Prions: epigenetics, evolution and disease

Anton Khmelinskii

Outline

- history of prions
- proteostasis and protein folding diseases
- prions as folding diseases
- prions in evolution

What is epigenetics?

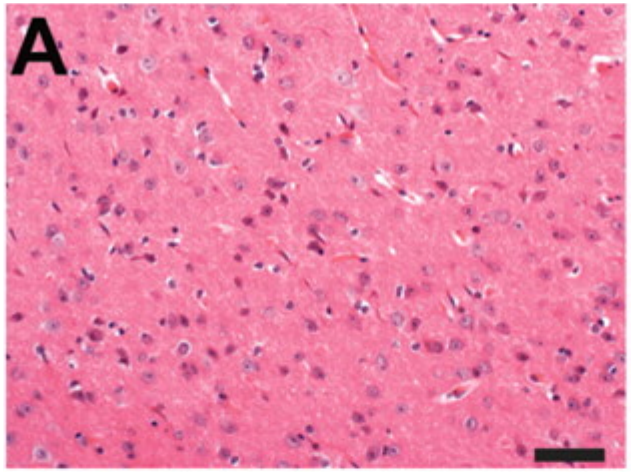
Institute of Molecular Biology

"**heritable** phenotype changes that do not involve alterations in the DNA sequence"

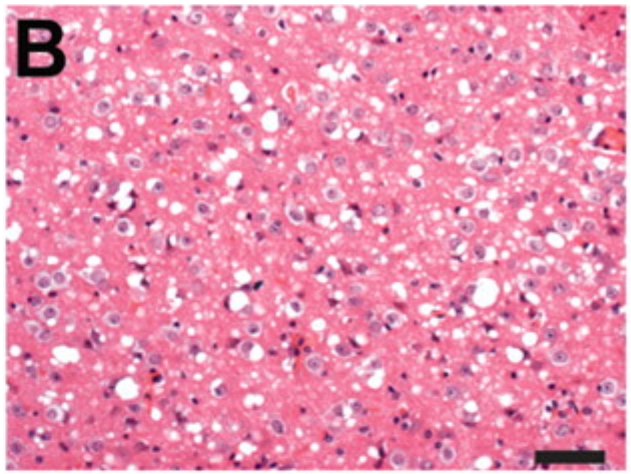
Epigenetics: Definition, Mechanisms and Clinical Perspective
Dupont et al. 2009 Semin Reprod Med

Transmissible spongiform encephalopathies

normal



disease



Wang et al. 2010 Science

disease	natural host
scrapie	sheep and goats
bovine spongiform encephalopathy ("mad cow" disease)	cattle
chronic wasting disease	elk and deer
kuru	human
Creutzfeldt-Jakob	
Gerstmann-Sträussler-Scheinker syndrome	
fatal familiar insomnia	

Transmissible spongiform encephalopathies

scrapie first documented in 1750s

some evidence for transmission
also between species!

kuru in Papau New Guinea, 1950s
funerary cannibalism

CJD described in 1920, familial cases
1970s cases linked to use
of surgical instruments

disease	natural host
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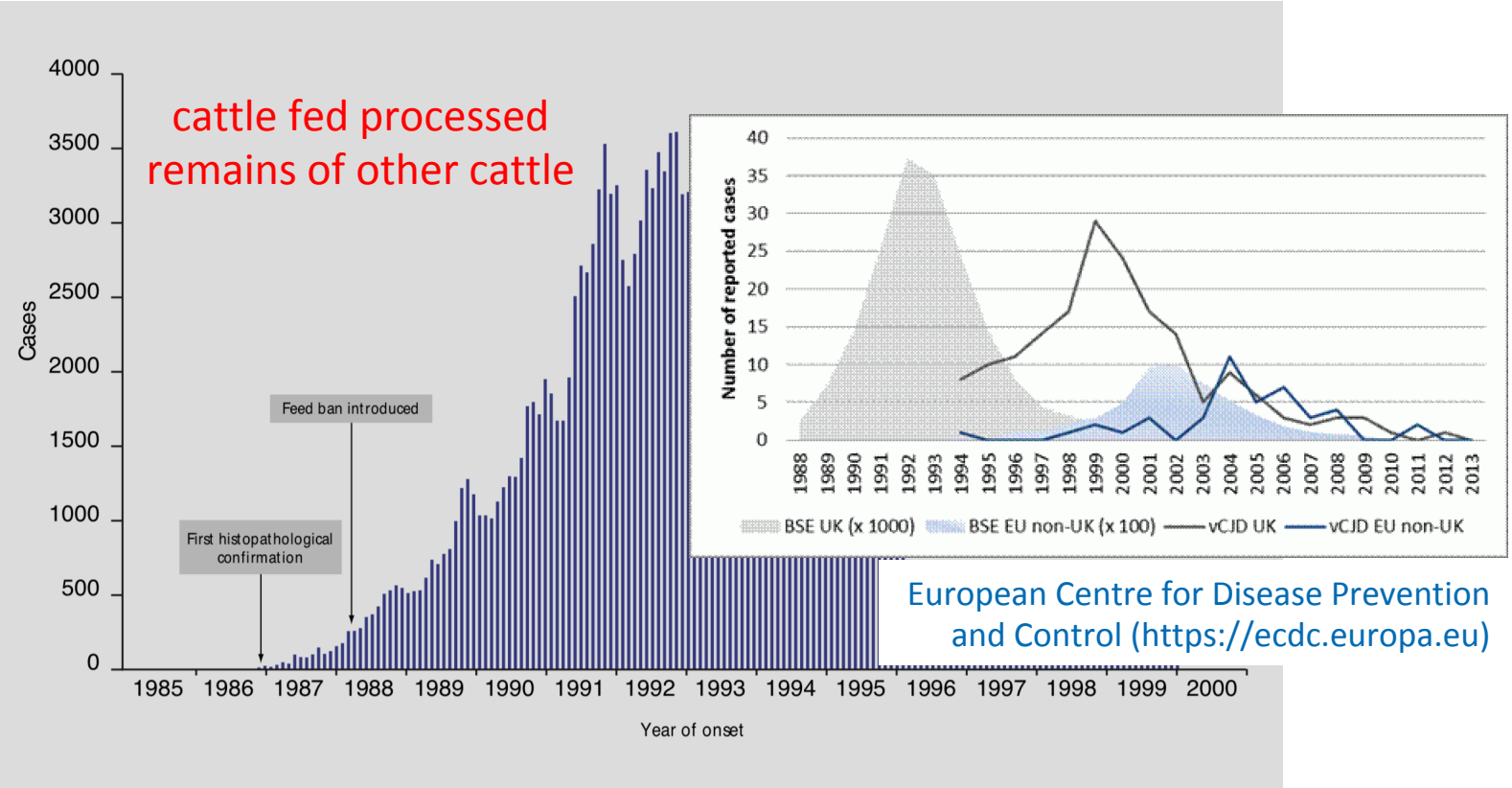
Bovine spongiform encephalopathy

BSE outbreaks in UK



European Centre for Disease Prevention and Control (https://ecdc.europa.eu)

Aguzzi 2001 Dialogues Clin Neurosci

CJD ~1 case per million people

Transmissible spongiform encephalopathies

what is the infectious agent?

