Biomarkers identification and validation

(example of the Alzheimer's Disease)

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Eq. Maladie d'Alzheimer : Modélisation, Biomarqueurs, Imageries Précliniques

http://mamobipet.free.fr/Teaching/Teaching.html

Overview

- Concepts of Biomarkers
- Overview on Alzheimer's disease
- Biomarkers in humans
  - Dubois Criteria / ADNI initiative
  - Cerebral atrophy (MRI)
  - Brain metabolism (PET)
  - Amyloid plaques (PET)
- Biomarkers in animal models: Why/how can we use of biomarkers in animal models?
  - Characterization of animal models
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    - Choice of marker versus biomarkers ?
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    - "Classical view" of translational medicine
    - Translational bridgesTherapeutic evaluations
  - Preparation of clinical trials

Diseases and therapies…

Step 1: Objective in humans: Cure the disease…

Disease →

→ Clinical outcome (Phenotype)

Ex. Cognitive alterations
Death, etc…

Therapy →

Empiric approaches: Is my drug treating the disease ?

Biomarqueurs: Un concept faussement "simple"
Biomarker Definition Working group (2001)

- CLINICAL ENDPOINT (critère ou marqueur clinique, ~symptôme?)
  - A characteristic or variable that reflects how a patient feels or functions, or how long a patient survives.

- BIOLOGICAL MARKER (BIOMARKER)
  - A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.
  - Replace a distal endpoint with a more proximal one, measured earlier
  - Can be measured more easily or frequently
  - Faster decision making

- 3 types of Biomarkers (Biomarker Def Working Grp, 2001)
  - Type 0 : **Reflects natural history of a disease**
  - Type I : **Reflects mechanism of action of an intervention**
  - Type II : **Predicts clinical benefit of a treatment (or toxicity)**

  (SURROGATE ENDPOINT (critère ou marqueur de substitution))

Traductions !

***Outcome* se rapporte à l'évolution ou à l'aboutissement d'un processus ou à l'état dans lequel se trouve un patient**	
• *Disease outcome* • *Pregnancy outcome* • *Patient outcome*	**Évolution**, **issue** d'une maladie, **Évolution**, **issue**, **devenir** d'une grossesse **Évolution de l'état de santé** du patient **Devenir** d'un patient, d'une population de patients
***Outcome* a trait à l'évaluation d'un traitement ou d'un processus quelconque**	
• *Clinical outcome, health outcome, outcome* • *Pharmaceutical outcome, outcome* • *Therapeutic outcome, treatment outcome, outcome* • *Outcome, outcome measure, outcome variable, endpoint* • *Outcome measure* • *Outcome event* • *Clinical endpoint, clinical outcome* • *Intermediary endpoint* • *Surrogate outcome, surrogate endpoint, surrogate marker*	**Résultat clinique** **Résultat du traitement médicamenteux** **Résultat thérapeutique** **Critère** (**de jugement, d'évaluation**), **facteur résultant**, **variable**, **paramètre, instrument de mesure des résultats** **Mesure des résultats** **Événement**, **événement cible** **Critère clinique*** **Critère intermédiaire*** **Critère de substitution***
* Bien souvent en anglais, on utilisera également *endpoint* pour désigner les résultats obtenus relativement à ces critères. Il faudra donc adapter la traduction en conséquence.	

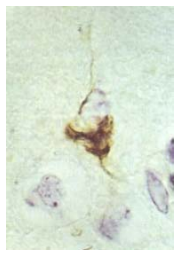
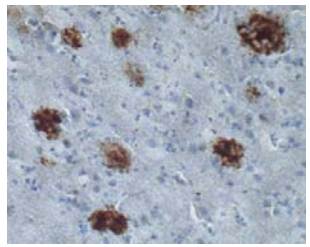
Diseases and therapies…

Step 2: Objective in humans: Natural history of the disease

Disease → Target → Endophenotypes → Clinical outcome (Phenotype)

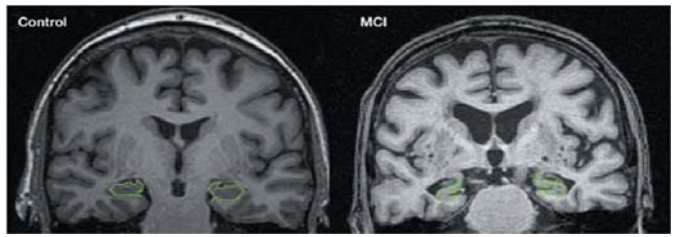
Ex. Cognitive alterations
Death, etc…

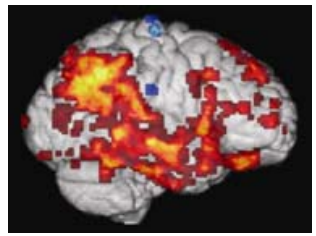
Markers


Biomarkers

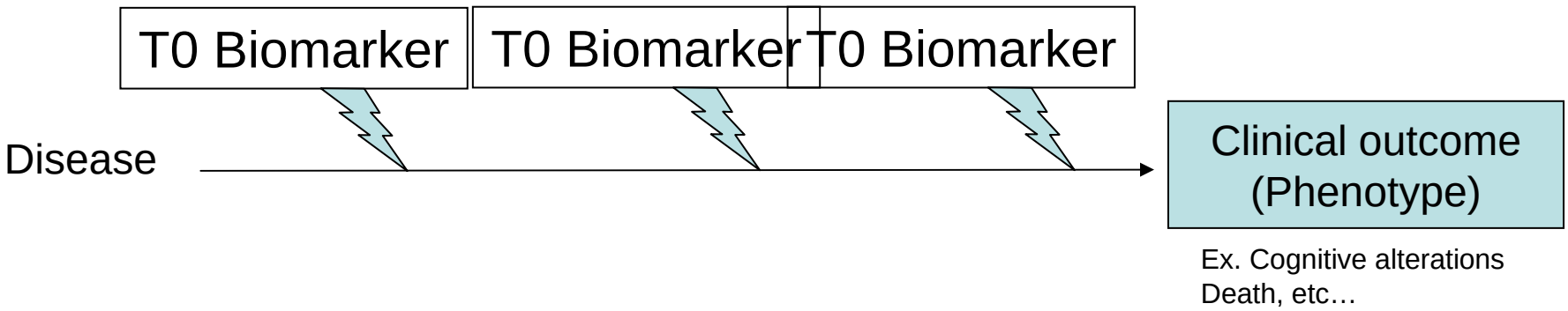
Diagnostic | **Longitudinal** | **Functional**





Understand the disease

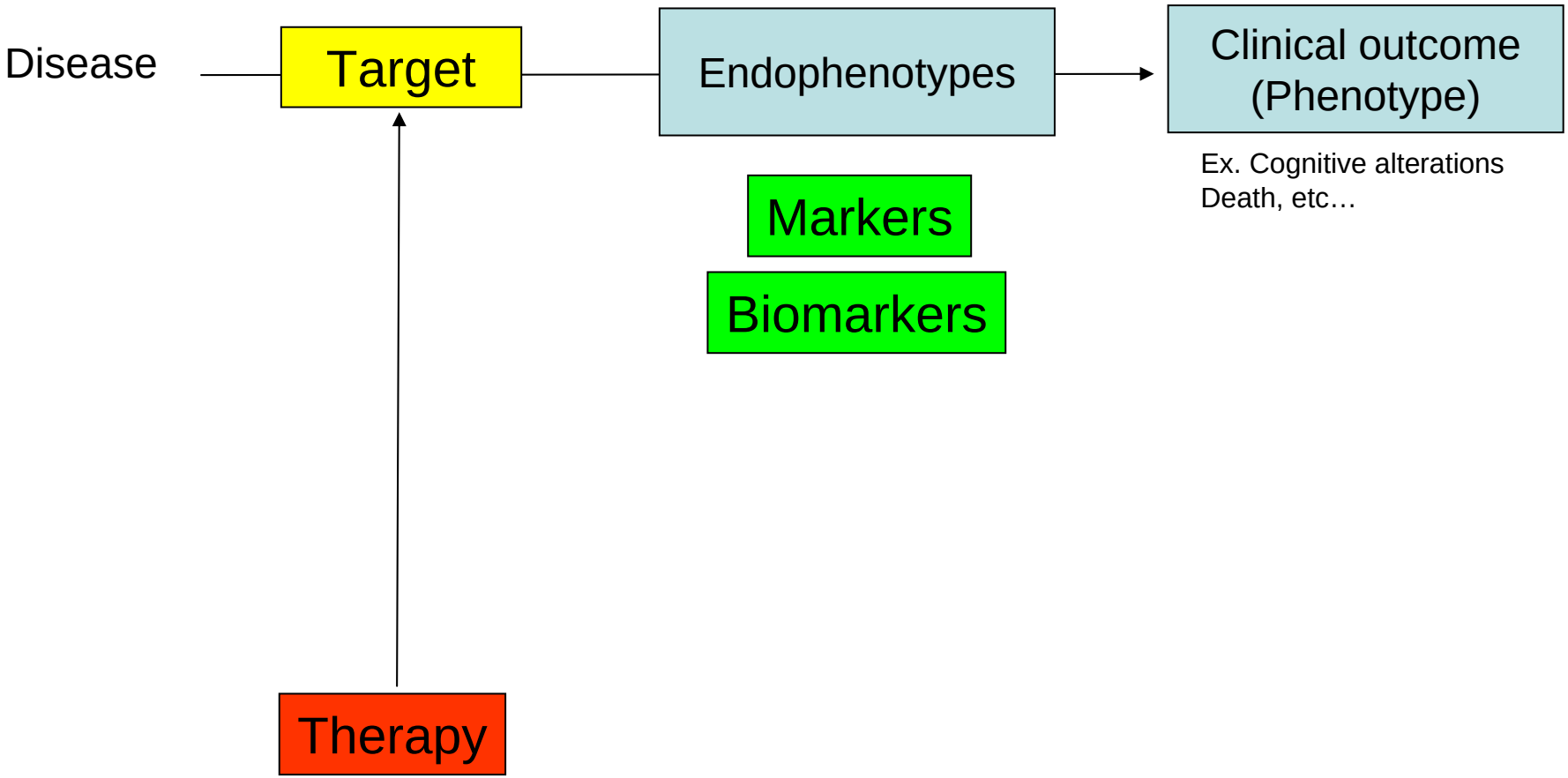
Type 0 Biomarker
Natural history of a disease



- Possible applications of T0 biomarkers
  - (Early) diagnosis
  - Clinical study enrichment, stratification of the patients

Diseases and therapies…

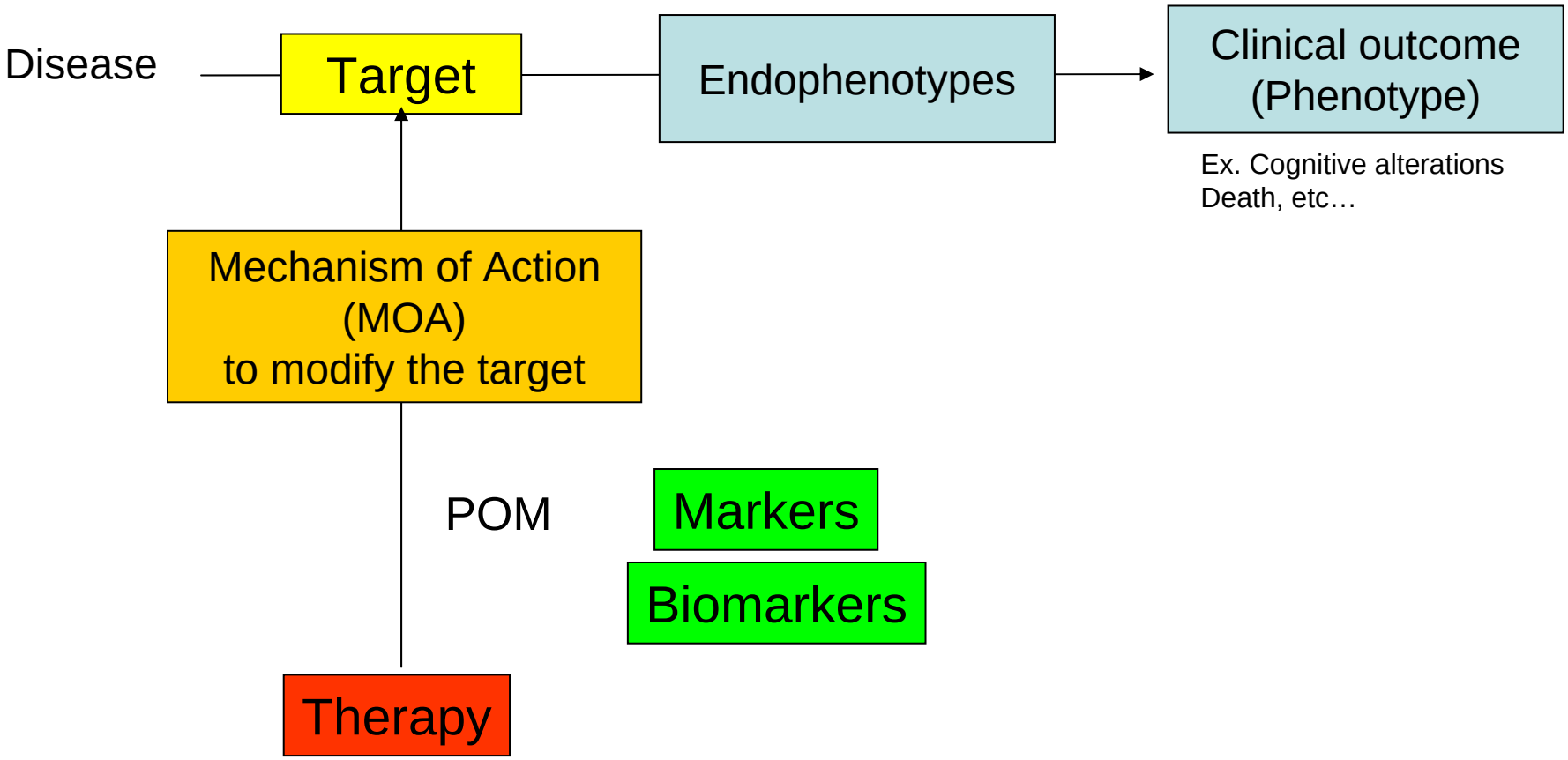
Step 3: Objective in humans: Isolate a target



Understand the disease → isolate a potential target

Diseases and therapies…

Step 4: Objective in humans: Understand how a drug works

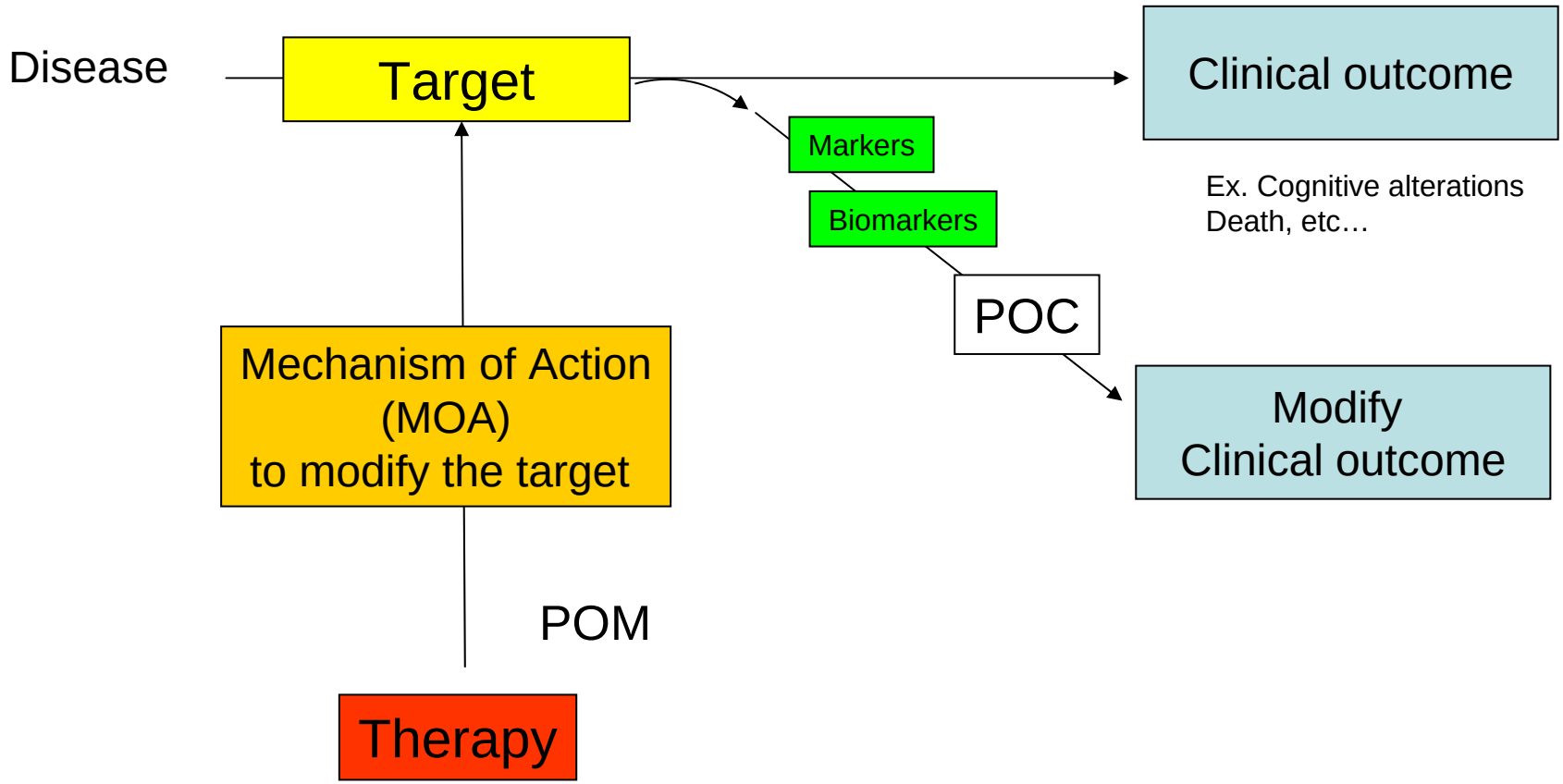


Proof of Mechanism (POM): Is my drug really active on the supposed mechanism ?

→ Type I biomarkers

Basis of translational medicine

Step 5: Objective in humans: If I modify the target, do I modify the disease ?

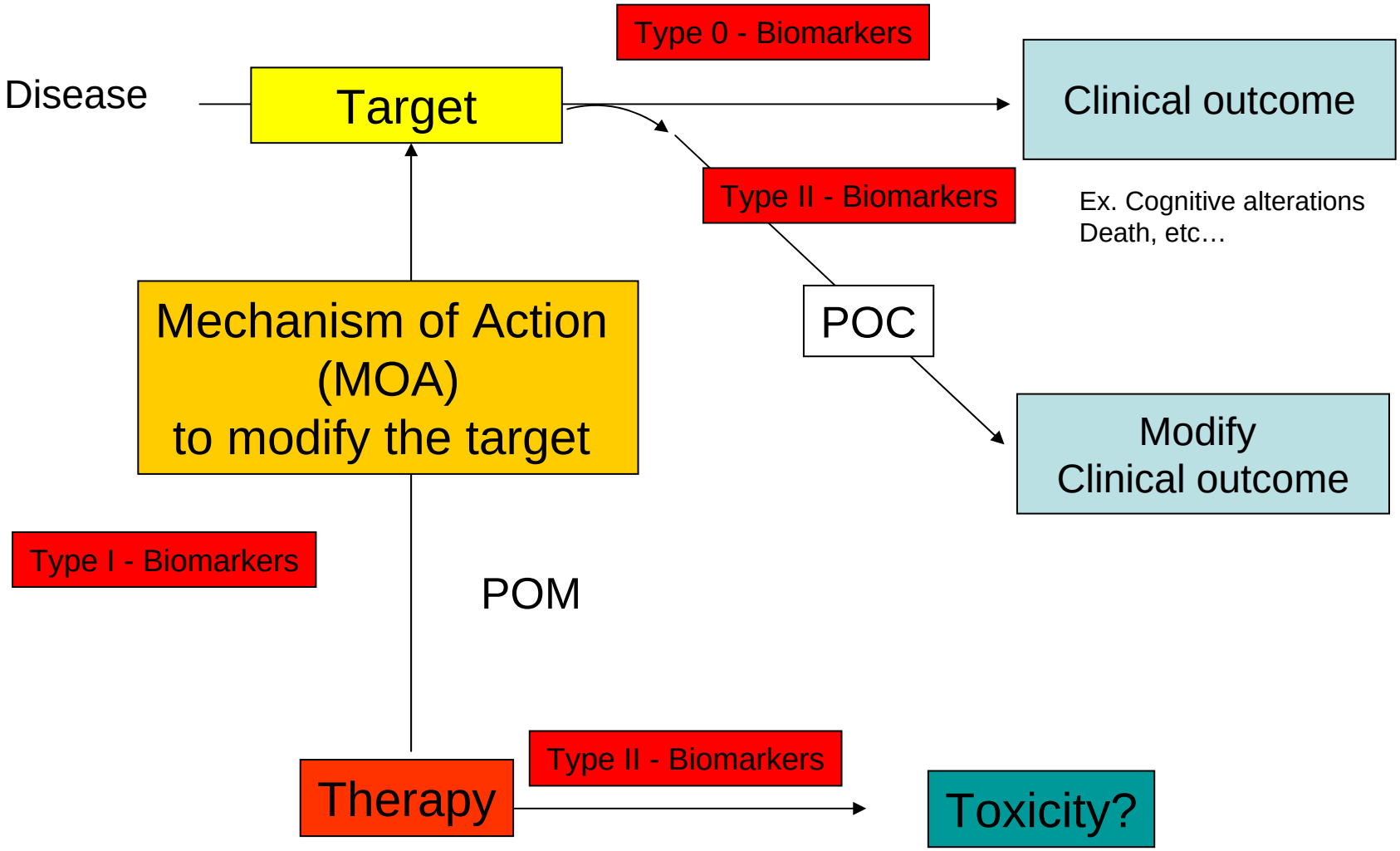


Proof of Mechanism (POM): Is my drug really active on the supposed mechanism ?

Proof of Concept (POC): If I modify the target, do I modify the disease ?

→ Type II biomarkers

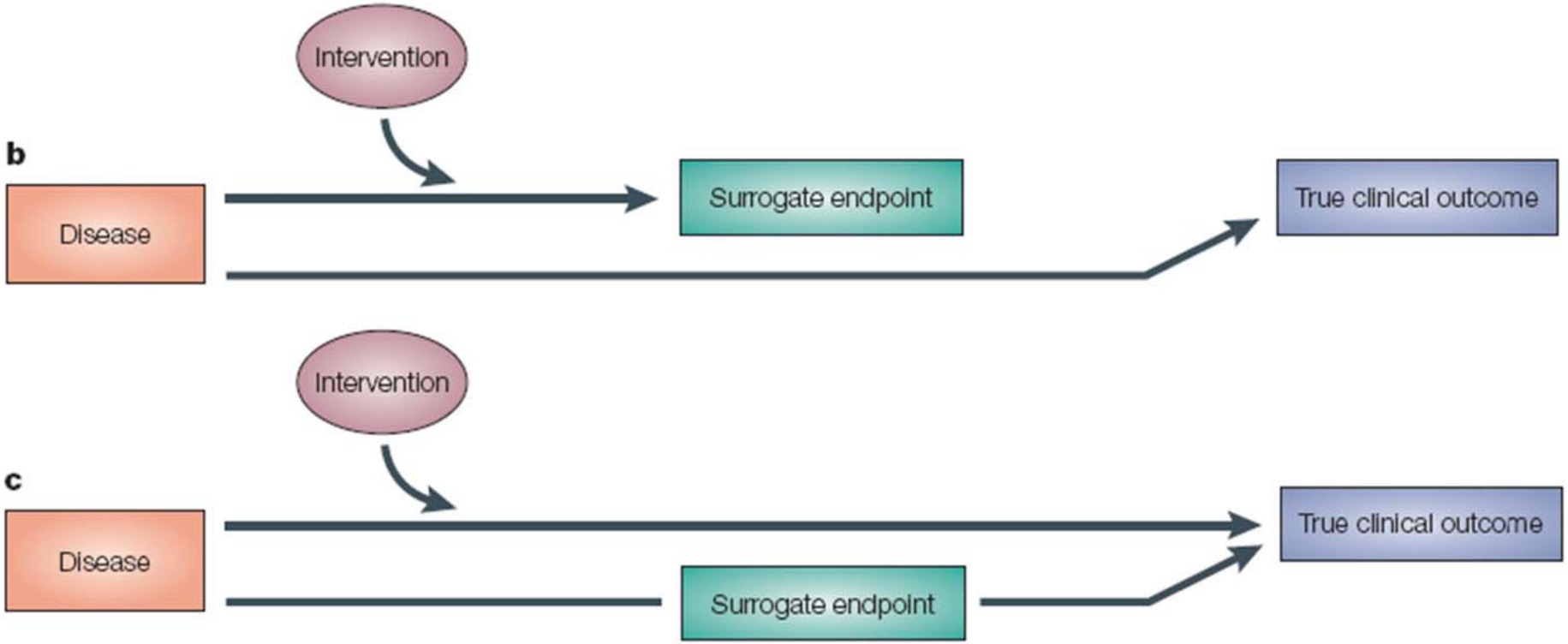
Basis of translational medicine



Proof of Concept (POC): If I modify the target, do I modify the disease ?

Proof of Mechanism (POM): Is my drug really active on the supposed mechanism ?

Many causes of Type II (surrogate) biomarker failure



Frank R, Hargreaves R. Clinical biomarkers in drug discovery and development. Nat Rev Drug Discov. 2003 Jul;2(7):566-80.

Example of validated Type II Biomarkers

Examples of Laboratory Markers

THERAPEUTIC CLASS	BIOMARKER/ SURROGATE	CLINICAL OUTCOME
ANTI-HIV DRUGS	↑ CD4; ↓VIRAL RNA	DELAY AIDS PROGRESSION
LIPID LOWERING DRUGS	↓ CHOLESTEROL	↓ CAD *
ANTI-DIABETIC DRUGS	↓ BLOOD GLUCOSE	↓ MORBIDITY
ANTIBIOTICS	NEG. CULTURE	CLINICAL CURE
DRUGS FOR PROSTATE CA	↓ PSA	TUMOR RESPONSE

*Coronary artery disease

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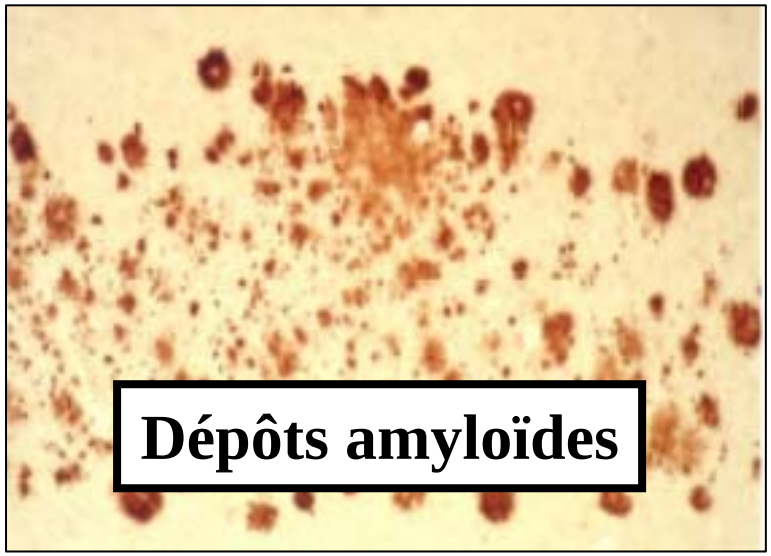
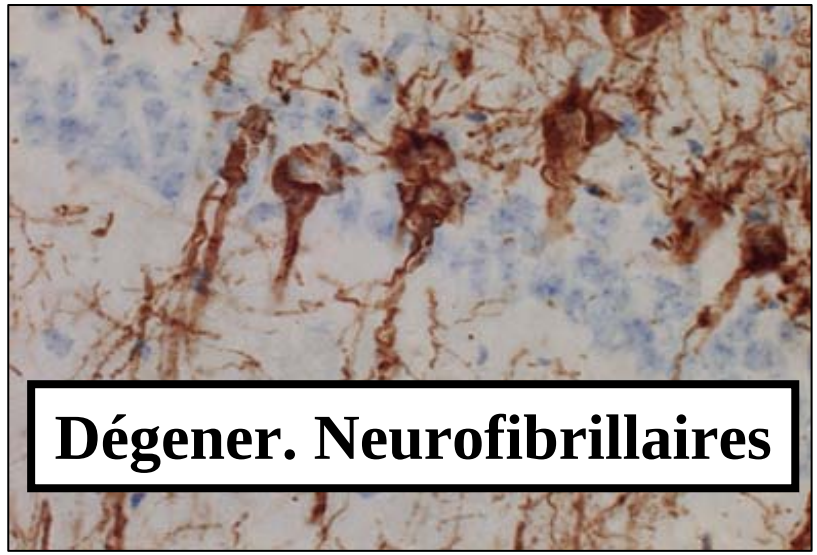
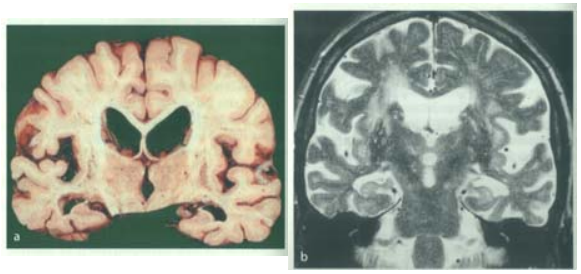
Maladie d'Alzheimer

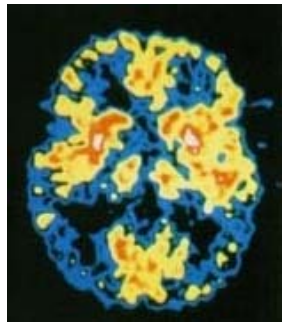




Atrophie cérébrale

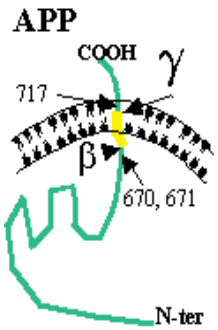


Altérations fonctionnelles

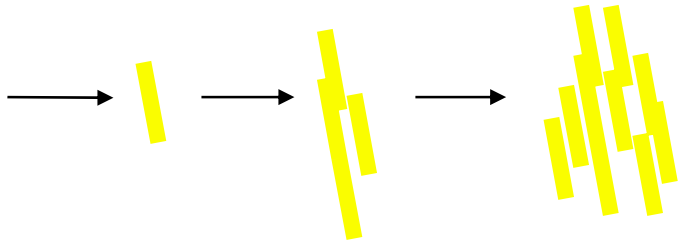


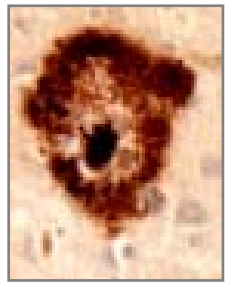
Altérations cognitives Démence

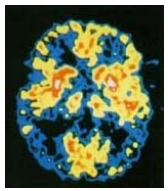
Amyloid cascade hypothesis (simplified)

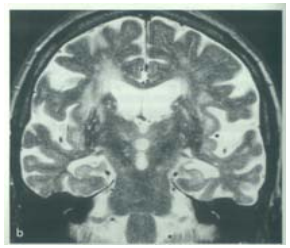


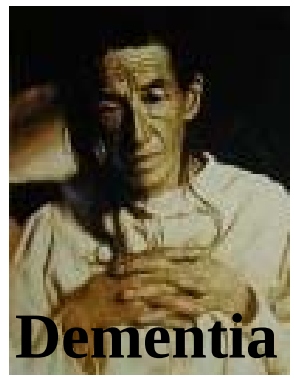
Beta Amyloid











CAA

NFT

Functional alterations

Atrophy Hippoc…

Dementia

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Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria

Bruno Dubois*, Howard H Feldman*, Claudia Jacova, Steven T DeKosky, Pascale Barberger-Gateau, Jeffrey Cummings, André Delacourte, Douglas Galasko, Serge Gauthier, Gregory Jicha, Kenichi Meguro, John O'Brien, Florence Pasquier, Philippe Robert, Martin Rossor, Steven Salloway, Yaakov Stern, Pieter J Visser, Philip Scheltens

Lancet Neurol 2007; 6: 734–46

- Episodic memory impairments

- Supportive features
  - Medial temporal atrophy
  - Alteration of the CSF
  - Alterations of the PET
    - Reduced glucose metabolism in bilateral temporal-parietal regions
    - Amyloid detection by PET (PIB-FDDNP…)

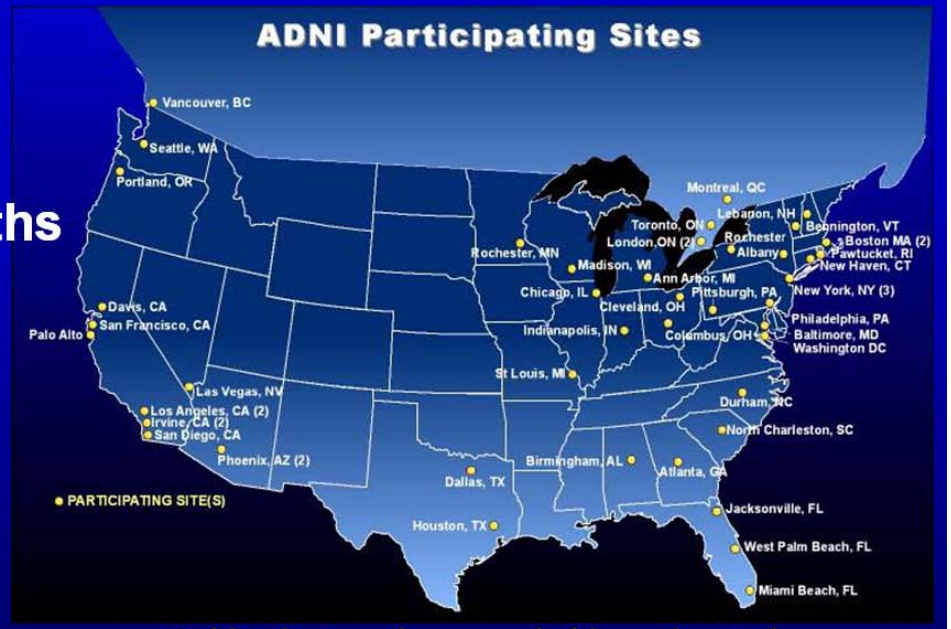
ADNI - Principle

Naturalistic study of AD progression

- 200 NORMAL 3 yrs
- 400 MCI 3 yrs
- 200 AD 2 yrs
- Visits every 6 months

- 57 sites
- Clinical, blood, LP
- Cognitive Tests
- 1.5T MRI

Some also have
- 3.0T MRI (25%)
- FDG-PET (50%)
- PiB-PET (approx 100)

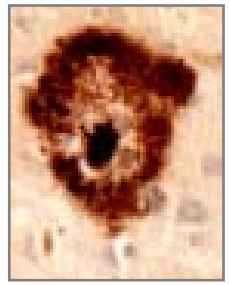


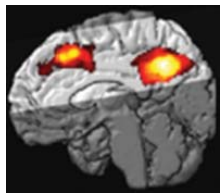
All data in public database: UCLA/LONI/ADNI: No embargo of data

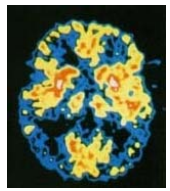
"sample size required to detect 25% change for a given biomarker (during one year)"

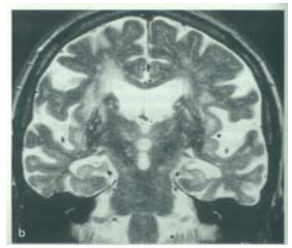
Biomarkers for Alzheimer's disease

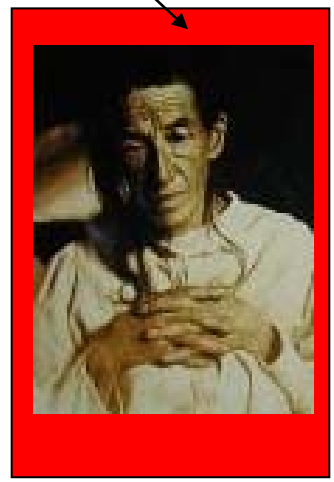
Dépôts Amyloïdes









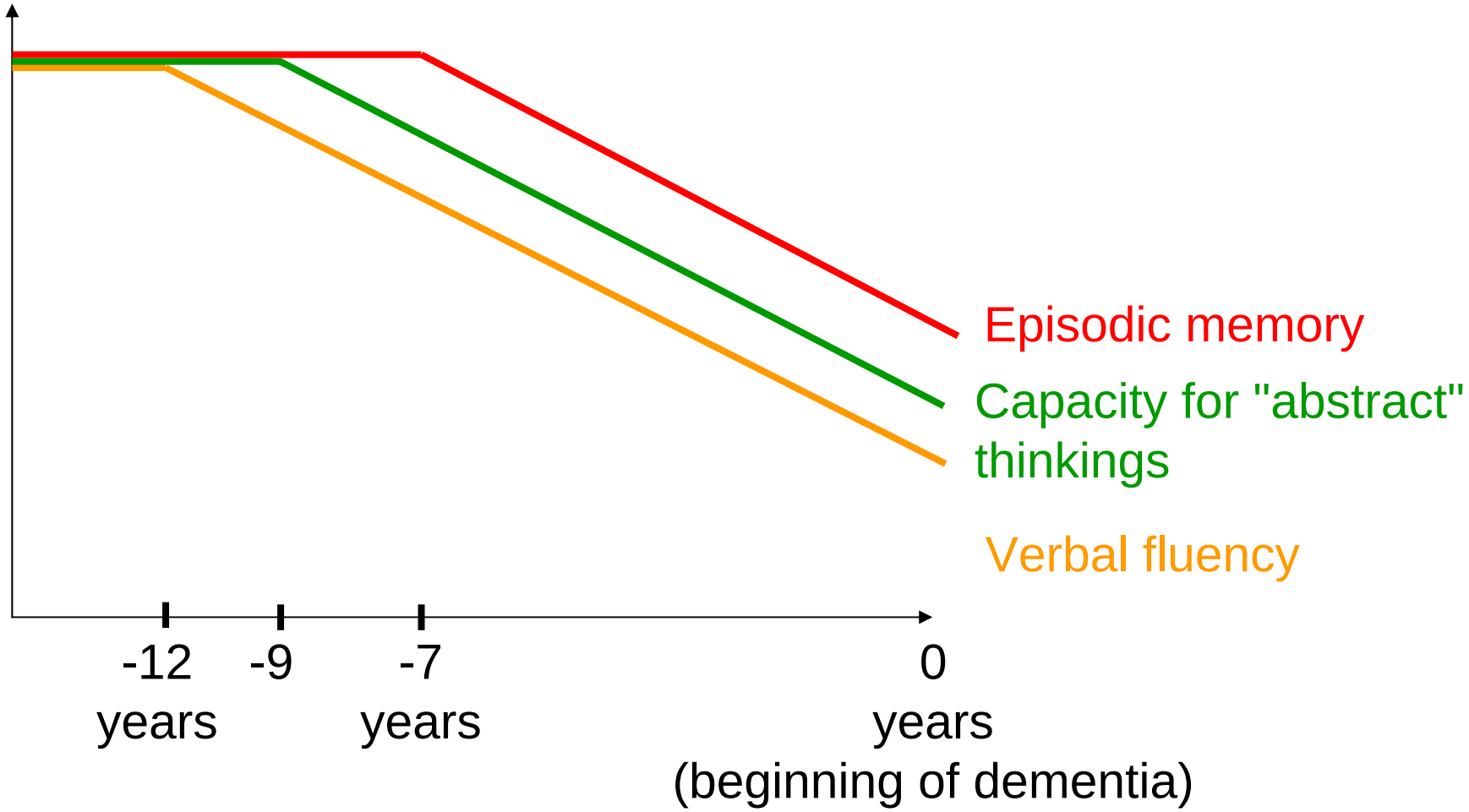


DNF

Altérations fonctionnelles

Atrophie

Cognitive alterations



Results from ADNI

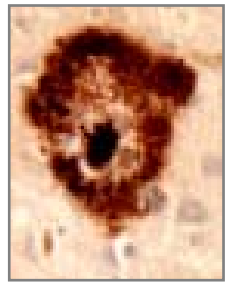
POWER OF CLINICAL/COGNITIVE TESTS 25% CHANGE 1YR STUDY (2 ARM) :

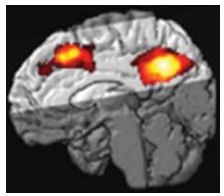
AD (155 Subjects)

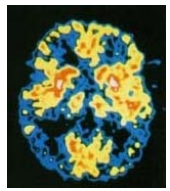
Test	Sample Size
MMSE	803
RAVLT	607
ADAS	592
CDR SOB	449

