Imaging Glucose Metabolism with ^{18}F-FDG

Mechanism

Glucose $\longrightarrow$ ^{18}F-FDG

FDG $\rightleftharpoons$ (Glucose Transporter) FDG $\xrightarrow{\text{Hexokinase}}$ FDG-6-PO$_4$ $\xrightarrow{\times}$ Glycolysis

Glucose-6- phosphatase

Plasma | Tissue
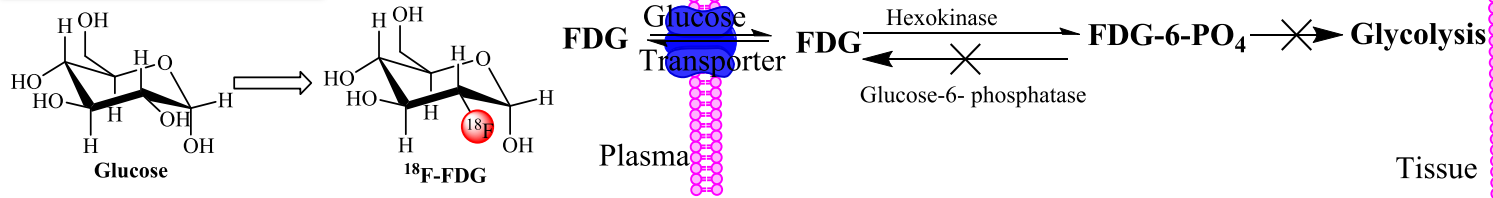
Application

^{18}F-FDG is the most widely used tracer for PET imaging in cancer, neurology, and cardiology. With more than two million ^{18}F-FDG PET scans performed annually in the U.S., ^{18}F-FDG applications include:
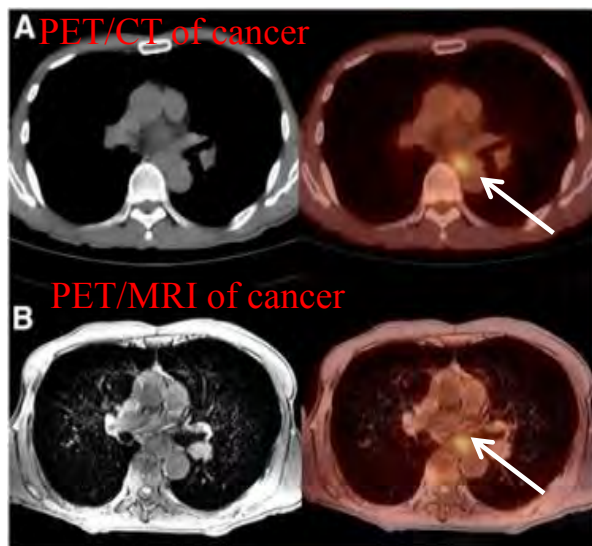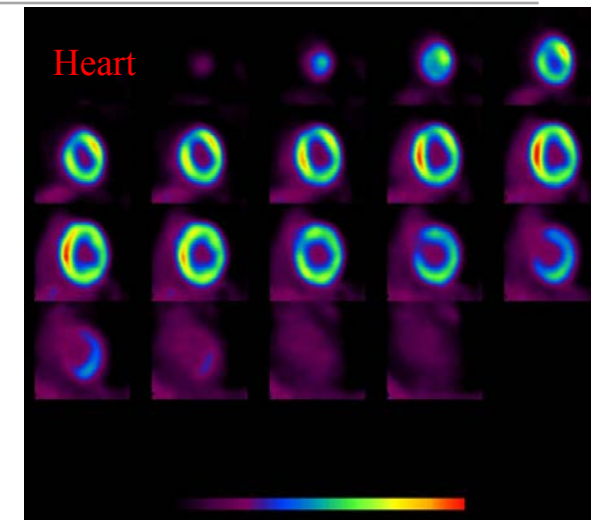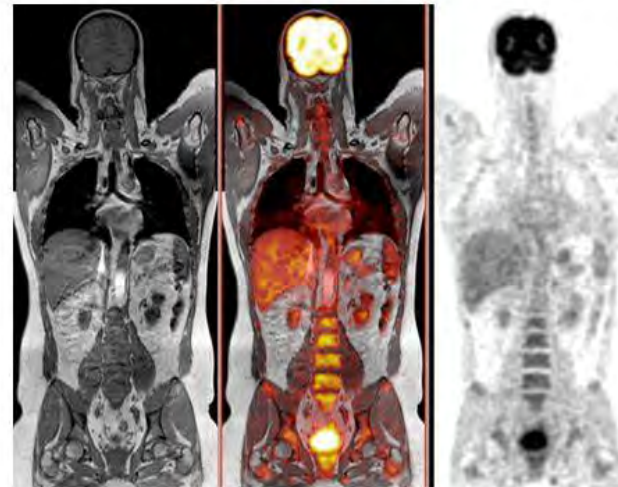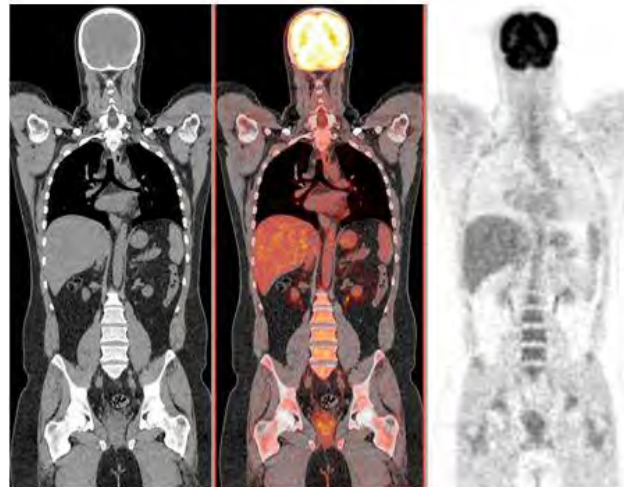
- Cancer diagnosis and therapy evaluation
- Neurodegenerative diseases
- Epilepsy
- Drug and alcohol addition
- Coronary artery diseases
- Drug discovery and development

^{18}F-FDG is an approved PET drug for human use. We produce it once we obtain its ANDA approval by the FDA.

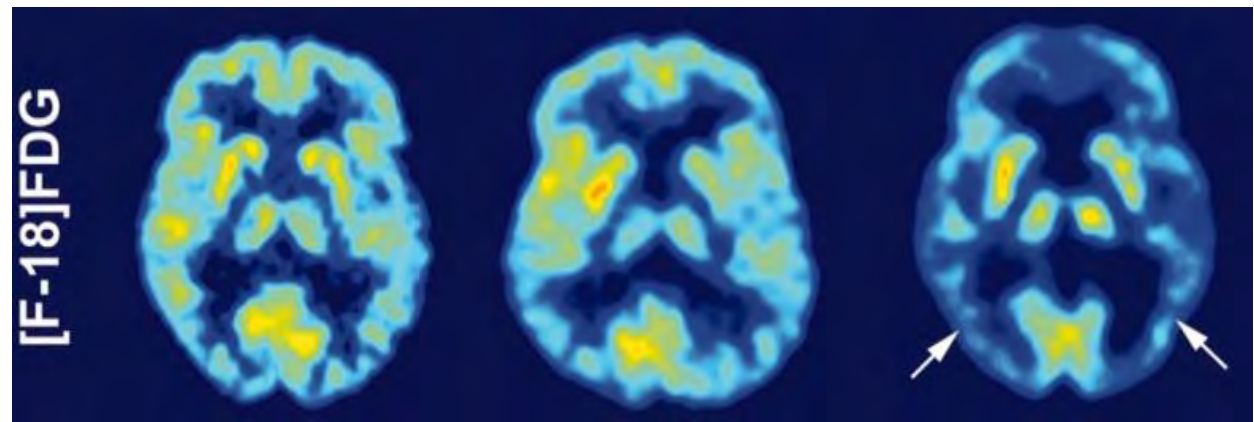# Examples of ^{18}F-FDG-PET imaging

PET-CT

PET-MR

Heart
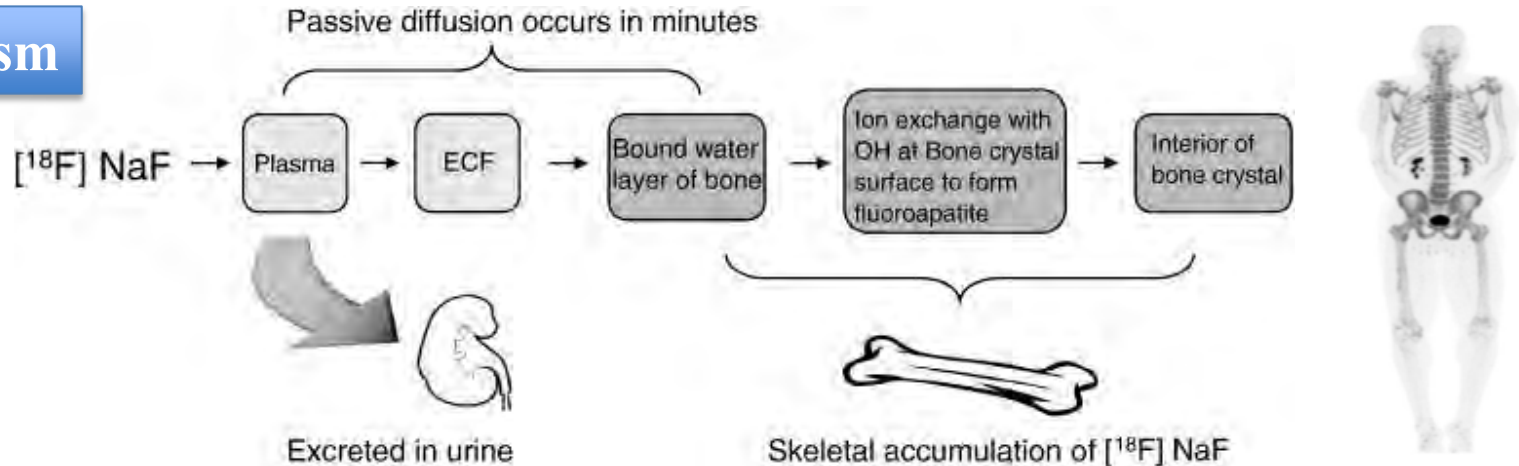
PET/CT of cancer

PET/MRI of cancer

Control   **MCI**   **AD patient**

[F-18]FDG

MCI: Mild cognitive impairment;   **AD**: Alzheimer's disease

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Imaging Bone with ^{18}F-NaF

Mechanism

Passive diffusion occurs in minutes

$[^{18}F]$ NaF → Plasma → ECF → Bound water layer of bone → Ion exchange with OH at Bone crystal surface to form fluoroapatite → Interior of bone crystal

Excreted in urine

Skeletal accumulation of $[^{18}F]$ NaF

Application

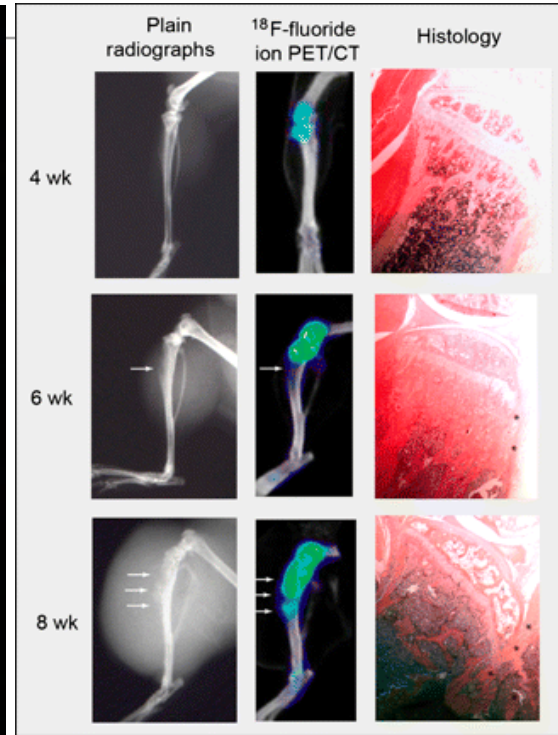➢ PET imaging with ^{18}F-NaF (sodium fluoride) is used to diagnose skeletal metastases from primary cancers elsewhere, particularly breast and prostate.

➢ Imaging other bone diseases, such as fractures, arthritis, Paget's disease of bone, or infection of the joints, joint replacements or bone.

^{18}F-NaF is an approved PET drug for human use. We produce it once we obtain its ANDA approval by the FDA.

