Proiect IMAGO-MOL: Dezvoltarea imagisticii funcționale în regiunea Nord-Est

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Nuclear medicine

- Originates in the mid-1920s in Freiburg, Germany, when George de Hevesy made experiments with radionuclides administered to rats, displaying metabolic pathways of these substances and establishing the tracer principle.
- In 1936, John Lawrence made the first application in patients of an artificial radionuclide when he used phosphorus-32 to treat leukemia.
- December 7, 1946 an article was published in the Journal of the American Medical Association by Sam Seidlin.
    - The article described a successful treatment of a patient with thyroid cancer metastases using radioiodine (I-131).
    - Iodine use was later expanded to imaging of the thyroid gland, quantification of the thyroid function, and therapy for hyperthyroidism.
    - Benedict Cassen develops the first rectilinear scanner and
    - Hal O. Anger's invents the scintillation camera (Anger camera).

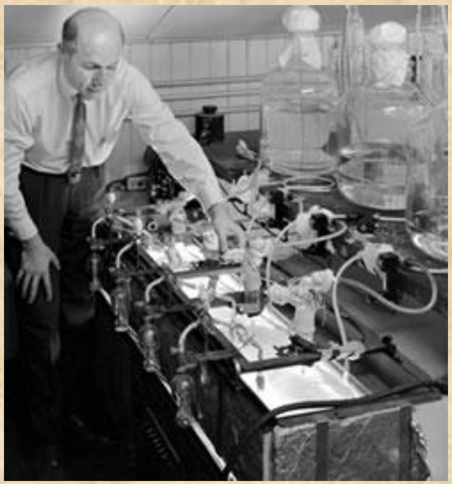


Figure 1. Samuel M. Seidlin, M. D. (1895-1955)

What is a good medical isotope?

For applications in medicine, nature and "man-made" physics approaches provide many different radionuclides to choose from.

The choice of radionuclide is critical for achieving successful diagnostic imaging and cancer treatment outcomes.

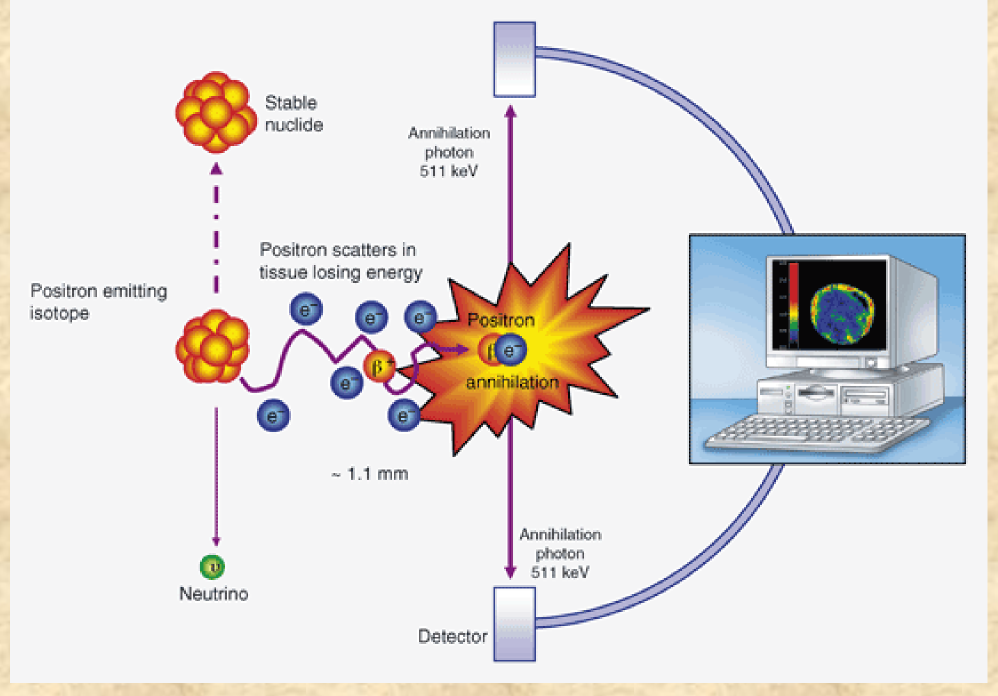
1) Diagnostic nuclear medicine: high quality images of activity in the patient, with low patient radiation dose

2) Therapeutic nuclear medicine: high amount of energy imparted to the target tissue (to destroy cancer cells) relative to critical normal organs and tissues (to prevent radiation damage and side-effects)

Medical isotope production methods

- Nuclear reactors
- Charged-particle accelerators
  - Proton cyclotrons, linear accelerators
  - Alpha-particle accelerators
  - Electron beam (x-ray) interactions
- Chemical separation from longer-lived parent isotopes

PET – positron emission tomography



Positron emission tomography (PET) is a test that uses a special type of camera and a tracer (radioactive chemical) to look at organs in the body.

A PET scan is often used to evaluate cancer, check blood flow, or see how organs are working.

