

IPFA/PEI 28th International Workshop on Surveillance and Screening of Blood-borne Pathogens

21 & 22 September 2022 | Porto, Portugal



**Donnons
au sang**
*Le pouvoir
de soigner*

Development of diagnostic tests for vCJD and other proteinopathies

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UMR 1058 Pathogénèse et Contrôle des Infections Chroniques et Emergentes
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WHAT ARE PRIONS ?

- Responsible for **Transmissible Spongiform Encephalopathies / prion diseases**

Slow, fatal, untreatable, transmissible neurodegenerative diseases



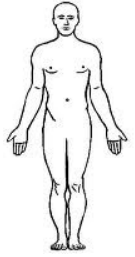
scrapie



BSE



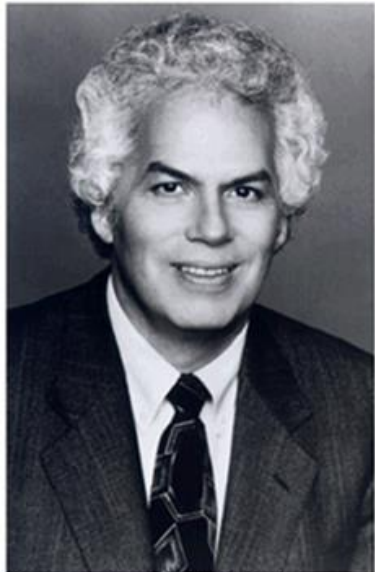
CWD



CJD

- A nonconventional agent : **an infectious protein...**

No immune response by the host / No nucleic acid



Stanley Prusiner - Prix Nobel 1997

Normal protein

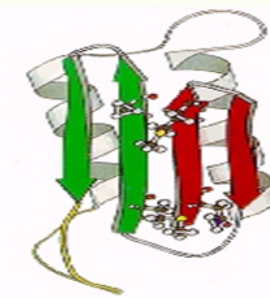


PrP^C

α - helix = 42 %
 β - sheet = 3 - 5 %

Misfolding

Infectious protein



PrP^{Sc} ou PrP^{TSE}

α - helix = 30 %
 β - sheet = 43 %

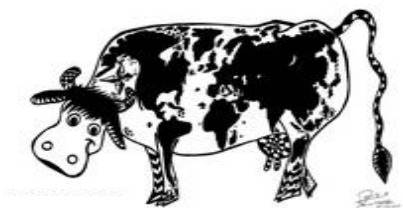
- Aggregation into amyloid structures
- Resistance to protease K → detection
- Hard to decontaminate



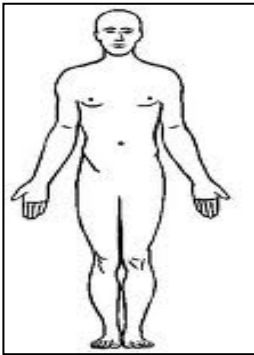
Prion rods

Prusiner et al., (1983), Cell, 35, 349-358

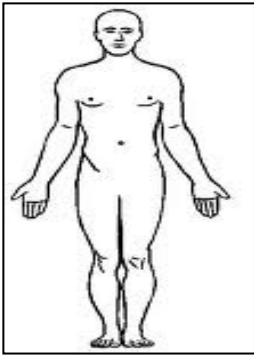
vCJD AND BLOOD SAFETY



BSE



vCJD



3 vCJD cases
+ 2 asymptomatic

VARIANT CJD CASES WORLDWIDE 5/7/2022			
COUNTRY	TOTAL NUMBER OF PRIMARY CASES (NUMBER ALIVE)	TOTAL NUMBER OF SECONDARY CASES: BLOOD TRANSFUSION (NUMBER ALIVE)	RESIDENCE IN UK > 6 MONTHS DURING PERIOD 1980-1996
UK	175 (0)	3 (0)	178 [§]
France	29 (0)	-	1
Republic of Ireland	4 (0)	-	2
Italy	3 (0)	-	0
U	233 cases worldwide		
C			
Saudi Arabia	1 (0)	-	0
Japan	1* (0)	-	0
Netherlands	3 (0)	-	0
Portugal	2 (0)	-	0
Spain	5 (0)	-	0
Taiwan	1 (0)	-	1

→ vCJD ∈ Red Agent (AABB classification, S Stramer et al. 2009)

→ Prevalence : UK 1/2 000 (95% IC : 1/3500 - 1/250)

France : 1/20 000 (estimated)

vCJD AND BLOOD SAFETY : preventive measures

- Donor deferral

Growth hormone treatment, history of transfusion, residence in the UK > 1 year ...