Examples of ^{18}F-NaF PET imaging
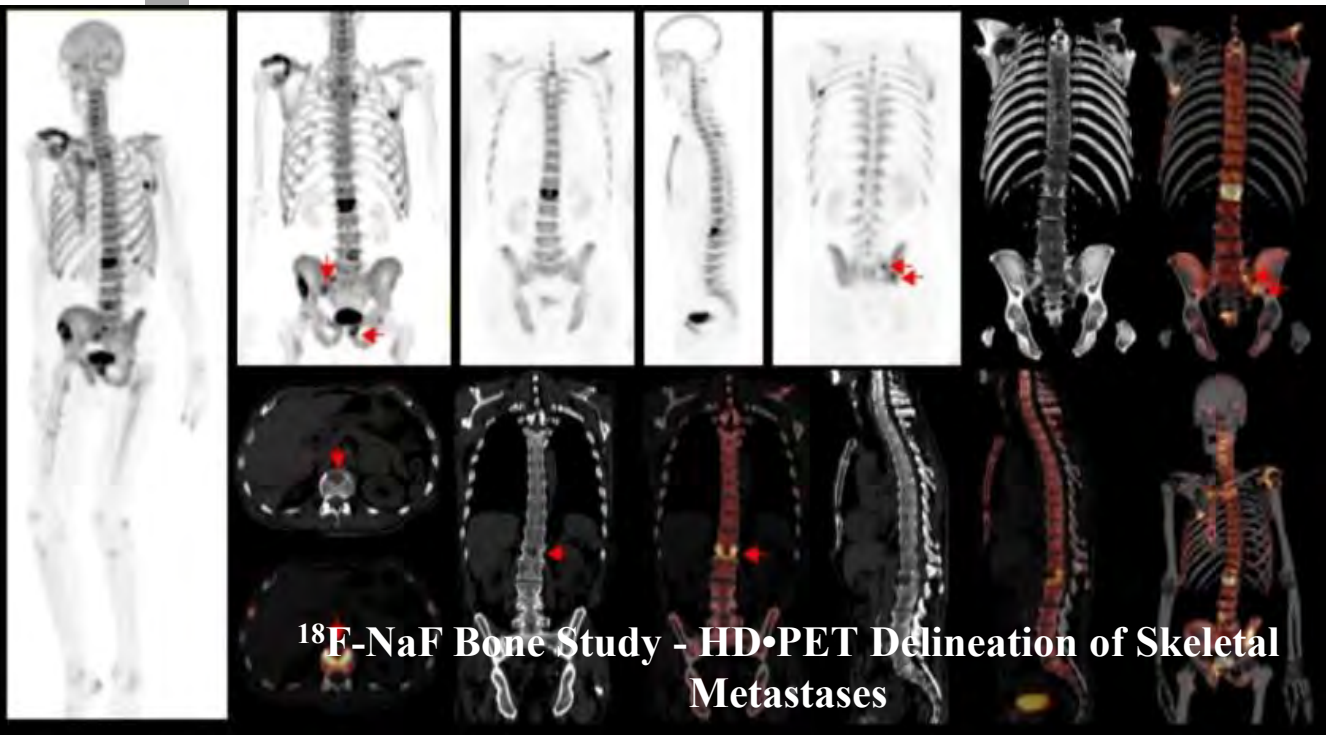
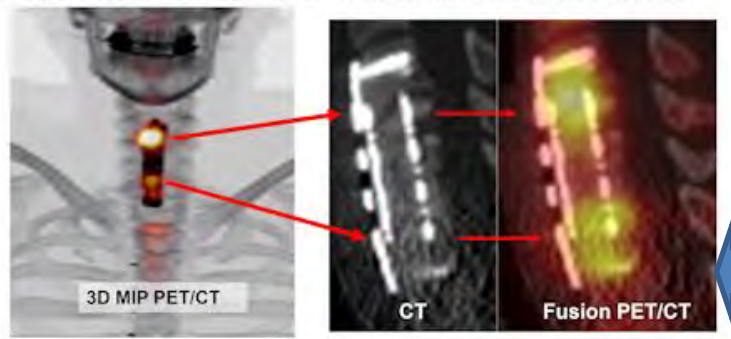^{18}F-NaF Bone Study - HD•PET Delineation of Skeletal Metastases

^{18}F-NaF PET/CT Evaluation of Cervical Spine Fixation Hardware

3D MIP PET/CT   CT   Fusion PET/CT

The clinical utility of PET/CT using a newly approved PET F-18 sodium fluoride (NaF) bone imaging agent to correctly pinpoint the cause of recurrent pain after surgical placement of spinal fixation hardware.

Radiographs (left), ^{18}F-NaF PET/CT scans (middle), and photomicrographs of histologic specimen (right). PET/CT images reveal osteoblastic lesion earlier (4 wk) than radiography (arrows denote bone lesions). Increasing ^{18}F-NaF uptake over time corresponds to increased bone formation seen on histology.
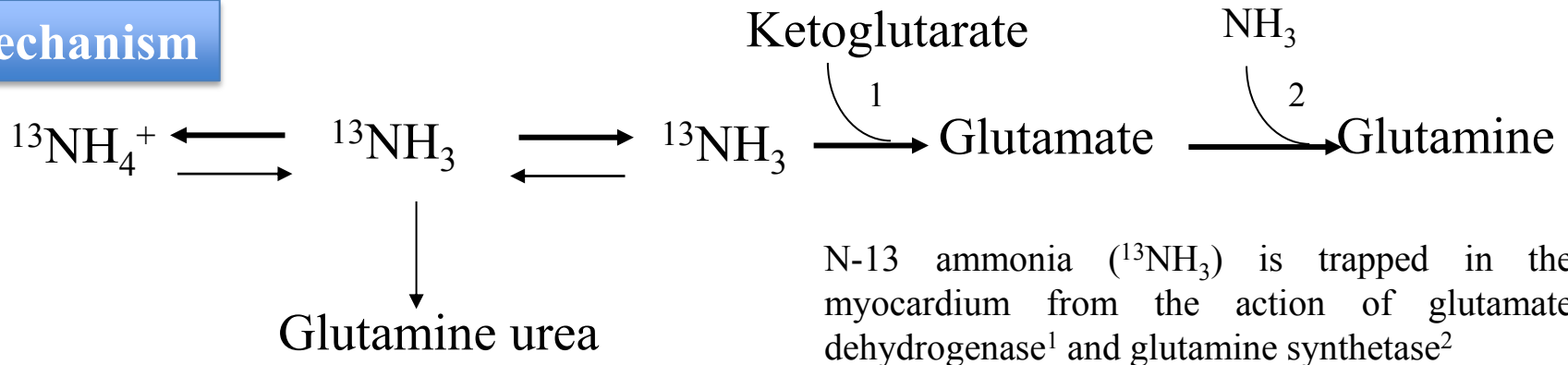
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Imaging Herat with N-13 Ammonia (^{13}N-NH$_3$)

Mechanism

$$^{13}NH_4^+ \rightleftharpoons {^{13}NH_3} \rightleftharpoons {^{13}NH_3} \xrightarrow{\text{Ketoglutarate}\;\;1} \text{Glutamate} \xrightarrow{\text{NH}_3\;\;2} \text{Glutamine}$$

$^{13}NH_3 \rightarrow$ Glutamine urea

N-13 ammonia ($^{13}NH_3$) is trapped in the myocardium from the action of glutamate dehydrogenase[1] and glutamine synthetase[2]
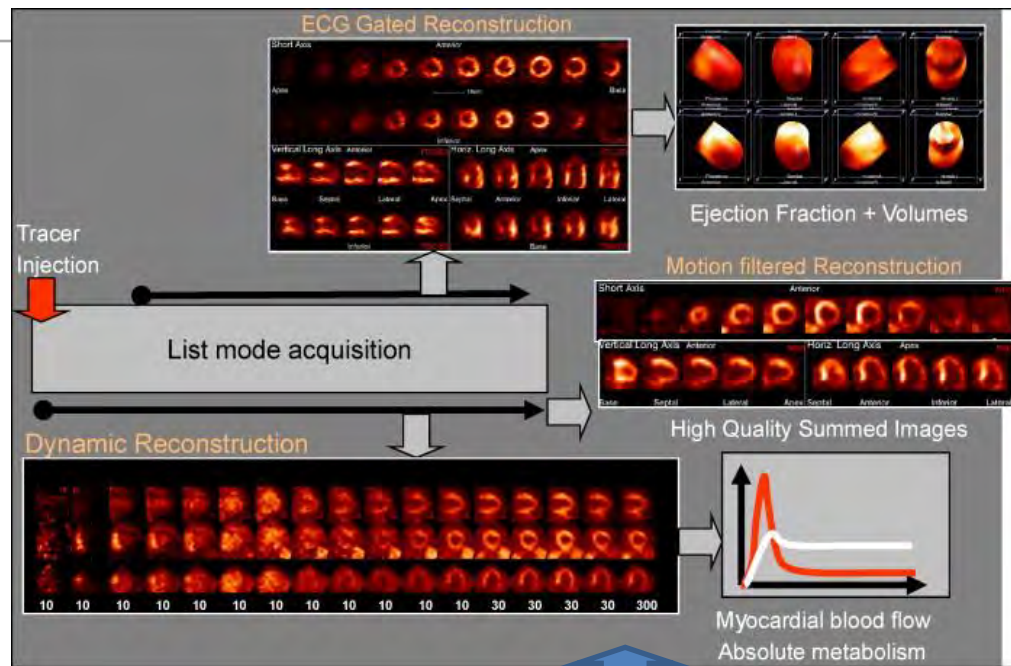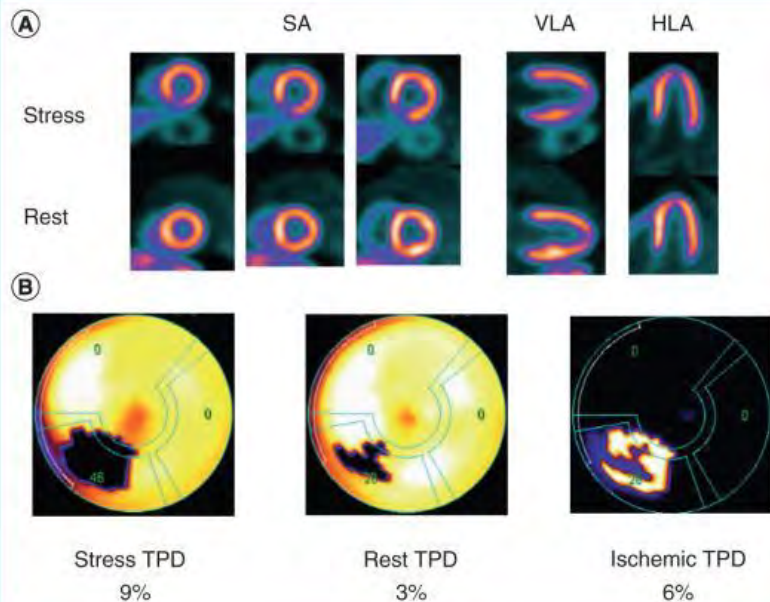
Application

➢ Myocardial perfusion imaging
➢ Imaging heart diseases, e.g. coronary artery disease
➢ Monitoring novel treatment therapies
➢ Assessment of glutamine synthetase activity by ^{13}N-NH$_3$ uptake

^{13}N-NH$_3$ is an approved PET drug for human use. We produce it once we obtain its ANDA approval by the FDA.

Examples of ^{13}N-NH$_3$ PET imaging
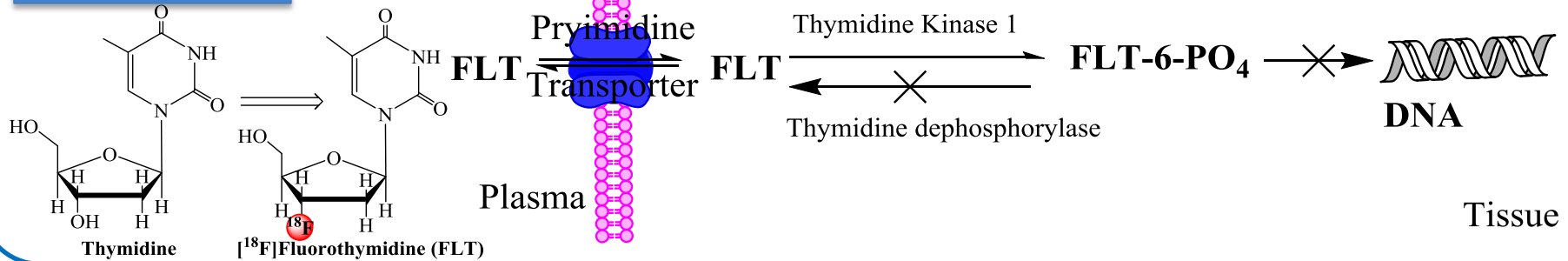

Abnormal ^{13}N-ammonia PET images and quantitative polar maps from a patient with 90% right coronary artery stenosis. A reversible perfusion defect is seen in the inferior wall both on the images **(A)** and the polar maps **(B)**. Stress and ischemic (reversible) TPD were 9 and 6%, respectively. HLA: Horizontal long axis; SA: Short axis; TPD: Total perfusion deficit; VLA: Vertical long axis.
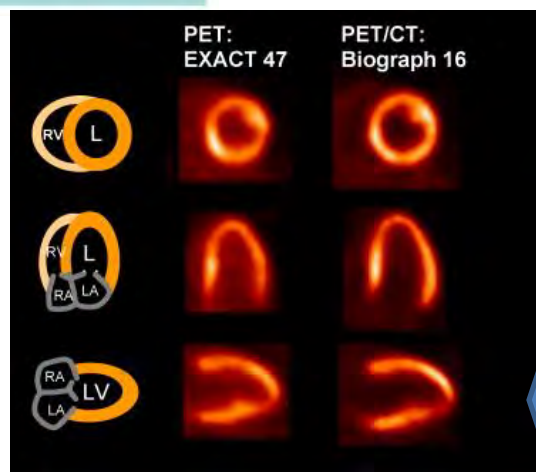
Generation of static, gated and dynamic data out of one single list-mode acquisition. Such an approach provides quantitative data without prolonging the acquisition time.

Comprehensive summary of the quantitative PET results from a NH3 rest/stress study in a female patient with three vessel disease resulting in significantly reduced flow reserve values and transient ischemic dilation.

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Imaging Cellular Proliferation with ^{18}F-FLT

Mechanism

$$FLT \xleftrightarrow[\text{Pyrimidine Transporter}]{} FLT \xrightleftharpoons[\text{Thymidine dephosphorylase}]{\text{Thymidine Kinase 1}} FLT\text{-}6\text{-}PO_4 \nrightarrow DNA$$

Plasma

Tissue

Thymidine

[^{18}F]Fluorothymidine (FLT)

Application

- ➤ FLT is an analog of thymidine. ^{18}F-FLT is trapped after phosphorylation by thymidine kinase 1, whose expression is upregulated in tumor cells.
- ➤ ^{18}F-FLT PET is used as a biomarker to assess *in vivo* cellular proliferation of malignant tumors and treatment response.

