

# Advancement in Personalized Imaging

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# Disclosure

- Avid Radiopharmaceuticals: consultant
- Navidea Radiopharmaceuticals: consultant
- Bayer Radiopharmaceuticals: consultant

# Objectives of this talk

- To understand the advantages and limitations of clinical radiotracer imaging
  - Radiotracer principle limits mass to be <1% of normal physiologic conditions
    - No pharmacologic effects should take place
    - Requires high affinity radioligands ( $K_d$  in nmolars or lower)
  - Novel technology such as CZT (for SPECT) and PET/MRI scanners
    - Still being validated in attenuation correction and texture density representation
  - Digital PET technology from Philips
    - High sensitivity and resolution

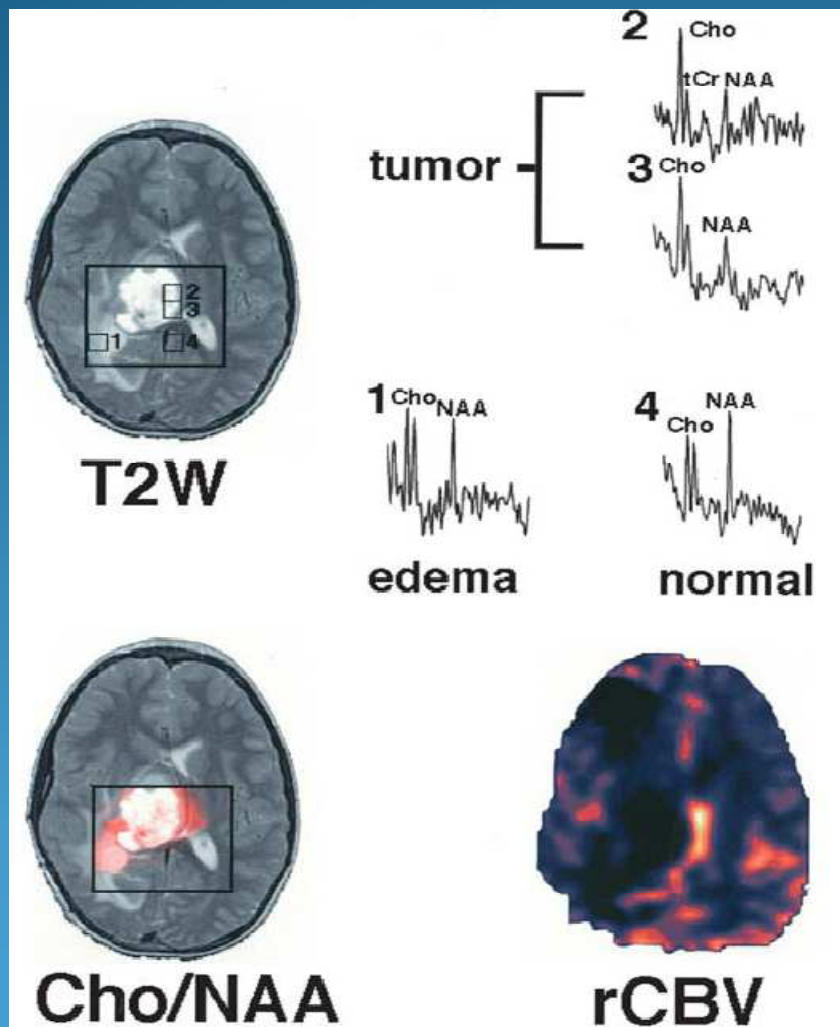
# Objectives of this talk (cont'd)

- What are the steps necessary for advancement
  - Development of new radioligands
    - translation of histopathologic staining into non-invasive clinical imaging
    - Validation with clinical outcome
      - Take years, maybe decades (e.g. FDG, choline for prostate CA)
- What else can we do?
  - New clinical applications of known radiotracers
    - Integrate old knowledge with new questions and challenges
- Given the limited time, can only sample some of the not so mainstream pre- and clinical efforts

# MRS Imaging in brain tumors

- Common metabolites used as biomarkers:
  - Reduced or absent: N-acetyl-aspartate (NAA) and total creatine (tCr) attributed to edema and necrosis
    - Only significant independent predictor of active tumor growth is tCr
  - increased: choline (Cho) reflecting cellular proliferation, altered phospholipid metabolism, and lactate due to metabolic acidosis
    - Cho peak includes water soluble Cho compounds, including phosphocholine (PCho), glycerophosphocholine (GPC), and free choline
- NAA in childhood tumors may reflect immature oligodendroglia

