PATHOPHYSIOLOGY AND MECHANISMS OF RADIOPHARMACEUTICAL LOCALIZATION__CONT.

20140721 morning meeting 胡蓮欣

The Pathophysiological basis of Nuclear Medicine 2nd ed. Springer.

The mechanisms of radioisotope localization

1. Isotope dilution — In vivo, MUGA, RBC scan
2. Capillary blockade — MAA lung perfusion
3. Physicochemical adsorption — MDP bone scan
4. Cellular migration and sequestration — WBC scan, denatured RBC spleen scan
5. Membrane transport — Xe-133 ventilation
   - Simple diffusion — HMPAO/ECD brain perfusion scan
     - Diffusion and intracellular metabolism/binding
     - Diffusion and mitochondrial binding — Tc-99m MIBI
     - Diffusion and increased capillary and plasma membrane permeability
   - Facilitated diffusion
   - Active transport
   - Phagocytosis
   - Receptor-mediated endocytosis
6. Metabolic Substrates and Precursors
   - Precursors: Radiolabeled Amino Acids
7. Tissue Hypoxia
8. Cell Proliferation
9. Specific Receptor Binding
   - Radiolabeled Peptides
   - Steroid Hormone Receptors
   - Adrenergic Presynaptic Receptors and Storage

Diffusion and increased capillary & plasma membrane permeability

- Gallium citrate: a carrier-free Ga-67
  - Still no general agreement on the exact mechanisms of localization in tumors
  - Bound exclusively to transferrin: two specific metal-binding sites of the iron-transport glycoprotein→ Ga-transferrin complex→ slowly transported through the capillary v. wall

  or exist as (under physiological pH 7.4)…

  - $Ga(OH)_4^-$: a soluble gallate ion→ rapidly leaves the blood compartment and equilibrates with the interstitial fluid (of normal & tumor tissue)

gallate: 鎵酸鹽

Gallium citrate

- Leaving blood vessel
  - Bounded form→ leaves BV slowly, by transport
  - Free form→ leaves BV rapidly and equilibrates with interstitial fluid
- Uptake by normal cells/tumor cells
  - Normal cells: strongly promoted by binding to transferin (沒有unbounded form可以進去的路)
  - Tumor cells: simple diffusion of unbounded or loosely bound form of Ga-67 (有unbounded form可以進去的路)
- Retention in cells
  - Tumor cell: very much dependent on Ga-67 binding to iron-binding proteins (lactoferin & ferritin, high affinity)→ prevent back diffusion of free Ga-67

- Increased capillary permeability and expanded extracellular space would augment the transport of the macromolecules (transferrin) across the BV
- Increased permeabiltiy of tumor cell membrane

Dissociation constant (Kd) vs. Affinity

The formation of a ligand-protein complex (C) can be described by a two-state process

$$\mathrm{C} \rightleftharpoons \mathrm{P} + \mathrm{L}$$

the corresponding dissociation constant is defined

$$K_d = \frac{[\mathrm{P}]\,[\mathrm{L}]}{[\mathrm{C}]}$$

The dissociation constant has molar units (M)

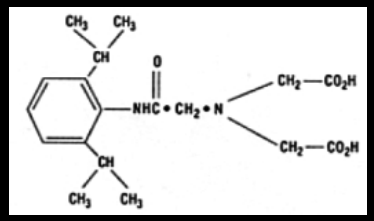
The smaller the dissociation constant, the more tightly bound the ligand is, or the higher the affinity between ligand and protein.

Kd越小，解離度越小 (親和力越高)

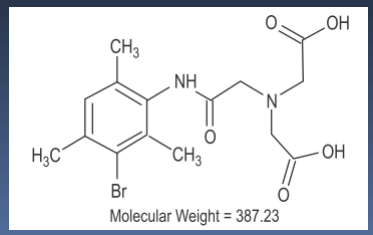
Facilitated diffusion

- F-18 FDG: facilitated diffusion
  - Glucose: Glucose transporter protein family (GLUT1-6)
- Hepatobiliary agents
  - IDA derivatives
  - Tc99m disofenin & Tc-99m mebrofenin
  - Blood v. to hepatocyte membrane:
    -diffuse through pores in endothelium lining
    -binding to the anionic membrane bound carriers
  - Hepatocyte membrane to intracellular:
    -facilitated by carrier-mediated, non-sodium-dependent, organic anionic pathways (similar to bilirubin)
  - Intracellular to biliary tract: passive

