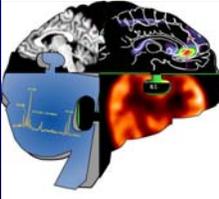


**Positron Emission Tomography:
Tool to Facilitate Drug Development and
to Study Pharmacokinetics**

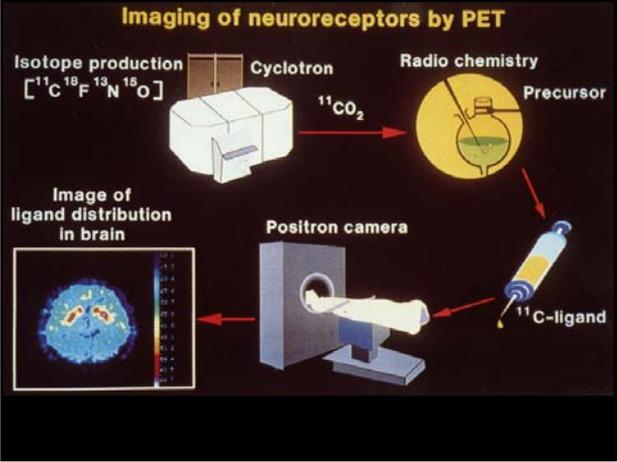


Robert B. Innis, MD, PhD
Molecular Imaging Branch
National Institute Mental Health

October 8, 2009

Outline of Talk

1. PET has high sensitivity and specificity
2. PET used in therapeutic drug development
3. Pharmacokinetic modeling of plasma concentration and tissue uptake can measure receptor density
4. Study drug distribution: "peripheral" benzodiazepine receptor
5. Study drug metabolism: inhibit defluorination



Positron Emission Tomography

PET vs. MRI

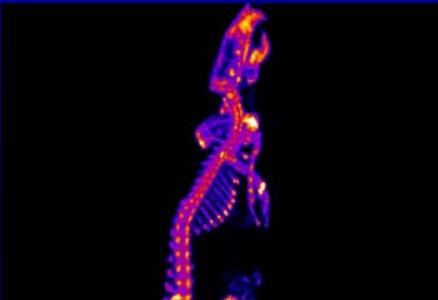
	PET	MRI
Spatial Resolution	2 - 6 mm	<< 1 mm
Sensitivity	10 ⁻¹² M	10 ⁻⁴ M
Temporal Resolution	minutes	<1 sec

Radionuclide (¹¹C): high sensitivity
 Ligand (raclopride): high selectivity
 Radioligand [¹¹C]raclopride: high sensitivity & selectivity

Radioligand = Drug + Radioactivity

- Drug administered at tracer doses**
 - No pharm effects
 - Labels <1% receptors
 - Labeled subset reflects entire population
- Radioligand disposed like all drugs**
 - Metabolism & distribution
- Radiation exposure**

**NIH Rodent PET Camera
¹⁸F bone uptake rat**

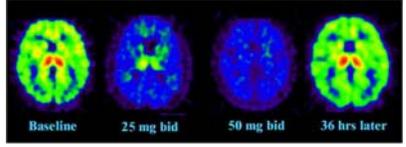


Developed By: Mike Green & Jurgen Seidel

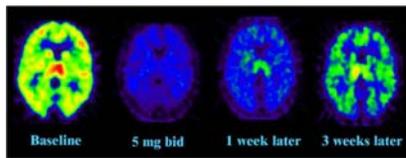
**PET: Tool in Therapeutic
Drug Development**

- Determine dose and dosing interval
- Identify homogeneous group
- Biomarker for drug efficacy
- Monitor gene or stem cell therapy

