Nuclear Physics Applied to Medicine:
Positron Emission Tomography (PET) as a Biomarker for Targeted Cancer Therapy

David A. Mankoff, MD, PhD*

Gerd Muehllehner Professor and Vice-Chair for Research
Department of Radiology
Perelman School of Medicine
University of Pennsylvania

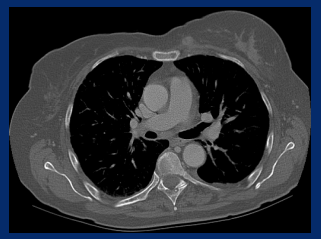
(* and Yale ’81 BS in Physics)

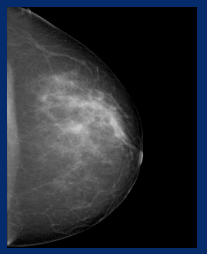
PET (and Applied Physics) as a Cancer Biomarker: Outline

- PET basics
  - Underlying principles
  - Progress in scanners and detector technology
- PET as a cancer imaging biomarker
  - Themes and goals
  - Estrogen Receptor PET as a predictive marker
  - Proliferation PET as an early response indicator
- Future Directions

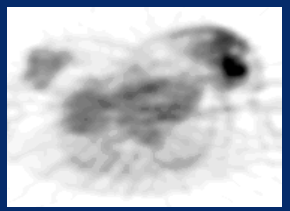
Anatomic versus Functional Imaging

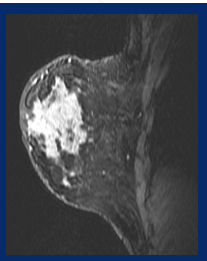
- **Anatomic Imaging**
  - **Relies on tumor size, shape, density**
    - **e.g., mammography, CT**
  - **Measures response by changes in size**



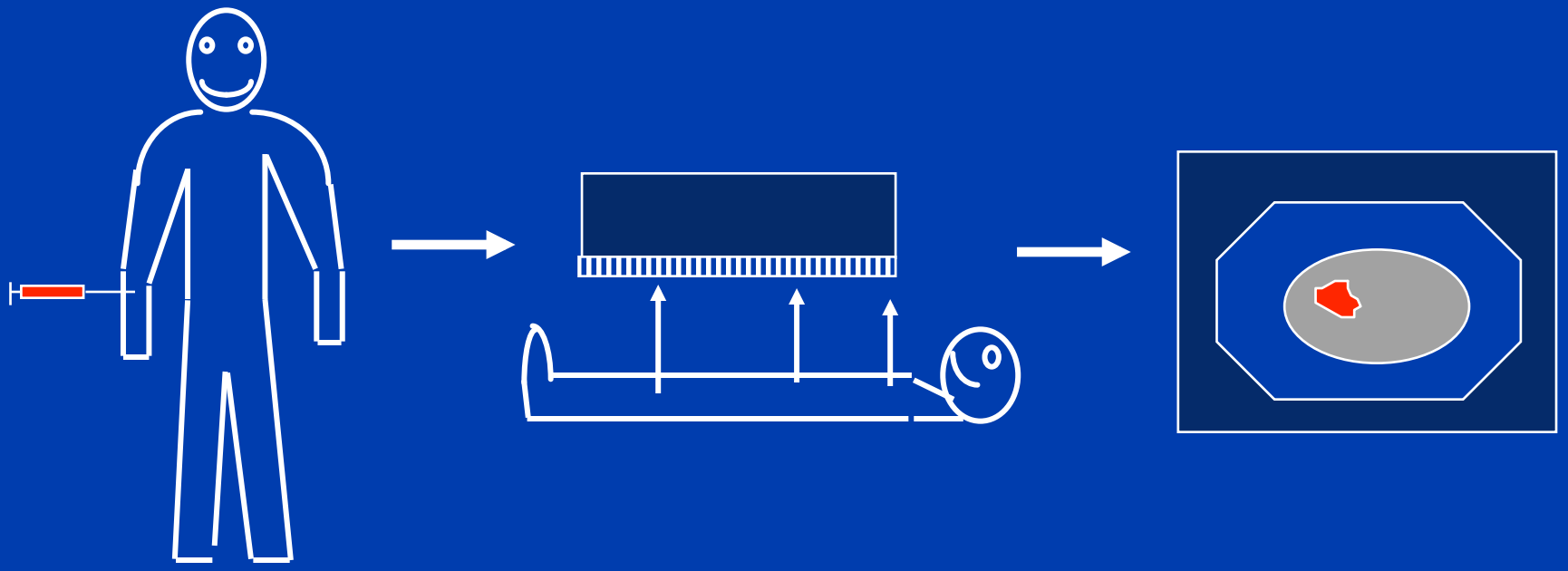


- **Functional/molecular imaging**
  - **Relies on in vivo tumor biology: perfusion, metabolism, molecular features**
    - **e.g., MRI, PET**
  - **Measures response by changes in functional/molecular processes**





Nuclear Medicine Principles

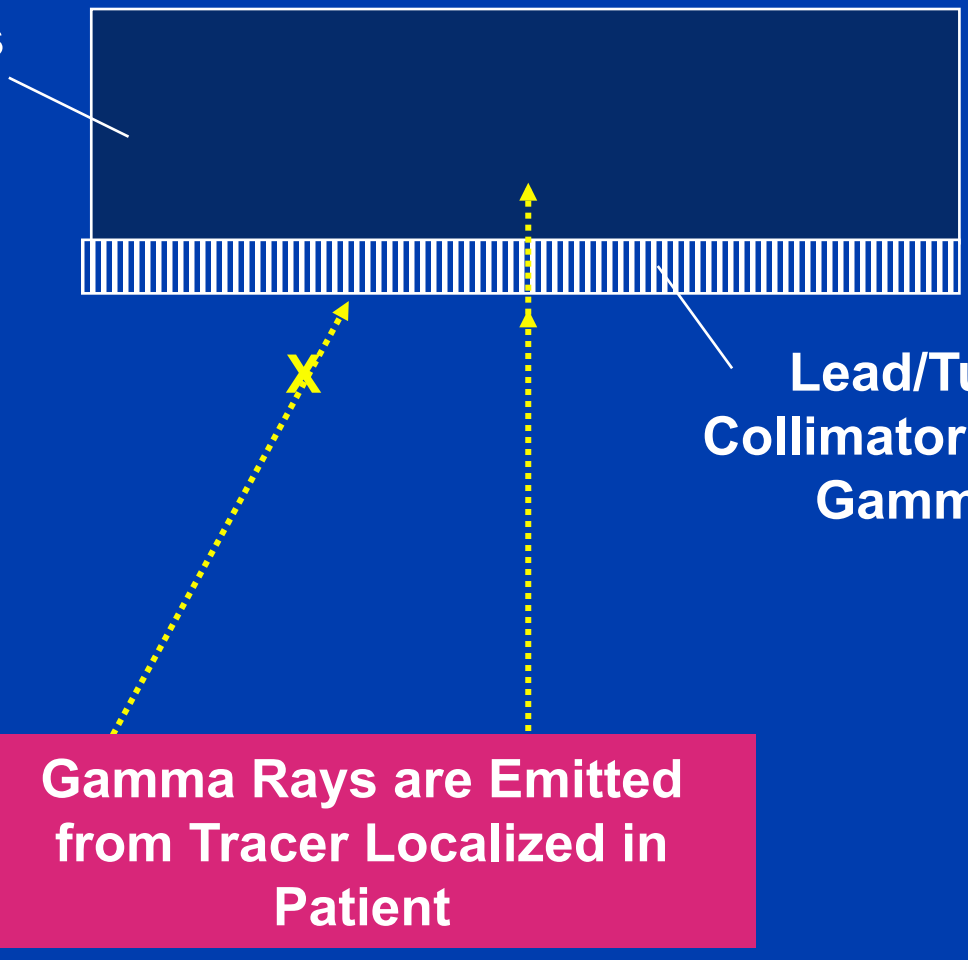


Inject Radioactive Tracer

Position-Sensitive Detection Device

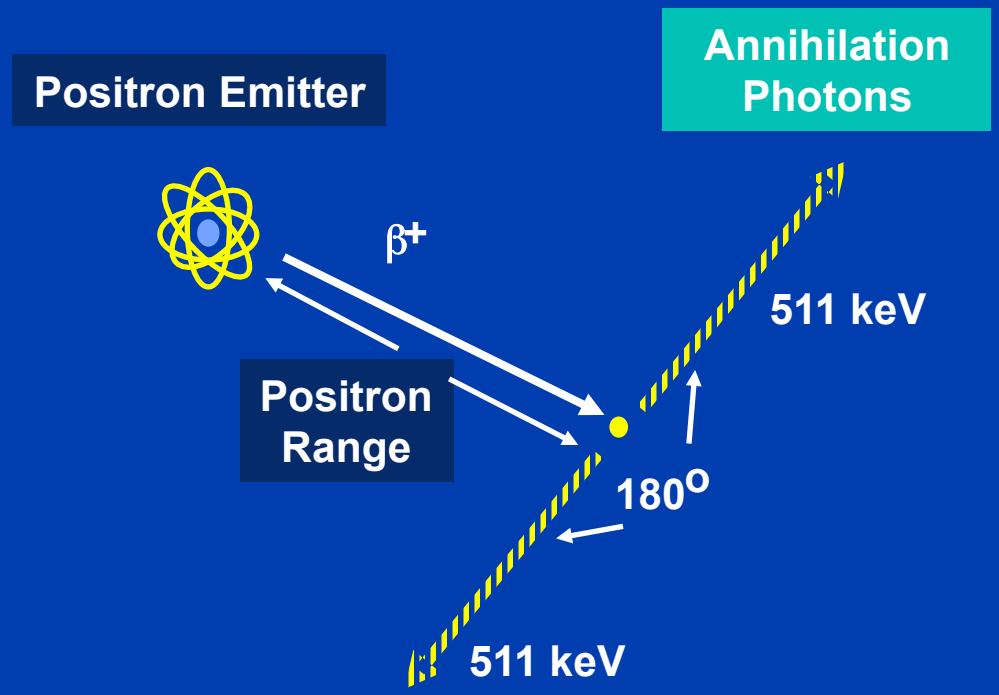
Image of Tracer Distribution

Single Photon Isotope Imaging
(egs., ^{99m}Tc, ^{123}I)

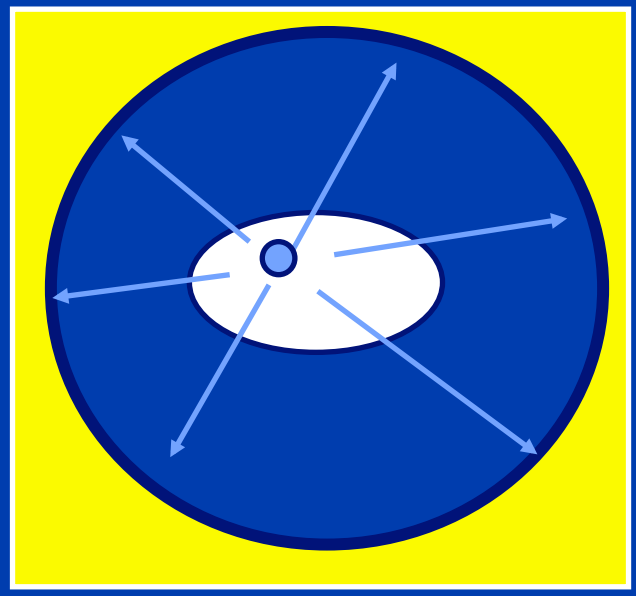


Positron Emission Tomography

(egs, ^{18}F, ^{68}Ga)



PET Tomograph



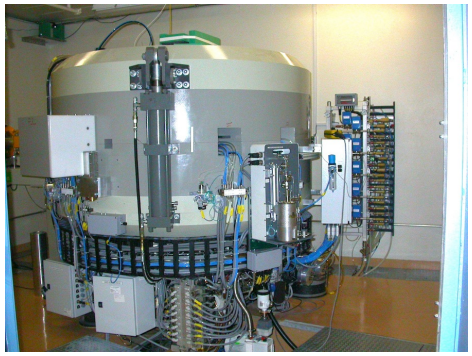
Why PET?

- **Greater sensitivity to isotope emissions**
  - "Electronic collimation" (versus physical collimation) uses greater fraction of emissions
  - Less image noise and/or lower patient radiation dose
- **Better quantitative imaging**
  - Exact correction for photon attenuation in the body using measured attenuation properties (e.g., by CT)
- **Larger range of radiopharmaceuticals for tracer imaging**
  - More "biologic" nuclei – ^{11}C, ^{15}O, ^{13}N ^{18}F
  - But …requires on-site (^{11}C, ^{15}O, ^{13}N) or regional (^{18}F) cyclotron

A Window on "In-the-Patient" Cancer Biology: Positron Emission Tomography (PET)

Physics and Chemistry Meet Biology

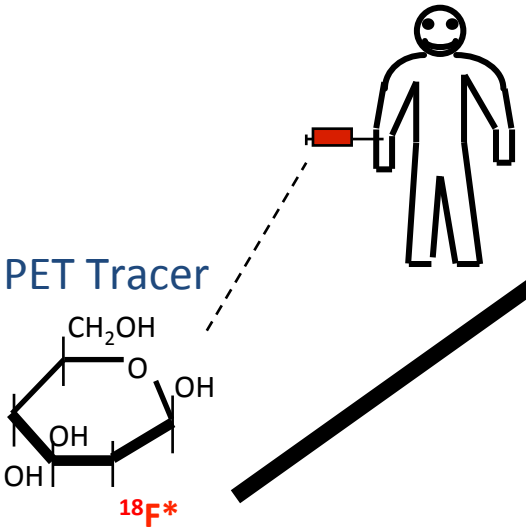
Cyclotron (IBA Cyclone):
Produces Isotope



$^{18}F^*$

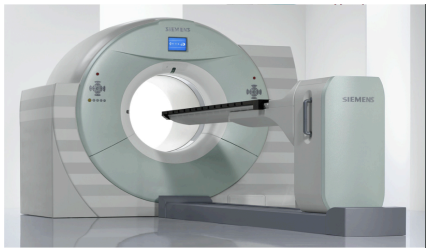
Automated "Hot Cell":
Synthesizes PET Tracer

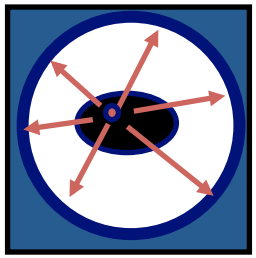
PET Tracer



^{18}F-Fluorodeoxyglucose (FDG):
a tracer of sugar metabolism

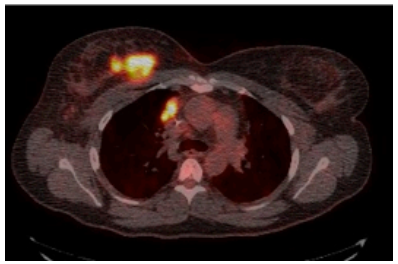
PET/CT Scanner (Siemens mCT):
Acquires and Reconstructs Tracer Image





Electron-Positron
Interactions

Result: Image of Tracer
Concentration



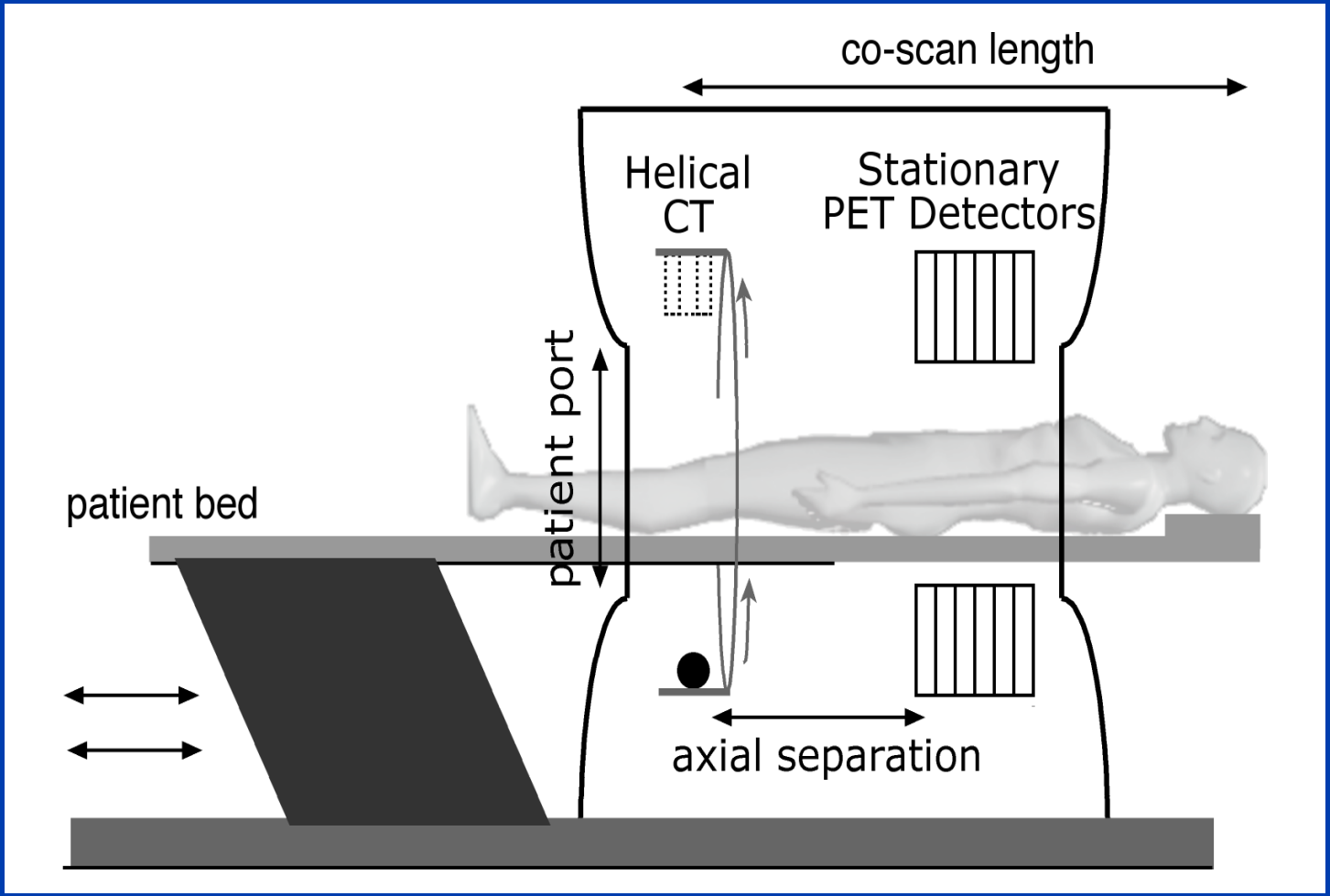
Why Radiotracer Imaging?
Answer: To achieve tracer conditions

- Example: Estrogen Receptor Imaging
  - Tracer specific activity 1000 mCi/umol
  - Injected activity dose: 5 mCi
  - Injected molar dose: 5 umol
  - Peak blood concentration: 1 nM

  (Typical estradiol blood concentration is nM)
- Radiographic, MR, or optical agents require mM (factor of 10^6 difference!)
- Therefore – PET can image biochemical processes without disturbing them

