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The Diabetic Dog as a Translational Model for Human Islet Transplantation

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The dog model has served as the primary method for early development of many diabetes therapies, including pancreatic islet transplantation techniques and immunosuppressive protocols. Recent trends towards the use of monoclonal antibody therapies for immunosuppression in human islet transplantation have led to the increasing use of primate models with induced diabetes. In addition to induced-disease models in large animals, scientists in many fields are considering the use of naturally-occurring disease models in client-owned pets. This article will review the applicability of naturally-occurring diabetes in dogs as a translational model for developing islet transplantation in the human diabetic patient.

INTRODUCTION

The dog has been used as a translational model for diabetes mellitus since the very advent of therapeutic trials, with Banting and Best performing their first experiments of pancreatic extracts therapy in diabetic dogs nearly one century ago [1,2]. Later, the dog served as an important large animal model for the development of advanced surgical techniques in whole pancreas transplantation and islet transplantation in human diabetics. With their similar pancreatic anatomy, common clinical signs of diabetes and readily available information on pharmacokinetics of immunosuppressive drugs, dogs were used to perform pre-clinical evaluation of the standard organ and cellular transplant procedures from their initiation in the 1960s to their wide clinical application in humans in the 1990s. The majority of these studies used dogs with surgically or chemically-induced diabetes, which served as convenient (if not accurate) models for type 1 diabetes mellitus in human patients. With the advent of transgenic animals, initial screening of targeted immunotherapy was carried out using knockout mouse models and the resulting monoclonal antibody therapies were species-specific. Pre-clinical testing in large animals often required the use of non-human primates (NHP†) where homology with humans was closer than that of dogs; human monoclonal antibodies could be tested directly in NHP for efficacy and safety. This switch in the standard pathway for testing

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†Abbreviations: NHP, non-human primate; NIH, National Institutes of Health; T1DM, Type 1 Diabetes Mellitus; GAD65, glutamic acid decarboxylase 65; IA2, islet antigen-2; CT, computerized tomography; MRI, magnetic resonance imaging.

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of transplant strategies had largely removed the dog from standard research models for the last decade. However, the NIH has recently recognized the value of using spontaneously occurring disease models in large animals to improve the likelihood of success during Stage 3 clinical trials in human patients and is supporting the development of these models for use in studies of regenerative medicine and cell transplantation (https://grants.nih.gov/grants/guide/pa-files/PAR-16-093.html). This has led to an interest in preclinical testing using companion animals as large animal models of naturally occurring disease. This perspective article will consider the advantages and disadvantages to the use of the client-owned dog with naturally occurring diabetes as an example of a potential untapped resource for studies of cell-based therapy for diabetes.

INCIDENCE OF DIABETES IN COMPANION ANIMALS

Many literary reviews of animal models of diabetes limit the discussion to inbred rodent models and chemically or surgically induced large animal models [3,4] and some even suggest that spontaneous diabetes is rare in larger animals, making their use impractical in studies of diabetes therapies [5]. While spontaneous diabetes is rare in the pig, NHP and to some degree, the purpose-bred dog, the incidence of the disease in the pet population is estimated to be 0.4 to 1.2 percent and is significantly higher in selected breeds with a known genetic predisposition [6,7]. According to estimates from the American Veterinary Medical Association (https://www.avma.org/kb/resources/statistics/pages/market-research-statistics-us-pet-ownership-demographics-sourcebook.aspx), there are an about 70 million pet dogs in the United States, translating to an estimated 700,000 pet dogs with naturally occurring diabetes that are available for therapeutic trials.

SIMILARITY OF NATURALLY OCCURRING DIABETES MELLITUS BETWEEN DOG AND HUMAN

Diabetes mellitus in the dog bears many phenotypic similarities to advanced human type 1 diabetes mellitus (T1DM), with the majority of affected animals having no detectable insulin at the time of diagnosis and pancreatic histology generally showing a complete lack of identifiable islets (Table 1). Dogs display classic signs of polyuria and polydipsia, although clinical onset is typically in adult animals. Due to the severity of insulin deficiency at the time of diagnosis, affected animals cannot survive without insulin therapy and will progress from profound hyperglycemia to life-threatening ketoacidosis. Cataract formation and secondary blindness are common. Standard therapy for canine diabetes equates to therapy for human TIDM and is centered around dietary management and insulin replacement, usually twice daily insulin injections administered subcutaneously; dosage is titrated based on blood glucose monitoring, urine glucose monitoring, and by clinical signs. Pork or human insulin products are both effective in managing canine diabetes, as the human insulin molecule differs from canine insulin by only one amino acid and both formulations have biological activity in the dog.