In place
France

- Leukoreduction

RBC and platelets 1998 – plasma 2001

OPEN ACCESS Freely available online

PLOS one

Impact of Leucocyte Depletion and Prion Reduction Filters on TSE Blood Borne Transmission

Caroline Lacroux¹, Daisy Bougard², Claire Litaize¹, Hugh Simmons³, Fabien Corbiere¹, Dominique Dernis⁴, René Tardivel⁵, Nathalie Morel⁶, Stephanie Simon⁶, Séverine Lugan¹, Pierrette Costes¹, Jean Louis Weisbecker⁷, François Schelcher¹, Jacques Grassi⁶, Joliette Coste², Olivier Andréoletti^{1*}



Removal



Screening

Under
development

VoxSanguinis

The International Journal of Transfusion Medicine

INTERNATIONAL FORUM

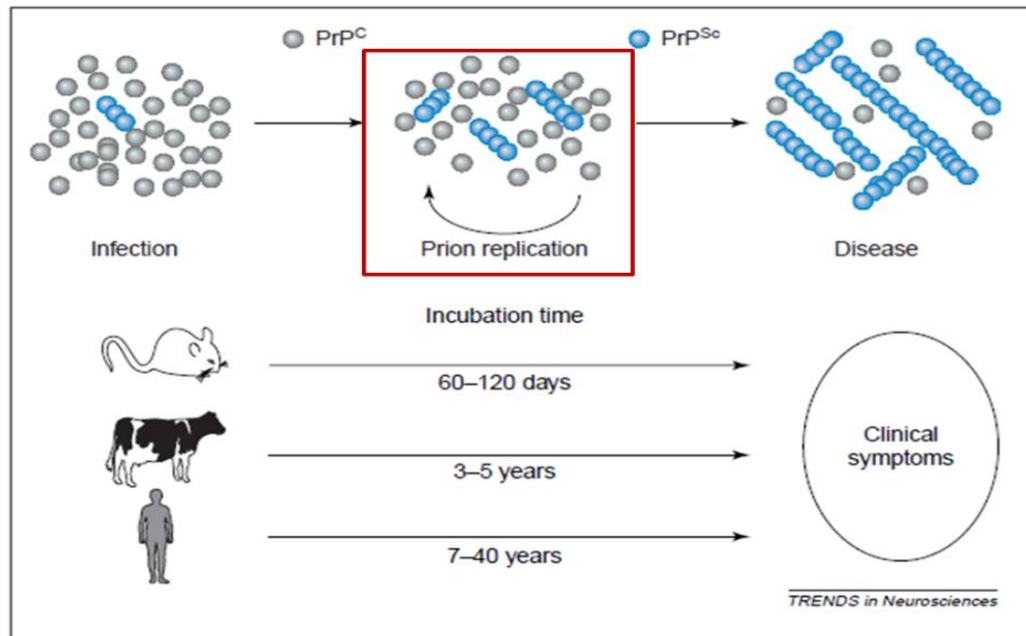
Prion reduction of red-blood-cells

J. Coste, C. Prowse, C. Grabmer, H. Schennach, P. Santos Prado Scuracchio, S. N. Wendel, M. Germain, G. Delage, T. Krusius, S. Ekblom-Kullberg, P. Tiberghien, J. O’Riordan, W. G. Murphy, Ø. Flesland, M. Turner, L. Williamson, L. Gregori, J. Epstein, D. Asher, S. Panzer & H. W. Reesink

