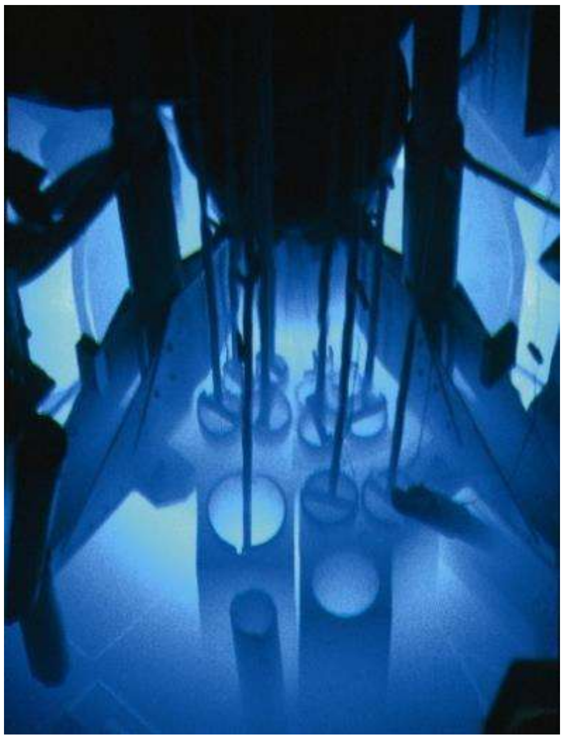
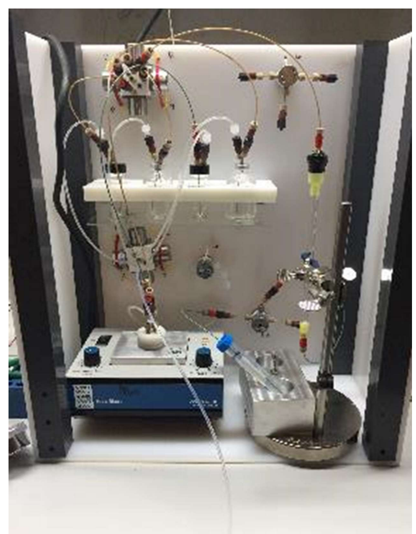
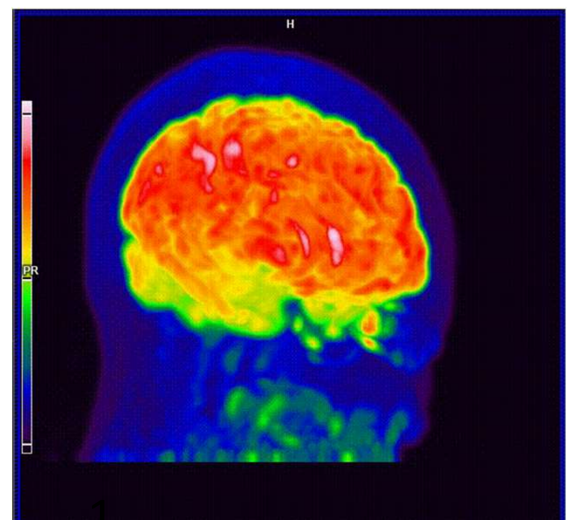
# Production of Medical Isotopes








## Graham Peaslee


**EBSS – June 8, 2022**

*** Thanks to Suzy Lapi for slides…**

# Production of Medical Isotopes

Outline

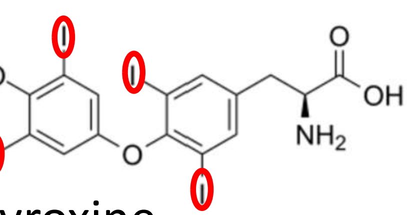
- Applied *vs*. Basic Nuclear Science
- Radioisotopes and Nuclear Medicine
  - Accelerator-based
  - Reactor-based
- Current Radioisotopes
- Where the Future Lies…

# Basic *vs*. Applied Science

# What is Nuclear Medicine?

The use of radioisotopes or nuclear technology to image or to treat disease…

Gamma Knife


Thyroxine


**40 million nuclear medicine procedures are performed each year (50% in US)…**
**Growing at 5 – 10% per year….**

# What is Nuclear Medicine?

- Imaging/diagnostic radioisotopes
- Therapeutic radioisotopes
- Theranostic radioisotopes

