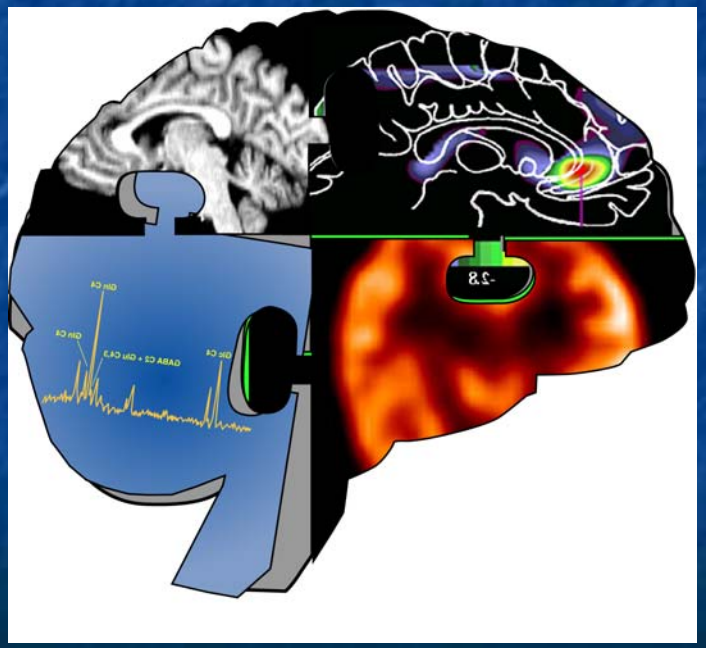
Positron Emission Tomography (PET) Imaging of Efflux Transporters



Robert B. Innis, MD, PhD
Molecular Imaging Branch
MIB: "Men In Black"
NIMH

Outline of Talk

* PET: high sensitivity and specificity
* Many PET ligands already exist to measure density of transporters – e.g., dopamine transporter in Parkinson's disease
* P-gp blocks brain entry of many drugs
* [^{11}C]loperamide: avid P-gp substrate but has radiometabolite; measures function
* [^{11}C]desmethyl-loperamide: metabolite is better than parent

Imaging of neuroreceptors by PET

Isotope production
[^{11}C ^{18}F ^{13}N ^{15}O]

Cyclotron

$^{11}CO_2$

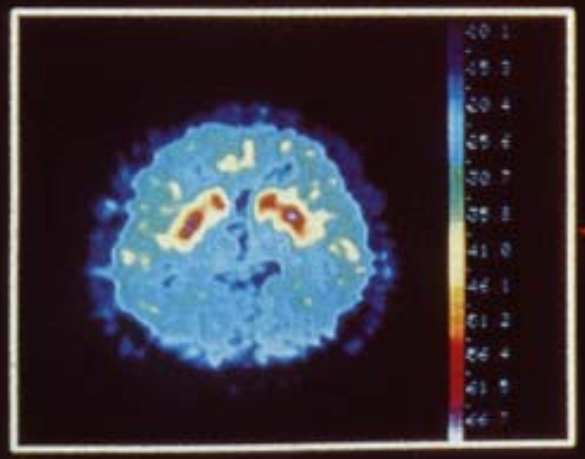
Radio chemistry

Precursor

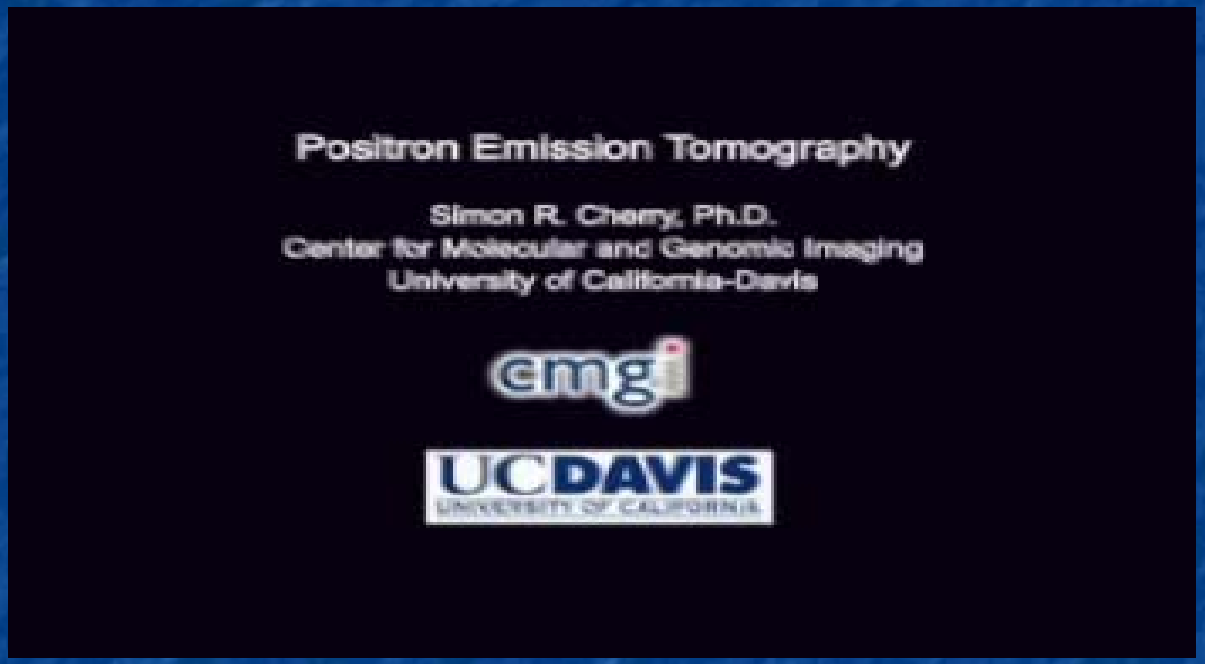
^{11}C-ligand

Positron camera

Image of
ligand distribution
in brain



Positron Emission Tomography



PET vs. MRI

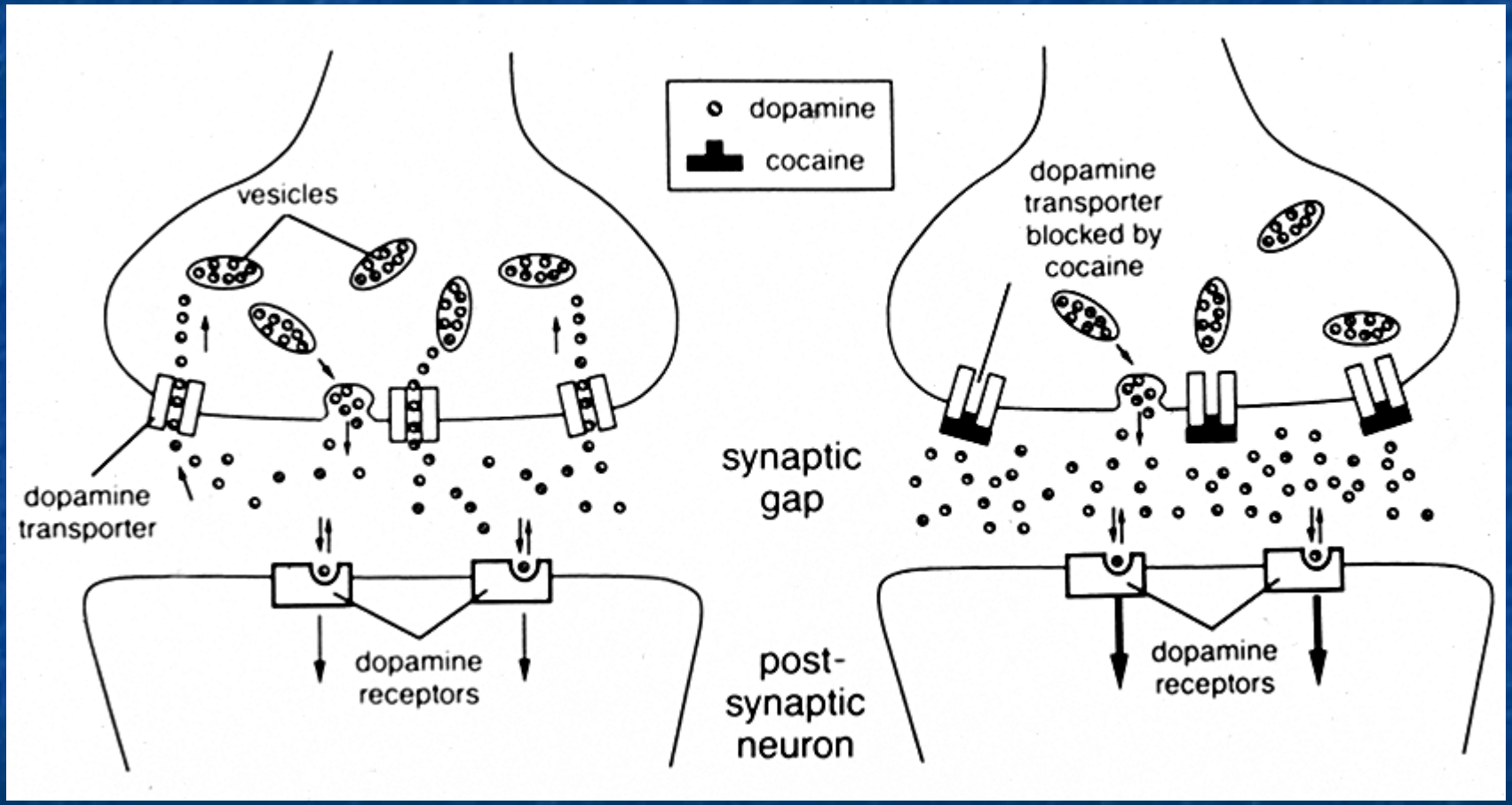
	PET	MRI
Spatial Resolution	2 – 6 mm	<< 1 mm
Sensitivity	10^{-12} M	10^{-4} M
Temporal Resolution	minutes	<1 sec

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

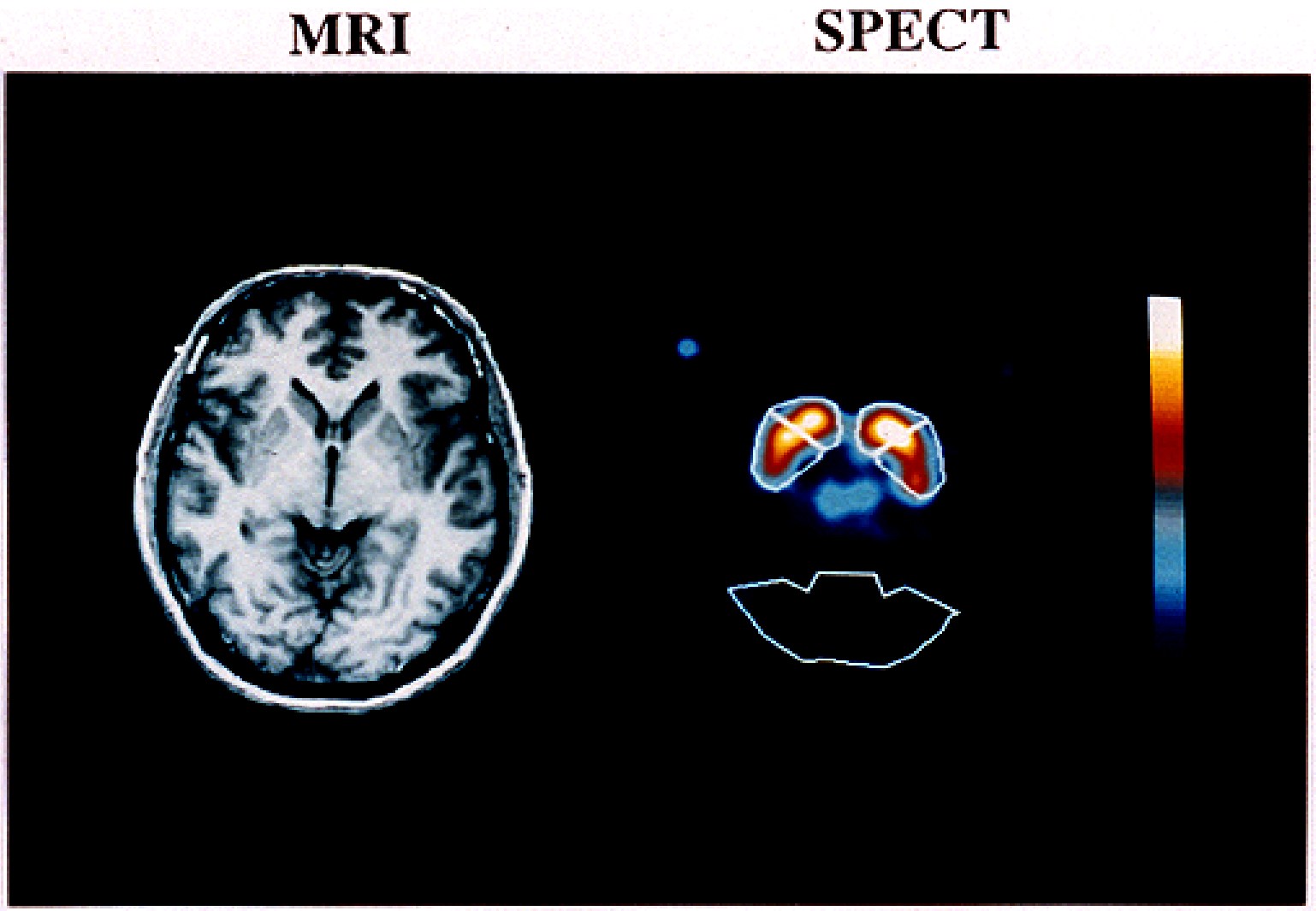
Radioligand = Drug + Radioactivity

1. **Drug administered at tracer doses**
   a) No pharm effects
   b) Labels <1% receptors
   c) Labeled subset reflects entire population
2. **Radioligand disposed like all drugs**
   a) Metabolism & distribution
3. **Radiation exposure**

