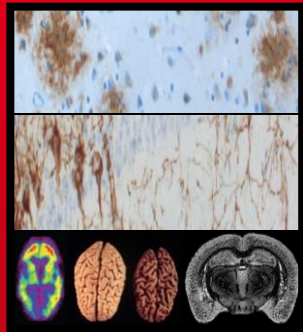


Transmission de la maladie d'Alzheimer

Hypothèse ou réalité?



DE LA RECHERCHE À L'INDUSTRIE

cea



Marc Dhenain

CNRS, CEA,
Molecular Imaging Research Center
Fontenay-aux-Roses, France



PREAMBULE

Peste noire
30 à 50 % des Européens
tués en cinq ans (1347-1352)



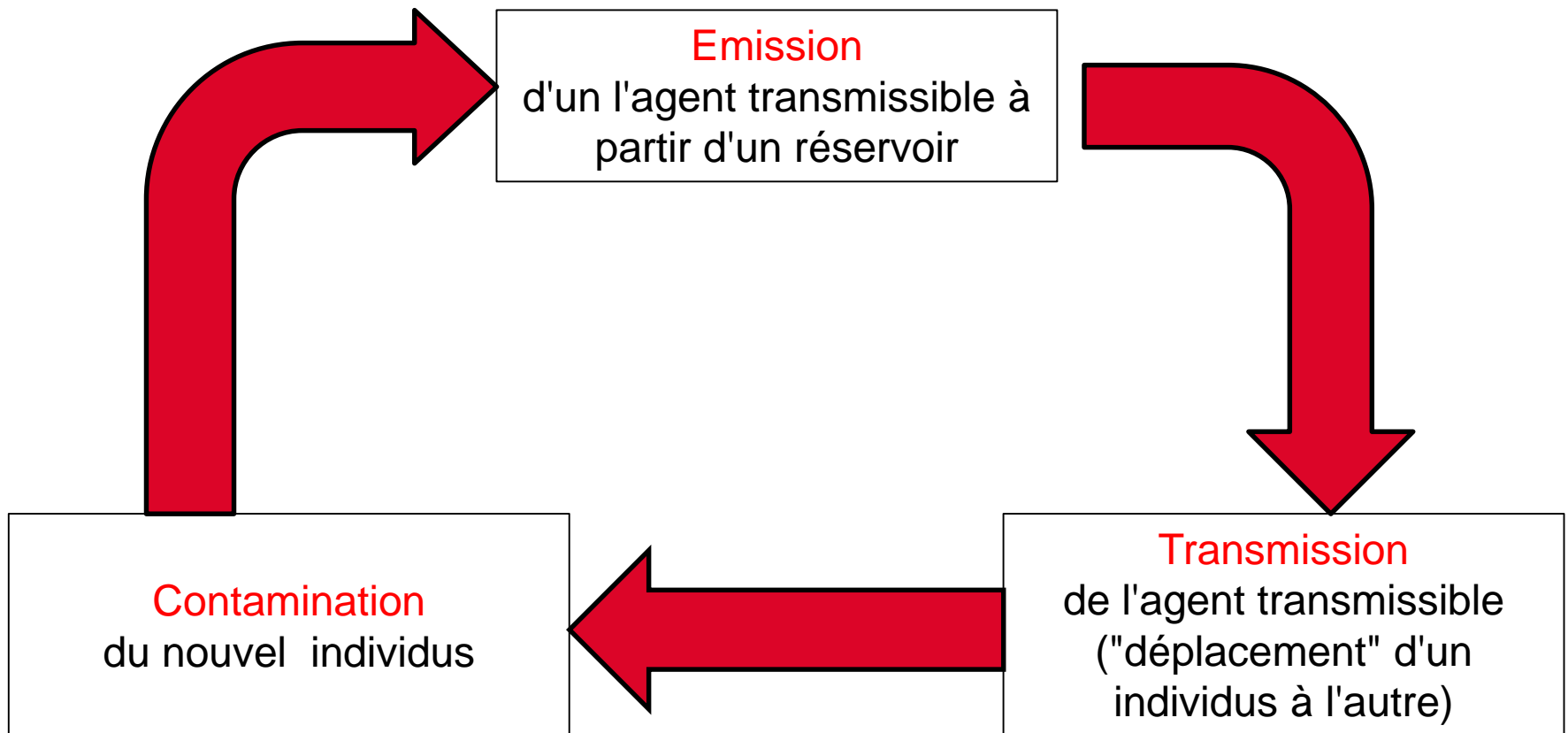
Grippe espagnole (1918)
50 millions de morts
2,5 à 5 % de la population
mondiale



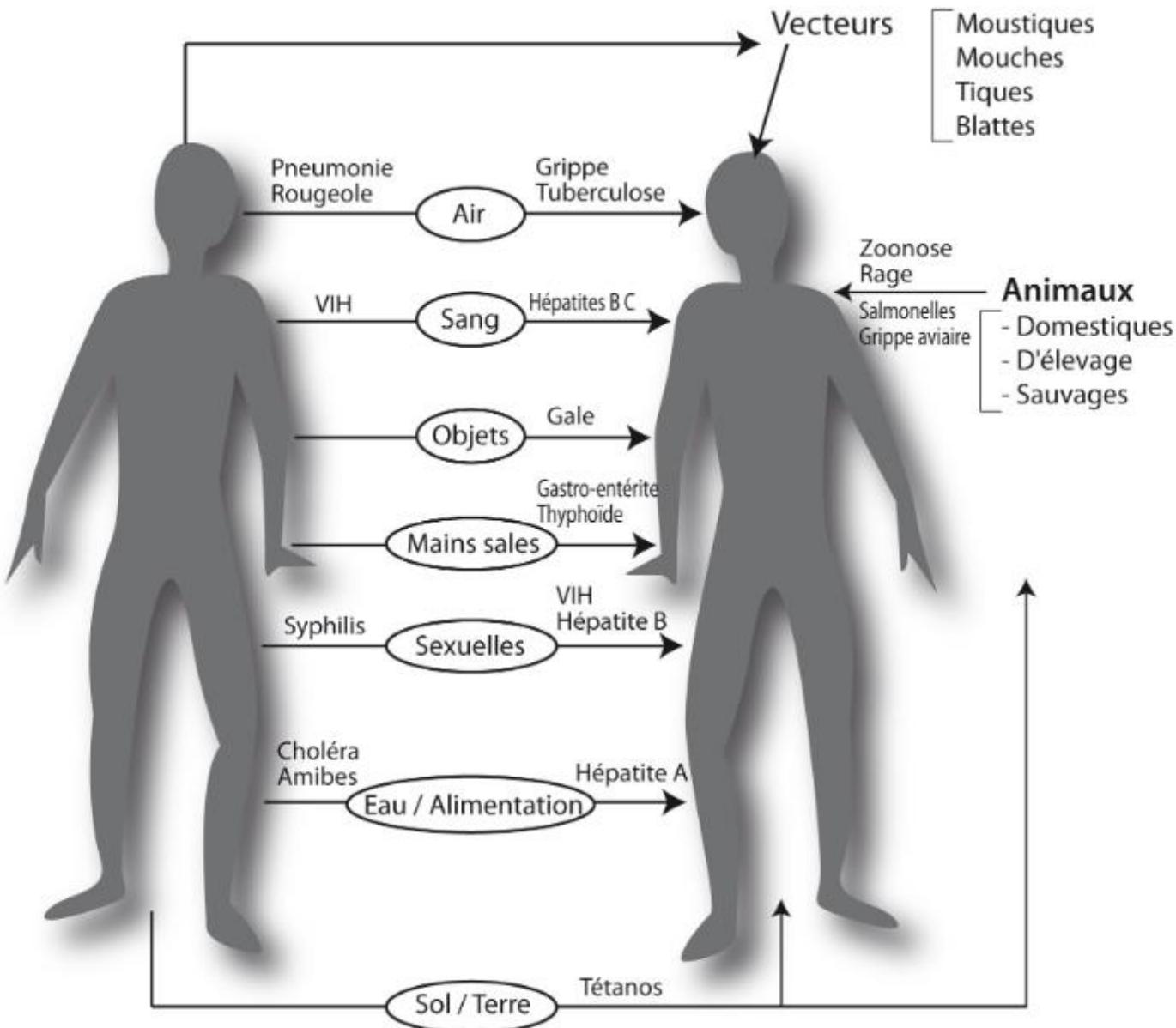
Je ne vais pas parler de ça...

QU'EST CE QU'UNE MALADIE TRANSMISSIBLE ?

Maladie qui passe d'une personne ou d'un animal infecté à une personne (ou un animal) auparavant non-infectée.



MODES DE TRANSMISSION ET DE CONTAMINATION



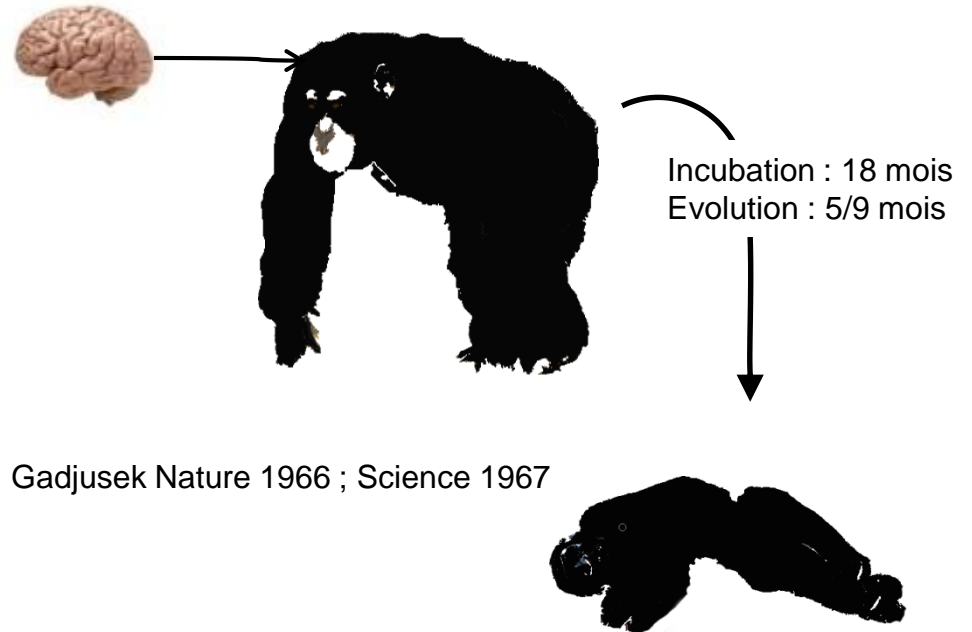
- Directes
- Indirectes
- Par vecteurs
- Iatrogènes



MALADIES A PRIONS - DES MALADIES "MIXTES" LE KURU : UNE MALADIE TRANSMISSIBLE



Kuru



Gadjusek Nature 1966 ; Science 1967



MALADIES DE CREUTZFELDT-JAKOB

FORMES TRANSMISSIBLES ET NON TRANSMISSIBLES

Formes sporadiques

Apparaissent de façon occasionnelles
et sans "raison apparente"

~ 13 000 cas/an dans le monde

Formes génétiques

Formes autosomales dominantes

~ 1000 cas/an dans le monde
(~5-10%)

