Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

PAUL SCHERRER INSTITUT

PET and SPECT: Physical Principles and Basic Strategies of Radiotracer Development for Pre-Clinical and Clinical Use

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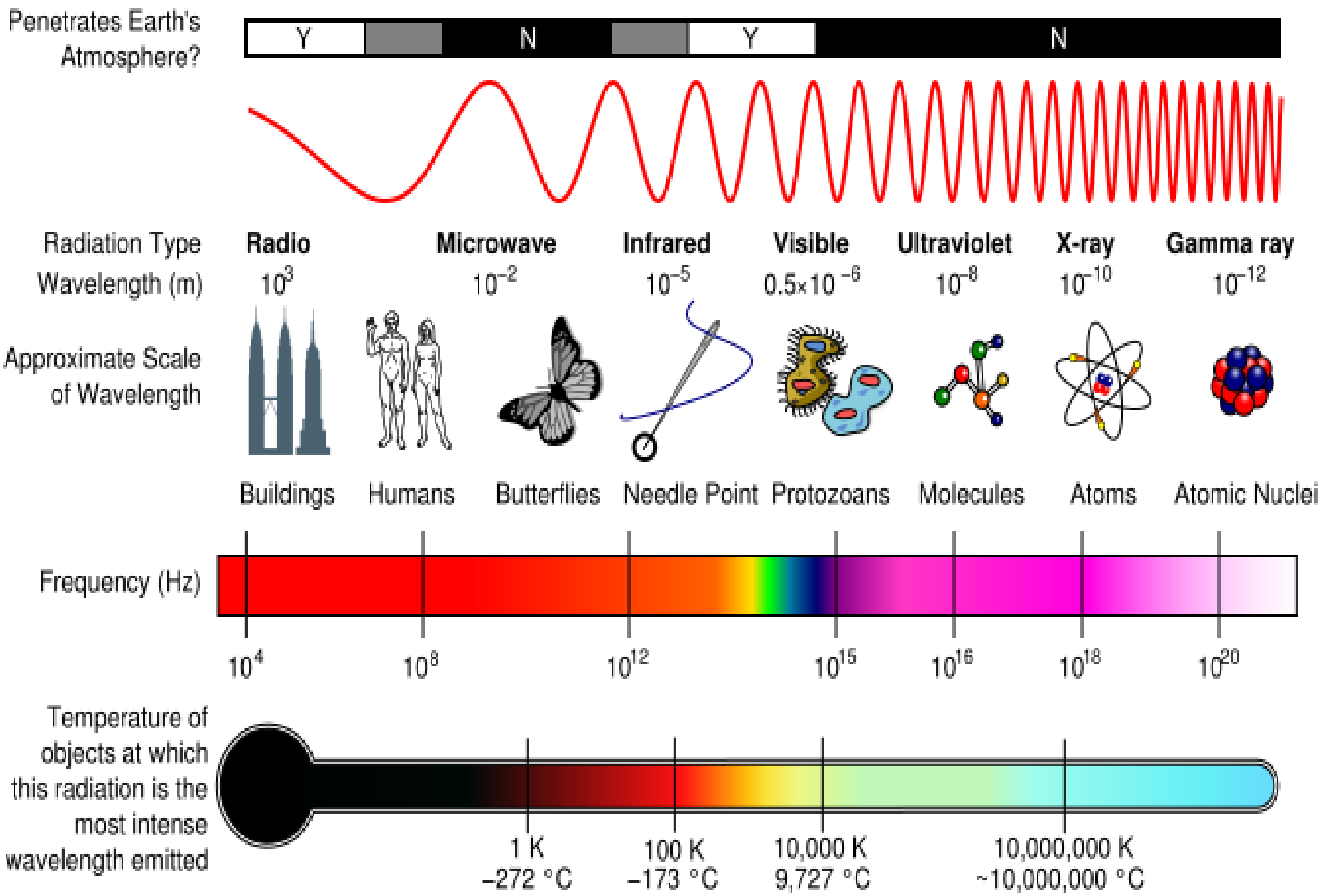
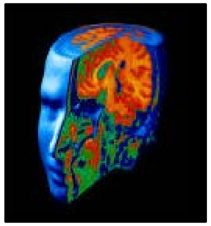


From wikipedia

Resolution and Sensitivity

Imaging Method	Spatial resolution	Sensitivity
Ultrasound	50 µm	10^{-3} Mol
CT	50 µm	10^{-3} Mol
MRI	100 µm	10^{-5} Mol
Bioluminescent	1-3 mm (depth!)	10^{-8} Mol
Nuclear*	***> 2 mm***	***10^{-9}-10^{-12} Mol***

Morphology

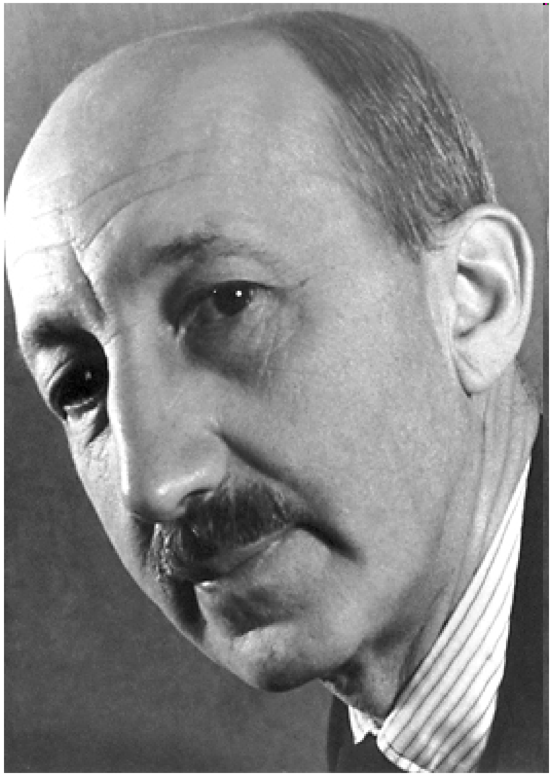


Function

* ***P**ositron **E**mission **T**omography - **PET***

S**ingle **P**hoton **E**mission **C**omputed **T**omography - **SPECT

The Tracer Principle



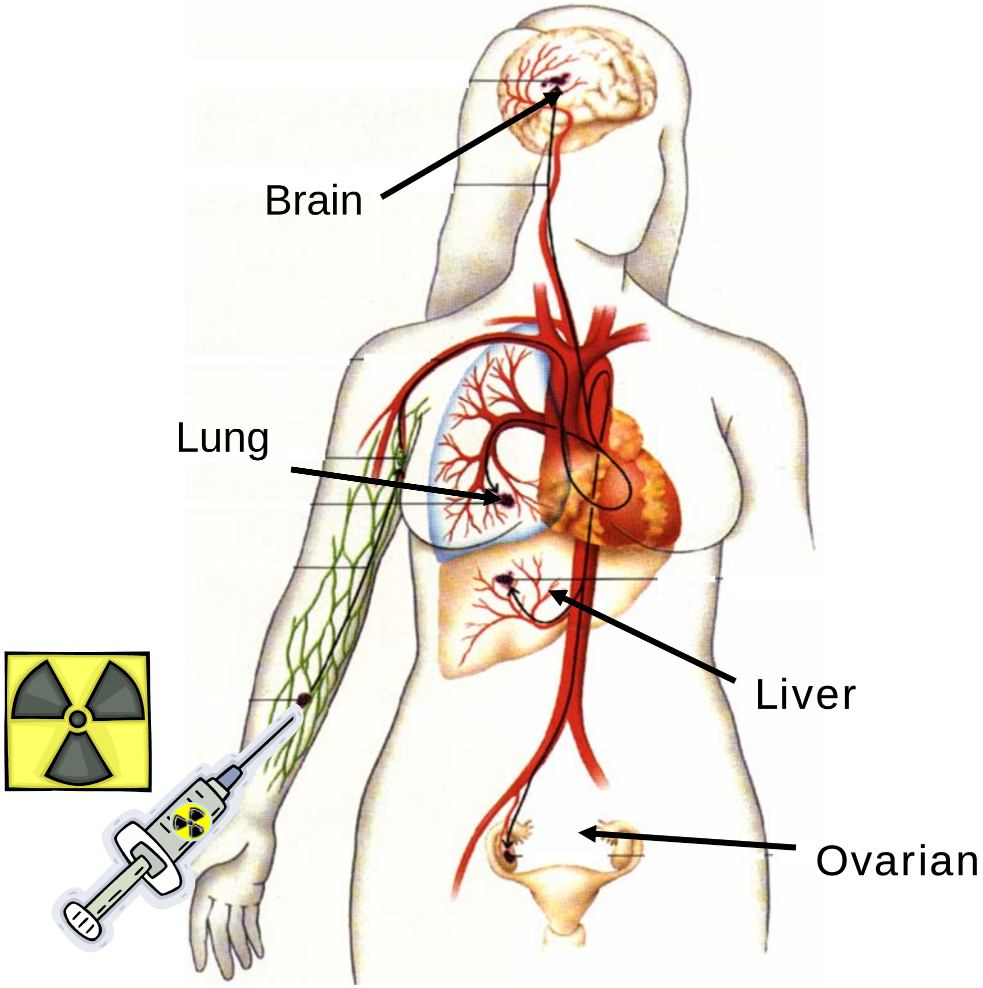
George de Hevesy (1885-1966);

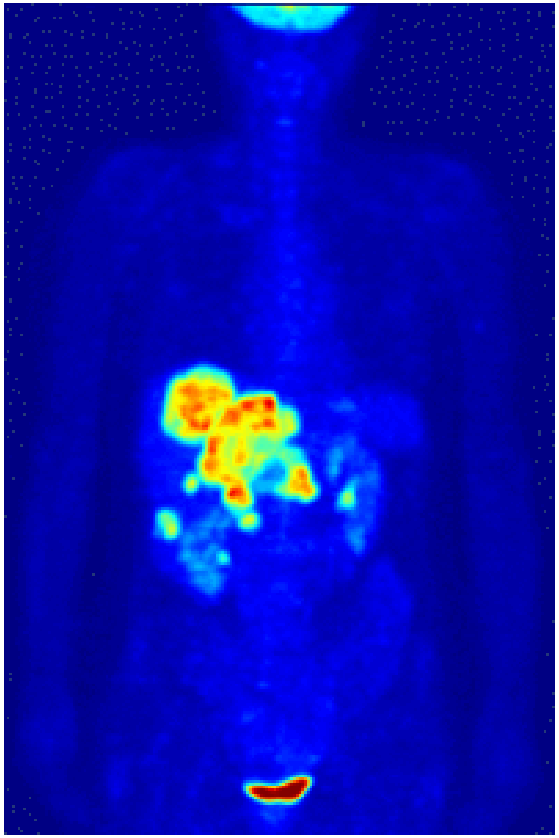
Nobel Prize for Chemistry in 1943

A radioactive tracer is a chemical compound in which one or more atoms have been replaced by a radioisotope. It is applied in minimal amounts, therefore, it has no pharmacologic effect in vivo. It can also be used to explore the mechanism of bio-/chemical reactions by tracing the path that the radioisotope follows from reactant to product

E.g. 370 MBq of ^{11}C-tracer necessary for a brain scan with ^{11}C-Raclopride (D2-receptor ligand) corresponds to 100 picogram total mass injected.