most infectious diseases are caused by viruses or bacteria

but with TSEs
- no obvious DNA involved
- no obvious RNA involved

disease	natural host
scrapie	sheep and goats
bovine spongiform encephalopathy ("mad cow" disease)	cattle
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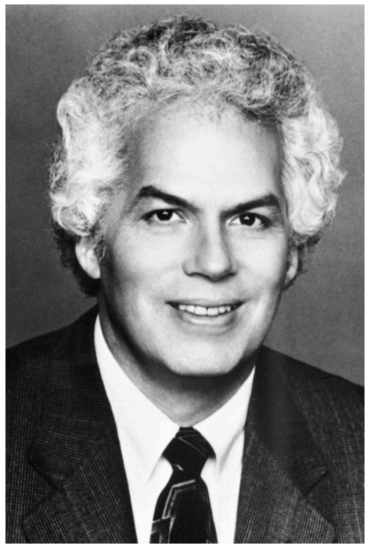
Gerstmann-Sträussler-Scheinker syndrome	
fatal familiar insomnia	

Prions

Novel Proteinaceous Infectious Particles Cause Scrapie

Stanley B. Prusiner

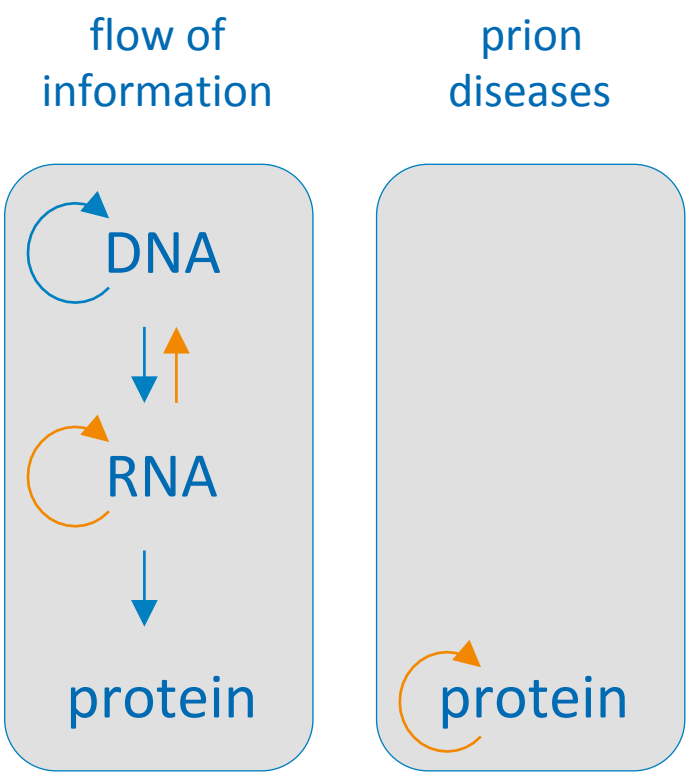
SCIENCE, VOL. 216, 9 APRIL 1982



"prion" pronounced *pree-on*
*pro*teinaceous *in*fectious particles

1997
Nobel Prize in Physiology or Medicine
"for his discovery of Prions - a new biological principle of infection."

Prions - against the central dogma?

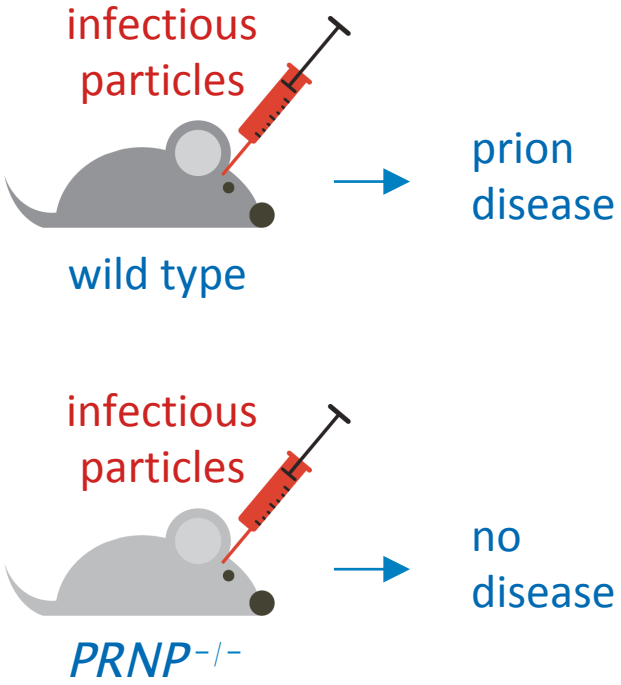


surprising etiology of prion diseases

- infection
- genetic -> infectious
- spontaneous -> infectious

Transmissible spongiform encephalopathies

disease	natural host	prion
scrapie	sheep and goats	PrP
bovine spongiform encephalopathy ("mad cow" disease)	cattle	PrP
chronic wasting disease	elk and deer	PrP
kuru	human	PrP
Creutzfeldt-Jakob		PrP
Gerstmann-Sträussler-Scheinker syndrome		PrP
fatal familiar insomnia		PrP

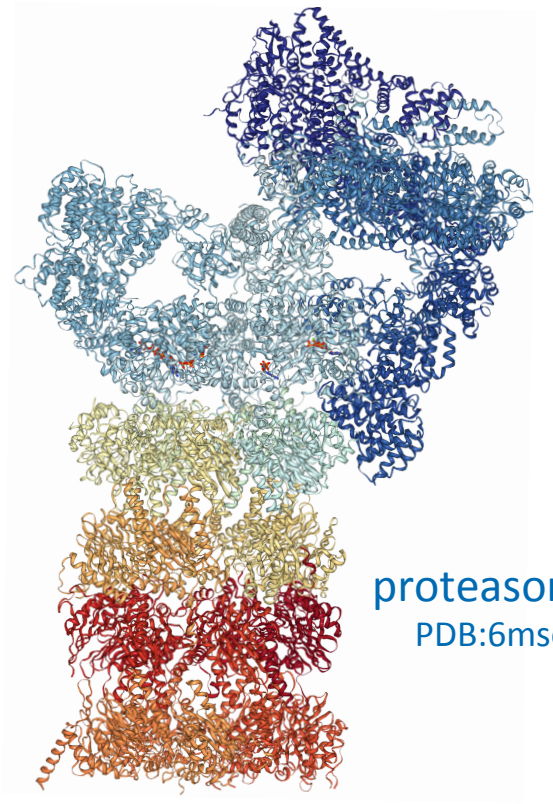


own protein required!

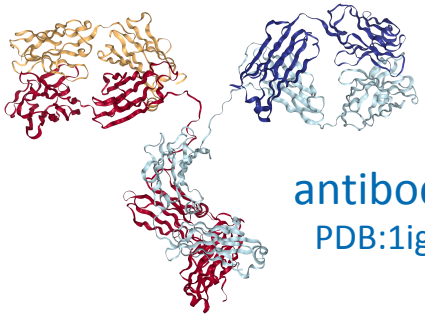
TSEs are protein folding diseases

Protein structure and function

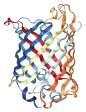
linear polypeptide -> 3D structure -> function