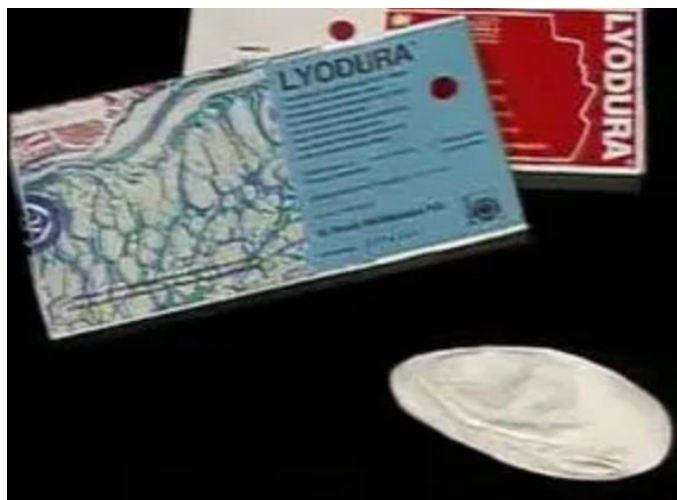
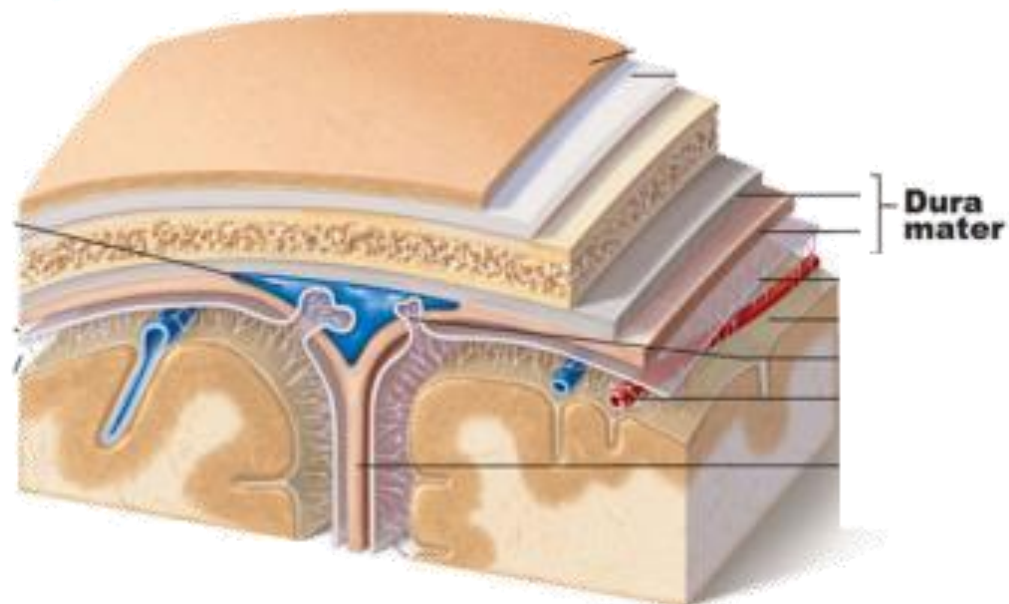
Formes transmissibles

- Iatrogènes (<1% des cas)
470 cas décrits
- Formes alimentaires
- ° Nouveau variant (228 cases)

TRANSMISSIBILITY OF PRION DISEASES

Origins of iatrogenic transmission (470 cases)

	Dura matter grafts / embolization
Total	228
	142 in Japan (20 000 batches/year)
Risk period	Before 1987 Banned in 1992
Incubation (years)	1.3-30



TRANSMISSIBILITY OF PRION DISEASES

Origins of iatrogenic transmission (470 cases)

20% of Lyodura use in the US was in nonneurosurgical applications

Creutzfeldt-Jakob disease after extracranial dura mater embolization for a nasopharyngeal angiofibroma

Article abstract—We report a 25-year-old man with Creutzfeldt-Jakob disease (CJD) who had received dura mater embolization in the external carotid artery for a nasopharyngeal angiofibroma 90 months earlier. The patient was heterozygous (Met/Val) at codon 129. This case suggests that dura mater embolization can be responsible for the CJD.

NEUROLOGY 1997;48:1451–1453

J.C. Antoine, MD; D. Michel, MD; P. Bertholon, MD; J.F. Mosnier, MD; J.L. Laplanche, PhD;
P. Beaudry, MD; J.J. Hauw, MD; and C. Veyret, MD

TRANSMISSIBILITY OF PRION DISEASES

Origins of iatrogenic transmission (470 cases)

20% of Lyodura use in the US was in nonneurosurgical applications

1: Non-neurosurgical uses of Lyodura in the United States*

- Development of ligaments to stabilise shoulder joints
- Replacement of the tracheal wall
- Covering pleura defects
- Securing bronchial stumps
- Repair of pericardium
- Repair of diaphragm defects (traumatic or congenital)
- Arthroplasties of the elbow
- Reinforcement of fascia in abdominal hernias
- Reinforcement of tendons or ligaments
- Plastic enlargement of the urinary bladder
- Other miscellaneous surgical uses

*Based on information from the US National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Ga.

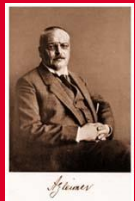
TRANSMISSIBILITY OF PRION DISEASES

Origins of iatrogenic transmission (470 cases)

	Surgical procedures				Medical procedures		
	Dura matter grafts / embolization	Surgical instruments *	EEG needles	Corneal transplants	Growth hormons	Gonadotropin	Packed red blood cells
Total	228	4	2	2	226	4	3
	142 in Japan (20 000 batches/year)				119 in France/ 1880 recipients		
Risk period	Before 1987 Banned in 1992				Before 1977 (USA) Before 1985 (Fce)		
Incubation (years)	1.3-30	1-2.3	1.3-27	1.5-27	5-42	12-16	6.5-8.3

Brown, Iatrogenic Creutzfeldt-Jakob Disease, Final Assessment. Emerging Infectious Diseases, 2012, 18: 901-907

* Prions are resistant to conventional methods of decontamination

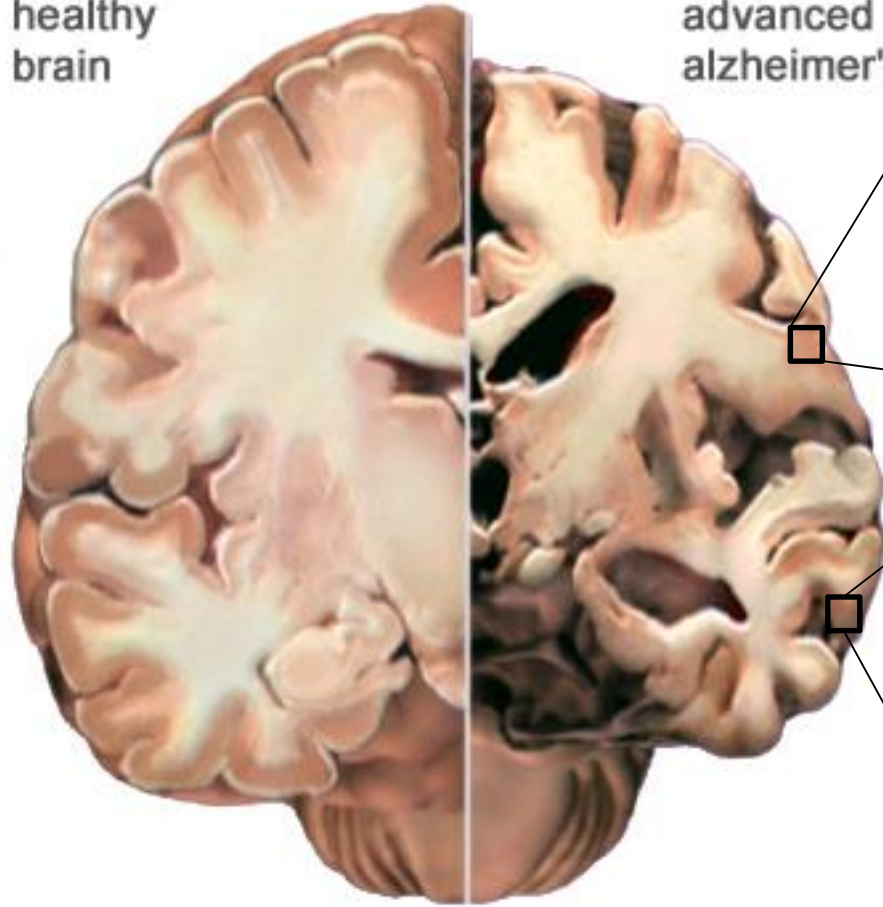


ALZHEIMER'S DISEASE

Cerebral atrophy

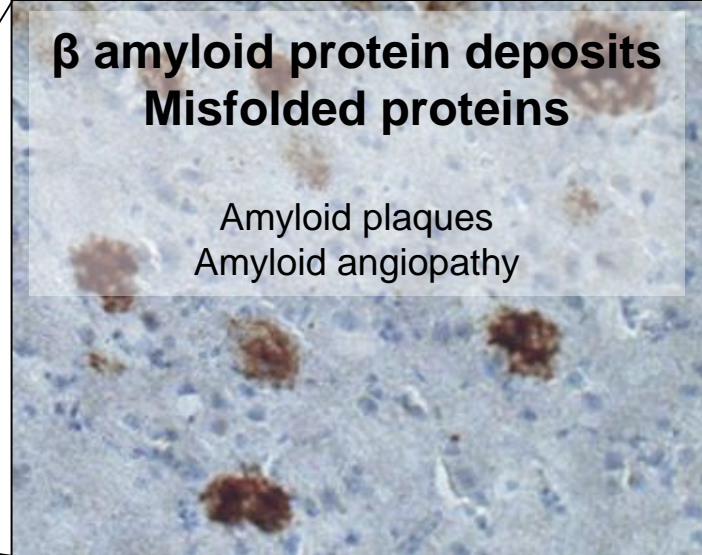
healthy brain

advanced alzheimer's



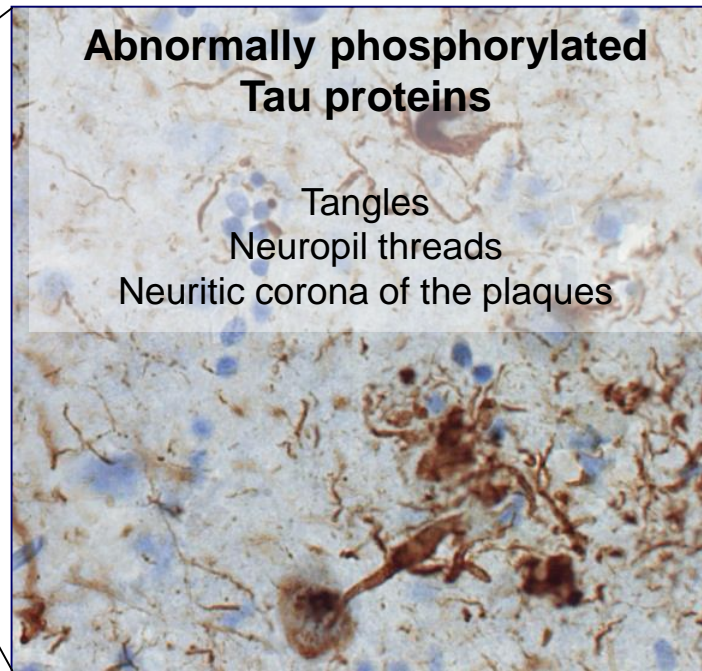
β amyloid protein deposits
Misfolded proteins

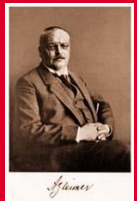
Amyloid plaques
Amyloid angiopathy



Abnormally phosphorylated
Tau proteins

Tangles
Neuropil threads
Neuritic corona of the plaques





ALZHEIMER'S DISEASE DIFFERENT FORMS



Sporadic Forms

Appearing at irregular intervals in time
occasional

~ 50 million / year

Genetic Forms

Autosomal dominant forms

~ 1 million / year
(~1%)

iatrogen forms ?