Principles in Nuclear Medicine





Gamma-Radiation of Scintigraphy and SPECT

$$^{99m}\mathbf{Tc} \longrightarrow {}^{99}\mathbf{Tc} + \gamma$$

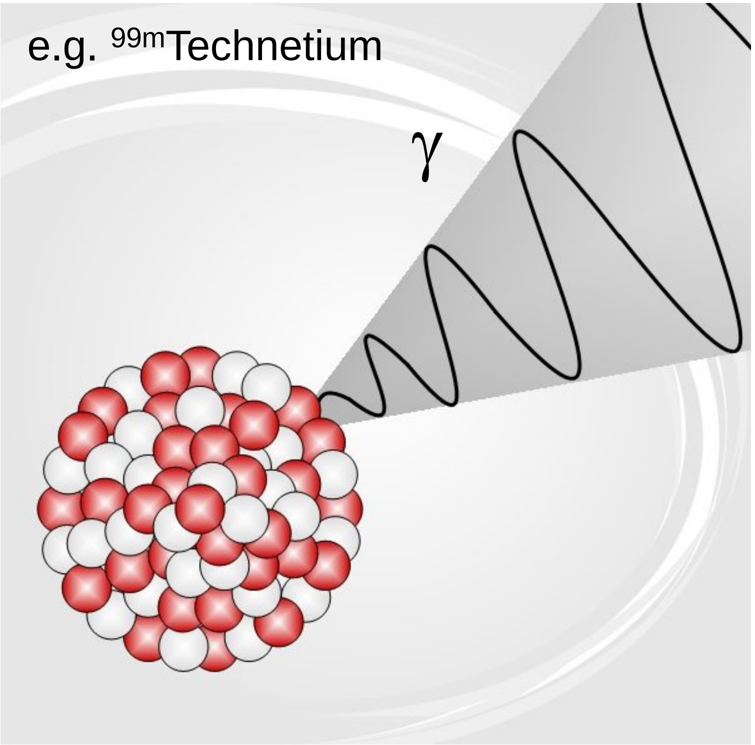
Nucleus in an exited state decays to ground state

$$^{111}\mathbf{In} \longrightarrow {}^{111}\mathbf{Cd} + \gamma$$

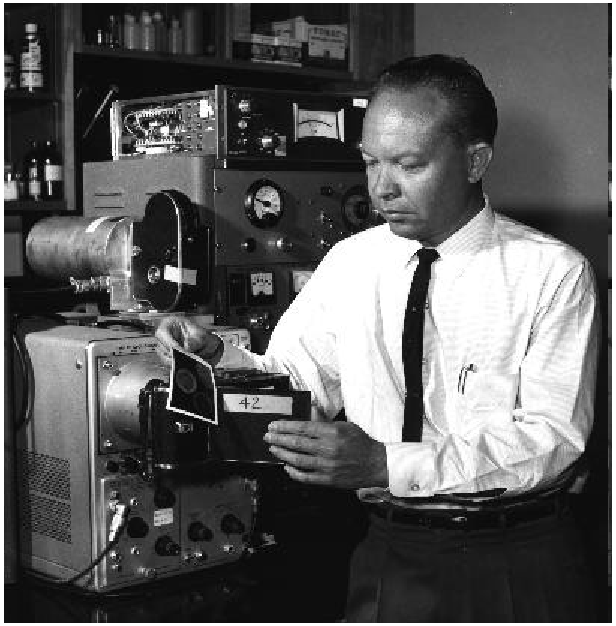
Electron capture: Nucleus possesses too many protons but is unable to emit a positron and instead captures an electron → exited state

$$^{67}\mathbf{Cu} \longrightarrow {}^{67}\mathbf{Zn} + e^- + \gamma$$

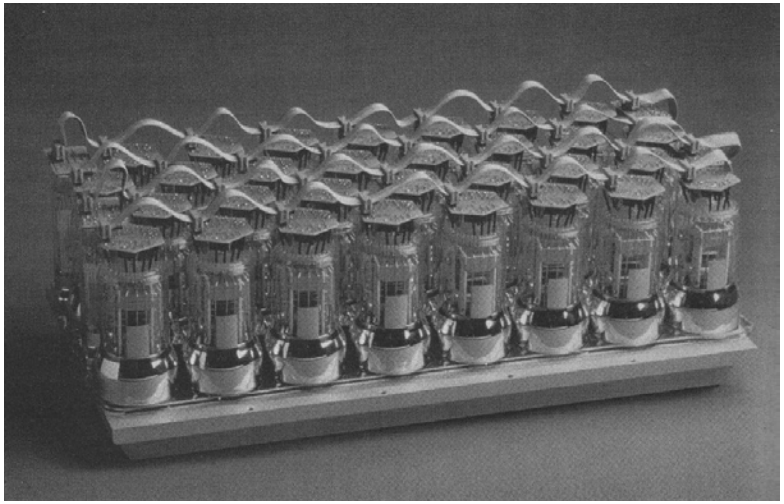
γ-emission after beta-decay



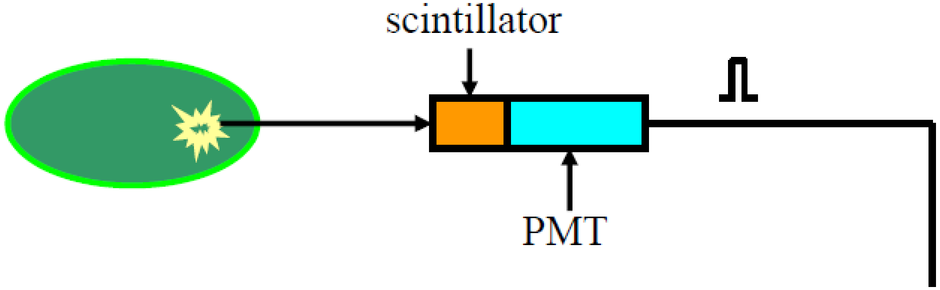
Anger Camera



Hal Oscar Anger (1920-2005)



Anger camera (NaI-scintillator and photo multipliers)



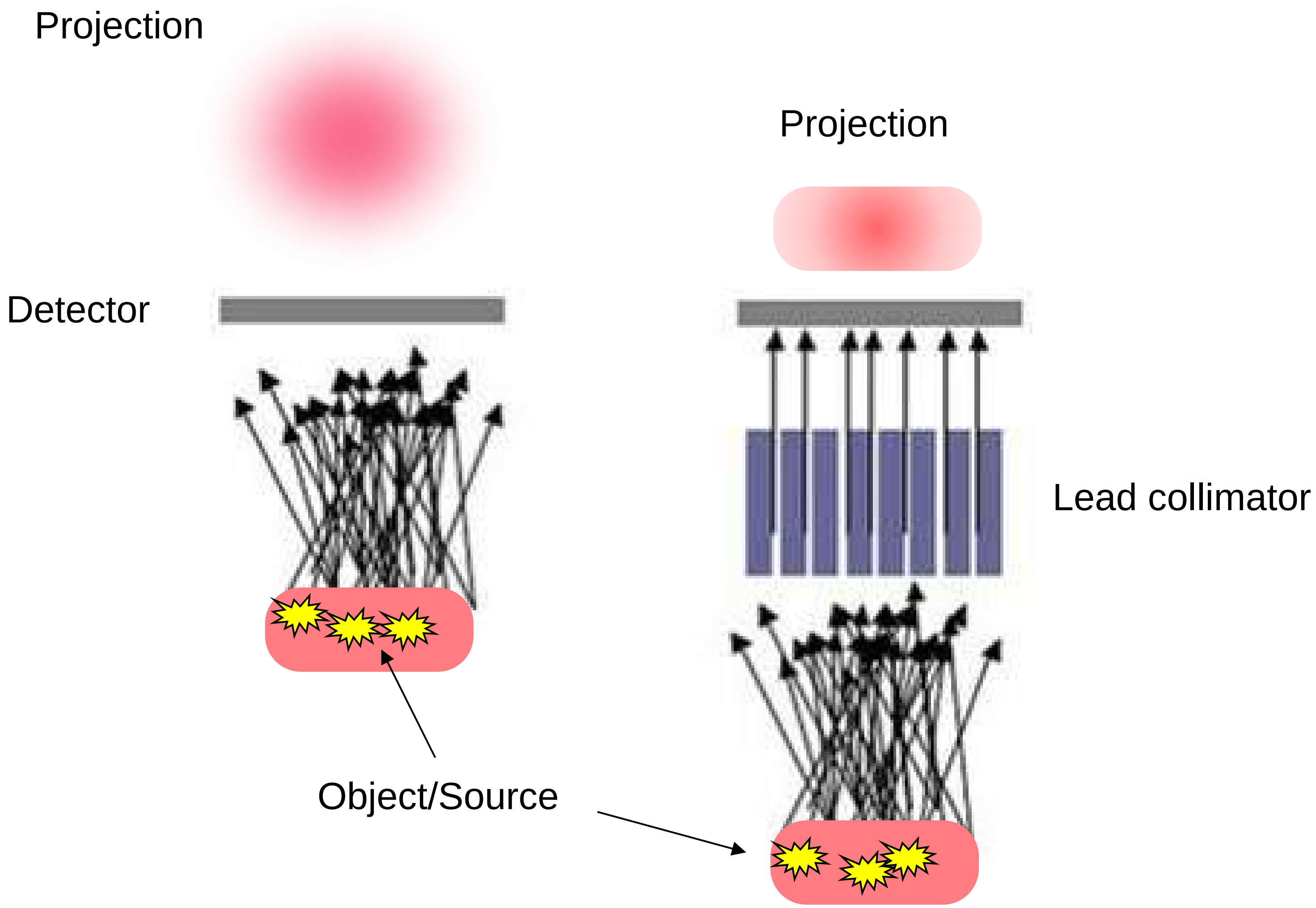
Signal detection

Scintillation Material

Scintillator	Density [g/cm^3]	Peak emission [nm]	Decay time [ns]	relative yield*
NaI(Tl)	3.67	415	230	100
CsI	4.51	315	16	4-6
CsF	4.64	390	3-5	5-7
CaF_2(Eu)	3.18	435	940	50
BaF_2	4.88	310	630	16
BGO	7.13	480	300	15-20
$CdWO_4$	7.90	350	28	130
$LaCl_3$(Ce)	3.79	350	28	130
$LaBr_3$(Ce)	5.29	380	16	160
YAP	5.37	347	28	40

*relativ to NaI(Tl)