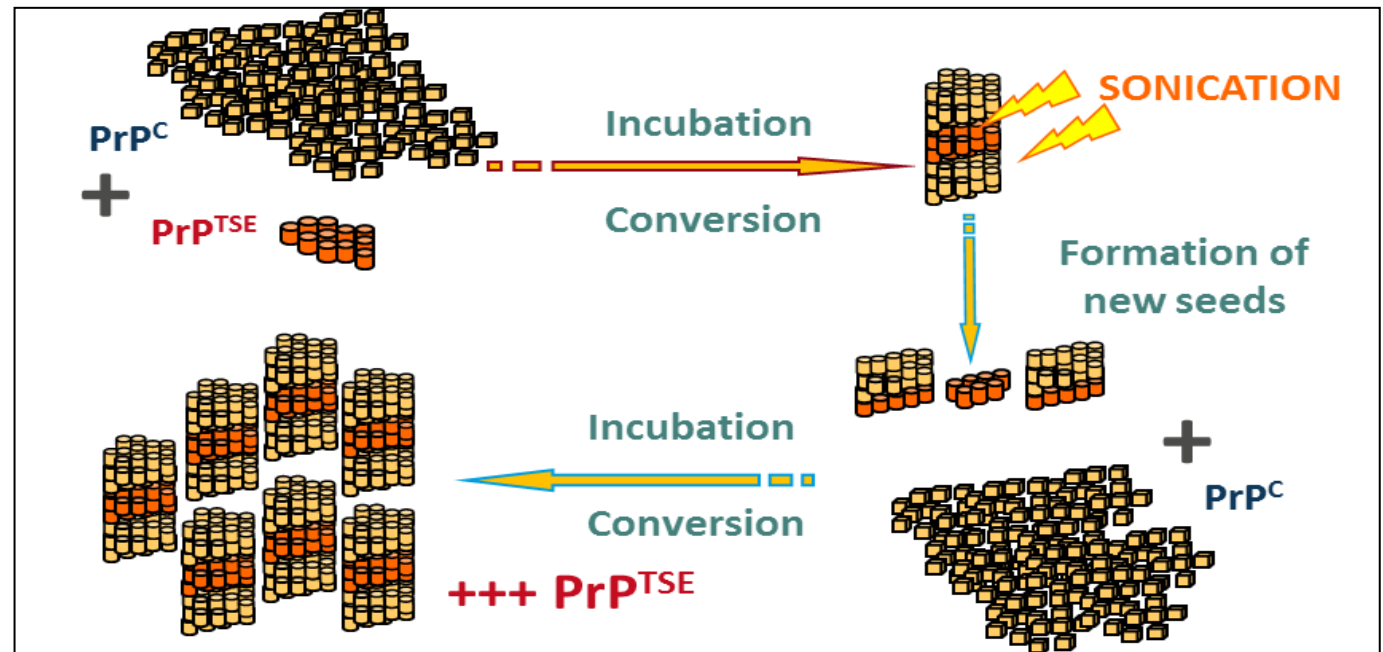
Need for a blood detection assay

DETECTION of vCJD : AMPLIFICATION

Prion replication during the incubation of disease



Protein Misfolding Cyclic Amplification (PMCA)

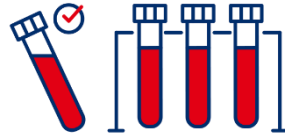


« Cyclic amplification of protein misfolding : application to prion-related disorders and beyond »

C Soto et al. Trends in Neurosciences, 2002 ; 25 : 390-394

DETECTION of vCJD IN BLOOD

A three-step assay :