- Study the brain's blood flow and metabolic activity.
- Alzheimer's disease, Parkinson's disease, multiple sclerosis, transient ischemic attack (TIA), amyotrophic lateral sclerosis (ALS), Huntington's disease, stroke, and schizophrenia.

- Evaluate cancers, especially lymphoma or cancers of the head and neck, brain, lung, colon, or prostate.

Find coronary artery disease.

Hungary – since 2007, Debrecen and Budapest

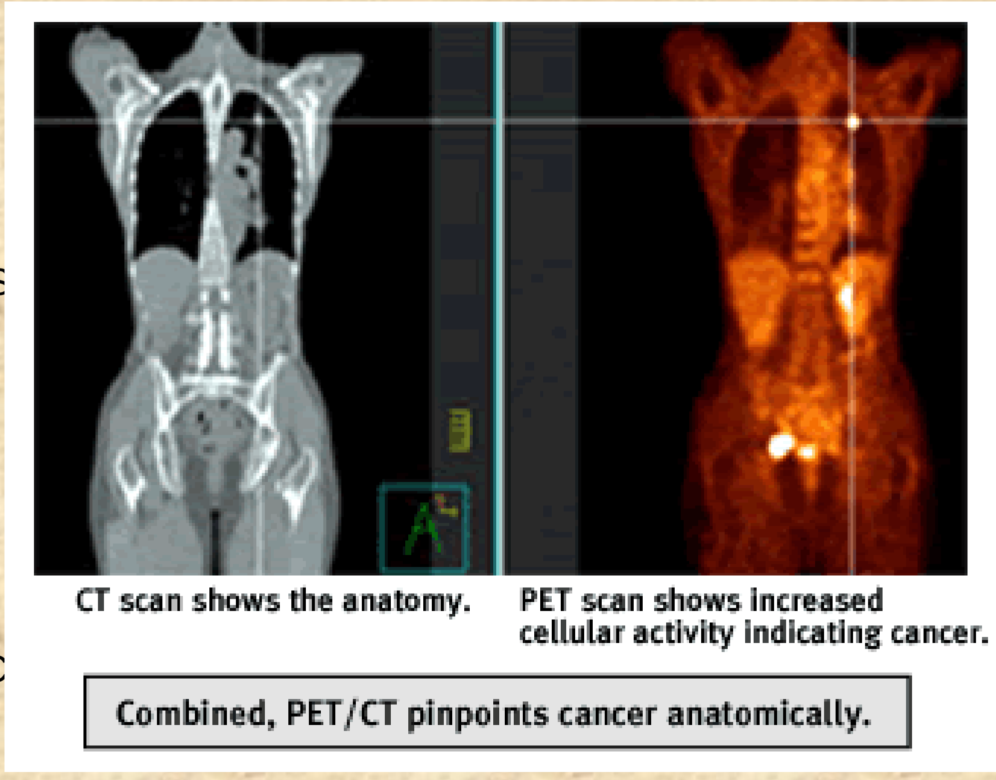
Bulgaria-

University Hospital "Alexandrovska".

Ukraine - Donetsk tumor center

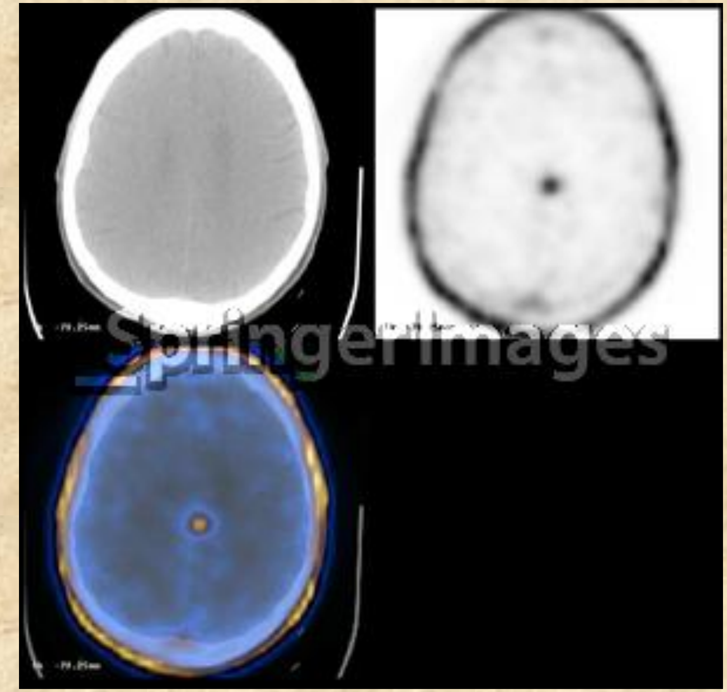
Positron emitters

- Cancer Metabolism and Functional Imaging
  - F-18-fluorodeoxyglucose (FDG) glucose analog, measures hexokinase activity (glucose metabolism), phosphorylated by hexokinase to F-18-FDG-6-PO4, elevated in tumor cells, chemically trapped in cells
  - F-18-amino acids (phenylalanine, tyrosine) image metastatic lesions
  - F-18-fluorothymidine measures thymidine kinase activity (DNA synthesis)
  - F-18-flouromisonidazol (FMISO) images tumor hypoxia
  - F-18-estradiol breast tumor detec



