Medical Isotope Production and Use

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Pacific Northwest
NATIONAL LABORATORY

Proudly Operated by Battelle *Since 1965*

Medical isotope production methods

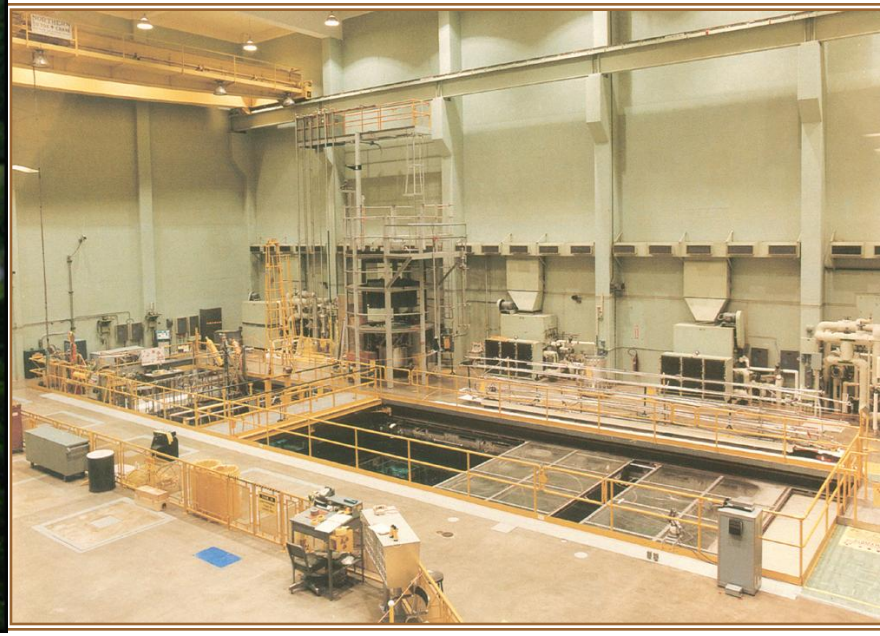
- Nuclear reactors
- Charged-particle accelerators
  - Proton cyclotrons, linear accelerators
  - Alpha-particle accelerators
  - Electron beam (x-ray) interactions
- Chemical separation from longer-lived parent isotopes
  - $^{90}Sr \rightarrow \beta^-$ + $^{90}Y \rightarrow \beta^-$ + ^{90}Zr (stable)
  - $^{224}Ra \rightarrow . . . \rightarrow {}^{212}Pb \rightarrow \beta^-$ + ^{212}Bi (alpha emitter)

Nuclear reactors

- National Research Universal (Chalk River, Ontario)
  - Operated by Chalk River Laboratories, AECL
  - 135 MW, low-enriched uranium fuel, high-enriched targets
  - Produces Mo-99, I-131, I-125, Xe-133, Ir-192
  - The major isotope-production facility in the world
  - Isotopes separated from targets and sold by MDS Nordion, Kanata, Ontario
  - Serves the isotope needs of 20 million patients per year

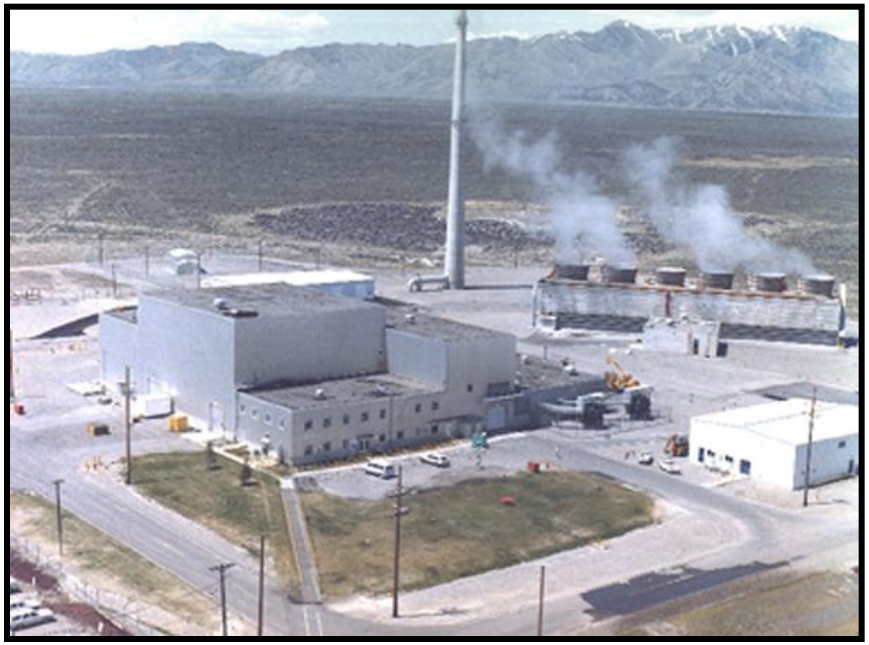
Nuclear reactors

- High-Flux Isotope Reactor (HFIR, Oak Ridge, TN)
  - Operated by Oak Ridge National Laboratory for DOE
  - Uses highly-enriched uranium fuel elements
  - 85 MW, 4E15 neutrons/cm^2-s^2, 26-day irradiation cycles
  - Produces Se-75, Cf-252, W-188/Re-188, Ni-63



