

REVIEW

Evolution of haematopoietic cell transplantation for canine blood disorders and a platform for solid organ transplantation

Scott S. Graves¹ | Rainer Storb^{1,2} 

¹ Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

² Department of Medicine, University of Washington School of Medicine, Seattle, Washington, USA

Correspondence

Rainer Storb, Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA.

Email: rstorb@fredhutch.org

Funding information

National Cancer Institute, Grant/Award Numbers: P30 CA015704, P01 CA078902

Abstract

Pre-clinical haematopoietic cell transplantation (HCT) studies in canines have proven to be invaluable for establishing HCT as a highly successful clinical option for the treatment of malignant and non-malignant haematological diseases in humans. Additionally, studies in canines have shown that immune tolerance, established following HCT, enabled transplantation of solid organs without the need of lifelong immunosuppression. This progress has been possible due to multiple biological similarities between dog and mankind. In this review, the hurdles that were overcome and the methods that were developed in the dog HCT model which made HCT clinically possible are examined. The results of these studies justify the question whether HCT can be used in the veterinary clinical practice for more wide-spread successful treatment of canine haematologic and non-haematologic disorders and whether it is prudent to do so.

KEYWORDS

canine, kidney, lymphoma, stem cell, transplantation

1 | INTRODUCTION

In humans, haematopoietic cell transplantation (HCT) is a well-established therapy for the treatment of not only malignant haematological diseases (Granot & Storb, 2020) but also non-malignant haematological disorders such as aplastic anaemia (Georges et al., 2018), hemoglobinopathies and immune-deficiency disease (Burrroughs & Woolfrey, 2010; Heimall et al., 2017). Moreover, immune tolerance following HCT can serve as a platform for solid organ allograft transplantation, thereby reducing morbidity and mortality associated with long-term immunosuppressive regimens (Sachs et al., 2011). Over 70 years, pre-clinical studies using various animal models have contributed to the successful application of clinical HCT protocols to treat human patients.

Canines have been an essential large animal model for the successful clinical development of HCT. There are several reasons why dogs have been so effective in this endeavour. Dogs are easily handled; share,

similarly to humans, a mixed gene pool; possess a diverse phenotype and have relatively long-life spans for a research animal (Ostrander & Wayne, 2005). They are not raised under gnotobiotic conditions, allowing for intestinal microbiota to affect HCT immunobiology in ways akin to the human condition (Noor et al., 2019). Dogs generally whelp large litters, which is important for finding suitable donor and recipient pairs that match or mismatch for the major histocompatibility complex (MHC) antigens, known as dog leukocyte antigens (DLA) (Dausset et al., 1971). In addition, human leukocyte antigen (HLA) and DLA class I and II genes share a high degree of gene structure similarity (Wagner et al., 1999).

In dogs, cancers develop spontaneously at rates comparable to or greater than in humans. Lymphomas for example, may occur in dogs at incident rates of 13–100 per 100,000 cases, sharing similarity with non-Hodgkin lymphoma in humans (Zandvliet, 2016). In general, cancers in humans and dogs share features such as histologic appearance, tumour genetics, biological behaviour, molecular target presentation,

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2021 The Authors. *Veterinary Medicine and Science* published by John Wiley & Sons Ltd.

therapeutic response and primary and metastatic microenvironments (Gordon et al., 2009). Several breeds of dogs are genetically predisposed to spontaneous diseases of haematologic origin and can be considered good candidates for HCT therapy.

Here, we briefly review the essential contributions the canine model has made towards the clinical application of HCT for human haematological malignant and non-malignant diseases. We suggest that a broader application of HCT in treating canine haematologic diseases should be considered in veterinary medicine. Although recent reviews on the application of stem cells for a variety of diseases in companion animals have been described, these reports focus almost exclusively on studies with mesenchymal stem cells (MSC) or adipose-derived stromal vascular fraction (AD-SVF) cells with little attention given to haematopoietic stem cells required for HCT (Fortier & Travis, 2011; Hoffman & Dow, 2016; Kang & Park, 2020).

Currently, HCT is being applied successfully for the treatment of canine lymphoma in veterinary practice on a limited scale. Dogs with non-malignant haematological pathologies have been successfully treated with HCT in pre-clinical studies, suggesting HCT for treatment of other haematopoietic diseases may be possible in veterinary clinics. In addition, evidence is offered to suggest that successful HCT-induced immune tolerance may replace the need for life-long immunosuppressive drugs required for solid organ transplantation.

2 | BACKGROUND OF HCT IN DOGS

The development of HCT in the canine pre-clinical research model has been well documented in recent reviews (Graves & Storb, 2020; Lupu & Storb, 2007). These observations span approximately six decades of investigation, with several important advancements having been successfully translated to human patients for the treatment of a variety of haematological disorders. The read-out for a majority of allogeneic canine HCT studies has been the successful establishment of stable mixed donor-host or 100% donor haematopoietic cell chimerism. Additionally, dogs with spontaneous leukaemia or lymphoma have been treated with HCT, resulting in instances of complete remission of disease (Appelbaum et al., 1985, 1986; Lupu et al., 2006; Suter et al., 2015; Warry et al., 2014; Weiden et al., 1978; Willcox et al., 2012).

The principles solved and the techniques used during this period included practical means of establishing DLA typing methods (Burnett et al., 1995; Wagner, Burnett, DeRose, et al., 1996; Wagner et al., 1998; Yu et al., 1994), optimizing recipient conditioning regimens including total body radiation (TBI) (Feinstein et al., 2001; Storb, Raff, et al., 1999; van Bekkum & de Vries, 1967), defining conditions for chemotherapy and radioimmunological therapy (Bethge et al., 2003; Chen et al., 2012), determining cell dose requirements (Appelbaum et al., 1978; Bodenberger et al., 1980), preventing or treating of graft-versus-host disease (GVHD) (Graves et al., 2017; Storb & Thomas, 1985; Storb et al., 1986; Yu et al., 1998) and demonstrating graft-versus-tumour (GVT) effects (Epstein et al., 1971; Weiden et al., 1978). Several of these studies can be considered important milestones towards the development of clinical HCT (Table 1).

TABLE 1 Critical advancements in canine haematopoietic cell transplantation (HCT)

	Literature, firstauthor
Graft vs. tumour (leukaemia/ lymphoma response)	Weiden (Weiden, Flournoy, et al., 1981)
	Appelbaum (Appelbaum et al., 1985)
	Weiden (Weiden et al., 1974)
DLA typing	Wagner (Wagner, Burnett, DeRose, et al., 1996)
	Wagner (Wagner et al., 1998)
	Graumann (Graumann et al., 1998)
Graft collection: marrow, mobilized PBMC	
Marrow transplantation	Appelbaum (Appelbaum, 1979)
Stem cell cryopreservation	Storb (Storb et al., 1967)
Mobilized PBMC	Storb (Storb, Epstein, LeBlond, et al., 1969)
Conditioning: non-myeloablative	De Revel (de Revel et al., 1994)
	Lupu (Lupu et al., 2008)
	Burroughs (Burroughs et al., 2005)
Chimerism analysis	Storb (Storb et al., 1997)
Post-grafting immunosuppression: GVHD	Storb (Storb, Yu, Barnett, et al., 1999)
rh CTLA4-Ig (abatacept)	Yu (Yu et al., 1994)
Tolerance: kidney, VCA	Storb (Storb et al., 1997)
	Zaucha (Zaucha, Yu, Zellmer, et al., 2001)
	Storb (Storb, Yu, Zaucha, et al., 1999)
Kidney	Yu (Yu et al., 2000)
VCA	
Reviews canine HCT	Kuhr (Kuhr et al., 2002)
	Mathes (Mathes et al., 2014)
	Lupu (Lupu & Storb, 2007)
	Graves (Graves & Storb, 2020)

Abbreviations: DLA, dog leukocyte antigens; HCT, haematopoietic cell transplantation; PBMC, peripheral blood mononuclear cells; rh CTLA4, recombinant human cytotoxic T-lymphocyte-associated antigen 4; VCA, vascularized composite allografts.

3 | DOG LEUKOCYTE ANTIGENS

An important milestone was the demonstration that serological matching donor and recipient pairs for DLA antigens was critical for the outcome of allogeneic HCT. Shortly thereafter, serological typing with multi-specific antisera (leuko-agglutination or trypan blue exclusion tests) was complemented by a cellular assay, the mixed leukocyte culture test (Epstein et al., 1968; Mollen et al., 1968; Rudolph et al., 1969). Later, the development of molecular typing methods for DLA using microsatellite markers specific to the polymorphic class I and II genes plus gene sequencing led to a highly effective and precise typing method of DLA matching for related and unrelated dog HCT

akin to what is performed in humans (Burnett et al., 1995; Francisco et al., 1996; Graumann et al., 1998; Venkataraman et al., 2007, 2017; Wagner, Burnett, DeRose, et al., 1996; Wagner et al., 1998; Wagner, Burnett, Works, et al., 1996).

Currently, there are recognized four complete class I genes, DLA-88, DLA-12, DLA-64 and DLA-79, and three class II genes, DRB1, DQA1 and DQB1. Two highly polymorphic canine microsatellite markers, one located in the class I region and one located in the class II region, suffice to select DLA-matched and -mismatched dogs within litters for tissue transplantation experiments though confirmation by gene sequencing should be done (Wagner et al., 1999). DLA-88 is considered the most polymorphic class I gene. A recent study showed that DLA-12 and DLA-64 are also polymorphic (Miyamae et al., 2018).

Typing methods of dogs within institutional colonies in which the genotypes of the female dog and sire are fully identified are straightforward for typing donor and recipient DLA-identical, DLA-haploidentical and fully DLA-mismatched pairs obtained from litters. However, DLA typing in the general population is complicated in cases where either one or both parents are not available for typing or the location of potential littermate donors is also limited. In 2006, Lupu et al. (2006) identified a DLA-identical cousin donor for a golden Labrador recipient requiring HCT for the treatment of spontaneously occurring lymphoma. Class I sequencing was done using primer pairs and the variable number tandem repeat-PCR standardized method (Wagner, Burnett, DeRose, et al., 1996). Because class II alleles may be difficult to differentiate using the single-strand conformation polymorphism (SSCP)-PCR method, confirmation of DRB1 alleles by sequencing and the use of a genetic analyzer were required. In this study, five potential HCT donors were identified by DLA typing of 29 family members from four generations of dogs in three countries.

Multigenerational-family molecular DLA typing for clinical allogeneic HCT needs to be a practical and routine laboratory procedure widely available to veterinary clinicians through commercialized laboratories or academic institutions with in-sourcing capabilities. Microsatellite primers are known for variable number tandem repeat-PCR methods to identify class I and II alleles and have been vetted for this purpose in a clinical setting for HCT therapy for canine lymphoma (Lupu et al., 2006).

4 | MONOCLONAL ANTIBODIES (mAb) AND RECOMBINANT PROTEINS

HCT progress has in part depended on the development of mAb, recombinant cytokines and recombinant fusion proteins specific to leukocytes and co-stimulatory molecules or their ligands. Some of these biologicals, developed for use in mice and humans, shared cross reactivity with canine lymphocytes and stem cells (Schuberth et al., 2007). Others required generation of molecules specific to canine leukocytes, an effort which has lagged behind production of the mouse and human equivalents (Table 2).

Anti-class II mAb (HB10a), when administered with TBI and methotrexate, improved HCT engraftment in a DLA-mismatched setting (Deeg et al., 1987). Similarly, mAb against CD44 on TBI-resistant marrow cells also facilitated engraftment in dogs given marrow from DLA-non-identical unrelated donors following 9.2 Gy TBI (F. Schuening et al., 1987, 1990, 1998).

Anti-CD34 mAb (2E9 or 1H6) binds 1%–3% of canine marrow cells with CD34+ cells showing marrow repopulating (stem cell) function in vivo (McSweeney et al., 1998). Anti-CD34 mAb has been used ex vivo to quantify stem cells within apheresis products used to transplant dogs with T-cell lymphoma (Warry et al., 2014).

CD28 is a critical costimulatory molecule for T-cell activation following antigen binding (Adams et al., 2016; Esensten et al., 2016). A blocking antibody directed against canine CD28 was produced with the aim of suppressing graft rejection and GVHD without downregulating the suppressive effects of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). The mAb was injected IV into normal dogs for evaluation of toxicity. Within 1 h, the antibody induced a cytokine storm in all three dogs tested (Rosinski, Stone, et al., 2015). A Fab of CD28 was safely tolerated in vivo, suggesting the possibility that safely targeting CD28 may be effective in preventing or treating GVHD or rendering the recipient of HCT tolerant against the donor graft. However, targeting the CD28 costimulatory pathway is complex and will require careful dissection before application is readily achieved (Esensten et al., 2016).

Inducible costimulatory molecule (ICOS) is upregulated on T cells in dogs with chronic GVHD (Sato et al., 2013). A murine mAb directed against canine ICOS was shown to temporarily reverse the progress of chronic GVHD in a canine model (Graves et al., 2018). Rabbit anti-thymocyte serum (ATS) was first successfully tested in dogs for the treatment of GVHD and for overcoming transfusion-induced sensitization to minor histocompatibility antigens and enhancing engraftment before progressing to the clinic (Storb et al., 1973; Storb, Gluckman, et al., 1974; Storb, Floersheim, et al., 1974; Weiden, Storb, Slichter, et al., 1976; Storb, Etzioni, et al., 1994). Despite great progress, uniform prevention and treatment of GVHD remains an important goal for the successful application of allogeneic HCT in treating canine diseases.