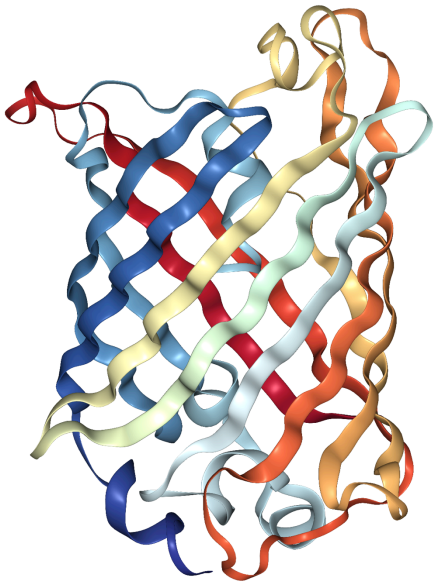
proteasome
PDB:6mse



antibody
PDB:1igt



GFP
PDB:1emb



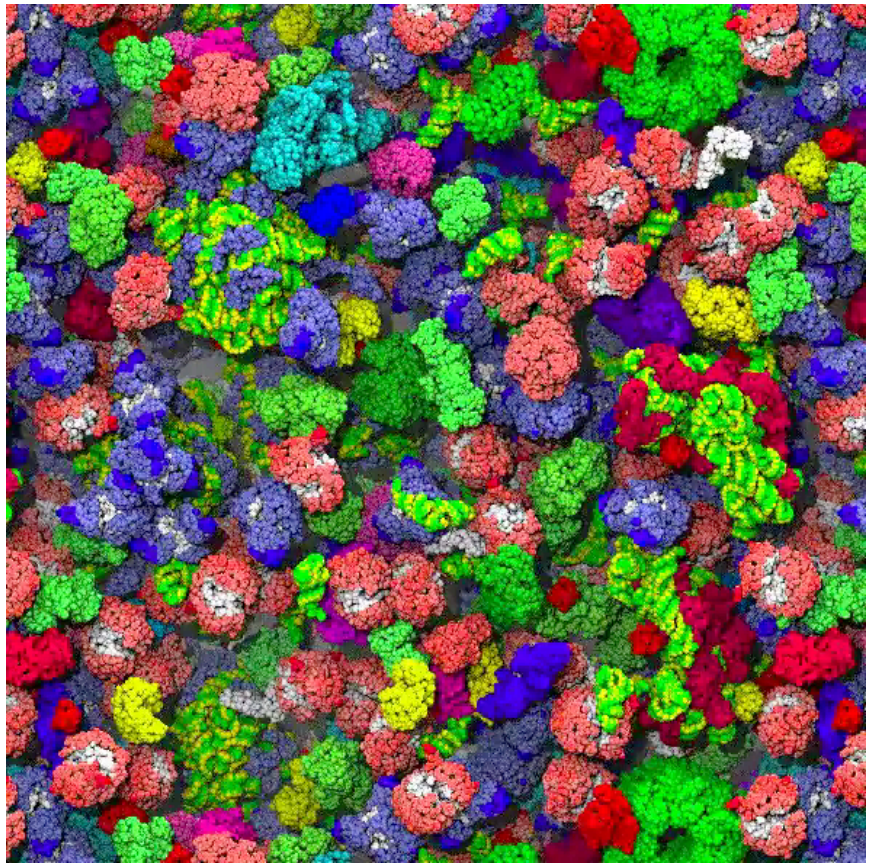
The challenge of protein folding


D. Allan Drummond

Saccharomyces cerevisiae
(baker's yeast)

~4000 different proteins
50 - 10^6 copies per cell
50 million protein molecules per cell

The challenge of protein folding



McGuffee and Elcock 2010 PLoS Comput Biol

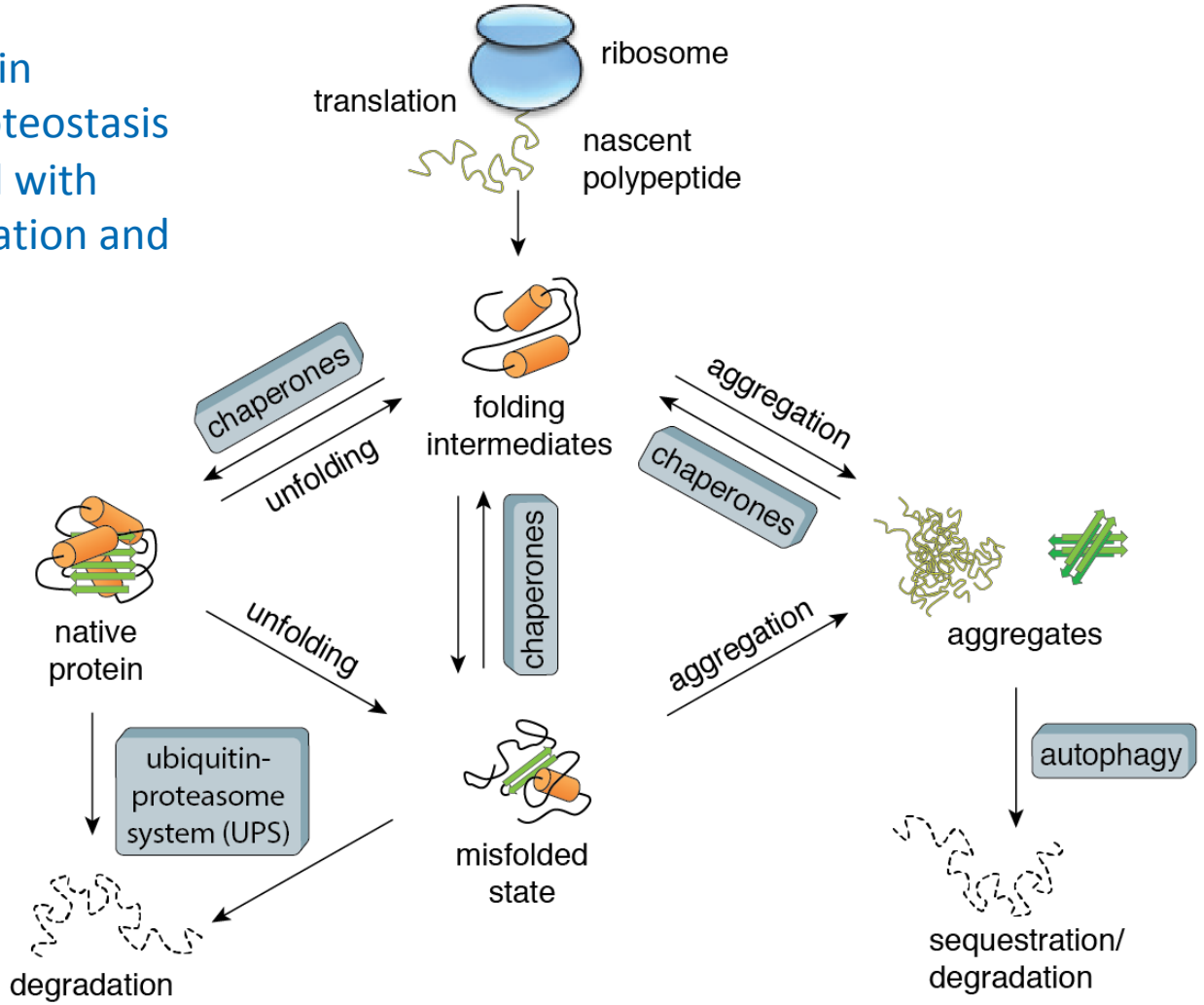
Saccharomyces cerevisiae
(baker's yeast)

~4000 different proteins
50 - 10^6 copies per cell
50 million protein molecules per cell

synthesis of >10000 proteins/s

Proteostasis network

- 5% of all protein involved in proteostasis
- loss associated with neurodegeneration and aging



