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Concise Review: Canine Diabetes Mellitus as a Translational Model for Innovative Regenerative Medicine Approaches

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ABSTRACT

Diabetes mellitus (DM) is a common spontaneous endocrine disorder in dogs, which is defined by persistent hyperglycemia and insulin deficiency. Like type 1 diabetes (T1D) in people, canine DM is a complex and multifactorial disease in which genomic and epigenomic factors interact with environmental cues to induce pancreatic β -cell loss and insulin deficiency, although the pathogenesis of canine DM is poorly defined and the role of autoimmunity is further controversial. Both diseases are incurable and require life-long exogenous insulin therapy to maintain glucose homeostasis. Human pancreatic islet physiology, size, and cellular composition is further mirrored by canine islets. Although pancreas, or isolated islets transplantation are the only clinically validated methods to achieve long-term normoglycemia and insulin-independence, their availability does not meet the clinical need, they target a small portion of patients and have significant potential adverse effects. Therefore, providing a new source for β -cell replacement is an unmet need. Naturally occurring DM in pet dogs, as a translational platform, is an untapped resource for various regenerative medicine applications that may offer some unique advantages given dogs' large size, longevity, heterogenic genetic background, similarity to human physiology and pathology and long-term clinical management. In this review, we outline different strategies for curative approaches, animal models used, and consider the value of canine DM as a translational animal/disease model for T1D in people. *STEM CELLS TRANSLATIONAL MEDICINE* 2019;00:1–6

SIGNIFICANCE STATEMENT

This Concise Review highlights (a) canine pancreatic islet physiology; (b) comparative pathology of T1D and spontaneous canine DM; (c) regenerative medicine approaches to cure T1D; (d) current state of regenerative medicine research in dogs; (e) major challenges in T1D-specific regenerative medicine translational research; and (f) future perspectives. Most importantly, the advantages and disadvantages of the canine DM model, and the opportunities to harness canine DM to facilitate the translation of novel regenerative medicine approaches to cure T1D in people are discussed.

DIABETES MELLITUS IN THE DOG—A COMPARATIVE APPROACH

Diabetes mellitus (DM) is a common spontaneous complex endocrine disorder in dogs, which affects middle age to geriatric dogs. It is estimated that the prevalence of DM within the pet dog population ranges between 0.2% and 1.2%, and is even higher in genetically predisposed breeds such as Samoyeds, Tibetan Terriers, Cairn Terriers, and others. Moreover, based on a 2.5 million canine patient's database, the prevalence of DM in dogs had increased in 79.7% since 2006 (Benfield's State of Pet Health, 2016 Report). Assuming an overall population

of 70 million dogs in U.S. only in 2012 [1], we predict a minimum of 165,000 diabetic dogs in U.S. only. A recent large-scale survey had further indicated that 1/10 diabetic dogs are being euthanized at the time of DM diagnosis, and 1/10 more will be euthanized within a year [2]. With an estimated \$70 per month expenses on insulin only, a (conservative) projected ~\$110 million per year market value is estimated.

Canine DM is defined by persistent hyperglycemia and insulin deficiency due to massive β -cell loss. The clinical consequences of insulin deficiency in dogs are similar to those observed in diabetic people and include polyuria, polydipsia, polyphagia, weight loss, and lethargy. Life-long

Table 1. Canine DM and human T1D comparative summary

Characteristic	Human T1D	Canine DM
Persistent hyperglycemia	+++	+++
Insulin deficiency	+++	+++
Time of onset	75% of T1D is diagnosed in children <18 years	Middle aged to geriatric (>8 years)
Etiology	Autoimmunity	Unknown. No consistent evidence of autoimmunity
Histology	Marked islet atrophy with β -cell loss and lymphocytic infiltration (aka insulinitis)	Marked islet atrophy with β -cell loss, insulinitis is an uncommon finding
Therapy	Life-long insulin	Life-long insulin
Common complications	DKA Microvascular disease Atherosclerotic cardiovascular disease (ASCVD)	DKA Cataract Retinopathy

