

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

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## **Outline of Talk**

PET has high sensitivity and specificity

PET used in therapeutic drug development

Pharmacokinetic modeling of plasma concentration and tissue uptake can measure receptor density

Study drug distribution: “peripheral” benzodiazepine receptor

Study drug metabolism: inhibit defluorination

## Imaging of neuroreceptors by PET

Illustration of requirements for PET: Isotope production, radiochemistry to create ligand, positron camera for imaging.

# Imaging of neuroreceptors by PET

Illustration of requirements for PET

# *Positron Emission Tomography*

Title slide for a talk on this topic by Simon R. Cherry at the University of California-Davis.

# PET vs. MRI

Chart comparing PET with MRI

Radionuclide ( $^{11}\text{C}$ ): high sensitivity

Ligand (raclopride): high selectivity

Radioligand [ $^{11}\text{C}$ ]raclopride: high sensitivity & selectivity

PET provides greater sensitivity but less spatial resolution than MRI.

## **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**

## **<sup>18</sup>F bone uptake rat**

PET scan image.

**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)**

Images of baseline, 25 mg bid, 50 mg bid, and 36 hours later.

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

Images at baseline, 5 mg bid, 1 week later and 3 weeks later.

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**Dopamine Transporter: Located on DA  
Terminals  
Removes DA from Synapse**

Illustration of this process at synapse.

# SPECT Imaging of Dopamine Transporter in Caudate and Putamen of Human Brain

MRI

SPECT

Illustration of imaging differences in MRI vs. SPECT.

## 123I- $\beta$ -CIT Dopamine Transporter SPECT: Decreased in Parkinson's Disease

Images of this activity in a healthy individual vs. a Parkinson Stage 1 patient.

# **PET: Tool in Therapeutic Drug Development**

**Determine dose and dosing interval**

**Identify homogeneous group**

**Biomarker for drug efficacy**

**Monitor gene or stem cell therapy**

## **Serial Dopamine Transporter Imaging in a Parkinson Patient**

Images comparing baseline with 22 months, 34 months, and 46 months with progressive reduction in dopamine transporter.

Institute for Neurodegenerative Disorders



# **PET Imaging of Amyloid: Biomarker for Alzheimer's Disease**

Images comparing AD to Control.

University of Pittsburgh  
PET Amyloid Imaging Group

## PET: Tool in Therapeutic Drug Development

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# 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

Illustration of gene therapy.

PET Dopamine Imaging in  
Hemi-Parkinson Monkey:  
Monitors gene for DA synthesis in right striatum

## **. PET Imaging to Monitor Embryonic Stem Cell Treatment of “Parkinson Disease” in Rats**

PET images of normal, unilateral lesions and embryonic stem cells in PET & MRI.

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

Illustration of brain drug levels in a patient compared with brain drug levels in a healthy subject over time.

## Brain Uptake of [ $^{18}\text{F}$ ]Fluoxetine: Measures Density of Serotonin Transporters & Affinity of Fluoxetine

Illustration of brain drug levels in a patient compared to brain drug levels in a healthy subject over time. Effect of injected activity (dose).



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

Illustration of a brain drug levels in a patient compared to brain drug levels in a healthy subject over time at different doses. Equal doses but different AUCs.

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

Illustration of brain drug levels in patient compared to brain drug levels in a healthy subject over time. Effect of body weight.

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

Illustration of brain drug in patient compared to brain drug in a healthy subject over time.  
Equal weight but different AUCs.

## Brain Uptake of [18F]Fluoxetine: Measures Density of Serotonin Transporters

Illustration of brain drug in patient compared to brain drug in a healthy subject over time.  
Effects of liver disease.

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**Binding Potential (BP): Receptor Density \* Affinity**  
**BP equals uptake in brain relative to how much drug**  
**is delivered in arterial plasma**

Chart illustrating the binding potential in the brain comparing drug in plasma with drug in brain.

