THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

Molecular Imaging: At the Forefront of Medicine, But Firmly Rooted in Nuclear Physics

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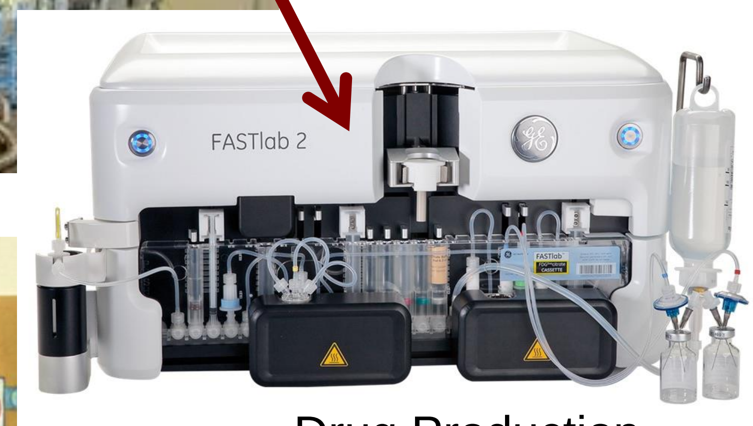
August 25, 2016

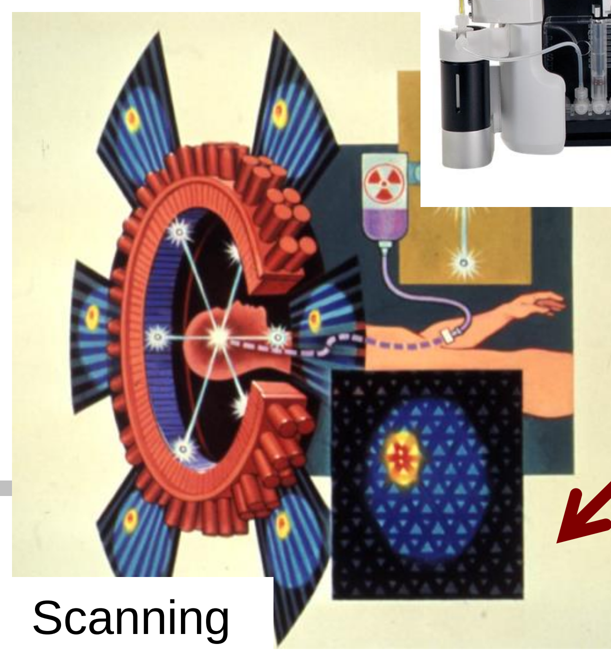
You are about to have a PET scan….

- Journey through a Radiology Nuclear Medicine Dept.
- Focus on PET, Positron Emission Tomography
- Start to finish: the influence of Nuclear Physics on patient care

Isotope production

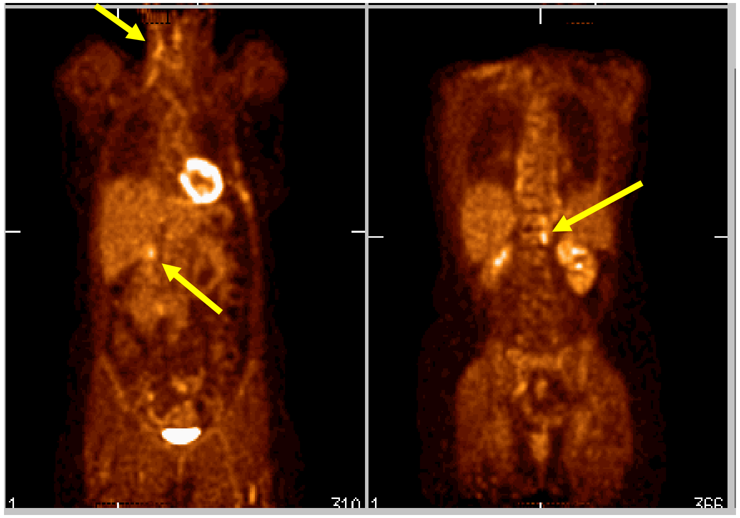


Drug Production

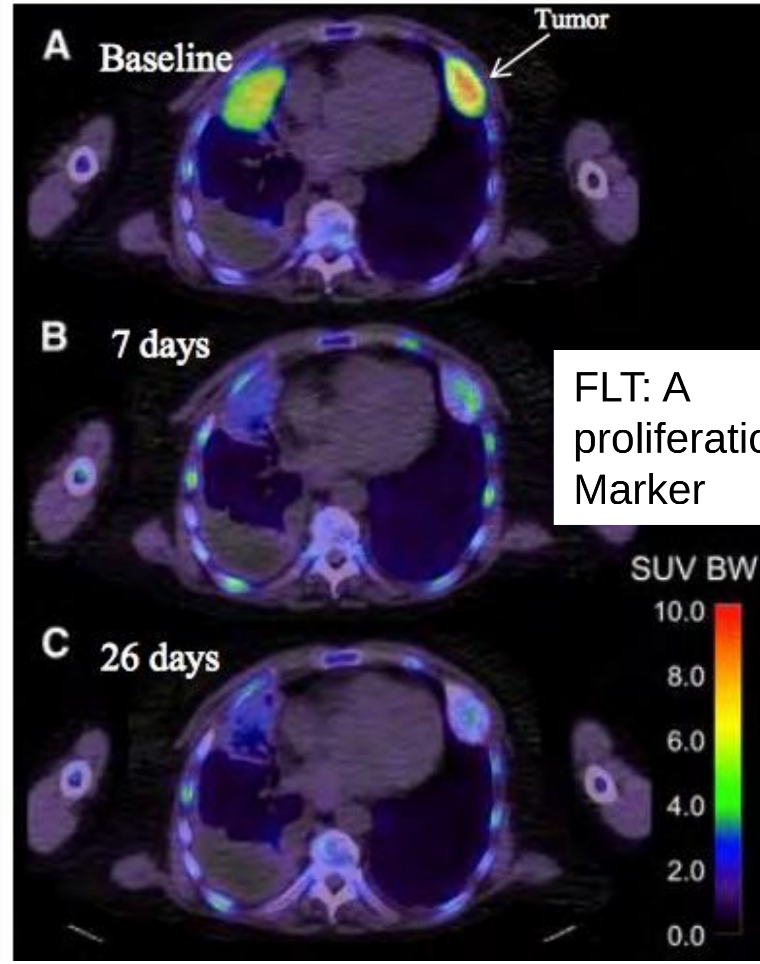


Scanning

What is so special about PET?



