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Novel Therapeutic Strategies for Prion Diseases

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Abstract. Prion diseases are a group of rare but invariably fatal neurodegenerative disorders caused by the misfolding of the normal cellular prion protein (PrPC) into its pathogenic isoform (PrPSc). The unique infectious nature of PrPSc, its ability to self-propagate, and the severe neuropathological changes it induces, including neuronal loss, spongiform degeneration, and gliosis, make these disorders particularly challenging to treat. Currently, there are no approved disease-modifying therapies, and clinical management remains entirely supportive. However, advances in molecular biology and translational neuroscience have led to promising therapeutic strategies. Antisense oligonucleotides have demonstrated efficacy in reducing PrP expression and slowing disease progression in preclinical models, while immunotherapy offers both preventive and therapeutic potential through antibody- or vaccine-based approaches. Small-molecule inhibitors, including compounds that disrupt prion aggregation or stabilize PrPC, also remain an area of active exploration. Despite these advances, major challenges persist: the inability of many therapeutic agents to cross the blood-brain barrier, prion strain variability that limits treatment generalizability, and the difficulty of diagnosing disease before significant neurodegeneration occurs. Future therapeutic success will depend on early detection, improved drug delivery systems, and combination therapies that simultaneously target multiple aspects of prion pathogenesis. Together, these developments highlight both the promise and the complexity of translating experimental prion therapeutics into viable clinical applications.

Keywords: Prion disease, therapeutics, Prp

1. Introduction

Prion diseases are fatal, transmissible neurodegenerative disorders caused by the misfolding of the normal cellular prion protein into its pathogenic isoform [1]. These disorders include Creutzfeldt-Jakob disease, fatal familial insomnia, kuru, and Gerstmann-Sträussler-Scheinker syndrome, all of which are characterized by rapid progression and severe neurological decline [1]. The central mechanism involves the templated misfolding of PrPC, leading to PrPSc accumulation, aggregation, and the subsequent spread of pathology within the nervous system [1]. Neuropathological hallmarks include spongiform degeneration, neuronal loss, gliosis, and the deposition of amyloid plaques in some cases [1].

One of the most unique and challenging aspects of prion diseases is their transmissibility, as PrPSc can act as an infectious agent without the need for nucleic acids, distinguishing prions from

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other protein misfolding disorders such as Alzheimer's and Parkinson's disease [2]. Additionally, prion strains demonstrate significant heterogeneity, with variations in incubation times, pathology, and host susceptibility, making therapeutic development more complex [2]. Currently, there are no approved disease-modifying treatments, and management remains supportive and palliative [1].

Ongoing research is focused on therapeutics that target PrP expression, block PrPSc propagation, or enhance cellular clearance of toxic aggregates [1]. Promising strategies include antisense oligonucleotides, immunotherapies, RNA interference, and small-molecule inhibitors, though each approach has distinct merits and challenges that require further study [2].

2. Antisense oligonucleotide therapy

Antisense oligonucleotides (ASOs) are short, chemically modified strands of nucleotides designed to bind specifically to complementary regions of mRNA, enabling degradation through RNAse H activity [3]. By targeting the Prnp mRNA, ASOs can reduce the synthesis of prion protein (PrP), a crucial step since PrP is necessary for disease progression [3]. ASOs used in prion research are chemically modified with features like phosphorothioate linkages and 2′-O-methyl groups to increase their stability, protect against degradation, and improve pharmacokinetics in the brain [4]. This approach, diverging from traditional protein-based therapeutics, enables direct intervention at the RNA level [4]. Notably, this strategy does not appear to promote the emergence of prion strains resistant to treatment [5].

Preclinical research demonstrates that ASOs are capable of lowering PrP across multiple prion disease subtypes, which is yet to be matched by any other therapeutic approach [5]. Initial studies demonstrated that ASOs targeting Prnp mRNA could extend the lifespan of prion-infected mice when administered shortly after infection, with one early example showing a 40% increase in survival [3]. More recent experiments significantly improved upon these results. Two ASOs targeting distinct regions of the Prnp gene (intron 2 and the 3′ UTR) were identified as highly effective [3]. When administered via intracerebroventricular bolus injections, these ASOs led to sustained reductions in Prnp mRNA and PrP protein across key brain regions like the cortex, hippocampus, and spinal cord [3]. Efficacy was observed not only in wild-type mice but also in susceptible genetic backgrounds [3].