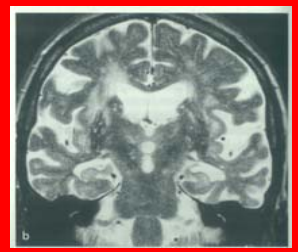
Biomarkers for Alzheimer's disease

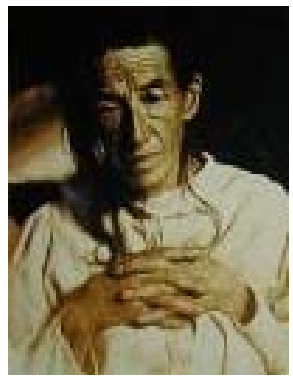
Dépôts Amyloïdes











DNF

Altérations fonctionnelles

Atrophie

Cerebral atrophy in humans with Alzheimer

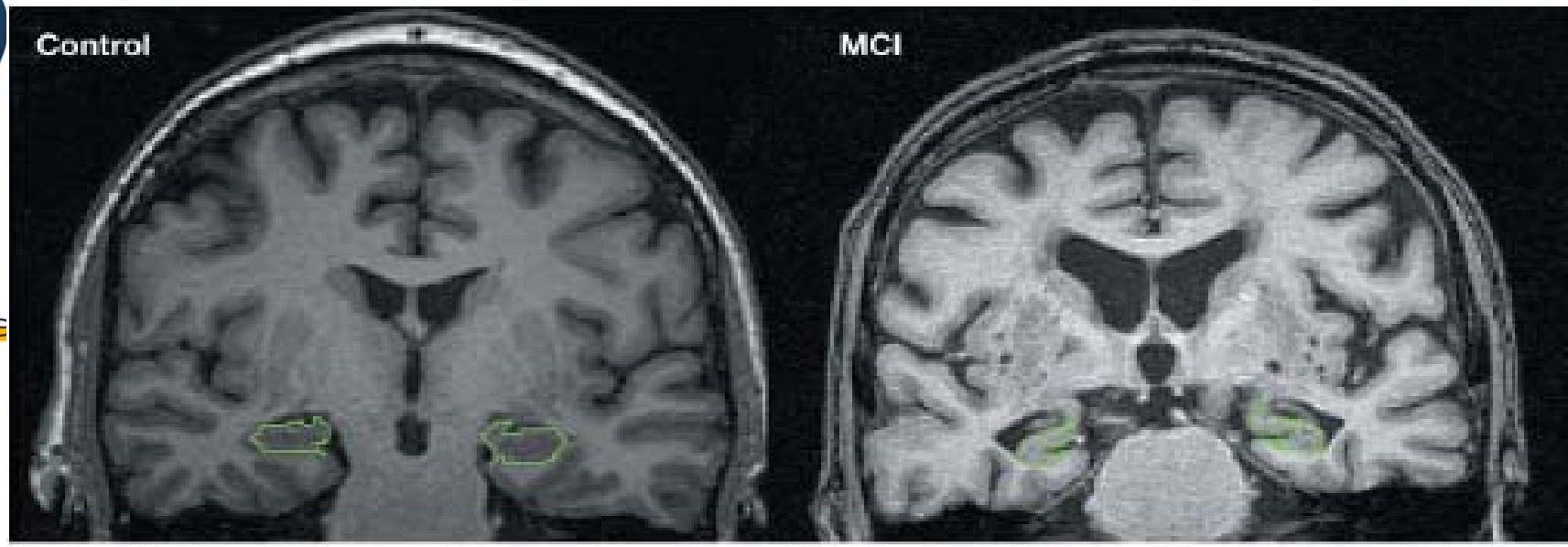
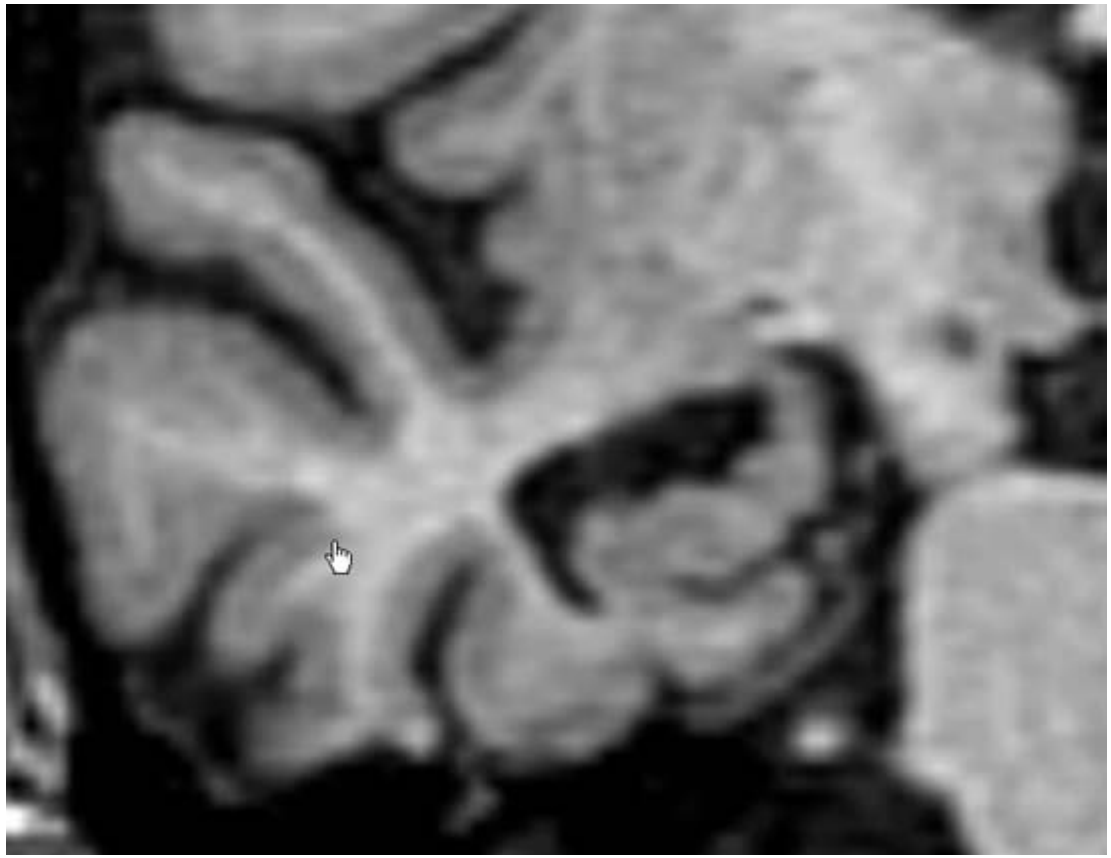


Figure 3 Comparable T1-weighted coronal MRI slices perpendicular to the long axis of the hippocampus showing a normal-sized hippocampus in a control person (total hippocampal volume uncorrected for head size 3,480 mm^3 right and 3,164 mm^3 left) and a smaller hippocampus in an MCI patient (total hippocampal volume uncorrected for head size 2,050 mm^3 right and 2,580 mm^3 left). Images courtesy of L. van der Pol, Alzheimer Center and Image Analysis Center, Vrije Universiteit Medical Center, Amsterdam, The Netherlands.

- Starts in the hippocampus then spread all over the brain

Cerebral atrophy in humans with Alzheimer

Progression from MCI to AD (10 years)



Clifford Jack, ISMRM, 2008

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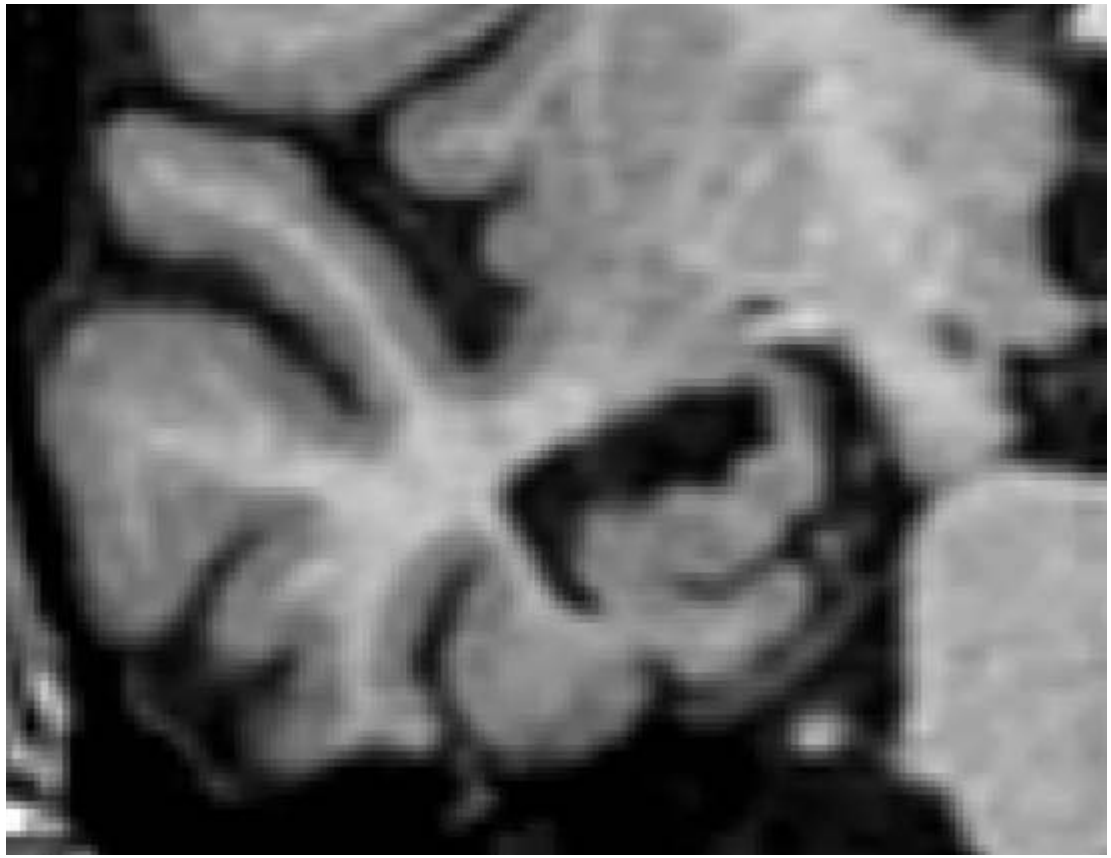

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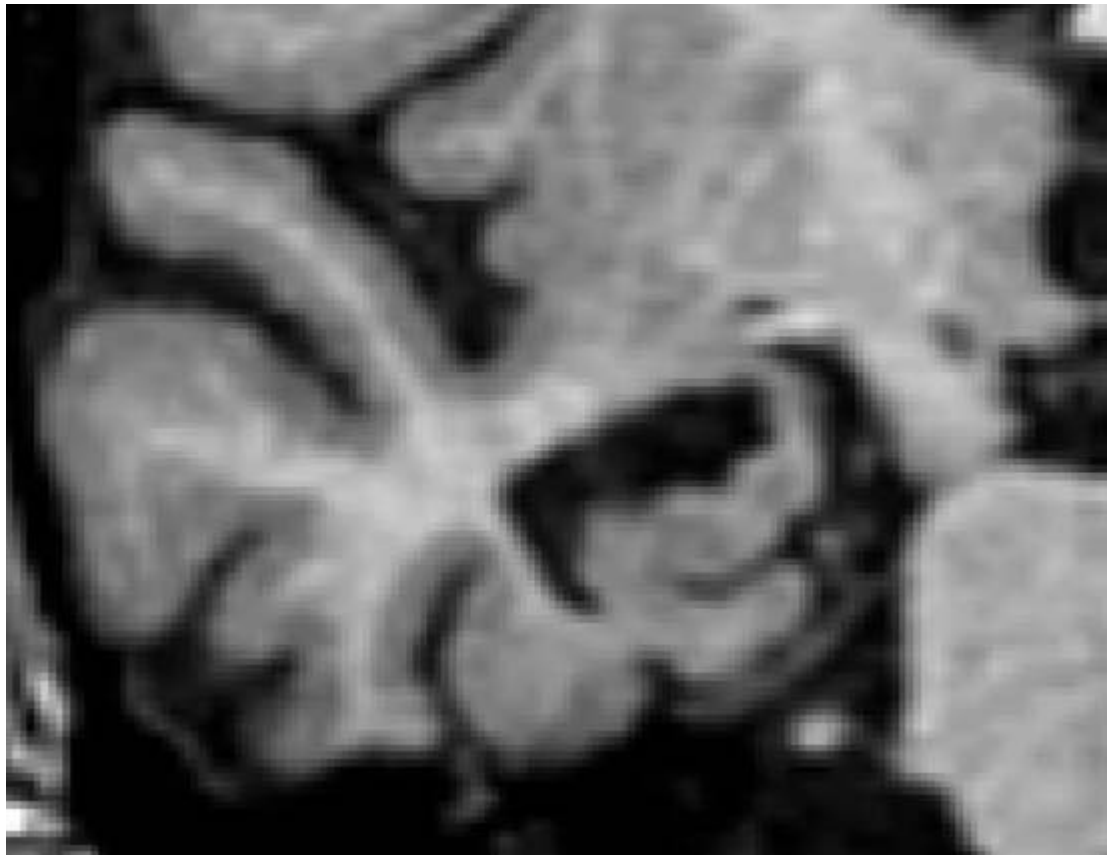

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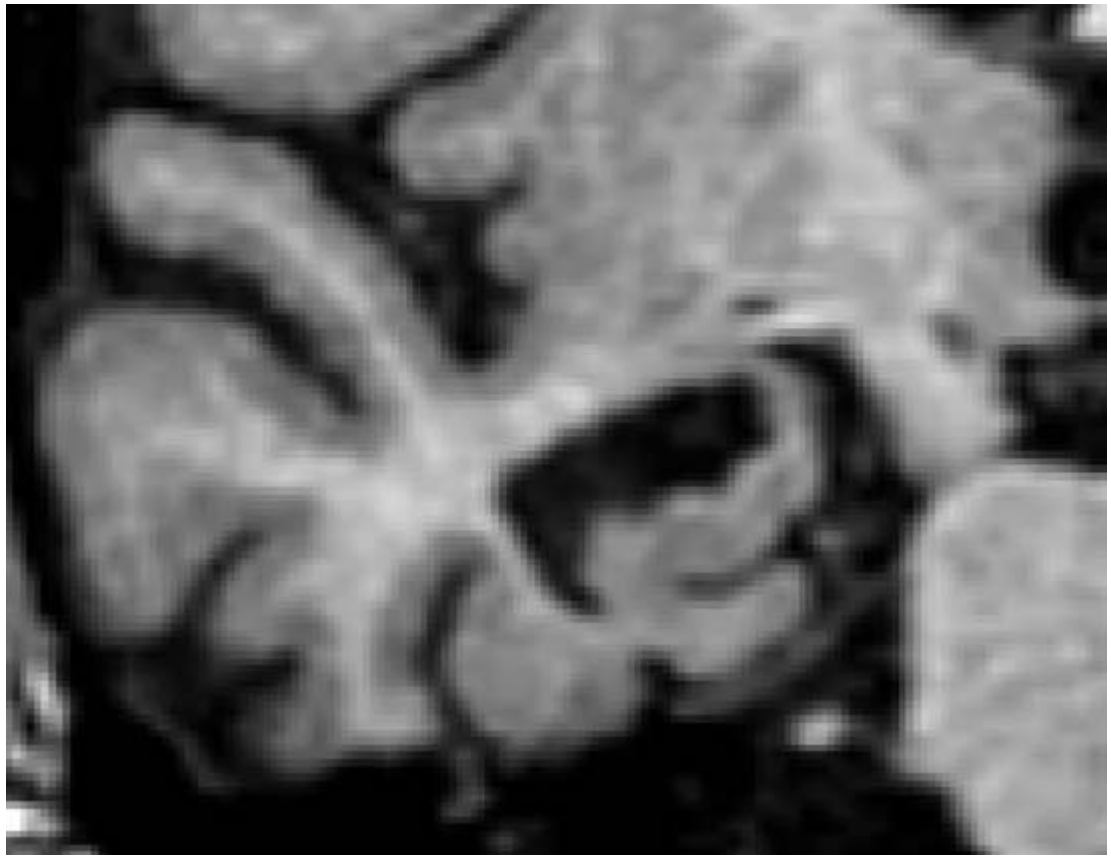

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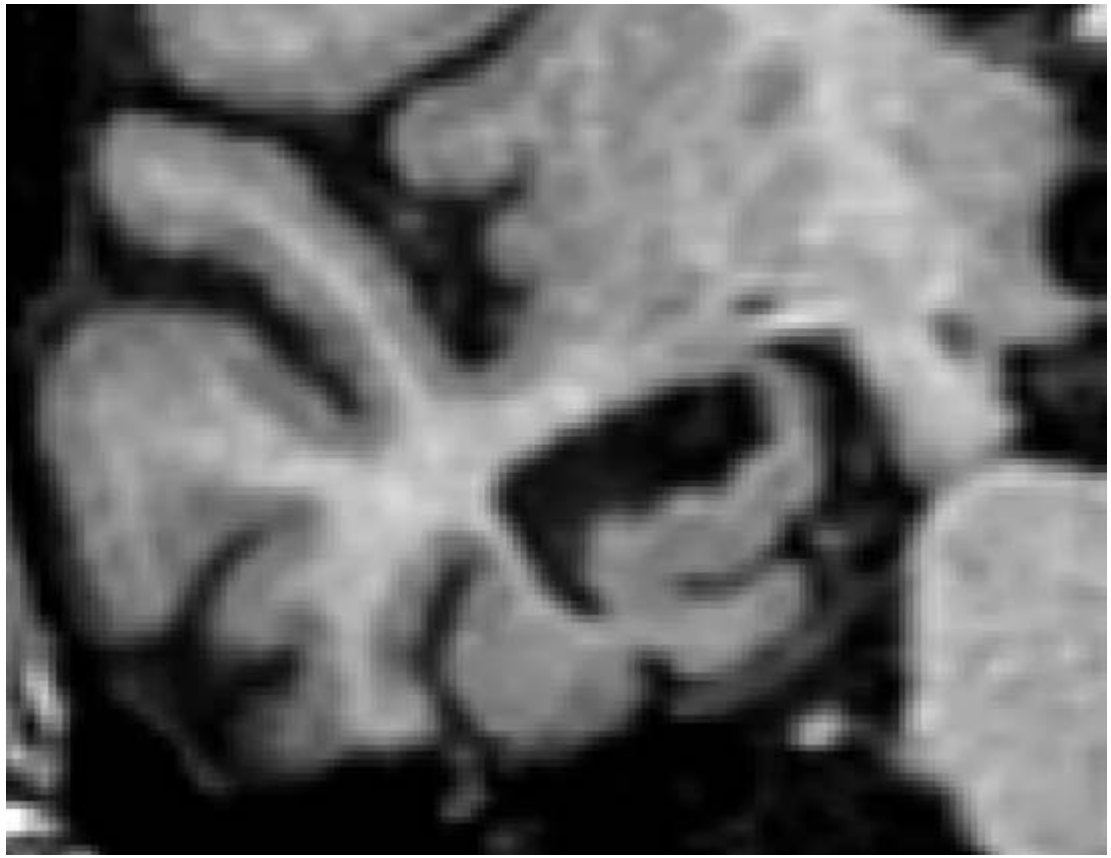

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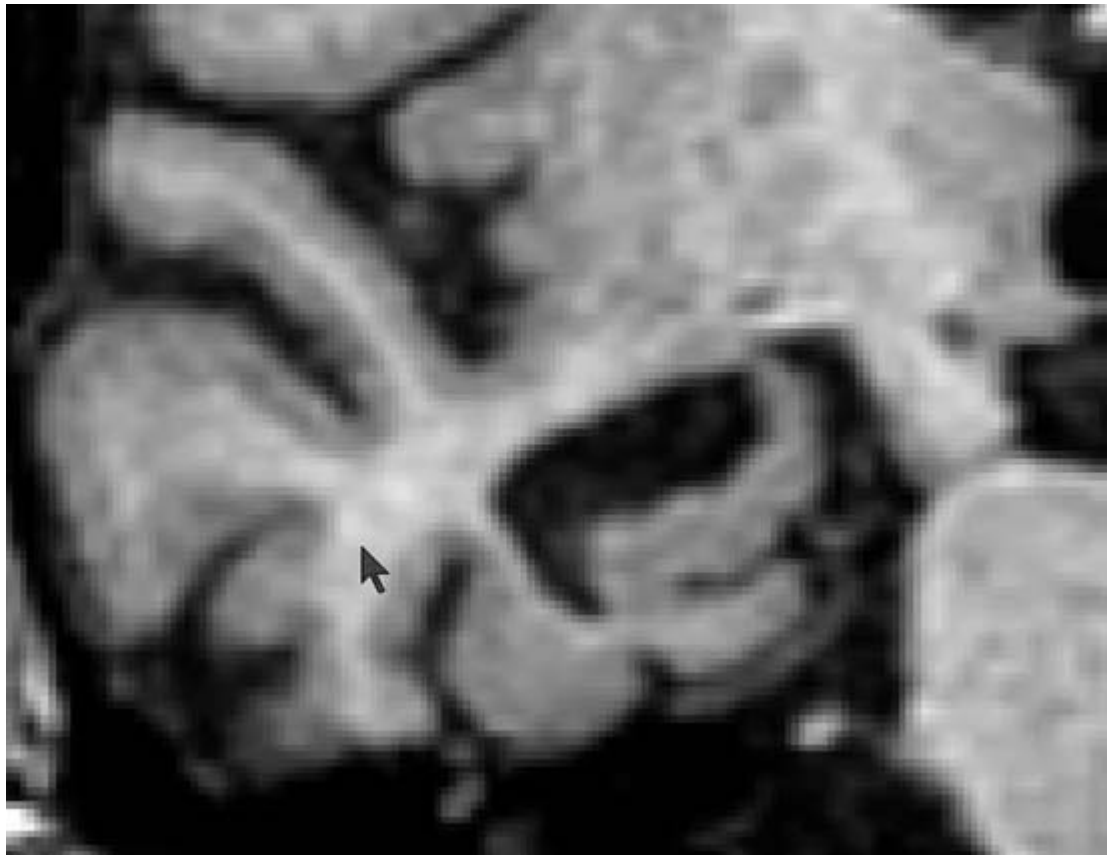

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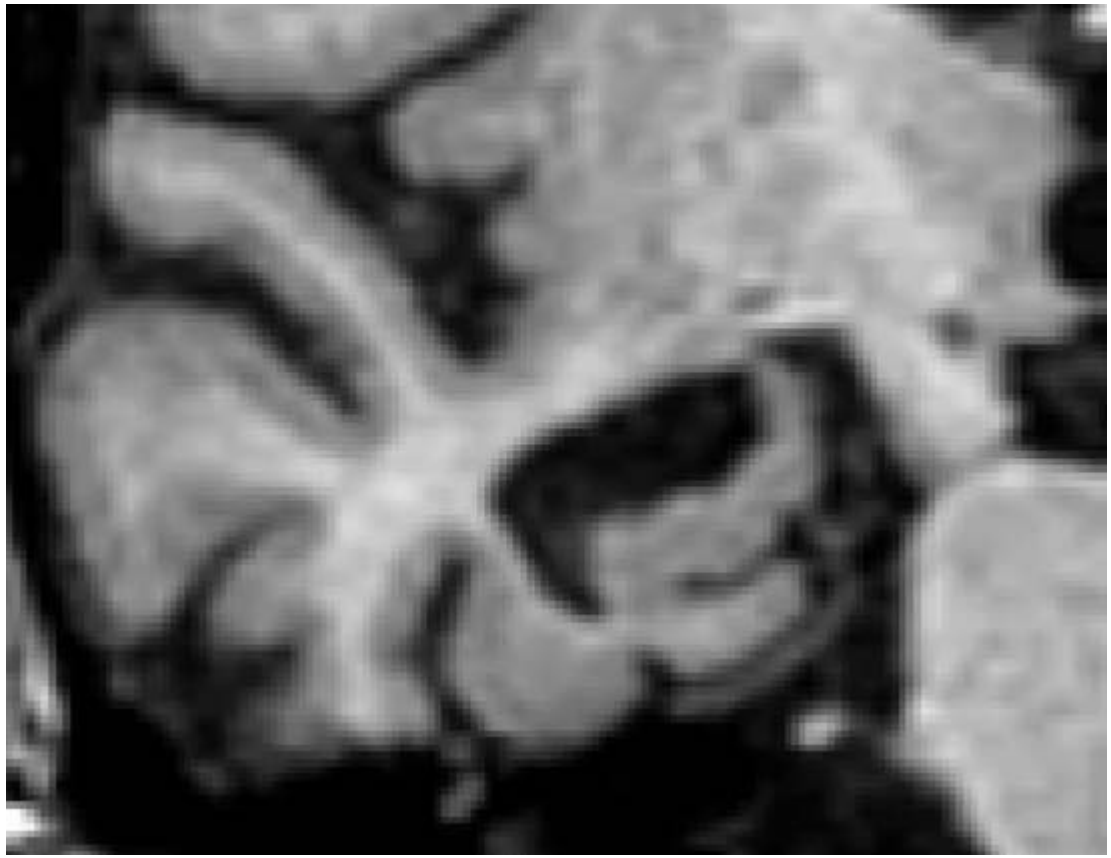

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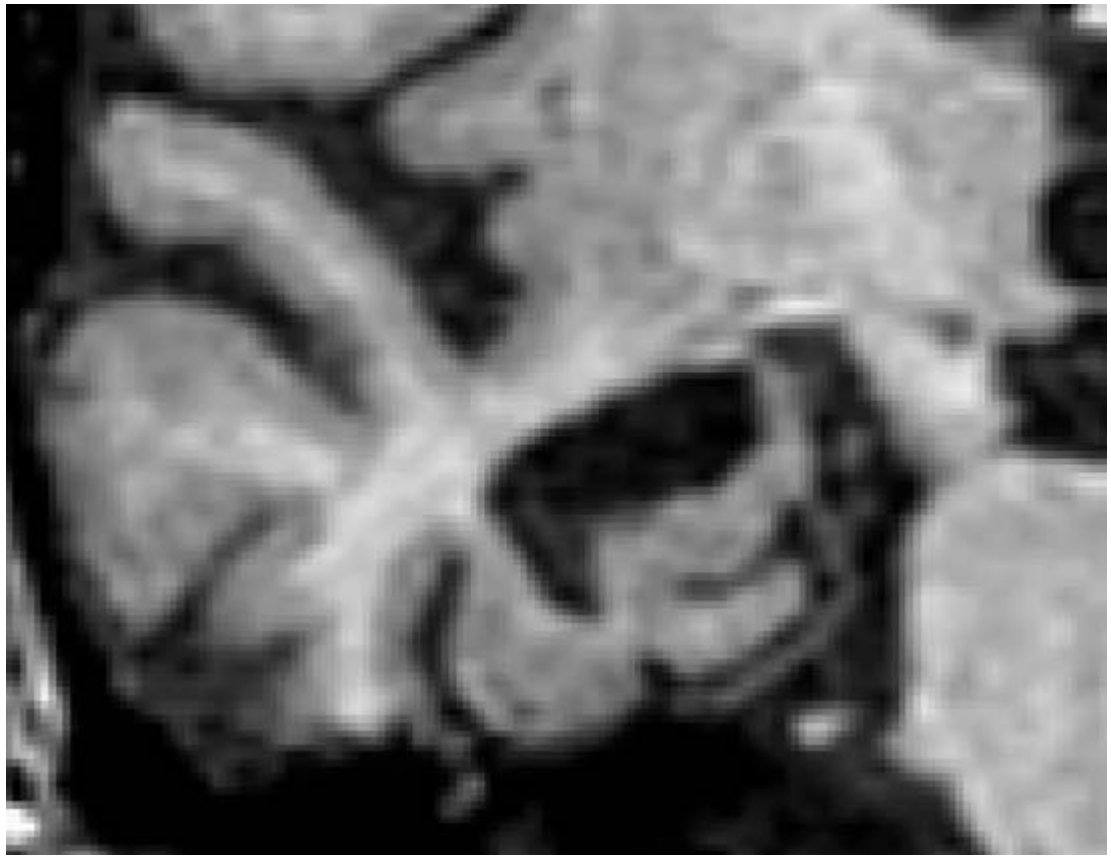
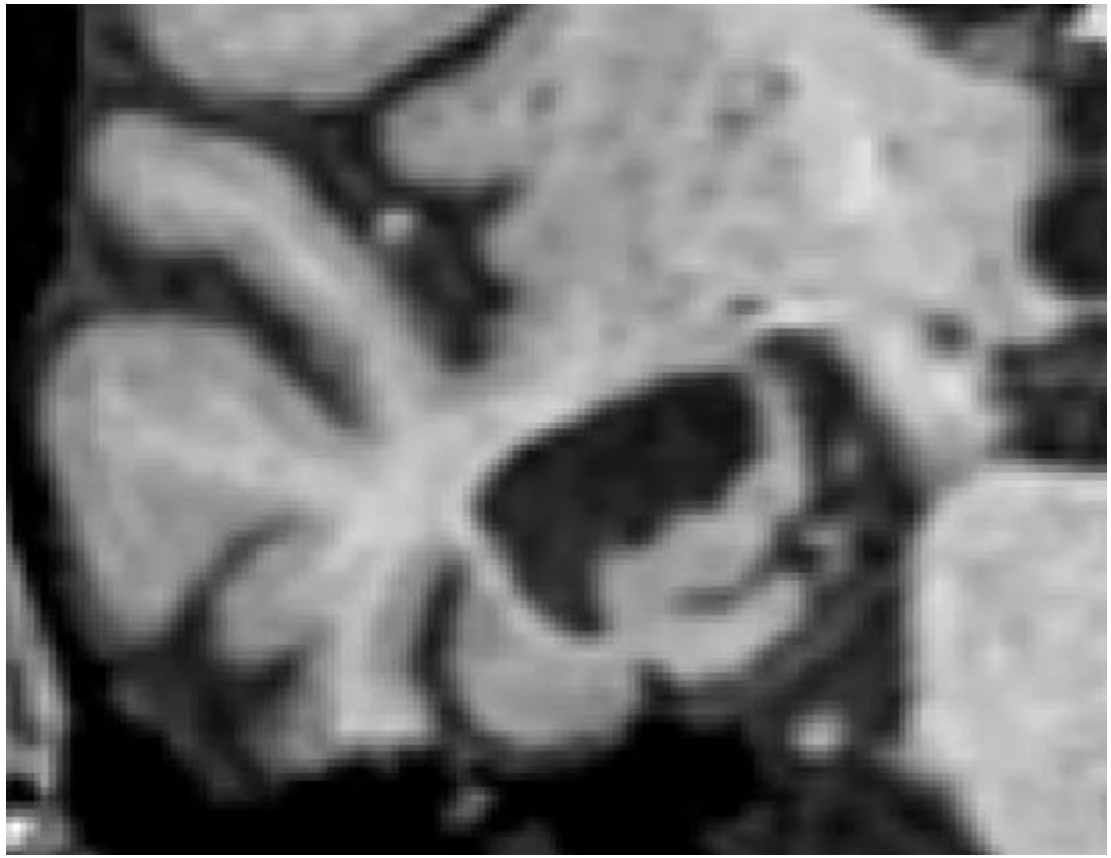


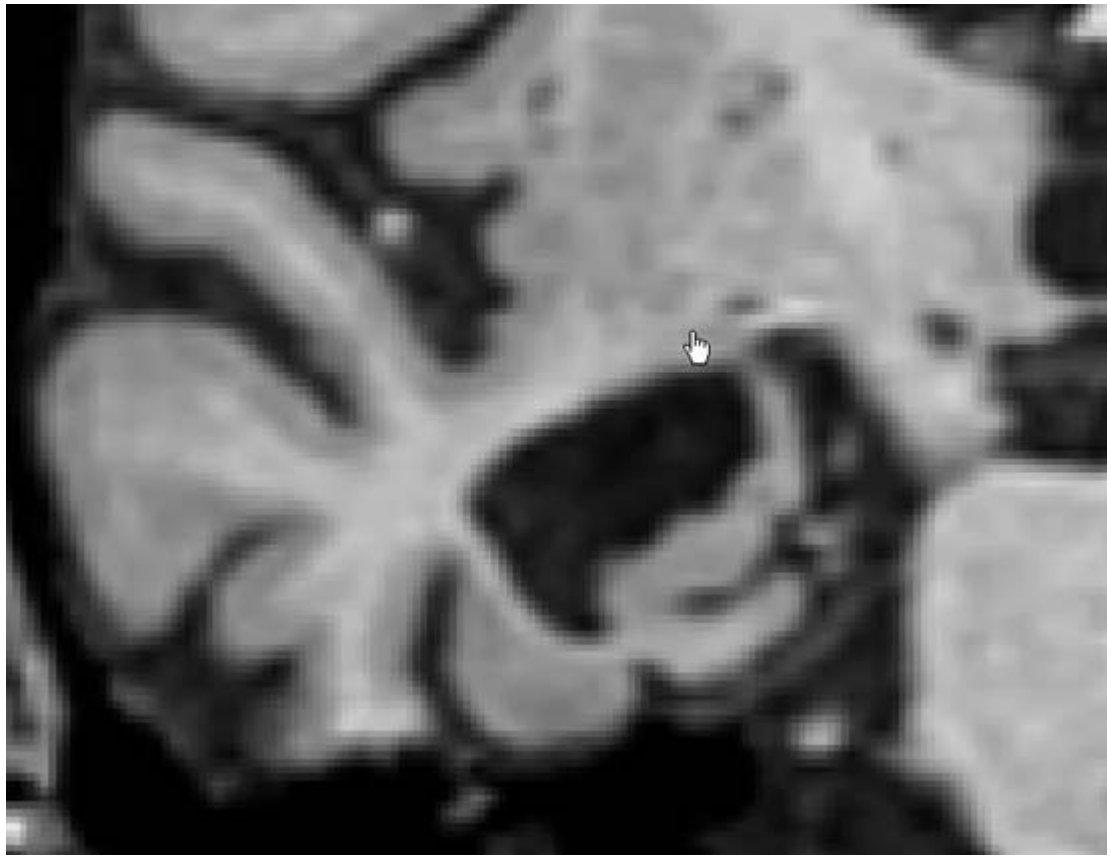
Clifford Jack, ISMRM, 2008

Progression from MCI to AD (10 years)



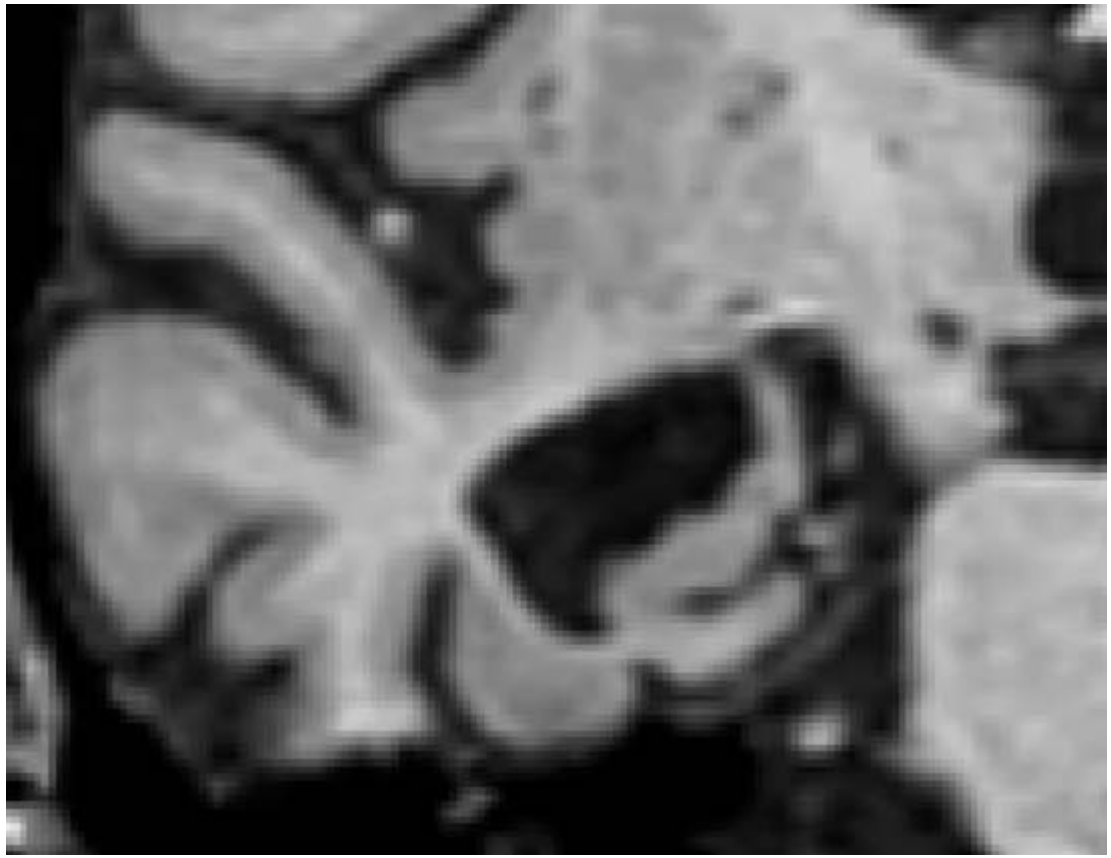
Clifford Jack, ISMRM, 2008

Progression from MCI to AD (10 years)



Clifford Jack, ISMRM, 2008

Progression from MCI to AD (10 years)



Clifford Jack, ISMRM, 2008

Results from ADNI

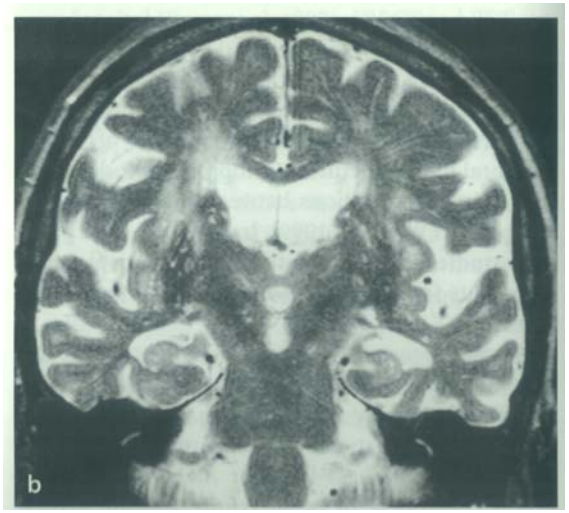
POWER OF EVALUATION OF BRAIN ATROPHY 25% CHANGE 1YR STUDY (2 ARM) :

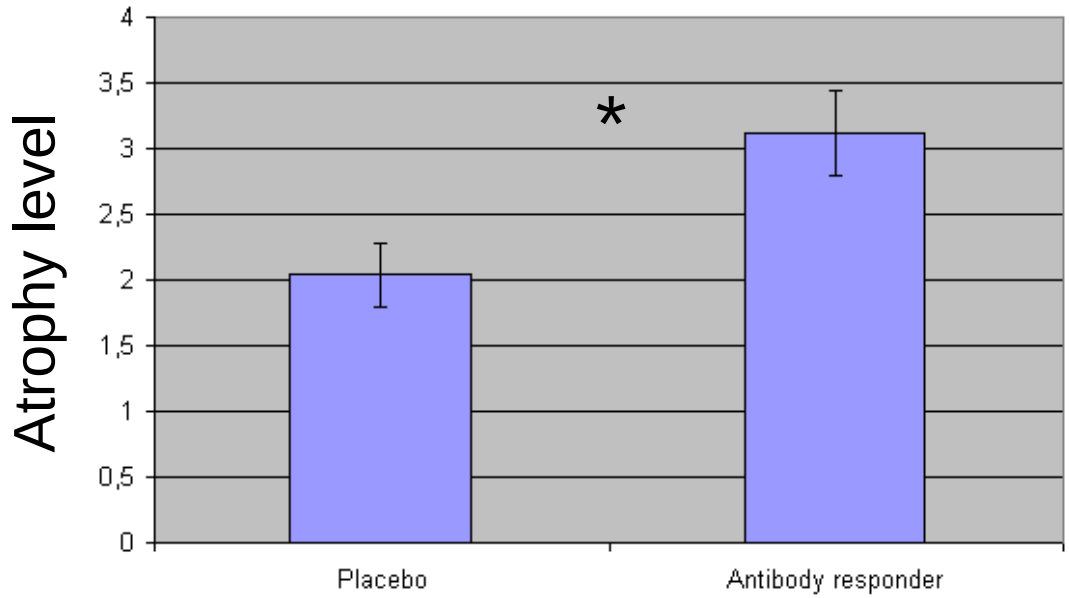
AD (69 Subjects)

Lab	Variable	SS/arm
Alexander	L. Hippo. Formation	334
Schuff - FS	Hippocampus	201
Dale	Hippocampus	126
Schuff - FS	Ventricles	119
Studhome	CV - % change	106
Fox	VBSI % change	105
Fox	BSI % change	71
Thompson	CV - % change	54

Effects of Aβ immunization (AN1792) on MRI measures of cerebral volume in Alzheimer disease

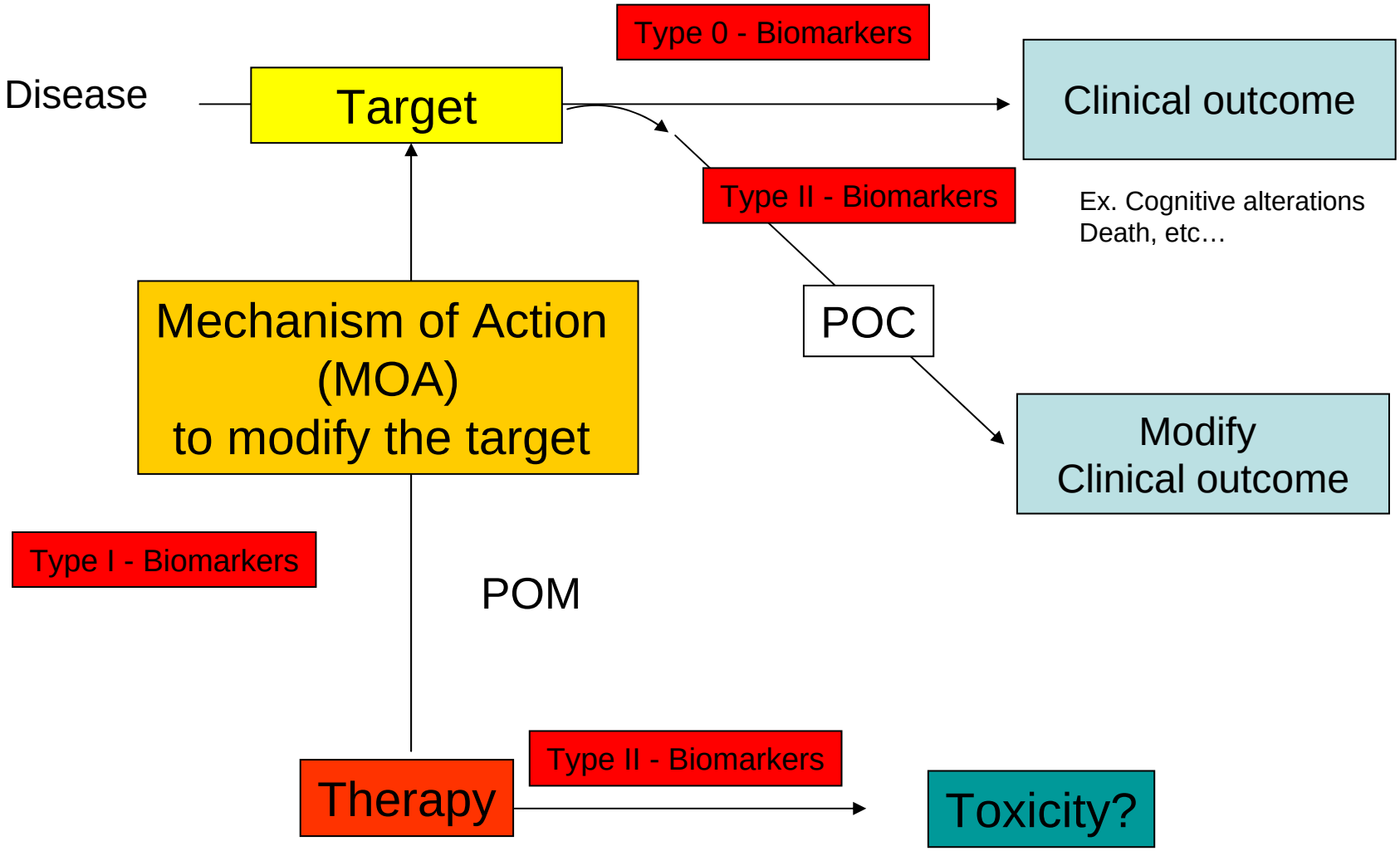
N.C. Fox, MD, FRCP; R.S. Black, MD; S. Gilman, MD, FRCP; M.N. Rossor, MD, FRCP; S.G. Griffith, MD, PhD, MRCP; L. Jenkins, PhD; and M. Koller, MD, MPH, for the AN1792(QS-21)-201 Study Team*





A good marker for the diagnosis (T0 biomarker)
can be questionable for therapeutic follow-up (T2 biomarker)

Cerebral atrophy ?