PROOFS FOR IATROGENIC TRANSMISSIONS

Methods based on triangulation

How to increase scientific certainty ?

Verifying results requires disparate lines of evidence — a technique called triangulation.

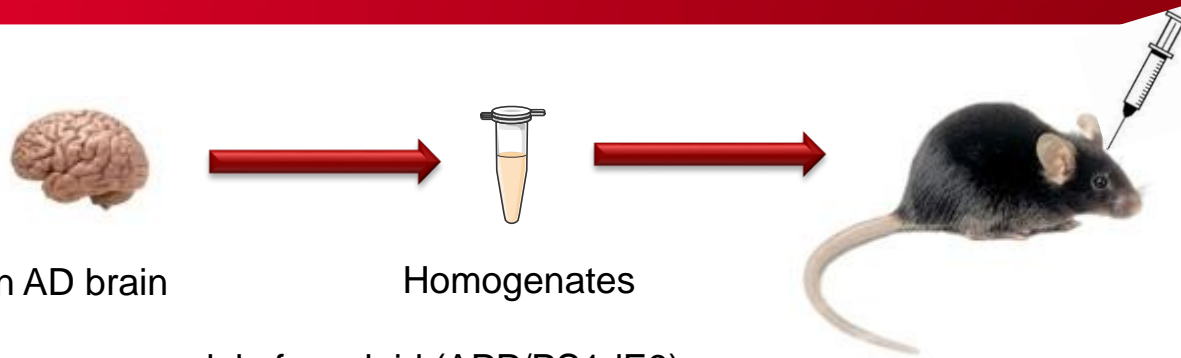
Studies
in rodent models



Studies
in primates

Studies
in humans

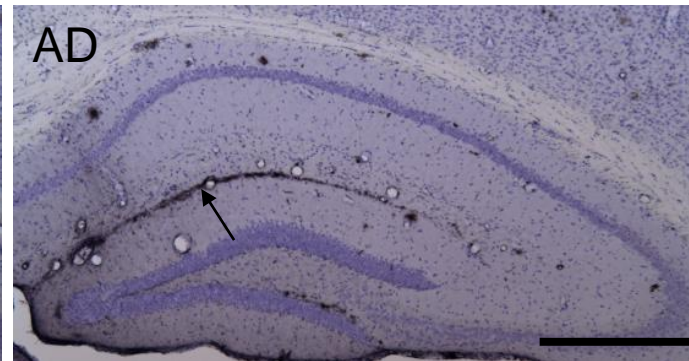
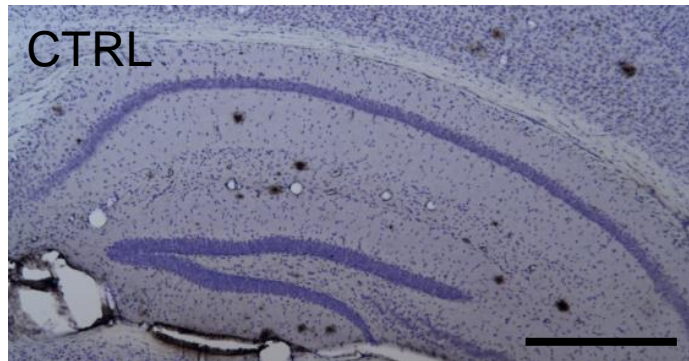
TRANSMISSION OF AMYLOID AND TAU IN TRANSGENIC RODENTS



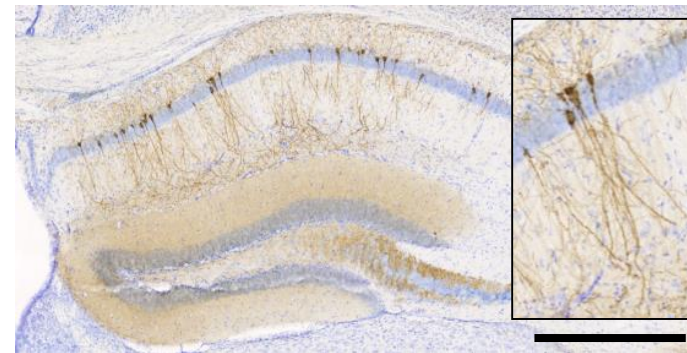
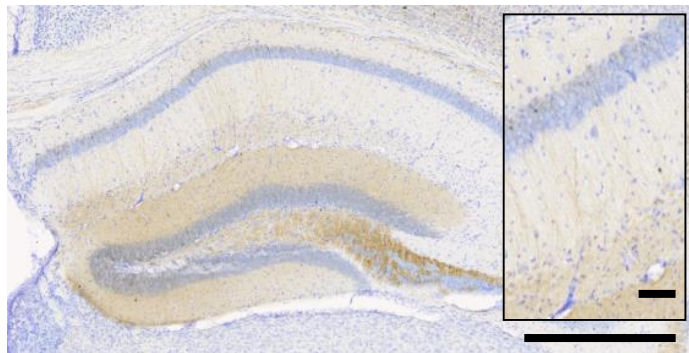
Human AD brain

Homogenates

Transgenic mouse model of amyloid (APP/PS1dE9)

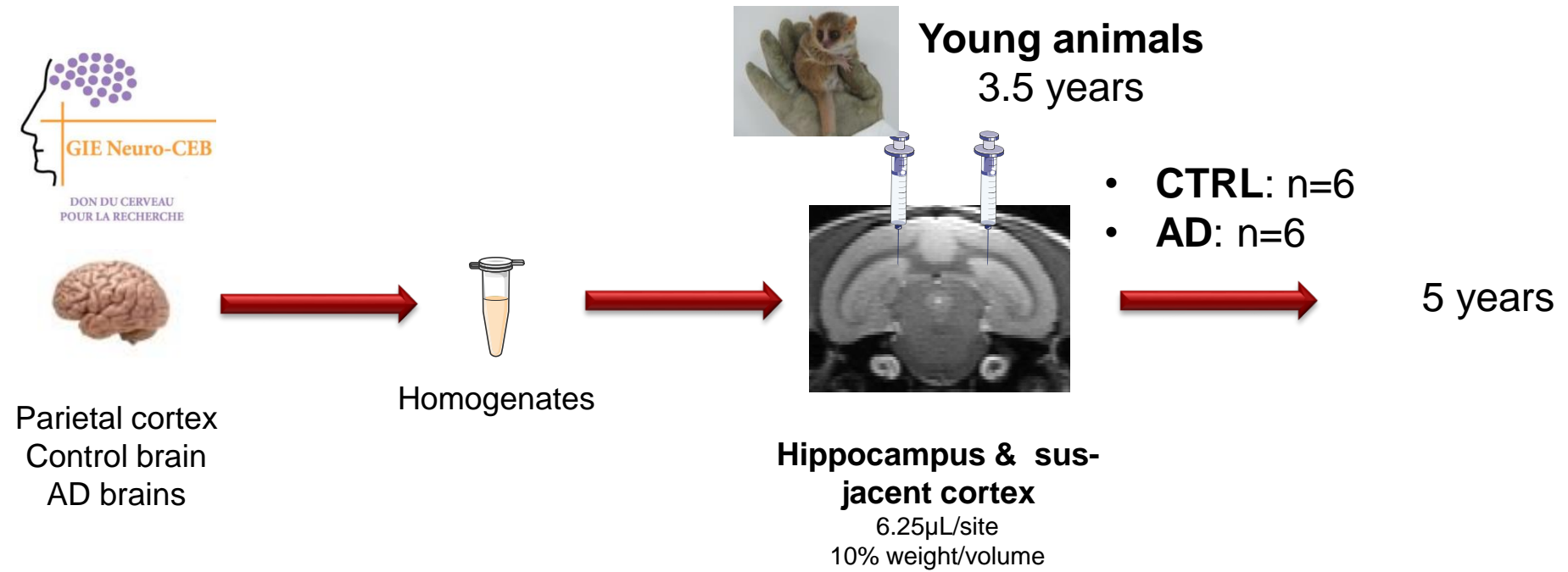


Transgenic mouse model of Tau (Tau30^{+/+})



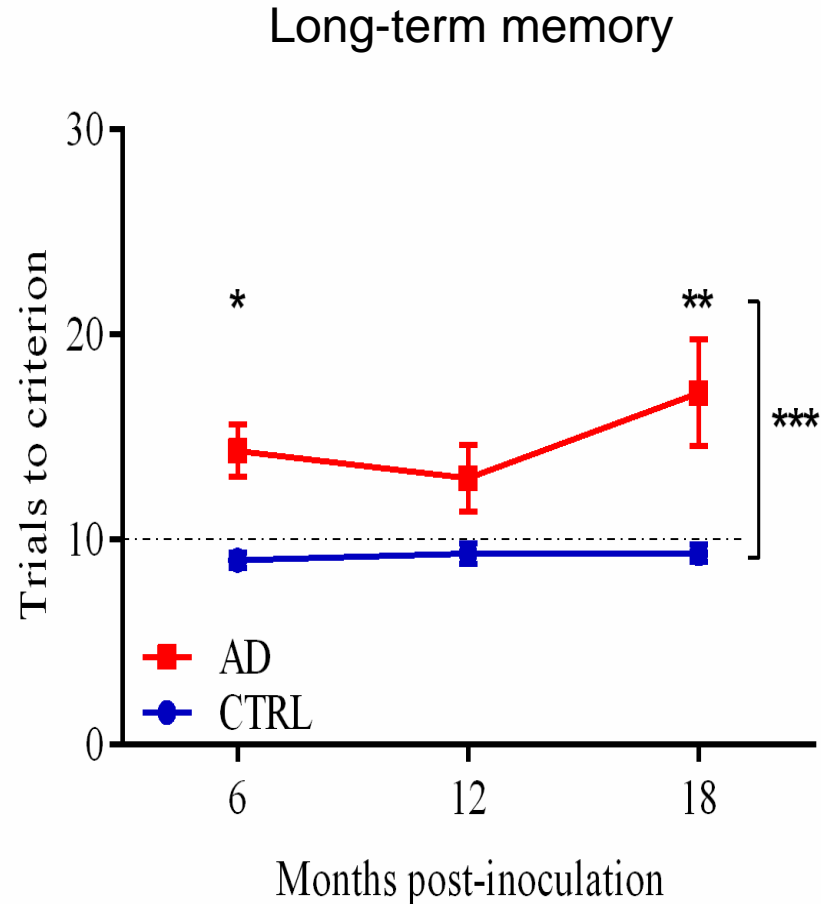
TRANSMISSION IN YOUNG MOUSE LEMUR PRIMATES ?