# 8 year-old male with right thalamic anaplastic astrocytoma using T2 weighted MR image

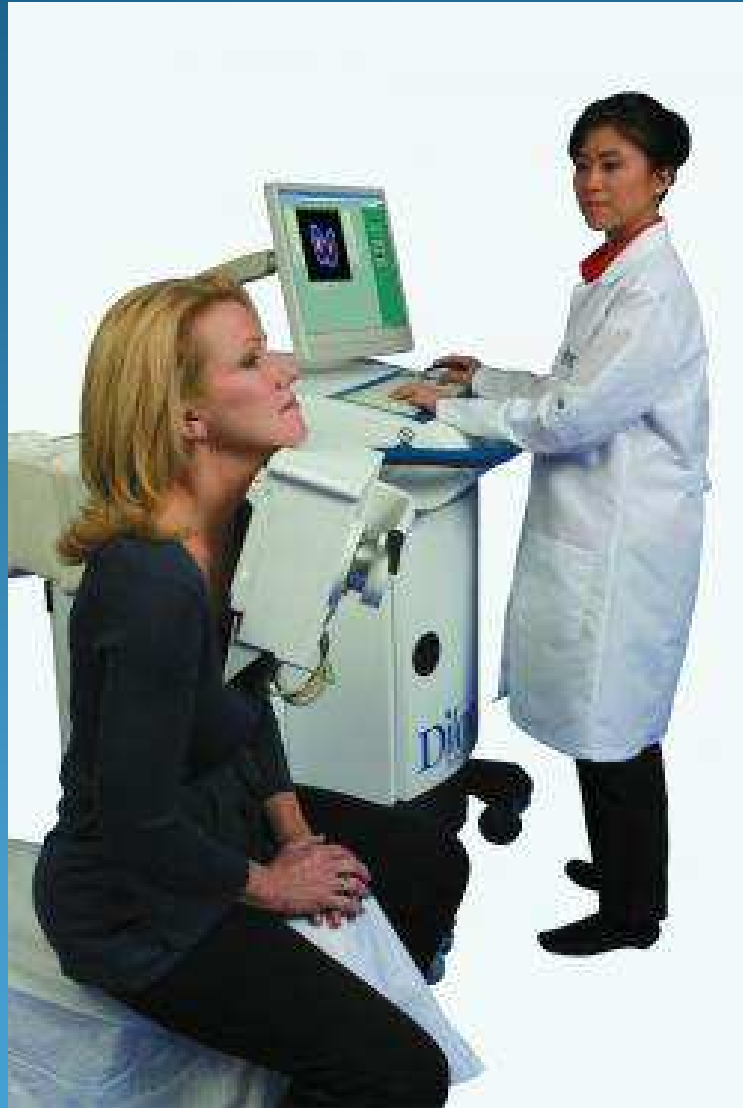


A Tzika *Intern J Oncol*  
32:517-526, 2008

# Breast specific $\gamma$ -camera

- 33 women with surgically proven DCIS had mammography and  $^{99m}\text{Tc}$ -tetrofosmin (740 MBq/20 mCi)
  - CZT (cadmium zinc telluride semiconductor) detector
  - Intrinsic spatial resolution = 1.6 mm
- Scintigraphy sensitivity in low-intermediate-grade DCIS is 100% (n=9) vs 91.3% in intermediate-high grade (n=24, NS)
- Scintigraphy demonstrated extent of disease better than mammography with microcalcifications (preoperatively)
- Overall, sensitivity between scintigraphy and mammography was not statistically significant

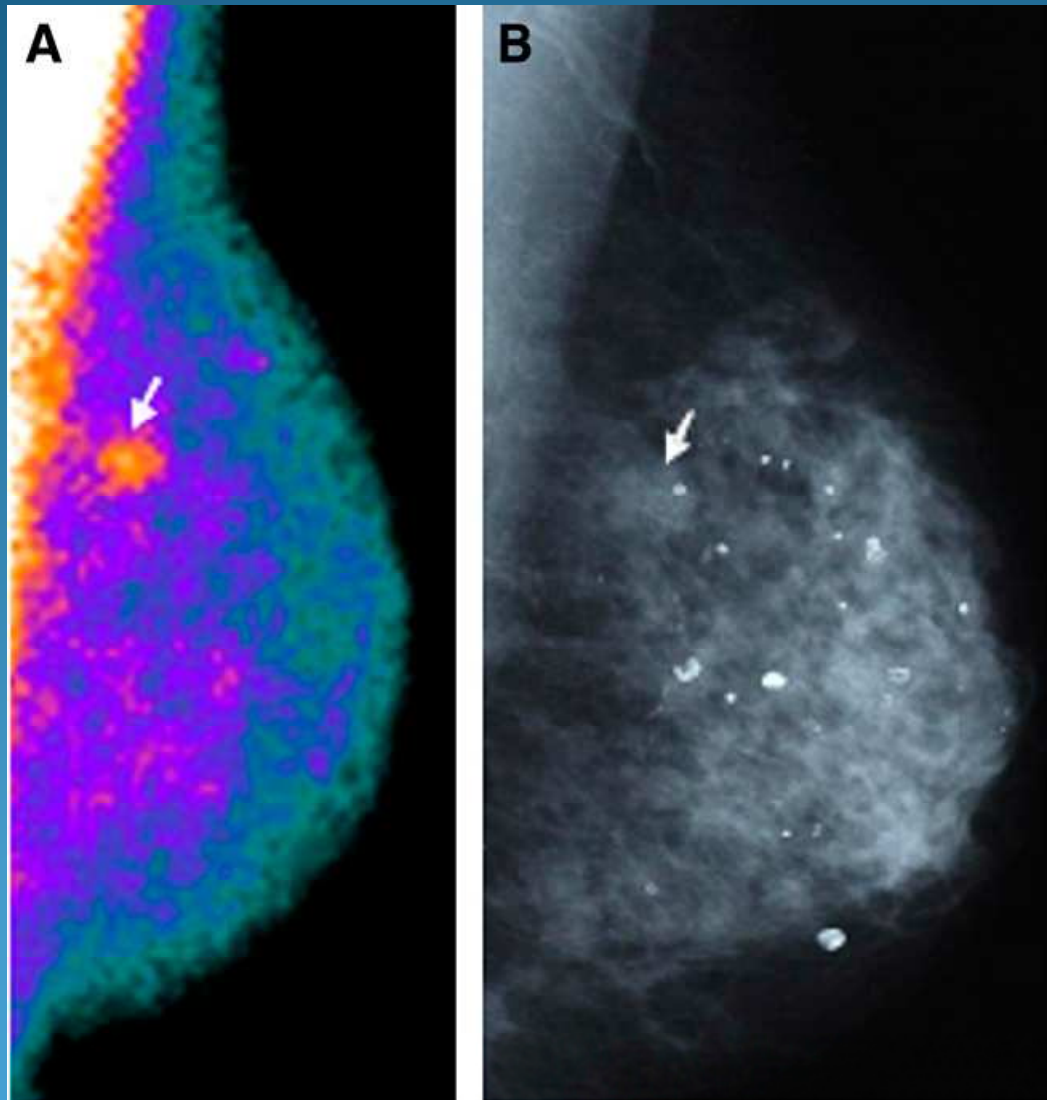
# Breast specific $\gamma$ -imaging (BSGI)