Nuclear reactors

- Advanced Test Reactor (ATR, near Idaho Falls, ID)
  - Operated by Idaho National Laboratory for DOE
  - 85 MW, 4E14 n/cm^2-s^2, large core volume, 57-d irradiation cycles
  - Hydraulic tube for short-term target irradiations
  - Produces mainly cobalt-60



Co-60 is produced for medical “gamma knife” irradiators for high-precision treatment by external radiation of brain tumors

Particle accelerators

- Brookhaven Linac Isotope Producer (BLIP) on Long Island, NY
  - Operated by Brookhaven National Laboratory
  - 200 MeV/150 μA proton beam drawn from the Alternating Gradient Synchrotron
  - System for target insertion/retrieval
  - Main isotopes produced:

    Ge-68/Ga-68, and Sr-82/Rb-82, also Zn-65, Mg-28, Fe-52, Rb-83
  - Considerable down-times

Particle accelerators

- Isotope Production Facility (IPF) at Los Alamos, NM
  - 100 MeV/250 μA proton beam from the LANSCE 0.5 mile linear accelerator at TA-53
  - Targets processed at TA-48
  - Available 30-40 weeks per year
  - Main isotopes: Ge-68/Ga-68 and Sr-82/Rb-82, and also smaller amounts of Al-26, Si-32

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}O, ^{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 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.
- Objectives:

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)

Broad categories

Radiopharmaceuticals

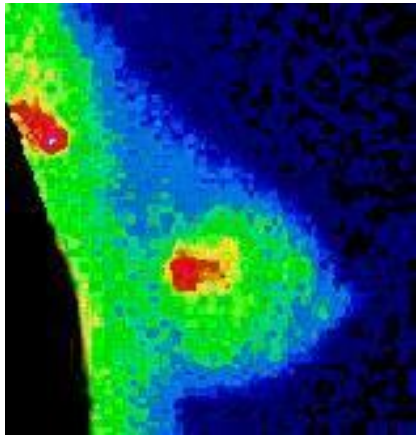
- Positron Emitters
- Beta/gamma Emitters
- Alpha Emitters

Medical Devices

- Sealed Sources
- Microsphere Applications
- Nanosphere Applications

Standard photon-emitter clinical imaging agents

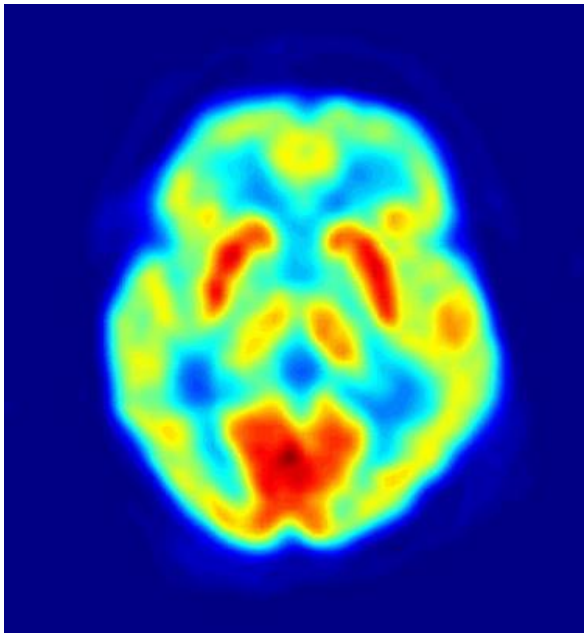
- Tc-99m (about 35 common diagnostic radiopharmaceuticals)
- I-131 sodium iodide
- In-111, I-123, Tl-201, Ga-67, Xe-133



Tc-99m-sestamibi scan shows breast tumor

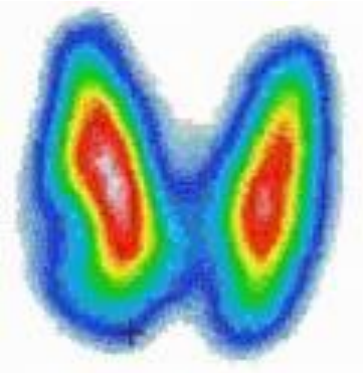
Positron emitters

- Cancer Metabolism and Functional Imaging
  - F-18-fluorodeoxyglucose (FDG) glucose analog, measures hexokinase activity (glucose metabolism), phosphorylated by hexokinase to F-18-FDG-6-PO_4, 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 detection