PET/CT

Combines Molecular and Anatomical Imaging



(Alessio, Rad Clin N Amer, 2005)

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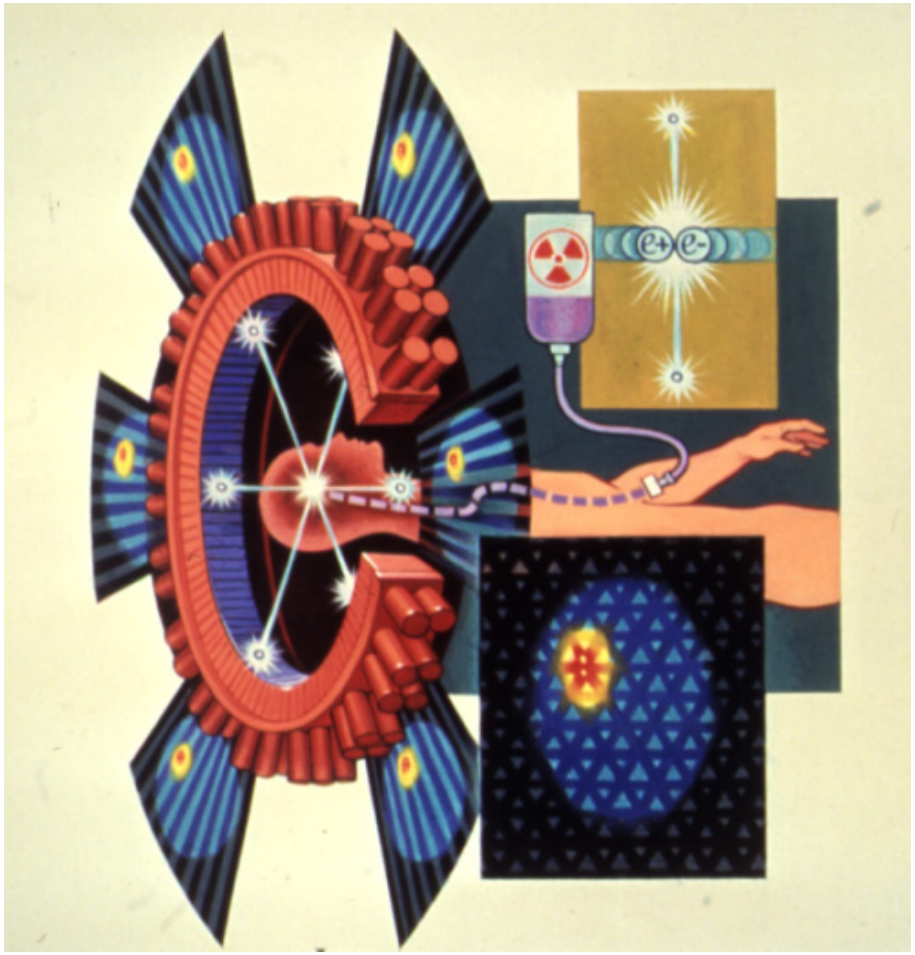
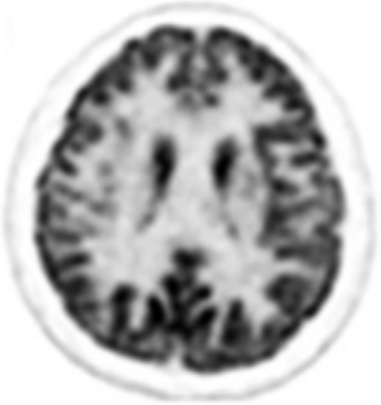
Positron Emission Tomography



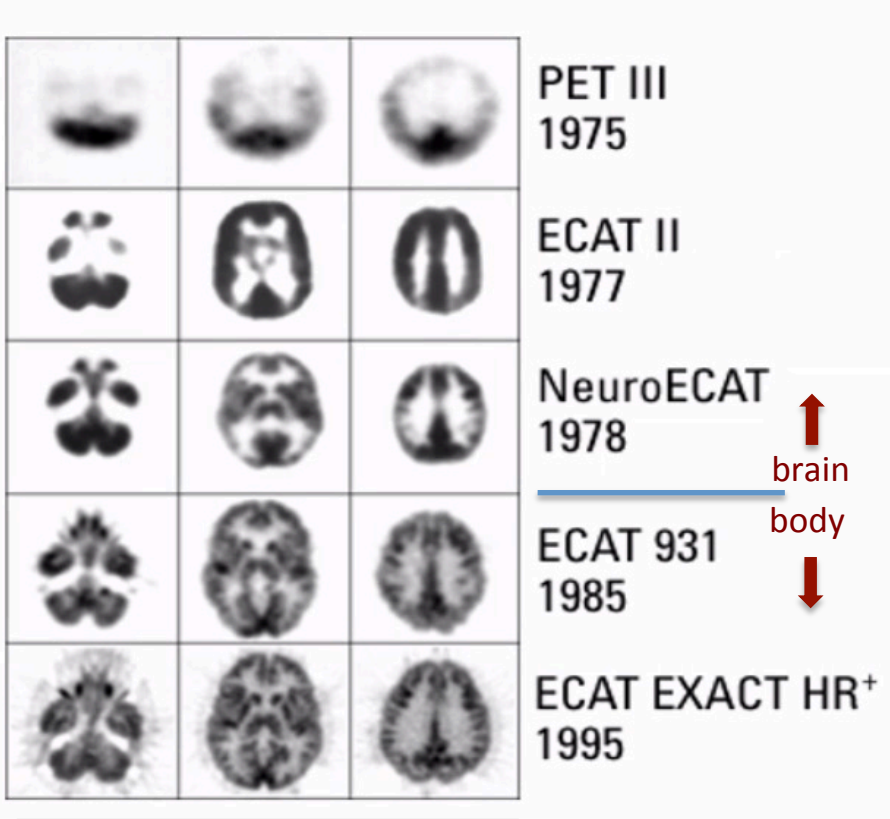
Tracer: [^{18}F]fluorodeoxyglucose
10 mCi = 370MBq

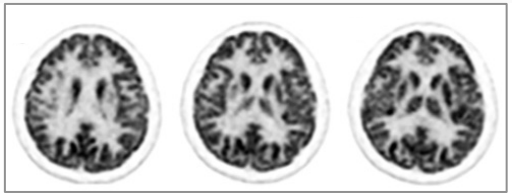


15-20 minute scan
PET : 1 rem (FDG)

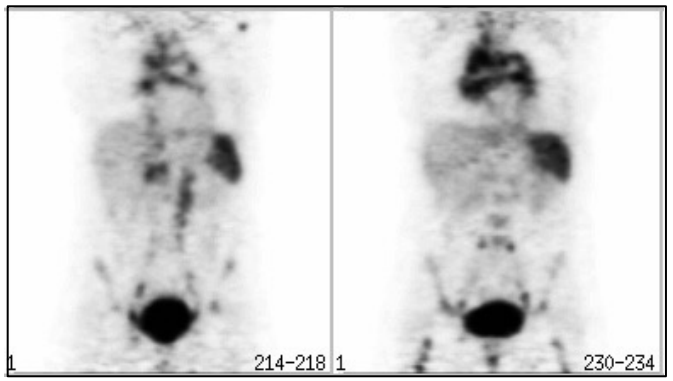
Advances in Image Quality

Wash U./UCLA/CTI

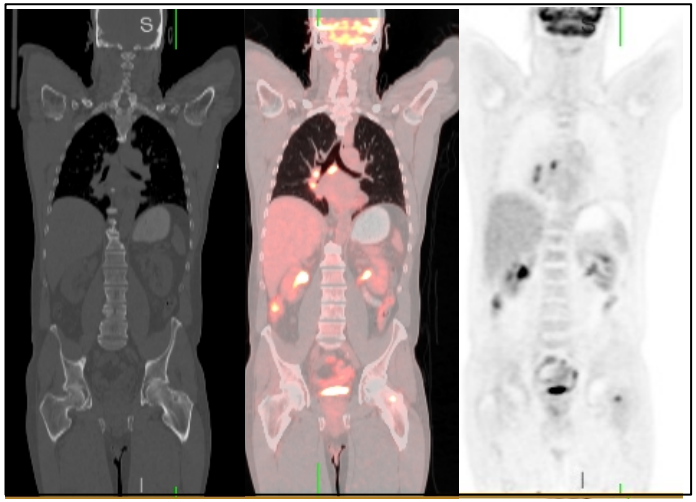




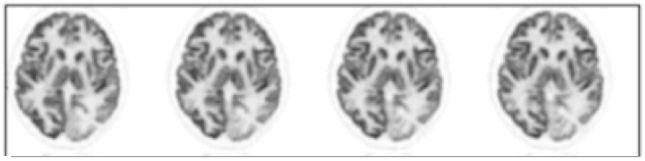
MD Anderson
2015

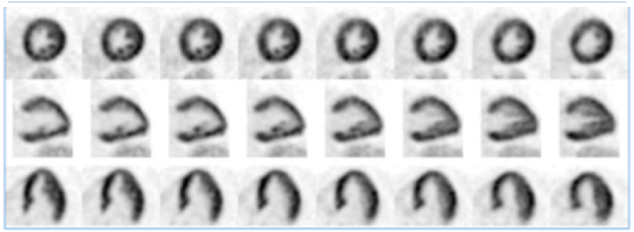


Penn-PET
1988

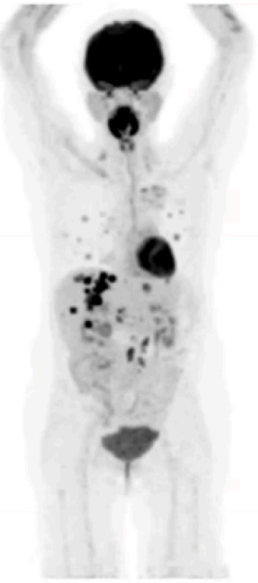


Philips
Gemini TF
2006



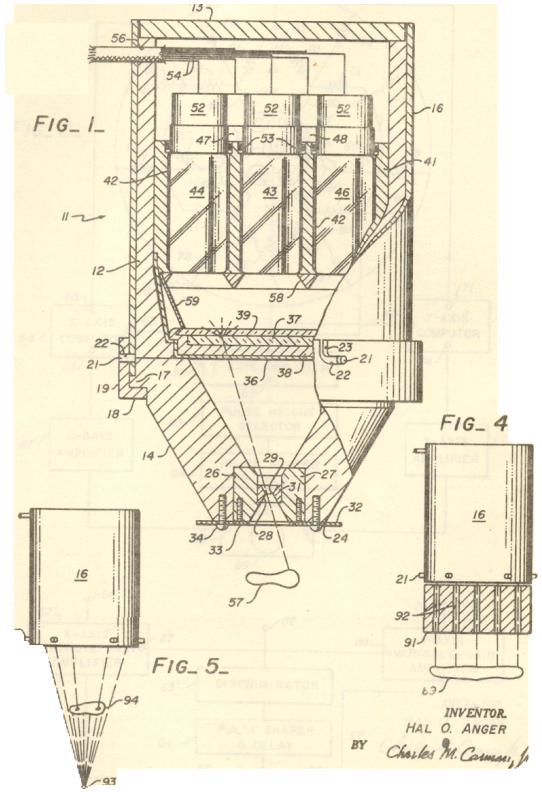


Philips Vereos 2015

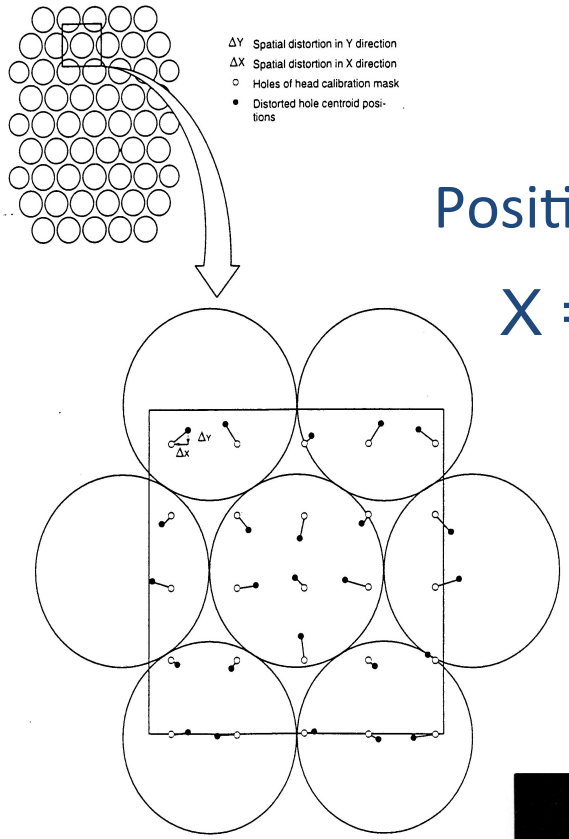


Position-Sensitive Scintillation Detector for Single-Photon Radioisotope Imaging: The Anger Camera

First camera had 7 PMTs coupled to NaI(Tl) scintillator

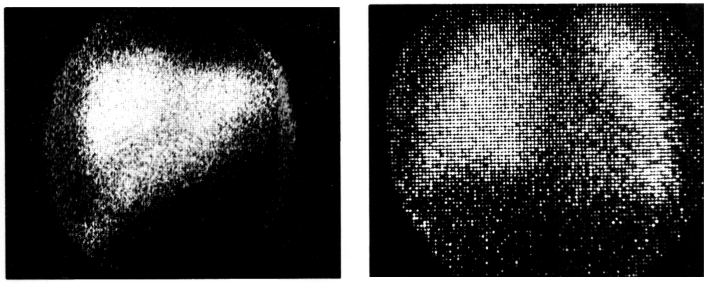


Planar Imaging: First commercial Anger camera was delivered by Nuclear Chicago to W. Myers, Ohio State 1962



Position: Weighted centroid

$$X = \Sigma x_i P_i / E \quad Y = \Sigma y_i P_i / E$$



Anger camera invented 1957

Scintillation Detectors for PET: Early Steps

Single Crystal-Single Tube (CsF)

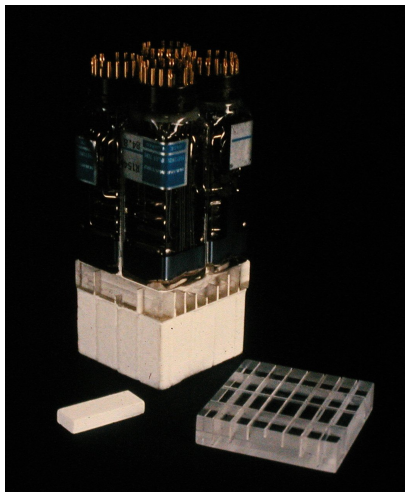
Wash. U. 1981-2

CsF 25 mm ϕ x 45 mm Crystal
28 mm ϕ PMT

Δt = 500 ps

1-to-1 coupling

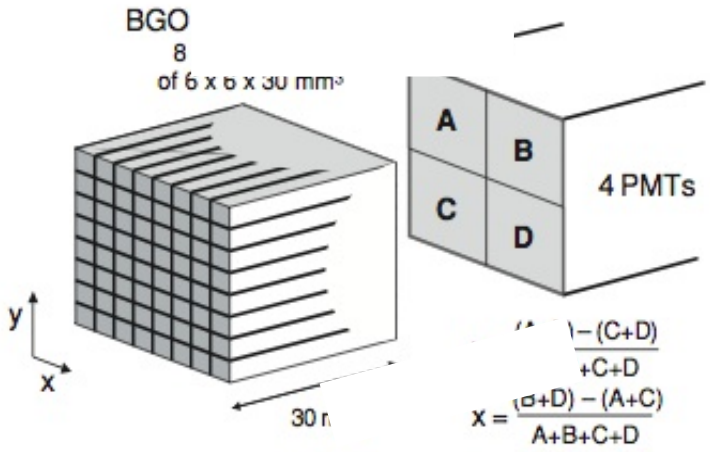
Block Detectors (BGO)



Casey, Nutt Block detector 1986

BGO scintillator	
+	High stopping power
-	Low light output
-	Slow scintillation decay

18,432 crystal elements *(32 rings)*
1,152 PMTs



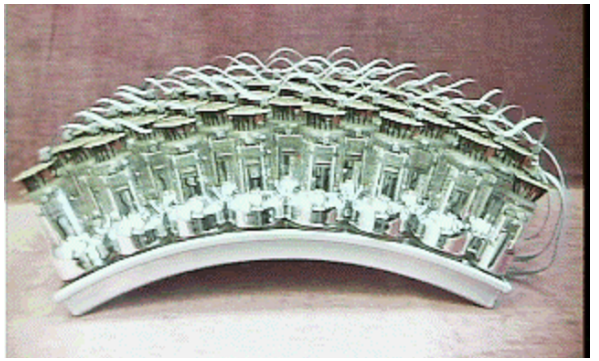
4 x 4 x 30 mm^3
19 mm PMTs (4)

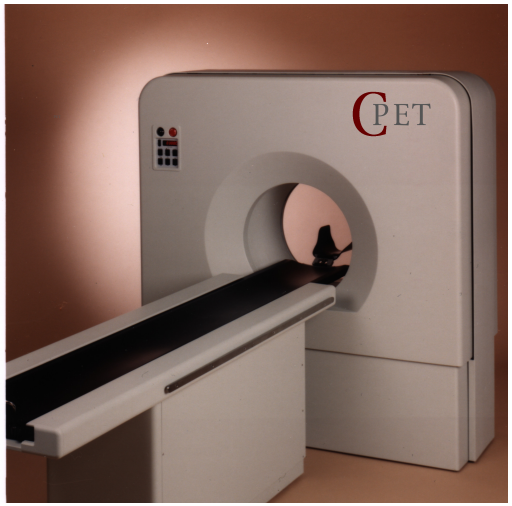
Scintillation Detectors for PET:

Large-Area Continuous Detectors

Flat Scintillator (NaI)