Tc-99m disofenin



Tc-99m mebrofenin



Active transport

- Against concentration gradient
- Requires energy
  - ATP (primary active transporters)
  - Electrochemical gradient of Na+ or H+ (secondary active transporters)
- If the energy source is inhibited or removed, the transport system will not function

Radioiodide and Tc-99m pertechnetate anions

- Thyroid
  - Actively traps certain anions: I-, TcO_4^- and ClO_4^- (same pathway)
  - Competitive to each other
  - Only iodine is used to synthesize thyroid hormone; others diffuse out of the gland
  - Affected by iodine containing medications, TSH levels, thyroid & nonthyroid drugs, total body iodine pool
- Salivary glands, stomach, bowel & GU tract
  - Also significant uptake (secretion) of radioiodide and pertechnetate

Thallous chloride (Tl-201) & Rubidium-82

- $Tl(OH)_2^+$ & Rb^+ act as K^+ ion
- Uptake of myocardium involves (Tl & Rb):
  - Passive diffusion
  - ATP-dependent pathways
- Uptake by tumor cells (Tl-201)
  - Increased blood flow and increased permeability
  - Na+/K+ ATPase

- Cellular uptake (Tl-201)
  - Na+/K+ ATPase ←(block) oubain, digitalis and furosemide
  - Chloride cotransport system ←(block) furosemid
  - Calcium-dependent ion channel: minimal amount

