



De la physique fondamentale à la physique appliquée

L'imagerie du petit animal:
une thématique pluridisciplinaire



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Point commun ?



Luigi Galvani



Thomas Young



Erwin Schrödinger



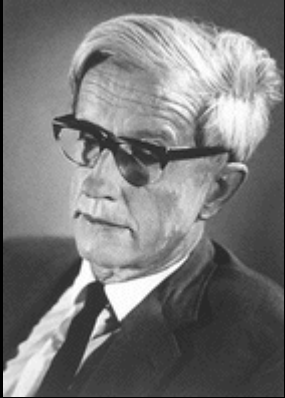
Ferdinand von Helmholtz



Niels Bohr

Ils ont tous osé s'aventurer dans " *l'espace* " qui unit la **physique** et la **biologie**

Exemple: parcours de Max Delbrück



Physicien de formation. Après sa thèse soutenue en 1930, il rejoint le laboratoire de Niels Bohr à Copenhague.

En 1932, Niels Bohr intervient, lors d'une conférence, sur le thème « la lumière et la vie », ce qui aura sur Delbrück une influence décisive et l'amènera à s'orienter vers la biologie, et plus précisément la nature du gène.

L'idée était que la vie ne pouvait être comprise que grâce à un point de vue complémentaire des approches existantes.

La première expérience est révélatrice de sa formation

En physique:

Etude de la matière = bombardement par des particules

En biologie:

Il décide d'étudier le gène par le biais de l'effet que des rayonnements induisent sur celui-ci

1935:

l'analyse de la fréquence des mutations permet d'estimer la dimension d'un gène (volume d'environ 10 distances atomiques de côté)

Delbrück interprète les mutations en termes quantiques

il propose que chaque mutation représente un saut quantique entre deux états stables du gène.

il s'est avéré que cette étude était incorrecte mais elle eut le mérite de démontrer que l'étude des gènes et du vivant était possible à l'aide d'outils et de démarches du domaine de la physique.

1937, départ pour les Etats-Unis

il est convaincu que le meilleur modèle d'étude du vivant doit être le plus simple possible.

➤ Etude du bactériophage (sa très faible taille l'assimile à un « gène pur »)

➤ Etude des mécanismes de réplication

➤ Mutations possibles chez les bactéries: naissance de la génétique bactérienne
Expérience la plus célèbre: *rôle de l'ADN et des protéines dans la transmission de l'information génétique*

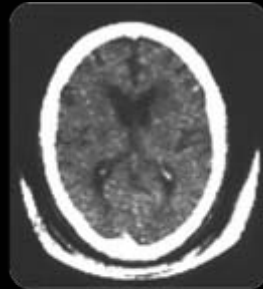
➤ Il partage en 1969 le prix Nobel de médecine avec Luria et Hershey

Mais encore...

1901: Röntgen obtient le premier prix Nobel de physique

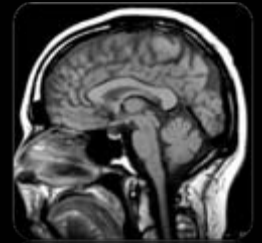


1979: Cormack et Hounsfield obtiennent le prix Nobel de médecine



1977: coupe de 10mm

2003: Lauterbur et Mansfield obtiennent le prix Nobel de médecine



Le 24 mars 2003, le Président de la République présente le Plan cancer

Objectifs: réduire de 20% la mortalité sur 5 ans

Moyens: 70 mesures, 600 M€

L'une des mesures: mieux structurer la recherche cancérologique en France

- 7 cancéropôles créées en 2003

- Création de l'INCa en 2005

2008, rapport de la Cour des Comptes

le plan cancer a constitué un cadre cohérent et que ses objectifs ont été largement atteints

1/3 des mesures pleinement concrétisées,

1/3 modérément et le dernier tiers peu/pas mis en œuvre

Le cancer reste aujourd'hui la première cause de mortalité en France avec 145 000 décès en 2008.

Février 2009: Rapport du Pr Jean-Pierre Grünfeld

" Recommandations pour le Plan Cancer 2009-2013 : pour un nouvel élan "

Diagnostic

*Examen clinique
Imagerie médicale
Agent de contraste*



Thérapie

*Radiothérapie (externe, interne, métabolique)
Hadronthérapie
La chimiothérapie (ciblée)
Chirurgie*

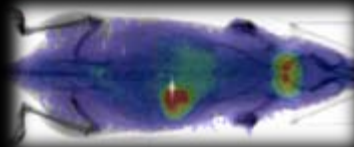
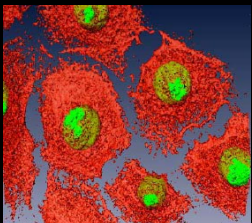


GDR MI2B

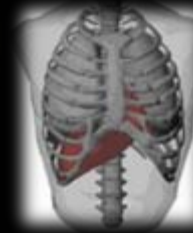
*Instrument et Méthodes
pour la lutte contre le cancer*

Recherche fondamentale

*Radiobiologie: interaction rayonnement / cellule
Imagerie in vitro
Imagerie cellulaire
Imagerie in vivo*



BioInformatique

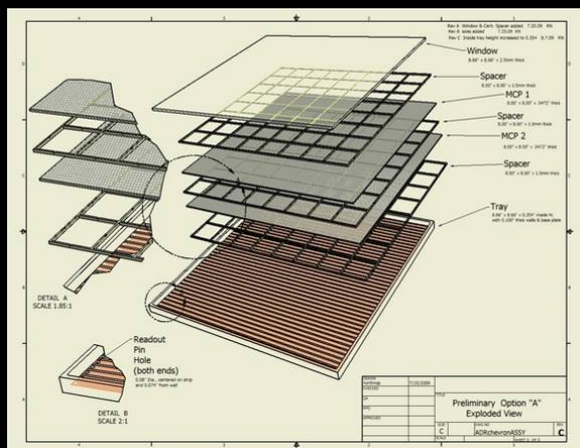


Diagnostic

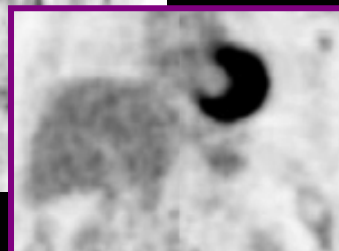
L'imagerie moléculaire doit être
Exacte (quantitative),
précoce,
prédictive.

Amélioration de la résolution spatiale et de
l'efficacité de détection en Tomographie
d'Emission de Positons (TEP)

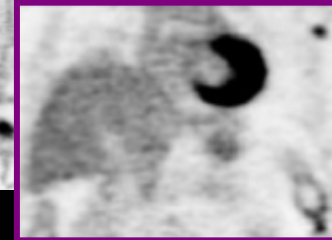
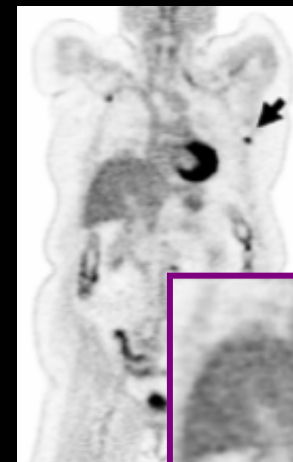
- Mesure du temps de vol (TOF)
- Electronique de lecture dédiée
- Couplage cristal/photodétecteur
- Instrumentation innovante (Sc-44 PET 3 γ)
- Algorithme de reconstruction



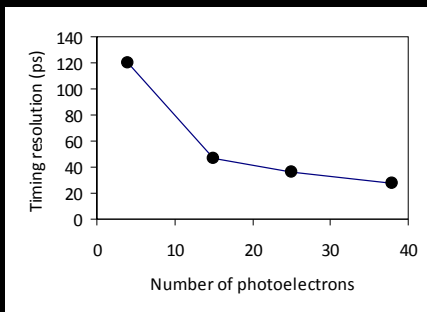
LAPPD Project (Fermilab, UC)



FORE + 2D OSEM



3D OSEM + TOF



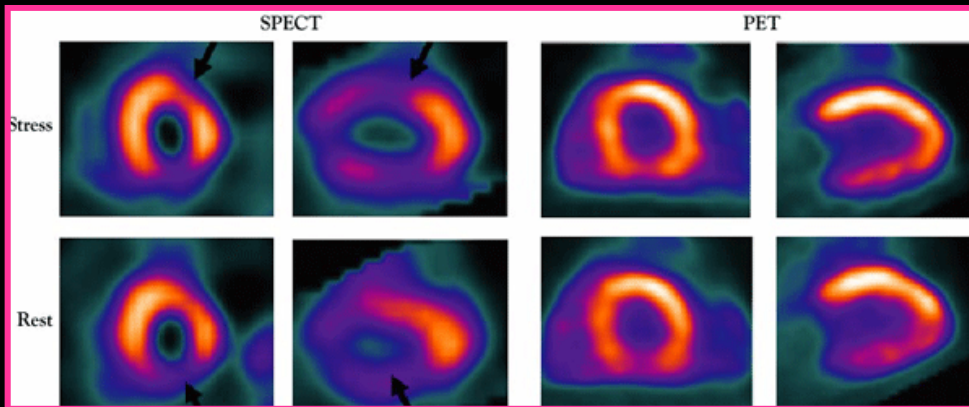
Diagnostic

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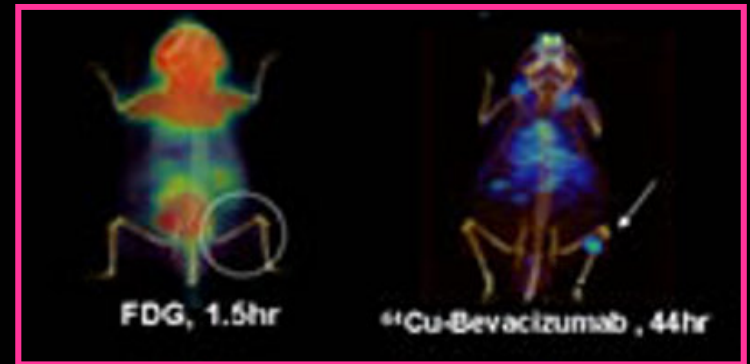


Développement de nouvelles molécules radiomarquées

- Deux centres de recherche et production (ARRONAX, IPHC)
- Radionucléide émergents pour la médecine nucléaire
 - Rb-82, Ge-68/Ga-68, Cu-64/67, Sc-44/47, Zr-89
- Recherche en radiochimie

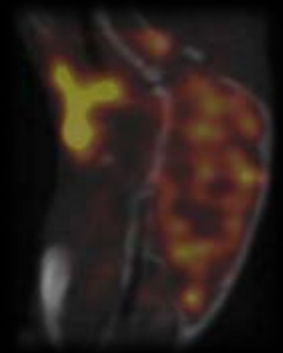
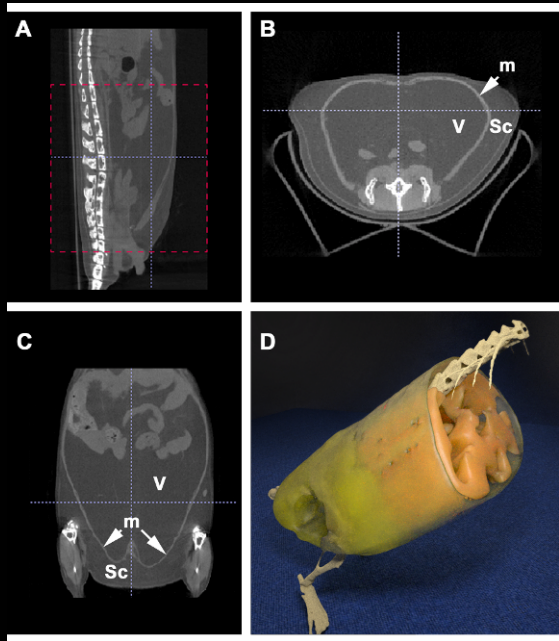
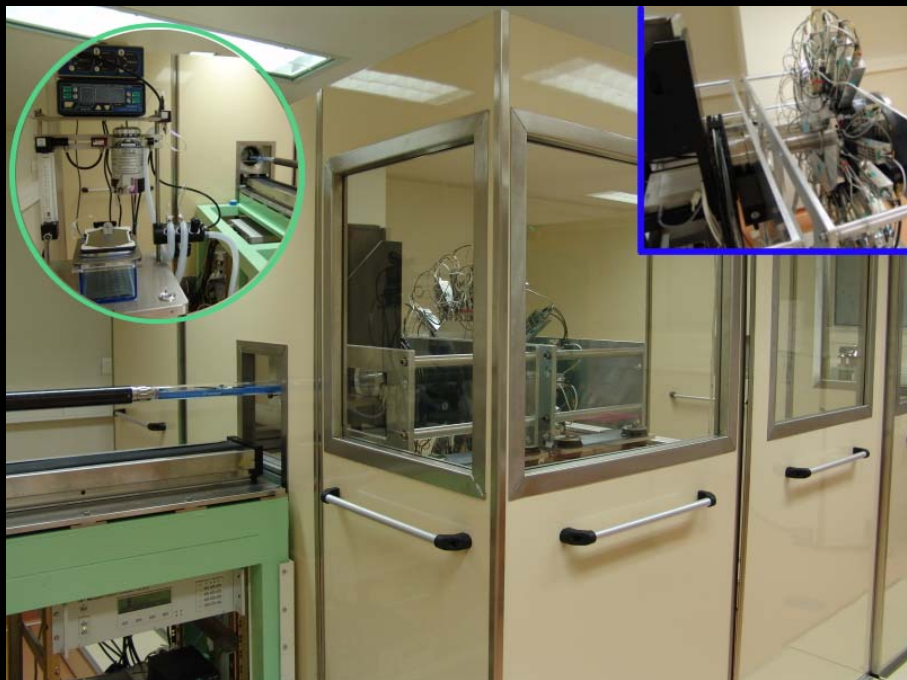


Tc-99m / Rb-82



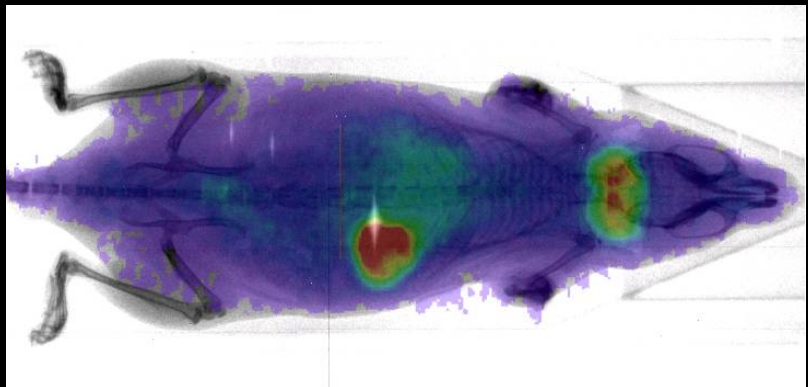
Tumor angiogenesis (FDG/Cu-DOTA)

Plate-forme d'imagerie du petit animal: approche séquentielle

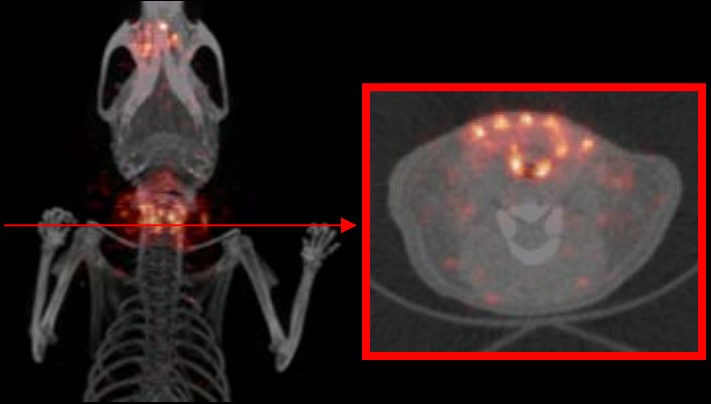


μ SPECT

μ CT

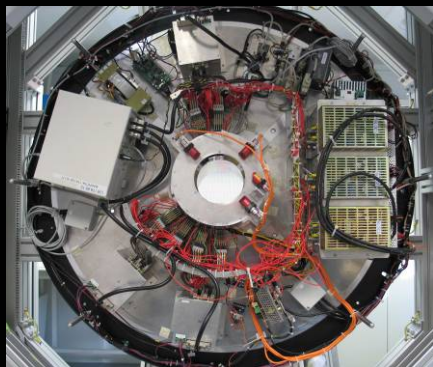


Criblage haut débit



IPHC

Plate-forme d'imagerie du petit animal: approche combinée



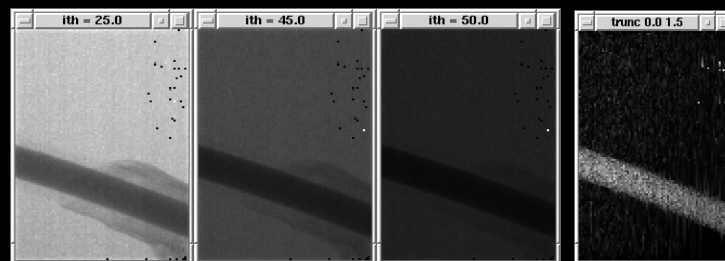
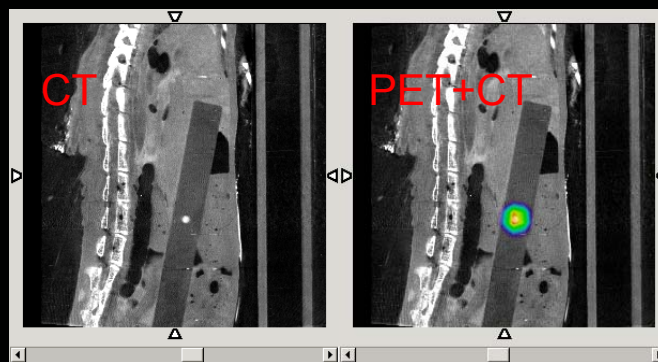
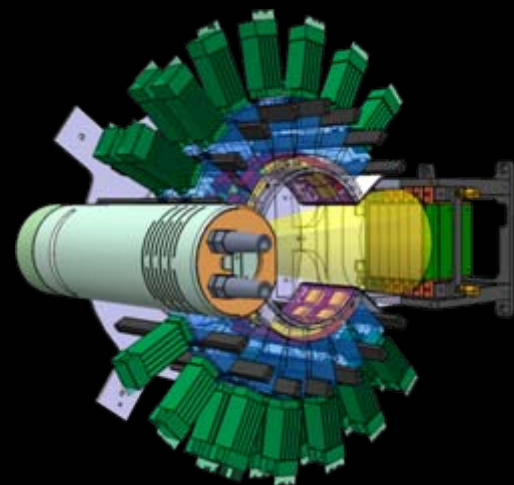
ClearPET (EPFL)

+

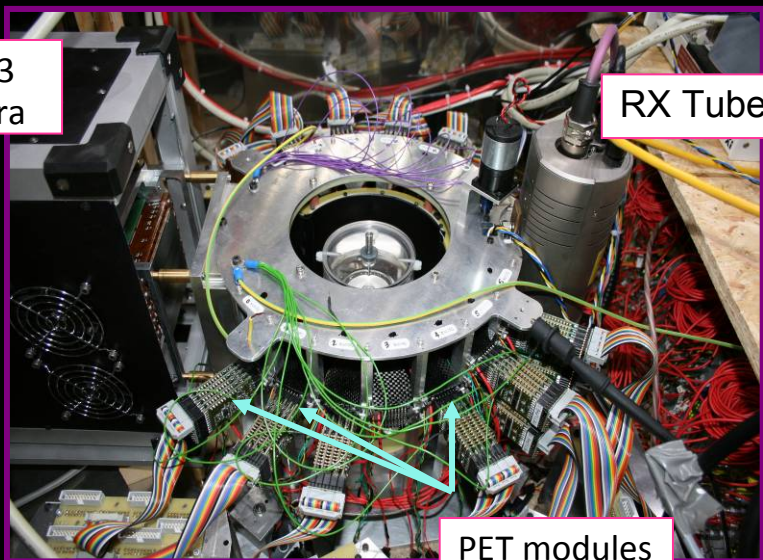


XPAD (CPPM)

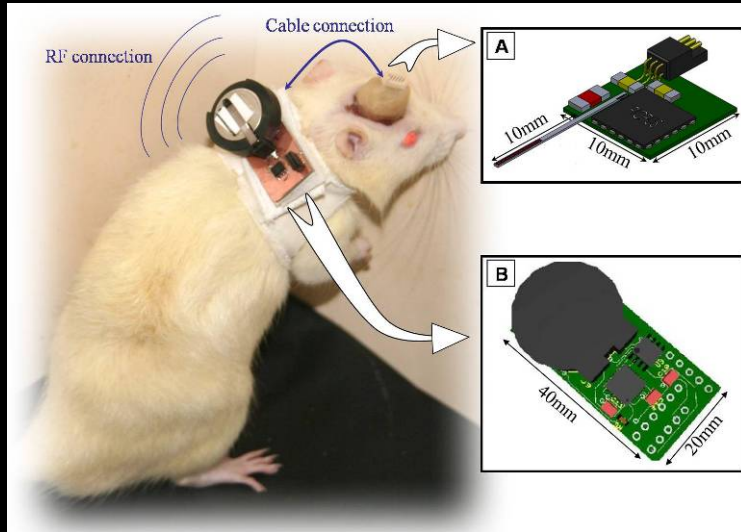
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Conventional CT / Spectral CT



