

# **New Tracers: New Challenges in SPECT**

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Royal Prince Alfred Hospital*

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# SPECT Radiotracers

increasing isotope availability



**C-11**

**F-18**

**I-123**

**Tc-99m**

Unchanged  
Substrate

F for H

I for H

Not  
Predictable

F for OH

I for OH

RF for H

I for CH<sub>3</sub>

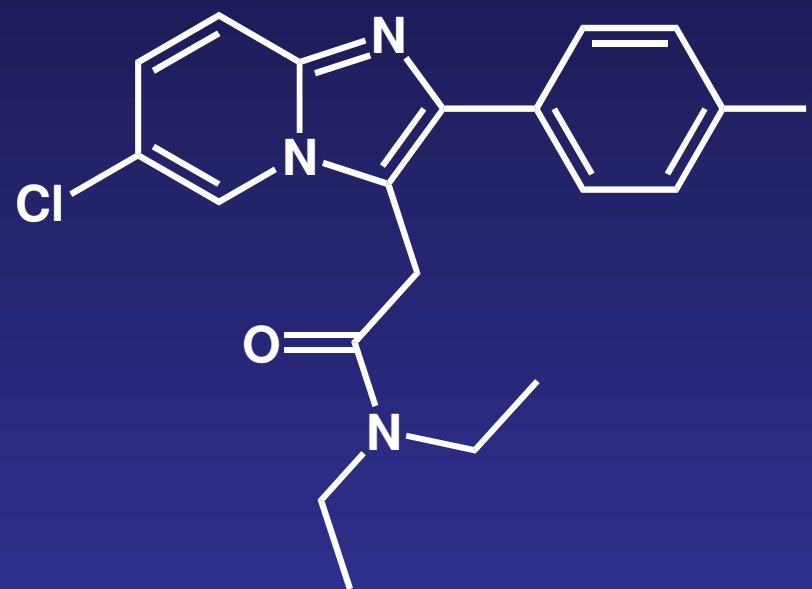
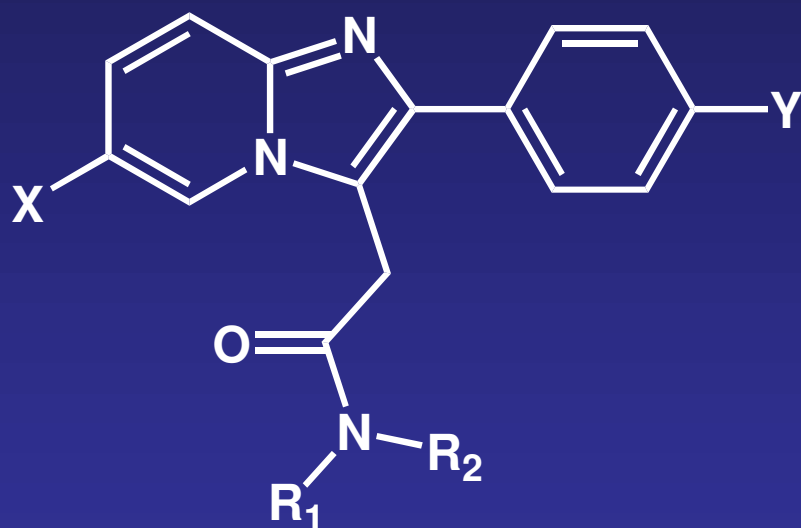
increasing physiological changes



# Peripheral Benzodiazepine Receptors (PBRs)

- Multimeric protein primarily located in the outer mitochondrial membrane
- Overexpressed in neurodegenerative disorders, malignant tumours, inflammatory gliosis
- Predominantly found in
  - Peripheral organs : heart, kidney, adrenals, gonads
  - Brain : glial cells
- Different in pharmacology, localisation and function to central benzodiazepine receptors

# Imidazopyridines as Ligands for the PBRs

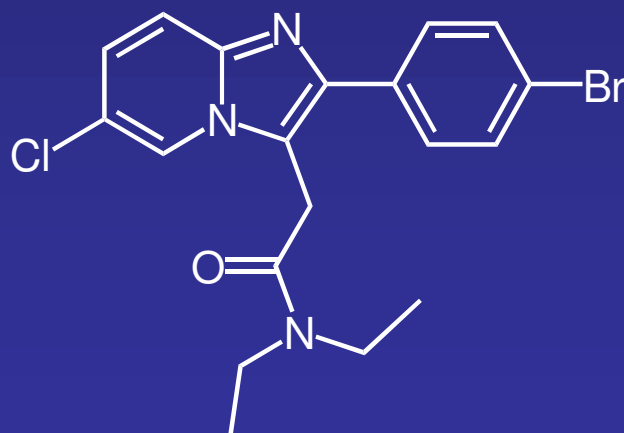
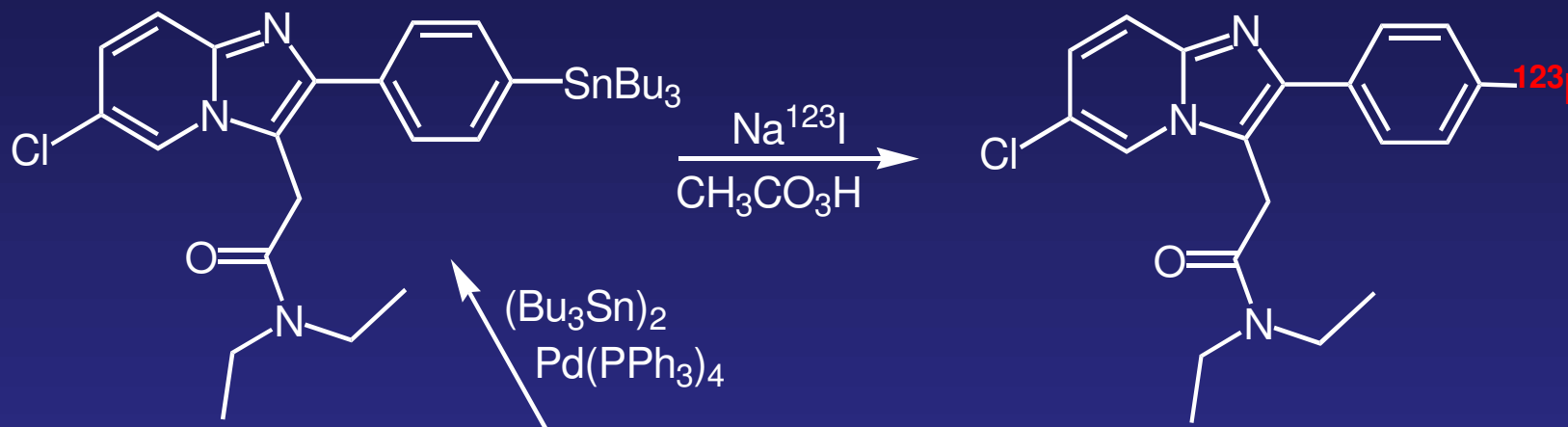


**CLINDE**

$IC_{50} = 450$  nM CBR

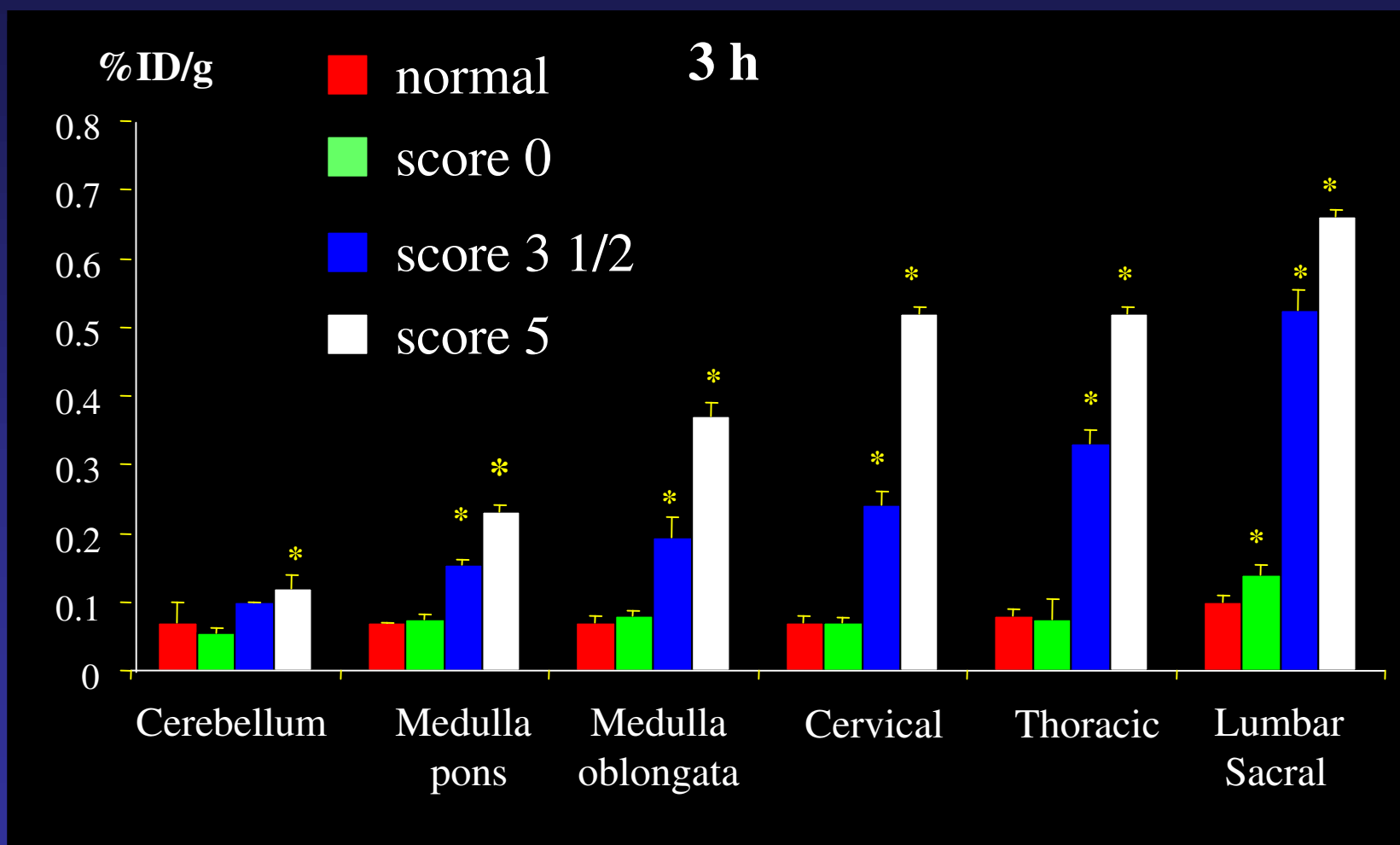
$IC_{50} = 1.70$  nM PBR

# Radiosynthesis of [<sup>123</sup>I]CLINDE



**RCY = 80-85%**

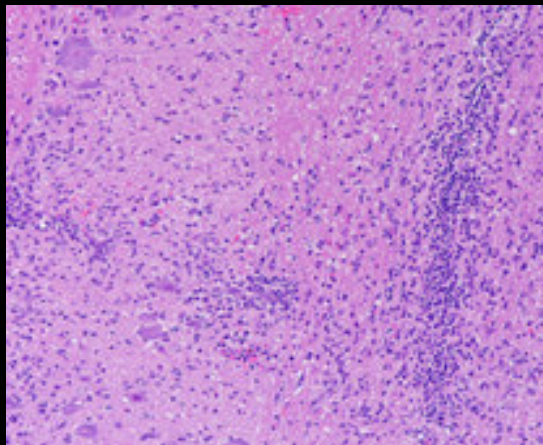
# CNS Biodistribution of [<sup>123</sup>I]CLINDE in Experimental Autoimmune Encephalomyelitis (EAE)



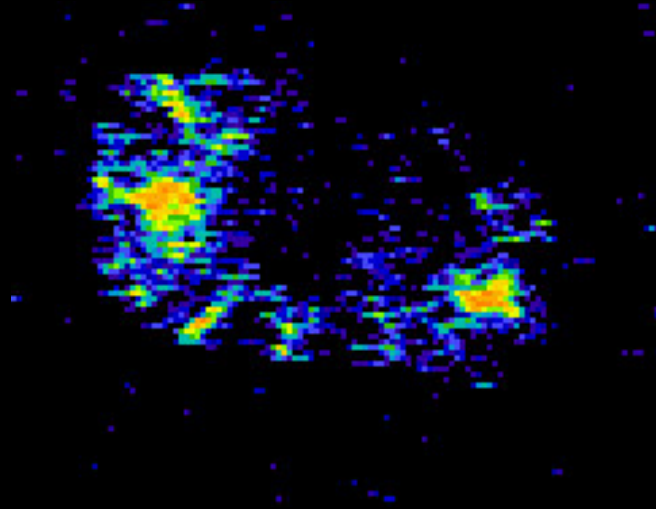
# *Ex -Vivo* Autoradiography of [<sup>123</sup>I]CLINDE