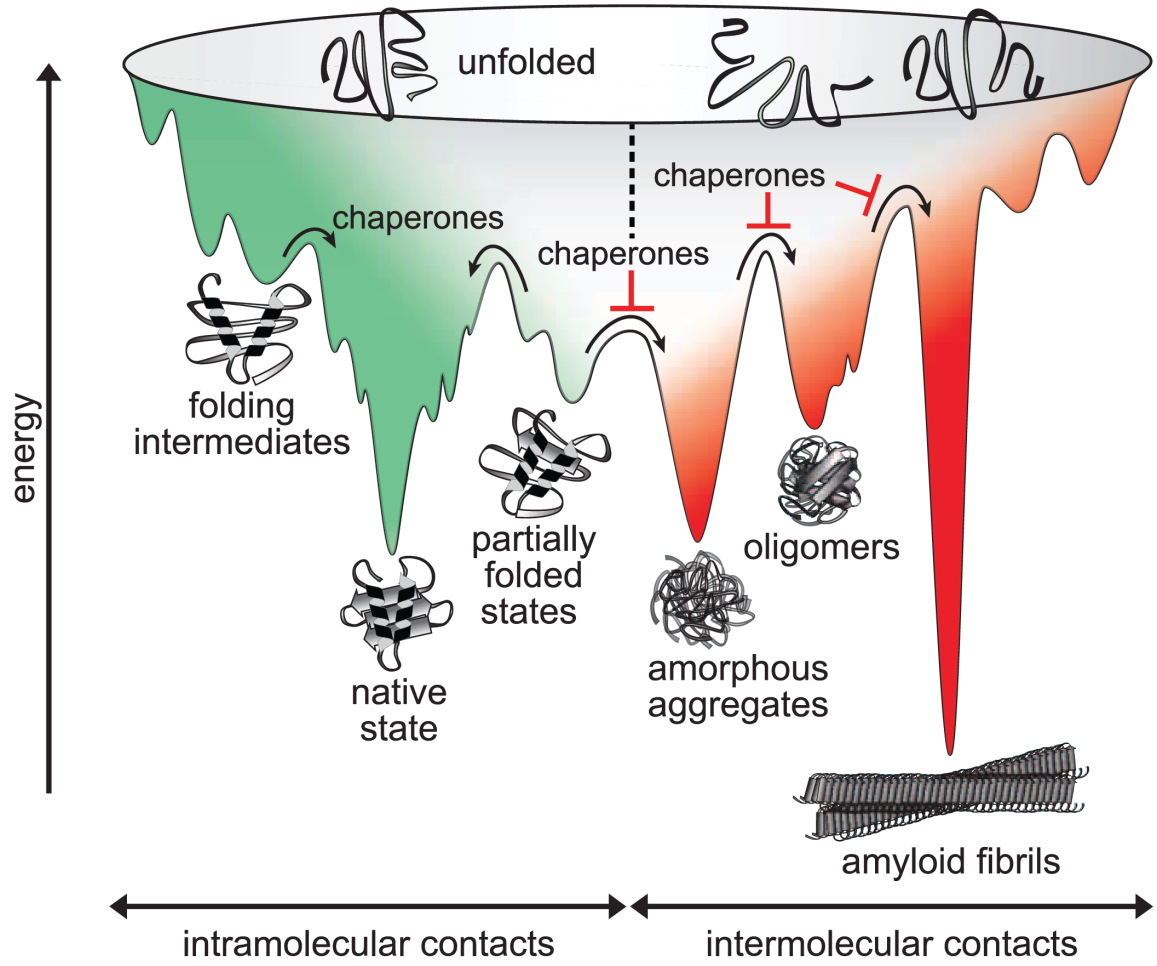
Hartl et al. 2010 Nature

Navigating the protein folding landscape

small polypeptide
~100 residues

↓

~10^{30} possible
conformations!



Balchin et al. 2016 Science

Protein folding diseases

loss-of-function diseases

"protein dysfunction due to mutations that may render proteins metastable and prone to degradation"

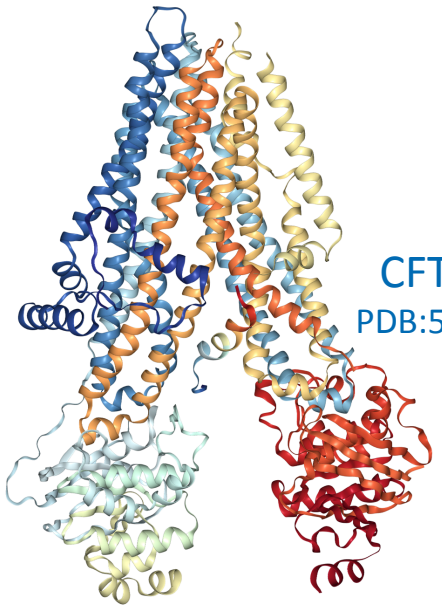
Hartl 2017 Annu Rev Biochem

cystic fibrosis

~2000 different mutations in the CFTR protein chloride channel

~70% of the cases - ΔF508 mutation
poor folding followed by degradation in ER

Lukacs and Verkman 2012 Trends Mol Med



CFTR
PDB:5uak

Protein folding diseases

toxic gain-of-function diseases

"metastable proteins undergo aggregation
in a process associated with cellular toxicity"

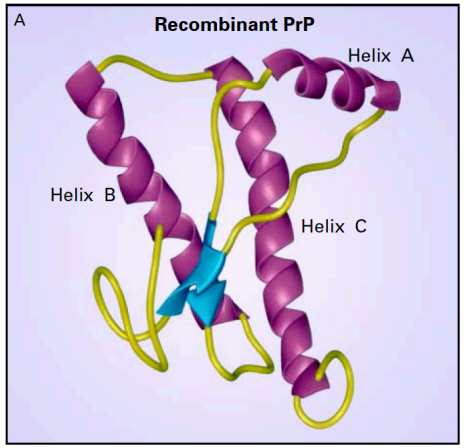
Hartl 2017 Annu Rev Biochem

Peptide or protein name	Number of residues[a]	Structure[b]	Associated diseases
Amyloid-β peptide (Aβ)	40 or 42[d]	Intrinsically disordered	Alzheimer disease Hereditary cerebral hemorrhage with amyloidosis
α-Synuclein (αs)[e]	140	Intrinsically disordered	Parkinson disease Parkinson disease with dementia Dementia with Lewy bodies Multiple system atrophy
Huntingtin exon 1 (HttEx1)[e]	~103–187[d]	Intrinsically disordered	Huntington disease
Transthyretin (TTR)	127	All-β, prealbumin-like	Senile systemic amyloidosis Familial amyloidotic polyneuropathy Familial amyloid cardiomyopathy Leptomeningeal amyloidosis
Islet amyloid polypeptide (IAPP)	37	Intrinsically disordered	Type II diabetes Insulinoma