insulin treatment (most commonly as subcutaneous injections that are given by the owner twice a day) is the standard-of-care. Poorly regulated DM can further lead to diabetic ketoacidosis (DKA), a severe and potentially life threatening metabolic derangement [3]. Common comorbidities and complications of DM in dogs such as cataracts, retinopathy, hyperadrenocorticism, urinary tract infection, dermatitis, otitis, pancreatitis, and hypothyroidism may further contribute to insulin resistance and a ketosis-prone metabolic state [3]. Furthermore, in humans with type 1 diabetes (hT1D) hypoglycemia unawareness, or impaired awareness of hypoglycemia (IAH), is associated with increased risk of hypoglycemic events frequency and severity, and is often used as an inclusion criterion for islet transplantation focused clinical trials. IAH can be defined by the lack of recognition of 3 groups of symptoms of hypoglycemia: autonomic (sweating, palpitation, and shaking and hunger) neuroglycopenic (confusion, drowsiness, odd behavior, speech difficulty, and incoordination), and malaise (nausea and headache) [4]. Although some of these are subjective and depend on self-reporting, some autonomic signs are quantifiable [5]. Dogs with poorly controlled DM have increased heart rate variability and decreased plasma norepinephrine (NE) concentrations [6]. Moreover, NE is negatively correlated with fructoseamine concentrations in poorly controlled diabetic dogs, suggesting impaired autonomic response [6]. These objective indicators may serve as objective surrogates for IAH in diabetic dogs, especially with the advent of new wearables monitors that can continuously record blood glucose, heart rate, and heart rate variability. These data suggest that while the true “awareness” of dogs may not be able to evaluate objectively, IAH may be modeled in dogs by continuous glucose monitoring coupled with continuous measurement of the sympathetic tone.

Although canine DM mirrors many of the hallmark phenotypic features of hT1D, there are also some key differences between the human and dog disease (Table 1). Notably, while cellular-mediated autoimmune destruction of the pancreatic β -cells is the underlying etiology of hT1D, canine DM etiology is

unknown and evidence of autoimmunity (i.e., autoantibodies and insulinitis) in canine DM are rarely reported [7]. The heterogeneity of the disease presentation and natural course of progression suggests that more than one pathological mechanism may contribute to the development DM in dogs [8]. Deep understanding of the advantages and disadvantages of each diabetes model is critical for optimal study design, which is tailored for the specific study's goals.

As opposed to naturally occurring DM in pet dogs, induced DM models in research dogs is typically induced by pancreatectomy and/or the use an islet cell toxic chemical, such as streptozotocin. Both options induce tissue damage to “bystander” nonislet tissues, and are poor models to evaluate long-term complication of the disease. DM in client owned dogs occurs spontaneously, and not only models β -cell depletion and insulin deficiency, but also models the health care system in which the clinical trial is being administered. Critical issues such as complex study design, regulations, patient recruitment and retention, and compliance may be modeled in a pet-dog based veterinary clinical trial.

REGENERATIVE MEDICINE APPROACHES TO CURE hT1D

Limited natural regenerative potential of the islets remains a major challenge to regenerative medicine approaches to cure hT1D [9]. Since the discovery of insulin and its isolation from canine pancreata in 1921, treatment of the first diabetic patient in 1922, large scale production of porcine insulin and finally the production of recombinant human insulin in 1978, the clinical treatment paradigm for patients with hT1D remained primarily symptomatic, and not curative. Here, we outline different curative strategies, animal models used, and consider the value of canine DM as a translational animal/disease model.

Transplantation of Whole Pancreas and Donor Derived Pancreatic Islets

Transplantation of whole pancreas, or isolated islets are the only clinically validated methods to achieve long-term normoglycemia and insulin-independence [10, 11]. It targets a small portion of patients with poorly controlled diabetes, that are often defined by having IAH.

More than 50,000 human pancreas transplantations have been performed to date worldwide [10]. Overall survival rates are >80% at 5 years post transplantation, with preclinical dog models playing an important role in this success [11]. More recently, 10-year actual insulin independence rates have been reported to range between 60% and 80% depending on specific surgical approach [10]. Whole pancreas transplantation involves significant complications including technical failures, acute rejection, and cytomegalovirus infection [10]. Islet transplantation is a less invasive procedure and may sustain normoglycemia and insulin independence in recipients (human) for years. Using immunosuppressive treatment, approximately 50% of patients remained insulin independent at 5 years after receiving a transplant [11].