ASO treatments delayed the onset of clinical symptoms by up to 99% and increased survival by up to 98% in treated animals compared to saline controls [3]. Importantly, these effects were reproducible when ASOs were administered at both early and later stages of infection, demonstrating their capacity to mitigate disease progression even after prions had accumulated in the brain [3]. The therapeutic benefit of ASOs was also shown to correlate directly with reductions in Prnp mRNA and PrP protein levels [3].

The bolus i.c.v. delivery method, shown to be well-tolerated with no significant neuroinflammatory response, mimics intrathecal injection used in human treatments, suggesting translatability to clinical practice [3]. Repeated dosing regimens (e.g., every 60-90 days) sustained therapeutic mRNA suppression over weeks, making periodic lumbar punctures a feasible delivery strategy [3].

When given repeatedly before symptoms or during very early pathological changes (≤78 dpi), ASOs extended the time to symptom onset by nearly threefold, an increase of about 290 days, by both prolonging healthy lifespan and slowing the initial decline [5]. Administering ASOs at slightly later stages, when early neuropathological signs appear (83-120 dpi), still lengthened survival, reversed some neuronal damage and astrocytosis, and partially restored early weight loss [5]. At

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these stages, the delay in reaching symptomatic disease was modest (around one month), but the delay to terminal disease was more substantial (about three months) [5].

The prolonged suppression of Prnp mRNA after a single bolus dose (up to 84 days), along with the ability to delay both disease onset and mortality, strongly support the advancement of ASOs to human trials [3]. Given their already validated use in other neurological conditions, ASOs have a promising future as a platform for treating not only sporadic prion diseases but also genetic forms where early intervention could be life-saving [3]. Further exploration of aptameric interactions, optimization of chemical modifications, and refinement of delivery regimens will be essential to fully realize the potential of this therapeutic class [3].

3. Doxycyclin

Doxycycline, a tetracycline antibiotic, has been shown to repress the expression of the normal prion protein, which is the essential substrate for pathogenic PrPSc replication [6]. In transgenic mouse models, administration of doxycycline at various doses and delivery routes led to a dose- and time-dependent suppression of PrPC expression, reaching nearly complete repression after seven days of treatment [6]. This repression was reversible: PrPC levels recovered within a week of doxycycline withdrawal, confirming that the drug acts as a regulator rather than a permanent silencer of prion protein synthesis [6]. Importantly, sustained suppression of PrPC over prolonged periods, exceeding a year in some experiments, was well tolerated, with no detectable neurological or histological side effects [6]. These findings demonstrated that PrPC is not essential for short-term neuronal survival and that its suppression can be pursued as a therapeutic approach without overt toxicity [6].

When administered prior to prion inoculation, doxycycline prevented the onset of clinical signs for over 380 days, while untreated controls developed progressive neurological decline within weeks [6]. Brain tissue from treated animals showed an absence of neurodegeneration, indicating that blocking PrPC expression halts PrPSc accumulation and prion disease progression [6]. These results reinforce the model that prion pathogenesis stems from the accumulation of PrPSc, rather than from the absence of PrPC function [6].

Several preclinical and clinical findings support doxycycline as a candidate therapy for prion diseases. In animal models, doxycycline and related tetracycline analogs extended survival when administered both peripherally and intracerebrally [7]. In human patients with Creutzfeldt-Jakob disease, retrospective analyses revealed that those who received oral doxycycline lived significantly longer than untreated controls [8,9]. Furthermore, chronic daily dosing of 100-200 mg was well tolerated, with no major adverse effects [8]. The drug's accessibility and established clinical use in other diseases also make it an attractive candidate for repurposing [8,9]. Its ability to cross the blood-brain barrier, albeit variably, supports its relevance for central nervous system disorders [9].

Doxycycline demonstrates clear proof-of-concept that pharmacological repression of PrPC can prevent prion replication and disease progression, at least in preclinical models and when treatment begins early [6]. Its favorable tolerability and oral availability further enhance its potential as a practical therapy [8,9]. However, clinical translation faces obstacles: low CNS penetration, insufficient dosing regimens, and the challenge of initiating therapy before irreversible neurodegeneration occurs [7,9].