Positron Emission Tomography (PET) $^{11}C$, $^{18}F$

Single Photon Emission Computerized Tomography (SPECT) $^{99m}Tc$, $^{67}Ga$

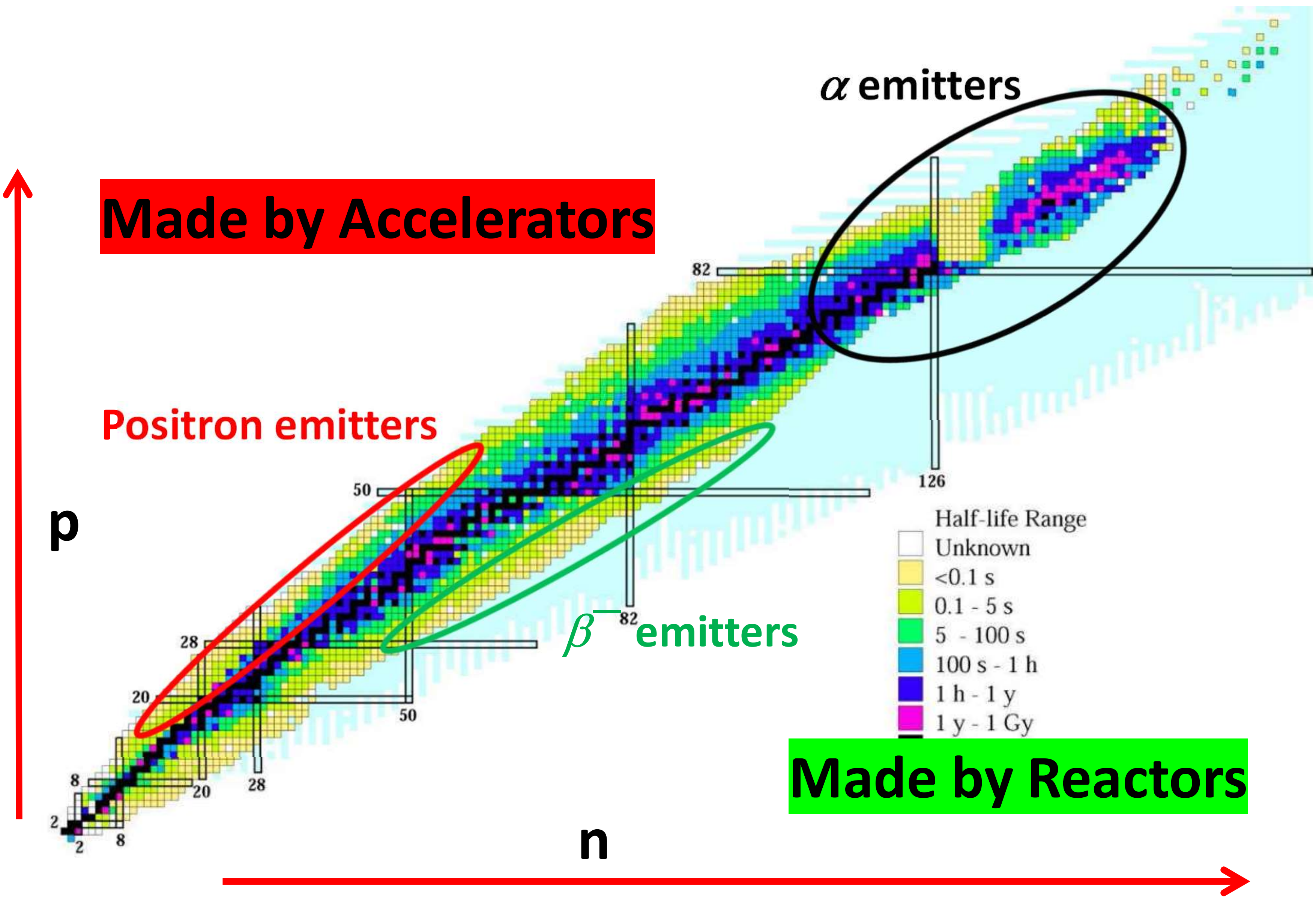
Brachytherapy $^{60}Co$, $^{125}I$

Radiopharmaceuticals $^{131}I$, $^{90}Y$

# What Makes a Good Radioisotope?

- **Radioisotopes have the same chemical properties and will behave similarly as non-radioactive isotopes – can be used as tracers…**
- **Appropriate half-life: not too short, not too long**
- **(both physical and biological half-life)**
- **Type of decay is important…**
- **Availability...**
- **Purity….**

# How to make Radioisotopes?



# Accelerator Methods of Production

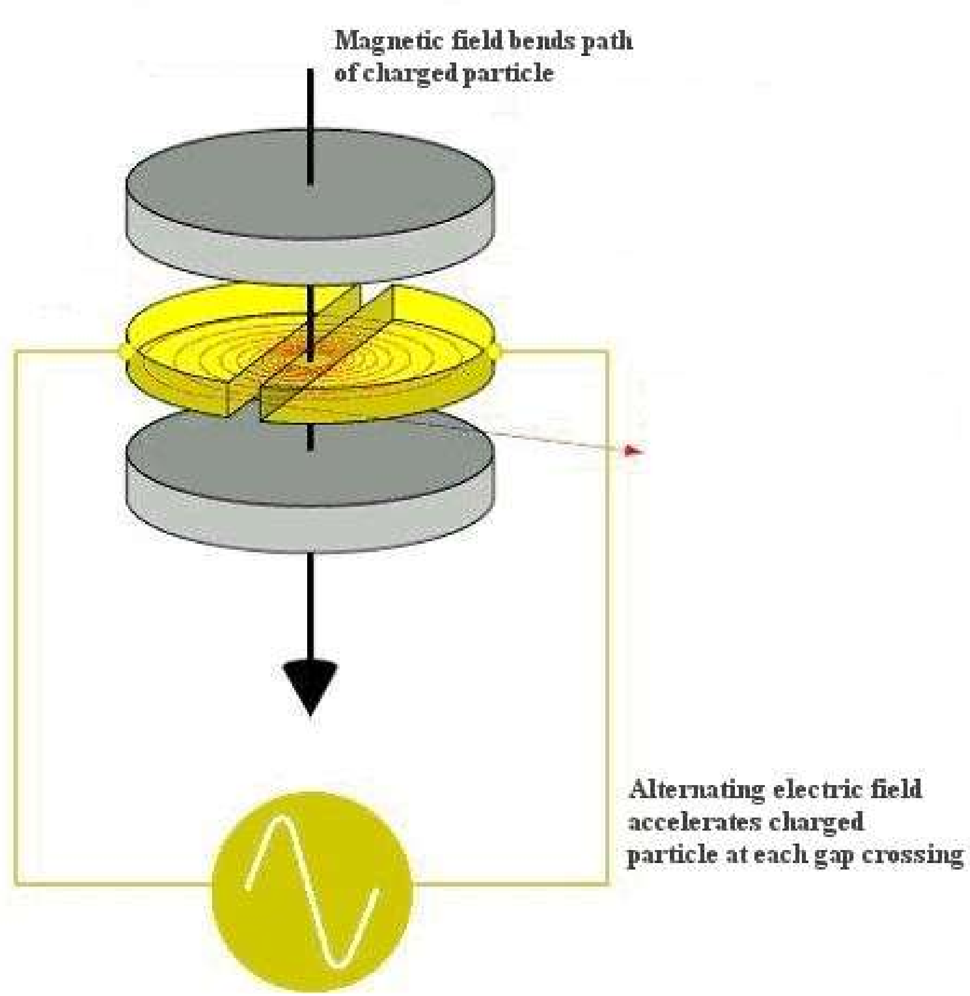
- Usually light-ion accelerators: protons (most common), $^{2}H$, $^{3}He$, $^{4}He$
- Typically accelerated by electric fields (electostatic accelerators & cyclotrons)
- Energy range of 10 – 25 MeV protons will result in spallation reactions = lots of isotopes
- Need targetry (gas, liquid and solid targets)
- Need radiochemical separation & purification

# Cyclotron Production of Medical Isotopes

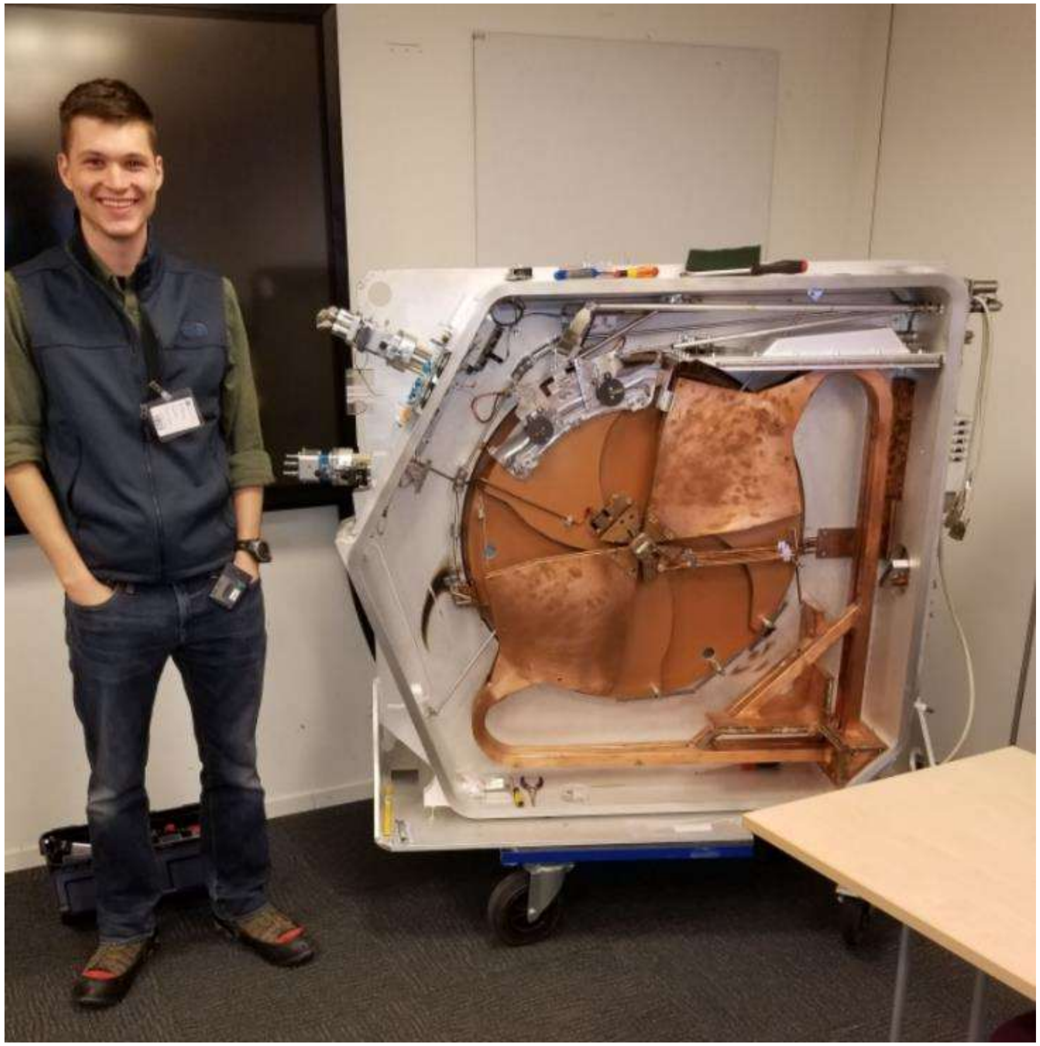
- Over 1500 cyclotrons world-wide dedicated to medical radioisotope production…(244 in US)

