Imagerie moléculaire des maladies Neurodégénératives

Etat de l'art et perspectives

Denis Guilloteau
CHRU Bretonneau Tours
Service de Médecine Nucléaire
INSERM U 930 « Imagerie et cerveau »

1 ères Journées Francophones de Médecine Nucléaire
La Rochelle 28-31 mai 2015

Imagerie moléculaire des maladies Neurodégénératives

Pourquoi?

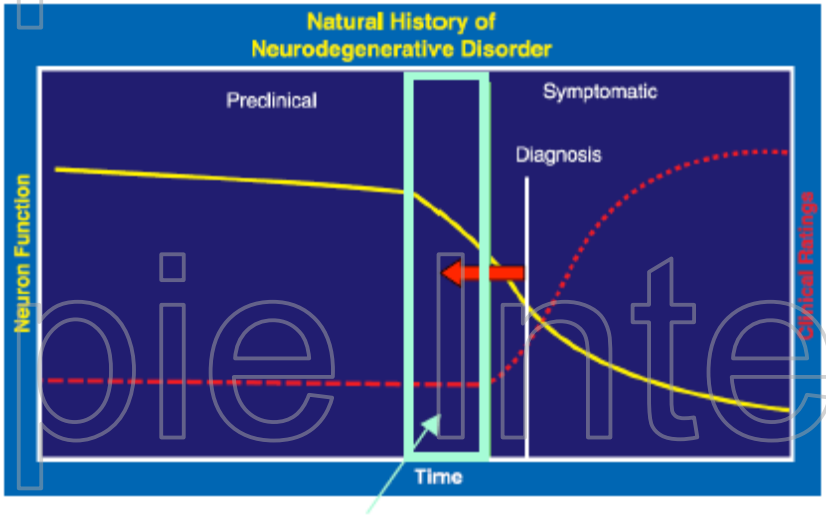
- Diagnostic précoce
- Diagnostic des populations à risque
- Appliquer le traitement aux bons patients

- Suivi efficacité des traitements

évolution cible (plaques..)

- Adapter la posologie
- Aide aux développements des traitements

Diagnostic Précoce des Maladies Neurodégénératives



Phase Asymptomatique

Modification des paramètres de la neurotransmission avant signes cliniques

Modified from DeKosky and Marek, Science 2003; 302:830

Notion biomarqueurs

« caractéristique qui est objectivement mesurée et évaluée comme un indicateur de processus
biologiques normaux ou pathologiques, ou de réponses pharmacologiques à une intervention thérapeutique»
(définition du *National Institute of Health*, US).

Notion Médecine Personnalisée / Stratifiée

terme consistant en un abus de langage à proscrire et à remplacer par le terme médecine « stratifiée » compte tenu du fait que la validation du couple marqueur/traitement est
fondée sur une approche populationnelle classique de validation de thérapeutique.

UNIVERSITÉ FRANÇOIS - RABELAIS

Instituts thématiques

Inserm

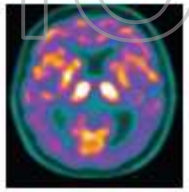
Institut national de la santé et de la recherche médicale

CHRU HÔPITAUX DE TOURS

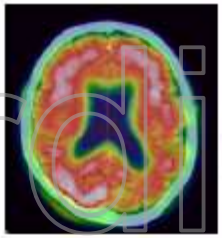
Où sommes nous en 2015?

UNIVERSITÉ FRANÇOIS - RABELAIS TOURS

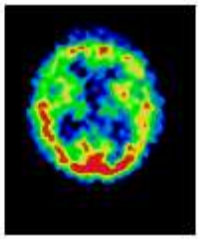
Pierre Payoux … (IRON)



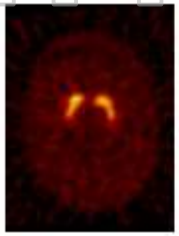
Glucose Metabolism
2000
FDG PET



?



Brain perfusion
1990 SPECT
HMPAO/ECD

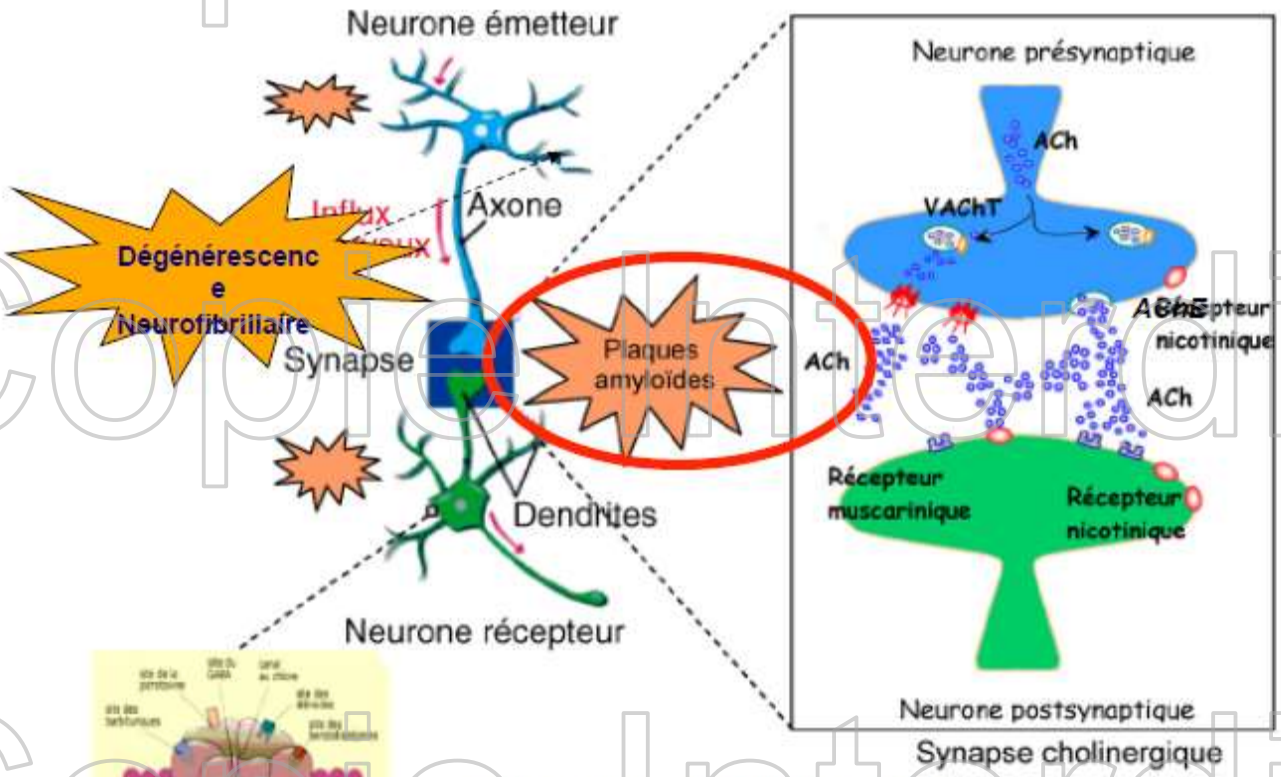


Dopamine transporter
2001
DaTSCAN (DLB & AD)

β amyloid plaques
2014 Florbetapir
Florbetaben
Flutemetamol
… /…

Cibles Moléculaires Maladie d'Alzheimer

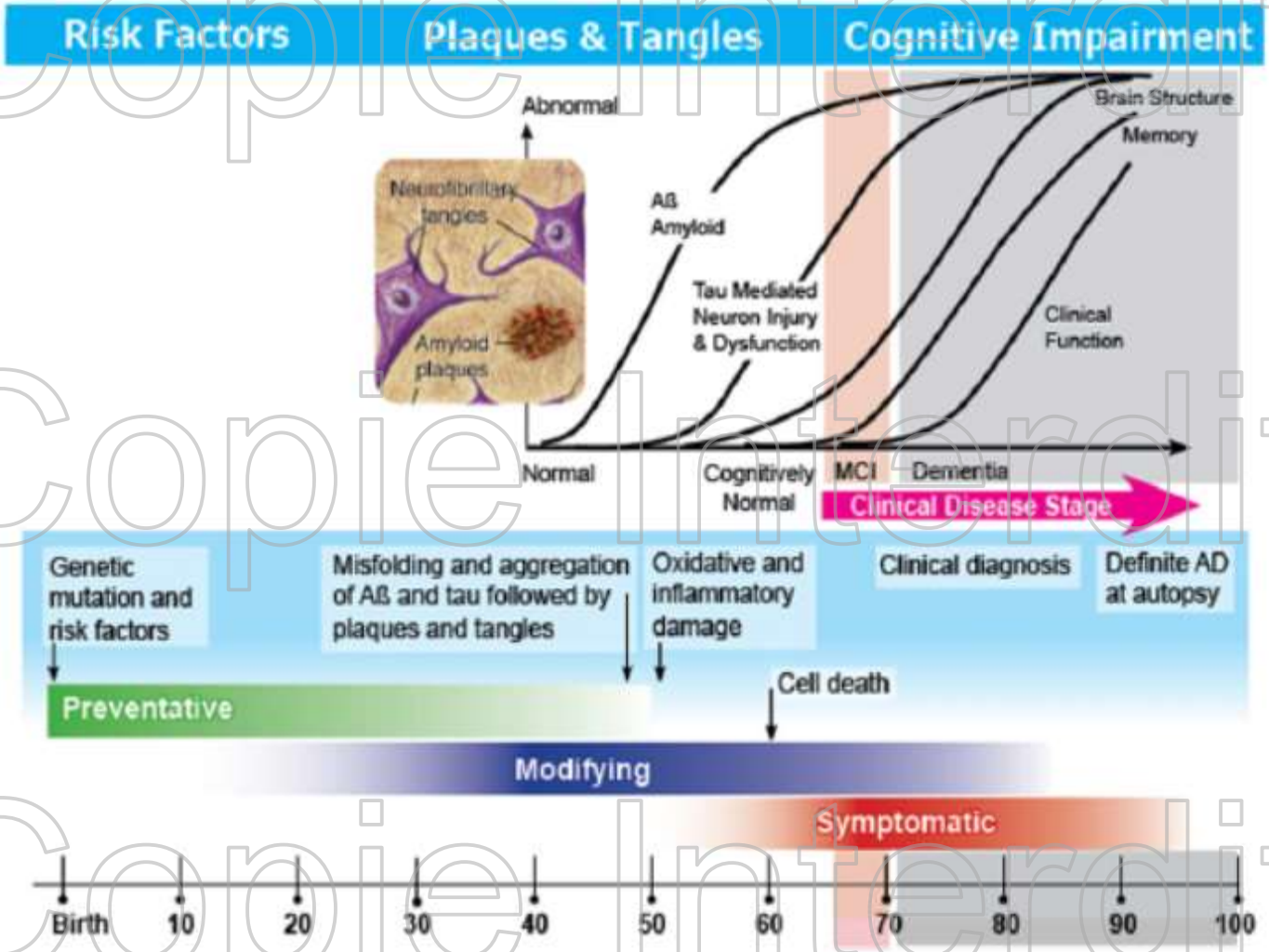
J. Vergote et al./Médecine Nucléaire xxx (2007) xxx–xxx



TSPO (Translocator Protien (18 kDa))

PBR (d'après http://lecerveau.mcgill.ca/flash/index_d.html)

CHRU HÔPITAUX DE TOURS



ure shows a hypothetical time line for the onset and progression of Alzheimer's disease (AD) neurodegeneration and cognitive impairmen

Revising the definition of Alzheimer's disease: a new lexicon

Bruno Dubois, et al

2010

Lancet Neurol. 2010 Nov;9(11):1118-27

- *1984 NINCDS–ADRDA criteria stipulated that diagnosis of AD during life could only be "probable", whereas a "definite" diagnosis required post-mortem histopathological confirmation (Neurology 1984; **34: 939–44.**)*
- *Over the past two decades, it has become increasingly possible to identify in-vivo evidence of the specific neuropathology of AD by use of validated and disease specific biomarkers*

Biomarqueurs de la Maladie d'Alzheimer

2010

	Pathophysiological markers	Topographical markers
Cerebrospinal fluid		
Amyloid β_{42}	Yes	No
Total tau, phospho-tau	Yes	No
PET		
Amyloid tracer uptake	Yes	No
Fluorodeoxyglucose	No	Yes
Structural MRI		
Medial temporal atrophy	No	Yes

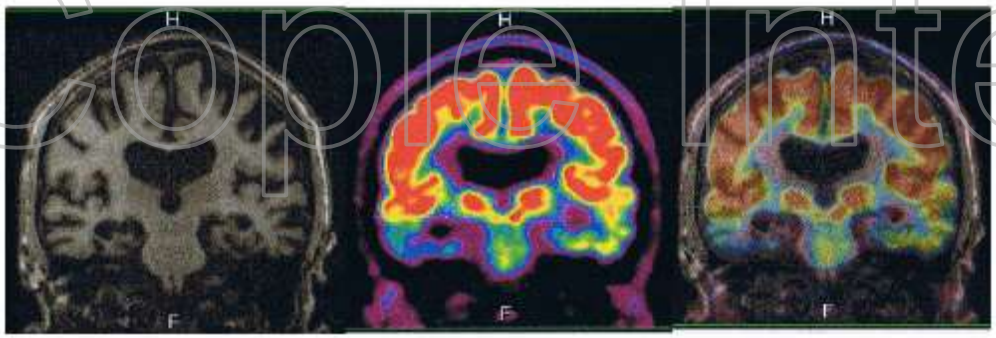
AD=Alzheimer's disease.

Table 1: Categorisation of the current, most-validated AD biomarkers

B Dubois et al. Lancet Neurol. 2010 Nov;9(11):1118-27

Maladie d'Alzheimer

IRM ^{18}F-FDG



sensibilité = 93%

spécificité = 63%

précision = 82%

Hoffman J et al, JNM 2000

Biomarqueurs de la Maladie d'Alzheimer

	Pathophysiological markers	Topographical markers
Cerebrospinal fluid		
Amyloid β_{42}	Yes	No
Total tau, phospho-tau	Yes	No
PET		
Amyloid tracer uptake	Yes	No
Fluorodeoxyglucose	No	Yes
Structural MRI		
Medial temporal atrophy	No	Yes

AD=Alzheimer's disease.

Table 1: Categorisation of the current, most-validated AD biomarkers

B Dubois et al. Lancet Neurol. 2010 Nov;9(11):1118-27

Maladie d'Alzheimer

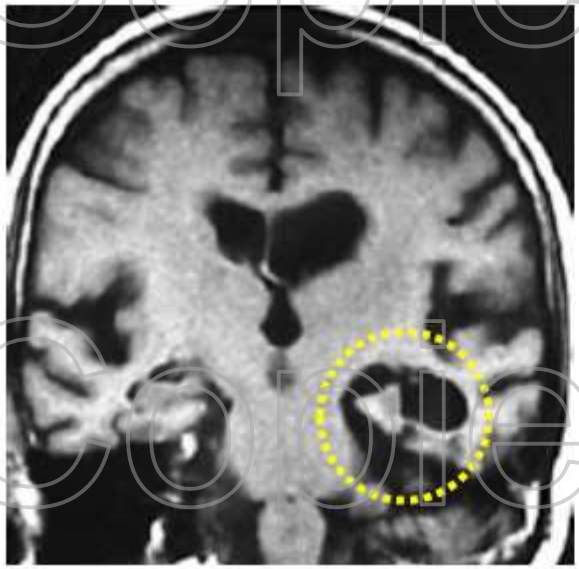
- Atrophie parenchymateuse et élargissement des ventricules (en relation avec densité neuronale)
- Réduction du volume hippocampique:

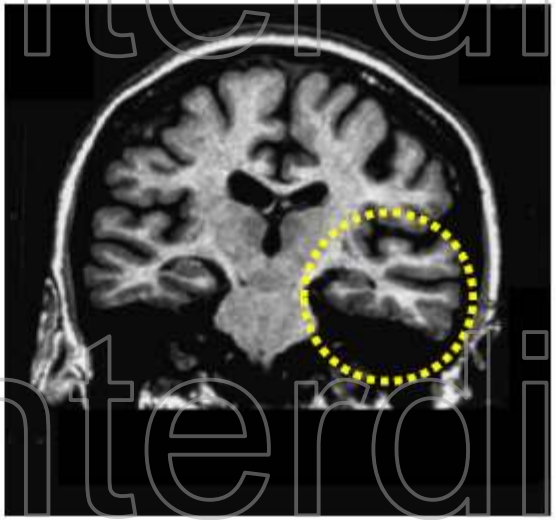
30-40% : formes modérées

20-30% : formes légères

10-12% : stade très précoce (MMS 27)

Jack Neurology 1992, 1999, Hampel J Neurol Sci 2002, Killiany Arch Neurol 1993, Cuenod Arch Neurol 1993, Lehericy AJNR 1994





Biomarqueurs de la Maladie d'Alzheimer

	Pathophysiological markers	Topographical markers
Cerebrospinal fluid		
Amyloid β_{42}	Yes	No
Total tau, phospho-tau	Yes	No
PET		
Amyloid tracer uptake	Yes	No
Fluorodeoxyglucose	No	Yes
Structural MRI		
Medial temporal atrophy	No	Yes

AD=Alzheimer's disease.