## Lumbar spinal cord

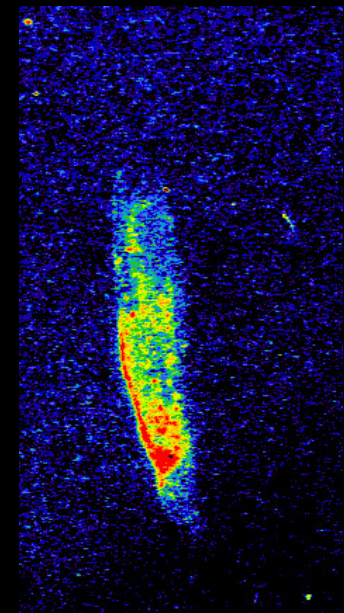
EAE - score 3



histopathology

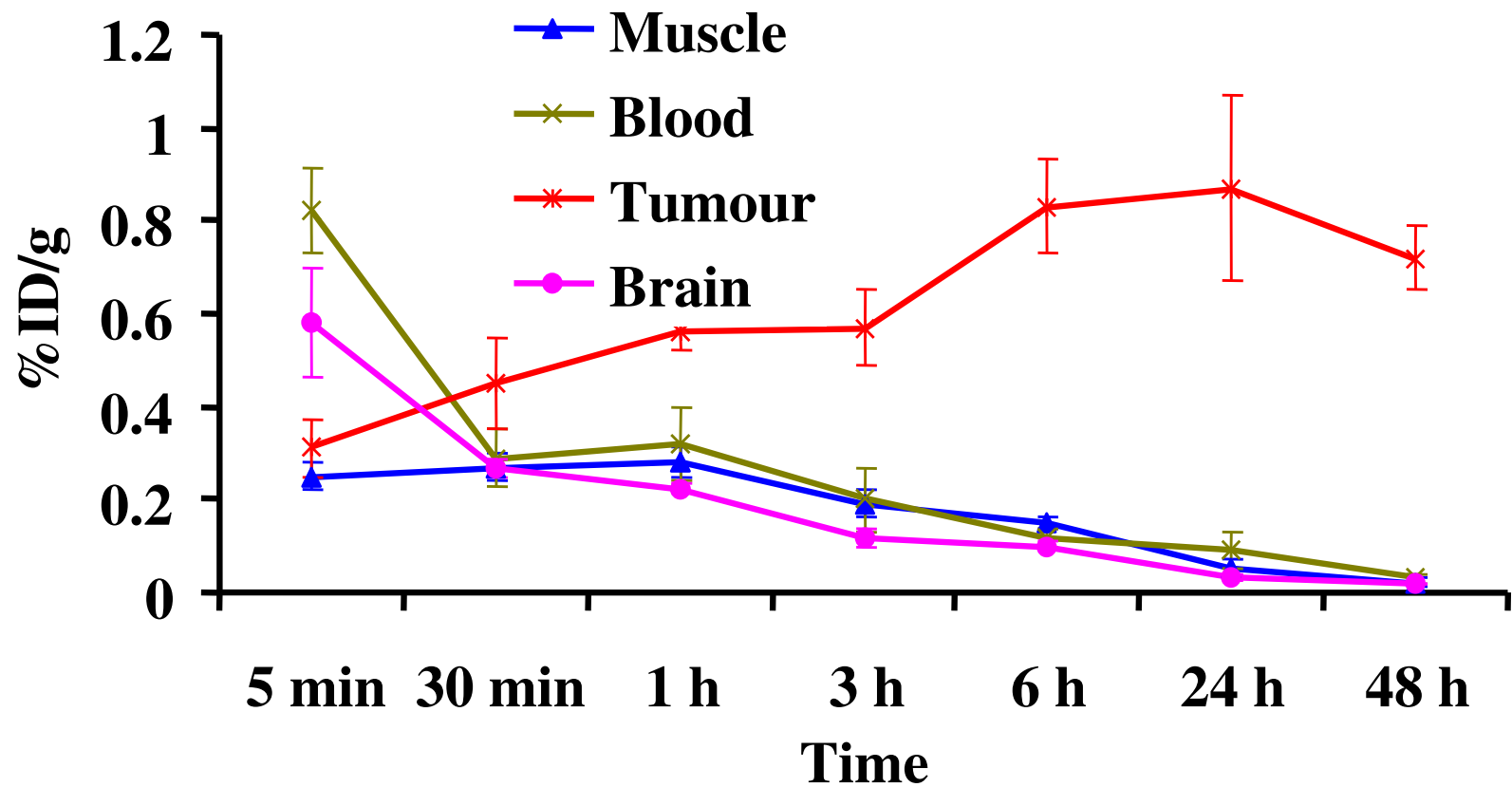


ARG sagittal section

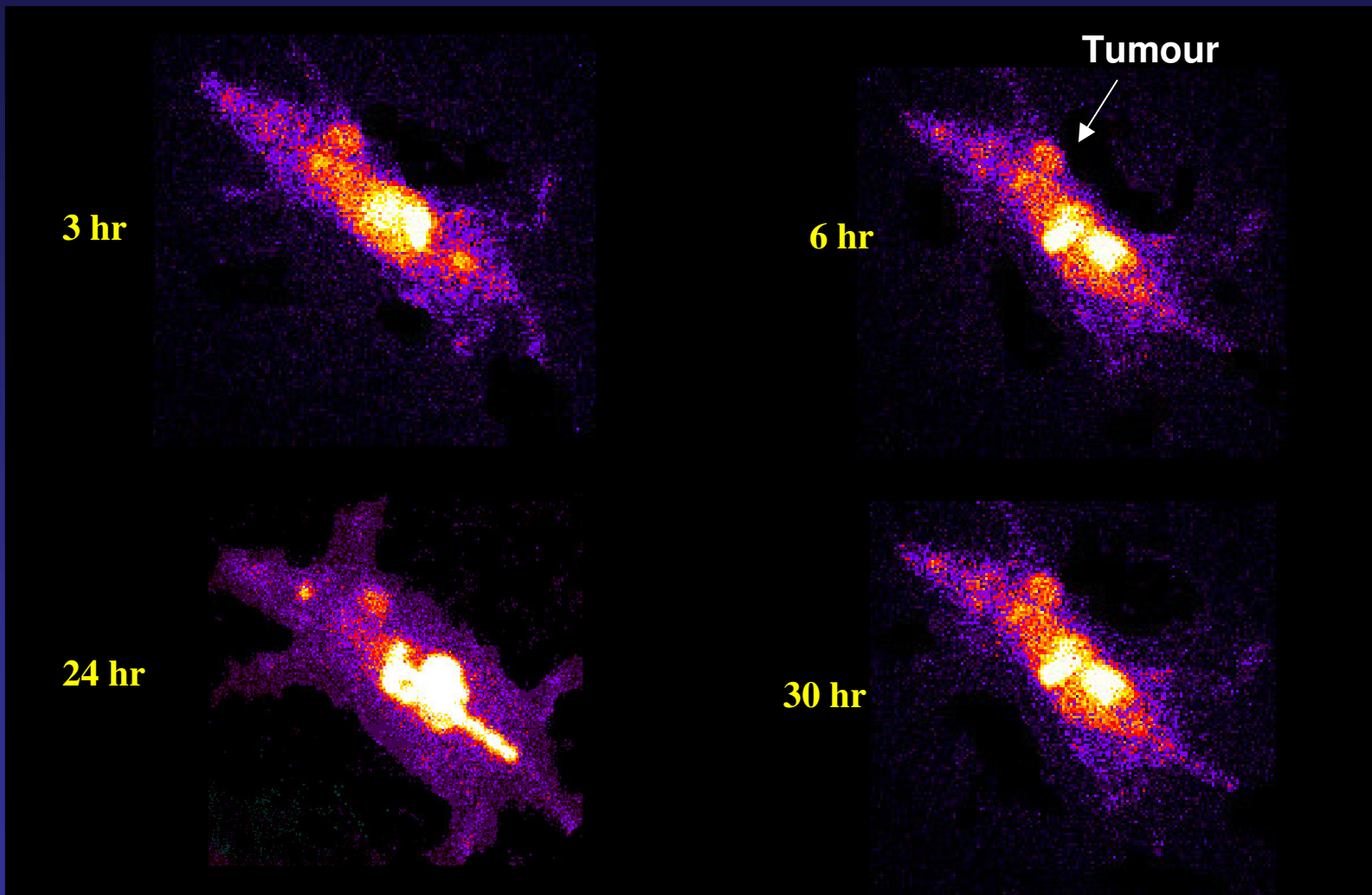


ARG longitudinal section

# Biodistribution of [<sup>123</sup>I]CLINDE in Rats Bearing Mammary Adenocarcinoma Tumours

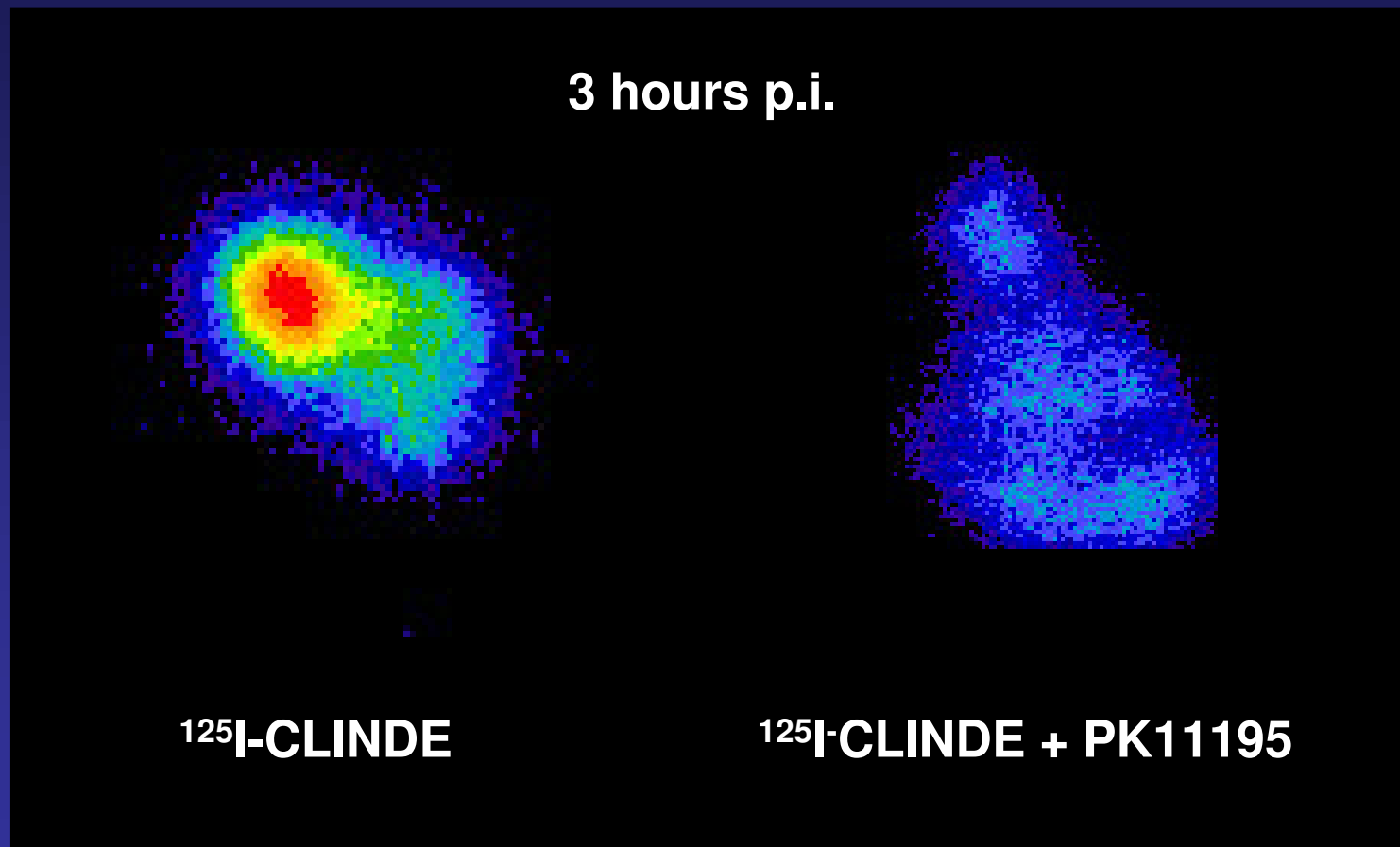


# Uptake of [ $^{123}\text{I}$ ]CLINDE in Rats with Mammary Adenocarcinoma

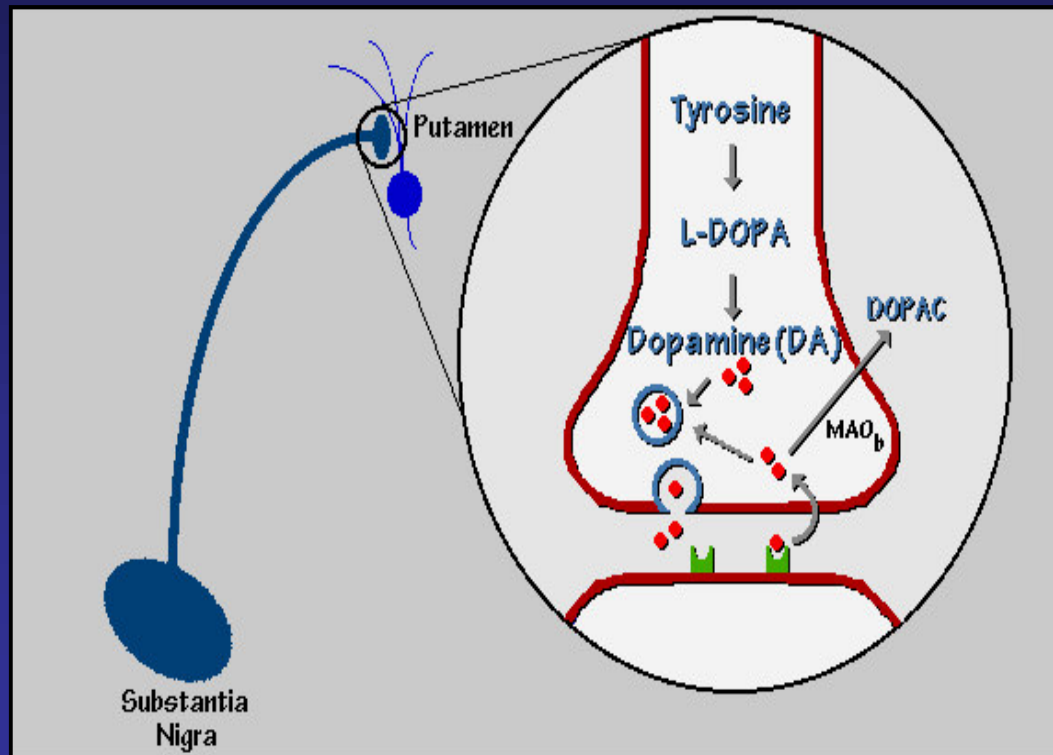


# *Ex -Vivo* Autoradiography of [ $^{125}\text{I}$ ]CLINDE

## Mammary Adenocarcinoma



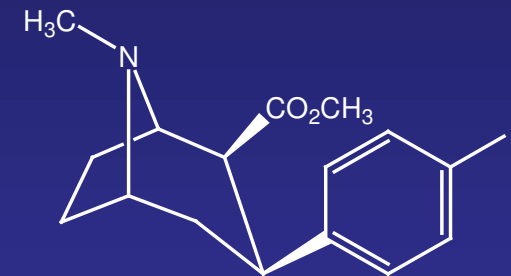
# DAT as a Marker for Diagnosis of Parkinson's Disease (PD)



