

ASHI

Quarterly



Third Quarter 2017

Volume 41, Number 3



2016 Paul I. Terasaki Lecture

Back to the Future — HLA Matching to Improve Outcomes

Peter Nickerson,

Department of Internal Medicine, University of Manitoba;

Department of Immunology, University of Manitoba;

and Diagnostic Services of Manitoba, Winnipeg,

Manitoba, Canada

Introduction

Today, solid organ transplantation reports one-year graft and patient survival that is remarkable due to calcineurin-based immunosuppression and solid-phase HLA antibody analysis to detect and avoid donor-specific immune memory prior to transplant. Despite this amazing success story, the field is confronted with the fact that long-term outcomes have only marginally improved.¹ Epidemiologic studies have found that the etiology of graft loss remains largely alloimmune based, reflected in the development of de novo donor-specific HLA antibodies (DSAs) leading to antibody-mediated rejection or related to premature death of the patient with a functioning graft due to metabolic, infectious or cancer complications – some of which are attributable to immunosuppression.²⁻⁴ Herein lies the delicate balance of modern-day transplantation – giving enough maintenance immunosuppression to control the alloimmune response while giving the least amount possible to avoid unwanted complications. The goal is to personalize immunosuppression to the lowest possible level. Unfortunately, the development of new, cheap and effective drugs with less toxic side effects has largely failed, as have attempts to minimize calcineurin-based immunosuppression predicated on quiescence of the immune system to the transplanted graft.^{5,6} Where does this leave the field? Is the only hope some future breakthrough in tolerance-inducing agents?

At the time, it is hard to appreciate how visionary some individuals are in anticipating where a field needs to go for transformational change. Paul I. Terasaki is one such individual, and while most cite his 1969 *New England Journal of Medicine* crossmatch paper⁷ or his lifelong pursuit to prove the humoral theory of graft loss⁸ as his most influential works, I have chosen instead in this lecture to highlight his 1971 *Tissue Antigens* paper as the most visionary of its time.⁹ In it, he observed that deceased donor transplants did well despite incompatibilities and he declared “the apparent inadequacy of simple match-mismatch criteria for selection of recipients” and that “empiric knowledge on the types of incompatibilities which can result in good graft survival must be developed.” Indeed, this paper, which came out in the very first issue of *Tissue Antigens*, was seen as at odds with the dogma of the day – warranting a dissenting editorial by the HLA community.¹⁰ However, as will be discussed, I believe the community failed to comprehend the essence of the “call to action” message Paul Terasaki was communicating and the evolution he foresaw that would be required for the transformational change we seek today: personalized immunosuppression based on precision medicine.

HLA Mismatching: Beyond Whole HLA Molecules

Since the beginning of kidney transplantation, the importance of HLA matching has been indisputable. Indeed, the identical twin transplants of the 1950s in Boston proved that genetic identity between donor and recipient negated the need for immunosuppression.¹¹ Ever since, giants in the field – Amos, Bodmer, Ceppellini, Dausset, Kissmeyer-Nielsen, Payne, Terasaki and van Rood – have published leading works in top journals (e.g., the *New England Journal of Medicine* and *The Lancet*) dissecting the relative importance of HLA compatibility at various loci with clinical outcomes. But even in his 1971 paper, Paul Terasaki foresaw that “we must now prepare for the second phase, in which more sophisticated measures of HLA compatibility should be developed for more accurate prediction of outcomes.”⁹

What evolved in the last 60 years to advance the field of transplant immunogenetics and histocompatibility has been the disciplines of molecular and structural biology. These disciplines allowed major progress in determining the molecular basis of antibody-antigen interaction. Specifically, in the context of alloimmunity, a recipient’s DSA heavy and light chain variable regions form six complementary determining regions (CDRs) that bind the surface on the donor’s HLA mismatched molecule. This entire antibody binding region, with a radius of 15Å on the HLA surface, is the “structural epitope” of the antigen and determines antibody avidity (Figure 1). The specific polymorphic amino acids of the donor HLA and the surrounding 5Å radius on the surface are bound by the H3 CDR of the antibody heavy chain, which determines antibody specificity, and is referred to as the “functional epitope” of the antigen. It is this structure-function understanding of the H3 CDR that led Rene Duquesnoy to develop his computational software (HLAMatchmaker) to predict potential polymorphic epitopes on the donor HLA surface in the context of the recipient’s HLA, for which he coined the term “eplet” mismatch.^{12,13}