Experimental design



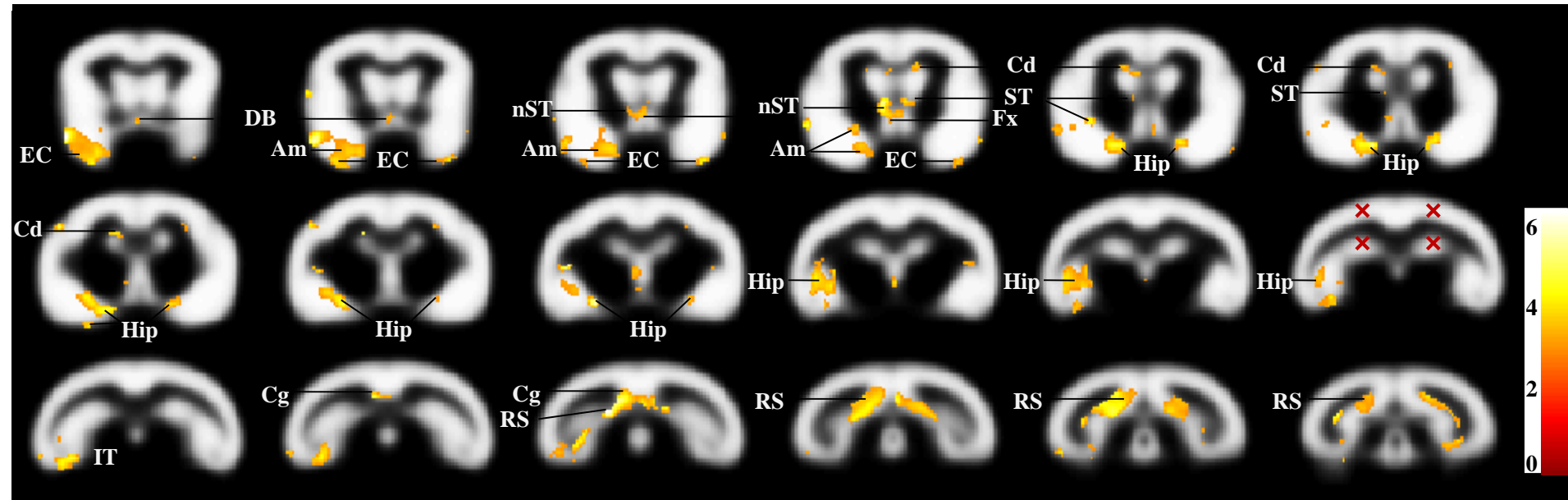
- Longitudinal follow-up (every 6 months)
- Functional impact (Behavior evaluation, EEG)
- Cerebral atrophy (MRI every 3 months)
- Neuropathological impact

COGNITIVE IMPAIRMENTS IN AD-INOCULATED ANIMALS

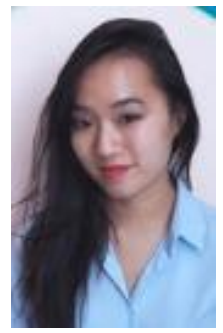
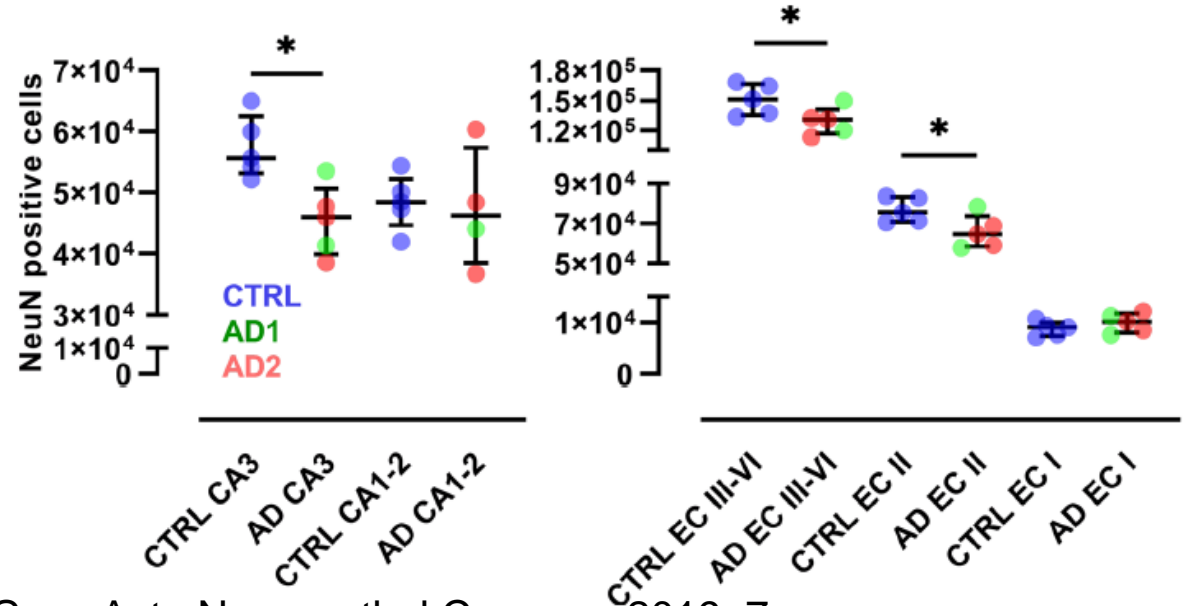
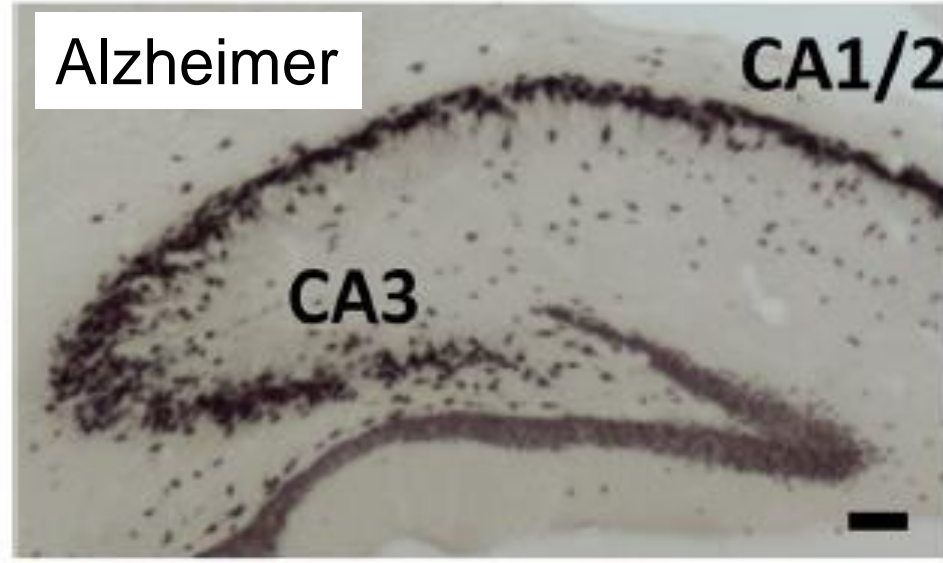
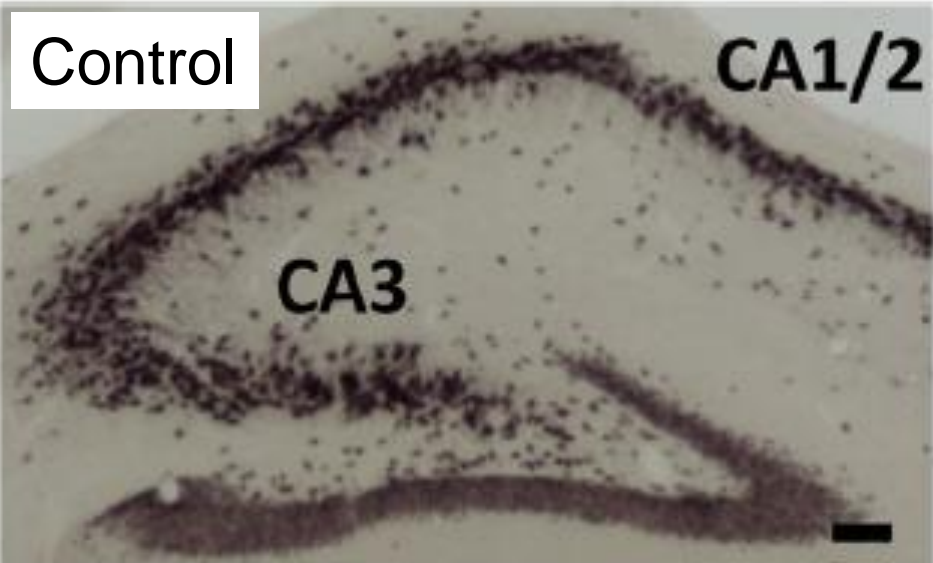


- AD brain homogenate inoculation progressively leads to learning and long-term memory impairments

