



UNIVERSITY OF TORONTO
FACULTY OF MEDICINE

NEW APPROACHES FOR IMAGING ALZHEIMER'S DISEASE AND CO-OCCURRING DISORDERS IN THE LIVING HUMAN BRAIN

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Outline

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- CAMH PET Program
- PET in Parkinson's Disease (PD)
- 5 new approaches for imaging Alzheimer's disease (AD)
 - ▣ Plaques
 - ▣ Neuroinflammation
 - ▣ Role of Metals
 - ▣ Cerebral amyloid angiopathy
 - ▣ Cholinergic system

CAMH and the TDRA

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1. Adverse cognitive effects of medications with anticholinergic properties (Dr. Bruce Pollock *et al.*)
2. Population pharmacokinetics of atypical antipsychotics and other medications in older patients
 - Pollock *et al.* published on all the atypicals used in the CATIE-AD trial
3. Alternatives to the use of atypicals for treatment of agitation & psychosis in dementia
 - pilot work has led to a substantial multi-site NIA-sponsored placebo-controlled trial of citalopram led by Pollock *et al.*
4. PET imaging and novel radioligand development (CAMH PET)

CAMH PET Group

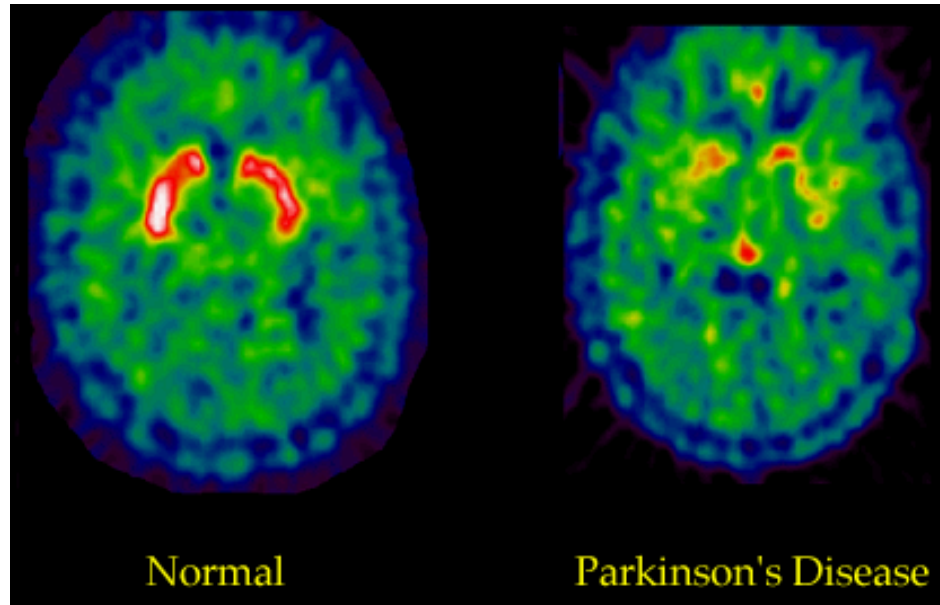
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- 28 PET radiotracers for human imaging
 - 12 were 1st use worldwide
 - 10 were 1st use in Canada
- Radiochemistry facilities
 - Patented ¹¹C-technology
 - 17 MeV cyclotron (only one in Toronto)
- 1 head-only scanner (HRRT) and 1 PET-CT
- Expansion highlights include:
 - fMRI
 - Small animal imaging
 - 2nd cyclotron (IBA cyclone; March 2011); new GMP labs
- Mood disorders, Schizophrenia, Addictions, PD, AD



[¹⁸F]FDOPA and Parkinson's disease

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- PD patients with gambling behaviour show increased release of dopamine in the ventral striatum during gambling
Strafella, *et al.*, *Brain*, **2009**
- CAMH discovered a D3 dopamine receptor-preferring ligand
Wilson, *et al.* *J. Med. Chem.* **2005**
- PD patients showed elevated D2 binding as expected, but decreased D3 binding
Boileau, Kish, *et al.*, *Brain*, **2009**

