Neuroimagerie et recherche translationnelle… from bed to bench* et vice versa

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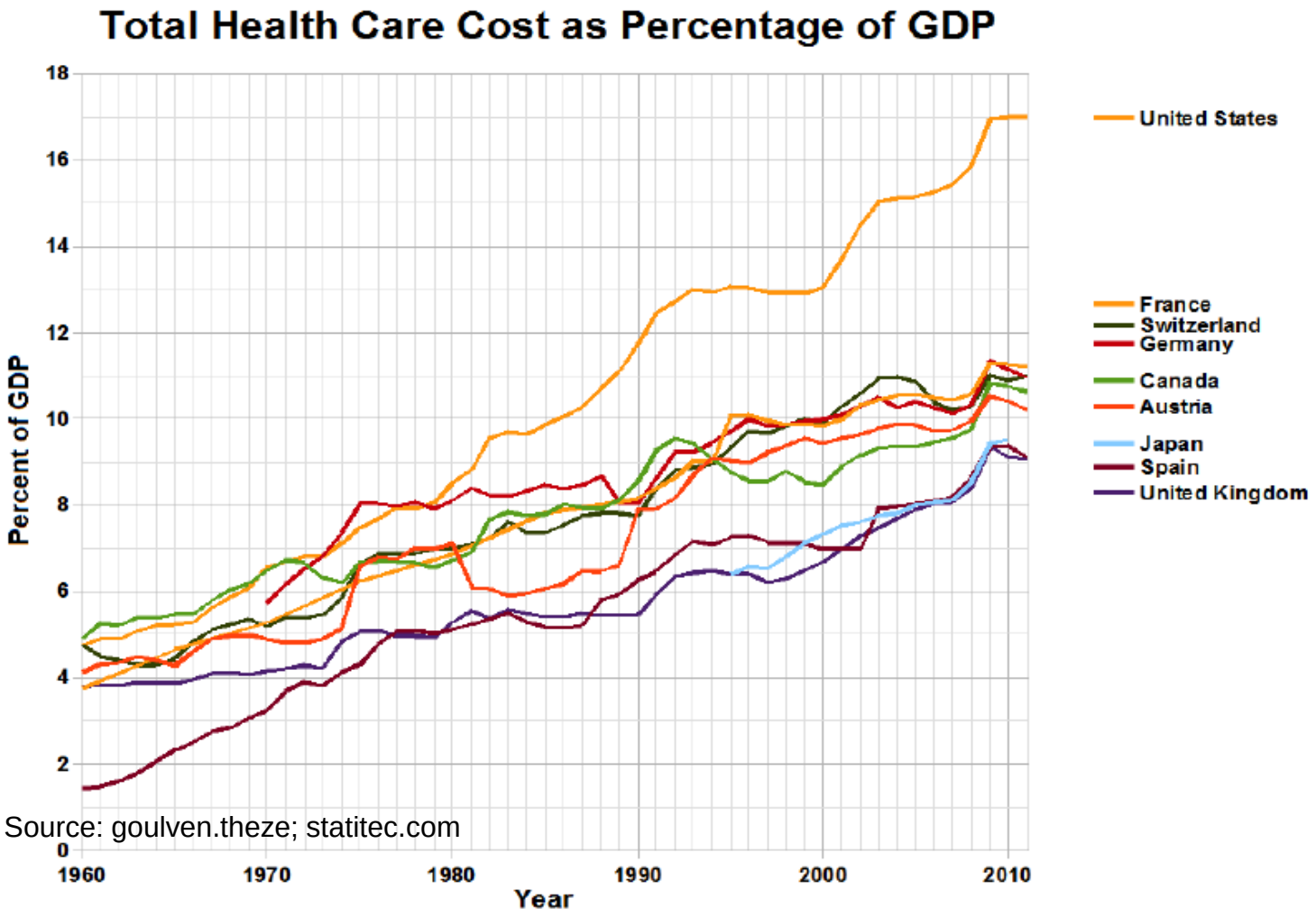
Multimodal Imaging
of Neurodegenerative Diseases and Therapies

Alzheimer's Disease Group:
Modelization, Biomarkers, Preclinical Imaging

*du lit à la paillasse

Increase healtcare costs since 50 years



"Can the pharmaceutical industry reduce attrition rates?" Kola and Landis, Nature Reviews Drug Discovery 2004; 3: 711-715.

High price of new drug development

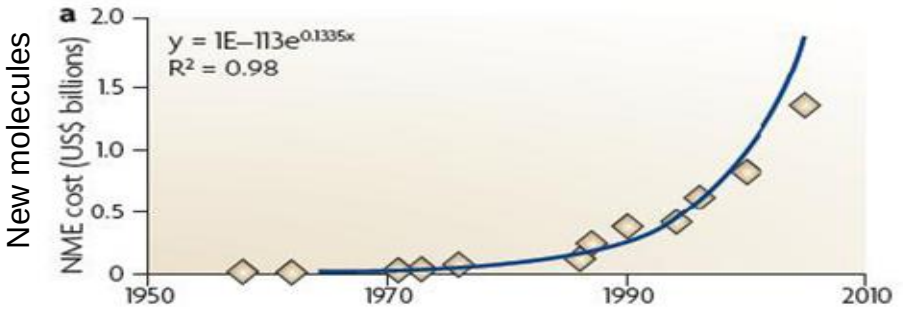
After

>15 years

>10^9 €

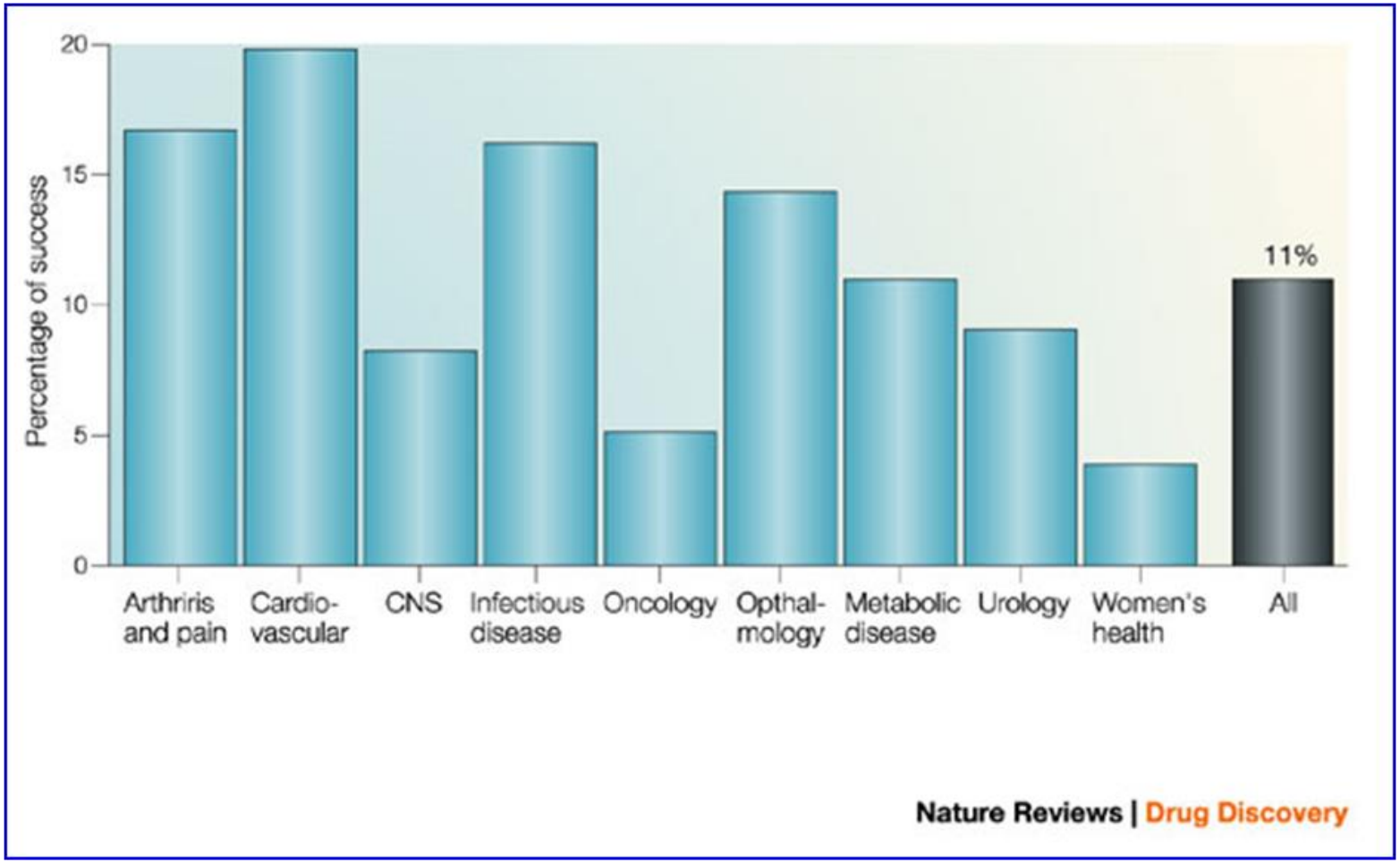
>3000 patients

Increased investissements in drug discovery



Source : Munos, B. (2009). Lessons from 60 years of pharmaceutical innovation. Nature Reviews Drug Discovery, 8(12), 959-968.

