Imaging: PET and SPECT

Positron Emission Tomography

Single Photon Emission Computed Tomography

PET and SPECT

Properties of ideal imaging nuclides, biological, chemical , physical

Production of radionuclides
- **Nuclear fission**
- **Charged particle bombardment**

The Tc-99m Generator

Chemistry
- **Chelators vs organic chemistry**

Delivery strategies
- **Blood brain barrier**
- **Metabolic pathways**
- **Chemical affinity**

Clinical applications
- **Tumor imaging and staging**
- **Cardiac imaging**
- **Gene therapy**
- **Brain function**
- **Dopamine pathways, addiction**

Imaging

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Radionuclides

SI unit is the Becquerel (Bq)

1 Bq = 1 dps (disintegration per second)

old unit is the Curie (Ci)

1 Ci = 3.7 X 10^{10} dps

Activity (A) = *rate of decay*

N_o = number of active nuclei at time t = 0

N(t) is the number of active nuclei at time 't'

λ is the *decay constant*

λ = 0.693/T (T = half-life)

$$dN/dt = -\lambda N(t)$$

$$N(t) = N_o e^{-\lambda t}$$

$$A(t) = A_o e^{-\lambda t}$$

Effective Half-Life

Physical half-life, T_P [radioactive decay]

Biological half-life, T_B [clearance from the body]

$$A = A_0 e^{-\lambda_{phys}\, t}\, e^{-\lambda_{biol}\, t}$$

$$A = A_0 e^{-(\lambda_P + \lambda_D)t} \qquad \lambda_P + \lambda_B = \lambda_E$$

$$\frac{1}{T_E} = \frac{1}{T_B} + \frac{1}{T_P} \quad or \quad T_E = \frac{T_P T_B}{T_P + T_B}$$

Effective Half-Life

E.g., for an isotope with a 6-hr half life attached to various carrier molecules with different biological half-lives.

T_P	T_B	T_E
6 hr	1 hr	0.86 hr
6 hr	6 hr	3 hr
6 hr	60 hr	5.5 hr
6 hr	600 hr	5.9 hr

Effective Half-Life

Assume 10^6 Bq localized in a tumor site, vary T

Nuclide	Half-life (T)	λ (sec^{-1})	N
1	6 sec	0.115	8.7×10^{7}
2	6 min	1.75×10^{-3}	5.7×10^{9}
3	6 hrs	3.2×10^{-5}	3.1×10^{11}
4	6 days	1.3×10^{-6}	7.7×10^{12}
5	6 years	4×10^{-9}	2.5×10^{15}

Effective Half-Life

Assume 10^{10} atoms of radionuclide localized in a tumor site, vary T

Nuclide	Half-life (T)	λ (sec^{-1})	Activity (Bq)
1	6 sec	0.115	1.15×10^{9}
2	6 min	1.75×10^{-3}	1.7×10^{7}
3	6 hrs	3.2×10^{-5}	3.2×10^{6}
4	6 days	1.3×10^{-6}	1.3×10^{4}
5	6 years	4×10^{-9}	40

Production of Radionuclides

Reactor production, Nuclear fission

- **Heavy nuclides (A > 230) capture a neutron; tend to fission**
- **Daughter nuclides of ~ half the parent mass are produced**
- **Possible to purify nuclides carrier free (chemically different)**
- **Nuclides generally neutron rich and decay by β^- emission**

Production of Radionuclides

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Production of Radionuclides

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Production of Radionuclides

Cyclotron production: Charged particle bombardment

- **Accelerates charged particles to high energies**
- **Nuclear reactions have threshold energies**
- **The product is different than the target**
- **Nuclides can be produced carrier-free**

Production of Radionuclides

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Properties of the ideal diagnostic radiopharmaceutical

1. Pure gamma emitter
2. 100 < gamma energy < 250 keV.
3. Effective half-life = 1.5 X test duration.
4. High target:nontarget ratio.
5. Minimal radiation dose to patient and Nuclear Medicine personnel
6. Patient Safety
7. Chemical Reactivity
8. Inexpensive, readily available radiopharmaceutical.
9. Simple preparation and quality control if manufactured in house.