Principle of Parallel Hole Collimator



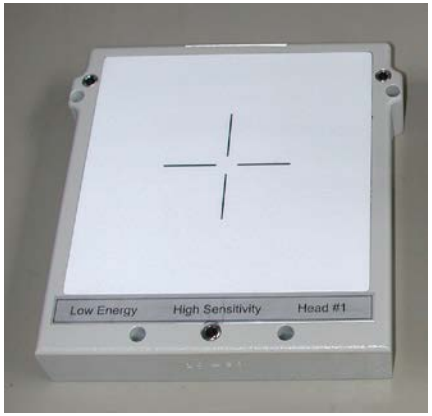
Principle of Parallel Hole Collimator

$$R = \frac{d_e * (L + H)}{L}$$

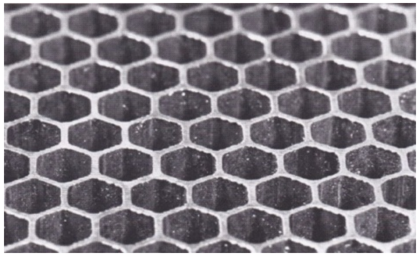
L = length of the holes

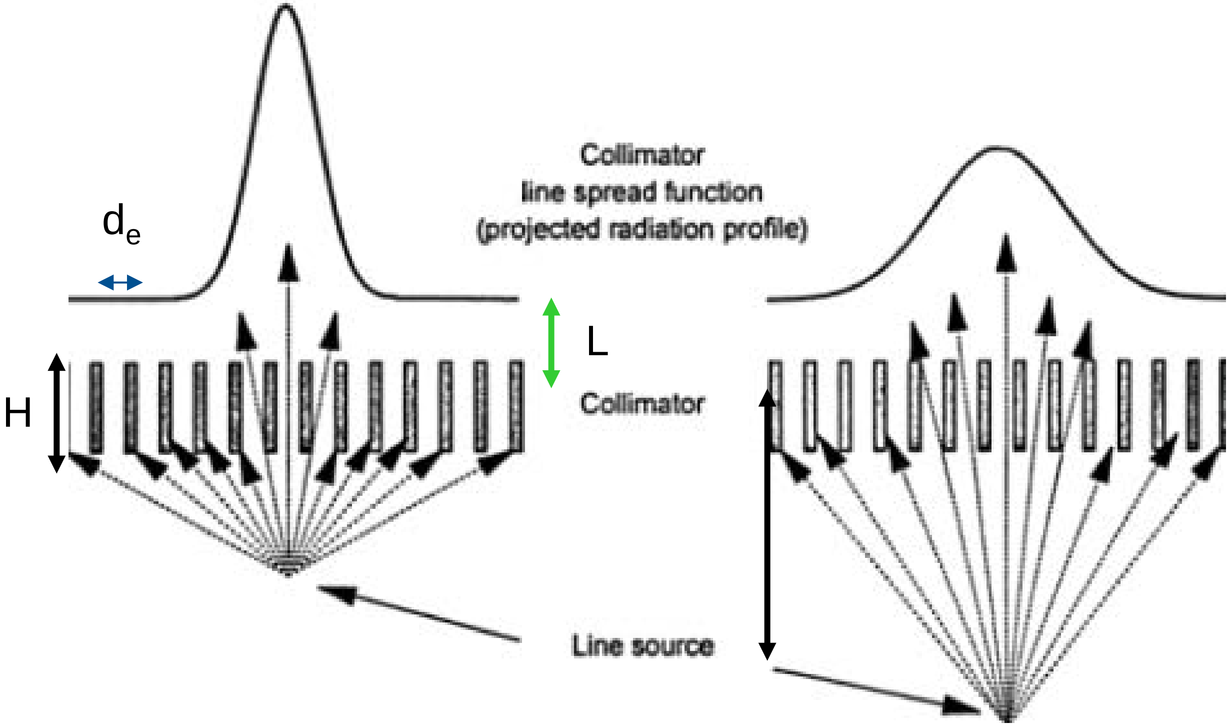
d_e = hole diameter

H = collimator to the source distance



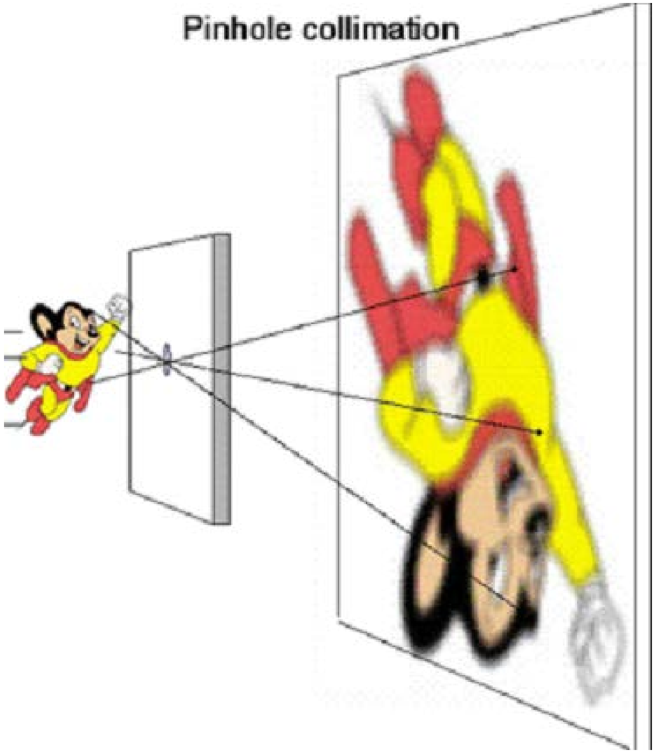
Lead collimator





Principle of a Pinhole Collimator

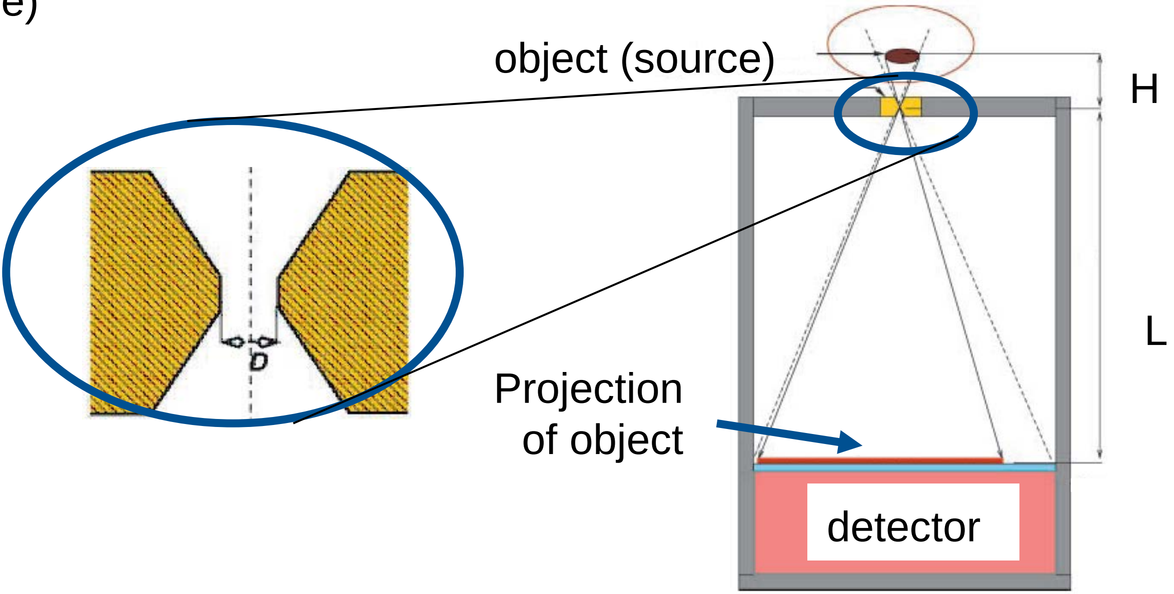
- Magnification of the projected object
- “*Camera Obscura*”



Resolution of a Pinhole Collimator

$$R = \sqrt{(d_e(1 + 1/M))^2 + (R_i/M)^2}$$

R = resolution
d_e = hole diameter
R_i = intrinsic resolution of the detector
M = magnification factor given by L/H (L the focal length of the pinhole; H the pinhole to the source distance)



object (source)

