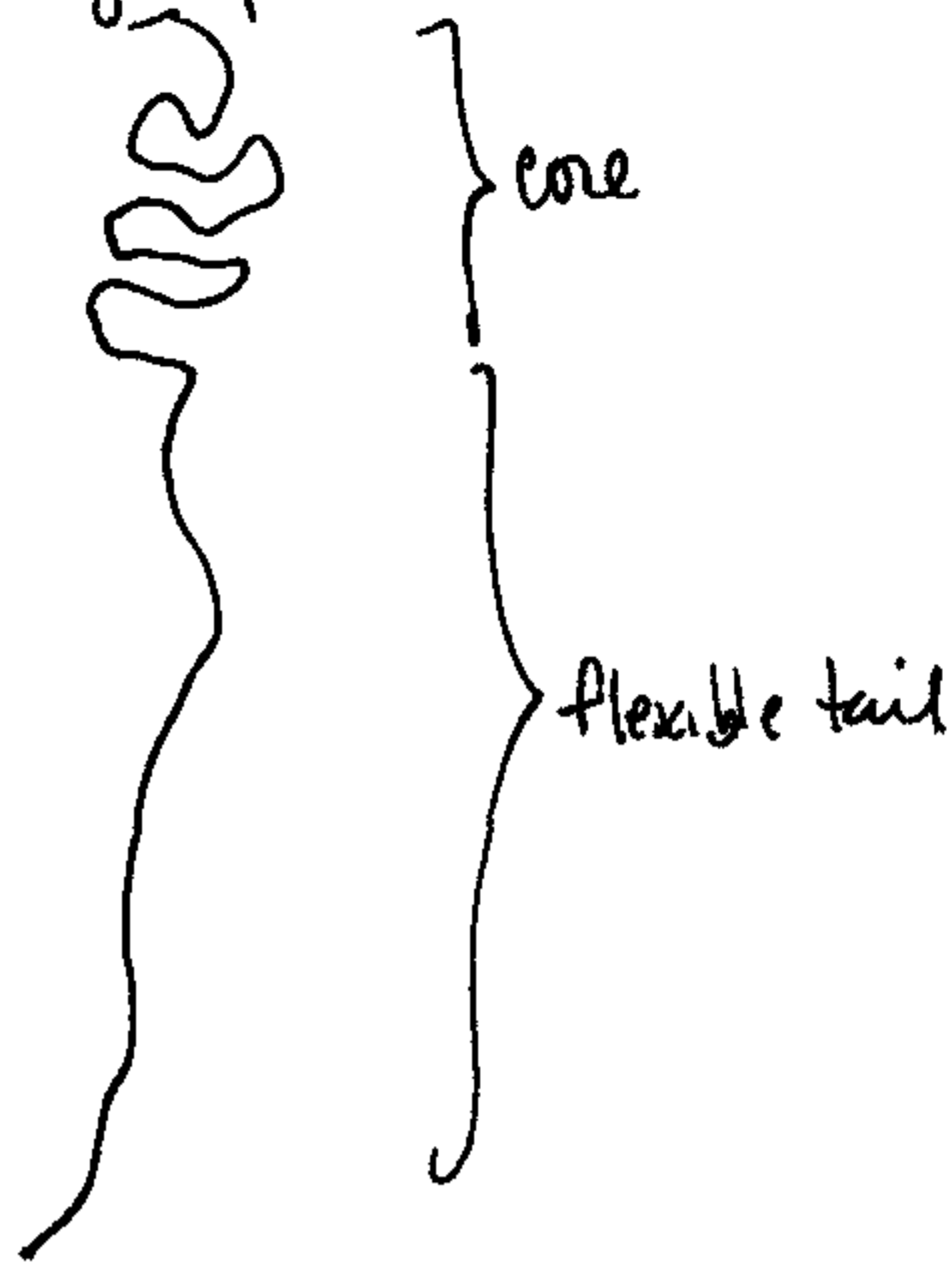


Full Length protein



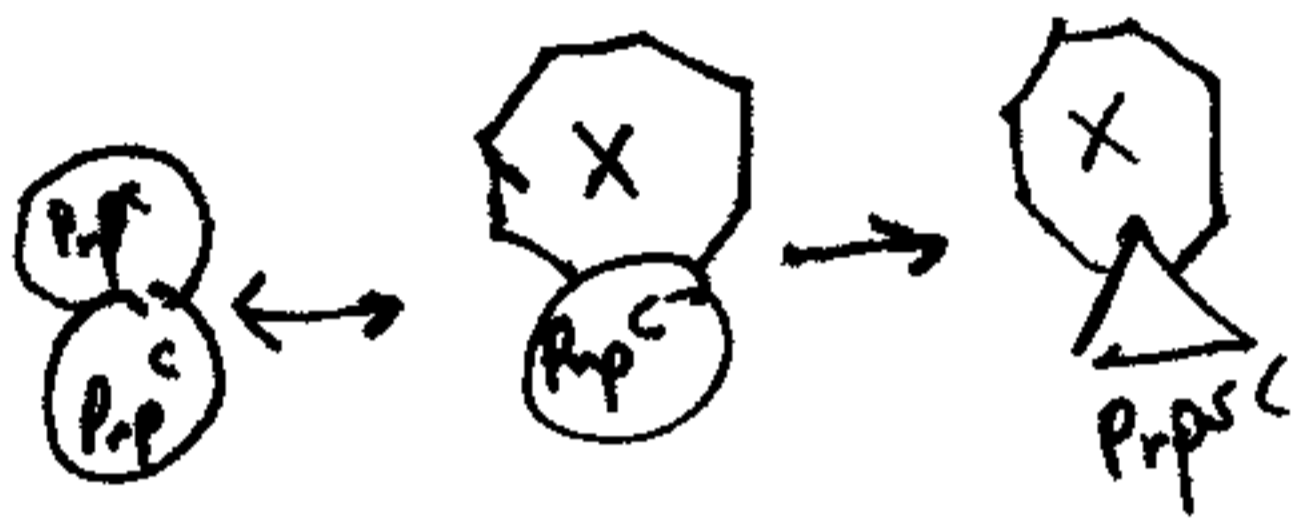
Prion Diseases Resemble

- ALS
 - Parkinson
 - Alzheimeres
- } sporadic forms

Suggests can tx. diseases by working at prot X.

Ethics of

- Some evidence suggests copper might interact w/ tail



Some evidence that there is another protein involved.