GRAY MATTER ATROPHY IN THE AD GROUP

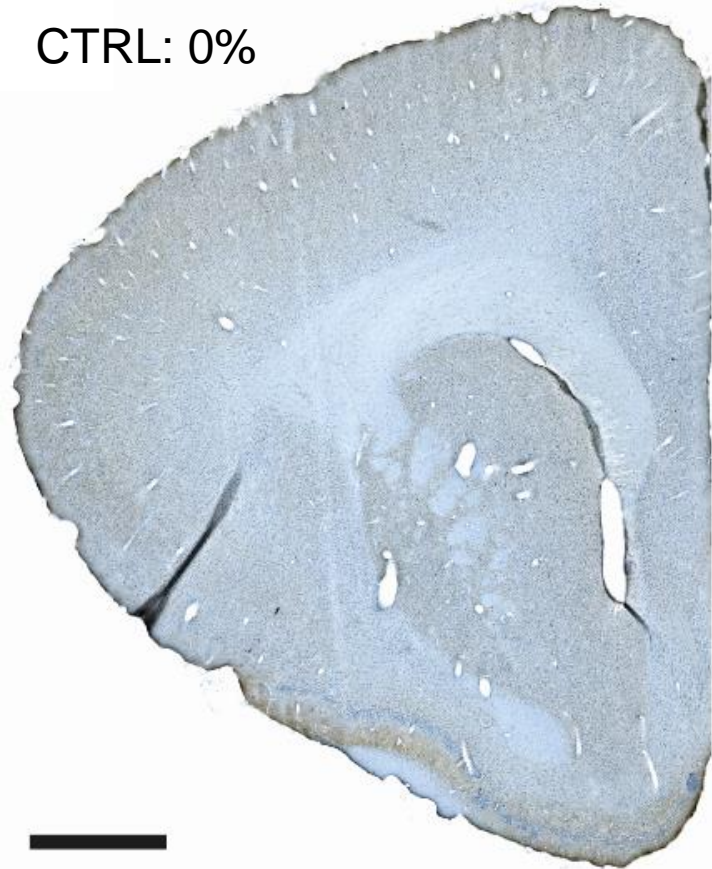


NEURONAL LOSS IN THE AD GROUP

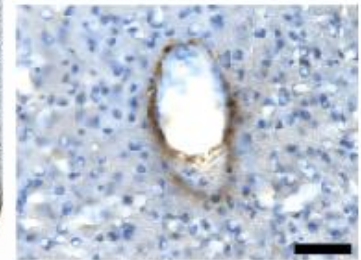
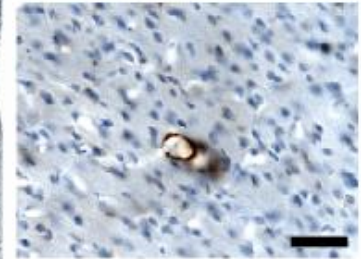
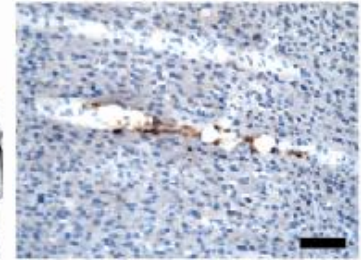
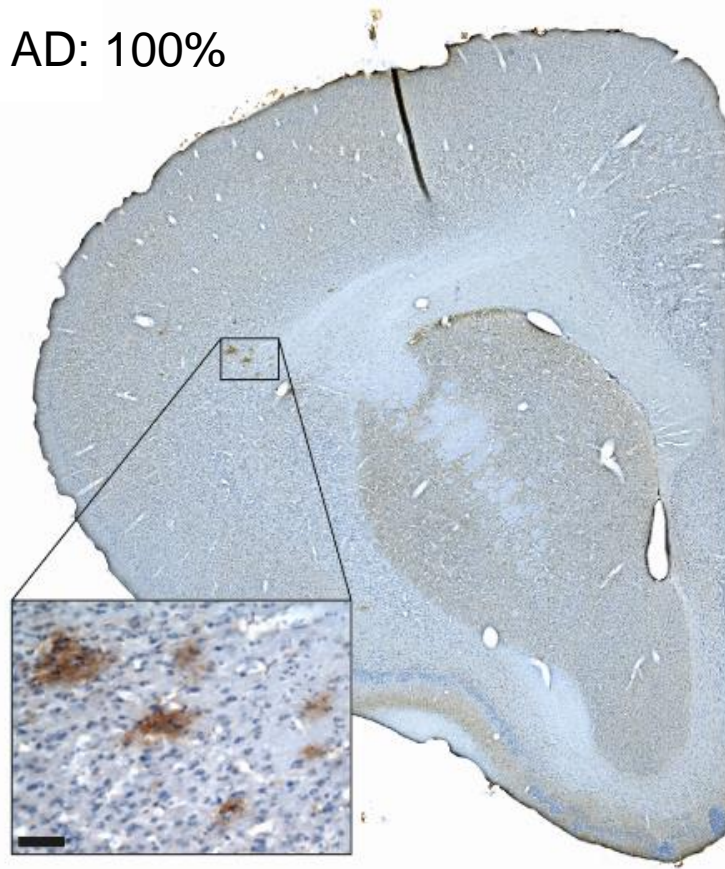


SPARSE AMYLOIDOSIS IN THE AD GROUP

CTRL: 0%

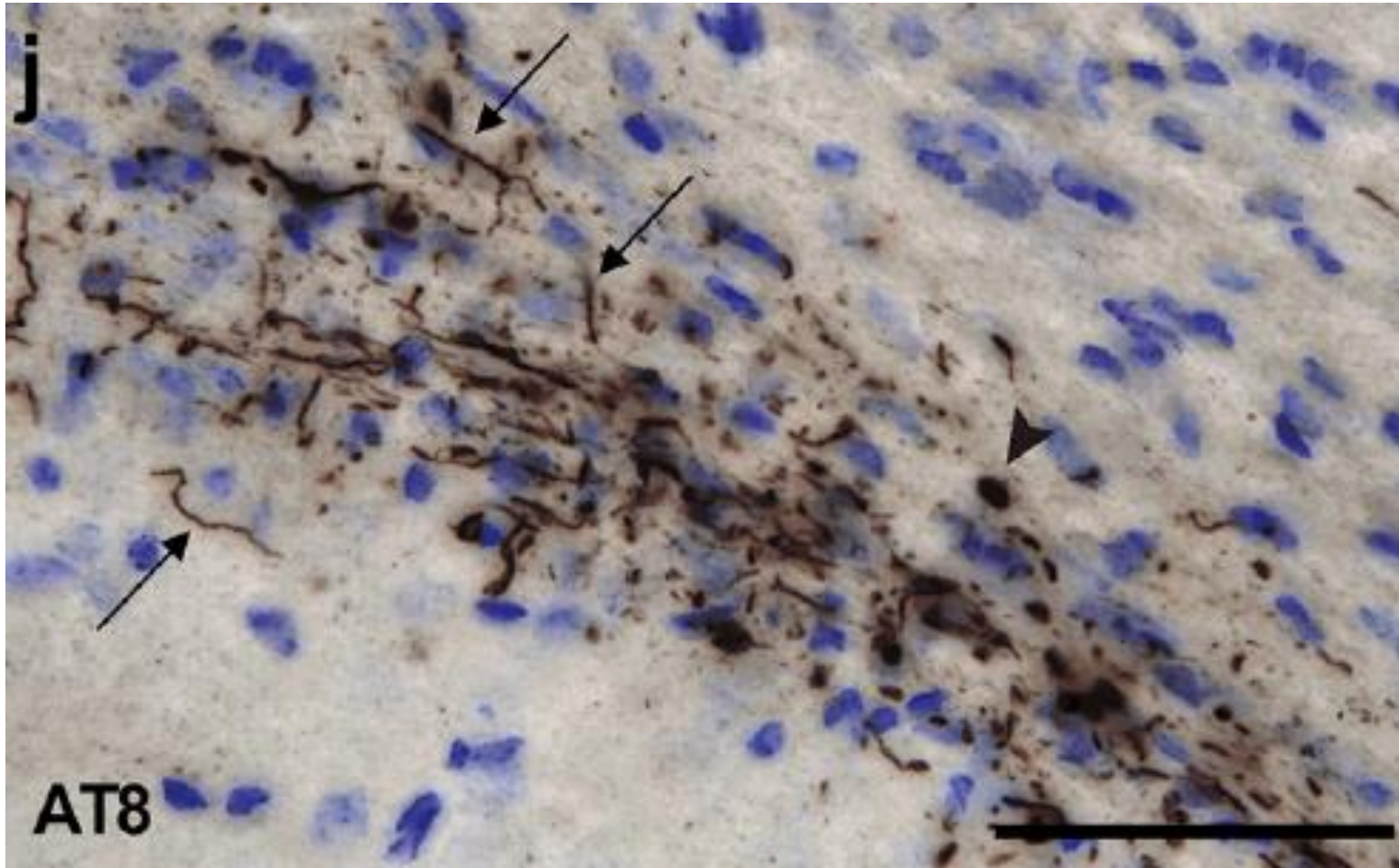


AD: 100%



TAU PATHOLOGY IN THE AD GROUP

CTRL: 0%; AD: 40% (2/5)



PROOFS FOR IATROGENIC TRANSMISSIONS

Methods based on triangulation

How to increase scientific certainty ?

Verifying results requires disparate lines of evidence — a technique called triangulation.

Studies
in rodent models



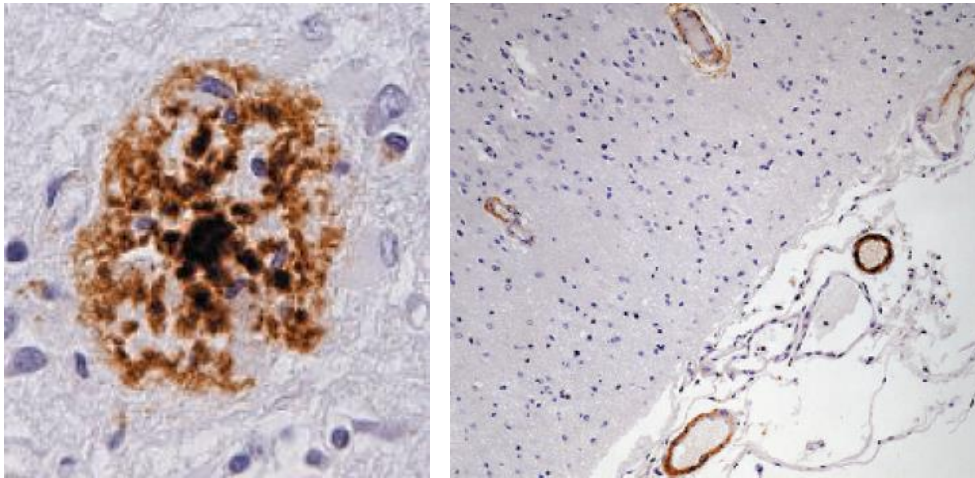
Studies
in primates

Studies
in humans

SUSPICION OF IATROGENIC TRANSMISSION OF AMYLOID

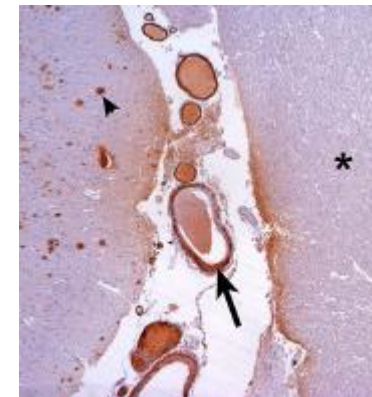
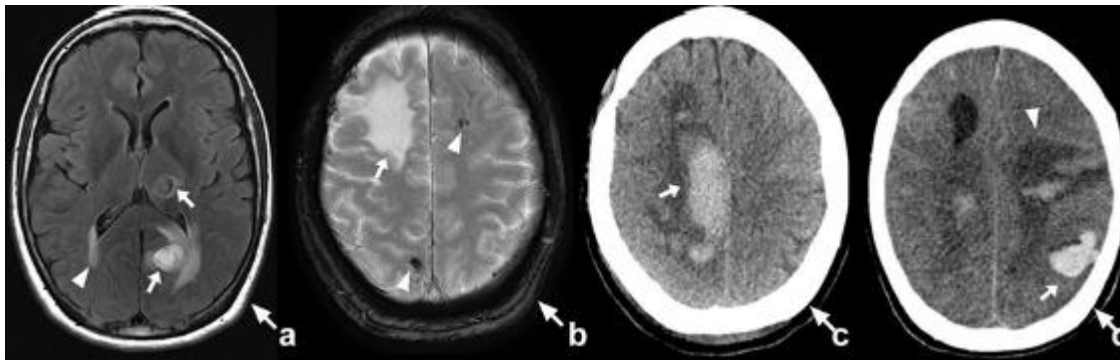
Contamination by dura matter grafts after cerebral surgery

- 2006: Preusser. Journal of Neurology Neurosurgery and Psychiatry 77: 413-416.