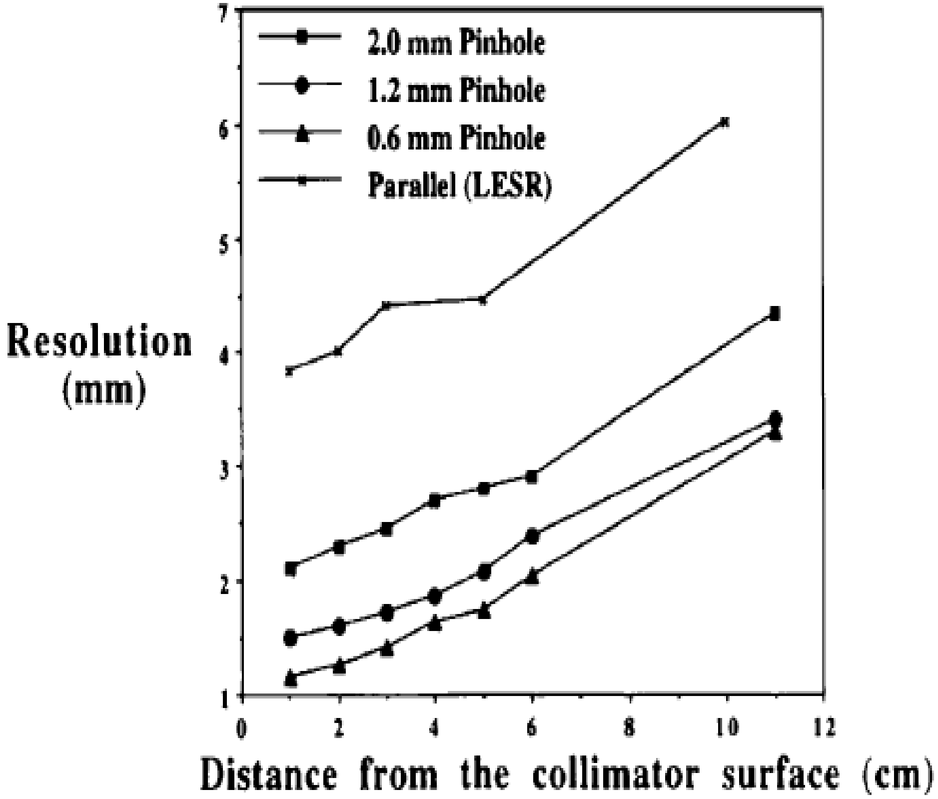
H

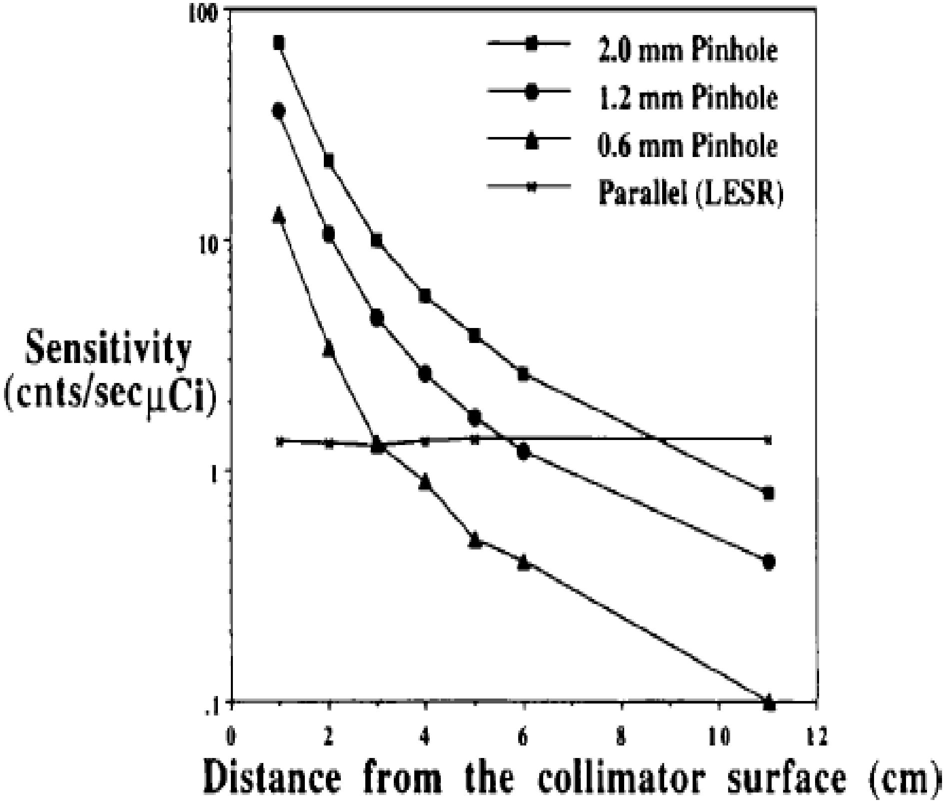
L

Projection of object

detector

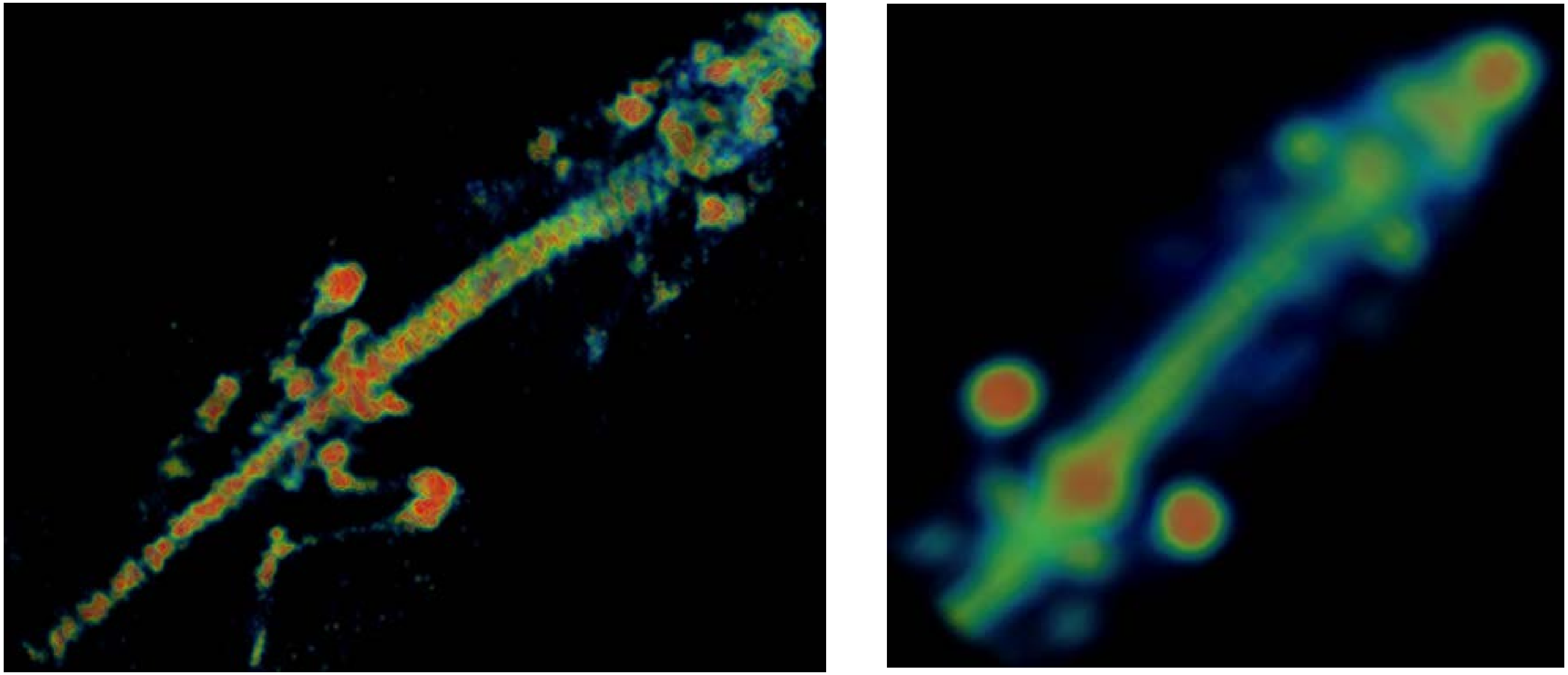
Effect of Pinhole Size and Object Distance on Resolution and Sensitivity





Results of Type of Collimators on Resolution

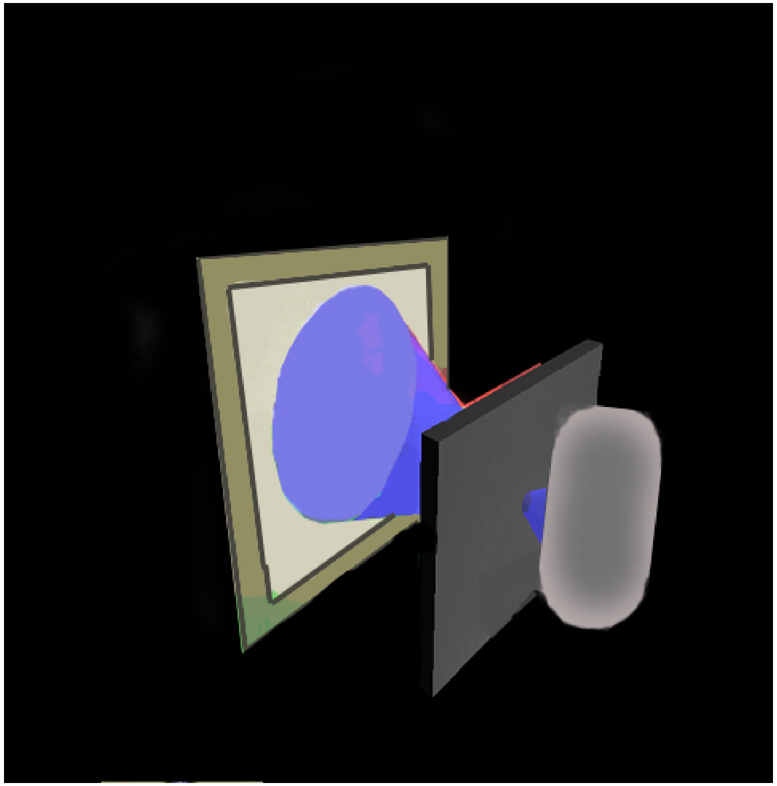
Pinhole: Parallel hole:



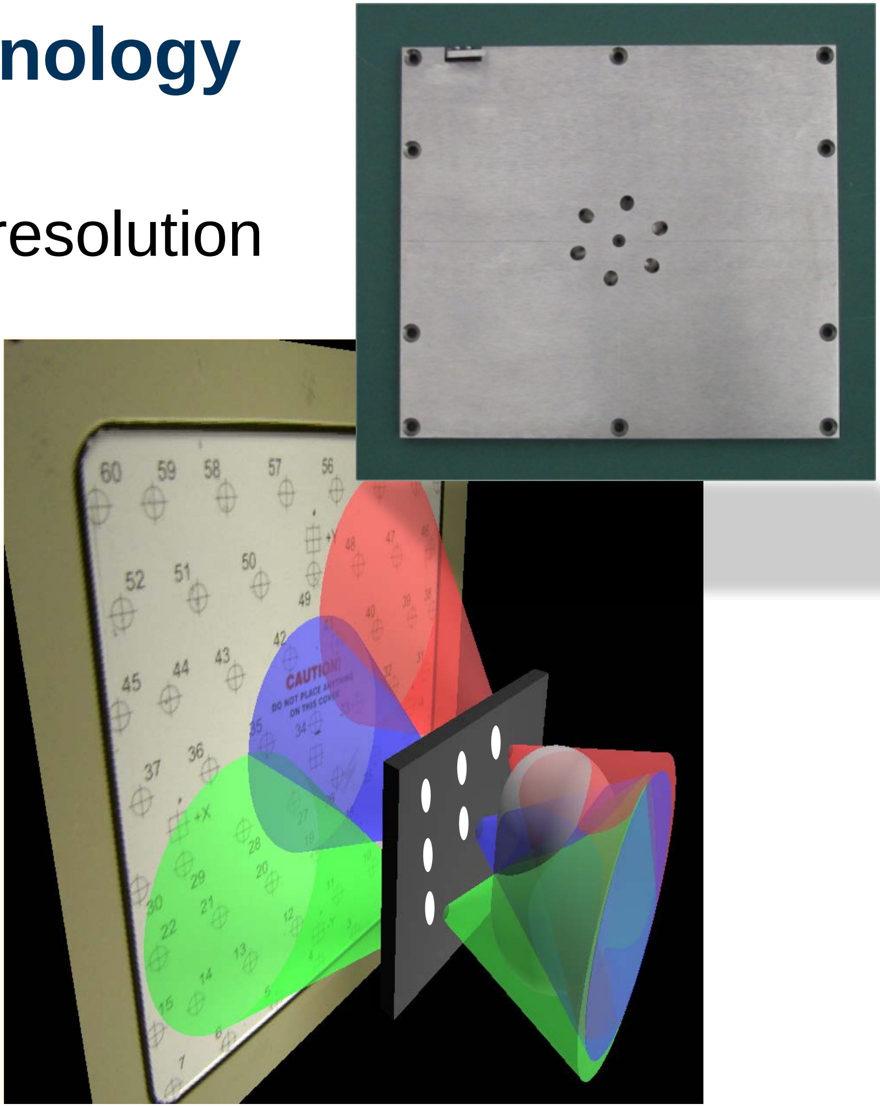
$^{177}LuCl_3$ bone scan in a normal mouse

Multi Pinhole SPECT Technology

- Higher sensitivity and better resolution



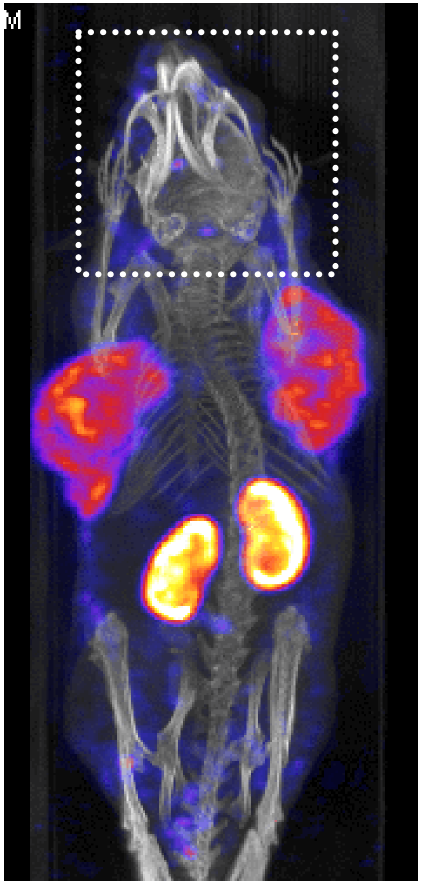
Single pinhole

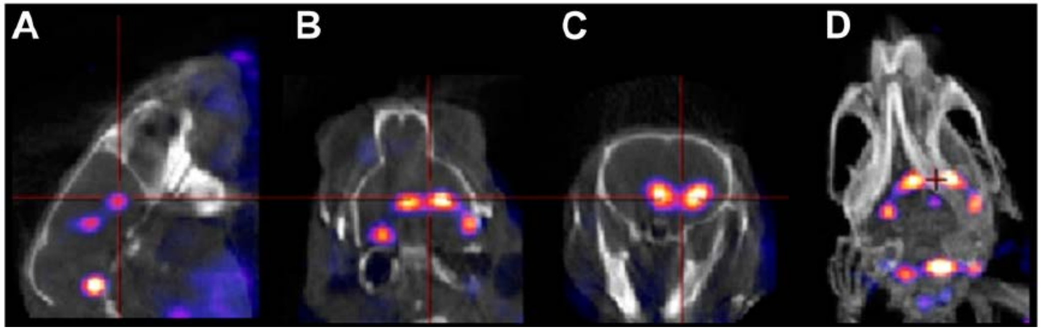


Multi pinhole

http://www.bioscan.com/

Performance of Multi Pinhole SPECT Technology





Choroid Plexus (folate receptor positive organ)

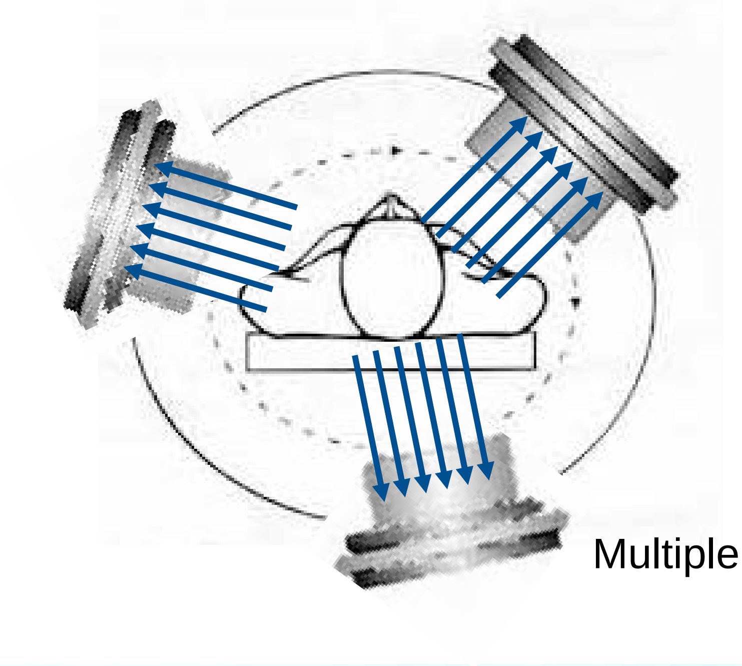
^{99m}Tc-Folate (tumor and kidney FR-positiv)

female nude mice with (human KB-cell

tumors, 24 h p.i.

