Interim report

OPTN/UNOS Histocompatibility Committee Meeting
O'Hare Airport Hilton Hotel, Chicago, IL
July 19, 2007
9:00 a.m. – 4:00 p.m. (CST)

1. Orientation to OPTN/UNOS Committees and Policy Development Process. Susie Leffell PhD, chair of the Histocompatibility Committee, began the meeting by welcoming the returning members and introducing incoming members to the Committee. Lori Gore, the Histocompatibility Committee Staff Liaison, provided the Committee with a brief orientation to the OPTN, and UNOS. Ann Harper, the Histocompatibility Committee Research Liaison, briefed the Committee on the progress made towards the HRSA Program goals. Alan Leichtman, M.D., representing the Scientific Registry of Transplant Recipients (SRTR) gave a brief synopsis of the SRTR's function in relation to the OPTN, NOTA and UNOS.

2. Minutes from May 14, 2007 Committee Meeting by Teleconference. The minutes were unanimously approved. (Committee vote: 15 For, 0 Against, 0 Abstentions)

3. Membership Issues and Report from the Membership and Professional Standards Committee (MPSC). The Committee reviewed key personnel changes in UNOS-approved HLA laboratories and made recommendations for Geof Land, Ph.D. to present to the MPSC on July 31, 2006.

4. Report from the Minority Affairs Committee (MAC). Steve Geier, PhD attended the MAC meeting on July 12, 2007. He reported that Ron Kerman Ph.D., Director of a Histocompatibility Laboratory in Texas (TXTH) made a presentation to the MAC, stating that the implementation of the calculated PRA (CPRA) would be a "further obstacle to minorities" who, in his opinion, are already are disadvantaged by OPTN/UNOS allocation policy. Dr. Kerman cited two abstracts that showed that a presence of donor specific antibody (DSA) in the face of a negative flow crossmatch had no adverse effect on kidney graft outcome. The first abstract, from the University of Texas, reported 44 candidates who had DSA and a negative cytotoxic and flow crossmatch against the kidney donor. These positive DSA/negative crossmatch recipients experienced an 11 percent incidence of rejection and had 91 percent allograft survival at one year, which was not different from those candidates who lacked DSA. The second study was from the UK; it reported similar results in 36 candidates with positive DSA and negative crossmatch. Both papers reported there was no higher incidence of delayed graft function, no difference in renal function, and no significant impact on graft survival of the recipients with positive DSA compared with those who lacked DSA. Dr. Kerman said these data were relevant to the MAC, since over 57 percent of those candidates who had DSA and negative crossmatches were minorities or women. He explained that the implementation of CPRA would require centers to list unacceptable antigens for their candidates prior to running a list of potential recipients. This could screen candidates from a kidney offer that may have viable results. Dr. Kerman believes this screening is a further obstacle to minorities who are already disadvantaged. He urged the MAC to exam the emerging data on the relevance of DSA and stop the implementation of a policy that he feels unfairly disenfranchises those who would seek an organ transplant.

   Dr. Geier responded to Dr. Kerman's assertions by explaining that the choice and criteria for listing unacceptable antigens are up to each center. Centers should only list as unacceptable those antigens that by their criteria would be a contraindication to transplant, whether that is by a likely positive CDC or flow crossmatch. He reported that, with a little experience in using solid phase assays, most laboratories should be able to gauge reactivity levels that will likely result in positive crossmatches.

   Secondly, Dr. Geier said, it should be remembered that only those candidates with CPRAs of 80 or higher will receive additional four points. Because minority candidates, particularly African

Americans, are generally sensitized to antigens common in the donor pool, they would benefit from the use of CPRA.

Dr. Geier reported the MAC received his comments favorably and as a whole supported the implementation of CPRA. He emphasized that the experience did illustrate the point that the Histocompatibility Committee needs to provide better education to the laboratories and centers about the implications of CPRA because there are misconceptions in the transplant community.

5. Response to Proposal out for public comment. The Committee reviewed the proposals that were out for public comment and choose to respond the Proposed Modifications to OPTN/UNOS Policy 4.0 (Acquired Immune Deficiency Syndrome (AIDS), Human Pituitary Derived Growth (HPDGH), and Reporting of Potential Recipient Diseases or Medical Conditions, including Malignancies, of Donor Origin. This proposal originated from the Operations Committee.