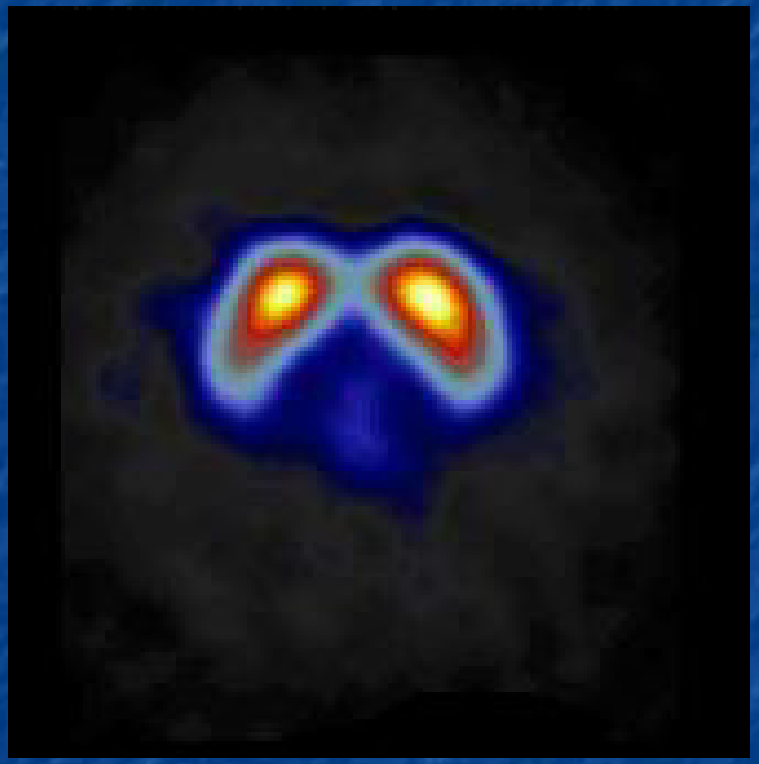
Dopamine Transporter: Located on DA Terminals Removes DA from Synapse



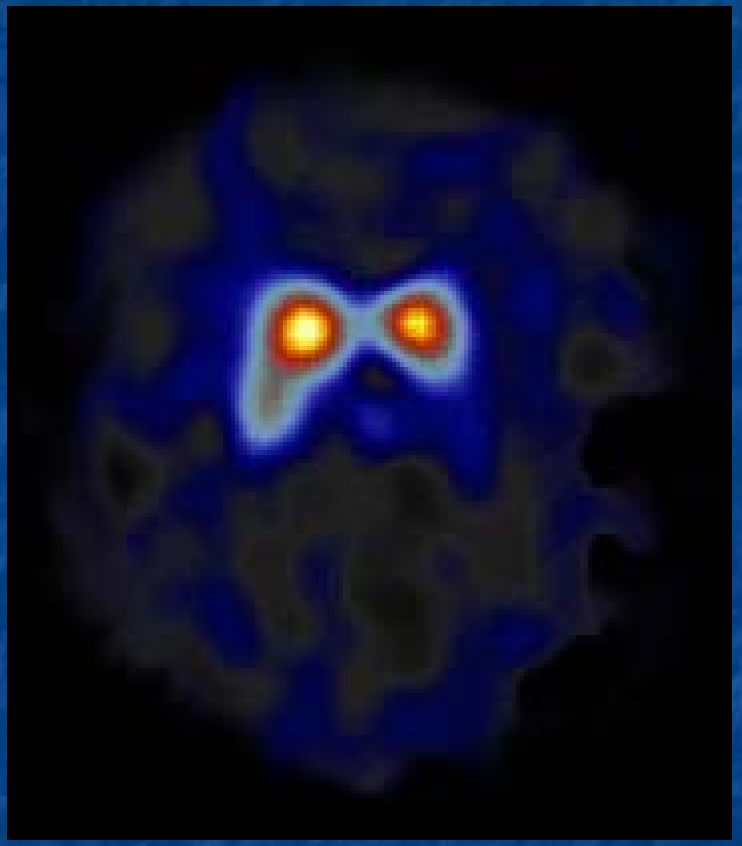
SPECT Imaging of Dopamine Transporter in Caudate and Putamen of Human Brain



^{123}I-β-CIT Dopamine Transporter SPECT: Decreased in Parkinson's Disease

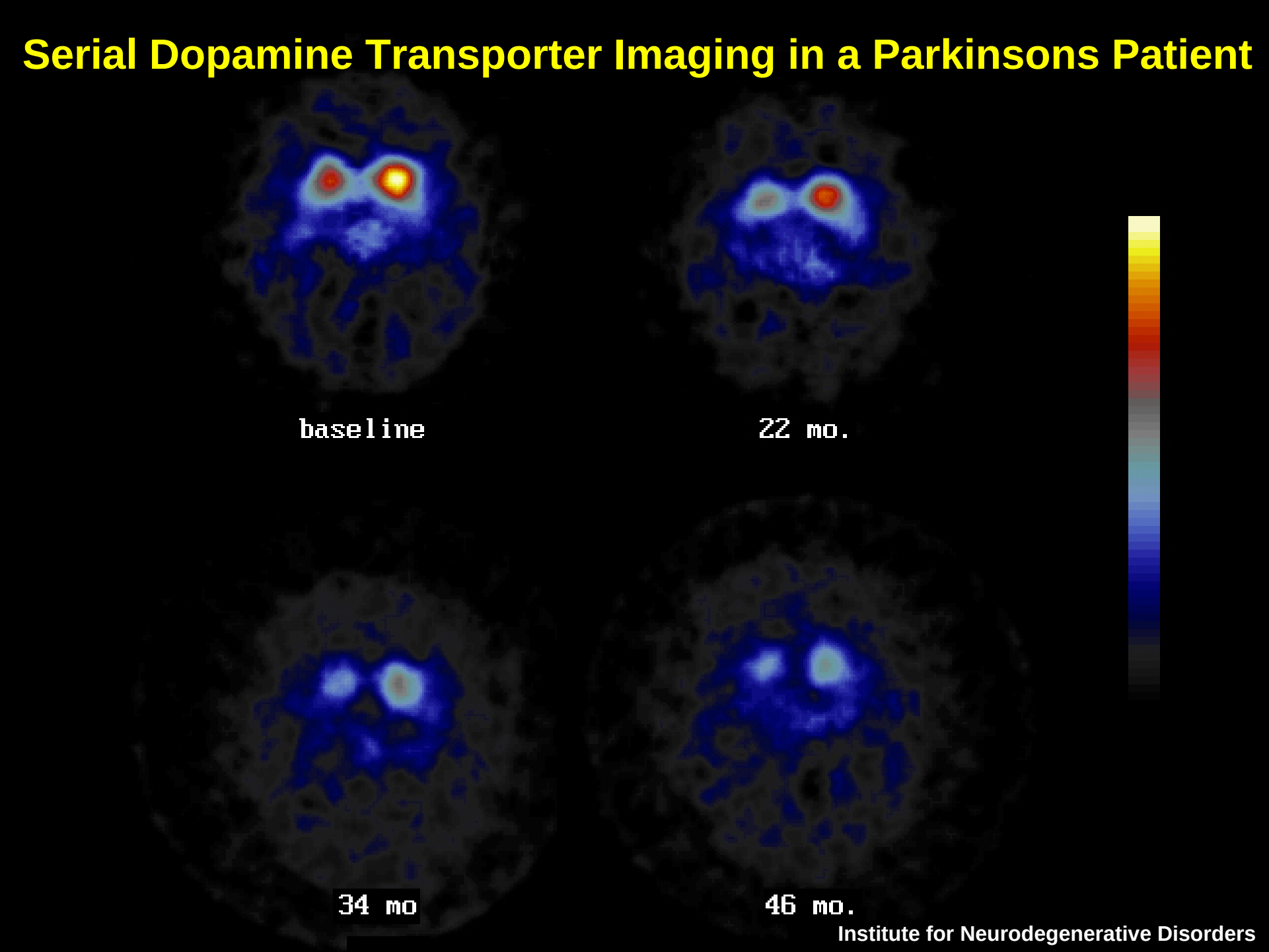


Healthy



Parkinson
Stage 1

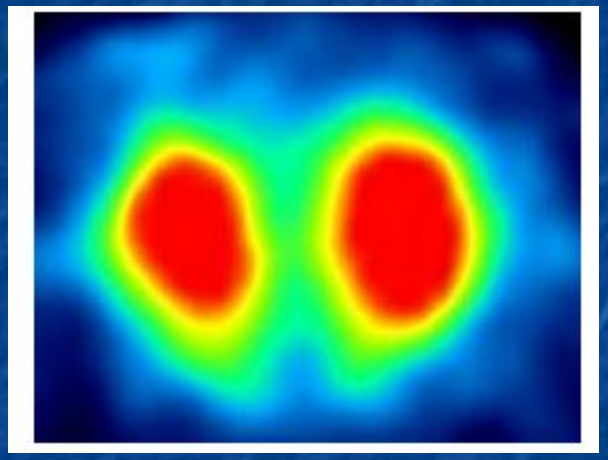
Serial Dopamine Transporter Imaging in a Parkinsons Patient



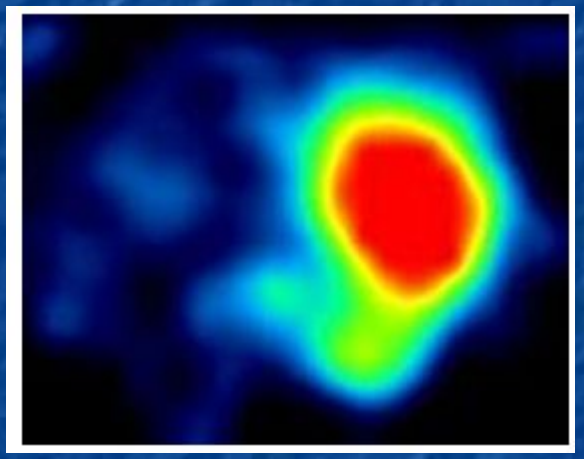
Institute for Neurodegenerative Disorders

PET Imaging to Monitor Embryonic Stem Cell Treatment of "Parkinson Disease" in Rats