Principle of SPECT

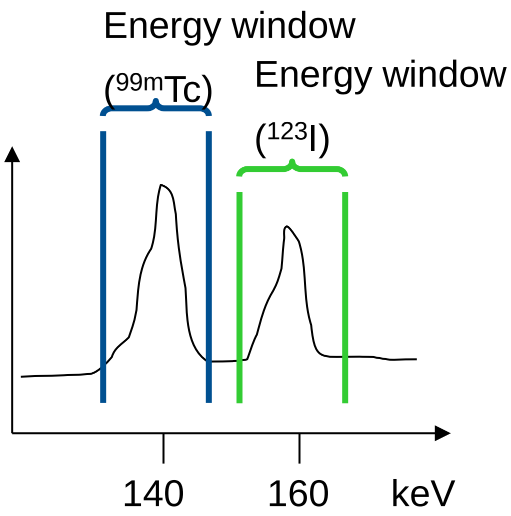
- Flat panel *head* used for detection
- Acquisition time depending on:
  - detector, collimator
  - size of the imaging region
  - amount of activity available.

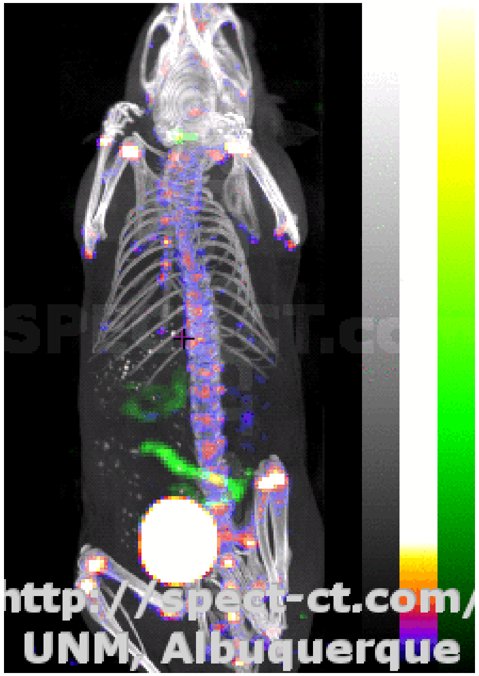


Multiple angle detection

Dual Isotope Imaging with SPECT

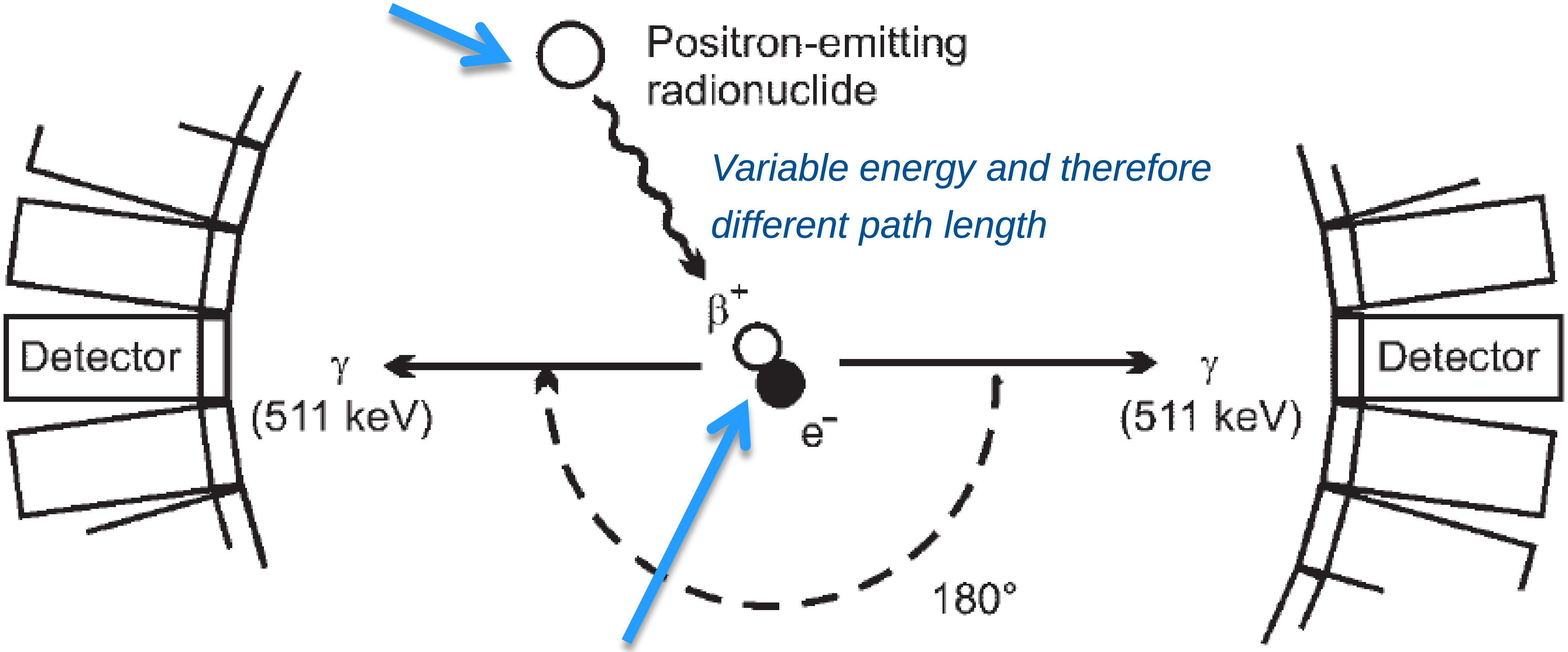
- Bone scan with ^{99m}Tc-MDP (red-blue) and Thyroid imaging with ^{123}I (green-yellow)
- ^{99m}Tc (140.5 keV)
- ^{123}I (159.0 keV)





Principle of PET

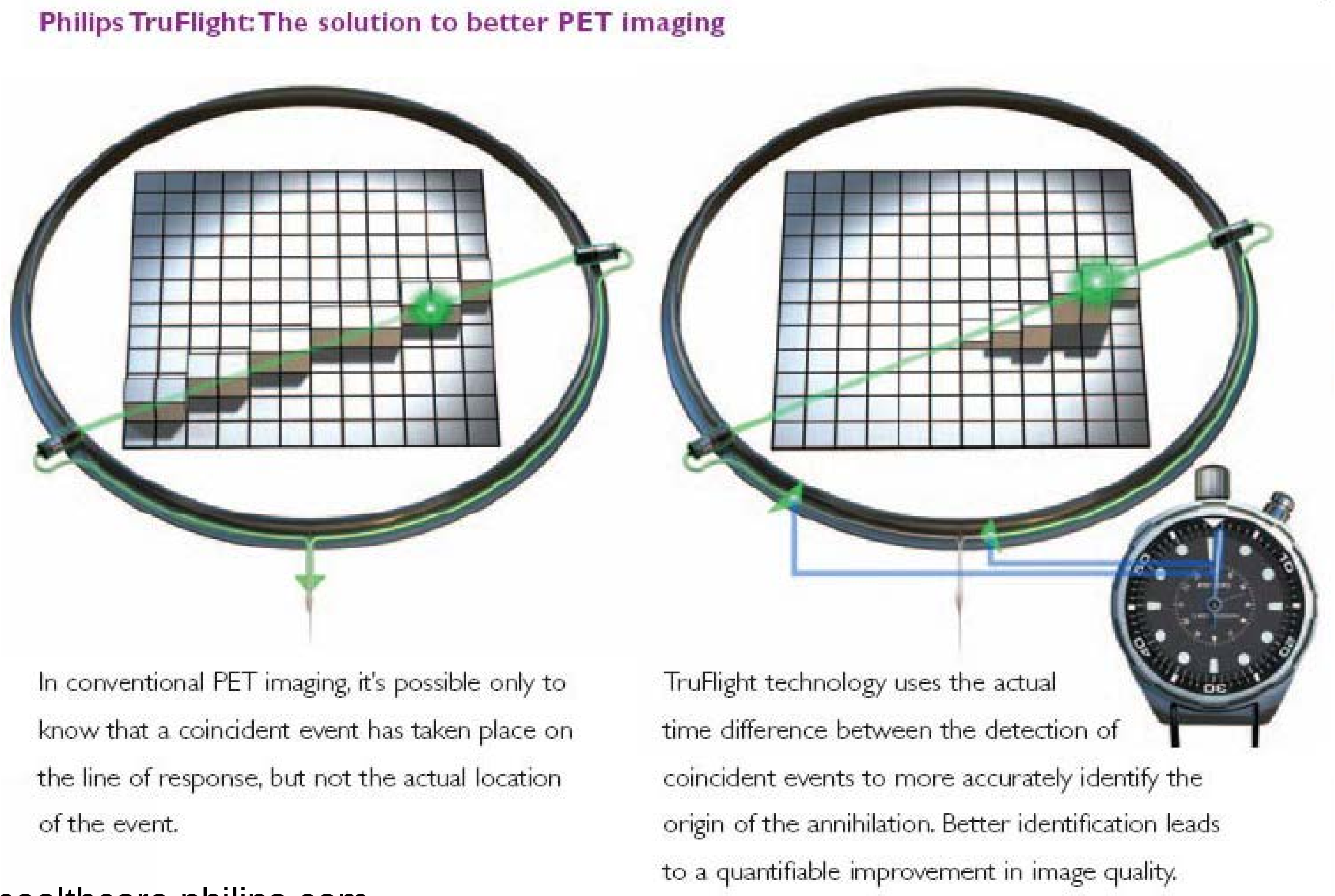
Site of radioactive decay



Variable energy and therefore different path length

Site of annihilation

Time-of-Flight PET (ToF-PET)



Philips TruFlight: The solution to better PET imaging

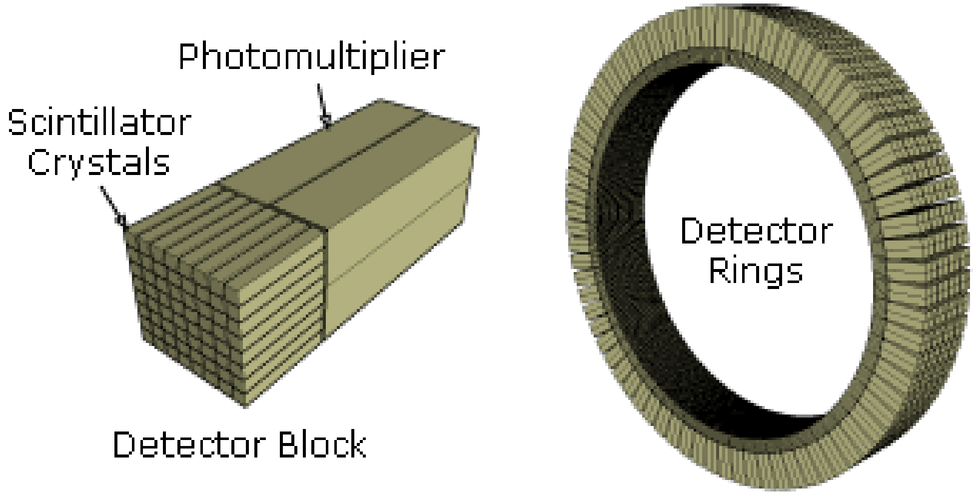
In conventional PET imaging, it's possible only to know that a coincident event has taken place on the line of response, but not the actual location of the event.