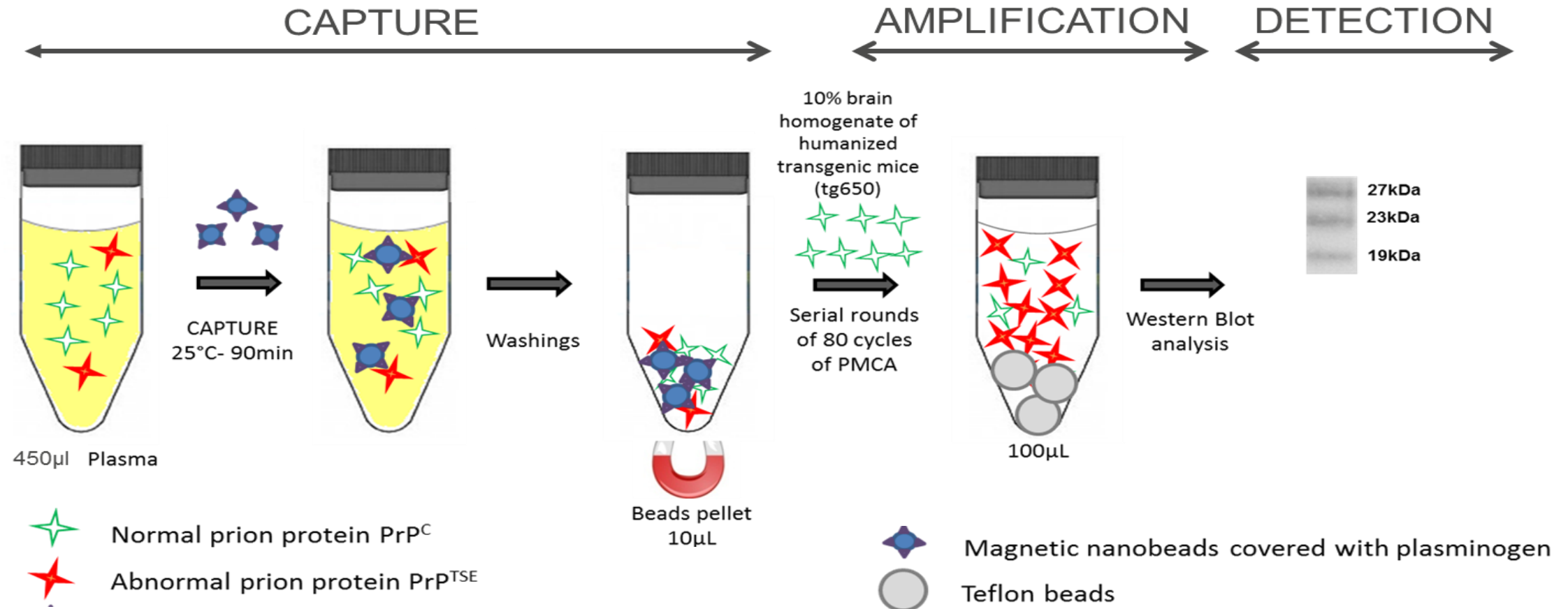
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

PRION DISEASES

Detection of prions in the plasma of presymptomatic and symptomatic patients with variant Creutzfeldt-Jakob disease

Daisy Bougard,^{1*} Jean-Philippe Brandel,^{2,3,4} Maxime Bélonrdade,¹ Vincent Béringue,⁵ Christiane Segarra,¹ Hervé Fleury,⁶ Jean-Louis Laplanche,^{4,7} Charly Mayran,¹ Simon Nicot,¹ Alison Green,⁸ Arlette Welaratne,³ David Narbey,⁹ Chantal Fournier-Wirth,¹ Richard Knight,⁸ Robert Will,⁸ Pierre Tiberghien,^{9,10} Stéphane Haïk,^{2,3,4} Joliette Coste^{1,9*}

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American Association
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of Science.



DETECTION of vCJD IN BLOOD

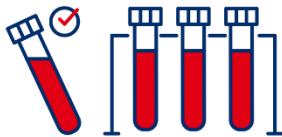


	Diagnosis	Patients with positive detection of Pr ^{TSE} in plasma samples no./total no.	Analytical performance % (95%CI)
Clinical CJD	Variant CJD	18/18	<i>Diagnostic sensitivity</i> 100% (81.5 - 100)
	Sporadic CJD	1/67	<i>Analytical specificity</i> 99.2% (95.9 - 100)
non CJD	Other neurodegenerative diseases	0/15	
	Alzheimer's disease	0/9	
	Lewy body dementia	0/3	
	Parkinson's disease	0/2	
	Fronto-temporal dementia	0/1	
	Other non-neurodegenerative diseases	0/52	
	Metabolic and toxic encephalopathies	0/14	
	Paraneoplastic encephalitis and cancer	0/12	
	Neurovascular disease	0/7	
	Infectious diseases	0/6	
	Autoimmune encephalopathies	0/3	
	Other disorders**	0/10	
Blood donors	Healthy controls From US (S Stramer)	0/104 0/112	<i>Diagnostic specificity</i> 100% 98.3 (96.5 - 100)

→ Presence of PrP^{TSE} in the plasma of all vCJD clinical cases

→ BEFORE ???