The traditional Edmonton immune suppression protocol includes induction with Daclizumab, followed by maintenance with Sirolimus and Tacrolimus [12]. Both immunosuppressive small molecules (i.e., Sirolimus and Tacrolimus) have been extensively used in dogs in various clinical and experimental

settings. Many of the more modern immunosuppressive protocols that are used for islet transplantation in humans are multi-drug approaches that include biologic reagents such as regulatory T cells (e.g., NCT03444064 and NCT03162237) and B cell depleting reagents such as humanized monoclonal antibodies and chimeric monoclonal antibodies (e.g., NCT00468442, NCT01049633, and NCT00434850).

To the best of our knowledge, there are only 2 canine-specific monoclonal antibodies that are approved by the U.S. Department of Agriculture and are commercially available: Blontress, an anti-CD20 antibody, and Tactress, an anti-CD52 antibody. Additional anti-canine CD20 [13] and anti-canine PD-L1 [14] monoclonal antibodies are under development. Furthermore, canine T regulatory cells may be isolated and expanded *ex vivo*, although their therapeutic use has not been determined yet in dogs. Finally, while several humanized monoclonal antibodies have been shown to crossreact with canine homologs (i.e., HER2, CSPG4, and vascular endothelial growth factor), a single amino acid substitution in the targeted antigen may result in complete lack of reactivity.

An additional approach to provide immune protection for transplanted islets in human patients, is the creation of a physical barrier which protects the allogeneic graft from alloimmunity on the one hand, and allows for oxygen and nutrient diffusion on the other hand. Both micro and macroencapsulation approaches for islet protection have been described and studied in dog models [15, 16].

Scarce organ donations and need of long-term use of immunosuppressive medication to control the auto or alloimmunity are factors that limit both procedures. Portal vein thrombosis, bleeding, liver steatosis and rapamune-induced mouth ulcers are amongst the complications of islet transplantation [11, 17]. Canine specific islet isolation protocols have been published, and more recently, a canine pancreas donor program was established to support islet transplantation in dogs [18]. Finally, allogeneic islet transplantation in a diabetic dog model has been described [16].

Dogs have a human leukocyte antigen system homolog, that is termed the dog leukocytes antigen (DLA) system, which includes the gene complex encoding the major histocompatibility complex genes [19]. Canine class II genes are classified as DLA-DQA1, DQB1, DRB1, and DRA. Except for DRA, class II genes are highly polymorphic, and historically, the DRB1 gene has been most extensively used for DLA-matching, due to its high level of polymorphism, its association with other DLA genes on chromosome 12 and its ease of genotyping [20]. DLA-88, DLA-12, DLA-79, and DLA-64 are traditional and long-established class I genes. A recent study by Venkataraman et al. demonstrates the discovery of new 13 novel canine DLA-88 alleles [21]. These data suggest that a basic solid understanding of DLA biology and DLA genotyping tools is available for transplantation studies in diabetic dogs.

Islet Cell Proliferation

The regenerative capacity of pancreas decreases drastically with age in rodents; more importantly, the adult human endocrine pancreas loses the potential to regenerate itself [22]. A number of studies have focused on induction of replication of existing β -cells using various strategies. Carbohydrate response element-binding protein, mTOR, AMP-activated protein kinase, Glycogen Synthase Kinase-3, and protein kinase C pathways

have been studied for their capacity to induce β -cell proliferation [22]. Numerous histologic studies of healthy, injured, pregnant, or obese adult human and canine pancreata have failed to document significant β -cell costaining with proliferative markers such as Ki-67 and PCNA [22, 23].

Differentiation of Pluripotent Stem Cells

The major breakthrough in 1998 that enabled *ex vivo* culture of human embryonic stem cells (hESC), and the discovery of induced pluripotent stem cells (iPSC) in 2006, opened new paths to regenerative medicine approaches by providing an unlimited source for “synthetic” human islets for transplantation. Soon after, protocols for *in vitro* differentiation of hESC to pancreatic β -like cells (SC- β), created a framework for more complex *in vitro* differentiation protocols that strive to recapitulate *in vitro* the complex β -cell developmental path [24]. The pancreas rises from the posterior foregut as dorsal and ventral buds fusing together to form the whole organ [25, 26]. More specifically, high levels of nodal drive development of endoderm from the anterior primitive streak, whereas FGFs, BMPs, and WNTs drive posterior streak development. Pancreatic and duodenal homeobox 1 (PDX1) and homobox protein Nkx6-1 (NKX6-1) are the master regulators of pancreas development [26]. The activation of retinoid signaling along with inhibition of hedgehog signaling induce PDX1-expressing epithelial progenitor cells, that give rise to different cell population within the pancreas. Inhibition of Notch signaling further plays a crucial role in pancreatic cell specification [26]. Neurog3 (NGN3), which marks the early precursors of pancreatic endocrine cells, is induced upon the inhibition of Notch signaling pathway. NGN3+ progenitor cells give rise to different pancreatic cell populations including α , β , δ , PP, and ϵ cells, which produce glucagon, insulin, somatostatin, pancreatic polypeptide, and ghrelin, respectively [27].

