Therapeutic targeting of cellular prion protein: toward the development of dual mechanism anti-prion compounds

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From the Contents

Abstract

PrP^{Sc}, a misfolded, aggregation-prone isoform of the cellular prion protein (PrP^C), is the infectious prion agent responsible for fatal neurodegenerative diseases of humans and other mammals. PrP^{Sc} can adopt different pathogenic conformations (prion strains), which can be resistant to potential drugs, or acquire drug resistance, posing challenges for the development of effective therapies. Since PrP^C is the obligate precursor of any prion strain and serves as the mediator of prion neurotoxicity, it represents an attractive therapeutic target for prion diseases. In this minireview, we briefly outline the approaches to target PrP^C and discuss our recent identification of Zn(II)-BnPyP, a PrP^C-targeting porphyrin with an unprecedented bimodal mechanism of action. We argue that in-depth understanding of the molecular mechanism by which Zn(II)-BnPyP targets PrP^C may lead toward the development of a new class of dual mechanism anti-prion compounds.

Key Words: anti-prion drug; anti-PrP^C antibody; antisense oligonucleotide; neurodegeneration; pharmacological chaperone; porphyrin; prion disease; PrP^C degrader; PrP^C shedding; zinc finger repressor

Introduction

Prion diseases, including Creutzfeldt-Jakob disease (CJD), fatal familial insomnia, and Gerstmann-Sträussler-Scheinker syndrome in humans, together with scrapie in sheep and goats, bovine spongiform encephalopathy (BSE), and chronic wasting disease (CWD) in cervids, are fatal brain disorders currently lacking a cure (Zerr et al., 2024). The infamous case of BSE in Britain during the 1990s, and the evidence of its transmission to humans, resulting in a variant form of CJD (vCJD), had a profound impact on public health. Fortunately measures to control BSE and its transmission to humans prevented vCJD from reaching epidemic proportions.

The rapid spread of chronic wasting disease in North America, with cases, also reported in South Korea and Europe, and the evidence that this disease can be transmitted to other animal species highlights the need for vigilance to prevent new zoonoses (Bartz et al., 2024).

Currently, human prion diseases acquired through infection – mostly transmitted iatrogenically through medical and surgical procedures – are extremely rare (< 1%). Approximately 85% of cases occur spontaneously with no known genetic or environmental trigger and are mostly sporadic CJD. The remaining 15% result from dominant, gain-of-function mutations in the *PRNP* gene encoding PrP^C.

Prion diseases have a devastating impact due to their unpredictable onset and exceptionally fast clinical course. Healthy adults suddenly experience neurological impairments, such as memory loss, ataxia, and motor dysfunction, rapidly advancing to severe dementia. Patients with sporadic CJD progress from the first symptom to death in less than 6 months, and most genetic prion disease patients die within a year from symptom onset.

Although prion diseases have different etiologies and variable clinical manifestations, spanning cognitive, motor, autonomic, or psychiatric domains, they all share a common pathogenic event: the conformational conversion of PrP^C to a misfolded aggregated isoform called PrP scrapie (PrP^{Sc}), or prion (Prusiner, 1998). This conversion can occur spontaneously or because of *PRNP* mutations, or can be triggered by contact with exogenous prions. Once formed, PrP^{Sc} self-propagates by

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inducing misfolding and aggregation of native PrP^{C}, ultimately leading to neuronal death. Inhibiting PrP^{Sc} propagation is therefore the primary aim of therapy.

Search Strategy

Studies cited in this narrative review published from 1998 to 2024 were searched on the PubMed database, Google and Google Scholar, using the following keywords: prion therapy, cellular prion protein, and prion conversion inhibitors. Further, we used Connected Papers (https://www.connectedpapers.com/) to create a map to follow any derivative or originating article.

Prions Occur in Different Strains That Can Become Drug-Resistant

A wealth of data indicates that PrP^{Sc} occurs in different conformations with distinctive physicochemical properties and multimeric assembly (Safar et al., 1998; Manka et al., 2023). These conformational variants, known as prion strains, encode the information that specifies the clinical and neuropathological characteristics distinguishing the different prion diseases.