While a number of the HLA eplets have been validated to correspond to HLA antibody binding sites, others remain purely theoretical. Nonetheless, this HLA eplet mismatch approach allows a molecular assessment of donor-recipient relatedness at a much more granular level compared to just considering an HLA whole molecule as matched or unmatched. For example, a given donor-recipient DR mismatch can have very few (e.g., zero

to five) eplet mismatches at a molecular level, whereas another donor–recipient DR mismatch can have many (e.g., 30 – 40) eplet mismatches and yet, at the whole antigen level, both are treated equivalent as a single DR mismatch. Clearly, large amounts of information about donor–recipient relatedness are lost with this latter approach, which we use every day in clinical practice.¹⁴

Donor–Recipient HLA Molecular Mismatch Correlates with Clinical Outcomes

Our laboratory and others have reported that donor–recipient Class II eplet mismatch in kidney transplantation is an independent correlate with Class II de novo DSA, antibody-mediated rejection, transplant glomerulopathy and graft loss.^{15–18} While Class II eplet mismatch is a continuous correlate with these outcomes, one can determine a threshold of eplet mismatch for DR and DQ loci to categorize an individual as at high or low risk for these outcomes.^{15,18} Applying this approach, we have demonstrated that those patients who are above these Class II eplet mismatch thresholds and who are non-adherent with immunosuppressive medication are at greatest risk for late rejection and graft loss.¹⁷ However, if patients are non-adherent but below these Class II eplet mismatch thresholds, they tolerated their non-adherence without developing late rejection and graft loss at the same rate. This suggests that Class II eplet mismatch thresholds may be a useful prognostic biomarker, which can be determined at the time of transplant, to assess an individual patient’s risk for a later alloimmune event.

Further proof of the potential utility of Class II eplet mismatch thresholds in clinical care comes from a recent National Institutes of Health–sponsored clinical trial in organ transplantation (CTOT-09).⁵ In this study, living donor kidney transplant recipients were treated with state-of-the-art immunosuppression for six months. If completely immune quiescent at six months (i.e., no acute rejection from zero to six months, no DSA at six months and normal histology at six months), then they were randomized to withdrawal of their calcineurin inhibitor tacrolimus. Unfortunately, the rates of clinical rejection and de novo DSA were excessive in the withdrawal arm, such that the Data Safety Monitoring Board halted the trial. The study proved that immune quiescence on a calcineurin inhibitor did not predict immune quiescence off a calcineurin inhibitor. However, in retrospect, it was determined that those patients forming de novo DSA off tacrolimus all had Class II eplet mismatches above our reported high-risk threshold, suggesting that Class II eplet mismatch assessment may have allowed a priori identification of low-risk patients for calcineurin inhibitor withdrawal – a hypothesis that requires a new randomized control trial to prove. Finally, in a recent report, our group found that Class II eplet mismatch modulates the trough levels of tacrolimus required to prevent de novo DSA formation in kidney transplant recipients.¹⁸

HLA Mismatch and Immunodominant Epitopes

While Class II eplet thresholds can be used for risk assignment, ideally one would know if individual allo-epitopes are specifically

at high risk for de novo DSA development. Again in the 1971 paper, Paul Terasaki envisioned this concept: “The complexities of relative antigenic differences in donors and recipients ... which cannot be overcome by immunosuppression still remain to be studied.”⁹ Unfortunately, it has been exceedingly difficult to study this concept of immunodominant epitopes. It requires consideration of the genetic background of the population under study; high-resolution, allele-level HLA typing; investigation of de novo DSA in patients on immunosuppression (most DSA specificity studies focus on patients off immunosuppression); a control group that does not form de novo DSA despite years of follow-up; knowledge of the level of immunosuppression in the individual to ensure adequacy (i.e., not just that de novo DSA is due to inadequate immunosuppression); and serial de novo DSA monitoring to assess timing of onset. Our laboratory took many of these issues into account and was able to identify a few DR and DQ epitopes that were more frequent than expected in leading to de novo DSA in our population, even if adherent with their immunosuppression.¹⁵ These epitopes, if validated by others, may ultimately come to be regarded as “immunodominant epitopes.”