Properties of the ideal diagnostic radiopharmaceutical

One nuclide comes close to being the ideal gamma-emitting nuclide

Technetium-99m (^{99m}Tc)

- **Half-life = 6 hr**
- **Almost a pure γ ray emitter**
- **E = 140 keV**
- **can be obtained at high specific activity and carrier free**

Nuclides

^{99m}Tc

^{99m}Tc is a decay product of the fission product ^{99}Mo

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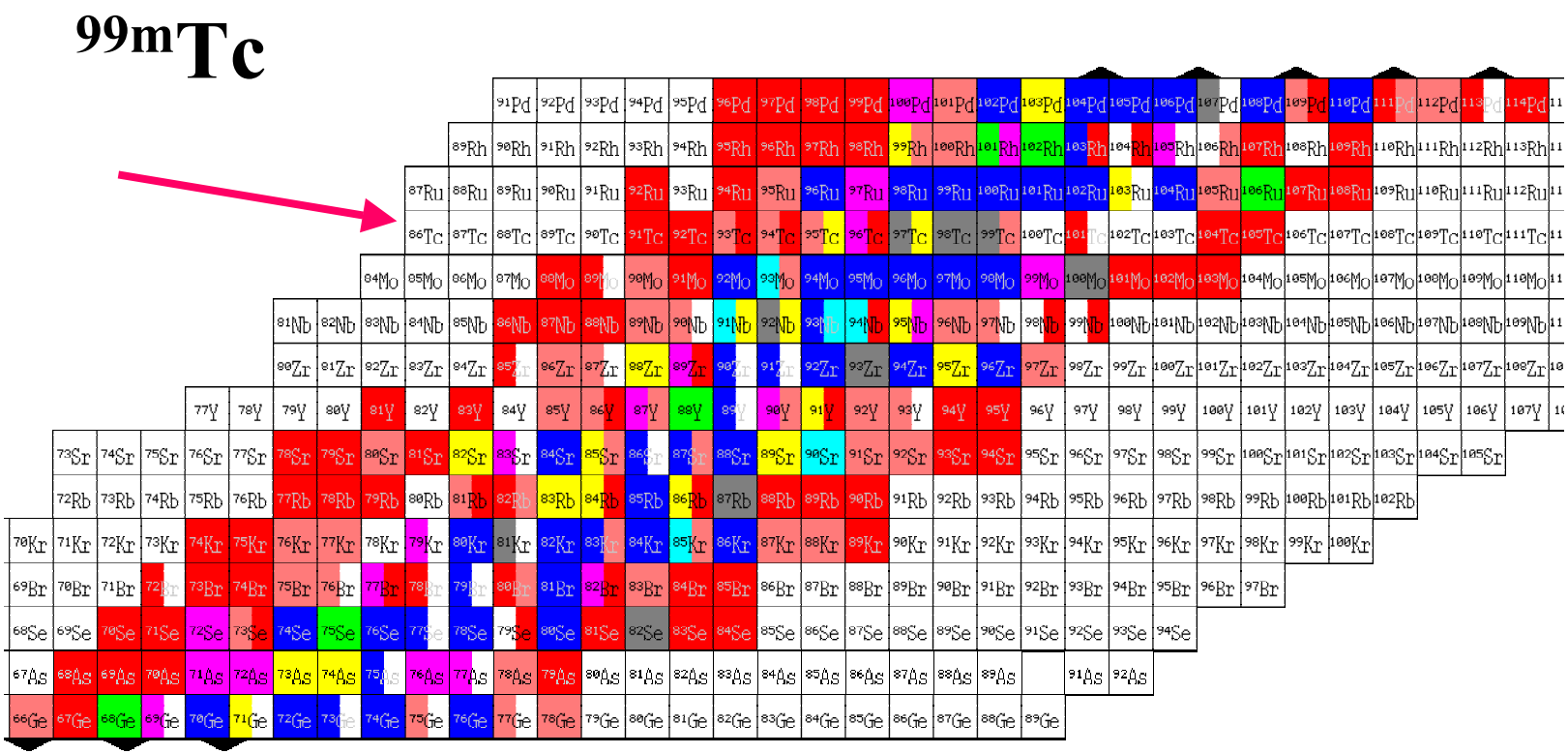
Table of the nuclides



Courtesy of Brookhaven National Laboratory.
(site no longer maintained -see http://www2.bnl.gov/CoN/)

