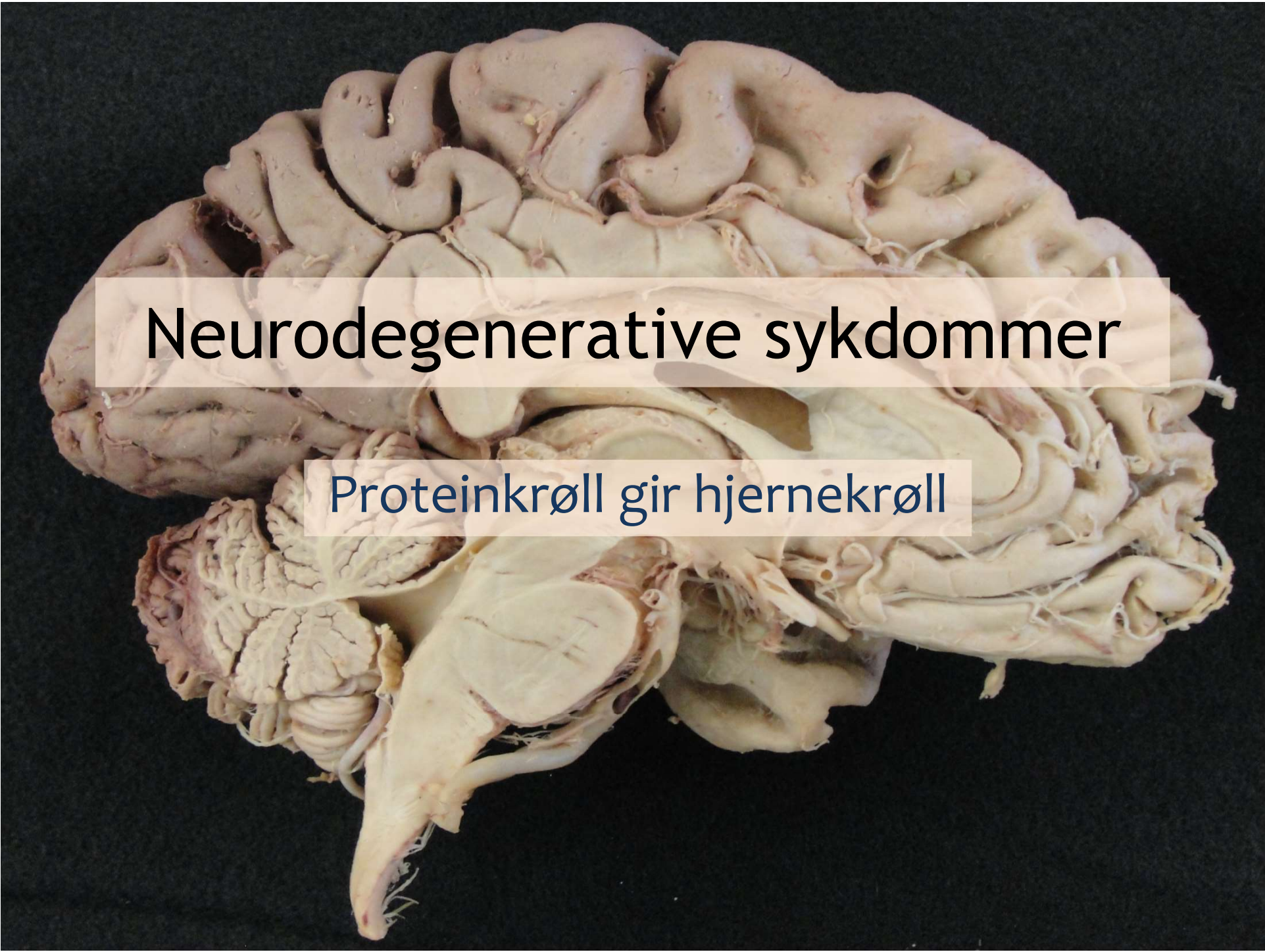


The image shows two human brains against a black background. The top brain is a coronal section, revealing internal structures like the ventricles and basal ganglia. The bottom brain is a smaller, more compact specimen, possibly a cerebellum or a smaller brain specimen. Both brains exhibit a pale, yellowish-tan color, suggesting they are preserved specimens. The text 'Neurodegenerative sykdommer' is overlaid on the top brain, and 'Proteinkrøll gir hjernekrøll' is overlaid on the bottom brain.

Neurodegenerative sykdommer

Proteinkrøll gir hjernekrøll

Sykdommen Kuru «Fryktskjelving»



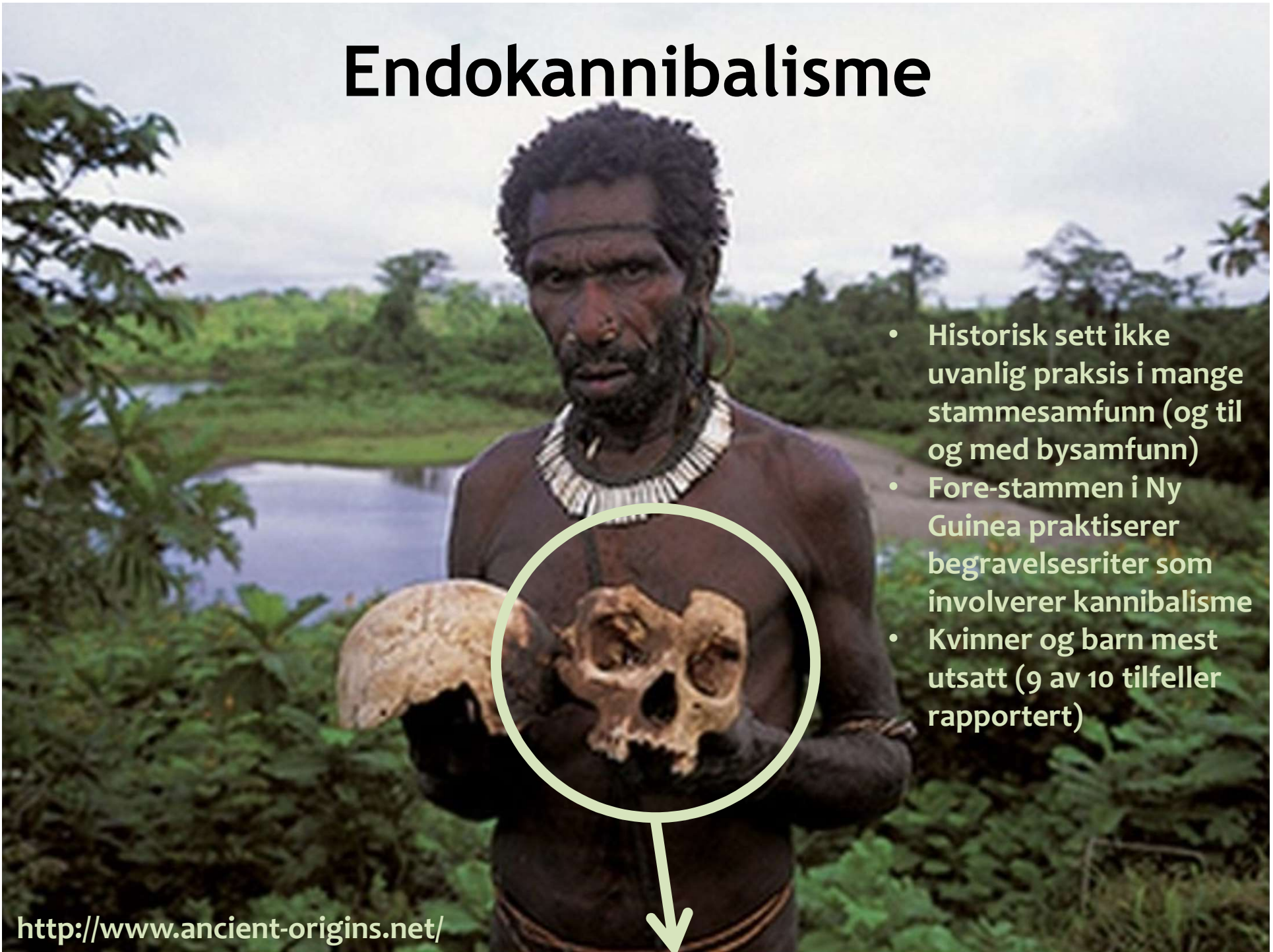
Symptomer og utbredelse



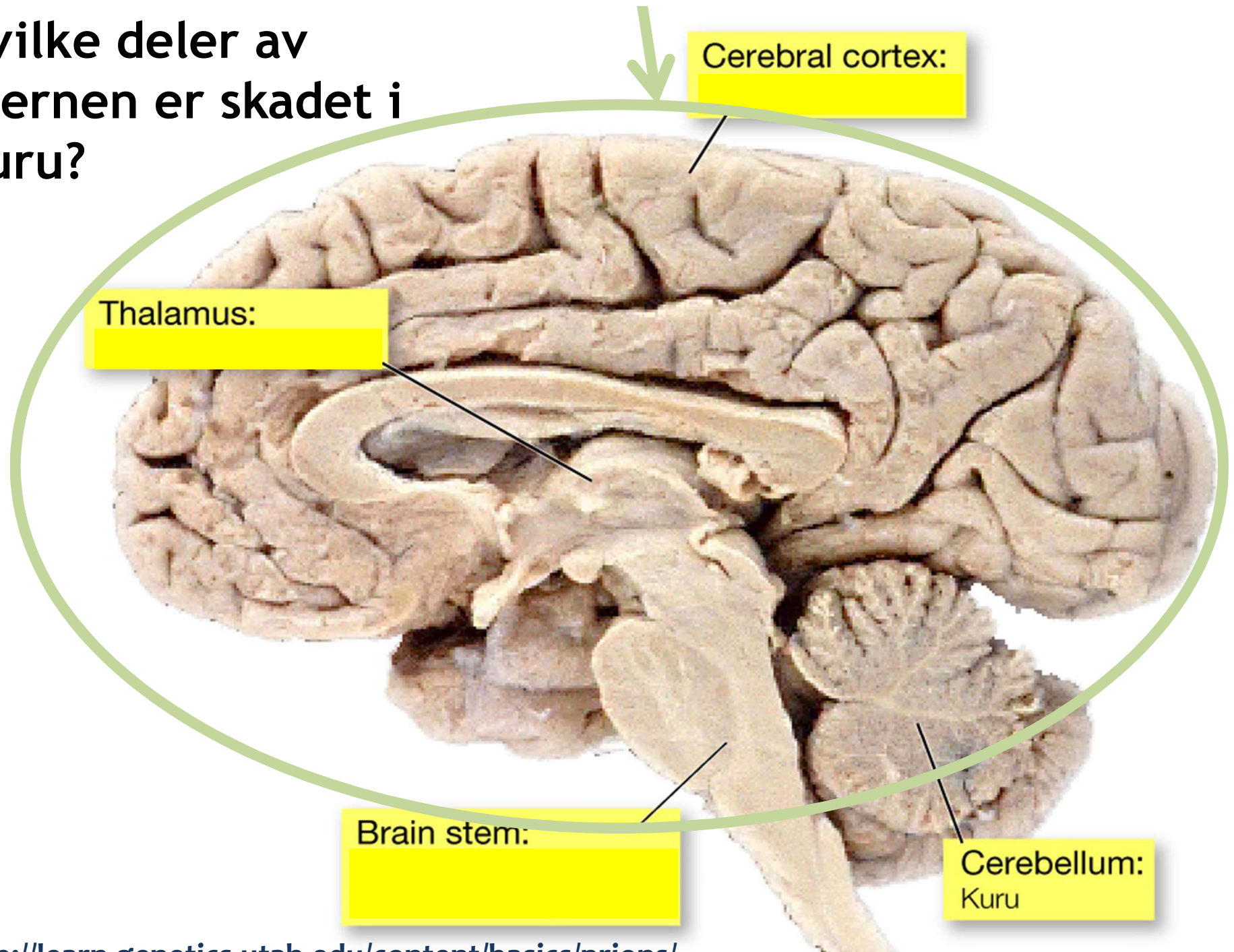
- Midten av 20. århundre: 3000 døde av en befolkning av 30 000
- Kvinner og barn mest utsatt (9 av 10 tilfeller rapportert)
- Tap av koordinering, skjelvinger, tap av evne til å svelge, «ufrivillig» gråt/latter

