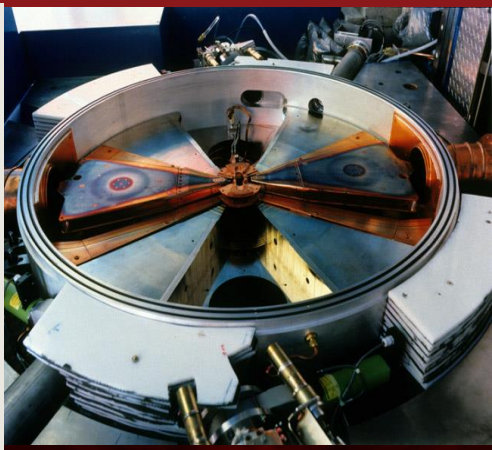
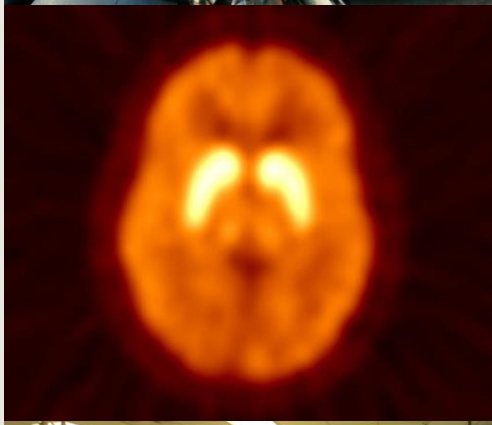
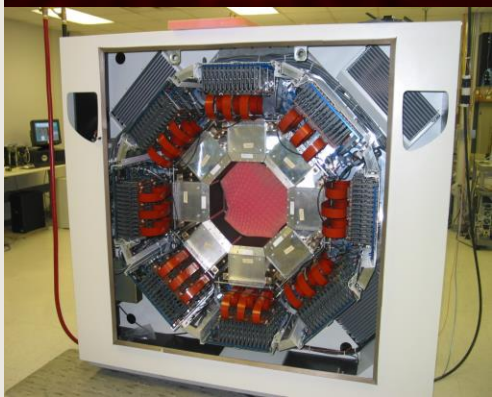
TRIUMF

Canada's National Laboratory for Particle and Nuclear Physics
Laboratoire national canadien pour la recherche en physique nucléaire et en physique des particules

From Vision to Seeing: Tracing brief history of positron emission tomography in BC and Canada.







Thomas J. Ruth, PhD
Senior Research Scientist , Emeritus
TRIUMF/BC Cancer Agency

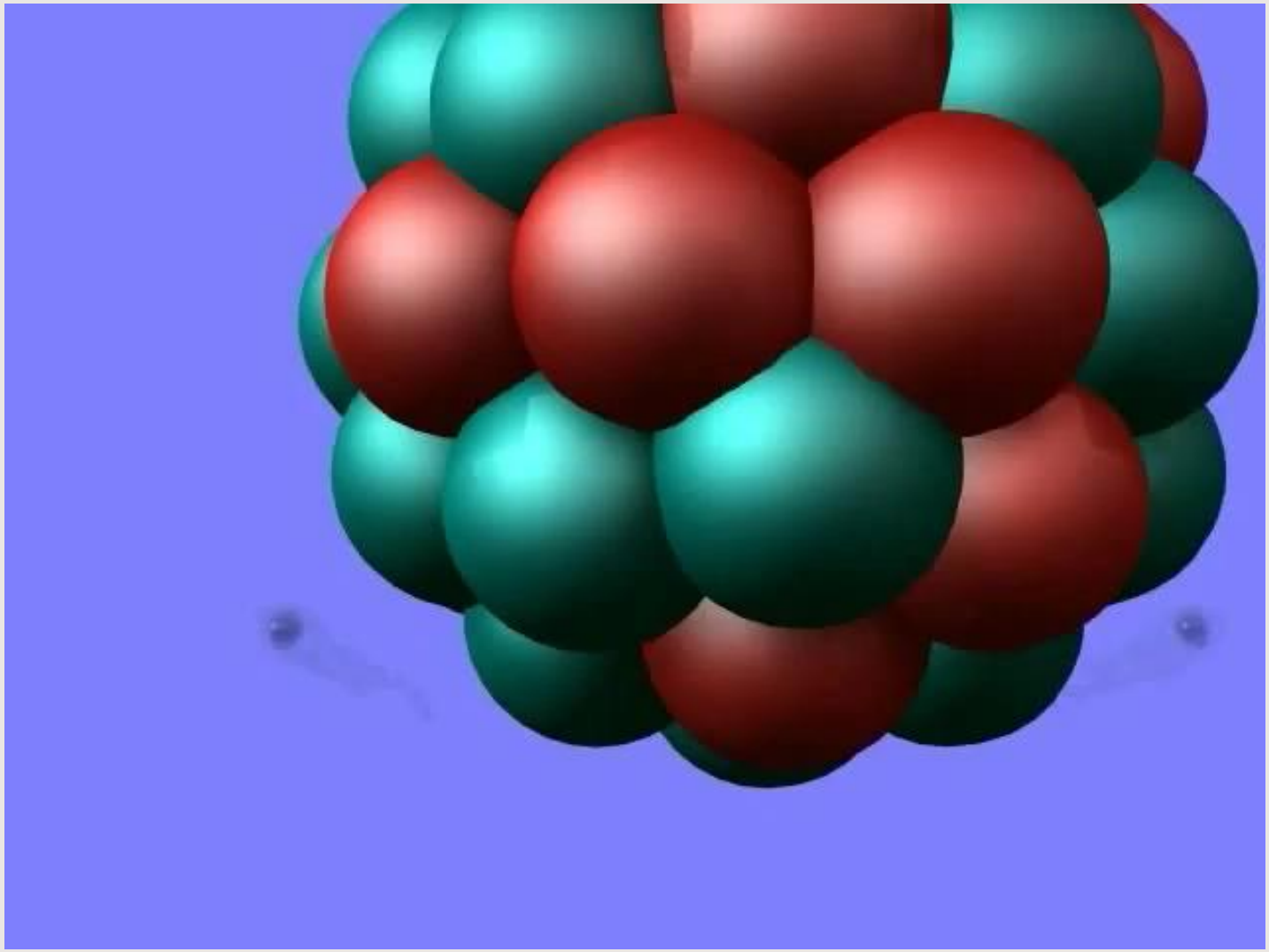
Disclosure:

I serve on the Scientific Advisory Board for α9oncology

Disclosure

Outline

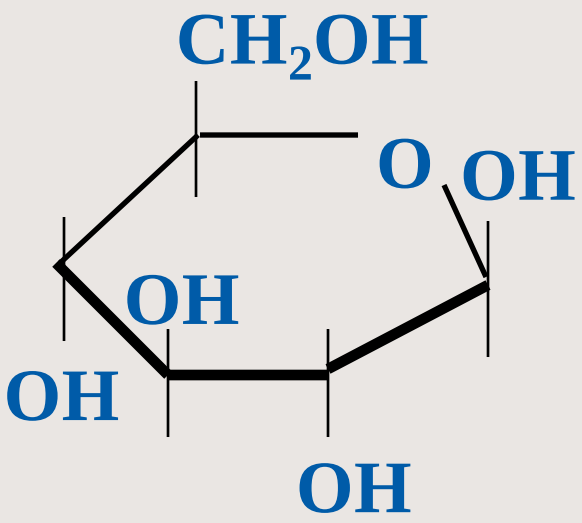
- History leading to FDG PET
- FDG PET
- BC and Canada's involvement
- TRIUMF/UBC Neuroscience Program
- BC Cancer establishing clinical PET
- Future of PET Scanning in Canada
- New Directions in cancer treatment
- Personalized Medicine
- Future of TRIUMF Isotope Program

- 

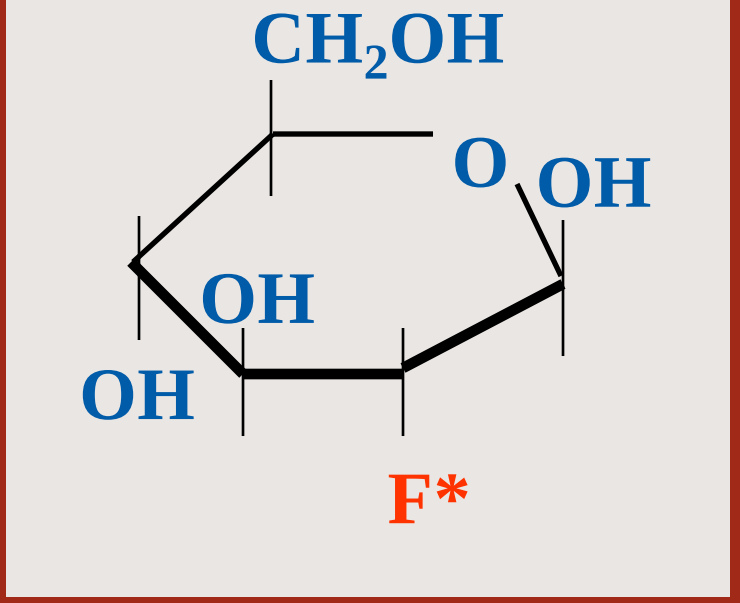
Brief History of PET

- 1950s – Brownell & Sweet at Harvard
- 1950s/60s – Hospital based cyclotron production of $H_2{}^{15}O$, Ter Pogossian, Wash. U.
- 1960s – ^{11}C-chemistry, Wolf team at BNL
- 1960s – ^{14}C-deoxyglucose, Sokoloff, NIH
- 1960s/70s – Kuhl & Edwards, MkIV camera
- 1970s – Phelps & Hoffmann, PET scanner, Wash. U.
- 1970s – ^{18}F-fluorodeoxyglucose, Wolf, Fowler, Ido
- 1970s – 1st FDG scan, Reivich, Kuhl, PENN
- 1980 – NIH funded 10 sites for NeuroPET

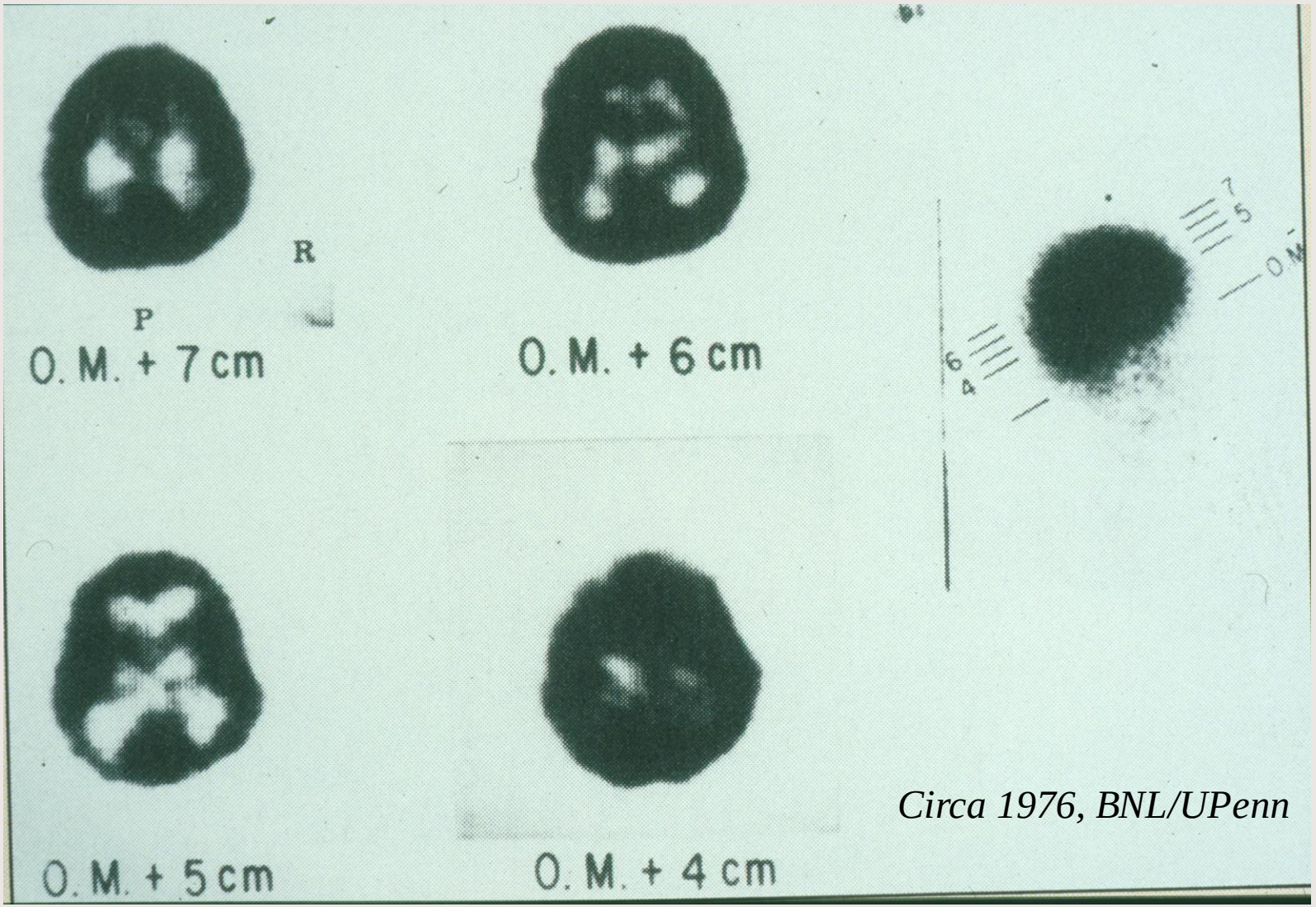
Glucose



Fluorodeoxyglucose (FDG)



FDG scan on MkIV – Kuhl,et al.



Circa 1976, BNL/UPenn

PET @ UBC/TRIUMF circa 1980

- Pat McGeer, Brian Pate, Bernie Reidel, Laurie Hall
- Building infrastructure:
  - CP-42 Beam Line
  - PETTVI Scanner
  - Pipeline

PETTVI Dedication 1982

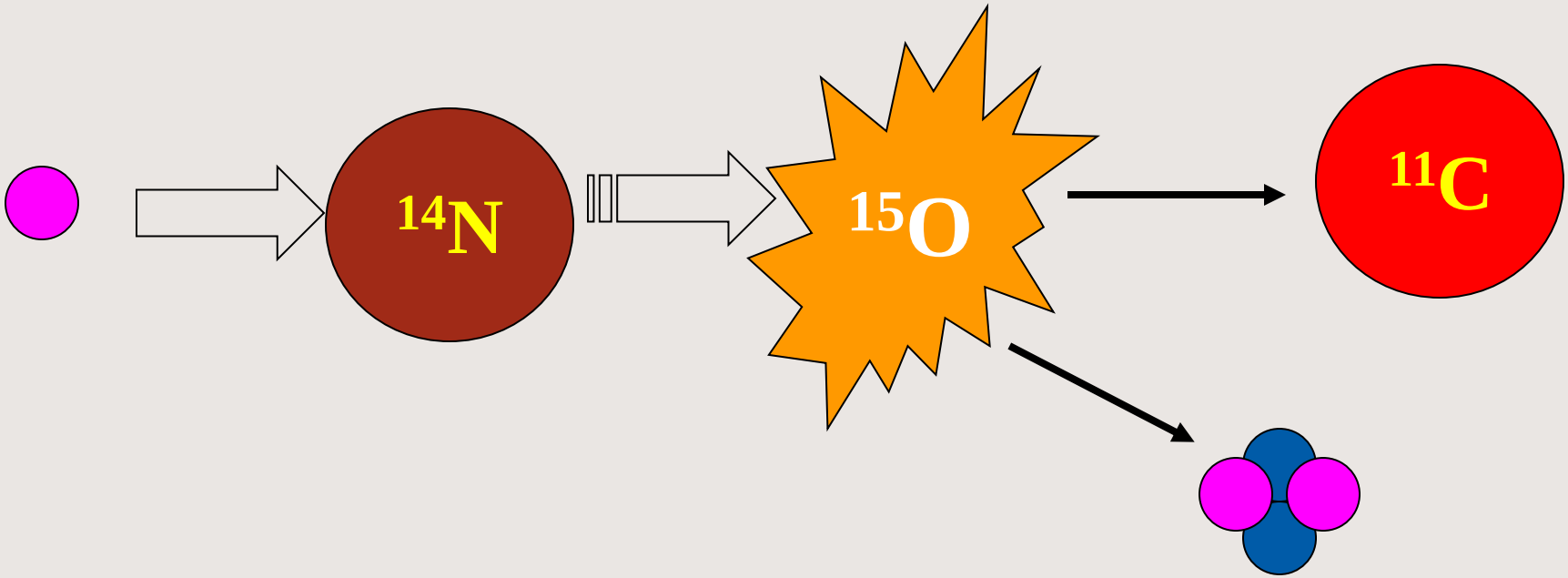
TRIUMF

That's Brian on the right!