Table 1: Categorisation of the current, most-validated AD biomarkers

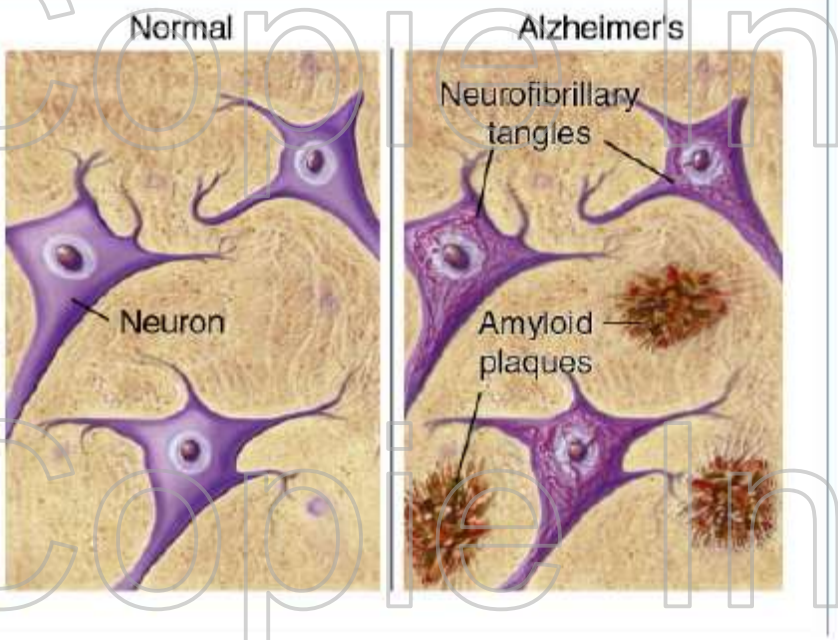
B Dubois et al. Lancet Neurol. 2010 Nov;9(11):1118-27

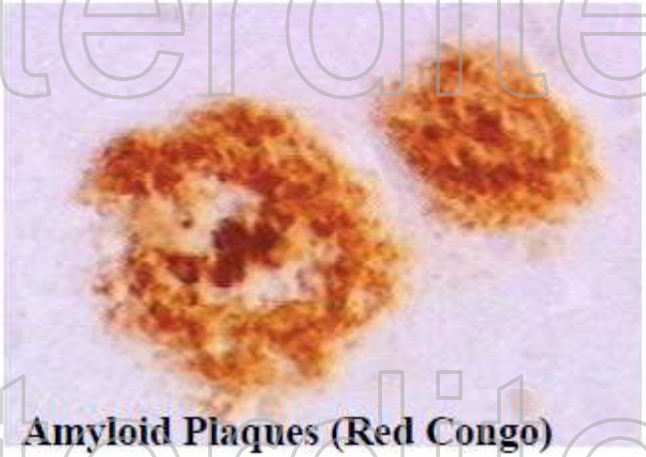
2 processus dégénératifs

Plaques et Tangles

Dégérecence Neurofibrillaire(DNF)

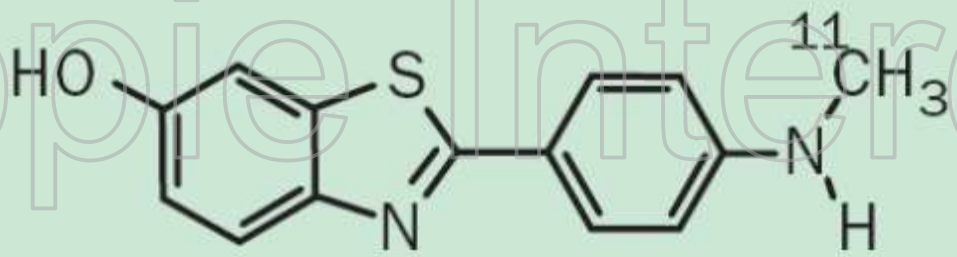
Plaques Amyloïdes





C-11 Radiopharmaceutical

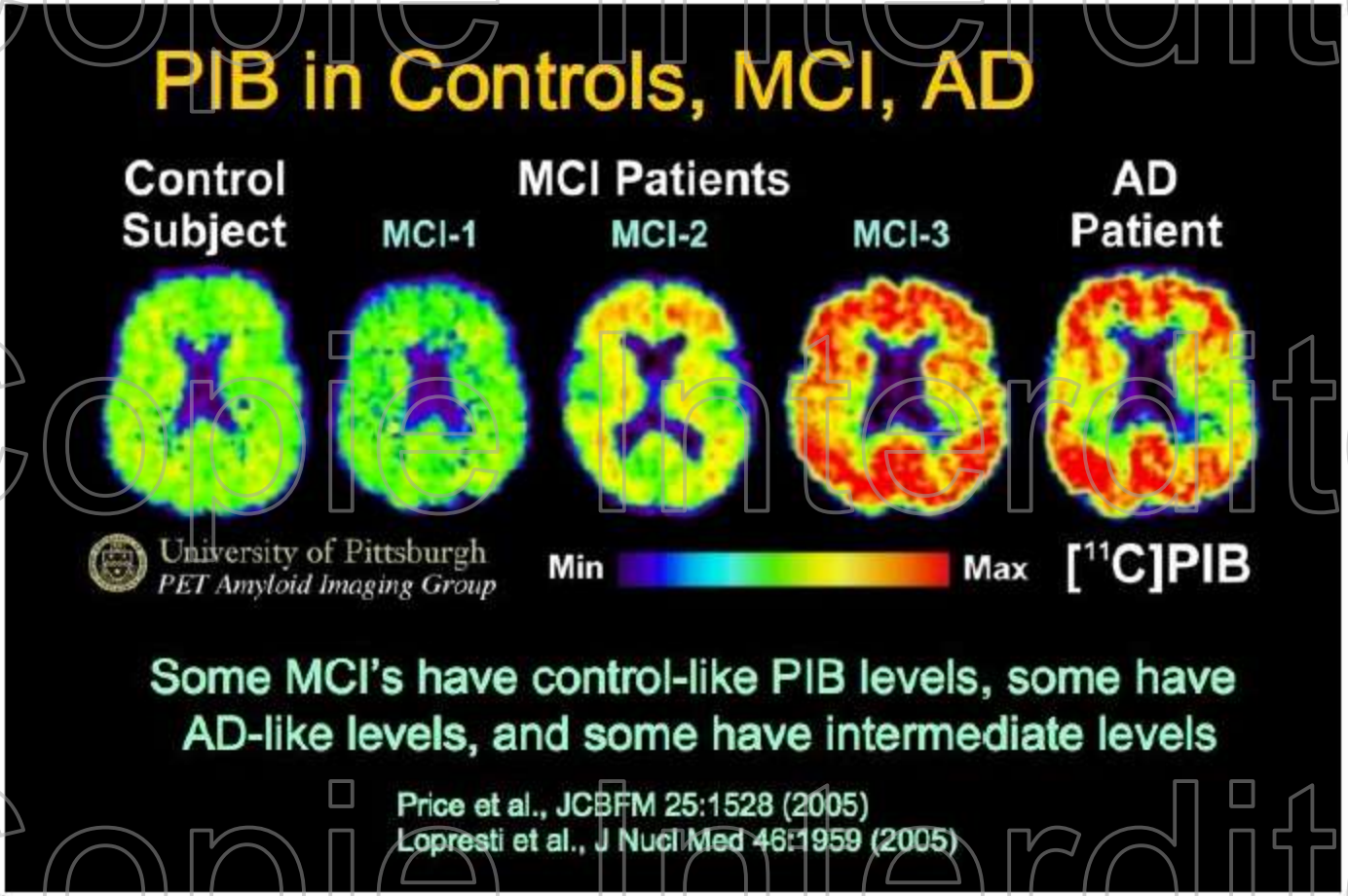
^{11}C-PIB



N-methyl-^{11}C-PIB

Benzothiazoles

Chester Mathis, Julie Price, Pittsburgh Pennsylvania



Courtesy: Julie Price

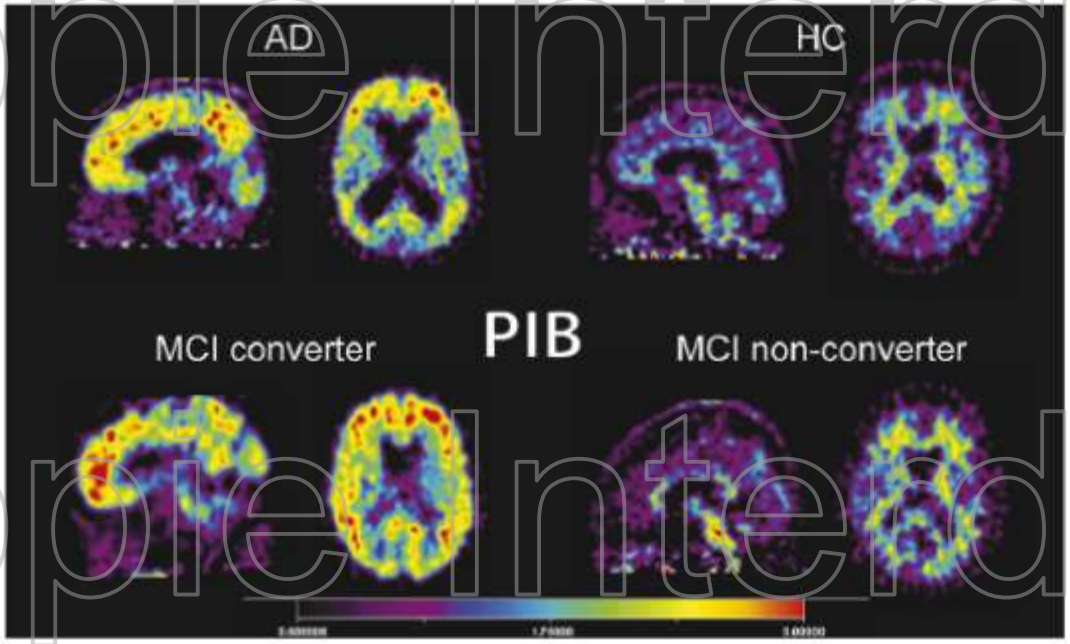


Fig. 2. PIB retention in one MCI converter, one MCI non-converter, one AD patient, and one healthy control. The PET scans show PIB retention at a sagittal and longitudinal section at the level of the basal ganglia. Red indicates high, yellow medium and blue low PIB retention. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

ELSEVIER

Neurobiology of Aging 29 (2008) 1456–1465

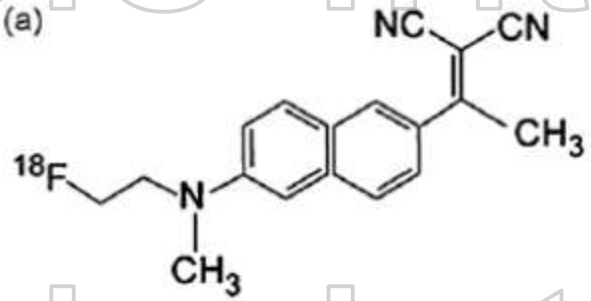
NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

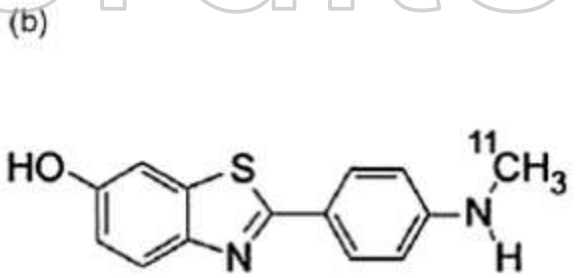
PET imaging of amyloid deposition in patients with mild cognitive impairment

Anton Forsberg [a], Henry Engler [c], Ove Almkvist [a,b,g], Gunnar Blomquist [d], Göran Hagman [b], Anders Wall [e], Anna Ringheim [e], Bengt Långström [e,f], Agneta Nordberg [a,b,*]

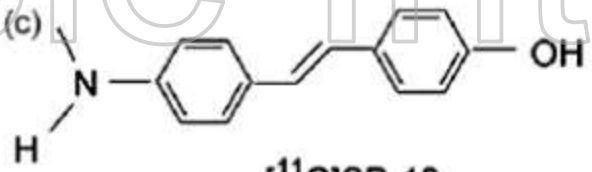
Amyloid Plaques tracers



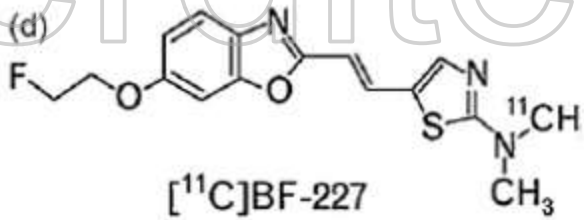
[18F]FDDNP



[*N*-methyl-^{11}C]PIB

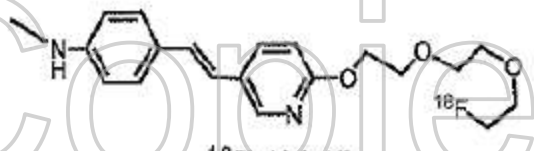


[11C]SB-13



[11C]BF-227

Stilbene



18F-AV-45

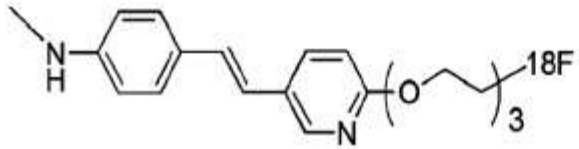
[18F]-BAY94-9172

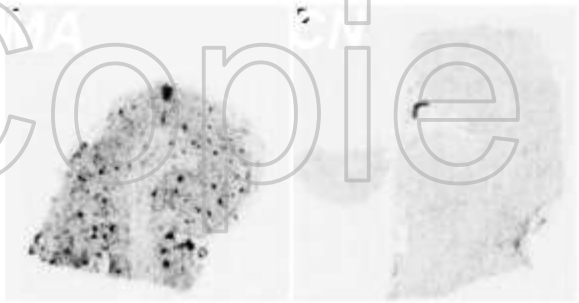
Imagerie des plaques amyloïdes

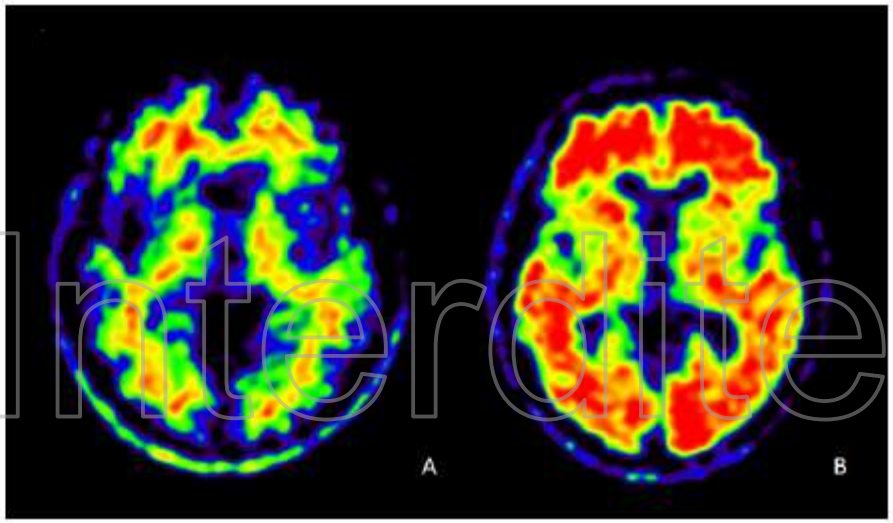
^{18}F-AV-45

(Florbetapir)