   The Committee opined that the intent of the proposal for Policy 4.0 was good, but failed to clarify the need to bring the standards of organ donor screening up to the level required for blood, tissue, progenitor cells and reproductive cells and tissues. Dr. Geier said this is the expectation of the community and a stated goal of many national and international medical and professional organizations and government agencies. He went on to say standardized donor screening should be completed prior to kidney transplantation. The Committee also said Policy 4.0 cannot be effective without appropriate modifications to Policy 2.0 (Minimum Procurement Standards for an Organ Procurement Organization (OPO).

   The Histocompatibility Committee did not support this proposal and appointed Dr. Geier and Dr. Eisenbrey to write an official response to the Operations Committee.

   Committee vote: 14 For, 0 Against, 0 Abstentions

6. Request for Incorporating CPRA into an Existing Alternative System for Kidneys.

   The OPTN/UNOS Board approved the following resolution in November 2006:

   > ** RESOLVED, that the modifications to Policy 3.5.11.3 (Panel Reactive Antibody) approved by the Board of Directors shall pertain to all OPOs operating with approved alternative systems for assigning priority in sensitized kidney candidates as well as the national kidney allocation system, unless application is made by an OPO to incorporate the use of a Calculated PRA (CPRA) into its existing alternative system. Such applications must be made in accordance with Policy 3.4.7.1 and be presented to the Histocompatibility Committee no later than February 1, 2007. OPOs may maintain the components of alternative systems that are not affected by the Histocompatibility Committee's implementation of CPRA as set forth in Policy 3.5.11.3

   Therefore, an OPO wanting to continue its alternative system for the allotment of sensitization points was required to make a formal request to continue its alternative system incorporating CPRA. Otherwise, an alternative system for assigning priority in sensitized candidates would convert to the national system described in Policy 3.5.11.3.

   The Tennessee Transplant Society (TTS), which uses a statewide sharing agreement for the allocation of kidneys, made a formal request to the OPTN/UNOS Histocompatibility Committee to incorporate CPRA into its alternative system. Currently, Tennessee gives four points to kidney transplant candidates with a PRA of 80 percent or higher, as is done in the national allocation system. TTS also assigns 2 points to candidates with a PRA of 40-79 percent.

   Request for Incorporating CPRA into an Existing Alternative System for Kidneys

Sensitized kidney waiting list candidates within the state of Tennessee with defined unacceptable HLA antigens that yield an 80 percent or greater probability of incompatibility with deceased donors (CPRA) would be assigned four points; and those candidates that have a CPRA value between 40 percent-79 percent will be assigned two points. This is of interest to the Histocompatibility and Kidney Committees because a gradation of points for PRA greater than 20 percent is being considered as part of the new kidney allocation proposal. The Histocompatibility Committee noted that this request is in the spirit intended for variances, because it is designed to test a specific research question for a specified period of time, as shown below.

The proposed alternative system is expected to be in place for a maximum of three years or until the OPTN/UNOS Kidney Transplantation Committee implements the new Kidney Allocation System, which is currently under development. The Histocompatibility and Kidney Committees will then analyze the alternative system and will make a request to the Board of Directors to continue, modify, or terminate the system.

The Histo Committee formed a subcommittee to write the responses to public comment. Dr. Eisenbrey, Mr. Hart and Mr. Friedlander volunteered.

7. Report from the Kidney and Pancreas Transplantation Committees Dr. Leffell, a member of both the Kidney and Pancreas Committees, updated the Histocompatibility Committee about the meetings of those Committees throughout the year. She reported that the emphasis of the Kidney Committee continues to be the development of a revised kidney allocation policy. In an effort to educate the new members of the Histocompatibility, she reviewed the history of the development plus some of the likely changes that will be occurring with the new kidney allocation system. She emphasized that the work on the actual proposal continues.