Different prion strains vary in their susceptibility to inhibitory drugs, and an initially drug-sensitive prion can become resistant with continuous exposure to a drug (Ghaemmaghami et al., 2009; Berry et al., 2013). This is because a prion strain is not a molecular clone, but a population of various PrP^{Sc} conformers, consisting of a major component and many variants, which are constantly generated and selected against a particular environment (Li et al., 2010). In the presence of an inhibitory drug, the most efficiently replicating variant becomes predominant. This 'mutability' of prions poses a major challenge to the development of treatment.

Targeting the PrP^{C} Precursor of the Prion

A more effective therapeutic approach to prevent prions from developing drug resistance would be to deprive them of their PrP^{C} precursor.

PrP^{C} is a cell surface glycoprotein found in most body cells, with its highest expression in neurons of the central nervous system. It is attached to the outer leaflet of the plasma membrane by a glycosyl-phosphatidyl-inositol anchor and consists of a flexible N-terminal tail containing four repetitions of eight amino acids each, referred to as octapeptide repeats (OR), and a C-terminal globular domain comprising three α-helices and two short anti-parallel β strands (Zahn et al., 2000).

PrP^{C} can undergo proteolytic events that release the whole polypeptide or N-terminal fragments into the extracellular space. The protein can also be internalized to an endocytic compartment from which it is either re-exposed on the cell surface or delivered to lysosomes for degradation (Prado et al., 2004).

PrP^{C} appears to be involved in many biological processes, including synaptic transmission, neuroprotection, myelin maintenance, and divalent metal homeostasis (Chiesa, 2015). Its genetic ablation in mammals is compatible with life, causing relatively mild phenotypic traits, the most severe being sensorimotor deficits in old age. Animals and humans lacking one functional *PRNP* allele are healthy.

There is compelling evidence that PrP^{C} is not only the substrate for conversion to PrP^{Sc}, but is also the mediator of prion neurotoxicity (Chiesa, 2015). Extracellular PrP^{Sc} is only toxic to neurons that express glycosyl-phosphatidyl-inositol-anchored PrP^{C}. One possible explanation is that a conformational change in PrP^{C} on contact with PrP^{Sc} activates a process of intracellular signaling that leads to cell death.

Surprisingly, PrP^{C} also mediates the toxicity of misfolded protein aggregates involved in other neurodegenerative diseases, including Aβ, tau, and α-synuclein (Laurén et al., 2009; Corbett et al., 2020). The molecular and signaling events involved in PrP^{C}-mediated neurotoxicity are not fully understood, but corruption of a PrP^{C} regulatory role in glutamate receptor function may be involved (Chiesa, 2015). PrP^{C}'s ability to mediate neurotoxic signaling should be borne in mind when thinking of PrP^{C}-directed therapeutics because some ligands, such as certain globular domain antibodies, may activate a neurotoxic response (Sonati et al., 2013).

Here we provide some examples of the strategies explored so far to target PrP^{C} for the treatment of prion disease (**Figure 1**).

Stabilize the native PrP^{C} fold

PrP^{C} needs to largely unfold to adopt the PrP^{Sc} conformation. Therefore a ligand that binds and stabilizes the folded domain of PrP^{C} may reduce the availability of unfolded PrP for prion propagation by acting as a pharmacological chaperone. PrP^{C} shows no obvious pocket for ligand binding, and only a few compounds have been identified that bind its globular domain. One example is meso-tetra(4-N-methylpyridyl) porphyne iron(III), or Fe(III)-TMPyP, which docks onto a shallow cleft made by the C terminus of the α3 helix and the first β-strand (Nicoll et al., 2010). Fe(III)-TMPyP stabilizes the native PrP^{C} fold, making the protein less prone to PrP^{Sc} conversion in protein misfolding cyclic amplification (PMCA), prion-infected cells, and organotypic brain slices (Nicoll et al., 2010; Masone et al., 2023).

Another example is N,N'-([cyclohexylmethylene]di-4,1-phenylene)bis(2-[1-pyrrolidinyl]acetamide), also known as medical chaperone, which binds to the PrP^{C} region composed of the α2 helix and the loop connecting α2 to α3. Medical chaperone inhibits recombinant PrP aggregation, prolongs the survival of prion-infected mice, and slows the development of symptoms in BSE-infected macaques (Yamaguchi et al., 2019). Certain anti-PrP^{C} antibodies, such as the mouse monoclonal antibody ICSM18, may also act as pharmacological chaperones. ICSM18 binds to residues 143-156 of human PrP^{C} and can delay disease onset in mice inoculated with prions peripherally (White et al., 2003).