The Team

(*circa 1981*)

Production of Radionuclides: True Alchemy



In short:

$^{14}N(p,\alpha)^{11}C$ $t_{1/2}$ = 20.3 min.

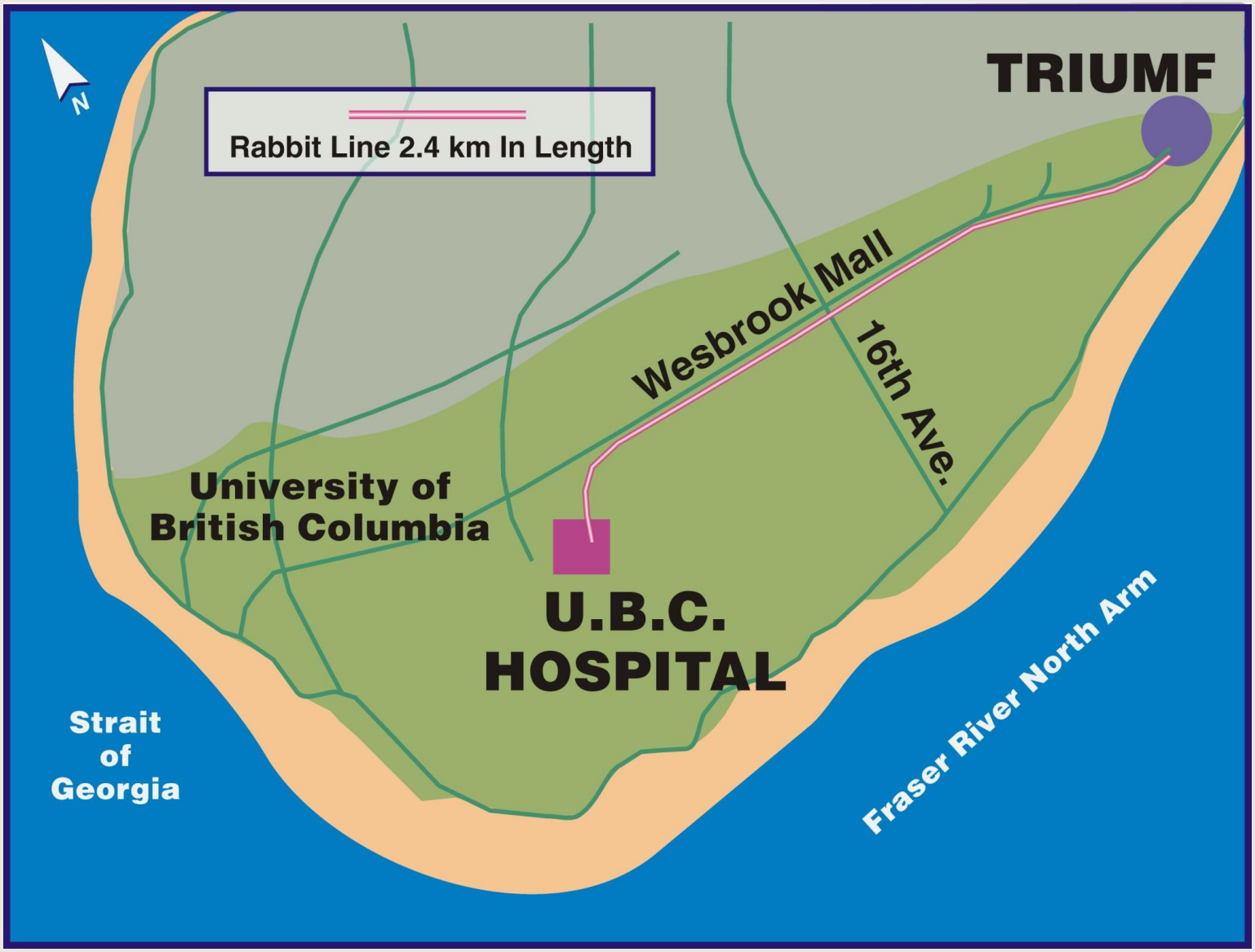
$^{18}O(p,n)^{18}F$ $t_{1/2}$ = 109.7 min.

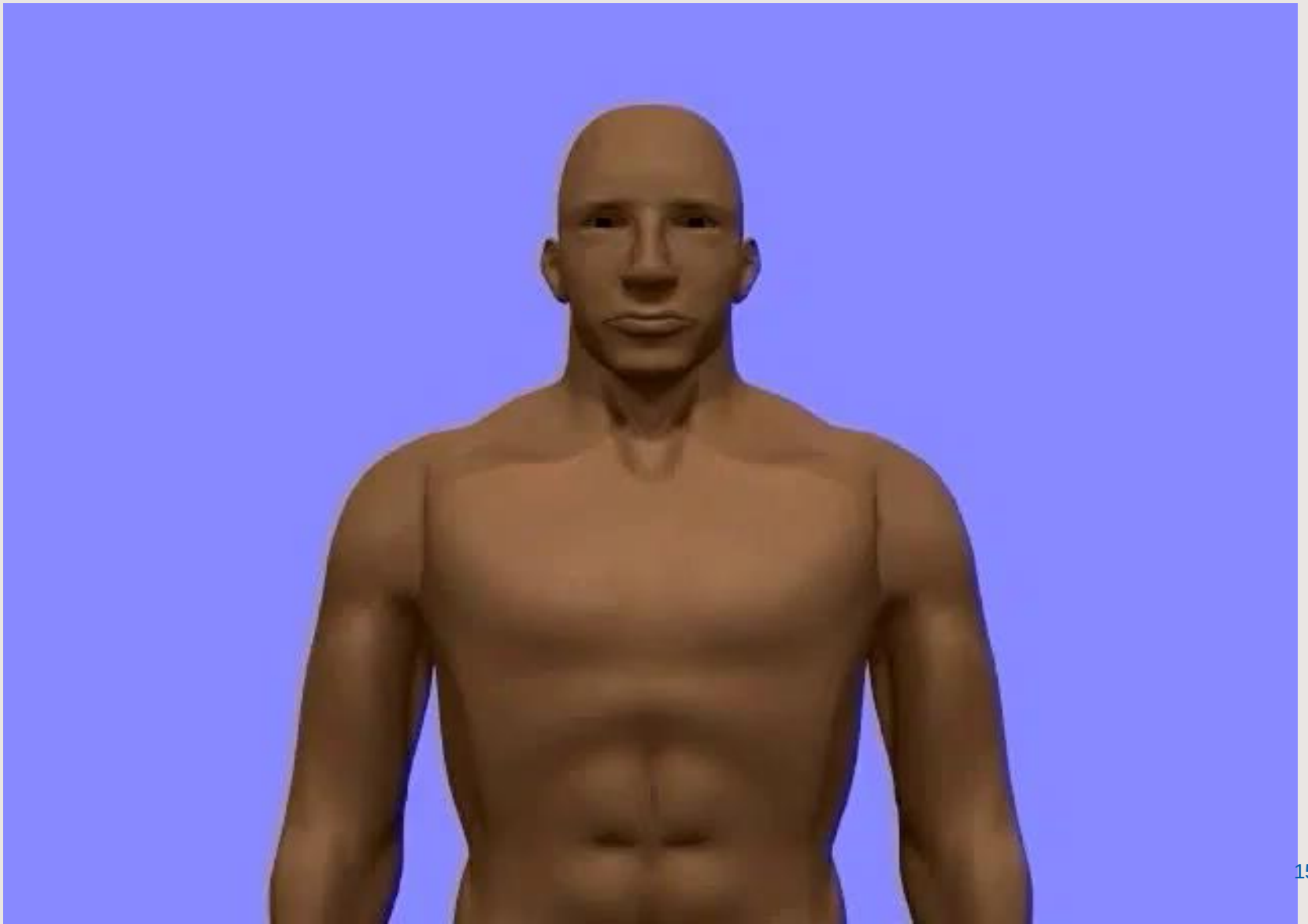
$^{64}Ni(p,n)^{64}Cu$ $t_{1/2}$ = 12.7 h

$^{16}O(p,\alpha)^{13}N$ $t_{1/2}$ = 9.97 min.

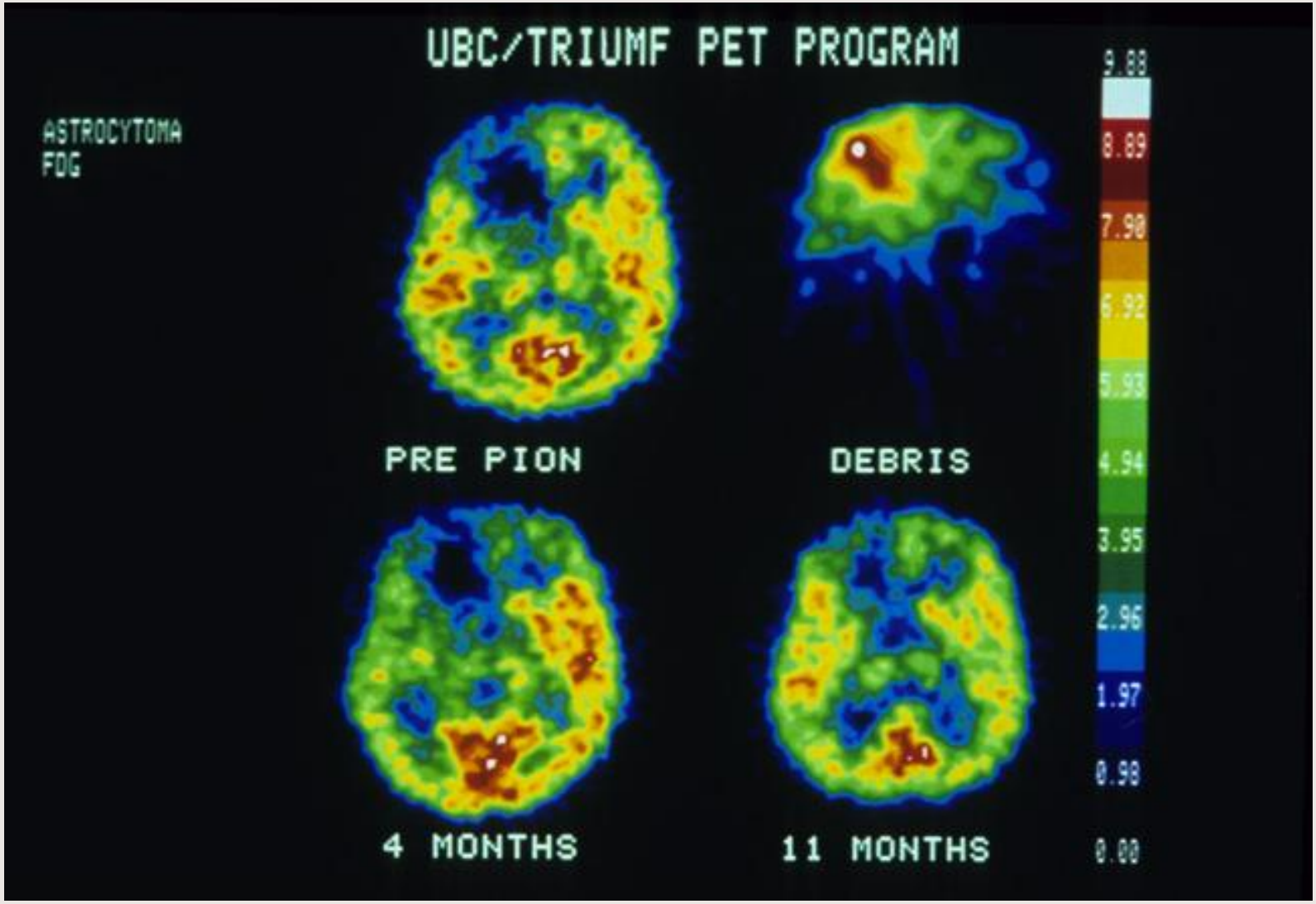
$t_{1/2}$ is the period during which half of the radioisotopes decay.

Pipeline 1983





Pion Therapy @ TRIUMF

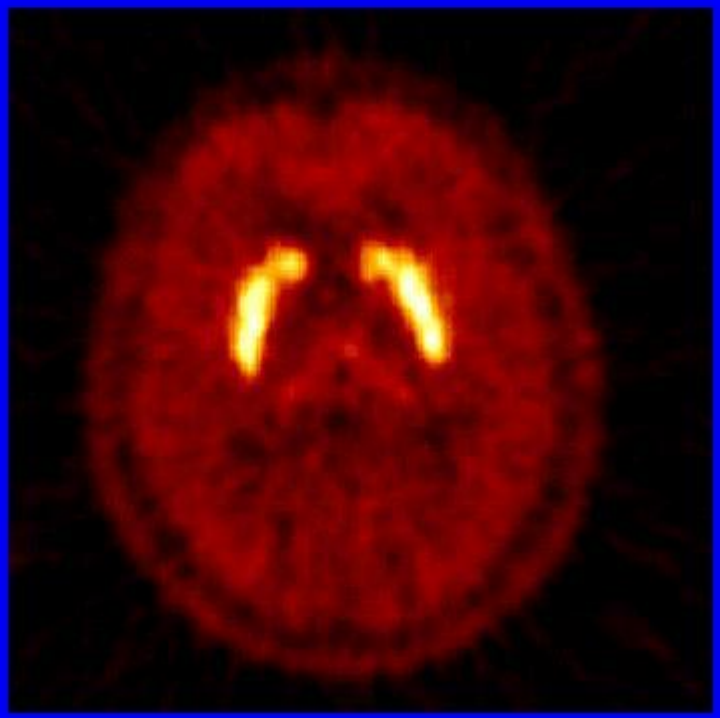


Parkinson's Disease

- A common neurodegenerative disorder
- Loss of dopamine neurons and nerve terminal causing loss of motor skills and speech
- Most common form of treatment is with L-dopa which is transformed into dopamine in the body