   Dr. Leichtman suggested to the Histocompatibility Committee that he believed the Kidney Committee was concerned that centers could manipulate the CPRA values of highly sensitized candidates in an effort to "game" the system. He expressed the concern that a center could choose to inadequately list the unacceptables used to calculate a candidates CPRA value and such a candidate would act as a "magnet," drawing organ offers that would most likely not be used in the intended recipient because of positive crossmatch. He said he believed this feeling was so strong within the transplant community that he was afraid it could "derail" the CPRA policy and advised the Committee to be proactive in fighting this perception.

   Dr. Leffell reminded the Committee that there are safe guards in place that would prevent that scenario from occurring. In order for a candidate to receive four points the center must list unacceptable antigens that would exclude the candidate from 80 percent of all organ offers. She said this number, in reality, would most likely be higher due to the effect of ABO compatibility. Secondly, the Histocompatibility Committee will monitor cases when an organ intended for a candidate was not placed with that candidate because of a positive crossmatch. She suggested that the Committee may consider a future proposal requiring that, when an organ is not placed with its intended recipient because of a positive cross match, every effort should be made to define the antigen that caused the positive reaction and require it be listed as an unacceptable.

   Dr. Baxter-Lowe expressed concern the cost of identifying unacceptable antigens would have on the national health care system. She said her laboratory was concerned that the cost of reagents could be prohibitively expensive, especially because her center has a very large waiting list.

   Dr. Leffell noted that the CPRA policy only requires the use of one solid phase test to identify unacceptable antigens. She suggested that a combination of tests be used to first identify the most sensitized candidates. The expensive tests would be used only for those candidates that warranted a more precise workup. She said her laboratory has been using this approach with success. Another approach might be to only do the expensive testing on those candidates who were near the top of the list and might realistically receive an organ offer. Several Committee members voiced the opinion that

laboratories are obligated to use the best technology available to serve their patients and suggested that the increased cost was justified.

Because of its ongoing work with the Kidney Committee to incorporate the sensitized candidate into the new kidney allocation scheme, the Committee reviewed the results of the latest simulation models made by the SRTR for the Kidney Committee. Dr. Leichtman presented the modeling results provided to the Kidney Committee at its meeting on May 20-21, 2007.

Dr. Leichtman said the Kidney Committee continued to explore the concept of life years following transplant (LYFT) as a component of a new allocation system. The Committee reviewed results that incorporated the concept of a continuous donor profile index (DPI). The DPI score for each donor would provide more information to patients and providers about the quality of donor kidneys. The Committee also examined possible alternative approaches to kidney allocation. Among these alternatives was an approach to divide candidates and donors into five categories (quintiles). These categories would provide a way of matching donors and recipients and would also facilitate more predictable waitlist management The Committee also examined an approach that would match candidates and donors based on age. Age matching and use of a DPI were suggestions made by participants at the February 2007 public forum held in Dallas, Texas.

Dr. Leichtman asked the Histocompatibility Committee if they had any requests they would like the SRTR to model. Dr. Baxter-Lowe asked if the SRTR had examined the long term effects of retransplantation on candidate sensitization. Dr. Leichtman answered that the SRTR was currently trying to understand the short term differences between the new and current system. As the Kidney Committee gets closer to forming a proposal, the SRTR plans to model the long-term impact of such variables as retransplantaion.

8. Research Requests to the SRTR The Histocompatibility Committee has proposed that CPRA be used as a factor for prorating sensitized candidates and be incorporated into the system for renal allocation by addition to the Life Years From Transplant (LYFT) score, plus any other modifications to the score, such as prorated waiting time. The allocation values for sensitized candidates would be derived by the following formula: CPRA x "Factor X" + LYFT score.

   The advantages of this approach include awarding some additional priority for low to moderately sensitized candidates who also experience reduced access to transplantation and a continuous ranking of sensitized candidates in contrast to current system with an arbitrary cut off at a PRAof 80.