Decay scheme for ^{99m}Tc

^{99}Mo decays to ^{99m}Tc by β - emission (^{99}Mo: T= 67 hrs)
^{99m}Tc excited nuclear state decays by γ emission (140 keV) to ground state ^{99}Tc (^{99m}Tc: T=6 hrs)
^{99}Tc (ground state) decays by β - emission to ^{99} Ru (stable isotope) (^{99}Tc: T=$2x10^5$ years)

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Radioactive equilibrium

Parent N_1 decays to daughter N_2, both are radioactive.
Special Case: Transient equilibrium

$N_1 \rightarrow N_2$
$T_1 > T_2$, but not greatly so. [$A = \lambda N$, $A = A_0 e^{-\lambda t}$]

$$\frac{dN_2}{dt} = \lambda_1 N_1 - \lambda_2 N_2 \quad \Rightarrow\Rightarrow A_2 = A_{10} \frac{\lambda_1}{\lambda_2 - \lambda_1}(e^{-\lambda_1 t} - e^{-\lambda_2 t}) + A_{20} e^{-\lambda_2 t}$$

Simplifying assumptions: $A_{20} = 0$; After ~10 half-lives, $e^{-\lambda_2 t} << e^{-\lambda_1 t}$

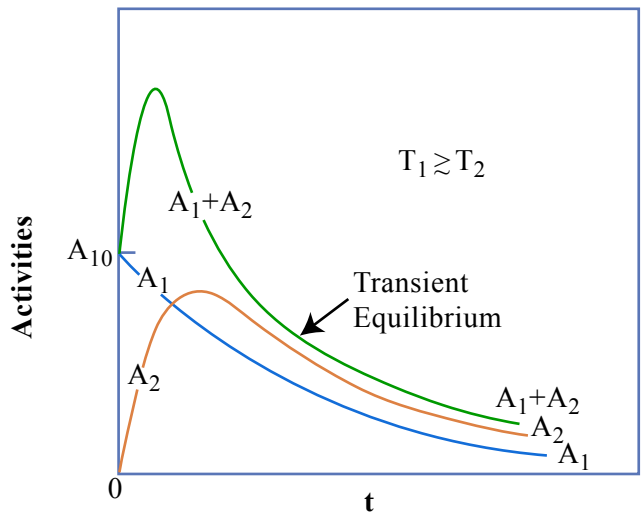
$$A_2 = A_{10} \frac{\lambda_1}{\lambda_2 - \lambda_1} e^{-\lambda_1 t} \qquad A_1 = A_{10} e^{-\lambda_1 t}$$

$$A_2 = A_1 \frac{\lambda_1}{\lambda_2 - \lambda_1} \qquad or \qquad \frac{A_2}{A_1} = \frac{\lambda_1}{\lambda_2 - \lambda_1}$$

Radioactive Decay

Example

^{99}Mo (T = 67 hrs)
^{99m}Tc (T = 6 hrs)



Activities as functions of time when T_1 is somewhat larger than T_2 ($T_1 \gtrsim T_2$) and $N_{20} = 0$. Transient equilibrium is eventually reached, in which all activities decay with the half-life T_1 of the parent.

Figure by MIT OCW.

The ^{99m}Tc Generator

^{99}Mo is adsorbed on an alumina column as ammonium molybdate (NH_4MoO_4)

^{99}Mo (T = 67 hrs) decays (by β -decay) to ^{99m}Tc (T = 6 hrs)

$^{99}MoO_4$ ion becomes the $^{99m}TcO_4$ (pertechnetate) ion (chemically different)

$^{99m}TcO_4$ has a much lower binding affinity for the alumina and can be *selectively eluted* by passing physiological saline through the column.

