Convergence of human and veterinary medicine: leveraging canine naturally occurring neurological disorders to develop regenerative treatments

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In recent years, large animal models of naturally occurring diseases have become increasingly studied, with the rationale that their disease attributes may better recapitulate the pathological features of corresponding human diseases as compared to induced disease models (Hoffman and Dow, 2016). Of the available naturally occurring disease models, the canine is increasingly recognized as a valuable pre-clinical animal model in translational medicine for the study of neurological diseases, including respiratory disease, and inflammatory disease (Kol et al., 2015; Hoffman and Dow, 2016). The canine is one of the most common causes of lifelong disability and has been shown to have a similar variation in the pathogenesis of SCI and the variability of lesion size and locale. Account for variability in clinical manifestations can be the result of a congenital defect, most notably meningoencephalitis, which has been shown to cause demyelination and degeneration. Though the heterogeneous nature of this pathology makes it difficult for clinical trials, the success of new strategies, such as a novel canine naturally occurring disease model would provide a meaningful approach to assess the function of therapeutics.

Canine CNS disorders:
Spinal cord injury (SCI): SCI is a devastating condition that afflicts both human and canine patients. SCI can be acquired via acute injury or by an early and acute onset, which may be more comparable to pediatric MS. Current treatment strategies for canine SCI are limited, which has been shown to have a strong association of dog leukocyte antigen class II, similar to HLA in human MS (Greer et al., 2021). Pugs specifically suffer from necrotizing leukoencephalitis, much like what is seen in human MS. The two pathological features of pediatric and adult MS are demyelination and inflammation, and therefore many animals are left with untreated lesions.

Postnatal repair in canines is being explored. It has been shown that recovery from SCI is substantially higher in neonates compared to adult and young animals (Boulond et al., 2013; Zuchner et al., 2018). One reason for this is that elevated adaptive plasticity is maintained in the spinal cord after birth, which has led to the introduction of plasticity-enhancing procedures into clinical trials on human SCI patients (Boulond et al., 2013). While the potentiality indicates the potential for a successful regenerative therapy for SCI, there are no existing animal models to study postnatal repair of SB. Additionally, for human SCI, the entwickingle of strategies that are not applicable for all cases, creating a clinical need for improved postnatal treatment strategies. Therefore, the English bulldog serves as a novel model to study postnatal repair to treat naturally occurring SB in human patients.

IBD: IBD has been shown to have similar phenotypes such as multiple sclerosis (MS) in humans (Vitale and Foss, 2019). The two pathological features of pediatric and adult MS are demyelination and inflammation caused by immune cell infiltration of the CNS (Bjelobaba et al., 2018). Mouse experimental autoimmune encephalitis is one of the most widely studied animal models for MS pathology and therapeutic intervention (Bjelobaba et al., 2018). While this induced model strongly resembles the inflammatory and demyelinated state associated with MS, it does not capture all the features of the naturally occurring disease. Canine IBD can generally be referred to as meningoencephalomyelitis of unknown origin (MUO). Several forms of MUO can be characterized by histopathological findings into several categories including granulomatous meningoencephalomyelitis, necrotizing meningoencephalitis, and necrotizing leukoencephalitis (Andersen-Ranberg et al., 2021). MUO is presumed to be an autoimmune disease with a genetic predisposition (Andersen-Ranberg et al., 2021). It has been shown that there is a central role of MHC II positive cells, T-cells, and macrophages in disease onset of granulomatous meningoencephalomyelitis and necrotizing leukoencephalitis, much like what is seen in human forms of MS pathology (Andersen-Ranberg et al., 2021). Pugs specifically suffer from necrotizing meningoencephalitis, which has been shown to have a strong association of dog leukocyte antigen class II, similar to HLA in human MS (Greer et al., 2010). Necrotizing meningoencephalitis in dogs has a strong autoimmune component and is an aggravating phenotype of disease that has an early and acute onset, which may be more comparable to pediatric MS. Current treatment strategies for canine IBD are limited, which has been shown to have a strong association of dog leukocyte antigen class II, similar to HLA in human MS (Greer et al., 2010). Necrotizing meningoencephalitis in dogs has a strong autoimmune component and