   The Committee requested an analysis of incorporation of CPRA in the models under discussion for possible revisions to renal allocation. However, in lieu of CPRA, which will not be available until after the revised PRA policy is implemented, the Committee recommended using the Peak PRA values in the registry database
   As a value for "Factor X", the Committee recommended starting with 4, which is the value currently used for candidates with PRAs of 80 or greater. The upper range of CPRAs that would receive points should not be limited to 80 percent, but other ranges should be tested (i.e., up to 100 percent); the lower bound could be tested at ranges such as 0 percent, 10 percent and 20 percent. As such, this would be a "sliding scale." The Committee recommends testing of other values to determine if there is a more appropriate, perhaps, lesser value that would award priority to sensitized candidates without bypassing non-sensitized candidates with equivalent or better LYFT scores. In this regard, the impact of waiting time must be considered, as highly sensitized candidates will often have substantial waiting time accrued.

   The Committee further recommended that data for these studies be limited to recent years, preferably the last five years. The introduction of solid phase immunoassays for antibody analyses has increased the sensitivity of antibody detection greatly. Currently, more than 30 percent of the waiting list candidates are sensitized and over 14 percent of these are highly sensitized with PRAs $\geq$ 80. Any simulations should reflect this proportion of sensitized candidates, therefore, the Committee said older data, obtained with less sensitive methods should not be used.

9. Collaboration with American Society of Histocompatibility and Immunogenetics (ASHI) and other professional organizations Dr. Leffell reported on a recent conference call she had with Karen Nelson, President; and Carol Pancoska, President-elect of ASHI. She assured them that the Histocompatibility Committee is eager to collaborate with ASHI in moving forward on issues of mutual concern between the organizations.

   Dr. Leffell reported ASHI is seeking funding for a national conference on the identification of HLA-specific antibodies and its application in clinical transplantation. As previously discussed, this is a vital area of mutual concern. She affirmed that the Histocompatibility Committee will enthusiastically endorse this initiative, and would like to help with the planning and implementation of the conference.

   Another goal of the Histocompatibility Committee is a set of guidelines and suggestions for the assignment of unacceptable antigens, which would be a useful educational tool for Histocompatibility laboratory personnel. The Committee will begin considering such guidelines during the coming year and will ask for input from ASHI.

   Dr. Land volunteered to serve as the liaison to the ASHI Board of Directors, in order to facilitate timely communication and collaboration. Dr. Eisenbrey agreed to serve as the liaison to the College of American Pathologists (CAP). Dr. Leffell said Dr. Allen Norin of ASHI had asked for Committee input on the ASHI Scientific Affairs Committee's consideration of histocompatibility testing guidelines for paired kidney donation programs. John M. Hart and Michael Gautreaux, Ph.D. volunteered as liaisons from the Committee to the ASHI Scientific Affairs Committee. Dr. Leffell also offered to share the draft guidelines for paired donation with Dr. Norin. These had been under consideration by the Histocompatibility Committee prior to the moratorium on paired donation. A recent ruling from the Justice Department found that paired donation programs do not violate the NOTA.

10. Implementation of Policy 3.5.11.3 Calculated Panel Reactive Antibody (CPRA). The Board approved the Histocompatibility Committee's proposed modifications to policy 3.5.11.3 at its December 2006 meeting. As a result, CPRA will replace PRA when determining kidney allocation.

    The Histocompatibility Committee recommended that implementation happen in three phases:

    - Phase One, allocation continues to be based on traditional PRA. OPOs, transplant centers, and HLA laboratories will be able to calculate and see CPRA on match runs. The CPRA calculator will become available to members at this time.

    - Phase Two, allocation will be based on CPRA. OPOs, transplants centers, and HLA laboratories will be able to enter and see traditional PRA on the waitlist if desired.

    - Phase Three, allocation is based on CPRA. Traditional PRA information will no longer appear on the waitlist.

    Dielita McKnight, from the UNOS IT Department, reported that programming for Policy 3.5.11.3 (CPRA) was on schedule. Phase One is scheduled to be implemented in fall 2007.

    The Committee decided that a specific timeframe should not be set between the implementation of Phase One and Phase Two. Rather, the Committee plans to monitor the reaction of the transplant community and the results of the implementation of Phase One before moving on to Phase Two.

    Dr. Diane Kumashiro and Dr. Lee Ann Baxter-Lowe volunteered to serve on the implementation subcommittee.

