OXFORD JOURNAL
OF STUDENT
SCHOLARSHIP

Monoclonal Antibodies, Oligonucleotides, and Metal Chelators Vary in their Effectiveness of Treating Prion Diseases

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ABSTRACT

This paper evaluates the effectiveness of monoclonal antibodies (mAbs), antisense oligonucleotides (ASOs), and metal chelators for the treatment of prion diseases. Using data from current scientific journals and from biomedical research databases such as PubMed, this review compares the efficiency, limitations, and current progress of each approach. Current evidence suggests that mAbs show the greatest therapeutic promise. However, all treatment strategies are associated with off-target effects, though their severity is under debate. This result suggests a need for further research, particularly into ASOs and metal chelators, due to limited available studies.

I. INTRODUCTION

A. Prion Diseases

Prion diseases are class of neurodegenerative diseases caused by uncontrolled accumulation of prion proteins (PrP), which lack genetic material and replicate by inducing misfolding in normal PrP (Prusiner, 1982). It is characterized by progressive deterioration of brain function. Unlike conventional pathogens, prions propagate without DNA or RNA. These prion diseases include bovine spongiform encephalopathy (BSE), chronic wasting disease (CWD) in deer and similar mammals, and Creutzfeldt-Jakob disease (CJD) in humans (Prusiner, 1998). Early signs often include subtle changes in personality, mood, or behavior, such as depression, anxiety, or irritability. As the disease progresses, patients may develop rapidly worsening dementia, memory loss, impaired judgment, and confusion. Motor symptoms such as muscle stiffness, involuntary movements (myoclonus), difficulty walking (ataxia), and speech disturbances are common. Visual disturbances and sleep abnormalities may also occur.

Diagnosis typically involves neurological examination, MRI brain imaging (which may show changes such as an increased signal in the basal ganglia), EEG (which can reveal abnormal electrical activity), and analysis of cerebrospinal fluid for specific biomarkers. Pathologically, prion diseases are marked by spongiform changes such as microscopic holes in brain tissue along with neuronal loss and gliosis. Prion disorders are classified as familial, sporadic, iatrogenic, or variant, based on their mode of origin.

Their exact pathogenic mechanism is still unclear, and the timescale of illness is variable but often rapid: symptoms may progress from onset to severe disability or death within months to a few years. No approved cure exists. This review evaluates the therapeutic efficacy of metal chelators, antisense oligonucleotides (ASOs), and monoclonal antibodies (mAbs) in treating prion diseases.

B. Structure and Function of Prion Protein

The cellular prion protein $PrP^{C`}$ is a non-pathogenic, cell surface glycoprotein composed of 253 amino acids (Oesch et al., 1985; Madore et al., 1999). Its C-terminal domain contains three α-helices, a short β-sheet, and key post-translational modifications including disulfide bonding (Cys179–Cys214) and N-linked glycosylation at Asn181 and Asn197 (Zahn et al., 2000; Haraguchi et al., 1989). These modifications are thought to stabilize PrP^{C} and reduce its conversion to the pathogenic isoform, PrP^{Sc}. (Bosques & Imperiali, 2003). The N-terminal region lacks defined secondary structure and features octapeptide repeats that bind Cu (II), primarily through glycine and histidine residues (Brown et al., 1997; Garnett & Viles, 2003). PrP^{C} also binds copper at a secondary site involving His96 and His111 (Jackson et al., 2001), though its role in oxidative stress regulation remains unclear. The prion protein ($PrP^{C)}$ has been suggested, in in vitro studies, to act similarly to an enzyme called superoxide dismutase (SOD). SOD protects cells by catalyzing the degradation of reactive oxygen species (ROS), harmful molecules generated during normal metabolism or in response to stress, into less toxic substances. If PrP^{C} truly has SOD-like activity, it could help neutralize these ROS and reduce oxidative stress in the brain. However, while this antioxidant function is interesting and could explain some protective roles of PrP^{C}, in vivo evidence does not support a significant antioxidant function (Brown et al., 1999; Hutter et al., 2003).

PrP^{C} is tethered to the plasma membrane via a GPI anchor (a molecule that attaches proteins to the cell surface), which directs it to caveolae-like domains, regions consisting of cholesterol and sphingolipids but lacking the caveolin protein characteristic of caveolae. This localization appears to influence PrP^{Sc}. formation, as GPI-anchored PrP is more susceptible to conversion than transmembrane forms (Kaneko et al., 1997; Walmsley et al., 2001).

