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The Special Issue on Immunobiology of Transplantation

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The era of organ transplantation began when Emerich Ullmann, an Austro-Hungarian professor of surgery, performed the first intestinal transplant (1889), for which he was regarded as "the father of intestinal transplantation" [1]. On March 7, 1902, he performed the first kidney transplant on a human, anastomosing a pig kidney into the cubital region of a woman with end-stage renal disease; the transplant failed. His 1914 monograph on the state of the art of transplantation, "Tissue and Organ Transplantation", summarized what then seemed the insurmountable immunological barriers to transplantation [1]. It would take almost 50 years before effective means of immunosuppression were developed, becoming available in the 1950s [2]. However, in 1902-Ullmann had successfully performed an autotransplant of a dog's kidney to its throat. In 1908, French surgeon Alexis Carrel performed the same auto transplant of a dog's kidney, showing that "such a transplant doesn't interfere with the kidney function," which meant that, at least as a matter of surgery, organ transplantation was a reality. This earned Carrel the Nobel Prize in 1912. Subsequently, several other Nobel laureates laid the foundation for the immunobiology of transplantation. They included Sir Peter B. Medawar, Sir F. Macfarlane Burnet, Baruj Benacerraf, Jean D.G.J. Dausset, George D. Snell, Joseph E. Murray and E. Donnall Thomas.

Medawar postulated immunobiological forces inhibited the survival of an allograft post-transplantation. The elucidation of inhibitory factors began with the discovery of transplantation antigens, called the "Human Leukocyte Antigens" (HLA). These antigens on the cell surface of an allograft are recognized by the recipient's immune components as "non-self," and immune attack commenced against the allograft. The reverse can also happen as in the case of bone marrow transplantation, where the immune cells of the allograft may recognize the recipient's cells as foreign and attack them, a phenomenon known as "Graft-Versus-Host Disease"(GvHD). Murray and Thomas suggested strategies to overcome organ, tissue or bone marrow rejection post-transplantation [3]. But we are yet to succeed in making the allo-organ accepted as "self". The first step necessary to reach that goal is a holistic perspective followed by a reductionist approach to the immunobiology of transplantation.

The articles presented in this special issue aim at that dual perspective. Five of them were conceived and written under the leadership of Paul I. Terasaki, one of the pioneers in the development of organ transplanation, who is well known for a wide array of contributions to the field of immunobiology of transplantation. First, he developed the cytotoxicity assay to match donors to recipients [4], exposing donor HLA-expressing cells to the recipient's sera. Second, he was the first to purify HLA molecules [5-7], and to prove their immunogenic capabilities [8,9] *in vivo*. Third, after recognizing the wide diversity of HLA alleles, he developed a reliable and reproducible methodology to monitor Donor-Specific HLA Antibodies (DSA); for this, he used microbeads coated with recombinant HLA molecules (both HLA class -I and-II) analyzed by a Luminex platform [10,11]. With this technology, he was able to capture critical moments of the immune rejection of an allo-organ, which was mediated by antibodies. As a result, Paul I Terasaki proposed the "Humoral Theory of Transplantation" [12,13]. This issue contains papers submitted by his team at the Terasaki Foundation Laboratory which highlight a few aspects of the immunobiology of transplantation.

In his manuscript, *"The Model of Chronic Allograft Injury in Alloantibody Positive Renal Transplant Patients"*, Matthew J. Everly summarizes the current concepts about chronic allograft injury and allograft failure in transplant patients who are positive for DSA. He uses renal transplantation as a model, and highlights several important observations that build upon Terasaki's Humoral theory of transplantation. Foremost, Everly indicates that the clinical appearance of de novo DSA in many transplant patients may be driven, primarily, by low immunosuppression states, namely non-adherence to immunosuppression or physician-directed immunosuppression minimization. This report makes it clear that there is a need for a better understanding of DSA in transplantation. By finding that 75% of DSA-positive patients have apparently normal intermediate-term allograft function, Everly suggests that either immunosuppression currently in use is working to suppress immunological injury or that there needs to be a clarification on the interaction of DSA with the allograft. Moving forward, Everly suggests that "completely" studying the alloimmune response and the longitudinal development of allograft injury may be the next necessary step toward better

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stratification of injury types undergone by the allograft after it is placed in the new microenvironment of the recipient.

Junchao Cai, with Everly, Cheng, Terasaki, et al., uses the UNOS registry to compare allograft survival in ABO-compatible intestinal transplants performed in the US, with that of ABO-identical transplants. The ABO-compatible recipients included blood group A and B patients who received allografts from O donors, and blood group AB patients who received transplants from A, B, or O donors. ABO-compatible intestinal transplant recipients experienced a significantly higher rate of acute rejection than did ABO-identical patients, possibly due to subjecting the ABO-compatible transplants to intense induction/ maintenance immunosuppressive therapies. Even more important than the need for increased immunosuppression, the Cai group found that ABO-compatible intestinal transplant recipients had a significantly higher rate of acute rejection, with a >40% higher graft loss than recipients in the ABO-identical group. The authors attribute that acute rejection to GvH antibodies that can be produced by viable graft-derived lymphocytes from lymphoid tissues of allografts. In ABO-compatible kidney transplantation, GvH antibodies have been shown to cause hemolysis 60% of the time. The Cai group also points out that the GvH reactions may damage host lymphoid tissues and produce profound immunosuppression leading to infection.

