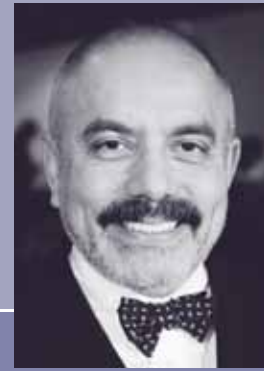


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· Translational Studies and Clinical Outcomes
Investigations in Transplantation



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FUNDING

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New immunosuppressive drugs improve the short-term survival of organ transplant recipients. However, long-term survival remains comparatively poor. This is likely due to the fact that immunosuppressive strategies are not tolerogenic. Transplant tolerance is likely to arise not from improved immunosuppressive regimens, but from improved understanding of the normal mechanisms that generate and maintain self-tolerance, and the ability to manipulate these mechanisms for the prevention and treatment of transplant rejection.

The overall goal of our research is two-fold:

1. Translational studies

Translational studies seek to apply the principles that are learned from basic science investigations to patient care.

Liver transplantation has progressed significantly since the first successful clinical trials performed in 1963, and has depended on improvements in organ preservation, immunosuppressive drug therapy, and improvements in surgical and peri-operative care. Survival has improved dramatically with the introduction of newer immunosuppressive drugs; however, though rejection of the transplanted organ is no longer a significant threat, the potential for infection and/or toxicity from drug therapy remains so given the lifelong need for treatment. Therefore, the ultimate goal is the acceptance of the transplanted organ without the need for lifelong drug therapy, a state called “tolerance.”

The University of Washington Medical Center is involved in a Phase II trial sponsored by the National Institutes of Health (NIH) that may give us insights into the mechanisms for the achievement of tolerance, as well as when to withdraw immunosuppression.

Over the last few years, Dr. Frances Malone, working in the Transplant Research Laboratory, has collaborated with Dr. Wei Li of the University of Washington to elucidate the roles of specific surface proteins and regulatory cells on the development of tolerance in murine liver transplantation. Dr. Malone has published two manuscripts on the roles of PD-L1 signaling and gamma delta lymphocytes in transplantation and was invited to present other work on the inverse expression of gamma delta T cells and Foxp3CD25CD4 T regulatory cells after murine liver transplant at the American Association of Immunologists Meeting (May, 2009). She has also designed a prospective clinical trial evaluating the changes in lymphocyte subsets between two standard immunosuppression protocols at the University of Washington Medical Center. This work is funded as an investigator-initiated proposal through Astellas Pharma; she is currently analyzing samples.

In order to prevent organ rejection, patients receiving liver transplants currently require life-long treatment with immune system-suppressing medications to prevent the rejection of the transplanted liver. However, these medications can cause long-term side effects, such as infection, kidney problems, diabetes and cancer. In patients infected with hepatitis C virus (HCV), these medications may increase the risk of HCV infection in the transplanted liver. The purpose of this study is to determine whether a slow withdrawal of immune system-suppressing medication is safe. The study also looks at whether slow withdrawal will help reduce the long-term side effects of immune system-suppressing medications and decrease the chance for HCV infection of the new liver in transplant patients with HCV. During and after the withdrawal phase, participants are closely monitored for liver allograft function, signs of

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rejection, levels of HCV in the blood and liver, and for the response of the immune system to the withdrawal of immunosuppression.

Being able to wean patients from their immunosuppressive medications would truly be an achievement, giving transplant recipients improved outcomes following transplantation and improve their health and quality of life.

2. Clinical outcomes investigations

A multitude of factors influence the outcome of each transplant procedure, including physiologic factors of the organ donor and recipient, surgical technique, logistics factors in transporting the donor organ for the recipient operation, the type of immunosuppressive medication, and geographic and sociological factors. Our clinical outcomes studies have been correspondingly broad in an effort to address several different ways in which transplant outcomes can be improved:

- **Eliminating health disparities for minorities undergoing solid organ transplantation** (Andre Dick, M.D.)
- **Weaning liver transplant recipients from immunosuppressive drug therapy in order to avoid the side effects of this therapy** (Jorge Reyes, M.D.)
- **Biliary Atresia and Intestinal Failure** (Frances Malone, Ph.D., A.R.N.P.). Two different mechanistic studies are underway to accompany two U01 proposals (Biliary Atresia and Intestinal Failure) one of which has been funded (U01-ChildREN NIDDK/U01 DK084575-01). Other current projects include finalizing manuscripts for three retrospective studies evaluating the clinical outcomes related to children with intestinal failure or requiring small bowel transplant, as well as a manuscript detailing the results of the Intestinal Care Program's use of omega-3 fatty acid supplementation in children with intestinal failure and liver disease. The data from each of these manuscripts have been presented at the 2009 International Small Bowel Transplant Symposium, the National Association of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), and other regional surgical/academic meetings.
- **Pediatric Intestinal Failure Consortium (PIFCON)** (Frances Malone, Ph.D., A.R.N.P.). This national research consortium has been established to study children with intestinal failure. The group has received R21 funding and submitted a U01 proposal based on retrospective data (NIDDK/ 1R21DK081059-01).
- **Factors influencing liver transplant survival rates, including recommendations on optimum MELD scores for liver transplantation** (James Perkins, M.D.)
- **Improving the quality of donor/recipient matching in liver transplantation** (Jeffrey Halldorson, M.D.)
- **Maximizing the experience of surgical residents for optimum learning of the principles and techniques of abdominal organ transplantation** (Ramasamy Bakthavatsalam, M.D.)

RELATED PUBLICATIONS

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DEPARTMENT CO-INVESTIGATORS

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