Curved Scintillator





Fast Detectors for Time-of-Flight (TOF) PET

Wash. U. 1981-2

CsF 25 mm ϕ x 45 mm Crystal
28 mm ϕ PMT

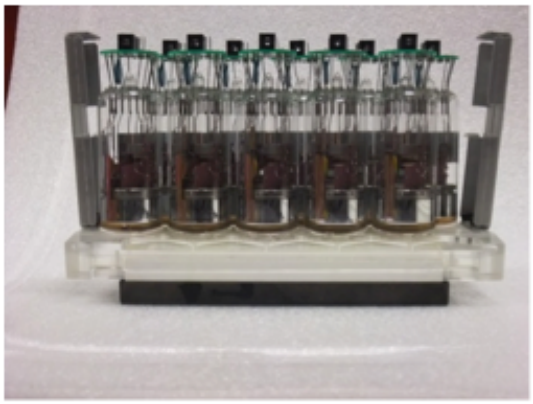
Δt = 500 ps

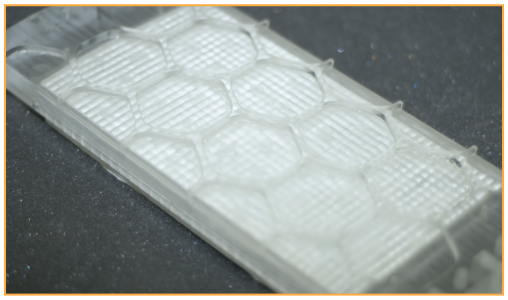
1-to-1 coupling

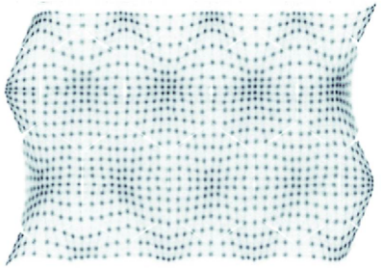
Philips 2005-2015

LYSO 4 mm x 4 mm Crystal
39 mm ϕ PMTs

Δt = 500 ps





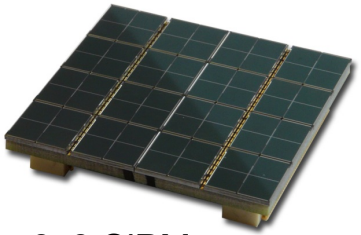


Crystal position flood

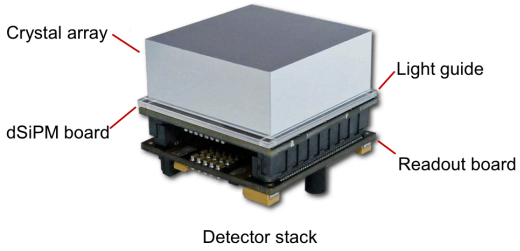
Philips 2015-

LYSO 4 mm x 4 mm Crystal
4 mm^2 SiPMs

Δt = 300 ps



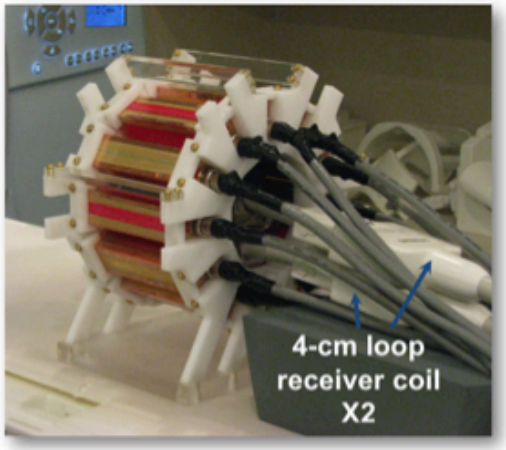
8x8 SiPM array



Silicon Photo-multipliers
2-D array of micro-cells (typically 1000's) operating in Geiger-mode

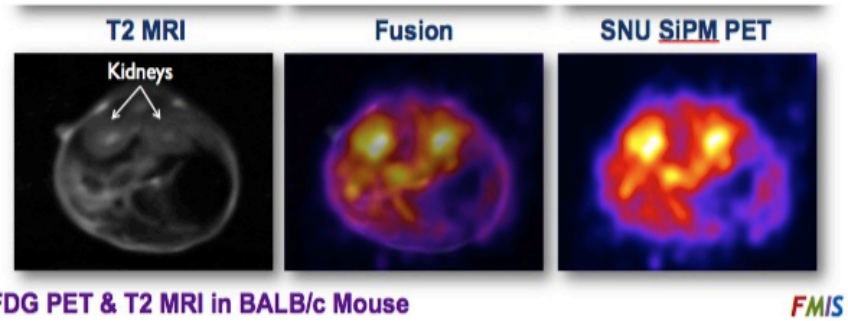
SiPM detectors in small animal and brain PET

Small animal PET/MR

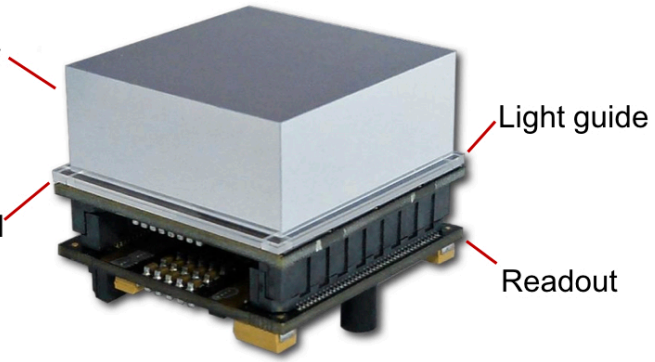


1.5 x 1.5 x 7 mm^3 LGSO
Hamamatsu MPPC

Seoul Nat' l University

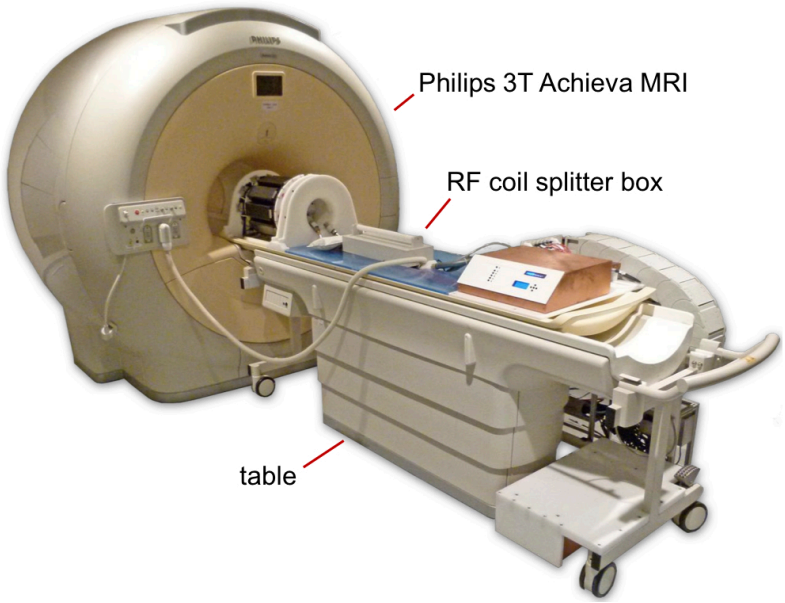


Yoon SNM 2011



30x30 array of 1-mm^2
LYSO crystals

8x8 array of 4-mm^2
dSiPM devices

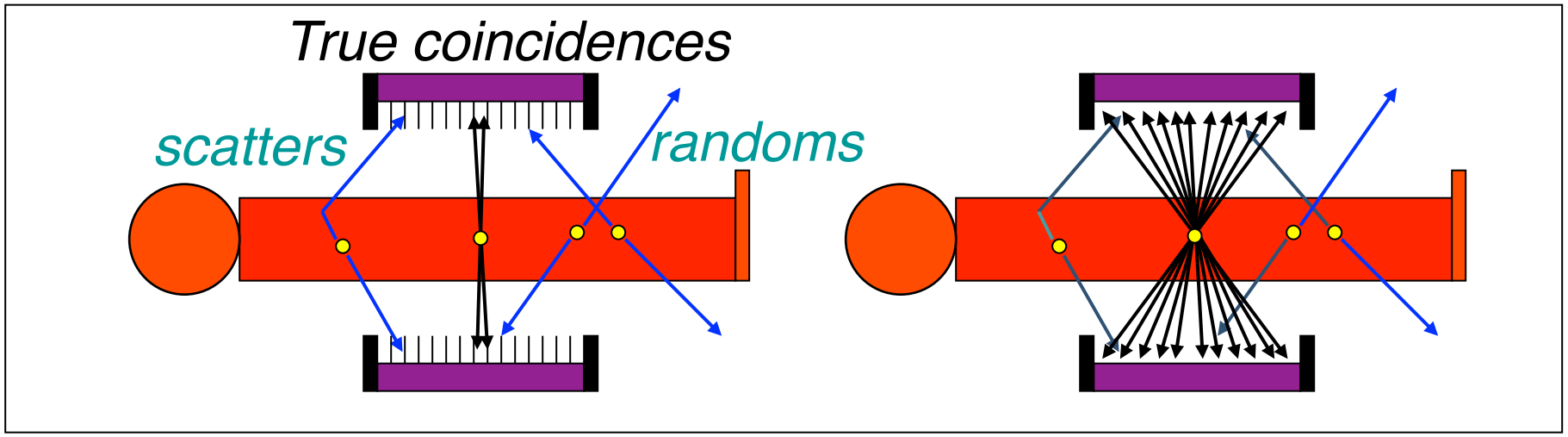


Weibler et al NSS/MIC 2012

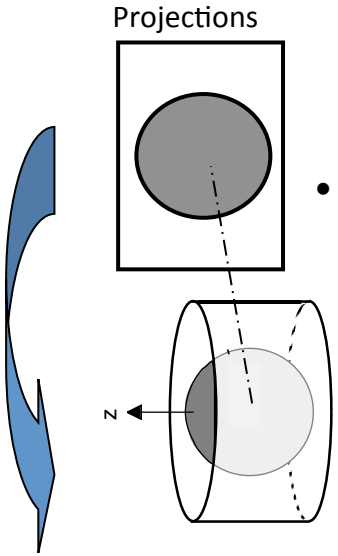
PET Instrumentation Advances Beyond Detectors

- True 3D imaging − improved sensitivity
- Iterative reconstruction − better system modeling, better images
- Time-of-flight (TOF) acquisition and reconstruction − decreased image noise, improved image quality
- Total-body PET imaging − building Explorer devices at UC David & Penn

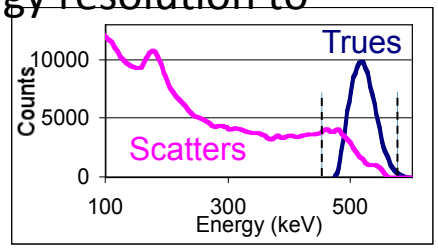
2D vs. 3D Imaging



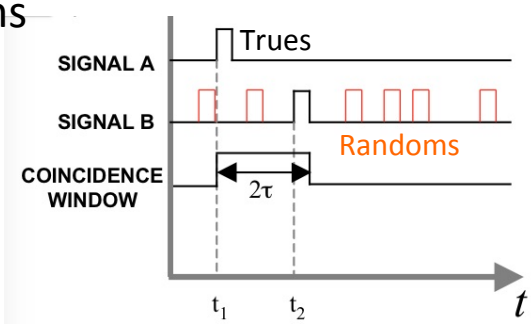
- 2D: *Low sensitivity*
  - septa allow mechanical rejection of scatter & randoms
  - requires more sophisticated reconstruction algorithm



- 3D: *High sensitivity*
  - requires good energy resolution to reject scatter

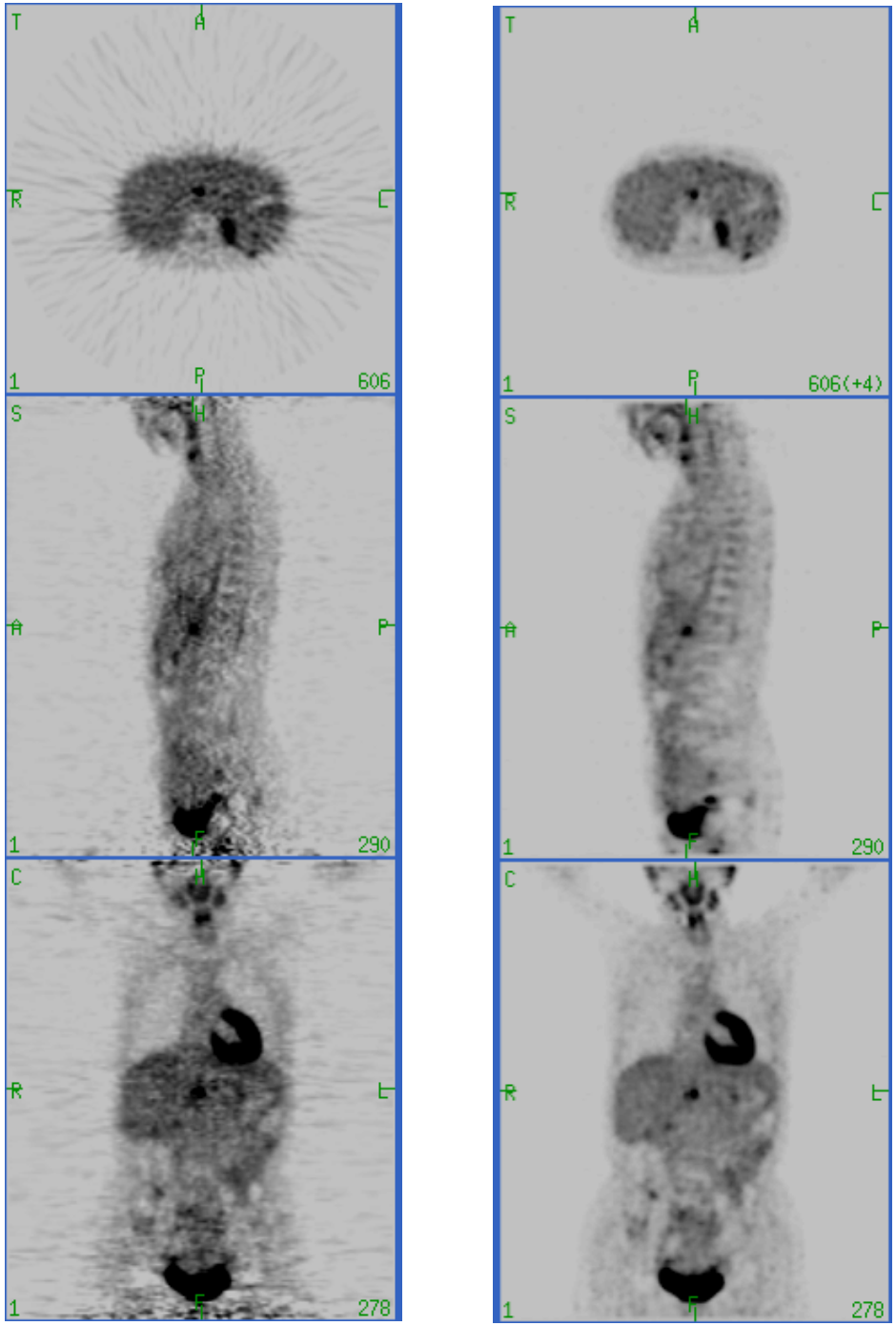


  - requires good timing resolution to reject randoms



Analytic Reconstruction: Filtered Backprojection

Filter trades off resolution and noise

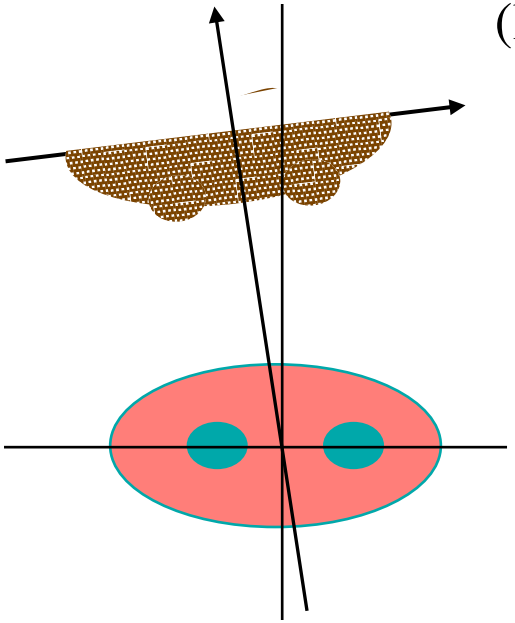


Iterative Reconstruction: EM Algorithm

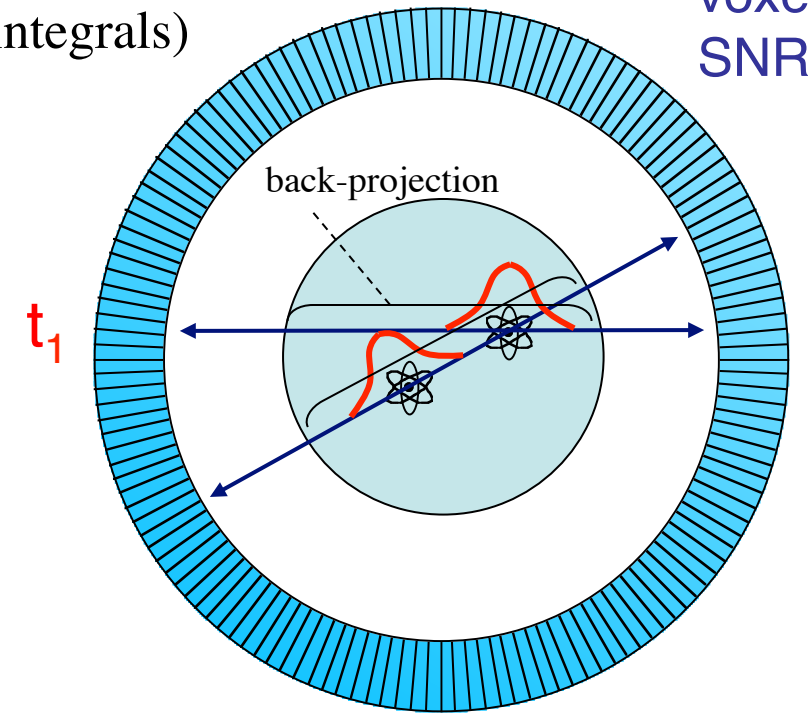
more accurate modeling of physical effects, including statistical nosie

Time-of-flight (TOF) assisted reconstruction

Image reconstruction from projections
(line-integrals)



Signals from different voxels are coupled
SNR ≠ N / $(N)^{1/2}$



$\Delta t = t_1 - t_2$

$\Delta x = c \cdot \Delta t/2$

TOF information reduces coupling, thus improves SNR

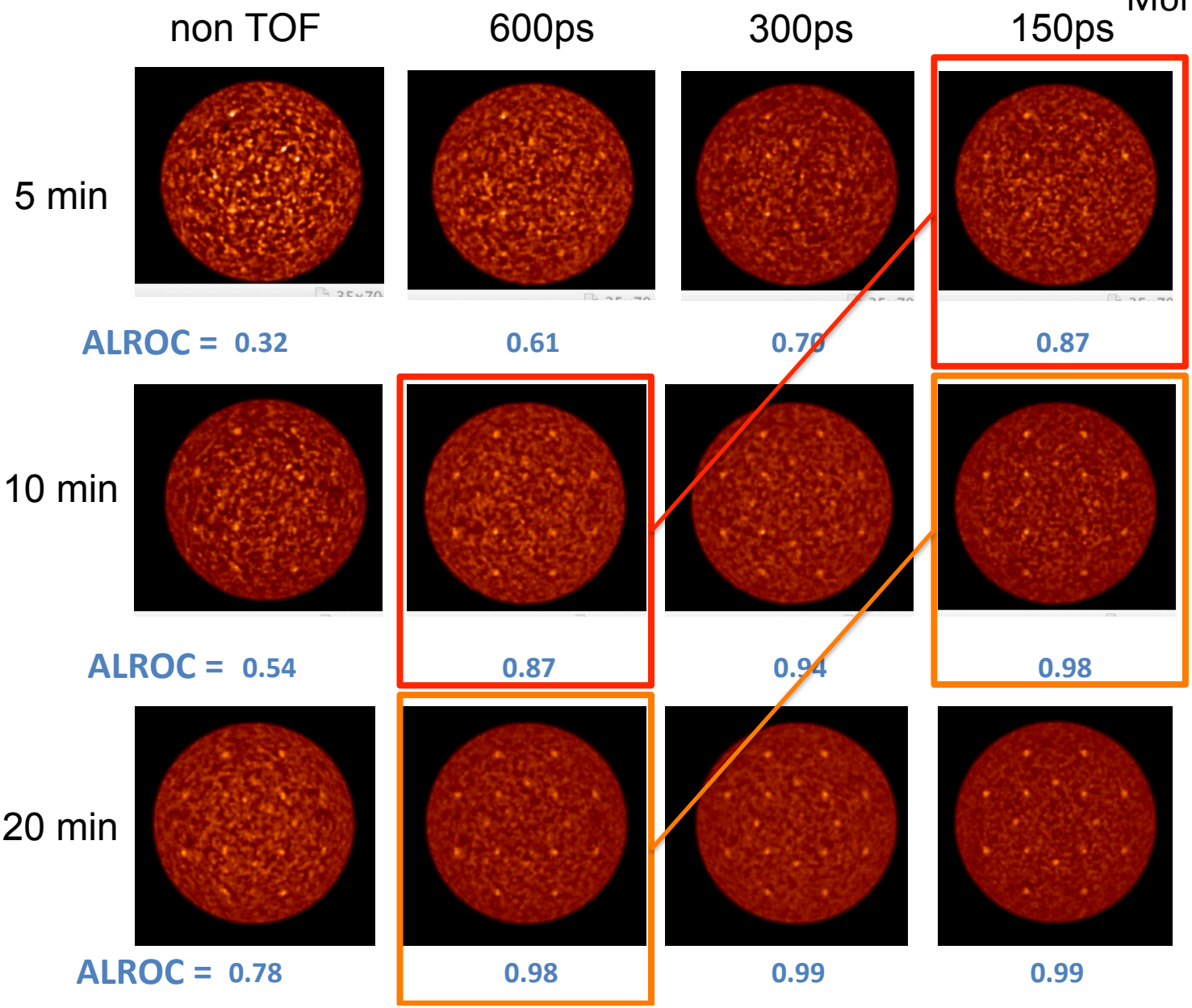
Gain in SNR ~ $(D/\Delta x)^{1/2}$ Δx = 9 cm @ Δt = 600 ps

Improved TOF – is it worth it?