Rapid recovery of lymphocytes and neutrophils is important in the application of HCT for veterinary medical treatment of haematological diseases. The first agent to show promise in this regard was recombinant human granulocyte colony stimulating factor (rhG-CSF). F. G. Schuening et al. (1989) reported that rhG-CSF administered for 10 days after 9.2 Gy TBI accelerated recovery of neutrophils, monocytes and lymphocytes from post-irradiation nadirs. Sustained haematopoietic cell recovery in four of five dogs was seen when rhG-CSF was administered for 21 days after an otherwise lethal dose of 4.0 Gy TBI. Dogs conditioned with 4.5–6.0 Gy TBI and injected with haematopoietic growth factors (G-CSF with or without stem cell factor) in addition to DLA-identical marrow showed improved survival over dogs given marrow alone (Storb, Raff, et al., 1994). Recombinant canine (rc)G-CSF is available in bulk quantities from Amgen or R & D Systems.

Turning to fusion proteins directed against costimulatory molecules, there are potential applications for improved HCT in the veterinary

TABLE 2 Biologics to canine leukocytes used in HCT

	Use	Literature, first author
Canine specific reagents		
Anti-CD3	Engraftment, genetic manipulation	Zaucha (Zaucha, Zellmer, et al., 2001) Georges (Georges et al., 1998)
Anti-CD4	Immune response characterization T-regs, T-cell depletion	Knueppl (Knueppel et al., 2012)
Anti-CD5	lymphoma, NKT cell phenotyping	Graves (Graves, Gyurkocza, et al., 2019) Bonfont-Rebeix (Bonfont-Rebeix et al., 2016)
Anti-CD8	Immune response characterization, depletion studies	Watson (Watson et al., 1994)
Anti-CD28	T-cell costimulation	Graves (Graves et al., 2011)
Anti-CD34	Stem cell purification	Niemeyer (Niemeyer et al., 2001)
Anti-CD44 (S5)	Targeting NK, radioimmunotherapy	Fukuda (Fukuda et al., 2006)
Anti-CD94	NKT/NK cell reactivity/expansion	Graves (Graves, Gyurkocza, et al., 2019)
Anti-ICOS	Detection/prevention of GVHD	Sato (Sato et al., 2013) Graves (Graves et al., 2018)
rcCD40-Ig	Costimulatory molecule blockade	Jochum (Jochum et al., 2008)
rcCTLA4-Ig	Costimulatory molecule blockade	Graves (Graves et al., 2009)
	Tolerance induction	Zaucha (Zaucha, Zellmer, et al., 2001)
Cross-reactive reagents		
Anti-hu CD154 (5C8)	Costimulatory molecule blockade	Jochum (Jochum et al., 2007)
rh CTLA4-Ig (abatacept)	Costimulatory molecule blockade	Storb (Storb, Yu, Zaucha, et al., 1999) Yu (Yu et al., 2000)

Abbreviations: GVHD, graft-versus-host disease; rh CTLA-4, recombinant human cytotoxic T-lymphocyte-associated antigen 4; rcCTLA4, recombinant canine cytotoxic T-lymphocyte-associated antigen 4.

clinic. Stable mixed haematopoietic chimerism was established in dogs conditioned with suboptimal non-myeloablative 1.0 Gy TBI in the DLA-identical HCT setting when recipients were first treated for 7 days with infusion of donor peripheral blood mononuclear cells (PBMC) and CTLA4-Ig in order to induce a state of host-versus-donor unresponsiveness. Marrow transplantation was given after TBI on day 0 and followed with post-grafting immunosuppression consisting of cyclosporine and mycophenolate mofetil (Storb, Yu, Zaucha, et al., 1999). The mechanism of action of CTLA4-Ig was inferred as inhibition of T-cell function which was supported by a later study that showed tolerance could be induced to T-cell dependent antigens, sheep red blood cells (SRBC), following co-infusion of rcCTLA4-Ig and SRBC (Graves et al., 2009). RcCTLA4-Ig did not suppress a canine mixed leukocyte reaction (MLR) any better than the human protein (abatacept, Bristol Myers Squibb), making the human recombinant molecule readily available for the veterinary practice.

5 | CONDITIONING FOR HCT

In cases of malignant disease, conditioning of the recipient before HCT is required to decrease tumour burden and suppress the recipient's immune responses, thereby enabling engraftment of the donor haematopoietic cells. Conditioning regimens include TBI, radioim-

munotherapy (RIT), chemotherapy, polyclonal and monoclonal antibodies alone or in combinations.

TBI has proven to be the most consistent and effective means to condition the recipient for HCT. Studies pioneered by Thomas and colleagues demonstrated recovery of haematopoiesis in normal (Deeg et al., 1981; Ferrebee et al., 1958; Kolb et al., 1979; Storb, Raff, Appelbaum, Schuening, Sandmaier, Graham, & Thomas, 1988; Storb et al., 1989; Thomas et al., 1970) and tumour-bearing dogs (Appelbaum et al., 1985; Escobar et al., 2012; Warry et al., 2014; Weiden et al., 1978; Willcox et al., 2012; Weiden, Storb, Deeg, & Graham, 1979) given myeloablative doses of TBI followed with infusion of autologous or allogeneic HCT. Dogs given a dose of 4.0 Gy without a marrow graft died from marrow aplasia (Thomas et al., 1970). Myeloablative doses of TBI were effective in eliminating non-cycling tumour cells but at the cost of killing normal marrow cells, thus requiring the inclusion of HCT for recovery of normal haematopoiesis. Efficacy of marrow toxic doses of TBI followed by infusion of autologous marrow collected and cryopreserved prior to irradiation was done in dogs with malignant tumours (Epstein et al., 1971; Weiden et al., 1975; Weiden, Storb, Deeg, Graham, & Thomas, 1979; Storb, Epstein, LeBlond, et al., 1969). A marrow toxic dose escalation study spanning 4.5, 6.0, 7.0 and 8.0 Gy TBI followed by infusion of DLA-identical marrow showed transient allogeneic marrow engraftment at lower TBI doses, while the risk of allogeneic graft failure was reduced with higher doses of TBI. Even in cases of

allogeneic graft failure, the graft appeared to provide haematopoietic support until autologous haematopoiesis could recover (Storb, Raff, Appelbaum, Schuening, Sandmaier, & Graham, 1988).

A review of several HCT studies for dogs with naturally occurring tumours showed that higher doses of TBI were required for reducing tumour burden. The conditioning doses for external beam TBI followed by HCT reported for dogs with leukaemia/lymphoma ranged between 8.0 and 12.0 Gy TBI (Appelbaum et al., 1986; Lupu et al., 2006; Warry et al., 2014; Weiden et al., 1975; Weiden, Storb, Deeg, Graham, & Thomas, 1979; Willcox et al., 2012). Less-intensive conditioning TBI regimens, first established in dogs, were translated to the human allogeneic HCT setting to treat elderly and medically infirm patients with haematologic malignancies for whom myeloablative conditioning regimens would be too toxic. This approach relied less on the effectiveness of the conditioning regimen to reduce the tumour burden but, rather, on GVT effects for eradicating malignant cells. Non-myeloablative TBI was effective because post-grafting immunosuppression with short courses of mycophenolate mofetil and cyclosporine enabled engraftment of allogeneic donor cells and mitigated GVHD both in the DLA-identical (Storb et al., 1997) and DLA-non-identical settings (Yu et al., 1998).

Conditioning protocols using RIT for HCT were first evaluated in dogs. Radionuclides conjugated to mAbs with either β -emitting or α -emitting radionuclides followed by HCT offered targeting specificity with few or no off-target effects. Several canine HCT studies using various mAb targeting agents validated RIT conditioning for HCT (Bethge et al., 2003; Chen et al., 2012; Sandmaier et al., 2002). This approach to conditioning has been translated to on-going Phase I-II, first-in-human clinical trials. Particularly attractive has been an alpha-emitter, Astatine 211 which has a $t_{1/2}$ of 7.2 h, extremely high energy and a path length of only 60 microns, thereby engendering minimal off-target effects. The isotope has been coupled to a mAb, directed at the haematopoietic-specific antigen CD45. This approach at RIT promises effective tumour cell-kill without causing toxic side effects typically seen with, say, systemic chemotherapy or external beam gamma irradiation. Currently, the generation of Astatine 211 is limited to a small number of specific cyclotrons. Moreover, the cost of production of the isotope, its short $t_{1/2}$ lives, and the complexity of conjugation methods currently makes RIT impractical for standard veterinary practices.

High-dose cyclophosphamide as a single agent was shown to be an effective replacement for TBI in dogs given allogeneic (Storb, Epstein, Rudolph, et al., 1969) or autologous HCT (Epstein et al., 1969). Busulfan has been administered as a single conditioning agent for HCT in the treatment of canine leukocyte adhesion deficiency (CLAD) in dogs given matched littermate HCT (Sokolic et al., 2005). An intravenously injectable variant of busulfan, dimethylmyleran (DMM), effectively induced marrow aplasia that was reversed with autologous HCT (Kolb et al., 1974). In the allogeneic setting, DMM was less successful on its own in promoting engraftment; however, when combined with an immunosuppressive agent such as rabbit ATS more consistent engraftment was obtained (Storb et al., 1977). In veterinary practices where TBI is not easily available, chemotherapy conditioning may be a possible alternative, especially in the treatment of non-malignant haemato-

logical diseases (Bauer et al., 2006). However, TBI is the preferred regimen in the treatment of lymphoid malignancies.

6 | GRAFT COLLECTION

In general, donor stem cells for HCT in canines are obtained by aspirating the long bones of dogs. Mobilization of haematopoietic cells into the peripheral blood using rcG-CSF and collection of PBMC by apheresis can effectively replace marrow aspiration methods. Apheresis has been reported using a COBE Spectrum blood separator and central dual-lumen catheter (reviewed in Lupu et al., 2008) or a Baxter-Fenwall CS-3000 Plus blood separator (Suter, 2011). A typical course of rcG-CSF for obtaining mobilized PBMC (G-PBMC) included subcutaneous injections starting 5–6 days prior to the day of apheresis and irradiation of the recipient (Lupu et al., 2008). Zauha, Zellmer, et al. (2001) showed that stable engraftment was observed in dogs conditioned with 1.0 Gy TBI and given DLA-identical G-PBMC followed with extended post-grafting immunosuppression. However, in the DLA-haploidentical transplantation setting, dogs initially engrafted after 2.0 Gy TBI followed by G-PBMC infusion and post-grafting immunosuppression but eventually rejected donor grafts. Rejection occurred because of relatively radioresistant recipient NK cell activity (Chen et al., 2011).

A CXCR-4 inhibitor, AMD3100 (Plerixafor), was developed for stem-cell mobilizing properties and tested in dogs before application in the clinic (Burroughs et al., 2005). A comparison study of AMD3100 and rcG-CSF showed that a combination of the two agents was superior to either agent alone in mobilizing stem cells to the peripheral blood (Kim et al., 2019). Mobilization of haematopoietic cells into the peripheral blood using both G-CSF and AMD3100 (SQ) was used to enhance in vivo gene therapy in dogs given foamy virus vector containing a corrected common gamma chain gene for x-SCID disease (Humbert et al., 2018). As noted earlier, rcG-CSF was used to mobilize donor marrow stem cells into the peripheral blood for collection by apheresis for transplantation into a DLA-identical recipient dog for treatment of lymphoma (Lupu et al., 2006). Sandmaier et al. (1996) reported that the incidence and severity of acute GVHD in dogs given allogeneic G-PBMC after TBI without post-grafting immunosuppression were not significantly different from that in dogs given marrow as a source of stem cells. Together these results indicate that generation and collection of G-PBMC through leukapheresis procedures can adequately replace bone marrow aspiration methods for collection of haematopoietic grafts. G-PBMC might be preferred over bone aspiration in the veterinary practice although the latter is less time-consuming.

7 | POST-GRAFTING IMMUNOSUPPRESSION FOR THE PREVENTION OF GVHD

Allogeneic HCT carries with it a risk of GVHD in dogs especially in cases of transplantation between DLA-haploidentical donor and recipient pairs. The DLA-mismatched dog HCT model has been used successfully to evaluate procedures to prevent or treat acute and

chronic GVHD (for review, see Graves & Storb, 2020; Lupu & Storb, 2007). Post-grafting immunosuppression significantly reduced the incidence of acute or chronic GVHD (Mielcarek et al., 2006; F. G. Schuening et al., 1997; Storb et al., 1986, 1993; Storb, Yu, Barnett, et al., 1999; Yu et al., 1998). Generally, interventions (immunosuppressive drugs, antibodies or fusion proteins) designed to reduce or eliminate GVHD have been tested in dogs given myeloablative TBI followed by infusion of marrow with or without 'buffy coat' cells from DLA-haploidentical or DLA-mismatched unrelated donors. In the DLA-matched littermate HCT setting, development of GVHD is less common, especially when post-grafting immunosuppression is employed. However, a case report by Schaefer et al. (2016) described the experimental study of a 2-year-old female beagle given HCT from a DLA-identical sibling following conditioning with 4.5 Gy TBI. Post-grafting immunosuppression consisted of a single agent, cyclosporine, days -1 through 35. GVHD developed by day 52 and was successfully treated with methylprednisolone, cyclosporine, antibiotics and analgesics. One week after discontinuation of the glucocorticoid therapy, GVHD returned and the dog required euthanasia. Had the post-grafting immunosuppression regimen included mycophenolate mofetil, methotrexate or sirolimus, shown to be synergistic with cyclosporine in preventing GVHD in non-myeloablative conditioning, this fatal outcome might have been prevented (Hogan et al., 2003; Yu et al., 1998). The importance of post-grafting immunosuppression was further illustrated in a study using G-PBMC as source of stem cells. In that study, dogs were conditioned with 9.2 Gy TBI and infused with either DLA-identical or DLA-haploidentical G-PBMC without post-grafting immunosuppression. All dogs promptly engrafted, but three of nine DLA-identical recipients and all DLA-haploidentical recipients developed fatal GVHD (Sandmaier et al., 1996). In conclusion, post-grafting immunosuppression is a possible solution for the prevention of GVHD in allogenic canine HCT recipients.

