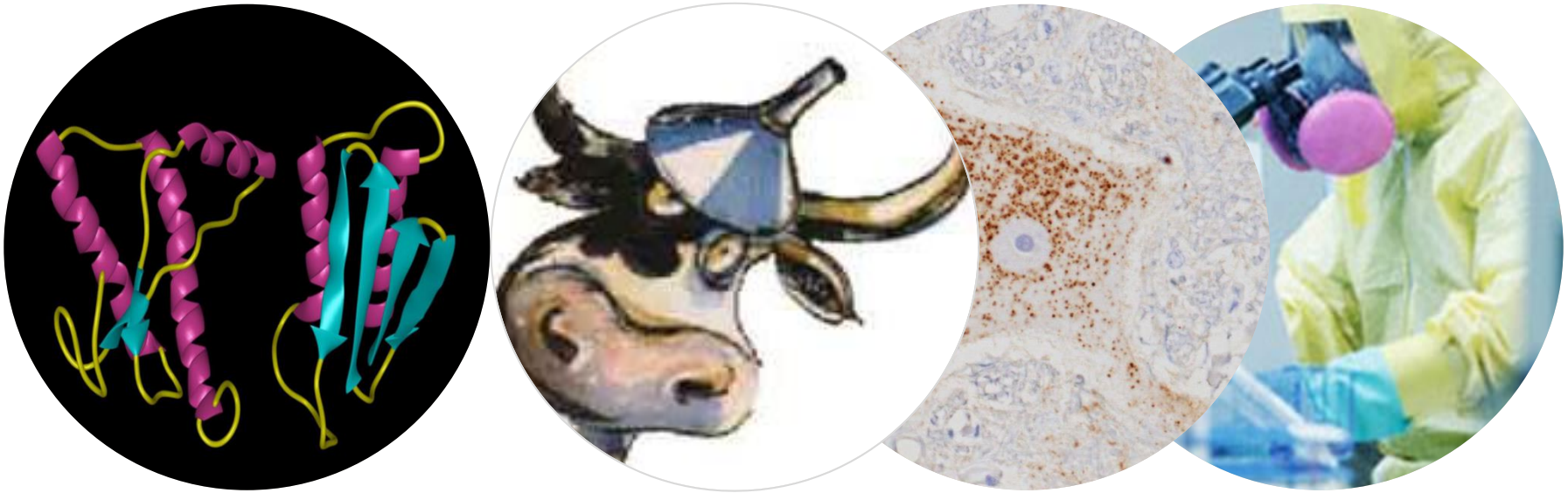
Gut: the gateway for prions to the Central Nervous System

Mini-symposium *Gut to Brain*, 15 May 2017

Alex Bossers, Wageningen Bioveterinary Research (WBVR)



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The Gut-Brain connection

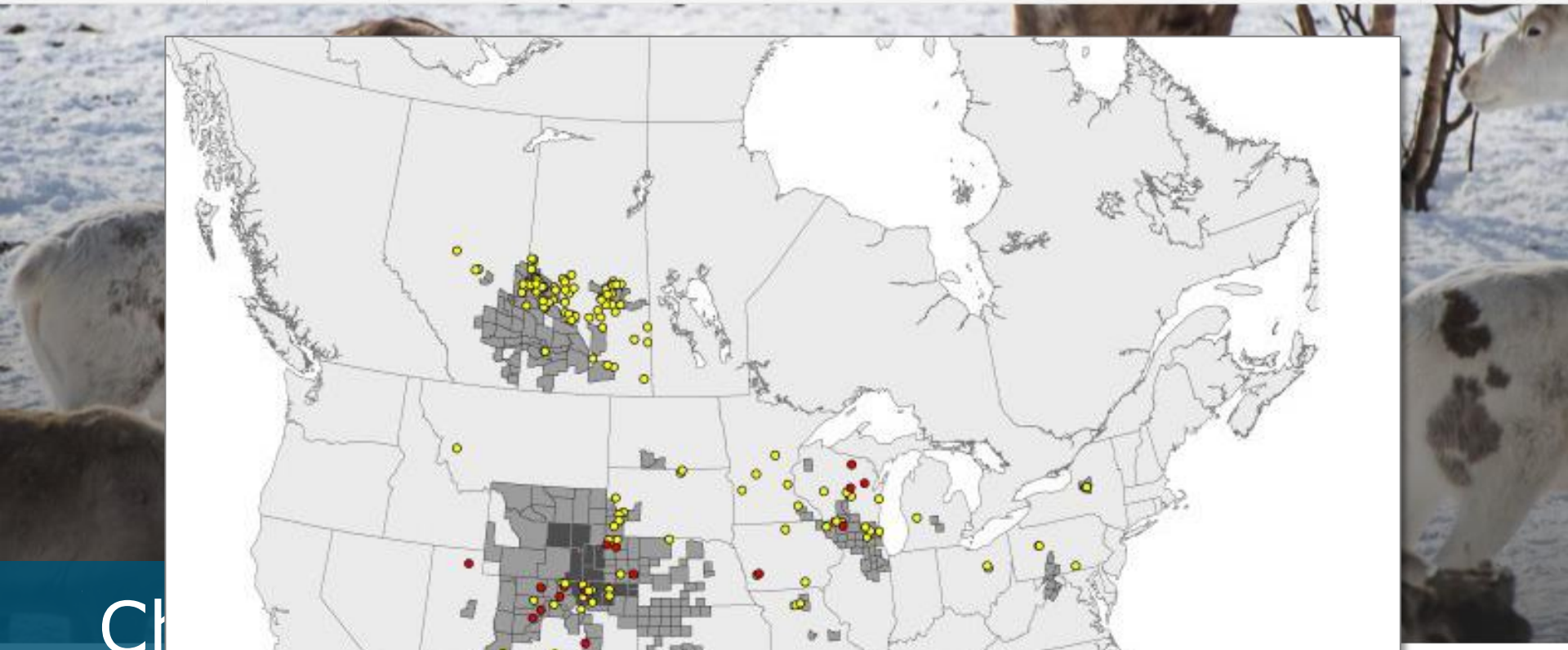
Prions...
Disease of Brain

BSE and scrapie
under control

Chronic Wasting Disease
came to Europe

NO
cure or vaccine

Prevention...
Role for the gut?



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Het ministerie van Landbouw heeft de opdracht gegeven om de kudde

Transmissible Spongiform Encephalopathies or Prion Diseases

Phenotypic expressions

Infectious forms

Creutzfeldt-Jacob Disease (iCJD/vCJD)	Human
Kuru	Human
Scrapie	Sheep/Goat
Bovine Spongiform Encephalopathy (BSE)	Cattle
Feline Spongiform Encephalopathy (FSE)	Cats
Chronic Wasting Disease (CWD)	Deer/Elk
Transmissible Mink Encephalopathy (TME)	Mink

'Genetic' forms

Creutzfeldt Jacob Disease (fCJD)	Human
Gerstmann-Straussler-Scheinker Syndrom (GSS)	Human
Fatal Familial Insomnia (FFI)	Human

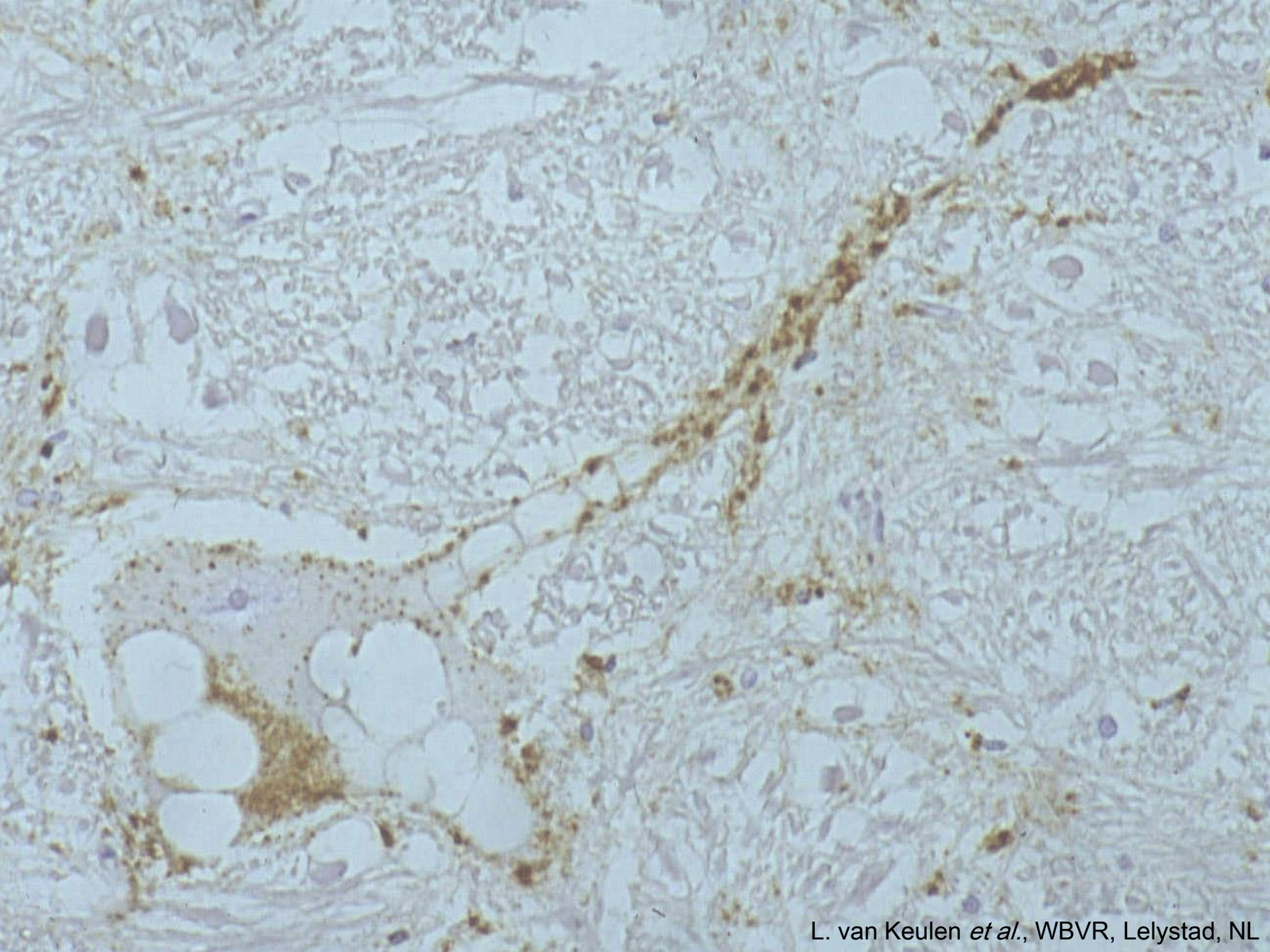
Sporadic forms

Creutzfeldt Jacob Disease (sCJD)	Human

Characteristics of prion diseases

- Neurodegeneration and vacuolization in the CNS
- Transmissible
- Protein misfolding disease
- Precipitation of pathological folded **host** protein (PrP)