35-cm diameter phantom, 1 cm lesions with 3:1 uptake

Monte Carlo Simulations

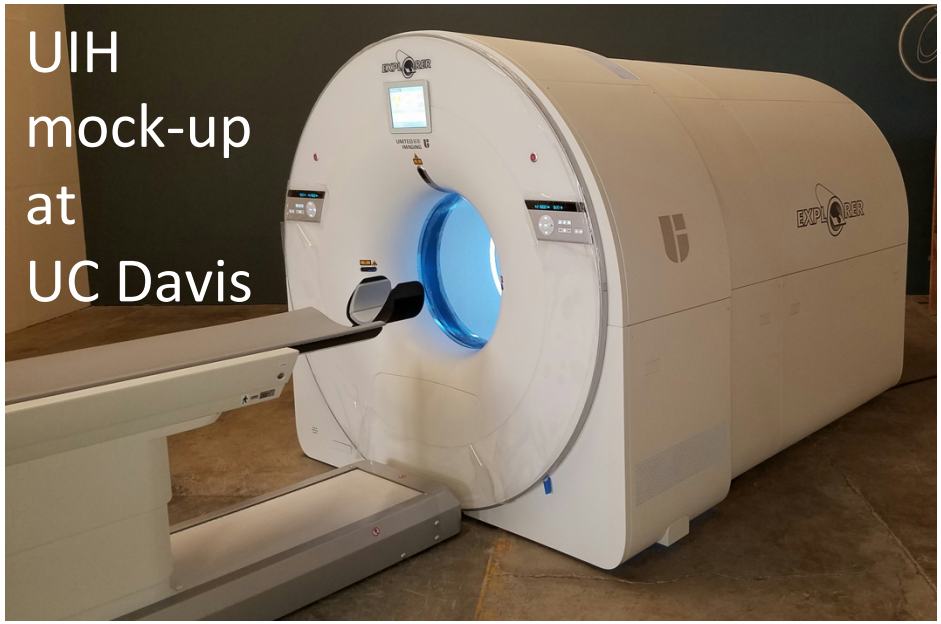
Surti et al, PMB 2013



Detectability depends on TOF and scan time (or activity)

… and the difficulty of the task

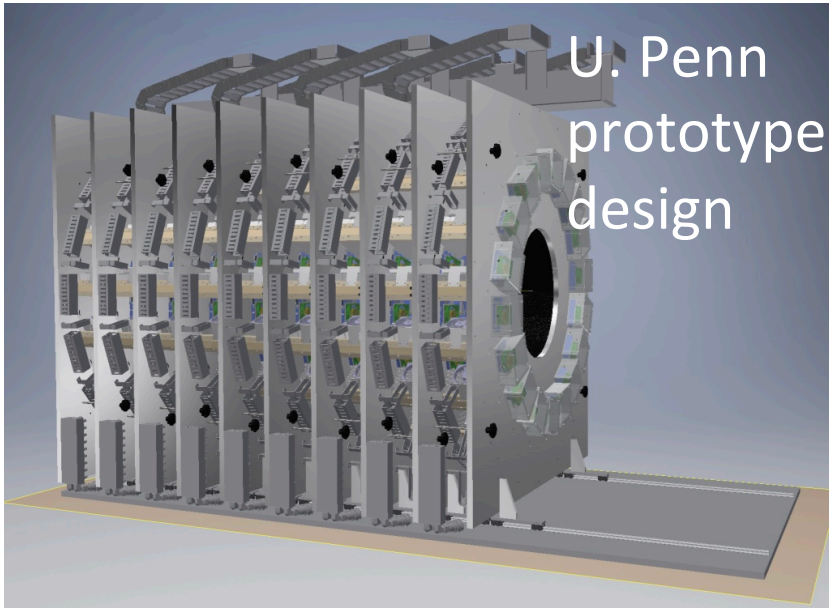
Explorer Whole-Body Scanners (UC Davis and U Penn)



- The detector modules: 2.76 x 2.76 x 18.1 mm LYSO
- Total of 564,480 crystals and 53,760 SiPMs
- Energy resolution of ~12.5%
- Timing resolution of ~400 ps
- Scanner diameter of 78.6 cm (bore 70 cm) and Axial FOV of 195 cm
- 64-slice CT in front

- The detector modules: 3.86 x 3.86 x 19 mm LYSO crystals
- Read out by digital SiPMs (1-to-1)

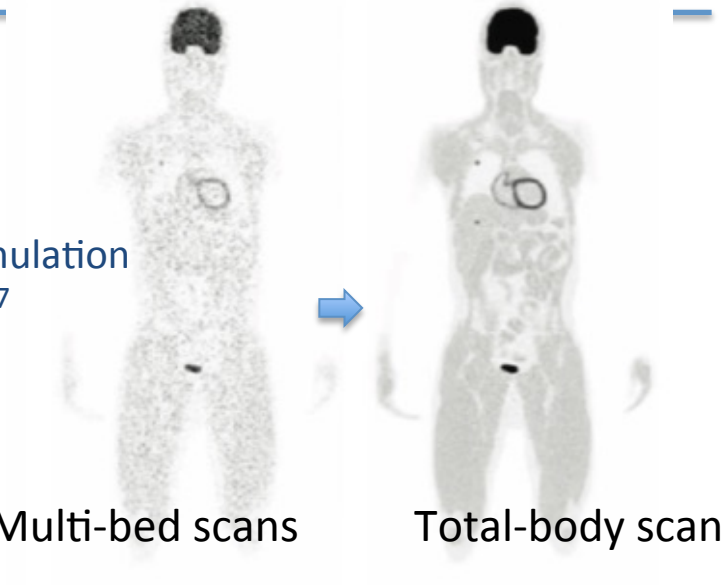
- Energy resolution of ~10%
- Timing resolution of ~250 ps
- Scanner diameter of 78.4 cm (bore 70 cm) and Axial FOV of 70 cm (3 rings), 140 cm (6 rings) or 210 cm (9 rings)
- 64-slice CT in front



Why a Whole Body Scanner?

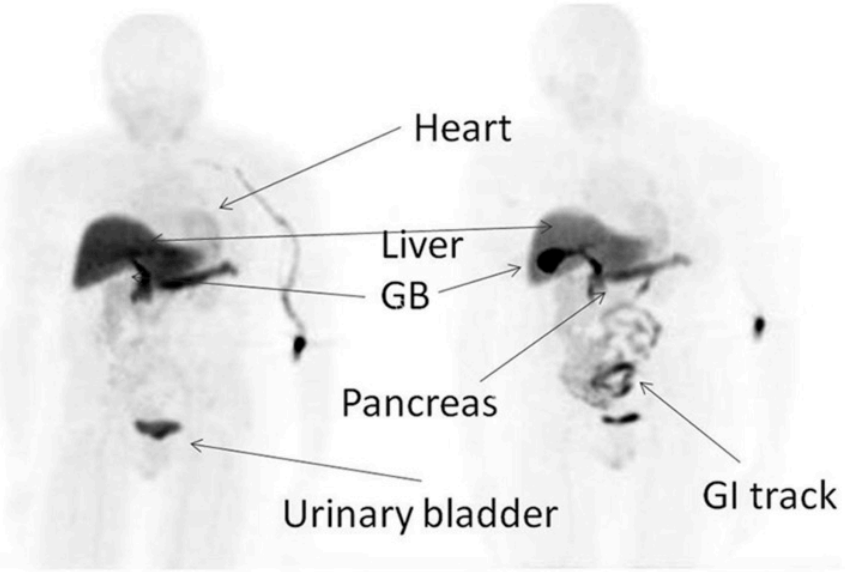
- High sensitivity ≈ $AFOV^2$
  - Lower dose
  - Pediatrics
  - Low $\beta+$ tracers, e.g., ^{90}Y

Monte Carlo Simulation
Zhang et al, PMB 2017



Multi-bed scans Total-body scan

- Simultaneous measures of multiple organs
  - Total body kinetics
  - Drug development



Dosimetry study of [^{18}F]ISO-1 : sequential scans
E. McDonald, R. Mach

20-40 min 140-160 min

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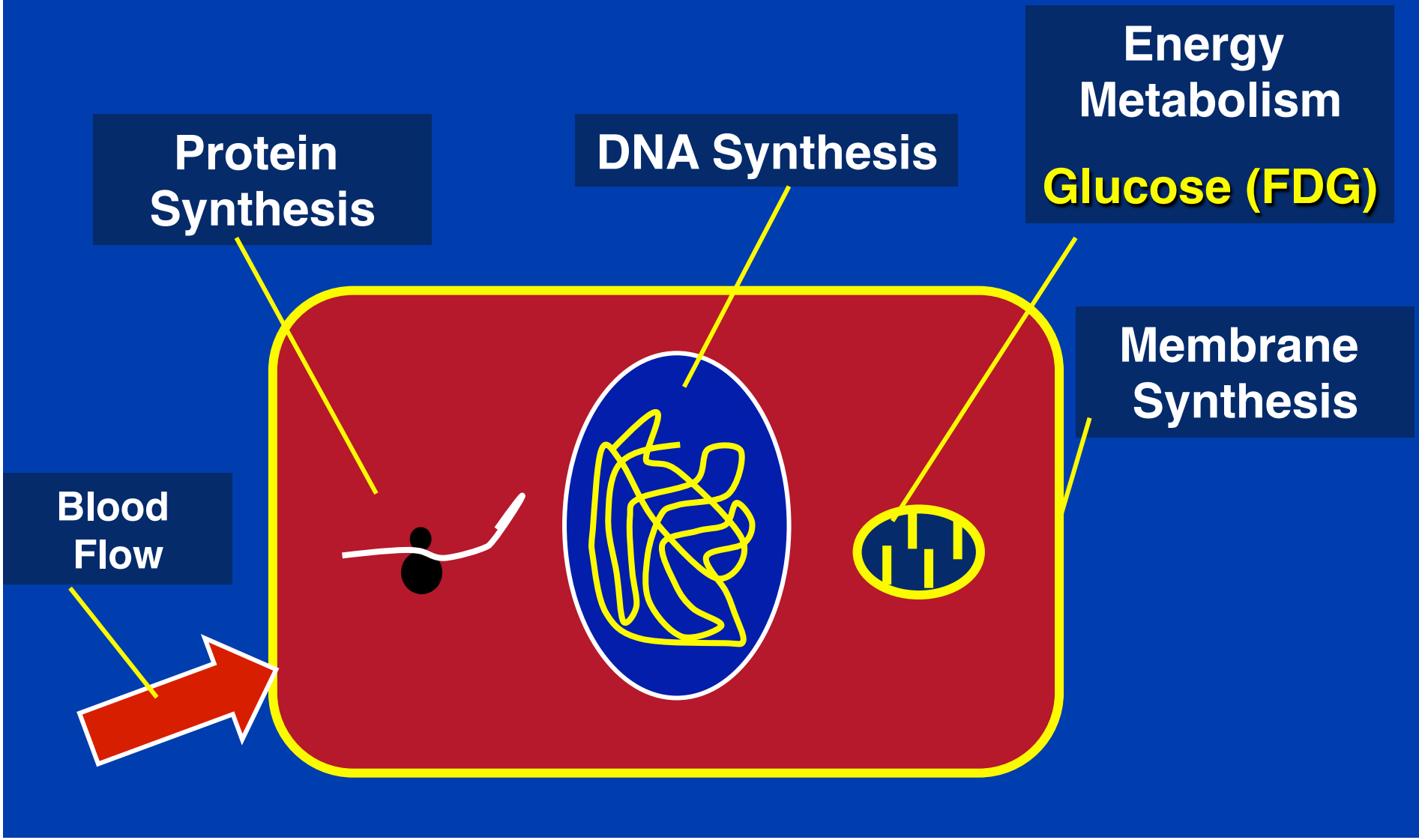
Cancer Imaging for Detection:

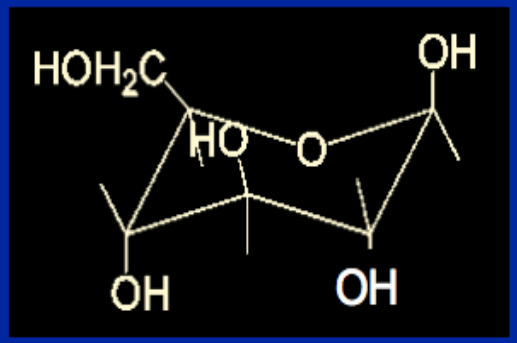
Targets for Detecting Tumor Cells

Higher in Tumor than Normal Tissue

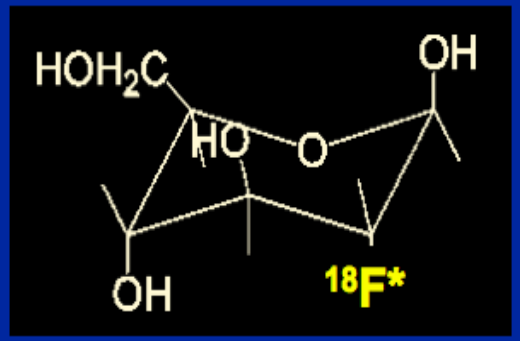


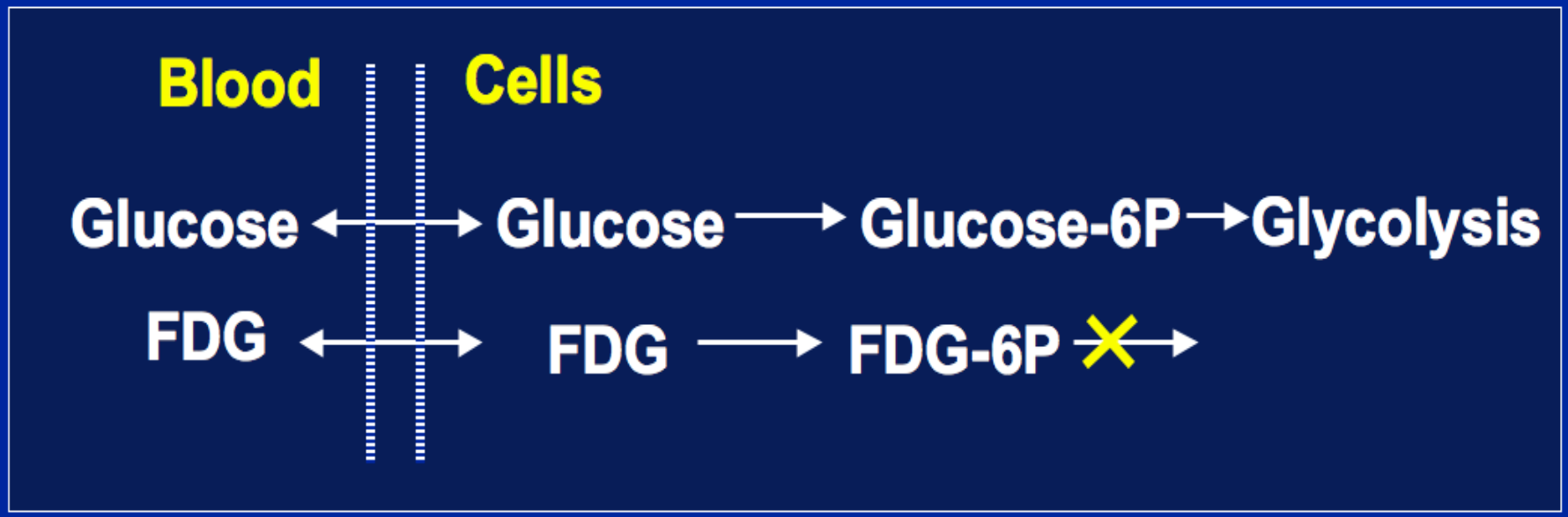
FDG: A Tracer of Glucose Metabolism

Glucose



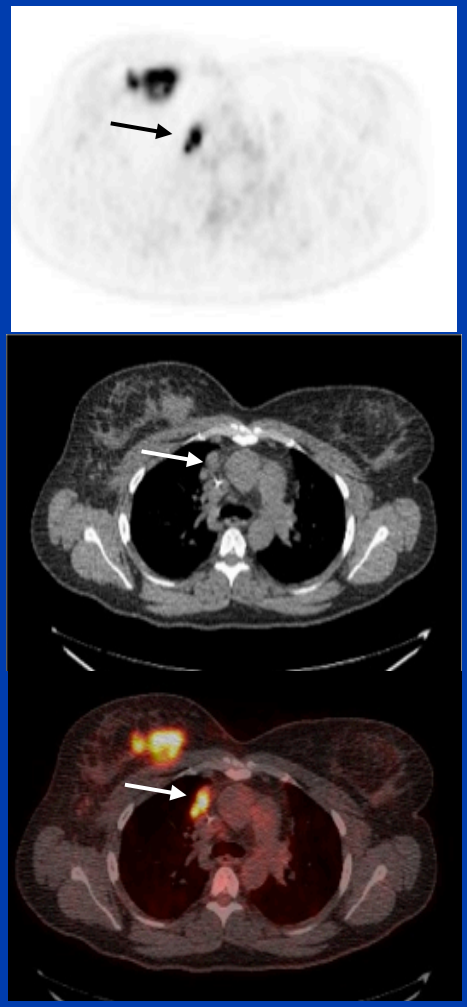
Fluorodeoxyglucose
(FDG)

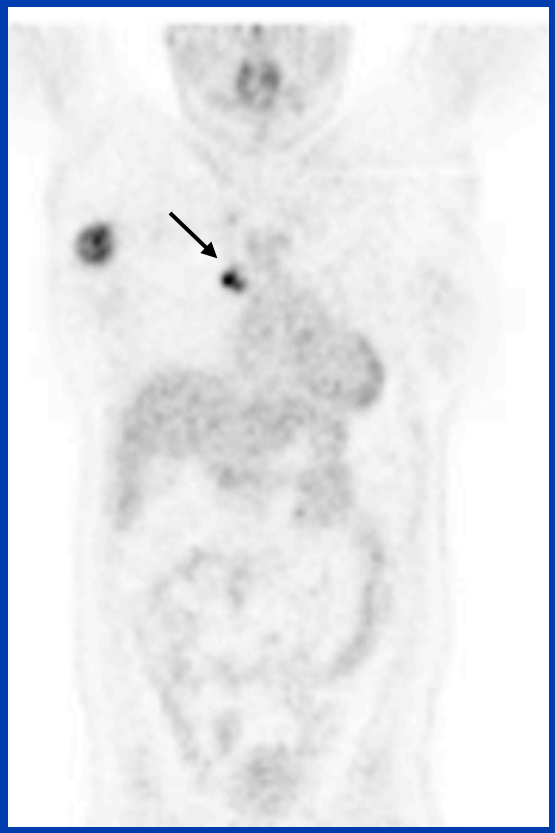




FDG PET/CT Detects Breast Cancer Outside the Breast and Axilla

axial





coronal

Can FDG PET Measure Response?
(answer = Yes!)