11. UNOS Research request The Histocompatibility Committee asked the UNOS Research Department to provide an analysis of the results of CPPA once CPRA (Phase I) has been implemented and

sufficient data have accumulated. The Committee would like to review a comparison of traditional PRA versus CPRA values by ethnicity, DSA, and other relevant factors. The Committee has also asked for an analysis of CPRA by Class I and Class II antibodies.

12. Memo to transplant community concerning the implementation of CPRA The Committee is aware of misconceptions within the transplant community surrounding the implementation of CPRA. Therefore, a notice will be sent to advise Transplant Centers and HLA laboratories of the anticipated time line for implementation of CPRA and to provide suggestions for centers to consider in setting their criteria for listing of unacceptable antigens.Dr. Leffell said this memo should include:

    a. Considerations for Criteria for Unacceptable Antigens

        i. Every Transplant Center has the right and responsibility to set criteria for the listing of unacceptable antigens in accordance with its clinical protocols. The CPRA is not intended to serve as a "virtual crossmatch". The intent is to eliminate candidates from match runs with donors who would not be compatible based on the Center's acceptance criteria. It is a requirement that HLA laboratories use at least one solid phase immunoassay in their antibody analyses, but it is ***not*** a requirement to list every HLA antigen to which a given candidate may have antibodies as unacceptable.

        ii. It is recommended that members of HLA laboratories meet with the transplant physicians and surgeons and determine what will constitute a contraindication to transplantation. Unacceptable antigen criteria can then be set accordingly. Using solid phase assays, many laboratories are defining the levels of reactivity that correspond to positive crossmatch tests in different assays. As an example, median fluorescence intensity (MFI) values can be correlated with flow cytometric or cytotoxicity crossmatch reactivity. Then, if a center's criterion for transplantation is a negative cytotoxicity crossmatch, only those antigens predicted to yield a positive cytotoxicity crossmatch would be listed as unacceptable. Conversely, if a center has very stringent criteria for acceptable crossmatch results, antigens to which there are only low levels of antibody could also be considered as unacceptable.

    b. CPRA Implementation

        i. CPRA will be implemented in three phases. Depending upon the completion of programming, the first phase will occur this in fall 2007. During the first phase, allocation will continue to be based on the traditional PRA, but the CPRA will also be listed on match runs. A "CPRA Calculator" will be available to transplant professionals through UNET and to candidates through the Transplant Living website. The first phase is anticipated to last from 3-6 months. In Phase Two, allocation will be based on CPRA, but the traditional PRA can still be entered and viewed on the wait list for comparison. In Phase Three, allocation will be based on CPRA and the traditional PRA information will no longer appear on the wait list. During all three phases, a joint Committee comprised of members from the Histocompatibility, Kidney Transplant, and Pancreas Transplant Committees will review listings of unacceptable antigens, comparisons of PRA and CPRA, and the incidence of unexpected crossmatch results (phases two and three). If there are any problems, the joint Committee will recommend changes in the policy and/or CPRA program.

- Analysis of Discrepant HLA Typings The Committee discussed the UNet^{SM} Discrepant HLA Typing report, as referenced in OPTN Policy Appendix 3C. Laboratories are asked to use this report to resolve discrepant donor and recipient HLA typings. A brief OPTN analysis revealed that 2,787 donor records and 2,079 recipient records were unresolved at this time. It also showed that the report was not working as intended, and that it was not being used by many laboratories. Several Committee members said that they did not know the report existed. Ms. Gore asked the

Committee for direction regarding the report, and a review of the original intent of and current need for the report. Given the high number of unresolved discrepancies shown, the Committee opined that the programming problems within the report should be resolved. The Committee also agreed that once the UNet[SM] report has been modified, laboratories should be notified that they are to resume using the report. Dr. Baxter-Lowe said UNOS should send out a systems notice reminding HLA laboratories of the existence of the report and remind them that the Histocompatibility Committee will be reviewing the unresolved discrepant HLA typings found annually.

13. Additional Unacceptable Antigen Equivalences to be used in the Calculated PRA (CPRA) The unacceptable antigen equivalence table approved for use in the renal allocation system (Appendix 3A) does not include equivalences for Bw4, Bw6, DR51, DR52, and DR53. However, equivalences are needed for these in order to calculate the CPRA. Therefore, the Committee approved a request that Appendix 3A be amended to include the following unacceptable equivalence table, which would be used solely in the calculation of the CPRA.

