Islet Replacement Approaches for Treatment and Management of Canine Diabetes

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INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder affecting humans as well as pets. Dogs present with Type-1-like or insulin dependent diabetes. Management of diabetes in pets is aimed at achieving good glycemic control via controlled insulin injection, diet, exercise and rigorous home monitoring which presents major challenges to pet owners. Consequently, a large percentage of owners (up to 60%) opt for pet euthanasia at diagnosis or within the first year of treatments. Likarda is exploring alternative, regenerative approaches for the management of diabetes in dogs and cats including islet transplants and stem-cell derived insulin producing beta-like cells capable of correcting the diabetic condition. Islets were microencapsulated using our patented Core-Shell Spherification™ (CSS) process in PEGDA-based hydrogels, after which microspheres were transplanted into the omentum of diabetic dogs. Likarda-patented hydrogel encapsulation technologies, as well as safety and efficacy studies in mice and dogs, have paved the way for clinical trials. Ongoing studies are aimed at better understanding islet dose requirements, potency, microsphere diffusion dynamics and host immune response as well as the in vivo stability of microspheres. Likarda is also exploring scalable sources of insulin producing cells from pluripotent and other stem cell sources. Current data from islet transplants and preliminary data from directed differentiation of stem cells indicates that regenerative approaches will be an economically feasible and easy to adopt for the treatment and management of diabetes in pets.

METHODS and RESULTS

Likarda Islet Transplant Service

- Pancreas procured from qualified donors
- Cheri’s Hope Organ Donation or vet clinic
- Islets are isolated from pancreas
- Encapsulated in hydrogel for immunoprotection
- QC and batch release testing completed
- Transplantation into omentum (via injection)

Diabetes: Humans and Canine

<table>
<thead>
<tr>
<th>Human</th>
<th>Canine</th>
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<tbody>
<tr>
<td>Type 1 Diabetes = Insulin Dependent</td>
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<tr>
<td>Incidence: Growing 3-5% / year</td>
<td>Incident Growing 3-4 fold</td>
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<tr>
<td>Genetic Predisposition (familial)</td>
<td>Genetic Predisposition (breed)</td>
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<tr>
<td>Immune Destruction of Beta-Cells</td>
<td>Immune Destruction of Beta-Cells</td>
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<td>Diagnosis Confirmed by Autoantibodies</td>
<td>Autoantibodies Data conflicting</td>
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<td>Typically Diagnosed in Youth</td>
<td>Disease of Middle-Aged and Older Dogs</td>
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Human Islet Transplant Procedure

- Canine pancreas are procured from dogs euthanized for other reasons and with owner’s consent.
- The islets are isolated in the lab using collagenase digestion and density gradient centrifugation and cultured in complete CMRL medium.
- Islets undergo qualitative and quantitative assessments including Islet Equivalent Counting (IEQ), viability, purity, metabolic status measured by ATP production, total Insulin measurements and DNA content.
- Islets are encapsulated in polyethylene glycol (PEGDA) or hyaluronic acid (HA) based hydrogels using Core-Shell Spherification™ (CSS), and implanted into the omentum or IP cavity.
- Animals are monitored for blood glucose and other health parameters and stained for histology at necropsy for inflammation and fibrosis.

CONCLUSIONS

We have established that PEGDA hydrogel microencapsulated canine islets survive and maintain function in vivo leading to high blood glucose correction. Dose and efficacy studies are underway in canine models. Scalable stem cell derived insulin producing cells are also under investigation for treatment of diabetes in pets.

REFERENCES