Addictive blockade effect

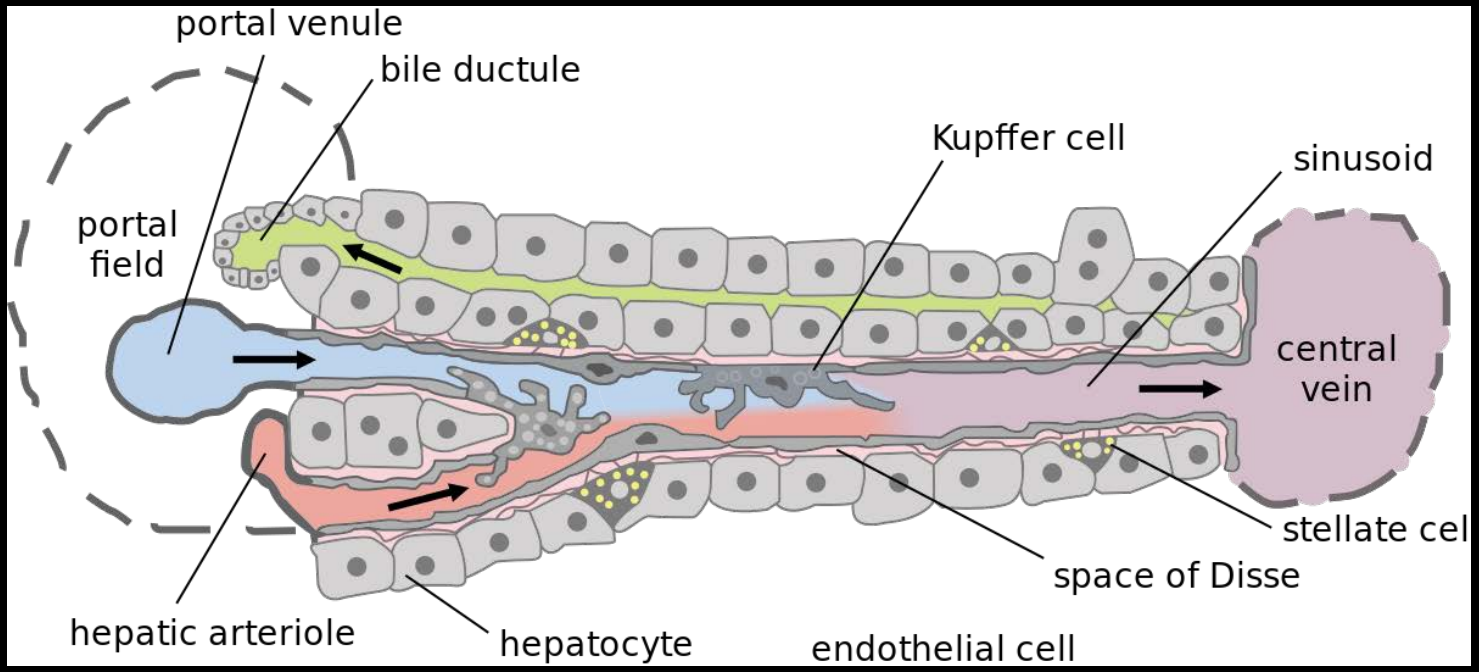
Renal agents

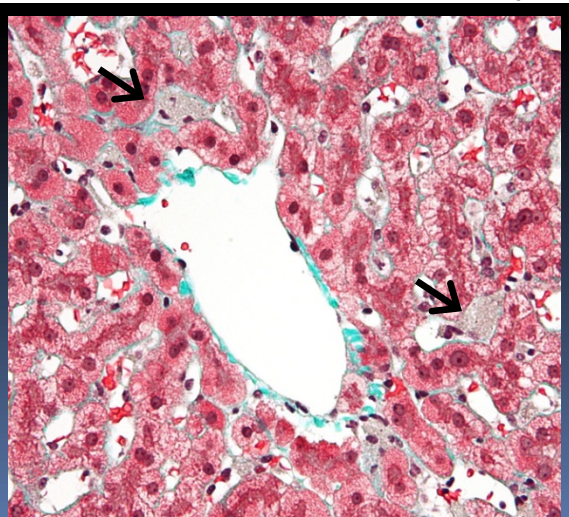
- Agents for GFR
  - I-125 iothalamate, Tc-99m DTPA, Cr-51 EDTA
  - Mostly filtered by glomerulus
  - No specific transport mechanism involved
  - Dependents on hydrostatic & colloid osmotic pressure
- Agents for ERPF
  - OIH and MAG_3
  - Partly filtered and mostly secreted by tubules
  - Actively transported by renal hippurate anionic transport system

Phagocytosis

- Tc-99m sulfur colloid (SC)
  - Size: 0.1-1.0 um
  - Opsonins (specific serum proteins) may interact with it, providing a coating to the SC particles
  - Be recongnized by receptors on the phagocytic cell surfaces (of RES, called Kupffer cells in liver sinusoids; reticular cells in spleen)
  - Engulf the colloid, remove it from circulation
  - → In SC scan, cold lesion in liver suggests tumor displacing the usual distribution of RES cells
  - → Similarly, radiation damage in liver & bone is seen as cold areas due to decrease RES function