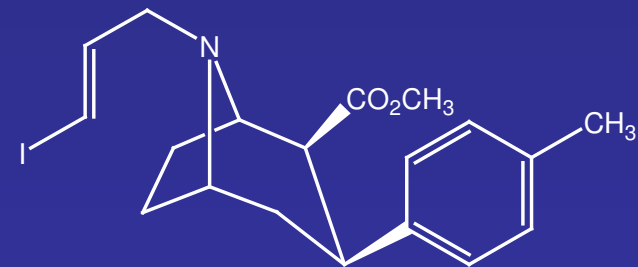
Dopaminergic synapse

PD – loss of presynaptic neurons

DAT↓ ~ DA neuron↓

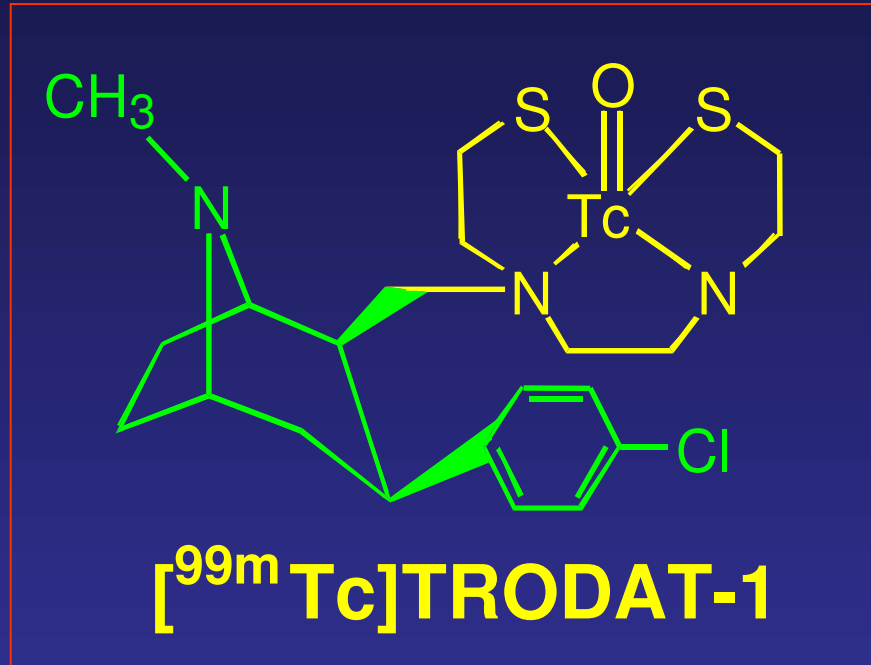


**β-CIT**



**PE2I**

# What is Tc-99m TRODAT-1?



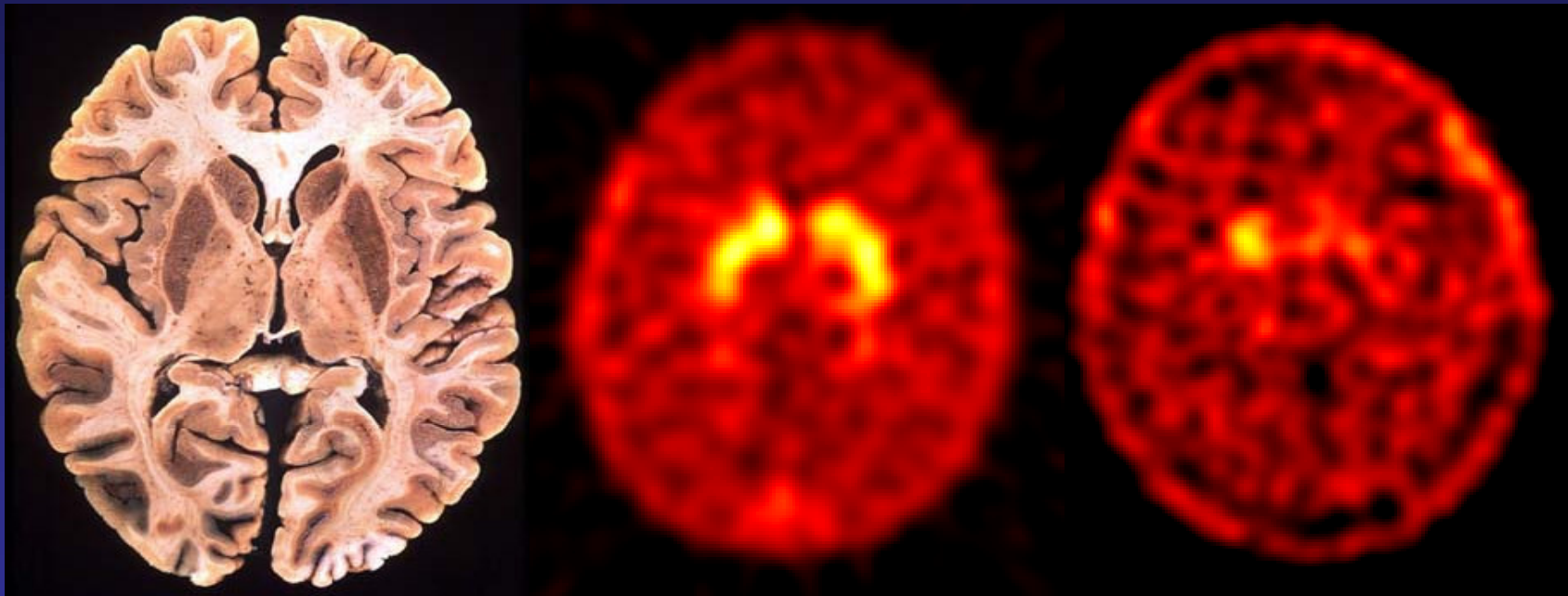
**TROPANE**

**DAT (DOPAMINE TRANSPORTER)**

**TRODAT**

Dr Hank.Kung UPenn

# SPECT Imaging of Tc-99m TRODAT-1 in Normal and Parkinson's Subjects



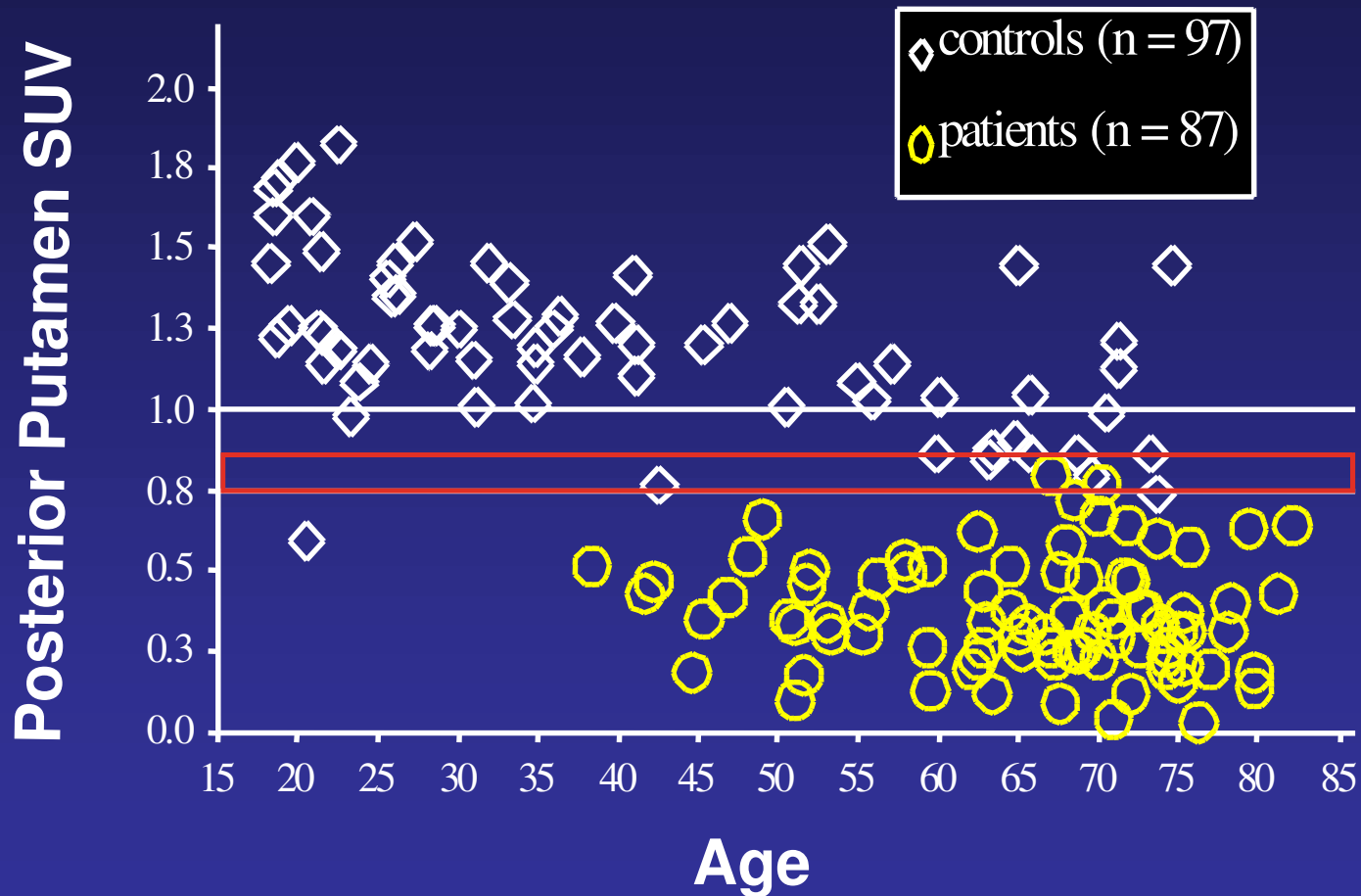
Histology

Healthy subject

Parkinson's patient

Transaxial, SPECT images of human brain at 3 hr. post iv injection of 20 mCi of [ $^{99m}\text{Tc}$ ]TRODAT-1 for normal and Parkinsonian subject, respectively.

# SPECT Imaging of Tc-99m TRODAT-1 in Normal and Parkinson's Subjects



Transaxial, SPECT images of human brain at 3 hr. post iv injection of 20 mCi of [<sup>99m</sup>Tc]TRODAT-1 for normal and Parkinsonian subject, respectively.