Imagerie du petit animal: approche éveillée



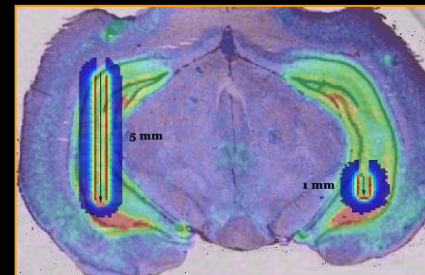
Premier test



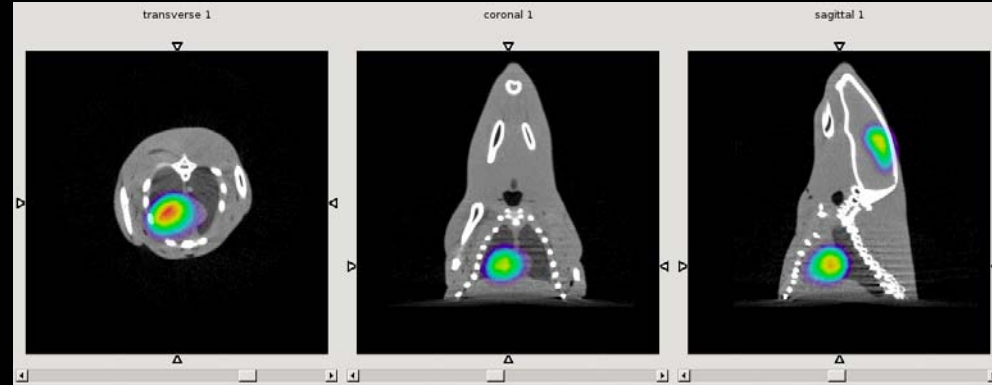
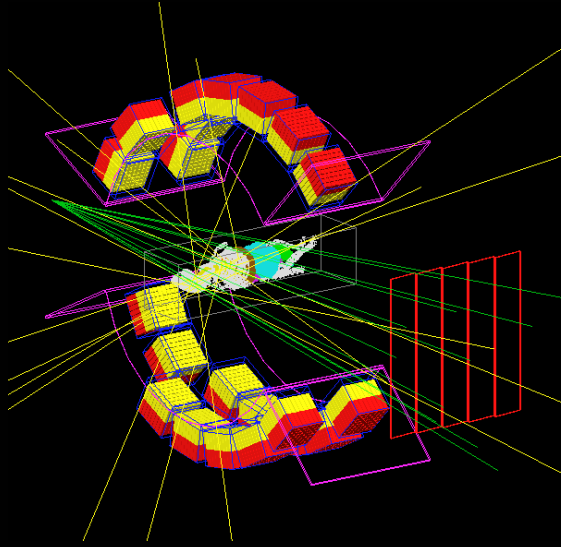
Premier prototype

Objectifs:

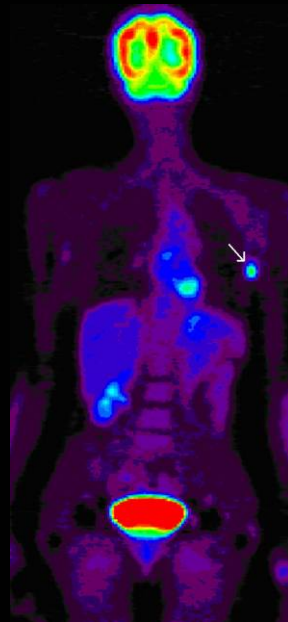
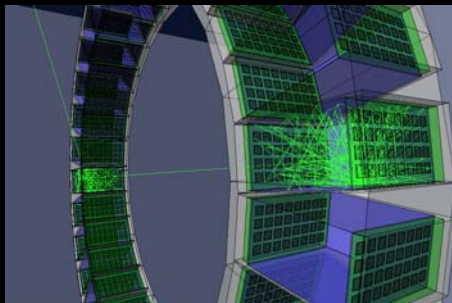
- Supprimer le biais introduit par l'anesthésie
- Etude du comportement en temps réel
- Approche multimodale



Outil de simulation pour l'imagerie d'émission (transmission): Gate



Courtesy of C Morel, CPPM



CEA/SHFJ

Conception:

- Prototypes

Optimisation:

- Protocoles d'acquisition
- Algorithmes de reconstruction

Amélioration:

- Quantification
- Corrections

Collaboration openGATE

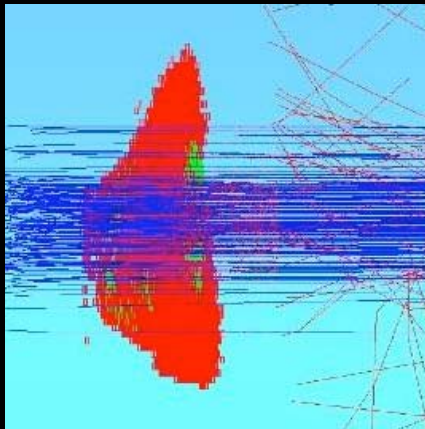
Outil de simulation pour la radiobiologie: Geant4-DNA

« A major challenge lies in providing a sound mechanistic understanding of low-dose radiation carcinogenesis »

L. Mullenders et al. (2009), Nature Reviews Cancer

Objectif : adapter la plate-forme de simulation généraliste Geant4 aux problématiques d'interactions du rayonnement avec les systèmes biologiques au niveau de la cellule, voire de l'ADN (« micro-dosimétrie »)

Exemple: simulation haute résolution de l'irradiation d'une cellule par un faisceau de particules alpha de 3 MeV.

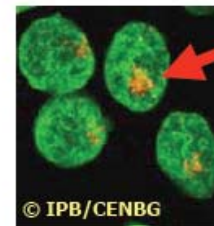


Validation par l'expérience

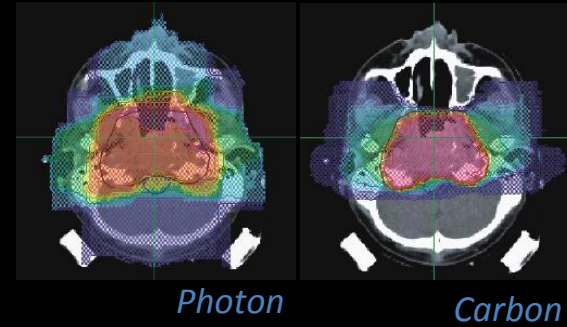
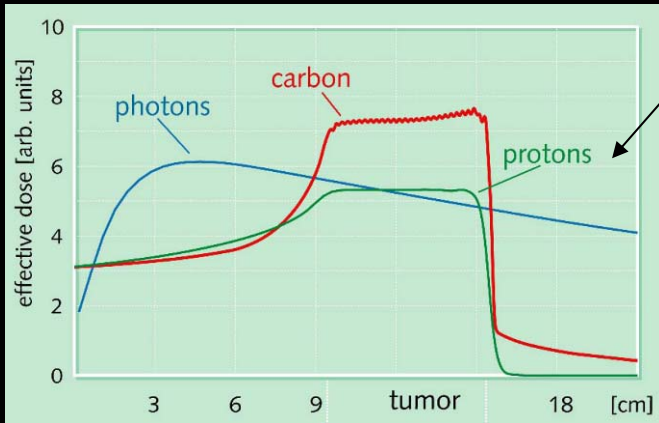


CENBG AIFIRA irradiation facility in Bordeaux, France

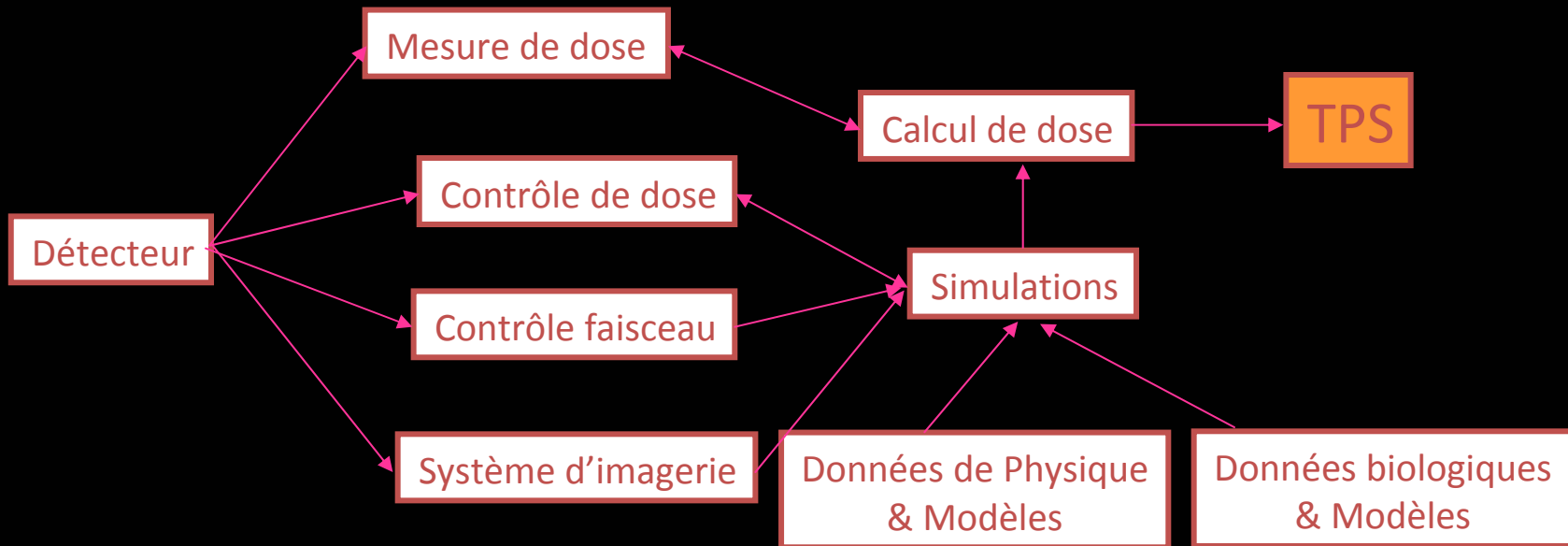
- AIFIRA equipped with a cellular irradiation microbeam line
- 3 MeV proton or alpha beam
- **single cell & single ion mode**
- Targeting accuracy on living cells **in air** : a few μm
- Able to quantify DNA damages like double strand breaks



Hadrontherapie



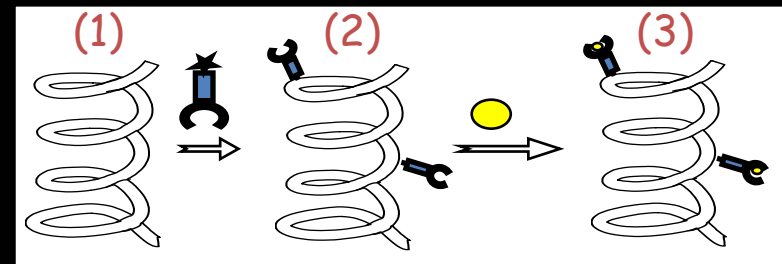
Objectif: Optimiser le plan de traitement (TPS) dans le cas du carbon



ETOILE, ARCHADE, ENVISION (FP7)

LPC Caen, LPC Clermont, IPNL, IMNC, IPHC, CPPM

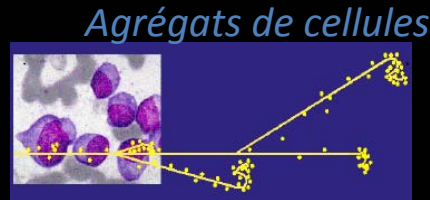
Thérapie: approche isotopique



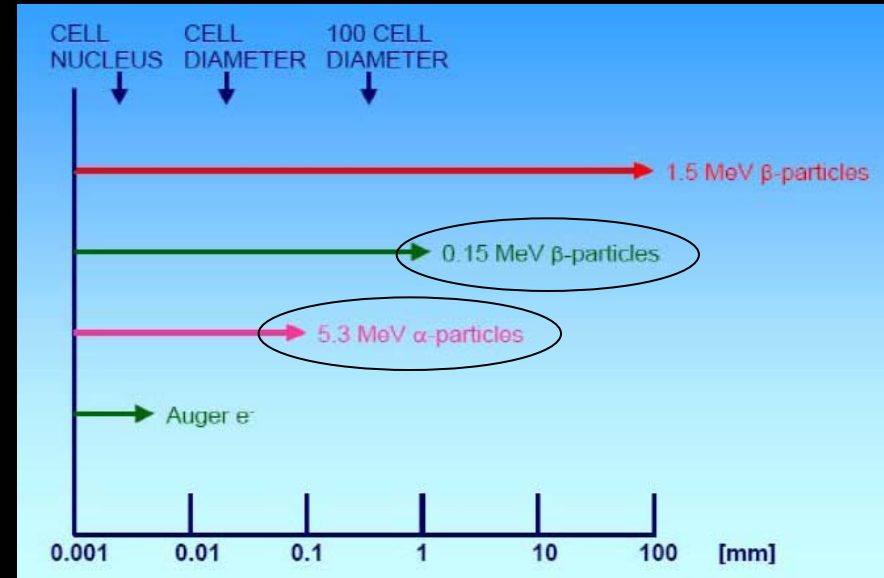
Principe de l'immunothérapie:

- (1) Reconnaissance spécifique de cellules cancéreuses (anticorps, fragments, peptides...)
- + (2) Chelate/Linker (dérivé du DTPA, DOTA)
- + (3) partie thérapeutique (particule chargée)

β^- : Cu-67, Sc-47



α : At-211



Applications de l'alpha-Immunotherapie:

- cancer mono-cellulaire (leucémie)
- Invasion micro-métastatique
- Faible résidu après chimiothérapie
- Faible résidu après chirurgie (excérèse tumorale)

Imagerie per-opératoire

Protocole du ganglion sentinelle

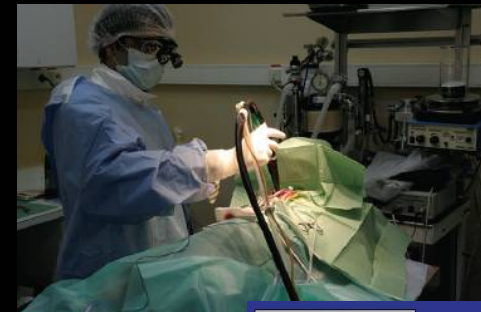


- 1- Vérifier avant l'intervention la distribution de la radioactivité (γ camera)
- 2- Localiser pendant l'intervention les ganglions (γ probe + γ camera)
- 3- Vérifier après l'intervention la qualité de l'exérèse (γ camera)

Tumeur du cerveau

Principalement dédié à la chirurgie des gliomes.

Objectif: Localiser puis exciser la tumeur pendant l'acte chirurgical



Détection optique + β
+
Outil d'exérèse

Thérapie

Radiothérapie (externe, interne, métabolique)
Hadronthérapie
La chimiothérapie (ciblée)
Chirurgie

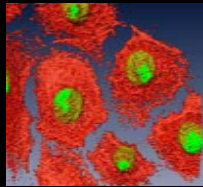
Diagnostic

Examen clinique
Imagerie médicale
Agent de contraste

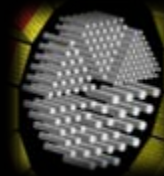


Recherche fondamentale

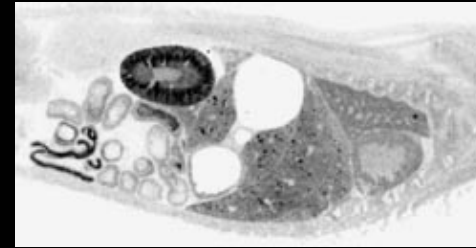
Radiobiologie: interaction rayonnement / cellule
Imagerie in vitro
Imagerie cellulaire
Imagerie in vivo



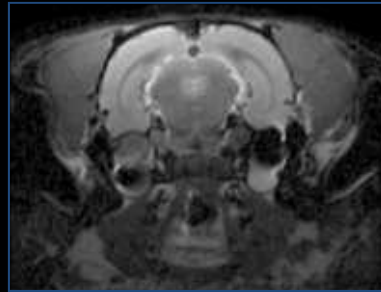
BioInformatique



Small Animal molecular Imaging

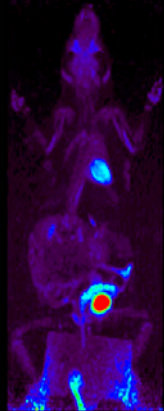


Autoradiography



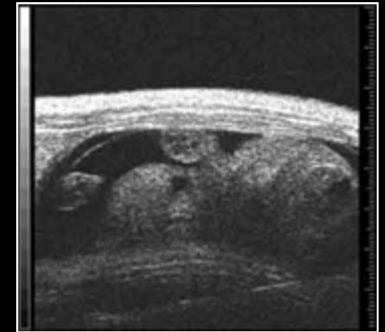
MRI

Unregistered HyperCam

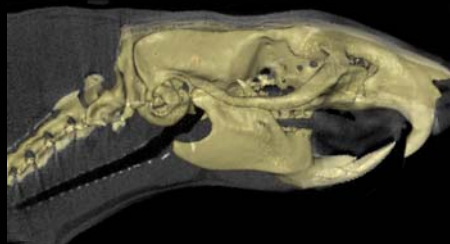


Manchester institute

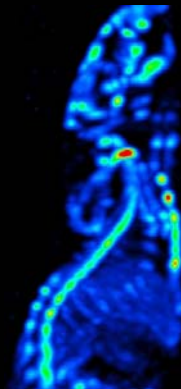
PET system



Ultrasound

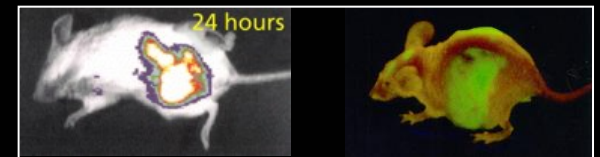


CT system



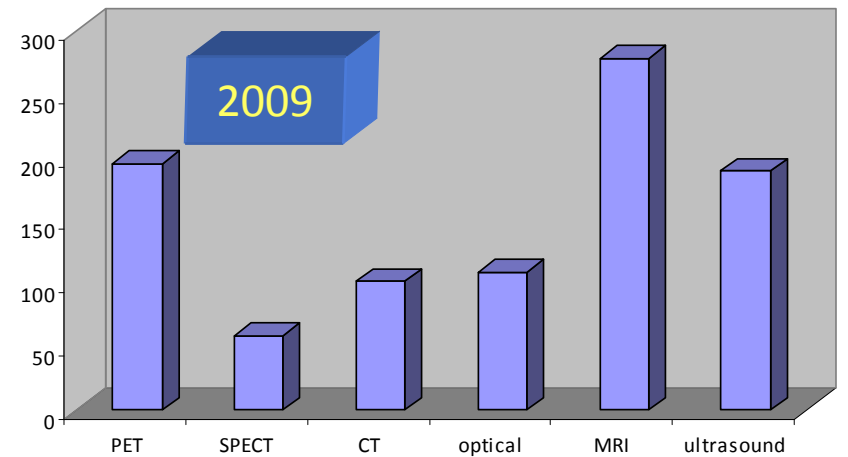
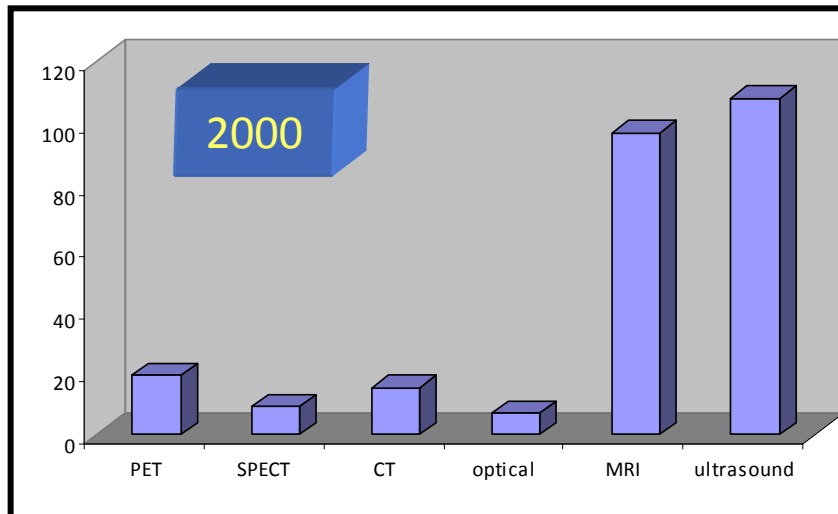
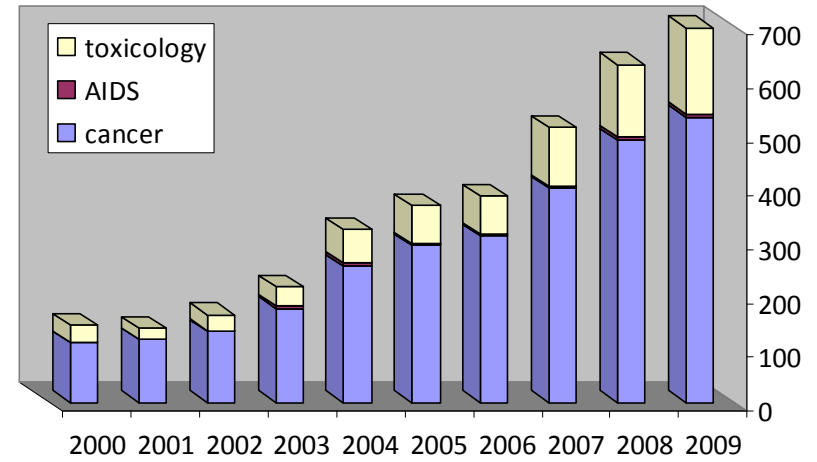
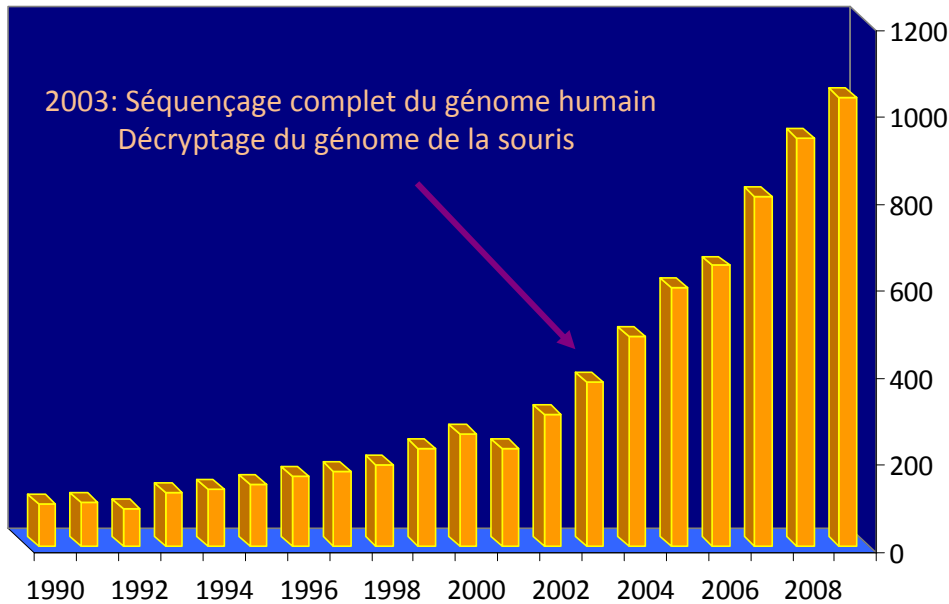
Julich Research center