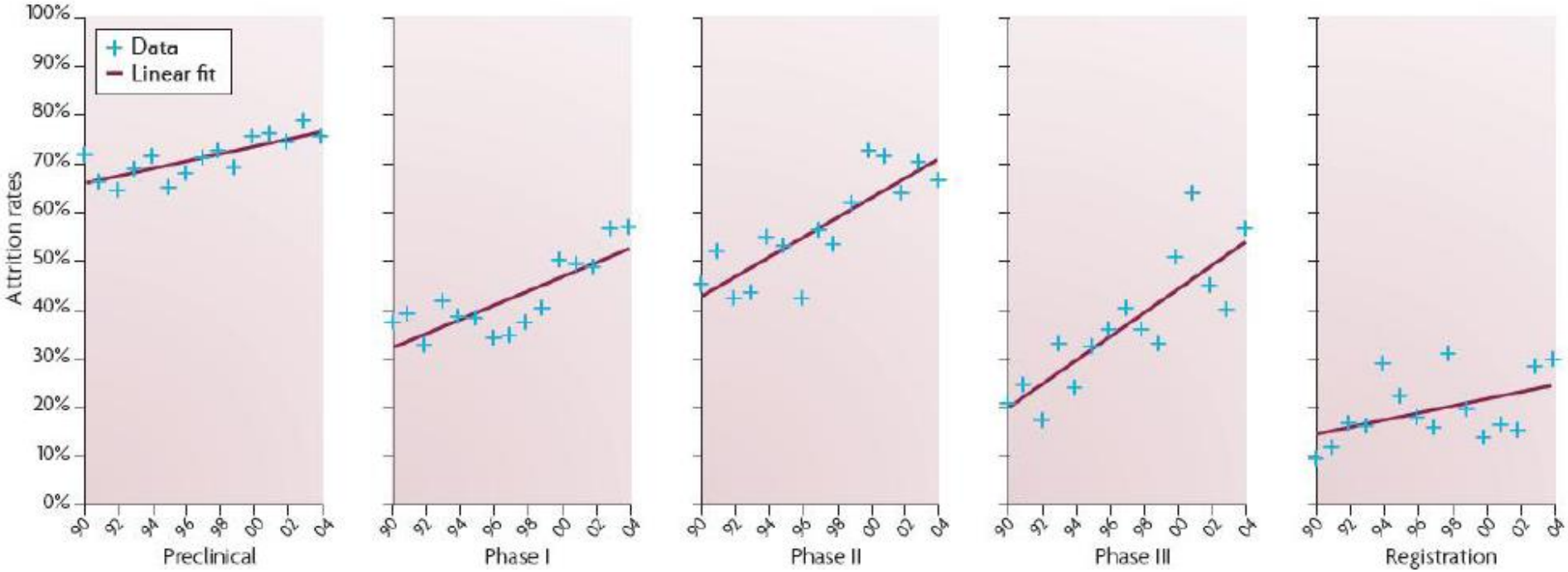
But high attrition in drug development



"Can the pharmaceutical industry reduce attrition rates?" Kola and Landis, Nature Reviews Drug Discovery 2004; 3: 711-715.

Attrition rate increases with time

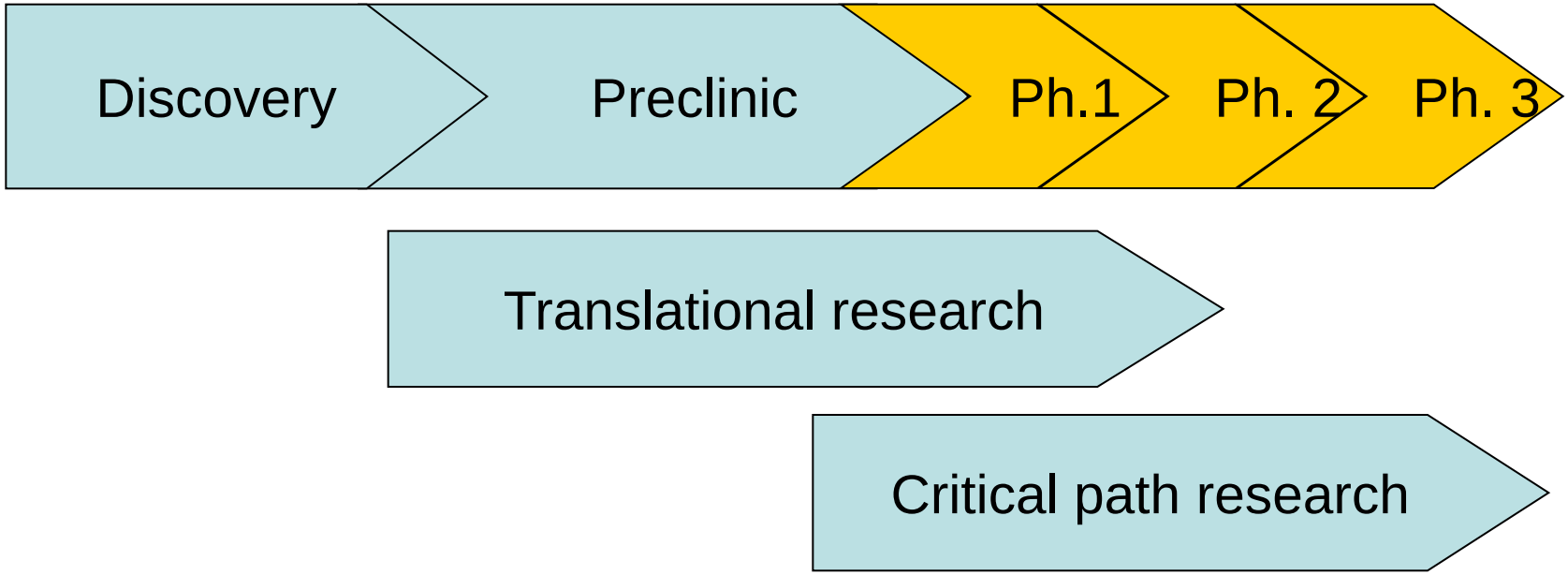
- Attrition rate increases in phases 2-3



- Drug development pipeline

Source : Pammolli, F., Magazzini, L., & Riccaboni, M. (2011). The productivity crisis in pharmaceutical R&D. Nature Reviews Drug Discovery, 10(6),

How to improve the discovery process? NIH definitions



G Finkelstein R,T Miller, and R Baughman,"The Challenge of Translational Research—A Perspective from the NINDS," *Nature neuroscience supplement*,Vol.5, **2002.**

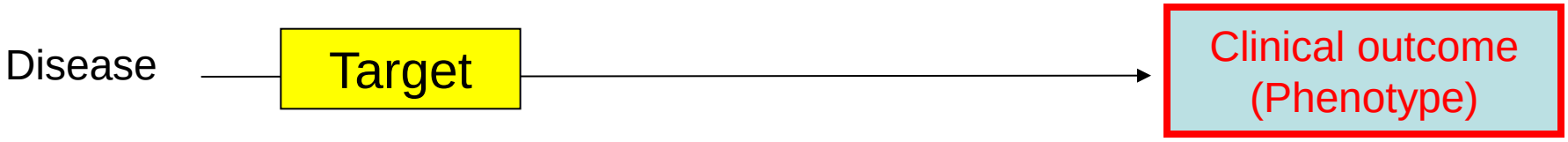
Diplôme universitaire

INNOVATION THÉRAPEUTIQUE ET RECHERCHE TRANSLATIONNELLE DANS LES MALADIES DU SYSTÈME NERVEUX:

COMMENT ÉTABLIR UN LIEN ENTRE LA RECHERCHE EXPÉRIMENTALE ET CLINIQUE?