Normal

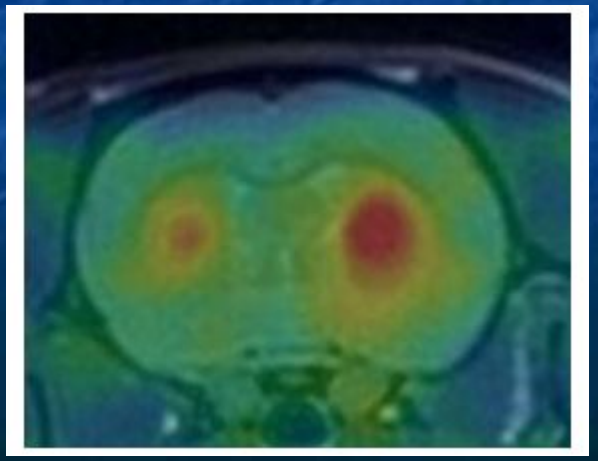


Unilateral Lesion



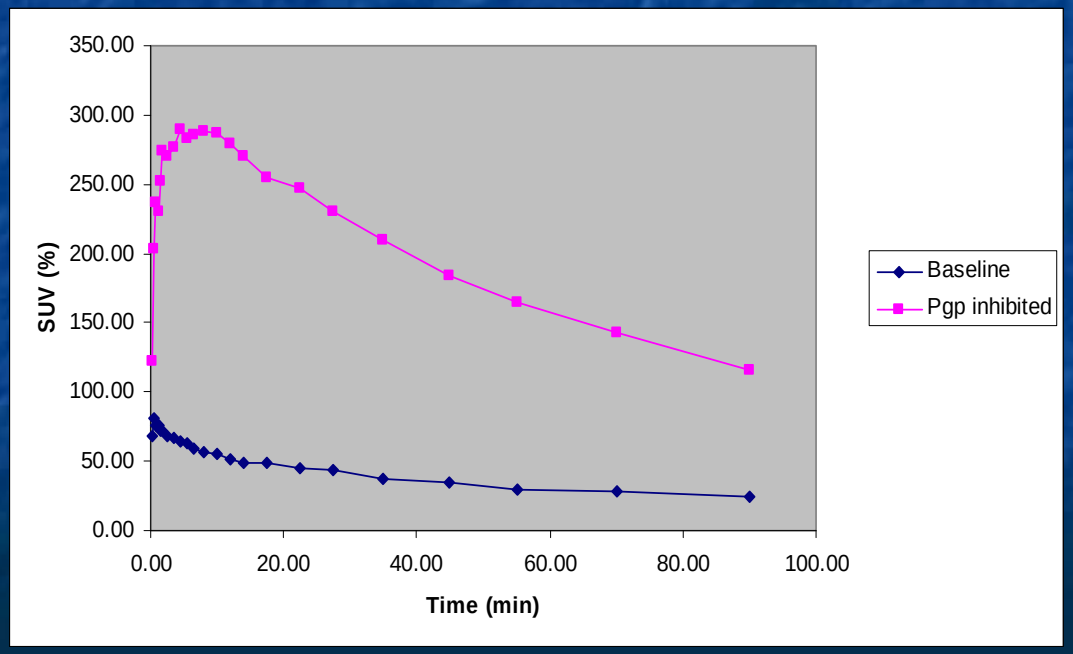
Embryonic Stem Cells

PET & MRI

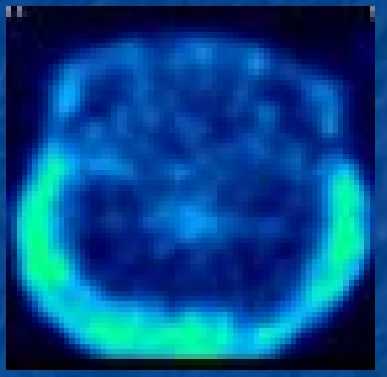


[^{11}C]RWAY Rat Brain P-gp Inhibition Increases Uptake

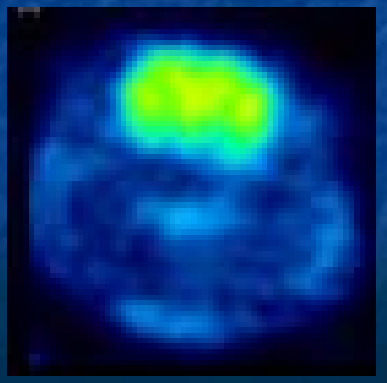
* P-glycoprotein efflux pump: removes many drugs from brain
* P-gp Inhibition: Cyclosporin-A given 30 min before tracer