# Imaging Gene Expression

Bicistronic vector



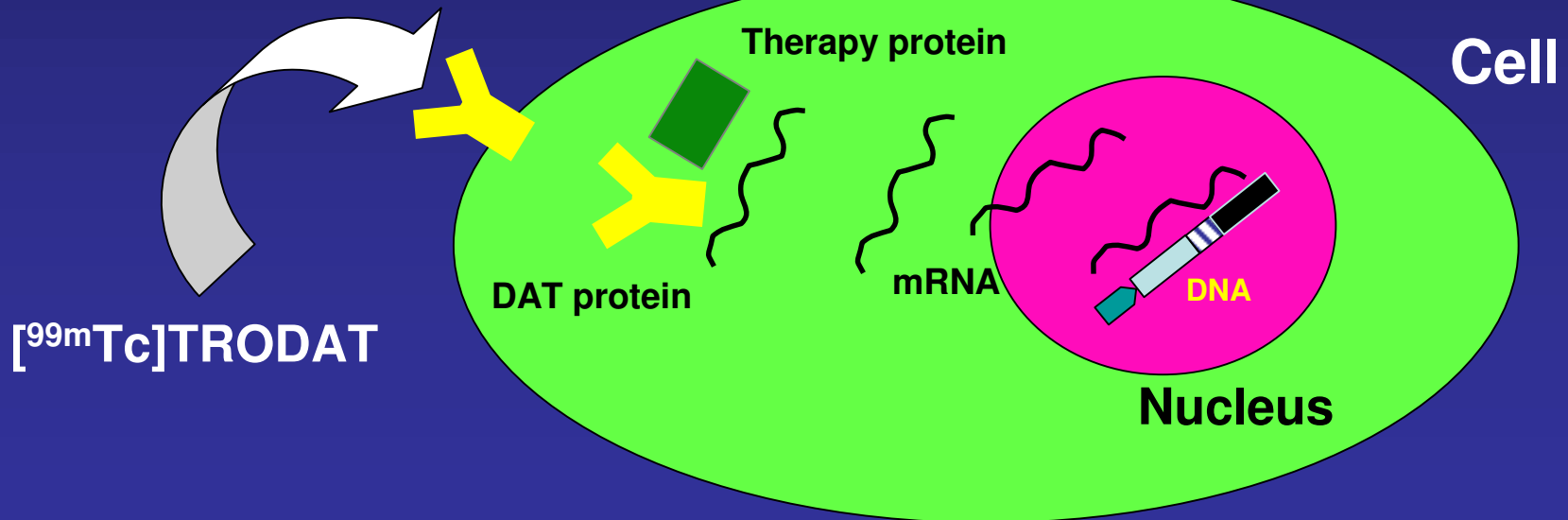
Promoter

therapy gene

IRES

reporter gene

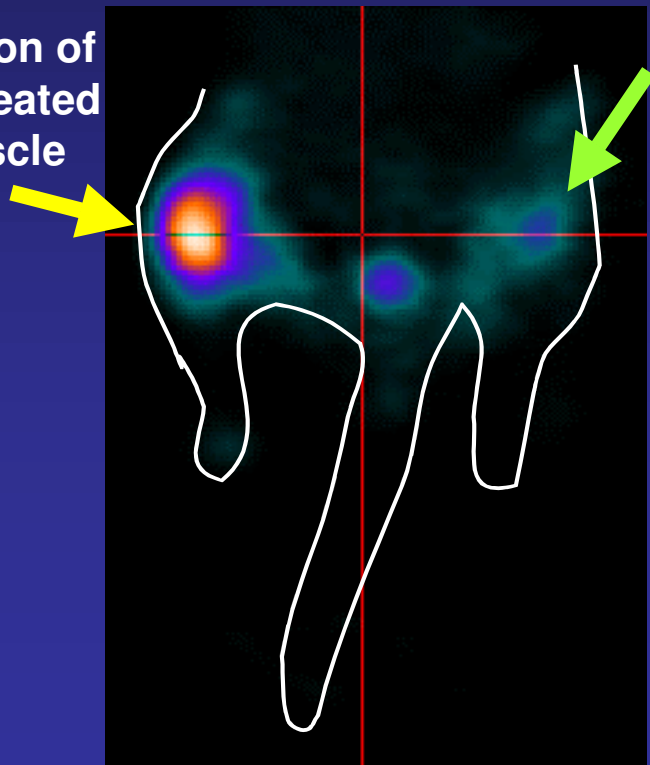
Transmembrane DAT



# Imaging of [<sup>99m</sup>Tc]TRODAT-1 in Mouse Leg Muscle Using Ultra-High Resolution SPECT

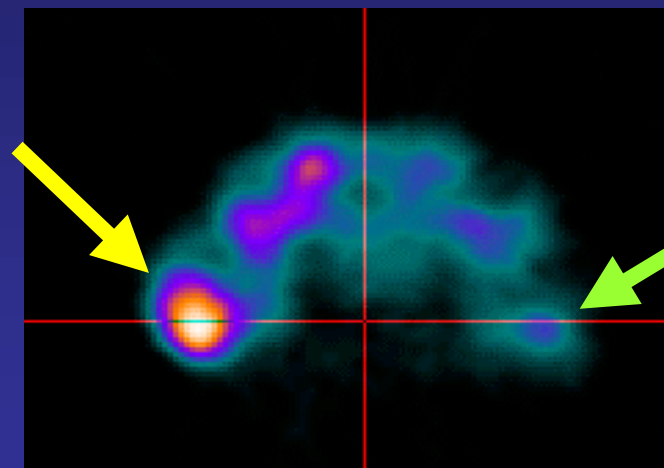
Transverse

Expression of  
DAT in treated  
leg muscle



Coronal

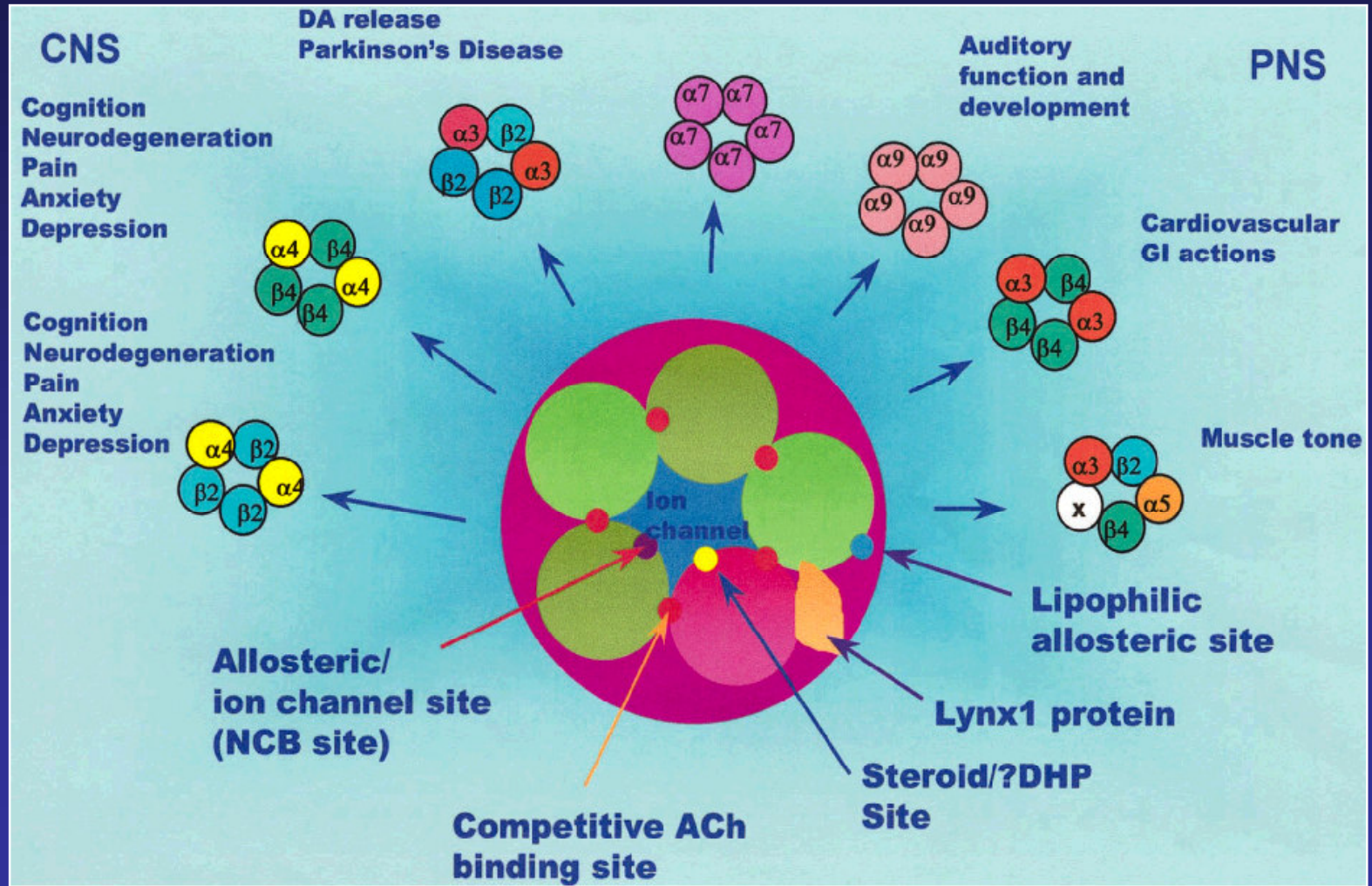
Low  
uptake of  
TRODAT in  
control  
muscle



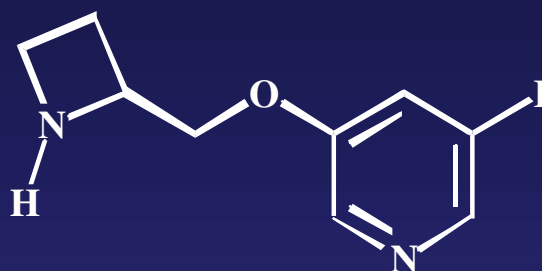
# Alzheimer's Disease

- Currently affects approximately 20 million worldwide, with 800 thousand and 360 thousand new cases in Europe and the USA each year
- AD imposes an annual economic burden of approximately US \$100 billion
- As life-expectancies in the developed world increase, so too will the prevalence of AD

# Nicotinic Acetylcholine Receptor (nAChR) Subtypes



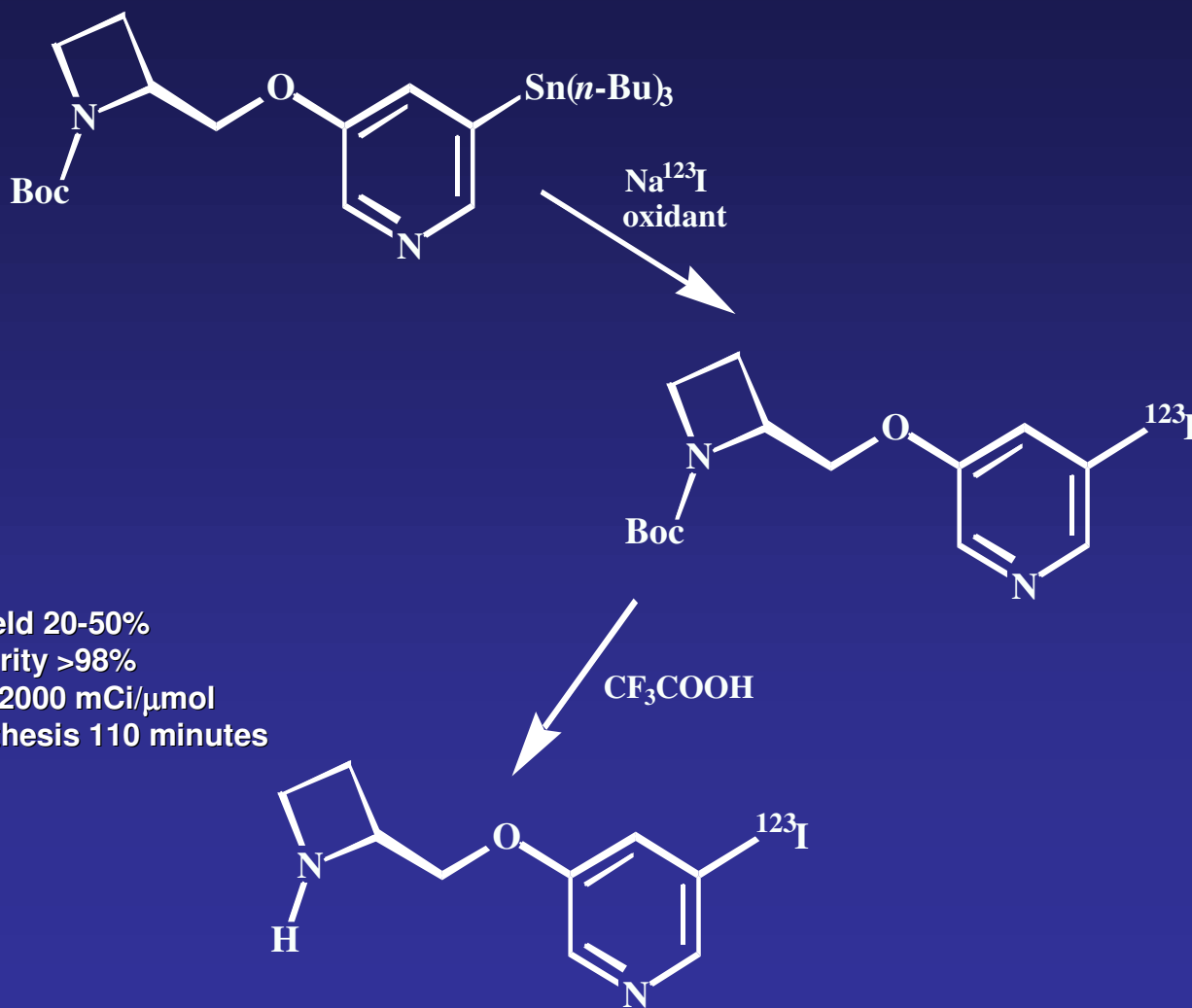
# 5-Iodo-A-85380



Ki at nAChR Subtypes (nM)

Ligand	$\alpha 4\beta 2$	$\alpha 3\beta 4$	$\alpha 7$	muscle
(-)-nicotine	0.84	100	130	1000
(±)epibatidine	0.008	0.049	4	7.5
A-85380	0.017	14	17	320
5-iodoA5380	0.01	51	250	1400

# Synthesis of 5-[<sup>123</sup>I]Iodo-A-85380



Radiochemical Yield 20-50%  
Radiochemical Purity >98%  
Specific Activity >2000 mCi/ $\mu\text{mol}$   
Total Time of Synthesis 110 minutes

# Animal Model of AD

## Surgical Lesioning

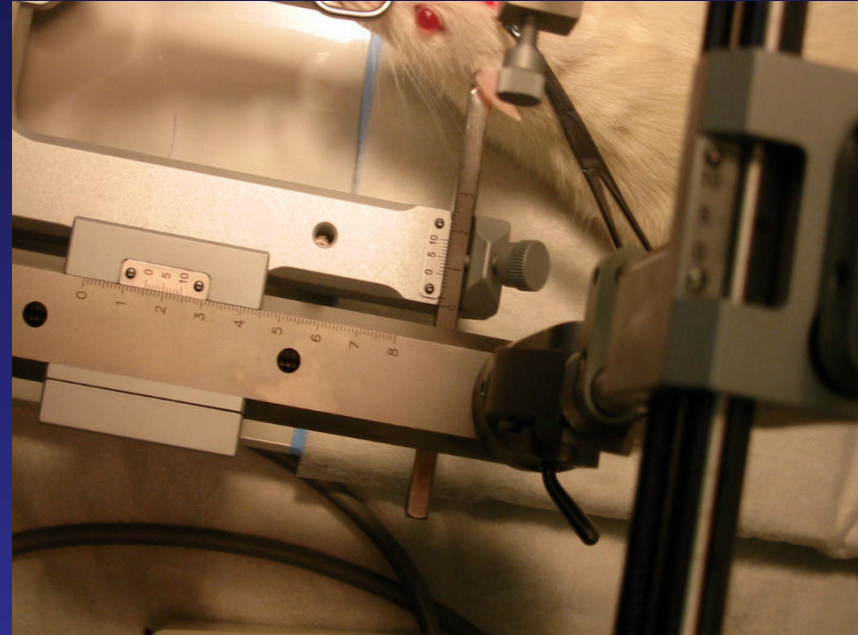
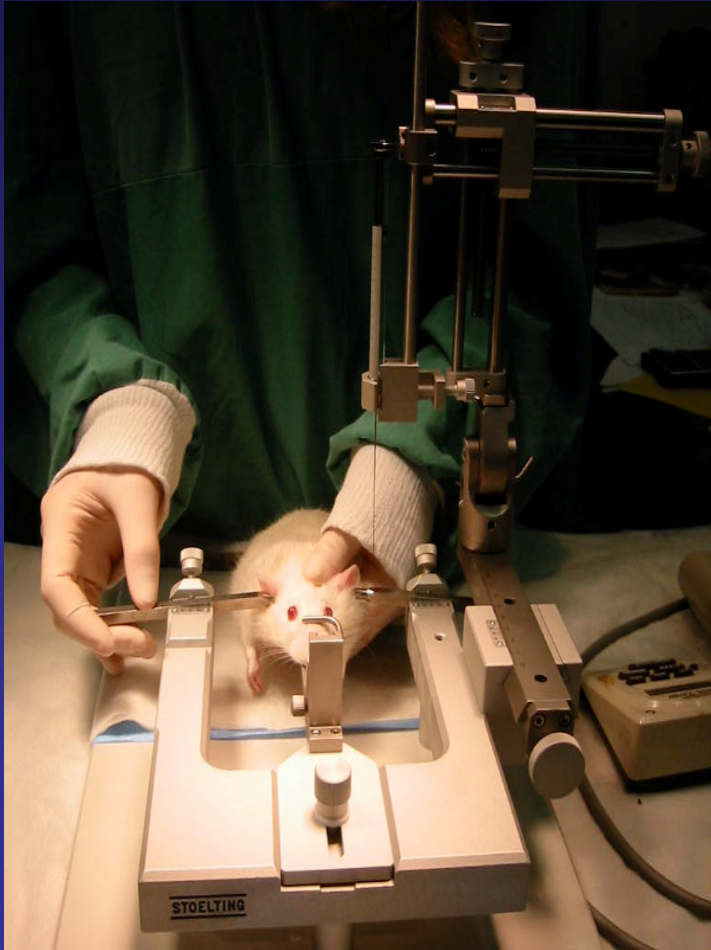


The animal is first anaesthetised...



# Animal Model of AD

## Surgical Lesioning



Then placed in a stereotaxic frame and a scalp incision made. An injection site is precisely located...(AP: -0.9mm, L: +/-1.5mm, DV: -3.4mm from Bregma according to Paxinos and Watson)

# Animal Model of AD

## Surgical Lesioning



A hole is drilled through the skull. The needle is lowered and the toxin slowly infused.

