and Parkinson's disease. Alzheimer's disease had been suspected to be transmissible for some time: an early report[9] of disease transmission to hamsters through white blood cells from people with Alzheimer's disease caused great consternation, but was never reproduced. Much more tantalizing evidence came from the discovery[10,11] that aggregates of the amyloid-β (Aβ) peptide found in the brain of people with Alzheimer's disease could be transmitted to the brain of mice engineered to produce large amounts of the Aβ precursor protein APP. Another study[12] has shown that healthy tissue grafted into the brain of people with Parkinson's disease acquires intracellular Lewy bodies — aggregates of the Parkinson's disease-associated protein α-synuclein. This suggests prion-like transmission of diseased protein from the recipient's brain to the grafted cells.

These findings[10–12] raise a provocative question. If protein aggregation depends on the introduction of 'seeds' and on the availability of the monomeric precursor, and if, as has been suggested[13], amyloid represents the primordial state of all proteins, wouldn't all proteins — under appropriate conditions — behave like prions in the presence of sufficient precursor?

Acceptance of this concept is gaining momentum. For one thing, an increasing wealth of traits is being found in yeast, fungi and bacteria that can best be explained as prion-like phenomena (see table). And now, Ren and colleagues[3] provide evidence for prion-like spread of polyglutamine (polyQ)-containing protein aggregates, which are similar to the aggregates found in Huntington's disease. They show that polyQ aggregates can be taken up from the outside by mammalian cells. Once in the cytosol, the polyQ aggregates can grow by recruiting endogenous polyQ.

Clavaguera *et al.*[4] report similar findings in a mouse model of tauopathy, a neurodegenerative disease caused by intraneuronal aggregation of the microtubule-associated tau protein. Injection of mutant human tau into the brain of mice overexpressing normal human tau transmitted tauopathy, with intracellular aggregation of previously normal tau and spread of aggregates to neighbouring regions of the brain. Notably, full-blown tauopathy was not induced in mice that did not express human tau. Assuming that tau pathology wasn't elicited by some indirect pathway (some mice overexpressing mutated human tau develop protein tangles even when exposed to unrelated amyloid aggregates[14]), this sequence of events is reminiscent of prions. Finally, Frost and colleagues[5] show that extracellular tau aggregates can be taken up by cells in culture. Hence, tau can attack and penetrate cells from the outside, sporting predatory behaviour akin to that of prions.

Yet there is one crucial difference between actual prion diseases and diseases caused by other prion-like proteins (let's call them prionoids) described so far (see table). The behaviour of prions is entirely comparable to that of any other infectious agent: for instance, prions are transmissible between individuals and often across species, and can be assayed with classic microbiological techniques, including titration by bioassay. Accordingly, prion diseases were long thought to be caused by viruses, and BSE created a worldwide panic similar to that currently being provoked by influenza. By contrast, although prionoids can 'infect' neighbouring molecules and sometimes even neighbouring cells, they do not spread within communities or cause epidemics such as those seen with BSE.

So, should any amyloid deserve an upgrade to a bone fide prion status? Currently, amyloid A (AA) amyloidosis may be the most promising candidate for a truly infectious disease caused by a self-propagating protein other than PrP^{Sc}. AA amyloid consists of orderly aggregated fragments of the SAA protein, and its deposition damages many organs of the body. Seeds of AA amyloid can be excreted in faeces[15], and can induce amyloidosis if taken up orally (at least in geese)[16]. Also, AA amyloid may be transmitted between mice by transfusion of white blood cells[17]. So, like enteroviruses and, perhaps, sheep scrapie prions, AA amyloid seems to display all the elements of a complete infectious life cycle, including uptake, replication and release from its host.

There are intriguing evolutionary implications to the above findings. If prionoids are ubiquitous, why didn't evolution erect barriers to their pervasiveness? Maybe it is because the molecular transmissibility of aggregated states can sometimes be useful. Indeed, aggregation of the Sup35 protein, which leads to a prion-like phenomenon in yeast, may promote evolutionary adaptation by allowing yeast cells to temporarily activate DNA sequences that are normally untranslated[18]. Mammals have developed receptors for aggregates, and ironically PrP^{C} may be one of them[19], although these receptors have not been reported to mediate protective functions. Therefore, we shouldn't be shocked if instances of beneficial prionoids emerge in mammals as well. ■

PRIONS AND POTENTIAL PRIONOIDS

Disease	Protein	Molecular transmissibility	Infectious life cycle
Prion diseases	PrP^{Sc}	Yes	Yes
Alzheimer's disease	Amyloid-β	Yes	Not shown
Tauopathies	Tau	Yes	Not shown
Parkinson's disease	α-Synuclein	Host-to-graft	Not shown
AA amyloidosis	Amyloid A	Yes	Possible
Huntington's disease	Polyglutamine	Yes	Not shown

Phenotype	Protein	Molecular transmissibility	Infectious life cycle
Suppressed translational termination (yeast)	Sup35	Yes	Not shown
Heterokaryon incompatibility (filamentous fungi)	Het-s	Yes	Not shown
Biofilm promotion (bacteria)	CsgA	Yes	Not shown

In humans and animals, infectious prion diseases are caused by PrP^{Sc}, which spreads by recruiting its monomeric precursor PrP^{C} into aggregates. Aggregates then multiply by breakage, a process that is termed molecular transmissibility. Other proteins involved in disease and in phenotypes of fungi and bacteria, can also undergo self-sustaining aggregation, but none of these 'prionoid' proteins behaves like typical infectious agents, nor do any of them enact a complete infectious life cycle — with the possible exception of AA amyloid.

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Correction
In the News & Views article "Immunology: Immunity's ancient arms" by Gary W. Litman and John P. Cannon (*Nature* **459,** 784–786; 2009), the name of the first author of the *Nature* paper under discussion was misspelt. The author's name is P. Guo, not Gou as published.