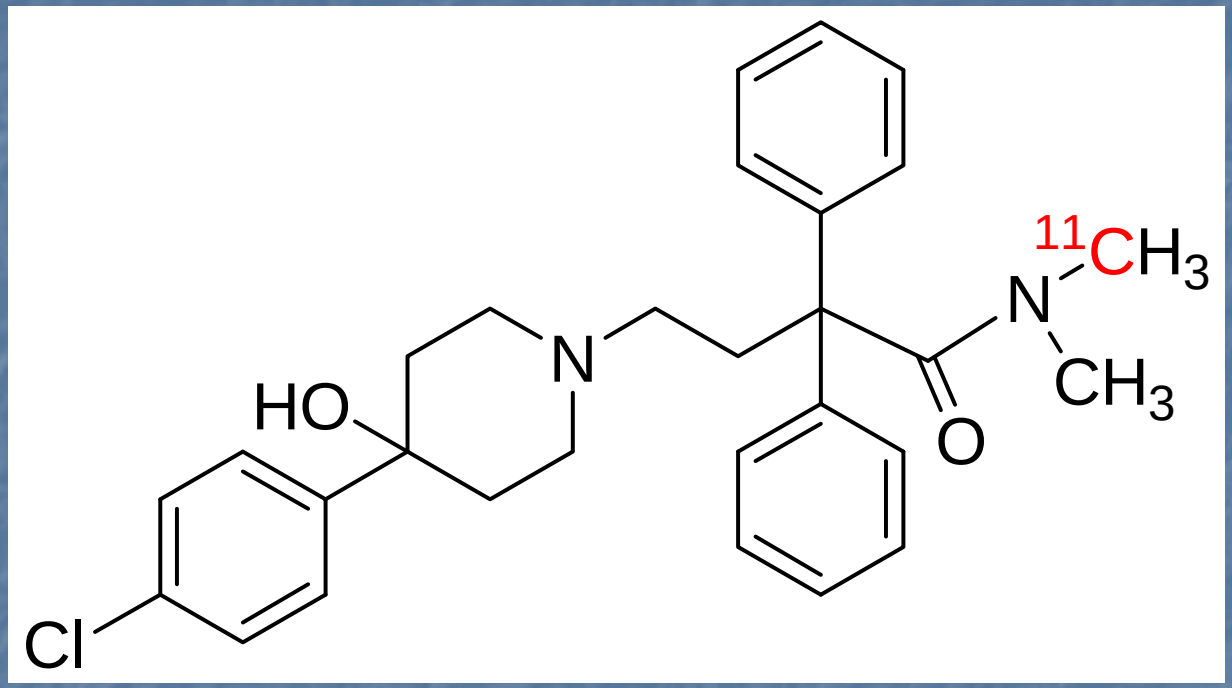
Baseline



Pgp blocked

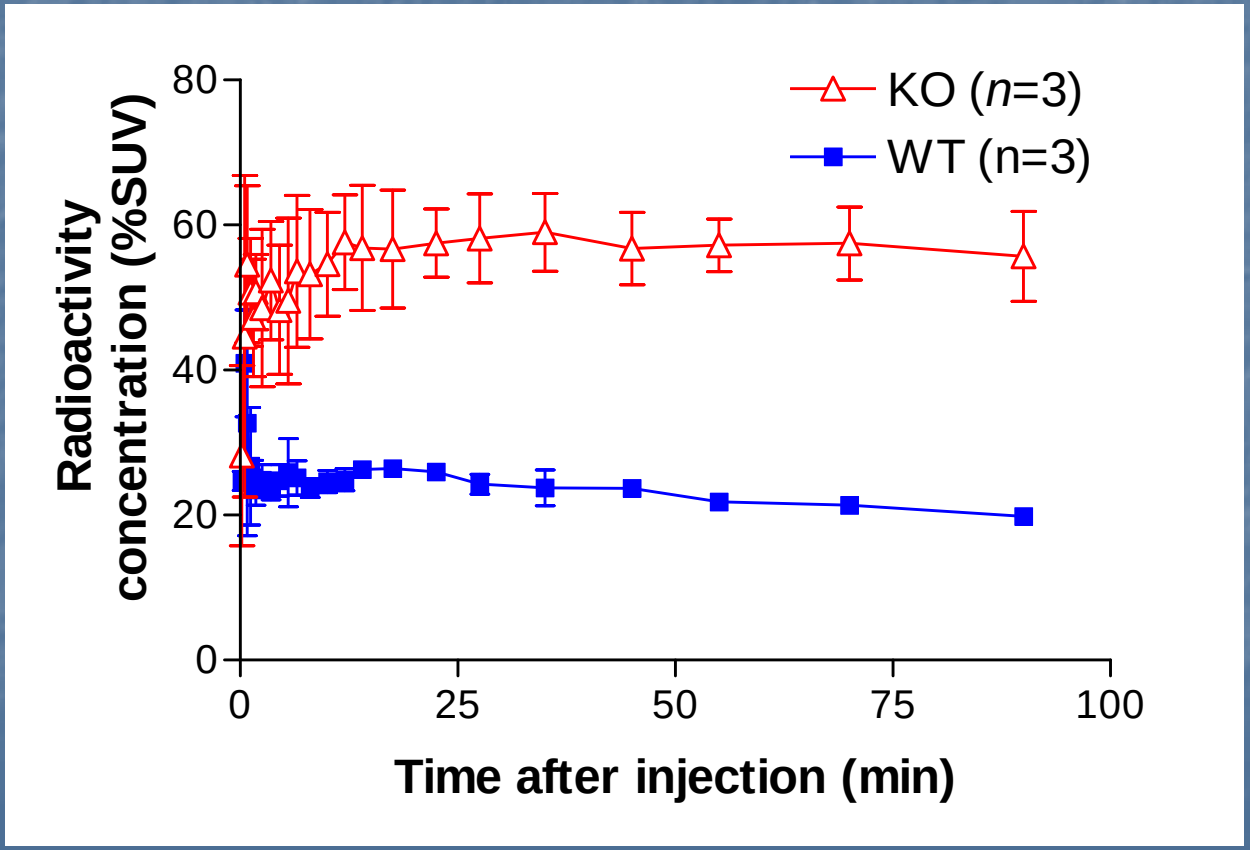


[^{11}C]Loperamide: Substrate for P-gp

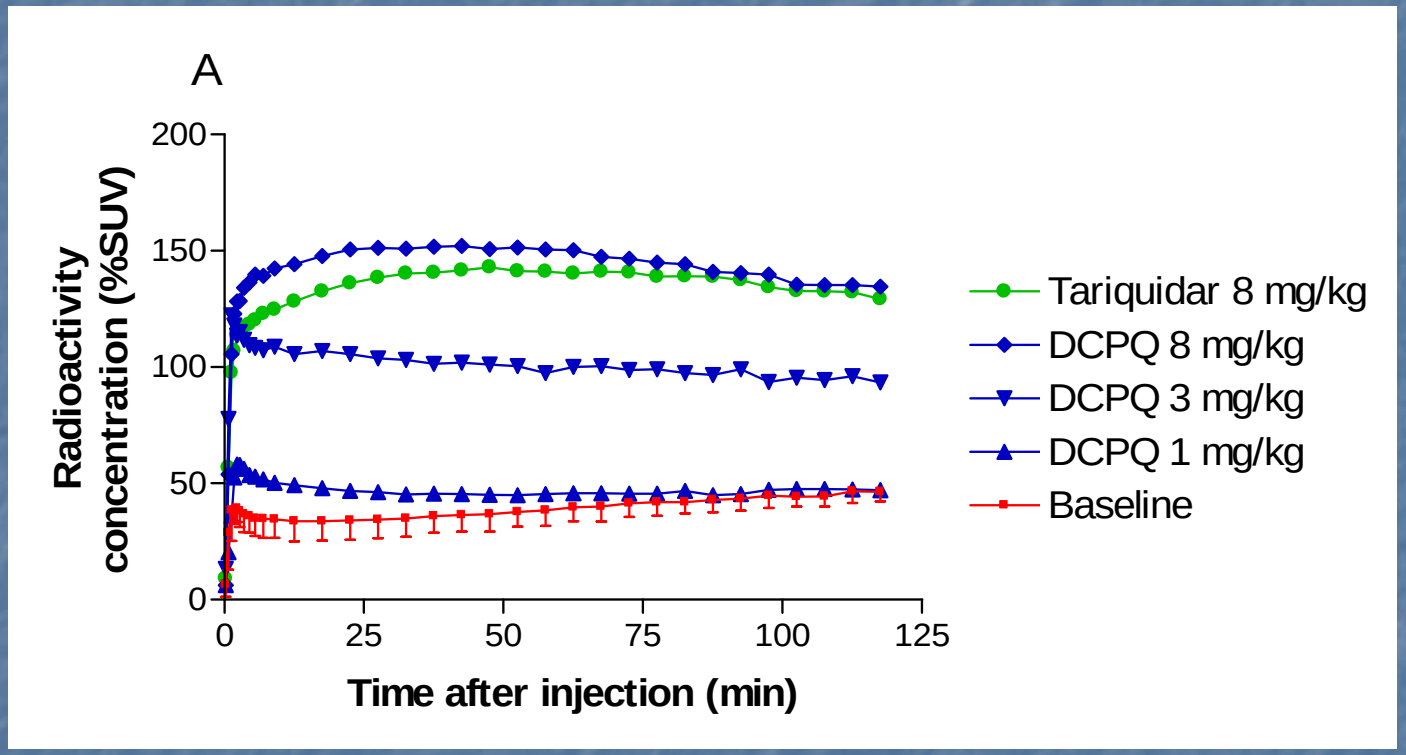


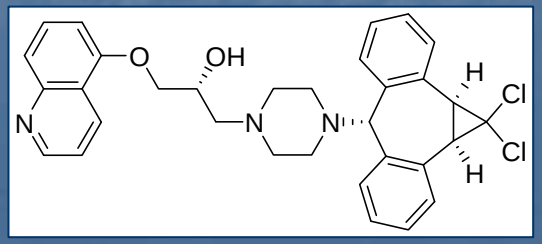
* Opiate agonist: antidiarrheal drug (Imodium®)
* Drug acts via opiate receptors on intestinal smooth muscle
* No drug CNS effects; P-gp blocks brain entry
* Easily labeled

PET with [^{11}C]Loperamide:
Brain Uptake in P-gp Knockout Mice is Twice that in Wild Type Mice



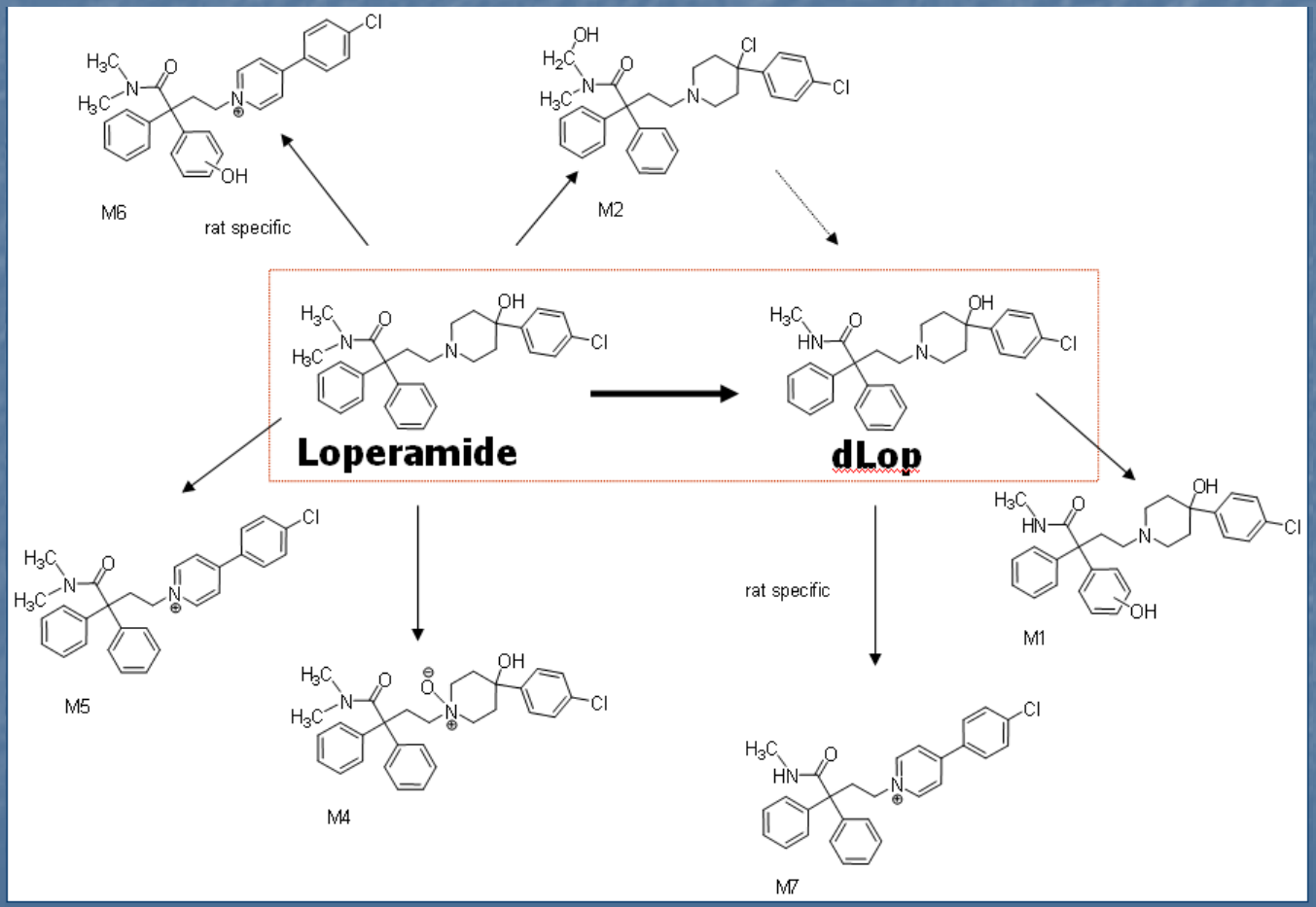
DCPQ or Tariquidar Increases Brain Uptake of Radioactivity in Monkey Given [^{11}C]Loperamide





DCPQ, K_i = 0.053 μM
Mol. Pharmacol. **61:** 974, 2002

Major Metabolites of Loperamide
in Rat and Human Liver Microsomes



Kalgutkar & Nguyen, *Drug Metab. & Disposition* 2004, 22, 943-952.

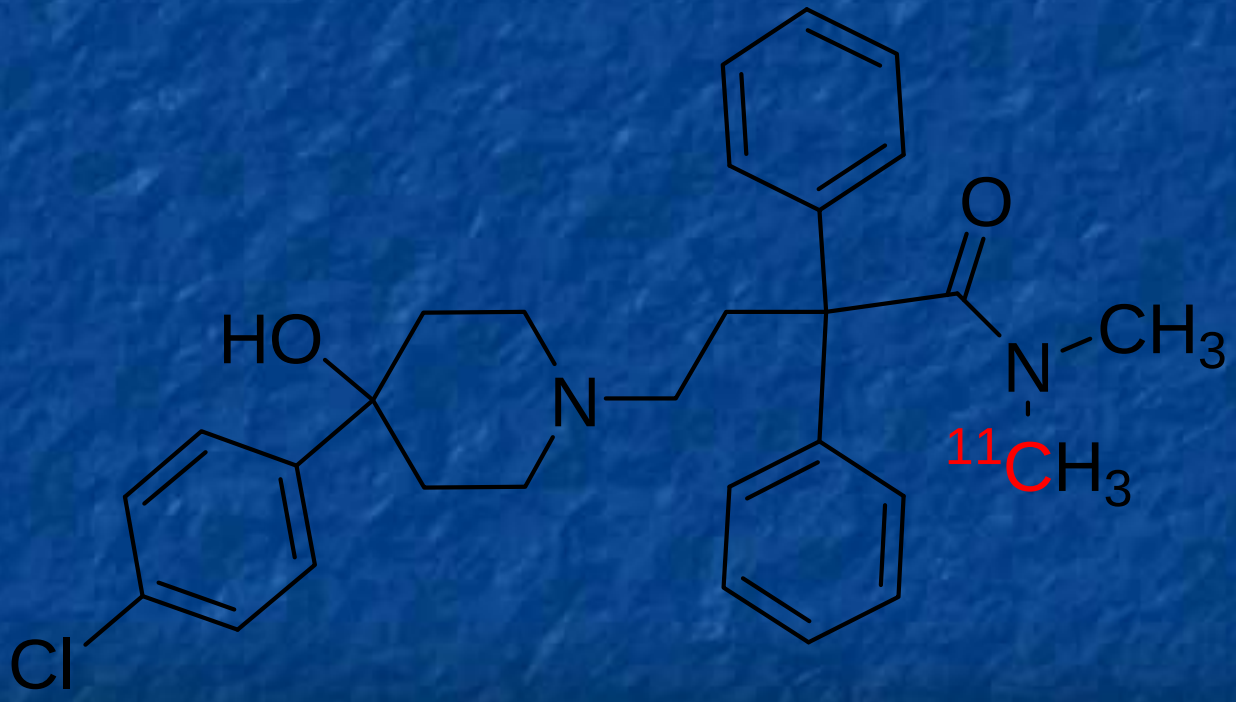
Injection of [^{11}C]Loperamide in P-gp Knockout and Wild Type Mice

	Brain		
	Concentration (%SUV)		% Brain Activity
Radiochemical Species	KO	WT	KO
[^{11}C]Loperamide	25	2	**50%**
[^{11}C]dLop	12	1	24%
Metabolites	14	11	26%
Total	51	14	100%

Five P-gp KO and five WT mice were killed 30 min after injection of [^{11}C]loperamide.

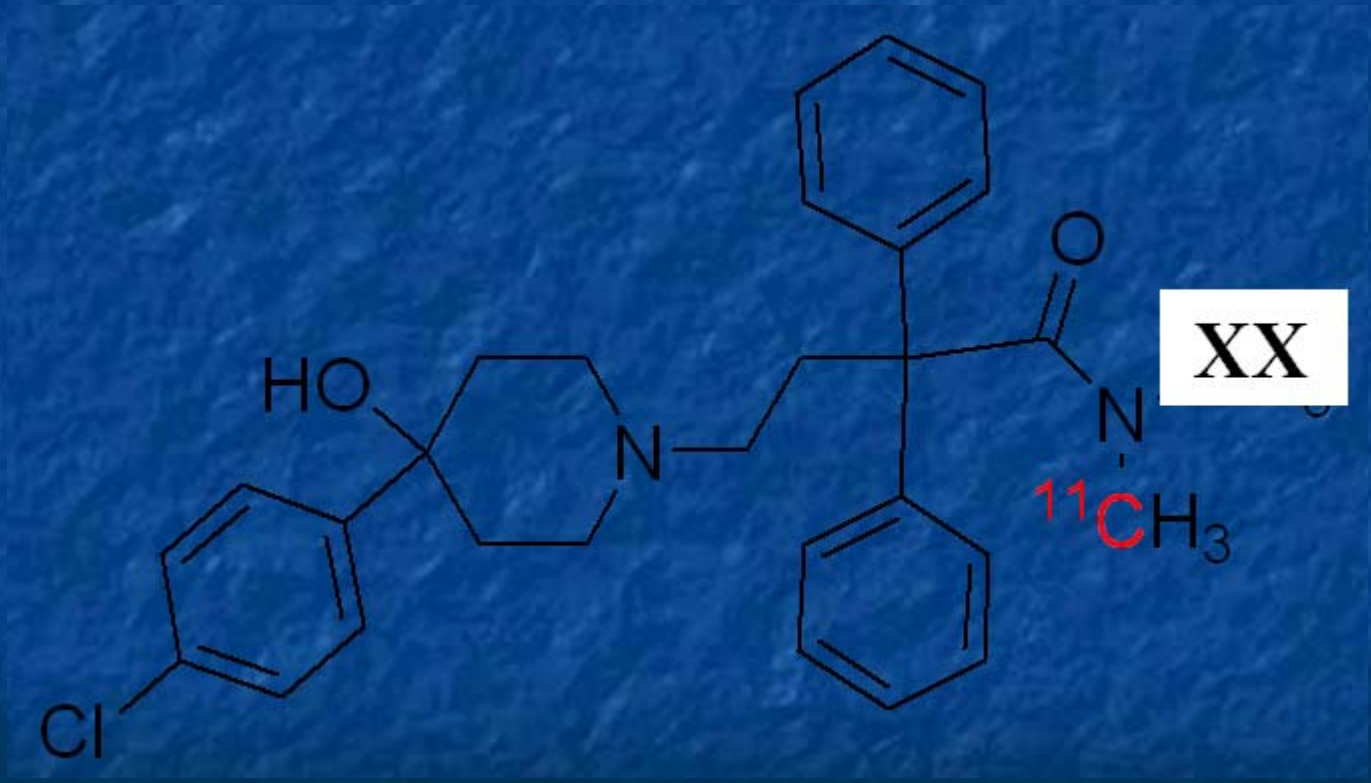
PROBLEM of [^{11}C]Loperamide
Radiometabolite (desmethyl) enters brain