C. Monoclonal Antibodies

Monoclonal antibodies (mAbs) are synthetic proteins that mimic the antigen-binding abilities of antibodies found in the immune system. They consist of two identical light and heavy chains forming a conserved Y-shaped configuration, irrespective of the amino acid sequences in the N-terminal region (Edelman et al., 1961). MAbs can have immune responses through several mechanisms, including complement-dependent cytotoxicity via Membrane Attack Complex formation, antibody-dependent cytotoxicity mediated by effector cells, and modulation of the cytokine environment-either by inhibiting interleukin production or prolonging cytokine half-life (Jenne et al., 1988; Brennan et al., 1989; Finkelman et al., 1993). Several mAbs, including T2, V5B2, 1.5D7, and 1.6F4, have demonstrated the ability to bind to PrP^{Sc} (Cordes et al., 2008; Curin Serbec et al., 2004; Shimizu et al., 2010).

D. Antisense Oligonucleotides

Antisense oligonucleotides (ASOs) are synthetic DNA sequences (18 to 30 base pairs in length) that modify the expression of target RNA and block production of a protein. Their mechanisms of action include RNase H-mediated degradation of protein mRNA (Donis-Keller, 1979), steric blocking of translation (Stephenson & Zamecnik, 1978), and modulation of splicing through exon skipping or inclusion (Hua et al., 2010; Takeshima et al., 2006). ASOs may also inhibit small non-coding RNAs such as miRNAs and siRNAs, restoring expression of their target genes (Davis et al., 2006). To optimize its pharmacokinetics, ASOs often undergo chemical modifications. Phosphorothioate (PS) and phosphorodiamidate morpholino (PMO) modifications improve nuclease resistance and support RNase H activity (Summerton, 1999; Crooke et al., 2017). The 2′-O-methoxyethyl (2′-MOE) modification increases binding affinity and allows pharmacokinetic fine-tuning (Geary et al., 2001). Finally, gapmer designs, which flank modified regions with PS-linked DNA, combine stability with RNase H activation while minimizing toxicity (Crooke et al., 2017). In general, nucleotide modifications may be used in ASOs individually or together to improve nuclease resistance as well as to fine tune the pharmacokinetics of a particular ASO.

E. Metal Chelators

The octapeptide repeat region of binds divalent metal cations such as copper and zinc via histidine-glycine motifs (Brown et al., 1997). Though estimates vary, PrP^C binds approximately 1.8 to 5.6 moles Cu/mole, with discrepancies likely due to differing experimental pH conditions (Brown et al., 2001; Miura et al., 1999). PrP^C also binds other transition metals, including iron and manganese (Kim et al., 2005; Brown et al., 2000). These metals can participate in Fenton and Haber-Weiss reactions, such as $Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + OH^- + OH$, and can generate highly reactive hydroxyl radicals that contribute to oxidative stress (Halliwell & Gutteridge, 1992; Brazier et al., 2014). In general, any multivalent metal cation M with possible charges M^n/M^{n+1} may participate in the following Fenton reaction $M^{n+1} + H_2O_2 \rightarrow M^{n+} + OH^- + OH$ to generate a highly oxidizing hydroxyl radical. Copper and iron may also participate in Haber-Weiss reactions given below (M represents a transition metal)

$$M^{n+1} + O_2^- \rightarrow M^{n+} + O_2$$

$$M^{n+} + H_2O_2 \rightarrow M^{n+1} + OH^- + OH$$

$$H_2O_2 + O_2^- \rightarrow O_2 + OH^- + OH$$

Metal chelators bind free metal ions thus preventing their participation in ROS-generating reactions. Compounds such as quinacrine derivatives (Doh-Ura et al., 2000) and EUK-189 (Brazier et al., 2008) have been proposed as potential therapies for prion disease considering these biochemical processes.

As discussed above, the misfolding of PrP^{C} into PrP^{Sc} is a hallmark of prion diseases. Monoclonal antibodies are designed to recognize and neutralize PrP^{Sc}, antisense oligonucleotides aim to reduce the synthesis of prion protein at the mRNA level, and metal chelators disrupt metal-mediated stabilization of pathogenic conformers. Figure 1 and 2 provides a structural diagram of this transformation and essential context for evaluating the mechanisms and effectiveness of these emerging treatments.