Faculté de Médecine du Kremlin-Bicêtre, Université Paris-Sud

Strategies to modify the clinical outcome? Isolate a target

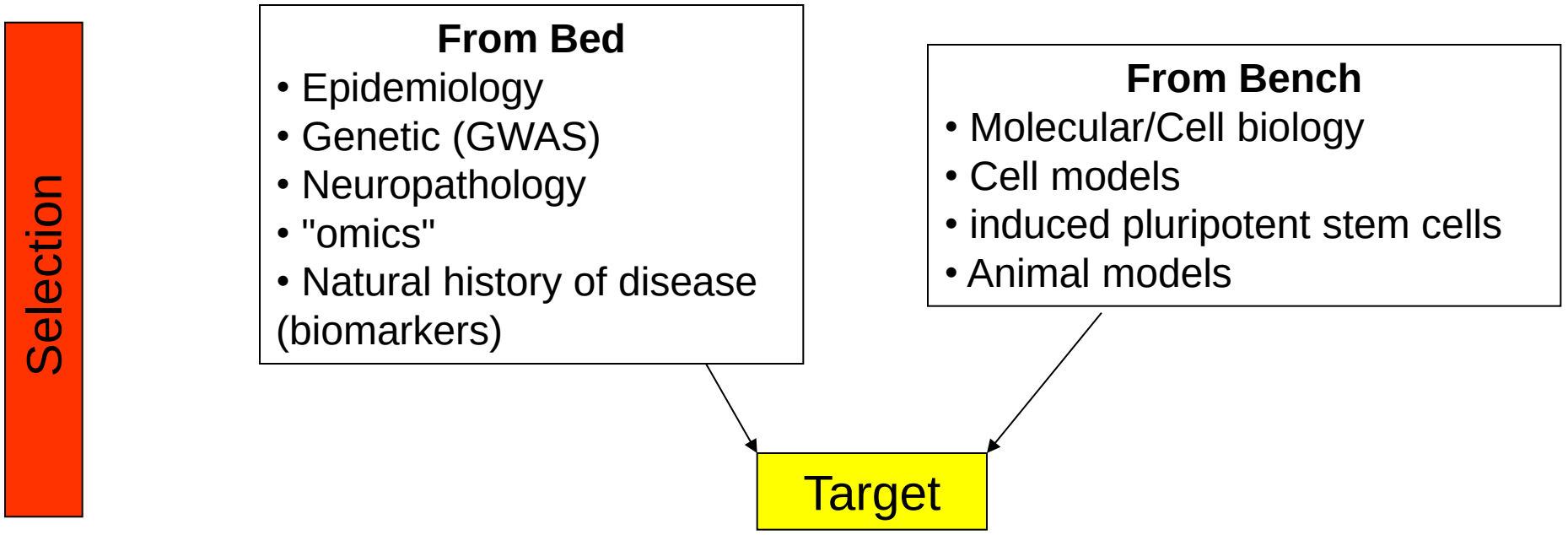


Validation

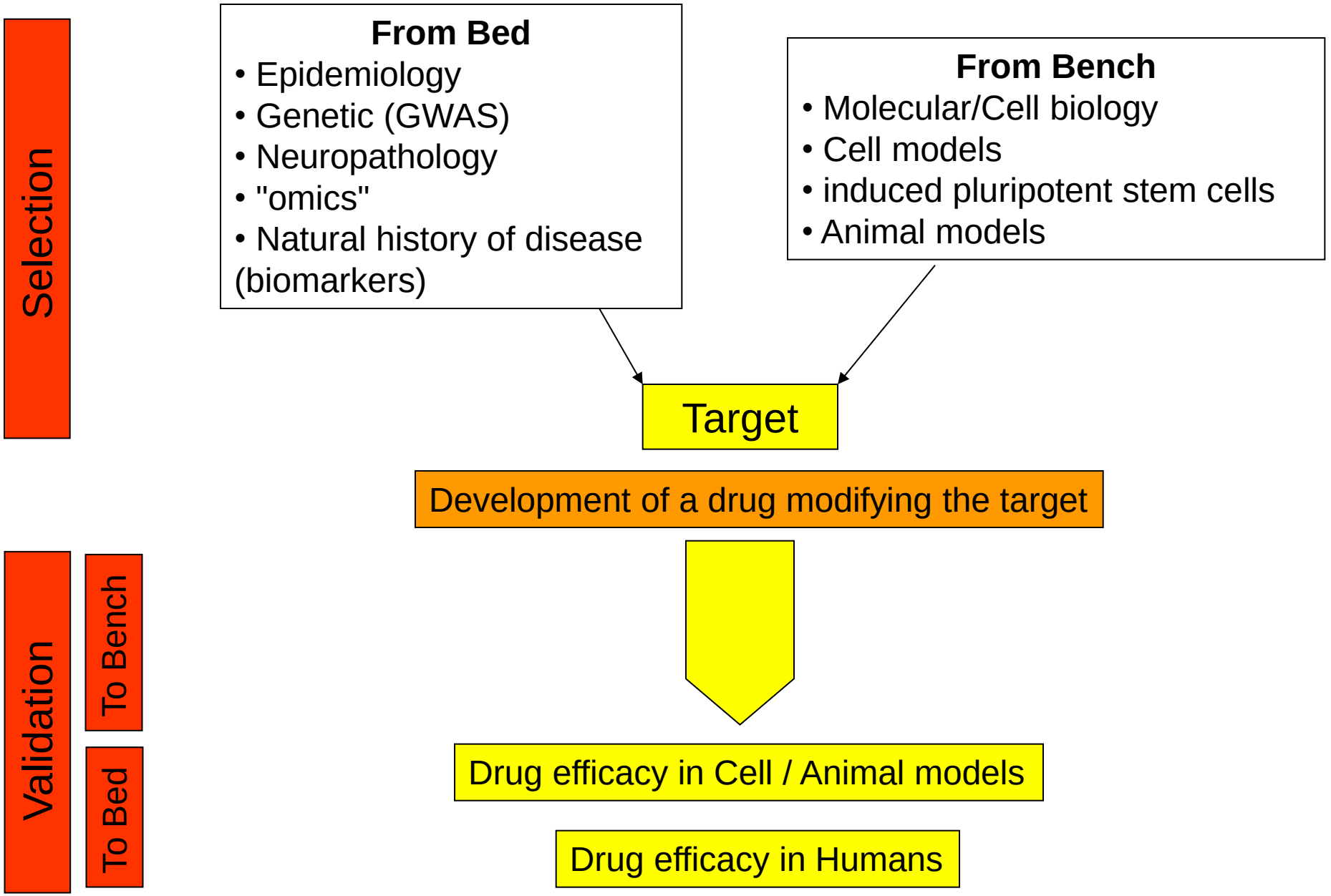
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

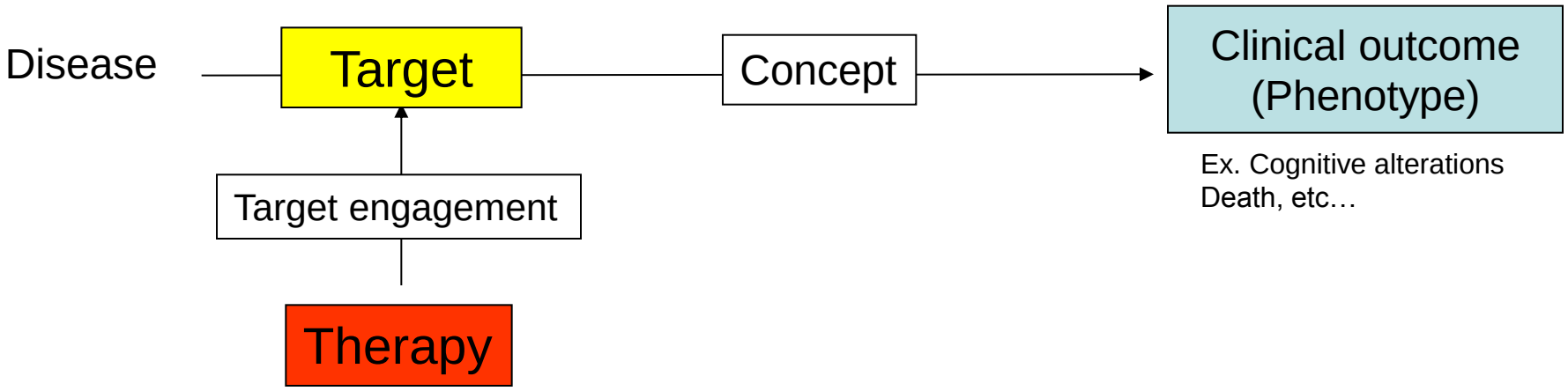
How to select / validate a target ?



How to select / validate a target ?



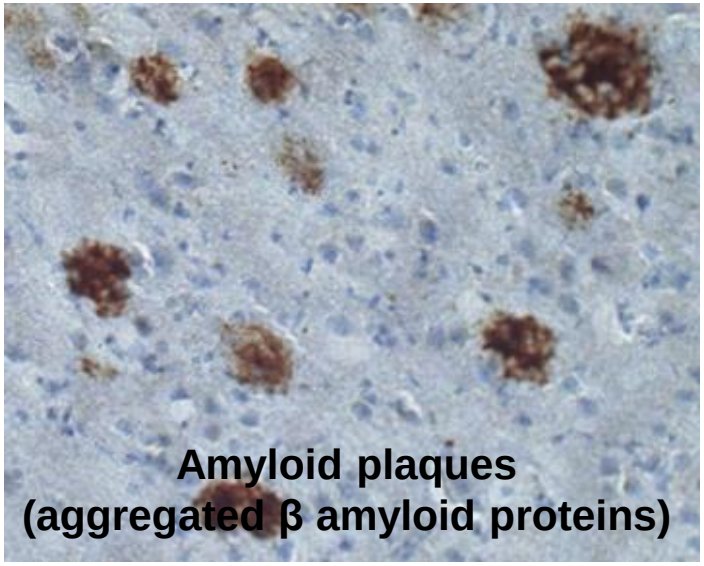
From drug to target, and from target to disease



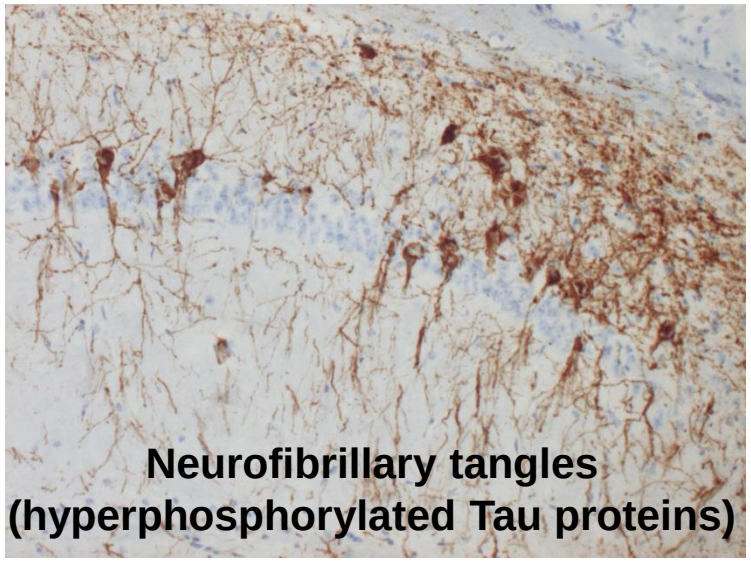
- Identify a target ?
- Is my therapy modifying/reaching the target ?
  - Target engagement, proof of mechanims (POM)
- If I modify the target, do I modify the clinical outcome ?
  - Proof of concept (POC)

Example in Alzheimer's disease

- Two main microscopic lesions



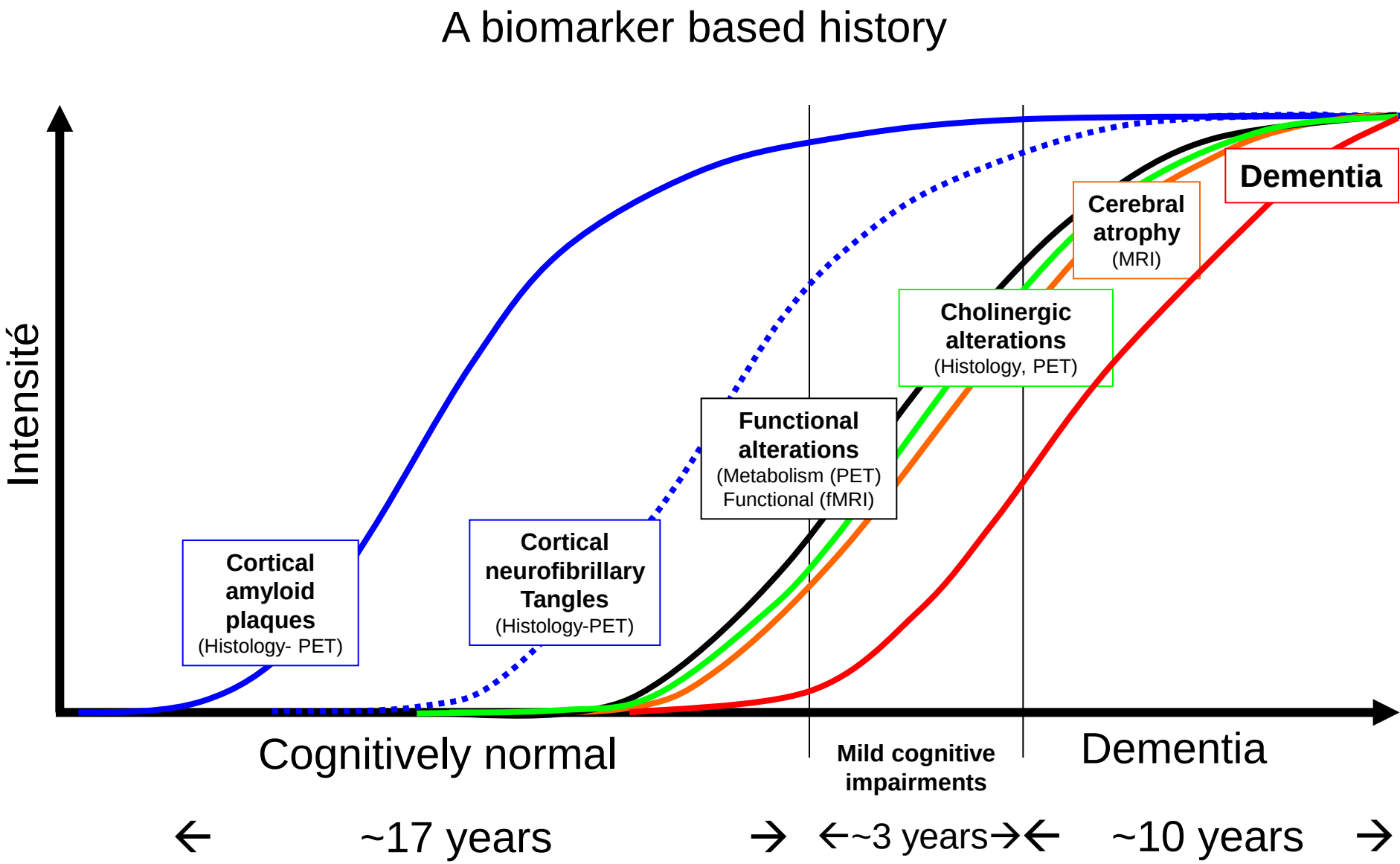
Amyloid plaques (aggregated β amyloid proteins)



Neurofibrillary tangles (hyperphosphorylated Tau proteins)

- No curative treatment
  - How can we discover a curative treatment ?