PET radiopharmaceuticals other than fluorine-18

- C-11-thymidine incorporates in DNA, indicates rapid metabolism
- C-11-choline incorporates in cell membrane phospholipids
- C-11-carbon monoxide indicates blood flow
- C-11-methionine amino acid uptake and protein metabolism
- C-11-acetate measures oxidative activity
- Ga-68-DOTATOC/DOTATATE imaging of somatostatin receptors in neuroendocrine tumors
- Cu-64-labeled antibody cancer receptor imaging
- Other positron-emitter antibody labels: Br-76, Br-77, As-72, Zr-89, I-124



Particle accelerators

► Commercial cyclotrons

- Accelerates charged hydrogen atoms (protons, deuterons)
- Energies 13-40 MeV and up to 100 MeV, current up to 2 mA
- Efficient, reliable, expensive to operate
- For production of proton-rich isotopes, including: ^{18}F, ^{82}Sr, ^{64}Cu, ^{15}C, ^{11}C, ^{77}Br, ^{77}Br, ^{124}I, ^{86}Y, ^{66}Ga, ^{60}Cu, ^{61}Cu, ^{89}Zr
- Several manufacturers: Ion Beam Applications (IBA, Belgium) Ebco Technologies (Canada) Sumitomo Heavy Industries, Ltd. (Japan) General Electric (United States) Siemens (Germany)

Left: 17 MeV GE PETtrace cyclotron

Right: Compact French 65 MeV cyclotron for proton and neutron therapy.

What are "compact systems"?

- "NEXT-GENERATION" APPROACH TO ISOTOPE PRODUCTION WHERE NUCLEAR REACTORS AND CYCLOTRONS ARE NOT AVAILABLE, TOO COMPLEX, OR TOO EXPENSIVE TO ACQUIRE AND OPERATE

Proton accelerators

Alpha accelerators

Neutron generators

Electron beam x-ray systems

Stable isotope plasma separation systems

Compact systems: proton accelerator

First U.S. 7 MeV proton linear accelerator for medical isotope production

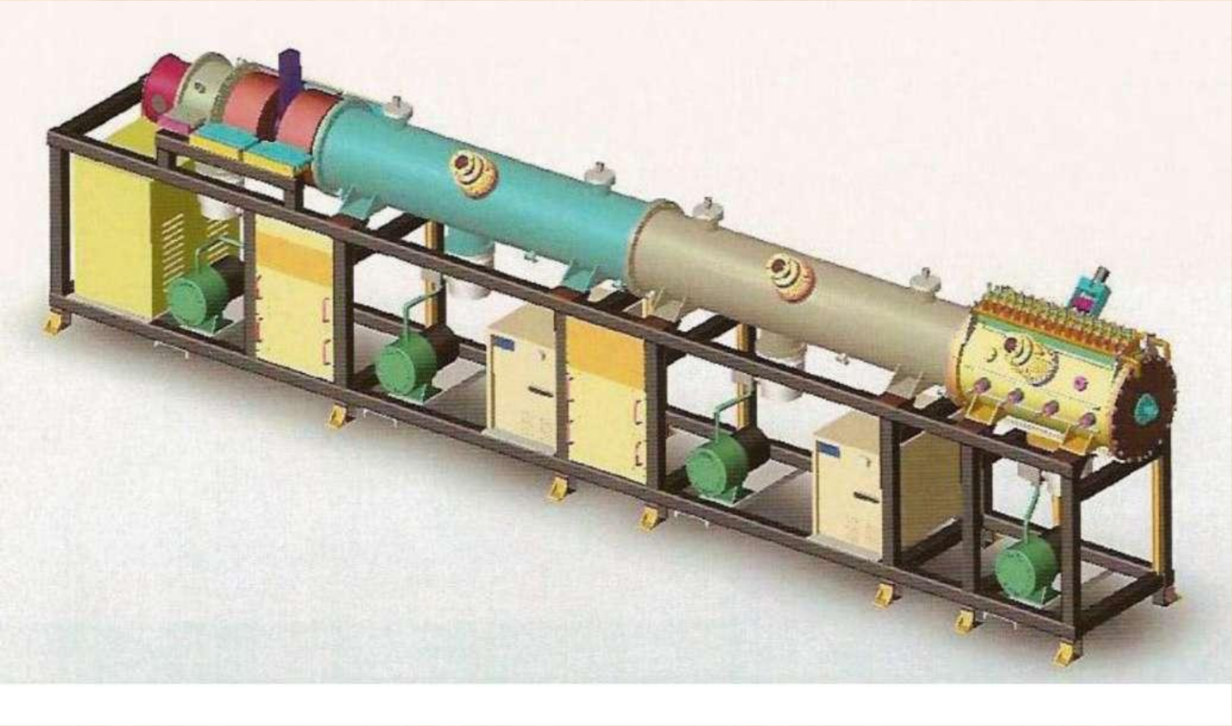
Up and running, producing ^{18}F for regional hospitals