TruFlight technology uses the actual time difference between the detection of coincident events to more accurately identify the origin of the annihilation. Better identification leads to a quantifiable improvement in image quality.

http://www.healthcare.philips.com

PET Detectors

- Scintillation detectors:
  - conversion of radiation to visible light, detected by PMT, SiPMT or APD-, PIN-Diodes

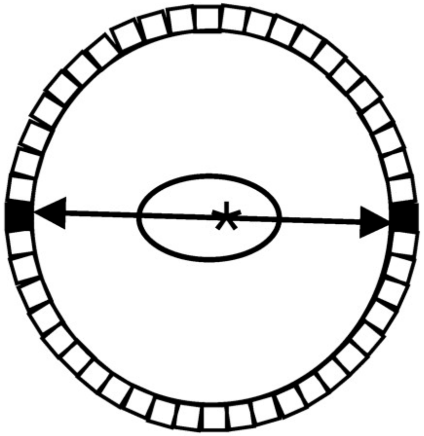


- Semiconductor detectors (CdTe or ZnCdTe)
- Multi-wire gas counters
- No collimators necessary!

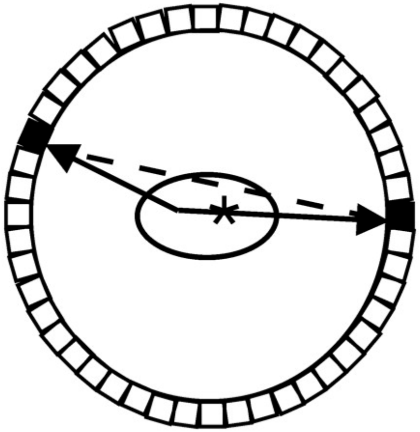
Possible Coincidence in PET

- ***True coincidences***, where the line drawn between the two hit detector elements for that event passes through the point of origin
- ***Scatter coincidences***, where one or both 511-keV photons undergo Compton scatter (unwanted)
- ***Random coincidences*** occur when two distinct radionuclei contribute one detected photon (unwanted)
- ***γ-coincidences*** occur when a 511 keV photon and a γ-photon are detected (unwanted)

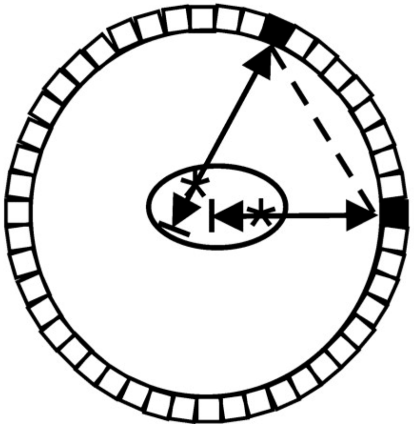
True coincidence



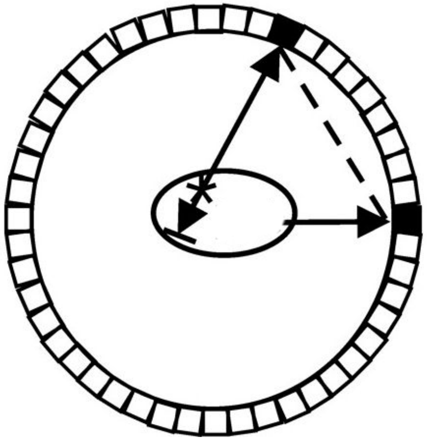
Scatter coincidence



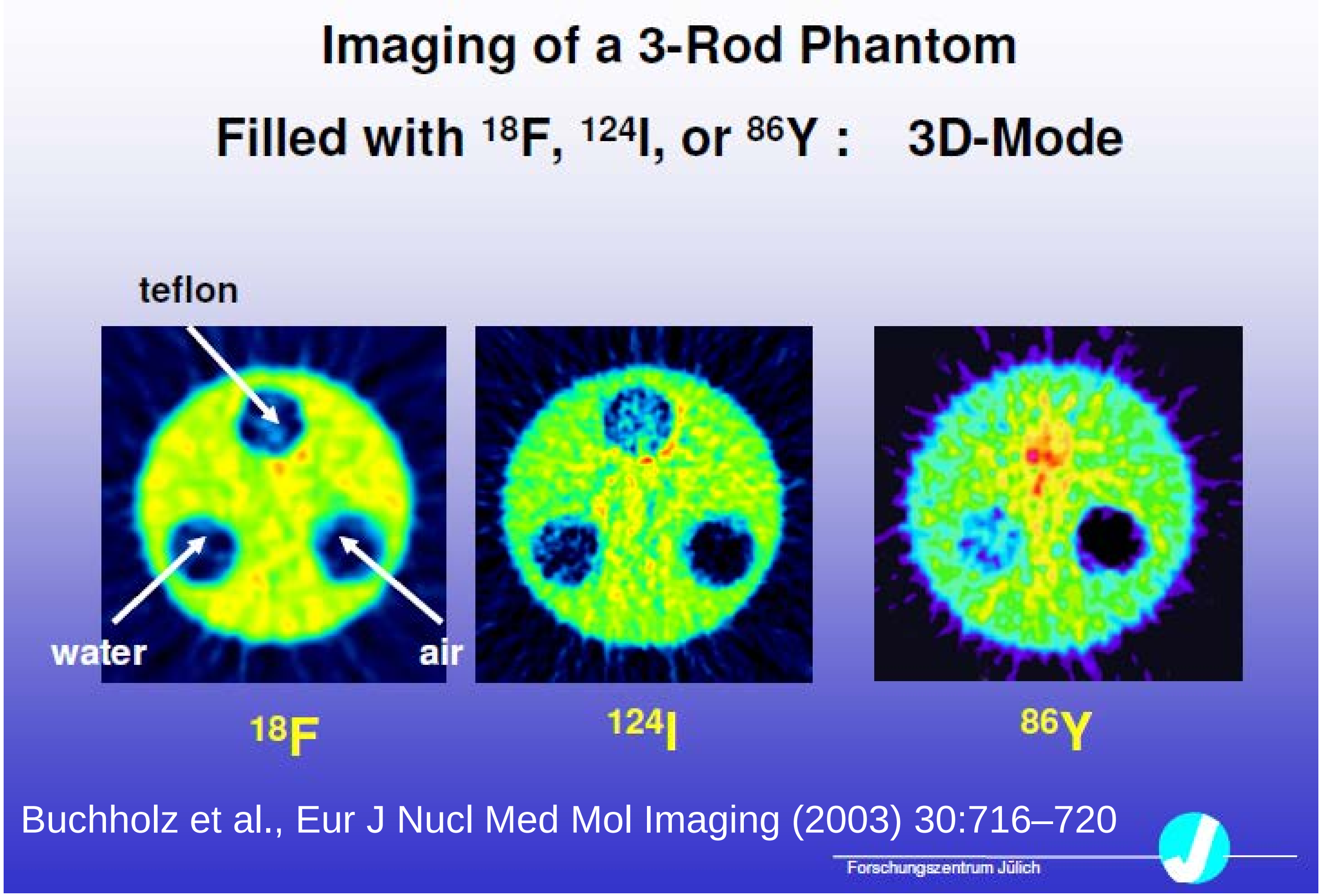
Random coincidence



γ-coincidence



Scatter Effects



Imaging of a 3-Rod Phantom

Filled with ^{18}F, ^{124}I, or ^{86}Y : 3D-Mode

^{18}F ^{124}I ^{86}Y

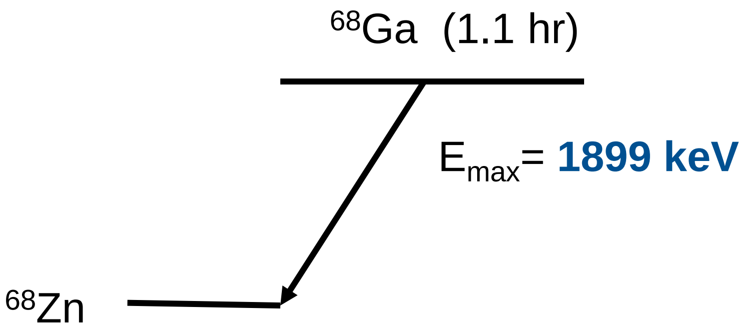
Buchholz et al., Eur J Nucl Med Mol Imaging (2003) 30:716–720

Forschungszentrum Jülich

Decay Properties of Selected Positron Emitters

	$T_{1/2}$ (min)	max. Positronen-energy (MeV)	mean distance in water (mm)
^{11}C	20.4	0.96	0.3
^{13}N	9.9	1.19	0.4
^{15}O	2.9	1.72	1.5
^{18}F	110	0.64	0.2
^{86}Y	870	3.14	3.2
^{124}I	5900	2.13	2.3

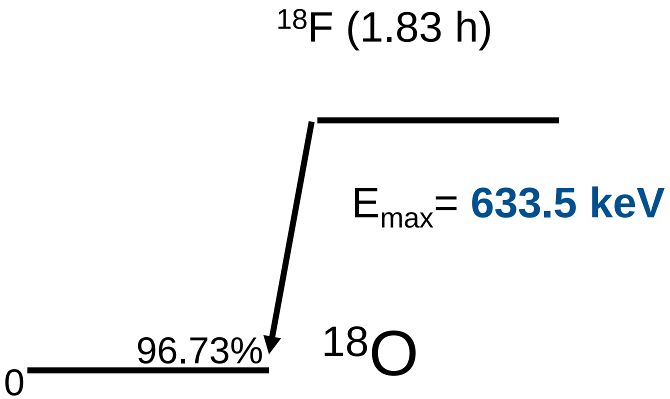
Influence of Positron Energy on Resolution



^{68}Ga (1.1 hr)

E_{max}= **1899 keV**

^{68}Zn



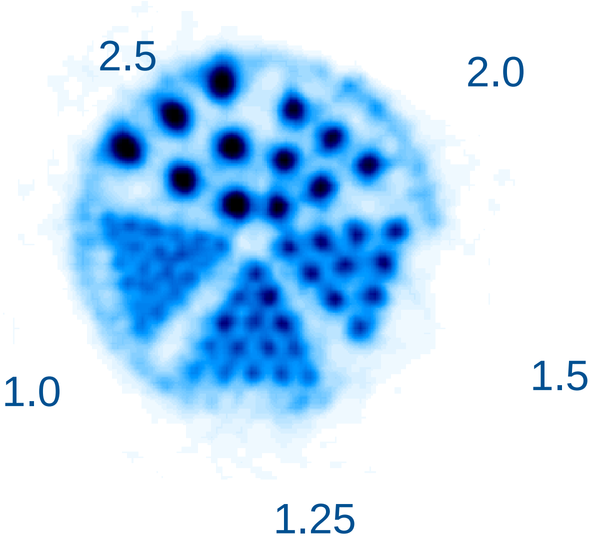
^{18}F (1.83 h)