The first human clinical trial using ESC-derived pancreatic progenitor cells for the treatment of hT1D was carried out by Viacyte in San Diego, California in 2014. A total of 19 patients received this cellular product subcutaneously loaded into a macroencapsulation device [28]. Poor cell survival due to hypoxia and a “foreign body”-like immune response were the main challenges, which led to pause of the trial [28].

Trans-Differentiation of Adult Non- β Cells into Insulin Secreting Cells and Insulin Gene Therapy

The term trans-differentiation implies the direct transformation of one adult cell phenotype into a second adult cell phenotype, without an intermediate pluripotent stem cell phase. Induction of 3 transcription factors, NGN3, PDX1, and MAFA, was shown to convert mice acinar cells to insulin+ cells [29]. These cells expressed NKX6.1, GLUT2, and glucokinase, while improving hyperglycemia in mice. Deletion of FOXO1 from human gut endocrine progenitor cells [30], and knocking out of FBW7 from duct cells [31] led to their conversion into insulin secreting cells. Deletion of FBW7 stabilizes a key regulator of endocrine cell differentiation, NGN3, and therefore facilitates trans-differentiation of the ductal cells to insulin secreting cells.

Given the use of viral vectors, transgenic DNA and *in vivo* trans-differentiation, massive immune activation and neoplastic transformation are the primary safety concerns in moving such an approach to clinical trials. As murine models have markedly different immune systems from humans [32], a realistic animal

model that will enable meaningful safety and efficacy studies would be highly valued [33].

Three-dimensional Tissue Bioprinting Potential for Application in hT1D

A contemporary approach to enhancing the viability of insulin secreting cells post transplantation may be the application of three-dimensional (3D) tissue bioprinting to generate pancreatic tissue-like organoids. These organoids could potentially incorporate microvasculature to limit post-transplantation cellular hypoxia [34–36].

Other potential benefits of bioprinting insulin producing cells may include the opportunity to provide an immunological barrier to donor cells, or incorporation of immunosuppressive molecules within the tissue construct. Similarly, the enhanced utility of 3D bioprinting in this context may also include the ability to modulate the physical characteristics of the bioprinted material to alter robustness, density and permeability. The function of bioprinted tissues could also be assessed prior to transplantation and can be retained in a localized site of implantation as the cells or islets are embedded or incorporated within the bioprinted material. A number of different bioprinting strategies have been used to enhance the transplantation of islets or insulin secreting cells. These include 3D printed devices, cell laden hydrogels, or composite devices [34–36].

Human islets that were loaded into a polylactic acid 3D printed encapsulation device were successfully transplanted into immunodeficient mice [35]. Song and Millman [36] reported incorporation of human stem cell derived β -cells embedded in a fibrin based hydrogel to support cell encapsulation and survival and enclosed in a PLA microporous device to provide structural integrity to enhance post transplantation survival.

Although the application of 3D bioprinting may provide opportunities for treatment hT1D, much more research is required to enhance the survival and function of transplanted islets, which are highly dependent on adequate oxygen supply [37].

CURRENT STATE OF REGENERATIVE MEDICINE RESEARCH IN DOGS

Canine ESC lines have been established by several groups from 5- to 10-day-old blastocysts [38]. Canine iPSC were further reprogrammed via lentivirus [39] or Sendai virus [40] vehicles delivering the human or canine Yamanaka factors (i.e., OKSM) or OKSM supplemented with LIN28 and NANOG [41]. Although standard human PSC require bFGF and mouse PSC require LIF stimulation during ex vivo culture, canine PSC require both bFGF and LIF for pluripotency maintenance and viability [39]. In only a few of the canine iPSC publications, spontaneous in vivo differentiation (i.e., teratoma formation) was demonstrated, and contribution of canine pluripotent stem cells to chimera formation has not been reported.

