



Prions

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Abstract

This presentation contains information regarding what prions are in the body, how they are formed, and what these changes do to the body. Prions were discovered by Stanley B. Prusiner and his team when he proclaimed that his team had discovered and confirmed theories that dated back to the 1960s. Prusiner went on to win the Nobel Prize in medicine. Prions, and the mechanisms of how they propagate are not fully understood.

The general information we now know about prions is being considered to be true, but is still being confirmed. Prions are found on the neurons and occur naturally in the body. The interesting thing about prions is the problems when they undergo a physical change. When prions change from their normal state to their misfolded state, neurons are effected. Not only humans have prions, animals have them as well. This process of prions folding is suspected to be an infectious process. When one prion has been misfolded, it is believed to come in contact with a normal prion, and force it to also misfold. This process continues on and each prion spreads then to others. Once spread, folded prions are suspected to cause different diseases or conditions in humans. But this still does not explain how the process of folding the prions begins. There are many suspected sources of folded prions. These include animals, mutation in the PRNP gene, infected tissue or organ transplant, or heredity.

There is still much to learn about prions and the things we know still only theories. But science is well on the way to understanding more to benefit our lives. Prions and other misfolded protein diseases could be the answer to many diseases we already encounter within our society. As we learn more, there could be new solutions to health problems, and a better understanding of our body.

PrP^{SC} is different then then the normal infectious agents such as bacteria, viruses, parasites, and fungi, in which they do not contain nucleic acid. This was shown be treating them with ultraviolet light, then placing them back in an animal to test infectivity. After the UV dose the prions were still able to infect the animal.

Studies in mice have shown that there is an important condition with PrP^{SC}. PrP^{SC} can not cause any disease if PrP^{SC} is nonexistent. No relationship exists between concentration of PrP^{SC} and severity of disease. Older mice have more of an affinity to developing neuronal loss symptoms spontaneously. As for inheritance, chromosome 20 carries the genes responsible for transmissible spongiform encephalopathy.



Protein X: the unknown protein designated "X" is believed to be a protein that binds to PrP^C and causes the change to PrP^{SC}. The idea is that the protein binds and causes changes in the folding of the protein.

The change in conformation of the protein is different than a virus or bacterial infection, in which it does not cause an immune response in the body. Prions were first thought to be a virus that infected it hosts slowly. There are no nucleotides that have been detected on the PrP^{SC} form. Also the sequence of amino acids does not change either, this is contrary to the belief that amino acids code for the conformation of the protein.

Diseases

Mad Cow Disease: caused by the contacts of cows, eating beef, and drinking unpasteurized milk

Creutzfeldt - Jakob disease: A fatal neurodegenerative disorder that usually affects older persons.

Kuru: Transmitted by eating the brains of dead persons who had the disease. It is found in New Guinea and occurs mainly in women and children.

Fatal Familial Insomnia (FFI): An autosomal dominant sleep disorder with pathological lesions in the thalamus.

Gertsmann-Straussler Scheinker Syndrome: Genetically determined, most have autosomal dominant inheritance, and very rare.

Scrapie: A fatal disease that affects the nervous system of sheep and goats.

Aplers Syndrome: is a name given to prion diseases in infants.

Huntington's disease: In this disorder, the repeated trinucleotide is CAG, which adds a string of glutamines (Gln) to the encoded protein (called huntingtin). The abnormal protein increases the lelep53 protein in brain cells causing their death by apoptosis.

Parkinson's disease: is a disorder of the central nervous system that often impairs the sufferer's motor skill and speech.

Alzheimer's: destroys brain cells, causing memory loss and problems with thinking and behavior severe enough to affect work, lifelong hobbies or social life.

Chronic Wasting Disease: a transmissible neurological disease of deer and elk that produces small lesions in brains of infected animals

There are several ways humans can get infected:

Hereditary: It's a dominant trait

Prions disease caused by a new mutation in the PRNP gene

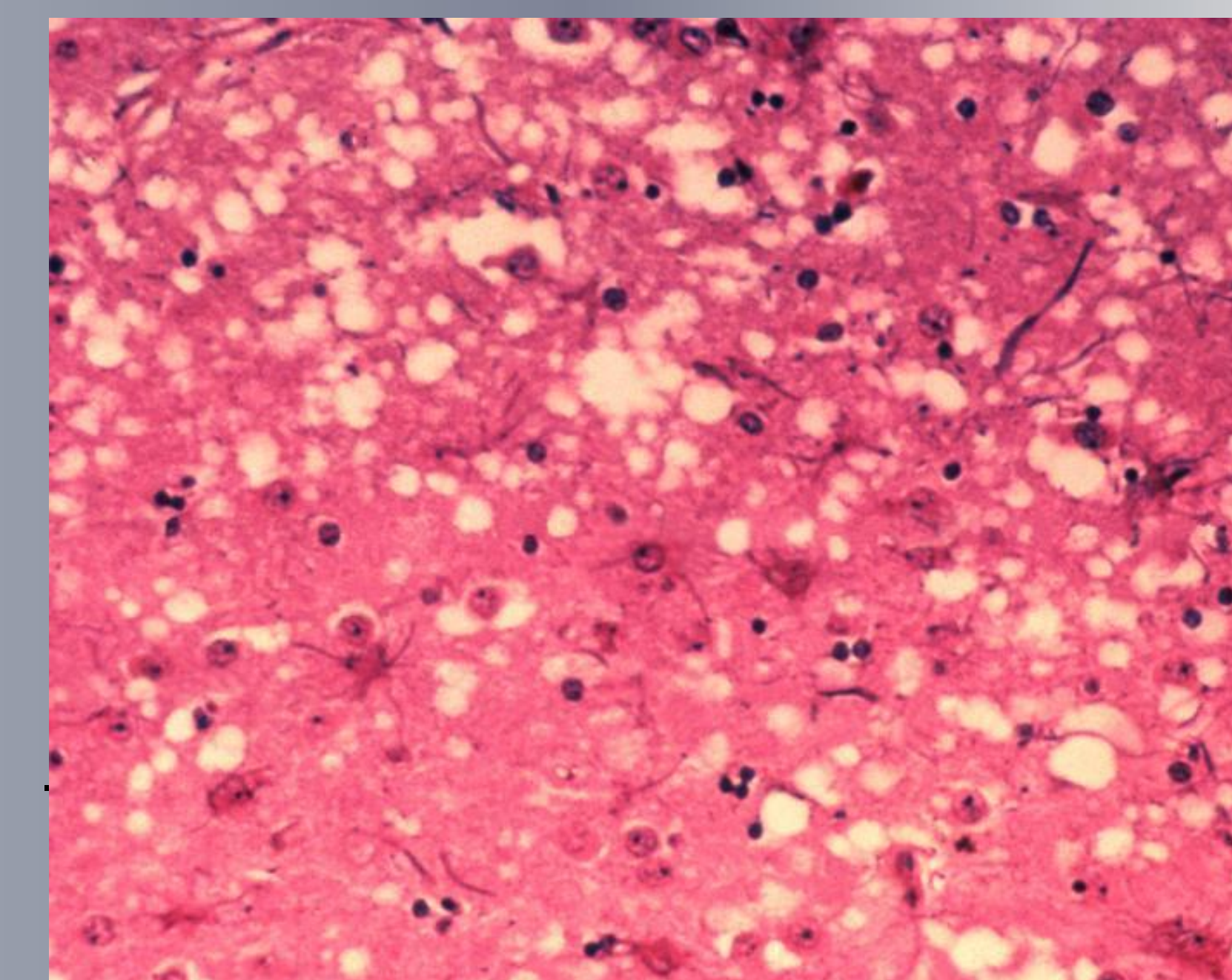
Prions disease can be transmitted by infected tissue

Prions disease can be transmitted via organ transplants and rarely by blood transfusion