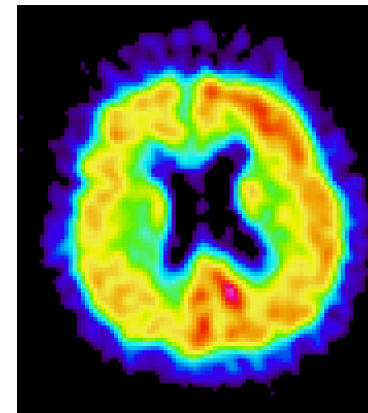
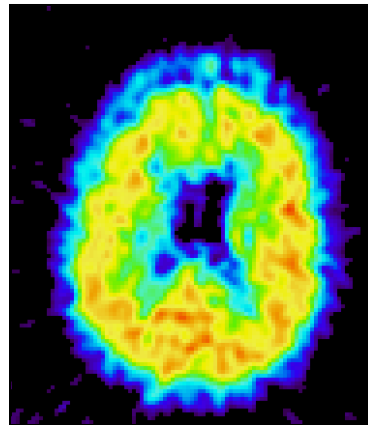
[¹¹C]PiB

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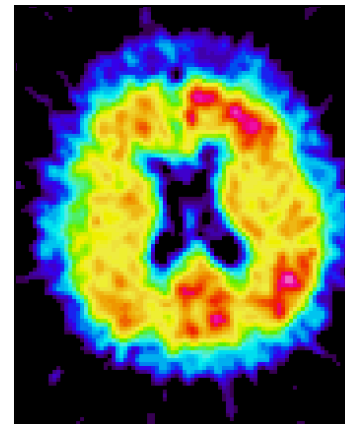
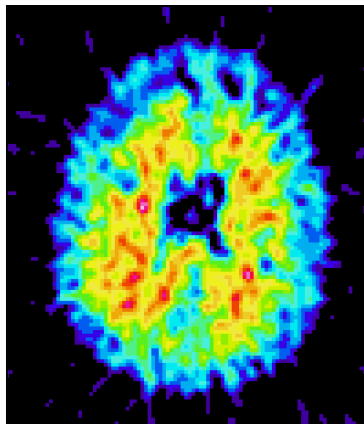
Control

Alzheimer's

0-30 minutes



30-120 minutes



Klunk W. *Science* 2002;297:752
Licenced by GE

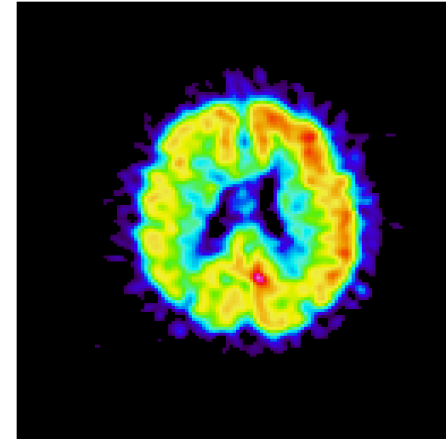
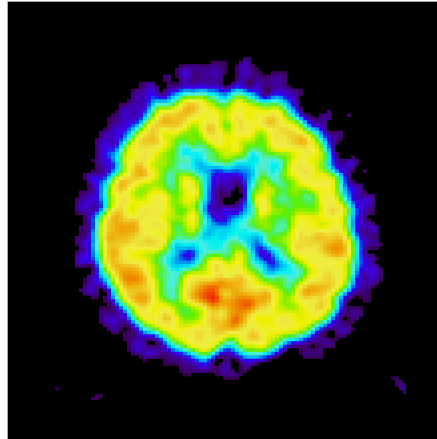
[¹¹C]SB-13 - discovered at CAMH