PRN100, a humanized version of ICSM18, was injected intravenously into six CJD patients following a dose-escalation protocol. PRN100 eventually reached the target concentration in the cerebrospinal fluid and brain, with no noticeable toxic effects (Mead et al., 2022). These promising results provide the basis for conducting formal efficacy trials of PRN100 in early symptomatic CJD patients and as prophylaxis in individuals at risk of genetic or iatrogenic prion diseases.

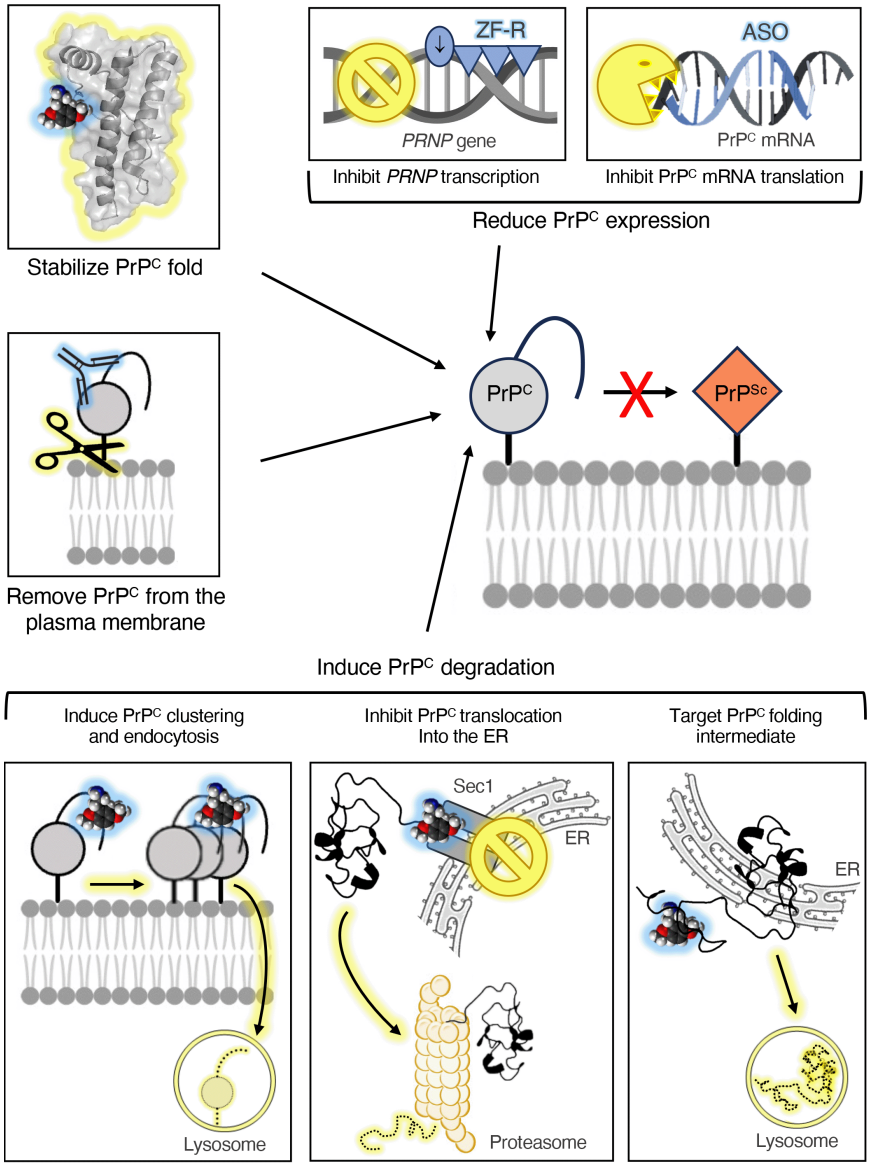

Figure 1 | Current strategies for PrP^C targeting in the treatment of prion disease.
The folded globular domain of PrP^C can be stabilized by molecules (e.g. Fe(III)-TMPyP, Medical Chaperone) and antibodies (e.g., PRN100). PrP^C synthesis can be blocked by (i) ZF-R repressing transcription of the *PRNP* gene; (ii) ASOs degrading PrP^C mRNA. PrP^C can be removed from the plasma membrane using antibodies inducing PrP^C shedding. PrP^C can be degraded by (i) molecules (e.g., hemin) and antibodies (e.g., POM2) stimulating PrP^C clustering, internalization, and lysosomal degradation; (ii) molecules (i.e. molecular gates) inhibiting the translocation of nascent PrP molecules through the Sec1 channel of the ER, diverting them to cytosolic proteasomes; (iii) molecules (e.g., SM875) binding to a PrP^C folding intermediate and diverting it from the ER to lysosomes. Created with Microsoft PowerPoint. ASOs: Antisense oligonucleotides; ER: endoplasmic reticulum; PrP^C: cellular prion protein; ZF-R: zinc finger repressors.