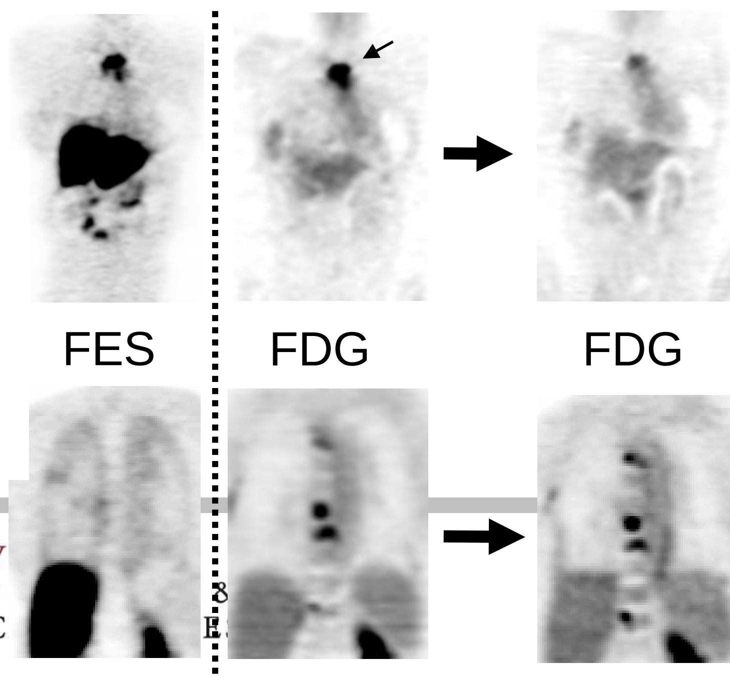
FDG: A glucose analog: workhorse of PET showing metabolic function



FLT: A proliferation Marker

Pre-Rx

Post-Rx

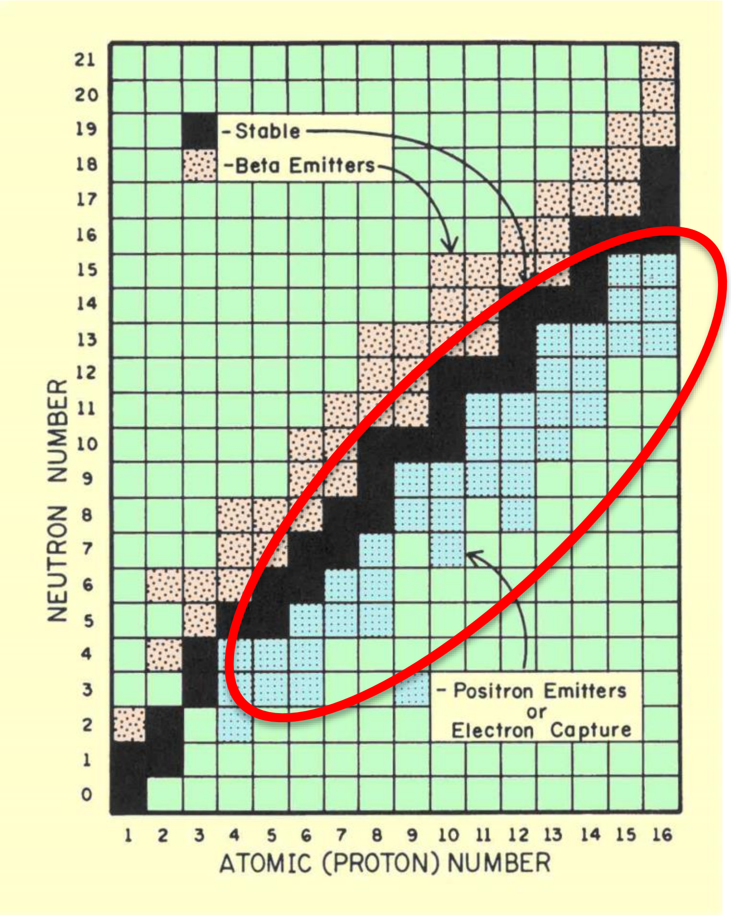


FES: Marker for respons e to therapy

What isotopes are used?

- ^{18}F fluoride (workhorse): ^{18}O (p,n) ^{18}F
  109.8 min, 6-20 Ci/run
- ^{18}F fluorine: $^{20}Ne(d, \alpha)^{18}F$
  109.8 min, 250-500 mCi/run
- $^{11}CO_2$: $^{14}N_2[+O_2](p, \alpha)^{11}CO_2$
  20 min, 4 Ci/run
- ^{13}N: $^{16}O(p, \alpha)^{13}N$
  10 min, ≈ 1 Ci maximum/run
- ^{15}O: $^{14}N(p,n)^{15}O$
  2 min , continuous production, 400 Ci/10'
- Other isotopes often used:
  - ^{64}Cu (12.7 hours)
  - ^{89}Zr (78.4 hours, 3.3 days)
  - ^{124}I (4.2 days)

Dominated by (p,n), (p, 2n), (p,α) reactions



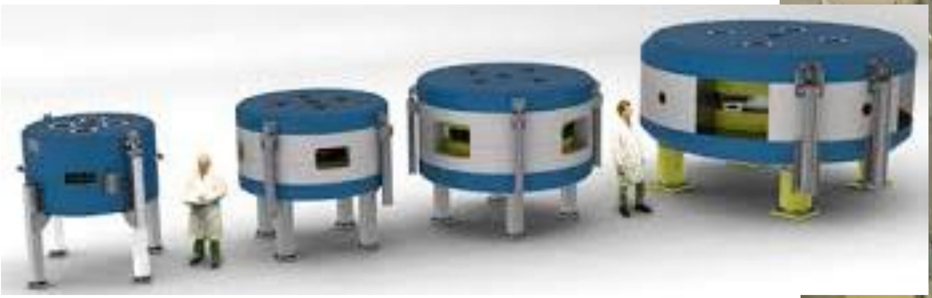
First Step: Isotope Production

(I guess all the time I worked on Stony Brook's 7 MV Van de Graaff was useful after all!)

Cyclotron Manufacturers

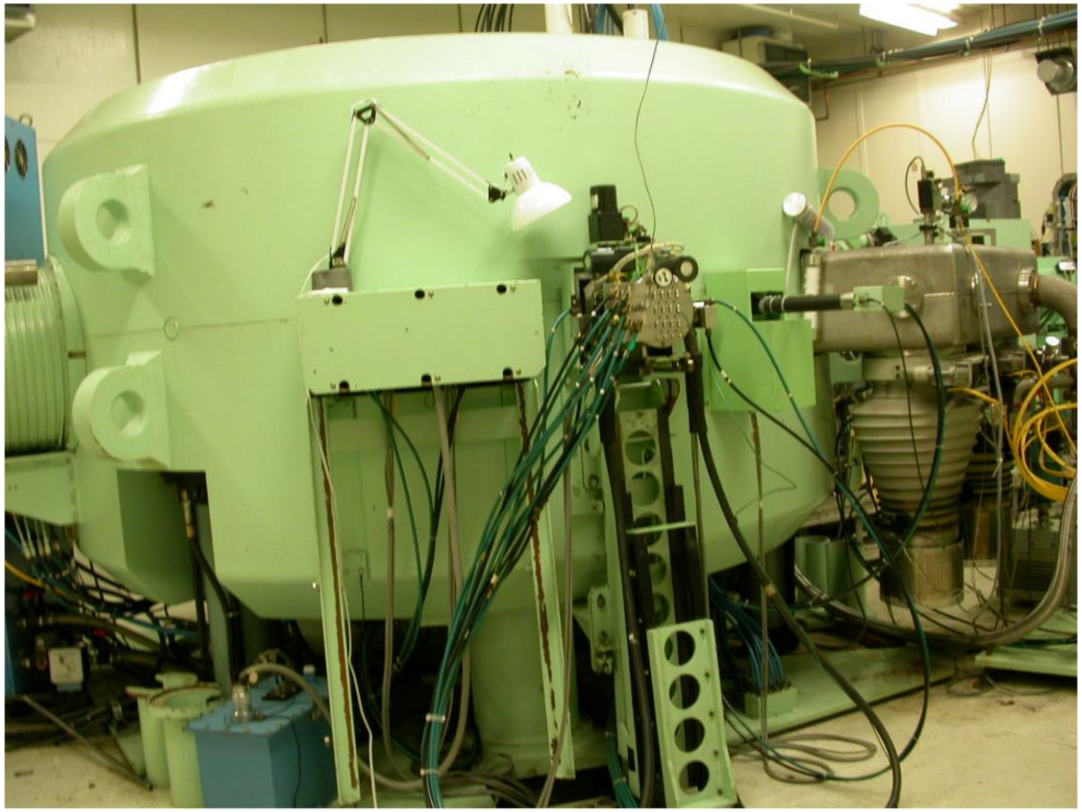
- GE
- ABT
- Sumitomo
- Best
- Siemens
- IBA
- ACSI
- Ionex (^{13}N)