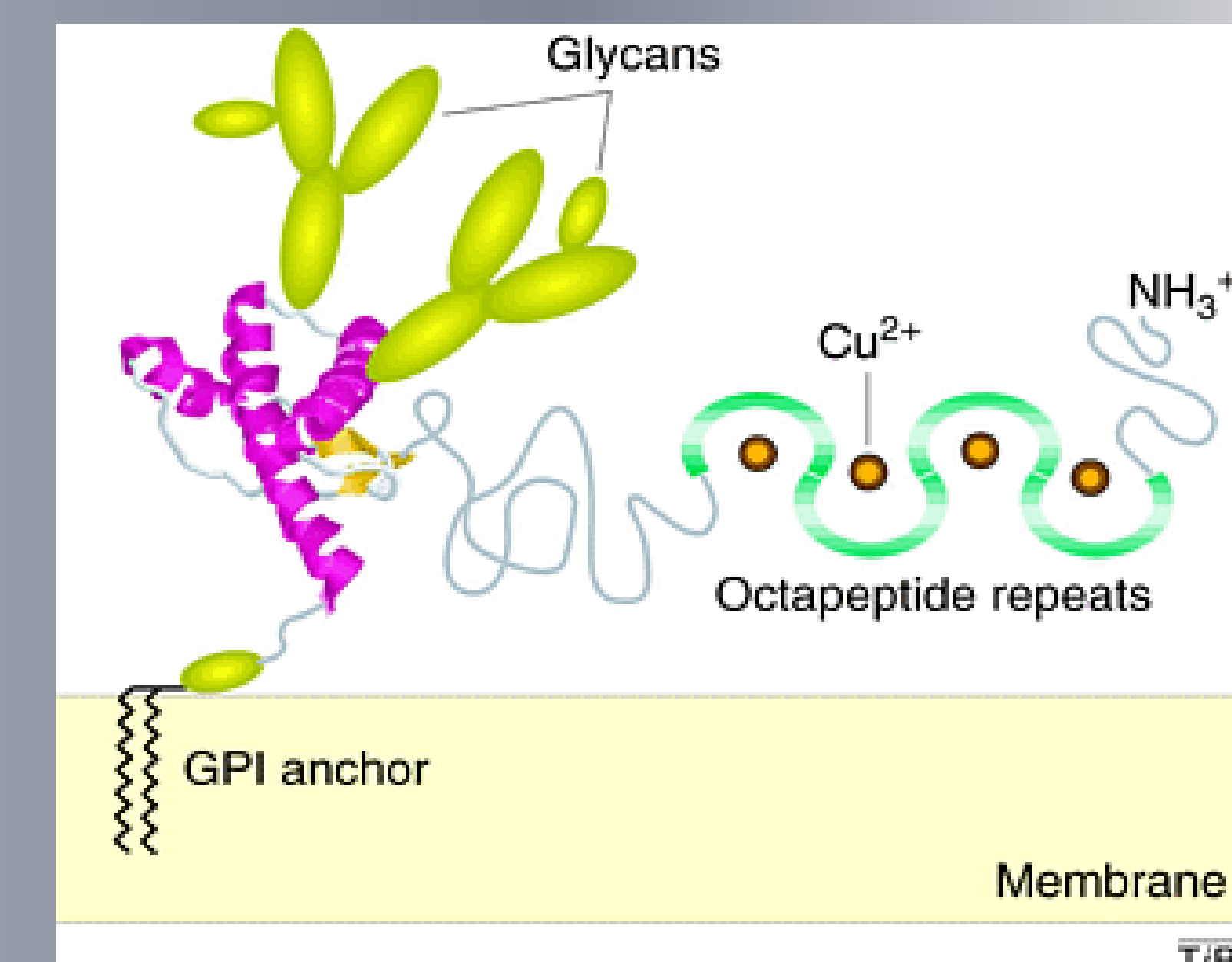
Prions diseases occur in mink, elk, deer, sheep and other mammals although its still not decided whether this disease can be transmitted to people who hunt, butcher, or eat affected animals.

The effects:

A prion disease causes heart damage in mouse. In humans the effects of prion diseases are ataxia, paralysis, pneumonia, death, brain damage, loss of coordination, loss of control, and dementia. There is no cure for Prion diseases.



