Médecine translationnelle et stratégies d'évaluation de médicaments de la cible à l'homme: Exemple de la maladie d'Alzheimer

Marc Dhenain

URA CEA CNRS 2210 – MIRCen - Fontenay aux Roses
Eq. Maladie d'Alzheimer : Modélisation, Biomarqueurs, Imageries Précliniques

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

Overview

- Overview on neurodegenerative diseases

- Strategies for the discovery of new therapies
  - From phenotypic to target based approaches
  - Biomarkers, POM, POC
  - Use of animal model: Target models, predictive models, and biomarkers

- Biomarkers in humans: From diagnostic to therapy evaluation tools
  - Dubois Criteria / ADNI initiative
  - Cerebral atrophy (MRI)
  - Brain metabolism (PET)
  - Amyloid plaques (PET)

- Animal models of Alzheimer's disease
  - Most used models of AD

  - Can we predict clinical efficacy of a drug with these models ?
    - "Classical view" of translational medicine
    - Translational bridges

- Conclusion

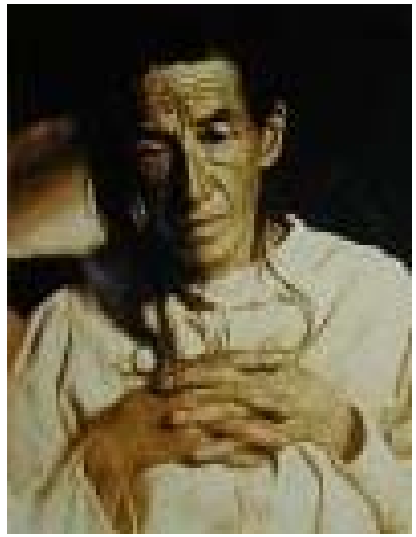
Neurodegenerative diseases

Disease	*Anatomy*	*Patients (Fr)*
Alzheimer	cortex	860 000
Parkinson	subst. nigra	80 000
Huntington	striatum	6 000
Spino-cereb. ataxia	cerebellum	<5 000
Amyotrophic Lat. Scler.	cortex, medulla	<5 000
Multiple Sclerosis	cortex, stem, medulla	60 000

No curative treatments available

Alzheimer's disease: Symptoms

Dementia

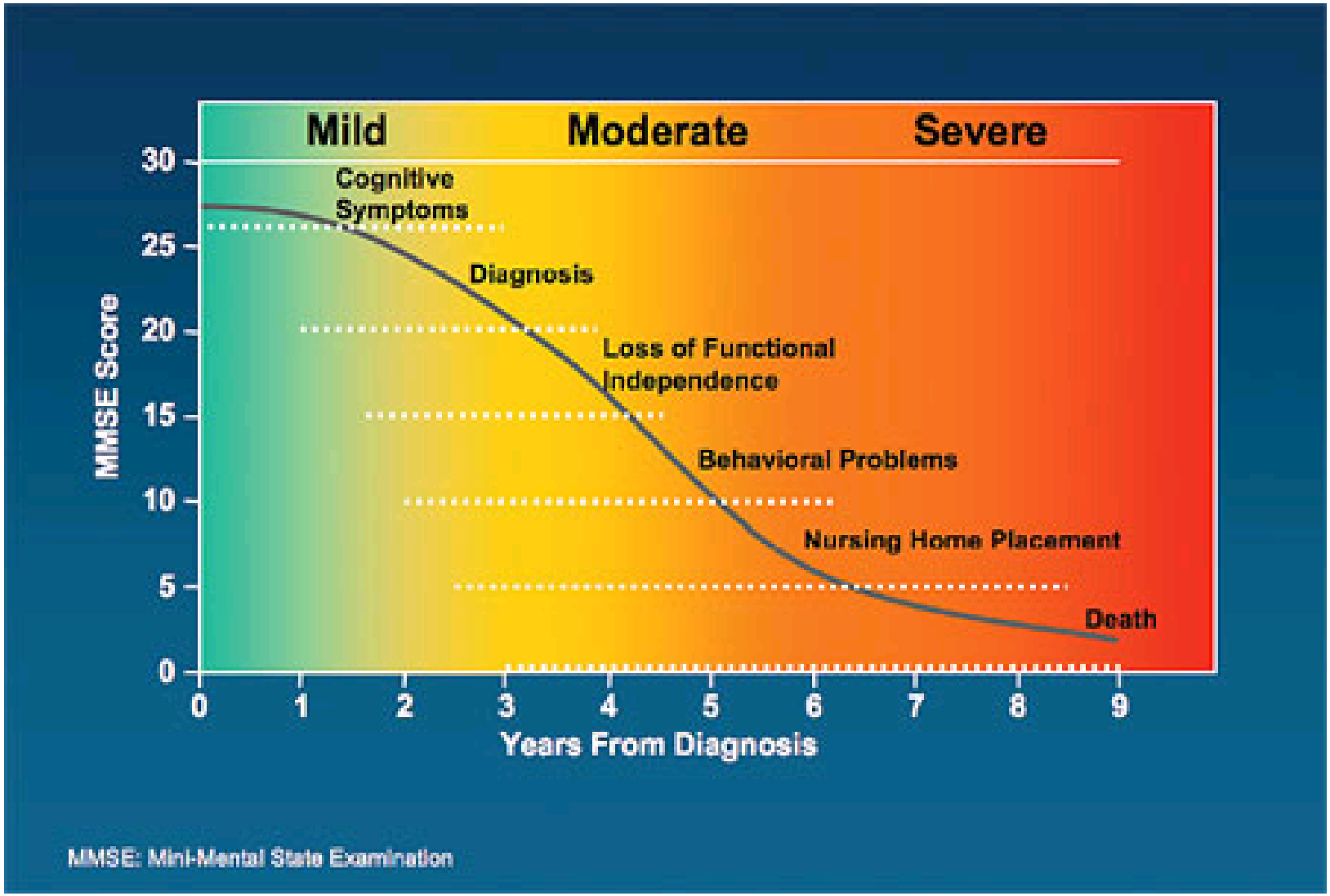


- spatio-temporal disorientation

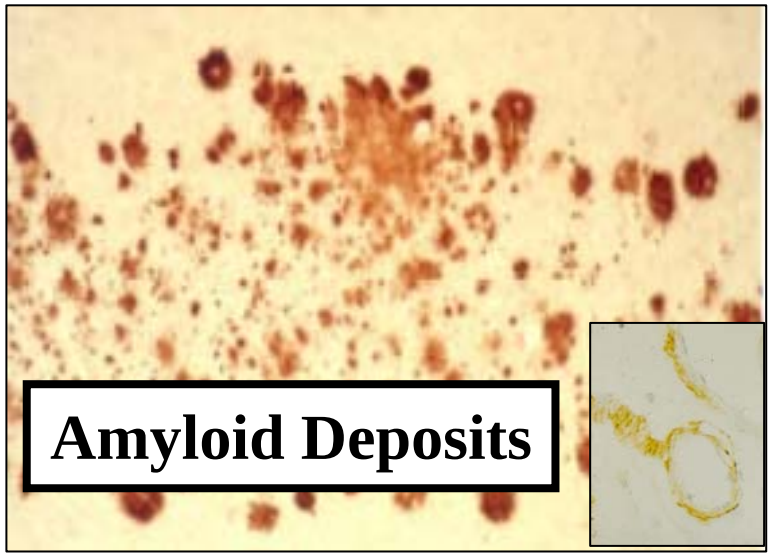
- Alteration of short term memory (episodic)

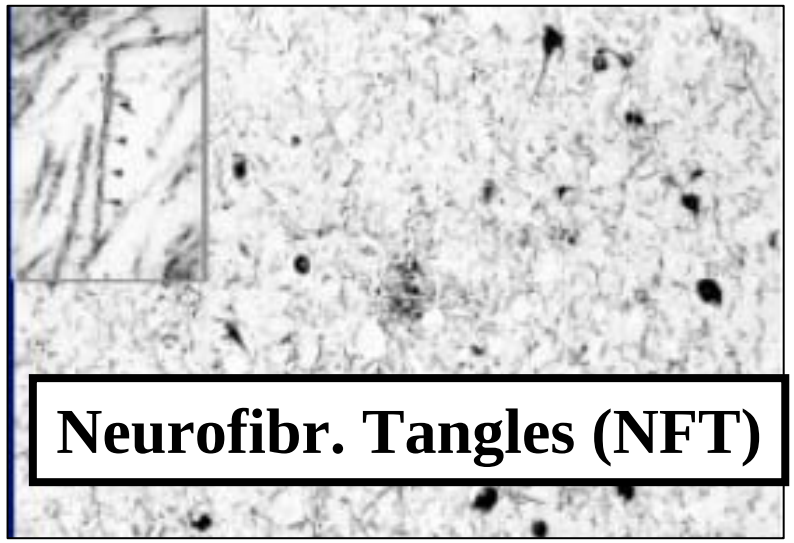
- language, visual recognition

Alzheimer's disease: disease evolution

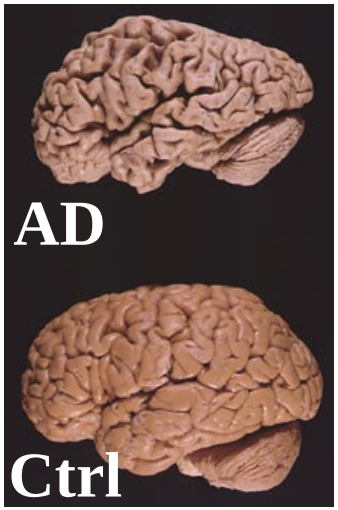


Alzheimer's disease: lesions

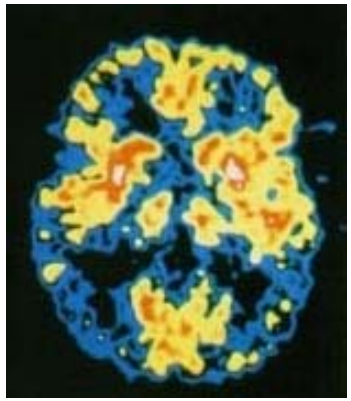




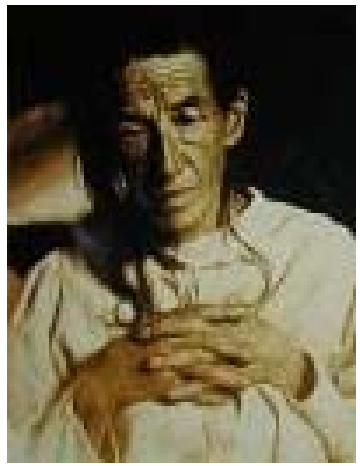
Cerebral atrophy



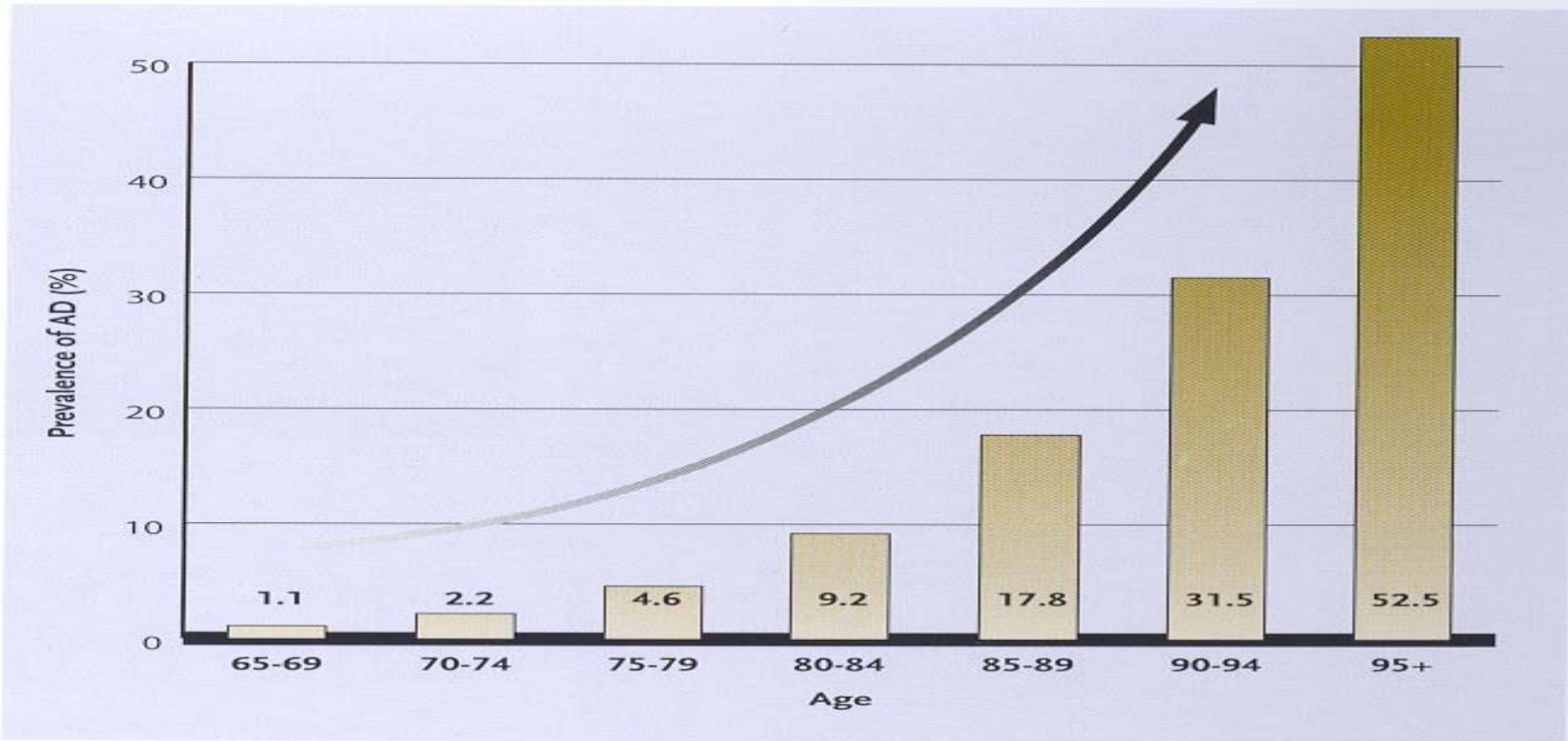
Functional alterations



Cognitive alterations



Alzheimer's disease: risk factors



Increased prevalence of Alzheimer's disease with age among US population.

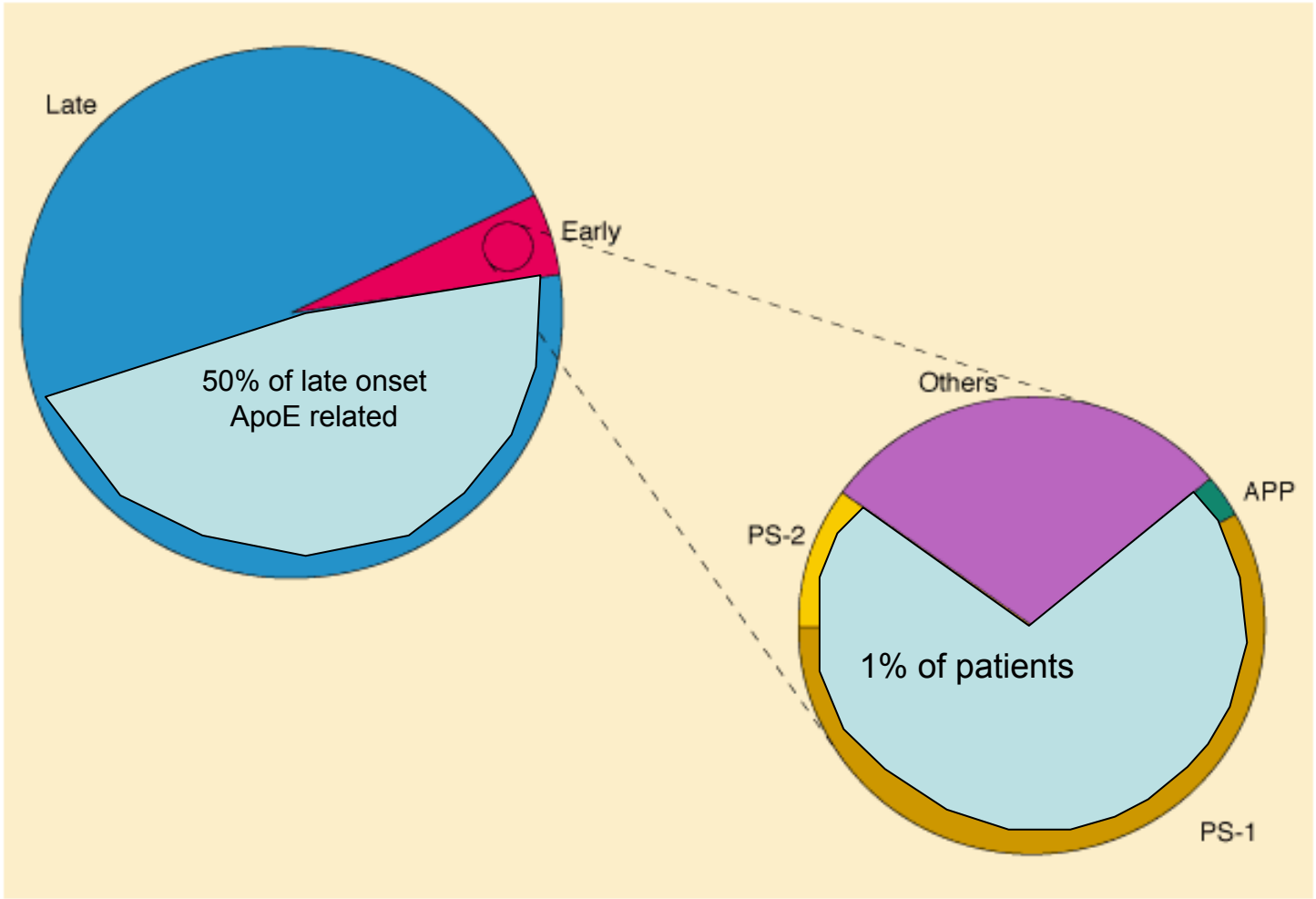
Adapted from: U.S. General Accounting Office/Health and Human Services (98-16). Alzheimer's Disease. Estimates of Prevalence in the United States.

Risk factors (Alzheimer)

- Age
- Education level
- Familial History
- Positive genotype Apolipoprotein E 4/4
- Arterial hypertension
- Hyperinsulinemia

Alzheimer's disease: Few genetic causes

Relative frequency of early and late-onset Alzheimer's and the proportion of early-onset cases attributed to mutations in specific genes such as APP, PS1, PS2 or others



From, Piecing Together Alzheimer's by Peter H St George-Hyslop.

Alzheimer's disease: currents therapies

Effet typique du traitement sur les capacités mnésiques
Exemple de Donepezil (Aricept)

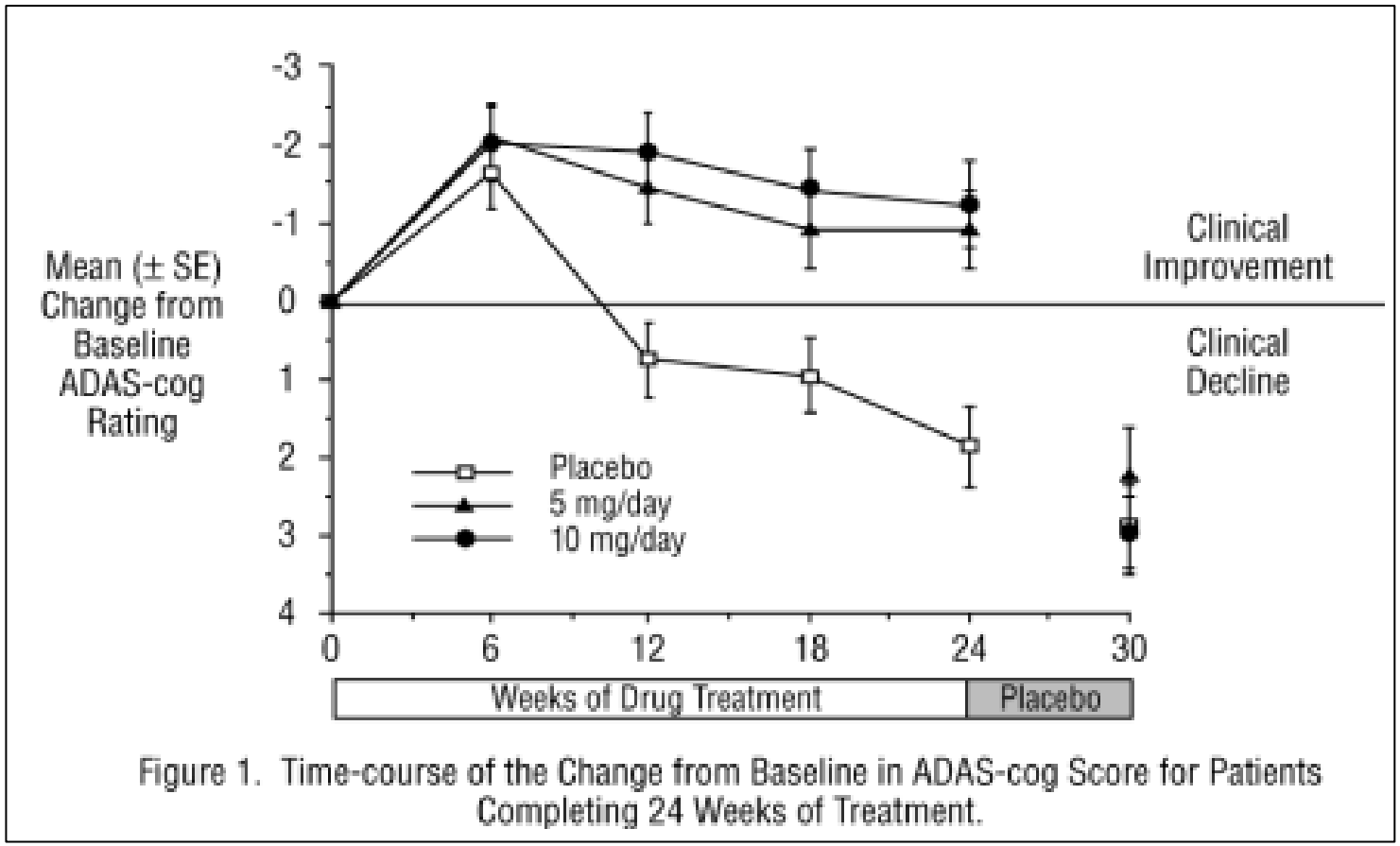
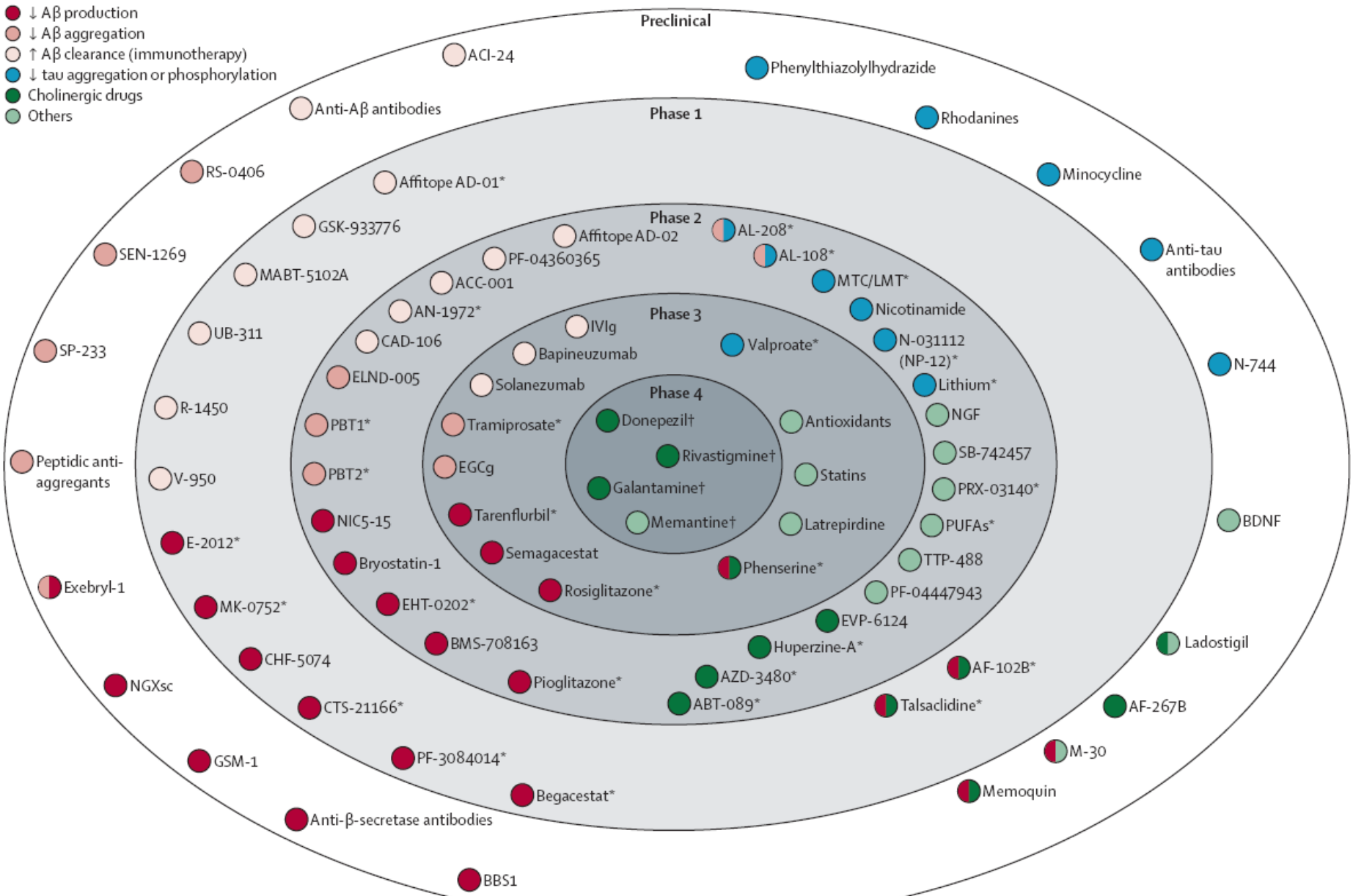


Figure 1. Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 24 Weeks of Treatment.