- Disease is progressive and always fatal
- Long incubation periods



L. van Keulen *et al.*, WBVR, Lelystad, NL

Characteristics of the infectious TSE agent

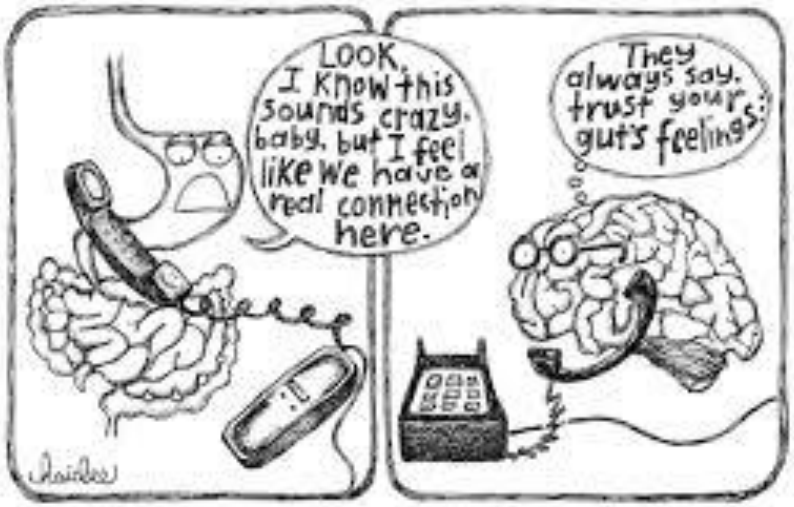
- Transmissible (natural/experimental)
- No prion agent-specific nucleic acid found
- Extreme resistant (heat, radiation, nucleic acid degradation)

- Enrichment for prion protein (PrP) increases agent titre
- Amplification (*in vitro*) of prion protein isoforms replicates infectivity

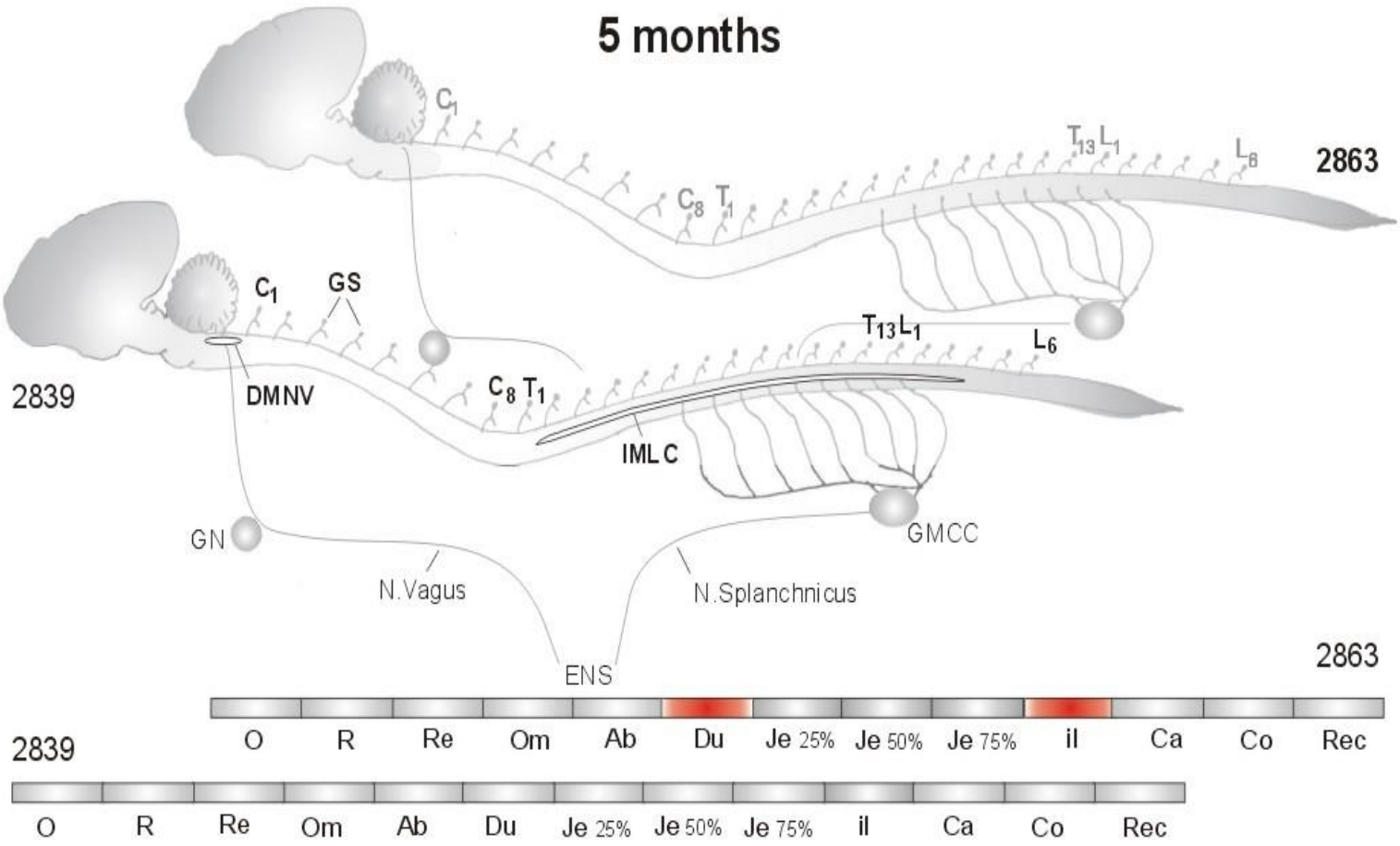
- TSE agent is largely if not entirely composed of abnormal forms of the host-encoded PrP (PrP^{Sc}). CONCEPT: infectious misfolded protein

PATHOGENESIS

How the gut and brain connect



PrP deposition within the ENS



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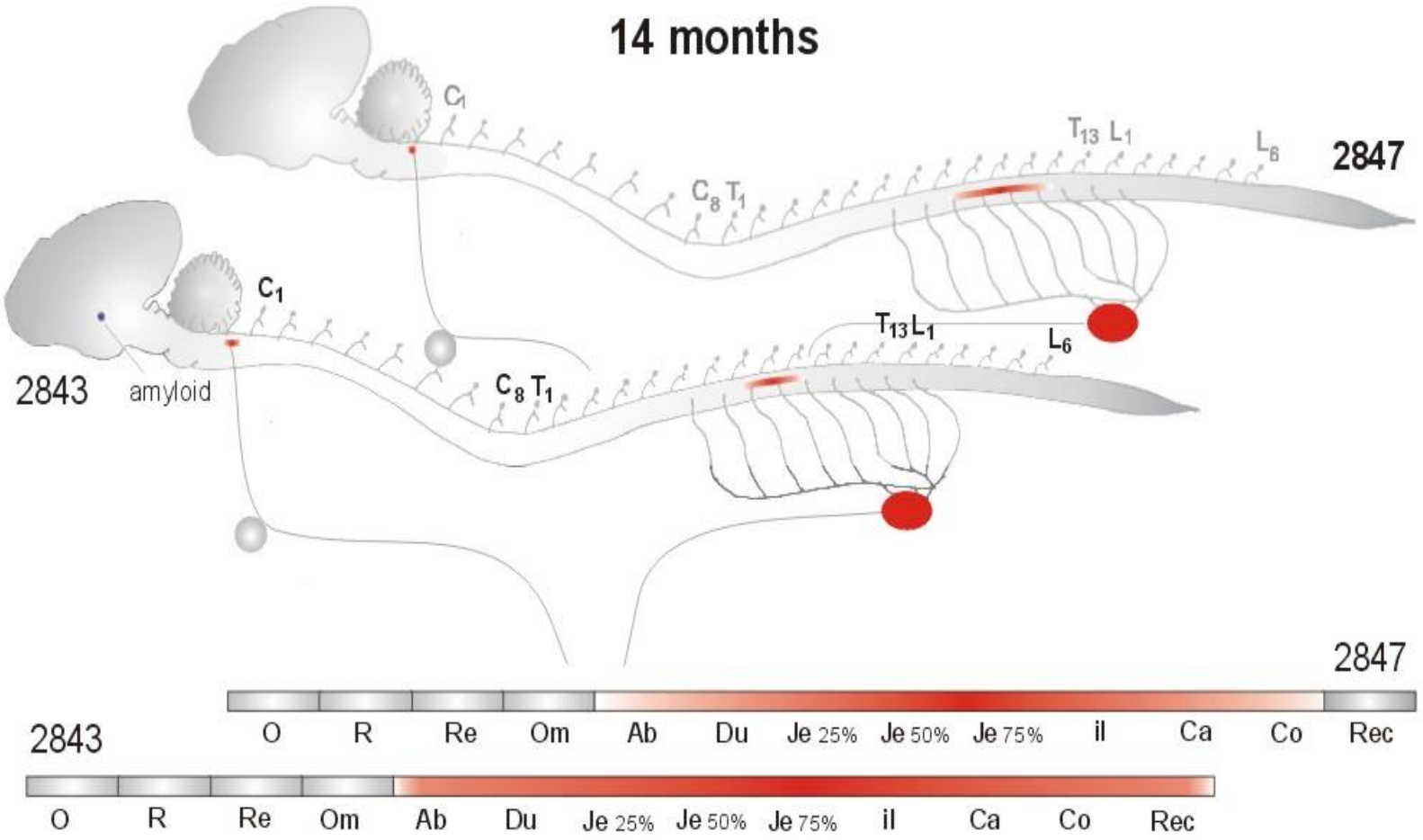
L. Van Keulen *et al.*