Amyvid





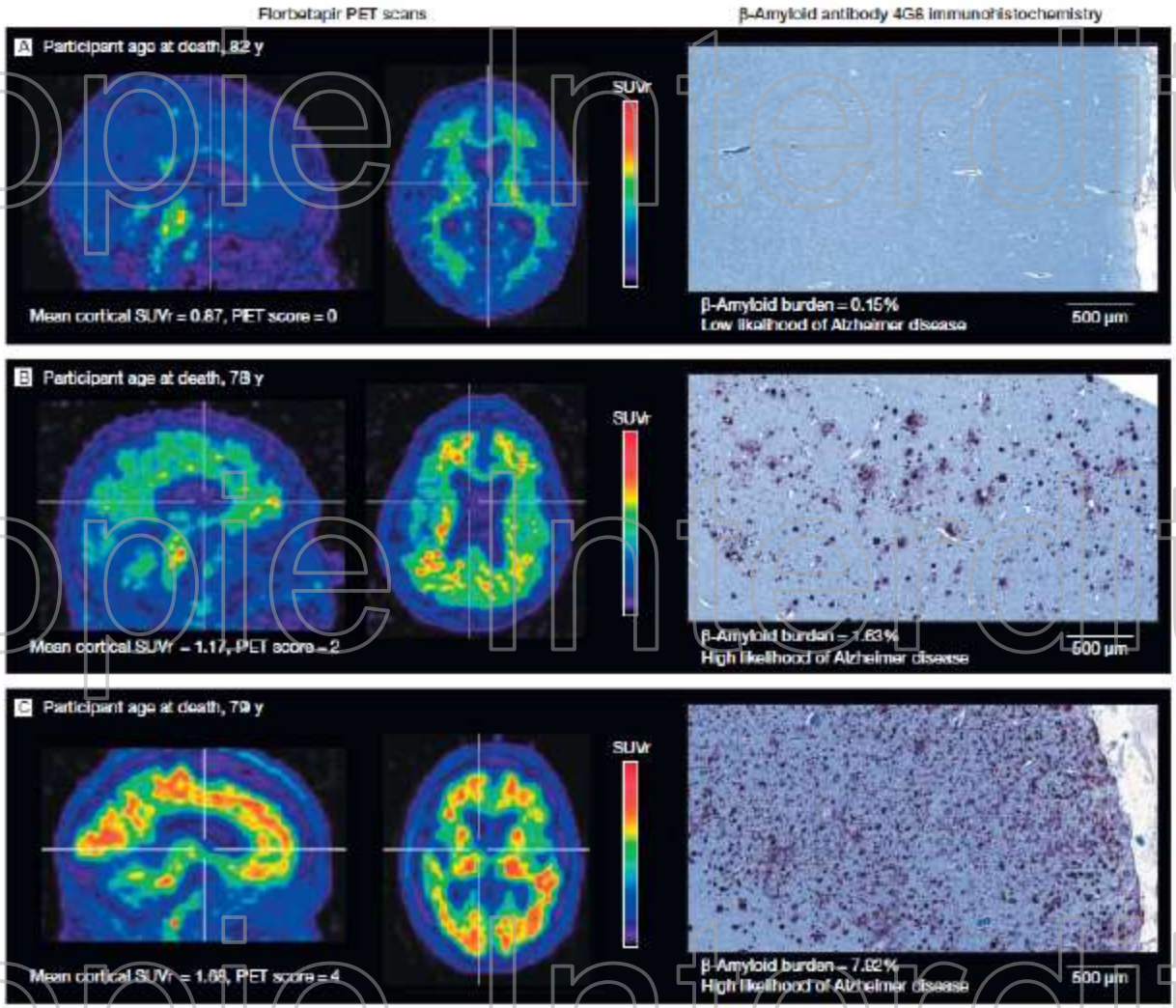


Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-011-2021-8

ORIGINAL ARTICLE

Using PET with ^{18}F-AV-45 (florbetapir) to quantify brain amyloid load in a clinical environment

V. Camus · F. Payoux · L. Barré · B. Desgranges · T. Voisin · C. Tauber · R. La Joie · M. Tafani · C. Hommet · G. Chételat · K. Mondon · V. de La Sayette · J. P. Cottier · E. Beaufils · M. J. Ribeiro · V. Gissot · L. Vierron · J. Vercouillie · B. Vellas · F. Eustache · D. Guilloteau

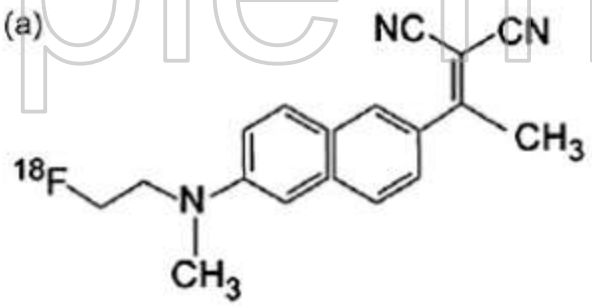


Sagittal and axial views of positron emission tomographic (PET) scans of representative patients. The vertical bars indicate the range of semiautomated quantitative analysis of the ratio of cortical to cerebellar signal (SUVr) scores. The maximum color (red) corresponds to an SUVr of approximately 2.2. The 4G8 immunohistochemistry shows precuneus gray matter with aggregated β-amyloid (red) using a 3-amino-9-ethylcarbazol chromogen stain and counterstained with acid blue 129 (original magnification ×5).

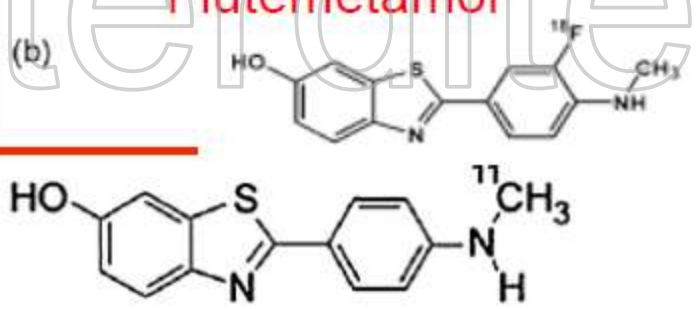
Traceurs des Plaques Amyloïdes

Benzothiazoles

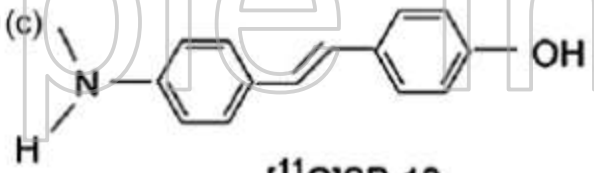
Flutemetamol



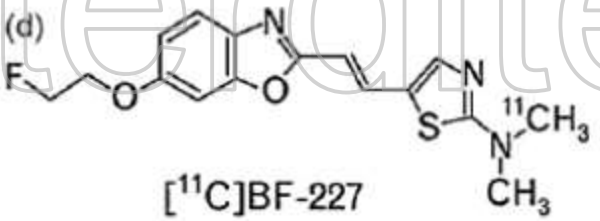
[18F]FDDNP



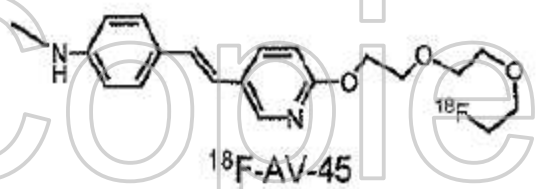
[*N*-methyl-^{11}C]PIB



[^{11}C]SB-13

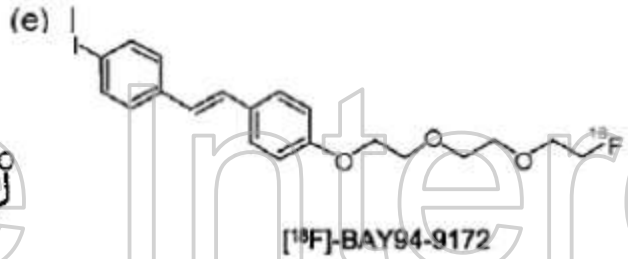


[^{11}C]BF-227



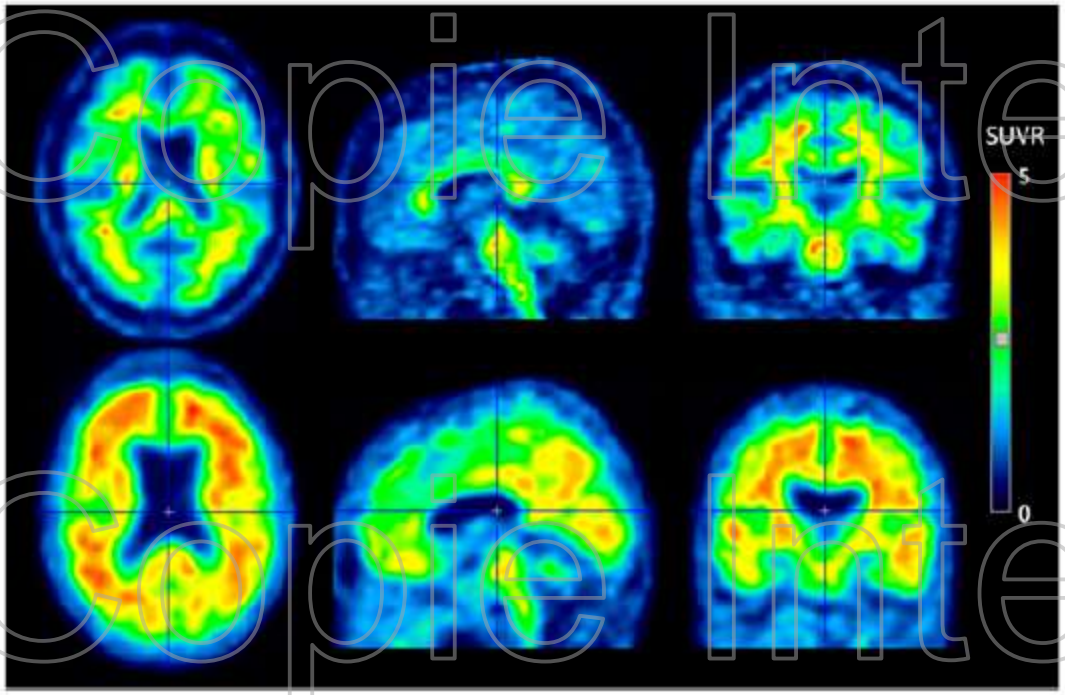
^{18}F-AV-45

Florbetapir



[^{18}F]-BAY94-9172

Florbetaben



GE-067

Flutemetamol

Vizamyl

FIGURE 2. Brain uptake distribution of ^{18}F-GE067 in healthy 64-y-old male subject (top), compared with 68-y-old male AD patient (bottom). Transverse, sagittal, and coronal sections indicate absence of specific gray matter uptake of ^{18}F-GE067 and aspecific uptake in white matter, pons, and thalamus. Images represent standardized uptake value [illegible] 85 and 105 min a[illegible]al study.

Whole-Body Biodistribution and Radiation Dosimetry of ^{18}F-GE067: A Radioligand for In Vivo Brain Amyloid Imaging

J Nucl Med 2009; 50:818–822

Michel Koole[1], Dewi M. Lewis[2], Christopher Buckley[2], Natalie Nelissen[3], Mathieu Vandenbulcke[4], David J. Brooks[2,5], Rik Vandenberghe[3,6], and Koen Van Laere[1]

CHRU HÔPITAUX DE TOURS

3 radiopharmaceutiques autorisés

AV45, Florbetapir, **Amyvid®**
Eli Lilly & Co. and Avid Radiopharmaceuticals Inc

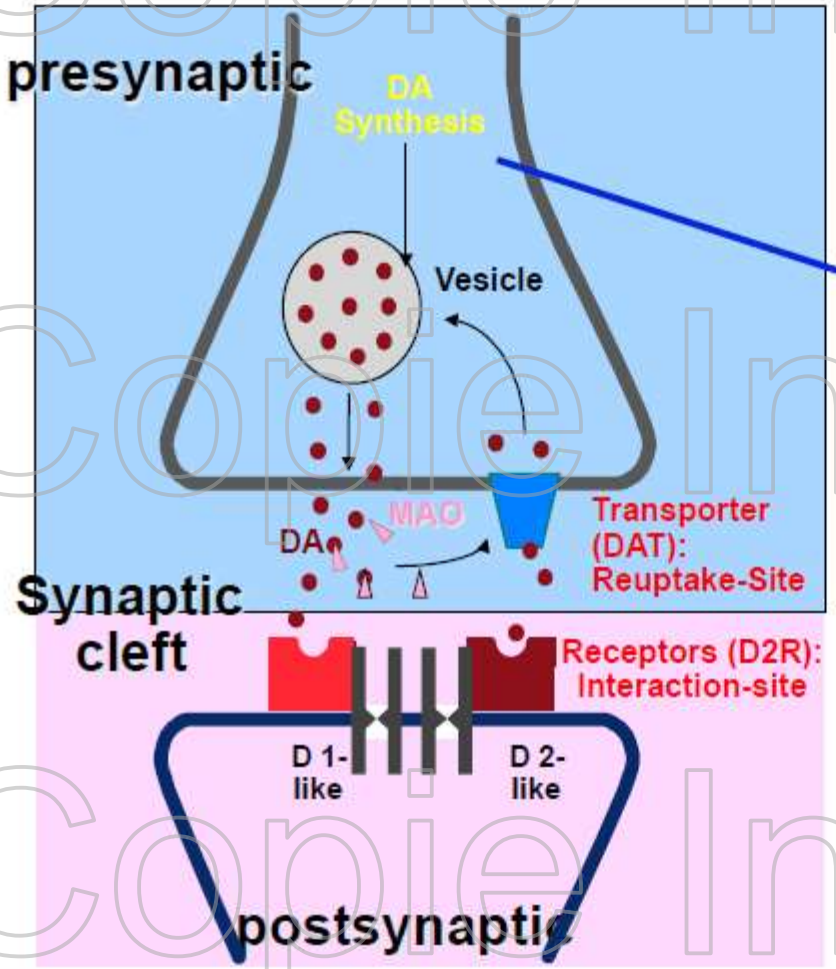
Flutemetamol **Vizamyl®,**
Healthcare, Medi-Physics IncGE

Florbetaben **Neuraceq®**
Piramal

Cibles Moléculaires
Maladie de Parkinson

Neurotransmission
Dopaminergique

Parkinson disease



Dopaminergic System Main targets:

- ***F-DOPA***
- ***DAT***
- ***D2 R***

Adapted from K. Tatsch, U. Munich, A Catafau, Barcelona

Maladie de Parkinson et Neurotransmission

Quels outils pour les D2R?