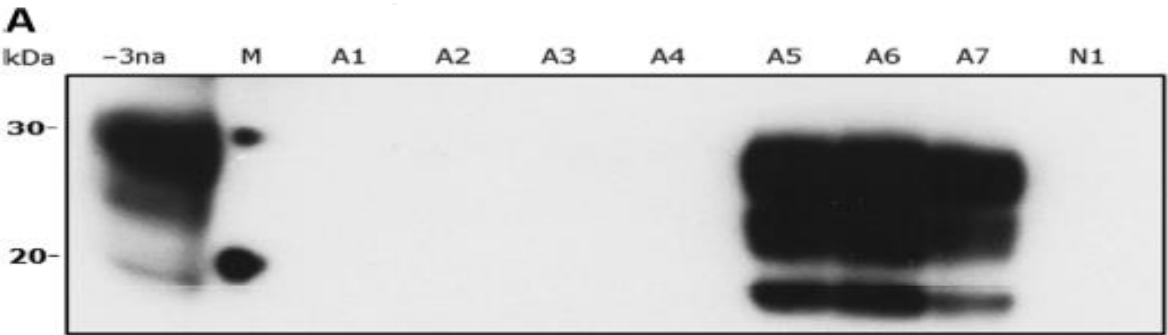
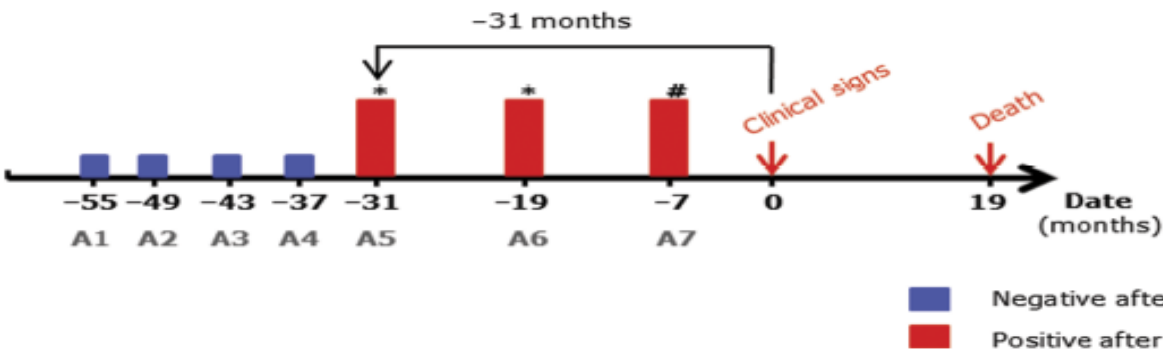
DETECTION of vCJD IN BLOOD : preclinical detection



France : 29 vCJD cases → 3 blood donors → 11 sequential archived plasma samples

Donor A

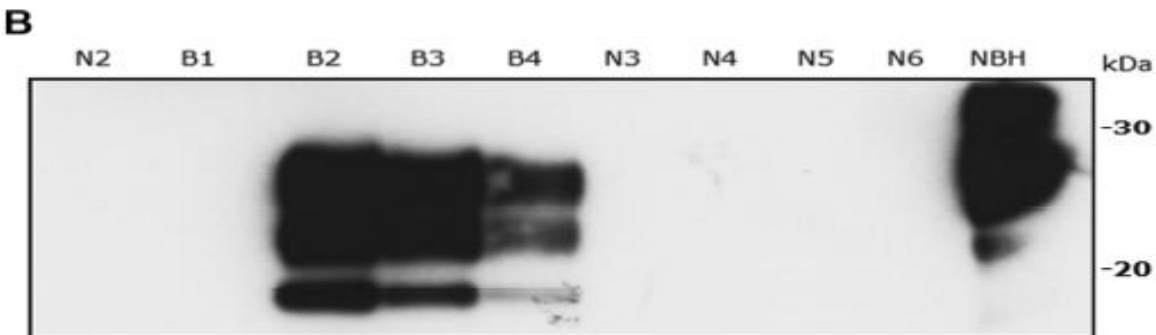
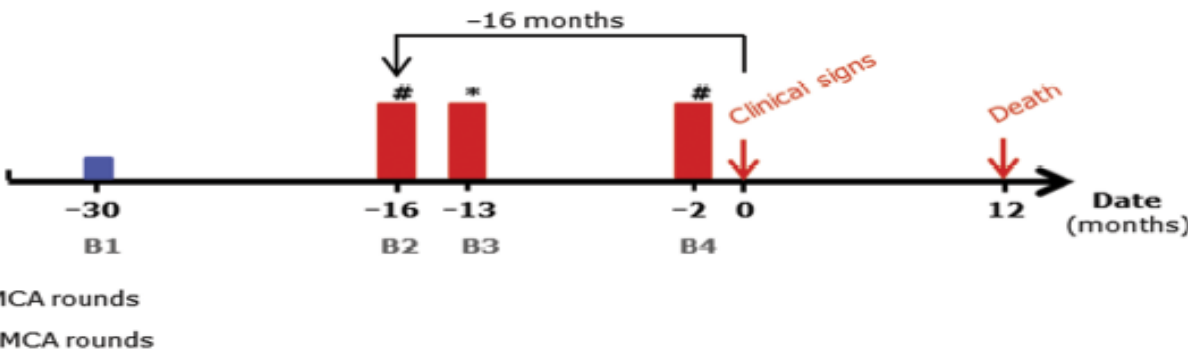
7 sequential plasma A1 to A7