8 | TREATMENT FOR CANINE MALIGNANT DISEASES

Dogs represent an appropriate model for the development of HCT therapies for spontaneous malignancies in a random bred species (Epstein et al., 1971). Canine malignancies share histopathological and biological characteristics with those in humans (MacEwen, 1990). Most canine tumours progress rapidly in a time frame in step with human tumours. Many canine and human cancers are associated with similar genetic alterations. For example, gene clustering analysis of genomic regions with alterations in copy number showed similarities in colorectal cancers in both man and dog (Tang et al., 2010). These alterations were correlated with tumour origin, progression and tumour subtype. Such findings demonstrate that the same or similar genetic pathways are likely affected in colorectal tumorigenesis in both species. Dogs with malignancies also have impaired humoral and/or cellular immune responses (Weiden et al., 1975) as observed in humans with neoplasia. For these reasons, canines have been responsible for many breakthrough studies. Having proven both pre-clinical and clinical efficacy of

HCT in treating haematological malignant and non-malignant diseases in both dogs and humans, it is now appropriate to consider HCT for treating such diseases in veterinary medicine.

9 | LYMPHOMA/LEUKAEMIA

Lymphomas are the most common haematopoietic neoplasia in dogs (Dobson, 2013; Dorn et al., 1967). A study of 40 dogs with occurring lymphomas revealed 78% were of B cell origin, 10% were of T cell origin and 12% were of non-T/non-B cell origin, a breakdown resembling that described for human lymphomas (Appelbaum et al., 1984). Breed specificity is a factor, with high indices of lymphoma in Doberman, Rottweiler, Boxer and Bernese Mountain Dogs (Comazzi et al., 2018). Complete remissions can be achieved in dogs with malignant lymphoma with combination chemotherapy usually consisting of cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine (Oncovin) and prednisone (CHOP). However, remissions are usually short lived unless followed up with high-dose TBI and HCT (Appelbaum et al., 1985; Deeg et al., 1985; Weiden, Storb, Deeg, Graham, & Thomas, 1979).

Autologous HCT following high-dose TBI has been used to treat spontaneous lymphoma as an intervention after standard chemotherapy or as a primary therapy (Appelbaum et al., 1985; Bowles et al., 1980; Deeg et al., 1985; Epstein et al., 1971; Weiden et al., 1978, 1975, 1977). Early studies by Weiden et al. (1975) showed that dogs with naturally occurring malignant lymphoma survived more than 25 days when treated with 1200 R (9.2 Gy) TBI followed by infusion of autologous marrow collected before TBI. One of eight dogs was tumour-free at the time of death. In a later study, dogs with lymphoma in clinical remission that were given 8.4 Gy TBI and autologous HCT experienced 24% long-term survival (Appelbaum et al., 1985). Chemotherapeutic drugs with or without TBI have been used to condition dogs for autologous HCT. For example, one study used conditioning with cyclophosphamide following a 12-week, five-drug chemotherapy protocol (Frimberger et al., 2006). This dose escalation study revealed dogs given 500 mg/m² cyclophosphamide conditioning had a median survival of 139 weeks compared to 43 and 68 weeks for dogs given 300 and 400 mg/m² IV cyclophosphamide, respectively. This suggests chemotherapy may replace TBI for conditioning for autologous HCT when a radiation source is unavailable.

Using autologous marrow for HCT in treating lymphoma is potentially risky as speculated by Bowles et al. (1980) who reported that minimal tumour burden and infusion of disease-free marrow were important factors in prolonging survival for dogs transplanted for spontaneous lymphoma. However, a study by Weiden et al. (1975) found that five of 25 dogs remained in complete remission of their lymphoma when given autologous marrow aspirated before 9.2 Gy TBI was administered. The investigators reported no apparent relationship between marrow status before TBI and survival beyond day 14. This suggested tumour involvement in marrow before autologous transplantation might not be an issue but the number of dogs studied was small. Given the documented GVT effects and the relative safety

of allogeneic HCT, selecting a DLA-identical graft over an autologous graft might be preferable.

Early studies in rodents indicated that transient engraftment of allogeneic HCT may result in an anti-leukemic effect in the recipient (Chester et al., 1977; Fefer, 1973). The question whether an allogeneic marrow graft provides a GVT effect or simply reconstitutes haematopoiesis following high-dose TBI in dogs with naturally occurring tumour was addressed by comparing the survival benefit of dogs given an autologous graft following 9.2 Gy TBI versus dogs given an allogeneic graft following the same dose of TBI. The number of allograft recipient dogs surviving more than 14 days that did not have tumours at the time of autopsy (88%) was significantly greater than dogs given an autologous graft (12%) (Weiden, Storb, et al., 1981). Although there were other factors that may have contributed to the difference in survival without tumour at the time of necropsy, the studies suggest allogeneic HCT may be superior to autologous HCT, likely due to recognition of tumour-associated and/or minor MHC antigens present on tumour cells as suggested in studies in humans (Nishida et al., 2009; Weiden, Flournoy, et al., 1981) and canines (Rosinski, Stone, et al., 2015).

Three additional early pre-clinical allogeneic HCT studies in dogs with spontaneous lymphoma are worth noting. In 1971, Epstein et al. (1971) reported on 29 dogs given allografts from DLA-matched or mismatched donors after 9.2 Gy TBI. Dogs received methotrexate for post-grafting immunosuppression. Seven dogs with lymphosarcoma survived beyond day 8. Although mortality rates were high, two dogs surviving 46 and 60 days post-transplant showed no signs of tumour on necropsy. Weiden et al. (1978) reported on dogs treated with 9.2 Gy TBI before transplant with unrelated marrow and given methotrexate and anti-lymphocyte serum as post-grafting immunosuppression. Sixteen dogs survived more than 14 days, and 14 of 15 dogs were free of disease at the time of necropsy. A later study revealed that two of eight dogs with spontaneous malignant lymphoma in chemotherapy-induced remission treated with 8.4 Gy TBI before infusion of marrow from unrelated donors initially survived transplantation but ultimately died from GVHD (Appelbaum et al., 1985). Collectively, these early studies indicated that allogeneic HCT can successfully cure dogs with lymphoma provided complications, such as GVHD, could be mitigated.

Recent individual case reports of dogs indicated that allogeneic HCT was a practical treatment option for leukaemia/lymphoma. In one report, a 2-year-old Cavalier King Charles Spaniel was diagnosed with large granular lymphocytic leukaemia. The dog responded well to induction chemotherapy and administration of 8 Gy TBI in two fractions followed by DLA-matched CD34+ cells obtained from a sibling donor. Post-grafting immunosuppression consisted of cyclosporine monitored and adjusted weekly. Haematopoietic donor cell chimerism was established 2 weeks after transplant and remained stable for more than 2 years, during which time the dog remained healthy (Suter et al., 2015). In 2006, Lupu et al. (2006) reported on HCT for treatment of a 7-year-old male Golden Retriever diagnosed with stage V T-cell malignant lymphoma. Clinical remission was first observed following two cycles of chemotherapy (cyclophosphamide, vincristine, cytosine arabinoside and prednisone, COAP). Eighteen weeks after diagnosis, a

TABLE 3 Equipment/methods generally required for allo-haematopoietic cell transplantation (HCT)

1. External beam radiation, (preferred)
2. Variable number tandem repeat-PCR testing
3. SSCP gel electrophoresis and DRB1 allelic sequencing
4. Haematopoietic chimerism analysis, microsatellite markers
5. Leukapheresis equipment, 'clean room'
6. Post-operative supportive care, 24/7 × 14 days

Abbreviations: SSCP, single-strand conformation polymorphism.

cousin donor was selected from 29 family members using molecular DLA typing methods. The dog was conditioned with two fractions of 4.0 Gy TBI for an infusion of G-PBMC. Post-grafting immunosuppression consisted of cyclosporine starting the day before HCT and ending 35 days after HCT. Blood chimerism analysis, measured until day 406, indicated the dog had stable full donor chimerism beginning by week 2 after transplant. The dog was tumour-free and eventually died of old age. Based on these studies, a compilation of the necessary equipment and steps needed for HCT for the treatment of leukaemia/lymphoma in dogs is provided in Table 3.

HCT for the treatment of lymphoma in dogs is available as a therapeutic option at a selected number of institutions within the United States. North Carolina State University Veterinary Hospital Medical Oncology programme performs marrow transplantation for canine lymphoma and leukaemia patients (NC State, Raleigh, NC). MedVet, located at Medical and Cancer Center for Pets, Columbus, Ohio, has recently completed its seventh transplantation in dogs with lymphoma (<https://www.medvetforpets.com/specialty/medical-oncology/>). The Bellingham Veterinary Clinic (Bellingham, WA), which specializes in canine oncology, also performs HCT for the treatment of haematological malignancies.

10 | NON-MALIGNANT HAEMATOLOGICAL DISORDERS

10.1 | Canine leukocyte adhesion deficiency (CLAD)

CLAD is a genetic immunodeficiency disease clinically manifested by recurrent bacterial infections and leucocytosis. The disease is caused by a single-point mutation within the CD18 gene preventing proper expression of a leukocyte adhesion proteins (Kijas et al., 1999). CLAD was first identified in an Irish Setter population in Europe. DNA sequencing from Irish Red and White Setters indicated the mutation for CLAD is also present in the United States and Australia (Fouremant et al., 2002; Jobling et al., 2003). As a haematopoietic disease, CLAD has been successfully treated with protocols using either 2.0 Gy TBI or busulfan for conditioning, marrow transplantation and post-grafting immunosuppression using cyclosporine and mycophenolate mofetil (Bauer et al., 2006; Sokolic et al., 2005). Additionally, CLAD has been successfully treated using non-myeloablative marrow transplantation

from DLA-identical littermates (Creevy et al., 2003). Bauer et al. (2005) reported 11 of 13 transplanted dogs had a reversal in their CLAD phenotype without evidence of GVHD. Dogs with less than 2% donor leukocyte chimerism presented with an attenuated CLAD phenotype suggesting gene therapy of a rather limited number of transduced autologous stem cells might also be a treatment for this disease (Gu et al., 2006).

10.2 | X-linked severe combined immunodeficiency

In humans, X-linked severe combined immunodeficiency (X-SCID) is the most common form of the disease and is caused by mutations in the common gamma chain associated with receptors for IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21. These receptors are required for the development and function of T, B and NK cells. HCT is an appropriate treatment that replaces the patient's defective immune system with donor T cells but with limited B cell numbers and function (Haddad et al., 1999). In dogs, the phenotype and progression of the disease are the same that of humans. X-SCID has been observed in Basset and Welsh Corgi dogs and is caused by two different mutations in the common gamma chain (Felsburg et al., 1999, 2003). Studies have shown that X-SCID dogs could be successfully transplanted with marrow or purified CD34+ cells from a normal DLA-identical donor with stable engraftment of donor B and T cells without the need of post-transplantation immunosuppression. Although normal T-cell development occurred, the study indicated B-cell reconstitution and antigen-specific B-cell function might be variable (Hartnett et al., 2002). However, two common problems need further investigation, resolution of the decline in the complexity of T cell diversity in XSCID dogs given HCT (Vernau et al., 2007) and prevention of the development of late onset cutaneous papillomavirus infection, a common side effect of marrow transplantation for the treatment of X-SCID in humans (Goldschmidt et al., 2006).

10.3 | Haemolytic anaemia

Severe hereditary haemolytic anaemia occurs in Basenji dogs as a result of a homozygous autosomal recessive defect in the pyruvate kinase (PK) gene. Erythrocytes from Basenji dogs with haemolytic anaemia are round spheres with uniform spicules on their surface that are absent on erythrocytes of normal dogs (Chandler et al., 1975). Complete correction of the disease could be obtained through HCT after myeloablative TBI using marrow from non-anaemic littermate dogs (Weiden, Storb, Graham, et al., 1976). Importantly, long-term observations showed a profound reduction in the liver iron overload over time after successful HCT (Weiden, Hackman, et al., 1981).

Non-myeloablative HCT to establish mixed donor haematopoietic cell chimerism was tested in Basenji PK-deficient dogs (Zaucha, Yu, Lothrop, et al., 2001). PK-deficient recipients were given a sublethal dose of TBI (2 Gy) before and post-grafting immunosuppression after infusion of marrow from healthy DLA-identical littermates. Of all five dogs engrafted, three dogs showed sustained mixed donor-host haematopoietic cell chimerism, while two dogs eventually rejected

their grafts. One of the three dogs died of pre-existing liver cirrhosis. Successful resolution of liver cirrhosis and myelofibrosis was observed in one of the dogs with the highest (85%) donor chimerism. The other dog had only 12% sustained donor chimerism and redeveloped severe haemolysis. A follow-up study using the same transplant protocol but, in addition, immunotherapy consisting of subsequent donor leukocyte infusions, was successful in increasing the level of donor chimerism to above 50%, with resulting resolution of haemolysis and avoidance of subsequent development of liver cirrhosis and myelofibrosis (Takutu et al., 2003). These studies indicated that DLA-identical HCT could be used to treat haemolytic anaemia in dogs, and that more than 50% donor chimerism was required for the cure of the disease. These canine studies and especially the observation of eventual resolution of liver iron overload set the stage for the first successful human allogeneic HCT in the treatment of thalassemia major (Thomas et al., 1982).

