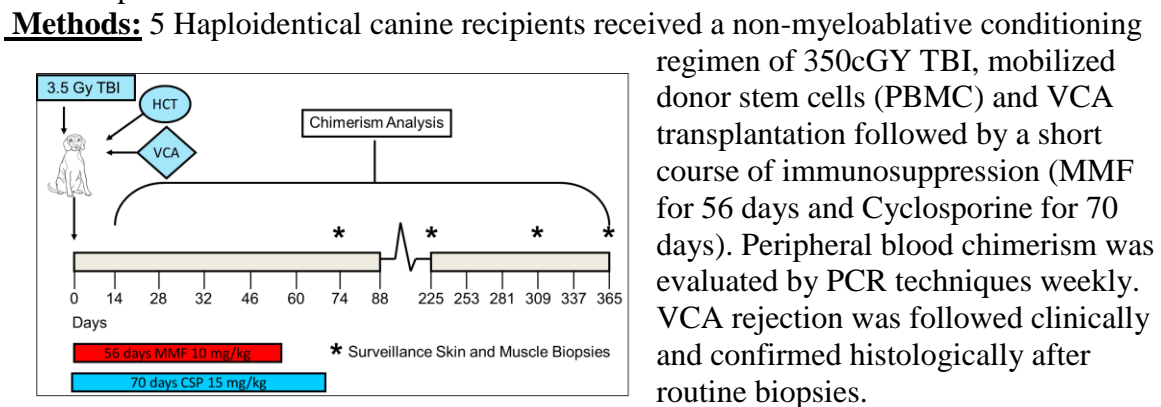


ACHIEVING TOLERANCE IN A MISMATCHED VCA TRANSPLANT WHILE REDUCING THE RISK OF GVHD: THE GOAL OF TRANSIENT CHIMERISM

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Background: Transplantation of vascularized composite allografts (VCA) offers the opportunity to restore form and function. Clinical application is limited due to the necessity of life-long immunosuppression. One promising method of inducing tolerance to an organ allograft is the development of mixed chimerism. We have demonstrated that a non-myeloablative stem cell transplant can lead to tolerance in a mismatched dog model. However, the application of this protocol has been limited by graft-versus-host disease (GVHD). We have observed several animals that, after an initial period of donor cell engraftment, lost their stem cell allograft but remained tolerant to the VCA. Conversely, animals that retained persistent donor cell chimerism inevitably developed GVHD. The hypothesis for this study was that our non-myeloablative hematopoietic stem cell transplant protocol could be used to induce tolerance to a recipient VCA without the need for persistent donor cell chimerism.



Results: All 5 animals tolerated the conditioning regimen. One dog rejected the PBMC at post-operative day (POD) 35 and went on to reject the VCA transplant following the cessation of immunosuppression (POD 84). One dog fully engrafted and converted to 100% donor chimerism and long-term tolerance to the VCA but developed GVHD. 3 dogs demonstrated a prolonged period of transient chimerism (7 to 10 weeks post-transplant) and went on to reject their donor stem cells after the cessation of immunosuppression without acute rejection of their donor VCAs. One of these dogs was euthanized for persistent fevers at POD 84 with no sign of rejection. The remaining two had long-term acceptance of their VCA (>200 days) with no evidence of acute rejection. However, later in the study both of these animals demonstrated evidence of chronic rejection. Neither developed GVHD.

Conclusions: In this study we demonstrate that our non-myeloablative protocol allows for selective rejection of donor stem cells and elimination of GVHD risks without acute rejection of the VCA transplant and that persistent donor chimerism can lead to GVHD.