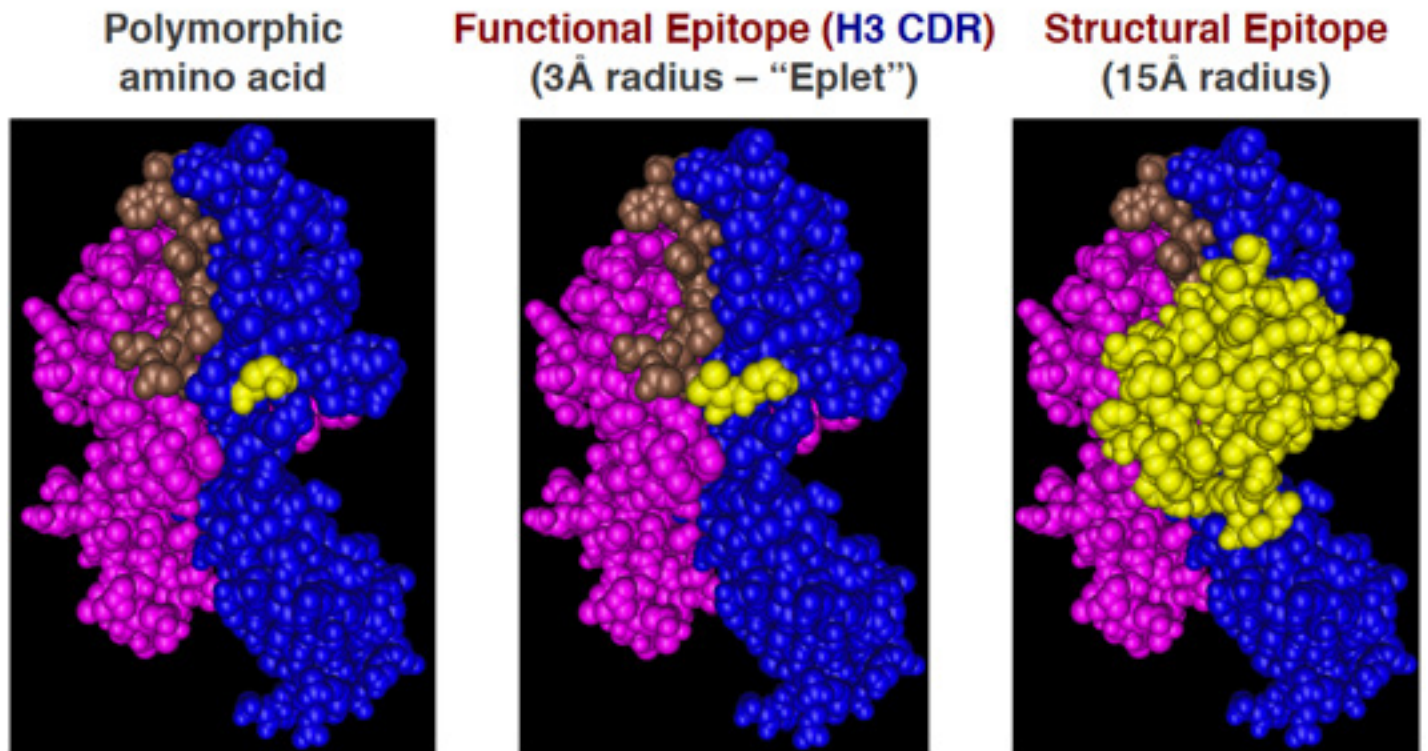
Summary

Today, we practice empiric immunosuppression post-transplant. By this, I mean we largely treat all patients with similar levels of baseline immunosuppression; we cannot tell in whom we may safely withdraw or minimize immunosuppression, and we only do so when we must to address a specific complication (e.g., infection or cancer). Unfortunately, not infrequently, we slowly lower immunosuppression based on how well someone is doing thinking we are acting in the best interest of the patient to minimize the risk of side effects until we are confronted with an adverse event (i.e., de novo DSA for which we have no proven effective therapy). Building on Paul’s vision, new basic science knowledge and novel computational tools, we now are at the brink of stratified medicine, where we assess risk at the time of transplant on the basis of HLA molecular mismatch (e.g., Class II eplets) to determine who is at high risk and therefore in whom we should avoid immunosuppression minimization unless absolutely required, and who is at low risk, where minimization may be an option. The future, as Paul foresaw, requires the community to map immunodominant epitope mismatches. With this knowledge, we truly will be in a position to practice personalized medicine with precision.