PRE-THERAPY POST-THERAPY
RESPONDER NON-RESPONDER
SUV 10 / 5 / 0
Chemo
FLT PET/CT Bone Marrow
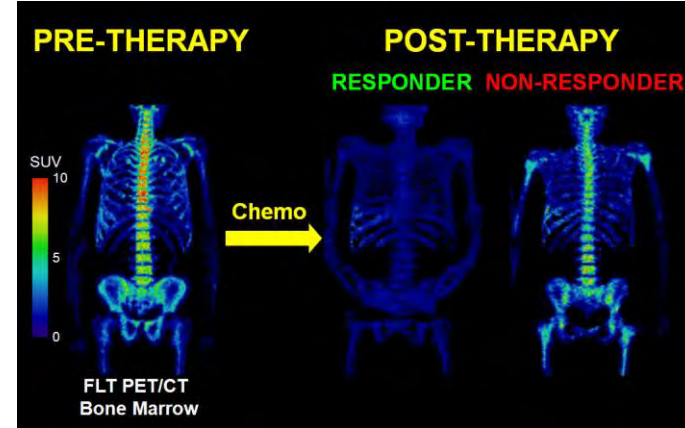
^{18}F-FLT will be made available for preclinical studies on campus as soon as the CRP becomes operational. We will file an IND application to the FDA for its human use.

Nature Med. 1998; 4, 1334 - 1336
J Nucl Med. 2013;54:903-912.

Examples of ¹⁸F-FLT PET/CT imaging

Fused ¹⁸F-FLT PET/CT image of patient with stage IV NSCLC with primary tumor in right lung and contralateral bone metastasis, at baseline (A) and 7 d (B) and 26 d (C) after start of treatment with erlotinib.
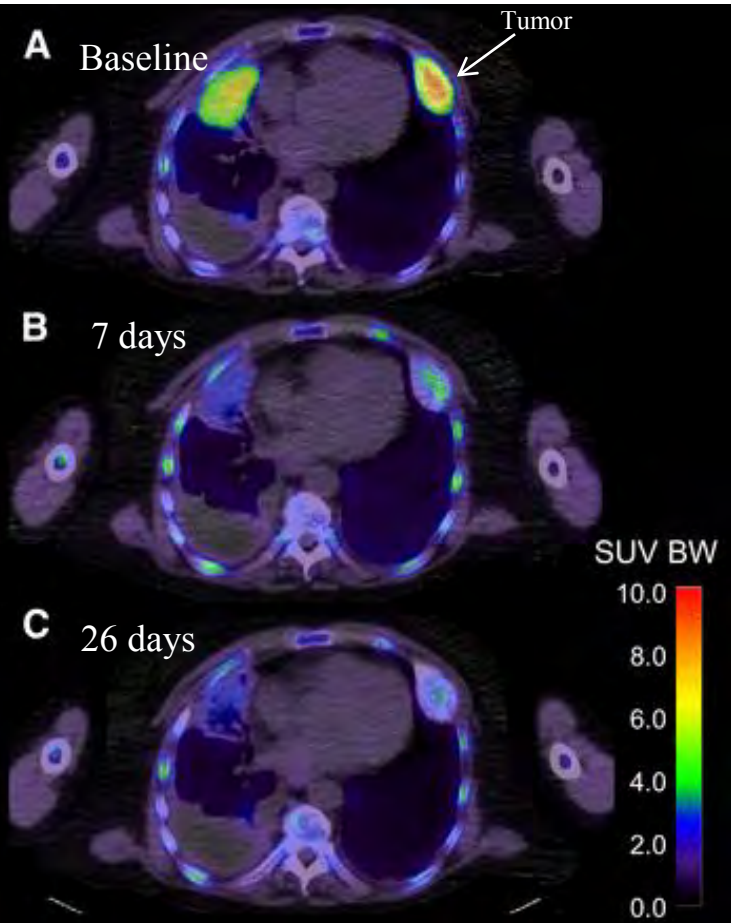

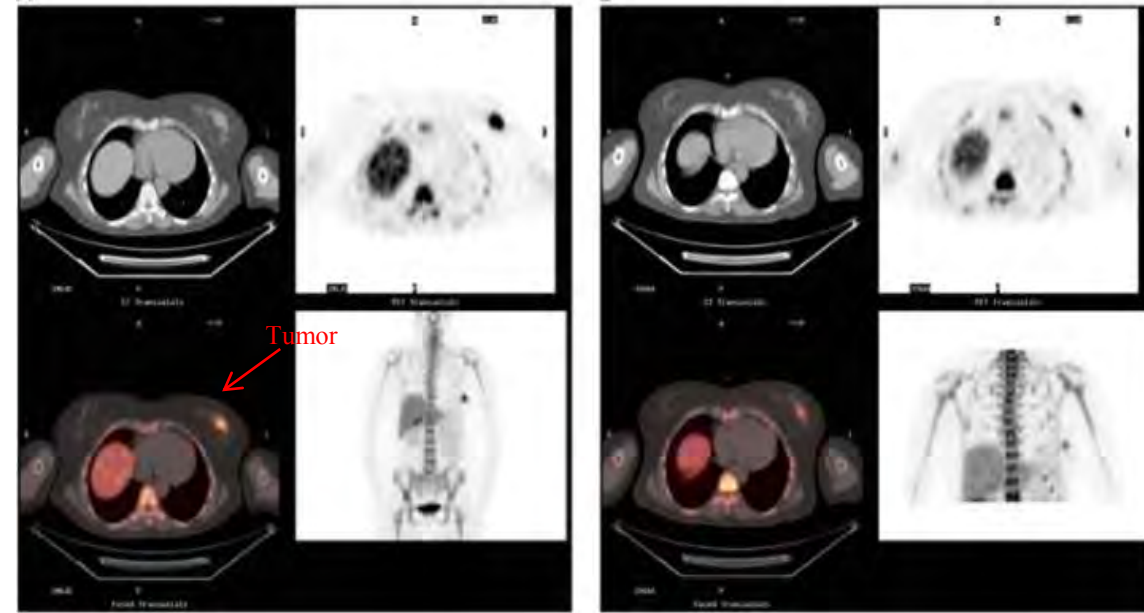A. a patient with aplastic anaemia.
B. a patient with myelodysplastic syndromes
C. a patient with myeloproliferative diseases
D. a patient with myelofibrosis
E. a patient with extramedullary haematopoiesis with β-

¹⁸F-FLT PET images representing SUV_{max} for a 55-year-old female with breast cancer. (A) pre-chemotherapy SUV_{max} 13 and Ki-67 of 59.5 (B) post 1 cycle of chemotherapy with a SUV_{max} 8.5 (-35%).

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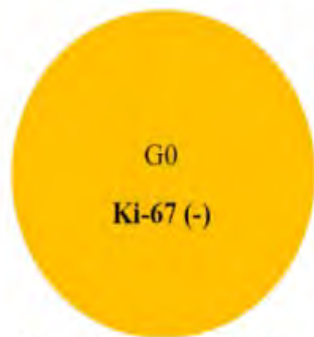
Imaging Cellular Proliferation with $[^{18}F]$ISO-1
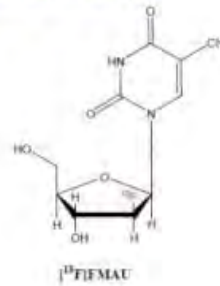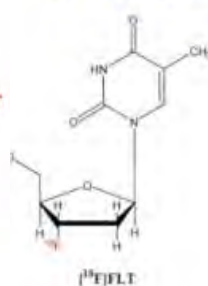
Mechanism
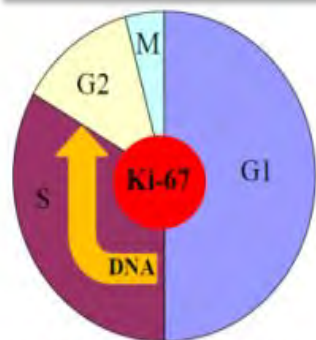
Proliferating Tumor Cell (P)

Quiescent Tumor Cell (Q)

G0 Ki-67 (-)

P:Q Ratio: Important for Treatment Planning

^{18}F-Labeled Thymidine Analogs

$[^{18}F]$FLT

$[^{18}F]$FMAU

^{18}F-Labeled Sigma-2 Radiotracer

$[^{18}F]$ISO-1
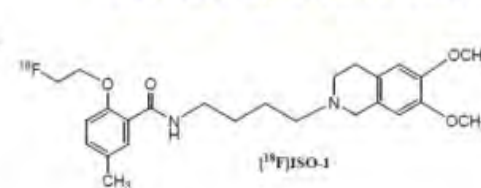
Application

➢ ^{18}F-FLT provides a measurement of the percentage of cells in S phase. It may underestimate the proliferative status of a solid tumor.

➢ The sigma-2 (σ2) receptor is overexpressed in a wide variety of solid tumors but with higher density in proliferating (P) tumor cells than quiescent (Q) ones.

➢ PET imaging with σ2 receptor ligand $[^{18}F]$ISO-1 is used as an attractive biomarker to assess the proliferative status (i.e., P:Q ratio) of solid tumors.

If interests arise in this radiotracer on campus, we will file an IND application to the FDA for its human use.

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Examples of [18F]ISO-1 PET/CT imaging
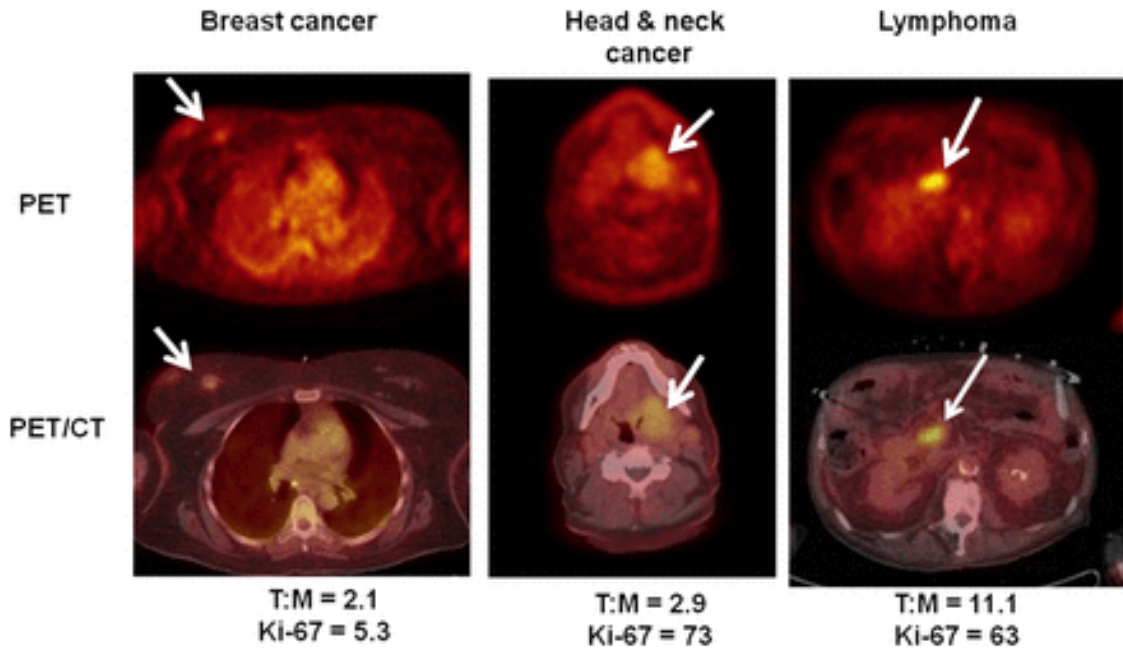
[18F]ISO-1 PET and PET/CT images of patients with breast cancer (left), head and neck cancer (middle), and lymphoma (right) showing different degrees of uptake in their tumors (arrows).
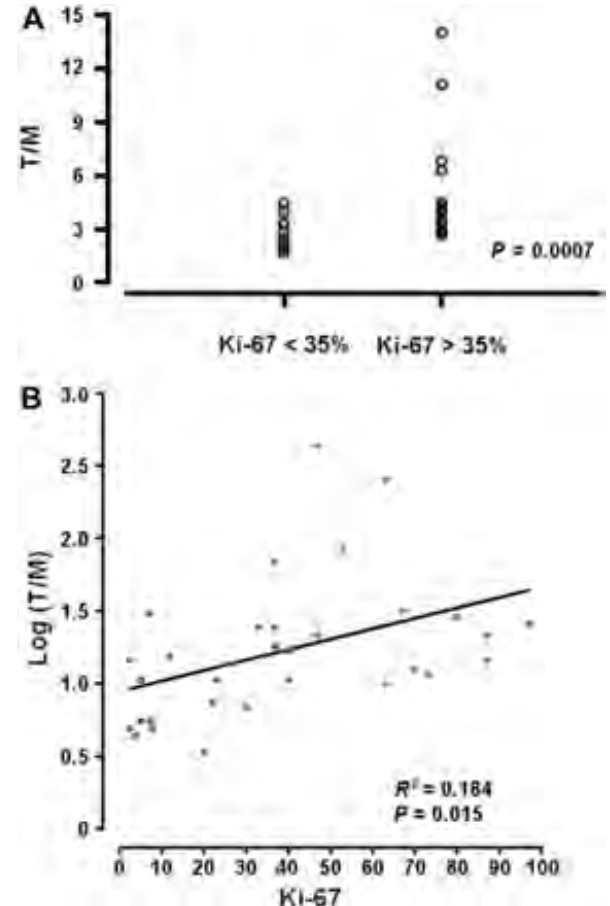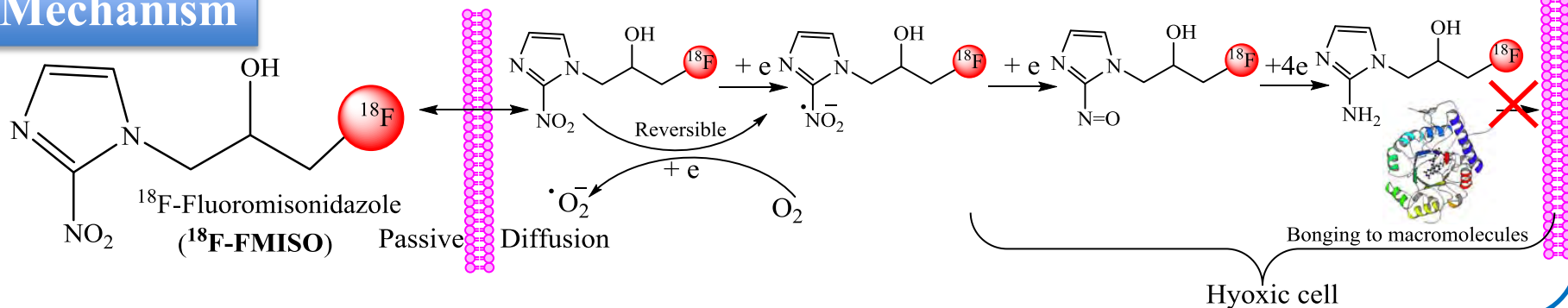
Correlation of [18F]ISO-1, as expressed by T/M, with low (<35%) and high (>35%) expression of Ki-67 (top).
Correlation of Ki-67 with [18F]ISO-1 expressed by T/M (bottom)