# Why Cyclotrons?

- Cyclic or repetitive application of force… allows small force to be used many times
- Small device
- High power



# GE PETtrace



# UAB TR24

# Which Nuclear Reactions?

- Governed by charged particle excitation functions
- Low energies = low σ usually
- σ usually increases to a maxima and then decreases due to competing reaction channels
- Usually much lower σ

than for neutron reactions

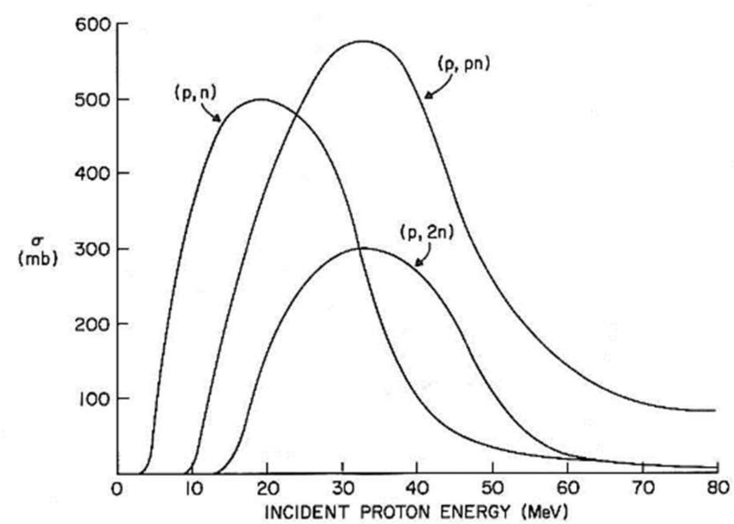



**Figure 4.4.** Excitation functions for several common proton-induced reactions on the same low-*Z* target nuclide.

# Production of Radioactive Nuclei

- Rate of production of a radioactive nucleus:

$$\frac{dN}{dt} = R - \lambda N$$

$$\frac{dN}{dt} = \sigma\Phi N_{tgt} - \lambda N$$

Rearranging gives:

$$\frac{dN}{\sigma\Phi N_{tgt} - \lambda N} = dt$$

Take the integral of both sides:

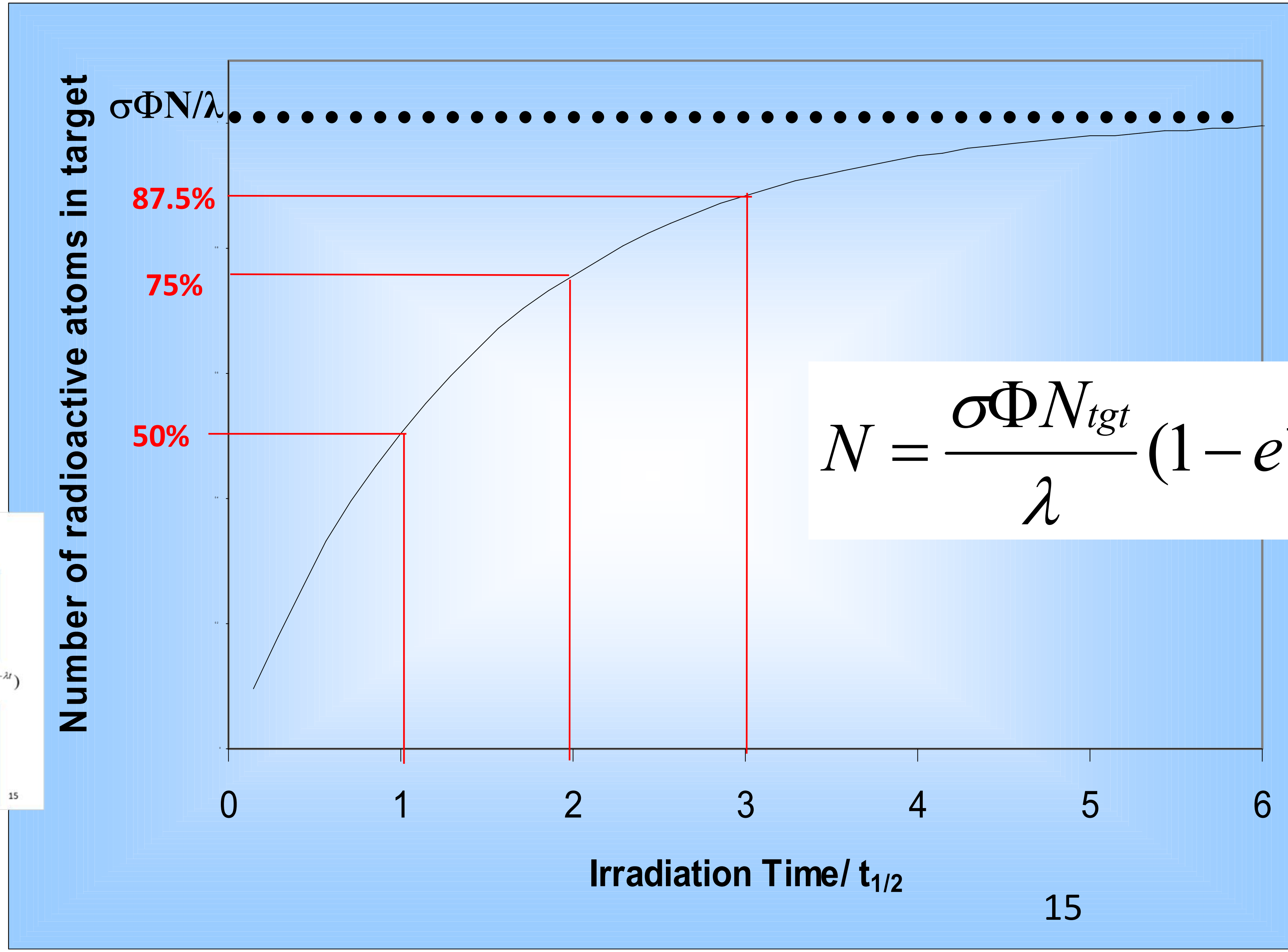
$$\int \frac{dN}{\sigma\Phi N_{tgt} - \lambda N} = \int dt$$

