Transplant Clinical Research Program

The advances achieved in transplantation over just a few decades have been incredible. Once viewed as a high risk, experimental procedure with less than optimal results, transplantation today is a routine procedure that offers many a new hope for a better and longer life. Underpinning all the advances to date, as well as all the hope for future advances, is research.

The foundation of our transplant center’s clinical research effort is our Clinical Research Program, which provides a ready infrastructure to facilitate the investigative efforts of our faculty. Initially started 15 years ago when the first research coordinator was charged with a study evaluating a new formulation of cyclosporine in kidney transplant recipients, our Clinical Research Program has grown and now consists of 7 research coordinators, a financial administrator, and a clinical research manager. Investigators from the Departments of Medicine, Surgery, Pediatrics as well as the College of Pharmacy, have all benefited from this resource, and studies have spanned all our transplant programs (Kidney, Liver, Pancreas, Heart, and Lung). While oversight of every individual research study is the responsibility of each lead investigator, Drs Diane Cibrik and John Magee serve as co-directors of the program, providing leadership in formulating policy and strategic planning. At present, the Clinical Research Program is involved in 22 active studies, 15 of which are currently enrolling patients. This translates to nearly 300 patients currently enrolled in studies in our transplant programs. Combined, these studies represent a total budget of approximately 4 million dollars. Current studies include...
Carrying out research involving patients is complex. Patient safety is paramount, and ethical concerns are ever present. Additionally, there are substantial regulatory requirements which must be followed. Providing a clear delineation of what constitutes standard clinical care vs. research is an increasingly important distinction, particularly with respect to the financial aspects of the research endeavor. I believe our group serves as a model of how research can be responsibly conducted. Indeed, members of our team have helped contribute to ongoing institutional efforts to examine how to better differentiate clinical and research costs.

While substantial challenges exist, the benefits of these research efforts are many. In addition to contributing to a better understanding of how to care for transplant patients, our research coordinators provide an extra set of eyes regarding clinical issues related to patients involved in studies, and an extra set of sympathetic ears for patient concerns. Additionally, participation in research provides our faculty with access to the newest knowledge and carefully controlled experience with the newest agents. The success of our Clinical Research Program rests on the hard work of well trained and dedicated professionals. We are fortunate to have them.

– John Magee, M.D.
Barbara has worked at the University of Michigan for more than 20 years; joining the transplant research team in 1995. She received her B.S. in Biology from Eastern Michigan University. When not working, Barb enjoys spending time with her son, painting still-life pictures and landscapes, quilting, reading, and listening to Reggae music.

Doug began his career at the University of Michigan in 1987, starting in Survival Flight and transferring to the Transplant Program in 1992. He received his B.A. in Biochemistry from Albion College, his BS degree in Nursing from Wayne State University, and his M.S. degree from the University of Michigan Public Health School. Doug is also the Director and co-founder of Camp Michitanki, a one-week summer camp for children who have received organ transplants. Doug is a new father (June 2006) and has put his travel, golf and volunteer firefighting activities on hold so he can spend more time with his new son.

Julie received her B.S. degree in Biology from the University of Michigan. She has worked with the transplant program since 1994 and in Transplant Clinical Research since 1997. When she's not busy coordinating research studies, she enjoys playing the cello with the Ypsilanti Symphony Orchestra, reading, and spending time with her husband and two cats.

Diane received her B.S. degree in Zoology and M.S. degree in Natural Resources from the University of Michigan. She started at the University Hospital in Emergency Services in 1983, worked in Pediatric Nephrology for five years and has been with Transplant since 2000. With three of her four children in college, Diane hopes to have more time for soccer, softball and reading plus volunteering as a Master Gardener and docent for Nichols Arboretum.

Peggy has worked at the University of Michigan for more than 17 years, joining the Transplant Research team in 1994. Peggy enjoys spending time with her two children, outdoor activities, and quilting.

Terri received her B.S. degree in Microbiology and Chemistry from Eastern Michigan University in 1985. Terri started at the University of Michigan in 1991, transferring to the Transplant Research Laboratoy in 1993. Terri began coordinating clinical trials in 1998. Terri is a member of the Association of Clinical Research Professionals and the American Association for the Study of Liver Diseases. In her spare time, Terri enjoys camping, fishing, snowmobiling and watching NASCAR with her fiancé Mitch. She also enjoys reading, gardening, beading, scrap booking and playing with her Weimaraner, Gunner, and her two cats, Sophie and Malcolm.