For production of ^{18}F, ^{111}In, ^{123}I, ^{11}C, ^{13}N, ^{15}O

May be upgraded to 10.5 MeV

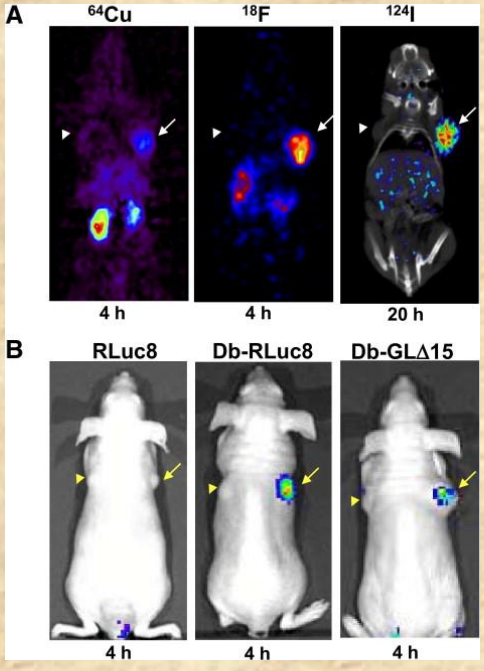
Compact systems: alpha linac

- Helium or deuterium accelerator up to 40 MeV at 1.5 mA m
- Radiofrequency quadrupole-driven confinement and acceleration
- Electron cyclotron resonant plasma source for helium ions
- For production of isotope such as: ^{117M}Sn, ^{225}Ac, ^{73}As, ^{55}Fe, ^{211}At, ^{109}Cd, ^{88}Y, ^{75}Se, ^{210}Po, etc.



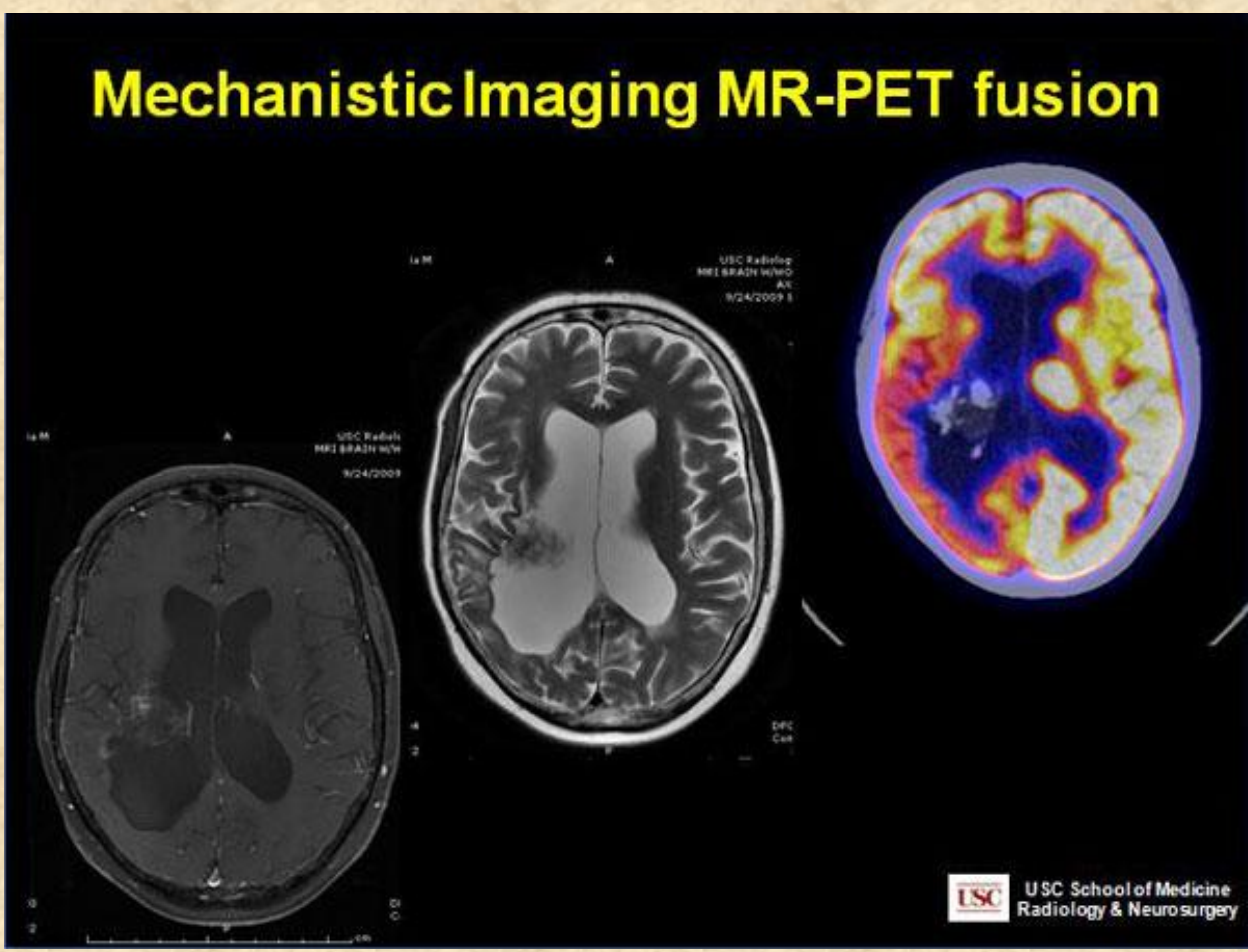
Estimated Costs for a medical cyclotrone