DIABETES ETIOLOGY IN DOGS

Much like the historical classification systems used in human diabetics, diabetes in companion animals has been described using phenotypic characteristics, such as insulin dependent or non-insulin dependent diabetes mellitus. In this system, it is clear that dogs are nearly uniformly affected by ß-cell deficiency and are therefore most aligned with human T1DM. Breed predispositions in Samoyeds, Tibetan Terriers, and Cairn Terriers suggested a genetic component that is analogous to ethnic predispositions in human diabetes and subsequent analyses of histocompatibility complex haplotypes (termed Dog Lymphocyte Antigens or DLAs) have demonstrated at least three haplotypes that are associated with increased risk while one other was shown to have a protective effect [7]. The fact that major histocompatibility complex alleles are associated with disease risk in dogs might suggest an immune-mediated etiology and reinforces the similarities with human T1DM [7]. Later studies evaluating single nucleotide polymorphisms in a large population of dogs suggested that several genes associated with human diabetes were found to increase susceptibility in dogs, further confirming the translational value of the canine diabetic model [8]. However, it must be noted that the DLA haplotypes and other candidate genes that are epidemiologically associated with diabetes in dogs can be found in both affected and control dogs within high risk breeds and may be the result of inbreeding or genetic drift [9]. In addition, despite the fact that canine genetic studies have been supportive of an immune-mediated disease, autoantibodies common islet associated antigens (GAD65 and IA2) are usually not found in the serum of affected dogs at the time of diagnosis [10-14]. Insulitis (lymphocytic infiltration of islets) is also an inconsistent finding in studies examining pancreatic histology of canine diabetics [15]. Some investigators have theorized that autoimmunity is present in dog with diabetes mellitus, but that they typically present in the late stages of disease, at a time when the complete lack of remaining islet tissue has led to a drop in circulating autoantibodies and to lack of inflammation in the pancreas [9]. An alternative

Table 1. Comparative Features of Diabetes Mellitus in the Human and the Dog.

Attributes	Human Type 1 Diabetes Mellitus	Canine Diabetes Mellitus
Time of onset	- Juvenile mode (childhood-adolescence) but can be diagnosed at any age (usually < 30-40)	- Middle aged to older (8 years)
Etiology	- Immune mediated - Known genetic predisposition	- Variable evidence of anti-islet Ab - May be secondary to pancreatitis - Etiology often not determined (diagnosed at end stage disease) - Genetic predisposition (Keeshond, Min. Schnauzer, Min. Poodle, Beagle)
Pancreatic Histology	- Beta cell deficiency - Insulitis (lymphocytic infiltration of islets) in early stages of disease	- Near complete absence of beta cells in majority of dogs at the time of diagnosis - Insulitis is rarely detected
Clinical presentation & secondary organ injury	- Ketosis-prone insulin dependent diabetes mellitus - Microvascular disease (retinopathy, nephropathy) and atherosclerosis	- Ketosis-prone insulin dependent diabetes mellitus - Cataract formation leading to blindness - Rarely: Atherosclerosis
Therapy	- Insulin therapy required - Dietary management is complementary	- Insulin therapy required - Dietary management is complementary

theory is that canine diabetes mellitus may arise secondary to diffuse, non-specific pancreatic injury secondary to pancreatitis, a relatively common condition in the dog. Acute hyperglycemia from this condition may lead to beta cell toxicity, which then progresses to beta cell deficiency and diabetes [9]. In summary, canine diabetes shares many phenotypic and genetic characteristics with human T1DM, although specific disease etiologies are heterogeneous in both populations and careful selection of certain populations of dogs may be required to provide the most valid models for specific human populations.

IMMUNOLOGY OF TRANSPLANTATION

The dog is a well-accepted model of human allograft and xenograft rejection, and canine allograft transplantation was used as an important model for the development of the triple drug immunosuppressive protocols required for immunosuppression in both dogs and human beings undergoing whole organ transplantation. With a complex MHC system consisting of four alleles and an outbred background in comparison to rodent strains, the dog model is a much more realistic and rigorous test for anti-rejection strategies [16,17]. Due to their historical use in the screening of anti-rejection drugs, pharmacokinetics and pharmacodynamics of commonly used immunosuppressive drugs such as cyclosporine, mycofenolate, and tacrolimus are well known and additional information can be obtained from their years of use in treating canine patients with immune mediated diseases [18-33]. As mentioned earlier, the primary difficulty in the use of the dog model is the inability to directly apply biologics such as monoclonal antibody therapies (basiliximab, daclizumab) without the developing of dog-specific therapies — a step that some companies may be unwilling to take due to the smaller perceived market for these drugs. However, many cell therapies for diabetes focus on the delivery of stem cells and the use of nanoporous devices or coatings that provide some degree of immunoisolation, with a goal of avoiding the use of immunosuppressive therapies altogether. The dog model is particularly relevant in evaluating these technologies and these also fit better with providing the quality of life that is desired by pet owner, avoiding daily immunosuppressive medications and potential side effects associated with standard islet allograft transplantation.