Darlene received her B.S. degree in Chemistry from Albion College and her Associates in Nursing from Washtenaw Community College. She joined the Transplant Center as a staff nurse in 1990 and transferred to Transplant Research in 1999. She enjoys spending time with her husband, son and 3 stepchildren. She also enjoys gardening, quilting, going to hockey, football and baseball games and playing with her dog, Bobby.

Jake received his BS degree in Nursing from Eastern Michigan University. He has worked for the University of Michigan for almost 5 years, transferring to Transplant Research three years ago. Jake recently built a house in the Pinckney area. Some of his interests include fishing, canoeing, skeet shooting, and skiing. He plans to learn how to snowboard next winter. Jake has been married for two years. He and his wife like to spend their time traveling and visiting friends and family.

Peggy received her B.S. degree in Microbiology and Chemistry from Eastern Michigan University in 1985. Peggy started at the University of Michigan in 1991, transferring to the Transplant Research Laboratoy in 1993. Peggy began coordinating clinical trials in 1998. Peggy is a member of the Association of Clinical Research Professionals and the American Association for the Study of Liver Diseases. In her spare time, Peggy enjoys camping, fishing, snowmobiling and watching NASCAR with her fiancé Mitch. She also enjoys reading, gardening, beading, scrap booking and playing with her Weimaraner, Gunner, and her two cats, Sophie and Malcolm.
Research on Female Transplant Outcomes and Noninvasive Methods of Diagnosing Acute Rejection

Dr. Diane Cibrik’s area of research focuses on female transplant outcomes and noninvasive methods of diagnosing acute rejection.

Previous studies have shown that post-menopausal females progress to end-stage renal disease faster than pre-menopausal women. In addition, female renal transplant patients have less chronic rejection than male renal transplant patients even though female renal transplant patients have more acute rejection, which is the major risk factor for developing chronic rejection. Gender differences are also seen in animal transplant models of chronic rejection. The goal of Dr. Cibrik’s research is to determine the factors that protect female renal transplant recipients from chronic rejection. Currently, she is surveying female transplant recipients on their gynecological history pre- and post-transplant and collecting hormone levels on these patients. This research is supported by a K12 BIRCWH scholar grant.

Dr. Cibrik has a long interest in noninvasive methods of diagnosing acute rejection. The gold standard of diagnosing acute rejection in renal transplant patients is a renal transplant biopsy which has potential risks including bleeding after the biopsy and loss of the transplant. In addition, patients cannot be followed longitudinally with this method. Along with Marielle Delnomdedieu, Ph.D. at Pfizer and Kent Johnson M.D. in Pathology, they are able to differentiate healthy individuals from renal transplant patients by urine NMR spectroscopy with multivariate analysis. More importantly, they are able to differentiate renal transplant patients with rejection from non-rejecting transplant recipients. Since urine NMR spectroscopy is noninvasive, renal transplant patients can be monitored longitudinally. With treatment of rejection, the urine spectrum from rejecting renal transplant patients returns to “normal” or the spectrum of non-rejecting renal transplant recipients. The current results of the study have been submitted for publication.

– Diane Cibrik, M.D.
The main obstacle to organ transplantation is graft rejection mediated by the immune system. There are two forms of graft rejection that may occur when T cells, the lymphocytes that orchestrate the immune system, recognize the transplant as foreign. **Acute rejection** generally occurs within the first year post-transplant and is a direct attack on the transplant by the immune system, resulting in destruction of the graft. Acute rejection can generally be controlled by additional immunosuppressive drugs. **Chronic rejection** is the major cause of late graft failure and is believed to result from low grade acute rejection episodes and resembles a wound healing process. As such, chronic rejection results in the scarring or “fibrosis” of the transplant, leading to the gradual loss of graft function. At present, the only effective therapy is re-transplantation – no current medications can prevent or reverse the disease process.

T cells are critical for the development of both acute and chronic rejection. However, the mechanisms by which T cells mediate acute graft damage and chronic fibrosis of the graft are not understood. T cells are capable of mediating multiple destructive “effector functions” but are also capable of developing into immunosuppressive or “regulatory T cells” which are beneficial in the setting of transplantation. A major focus of our research is determining how to prevent the development of deleterious T cell effector functions while promoting the development of beneficial regulatory T cells. Continued research will be required to fully understand these processes and to determine whether these findings may be translated clinically to human transplant patients.