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

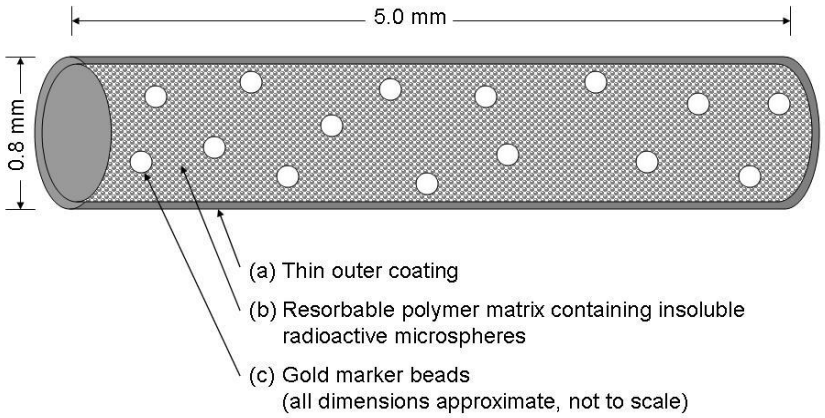
- Myeloproliferative diseases (bone marrow)
  - P-32 sodium phosphate (targets trabecular bone surfaces)
  - P-32 orthophosphate for polycythemia vera
  - Ho-166-DOTMP plus melphalan for multiple myeloma

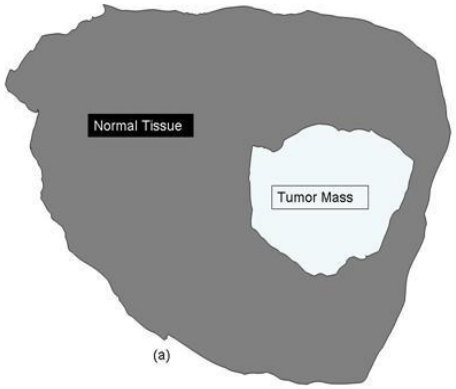
- Malignant ascites (intraperitoneal cavity)
  - P-32 chromic phosphate colloid
  - Y-90 silicate, colloidal suspensions
  - Y-90-labeled anti-ovarian-cell antibodies
    - Targets cell-surface antigens
    - Problem achieving sufficiently high, uniform radiation doses

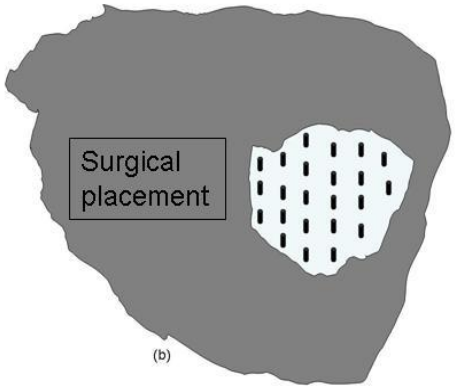
Sealed-source medical devices

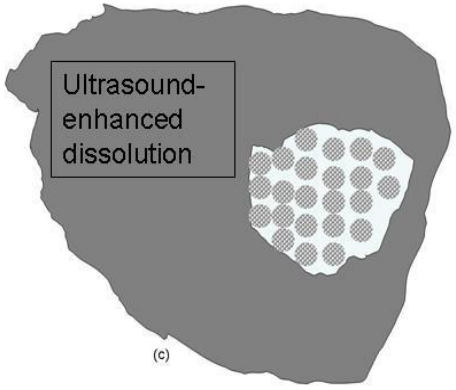
- Intra-uterine, cervical brachytherapy
  - Ir-192, Cs-137 sealed sources
- Seed implants
  - I-125, Pd-103, Cs-131, Au-198
- Y-90 microspheres (liver tumors)
- Y-90 eye plaques
- Y-90 intraocular therapy sources (wet age-related macular degeneration)

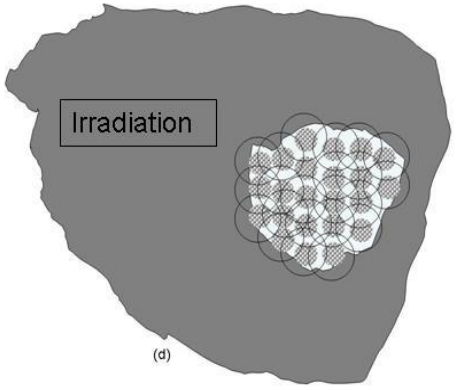
Next-generation Y-90 microsphere brachytherapy seed (prostate, brain, liver)