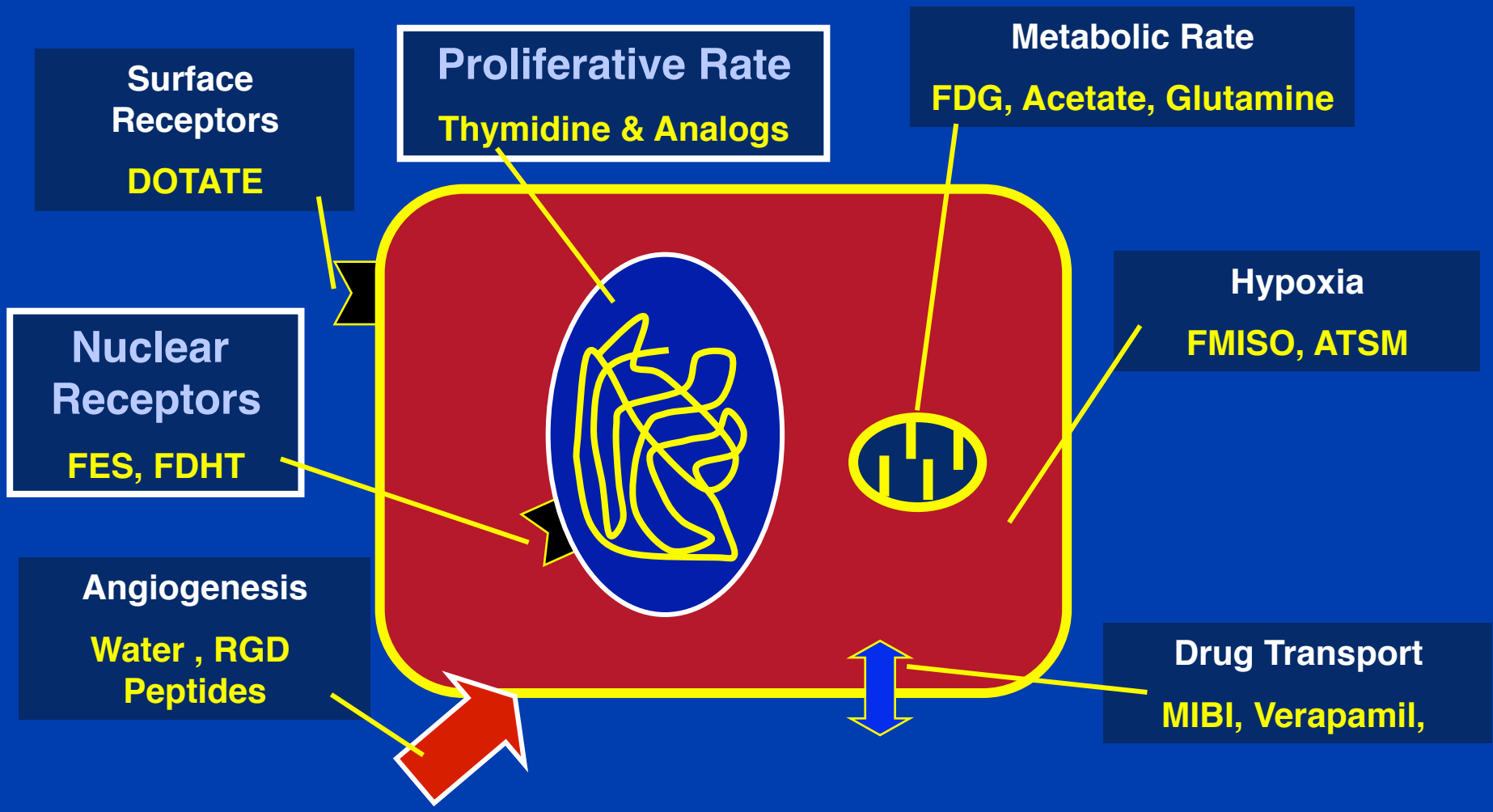
Pre-Therapy

4 weeks of Therapy

Imaging to Guide Targeted Therapy
Help Match Therapy to Tumor Biology

- **Goals in cancer treatment**
  - Characterize tumor biology pre-Rx
  - Individualized, specific therapy
  - Static response may be acceptable
- **The implied needs for cancer imaging**
  - Characterize in vivo tumor biology - predict behavior
  - Identify targets, predict response
  - Identify resistance mechanisms
  - Measure tumor response (early!)

Emerging Cancer Imaging Paradigm:
Measure Factors Affecting Response
Variable Levels in Tumor



Imaging and Cancer Therapy
Clinical Questions for Biomarker Imaging

- Choosing the right patients
  - Is the therapeutic target present?
- Choosing the right drug
  - Does the drug reach the target?
- Getting the right result
  - Is there a early response?
- Predicting the outcome
  - Will response lead to better patient survival?

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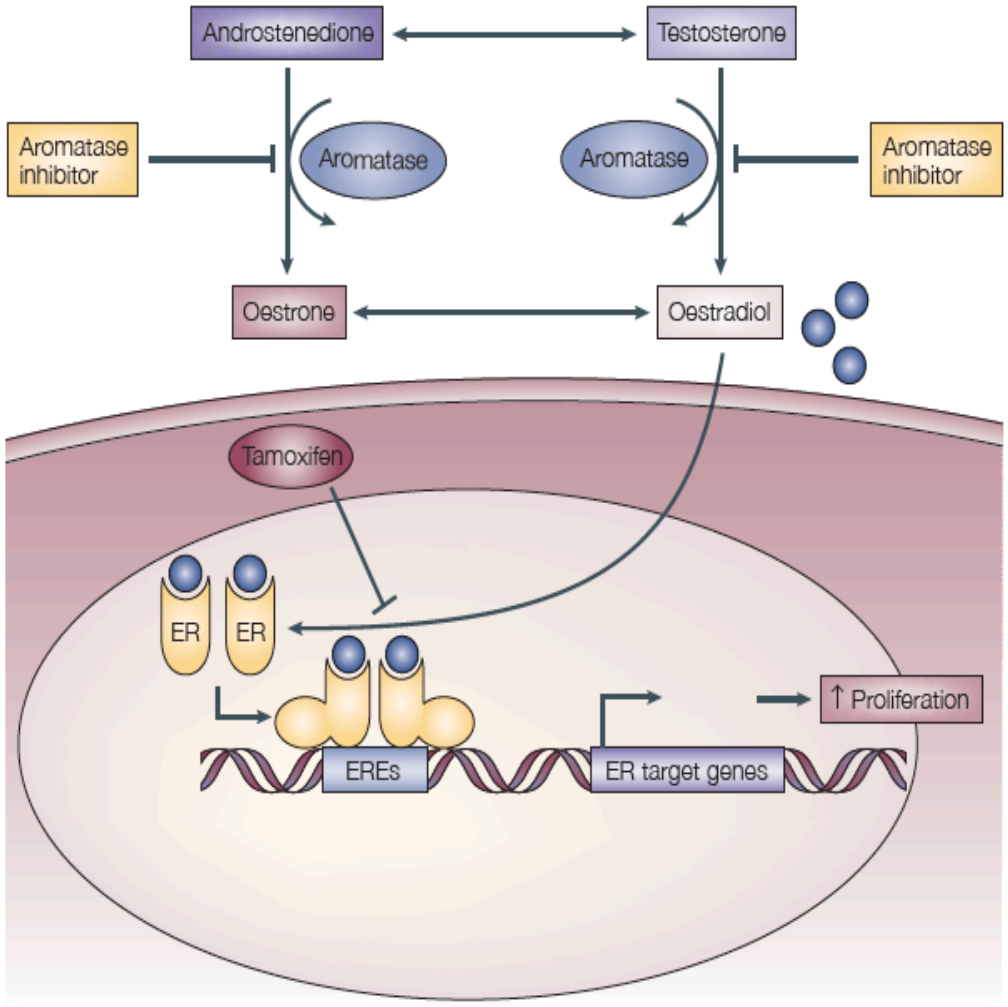
Targeted Breast Cancer Therapy:
The Estrogen Receptor (ER) and Endocrine Treatment



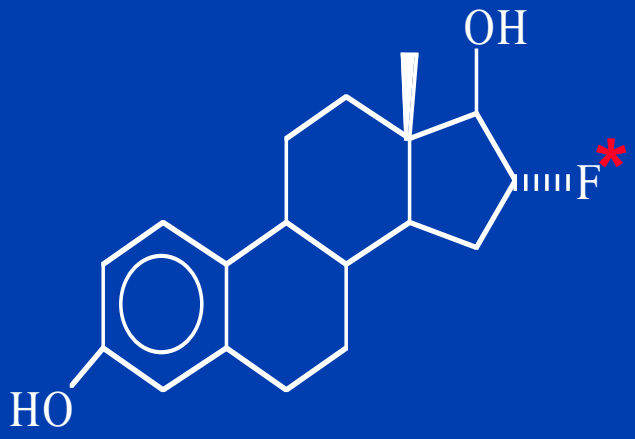
Endocrine Therapy Response Rate:

ER -	< 5%
ER +	50% - 75%

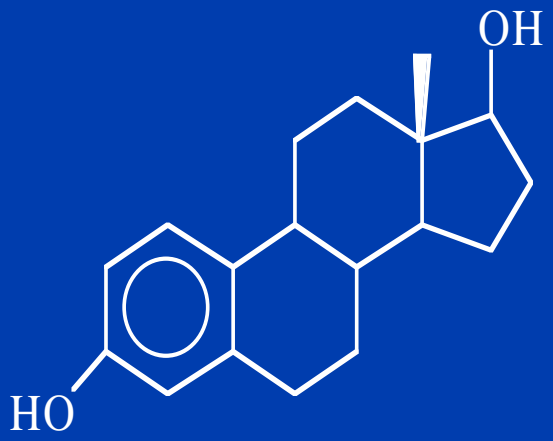
(Johnson and Dowsett, Nat Rev Cancer 3:821, 2002)

[F-18]-Fluoroestradiol (FES): PET Estrogen Receptor (ER) Imaging

FES



Estradiol



	Relative Binding (FES vs Estradiol)
ER	0.9
SHBG	0.2 - 0.8

(Kieswetter, J Nucl Med, 1984)

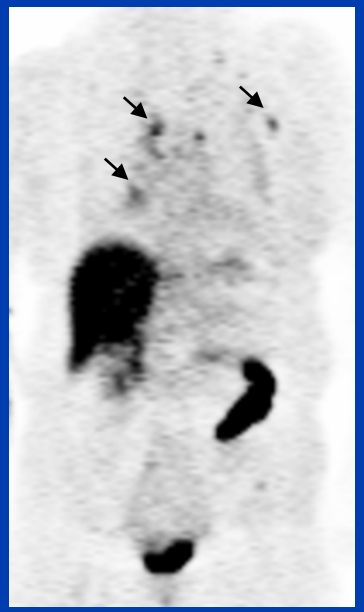
^{18}F-Fluoroestradiol (FES) PET Imaging of ER Expression in Breast Cancer

Peterson, Mol Imag Biol 16:431, 2014

University of Washington, NCI CIP Phase I/II Program

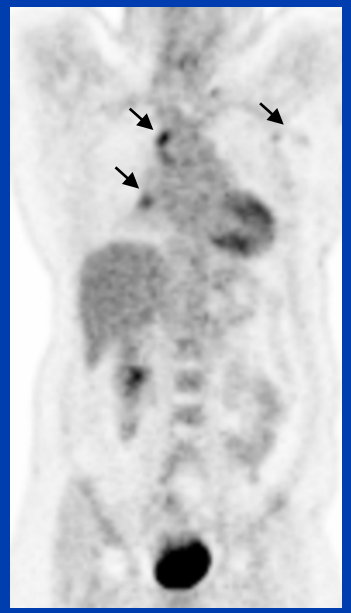
Patient A
Biopsy = ER+

FES



Estradiol Binding

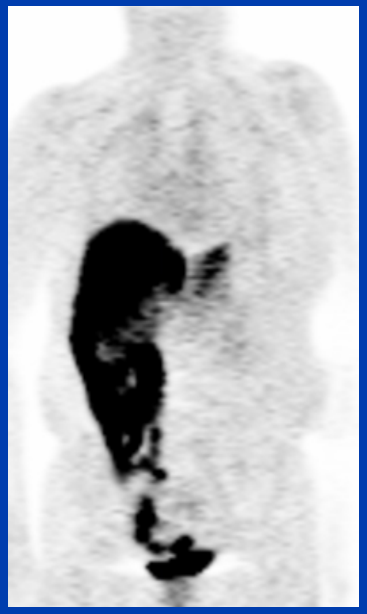
FDG



Glucose Metabolism

Patient B
Biopsy = ER-

FES



Estradiol Binding

FDG

Glucose Metabolism

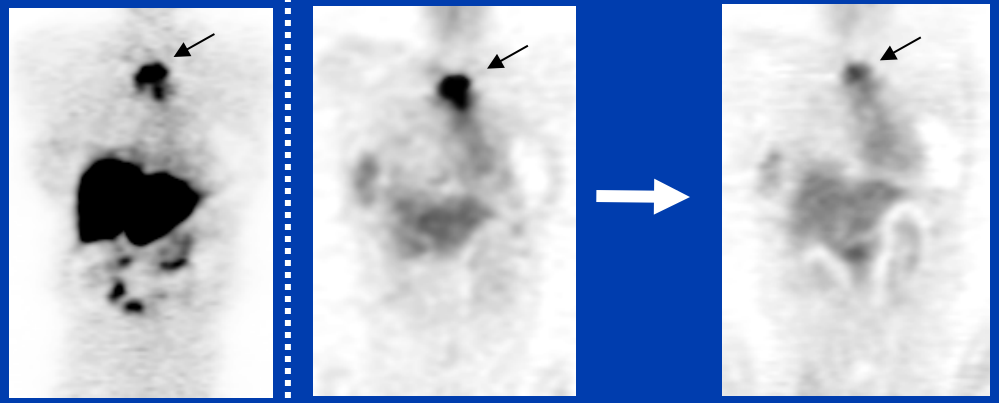
Is the Target Present?

FES Uptake Predicts Breast Cancer Response to Hormonal Therapy

Example 1

- Recurrent sternal lesion
- ER+ primary
- Recurrent Dz strongly FES+

Pre-Rx **Post-Rx**

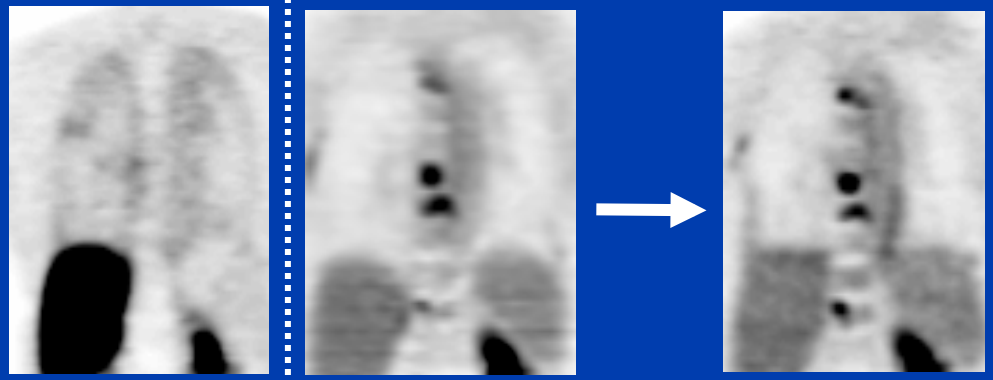


Excellent response after 6 wks Letrozole

Example 2

- Newly Dx'd met breast CA
- ER+ primary
- FES-negative bone mets

FES **FDG** **FDG**



No response to several different hormonal Rx's

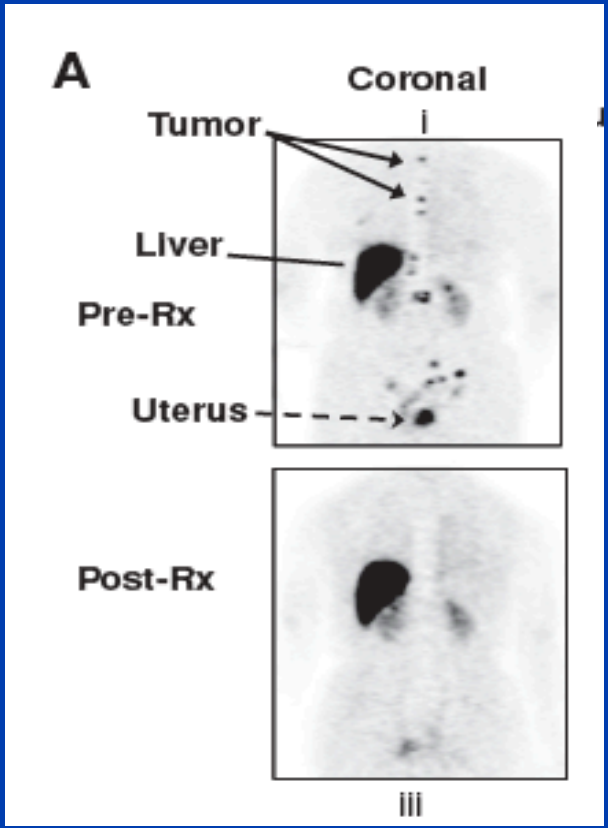
University of Washington

(Linden, J Clin Onc, 24:2793, 2006)