Hepatic lobule, sinusoid and Kupffer cells





Centrilobular **Kupffer cells**, with a grey granular cytoplasm, in a resolving liver injury. Liver biopsy. Trichrome stain.

From WikiPedia, Kupffer cell

溶液的分類

- 以溶劑分類:水溶液←→非水溶液
- 以型態分類:氣態溶液(一般稱混合氣體)/液態溶液(簡稱溶液)/固態溶液(亦稱固溶體)
- 以溶液導電性分類:電解質溶液←→非電解質溶液
- 以溶質粒子大小分類

真 溶 液	膠 體 溶 液
溶液的粒子為分子或離子	溶液的粒子為高分子、結合的粒子或吸附於溶劑分子的離子所構成的原子團, 含有原子數目達10^3～10^9個
粒子的直徑為10^{-10}公尺，即1A	粒子的直徑為10^{-9}～10^{-7}公尺 0.001-0.1 um
溶質	分散質
溶劑	分散媒
如:糖水、食鹽水、碘酒等	如:咖啡、牛奶、豆漿及澱粉液等

Phagocytosis–

Sentinel LN mapping:

- Particles <0.1 um: rapid clearance from the interstitial space into lymphatic vessels and significant retention
- Normal LNs→ hot spots
- Cancerous nodes→ cold (not sequest SC), FP result

Lymphoscintigraphy:

- Ideal agents for their small size:
  - Tc-99m antimony: 0.002-0.015 um
  - Tc-99m human serum albumin: 0.001-0.002 um
- A replacement that needs filter (0.2 um filter)
  - Tc-99m SC: 0.1-1.0 um

→Not available in the U.S.