Donald B Calne
1981

^{18}F-Fluorodopa PET Scan



Normal

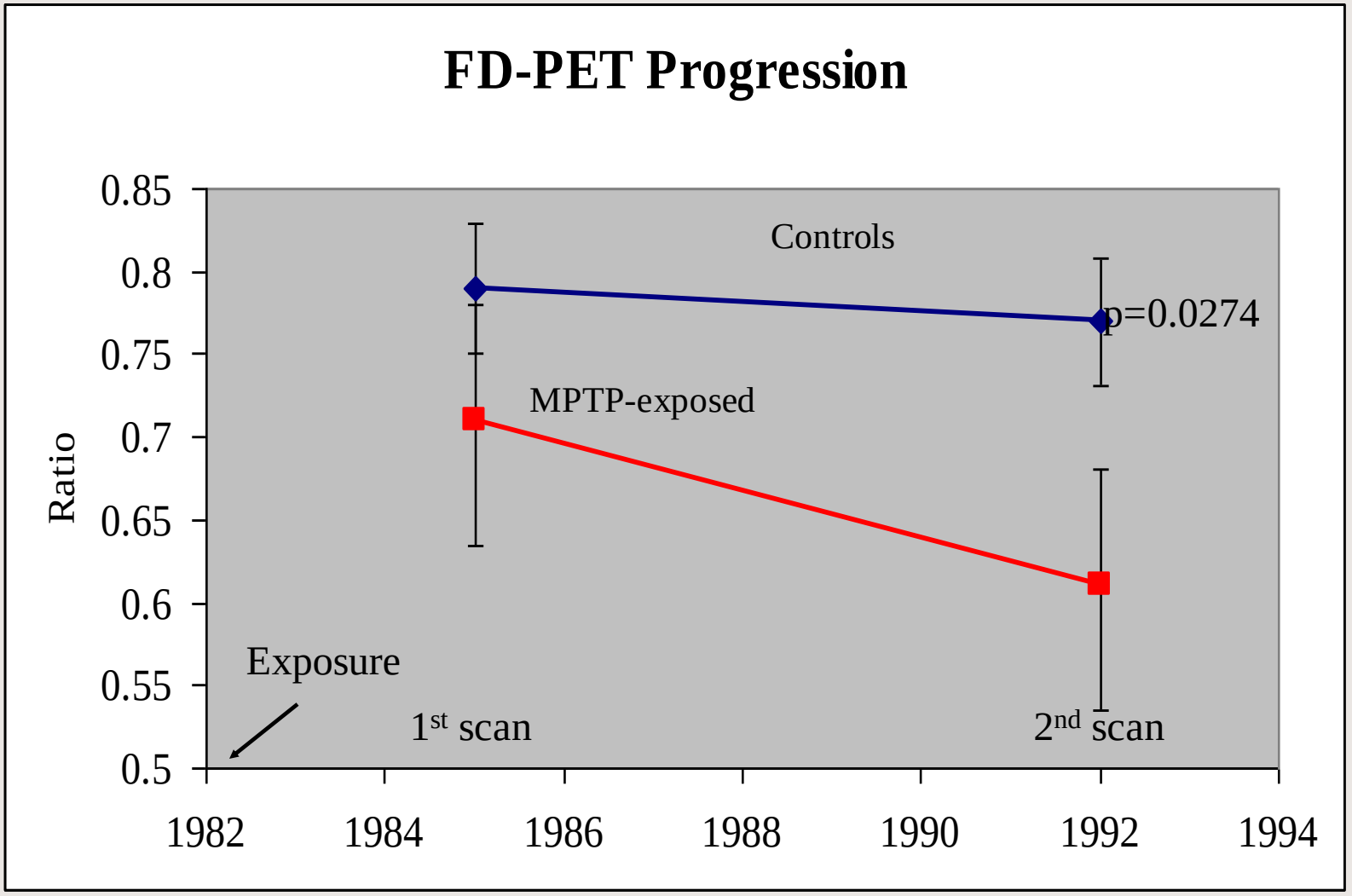
Parkinson's Disease

UBC/TRIUMF PET Program

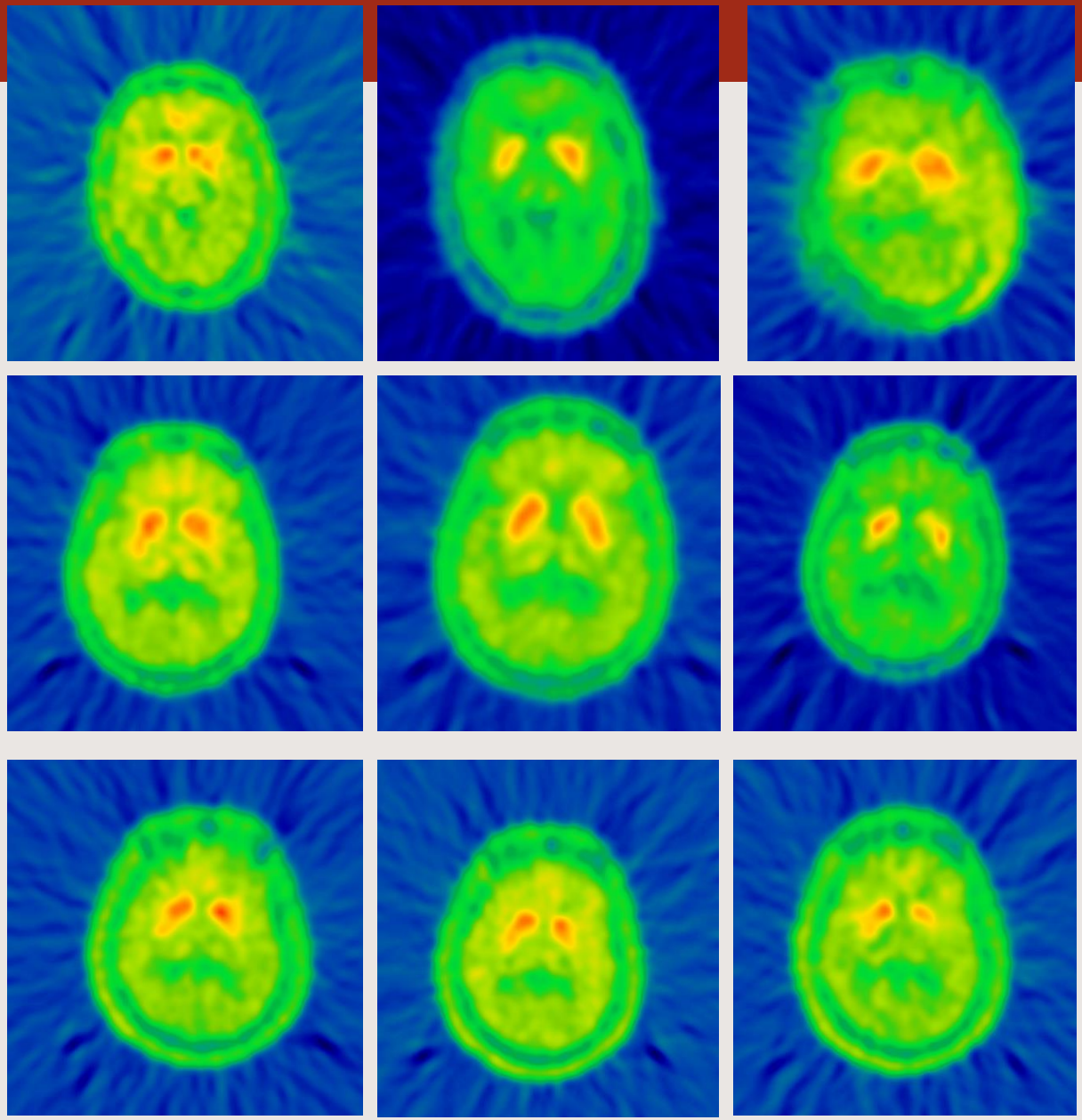
MPTP

In the 1980's a designer drug with a small contaminant (MPTP) causing Parkinsonian symptoms was sold to several to drug users.

Normal Progression vs MPTP Exposure



Pre- transplant 1 yr after 2yrs after



4 donor- group

1-donor group

placebo

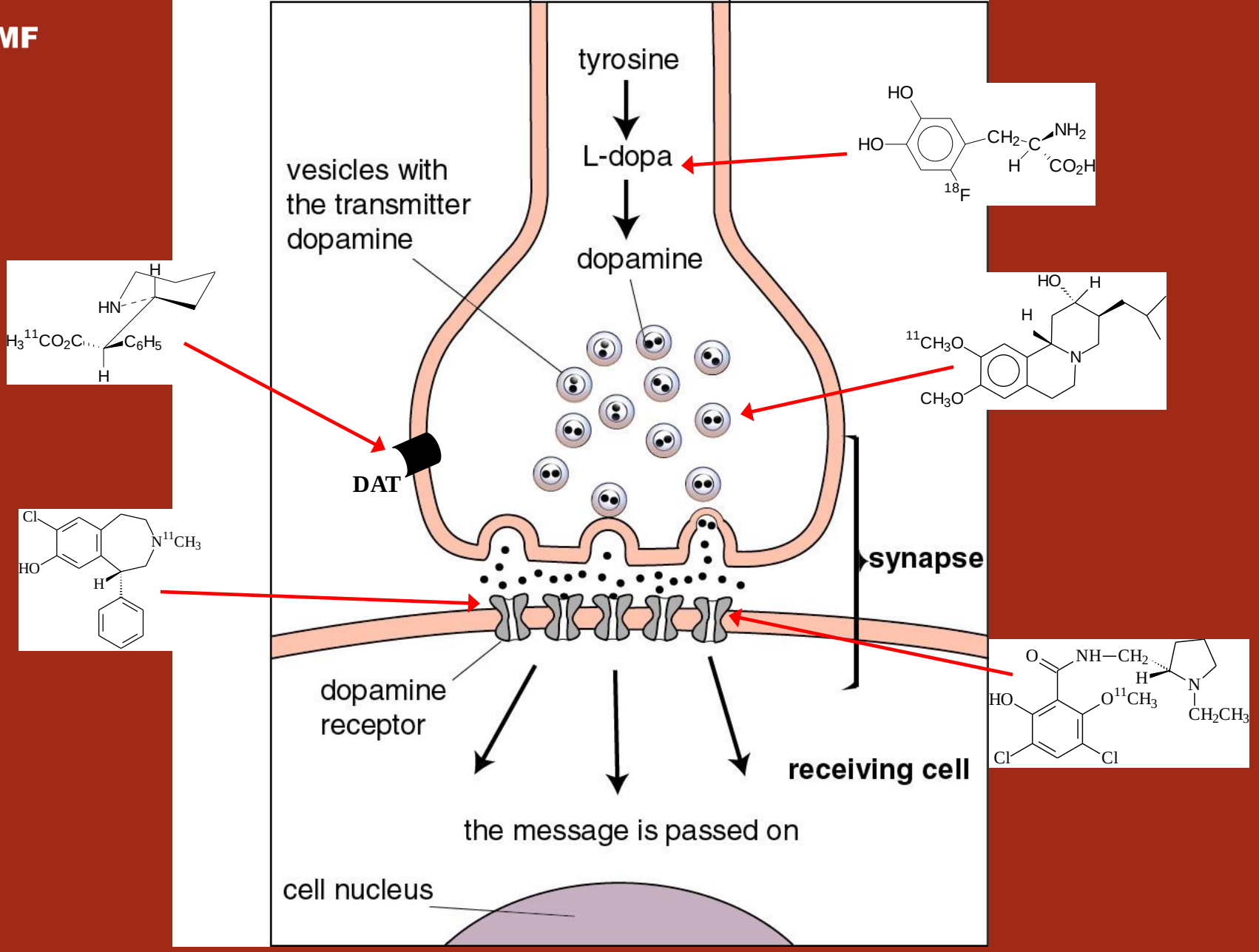
Pacific Parkinson's Research Centre

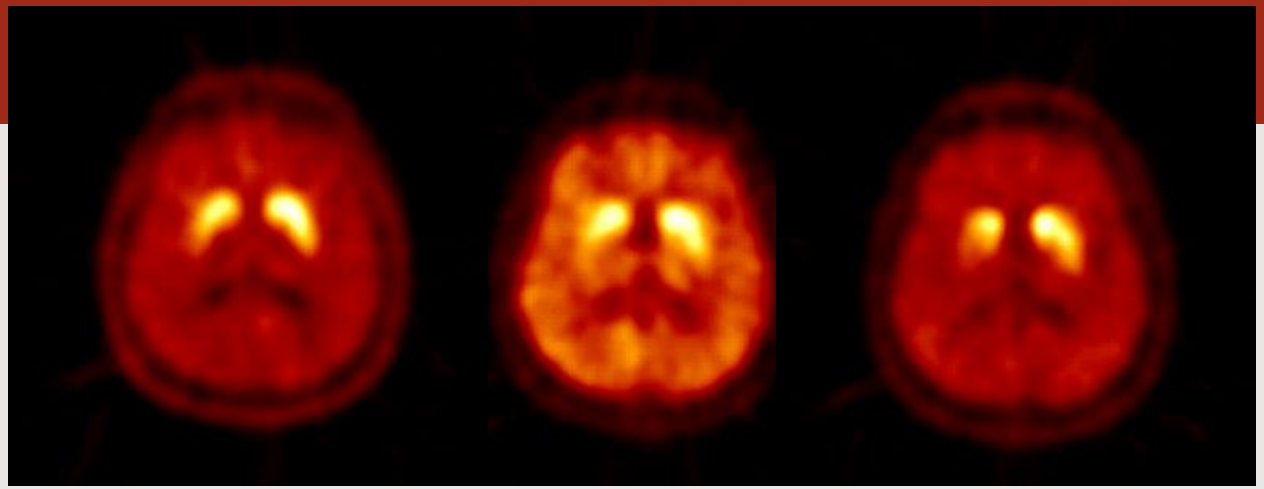
- Goals:
  - Determine the origins of PD
  - Follow natural history of disease (Progression)
  - Develop treatments
  - Control complications of treatment

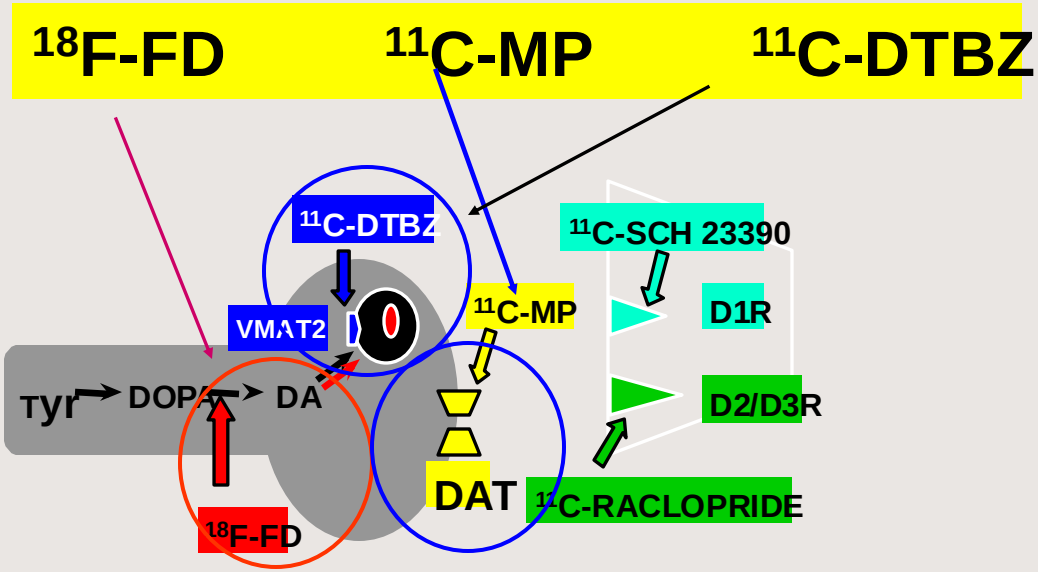
A. Jon Stoessl - Director

Radiopharmaceuticals

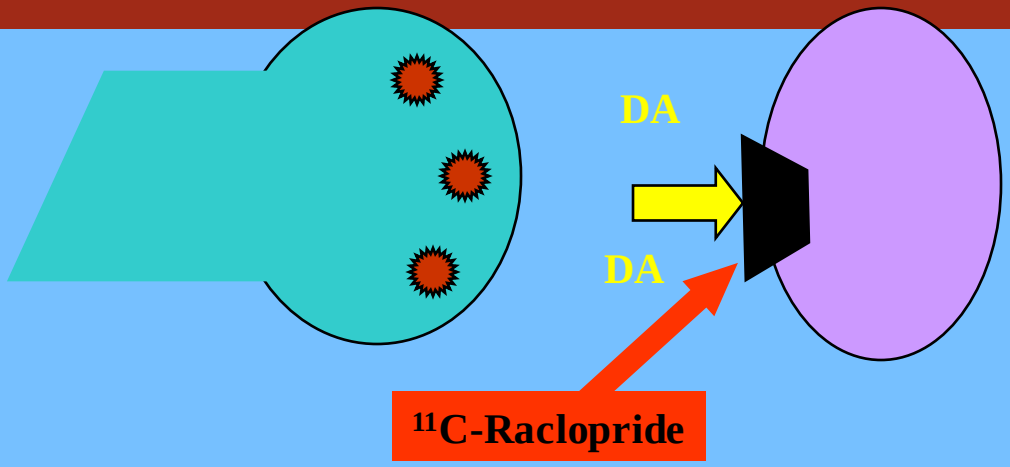
- Dopamine system
  - ^{18}F-FDOPA
  - ^{11}C-Methylphenidate
  - ^{11}C-Dihydrotetrabenazine
  - ^{11}C-Raclopride


tyrosine
L-dopa
dopamine
vesicles with
the transmitter
dopamine
DAT
synapse
dopamine
receptor
receiving cell
the message is passed on
cell nucleus

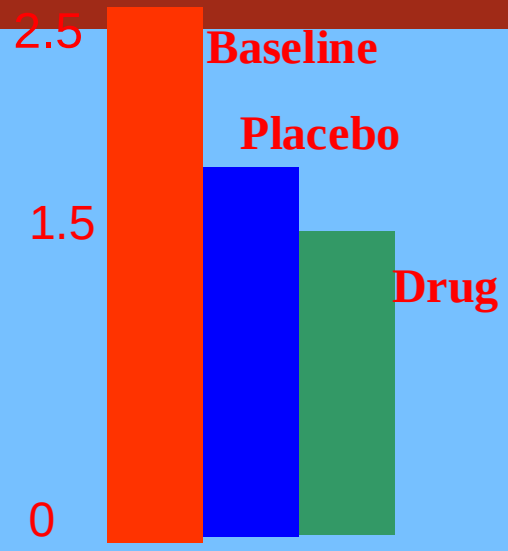



18F-FD
11C-MP
11C-DTBZ
11C-DTBZ
VMAT2
Tyr
DOPA
DA
18F-FD
11C-MP
DAT
11C-SCH 23390
D1R
D2/D3R
11C-RACLOPRIDE

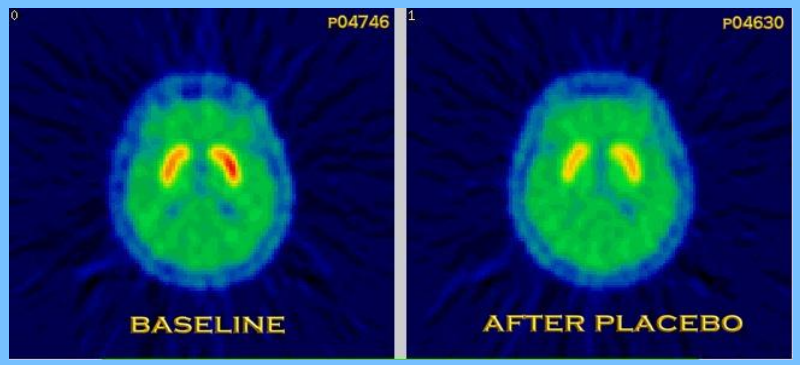
In vivo assessment of endogenous DA concentration



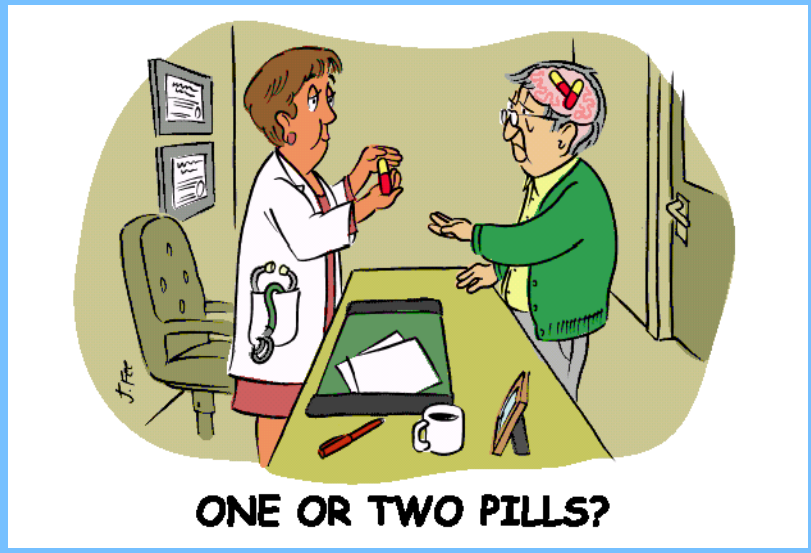
Endogenous DA competes with raclopride for the D2 receptor



Apomorphine-induced changes in raclopride binding



Lower raclopride binding indicates higher dopamine concentration



What have we learned about Parkinson's Disease thus far?

