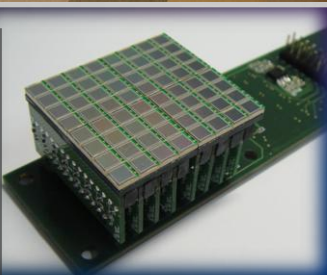
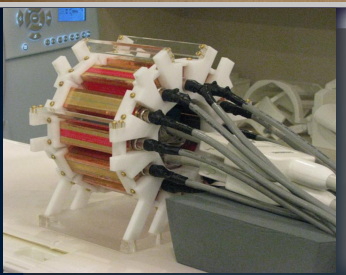
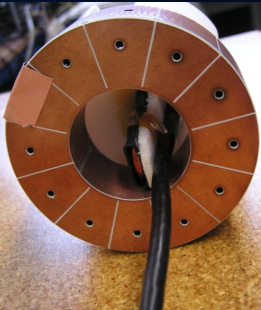
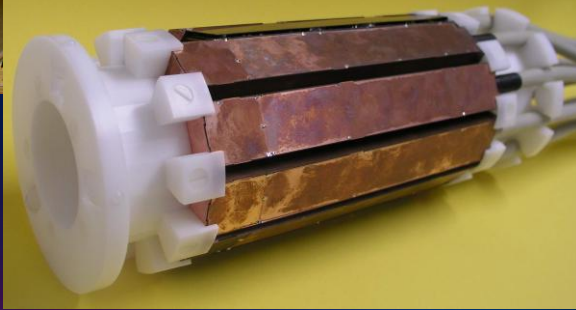
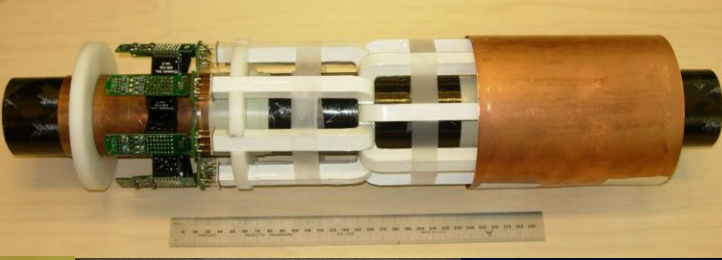


# PET/MRI: The Birth and Rebirth of PET/MRI

Simon R. Cherry, Ph.D.

Center for Molecular and Genomic Imaging  
Department of Biomedical Engineering  
University of California, Davis



# Early History



1986

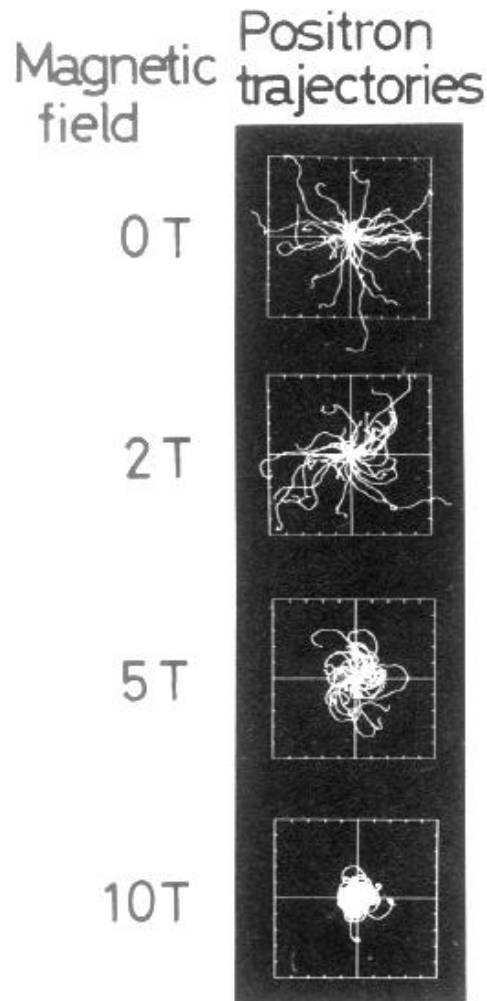
# Use of Magnetic Field to Reduce Positron Range

IEEE Transactions on Nuclear Science, Vol. 33, No. 1, February 1986

A SIMULATION STUDY OF A METHOD TO REDUCE POSITRON ANNIHILATION SPREAD DISTRIBUTIONS USING A STRONG MAGNETIC FIELD IN POSITRON EMISSION TOMOGRAPHY

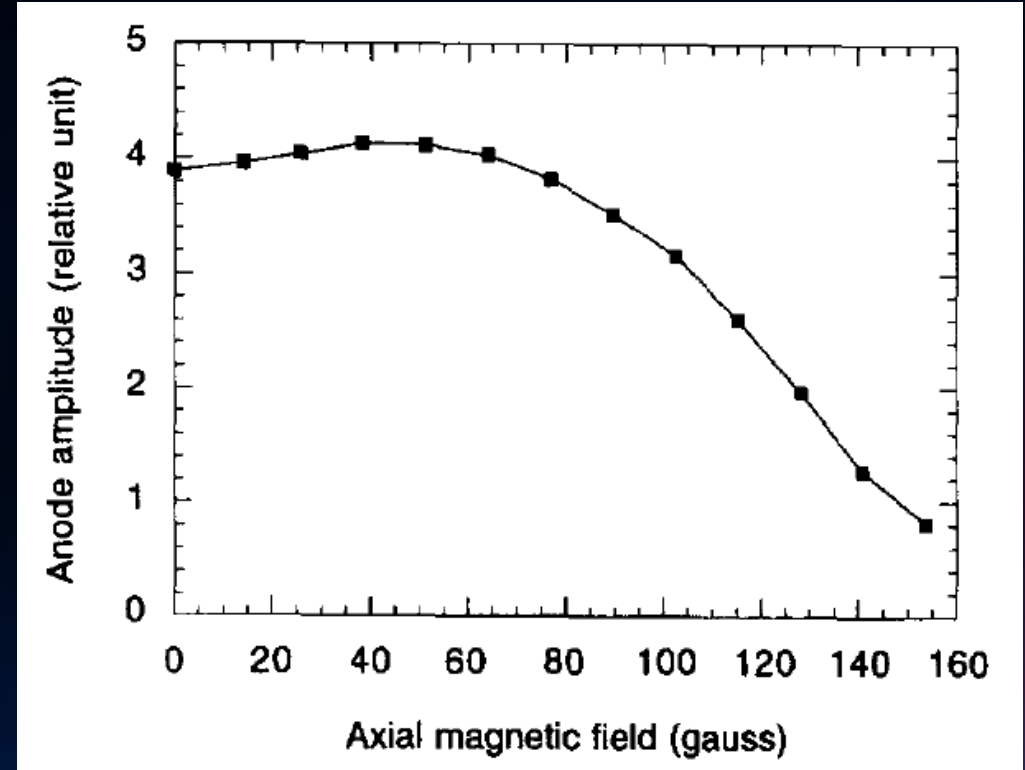
H. IIDA, I. KANNO, S. MIURA, M. MURAKAMI,  
K. TAKAHASHI AND K. UEMURA.

Department of Radiology and Nuclear Medicine  
Research Institute for Brain and Blood Vessels  
6-10 Senshu-Kubota-machi, Akita, 010, Japan



Unfortunately, since the required magnetic field to reduce the spread of positron annihilations was found to be terribly high, it will be pessimistic to apply the idea to the present practical PET, because we cannot use photo-multiplier tubes without gaudy magnetic shields. But in future, a new detector might be invented having good spatial resolution being unperturbed even by strong external magnetic fields.

# PMT Sensitivity to Magnetic Fields



Courtesy Hamamatsu Corp.

1T = 10,000 gauss!

# PET/MRI first proposed?

**United States Patent** [19]  
**Hammer**

[11] **Patent Number:** 4,939,464  
 [45] **Date of Patent:** Jul. 3, 1990

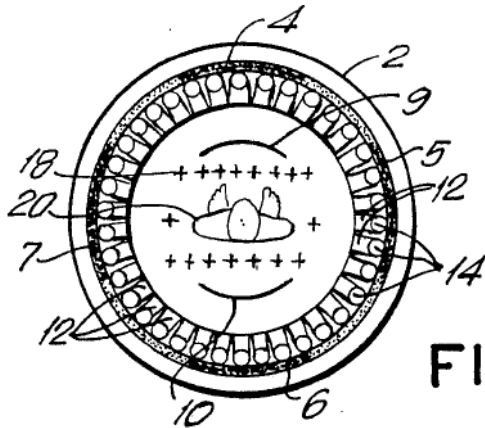
- [54] **NMR-PET SCANNER APPARATUS**
- [75] **Inventor:** Bruce E. Hammer, Latham, N.Y.
- [73] **Assignee:** Intermagnetics General Corporation, Guilderland, N.Y.
- [21] **Appl. No.:** 378,396
- [22] **Filed:** Jul. 11, 1989
- [51] **Int. Cl.<sup>5</sup>** ..... G01R 33/20
- [52] **U.S. Cl.** ..... 324/318; 128/653 R; 250/363.03; 250/368
- [58] **Field of Search** ..... 324/300, 307, 318; 250/363.03, 368; 128/653 R, 653 SC
- [56] **References Cited**

**FOREIGN PATENT DOCUMENTS**

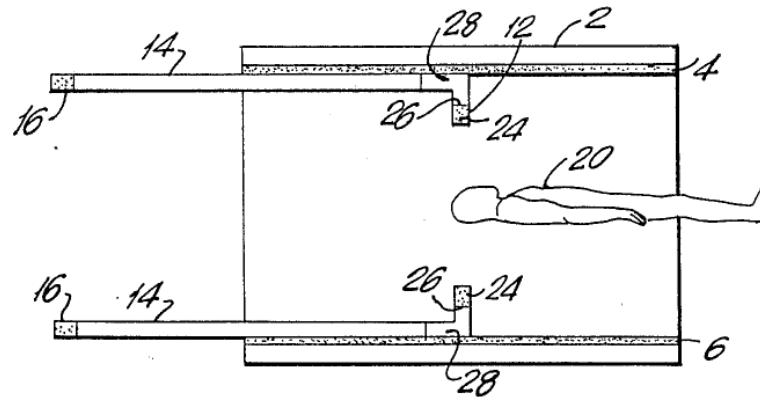
*Primary Examiner*—Michael J. Tokar  
*Assistant Examiner*—Kevin D. O'Shea  
*Attorney, Agent, or Firm*—Helfgott & Karas

[57] **ABSTRACT**

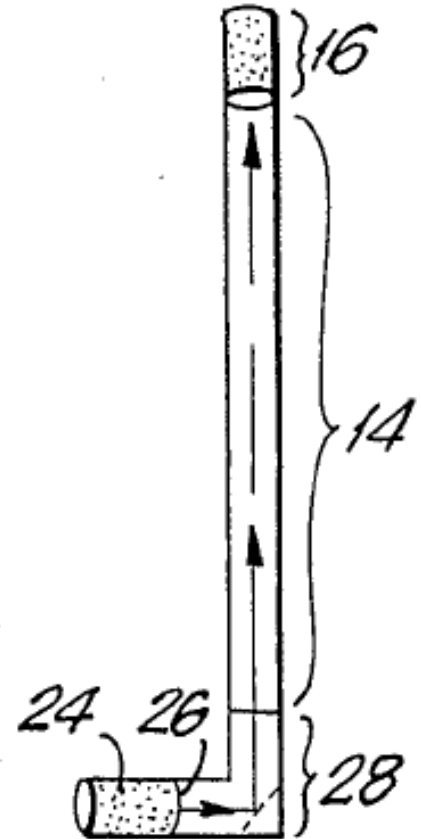
NMR-PET scanner apparatus is provided wherein a PET detector is disposed within a magnetic imaging structure of an NMR device. The output of the PET detector is conveyed through light pipes to photodetectors which are shielded and disposed without the magnetic imaging structure of the NMR device to avoid interaction between the photodetectors and the magnetic field generated by the magnetic imaging structure of the NMR device.



**FIG. 1**



**FIG. 2**



**FIG. 4**

1991

# Early Experimental Studies

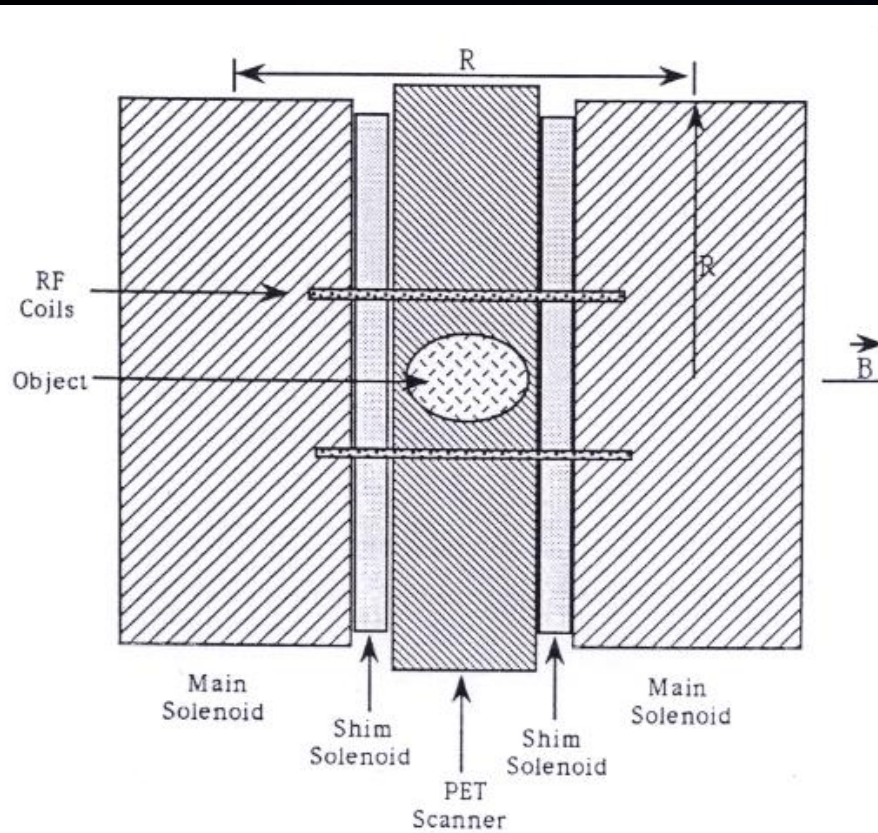
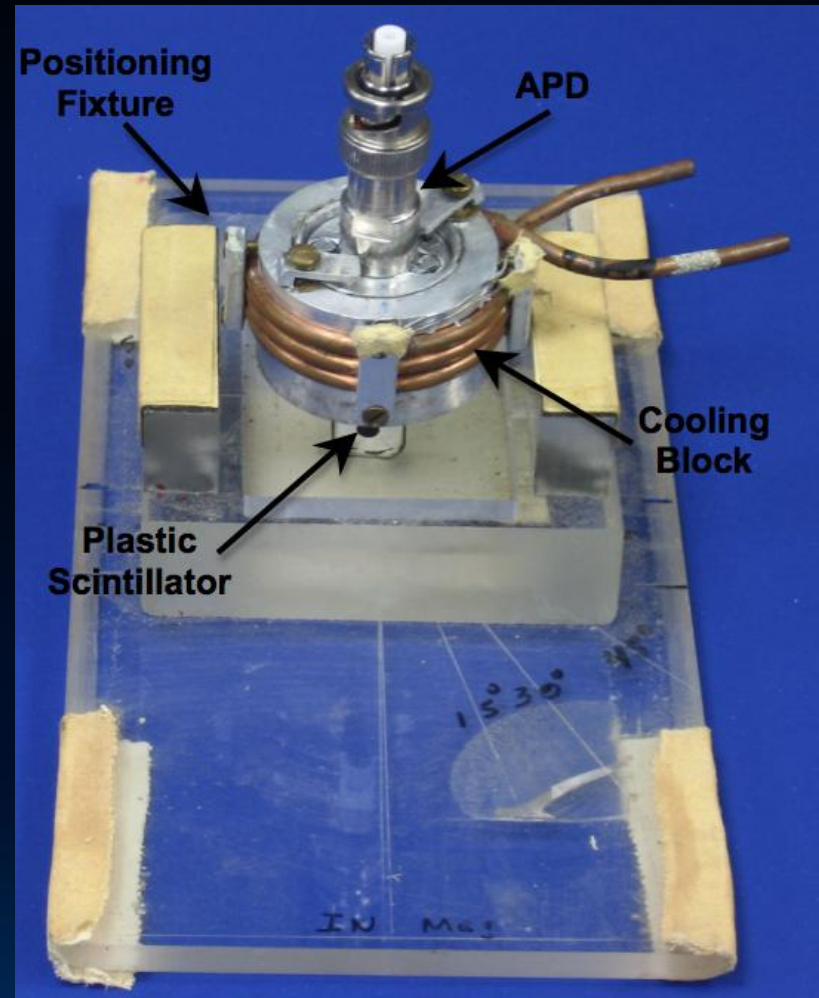


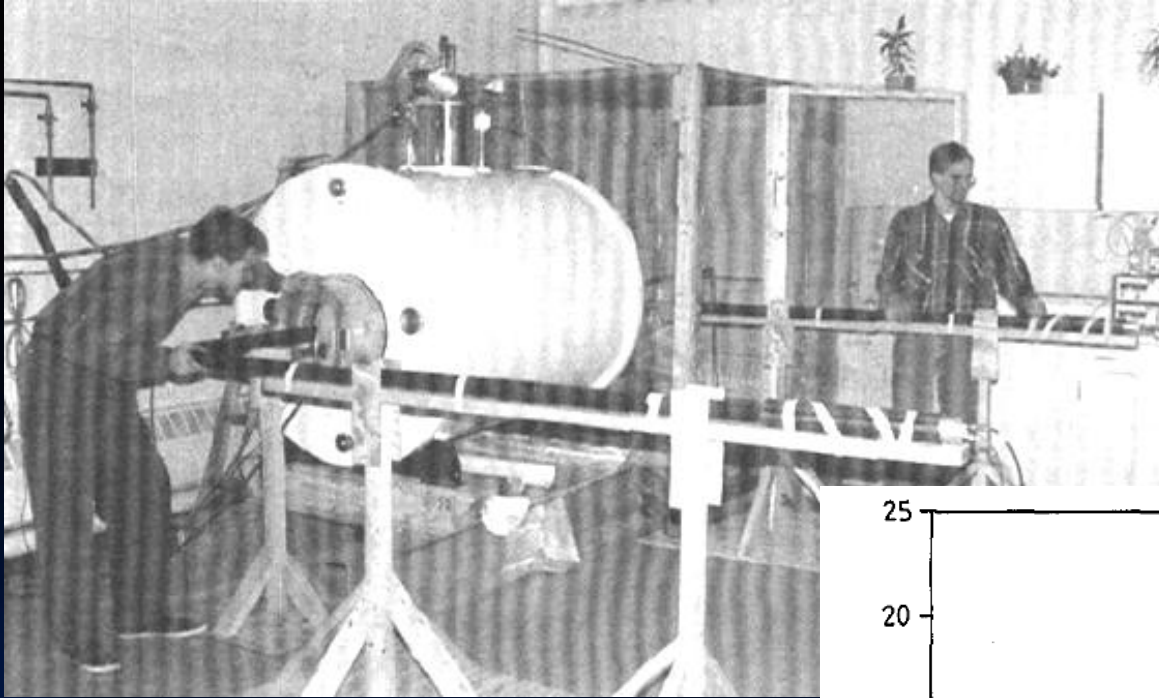
Figure IX.5: A schematic of the combined PET-MRI scanner.