Receptor-mediated endocytosis

- Ga-67 and Fe-59 uptake by tumor involves the transferrin receptors
  - Pro.:
    - In vitro: low concentration of transferrin (<0.1 mg/ml) stimulated and increased tumor uptake of Ga-67
    - Transferrin receptors in tumor cells are 10X than in normal cells
  - Against:
    - In vivo: conflicting data from animal studies
    - Ga-67 tumor uptake also was observed in mice with congenitally absent transferrin (hypotransferrinemic)

  → The exact connection bt transferrin receptors & Ga-67 tumor uptake in vivo has not been established
- Also see Diffusion and increased capillary & plasma membrane perme…

6. Metabolic Substrates and Precursors—metabolic trapping of FDG

- FDG: F-18-2-deoxy-2-fluoro-d-glucose
- Developed in 1977, by Some et al.
- Transported into cell by facilitated diffusion (see also Facilitated diffusion)
- FDG $\xrightarrow[\text{hexokinase}]{}$ FDG-6-P

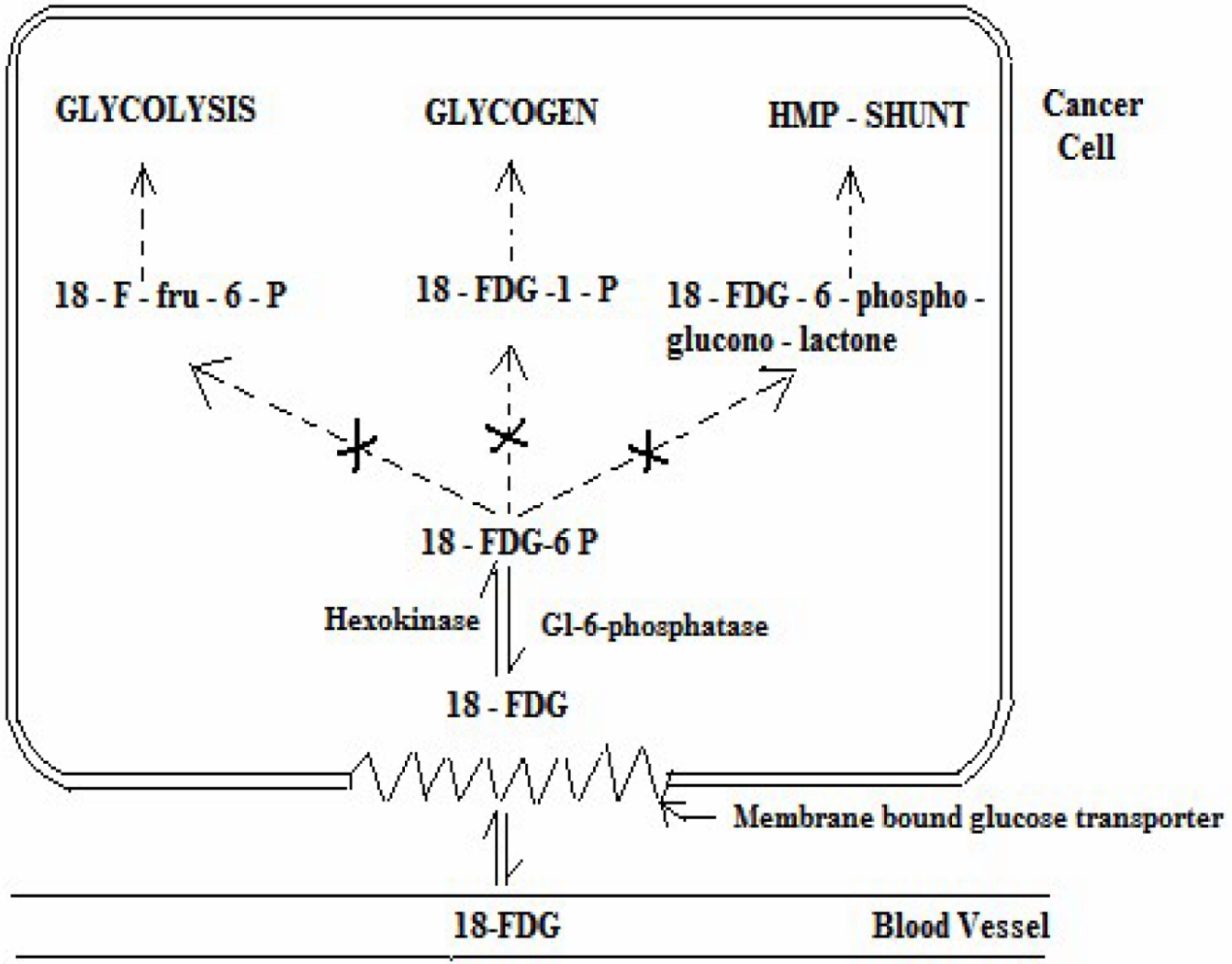
- FDG-6-P $\xrightarrow[\text{Glucose-6-phosphate isomerase}]{\text{⊘}}$ fructose-6-P