Imaging Technology News,  
May 15, 2013

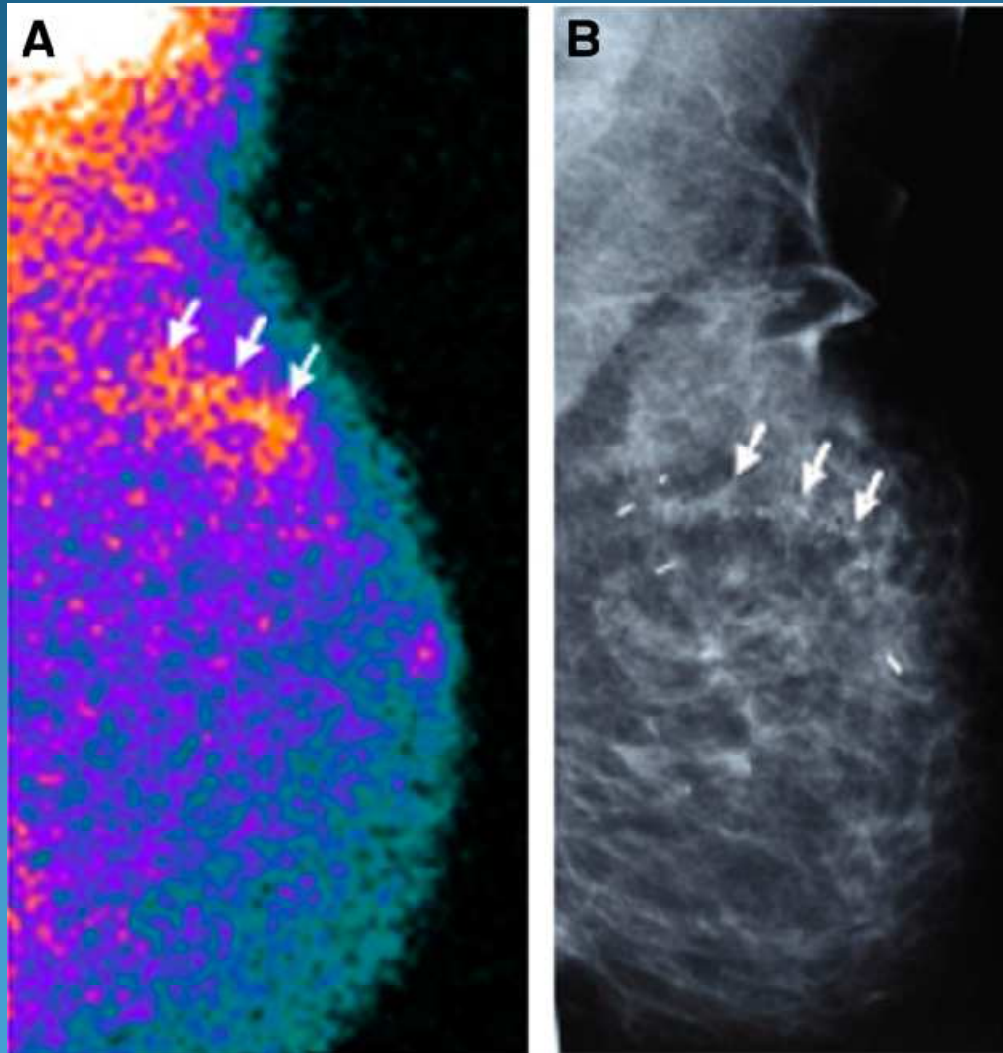


75 year-old female with intermediate-grade papillary-type DCIS (8 mm) also seen on mammography (B)