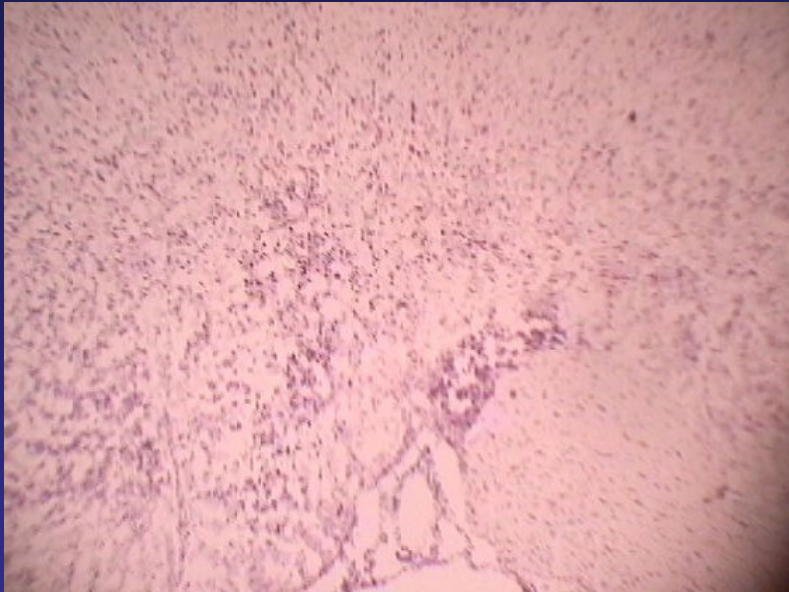
# Animal Model of AD

## Surgical Lesioning



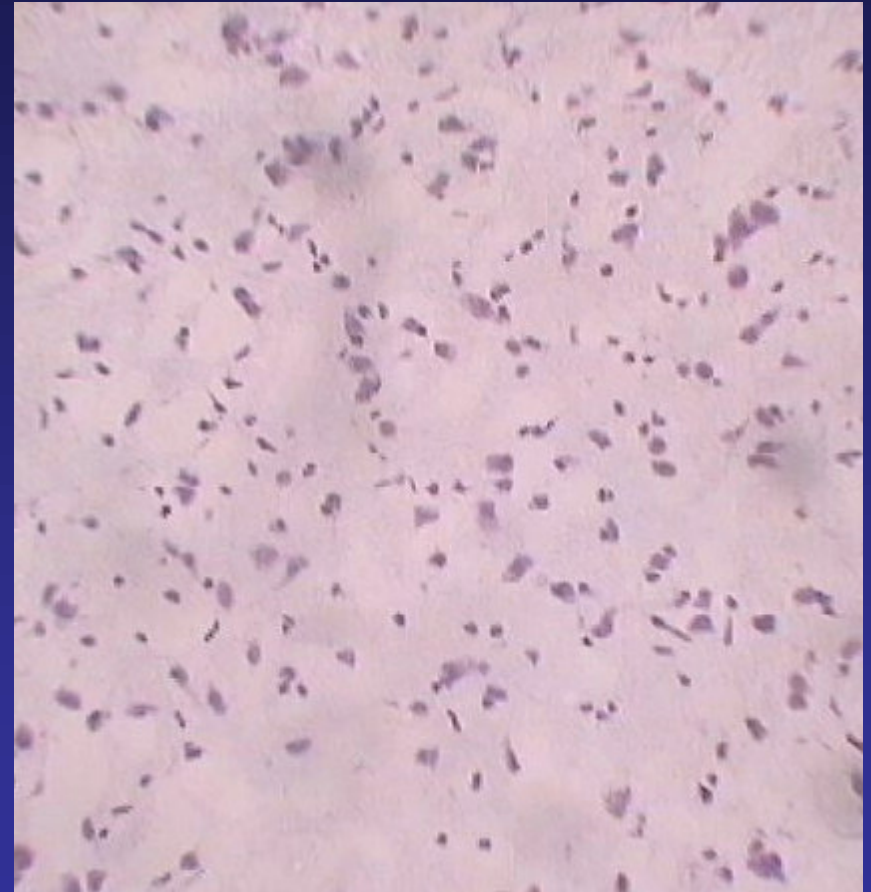
Finally, the needle is withdrawn and the scalp incision is sutured.

# *In Vitro* Studies



**4x**

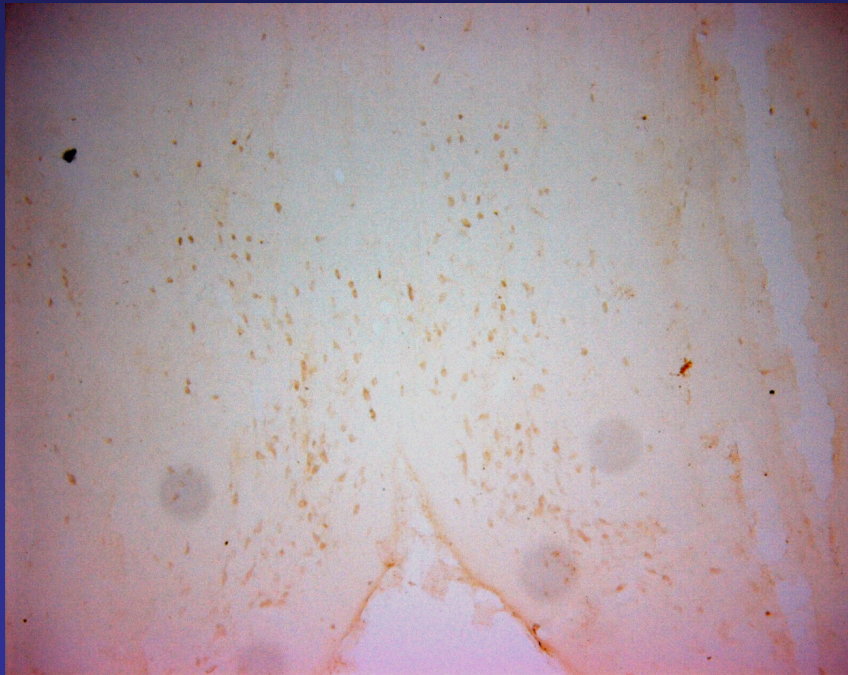
Cresyl violet histology section showing tissue morphology at Bregma -1.4 mm



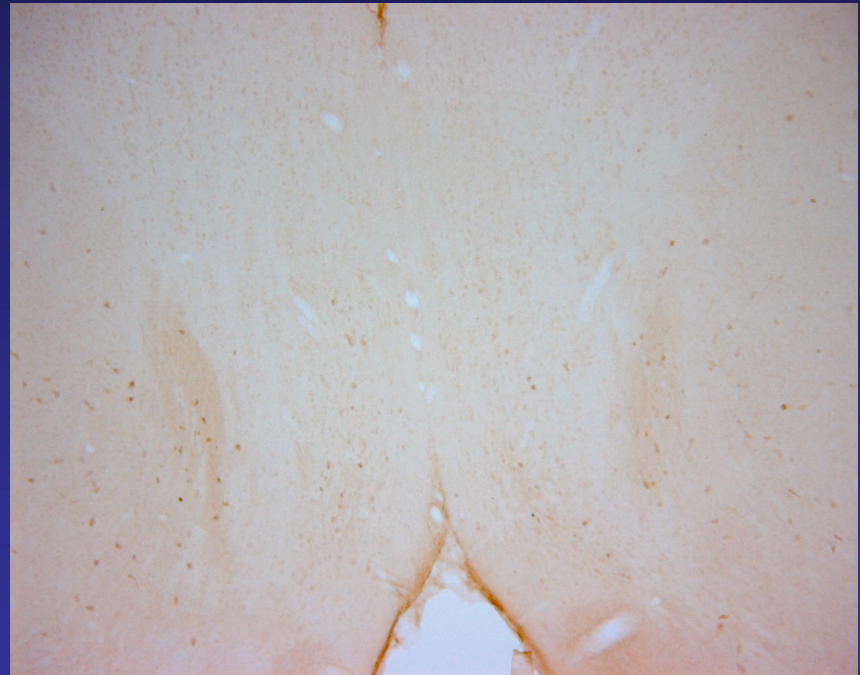
**20x**

# *In Vitro* Studies

**Sham lesioned**



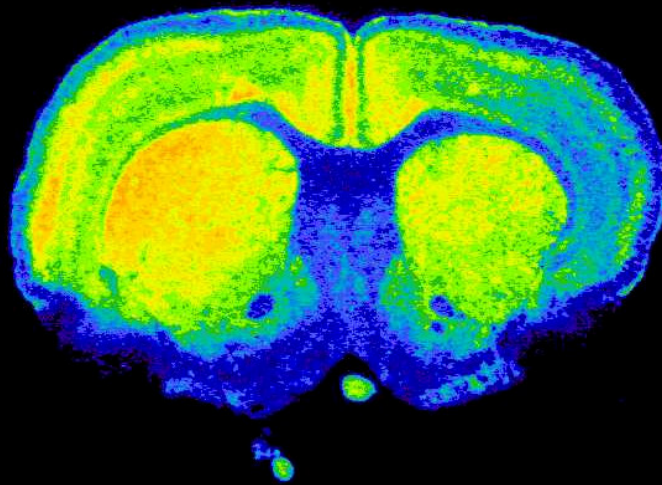
**IgG-saporin lesioned**



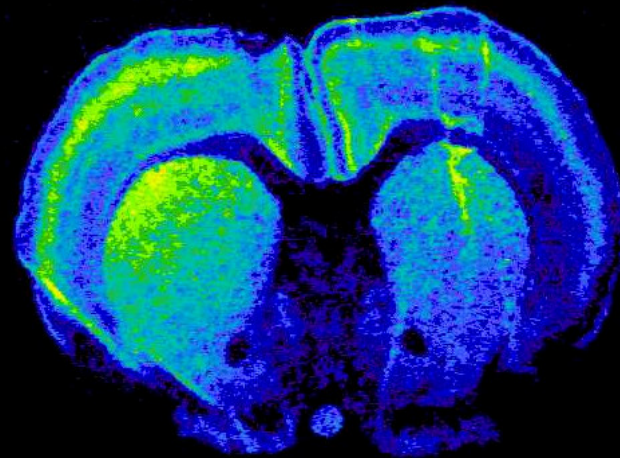
ChAT (choline acetyltransferase) immunohistochemistry section showing cholinergic neurons

# *In Vitro* Studies

Sham lesioned

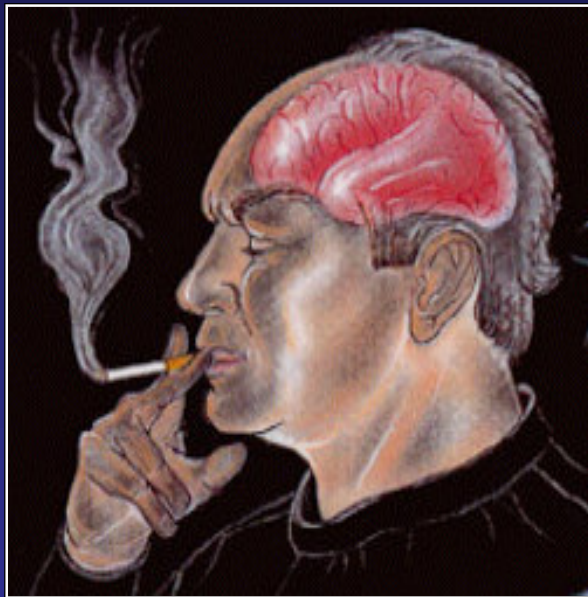


IgG-Saporin lesioned



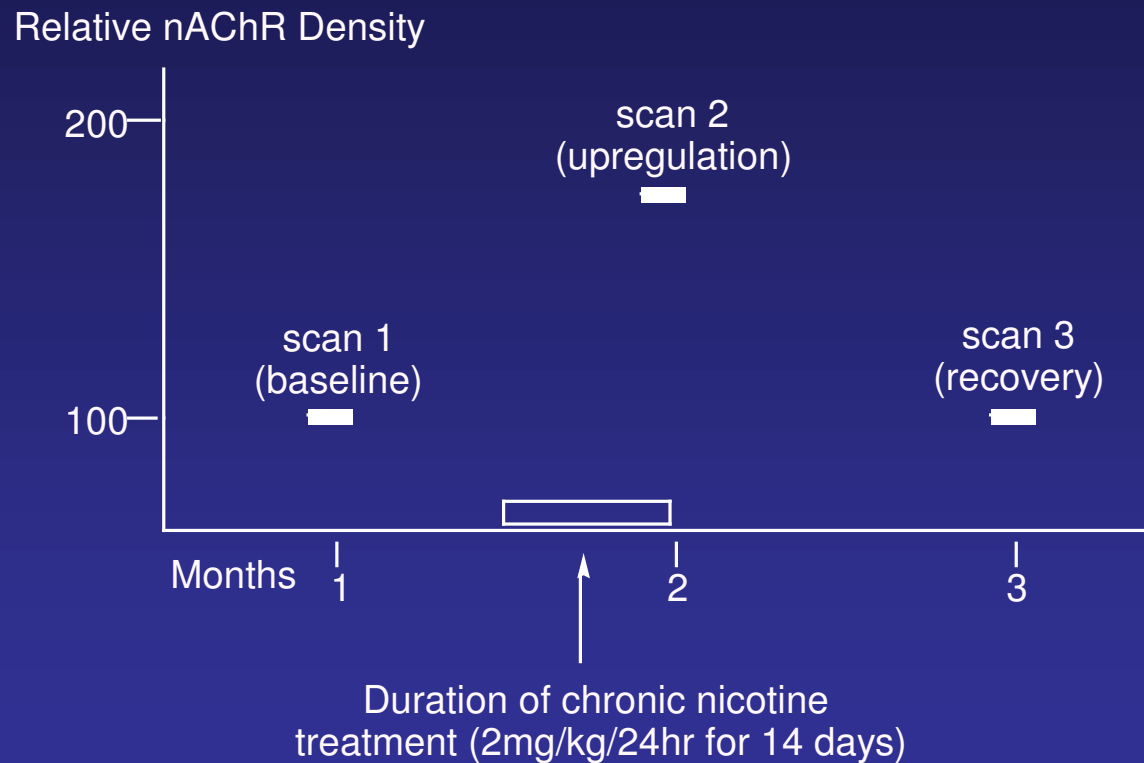
5-iodo[<sup>125</sup>I]-A-85380 autoradiography

# nAChRs - Smoking



- nAChR's increased in ctx, cb, hip and thal homogenates of autopsied brain samples from smokers.
- Positive correlation between cigarette consumption and nAChR increase, indicating dose dependent increase
- Smokers who had stopped smoking at least 2 months before death had nAChR levels similar to those of non-smokers.