Différentes familles

Benzamide
Butyrophenone
Ergolene

Dopamine D2 receptors

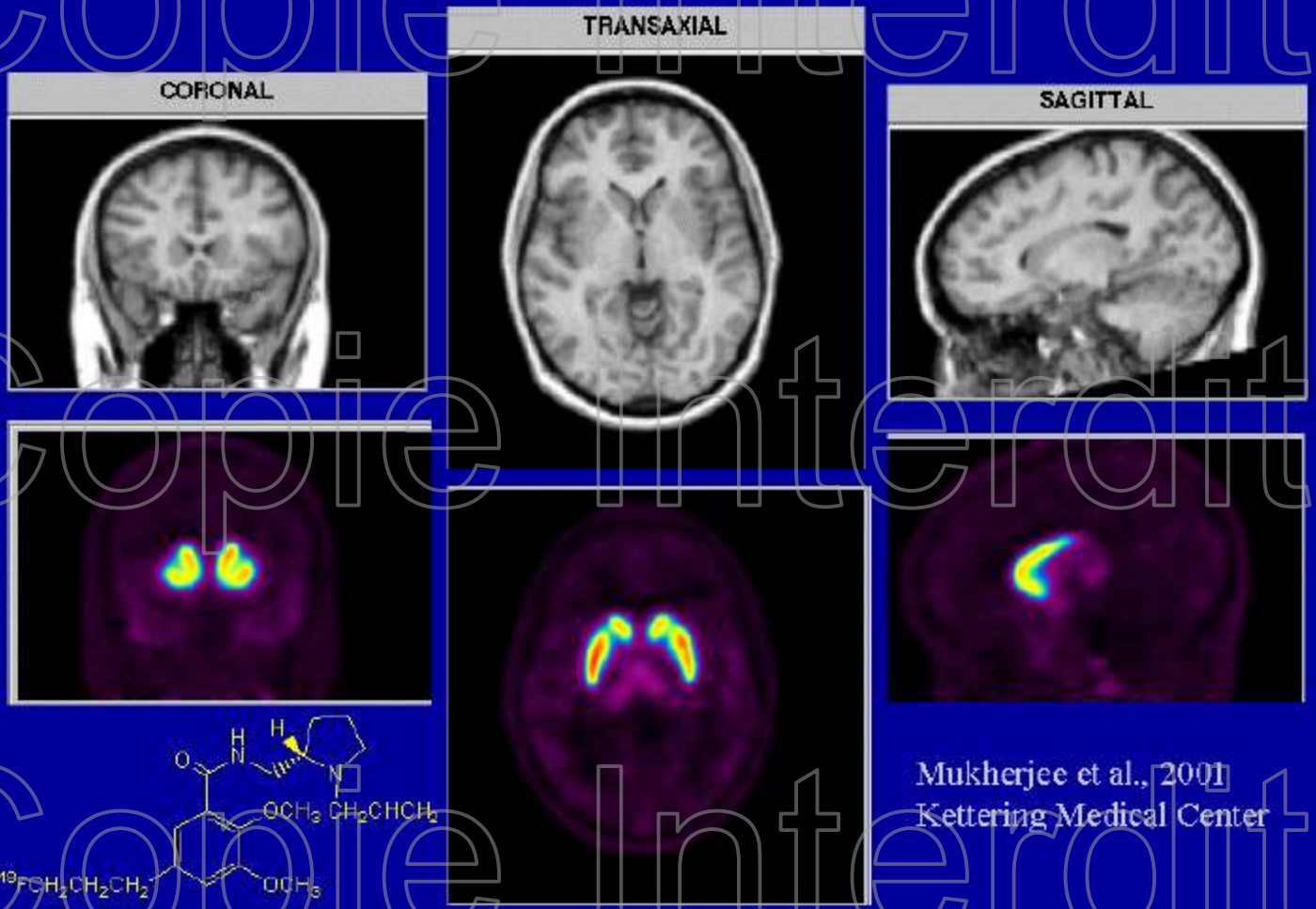
PET *[18F]fallypride*

SPECT

[123I]IBZM

Preparations magistrales

^{18}F-Fallypride in a Normal Volunteer

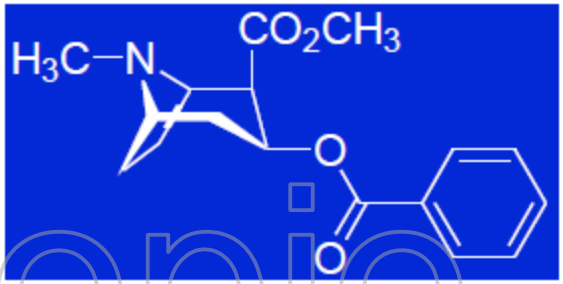


Mukherjee et al., 2001
Kettering Medical Center

Maladie de Parkinson
et
Neurotransmission
Quels outils pour
le DAT

derivés Cocaïne

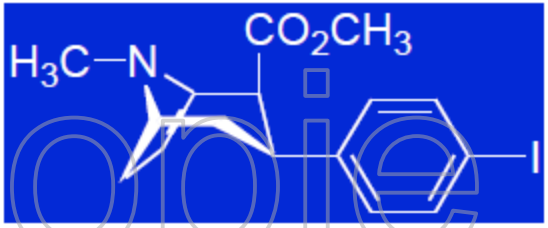
TROPANE : COCAINE et ANALOGUES



Cocaine

Faible spécificté:
Affinité DAT, SERT, NET

Rapide in vivo Métabolisme



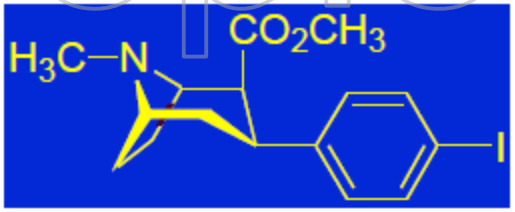
β-CIT

Faible Sélectivité:
Affinité : Ki_{DAT}= 27nM, Ki_{SERT}= 3 n

Stable In vivo

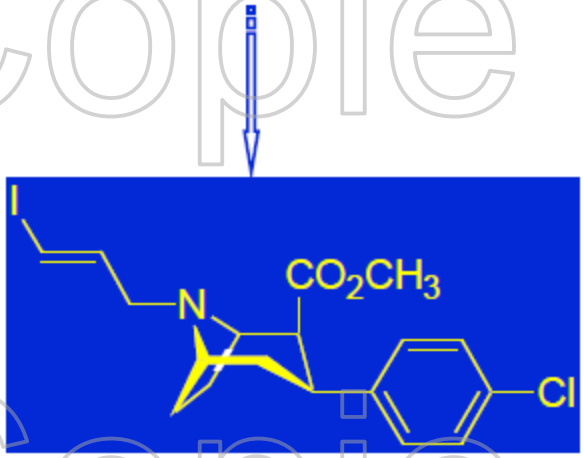
Boja *et al*. 1991; Innis *et al*.1993

TROPANE : COCAINE et ANALOGUES



β-CIT

Boja *et al.* 1991; Innis *et al.*1993



IPT

Goodman *et al.* 1994; Kung *et al.* 1995

- High affinity for the DAT
- Usable in vivo in human

Inconvenient:

- High affinity for the 5-HTT
- In vivo kinetics

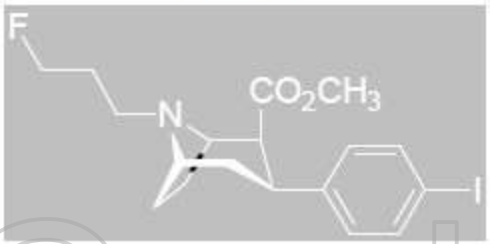
Improved selectivity for the DAT

COCAINE DERIVATIVES

Improved selectivity for the DAT

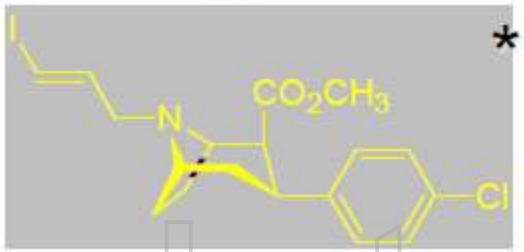
β-CIT

FP-β-CIT



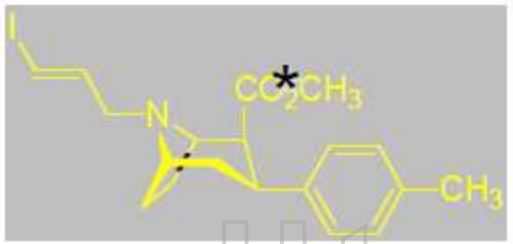
Neumeyer et al 1994
« Datscan »

IPT



Goodman *et al.* 1994; Kung *et al.* 1995

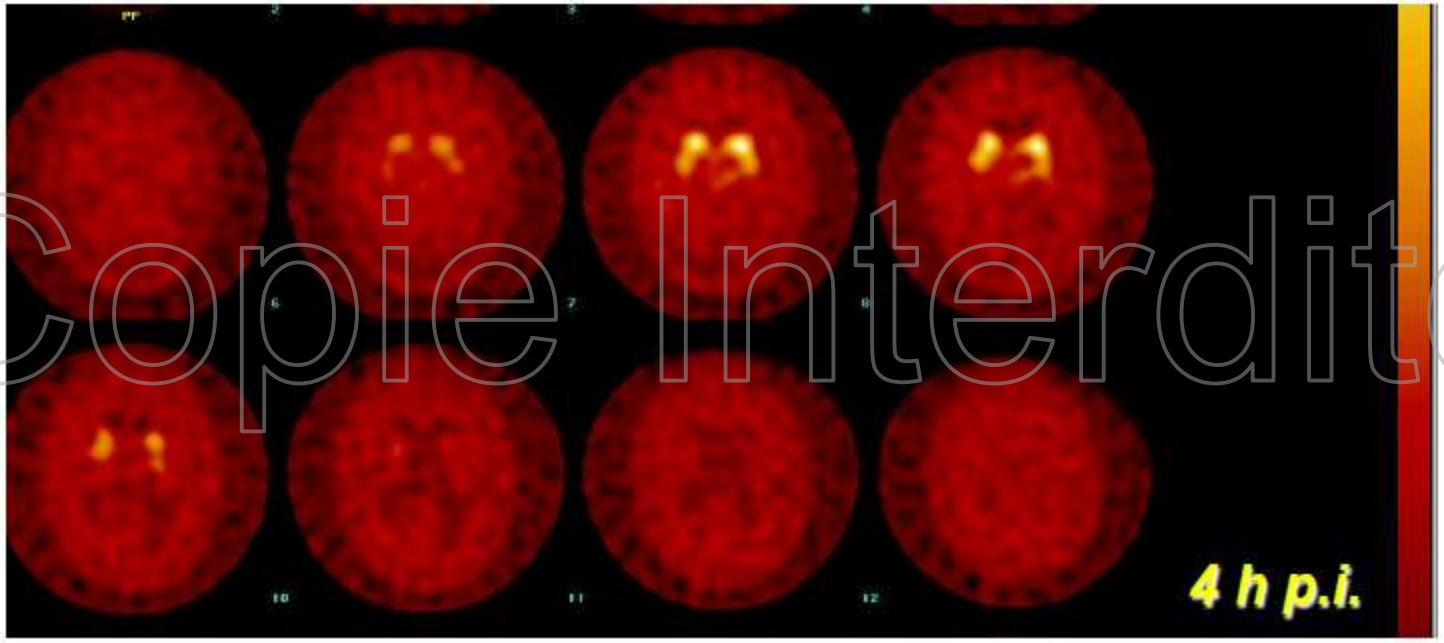
PE2I



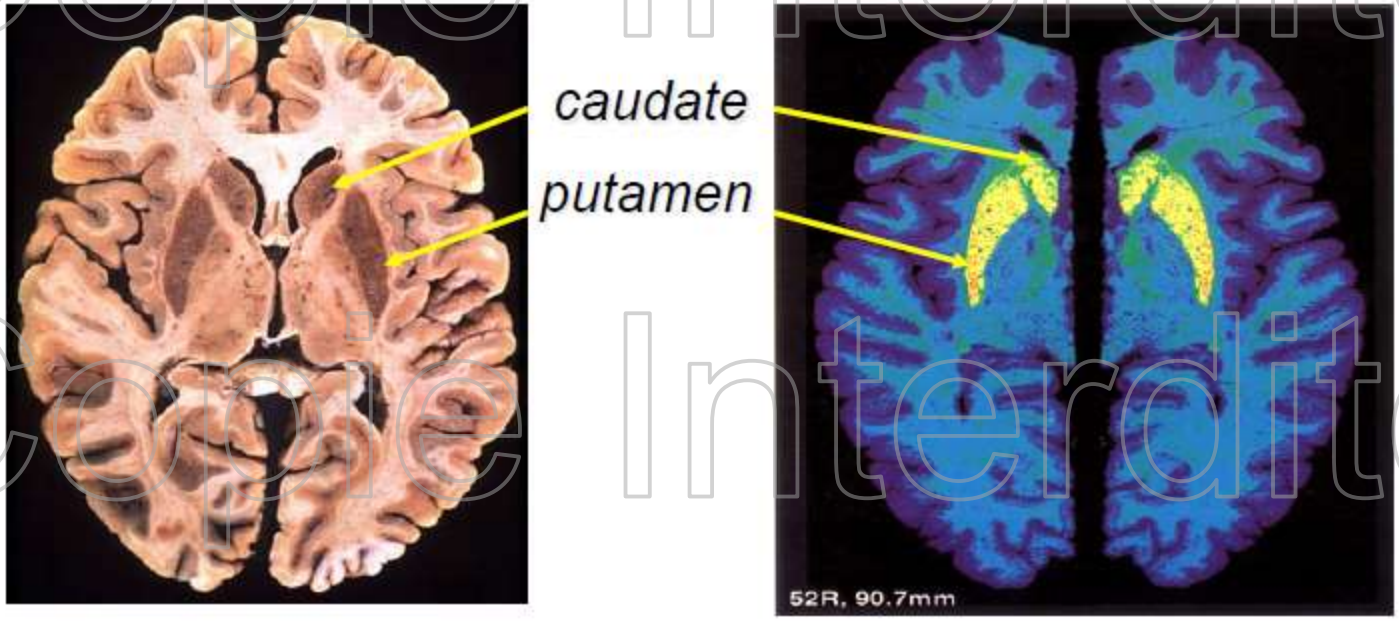
Emond et al,J Med chem 1997
Guilloteau et al, Nucl Med Biol 1998

Very high selectivity

^{123}I-FP-CIT (Datscan)



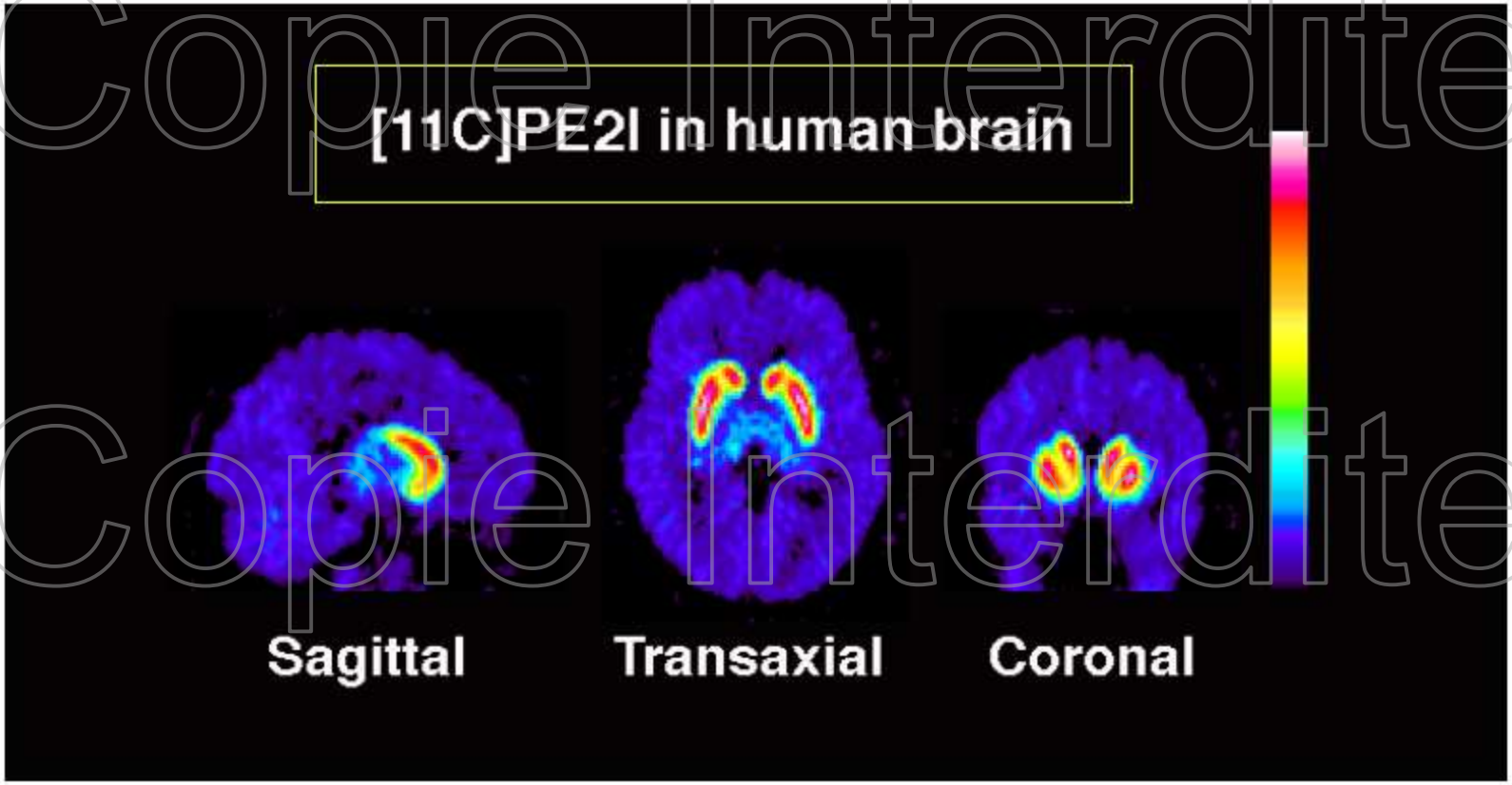
125I-PE2I



Histologie

Autoradiographie Post Mortem (Homme)

U 619 Tours et KI Stockholm



Human brain scintigraphy:

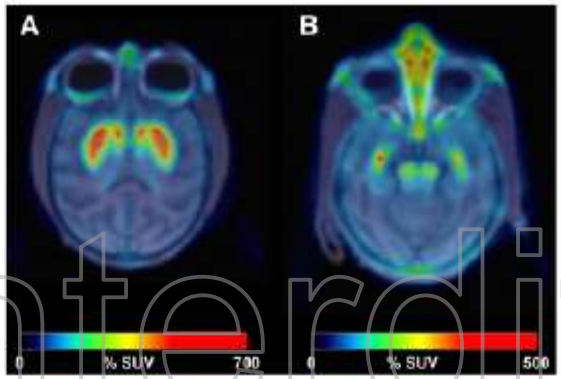
10 to 60 min after of 293 MBq [11C]-PE2I

Karolinska Institut and CHU Tours *Eur J Nucl Med Mol Imaging. 2003*

Traceur 18F pour le DAT

LBT-999

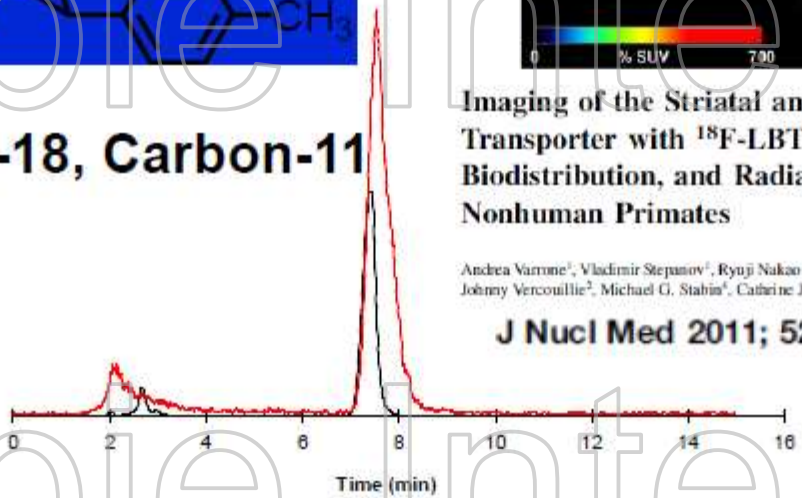
Fluorine-18, Carbon-11



Imaging of the Striatal and Extrastriatal Dopamine Transporter with ^{18}F-LBT-999: Quantification, Biodistribution, and Radiation Dosimetry in Nonhuman Primates

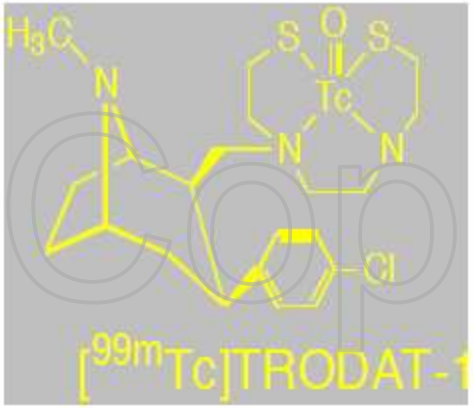
Andrea Varrone[1], Vladimir Stepanov[1], Ryuji Nakao[1], Miklós Tóth[1], Balázs Gulyás[1], Patrik Emond[2], Jean Bernard Deloye[3], Johnny Vercouillie[2], Michael G. Stabin[4], Catherine Jonsson[5], Denis Guilloteau[*2], and Christer Halldin[*1]

J Nucl Med 2011; 52:1313–1321



U 930, Cyclopharma

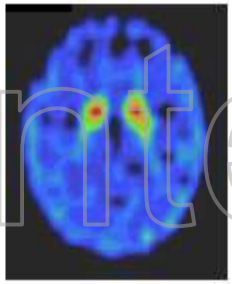
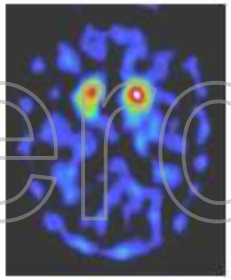
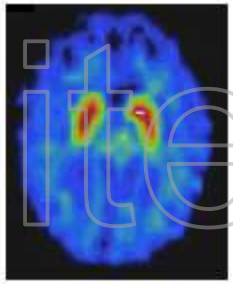
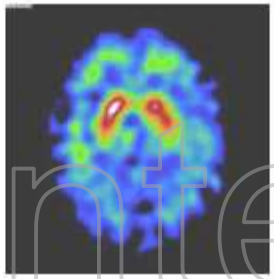
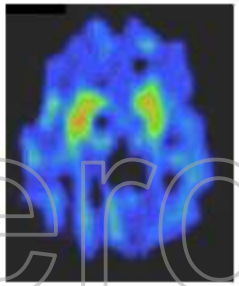
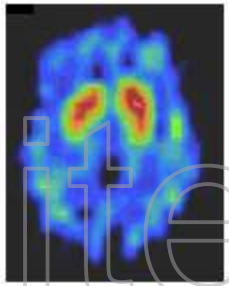
SPECT Imaging of Tc-99m TRODAT-1 in Normal and Parkinson's Subjects



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

Hank Kung et al

SPECT du Système Dopaminergique dans la Maladie de Parkinson

	PD	PSP MSA	ET
Pre-synaptic: DAT ^{123}I-FP-CIT			
Post-synaptic: D_2 R ^{123}I-IBZM			

Imagerie moléculaire des maladies Neurodégénératives

Perspectives

1 ères Journées Francophones de Médecine Nucléaire
La Rochelle 28-31 mai 2015

Traceurs des Plaques

2 eme Génération?