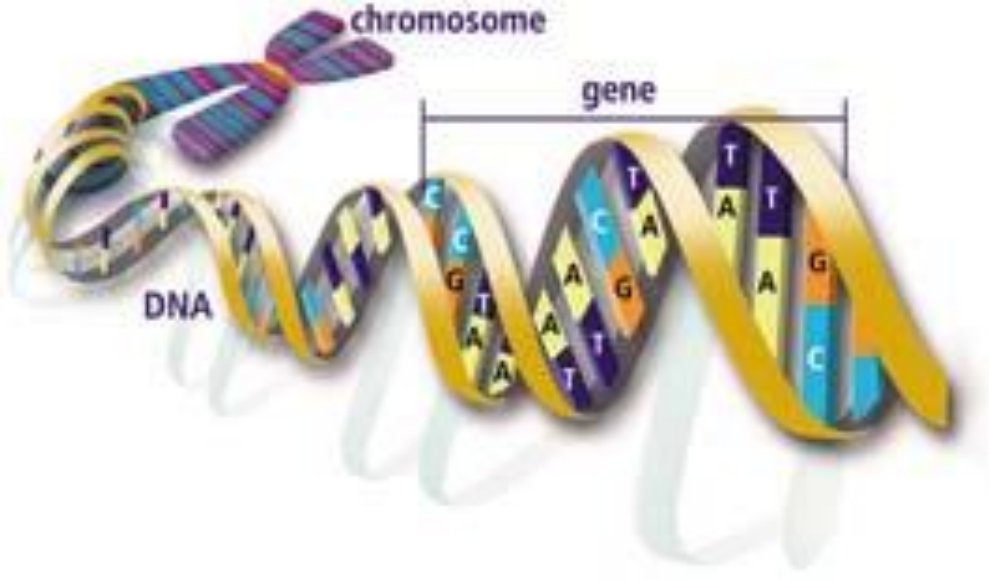
- Preclinical changes in PET indices.
- Asymptomatic patients progress to disease.
- Early signs of compensation.
- Singular events can cause parkinsonism.
- Evidence of our *Event* hypothesis including progression.

Even with accurate PET measures with today's tracers we are still looking at the consequence of disease.

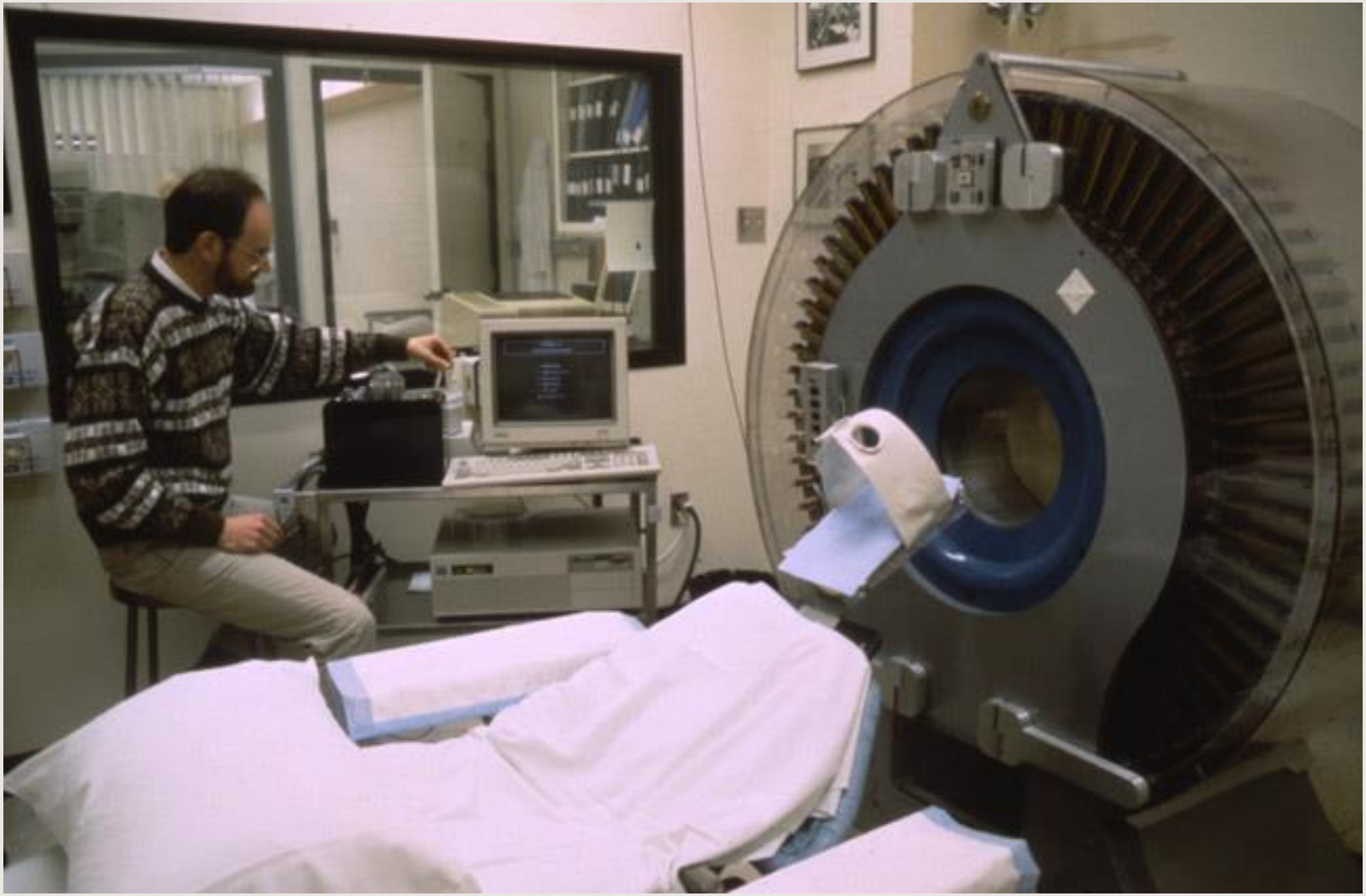
We need access to the disease process itself.

Future of Research PET

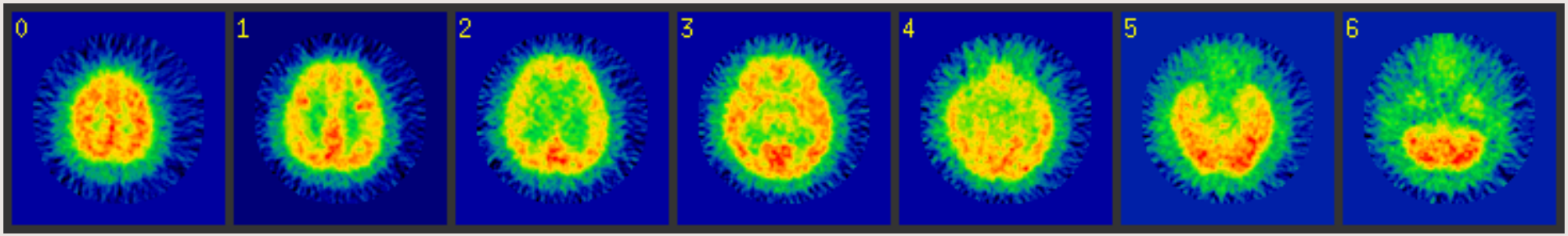
- The tracers we presently use *look* at the system response to disease.
- What we need are tracers that *look* at the disease process itself.
- We need to get closer to the *action*!
- This will provide the basis for personalized medicine.



PETTVI Scanner



PETTVI – FDG image



PETTVI:

4 detector rings separated by septa: 7 imaging planes

In plane spatial resolution 9.2 cm

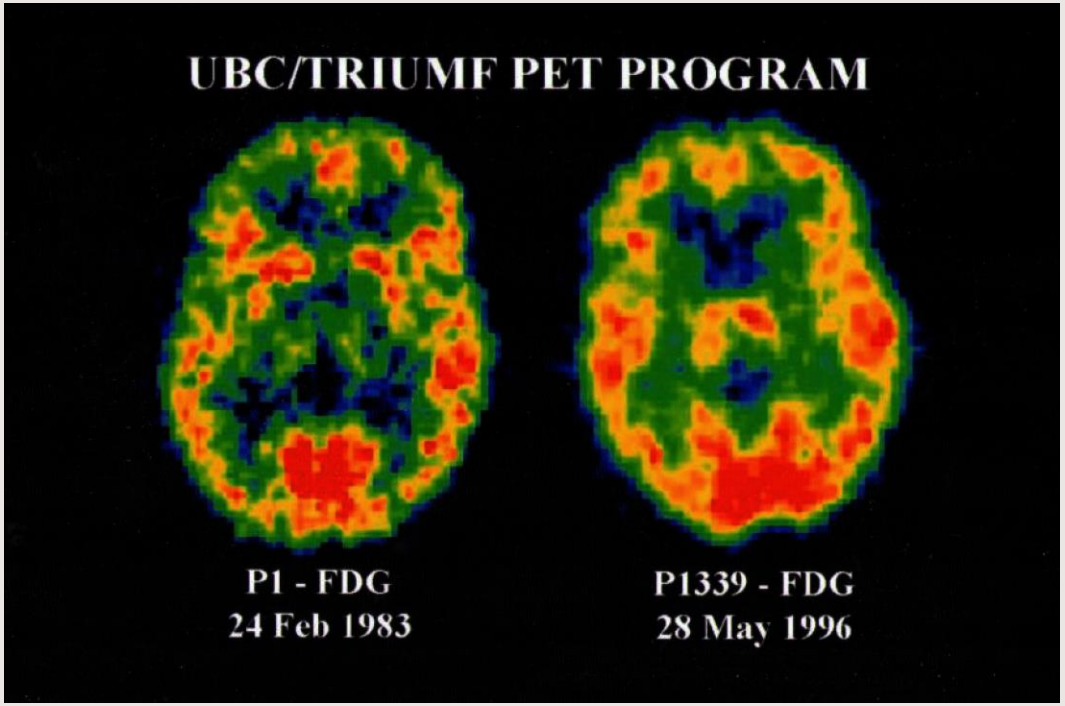
Axial slice width: 11.6 mm

Slice – to –slice distance: 14.4 mm

Sensitivity < 0.5%

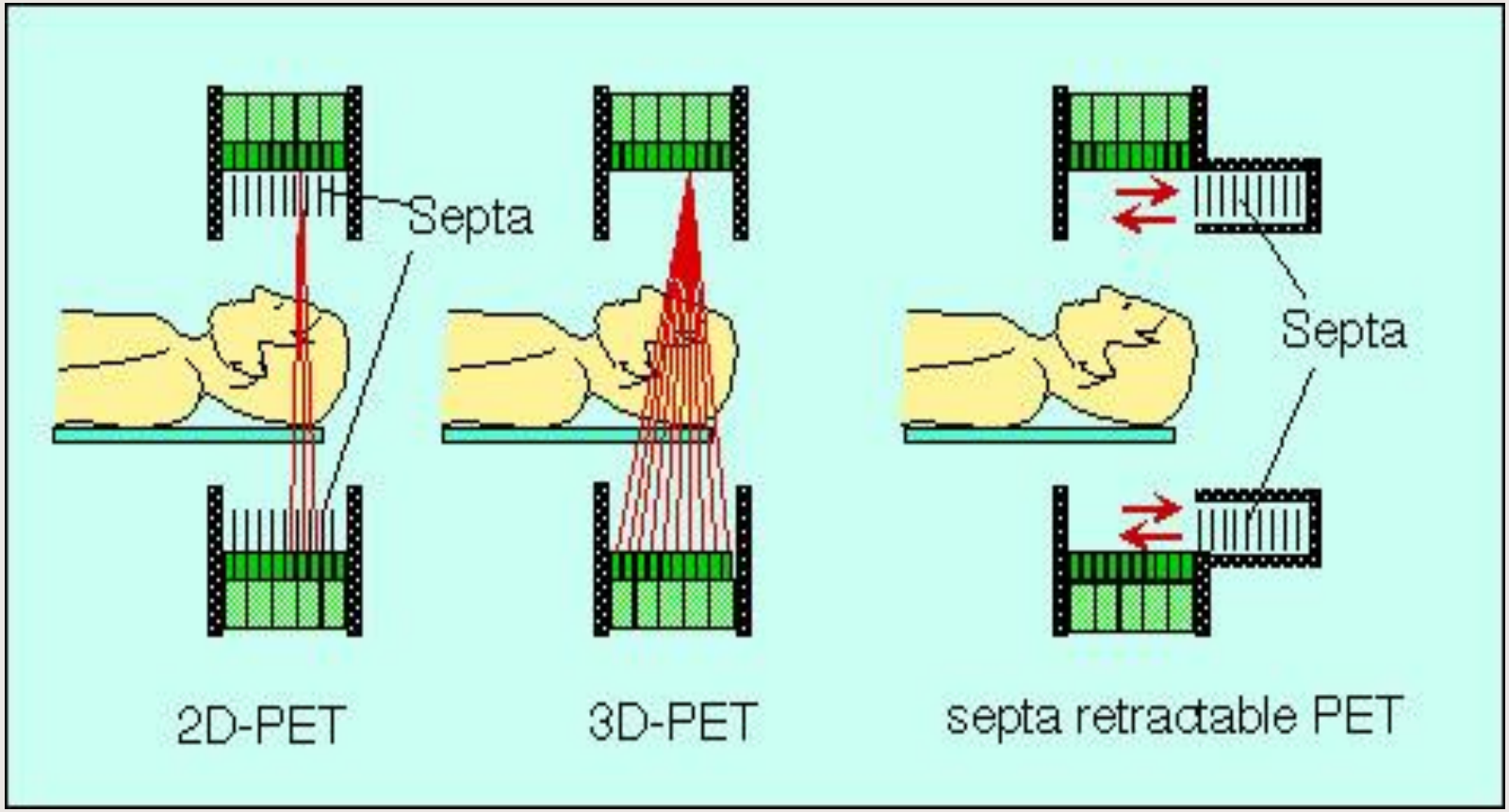
It wobbled!