11 | LYSOSOMAL STORAGE DISEASES

Mucopolysaccharidosis I (MPS I) is an inherited autosomal recessive mutation that is relatively rare but spread across many breeds of dogs including German Shepherds, Flat Hounds, Labrador Retrievers, Welsh Corgis, Miniature Pinchers and Miniature Schnauzers. The disease is a result of the accumulation of uronic acid-containing glucosamine glycosans (GAG), heparin sulphate and dermatan sulphate in lysosomes of cells in many tissues. Standard treatment for MPS I includes enzyme replacement and fibroblast or amniotic epithelial cell transplantation, but these procedures have not met expectations in patients (Gibbs et al., 1983; Yeager et al., 1985).

Dogs with MPS I share many clinical symptoms with similarly affected humans and serve as a model for evaluating therapeutic interventions, including HCT, for this disease. The rationale has been that stem cell progeny could provide a source of self-renewing cells capable of producing the deficient enzyme, alpha L-iduronidase. Shull et al. (1987) reported on five dogs with MPS I that were treated with 7.5–8.5 Gy TBI and transfused with marrow from DLA-identical littermates with methotrexate as post-grafting immunosuppression. Reduction of GAG was seen in liver, cerebral cortex and cerebral spinal fluid in treated versus untreated controls. Ultrastructural analysis of brain tissue showed a reduction in lysosomal distention after HCT. GAG was cleared from surrounding blood vessels, and urinary excretion of GAG was normal by 5 months after HCT. In a similar HCT study, long-term effects of decreased neuronal vacuolization, arterial medial thickening, and severity and incidence of degenerative arthropathy were seen 20 months after HCT in MPS I affected dogs (Breider et al., 1989).

12 | TOLERANCE FOR SOLID ORGAN TRANSPLANTATION

Solid organ transplantation for canines is an uncommon procedure in veterinary practice; however, kidney transplantation per se provides a solution in dogs afflicted with kidney disease when dietary restrictions fail (Aronson, 2016). Dog breeds prone to kidney disease include

the English Cocker Spaniel, Bull Terrier, German Shepherd, Golden Retriever, Samoyed and Cairn Terrier. Dogs poisoned with ethylene glycol may also be considered as kidney transplant candidates (Berg et al., 1971). Cats are amenable to standard kidney transplantation with post-transplant immunosuppression but without HCT, while dogs generally do not fare as well with this treatment.

Mathews and Holmberg (2000) reported that dogs transplanted with kidneys from erythrocyte antigen typed and cross-matched donors survived a median period of 8 months when recipients were given post-grafting immunosuppression consisting of rabbit ATS, azathioprine and prednisone for the prevention of rejection. In general, kidney transplantation in dogs without tolerance induction was associated with high morbidity and mortality and thromboembolic complications, which were major causes of death (Hopper et al., 2012). A solution to this problem was the inclusion of DLA-identical HCT for induction of immune tolerance to replace life-long immunosuppression for allograft survival (for review, see Graves, Mathes, et al., 2019). Decades of canine studies successfully reduced conditioning toxicity, improved HCT engraftment and prevented GVHD, making immune tolerance through HCT a viable alternative to life-long immunosuppressive drug therapy for the prevention of solid organ graft rejection.

Several studies have reported long-term kidney allograft survival in dogs rendered tolerant using donor HCT using both DLA-identical (Kuhr et al., 2002, 2007; Tillson et al., 2006) and DLA-haploidentical donors (Niemeyer et al., 2005). In addition to kidney transplantation, other more immunogenic organs such as skin, (Tillson et al., 2006; Yunusov et al., 2006), gut (Yunusov et al., 2002), lung (Nash et al., 2009) and vascularized composite allografts (VCA), (Mathes et al., 2011, 2014) have been successfully transplanted in dogs rendered immune tolerant through HCT. In several of these studies, it was the development of the non-myeloablative conditioning (2.0 Gy TBI before and a short course of immunosuppression after allogeneic HCT) that made kidney or other organ transplantation well tolerated and possible.

Tolerance has been induced with HCT given before the organ graft (Kuhr et al., 2002; Mathes et al., 2014; Tillson et al., 2006) or with HCT given months after kidney transplantation once the proinflammatory effects of surgery have dissipated (Chang et al., 2016). Additionally, Graves et al. (2012) demonstrated that donor haematopoiesis could be reversed to host haematopoiesis without rejection of the DLA-identical kidney allograft by treating the recipient with a second small dose of TBI followed by an infusion of recipient G-PBMC cryopreserved before allogeneic HCT. This manoeuvre forestalled the risk of GVHD. Collectively, these studies indicated that successful permanent engraftment of an allogeneic kidney can be significantly improved by incorporating donor HCT before or following surgery. Successful transplantation of other less tolerated (more immunogenic) organs is less assured.

13 | DISEASES FOR WHICH HCT WAS NOT SUCCESSFUL

HCT proved unsuccessful for solid tumours in dogs. Autologous HCT for non-haematologic tumours was carried out after 9.2 Gy

TBI (Weiden et al., 1975). None of the 14 evaluable dogs with solid malignancies reached complete remission of the disease. This was likely because solid tumours had greater radiation resistance than, say, lymphoma. Similar negative results were seen with allogeneic HCT for canine solid tumours (Weiden et al., 1978). These results indicated HCT to be of minimal or of no practical value in treating dogs with solid malignancies.

HCT has also been ineffective in treating dogs with Duchenne muscular dystrophy (Dell'Agnola et al., 2004), haemophilia (factor VIII deficiency) (Storb et al., 1972), GM1 gangliosidosis (O'Brien et al., 1990) and ceroid lipofuscinosis (Batten's disease) (Deeg et al., 1990).

14 | WHAT THE FUTURE HOLDS

Recently, several novel approaches in the treatment of cancer in veterinary medicine have been described (for review, see Regan et al., 2016). The current review indicates pre-clinical and clinical studies that HCT offers a superior solution to treating lymphoma compared to chemotherapy alone and should be considered as a reasonable approach for canine haematological malignancies in veterinary medicine. There are three areas of future development that should be considered as complementary to standard HCT in this application.

The first is improving allogeneic HCT engraftment and reducing the rate of GVHD, perhaps through checkpoint blockade such as anti-CD28 and anti-CD154 or by combining mycophenolate mofetil, cyclosporine and sirolimus in a three-drug regimen as recently established in a phase III clinical trial (Sandmaier et al., 2019). It is plausible that conditioning intensity and associated toxicities can be reduced by using mAbs. For example, a mAb directed against CD154 was effective in promoting allogeneic HCT engraftment in recipients conditioned with the suboptimal dose of 100 cGy TBI (Jochum et al., 2007). A Fab fragment of anti-CD28 mAb was given safely and capable of blocking CD28 without interfering with the down regulatory mechanism of CTLA-4. Perhaps, such an agent will also be useful in treating chronic GVHD (Graves et al., 2017; Rosinski, Storb, et al., 2015). The check-point inhibitor, PD-1L, has been identified on several canine tumours including lymphoma cell lines, and blocking that signal may improve the GVT effect (Shosu et al., 2016). An anti-canine mAb specific to PD-1 has been produced that binds to and prevents T-cell suppression mediated by tumour cell explant fragments (Coy et al., 2017).

A second area of interest is using mAb specific to canine tumour antigens to supplement HCT therapy. While rituximab, anti-human CD20, administered after autologous HCT provided improved progression-free survival in human patients with mantle cell lymphoma (Epperla et al., 2015), it was not found to reduce the relapse risk when used peri-transplantation in allogeneic HCT for a human lymphoma (Granot et al., 2020). Moreover, rituximab fails to bind to canine lymphocytes (Impellizeri et al., 2006). Rue et al. (2015) described a rituximab-like anti-canine CD20 with ADCC activity as a possible candidate for B-cell lymphoma. Anti-canine CD20 chimeric antibody with antibody dependent cell cytotoxicity (ADCC) suppressed the growth of CLBL-1 tumours in mice (Mizuno et al., 2020). In conclusion,

it is not clear whether anti-canine CD20 would be useful following HCT for the treatment of B-cell lymphoma in dogs.

A third area of tumour immunotherapy is the ex vivo engineering of autologous T cells, specifically CAR T cells, which is a recent approach for treating primarily B-cell human malignancies. However, allogeneic HCT still may play a role in order to consolidate CAR T-cell-induced disease remissions (Bouziana & Bouzianas, 2020). It is reasonable to speculate that CAR T-cell therapy may eventually find application in the veterinary clinic and be supported by HCT for B-cell malignancies.

In terms of non-malignant haematological disorders, HCT has made progress in treating canine x-SCID, haemolytic anaemia and metabolic disorders. The contributions the dog HCT model has made towards developing protocols for human patients are important. However, improved practices such as outbreeding to diversify a breed and eliminate mutant gene carriers from the gene pool are superior cost-effective measures to eliminate these diseases.

HCT for the induction of immune tolerance towards kidney transplantation in dogs should be considered as an approach which is superior to lifelong immunosuppression. Simultaneous transplantation of marrow and a kidney from a DLA-identical littermate has a high level of success with minimal risk of GVHD. A similar approach could be used for partial liver transplantation.

Finally, cost of HCT is a concern. However, in many cases the dog is considered a member of the family, and extending the life of the animal may not be a difficult decision to make for those who can afford the treatment. Costs can be curtailed by using autologous marrow for transplantation for haematological malignancies, which eliminates the need for DLA-typing, location and transport of stem cells from a suitable donor. For allogeneic donors, genetic sequencing efficiency and availability are improving, while costs are decreasing every year. Finally, canine HCT in the United States is covered by many major pet insurance policies, in some cases up to 80%–90% of costs. In conclusion, it may be time to consider the benefits of HCT in mainstream veterinary medical practices.

ACKNOWLEDGEMENTS

The authors wish to thank Alix McPhearson, Michele Spector, DVM and the Fred Hutchinson Cancer Research Center's animal technicians, past and present for their assistance in these studies. Stacy Zellmer and Debe Higginbotham for DLA-typing and chimerism analysis; and Helen Crawford for manuscript preparation. This work was supported by grants P30 CA015704 and P01 CA078902 from the National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, which had no involvement in the study design; the collection, analysis and interpretation of data; the writing of the report; nor in the decision to submit the article for publication.

ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this is a review article with no original research data.

CONFLICT OF INTEREST

There are no conflicts of interest to report.

AUTHOR CONTRIBUTIONS

Scott S. Graves and Rainer Storb shared equally in conceptualization, visualization, original draft preparation, review, and editing. Rainer Storb was responsible for supervision and project administration.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1002/vms3.601>

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed for this review.

ORCID

Rainer Storb  <https://orcid.org/0000-0002-9343-4099>

REFERENCES

- Adams, A. B., Ford, M. L., & Larsen, C. P. (2016). Costimulation blockade in autoimmunity and transplantation: The CD28 pathway. *Journal of Immunology*, 197(6), 2045–2050.
- Appelbaum, F. R. (1979). Hemopoietic reconstitution following autologous bone marrow and peripheral blood mononuclear cell infusions. *Experimental Hematology*, 7(5), 7–11.
- Appelbaum, F. R., Deeg, H. J., Storb, R., Graham, T. C., Charrier, K., & Bensinger, W. (1986). Cure of malignant lymphoma in dogs with peripheral blood stem cell transplantation. *Transplantation*, 42(1), 19–22.
- Appelbaum, F. R., Deeg, H. J., Storb, R., Self, S., Graham, T. C., Sale, G. E., & Weiden, P. L. (1985). Marrow transplant studies in dogs with malignant lymphoma. *Transplantation*, 39(5), 499–504.
- Appelbaum, F. R., Herzog, G. P., Graw, R. G., Bull, M. I., Bowles, C., Gorin, N. C., & Deisseroth, A. B. (1978). Study of cell dose and storage time on engraftment of cryopreserved autologous bone marrow in a canine model. *Transplantation*, 26(4), 245–248.
- Appelbaum, F. R., Sale, G. E., Storb, R., Charrier, K., Deeg, H. J., Graham, T., & Wulff, J. C. (1984). Phenotyping of canine lymphoma with monoclonal antibodies directed at cell surface antigens: Classification, morphology, clinical presentation, and response to chemotherapy. *Hematological Oncology*, 2(2), 151–168.
- Aronson, L. R. (2016). Update on the current status of kidney transplantation for chronic kidney disease in animals. *Veterinary Clinics of North America. Small Animal Practice*, 46(6), 1193–1218.
- Bauer T. R. Jr., Gu, Y. C., Tuschong, L. M., Burkholder, T., Bacher, J. D., Starost, M. F., Donahue, R. E., Sokolic, R. A., & Hickstein, D. D. (2005). Nonmyeloablative hematopoietic stem cell transplantation corrects the disease phenotype in the canine model of leukocyte adhesion deficiency. *Experimental Hematology*, 33(6), 706–712.
- Bauer T. R. Jr., Hai, M., Tuschong, L. M., Burkholder, T. H., Gu, Y.-C., Sokolic, R. A., Ferguson, C., Dunbar, C. E., & Hickstein, D. D. (2006). Correction of the disease phenotype in canine leukocyte adhesion deficiency using ex vivo hematopoietic stem cell gene therapy. *Blood*, 108(10), 3313–3320.
- Berg, P., Nunamaker, D., Amand, W., Harvey, C., & Klide, A. (1971). Renal allograft in a dog poisoned with ethylene glycol. *Journal of the American Veterinary Medical Association*, 158(4), 468–471.
- Bethge, W. A., Wilbur, D. S., Storb, R., Hamlin, D. K., Santos, E. B., Brechbiel, M. W., Fisher, D. R., & Sandmaier, B. M. (2003). Selective T-cell ablation with bismuth-213-labeled anti-TCR α as nonmyeloablative conditioning for allogeneic canine marrow transplantation. *Blood*, 101(12), 5068–5075.