Endokannibalisme

- Historisk sett ikke uvanlig praksis i mange stammesamfunn (og til og med bysamfunn)
- Fore-stammen i Ny Guinea praktiserer begravelsesriter som involverer kannibalisme
- Kvinner og barn mest utsatt (9 av 10 tilfeller rapportert)

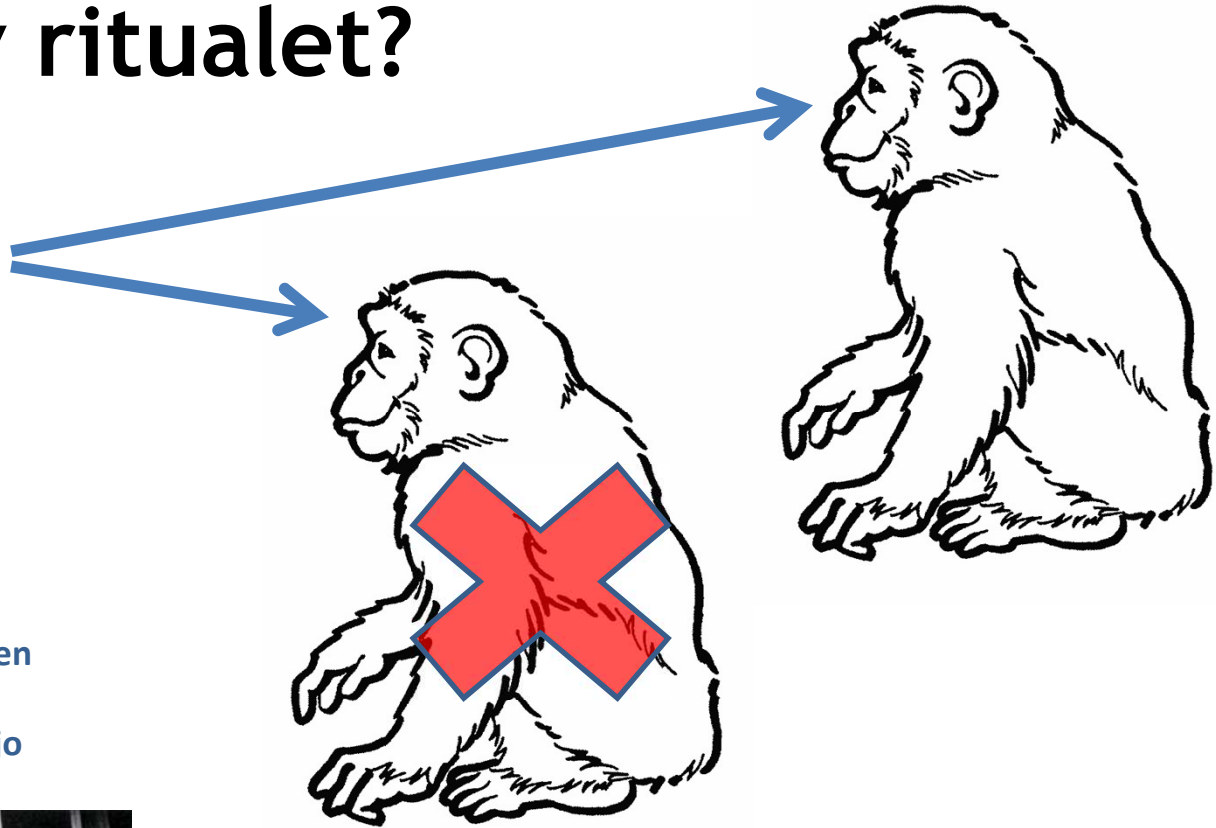


Hvilke deler av
hjernen er skadet i
Kuru?

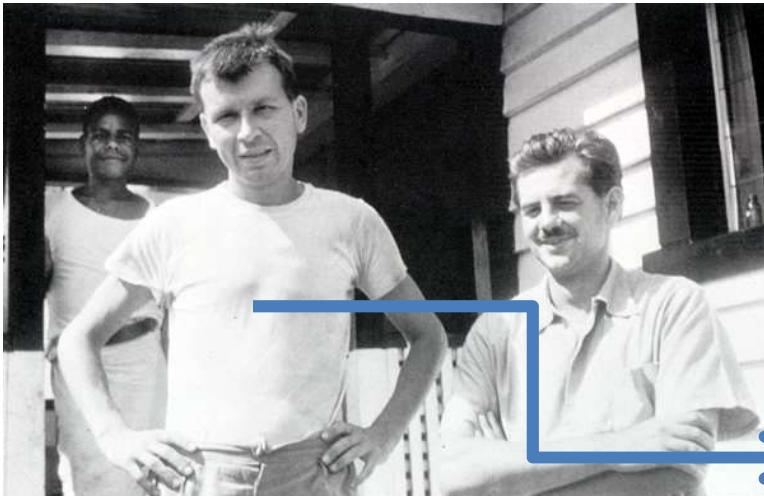


Var smittestoffet i hjerne, som ble spist som en del av ritualet?

Hjernemasse fra
avdøde Kuru-
pasienter.



Dr. Gajdusek (fornt left). New York: Raven
Press Books, 1981 and
<https://becker.wustl.edu/about/news/journals-dr-carleton-gajdusek>



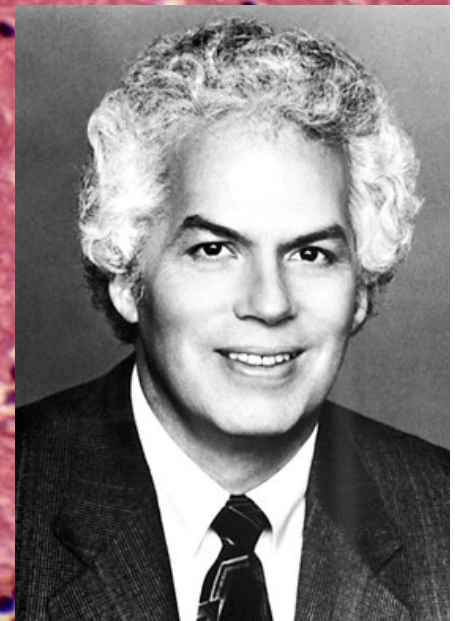
- Via diett og sår/kutt på hendene – forklarer hvor det var mest kvinner og barn som fikk sykdommen
- «Slow virus» mistenkt som smittestoff
- Forklarer hvorfor kvinner og barn var mest utsatt (9 av 10 tilfeller rapportert)