- \$1.2M - IBA 18/9 with ^{18}F targets, $^{18}F_2$, ^{11}C-CO_2, ^{11}C-CH_4, ^{13}N-NH4+ ^{15}O-H^2O, HCN module, H_2O module.
- \$400000 - vault and door
- \$100000 - one MIP4 double hot cell for research
- Synthesis modules are priced between \$60k and \$150k.



Neuroimaging

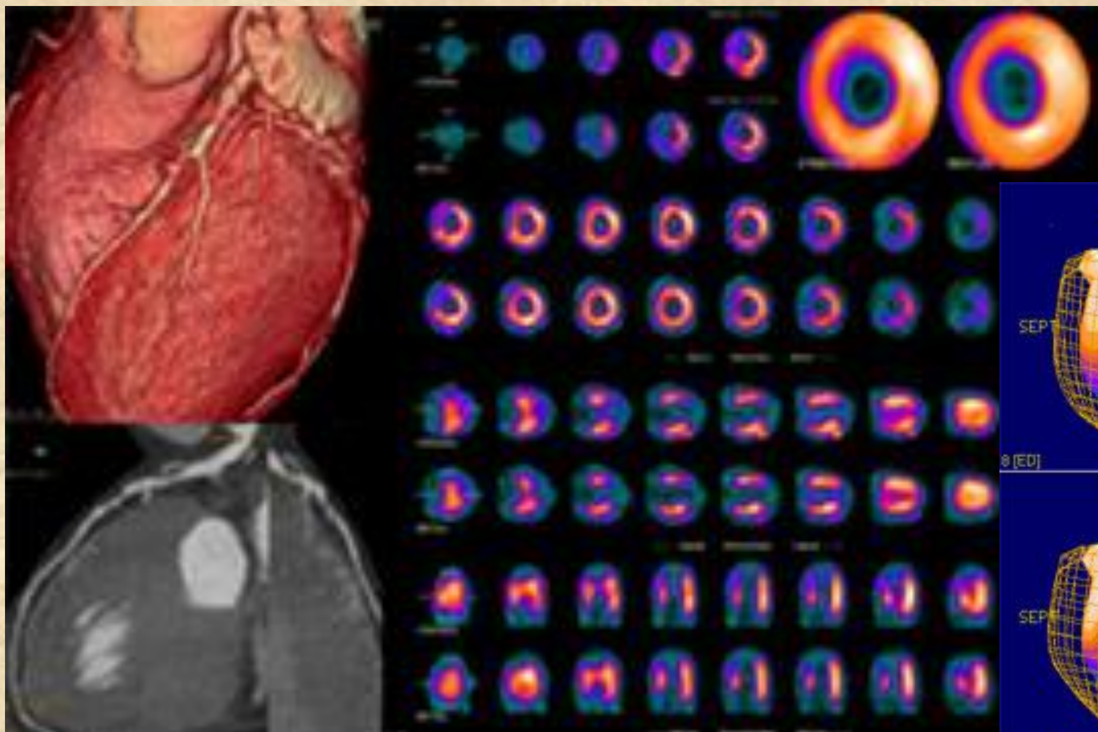
- F-18-FDG glucose metabolism, brain activity
- F-18-PIB binds amyloid placque in Alzheimer's disease
- F-18-fallypride targets dopamine receptors in neuropsychiatric disease and addiction
- C-11-raclopride dopamine receptors in addiction, alcoholism
- [C-11-]-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-Denzonitrile (DASB) binds to serotonin transporter for imaging depression