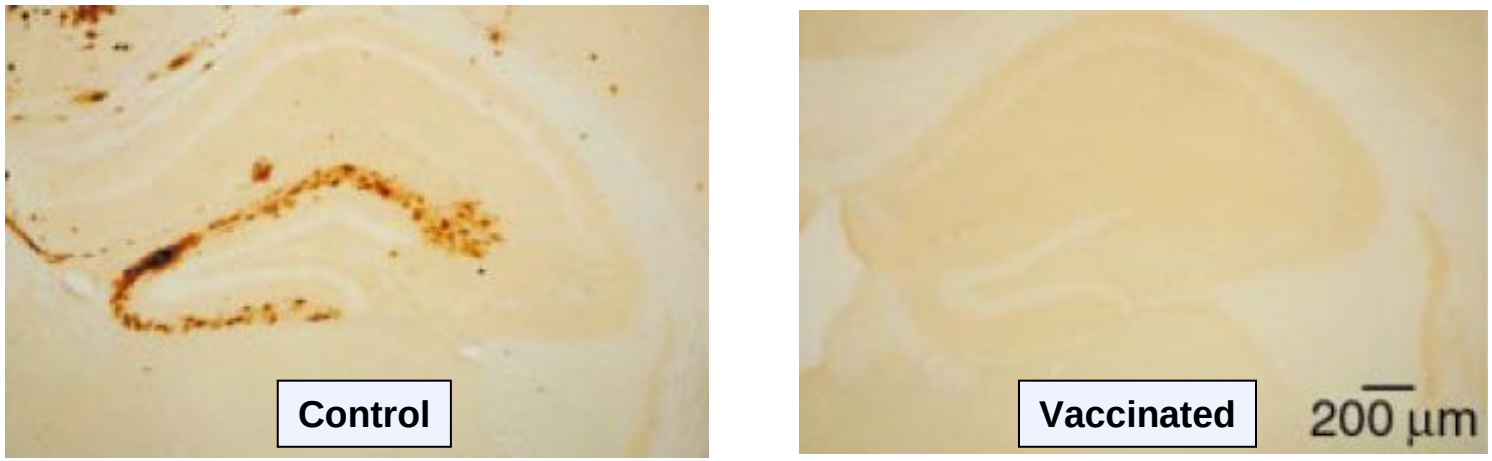
Alzheimer's disease: Therapies in development



Mangialasche F. 2010. *Lancet Neurol* 9, 702-716.

Alzheimer's disease: Concept of immunotherapy

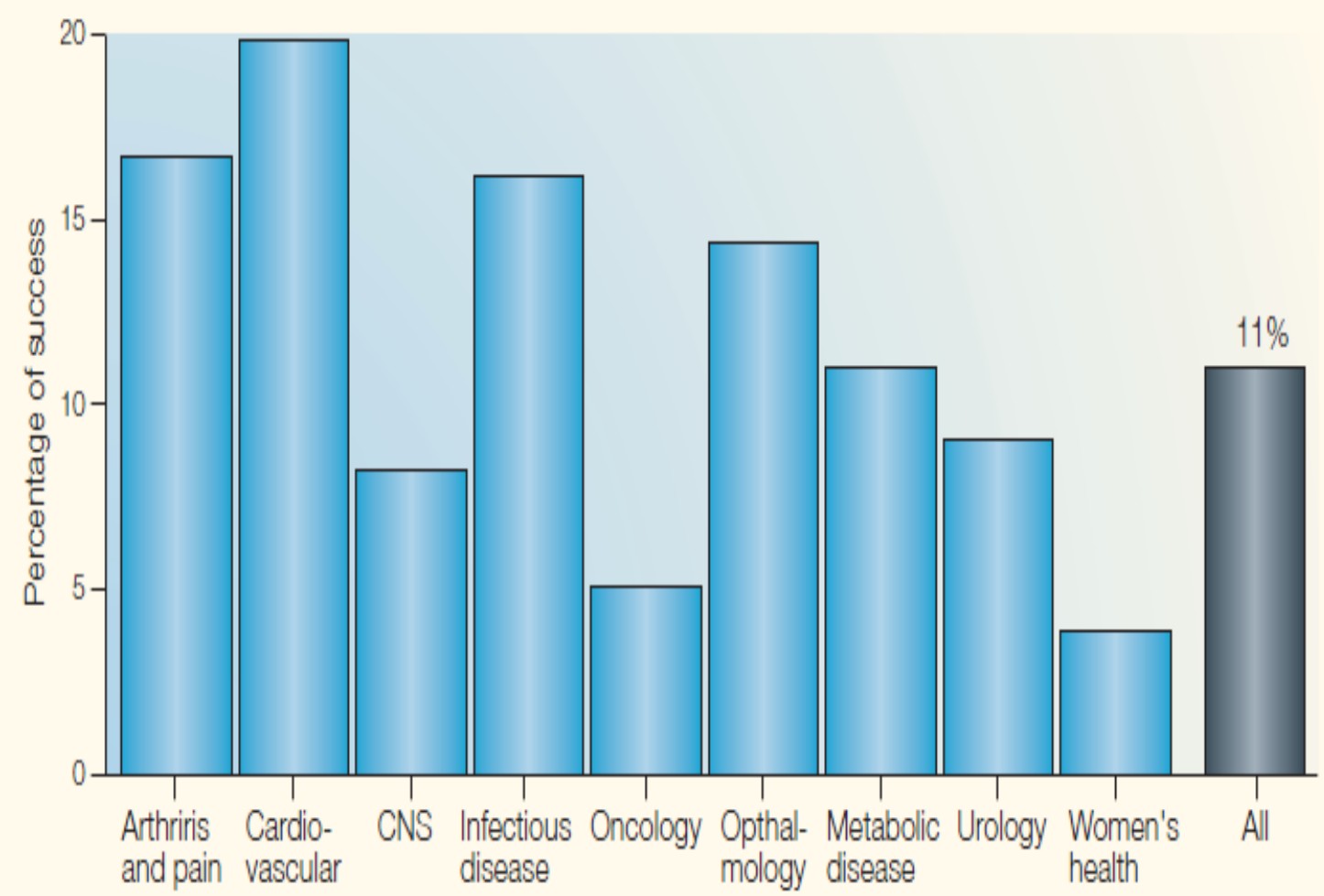
- Principles of anti-Aβ immunotherapy
  - Inoculation of Ab peptides or derivatives in an immune adjuvant
  - Administration of anti-amyloid monoclonal antibody
- Reduction of amyloid load (in mice)



(Schenk et al, 1999)

- Lack of cognitive improvement in humans

Difficulties in therapy trials



Percentage of success after the first test in humans

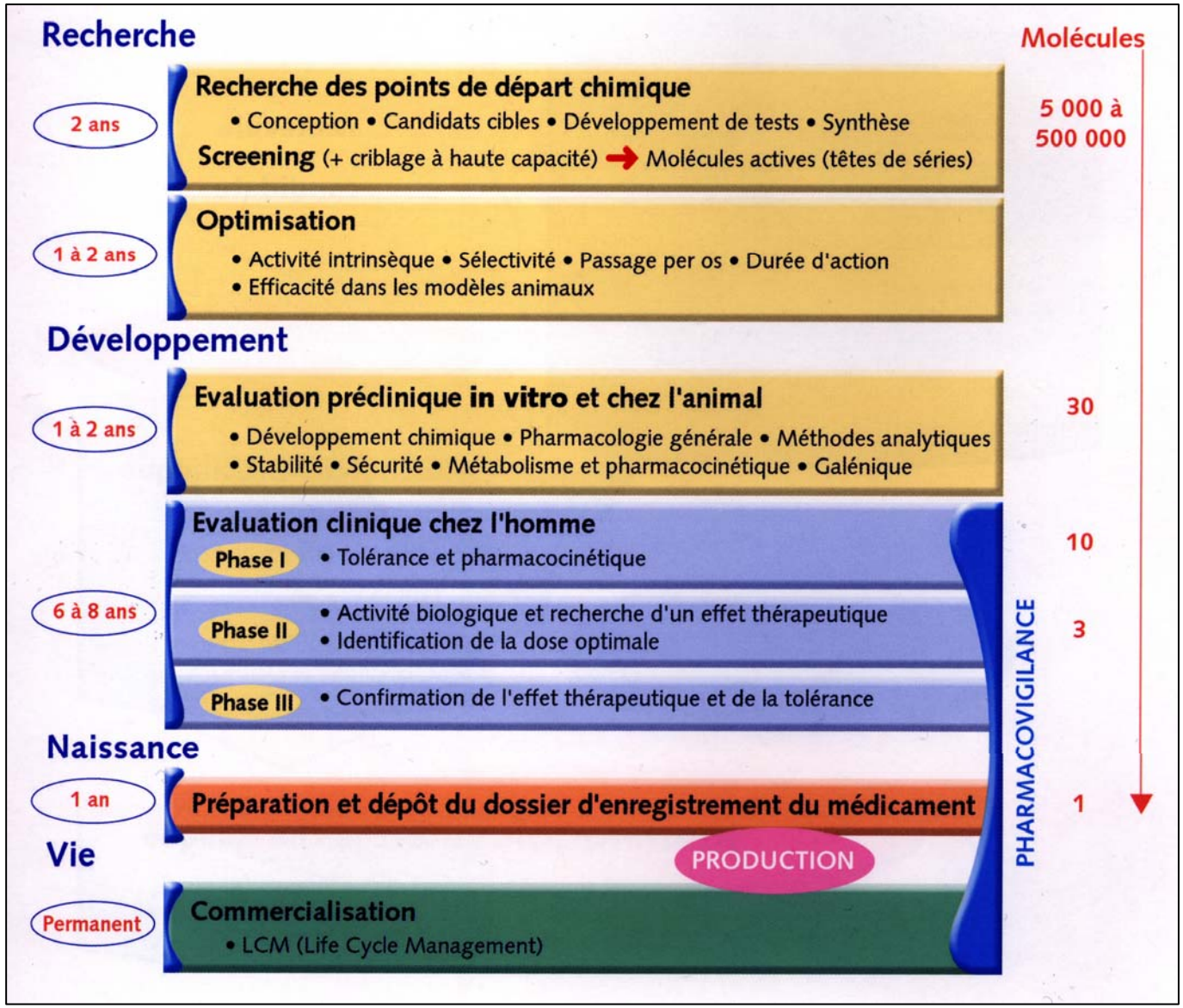
Kola, I. and J. Landis (2004). Nat Rev Drug Discov **3**(8): 711-5.

Développement d'un médicament

Après

- Plus de 16 ans
- Plus de 1 000 000 000€
- Plus de 3000 patients

Schéma de naissance d'un médicament



Overview

- Overview on neurodegenerative diseases
- Strategies for the discovery of new therapies
  - From phenotypic to target based approaches
  - Biomarkers, POM, POC
  - Use of animal model: Target models, predictive models, and biomarkers
- Biomarkers in humans: From diagnostic to therapy evaluation tools
  - Dubois Criteria / ADNI initiative
  - Cerebral atrophy (MRI)
  - Brain metabolism (PET)
  - Amyloid plaques (PET)
- Animal models of Alzheimer's disease
  - Most used models of AD
  - Can we predict clinical efficacy of a drug with these models ?
    - "Classical view" of translational medicine
    - Translational bridges
- Conclusion

Diseases and therapies: From phenotypic to target based approaches

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 ?
Phenotypic screening

Diseases and therapies: Discovery directly in humans

Step 1: Objective in humans: Cure the disease…

Disease

Clinical outcome (Phenotype)

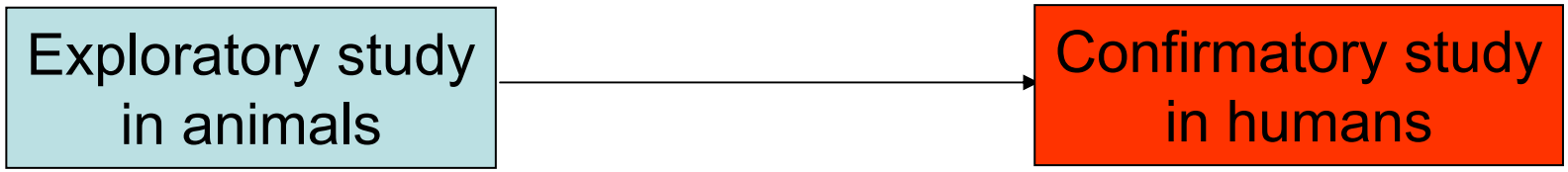
Ex. Sleep, Pain

Opium, Morphine

Empiric approaches: Is my drug treating the disease ?
Phenotypic screening in humans

Diseases and therapies: Discovery directly in animal

Step 1: Objective in humans: Cure the disease…



Reduced cost
Reduced risks

But need to have a predictive animal model

Drugs discovered after phenotypic approaches in animals
Ex. Taxol – Anti-cancer therapy

Most drugs that can be discovered on the basis
of phenotypic approaches have already been discovered…

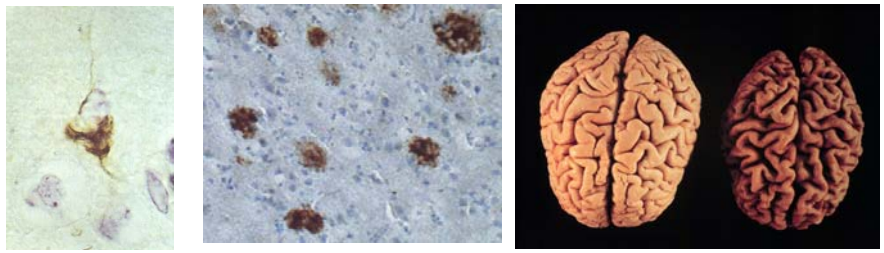
Diseases and therapies…

Step 2: Objective in humans: Natural history of the disease and target selection

Disease → Target → Endophenotypes → Clinical outcome (Phenotype)

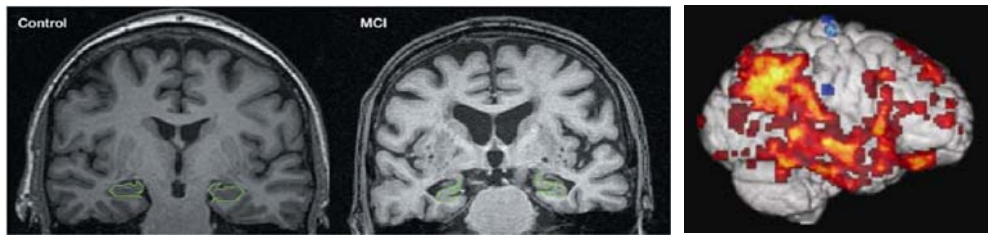
Ex. Cognitive alterations
Death, etc…

Markers



Biomarkers

Diagnostic | Longitudinal | Functional



Understand 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))

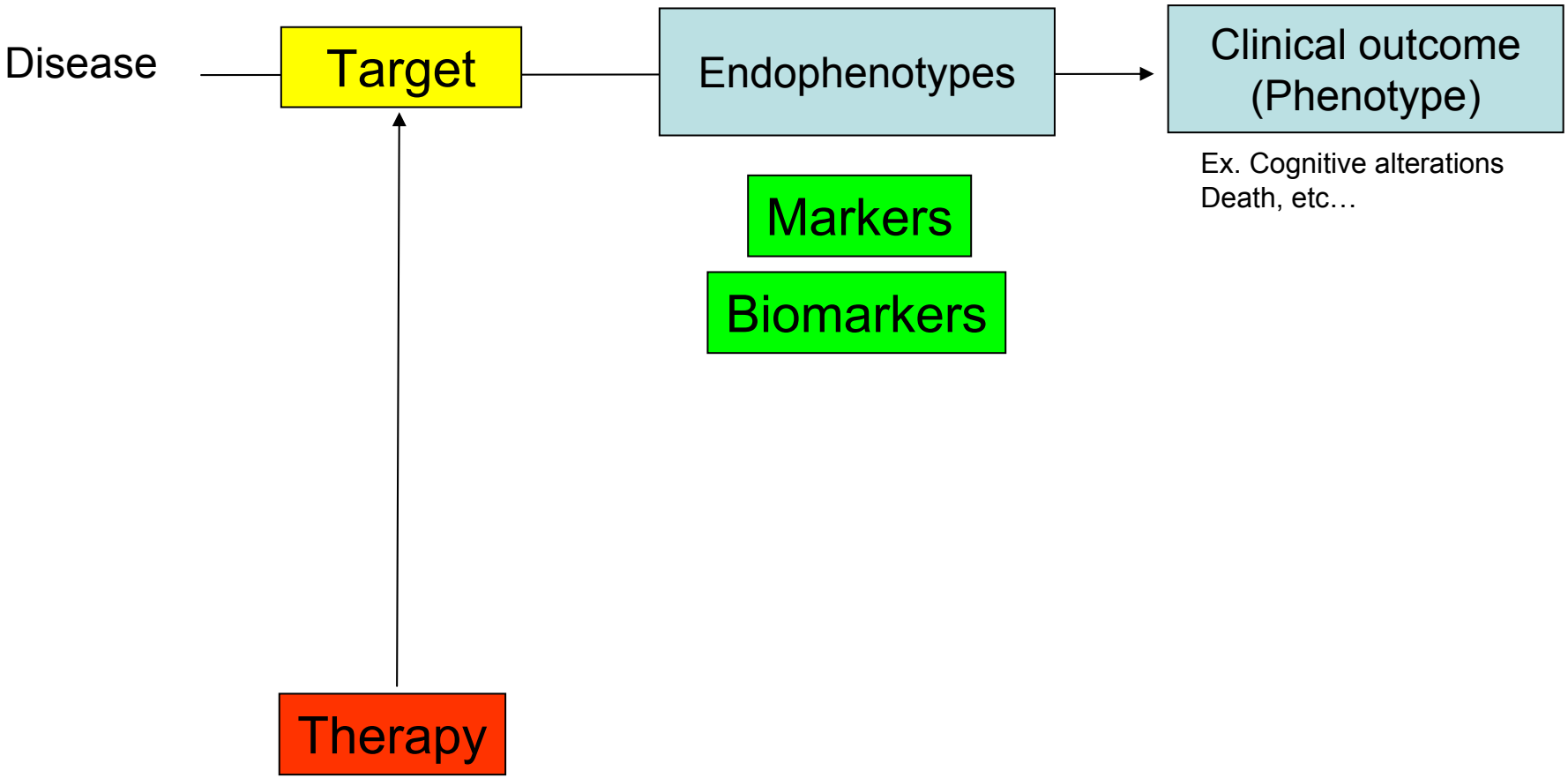
Traductions !

***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…

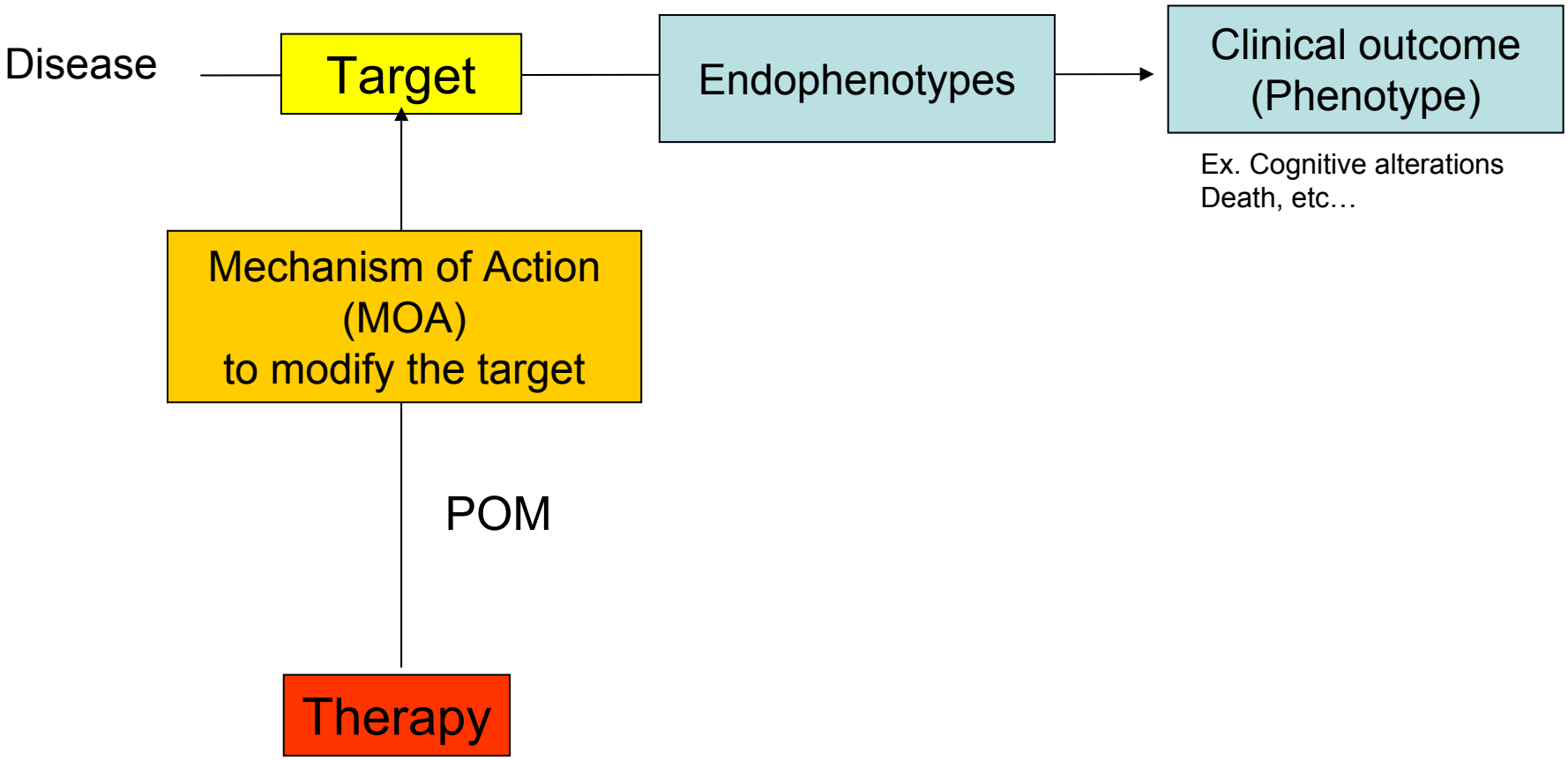
Step 3: Objective in humans: Isolate a target



Understand the disease → isolate a potential target

Diseases and therapies…

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

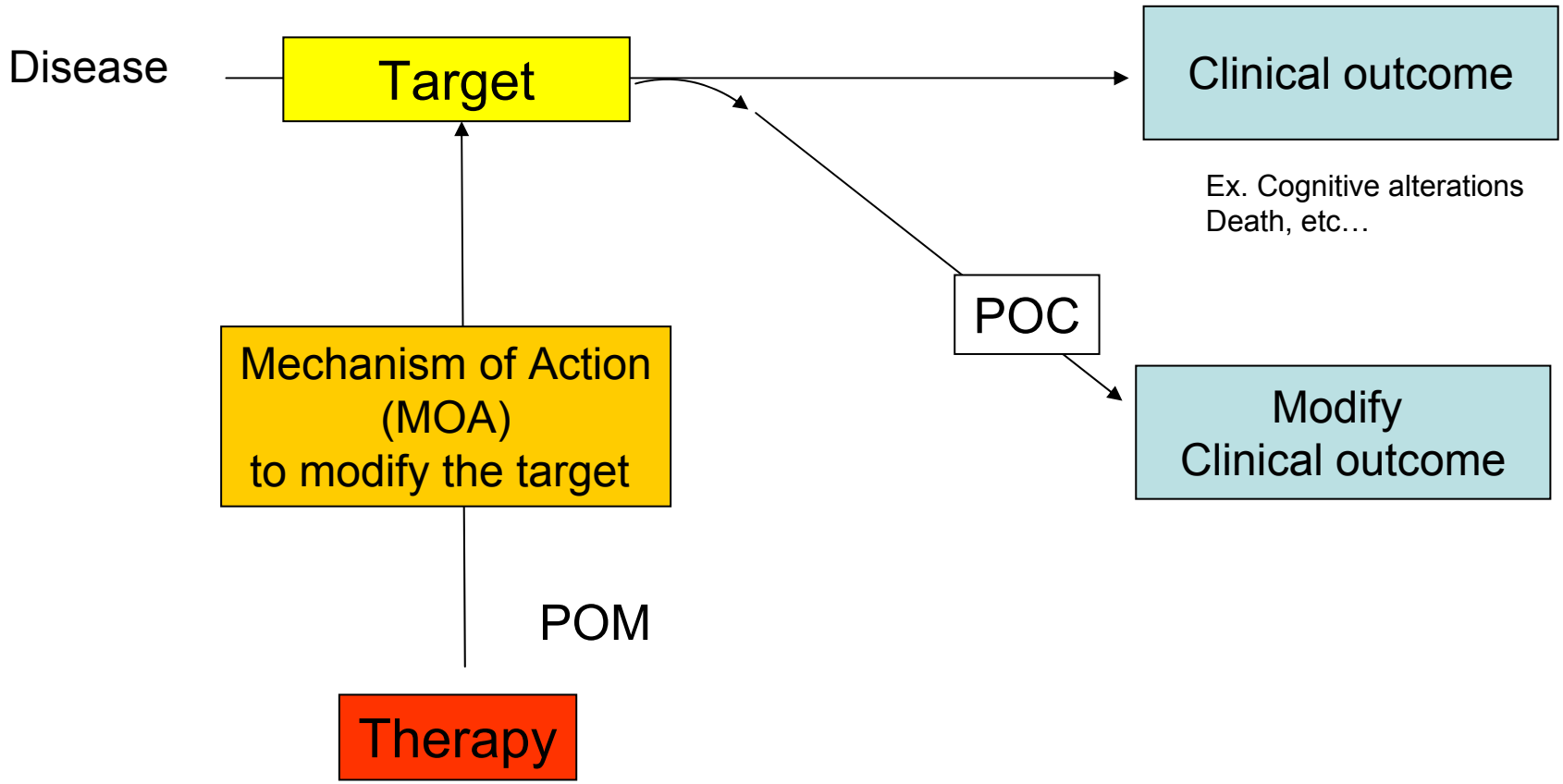


Proof of Mechanism (POM): Is my drug really active on the supposed mechanism ?