PrP deposition within the ENS & CNS



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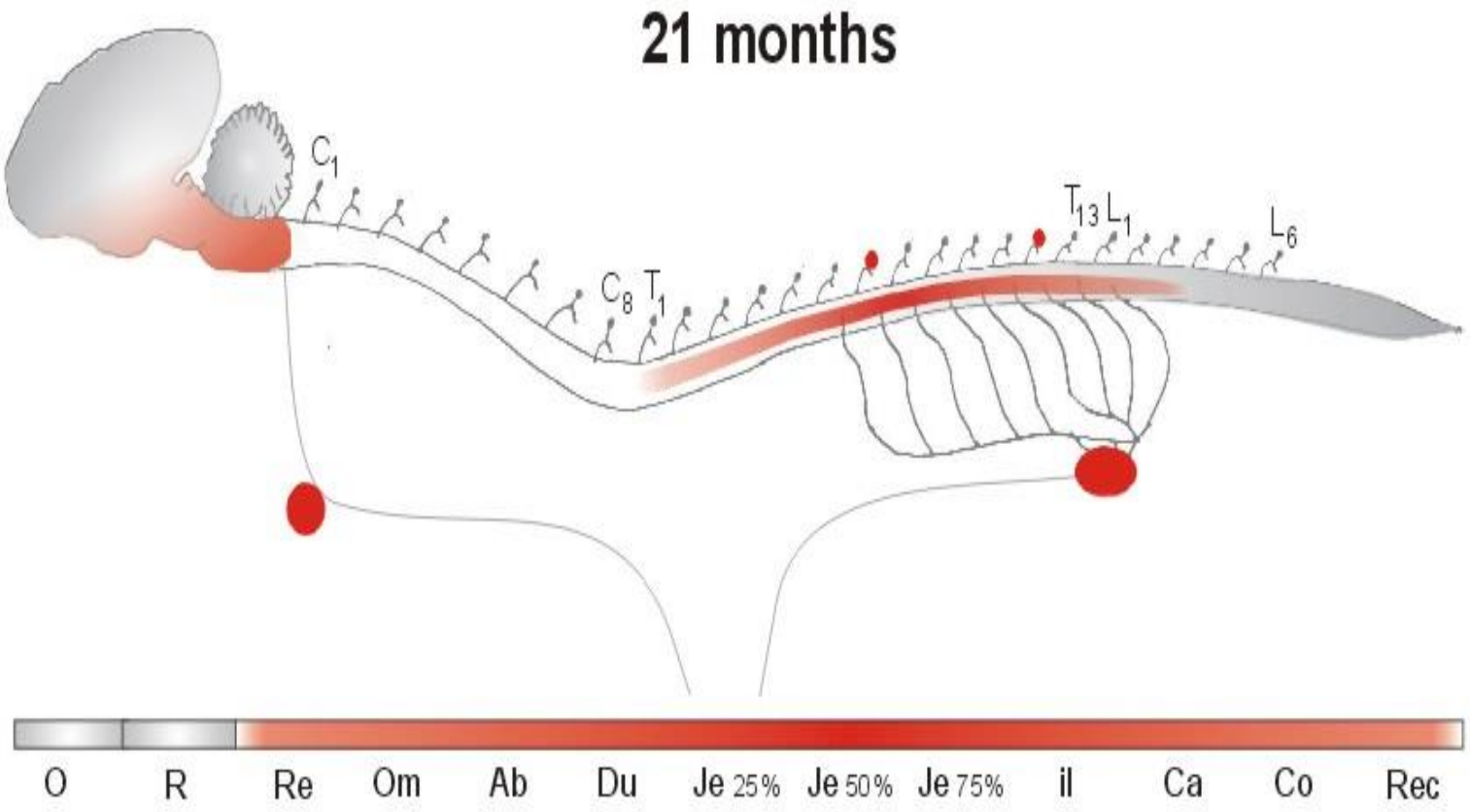
L. Van Keulen *et al.*

PrP deposition within the ENS & CNS



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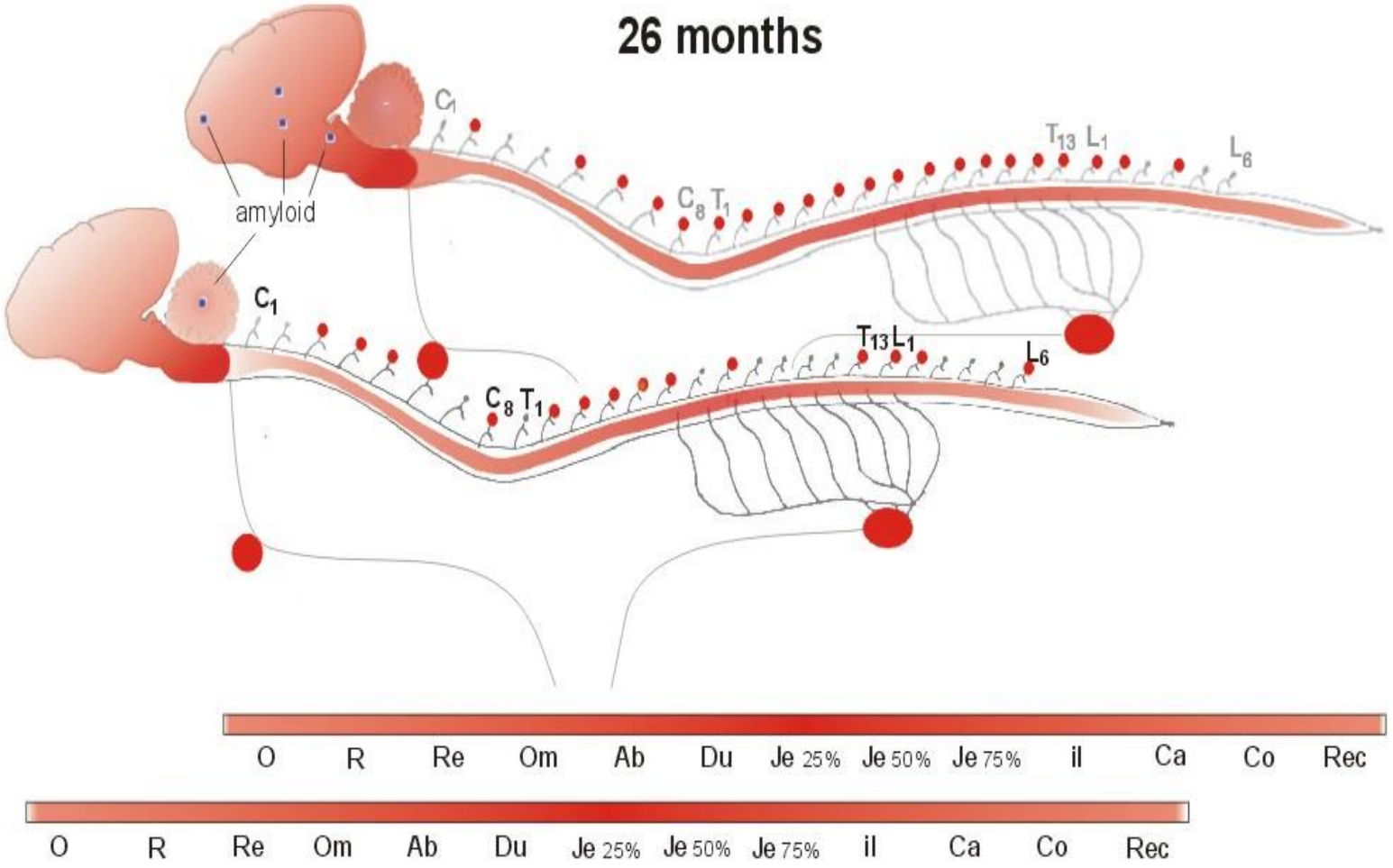
L. Van Keulen *et al.*