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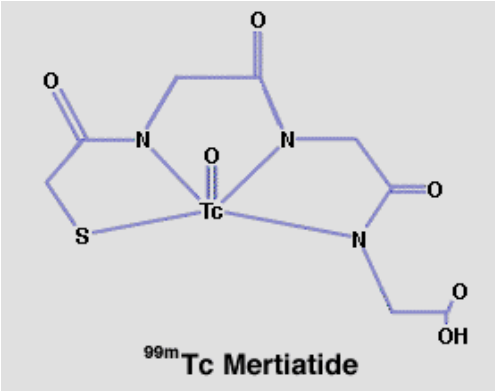
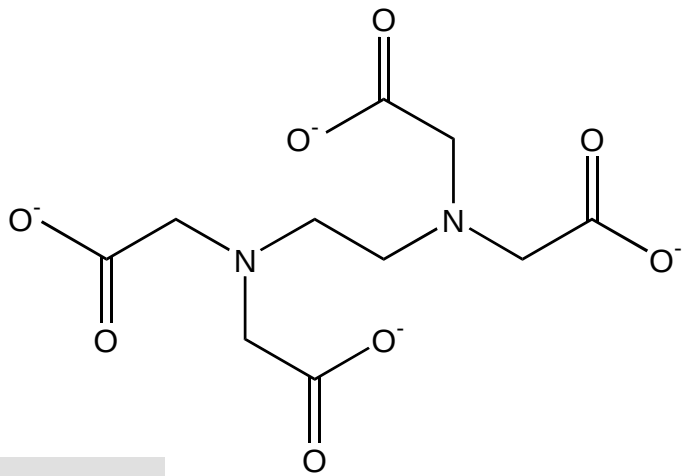
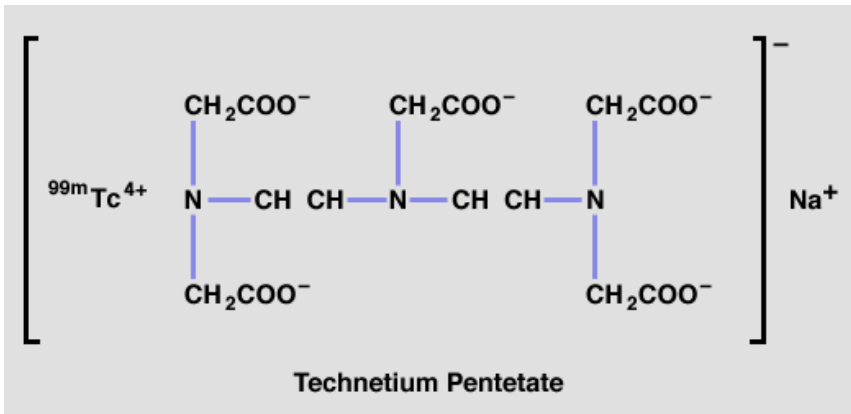
Chelators

EDTA
ethylenediaminetetraacetate



^{99m}Tc Mertiatide





DTPA

Chelators

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Production of Radionuclides

Cyclotron production

- Products are proton rich, neutron deficient
- Decay by β+ decay
- Positron emitters