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Hypoxia Imaging with ^{18}F-FMISO

Mechanism

^{18}F-Fluoromisonidazole
(^{18}**F-FMISO**)

Passive Diffusion

Reversible

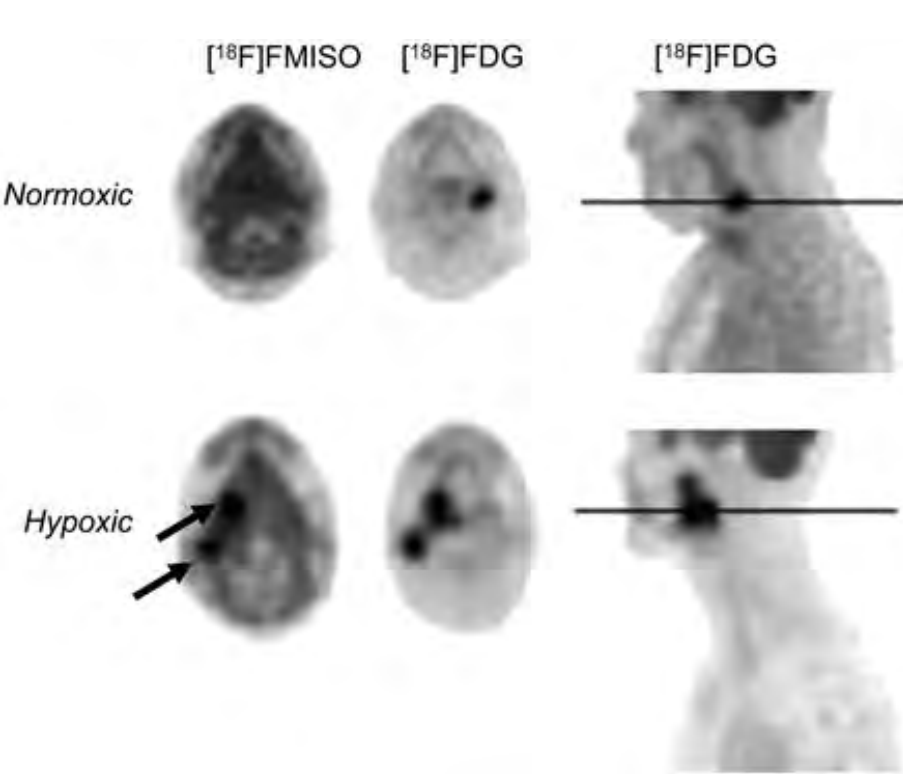Hyoxic cell

Bonging to macromolecules

Application

➢ Identification of tumor hypoxia as a prognostic indicator of treatment outcome.

➢ Determination of the spatial distribution of hypoxia for the purpose of treatment planning.

➢ Identification of hypoxic and viable tissue in stroke.

➢ **Other PET hypoxia agents** include ^{18}F-FAZA, ^{64}Cu-ATSM, ^{18}F-HX4.

^{18}**F-FMISO will be made available for preclinical studies on campus as soon as the CRP becomes operational. We will file an IND application to the FDA for its human use.**

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Examples of ^{18}F-FMISO PET/CT imaging

^{18}F-FMISO PET/CT guided Radiation Therapy in the Treatment of Head and Neck Cancer
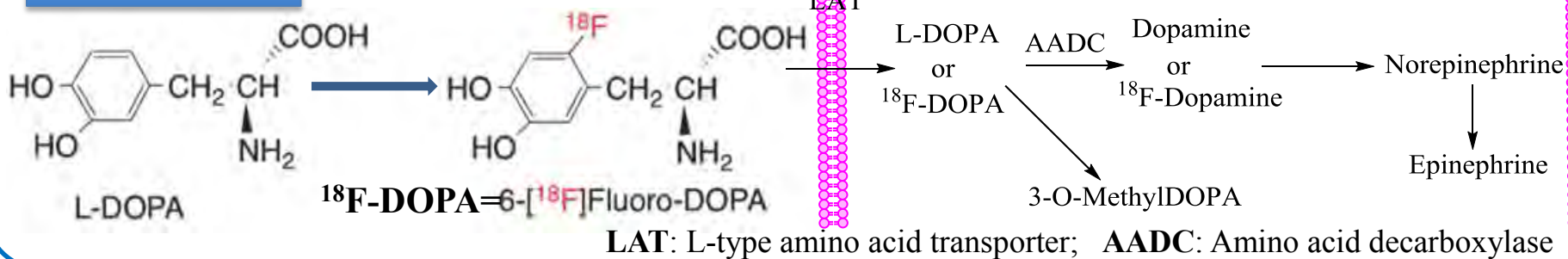

Transaxial ^{18}F-FMISO and ^{18}F-FDG PET images, and sagittal ^{18}F-FDG PET images of patients with normoxic (upper) and hypoxic tumors (lower). ^{18}F-FMISO preferentially accumulates in hypoxic tumors (arrows) but not in normoxic ones.
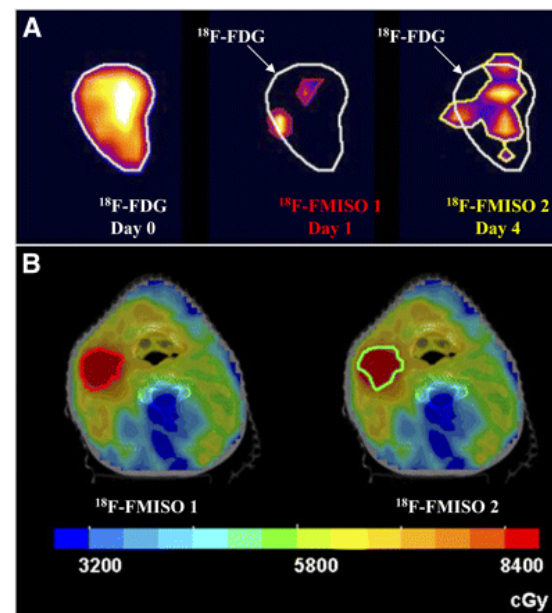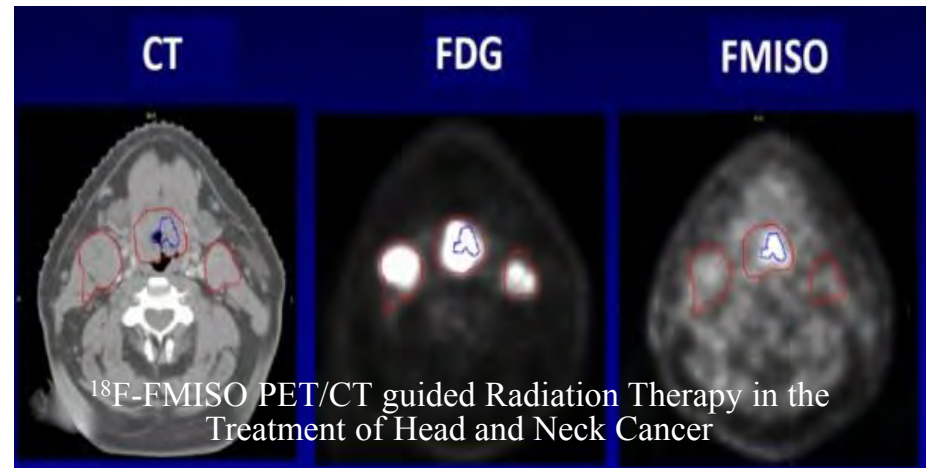
(A) ^{18}F-FMISO PET scans obtained 3 d apart in a patient with head and neck cancer show large variations in size and distribution of hypoxic regions between scans. Tumor volume was defined by viable tumor tissue that showed ^{18}F-FDG uptake. (B) Intensity-modulated radiotherapy dose distributions in color-wash display of a patient whose sequential ^{18}F-FMISO PET scans were similar.

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Imaging Dopaminergic Function with ^{18}F-DOPA

Mechanism

^{18}F-DOPA=6-[^{18}F]Fluoro-DOPA

LAT

L-DOPA or ^{18}F-DOPA → AADC → Dopamine or ^{18}F-Dopamine → Norepinephrine → Epinephrine

→ 3-O-MethylDOPA

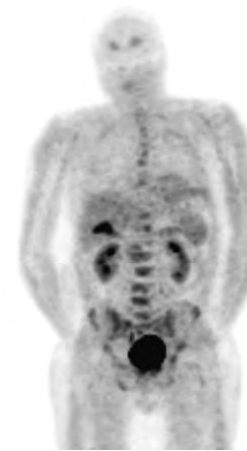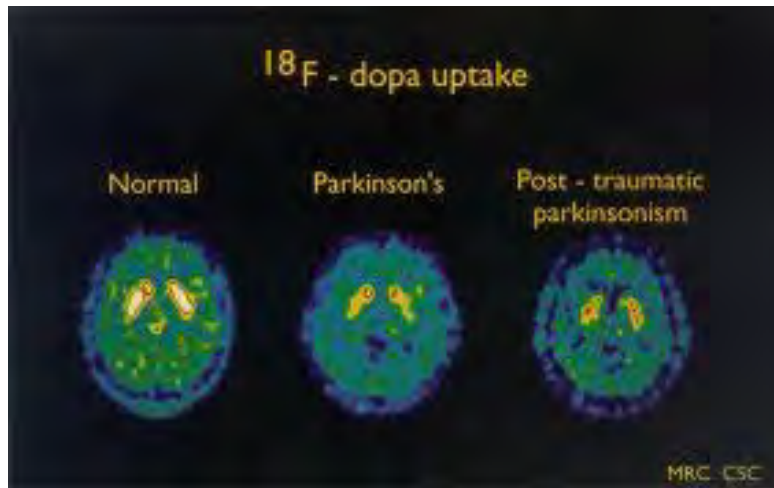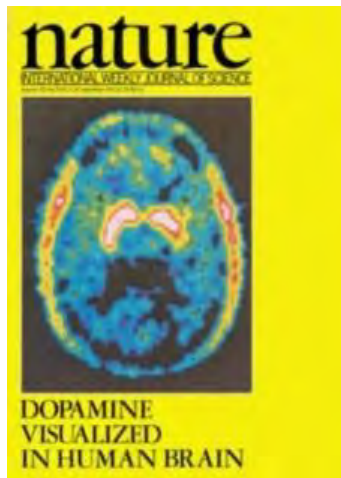**LAT**: L-type amino acid transporter;   **AADC**: Amino acid decarboxylase

Application

➤ Neurology/Psychiatry: Detect regional distribution of neurotransmitter dopamine in the brain.

➤ Oncology: Imaging amino acid uptake and metabolism in tumors including brain tumor, neuroendocrine tumors (NET).

➤ Non-invasive imaging of beta-cell mass in humans.