ISLET TRANSPLANTATION TECHNIQUES AND IMAGING STUDIES

One of the ongoing challenges in islet transplantation therapy is evaluation of islet transplant techniques and implantation sites in an appropriate large animal model [34-49]. While human islet transplantation has focused on the intraportal implantation of islets for many years, this technique results in an immediate blood-mediated inflammatory reaction and varying degrees of thromboembolism of the hepatic portal system. Many advances have been made in reducing the IBMIR, although study of these techniques in a rodent model is technically challenging due to their small size and cannot be performed using interventional radiology as would occur in human diabetics. On the contrary, the dog has been used to study and develop the intraportal, intraperitoneal, splenic, pancreatic, and bone marrow sites of implantation and for the investigation of various encapsulation methods cur-

rently being used in human diabetics [34-49]. For similar reasons, the dog would serve as a potential candidate for the investigation of novel imaging and cell tracking techniques to identify the fate of islet graft as they are ideally sized for imaging in human clinical CT and MRI units. Facilities for interventional radiology, minimally invasive surgery, and advanced imaging (CT or MRI) are available at most veterinary referral centers and teaching hospitals in the United States so that clinical trials in dogs with diabetes could be performed using dedicated equipment for companion animals.

EASE OF MONITORING

Blood sampling from peripheral veins is routine in pet dogs and adequate volumes of blood or plasma can be obtained for use in complete characterization of diabetes therapies. Diabetes monitoring of client owned dogs can include home monitoring, such as blood glucose sampling using a lancet or urine glucose monitoring [50,51]. Standard hospital techniques like 24-hour glucose curves and measurement of glycosylated hemoglobin can provide information on both short and long-term glycemic control [51,52]. Interstitial glucose monitors have even been validated in dogs and can provide continuous glucose monitoring for up to 14 days after application, an excellent tool for objective documentation of glycemic control on a moment to moment basis [53-57]. Kits for measurement of canine insulin and c-peptide are readily available as an additional method for monitoring islet graft function after transplantation in the dog model. Additional monitoring of the immune system has become routine and predictive of islet allograft rejection in human transplant recipients. Techniques for mixed lymphocyte reactivity [58-60] and measurement of autoantibody titers to IA-2A or GADA have been described in dogs [11] and would greatly add to the translational information obtained in canine clinical studies.

SOURCES FOR DONOR TISSUES IN COMPANION ANIMALS

Islet transplantation can never be a realistic option in pet dogs without identification of an acceptable source of donor animals. Veterinary researchers are presented with a unique opportunity for planned tissue collection from dogs that are euthanized for unrelated reasons. While numerous studies have shown that high quality islets can be obtained after pancreatectomy in anesthetized research dogs [61-64], our laboratory has made some of the first strides in accessing a more widely available tissue source by developing methods for islet isolation from dogs following standard euthanasia with barbiturates [65,66]. As expected, islet yields are lower from these cadaveric donors, although tissue availability from planned euthanasia far exceeds current demand for islet transplantation research and the use of multiple organs for each recipient is not a limiting factor. Tissue typing services and reagents are available for dogs (https://sharedresources.fredhutch.org/services/dla-typing-services), allowing MHC compatibility testing, although a national system for tissue matching and quality control has not been established for companion animals. Much like the future of human diabetes therapy, use of porcine xenografts or stem cells will provide a more reliable and consistent source of beta cells. Our laboratory is actively pursuing all of these areas with clinical trials in companion animals with naturally-occurring diabetes. Future work will need to establish whether islet allograft or xenograft transplantation provides improved glycemic control in dogs with naturally occurring DM.

POTENTIAL DUAL MARKET FOR COMMERCIALIZATION OF PRODUCTS

Clinical trials in companion animals have to the unique ability to rapidly commercialize a product in a veterinary market while concurrently obtaining efficacy and safety data to support eventual application for approval in the human market [67]. While the potential for revenue generation in the veterinary market is admittedly limited when compared to the human market, small start-up companies and entrepreneurial researchers at universities are now recognizing that up to 700,000 diabetic pet dogs constitutes a legitimate market for cell therapy products. Companies can use this revenue to access capital far earlier in the process than would be realized in direct development of a human medical device or cell product, as approval of veterinary products can be achieved with relatively low cost. The lack of third party payment in veterinary medicine leads to the client paying direct costs for most therapies that are performed in companion animals and can limit both the market size and the potential revenue gained by companies working in this area. However, this requirement has not suppressed the market for veterinary specific products used in advanced procedures such as total hip replacement, interlocking nails, ring fixators, and stents used in interventional procedures. Indeed, veterinary stem cell therapy is an active area of corporate interest and shows that cell based therapies can be economically viable in veterinary medicine [68]. The adoption of a broad One Health approach that includes naturally occurring disease models in companion animals is one of the key methods to reducing the high failure rate of medications and therapies in late stage human clinical trials [67].

CONCLUSIONS AND OUTLOOK

While the use of client-owned animals cannot substitute for all of the current steps in pre-clinical screening of diabetes therapeutics, there are a variety of economic and scientific advantages to using a naturally-occurring disease model in pet animals as an important component of that process. An increasing number of translational researchers are focusing their research programs around spontaneous osteoarthritis, cancer, and diabetes models in companion animals [67]. Veterinary researchers are currently focusing on identifying a safe and dependable source of beta cells for use in transplantation studies. Collaboration from established human transplant programs and from companies with novel technologies will be essential in leveraging the dog diabetes model as a mechanism to advance diabetes care in both animals and in human beings.

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