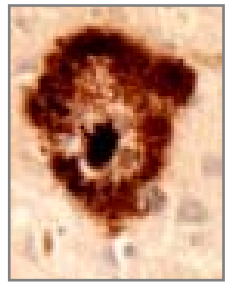


Proof of Concept (POC): If I modify the target, do I modify the disease ?

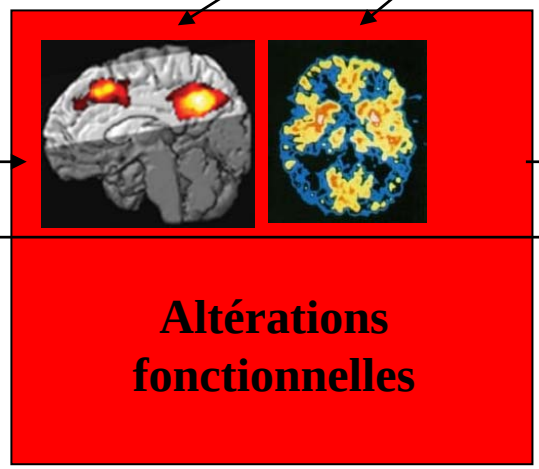
Proof of Mechanism (POM): Is my drug really active on the supposed mechanism ?

Maladie d'Alzheimer : Quels biomarqueurs ?

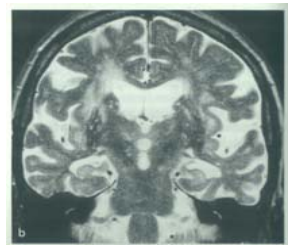
Dépôts Amyloïdes



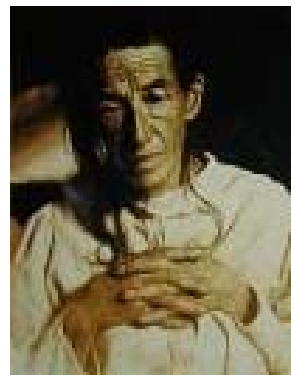
DNF



Altérations fonctionnelles

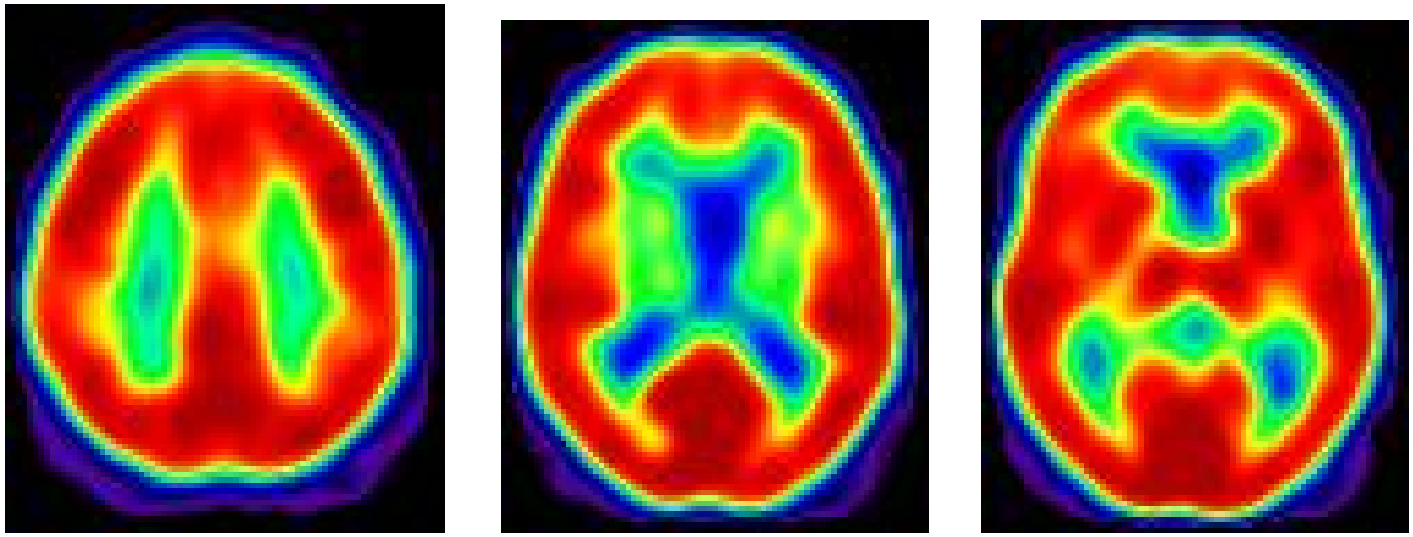


Atrophie

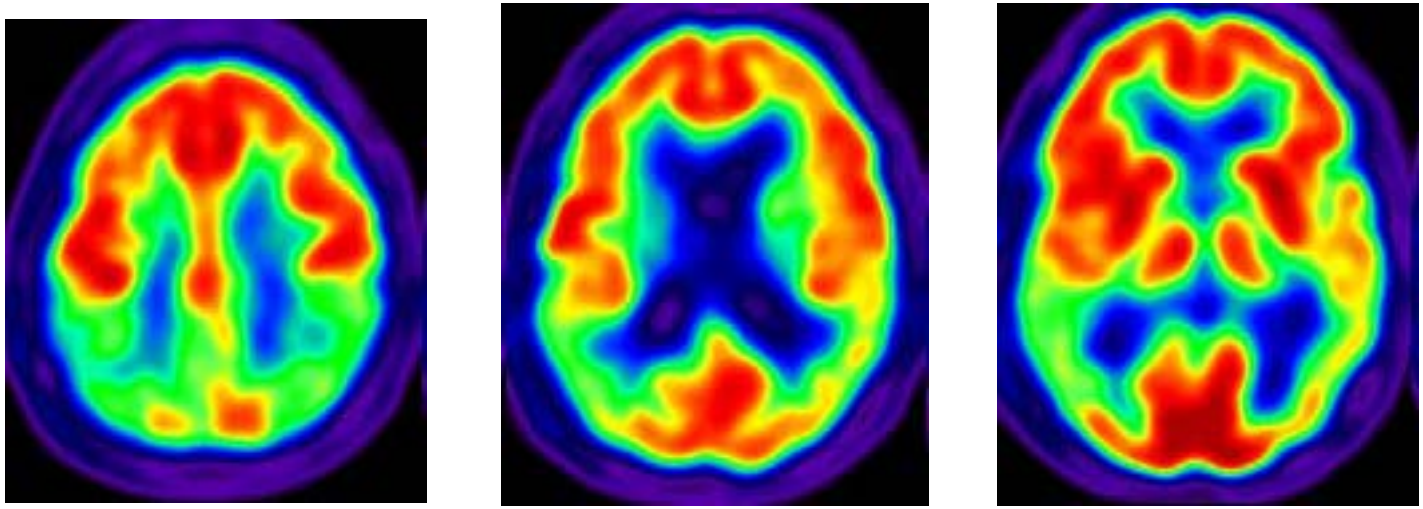


Cerebral metabolism

Normal



AD

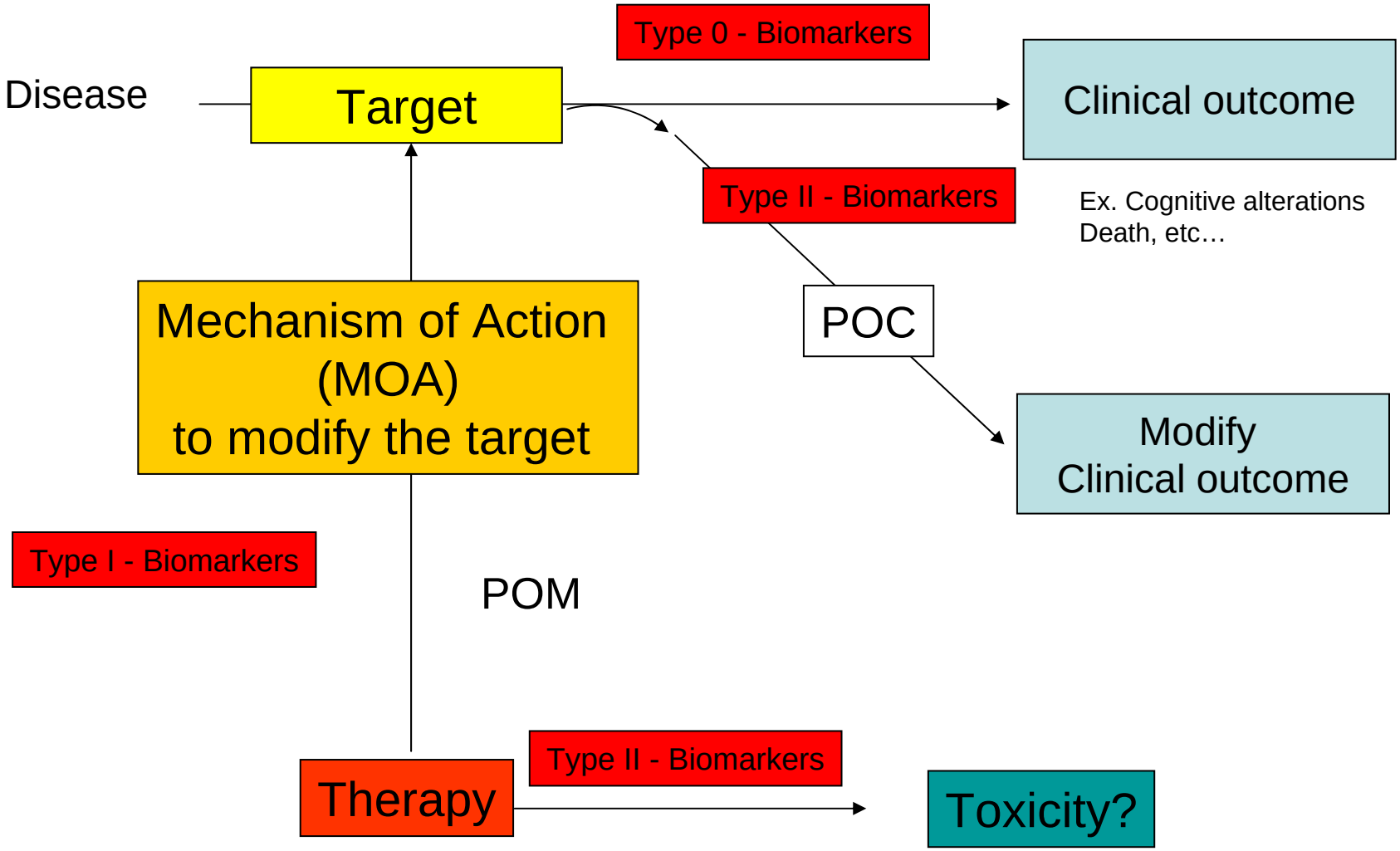


POWER OF EVALUATION OF BRAIN METABOLISM 25% CHANGE 1YR STUDY (2 ARM) :

AD (36 Subjects)

Lab	Variable	SS/arm
Foster	hypometabolism1	638
Foster	hypometabolism2	549
Jagust	ROI-avg	412
Reiman	CV-fROI	96

Cerebral metabolism ?



Proof of Concept (POC): If I modify the target, do I modify the disease ?

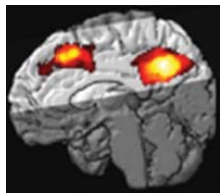
Proof of Mechanism (POM): Is my drug really active on the supposed mechanism ?

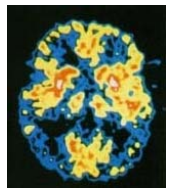
Cerebral metabolism

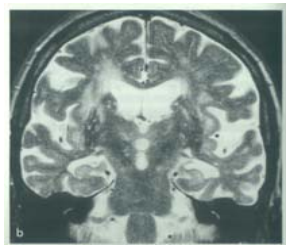
- Reflect clinical history of the disease
  - Disease progression biomarker (Type 0)
- Can be a better marker of clinical amelioration following treatment as compared to MRI

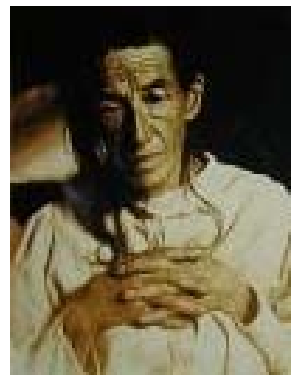
Biomarkers for Alzheimer's disease

Dépôts Amyloïdes







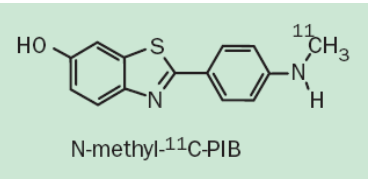


DNF

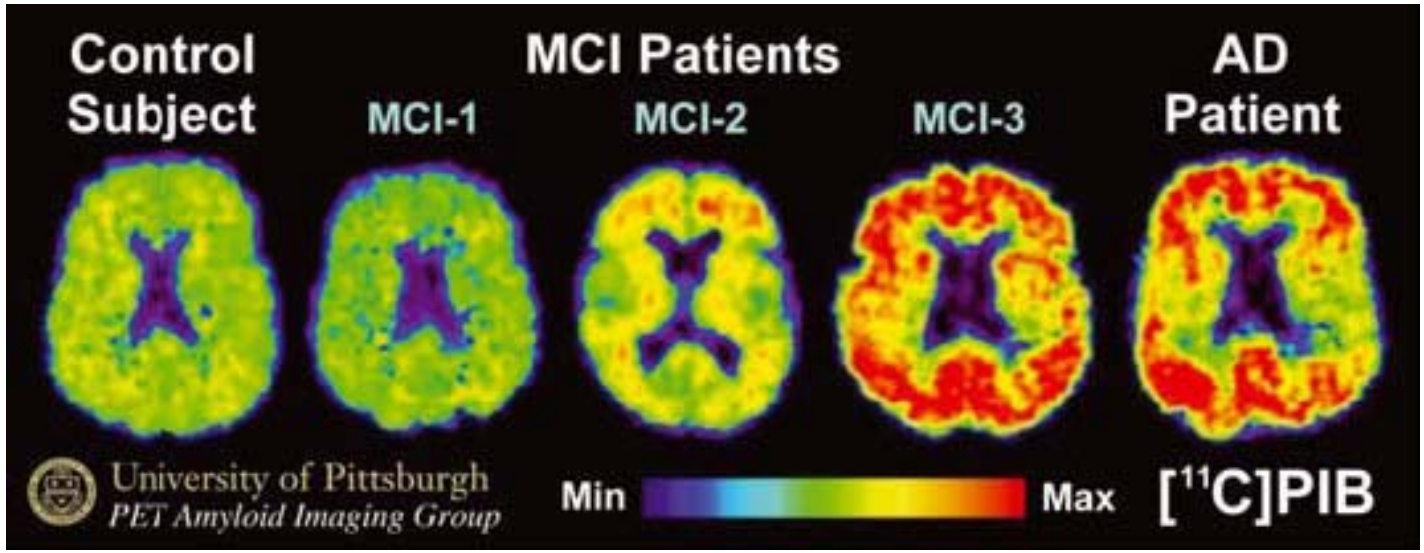
Altérations fonctionnelles

Atrophie

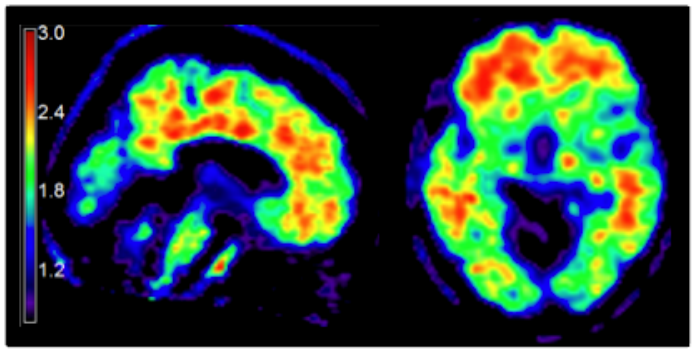
Amyloid imaging in humans (by PET)



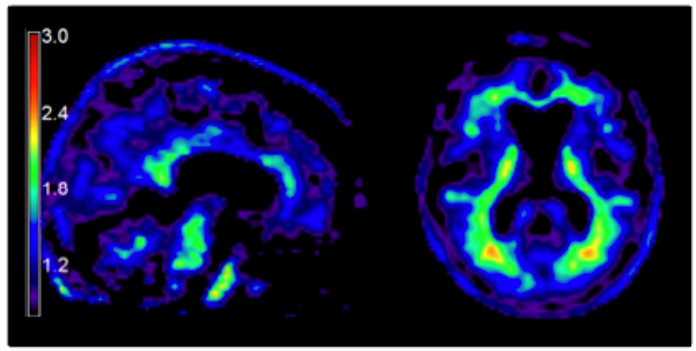
N-methyl-^{11}C-PIB



Amyvid

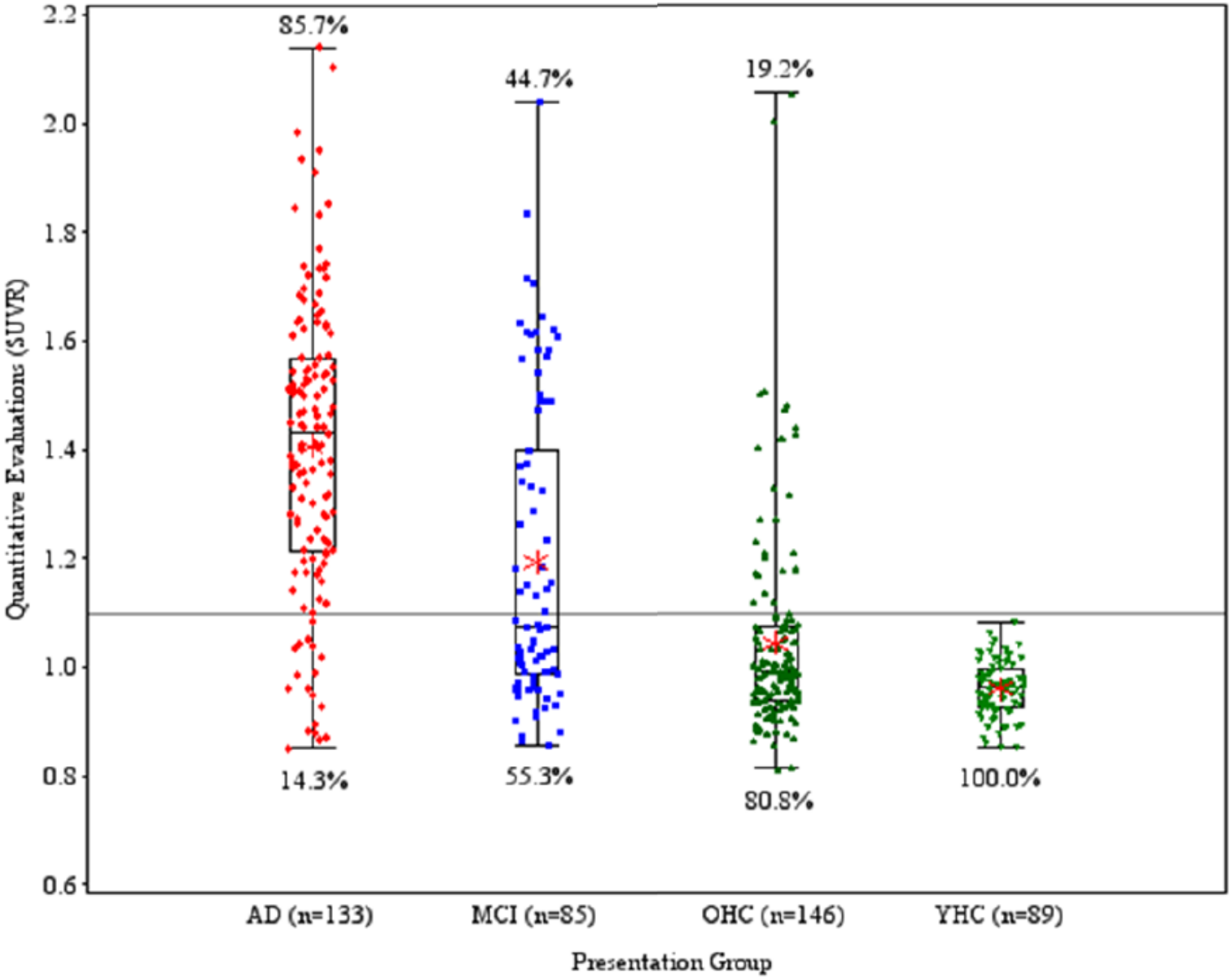


"Probable AD" Patient



Cognitively Normal Elderly

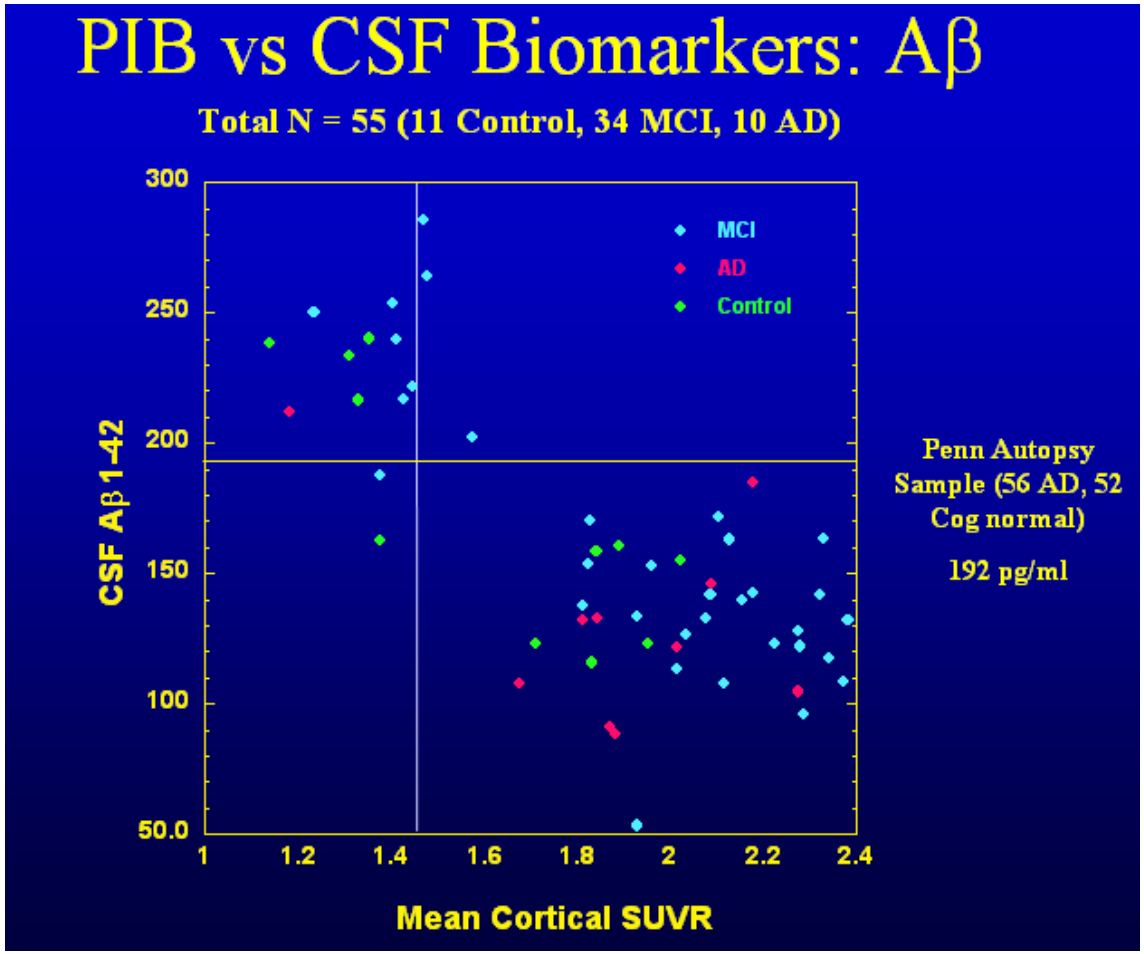
Figure 5: Distribution of Quantitative SUVR Values by Presentation Group



Amyloid load

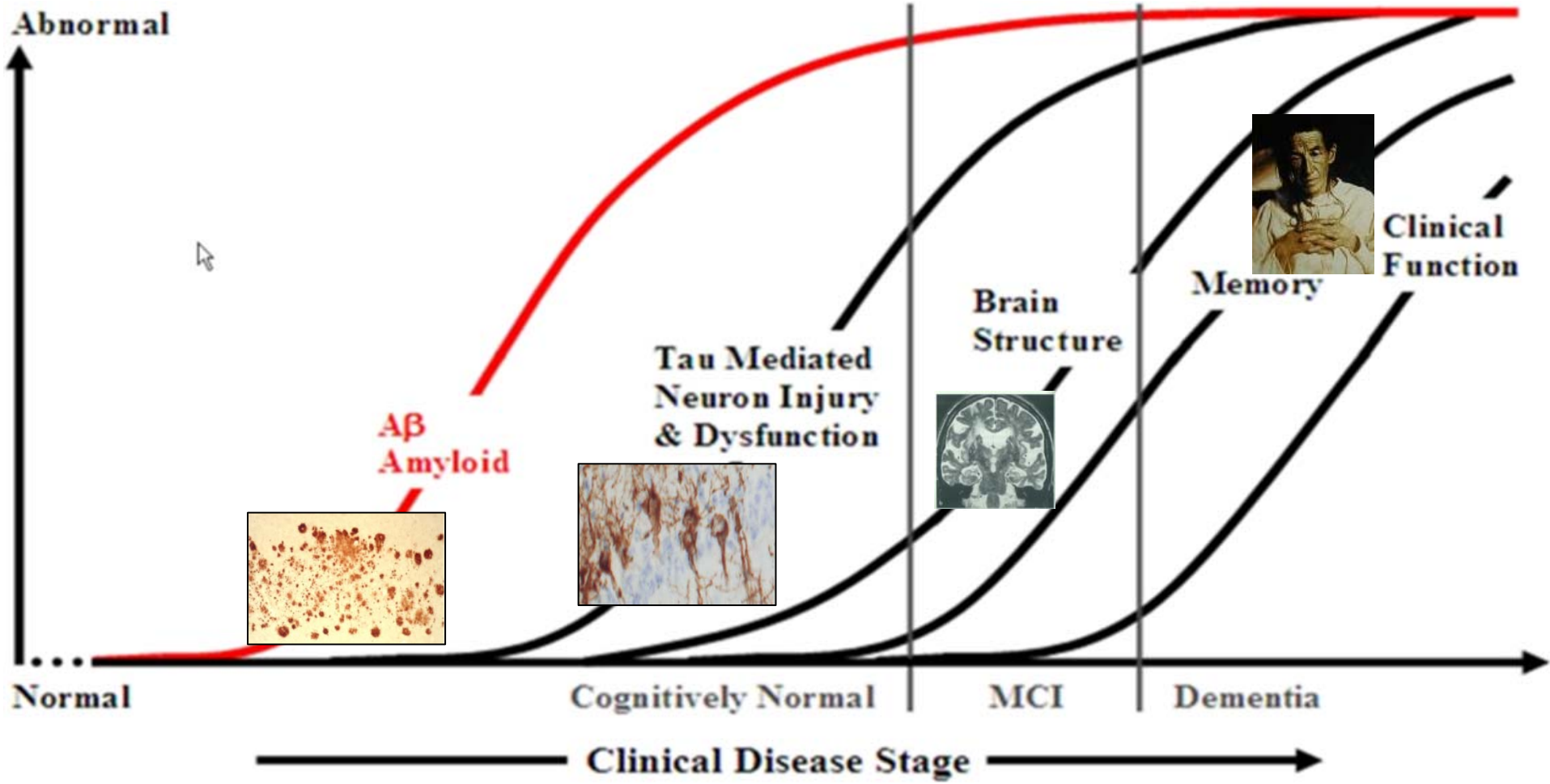
- Reflect early history of the disease ?
  - But is not a disease progression biomarker
- Related to therapy (for amyloid reducing therapies = Type II)

PIB versus CSF biomarkers



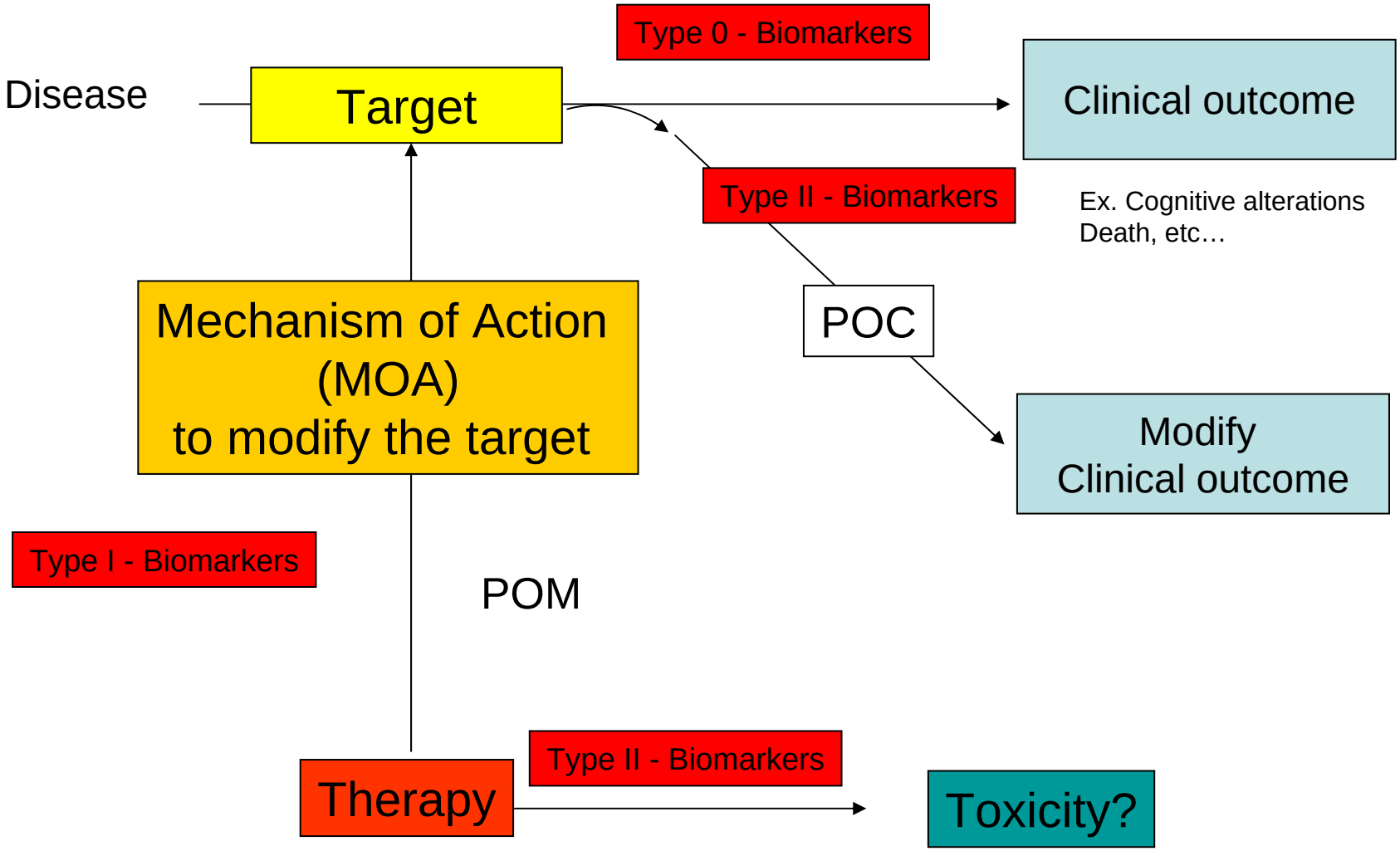
- PIB gives info similar to LP
- But LP gives more than amyloid
- Price is not the same…

Biomarker – Chronology in the disease



Jack CR, Jr. (2010). Lancet Neurol 9:119-128.

Amyloid plaques ?



Proof of Concept (POC): If I modify the target, do I modify the disease ?

Proof of Mechanism (POM): Is my drug really active on the supposed mechanism ?

Overview

- Concepts of Biomarkers
- Overview on Alzheimer's disease
- Biomarkers in humans
  - Dubois Criteria / ADNI initiative
  - Cerebral atrophy (MRI)
  - Brain metabolism (PET)
  - Amyloid plaques (PET)
- Biomarkers in animal models: Why/how can we use of biomarkers in animal models?
  - Characterization of animal models
    - Identification of biological mechanisms and targets
    - Choice of marker versus biomarkers ?
  - Therapeutic evaluations
    - "Classical view" of translational medicine
    - Translational bridgesTherapeutic evaluations
  - Preparation of clinical trials

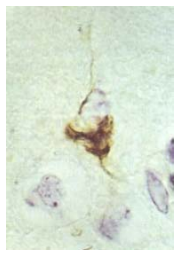
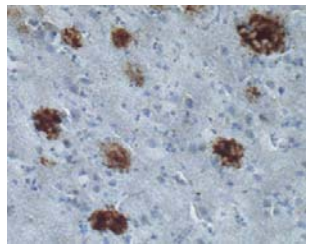
Phenotyping and endophenotyping in humans

Natural history of the disease

Disease → Target → Endophenotypes → Clinical outcome (Phenotype)

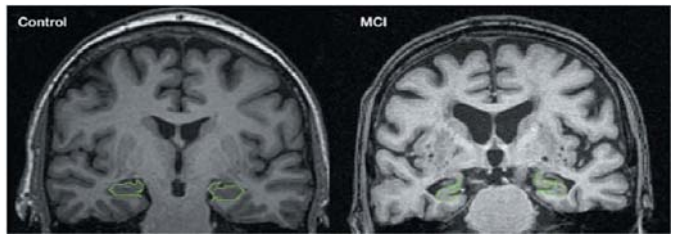
Ex. Cognitive alterations
Death, etc…

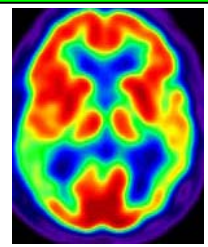
Markers


Biomarkers

Diagnostic | Longitudinal | Functional





Understand the disease

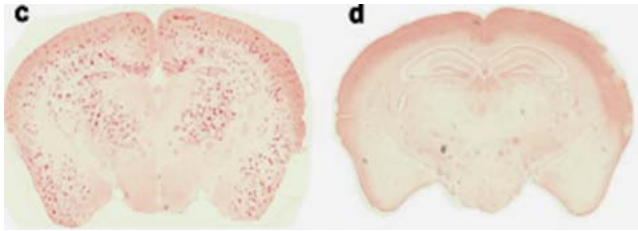
Identification of biological mechanisms and targets

Phenotyping and endophenotyping in animal studies

Disease → Target → Endophenotypes → Clinical outcome (Phenotype)

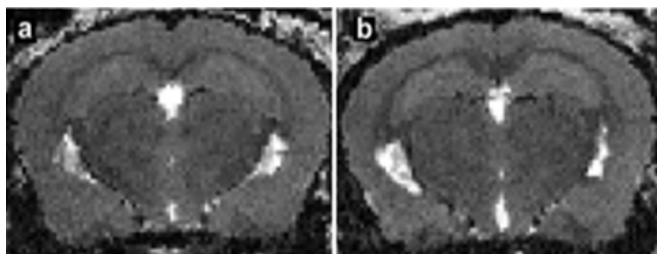
Ex. Cognitive alterations
Death, etc…

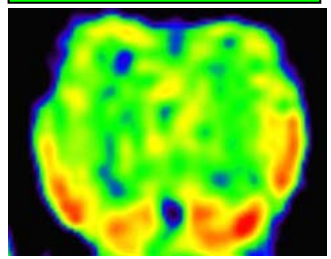
Markers



Biomarkers

Diagnostic | **Longitudinal** | **Functional**





-Non invasive
-Slightly invasive

Understand the disease

Why/how can we use of biomarkers in animal models

- Characterization of animal models
  - Identification of biological mechanisms and targets
    - Choice of marker versus biomarkers ?
    - Non invasive studies in animal

- Therapeutic evaluations
  - "Classical view" of translational medicine
  - Translational bridges
    - Evaluation of efficacy in animals
    - Evaluation of toxicity in animals

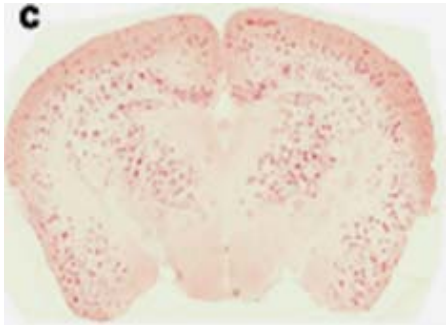
- Therapeutic evaluations
  - Preparation of clinical trials

Characterization of animal models:
Ex of the detection of amyloid plaques

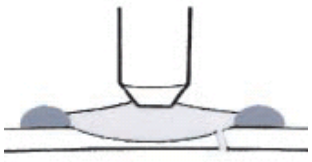
Markers

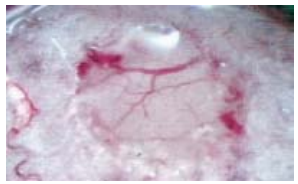
Biomarkers

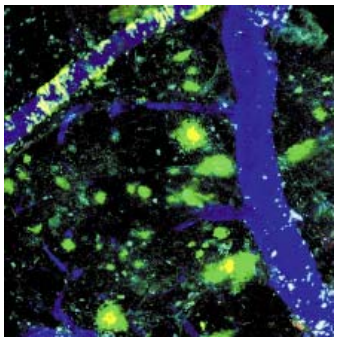
Histology



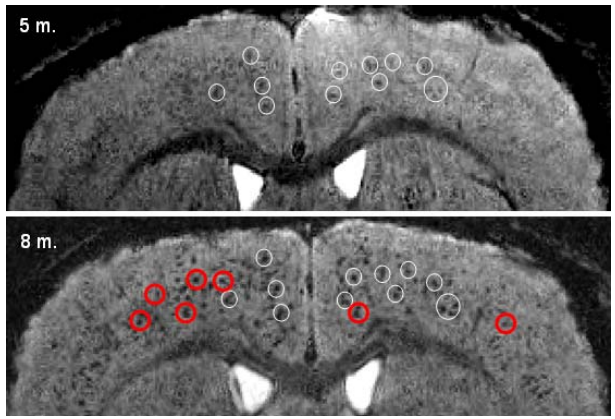
Multiphoton microscopy



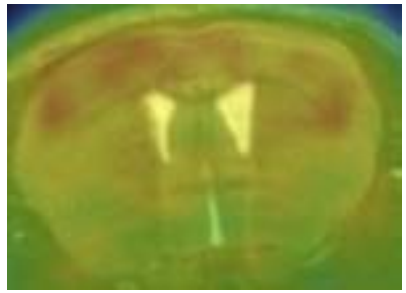




MRI



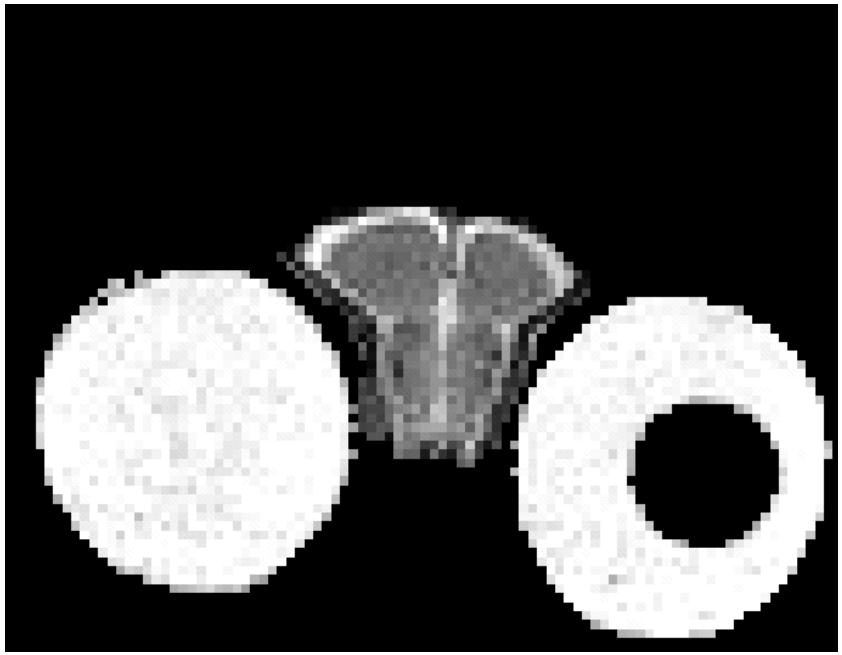
PET

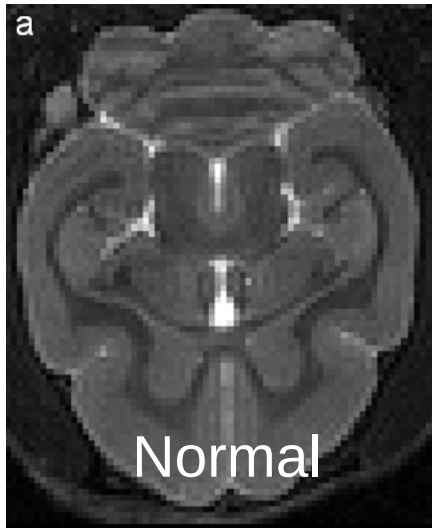


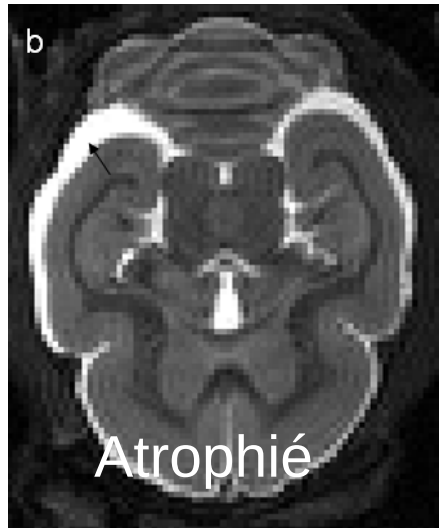
Characterization of animal models
Ex. of the Evaluation of cerebral atrophy in mouse lemurs

Characterization of animal models

- Precious animal







- Selection of animals to be included in therapeutic studies
  - Stratification

Why/how can we use of biomarkers in animal models?