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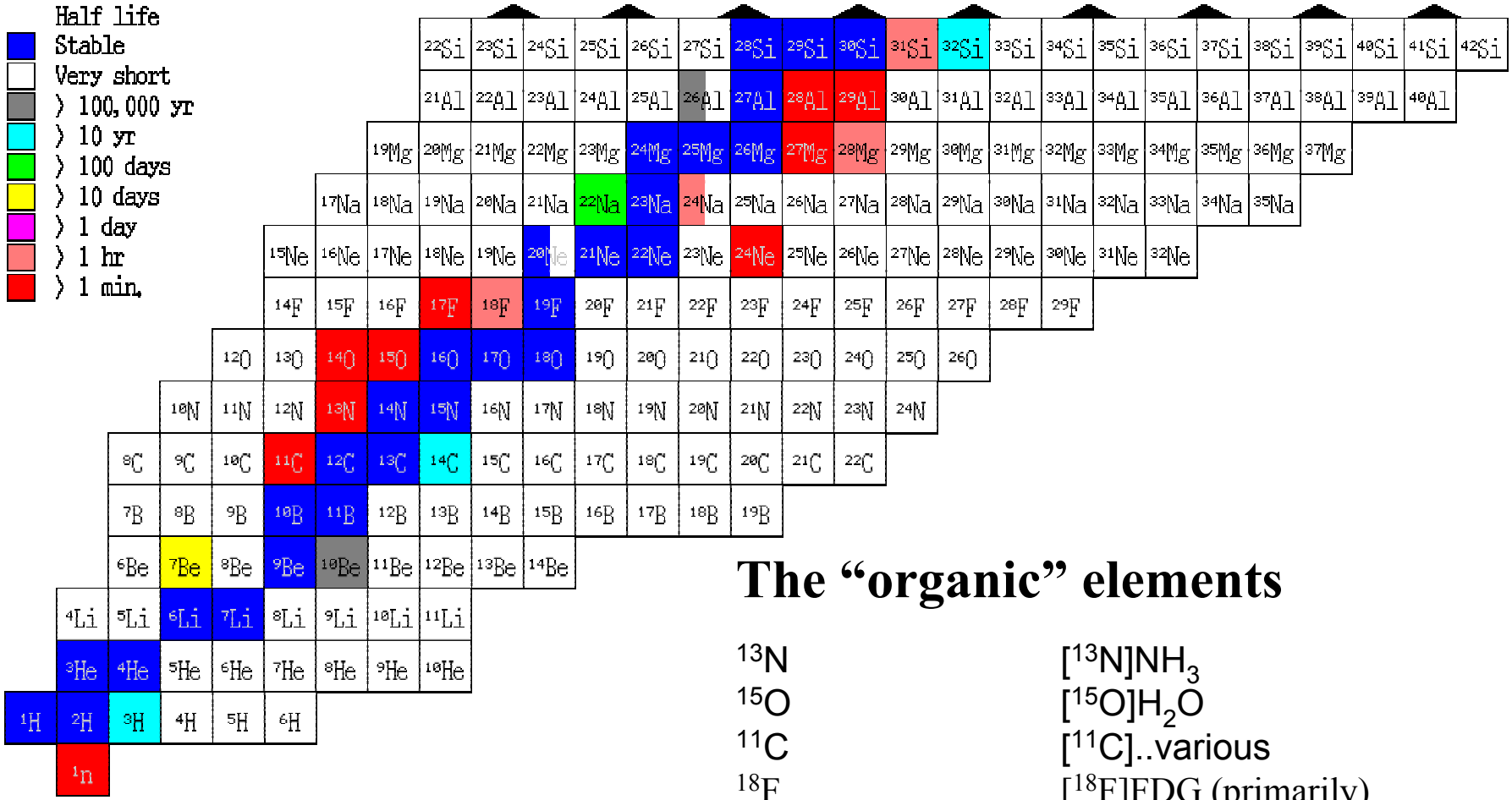
Chart of the Nuclides



The "organic" elements

^{13}N	$[^{13}N]NH_3$
^{15}O	$[^{15}O]H_2O$
^{11}C	$[^{11}C]$..various
^{18}F	$[^{18}F]$FDG (primarily)

Courtesy of Brookhaven National Laboratory.
(site no longer maintained -see http://www2.bnl.gov/CoN/)

Cyclotron Production

Targets

O-15: $^{14}N(d,n)^{15}O$; deuterons on natural N_2 gas; $^{15}O_2$ directly or $C^{15}O_2$, by mixing 5% carrier CO_2 gas.

C-11: $^{14}N(p,\alpha)^{11}C$; protons on natural N_2 gas: including 2% O_2 produces $^{11}CO_2$

N-13: $^{16}O(p,\alpha)^{13}N$; protons on distilled water

F-18: $^{18}O(p,n)^{18}F$; protons on ^{18}O-enriched water ($H_2{}^{18}O$),. Fluoride is recovered as an aqueous solution. For nucleophilic substitution.

F-18: $^{20}Ne(d,\alpha)^{18}F$; deuterons on neon gas. For electrophilic substitutions.

PET Radiopharmaceuticals

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PET Radiopharmaceuticals

- $^{11}CO_2$ from the target is converted into a highly reactive methylating agent: $^{11}CH_3I$ or $^{11}CH_3Tf$
- Elapsed time is 12 minutes..
- The radiochemical yield, based on $^{11}CO_2$ is about 90%.
- Specific activities of more than 6 Ci/μmol (220 GBq/μmol) can be obtained.
- ^{11}C-Methylation of ***various precursors*** is performed in the second reaction vessel within a few minutes.
- After methylation, the reaction product is separated via a semi preparative Radio-HPLC, purified via a solid phase extraction unit, followed by formulation of the radiotracer as an injectable saline solution.

Delivery strategies

Blood brain barrier
Metabolic pathways
Biological affinity

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Late 19th century
German chemist Paul Ehrlich demonstrates that certain dyes injected i.v. do not stain the brain.
The same dyes, when injected into the cerebral spinal fluid, stain the brain and spinal cord, but no other tissues.

The Blood-Brain Barrier

Function

Provide neurons with their exact nutritional requirements.