^{18}**F-DOPA will be made available for preclinical studies on campus as soon as the CRP becomes operational. We will file an IND application to the FDA for its human use.**
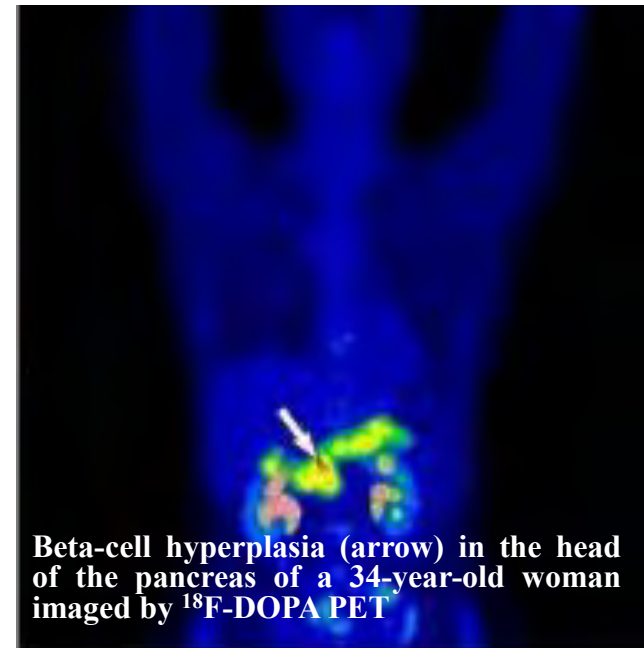
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Examples of ^{18}F-DOPA PET imaging

^{18}F - dopa uptake

Normal   Parkinson's   Post - traumatic parkinsonism

MRC CSC

^{18}F-DOPA PET projection image in patient with **Cushing's disease** and in whom all imaging had failed to find source of corticotropin overproduction. PET showed significant bone marrow uptake, which proved to be metastatic prostate cancer with neuroendocrine differentiation after biopsy.
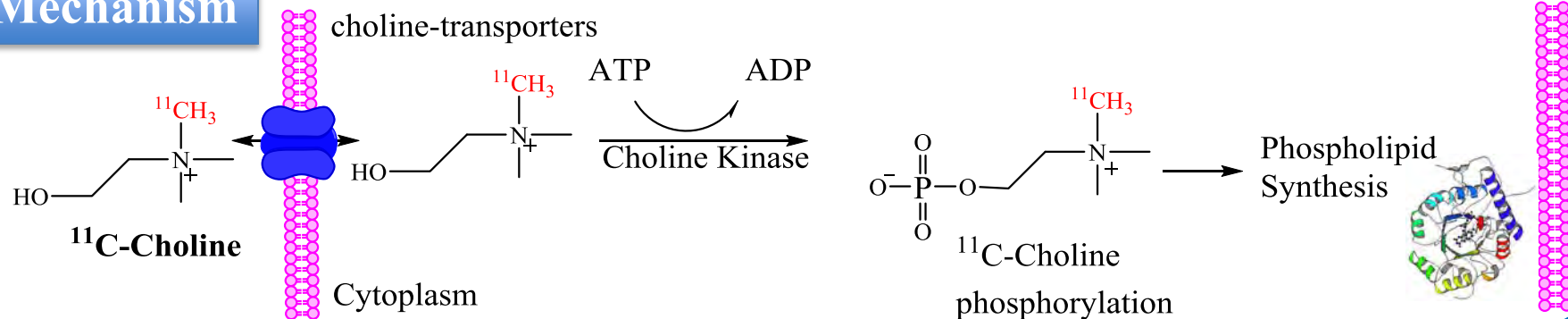

^{18}F-FDOPA uptake in gliomas.
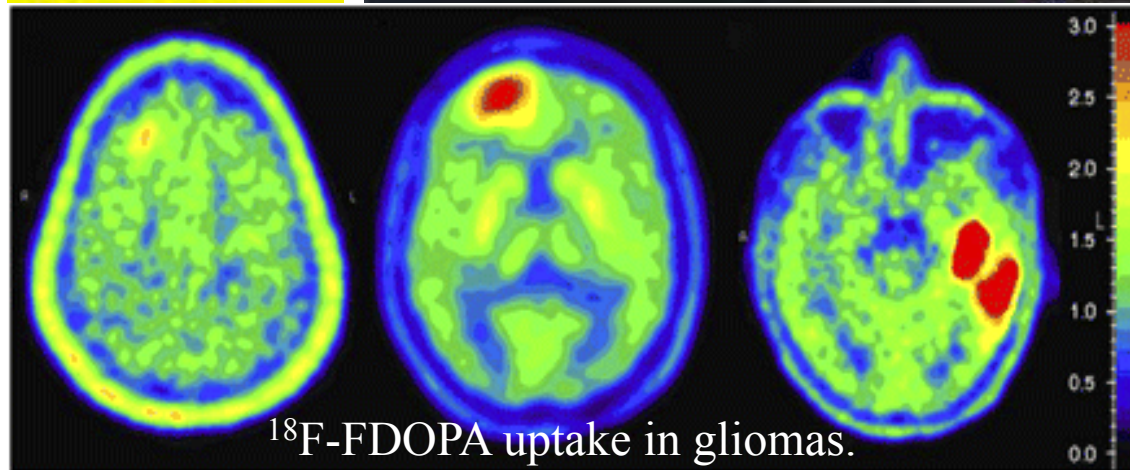
WHO grade:	II	III	IV
Histology:	oligodendroglioma	oligoastrocytoma	glioblastoma
Ki-67:	1%	25%	40%
SUVmax:	2.39	3.49	6.42

Beta-cell hyperplasia (arrow) in the head of the pancreas of a 34-year-old woman imaged by ^{18}F-DOPA PET

Nature 1983, 305, 137. Neurology 1997, 49: 183-189.
J Nucl Med. 2010,51:1532-1538.

J Nucl Med. 2008, 49, 573-586.
J Clin Endocrinol Metab. 2007, 92,1237-1244.

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Imaging Lipid Synthesis with ^{11}C-Choline

Mechanism

choline-transporters

^{11}CH$_3$

HO — N$^+$

^{11}C-Choline

Cytoplasm

ATP   ADP

^{11}CH$_3$

HO — N$^+$

Choline Kinase

^{11}CH$_3$

O$^-$—P—O— N$^+$
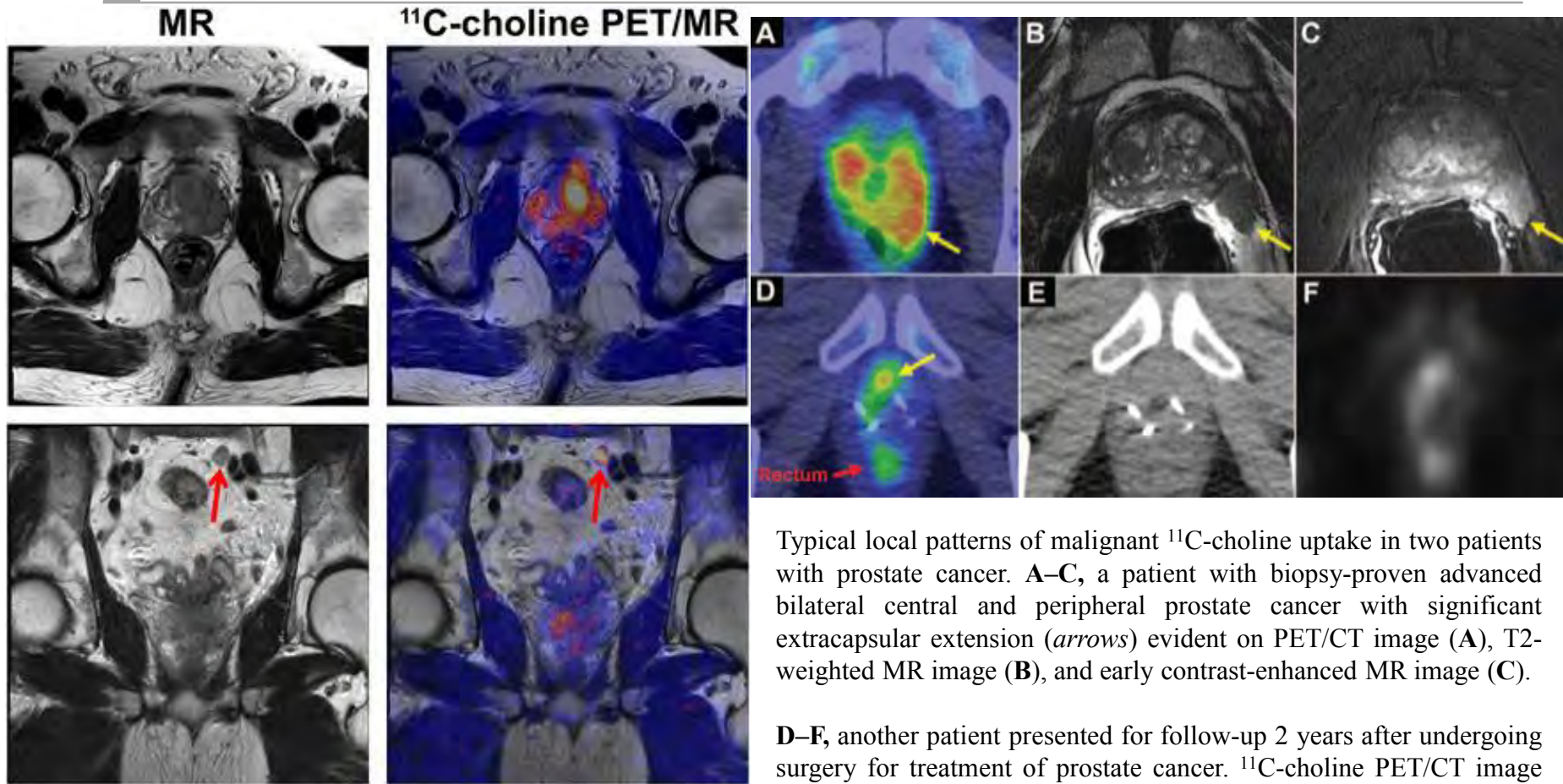
^{11}C-Choline
phosphorylation

Phospholipid
Synthesis

Application

➤ Cancer promotes alterations in choline transport and its utilization, leading to increased uptake of choline.

➤ ^{11}C-Choline PET is an effective noninvasive method for detecting nodal invasion, distal metastases, and local relapse of prostate cancer.

^{11}**C-Choline is an FDA approved PET drug for imaging of patients with prostate cancer. We will file an IND or ANDA to the FDA if interests in it arise on campus.**

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Examples of ^{11}C-Choline PET/MRI and PET/CT imaging

Typical local patterns of malignant ^{11}C-choline uptake in two patients with prostate cancer. **A–C,** a patient with biopsy-proven advanced bilateral central and peripheral prostate cancer with significant extracapsular extension (*arrows*) evident on PET/CT image (**A**), T2-weighted MR image (**B**), and early contrast-enhanced MR image (**C**).
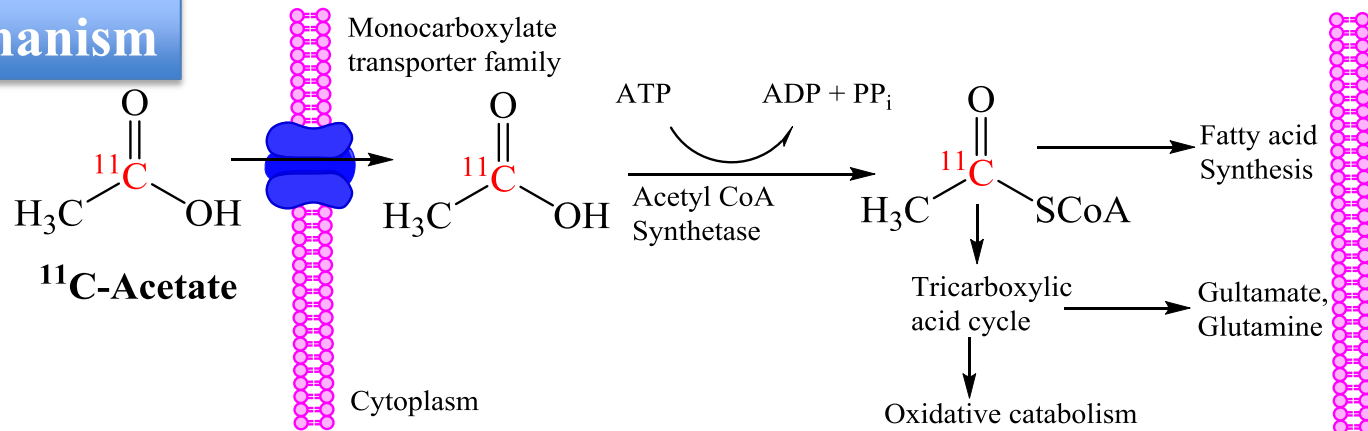
D–F, another patient presented for follow-up 2 years after undergoing surgery for treatment of prostate cancer. ^{11}C-choline PET/CT image (**D**), CT image (**E**), and ^{11}C-choline PET image (**F**) are shown. PET/CT image shows recurrence in prostatectomy bed (*yellow arrow*, **D**). MRI (not shown) was performed for restaging, but images were very difficult to interpret because of distorted postoperative anatomy.

58-y-old man with prostate cancer. ^{11}C-choline PET/MR image shows primary cancer in prostate gland (upper row) as well as pelvic lymph node metastasis (bottom row, arrow). This example emphasizes value of PET/MR imaging in oncologic diagnostics because high-resolution MR imaging can be combined with specific PET tracers.

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Acetate Metabolism Imaging with ^{11}C- Acetate

Mechanism

Monocarboxylate transporter family

^{11}C-Acetate

Cytoplasm

ATP   ADP + PP$_i$

Acetyl CoA Synthetase

Fatty acid Synthesis

Tricarboxylic acid cycle

Gultamate, Glutamine

Oxidative catabolism

Application

➤ ^{11}C-Acetate PET is used as a metabolic marker in the assessment of various cardiologic and oncologic diseases.

➤ ^{11}C-Acetate PET for myocardial oxygen metabolism/ myocardial perfusion.

➤ Prostate cancer imaging

We will file an IND application to the FDA if interests in this radiotracer arise on campus.