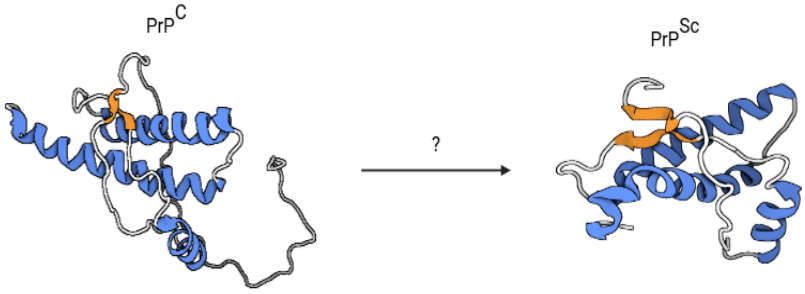

Figure 1. Structural Diagram of Alterations in Secondary Structure in Conversion of PrP^{C} to PrP^{Sc}

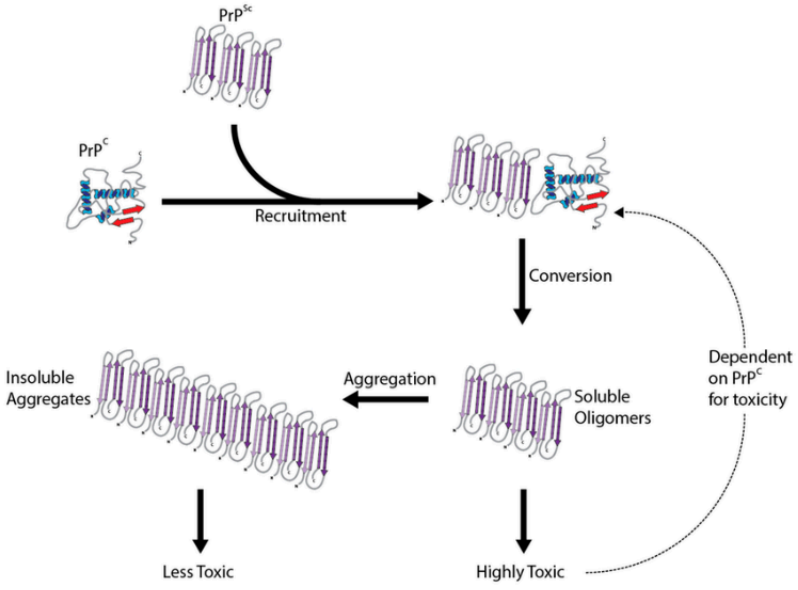

Figure 2. Structural Diagram in conversion of PrP^{C} to PrP^{Sc}

II. THE RESEARCH QUESTION

To what extent are monoclonal antibodies, antisense oligonucleotides, and metal chelators viable candidates for clinical translation in the treatment of prion diseases?

III. METHODOLOGY AND STUDY

A. Study Design

A narrative review was performed to address the limited and heterogeneous nature of studies on monoclonal antibodies (mAbs), antisense oligonucleotides (ASOs), and metal chelators in prion disease. The primary objective was to evaluate their mechanisms of action and therapeutic efficacy.

A comprehensive search was conducted in PubMed and in journals such as *Acta Neuropathologica*, *Cell*, and *Nature Neuroscience*, using adapted keyword combinations related to prion diseases and the three treatment classes. Reference lists of key articles were also screened for additional studies.

B. Study Selection Criteria

Only English-language peer-reviewed primary studies were included. Eligible studies met at least one of the following criteria:

- Reported in vitro or mechanistic data assessing anti-prion activity using cell lines or biochemical assays.
- Reported in vivo findings from animal or human models evaluating survival time, concentration of PrP^{Sc} levels when compared to PrP^{C}, and neurological outcomes.