Elaine Y. Cheng, with Terasaki, reviewed the literature on immune tolerance mechanisms observed in liver allograft recipients. The liver allograft has a lower incidence of rejection than do other solid organ transplants. The spontaneous acceptance of the liver allograft after discontinuation of immunosuppression (in 20% of allograft recipients) sheds light on how current research has advanced our hopes of achieving transplantation tolerance. The authors elaborate in detail the putative immune mechanisms underlying graft acceptance. These include sheltering donor-derived hematopoietic cells, called "passenger" leukocytes, by the liver allograft from the host immune attack; the persistence of donor cells and nucleic acid in the blood and tissues of the recipient, an illustration of donor microchimerism; and the modulation of the T-cell response by hepatocytes and nonparenchymal cells within the allograft. Based on these findings, the authors propose immune strategies to promote overall graft survival in organ transplantation; one such strategy involves elucidating the effects of donor bone marrow infusion in solid organ transplantation. The authors discuss recipients' allograft-infiltrating, T-cell-mediated immune mechanisms to circumvent rejection and the role of regulatory T cells in suppressing alloreactive T cells. They also discuss in light of experiments done on animal models and observations in human transplantation-the high-dose antigen hypothesis, highlighting the graft-protecting role of larger liver allografts with an antigen load. Finally, the authors emphasize the importance of the role played in tolerance induction by the soluble non-classical HLA molecule, HLA-G, and its potential as a therapeutic agent.

Vadim Jucaud, with Terasaki and Ravindranath, elucidates the transplantation immunobiology of HLA class Ib molecules, which were recognized 25 years ago. The authors show from the literature that, the HLA-Ib molecules (HLA-E, HLA-F and HLA-G) have been emerging as potential immune regulators of transplantation, functioning as ligands for immunomodulatory cell-surface inhibitory and activating receptors expressed by the subsets of NK and CD8+ T cells-the major players in allograft rejection. Jucaud, et al, underscores that this interaction is dependent on the nature and source of peptides presented. When HLA-Ia-derived peptides are presented by HLA-E, then the HLA-E molecule interacts with inhibitory receptors to block the cytotoxic cell functions-thereby promoting graft survival. However, when presenting with the HLA-G leader sequence or viral or bacterial peptides, HLA-E interacts with activating receptors to activate the cytotoxic cells, leading to graft rejection. The authors show how other HLA-Ib molecules (HLA-G and HLA-F) may promote graft acceptance by binding to different families of receptors. In contrast, the overexpression of HLA-Ib may promote GvHD in non-HLA-Ib-matched patients undergoing cell transplantation. Indeed, HLA-Ib molecules can become "non-self" antigenic targets recognized by the donors' cells when donors and recipients are not HLA-Ib identical. The occurrence of HLA-Ib with or without β2-microglobulin (β2m) and being in a soluble HLA-Ib state promotes greater immune modulation and recognition. HLA-Ib exposes epitopes to different immune components, contributing to the production of both monospecific and polyreactive antibodies with different functions, mediated by signal transduction.

Ravindranath, with Terasaki and Jucaud, review the literature about the immunobiology of HLA in the allograft microenvironment. We restrict our review to HLA-Ia and HLA-II, reporting that HLA molecules can promote allograft escape from cytotoxic killing and also provide cellular/ humoral immune pressure to an allograft. The physicochemical structure of HLA-I and HLA-II are elucidated to understand their functional potential. The importance of glycosylation of HLA molecules is emphasized to compensate for the hitherto lack of attention to glycol residues in transplantation immunology. The location and size of such residues indicate that they may impact the mode of antigen presentation and elicit anti-allograft antibodies, taking into account that the nature of glycans on HLA may vary with cell types and viremic conditions. It is shown that HLA-I can occur with or without β2m both on the cell surface and in body fluids, and that the increase of soluble β2m-free HLA post-transplantation and the interaction of that HLA with CD8 receptors on alloreactive cytotoxic T cells can induce apoptosis of alloreactive CD8+ T cells. This impact of soluble HLA is lost, once anti-HLA antibodies bind to them to form immune complexes, which may lead to arteriosclerosis during acute rejection. HLA antibodies formed against donor-specific HLA can be both pathogenic and non-pathogenic so there is a need to demarcate them by sensitive immunoassays. The pitfalls in monitoring donor-specific HLA antibodies post-transplantation are also discussed.

In all, these five manuscripts precisely fit this special issue on the "Immunobiology of Transplantation". We thank the Editor in Chief of SOJ Immunology for conceiving and projecting this special issue, with special thanks to Ellen Spencer, editorial assistant, for inviting me to organize our contributions.

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