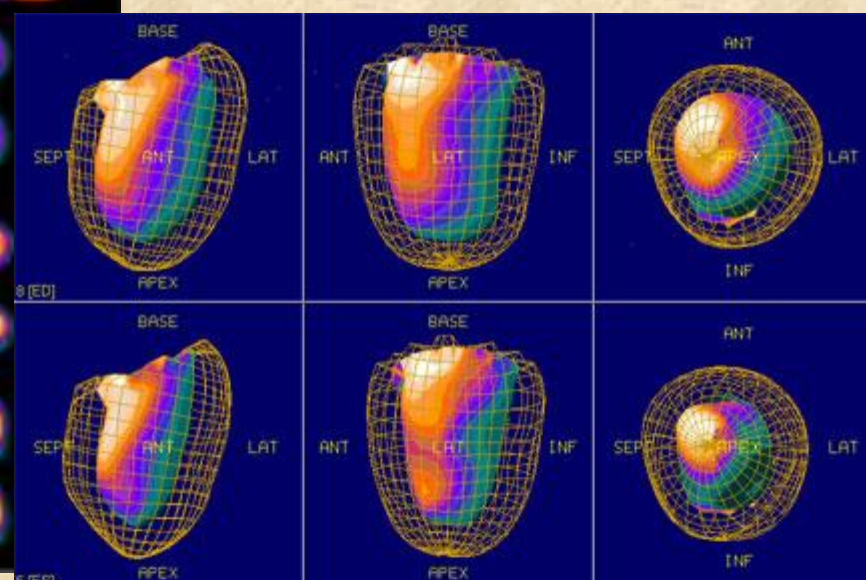


PET heart imaging

Cardiac Imaging

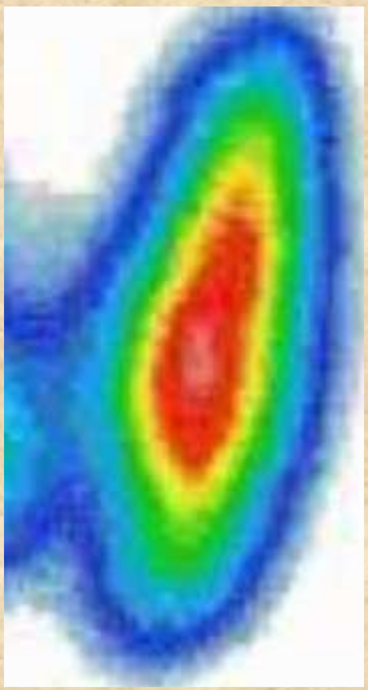
- F-18-FDG myocardial viability
- Ru-82-chloride (Sr-82) myocardial perfusion studies
- N-13-amonnia for assessing myocardial blood perfusion in the evaluation of coronary artery disease
- 0-15-water myocardial imaging
- C-11-palmitate and 11 -acetate for myocardial metabolism



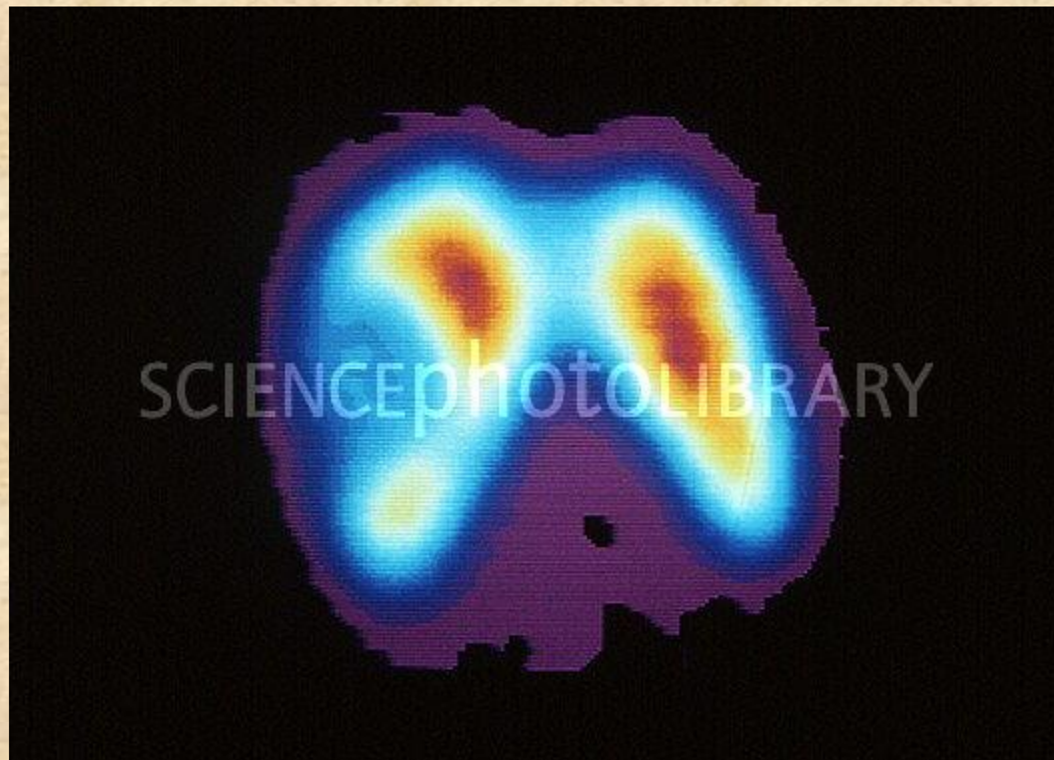


Therapy agents

- ► THYROID DISEASE (BENIGN AND MALIGNANT)
  - ■ IODINE-131 SODIUM IODIDE, ORAL
  - ■ TARGETS THYROID (HORMONE-SECRETING) TISSUES, SALIVARY GLANDS, CANCER METASTASES