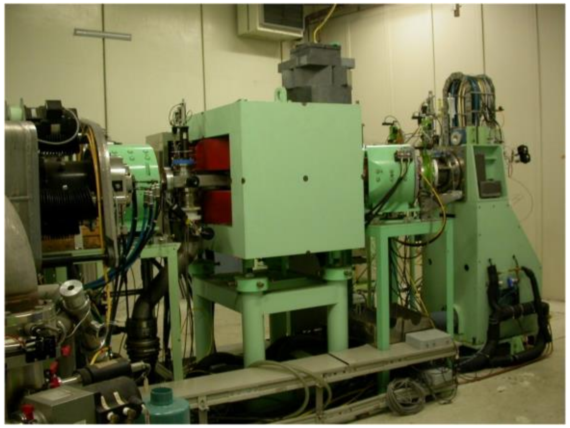





My Favorite (an older machine, 1985)

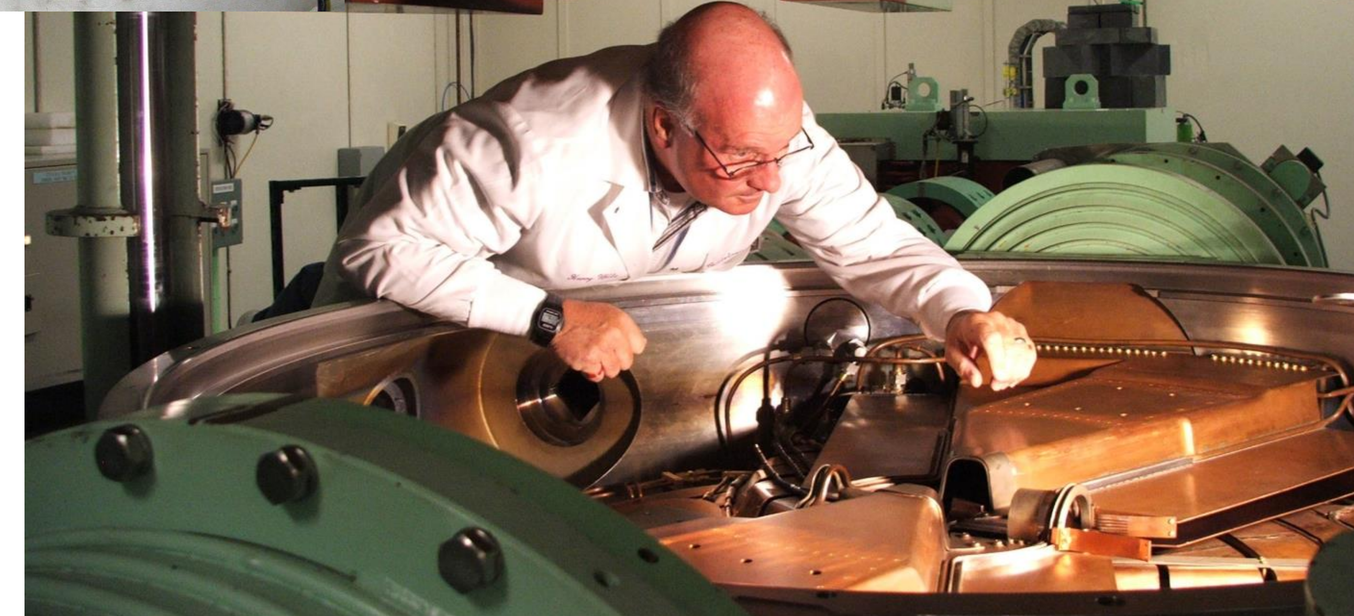
- *University of Penna.*, JSW 15, 22, 30 MeV p's
- d, ^{3}He, ^{4}He, external beam line, 6 production tgts
- Unshielded machine, in a 40' x 20' x 20' vault





Positive ion machine with deflector (hot).

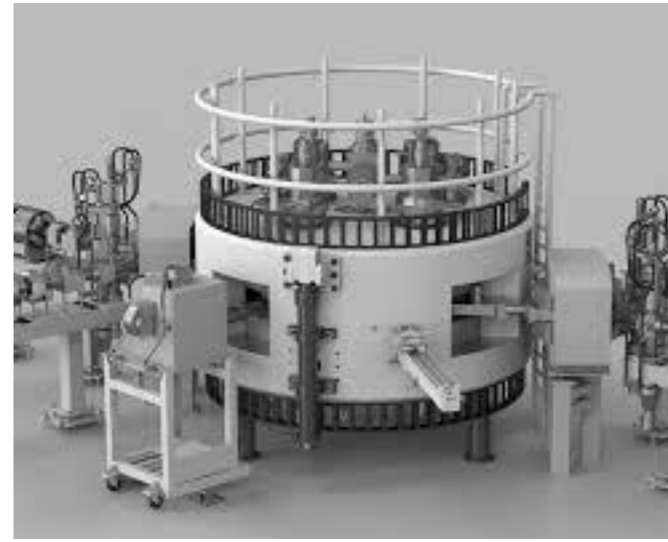
A look inside

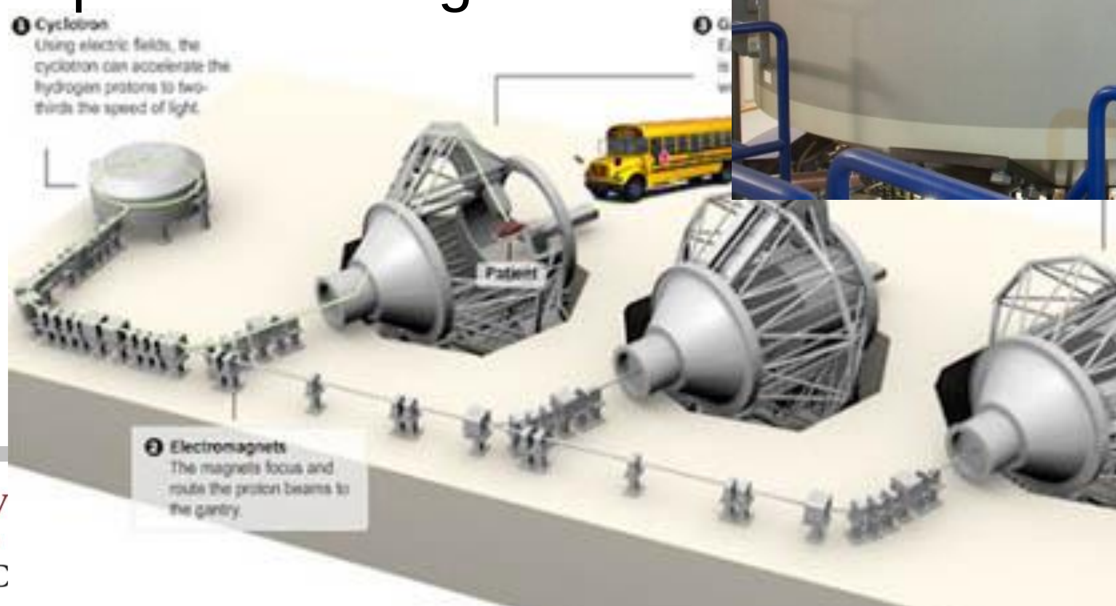


Old doesn't mean obsolete, just needs a little TLC

More Cyclotrons!