- Bodenberger, U., Kolb, H. J., Rieder, I., Netzel, B., Schäffer, E., Kolb, H., & Thierfelder, S. (1980). Fractionated total body irradiation and autologous bone marrow transplantation in dogs: Hemopoietic recovery after various marrow cell doses. *Experimental Hematology*, 8(4), 384–394.
- Bonnefont-Rebeix, C., Fournel-Fleury, C., Ponce, F., Belluco, S., Watrelot, D., Bouteille, S. E., Rapiteau, S., Razanajaona-Doll, D., Pin, J. - J., Leroux, C., & Marchal, T. (2016). Characterization of a novel canine T-cell line established from a spontaneously occurring aggressive T-cell lymphoma with large granular cell morphology. *Immunobiology*, 221(1), 12–22.
- Bouziana, S., & Bouzianas, D. (2020). Exploring the dilemma of allogeneic hematopoietic cell transplantation after chimeric antigen receptor T cell therapy: To transplant or not? *Biology of Blood and Marrow Transplantation*, 26(8), e183–e191.
- Bowles, C. A., Bull, M., McCormick, K., Kadin, M., & Lucas, D. (1980). Autologous bone marrow transplantation following chemotherapy and irradiation in dogs with spontaneous lymphomas. *Journal of the National Cancer Institute*, 65(3), 615–620.
- Breider, M. A., Shull, R. M., & Constantopoulos, G. (1989). Long-term effects of bone marrow transplantation in dogs with mucopolysaccharidosis I. *American Journal of Pathology*, 134(3), 677–692.
- Burnett, R. C., Francisco, L. V., DeRose, S. A., Storb, R., & Ostrander, E. A. (1995). Identification and characterization of a highly polymorphic microsatellite marker within the canine MHC class I region. *Mammalian Genome*, 6(9), 684–685.
- Burroughs, L., Mielcarek, M., Little, M. T., Bridger, G., Macfarland, R., Fricker, S., Labrecque, J., Sandmaier, B. M., & Storb, R. (2005). Durable engraftment of AMD3100-mobilized autologous and allogeneic peripheral blood mononuclear cells in a canine transplantation model. *Blood*, 106(12), 4002–4008.
- Burroughs, L., & Woolfrey, A. (2010). Hematopoietic cell transplantation for treatment of primary immune deficiencies. *Cellular Therapy and Transplantation*, 2(8). <https://doi.org/10.3205/ctt-2010-en-000077.000001>
- Chandler F. W. Jr., Prasse, K. W., & Callaway, C. S. (1975). Surface ultrastructure of pyruvate kinase-deficient erythrocytes in the Basenji dog. *American Journal of Veterinary Research*, 36(10), 1477–1480.
- Chang, J., Graves, S. S., Butts-Miwongtum, T., Sale, G. E., Storb, R., & Mathes, D. W. (2016). Long-term tolerance towards haploidentical vascularized composite allograft transplantation in a canine model using bone marrow or mobilized stem cells. *Transplantation*, 100(12), e120–e127.
- Chen, Y., Fukuda, T., Thakar, M. S., Kornblit, B. T., Storer, B. E., Santos, E. B., Storb, R., & Sandmaier, B. M. (2011). Immunomodulatory effects induced by cytotoxic T lymphocyte antigen 4 immunoglobulin with donor peripheral blood mononuclear cell infusion in canine major histocompatibility complex-haplo-identical non-myeloablative hematopoietic cell transplantation. *Cytotherapy*, 13(10), 1269–1280.
- Chen, Y., Kornblit, B., Hamlin, D. K., Sale, G. E., Santos, E. B., Wilbur, D. S., Storer, B. E., Storb, R., & Sandmaier, B. M. (2012). Durable donor engraftment after radioimmunotherapy using alpha-emitter astatine-211-labeled anti-CD45 antibody for conditioning in allogeneic hematopoietic cell transplantation. *Blood*, 119(5), 1130–1138.
- Chester, S. J., Esparza, A. R., Flinton, L. J., Simon, J. D., Kelley, R. J., & Albala, M. M. (1977). Further development of a successful protocol of graft versus leukemia without fatal graft-versus-host disease in AKR mice. *Cancer Research*, 37(10), 3494–3496.
- Comazzi, S., Marelli, S., Cozzi, M., Rizzi, R., Finotello, R., Henriques, J., Pastor, J., Ponce, F., Rohrer-Bley, C., Rütgen, B. C., & Teske, E. (2018). Breed-associated risks for developing canine lymphoma differ among countries: A European canine lymphoma network study. *BMC Veterinary Research*, 14(1), 232.
- Coy, J., Caldwell, A., Chow, L., Guth, A., & Dow, S. (2017). PD-1 expression by canine T cells and functional effects of PD-1 blockade. *Veterinary and Comparative Oncology*, 15(4), 1487–1502.
- Creevy, K. E., Bauer T. R. Jr., Tuschong, L. M., Embree, L. J., Silverstone, A. M., Bacher, J. D., Romines, C., Garnier, J., Thomas, M. L., Colenda, L., & Hickstein, D. D. (2003). Mixed chimeric hematopoietic stem cell transplant reverses the disease phenotype in canine leukocyte adhesion deficiency. *Veterinary Immunology and Immunopathology*, 95(3–4), 113–121.
- Dausset, J., Rapaport, F. T., Cannon, F. D., & Ferrebee, J. W. (1971). Histocompatibility studies in a closely bred colony of dogs. 3. Genetic definition of the DL-A system of canine histocompatibility, with particular reference to the comparative immunogenicity of the major transplantable organs. *Journal of Experimental Medicine*, 134(5), 1222–1237.
- de Revel, T., Appelbaum, F. R., Storb, R., Schuening, F., Nash, R., Deeg, J., Mcniece, I., Andrews, R., & Graham, T. (1994). Effects of granulocyte colony stimulating factor and stem cell factor, alone and in combination, on the mobilization of peripheral blood cells that engraft lethally irradiated dogs. *Blood*, 83, 3795–3799.
- Deeg, H. J., Appelbaum, F. R., Weiden, P. L., Hackman, R. C., Graham, T. C., & Storb, R. (1985). Autologous marrow transplantation as consolidation therapy for canine lymphoma: Efficacy and toxicity of various regimens of total body irradiation. *American Journal of Veterinary Research*, 46(9), 2016–2018.
- Deeg, H. J., Sale, G. E., Storb, R., Graham, T. C., Schuening, F., Appelbaum, F. R., & Thomas, E. D. (1987). Engraftment of DLA-nonidentical bone marrow facilitated by recipient treatment with anti-class II monoclonal antibody and methotrexate. *Transplantation*, 44(3), 340–345.
- Deeg, H. J., Shulman, H. M., Albrechtsen, D., Graham, T. C., Storb, R., & Koppang, N. (1990). Batten's disease: Failure of allogeneic bone marrow transplantation to arrest disease progression in a canine model. *Clinical Genetics*, 37(4), 264–270.
- Deeg, H. J., Storb, R., Weiden, P. L., Schumacher, D., Shulman, H., Graham, T., & Thomas, E. D. (1981). High-dose total-body irradiation and autologous marrow reconstitution in dogs: Dose-rate-related acute toxicity and fractionation-dependent long-term survival. *Radiation Research*, 88(2), 385–391.
- Dell'Agnola, C., Wang, Z., Storb, R., Tapscott, S. J., Kuhr, C. S., Hauschka, S. D., Lee, R. S., Sale, G. E., Zellmer, E., Gisburne, S., Bogan, J., Kornegay, J. N., Cooper, B. J., Gooley, T. A., & Little, M.-T. (2004). Hematopoietic stem cell transplantation does not restore dystrophin expression in Duchenne muscular dystrophy dogs. *Blood*, 104(13), 4311–4318.
- Dobson, J. M. (2013). Breed-predispositions to cancer in pedigree dogs. *ISRN Veterinary Science*, 2013, 941275.
- Dorn, C. R., Taylor, D. O., & Hibbard, H. H. (1967). Epizootiologic characteristics of canine and feline leukemia and lymphoma. *American Journal of Veterinary Research*, 28(125), 993–1001.
- Epperla, N., Fenske, T. S., Lazarus, H. M., & Hamadani, M. (2015). Post-autologous transplant maintenance therapies in lymphoid malignancies: Are we there yet? *Bone Marrow Transplantation*, 50(11), 1393–1404.
- Epstein, R. B., Graham, T. C., Storb, R., & Thomas, E. D. (1971). Studies of marrow transplantation, chemotherapy and cross-circulation in canine lymphosarcoma. *Blood*, 37(3), 349–359.
- Epstein, R. B., Storb, R., Clift, R. A., & Thomas, E. D. (1969). Autologous bone marrow grafts in dogs treated with lethal doses of cyclophosphamide. *Cancer Research*, 29(5), 1072–1075.
- Epstein, R. B., Storb, R., Ragde, H., & Thomas, E. D. (1968). Cytotoxic typing antisera for marrow grafting in littermate dogs. *Transplantation*, 6(1), 45–58.
- Escobar, C., Grindem, C., Neel, J. A., & Suter, S. E. (2012). Hematologic changes after total body irradiation and autologous transplantation of hematopoietic peripheral blood progenitor cells in dogs with lymphoma. *Veterinary Pathology*, 49(2), 341–343.
- Esensten, J. H., Helou, Y. A., Chopra, G., Weiss, A., & Bluestone, J. A. (2016). CD28 costimulation: From mechanism to therapy. *Immunity*, 44(5), 973–988.
- Fefer, A. (1973). Adoptive tumor immunotherapy in mice as an adjunct to whole-body X-irradiation and chemotherapy. A review. *Israel Journal of Medical Sciences*, 9(3), 350–365.
- Feinstein, L., Sandmaier, B., Maloney, D., Mcsweeney, P. A., Maris, M., Flowers, C., Radich, J., Little, M.-T., Nash, R. A., Chauncey, T., Woolfrey, A.,

