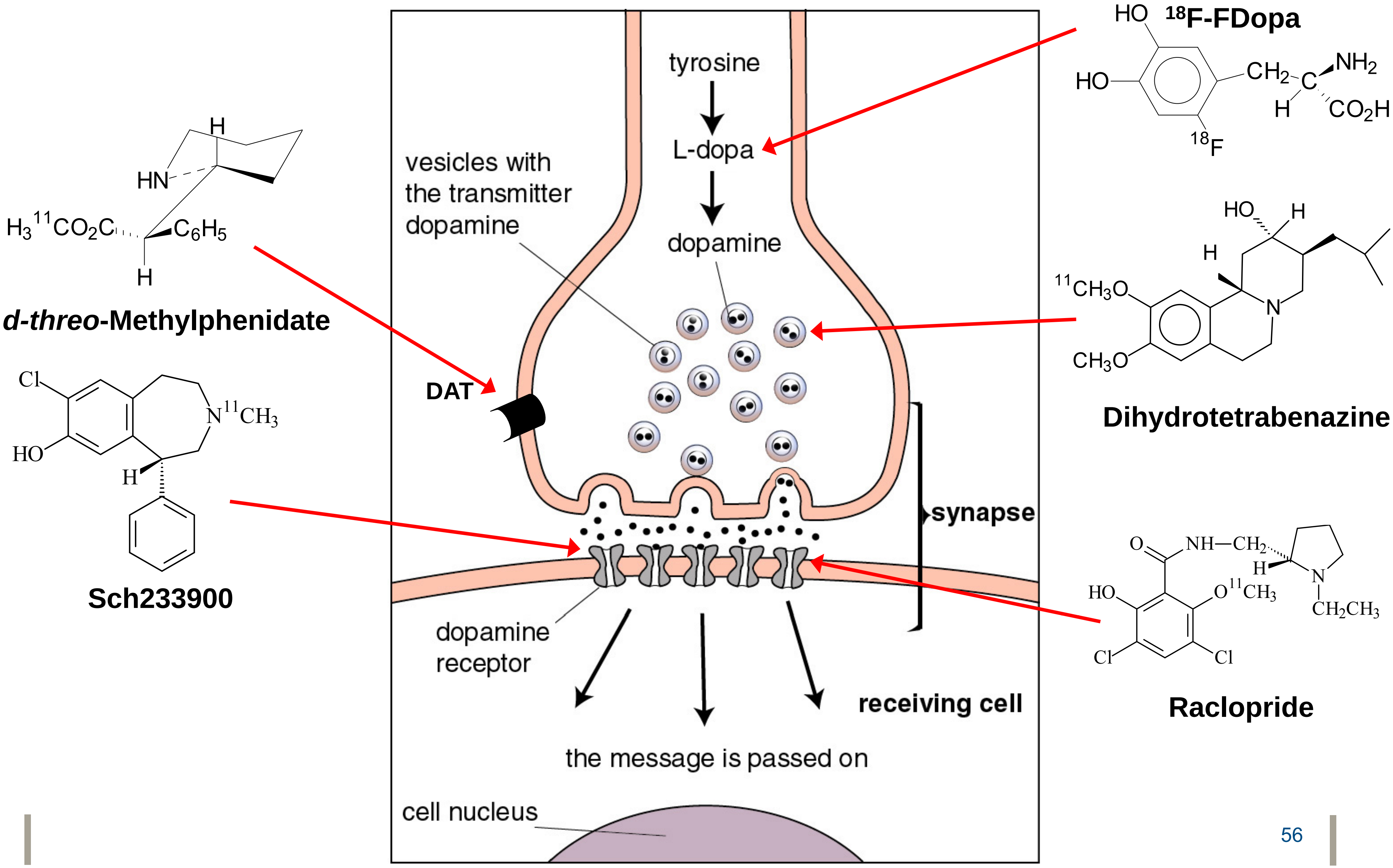
FLT
- Oncology
- Thymidine Kinase



TRIUMF

PPRC: Probing the Dopamine System





Infrastructure Upgrades: GMP Facilities

- WD Canada: $911,000 (retrofit GMP upgrade)
  - Thanks to: Nuc. Med. Team, Tim Meyer, Shirley Reeve

Not present:
Linda Graham,
James Inkster,
Tom Morley

Photos by: Mindy Hapke

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Edmonton (S McQuarrie, D Abrams, K Gagnon, J Wilson)

Lawson (F Prato, M Kovacs)

Sherbrooke (B Guerin)

CPDC (J Valliant), AAPS (C Campbell)

Advanced Cyclotron Systems, Inc.

GE Healthcare

NSERC CRSNG

CIHR IRSC Canadian Institutes of Health Research Instituts de recherche en santé du Canada

Natural Resources Canada Ressources naturelles Canada

Canada

Thank You!

Merci!