- Characterization of animal models
  - Identification of biological mechanisms and targets
    - Choice of marker versus biomarkers ?
    - Non invasive studies in animal

- Therapeutic evaluations
  - "Classical view" of translational medicine
  - Translational bridges
    - Evaluation of efficacy in animals
    - Evaluation of toxicity in animals

- Therapeutic evaluations
  - Preparation of clinical trials

"Classical view" of translational medicine

Tests in animal models

Markers and biomarkers

Enough argument to validate the efficacy / lack of toxicity in animal
Arguments for a predictivity in humans

Go/No Go in humans

The drug should be efficient in humans…

This view is simplistic. It requires

Predictive animal models

Pertinent use of biomarkers

Different signification of biomarkers in animals and humans

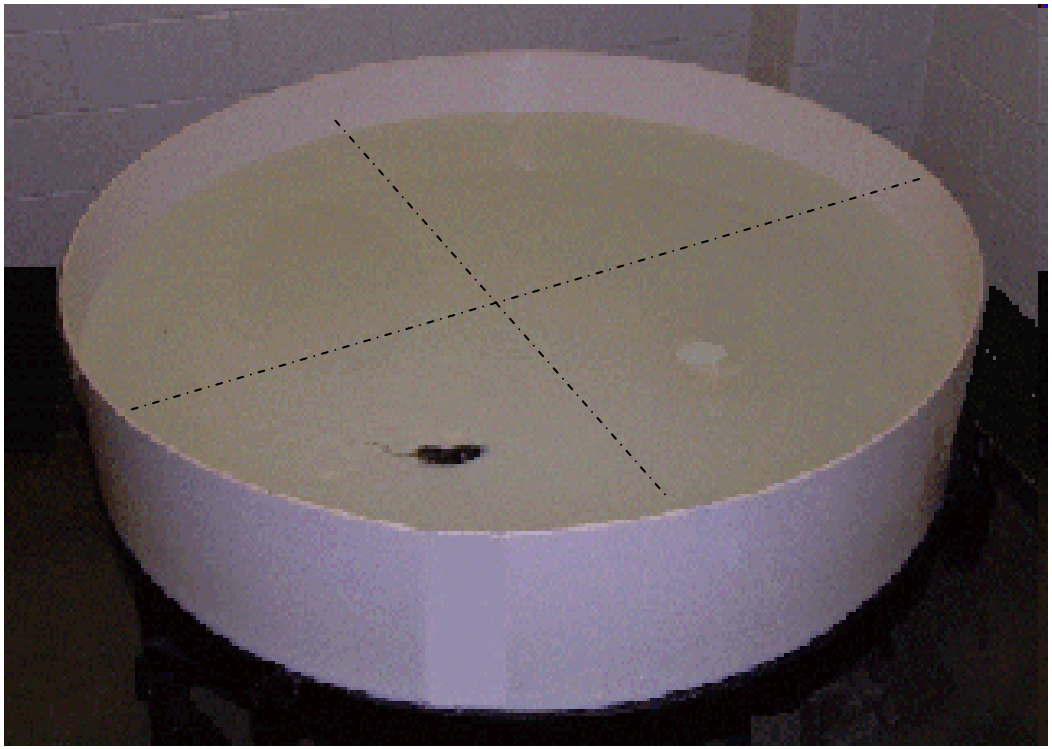
Example of behavioral studies

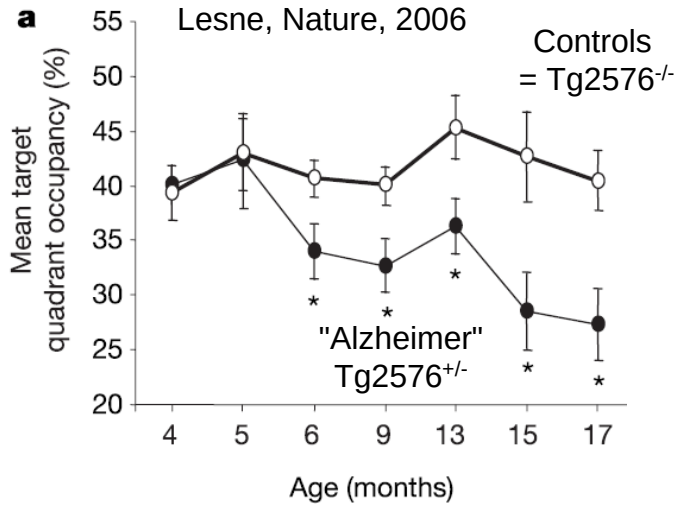
Alzheimer is a dementia
Let's look a behavioral alterations in animals to predict drug efficacy…

Altérations comportementales chez les rongeurs

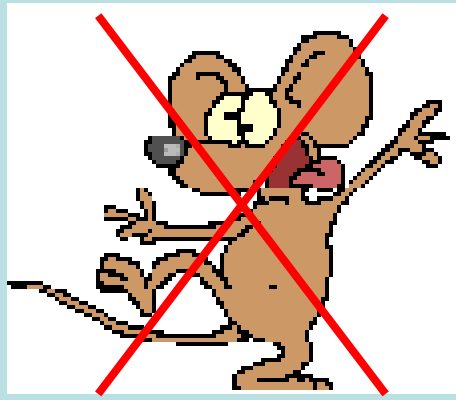
Ex. Piscine de Morris – Navigation Spatiale

- Mémoire spatiale de référence
- Intégrité de l'hippocampe
- Couramment utilisée





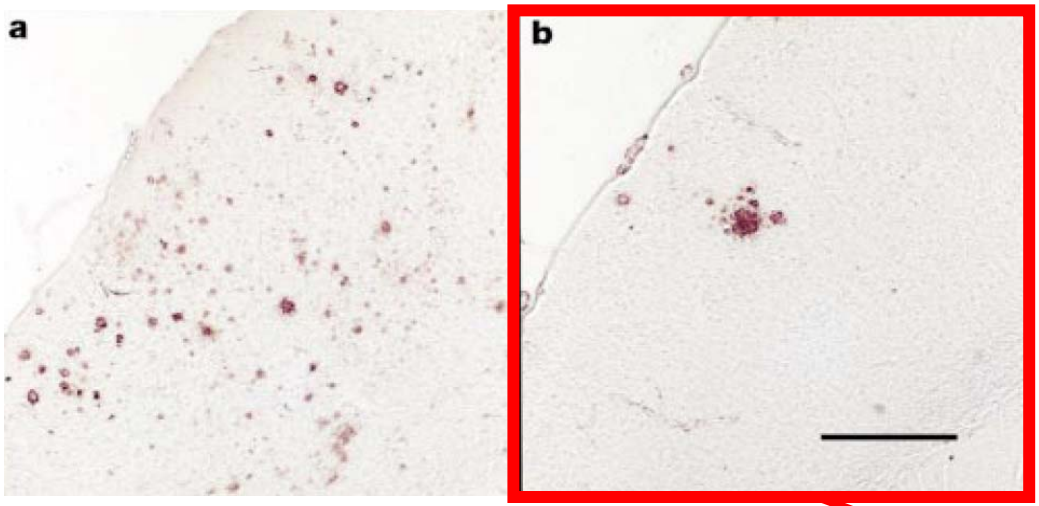
Altérations mnésiques mais pas de "démence"

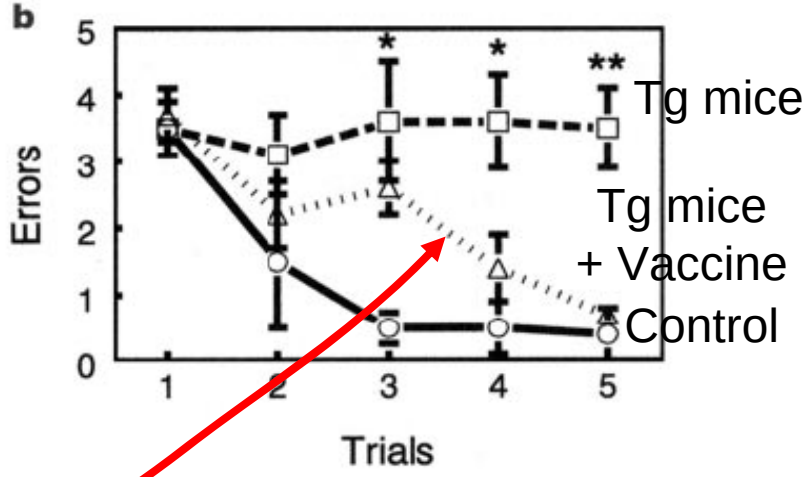


Predictivité des effets chez l'homme

- AN1792

Radial arm water maze





Morgan et al. (2000). Nature, 408(6815), 982-5.

- In humans
  - Efficiency to reduce amyloid load
  - No effect on behavioral alterations

Différence majeure cpt souris / Homme

Biais de raisonnement

Les troubles comportementaux des rongeurs n'ont pas la même origine que ceux de l'homme Alzheimer

Troubles comportementaux modérés

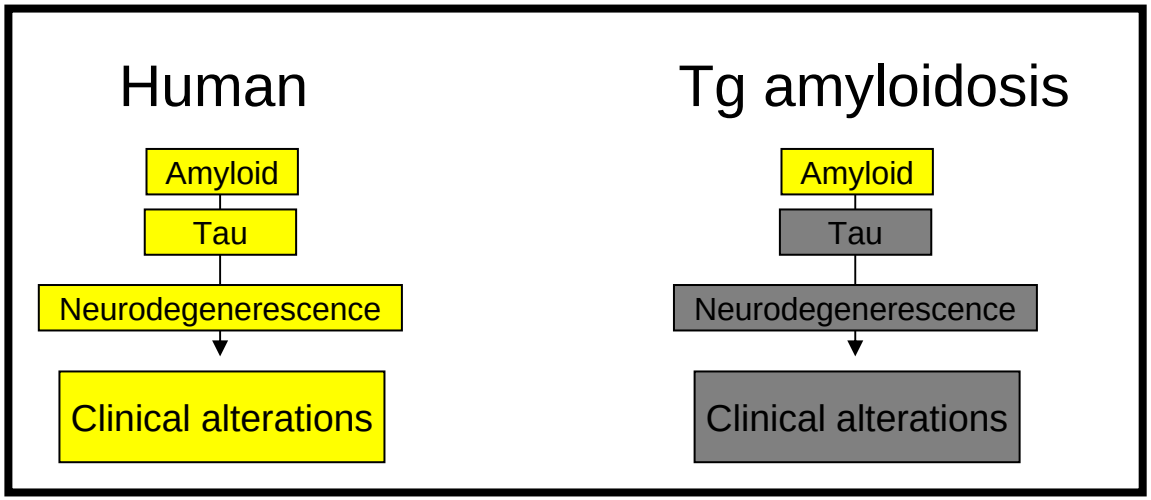
Origine Troubles Comportementaux = DNF

Origine Troubles Comportementaux = Oligomères

Validity of mouse models of amyloidosis

- Construct validity
  - Genetic

- Face validity: a truncated model ?
  - Extracellular amyloid deposits (but no downstream lesions)
  - Intracellular amyloid deposits
  - Lack of cerebral atrophy
  - Behavioral alterations not related to Tau pathology



- The same biomarker does not reflect the same underlying pathology in humans and animals

- The mouse model is not predictive of the full Alzheimer's disease pathology

Translational bridges

Clinical outcome

Endophenotypes

POC in animals

Target

POM in animals

Therapy

Clinical outcome

Endophenotypes

POC in Humans

Target

POM in human

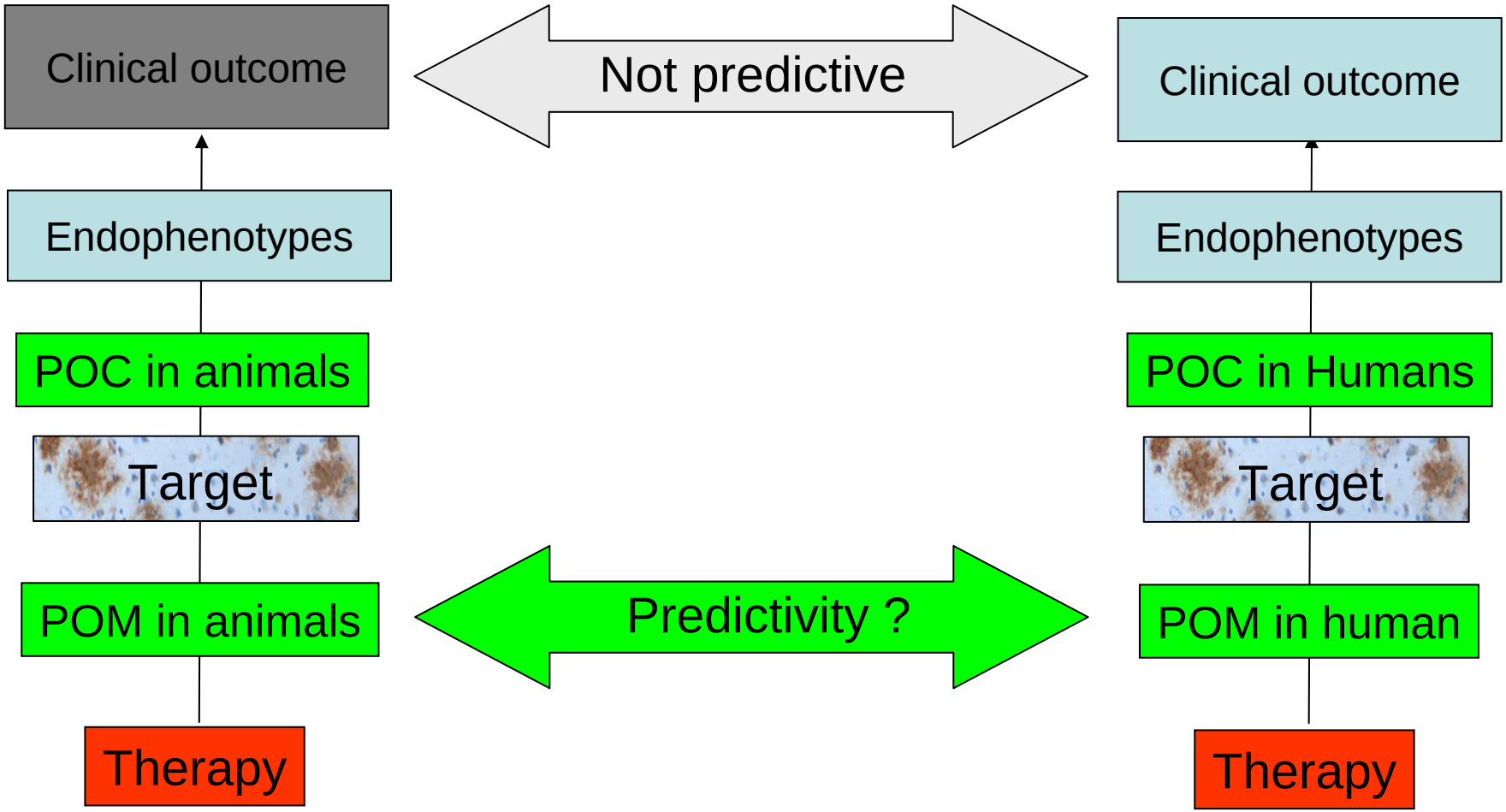
Therapy

Proof of Mechanism (POM): Is my drug really active on the supposed mechanism ?

Proof of Concept (POC): If I modify the target, do I modify the disease ?

Pivotal : Is the disease modification in animals predictive of results in humans ?

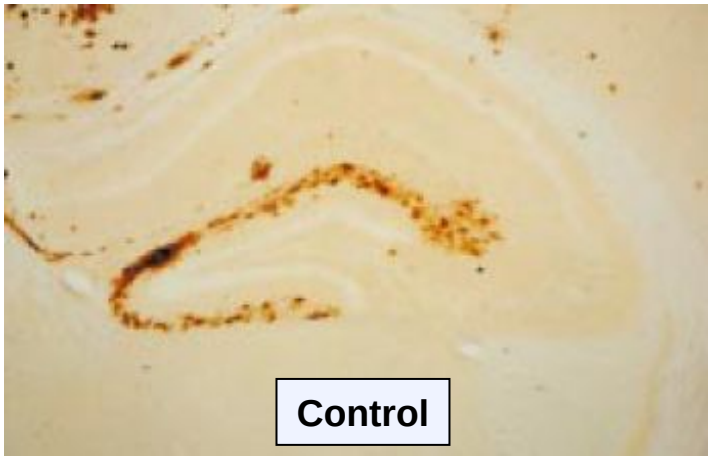
Translational bridges



Proof of Mechanism (POM): Is my drug really active on the supposed mechanism ?

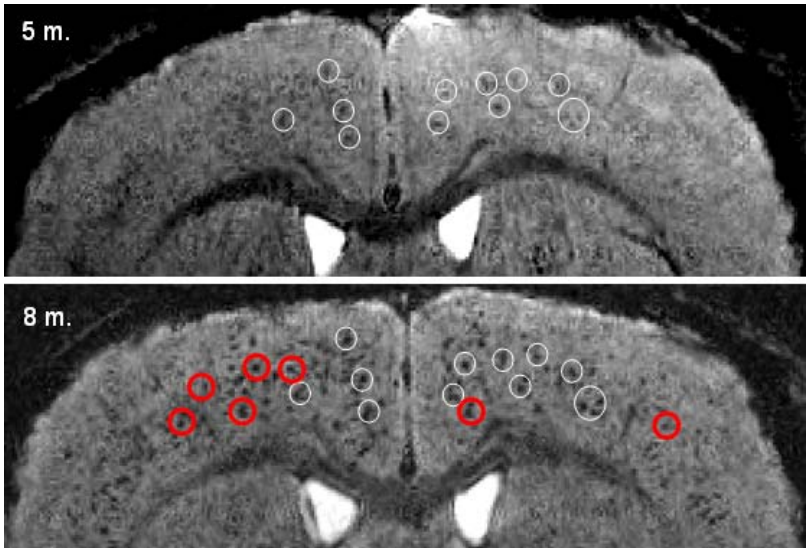
Immunotherapies in amyloid mice

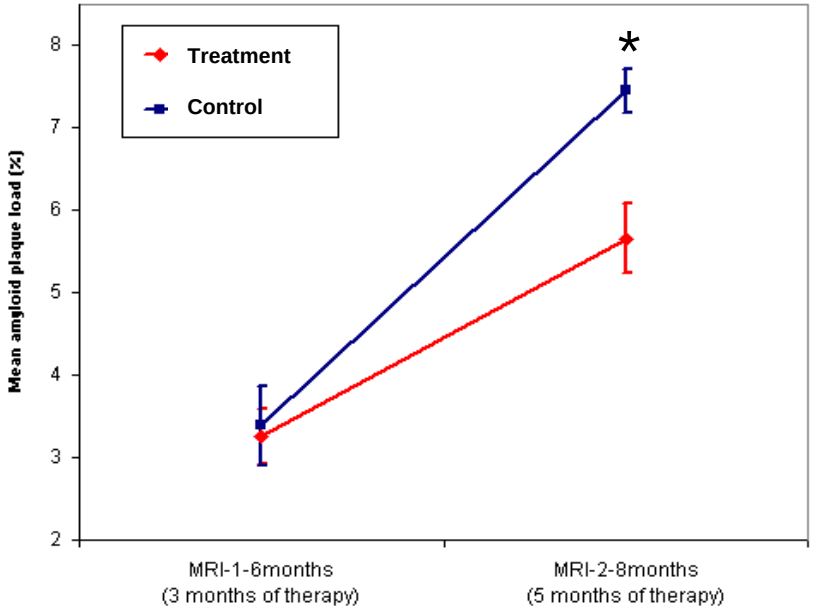
- Marker of amyloid load (Histology)



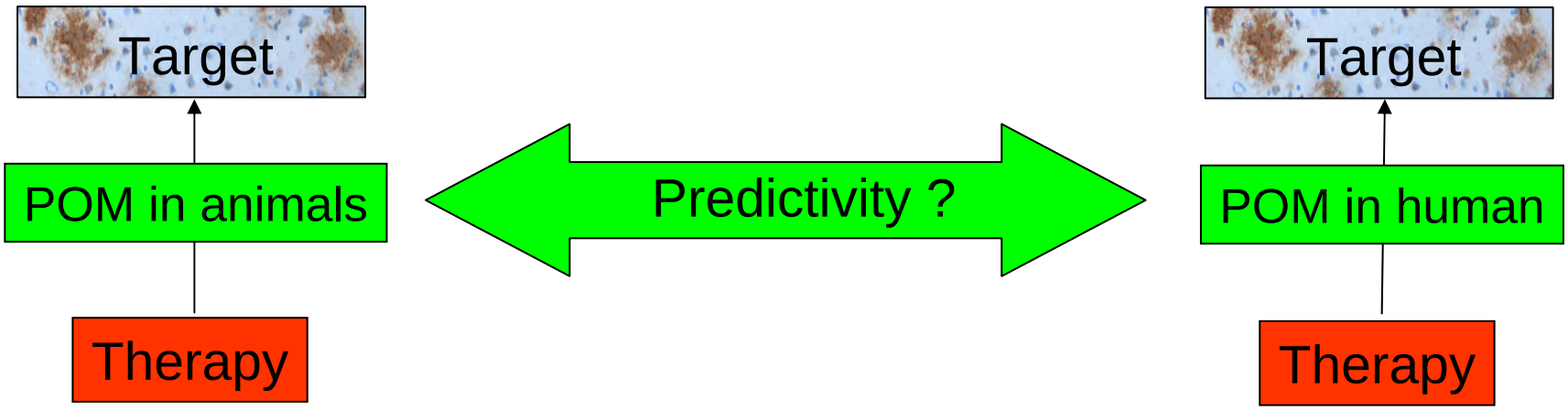
(Schenk et al, 1999)

- Biomarker of amyloid load (MR`



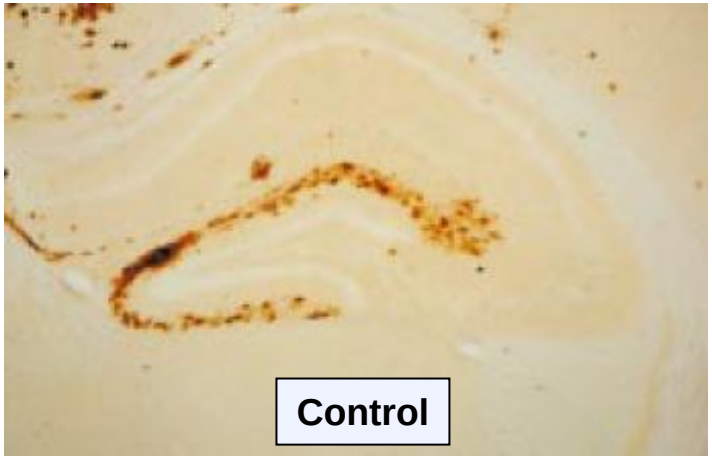


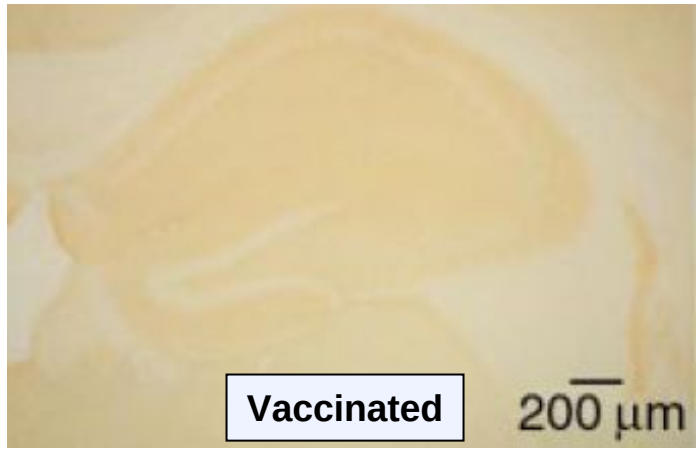
Translational bridges



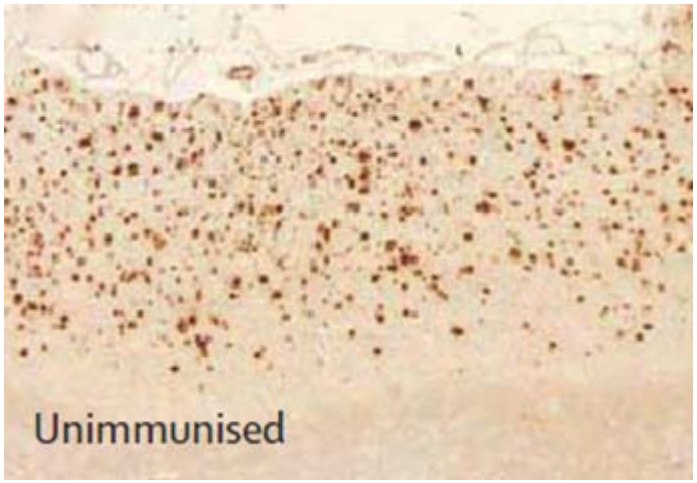
- It is reasonable to think that the treatment will reduce amyloid load in humans

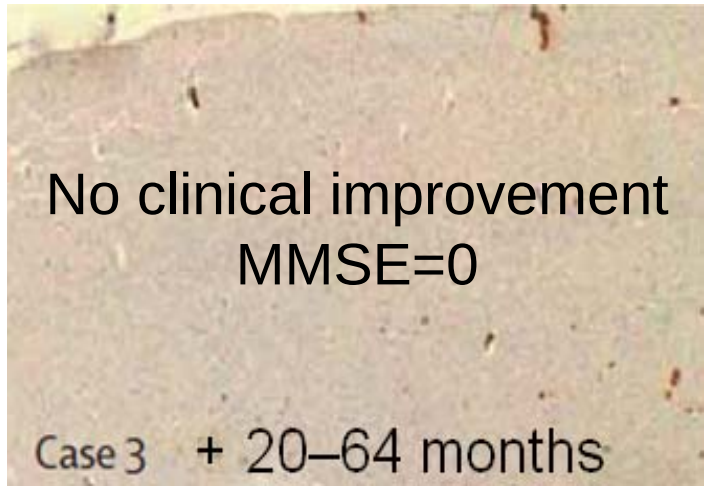
Discovery of new therapy strategies in amyloid mice





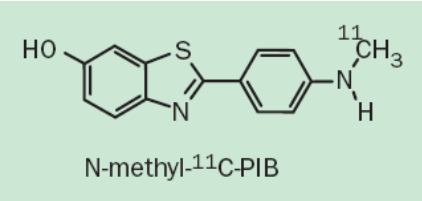
(Schenk et al, 1999)



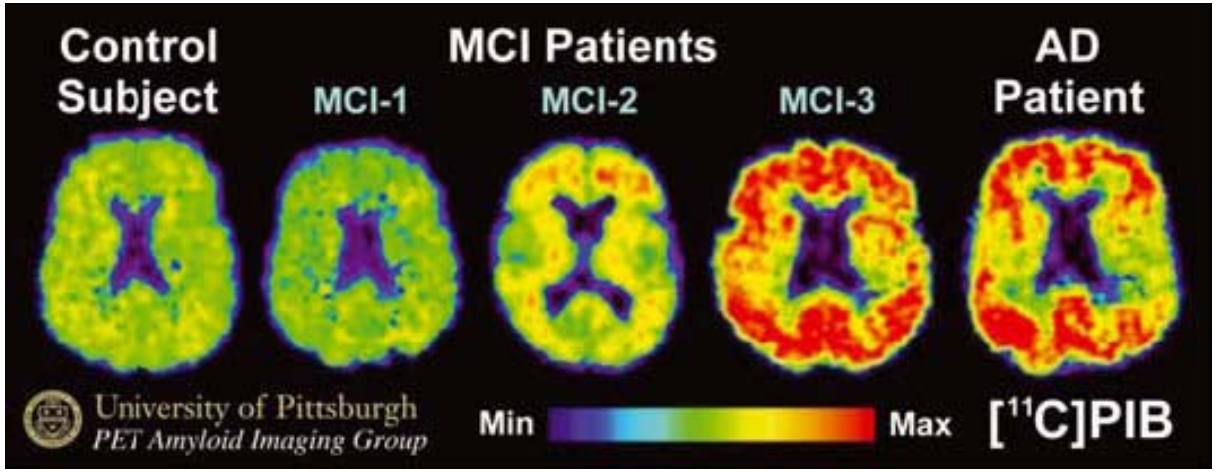


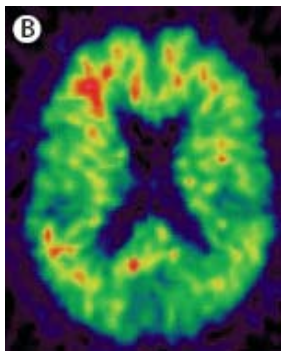
(Holmes et al, 2008)

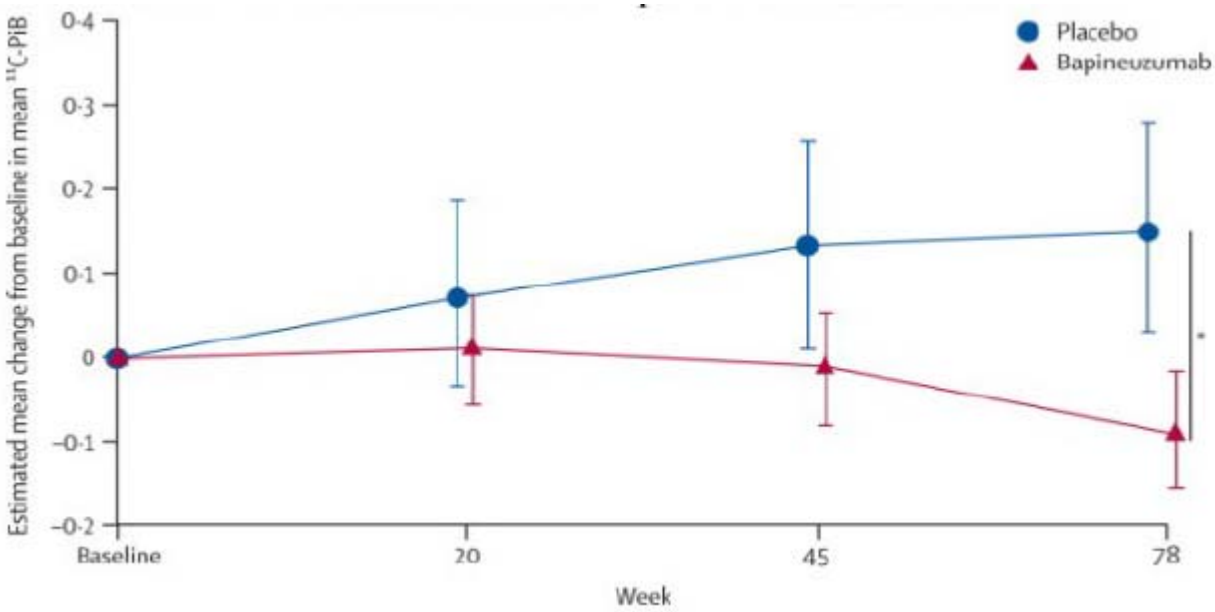
Amyloid imaging in humans (by PET)

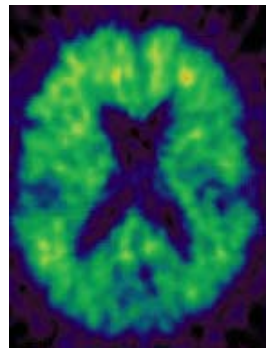


N-methyl-^{11}C-PIB

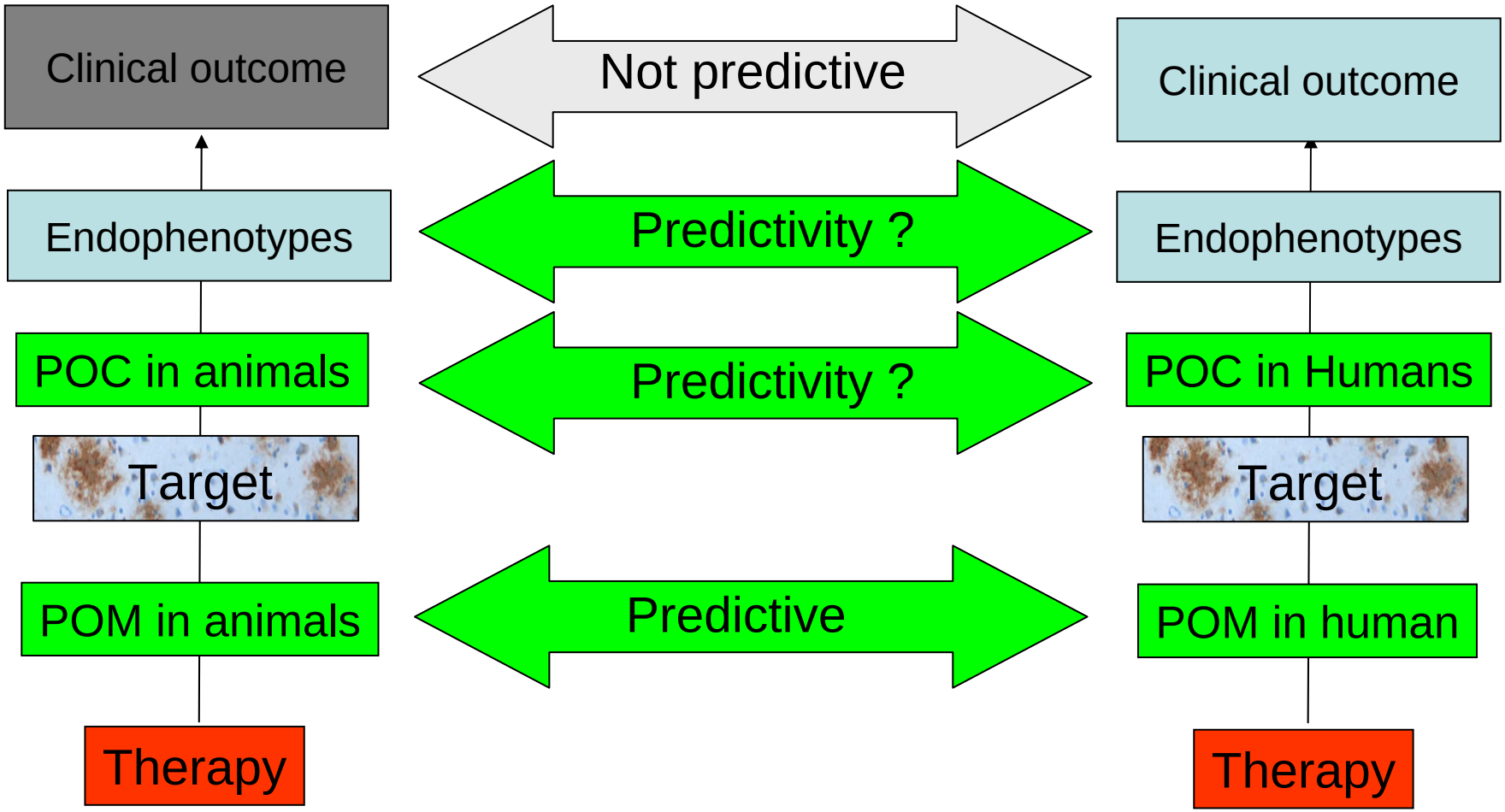








Translational bridges



Proof of Mechanism (POM): Is my drug really active on the supposed mechanism ?