- Georges, G., Kiem, H.-P., Zaucha, J. M., Blume, K. G., Shizuru, J., Niederwieser, D., & Storb, R. (2001). Nonmyeloablative hematopoietic cell transplantation: Replacing high-dose cytotoxic therapy by the graft-versus-tumor effect. *Annals of the New York Academy of Sciences*, 938, 328–337.
- Felsburg, P. J., Hartnett, B. J., Gouthro, T. A., & Henthorn, P. S. (2003). Thymopoiesis and T cell development in common gamma chain-deficient dogs. *Immunologic Research*, 27(3-Feb), 235–246.
- Felsburg, P. J., Hartnett, B. J., Henthorn, P. S., Moore, P. F., Krakowka, S., & Ochs, H. D. (1999). Canine X-linked severe combined immunodeficiency. *Veterinary Immunology and Immunopathology*, 69(4-Feb), 127–135.
- Ferrebee, J. W., Lochte H. L. Jr., Jaretzki A. III, Sahler, O. D., & Thomas, E. D. (1958). Successful marrow homograft in the dog after radiation. *Surgery*, 43, 516–520.
- Fortier, L. A., & Travis, A. J. (2011). Stem cells in veterinary medicine. *Stem Cell Research & Therapy*, 2(1), 9.
- Fouremant, P., Whiteley, M., & Giger, U. (2002). Canine leukocyte adhesion deficiency: Presence of the Cys36Ser beta-2 integrin mutation in an affected US Irish Setter cross-breed dog and in US Irish Red and White Setters. *Journal of Veterinary Internal Medicine*, 16(5), 518–523.
- Francisco, L. V., Langston, A. A., Mellersh, C. S., Neal, C. L., & Ostrander, E. A. (1996). A class of highly polymorphic tetranucleotide repeats for canine genetic mapping. *Mammalian Genome*, 7(5), 359–362.
- Frimberger, A. E., Moore, A. S., Rassnick, K. M., Cotter, S. M., O'Sullivan, J. L., & Quesenberry, P. J. (2006). A combination chemotherapy protocol with dose intensification and autologous bone marrow transplant (VELCAP-HDC) for canine lymphoma. *Journal of Veterinary Internal Medicine*, 20(2), 355–364.
- Fukuda, T., Kerbauy, F. R., Gooley, T., Santos, E. B., Storb, R., & Sandmaier, B. M. (2006). Dog leukocyte antigen-haploidentical stem cell allografts after anti-CD44 therapy and nonmyeloablative conditioning in a preclinical canine model. *Transplantation*, 82(3), 332–339.
- Georges, G. E., Doney, K., & Storb, R. (2018). Severe aplastic anemia: Allogeneic bone marrow transplantation as first-line treatment. *Blood Advances*, 2(15), 2020–2028.
- Georges, G. E., Storb, R., Brunvand, M. W., Kiem, H.-P., Moore, P. F., Malik, P., Ennist, D., & Nash, R. A. (1998). Canine T cells transduced with a herpes simplex virus thymidine kinase gene: A model to study effects on engraftment and control of graft-versus-host disease. *Transplantation*, 66(4), 540–544.
- Gibbs, D. A., Spellacy, E., Tompkins, R., Watts, R. W., & Mowbray, J. F. (1983). A clinical trial of fibroblast transplantation for the treatment of mucopolysaccharidoses. *Journal of Inherited Metabolic Disease*, 6(2), 62–81.
- Goldschmidt, M. H., Kennedy, J. S., Kennedy, D. R., Yuan, H., Holt, D. E., Casal, M. L., Traas, A. M., Mauldin, E. A., Moore, P. F., Henthorn, P. S., Hartnett, B. J., Weinberg, K. I., Schlegel, R., & Felsburg, P. J. (2006). Severe papillomavirus infection progressing to metastatic squamous cell carcinoma in bone marrow-transplanted X-linked SCID dogs. *Journal of Virology*, 80(13), 6621–6628.
- Gordon, I., Paoloni, M., Mazcko, C., & Khanna, C. (2009). The comparative oncology trials consortium: Using spontaneously occurring cancers in dogs to inform the cancer drug development pathway. *Plos Medicine*, 6(10), e1000161.
- Granot, N., Rezvani, A. R., Pender, B. S., Storer, B. E., Sandmaier, B. M., Storb, R., & Maloney, D. G. (2020). Impact of rituximab and host/donor Fc receptor polymorphisms after allogeneic hematopoietic cell transplantation for CD20+ B-cell malignancies. *Biology of Blood and Marrow Transplantation*, 26(10), 1811–1818.
- Granot, N., & Storb, R. (2020). History of hematopoietic cell transplantation: Challenges and progress. *Haematologica*, 105(12), 2716–2729.
- Graumann, M. B., DeRose, S. A., Ostrander, E. A., & Storb, R. (1998). Polymorphism analysis of four canine MHC class I genes. *Tissue Antigens*, 51(4 Pt 1), 374–381.
- Graves, S. S., Gyurkocza, B., Stone, D. M., Parker, M. H., Abrams, K., Jochum, C., Gallo, S., Saad, M., Johnson, M. M., Rosinski, S. L., & Storb, R. (2019). Development and characterization of a canine-specific anti-CD94 (KLRD-1) monoclonal antibody. *Veterinary Immunology and Immunopathology*, 211, 10–18.
- Graves, S. S., Mathes, D. W., Georges, G. E., Kuhr, C. S., Chang, J., Butts, T. M., & Storb, R. (2012). Long-term tolerance to kidney allografts after induced rejection of donor hematopoietic chimerism in a preclinical canine model. *Transplantation*, 94(6), 562–568.
- Graves, S. S., Mathes, D. W., Storb, R. (2019). Induction of tolerance towards solid organ allografts using hematopoietic cell transplantation in large animal models. *OBM Transplant*, 3(3), 24.
- Graves, S. S., Parker, M. H., Stone, D., Sale, G. E., Pillai, S. P. S., Johnson, M. M., & Storb, R. (2018). Anti-inducible costimulator monoclonal antibody treatment of canine chronic graft-versus-host disease. *Biology of Blood and Marrow Transplantation*, 24(1), 50–54.
- Graves, S. S., Rezvani, A., Sale, G., Stone, D., Parker, M., Rosinski, S., Spector, M., Swearingen, B., Kean, L., & Storb, R. (2017). A canine model of chronic graft-vs.-host disease. *Biology of Blood and Marrow Transplantation*, 23(3), 420–427.
- Graves, S. S., Stone, D. M., Loretz, C., Peterson, L. J., Lesnikova, M., Hwang, B., Georges, G. E., Nash, R., & Storb, R. (2011). Antagonistic and agonistic anti-canine CD28 monoclonal antibodies: Tools for allogeneic transplantation. *Transplantation*, 91(8), 833–840.
- Graves, S. S., Stone, D., Loretz, C., Peterson, L., Mccune, J. S., Mielcarek, M., & Storb, R. (2009). Establishment of long-term tolerance to SRBC in dogs by recombinant canine CTLA4-Ig. *Transplantation*, 88(3), 317–322.
- Graves, S. S., & Storb, R. (2020). Developments and translational relevance for the canine hematopoietic cell transplantation preclinical model. *Veterinary and Comparative Oncology*, 18(4), 471–483.
- Gu, Y. C., Bauer, T. R., Sokolic, R. A., Hai, M., Tuschong, L. M., Burkholder, T., Bacher, J., Starost, M. F., & Hickstein, D. D. (2006). Conversion of the severe to the moderate disease phenotype with donor leukocyte microchimerism in canine leukocyte adhesion deficiency. *Bone Marrow Transplantation*, 37(6), 607–614.
- Haddad, E., Le Deist, F., Aucouturier, P., Cavazzana-Calvo, M., Blanche, S., De Saint Basile, G., & Fischer, A. (1999). Long-term chimerism and B-cell function after bone marrow transplantation in patients with severe combined immunodeficiency with B cells: A single-center study of 22 patients. *Blood*, 94(8), 2923–2930.
- Hartnett, B. J., Yao, D., Suter, S. E., Moore, P. F., Krakowka, S., & Ochs, H. D. (2002). Transplantation of X-linked severe combined immunodeficient dogs with CD34+ bone marrow cells. *Biology of Blood and Marrow Transplantation*, 8(4), 188–197.
- Heimall, J., Puck, J., Buckley, R., Fleisher, T. A., Gennery, A. R., Neven, B., Slatyer, M., Haddad, E., Notarangelo, L. D., Baker, K. S., Dietz, A. C., Duncan, C., Pulsipher, M. A., & Cowan, M. J. (2017). Current knowledge and priorities for future research in late effects after hematopoietic stem cell transplantation (HCT) for severe combined immunodeficiency patients: A consensus statement from the Second Pediatric Blood and Marrow Transplant Consortium International Conference on Late Effects after Pediatric HCT. *Biology of Blood and Marrow Transplantation*, 23(3), 379–387.
- Hoffman, A. M., & Dow, S. W. (2016). Concise review: Stem cell trials using companion animal disease models. *Stem Cells*, 34(7), 1709–1729.
- Hogan, W. J., Little, M. T., Zellmer, E., Friedetzky, A., Diaconescu, R., Gisburne, S., Lee, R., Kuhr, C., & Storb, R. (2003). Postgrafting immunosuppression with sirolimus and cyclosporine facilitates stable mixed hematopoietic chimerism in dogs given sublethal total body irradiation before marrow transplantation from DLA-identical littermates. *Biology of Blood and Marrow Transplantation*, 9(8), 489–495.
- Hopper, K., Mehl, M. L., Kass, P. H., Kyles, A., & Gregory, C. R. (2012). Outcome after renal transplantation in 26 dogs. *Veterinary Surgery*, 41(3), 316–327.

- Humbert, O., Chan, F., Rajawat, Y. S., Torgerson, T. R., Burtner, C. R., Hubbard, N. W., Humphrys, D., Norgaard, Z. K., O'donnell, P., Adair, J. E., Trobridge, G. D., Scharenberg, A. M., Felsburg, P. J., Rawlings, D. J., & Kiem, H. P. (2018). Rapid immune reconstitution of SCID-X1 canines after G-CSF/AMD3100 mobilization and in vivo gene therapy. *Blood Advances*, 2(9), 987–999.
- Impellizzeri, J. A., Howell, K., McKeever, K. P., & Crow, S. E. (2006). The role of rituximab in the treatment of canine lymphoma: An ex vivo evaluation. *Veterinary Journal*, 171(3), 556–558.
- Jobling, A. I., Ryan, J., & Augusteyn, R. C. (2003). The frequency of the canine leukocyte adhesion deficiency (CLAD) allele within the Irish Setter population of Australia. *Australian Veterinary Journal*, 81(12), 763–765.
- Jochum, C., Beste, M., Stone, D., Graves, S. S., & Storb, R. (2008). Development and in vitro characterization of canine CD40-Ig. *Veterinary Immunology and Immunopathology*, 123(4-Mar), 260–265.
- Jochum, C., Beste, M., Zellmer, E., Graves, S. S., & Storb, R. (2007). CD154 blockade and donor-specific transfusions in DLA-identical marrow transplantation in dogs conditioned with 1-Gy total body irradiation. *Biology of Blood and Marrow Transplantation*, 13, 164–171.
- Kang, M. H., & Park, H. M. (2020). Challenges of stem cell therapies in companion animal practice. *Journal of Veterinary Science*, 21(3), e42.
- Kijas, J. M., Bauer T. R. Jr., Gafvert, S., Marklund, S., Trowald-Wigh, G., Johansson, A., Hedhammar, Å., Binns, M., Juneja, R. K., & Hickstein, D. D., Andersson, L. (1999). A missense mutation in the beta-2 integrin gene (ITGB2) causes canine leukocyte adhesion deficiency. *Genomics*, 61(1), 101–107.
- Kim, S., Hosoya, K., Kobayashi, A., & Okumura, M. (2019). Comparison of three mobilization protocols for peripheral blood stem cell apheresis with Spectra Optia continuous mononuclear cell protocol in healthy dogs. *Veterinary and Comparative Oncology*, 17(1), 61–68.
- Knueppel, A., Lange, S., Altmann, S., Sekora, A., Knuebel, G., Vogel, H., Lindner, I., Freund, M., & Junghanss, C. (2012). Upfront denileukin diftitox as in vivo regulatory T-cell depletion in order to enhance vaccination effects in a canine allogeneic hematopoietic stem cell transplantation model. *Veterinary Immunology and Immunopathology*, 145(1-2), 233–240.
- Kolb, H. J., Rieder, I., Bodenberger, U., Netzel, B., Schaffer, E., Kolb, H., & Thierfelder, S. (1979). Dose rate and dose fractionation studies in total body irradiation of dogs. *Pathologie Biologie*, 27(6), 370–372.
- Kolb, H. J., Storb, R., Weiden, P. L., Ochs, H. D., Kolb, H., Graham, T. C., Flossheim, G. L., & Thomas, E. D. (1974). Immunologic, toxicologic and marrow transplantation studies in dogs given dimethyl myleran. *Biomedicine*, 20(5), 341–351.
- Kuhr, C. S., Allen, M. D., Junghanss, C., Zaucha, J. M., Marsh, C. L., Yunusov, M., Zellme, E., Little M.-T., Torok-Storb, B., & Storb, R. (2002). Tolerance to vascularized kidney grafts in canine mixed hematopoietic chimeras. *Transplantation*, 73(9), 1487–1493.
- Kuhr, C. S., Yunusov, M., Sale, G., Loretz, C., & Storb, R. (2007). Long-term tolerance to kidney allografts in a preclinical canine model. *Transplantation*, 84(4), 545–547.
- Lupu, M., Gooley, T., Zellmer, E., Graves, S. S., & Storb, R. (2008). Principles of peripheral blood mononuclear cell apheresis in a preclinical canine model of hematopoietic cell transplantation. *Journal of Veterinary Internal Medicine*, 22(1), 74–82.
- Lupu, M., & Storb, R. (2007). Five decades of progress in haematopoietic cell transplantation based on preclinical canine model. *Veterinary and Comparative Oncology*, 5(1), 14–30.
- Lupu, M., Sullivan, E. W., Westfall, T. E., Little, M. -T., Weigler, B. J., Moore, P. F., Stroup, P. A., Zellmer, E., Kuhr, C., & Storb, R. (2006). Use of multigeneration-family molecular dog leukocyte antigen typing to select a hematopoietic cell transplant donor for a dog with T-cell lymphoma. *Journal of the American Veterinary Medical Association*, 228(5), 728–732.
- MacEwen, E. G. (1990). Spontaneous tumors in dogs and cats: Models for the study of cancer biology and treatment. *Cancer and Metastasis Reviews*, 9(2), 125–136.
- Mathes, D. W., Chang, J., Hwang, B., Graves, S. S., Storer, B. E., Butts-Miwongtum, T., Sale, G. E., & Storb, R. (2014). Simultaneous transplantation of hematopoietic stem cells and a vascularized composite allograft leads to tolerance. *Transplantation*, 98(2), 131–138.
- Mathes, D. W., Hwang, B., Graves, S. S., Edwards, J., Chang, J., Storer, B. E., Butts-Miwongtum, T., Sale, G. E., Nash, R. A., & Storb, R. (2011). Tolerance to vascularized composite allografts in canine mixed hematopoietic chimeras. *Transplantation*, 92(12), 1301–1308.
- Mathews, K. A., & Holmberg, D. L. (2000). Kidney transplantation in dogs with naturally occurring end-stage renal disease. *Journal of the American Animal Hospital Association*, 36(6), 475.
- McSweeney, P. A., Rouleau, K. A., Wallace, P. M., Bruno, B., Andrews, R. G., Krizanac-Bengez, L., Sandmaier, B. M., Storb, R., Wayner, E., & Nash, R. A. (1998). Characterization of monoclonal antibodies that recognize canine CD34. *Blood*, 91(6), 1977–1986.
- Mielcarek, M., Georges, G. E., & Storb, R. (2006). Denileukin diftitox as prophylaxis against graft-versus-host disease in the canine hematopoietic cell transplantation model. *Biology of Blood and Marrow Transplantation*, 12(9), 899–904.
- Miyamae, J., Suzuki, S., Katakura, F., Uno, S., Tanaka, M., Okano, M., Matsumoto, T., Kulski, J. K., Moritomo, T., & Shiina, T. (2018). Identification of novel polymorphisms and two distinct haplotype structures in dog leukocyte antigen class I genes: DLA-88, DLA-12 and DLA-64. *Immunogenetics*, 70(4), 237–255.
- Mizuno, T., Kato, Y., Kaneko, M. K., Sakai, Y., Shiga, T., Kato, M., Tsukui, T., Takemoto, H., Tokimasa, A., Baba, K., Nemoto, Y., Sakai, O., & Igase, M. (2020). Generation of a canine anti-canine CD20 antibody for canine lymphoma treatment. *Scientific Reports*, 10(1), 11476.
- Mollen, N., Cannon, F. D., Ferrebee, J. W., & St John, D. (1968). Lymphocyte typing in allografted beagles. *Transplantation*, 6(8), 939–940.
- Nash, R. A., Yunusov, M., Abrams, K., Hwang, B., Castilla-Llorente, C., Chen, P., Farivar, A. S., Georges, G. E., Hackman, R. C., Lamm, W. J. E., Lesnikova, M., Ochs, H. D., Randolph-Habecker, J., Ziegler, S. F., Storb, R., Storer, B., Madtes, D. K., Glenny, R., & Mulligan, M. S. (2009). Immunomodulatory effects of mixed hematopoietic chimerism: Immune tolerance in canine model of lung transplantation. *American Journal of Transplantation*, 9(5), 1037–1047.
- Niemeyer, G. P., Hudson, J., Bridgman, R., Spano, J., Nash, R. A., & Lothrop, C. D. (2001). Isolation and characterization of canine hematopoietic progenitor cells. *Experimental Hematology*, 29(6), 686–693.
- Niemeyer, G. P., Welch, J. A., Tillson, M., Brawner, W., Rynders, P., Goodman, S., Dufresne, M., Dennis, J., & Lothrop, C. D. (2005). Renal allograft tolerance in DLA-identical and haploidentical dogs after nonmyeloablative conditioning and transient immunosuppression with cyclosporine and mycophenolate mofetil. *Transplantation Proceedings*, 37(10), 4579–4586.
- Nishida, T., Hudecek, M., Kostic, A., Bleakley, M., Warren, E. H., Maloney, D., Storb, R., & Riddell, S. R. (2009). Development of tumor-reactive T cells after nonmyeloablative allogeneic hematopoietic stem cell transplant for chronic lymphocytic leukemia. *Clinical Cancer Research*, 15(14), 4759–4768.
- Noor, F., Kaysen, A., Wilmes, P., & Schneider, J. G. (2019). The gut microbiota and hematopoietic stem cell transplantation: Challenges and potentials. *Journal of Innate Immunity*, 11(5), 405–415.
- O'Brien, J. S., Storb, R., Raff, R. F., Harding, J., Appelbaum, F., Morimoto, S., Kishimoto, Y., Graham, T., Ahern-Rindell, A., & O'Brien, S. L. (1990). Bone marrow transplantation in canine GM1 gangliosidosis. *Clinical Genetics*, 38(4), 274–280.
- Ostrander, E. A., & Wayne, R. K. (2005). The canine genome. *Genome Research*, 15(12), 1706–1716.
- Regan, D., Guth, A., Coy, J., & Dow, S. (2016). Cancer immunotherapy in veterinary medicine: Current options and new developments. *Veterinary Journal*, 207, 20–28.
- Rosinski, S. L., Stone, B., Graves, S. S., Fuller, D. H., De Rosa, S. C., Spies, G. A., Mize, G. J., Fuller, J. T., & Storb, R. (2015). Development of a minor