Binding Potential: Independent of Injected Dose\*

Double Plasma Input => Double Brain Response

\*If ligand does not saturate receptors - i.e. if tracer doses  
used

Charts illustrating this.

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

Formula for this calculation.

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

Formula for binding potential.



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

## **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.**

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## Translocator Protein (18 kDa) a.k.a. “peripheral benzodiazepine receptor”

Mitochondrial protein highly expressed in macrophages and activated microglia

Exists in periphery and brain

Multiple potential functions: steroid synthesis, nucleotide transport

Distinct from typical benzodiazepine GABA<sub>A</sub> receptor in brain

Marker for cellular inflammation

## Receptor Blockade [<sup>11</sup>C]PBR28 in Monkey Brain: more radioligand in plasma and brain

Chart illustrating this and comparing baseline with receptors blocked.

MONKEY WHOLE BODY SCANS [<sup>11</sup>C]PBR28  
Receptor blockade displaces from lung & kidney  
Drives more to metabolism (liver) and excretion (urine)

Whole body scans of monkey at baseline and after blockade.

## Human with low uptake is similar to monkey with receptor blockade

Compares A) regular healthy subject with B) odd healthy subject.  
Graphic illustration.

**Some HEALTHY Subjects May have No Receptor Binding of [<sup>11</sup>C]PBR28**

Images of organs that demonstrate this occurrence.

**Nonbinders showed a trend of higher plasma [<sup>11</sup>C]PBR28**



# Focal and Global Increase of Inflammation

## Inflammation Imaging

Brain scans of the effects of healthy vs. diseased

## Disease

### Epilepsy

Focal increase in epileptogenic focus

### Alzheimer's disease

Global increase of inflammation

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[<sup>18</sup>F]FCWAY: Defluorination  
Bone uptake: human skull at 2 h

## **Miconazole Inhibits Defluorination & Bone Uptake**

Images of defluorination and bone uptake at various times.

## Disulfiram: Decreases Skull Activity & Increases Brain Uptake

Images of this at baseline and with Disulfiram.

Disulfiram: Decreases skull uptake of fluoride &  
Increases brain uptake of [<sup>18</sup>F]FCWAY

Charts comparing this uptake in the skull and the temporal cortex.

**Disulfiram: Decreases plasma fluoride &  
Increases plasma radiotracer [<sup>18</sup>F]FCWAY**

Charts that illustrate this activity.

## **Summary**

PET has high sensitivity and specificity

PET used in therapeutic drug development

Pharmacokinetic modeling of plasma concentration and tissue uptake can measure receptor density

Study drug distribution: block distribution to periphery and increase distribution to brain

Study drug metabolism: inhibit defluorination



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.

## **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.”

## Copy of website for the Foundation for the NIH

<http://www.fnih.org/>

The website for the Biomarkers Consortium

Information for this initiative can be found at  
[http://www.cancer.gov/ncicancerbulletin/NCI\\_Cancer\\_Bulletin\\_101006/page3](http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_101006/page3)

# Quantification of receptor density

## Distribution volume

Uptake in brain relative to how much drug is delivered via arterial plasma

# $^{18}\text{F}$ -SP203 in Human: Quantification went well

Calculations for regions, temporal cortex and cerebellum

Brown et al. 2008

Quantification of receptor density  
Equilibrium method  
Distribution volume

Concentration ratio of tissue to plasma under equilibrium

Line graph examples of Bolus injection and the equilibrium method



## Advantages of equilibrium method

Determine VT directly from concentration ratio of tissue to plasma under equilibrium

Less invasive

Rapid equilibrium can be achieved with bolus and constant infusion

# Rapid equilibrium with bolus plus constant infusion

From pharmacokinetic course 2009 by R.E. Carson

## Radioactivity became stable in plasma and brain with bolus plus constant infusion

Temporal cortex

Thalamus

Plasma parent