[^{11}C]Loperamide



Solution: Remove the nonradioactive methyl group

[^{11}C]Desmethyl-loperamide: Better radioligand? Demethylation product does not enter brain



[^{11}C]dLop as a Prospective PET Radiotracer of P-gp Function

* Our study of [^{11}C]loperamide shows [^{11}C]dLop is an avid substrate for P-gp
* dLop, as a metabolite of loperamide (Imodium), would be safe to give to human subjects
* dLop is extensively metabolized by demethylation. Thus, [^{11}C]dLop might be expected to give mainly polar one-carbon radiometabolites

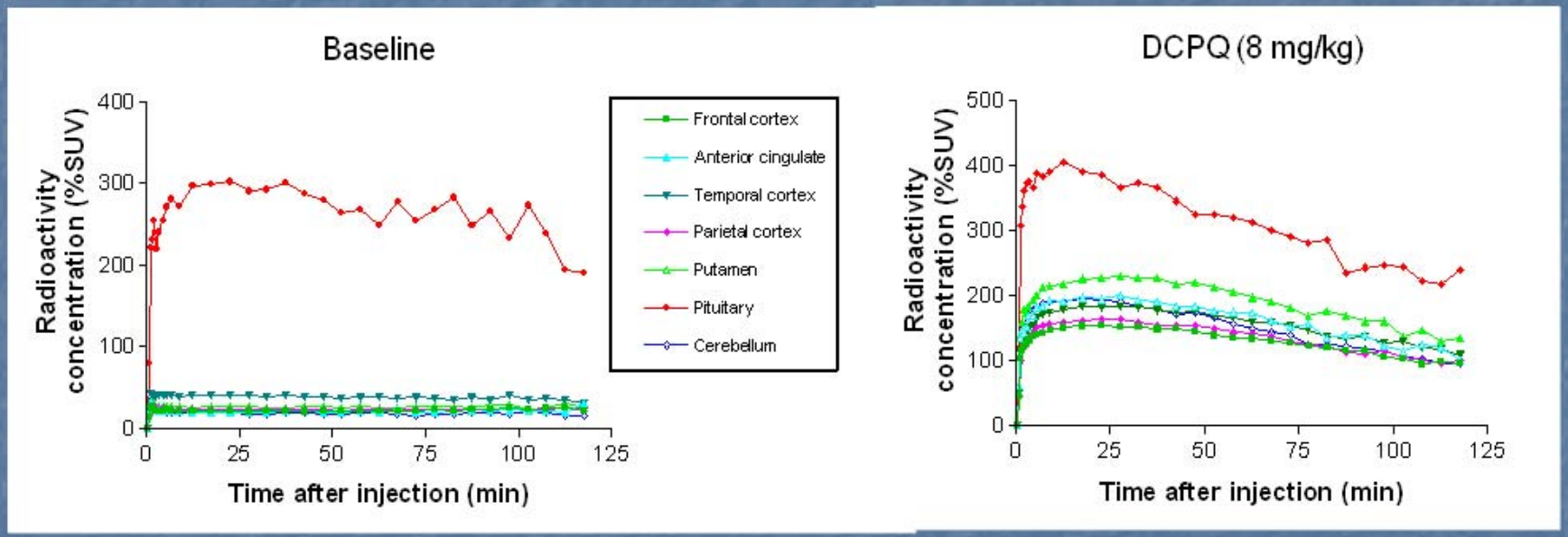
Injection of [^{11}C]*N*-desmethyl-Loperamide in P-gp Knockout and Wild Type Mice

	Brain		
	Concentration (%SUV)		% Brain Activity
Radiochemical Species	KO	WT	KO
[^{11}C] dLop	36	2	**92 %**
Metabolites	3	3	8 %
Total	39	5	100 %

Three P-gp KO and three WT mice were killed 30 min after i.v. injection of [^{11}C]dLop.