References

1. Lamb KE, Lodhi S, Meier-Kriesche HU. Long-term renal allograft survival in the United States: a critical reappraisal. *Am J Transplant.* 2011;11(3):450-462.
2. El-Zoghby ZM, Stegall MD, Lager DJ, et al. Identifying specific causes of kidney allograft loss. *Am J Transplant.* 2009;9(3):527-535.
3. Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Evolution and clinical pathologic correlations of de novo donor-specific HLA antibody post kidney transplant. *Am J Transplant.* 2012;12(5):1157-1167.

Fig. 1:



4. Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Rates and determinants of progression to graft failure in kidney allograft recipients with de novo donor-specific antibody. *Am J Transplant.* 2015;15(11):2921-2930.
5. Hricik DE, Formica RN, Nickerson P, et al; Clinical Trials in Organ Transplantation-09 Consortium. Adverse outcomes of tacrolimus withdrawal in immune-quiescent kidney transplant recipients. *J Am Soc Nephrol.* 2015;26(12):3114-3122.
6. Gatault P, Kamar N, Büchler M, et al. Reduction of extended-release tacrolimus dose in low-immunological risk kidney transplant recipients increases risk of rejection and appearance of donor-specific antibodies: a randomized study. *Am J Transplant.* 2017;17(5):1370-1379.
7. Patel R, Terasaki PI. Significance of the positive crossmatch test in kidney transplantation. *N Eng J Med.* 1969;280(14):735-739.
8. Terasaki PI. Humoral theory of transplantation. *Am J Transplant.* 2003;3(6):665-673.
9. Mickey MR, Kreisler M, Albert ED, Tanaka N, Terasaki PI. Analysis of HL-A incompatibility in human renal transplants. *Tissue Antigens.* 1971;1(2):57-67.
10. Kissmeyer-Nielsen F. The HL-A system and renal transplantation. *Tissue Antigens.* 1971;1(2):53-56.
11. Merrill JP, Murray JE, Harrison JH, Guild WR. Successful homotransplantation of the human kidney between identical twins. *J Am Med Assoc.* 1956;160(4):277-282.
12. Duquesnoy RJ. A structurally based approach to determine HLA compatibility at the humoral immune level. *Hum Immunol.* 2006;67(11):847-862.
13. Duquesnoy RJ, Askar M. HLAMatchmaker: a molecularly based algorithm for histocompatibility determination. V. Eplet matching for HLA-DR, HLA-DQ, and HLA-DP. *Hum Immunol.* 2007;68(1):12-25.
14. Wiebe C, Nickerson P. Strategic use of epitope matching to improve outcomes. *Transplantation.* 2016;100(10):2048-2052.
15. Wiebe C, Pochinco D, Blydt-Hansen TD, et al. Class II HLA epitope matching—a strategy to minimize de novo donor-specific antibody development and improve outcomes. *Am J Transplant.* 2013;13(12):3114-3122.
16. Sapir-Pichhadze R, Tinckam K, Quach K, et al. HLA-DR and -DQ eplet mismatches and transplant glomerulopathy: a nested case-control study. *Am J Transplant.* 2015;15(1):137-148.
17. Wiebe C, Nevins TE, Robiner WN, Thomas W, Matas AJ, Nickerson PW. The synergistic effect of class II HLA epitope-mismatch and nonadherence on acute rejection and graft survival. *Am J Transplant.* 2015;15(8):2197-2202.
18. Wiebe C, Rush DN, Nevins TE, et al. Class II eplet mismatch modulates tacrolimus trough levels required to prevent donor-specific antibody development. *J Am Soc Nephrol.* Published Online: July 20, 2017 (doi:10.1681/ASN.2017030287).