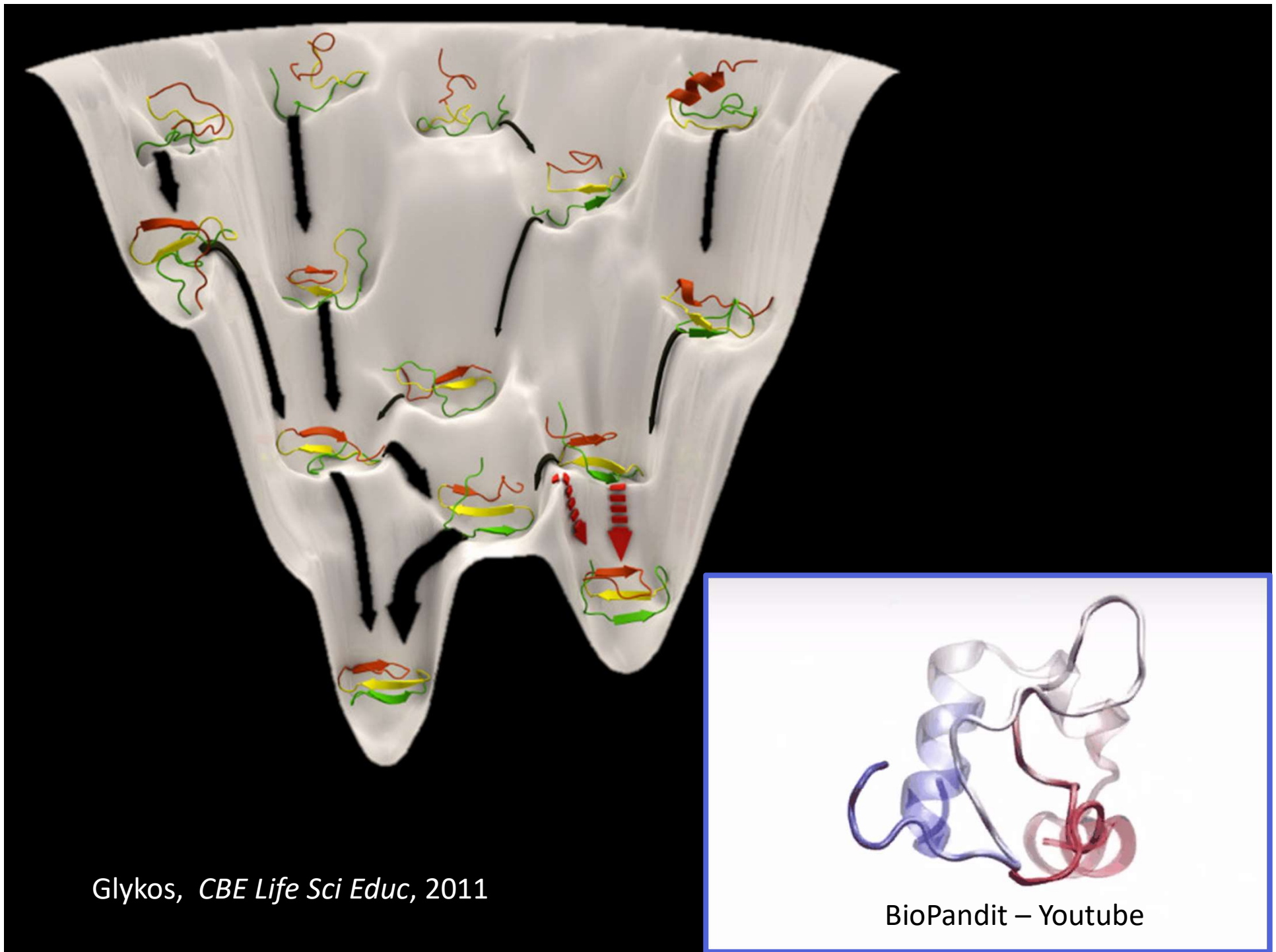
Nobel Prize in Medicine, 1976

Hva er smittestoffet?

- Mange uvanlige ting med smittestoffet
 - Irradiering ineffektivt
 - Nukleaser ineffektive
 - Tilsynelatende ingen bakterier eller virus assosiert med smitte
- PrP, et protein, assosiert med påvirket vev (post-mortem)
- Covarierer med smitte, sånn omtrentlig

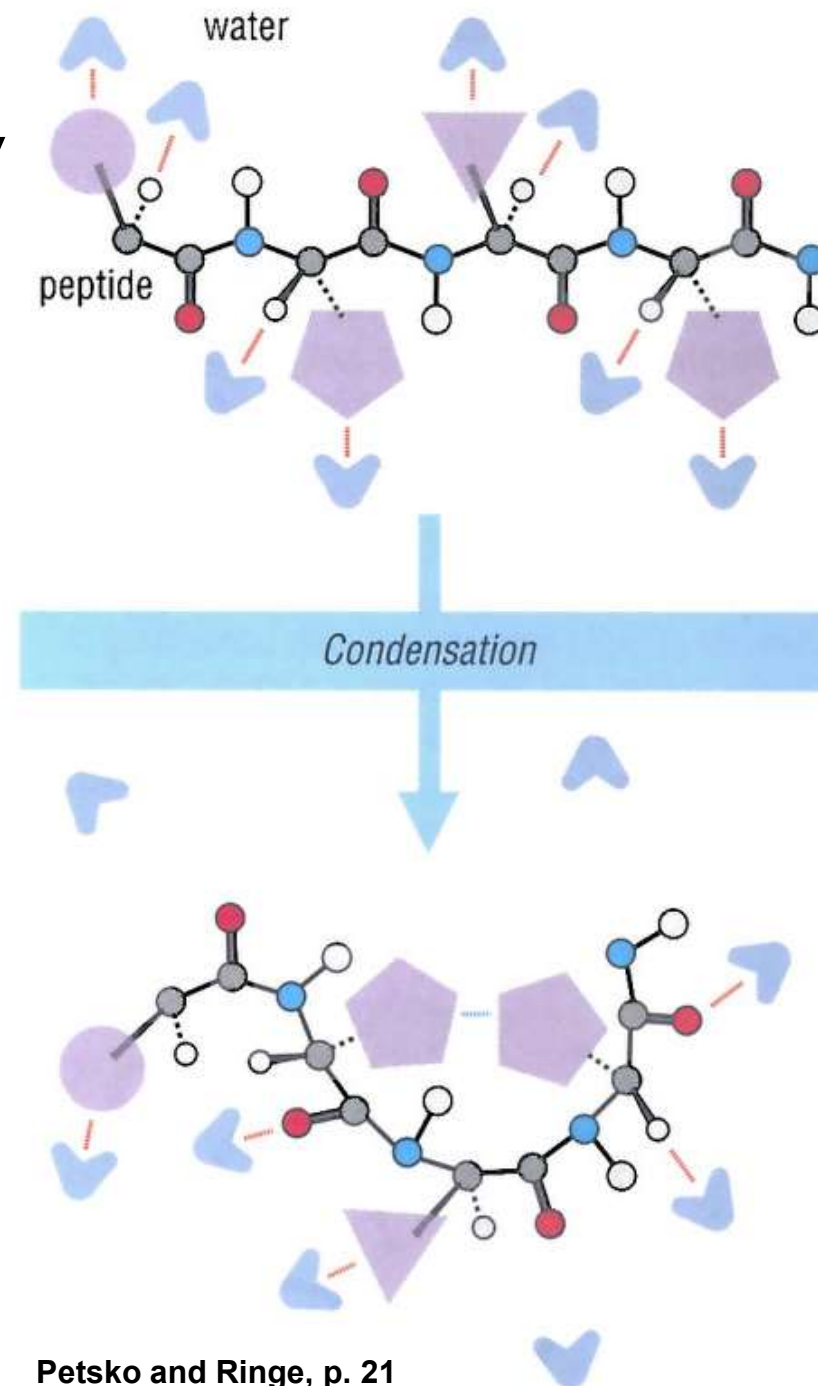
Stanley B. Prusiner
The Nobel Prize in
Physiology or
Medicine 1997





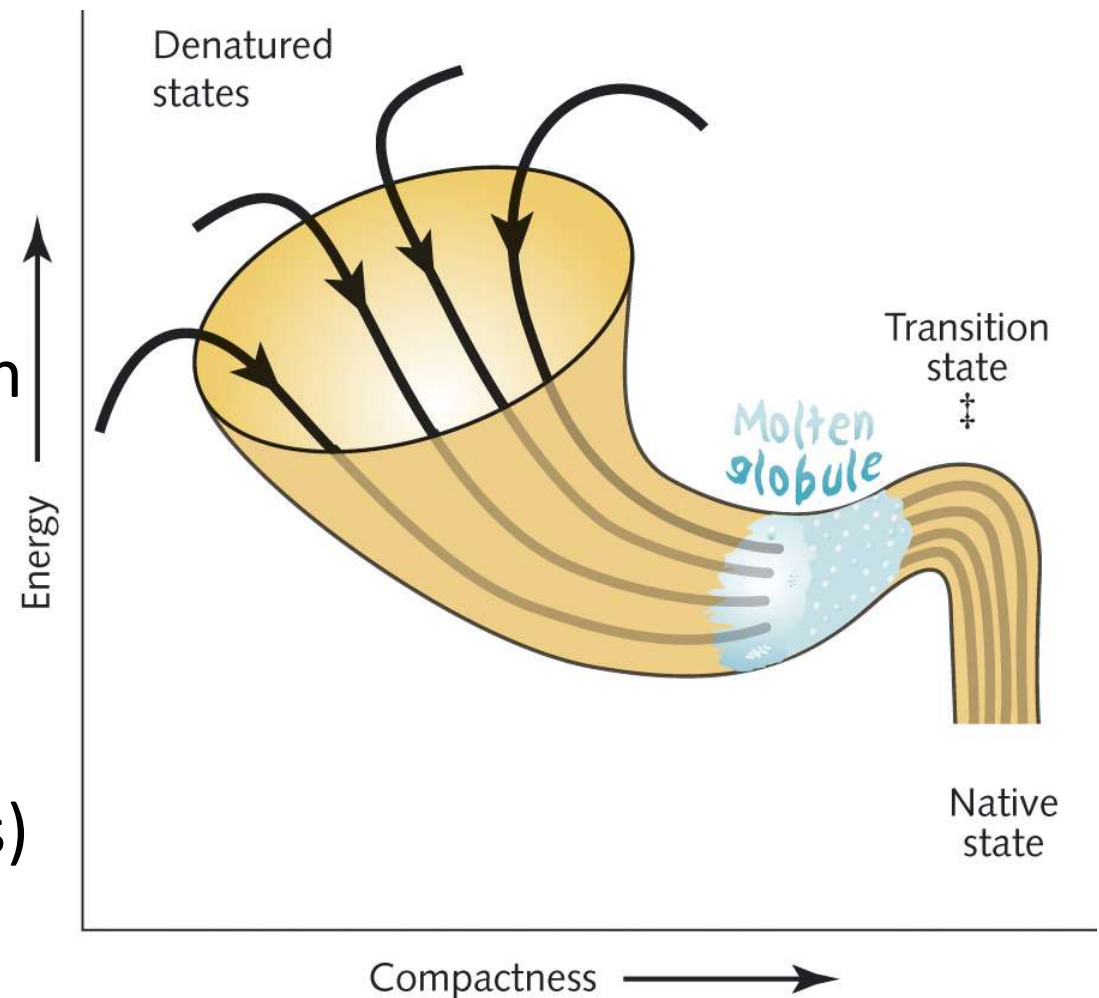
Vekselvirkninger/ bindingsdannelse i løpet av folding vil:

- Make small groups of hydrophobic residues
- Link distant parts of the polypeptide
- Expel water
- Sort residues into core and surface arrangement
- Optimize local configuration of backbone and sidechains
- Form secondary structure to provide H-bond opportunities for the backbone
- Continuously compensate for loss of entropy by releasing heat from bond-formation