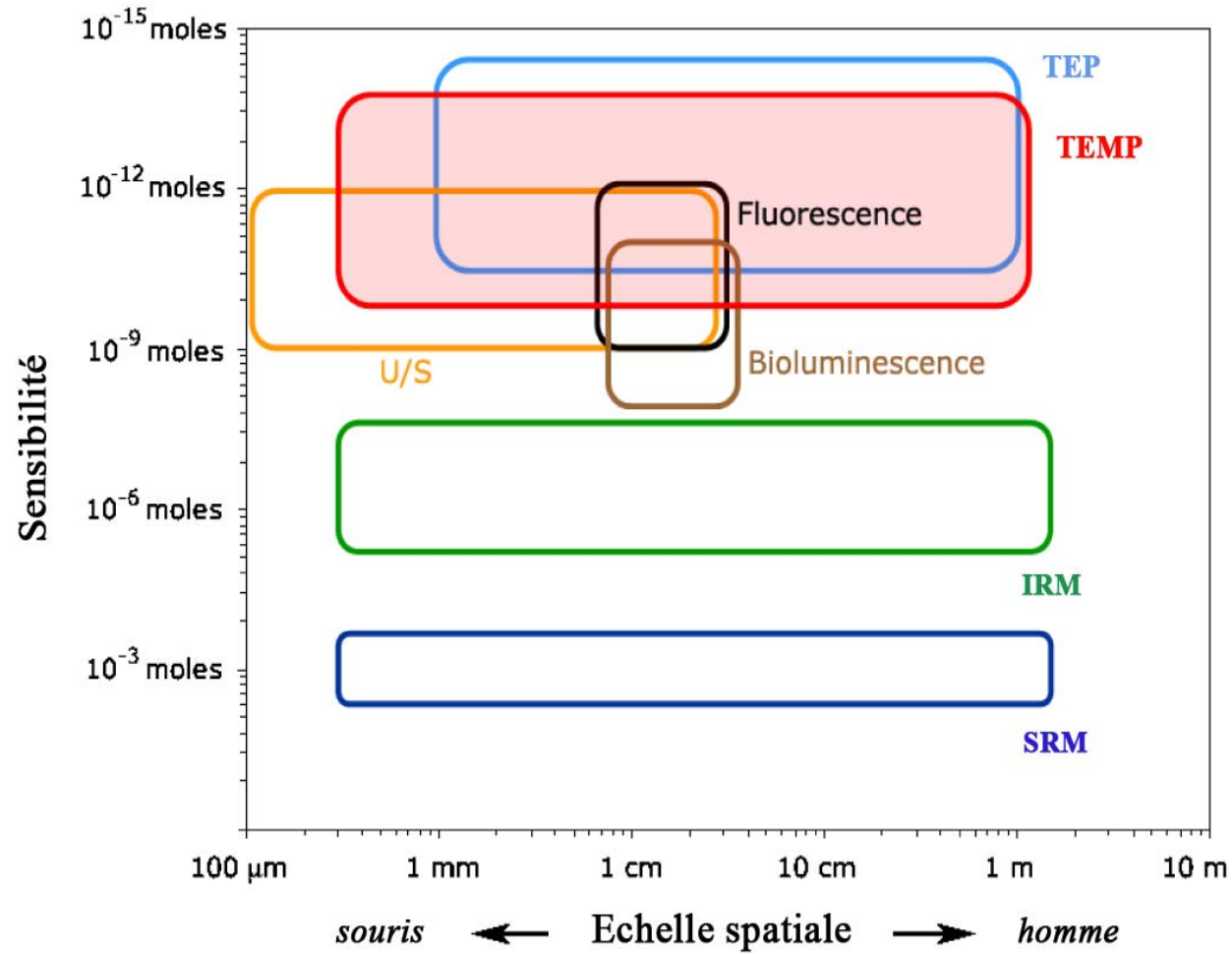
SPECT system



Optical system

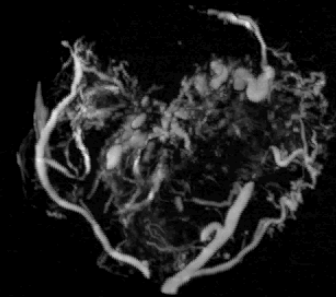
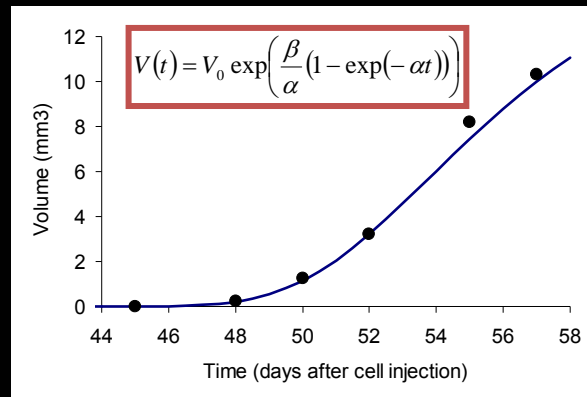
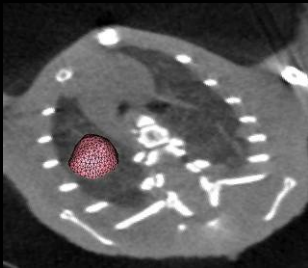
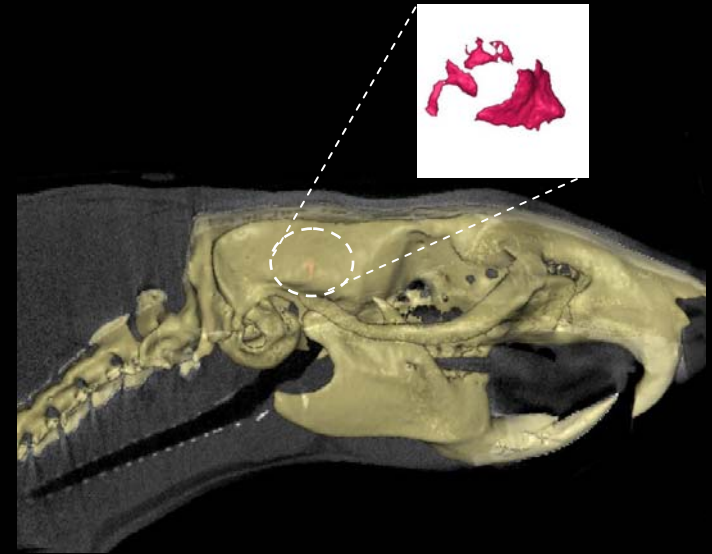
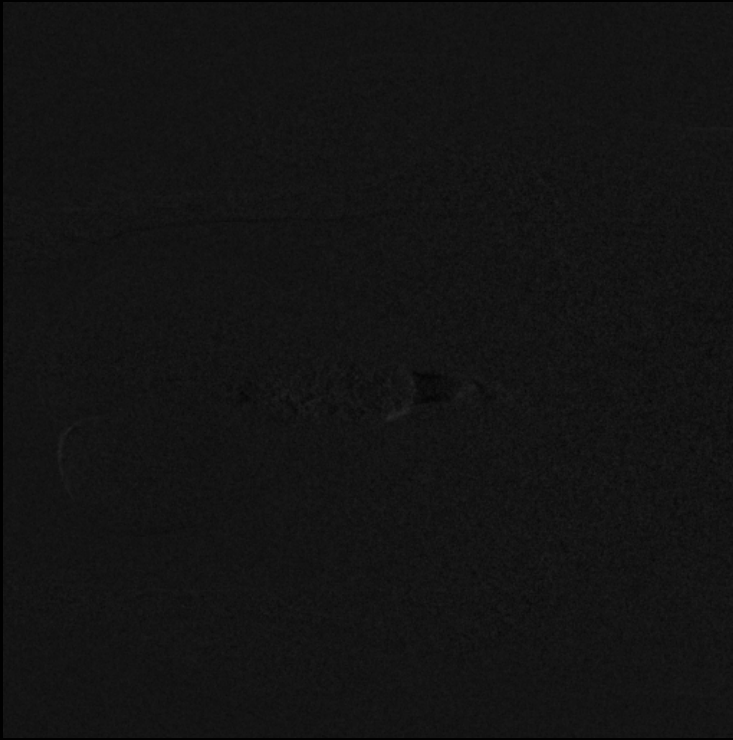
Small animal imaging key word in pubmed



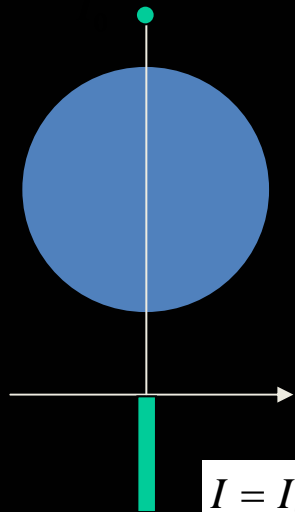
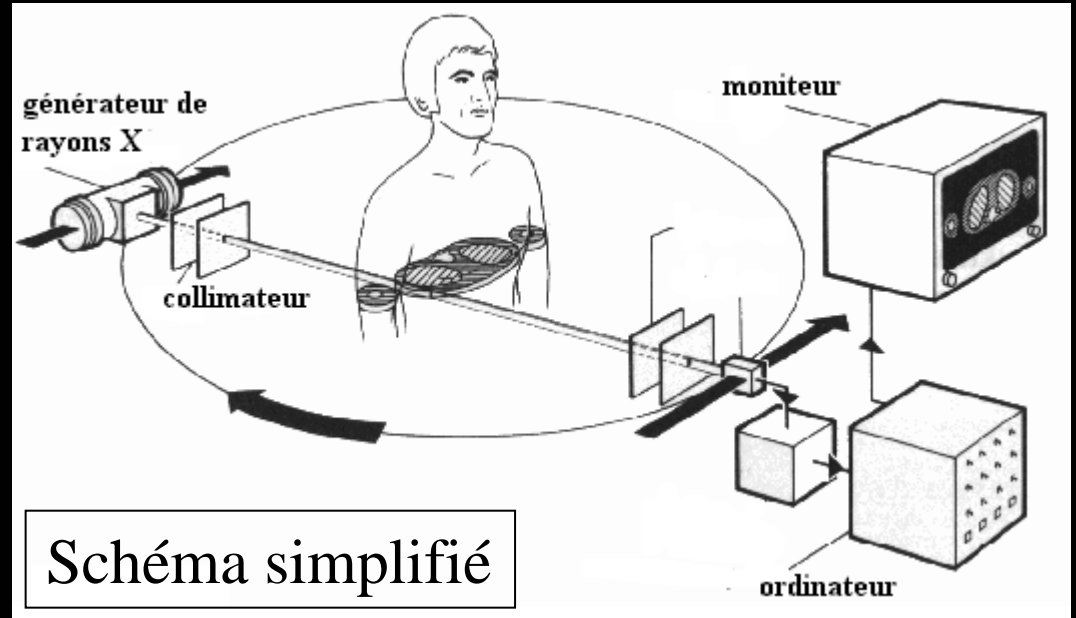
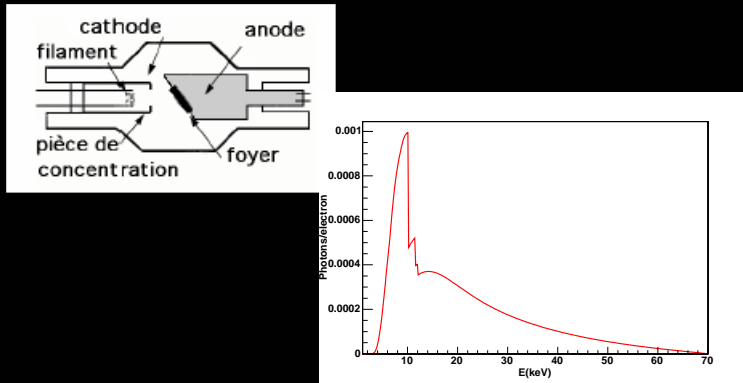


Meikle et al, PMB 50, 2005

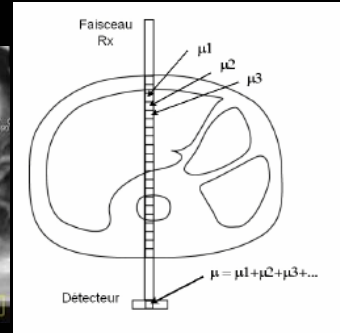
Loupe sur la μ CT



Imagerie par transmission



$$I = I_0 e^{-\mu d}$$

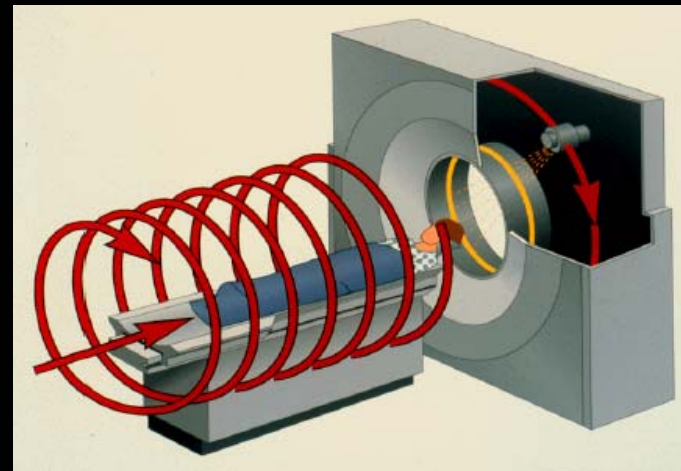
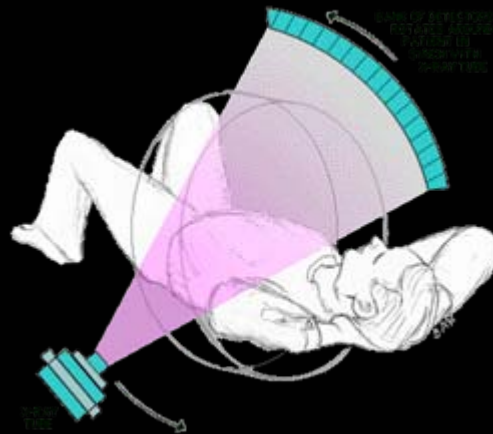


$$I = I_0 e^{-\int_L \mu_E(x,y,z) dL}$$

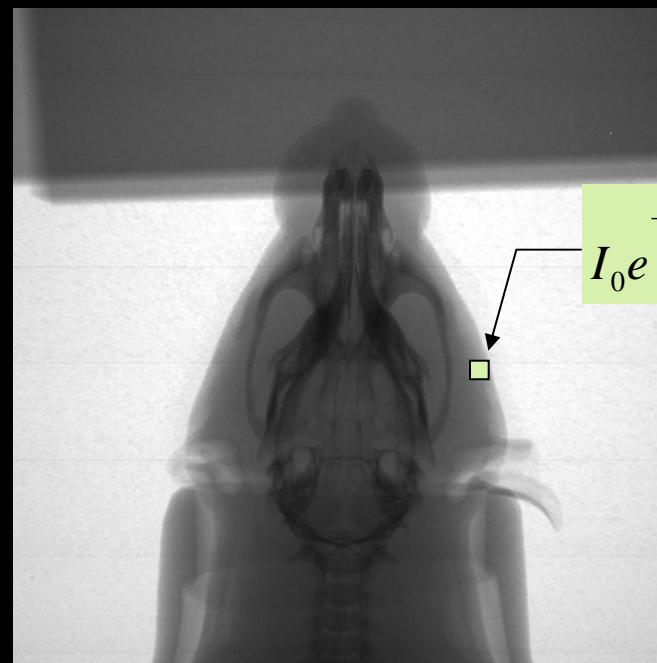
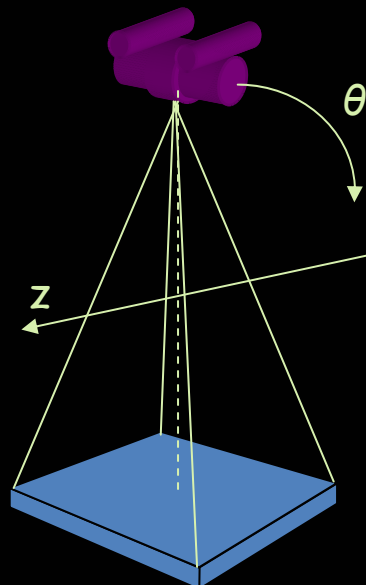
$$\int_L \mu_E(x, y, z) dL = \ln \frac{I_0}{I}$$

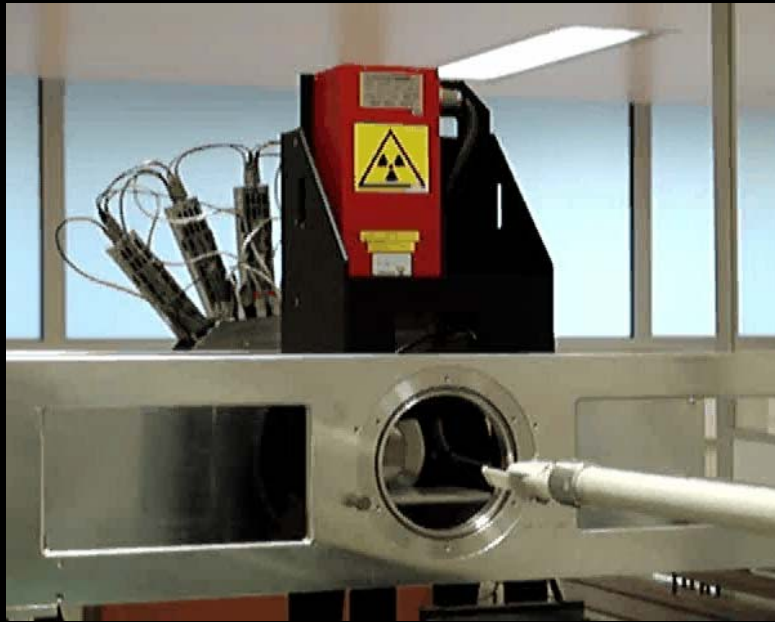
Hypothèse: E constante

Systeme
homme



Systeme
murin

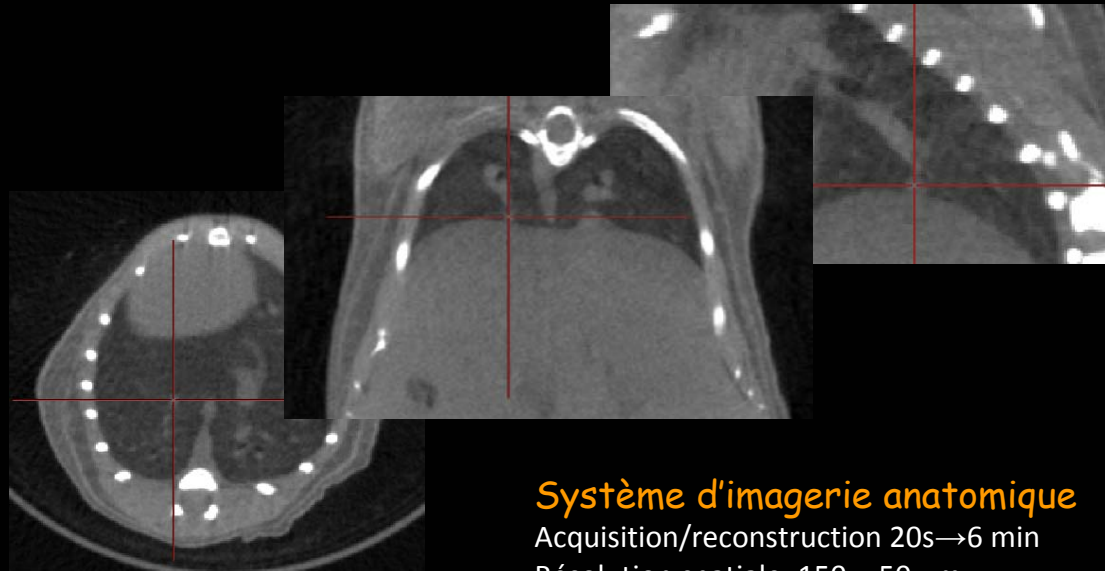




~1000 projections / 360°



GPU Board



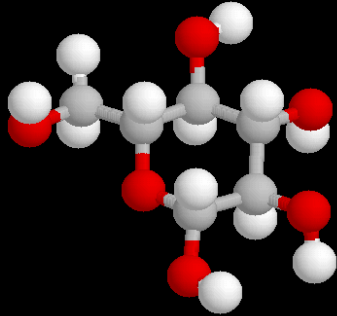
Système d'imagerie anatomique

Acquisition/reconstruction 20s → 6 min

Résolution spatiale: 150 → 50 μm

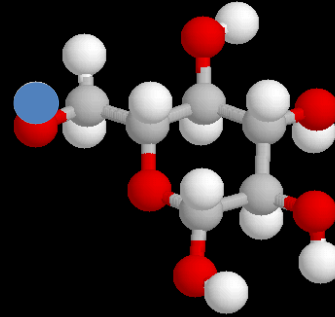
Principe de l'imagerie d'Emission

Step I



Trouver la molécule d'intérêt

Step II

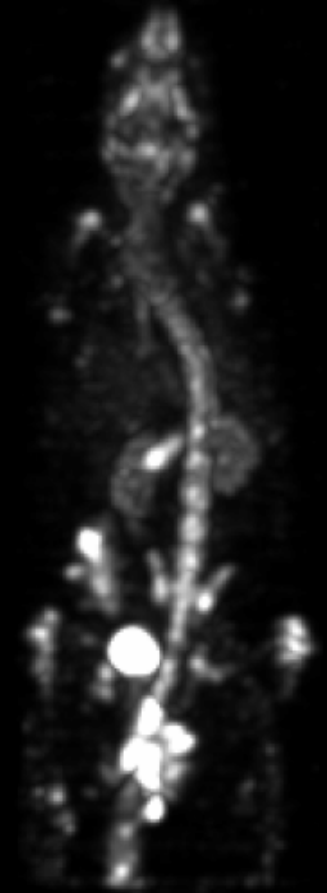


Insérer un isotope radioactif

Step III



Etudier la biodistribution après injection



Isotopes fréquemment utilisés

Isotope	Energie	Période
---------	---------	---------

Émetteurs γ

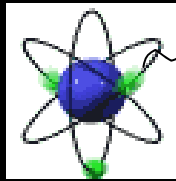
Technetium 99m	140 keV (89%)	6,02 hours
Iode 123	27 (71%) 159 keV (83%)	13,2 hours
Thallium 201	71 keV (47%)	73 hours