→ Type I biomarkers

Basis of translational medicine

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

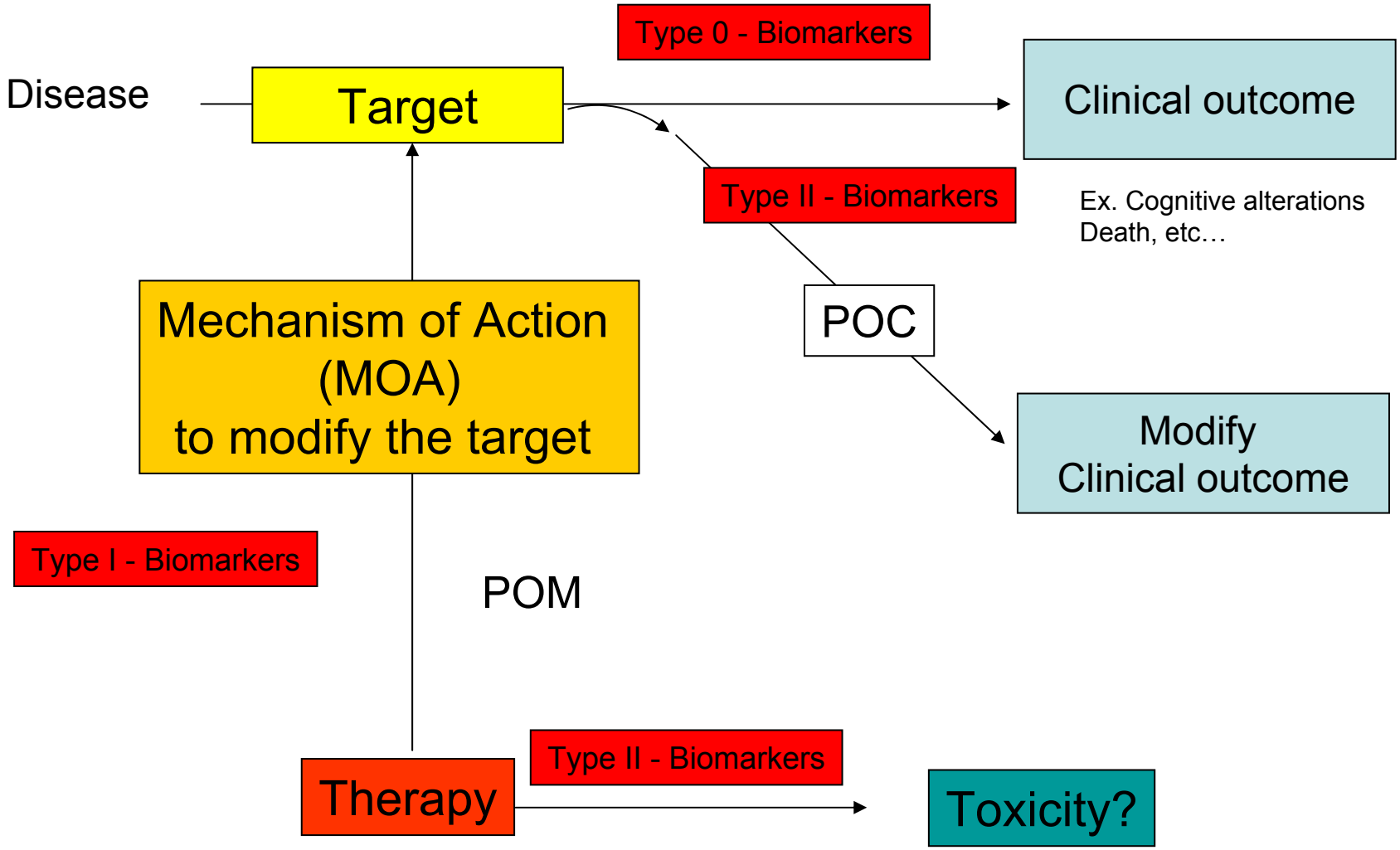


Proof of Mechanism (POM): Is my drug really active on the supposed mechanism ?

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

→ Type II biomarkers

Basis of translational medicine

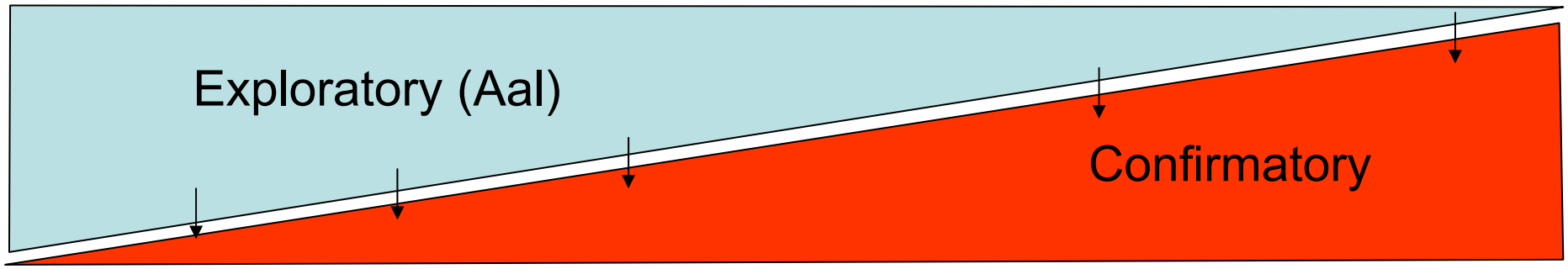


Proof of Concept (POC): If I modify the target, do I modify the disease ?

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

Diseases and therapies…

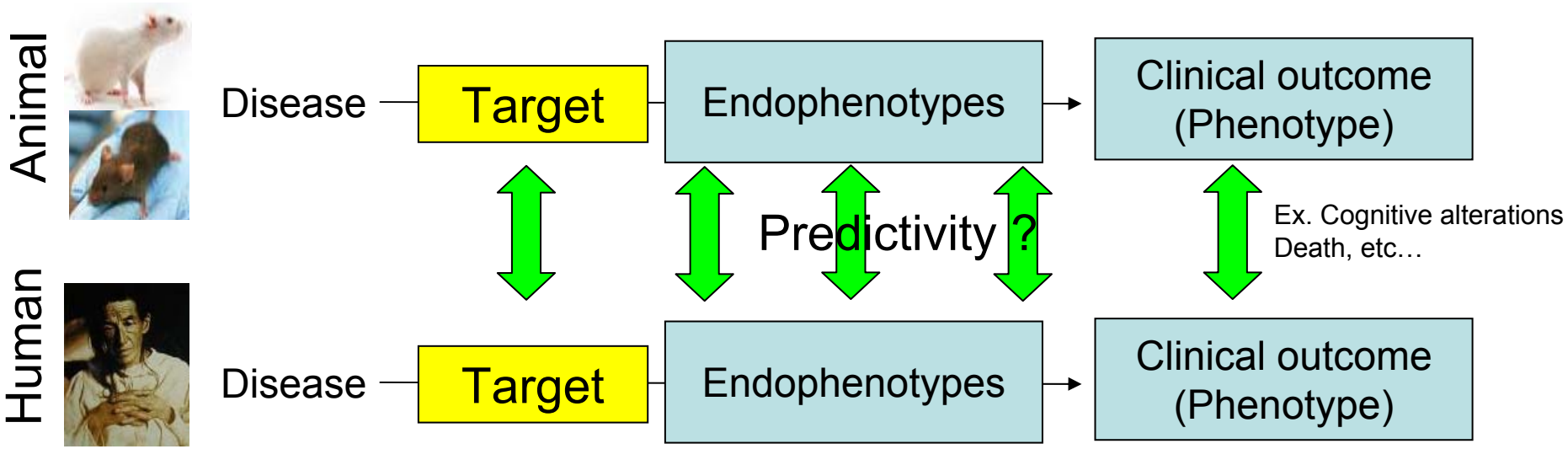
Step 6: Use animal models to predict drug efficacy



Preclinical phase

Phase 1 – Phase 2 – Phase 3

Necessity to establish a paralle between animal and human studies



Overview

- Overview on neurodegenerative diseases
- Strategies for the discovery of new therapies
  - From phenotypic to target based approaches
  - Biomarkers, POM, POC
  - Use of animal model: Target models, predictive models, and biomarkers
- Biomarkers in humans: From diagnostic to therapy evaluation tools
  - Dubois Criteria / ADNI initiative
  - Cerebral atrophy (MRI)
  - Brain metabolism (PET)
  - Amyloid plaques (PET)
- Animal models of Alzheimer's disease
  - Most used models of AD
  - Can we predict clinical efficacy of a drug with these models ?
    - "Classical view" of translational medicine
    - Translational bridges
- Conclusion

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…)

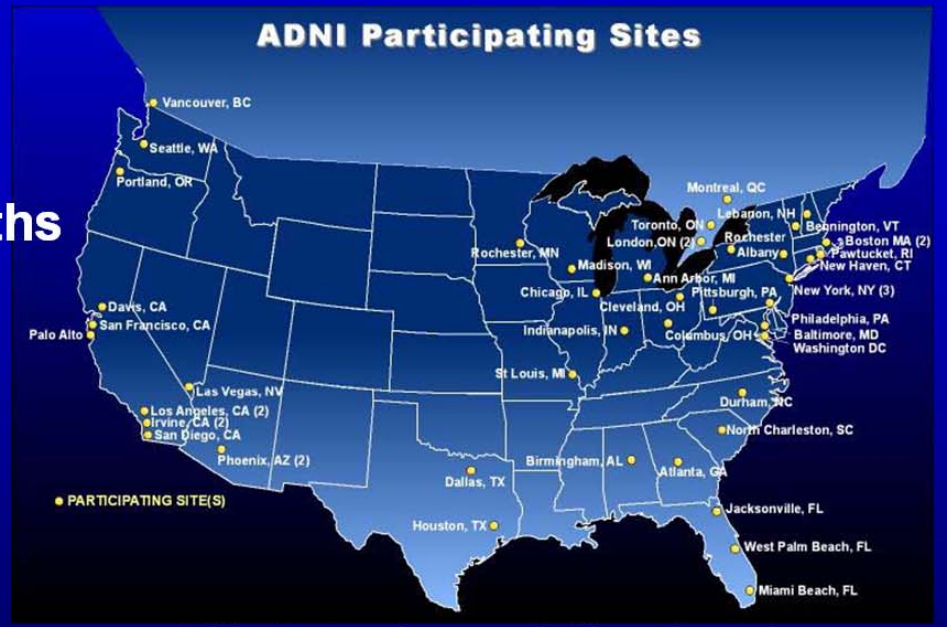
ADNI - Principle

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)

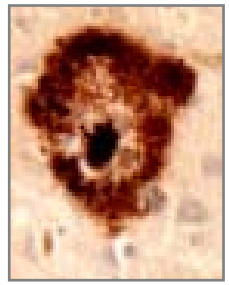


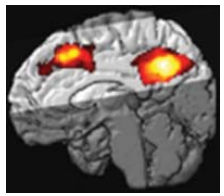
All data in public database: UCLA/LONI/ADNI: No embargo of data

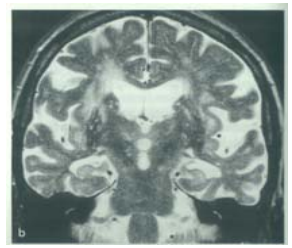
"sample size required to detect 25% change for a given biomarker (during one year)"

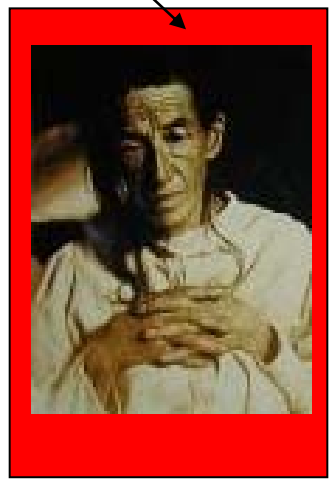
Biomarkers for Alzheimer's disease

Dépôts Amyloïdes







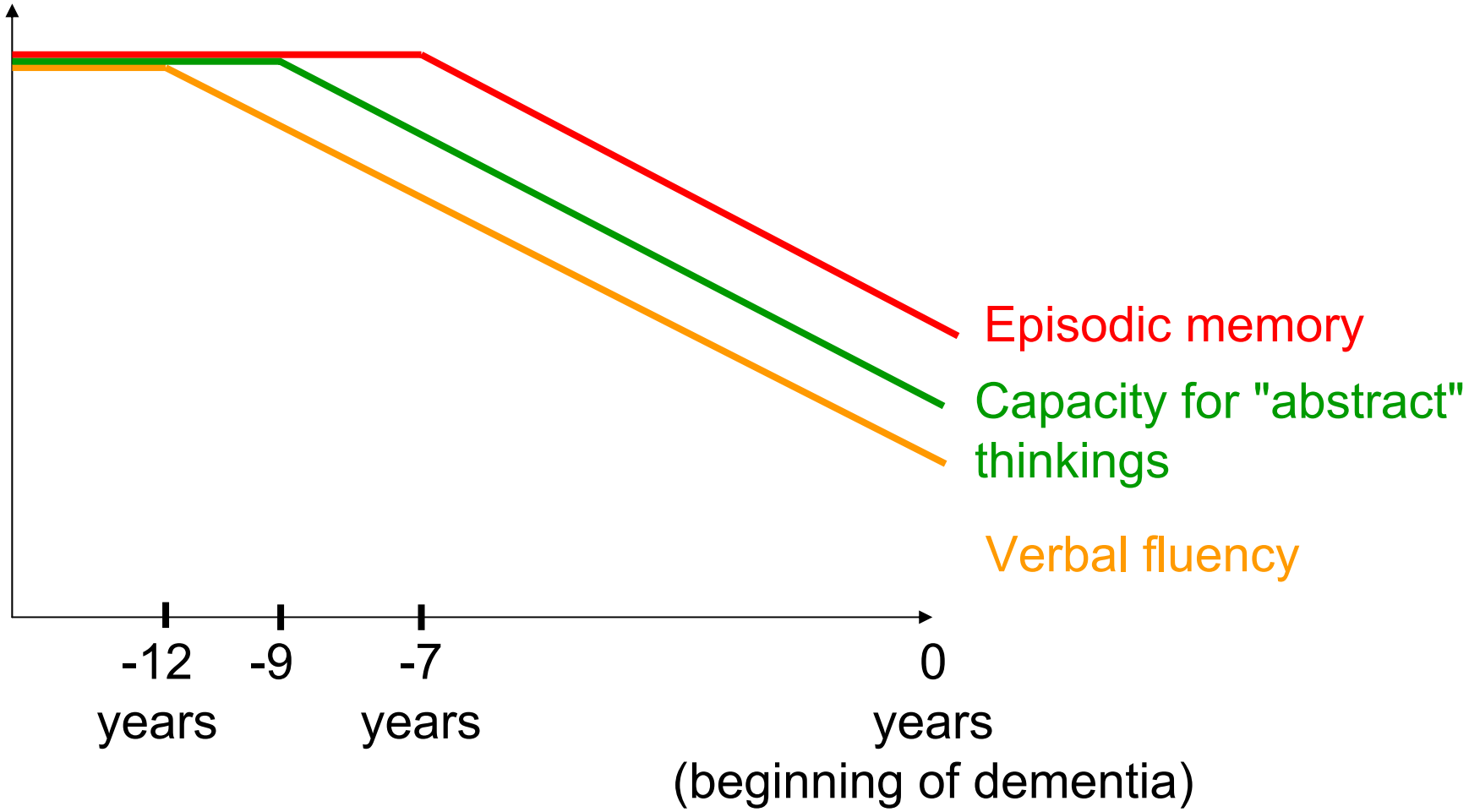


DNF

Altérations fonctionnelles

Atrophie

Cognitive alterations



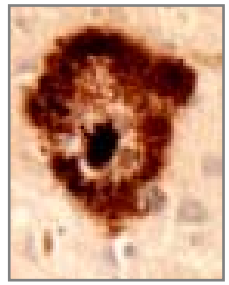
POWER OF CLINICAL/COGNITIVE TESTS
25% CHANGE 1YR STUDY (2 ARM) :

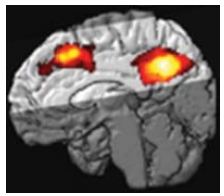
AD (155 Subjects)

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

Biomarkers for Alzheimer's disease

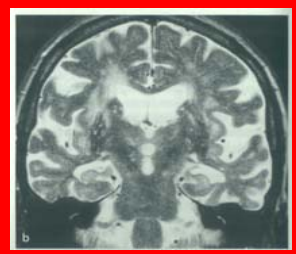
Dépôts Amyloïdes



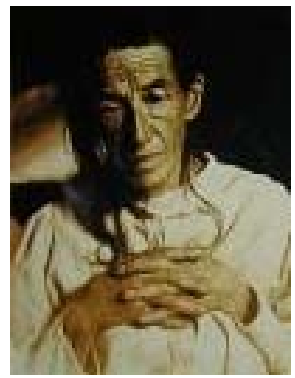


DNF

Altérations fonctionnelles



Atrophie



Cerebral atrophy in humans with Alzheimer

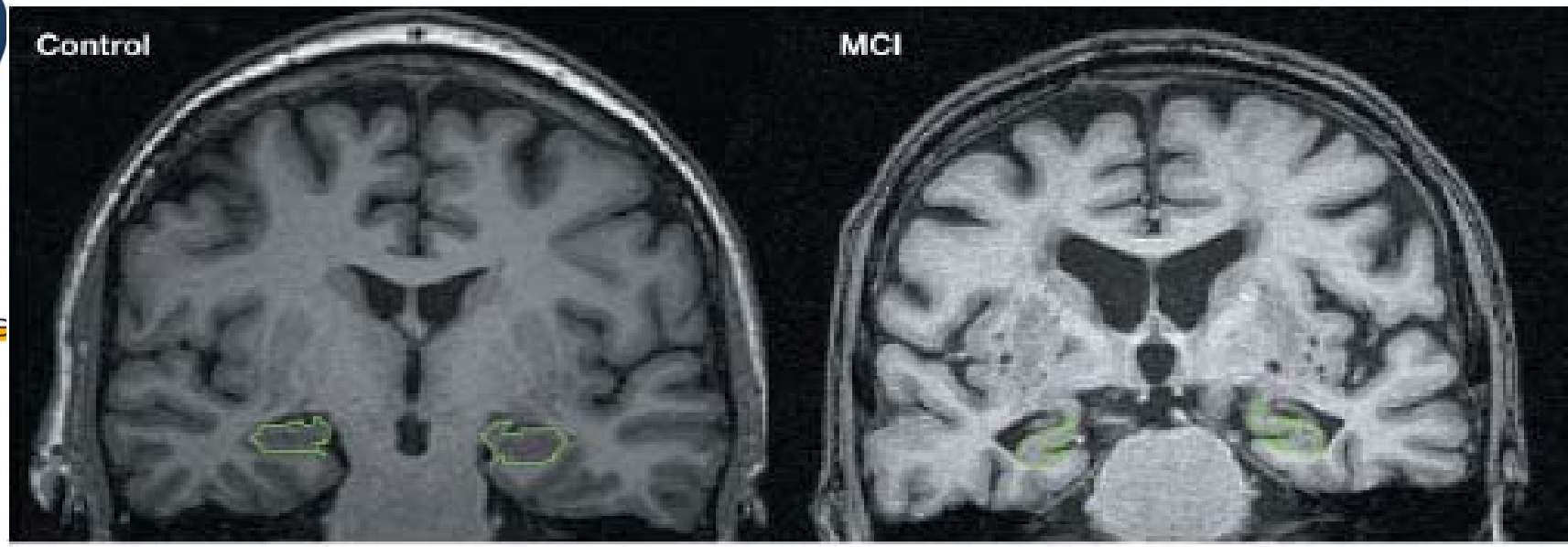
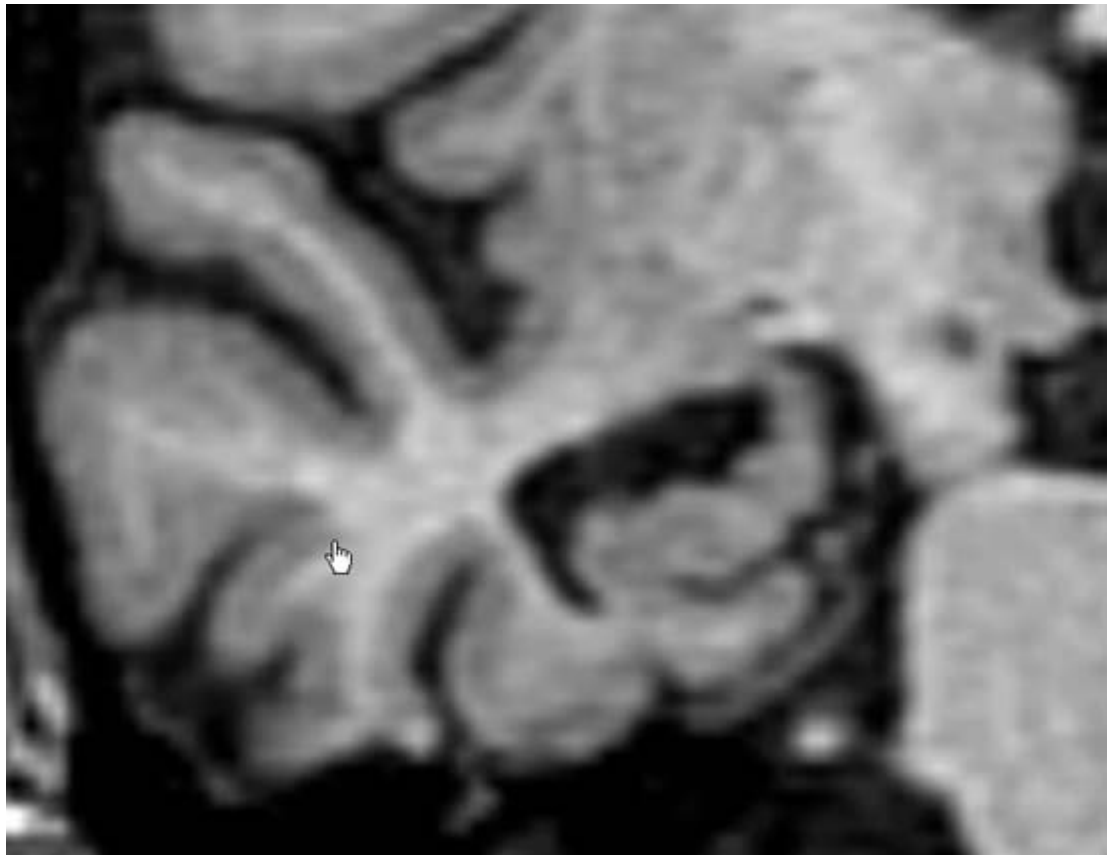


Figure 3 Comparable T1-weighted coronal MRI slices perpendicular to the long axis of the hippocampus showing a normal-sized hippocampus in a control person (total hippocampal volume uncorrected for head size 3,480 mm^3 right and 3,164 mm^3 left) and a smaller hippocampus in an MCI patient (total hippocampal 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

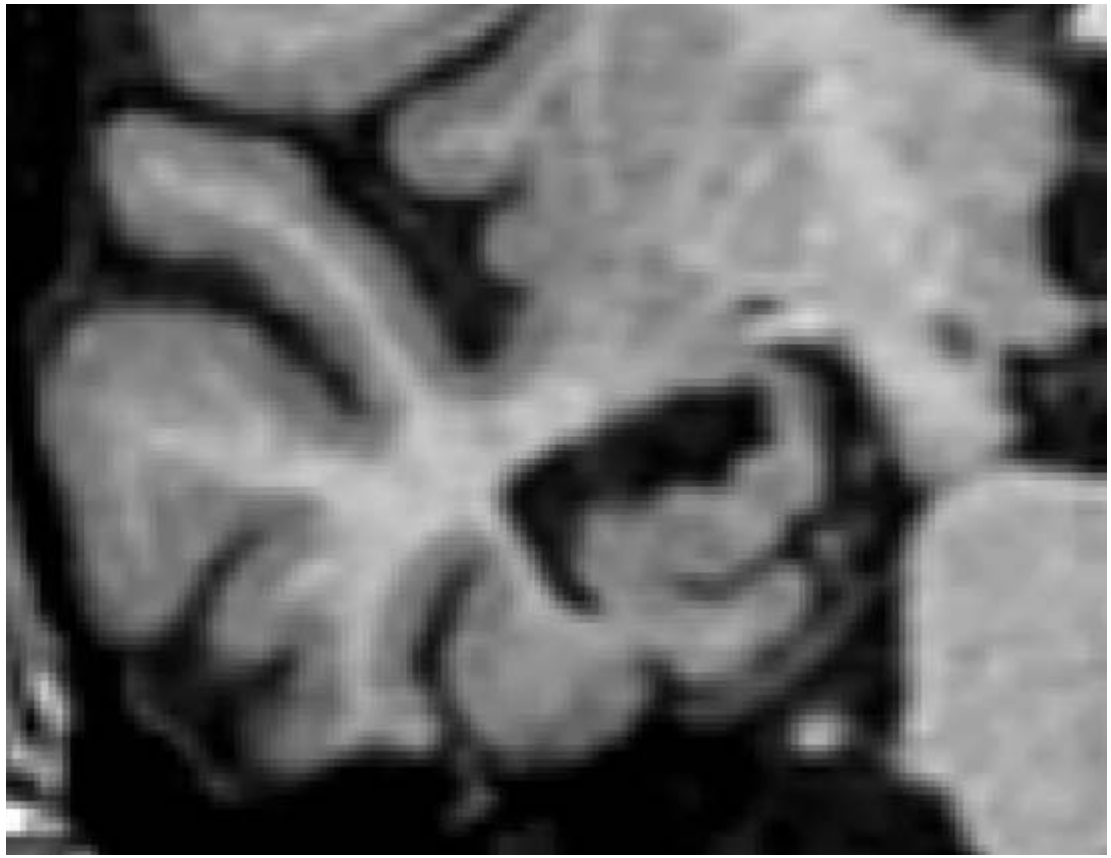
Cerebral atrophy in humans with Alzheimer

Progression from MCI to AD (10 years)



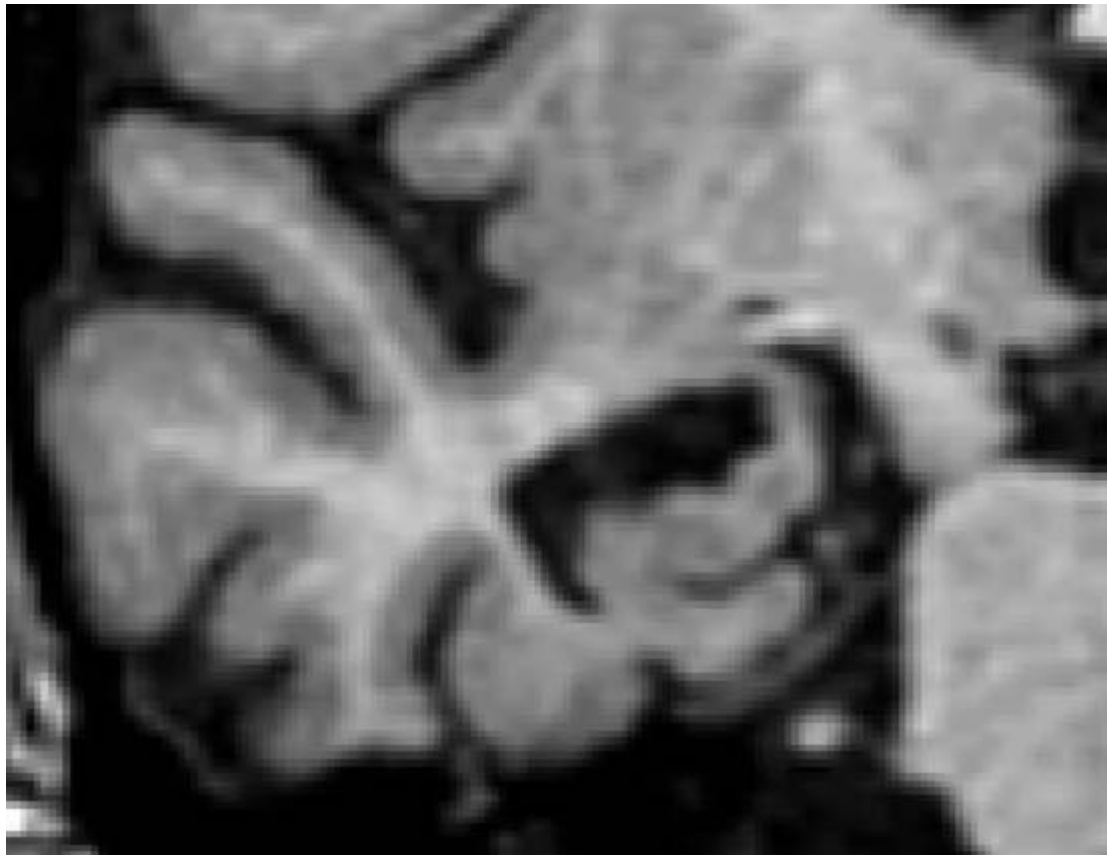
Clifford Jack, ISMRM, 2008

Progression from MCI to AD (10 years)