- 2.6 years

Donor B

4 sequential plasma B1 to B4



- 1.3 years

DETECTION of vCJD IN BLOOD



2020

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE



Variant Creutzfeldt–Jakob Disease Diagnosed 7.5 Years after Occupational Exposure

N ENGL J MED 383;1 NEJM.ORG JULY 2, 2020

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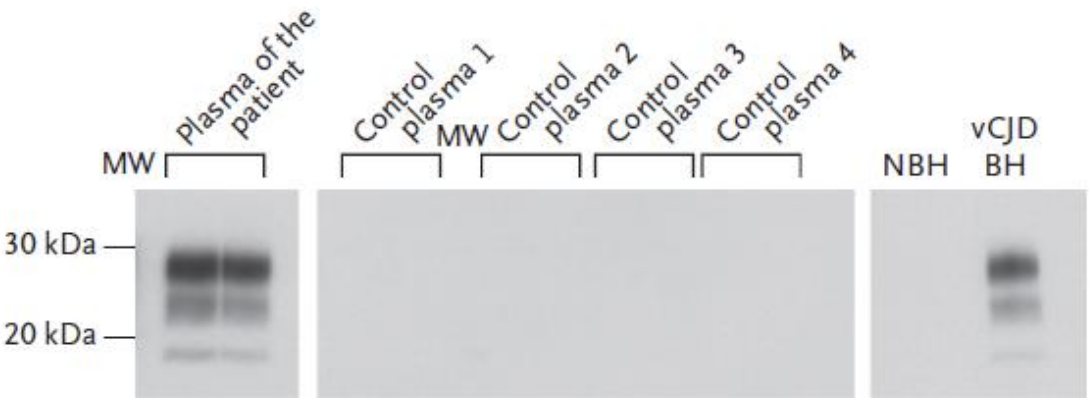
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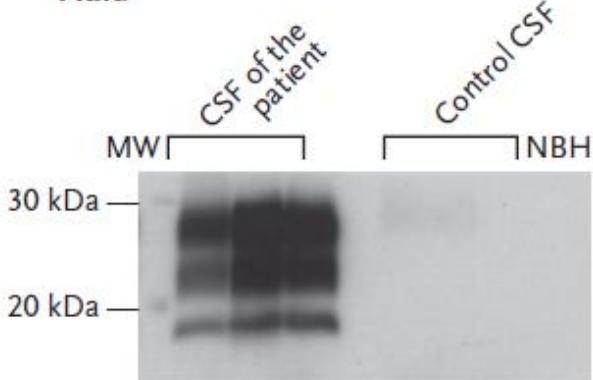
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A Abnormal Prion Protein in Plasma



B Abnormal Prion Protein in Cerebrospinal Fluid



CONCLUSIONS – PERSPECTIVES vCJD

- vCJD diagnostic assay available in the blood
- Able to detect before clinical signs

➡ **Diagnosis ante-mortem possible**

➡ **Risk assessment (prevalence / high-risk population)**

PERSPECTIVES « Prions »

Detection of Infectivity in Blood of Persons with Variant and Sporadic Creutzfeldt-Jakob Disease

Jean Yves Douet, Saima Zafar,
Armand Perret-Liaudet, Caroline Lacroux,
Séverine Lugan, Naima Aron, Herve Cassard,
Claudia Ponto, Fabien Corbière,
Juan Maria Torres, Inga Zerr,
and Olivier Andreoletti

Emerg Infect Dis 2014

SYNOPSIS

Sporadic Creutzfeldt-Jakob Disease in 2 Plasma Product Recipients, United Kingdom

Patrick Urwin, Kumar Thanigaikumar, James W. Ironside, Anna Molesworth, Richard S. Knight,
Patricia E. Hewitt, Charlotte Llewelyn, Jan Mackenzie, Robert G. Will

Emerg Infect Dis 2017

Sporadic CJD & blood ?