I-131 scan of normal thyroid



Therapy agents

- Myeloproliferative diseases (bone marrow)
  - P-32 sodium phosphate (targets trabecular bone surfaces)
  - P-32 orthophosphate for polycythemia vera
  - Ho-166-DOTMP plus melphalan for multiple myeloma
- Malignant ascites (intraperitoneal cavity)
  - P-32 chromic phosphate colloid
  - Y-90 silicate, colloidal suspensions
  - Y-90-labeled anti-ovarian-cell antibodies
    - Targets cell-surface antigens
    - Problem achieving sufficiently high, uniform radiation doses

Therapy agents

Neuroendocrine tumors

- Radiolabeled somatostatin analog peptides (peptide receptor radionuclide therapy, PRRT)
- Target somatostatin receptors overexpressed on hormone-secreting tumors, internalizing
- Somatostatin, gastrin, bombesin, calcitonin, VIP, PACAP, GRP, oxytocin, a-MSH, GLP-1
- Conjugated with In-111, Y-90, Lu-177
- Y-90-DOTA-Tyr^3-Octreotides, octreotates

► Liver cancer

- P-32 albumin colloids (1970s)
- I-131- or Re-188-HDD-lipiodol fatty acid ester for treating nonresectable hepatocellular carcinoma by endocytosis (not effective for metastases, diffuse disease)

Y-90 silicate microspheres (Theraspheres, SIR-spheres) administered intra-arterially with lung shunt

Bone pain agents

P-32-orthophosphate
Sr-89 chloride (Metastron)
Sm-153-EDTMP phosphonate (Quadramet)
Ho-166-EDTMP phosphonate \ Sn-
117m(stannic 4+)-DTPA •Lu-177
DOTMP/EDTMP Re-188-hydroxyethylidene
diphosphonate (HEDP)
Re-186, -188-HEDP hydroxyethylidene
diphosphonate
Re-188 dimercaptosuccinic acid 1-131 –
α-amino(4-hydroxybenzylidene)-
disphosphonate Y-90
chloride
Ra-223-chloride (**AlphaRadin**)