IV. RESULTS

A. In Vitro

Several monoclonal antibodies (mAbs), including 31C6, 6D11, T1, T2, 44B1, 6H10, and ICSM 18, have been evaluated for their ability to inhibit or bind prion proteins in vitro. Sadowski et al. (2009) reported that mAb 6D11 binds both human and murine PrP^{Sc} (22L strain) with high and comparable affinities ($10.1 \pm 0.09 \times 10^{-11}$ M and $8.5 \pm 0.18 \times 10^{-11}$ M, respectively), like mAb 3F4, which binds recombinant human PrP but not murine PrP. In FDC-P1/22L and N2a/22L cell models, 6D11 inhibited conversion of PrP^{C} to PrP^{Sc}, with IC_{50} (The concentration of a drug needed to inhibit a biological process by 50%. Lower IC_{50} means higher potency) values of 0.025 ± 0.01 µg/mL and 0.07 ± 0.02 µg/mL, respectively. This inhibition persisted without reappearance of PrP^{Sc} and did not negatively affect cell viability. Pankiewicz et al. (2019) demonstrated that 6D11 facilitated lysosomal degradation of PrP^{Sc}, with significant reduction in total PrP levels observed 72 hours after treatment. Fluorescence microscopy showed increased internalization of labeled 6D11 in infected cells compared to uninfected

cells, along with increased co-localization with Rab7 and cathepsin D. Knockdown of PrP^{C} using siRNA only reduced PrP^{Sc} when combined with 6D11, indicating a synergistic effect.

Horiuchi et al. (2009) found that mAb 6H10, which targets a conformational epitope, had stronger reactivity to PrP^{Sc} than mAbs 31C6, 72, 44B1, and KLH. Immunoprecipitation using 6H10 shifted PK-resistant PrP^{Sc} from the supernatant to the precipitate. This antibody successfully precipitated PrP^{Sc} from Obihiro- and Chandler-infected mice, scrapie-infected sheep, and BSE-infected cattle, unlike mAb 31C6. Shimizu et al. (2010) reported that mAb T2, but not T1, significantly inhibited PrP^{Sc} accumulation in ScN2a cells, reducing PrP^{Sc} levels to 3.6 ± 0.5 percent of untreated controls at a concentration of 10 µg/mL. Yamasaki et al. (2014) studied mAb 44B1 and observed a concentration-dependent reduction in PrP^{Res}, nearly eliminating detectable levels at 7.5 µg/mL. After 72 hours, PrP^{Res} in treated ScN2a cells was approximately 40 percent of untreated controls, while PrP^{C} increased to around 250 percent. Reilly et al. (2022) showed that ICSM 18 protected primary hippocampal neurons from RML-induced neurotoxicity. ICSM 18 prevented neurite degeneration, dendritic spine loss, and neuron death, with EC_{50} values ranging from 7.7 to 20 nM and did not harm uninfected neurons. BRIC222 showed no such protective effect.

ASO-based interventions were also investigated. Reidenbach et al. (2019) exposed RML-infected ScN2a cells to PrP-lowering ASOs without transfection. These ASOs reduced PrP mRNA and protein levels only at micromolar concentrations due to limited uptake. Both targeting and control ASOs partially inhibited PrP^{Sc}, although substantial clearance required prolonged exposure. In a separate study, Nazor Friberg et al. (2012) screened 78 ASOs and identified ASOs 742, 747, and 771 as the most effective. At 200 nM, these ASOs reduced PrP mRNA in b.END cells by 94 to 97 percent. In N2a and ScN2a cells, ASOs 742, 747, and 771 reduced PrP^{Sc} core (PrP27–30) by 81, 63, and 57 percent respectively after seven days. ASO 771 demonstrated an EC_{50} of 4 nmol/L for PrP^{Sc}, while control ASO 923 had an EC_{50} of 10 nmol/L. No in vitro studies to date have directly tested metal chelators as treatments, although some have used them to assess the influence of transition metals on PrP biology.

Table 1: In Vitro Efficacy of Therapeutic Strategies Against Prion Disease

The efficacy metrics reported in this review (such as IC_{50}/ EC_{50} values, percent reduction in prion protein levels) are drawn from studies using different experimental models, prion strains, doses, and endpoints. Direct comparisons between these values should be interpreted with caution, as they may not reflect equivalent conditions or outcomes across studies.

