**Assessing the feasibility of allogeneic stem cell therapy for canine dilated cardiomyopathy**

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Dilated cardiomyopathy (DCM) causes significant morbidity and mortality with the prevalence in European Dobermans >8 years at 44%. Clinical manifestations include a dilated phenotype with congestive heart failure or malignant arrhythmia causing sudden cardiac death. As treatment options are limited, there is interest in using cardiac stem cells. Cardiosphere-derived cells (CDCs) are an adult cardiac progenitor cell population that can be derived in large numbers from myocardial biopsies. Administration of CDCs to murine models of DCM showed improved survival and to Dobermans marginally increased systolic function. Allogeneic CDC therapy avoids obtaining cells from unhealthy donors and allows access to large cell numbers. Mesenchymal stem cells (MSCs) have been shown to induce an immune-tolerant phenotype in recipients from unrelated donors. However, MSCs are inferior to CDCs in their cardiac regenerative capability and it is currently unknown if canine CDCs possess a similar immune-privileged status.

Our aim was to characterise the immune-regulatory status of canine CDCs.

Cardiosphere-derived cells (CDCs), MSCs and lymph node cells (LNCs) were obtained from five dogs immediately post-mortem with owners’ consent and University ethical approval. These cells were isolated as previously published. The ability of CDCs to form clones, self-renew and commit to multiple lineages was assessed. Dogs were genotyped for DLA-88 and DRB-1 and cells assessed for MHC antigens by flow cytometry. Mixed lymphocyte reactions (MLR) incorporating responder LNCs and allogeneic stimulator CDCs or MSCs were performed. LNCs were also cultured alone or in combination with concanavalin A. Proliferation was assessed by 3H-thymidine uptake.

Canine CDCs demonstrated the ability to self renew, form clonal colonies and commit to multiple lineages (myocardial, endothelial and smooth muscle). All dogs in the study were heterozygous for both DLA-88 and DRB-1 and varied in haplotype. In MLR assays, lymphocyte proliferation ability was confirmed by response to concanavalin A stimulation. CDCs did not produce a significant proliferation in responder LNCs when compared to non-stimulated LNCs (P = 0.36). This lack of response was confirmed across multiple donor and responder cells with mismatched MHC I and II haplotypes. Interestingly, allogeneic MSCs stimulated a response in LNCs when compared to non-stimulated cell LNCs (P = 0.011).

These results show that CDCs do not produce an immunological response in an in vitro model of transplant immune-reactivity. This demonstrates that CDCs possess immune-privileged status. Our study provides evidence for the safe use of allogeneic CDCs to treat canine DCM.