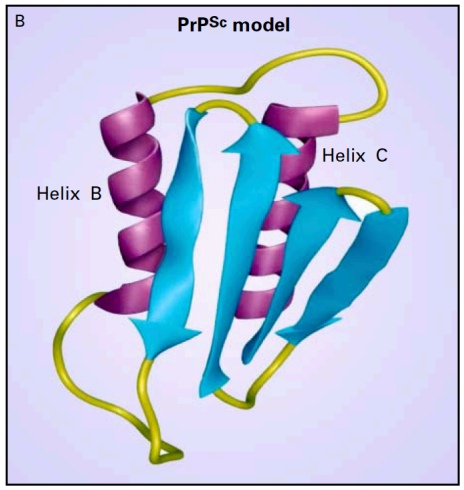
Chiti and Dobson 2017
Annu Rev Biochem

Prions as protein folding diseases

normal conformation

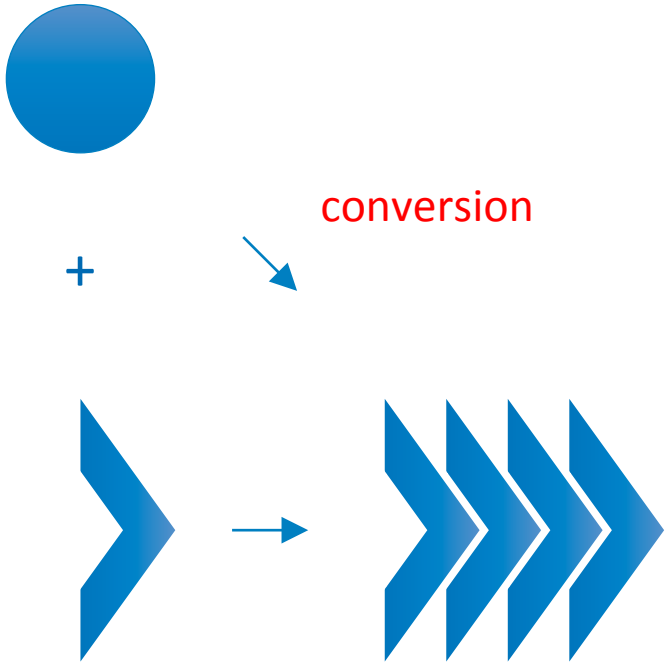


prion conformation (model)



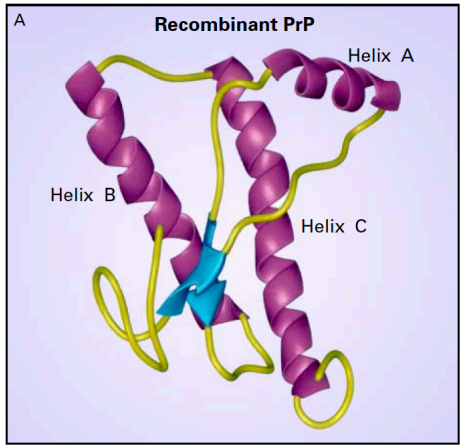
Prusiner 2001 N Engl J Med

- *PRNP* encodes a 253res PrP polypeptide
- function not well understood

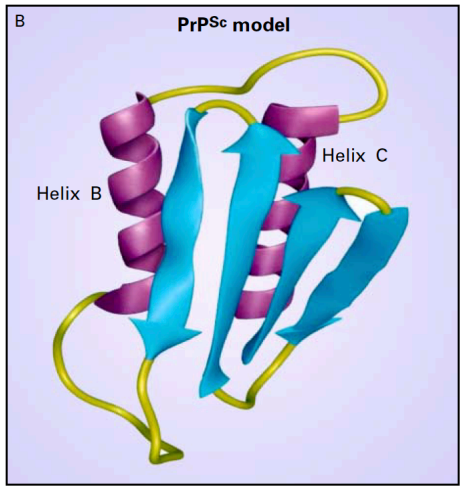


Prions as protein folding diseases

normal conformation

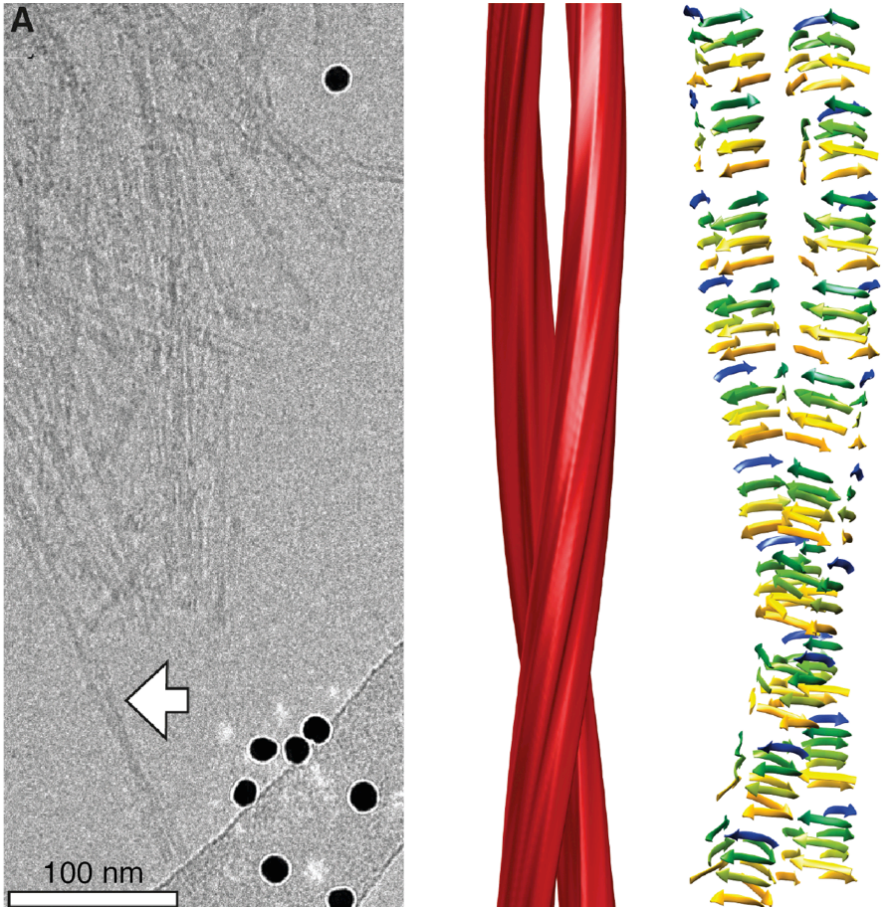


prion conformation (model)