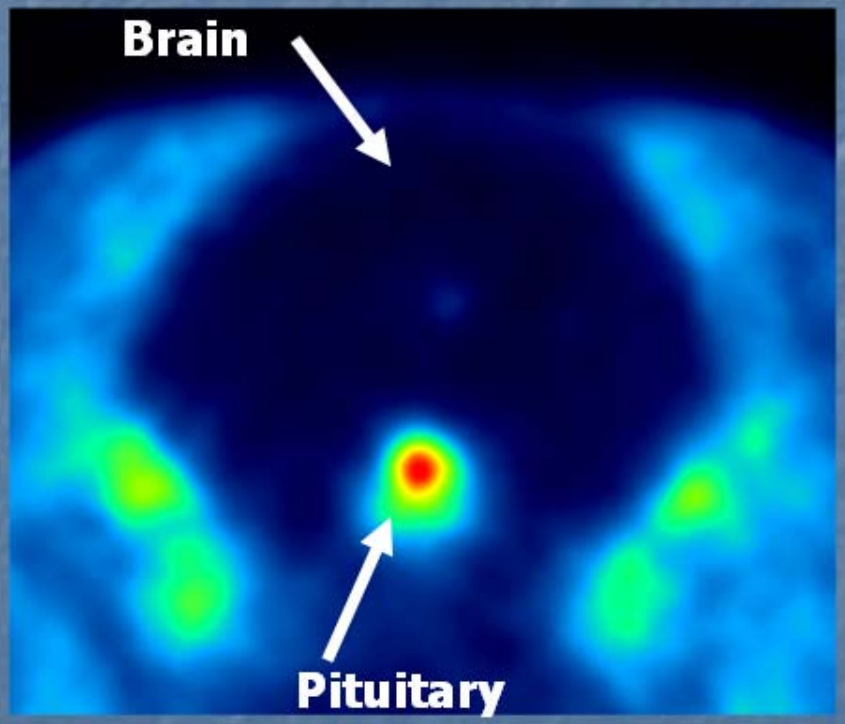
[^{11}C]dLop in Rhesus Monkey

under Baseline and P-gp Blocked Conditions

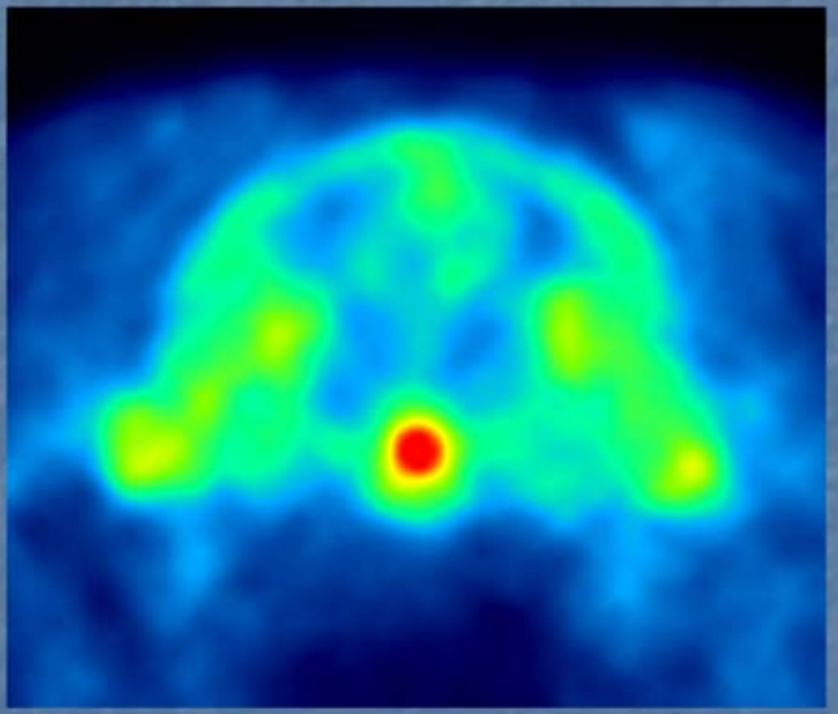


[^{11}C]dLop in Rhesus Monkey

Baseline

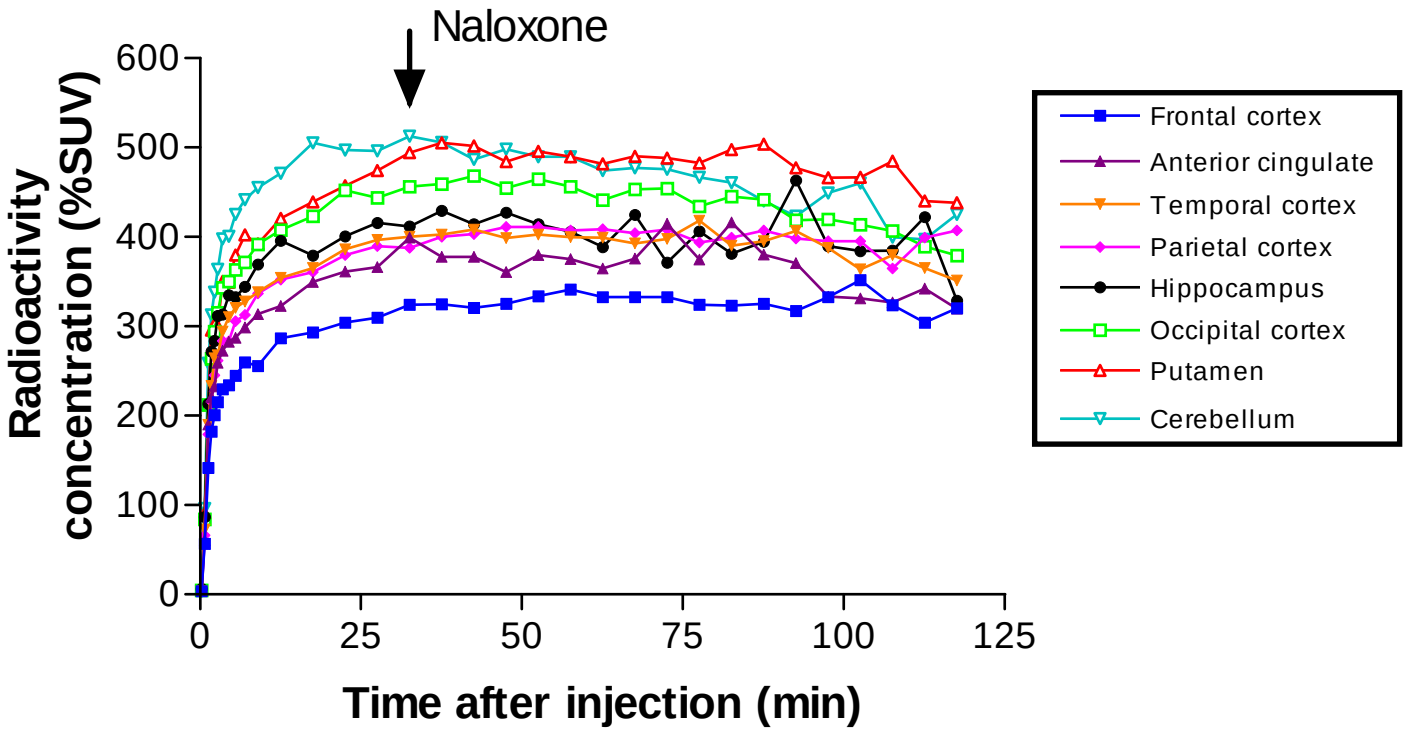


P-gp blocked



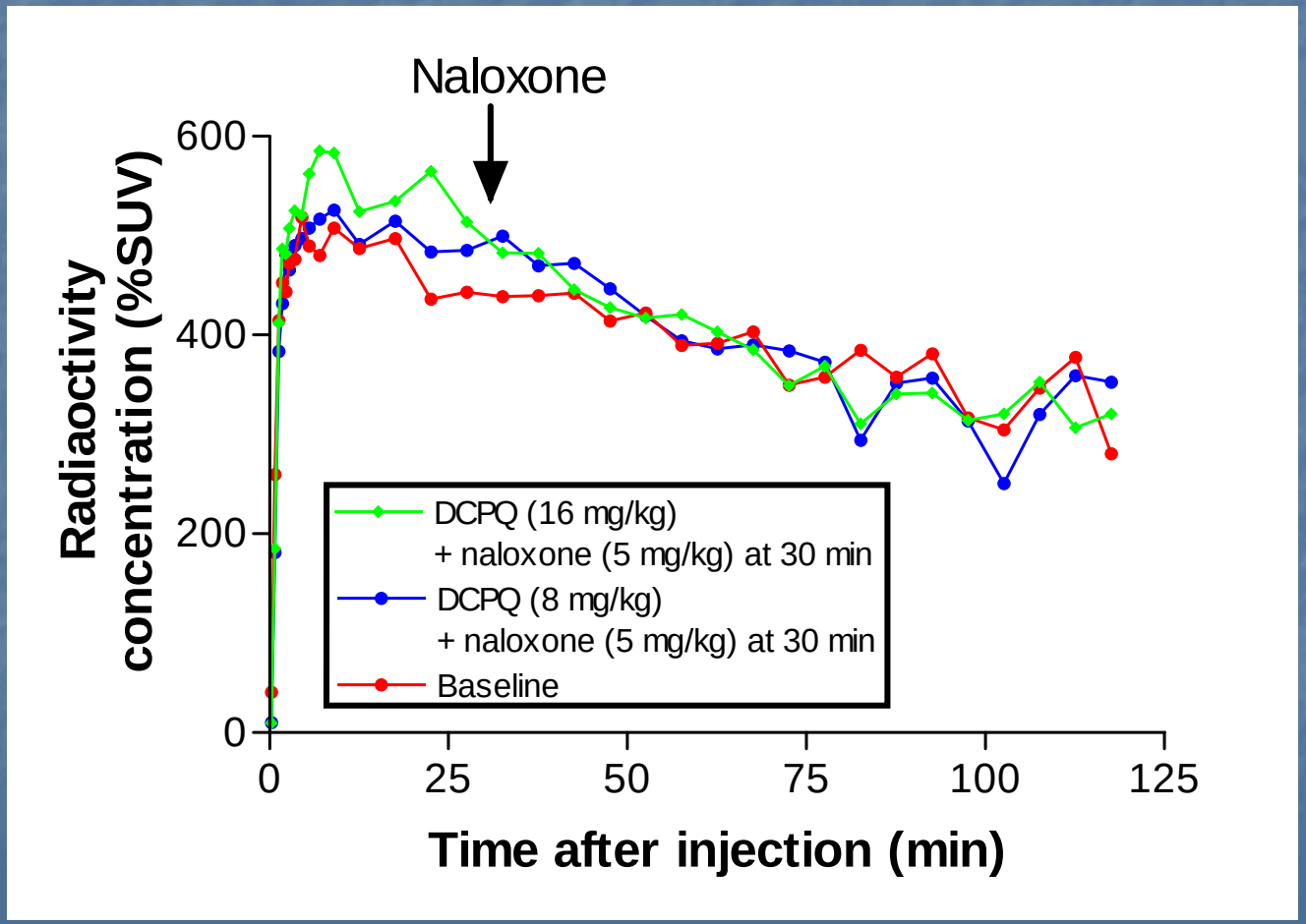
P-gp blocked with DCPQ

[^{11}C]dLop in Monkey:
P-gp Blockade Followed by Naloxone



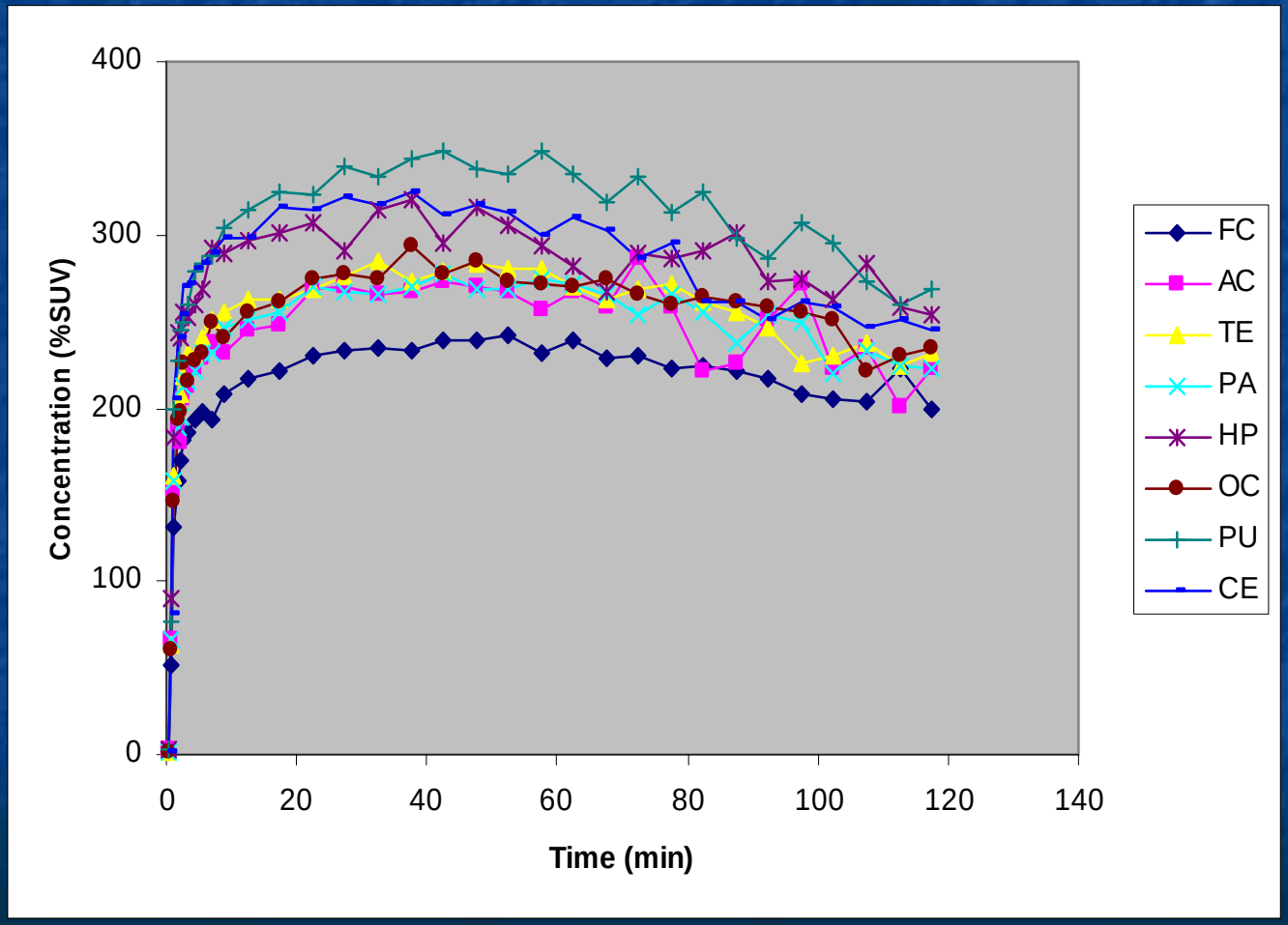
DCPQ 16 mg/kg, Naloxone 5 mg/kg (30 min after injection)

[^{11}C]dLop: High Uptake in Pituitary is not Increased by DCPQ or Displaced by Naloxone



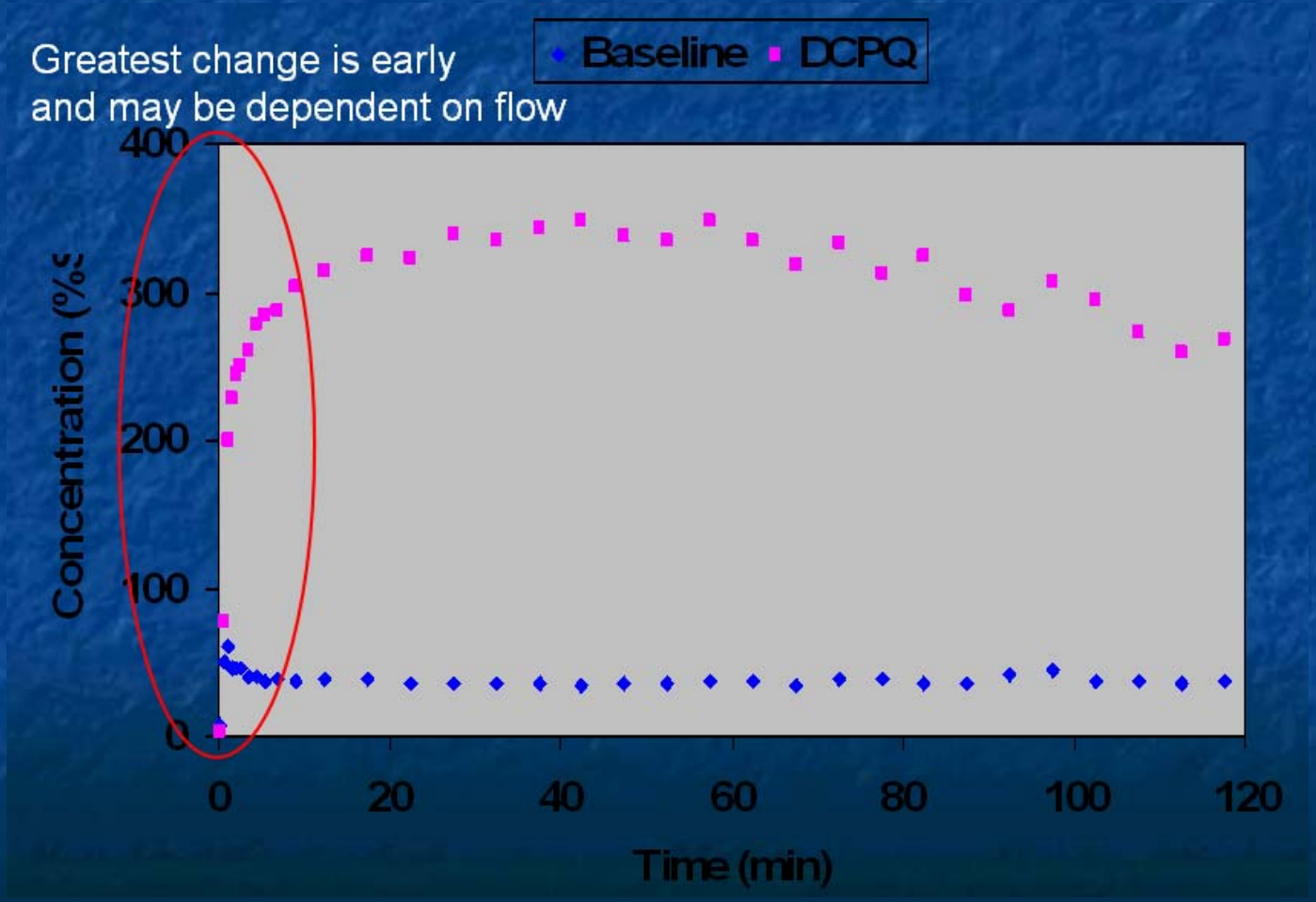
Is P-gp function uniformly distributed in the brain?