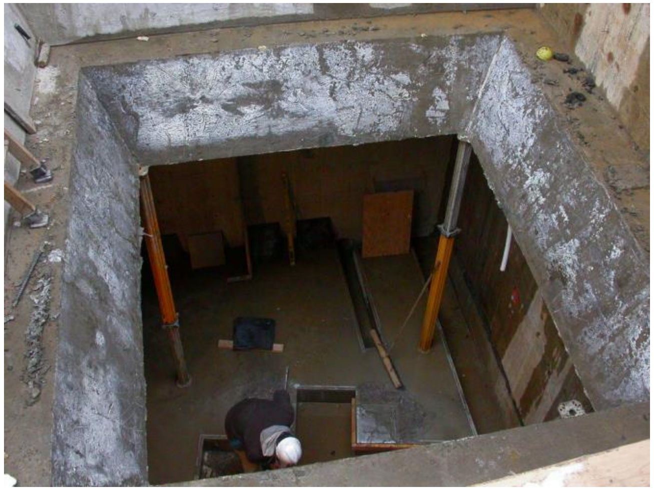
- ^{82}Sr/^{82}Ru (generator) needs 70 MeV
  ^{85}Ru(p,4n)^{82}Sr
- Proton therapy (roots at Stanford, GSI, Paul Scherrer and elsewhere)
  – Normal
  – Superconducting





Always the need to expand ….

- PET is still growing
- With 10 - 200 Ci/day still need to expand
- Not the scale of CERN/GSI
- Small team
- $8.5M (twice!)
- 10 months construction
- Major project for a Radiology Department



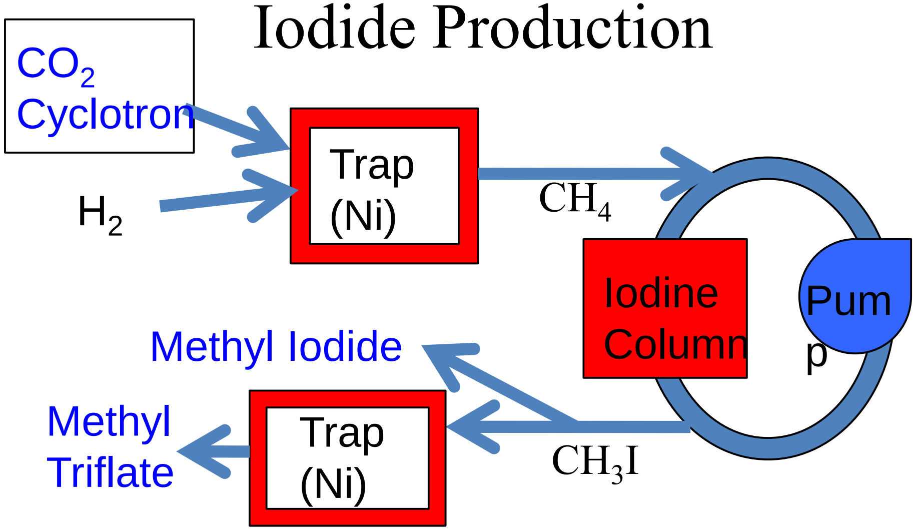
Step Two: Radiopharmaceutical Production

(Who would have thought that I would have to learn chemistry?)

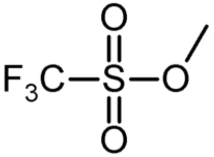
Elements to Radiopharmaceutical production

- Synthesis (automated, hand)
  - Time to synthesize
  - Complexity
- QC/QA
  - Every time you activate the machine: a new lot
- Regulatory (FDA)
- Approved drugs vs. investigational drugs

Look at a hard example: ^{11}C Methyl Iodide Production



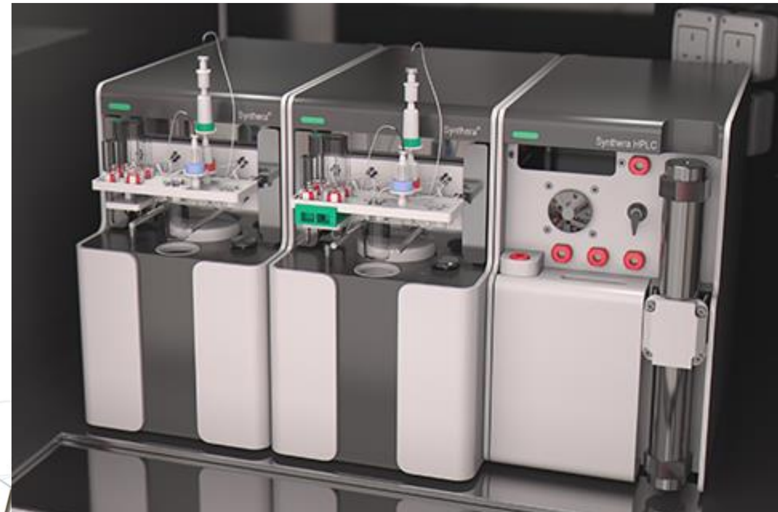
Methyl trifluoromethansulfonate

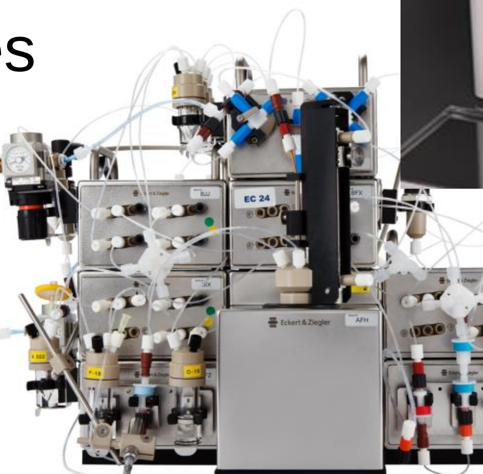


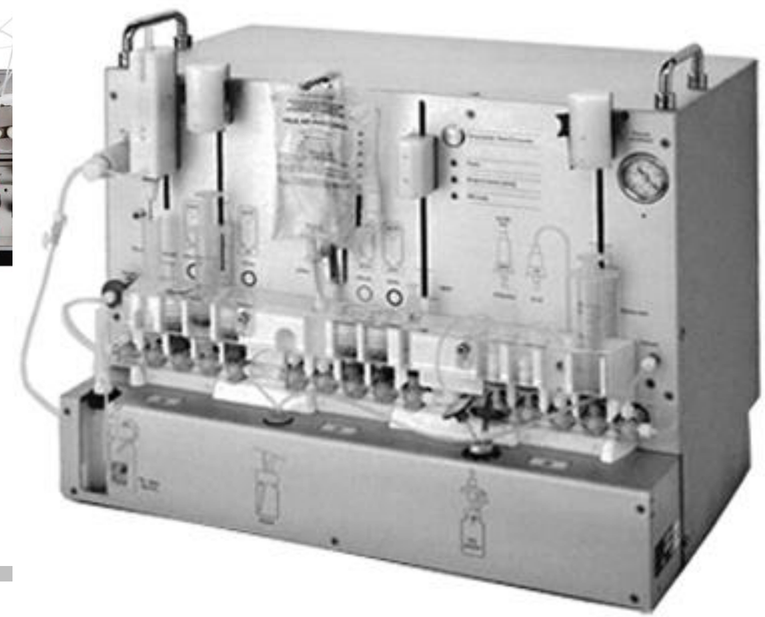
Takes 2 half-lives, start with 3 Ci of ^{11}C, end up with a 60 mCi Dose

Automated chemistry synthesis units

- Most ^{18}F chemistry can be automated
- All radiochemistry is <u>trace</u> chemistry
- Automation removes operator error, increases reliability
- Automation more compatible with norms in Pharma
- Probably hardest part of the three (for research)



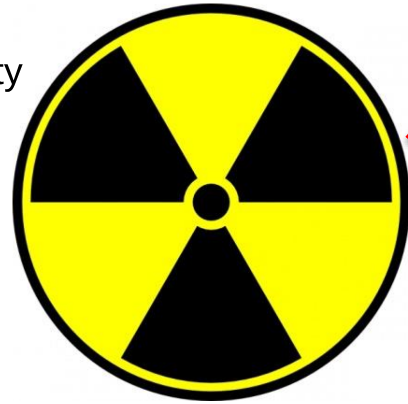




(Isotope production, radiochemistry, Scanners)

Radiochemistry: Compliance!