PrP deposition within the ENS & CNS

Clinical end point



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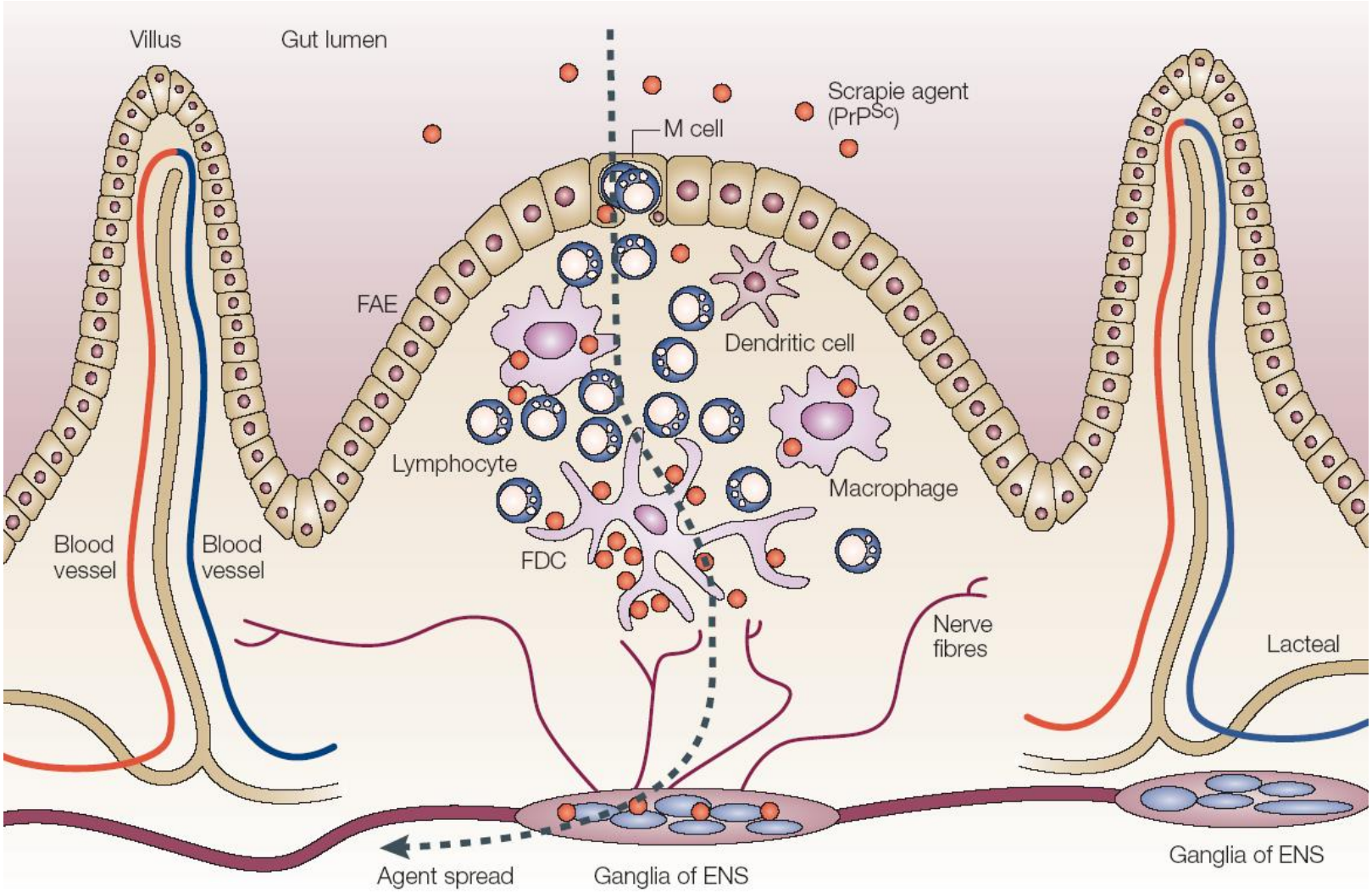
L. Van Keulen *et al.*

Entry of TSE agent at cellular level



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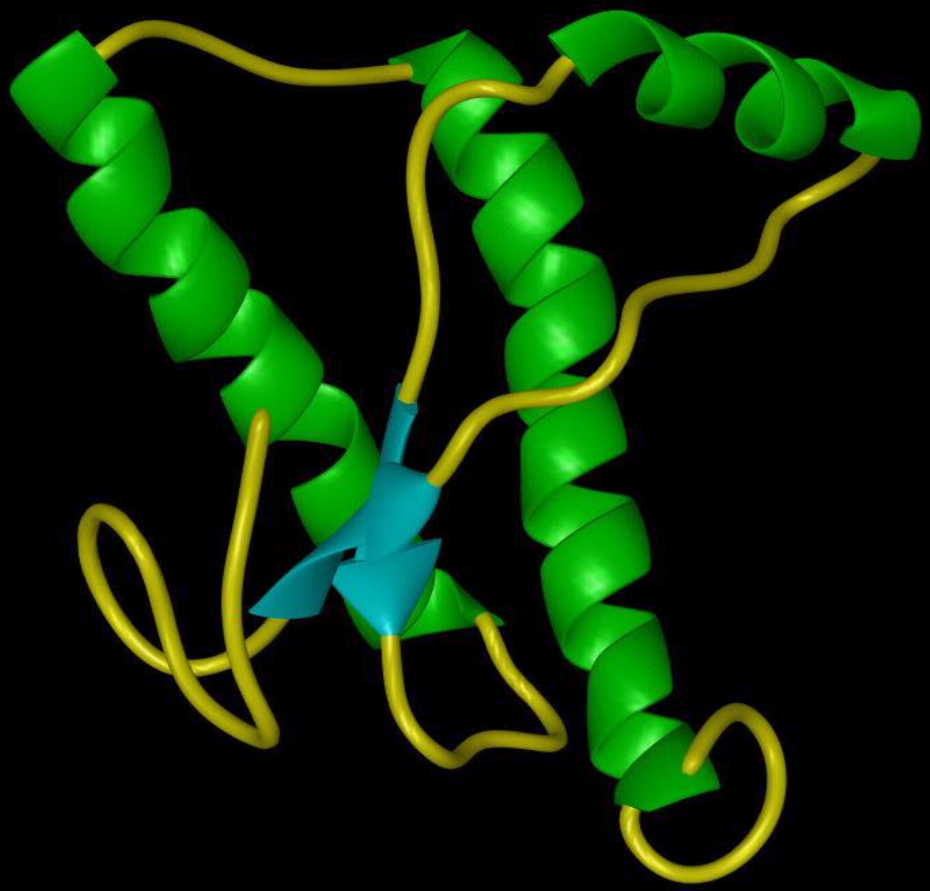
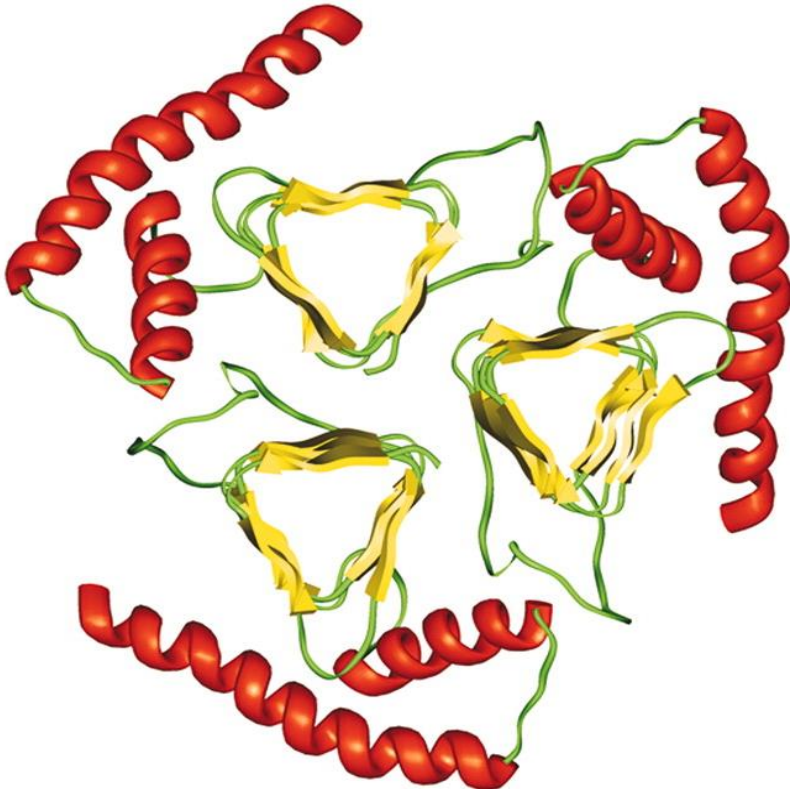
Cashman & Caughey, *Nature Rev*

