PET Imaging for Clinical and Preclinical Imaging

Robert S. Miyaoka, PhD
Department of Radiology
University of Washington

Disclosures

1) Research contract with Philips Healthcare
2) NIH Academic industrial partnership: Philips Healthcare (PI)
3) NIH Academic industrial partnership: GE Healthcare (co-inv)
4) NIH STTR: PETX LLC (sub contract: PI)

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Advanced PET Instrumentation Developments

1) Digital photon counting PET detectors
2) Time-of-flight PET/MRI scanners
3) Time-of-flight with depth of interaction PET detectors
4) Advance motion correction methods
5) Advance image reconstructions
6) Organ specific imaging systems (e.g., breast)
7) Operator friendly, desktop pre-clinical PET imaging systems

Advanced PET Instrumentation Developments

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5) ~~Advance image reconstructions~~
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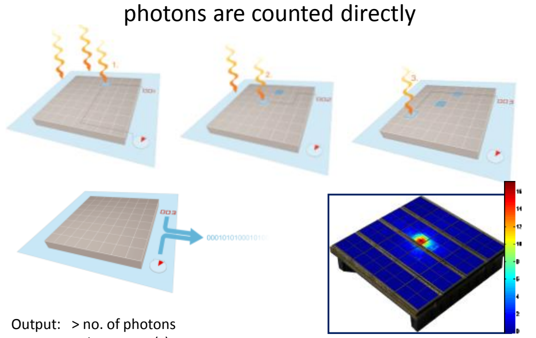
dSiPM – With Digital Photon Counting (DPC) photons are counted directly

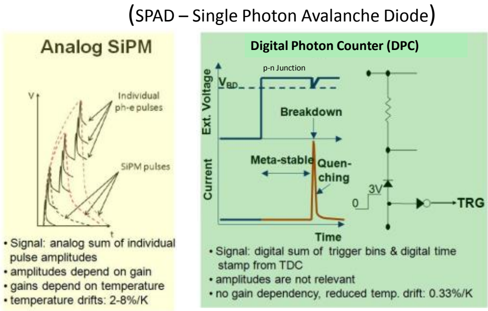


Output: > no. of photons
> time stamp(s)

No analog post-processing necessary!

PHILIPS

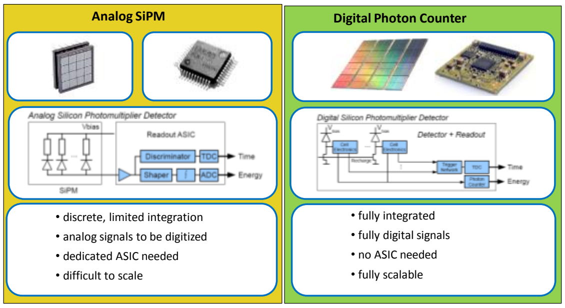
dSiPM - DPC uses intrinsic binary nature of SPADs (SPAD – Single Photon Avalanche Diode)



"Therefore, while the APD is a linear amplifier for the input optical signal with limited gain, the SPAD is a trigger device so the gain concept is meaningless." *(source: Wikipedia)*

PHILIPS

Digital Photon Counter is an integrated, scalable solution



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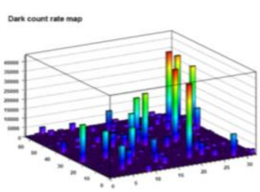
DPC: dark count management by digitization



- Silicon based light sensors have background noise (dark counts), varying with temperature.
- In digital SiPMs every cell can be addressed individually.
- Cells with high dark counts can be switched off.
- A few cells switched off (1-5%) reduces dark count levels by orders of magnitude.