From: Ray Raylman, PhD Thesis, "Reduction of positron range effects by use of a magnetic field: use in positron emission tomography", University of Michigan (1991)

1994-95

# Positron Range Reduction



Hammer et al.

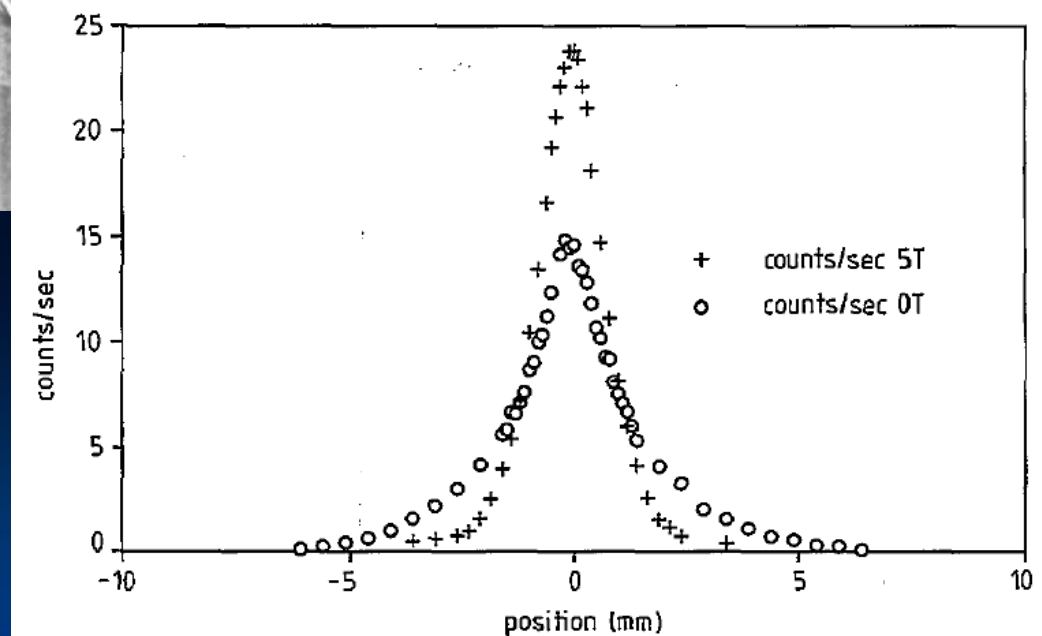
*Med Phys* 21; 1917-20 (1994)

Christensen et al.

*Phys Med Biol* 40; 691-7 (1995)

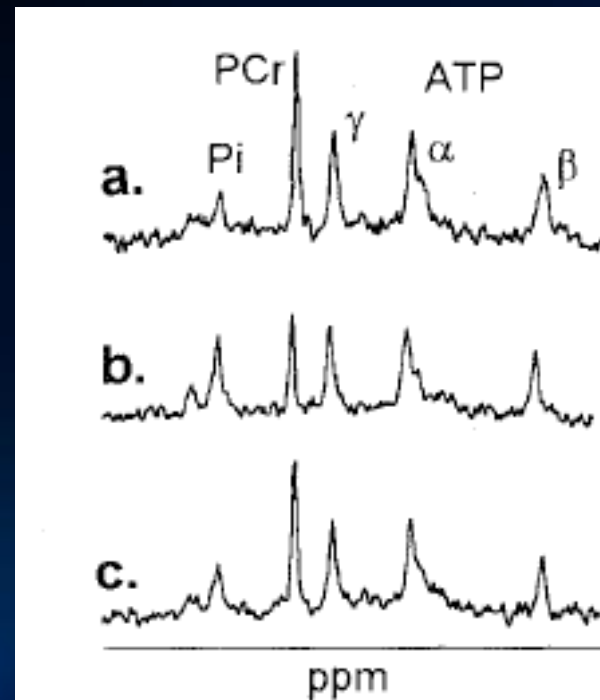
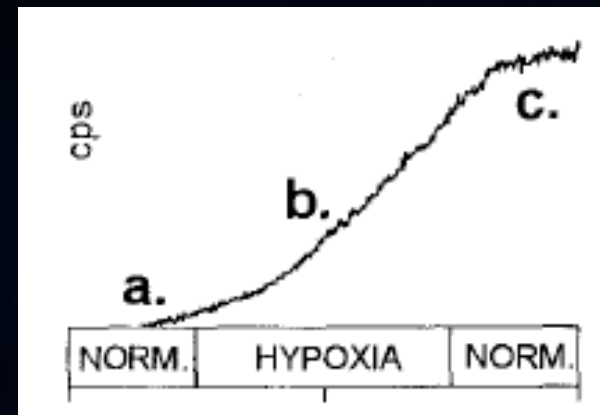
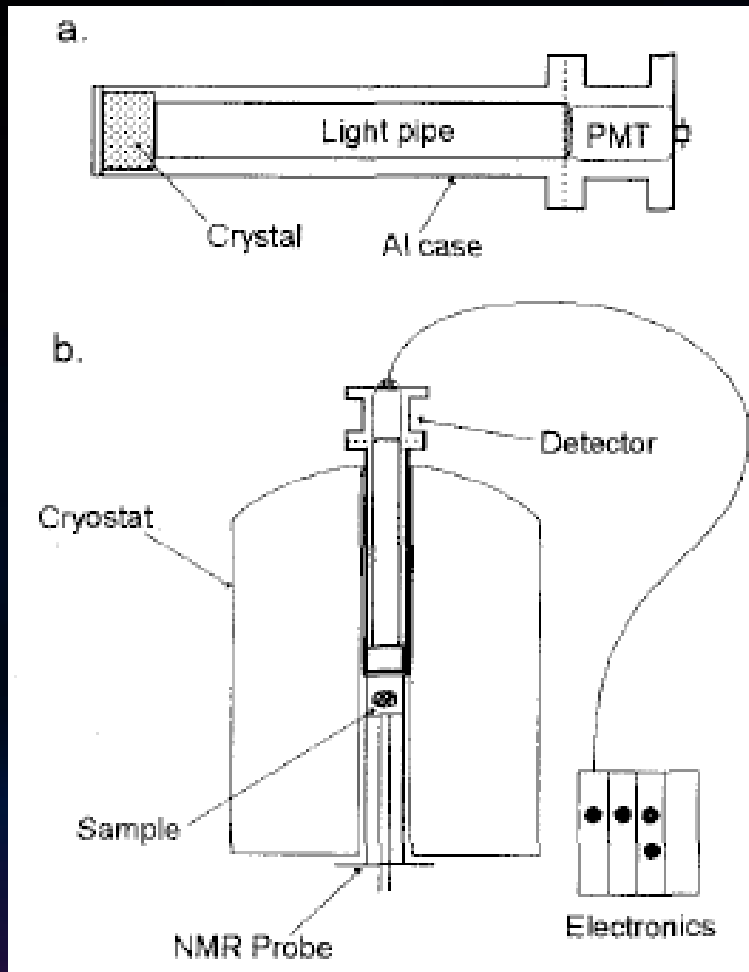
Hammer et al.

*IEEE Trans Nucl Sci* 42; 1371-6 (1995)



1995

# First Biomedical Experiments



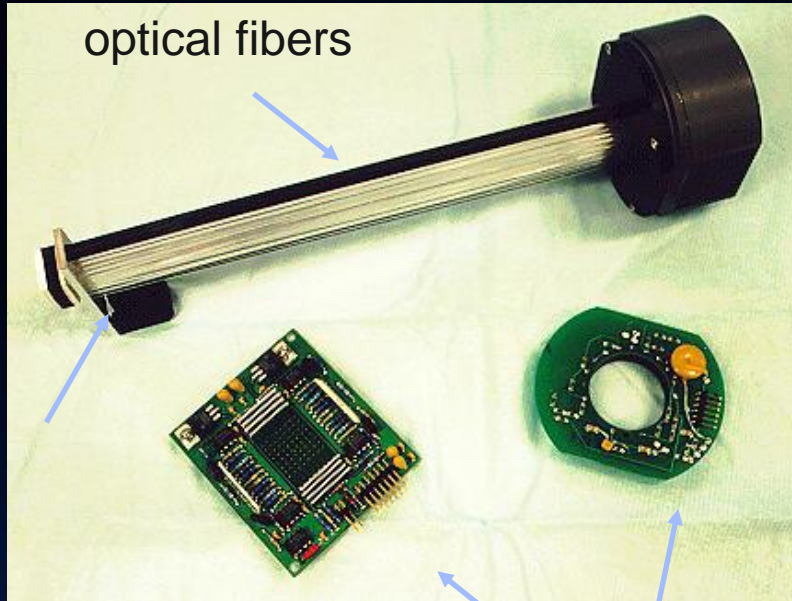
Buchanan M, Marsden PK et al.  
*IEEE Trans Nucl Sci* 43; 2044-8 (1996)

1994-96

# microPET

multichannel PMT

optical fibers



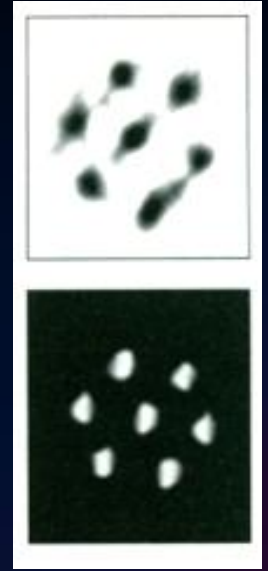
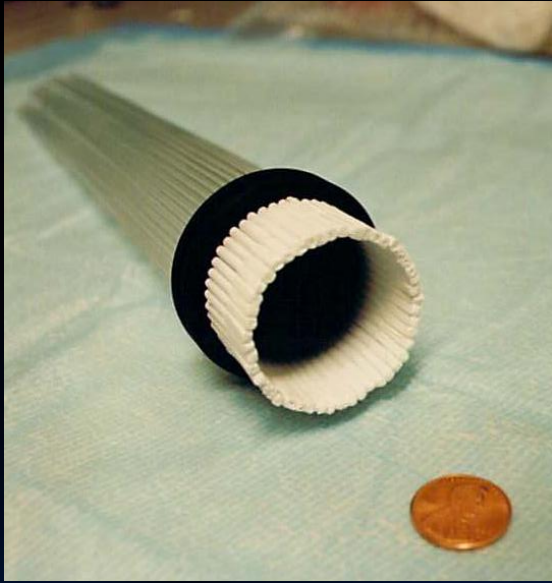
8x8 LSO  
array  
2x2x10 mm  
elements

readout  
electronics



1996

# Simultaneous PET/MR Images



Shao Y, Cherry SR, Farahani K et al.  
*Phys Med Biol* 42: 1965-70 (1997)

## MEDICAL IMAGING

## New Dynamic Duo: PET, MRI, Joined for the First Time

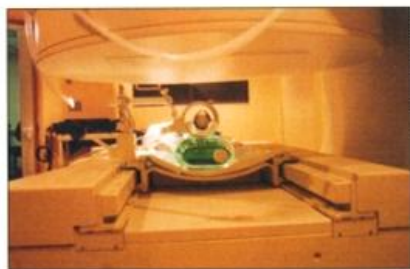
Looks will only get you so far, at least when it comes to medical imaging. Connecting the appearance of internal tissues to their function is an ongoing struggle for imaging researchers. Magnetic resonance imaging (MRI) excels at providing high-resolution anatomical maps, while positron emission tomography (PET) can better gauge the actual function of tissues by using a radioactive tracer to highlight metabolism. But never have the twin met in one machine: The powerful magnetic fields generated by MRI wreak havoc with the electronic detectors of PET scanners. That has made it hard on researchers studying the effects of drugs on particular tissues, for example. Now, however, things finally seem to be coming together.

A team of researchers at the Crump Institute for Biological Imaging at the University of California, Los Angeles (UCLA), has created a small PET prototype that is able to distance its vital electronics from MRI's high magnetic fields, thanks to fiber optic lines and highly sensitive detectors based on a crystalline material never before used in PET. This week, at the Society of Nuclear Medicine meeting in Denver, the team demonstrated its results: the first-ever simultaneous PET and MRI images, which show both structural features of a test object and PET-detected radioactivity highlighting those features.

"It's absolutely fascinating work," says Michael Green, an imaging physicist at the National Institutes of Health's Clinical Center in Bethesda, Maryland. Currently, researchers and clinicians must make the two kinds of images separately, then use mathematical techniques to weave them together, "a nontrivial task" that is prone to errors, Green says. But with the new setup, "you can relate functional changes to pieces of anatomy without ambiguity." Some scientists do caution that while the system should work well for animals, it may lose sensitivity when scaled up to human size. Still, "doing something like this has been discussed in the community for a long time," says Paul Lauterbur, an MRI expert at the University of Illinois, Urbana-Champaign.

This attempt at synergy was not the group's original goal, says UCLA physicist Simon Cherry, who led the team. It came as a by-product of their pursuit of a higher resolution PET scanner. PET scanners distinguish between metabolically active and inactive tissue by picking up gamma rays from a radioactive

compound that is injected into a subject and taken up by active tissues. An array of detectors—typically made from crystals of a bismuth, germanium, and oxygen (BGO) compound—surround the subject, and these crystals give off a burst of photons when they are hit by the



**Two for one.** A new type of PET detector can be integrated with MRI (above), yielding aligned images of both structure (right, top) and PET-related activity (below) in a test sample.



gamma rays. These photons are picked up by photomultiplier tubes (PMTs) that amplify the weak emission so it can be converted into an electric signal and ultimately integrated by a computer into an image of the active tissue.

But PET scanners with BGO-based detectors currently can only resolve the source of a signal to within a volume of about 64 cubic millimeters—about the size of a pencil eraser. That limit is not quite sharp enough to distinguish between tissues in the tiny organs of mice and rats, animals used to model drug activity of disease. To improve this situation, Cherry and his colleagues wanted to halve the size of the crystals—they are usually about 4 millimeters on a side—and pack them closer together. "That's possible to do" with BGO, says Cherry. But because the PMTs normally sit just behind the crystals, the tubes would also have to shrink if the crystals were packed more tightly. There's the rub, says Cherry: "There are no photomultiplier tubes that are that small."

Cherry and his colleagues realized that they could get around this size constraint by connecting 2-millimeter-thick optical fibers to the back side of their reduced crystals and

piping photons to PMTs tens of centimeters away. That, however, created another problem: Optical fibers absorb some photons, and BGO doesn't emit many to begin with, so there aren't enough left at the end of the line to drive the PMTs. To get past this obstacle, the UCLA team decided to use alternative crystals that can emit four times as many photons as BGO does after each gamma ray absorption. The new crystals, made from lutetium, silicon, and oxygen, or LSO, were discovered 6 years ago by Chuck Melcher and his colleagues at Schlumberger Limited, an oil services conglomerate that specializes in precision measurement.

LSO, says Cherry, "allowed all of the pieces to fit together." The new, closely packed detectors have a resolution of approximately 6 cubic millimeters, or about 10 times sharper than current detectors. And by arranging their detectors in a ring and using the long fiber optic lines to place the rest of the PET electronics a safe distance away, the researchers were able to put the ring inside an MRI machine and get PET and MRI images at the same time. They produced aligned cross-sectional images of a plastic cylinder drilled with a series of 1-millimeter-diameter holes, each of which was filled with a radio-labeled fluorine solution.

The group is still assembling a machine with a more complex array of detectors for a series of studies with small laboratory animals, such as investigating the interactions of cocaine with certain dopamine-producing cells in the brain. But performing related feats in people may be difficult, says Z. H. Cho, an MRI and PET expert at the University of California, Irvine. Among the problems, says Cho, is that to get a high-resolution image, each PET crystal must pick up a high density of gamma ray hits. The UCLA scanner accomplishes this in part by shrinking the diameter of its ring of detectors—which means each detector covers a relatively large percentage of the ring and collects more gamma rays. But the researchers will have to enlarge the ring to accommodate people, dropping the number of gamma rays that hit each detector.

One way around this would be just to add more detectors, says Cherry, although he concedes that this could make the machines overly expensive. So the device may not be able to do everything. Researchers may have to settle for two things at once.

—Robert F. Service

“...but performing related feats in people may be difficult.”