**Lazabemide blocks [¹¹C]deprenyl
binding to monoamine-oxidase-B (MAO-B)**

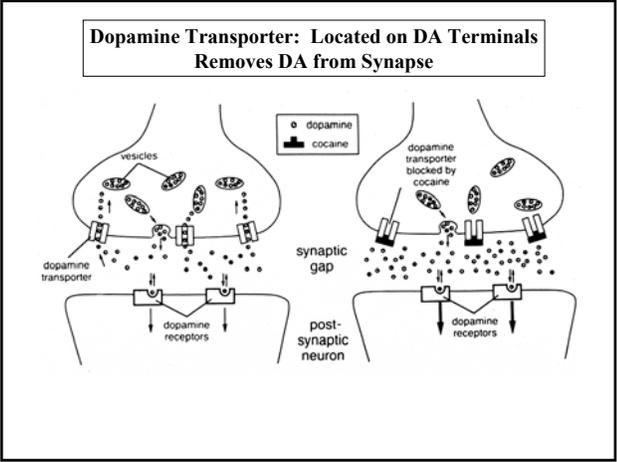


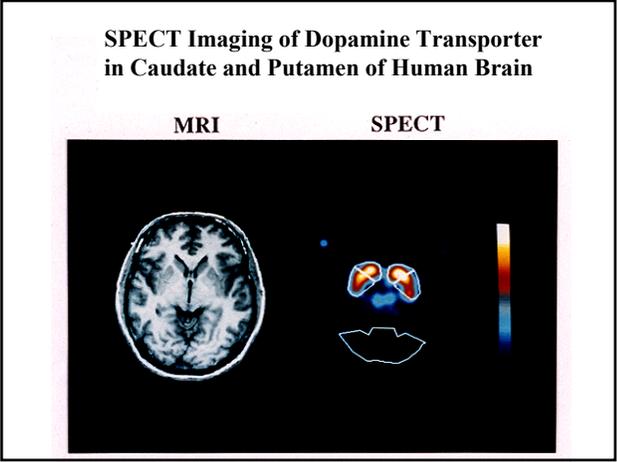
**Selegilene is more potent and longer acting
than lazabemide**

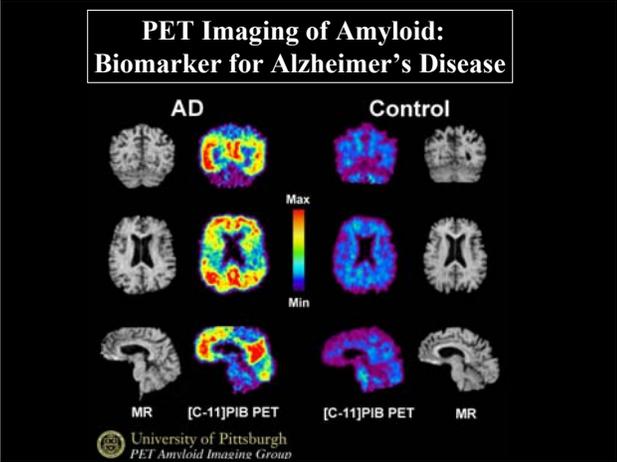


PET: Tool in Therapeutic Drug Development

- Determine dose and dosing interval
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- Biomarker for drug efficacy
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PET: Tool in Therapeutic Drug Development

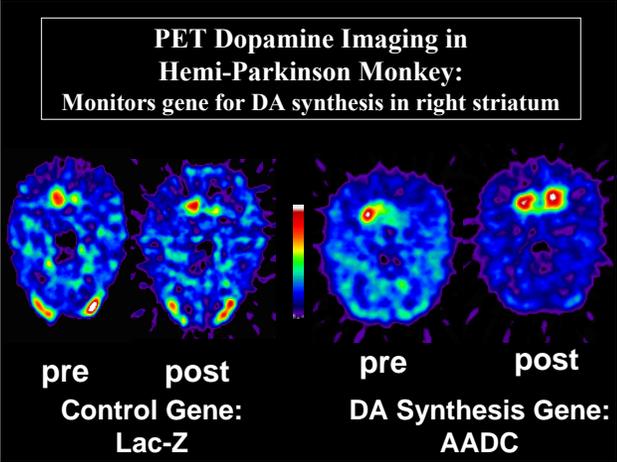
- Determine dose and dosing interval
- Identify homogeneous group
- Biomarker for drug efficacy
- **Monitor gene or stem cell therapy**