# Baboon (-)-Nicotine Dosing and Imaging Protocol



In humans, a daily dose of 30mg/24hr of (-)-nicotine results in plasma nicotine levels similar to those found in smokers. This is approximately 0.5mg/kg/24hr. Assume the baboon clears (-)-nicotine 4 times faster than humans, the comparable dose in baboon would be 2mg/kg/24hr (personal communication, Neal Benowitz)

# Implantation of Osmotic Pump



# Implantation of Osmotic Pump



# (-)-Nicotine and Cotinine Levels in Baboon Plasma



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(-)-Nicotine dose – 2 mg/kg/24hr (626 mg)

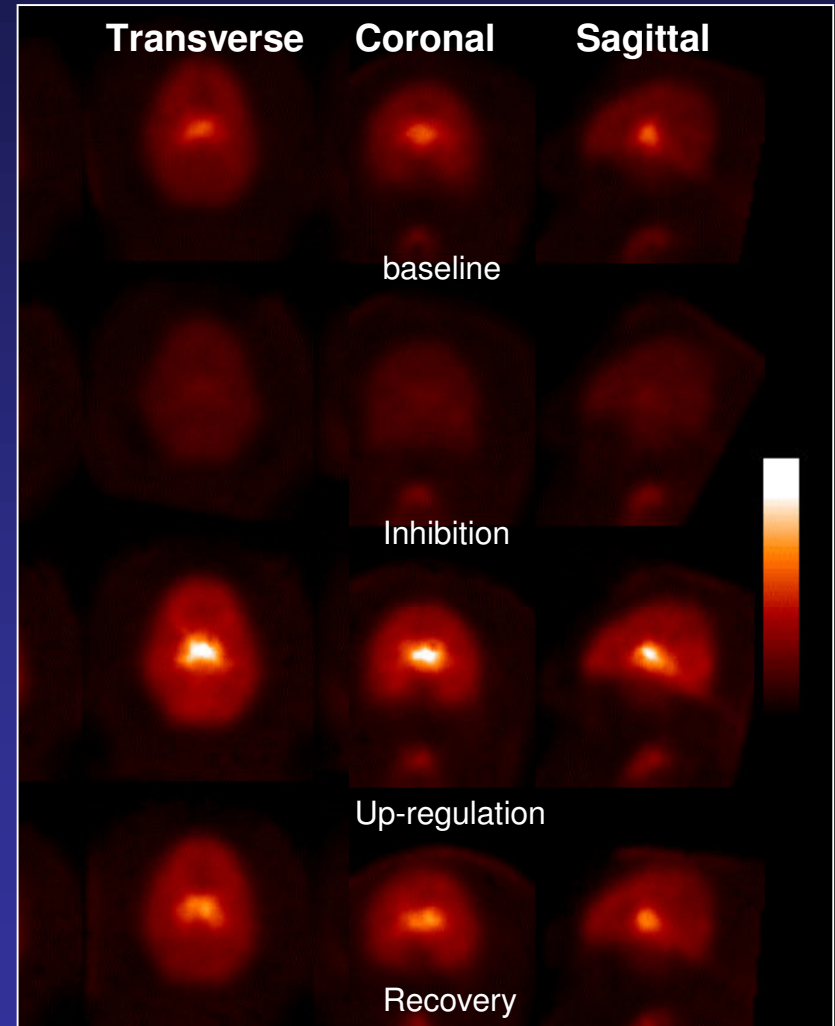
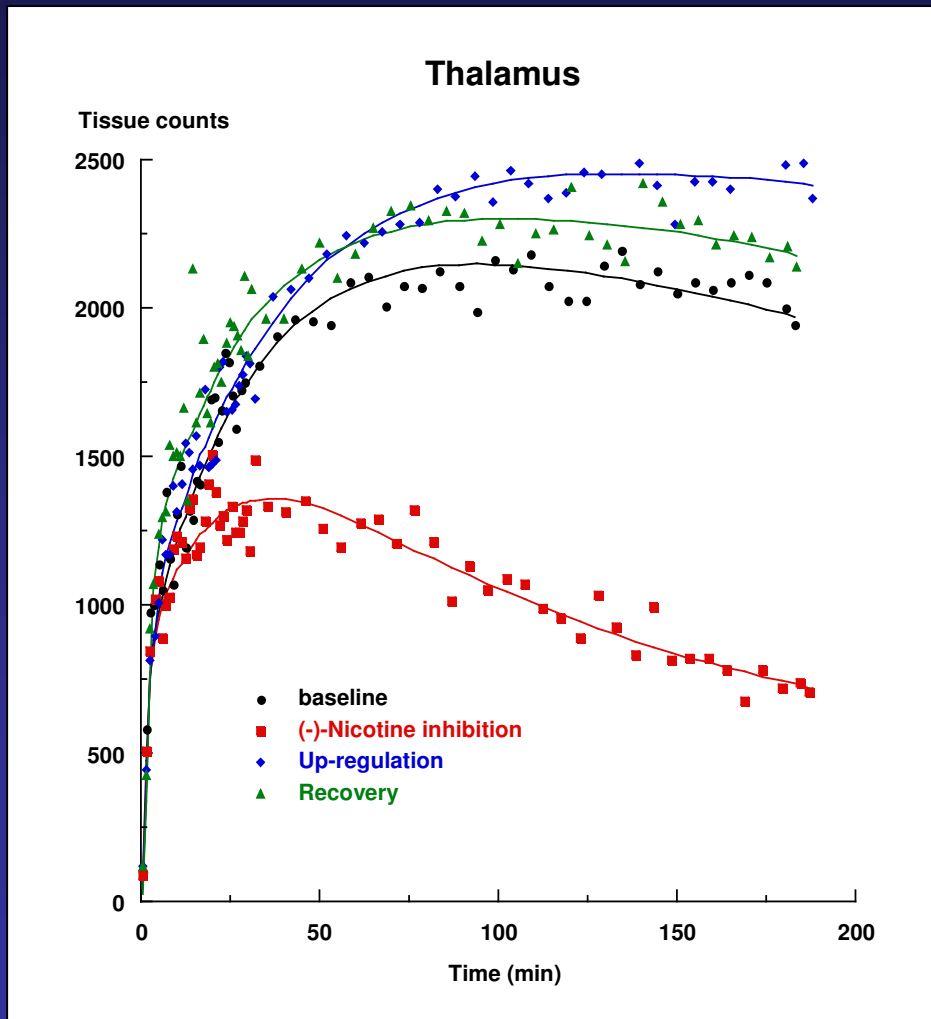
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Day of Infusion	(-)-Nicotine (ng/mL)	Cotinine (ng/mL)
2	27.3	238
15	26.4	191
Day 7 post infusion	*	ND

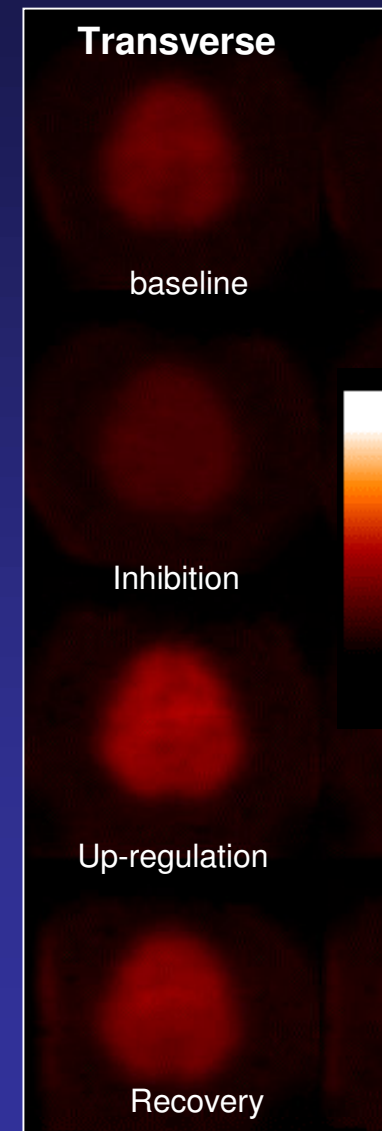
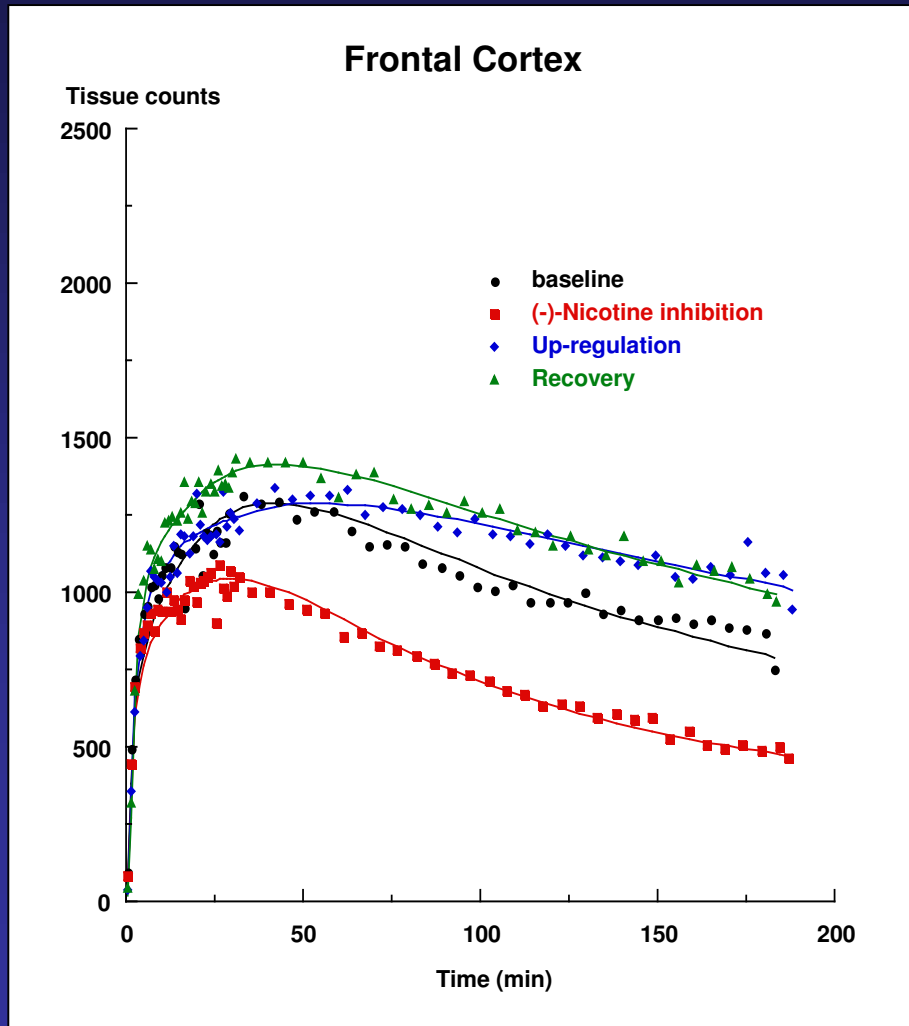
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ND means the analyte was not detected. \* means the analyte was below the limit of quantification (1.0 ng/mL for (-)-nicotine).

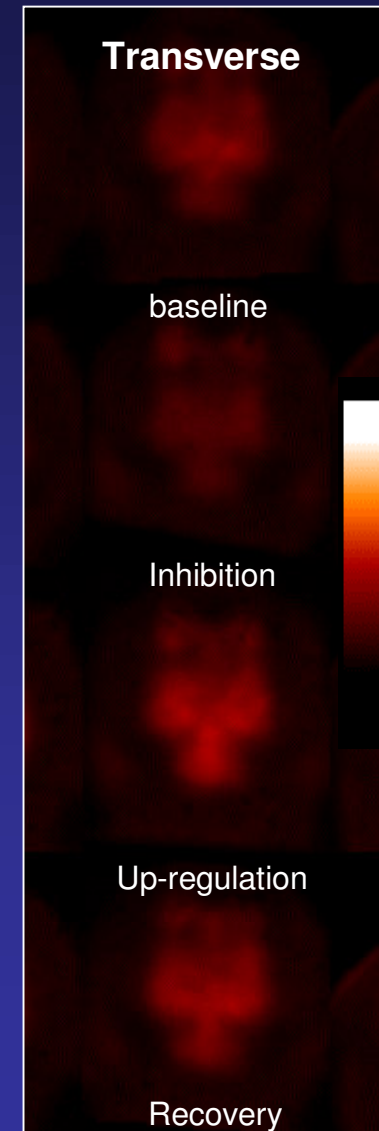
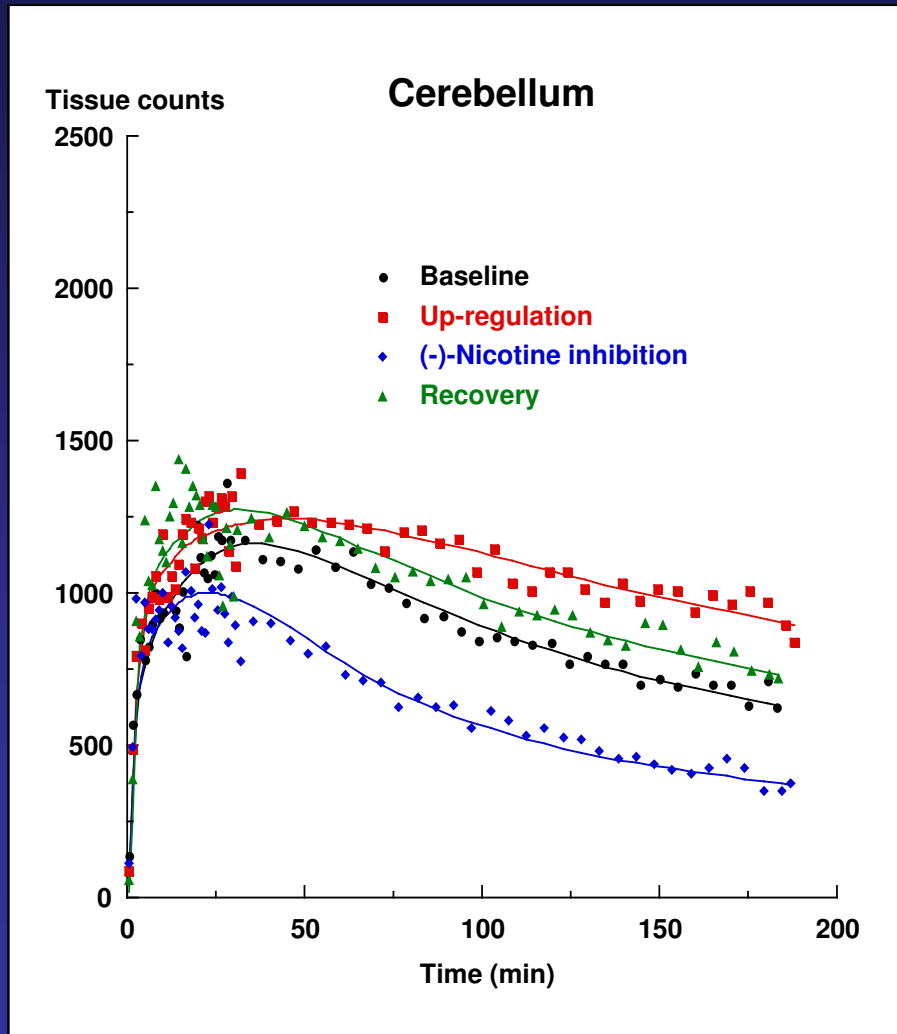
# 5-[<sup>123</sup>I]Iodo-A-85380 SPECT in Baboon (*Papio hamadryas*)