Émetteurs β^+

Oxygen 15	1738 keV	2,1 minutes
Carbone 11	960 keV	20,4 minutes
Fluor 18	634 keV	109,8 minutes
Brome 76	3980 keV	972 minutes

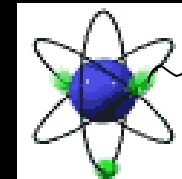
Systemes d'imagerie associés

Eméteurs γ



γ

Eméteurs β^+

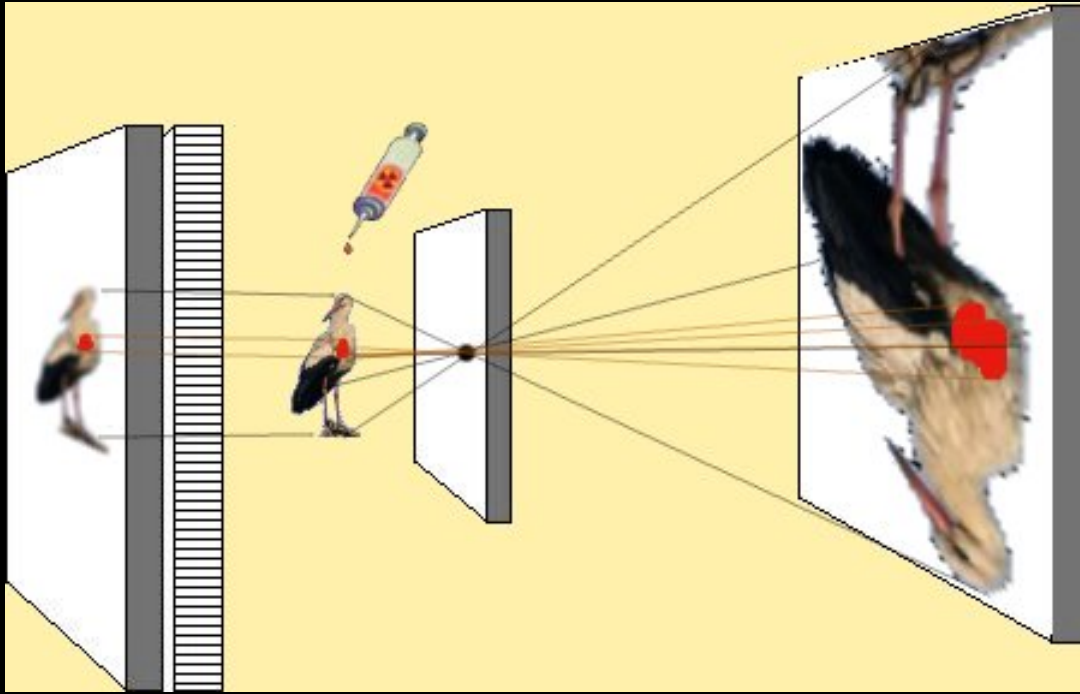


β^+

Tomographie d'Emission
Monophotonique
(TEMP)

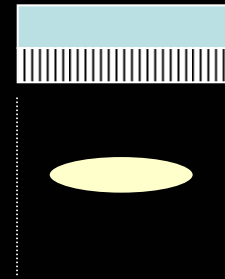
Tomographie d'Emission
de Positons
(TEP)

Instrumentation TEMP

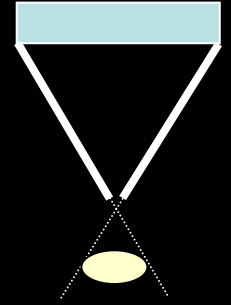


Injection du radiotracteur
Emission isotropique
Première étape:
Selection des bons candidats

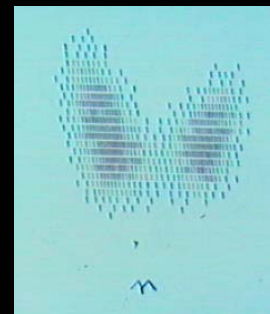
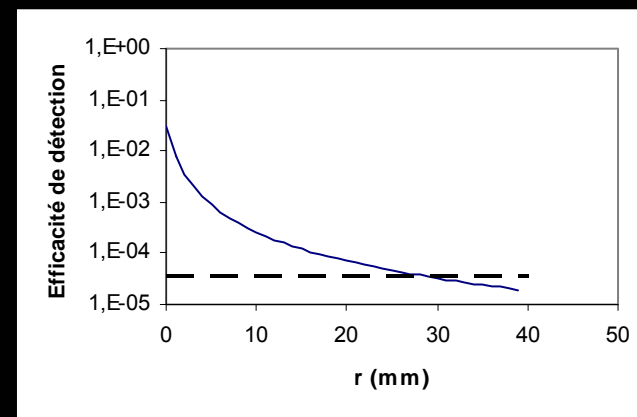
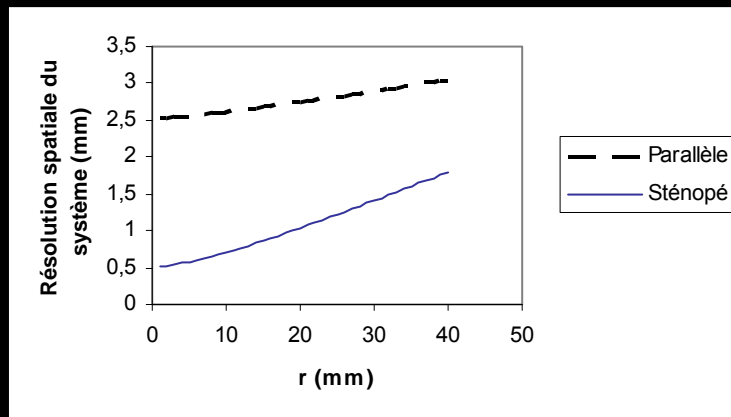
parallèle

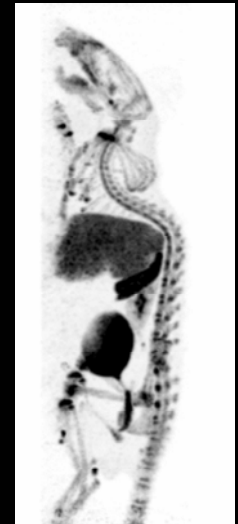
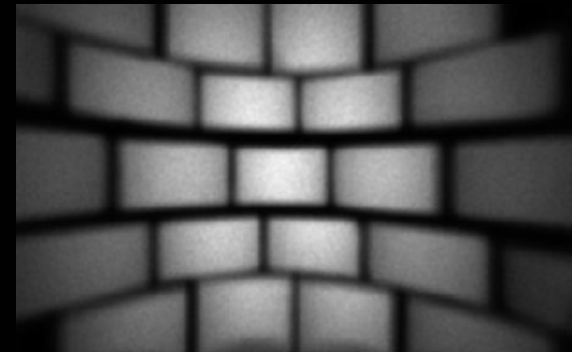
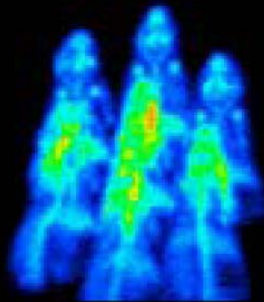
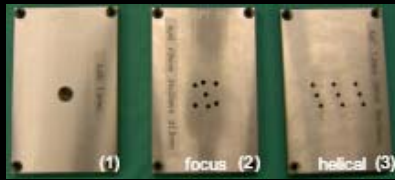


Sténopé



$$R_i = 2,3 \text{ mm}$$





NanoSPECT @ Bioscan

U-SPECT @ MILabs

Sub-mm total body U-SPECT imaging

Rat collimator



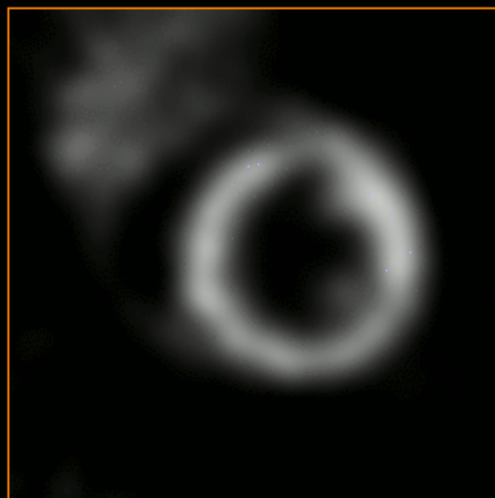
Mouse collimator



U-SPECT gated mouse cardiac perfusion imaging



Beating

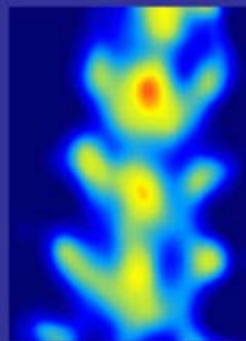


ED

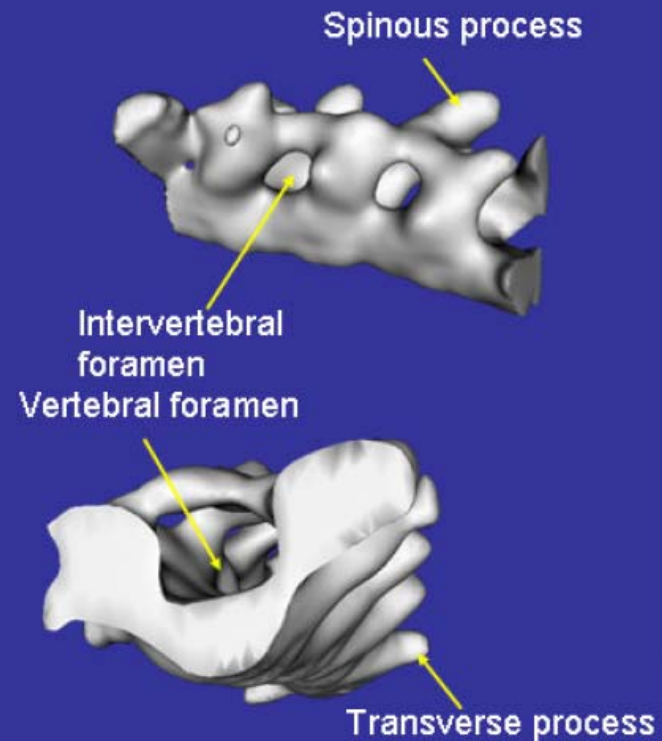
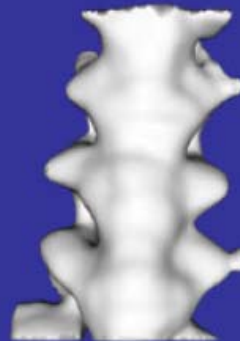


ES

U-SPECT-I: Mouse Spine



5 mm

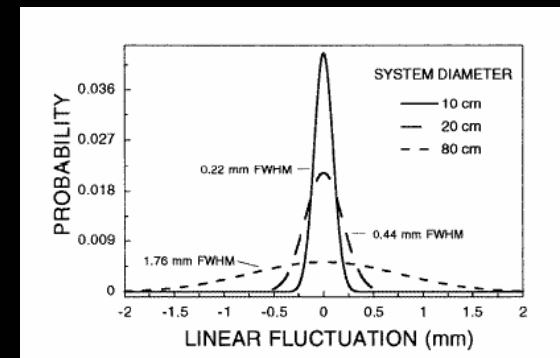
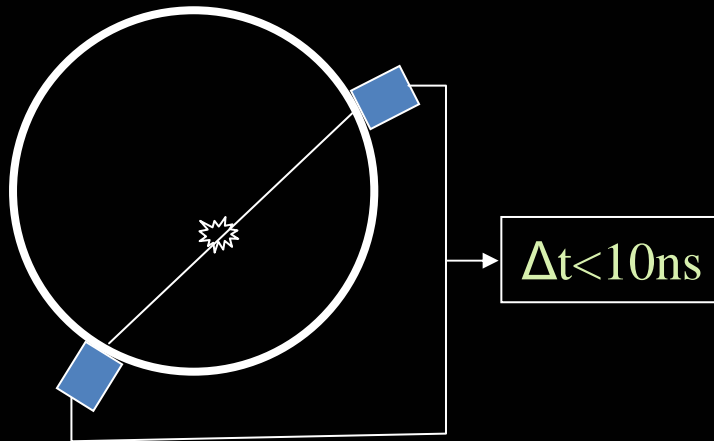
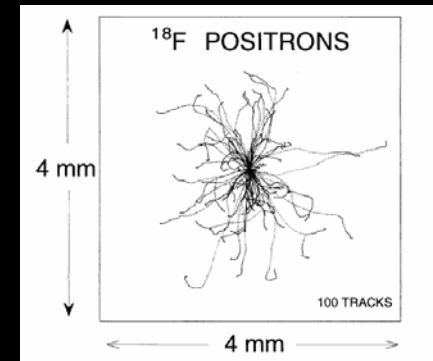
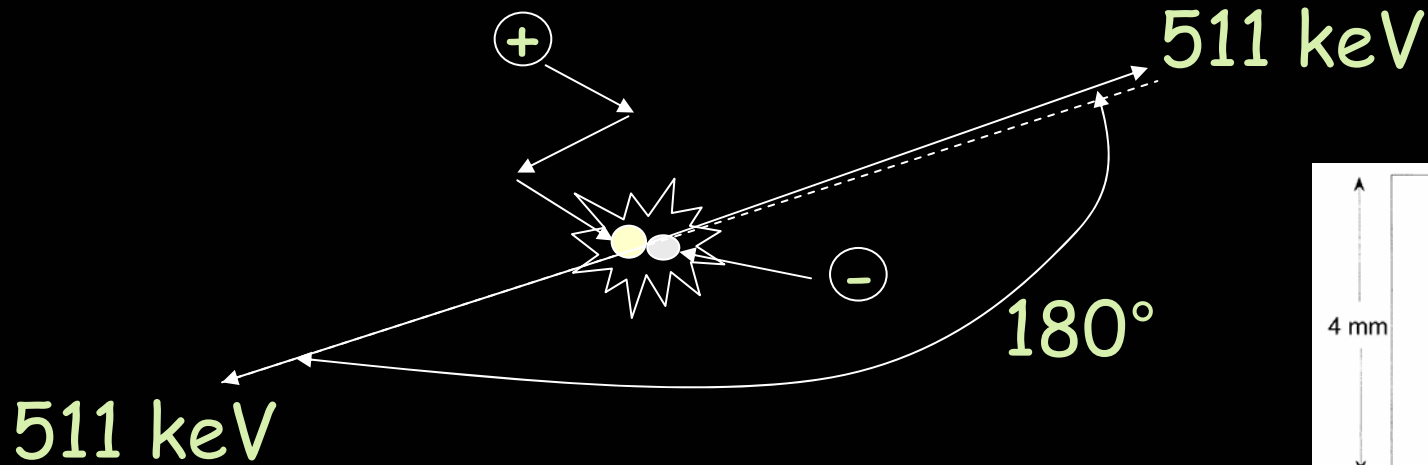
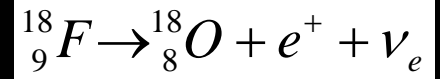


- Four mCi (99m)Tc-HDP
- Acquisition time: 22 min.
- 75 gold pinholes, $\varnothing = 0.6\text{mm}$
- Iso-surface renderings of SPECT data

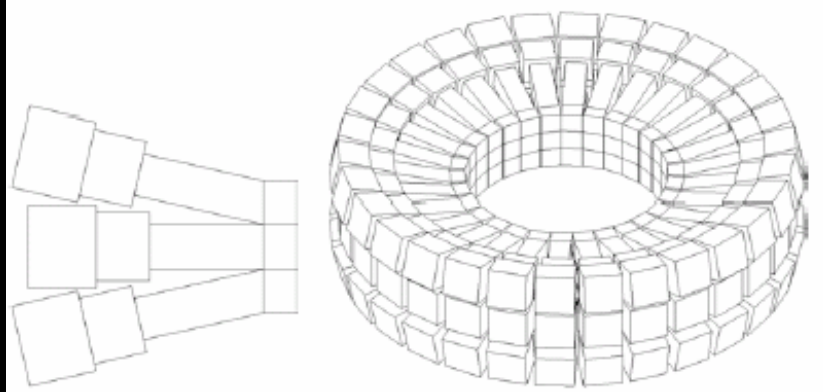
Instrumentation TEP



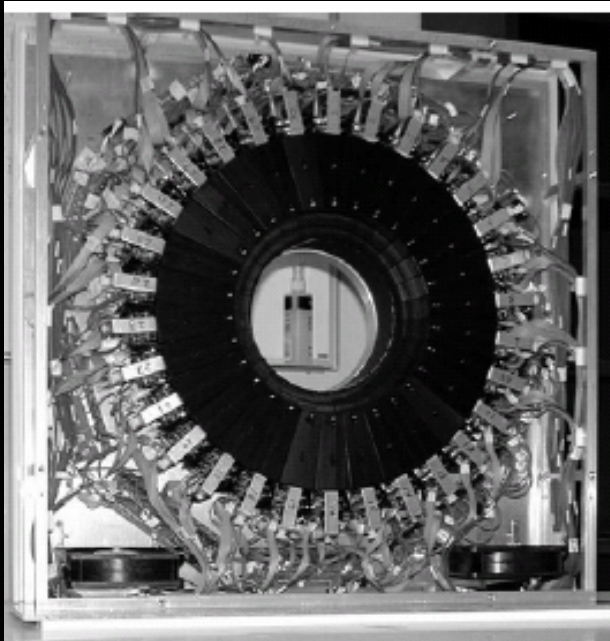
Exemple



Anatomie d'un système TEP

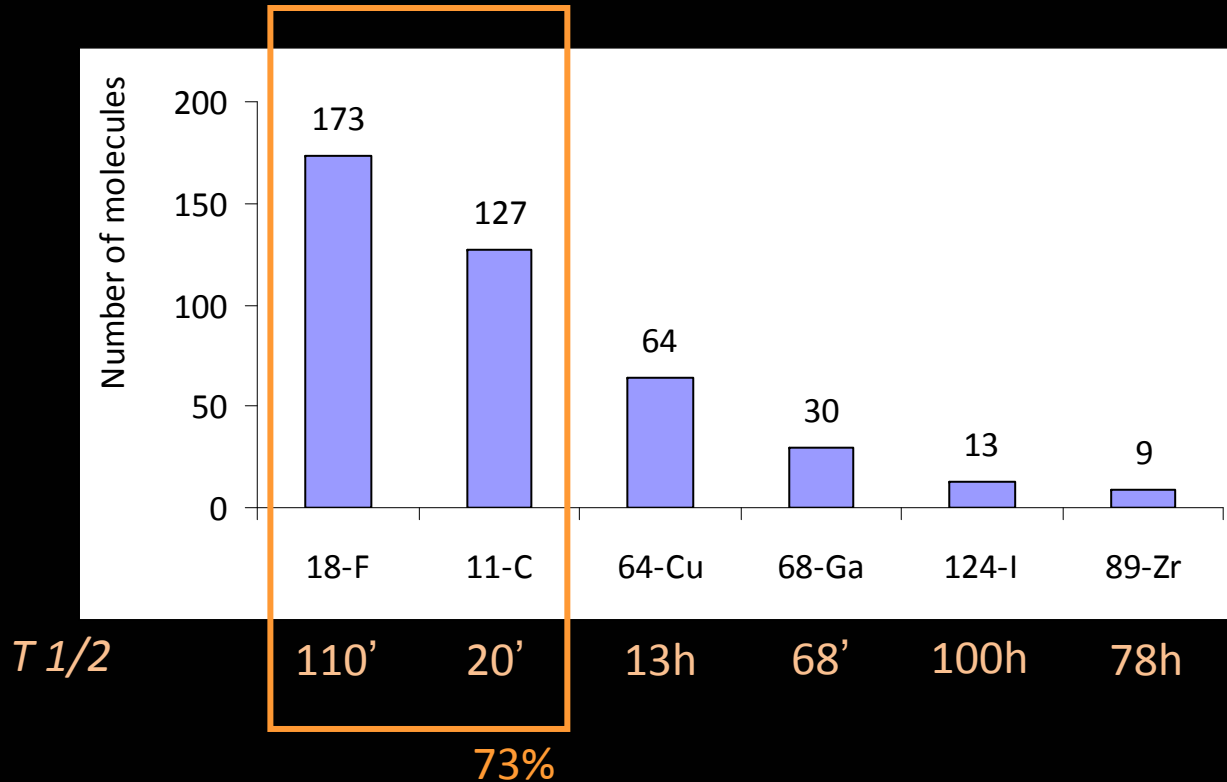


Detector diameter:	160 mm
FOV diameter:	80 mm
Axial FOV:	49 mm (3D)
Type:	90 modules (3 couronnes) de 14 x 14 cristaux
Crystal:	LSO
Photodetector :	MA-PMT
Crystal size:	0,975 x 0,975 x 12,5 mm ³
Absolute sensitivity:	2,26 % (> 250 keV)
Resolution tr (@centre):	0,83 mm
Resolution axial:	1,25 mm

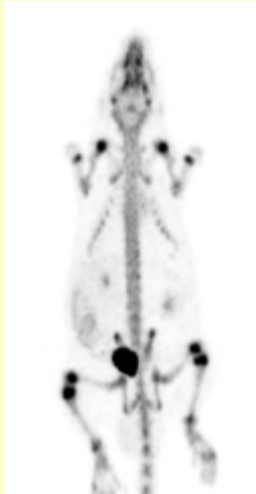


MICAD: Molecular Imaging and Contrast Agent Database

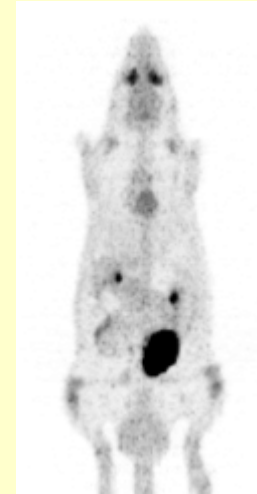
June, 2011, 407 molecules



Rat's movie as measured with the Sherbrooke small animal PET scanner and ^{18}F -, which is trapped in bones.