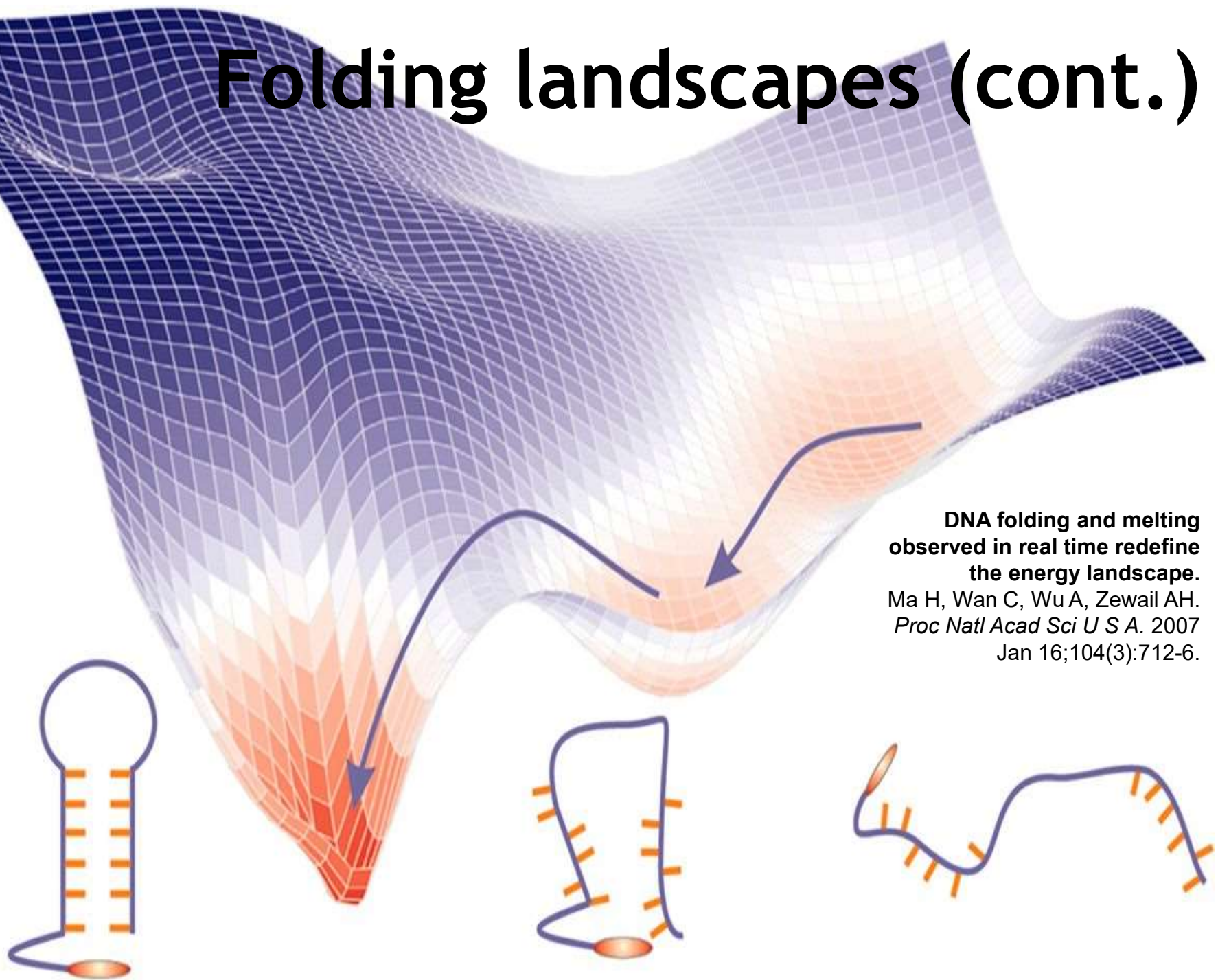


At the level of the protein structural hierarchy, folding involves...

- Fast collapse and secondary structure formation (typical timescale ms)
- Molten globule formation
- Appearance of tertiary structure, sidechains still mobile (timescale ms-s)
- Final “crystallization” to native state (timescale <s)



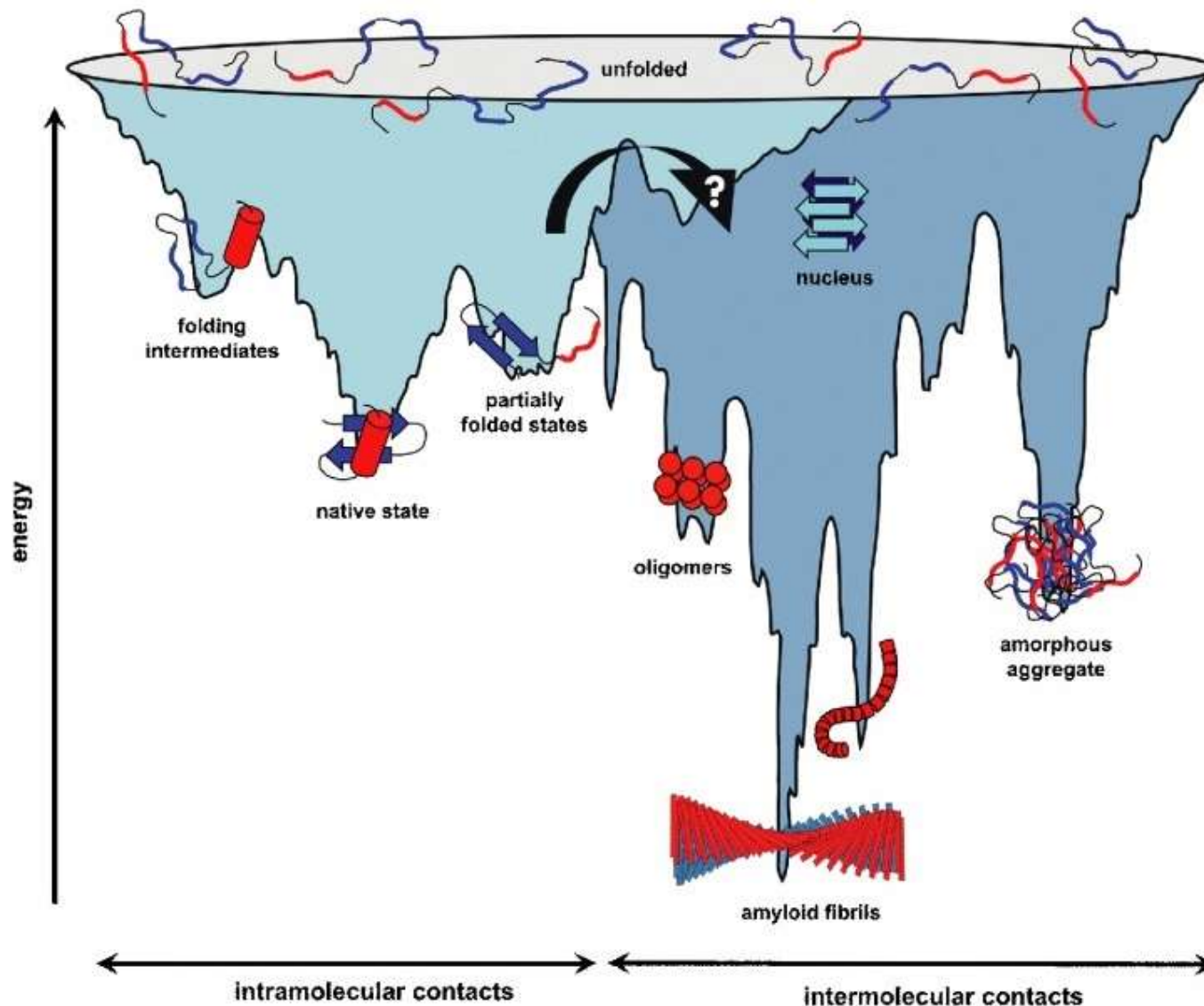
Folding landscapes (cont.)



**DNA folding and melting
observed in real time redefine
the energy landscape.**

Ma H, Wan C, Wu A, Zewail AH.
Proc Natl Acad Sci U S A. 2007
Jan 16;104(3):712-6.

Men hva skjer dersom noe «misfolder»?



Misfolding may lead to loss of function but also gain of toxic “function”

Og hva om noe promoterer misfoldede konfigurasjoner?



PrPC

Normalt fungerende protein, aktivt i mange vevstyper.

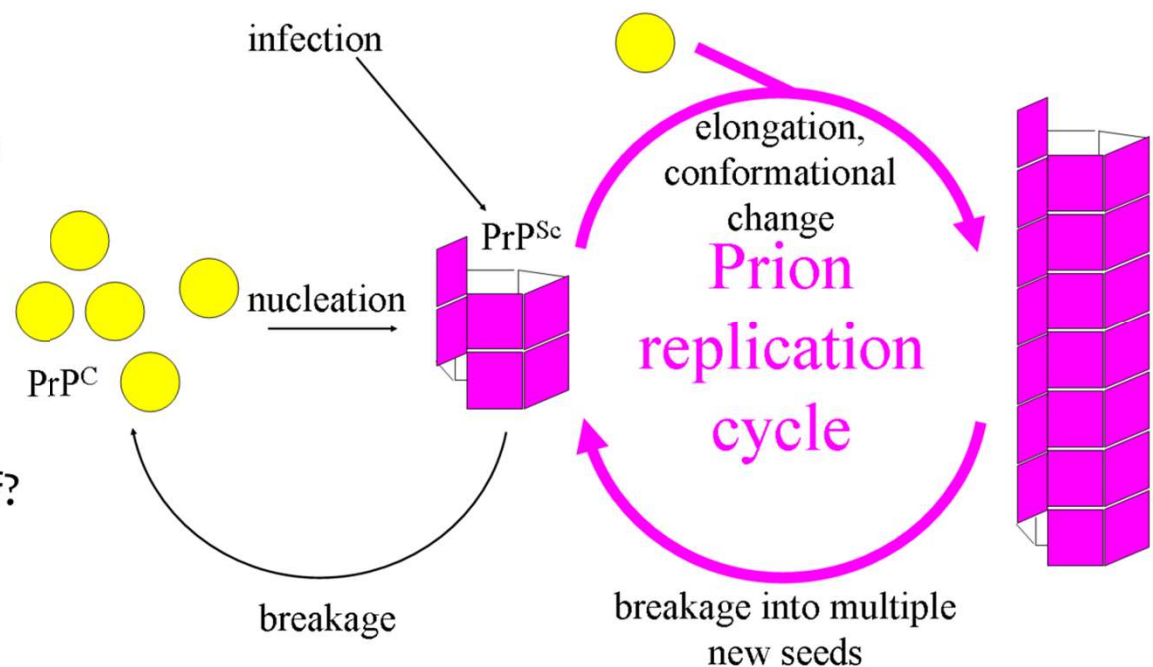
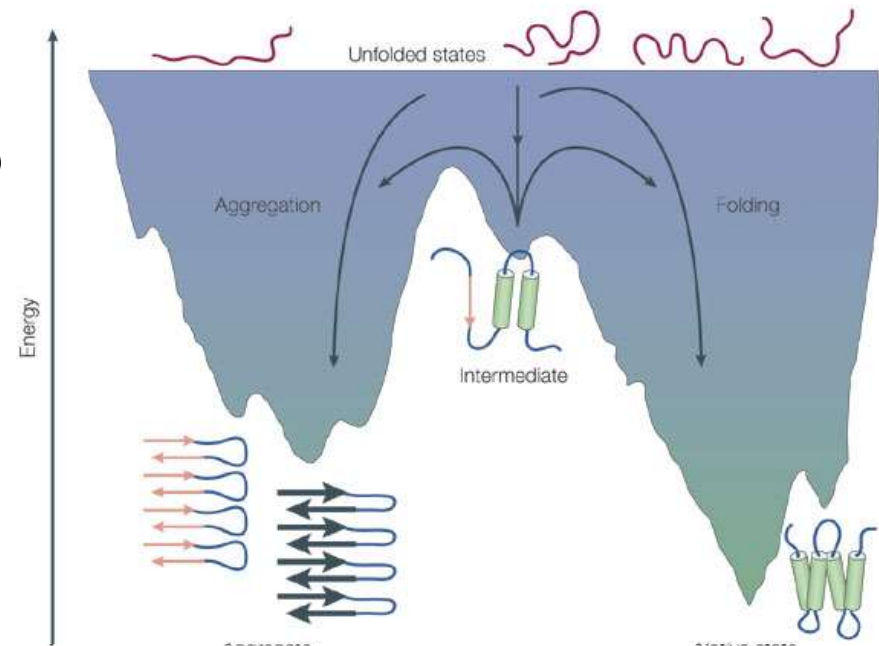
PrP^{Sc}