The development of regulatory T cells is promoted by the immunosuppressive cytokine, transforming growth factor beta (TGFβ). In addition, regulatory T cells mediate their suppressive function in part through the secretion of TGFβ. Hence, TGFβ has beneficial activities in the transplant setting. However, the dark side of TGFβ is that it promotes fibrosis. Indeed, we have recently published that TGFβ production is tightly associated with the development of chronic rejection. The important hypothesis that we are exploring is whether the beneficial suppressive activities of TGFβ may be spared while eliminating the fibrosis-inducing activities of TGFβ. We have also reported that TGFβ mediated chronic rejection is associated with the production of an additional cytokine, connective tissue growth factor (CTGF). CTGF is induced by TGFβ and is responsible for the fibrotic activity of TGFβ. Importantly, CTGF is not responsible for the immunosuppressive activities of TGFβ. Future studies will test the exciting possibility that selective targeting of CTGF may serve as a therapeutic tool for preventing chronic graft rejection while sparing the beneficial suppressive activities of TGFβ.

Our research is also focusing on translating our findings in the experimental mouse transplant model to the human transplantation. While experimental models are essential in identifying immune mechanisms that are critical to graft acceptance vs. rejection, the application of this knowledge to the clinical setting must be verified. Currently, we are unable to predict which recipients will experience acute and/or chronic rejection. The identification of reliable predictors of these processes could provide valuable information to guide post-transplant management. For example, the presence of immune indicators of rejection may dictate a more aggressive approach to immunosuppression while the absence of these indicators may indicate that the level of immunosuppression a patient receives may be reduced. These studies will require close interactions between the Transplant Immunology Research Laboratory and the transplant surgeons and physicians.

– D. Keith Bishop, Ph.D.
The Data Coordinating Center (DCC) for a large multi-center study of adult-to-adult living donor liver transplantation (AALDL T) resides here at the University of Michigan under the leadership of its principal investigator, transplant surgeon Robert M. Merion, MD. The study is sponsored by the National Institutes of Health and is the first large study of living donor liver transplantation in the country.

Prior to 1998, living liver donation was predominantly used for pediatric liver transplantation; when an adult donates a portion of his or her liver to a child. The liver is the only organ that will grow after donation and transplantation. The remnant liver regenerates in the donor, and the donated portion grows in the recipient. As the number of adults on the transplant waiting list grew, many were dying while waiting for a liver from a deceased donor. Caregivers began to seek new options for their patients, and in the late 1990's surgeons did the first adult-to-adult living donor liver transplant. Although still a small number relative to the several thousand adult deceased donor liver transplants performed annually, AALDLT is changing the face of liver transplantation. Too few cases have been performed at any one center and approaches to the patient and donor were too diverse across centers to provide generalized information on donor and recipient outcomes from individual centers.

In 2002, Dr. Merion and his team competed with other groups across the country to become the DCC for the Adult-to-Adult Living Donor Transplantation Cohort Study (A2ALL). The University of Michigan was awarded the 7-year grant. The information collected in this study is needed to aid decisions made by physicians, patients, and potential donors. Along with the DCC, there are 9 clinical transplant centers from across the country participating in this groundbreaking research consortium. The study is researching outcomes associated with recipients of living donor liver transplant compared to those who either received a deceased donor transplant and those who did not receive a transplant. For living liver donors, the researchers are evaluating medical outcomes and quality of life following donation. The group
Dr. Englesbe, the lead author of the article, says that he and Dr. Campbell have received a lot of feedback from centers interested in participating in a pilot network of Transplant Centers that would establish the framework for a national program. However, not all members of the Transplant community support the need for such a program, and many are concerned about who will pay for the infrastructure that such a network would require. Englesbe and his group point to data showing that improvements in quality have consistently resulted in decreased costs for hospitals and insurance companies. It is his hope that these groups will be willing to underwrite the cost of a national program in order to reduce their own costs. Many large insurance companies have already demonstrated their interest in this concept by funding similar projects aimed at improving the quality of medical care, while reducing the cost of care at the same time.

– Jeffrey D. Punch, M.D.