Glucose

- **Sole source of energy (adult brain consumes ~100 g of glucose/day)**
- **Neurons need a steady supply at an exact concentration**

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The BBB is selective

- **Glucose and other nutrients are transported through**
- **Proteins, complex carbohydrates, all other foreign compounds are excluded.**
- **Ion concentrations are tightly regulated**

Drug Delivery

Tumors do not have a blood tumor barrier

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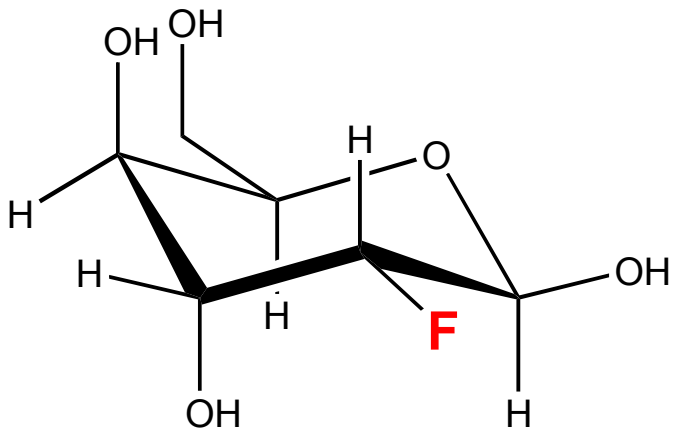
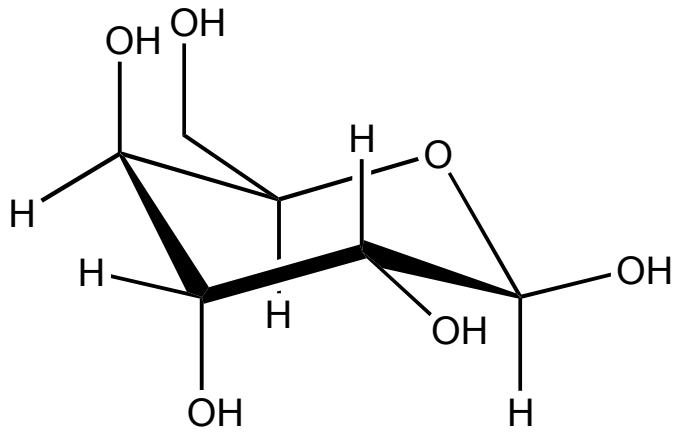
Delivery Strategies: Metabolic pathways

FDG
2-fluoro-2-deoxy-glucose



B-D-glucose



Delivery Strategies: Metabolic pathways

Glu → G6P→ F6P→FBP

- **FDG is transported into the cells**
- **FDG is phosphorylated to FDG-6P (charged molecules cannot diffuse out)**
- **FDG is NOT a substrate for the enzyme that catalyzes the next step in glycolysis.**

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Mapping Human Brain Function

^{18}F-FDG PET scans show different patterns of glucose metabolism related to various tasks.

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FDG in Oncology

- FDG transport into tumors occurs at a *higher* rate than in the surrounding normal tissues.
- FDG is de-phosphorylated and can then leave the cell.
- The dephosphorylation occurs at a *slower* rate in tumors.

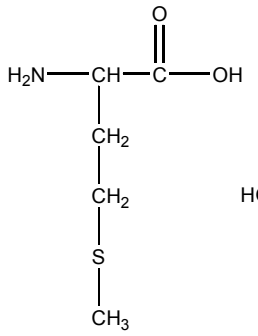
Applications of FDG

- Locating unknown primaries
- Differentiation of tumor from normal tissue
- Pre-operative staging of disease (lung, breast, colorectal, melanoma, H&N, pancreas)
- Recurrence vs necrosis
- Recurrence vs post-operative changes (limitations with FDG)
- Monitoring response to therapy

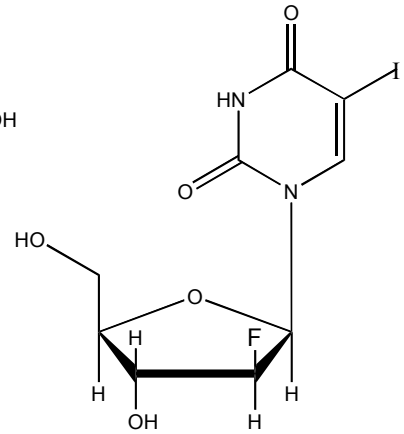
Delivery Strategies: Metabolic pathways

PET can provide highly specific metabolic information.