A Spanu et al. *JNM*  
53(10):1528-1533, 2012

52 year-old female with high-grade comedo-type DCIS as scattered microcalcifications



A Spanu et al. JNM  
53(10):1528-1533, 2012

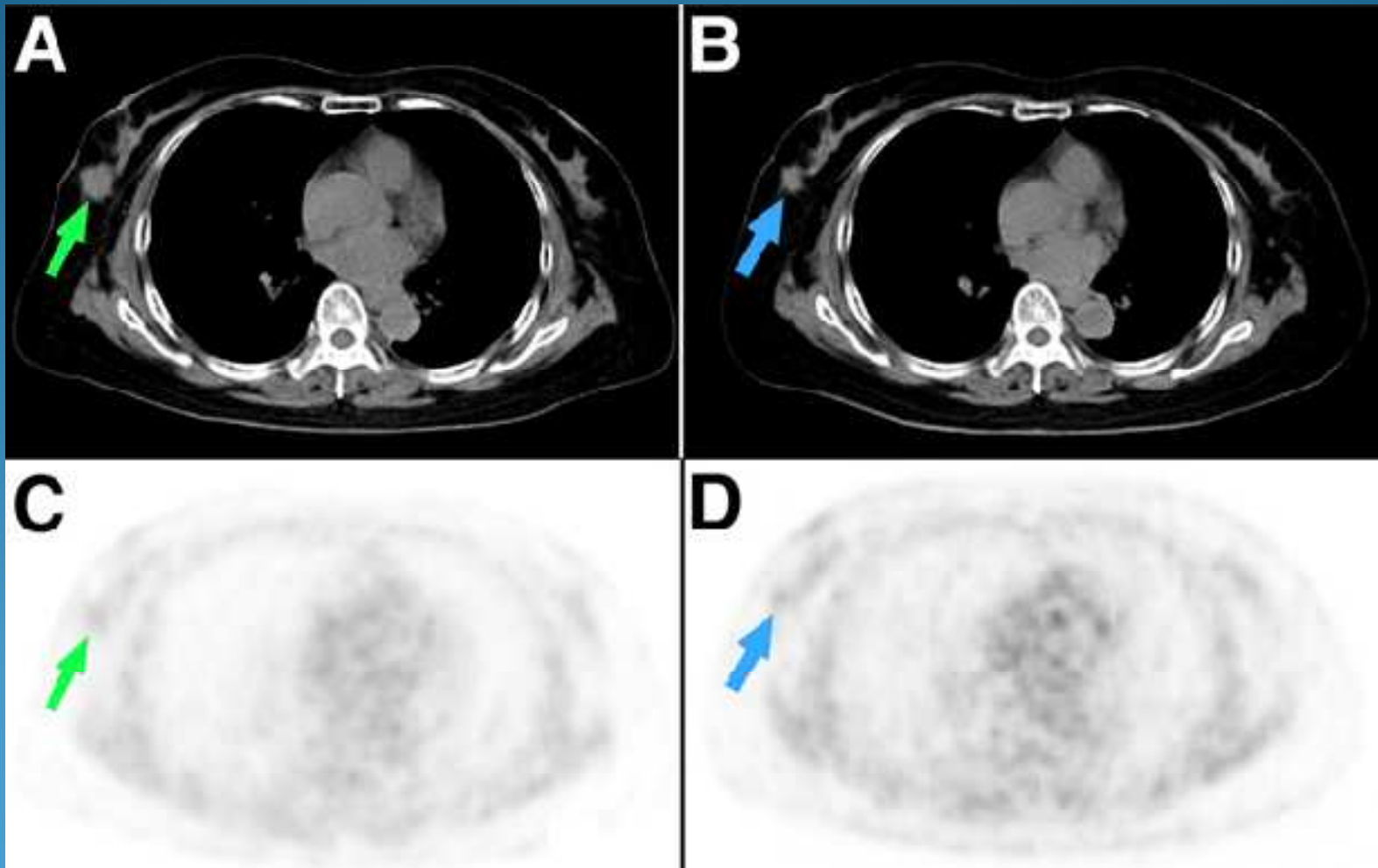
# $^{18}\text{F}$ -Fluoromisonidazole imaging

- $^{18}\text{F}$ -FMISO PET/CT imaging has been used to assess hypoxia (370 MBq/10 mCi)
  - Hypoxia significantly reduces growth effects of E2 and the inhibitory effects of anti-estrogen receptors (Kurebayashi et al, *Jpn J Cancer Res* 92:1093-1101, 2001)
- Hypoxia induced factor (HIF-1 $\alpha$ ) associated with resistance to treatment (Generali et al, *Clin Cancer Res* 12:4562-4568, 2006)
- Pharmacokinetics of FMISO is poor and via diffusion with mean tumor-to-background ratios of 1.15 (SUVavg 1.85) at 2 hours and 1.22 (SUVavg 1.80) at 4 hours
  - 20 post-menopausal female patients with ER- $\alpha^+$  stage II-IV breast cancers (J Cheng et al, *JNM* 54:333-340, 2013)