Mesenchymal stem/stromal cells (MSCs): MSC-based regenerative therapy has become progressively popular in both human and veterinary patients (Carrade and Borjesson, 2013; Kol et al., 2015). MSCs are known to possess potential immunomodulatory, neuroprotective, and regenerative properties through the secretion of bioactive mediators (Carrade and Borjesson, 2013). However, the mechanisms by which canine MSCs achieve these effects for humans are not yet fully characterized. MSCs may play a pivotal role in neuroregeneration by secretion of neuroprotective, anti-inflammatory, and neurotrophic factors/mediators and act as repair elements. MSCs may also possess the ability to induce endogenous neuronal growth, promote neurogenesis, encourage synaptic connection from damaged neurons, recruit local olfactory glial progenitors, and stimulate angiogenesis, reduce demyelination and oxidative stress, and regulate neuroinflammation by modulating innate and adaptive immune responses.

MScs therapy for canine CNS disorders: MSCs have immune-modulatory and regenerative properties which have been demonstrated in several animal species. Research-induced disease modeling, using synthetic, genetic, and technical manipulation provides critical preclinical insights for disease study, but has significant limitations modeling the complexity of native pathological features of biological diseases. This likely contributes to the high failure rate of rodent disease models transitioning to human phase I clinical trials (Kol et al., 2015). Therefore, naturally occurring canine animal models may better recapitulate the heterogeneous features associated with human disease pathology.

Utilizing MSC therapy for the treatment of canine CNS disorders in the dog has become of high interest in recent years. The ability to provide critical insights to the use ofMSCs and MSC-derived extracellular vesicles as potential drug candidates for canine diseases is well. Clinical trials have already been employed in the canine using adult tissue-derived MSCs for several neurologic indications including, IVD and MUO (Hoffmann and Dow, 2016). It has previously been reported that canine MSCs derived from adult and fetal tissue have comparable functional properties feasible for the treatment of neurological disorders; however, canine MSCs have superior immunomodulatory properties making them an ideal drug candidate.
candidate. Investigating the therapeutic functions of canine PMSCs in treating canine neurological disorders will not only benefit canine patients but will also serve as preclinical data to accelerate the development of human counterpart PMSCs as a therapeutic for human patients. MSCs are also currently being evaluated for the treatment of MS. However, the heterogeneous nature of MS pathology poses a large challenge for the development of intervention strategies. Utilizing naturally occurring canine SCI, SB and MUO may better direct treatment plans for future human clinical trials.

To assess the clinical feasibility of an MSC product for the treatment of canine neurologic diseases, clinical trials will be necessary. Studies utilizing canine MSCs to evaluate safety and efficacy in the form of a veterinary clinical trial would allow for a new standard of care for these patients. Determining outcomes of these studies will utilize analogous deficits observed in both canine and human patients. For many CNS disorders, ambulatory defects, incontinence, and impaired cognitive functions are typically observed in patients. The need for strategies to improve clinical outcomes for neurodegenerative diseases is warranted in both the veterinary and human medical fields. Large-scale clinical trials evaluating the safety and efficacy of stem cell–based treatments long-term in canines provide unique opportunities to address clinical needs for both companion animals and their human counterparts. A schematic overview of studies utilizing in vitro models, research-induced disease models, and naturally occurring veterinary disease models to develop regenerative treatments for both veterinary and human patients is shown in Figure 1. This approach will be a significant step toward translating this cellular therapy to human patients.

Conclusions: Findings from these studies would be relevant to companion animal health as these results will provide clinical utility to several populations of dogs that do not have a treatment available in most cases. These animals will typically be euthanized due to the lack of standard care and intensive care required for their survival. Due to the immunomodulatory and regenerative properties of stem cells, there is a wide range of pathologies these therapies can be utilized for. PMSCs are a unique subset of cells that may have efficacious therapeutic outcomes for neurodevelopmental disorders due to their potent immunomodulatory and neuroprotective functions. In conclusion, the canine is becoming a significant translational model for human disease and may be a better predictor of clinical outcomes in humans, compared to traditional research-induced disease models, and will provide unique insights into translational therapies for human patients.

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