Major Source of Radioactivity



City, State, and Federal Regulations

How to organize and manage ???

- Admin
- Procurement
- Regulatory Affairs
- Facilities
- Safety
- Radiation Safety

$$$

Major commitment of monetary resources

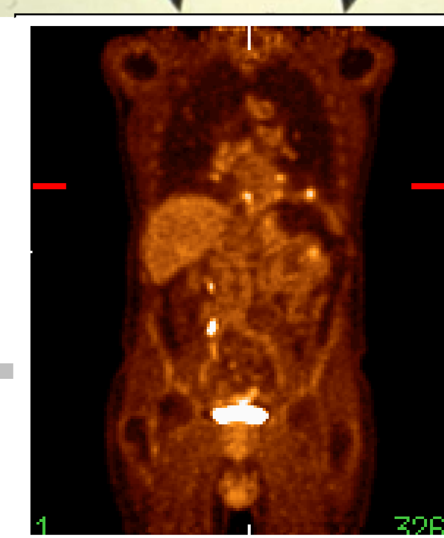
Resources:
Space
Manpower
Equipment

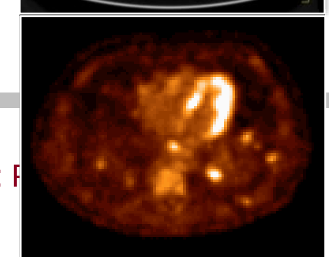
Step Three:
The scanner

(This is the most fun part of the business)

Some basics

- Injected activity ≈ 15 mCi (550 MBq)
- Body attenuation @ 511 keV ≈ 20x
- Low dose CT for attenuation correction
- ½ rem for CT
- 1 rem for PET
- 20 minutes for a whole-body scan

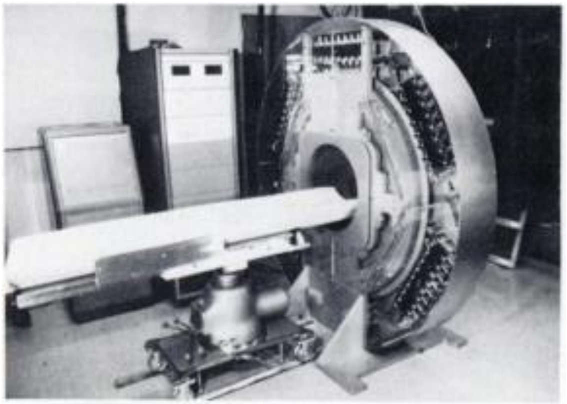


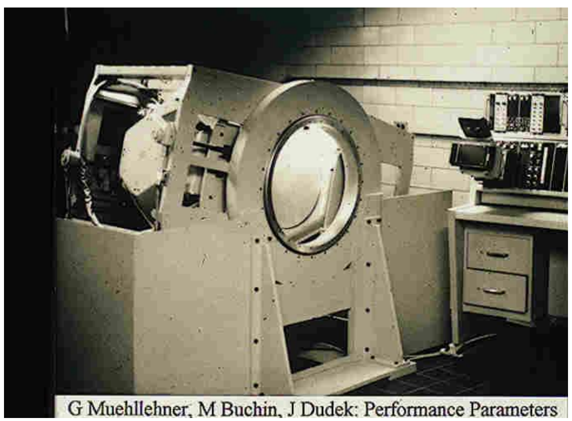


We've come a long way….

mid 1970's

Washington University





University of Chicago

4 decades…

Single-slice

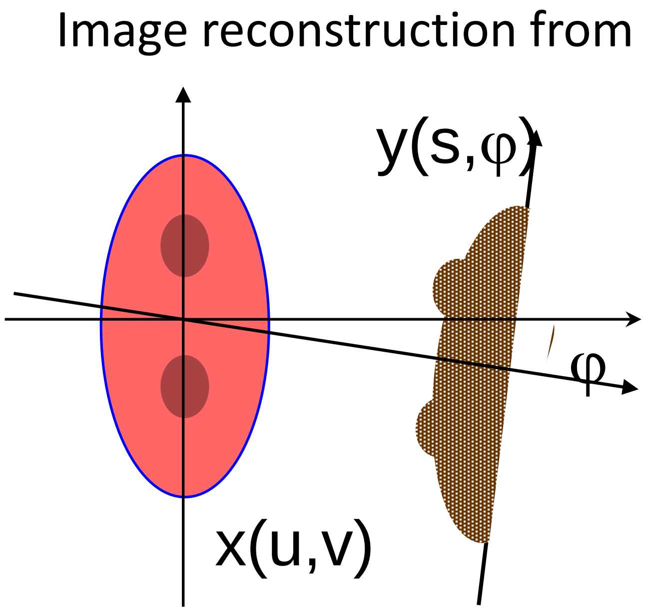
Large, 2D detectors 3D acq.

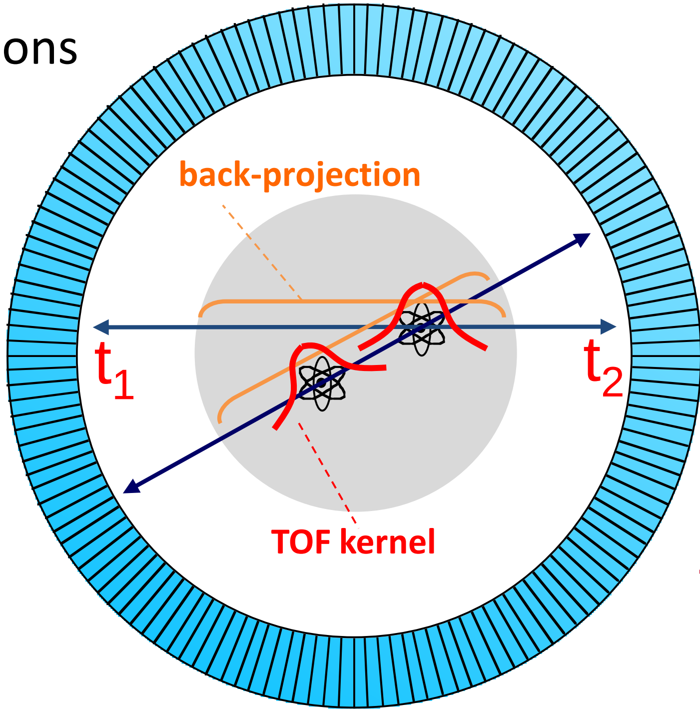
2015

PET/CT

- Fully-3D
- Iterative reconstruction
- Improved scintillators – fast, dense, bright
- Time-of-flight