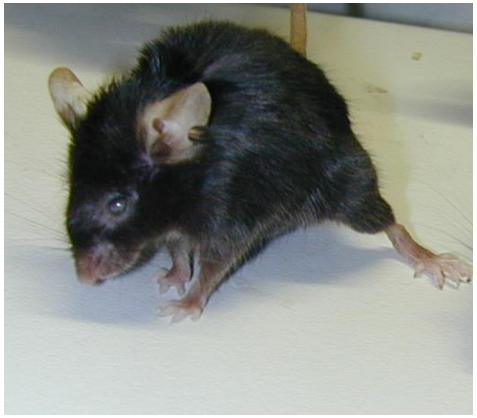
Natural history of Alzheimer's disease → amyloid as a target



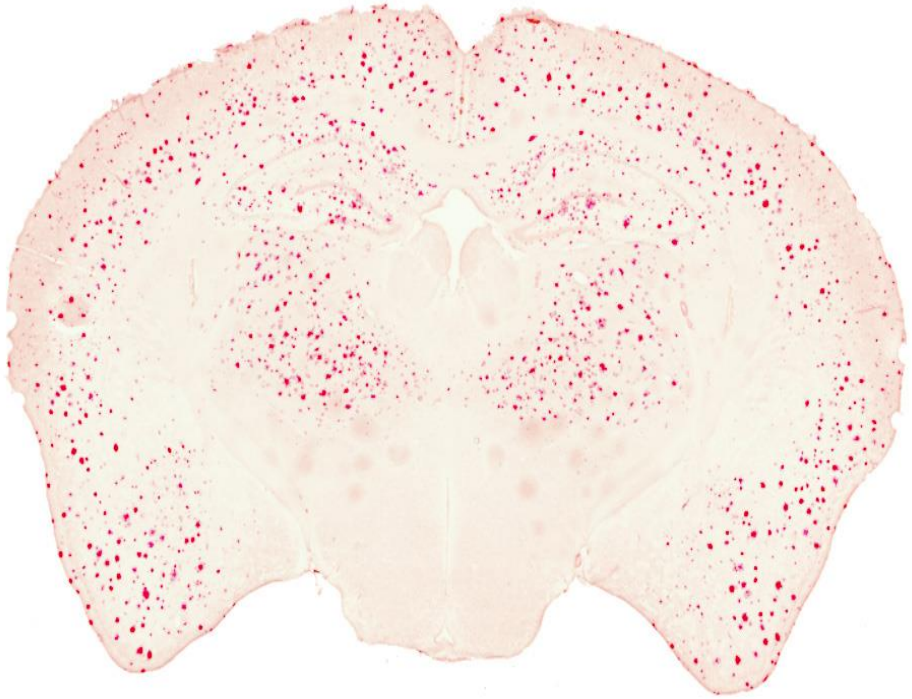
Jack et al, 2013

From bed to bench…

Mouse model of amyloid

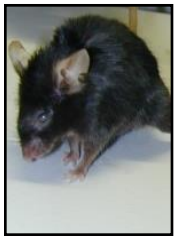


APP/PS1

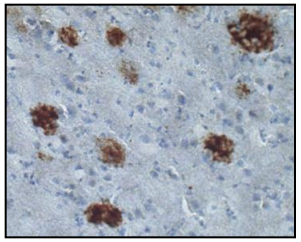


Model of amyloidosis
→ Evaluation of anti-amyloid drugs

Amyloid induce cognitive alterations in animals
Improvement with therapies



Cognitive alterations



Amyloid

Immunotherapies

Cognitive improvement

(Morgan et al., 2000)

(Schenk et al, 1999)

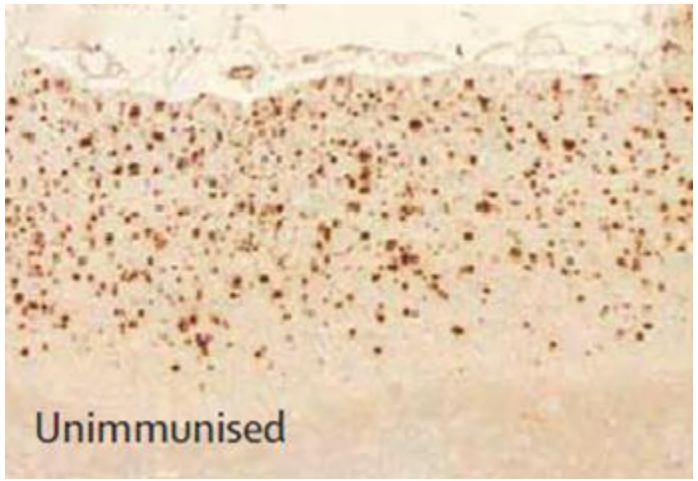
2010-2013 : Failure of anti-amyloid therapies in humans

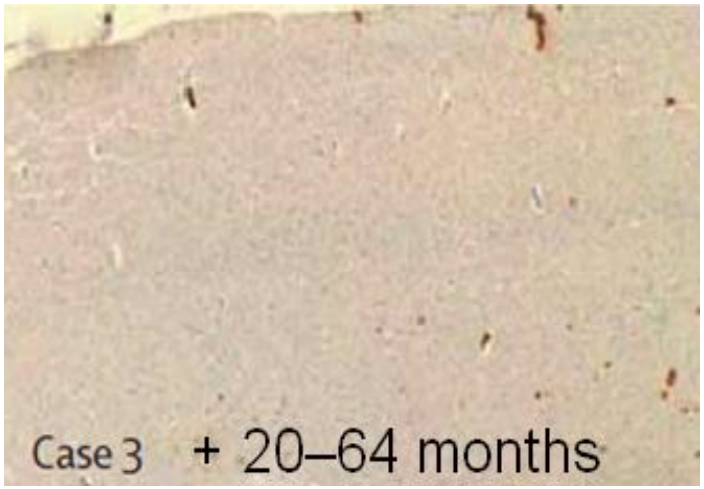
- Immunotherapies
  - Bapineuzumab: antiAß1-5 (Wyeth/Elan – Pfizer/Janssen)
    - Fall in phase III - 2012
  - Solaneuzumab: antiAß13-5 (Eli Lilly)
    - Fall in phase III - 2012
  - Gammagard : immunoglobulin I.V. (IVIG) (Baxter International Inc.)
    - Fall in phase III - 2013

- Other anti-amyloid therapies
  - γ-secretase inhibitor (LY450139 -Semagacestat - Eli Lilly)
    - Fall in Phase III - 2010
  - ß-secretase inhibitor (LY2886721 - Eli Lilly)
    - Fall in Phase II - 2013

These therapies are able to reduce amyloid load in humans

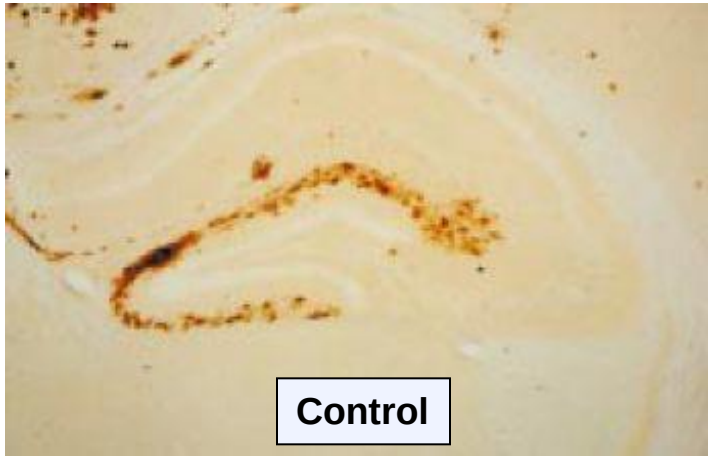
Humans

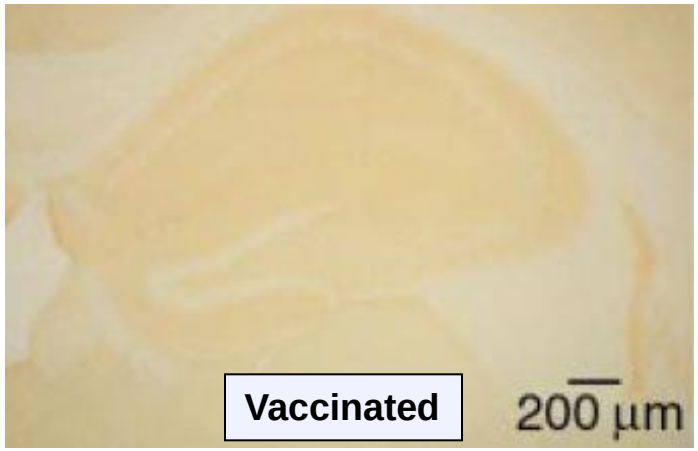




(Holmes et al, 2008)

Mice



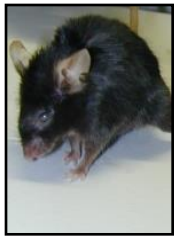


(Schenk et al, 1999)

→Effect on the target

→ No effect on clinical outcome

Different origin of cognitive alterations in animals and humans



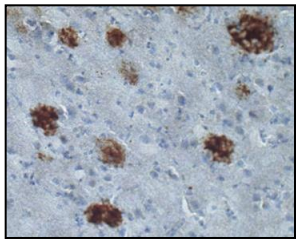
Animal

Cognitive alterations
(non homologous
To human alterations)

oligomers

Lack of Tau

Amyloid



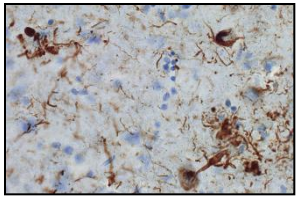
Homol
Predictive

Homol
Predictive

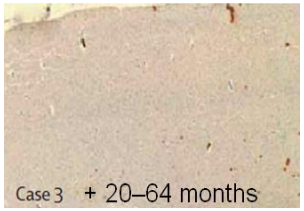
Homme

Cognitive alterations

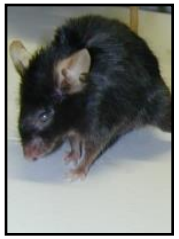
Tau



Amyloid



Biomarkers and animal/human comparisons



Animal

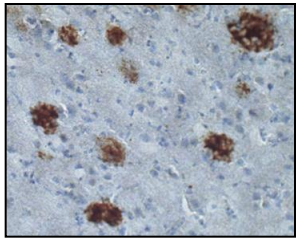
Cognitive alterations
(not homologous
To human alterations)

Atrophy

Functional alterations

Lack of Tau

Amyloid



Homol
Predictive

?

