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 healthcare costs since 50 years

Source: goulven.theze; statitec.com

High price of new drug development

After
>15 years
>10^9 €
>3000 patients

Increased investissements in drug discovery

But high attrition in drug development

Attrition rate increases with time

- Attrition rate increases in phases 2-3

- Drug development pipeline

How to improve the discovery process?

NIH definitions

Diplôme universitaire

INNOVATION THÉRAPEUTIQUE ET RECHERCHE TRANSLATIONNELLE DANS LES MALADIES DU SYSTÈME NERVEUX: COMMENT ÉTABLIR UN LIEN ENTRE LA RECHERCHE EXPÉRIMENTALE ET CLINIQUE?

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Strategies to modify the clinical outcome? Isolate a target

Disease → Target → Clinical outcome (Phenotype)
How to select / validate a target?

**From Bed**
- Epidemiology
- Genetic (GWAS)
- Neuropathology
- "omics"
- Natural history of disease (biomarkers)

**From Bench**
- Molecular/Cell biology
- Cell models
- induced pluripotent stem cells
- Animal models

Target
How to select / validate a target?

From Bed
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Target

Development of a drug modifying the target

Drug efficacy in Cell / Animal models

Drug efficacy in Humans
From drug to target, and from target to disease

- Identify a target?
- Is my therapy modifying/reaching the target?
  - Target engagement, proof of mechanisms (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

A biomarker based history

Cortical amyloid plaques (Histology-PET)

Cortical neurofibrillary Tangles (Histology-PET)

Functional alterations (Metabolism (PET) Functional (fMRI))

Cerebral atrophy (MRI)

Cholinergic alterations (Histology, PET)

Mild cognitive impairments

Cognitively normal

~17 years

~3 years

~10 years

Dementia

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

Cognitive improvement

Immunotherapies

(Morgan et al., 2000)

(Schenk et al., 1999)
2010-2013: Failure of anti-amyloid therapies in humans

- Immunotherapies
  - Bapineuzumab: antiAβ1-5 (Wyeth/Elan – Pfizer/Janssen)
    - Fall in phase III - 2012
  - Solaneuzumab: antiAβ13-5 (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
  - β-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)

Lack of Tau

Amyloid

Homol Predictive

Oligomers

Homme

Cognitive alterations

Homol Predictive

Tau

Amyloid

Case 3 + 20–64 months
Biomarkers and animal/human comparisons

Animal

Cognitive alterations
(not homologous To human alterations)

Atrophy

Functional alterations

Lack of Tau

Amyloid

Human

Cognitive alterations

Atrophy

Functional alterations

Tau

Amyloid

Homol Predictive

Homol Predictive

Case 3 + 20–64 months
Cerebral atrophy in humans with 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
Brain and hippocampal growth even in the presence of amyloid deposits...
Cerebral atrophy

Animal

Cognitive alterations
(not homologous To human alterations)

Atrophy

Functional alterations

Lack of Tau

Amyloid

Human

Cognitive alterations

Atrophy

Functional alterations

Tau

Amyloid

Homol
Predictive

Homol
Predictive

Homol
Predictive

Case 3  20–64 months
Cognitive alterations (not homologous to human alterations)

- Atrophy
- Functional alterations
- Lack of Tau
- Amyloid

Homologous Predictive

Functional alterations

Perfusion MRI

FDG PET

Atrophy

Cognitive alterations

Homologous Predictive

Functional alterations

Tau

Amyloid

Animal

Human

Case 3: 20-64 months
Perfusion measurements from MRI

ASL-MRI provides overlapping information with FDG-PET

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

Increased glucose uptake in regions surrounding amyloid plaques in mice

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

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

In-vivo follow-up of amyloid load

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

APP/PS1

Control

29*29*117 µm³
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
Comparison with 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 un patient
Ceci n'est pas une souris
Ceci est une cible

Merci …