- **FDG, MET, FLT are incorporated via transporters**
- **Uptake is indicative of tumor grade.**



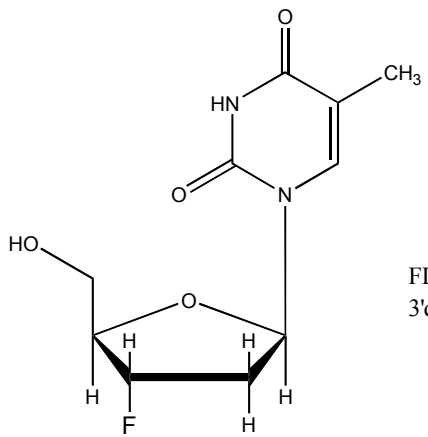
methionine



FIAU
2'-fluoro-2'-deoxy-1-*B*-D-arabinofuranosyl-5-[^{124}I]-uracil

^{11}C-methionine

- **specific for tumor**
- **avoids high brain background problem seen with FDG**
- **no significant uptake in chronic inflammatory or radiogenic lesions**
- **MET better than FDG in low-grade gliomas**



FLT
3'deoxy-3-'fluoro-[^{18}F]-L-thymidine

Functional imaging of gliomas

Imaging objectives

- **Location and relation to surrounding brain activity**
- **Biological activity = malignancy**
- **Response to therapy**

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Tumor recurrence vs post-radiotherapy changes

FDG uptake indicates recurrence

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Left: MRI
Center: PET
Right: fused image

Functional Imaging

Tumor vs functional brain

^{11}C-MET + MRI delineates tumor (GREEN)

[^{15}O]H_2O PET delineates function (blood flow)

Stimulation of brain regions causes increased blood flow (RED)
- **finger tapping (A)**
- **verb generation (B)**

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Pre-surgical analysis to guide surgery.

Tumors cause swelling and deformation of brain anatomy: mapping function is critical.

Intra-operative electrical stimulation causes aphasia: correlated well with area mapped by [^{15}O]H_2O PET.

Information can be displayed in neuro-navigation software during surgery.

Recurrent tumor vs necrosis

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MRI (right) indicates necrosis
^{11}C-MET (left) shows tumor recurrence

Image correlation with different modalities

High-grade glioma: three-dimensional determination of

- **Localization**
- **Extent**
- **Metabolism**

Image removed due to copyright restrictions.

Top: MRI
Middle: ^{11}C-MET
Bottom: ^{18}FDG

[Note lower ipsilateral glucose metabolism.]

Bone scanning

Bone scans are the second most frequent nuclear medicine procedure.

Clinical uses:

- **Detection of primary and metastatic bone tumors**
- **Evaluation of unexplained bone pain**
- **Diagnosis of stress fractures or other musculoskeletal injuries or disorders.**

E.g.,

Prostate cancer:

- **Incidence is rising**
- **Most common cause of death in males in many western countries**
- **Of prostate deaths, 85% have mets in bone**
- **60% of new cases have mets**
- **Bone metastases are painful and debilitating**
- **Diagnosis of bone mets is part of the staging process that determines treatment**

Breast cancer:

- **Bone is the most common site of metastasis**
- **8% of all cases develop bone mets**
- **70% of advanced cases experience bone mets**

Bone

Bone is a living tissue comprised of a crystalline matrix of hydroxyapatite $Ca_5(PO_4)_3OH$ in a collagen matrix.

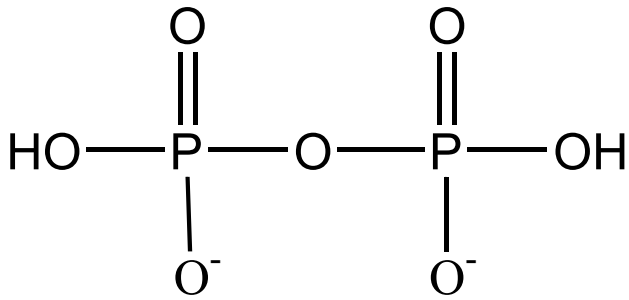
Osteoblasts: responsible for new bone formation, repair of damaged sites, lay down new crystalline hydroxyapatite.

Osteoclasts: responsible for bone resorption, dissolve bone. Osteoclasts are more active in metastatic tumor sites.