PROTEINOPATHIES

Neurodegenerative Diseases: Expanding the Prion Concept

Lary C. Walker^{1,2} and Mathias Jucker^{3,4}
Annu. Rev. Neurosci. 2015

NEURODEGENERATION

Alzheimer's and Parkinson's diseases: The prion concept in relation to assembled A β , tau, and α -synuclein

Michel Goedert* *Science*, 08/07/2015

LETTER

Nature, 09/10/2015

doi:10.1038/nature15369

Evidence for human transmission of amyloid- β pathology and cerebral amyloid angiopathy

Zane Jaunmuktane¹, Simon Mead^{2,3,4}, Matthew Ellis³, Jonathan D. F. Wadsworth^{2,3}, Andrew J. Nicoll^{2,3}, Joanna Kenny^{2,4},
Francesca Launbury³, Jacqueline Linehan², Angela Richard-Loendt³, A. Sarah Walker⁵, Peter Rudge^{2,4},
John Collinge^{2,3,4} & Sebastian Brandner^{1,2,3}

Session 14 - Blood safety - Infectious perspectives 2022

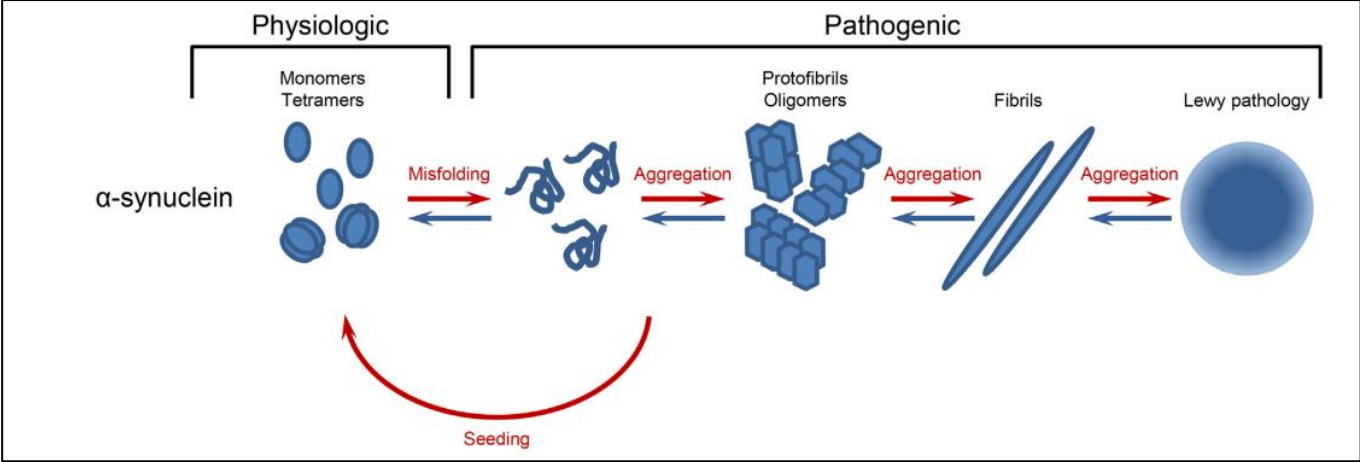
Association between the occurrence of intracerebral haemorrhage in blood donors and their recipients: Evidence of possible transfusion-transmitted cerebral amyloid angiopathy?

J. Zhao¹, E. Lauwers², K. Rostgaard³, T. Dahlén¹, B. De Strooper^{2,4,5}, R.
Lemmens^{2,4,6}, H. Hjalgrim^{3,7,8}, G. Edgren¹

Proteinopathy	Aggregated proteins	Diseases (examples)
Prion diseases	PrP	CJD , Kuru, GSS
Synucleinopathies	Alpha-synuclein	Parkinson's disease Multiple system atrophy
Tauopathies	Tau	Alzheimer's disease Pick's disease
B-amyloid pathologies	A β	Alzheimer's disease Cerebral amyloid angiopathy

- No blood test
- No treatment
- Inter-human transmissibility ??