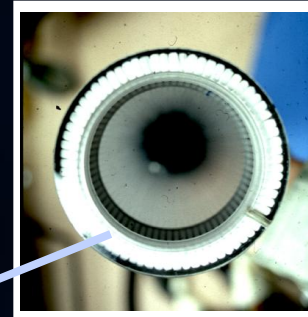
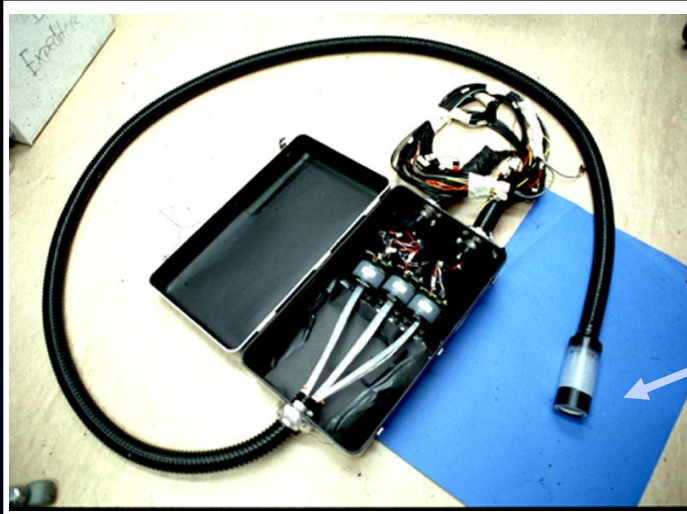
Z.H. Cho

“...doing something like this has been discussed in the community for a long time”

Paul Lauterbur

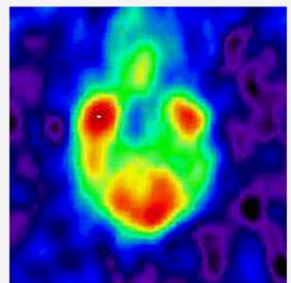
1997

# Simultaneous In Vivo Images

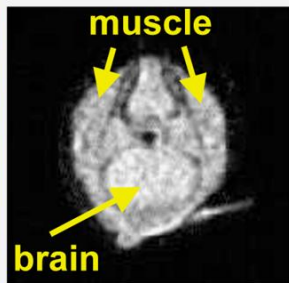


56 mm ring diameter  
72 2x2x25 mm LSO scintillators

200 g Rat -  $^{18}\text{F}$ -FDG Brain Study



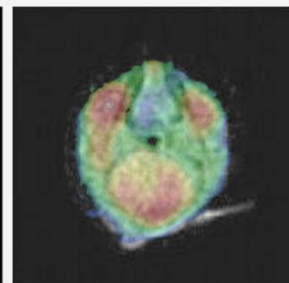
PET



brain

muscle

MRI

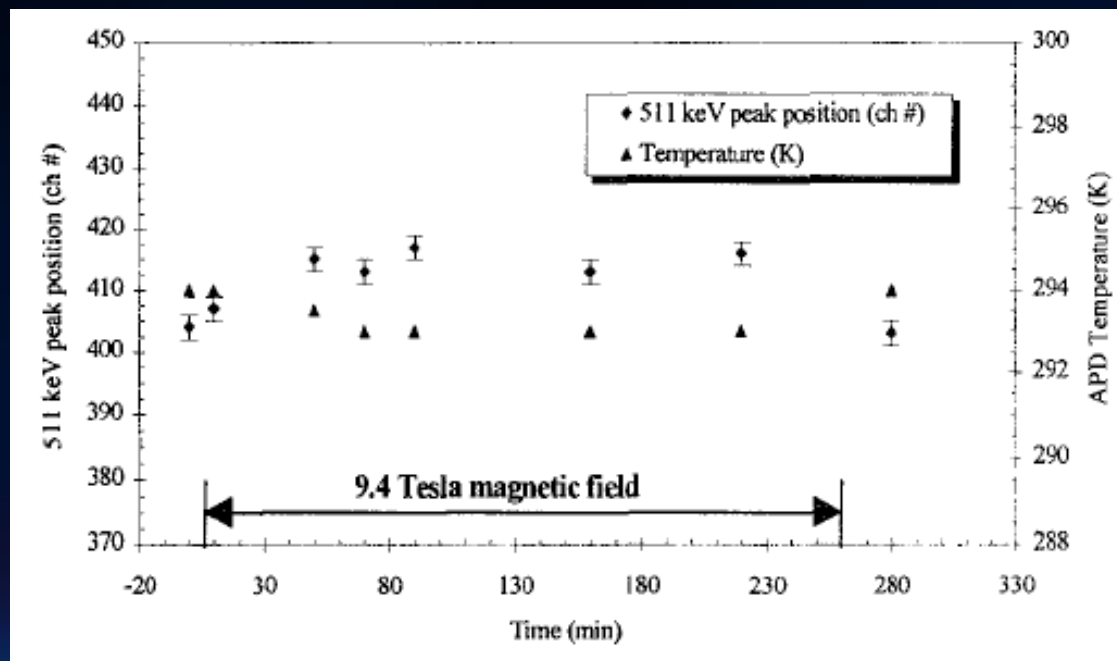
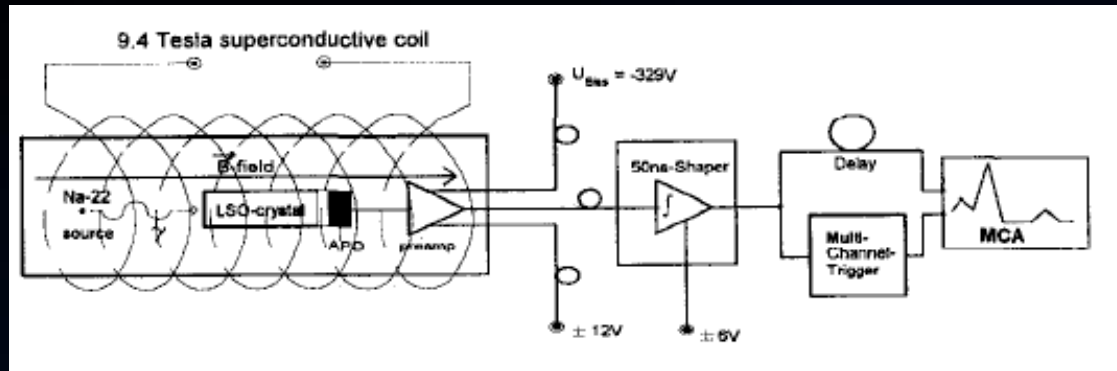


fused PET/MRI



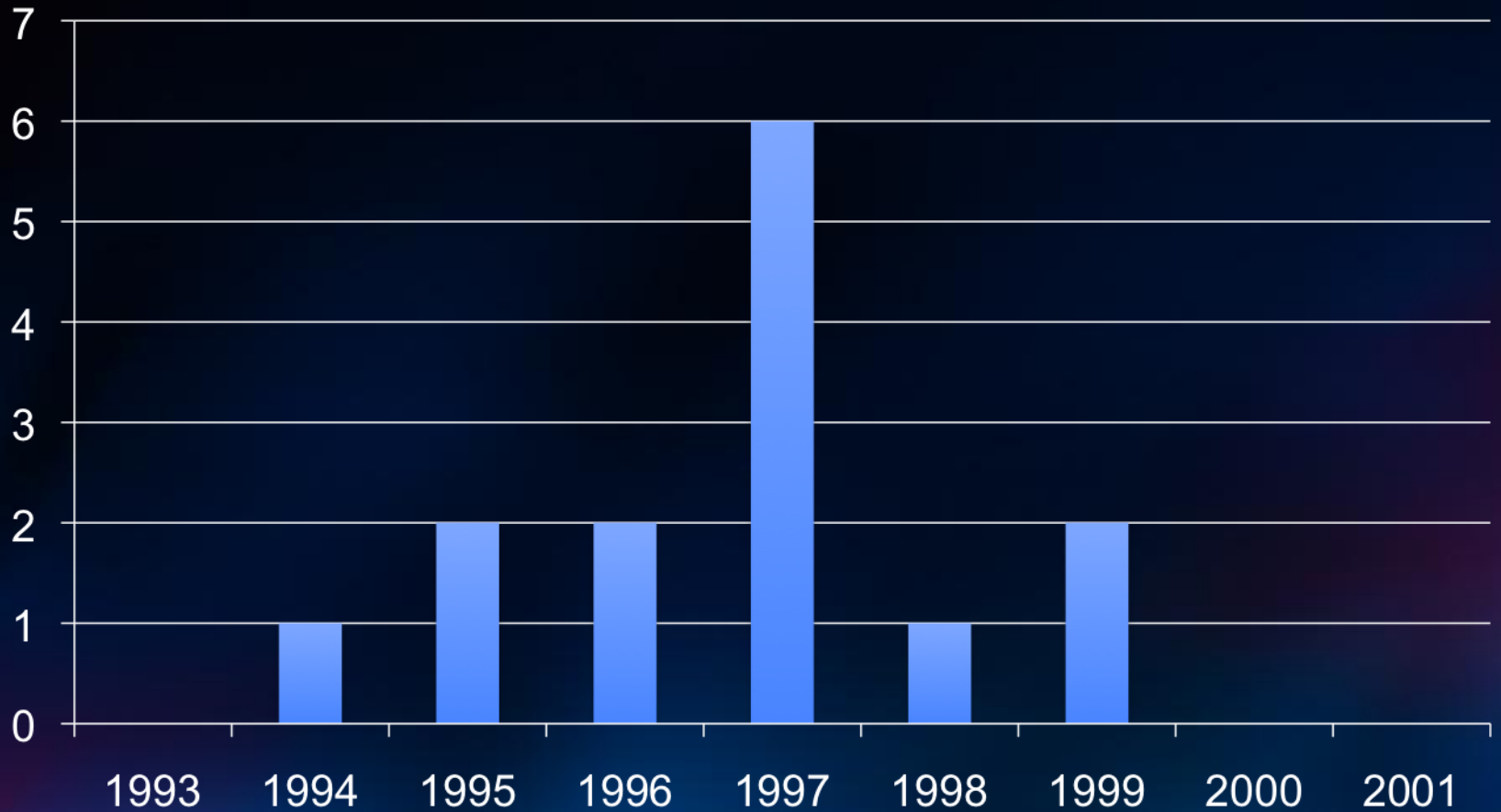
1997

# LSO-APD Detector at 9.4T



Pichler BJ, Lorenz E, Mirzoyan R, Pimpl W, Roder F, Schwaiger M, Ziegler SI.  
 1997 IEEE Medical Imaging Conference Record pp. 1237-9, (1998)

# PET/MR Publications versus Year



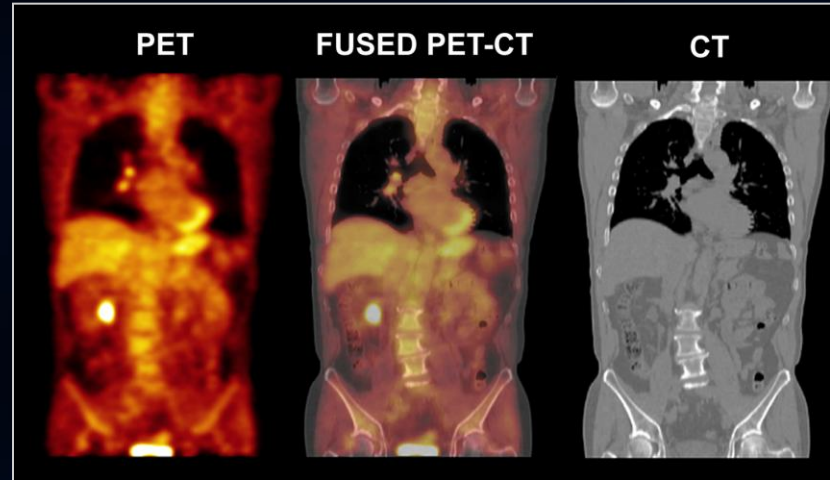
# The Dark Ages



# The Invasion of PET/CT



Courtesy GE Medical Systems



Images courtesy of David Townsend, University of Tennessee



Courtesy Siemens Preclinical Solutions

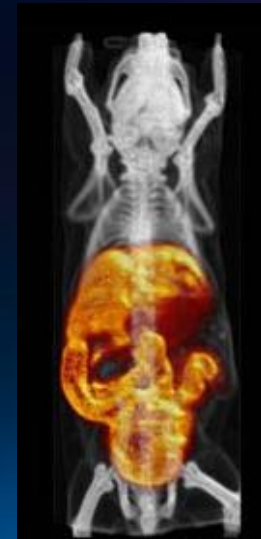
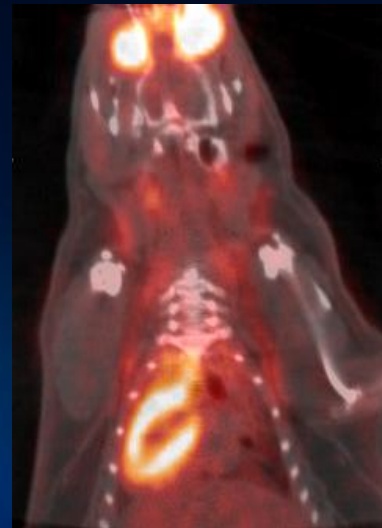
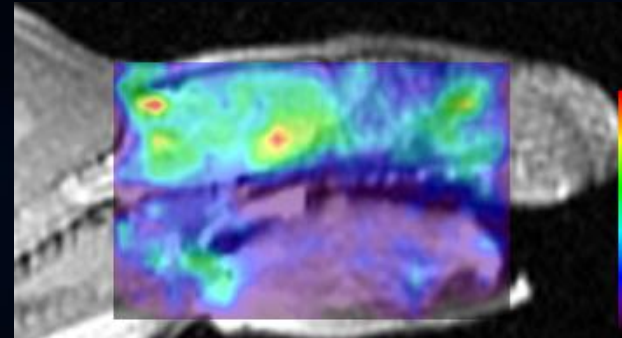
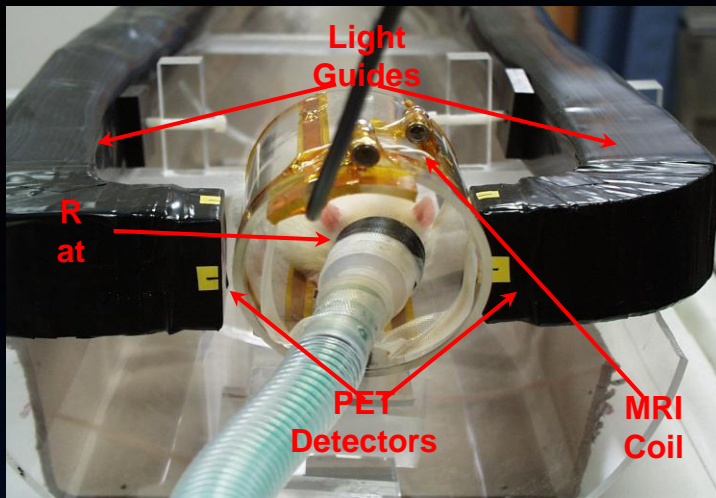


Image courtesy UCLA

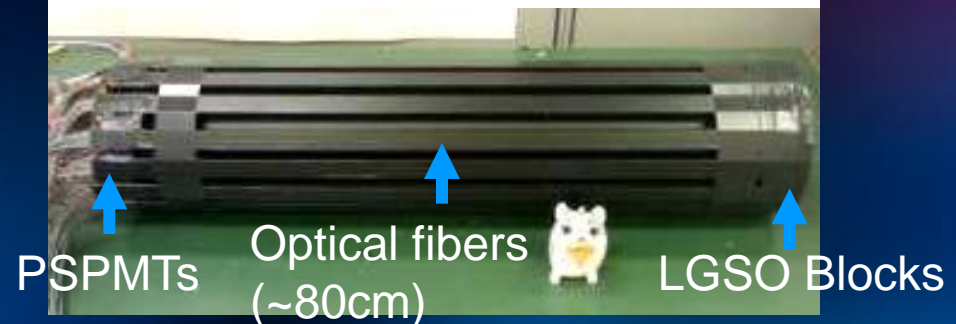
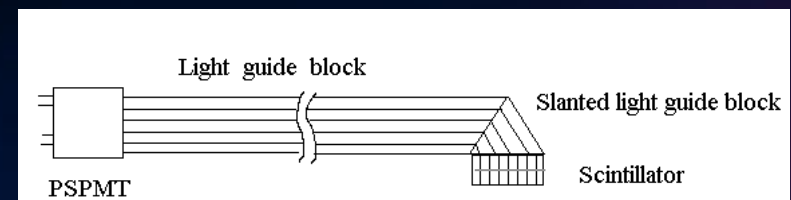
# The Renaissance



# Fiber-Optically Coupled PET/MRI

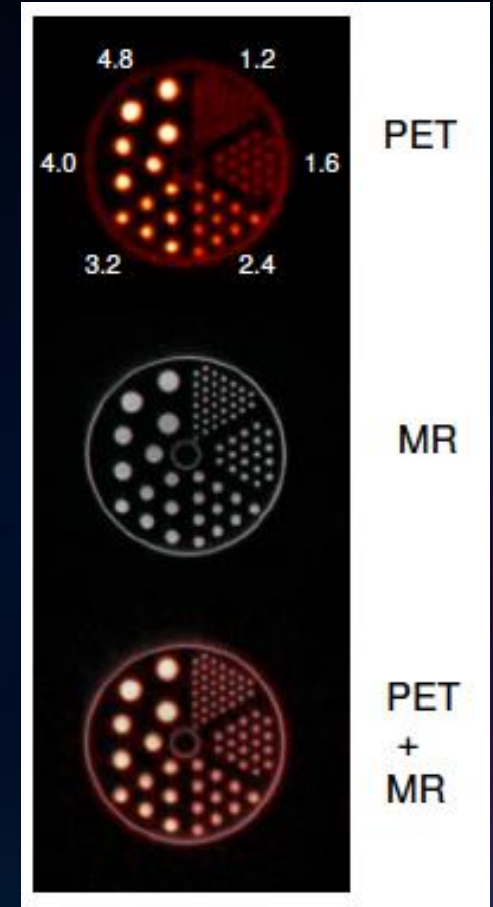
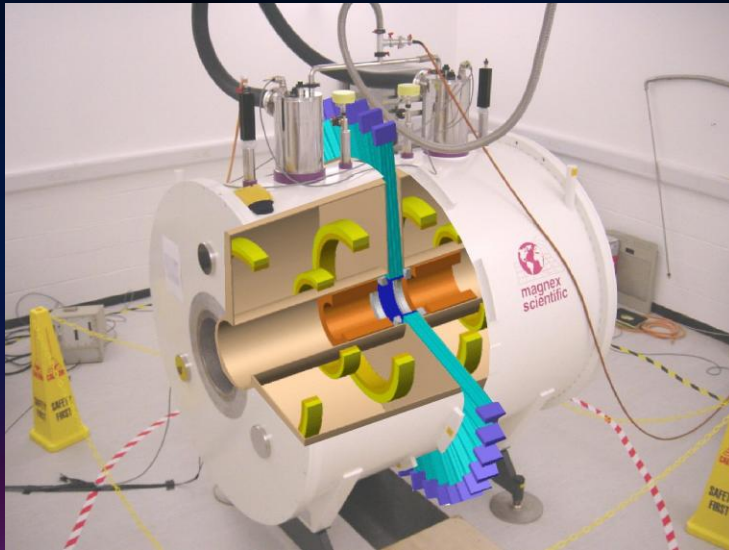
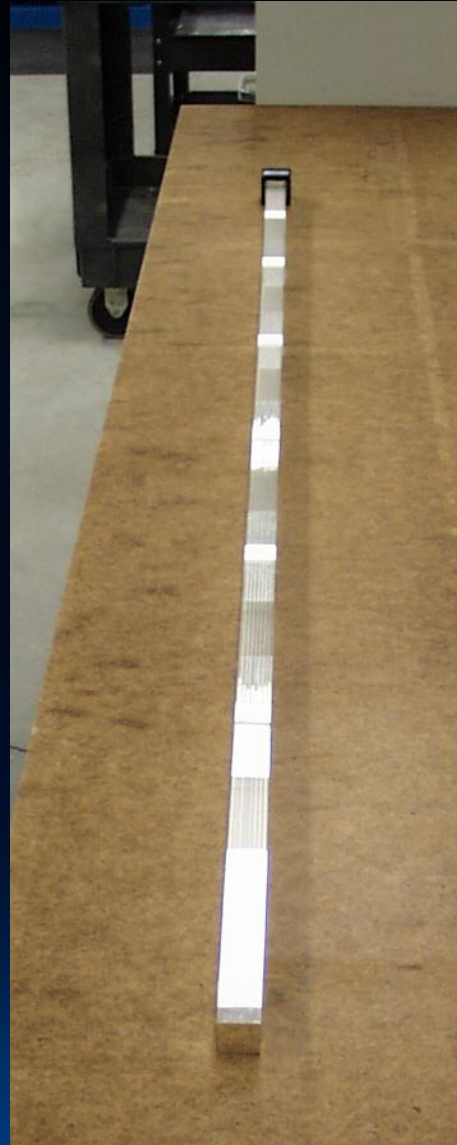


courtesy of Ray Raylman, West Virginia University  
*Phys Med Biol*, 2006;51:6371-6379 and *NIMA*, 2006;569(2):306-309.