Despite their potential, pharmacological chaperones face challenges in clinical translation, including poor blood–brain barrier (BBB) permeability (as with Fe(III)-TMPyP), heterogeneous brain distribution (as with medical chaperone), and the absence of a measurable indicator of target engagement *in vivo*. The lack of a target engagement biomarker makes it hard to optimize dosing regimens and maximize therapeutic potential while minimizing side effects.

Reduce PrP^C expression

There is ample evidence that lowering PrP^C levels is highly beneficial in prion disease. PrP knockout mice are resistant to prions, and heterozygotes show a significant delay in disease onset, surviving more than twice as long as wild-type mice. In addition, conditional PrP knockout in neurons of mice in the early stage of prion disease rescues clinical signs and prevents neurodegeneration (Chiesa, 2015). These findings, with the fact that ablation of PrP^C has no major detrimental effects, support a strategy aimed at inhibiting PrP^C synthesis.

Sangamo Therapeutics is pursuing a strategy to achieve a rapid and sustained reduction of brain PrP^C using an engineered zinc finger repressor of *PRNP* gene transcription delivered to the brain through adeno-associated viral vectors. They reported that neuronally restricted zinc finger repressor expression led to widespread 50% reductions in PrP^C mRNA and protein levels, significantly prolonging the survival of prion-infected mice (Zeitler et al., 2022).

Silencing *PRNP* gene expression by intraventricular injection of antisense oligonucleotides (ASOs) had beneficial effects in prion-infected mice, with no noticeable side effects (Minikel et al., 2020). Ionis Pharmaceuticals recently started a phase I–II clinical trial to test the safety and tolerability of repeated intrathecal ASO in early-stage prion disease patients (https://www.clinicaltrials.gov/study/NCT06153966). *PRNP* ASOs are extremely promising, but there are still uncertainties about their ability to reach all regions of the human brain – prion disease is a whole-brain disease – and possible off-target effects cannot be excluded.

Remove PrP^C from the plasma membrane

Conformational conversion of PrP^C starts on the cell surface, where PrP^C interacts with exogenous PrP^{Sc}. Reducing the amount of cell surface PrP^C available for conversion should therefore limit PrP^{Sc} propagation and inhibit PrP^C-mediated prion neurotoxicity. PrP^C is physiologically released from the cell surface by the ADAM10 metalloprotease. This process, referred to as shedding, can be stimulated by several anti-PrP^C antibodies (Linsenmeier et al., 2021). The next step will now be to identify smaller ligands that stimulate ADAM10-mediated PrP^C shedding and test them in animal models of prion disease.

Another possible way to remove PrP^C from the cell surface is to stimulate its re-localization to intracellular compartments. Some compounds, such as chlorpromazine, an anti-psychotic drug that inhibits prion replication in cultured cells, induced re-localization of PrP^C from the plasma membrane through mechanisms not involving any direct interaction with PrP^C (Biggi et al., 2020). Chlorpromazine's ability to cross the BBB makes it a potential candidate for repurposing in prion disease therapy. However, preliminary tests in prion-infected mice, and iatrogenic CJD and FFI patients did not provide evidence of efficacy (Barret et al., 2003; Benito-León, 2004; Martínez-Lage et al., 2005).

Induce PrP^C degradation

The natural porphyrin hemin interacts with the N-terminal region of PrP^C, causing oligomerization, endocytosis, and lysosomal degradation of the cell surface PrP^C (Lee et al., 2007). So does the anti-PrP antibody POM2, which recognizes repetitive epitopes in the OR region and stimulates multimeric clustering of cell surface PrP^C (Linsenmeier et al., 2021). Thus, molecules that stimulate PrP^C clustering on the plasma membrane may ultimately lead to its degradation. However, one must be careful in trying to exploit this PrP^C lowering strategy for therapy, since ligand-induced PrP^C crosslinking may be extremely neurotoxic (Solforosi et al., 2004).