- histocompatibility antigen vaccine regimen in the canine model of hematopoietic cell transplantation. *Transplantation*, 99(10), 2083–2094.
- Rosinski, S. L., Storb, R., Strong, R. K., Sale, G. E., Stone, D. M., Gewe, M. M., Friend, D. J., Abrams, V. K., Randolph-Habecker, J., & Graves, S. S. (2015). Anti-CD28 antibody-initiated cytokine storm in canines. *Transplant Direct*, 1(2), e7 <https://doi.org/10.1097/TXD.0000000000000516>
- Rudolph, R. H., Hered, B., Epstein, R. B., & Thomas, E. D. (1969). Canine mixed leukocyte reactivity and transplantation antigens. *Transplantation*, 8(2), 141–146.
- Rue, S. M., Eckelman, B. P., Efe, J. A., Bloink, K., Deveraux, Q. L., Lowery, D., & Nasoff, M. (2015). Identification of a candidate therapeutic antibody for treatment of canine B-cell lymphoma. *Veterinary Immunology and Immunopathology*, 164(3–4), 148–159.
- Sachs, D. H., Sykes, M., Kawai, T., & Cosimi, A. B. (2011). Immunointervention for the induction of transplantation tolerance through mixed chimerism. *Seminars in Immunology*, 23(3), 165–173.
- Sandmaier, B. M., Bethge, W. A., Wilbur, D. S., Hamlin, D. K., Santos, E. B., Brechbiel, M. W., Fisher, D. R., & Storb, R. (2002). Bismuth 213-labeled anti-CD45 radioimmunoconjugate to condition dogs for nonmyeloablative allogeneic marrow grafts. *Blood*, 100(1), 318–326.
- Sandmaier, B. M., Kornblit, B., Storer, B. E., Olesen, G., Maris, M. B., Langston, A. A., Gutman, J. A., Petersen, S. L., Chauncey, T. R., Bethge, W. A., Pulsipher, M. A., Woolfrey, A. E., Mielcarek, M., Martin, P. J., Appelbaum, F. R., Flowers, M. E. D., Maloney, D. G., & Storb, R. (2019). Addition of sirolimus to standard cyclosporine plus mycophenolate mofetil-based graft-versus-host disease prophylaxis for patients after unrelated nonmyeloablative haemopoietic stem cell transplantation: A multicentre, randomised, phase 3 trial. *The Lancet Haematology*, 6(8), e409–e418.
- Sandmaier, B. M., Storb, R., Appelbaum, F. R., Gallatin, W. M. (1990). An antibody that facilitates hematopoietic engraftment recognizes CD44. *Blood*, 76(3), 630–635.
- Sandmaier, B. M., Storb, R., Bennett, K. L., Appelbaum, F. R., & Santos, E. B. (1998). Epitope specificity of CD44 for monoclonal antibody dependent facilitation of marrow engraftment in a canine model. *Blood*, 91(9), 3494–3502.
- Sandmaier, B. M., Storb, R., Santos, E. B., Krizanac-Bengez, L., Lian, T., Mcsweeney, P. A., Yu, C., Schuening, F. G., Deeg, H. J., & Graham, T. (1996). Allogeneic transplant of canine peripheral blood stem cells mobilized by recombinant canine hematopoietic growth factors. *Blood*, 87(8), 3508–3513.
- Sato, M., Storb, R., Loretz, C., Stone, D., Mielcarek, M., Sale, G. E., Rezvani, A. R., & Graves, S. S. (2013). Inducible costimulator (ICOS) up-regulation on activated T cells in graft-versus-host disease after dog leukocyte antigen-nonidentical hematopoietic cell transplantation: A potential therapeutic target. *Transplantation*, 96(1), 34–41.
- Schaefer, S., Werner, J., Lange, S., Machka, C., Knuebel, G., Sekora, A., Roof, C., Winkler, T., Murua Escobar, H., Nolte, I., & Junghanss, C. (2016). Graft-versus-host disease in a dog after reduced-intensity hematopoietic stem cell transplantation from a DLA-identical littermate. *In Vivo*, 30(4), 427–432.
- Schuberth, H. J., Kucinskiene, G., Chu, R. M., & Faldyna, M. (2007). Reactivity of cross-reacting monoclonal antibodies with canine leukocytes, platelets and erythrocytes. *Veterinary Immunology and Immunopathology*, 119(1–2), 47–55.
- Schuening, F. G., Storb, R., Goehle, S., Graham, T. C., Appelbaum, F. R., Hackman, R., & Souza, L. M. (1989). Effect of recombinant human granulocyte colony-stimulating factor on hematopoiesis of normal dogs and on hematopoietic recovery after otherwise lethal total body irradiation. *Blood*, 74(4), 1308–1313.
- Schuening, F. G., von Kalle, C., Kiem, H. P., Appelbaum, F. R., Deeg, H. J., Pepe, M., Gooley, T., Graham, T. C., Hackman, R. C., & Storb, R. (1997). Effect of recombinant canine stem cell factor, a c-kit ligand, on hematopoietic recovery after DLA-identical littermate marrow transplants in dogs. *Experimental Hematology*, 25(12), 1240–1245.
- Schuening, F., Storb, R., Goehle, S., Meyer, J., Graham, T. C., Deeg, H. J., Appelbaum, F. R., Sale, G. E., Graf, L., & Loughran, T. P. (1987). Facilitation of engraftment of DLA-nonidentical marrow by treatment of recipients with monoclonal antibody directed against marrow cells surviving radiation. *Transplantation*, 44(5), 607–613.
- Shosu, K., Sakurai, M., Inoue, K., Nakagawa, T., Sakai, H., Morimoto, M., Okuda, M., Noguchi, S., & Mizuno, T. (2016). Programmed cell death ligand 1 expression in canine cancer. *In Vivo*, 30(3), 195–204.
- Shull, R. M., Hastings, N. E., Selcer, R. R., Jones, J. B., Smith, J. R., Cullen, W. C., & Constantopoulos, G. (1987). Bone marrow transplantation in canine mucopolysaccharidosis I. Effects within the central nervous system. *Journal of Clinical Investigation*, 79(2), 435–443.
- Sokolic, R. A., Bauer, T. R., Gu, Y. C., Hai, M., Tuschong, L. M., Burkholder, T., Colenda, L., Bacher, J., Starost, M. F., & Hickstein, D. D. (2005). Nonmyeloablative conditioning with busulfan before matched littermate bone marrow transplantation results in reversal of the disease phenotype in canine leukocyte adhesion deficiency. *Biology of Blood and Marrow Transplantation*, 11(10), 755–763.
- Storb, R., Epstein, R. B., LeBlond, R. F., Rudolph, R. H., & Thomas, E. D. (1969). Transplantation of allogeneic canine bone marrow stored at -80 degrees C in dimethyl sulfoxide. *Blood*, 33(6), 918–923.
- Storb, R., Epstein, R. B., Ragde, H., & Thomas, E. D. (1967). Marrow engraftment by allogeneic leukocytes in lethally irradiated dogs. *Blood*, 30(6), 805–811.
- Storb, R., Epstein, R. B., Rudolph, R. H., & Thomas, E. D. (1969). Allogeneic canine bone marrow transplantation following cyclophosphamide. *Transplantation*, 7(3), 378–386.
- Storb, R., Etzioni, R., Anasetti, C., Appelbaum, F. R., Buckner, C. D., Bensinger, W., Bryant, E., Clift, R., Deeg, H. J., & Doney, K. (1994). Cyclophosphamide combined with antithymocyte globulin in preparation for allogeneic marrow transplants in patients with aplastic anemia. *Blood*, 84(3), 941–949.
- Storb, R., Floersheim, G. L., Weiden, P. L., Graham, T. C., Kolb, H. J., Lerner, K. G., Schroeder, M. L., & Thomas, E. D. (1974). Effect of prior blood transfusions on marrow grafts: Abrogation of sensitization by procarbazine and antithymocyte serum. *Journal of Immunology*, 112(4), 1508–1516.
- Storb, R., Gluckman, E., Thomas, E. D., Buckner, C. D., Cliff, R. A., Fefer, A., Glucksberg, H., Graham, T. C., Johnson, F. L., Lerner, K. G., Neiman, P. E., & Ochs, H. (1974). Treatment of established human graft-versus-host disease by antithymocyte globulin. *Blood*, 44(1), 57–75.
- Storb, R., Kolb, H. J., Deeg, H. J., Weiden, P. L., Appelbaum, F., Graham, T. C., & Thomas, E. D. (1986). Prevention of graft-versus-host disease by immunosuppressive agents after transplantation of DLA-nonidentical canine marrow. *Bone Marrow Transplantation*, 1(2), 167–177.
- Storb, R., Kolb, H. J., Graham, T. C., Kolb, H., Weiden, P. L., & Thomas, E. D. (1973). Treatment of established graft-versus-host disease in dogs by antithymocyte serum or prednisone. *Blood*, 42(4), 601–609.
- Storb, R., Marchioro, T. L., Graham, T. C., Willemin, M., Hougie, C., & Thomas, E. D. (1972). Canine hemophilia and hemopoietic grafting. *Blood*, 40(2), 234–238.
- Storb, R., Raff, R. F., Appelbaum, F. R., Deeg, H. J., Fitzsimmons, W., Graham, T. C., Pepe, M., Pettinger, M., Sale, G., Van Der Jagt, R., & Schuening, F. G. (1993). FK-506 and methotrexate prevent graft-versus-host disease in dogs given 9.2 Gy total body irradiation and marrow grafts from unrelated dog leukocyte antigen-nonidentical donors. *Transplantation*, 56(4), 800–807.
- Storb, R., Raff, R. F., Appelbaum, F. R., Deeg, H. J., Graham, T. C., Schuening, F. G., Shulman, H., Yu, C., Bryant, E., & Burnett, R. (1994). DLA-identical bone marrow grafts after low-dose total body irradiation: the effect of canine recombinant hematopoietic growth factors. *Blood*, 84(10), 3558–3566.
- Storb, R., Raff, R. F., Appelbaum, F. R., Graham, T. C., Schuening, F. G., Sale, G., & Pepe, M. (1989). Comparison of fractionated to single-dose total body