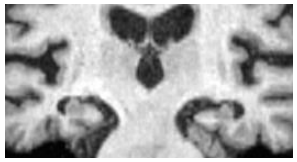
?

Homol
Predictive

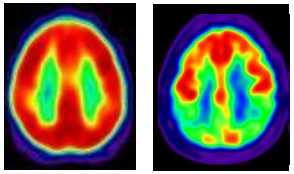
Human

Cognitive alterations

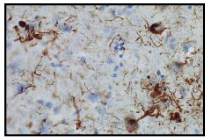
Atrophy



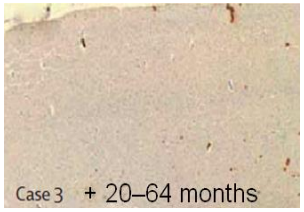
Functional alterations



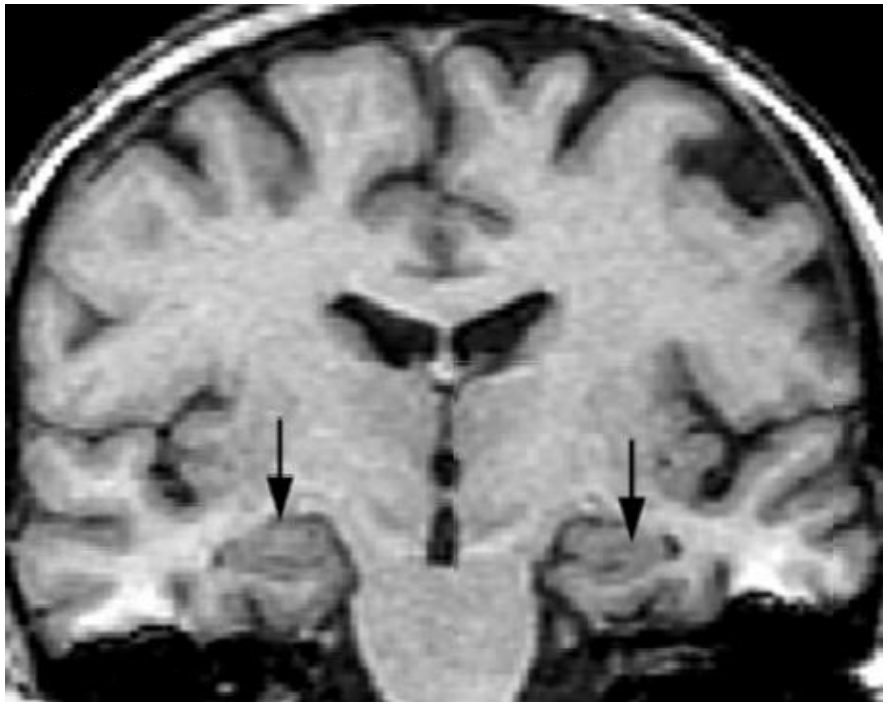
Tau



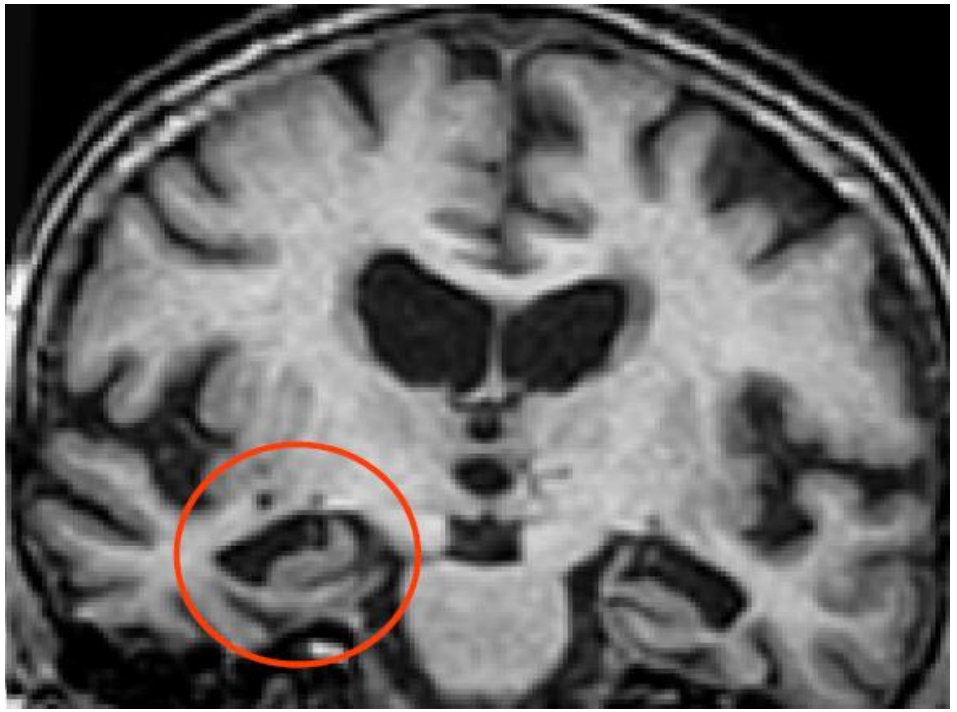
Amylod



Cerebral atrophy in humans with Alzheimer



Normal aging



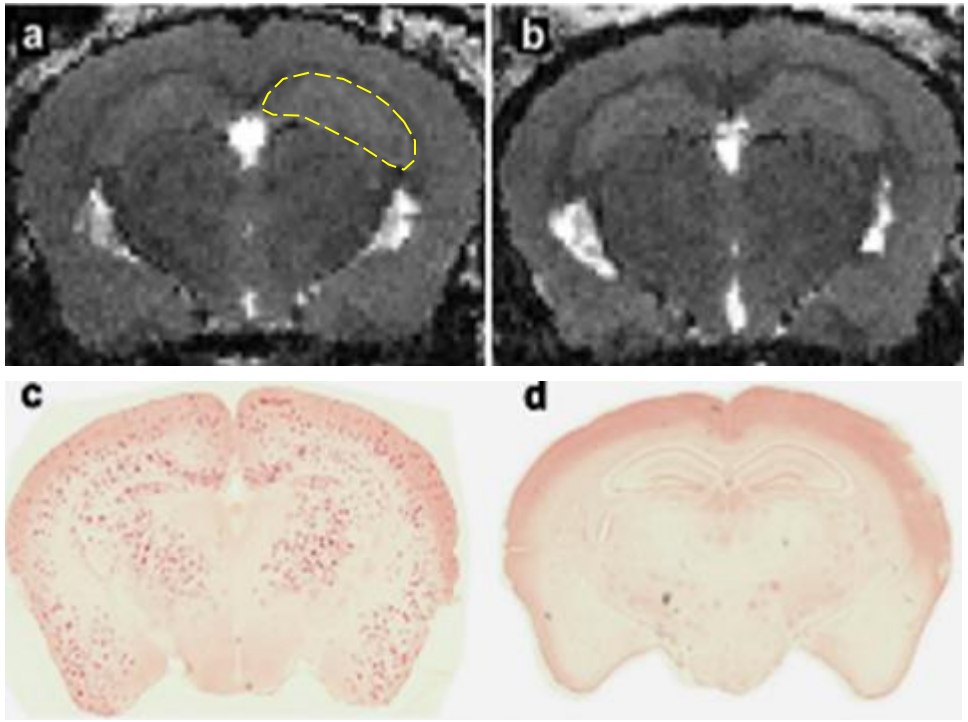
Alzheimer

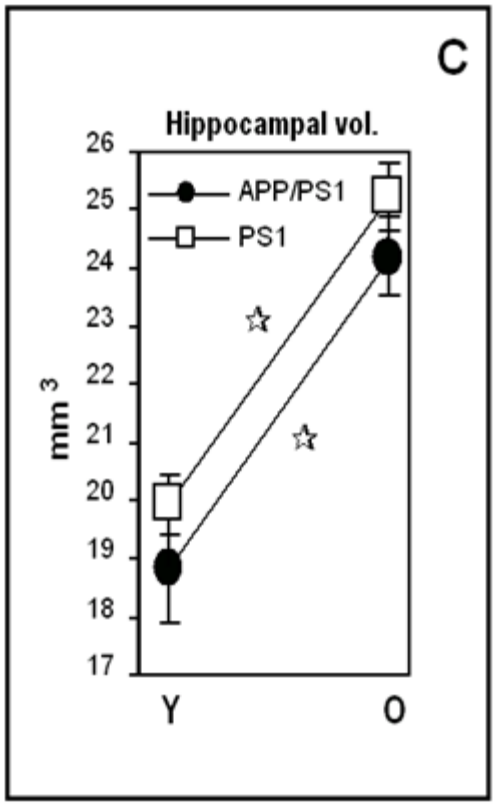
Starts in the hippocampus then spreads all over the brain

Evaluation of cerebral atrophy in animal models of AD

Images provided by Dr. S. Lehericy

Cerebral atrophy in transgenic mouse model of amyloidosis

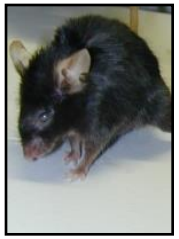




Brain and hippocampal growth
even in the presence of amyloid deposits…

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

Cerebral atrophy



Animal

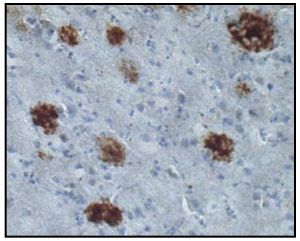
Cognitive alterations
(not homologous
To human alterations)

Atrophy

Functional alterations

Lack of Tau

Amyloid



Homol
Predictive

Homol
Predictive

Homol
Predictive

Human

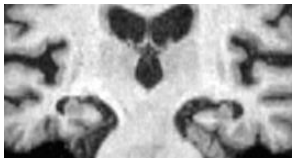
Cognitive alterations

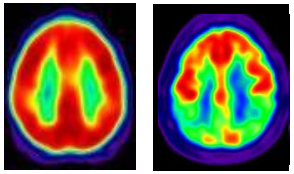
Atrophy

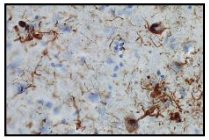
Functional alterations

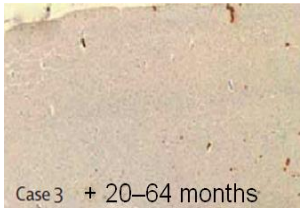
Tau

Amylod

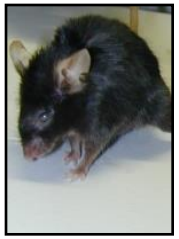








Functional alterations ?