65 year-old female with R-breast primary using  $^{18}\text{F}$ -FMISO pre and post 3 mo tx with Letrozol (JNM, 2013)

Pre

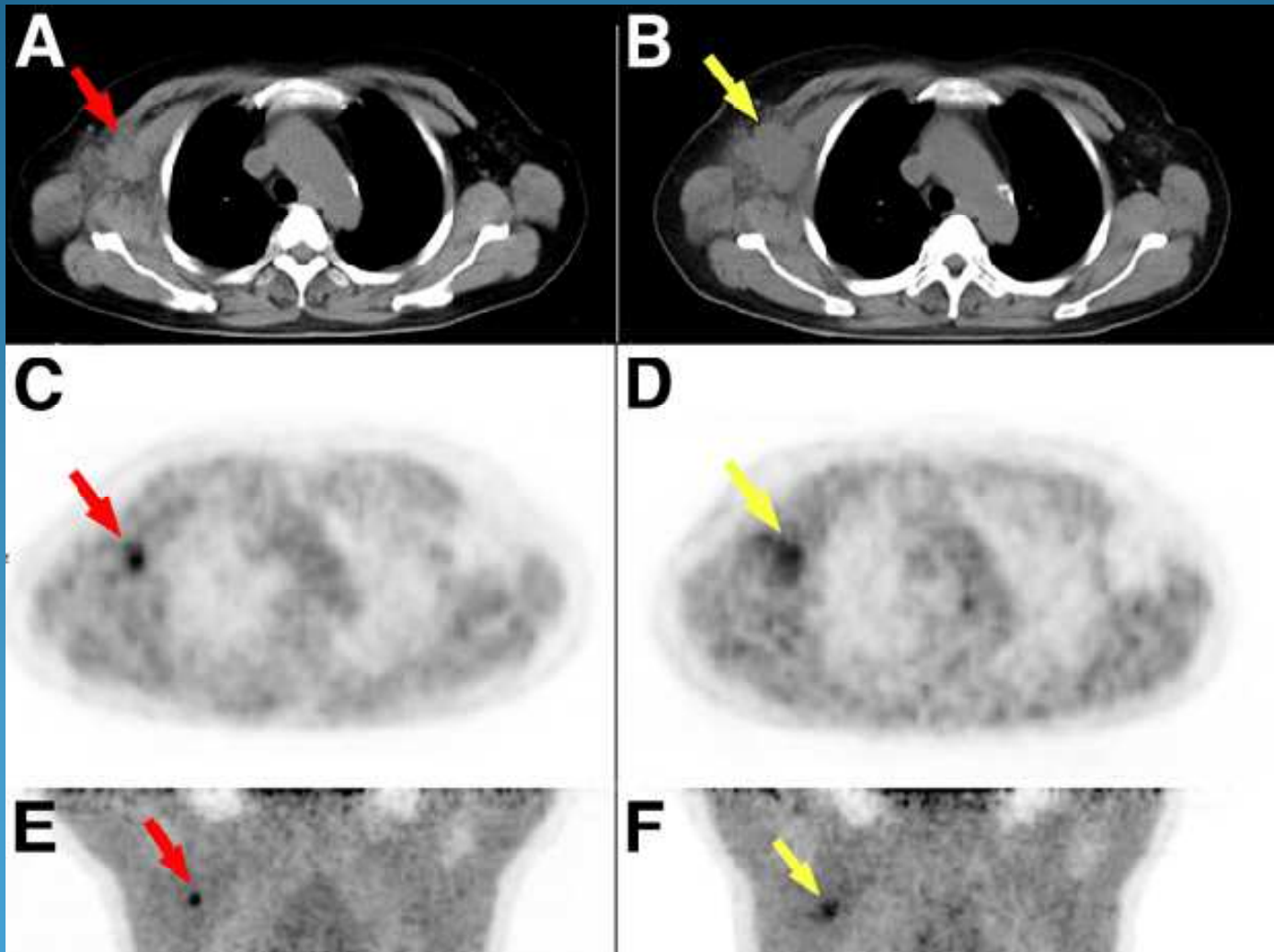
Post



58 year-old female with R-axillary LN using  $^{18}\text{F}$ -FMISO pre- and post 3 mo tx with Letrozol (JNM 2013)