Time of Flight Scanners



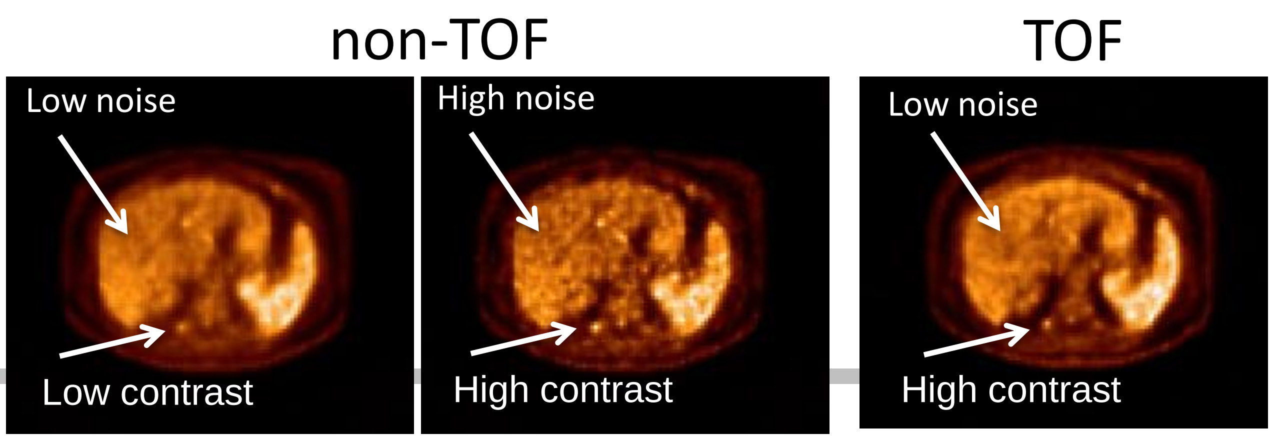


$\Delta t = t_1 - t_2$

$\Delta x = c \cdot \Delta t/2$

7.5 cm ~ 500 ps

- TOF information improves SNR
- Large benefit for high Body Mass Index Patients



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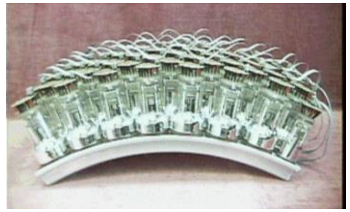
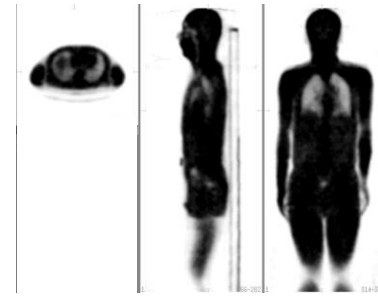
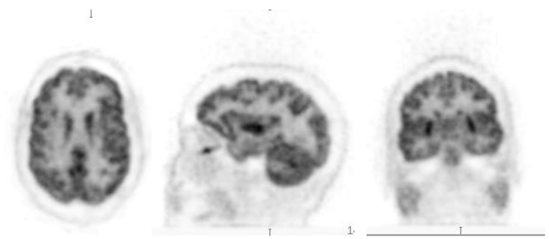
Unique Scintillators

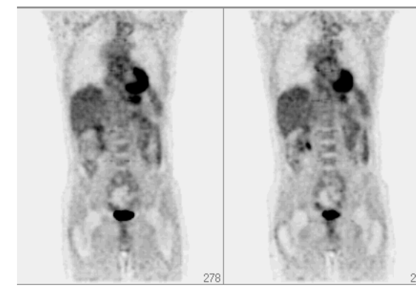
- C-PET – Na(Tl)
  Curved plate
  detectors



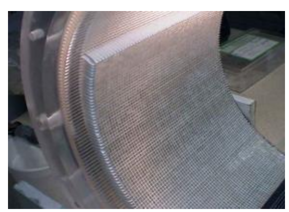


- G-PET brain / Allegro body – pixelated
  GSO detectors





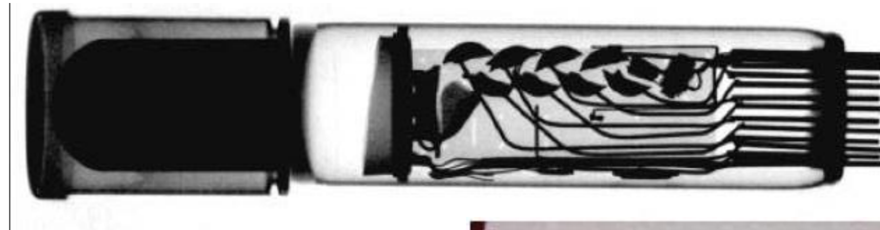
- Mosaic small animal – LYSO
  pixilated detectors

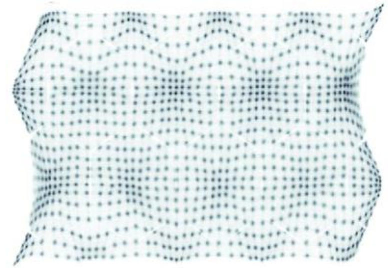


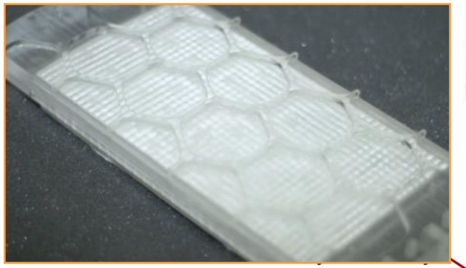
- La-PET – time-of-flight
  PET - $LaBr_3$ detectors

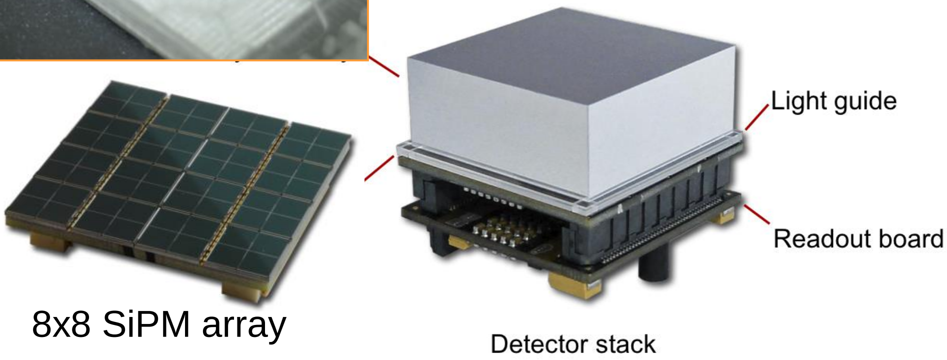
Unique Light Detectors – Suitable for TOF

- Wash Univ. 1981-2
  - 1 to 1 coupling
  - CsI (Δt = 500 ps)
- 2005-2015
  - LYSO, 4 x 4 mm^2
  - Large arrays (Δt = 500 ps)
- 2015 –
  - SiPM: analog and digital (Δt = 300 ps)
  - Newer scintillators





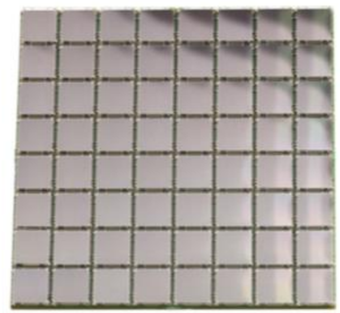




Improving on Δt = 300 ps?