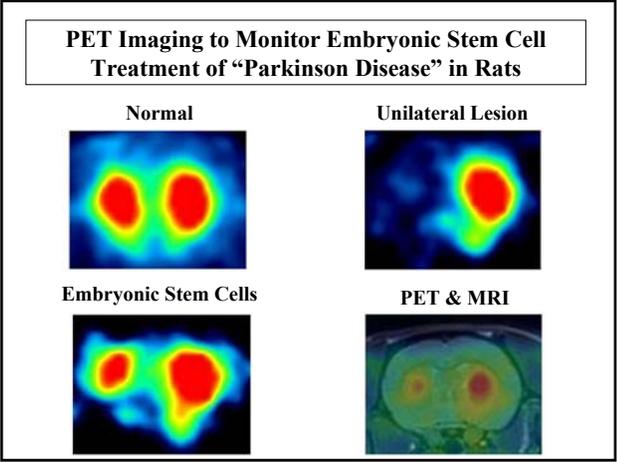
Gene Therapy Using Viral Vectors

Viral vectors deliver gene that synthesizes dopamine (DA)
 Infuse virus into striatum (target cells)

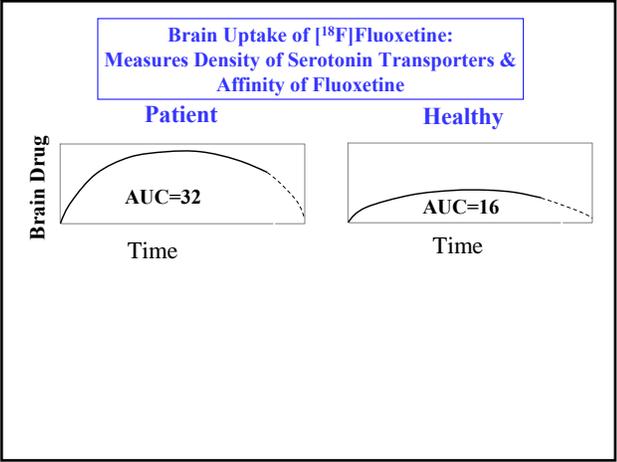
Target cells express the DA gene

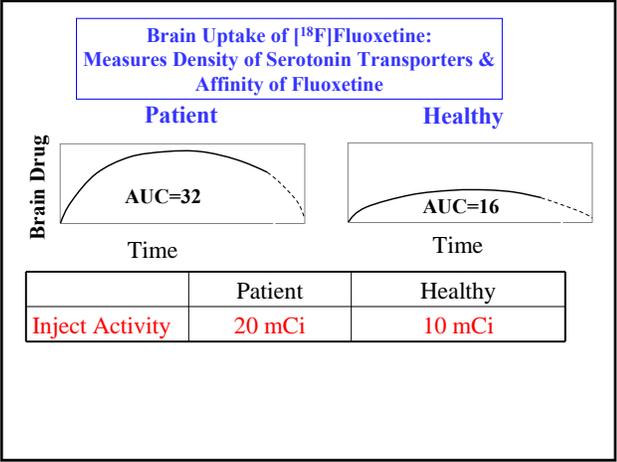
DNA (Gene) Gene encapsulated in AAV AAV releases gene into cell Patient cell Gene expresses proteins Therapeutic protein