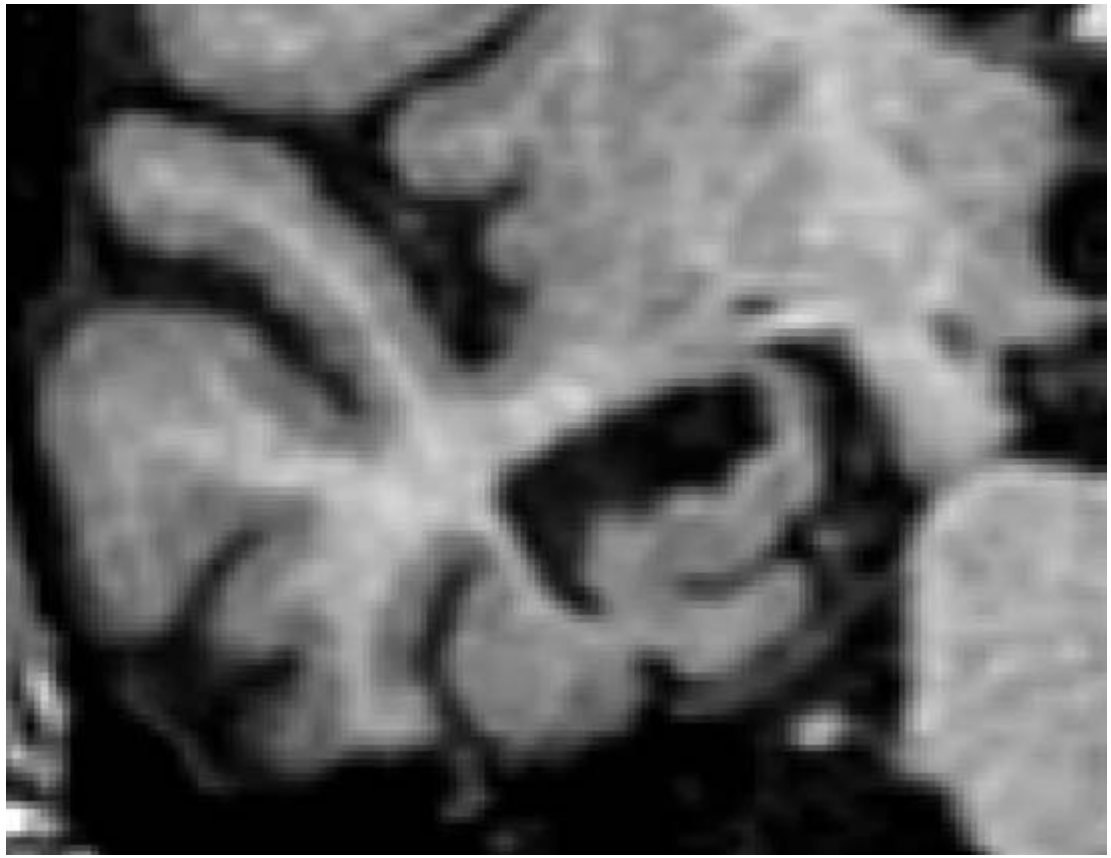
Clifford Jack, ISMRM, 2008

Progression from MCI to AD (10 years)



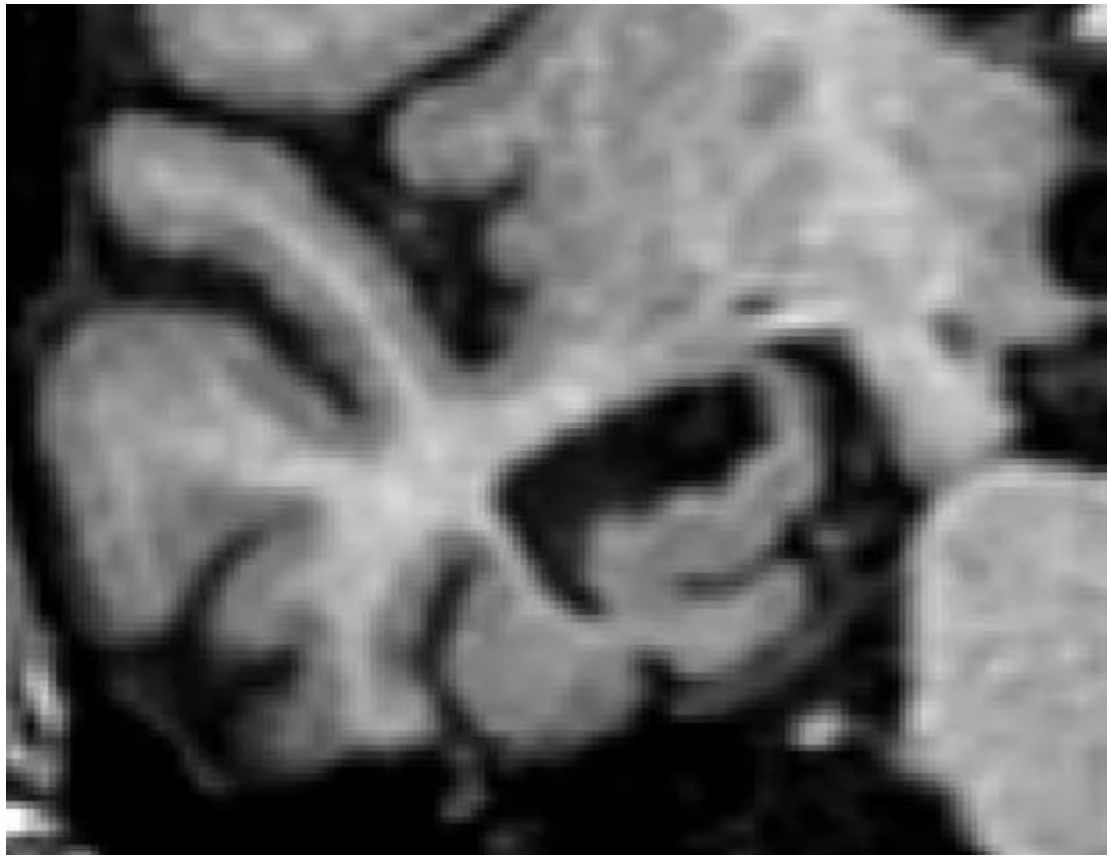
Clifford Jack, ISMRM, 2008

Progression from MCI to AD (10 years)



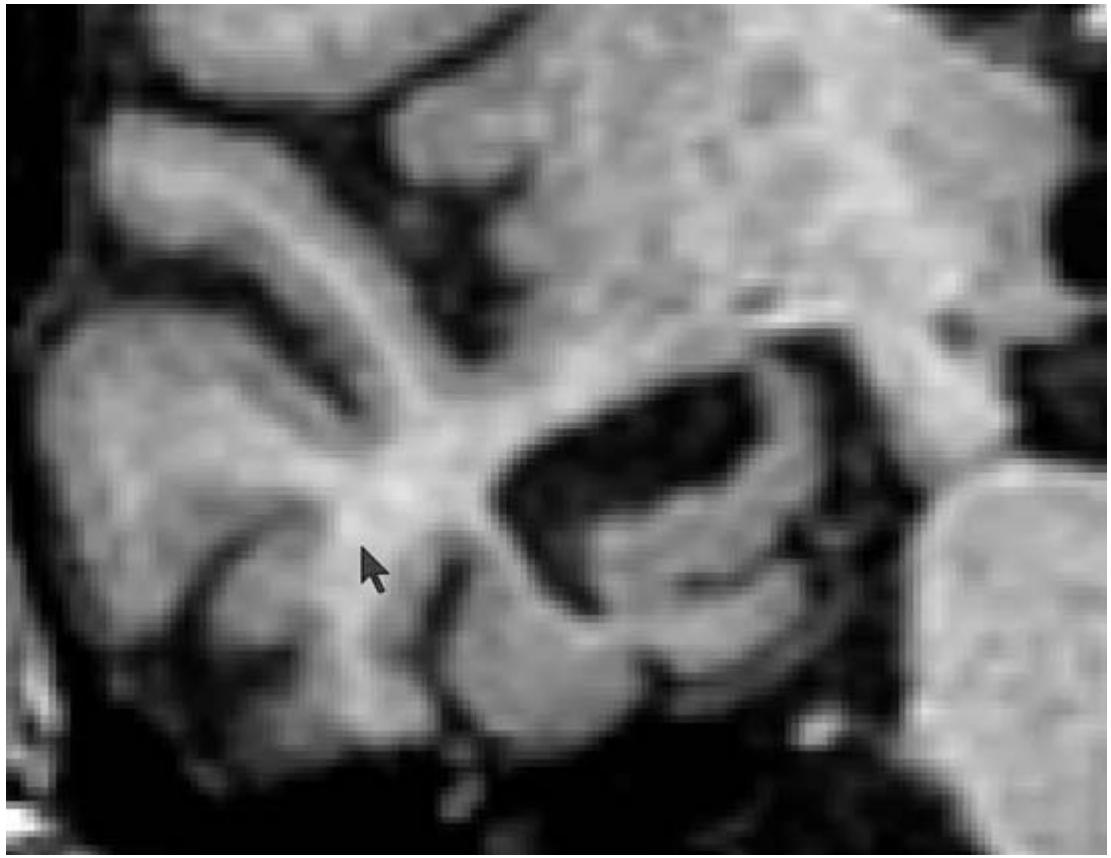
Clifford Jack, ISMRM, 2008

Progression from MCI to AD (10 years)



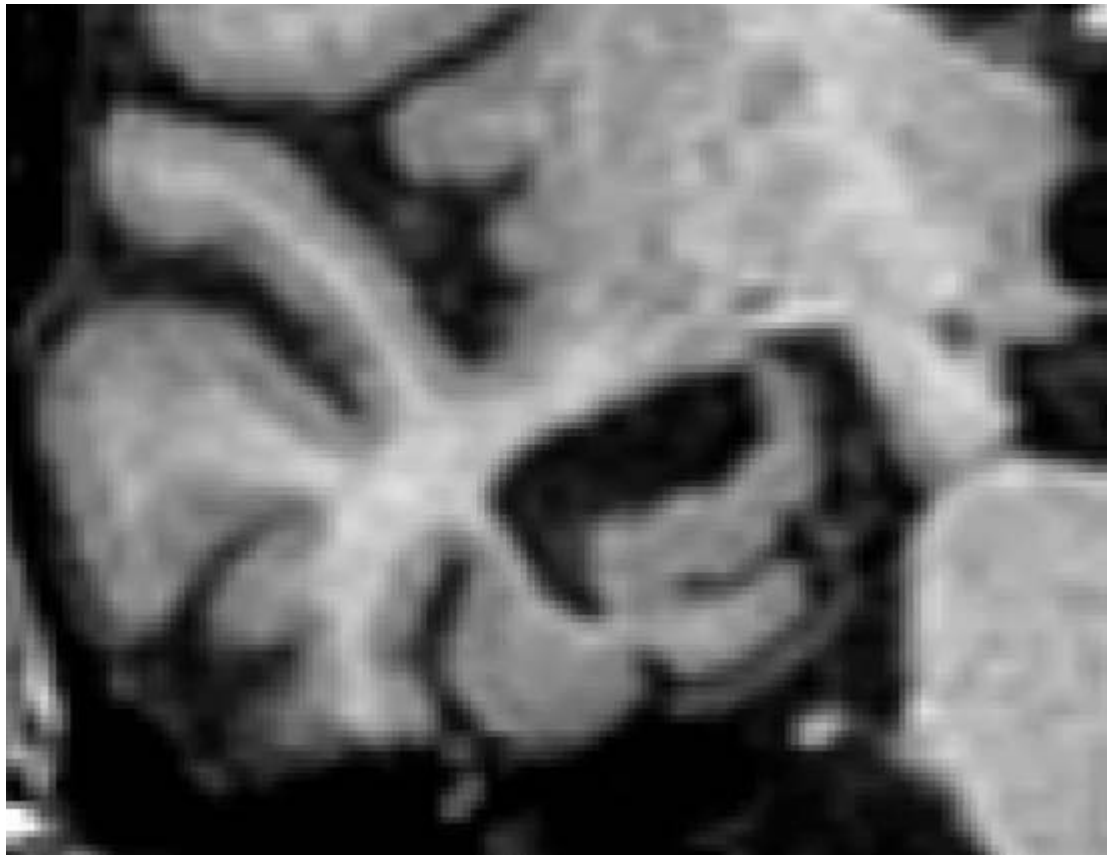
Clifford Jack, ISMRM, 2008

Progression from MCI to AD (10 years)



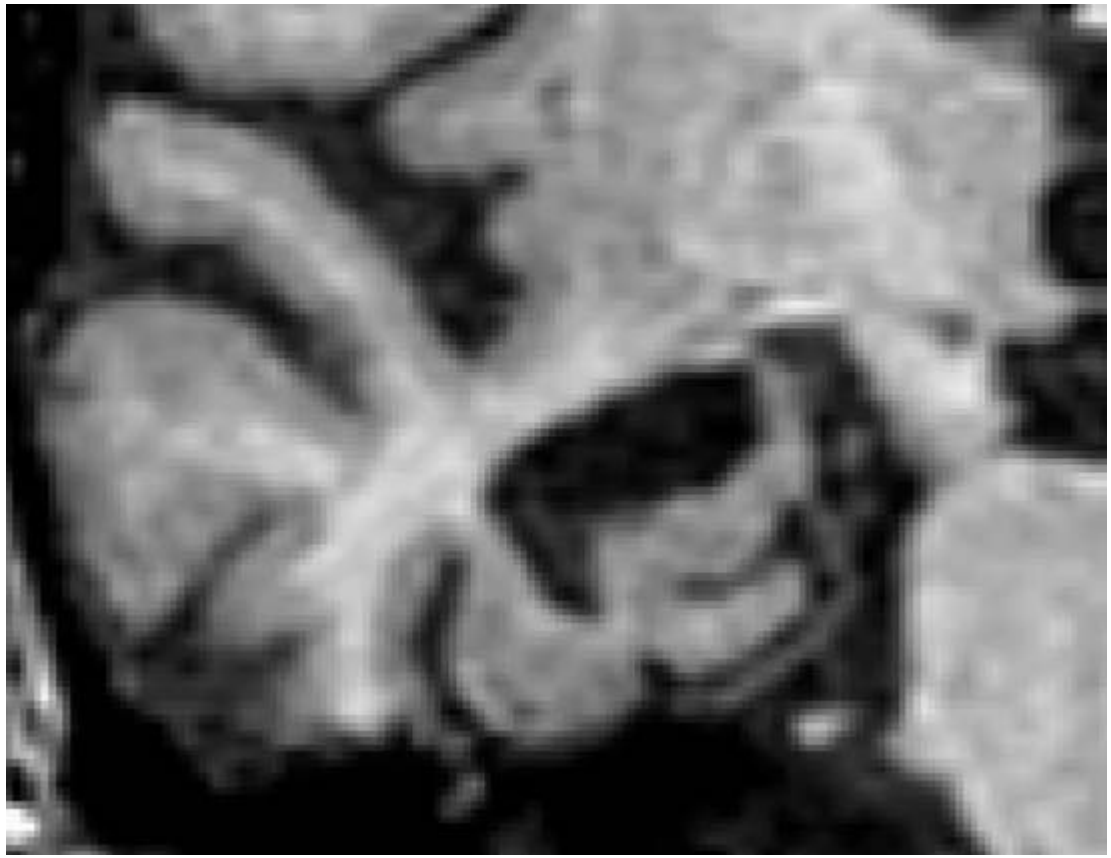
Clifford Jack, ISMRM, 2008

Progression from MCI to AD (10 years)



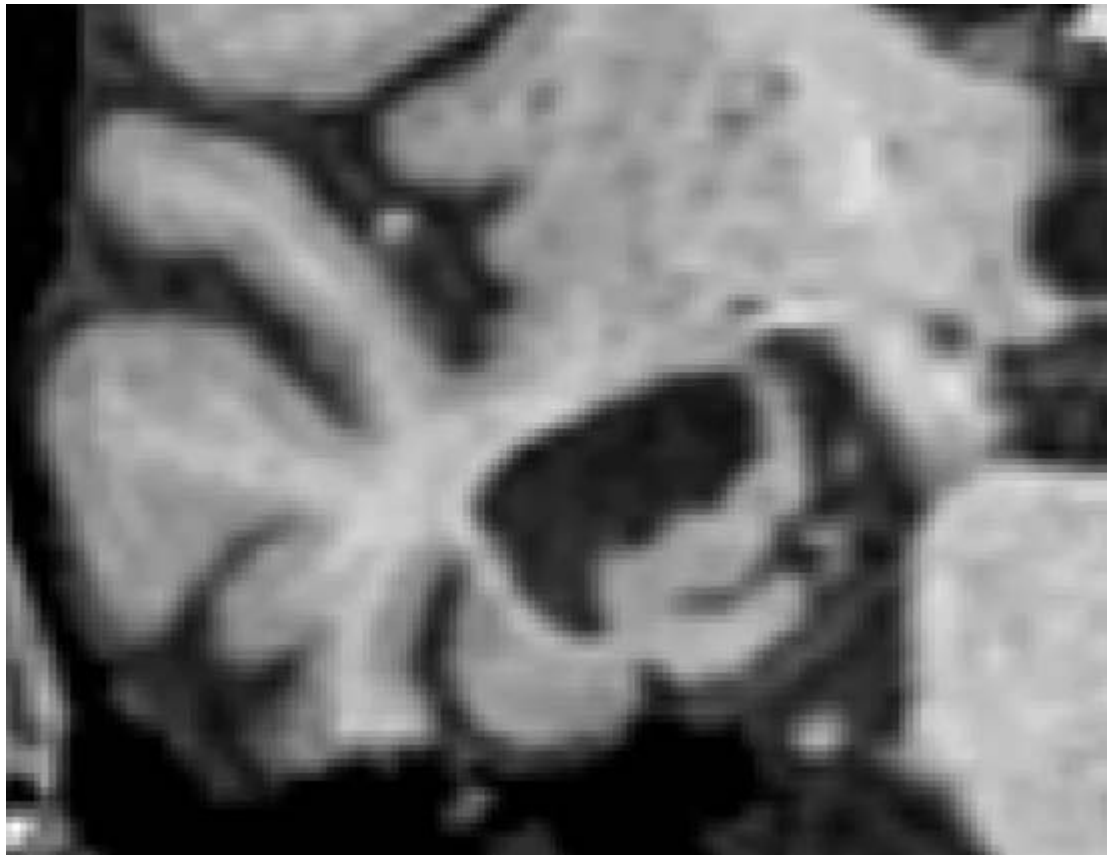
Clifford Jack, ISMRM, 2008

Progression from MCI to AD (10 years)



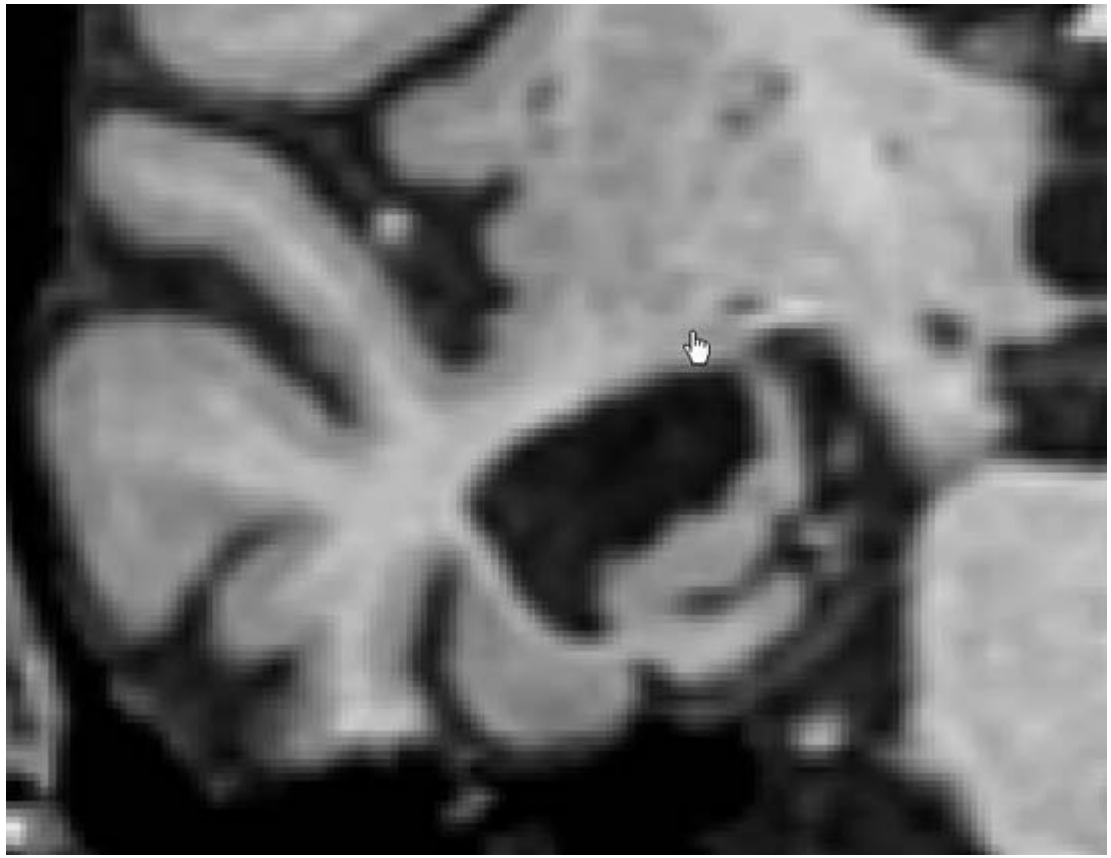
Clifford Jack, ISMRM, 2008

Progression from MCI to AD (10 years)



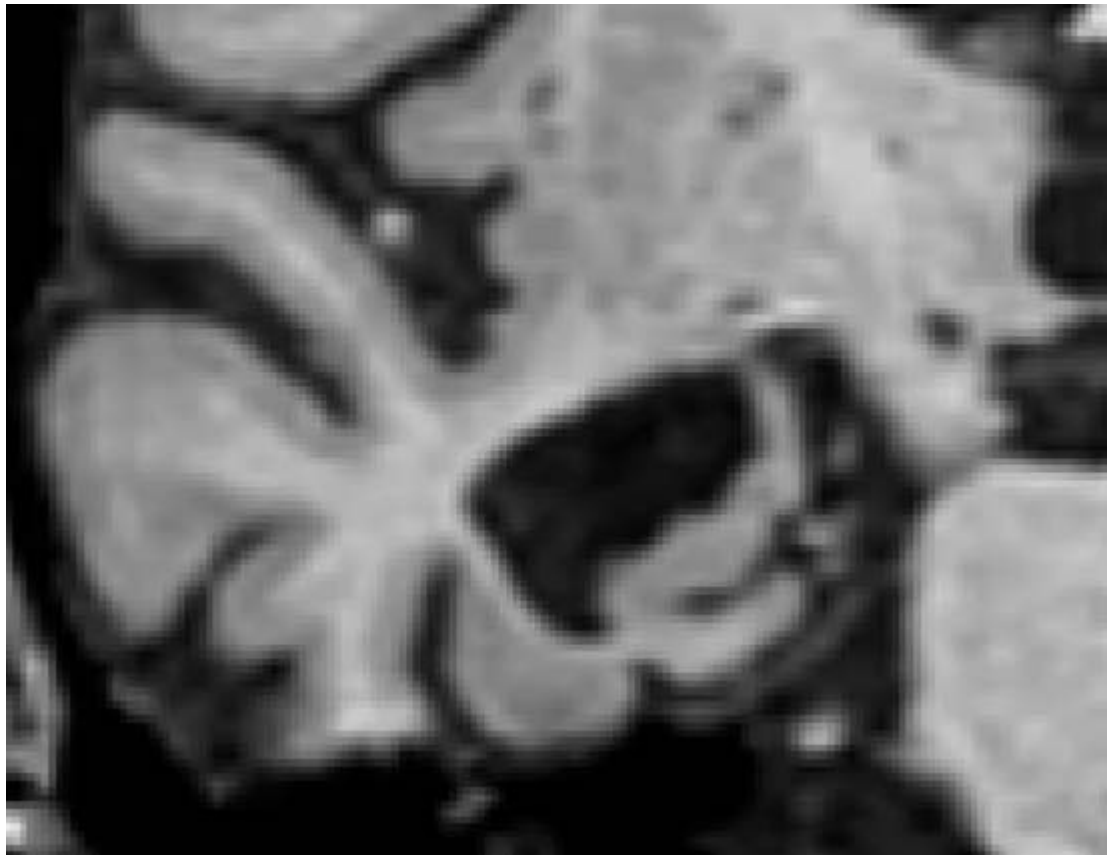
Clifford Jack, ISMRM, 2008

Progression from MCI to AD (10 years)



Clifford Jack, ISMRM, 2008

Progression from MCI to AD (10 years)



Clifford Jack, ISMRM, 2008

Results from ADNI

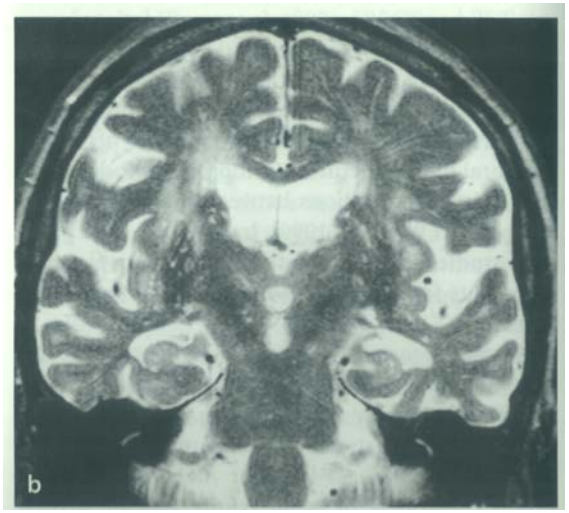
POWER OF EVALUATION OF BRAIN ATROPHY 25% CHANGE 1YR STUDY (2 ARM) :

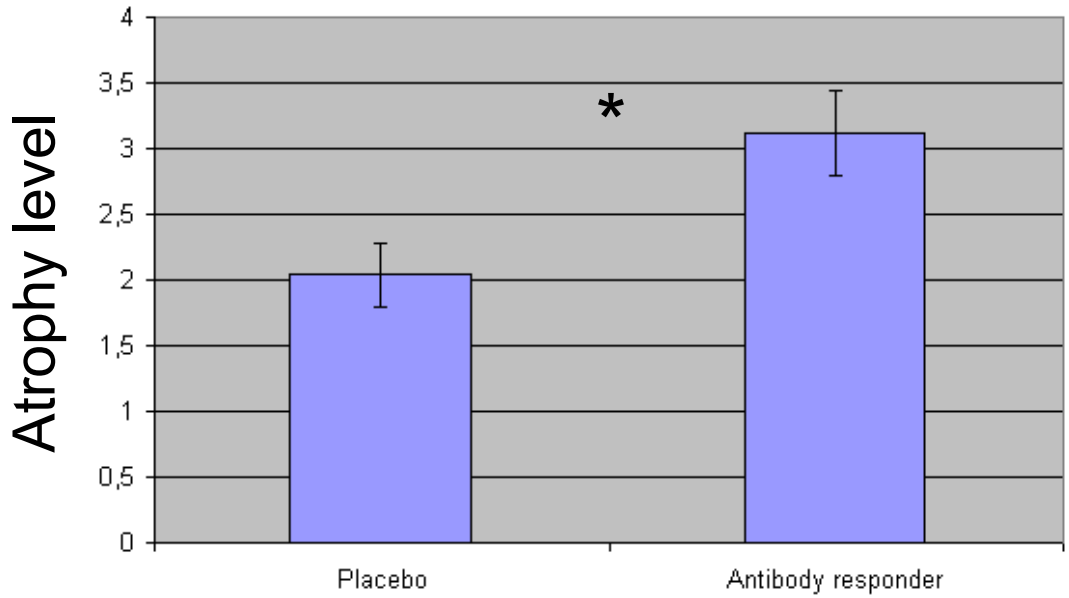
AD (69 Subjects)

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*

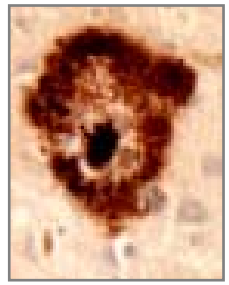




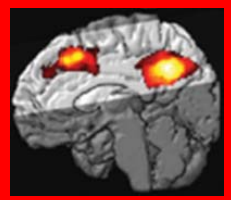
A good marker for the diagnosis (T0 biomarker)
can be questionable for therapeutic follow-up (T2 biomarker)

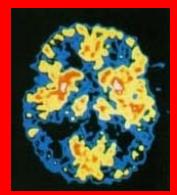
Maladie d'Alzheimer : Quels biomarqueurs ?