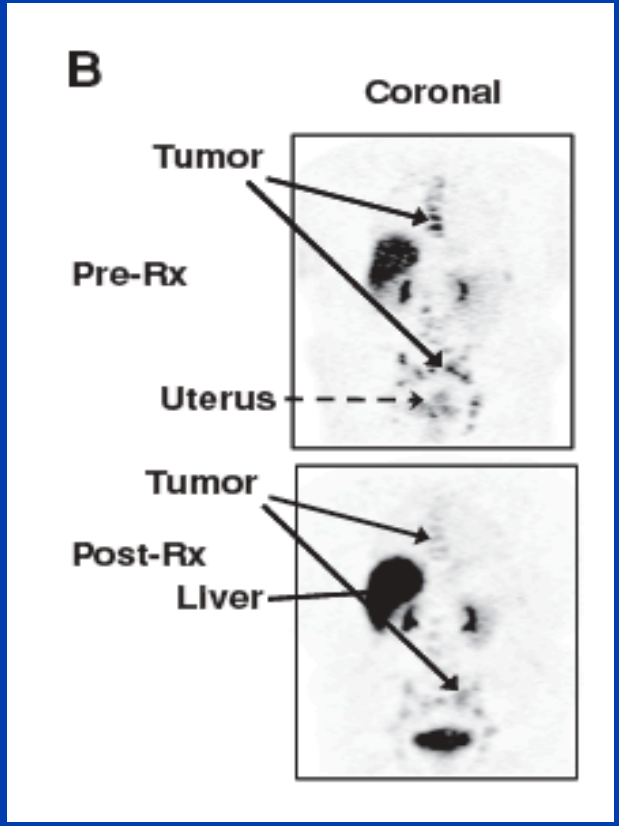
Serial FES PET Measures Endocrine Therapy Impact on Tumor Estrogen Binding

(Linden, Clinical Cancer Res, 17:4799, 2011)

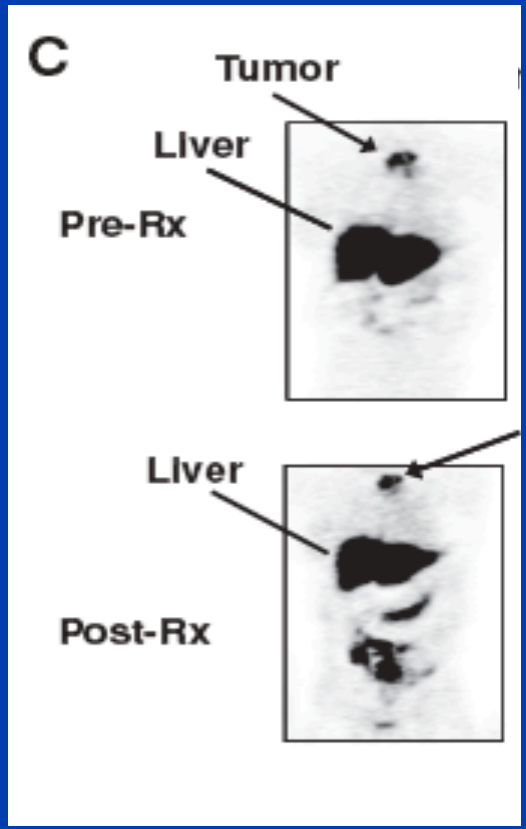
Tamoxifen
(blocks receptor)



Letrozole
(lowers estrogen)



Fulvestrant
(blocks receptor)

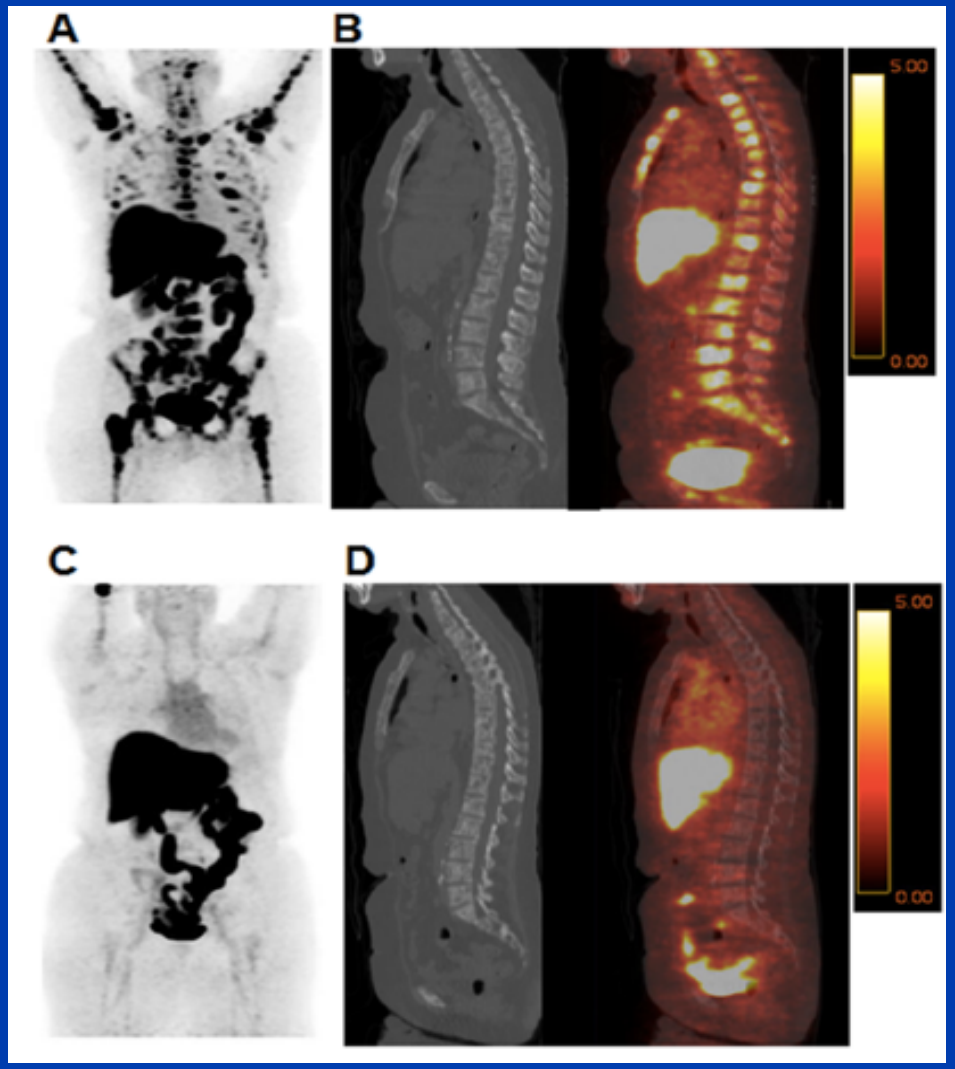


FES PET Applied to a New ER-Targeted Agent: Novel Estrogen Blocking Drug (SERD; ARN-810)

Yang, Clinical Cancer Res, epub, 2017

Pre-therapy

Post-ARN-810
(ER Blcoker)



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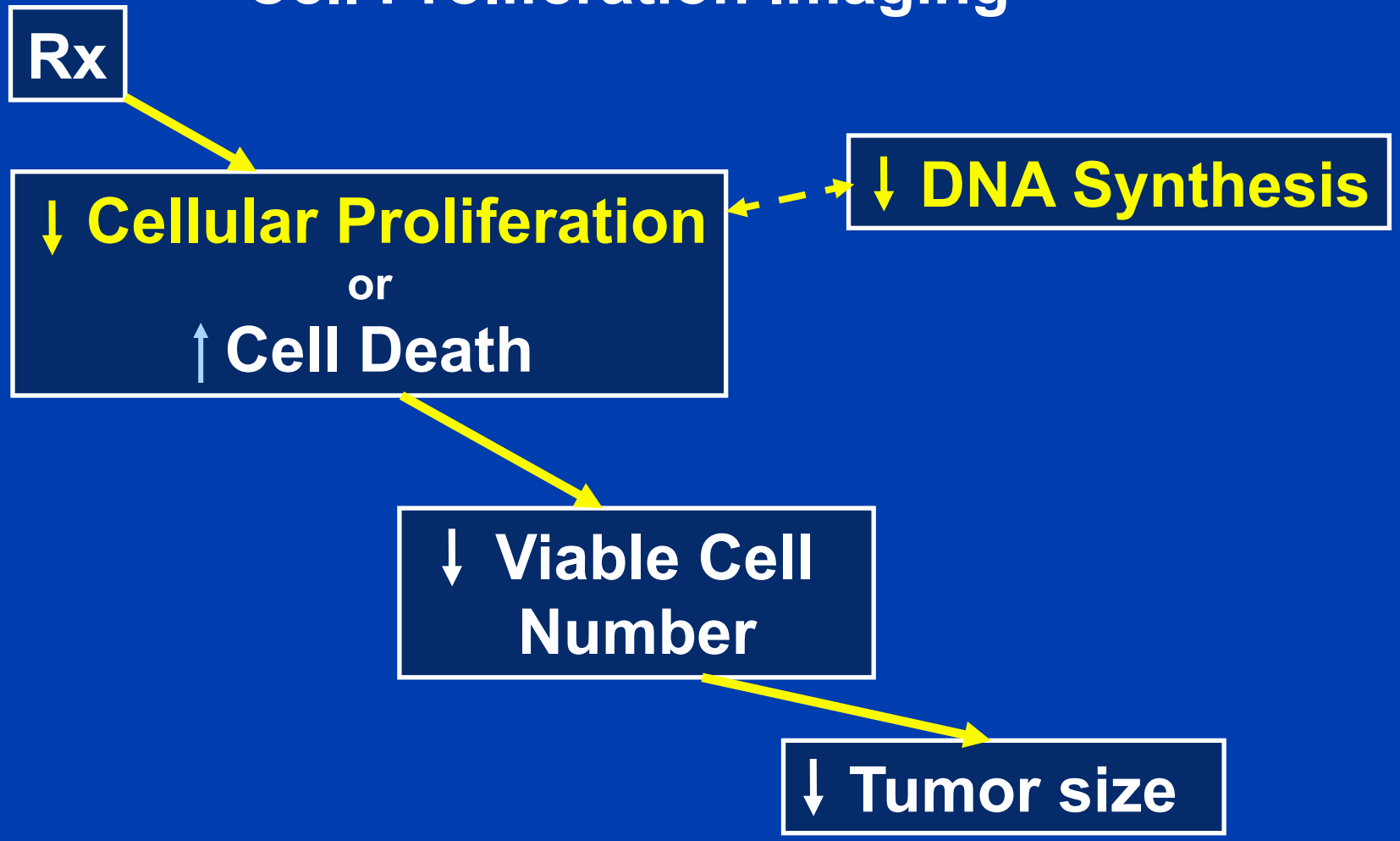
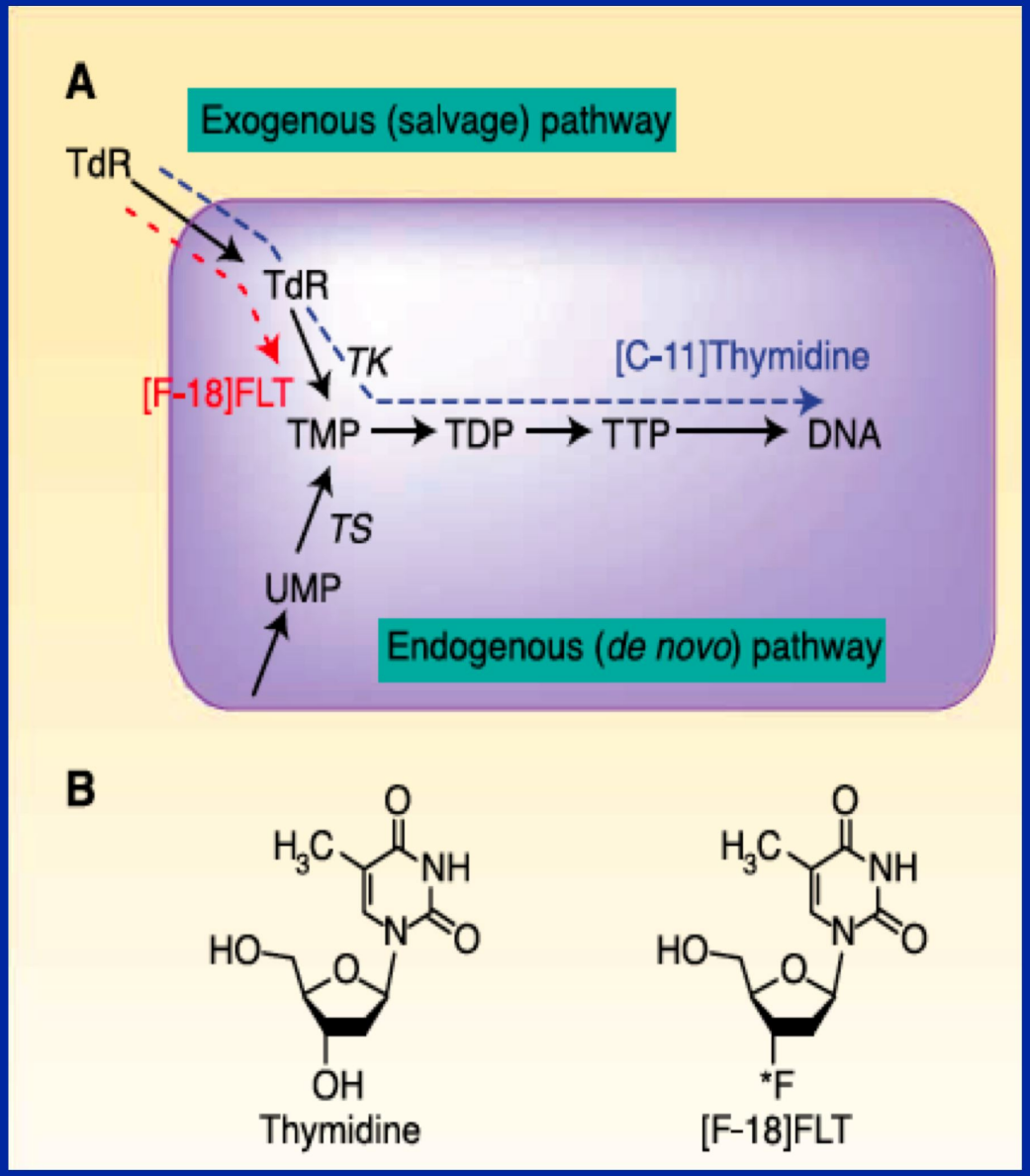
Biologic Events in Response to Successful Cancer Therapy

Rationale for Measuring Early Response by Cell Proliferation Imaging



Thymidine Incorporation Pathways

Imaging Tumor Proliferation



(Mankoff and Eary, Clin Cancer Res 14: 7159, 2008)

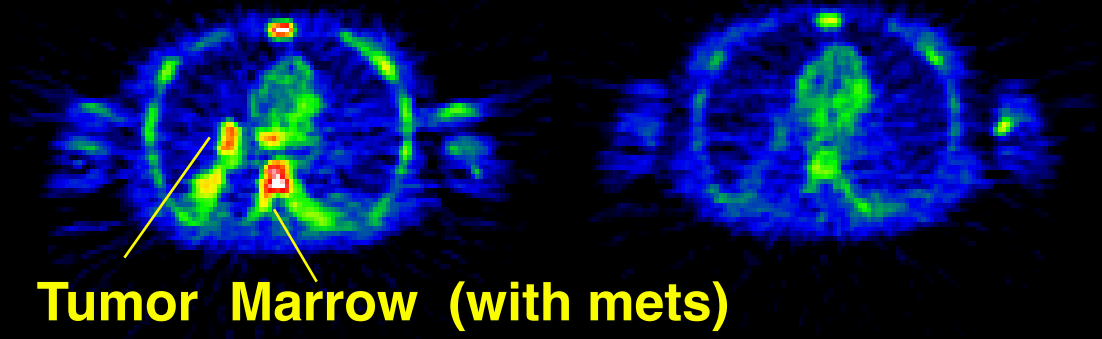
Small Cell Lung Cancer:

PET Imaging Pre-and Post One Cycle of Rx

Pre-Rx **Post-Rx**

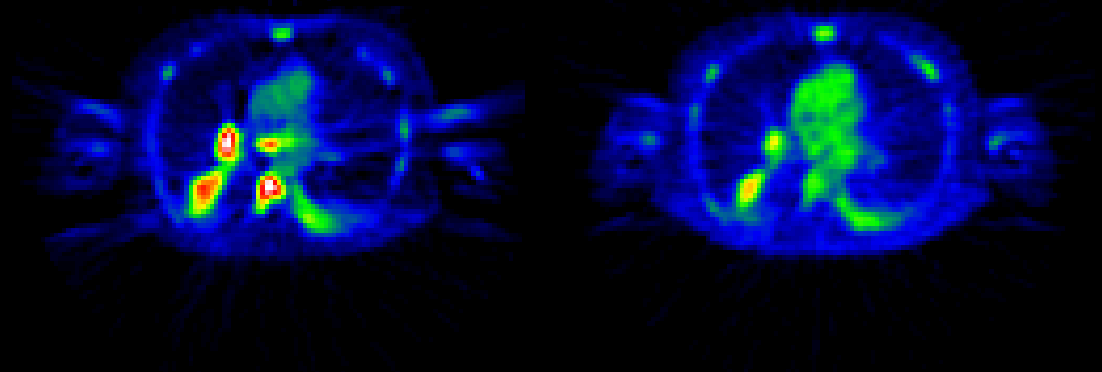
Thymidine

(proliferation)



FDG

(Glucose Metabolism)



7 days

(Shields, J Nucl Med, 1998)

Compartmental Model for 2-^{11}C-Thymidine (TdR)

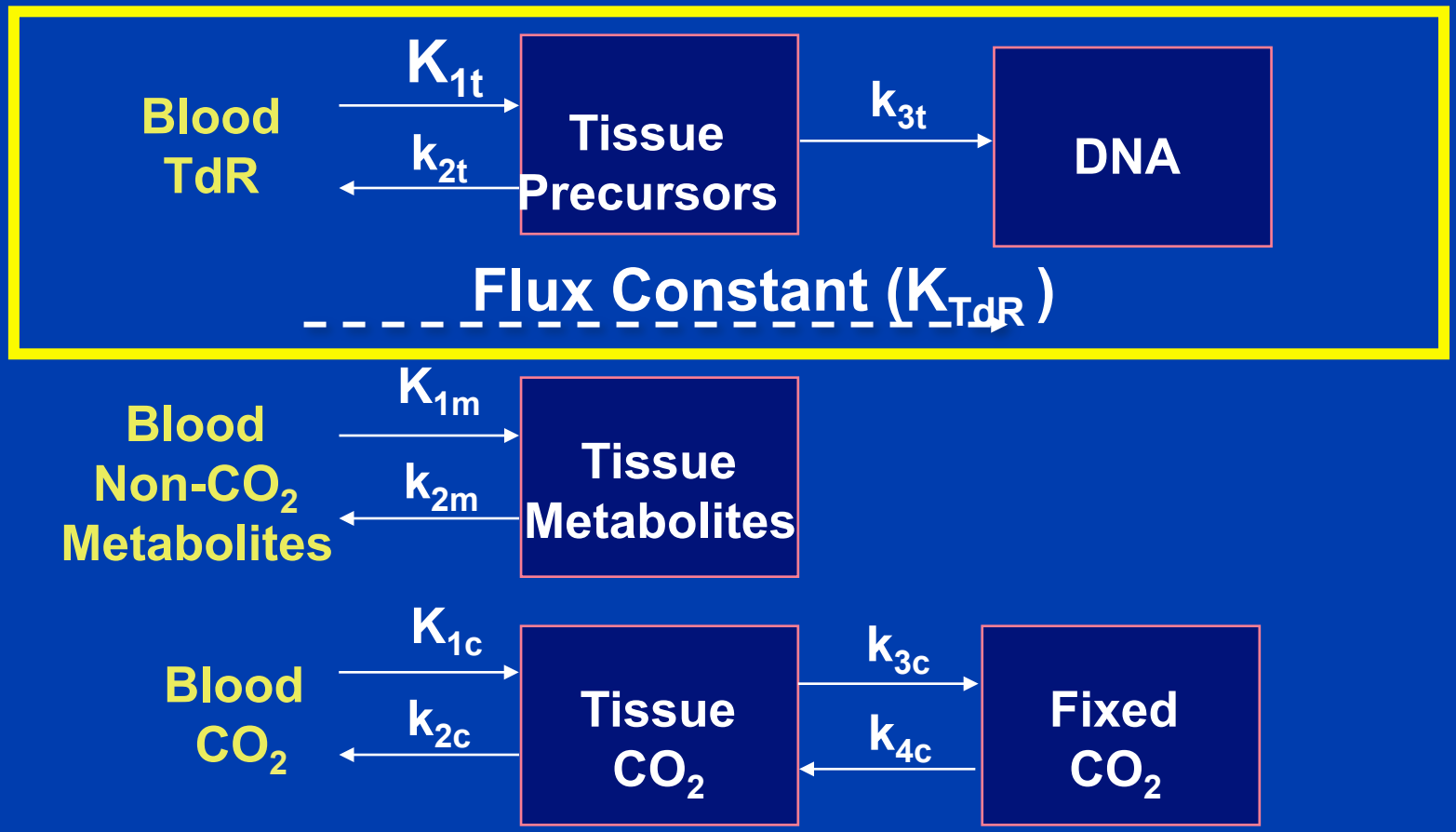


Image Total = Sum(Tissue Compartments) + V_b(Blood Total)