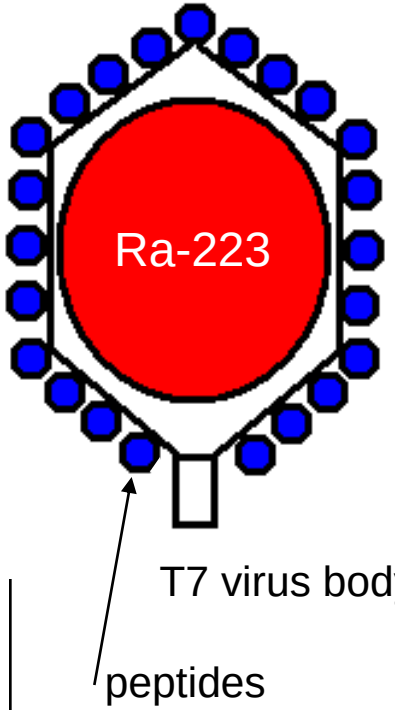




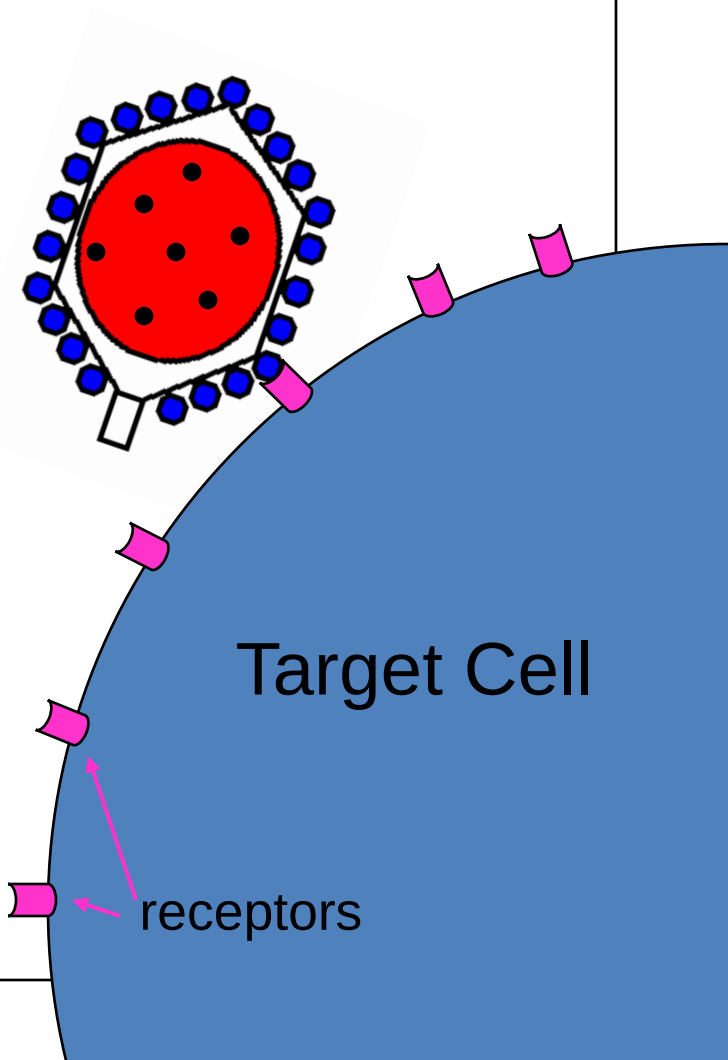


Advantage: controlled delivery of Y-90 microspheres

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



Radioisotopes used in diagnostic applications

Beta/gamma Emitters

Technetium-99m	Iodine-131	Indium-111	Thallium-201

Positron Emitters

Fluorine-18	Carbon-11	Oxygen-15	Nitrogen-13
Rubidium-82	Germanium-68	Copper-64	Copper-60
Copper-61	Bromine-76	Bromine-77	Iodine-124
Technetium-94m	Yttrium-86	Zirconium-89	Gallium-66

Auger-electron Emitters

Indium-111	Iodine-123	Iodine-125

Radioisotopes used in cancer treatment

Beta Emitters

Iodine-131	Strontium-89	Samarium-153	Holmium-166
Yttrium-90	Lutetium-177	Promethium-149	Gold-199
Copper-64	Rhenium-186	Rhenium-188	Others?
Copper-67	Tin-117m	Phosphorus-32	

Alpha Emitters

Astatine-211	Radium-223	Actinium-225	Terbium-149
Radium-224	Bismuth-212	Bismuth-213	Thorium-227

Auger-electron Emitters

Bromine-77	Indium-111	Iodine-123	Iodine-125