PHILIPS

Performance comparison: Analog versus Digital PET

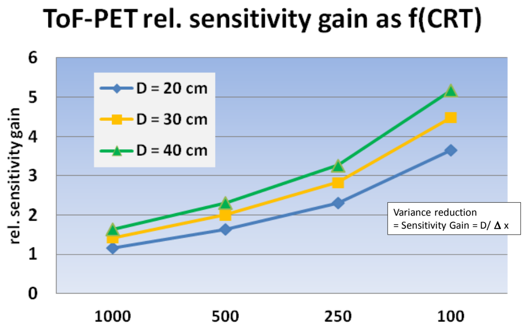
	Analog*	Digital**
Coincidence timging (psec)	591	307
Image resolution (FWHM, mm)	4.7	4.0
Energy resolution (@511 keV)	13.0%	11.2%

* Philips Gemini Time-of-flight PET; ** Philips Vereos digital PET/CT

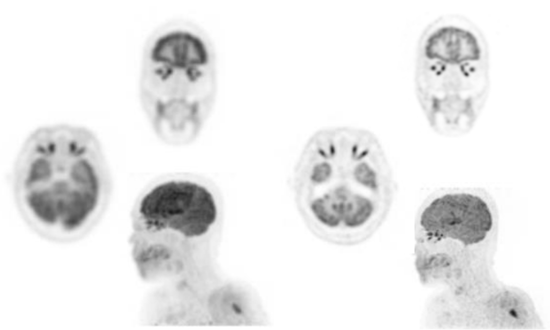
Miller M, et al. 2014 SNMMI, St Louis, Mo

PHILIPS

Motivation PET: clinically useful sens. gain

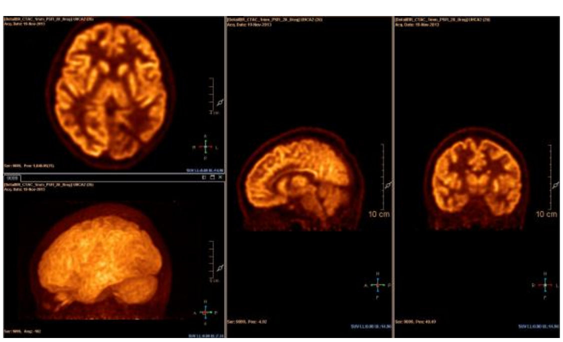


*Data calculated after: J.S. Karp et.al. JNM, **49/3**, 462-470, 2008*



Analog (TOF) Digital (TOF)

Images courtesy of University Hospital Cleveland



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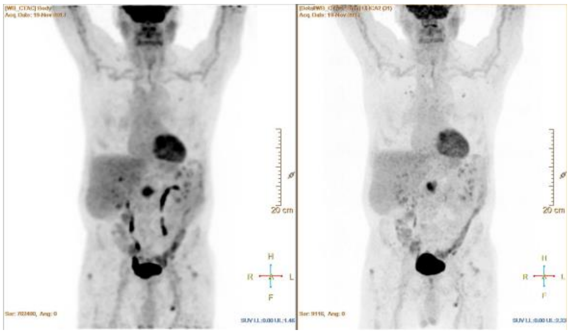


Analog (TOF) Digital (TOF)

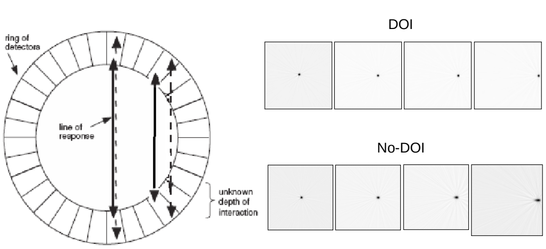
Images courtesy of University Hospital Cleveland

Why add depth of interaction?

1) Depth of interaction reduces positioning paralax errors
2) PET/MRI smaller detector ring diameters
3) Smaller detector ring diameters to reduce cost of systems
4) Future generation, long axial field of view systems

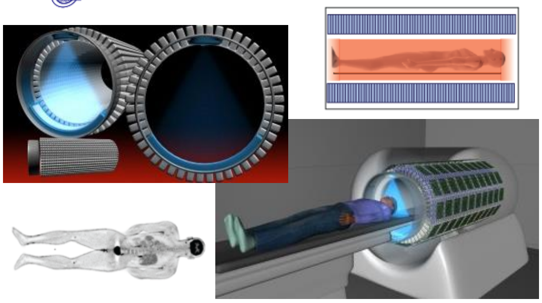
Parallax Error

- Depth-of-interaction (DOI)



Smaller detector ring diameter and longer axial FOV accentuate spatial resolution blurring from parallax errors.