Aktivt skadelig, antatt å være smittesubstans

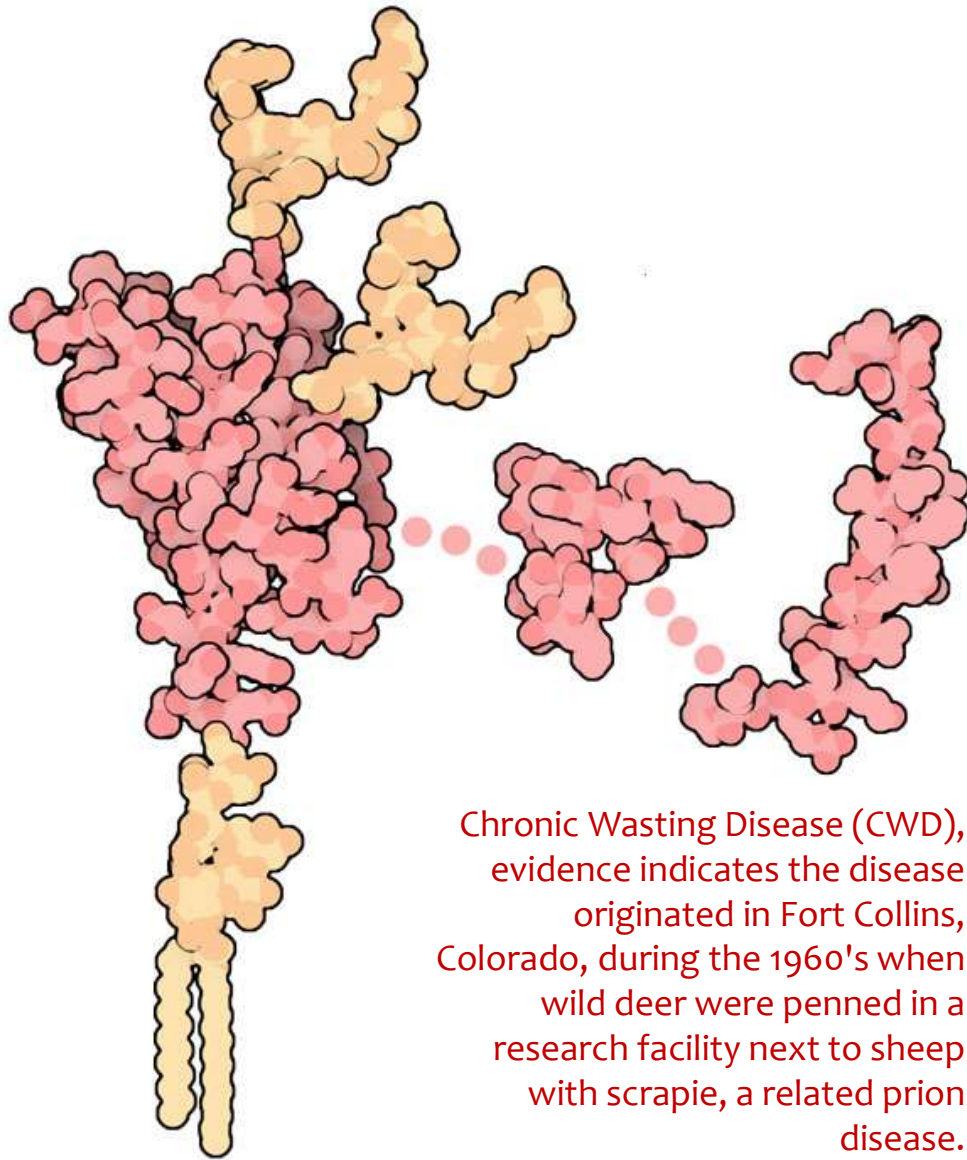
PrP^{Res}

PrP som er resistent mot proteaser, ikke-funksjonelt. Smittestoff?

based on pdb-structure 1AG2,
org/pdb/explore/explore.do?structureId=1ag2



Prioner i nyhetene



Chronic Wasting Disease (CWD), evidence indicates the disease originated in Fort Collins, Colorado, during the 1960's when wild deer were penned in a research facility next to sheep with scrapie, a related prion disease.



<http://www.sciencemag.org/news/2017/04/norway-plans-exterminate-large-reindeer-herd-stop-fatal-infectious-brain-disease>



<http://www.deerfriendly.com/deer-disease>

2200 rein skal slaktes

Ti prosent av den norske villreinstammen skal slaktes ned i Nordfjella, og hele området blir lagt øde i mange år. Frykten for at skrantesyken skal spre seg er årsaken.



Her er det funnet dyr med skrantesyke

Elgku fra Selbu i mai 2016



Tre reinsdyr fra Nordfjella villreinområde fikk påvist sykdommen i 2016.



SKRANTESJUKE (CWD) I NORDFJELLA

CHRONIC WASTING DISEASE (CWD) IN NORDFJELLA / AUSZEHRKRANKHEIT (CWD) IM NORDFJELLA



Hjortedyrene i Nordfjella kan være smittet av skrantesyke (CWD). Hjelp oss å hindre at smitten sprer seg til andre områder.

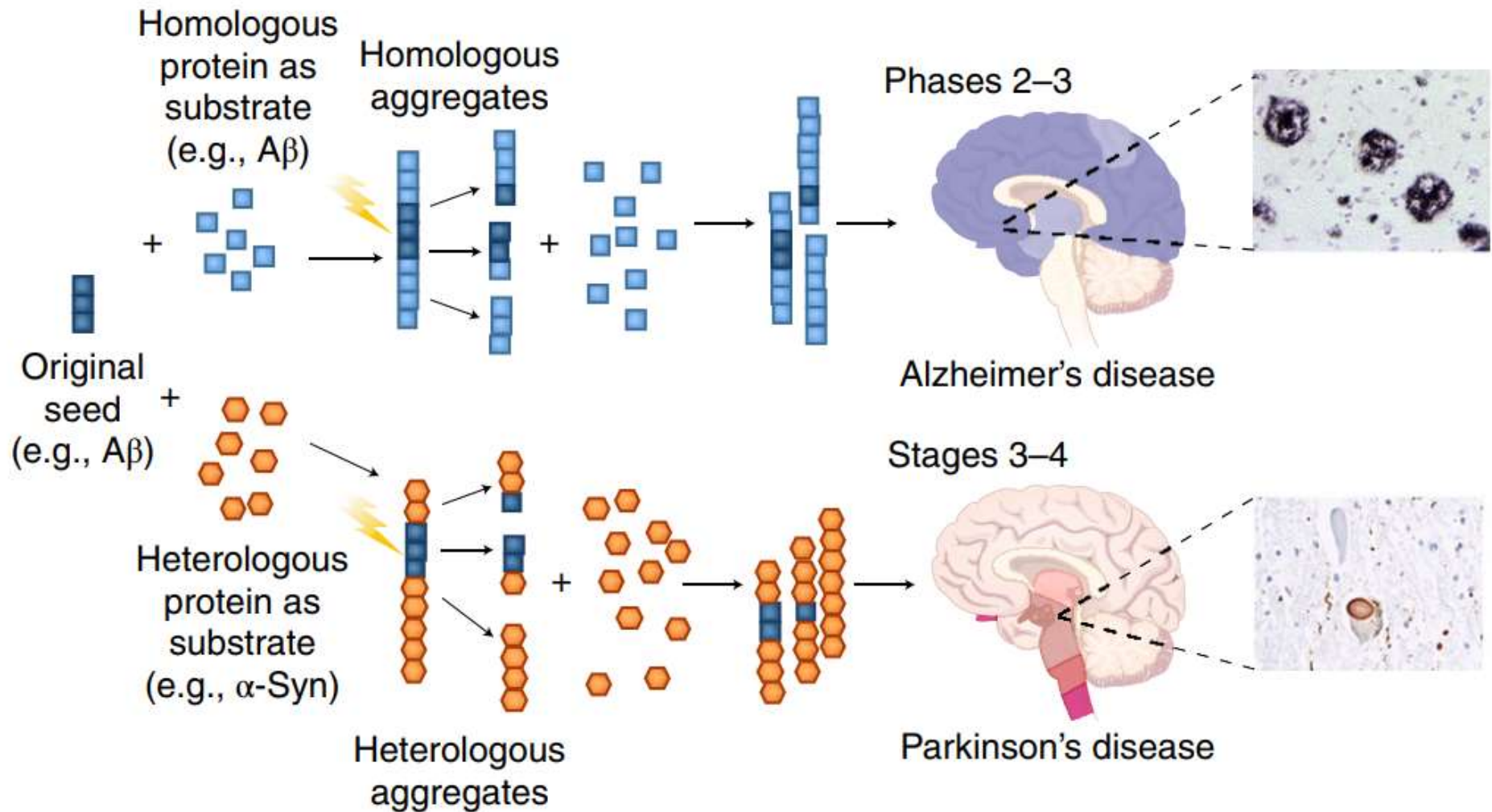
Cervids in the Nordfjella area may be infected with chronic wasting disease (CWD). Please help us to prevent the infection from spreading to other areas.
Der Hirschbestand im Bereich des Nordfjella ist möglicherweise von der Auszehrkrankheit (CWD = Chronic Wasting Disease) befallen. Bitte helfen Sie uns zu verhindern, dass die Erkrankung sich in andere Gebiete ausbreitet!