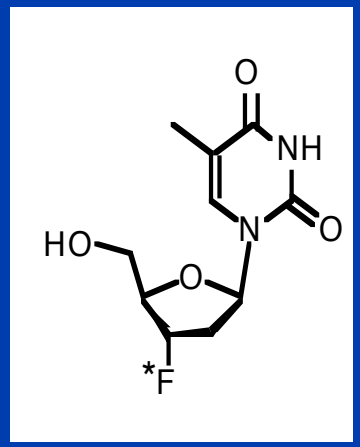
$$\text{Flux} = [\text{TdR}]K_{TdR} = [\text{TdR}]\frac{K_{1t}\,k_{3t}}{(k_{2t} + k_{3t})}$$

(Mankoff, J Nucl Med, 1998)

Thymidine Analogs for PET Cell Proliferation Imaging

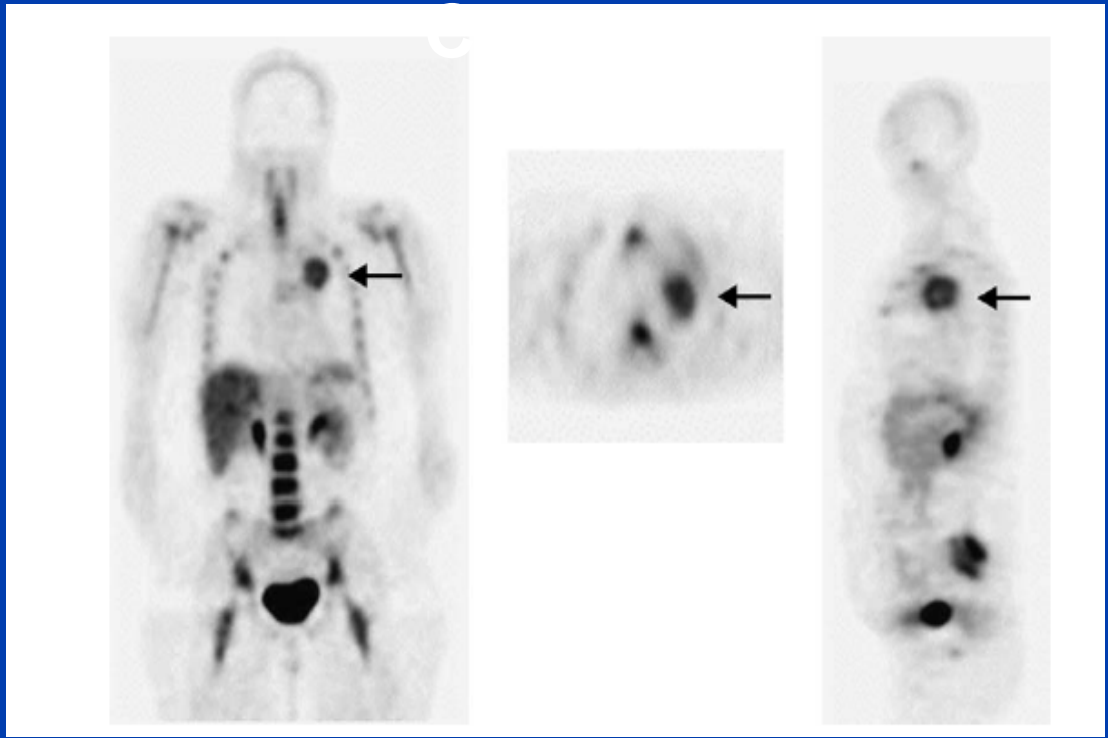
Clinically Feasible Isotope and Imaging Protocol

^{18}F-Fluoro-L-thymidine (FLT)



(Grierson, Nucl Med Biol 27:143, 2000)

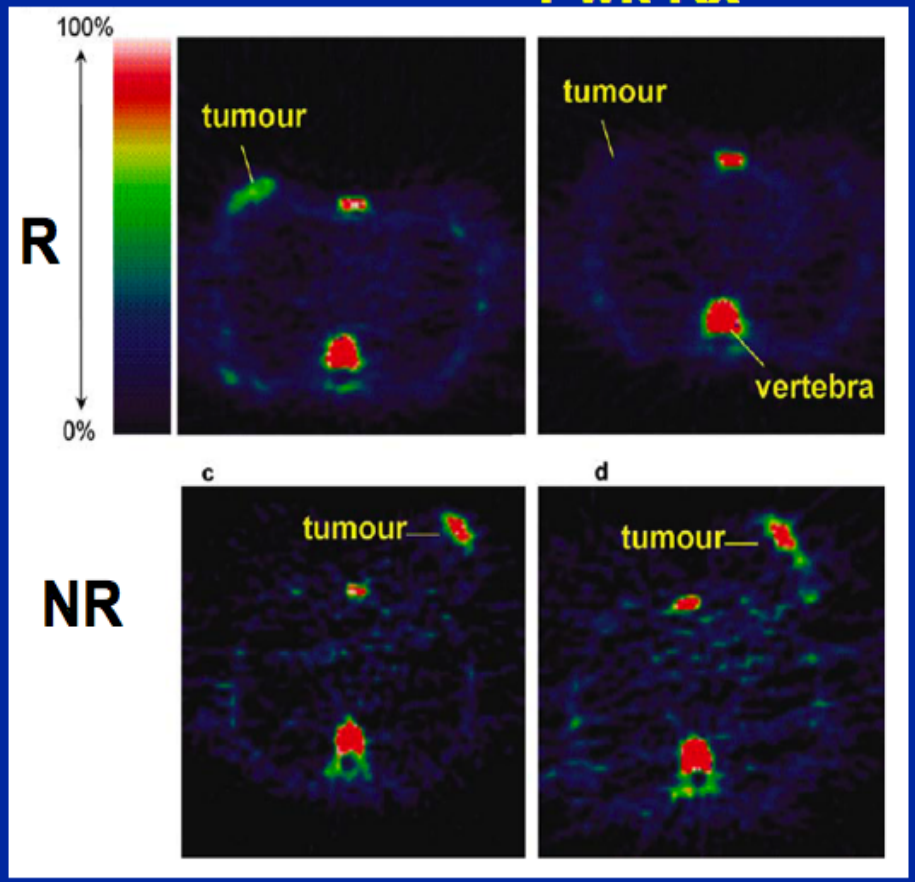
FLT PET Images of Lung



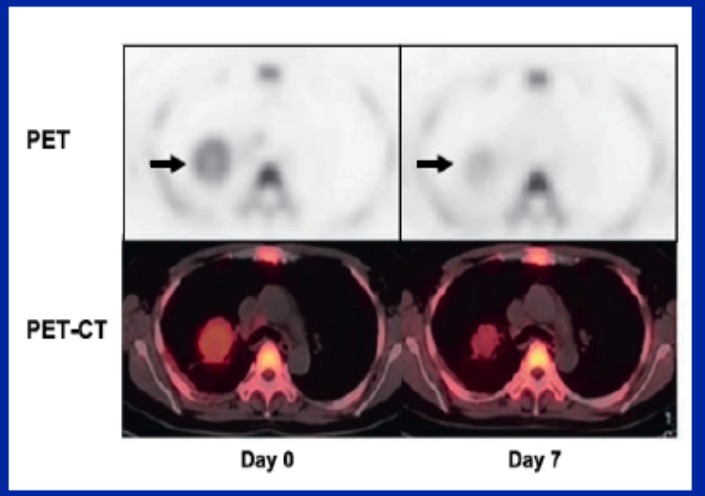
(Shields AF, from Mankoff, Shields, and Krohn, Rad Clin N Amer 43:153, 2005)

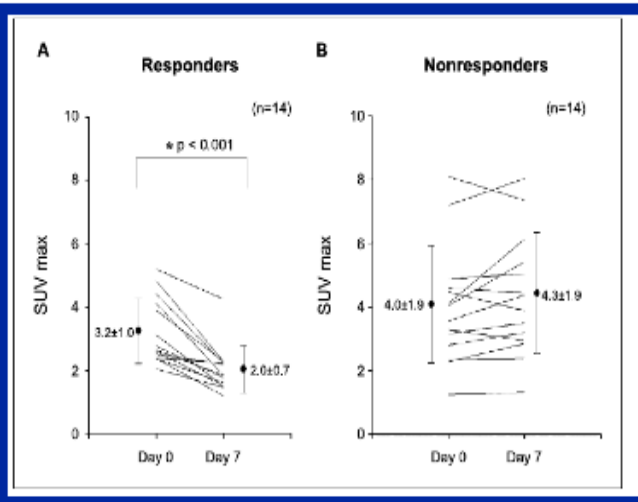
Early Response Measured by ^{18}F-fluorothymidine (FLT) PET

Breast CA, ChemoRx
(Kenny, EJNMMI 34:1339, 2007)

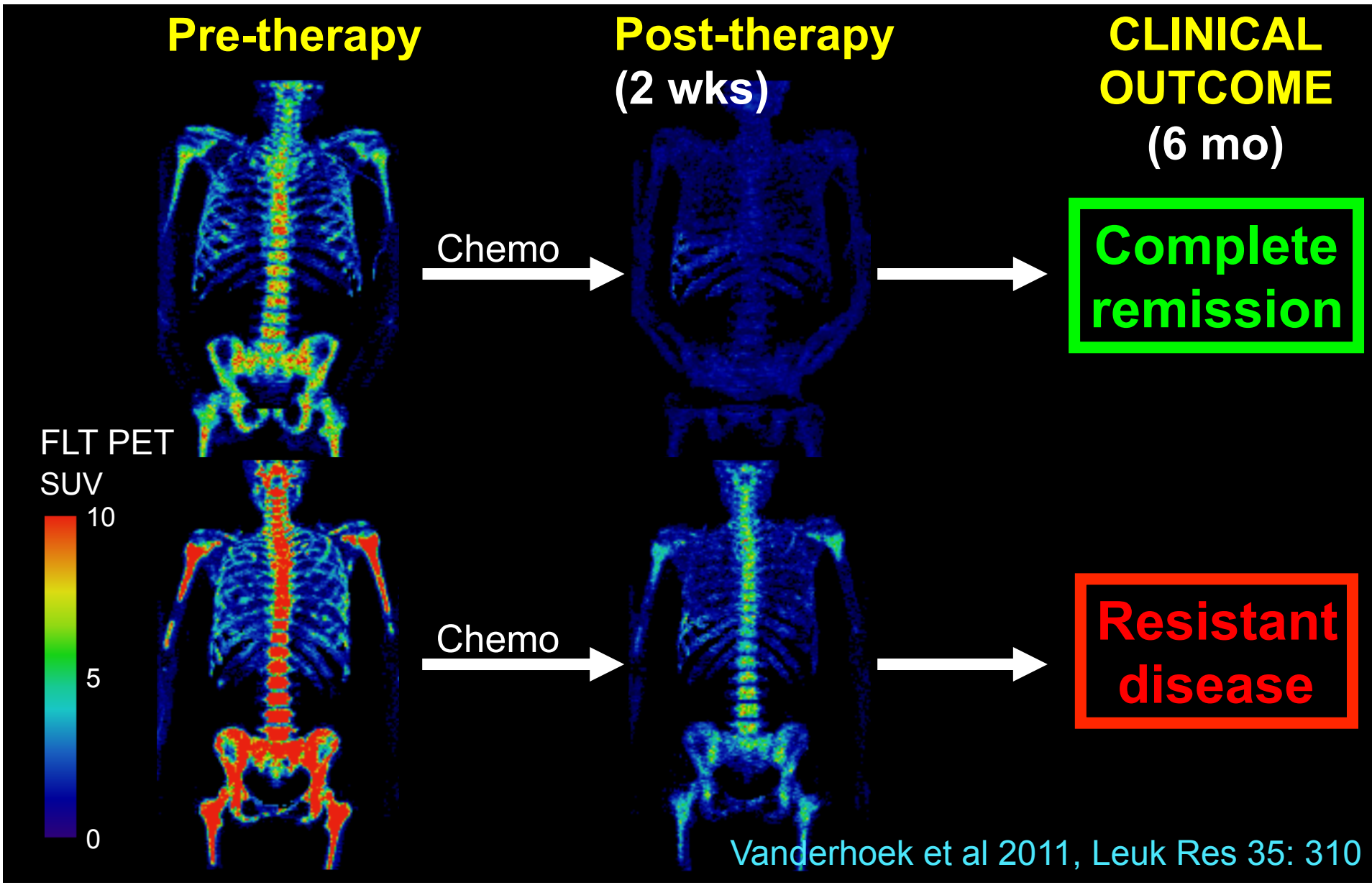


Lung CA, Genfitinib Rx
(Sohn, Clin Cancer Res 14: 7423, 2008)





FLT PET as a response biomarker



Vanderhoek et al 2011, Leuk Res 35: 310

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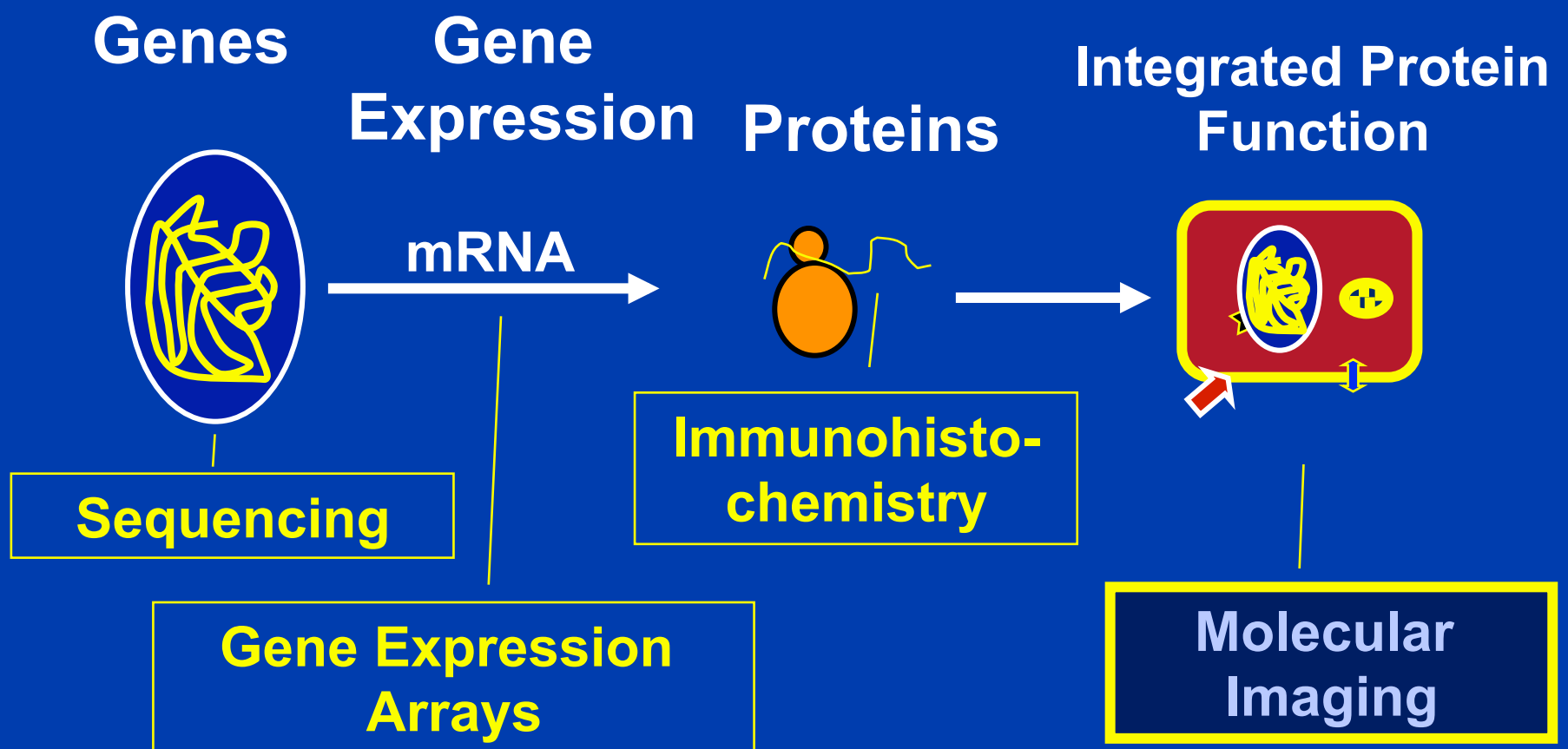
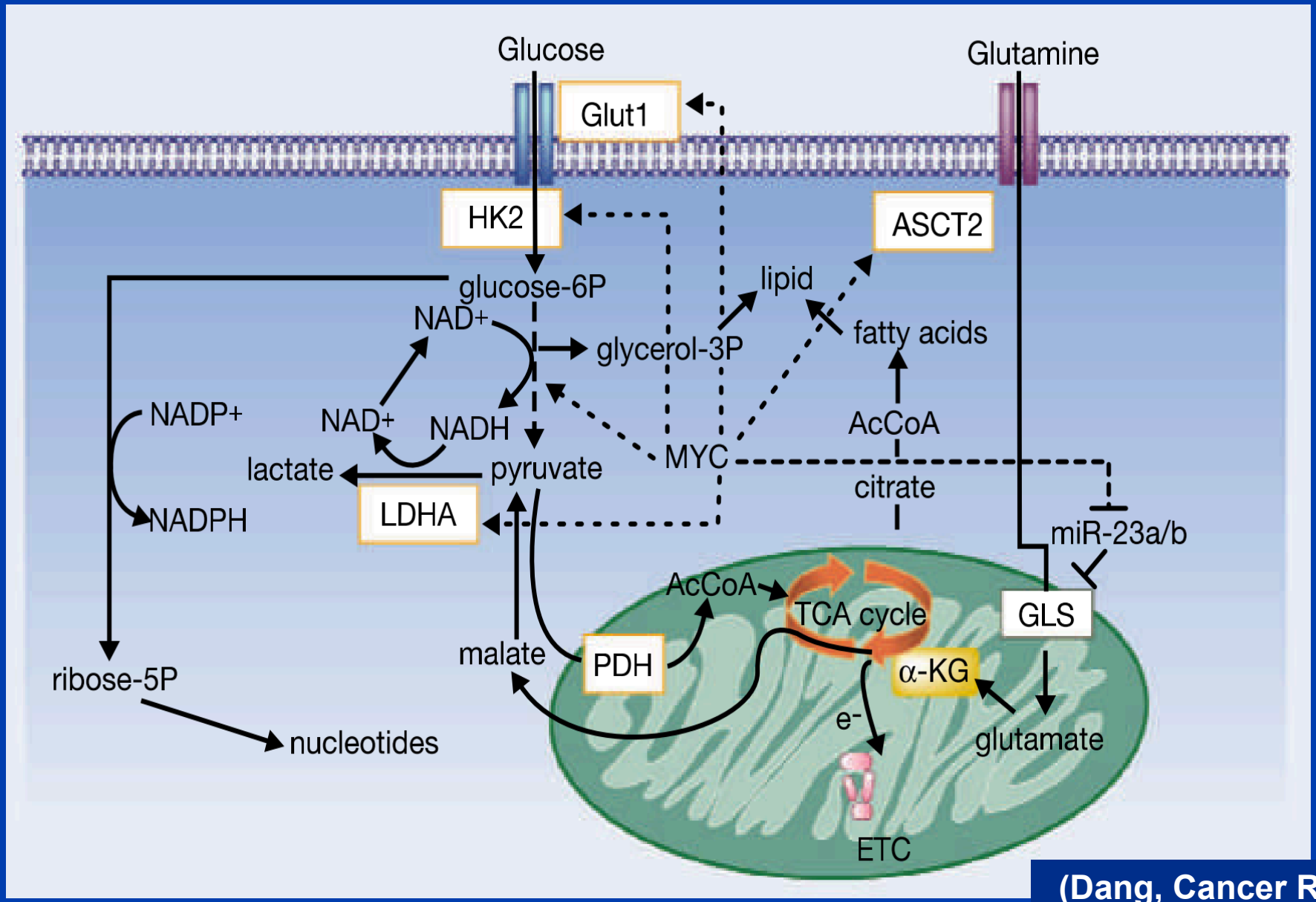
Molecular Imaging:
A Tool for Measuring In Vivo Cancer Biology