courtesy of Seichi Yamamoto, Kobe, Japan

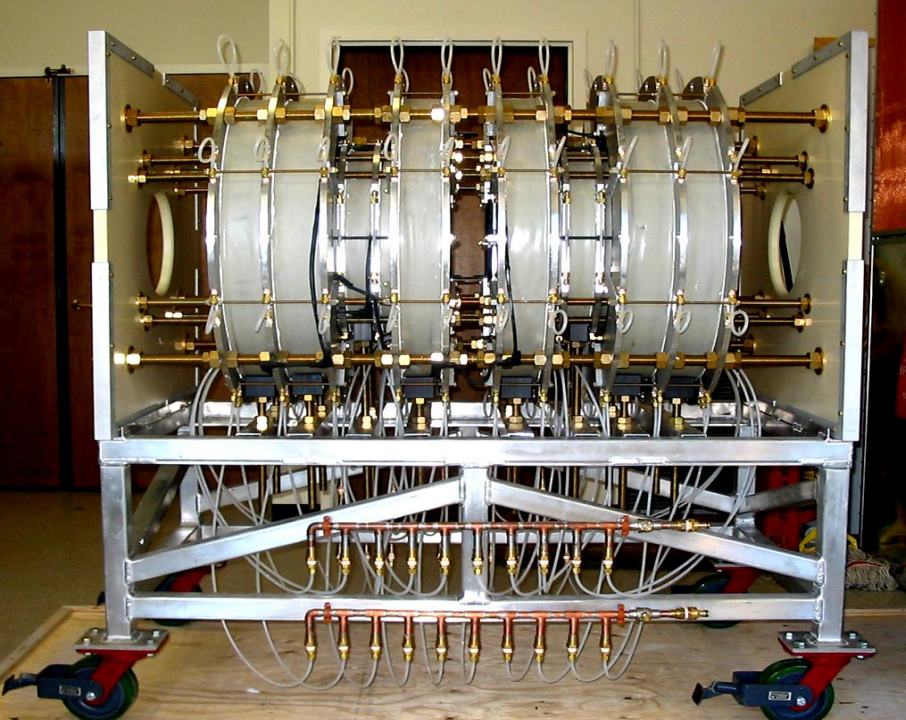
# Split Magnet PET/MRI



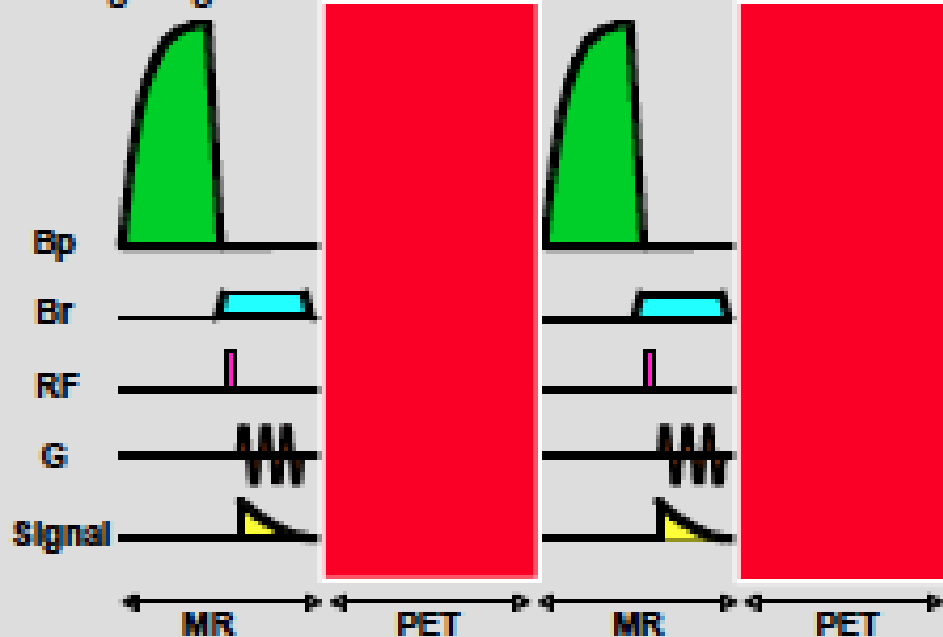
*A Lucas, R. Hawkes, P Guerra, R Ansorge, R Nutt, J Clark, T Fryer, A Carpenter.*



**UNIVERSITY OF  
CAMBRIDGE**



timing diagram:

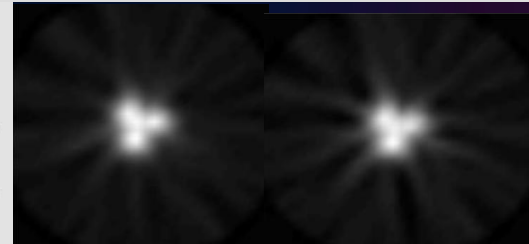
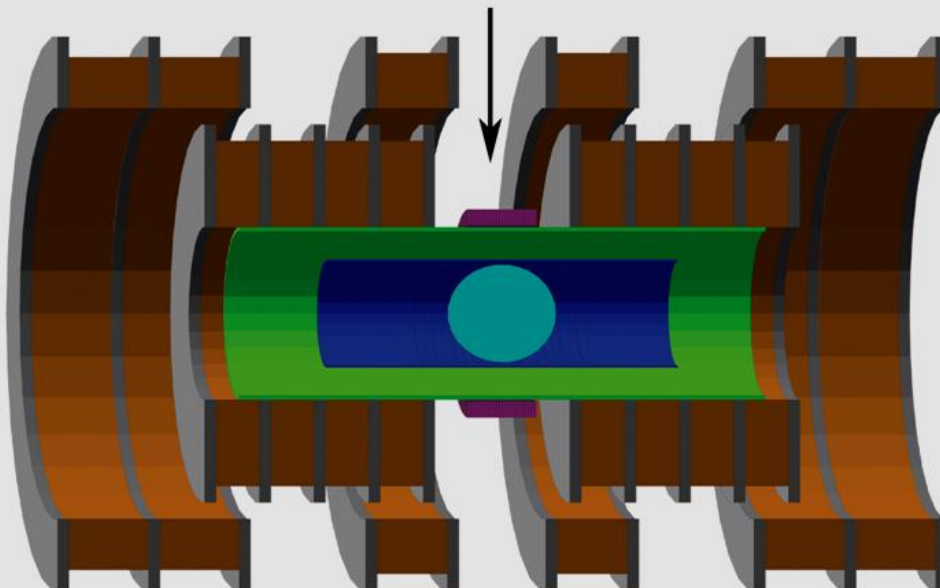


microPET scintillators

Readout Magnets

Polarizing Magnets

Gradients, RF etc  
around spherical  
sample

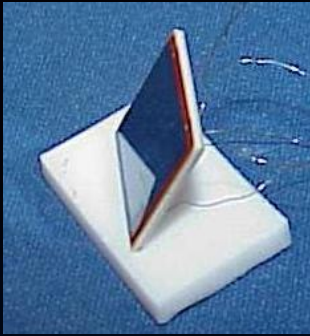


Field-Cycled MRI  
for MRI/PET

Blaine Chronik

University of Western  
Ontario

# MR-Compatible PET Detector based on APDs



Si avalanche photodiode with position-sensitive resistive anode, field tolerant beyond 9.4 T

**RMD**

scintillator array

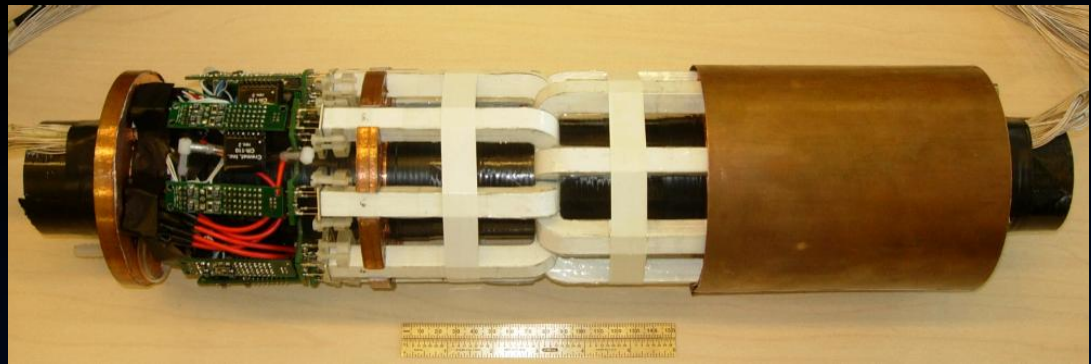
optical fiber bundle

PSAPD

preamplifiers



# PET Insert

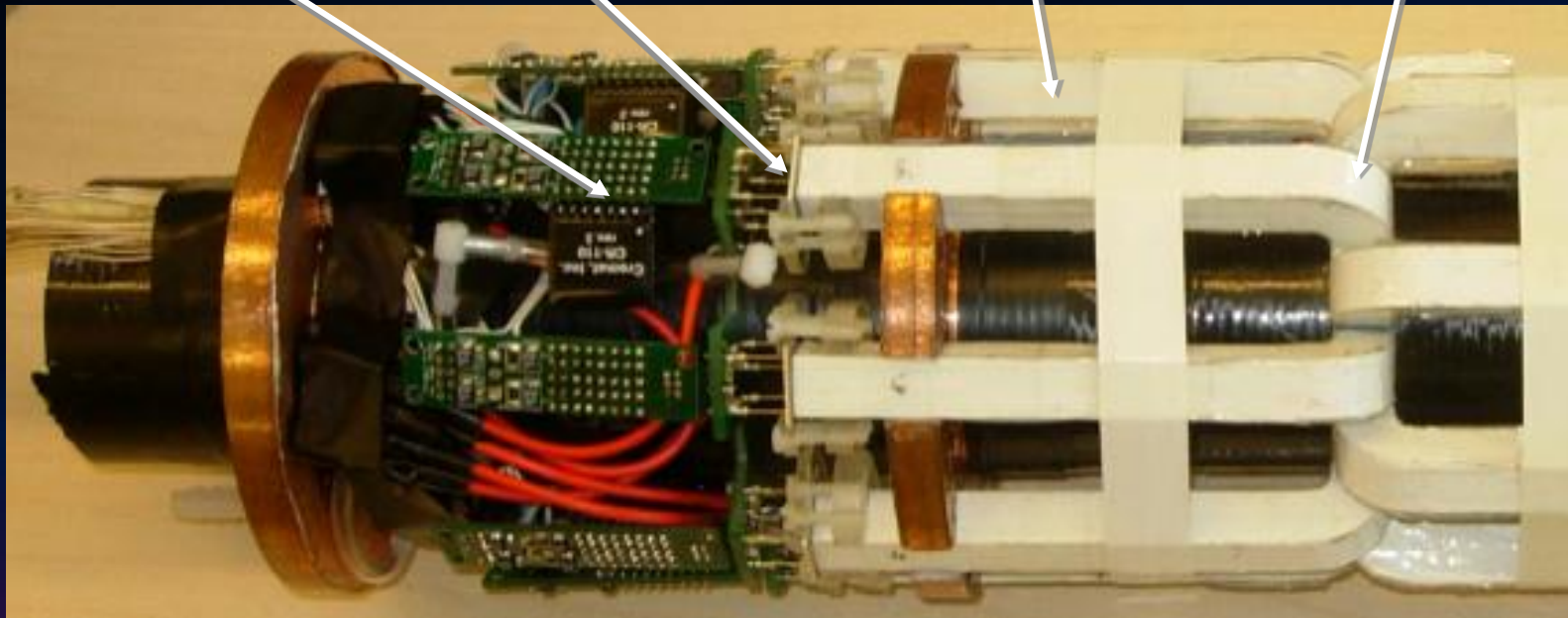


preamplifiers

PSAPDs

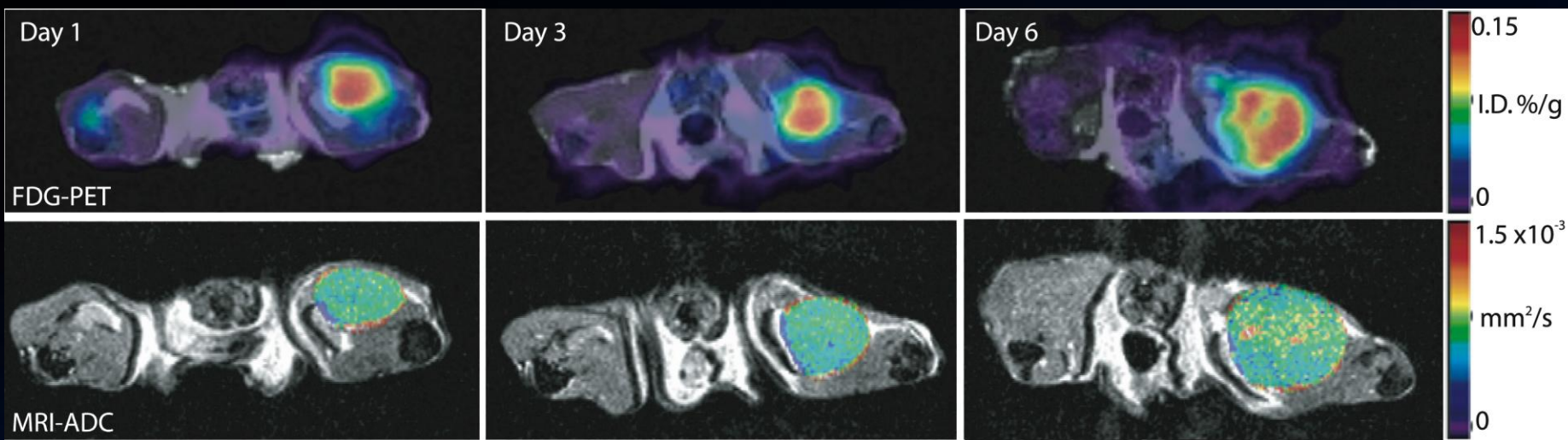
optical fibers

scintillator ring

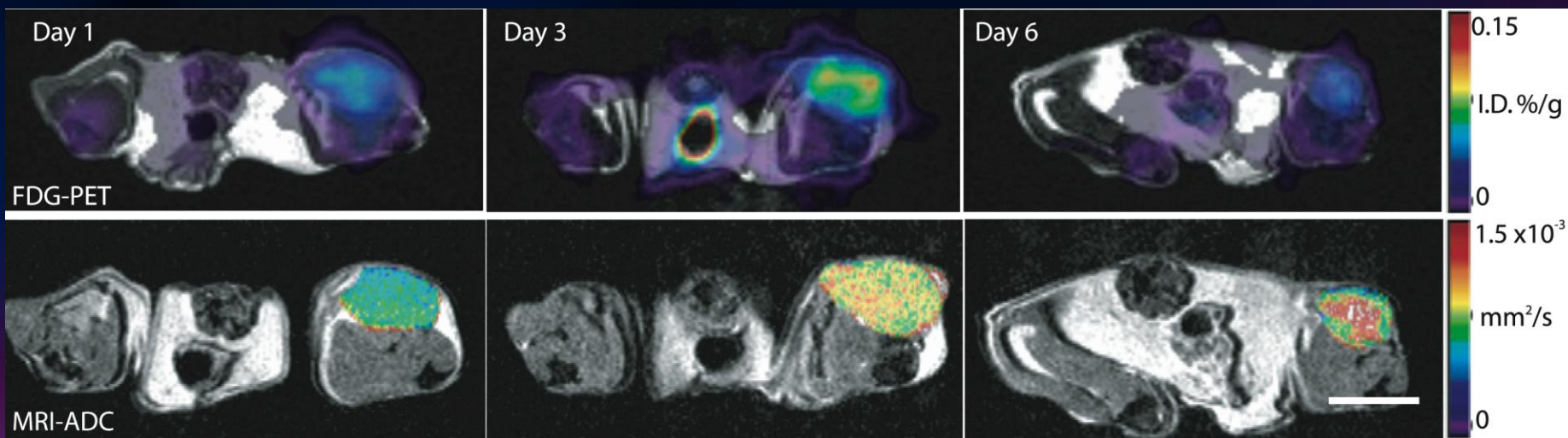


# Therapeutic Monitoring with PET/MRI

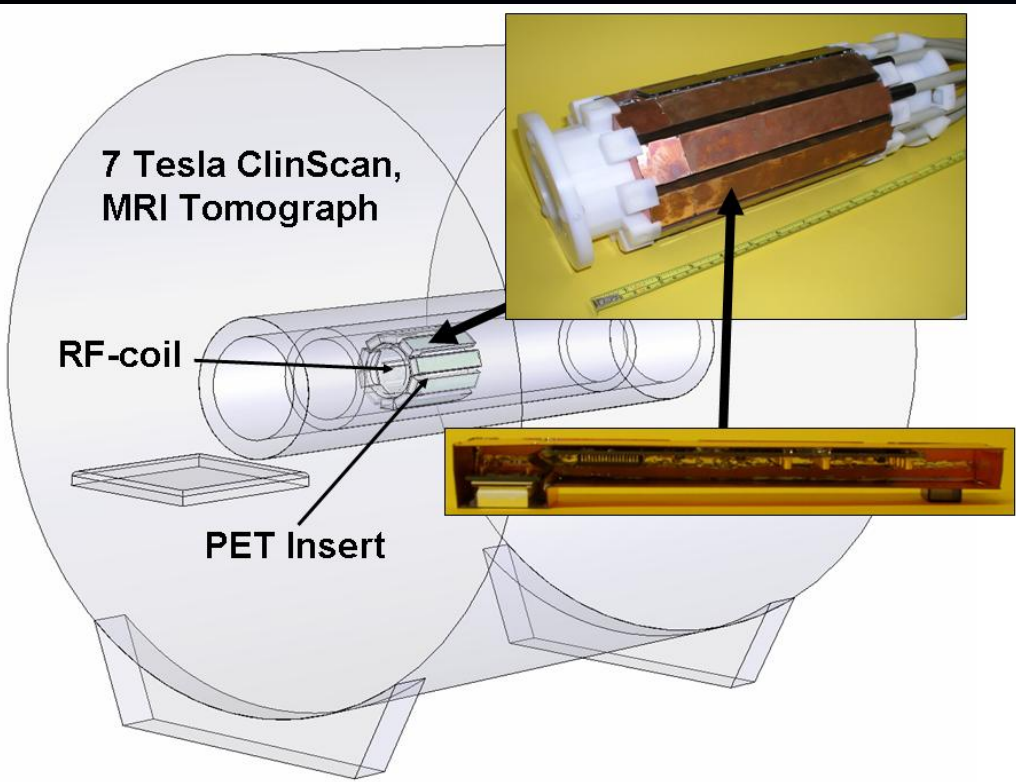
Control



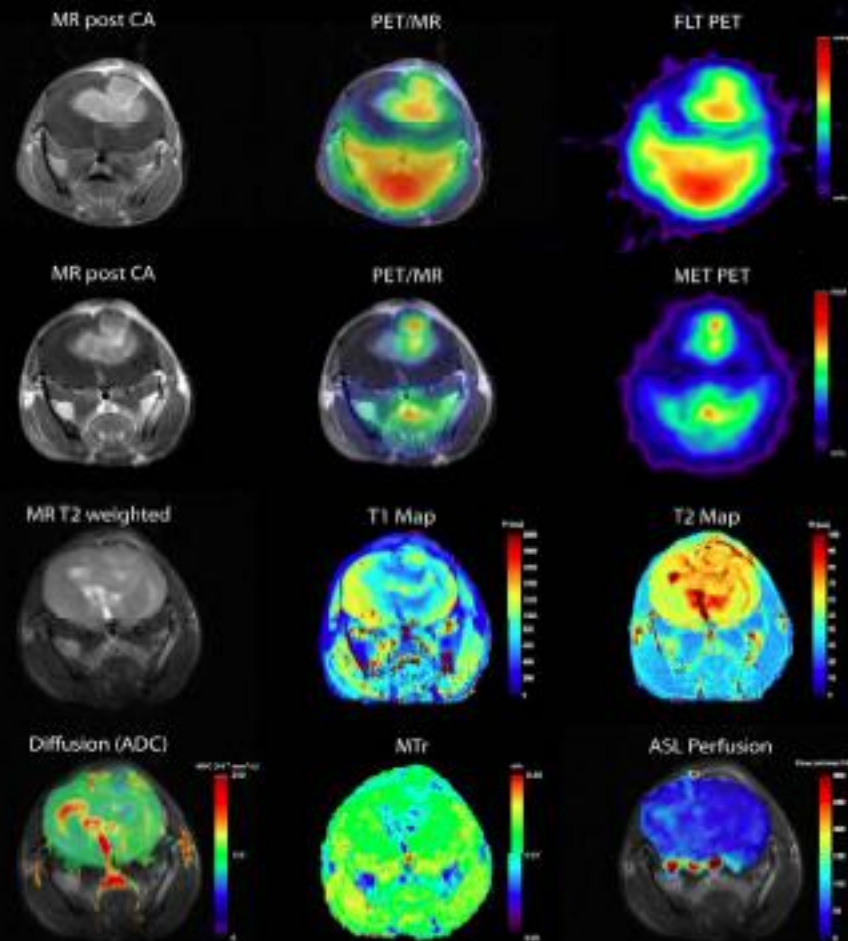
Treated "IT101" Camptothecin /  $\beta$ -cyclodextrin nanoparticle Prof. Mark Davis Caltech