此反應無法進行，因為G6P isomerase的structural & geometric demand很嚴格

- FDG-6-P $\xrightarrow[\text{Glucose-6-phosphatase}]{}$ FDG

此反應所需enzyme很少或幾乎沒有

FDG Mechanism in functional imaging



Metabolic Substrates and Precursors—radiolabeled amino acids

- Amino acid transport
  - L-[methyl- 11 C]methionine (MET)
  - L-O-[2- 18 F]fluorethyl-tyrosine (FET)
- Protein synthesis
  - L-[1- 11 C]tyrosine (TYR)
  - L-[2- 18 F]fluorotyrosine (FTyr)
  - L-4-[18 F]fluoro-m-tyrosine
  - L-[3- 18 F]-a-methyltyrosine (FMT): relatively easy to synthesize, high in vivo stability (75% inj. dose appears unmetabolized form in the circulation)
- Unnatural amino acids (nonmetabolized)
  - C-11 ACBC ([11 C]a-aminocyclobutane carboxylic acid)
  - F-18 ACBC
  - In astrocytoma & glioblastoma

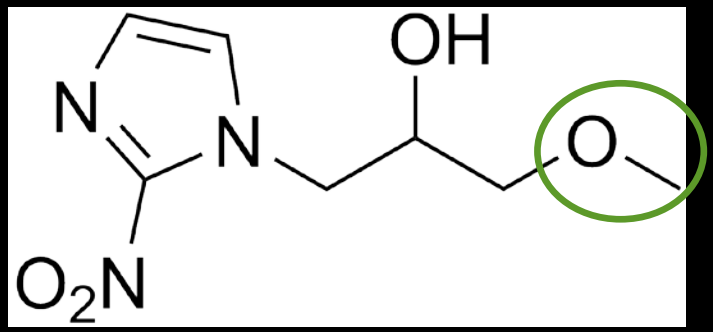
7. Tissue Hypoxia

造影/uptake原理

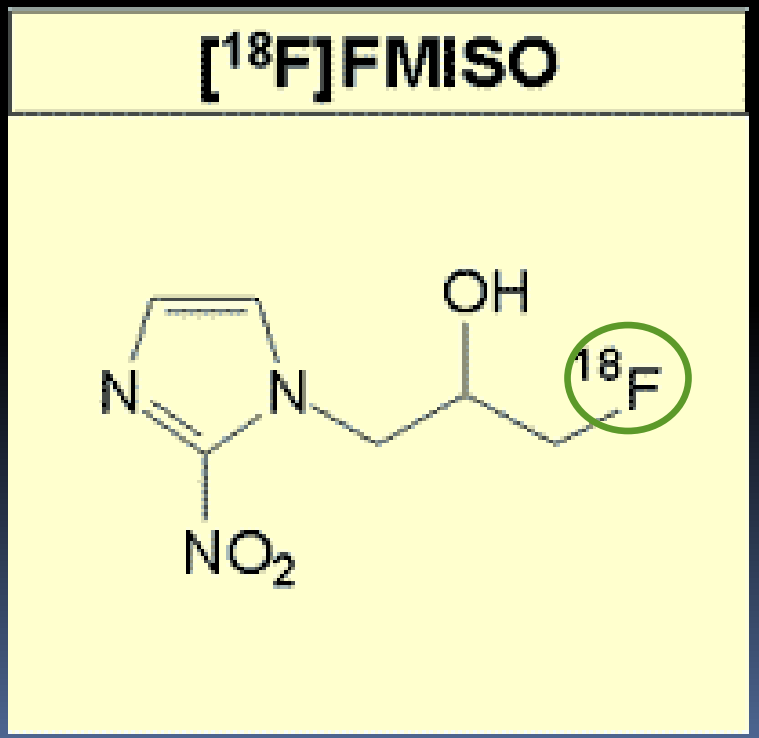
- MISO (misonidazole)
  - A radiosensitizer used in radiation therapy to cause normally resistant hypoxic tumor cells to become sensitive to the treatment ***Wikipedia***
  - With radiosensitizing and antineoplastic properties. Exhibiting high electron affinity, misonidazole induces the formation of free radicals and depletes radioprotective thiols, thereby sensitizing hypoxic cells to the cytotoxic effects of ionizing radiation. This single-strand breaks in DNA induced by this agent result in the inhibition of DNA synthesis.