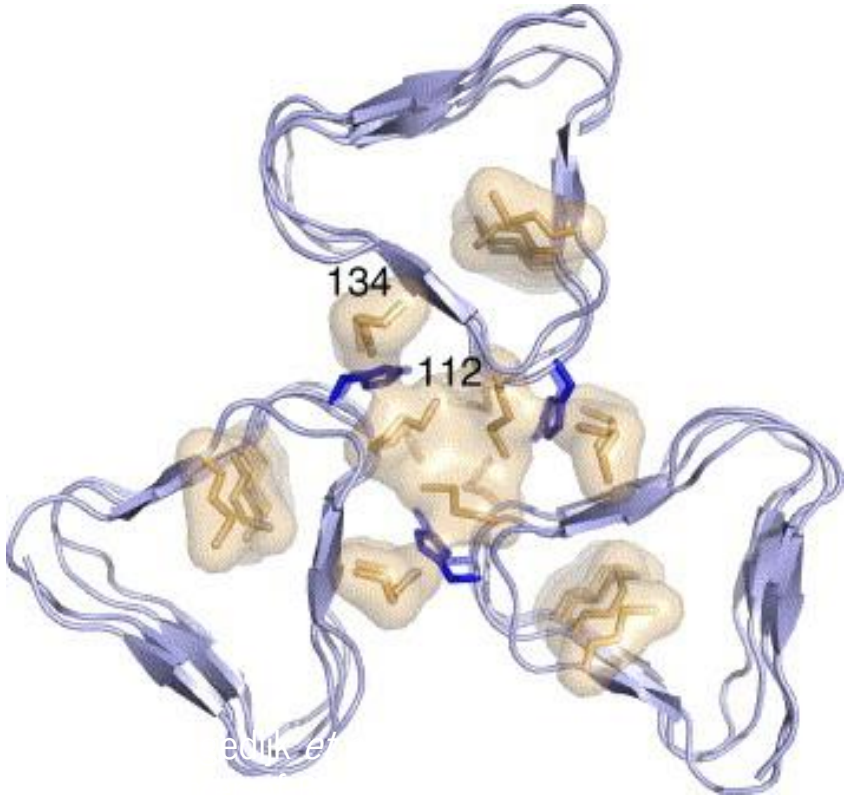
Prion replication



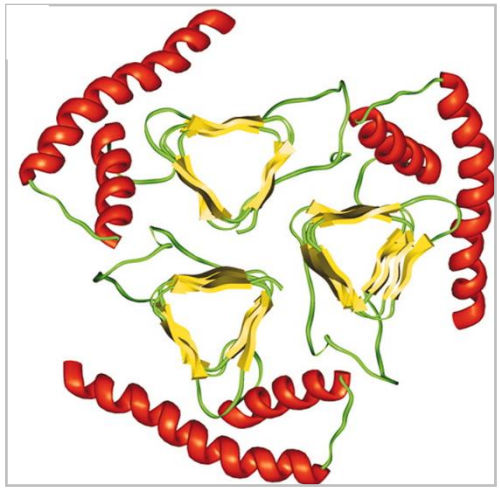
PrP^C

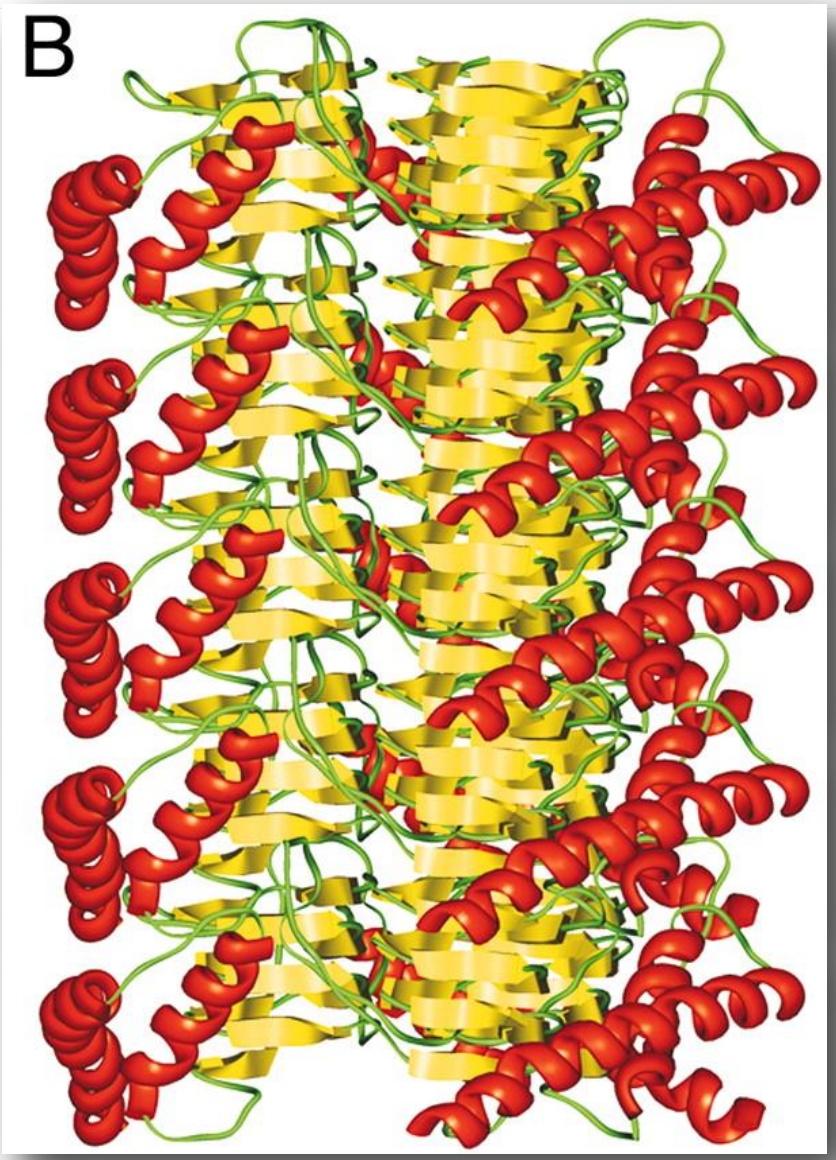
PrP^{Sc} trimers ~ one disc of PrP^{Sc}





Stacked PrP trimer-discs into stable polymer

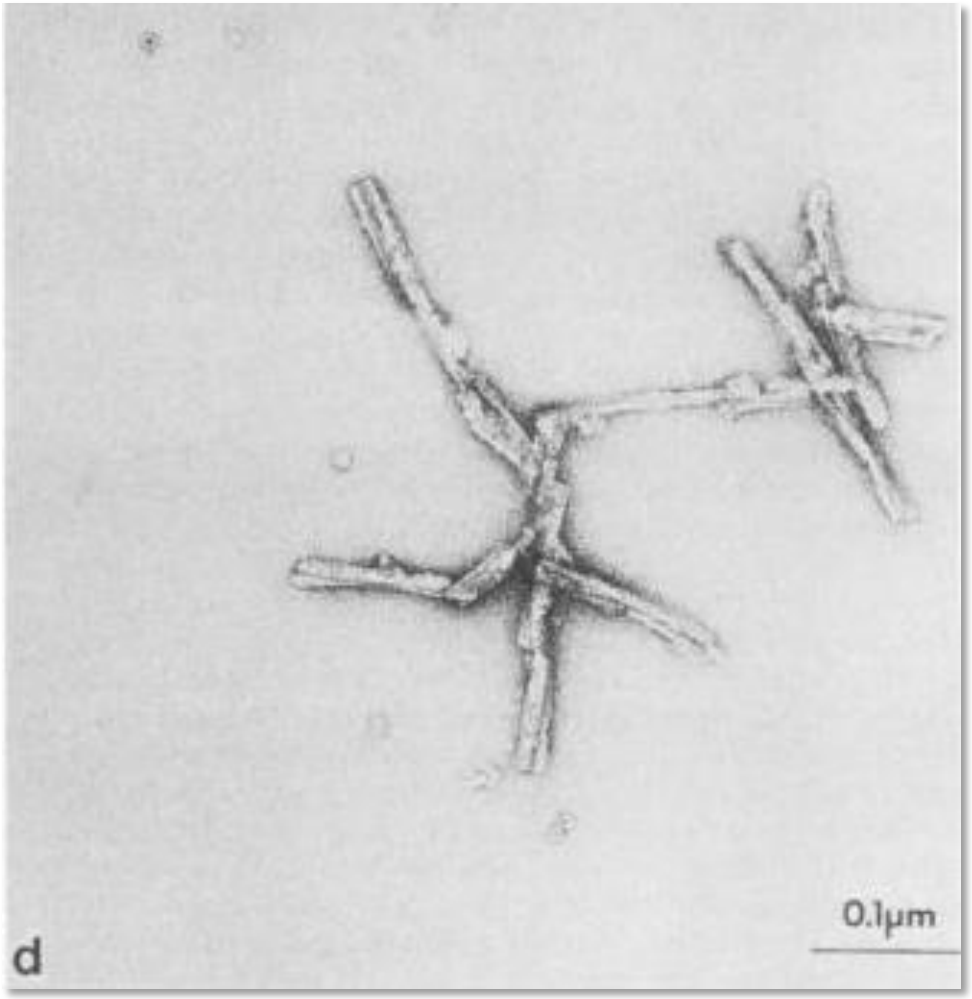




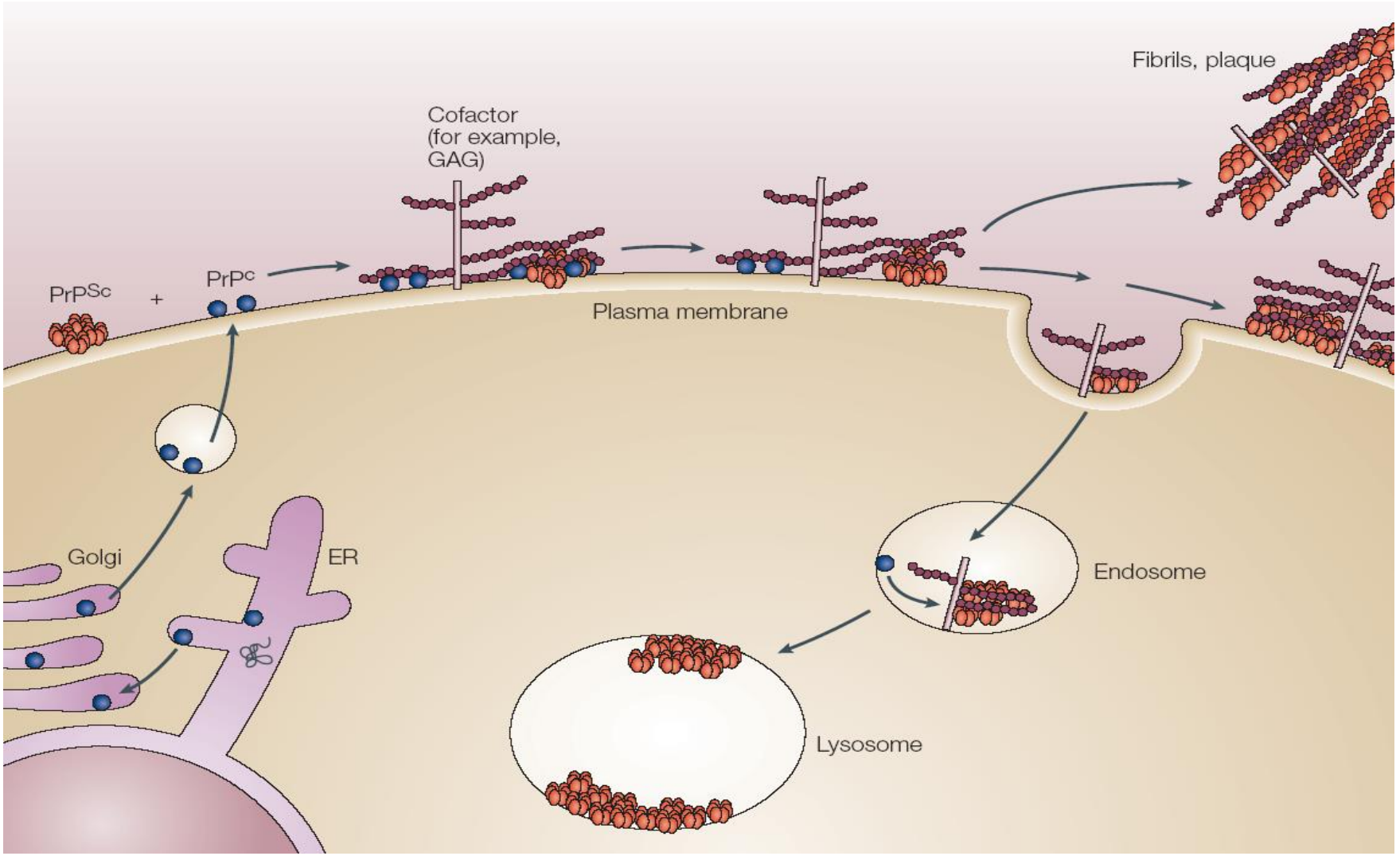
Govaerts *et al.* 2004 PNAS

SAFs: Scrapie Associated Fibrils

EM image of purified scrapie rods