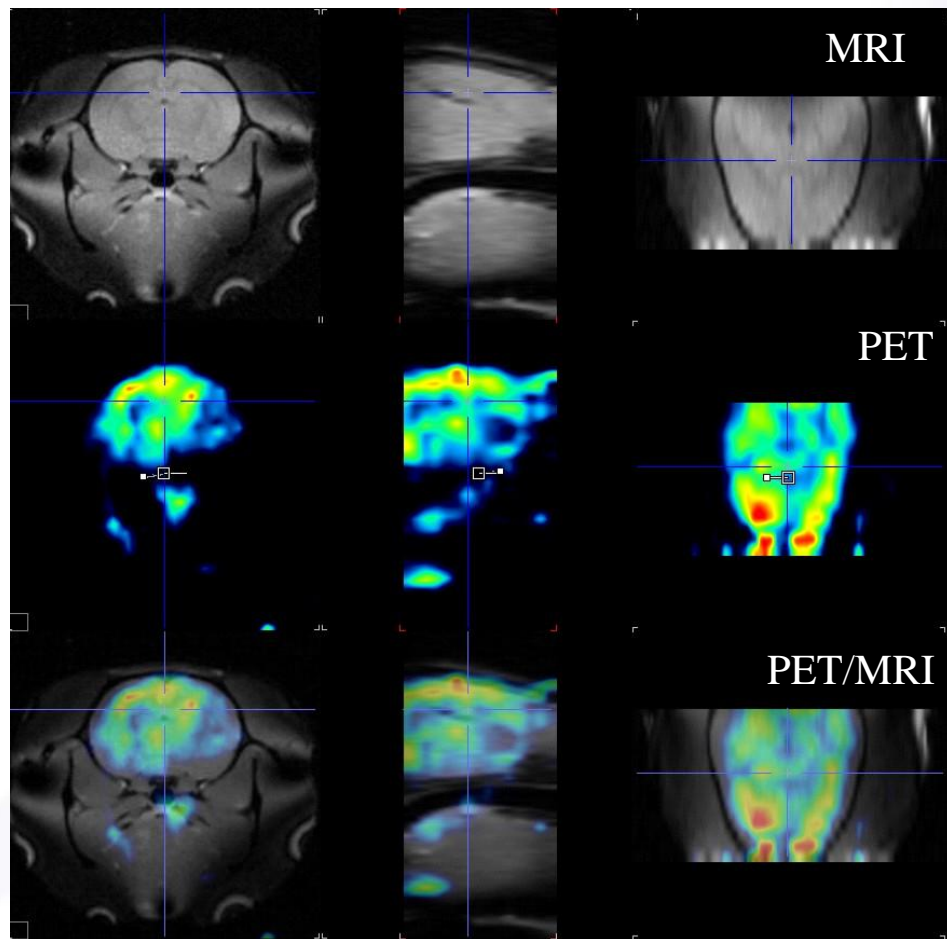
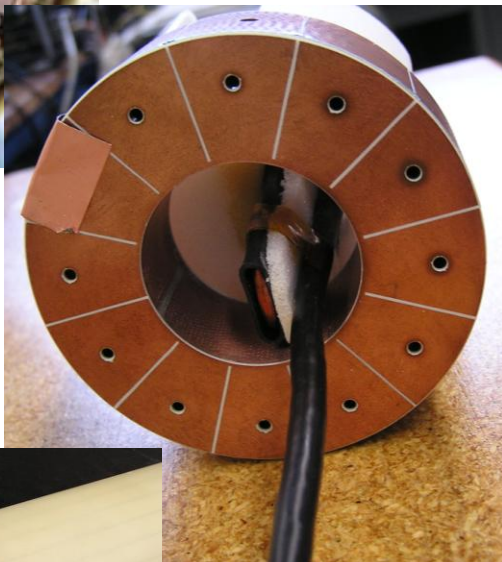
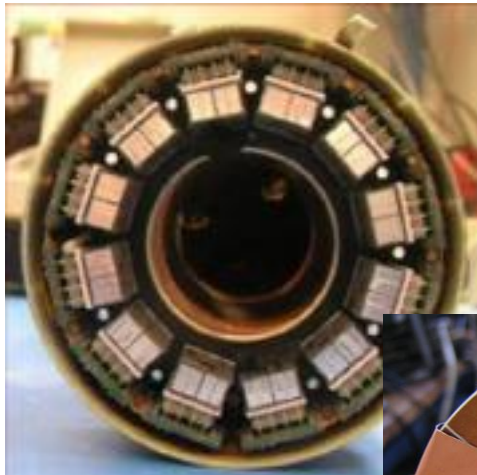
# APD-Based PET/MRI



Mouse glioma model imaged with  $^{18}\text{F}$ -FLT,  $^{11}\text{C}$ -methionine and various MR sequences

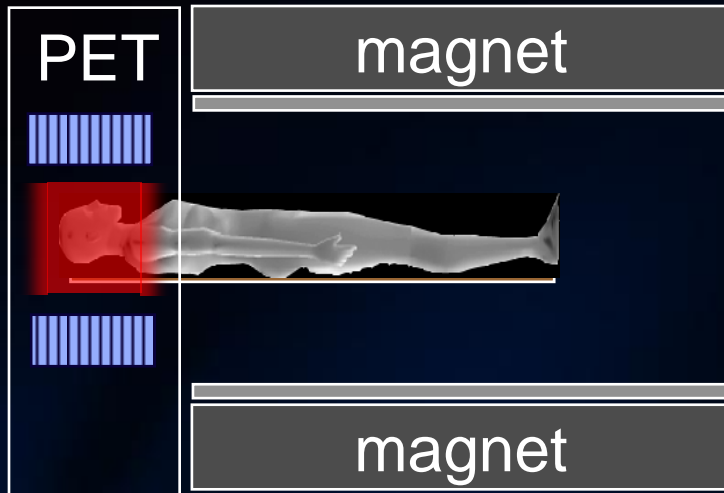


# APD-Based PET/MRI



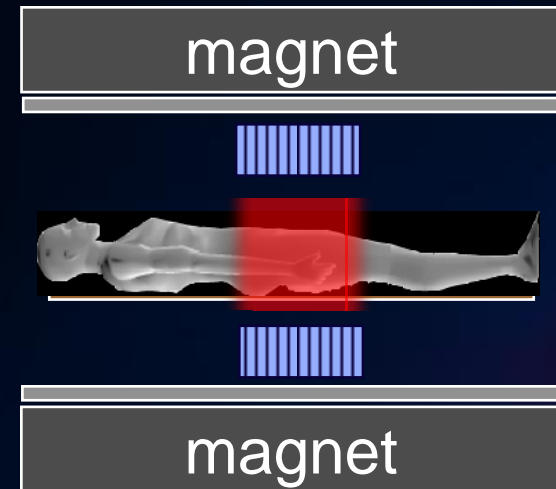
# Approaches to PET/MRI

## “tandem” PET/MRI



- + interference easier to avoid
- + largely use existing hardware
- + least expensive

## “integrated” PET/MRI



- + simultaneous PET/MRI possible
- + higher throughput/easier scheduling
- + best image registration

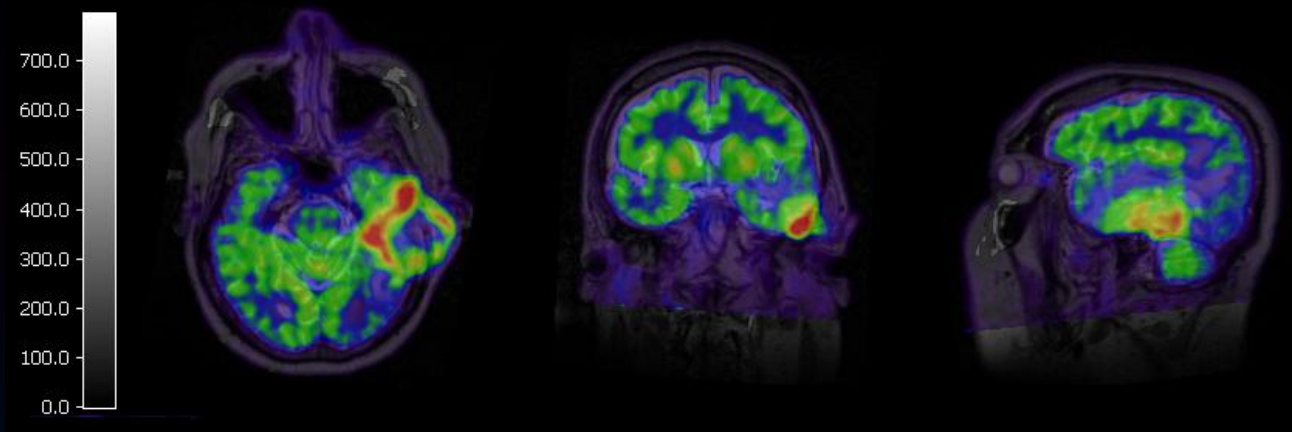
# Sequential PET/MRI



# Industrial Revolution



# Human Brain PET/MR

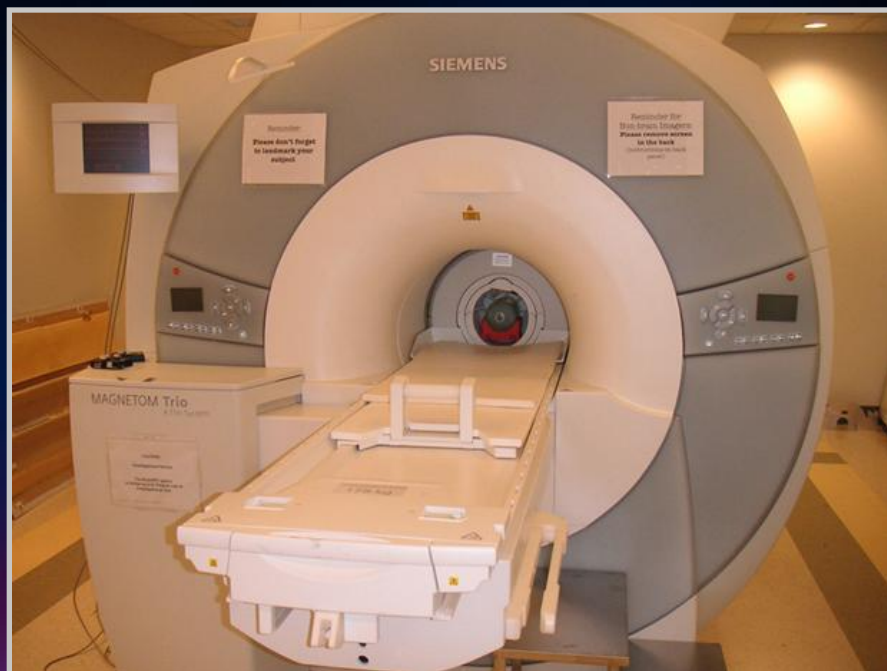


## PET

- 5.45 mCi FDG injected approx. 2.5 hours prior to acquisition
- OSEM 3D reconstruction
- Attenuation correction performed based on MR data

## MR

- T1 MP-RAGE, T2 SPACE (shown), FLAIR, DTI, CSI, SVS sequences run simultaneously
- CP coil

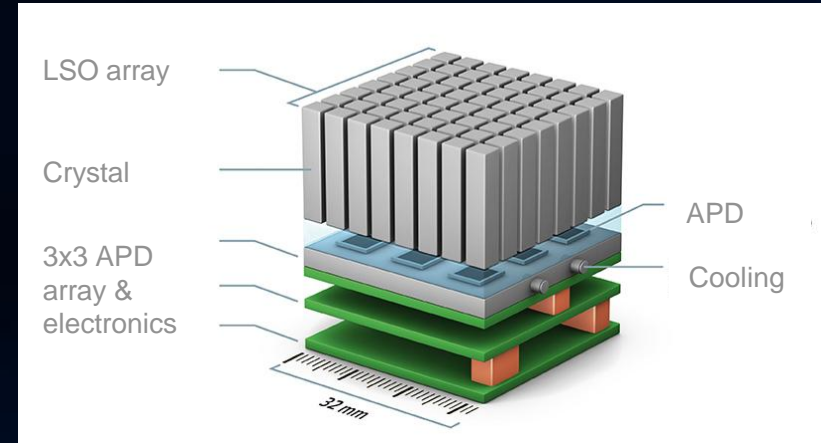


# Clinical PET/MRI

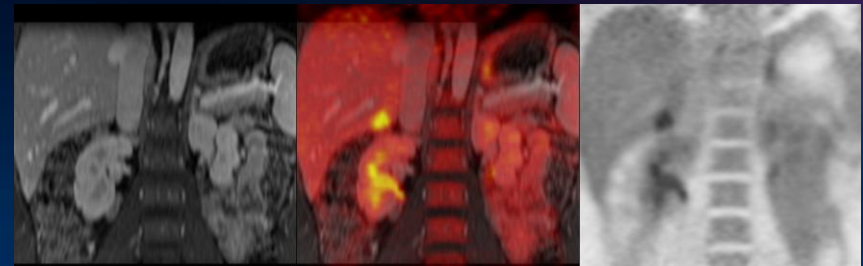
mMR, clinical whole body PET/MRI system at 3 Tesla



*Courtesy of Siemens*

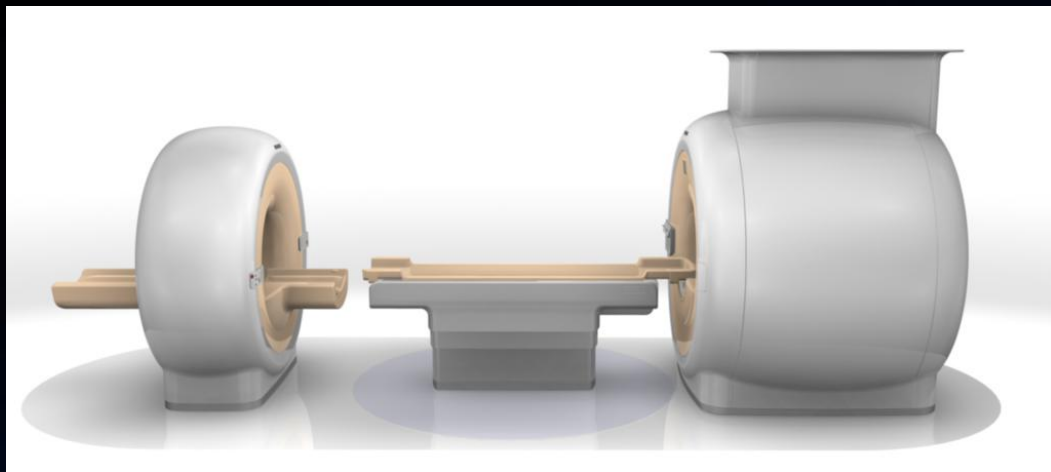


- APD based LSO Block detector ( $4 \times 4 \text{mm}^2$ )
- Fully integrated with MRI system
- Shared cooling system

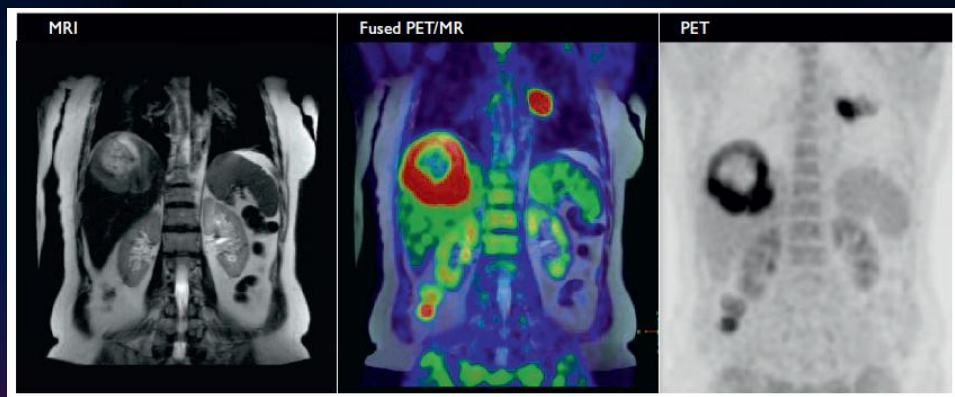


Courtesy of Henrik Michaely & Alex Guimaraes, MGH

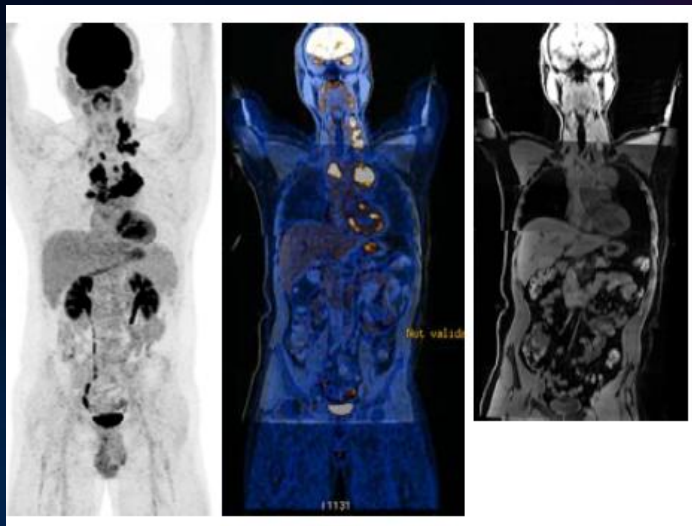
# Whole-Body PET/MR (Sequential)