Therapeutic Strategy	Agent(s) & Dose/Concentration	Efficacy (IC_{50}/EC_{50})	Limitations/Notes
Monoclonal Antibodies	6D11 (0.025 ± 0.01 µg/mL, 0.07 ± 0.02 µg/mL), 3F4, 6H10, T2, 44B1, ICSM 18	6D11: IC_{50} = 0.025 ± 0.01 µg/mL (FDC-P1/22L), 0.07 ± 0.02 µg/mL (N2a/22L); EC_{50} = 10.1 ± 0.09 × 10^{-11} M (human), 8.5 ± 0.18 × 10^{-11} M (murine); 44B1: ~7.5 µg/mL nearly eliminates PrPRes; ICSM 18: EC_{50} = 7.7–20 nM	High efficacy; some mAbs ineffective (e.g., BRIC222); cell uptake and CNS penetration not addressed in vitro
Antisense Oligonucleotides	742, 747, 771 (200 nM, 4 nmol/L)	742, 747, 771: PrP mRNA reduced by 94–97%; PrPSc core reduced by 81%, 63%, 57%; ASO 771: EC_{50} = 4 nmol/L; control ASO 923: EC_{50} = 10 nmol/L	High concentrations required due to limited uptake; partial inhibition unless prolonged exposure
Metal Chelators	(No direct agents tested in vitro)	No direct in vitro efficacy data	Lack of direct studies; only indirect effects assessed

B. In Vivo

Multiple in vivo studies have evaluated the efficacy and safety of monoclonal antibodies (mAbs), antisense oligonucleotides (ASOs), and metal chelators in murine models of prion disease.

Passive immunization with mAb 6D11 in CD-1 mice infected with the 22L prion strain extended the incubation period up to 58 days and reduced CNS PrP^{Sc} levels by 79%. However, once treatment ceased, PrP^{Sc} levels in lymphoid tissues rebounded, suggesting a transient therapeutic effect. GFAP-reactive astrogliosis (An increase in the number or size of astrocytes which are support cells in the brain in response to injury), while elevated in treated mice compared to non-infected controls, was significantly lower than in vehicle- and IgG-treated groups.

In a separate study, pre-incubation of the Obihiro prion strain with mAb 6H10 prolonged incubation by 19 days, corresponding to over a 95% reduction in infectivity. mAbs 31C6 and 110 failed to produce significant effects. mAb W226, recognizing both PrP^{C} and PrP^{Sc}, showed limited therapeutic benefit: intracerebral or extended intraperitoneal administration only modestly prolonged survival. Nonetheless, individual mice survived up to 694 days post-infection following treatment cessation at day 320, though overall differences were statistically significant but therapeutically minimal. Peripheral administration of fluorophore-labelled mAb 31C6 showed some brain penetration in infected mice but not in

uninfected controls. Survival benefit was minimal (average ~5 days), with variability in response depending on brain distribution of the antibody. PrP^{Sc} accumulation was slightly attenuated during disease progression but was comparable between treated and control groups at terminal stages. No significant differences were observed in microglial activation, astrogliosis, or vacuolation.

Dose-escalation studies of mAbs D13 and ICSM18 revealed dose-dependent neurotoxicity, with intracerebral injections above 6 µg inducing hyperintense lesions, edema, and neuronal damage without significant apoptosis. Safe upper limits were estimated at 3.7–5.4 µg for D13 and 3.1 µg for ICSM18.ASO-based therapies showed more promising outcomes. ASOs 742, 747, and 771 were well-tolerated in FVB mice, with no clinical or biochemical abnormalities. At 50 mg/kg/week intraperitoneally, ASO 742 reduced Prnp mRNA and PrP^{C} levels in the liver by 75% and 65%, respectively; ASO 771 achieved 30% and 50% reductions. Intracerebroventricular administration (75 µg/day for 21 days) reduced Prnp mRNA in the brain by 60% and PrP^{C} by 30–70%, depending on the ASO. A 100 µg/day dose of ASO 742 caused toxicity, while 75 µg/day was well-tolerated. ASO 771 reduced PrP^{Sc} levels by 96% and extended incubation by 40%, though delayed administration (60 days post-infection) caused toxicity, indicating a critical treatment window.

Further studies showed that ASOs 1 and 2, administered prophylactically in RML-infected mice, delayed clinical onset by 82% and 99%, respectively. ASO 1 also extended survival by 55% and tripled the symptomatic phase duration, while ASO 2 was not tolerated when administered at 120 days post-infection. Histopathology showed reduced PrP deposition and spongiform changes in treated mice, but terminal-stage pathology remained like controls. In 2020, ASOs 5 and 6 prolonged survival by 108% and 80%, respectively, in prophylactically treated mice, with dose-dependent reductions in cortical Prnp mRNA. ASO 1 extended survival by 57–184% across five prion strains in both Prnp^+/− and wild-type mice. However, ASO treatment sometimes increased GFAP-reactive astrogliosis. Delayed treatment with ASO 6 offered partial functional recovery but was effective only in a minority of mice.