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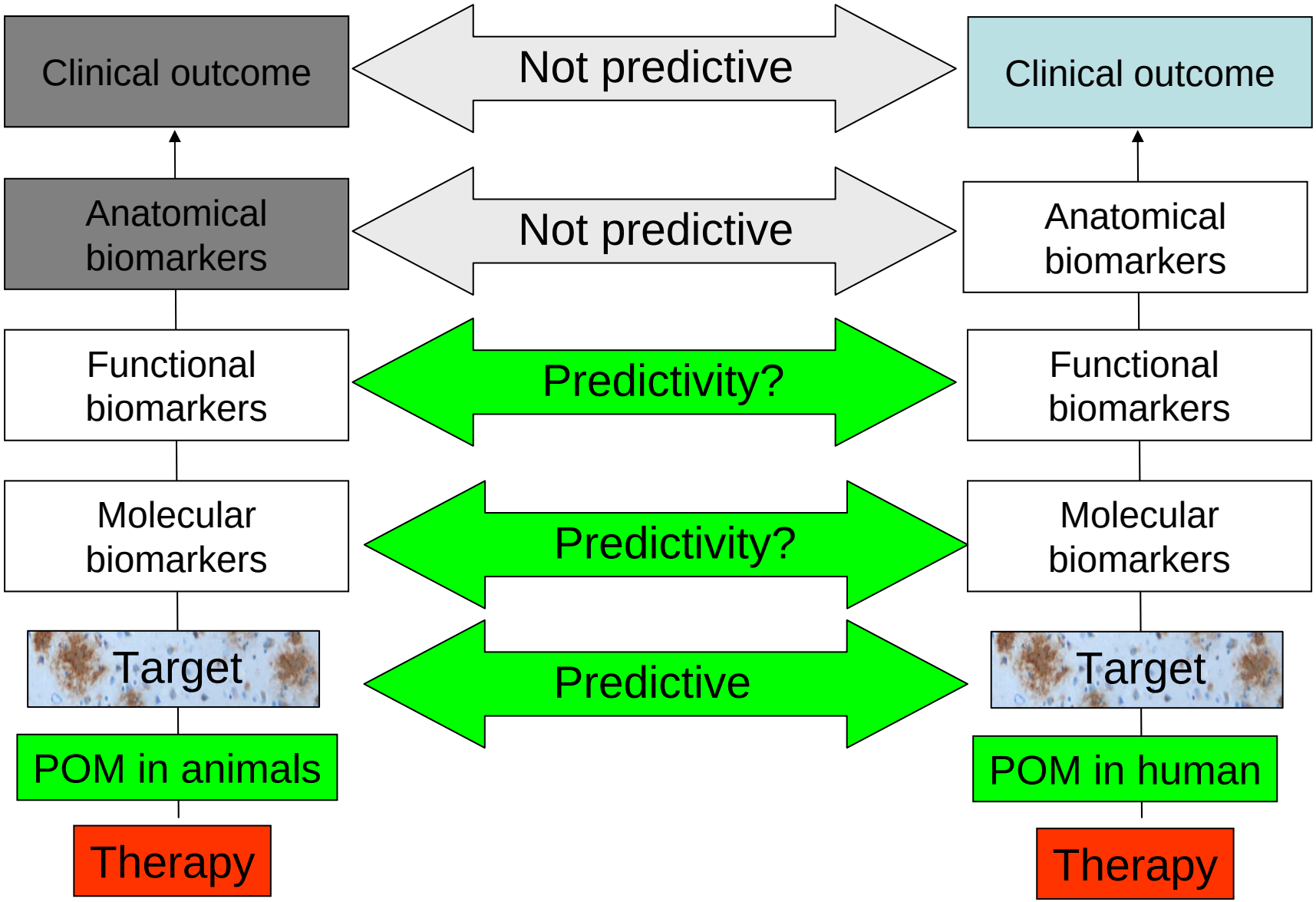
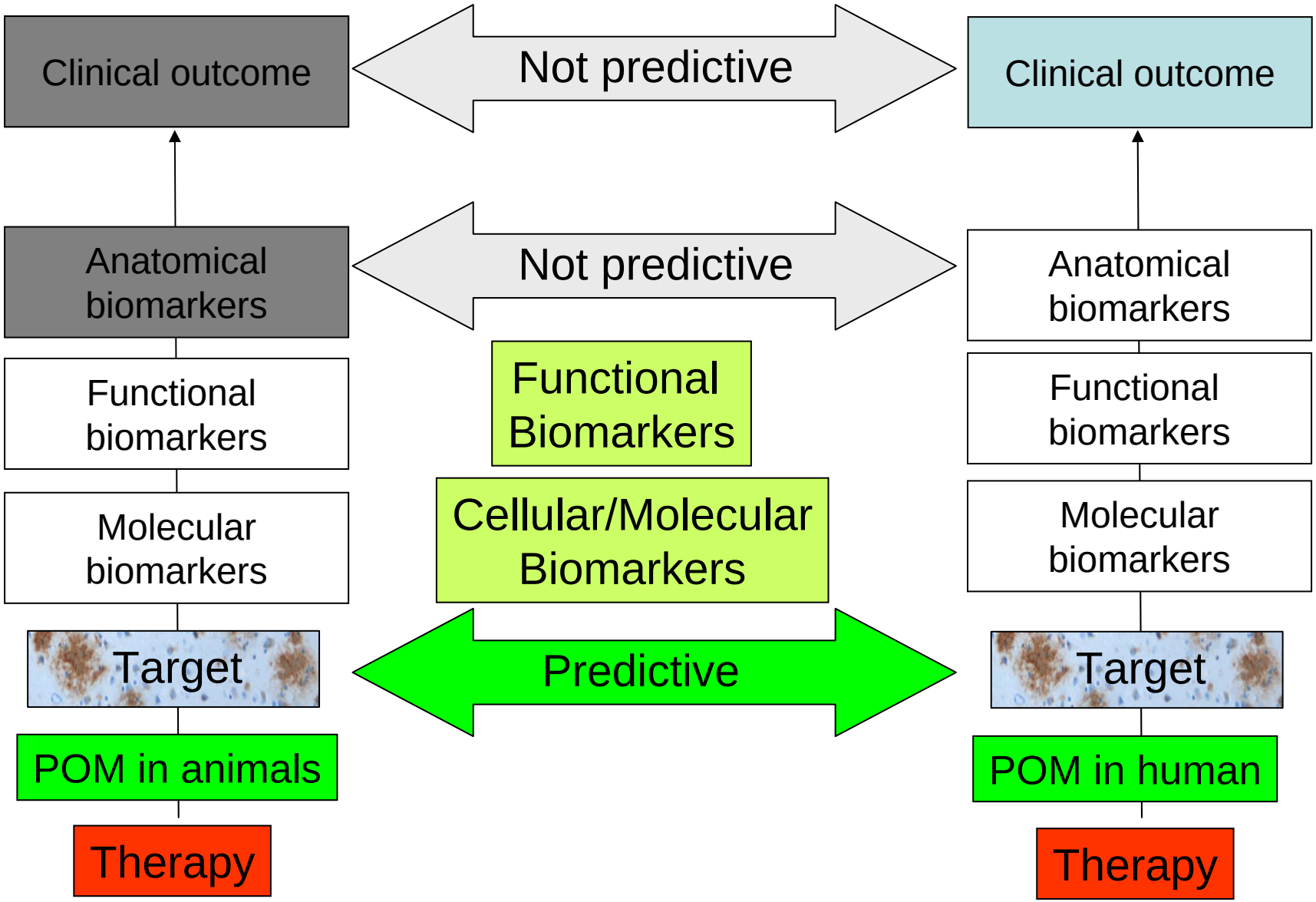
Pivotal : Is the disease modification in animals predictive of results in humans ?

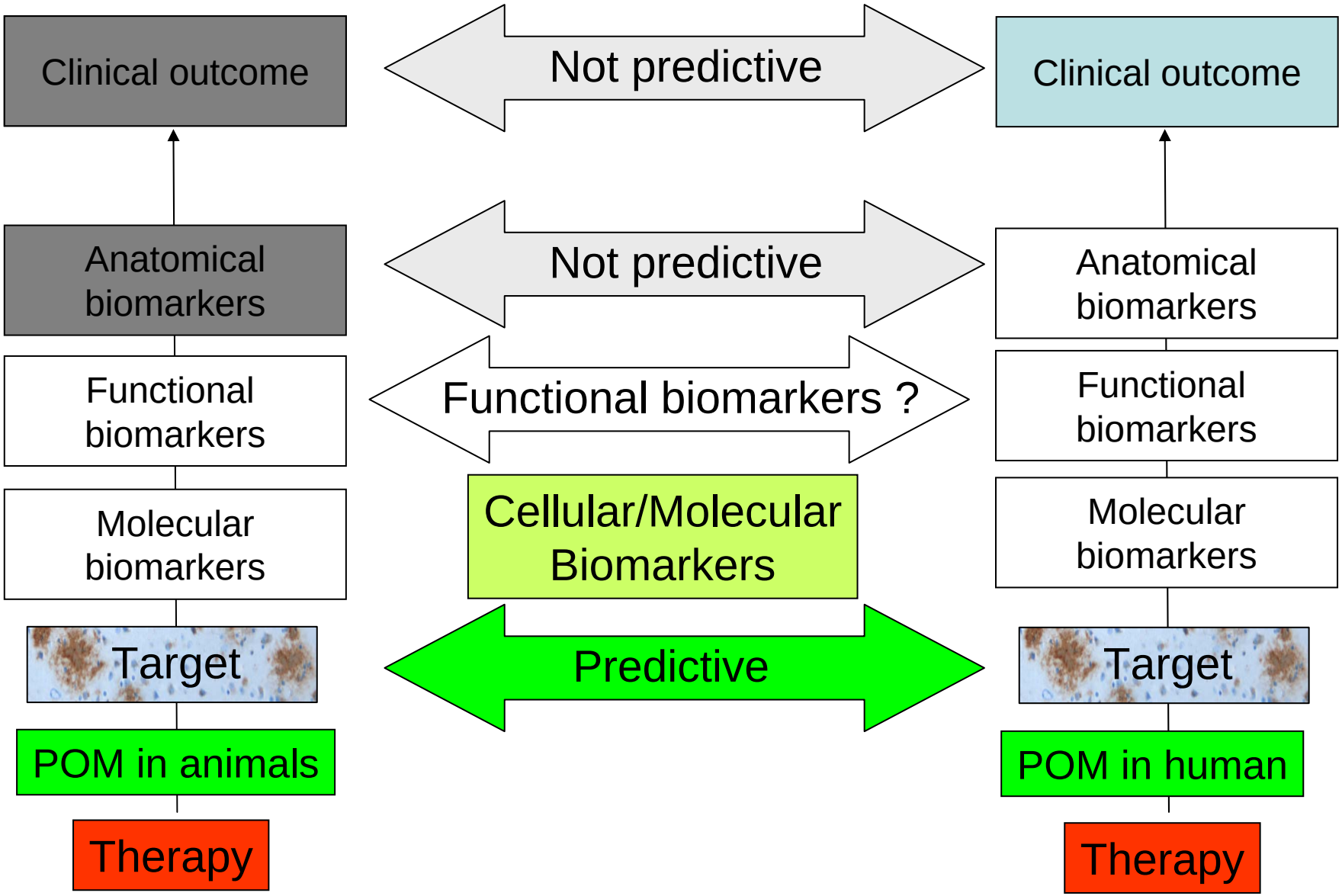
Use of biomarkers to add translational bridges between humans and animals ?



Use of biomarkers to add translational links between humans and animals ?



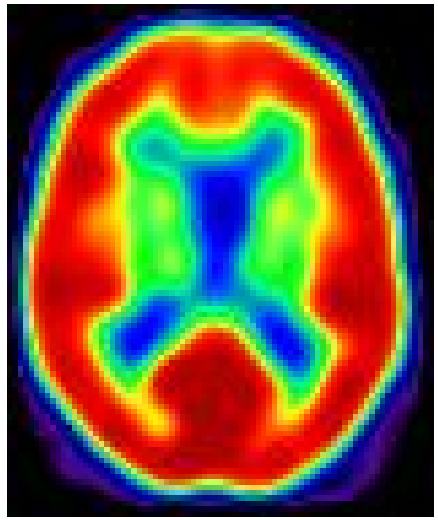
Use of biomarkers to add translational links between humans and animals ?



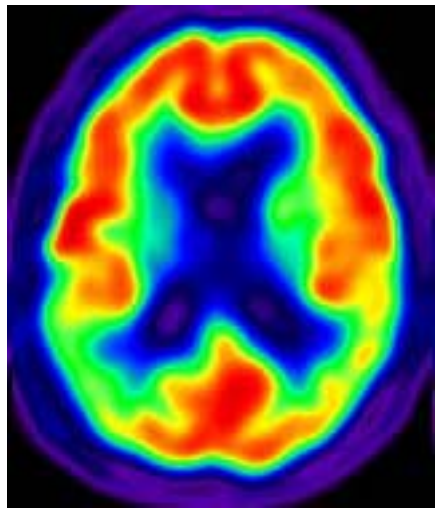
Cerebral metabolism

Glucose metabolism (PET)
Edison P et al.
Neurology, 2007

Normal

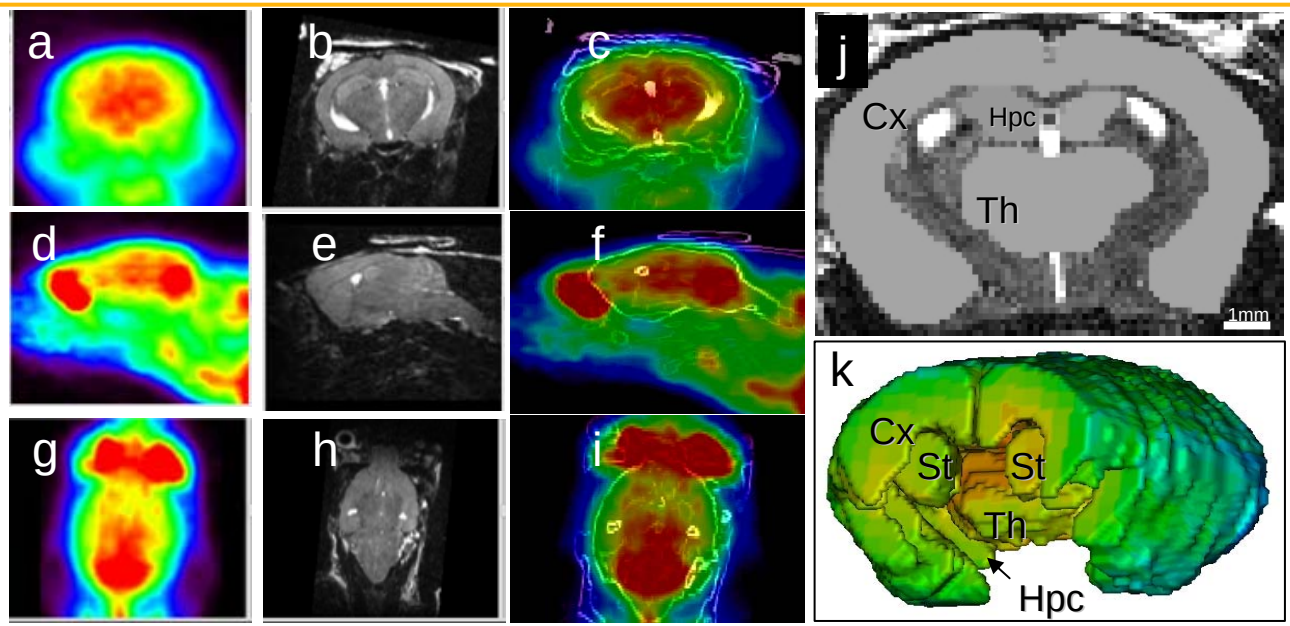


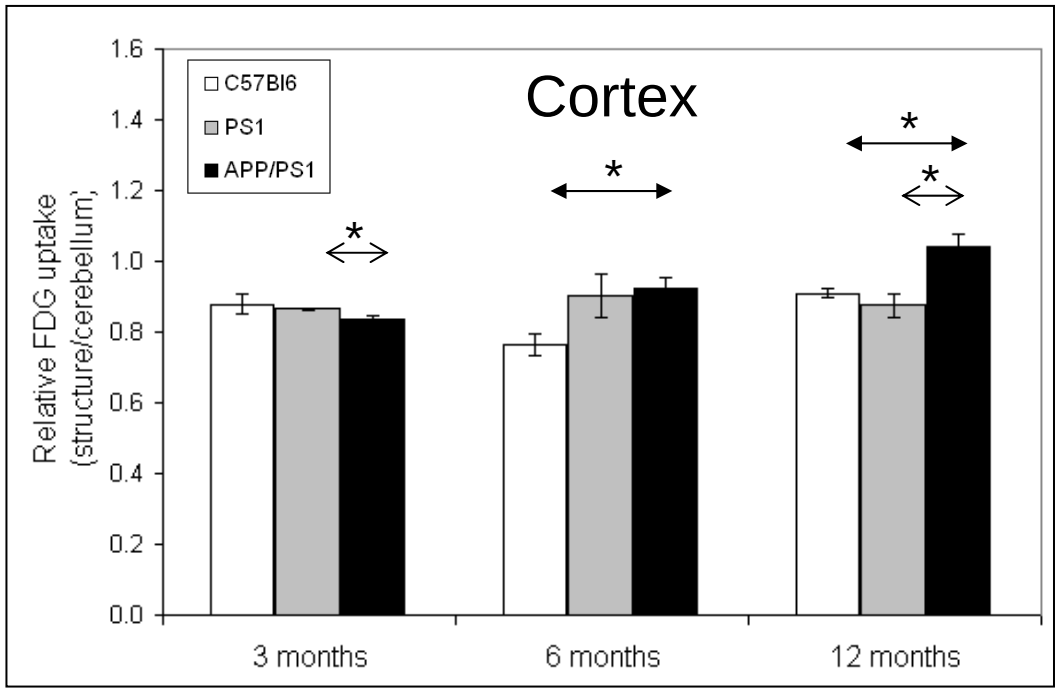
AD



Amyloid is associated to an increased glucose uptake in Tg mice

FDG-PET study

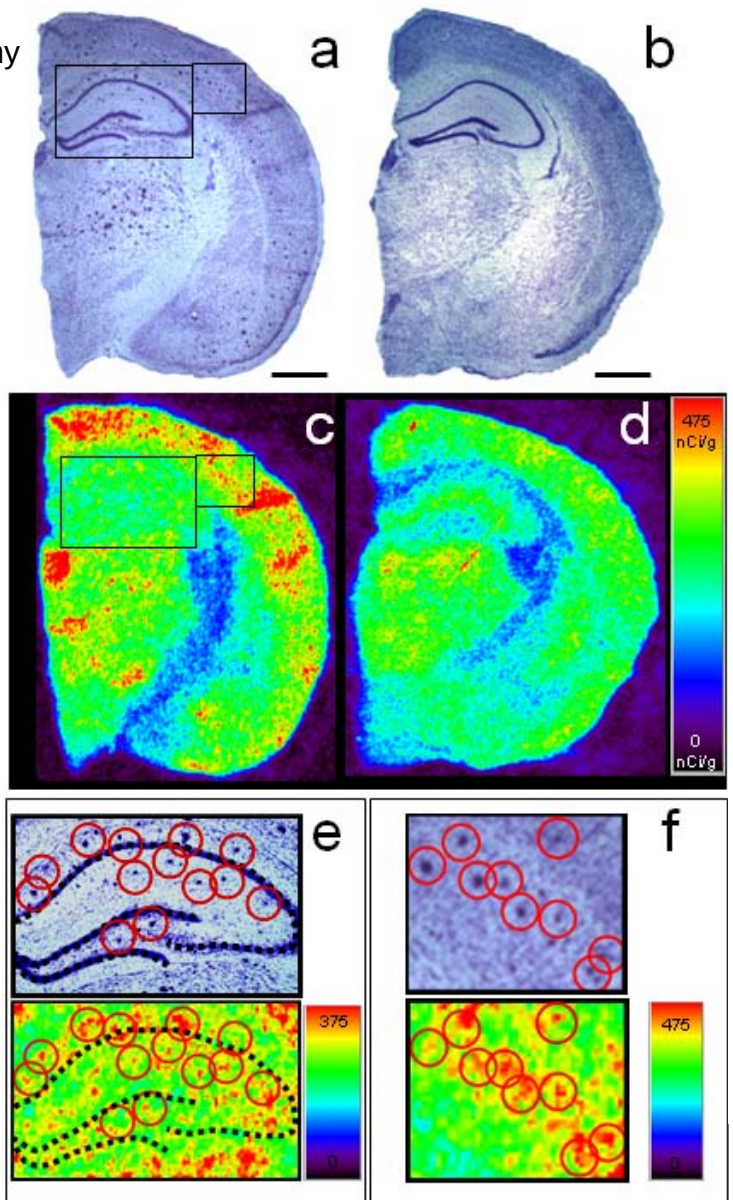


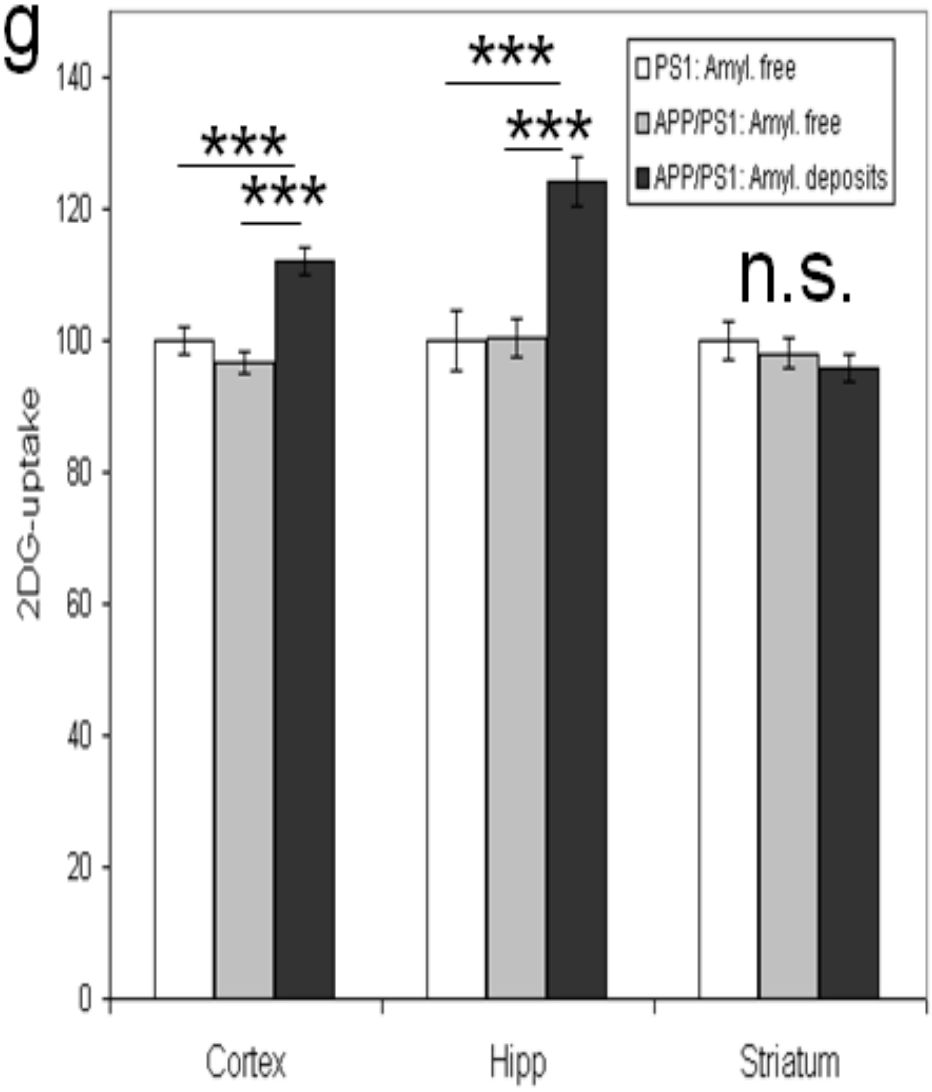


G. Poisnel et al,
Neurobiology of Aging, 2012

Amyloid plaques are associated to an increased glucose uptake

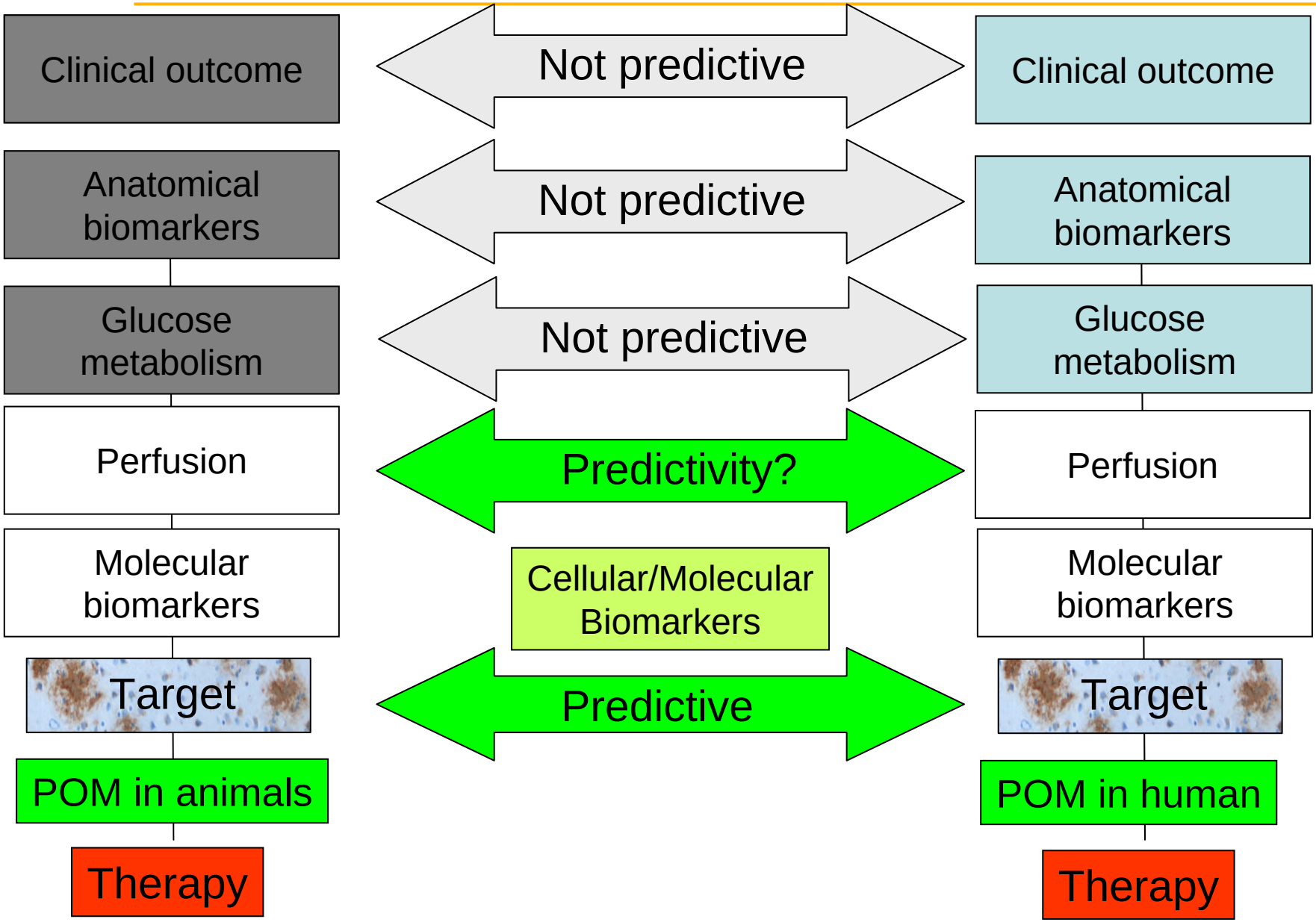
2DG autoradiography





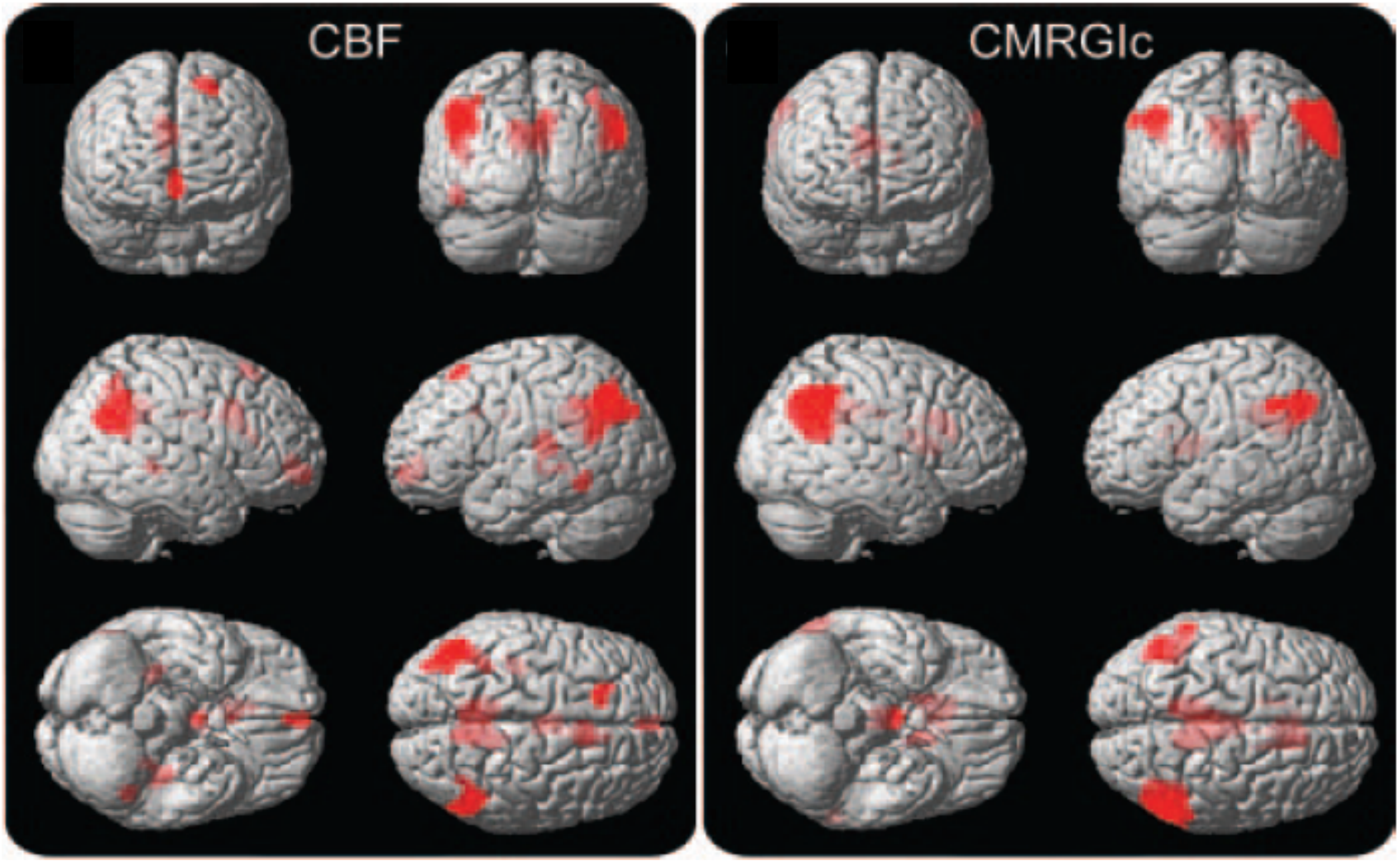
G. Poisnel et al, Neurobiology of Aging, In press

Use of biomarkers to add translational links between humans and animals ?



Perfusion measurements from MRI

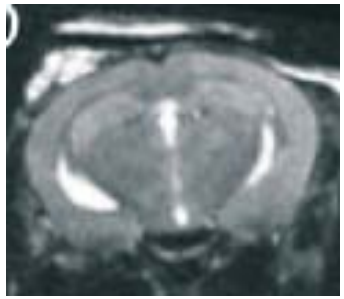
ASL-MRI provides overlapping information with FDG-PET

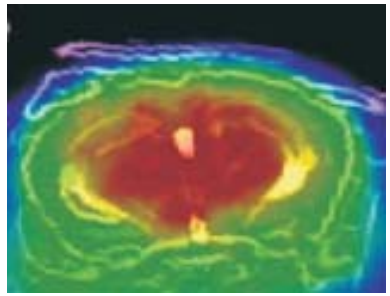


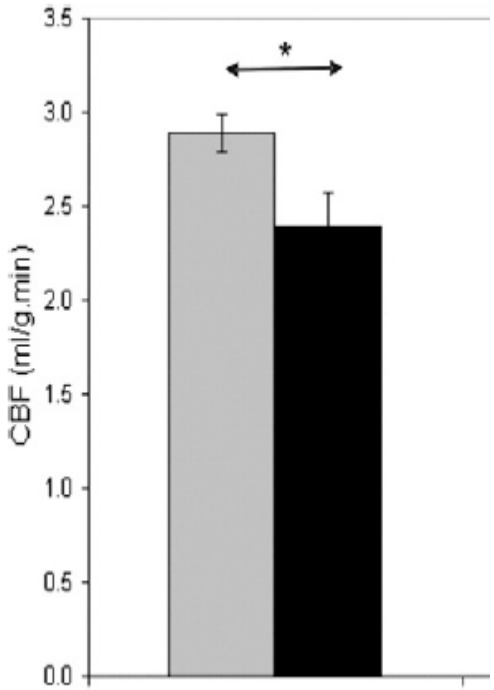
ASL-MRI FDG-PET

Chen Y et al. Neurology 77, 1977-85; 2011.

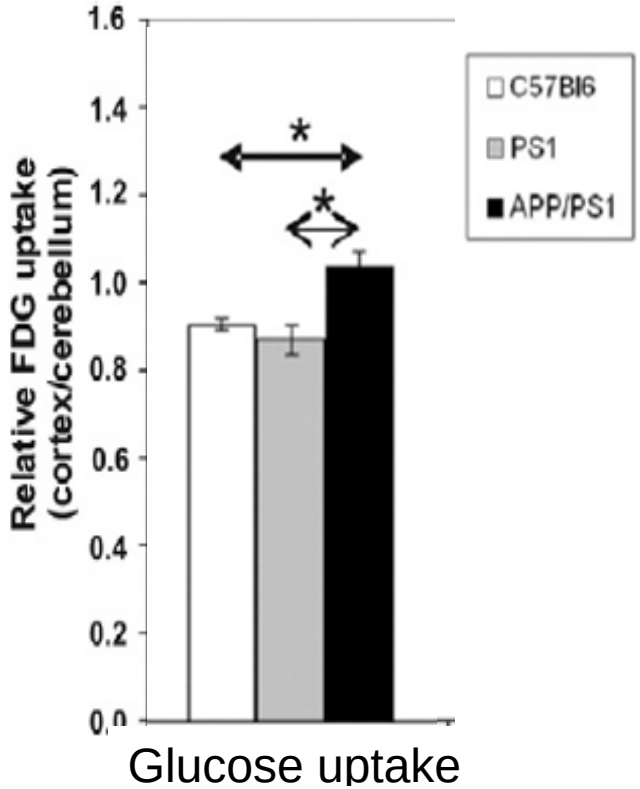
Dissociation between perfusion and glucose uptake in mouse models of amyloidosis







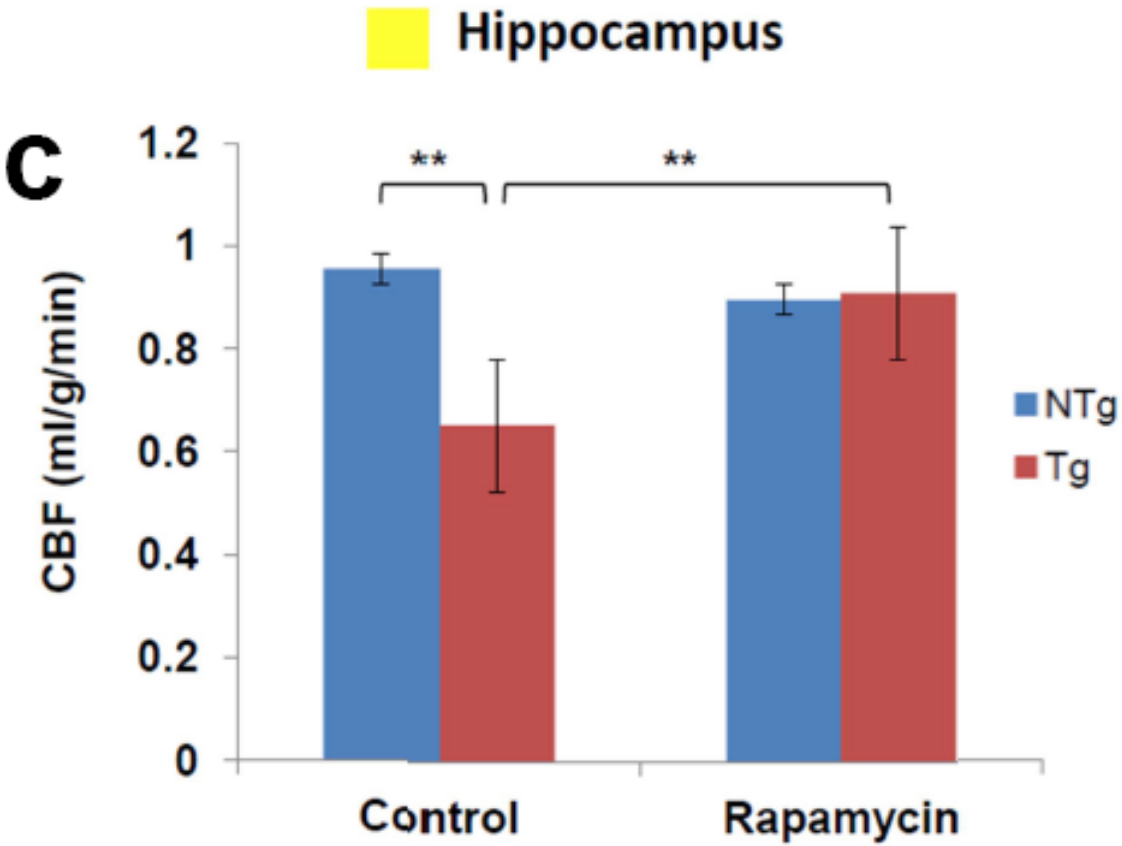
Perfusion



Glucose uptake

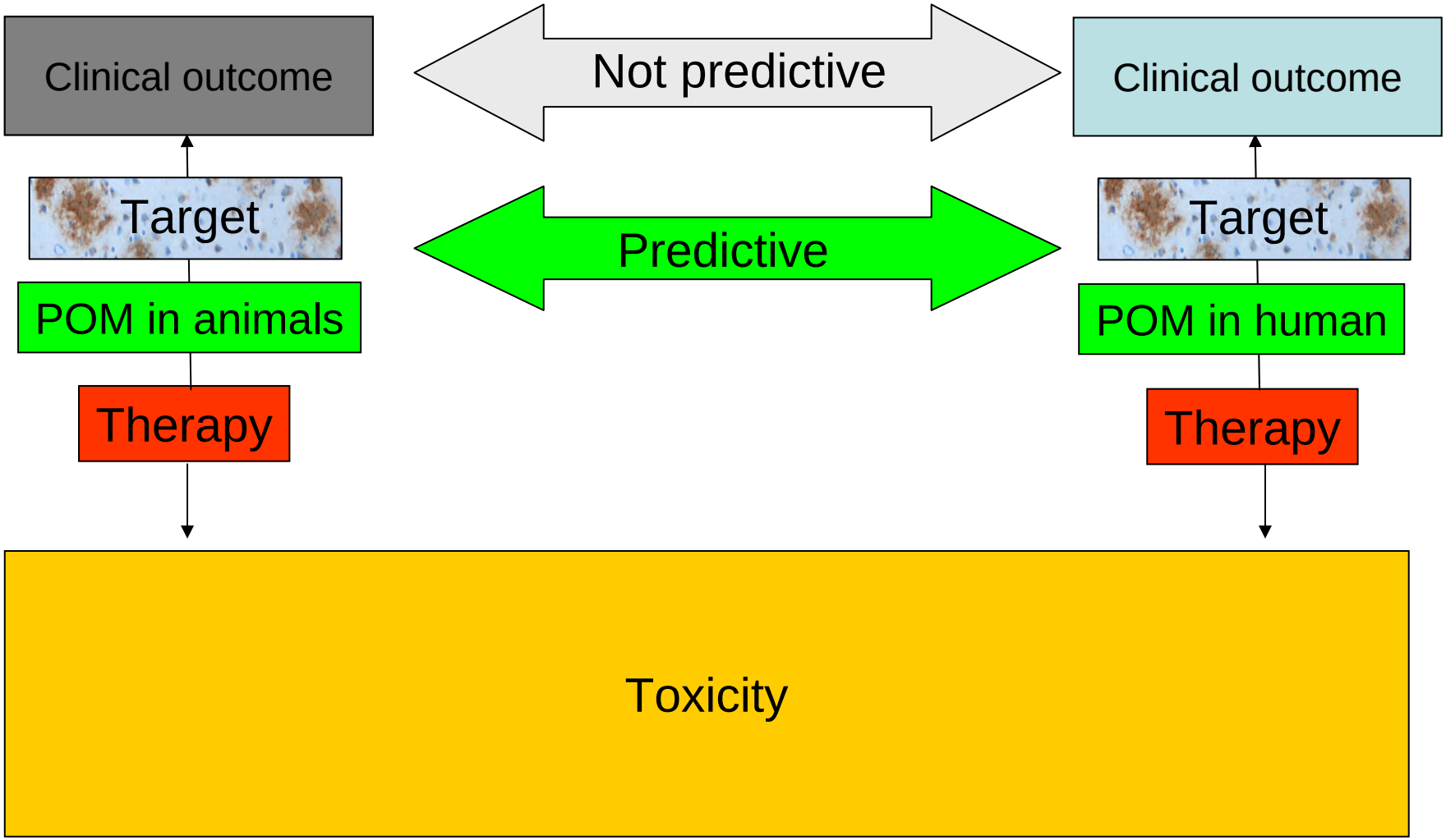
Poisnel G et al. Neurobiology of Aging. Ahead of Print.

Application for therapeutic evaluation



Ai-Ling Lin et al. ISMRM2012. 586.