[^{11}C]dLop time activity curves in rhesus monkey brain by region

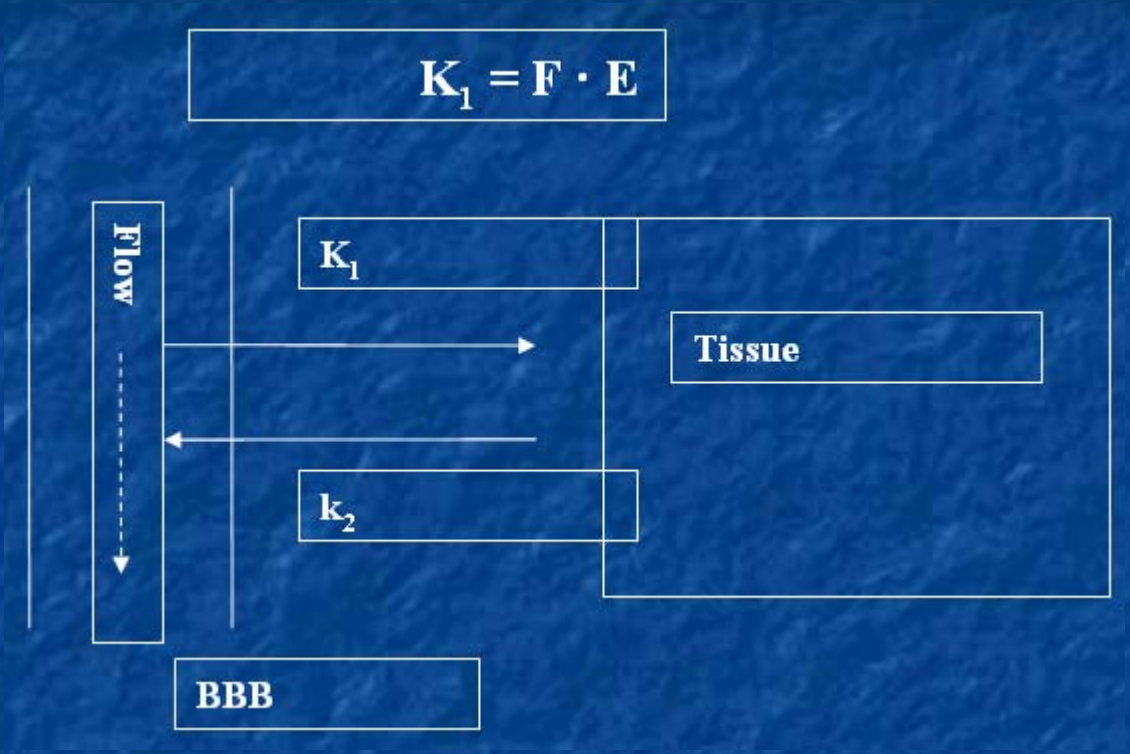


FC=Frontal Cortex, AC=Anterior Cingulate Gyrus, TE=Temporal Cortex , PA=Parietal Cortex, HP=Hippocampus, OC= Occipital Cortex, PU=Putamen, CE=Cerebellum

Brain uptake is rapid and stable at baseline and after blockade with the P-gp inhibitor DCPQ



[^{11}C]dLop has high single pass extraction (E)

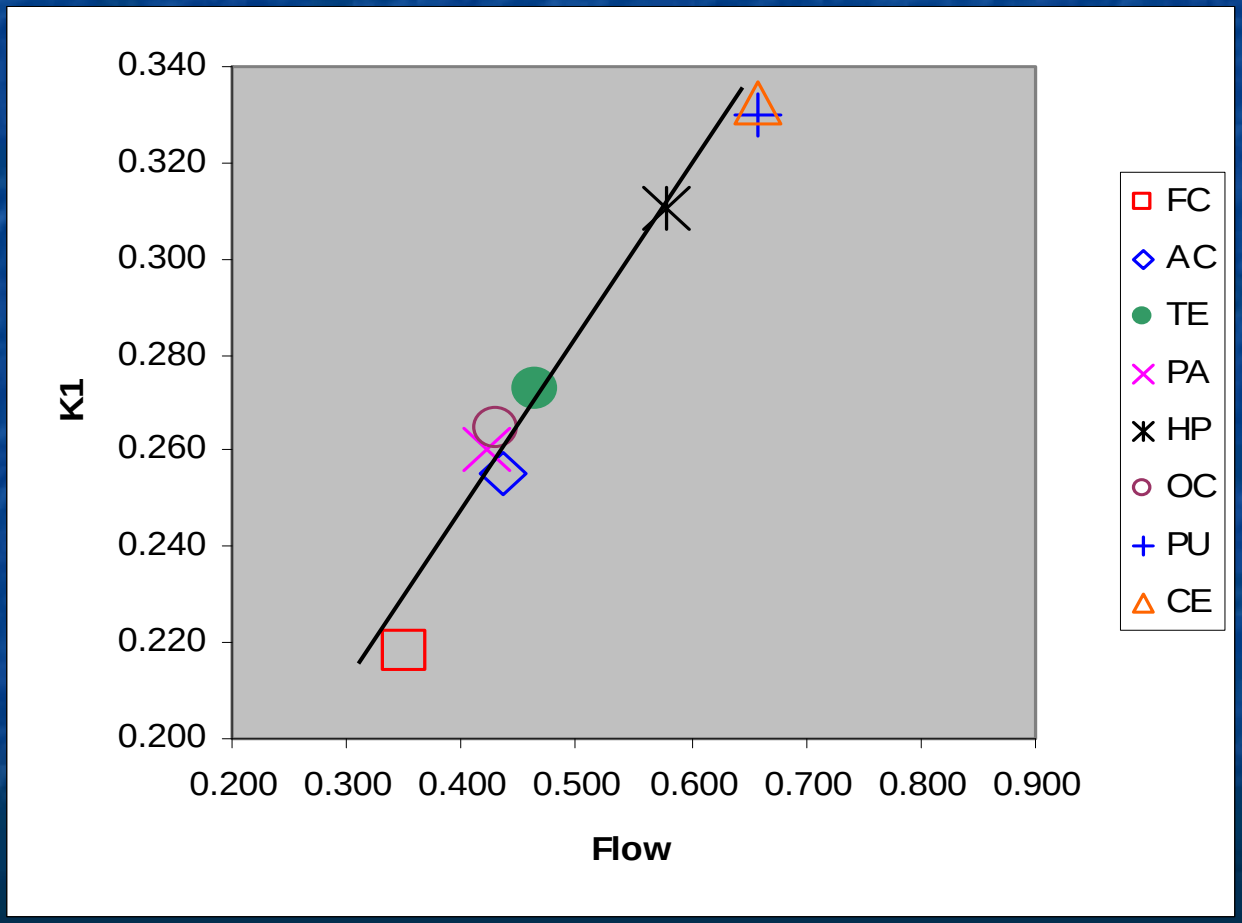


Flow (F) for anesthetized monkey = 0.5 mL · g^{-1} · min^{-1}

Mean measured K_1 = 0.28 mL · mL^{-1} · min^{-1}

So, single pass Extraction (E) = 56%

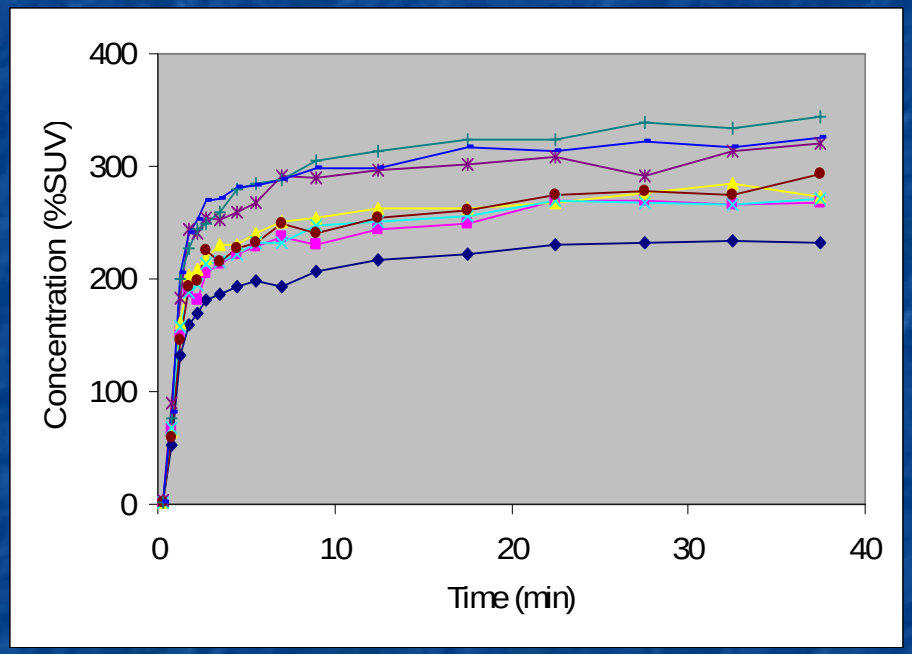
Regional K_1 increases linearly with relative blood flow



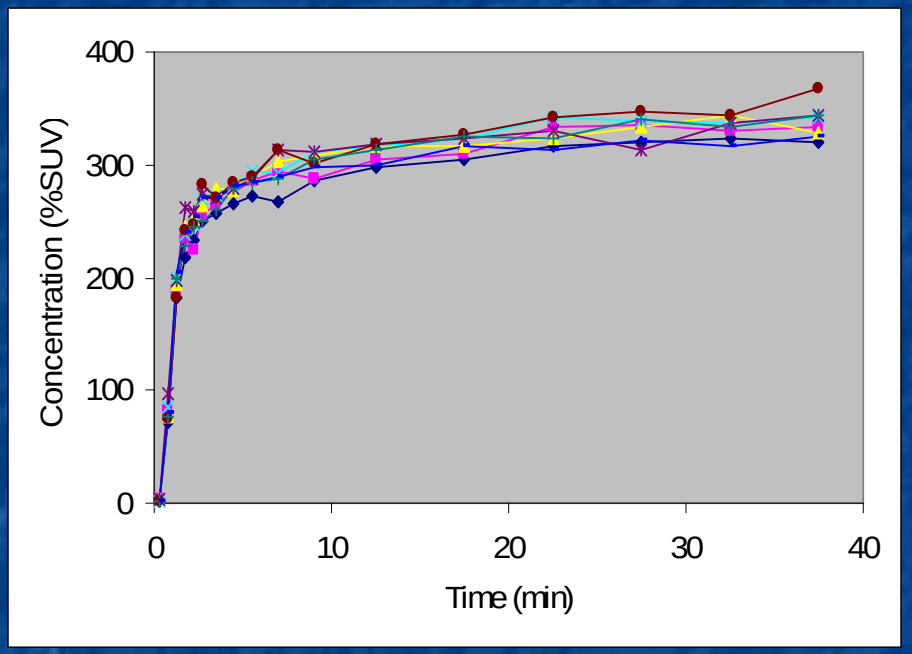
FC=Frontal Cortex, AC=Anterior Cingulate Gyrus, TE=Temporal Cortex , PA=Parietal Cortex, HP=Hippocampus, OC= Occipital Cortex, PU=Putamen, CE=Cerebellum

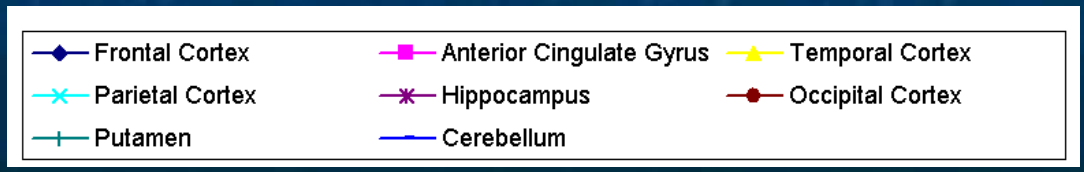
After correction for relative blood flow, [^{11}C]dLop uptake is uniform among brain regions