Metal chelation studies showed mixed results. D-penicillamine significantly delayed disease onset, particularly in mice inoculated with a 1000-fold dilution of infected brain homogenate. Brain copper levels decreased by up to 32%, and proteinase K resistance of PrP^{Sc} was reversed by D-penicillamine in vitro, supporting a copper-mediated mechanism. In contrast, $Na_2CaCDTA$, a manganese chelator, selectively reduced Mn^{2+} levels by 50% and increased survival in low-dose prion-inoculated mice ($p = 0.002$) but had no benefit in high-dose infections.

Table 2: In Vivo Efficacy of Therapeutic Strategies Against Prion Disease

The efficacy metrics reported in this review (such survival extension, and percent reduction in prion protein levels) are drawn from studies using different experimental models, prion strains, doses, and endpoints. Direct comparisons between these values should be interpreted with caution, as they may not reflect equivalent conditions or outcomes across studies.

Strategy	Agent(s) & Dose/Concentration	Efficacy	Limitations/Notes
Monoclonal Antibodies	6D11, 6H10, W226, D13, ICSM18	6D11: Incubation extended by 58 days, CNS PrPSc reduced by 79%; 6H10: Incubation extended by 19 days, >95% reduction in infectivity; W226: modest survival benefit; D13/ICSM18: safe upper limits 3.7–5.4 µg/3.1 µg	Transient effect; rebound in lymphoid tissues; poor CNS penetration; dose-dependent neurotoxicity
Antisense Oligonucleotides	742, 747, 771, 1, 2, 5, 6	Prnp mRNA/PrPC reduced by up to 75%/70%; PrPSc reduced by 96%; incubation extended by up to 184%; delayed onset by up to 99%	Toxicity at high doses/delayed administration; critical treatment window; increased astrogliosis in some cases
Metal Chelators	D-penicillamine, $Na_2CaCDTA$	D-penicillamine: delayed onset, copper reduced by 32%; $Na_2CaCDTA$: Mn^{2+} reduced by 50%, increased survival in low-dose	Benefit only in early/low-dose disease; no effect in advanced/high-dose; risk of metal imbalance

V. DISCUSSION

A. Monoclonal Antibodies

Monoclonal antibodies (mAbs) showed substantial invitro efficacy against prion diseases, with mAbs such as 6D11, T2, 6H10, 44B1, and ICSM18 significantly reducing PrP^{Sc} levels. Among these, 6D11 appeared most effective, fully inhibiting PrP^{Sc} propagation via lysosomal degradation, as measured by co-localization with Rab7 and cathepsin D. In vivo results were more variable: 6D11 reduced PrP^{Sc} levels and hallmark prion disease lesion in the cingulate cortex. However, PrP^{Sc} levels rebounded post treatment in the lymphoreticular system. Efficacy was further limited by poor CNS penetration due to the blood-brain barrier, as seen with mAb 31C6. Additionally, high-dose administration of ICSM18 and D13 induced neurotoxicity. These findings highlight the need for further research to optimize CNS delivery, define safe dosage ranges, and evaluate long-term efficacy of mAbs in vivo.

B. Antisense Oligonucleotides

Antisense oligonucleotides (ASOs) have demonstrated efficacy in reducing PrP^{C}, PrP^{Sc}, and Prnp mRNA levels. In vitro, ASOs 771, 742, and 747 significantly reduced both PrP^{C} and protease-resistant

PrP27–30 levels, with ASO 771 showing an EC_{50} of 4 nmol/ less than half that of control ASO 923. In vivo, ASOs 771 and 742 at 75 µg/day significantly reduced PrP^{Sc}, in the CNS, and ASO 771 extended incubation time by up to 40%. ASO 1 also prolonged symptom onset and survival (Raymond et al., Minikel et al.). However, efficacy appears dose-dependent: Reidenbach et al. reported significant reductions only at near-micromolar concentrations. At these levels, some ASOs especially 2'-MOE, have been linked to caspase-3 activation and inhibited cell proliferation at ~100 nM. Additionally, some ASOs induced GFAP-reactive astrogliosis, which may impair CNS healing process. These conflicting results underscore the need for further research to define safe, effective dosing and assess the impact of backbone modifications on cytotoxicity.