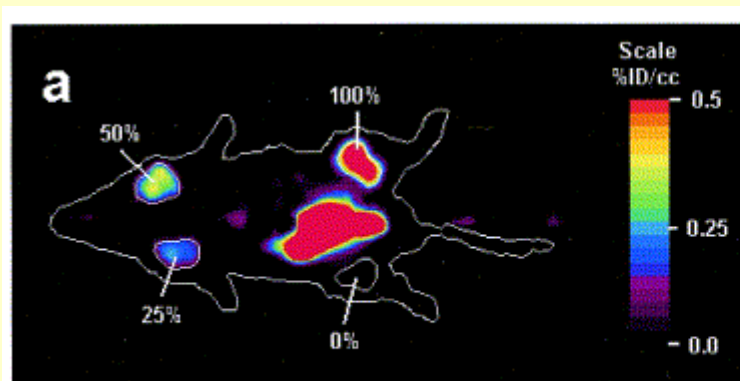


Rat's movie as measured with the Sherbrooke small animal PET scanner and ^{18}F FDG, which is trapped in tissue.

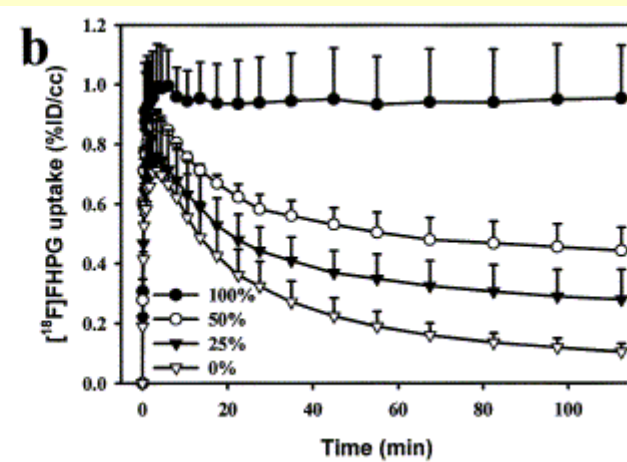


Sherbrooke University

Evaluation of $[^{18}\text{F}]\text{FHPG}$ as PET tracer for HSVtk gene expression



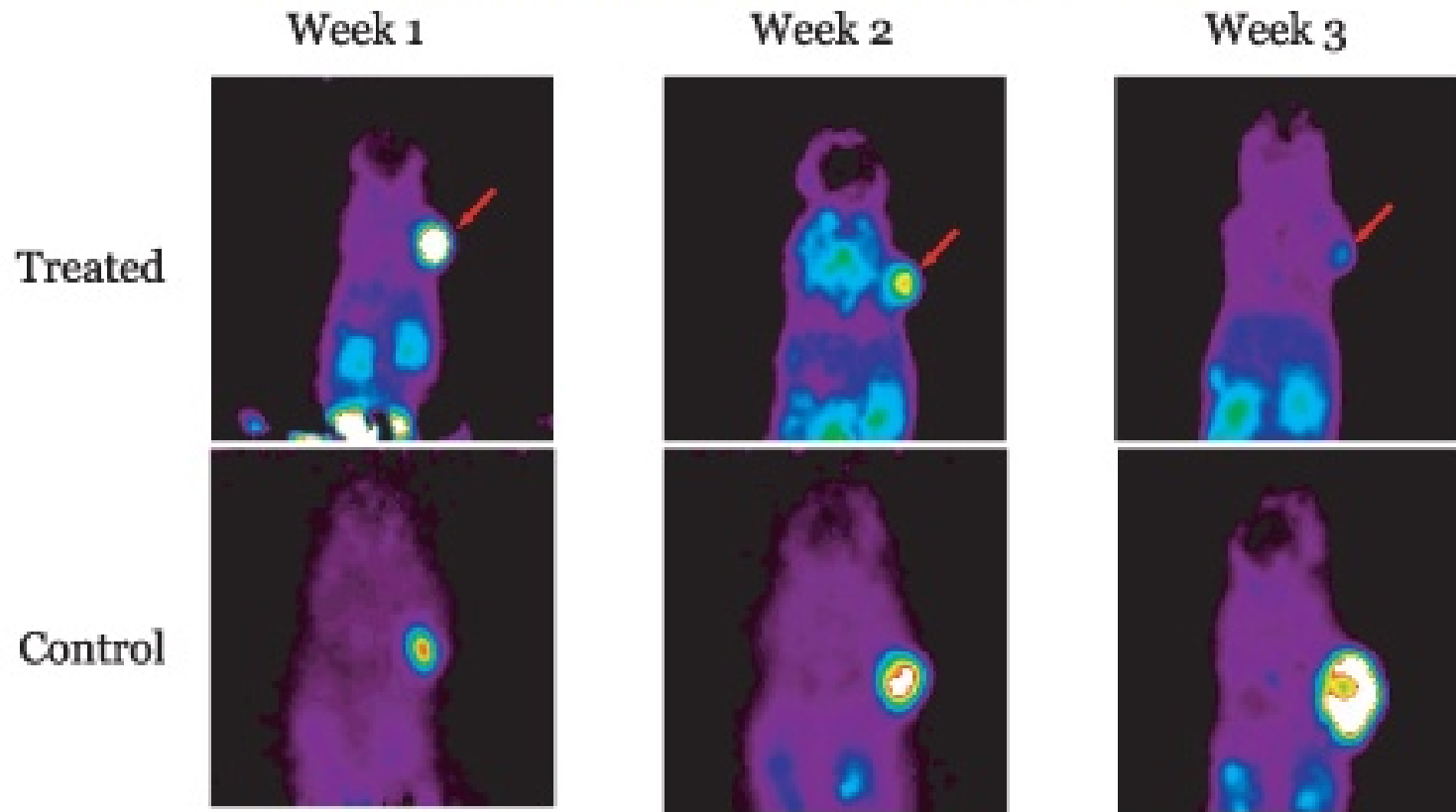
Percentage of C6tk cells injected at the tumor site



PET imaging of HSVtk enzyme activity 105-120 min after i.v. injection of $[^{18}\text{F}]\text{FHPG}$

FLT: 3'-deoxy-3'-¹⁸F-fluorothymidine

FLT Measurements of DNA Synthesis



Effects of PKI-166 on A-431 Vulvar Carcinoma Monitored with [¹⁸F]fluorothymidine (FLT)

MicroPET enables longitudinal imaging of the same subject over time, significantly reducing the number of animals required. Allows for better statistical paired testing.

Waldberr et al. Ahmanson Biological Mouse Imaging Clinic

Possibilités d'amélioration ?

En termes de

Instrumentation ?

Molécules ?

Méthodologie ?

La collimation est l'une des clés en imagerie TEMP

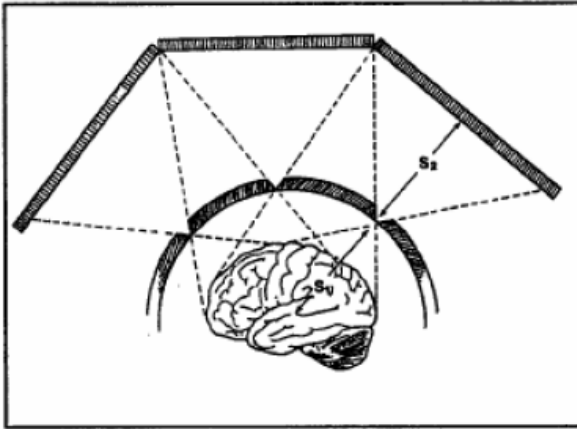


Figure 2: System without overlapping projections. Only a few pinholes can be used because of large magnification and poor detector resolution [7].

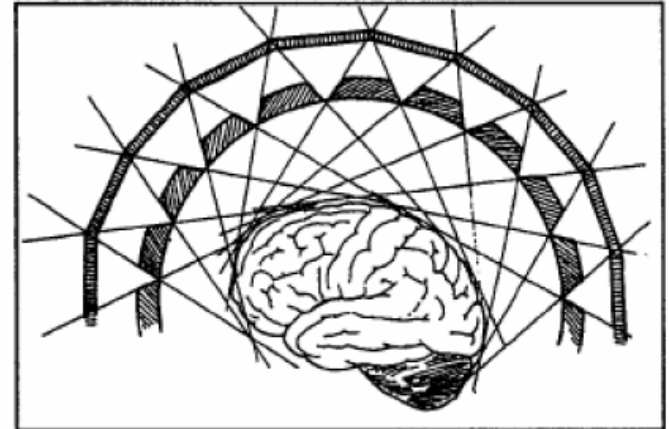


Figure 3: System without overlapping projections. Many pinholes can be used because of small magnification and good detector resolution [7].

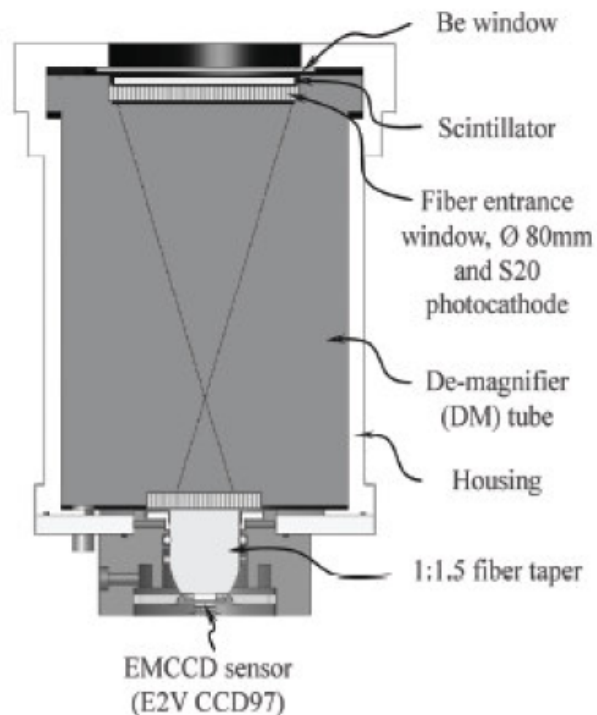
Meilleure efficacité

Meilleure résolution spatiale

Etudes dynamiques

Animal éveillé ?

Nécessite des détecteurs hautement résolus



- Ultra-high resolution gamma camera based on EMCCD sensor and DM tube
- 100 μm pinhole
- **60 μm intrinsic resolution**

Image of “heart” phantom

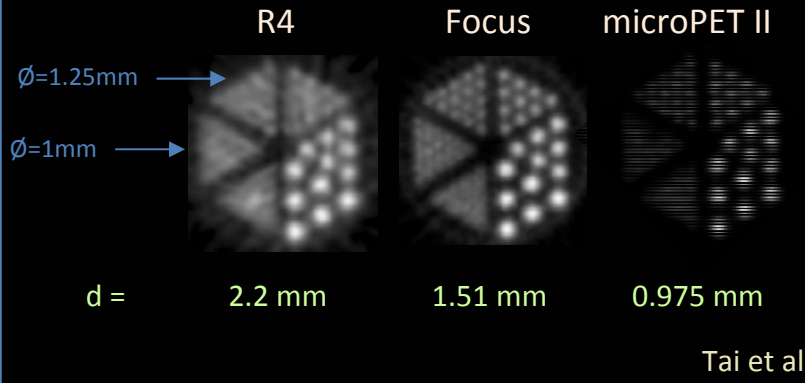
450 μm

Co-registered SPECT/CT image of a mouse thyroid lit up due to the uptake of I-125 NaCl solution



LJ Meng et al, Preliminary imaging performance of an ultra-high resolution pinhole SPECT system using an intensified EMCCD camera, 2006 IEEE NSS/MIC

Section du cristal

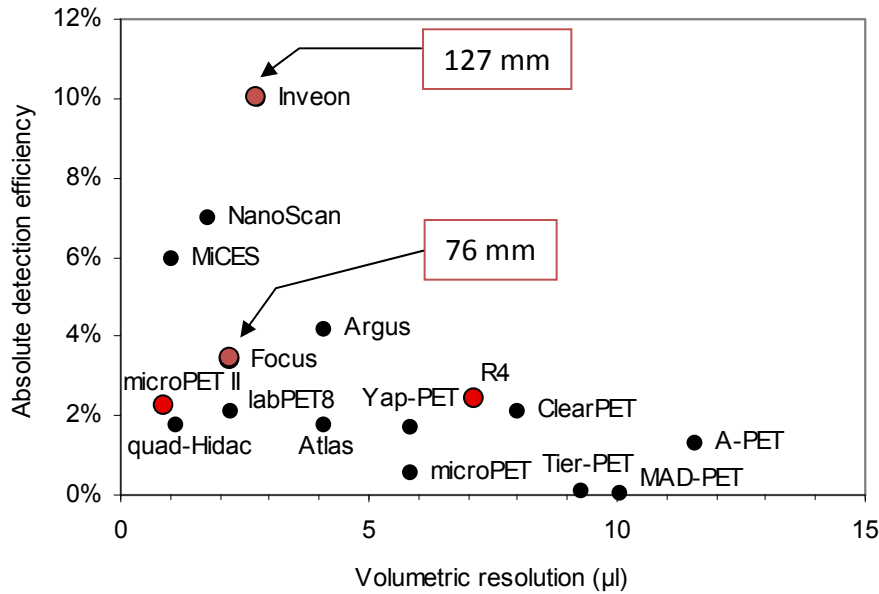
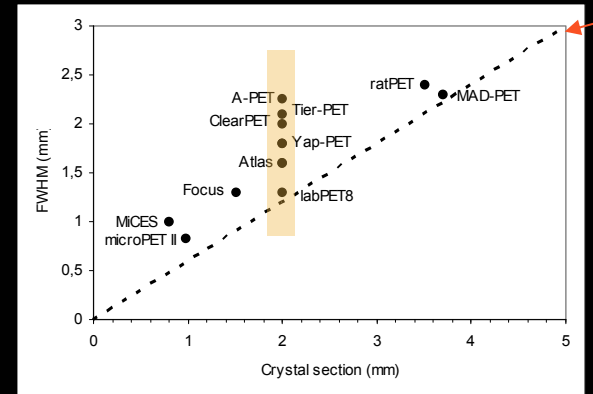


Type du cristal

Mainly LSO:Ce

Codage

$$LTMH = k \sqrt{\left(\frac{d}{2}\right)^2 + (0,0022D)^2 + r_p^2 + b^2}$$



Champ de vue axial



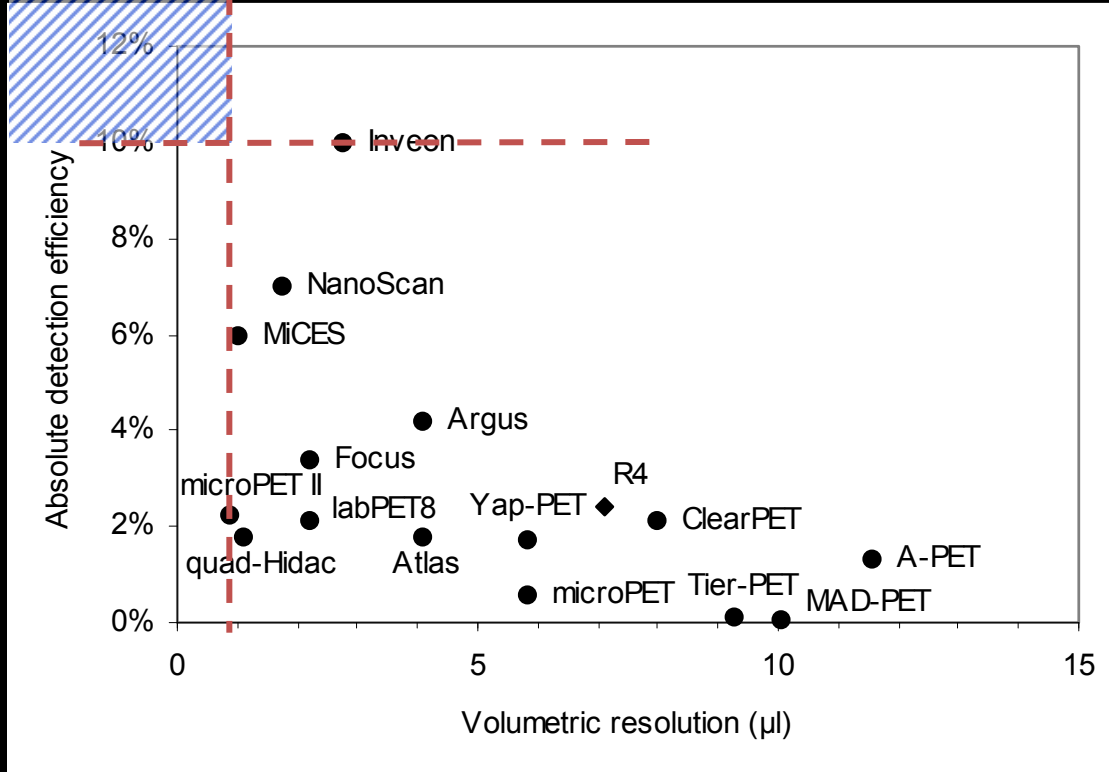
Comment atteindre cette zone ?