Examples of ^{11}C-Acetate PET/CT imaging
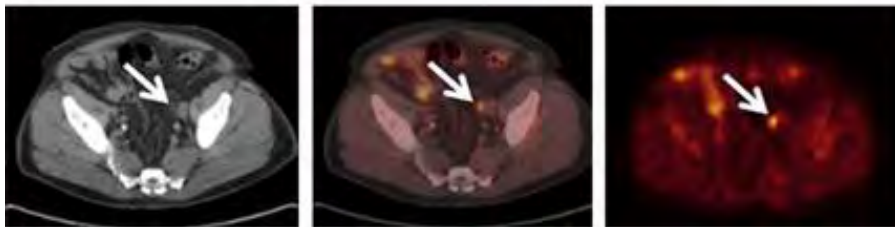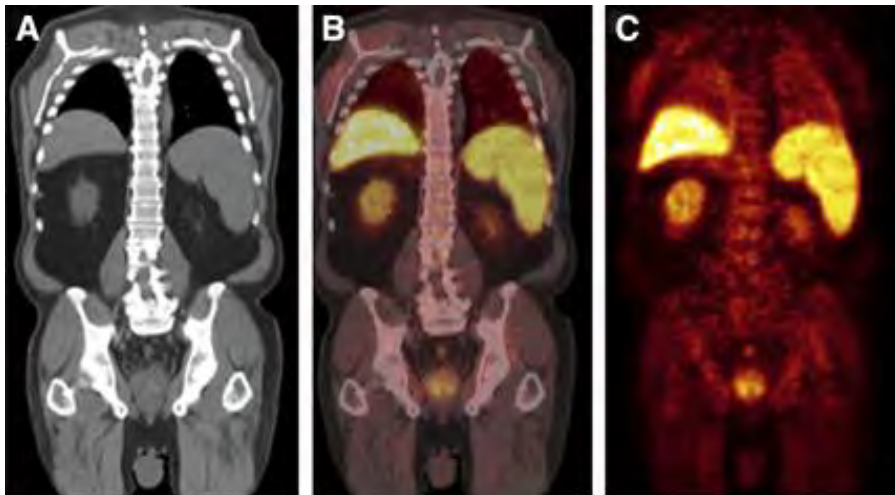
Representative images of CT (A), ^{11}C-acetate PET/CT (B) and PET (C) in a patient with prostate cancer in 4 quadrants and unsuspected LN metastasis. Diffusely increased ^{11}C-acetate uptake was noted within prostate gland and was most intense in right lobe (short arrow). Long arrows point to normal-sized left external iliac LN.
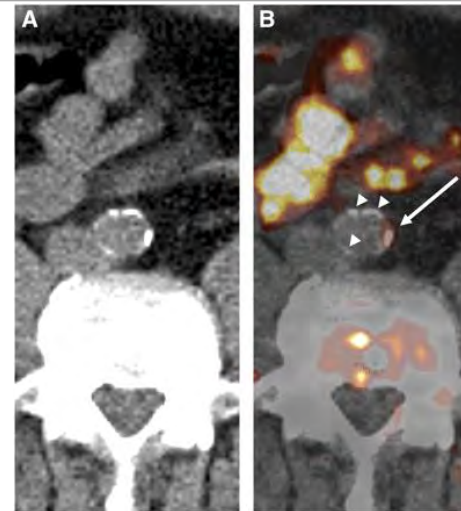
Transaxial ^{11}C-acetate PET/CT images of abdominal aorta of a man: CT image (A) and coregistered and fused PET/CT image (B).^{11}C-acetate uptake in vessel wall alteration coincided with calcification. Other calcified plaques of comparable size did not accumulate ^{11}C-acetate. Arrow = tracer uptake site; arrowheads = calcifications.
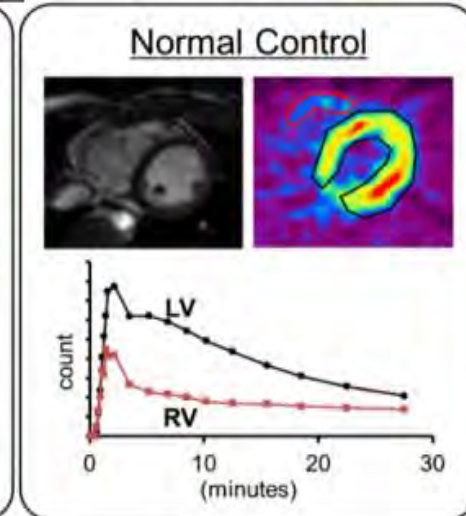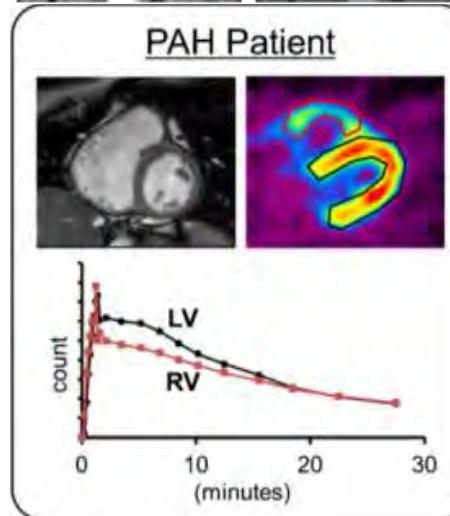
^{11}C-Acetate myocardial PET imaging of a pulmonary hypertension (PAH) patient and a normal control.

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β-Amyloid Imaging with PET Radiotracers

Mechanism

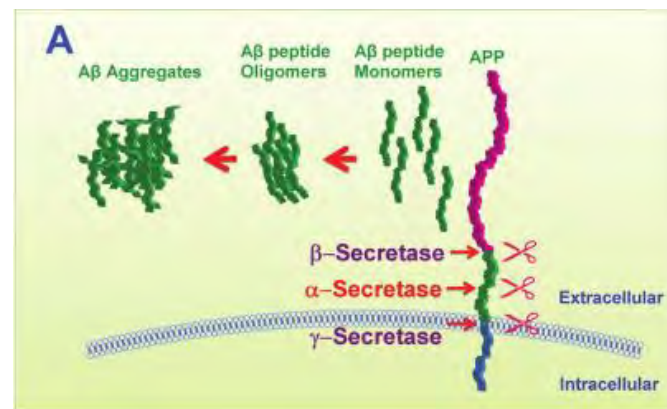β-Amyloid (aβ) plaque is a hallmark of Alzheimer's Disease (AD) pathology. The Aβ plaque specific PET radioligand ^{11}C-PIB has been established for imaging Aβ plaques in human brain.
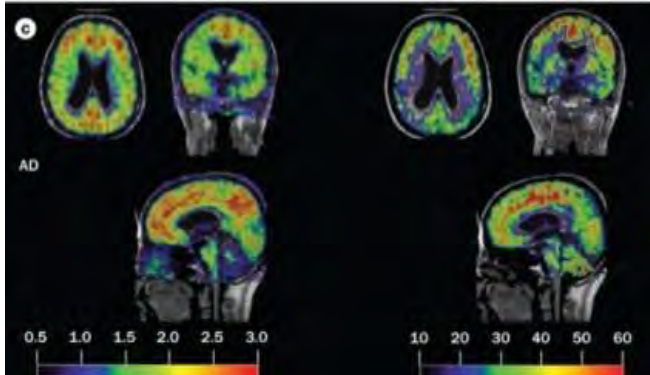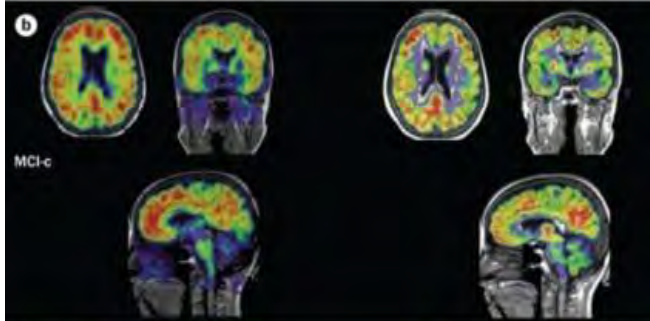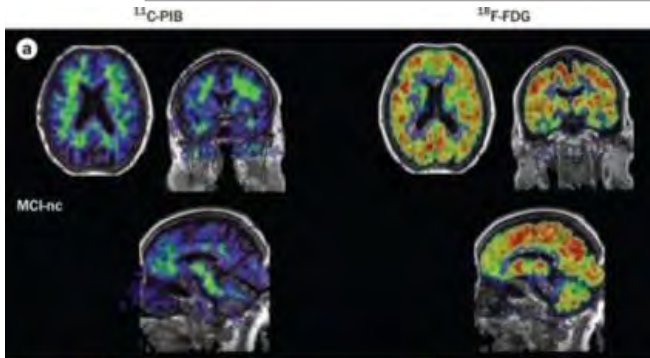

Application

➤ Noninvasive imaging tool for the detection of suspected AD or other neurodegenerative diseases.

➤ Evaluation of anti- Aβ therapy response.

➤ Potential use for other diseases, such as TBI.

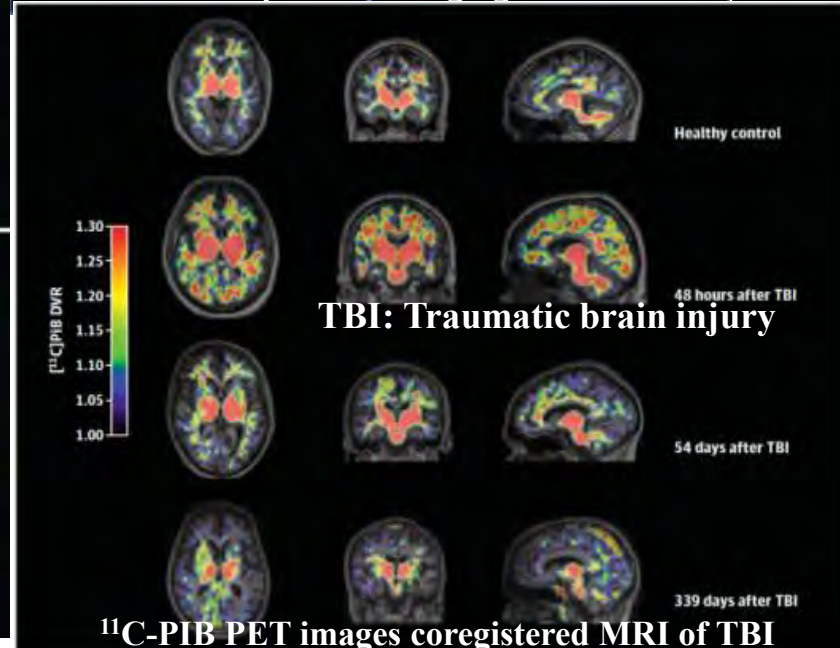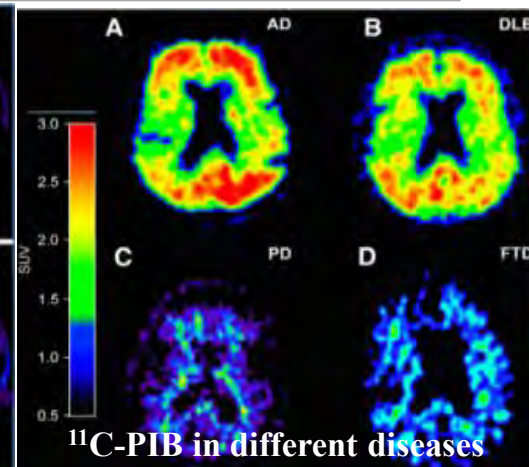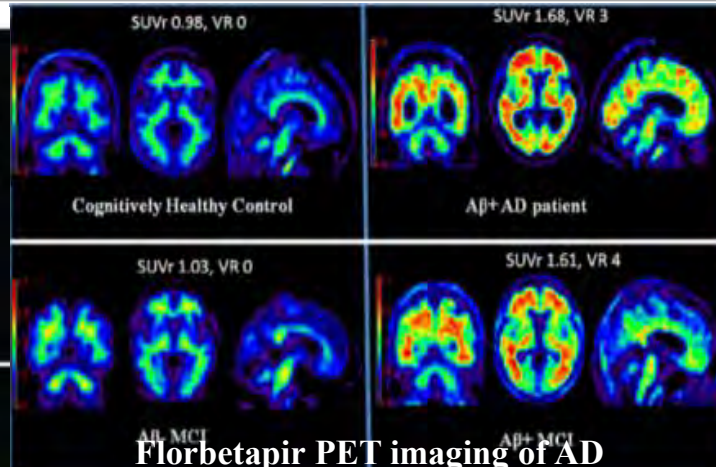**FDA-approved Aβ PET drugs:** ^{18}F-florbetaben, ^{18}F-florbetapir, and ^{18}F-flutemetamol

We will file an IND application to the FDA if interests in ^{11}C-PIB arise on campus.

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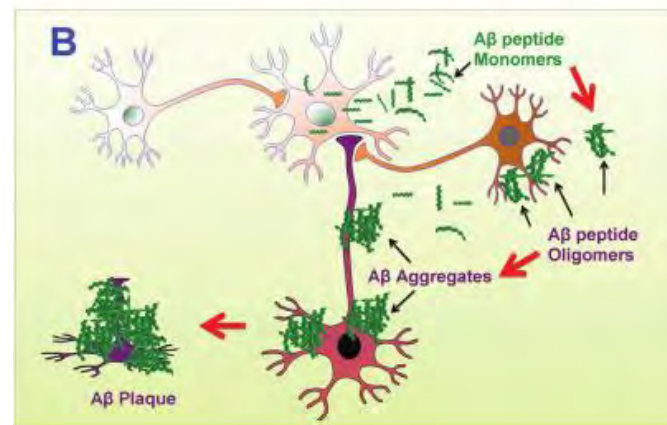
Examples of β-Amyloid PET Imaging

Fusion images from coregistered PET/MRI

Florbetapir PET imaging of AD

^{11}C-PIB in different diseases
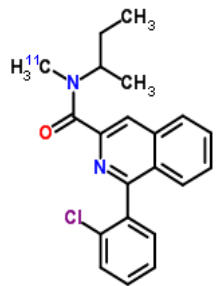

TBI: Traumatic brain injury

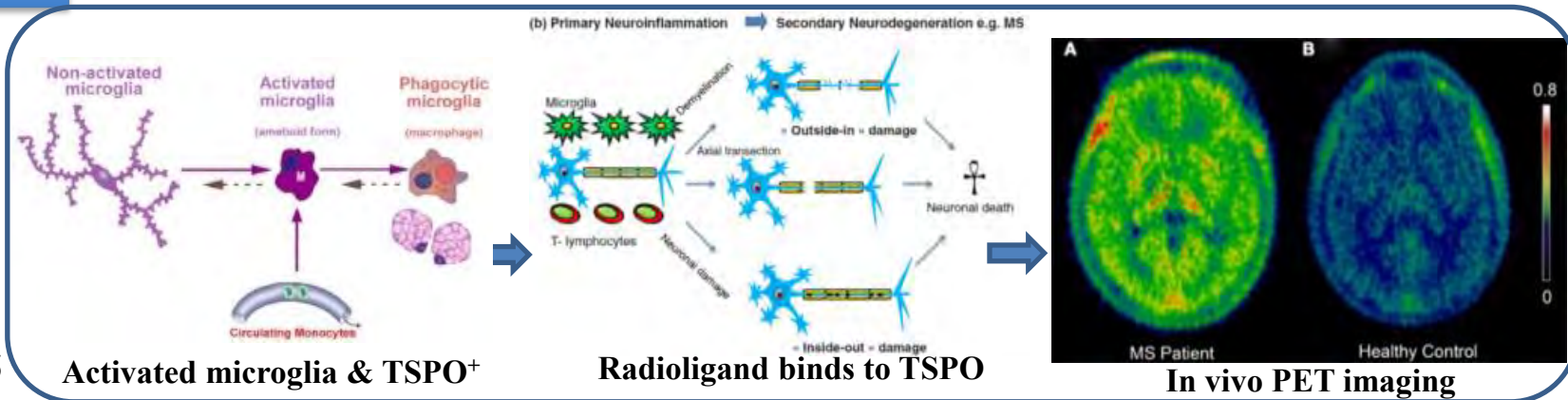^{11}C-PIB PET images coregistered MRI of TBI

High PIB retention was observed in patients with Alzheimer's disease (**A**) and patients with Lewy bodies (**B**). In contrast, low PIB retention was observed in patients with Parkinson disease (**C**) and in patients with frontotemporal dementia (**D**).