Dépôts Amyloïdes

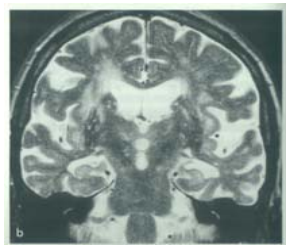


DNF

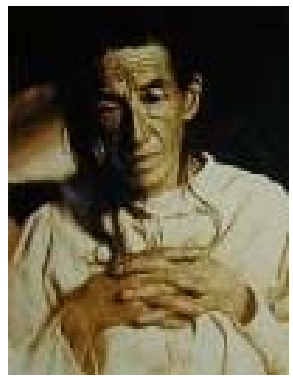




Altérations fonctionnelles

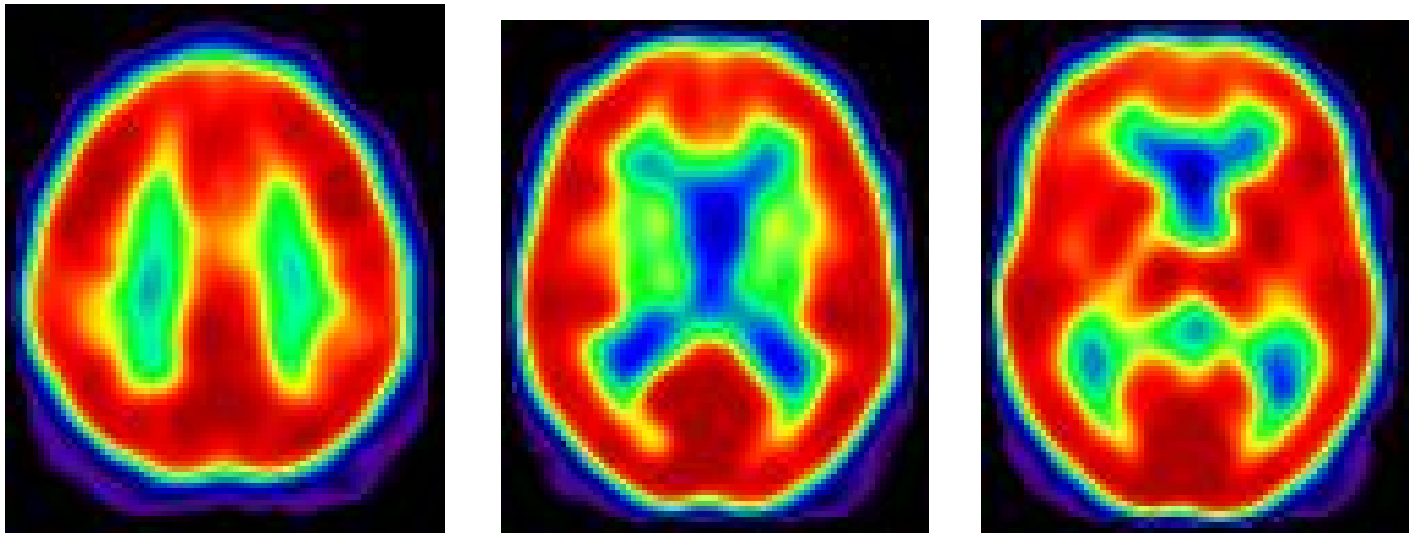


Atrophie

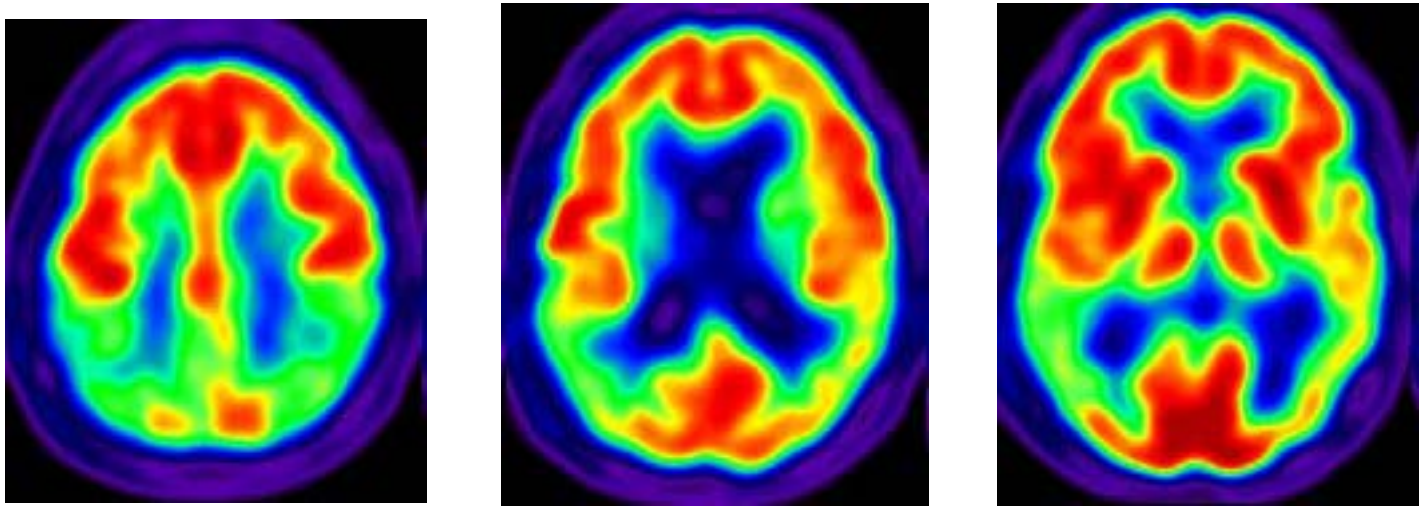


Cerebral metabolism

Normal



AD



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

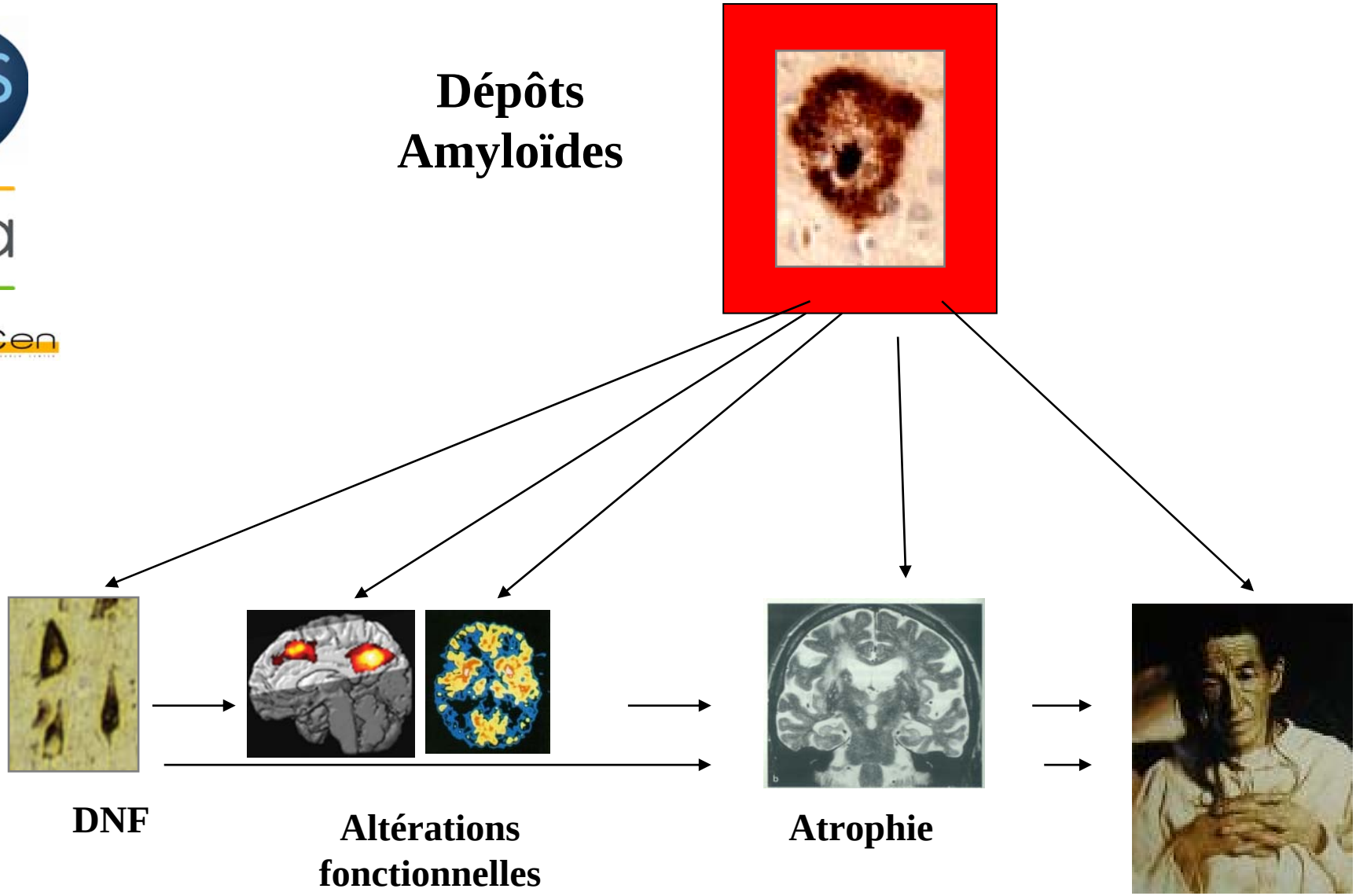
AD (36 Subjects)

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

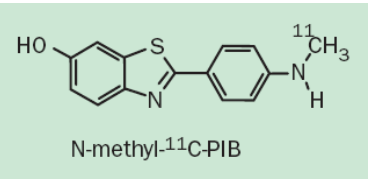
Cerebral metabolism

- 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

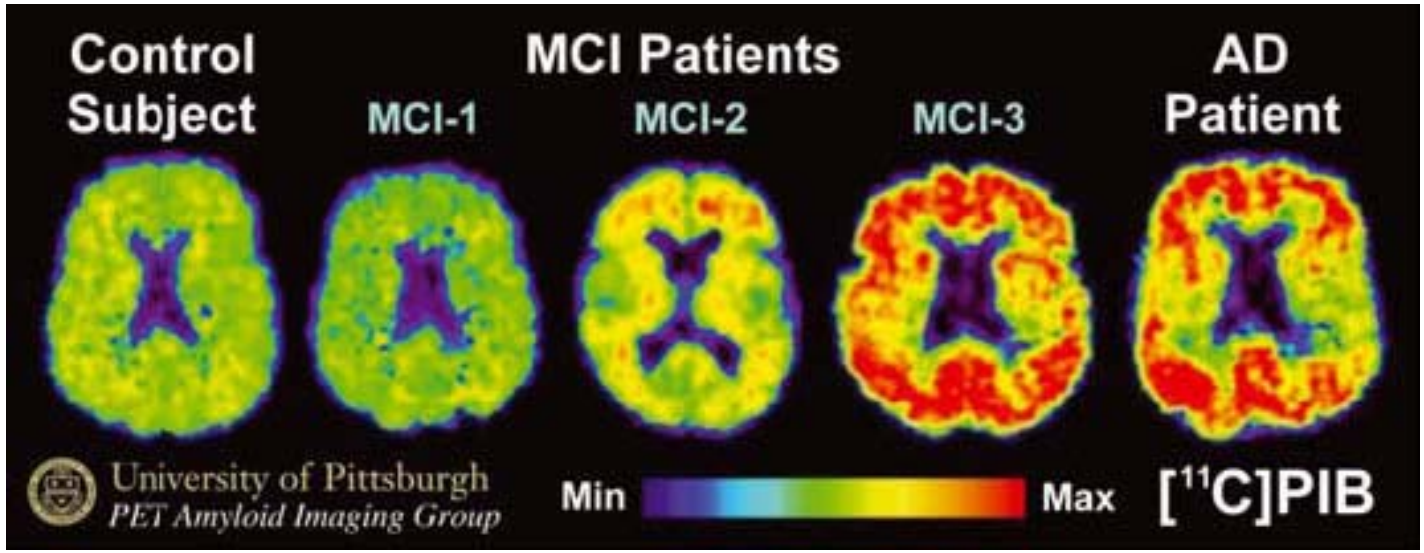
Biomarkers for Alzheimer's disease



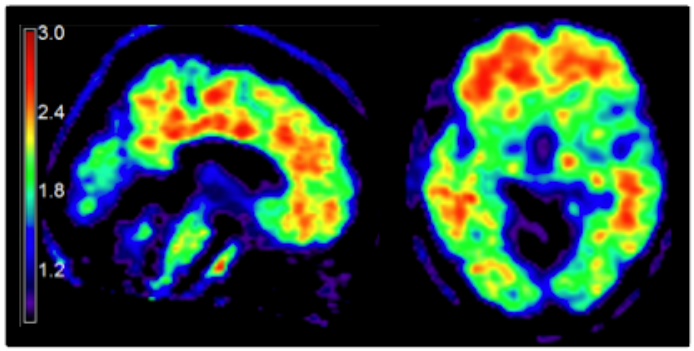
Amyloid imaging in humans (by PET)



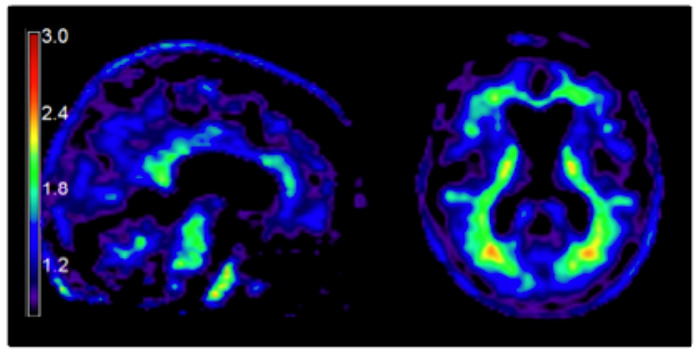
N-methyl-^{11}C-PIB



Amyvid

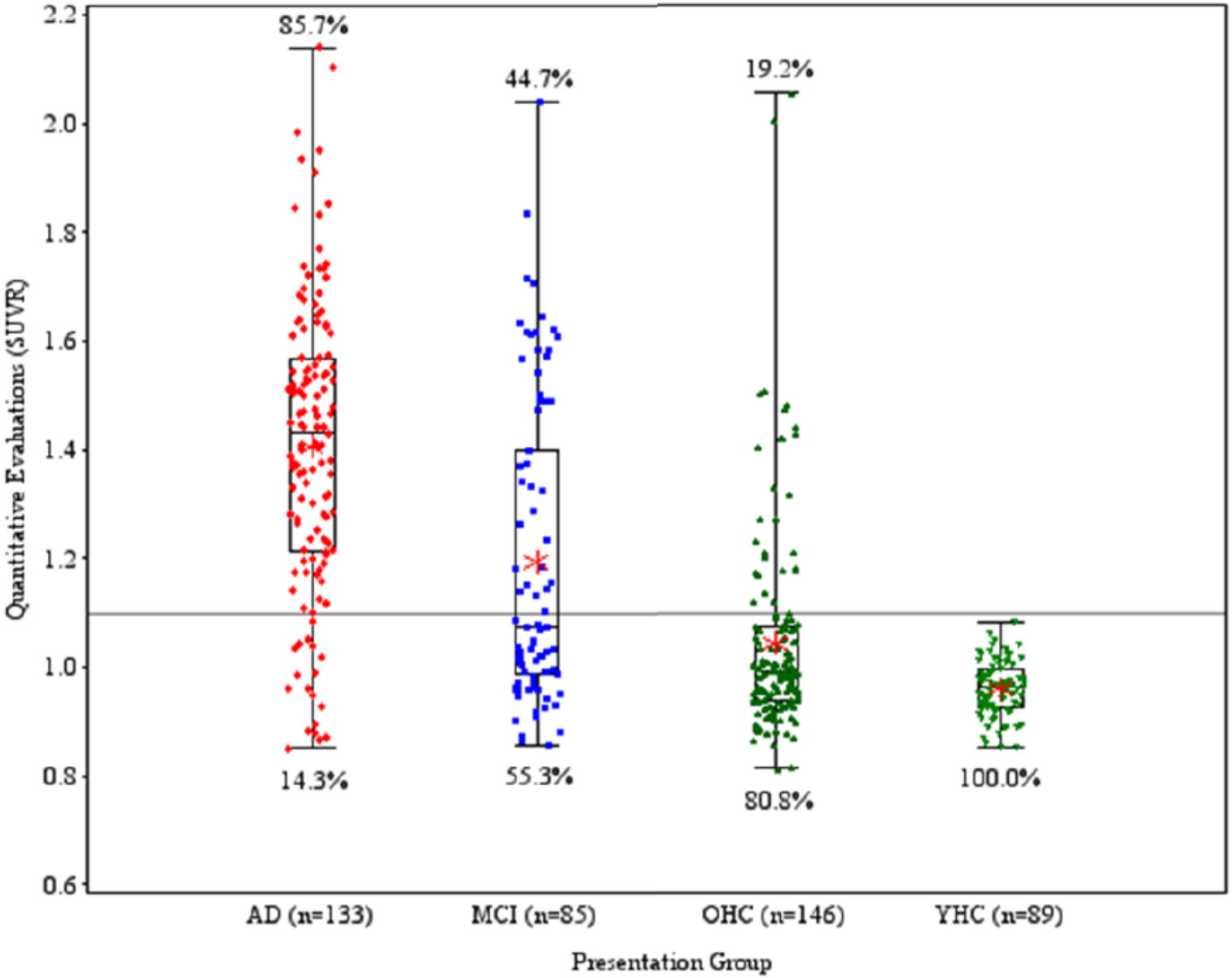


"Probable AD" Patient

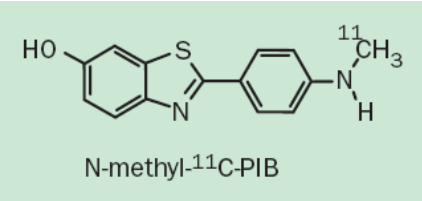


Cognitively Normal Elderly

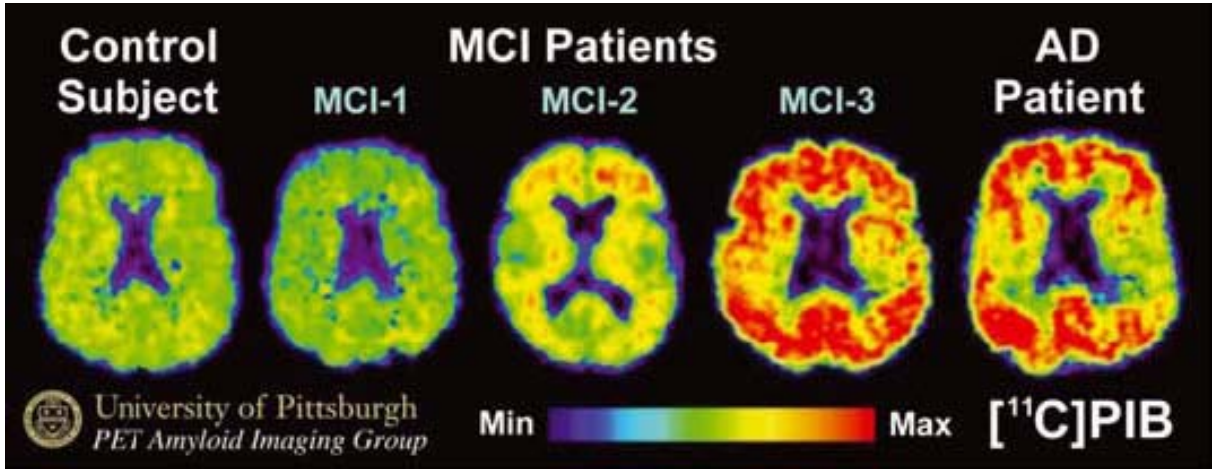
Figure 5: Distribution of Quantitative SUVR Values by Presentation Group

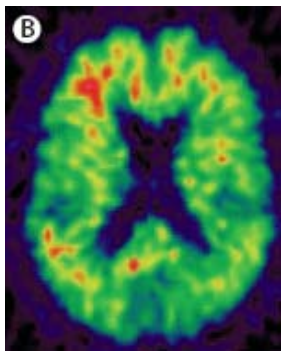


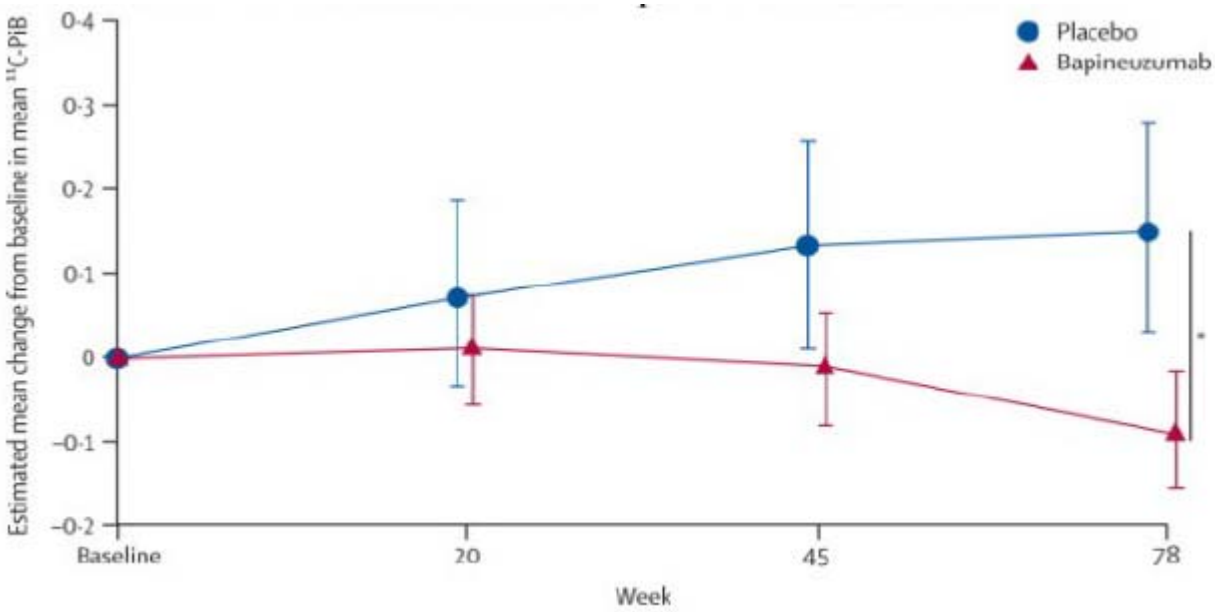
Amyloid imaging in humans (by PET)