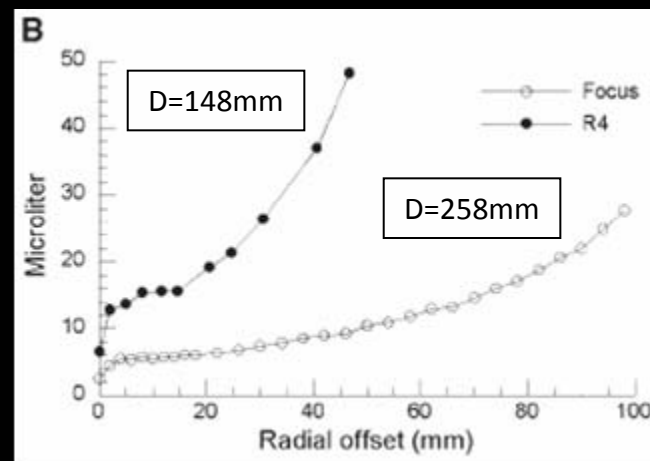
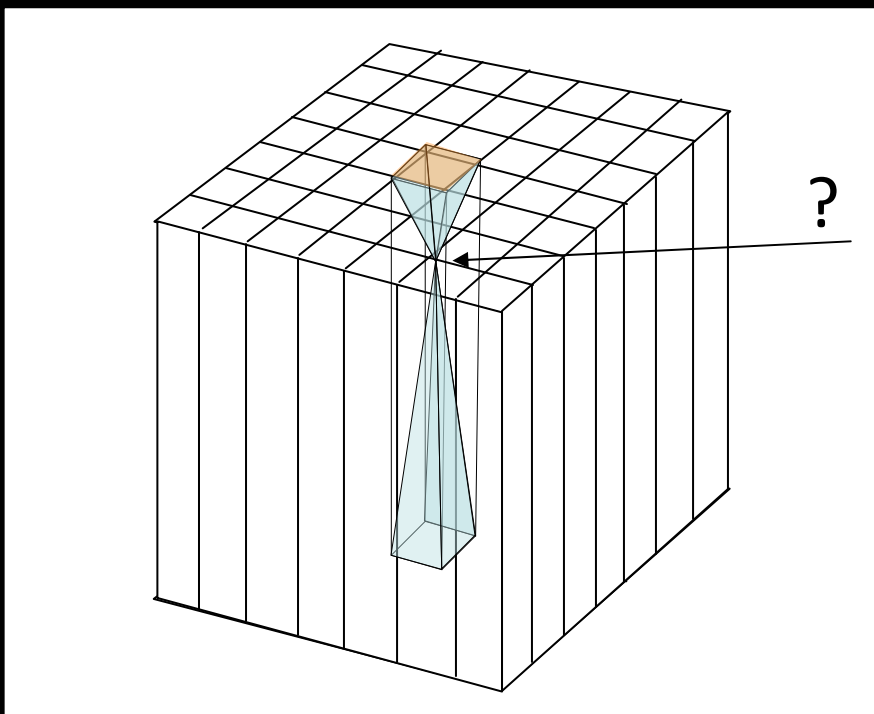
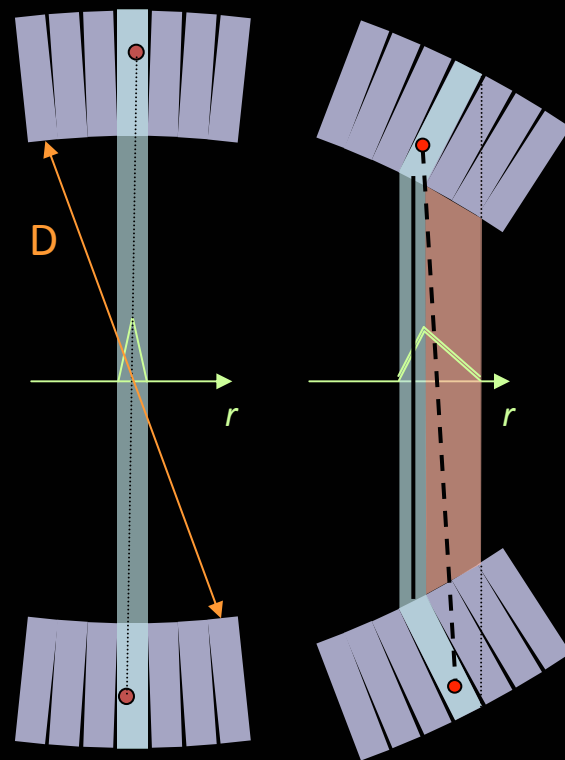
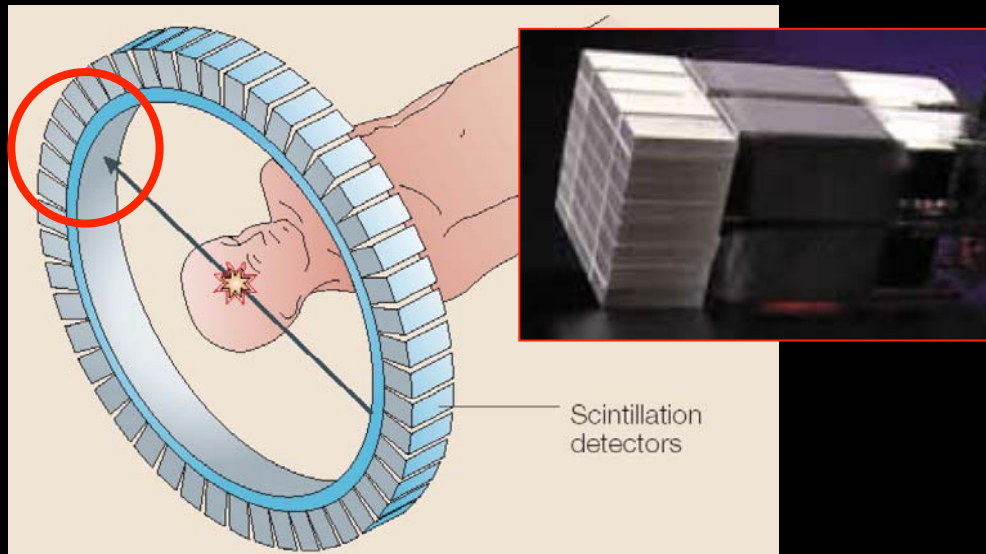
Résolution spatiale: 1 μl

→ Section du cristal: 0,975 mm

Efficacité de détection: 10 %

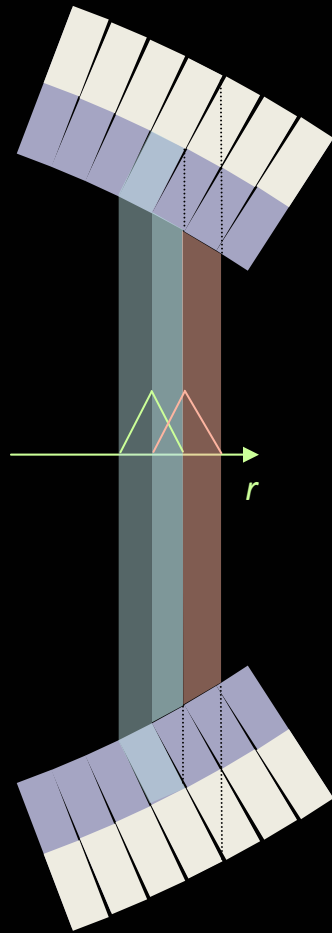
→ Champ de vue axial: 127 mm



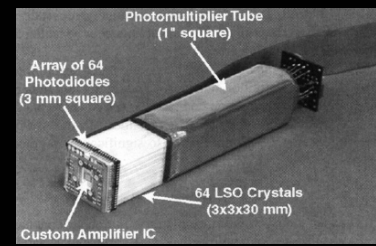


Profondeur d'interaction (DOI)

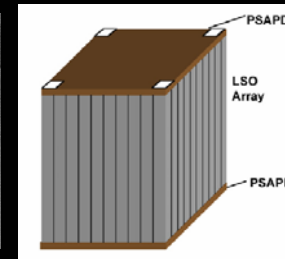
Compromis entre résolution spatiale et efficacité de détection



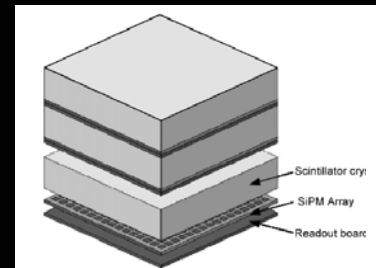
Aller d'un détecteur 2D au 3D



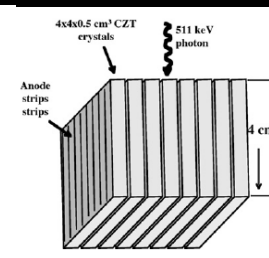
Lawrence Berkley Laboratory



UC Davis



INFN, Pisa University



Stanford University

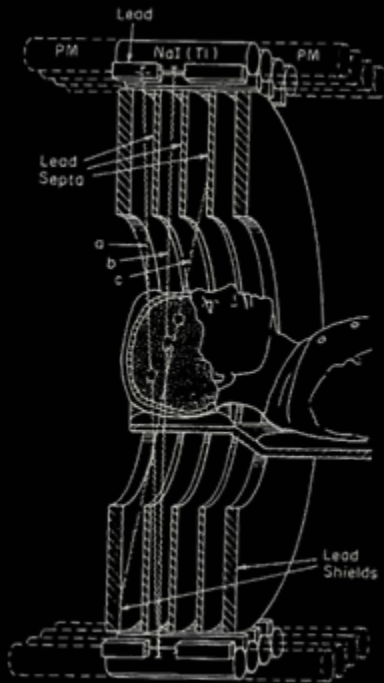
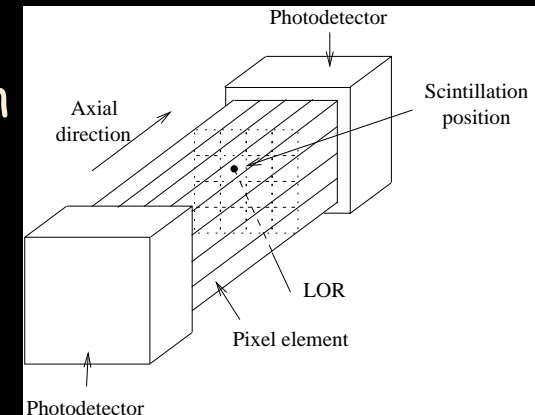


Quid de la géométrie axiale ?

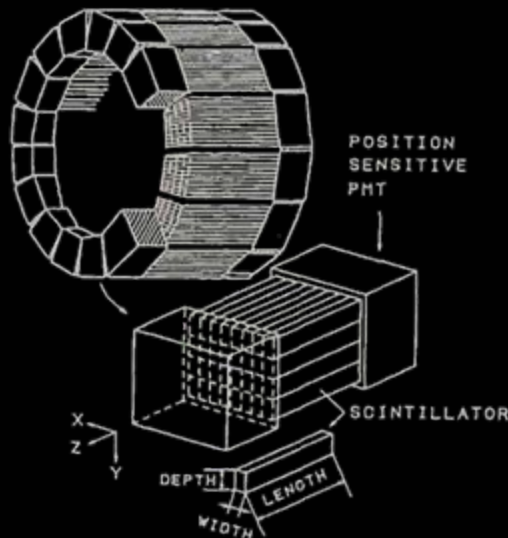
Géométrie axiale:

Résolution spatiale----X---- Efficacité de détection

Ter-Pogossian *et coll.* 1978, Shimizu *et coll.* 1988



$R_L \approx 3-4 \text{ cm}$



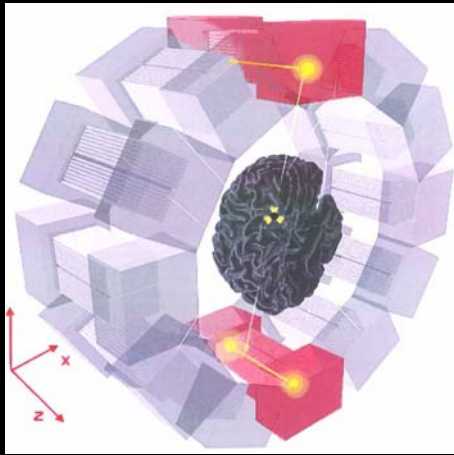
$R_L = 1 \text{ cm}$

- 😊 Pas d'erreur de parallaxe
- 😊 Echantillonnage continu en z
- 😊 Améliore l'efficacité de détection (proche de l'angle solide)
- 😞 Double le nombre de voies
- 😞 La résolution axiale dépend des caractéristiques du cristal

Quelques tentatives

YAP + HPDs

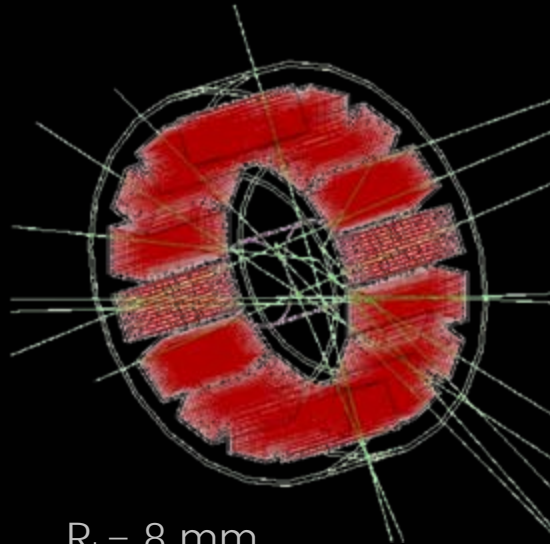
(Vilardi *et al.* 2006)



$R_L = 1.4 \text{ cm}$

Liquid Xenon + PMT

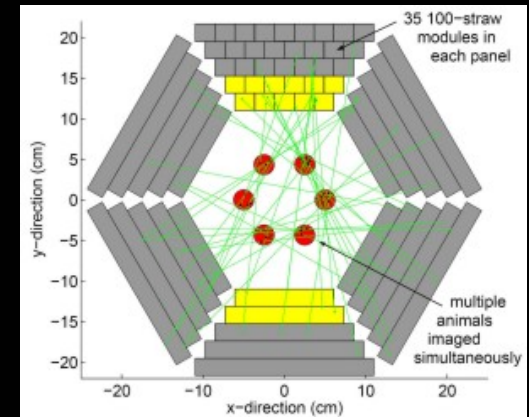
(Gallin-Martel *et al.* 2005)



$R_L = 8 \text{ mm}$

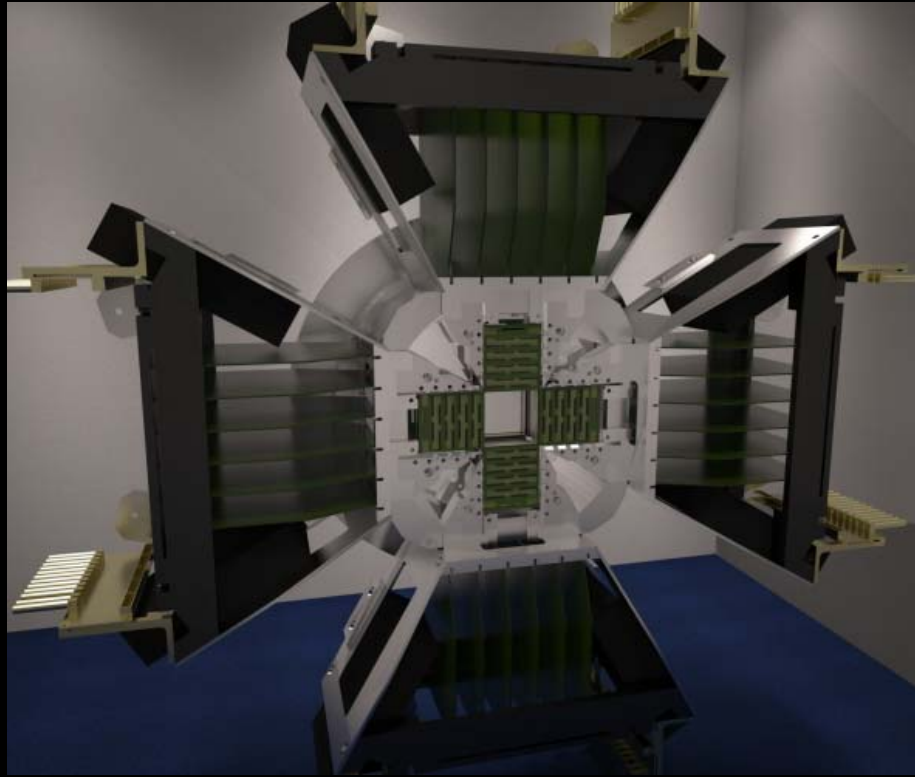
Tungsten tube

(LWS, Proportional Technologies, 2008)

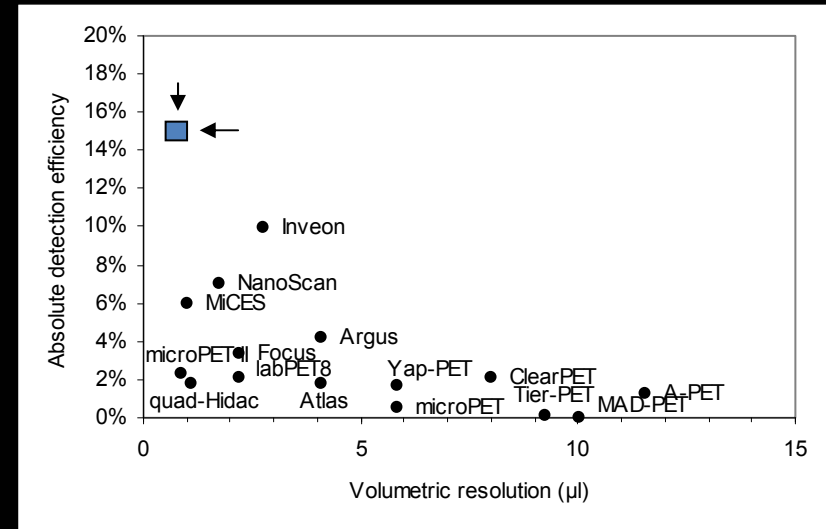
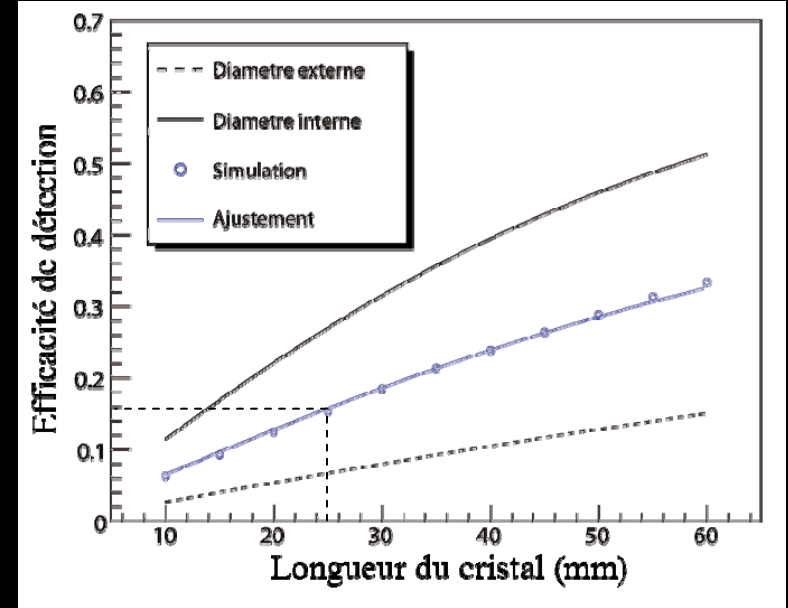


$R_L = 1 \text{ mm}$

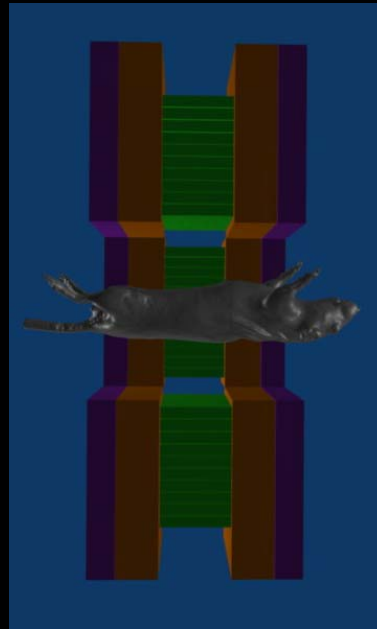
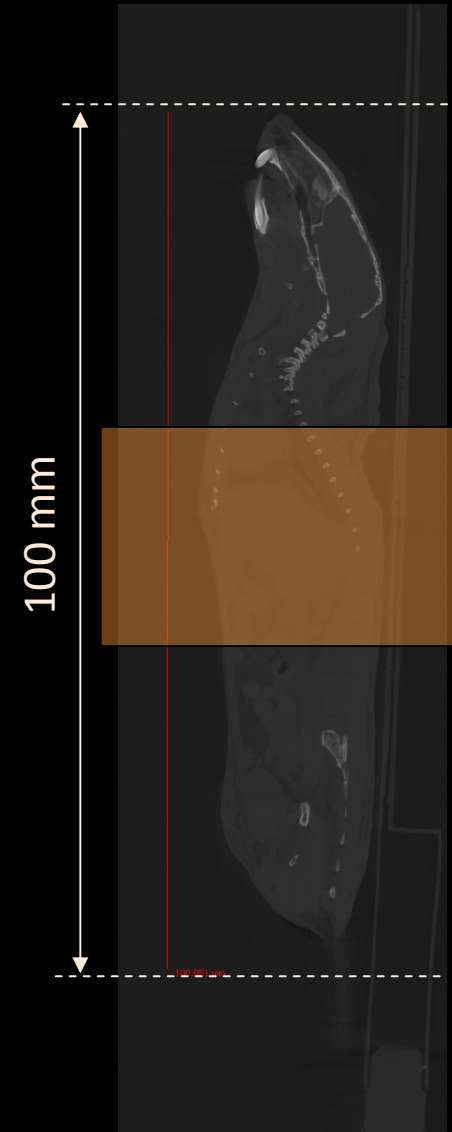
La solution proposée



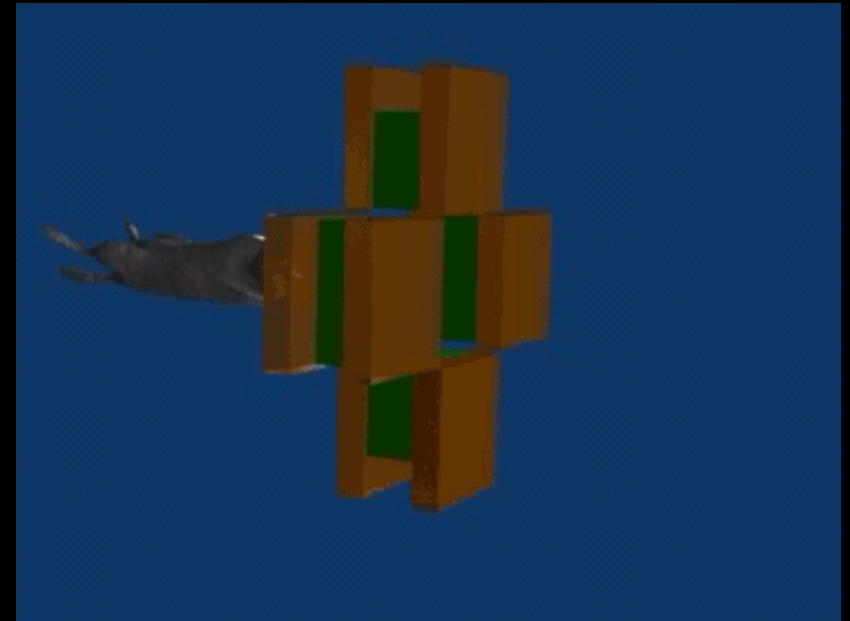
Résolution spatiale: $1 \mu\text{l}$
 Fenêtre de temps: $< 2 \text{ ns}$
 Efficacité de détection: 15 %



Le talon d'Achille: le champ de vue axial



Acquisition en mode continu...