A safer way to down-regulate PrP^C would be through small molecules that stimulate its cellular disposal without inducing potentially toxic PrP^C aggregates. Membrane proteins like PrP^C are first translocated into the endoplasmic reticulum by the Sec61 complex before reaching the cell surface by vesicular trafficking. Substrate-selective inhibition of Sec61 may offer the possibility of downregulating disease-related proteins (Wenzell et al., 2024). Gate Bioscence is developing a small molecule Sec61 inhibitor, referred to as a "molecular gate" that specifically prevents the translocation of nascent PrP molecules into the endoplasmic reticulum, leading to their disposal by the cytosolic proteasomes. This approach not only lowers PrP^C, but may also promote the production of short-lived neuroprotective untranslocated PrP (Restelli et al., 2010).

A computational method to investigate the folding pathway of PrP^C led to the identification of a folding intermediate that was subjected to virtual screening of a chemical library (Spagnolli et al., 2021). The hypothesis was that a ligand that stabilizes the folding intermediate could promote its degradation by the cell's quality control machinery, which would recognize it as an improperly folded form. This led to the discovery of the small molecule SM875, which diverts newly synthesized PrP from the endoplasmic reticulum to lysosomes for degradation (Spagnolli et al., 2021). SM875 has some intrinsic toxicity and low potency, and needs to be optimized before testing in prion-infected mice.

Finally, Schmitt-Ulms and colleagues developed an indirect targeting approach to induce degradation of plasma membrane PrP^C. They found that PrP^C is close to Na,K-ATPases, and exposing cells to cardiac glycosides, the natural inhibitors of Na,K-ATPases, induces their turnover along with PrP^C (Mehrabian et al., 2022). Some cardiac glycosides have favorable pharmacological characteristics for brain applications and might potentially be repurposed for treating prion disease.

Zn(II)-BnPyP – a PrP^C Degrader and Inhibitor of PrP^{Sc} Conversion

We recently demonstrated that native PrP^C can be targeted with a ligand that simultaneously inhibits conversion to PrP^{Sc} and stimulates PrP^C degradation. Zn(II)5,10,15,20-tetra(N-benzyl-4-pyridyl)porphyrin tetra-chloride, referred to as Zn(II)-BnPyP, binds to two distinct regions of native PrP^C: (i) the globular domain, on the surface made by the α2 helix and the C-terminus of the α3 helix; and (ii) the N-terminal tail, by virtue of Zn(II)-mediated interactions with the imidazole rings of histidines in the OR region. We found that the interaction of Zn(II)-BnPyP with the globular domain destabilized its fold and was sufficient to inhibit PrP^C conversion to PrP^{Sc}, whereas binding to the OR motif disrupted intramolecular interactions between the N- and C-terminal domains, triggering PrP^C endocytosis and lysosomal degradation (**Figure 2**; Masone et al., 2023). This dual effect on the prion precursor gives Zn(II)-BnPyP potent, strain-independent anti-prion activity in PMCA reactions, prion-infected cells, and organotypic brain cultures.

Several aspects of how Zn(II)-BnPyP targets PrP^C merit consideration. First, Zn(II)-BnPyP inhibits PrP^C conversion by destabilizing the native protein fold, as opposed to increasing the protein stability, indicating a new paradigm for anti-prion drug development. Second, in contrast to other N-terminal tail ligands such as hemin, which induces PrP^C degradation by promoting its clustering, Zn(II)-BnPyP does not induce PrP^C aggregation. Moreover, Zn(II)-BnPyP does not interfere with PrP^C biosynthesis and folding, but targets natively folded cell surface PrP^C, stimulating the normal process of clathrin-mediated PrP^C endocytosis and lysosomal degradation. Finally, Zn(II)-BnPyP is not neurotoxic like other globular domain ligands; in fact, its ability to interact also with the N-terminal tail implies that it may even have neuroprotective effects (Sonati et al., 2013).

All these features make Zn(II)-BnPyP a promising therapeutic candidate for prion disease and other protein-misfolding neurodegenerative disorders, which are thought to involve PrP^C-mediated neurotoxicity. However, pharmacokinetic studies indicate that Zn(II)-BnPyP, like other porphyrins, does not cross the BBB efficiently, hampering preclinical efficacy tests in animal models (Masone et al., 2023). In principle, the BBB penetration of Zn(II)-BnPyP might be boosted using brain-targeted nanocarriers. However, a more drug-like molecule with the same dual anti-prion effect would be desirable.