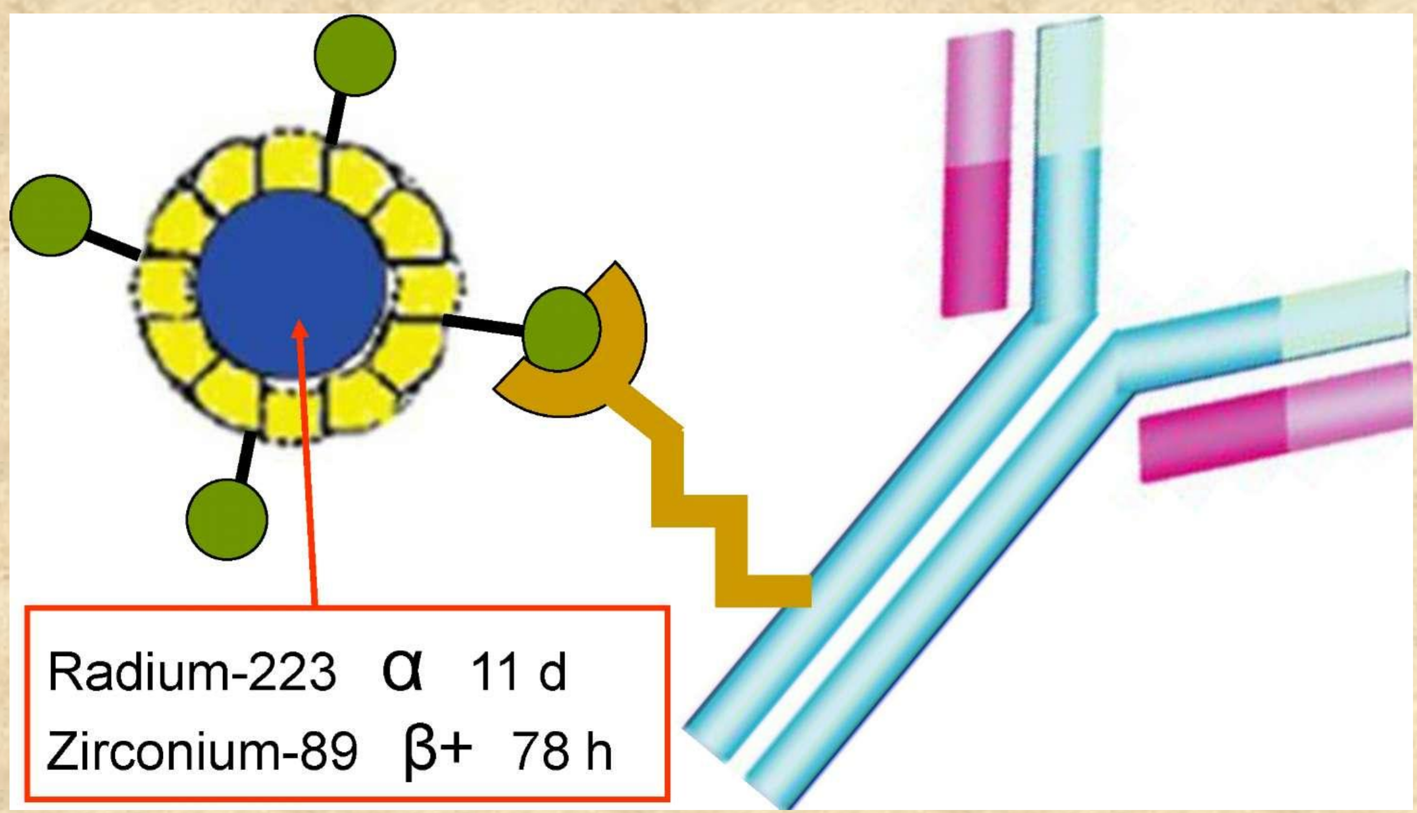
Radiogel polymer composites

- Direct injection/perfusion of non-resectable solid tumors
- Temperature-sensitive gelation
- Very high absorbed radiation doses achievable with sparing of adjacent normal tissues
- Improved localized distribution of radiation dose
- Applications in therapy of cancers of the prostate, brain, liver, pancreas, colon, kidney
- May be combined with imaging agents for ultrasound, MRI, gamma-camera, and PET

Sealed-source medical devices

- Intra-uterine, cervical brachytherapy
  - Ir-192, Cs-137 sealed sources
- Seed implants
  - 1-125, Pd-103, Cs-131, Au-198
- Y-90 microspheres (liver tumors)
- Y-90 eye plaques
- Y-90 intraocular therapy sources (age-related macular degeneration)

Novel immunoconjugate constructs



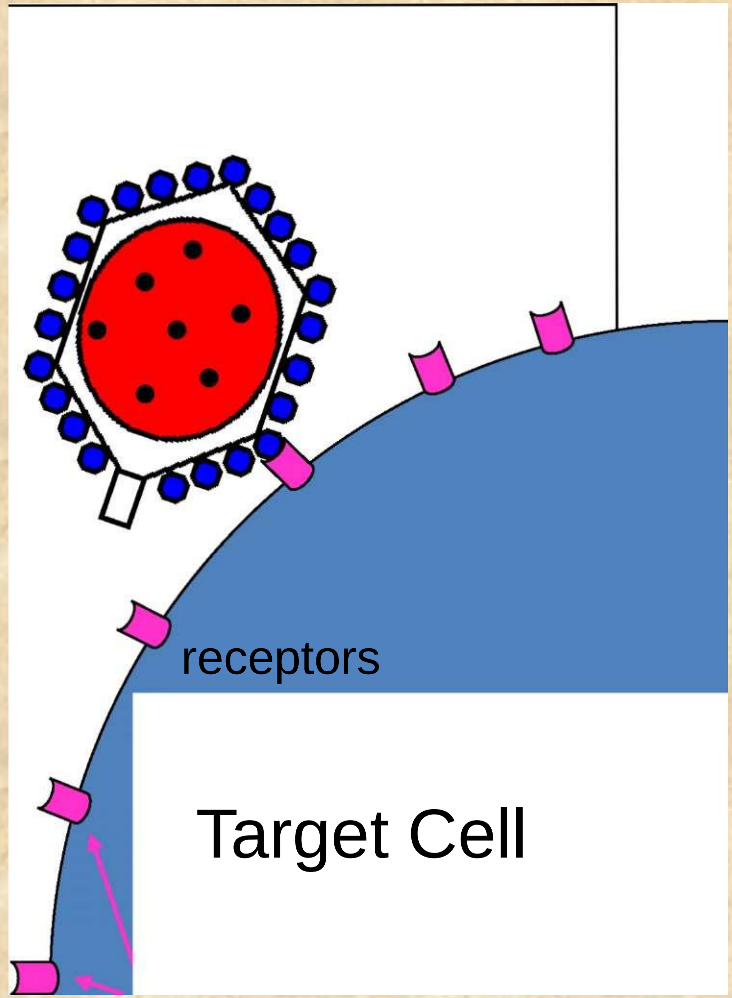
Apoferitin nanoparticle-biotin-streptavidin-antibody

Nanoparticle virus phage capsid

1. Fuse an affinity reagent by phage display or protein expression

2. Remove DNA

3. Replace with an insoluble radioisotope core



Project for IMAGO-MOL (Cyclotrone for PET and short-lived isotopes)

- **Diagnosis**
  - Hospitals
    - Neuroimaging
    - Heart imaging
  - Oncology Institute
  - PET, PET-CT, MRI-CT for the whole area, and for the whole country
- **Therapy**
  - Hospital
    - Endocrinology
  - Oncology institute
- **Research**
  - University of Medicine
    - Drug factories – radiolabeling, follow-up
    - Medical companies to produce brachytherapy implants
    - Chemistry research institutes
    - Pain research laboratories
      - Radiotracers
      - In vivo/in vitro experimentation
      - PET for small animals