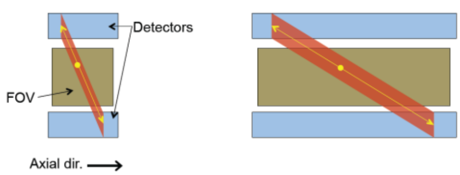
Explorer



Explorer

- Combining time-of-flight (TOF) and depth-of-interaction (DOI) especially important for long axial field-of-view PET scanners.
- Long LORs have axial DOI blurring
- High attenuation introduces need for TOF

Typical PET scanner **Long axial FOV PET**



Explorer

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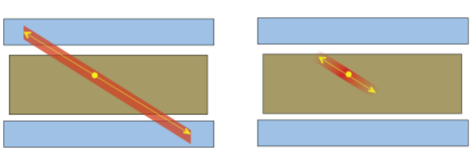
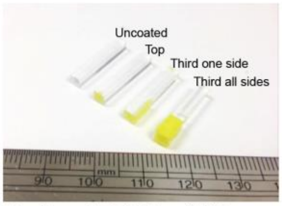
Long axial FOV PET **Long axial FOV PET**



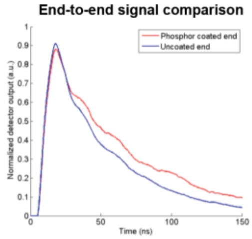
DOI TOF and DOI

Explorer
(depth of interaction)



Phosphor coated 3x3x20 mm³ LYSO crystals

Phosphor (YAG:Ce) coated



Decay time of collected light varies with depth

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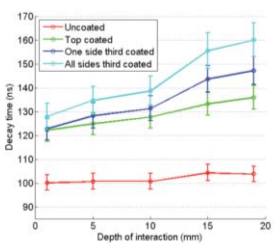
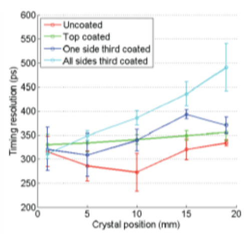
Explorer
(DOI, TOF)

DOI Resolution (mm)

	PMT	SiPM
Top coated	12.3	14.5
One side third coated	7.5	9.1
All sides third coated	6.6	8.2





Head-on Coincidence Timing Resolution (ps)

	Before correction	After correction
Uncoated	373 +/- 24	373 +/- 24
Top coated	391 +/- 15	388 +/- 11
One side third coated	433 +/- 25	394 +/- 29
All sides third coated	592 +/- 26	448 +/- 39

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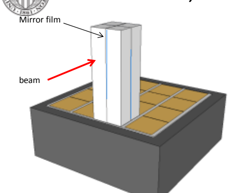
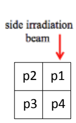
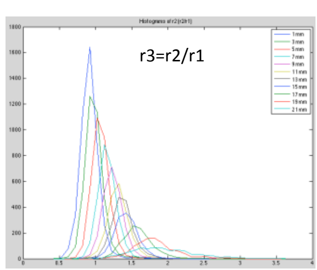
TOF, DOI PET Detector

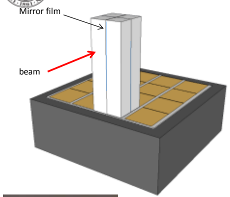


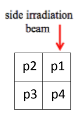


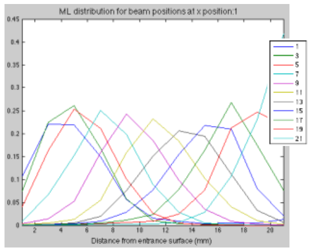


Events in pix 1
r1=p1/p2
r2=p1/p4
r3=r2/r1

TOF, DOI PET Detector







Effective FWHM: ~6 mm

Coincidence timing resolution: ~370 psec

PET Imaging of Breast Cancer

Avril, et al. *JCO* 2000

"Partial volume effects and varying metabolic activity (dependent on tumor type) seem to represent the most significant limitations for the routine diagnostic application of PET. The number of invasive procedures is therefore unlikely to be significantly reduced by PET imaging in patients presenting with abnormal mammography.