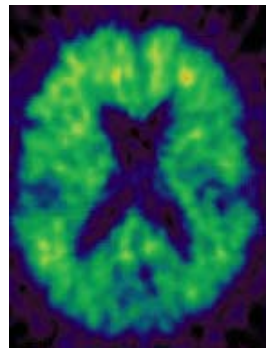


N-methyl-^{11}C-PIB





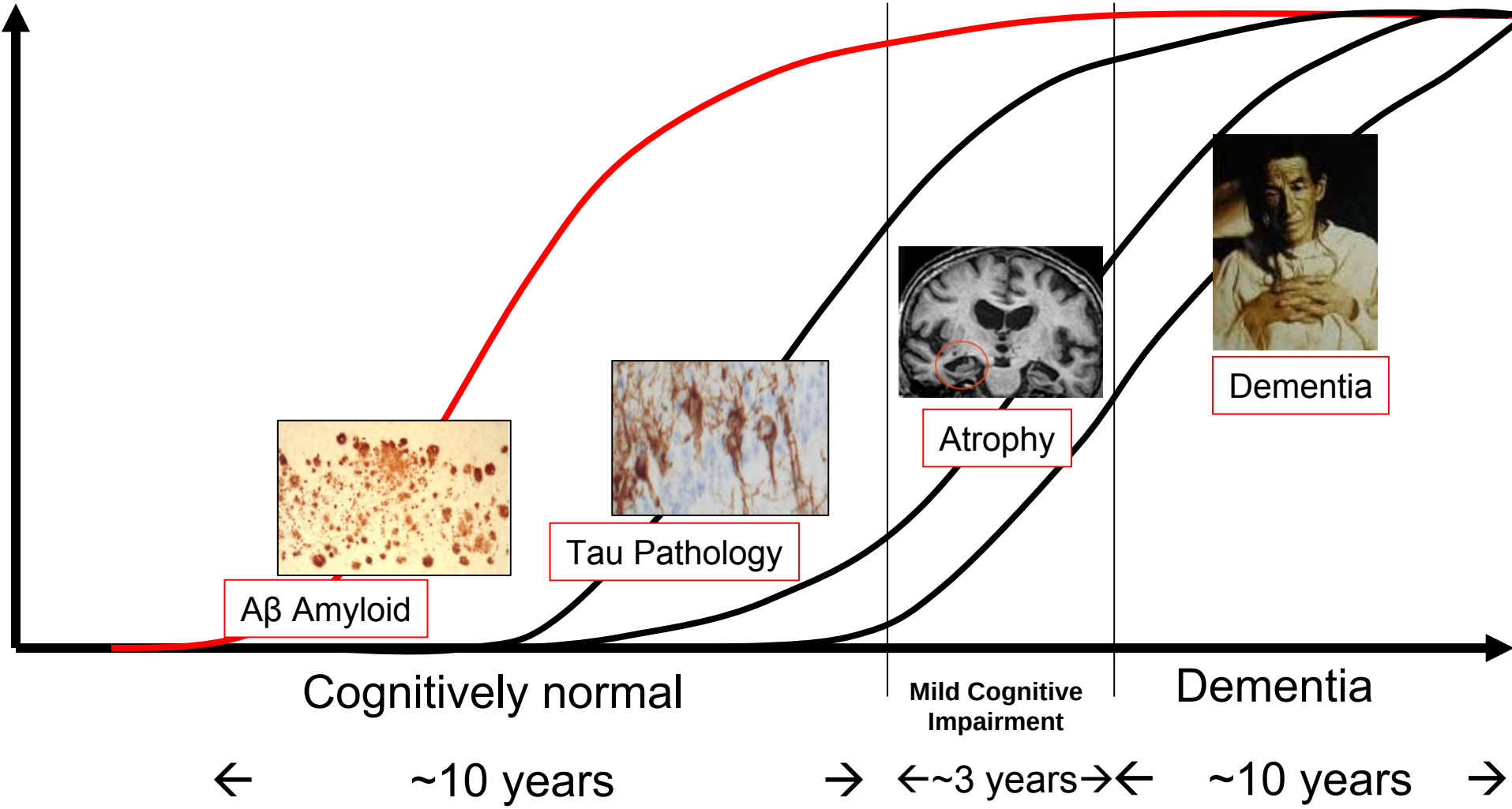




Amyloid load

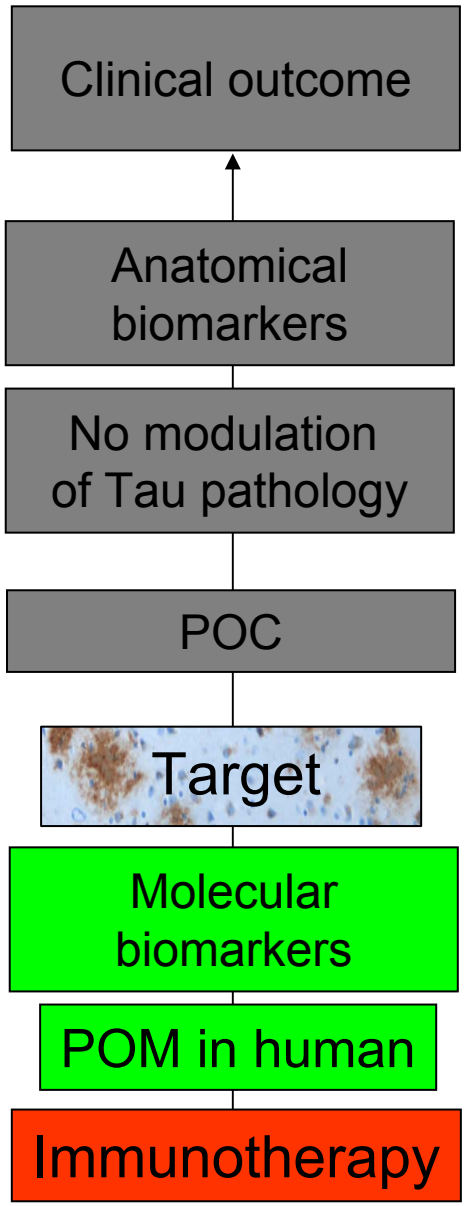
- Reflect early history of the disease ?
  - But is not a disease progression biomarker
- Related to therapy (for amyloid reducing therapies = Type II)

Biomarker – Chronology in the disease



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

Biomarker – Immunotherapy evaluation



No cognitive improvement

No Modulation of cerebral atrophy

No Modulation of Tau pathology

No POC

Reduced amyloid load

POM

Conclusion: Biomarkers in humans

- Better exploration of the natural history of the disease
  - Amyloid as an early event in the course of the disease
- Reduction of the patients to be involved in (preliminary) therapeutic trials
- Milestones on the follow of immunotherapies

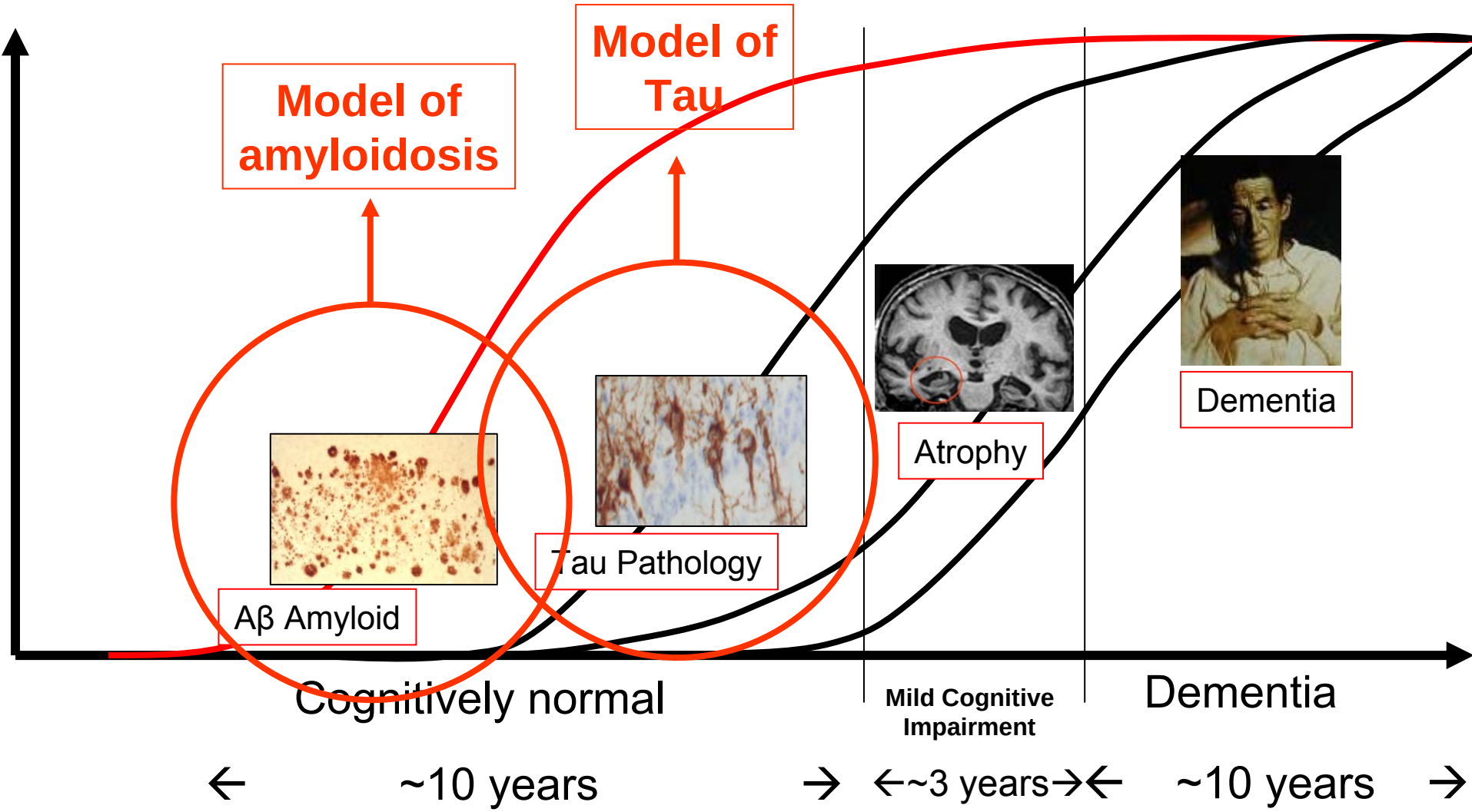
Overview

- Overview on neurodegenerative diseases
- Strategies for the discovery of new therapies
  - From phenotypic to target based approaches
  - Biomarkers, POM, POC
  - Use of animal model: Target models, predictive models, and biomarkers
- Biomarkers in humans: From diagnostic to therapy evaluation tools
  - Dubois Criteria / ADNI initiative
  - Cerebral atrophy (MRI)
  - Brain metabolism (PET)
  - Amyloid plaques (PET)
- Animal models of Alzheimer's disease
  - Most used models of AD
  - Can we predict clinical efficacy of a drug with these models ?
    - "Classical view" of translational medicine
    - Translational bridges
- Conclusion

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

How can we create a model of Alzheimer's disease ?



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

Animal models of AD

Reproduction, Easy acces

→ Genetic

Non-transgenic → SAMP8 mice, rats

Transgenic mice → 90', familial forms of AD

- genetic, mecanistic

- Therapeutic evaluations but limit of the models = genetic distance to humans

→ Therapeutic evaluation

Life span

2-3 months

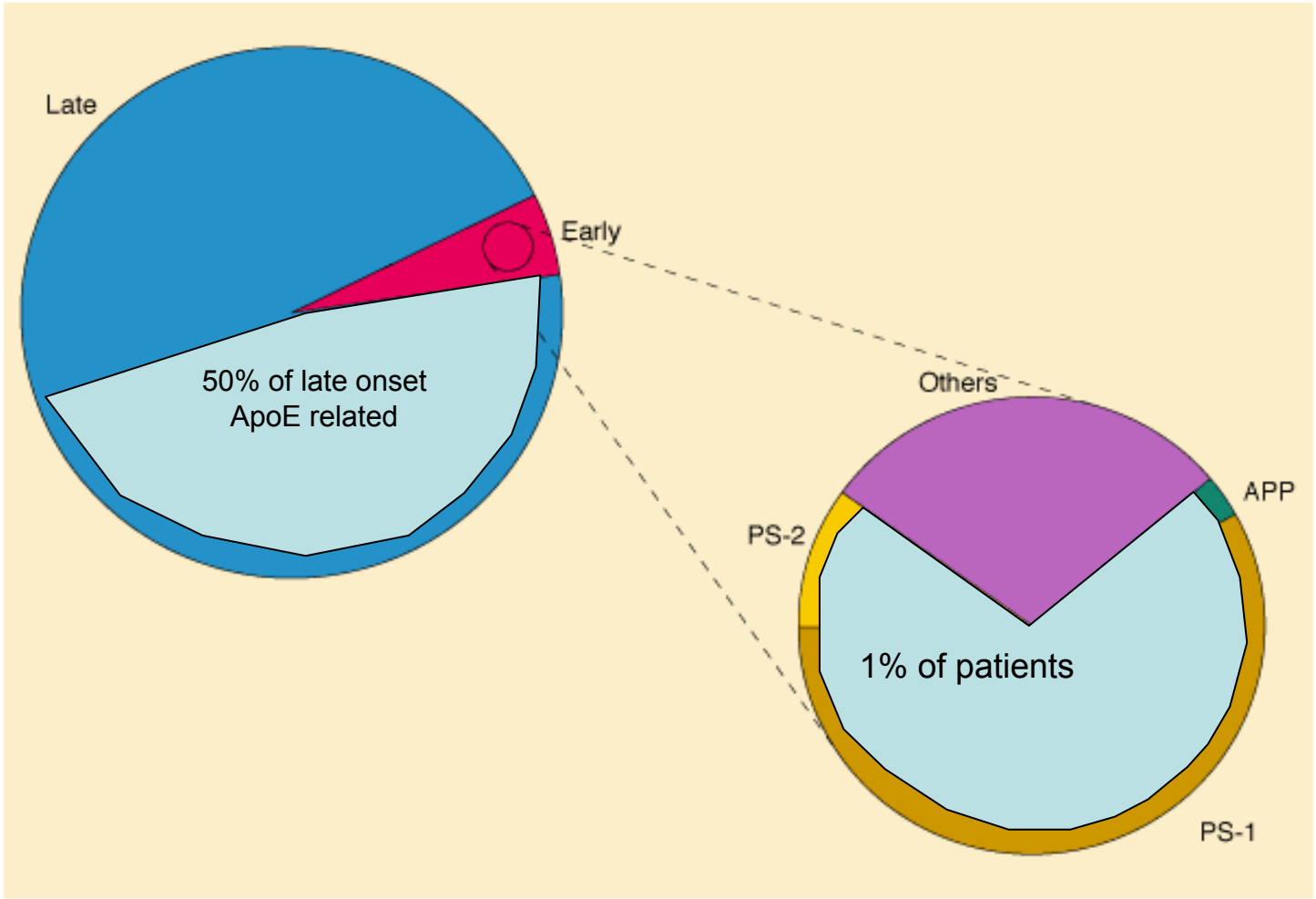
2-3 years

30 years

Duyckaerts C. et al., Acta Neuropathol 2008 ; Woodruff-Pak S.D., J Alzheimers Dis 2008 ; Philipson O. *et al.,* FEBS Journal 2010

Alzheimer's disease: Few genetic causes

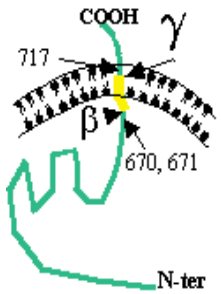
Relative frequency of early and late-onset Alzheimer's and the proportion of early-onset cases attributed to mutations in specific genes such as APP, PS1, PS2 or others



From, Piecing Together Alzheimer's by Peter H St George-Hyslop.

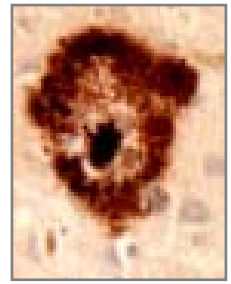
Mouse models of Amyloidosis

APP

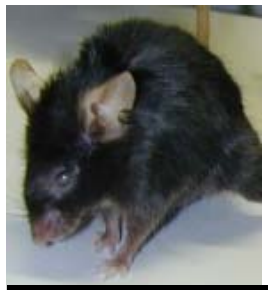


Beta Amyloid

Plaque



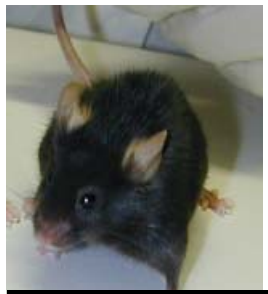
Mutations:
APP_{751SL} + $PS1_{M146L}$



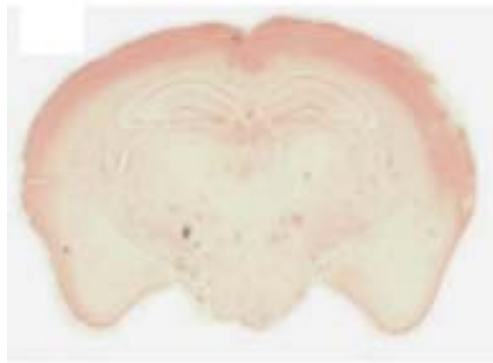
APP/PS1

No Tau Pathology …

Mutation:
$PS1_{M146L}$ alone



PS1

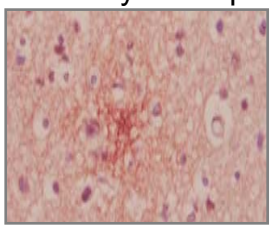


Risk factors (Alzheimer)

- Age
- Education level
- Familial History
- Positive genotype Apolipoprotein E 4/4
- Arterial hypertension
- Hyperinsulinemia

A model of cerebral aging/AD?

Diffuse amyloid deposits



Bons et al., Neurobiology of aging, 1991

Small size

Facilitates breeding, manipulation, experimentation

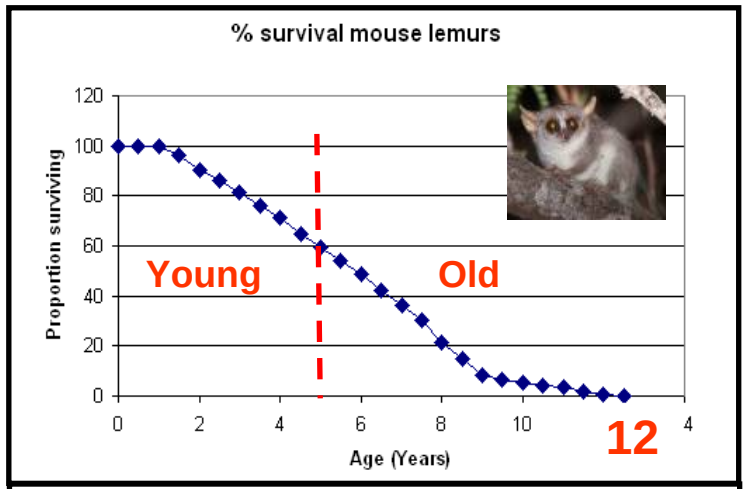
Primate

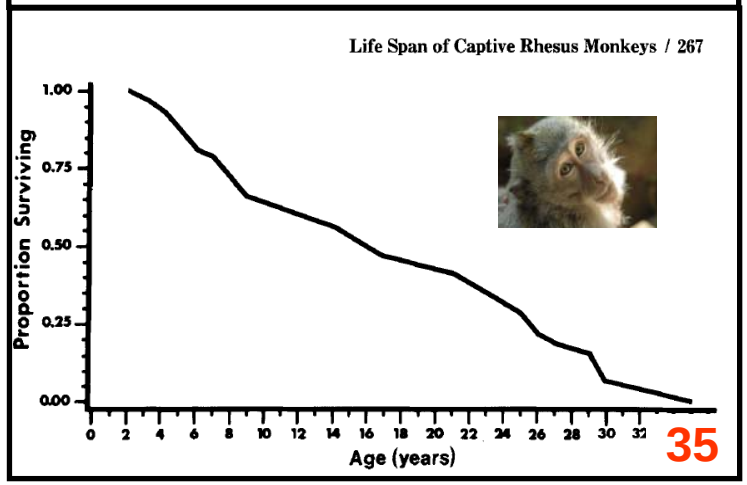
Phylogenic proximity with humans

Lack of severe zoonoses

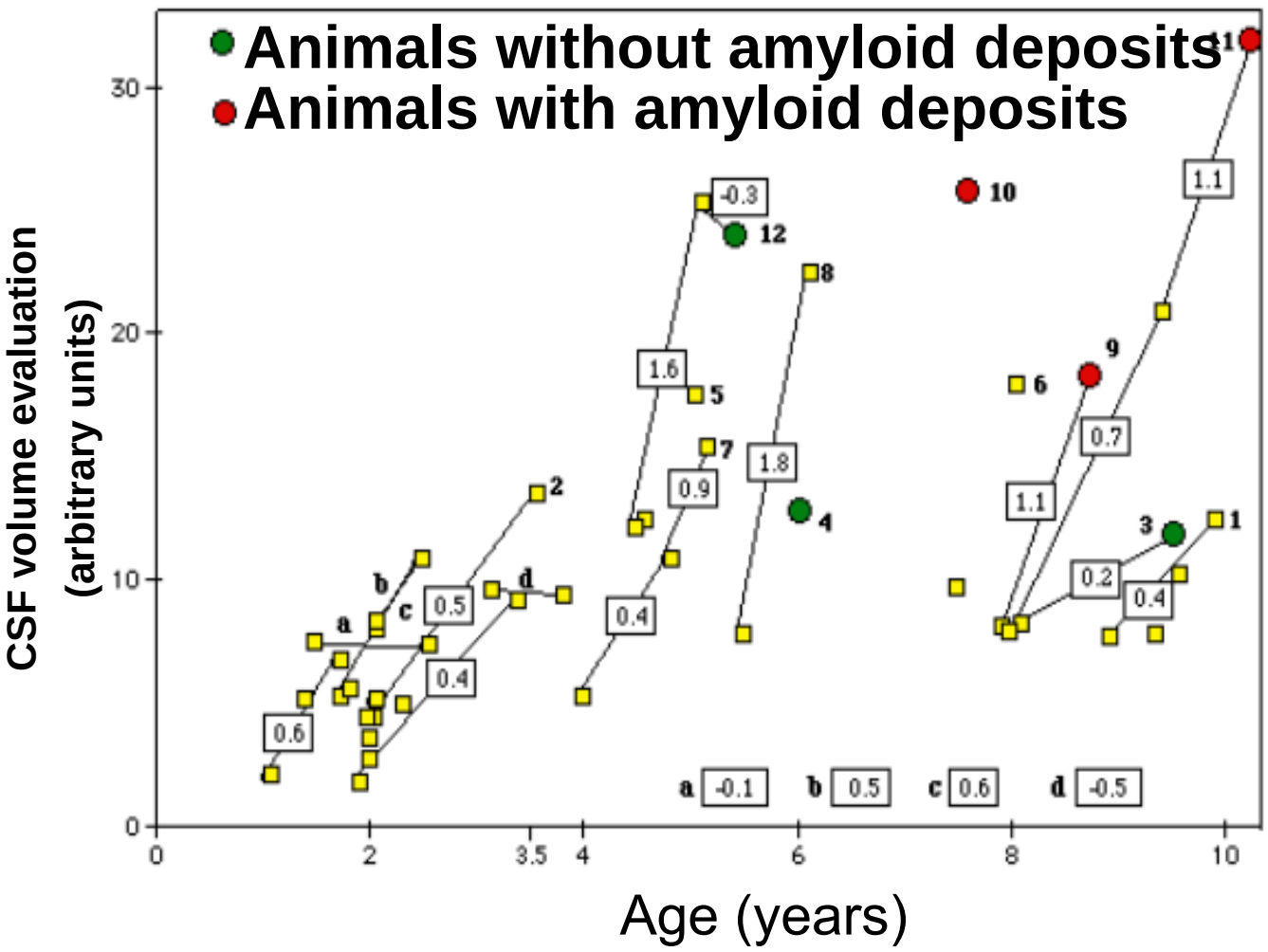
Small cost

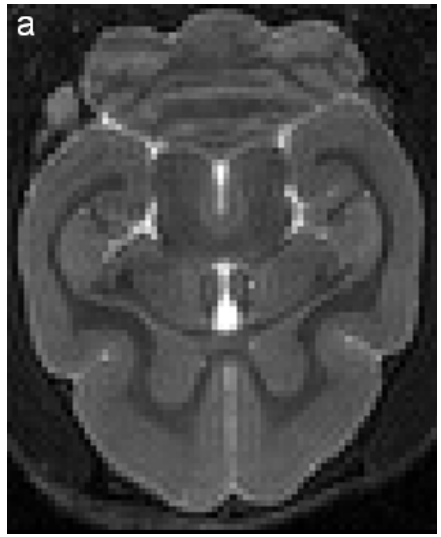
Short life span

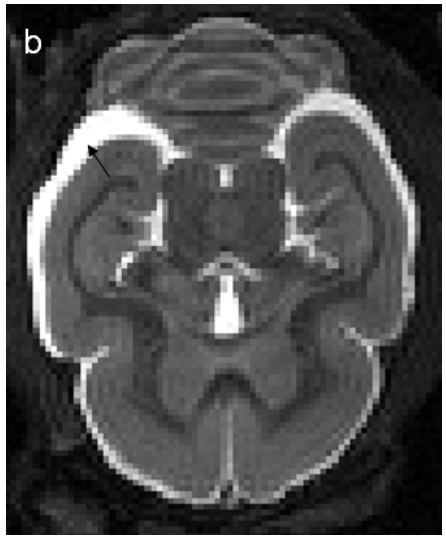




cerebral atrophy



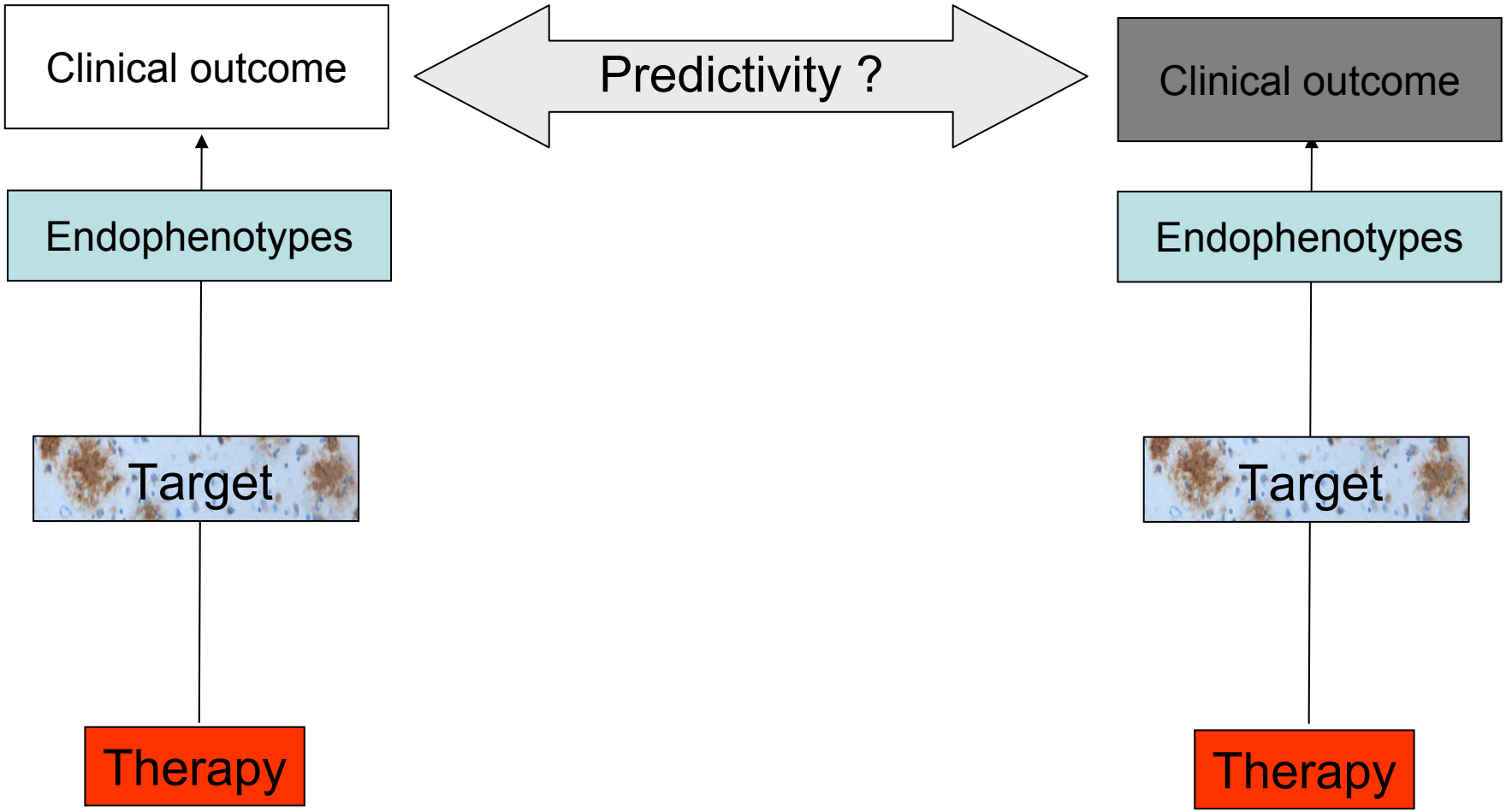




Dhenain et al. Neurobiol Aging. 2000;21(1):81-8.

Can we predict the clinical efficacy of a drug with these models ?

Translational bridges: Focus on the clinical outcome ?