Philips Gemini TF (PET) and Achieva 3T (MRI)

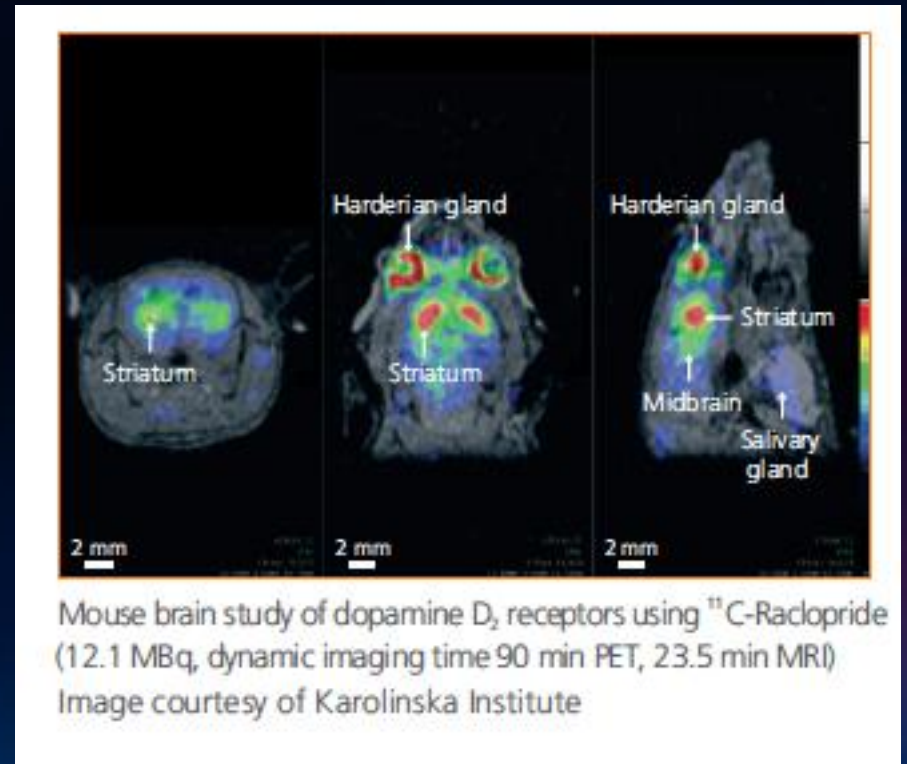


Courtesy Philips and University Hospital of Geneva



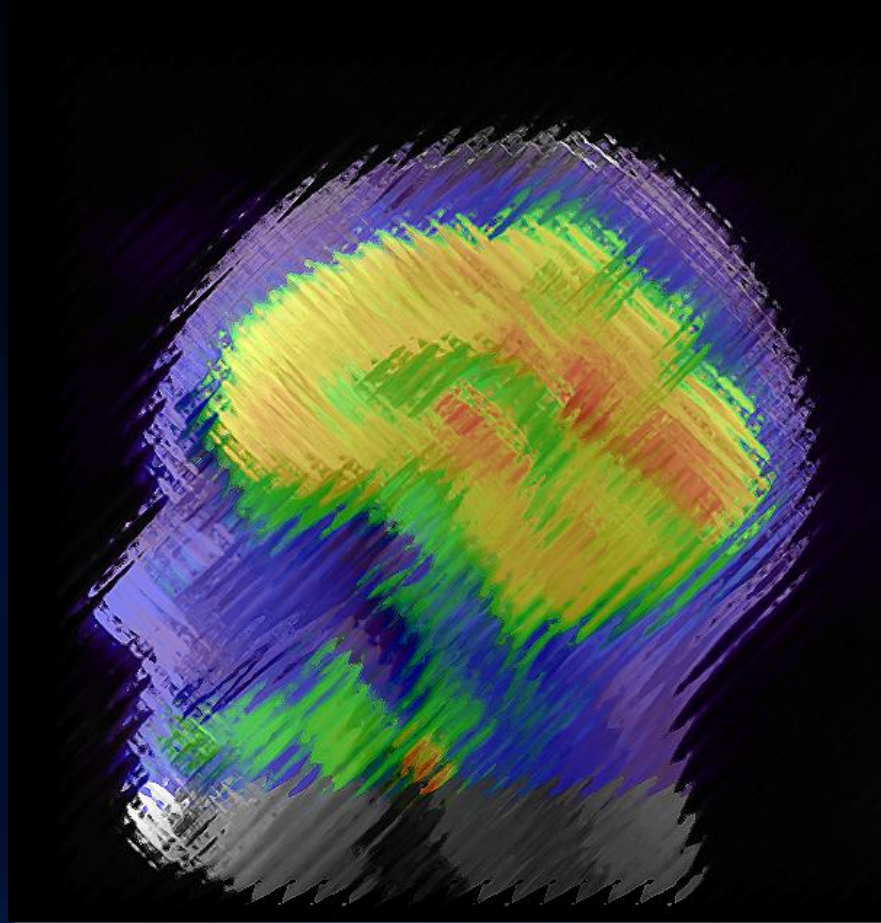
Courtesy GE Healthcare and Gustav von Schultess, University Hospital Zurich

# Preclinical PET/MRI (Sequential)

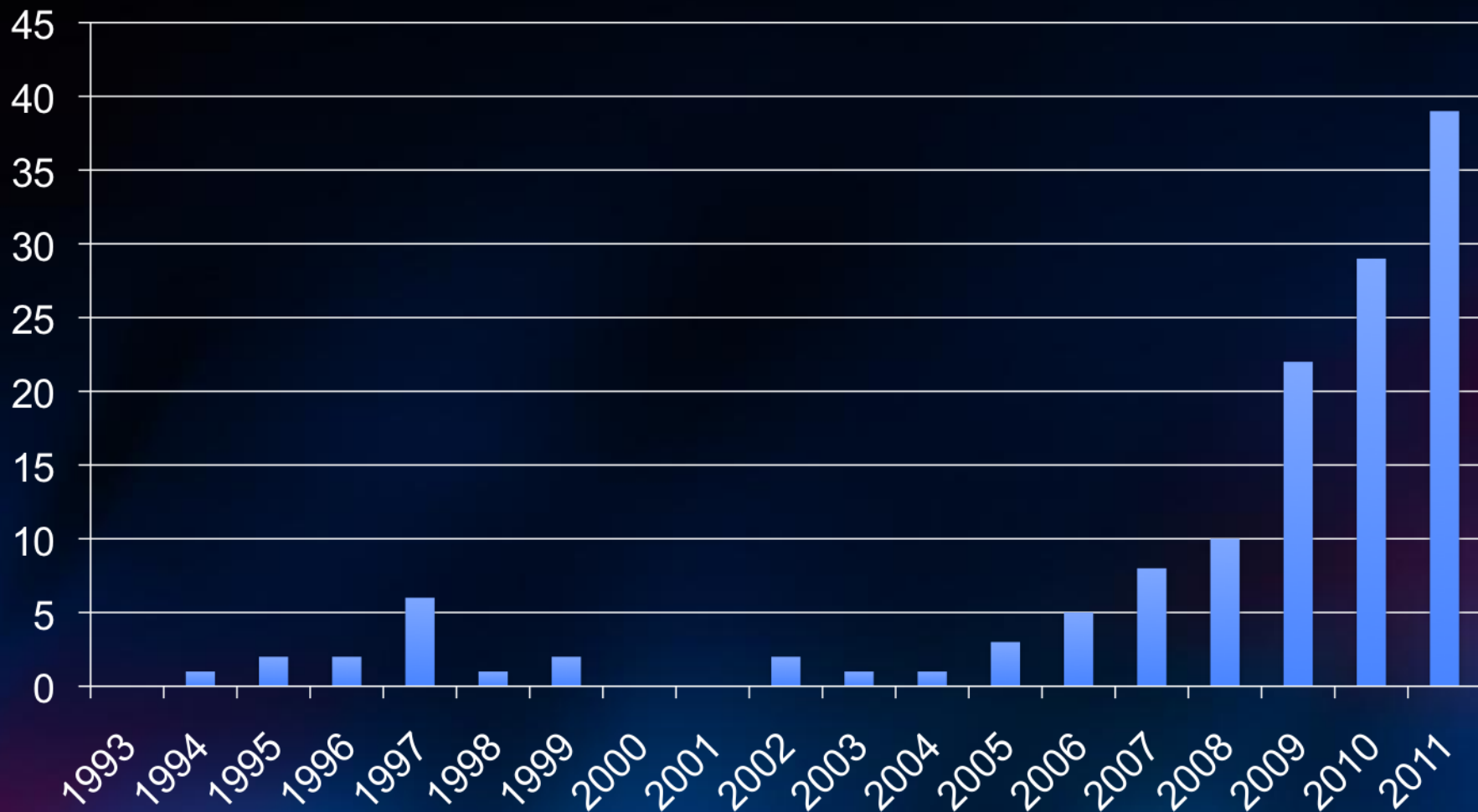


Mouse brain study of dopamine D<sub>2</sub> receptors using <sup>11</sup>C-Raclopride (12.1 MBq, dynamic imaging time 90 min PET, 23.5 min MRI)  
Image courtesy of Karolinska Institute

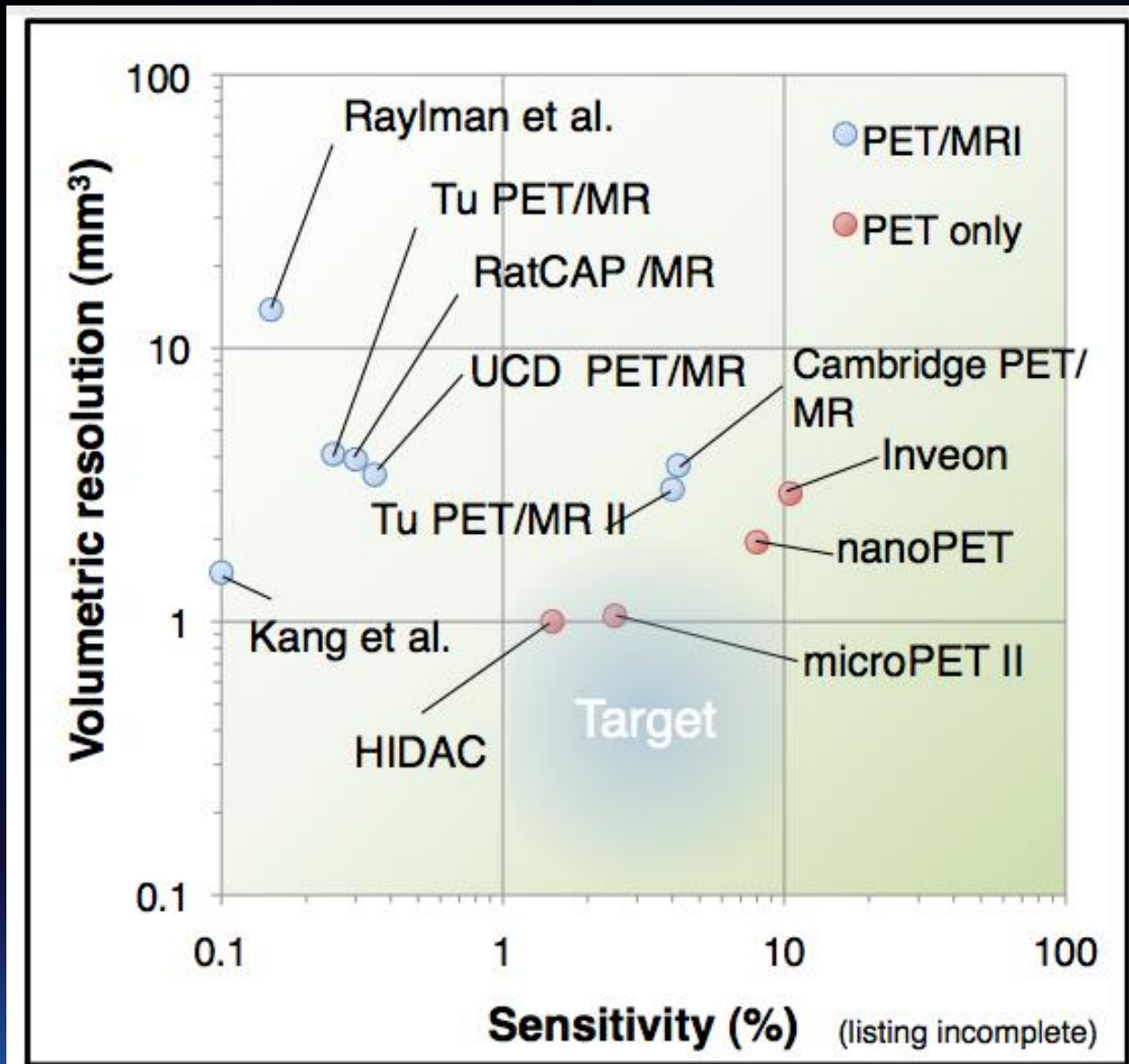
# The Modern Era



# PET/MR Publications versus Year

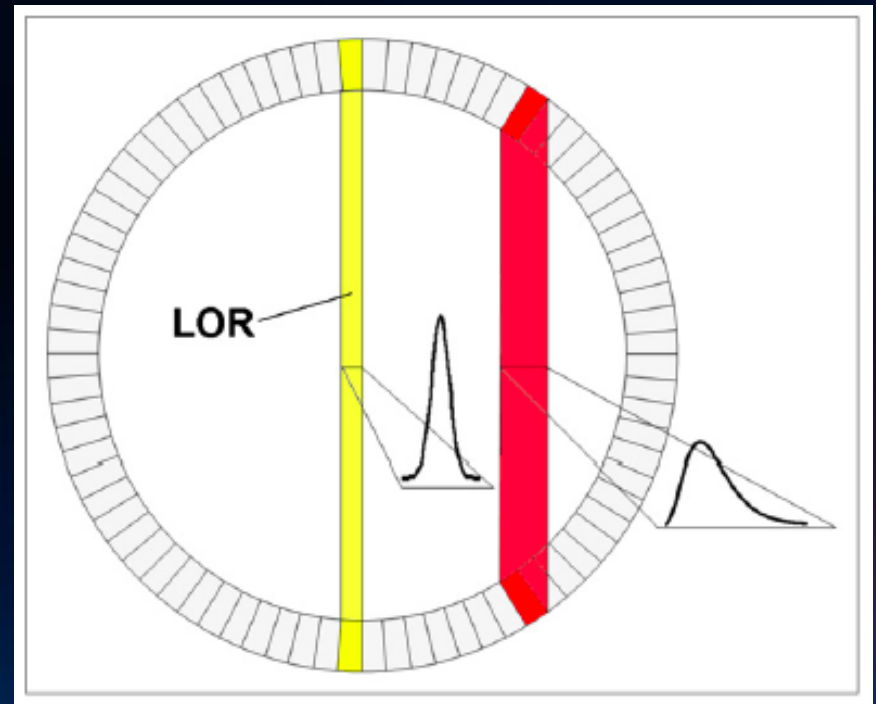


# Preclinical PET/MRI Systems so far...



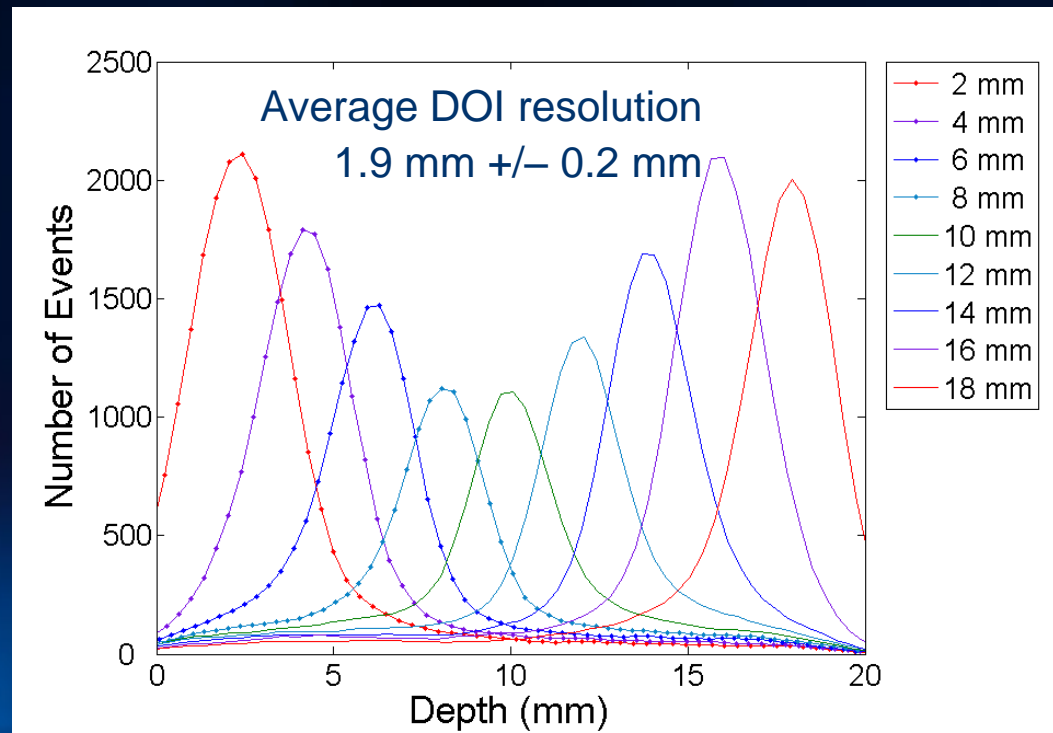
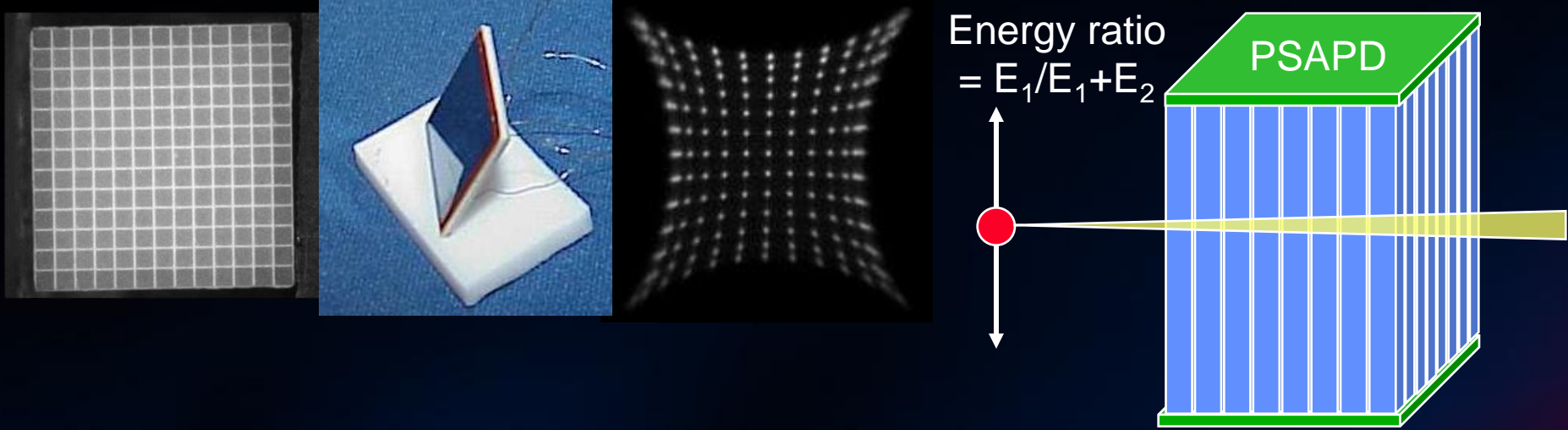
# Depth of Interaction Problem