However, the high positive-predictive value, resulting from the increased metabolic activity of malignant t... ent of disease or to assess therapy response."

Eubank & Mankoff, *Sem Nucl Med* 2003

18... staging, and response monitoring in breast cancer patients. Although studies have proven its accuracy in detection of the primary tumor and axillary staging, its most important current clinical application is in detection and defining the ext... tary to conventional methods of staging in that it provides better sensitivity in detecting nodal and lytic bone metastases; however, it should not be considered a substitute for conventional staging studies, including computed tomography and bone scintigraphy. FDG uptake in the primary tumor carries prognostic information, but the underly... elucidated. Future work using other PET tracers besides FDG will undoubtedly help our understanding of tumor biology and help tailor therapy to individual patient by improving our ability to quantify the therapeutic target, identify drug resistance factors, and measure and predict early response.

Whole-body PET

- spatial resolution is not sufficient for imaging early-stage breast cancer
- potential for detection of recurrence
- potential for selection/monitoring therapy

restricted to relatively advanced disease

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The Problem: Variable Responses

- Despite several biomarker targets (e.g., tumor phenotype, receptor status) used to characterize the cancer and help determine treatment, **cancer therapy efficacy is highly variable**
- As of 2007, there were 30 approved breast cancer therapies, the most of any cancer
- There are limited means for early evaluation of the success of therapy
  ➔ typically takes months after surgery to measure response with imaging

  Consequences in cases of ineffective therapies:
  - delays effective treatment; earlier treatment is known to improve outcomes
  - patients suffer side-effects associated with the ineffective therapy without benefits
  - treatments are very costly

Over 200,000 women in the United States are diagnosed each year with breast cancer (~40,000 mortalities/yr)

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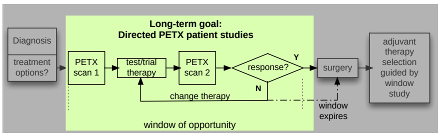
PET/X Proposed Clinical Paradigm

After diagnosis, use PET tracer uptake as therapy assessment biomarker



Duration of 'window of opportunity' will be case/patient dependent
(e.g. see Gebhart et al., *JNM* 2013)

Related ongoing research at UW

- "**Early Assessment of Response** to Aromatase Inhibitor (AI) Therapy", Linden, et al., *ASCO* 2009
- "Fluoroestradiol (FES) Positron Emission Tomography **(PET) Reveals Differences In Pharmacodynamics Of Aromatase Inhibitors**, Tamoxifen, And Fulvestrant In Patients With Metastatic Breast Cancer", Linden et al., *Clin Cancer Res* 17(14):4799-4805, 2011
- "Quantitative Fluoroestradiol Positron Emission Tomography **Imaging Predicts Response to Endocrine Treatment** in Breast Cancer", Linden et al., *JCO* 24(18):2793-2799, 2006

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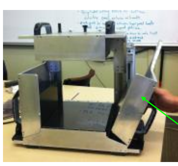
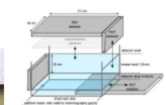
Prototype PET/X Mounting Stage

Modular 4-sided detector assembly





attachable biopsy-guidance system

Prototype PET detector mounting system; GE Essential Senographe

partially assembled on Essential Senographe

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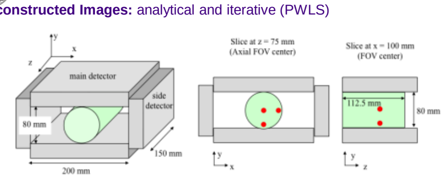
Design Optimization via Simulations

Reconstructed Images: analytical and iterative (PWLS)