Additional Unacceptable Antigen Equivalences to be used in the Calculated PRA Only
Bw4: B5, B13, B17,B27, B37, B38, B44, B47, B49, B51,B52, B53, B57, B58, B59, B63, B77
Bw6: B7, B8, B14, B18, B22, B35, B39, B40, B41, B42, B45, B46, B48, B50 (B*4005), B54, B55, B56, B60, B61, B62, B64, B65, B67, B70, B71, B72, B73, B75, B76, B78, B81
DR51: DR2, DR15, DR16
Dr52: DR3, DR5, DR6, DR11, DR12, DR13, DR14, DR17, DR18
Dr53: DR 4, DR7, DR9

(Committee vote: 15 For, 0 Against, 0 Abstentions)

14. Requests from members. The Committee received request from a member that the HLA antigen data fields in UNet (both for renal recipients and organ donors) be modified to (1) accept molecular nomenclature in addition to the serologic nomenclature and (2) that the molecular nomenclature would automatically convert to the serologic equivalents when generating a match run.

Several members of the Committee thought this was an excellent suggestion. The Committee reviewed and approved these ideas in concept. Incorporation of molecular nomenclature with automatic conversion to serologic equivalents would, however, require substantial programming. The Committee designated a sub-Committee that would consider the suggestions further and will specifically address the requirements and potential time line for possible implementation. Drs. Eisenbrey and Baxter-Lowe volunteered to work on this subcommittee.

The Committee also received a request to clarify the reporting of the null allele in the UNet system. The Committee discussed the issue of reporting DR53 when the DRB4*0103n allele cannot be excluded as a possible assignment. The Committee appreciates the problem that arises when a low resolution typing platform cannot confirm either the presence or absence of an allele. The Committee also agrees that, while linkage disequilibrium information is helpful in making assignments, it should not be considered as definitive. However, reporting the presence of an antigen when a null allele is in fact present is more problematic, since it could exclude candidates from consideration in donor allocation.

The Committee agrees with the recent policy adopted by the ASHI Accreditation Review Board that will require resolution of certain frequently observed null alleles, including DRB4*0103n. This policy is currently only recommended by ASHI, but it is their intention to make this a requirement once there has been sufficient time for laboratories to come into compliance. The Histocompatibility Committee will likely follow suit and require resolution of these null alleles. Therefore, it is the recommendation of the Committee to pursue expansion of typing platforms to include these alleles.

15. New Business

Dr. Leffell asked the Committee to consider developing a policy that would require transplant centers to share the data from candidates who have been transferred from one center to another. This information would include previous transplant HLA and previous PRA. The problem that the Committee wished to address is that some laboratories do not maintain data or will not share it in a timely fashion. Dr. Land mentioned that institutions are confused about HIPAA regulations and patient confidentiality. The Committee agreed that there was a need for a policy proposal.

Dr. Leffell first asked if the Committee thought it should require that laboratories maintain histocompatibility records on transplanted candidates for the life of that candidate and that these records must be provided to the laboratory of another transplant center in the event that the candidates transfers to another center.

Committee members said they thought this requirement would place too much of a burden on the transplant center. The Committee opined that patient records should only be kept for the amount of time that the government or the Clinical Laboratory Improvement Amendments (CLIA) requires.

Dr. Leffell then asked the Committee if laboratories should be required to share historic serum samples for candidates that transfer to another center. The Committee felt that it could "highly recommend" that laboratories facilitate re-transplantation of transfer candidates by sharing historic serum samples when appropriate, but that it should not be required.

The Committee voted to move forward with the proposal, but in the interest of time tabled further discussion till the next meeting.

Dr. Leffell asked the Committee if they wished to develop a Committee-sponsored alternative system for kidney candidates who have under gone a desentization protocol. Members of the Committee said they would like to see what the need for such a proposal was before the moving forward. Dr. Leffell said she would contact Stan Jordan, M.D. of Cedar- Sinai Medical Center in Los Angles, who made the initial request for an alternative system, to discuss the scope of the issue. In the interest of time further discussion was tabled.