Du som ferdes i området må:

People who use the area must take the following precautions/Wenn Sie sich in diesem Gebiet aufhalten:



Misfolding and seeding is a shared feature of many neurodegenerative diseases

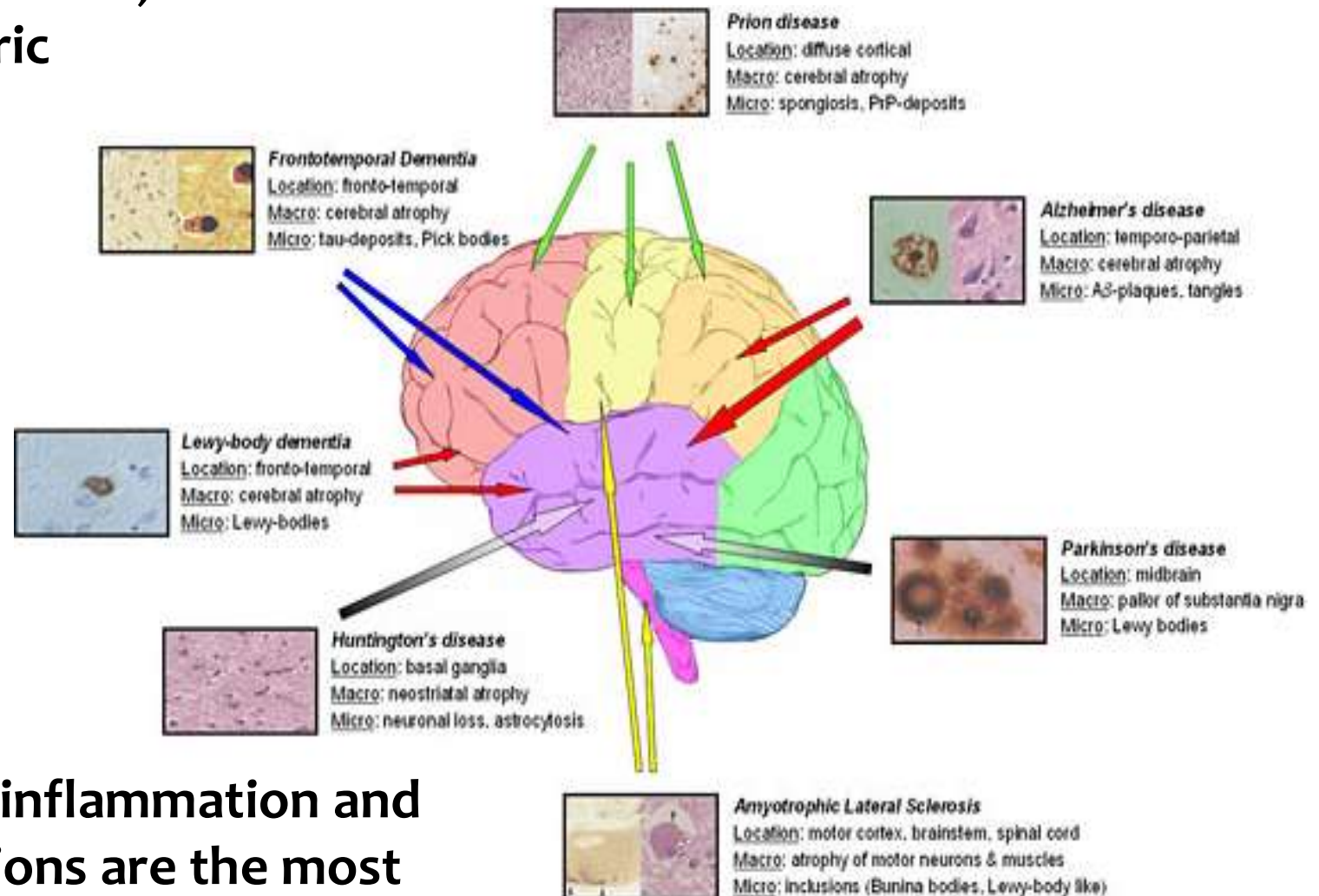


Soto and Pritzkow, *Nature Neuroscience*, 2018. Also, Martin Jakubec

Neurodegenerative diseases including Prionic Diseases

Loss of neurons and neural connections, gain of motoric symptoms

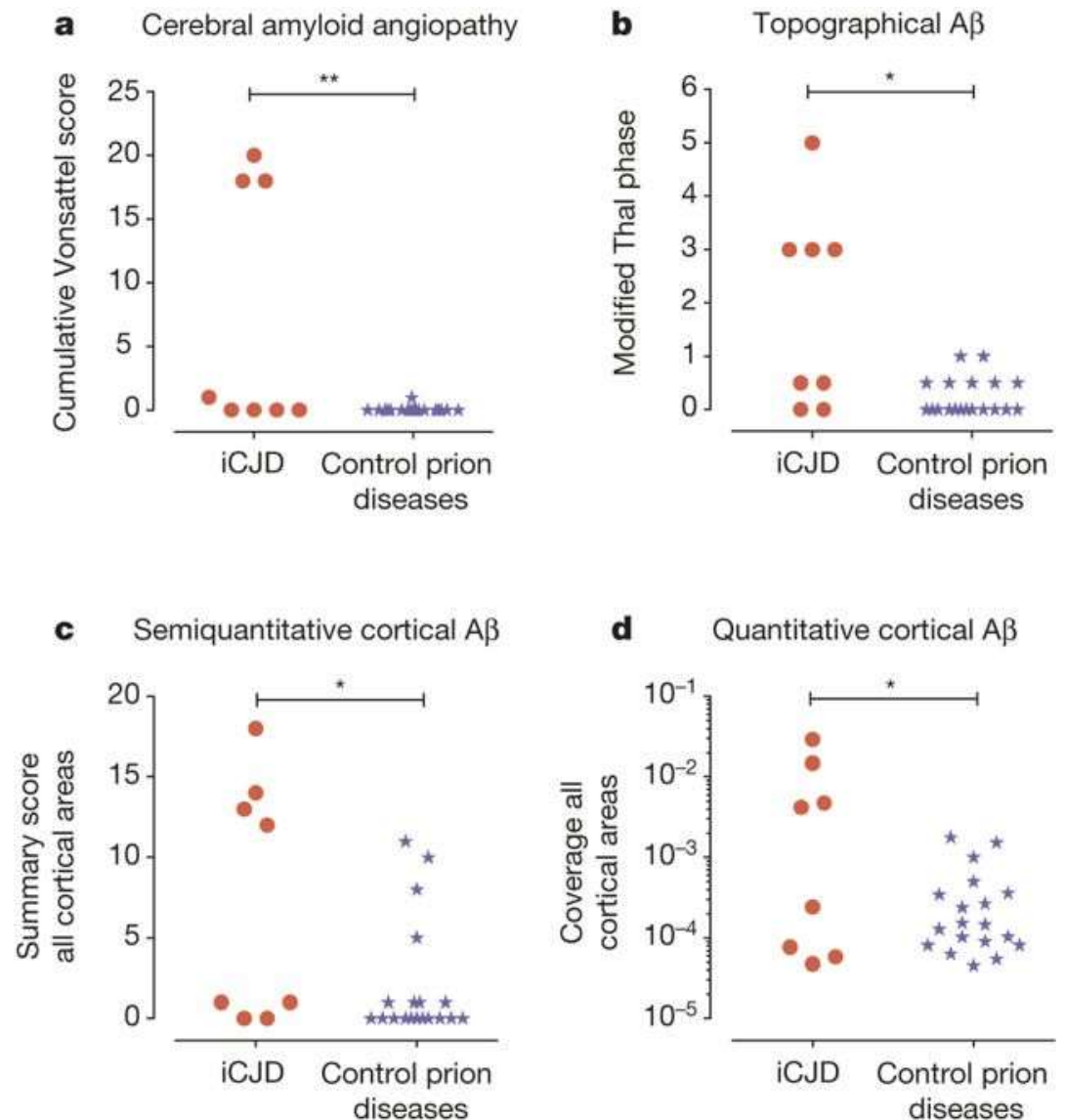
Bertram and Tanzi, 2005



Age, lifestyle, inflammation and genetic variations are the most important risk factors.