No Flow Correction



With Flow Correction





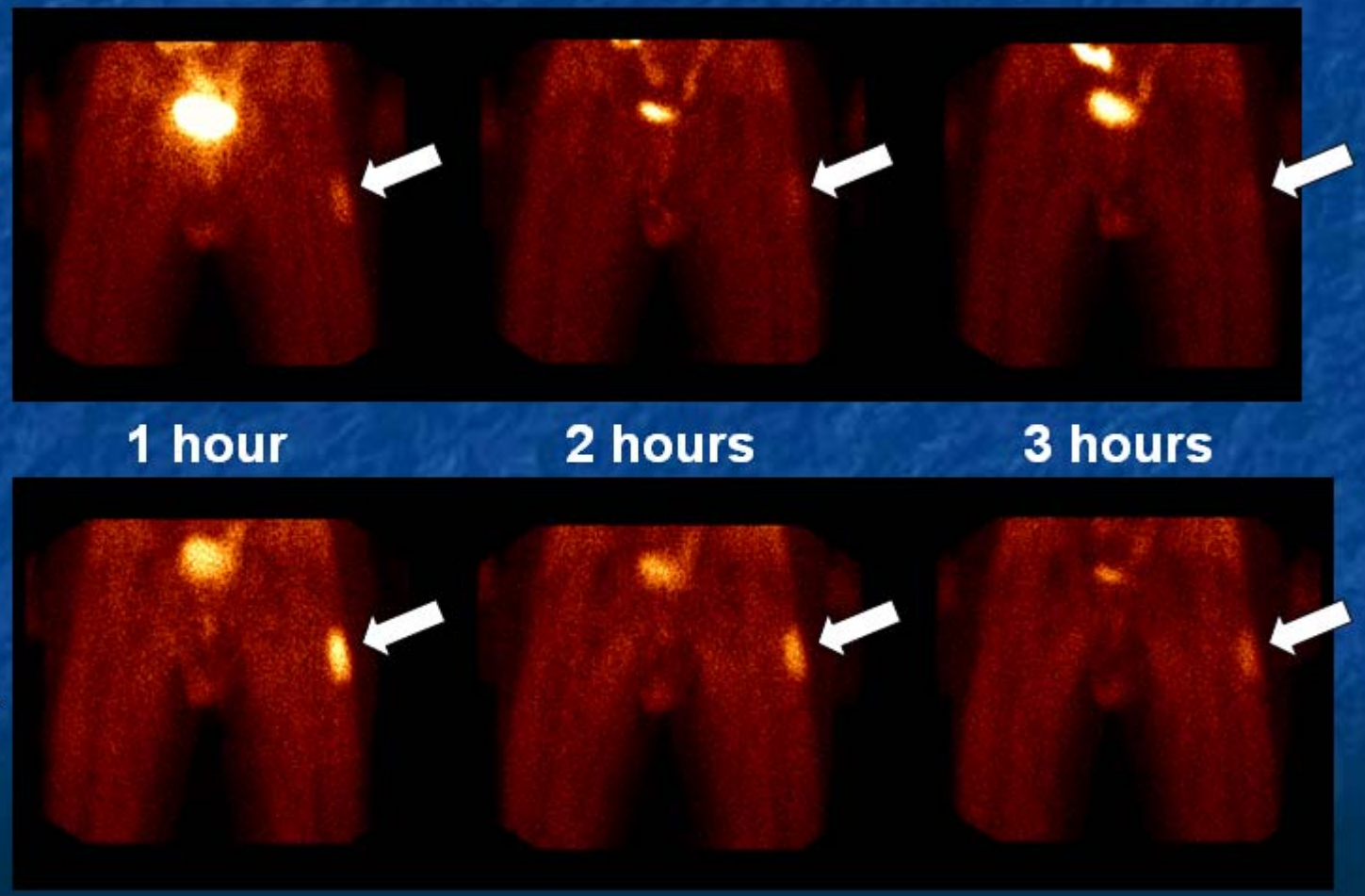
Conclusions

* [^{11}C]Loperamide: avid P-gp substrate
* [^{11}C]dLop is also P-gp substrate & measures function
* [^{11}C]dLop: avoids one metabolite problem of [^{11}C]loperamide
* After P-gp blockade, single pass uptake of [^{11}C]dLop into brain is high and, therefore, shows dependence on blood flow

Future Directions

* BRAIN: Potential dysfunction of P-gp at blood-brain barrier: epilepsy, Alzheimer's disease
* PERIPHERY: P-gp over expression in multidrug resistance in cancer

Renal Cell Carcinoma
^{99m}Tc-Sestamibi Uptake in Left Thigh Metastasis
Effect of Tariquidar



Future Directions

* Radioligands for P-gp are useful biomarkers for brain and periphery
* Biomarkers Consortium: FDA, NIH, and industry collaborate to develop biomarkers to facilitate therapeutic drug development

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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(Science Magazine Nov. 17, 2006)

Public-Private Partnership Launched To Determine Therapeutic Benefits of Schizophrenia Medication

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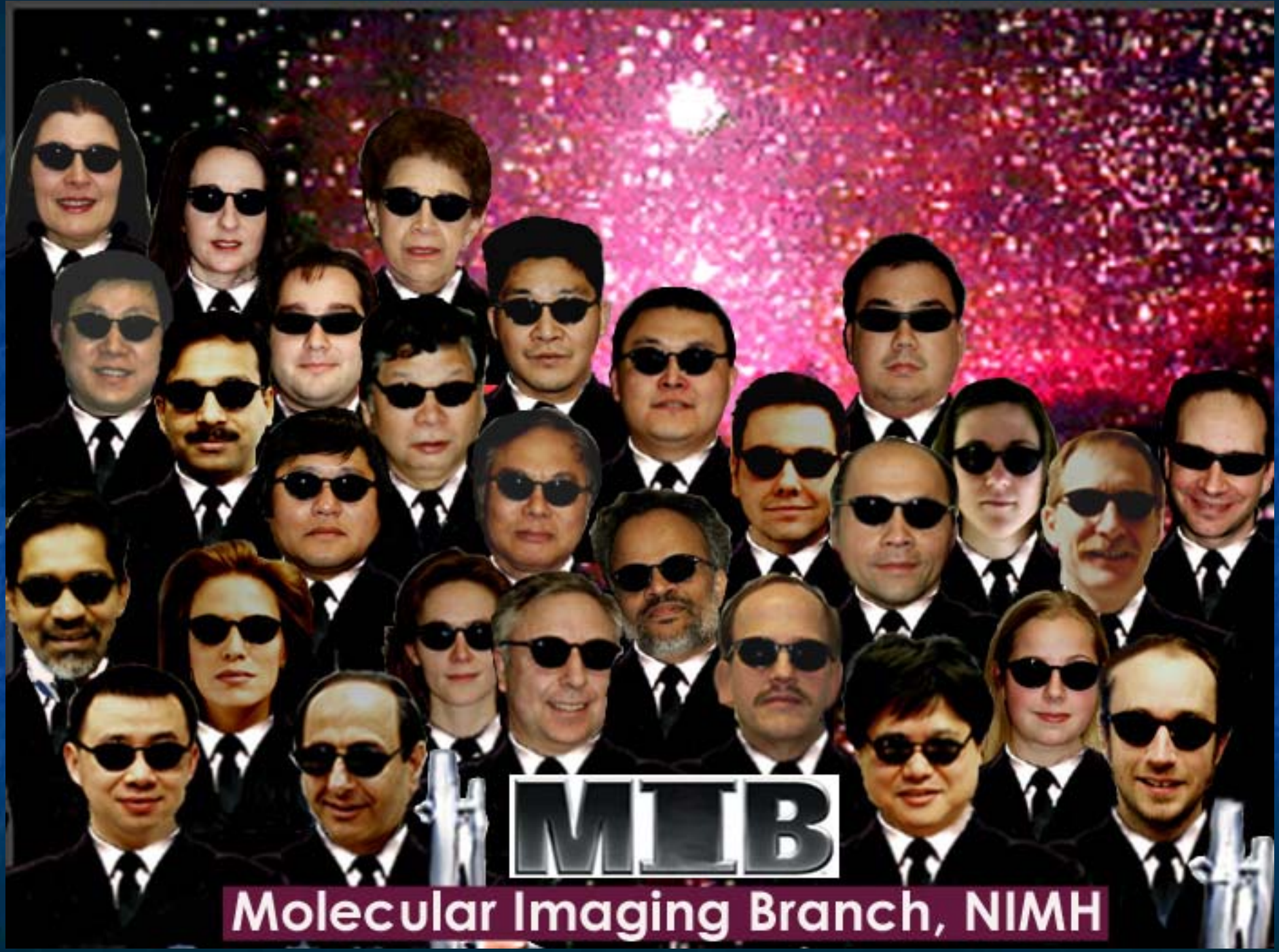
THE BIOMARKERS CONSORTIUM
ADVANCING MEDICAL SCIENCE

The Biomarkers Consortium is a public-private biomedical research partnership of the Foundation for the National Institutes of Health, Inc. that involves a variety of public and private stakeholders including the National Institutes of Health (NIH); Food and Drug Administration (FDA); Centers for Medicare & Medicaid Services (CMS); the pharmaceutical, biotechnology, diagnostics, and medical device industries; non-profit organizations and associations; and advocacy groups (News/Events).

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.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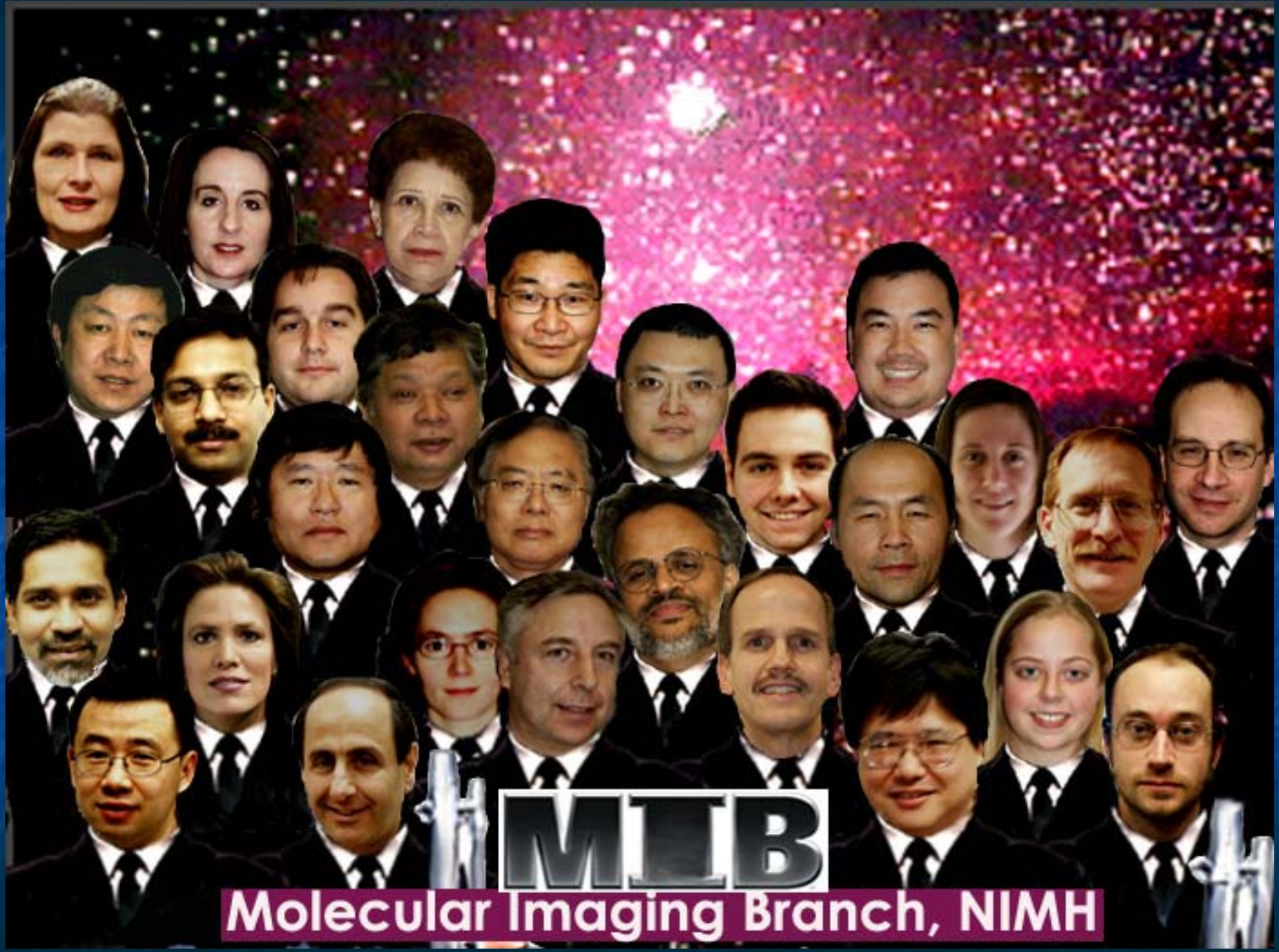
MIB
Molecular Imaging Branch, NIMH

Self-Assessment Quiz: True or False?

* Loperamide, an antidiarrheal drug, lacks central nervous system opiate effects because P-gp (Permeability-glycoprotein) blocks its entry into brain.
* Positron emission tomography (PET) can measure the function of P-gp *in vivo* by using a radiolabeled P-gp substrate such as [^{11}C]loperamide.
* PET can monitor the *in vivo* metabolism of radioligands. By measuring P-gp function, PET can also monitor drug distribution.