Prusiner 2001 N Engl J Med

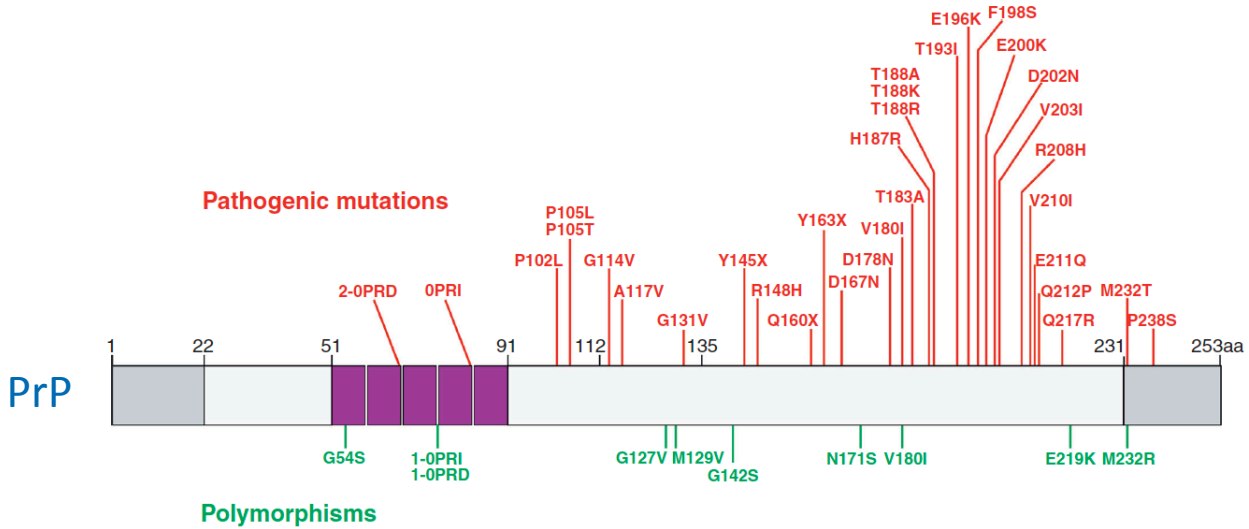
amyloid fibers



Vázquez-Fernández et al. 2016 PLoS Pathog

Prions as protein folding diseases

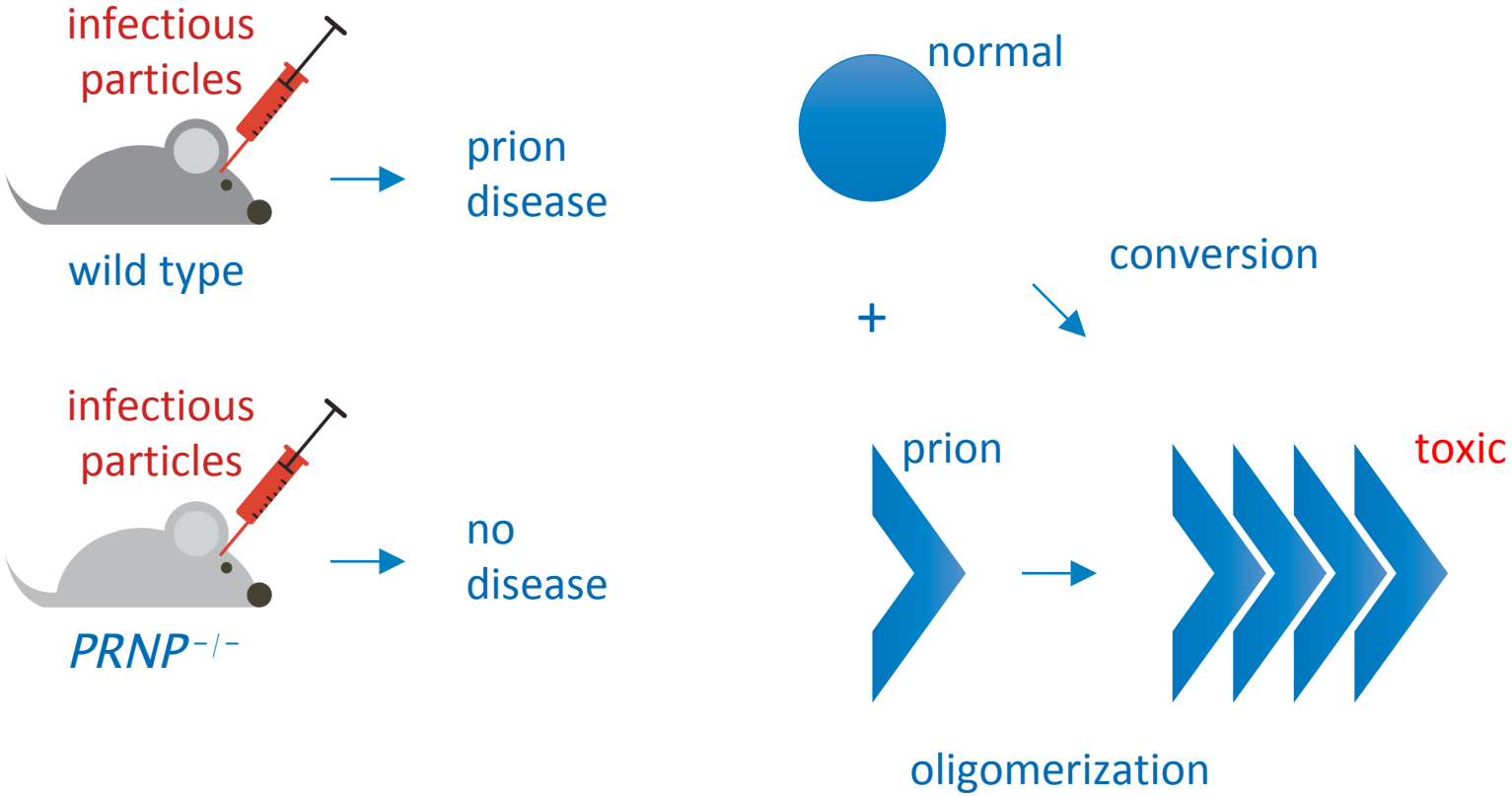
mutations that promote
the prion conformation (dominant)



Lloyd et al. 2013 Curr Opin Genet Dev

Prions as protein folding diseases

- *PRNP* encodes a 209aa PrP protein
- cell-cell communication in the brain



Take home messages (I)

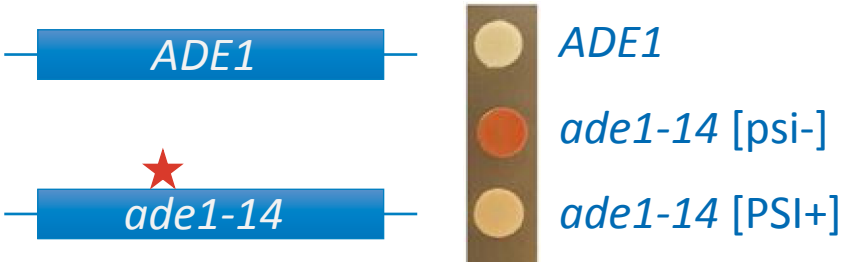
- prions are protein folding diseases
- caused by an abnormal PrP conformation (PrP^{Sc})
- PrP misfolding is spontaneous or enhanced by mutations
- in theory a single PrP^{Sc} molecule can start the disease

- what is the prion structure in different diseases?
- why are aggregates toxic?
- cure by interfering with aggregation?

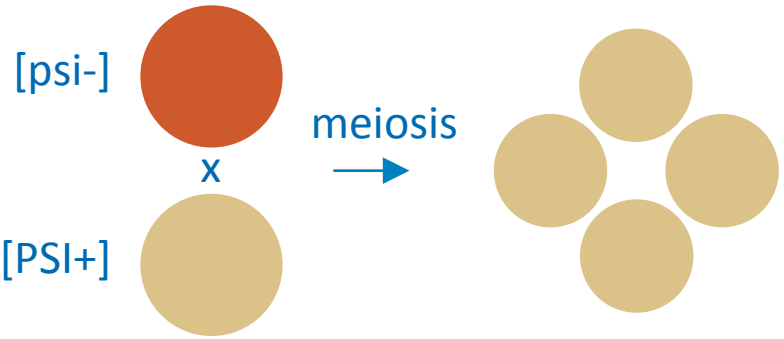
Prions in yeast

[PSI+] phenotype (1965)