- Kovacs et al. Acta Neuropathol. 2016
- Frontzek, K. Swiss Med Wkly. 2016
- Hamaguchi, Acta Neuropathol. 2016

- Induction of clinical signs : Cerebral haemorrhages



- Herve et al. 2018

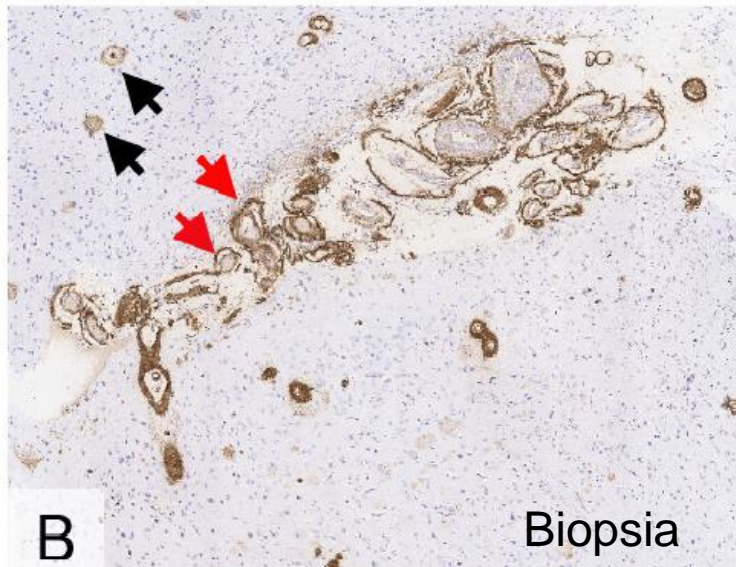
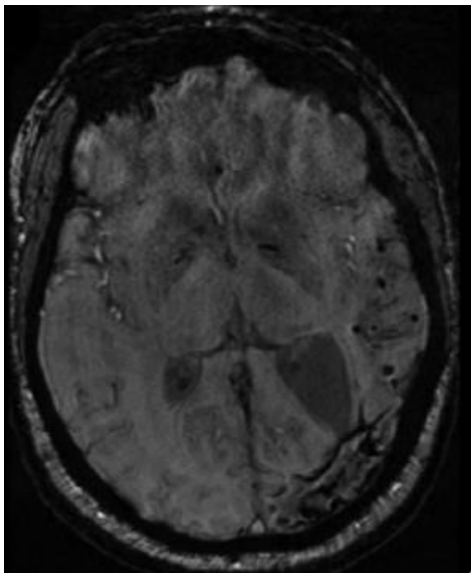
SUSPICION OF IATROGENIC TRANSMISSION OF AMYLOID

Contamination by dura matter grafts after embolization

- Parotid cavernous hemangioma: at 2 and 6 years → Embolization with dura matter

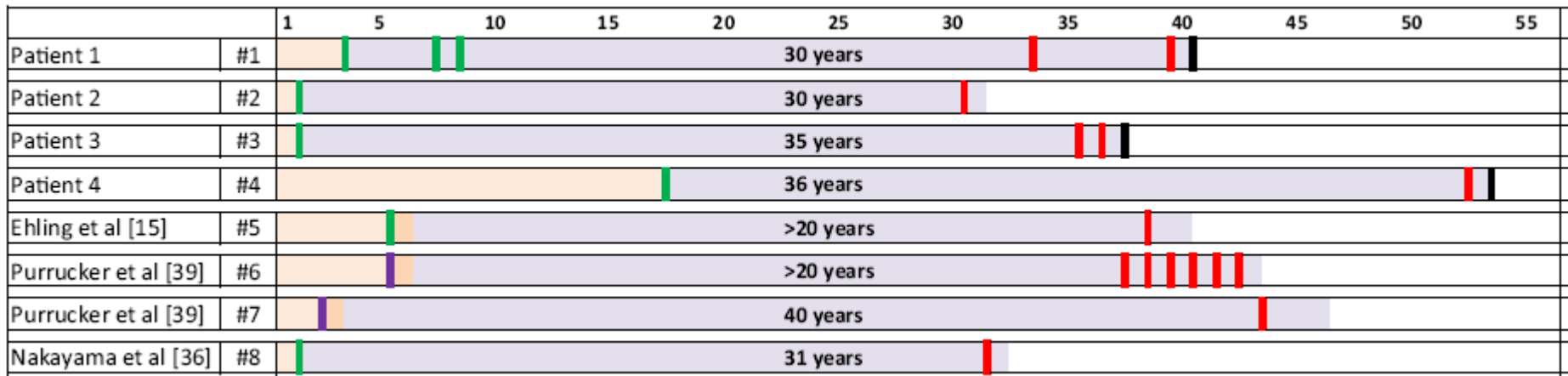


- At 27, 31, 33, 35 years: Haemorrhages



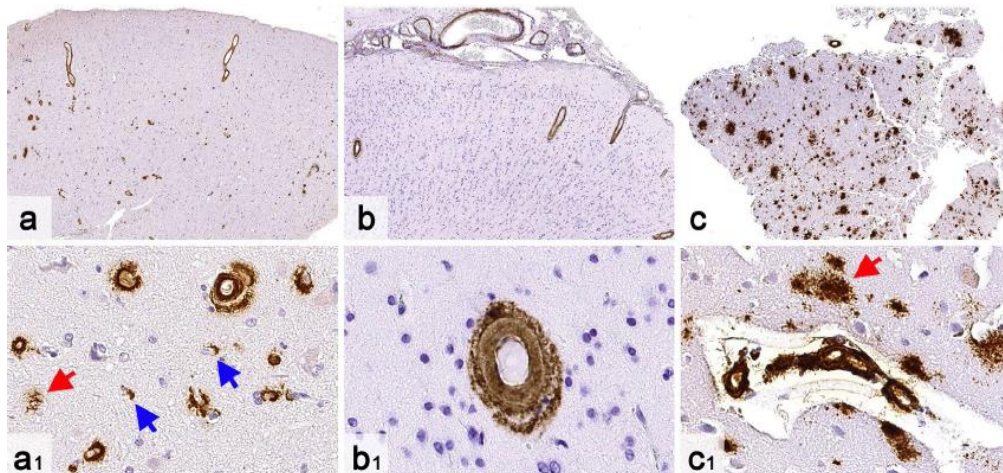
SUSPICION OF IATROGENIC TRANSMISSION OF AMYLOID IN HUMANS

Contamination by surgical intervention



■ Surgery ■ Head trauma

■ Haemorrhage ■ Death

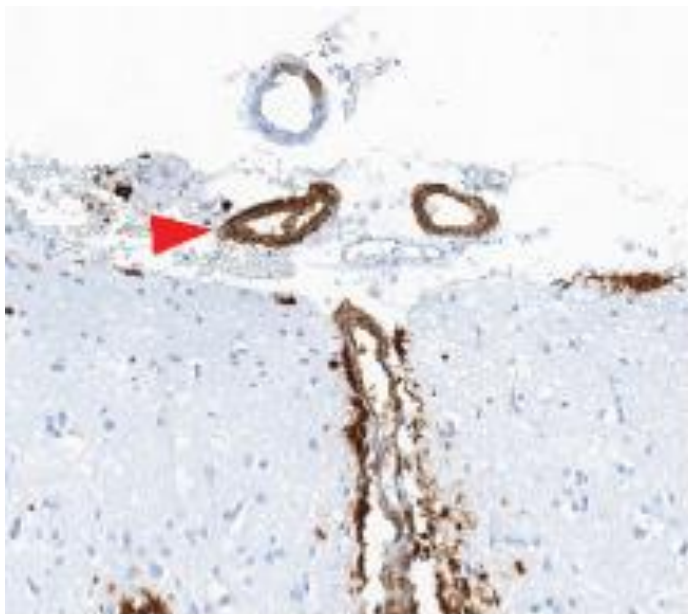


- Jaunmuktane. Evidence of amyloid-beta cerebral amyloid angiopathy transmission through neurosurgery. *Acta Neuropathol* 2018. 135: 671-679.

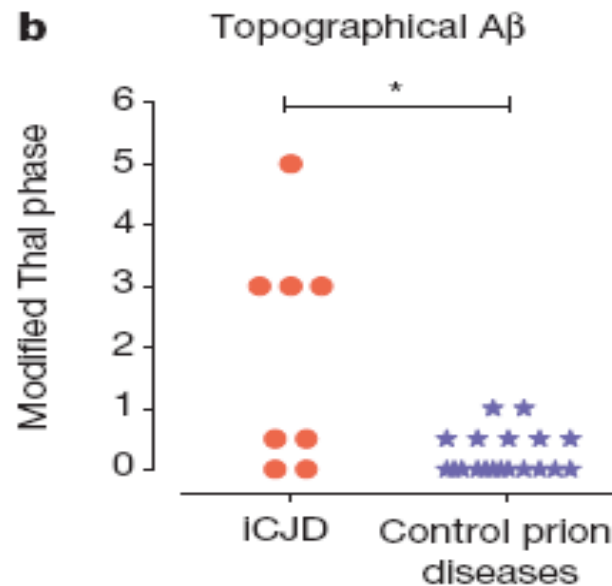
SUSPICION OF IATROGENIC TRANSMISSION OF AMYLOID IN HUMANS

Contamination with growth hormone

- Presence of A β and tau in injected c-hGH (Duyckaerts et al. 2018, Purro 2018)
- Amyloidosis in iatrogenic persons inoculated with growth hormone
 - Who died from Creutzfeldt-Jakob disease (Jaunmuktane, Nature. 2015)



Amyloid β



- Who died from other causes (Ritchie, Acta Neuropathologica, 2017)
- Amyloid plaques, amyloid angiopathy (and Tau ?)

PRION AND ALZHEIMER'S DISEASE

Cases of iatrogen transmission

	Surgical procedure				Medical procedures		
	Dura matter grafts	Surgical instruments	EEG needles	Corneal transplants	Growth hormons	Gonadotropin	Packed red blood cells
Prion	228	4	2	2	226	4	3
470 cases	142 in Japan (20 000 batches/year)				119 in France/ 1880 recipients		
	Dura matter grafts	Surgical instruments	EEG needles	Corneal transplants	Growth hormons	Gonadotropin	Packed red blood cells
Alzheimer	22	8	0	0	39	0	0
	Preusser, 2006 Frontzek, 2016 Kovacs 2016 Hamaguchi, 2016 Herve, 2018 Banerjee, 2019	Jaunmuktane, 2018			Jaunmuktane, 2015 Duyckaerts, 2018 Ritchie, 2017 Cali, 2018		
72 cases	4 cases Haemorrhages	8 cases Haemorrhages					

Only 5 years of studies: No doubt on future (exponential) increase of cases reported for AD

PUBLIC HEALTH ISSUES

CURRENT POTENTIAL RISK ?

- Dura mater is not used anymore
- Growth hormon is not used anymore

- Cerebral surgery
 - Procedures for prion patients
 - Identification of patients at risk for having a prion disease before they undergo surgical procedures.
 - Increased procedures for surgical tools desinfection (World Health Organization (WHO), 1999)
 - <https://www.cdc.gov/prions/cjd/infection-control.html>
 - **Procedure for Alzheimer patients ?**
 - Today is there an identification of patients at risk for having AD before surgery?
 - Increased procedures for surgical tools desinfection
 - Wisdom: Exclude from donor programs patients with amyloid/tau lesions.
(Duyckaerts, Curr Opin Neurol. 2019; 32: 266-271)

PUBLIC HEALTH ISSUE

PATIENTS WHO HAD AT-RISK PROCEDURES IN THE YEARS ~1980

- Follow-up of patients
 - Surgery
 - Cerebral surgery in general
 - Dura mater graft
 - **Non neurosurgical use of dura mater (~20% use of Lyodura)**

2: Features of the five Australian cases of Creutzfeldt–Jakob disease associated with Lyodura

Removal of frontal meningioma

Removal of cerebellar astrocytoma

Craniocervical decompression

Removal of cerebellar astrocytoma

Removal of acoustic neuroma

ORIGINE PERIPHERIQUE DES CONTAMINATIONS ?