1 ères Journées Francophones de Médecine Nucléaire
La Rochelle 28-31 mai 2015

Journal of Neurochemistry

JOURNAL OF NEUROCHEMISTRY | 2009 | 108 | 1173–1185 doi: 10.1111/j.1471-4159.2008.05861.x

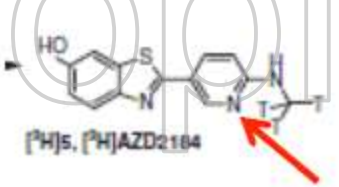
CHRU HÔPITAUX DE TOURS

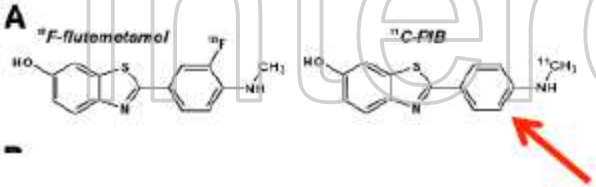
AZD2184: a radioligand for sensitive detection of β-amyloid deposits

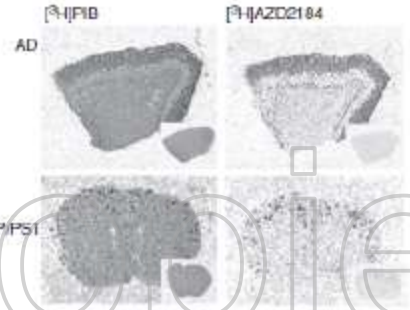
Allan E. Johnson,* Fredrik Jeppsson,† Johan Sandell,‡ David Wensbo,‡ Jan A. M. Neelissen,§ Anders Juréus,* Peter Ström,‡ Henrietta Norman,† Lars Farde¶·** and Samuel P. S. Svensson†

*Disease Biology, †Molecular Pharmacology, ‡Medicinal Chemistry, §DMPK and ¶Discovery Medicine, AstraZeneca R&D, Södertälje, Sweden

**Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden



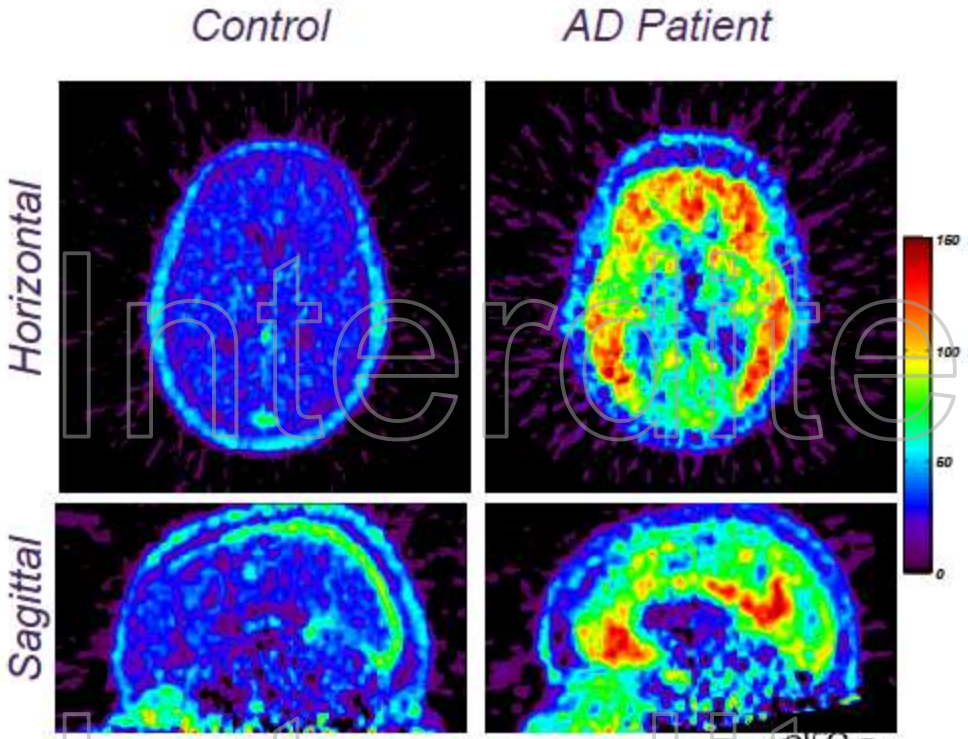




Very low white matter binding!

[11C]AZD2184 – in human subjects

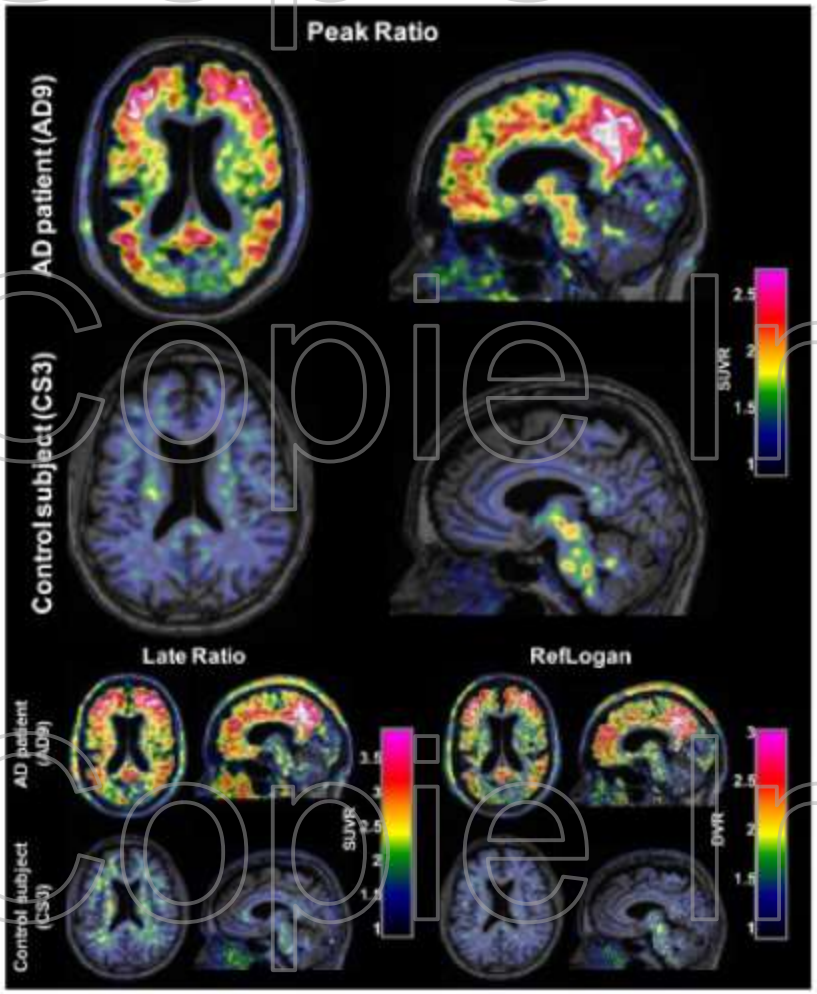
- Uniform low uptake in control subjects
- In AD patients high binding in brain regions with expected deposition of amyloid plaques
- Low binding in regions not associated with amyloid plaques



Christer Halldin,
Karloinska Institutet

Marie Curie Award 2009

[18F]-AZD4694 – in human subjects



Clinical Validation of ^{18}F-AZD4694, an Amyloid-β–Specific PET Radioligand

Zsolt Cselényi[1,2], Maria Eriksdotter Jönhagen[3,4], Anton Forsberg[2], Christer Halldin[2], Per Julin[1], Magnus Schou[1,2], Peter Johnström[1,2], Katarina Varnäs[2], Samuel Svensson[2], and Lars Farde[1,2]

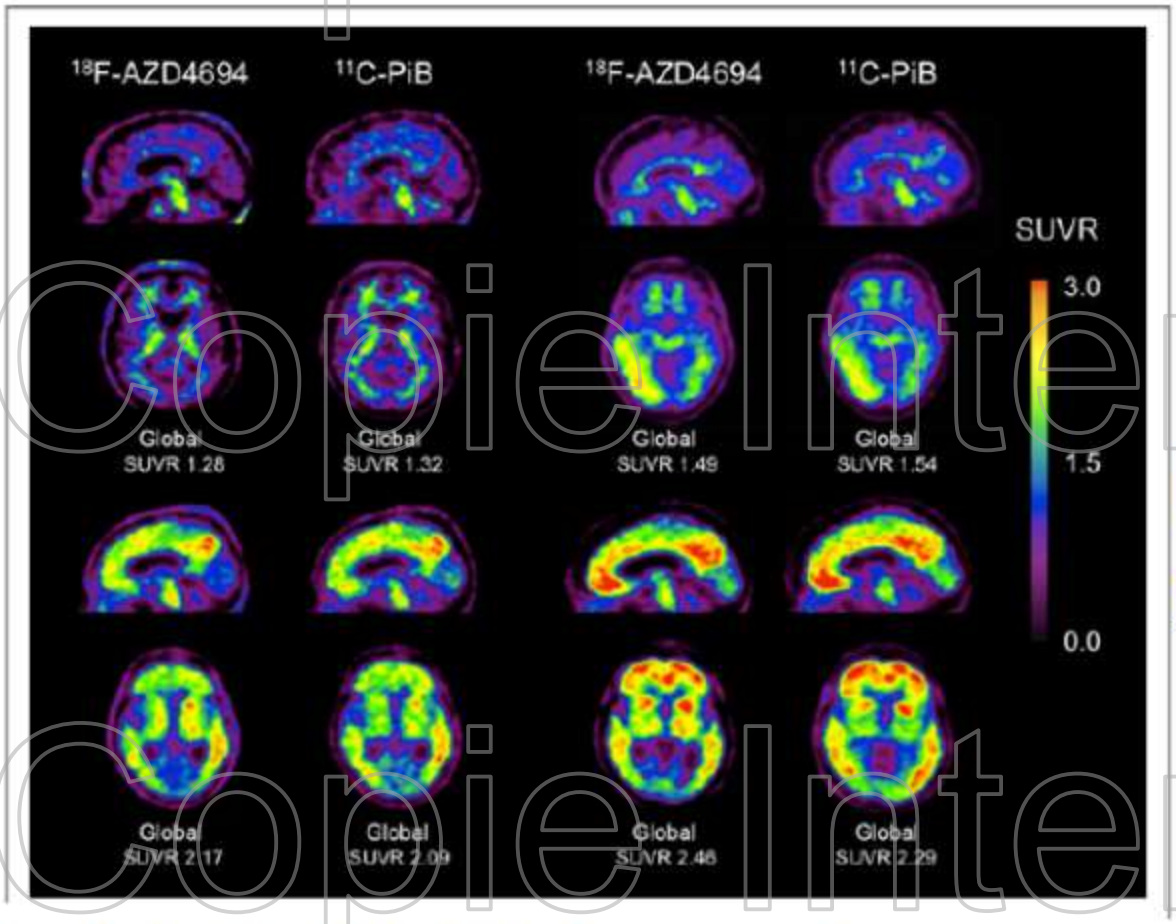
[1]*Neuroscience Research and Therapy Area, AstraZeneca Research and Development, Södertälje, Sweden;* [2]*Center for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden;* [3]*Clinical Geriatrics, Department of Neurobiology, Caring Sciences and Society, Karolinska Institutet, Stockholm, Sweden; and* [4]*Department of Geriatric Medicine, Karolinska University Hospital, Stockholm, Sweden*

J Nucl Med 2012; 53:415–424

FIGURE 3. Sample horizontal and sagittal slices of ^{18}F-AZD4694 peak ratio (21–33 min), late ratio (51–63 min) SUVR, and reference Logan DVR images overlaid on MR images for AD patient and CS. SUVR images were smoothed for visualization with gaussian filter with full width at half maximum of 5 mm. Color scale windows were set in such a way that cortical binding in AD patient appears comparable between methods.

[18F]-AZD4694 – in human subjects

J Nucl Med 2013; 54:1–7



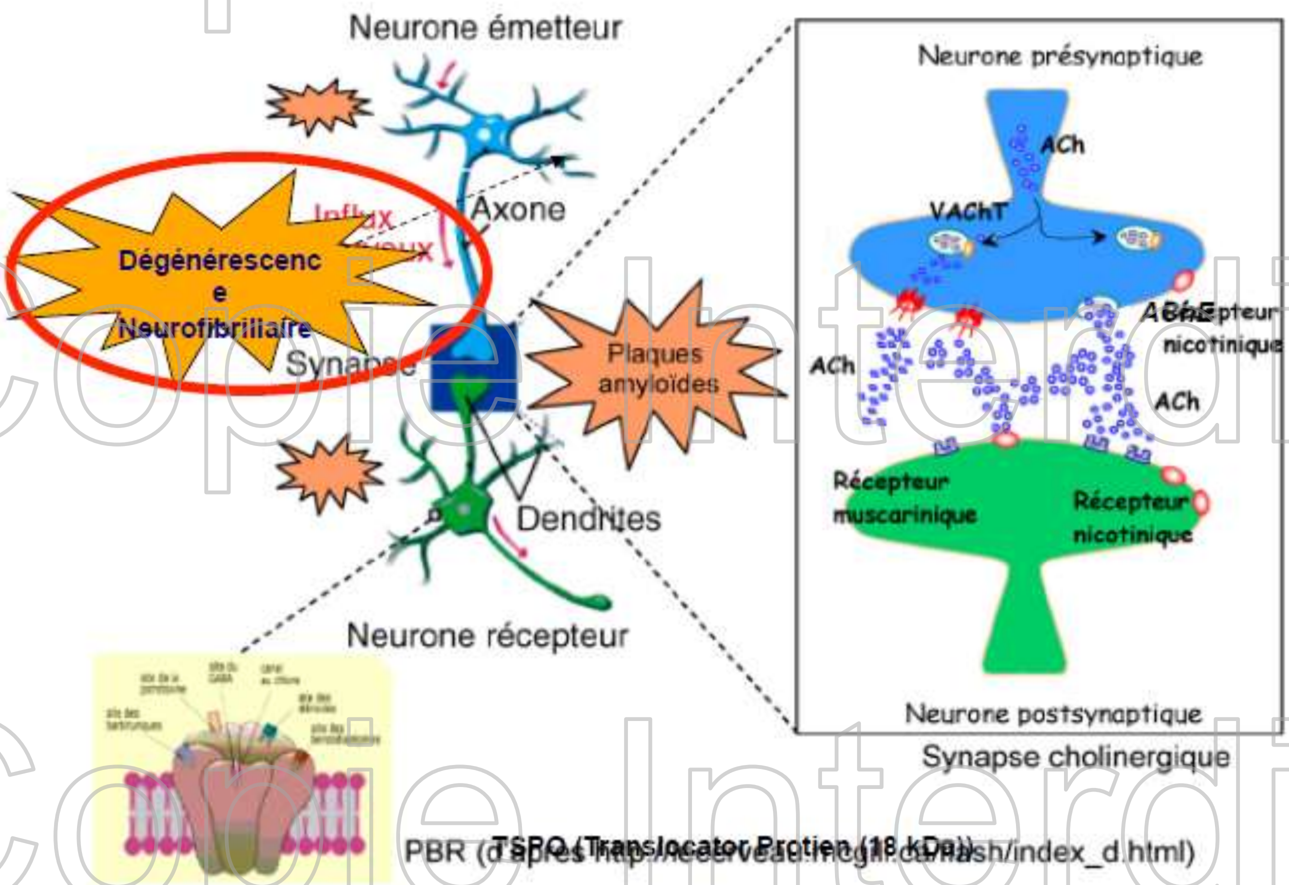
^{18}F-AZD4694 and ^{11}C-PiB PET imaging in 4 subjects