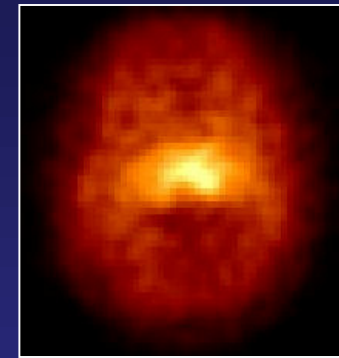
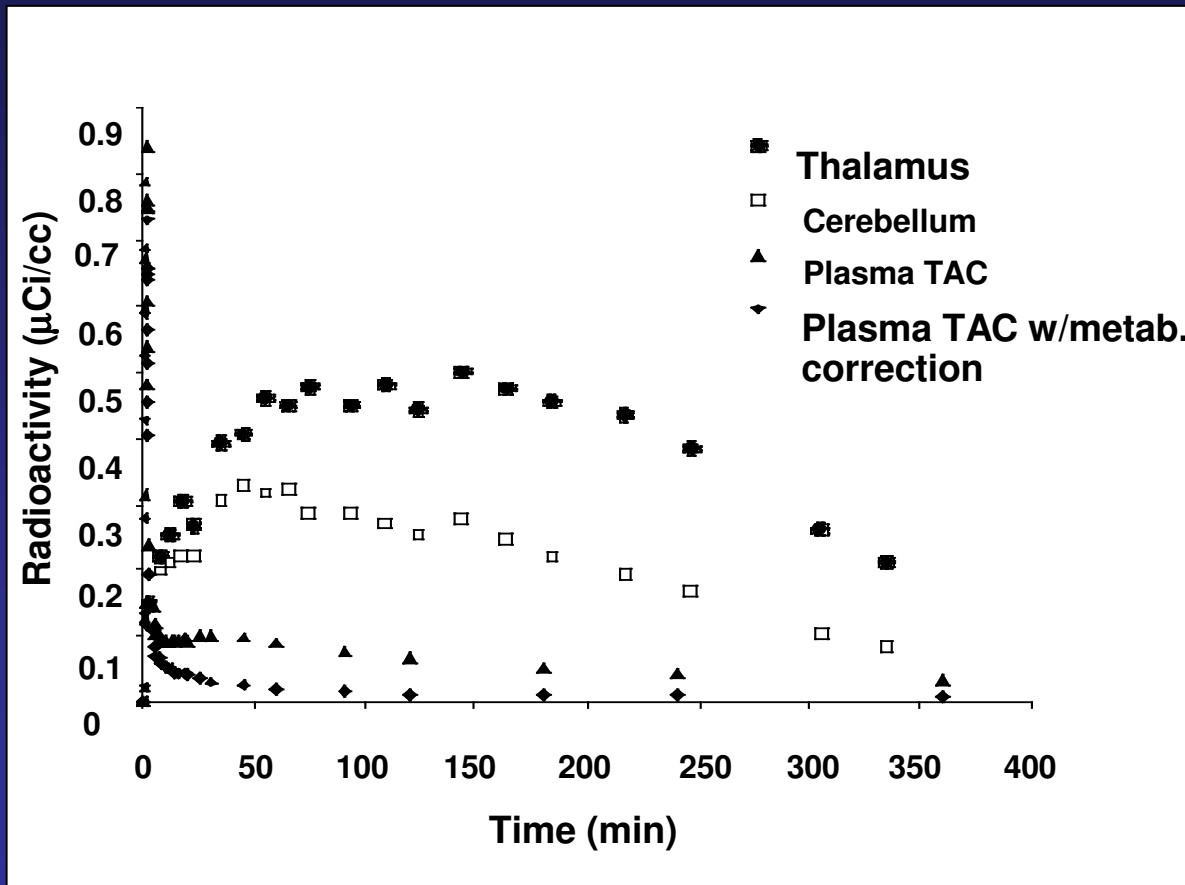
# 5-[<sup>123</sup>I]Iodo-A-85380 SPECT in Baboon (*Papio hamadryas*)



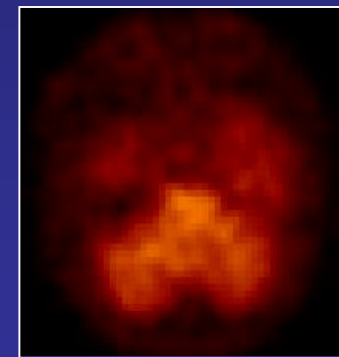
# 5-<sup>[123I]</sup>Iodo-A-85380 SPECT in Baboon (*Papio hamadryas*)



# 5-[<sup>123</sup>I]Iodo-A-85380 SPECT in Human



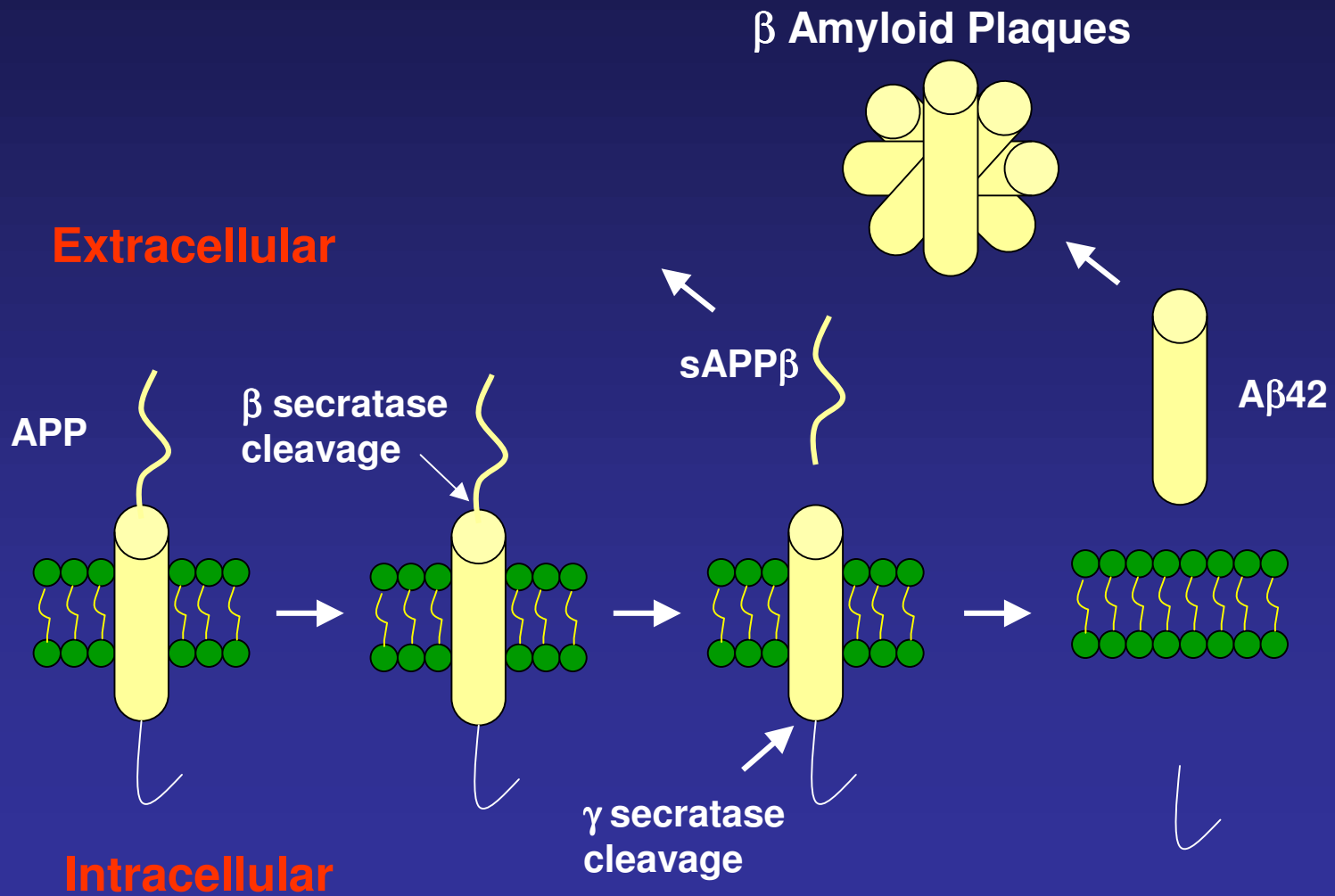
Thalamus



Cerebellum

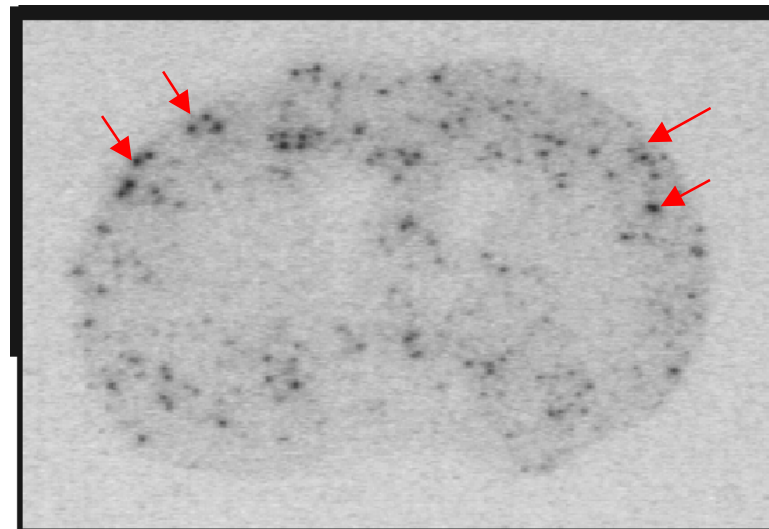
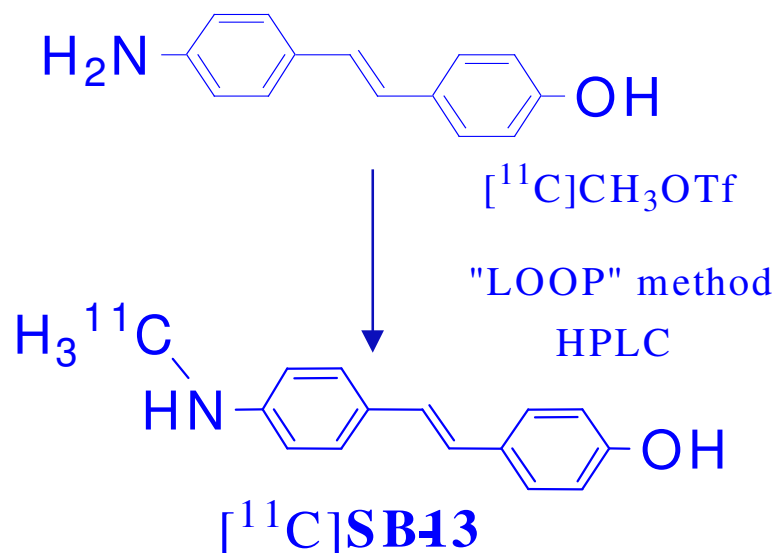
# $\beta$ Amyloid Plaques

## Cleavage of Amyloid Precursor Protein (APP)



# [<sup>11</sup>C]SB-13 for Imaging Aβ Plaques

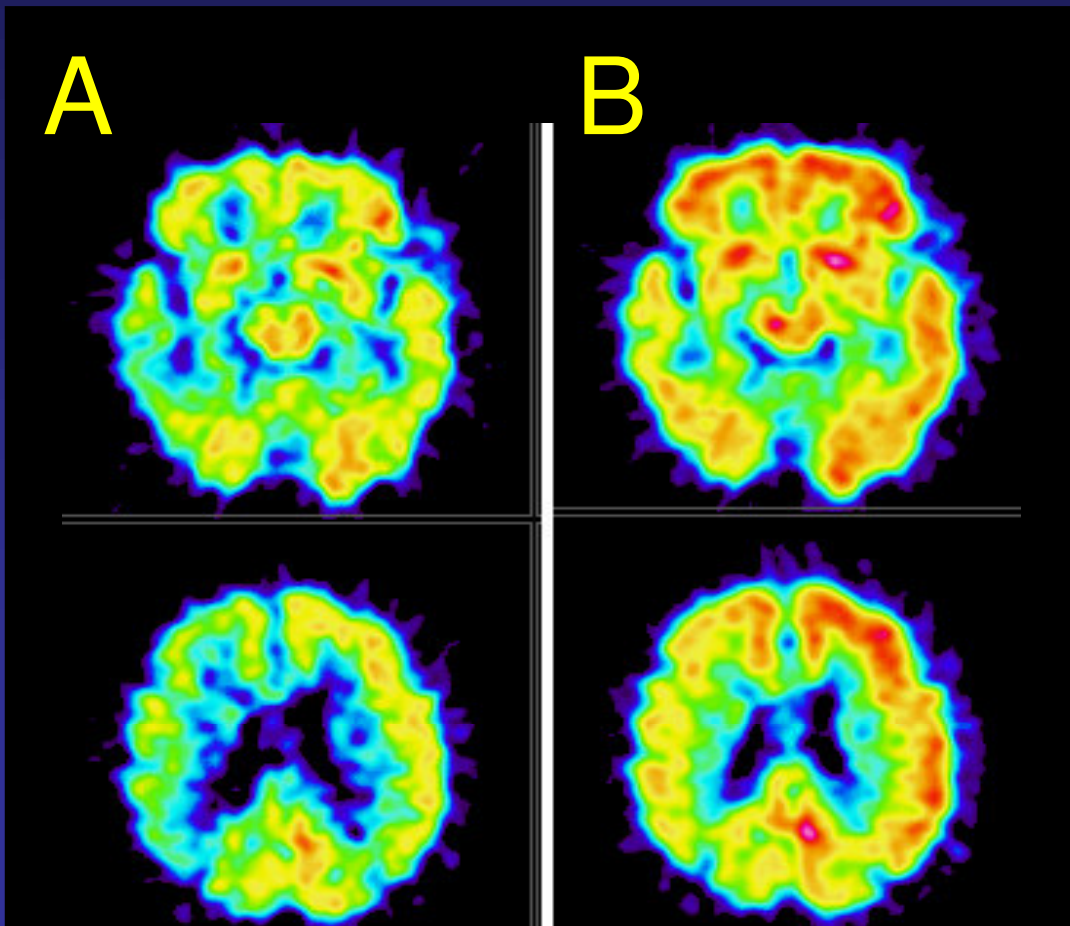
Dr. Alan Wilson, Univ Toronto, [<sup>11</sup>C]SB-13 was prepared by the following reaction:



In vitro autoradiography of brain sections of Tg mice suggests that [<sup>11</sup>C]SB-13 displayed selective binding to Aβ plaques.