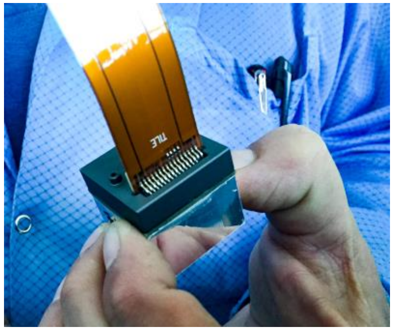
- Improved photo-detectors and scintillators
  - More compact
  - MRI compatible
  - Lower encoding
  - Depth of interaction

Analog SiPM or Digital SiPM



SensL

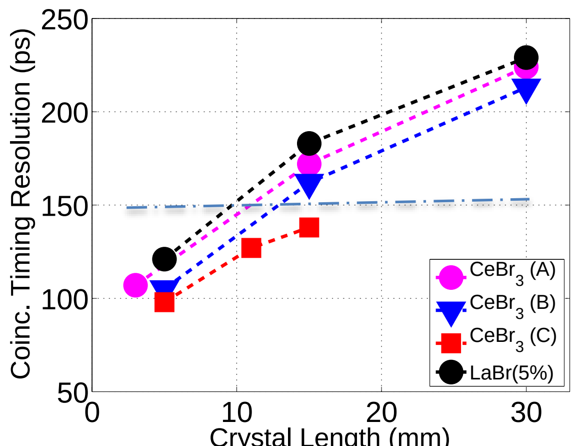
300 ps



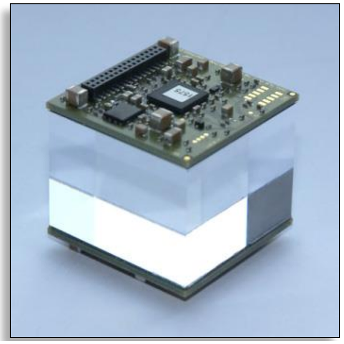
PDPC

64-channel crystal/SiPM array

Halide scintillators with FBK SiPM



Schmall et al



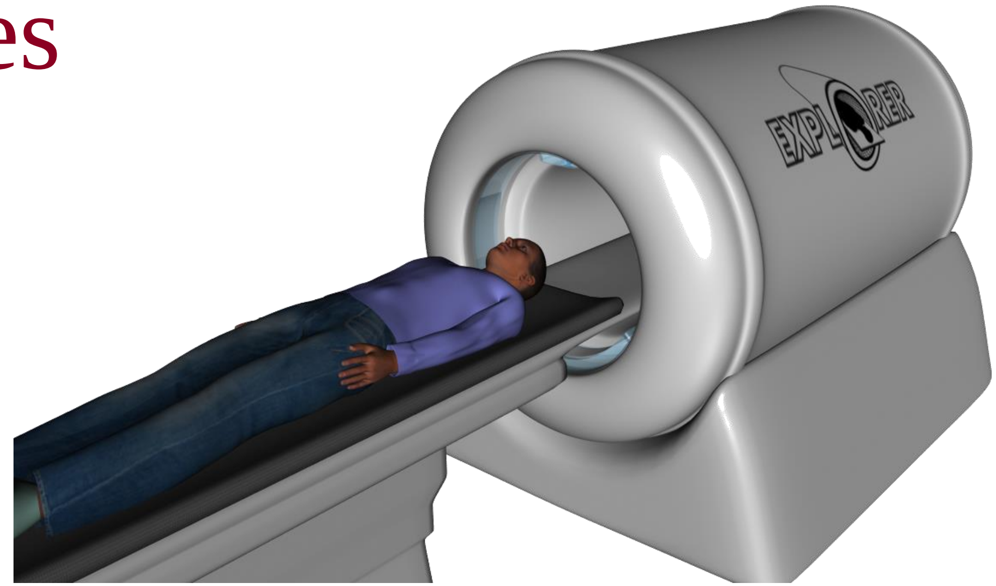
32 mm x 32 mm x 22 mm commercial-grade LYSO:Ce with double-sided dSiPM readout

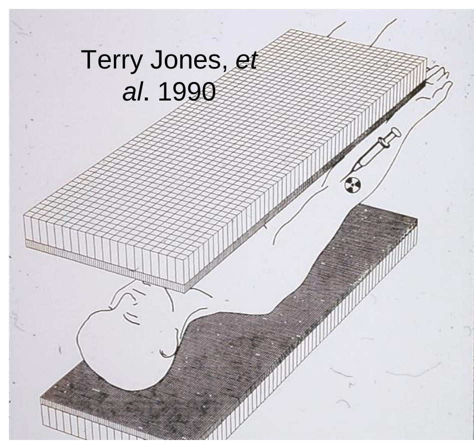
150 ps

Peet et al, SNM 2015, Borghi et al PMB 2016

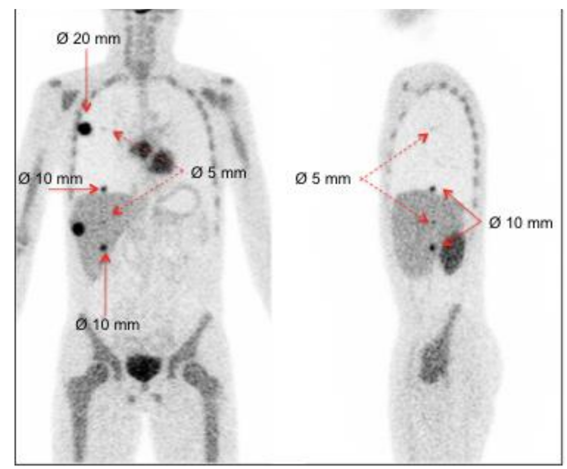
Newer Geometries

- Long whole-body scanner, 2 m
- Old idea, new implementation
- Lower dose, higher sensitivity, larger axial field of view
- Total body kinetics
- Consortium: UC Davis (lead), Penn, LBNL
- Large datasets, special algorithms