Solution:

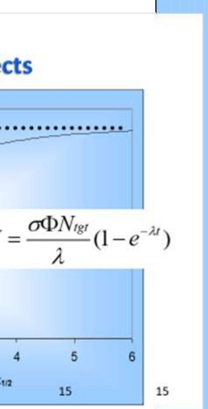
$$N = \frac{\sigma\Phi N_{tgt}}{\lambda}(1 - e^{-\lambda t})$$

$$A = \sigma\Phi N_{tgt}(1 - e^{-\lambda t})$$

# Saturation Effects

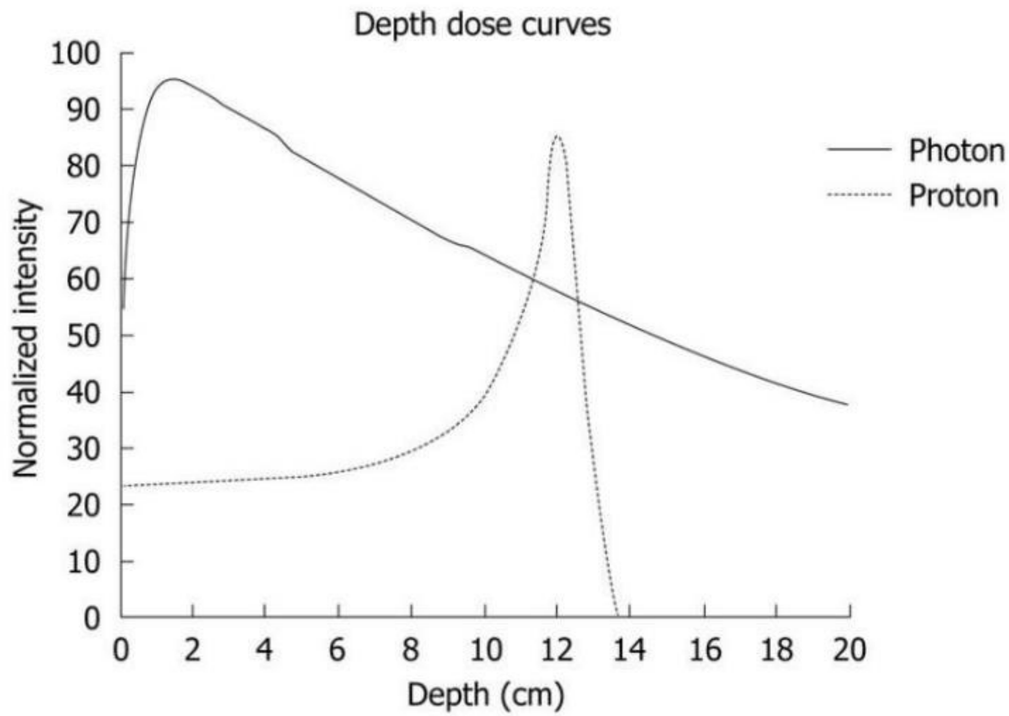



$$N = \frac{\sigma \Phi N_{tgt}}{\lambda}(1 - e^{-\lambda t})$$



# Targetry: Interation of Radiation & Matter

- Bragg Peak, high energy deposition in a very small area



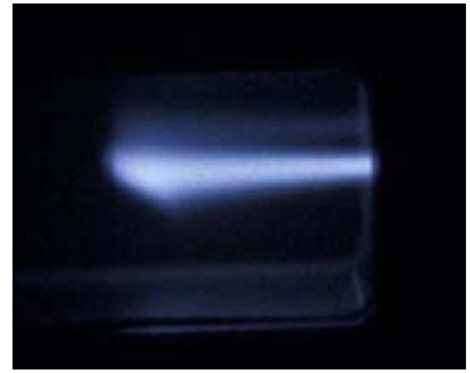

- Charged particle range depends on energy, mass, charge and target material

# Accelerator Targets

1. **Gases:**

   $^{14}N(d,n)^{15}O$ — ($^{14}N_2$)

   $^{14}N(p,\alpha)^{11}C$ — ($^{14}N_2$)



2. **Liquids:**

   $^{16}O(p, \alpha)^{13}N$ — ($H_2{}^{16}O$)

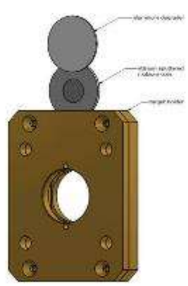
   $^{18}O(p,n)^{18}F$ — (enriched $H_2{}^{18}O$)

3. **Solids**:

   $^{64}Ni(p,n)\ ^{64}Cu$ — (enriched metallic $^{64}Ni$)

   $^{89}Y(p,n)^{89}Zn$ — (metallic $^{89}Y$)

   $^{68}Zn(p,2n)^{67}Ga$ — (enriched metallic $^{68}Zn$)



# Accelerator Targets

- Solid Target Materials:
  - Thermally conducting
  - High melting point
  - Low amount of “activation”
  - Easy to machine
  - Non-toxic
  - Separable from desired radioisotope…

# Solid Target Issues

- Less common
- Often use enriched materials ($$$)
- Heating issues
- Wide variety of isotopes possible
- Usually, more chemistry required for the separation (begin with dissolution or distillation)

# Solid Targets

| Radionuclide | Half-life | Decay | Production Reaction | Medical Use |
|---|---|---|---|---|
| Copper-64 | 12.7 h | EC/$\beta^-$/$\beta^+$ | Cyclotron | Imaging/Therapy |
| Copper-67 | 2.58 d | $\beta^-$ (γ, 184.6 keV) | High Energy Accelerator | Therapy |
| Gallium-67 | 3.26 d | EC (γ, 184.6 keV) | Cyclotron | Imaging |
| Bromine-76 | | | | |
| Yttrium-86 | 14.7 h | EC/$\beta^+$ | Cyclotron | Imaging |
| Zirconium-89 | 3.27 d | EC/$\beta^+$ | Cyclotron | Imaging |
| Indium-111 | 2.80 d | EC (γ, 171.3 keV) | Cyclotron | Imaging |
| Thallium-201 | 3.04 d | EC (γ,167.4 keV) | Cyclotron | Imaging |

# Radiopharmaceuticals

- A **radiopharmaceutical** is a drug labeled with a radionuclide to image a biological process or to deliver therapy to a specific disease site
  - the overall chemical structure determines biological properties
  - the radionuclide determines imaging or therapeutic properties