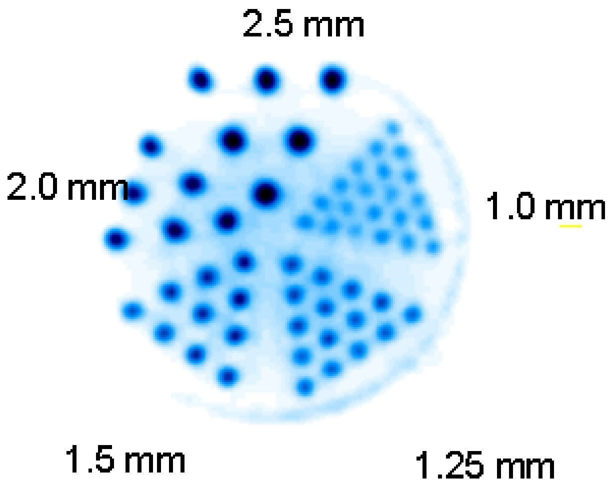
E_{max}= **633.5 keV**

96.73%

0

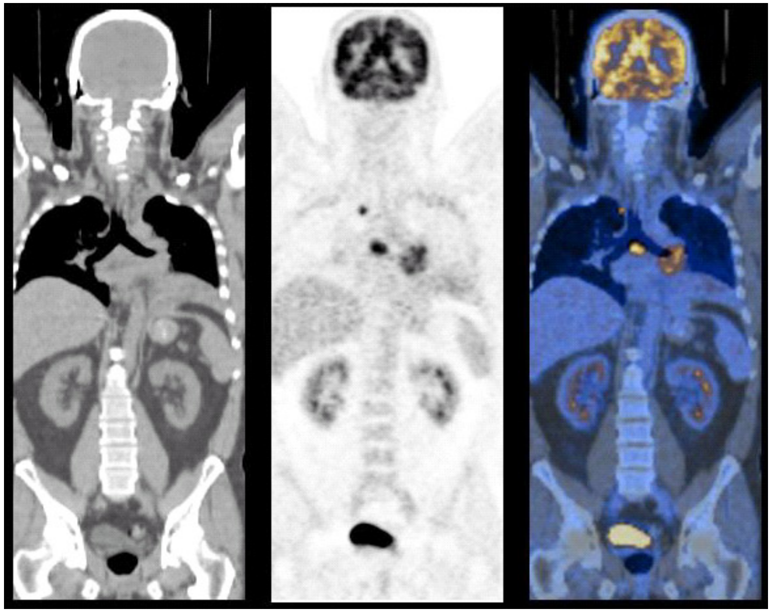
^{18}O





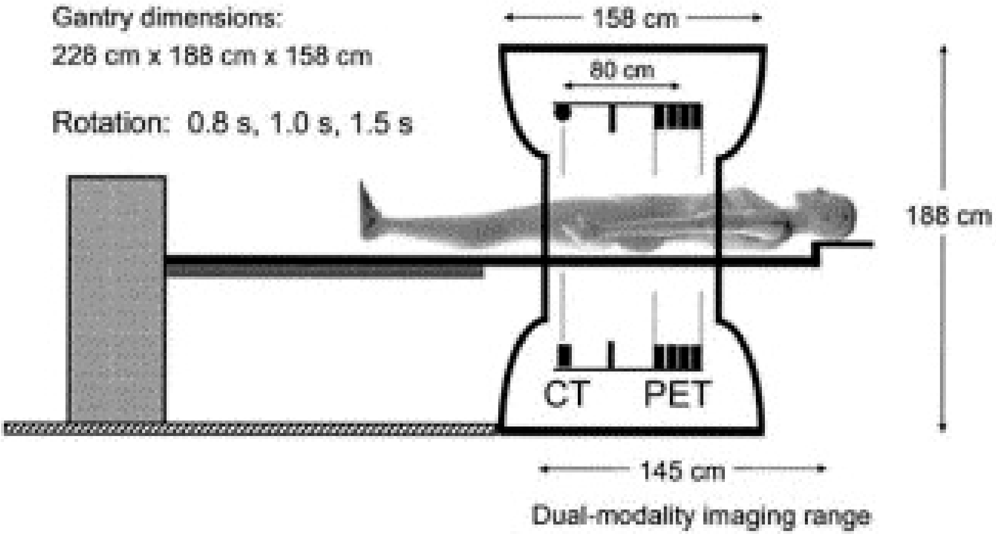
Hybrid Imaging: PET/CT, SPECT/CT, PET/MR

- Combine functional imaging with morphologic imaging



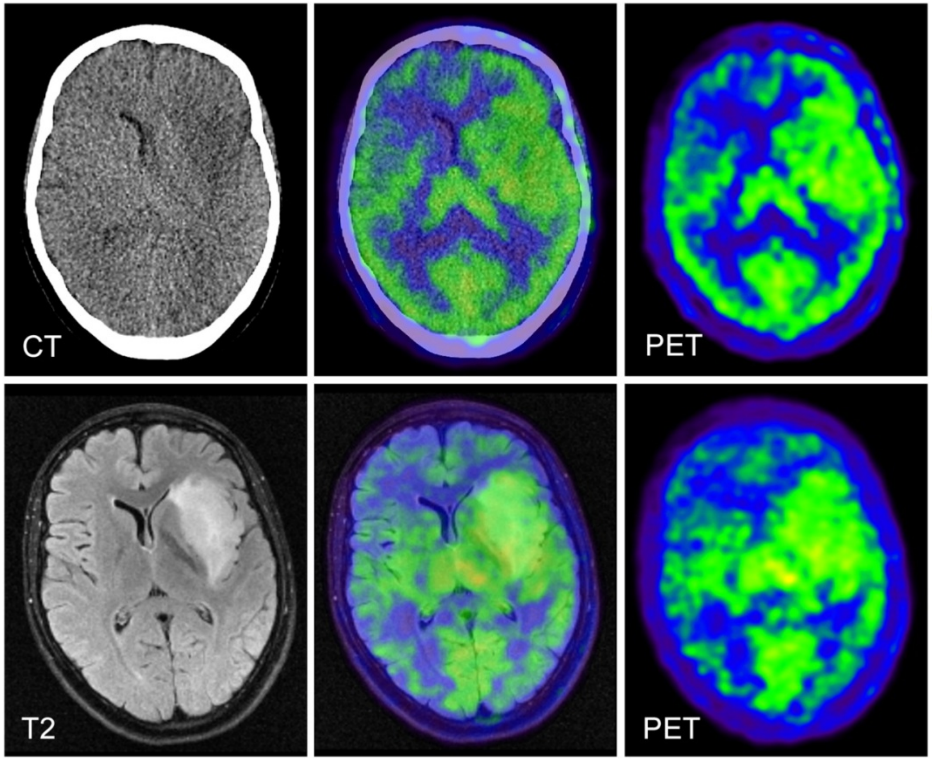
CT PET PET/CT

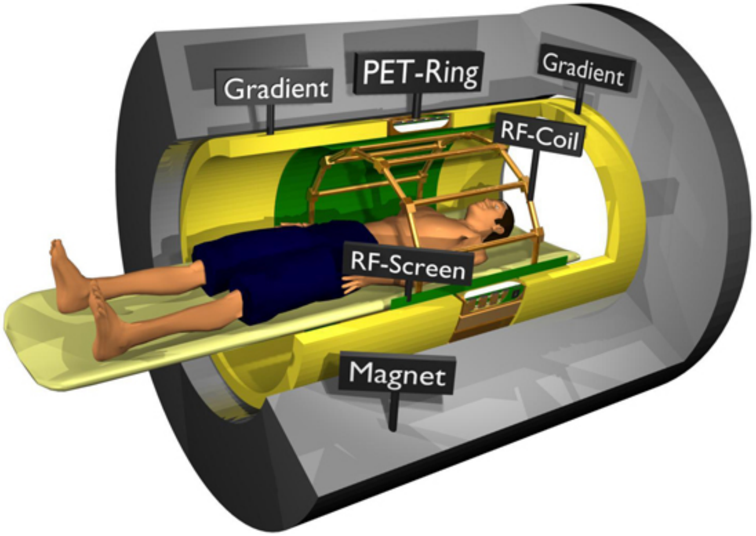
(^{18}F-FDG); source USZ



David W et al.. Seminars in Nuclear Medicine, Volume 33, Issue 3 2003 193.

Integrated PET/MR vs. PET/CT





www.hybrid-pet-mr.eu

Boss et al. *J Nucl Med, 2010, 51;1198.*

Important Radionuclides for SPECT

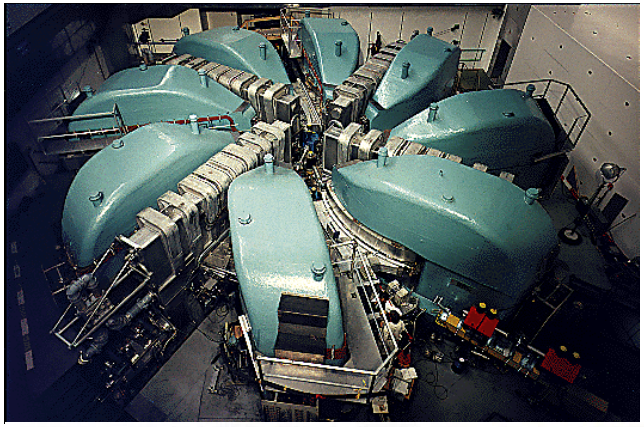
Radionuclide	Main Emission Energy	$T_{1/2}$
^{67}Ga	93, 185 keV	3.3 days
^{99m}Tc	140 keV	6.02 h
^{123}I	159 keV	13.3 h
^{111}In	171, 245 keV	2.8 days
^{201}Tl	135, 167 keV	3.0 days
^{131}I	364 keV	8.2 days

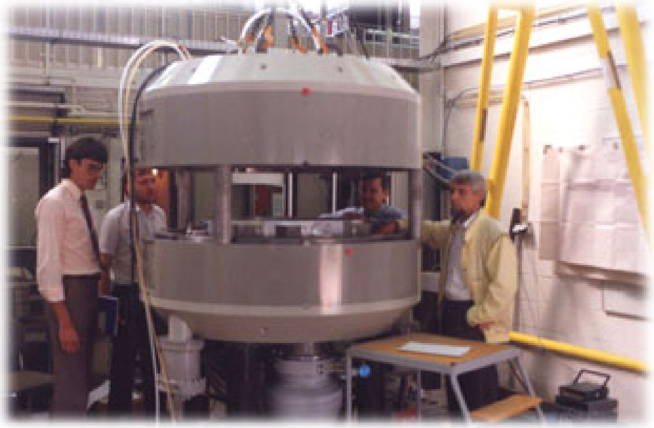
Important Radionuclides for PET

Radionuclide	$T_{1/2}$	Mean β^+ energy (keV)	Resolution (mm)
^{11}C	20 min	386	1.1
^{15}O	2 min	735	1.5
^{18}F	110 min	250	0.7
^{64}Cu	12.7 h	278	0.7
^{68}Ga	1.1 h	830	2.4
^{76}Br	16.3 h	1180	3.2
^{124}I	4.17 d	820	2.3
^{89}Zr	3.27 d	396	1.1

Radionuclide Production

Cyclotron





E.g.:

C-11

N-13

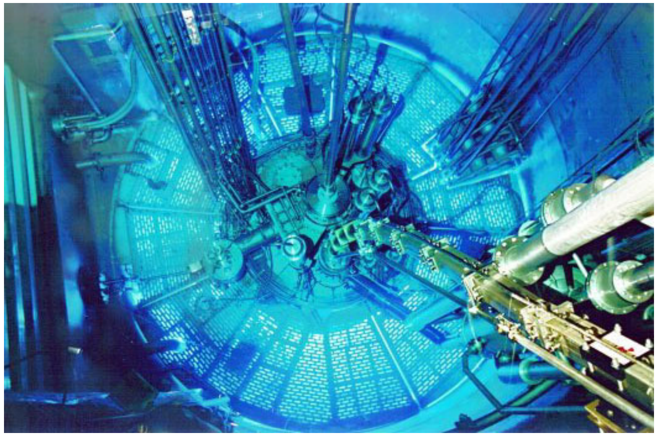
F-18

Cu-64/67

In-111

I-123

Reactor: Neutron bombardment



E.g.:

I-131

Sm-153

Ho-166

Lu-177

W-188

On-site generators

E.g.:

Ga-68 Tc-99m

Re-188

Radionuclide Production

nuclear reaction

^{11}C: ^{14}N(p,α)^{11}C

^{13}N: ^{13}C(p,n)^{13}N ; ^{12}C(d,n)^{13}N

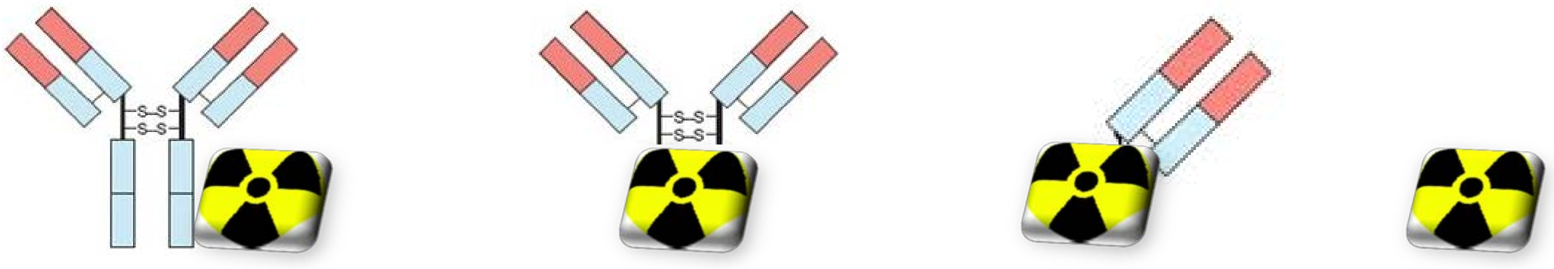
^{15}O: ^{14}N(d,n)^{15}O ; ^{15}N(p,n)^{15}O

^{18}F: ^{18}O(p,n)^{18}F

^{111}In: ^{111}Cd(p,n)^{111}In

^{131}I: ^{130}Te(n,γ)^{131}Te $\rightarrow$ ^{131}I

Do We Need So Many Different Radionuclides?