Monte Carlo Simulation
S. Vandenberghe, U. Ghent

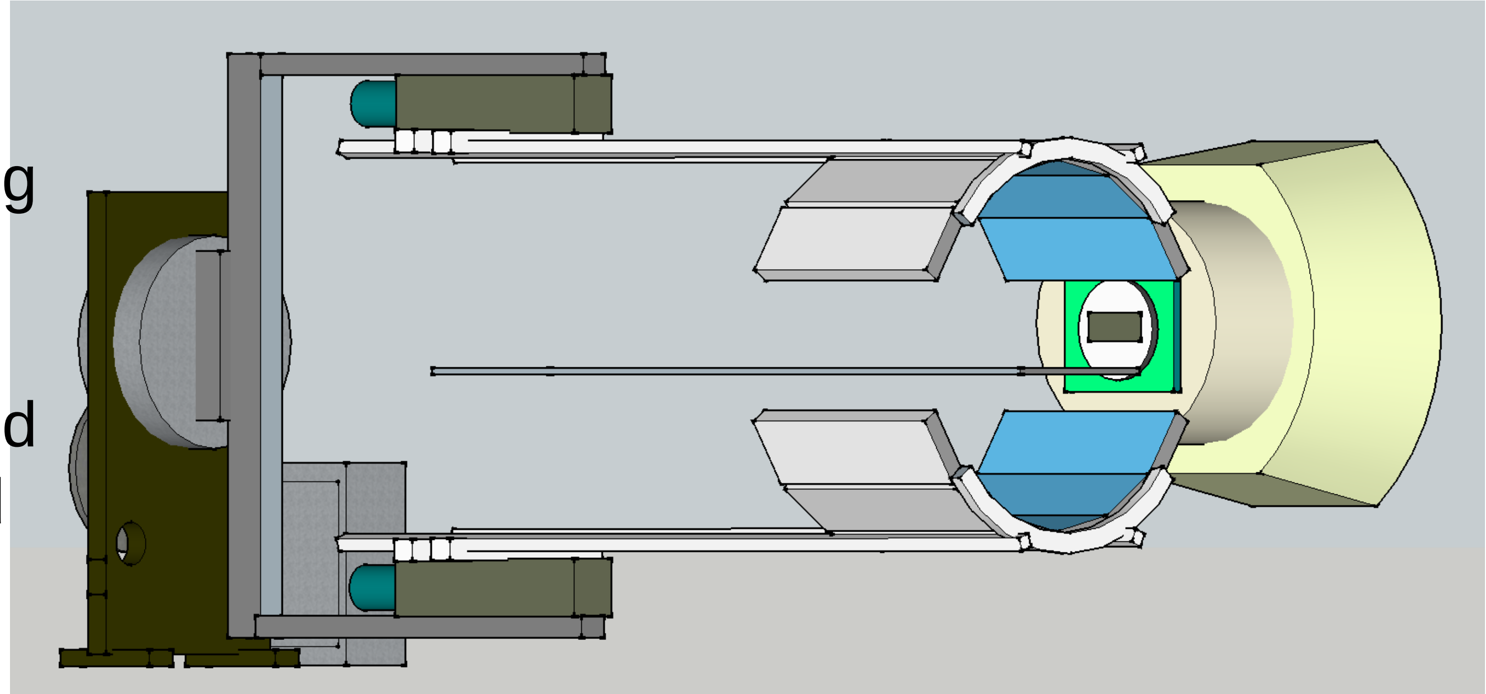


12 minutes, 40 MBq activity x10 reduction

Proton Dose Monitoring with PET

- GSI late 1980's
- Incomplete field of view
- Not for beam monitoring
- Matching FDG image and irradiated area

Needs: handling of large number of detectors, big data sets, improve algorithms



What haven't I discussed?

- Advances in Reconstruction Algorithms
- Quantitative corrections
- Attenuation Correction methods
- PET/MRI
- Acquisition time vs. Time resolution in the Clinic
- Modeling
- Normalization, time and energy calibrations

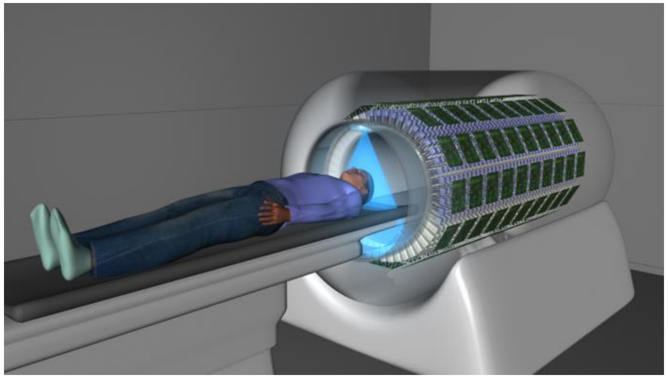
Conclusions

- At almost every step of the process from radioisotope production through chemistry and ending with scanning, nuclear physics has made this non-invasive technology possible.
- Cyclotrons: many different designs
  - Different capabilities and capacities, academia vs. commercial
  - Novel radioisotopes lead to novel radio-ligands
- Radiochemistry
  - Toughest part for non-standard research ligands, trace chemistry
  - Wide pallet of compounds but only a few are FDA approved
- Scanner technology – Nuclear physics pervades throughout
  - Novel scintillators: large area, high pixilation, high light output
  - Novel light detectors: SiPM - analog/digital
  - Time of flight: 300ps time resolution with possible improvements
  - Larger geometries for higher geometric and system sensitivity
  - In-beam monitoring: Limited angles improved by TOF, reduction of irradiation of margins and surrounding tissue

Cyclotrons for Medical Isotope production

- Patient dose: 10-15 mCi
- Academic production: 6 – 15 Ci/day
- Commercial production: 20 – 300 Ci/day
- Rad. Safety, ALARA, shielding (Hot Cells)
- Solid Targetry for:
  - ^{64}Cu, ^{77}Br, ^{124}I, ^{89}Zr
  - ^{99m}Tc
  - etc.

Technically challenging

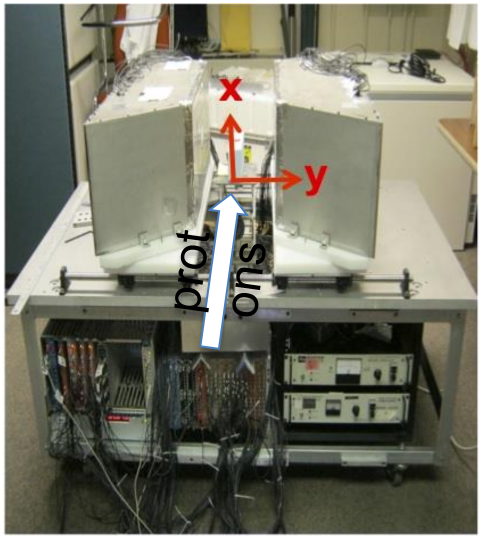


- Detector hardware, electronics
  - 300,000 detector elements (~10 scanners)
  - Performance trade-offs; e.g. TOF vs. spatial resolution
  - Terabytes data per patient
- Calibrations and data correction
  - Attenuation correction
  - Normalization - detector efficiency correction
  - Scatter correction
  - Quantitative accuracy over wide range of activity
- Image reconstruction
  - Billions of coincidence lines-of-response, large acceptance angle
  - Time-of-flight with full system modeling

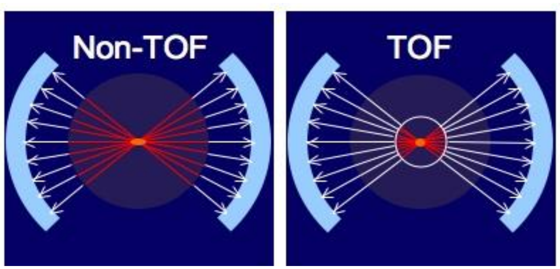
Limited Angle Reconstruction w/ TOF

S. Krishnamoorthy, K. Teo, S. Surti

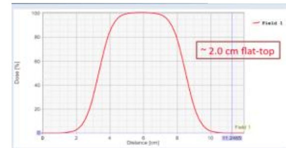
Proto-type PET system



Small-FOV proto-type system
2 $LaBr_3$ PET detectors
TOF resolution 400 ps



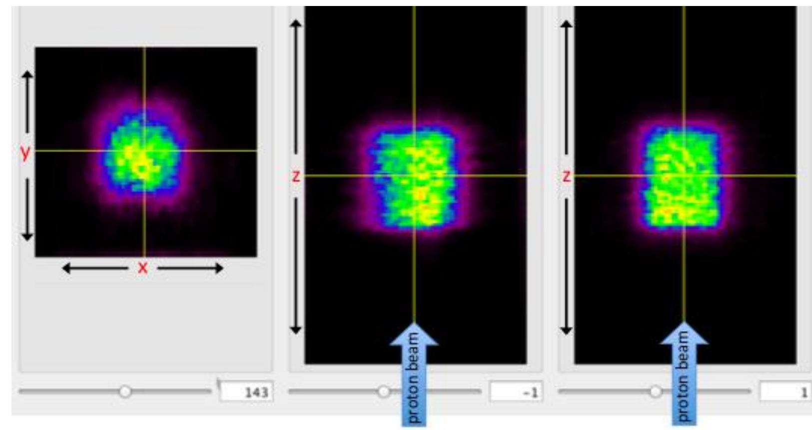
TOF a benefit with limited angle data



Beam profile, 2 Gy irradiation

Carbon-rich polyethylene phantom

92 MeV protons



Oxygen-rich water gel phantom

54 MeV protons