Doxycycline provides an essential foundation for the development of prion-targeted treatments [6-9]. By highlighting the feasibility of PrPC repression and its safety over extended durations, doxycycline studies lay the groundwork for next-generation interventions that combine tetracyclines with complementary strategies to maximize efficacy in both preventive and therapeutic contexts [6-9].

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4. Immunotherapy

Immunotherapy offers a rational approach to prion diseases because the misfolded prion protein is a well-established disease-causing agent and a valid therapeutic target [10]. Since PrP is localized on the cell surface and its conversion to PrPSc occurs on the membrane or endocytic pathway, it is accessible to therapeutic antibodies or immune responses [10]. Immunotherapy works by generating immune recognition of these abnormal proteins, either through direct administration of antibodies (passive immunization) or by eliciting polyclonal antibody responses via vaccination (active immunization) [10]. Experimental approaches such as the use of anti-PrP antibodies, dendritic cells loaded with PrP peptides, or sensitized CD4+ T cells from PrP-deficient donors have demonstrated that tolerance to the prion protein can be overcome and protective immune responses can be induced [11].

The advantages of immunotherapy stem from its strong specificity and relatively low risk of systemic side effects compared with small molecules [10]. Vaccination approaches are attractive because polyclonal responses can target multiple epitopes across PrPSc, making them more resilient to the structural variations between different prion strains [10]. In animal models, active immunization was able to reduce peripheral PrPSc accumulation, which is crucial not only for slowing disease progression but also for limiting prion shedding and transmission, as seen in chronic wasting disease [10]. In uninfected animals, the presence of anti-PrP antibodies in peripheral tissues could prevent infection by blocking natural entry routes [10]. Some monoclonal antibodies, such as ICSM18 and ICSM35, produced striking benefits when administered early, with mice surviving well beyond 500 days without disease signs [10]. These results demonstrate that appropriately timed immunotherapy can both prevent disease onset and extend survival [10].

Immunotherapy against prion diseases illustrates both promise and challenge. Vaccines and antibody therapies show that the immune system can, in principle, recognize and neutralize PrPSc [10]. But prion diseases often remain asymptomatic for years before diagnosis [12]. For this reason, prophylactic immunotherapies are more likely to be targeted to high-risk groups, such as carriers of pathogenic Prnp mutations, rather than the general population [11].

Looking forward, future work must focus on overcoming the blood-brain barrier problem, improving specificity for PrPSc, and clarifying which immune mechanisms confer true protection [10,11]. Combining immunotherapy with other strategies, such as molecules that reduce PrPC expression, may also enhance efficacy [10]. While no immunotherapy has yet advanced to a definitive clinical treatment for human prion diseases, ongoing studies continue to refine our understanding of how immune-based strategies could one day provide both prophylactic and therapeutic benefit [10,11].

5. RNA interference

RNA interference (RNAi) is a highly conserved, sequence-specific, post-transcriptional gene-silencing mechanism in which small interfering RNAs (siRNAs) guide the degradation of homologous mRNA, preventing translation into protein [13]. In prion diseases, RNAi is applied to target the mRNA encoding the cellular prion protein, which is essential for replication of the pathogenic isoform [14]. In the absence of PrPC, PrPSc cannot propagate, making PrPC a validated therapeutic target [14]. Lentiviral vectors can deliver short hairpin RNAs (shRNAs) into neurons, where they are transcribed into double-stranded RNA and processed into siRNAs that direct the RNA-induced silencing complex to degrade PrP mRNA [14]. The use of lentivectors is especially

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suited to the central nervous system because they integrate into both dividing and non-dividing cells, enabling long-term, stable shRNA expression [13].

Preclinical studies have demonstrated that lentiviral iRNA targeting PrP can significantly modify disease progression, even when treatment is initiated after prion infection is established. One optimized lentiviral shRNA vector, LVsh512, has been shown to reduce PrPC expression by more than 90% in vitro [15]. When tested in N2a cells chronically infected with prions (ScN2a cells), LVsh512 treatment led to a stable and substantial decrease in PrPSc accumulation compared with controls [15]. The same vector also efficiently silenced PrPC in primary neuronal cultures, even in cells with long-standing scrapie infection, and suppressed the build-up of PrPSc in these chronically infected neurons [15].