Pre

Post



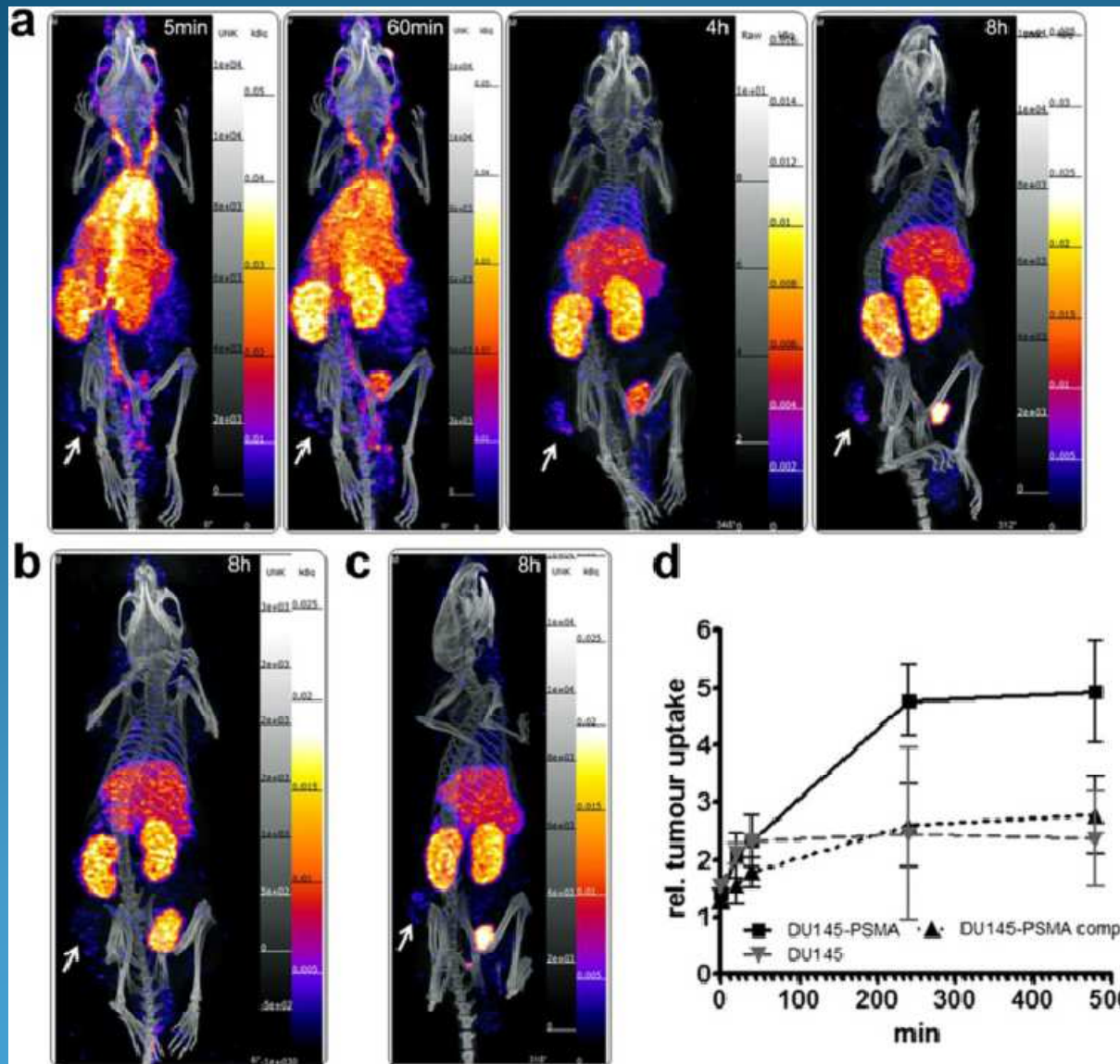
# Prostate Specific Membrane Antigen (PSMA) imaging

- <sup>111</sup>In-Prostascint (Capromab) is a murine monoclonal anti-PSMA within cytoplasmic domain
  - Pharmacokinetics is slow with low tumor-to-background ratio
- PSMA present in neovasculature of gastric and colorectal adenocarcinomas (Haffner et al, *Human Path* 40:1754-1761, 2009)
- PSMA present in neovasculature of (clear cell) renal cell carcinoma (Baccala et al, *Urology* 70:385-390, 2007)
- Humanized J591 (mAb) is directed against extracellular epitope of PSMA
  - Usage limited by slow pharmacokinetics

# PSMA imaging using diabody

- J591C is bivalent homodimeric  $V_H$ - $V_L$  domains with added cysteine at or near the C-terminus for stability
  - Connected by 5-8 amino acid linker
  - Intermediate size of 55kDa
  - Relatively rapid circulation, tissue penetration and systemic clearance
- $^{99m}\text{Tc}$  is directly chelated by tricarbonyl moiety (His)<sub>6</sub>-tag