# Comparison of [ $^{11}\text{C}$ ]SB-13 PET Imaging

## Control vs AD Patient



**A:** 68 yo healthy female;  
10 mCi of [ $^{11}\text{C}$ ]SB-13; 0-2 hr

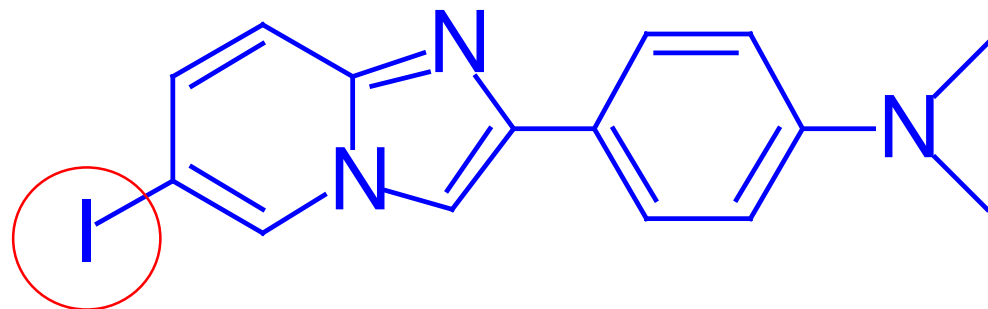
**B:** 74 yo female mild AD  
10 mCi [ $^{11}\text{C}$ ]SB-13; 0-2 hr

*Wilson, Verhoeff and Houle  
University of Toronto*



# New Probes for Imaging A $\beta$ Plaques

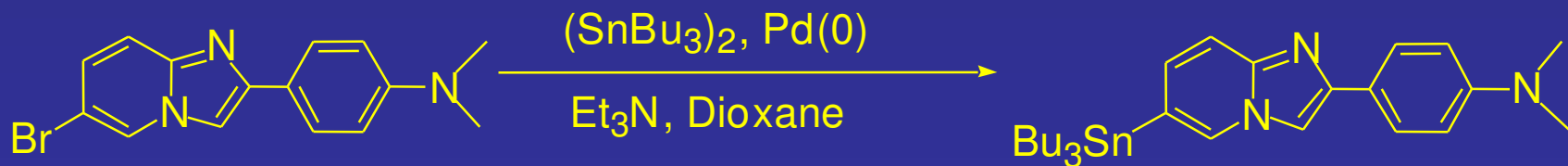
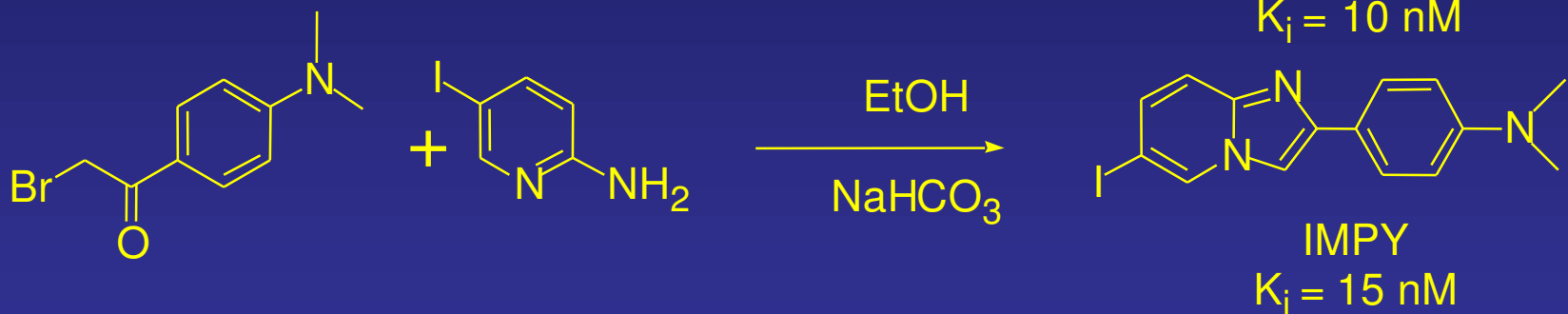
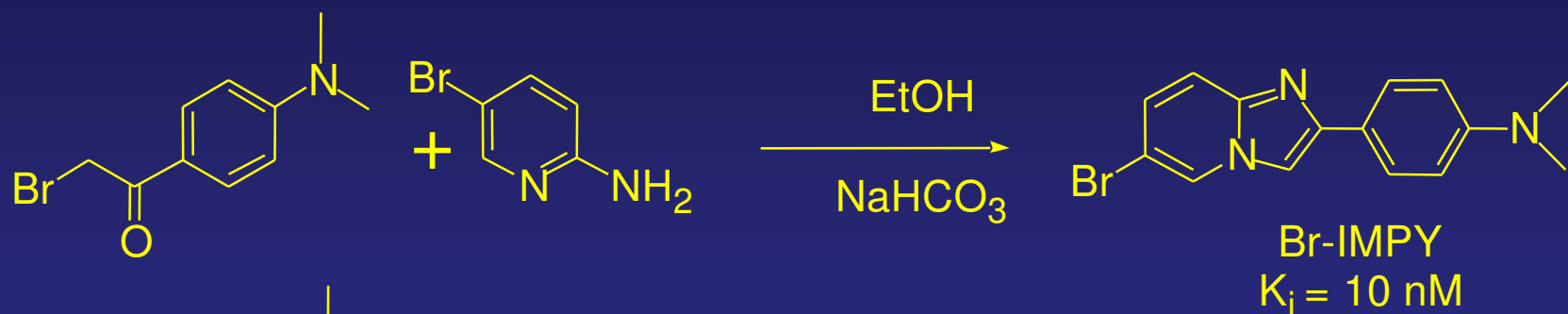
6-Iodo-2-(4'-dimethylamino-)phenyl-  
imidazo[1,2- $\alpha$ ]pyridine (IMPY)



IMPY

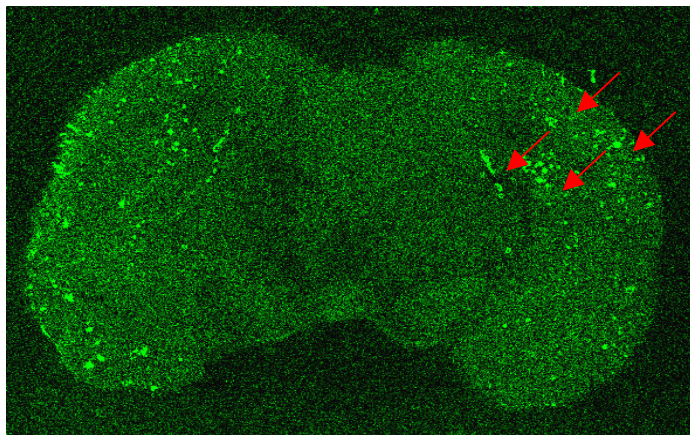
$K_i = 15$  nM

# New Probes for Imaging A $\beta$ Plaques: Synthesis of IMPY

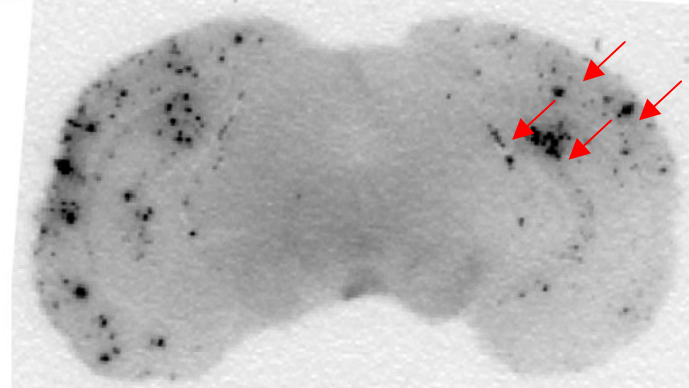
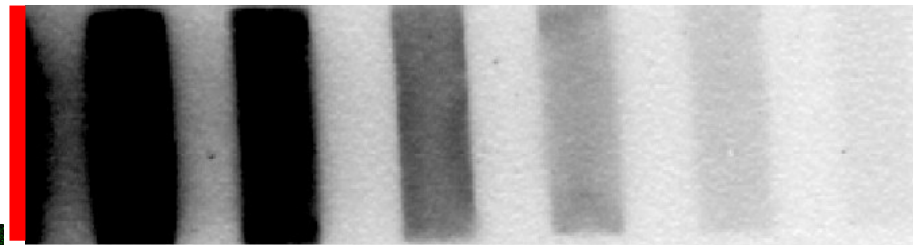


# In Vitro Autoradiography [<sup>125</sup>I]IMPY in Transgenic Mice (Tg 2576)

0.5 cm



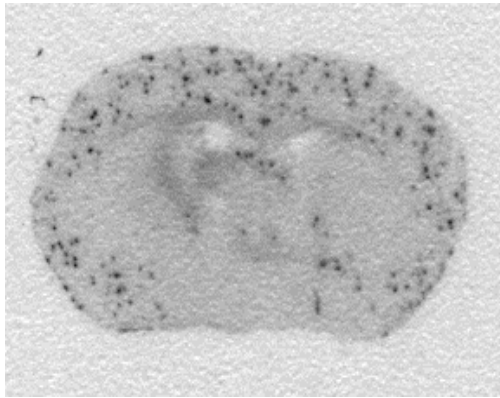
Thioflavin S



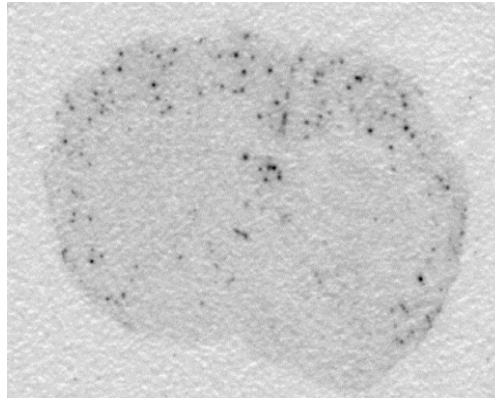
[<sup>125</sup>I]IMPY

# *In vivo* labeling autoradiography of [<sup>125</sup>I]IMPY in transgenic mice

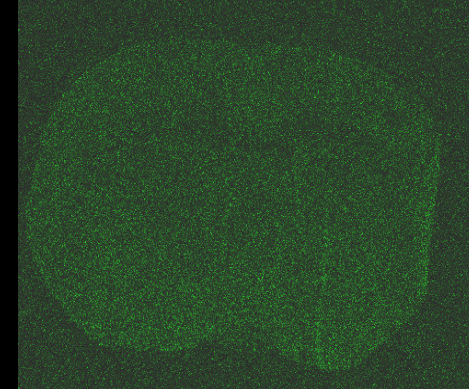
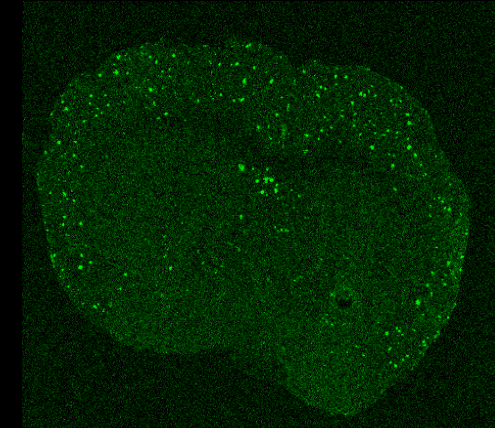
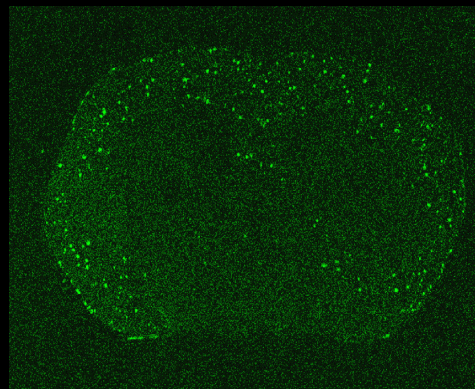
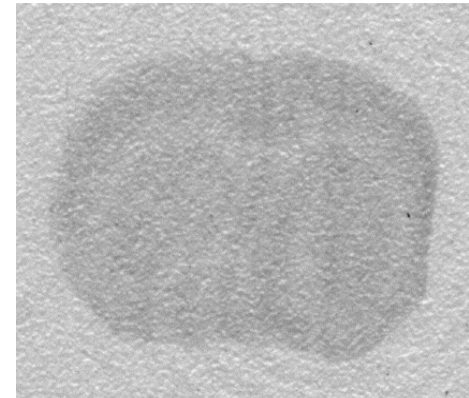
I-125 IMPY 0.5hr  
(TT4609-42)



I-125 IMPY 3hr  
(TT4364-56)

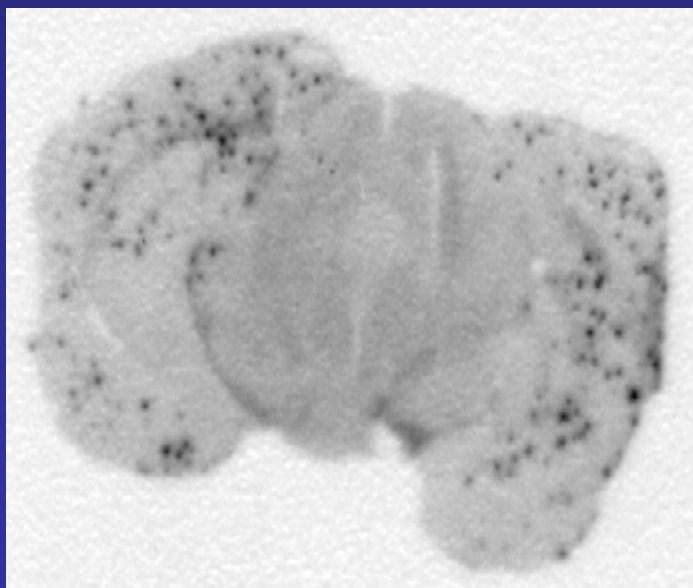
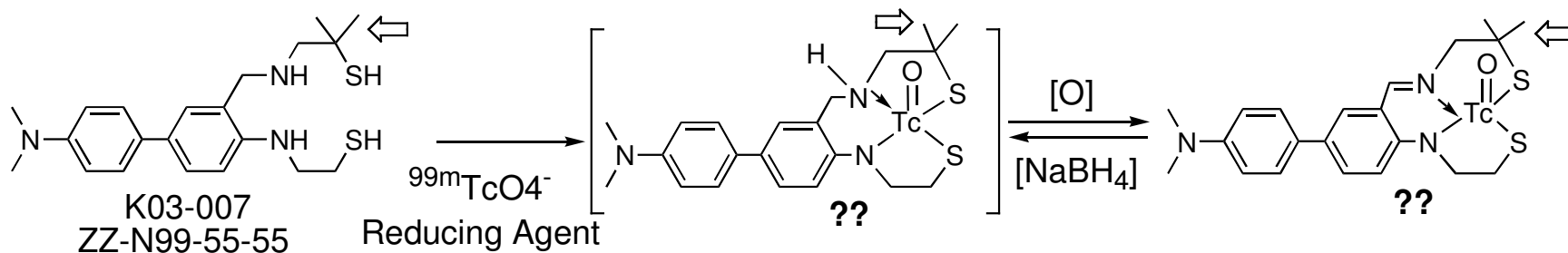


I-125 IMPY 3hr  
(WWD-52)



**Preparation of [<sup>99m</sup>Tc]K03-007 was achieved. *In vitro* Tg mouse brain tissue labelling showed clear and distinctive labelling to the Aβ plaques.**

New <sup>99m</sup>Tc Compound K03-007 with added gem-dimethyl groups to stabilize the TcO(N<sub>2</sub>S<sub>2</sub>) complex



Brain section labeled with  
[<sup>99m</sup>Tc] K03-007 in Transgenic  
mouse PDAPP (in vitro)

# SPECT Radiotracers

## Summary

- Significant progress has been made in the development of I-123 and Tc-99m SPECT radiotracers
- From a chemistry perspective I-123 has advantages: easier to prepare ligands and structure-activity relationships are more straight forward
- On a practical level, because of ease of use and optimal physical characteristics, there is a greater urgency and demand for Tc-99m labelled imaging agents in nuclear medicine clinics