Animal

Human

Cognitive alterations
(not homologous
To human alterations)

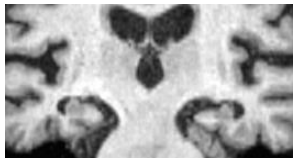
~~Homol~~
~~Predictive~~

Cognitive alterations

Atrophy

~~Homol~~
~~Predictive~~

Atrophy

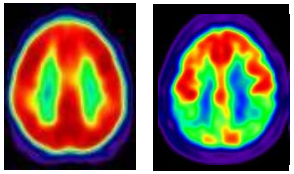


Functional alterations

Perfusion MRI

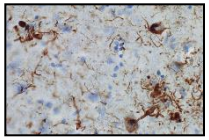
FDG Pet

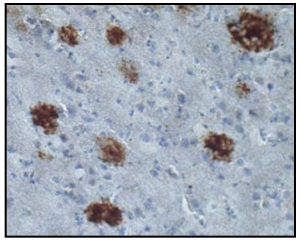
Functional alterations



Lack of Tau

Tau

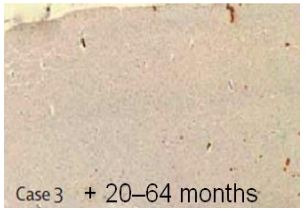




Amyloid

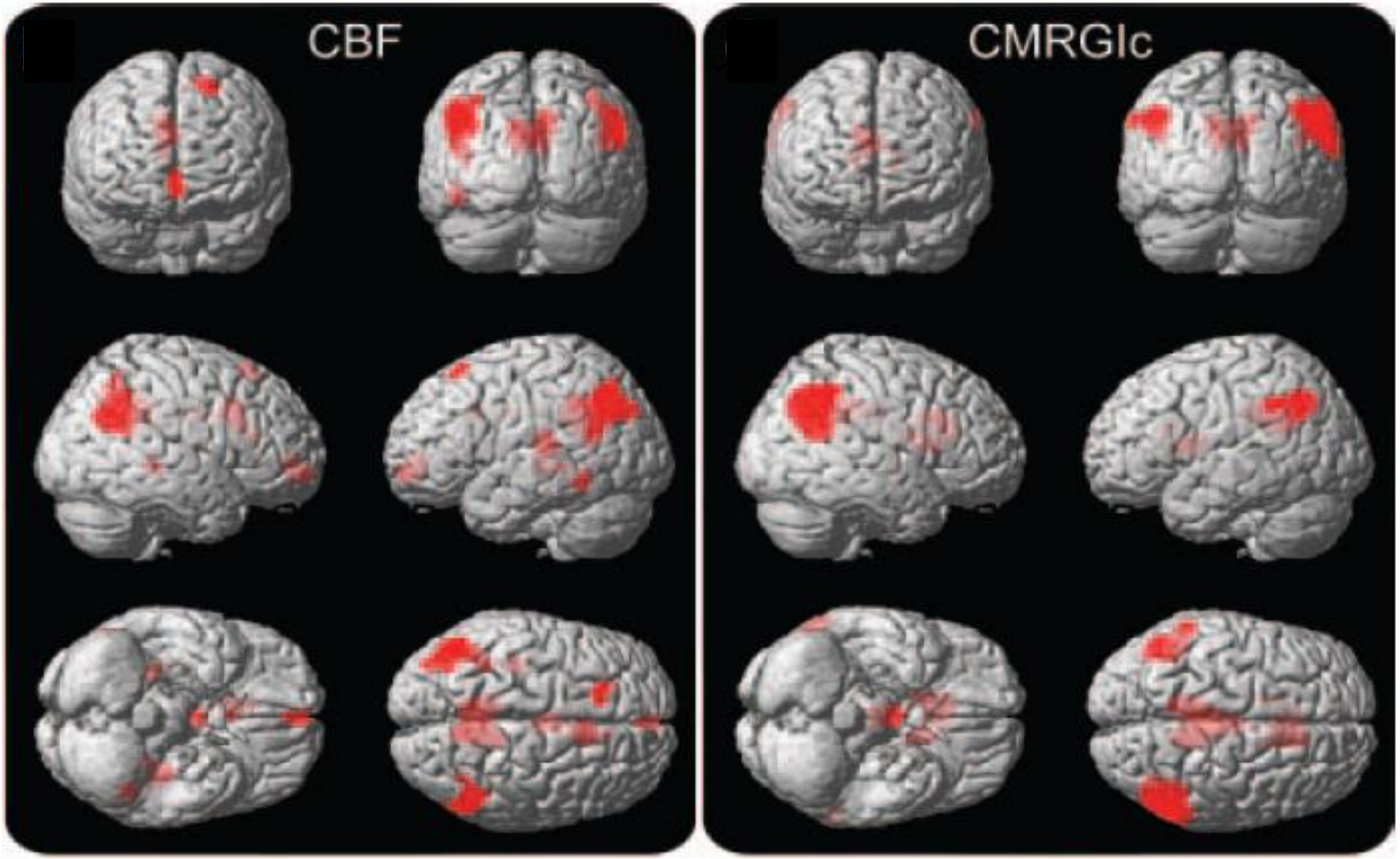
Homol
Predictive

Amylod



Perfusion measurements from MRI

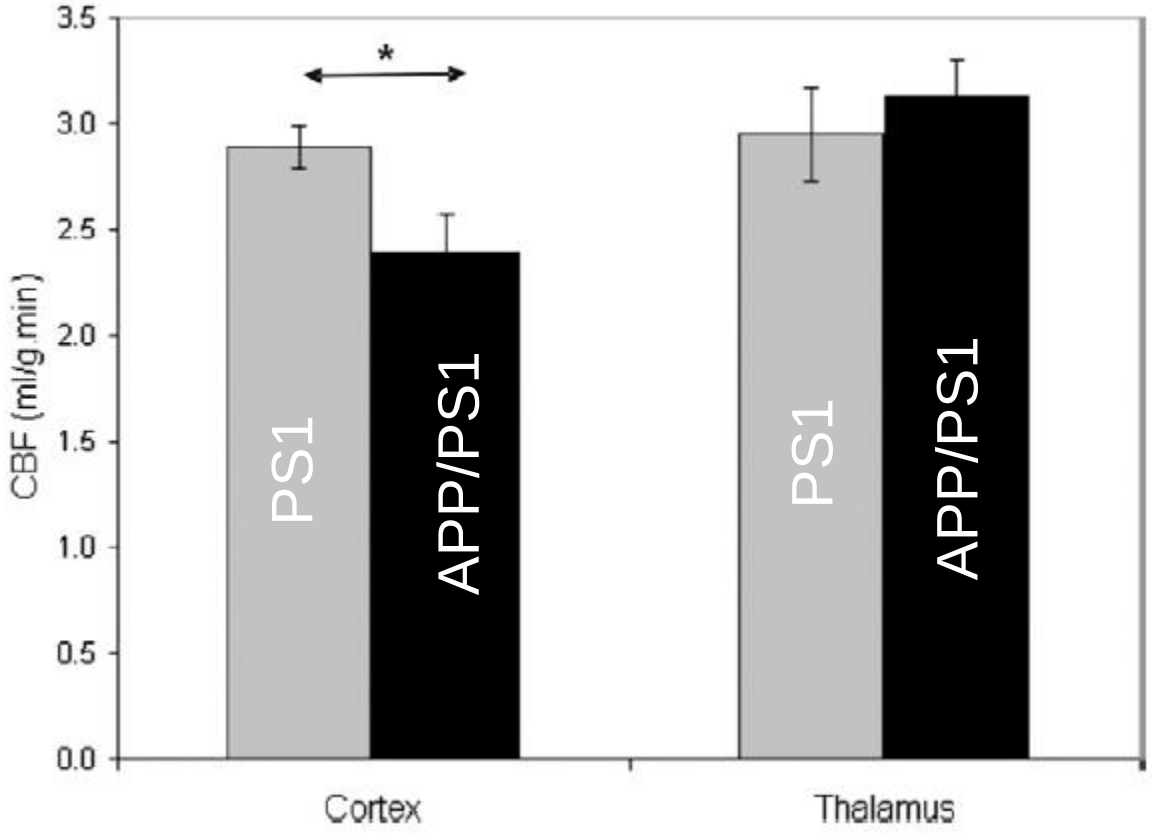
ASL-MRI provides overlapping information with FDG-PET



ASL-MRI FDG-PET

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

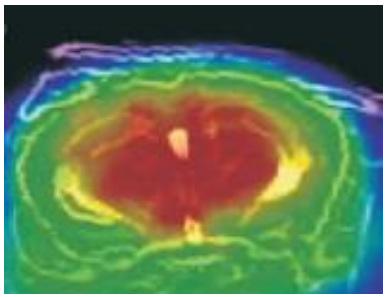
Effects of amyloid on cerebral perfusion?