"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

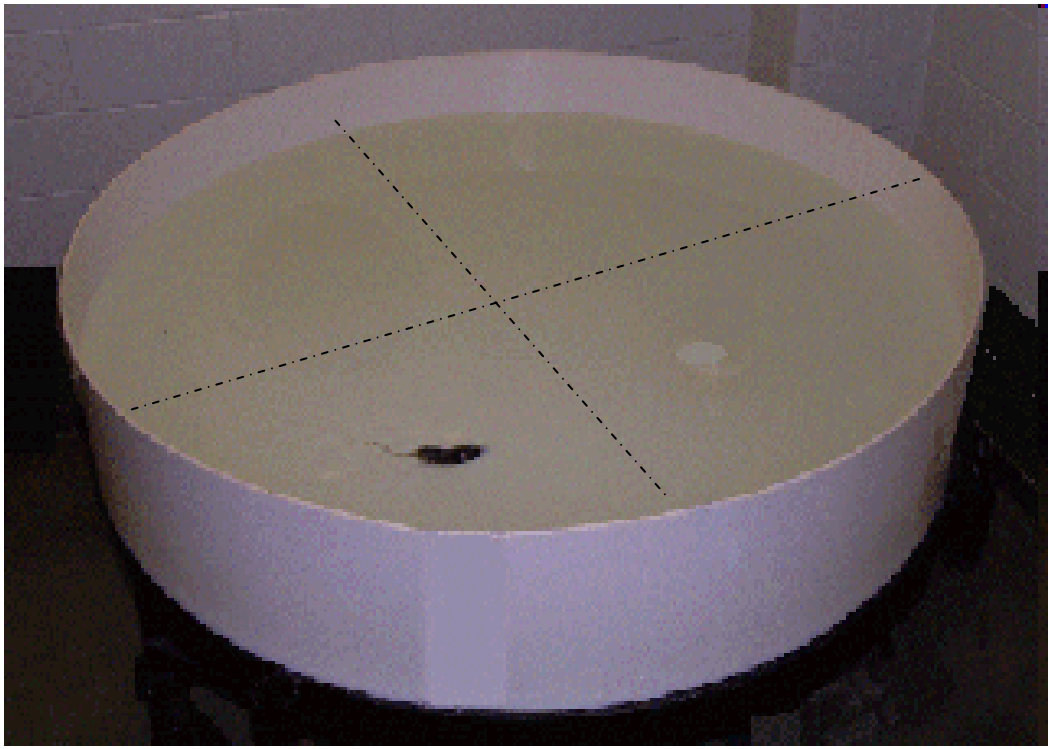
Example of behavioral studies to evaluate drug efficacy in mice

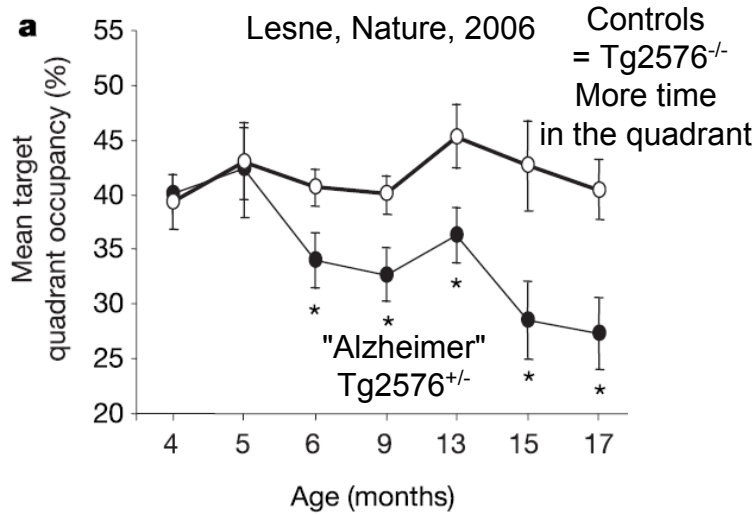
Alzheimer is a dementia
Let's look a behavioral alterations in animals to predict drug efficacy…

Altérations comportementales chez les rongeurs

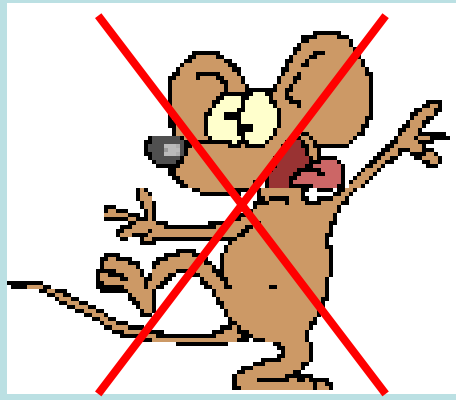
Ex. Piscine de Morris – Navigation Spatiale

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



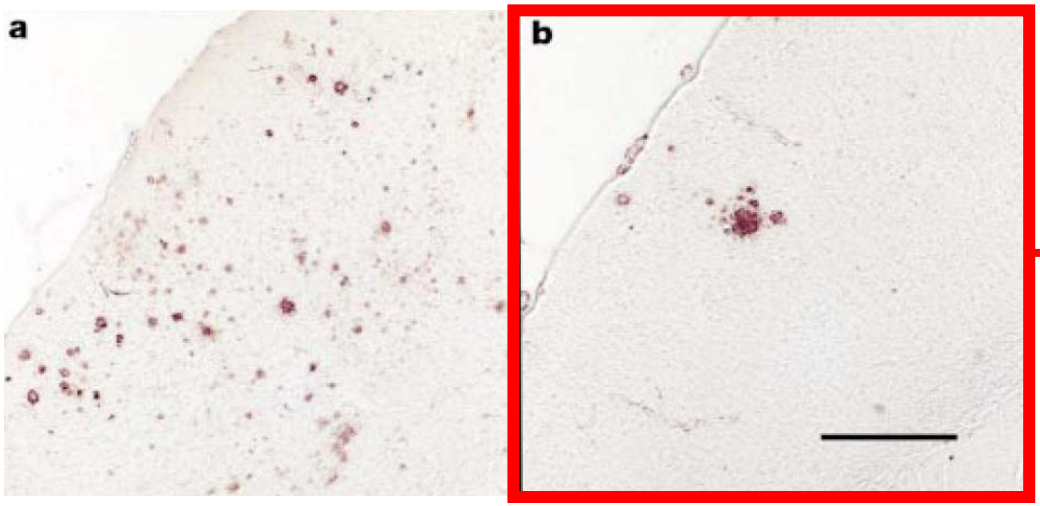


Altérations mnésiques
mais pas de "démence"



Predictivité des effets chez l'homme

- AN1792



Improve cognitive alterations

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

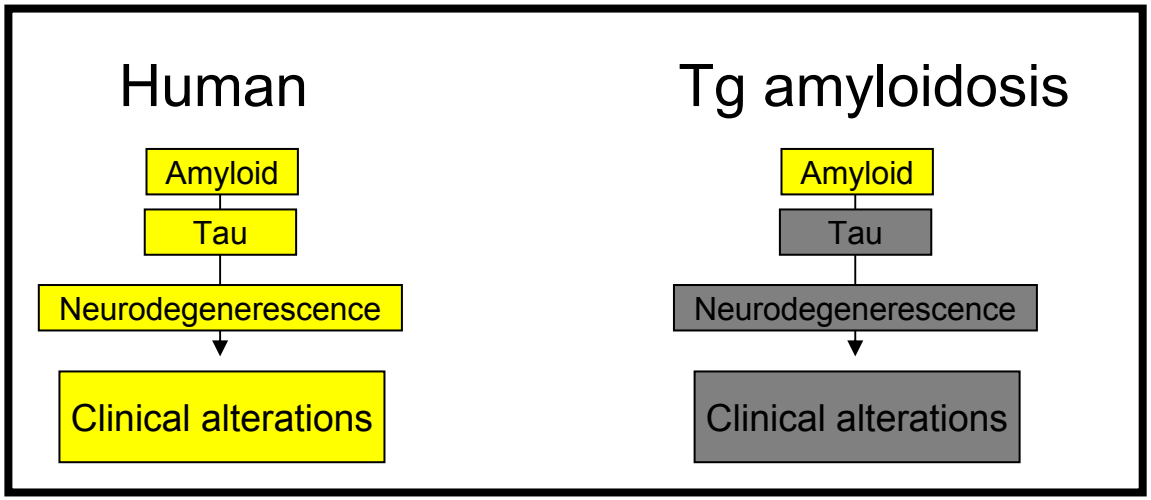
Origine Troubles Comportementaux = DNF

Troubles comportementaux modérés

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 does not reflect the full Alzheimer's disease pathology and is not predictive of treatment efficacy at the clinical level

From mice to humans: Translational bridges

Clinical outcome

Endophenotypes

POC in animals

Target

POM in animals

Therapy

Clinical outcome

Endophenotypes

POC in Humans

Target

POM in human

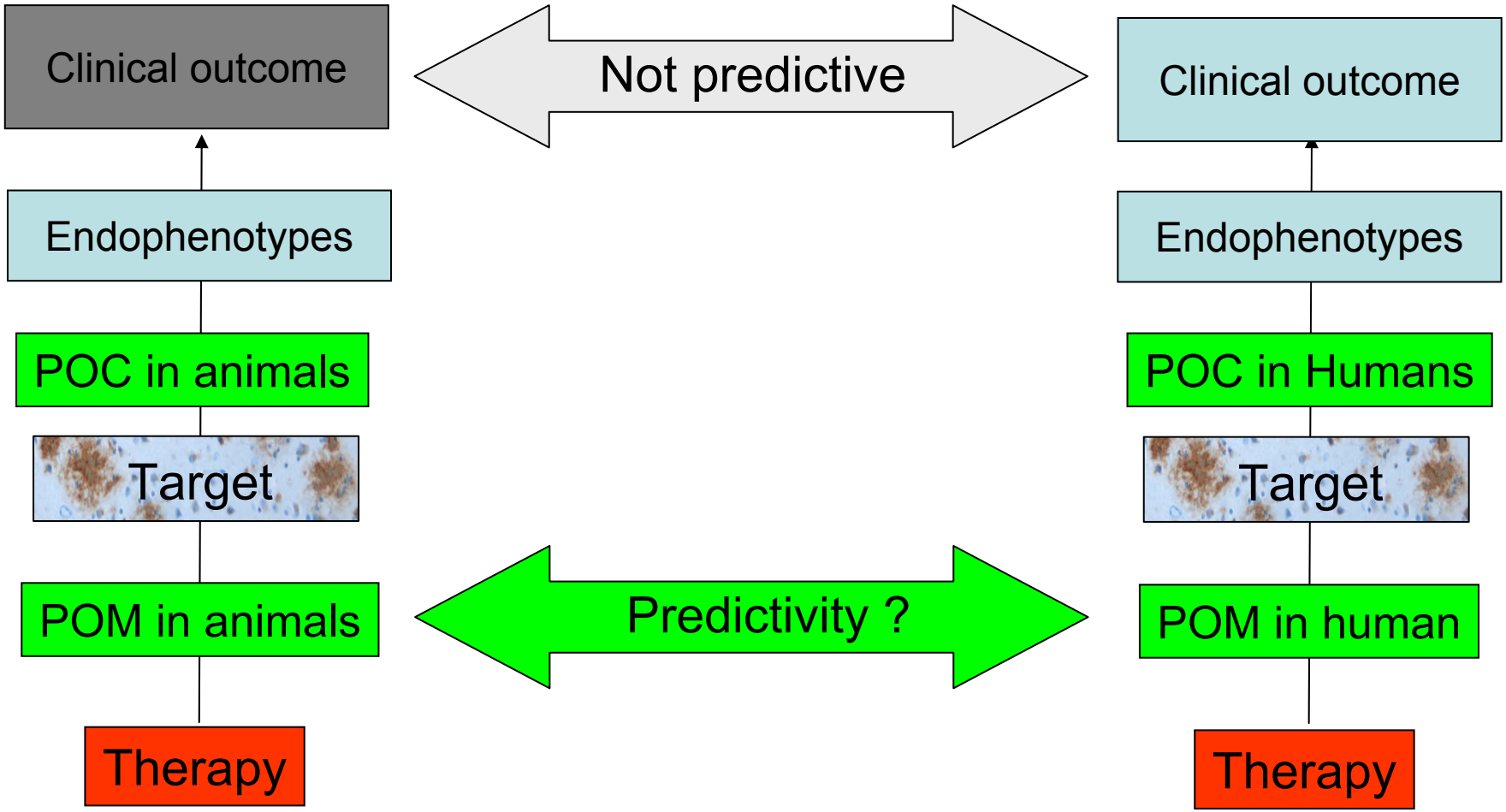
Therapy

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 ?

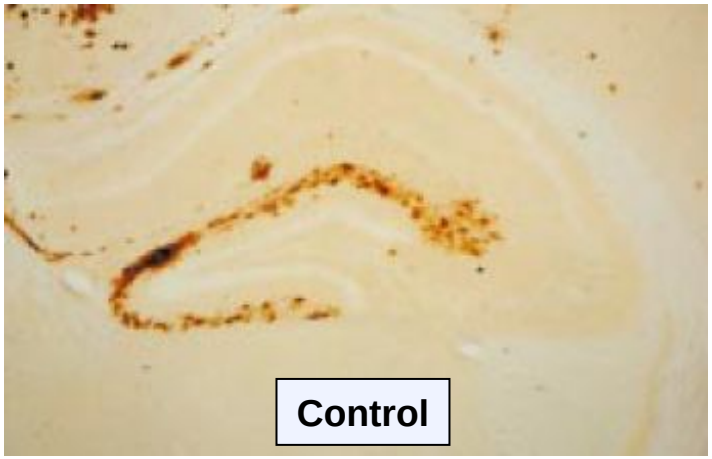
Translational bridges



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

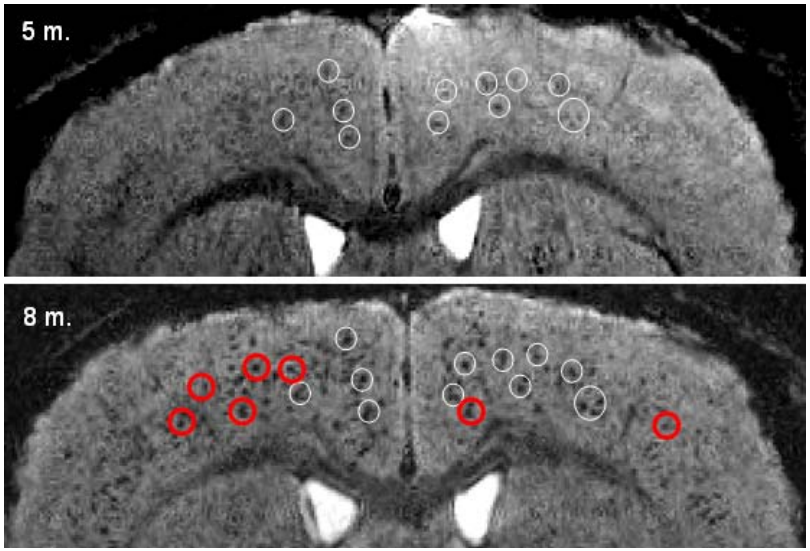
Immunotherapies in amyloid mice

- Marker of amyloid load (Histology)

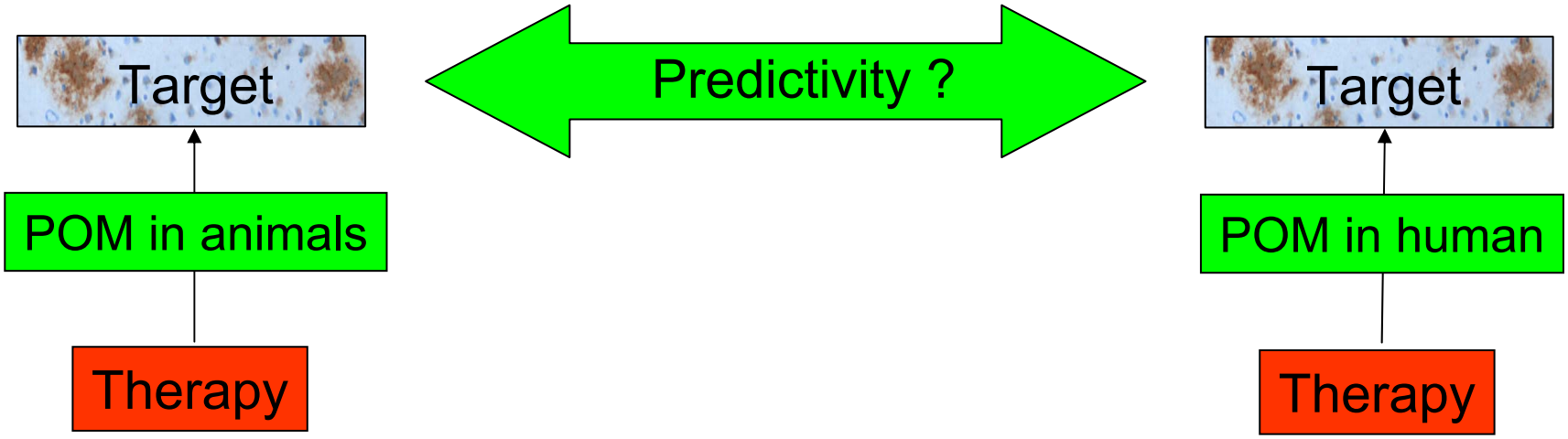


(Schenk et al, 1999)

- Biomarker of amyloid load (MRI)

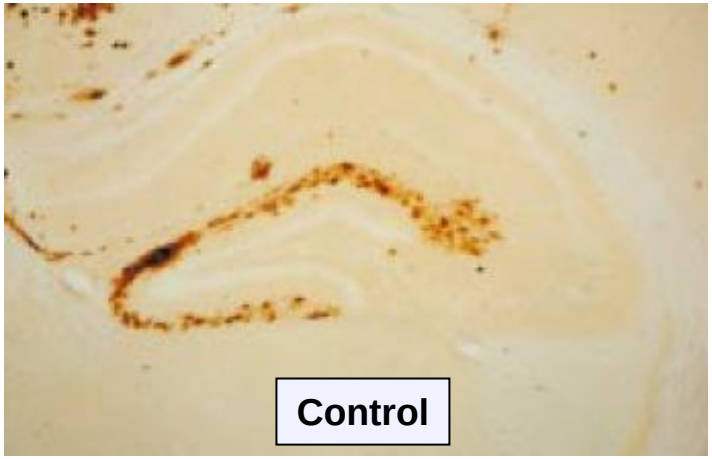


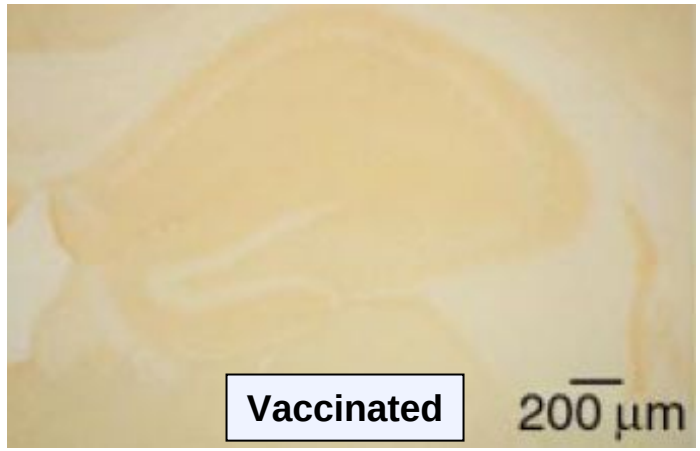
Translational bridges



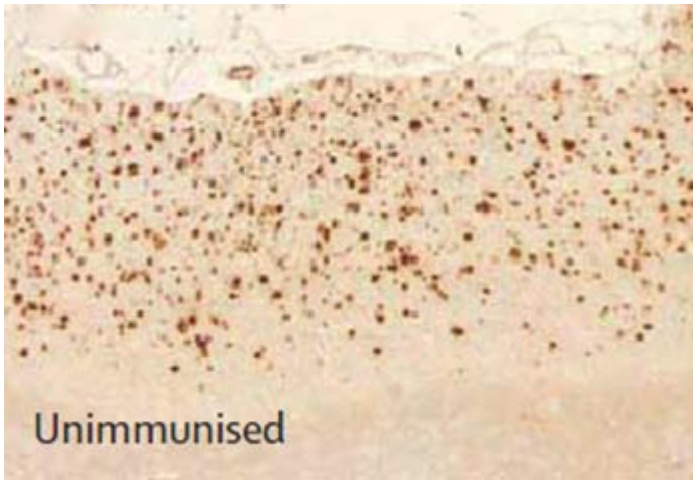
- It is reasonable to think that the treatment will reduce amyloid load in humans?

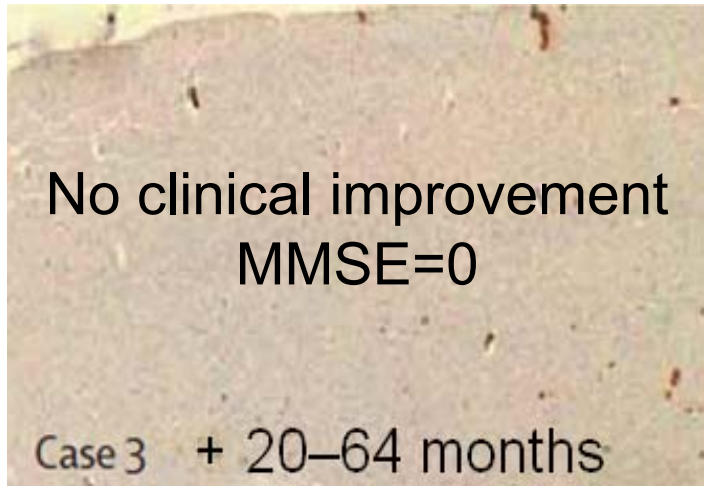
Discovery of new therapy strategies in amyloid mice





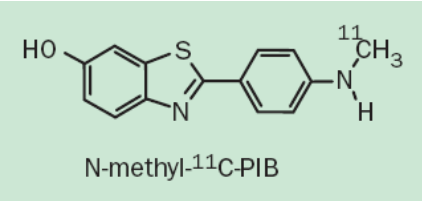
(Schenk et al, 1999)



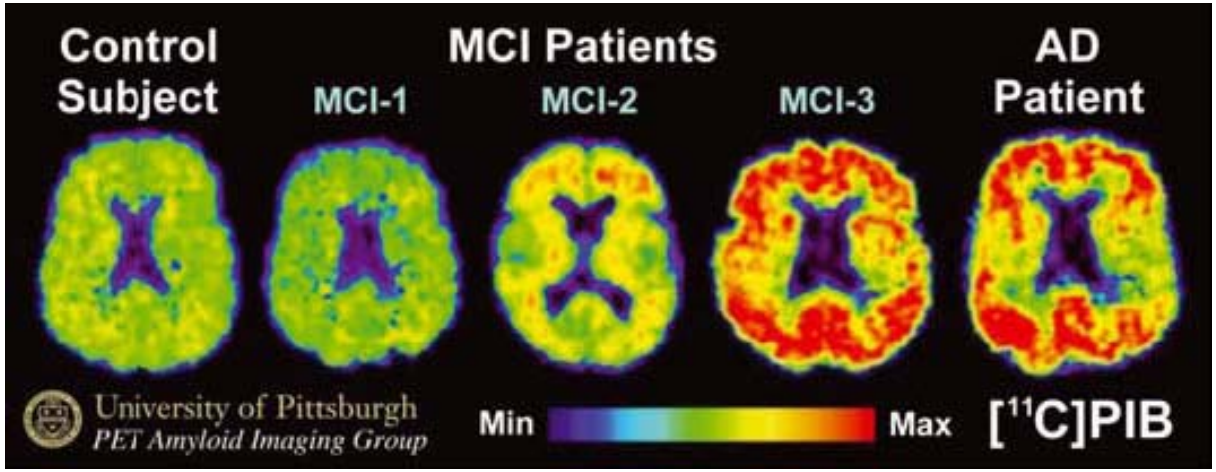


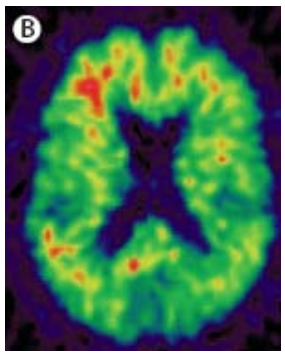
(Holmes et al, 2008)

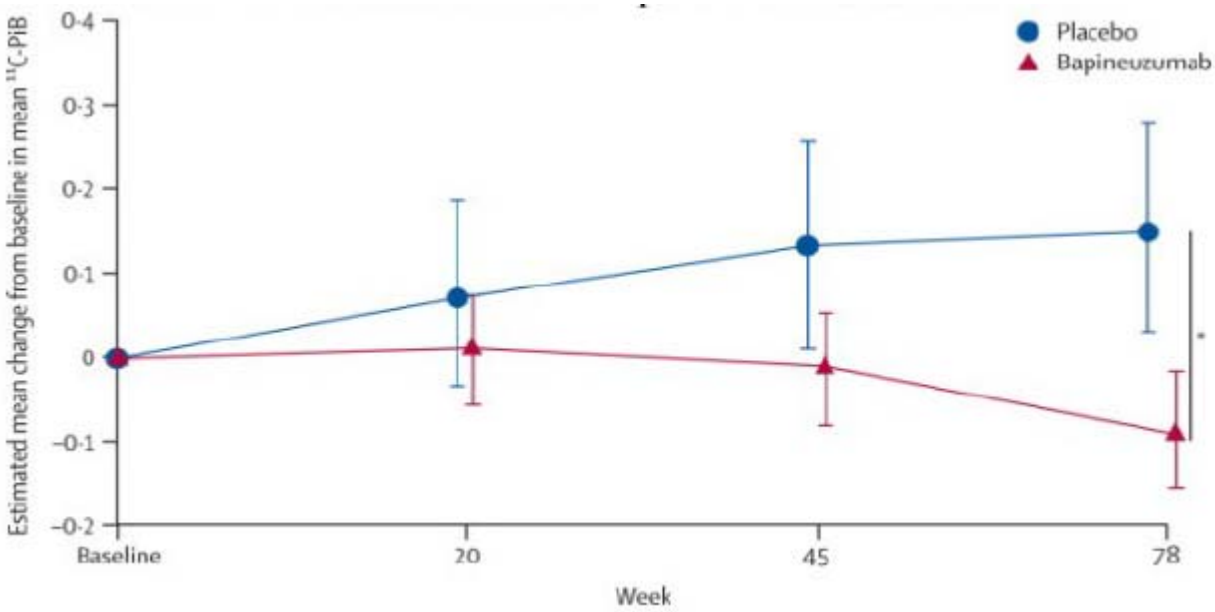
Amyloid imaging in humans (by PET)