- read-through at stop codons



- non-mendelian inheritance

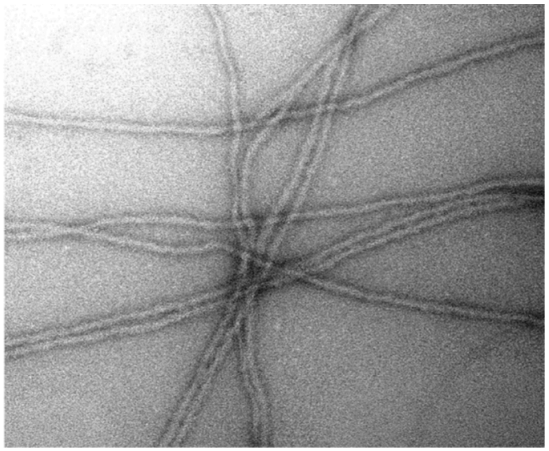


[PSI+] is the prion form of Sup35

[PSI+] is the prion form of the translation termination factor Sup35

Wickner 1994 Science

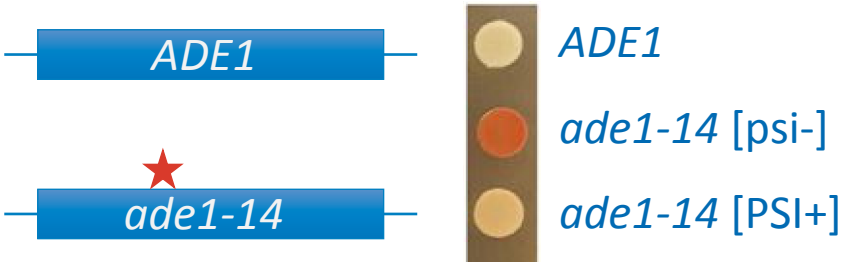
Sup35NM fibers



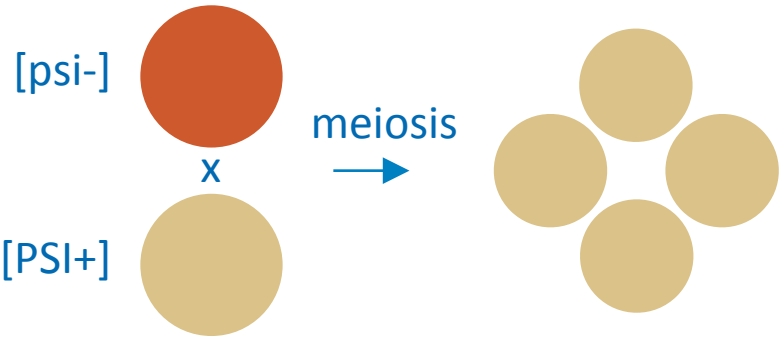
power of yeast genetics to the study prions!

[PSI+] phenotype (1965)

- read-through at stop codons



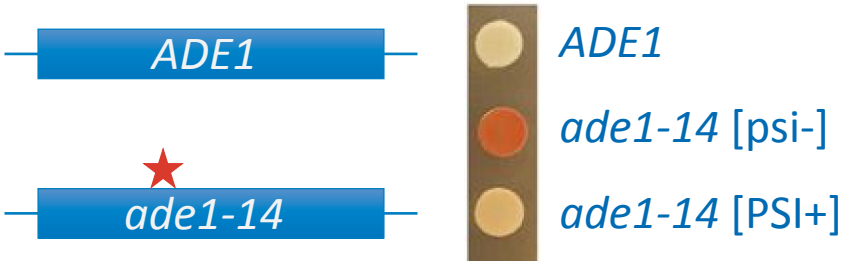
- non-mendelian inheritance



transgenerational inheritance

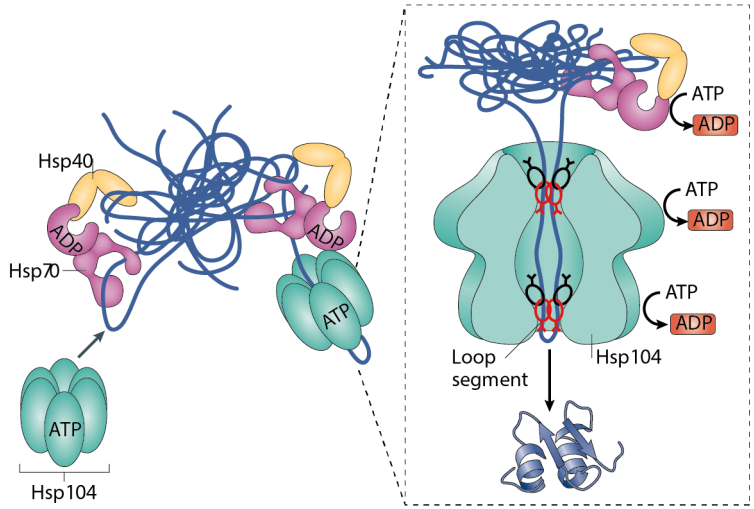
[PSI+] appearance and propagation

- Sup35 overexpression increases frequency of [PSI+] appearance



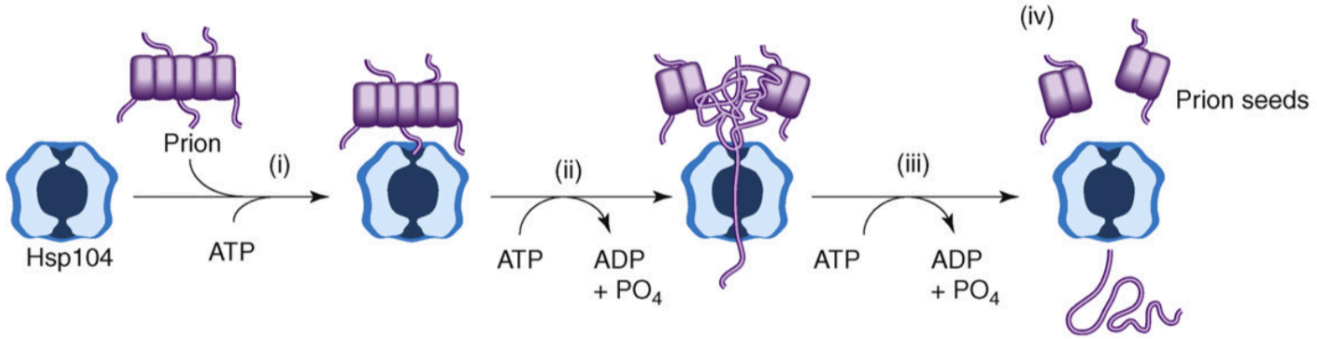
- [PSI+] is cured by transient treatment with GuHCl
- [PSI+] is cured by *hsp104Δ*
- [PSI+] is cured by Hsp104 overexpression