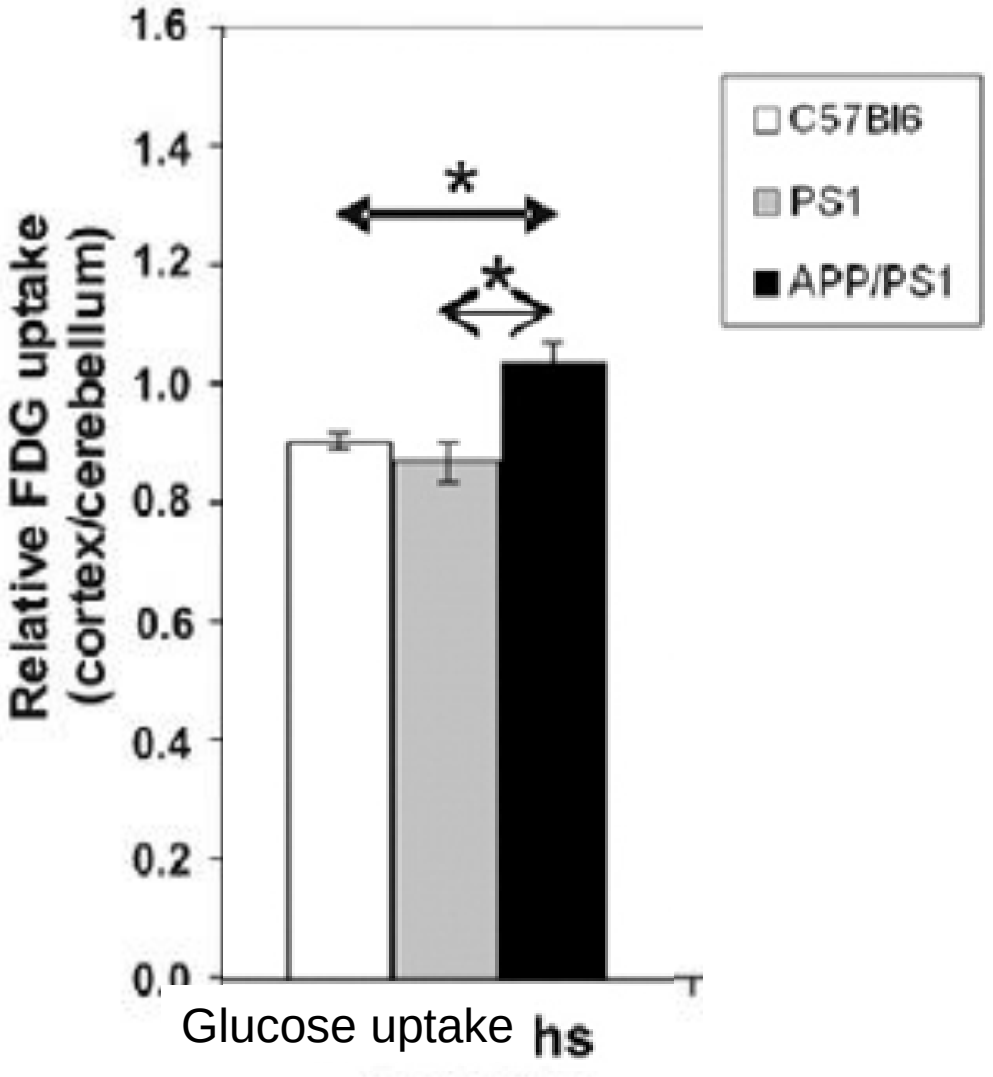
Amyloid induce cortical hypoperfusion

Poisnel et al, Neurobiology of Aging, 2012

Dissociation between perfusion and glucose uptake in mouse models of amyloidosis

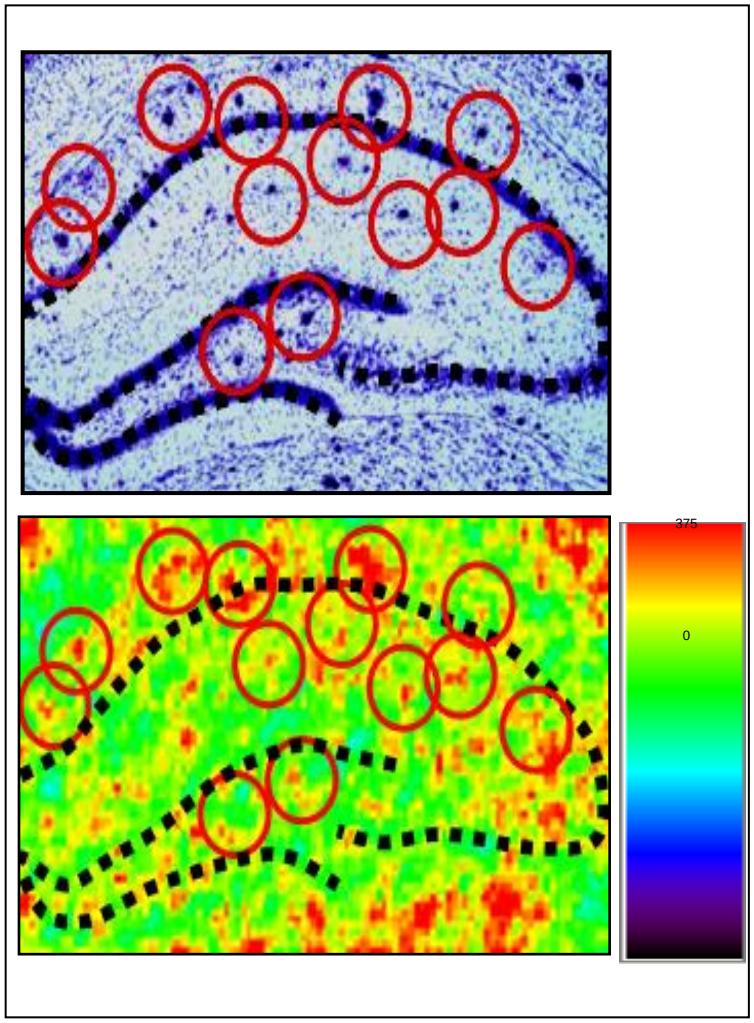


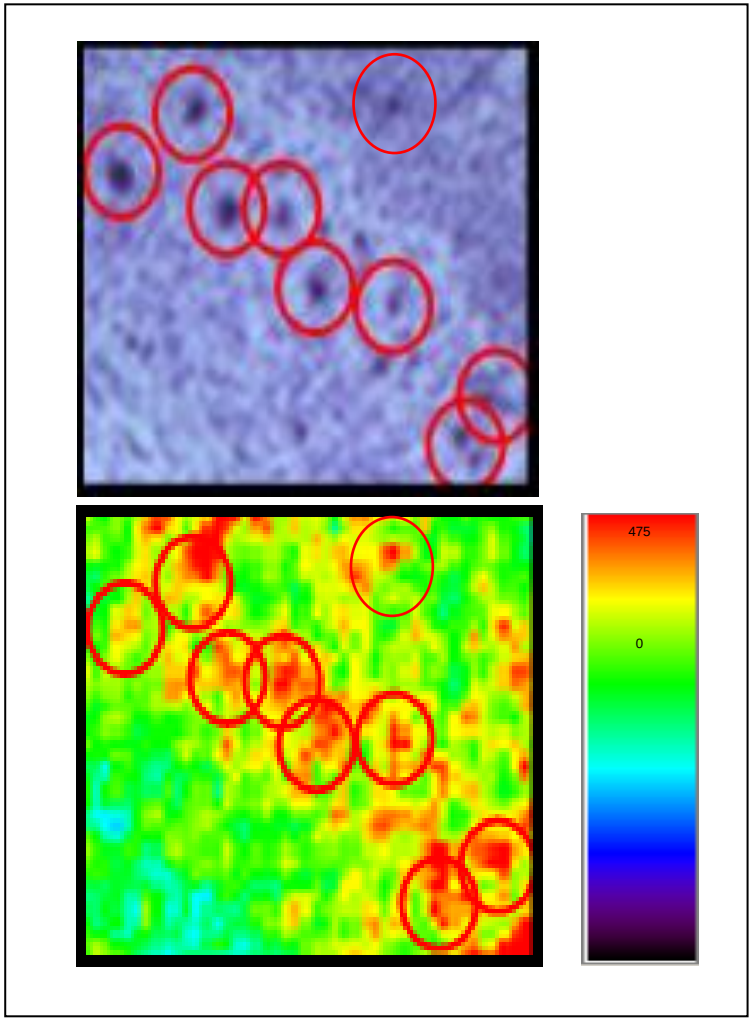
PET-FDG



Poisnel G et al. Neurobiology of Aging. 2012.

Increased glucose uptake in regions surrounding amyloid plaques in mice





2DG autoradiography

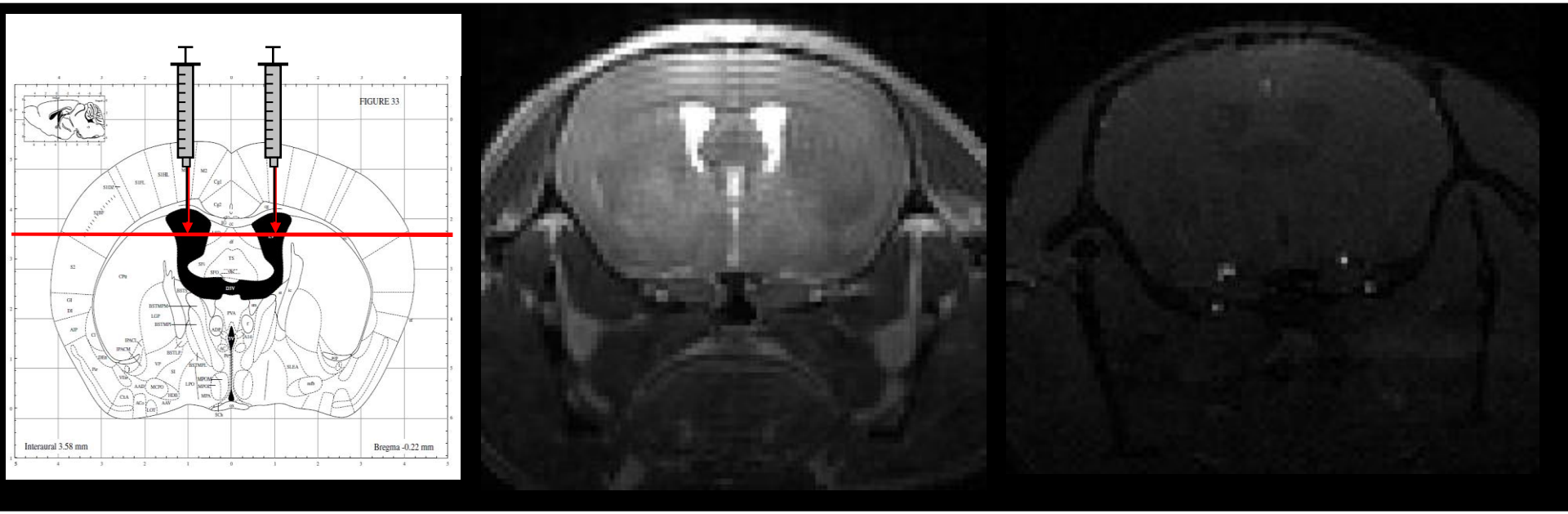
G. Poisnel et al, Neurobiology of Aging, 2012

MR Imaging from bench to bed… (maybe)

In vivo Gadolinium-Staining method

- Intra-cerebro-ventricular (ICV) administration of Gadolinium contrast agent
  - Commonly used procedure in experimental research