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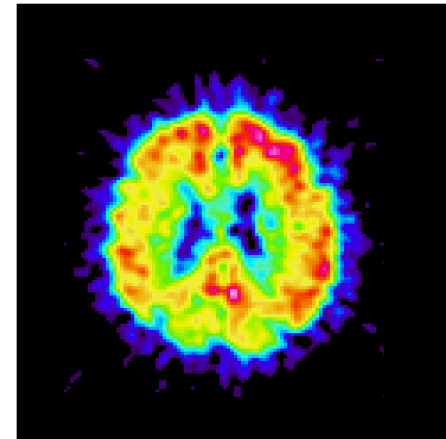
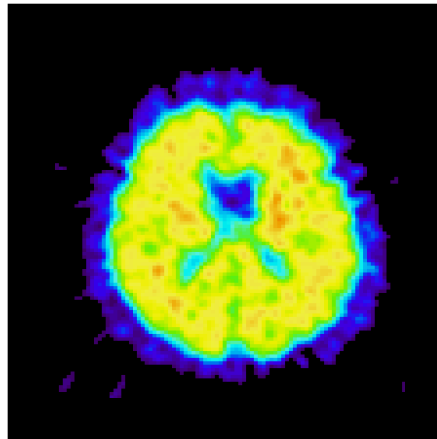
Control

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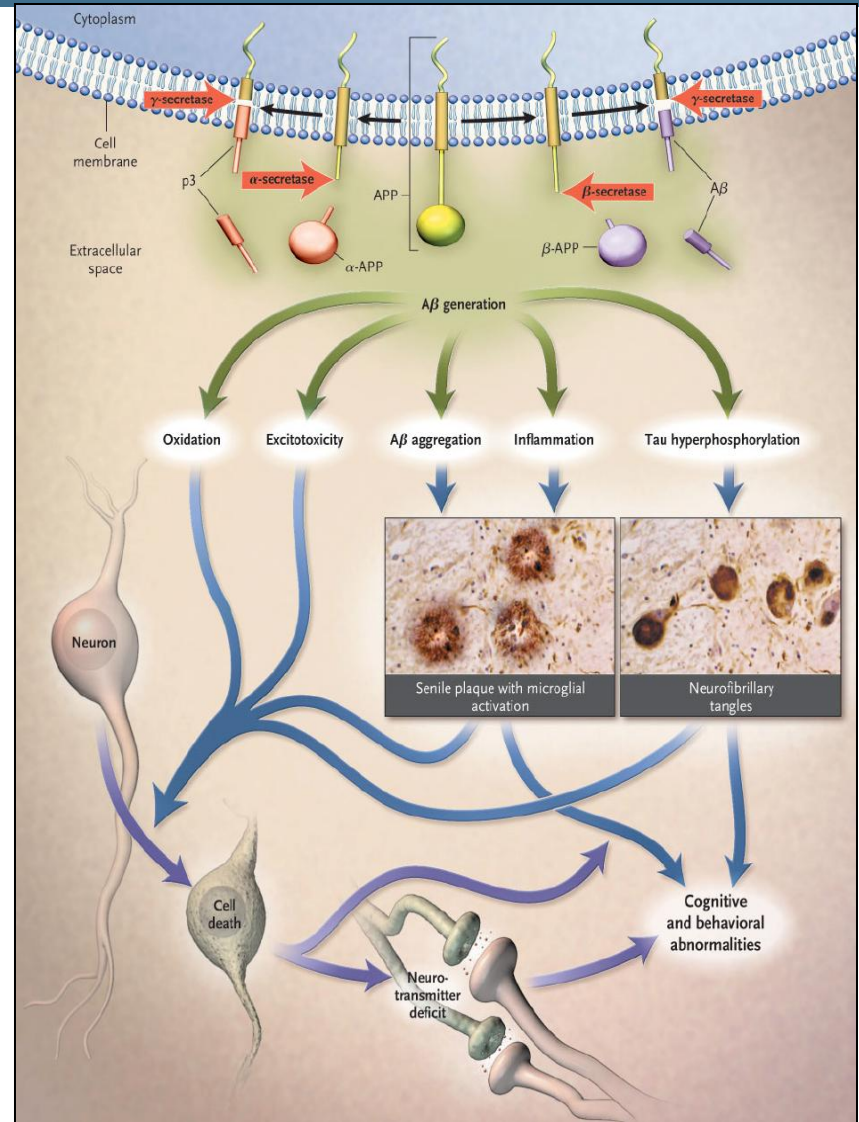