Histological analysis showed that lentivirus-transduced (EGFP-positive) cells were present throughout multiple brain regions, with the highest concentration in the posterior cerebrum, including the hippocampus and cerebellum [15]. In prion-infected mice, hippocampal PrP mRNA expression was reduced by up to 80% after a single administration of the therapeutic lentivirus, halting early pathological changes [14]. This localized knockdown prevented the spread and replication of prions within the targeted area, reduced PrPSc accumulation, preserved neuronal architecture, and maintained behavioral performance such as burrowing activity and object recognition memory [14]. Quantitative neuronal counts confirmed the preservation of CA1 pyramidal neurons in treated animals compared with controls [14]. These functional and structural protections translated into a 23.5% increase in mean lifespan for treated mice. Importantly, a single focal administration was sufficient to delay the onset of the first behavioral deficits, underscoring the potency of targeted PrP suppression [14].

RNAi represents a rational and genetically validated strategy for prion disease therapy by directly targeting the sole host factor required for prion replication [14]. The demonstrated ability to reverse early neuronal dysfunction, protect against neurodegeneration, and prolong survival underscores its therapeutic potential [14]. Combining RNAi with other agents may produce synergistic benefits, addressing both prion replication and downstream neurotoxicity [13]. Continued development of improved vectors and delivery strategies could eventually position RNAi as a cornerstone in the treatment of prion and other protein misfolding diseases.

6. Discussion

However, earlier ASO studies encountered several limitations [3]. In one case, it was unclear whether observed benefits were due to PrP suppression or off-target interactions (aptameric effects), highlighting the need for reliable biomarkers [3]. Additionally, continuous infusion via osmotic pumps caused high rates of complications and death, limiting its clinical potential [3]. These issues were addressed in later studies through bolus dosing, which proved both safer and more effective [3]. Another major concern has been that many anti-prion therapies only work in early stages [3]. In animals treated at clear symptomatic stages (132-143 dpi), roughly one-third experienced a delay of around 85 days before terminal decline, though functional and weight loss deficits persisted [5]. By the most advanced stage (156 dpi), treatment offered no measurable benefit [5]. This is likely because, while ASOs begin engaging their RNA targets within a week, the beneficial effects on established disease appear only after an estimated three-week delay [5].

ASO treatment demonstrated efficacy even when administered well after infection, marking a substantial improvement over previous strategy [3]. The prolonged suppression of Prnp mRNA after a single bolus dose (up to 84 days) and the ability to delay both disease onset and mortality strongly support the advancement of ASOs to human trials [3]. Given their already validated use in other

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neurological conditions, ASOs have a promising future as a platform for treating not only sporadic prion diseases but also genetic forms where early intervention could be life-saving [3]. Further exploration of aptameric interactions, optimization of chemical modifications, and refinement of delivery regimens will be essential to fully realize the potential of this therapeutic class [3].

Referring to doxycycline, significant limitations remain. In animal studies, doxycycline showed limited therapeutic effect when administered after the onset of neurological symptoms, even when delivered directly into the cerebroventricular system in liposomal formulations [7]. This suggests that doxycycline is primarily effective as a preventive or very early-stage intervention but has little impact once prion-related pathology is established [7]. Clinical findings also highlight mixed outcomes. While retrospective analyses suggested survival benefits, more rigorous prospective trials failed to demonstrate significant life extension at standard doses of 100 mg per day [9]. Pharmacokinetic studies indicate that these doses may not achieve sufficient brain concentrations to fully suppress PrPC expression or to halt PrPSc accumulation [9]. Thus, insufficient penetration into brain tissue and late initiation of treatment are major barriers to therapeutic success [7,9].

The future of doxycycline in prion therapy will likely hinge on three strategies. First, improving CNS delivery, through liposomal encapsulation, chemical modification, or combination therapy with agents that enhance blood-brain barrier penetration [7,9]. Second, employing higher or sustained dosing regimens while monitoring safety profiles [9]. Third, targeting populations at the presymptomatic stage, such as genetic prion disease carriers, where preventive therapy may hold the most promise [9]. Recent research has emphasized two key directions: dose optimization and early intervention [9]. Quantification of brain doxycycline levels suggests that higher doses may be necessary for efficacy, and new clinical trials are exploring whether increased dosing regimens can improve outcomes [9]. Preventive trials are also underway, including long-term studies in asymptomatic carriers of fatal familial insomnia, where doxycycline is administered prophylactically over a decade to test whether early, sustained PrPC repression delays or prevents disease onset [9]. Although results are pending, these trials represent an important step toward evaluating doxycycline's utility in genetic prion diseases, where at-risk populations can be identified before symptoms appear [9].