Delivery Strategy

Pyrophosphate

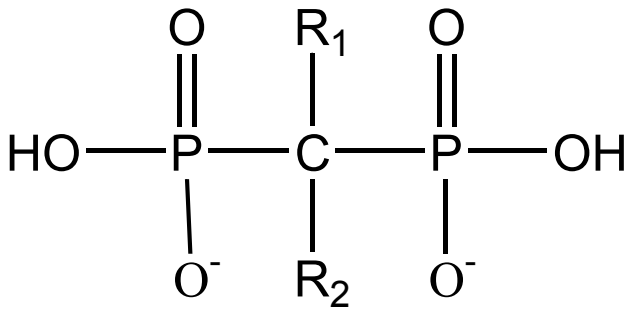
Normal metabolite from ATP hydrolysis
Source of phosphate in bone.



pyrophosphate

Bisphosphonates

- **have an affinity for the hydroxyapatite component of bone**
- **are incorporated into the crystalline matrix during bone remodeling or repair.**
- **are used to slow or prevent bone density loss leading to osteoporosis**



bisphosphonate

Bone Scans

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Normal pediatric bone image

Bone scans

SCHAPHOID fracture

- **48 y. o. woman presenting with with painful wrist 2 weeks after fall onto outstretched hand.**
- **X rays normal**
- **Blood flow ($^{13}NH_3$) increased to the left wrist (top)**
- **Left scaphoid fracture revealed on ^{99m}Tc-MDP image (bottom)**

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Active metastatic disease

41 y.o. male with lung carcinoma presents with pain in upper right humerus, 2-3 months of bilateral rib pain, 3 weeks of left knee pain.

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Scan shows multiple focal sites of abnormal tracer uptake

- **Right humerus**
- **Multiple ribs**
- **Left femur**
- **Sacral and lumbar vertebrae**

Coronary artery disease

Use PET and/or SPECT imaging to assess information on:

- **perfusion**
- **metabolism**
- **distinguish viable from non-viable myocardium.**

Cardiac Imaging

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The Cardiac Stress Test

Exercise causes

- **Increased HR, contractility, BP**
- **Increased O_2 demand**
- **Coronary vasodilation**

Increased myocardial blood flow

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Gene Therapy

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Gene Therapy

Use of PET to confirm vector gene expression

Specific retention of FIAU PET signal at 68 hrs (left) indicates phosphorylation by HSV TK.

Same area shows necrosis after treatment with ganciclovir (right).

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PET in studies of substance abuse

Drugs of abuse

- Why are they pleasurable?
- What brain changes reinforce usage and lead to addiction?

Brain Function

Changes in specific components of this system present in various disease states.

Parkinsons Disease
aging
substance abuse
depression.

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Brain Function

Quantitative PET

•Signal intensity in regions of interest is monitored as a function of time.

•Concurrent sampling of arterial blood allows correlation of signal to blood concentration.

•Pharmacologic doses of antagonist block PET tracer uptake.

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Drug Addiction

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•Cocaine: one of the most reinforcing drugs of abuse
•Cocaine binds to the DA re-uptake transporter (DAT)
•DAT blockade results in increased DA concentrations. Effect is greatest in brain regions rich in DA neurons (e.g., basal ganglia).

Drug Addiction

Control **1 week de-tox** **3 months de-tox**

Image removed due to copyright restrictions.

FDG PET: Low frontal metabolism may underlie the loss of control in cocaine addiction.

Drug Addiction

Image removed due to copyright restrictions.

Cocaine and methylphenidate (Ritalin)

Image removed due to copyright restrictions.

^{11}C-cocaine

^{11}C-methylphenidate

- **show identical distribution**
- **highest in basal ganglia (highest DAT concentrations)**
- **binding to the same receptors**
- **cold cocaine blocks ^{11}C-methylphenidate uptake**
- **cold methylphenidate blocks ^{11}C-cocaine uptake**

Cocaine and methylphenidate (Ritalin)

Image removed due to copyright restrictions.

Slow on-rate of oral methylphenidate does not produce a high

Peak DAT blockade

i.v. cocaine:	**4-6 min**
i.v. methylphenidate:	**8-10 min**
oral methylphenidate	**60 min**

Slow off-rate for methylphenydate does not lead to "binging" behavior. Second dose would not produce a high.