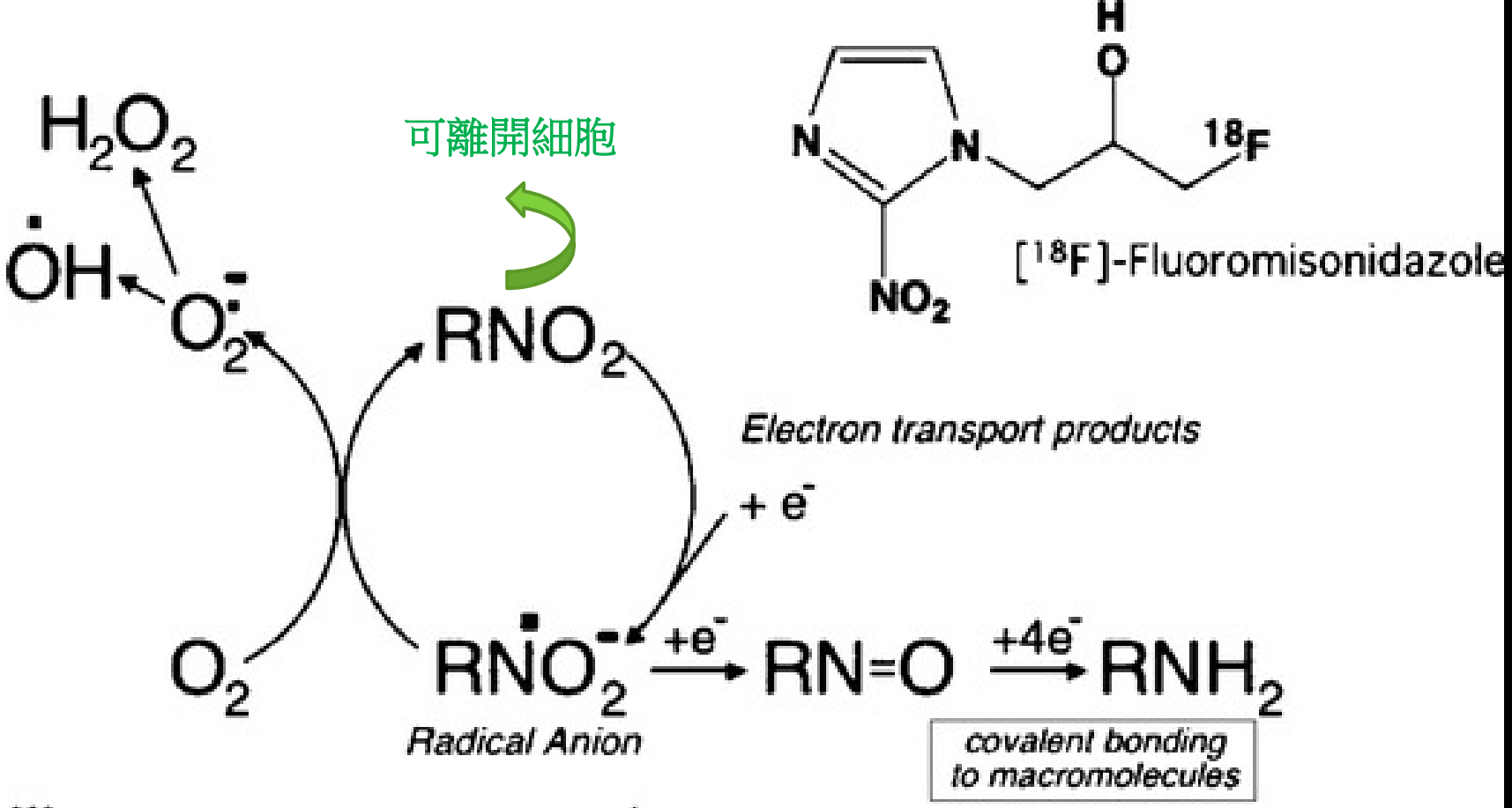
NCI Drug Dictionary

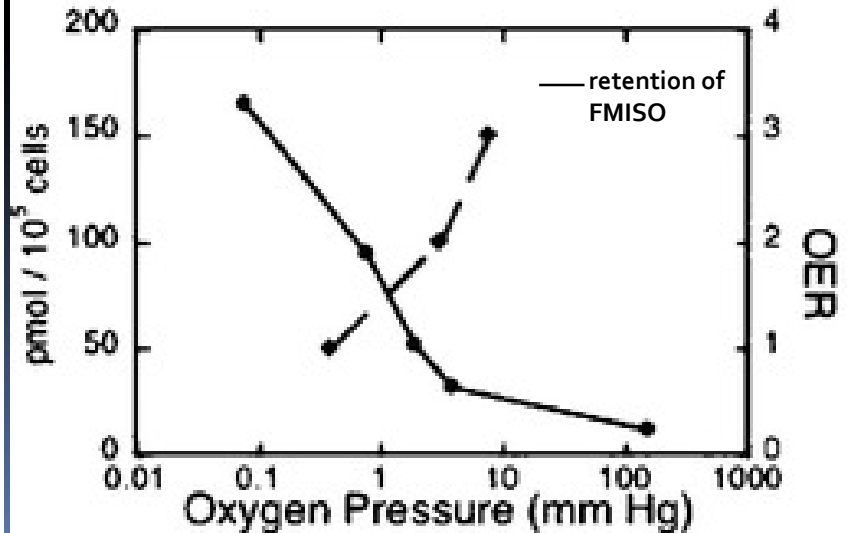
MISO

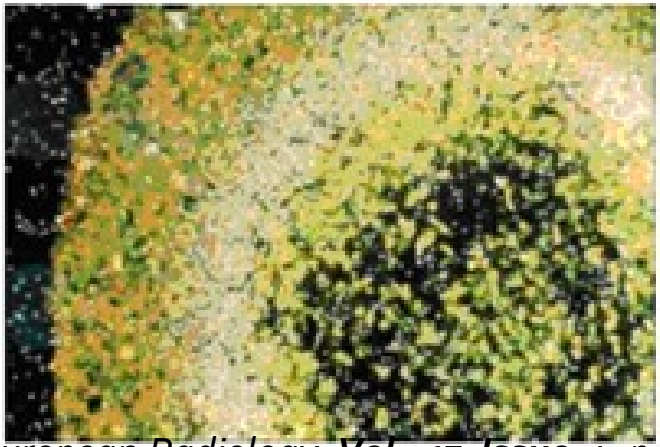


[^{18}F]FMISO









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Tracers in tissue hypoxia

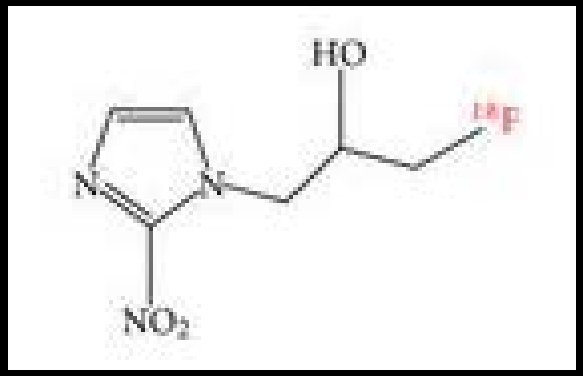
- PET F-18 FMISO (F-18 fluoromisonidazole)
- PET Cu-64 ATSM (Cu-diacetylbis-(N4-methylthiosemicarbazone)
- SPECT I-123 IAZA (I-123 iodoazomycin arabinoside)
- SPECT Tc-99m PnAO (TcO(PnAO-1-(2-nitroimidazole))
  - a Tc-99m propylene amine oxime derivative of 2-nitroimidazole)
  - a.k.a. BMS181321