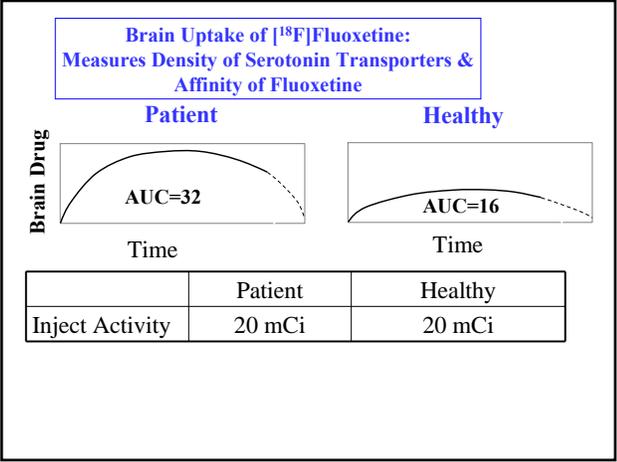




- Outline of Talk**
1. PET has high sensitivity and specificity
 2. PET used in therapeutic drug development
 3. Pharmacokinetic modeling: plasma concentration and tissue uptake
 4. Study drug distribution: "peripheral" benzodiazepine receptor
 5. Study drug metabolism: inhibit defluorination







**Brain Uptake of [¹⁸F]Fluoxetine:
Measures Density of Serotonin Transporters &
Affinity of Fluoxetine**

Patient

AUC=32

Healthy

AUC=16

	Patient	Healthy
Inject Activity	20 mCi	20 mCi
Weight	50 kg	100 kg

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Measures Density of Serotonin Transporters &
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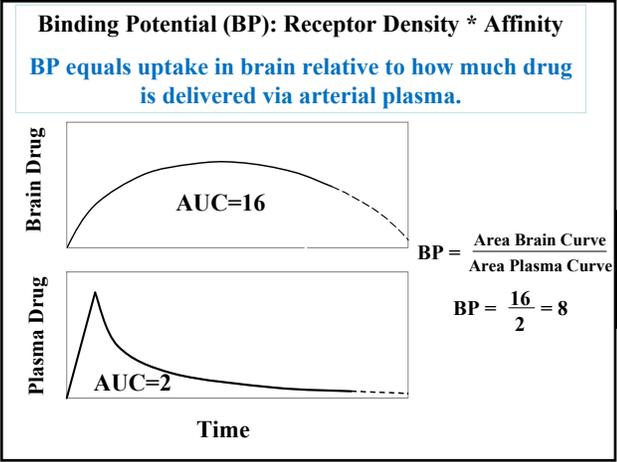
Patient

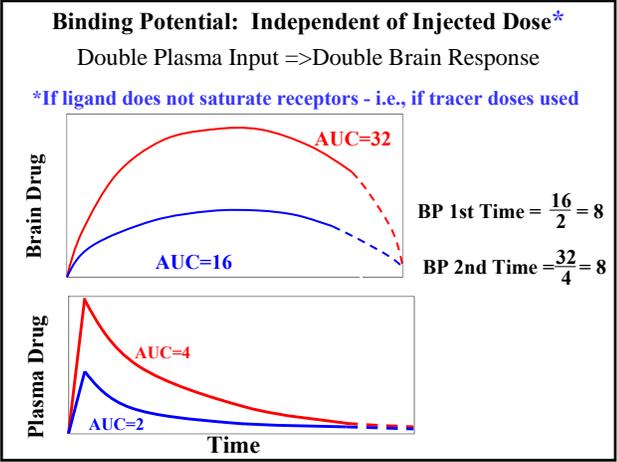
AUC=32

Healthy

AUC=16

	Patient	Healthy
Inject Activity	40 mCi	20 mCi
Weight	100 kg	100 kg
Liver disease	Yes	No





BP can be calculated from the Area Under Curve (math integral) as well as rate constants (math differential).

From curves of plasma and brain radioactivity over time, estimate rate constants of entry and removal to/from tissue.