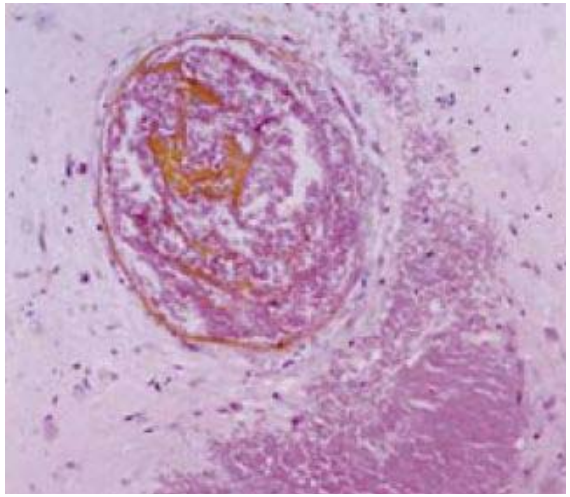
Biomarkers of toxicity



Imaging biomarkers of Toxicity
Example of the immunotherapy

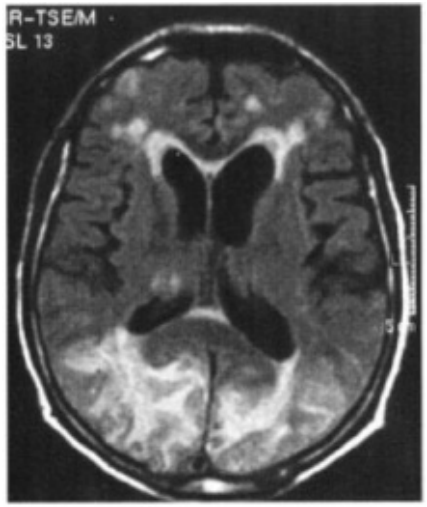
Severe side effects detected in human studies

Microhemorrhages



Ferrer I et al.
Brain Pathol, 2004

Meningoencephalitis

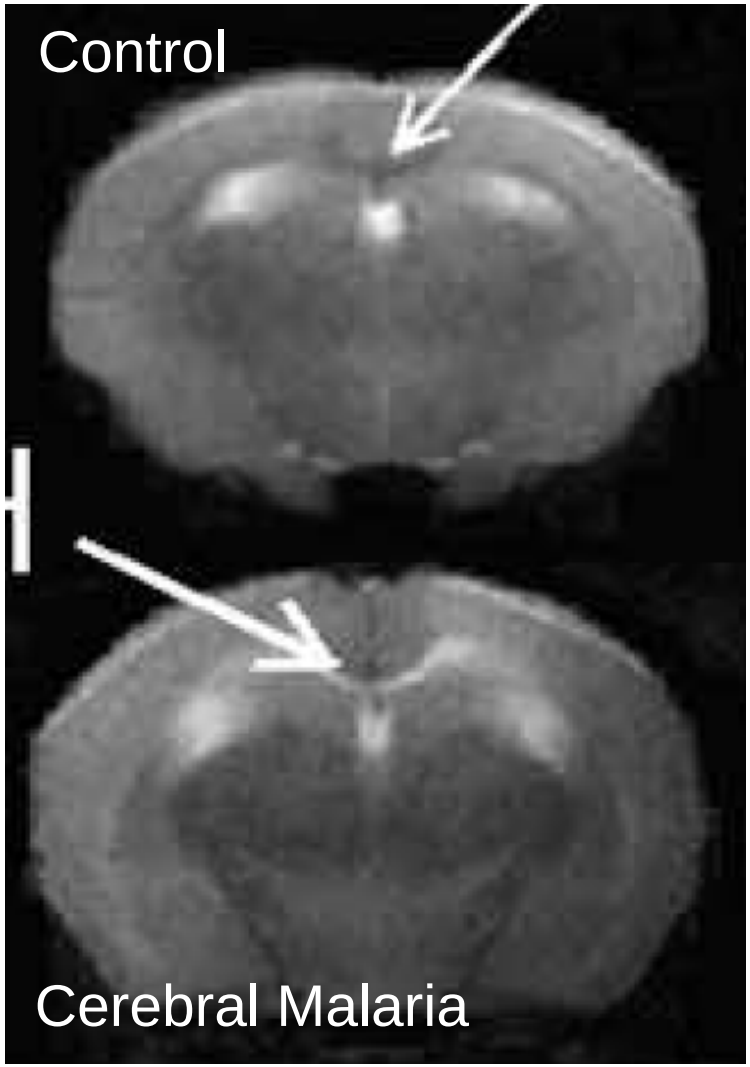


Orgogozo JM et al.
Neurology, 2003

Vasogenic edema

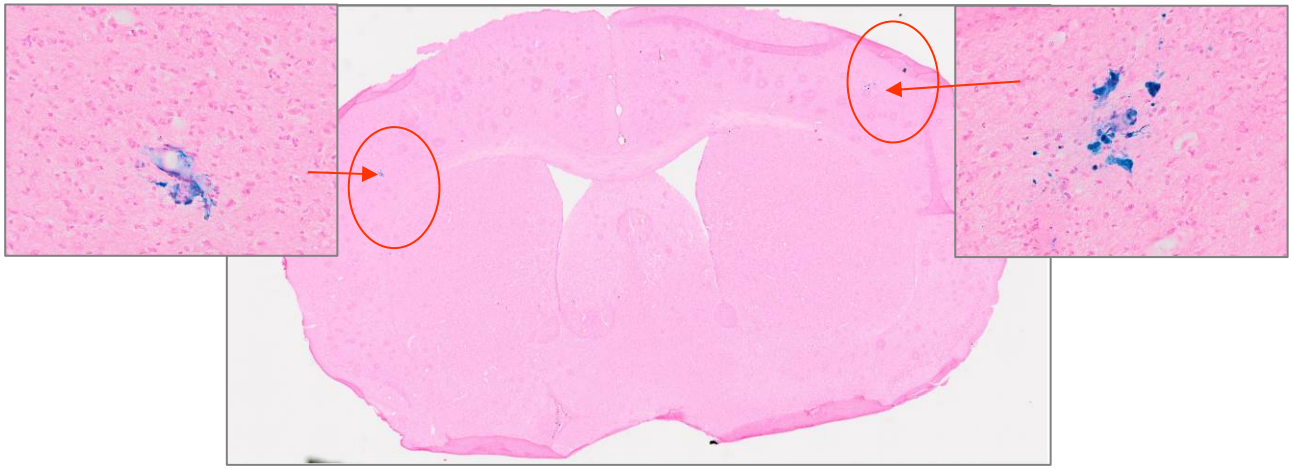
Salloway S et al.
Neurology, 2009

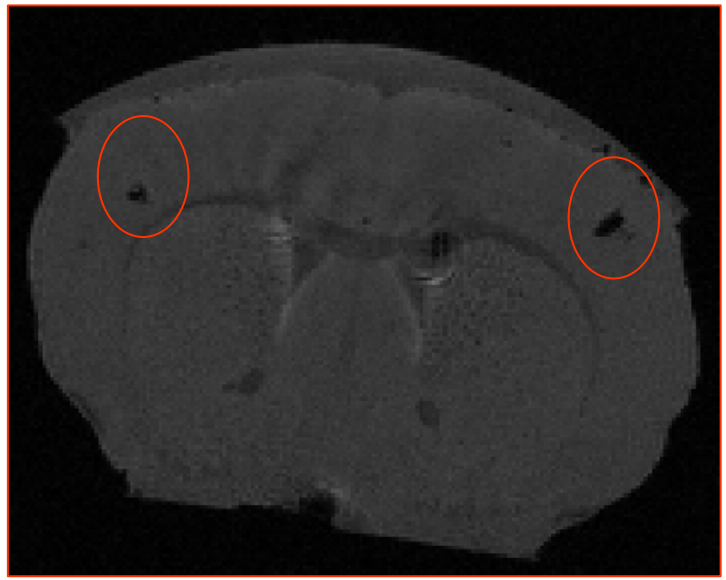
Marqueurs toxicologiques chez l'animal
Neuroinflammation



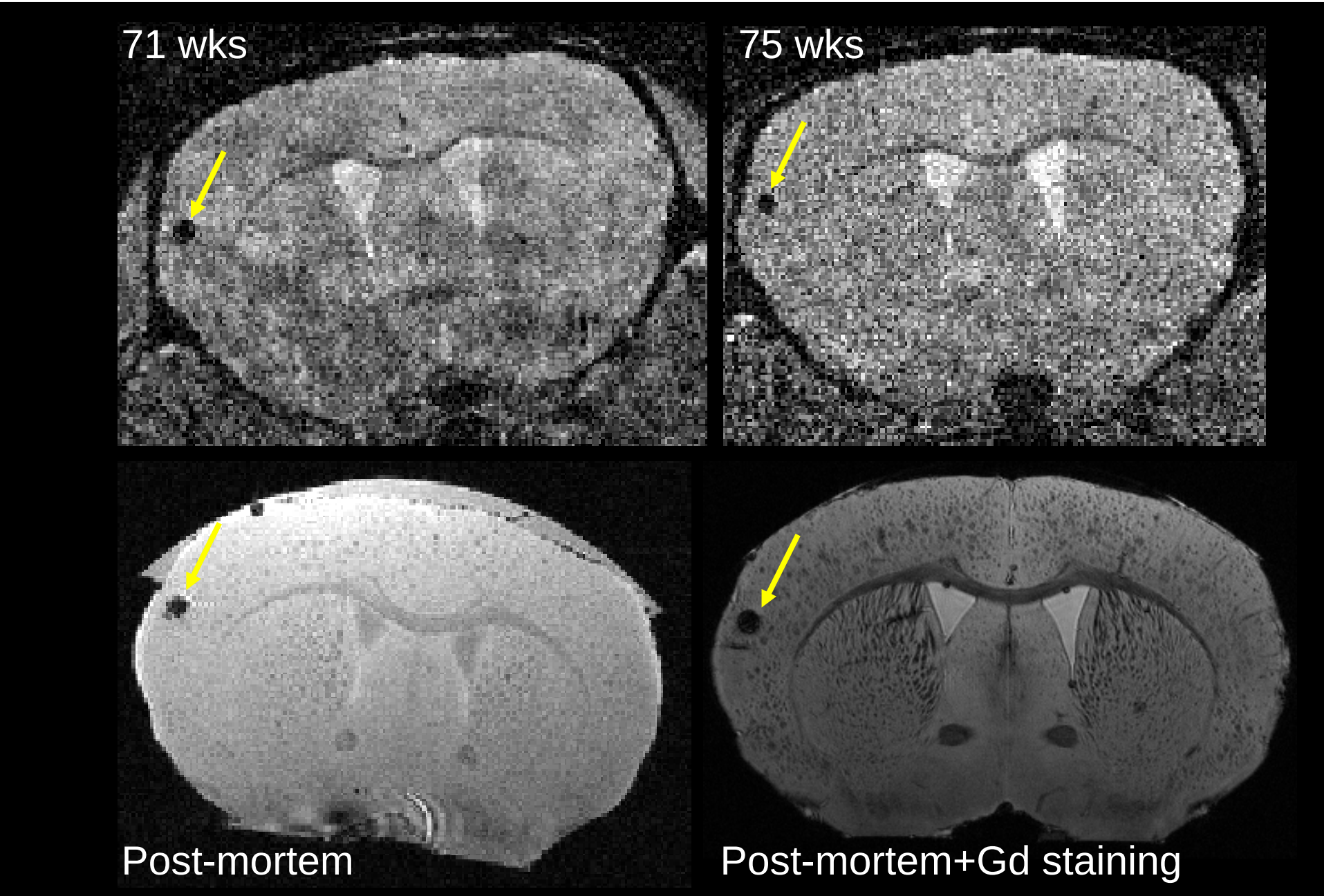
Penet, M. F.. (2005).
J Neurosci **25**(32): 7352-8.

Marqueurs toxicologiques chez l'animal
Microhémorragies cérébrales





Detection of cerebral microhemorrhages by MRI



Why/how can we use of biomarkers in animal models

- Characterization of animal models
  - Identification of biological mechanisms and targets
    - Choice of marker versus biomarkers ?
    - Non invasive studies in animal
- Therapeutic evaluations
  - "Classical view" of translational medicine
  - Translational bridges
    - Evaluation of efficacy in animals
    - Evaluation of toxicity in animals
- Therapeutic evaluations
  - Preparation of clinical trials

Objective for preparation of clinical trials

- Define best animal models
- Define best endophenotype/biomarkers that will allow to predict results in humans
- This requires to understand the targets

Translational bridges

Validity of the animal model

Validity of the marker/biomarkers

Validity of the disease/target hypothesis

Clinical outcome

Endophenotypes

POC in animals

Target

POM in animals

Therapy

Clinical outcome

Endophenotypes

POC in Humans

Target

POM in human

Therapy

A good animal model

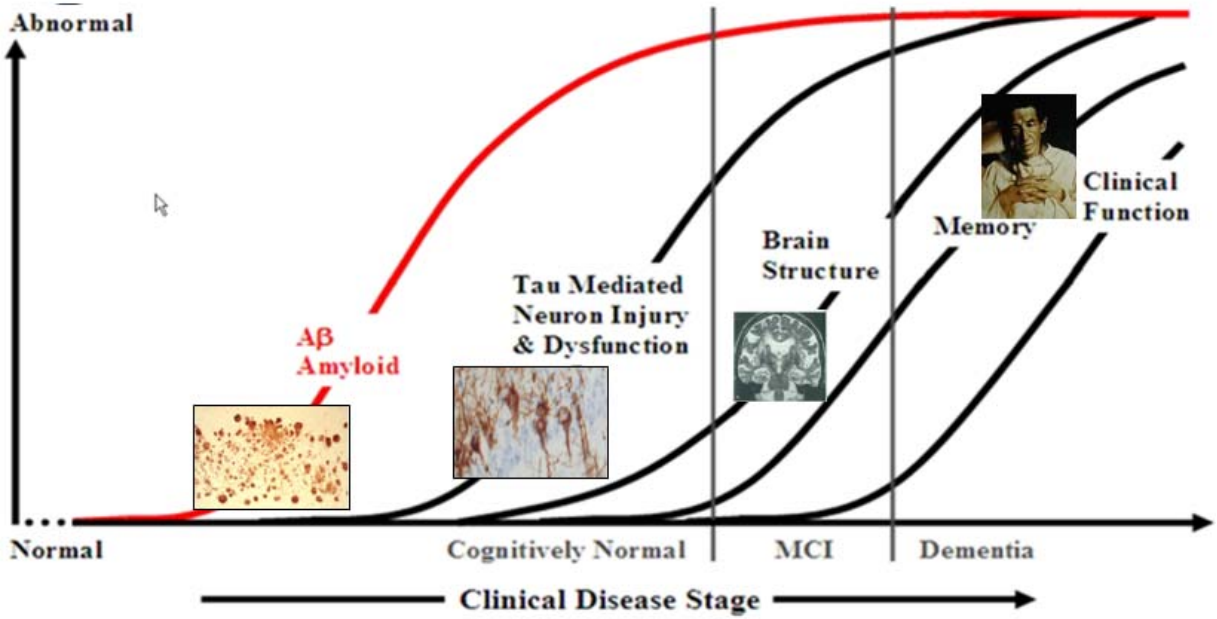
- Construct validity
  - Biological (aging…)
  - Lesions: chemical, mechanical….
  - Mechanistic (drug, etc…)
  - Genetic (transgenic: standard, conditional, tissue specific…)
- Face validity
  - Lesional: Amyloid then Tau then Neurodegerescence
  - Endophenotyping
    - Functional
    - Electrophysiological alterations
  - Phenotyping (behaviour)
- Prediction validity
  - Mecanistic (target engagement, downstream effects)
  - POM
  - POC
  - Pivotal
  - Toxicity
- Easy to use
  - Access (reproducibility, ability to use the model, community)
  - Homogeneity of the model
  - Techniques available to evaluate the model

A good translational biomarker

- Construct validity
  - Biological relevance
  - Biological parameter can be measured in humans and animals
    - With exactly the same method (pb of scale-up)
    - Similar methods (ex. amyloid plaque imaging)
- Face validity
  - Same behavior in animals and humans
    - Evolution with disease evolution
- Prediction validity
  - Same modulation with same treatment in humans and animals (if validated modelization in animal).
- Easy to use
  - Access (reproducibility, price, community)
  - Homogeneity of the results

Validity of the disease/target hypothesis

- Construct validity
  - Biological relevance
  - Constructed from human data
- Prediction validity
  - Predicts the effects of treatments in humans.



Thank you…

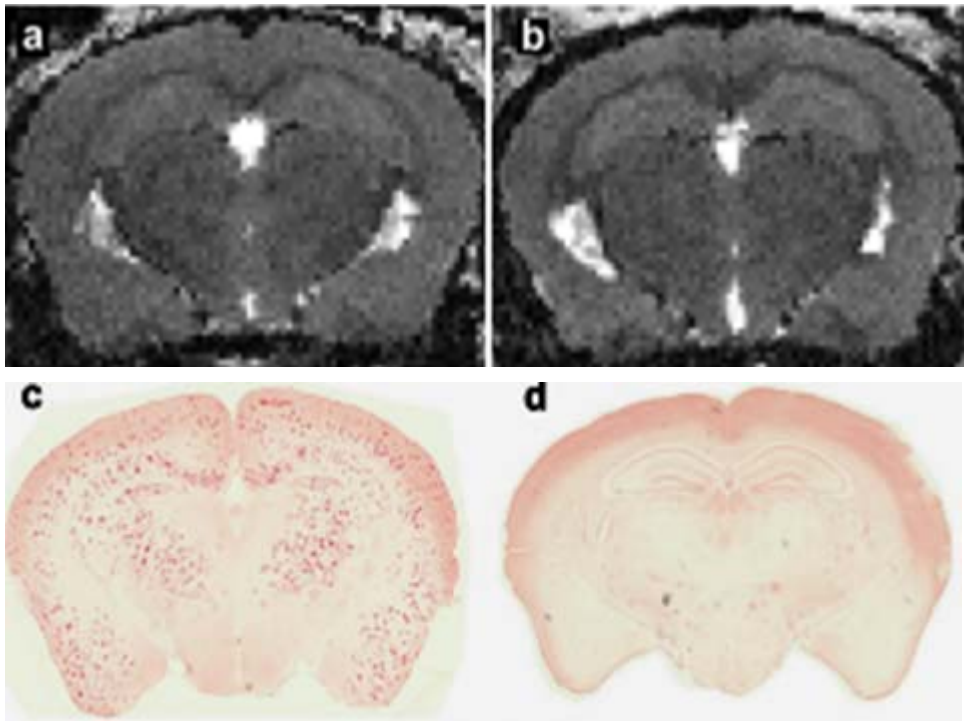
http://mamobipet.free.fr/Teaching/Teaching.html

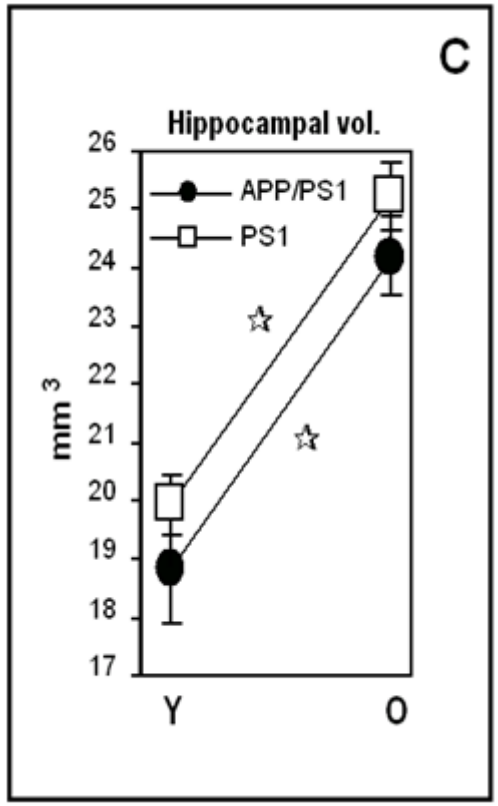
Annex
other potential biomarkers in animals

- Cerebral atrophy
- Other biomarkers of beta amyloid
  - Liquides périphériques
    - LCR
    - Sang
  - Le cerveau
    - PET
    - Imagerie optique
    - IRM
  - Les yeux
- Synaptic activity
  - MEMRI
- Neuronal death

Cerebral atrophy

CSF and brain volumes in mice





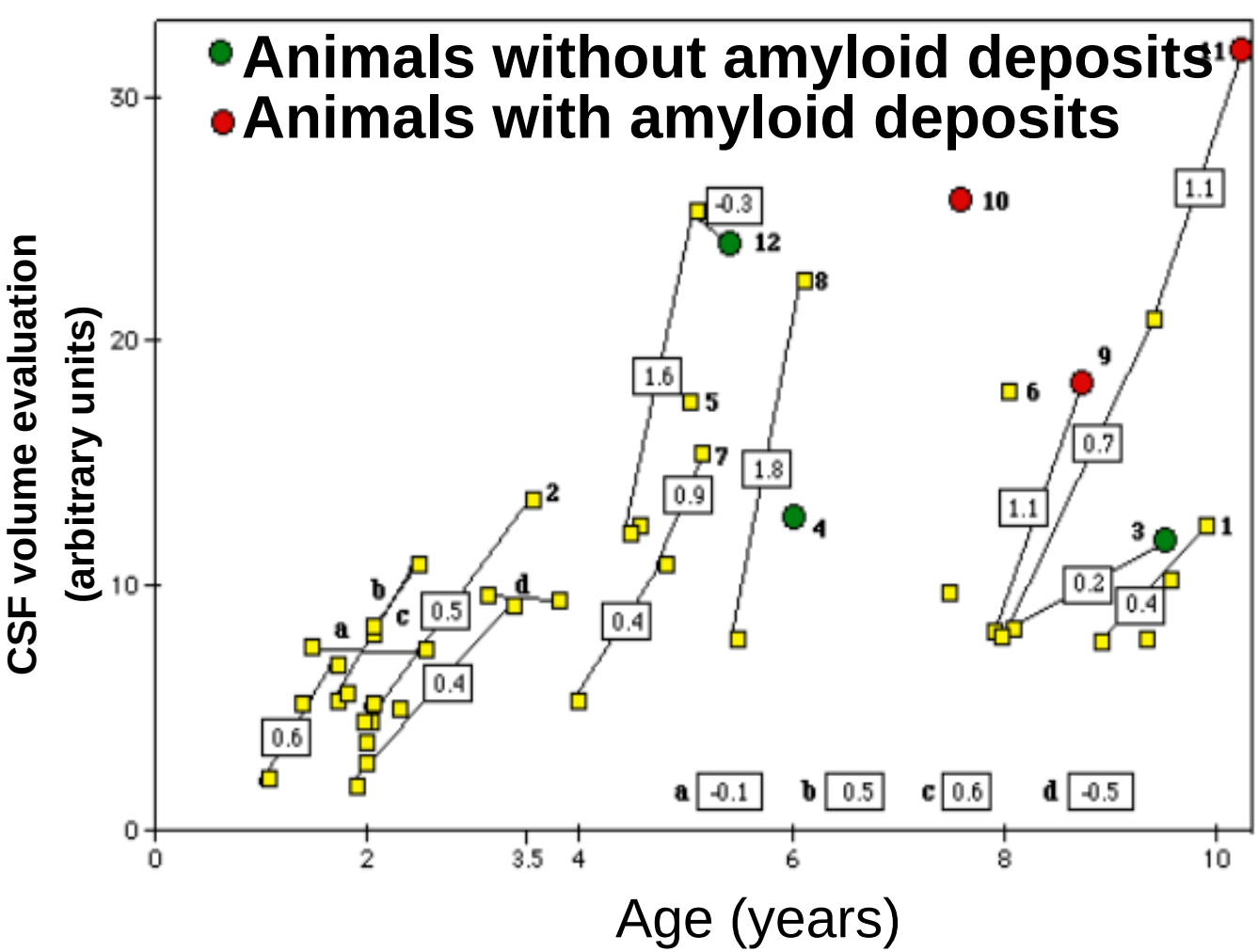
Brain and hippocampal growth
even in the presence of amyloid deposits…

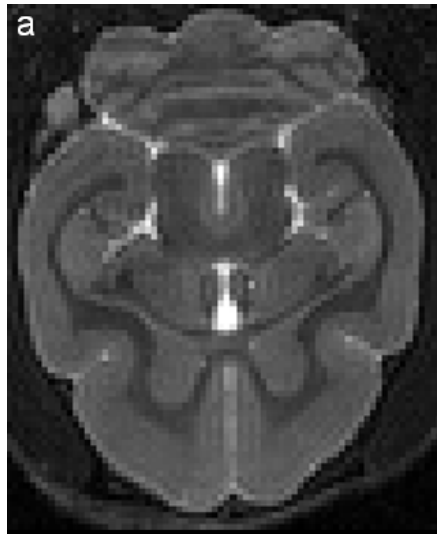
Delatour et al. (2006). Neurobiol Aging, 27(6), 835-847.

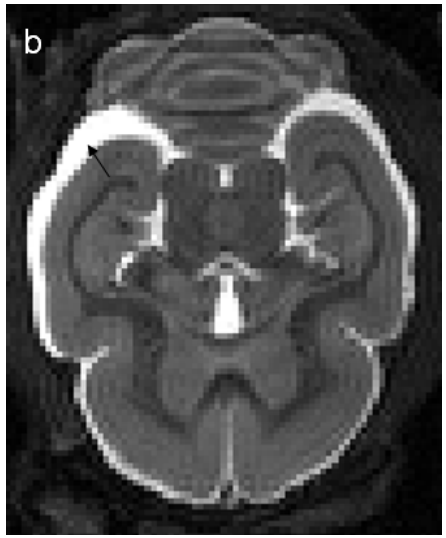
Conclusion atrophie souris

Biomarker	Use in animals		Use in humans	
	Detection of AD-like pathology	Preclinical evaluation of drugs	Clinical diagnostic	Clinical endpoint True benefits of a drug
Cerebral atrophy	No	No	Yes	No

Longitudinal follow-up of temporo-parietal atrophy





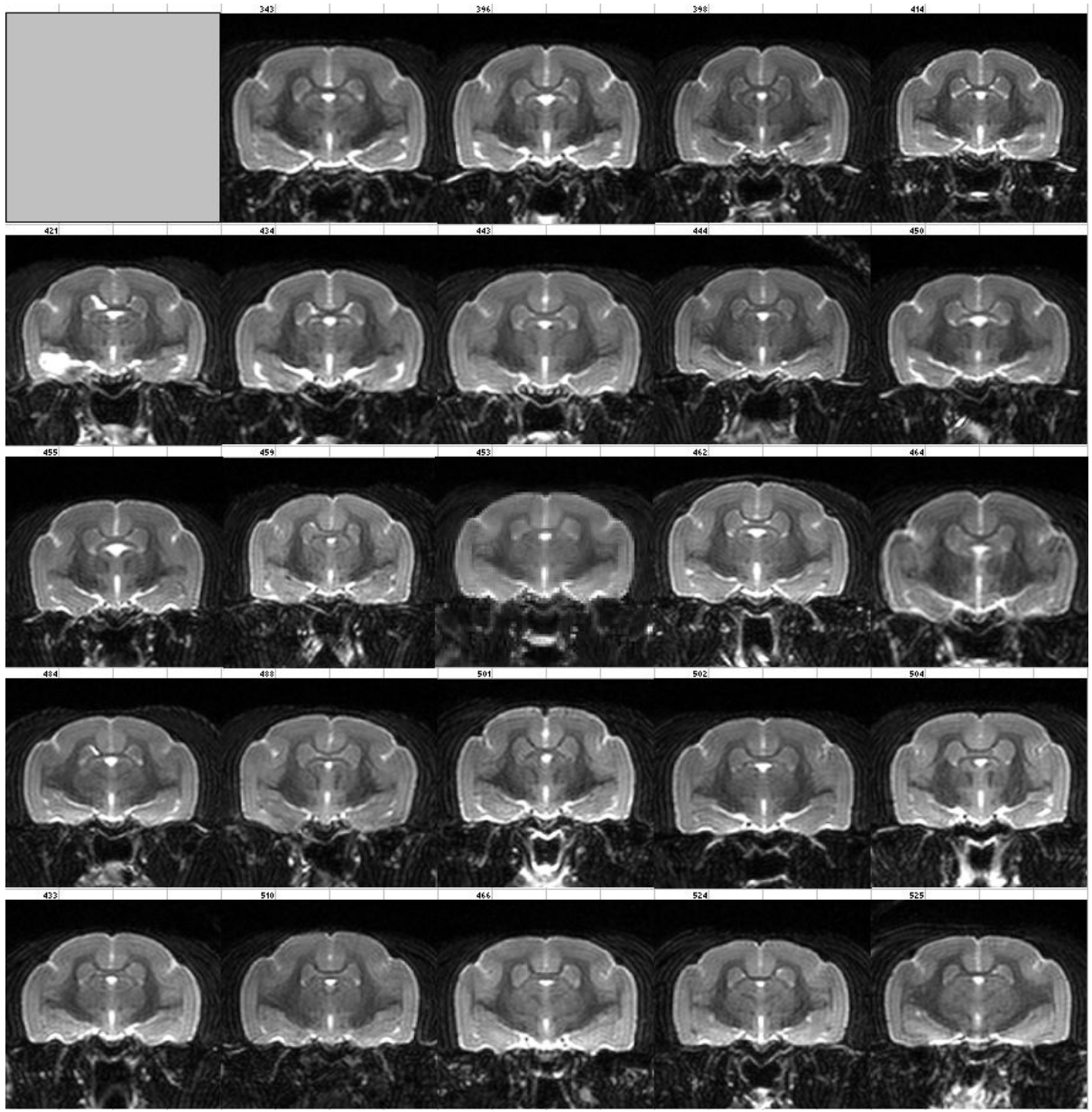


- Quick evolution once started

Dhenain et al. Neurobiol Aging. 2000;21(1):81-8.

Use of atrophy to select animals involved in therapeutic trials

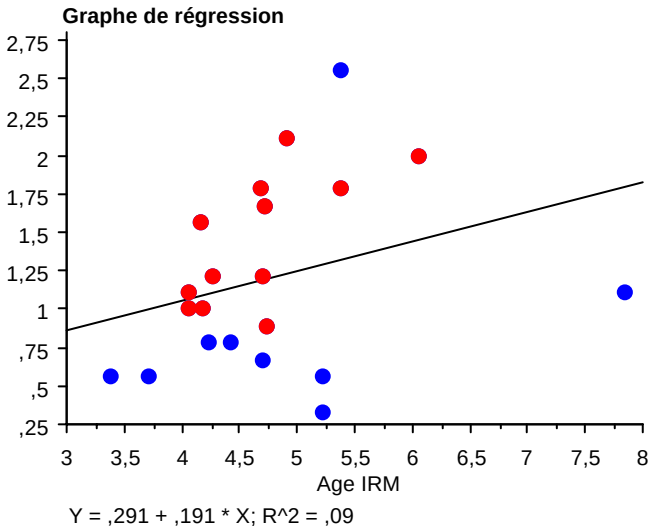
- 25 animals scanned

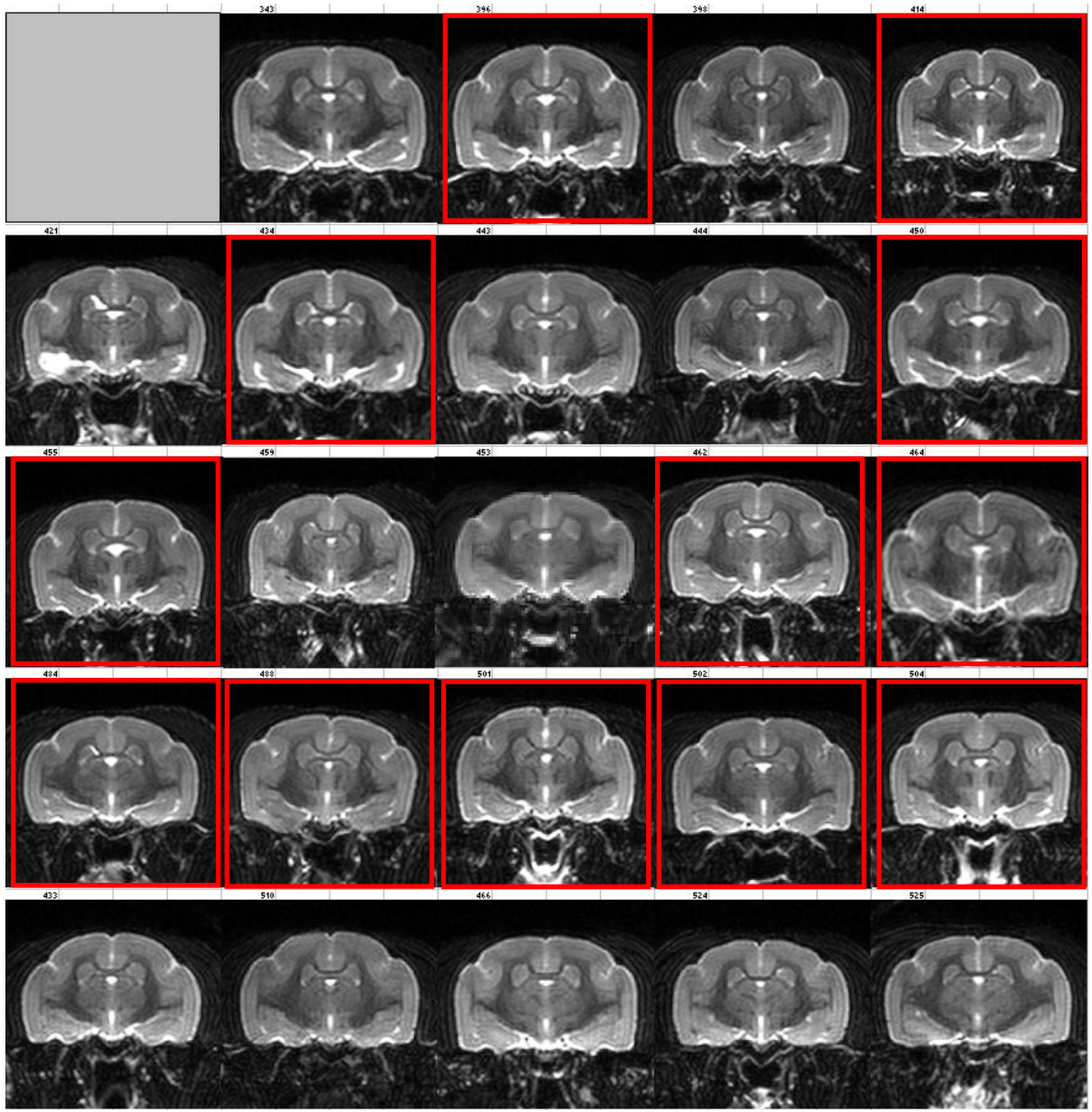


Nelly Joseph-Mathurin

Animals Screening

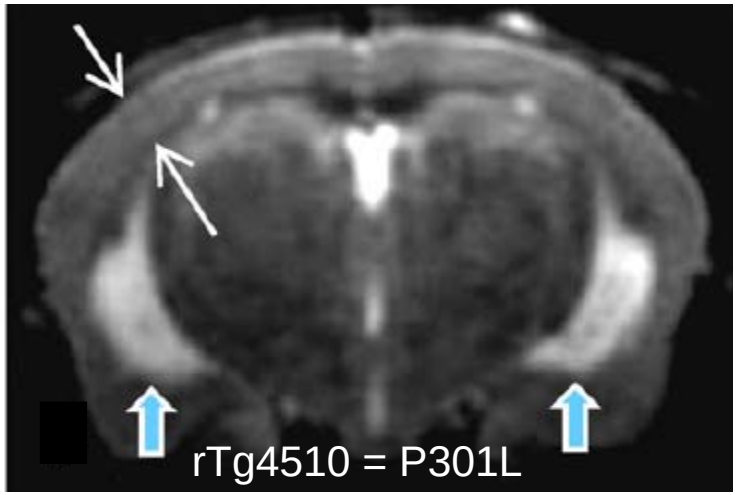
- 12 animals selected

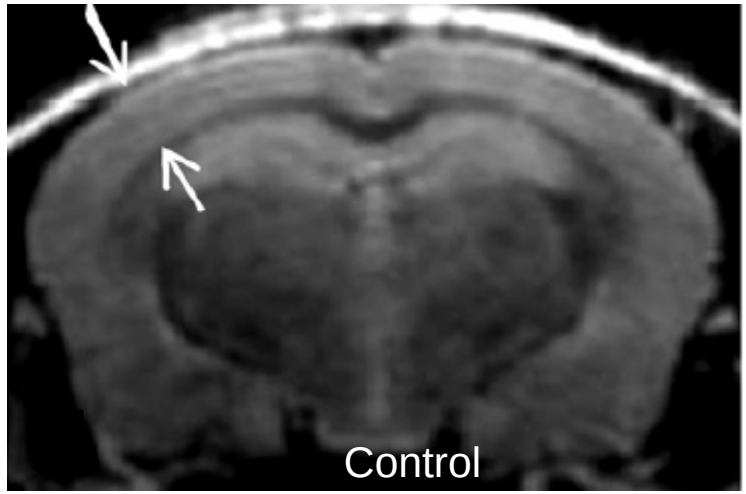


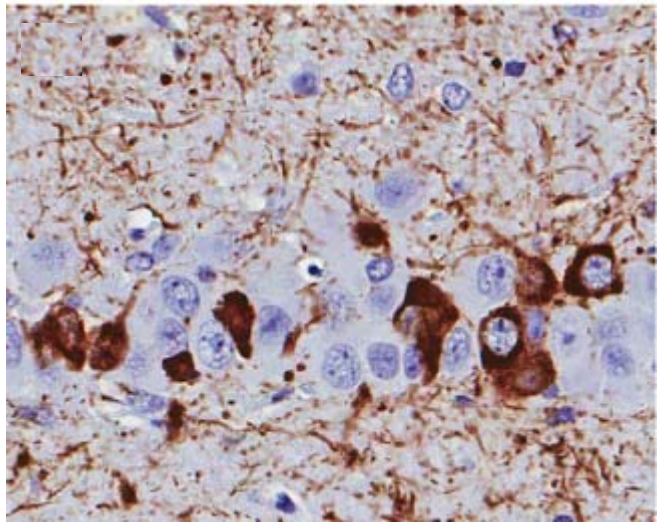


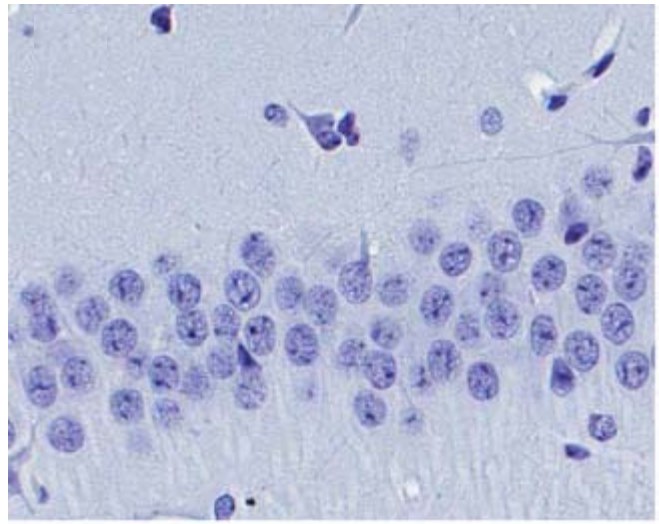
Nelly Joseph-Mathurin

Cerebral atrophy in Tau mice









Suggests that atrophy is a marker of Tau pathology

Yang D et al. Neuroimage. 2011 (rTg4510 = P301L mice)

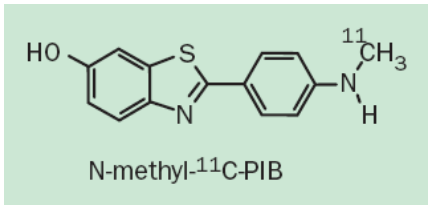
Biomarqueurs de l'Amyloïde béta

- Liquides périphériques
  - LCR
  - Sang
- Le cerveau
  - PET
  - Imagerie optique
  - IRM
- Les yeux

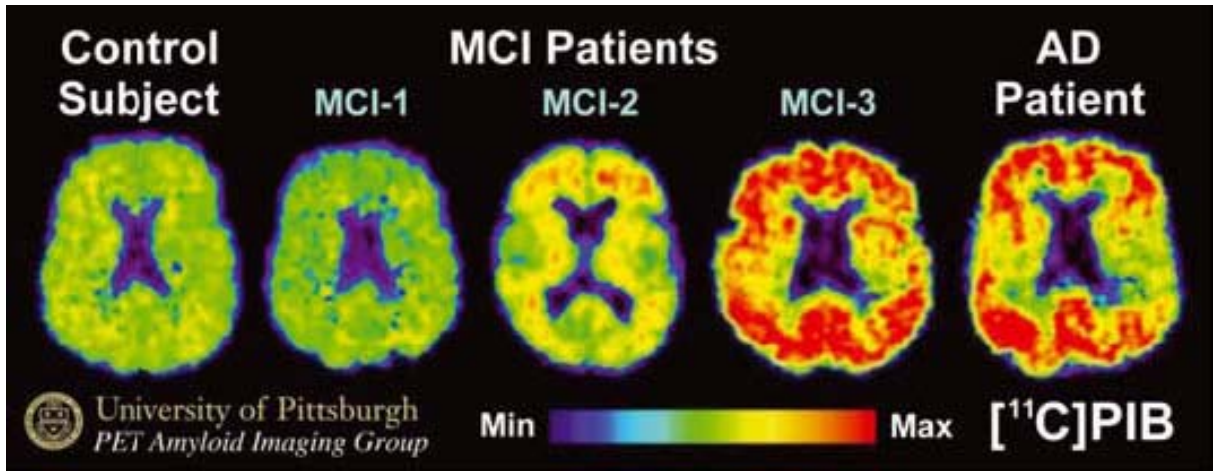
Où chercher l'Amyloïde béta

- Liquides périphériques
  - LCR
  - Sang
- Le cerveau
  - PET
  - Imagerie optique
  - IRM
- Les yeux

Amyloid imaging in humans (by PET)



N-methyl-^{11}C-PIB



10598 • The Journal of Neuroscience, November 16, 2005 • 25(46):10598–10606

Cellular/Molecular

Binding of the Positron Emission Tomography Tracer Pittsburgh Compound-B Reflects the Amount of Amyloid-β in Alzheimer's Disease Brain But Not in Transgenic Mouse Brain

William E. Klunk,[1] Brian J. Lopresti,[2] Milos D. Ikonomovic,[3] Iliya M. Lefterov,[4] Radosveta P. Koldamova,[5] Eric E. Abrahamson,[3] Manik L. Debnath,[1] Daniel P. Holt,[2] Guo-feng Huang,[2] Li Shao,[1] Steven T. DeKosky,[3] Julie C. Price,[2] and Chester A. Mathis[2]

Departments of [1]Psychiatry, [2]Radiology, [3]Neurology, [4]Environmental and Occupational Health, and [5]Pharmacology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213

European Journal of Nuclear Medicine and Molecular Imaging

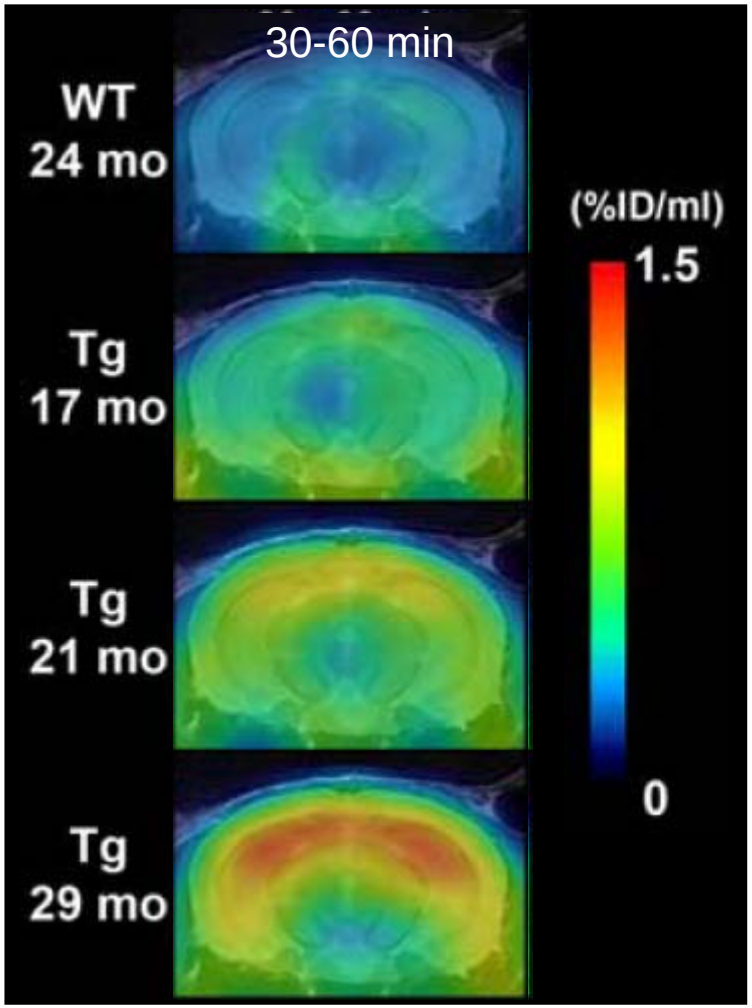
10.1007/s00259-005-1780-5

Molecular Imaging

PET imaging of brain with the β-amyloid probe, [^{11}C]6-OH-BTA-1, in a transgenic mouse model of Alzheimer's disease

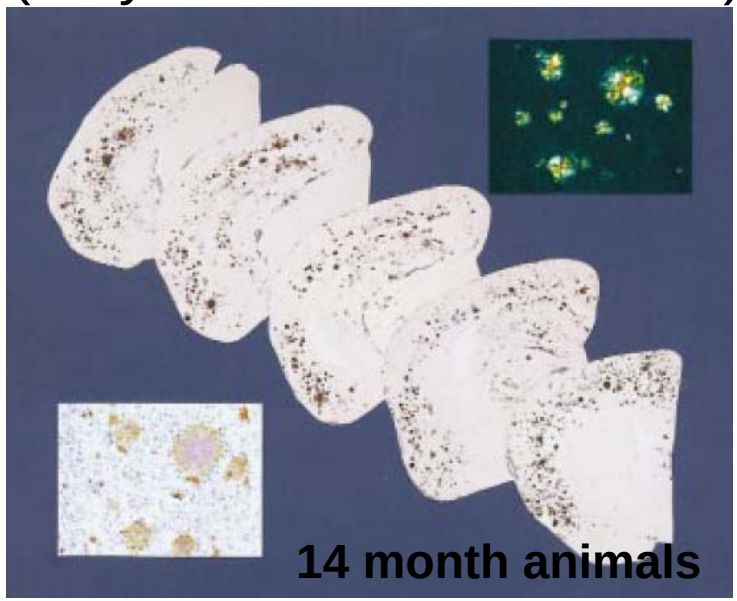
Hiroshi Toyama[1, 2], Daniel Ye[3], Masanori Ichise[2], Jeih-San Liow[2], Lisheng Cai[2], David Jacobowitz[4], John L. Musachio[2], Jinsoo Hong[2], Mathew Crescenzo[2], Dnyanesh Tipre[2], Jian-Qiang Lu[2], Sami Zoghbi[2], Douglass C. Vines[2], Jurgen Seidel[5], Kazuhiro Katada[1], Michael V. Green[5], Victor W. Pike[2], Robert M. Cohen[3] and Robert B. Innis[2]

PIB Mice – Very late marker (if marker)



Maeda, J., B. Ji, et al. (2007).
J Neurosci **27**(41): 10957-68.