Prion protein conversion at the cellular level



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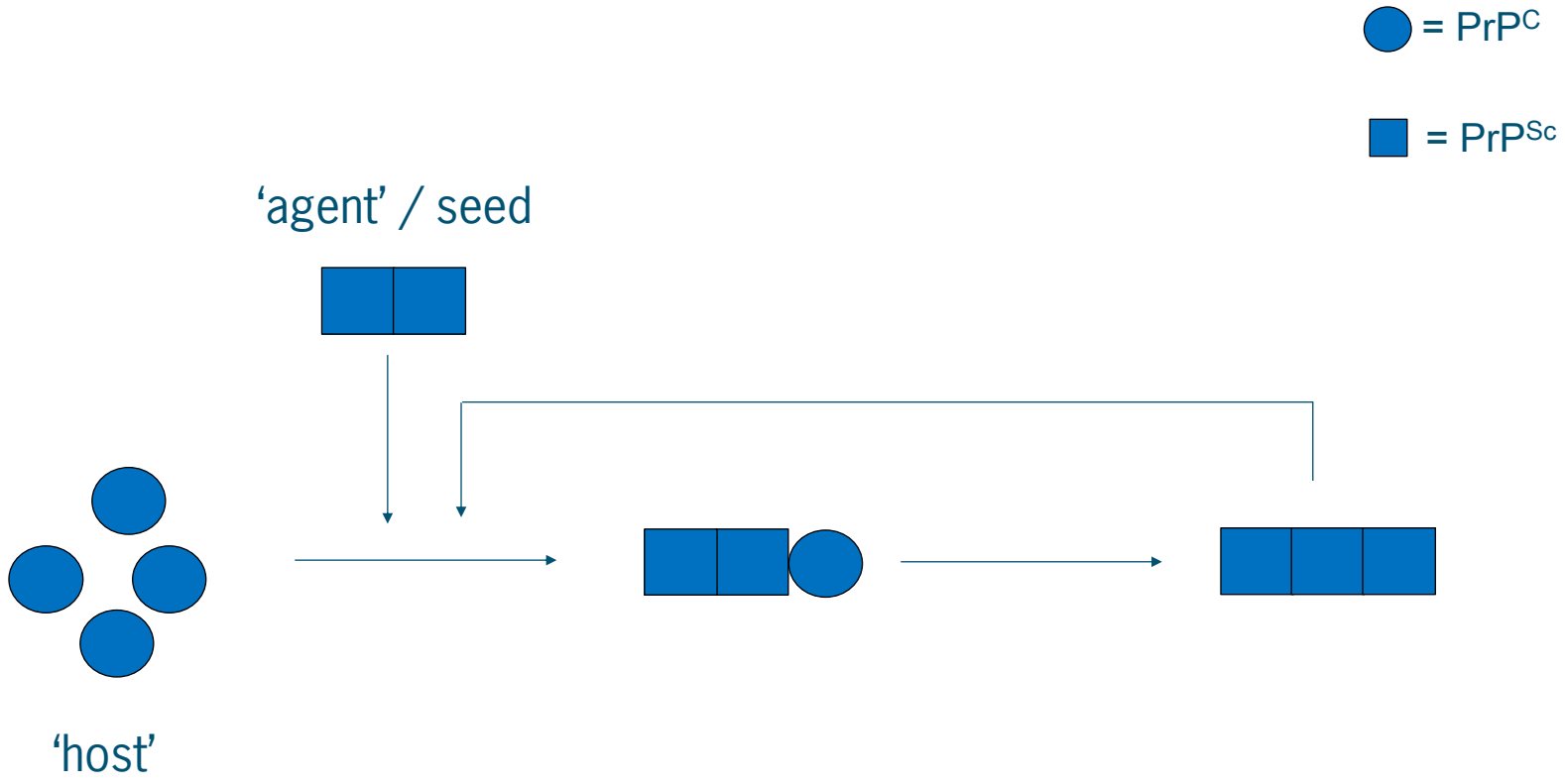
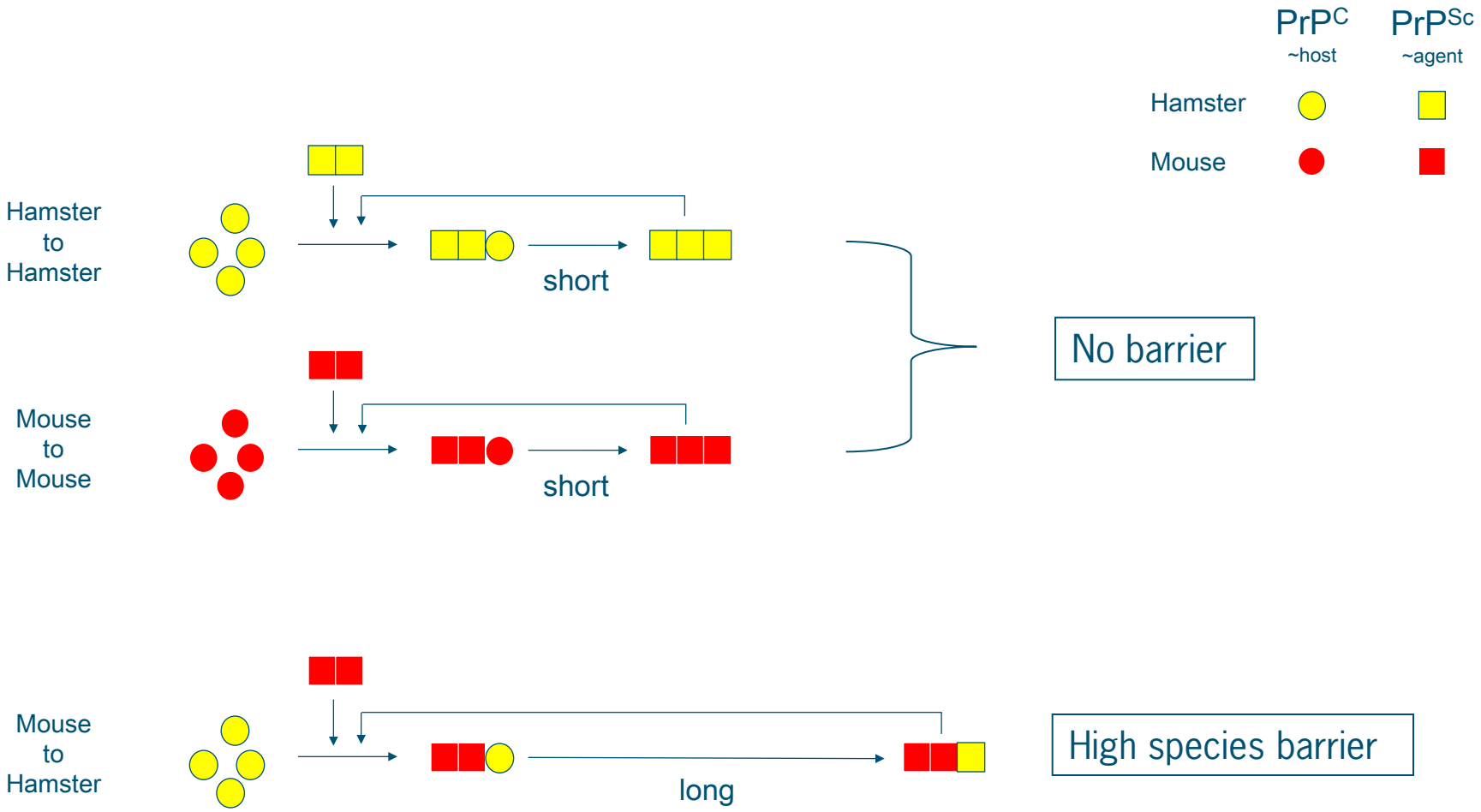
Priola *et al.* 2003 *Science*
Cashman & Caughey, 2004, *Nature Rev*

TSE agent replication :: prion protein conversion

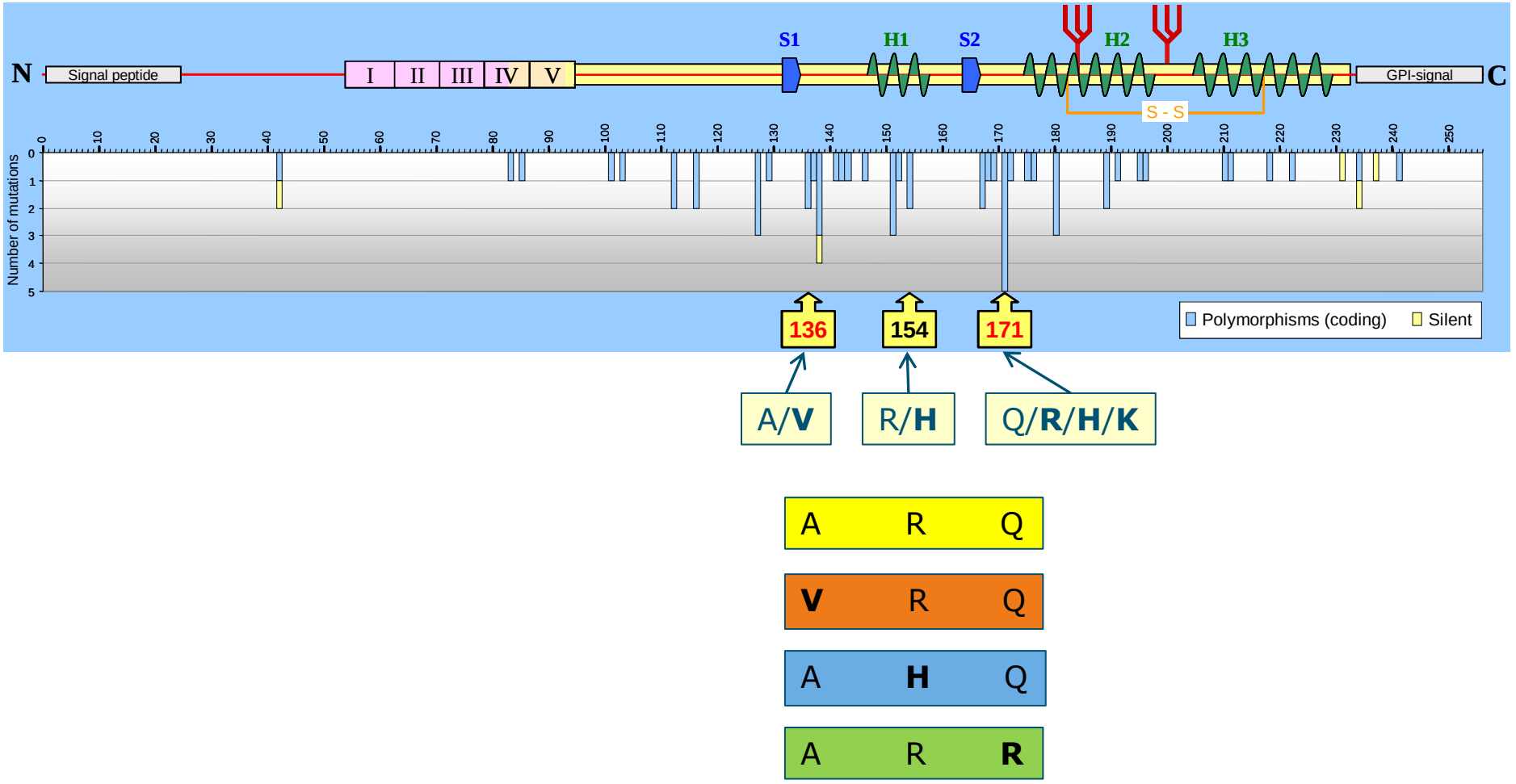
Prion hypothesis: refolding or seeded-polymerization