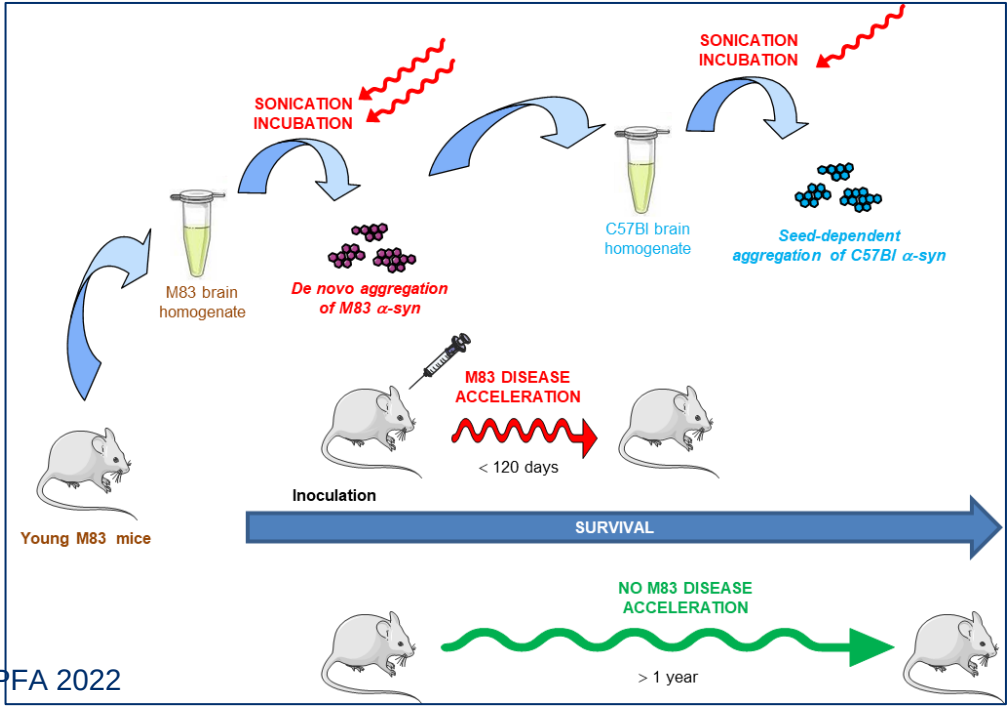
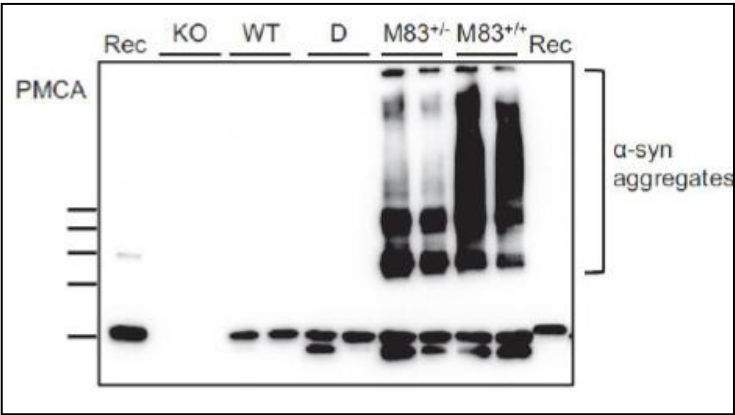
PROTEINOPATHIES : detection of α -synuclein



Seeded propagation of α -synuclein aggregation in mouse brain using protein misfolding cyclic amplification

Simon Nicot,* J  r  my Verch  re,* Maxime B  londrade,* Charly Mayran,* Dominique B  temps,* Daisy Bougard,* and Thierry Baron*¹

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PROTEINOPATHIES : conclusions – future developments

- amplification of α -syn was obtained

- ➡ Development of a blood-detection assay

- ➡ Evaluation of the possible transfusion-transmission of alpha-synuclein pathologies

- ➡ Application to Tau and A β

- ➡ **surveillance ...**