- High sensitivity requires thick detector crystals
- Thick detector crystals leads to a loss in spatial resolution with increasing severity for
  - increasing radial location from center of scanner
  - small diameter scanners (such as found in PET/MR)



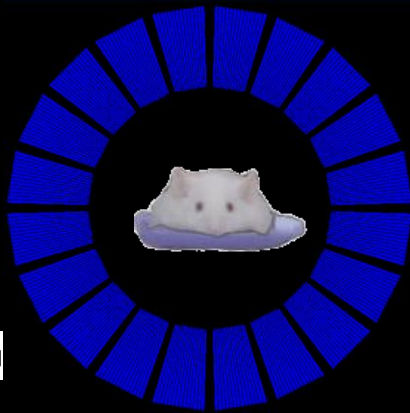
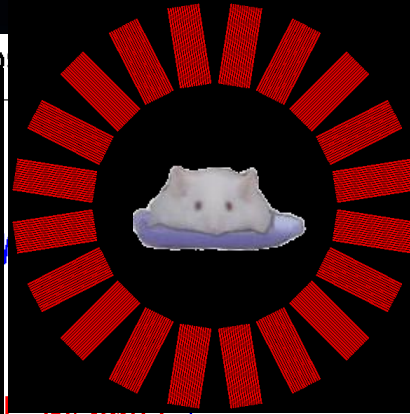
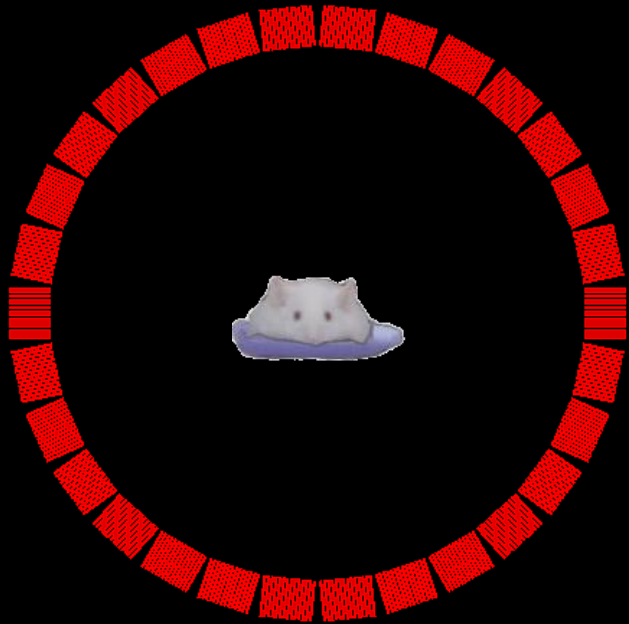
*courtesy Bernd Pichler*

# High Resolution Depth Encoding Detectors

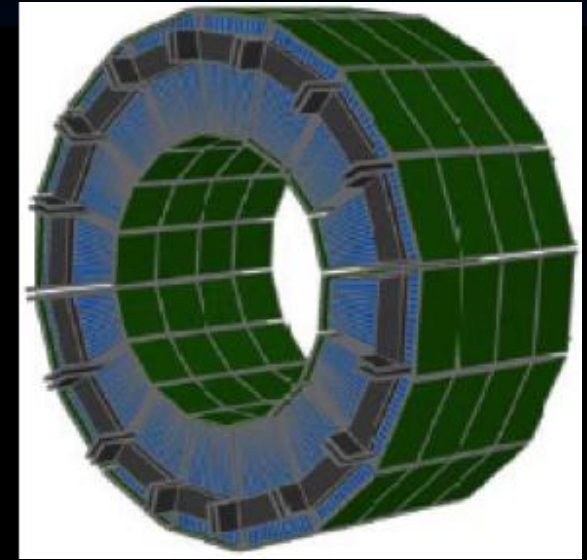


# New Small Animal PET/MR Design

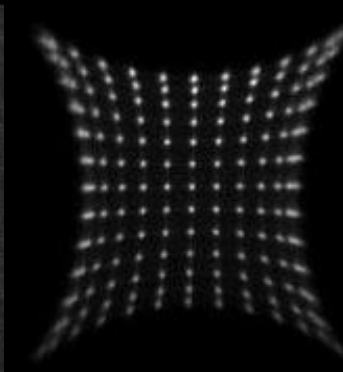
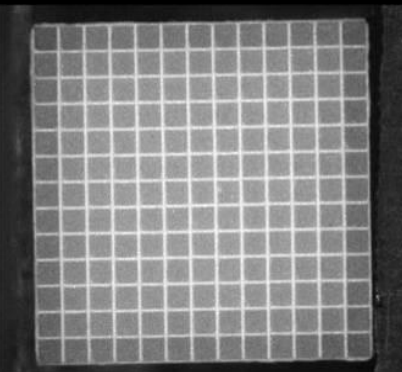
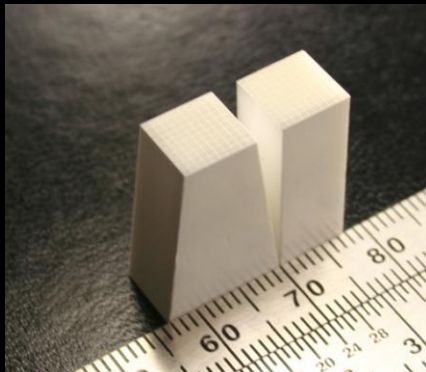
Sensitivity Across



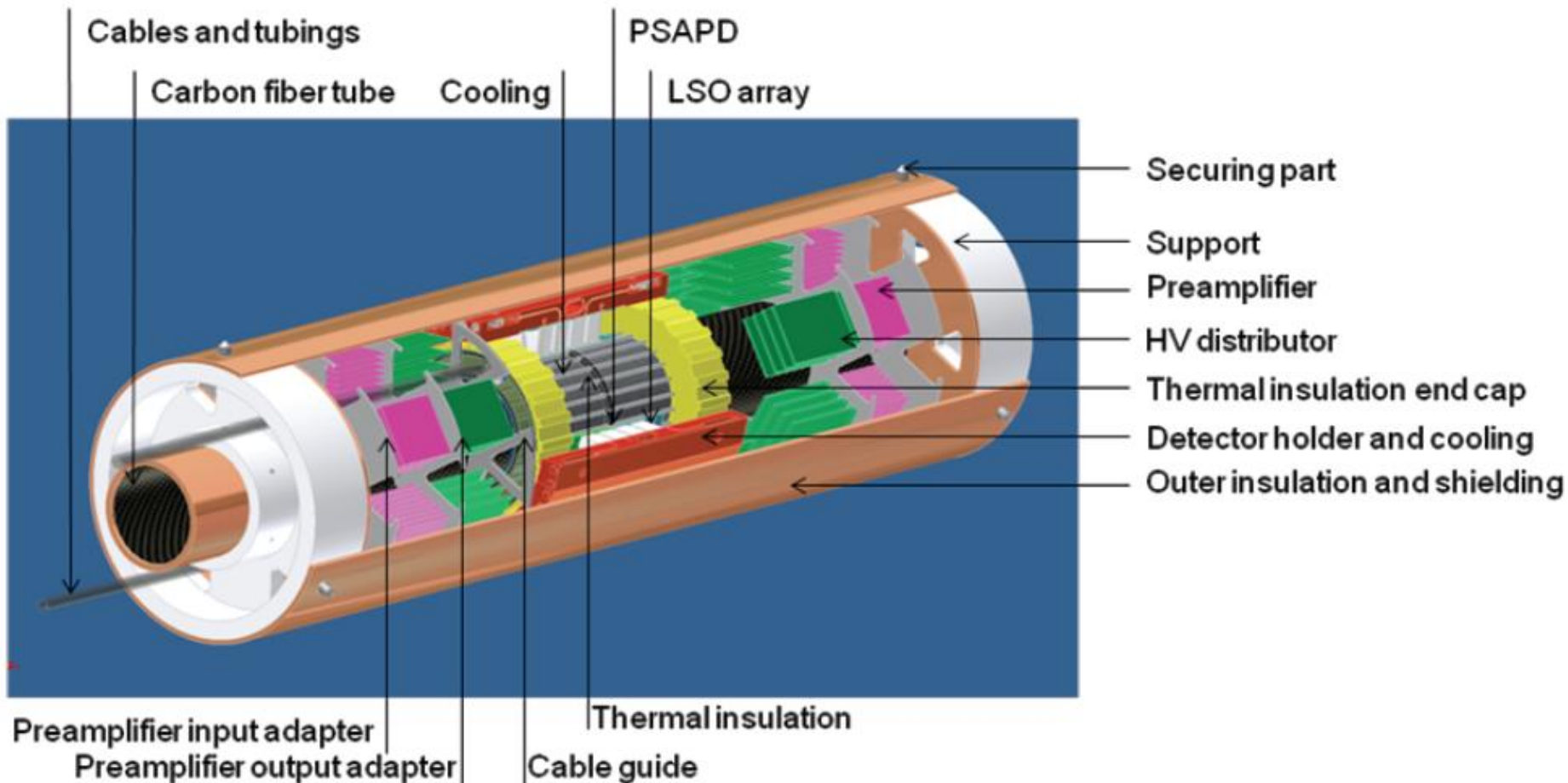
X Position



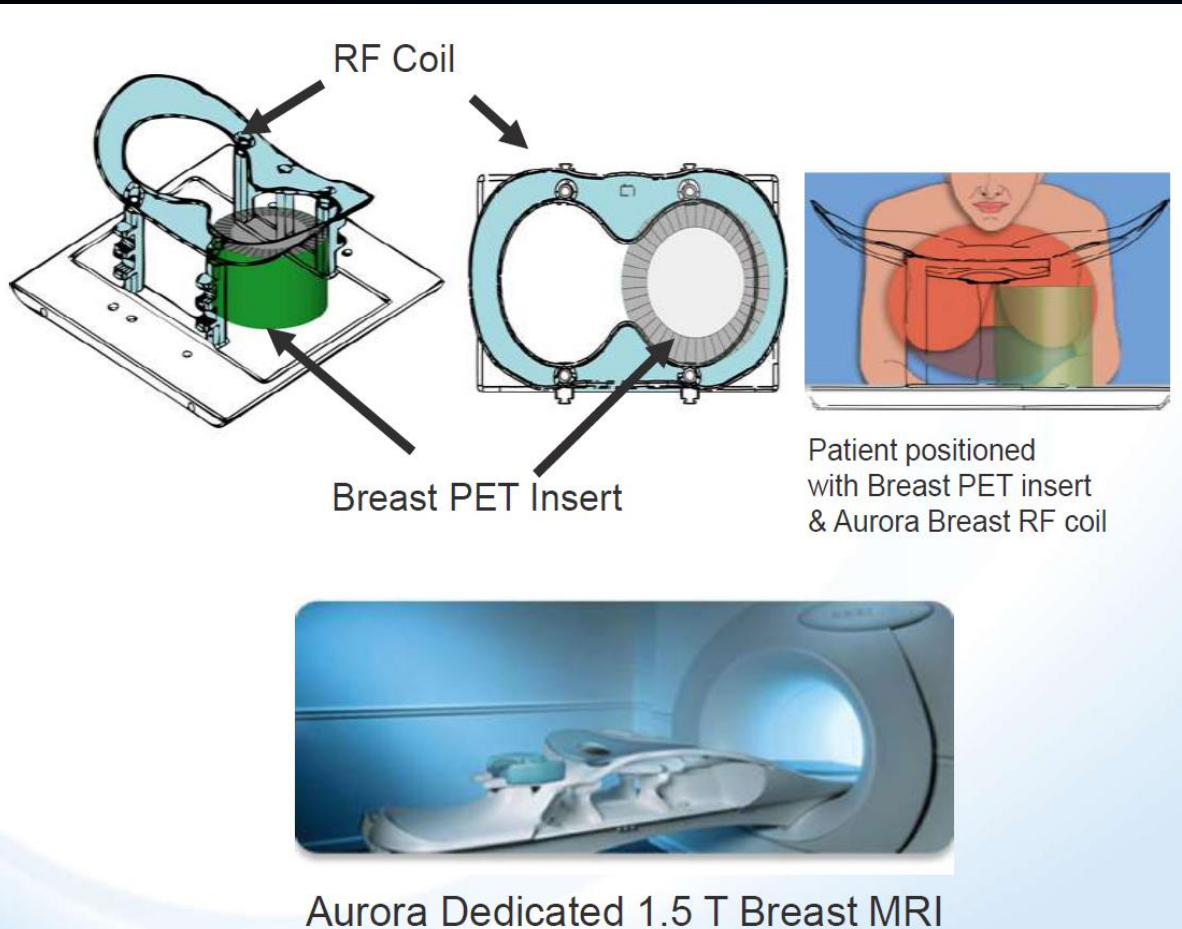
Detector modules: 64  
PSAPDs: 128  
Channels: 512  
Crystals: 10,816



# New PET Insert Design



# Dedicated Breast PET/MRI



- Dedicated system for breast PET/MRI
- Uses modified version of the "RatCAP" PET detector
- Based on APDs and LYSO crystals ( $2.2 \times 2.2 \times 15 \text{ mm}^3$ )
- Operates inside 1.5 T MRI

*Slide Courtesy: B. Ravindranath, D. Schlyer, Brookhaven National Laboratory*

# Brain PET/MR at 9.4T



0T



9.4T

Courtesy of Hans Herzog, Jülich

Brain Phantom: H. Iida et al., J. Nucl. Med. 50, Suppl. 2, 123P, 2009.

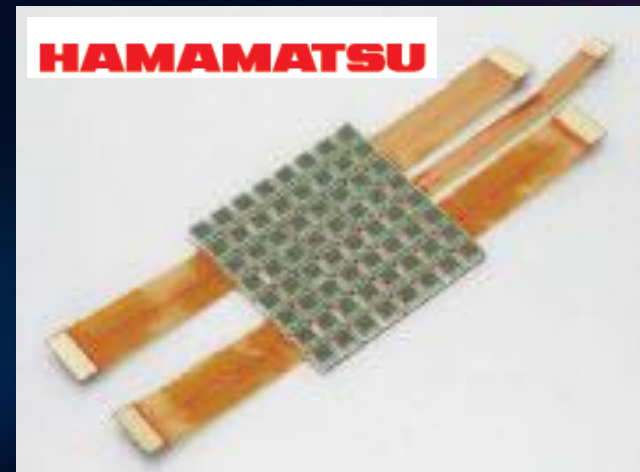
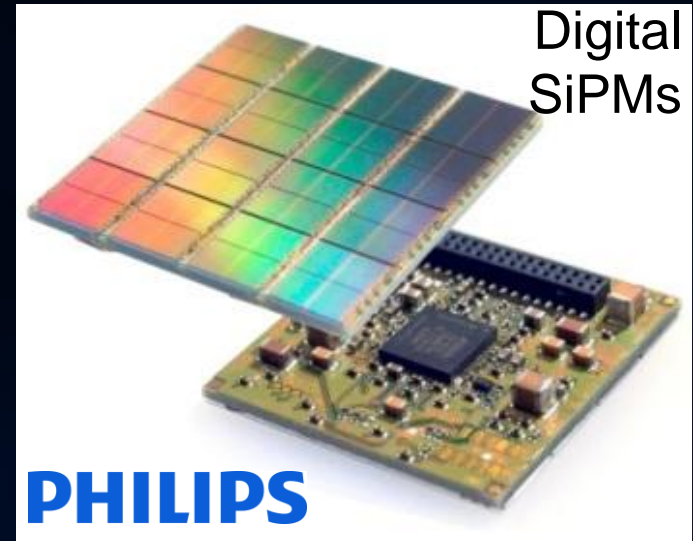
# Silicon Photomultipliers: the future for PET/MRI?