Species barriers :: incompatibility of PrP protein sequences



Mutations in the sheep prion protein gene coding region



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Hunter & Bossers, 2006

Genetically determined susceptibility of sheep

PrP genotype

VRQ / VRQ
VRQ / ARQ
ARQ / ARQ

VRQ / ...
ARQ / ...
ARH / …

AHQ / …

ARR / ARR

Highly susceptible

Resistant

In ... efficiency

AR

F

letters to nature

Molecular assessment of the potential transmissibilities of BSE and scrapie to humans

Gregory J. Raymond*, James Hope†, David A. Kocisko*‡, Suzette A. Priola*, Lynne D. Raymond*, Alex Bossers§, James Ironside‖, Robert G. Will‖, Shu G. Chen¶, Robert B. Petersen¶, Pierluigi Gambetti¶, Richard Rubenstein#, Mari A. Smits§, Peter T. Lansbury Jr‡* & Byron Caughey*

* Rocky Mountain Laboratories, NIAID, National Institutes of ...
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† BBSRC Institute for Animal Health, Com...
Berkshire RG20 7NN, UK
‡ Massachusetts Institute ...
Massachusetts 0...
§ Dep...

be correlated with the *in vivo* transmissibility of BSE to that host. This correlation encouraged us to look for an *in vitro* indication of the transmissibility of BSE to humans, using a PrP^{BSE}/human PrP-sen conversion assay.

Wild-type human (h) PrP has two common allelic fo... encode either methionine (hPrP-M) or valine (hP... 129 (ref. 18). Hence we tested both types of ... experiments. PrP^{BSE} converted th... hPrP-M and ^{35}S-hPrP-V ... compatible with th... the human ... m...

Proc. Natl. Acad. Sci. USA
Vol. 94, pp. 4931–4936, May 1997
Biochemistry

Scrapie susceptibility-linked polymorphisms modulate the *in vitro* conversion of sheep prion protein to protease-resistant forms

(allelic variants/protein conformation/spongiform encephalopathy/proteinase K resistant)

ALEX BOSSERS*, PETER B. G. M. BELT†, GREGORY J. RAYMOND‡, BYRON CAUGHEY‡, RUTH DE VRIES*, AND MARI A. SMITS*§

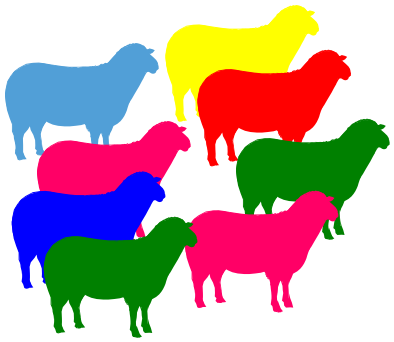
*Department of Bacteriology, and †Department of Production, DLO-Institute for Animal Science and Health, P.O. Box b5 8200 AB Lelystad, The Netherlands; and ‡Laboratory of Persistent Viral Diseases, Rocky Mountain Laboratories, National Institute of Allergies and Infectious Diseases, Hamilton, MT 59840

ARR BOV

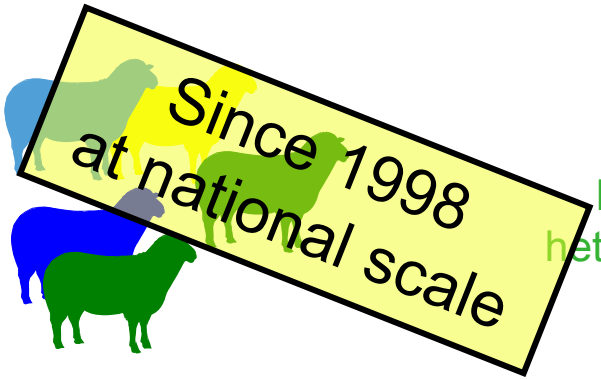
PrP-C variants

Bossers *et al.* 1996, 1997, 2000; Priem *et al.* 2013

Scrapie eradication by genetic selection



Counter selection

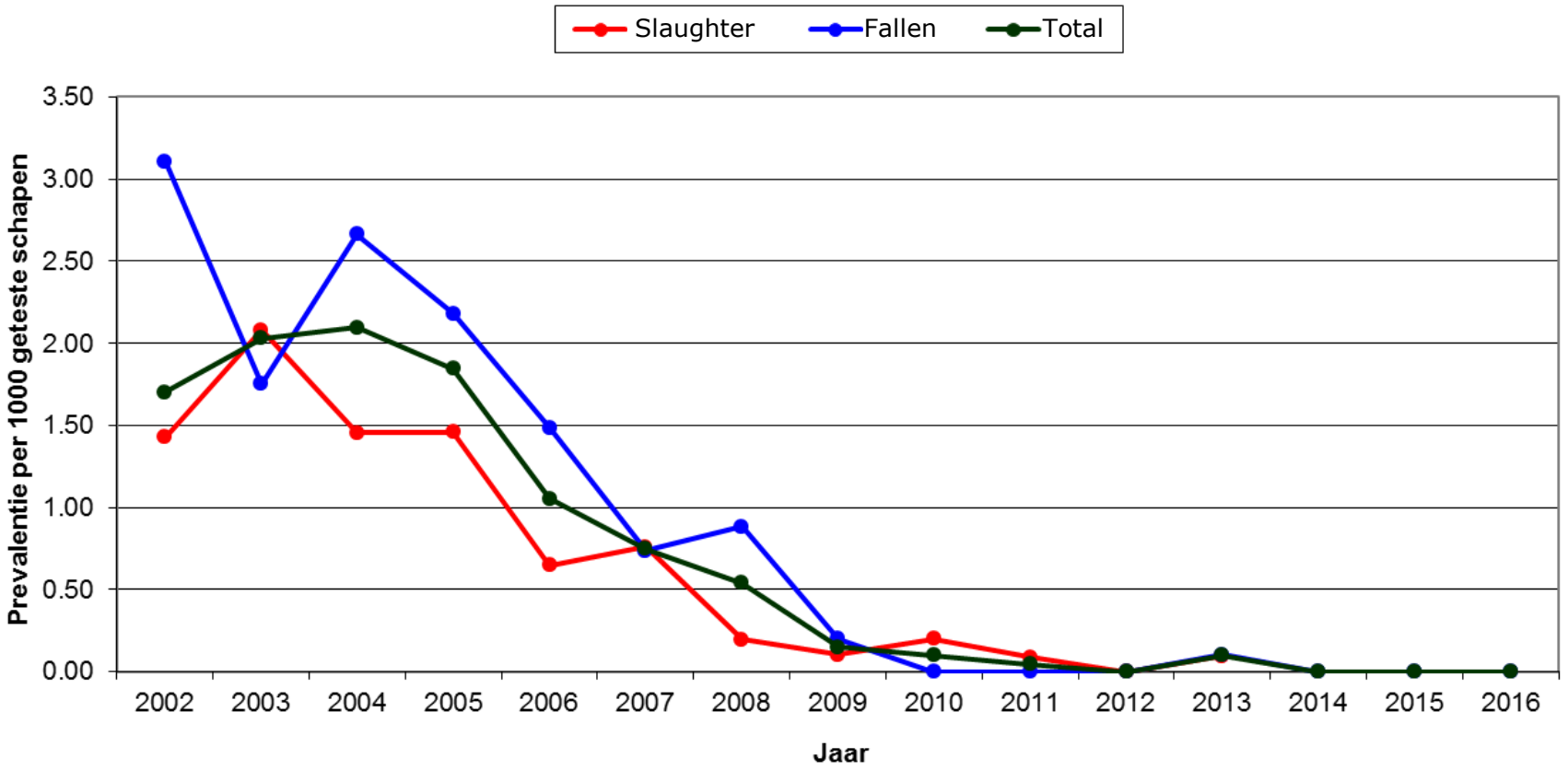


Long
but more
heterogeneous

Direct selection

Rapid
but risk of
Inbreeding!