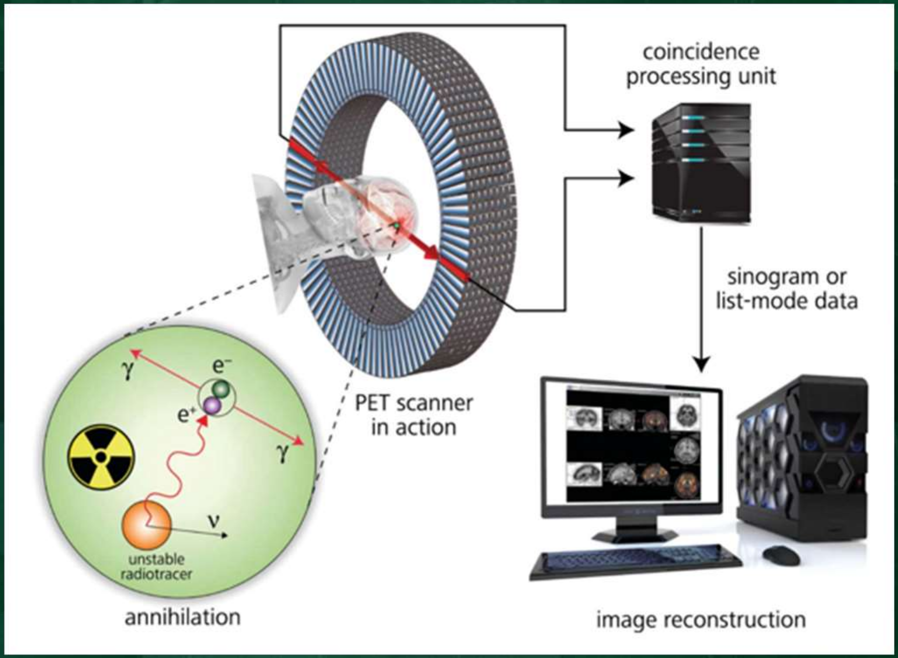


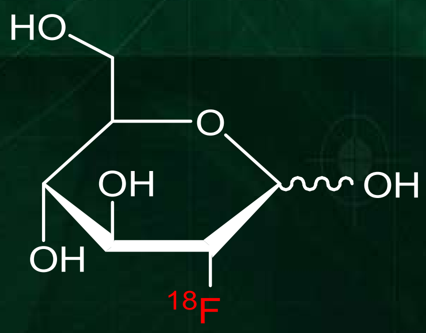
D-glucose

2-[$^{18}$F]fluoro-2-deoxy-D-glucose (FDG)

# Positron Emission Tomography

PET imaging is a very sensitive tool capable of providing quantitative information about biochemical and physiological processes in a non-invasive manner.




2-[$^{18}$F]fluoro-2-deoxy-D-glucose (FDG)

# Positron Emission Tomography

**FDG: 59-year-old woman with T-cell lymphoma**


Initial study


4 months later,
after chemotherapy

# Why Develop New Imaging Agents?

- Imaging more than detection of disease:
  - Oncology
  - Neurology
  - Cardiology
- Imaging can provide more information: detection, cell proliferation, amyloid burden, receptor status, oxygenation, microenvironment, immune cell infiltration…………
- **Prediction of treatment response.**

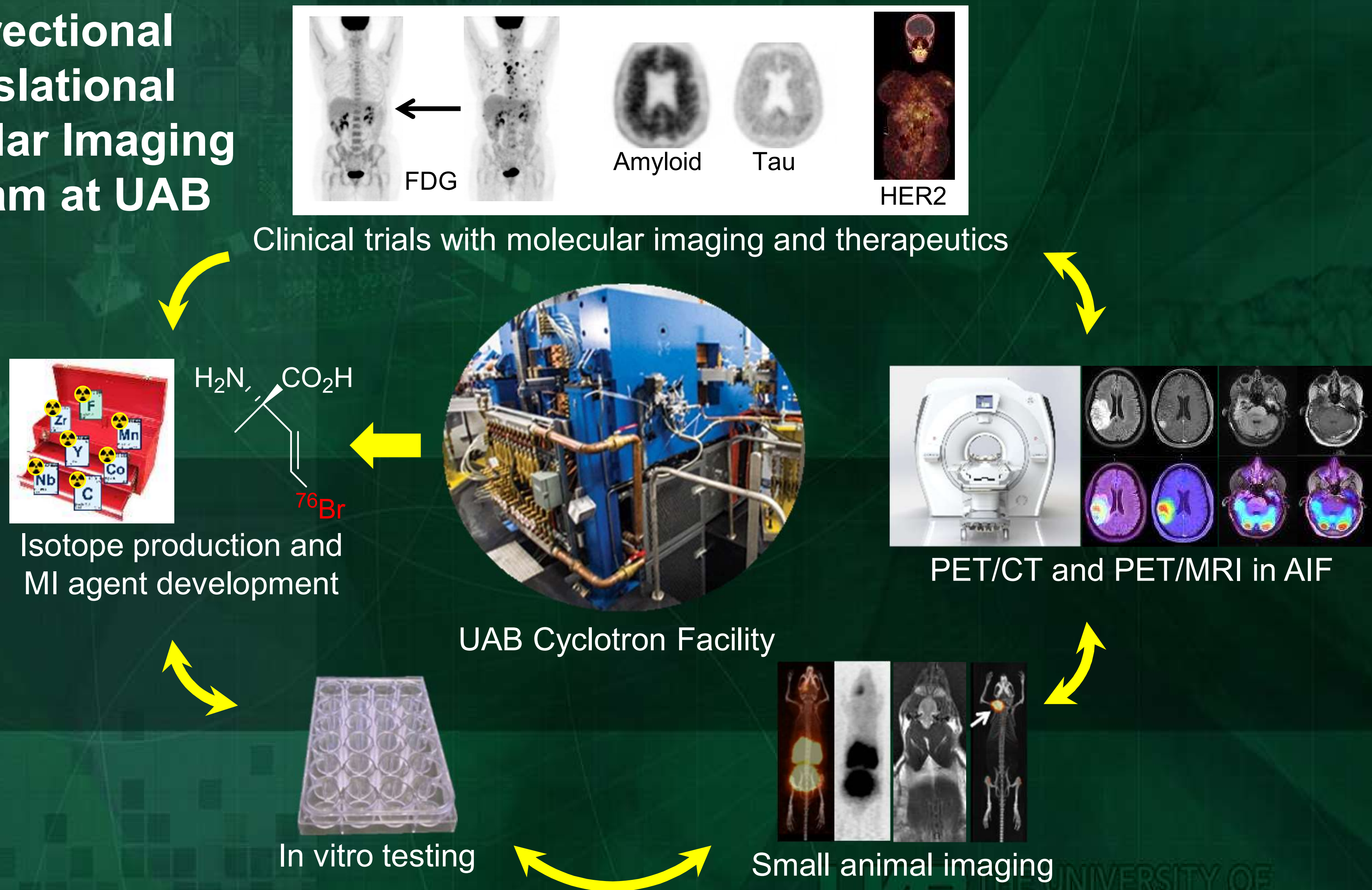
# Expanding the Toolbox of Imaging Agents