## Characteristics:

High gain, fast, compact, low bias voltage, magnetic field tolerant, scaleable

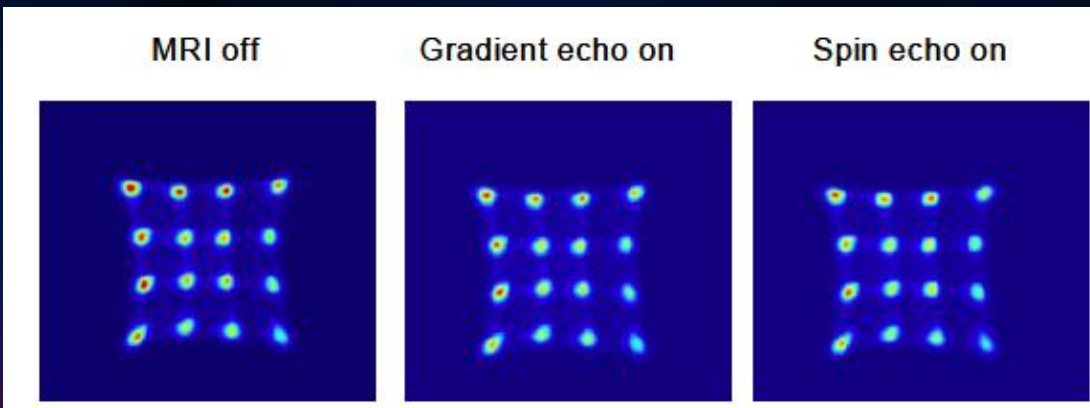
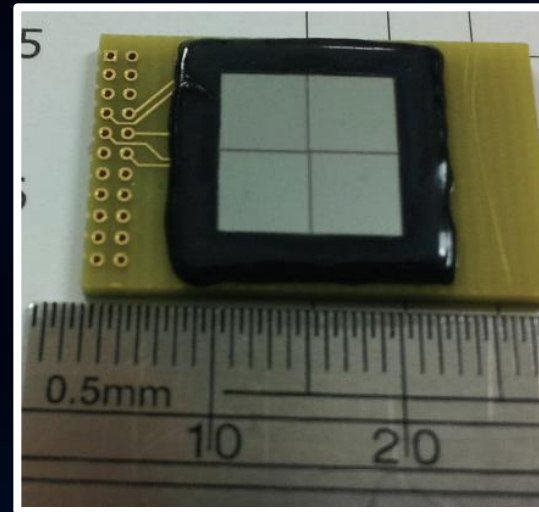
## Challenges:

Cost per cm<sup>2</sup>, dark rate, optical crosstalk, afterpulsing, recovery time,

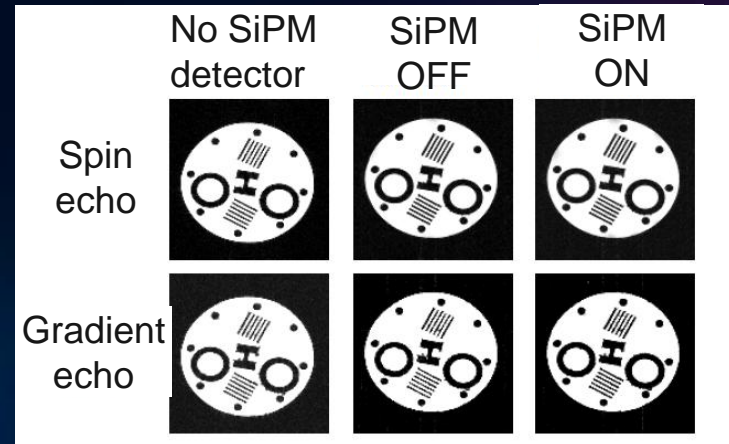


# Position-Sensitive SiPMs

- Continuously position-sensitive
- Up to 10 x 10 mm in size



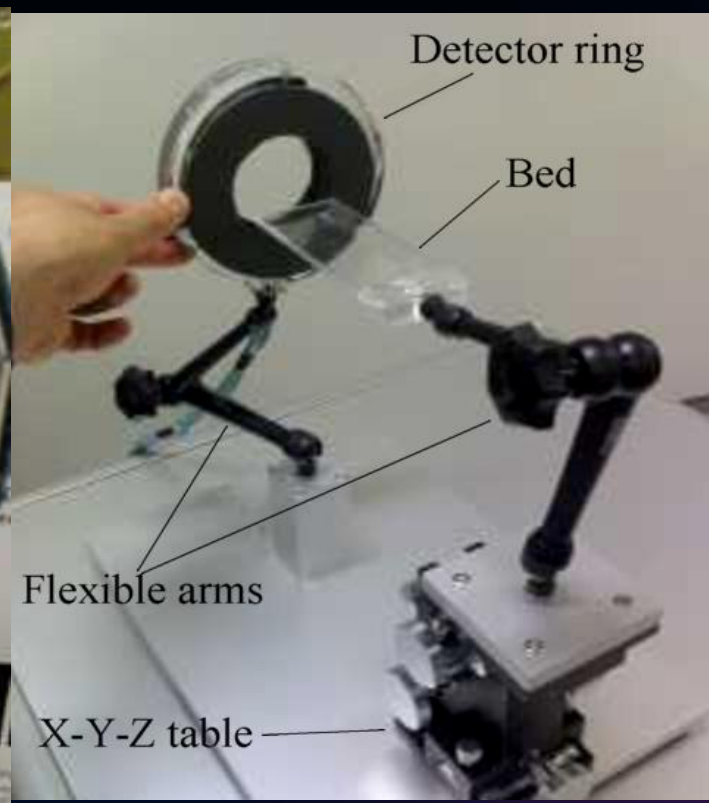
4 x 4 LSO array, 1.5 mm elements on position-sensitive SiPM



Courtesy of Purushottam Dokhale, RMD

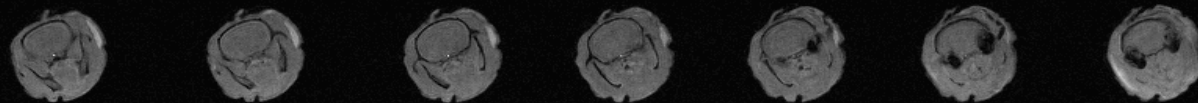
# SiPM-based PET/MRI

Courtesy of  
Seiichi Yamamoto  
Kobe, Japan

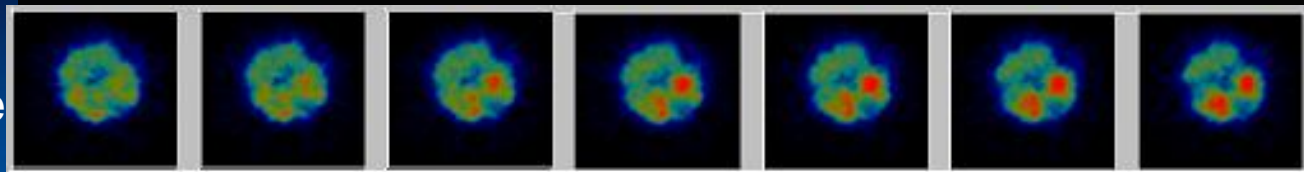


*Simultaneously measured Si-PM-PET and 0.15T MRI*

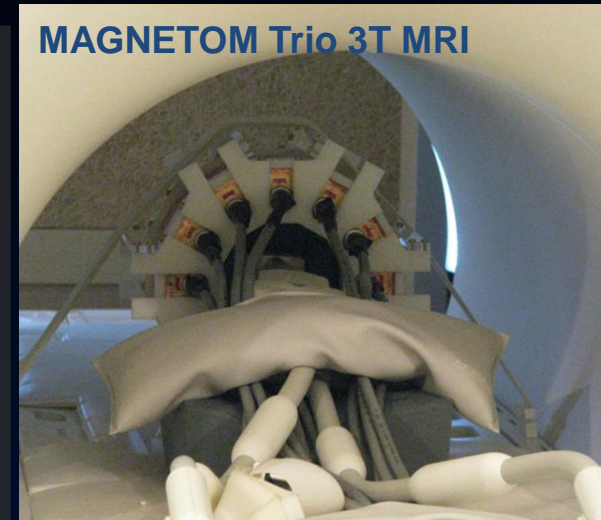
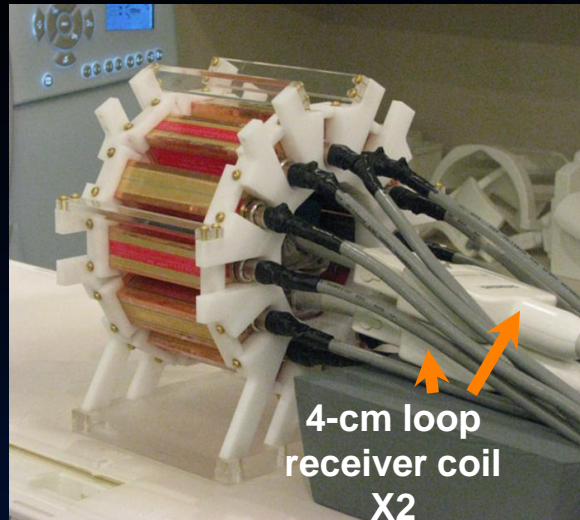
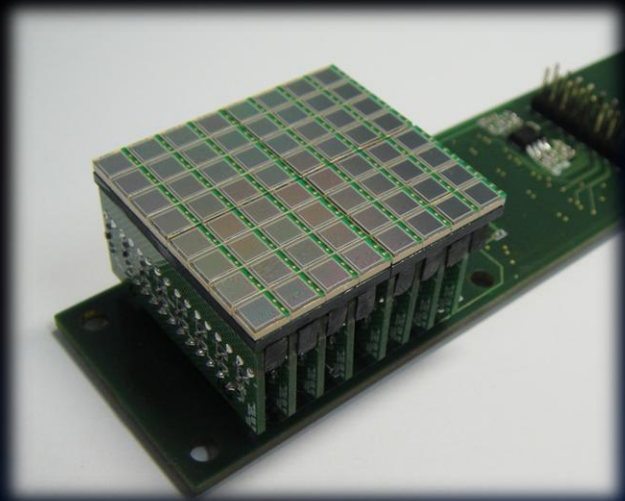
MR-images  
with PET



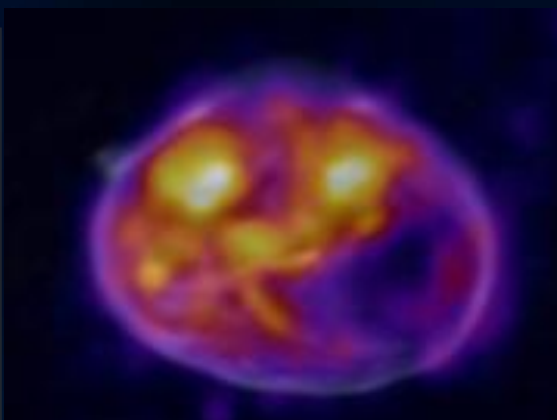
PET images  
(FDG) inside  
MRI w RF



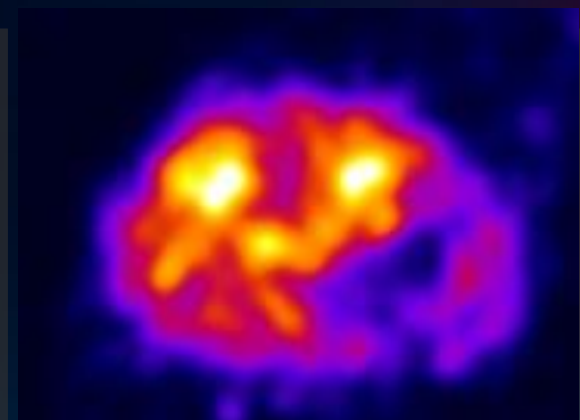
# SiPM-based PET/MR



**T2 MRI**



**Fusion**

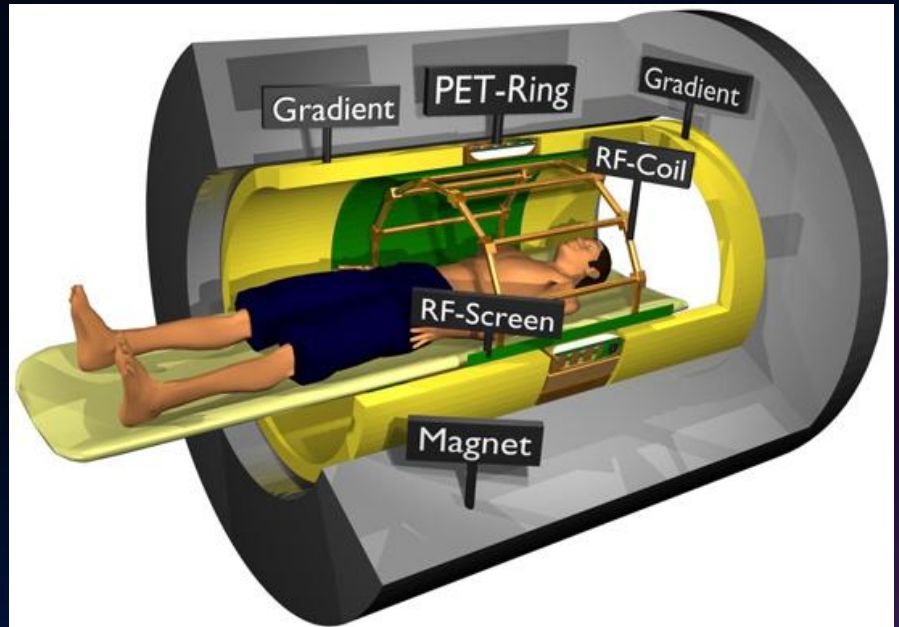
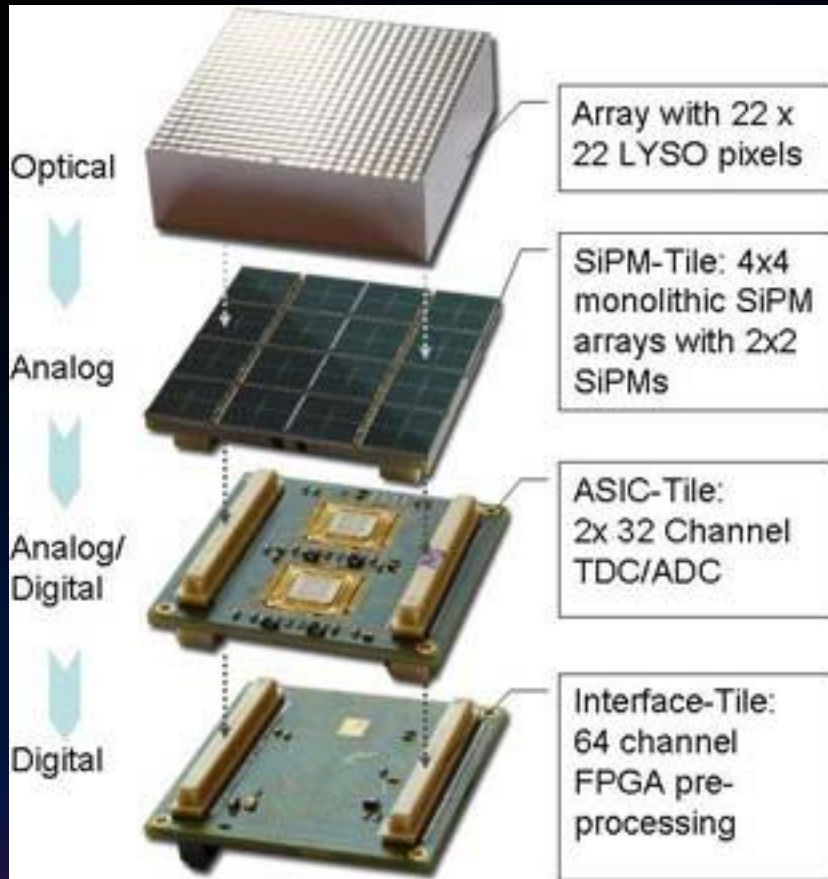


**SNU SiPM PET**

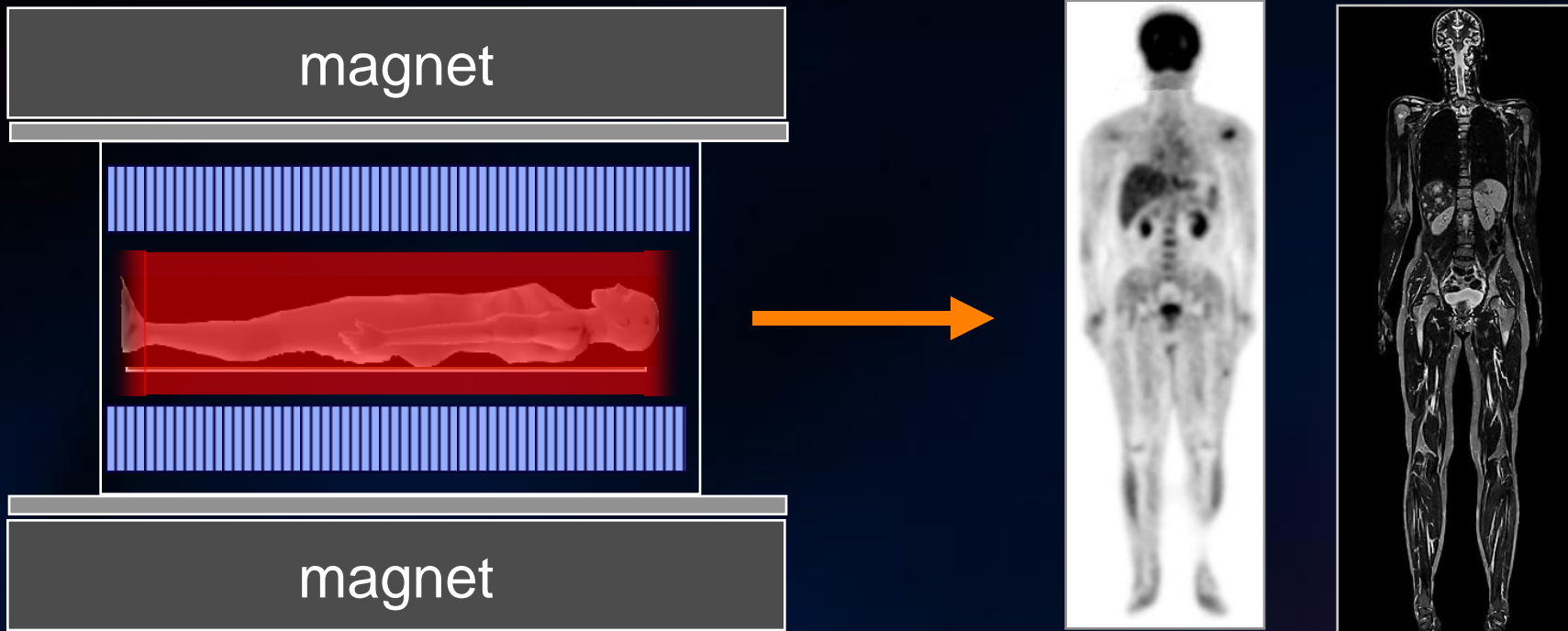


Courtesy of Jae Sung Lee,  
Seoul National University

# Human TOF PET/MRI based on SiPMs



# The Molecular Imaging Scanner of the Future?



- Very long axial FOV
- Time of flight
- x100-fold reduction in variance, x10 improvement in SNR
- Whole-body MRI

# PET/MRI

## endless possibilities

### MRI

#### Structural imaging

fMRI

DCE MRI

DTI

MR Spectroscopy

paraCEST

Hyperpolarized  $^{13}\text{C}$

...

### PET

#### Metabolic imaging

Blood flow

Receptor ligands

Hypoxia

Proliferation

Amyloid imaging

Cell trafficking

...

## PET/MRI

# Summary

- PET/MRI has a long history!
- PET/MRI systems have been successfully developed for small animal and human imaging
- PET/MRI is a powerful multimodality platform for biomedical research – commercial systems for preclinical and human imaging now available
- Although most current systems are based on APDs, SiPMs appear to offer many advantages for hybrid PET/MR systems
- To what extent simultaneous PET/MR is required for emerging clinical applications is being debated

# Acknowledgments

Our PET/MR research:

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Yibao Wu

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Bernd Pichler

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Daniel Procissi

Thomas Ng

Bo Peng

Kanai Shah

Jinyi Qi

Robert Silverman

Kun Di

Xiaowei Bai

Angelique Louie

Richard Farrell

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Seiichi Yamamoto

David Schlyer

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Adrian Carpenter

Hans Herzog

Blaine Chronik

Siemens

GE

Philips

Mediso