Hsp104 disaggregase

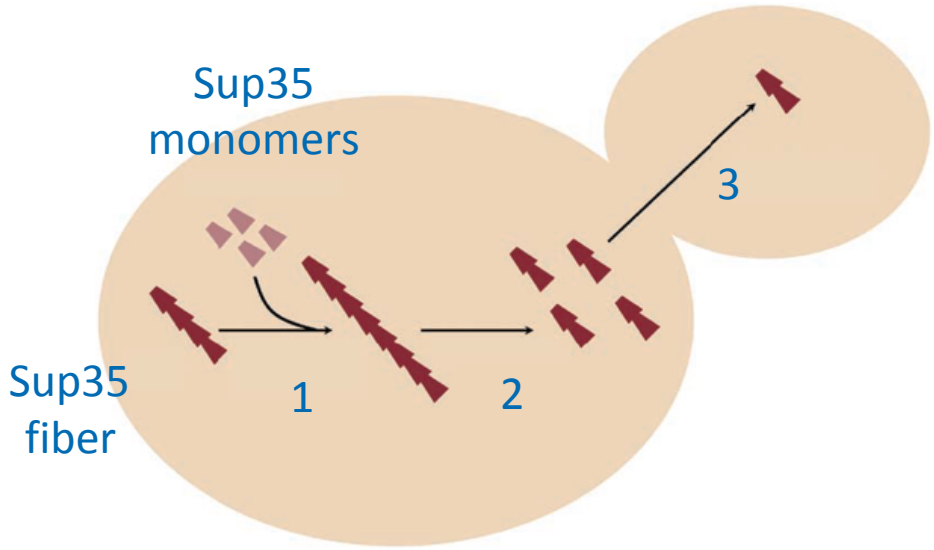


Tyedmers et al. 2010 Nat Rev Mol Cell Biol

[PSI+] appearance and propagation



Doyle and Wickner 2009 Trends Biochem Sci

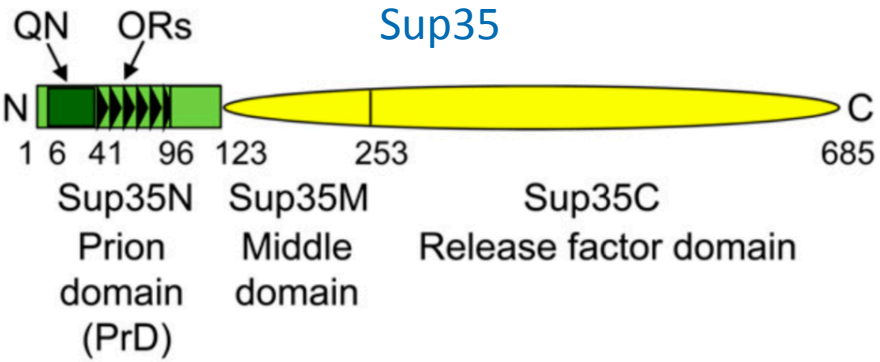


1. fiber growth
2. fiber division
   requires Hsp104 activity!
3. prion inheritance

Verges et al. 2011 Nat Struct Mol Biol

Sequence features of prions

- intrinsically disordered domains
- glutamine/asparagine-rich regions



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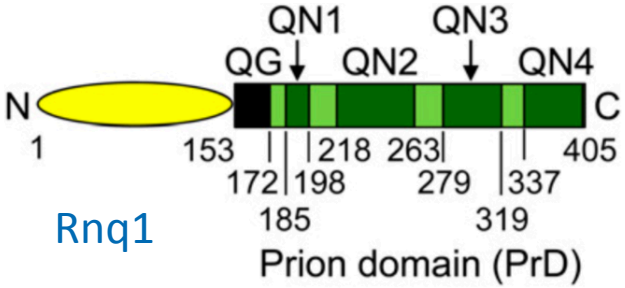
YSGYQQGGYQQYNPDAGYQQQYNPQGGYQQYNPQGGYQQQFNPQGGRGNYKNF
NYNNNLQGYQAGFQPQSQG

trend but not a rule



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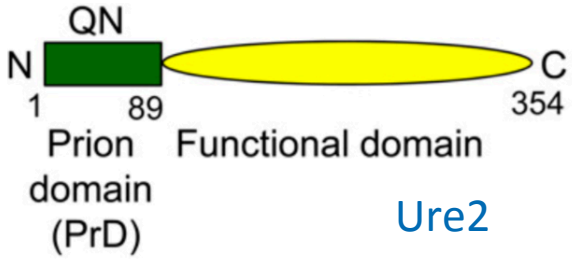

MMNNNGNQVSNLSNALRQVNIGNRNSNTTTDQS
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SQNNDNENNIKNTLEQHRQQQQ

Search for new prions

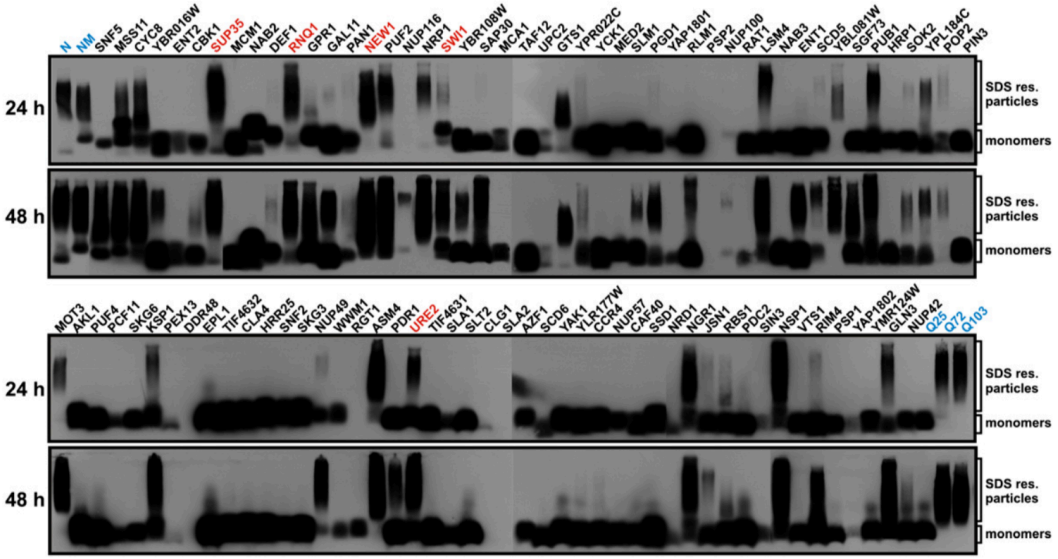
2009

A Systematic Survey Identifies Prions and Illuminates Sequence Features of Prionogenic Proteins

Simon Alberti,[1,5] Randal Halfmann,[1,3,5] Oliver King,[1,4] Atul Kapila,[1,3] and Susan Lindquist[1,2,3,*]

~200 proteins with candidate prion domains in S. cerevisiae

24 domains with prion behavior



strongly enriched for proteins involved in gene expression

- transcription factors
- RNA-binding proteins

Are yeast prions diseases?

ARTICLE 2012
doi:10.1038/nature10875

Prions are a common mechanism for phenotypic inheritance in wild yeasts

Randal Halfmann[1,2]†*, Daniel F. Jarosz[1]*, Sandra K. Jones[1]†, Amelia Chang[1,2]†, Alex K. Lancaster[1] & Susan Lindquist[1,2,3]

in 10/690 wild strains

in 43/690 wild strains

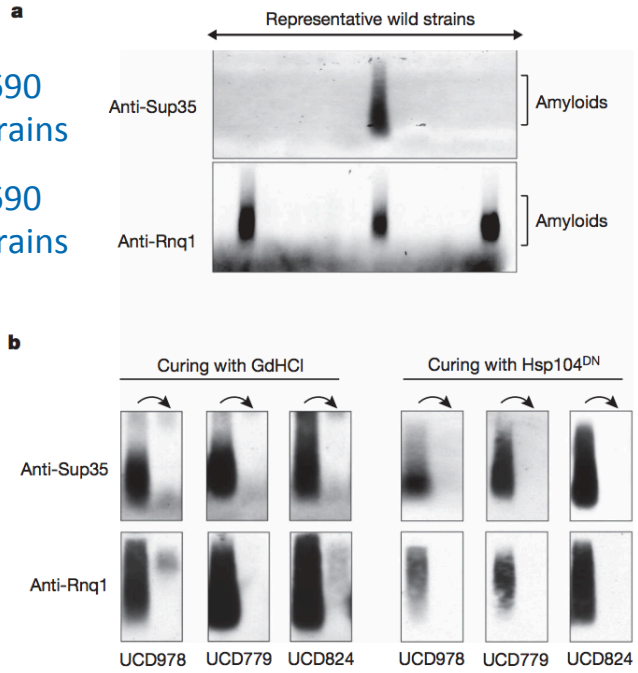


Figure 1 | Identification and verification of prions in wild yeast.

- frequency too high to be a disease
- cured strains grew differently in 37% of the cases (255/690)
- for almost half, cured strain was at a disadvantage!

Take home messages (II)

- prion inheritance is epigenetics beyond the chromosome

(no changes in DNA sequence and no role for chromatin)

- yeast is an excellent system for mechanistic studies of prions
- prion propagation (often) depends on Hsp104
- sequence features of prion domain
- prions are a common mechanism of phenotypic inheritance