How to Make Zn(II)-BnPyP a Drug?

We have already clarified many aspects of the Zn(II)-BnPyP interaction with PrP^C and the consequences of binding on the protein structure (Masone et al., 2023). Zn(II)-BnPyP binds to a C-terminal pocket comprising the α2 and α3 helices and establishes hydrophobic interactions with the aromatic side chains of Y226 and Y225, destabilizing the hydrophobic core of the globular domain (**Figure 3**). Zn(II)-BnPyP also interacts with the flexible N-terminal tail through Zn(II)-mediated coordination of the OR histidine side chains (H61, H69, H77, and H85), and π-π interactions between the BnPyP scaffold and the OR tryptophan side chains (W65, W73, W81, and W89). This counteracts the intramolecular interactions between the N- and C-terminal domains of PrP^C, favoring a less compact fold (**Figure 3**; Masone et al., 2023).

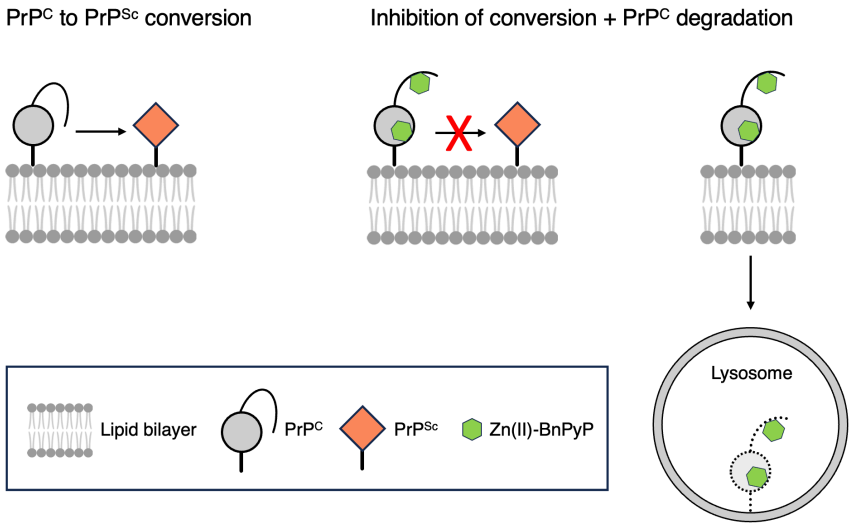

Figure 2 | Scheme illustrating the dual anti-prion activity of Zn(II)-BnPyP.
Zn(II)-BnPyP binds to both the globular domain and the N-terminal tail of PrP^C, simultaneously inhibiting conversion to PrP^{Sc} and stimulating PrP^C endocytosis and lysosomal degradation. Created with Microsoft PowerPoint. PrP^C: Cellular prion protein.