Plasma $\xrightleftharpoons[k_2]{K_1}$ Brain

$$BP = \frac{K_1}{k_2}$$

Tissue uptake is proportional to density of receptors and the affinity of the drug

Binding Potential $BP = \frac{B_{max}}{K_D} = B_{max} \times \frac{1}{K_D} = B_{max} \times \text{affinity}$

B_{max} = receptor density
 K_D = dissociation binding constant
 $\frac{1}{K_D}$ = binding affinity drug

SUMMARY PET KINETICS

- Organ uptake is proportional to receptor density and affinity of drug
- Binding Potential (BP) = density X affinity
- "Drug Exposure" to tissue is AUC of: plasma concentration vs. time
- "Response" (uptake) of tissue is AUC of: tissue concentration vs. time

$$BP = \frac{\text{Response}}{\text{Exposure}} = \frac{AUC_{\text{tissue}}}{AUC_{\text{plasma}}}$$

- BP also equals ratio of rate constants of entry and removal to/from tissue

$$BP = \frac{k_1}{k_2}$$

Major Point of PET Pharmacokinetics (in words)

- Plasma pharmacokinetics provides a limited view of what's happening to drug in plasma.
- PET provides a limited view of what's happening to drug in tissue.
- **Concurrent measurement of drug in plasma and of drug in tissue allows quantitation of the target of drug action – i.e., receptor.**

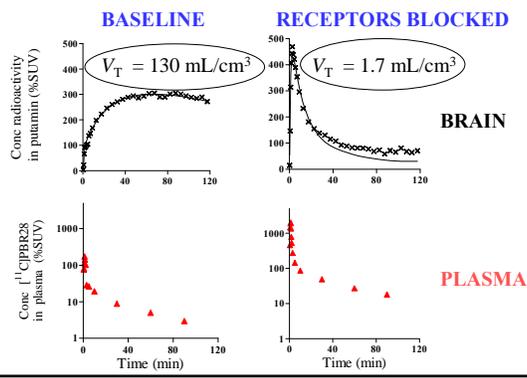
Outline of Talk

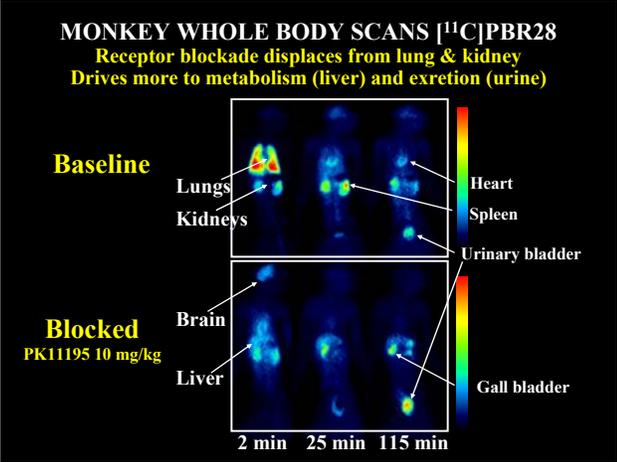
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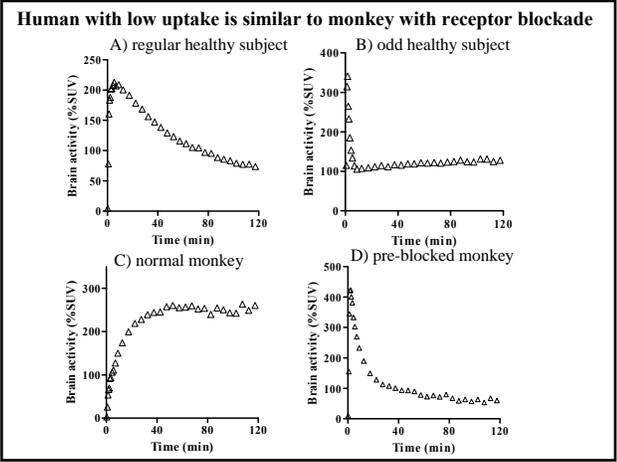
Translocator Protein (18 kDa) a.k.a. "peripheral benzodiazepine receptor"