In the Brain

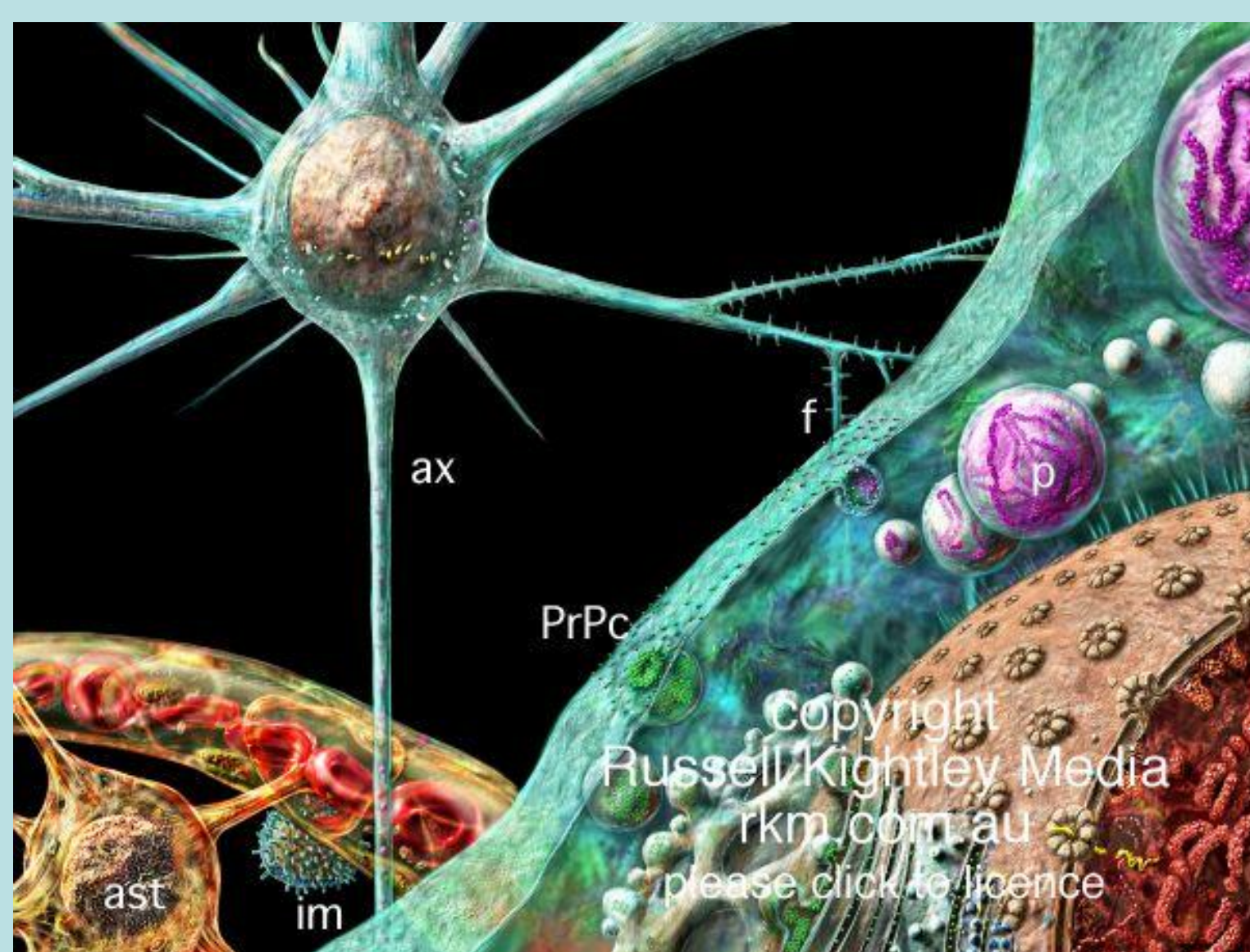


How Prions Are Spread in The Body

Prions exist in their normal form (PrP^C) on nerve cells. When the prion changes to the misfolded form (PrP^{SC}) they start spreading and changing from the normal PrP^C into misfolded PrP^{SC} form. The the change in the proteins then causes the formation of amyloid plaques. These plaques cause the neurons to malfunction. The normal form consists in a tertiary structure of about 40% alpha helical structure and a small amount of beta sheets. The protein structure changes to 30% alpha helical and 45% beta sheet structure which is the misfolded PrP^{SC} form .(Prusiner 1997)

How this change occurs is not completely understood. There are theories on how the transformation is caused, the Template-assisted prion formation theory and the Protein X theory. Also when cells are stressed it can cause the protein to denature and cause misfolding.

Template-assisted Prion Formation: In this theory it is believed that PrP^{SC} acts as a template to cause a reaction in PrP^C that changes the conformation of the protein. When the two proteins interact, the PrP^{SC} changes PrP^C into the altered state and acts as a catalyst.



Prion replication and spread at the cellular level

What Prions Do

Prions are very unique in the sense that they rely on mutated proteins in mammals. A prion is a proteinaceous infectious particle. The protein affected by prions are the PrP^C proteins, which reside in the central nervous system, leukocytes, and in the gut. Prions can be transferred infectiously, sporadically, or inherited.

Normally the ubiquitin-proteasome system is able to break down the PrP^C proteins. However, when these proteins become mutated, and transform to PrP^{SC}, this system is ineffective, causing them to build up in the body. However if this system becomes nonfunctional, misfolded PrP^C will build in the cytosol, causing similar effects as with PrP^{SC} (cell death).

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