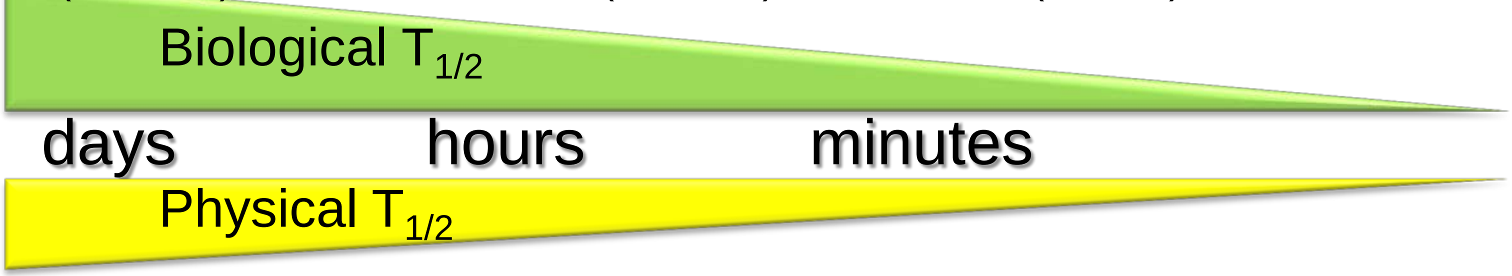


intact Ab (150kDa)

$F(ab)_2$ (100kDa)

F(ab) (50kDa)

Small molecules



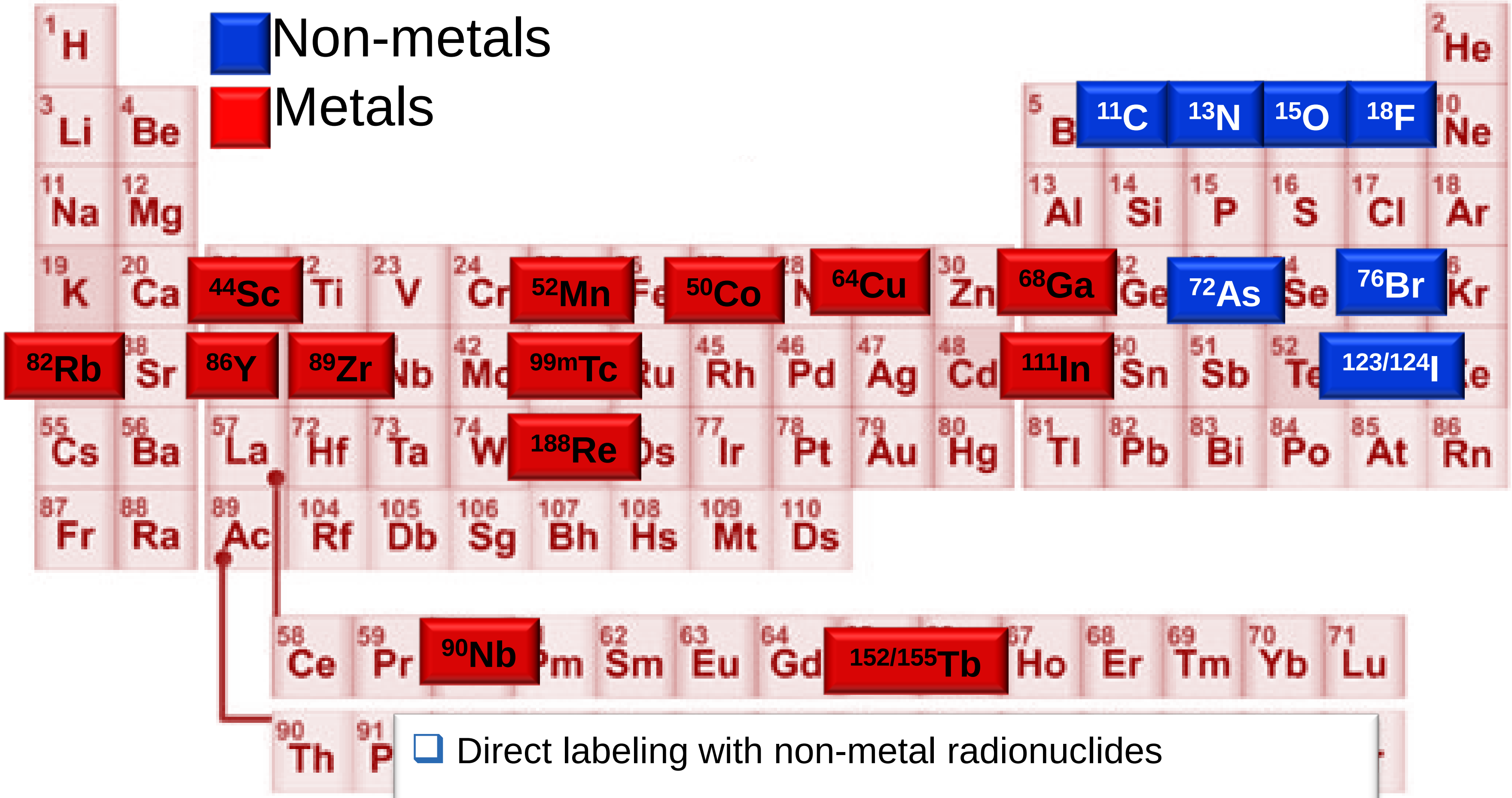
Biological $T_{1/2}$

days hours minutes

Physical $T_{1/2}$

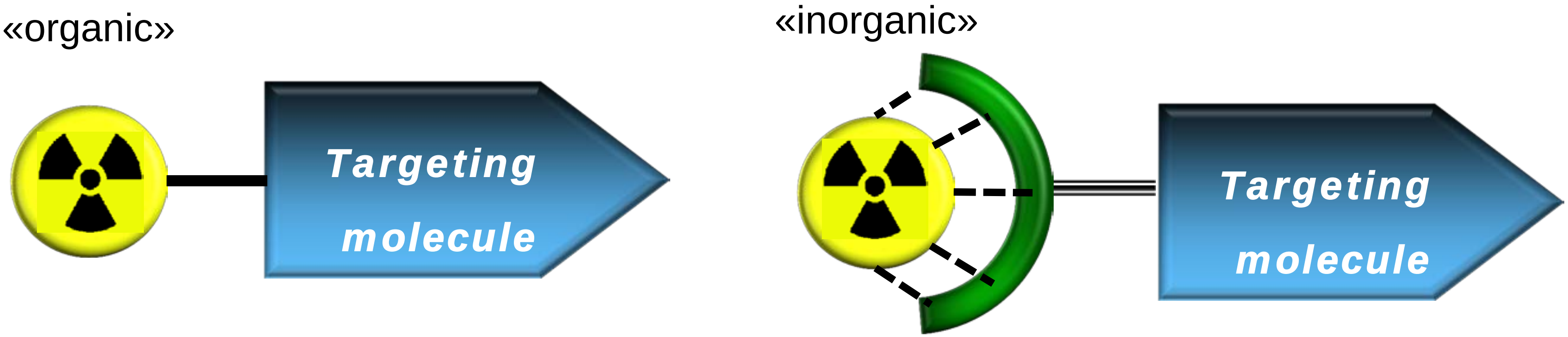
^{89}Zr	3.2 d	^{99m}Tc	6 h	^{11}C	20 min
^{111}In	2.8 d	^{64}Cu	12.7 h	^{18}F	1.9 h
^{67}Ga	3.2 d	^{76}Br	16.3 h	^{68}Ga	1.1 h
^{124}I	4.2 d	^{123}I	13.3 h		

Suitable Radionuclides for Diagnosis


🟦 Non-metals
🟥 Metals

- ☐ Direct labeling with non-metal radionuclides
- ☐ Indirect labeling strategies via bifunctional chelators
- ☐ 60 % of suitable radionuclides are metals!

Critical Issues for Functionalization and Radiolabeling of Molecules

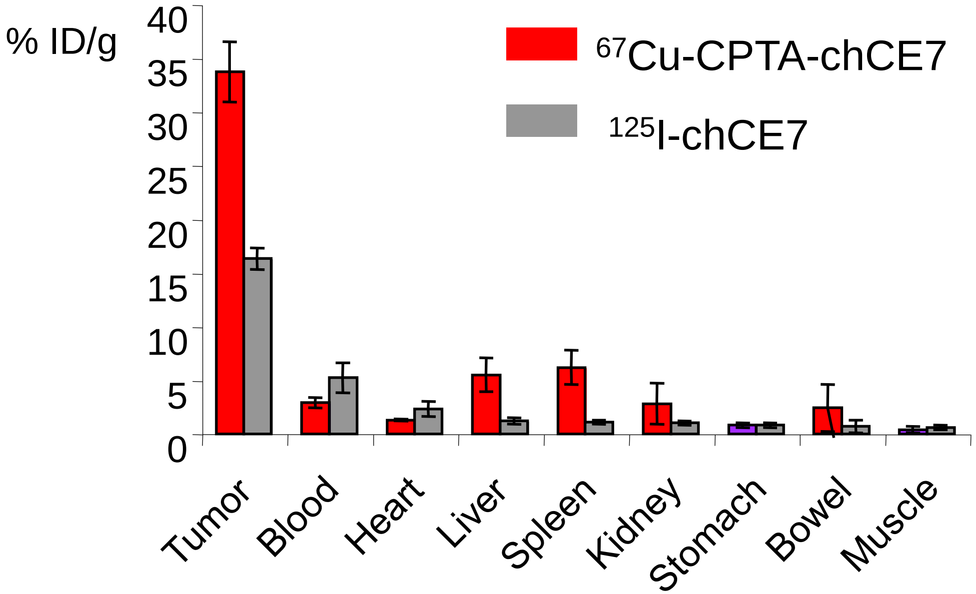

«organic»

«inorganic»

- Labeling yields
- Synthetic steps
- Avoid cross reactivity with other functional groups
- Avoid mixtures of products and formation of isomers
- Optimal pharmacokinetic
- Retention of biological activity and integrity

Potential Drawbacks of Iodine Radioisotopes

- Expensive isotopes with suboptimal decay and imaging characteristics
  - half-live too long for imaging (^{124}I)
  - decay energy too low for imaging (^{125}I)
  - high dose burden (^{124}I/ ^{131}I)
- In vivo de-iodination via hepatic deiodases (Tyr only)



Biodistribution of ^{67}Cu-labeled vs ^{125}I-labeled antineuroblastoma mAb chCE7 in tumor-bearing nude mice: higher tumor uptake of radiocopper labeled antibody

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PET Tracer Production

Interesting References

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