Scrapie control by genetic selection successful



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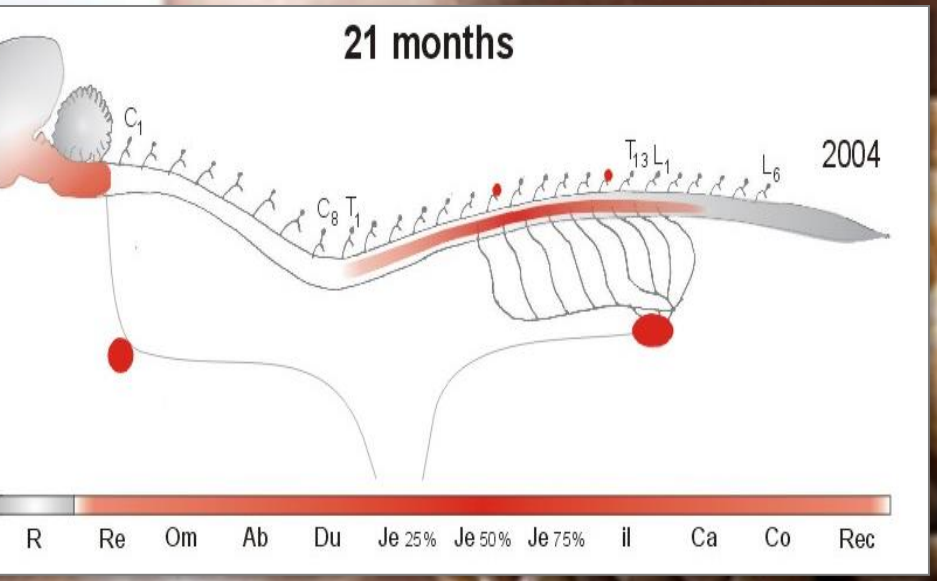
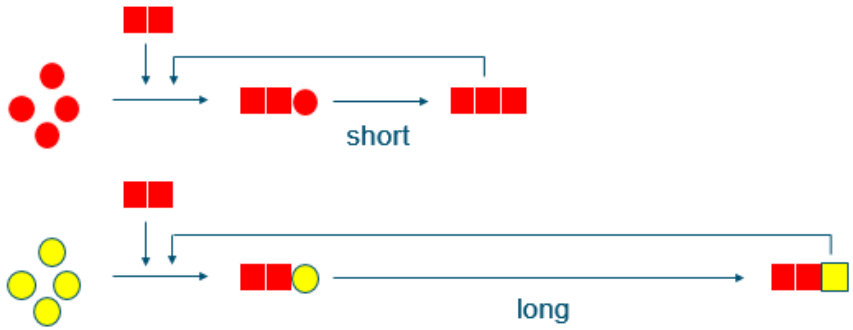
Van Zijderveld *et al.*, 2016

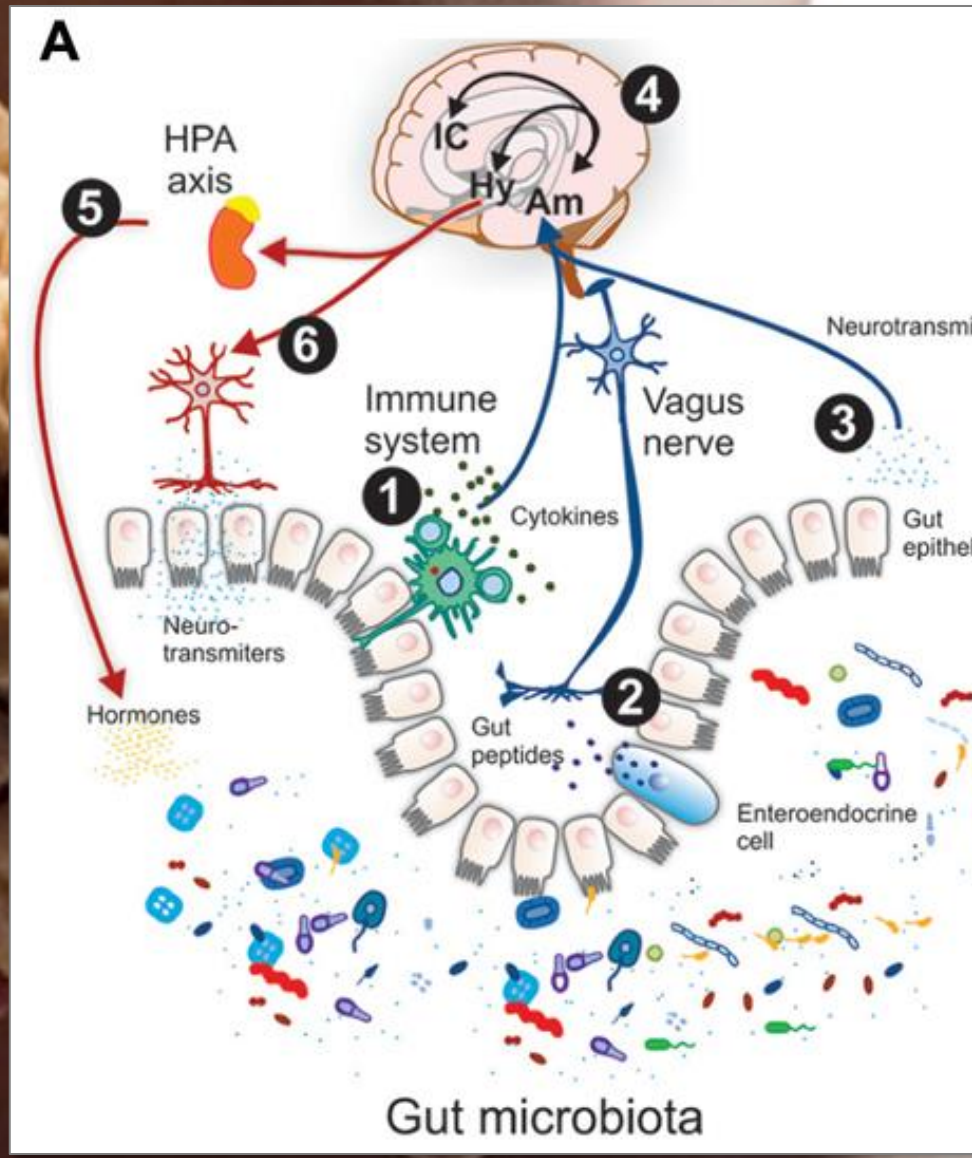
Prion mystery solved?

- Genetic predisposition sheep -> breeding -> eradication
- Not possible for humans, cattle, ...
- NO cure / therapy
    - Inactivate prions *in vivo*
        - Dissociate prion aggregates (PPS)
    - Interfere with PrP^{C} to PrP^{Sc} binding
        - PrP knockout
        - Peptides / antibodies
    - Increase clearance
- Prevent prion uptake by increasing intestinal health?

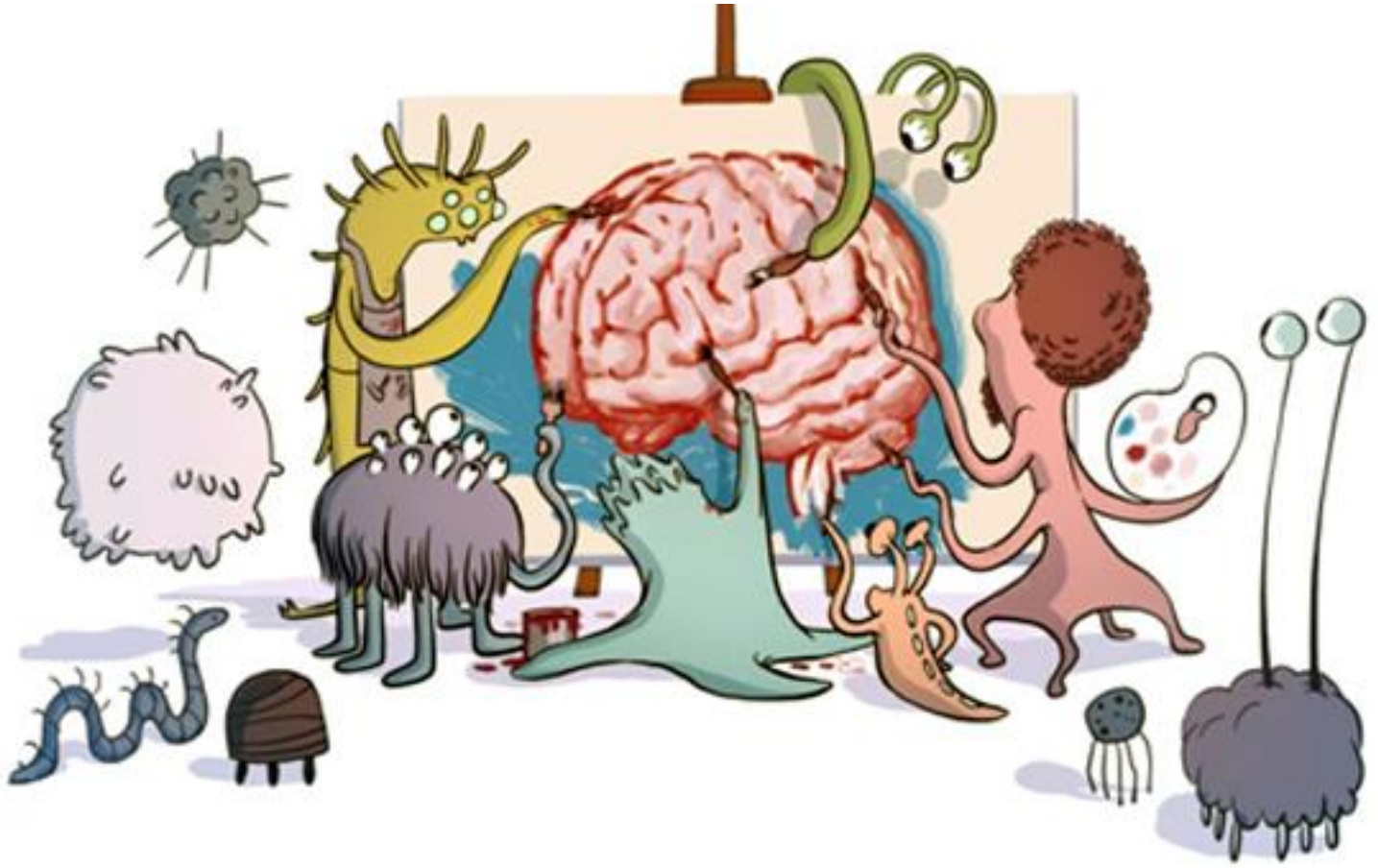
The Gut-Brain connection







Questions?



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