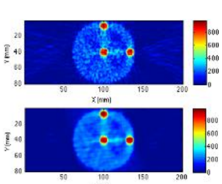


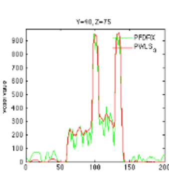
Recovery Coefficients (ROImax):
10 mm sphere diameters
Idealized condition: 40mm crystals; perfect LOR, no detector blur modeled

Reconstruction

Sph.#	Analytical
1 (3 o'clock)	1.064
2 (center)	1.103
3 (12 o'clock)	1.080

Sph.#	Iterative
1 (3 o'clock)	0.913
2 (center)	0.889
3 (12 o'clock)	0.925





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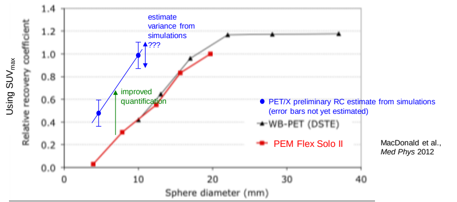
PET/X Performance Goals

Target: measure 20% change (95% CI) in SUV, for 5 mm lesion with SUV = 5



MacDonald et al., *Med Phys* 2012

WB-PET
- Full quantitative data corrections are applied
- RC limited by spatial resolution (partial volume effect)

PEM
- Improved spatial resolution ('in-plane')
  - limited-angle tomosynthesis
- Quantitative data corrections *not* applied
  - attenuated photons
  - scattered photons
  - random coincidences
  - dead-time count-loss

PET/X
Under development
- target FWHM resolution < 2 mm
- quantitative accuracy goals given above

macdon@uw.edu

Summary: PET/X

Quantitative Breast PET as a Cancer Biomarker

- Many targeted breast cancer therapies exist
  - efficacy is variable
  - cost is high
- Primary tumor is resected; recurrence or lack thereof determines therapy efficacy
  - failure of first-line therapy means
    - effective treatment is delayed, degrading outcomes
    - suffer side-effects with no benefit
    - high cost to healthcare system and patients
- Quantitative PET is showing promise for predicting therapy response earlier than existing methods in several cancers
  - WB-PET spatial resolution deemed insufficient for tumors <~ 2-3 cm
  - majority of new BC cases present with tumors <~ 2 cm
- PET/X detector design photon sensitivity vs. spatial resolution trade-off will favor quantitative accuracy and precision
- Most dedicated breast PET systems have focused on detection/diagnosis task
  - this is changing as developers now implement quantitative corrections
- Not discussed: integration with mammography and x-ray tomosynthesis
  - x-ray image may play important role in PET attenuation correction

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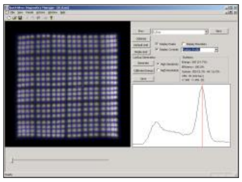
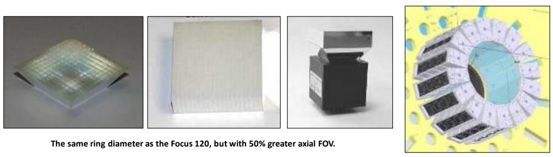
Clinical to Pre-clinical Imaging Systems

SIEMENS

Siemens Inveon PET



- 20x20 LSO Array
- 1.59x1.59x10mm pixel
- Short, Tapered Light Guide
- Hamamatsu C-12 PS-PMT
- Highest packing fraction detector ring
- 25,600 Detector elements



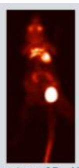
The same ring diameter as the Focus 120, but with 50% greater axial FOV.

SIEMENS

Siemens Inveon PET

The highest resolution PET system:
<1.4mm
The highest sensitivity PET system:
>10.5%
The highest countrate PET system:
>2.0Mcps peak NEC
The largest FOV:
12.7cm axial x 10cm dia.
Best timing resolution:
1.3 nsec *(in the system)*
Best energy resolution:
15% ER *(in the system)*
The only source based attenuation correction in preclinical imaging

All performance specifications are derived from customer evaluation per proposed NEMA standards.