APP 23 mice
(Amyloid starts at 6 months)



Binding of the Positron Emission Tomography Tracer Pittsburgh Compound-B Reflects the Amount of Amyloid-β in Alzheimer's Disease Brain But Not in Transgenic Mouse Brain

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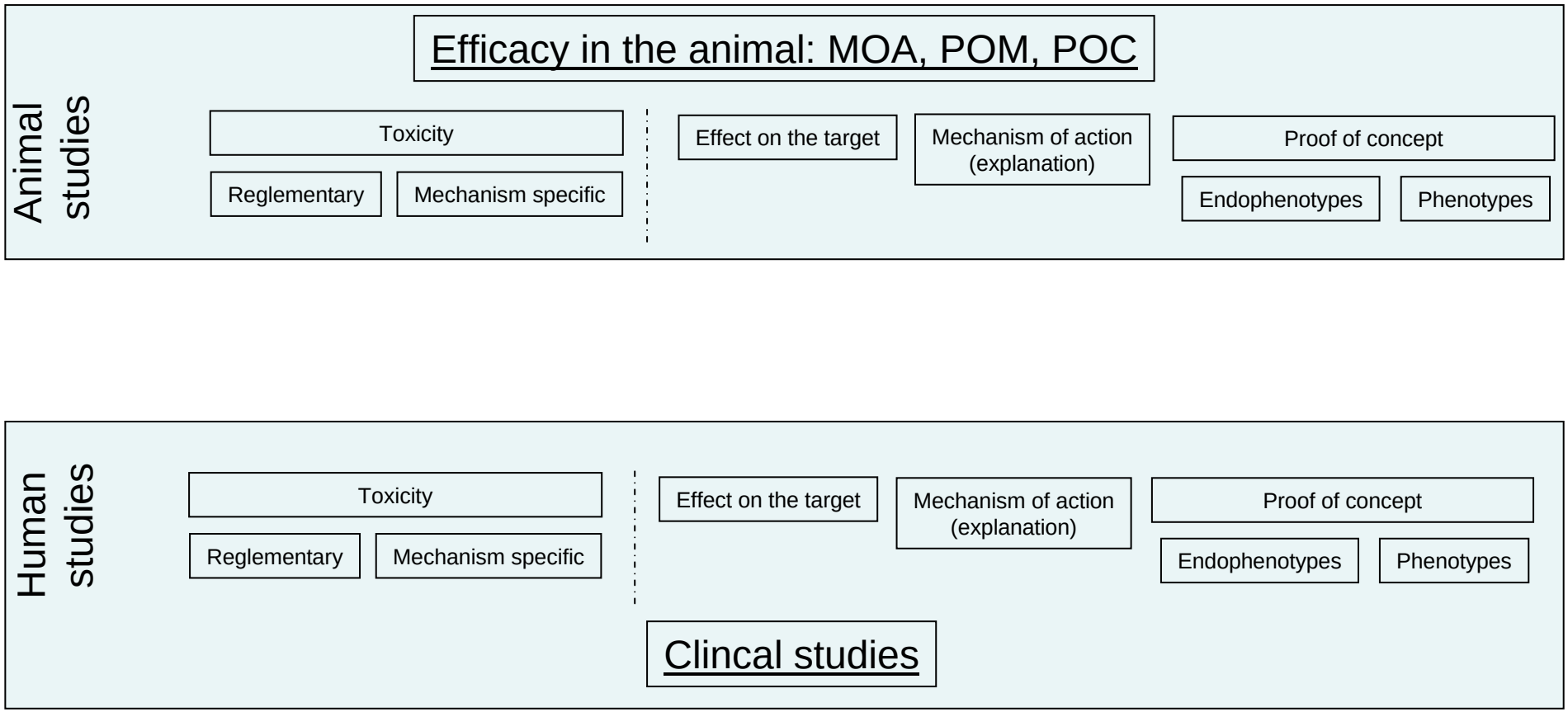
Departments of [1]Psychiatry, [2]Radiology, [3]Neurology, [4]Environmental and Occupational Health, and [5]Pharmacology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213

Klunk, W. E., B. J. Lopresti, et al. (2005).
J Neurosci **25**(46): 10598-606.

Conclusion: amyloid detection - PET

Biomarker	Use in animals		Use in humans	
	Detection of AD-like pathology	Preclinical evaluation of drugs	Clinical diagnostic	Clinical endpoint True benefits of a drug
Amyloid (Aggregated - PET + PIB)	Yes	No	Yes	No
Futur contrast agents ?	Yes ?	Yes ?	Yes	No

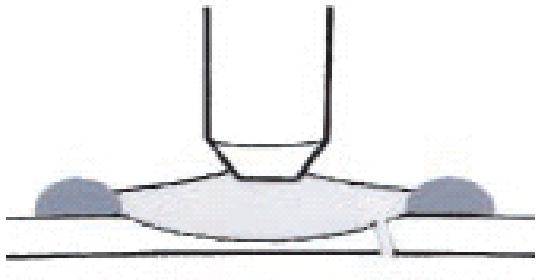

Animal studies
Efficacy in the animal: MOA, POM, POC
Toxicity
Reglementary
Mechanism specific
Effect on the target
Mechanism of action (explanation)
Proof of concept
Endophenotypes
Phenotypes
Human studies
Toxicity
Reglementary
Mechanism specific
Effect on the target
Mechanism of action (explanation)
Proof of concept
Endophenotypes
Phenotypes
Clincal studies

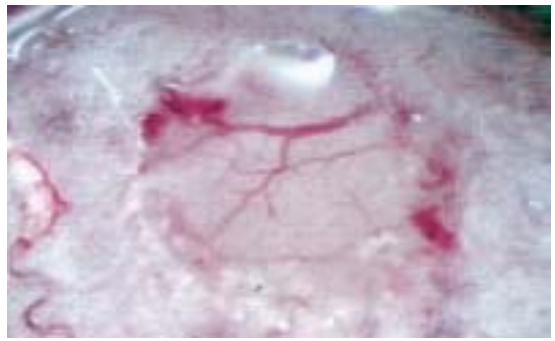
Où chercher l'Amyloïde béta

- Liquides périphériques
  - LCR
  - Sang
- Le cerveau
  - PET
  - Imagerie optique
    - Multiphoton microscopy
    - Near Infra red imaging
  - IRM
- Les yeux

Multiphoton microscopy

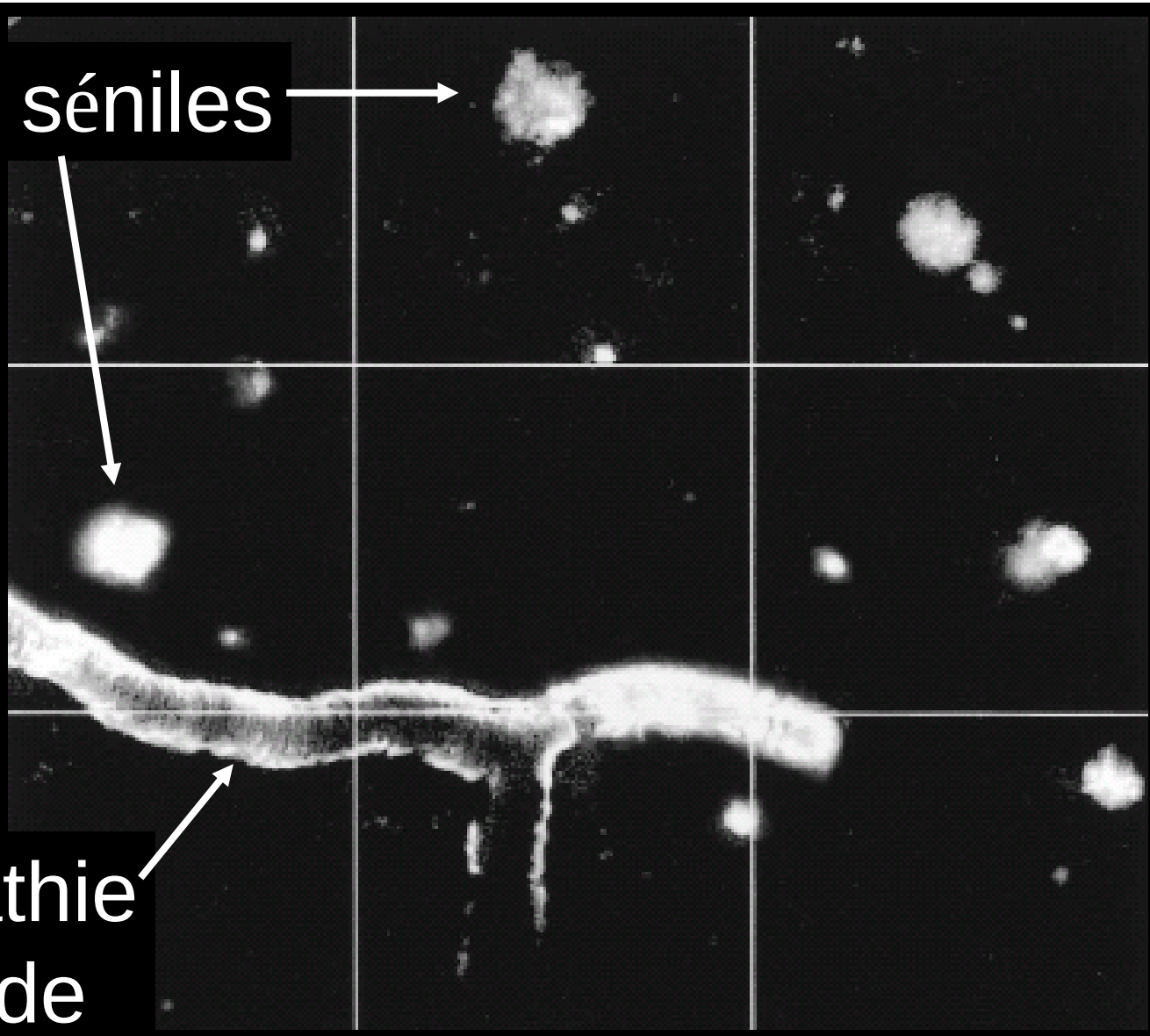
- Fenêtre sur le cerveau





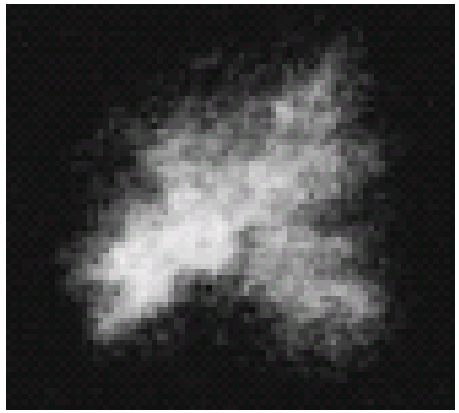
- Marquage par un fluorophore
  - Thioflavine S (par exemple)
- Résolution = 1 µm
- Profondeur = 150 µm

Multiphoton microscopy

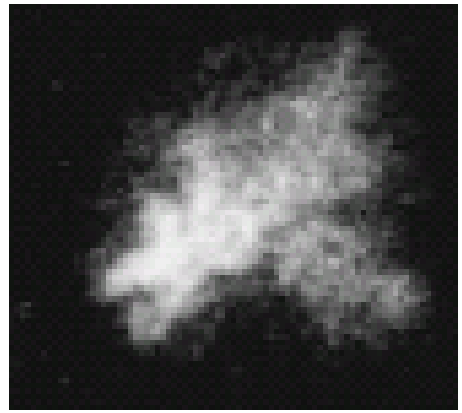


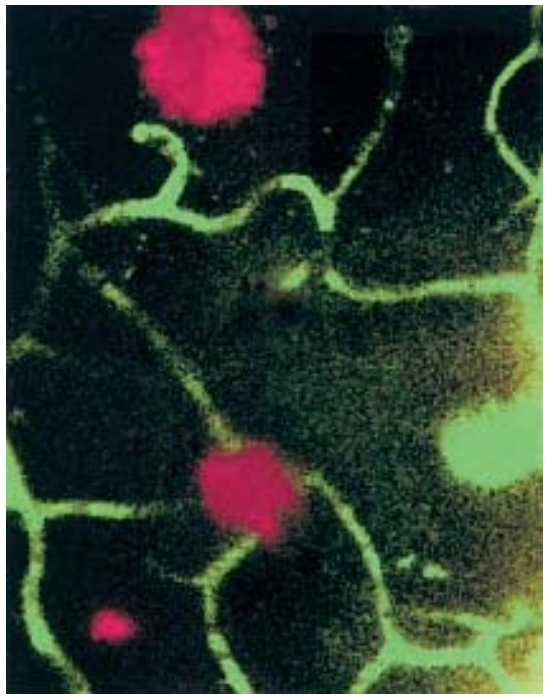
Christie R. H. et al., The Journal of Neuroscience, 21(3), 858-864, 2001

Multiphoton microscopy: Longitudinal follow up of plaque turn over

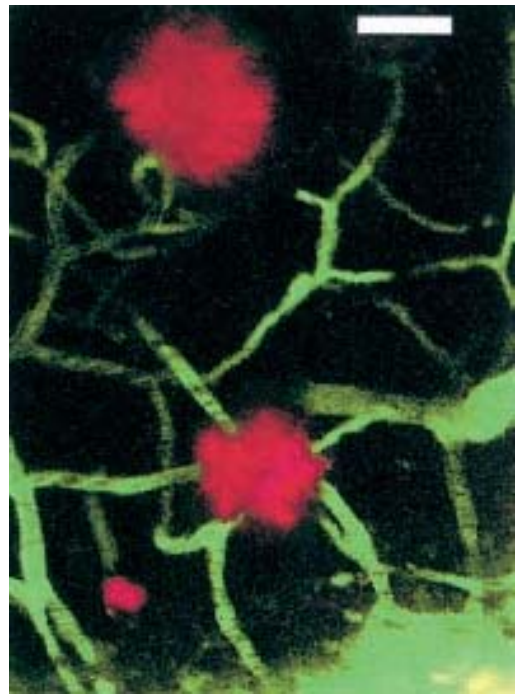


+ 2 jours





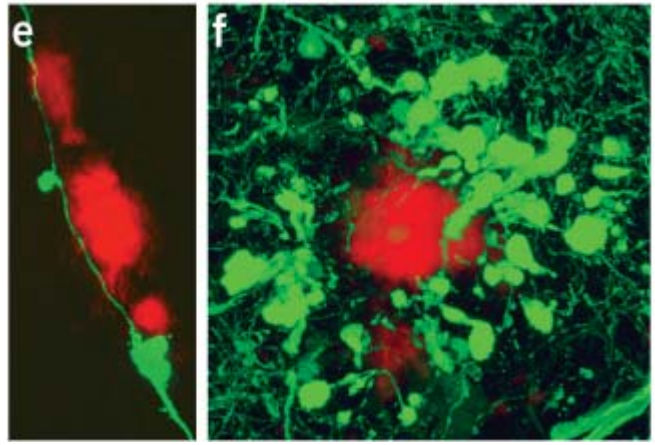
+ 104 jours



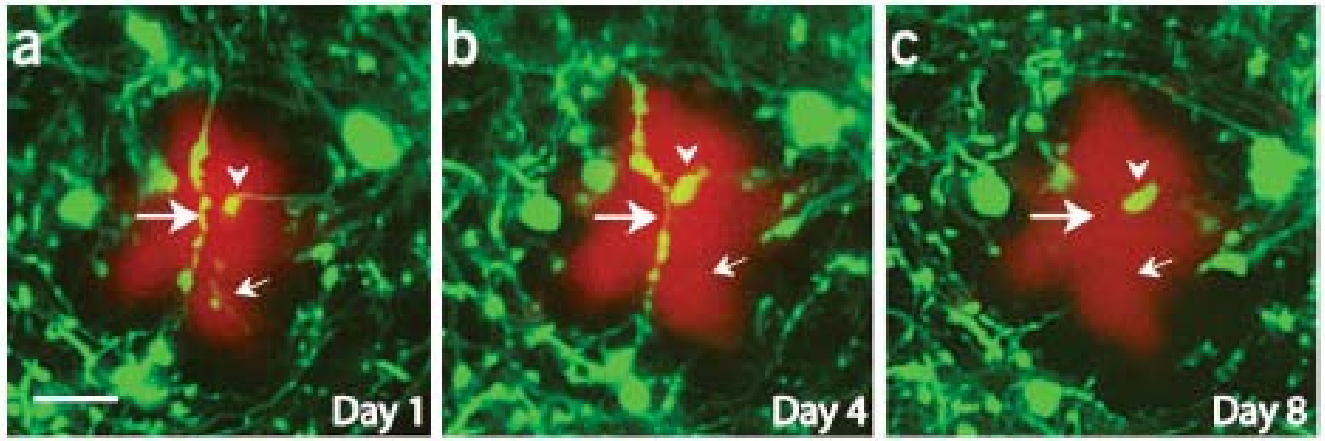
Christie R. H. et al., The Journal of Neuroscience, 21(3), 858-864, 2001

Multiphoton microscopy: Longitudinal follow up of plaque toxicity

- Neuronal varicosities associated to amyloid plaques



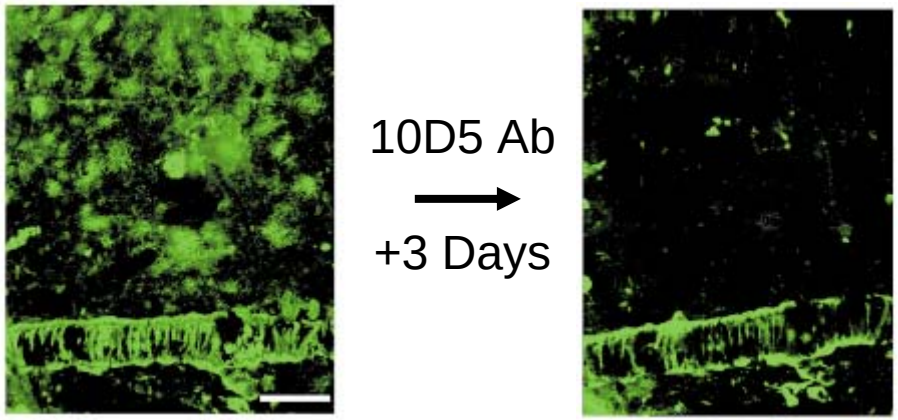
- Neurite breakage close to amyloid plaques



Tsai, J., J. Grutzendler, et al. (2004). Nat Neurosci 7(11): 1181-3.

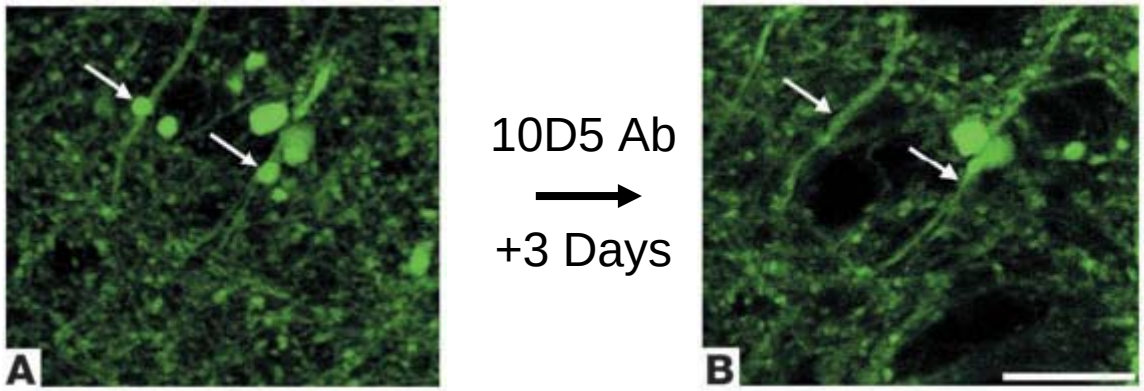
Multiphoton microscopy: Use to evaluate experimental therapies

- Détection of amyloid clearance following immunotherapy



Bacskai, B. J., et al. (2001). Nat Med 7(3): 369-72.

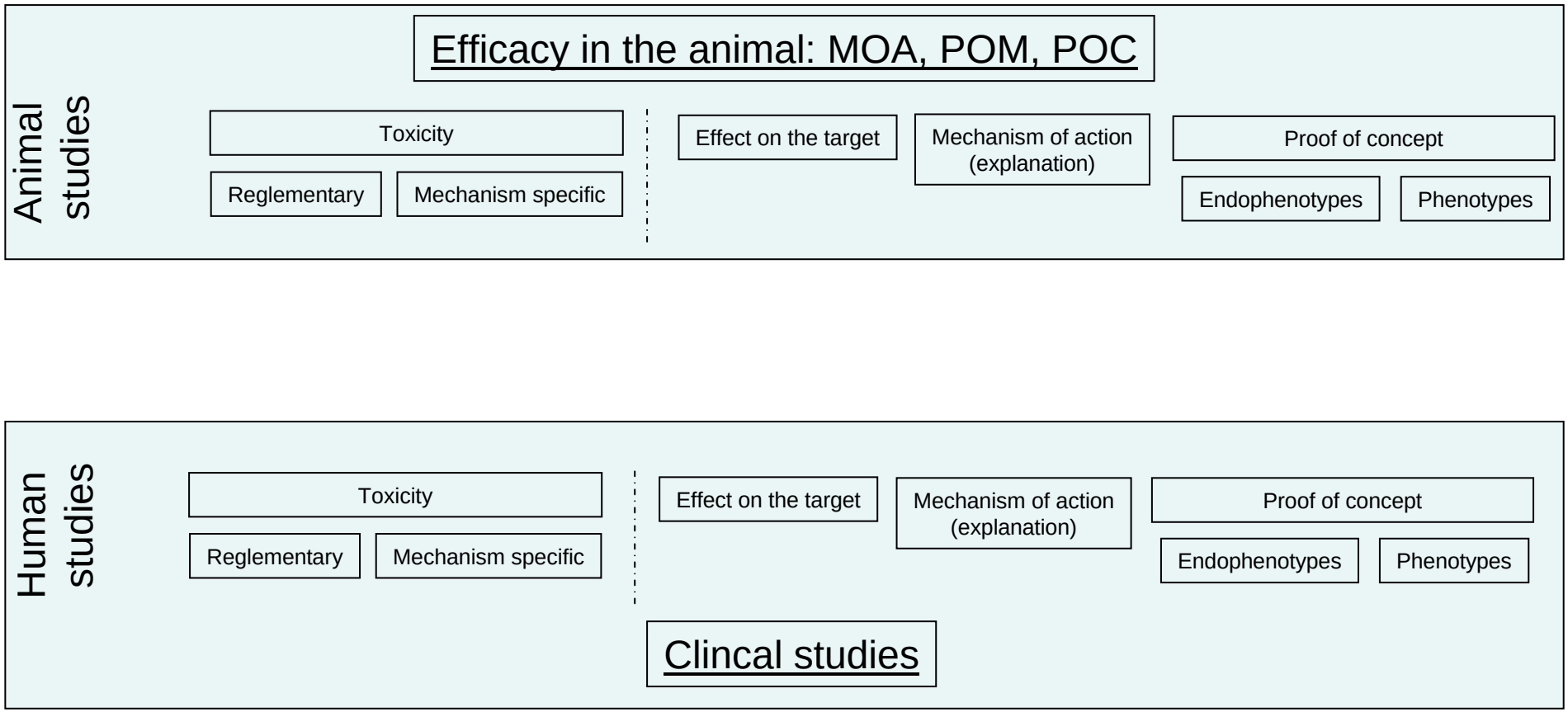
- Détection of effects of treatments on amyloid-associated neuronal modifications



Brendza, R. P., (2005). J Clin Invest **115**(2): 428-33.

Conclusion: amyloid detection – Multiphoton and NIR

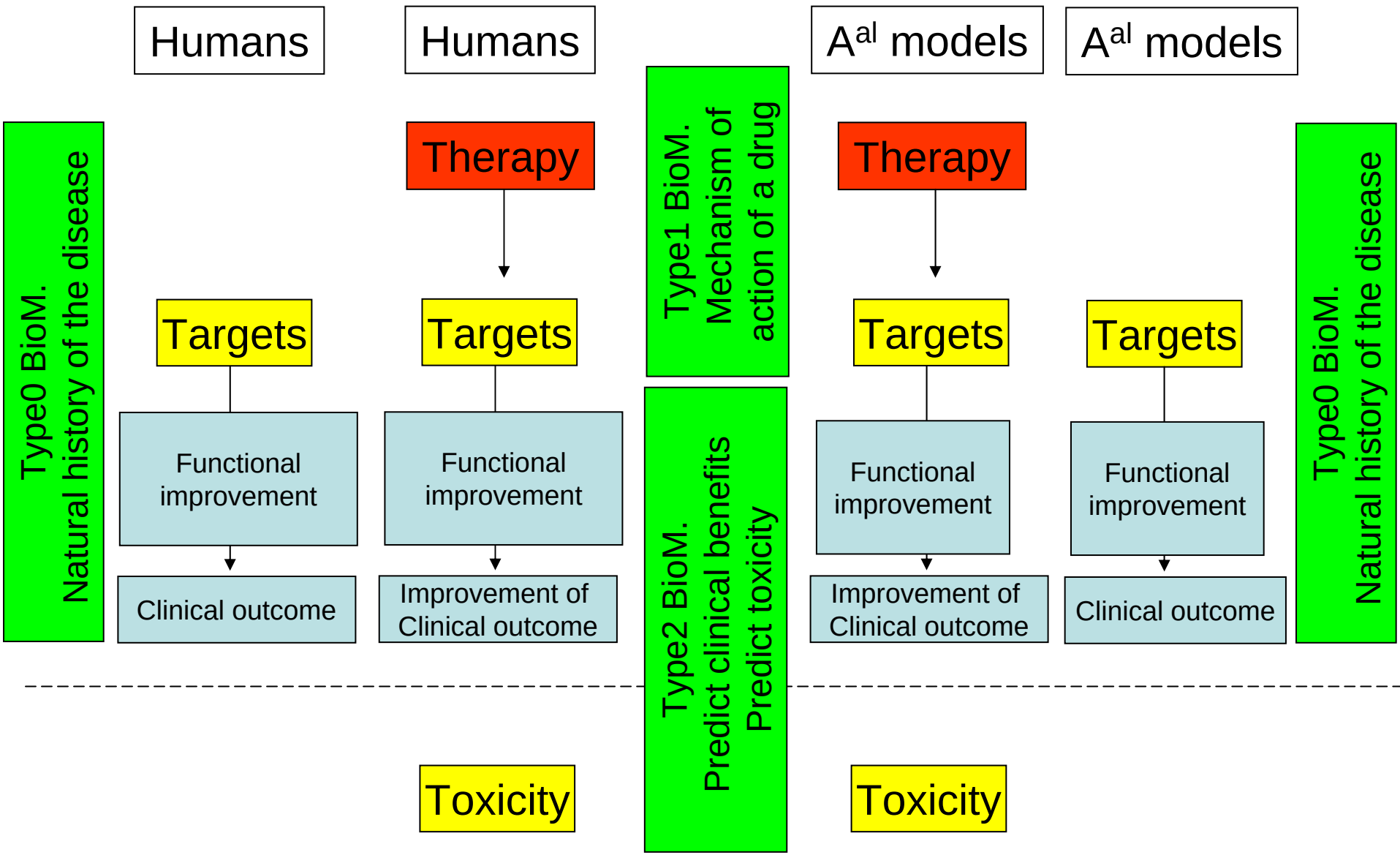
Biomarker	Use in animals		Use in humans	
	Detection of AD-like pathology	Preclinical evaluation of drugs	Clinical diagnostic	Clinical endpoint True benefits of a drug
Amyloid (Aggregated - PET + contrast agent)	Yes	No	Yes	No
Multiphoton	Yes	Yes	No	No
NIR	Yes	Yes	No	No


Animal studies
Efficacy in the animal: MOA, POM, POC
Toxicity
Reglementary
Mechanism specific
Effect on the target
Mechanism of action (explanation)
Proof of concept
Endophenotypes
Phenotypes
Human studies
Toxicity
Reglementary
Mechanism specific
Effect on the target
Mechanism of action (explanation)
Proof of concept
Endophenotypes
Phenotypes
Clincal studies

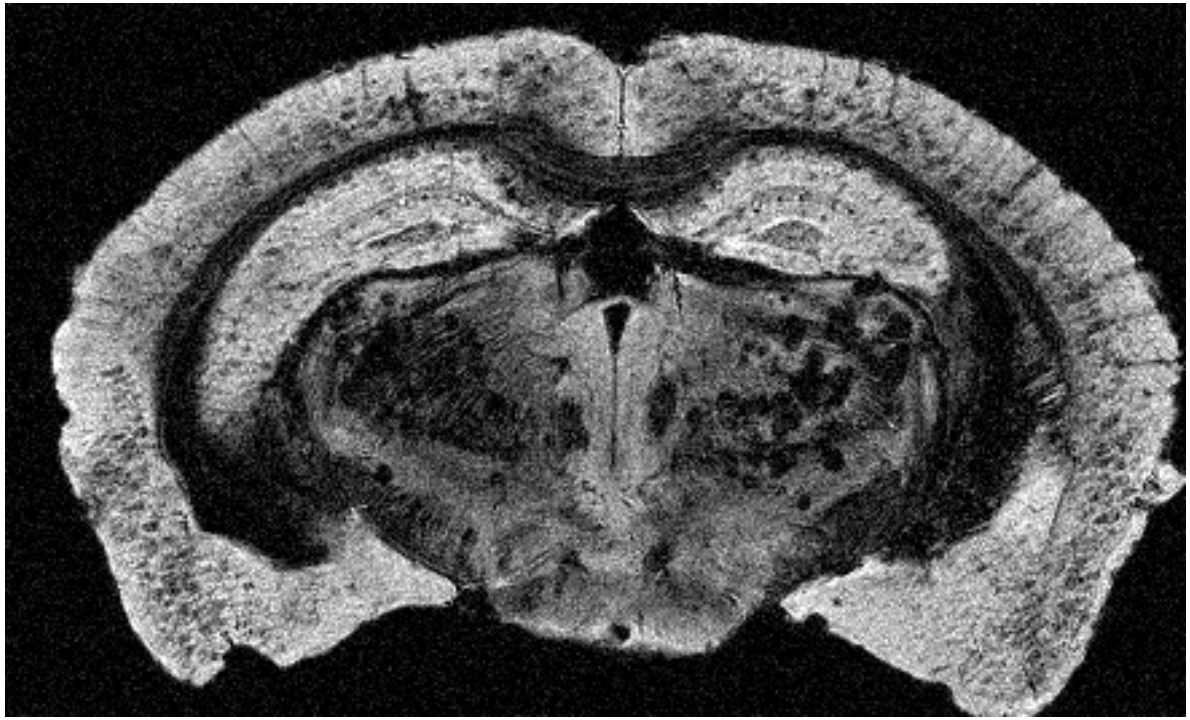
Où chercher l'Amyloïde béta

- Liquides périphériques
  - LCR
  - Sang
- Le cerveau
  - PET
  - Imagerie optique
  - IRM
- Les yeux

Conclusion

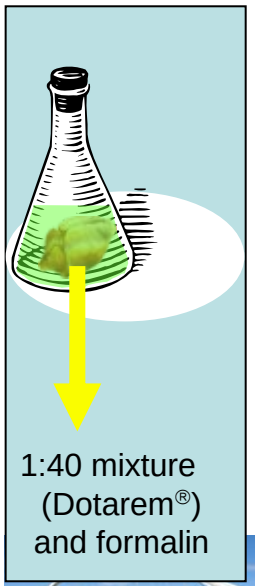

Humans
Humans
A^al models
A^al models
Type0 BioM. Natural history of the disease
Therapy
Therapy
Type1 BioM. Mechanism of action of a drug
Targets
Targets
Targets
Targets
Type0 BioM. Natural history of the disease
Functional improvement
Functional improvement
Functional improvement
Functional improvement
Clinical outcome
Improvement of Clinical outcome
Improvement of Clinical outcome
Clinical outcome
Type2 BioM. Predict clinical benefits Predict toxicity
Toxicity
Toxicity

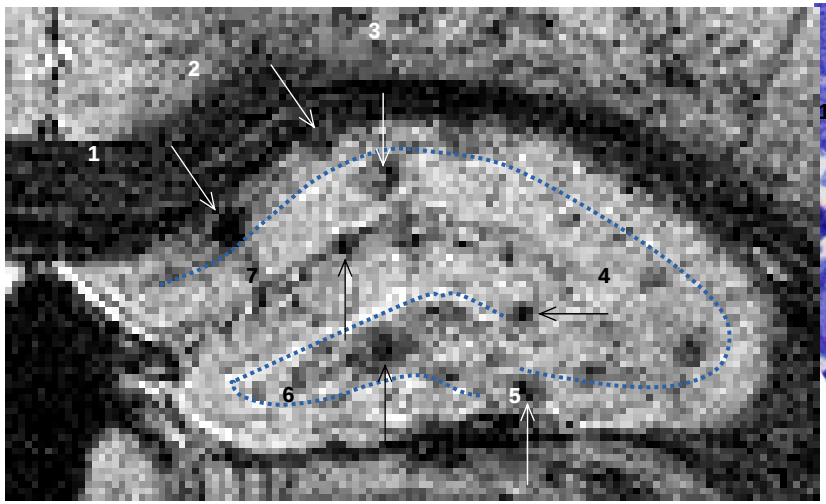
Optimisation of plaque imaging thanks to contrast agents

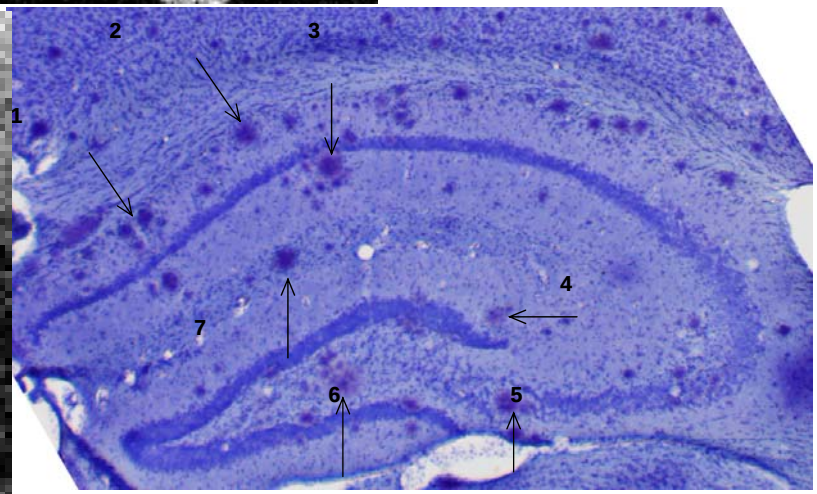


7T Clinical Scanner
Siemens
23.4 x 23.4 x 90 µm^3
Tacq = 13 hours 50 min
Sequence: GRE

Alexandra Petiet
Anne Bertrand
Chris Wiggins

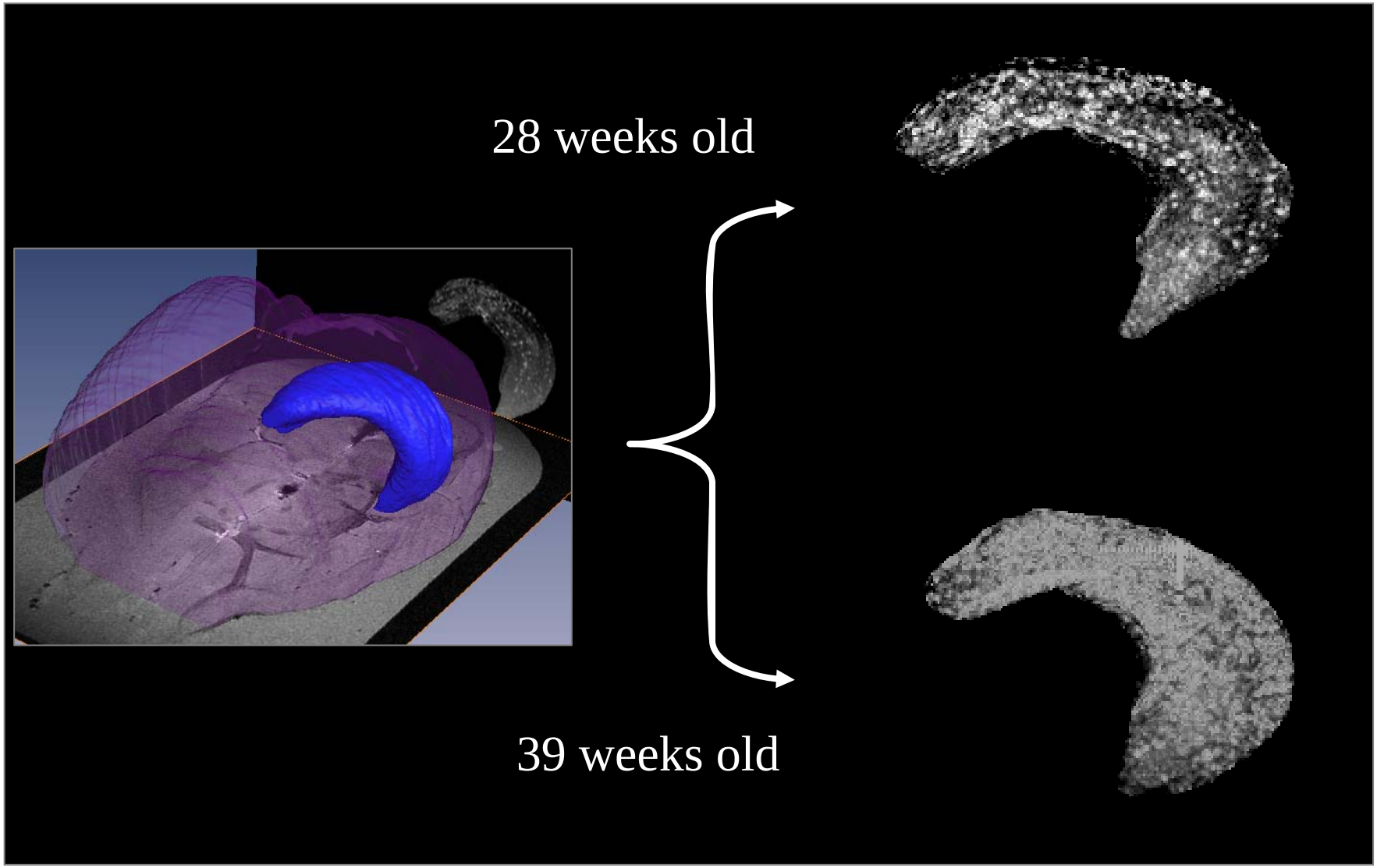






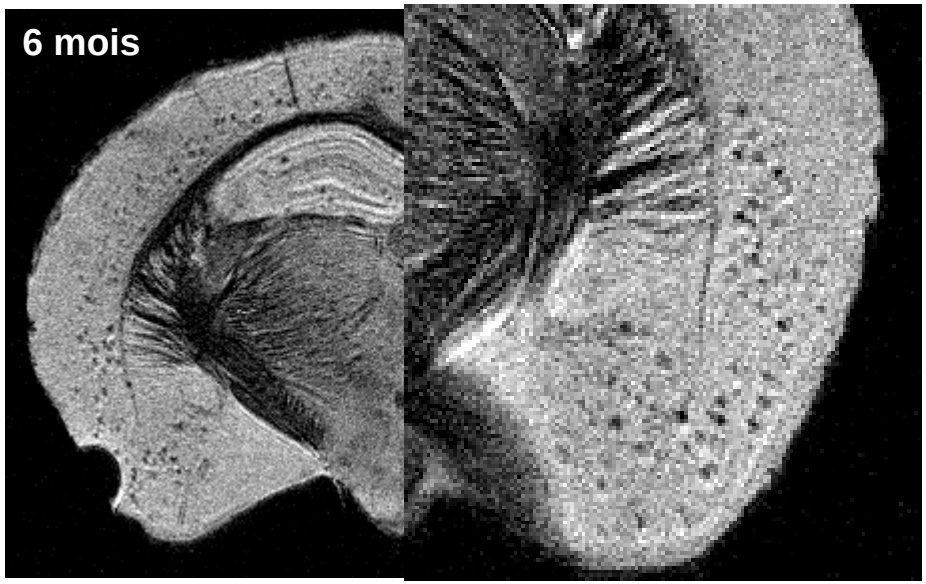
Dhenain M, et al. MRM. 55. 687-693. 2006.