Verhoeff et al, *Am J Geriatr Psychiatry*, 2004
Not Patented

Pathophysiology of AD

- Plaques are a heterogeneous clusters
- Formation of tau
- Oxidative stress
- Microglia activation
- Neurotransmitter impairment
- Signal transduction pathways
- Inflammatory reactions
- Cholinergic pathway
- Role of metals in plaques
- Cerebral amyloid angiopathy

(Cummings, 2004)



Many hypotheses bring many radiotracers: Ideal amyloid imaging agent

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- Lipid soluble (crosses BBB)
- High affinity and selectivity for A β plaques
- Slow dissociation from binding site
- Rapidly cleared from blood
- Not metabolized
- Provide quantitative and reproducible information about A β burden in the brain
- Easily labeled with ^{18}F , ^{11}C , $^{99\text{m}}\text{Tc}$, ^{123}I

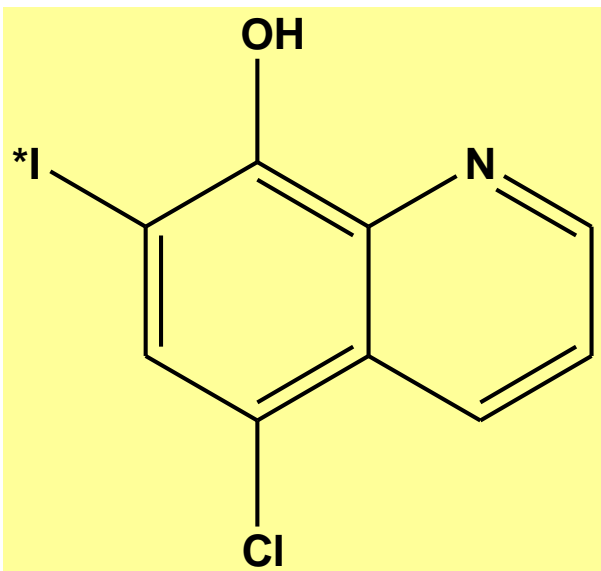
Advantages of fluorine-18

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- Half-life: ^{18}F (109.7 min) vs. ^{11}C (20.4 min)
 - ▣ Multiple scans from one synthesis
 - ▣ Supply neighboring hospitals
- Radiochemistry can be facilitated
- Match pharmacokinetics of binding to lifetime of the radiotracer