- irradiation in conditioning canine littermates for DLA-identical marrow grafts. *Blood*, 74(3), 1139–1143.
- Storb, R., Raff, R. F., Appelbaum, F. R., Schuening, F. W., Sandmaier, B. M., & Graham, T. C. (1988). The influence of transfusions from unrelated DLA-matched or mismatched donors upon marrow grafts between DLA-identical canine littermates. *Transplantation*, 46(2), 334–336.
- Storb, R., Raff, R. F., Appelbaum, F. R., Schuening, F. W., Sandmaier, B. M., Graham, T. C., & Thomas, E. D. (1988). What radiation dose for DLA-identical canine marrow grafts? *Blood*, 72(4), 1300–1304.
- Storb, R., Raff, R. F., Graham, T., Appelbaum, F. R., Deeg, H. J., Schuening, F. G., Sale, G., & Seidel, K. (1999). Dose rate-dependent marrow toxicity of TBI in dogs and marrow sparing effect at high dose rate by dose fractionation. *Biology of Blood and Marrow Transplantation*, 5(3), 155–161.
- Storb, R., & Thomas, E. D. (1985). Graft-versus-host disease in dog and man: The Seattle experience. *Immunological Reviews*, 88, 215–238.
- Storb, R., Weiden, P. L., Graham, T. C., Lerner, K. G., Nelson, N., & Thomas, E. D. (1977). Hemopoietic grafts between DLA-identical canine littermates following dimethyl myleran. Evidence for resistance to grafts not associated with DLA and abrogated by antithymocyte serum. *Transplantation*, 24(5), 349–357.
- Storb, R., Yu, C., Barnett, T., Wagner, J. L., Deeg, H. J., Nash, R. A., Kiem, H. P., Mcsweeney, P., Seidel, K., Georges, G., & Zaucha, J. M. (1999). Stable mixed hematopoietic chimerism in dog leukocyte antigen-identical littermate dogs given lymph node irradiation before and pharmacologic immunosuppression after marrow transplantation. *Blood*, 94(3), 1131–1136.
- Storb, R., Yu, C., Wagner, J. L., Deeg, H. J., Nash, R. A., Kiem, H. P., Leisenring, W., & Shulman, H. (1997). Stable mixed hematopoietic chimerism in DLA-identical littermate dogs given sublethal total body irradiation before and pharmacological immunosuppression after marrow transplantation. *Blood*, 89(8), 3048–3054.
- Storb, R., Yu, C., Zaucha, J. M., Deeg, H. J., Georges, G., Kiem, H. - P., Nash, R. A., Mcsweeney, P. A., & Wagner, J. L. (1999). Stable mixed hematopoietic chimerism in dogs given donor antigen, CTLA4Ig, and 100 cGy total body irradiation before and pharmacologic immunosuppression after marrow transplant. *Blood*, 94(7), 2523–2529.
- Suter, S. E. (2011). Collection of peripheral blood CD34+ progenitor cells from healthy dogs and dogs diagnosed with lymphoproliferative diseases using a Baxter-Fenwal CS-3000 Plus blood cell separator. *Journal of Veterinary Internal Medicine*, 25(6), 1406–1413.
- Suter, S. E., Hamilton, M. J., Sullivan, E. W., & Venkataraman, G. M. (2015). Allogeneic hematopoietic cell transplantation in a dog with acute large granular lymphocytic leukemia. *Journal of the American Veterinary Medical Association*, 246(9), 994–997.
- Takatu, A., Nash, R. A., Zaucha, J. M., Little, M.-T., Georges, G. E., Sale, G. E., Zellmer, E., Kuhr, C. S., Lothrop, C. D., & Storb, R. (2003). Adoptive immunotherapy to increase the level of donor hematopoietic chimerism after nonmyeloablative marrow transplantation for severe canine hereditary hemolytic anemia. *Biology of Blood and Marrow Transplantation*, 9(11), 674–682.
- Tang, J., Le, S., Sun, L., Yan, X., Zhang, M., Macleod, J., Leroy, B., Northrup, N., Ellis, A., Yeatman, T. J., Liang, Y., Zwick, M. E., & Zhao, S. (2010). Copy number abnormalities in sporadic canine colorectal cancers. *Genome Research*, 20(3), 341–350.
- Thomas, E. D., Buckner, C. D., Sanders, J. E., Papayannopoulou, T., Borgna-Pignatti, C., De Stefano, P., Clift, R., Sullivan, K., & Storb, R. (1982). Marrow transplantation for thalassaemia. *Lancet*, 2(8292), 227–229.
- Thomas, E. D., LeBlond, R., Graham, T., & Storb, R. (1970). Marrow infusions in dogs given middlelethal or lethal irradiation. *Radiation Research*, 41(1), 113–124.
- Tillson, M., Niemeyer, G. P., Welch, J. A., Brawner, W., Swaim, S. F., Rynders, P., Lenz, S. D., Dean, B., & Lothrop, C. D. (2006). Hematopoietic chimerism induces renal and skin allograft tolerance in DLA-identical dogs. *Experimental Hematology*, 34(12), 1759–1770.
- van Bekkum, D. W., & de Vries, M. J. (1967). *Radiation chimaeras*. Logos Press Limited.
- Venkataraman, G. M., Kennedy, L. J., Little, M. E., Graves, S. S., Harkey, M. A., Torok-Storb, B. J., & Storb, R. (2017). Thirteen novel canine dog leukocyte antigen-88 alleles identified by sequence-based typing. *HLA*, 90(3), 165–170.
- Venkataraman, G. M., Stroup, P., Graves, S. S., & Storb, R. (2007). An improved method for dog leukocyte antigen 88 typing and two new major histocompatibility complex class I alleles, DLA-88*01101 and DLA-88*01201. *Tissue Antigens*, 70(1), 53–57.
- Vernau, W., Hartnett, B. J., Kennedy, D. R., Moore, P. F., Henthorn, P. S., Weinberg, K. I., & Felsburg, P. J. (2007). T cell repertoire development in XSCID dogs following nonconditioned allogeneic bone marrow transplantation. *Biology of Blood and Marrow Transplantation*, 13(9), 1005–1015.
- Wagner, J. L., Burnett, R. C., DeRose, S. A., Francisco, L. V., Storb, R., & Ostrander, E. A. (1996). Histocompatibility testing of dog families with highly polymorphic microsatellite markers. *Transplantation*, 62(6), 876–877.
- Wagner, J. L., Burnett, R. C., & Storb, R. (1999). Organization of the canine major histocompatibility complex: Current perspectives. *Journal of Heredity*, 90(1), 35–38.
- Wagner, J. L., Burnett, R. C., Works, J. D., & Storb, R. (1996). Molecular analysis of DLA-DRBB1 polymorphism. *Tissue Antigens*, 48(5), 554–561.
- Wagner, J. L., Works, J. D., & Storb, R. (1998). DLA-DRB1 and DLA-DQB1 histocompatibility typing by PCR-SSCP and sequencing. *Tissue Antigens*, 52(4), 397–401.
- Warry, E. E., Willcox, J. L., & Suter, S. E. (2014). Autologous peripheral blood hematopoietic cell transplantation in dogs with T-cell lymphoma. *Journal of Veterinary Internal Medicine*, 28(2), 529–537.
- Watson, C. J., Cobbold, S. P., Davies, H. S., Rebello, P. R. U. B., Thiru, S., Mcnair, R., Rasmussen, A., Waldmann, H., Calne, R. Y., & Metcalfe, S. M. (1994). Immunosuppression of canine renal allograft recipients by CD4 and CD8 monoclonal antibodies. *Tissue Antigens*, 43(3), 155–162.
- Weiden, P. L., Flournoy, N., Thomas, E. D., Fefer, A., & Storb, R. (1981). Antitumor effect of marrow transplantation in human recipients of syngeneic or allogeneic grafts. In J. Okunewick & R. Meredith (Eds.), *Graft-versus-leukemia in man and animal models* (pp. 11–23). CRC Press Inc.
- Weiden, P. L., Hackman, R. C., Deeg, H. J., Graham, T. C., Thomas, E. D., & Storb, R. (1981). Long-term survival and reversal of iron overload after marrow transplantation in dogs with congenital hemolytic anemia. *Blood*, 57(1), 66–70.
- Weiden, P. L., Storb, R., & Deeg, H. J. (1981). Antitumor effect of marrow transplantation in randomly bred species: Studies in dogs with spontaneous lymphoma. In J. Okunewick & R. Meredith (Eds.), *Graft-versus-leukemia in man and animal models* (pp. 127–138). CRC Press Inc.
- Weiden, P. L., Storb, R., Deeg, H. J., & Graham, T. C. (1979). Total body irradiation and autologous marrow transplantation as consolidation therapy for spontaneous canine lymphoma in remission. *Experimental Hematology*, 7(5), 160–163.
- Weiden, P. L., Storb, R., Deeg, H. J., Graham, T. C., & Thomas, E. D. (1979). Prolonged disease-free survival in dogs with lymphoma after total-body irradiation and autologous marrow transplantation consolidation of combination-chemotherapy-induced remissions. *Blood*, 54(5), 1039–1049.
- Weiden, P. L., Storb, R., Graham, T. C., & Schroeder, M. L. (1976). Severe hereditary haemolytic anaemia in dogs treated by marrow transplantation. *British Journal of Haematology*, 33(3), 357–362.
- Weiden, P. L., Storb, R., Kolb, H. J., Ochs, H. D., Graham, T. C., Tsoi, M.-S., Schroeder, M.-L., & Thomas, E. D. (1974). Immune reactivity in dogs with spontaneous malignancy. *Journal of the National Cancer Institute*, 53(4), 1049–1056.
- Weiden, P. L., Storb, R., Lerner, K. G., Kao, G. F., Graham, T. C., & Thomas, E. D. (1975). Treatment of canine malignancies by 1200 R total body

- irradiation and autologous marrow grafts. *Experimental Hematology*, 3(2), 124–134.
- Weiden, P. L., Storb, R., Sale, G. E., Graham, T. C., & Thomas, E. D. (1978). Allogeneic hematopoietic grafts after total-body irradiation in dogs with spontaneous tumors. *Journal of the National Cancer Institute*, 61(2), 353–357.
- Weiden, P. L., Storb, R., Shulman, H., & Graham, T. C. (1977). Dimethyl myleran and autologous marrow grafting for the treatment of spontaneous canine lymphoma. *European Journal of Cancer and Clinical Oncology*, 13(12), 1411–1415.
- Weiden, P. L., Storb, R., Slichter, S., Warren, R. P., Sale, G. E. (1976). Effect of six weekly transfusions on canine marrow grafts: Tests for sensitization and abrogation of sensitization by procarbazine and antithymocyte serum. *Journal of Immunology*, 117(1), 143–150.
- Willcox, J. L., Pruitt, A., & Suter, S. E. (2012). Autologous peripheral blood hematopoietic cell transplantation in dogs with B-cell lymphoma. *Journal of Veterinary Internal Medicine*, 26(5), 1155–1163.
- Yeager, A. M., Singer, H. S., Buck, J. R., Matalon, R., Brennan, S., O'toole, S. O., Moser, H. W., Opitz, J. M., & Reynolds, J. F. (1985). A therapeutic trial of amniotic epithelial cell implantation in patients with lysosomal storage diseases. *American Journal of Medical Genetics*, 22(2), 347–355.
- Yu, C., Linsley, P., Seidel, K., Sale, G., Deeg, H. J., Nash, R. A., & Storb, R. (2000). Cytotoxic T lymphocyte antigen 4-immunoglobulin fusion protein combined with methotrexate/cyclosporine as graft-versus-host disease prevention in a canine dog leukocyte antigen-nonidentical marrow transplant model. *Transplantation*, 69(3), 450–454.
- Yu, C., Ostrander, E., Bryant, E., Burnett, R., & Storb, R. (1994). Use of (CA)n polymorphisms to determine the origin of blood cells after allogeneic canine marrow grafting. *Transplantation*, 58(6), 701–706.
- Yu, C., Seidel, K., Nash, R. A., Deeg, H. J., Sandmaier, B. M., Barsoukov, A., Santos, E., & Storb, R. (1998). Synergism between mycophenolate mofetil and cyclosporine in preventing graft-versus-host disease among lethally irradiated dogs given DLA-nonidentical unrelated marrow grafts. *Blood*, 91(7), 2581–2587.
- Yunusov, M. Y., Kuhr, C. S., Georges, G. E., Hogan, W. J., Taranova, A. G., Lesnikova, M., Kim, Y.-S., Abrams, K., Hwang, B., Sale, G. E., Storer, B., Storb, R., & Nash, R. A. (2006). Partial donor-specific tolerance to delayed skin grafts after rejection of hematopoietic cell graft. *Transplantation*, 82(5), 629–637.
- Yunusov, M. Y., Kuhr, C., Georges, G. E., Sale, G. E., Spector, M., Lesnikova, M., Lee, R., Little, M.-T., Gass, M. J., Weber, K., Joslyn, A., Storb, R., & Nash, R. A. (2002). Survival of small bowel transplants in canine mixed hematopoietic chimeras: preliminary results. *Transplantation Proceedings*, 34(8), 3366–3367.
- Zandvliet, M. (2016). Canine lymphoma: A review. *Veterinary Quarterly*, 36(2), 76–104.
- Zauch, J. M., Yu, C., Lothrop, C. D. Jr., Nash, R. A., Sale, G., Georges, G., Kiem, H.-P., Niemeier, G. P., Dufresne, M., Cao, Q., & Storb, R. (2001). Severe canine hereditary hemolytic anemia treated by nonmyeloablative marrow transplantation. *Biology of Blood and Marrow Transplantation*, 7(1), 14–24.
- Zauch, J. M., Yu, C., Zellmer, E., Takatu, A., Junghans, C., Little, M.-T., & Storb, R. (2001). Effects of extending the duration of postgrafting immunosuppression and substituting granulocyte-colony-stimulating factor-mobilized peripheral blood mononuclear cells for marrow in allogeneic engraftment in a nonmyeloablative canine transplantation model. *Biology of Blood and Marrow Transplantation*, 7(9), 513–516.
- Zauch, J. M., Zellmer, E., Georges, G., Little, M. T., Storb, R., Storer, B., & Torok-Storb, B. (2001). G-CSF-mobilized peripheral blood mononuclear cells added to marrow facilitates engraftment in non-myeloablated canine recipients: CD3 cells are required. *Biology of Blood and Marrow Transplantation*, 7(11), 613–619.

How to cite this article: Graves, S. S., & Storb, R. (2021). Evolution of haematopoietic cell transplantation for canine blood disorders and a platform for solid organ transplantation. *Veterinary Medicine and Science*, 7, 2156–2171. <https://doi.org/10.1002/vms3.601>