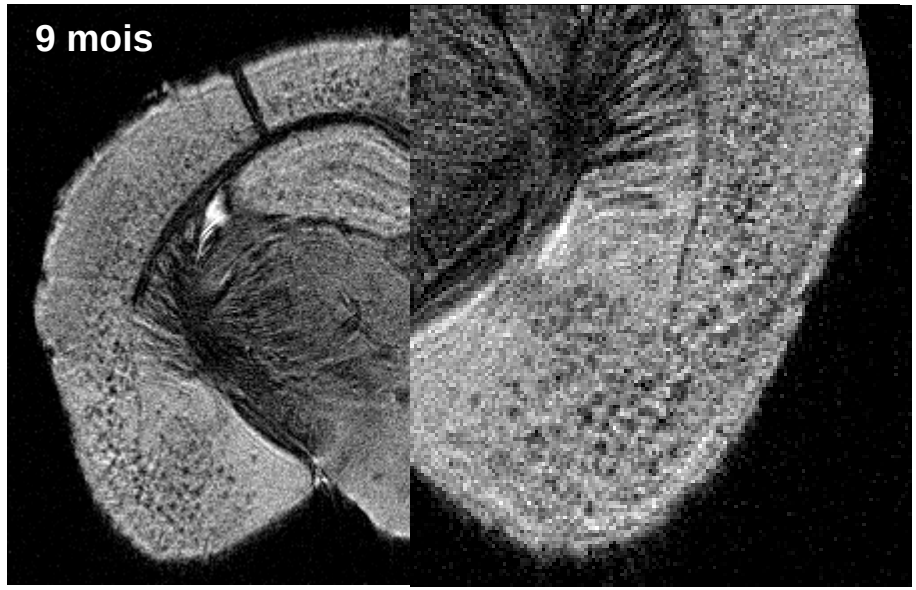
Passive staining: 3D Reconstructions

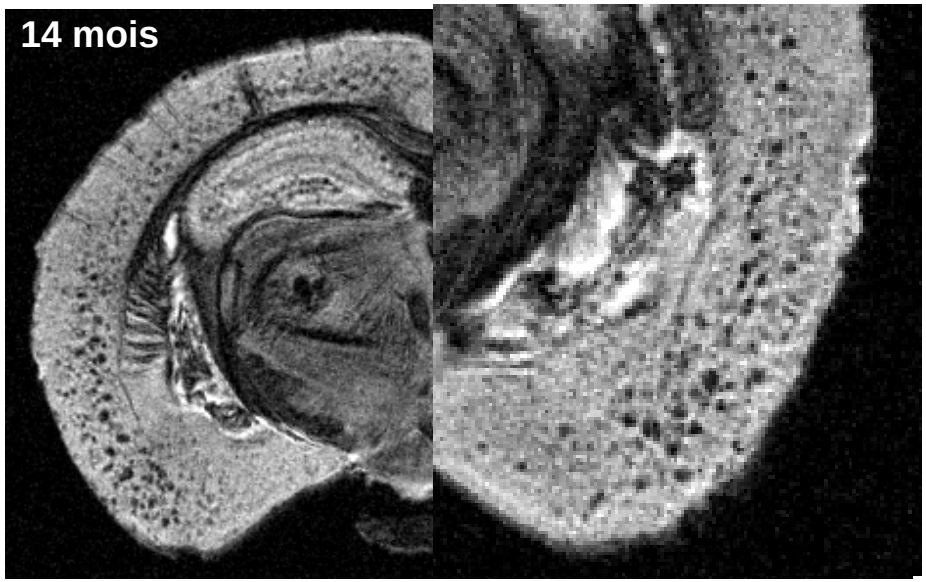


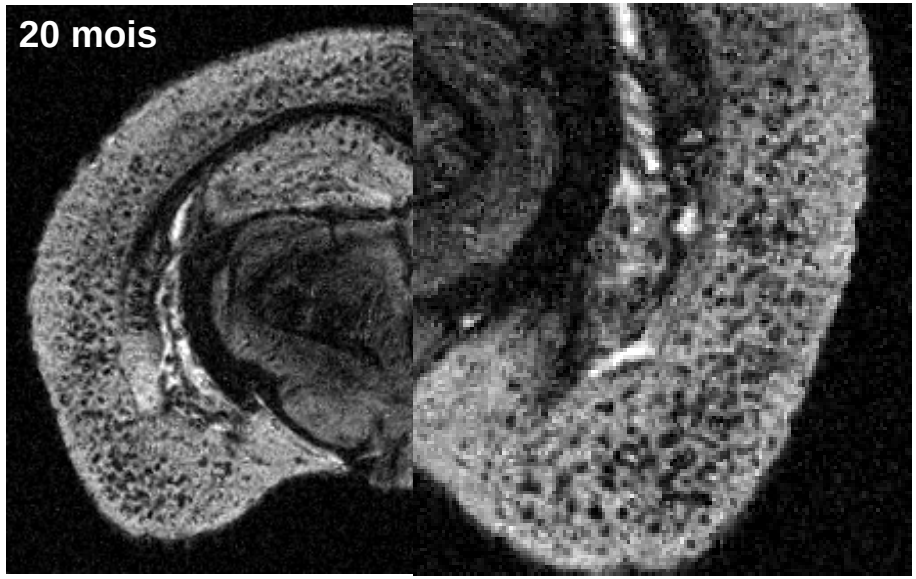
Dhenain M, et al. MRM. 55. 687-693. 2006.

Evaluation des plaques amyloïdes

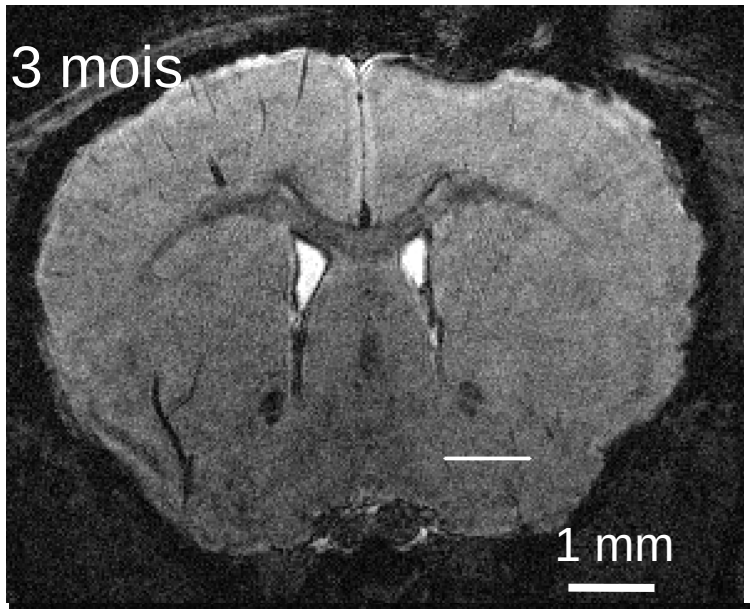


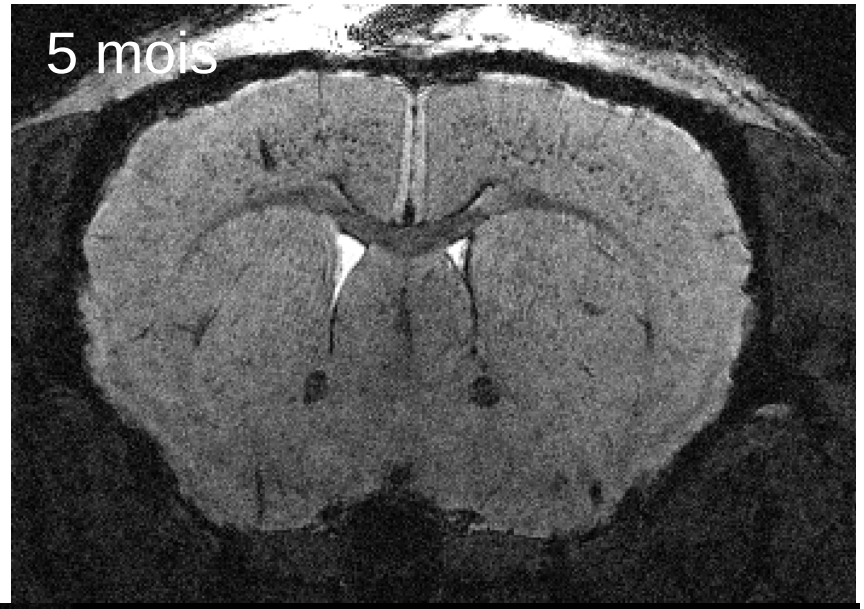


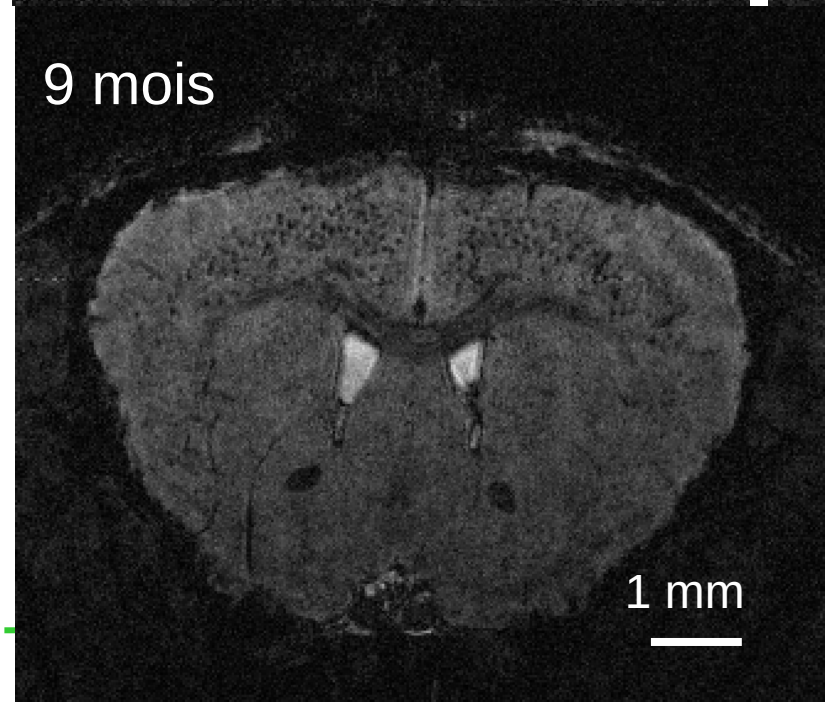


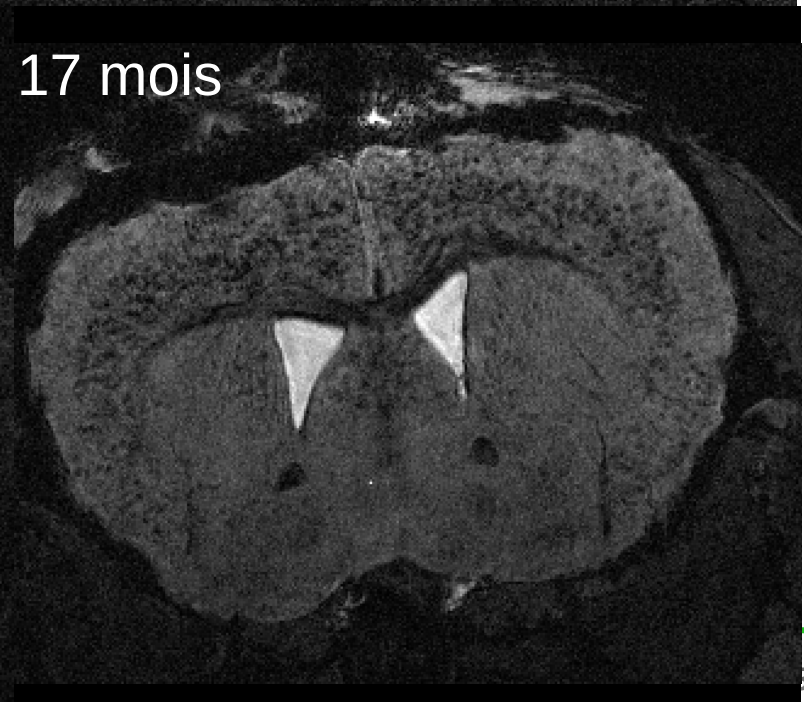


In-vivo follow up of amyloid load









Conclusion: amyloid detection - MRI

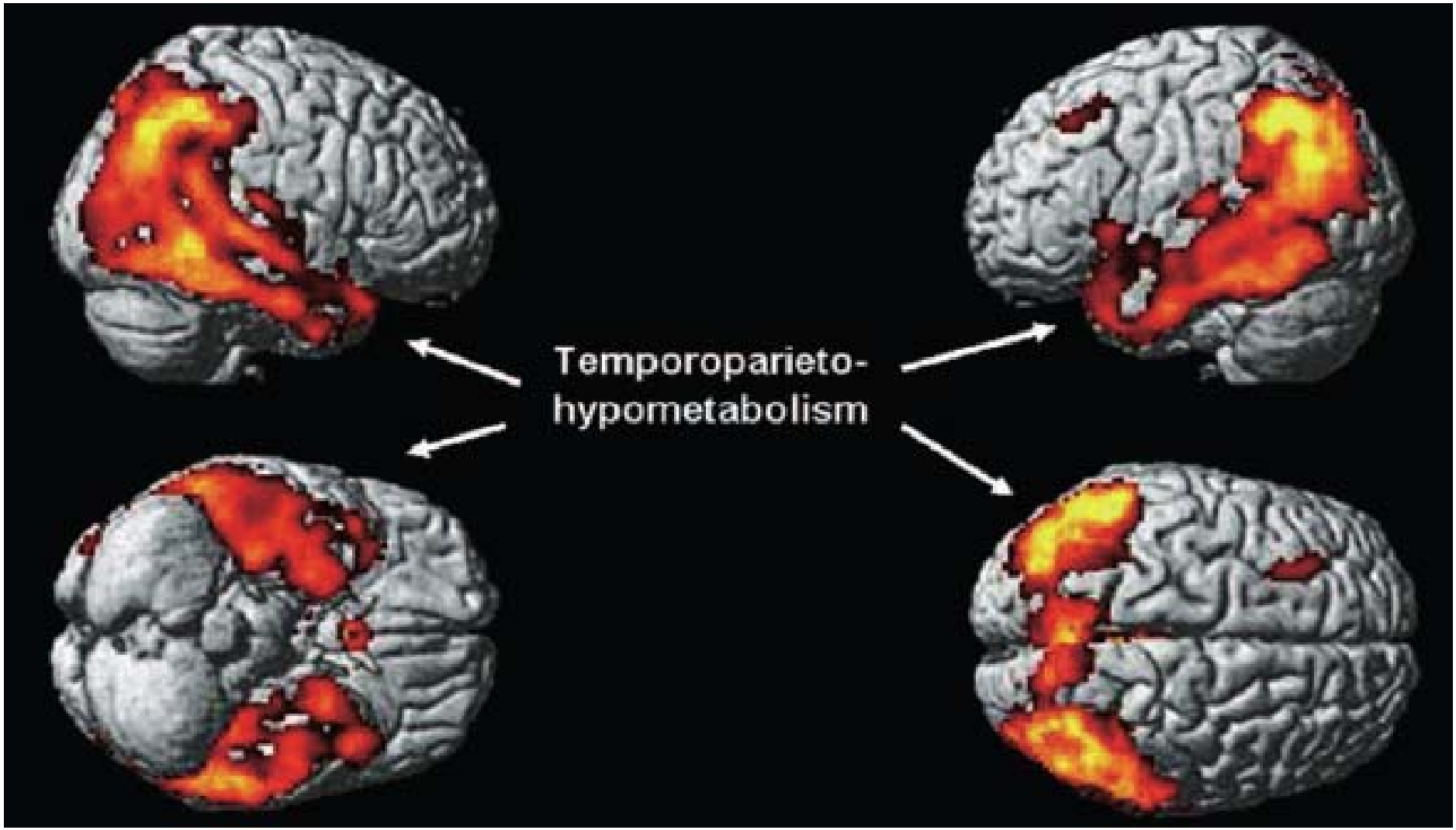
Biomarker	Use in animals		Use in humans	
	Detection of AD-like pathology	Preclinical evaluation of drugs	Clinical diagnostic	Clinical endpoint True benefits of a drug
Amyloid (MRI + contrast agent)	Yes	Yes	No	No

Dhenain, MR Insights, 2008 (http://www.la-press.com/)

Altérations fonctionnelles associées à la MA

- Métabolisme cérébral
- Perfusion cérébrale
- Transport neuronal

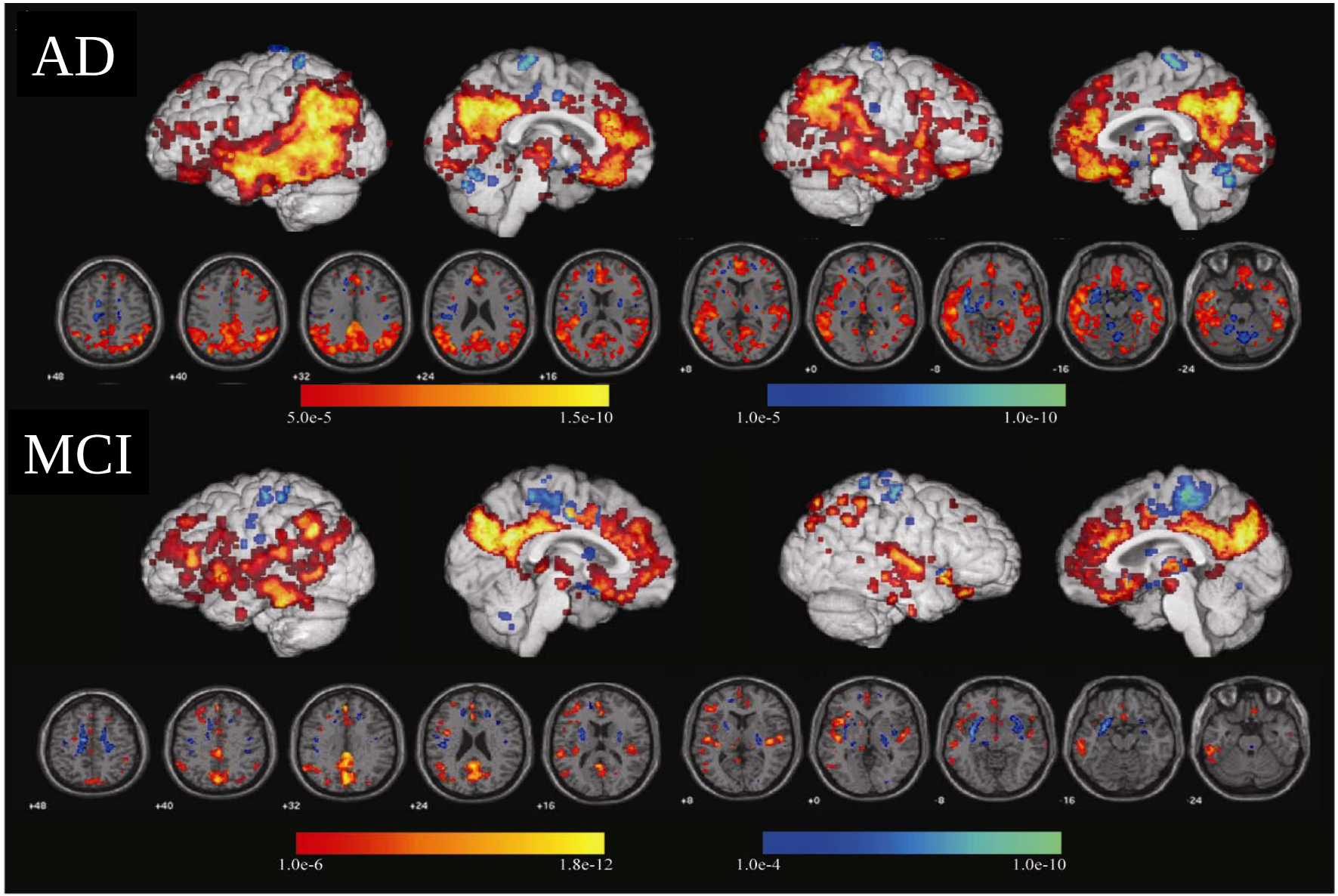
Alteration of glucose metabolism in AD



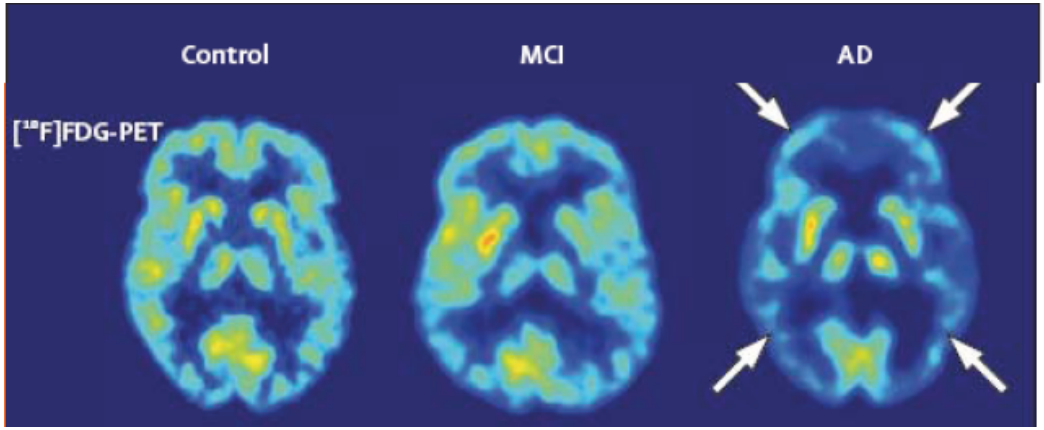
Fluorodeoxyglucose (FDG)-PET

Edison P et al. Neurology. 68(7):501-8; 2007

Cerebral metabolism



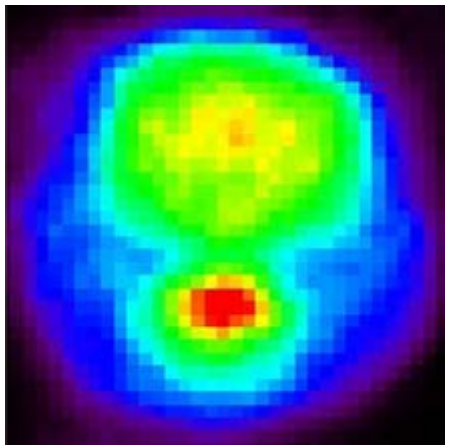
Imagerie du métabolisme cérébral

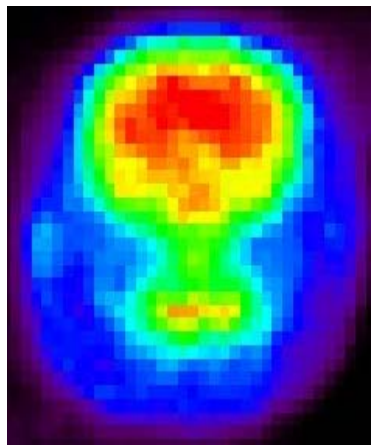


Images [^{18}F]-FDG-TEP de cerveaux présentant des altérations cognitives.
Kepe et al., 2006

µPET Focus 220

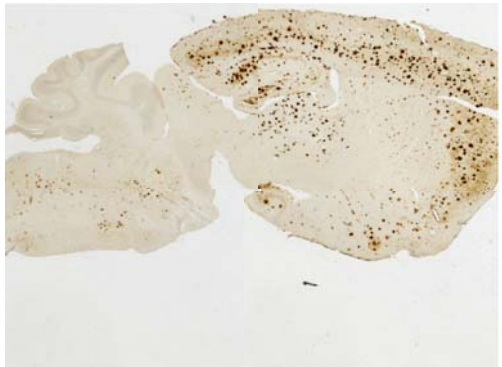
[18F]-FDG et µTEP
Hypermétabolisme chez les Souris APP_PS1/TG69



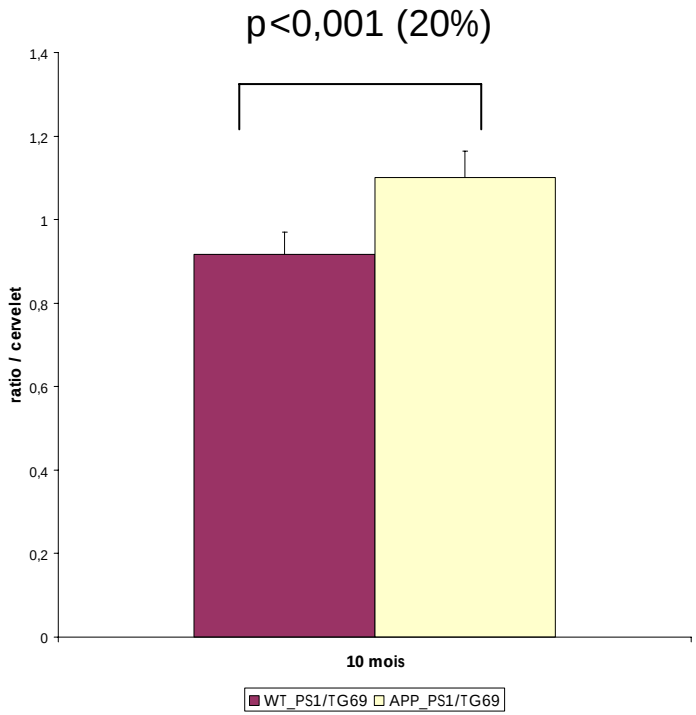


WT_PS1/TG69 de 10 mois

APP_PS1/TG69 de 10 mois



9 months



Augmentation de la rétention de [18F]-FDG chez APP_PS1/TG69 vs contrôles (p<0,001, toutes structures confondues)

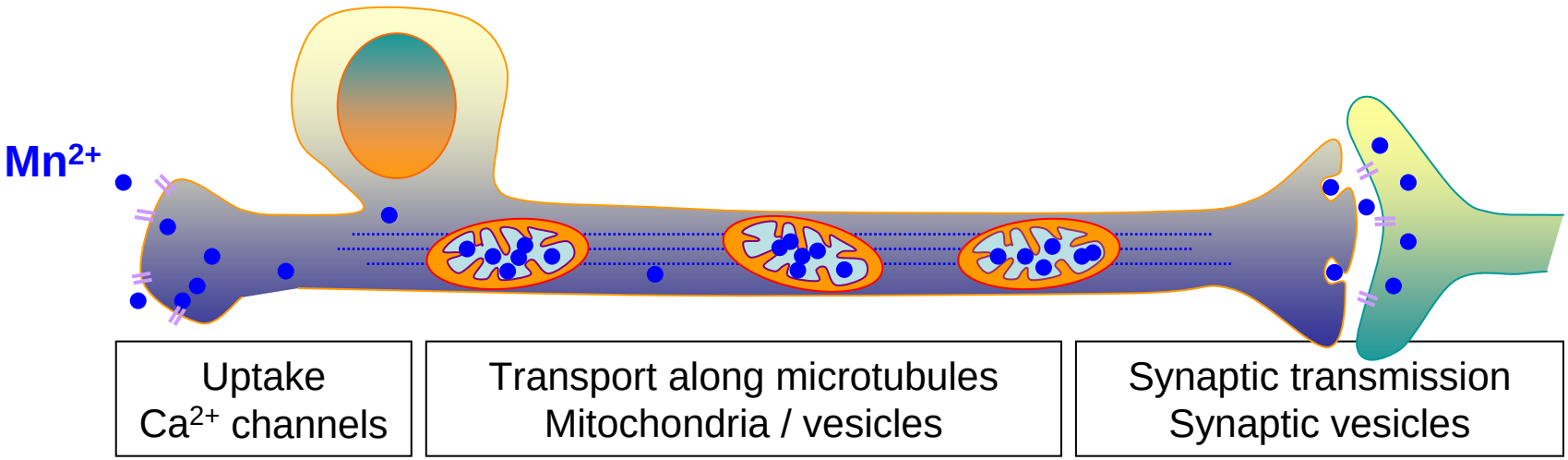
Poisnel et al. Neurobiology of Aging, In press

Conclusion: Functional biomarkers

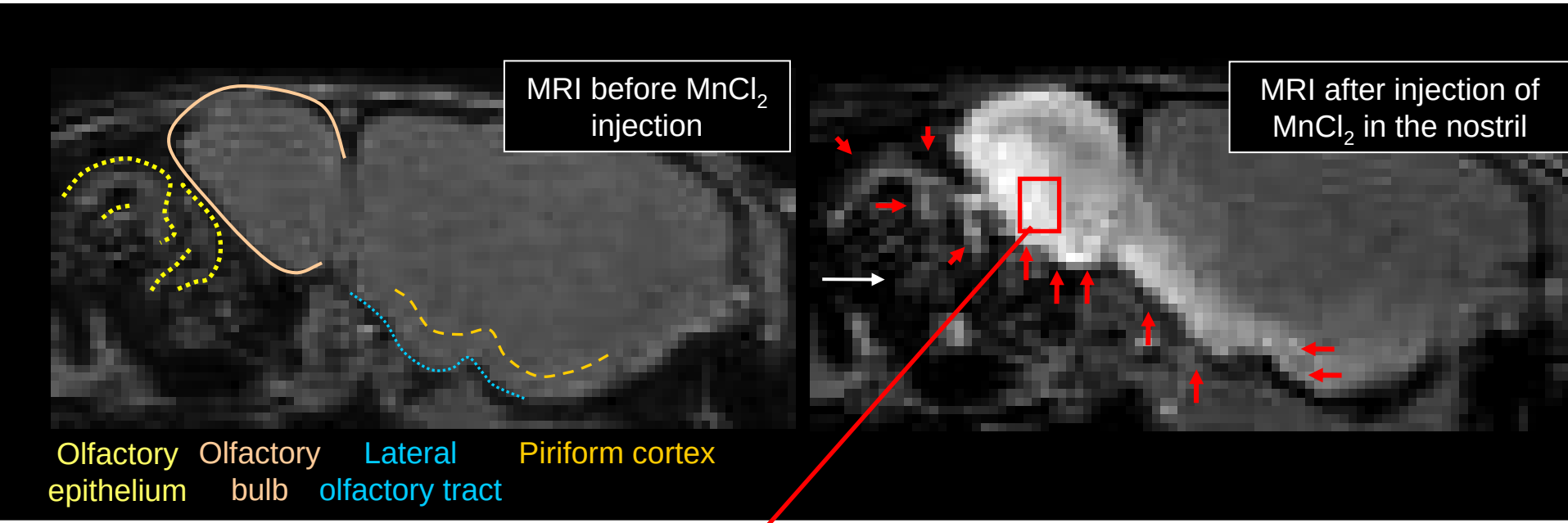
Biomarker	Use in animals		Use in humans	
	Detection of AD-like pathology	Preclinical evaluation of drugs	Clinical diagnostic	Clinical endpoint True benefits of a drug
Cerebral Metabolism (PET + FDG)	Yes ?	No	Yes	No

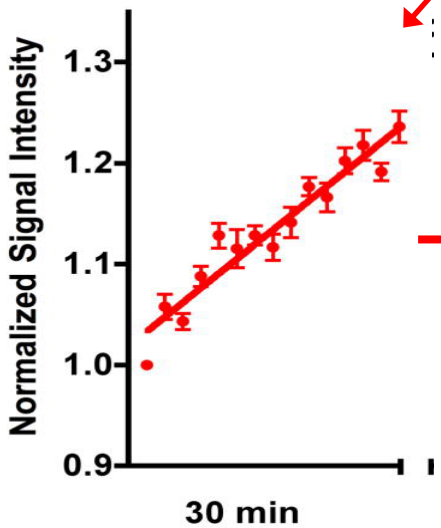
MEMRI

Manganese-enhanced MRI (MEMRI) & neuronal transport



MEMRI & neuronal transport



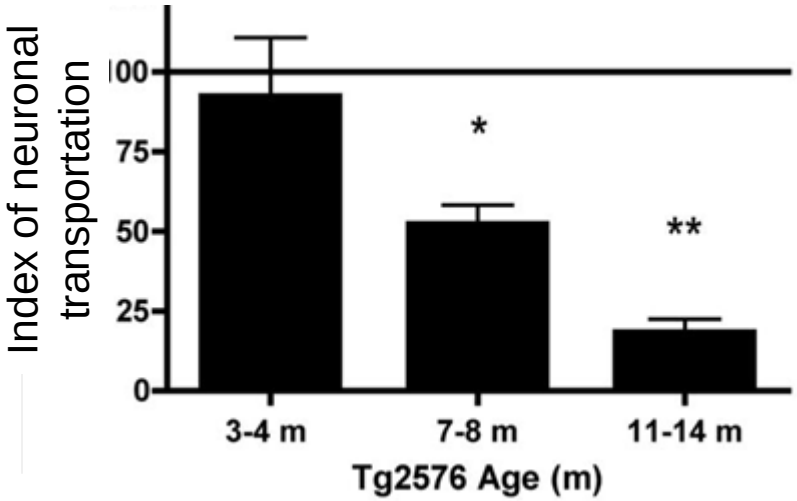


Index of the speed of neuronal transportation

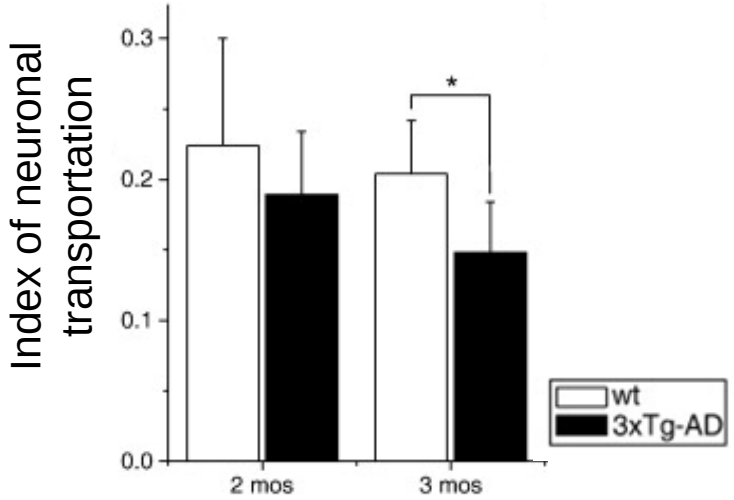
Smith KD et al.
Neuroimage. 2007

Alteration of neuronal transport in animal models of Alzheimer's disease

Amyloid	Tau + Amyloid
APP_{Swe}	$PS1_{M146V}$ + APP_{Swe} + Tau_{P301L}

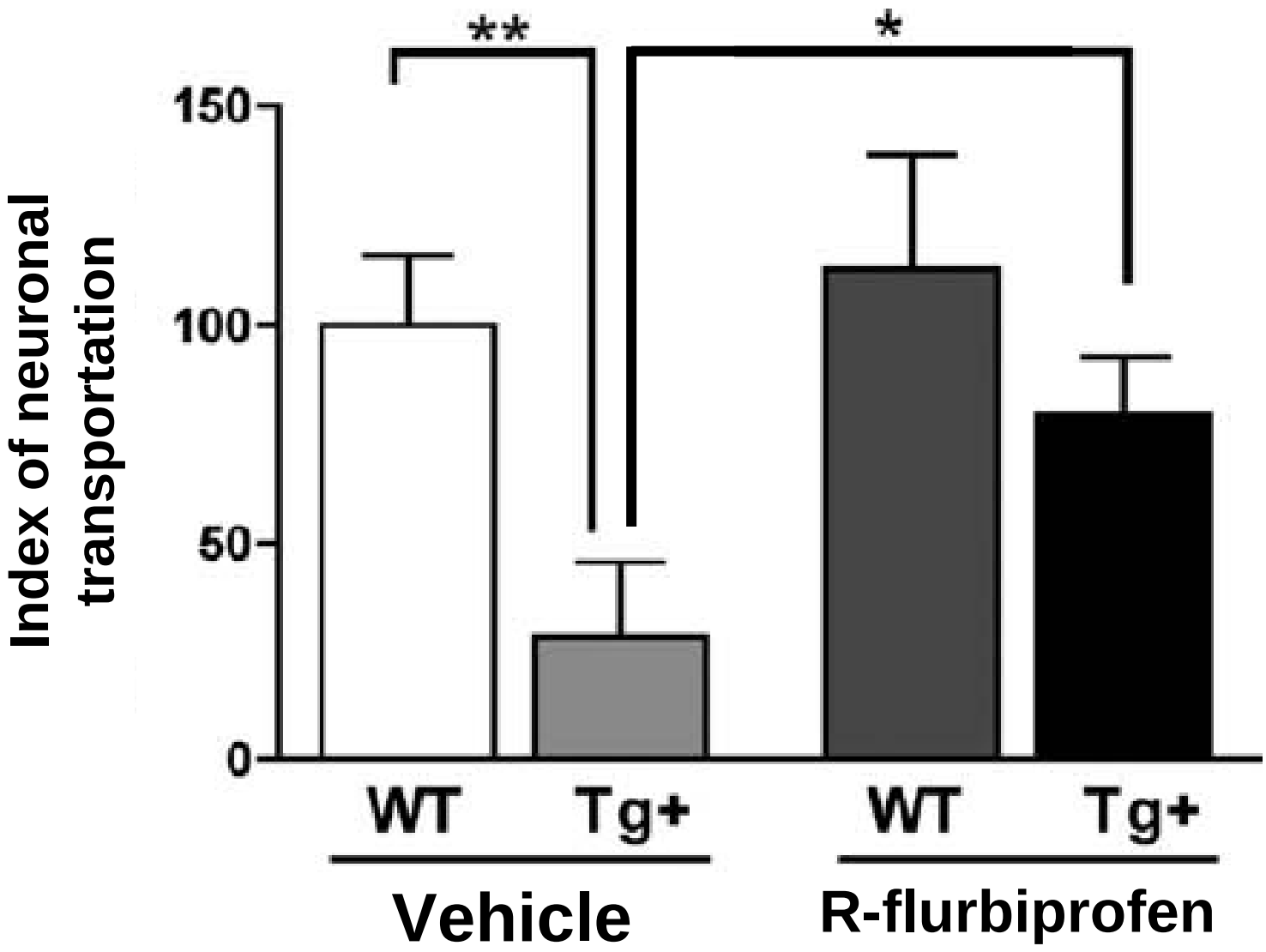


Smith KD et al. Neuroimage *2008*



Kim J et al. Neuroimage 2011

MEMRI studies and therapeutic evaluations



Smith KD et al. Magn Reson Med 65, 1423-9; 2011