[$^{18}$F]FDG


[$^{68}$Ga]DOTATATE

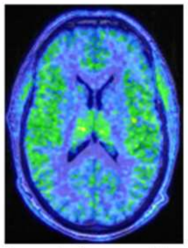
*Courtesy J. McConathy, UAB*

# Bidirectional Translational Molecular Imaging Program at UAB

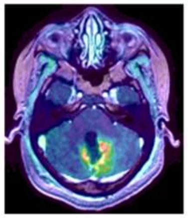


# Status of Active Radiotracers for Human Use at UAB

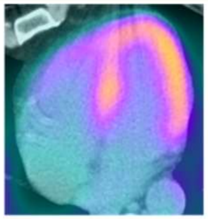
| Radiopharmaceutical | Use |
|---|---|
| [$^{18}$F]FLT | Proliferation |
| [$^{13}$N]$NH_3$ | Cardiac blood flow |
| [$^{68}$Ga]DOTATATE | SSTR status |
| [$^{18}$F]FMISO | Hypoxia |
| [$^{89}$Zr]Trastuzumab | HER2 status (breast cancer) |
| [$^{18}$F]FET | Amino acid transport |
| [$^{11}$C]PiB | Amyloid |
| [$^{18}$F]DPA-714 | TSPO (neuroinflammation) |
| [$^{68}$Ga]PSMA-11 | PSMA status (prostate cancer) |
| [$^{89}$Zr]Panitumumab | EGFR status (colon cancer) |
| [$^{18}$F]AV1451 | Tau protein |
| [$^{68}$Ga]GZP* | Granzyme B (Immune Activation) |
| [$^{11}$C]Acetate | Cardiac Metabolism |
| [$^{89}$Zr]Oxine/White Blood Cells* | WBC tracking |
| [$^{18}$F]FES | Estrogen receptor |
| [$^{68}$Ga]FAP-2286 | Fibroblast Activation Protein |



Neuroinflammation through TSPO in microglia
[$^{18}$F]DPA-714



Amino acid transport in neuro-oncology
[$^{18}$F]FET

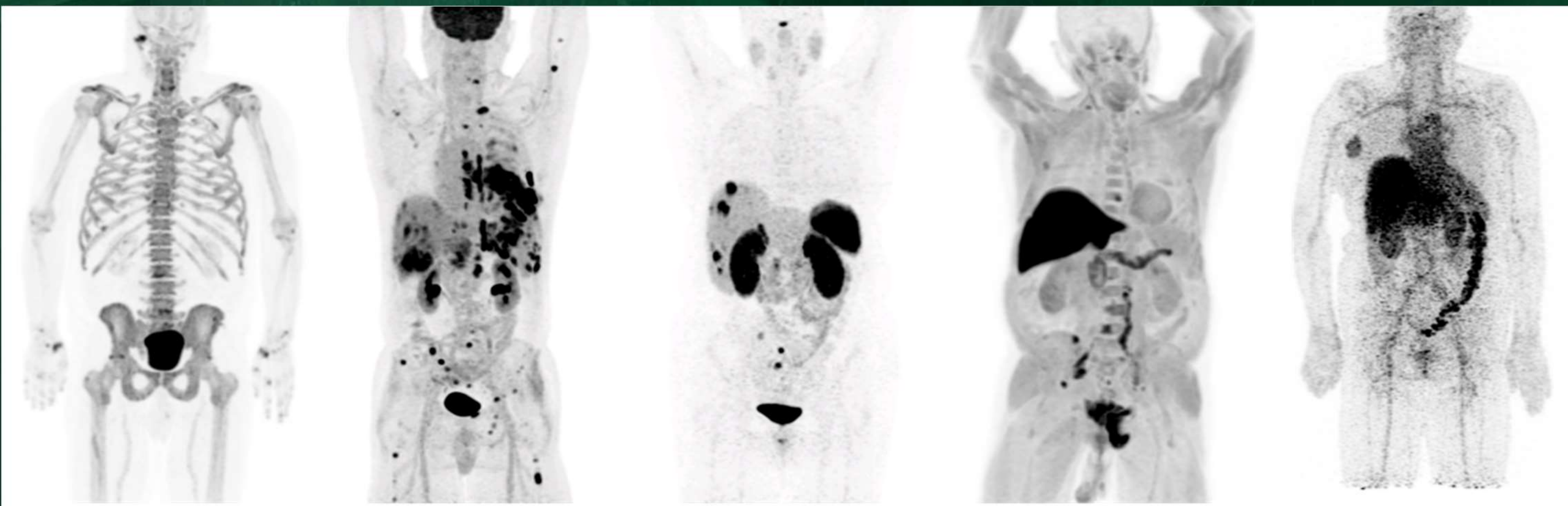


Myocardial perfusion
[$^{13}$N]ammonia

HER2 as a target for therapy in breast cancer
[$^{89}$Zr]trastuzumab

*First in human compound

# Whole body PET tracers in use at UAB for oncology



Bone turnover in skeletal metastases [$^{18}$F]fluoride

Glucose metabolism in many cancers [$^{18}$F]FDG

Somatostatin receptors in neuroendocrine cancers [$^{68}$Ga]DOTATATE

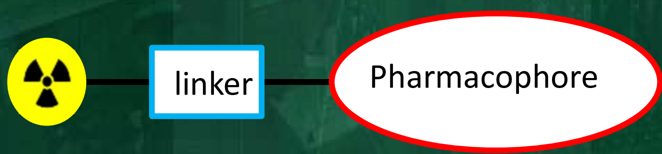
Amino acid transport in prostate cancer [$^{18}$F]fluciclovine

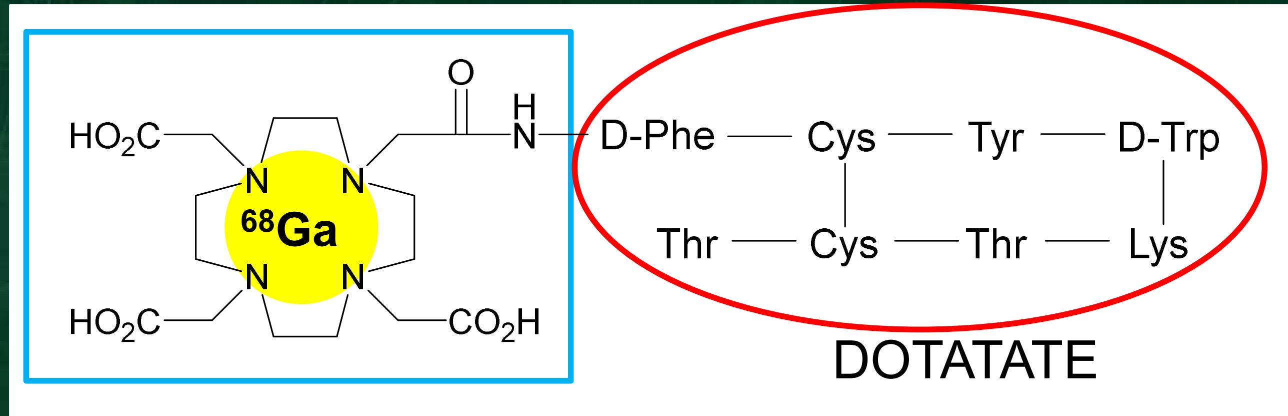
HER2 as a target for therapy in breast cancer [$^{89}$Zr]trastuzumab

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Knowledge that will change your world

# Theranostics and radionuclide therapy for cancer



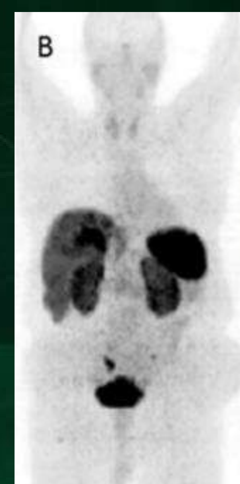




- Some radiopharmaceutical can be labeled for imaging and for therapy: **theranostic approach**

- Radionuclide therapies can succeed after other therapies fail.