- SPECT Tc-99m HL91 (4,9-diaza-3,3,10,10-tetramethyldodecan-2,11-dione dioxime)

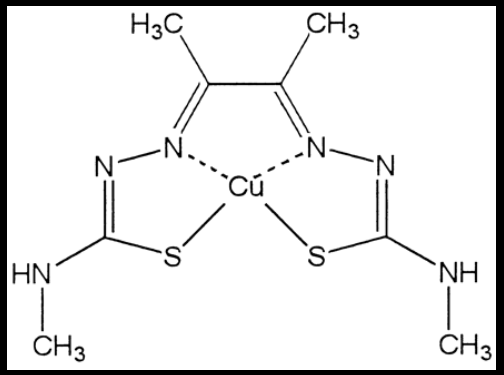
NO_2 moiety related

NO_2 moiety Non-related

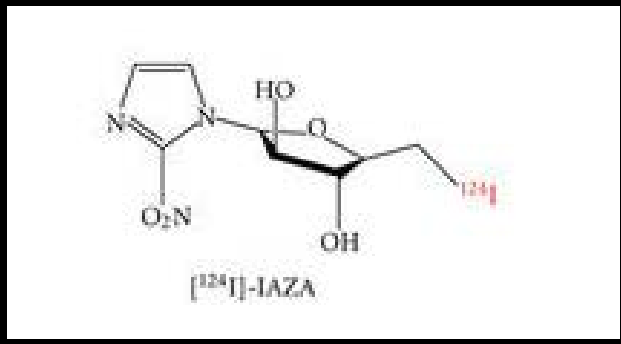
F-18 FMISO

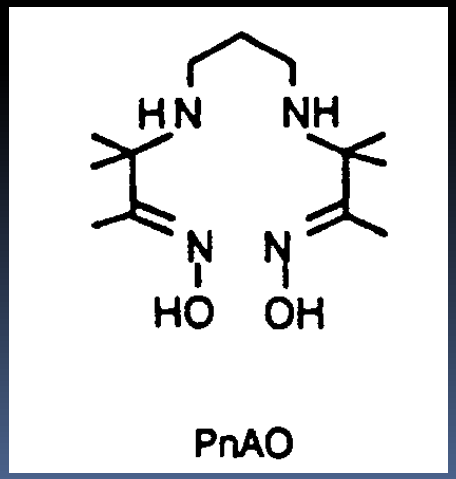


Cu-64 ATSM



I-123 IAZA





Tc-99m PnAO

Tc-99m HL91

Hypoxia & tumor pH

- Tumor cells have increased rates of anaerobic & aerobic glucose metabolism… 1925, by Warburg
- If aerobic respiration is not available, pyruvate (end product of glycolysis) turned into lactic acid by LDH (lactate dehydrogenase) and accumulates→ pH of tumor cell is lightly acidic, as compared with normal tissue pH of 7.4