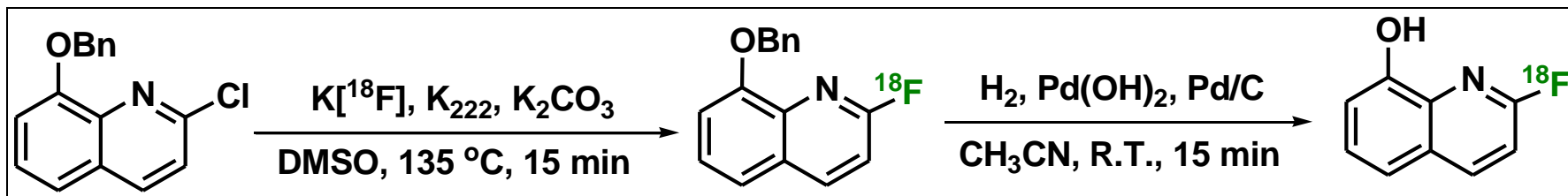
Class 1. Metals Hypothesis

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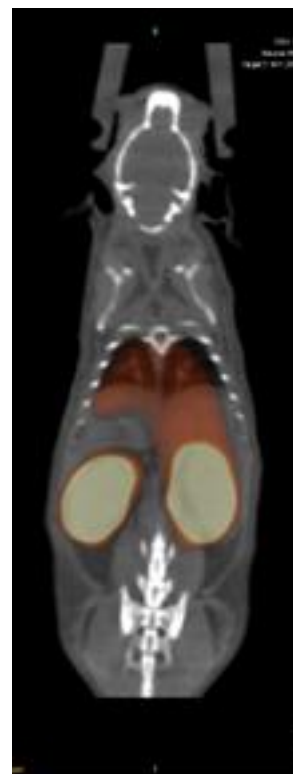
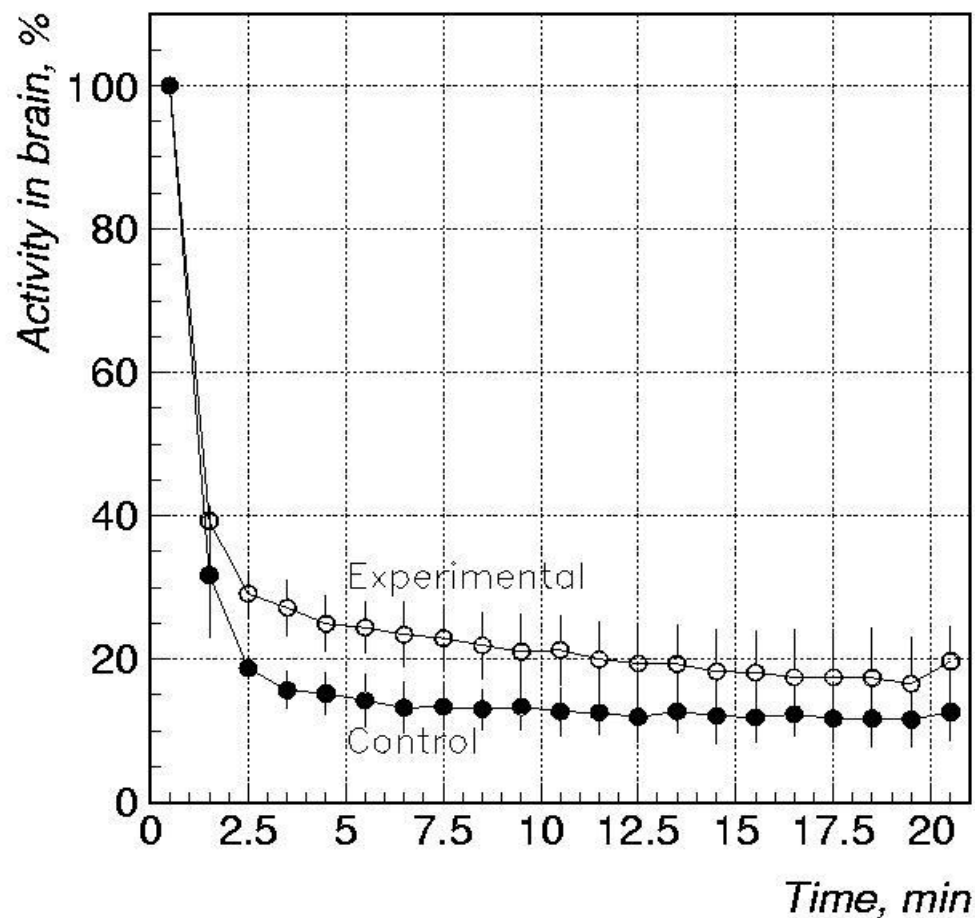
• Chelates Zn^{2+} and Cu^{2+} in plaques

- Opazo, C., et al. *Aging Cell*. **2006**, 5, 69.
- Kulkarni, P.; et al., *J. Nucl. Med.* **2006**, 47, 218P

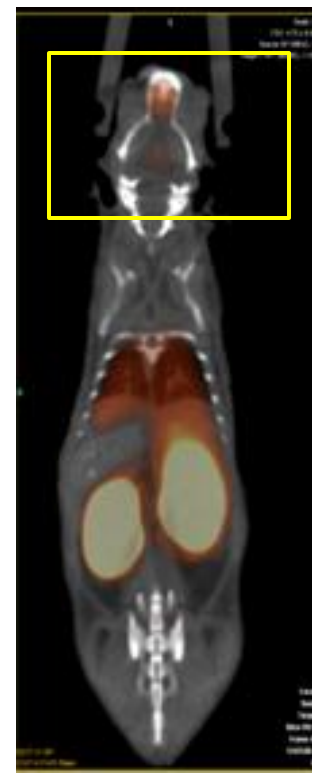


Control mouse vs. A β -aggregate injected into hippocampus and PET-CT images (control vs. AD trans)

