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Awards in Transplantation Science Recognize the Best Manuscripts Published in *Transplantation*

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The Transplantation Science Committee together with The Transplantation Society and *Transplantation* are pleased to announce the best manuscripts submitted to the Journal in 2015.

Named after 2 pioneering giants, a selection committee that included editors of *Transplantation*, The Transplantation Society, in addition to members and chairs of The Transplantation Science Committee selected 2 winners amongst a very competitive group of applicants.

The **Leslie Brent Award** for the best publication in basic transplantation research went to **Naohiro Takemoto and co-workers** from Kyoto University for their work showing that “coaggregates” of pancreatic islets and regulatory T cells resulted in improved transplant outcomes in experimental models of islet transplantation. The **Anthony P. Monaco Award** that recognizes the best translational submission went to **Donna Lucas and co-workers** from Johns Hopkins University for their clinical study investigating antibody responses in renal patients across different MHC mismatches, with the aim of improving donor-patient matching and to better apply immunosuppression.

The **Leslie Brent Award**: ‘Sticking out of trouble’ – *Treg therapy for immunosuppression free islet transplant survival*.

The **Leslie Brent Award** for the most outstanding paper for 2016 goes to **Takemoto and colleagues¹** for their manuscript entitled “Coaggregates of Regulatory T Cells and Islet Cells Allow Long-term Graft Survival in Liver Without Immunosuppression.” Transplantation relies on the use of heavy immunosuppression to maintain graft survival. However, associated toxicities and negative aspects of immunosuppression mitigate the success of

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transplantation. The limits imposed by immunosuppression are evident in islet cell transplantation. Islet transplantation is emerging in many centers as a treatment for patients with type 1 diabetes and hyperglycemic unawareness². At this stage this treatment is restricted to adults with severe complications due to the need for immunosuppression. Whereas it is clear from the DCCT (Diabetes Case Control Trial) studies that the improved glycemic control imposed by an islet cell transplant would provide substantial protection from long term diabetic complications, and could thus be reasonably considered as a protective treatment for young subjects with type 1 diabetes. The application of regulatory T cells (Treg) may be one pathway to mitigate the need for heavy immunosuppression and open a path for applying islet transplantation to extended groups of patients. Treg are key controllers of immunity and when applied in islet experimental transplant models can allow impressive islet transplant survival across a MHC-barrier^{3,4}. Clinical trials have begun to test the use of large numbers of expanded and/or enriched Treg applied therapeutically for autoimmunity and transplantation^{5,6}. However, systemic approaches raise safety concerns, including the possibility of blunting protective immunity⁶. To circumvent this potential complication Takemoto and colleagues¹ developed a technology to fuse Treg with pancreatic islets to form “coaggregates”, such that after infusion, the 2 cell products would be delivered to the same locale. The rationale being that local Treg would provide at site immune regulation without the potential complication of systemic suppression. Further to this, it was reasoned this approach might reduce the numbers of Treg needing to be infused and thus reduce the cost of cell manufacturing. Using the more robust mouse model of intra-portal islet transplantation, Takemoto and colleagues show that co-transplantation of allogeneic islets with peripheral Treg (CD4+ CD25+ T cells) allowed long term survival (>100 days) for the majority of islet grafts, whereas all control grafts are rapidly rejected. The islet-Treg coaggregates also provided normal glycemic control throughout the experimental period.

These experimental data provide a novel solution to the use of Treg and support further testing with human islets and Treg to determine whether human cells would form functional coaggregates. The liver is coming under increasing scrutiny as the preferred site for clinical islet transplantation and it would be interesting to test whether coaggregates with Treg improved islet engraftment in the liver, and prevented the early loss of islet mass, as well as the appearance of liver pathology around islet grafts. The success of Takemoto and colleagues in forming islet coaggregates suggests the possibility of forming much more complex cell mixtures, including the addition of Treg as well as endothelial precursors (ePC's) to promote vascularization⁷. Such a combination could form a superior product for implanting islets in other sites such as the omental pouch⁸ free of immediate blood contact and without potential risk to the liver.

Shane T Grey, PhD

The **Anthony P. Monaco Award**: *A deeper understanding of HLA immunogenicity.*

The **Anthony P. Monaco Award** for the most outstanding translational paper for 2016 goes to **Lucas and colleagues**⁹ for their manuscript entitled “Differences in Immunogenicity of HLA Antigens and the Impact of Cross-Reactivity on the Humoral Response.” The de novo development of anti-HLA antibodies after transplantation is closely associated with an

increase in the risks of both acute rejection and chronic allograft dysfunction in all solid organ transplants^{10–12}. It therefore follows that a mismatch in HLA types between donor and recipient will contribute to the development of these antibodies, and that HLA matching improves outcomes after transplantation. However, irrespective of the development of donor-specific antibodies, sensitisation to a single donor HLA antigen can be detrimental to future re-transplantation¹³. The sensitisation that develops does not necessarily correlate with the overall HLA mismatch, because the immunogenicity of a specific epitope is dependent on multiple factors. However, identification of epitope mismatches is neither practical nor necessarily predictive of overall response, as multiple epitopes can contribute to antibody development and immunogenicity can be determined by the physiochemical properties of the amino acids that make up the epitope. For these reasons, a broader evaluation of the immunogenicity of specific HLA antigens is useful as this may provide insight beyond those gleaned from knowledge of the HLA mismatch alone. In the award winning study from Lucas and co-workers, de novo donor-specific antibody frequency data were examined from 703 renal transplant patients at the Johns Hopkins Comprehensive Transplant Center¹⁴. Sera were tested using multiplexed bead assays supplemented with phenotype panels and the frequencies of antibodies to each mismatched antigen determined. A large amount of variability in immunogenicity of different HLA antigens was observed, and interestingly, antibody frequencies were reduced for some specificities in the presence of cross-reactive antigens in the patient's phenotype. Globally, the mean frequency of antibodies in the serum which were reactive to HLA-B antigens were lower than those to HLA-A, -DR and -DQ antigens. Moreover, the mean frequency of antibodies to DR51, DR52 or DR53 was higher than those to DRB1 locus antigens. The impact of specific HLA haplotype mismatches has, for many years, been proposed to be important in predicting transplantation outcomes^{10,15,16}. A deeper understanding of how immunogenicity of specific HLA antigens may differ is important as it may help predict how a patient may respond to a re-transplant. A larger bank of data (ideally across multiple centres and countries) are required in order to provide more confidence in this predictive power. It is therefore possible that in the future, information on antigen immunogenicity is considered during the matching process, particularly in sensitised patients. At the very least, it may be prudent to more closely monitor 'at risk' patients. Whether the differences in humoral immunogenicity demonstrated in this study are related to previous environmental factors is not known. The authors concede that prior pregnancy and transfusion may contribute to sensitisation to specific HLA antigens, although it is not clear why this should be the case for only these specific haplotypes. Perhaps there are other factors at play, such as previous responses to pathogens (and thus cross-reactivity or heterologous immunity) which may explain some of the consistency observed among patients in their responses against specific HLA antigens. Overall, the observations made by Lucas and colleagues are likely to be clinically important and we would encourage our readers to take a closer look at this paper.

Fadi Issa, DPhil

Both the Leslie Brent and the Anthony P. Monaco Award are wonderful opportunities to highlight outstanding publications in *Transplantation*.

We are presently looking forward to review the best submissions of 2016 and will accept applications until June 30th, 2017.

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(Chair and Co-Chair, The Transplantation Science Committee, TTS)

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