For immunotherapy, it faces major obstacles. The most notable limitation is that antibodies are generally too large (~150 kDa) to cross the blood-brain barrier, making them ineffective once infection has reached the central nervous system [10]. Studies have shown that while peripherally administered antibodies can eliminate disease after peripheral inoculation, they fail to protect against intracerebral infection [10]. Attempts to overcome this with intraventricular infusion of antibodies have produced only modest survival benefits, highlighting the restricted CNS penetration of these therapies [10]. Another concern is the risk of adverse effects: polyclonal antibodies generated through active immunization could inadvertently target normal PrPC epitopes, leading to neurotoxicity [10]. While using conformationally distinct immunogens that mimic PrPSc may reduce this risk, there remains no confirmed antibody that exclusively targets PrPSc without reacting with PrPC [10]. Finally, uncertainty about which immune responses, humoral vs. cellular, or mucosal vs. peripheral, are most protective complicates vaccine optimization [11].

Recent studies are exploring strategies to bypass these limitations. Nanobody technology, with smaller antibody fragments, offers the potential for better CNS penetration, though no PrPSc-specific nanobody has yet been identified [10]. Vaccination with disease-specific epitopes has also shown promise by eliciting strong immune responses that discriminate against misfolded proteins [12]. In addition, dendritic cell-based immunization and adoptive T cell transfer have provided proof-of-concept for breaking immune tolerance to PrP [11]. However, these strategies remain at the

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experimental stage, and translation into human trials has not yet been achieved [11]. Other adjunctive approaches, such as pentosan polysulfate, have been tested for prion disease treatment, but their benefits in humans have been limited by inconsistent dosing regimens and complications with delivery [12].

RNAi therapy also faces several obstacles. Earlier studies have shown that iRNA reduced PrPs, but did not achieve long-term PrP suppression in a stable cell line [16]. Expression of dsRNAs, including shRNAs, can activate the innate immune system, inhibit non-target genes, or saturate the RNAi machinery, potentially causing toxicity [13]. Safe and efficient delivery of dsRNAs into the brain remains the greatest challenge [13]. Lentivectors require high-titer viral stocks, may have unknown consequences in recipients infected with related retroviruses, and can undergo silencing of integrated copies, reducing long-term effectiveness [13]. Current focal delivery methods limit knockdown to the injection site, leaving other brain regions susceptible to prion spread [14]. Additionally, some studies have shown only modest survival benefits, for example, extending lifespan to 231 days compared to 167 days in controls, indicating a need for improved lentivector design to achieve broader neuronal transduction and higher shRNA expression [13].

Advances in vector engineering may help achieve brain-wide transduction with improved safety profiles [13]. Optimizing timing and extent of PrP knockdown will be crucial, as intervention during reversible neuronal dysfunction yields the greatest benefit [14]. Combining RNAi with other therapies, such as polyanionic compounds, porphyrins, or protein-processing stabilizers may enhance therapeutic outcomes [13]. Moreover, expanding delivery to cover multiple brain regions could prevent prion spread beyond localized treatment zones [14]. The focal delivery model also provides a valuable platform for studying mechanisms of neuronal toxicity and recovery in neurodegeneration [14].

7. Conclusion

The search for effective prion therapeutics has made significant strides, particularly in strategies targeting PrP itself through genetic suppression or immune-based interventions. However, challenges remain in ensuring CNS delivery, overcoming prion strain diversity, and initiating treatment early enough to alter disease trajectory. Preclinical data suggest that therapies can extend survival and delay symptom onset, but translation to clinical benefit in humans has not yet been realized. Continued refinement of delivery methods, biomarker development for earlier detection, and integration of cross-disciplinary approaches will be essential. Looking forward, the convergence of molecular therapeutics and precision medicine offers a path toward viable treatments for these devastating disorders.