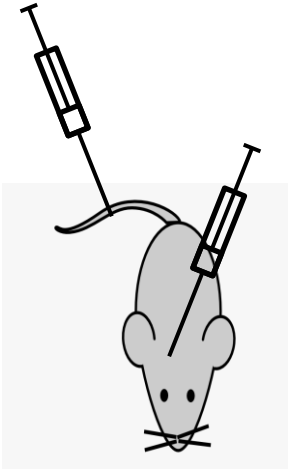
Voie	% efficacité	Dilution
Intra-cérébrale	100%	1:10
Intra-péritonéale	100%	>1:10
Intra-veineuse	0%	1:100
Intra-oculaire	0%	1:10
Orale	0%	1:10
Intranasale	0%	1:10

Intra-péritonéale :
Cluster de Aβ₄₂ proche
des vaisseaux



RISQUES DE CONTAMINATION POUR LE PERSONNEL DE LABORATOIRE ?

Contamination chez les modèles cellulaires et animaux

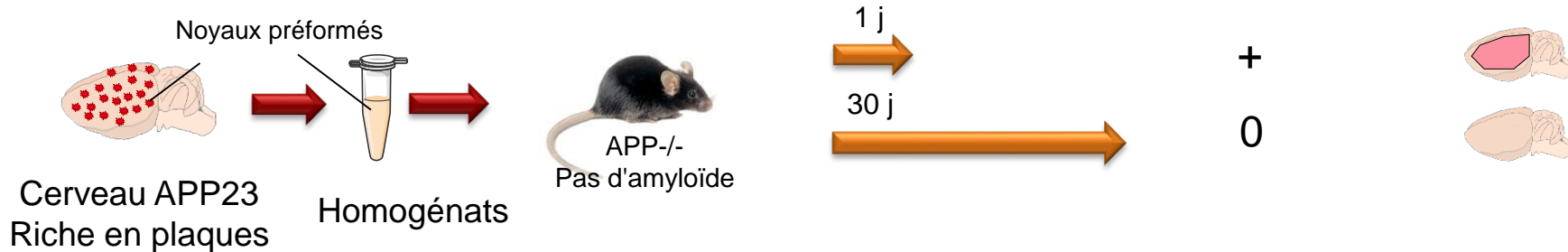


	intracérébrale	Intrapéritonéale	intramusculaire	intraveineux	Oral/voie aériennes
A-beta	++	Oui	Pas de données	0/6	0/6
Tau	++ (2,5 µl)	2x100µl 1 week interval	Pas de données	Pas de données	?
Synucléine	++	?	+ souris transgéniques	+/- souris transgéniques	+/- souris transgéniques

ACCÉLÉRATION DE L'AMYLOÏDOSE APRÈS INJECTION D'HOMOGÉNATS SANS AMYLOÏDE DETECTABLE

Première transmission

Mesures biochimiques de l'amyloïde

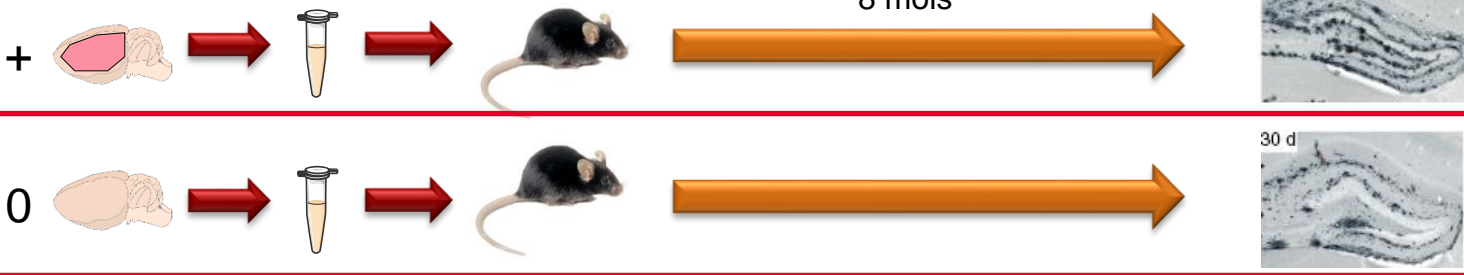


Deuxième transmission

APP23: Modèle d'amyloïdose

8 mois

APP-/-

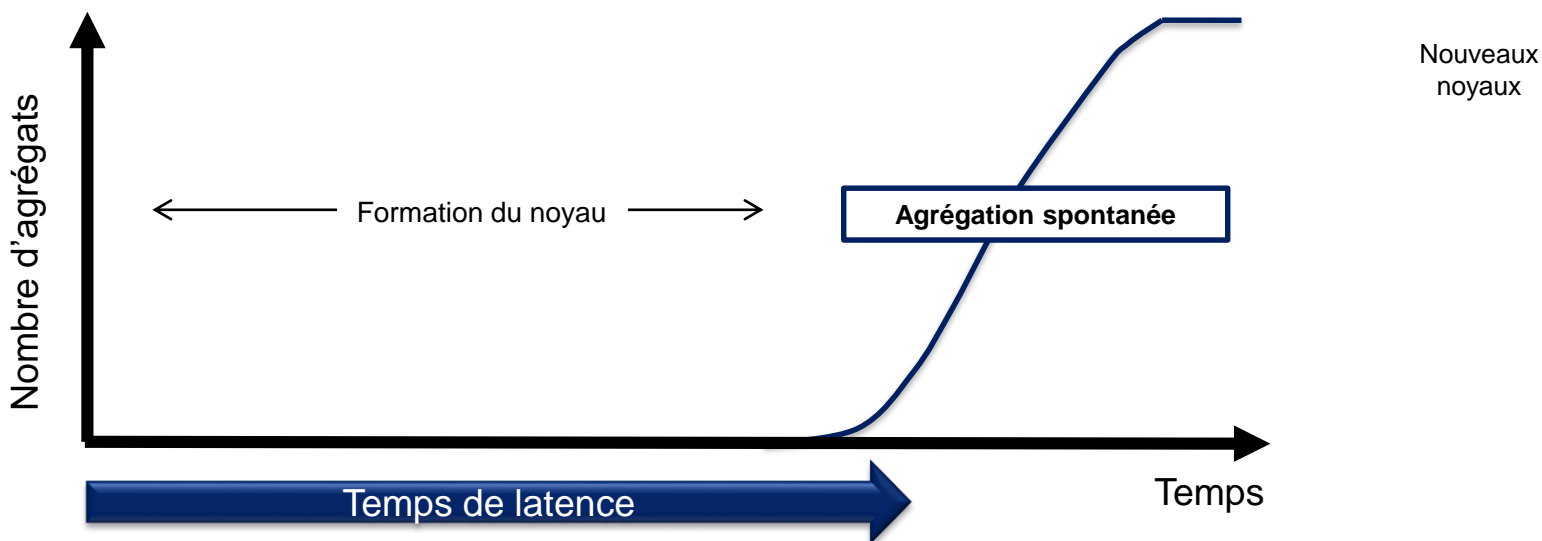
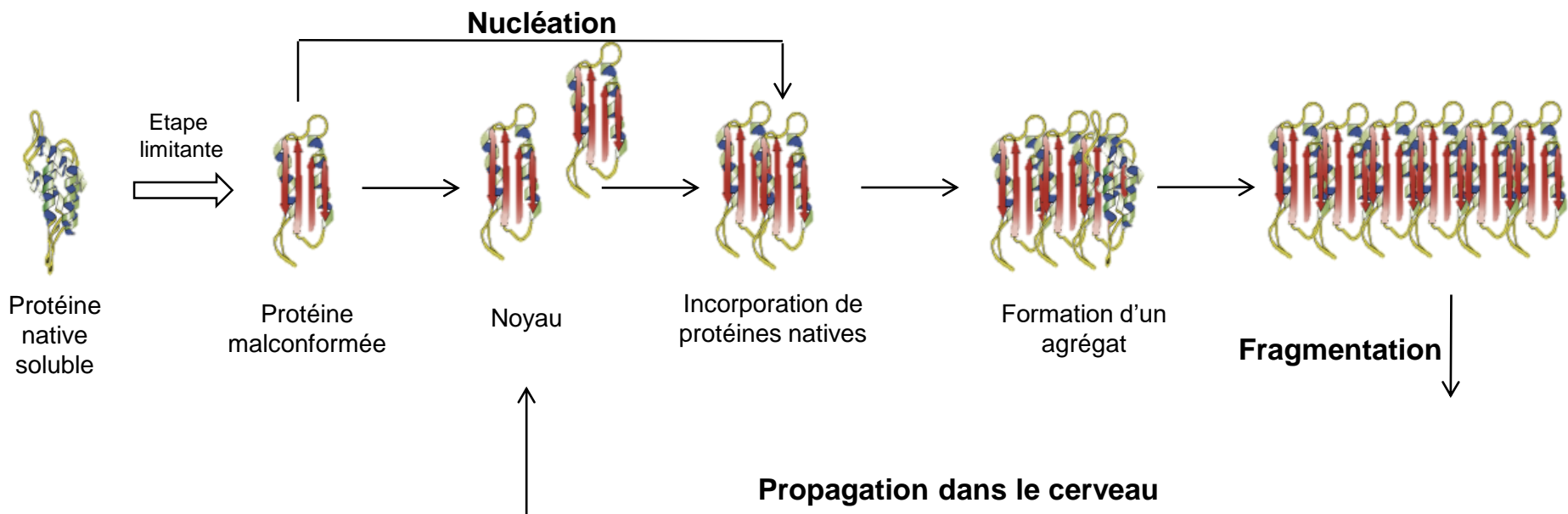