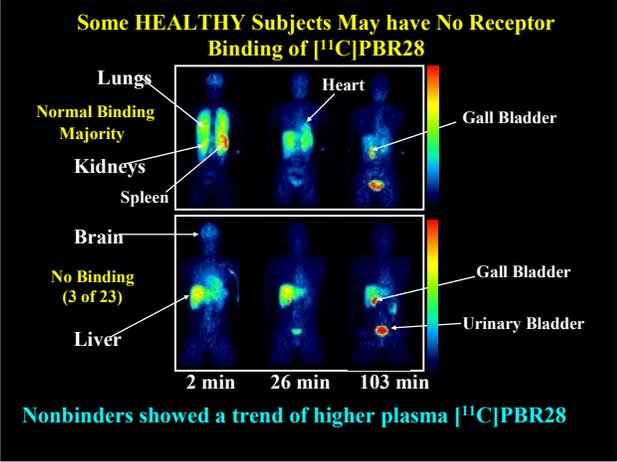
- 1. Mitochondrial protein highly expressed in macrophages and activated microglia
- 2. Exists in periphery and brain
- 3. Multiple potential functions: steroid synthesis, nucleotide transport
- 4. Distinct from typical benzodiazepine GABA_A receptor in brain
- 5. Marker for cellular inflammation

Receptor Blockade [¹¹C]PBR28 in Monkey Brain: more radioligand in plasma and brain









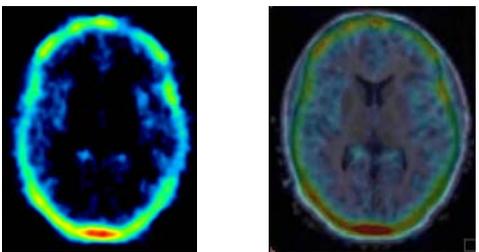
INFLAMMATION IMAGING
On-going Studies

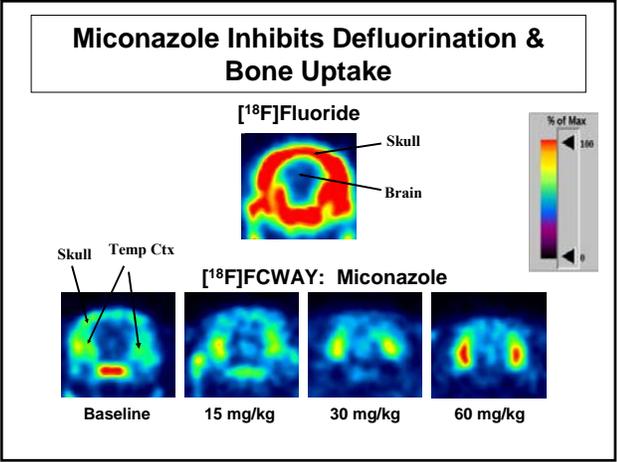
- Neurocysticercosis
- Multiple sclerosis
- HIV with cognitive impairment
- Alzheimer's disease
- Atherosclerosis