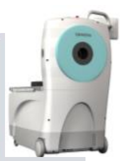
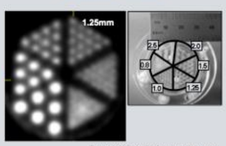


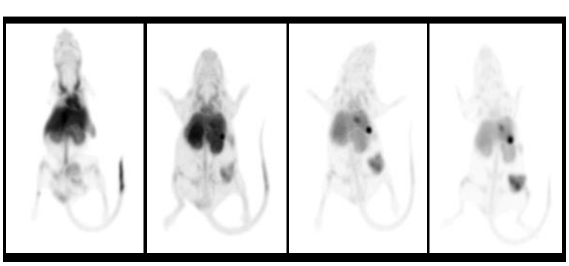
Image Courtesy of Dr. J Wiechert
U. Wisconsin, Madison



Innovation is in our genes.

SIEMENS

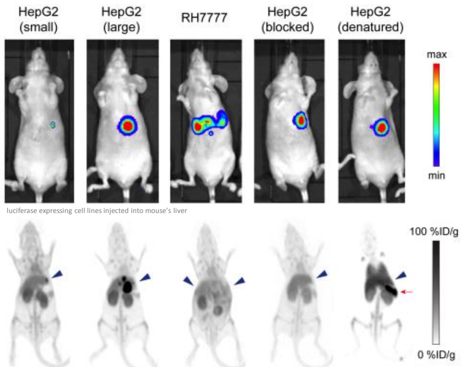
Glypican-3–Targeted ^{89}Zr PET Imaging of Hepatocellular Carcinoma



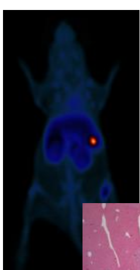
Day 0 Day 1 Day 3 Day 5

Sham, Kievit, Grierson, Miyaoka, Yeh, Zhang, Yeung, Minoshima, Park. J Nucl Med, 55:799-804, 2014.

In Vivo ^{89}Zr-Antibody Targeting

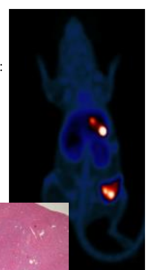


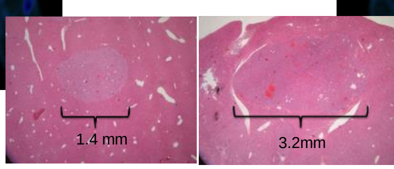
Absolute Tumor Size

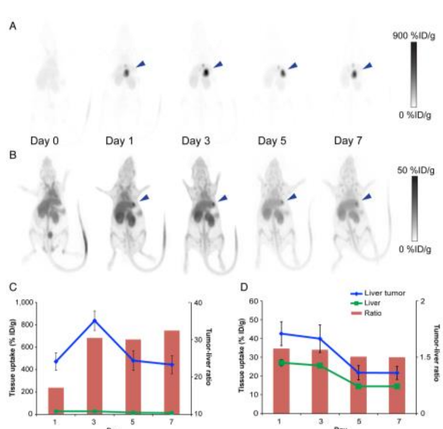


- Tumor Dimensions: 1.4 x 1.0 mm
- Tumor volume: ~0.71 mm^3

- Tumor Dimensions: 3.2 x 1.6 mm
- Tumor volume: ~6.43 mm^3







Small Animal PET

Bruker

TriFoil Imaging

nanoScan PET/CT
Mediso Medical Imaging Systems

SOFIEBIOSCIENCES
G4 PET/X-ray

G8 PET/CT

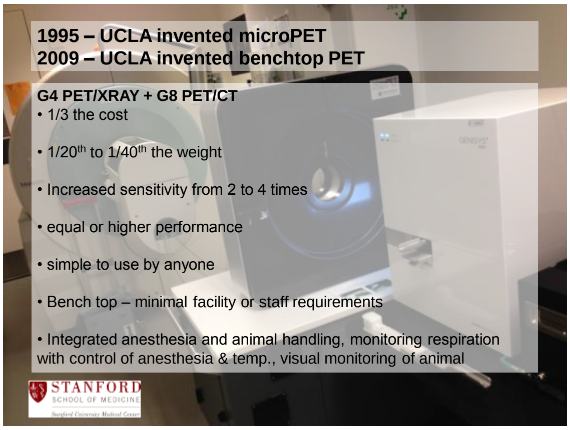
SOFIEBIOSCIENCES

IMAGING PAIN POINT

High cost and complexity of current PET scanners limit use, access, throughput and require significant support resources