C. Metal Chelators

Due to limited research, the efficacy of metal chelators in treating prion disease remains uncertain. Existing studies suggest they may be beneficial in early-stage disease when PrP^{Sc} levels are low. Sigurdsson et al. observed delayed symptom onset only in mice given a 1000-fold diluted prion inoculum, and Brazier et al. reported prolonged survival only with low-dose prion exposure. These findings indicate that metal chelators may slow disease progression during early pathogenesis but are likely ineffective once PrP^{Sc} level is high. This limits their clinical utility, as symptoms typically emerge after PrP^{Sc} has already plateaued (Mays et al., 2015).

A key advantage is their target specificity brain concentrations of non-target metals remained unchanged, potentially reducing off-target toxicity. However, Sigurdsson reported up to a 35% reduction in blood copper levels, raising concerns about significant metal imbalance. Given these findings, further investigation is needed to assess safety, optimize dosing, and determine the efficiency of metal chelators in both early and advanced stages of prion disease.

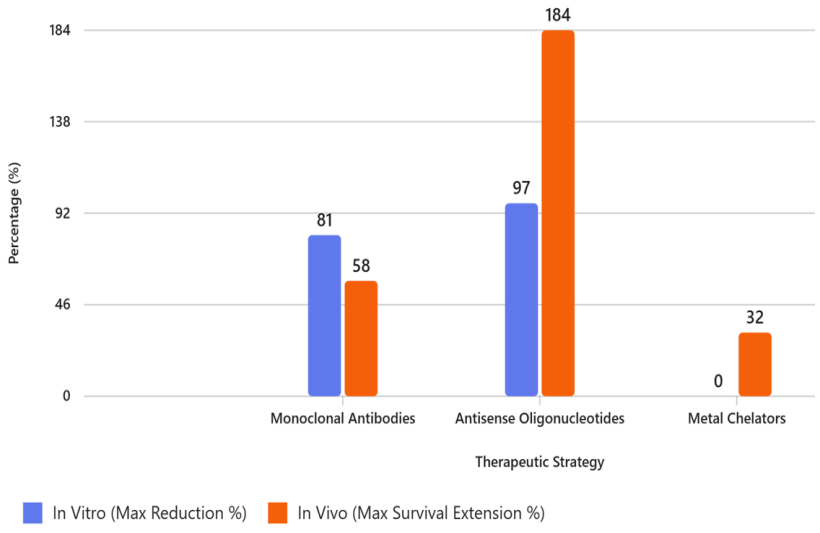

Figure 3. Max Reduction and Survival Extension in Percentage for In Vitro and In Vivo.

Max Reduction %, Survival Extension% shown in this figure are drawn from studies using different experimental models, prion strains, doses and endpoints. Direct comparisons between these values must be interpreted with caution ad they may not reflect equivalent conditions or outcomes across studies.

VI. CONCLUSION

When comparing the three therapeutic modalities monoclonal antibodies (mAbs), antisense oligonucleotides (ASOs), and metal chelators their mechanisms of action are distinct yet complementary. MAbs are designed to specifically recognize and neutralize the misfolded prion protein (PrP^{Sc}), either by promoting its degradation or blocking its propagation. ASOs act upstream by reducing the synthesis of prion protein at the epigenetic level, lowering both normal and pathogenic forms. Metal chelators target the biochemical environment, binding free metal ions (such as copper and manganese) that stabilize pathogenic prion conformers and contribute to oxidative stress.

Mechanistically, mAbs offer targeted neutralization but face challenges in crossing the blood-brain barrier and may induce immune responses. ASOs provide gene-level suppression, with potential for broad efficacy but risk of off-target effects and toxicity at high doses. Metal chelators may slow disease progression in initial stages by disrupting metal-mediated prion stabilization, but their effectiveness diminishes as disease advances, and they may cause systemic metal imbalances. Each approach has unique advantages and limitations, and future therapies may benefit from combining modalities to address multiple aspects of prion pathogenesis.

VII. REFERENCES

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