1st and Last Scans on the PETTVI



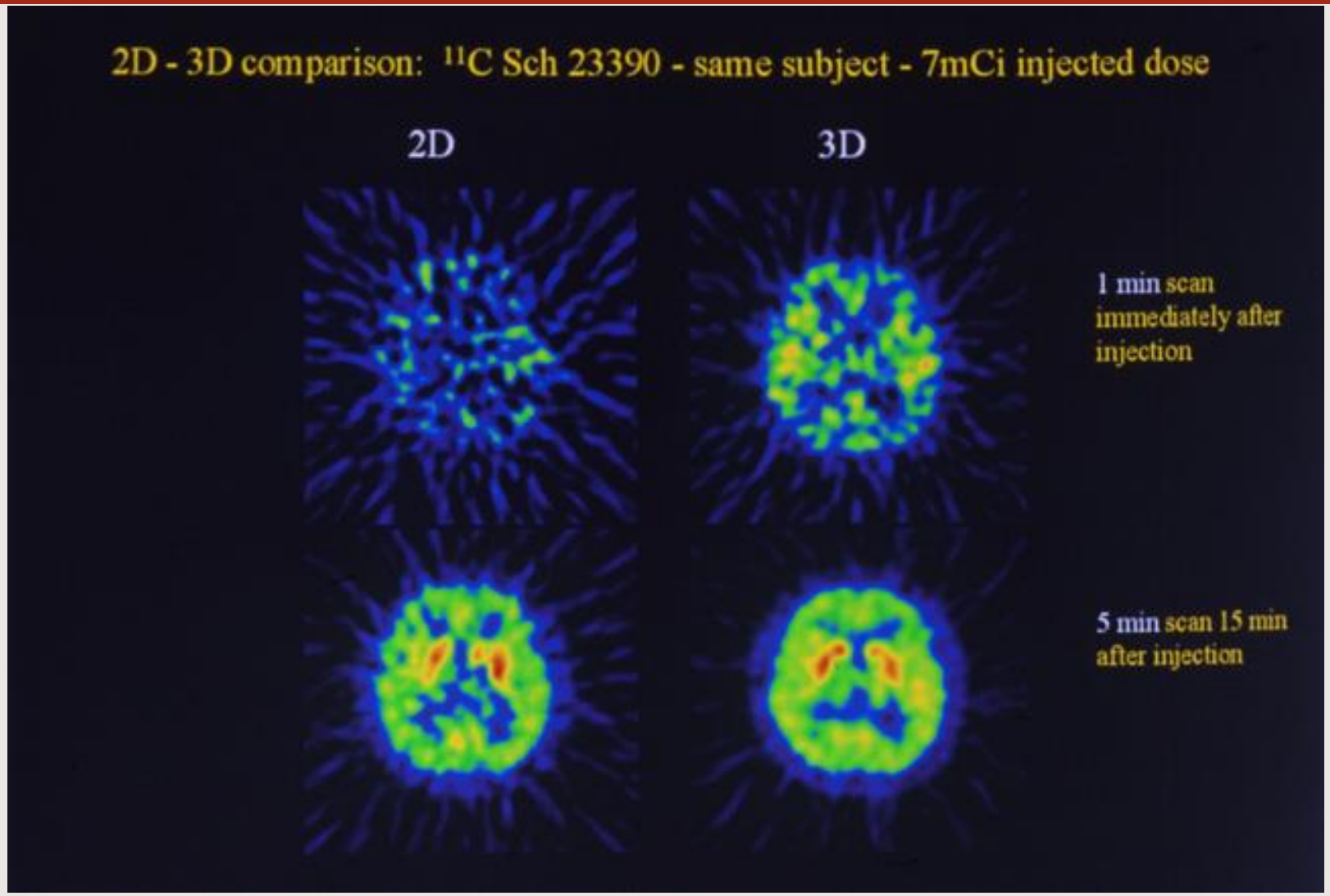
ECAT 953B, Ruth, Miller, Gardner

ECAT 953B Scanner

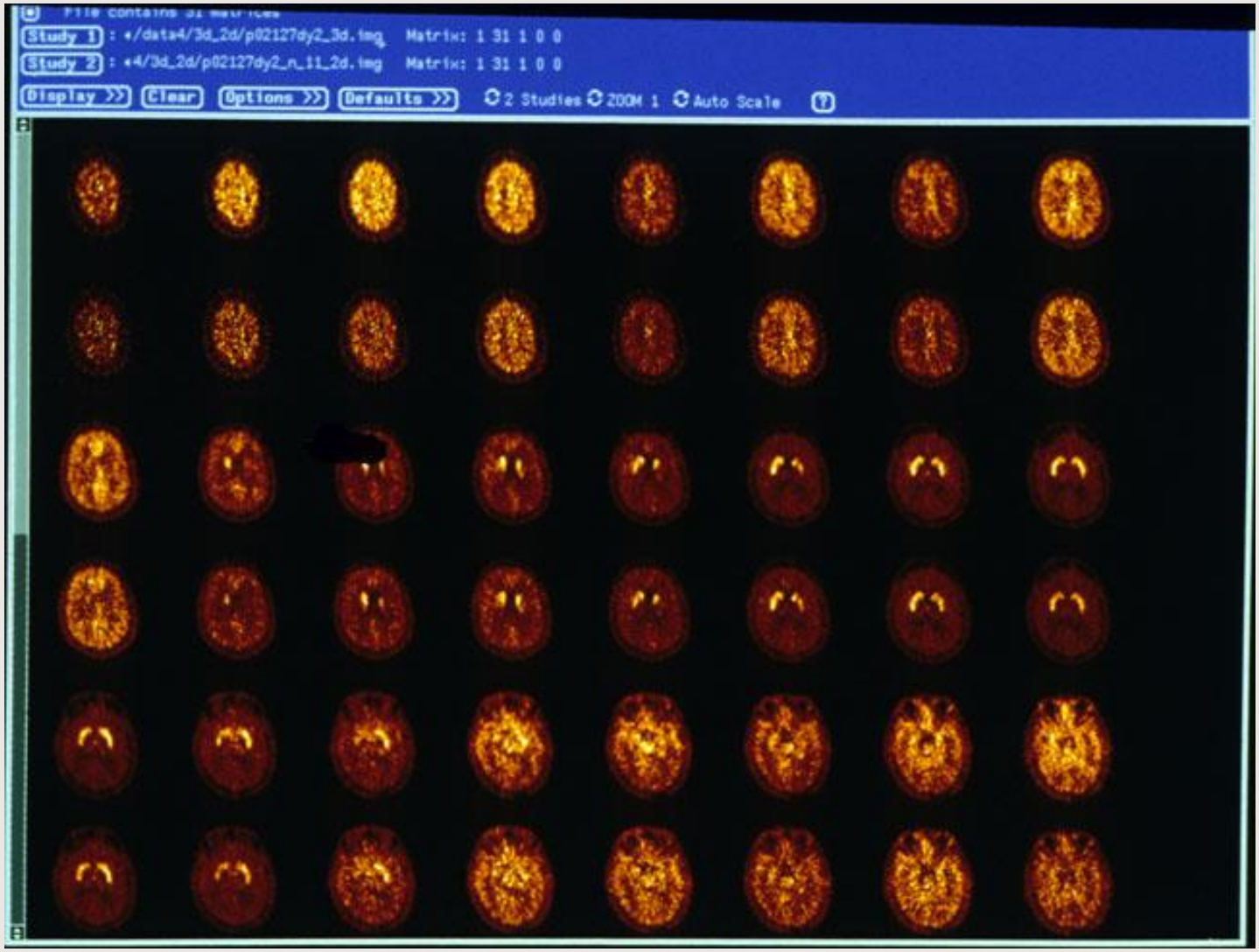


Paul Kinahan, UBC MSc student developed first 3D reconstruction code

Early 3D Scans – ECAT 953



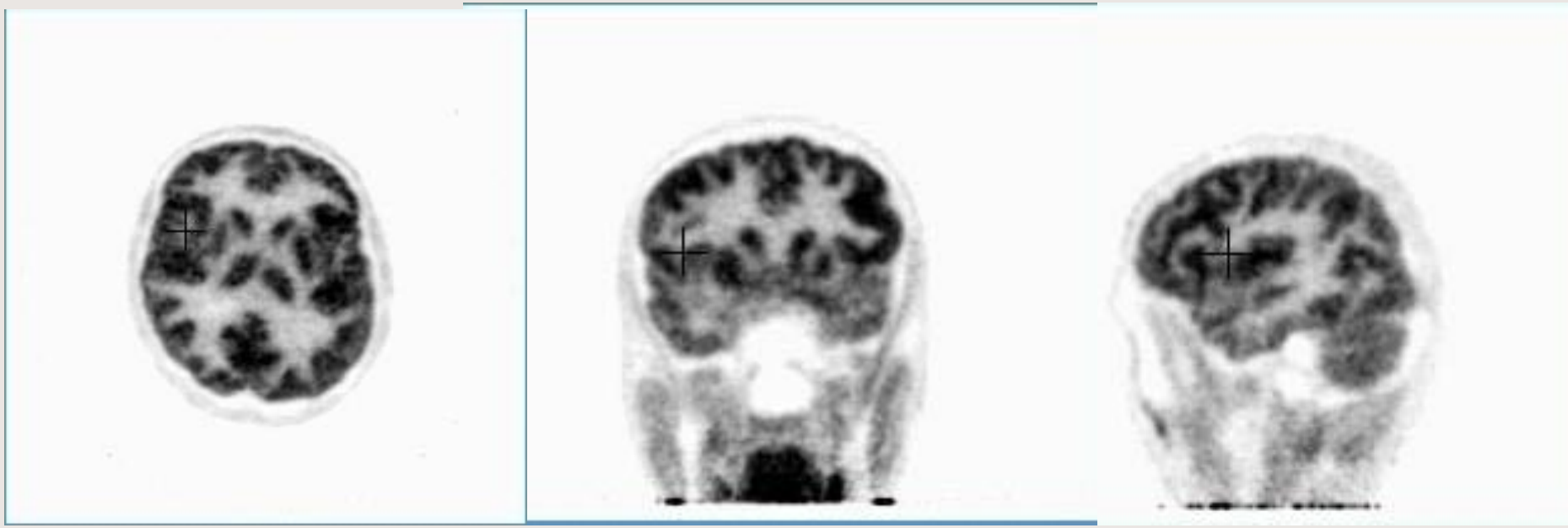
Screenshot from ECAT 953B



High Resolution Research Tomograph

- 119,000 detector elements
- 4,000,000,000 lines of response
- > 1Gbyte of data per image frame

FDG Images from the HRRT



Axial

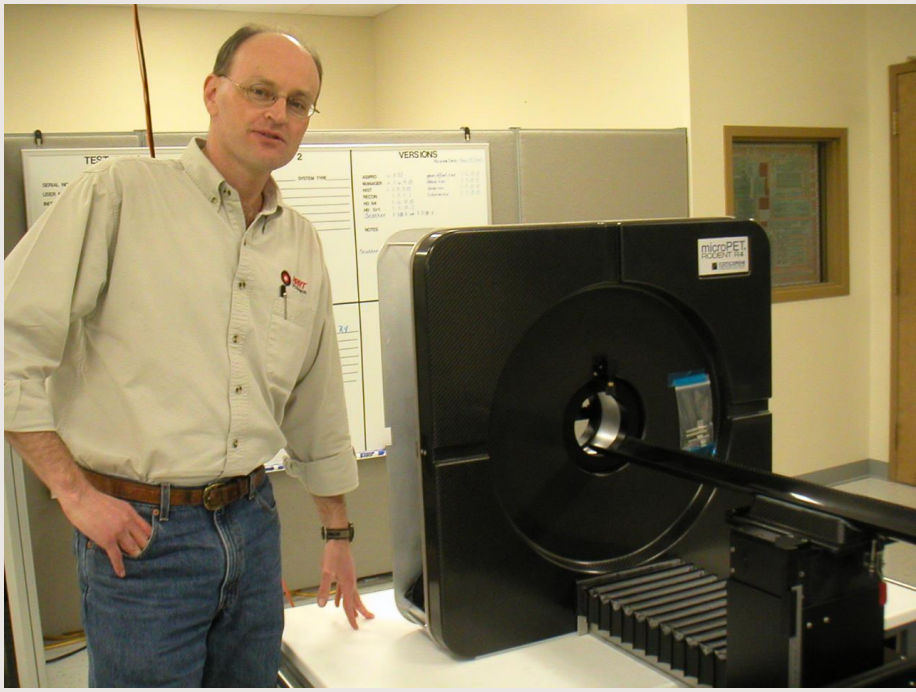
Coronal

Sagittal

microPET

10 April 2003

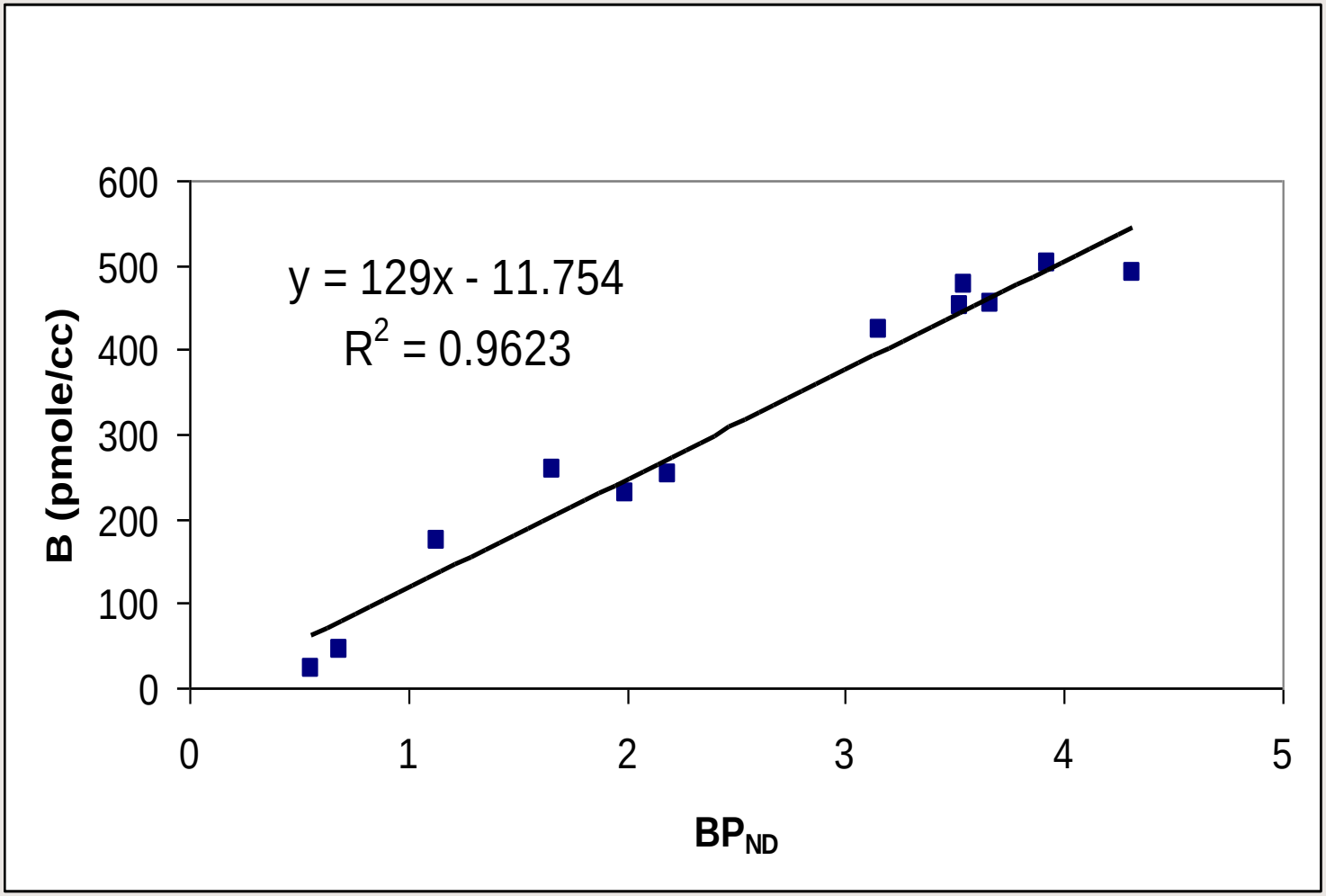
- 32 detector modules (8x8)
- 1920 individual LSO elements
- ring diameter 17.2 cm
- 10 cm transaxial FOV
- 1.8 cm axial FOV
- volume resolution ~ 8 mL
- sensitivity: 200 cps/µCi
- cost ~ $ 450K USD



Validation of Tracers

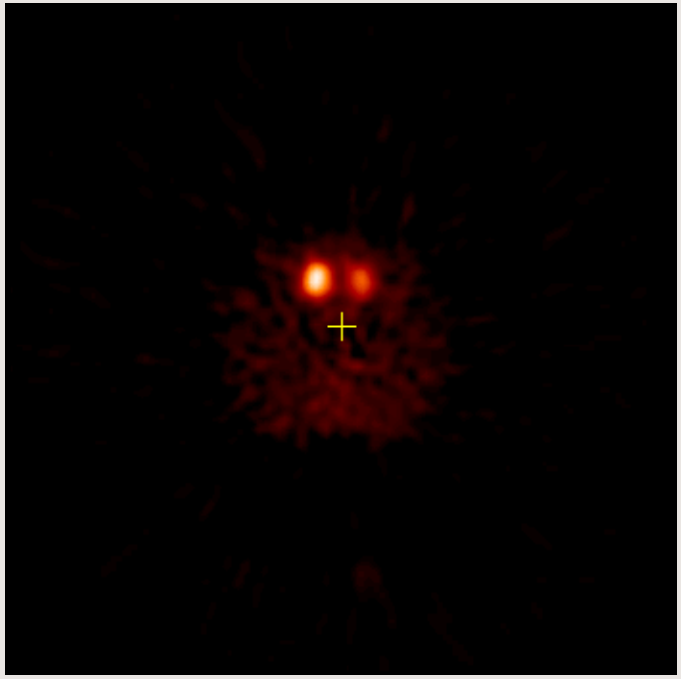
- From the very beginning we validated the tracers we used
- We calibrated the scanners so that the regions of interest could be viewed as Bq/cm^3
- With modelling the results could be interpreted with quantitative biological metrics