- Imaging often guides therapy by demonstrating the entire tumor burden expresses the therapeutic target

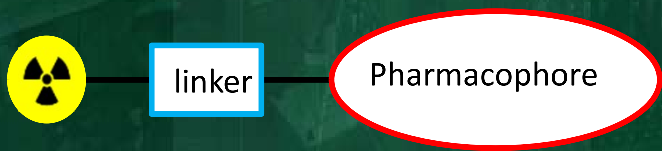
[$^{68}$Ga]DOTATATE for imaging (NETSPOT)

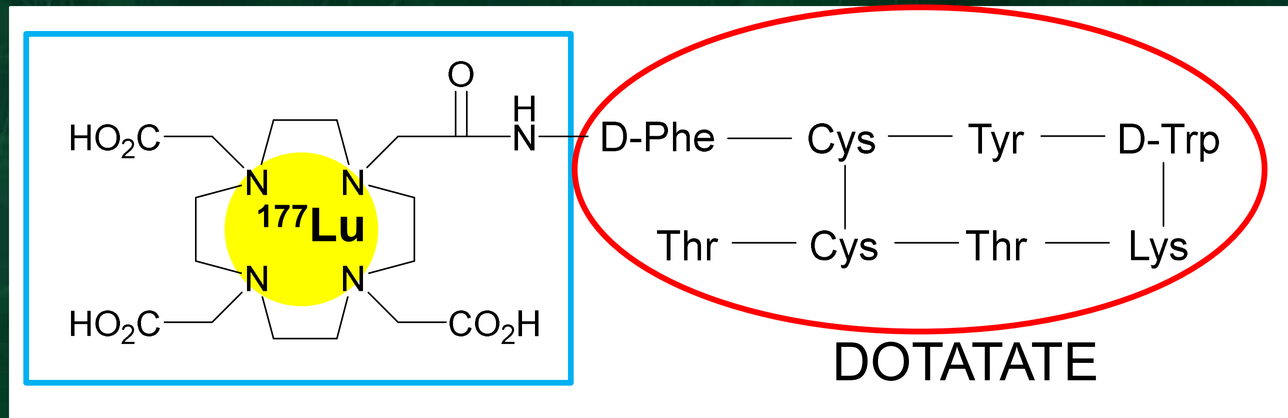



[$^{68}$Ga]DOTATATE


[$^{177}$Lu]DOTATATE

# Theranostics and radionuclide therapy for cancer



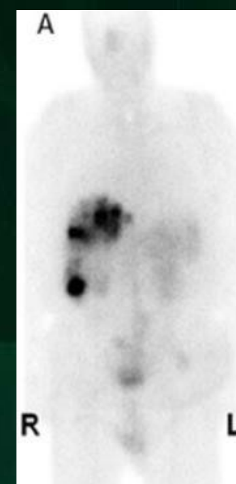

- Some radiopharmaceutical can be labeled for imaging and for therapy: **theranostic approach**

- Radionuclide therapies can succeed after other therapies fail.

- Imaging often guides therapy by demonstrating the entire tumor burden expresses the therapeutic target

[$^{68}$Ga]DOTATATE for imaging (NETSPOT)


[$^{68}$Ga]DOTATATE




[$^{177}$Lu]DOTATATE

**[$^{177}$Lu]DOTATAE for imaging (Lutathera)**

# Heavy Ion Production @ Notre Dame

A HEAVY-ION APPROACH TO RADIOMEDICINE

A Dissertation

Submitted to the Graduate School

of the University of Notre Dame

in Partial Fulfillment of the Requirements

for the Degree of

Doctor of Philosophy

by

Sean R. McGuinness

2021

# Heavy Ion Production @ Notre Dame

$$ {}^{4}_{2}He + {}^{75}_{33}As \rightarrow {}^{79}_{35}Br^{*} \rightarrow {}^{77}_{35}Br + 2n $$

$$ {}^{1}_{1}H + {}^{78}_{34}Se \rightarrow {}^{79}_{35}Br^{*} \rightarrow {}^{77}_{35}Br + 2n $$

$$ {}^{16}\mathrm{O} + {}^{63}\mathrm{Cu} \longrightarrow {}^{79}\mathrm{Rb}^{*} \longrightarrow {}^{77}\mathrm{Kr} + p + n $$

$$ {}^{16}\mathrm{O} + {}^{63}\mathrm{Cu} \longrightarrow {}^{79}\mathrm{Rb}^{*} \longrightarrow {}^{76}\mathrm{Kr} + p + 2n $$

$$ {}^{16}\mathrm{O} + {}^{63}\mathrm{Cu} \longrightarrow {}^{79}\mathrm{Rb}^{*} \longrightarrow {}^{76}\mathrm{Br} + 2p + 2n $$

$$ {}^{16}\mathrm{O} + {}^{65}\mathrm{Cu} \longrightarrow {}^{81}\mathrm{Rb}^{*} \longrightarrow {}^{77}\mathrm{Kr} + p + 3n $$

$$ {}^{16}\mathrm{O} + {}^{65}\mathrm{Cu} \longrightarrow {}^{81}\mathrm{Rb}^{*} \longrightarrow {}^{76}\mathrm{Br} + 2p + 3n $$