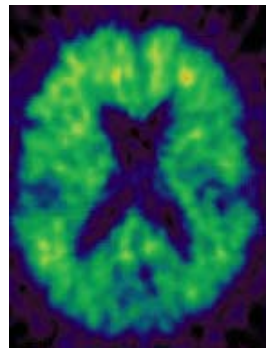


N-methyl-^{11}C-PIB

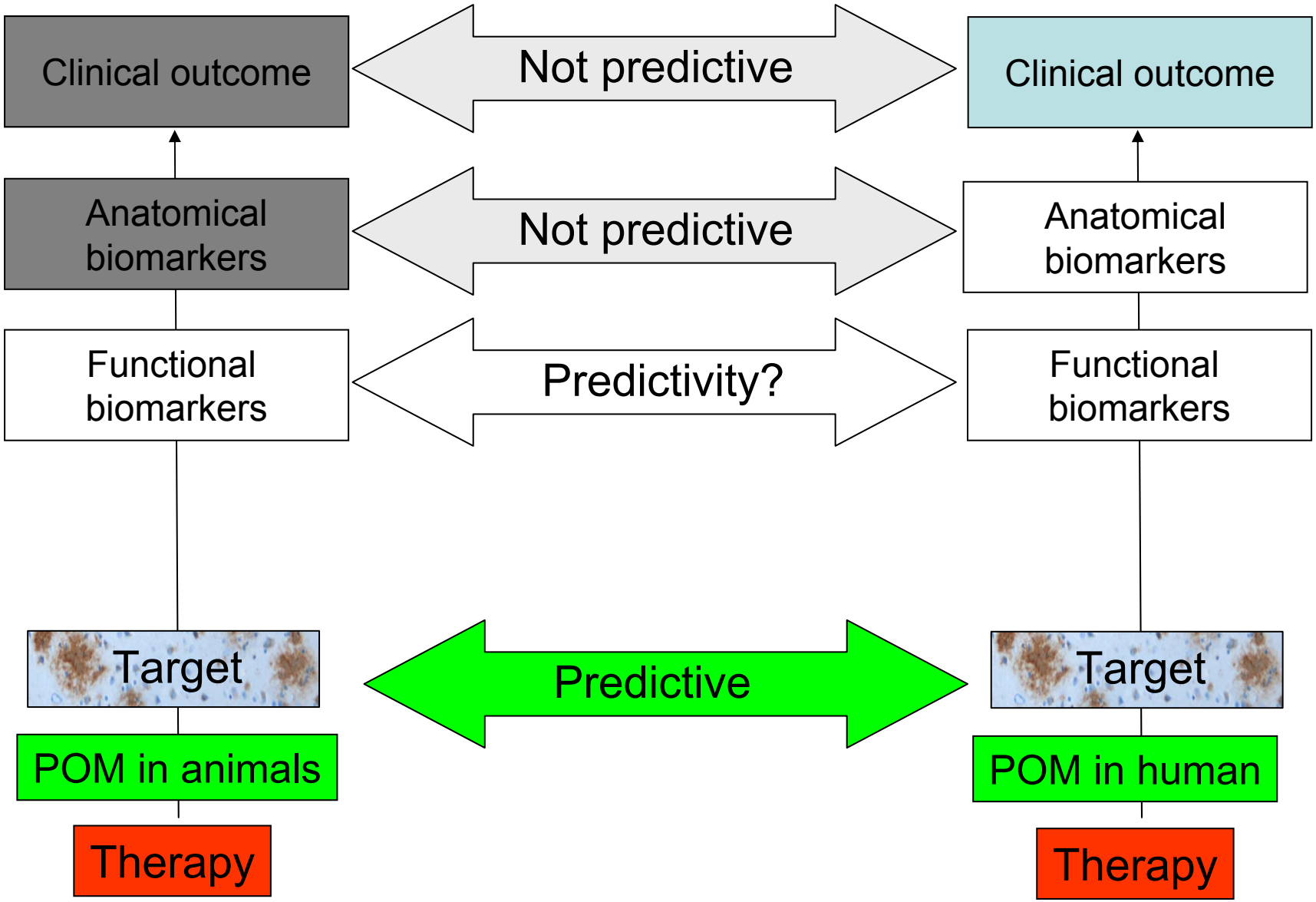








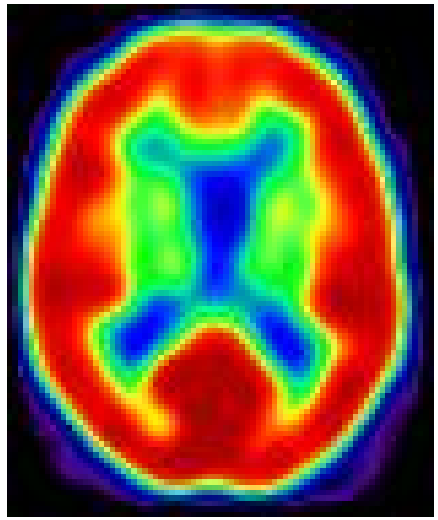
Use of biomarkers to add translational bridges between humans and animals ?



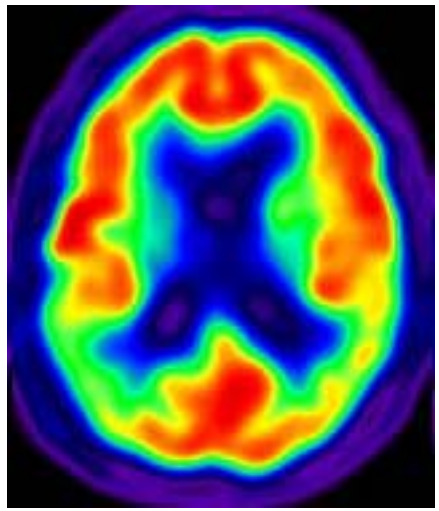
Cerebral metabolism

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

Normal

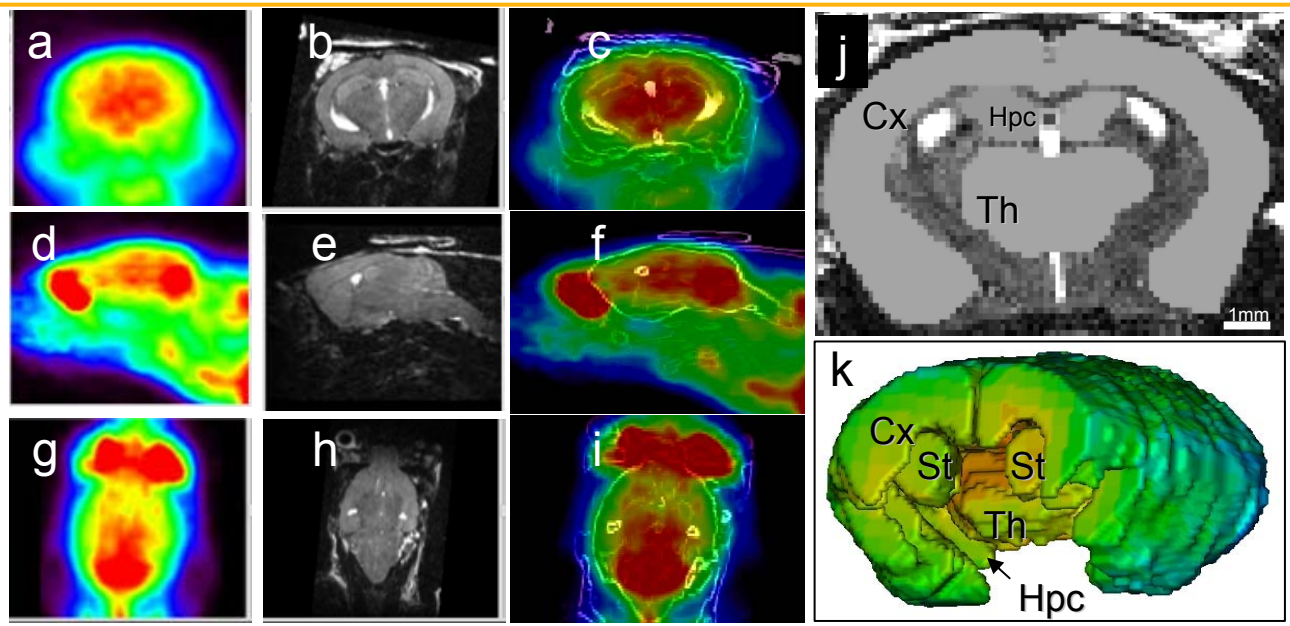


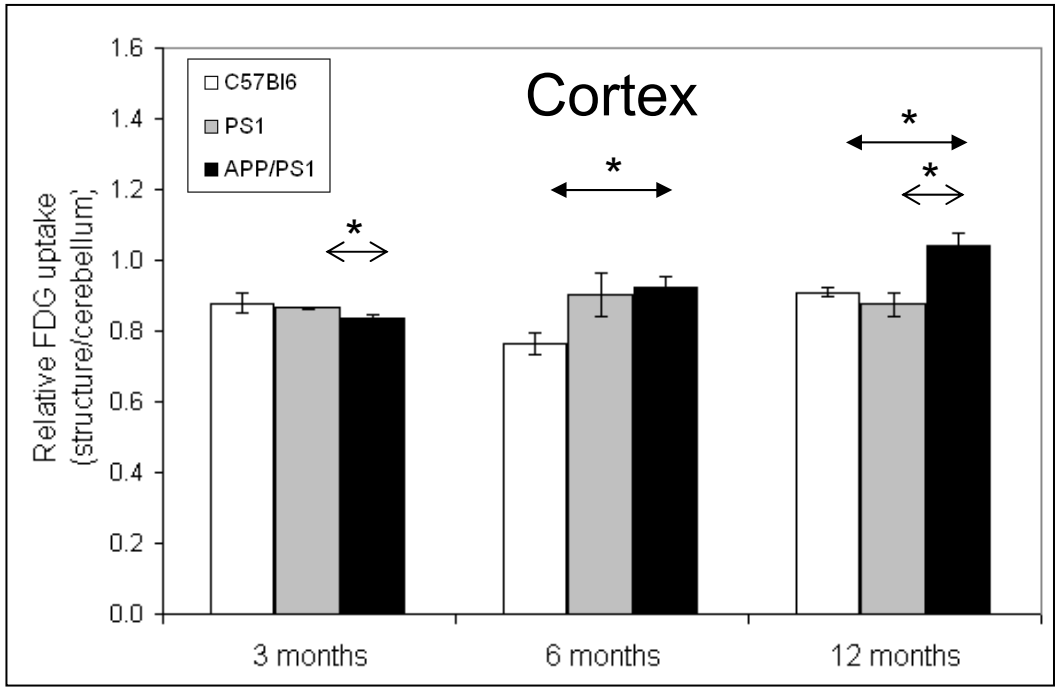
AD



Amyloid is associated to an increased glucose uptake in Tg mice

FDG-PET study

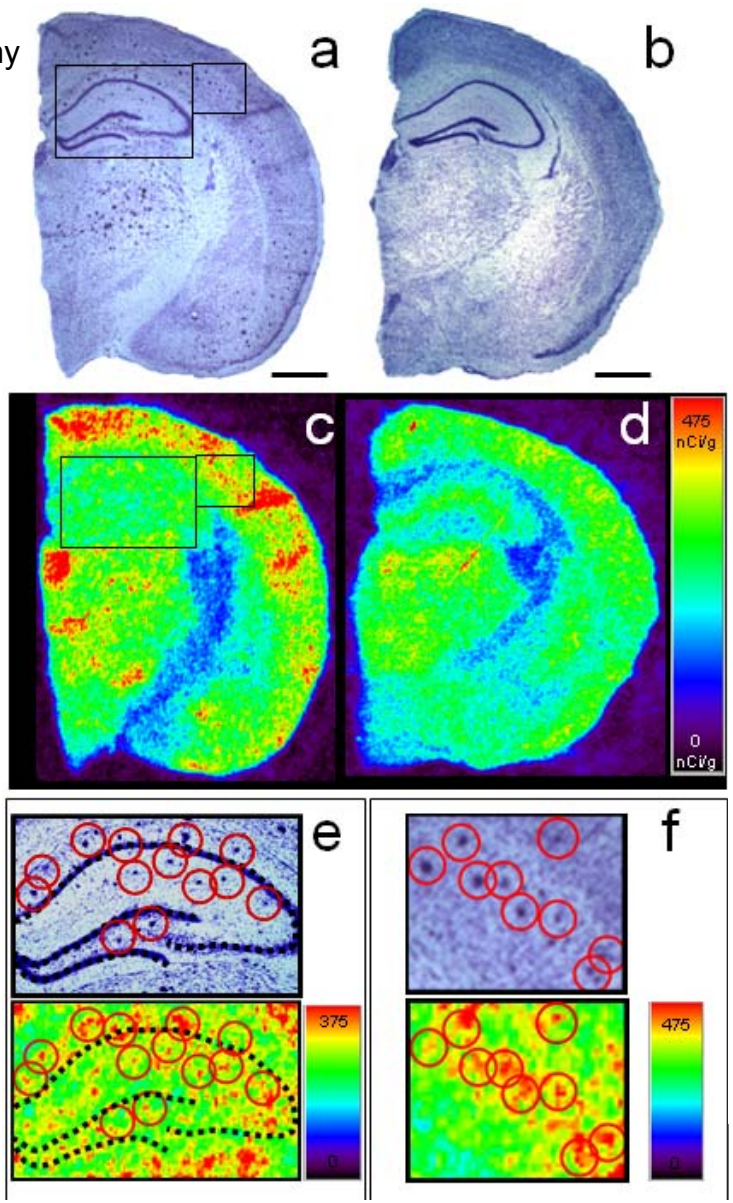


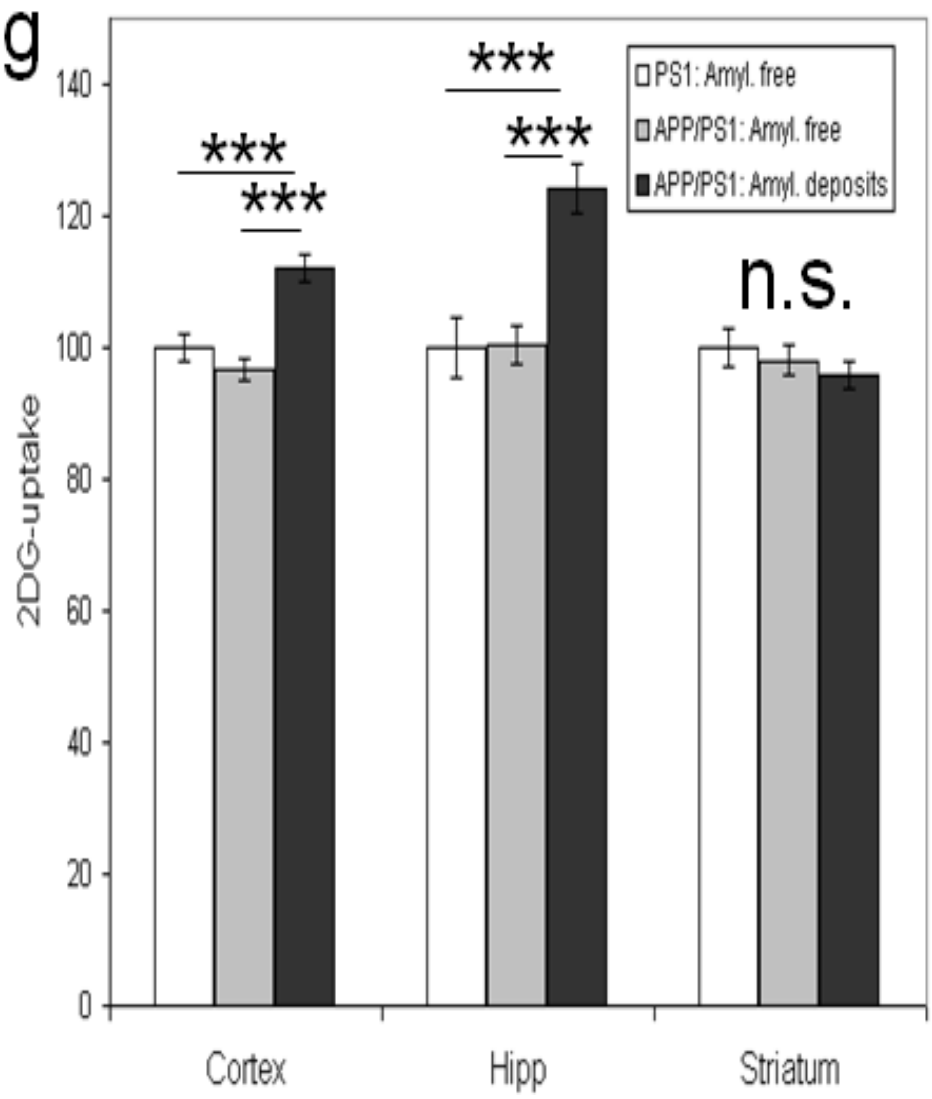


G. Poisnel et al,
Neurobiology of Aging, 2012

Amyloid plaques are associated to an increased glucose uptake

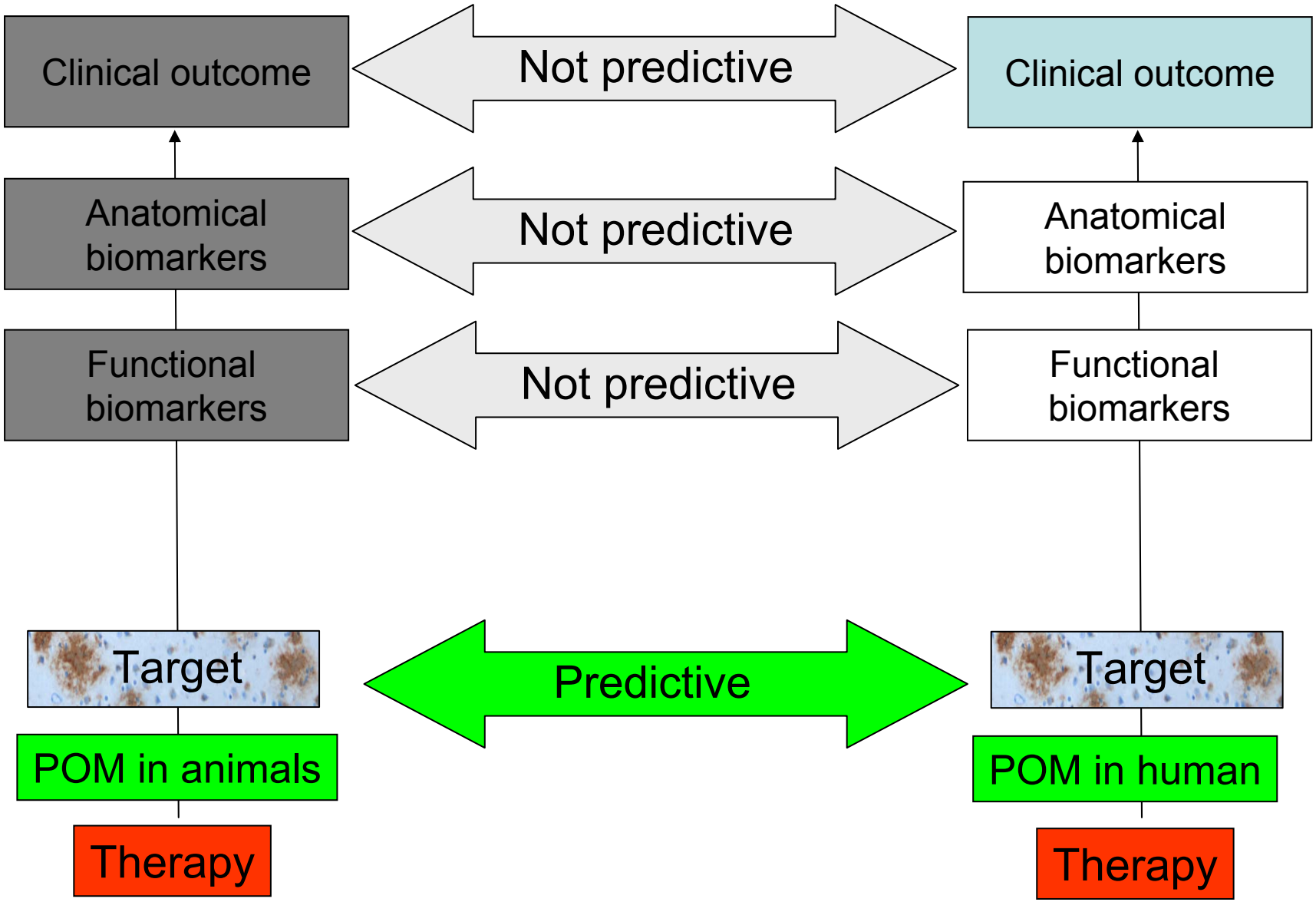
2DG autoradiography





G. Poisnel et al, Neurobiology of Aging, 2012

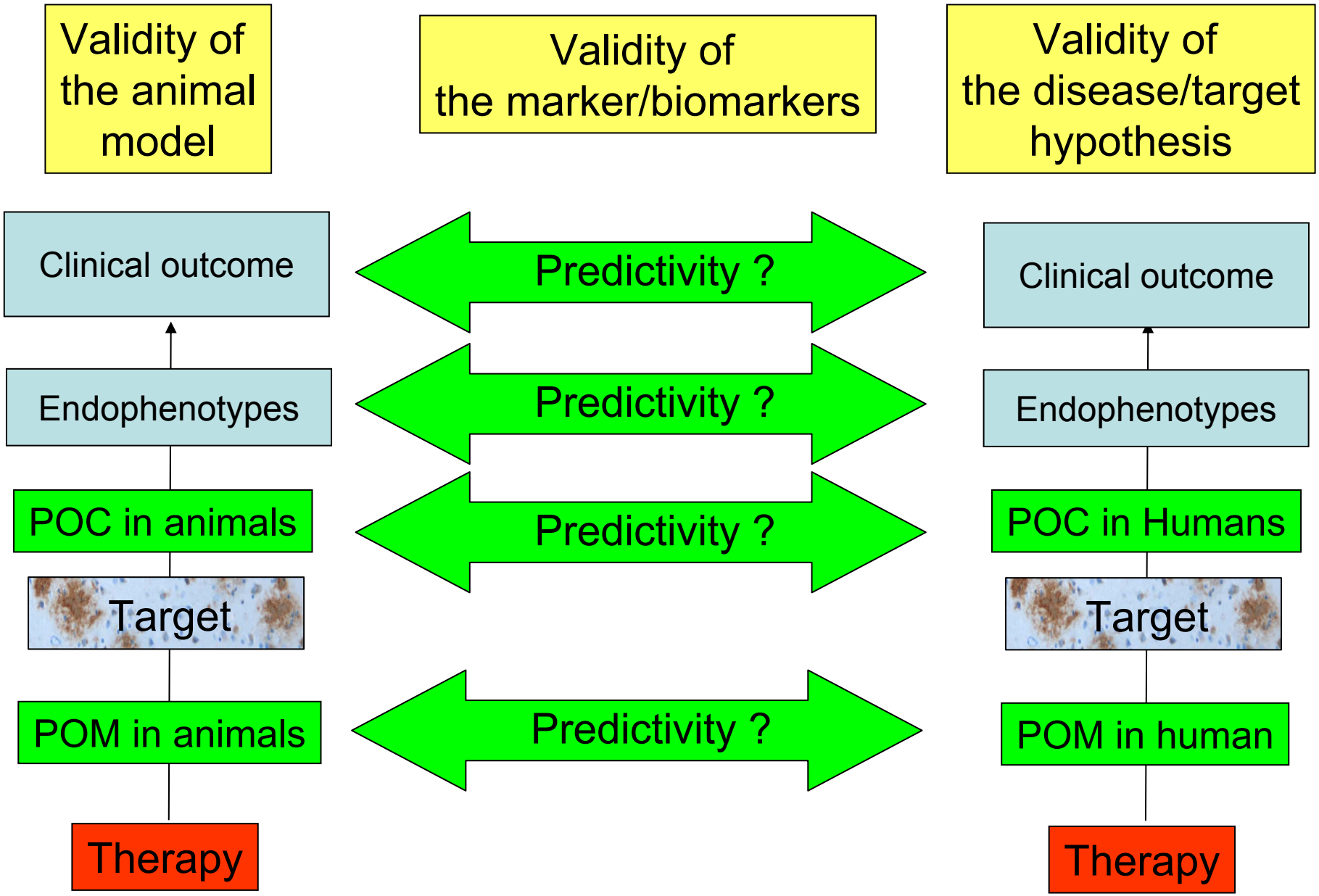
Use of biomarkers to add translational bridges between humans and animals ?



Overview

- Overview on neurodegenerative diseases
- Strategies for the discovery of new therapies
  - From phenotypic to target based approaches
  - Biomarkers, POM, POC
  - Use of animal model: Target models, predictive models, and biomarkers
- Biomarkers in humans: From diagnostic to therapy evaluation tools
  - Dubois Criteria / ADNI initiative
  - Cerebral atrophy (MRI)
  - Brain metabolism (PET)
  - Amyloid plaques (PET)
- Animal models of Alzheimer's disease
  - Most used models of AD
  - Can we predict clinical efficacy of a drug with these models ?
    - "Classical view" of translational medicine
    - Translational bridges
- Conclusion

Critical steps in translational medicine

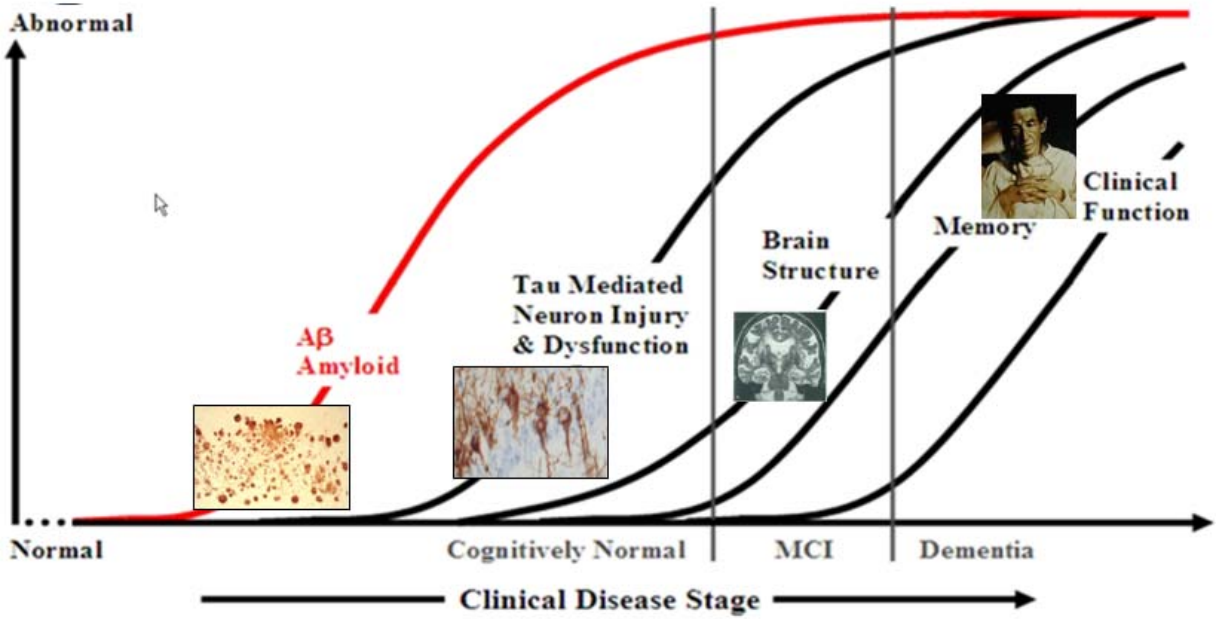


A good translational biomarker

- 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.



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

Conclusion

- Biomarkers in humans
  - Raffine the natural history of the disease → New hypothesis
  - Position milestones to evaluate the effects of a drug
- Animal models
  - Dissociate target model and predictive models
- Use translational bridge to compare early events of disease evolution in humans and animals



Thank you…

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