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Because all Kidney Transplant Recipients are not Alike, we must Find Better Surrogates of Early, Subclinical Immunologic Injury

Carlos E Marroquin[1], **Pam Gibson**[2], **Jon Boyson**[1] **and Mark Fung** [2]

[1]*University of Vermont College of Medicine, Department of Surgery, Division of Transplant, Immunology and Hepatobiliary Surgery, Burlington VT, USA*

[2]*University of Vermont College of Medicine, Department of Pathology, Burlington VT, USA*

[*]**Corresponding author:** Carlos E Marroquin, University of Vermont College of Medicine, Department of Surgery, Division of Transplant, Immunology and Hepatobiliary Surgery, Burlington VT, USA, Tel: 802847-4774; Fax: 802847-3619; E-mail: Carlos.Marroquin@uvmhealth.org

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Transplant Recipients

Not all transplant recipients are alike. Therefore, it is impossible to imagine any given immunosuppression protocol is equally effective for all recipients. If we were to look at age-related differences, we would find differences in the nutritional fortitude of each patient. This is compounded by the natural senescence of our organ systems. Young hyper-cellular bone marrows become effaced with fatty infiltration with age. As such, the functional capacity of each person's bone marrow and health of their central and peripheral immune system is affected by both aging and a given individual's nutritional status. Moreover, aging results in progressive deconditioning that contributes to injuries and frailty and both have an effect on immunity.

Therefore, the combination of these factors: age, nutrition, conditioning, and progressive frailty have the ability to affect the amount of immunosuppression a given patient requires. Yet, we continue to wean immunosuppression based on clinical protocols. While this is the best we have, we are not using the power of the science at our disposal. It is virtually impossible to develop an accurate and effective model to predict immunity base on the previously mentioned factors. Moreover, immunosuppression is not without its risks and many patients receive too much immunosuppression resulting in opportunistic infections, life threatening malignancies and side effects that also result in injury to the allograft and increased morbidity to the host such as new onset diabetes, worsening hypertension and dyslipidemias increasing their cardiovascular mortality. Conversely, other transplant recipients receive too little immunosuppression exposing them to increased risk of ongoing insults from acute and chronic allograft injury and eventual graft loss. We should be able to find reasonable surrogates that will help wean immunosuppression and its side effects while avoiding immunologic events and premature graft loss.

Clinical acute rejection rates within the first year post transplant have been stable, around 10%, for the last decade [1]. Unfortunately, subclinical rejection episodes continue to occur over the lifespan of an allograft contributing to an appreciable five-year acute rejection incidence [2,3]. Interstitial fibrosis and tubular atrophy (IFTA) is a marker of chronic rejection secondary to ineffective immunosuppression. Programs that perform protocol biopsies suggest the incidence of IFTA is on the order of 20 to 30%, and approximately 20 to 25% of patients biopsied on biopsy protocols may be found to have subclinical rejection. While the incidence of catastrophic events is low with protocol biopsies, any graft loss or poor outcome that occurs from a protocol biopsy is unacceptable. Moreover, what we really need is to be able to follow changes over time and to be able to identify the "sweet spot" for maintenance immunosuppression that is based on an objective, non-invasive assay.

As transplant specialists, we identify our Achilles heal as the lack of organ supply and the growing disparity between supply and demand. One reason the disparity between organ supply and demand continues to grow is that many patients are being re-listed for a second, third and occasionally fourth transplant. We would argue that a critical way to impact the ever-growing disparity between supply and demand is to mitigate graft losses and the need to re-list. The new renal allocation policy is a great testament to our ability to consider the biology of transplanting beyond the technical exercise. A necessary next step is to impact graft loss by improving our ability to detect sub-clinical events and avoid weaning immunosuppression while patients are at increased risk of rejecting.

"Goldilocks" was fictional; however, the concept is real and timely in our specialty. We must be able identify the "right amount" of immunosuppression for each person. The key is finding a non-invasive approach that has high fidelity. Molecular diagnostics need to be developed to allow an individualized approach to immunosuppression that caters to the specific patient being treated in a cost effective manner. While there are still limitations to the non-invasive assays that have been developed to date, several groups have demonstrated the ability to detect acute rejection with molecular techniques using peripheral blood [4-10]. Kurian et al. recently demonstrated that peripheral blood gene expression has the capacity to distinguish between acute rejection, acute dysfunction with no rejection and a well-functioning allograft [11]. More work is critical to advancing our field as immune mediated events are a dynamic process and management of immunosuppression requires serial monitoring and establishing trends that are not provided with biopsies, but may be provided by these non-invasive assays.

In addition to using peripheral blood, some groups have effectively used urinary cell levels of mRNA to distinguish between acute cellular rejections, antibody mediated rejection and borderline rejection [12]. This group found that a three gene signature of normalized levels of CD3ε mRNA, interferon inducible protein 10 (IP-10) mRNA, and 18S rRNA could distinguish between acute rejection and no rejection [13]. Moreover, their assay was predictive and was able to distinguish between groups who went on to develop acute rejection in contrast to those who did not. In a similar fashion, Hricik et al. demonstrated that urine levels of the chemokine CXCL9 were significantly higher in patients found to have biopsy proven rejection and were non-existent in patients at low risk for a rejection episode [14]. This has the advantage of allowing one to augment the amount of immunosuppression to prevent a rejection episode and its insidious

harm before they occur. Perhaps some combination of peripheral blood and urine assays may yield the ideal positive predictive and negative predictive analyses.

It is clear we are entering a new era of molecular diagnostics based on blood and urine samples that will permit us to move away from biopsy specimens and allow us to track a patient's course more reliably. These assays will allow us to balance maintenance immunosuppression in an objective manner and minimize the risks of lethal infections and malignancies that result from over immunosuppression. As we continue to develop and advance these new non-invasive diagnostics, other factors must be evaluated such as utility, cost, delivery and clinical validation with a focus on outcomes and survival. Given the lack of funding in the current era, we will need to develop a pragmatic collaboration between the private and public sectors to bring these tools to the clinical setting.

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