Développé par Navidea

Autre cibles moléculaires
Maladie d'Alzheimer

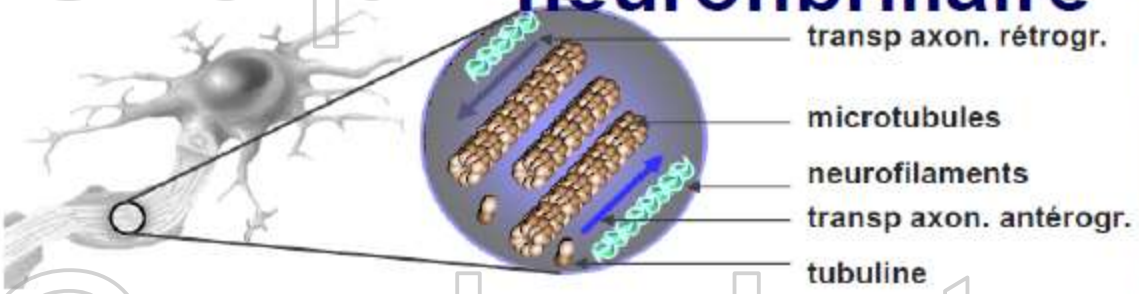
Cibles Moléculaires Maladie d'Alzheimer

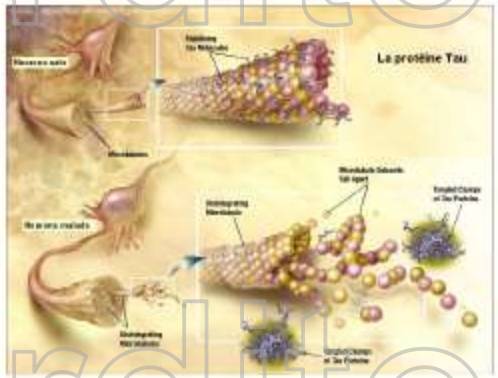
J. Vergote et al. Médecine Nucléaire xxx (2007) xxx–xxx



CHRU
HÔPITAUX DE TOURS

Marqueurs de dégénérescence neurofibrillaire





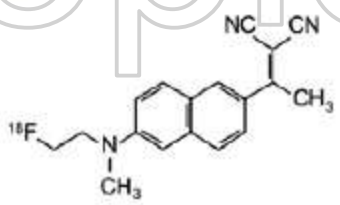
Protéine Tau (Tubulin Associated Unit)

- **associée aux microtubules** : rôle physiologique dans la stabilisation des microtubules (permet croissance, transport axonal…)
- fonction régulée par des mécanismes de **phosphorylation**

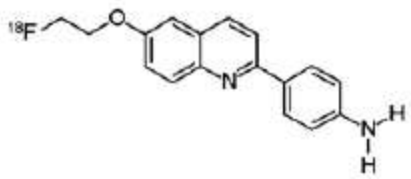
Protéine Tau phosphorylée

Dans la MA : **Hyperphosphorylation anormale** de la protéine Tau

- **agrégation** intraneuronale sous forme de DNF
- **lyse** neuronale

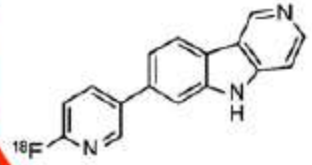


18F-FDDNP

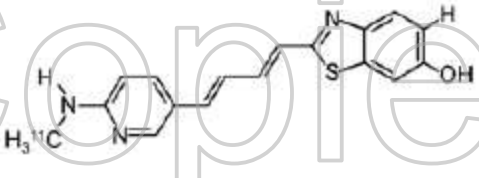


18F-THK-523

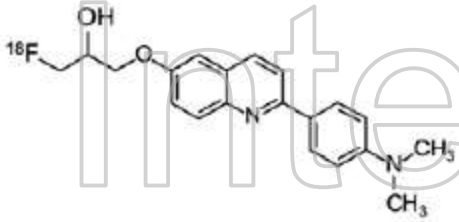
18F-AV-1451 (Avid)



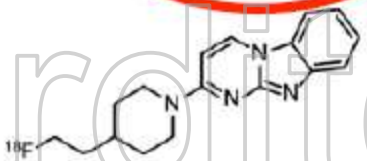
18F-T807



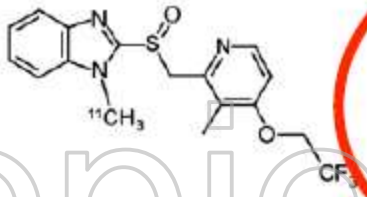
11C-PBB3



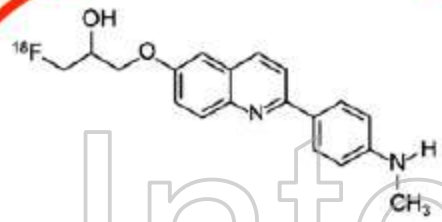
18F-THK-5105



18F-T808



11C-N-Methyl Lansoprazole

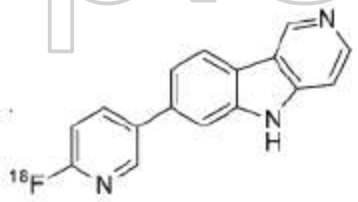


18F-THK-5117

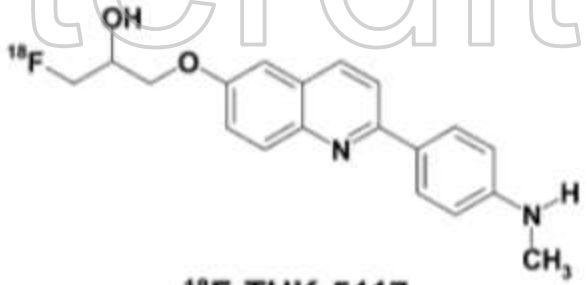
Fig. 1. Chemical structure of currently available tau radiotracers. Most of them have been evaluated in clinical studies.

Imagerie moléculaire
TAU

American group (AVID): [^{18}F]-T807
Japan group :[^{18}F]-THK-5117



[F-18]-T807



^{18}F-THK-5117

Traceurs Spécifiques des DNF

doi:10.1093/brain/awr038 Brain 2011: 134; 1089–1100 | 1089

BRAIN
A JOURNAL OF NEUROLOGY

^{18}F-THK523: a novel *in vivo* tau imaging ligand for Alzheimer's disease

Michelle T. Fodero-Tavoletti,[1,2] Nobuyuki Okamura,[3] Shozo Furumoto,[3] Rachel S. Mulligan,[4] Andrea R. Connor,[1,2] Catriona A. McLean,[5] Diana Cao,[6] Angela Rigopoulos,[6] Glenn A. Cartwright,[6] Graeme O'Keefe,[4] Sylvia Gong,[4] Paul A. Adlard,[1,7] Kevin J. Barnham,[1,2,7] Christopher C. Rowe,[4] Colin L. Masters,[7] Yukitsuka Kudo,[8] Roberto Cappai,[1,2] Kazuhiko Yanai[3] and Victor L. Villemagne[4,7]

1 Department of Pathology, The University of Melbourne, Victoria, 3010, Australia
2 Bio21 Molecular and Biotechnology Institute, The University of Melbourne, Victoria, 3010, Australia
3 Department of Pharmacology, Graduate School of Medicine, Tohoku University, Sendai, 980-8575, Japan
4 Department of Nuclear Medicine and Centre for PET, University of Melbourne, Austin Health, Victoria, 3084, Australia
5 Department of Anatomical Pathology, The Alfred Hospital, Victoria, 3181, Australia
6 Ludwig Institute for Cancer Research, Austin Hospital, Victoria, 3084, Australia
7 The Mental Health Research Institute, Victoria, 3010, Australia
8 Innovation of New Biomedical Engineering Centre, Tohoku University, Sendai, 980-8575, Japan

Correspondence to: Victor L. Villemagne,
Austin Health, Department of Nuclear Medicine and Centre for PET,
145 Studley Road,
Heidelberg,
VIC, 3084, Australia
E-mail: villemagne@petnm.unimelb.edu.au

CHRU
HÔPITAUX DE TOURS

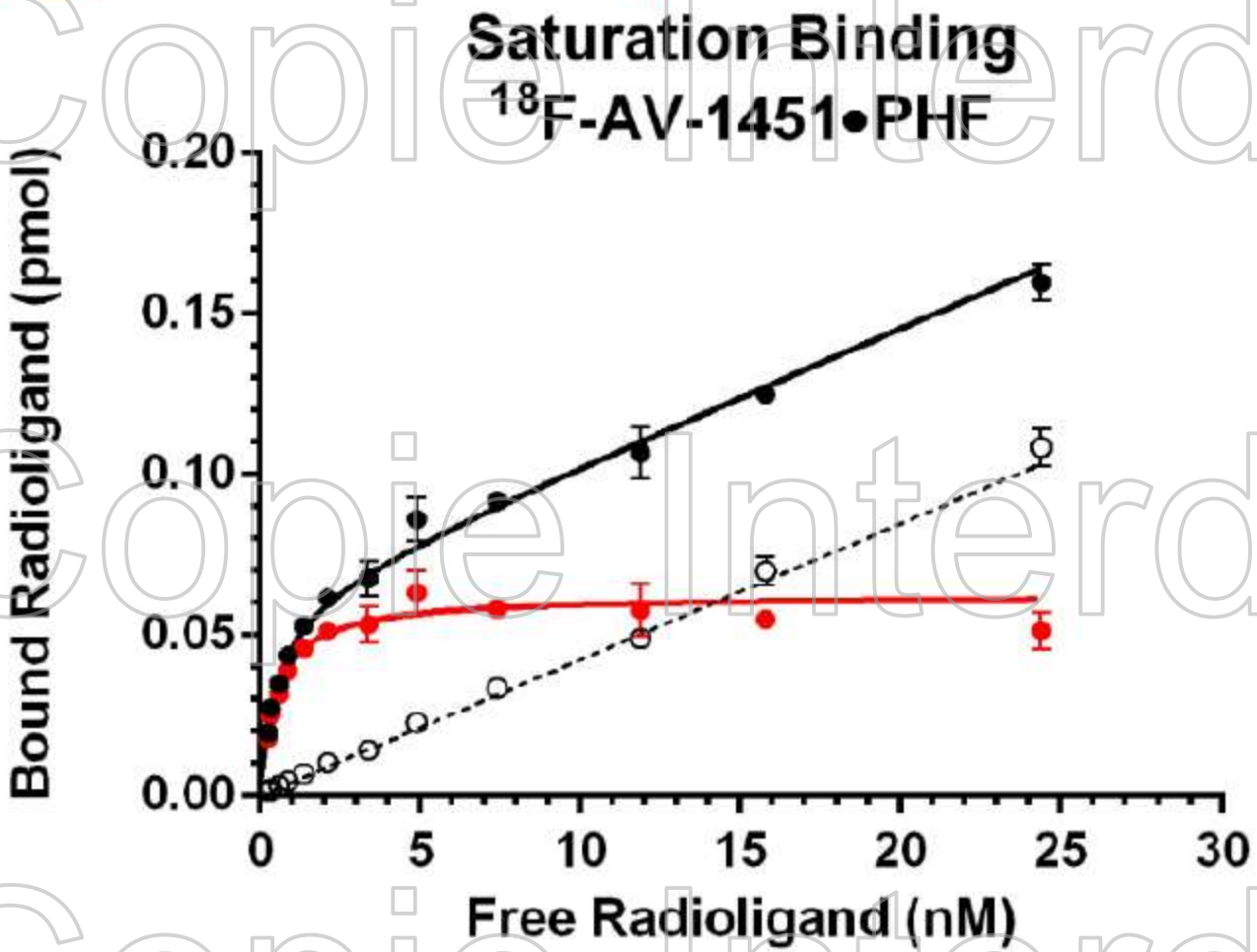
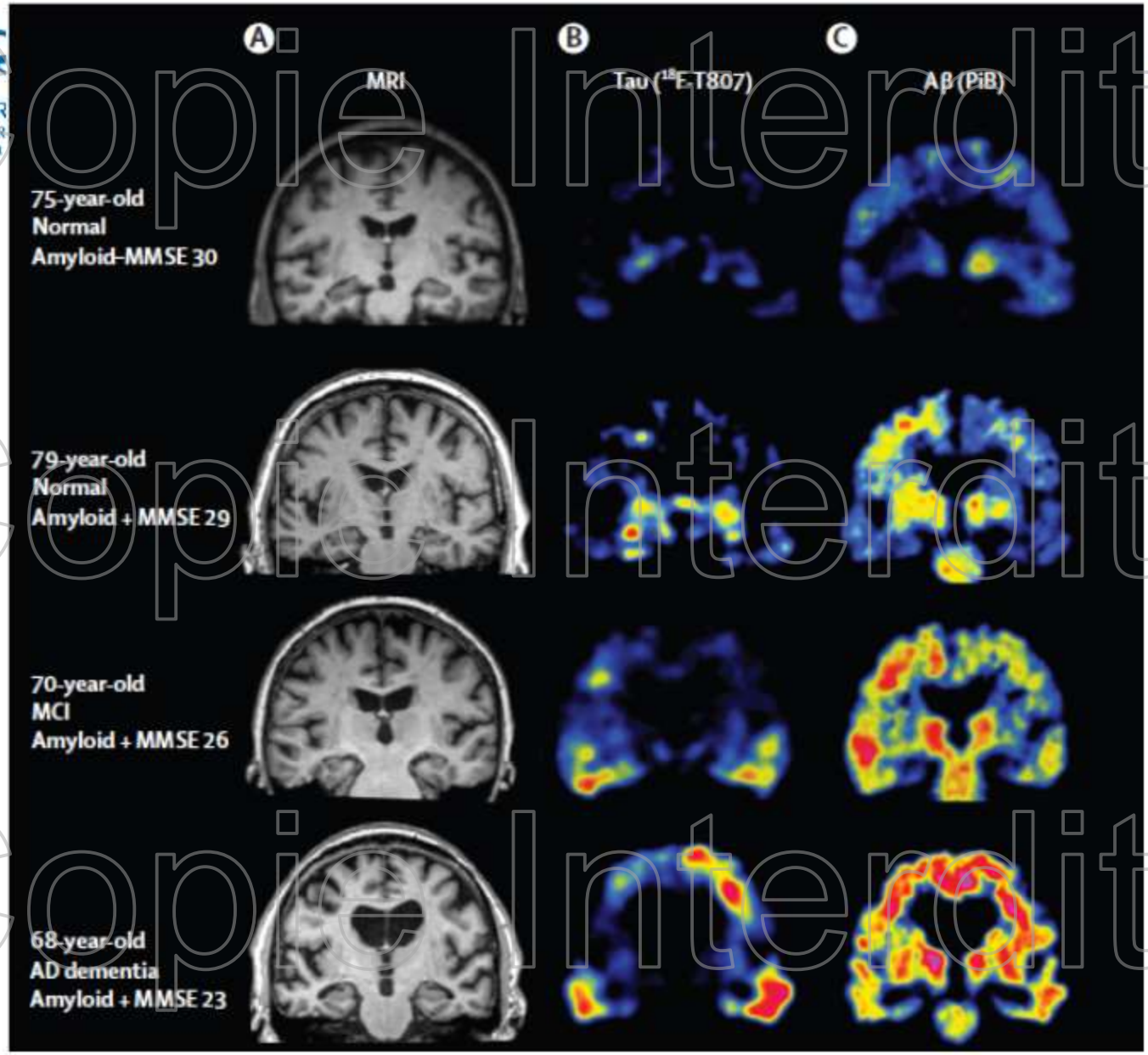


Figure 4: **Representative Saturation Binding Isotherm of 18F-AV-1451 to PHF tau extracted from AD brain.**



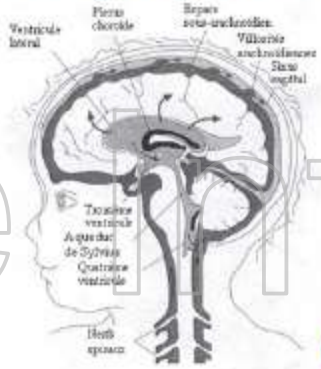
Dosage LCR/Imagerie Moléculaire

Complémentarité/Compétition?