Multipotent stromal cells (MSC) have potent immunomodulatory, angiogenic, antiapoptotic, and trophic properties which position them as excellent cell candidates to support regeneration in response to tissue injury [42]. Co-transplantation of MSC with pancreatic islets as a measure to increase islet engraftment and viability has also been explored [43]. Canine MSC have been isolated and expanded from various tissue sources such as fat, umbilical cord, and bone marrow. Such cells have been

applied in veterinary clinical trials to numerous diseases such as inflammatory bowel disease, spinal cord injury, osteoarthritis, and many more [44]. Other canine adult stem cell types such as epidermal neural crest stem cells, cardiac stem cells, and hematopoietic stem cells have been identified, characterized and used in veterinary clinical research [44].

Pioneering translational research in the gene therapy and immunotherapy fields was conducted in dogs with hemophilia B [45], Duchenne muscular dystrophy [46] and cancer [47], respectively. Such pioneering projects in dog models have accelerated the development of groundbreaking novel therapeutics for the parallel human disease [33].

Finally, well-defined and specific inclusion/exclusion criteria and primary outcome measures will be critical for any veterinary clinical trial. Eligibility for canine clinical trials frequently includes commitment by the owner to various follow up hospital visits, as determined by the investigator, in which additional samples such as blood, tissue biopsies and imaging will be taken. Finally, necropsies are often performed on animals that have participated in a clinical trial and have died, as determined by the investigator.

MAJOR CHALLENGES IN hT1D-SPECIFIC REGENERATIVE MEDICINE TRANSLATIONAL RESEARCH

Development of iPSC-derived therapeutic products for wide spread clinical use entails several unique key challenges, primarily graft-recipient immune interaction, graft integration, graft survival over time, production “scale-up” and overall biocompatibility [48]. Ectopic tissue formation and worse, neoplastic transformation, are the most significant potential safety concerns, given iPSCs inherent capacity to establish teratomas in vivo. It is extremely important to minimize safety concerns prior to widespread use of iPSC-derived grafts in clinical trials. Malignant transformation of an iPSC-derived graft within a treated patient may have catastrophic effects not only on the affected patient, but on the entire field in general. Moreover, it is critical that the potential for malignant transformation of an iPSC-based therapeutic product candidate be tested in immunocompetent animals. Nevertheless, transplantation of human iPSC-derived cellular products into an immunocompetent animal model would be a poor model, as transplanted cells will be recognized as xenografts and induce a robust (and nonrepresentative) immune response. Given the conflicting evidence regarding the immunogenicity of iPSC derived cellular products [49], current iPSC-based trials in humans include an immunosuppressive protocol (e.g., Kyoto Trial to Evaluate the Safety and Efficacy of iPSC-derived dopaminergic progenitors in the treatment of Parkinson’s Disease, UMIN000033564). Furthermore, translational research using iPSC based cellular products will illuminate the nature of the immune response toward such cellular products.

FUTURE PERSPECTIVE

Canine DM is a common spontaneous disease that recapitulates much of the complexity that is noted in hT1D, and may offer a valuable untapped resource as a realistic translational disease/animal model. Pet dogs share with their owners environmental factors such as intestinal microbiota, infections, sedentary lifestyle, industrialized diets, and environmental toxins that are key in the development of diabetes [50]. Furthermore,

state-of-the-art academic veterinary hospitals are able to provide excellent diagnostic and long-term therapeutic care for owners who seek the best medical care for their pets, setting the foundation for clinically relevant, large-scale veterinary clinical trials. Translational research in companion dogs with naturally occurring diabetes could therefore bridge the gap between laboratory animal disease models and human clinical trials.

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There are many remarkable studies to cite, we apologize that we were not able to mention them all due to the space limitation.

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AUTHOR CONTRIBUTIONS

M.M.: conception and design, collection and/or assembly of data, manuscript writing; B.T., C.G., K.P., P.W., and L.L.A.: manuscript writing; P.S.: conception and design, collection and/or assembly of data, manuscript writing, financial support; A.K.: conception and design, collection and/or assembly of data, manuscript writing, financial support, final approval of the manuscript.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

P.W. declared employment and honoraria from the University of Sydney. The other authors indicated no potential conflicts of interest.

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