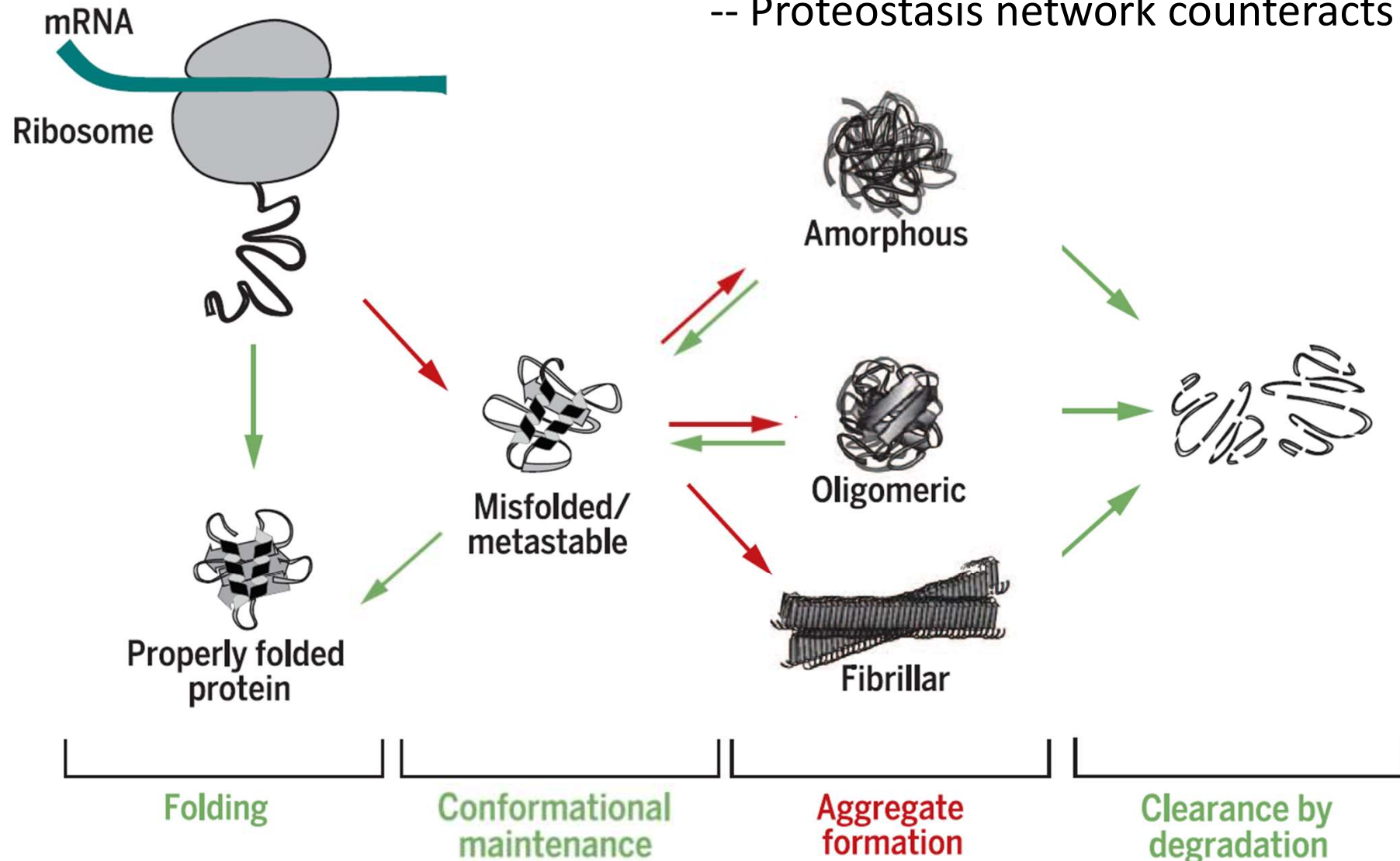
Prion-Alzheimer link

- 200 individuals has developed Creutzfeldt–Jakob disease (CJD) worldwide from treatment with growth hormone contaminated with prions.
- This continues to emerge due to long incubation times of prionic diseases.
- Autopsies of 4 patients showed amyloid- β ($A\beta$) pathology in grey matter and in brain blood vessels.
- Did not co-localize with prion protein deposition.



Protein misfolding affects 1 in 7 proteins in the cell

-- Proteostasis network counteracts this

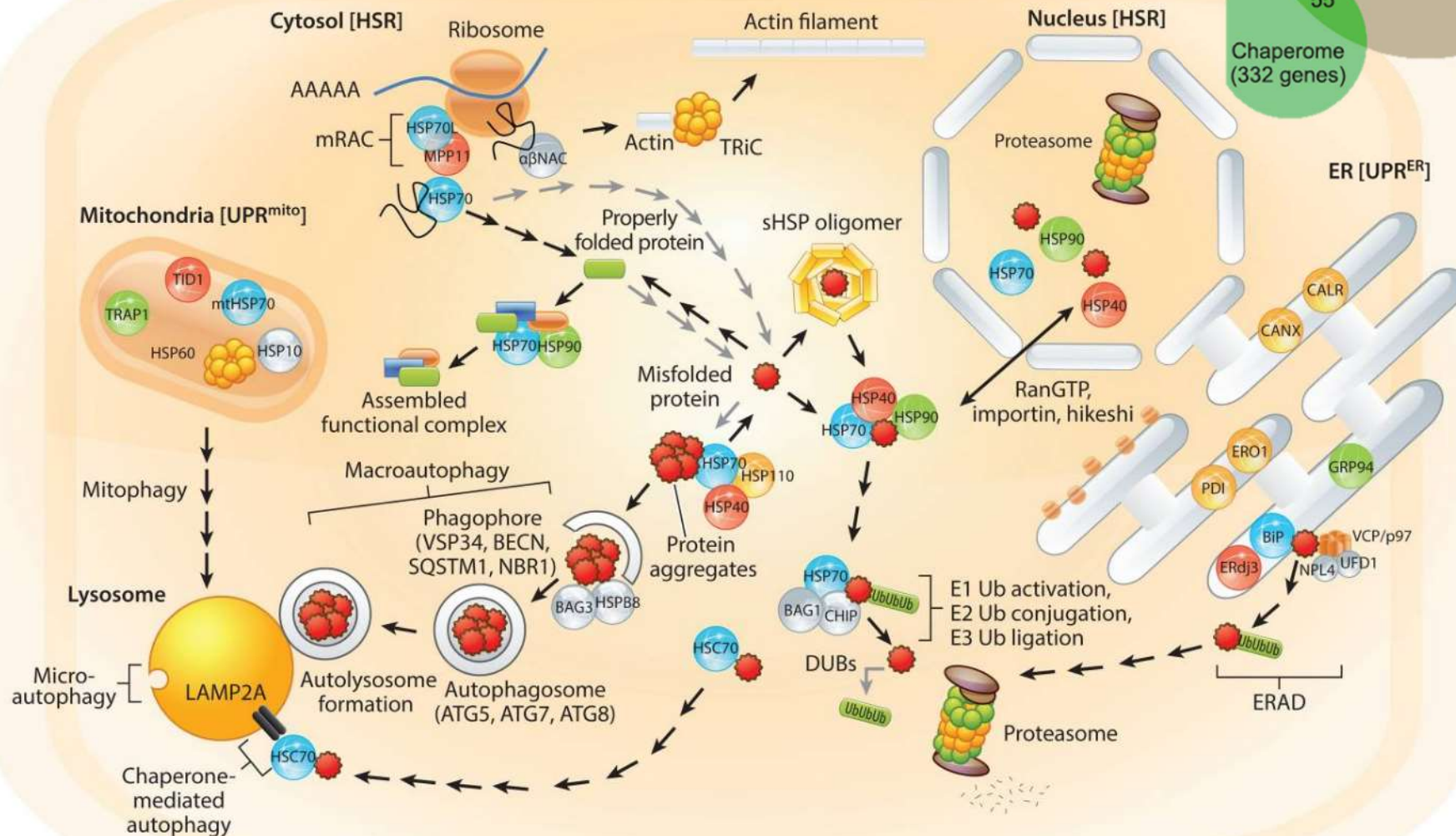


The proteostasis network - robust and complex

Core fitness genes
of K562 cells
(1658 genes)

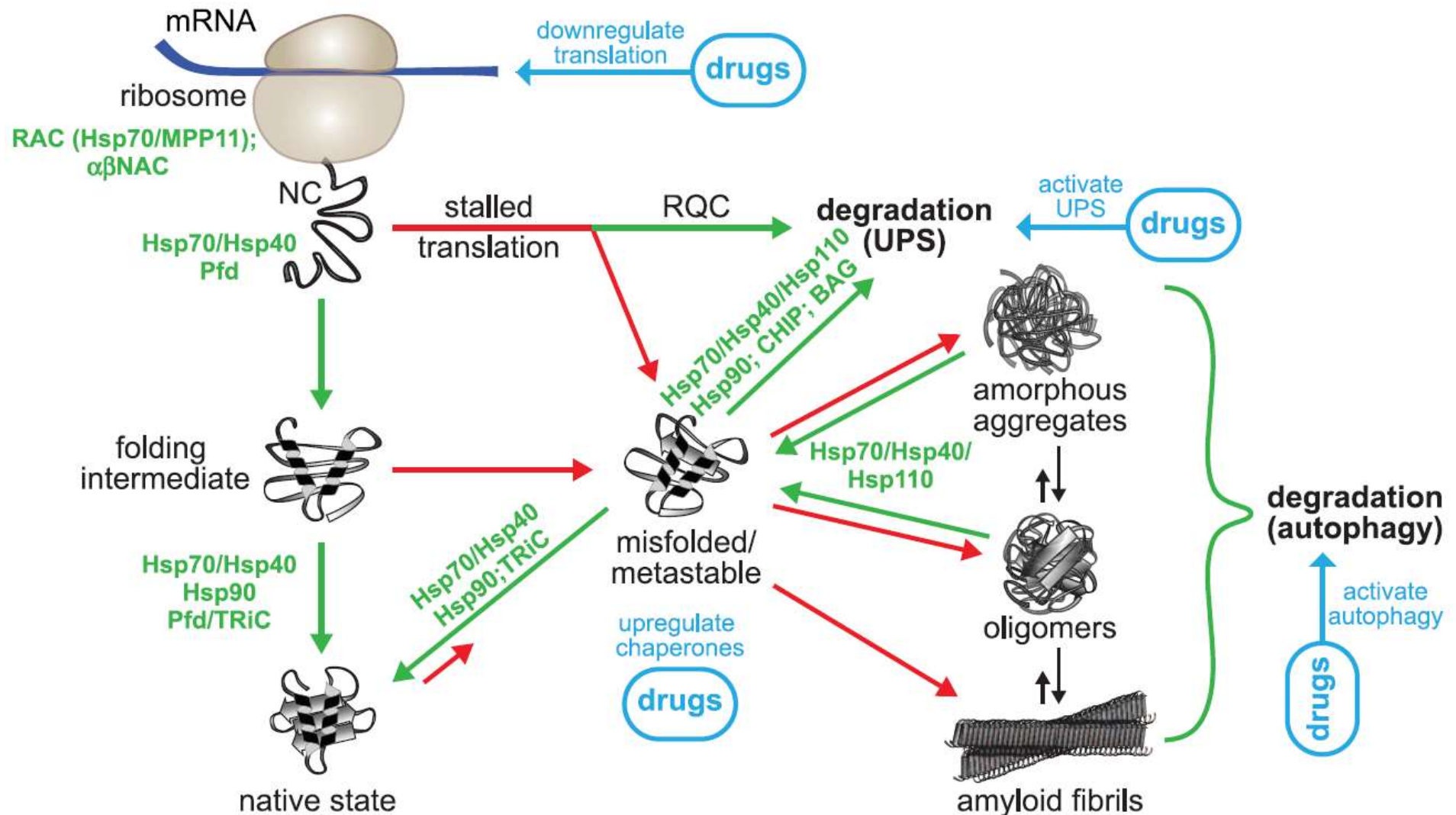
55

Chaperome
(332 genes)



Are there any cures for misfolding?