Analyse des coûts

Lésions microscopiques de la MA

Conséquences dans le Liquide Céphalo-Rachidien LCR



↓ *β-amyloïde*

↑ *TAU et P-TAU*

= marqueurs biologiques de la maladie d'Alzheimer

DOSAGE POSSIBLE

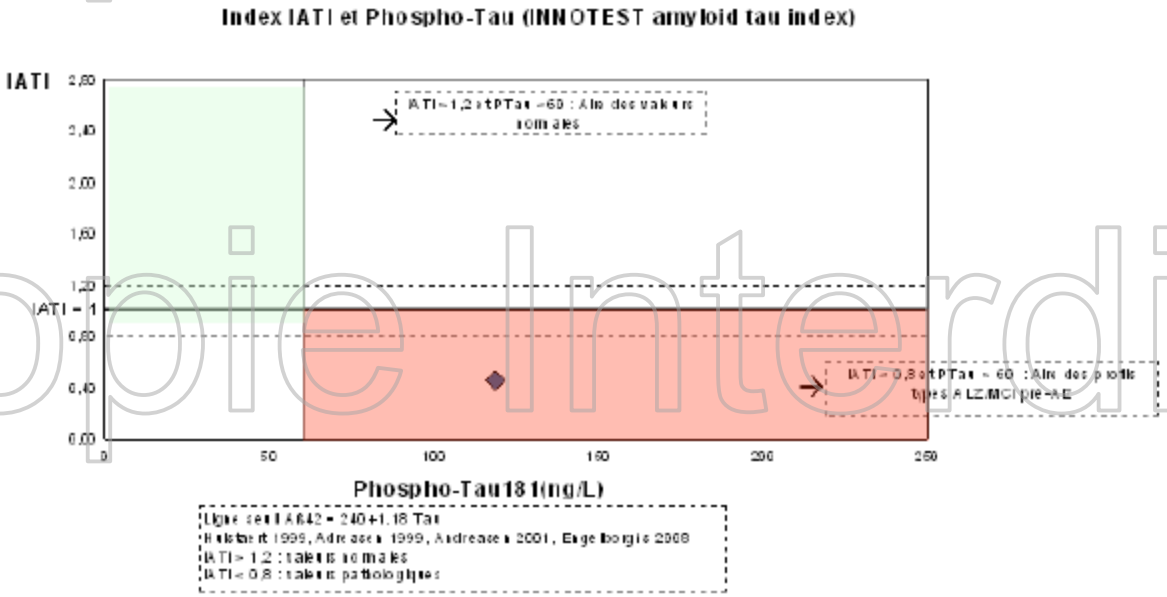
Objectif des dosages ? Pour qui ?

Apporter une aide pour le diagnostic de la maladie d'Alzheimer

*Recommandations de la **HAS** de 2011*
« Le dosage dans le LCR des protéines Tubulin Associated Unit (TAU) totales, phospho-TAU et Aβ1-42 peut être réalisé en cas de doute diagnostique et en particulier chez les patients jeunes »

HAS
HAUTE AUTORITÉ DE SANTÉ

Interprétation des résultats



*Aβ42, TAU et p-TAU normales : **profil biochimique normal***

*Aβ42 < N, TAU et p-TAU > N : **profil biochimique MA ou MA pré-démentielle***

Stratégie de dosages des marqueurs du LCR dans la MA

Principe tests : technique immunoenzymatique type ELISA

Dosages conjoints :

- β-amyloïde$_{1-42}$
- Tau

Sensibles mais peu spécifiques

- p-Tau

Spécifique mais peu sensible

=> Combinaison des 3 dosages :
- sensibilité : 77 à 90%
- spécificité : 90 à 97%
(Blennow et al., 2006; Gabelle et al., 2013)

UNIVERSITÉ FRANÇOIS - RABELAIS TOURS

Instituts thématiques Inserm Institut national de la santé et de la recherche médicale

CHRU HÔPITAUX DE TOURS

2014

Position Paper

Place des biomarqueurs

Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria

Bruno Dubois, Howard H Feldman, Claudia Jacova, Harald Hampel, José Luis Molinuevo, Kaj Blennow, Steven T DeKosky, Serge Gauthier, Dennis Selkoe, Randall Bateman, Stefano Cappa, Sebastian Crutch, Sebastiaan Engelborghs, Giovanni B Frisoni, Nick C Fox, Douglas Galasko, Marie-Odile Habert, Gregory A Jicha, Agneta Nordberg, Florence Pasquier, Gil Rabinovici, Philippe Robert, Christopher Rowe, Stephen Salloway, Marie Sarazin, Stéphane Epelbaum, Leonardo C de Souza, Bruno Vellas, Pieter J Visser, Lon Schneider, Yaakov Stern, Philip Scheltens, Jeffrey L Cummings

Lancet Neurol 2014; 13: 614–29

Panel 1: IWG-2 criteria for typical AD (A plus B at any stage)

A Specific clinical phenotype

- Presence of an early and significant episodic memory impairment (isolated or associated with other cognitive or behavioural changes that are suggestive of a mild cognitive impairment or of a dementia syndrome) that includes the following features:
  - Gradual and progressive change in memory function reported by patient or informant over more than 6 months
  - Objective evidence of an amnestic syndrome of the hippocampal type,* based on significantly impaired performance on an episodic memory test with established specificity for AD, such as cued recall with control of encoding test

B In-vivo evidence of Alzheimer's pathology (one of the following)

- Decreased $A\beta_{1-42}$ together with increased T-tau or P-tau in CSF
- Increased tracer retention on amyloid PET
- AD autosomal dominant mutation present (in *PSEN1*, *PSEN2*, or *APP*)

UNIVERSITÉ FRANÇOIS - RABELAIS TOURS

Instituts thématiques Inserm Institut national de la santé et de la recherche médicale

CHRU HÔPITAUX DE TOURS

Movement disorders 2

Imaging insights into basal ganglia function, Parkinson's disease, and dystonia

A Jon Stoessl, Stephane *Lehericy, Antonio P Strafella*

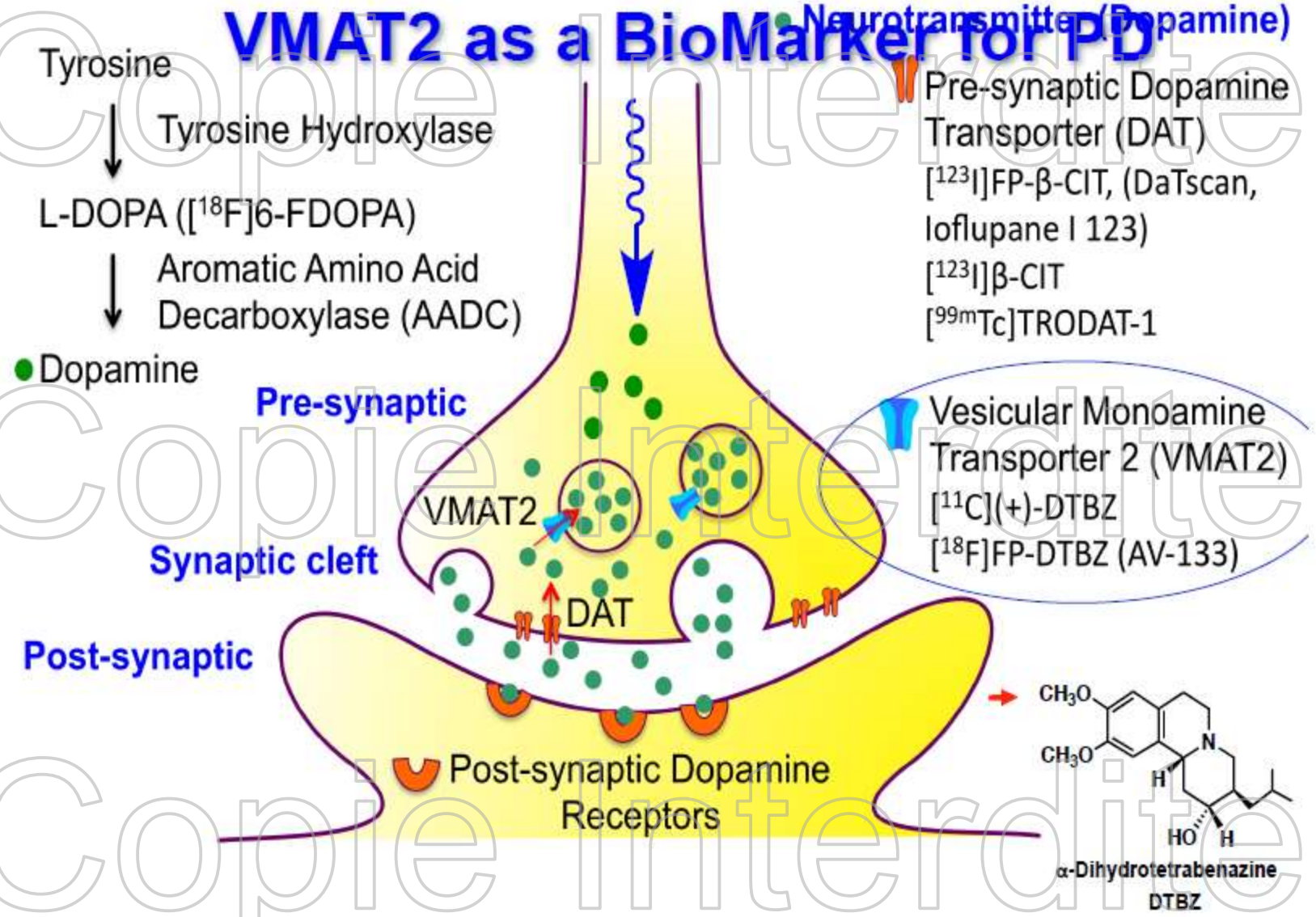
Lancet 2014

« Recent advances in structural and functional imaging have greatly improved our ability to assess normal functions of the basal ganglia, diagnose parkinsonian syndromes, understand the pathophysiology of parkinsonism and other movement disorders, and detect and monitor disease progression.

« Radionuclide imaging is the best way to detect and monitor dopamine deficiency, and will probably continue to be the best biomarker for assessment of the effects of disease-modifying therapy »

Perspectives
VMAT2

VMAT2 as a BioMarker for PD



Neuro–degenerative Diseases

Neurodegenerative Dis
DOI: 10.1159/000334535

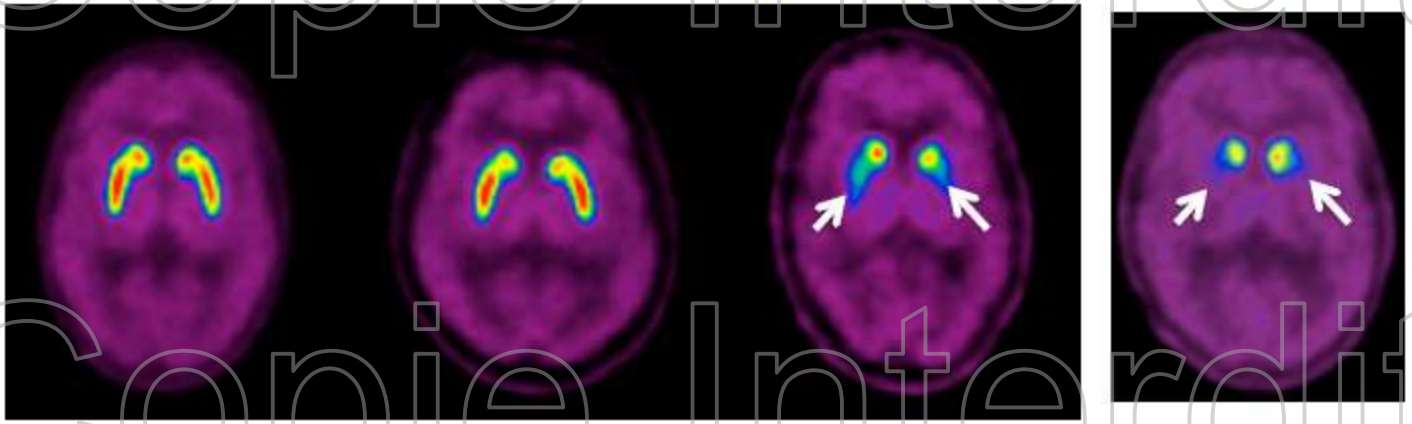
Received: June 28, 2011
Accepted after revision: Oct
Published online: January 1

Differential Diagnosis in Alzheimer's Disease and Dementia with Lewy Bodies via VMAT2 and Amyloid Imaging

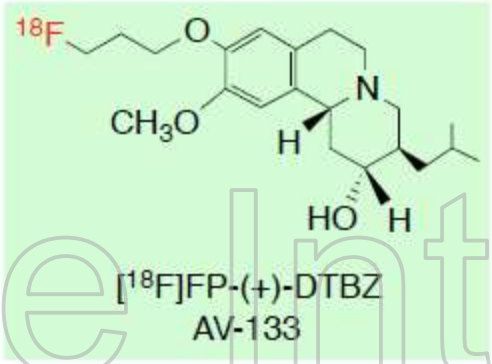
Victor L. Villemagne[a, d] Nobuyuki Okamura[e] Svetlana Pejoska[d] John Drago[b, c]
Rachel S. Mulligan[d] Gaël Chételat[d, f] Graeme O'Keefe[d] Gareth Jones[d]
Hank F. Kung[g] Michael Pontecorvo[h] Colin L. Masters[a] Daniel M. Skovronsky[g, h]
Christopher C. Rowe[d]

[a]Mental Health Research Institute, [b]Howard Florey Institute, and [c]Centre for Neuroscience, University of Melbourne, and [d]Department of Nuclear Medicine and Centre for PET, Austin Health, Melbourne, Vic., Australia; [e]Department of Pharmacology, Tohoku University School of Medicine, Sendai, Japan; [f]Inserm-EPHE-Université de Caen/Basse-Normandie, Unité U923, GIP Cyceron, CHU Côte de Nacre, Caen, France; [g]Radiology, University of Pennsylvania, and [h]Avid Radiopharmaceuticals Inc., Philadelphia, Pa., USA