Ye et al,
Nature Neuroscience, 2015

ORIGIN

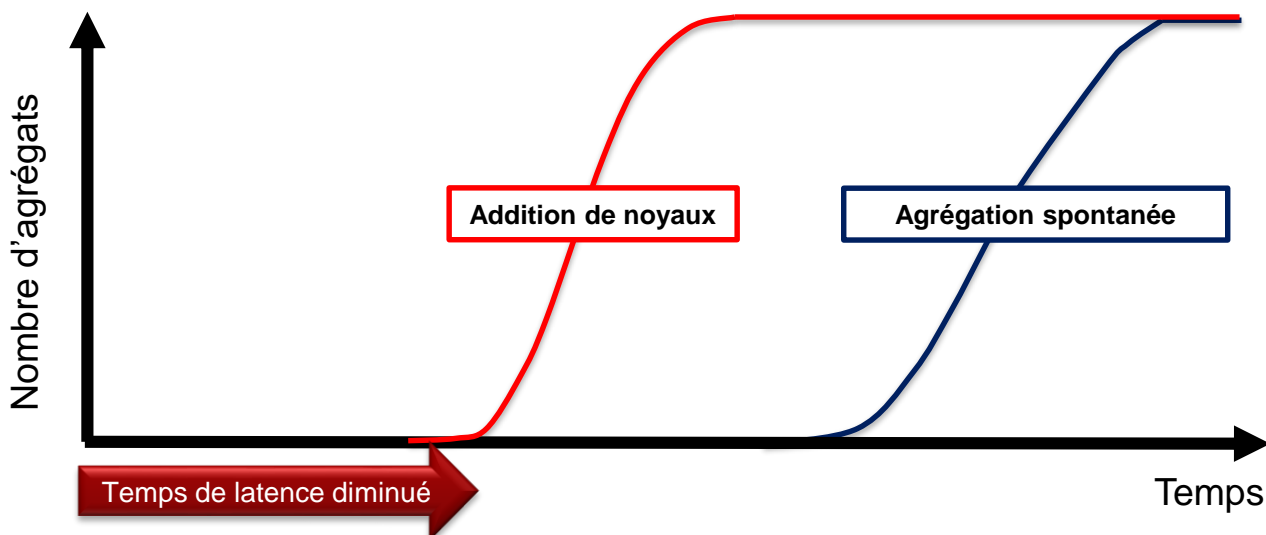
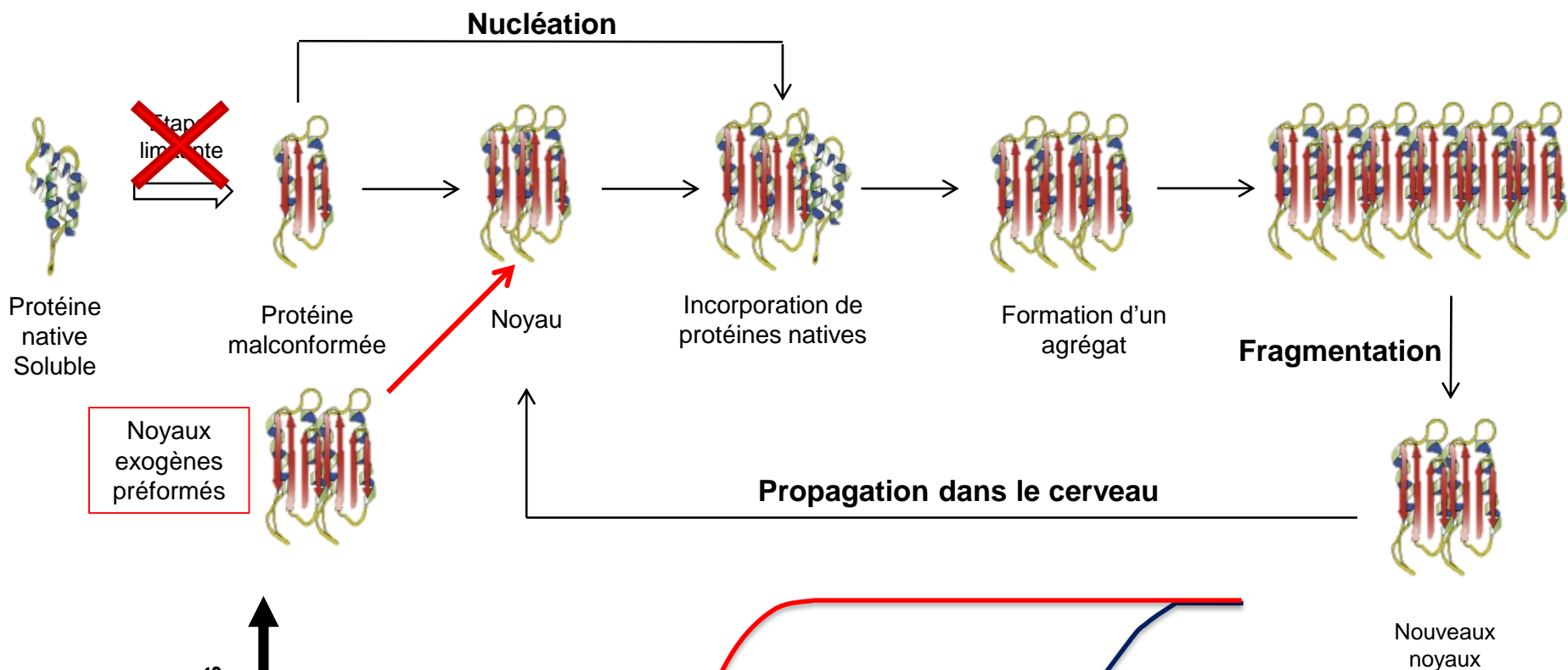
HYPOTHESE PRION

MÉCANISMES DE NUCLÉATION/PROPAGATION



HYPOTHESE PRION

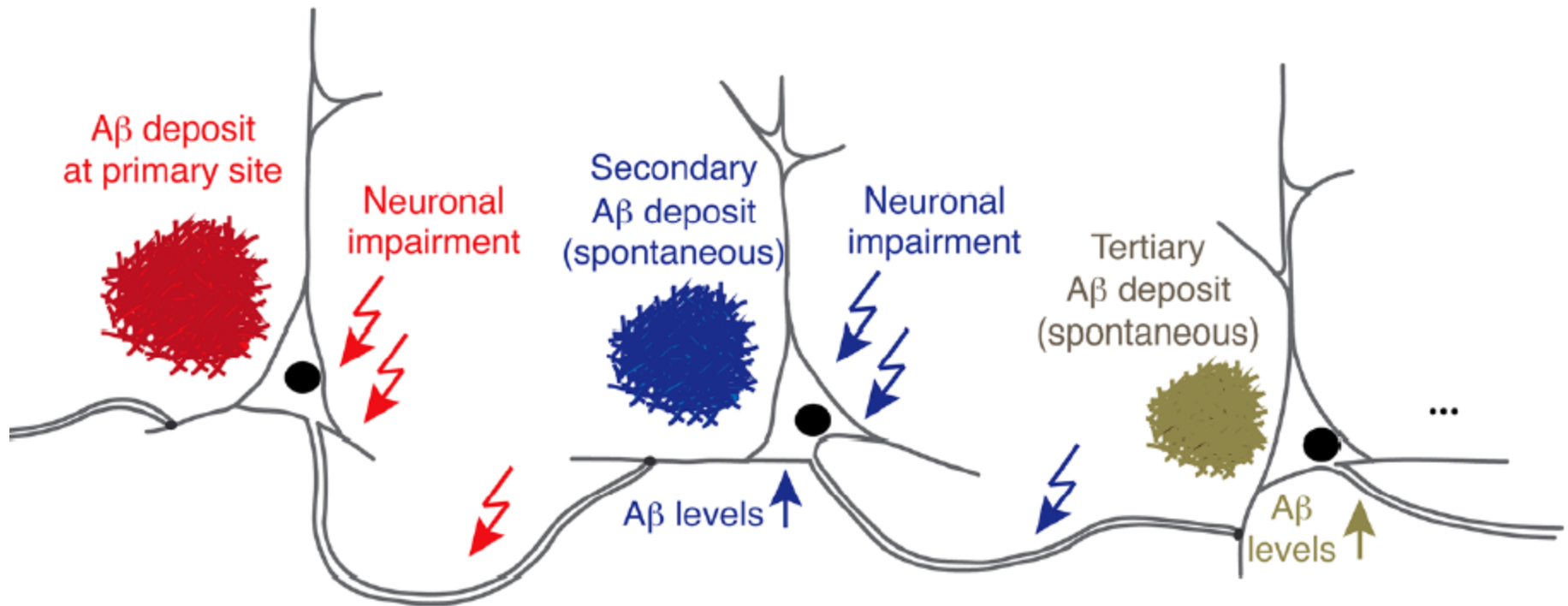
MÉCANISMES DE NUCLÉATION/PROPAGATION



HYPOTHESE

SYNTHESE D'AMYLOÏDE EN REPONSE A UNE SOUFFRANCE CELLULAIRE

Indirect effect: neuronal impairment leads to increased A β levels



Eisele YS, Duyckaerts C (2016)

Propagation of A β pathology: hypotheses, discoveries, and yet unresolved questions from experimental and human brain studies. *Acta Neuropathol* 131: 5-25.

L'HYPOTHESE IMMUNOLOGIQUE ARIA

Amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with bapineuzumab: a retrospective analysis



Reisa Sperling, Stephen Salloway, David J Brooks, Donatella Tampieri, Jerome Barakos, Nick C Fox, Murray Raskind, Marwan Sabbagh, Lawrence S Honig, Anton P Porsteinsson, Ivan Lieberburg, H Michael Arrighi, Kristen A Morris, Yuan Lu, Enchi Liu, Keith M Gregg, H Robert Brashear, Gene G Kinney, Ronald Black, Michael Grundman

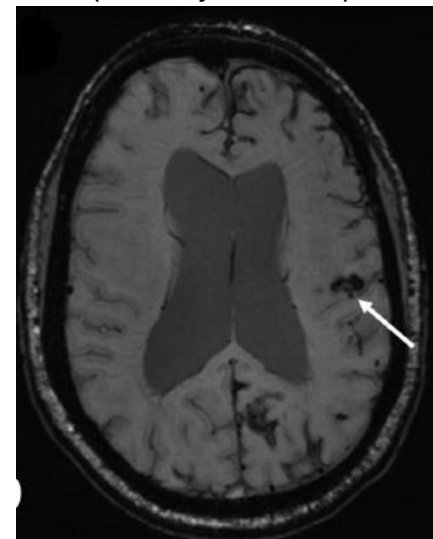
Summary

Background Amyloid-related imaging abnormalities (ARIA) have been reported in patients with Alzheimer's disease *Lancet Neurol* 2012; 11: 241-49

ARIA-H: Microhemorrhages



Patient with dura matter graft
(Banerjee 2019)



CONCLUSION

- Identification de transmission iatrogène de lésions associées à la maladie d'Alzheimer
 - Angiopathie amyloïde iatrogène
 - Autres formes possibles
- Risque associé aux greffes de dure mère et d'hormone de croissance est derrière nous

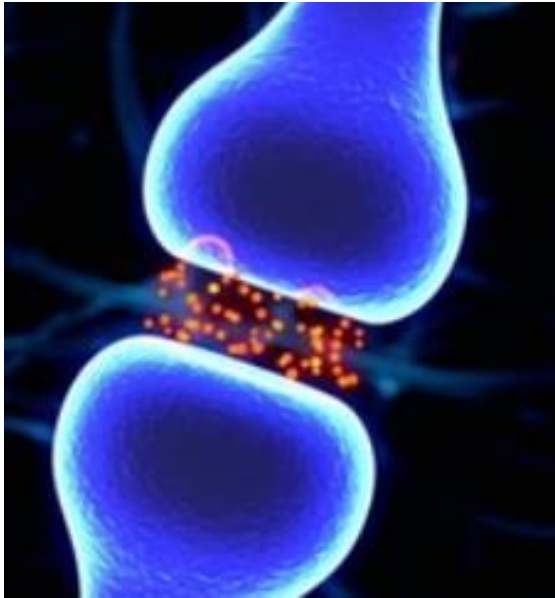


Angiopathie iatrogène → ●

PERSPECTIVES

"OUTILS" POUR ÉTUDIER LES MALADIES NEURODÉGÉNÉRATIVES

Inoculation de cerveaux Alzheimer module les synapses et la tauopathie



Explication de l'hétérogénéité de la maladie d'Alzheimer

- ° Atteinte différentielle des synapses
- ° Explication de l'épilepsie liée à la maladie d'Alzheimer

ACKNOWLEDGMENTS

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Fanny Petit

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Sebastien Piluso

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Charlotte Gary

Clément Garin

Nachiket Nadkarni

Salma Bougacha

James Koch

Lisa Ciaptacz

Zoé Hanss

Clemence Duffeffant

Michel Vandenberghe

Yael Balbastre

Zhenzhen You

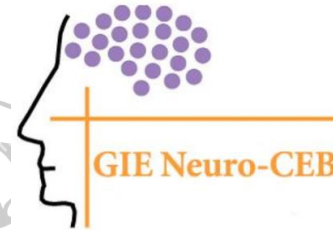
Clément Bouvier

Cedric Clouchoux



MIIND

Multimodal Imaging of
Neurodegenerative Diseases
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DON DU CERVEAU
POUR LA RECHERCHE



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