References

[1] Liu, F., Lu, W., & Liu, L. (2024). New implications for prion diseases therapy and prophylaxis. Frontiers. https: //www.frontiersin.org/journals/molecular-neuroscience/articles/10.3389/fnmol.2024.1324702/full

[2] Shim, K. H., Sharma, N., & An, S. S. A. (2022). Prion therapeutics: Lessons from the past. PMC. https: //pmc.ncbi.nlm.nih.gov/articles/PMC9754114/

[3] Raymond, G. J., Zhao, H. T., Race, B., Raymond, L. D., Williams, K., Swayze, E. E., Graffam, S., Le, J., Caron, T., Stathopoulos, J., O'Keefe, R., Lubke, L. L., Reidenbach, A. G., Kraus, A., Schreiber, S. L., Mazur, C., Cabin, D. E., Carroll, J. B., Minikel, E. V., Kordasiewicz, H., & Caughey, B. (2019). Antisense oligonucleotides extend survival of prion-infected mice. PMC. https: //pmc.ncbi.nlm.nih.gov/articles/PMC6777807/

[4] Cantara, S., SImoncelli, G., & Ricci, C. (2024). Antisense Oligonucleotides (ASOs) in Motor Neuron Diseases: A Road to Cure in Light and Shade. PMC. https: //pmc.ncbi.nlm.nih.gov/articles/PMC11083842/

DOI: 10.54254/2753-8818/2025.AU27102

[5] Minikel, E. V., Zhao, H. T., Le, J., O'Moore, J., Pitstick, R., Graffam, S., Carlson, G. A., Kavanaugh, M. P., Kriz, J., Kim, J. B., Ma, J., Wille, H., Aiken, J., McKenzie, D., Doh-ura, K., Beck, M., O'Keefe, R., Stathopoulos, J., Caron, T., … Vallabh, S. M.. (2020). Prion protein lowering is a disease-modifying therapy across prion disease stages, strains and endpoints. Oxford Academic. https: //academic.oup.com/nar/article/48/19/10615/5878830

[6] Tremblay, P., Meiner, Z., Galou, M., Heinrich, C., Petromilli, C., Lisse, T., Cayetano, J., Torchia, M., Mobley, W., Bujard, H., DeArmond, S. J., & Prusiner, S. B. (1998). Doxycycline control of prion protein transgene expression modulates prion disease in mice. PMC. https: //pmc.ncbi.nlm.nih.gov/articles/PMC22873/

[7] Teruya, K., & Doh-ura, K. (2017). Insights from Therapeutic Studies for PrP Prion Disease. PMC. https: //pmc.ncbi.nlm.nih.gov/articles/PMC5334251/

[8] Forloni, G. (2025). Doxycycline: An essential tool for Alzheimer's disease. PMC. https: //pmc.ncbi.nlm.nih.gov/articles/PMC12165865/

[9] Fede, G. D., Giaccone, G., Salmona, M., & Tagliavini, F. (2018). Translational Research in Alzheimer's and Prion Diseases. PMC. https: //pmc.ncbi.nlm.nih.gov/articles/PMC5869996/

[10] Ma, Y., & Ma, J. (2020) Immunotherapy against Prion Disease. PMC. https: //pmc.ncbi.nlm.nih.gov/articles/PMC7157205/

[11] Napper, S., & Schatzl, H. M. (2023). Vaccines for prion diseases: a realistic goal?. PMC. https: //pmc.ncbi.nlm.nih.gov/articles/PMC9918406/

[12] Burchell, J. T., & Panegyres, P. K. (2016). Prion diseases: immunotargets and therapy. PMC. https: //pmc.ncbi.nlm.nih.gov/articles/PMC4970640/

[13] Kong, Q. (2006). RNAi: a novel strategy for the treatment of prion diseases. PMC. https: //pmc.ncbi.nlm.nih.gov/articles/PMC1679715/

[14] White, M. D., Farmer, M., Mirabile, I., Brandner, S., Collinge, J., & Mallucci, G. R. (2008). Single treatment with RNAi against prion protein rescues early neuronal dysfunction and prolongs survival in mice with prion disease. PMC. https: //pmc.ncbi.nlm.nih.gov/articles/PMC2474561/

[15] Pfeifer, A., Eigenbrod, S., Al-Khadra, S., Hofmann, A., Mitteregger, G., Moser, M., Bertsch, U., & Kretzschmar, H. (2006). Lentivector-mediated RNAi efficiently suppresses prion protein and prolongs survival of scrapie-infected mice. JCI. https: //www.jci.org/articles/view/29236

[16] Golding, M. C., Long, C. R., Carmell, M. A., Hannon, G. J., & Westhusin, M. E. (2006). Suppression of prion protein in livestock by RNA interference. PNAS. https: //www.pnas.org/doi/full/10.1073/pnas.0600813103