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Inflammation Imaging with ^{11}C-PK11195

^{11}C-PK11195   **Activated microglia & TSPO$^+$**   **Radioligand binds to TSPO**   **In vivo PET imaging**

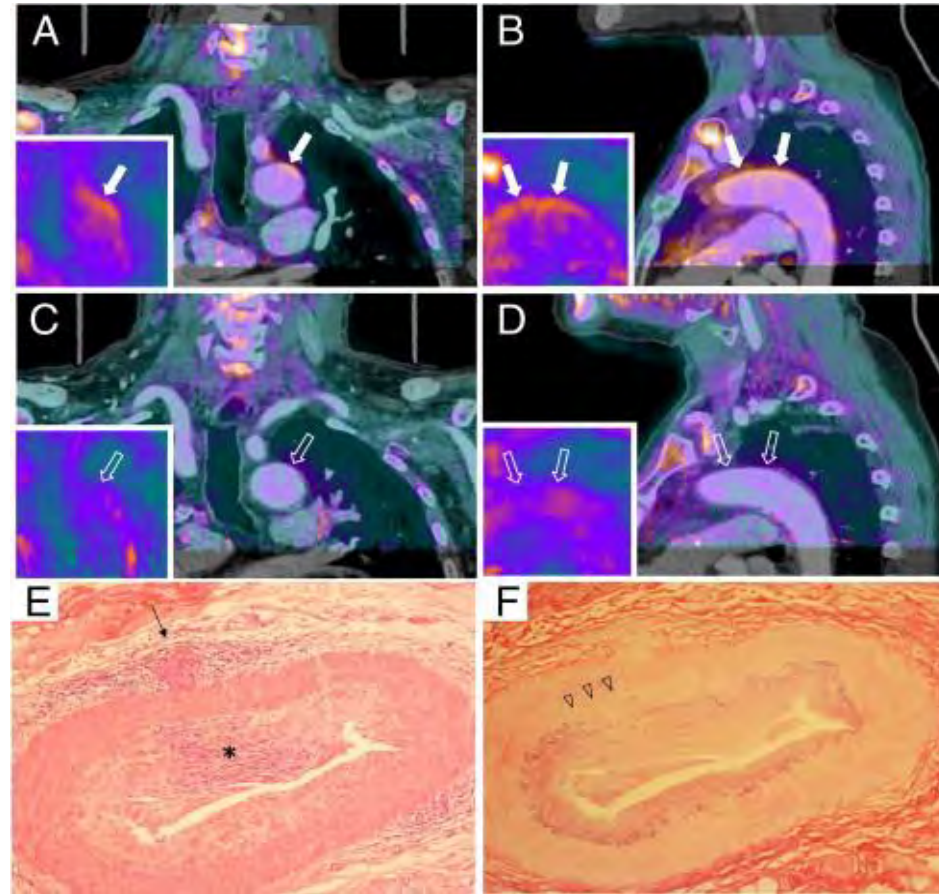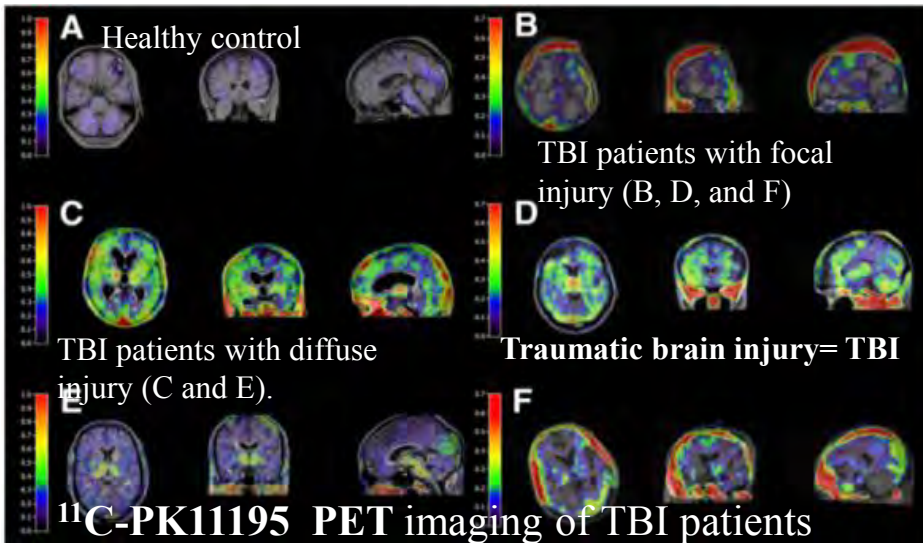**Application**

- ^{11}C-PK11195 binds to an 18-kDa translocator protein (TSPO) found on activated microglia.
- PET with ^{11}C-PK11195, as a biomarker of activated microglia, has been proposed to visualize in vivo inflammation in human disorders including Rasmussen's encephalitis, MS, AD, PD, amyotrophic lateral sclerosis, HD, HIV, herpes encephalitis, and neuropsychiatric disorders such as schizophrenia.
- **Other TSPO PET tracers:** ^{11}C-DAA1106, ^{11}C-PBR28, ^{18}F-DPA-714, ^{18}F-FEDAA1106.

We will file an IND application to the FDA if interests in ^{11}C-PK11195 arise on campus.

Insights Imaging.2012, 3:111–119.

Examples of ^{11}C-PK11195 PET Imaging

Healthy control

TBI patients with focal injury (B, D, and F)

TBI patients with diffuse injury (C and E).

Traumatic brain injury= TBI

[11]**C-PK11195 PET** imaging of TBI patients

PET/MRI   **FA**

[11]**C-PK 11195-PET overlaid on T1-weigthed MRI (left) and fractional anisotropy image showing fiber tracts (right).**

[11]C-PK11195 PET/CT images were obtained before **(A & B)** and after **(C & D)** a 20-week treatment with oral corticosteroids. After treatment, comparable image planes **(C and D)** demonstrate a marked reduction in [^{11}C]-PK11195 uptake. Aortic wall target-to-background ratios decreased from 1.63 to 0.87.**(E)** Temporal artery biopsy specimens stained with hematoxylin and eosin. **(F)** Elastica van Gieson staining (arrowheads).
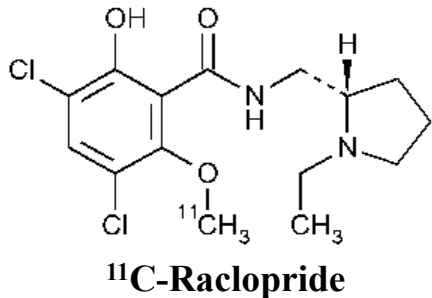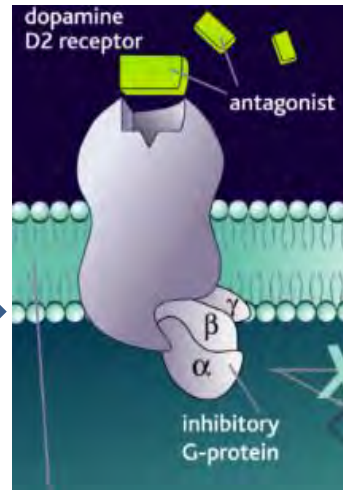
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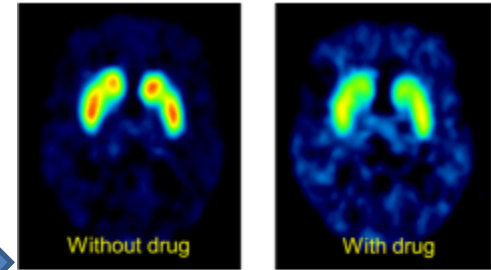# Dopamine Receptor (D2) Imaging with ^{11}C-Raclopride

Mechanism

Raclopride is a compound that acts as an antagonist on D2 dopamine receptor. ^{11}**C-Raclopride** is a PET tracer that binds to the receptor.

^{11}**C-Raclopride**

"Happy receptor"

Radioligand binding D2 Dopamine Receptor

Reduction of ^{11}C-raclopride binding in striatum occurs when drug is administered (right image).

In vivo PET imaging

Application

➢ Noninvasively assess the degree of dopamine binding to the D_2 Dopamine receptor.

➢ ^{11}C-raclopride is commonly used to determine the efficacy and neurotoxicity of dopaminergic drugs.

We will file an IND application to the FDA if interests in ^{11}C-Raclopride arise on campus.

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Examples of ^{11}C-Raclopride PET Imaging
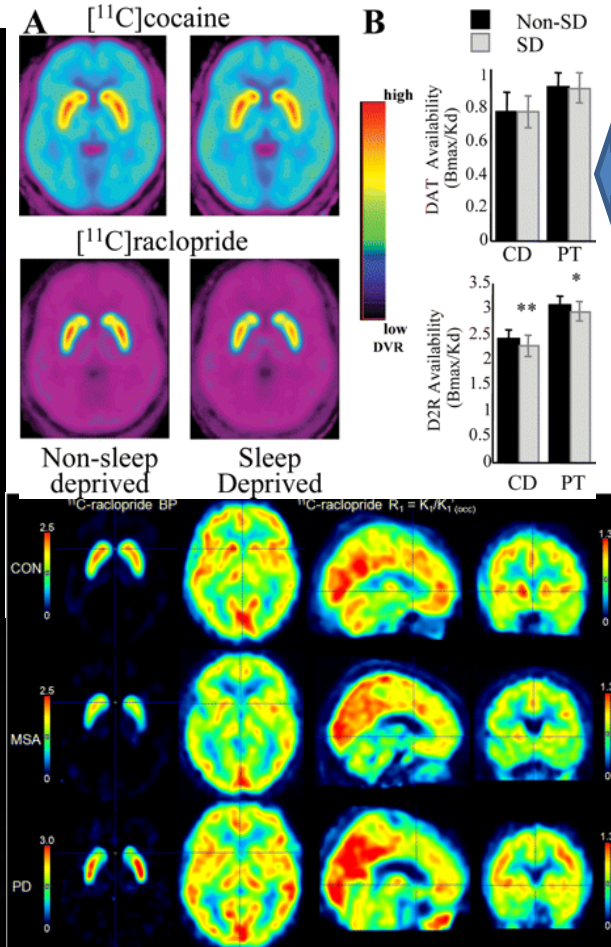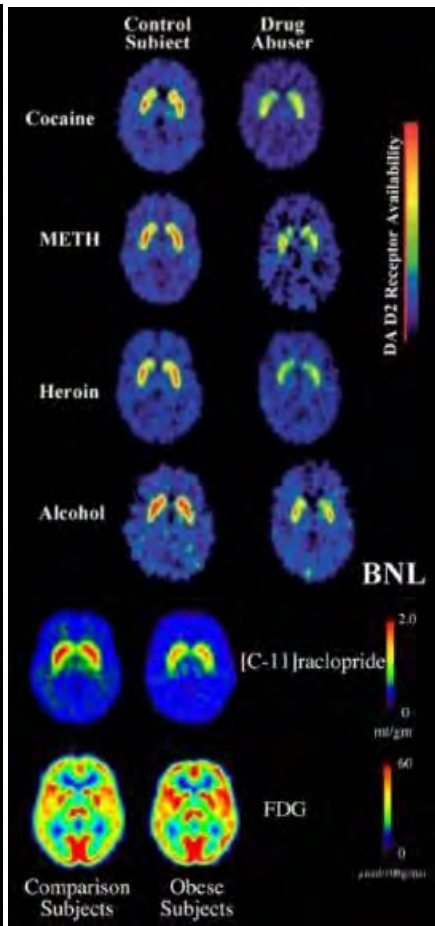
Averaged brain images of the distribution volume ratio for ^{11}C-cocaine (dopamine transporter radioligand) and for ^{11}C-raclopride at the level of the striatum for non-SD and SD (sleep deprivation) conditions.
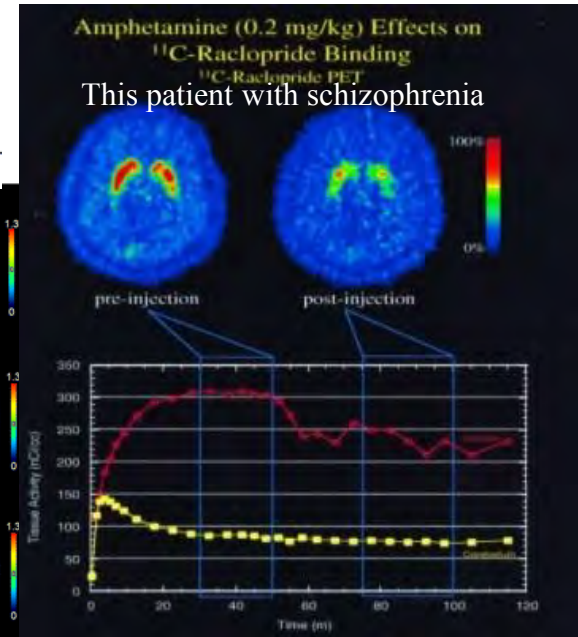
This patient with schizophrenia

Images of **^{11}C-Raclopride** in subjects addicted to different drugs. Dopamine D2 Receptors are lower in addiction.