VMAT in lesioned rat (comparing postmortem to Binding Potential (PET))

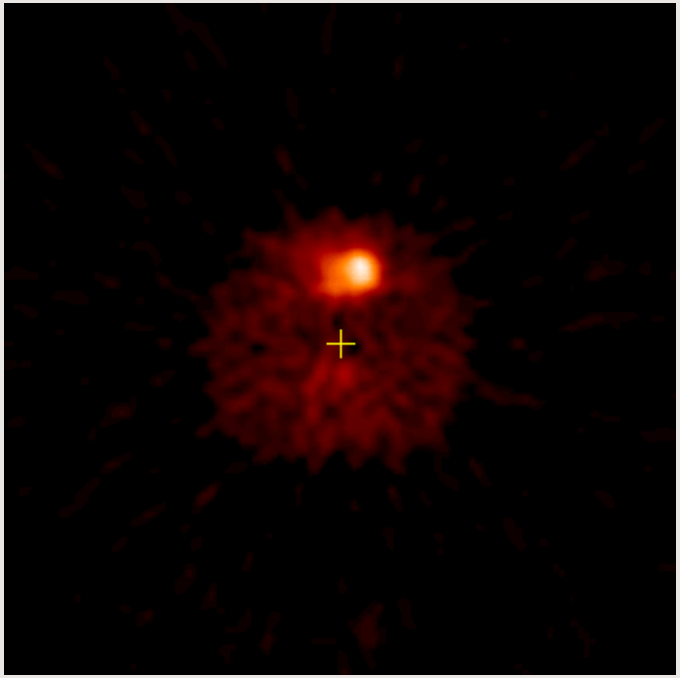


microPET

^{11}C-DTBZ (rat)



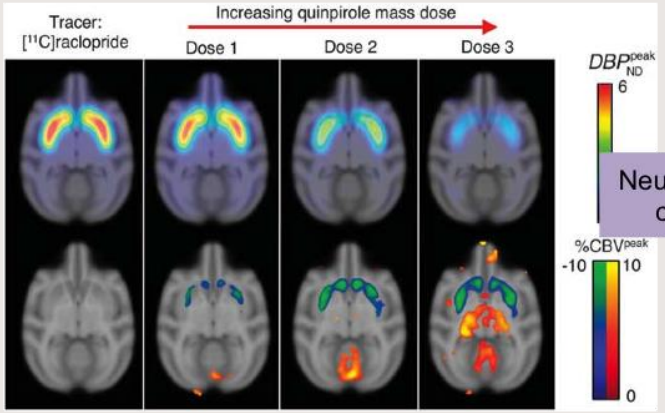
^{11}C-raclopride in same rat.



Additional Questions for PET:

- New drugs for diabetes
- Spinal cord research
- Enzymology
- The mouse genome and knock in/out models
- Learning
- Dyskinesia
- Cancer research

Hybrid PET/MR scanner: – data can be acquired simultaneously, ideal to investigate several aspects of **brain connectivity**



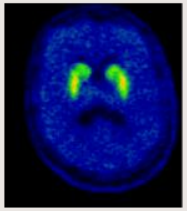
Interaction between metabolic and hemodynamic networks

Neurovascular coupling

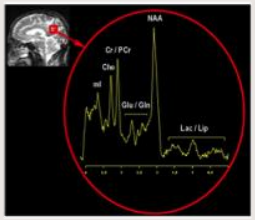
Bioenergetics

Network Degeneration Hypothesis

Neurochemistry



- Metabolism
- Neurotransmission
- Protein aggregation
- NeuroInflammation



- MRS

Data fusion

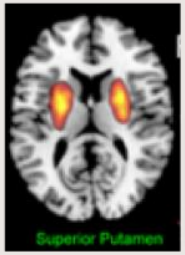
Functional MRI

PET/MRI

PET

MRI

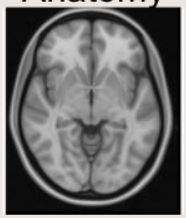
Rs-fMRI



- Hemodynamics
- Functional networks
- (rs)-FMRI

- Anatomical structures
- Structural connectivity

Anatomy



Multimodal imaging PET/MRI at UBC: applications

GE Signa

Inflammation

Abnormal protein aggregation

Abnormal neurotransmitter release and connectivity

Abnormal brain energetics and connectivty

Healthy aging

Abnormal brain energetics and connectivity

Inflammation

Abnormal protein aggregation

PD

neuroprotection

AD and dementia

Inflammation

Abnormal brain energetics and connectivity

Multiple sclerosis

Mood disorders

Abnormal neurotransmitter release and connectivity

Abnormal brain energetics and connectivity

Addiction

Abnormal neurotransmitter release and connectivity

+ **Algorithms development**

Collaborations Beyond UBC/TRIUMF PET: *^{18}F & FDG Supply*

Alberta Cancer Board

$^{18}F^-$

FDG

μPET

BC Cancer Agency
CARE & RESEARCH

LION'S GATE HOSPITAL
Nuclear Medicine

VANCOUVER HOSPITAL
& Health Sciences Centre
Division of Nuclear Medicine

St. Paul's Hospital
Department of Nuclear Medicine

PETscan
vancouver

PET/CT

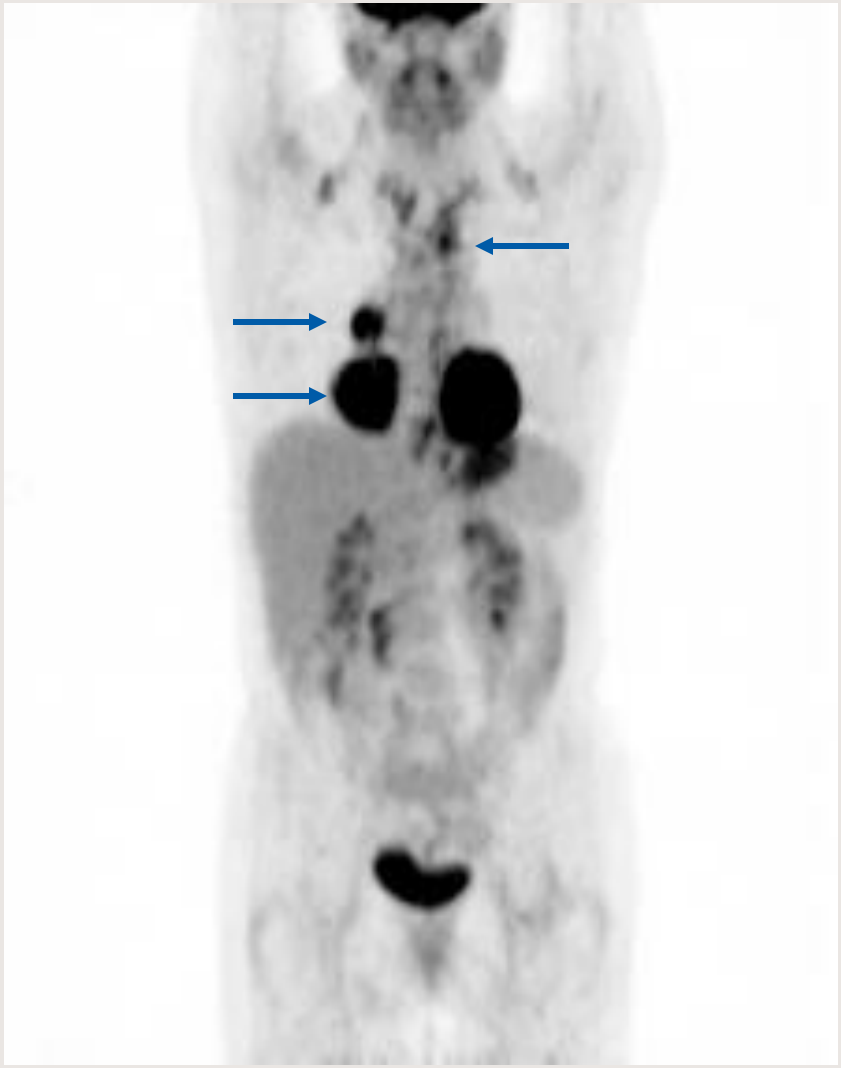
The Centre of Excellence for Functional Cancer Imaging

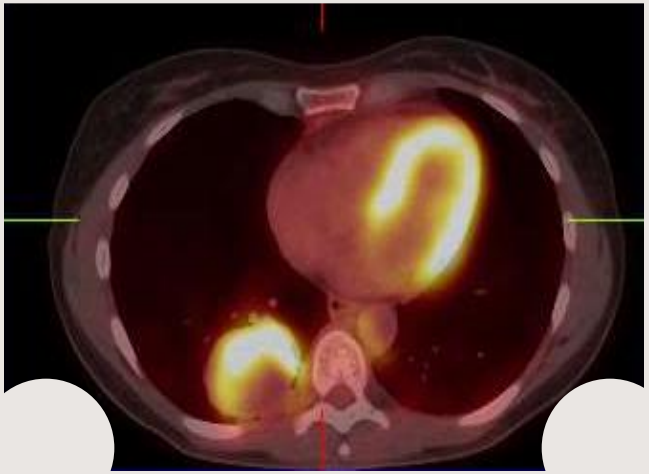
Phase A
- Clinical PET/CT

Phase B
- Cyclotron
- Radiopharmacy

47

61 yo female NSCLC pre-operative staging

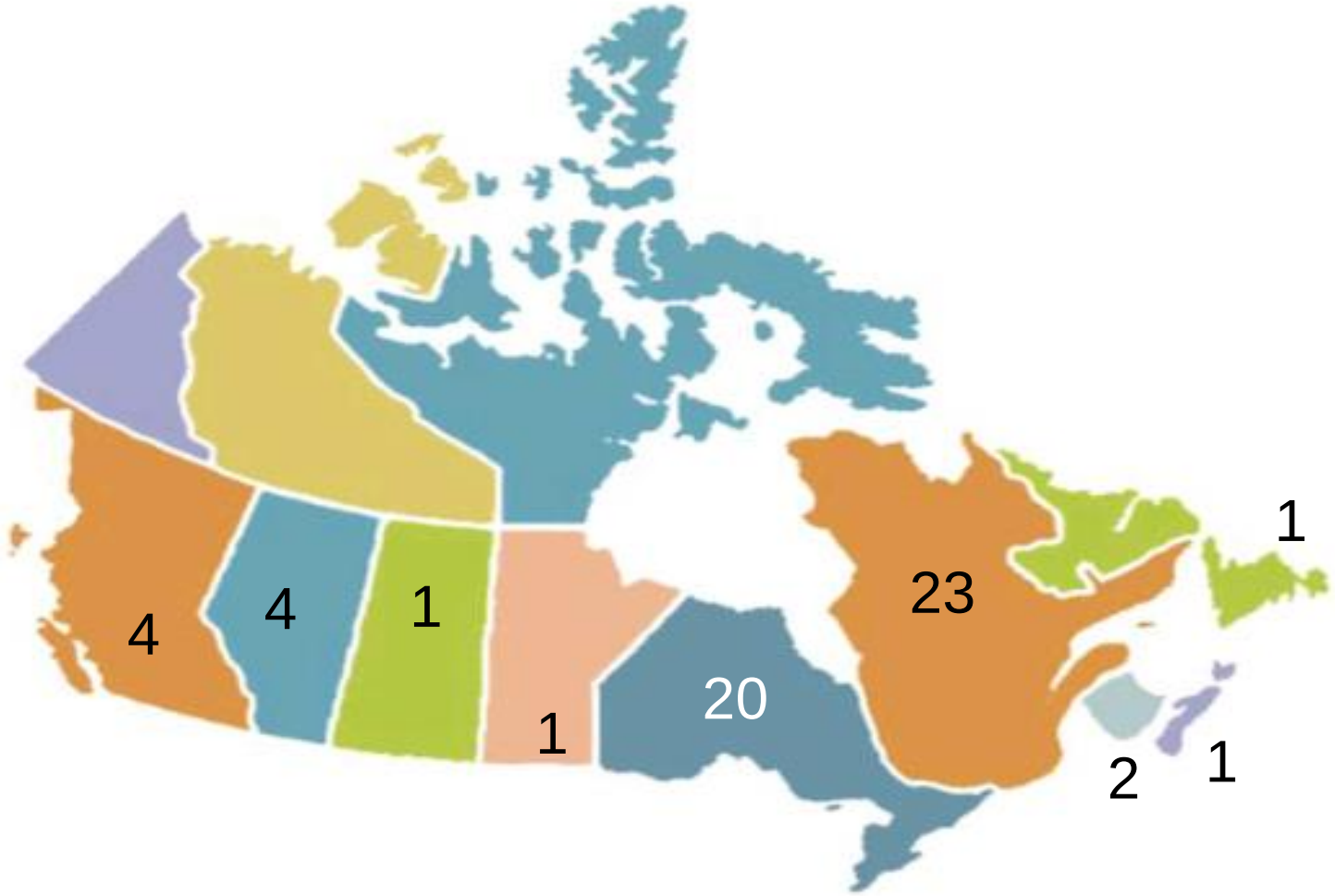




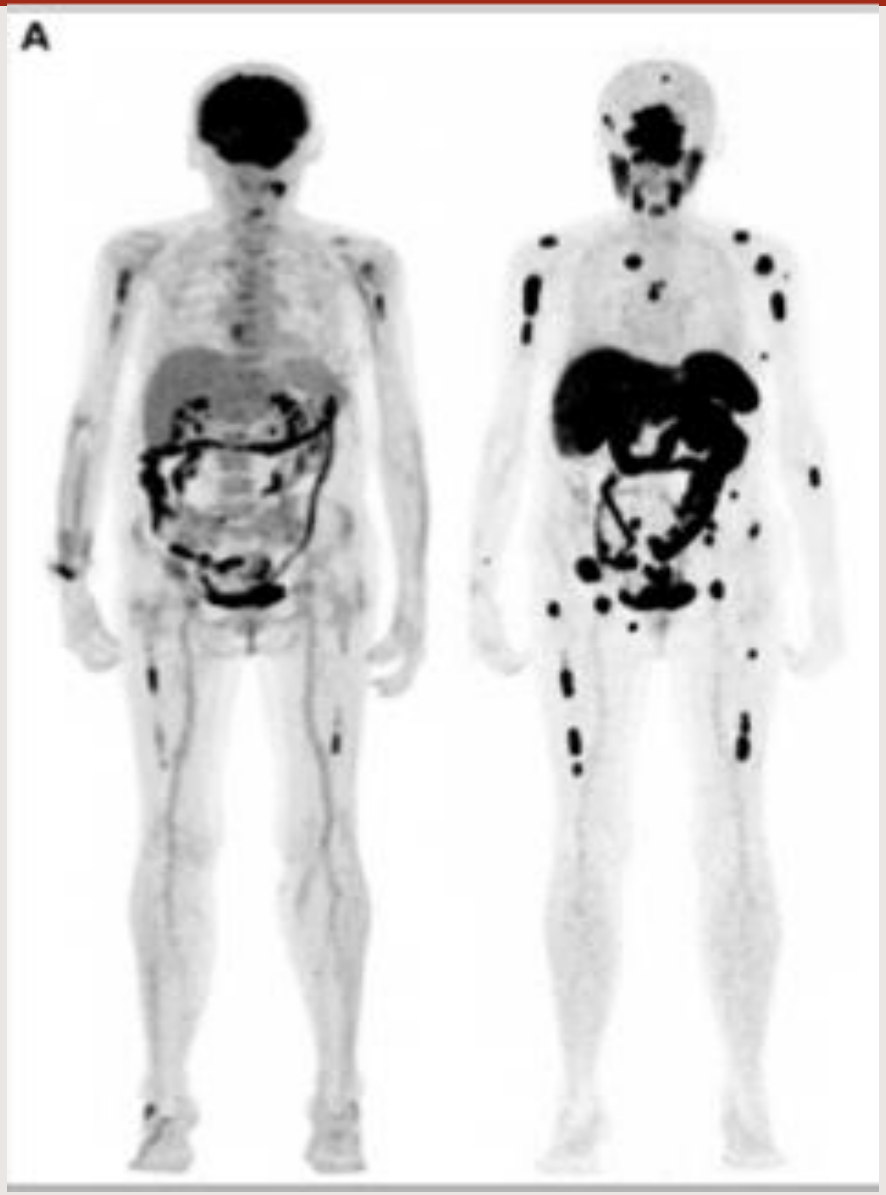
Clinical PET Scanner

Public PET Cameras

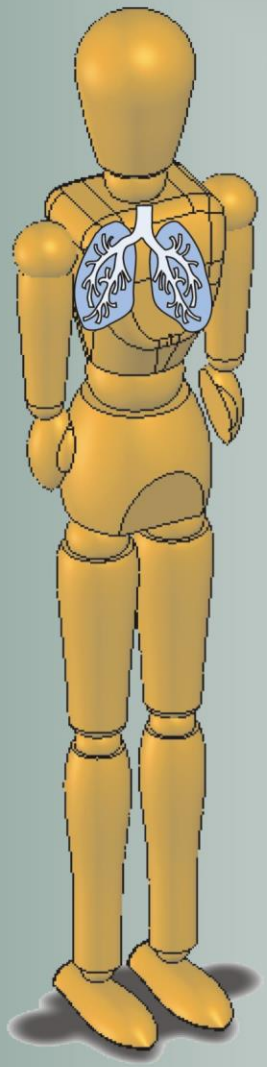
https://www.triumf.ca/sites/default/files/TRIUMF-AAPS-Martinuk-PET-Across-Canada-REPORT.pdf



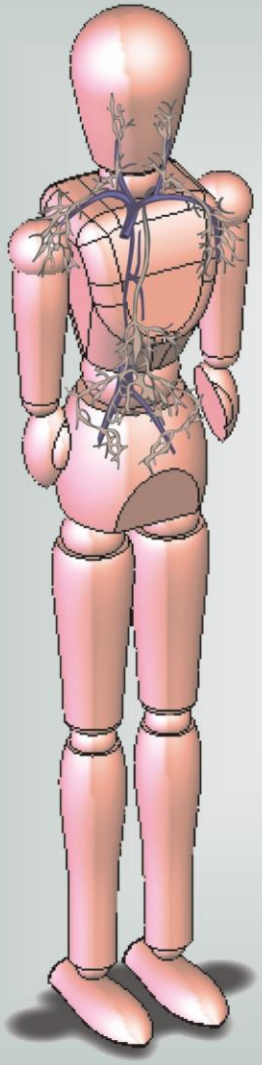
Tracer selection Important: ^{18}F-FDG Compared with ^{68}Ga-PSMA-11



Will Trace developments combined with genomics provide Personalized Medicine?