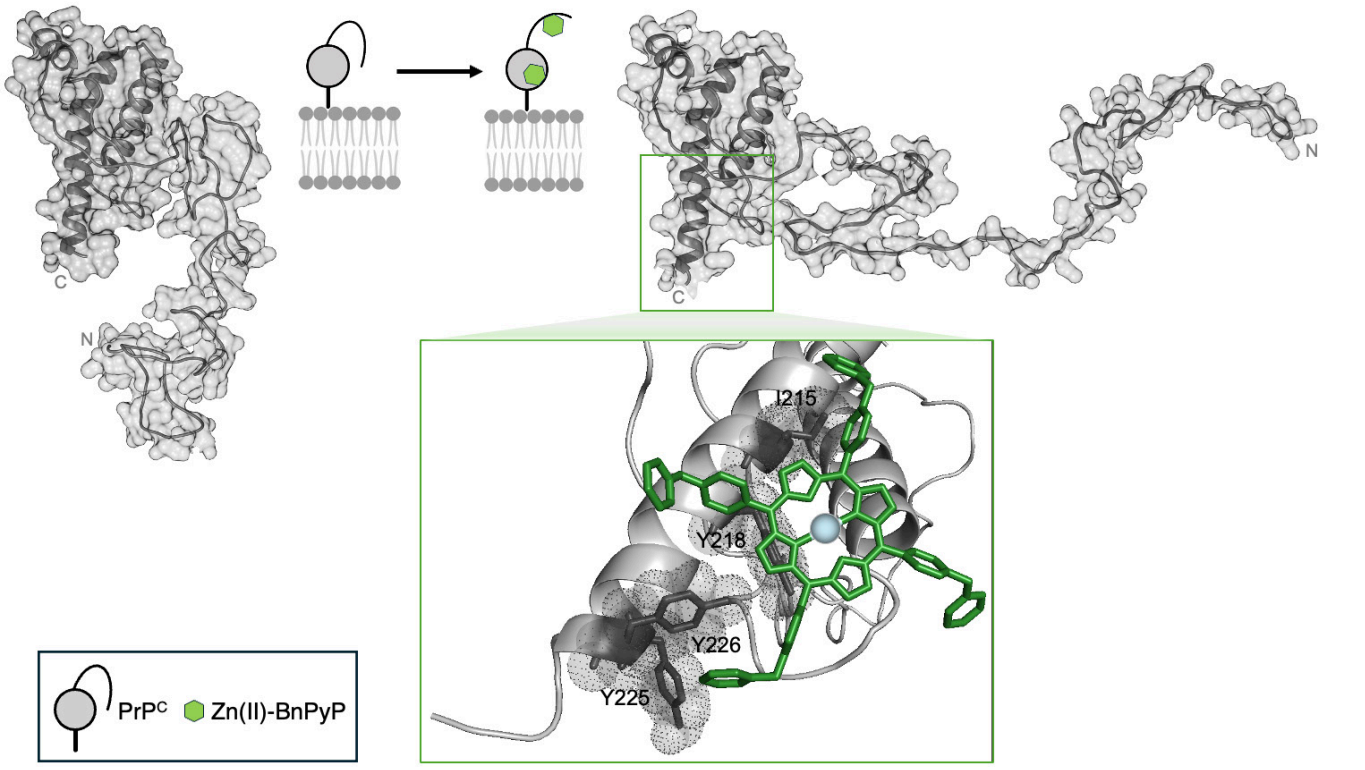

Figure 3 | Conformational effect of Zn(II)-BnPyP on PrP^C.
Illustrative PrP^C structures obtained from Ensemble Optimization Method analysis of Small-Angle X-ray Scattering data, describing the structure of PrP^C alone (upper left) and with Zn(II)-BnPyP (upper right). Zn(II)-BnPyP binding to the PrP^C N-terminal tail and globular domain induces a conformational switch towards more opened structures. In the globular domain Zn(II)-BnPyP binds to the C-terminal region (green box). A docking model of PrP^C globular domain in complex with Zn(II)-BnPyP (lower middle) based on NMR data and computational methods highlights the hydrophobic interactions between the ligand and the protein. The stoichiometry and the mode of binding of Zn(II)-BnPyP to PrP^C N-terminal tail are still not known. Created with Microsoft PowerPoint. PrP^C: Cellular prion protein.

However, to design more drug-like compounds it is important to determine which residues of PrP^C and which chemical moieties of the porphyrin are essential for its bimodal activity. This can be achieved in structure-activity studies involving the synthesis of Zn(II)-BnPyP variants with modified scaffolds and different coordination metals, and PrP^C mutants with hypothesis-driven amino acid substitutions. Another important point will be to determine the structure of the OR motif in complex with Zn(II)-BnPyP and its variants. The information gained from these studies will permit rational modification of Zn(II)-BnPyP to improve its pharmacokinetic properties and BBB passage, and/or to design more drug-like small molecules with the same dual mechanism of action as Zn(II)-BnPyP.

Conclusions

There is an urgent need for effective therapies for prion disease patients and to prevent disease in individuals at iatrogenic or genetic risk. Promising new therapeutics targeting PrP^C gene, mRNA or protein are emerging, including antibodies and antisense oligonucleotides, whose initial clinical evaluation is underway. However, these therapeutics may encounter challenges related to delivery and distribution inherent to their nature. A small molecule capable of crossing the BBB and selectively targeting PrP^C could offer significant clinical advantages and potentially complement an antibody or ASO therapy. We believe that drugs with a dual mechanism of action similar to Zn(II)-BnPyP hold great promise for combating prion diseases. Further exploration and development of such compounds are warranted to address this pressing medical need.

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