AV-133 (Florbenazine) VMAT2 PET Imaging



HC AD DLB PD

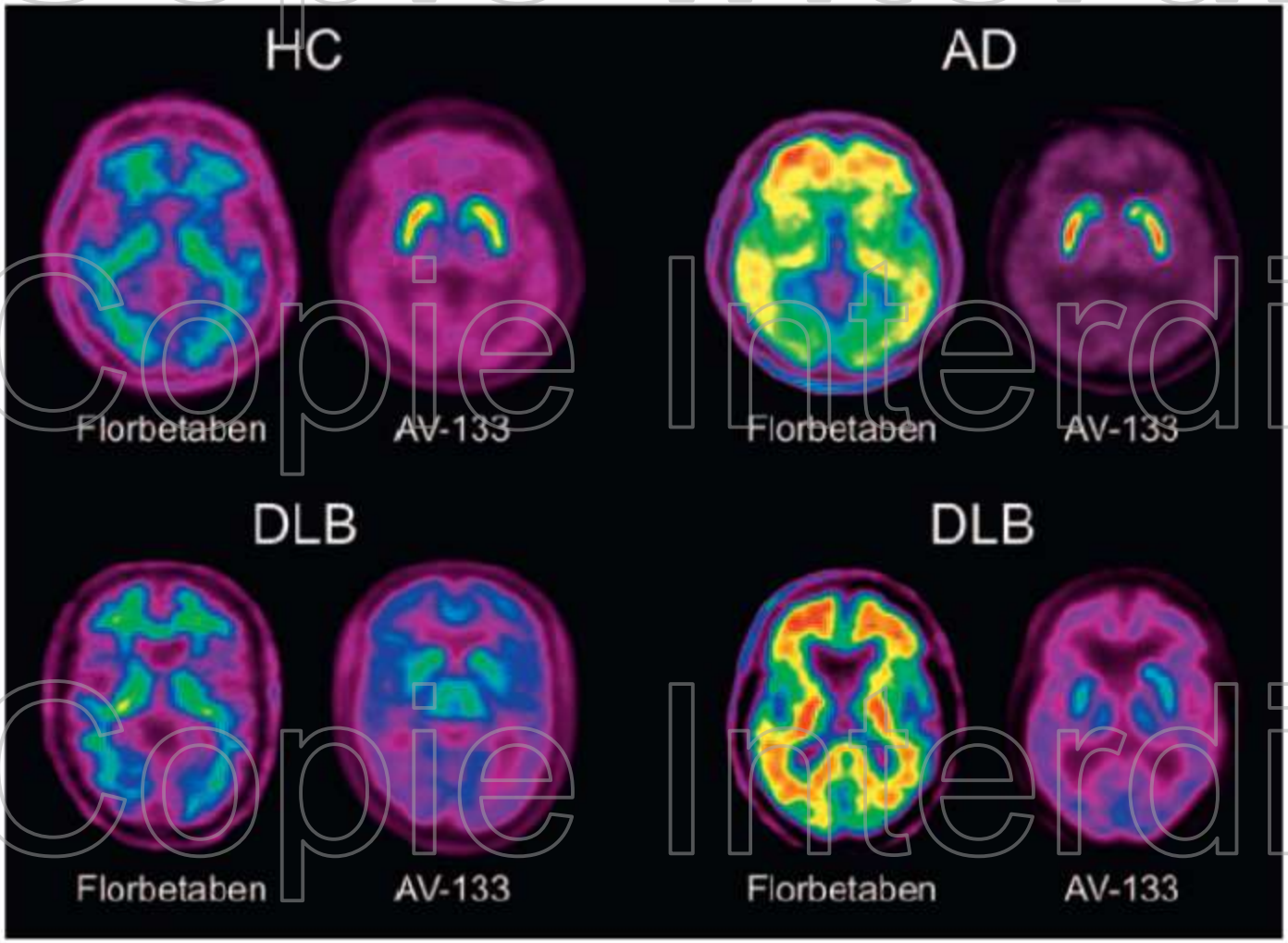


[^{18}F]FP-(+)-DTBZ
AV-133

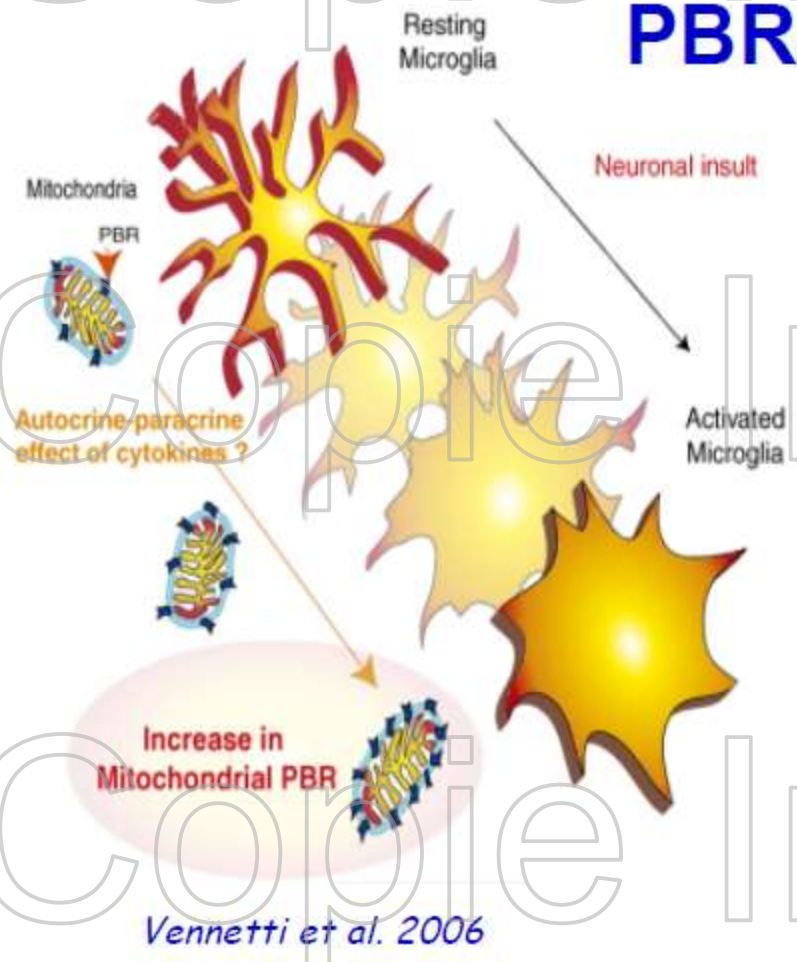
Neuro-degenerative Diseases

Neurodegenerative Dis
DOI: 10.1159/000334535
Received: June 28, 2011
Accepted after revision: October 3, 2011
Published online: January 17, 2012

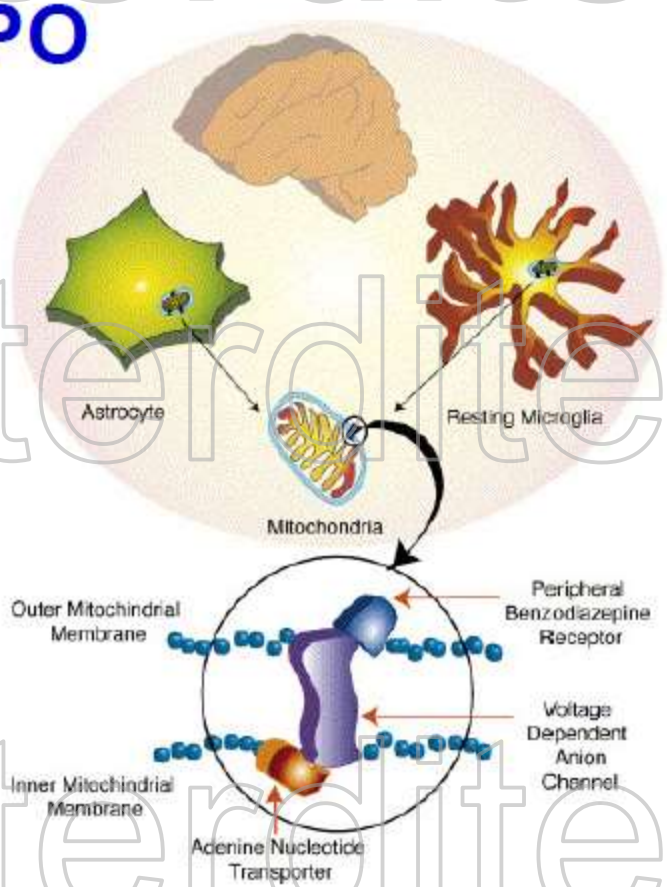
Differential Diagnosis in Alzheimer's Disease and Dementia with Lewy Bodies via VMAT2 and Amyloid Imaging



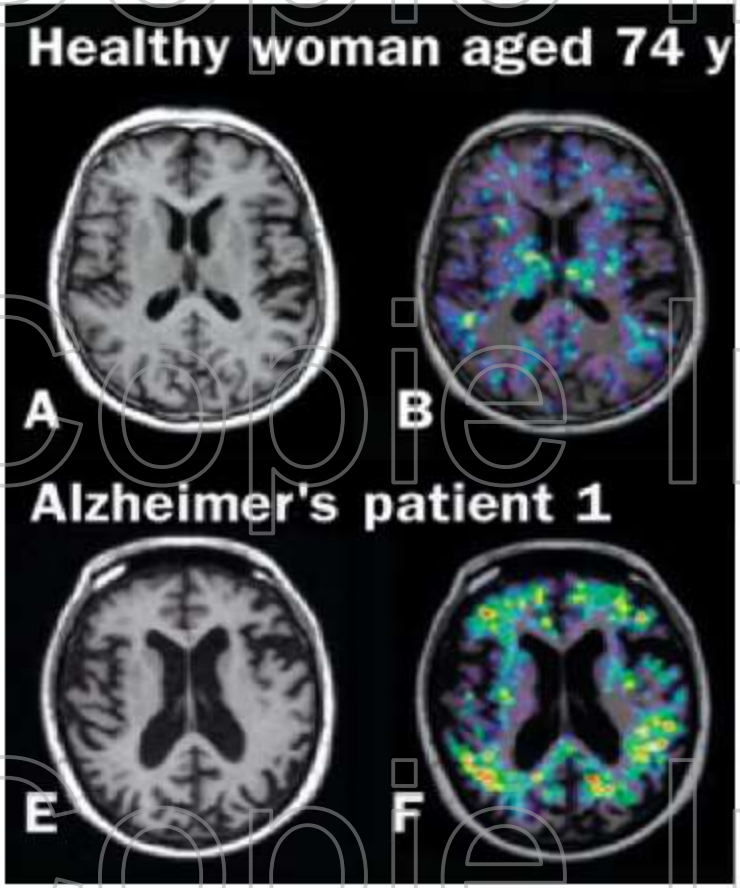
Imagerie moléculaire de la neuroinflammation PBR/TSPO



Vennetti et al. 2006

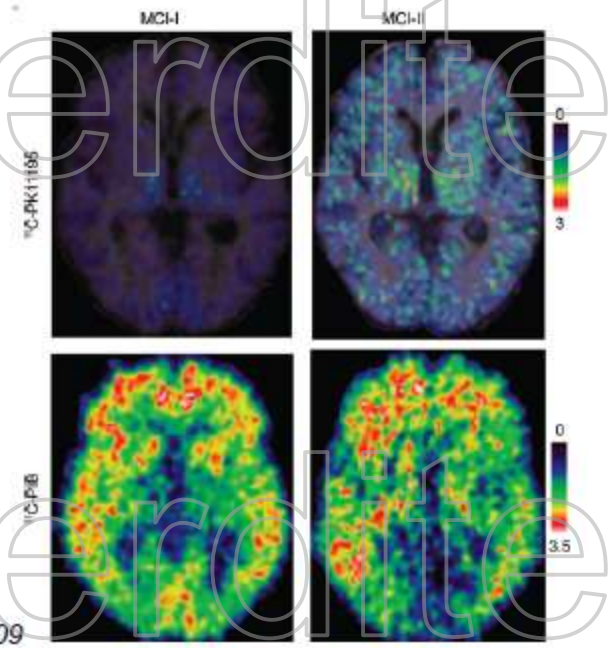


Maladie d'Alzheimer



Cagnin, Lancet, 2001

PK 11195



Okello, Neurology, 2009

Imagerie moléculaire de la neuroinflammation PBR/TSPO

Résultats controversés

Dépendants de la phase de la maladie?

Evidence for Astrocytosis in Prodromal Alzheimer Disease Provided by ^{11}C-Deuterium-L-Deprenyl: A Multitracer PET Paradigm Combining ^{11}C-Pittsburgh Compound B and ^{18}F-FDG

Stephen F. Carter*[1], Michael Schöll*[1], Ove Almkvist[1,2], Anders Wall[3], Henry Engler[3,4], Bengt Långström[5,6], and Agneta Nordberg[1,7]

J Nucl Med 2012; 53:37–46

CHRU HÔPITAUX DE TOURS

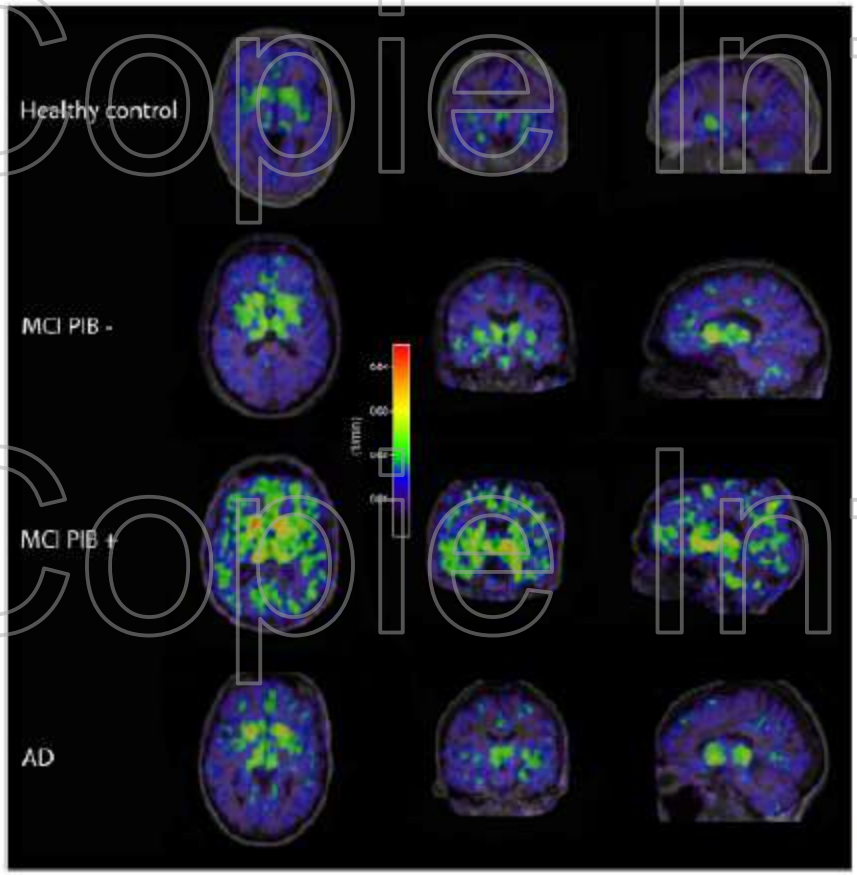
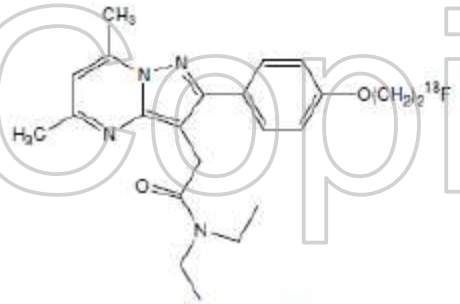


FIGURE 2. Representative parametric images of ^{11}C-DED binding (slope).

Evidence for Astrocytosis in Prodromal Alzheimer Disease Provided by ^{11}C-Deuterium-L-Deprenyl: A Multitracer PET Paradigm Combining ^{11}C-Pittsburgh Compound B and ^{18}F-FDG

Stephen F. Carter*[1], Michael Schöll*[1], Ove Almkvist[1,2], Anders Wall[3], Henry Engler[3,4], Bengt Långs and Agneta Nordberg[1,7]

J Nucl Med 2012; 53:37–46



DPA-714, a New Translocator Protein–Specific Ligand: Synthesis, Radiofluorination, and Pharmacologic Characterization

Michelle L. James[1], Roger R. Fulton[2], Johnny Vercoullie[3], David J. Henderson[2], Lacette Garreau[3], Sylvie Chalon[3], Frederic Dolle[4], Silvia Selleri[5], Denis Guilloteau[3], and Michael Kassiou[6–8]

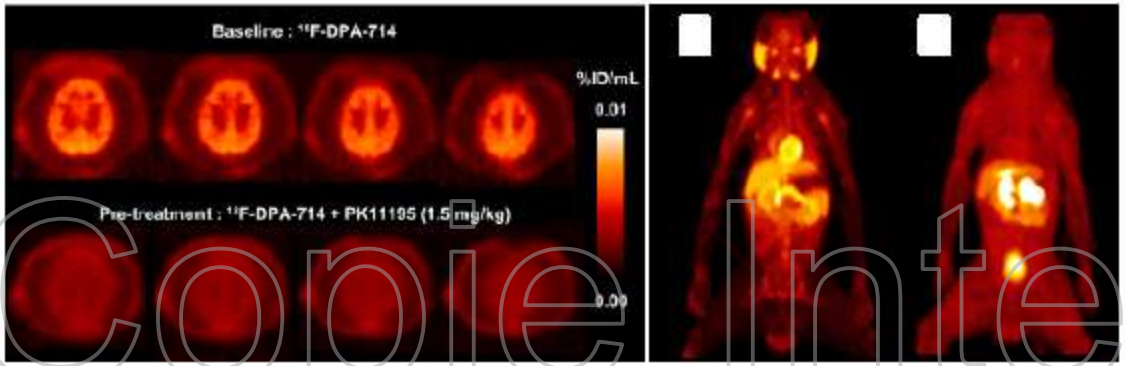
The University of Sydney

brain&mind RESEARCH INSTITUTE

UNIVERSITÉ FRANÇOIS - RABELAIS TOURS

Inserm

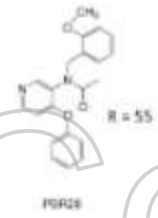
CHRU HÔPITAUX DE TOURS

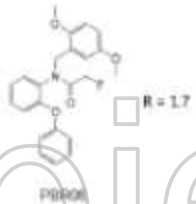


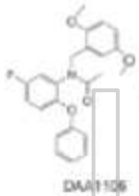
TSPO binder / non binder

Mixed-Affinity Binding in Humans with 18-kDa Translocator Protein Ligands

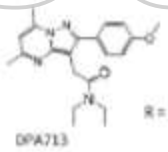
Phenoxyphenyl acetamid derivatives

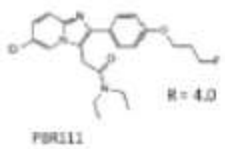




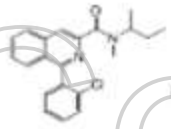


Bicyclic linker derivatives





Phenyl-isoquinolinecarboxamide derivative



Ratio of Specific Signal for HABs, MABs, and LABs with Different TSPO Ligands

Ligand	LAB	MAB	HAB
PBR28	1	28.2	55.3
PBR06	1	9.2	17.3
DAA1106	1	2.9	4.7
PBR111	1	2.5	4.0
DPA173	1	2.7	4.4
PK11195	1	0.9	0.8

Knowledge of subjects' binding patterns will be required to accurately quantify TSPO expression in vivo using PET.

Projet Européen In Mind

Imaging of NeuroinflaMmation In Neurodegenerative Diseases

*7ème programme cadre de recherche et développement (**PCRD**)*

Imagerie moléculaire des maladies Neurodégénératives

Perspectives

Et nous aurions pu parler de

Alpha –synucléine

mGluR5

…….

CONCLUSION

A Jon Stoessl, Stephane Lehericy, Antonio P Strafella
Lancet 2014

Radionuclide imaging is the best way to detect and monitor dopamine deficiency, and will probably continue to be the best biomarker for assessment of the effects of disease-modifying therapies

Le Chemin est encore long…

... mais on peut espérer!

Remerciements

Maria-Joa Ribeiro Tours
Vincent Camus Tours
Nicolas Arlicot`

Daniel Skovronsky , AVID,Philadelphia
Hank Kung, Philadelphia
Jorge Barrio, UCLA
Julie Price, Pittsburg
Chris Rowe, Austin, Melbourne
Christer Halldin, KI, Stockholm

Pierre Payoux Toulouse