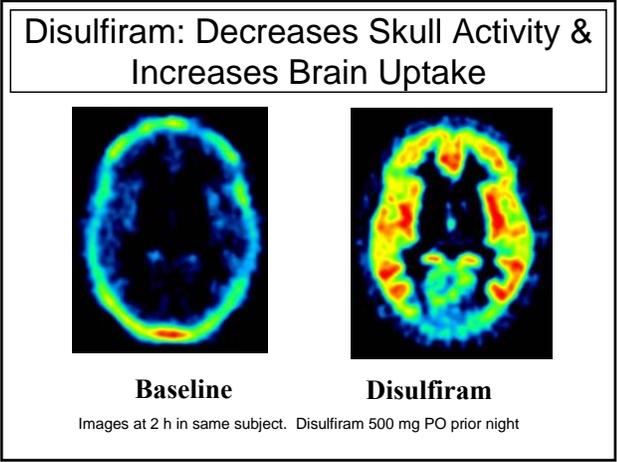
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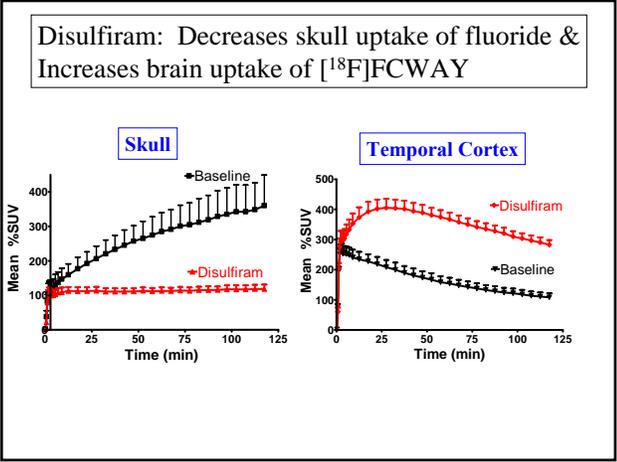
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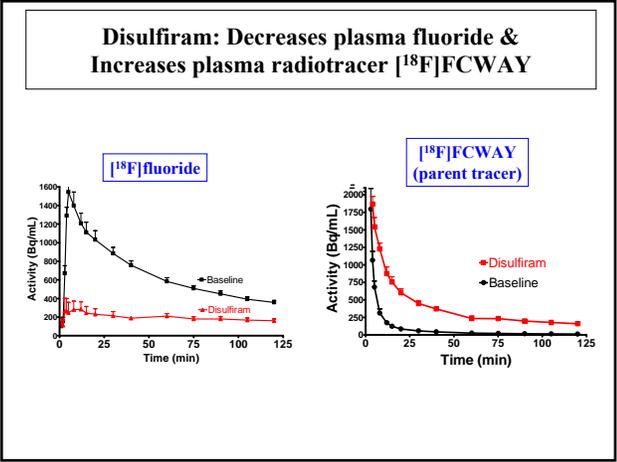
[¹⁸F]FCWAY: Defluorination
Bone uptake: human skull at 2 h











- Summary of Talk**
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- FDA Critical Path Initiative**
- Approvals for new drugs declining
 - R&D funding by industry and NIH is increasing
 - Problem: tools are inadequate for efficient evaluation of new drugs in the “critical path” of development
 - Still using old tools like liver enzymes and hematocrit to evaluate safety and efficacy
 - Need new **Product Development Toolkit**

CRITICAL PATH to New Medical Products
 FDA, March 2004

“There is currently an urgent need for additional **public-private collaborative work** on applying technologies such as ... new imaging technologies.

Opportunity: **Imaging technologies**, such as molecular imaging tools in neuropsychiatric diseases or as measures of drug absorption and distribution, may provide powerful insights into the distribution, binding, and other biological effects of pharmaceuticals.”

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 National Institutes of Health

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The Consortium will search for and validate new biological markers—biomarkers—to accelerate dramatically the competitive delivery of successful new technologies, medicines, and therapies for prevention, early detection, diagnosis, and treatment of disease. Biomarkers are molecular, biological, or physical characteristics that indicate a specific, underlying physiologic state. For example, cholesterol and blood pressure are perhaps the most well known biomarkers; these biomarkers are indicators of cardiovascular health.

**Self-Assessment Quiz:
True or False?**

- Positron emission tomography (PET) studies involve the injection of a radioactively labeled drug that emits a particle called a positron.
- PET shows the location of radioactivity in a cross section (or tomograph) of the body.
- PET can be used to quantify the density of specific proteins in the body.
- Compartmental modeling of PET data typically uses measurements over time of 1) PET images of the target tissue and 2) concentrations of unchanged parent radioligand in plasma.