# Heavy Ion Production @ Notre Dame

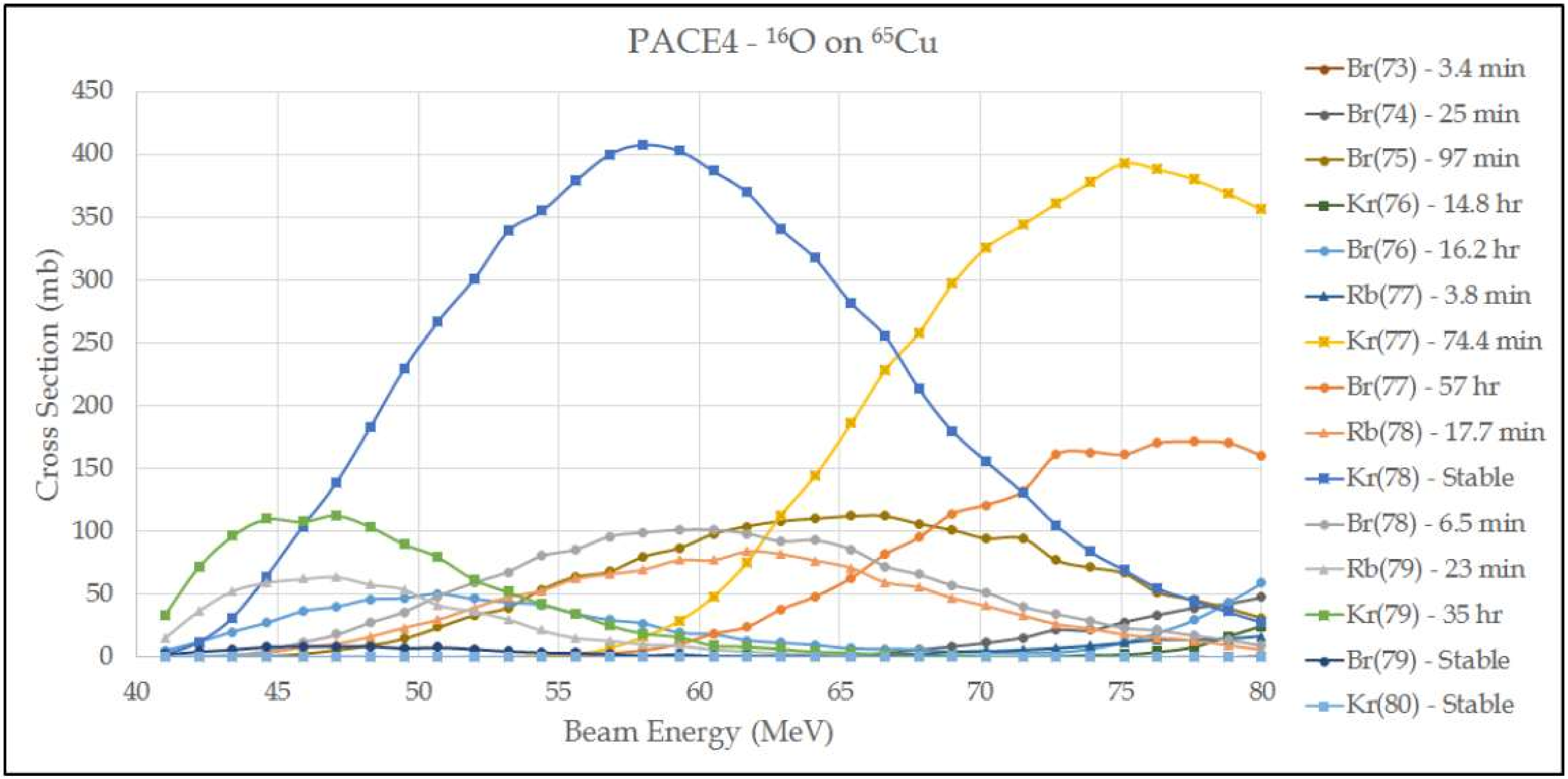
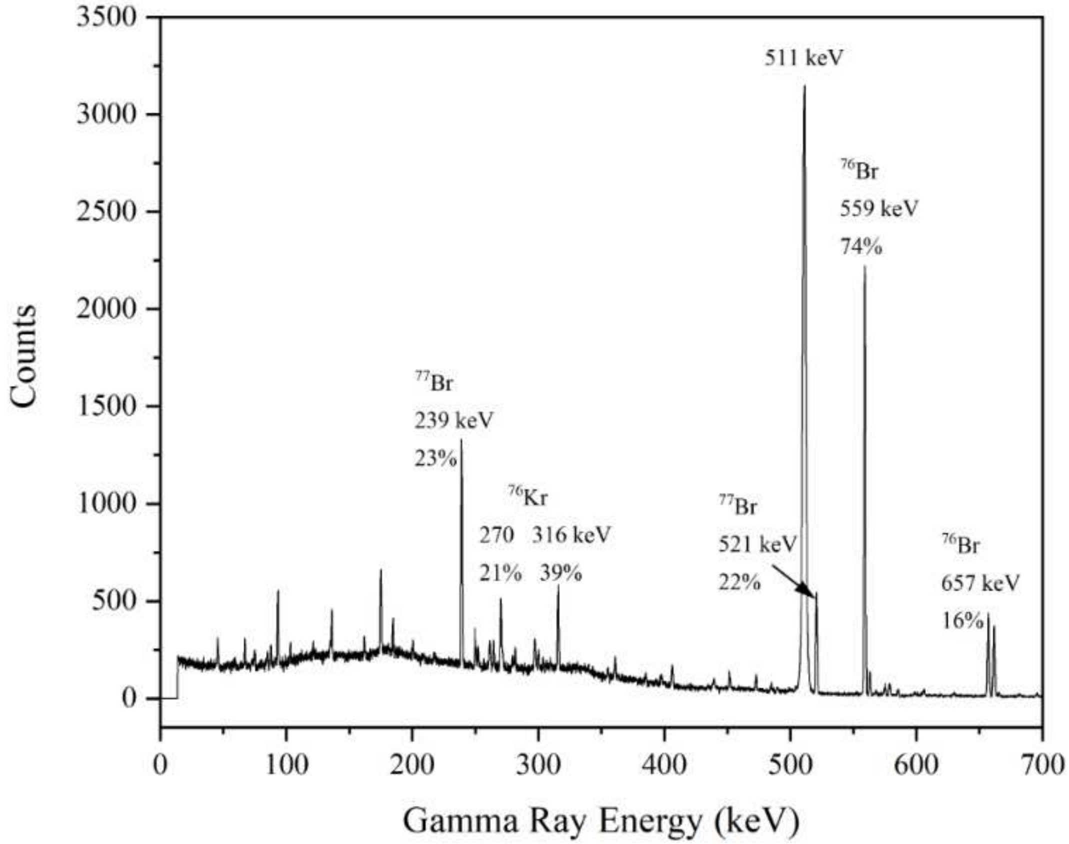



Figure 3.6. PACE4 predicted cross sections for $^{16}O$ on $^{65}Cu$.

# Heavy Ion Production @ Notre Dame

72 MeV $^{16}O$ on $^{nat}Cu$ - 16 hr EOB




| $^{16}O$ on $^{nat}Cu$ 72.0 MeV | | $^{16}O$ on $^{nat}Cu$ 55.0 MeV | |
|---|---|---|---|
| 1500 s | 111 pnA | 1200 s | 8.4 pnA |
| Predicted | Measured | Predicted | Measured |
| $1281^* \pm 260$ | <LOD* | 44.7±9 | 51.5±0.04 |
| 9.21*±1.8<br>37.7**±7.5 | 5.0*±1.4 | 0.33±0.1 | 1.0±0.5 |
| 139±28 | 18.9±4.5 | 1.05±0.2 | 0.95±0.3 |
| 134±27 | 34.6±3.5 | 1.74±0.4 | 2.1±1.4 |

# Summary

- Radioisotopes continue to play an important role in medicine and other areas of science. This role is expanding.
- A wide variety of half-lives, imaging characteristics and chemistries leads to a unique toolbox for the development of new nuclear medicine imaging and therapeutic agents.
- Development and increased use of these agents will require collaborations between chemists, biologists, physicists and physicians.

*gpeaslee@nd.edu*