Chimeric genes

- mouse/human chimeras provide evidence for prot X

- Dominant negatives can be made which are un Infectible

Human disease

- sporadic
- genetic
- infections

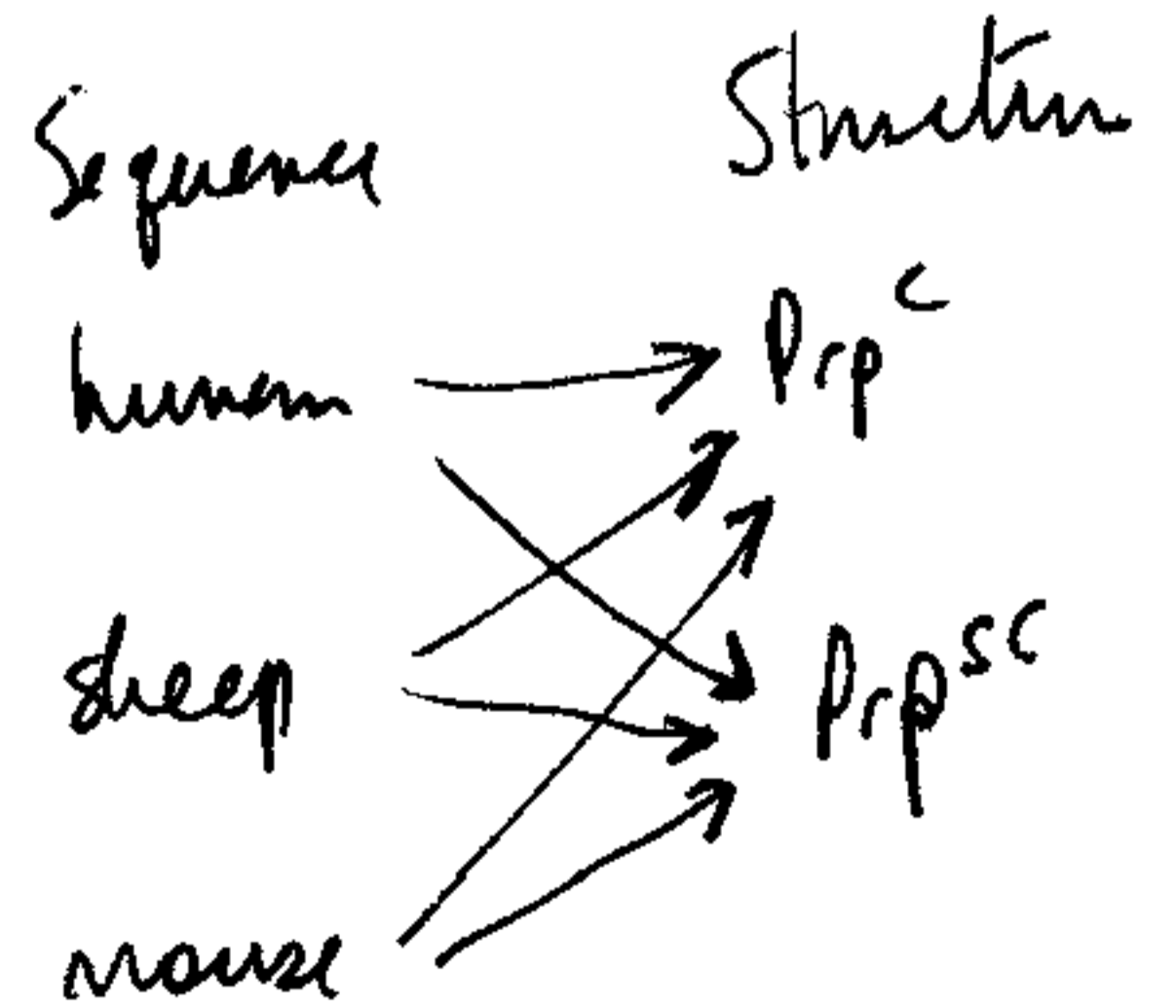
Mad Cow Disease

- ~25 cases in humans
- all young people

20 known PrP mutations

Strains

- how can they exist w/o nucleic acids



- all proteins can make PrP^C structure and PrP^{Sc} structure

Stan Prusiner - 2nd Charley Yanofsky award

Diseases

Autosomal
Dominant

- Kuru - human
- CSD - human -- can be transmitted to some animals
- BSS - human
- FFI - human - fatal familial insomnia
- Scrapie - sheep + goats in wild, can be transmitted to some animals
- Mad Cow

PrP ^C vs PrP ^{Sc}		
42%	alpha	30%
37%	Bsheet	43%
-	infective	+

All can be both genetic + infectious

History (or how the study of prions could have developed)

- 1930's Genetics
- shows in 1960's that it could be infectious
- what about sporadic forms... also common (maybe somatic mutations)

Transmission

- agent is small
- UV irradiation inactivation spectrum
- amt of inactivation at 260 = 280 (suggested might be nucleic acid)
- but reqs tons of UV
- action spectrum similar to some proteins

Mice deficient in PrP^C are resistant
 -> PrP^{Sc} is reqd for infection

Bioassay...

- used to isolate protease resistant protein
- those methods that modify proteins could reduce activity
- " " " " nucleic acids did not reduce activity
- microsequence protein
- single exon

Two mice strains

- one long incubation
- one short " " } the genetics of this showed linkage w/ PrP gene
2 aa differences in PrP

Normal vs infected

- No differences in PrP tx
- No alternative splicing (1 exon)
- No detectable chemical modifications
- concluded that they were conformationally different

Fred Cohen

- predictions of 2ary structure