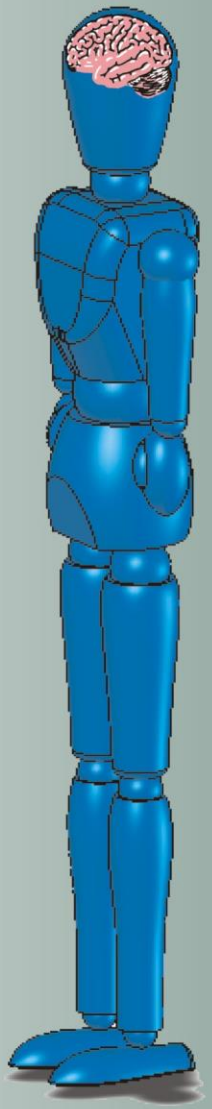
Lungs



Lymph System

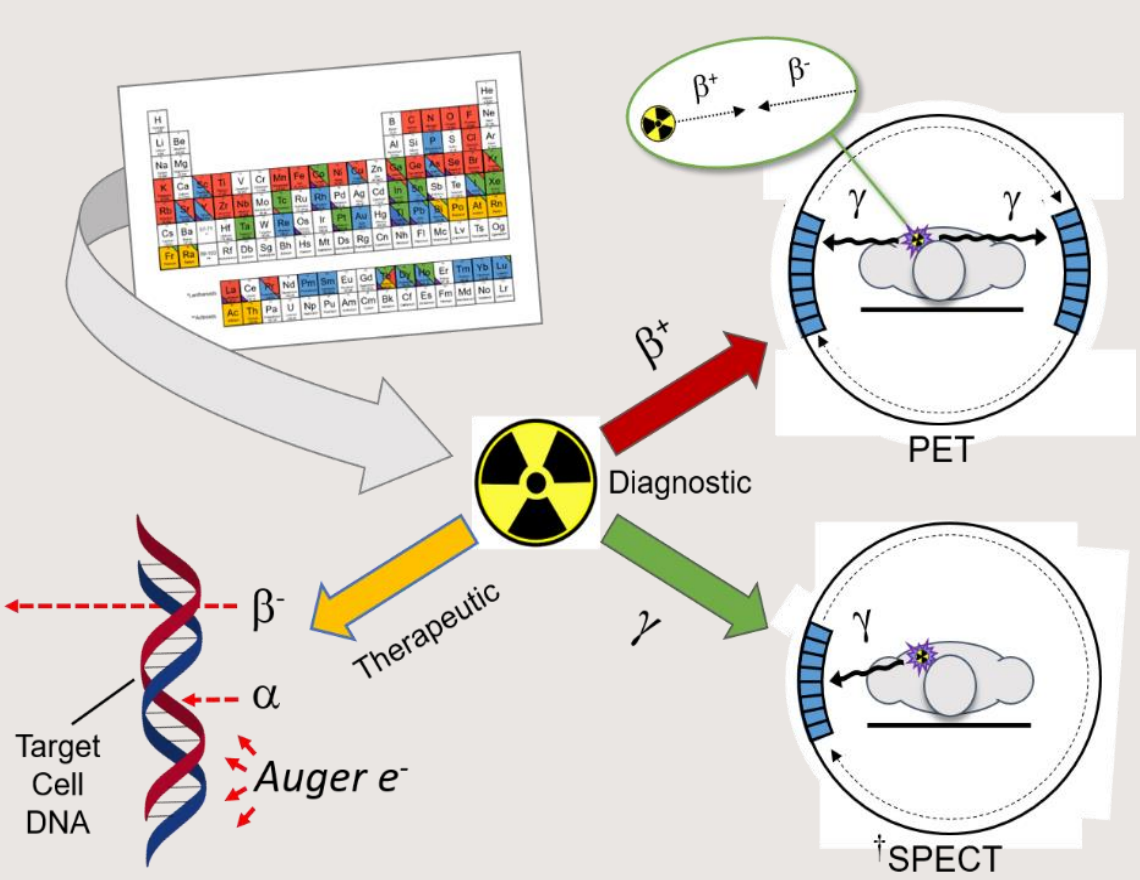
Heart

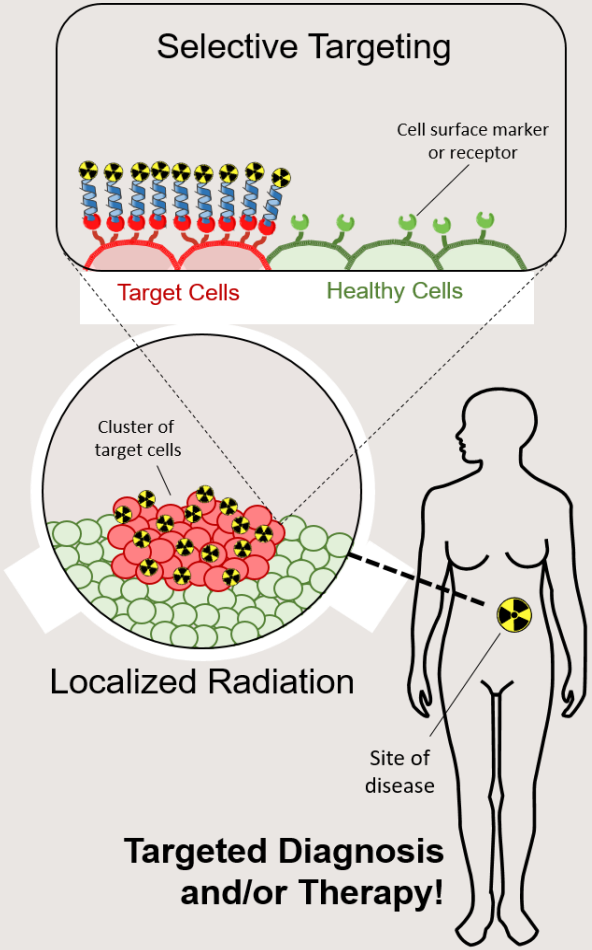
Nervous System



Brain

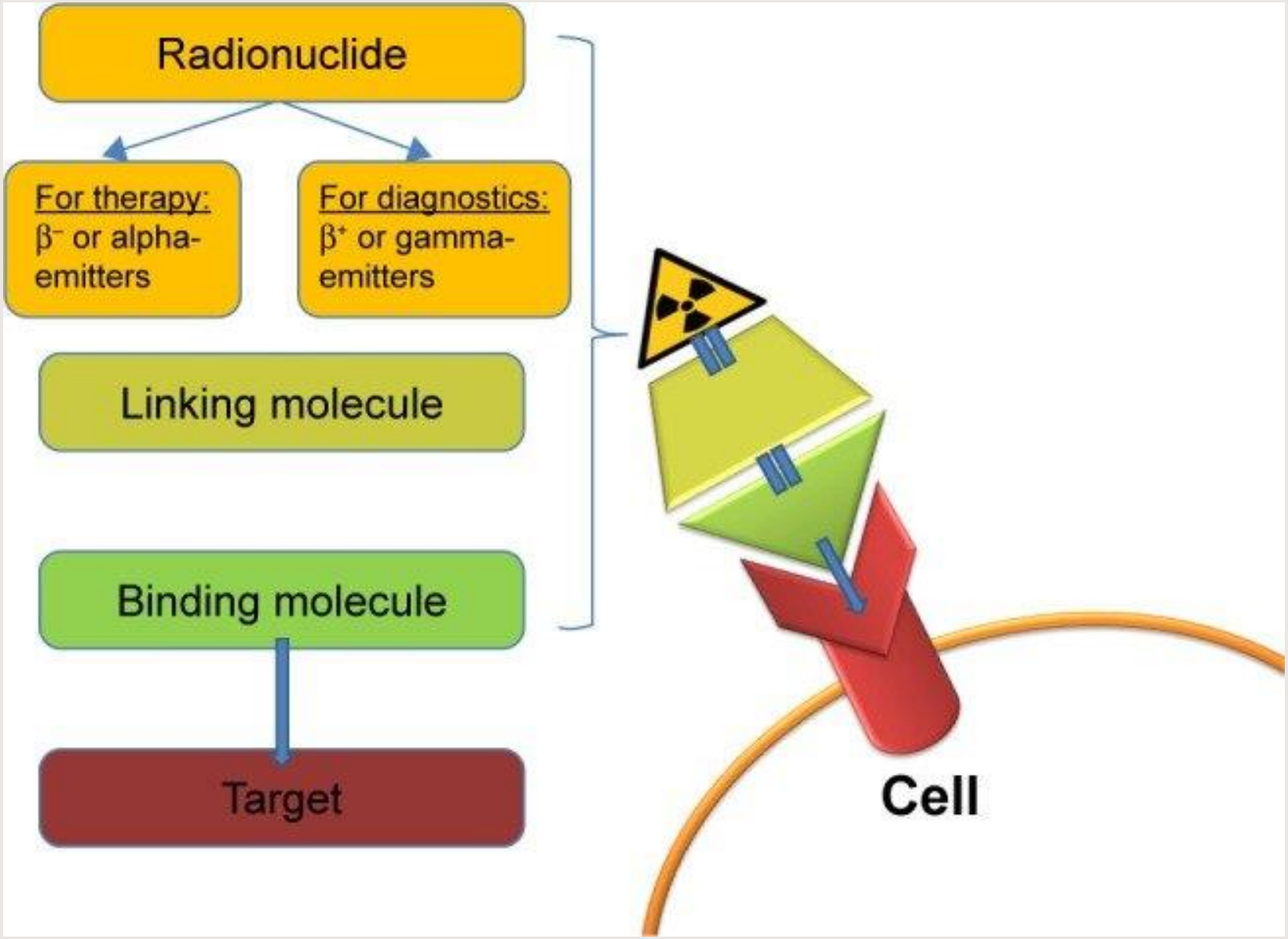
2025-2030: Applying Physics to Life



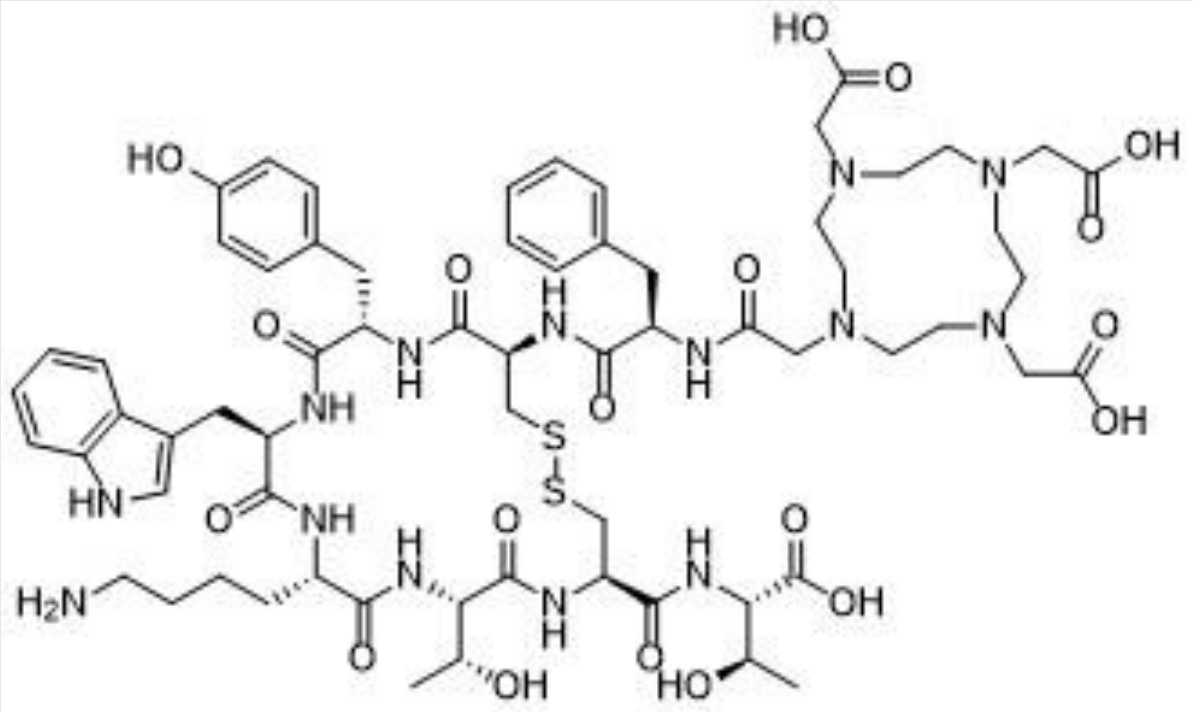


T. I. Kostelnik, C. Orvig *Chem. Rev.* **2019**, *119*, 902
invited for **Metals in Medicine** issue
Pouget et al. Nat. Rev. Clin. Oncol. 2011, 8, 720-734