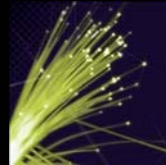


...augmente artificiellement le champ de vue axial

Cristaux

Scintillateurs	Densité (g/cm ³)	Rendement (ph/511keV)	Décroissance (ns)	μ @511 keV (cm ⁻¹)
NaI:Tl	3,67	19400	230	0,34
LSO:Ce	7,40	~ 13000	~ 47	0,88
LaBr ₃ :Ce	5,29	32000	16	0,45
LaCl ₃ :Ce	3,86	23000	25	0,36
LYSO:Ce	7,11	17300	41	0,83

Problèmes: hygroscopique
disponible pour section > 4 mm

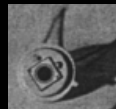


Photodétecteurs

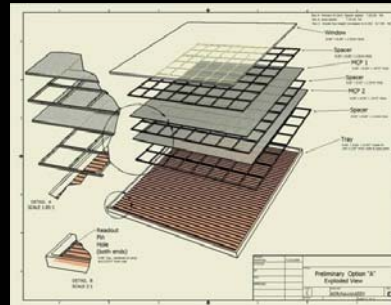
Candidats potentiels



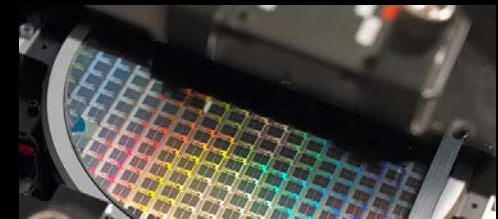
Matrice APD



SiPM

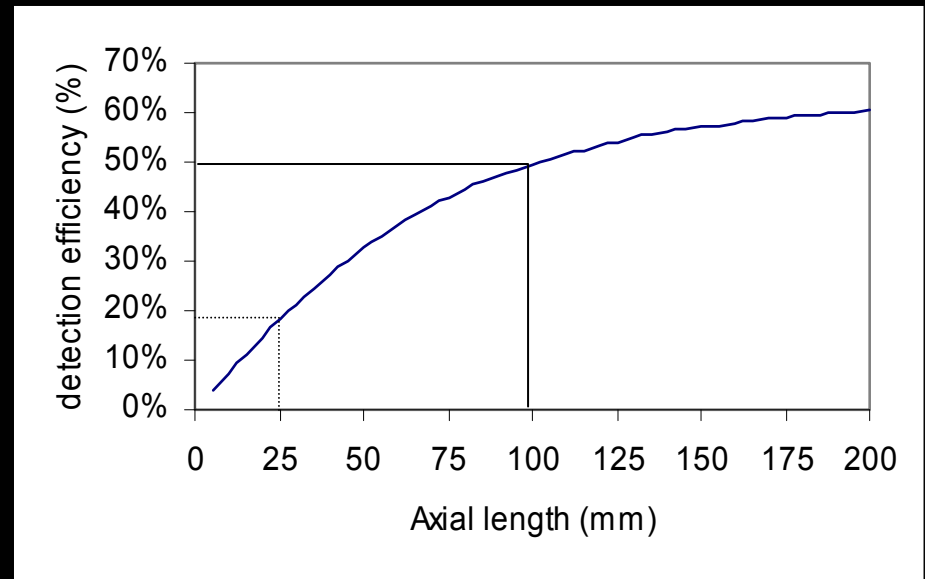
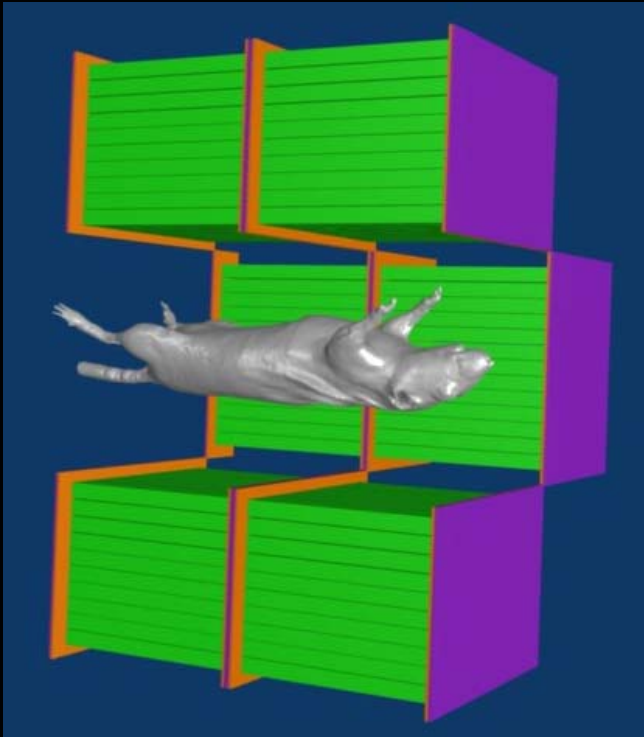


LAPPD Project (Fermilab, UC)



SiPM digitaux

Géométrie axiale: ...une ouverture possible

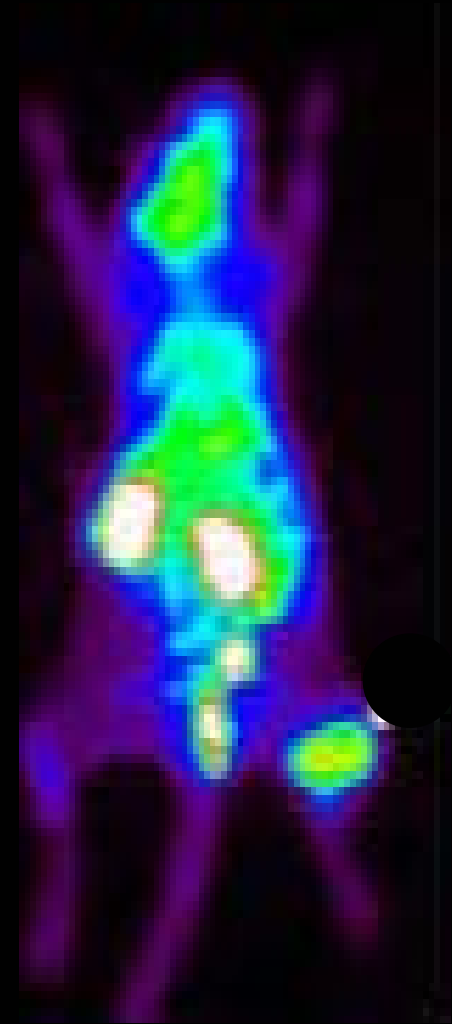


Champ de vue axial: 100 mm
Résolution spatiale: 1 μ l
Efficacité de détection: 50 %

Un exemple de mauvaise résolution TEP...



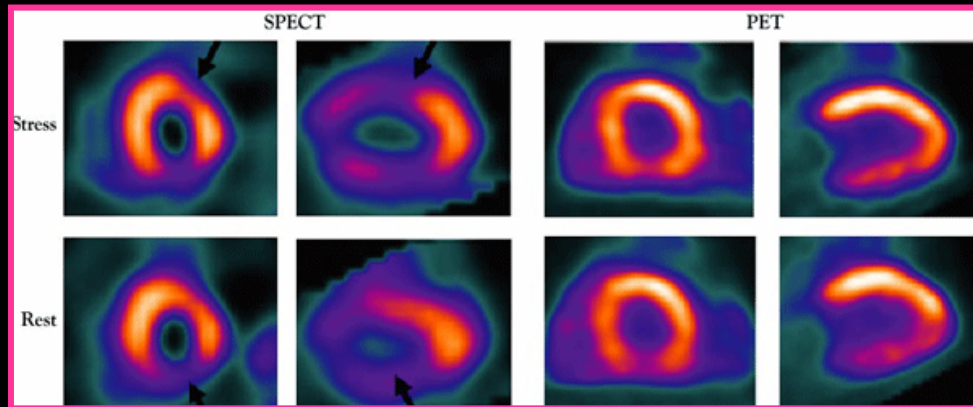
Courtesy of Crump Institute



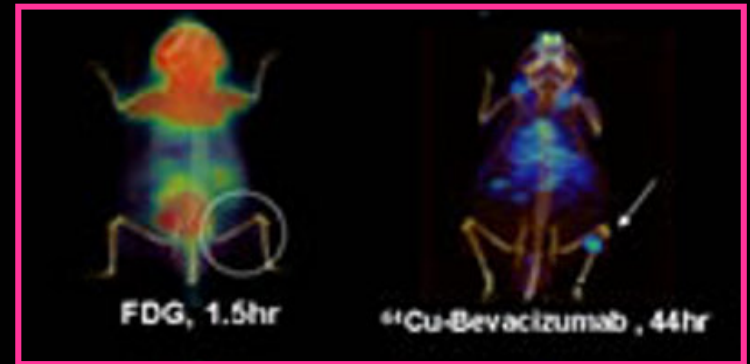
...une histoire de molécule.

Isotopes émergents...

Rb-82, Ge-68/Ga-68, Cu-64/67, Sc-44/47, Zr-89

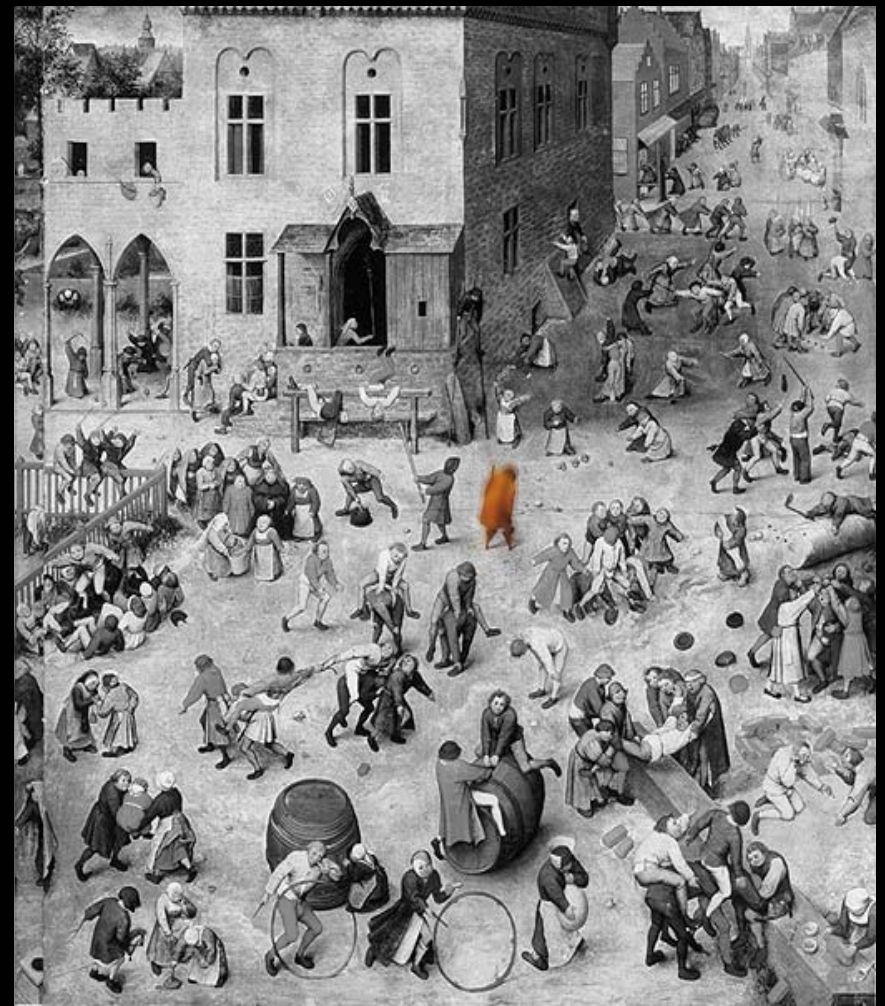


Tc-99m / Rb-82



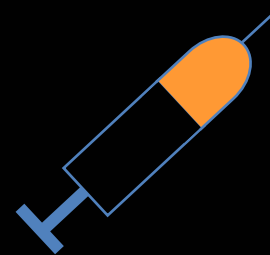
Tumor angiogenesis (FDG/Cu-DOTA)





P. Brueghel

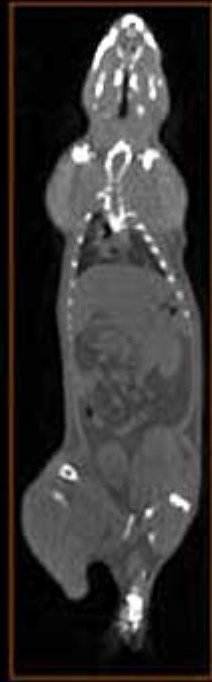
Anatomie



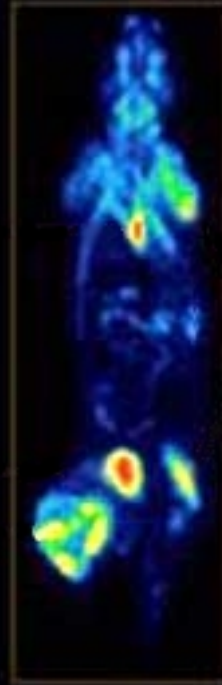
Fonction

Approche multimodale

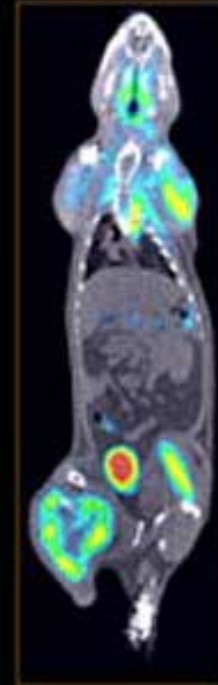
TEP/CT



CT

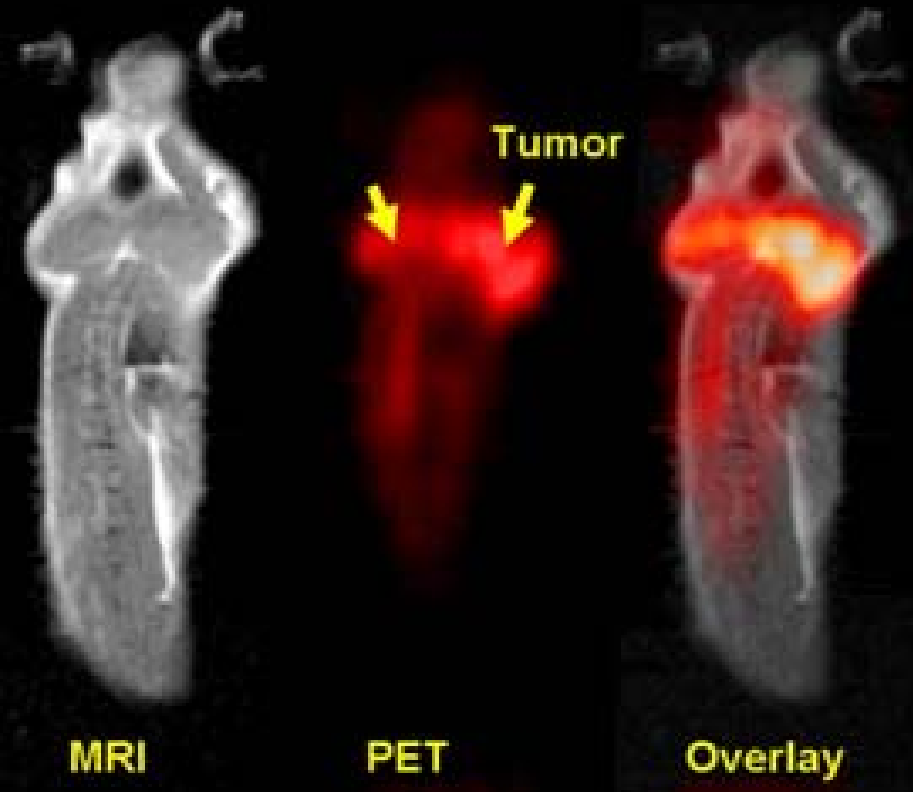


FDG-PET



Approche multimodale

TEP/IRM



Approche multimodale

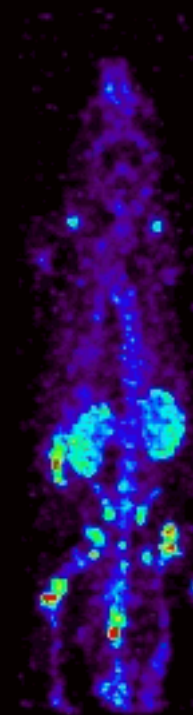
TEMP/CT



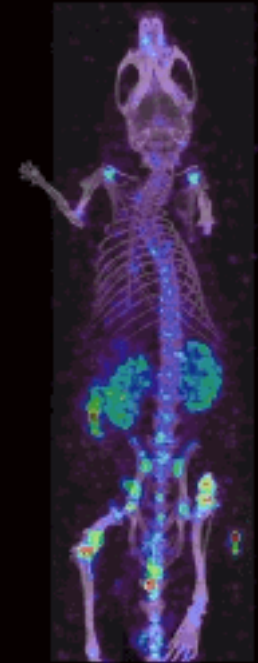
AMISSA Platform (IPHC)



CT

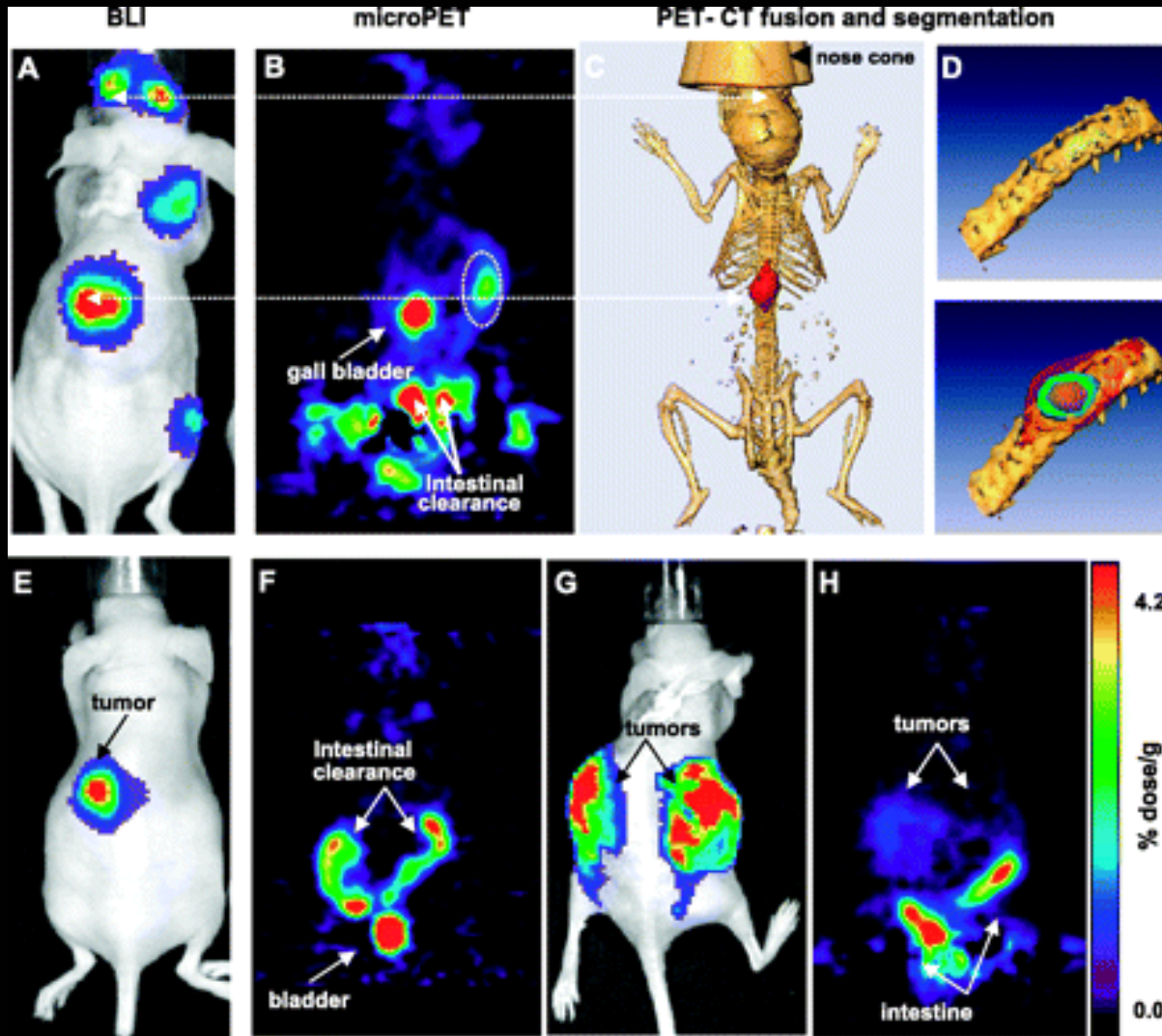


SPECT



Approche multimodale

CT/BLI/TEP



Performances / Coûts / Impact...

Avons nous besoin de résolution spatiale ?