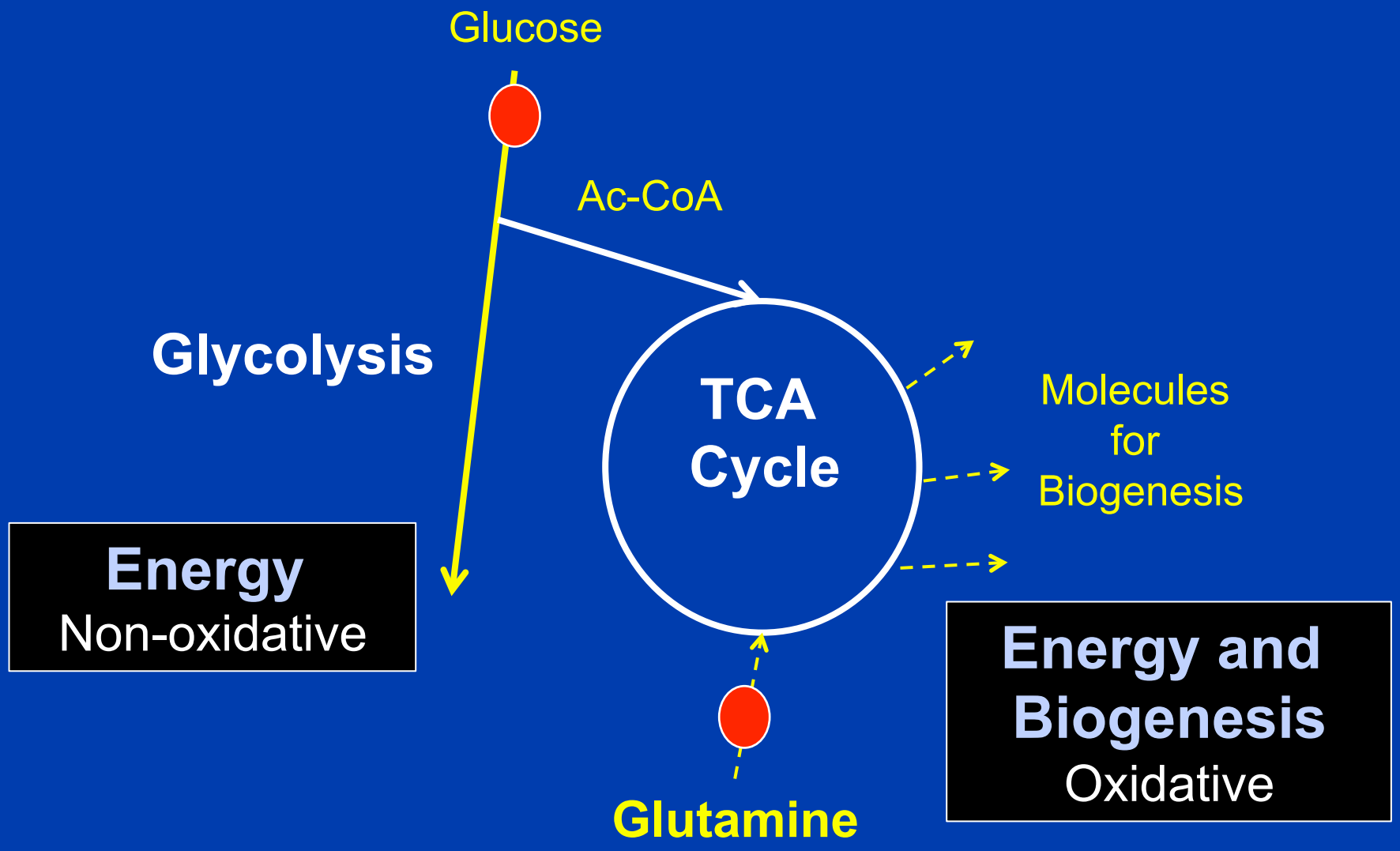
Simplified Cancer Metabolism Roadmap



(Dang, Cancer Res 70:859, 2010)

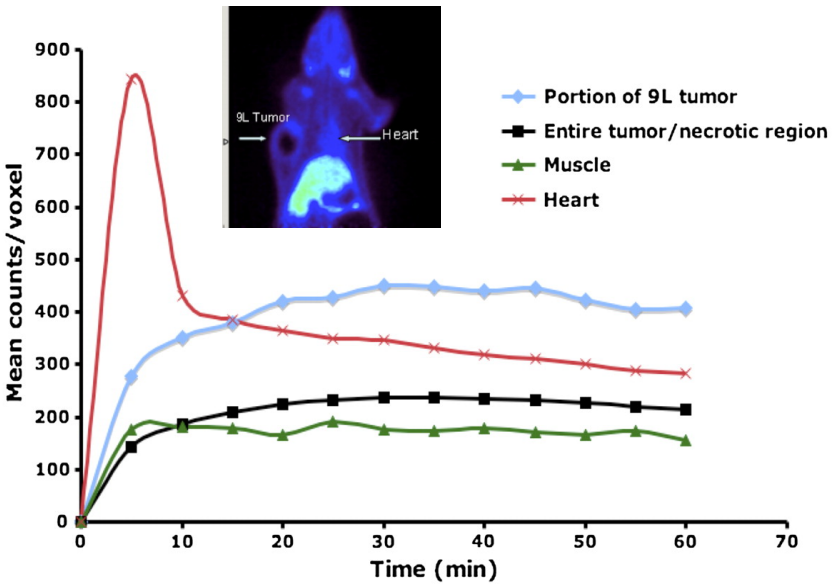
Energy Metabolism & Biogenesis

Aggressive Tumors Can Use Both Glutamine and Glucose as Fuel



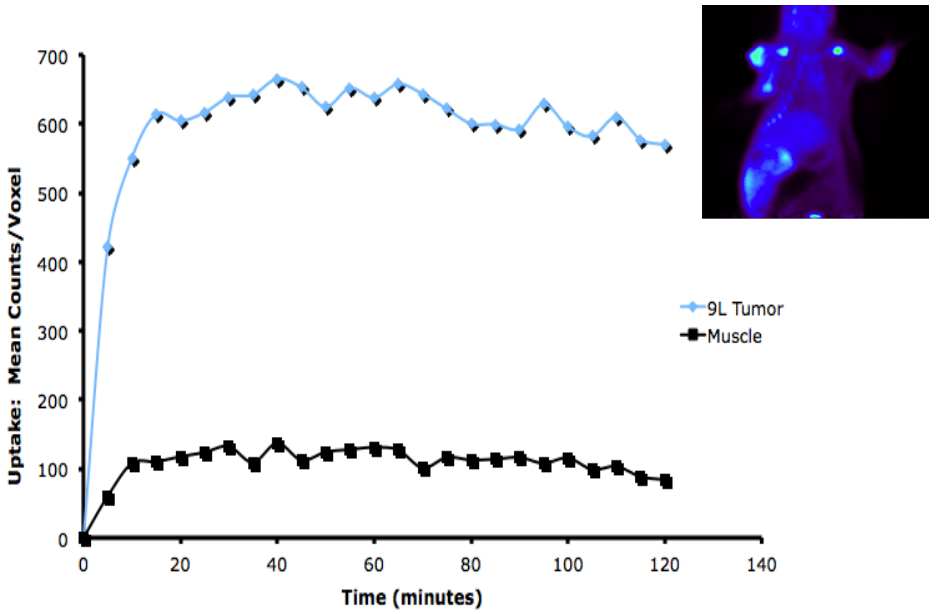
PET Tracer for Imaging Glutamine Metabolism
Pre-Clinical Studies in a Rat Brian Tumor Model

L-5-^{11}C-glutamine



(Qu, JNM 2012: 53; 98-105)

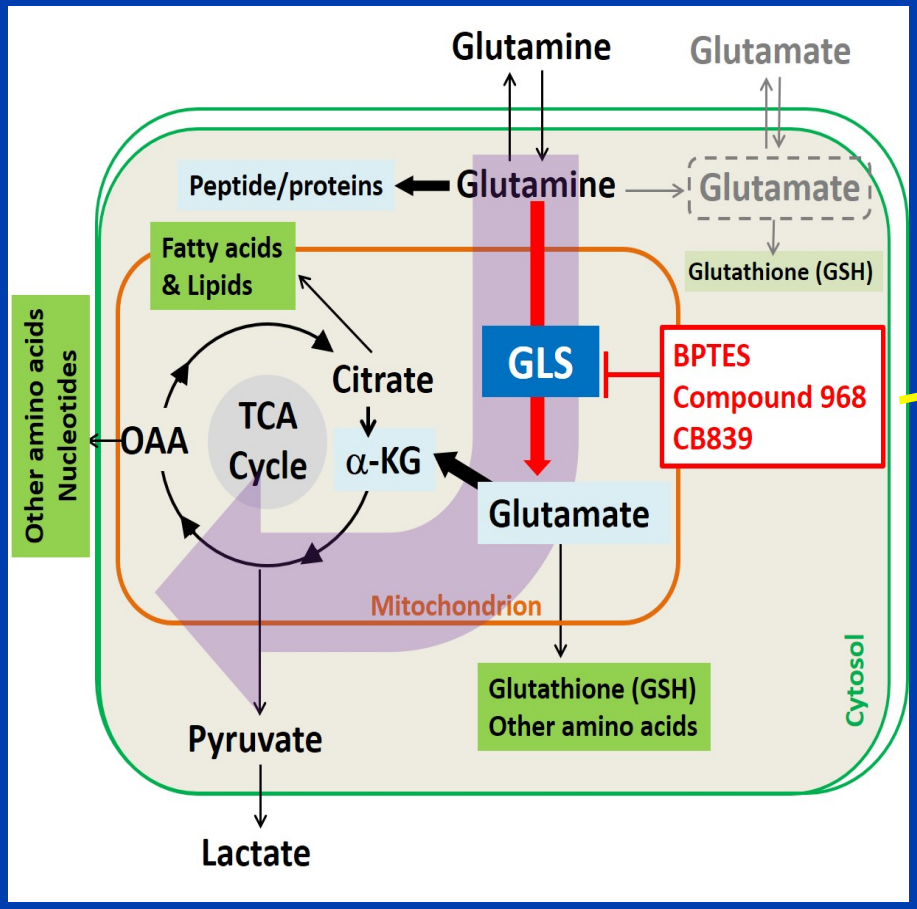
[^{18}F](2S,4R)-4F-Glutamine



(Lieberman, J Nucl Med 52:1947, 2011)

(courtesy of Hank Kung and Bob Mach, U Penn)

Glutamine Kinetics & Impact of Blocking Glutaminase (GLS)



Block GLS

Glutamine ↑

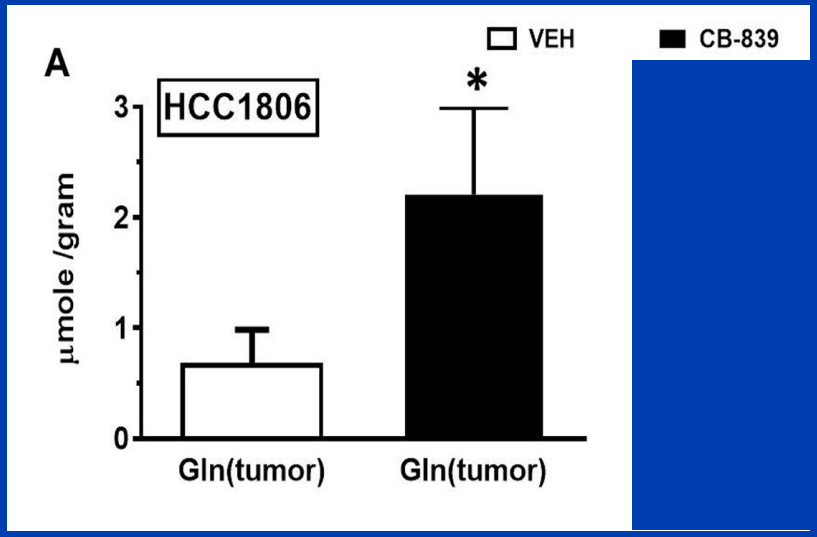
Glutamate ↓

Zhou, Pantel, Mankoff

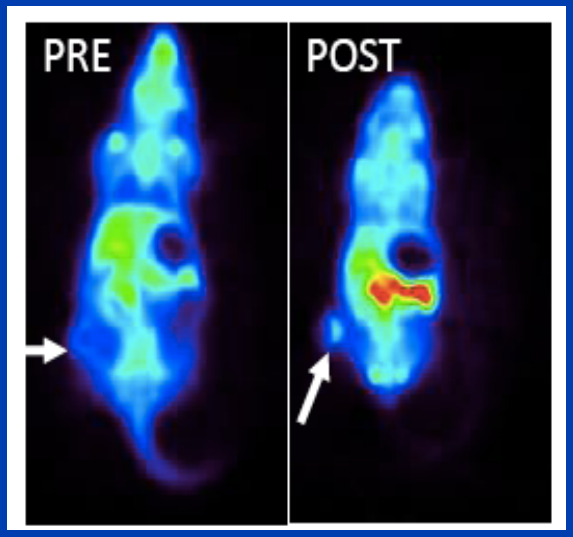
[^{18}F]Fluoroglutamine to Measure *GLS* Inhibition in a Breast Cancer Mouse Model

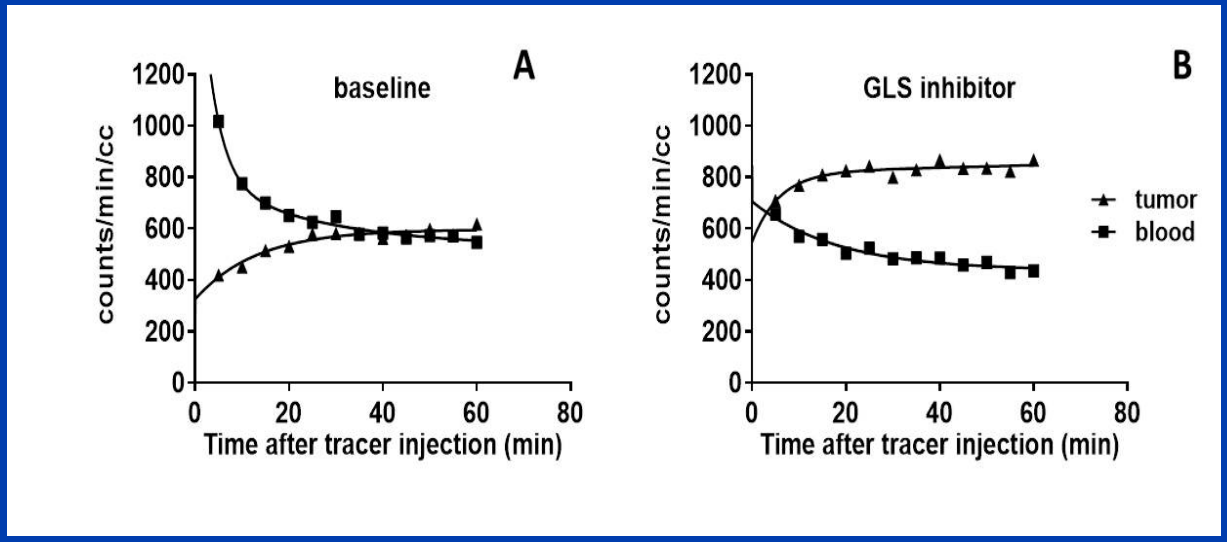
Zhou, Cancer Research, 2017

Glutamine Pool Size by ^{1}H NMR



[^{18}F]Fluoroglutamine PET Uptake





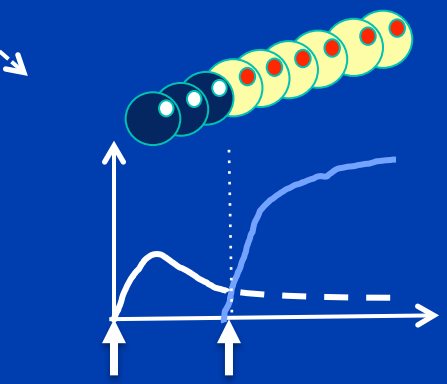
Imaging Glutamine and Glucose Metabolism in a Single Imaging Session

NIH R33CA225310 (Cancer Moonshot Program)

Large-Volume PET Tomograph

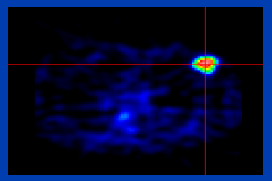
Dual Tracer injection

Dynamic Imaging



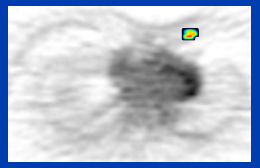
Segmentation and Mixture Analysis

Parametric Images (Glutamine/Glucose Ratio)



Regional Quantitative Biology

Feature Extraction



Biologic Heterogeneity

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