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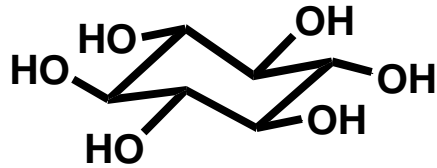


Control
(3.5 min pi)

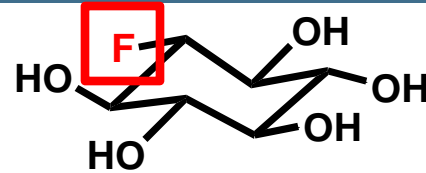


APP/Ps1

Class 2: *scyllo*-Inositol and CAA



scyllo-inositol



1-deoxy-1-fluoro-*scyllo*-inositol

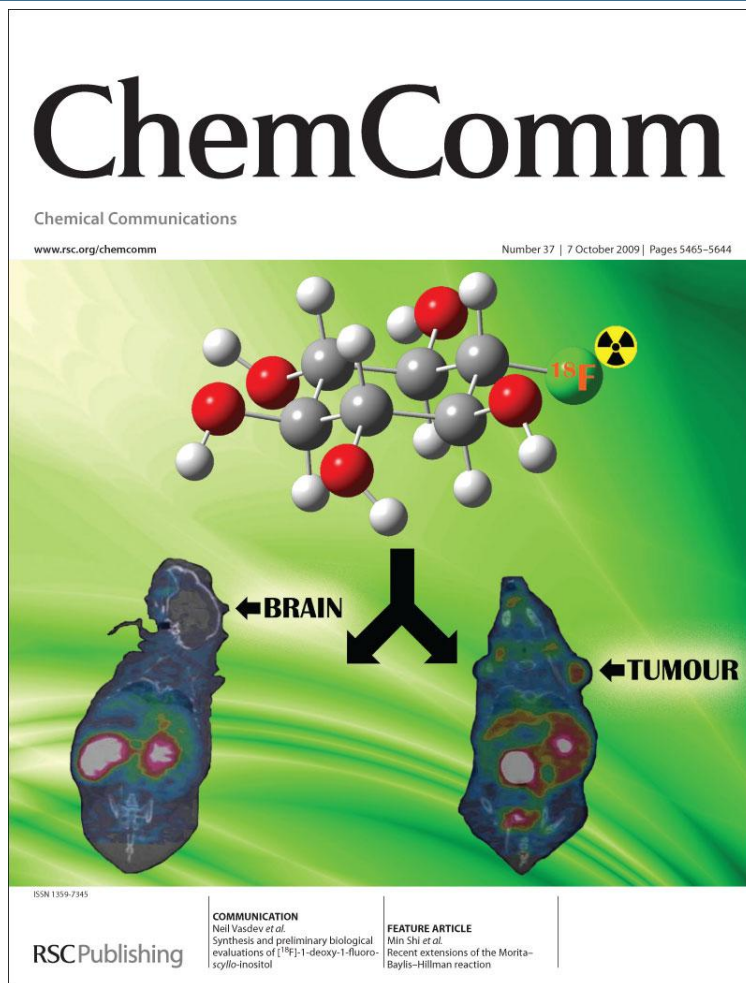
- Phase II clinical trials for AD
- Crosses BBB
- Interact with $A\beta_{42}$ peptide in vitro/in vivo

Why does it work?

- ▣ Targets cerebral amyloid angiopathy (CAA)
CAA: Amyloid deposits form in the walls of the blood vessels of the CNS
- **Our goal was to label with fluorine-18**
 - ▣ ***3 other groups also had the same goal***

[¹⁸F]scyllo-Inositol did not penetrate the brain!