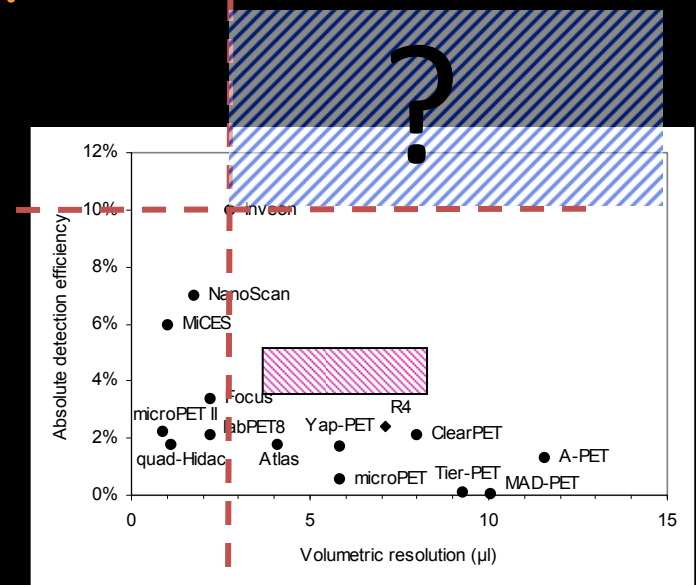
- dosimétrie (résolution au niveau de l'organe)

Modèle animal?

- Souris génétiquement modifiée: 90% des études
-> système dédié, bas coût

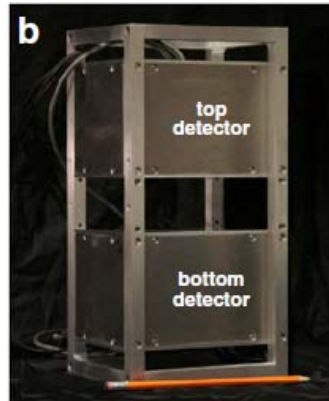
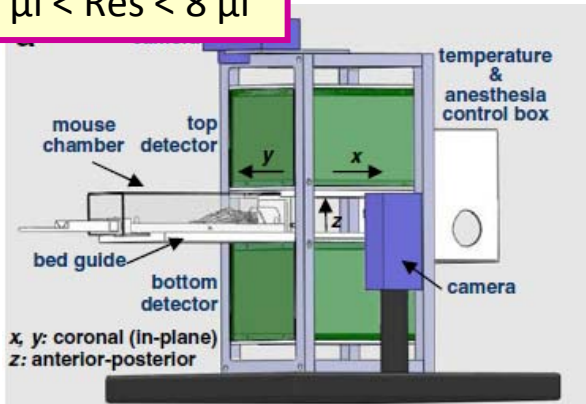
Activité injectée ?

- réduire l'activité car impact sur la mesure

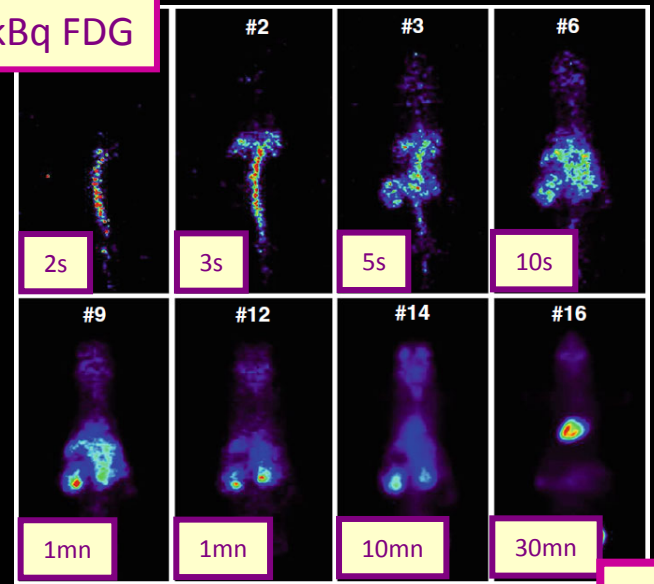


Chatziioannou et al, 2010: PETBox

S = 4% au centre
4 µl < Res < 8 µl



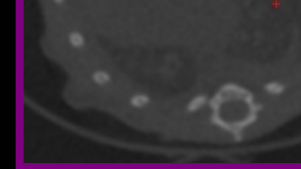
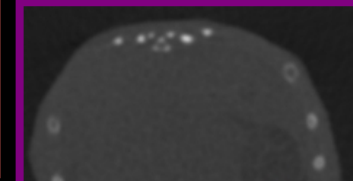
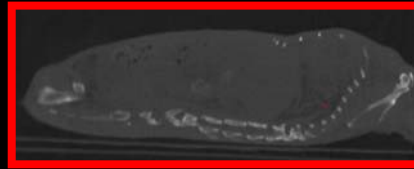
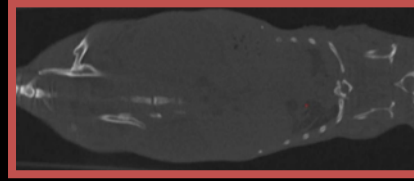
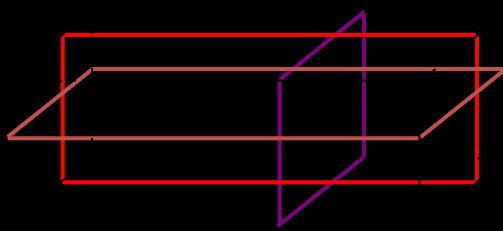
740 kBq FDG



...1h

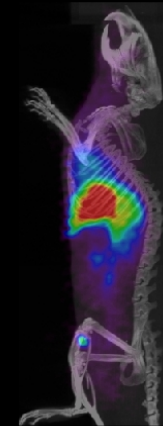
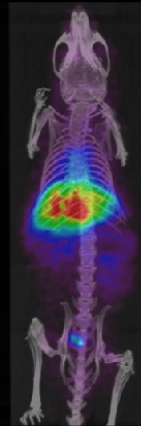
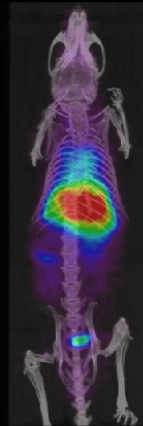
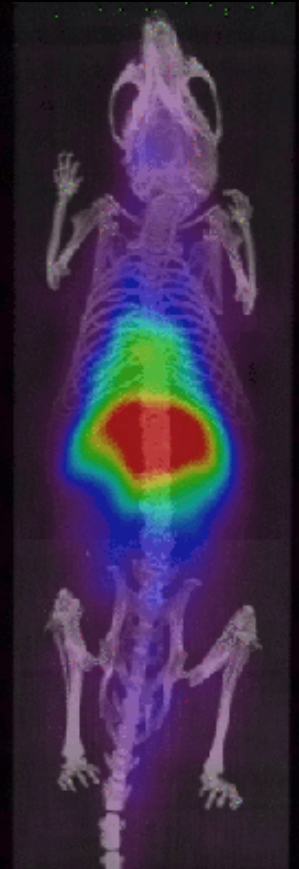
Méthodologie en TEMP

- Acquisition uCT: < 1min., résolution 100 μm , dose = 6 mGy



➡ Localisation 3D, corrections, positionnement anatomique

- Acquisition 2D: scintigraphie <3 min., résolution 1 mm (2D)



Left

Top

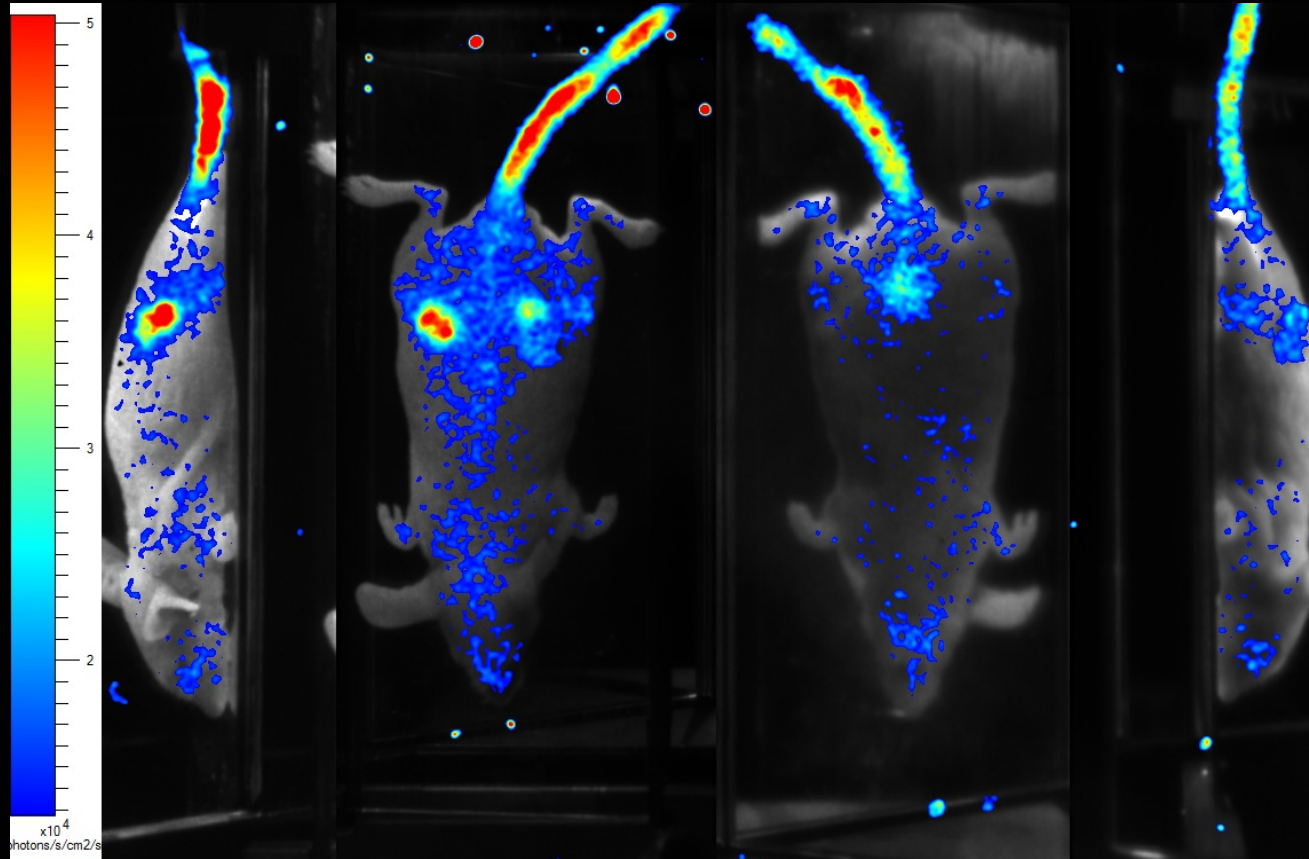
Bottom

Right



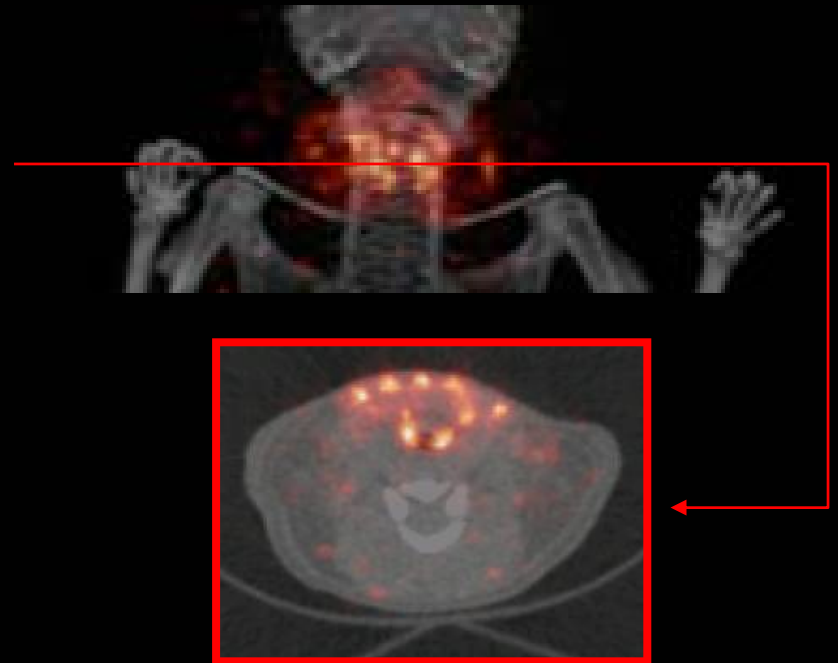
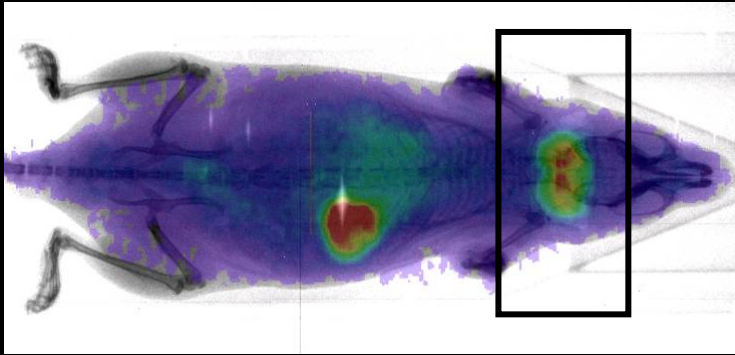
Méthodologie en TEP

- 2D Acquisition: imagerie Cerenkov <5 min., resolution 1 mm (2D)



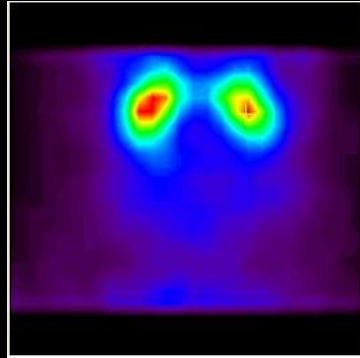
1,6 MBq P32 IV injection

- Acquisition TEMP 3D: 10 min., résolution 0,8 mm (3D)



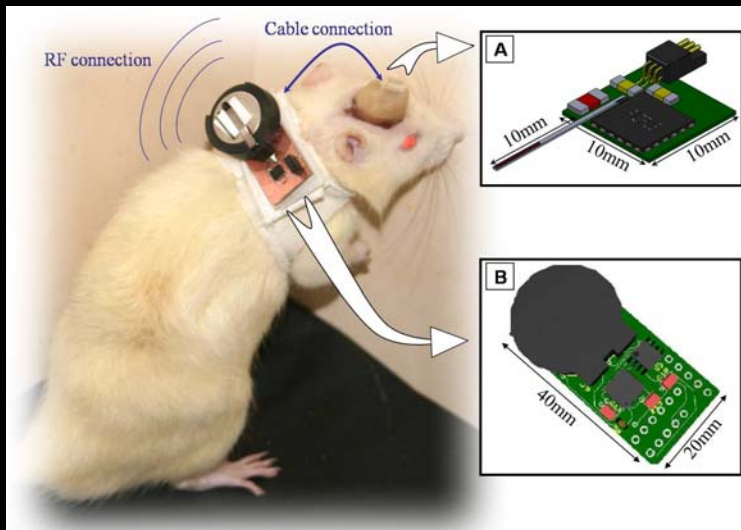
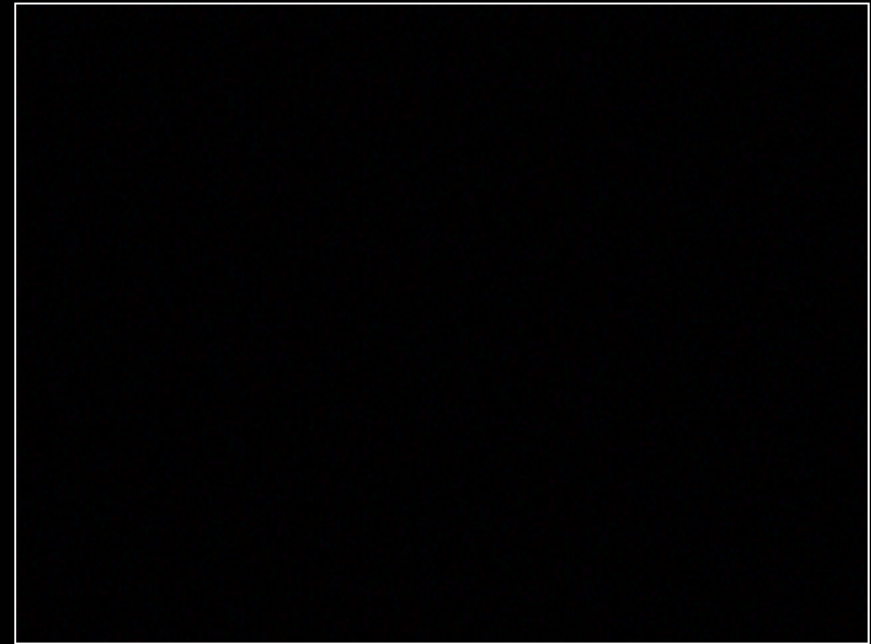
Etude sur animal éveillé

RatCap Project (BNL)

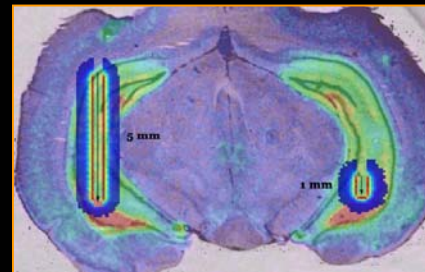


C11-raclopride

Courtesy of C. Woody, BNL

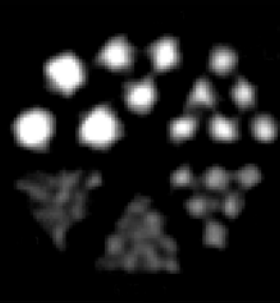
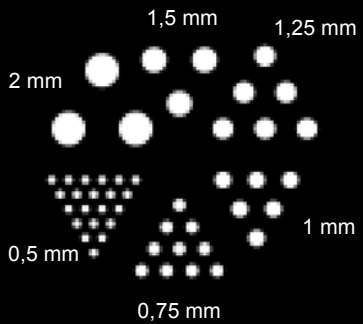
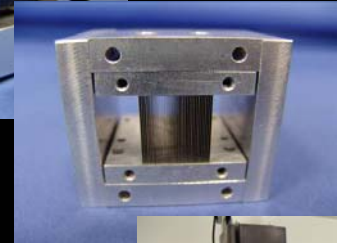
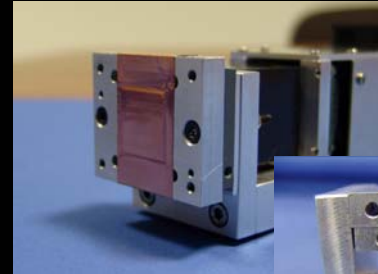
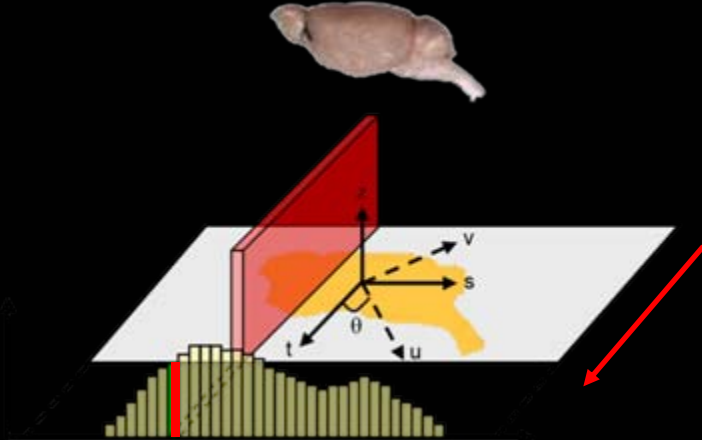
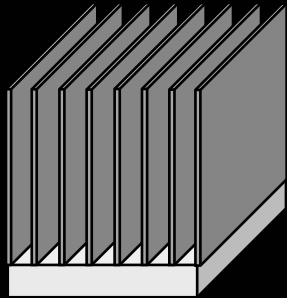


Travaux réalisés par M Savinaux (Biospace, Central Paris)

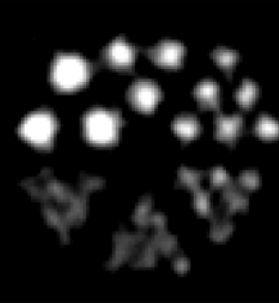


PixSic Project (IMNC, CPPM, CERMEP, NPS)

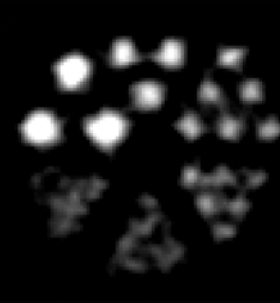
En TEMP ?... Un problème de collimation



0 cm

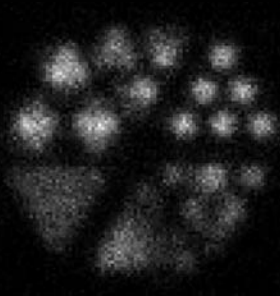


1 cm

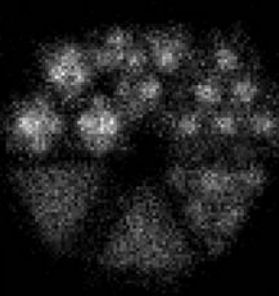


2 cm

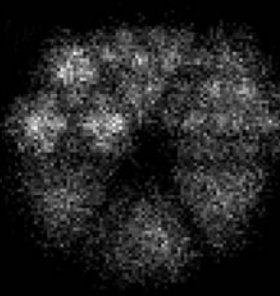
prototype



0 cm



1 cm



2 cm

γ caméra

Conclusion

Cluster de compétences autour de l'Imagerie Moléculaire