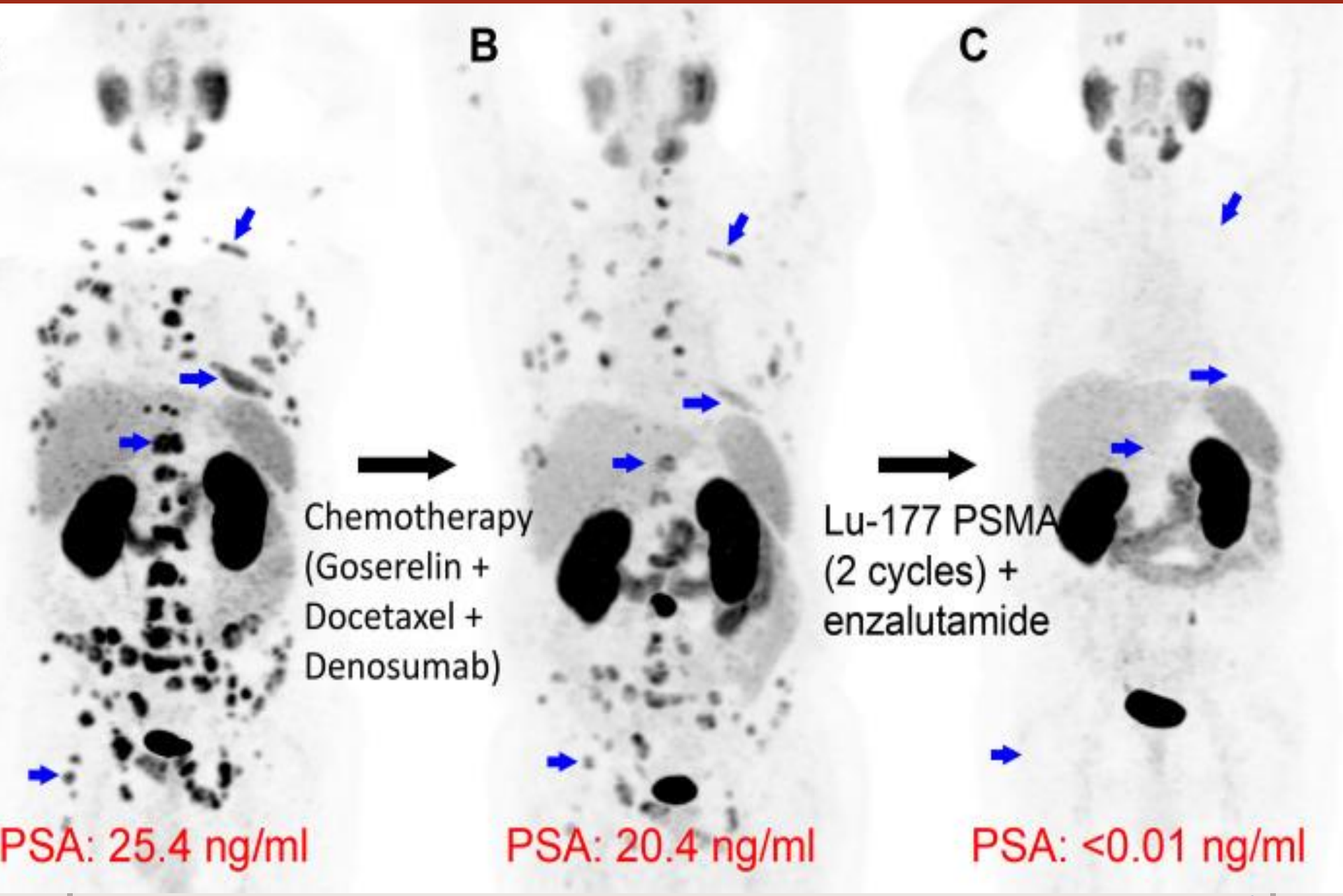
Combining Diagnoses and Therapy: Theranostics



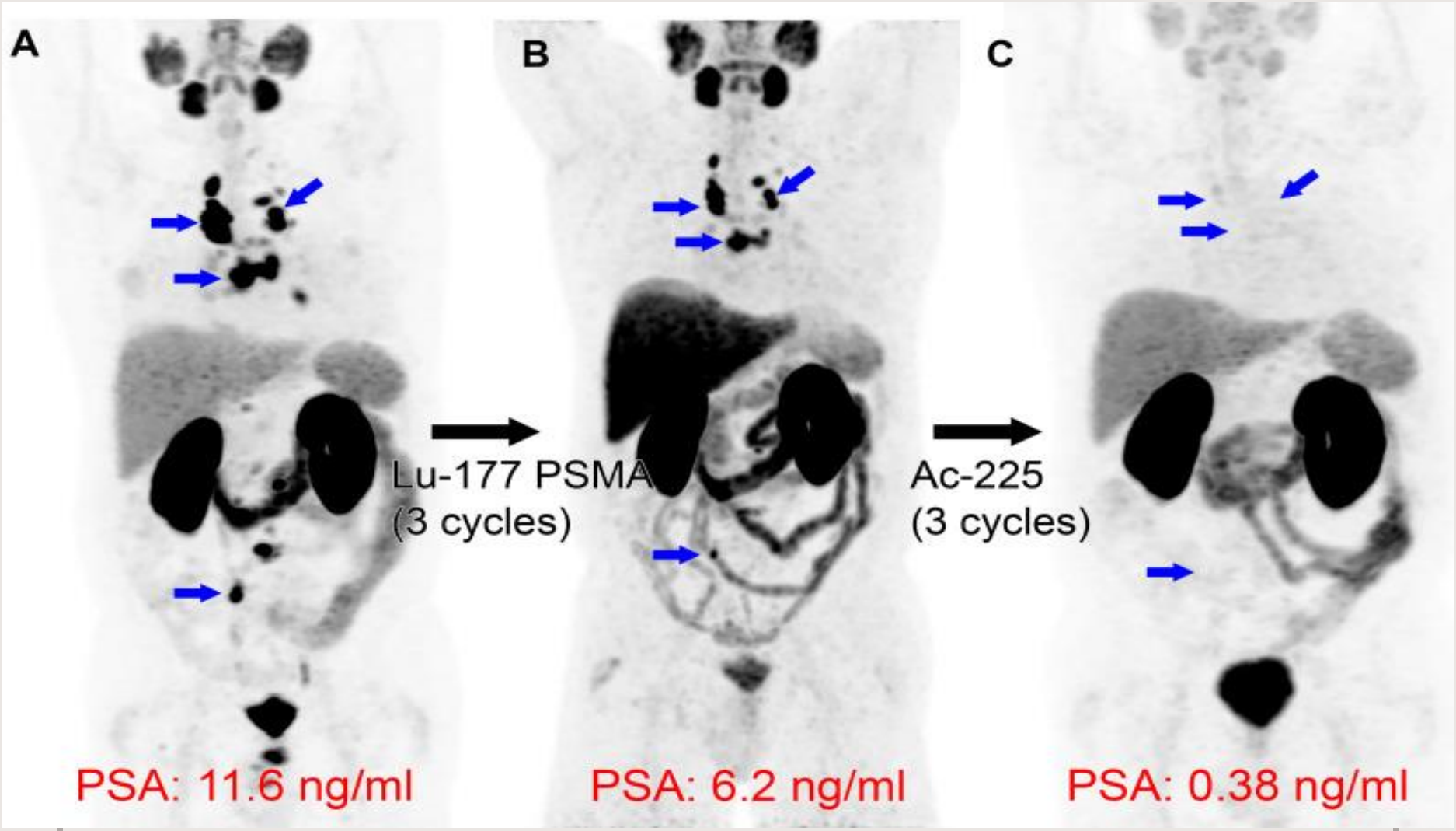
Theranostic Chemical Construct



Ballal, S. et al. J. Nucl. Med. 2023,64,211.


B
C
Chemotherapy
(Goserelin +
Docetaxel +
Denosumab)
Lu-177 PSMA
(2 cycles) +
enzalutamide
PSA: 25.4 ng/ml
PSA: 20.4 ng/ml
PSA: <0.01 ng/ml

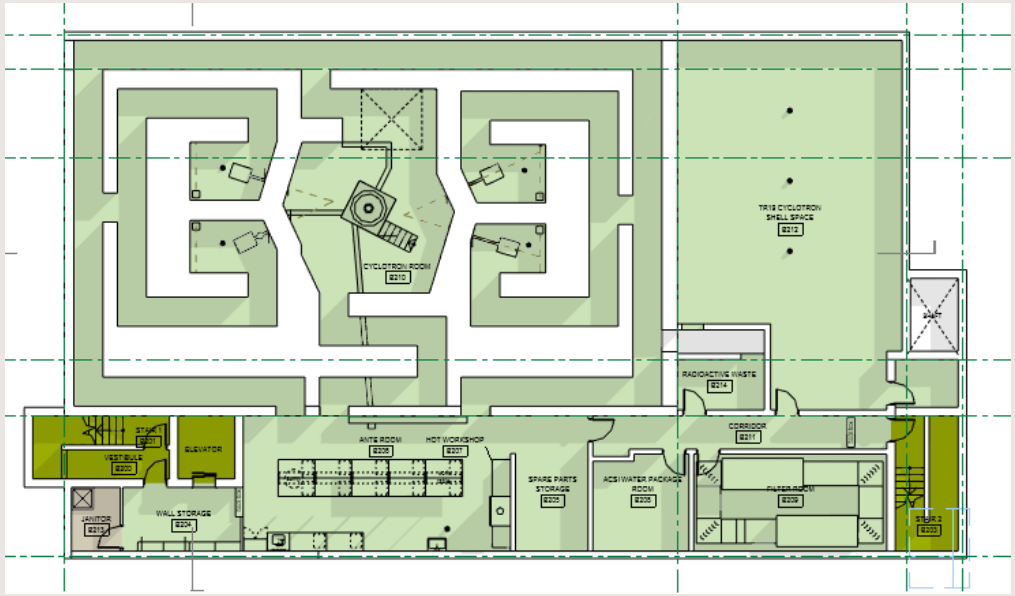
Radiol. Imaging Cancer. (2023); 5:e220157.

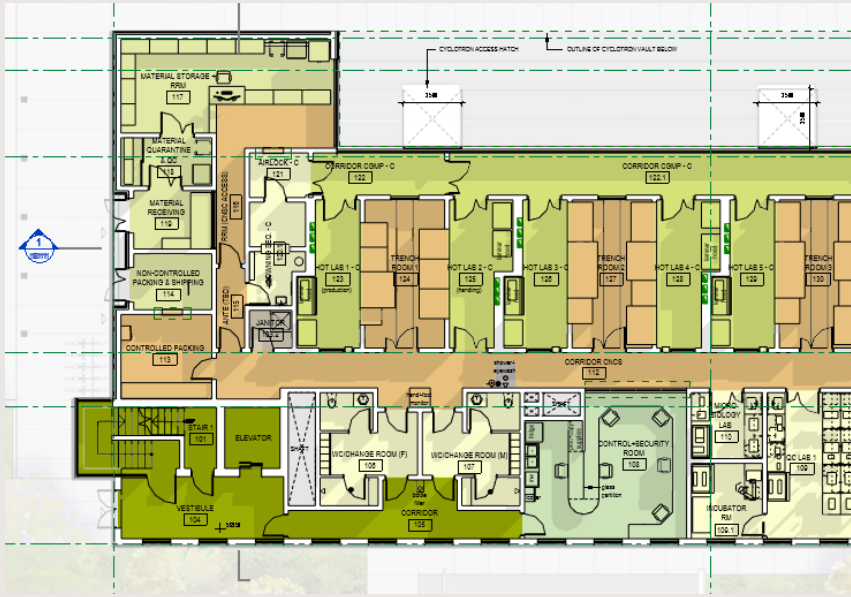


IAMI

Institute for Advanced Medical Isotopes

- BC Provincial Health Authority will be placing 2nd cyclotron in facility; additional lab space to support expanding provincial PET program
- Additional funding requests continue in discussion with provincial funding ministries





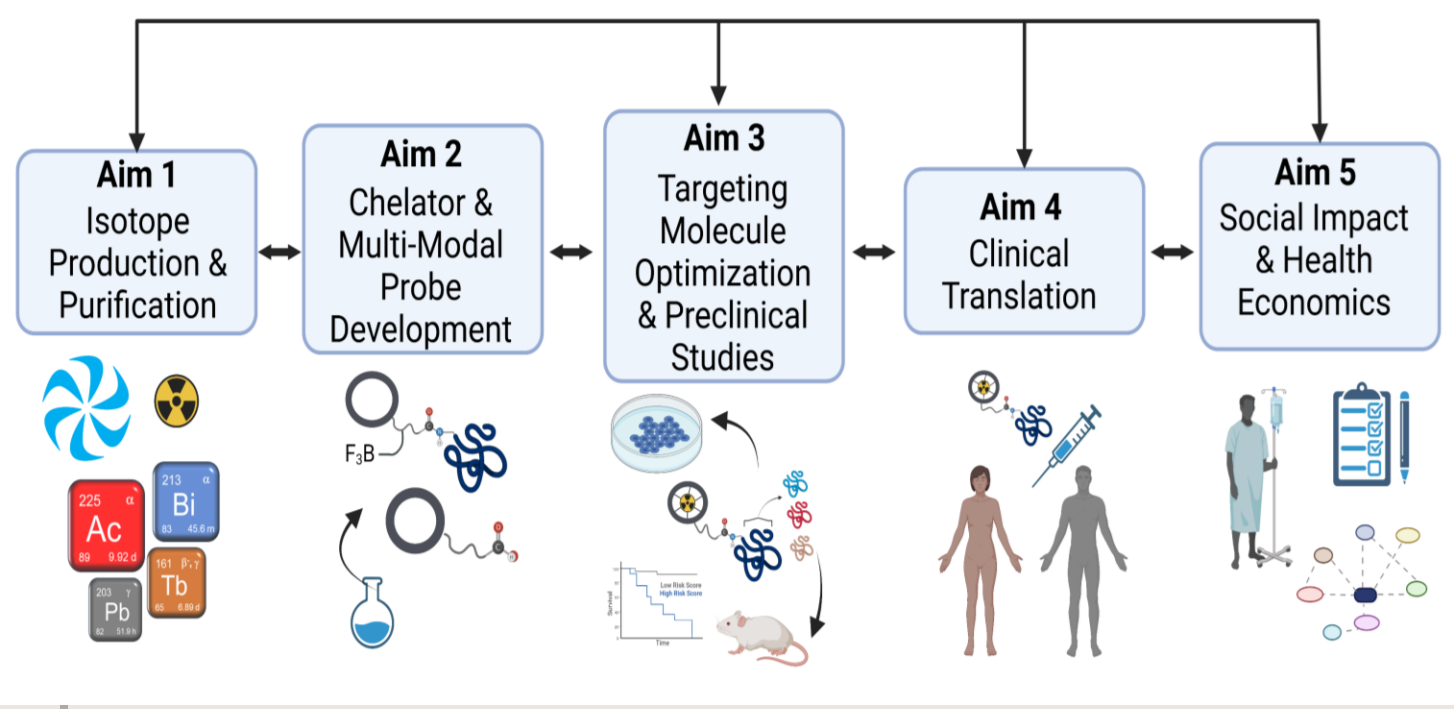
NFRF-Transformation: Rare Isotopes to Transform Cancer Therapy

New Frontiers in Research Fund
Fonds Nouvelles frontières en recherche

$23.7 M over 6 years

- NPI: Bénard (UBC/BC Cancer)
- Co-PI: Ramogida (SFU/TRIUMF)

TRIUMF Team: Hoehr, Radchenko, Schaffer, Yang



We face an enormous challenges with these projects

TRIUMF

But the view will be stunning!

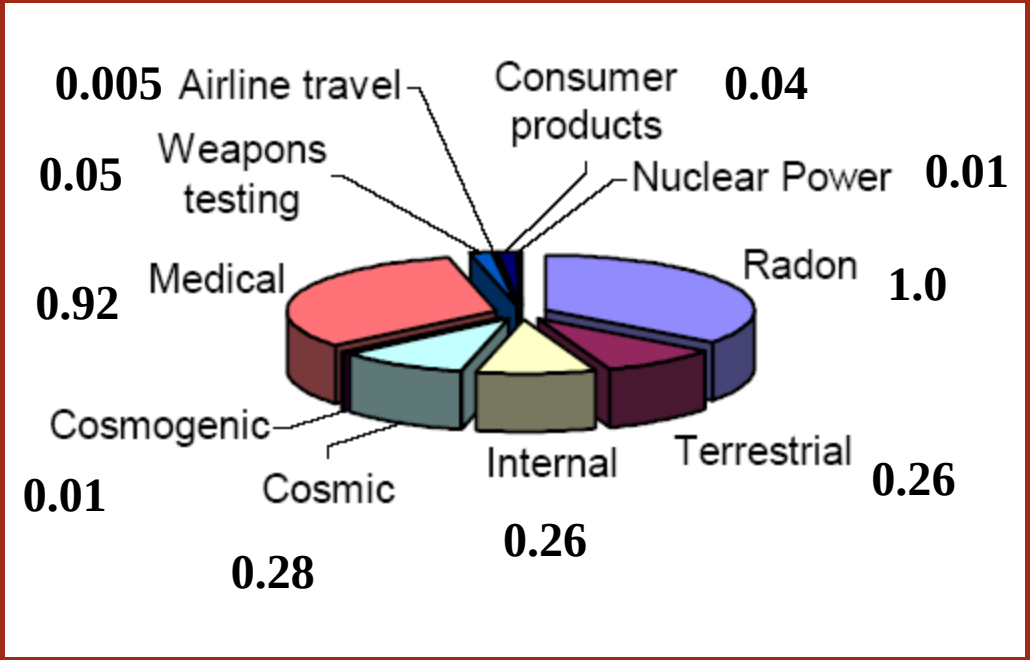
Acknowledgements

Thank you!
Merci!

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

Background Radiation

Average population exposure – 2.8 mSv/year



This can vary significantly depending upon life style and living location.

Loss of Life Expectancy Due to Various Risk - Days

- Being unmarried male - 3500
- Smoking – 2250
- Heart diseases – 2100
- Being unmarried female – 1600
- Coal Miner - 1100
- Cancer – 980
- Being poor - 700
- Stroke – 520
- All accidents - 435
- Motor vehicle accidents - 207
- Home accidents - 95
- Safest jobs – 30
- Bicycle – 5
- All catastrophes combined- 3.5
- **PET scan – 1 hour**
- Smoking 1 cigarette – 10 min.
- Pap test – (- 4 days)
- Air bags – (- 50 days)

Adapted from TRIUMF Radiation Safety Manual