# $^{99m}\text{Tc}$ -J591Cdia Imaging



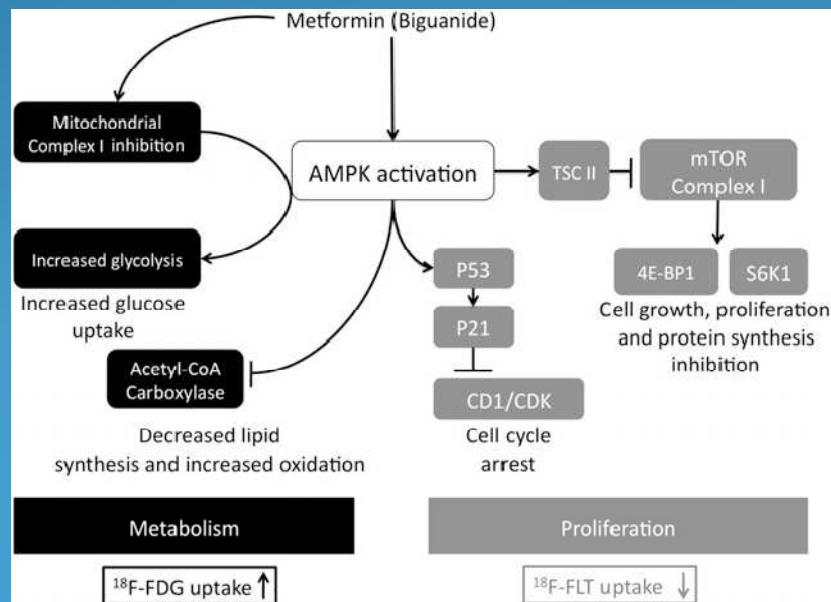
- a) Serial imaging with DU145-PSMA tumor
- b) PSMA-negative DU145 tumor
- c) PSMA-positive DU145 tumor plus 20X cold competition
- d) Time-activity curves

Kampmeier et al, *EJNMMI Res* 4:13, 2014



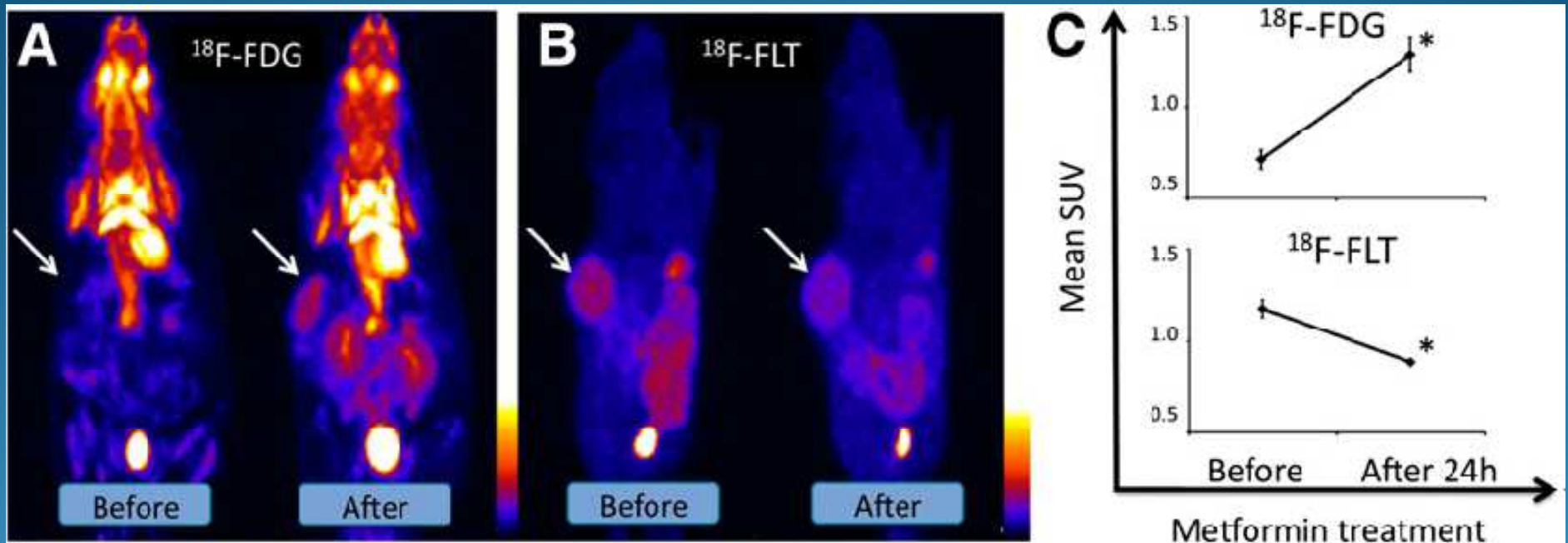
# Metformin as adjunct therapy

- Metformin (MET) is an adenosine monophosphate-activated protein kinase (AMPK) activator
  - commonly used in the treatment of diabetes
  - can improve progression-free survival of patients with multiple cancers
- AMPK may have opposite effects on glucose uptake versus proliferation



Habibollahi et al,  
*JNM* 54:252-258, 2013)