ICV-Gd-Staining | Control

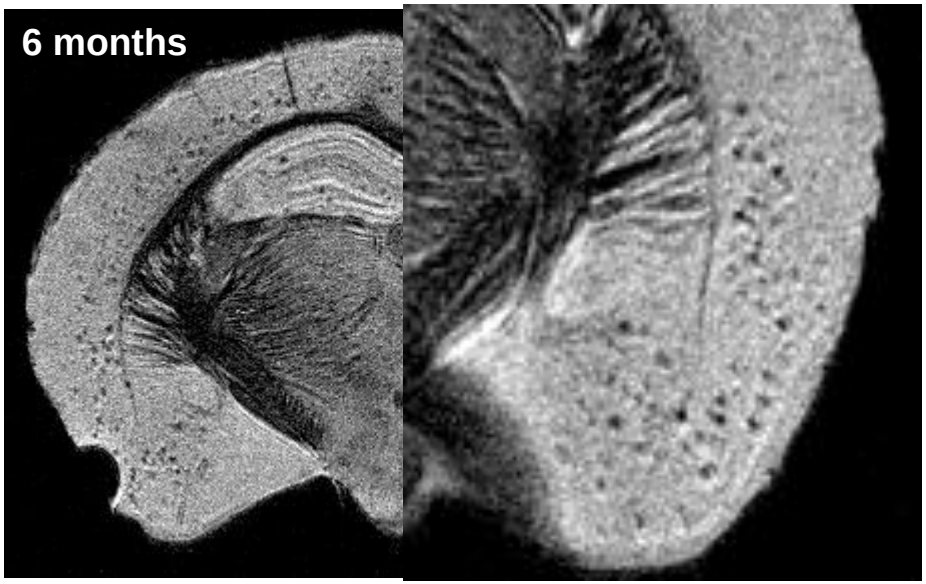


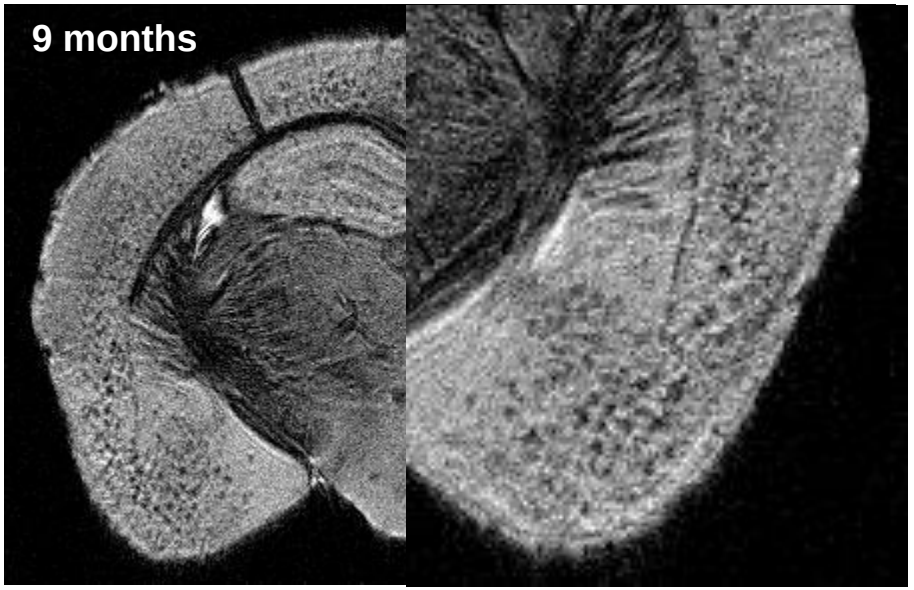
→Diffusion of Gadolinium in the brain
→Increased signal to noise ratio

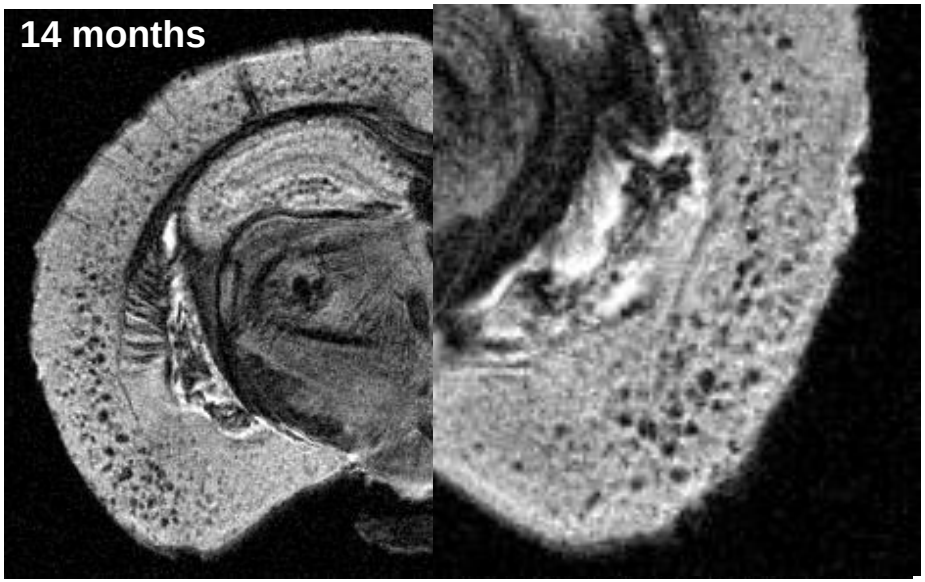
Detection of amyloid plaques thanks to non targeted contrast agents

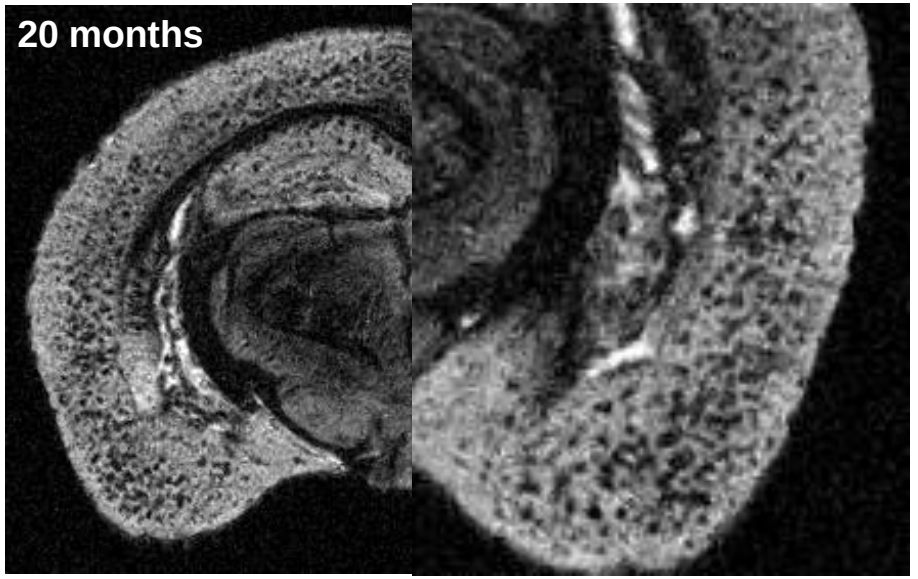
- Increase the signal in the brain
  - Allow to record images with a better resolution or faster
- Increase the contrast between amyloid plaques and the parenchyma

Detection of amyloid plaques by MR microscopy









Petiet A. et al. Neurobiology of Aging, 2012, 33 - 1533-1544

In-vivo follow-up of amyloid load

Detection of amyloid plaques by "*In-vivo* Gadolinium staining"

APP/PS1

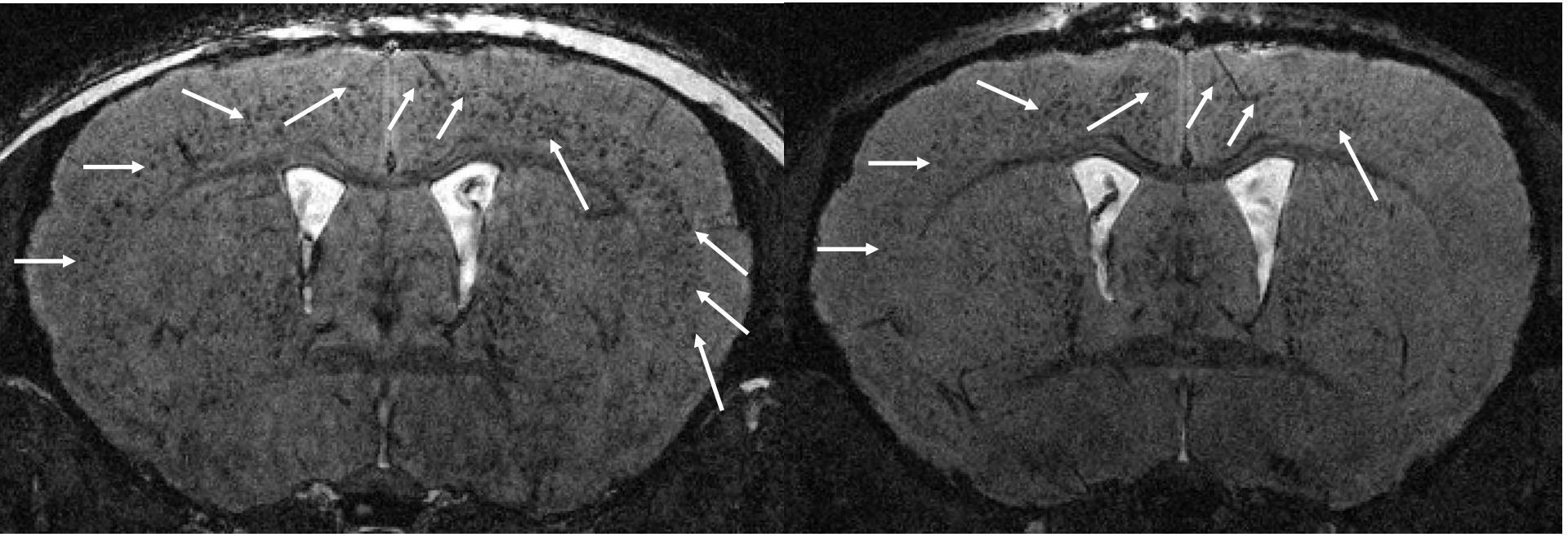
Control

29*29*117 μm^3
Acq Time can be 32 min

How to by-pass the blood brain barrier after IV injection?

- Opening of the blood brain barrier thanks to ultrasounds and microbubbles
  - *Hynynen K. et al. Noninvasive MR imaging-guided focal opening of the blood-brain barrier in rabbits. Radiology 2001, 220, 640-6.*

Comparison with ICV-Gd staining



US-Gd-Staining

ICV-Gd-Staining

Santin et al. NeuroImage 2013

Conclusion

- Do not use the term "animal model of Alzheimer's disease"
  - Prefer "model of amyloidosis"
- Do not limit exploration of animal models to phenotypes
  - Endophenotypes, revealed by biomarkers are critical
- Accept and assume that clinical outcome can not be predicted with current models
- Possibility to detect amyloid plaques by MRI


Magritte
Ceci n'est pas une pipe.


Ceci n'est pas un patient
Ceci n'est pas une souris
Ceci est une cible

Merci …