A2ALL Study continued from page 6

has completed a retrospective study of outcomes of recipient and donor candidates from 1998 through 2003, and has begun a prospective study that will collect data from 2003 through 2009. There are currently more than 1,000 subjects enrolled in the main study.

The DCC’s role is vital in developing common protocols, an innovative web-based data entry and bio sample tracking system, and a study website. The website (www.nih-a2all.org) has information for patients and their families to learn more about the study and its research goals.

Another critical role of the A2ALL DCC is overseeing the collection and maintenance and performing the statistical analysis of the complex data that is produced by the study. There are over 20,000 unique variables in the main study. The DCC’s analysis has enabled the researchers to begin to answer their research questions and share those results with colleagues. Several abstracts and manuscripts have been published and presented at national meetings. These findings have been met with critical acclaim by the hepatology and transplantation communities.

Vita Redita – Life Restored

The Vita Redita (which means Life Restored) is an annual Black Tie Dinner and Auction which benefits the University of Michigan Transplant Center.

The event is being held at the Polo Fields Golf and Country Club of Ann Arbor at 6 p.m. on September 30, 2006. For further information or to purchase tickets to attend this enjoyable event, please contact Crystal Sprang at 734-936-0351.
On April 11, 2006, Secretary of State Terri Lynn Land honored renal transplant physician Alan Leichtman of the University of Michigan Health System with a Shining Star award in recognition of his “exemplary leadership” in organ and tissue donation. Many friends, associates and colleagues attended the ceremony to witness the award presentation and show their respect for Dr. Leichtman’s accomplishments. T. Anthony Denton, senior associate director and chief operating officer for the University of Michigan Hospitals and Health Center, opened the ceremony expressing his pleasure in representing the University of Michigan Health System, in introducing Secretary Land, and in joining her to recognize the important efforts of Dr. Leichtman.

Secretary Land created the Shining Star award to acknowledge those whose exceptional efforts encourage greater organ donor awareness.

“Out of many deserving candidates, Dr. Leichtman was chosen because of his exemplary leadership in organ donation,” said Land. “He is a recognized expert in transplantation and has increased awareness of the importance of participation in donor registries. He has also worked to improve the fairness of the apportionment process for the thousands of people who are waiting for transplants.”

Dr. Leichtman is a professor of internal medicine and has been medical director of transplantation for the kidney/pancreas program at the University of Michigan since 1989. He is director of the UM Transplant Nephrology Fellowship Training Program and a member of the UM Transplant Center Executive Committee.

He was appointed to chair the Organ and Procurement Transplant Network’s Kidney and Pancreas Transplantation Committee, which is the principal committee advising the federal government and the national organ procurement group that directs kidney and pancreas allocation policy. He is also one of seven co-principal investigators for the Scientific Registry of Transplant Recipients, which tracks outcomes and compiles statistics of transplant programs and organ procurement organizations and reports annually on the state of transplantation in the United States. Leichtman has co-authored numerous articles in the area of renal transplantation. He earned his medical degree from Michigan State University in 1978.

Dr. Leichtman was nominated by Dr. Timothy J. Laing, associate professor and vice chair of the Department of Internal Medicine at the University of Michigan Health System.

“Alan is dedicated to his work and has had a profoundly positive impact on the lives of many patients,” said Dr. Frank Brosius, professor of internal medicine and physiology and co-director of the Nephrology Training Program at the University of Michigan. “His leadership has directly resulted in major changes in transplant allocation that have made kidney and pancreas transplantation fairer and more inclusive.”

Congratulations Dr. Leichtman – on a job well done! <3
WHAT DO YOU THINK?

We welcome your feedback Please share with us your thoughts on the Transplant Center Newsletter. Whether you wish to share your thoughts on a published article, make a suggestion, share news of your area, tell us what subjects you find interesting or valuable, we are interested in hearing from you!

Send your thoughts to Mary Kruger at mckruger@umich.edu. Please include your name and telephone number so we can explore potential stories.

Transplant Center’s Mission

The Transplant Center’s clinical mission is to provide our patients with the best possible medical care in a setting that emphasizes excellence, compassion, accessibility, responsiveness and prompt delivery of care.

University of Michigan Transplant Center Contact Information

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Heart Transplant Programs

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Kidney and/or Pancreas Transplant Programs

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Lung Transplant Program

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