Could we target all or parts of the folding/misfolding/regulation complexity?



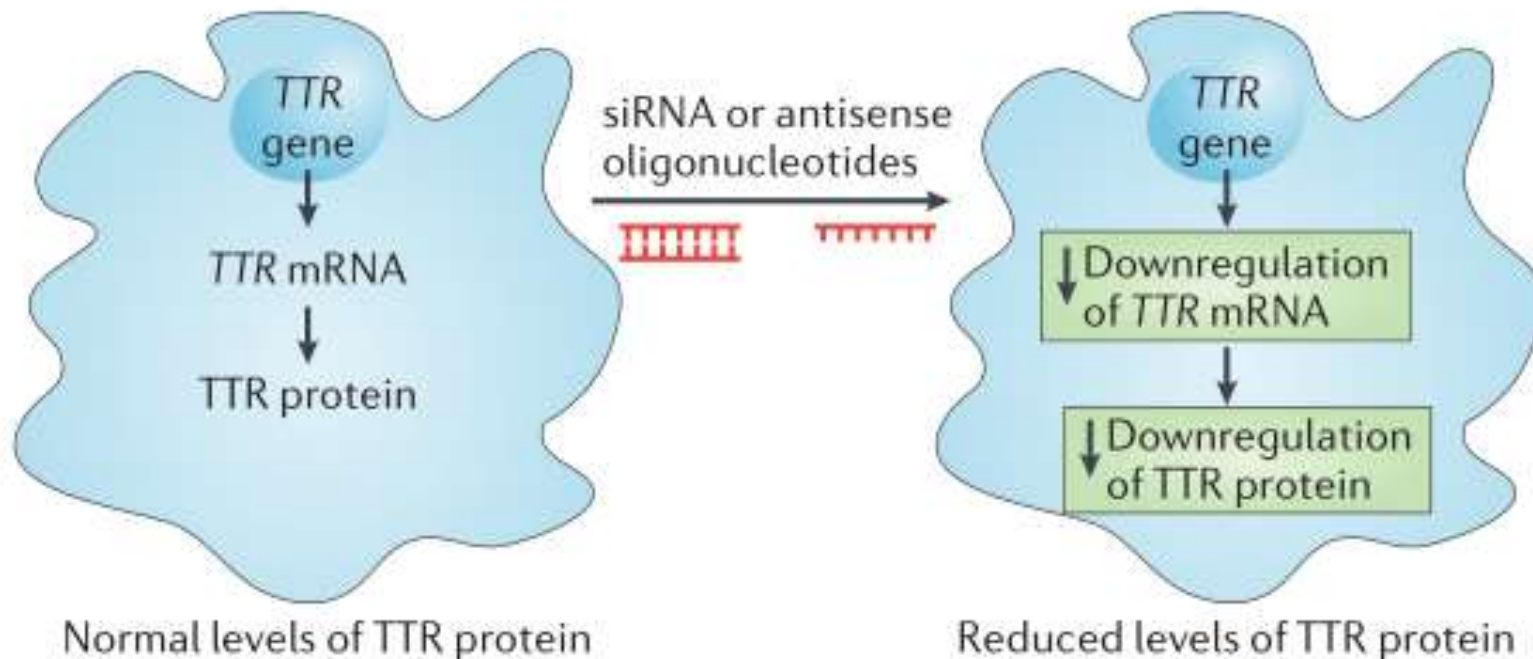
From Balchin *et al.*, *Science*, 2016

Downregulate translation drugs

Transthyretin Amyloidosis – an amyloid disease

- mRNA reduction– Preclinical –Coelho *et al.*, *N Engl J Med*, 2013
- RNAi antisense oligonucleotides – Clinical Trials –Benson *et al.*, *Amyloid*, 2010

e Degrading TTR mRNA to ameliorate TTR amyloidosis



Stabilization of correct fold

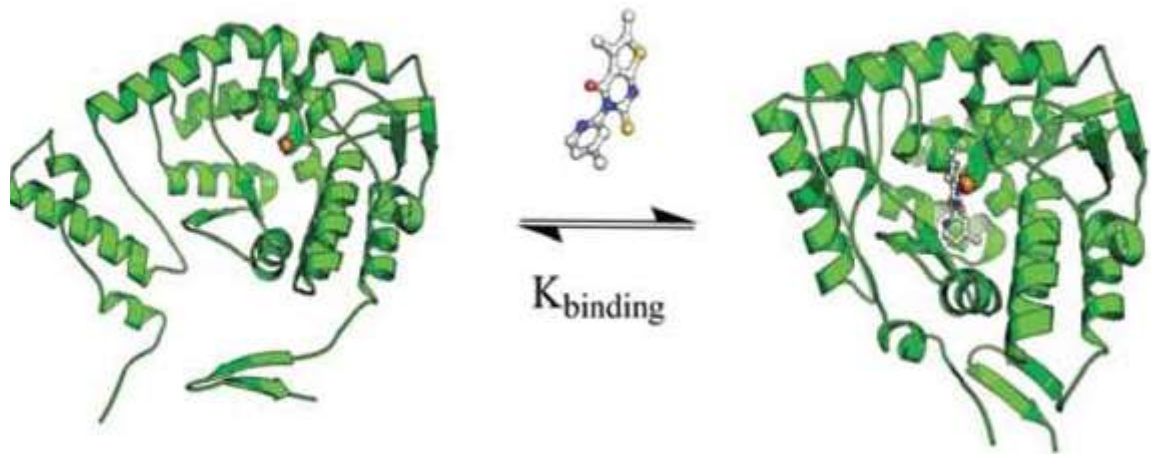
Aromatic amino acid hydroxylase – enzyme family

Phenylketonuria –hereditary diseases in some cases code for marginally stable proteins

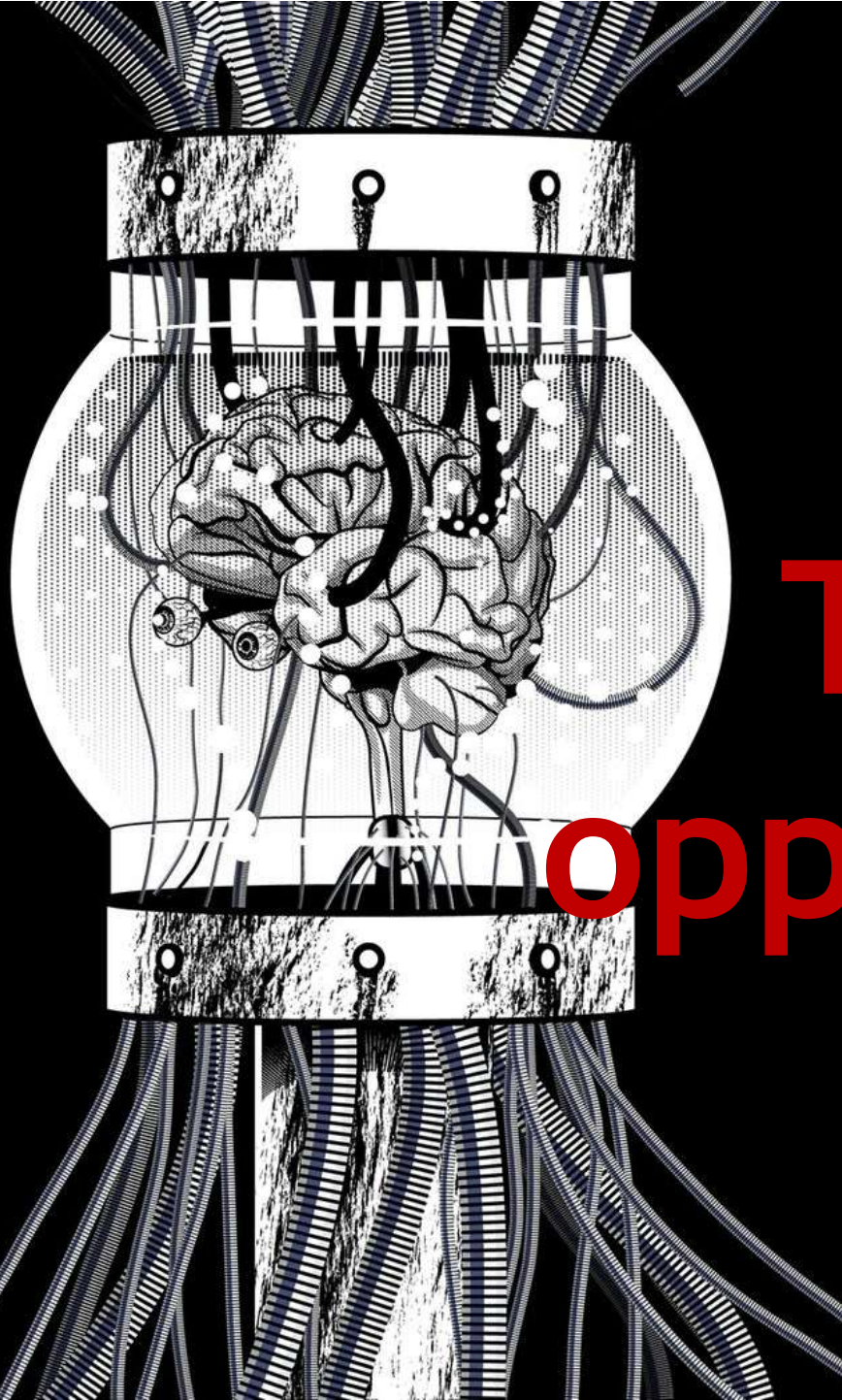
Small molecular chaperons – Preclinical trial



Aurora Martinez



Hole et al., *Current Drug Targets*, 2016



Takk for
oppmerksom-
heten!