Representative transverse slices of ^{11}C-raclopride BP and orthogonal slices of ^{11}C-raclopride R_1 (parametric maps) in a healthy volunteer, multiple-system atrophy (MSA) patient, and a PD (Parkinson disease) patient. Images are in radiologic orientation. CON = control; OCC = occipital.

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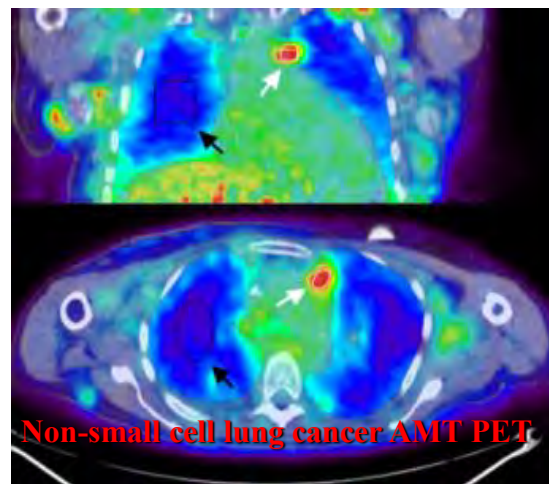Medical Center
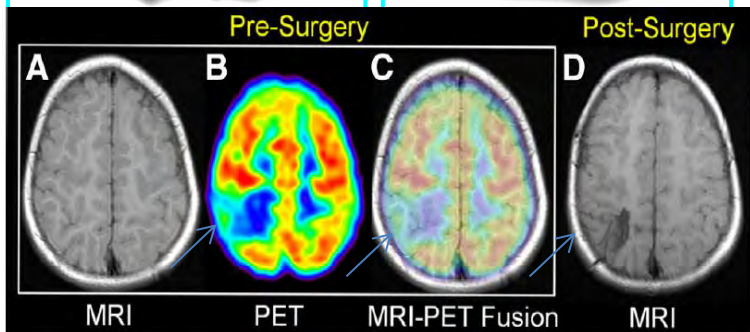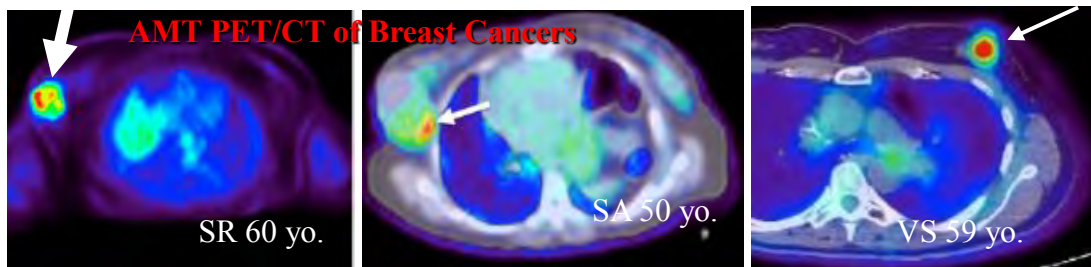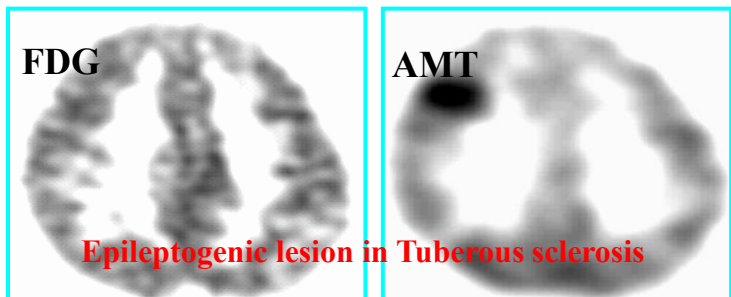
Amino Acid Metabolism Imaging with ^{11}C-AMT

Mechanism
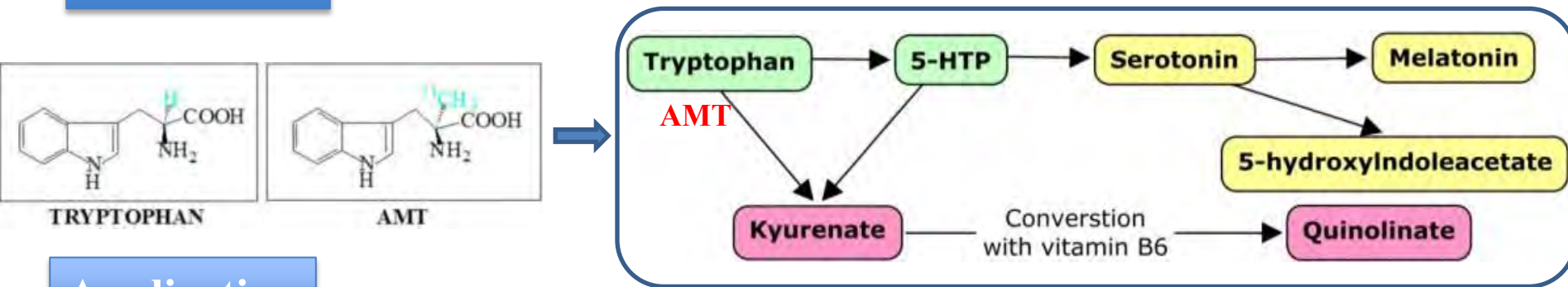
Application

➤ **α-[^{11}C]methyl-L-tryptophan (AMT)** is an analog of tryptophan.

➤ AMT-PET can measure serotonin synthesis capacity and tryptophan metabolism via the kynurenine pathway in humans.

➤ AMT-PET uptake is used to identify epileptogenic foci, as a biomarker in autism, and tryptophan metabolism in human cancer.

We will file an IND application to the FDA if interests in ^{11}C-AMT arise on campus.

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FDG

AMT

Epileptogenic lesion in Tuberous sclerosis

Pre-Surgery — Post-Surgery

A — B — C — D

MRI — PET — MRI-PET Fusion — MRI

AMT

MRI+FDG

Rt — Lt

AMT PET in patients with failed epilepsy surgery

AMT PET/CT of Breast Cancers

SR 60 yo. — SA 50 yo. — VS 59 yo.

Non-small cell lung cancer AMT PET

Tumor

Lung

AMT-PET image of Brain Tumor

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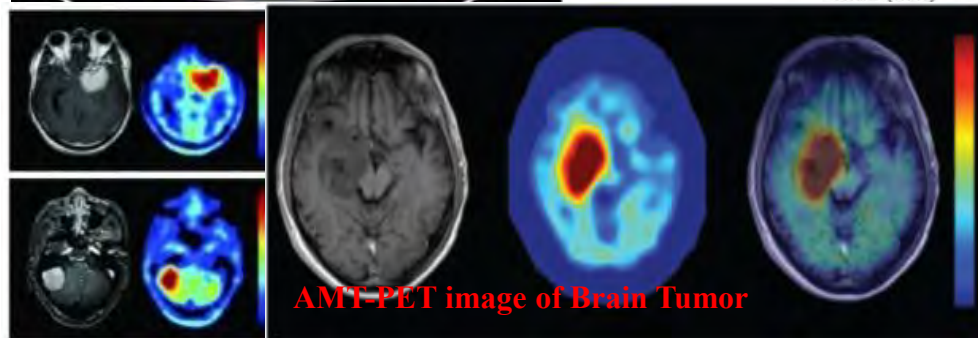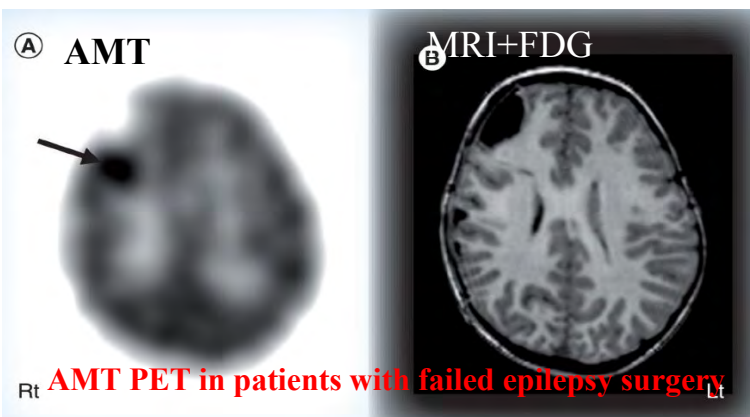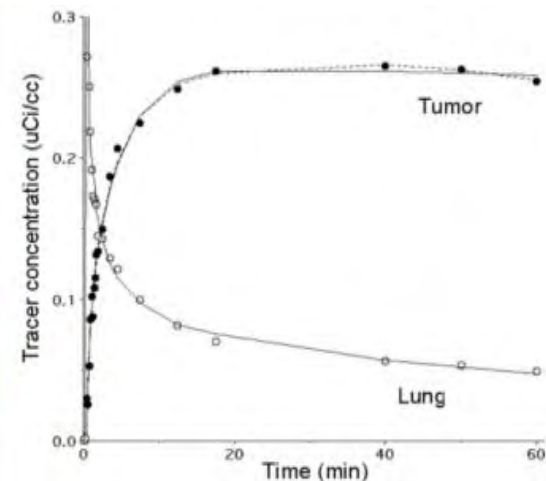
Opportunities in Biomolecules and Nanomedicine

➢ Recently, biologics (peptide, affibody, antibody, protein, nanoparticle) based drug research grows rapidly and considerably.

➢ PET imaging can track and quantify "biologics" in a longitudinal manner over a relatively long time course. It provides "look before you treat" as companion diagnostics for therapeutic "biologics" .

➢ PET imaging of "Biologics" requires long-lived radionuclides, such as ^{64}Cu ($t_{1/2}$ = 12.7 h) and ^{89}Zr ($t_{1/2}$ = 78.4 h)

1 h   3 h   24 h
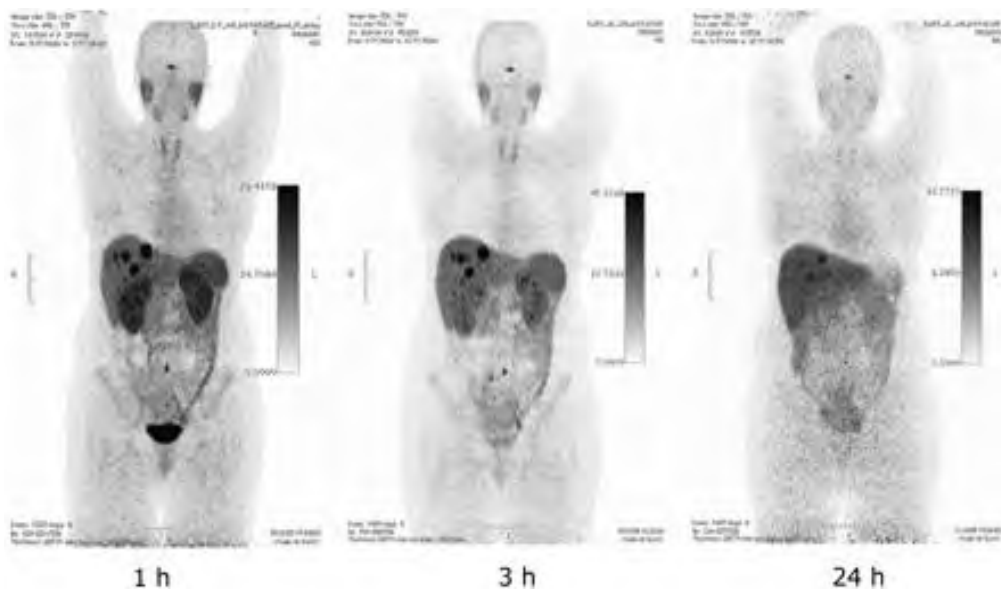
^{64}Cu-DOTATATE PET images (out to 24 h) of a patient with gastroenteropancreatic NET with liver metastases
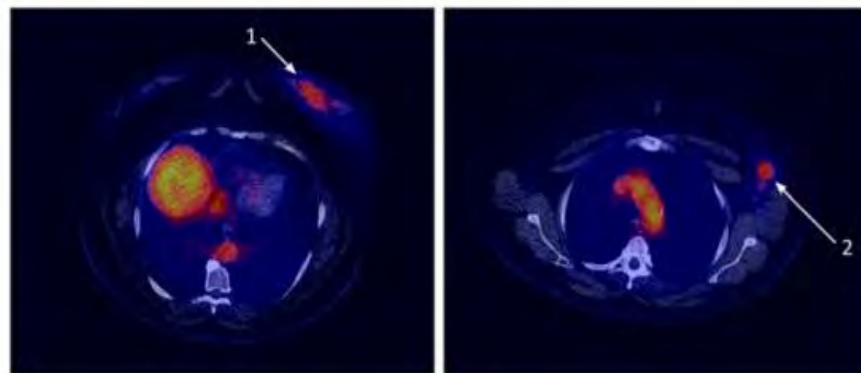
^{89}Zr-bevacizumab PET of a patient with primary breast tumor (1) and lymph node metastasis (2).

The clinical use of ^{64}Cu or ^{89}Zr "biologics" requires eIND or IND approvals by the FDA.

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