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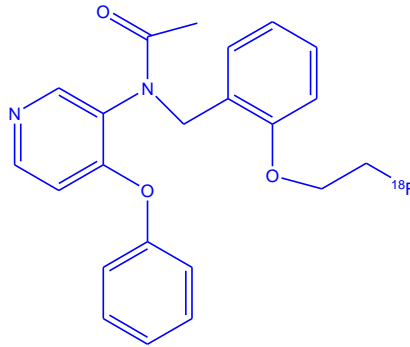
Our paper was featured on the cover page of *Chemical Communications*

Vasdev *et al.*, 2009

Class 3: Radiotracers for imaging neuroinflammation: [^{18}F]FEPPA

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- Targets the translocator protein (18 KDa) a.k.a. the peripheral benzodiazepine receptor
- [^{18}F]FEPPA developed by our laboratory

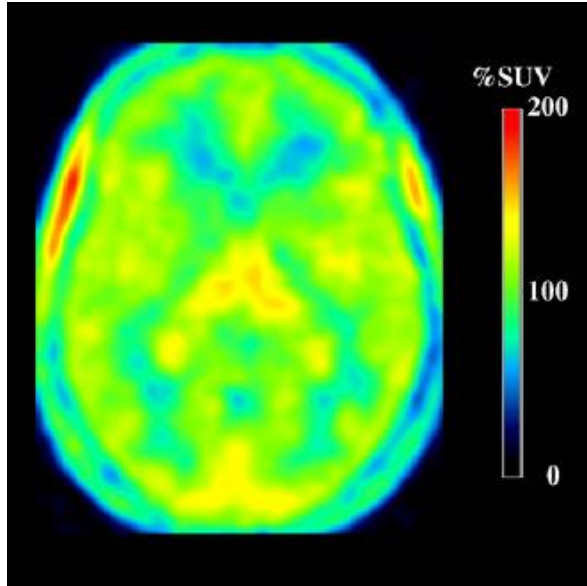


Wilson, A.A.; Garcia, A.; Parkes, J.; Stephenson, K.A.; Houle, S.; Vasdev, N. et al. *Nucl. Med. Biol.* **2008**, 35, 305.

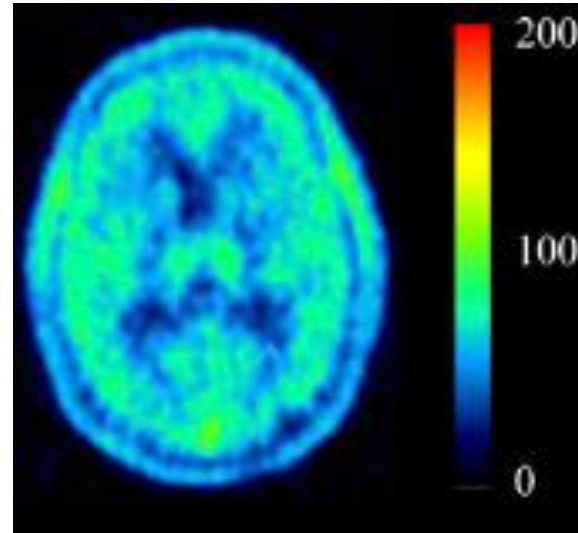
- Used in human subjects in Toronto
- Recent work will focus on [^{18}F]FEPPA for imaging neuroinflammation in patients suffering from AD

[¹⁸F]FEPPA – human imaging studies underway

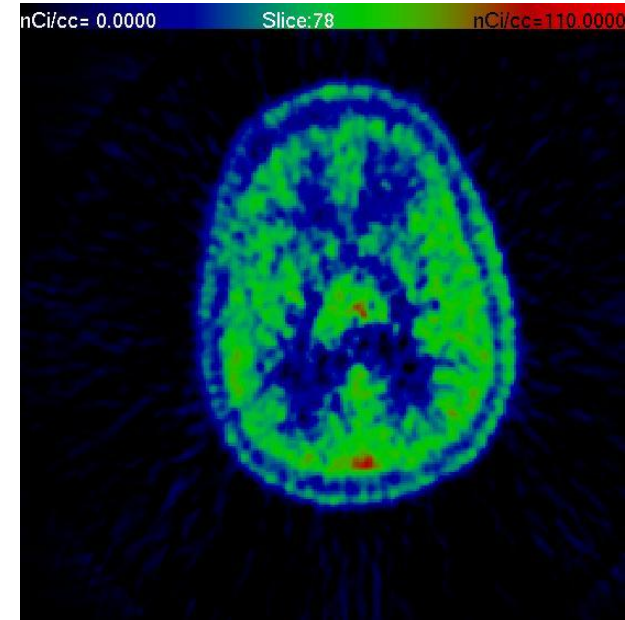
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[¹¹C]-PBR28
Fujita 2007