New users see PET as too complicated, too expensive, lacks diversity and requires one deal with radiation

- Economic challenges effect everyone
- $700k - $1M PET scanners represents only a fraction of cost, including service contracts of $70 - $100k/yr
- Further automation of imaging process to allow experts to focus on more important things
- Provide routine, more affordable access to non-FDG probes
- Technology to remove fears of radioactivity



1995 – UCLA invented microPET
2009 – UCLA invented benchtop PET

G4 PET/XRAY + G8 PET/CT
- 1/3 the cost
- 1/20th to 1/40th the weight
- Increased sensitivity from 2 to 4 times
- equal or higher performance
- simple to use by anyone
- Bench top – minimal facility or staff requirements
- Integrated anesthesia and animal handling, monitoring respiration with control of anesthesia & temp., visual monitoring of animal

STANFORD
SCHOOL OF MEDICINE

SPACE IS PRECIOUS

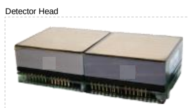
BREAKING AWAY FROM CONVENTIONAL RING BASED GEOMETRY

14% Sensitivity
1.4 mm Spatial Resolution

Surround the animal with panel detectors

Composed of four detector heads closely placed together, which yields very high sensitivity from the large coverage (3D solid angle) on the animal.

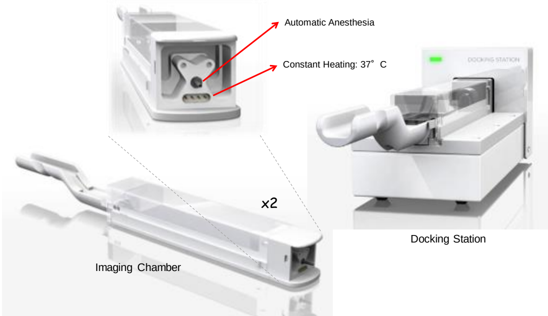
Detector Head



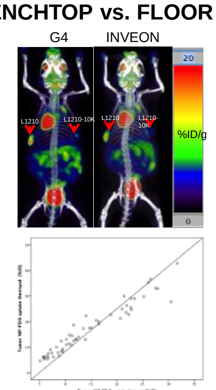
- Composed of
  - 52 × 24 BGO array (1248 pixels per head)
  - Two 64-Channel PSPMTs
- Detector Element Size: 1.75 mm x 1.75 mm x 7.2 mm
- Field of View (FOV): 9.5 cm x 4.5 cm

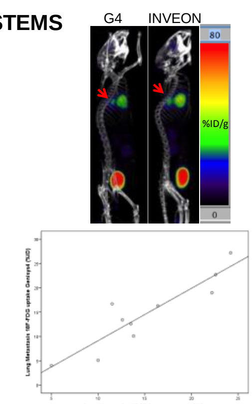
AUTOMATION & LIVE LINK TO THE ANIMAL

- Automatic hook-up for anesthesia and heating
- No more cables
- System takes care of the animal for you

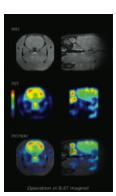


BENCHTOP vs. FLOOR SYSTEMS



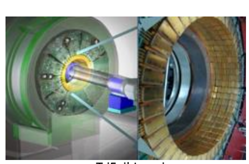


PET/MRI



Mediso Medical

MR Soultions



TriFoil Imaging

Future Systems/Applications

- PET combined with fluorescence imaging
- Dual radioisotope PET imaging
- PET for proton and hadron therapy
- PET for neutron therapy
- PET combined with micro-irradiators
- Dedicated organ specific imaging systems
  - brain
  - breast
  - prostate

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