# $^{18}\text{F}$ -FDG versus $^{18}\text{F}$ -FLT effects of Metformin

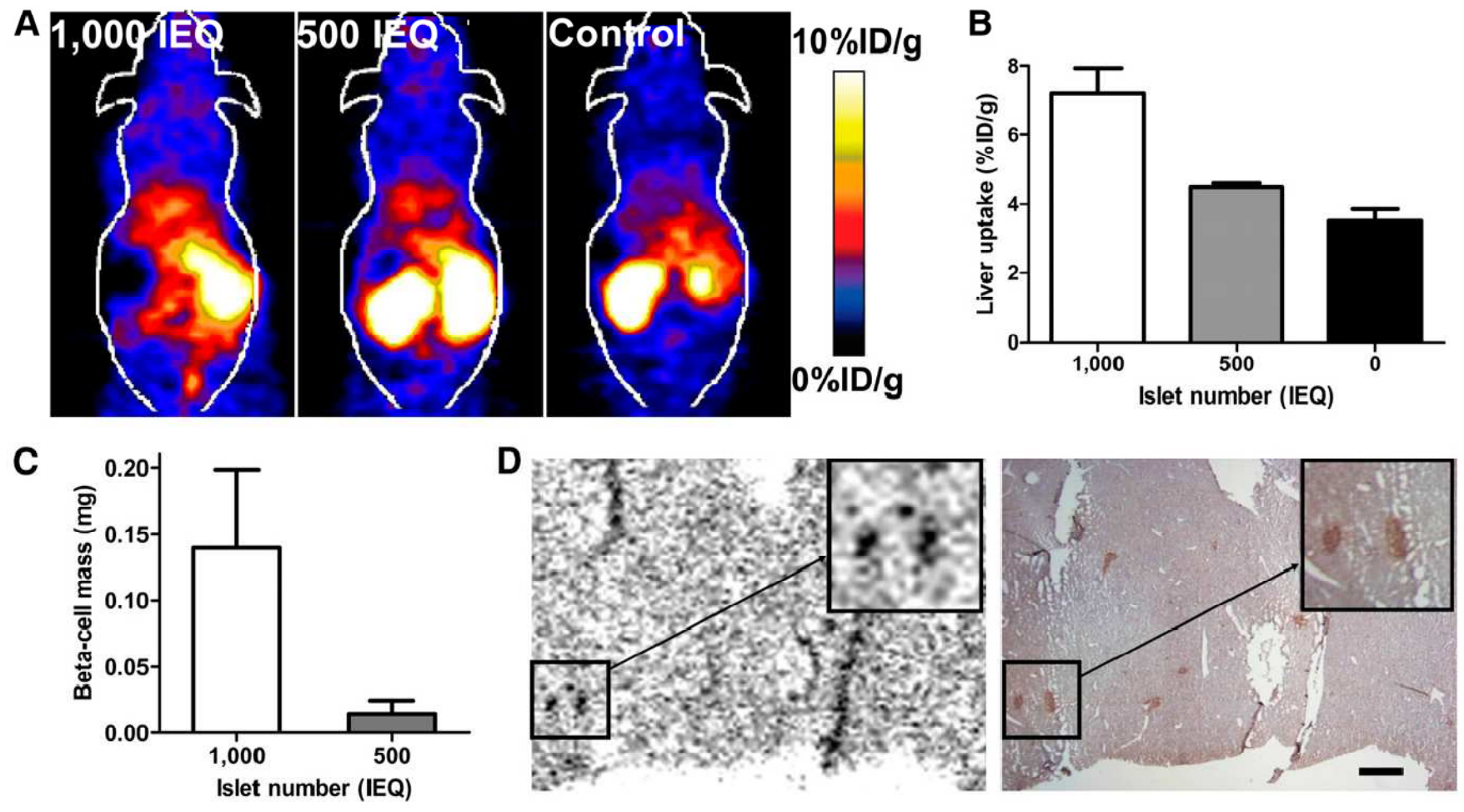


FDG = 2-deoxy-2- $^{18}\text{F}$ -fluoro-D-glucose  
FLT = 3'-deoxy-3'- $^{18}\text{F}$ -fluorothymidine

# Post islet cell transplant imaging

- Post islet transplant patients can achieve insulin independent glycemic control in type 1 diabetes
  - only 10% is sustained over 5 years
- Glucagon-like peptide 1 (GLP-1) is an incretin peptide released from the intestine in response to nutrient ingestion
  - augments glucose-induced insulin secretion from pancreatic  $\beta$ -cells
  - receptor-bound GLP-1 (GLP-1R) localizes to pancreatic duct cells and expressed only in  $\beta$ -cells
- Exendin-4 shows similar biologic properties as human GLP-1
  - Shares 53% sequence identity with greater stability

# $^{18}\text{F}$ -TTCO-exendin-4 imaging post-intraportal islet cell transplantation



# Summary

- It is an exciting time to integrate and translate scientific knowledge into clinical practice
  - Understand basic principles in order to differentiate promising efforts from confusing flawed data
  - New technology and radiotracers need time for validation
    - Need wide participation in these efforts to avoid biases from selected groups
  - Cost in research and development is a big factor
    - Choose judiciously of the project you wish to invest your time
    - Frequent exchanges between colleagues can be invaluable

# Sidra Medical and Research Center



# Entrance - Lobby



# Nursing Station





The image features a solid blue background with a wavy, lighter blue gradient at the top. The text "Thank you" is centered in a bright yellow, sans-serif font.

Thank you