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# Diabetes-Related Islet and Hematopoietic Cell Transplantation That Cures the Condition in Mice without Harmful Bone Marrow Conditioning

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## Abstract

The immunological tolerance of donor-matched transplanted tissues, such as pancreatic islets, can be enhanced by mixed hematopoietic chimerism. Adoption of this approach is, however, constrained by the toxicity of conventional therapies that allow donor hematopoietic cell engraftment. Here, we address these issues by using a non-myeloablative conditioning regimen that promotes allograft tolerance and hematopoietic chimerism across totally mismatched major histocompatibility complex (MHC) barriers. Immunocompetent mice treated with a CD117 antibody that targets the c-Kit protein along with T cell-depleting antibodies and low-dose radiation are able to develop permanent multi-lineage chimerism after hematopoietic cell transplantation. Co-transplantation of donor-matched islets and hematopoietic cells effectively reverses diabetes in diabetic mice without causing persistent immunosuppression or significant graft-versus-host disease (GVHD). Allotolerance is most likely mediated by peripheral regulatory T cells produced from the host and donor-derived thymic antigen-presenting cells.

**Keywords:** Immunologic tolerance; Islet transplantation ; Mixed chimerism; Transplantation of Hematopoietic stem cells; Diabetes; Allogeneic transplant blood marrow

## Introduction

Effective treatment for diabetes after pancreatic beta-cell loss is the transplantation of pancreatic islets from MHC-mismatched (allogeneic) donors, however this procedure necessitates long-term immunosuppression to prevent islet rejection. Corticosteroids and T cell inhibitors are commonly used in immunosuppression, although they have nephrotoxic and diabetogenic side effects and raise the risk of cancer and opportunistic infections. Therefore, it would be a significant advancement to achieve islet transplantation tolerance without systemic immunosuppression [1].

Solid organ transplantation experiments have shown that mixed chimerism, in which hematopoietic stem cells (HSCs) of the host and donor origin coexist, is a viable strategy for obtaining long-lasting. Current conditioning protocols use high-dose radiation and/or DNA-damaging chemotherapeutic drugs like busulfan and melphalan to prime host bone marrow for engraftment by donor HSCs. Such rigorous regimens are thought to be too dangerous for widespread use in islet transplantation and pose the risk of serious chronic morbidities. However, failure of HSC engraftment might occur if myeloablative drug dosages are only decreased to reduce conditioning intensity. In light of this, safer NMA conditioning protocols [2].

## Mixed chimerism increases the tolerance to allogeneic islets

We looked at whether donor-matched islet allograft tolerance was enhanced by the emergence of mixed chimerism between totally MHC mismatched strains after NMA conditioning. Mice with mixed chimerism or conditioned controls were given islets from sex-matched B6 and BALB/c or third-party FVB (H2q) donors in order to study both acute immunity and long-term tolerance.; In mice with mixed BALB/c chimerism, the BALB/c islet grafts persisted two weeks after transplantation with minimal to no CD3+ T cell infiltration and scarce CD45+ immune cell infiltration. In contrast, islet grafts from unrelated FVB donors had a high level of CD3+ and CD45+ cell infiltration. Grafts from BALB/c were [3].

We employed B6 RIP-DTR mice to test whether simultaneous HCT and islet transplantation could help overtly diabetic recipients get over the barrier of full MHC mismatch. These are homozygous for Ptprca and have the Ins2-HBEGF transgene. After receiving a single dose of diphtheria toxin (DT; STAR Methods), islet beta-cell ablation causes the mouse to become severely insulin-dependent and diabetic. Prior to NMA conditioning, male and female B6 RIP-DTR mice were given DT on day 4.5 and became diabetic. Conditioned mice got an islet transplant from a B6, BALB/c, or FVB sex-matched donor on day 0 and a BALB/c sex-matched donor's HCT on day 0. Following transplantation, mice were observed for 20 weeks (cohort 1) or 16 weeks (cohort 2). By 4 weeks following the transplant [4].

FVB islet recipients initially experienced euglycemia, but after a mean of 78 days (n = 4; Figure 3G), they spontaneously relapsed to hyperglycemia. Destruction of the transplanted FVB islets was confirmed by graft recovery and histological analysis. The FVB graft function lasted longer than the typical 2-week period of islet rejection in immunocompetent normal mice. We hypothesise that this delay is caused by a number of variables, including as transitory immunosuppression in graft recipients, the maturation period for de novo effector T cells, and potential interactions between indigenous immune cells and transplanted islets. However, the final rejection of islet allografts from a different source showed that mixed chimaeras had retained immunocompetence [5].

## Discussion

Mixed hematopoietic chimerism can produce donor-specific

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tolerance, according to prior studies, but harsh conditioning methods and previously employed hematopoietic cell preparations have impeded practical translation. After NMA conditioning, we were able to produce mixed donor chimerism and long-lasting islet tolerance in this case. Diabetes remission without ongoing immunosuppression was achieved after donor-matched islet transplantation, leading to high functional status. We also found evidence of central and peripheral pathways mediating donor-specific tolerance in mice with stable mixed chimerism. The advances made in this area point the door to safer clinical techniques for a wider application of islet transplantation in diabetes [6].

For HCT conditioning, DNA alkylating medications and high doses of radiation are linked to a number of morbidities, including chronically reduced fertility and endocrine function (Couto-Silva et al., 2001). These issues call for intensive counselling and care. Here, we showed that a small cohort of mice maintained good breeding performance and remained fertile after NMA conditioning, and that diabetes could be reversed after islet allotransplantation and HCT. It is necessary to conduct more research with bigger male and female cohorts to see whether quality-of-life indicators are maintained following CD117-based training [7, 8].

GVHD is a potentially fatal side effect of HCT and a barrier to increasing the usage of HCT (Flowers and Martin, 2015). The degree of bone marrow conditioning and the source and composition of HSCs are significant risk factors for GVHD; in this study, we focused on both risk variables. First off, our conditioning programme is NMA, rather gentle, and highly effective. Second, rather than transplanting complete bone marrow, we used enhanced hematopoietic stem and progenitor cells (HSPCs), which have been stripped of their mature effector cells. Clinically, CD34+ cell purification utilising tried-and-true sorting techniques results in HSPC enrichment. HSPC preparations can lower the risk of GVHD, but since they lack immunological and other supporting cells, they do not engraft as well as WBM [9].

## Conclusion

The figure legends and results section contains statistical information about each experiment, including the value of n. All data are displayed as means with standard error of the mean (SEM), where n is the number of animals. The experimental groups were divided up into animals at random, and each sample is a biological replicate. The Prism 8 statistical analysis programme was used. Welch's correction was applied to the unpaired, two-tailed Student's t-test to analyse differences between the means of the two groups. The outlier function in Prism 8 eliminated some data. Estimates of the sample size weren't used. Statistical significance was defined as a p value of 0.05 or less. $*p < 0.05$, $**p < 0.01$ [10].

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## Potential Conflicts of Interest

No conflict or competing interests in the publication of this paper.

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