[¹⁸F]-PBR06
Fujimura 2009



[¹⁸F]-FEPPA
Mizrahi 2009
CAMH

- Summated PET images with activity present in cortices, striatum, pons, and maximum activity in the thalamus with all radiotracers

Class 4: Cholinergic Hypothesis

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- Dr. Bruce Pollock *et al.* conducted seminal studies on the role of the cholinergic system in dementia patients
- Loss of cholinergic function in the CNS contributes to the cognitive decline associated with AD
- Cholinergic neurons release Ach which can bind **muscarinic** ACh receptors (M1 – M5)

[¹⁸F]FP-TZTP is used to image M2 in human brain

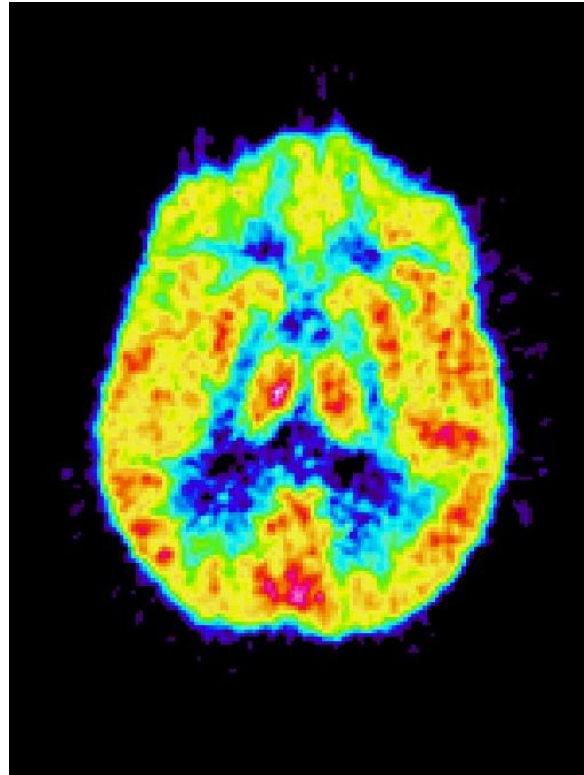
Kiesewetter, D. O., et al., 1995..J. Med. Chem. 38, 5.

- ▣ Our lab recently optimized the synthesis for human use

vanOosten, E. M.; Wilson, A. A.; Stephenson, K. A. Mamo, D. C., Pollock, B. G., Mulsant, B. H., Yudin, A. K., Houle, S., Vasdev, N., *Appl Radiat Isot*, **2009**, 67, 611.

[¹⁸F]FP-TZTP in human brain

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- To be presented by Dr. Tiffany Chow

CAMH and the TDRA

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2. Population pharmacokinetics of atypical antipsychotics and other medications in older patients
3. Alternatives to the use of atypicals for treatment of agitation & psychosis in dementia
4. PET imaging and novel radioligand development (CAMH PET):
 - [^{11}C]PHNO, [^{11}C]SB-13, [^{18}F]-FEPPA, [^{18}F]FP-TZTP, [^{18}F]hydroxyquinoline, [^{18}F]scyllo-inositol

Novel approaches for imaging Alzheimer's disease and co-occurring disorders are underway at CAMH and the University of Toronto

Acknowledgements

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- Dr. Alan A. Wilson, Dr. Sylvain Houle, and staff/students at the CAMH PET Centre
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- Dr. Bruce Pollock, Dr. Tiffany Chow, Dr. David Mamo and Dr. Benoit Mulsant

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