

SECTION OF ORGAN TRANSPLANTATION AND IMMUNOLOGY

FACULTY

Professor and Chief of Section

Marc I. Lorber, M.D., (Rush Medical College)

Associate Professor

David Cronin, II, M.D., Ph.D. (Mt. Sinai School of Medicine)

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Assistant Professor

Lisa A. Geiselhart, PhD., (Albany Medical College)

Description of Program

The Section of Organ Transplantation and Immunology is committed to a vigorous clinical program in multi-organ transplantation, as well as research focusing upon problems relevant to clinical transplantation and transplant biology. The current clinical effort includes renal and pancreatic transplant programs. Present transplant activity level approximates 100 transplants yearly, and we expect growth will continue at a moderate rate. Also, integrally related to the Section's mission is the activity of the clinical Histocompatibility and Immune Evaluation Laboratory where more than 5,000 procedures are performed annually in support of clinical transplantation efforts throughout the institution. Vigorous research efforts are ongoing with work focusing on several areas of transplant biology including T lymphocyte control of alloimmunity, acute and chronic graft arterial injury, pharmacological control of allograft rejection, and the biology of rejection.

Accomplishments

The central mission of outstanding clinical care, education and new knowledge generation has remained the Section's focus. The transplant referral base remains steady and vibrant in the areas of renal and pancreas transplantation, and volume has remained strong. The program in laparoscopic living renal donation continues to grow under the leadership of Dr. Amy Friedman. The Section has recently completed recruitment of Dr. David C. Cronin to lead our efforts in Liver Transplantation. Dr. Cronin will soon join us from The University of Chicago where he has been active in Adult and Pediatric Liver Transplantation. He also holds a PhD Immunobiology, and he has been active nationally and internationally in areas of Transplant Ethics. Dr. Cronin represents the initial recruit into the Interdisciplinary, Yale-New Haven Organ Transplant Center (YNOT), directed by Dr. Lorber and co-directed by Dr. Fadi Lakkis (Nephrology). YNOT members from the Departments of Surgery, Pathology, Internal Medicine, Pediatrics, and Anesthesiology are continuing recruiting efforts in many areas. The YNOT continues its close collaboration with the Interdepartmental Research Program in Vascular Biology and Transplantation (VBT), providing the institutional infrastructure for clinical, research and educational programs in transplantation across many disciplines. The successful, 2nd annual joint YNOT and VBT retreat was held during the fall, and the weekly seminar series focusing on scientific and clinical topics relevant to transplantation have remained quite successful.

Clinical and laboratory research have remained vigorous with continuing externally funded clinical research focusing on new approaches to post transplant immunosuppression. Dr. Formica's (Transplant Nephrology) hypertension project has completed patient enrollment as a collaboration between members of the Sections of Nephrology and Organ Transplantation and Immunology, and active follow up is ongoing. Again this year, laboratory based projects have been similarly strong, continuing to receive external funding. Drs. Lorber and Geiselhart continue work on several funded projects focused on allograft arterial disease, histocompatibility and immune evaluation.

Research in Progress

Dr. Marc I. Lorber focuses his research in the general area of transplantation immunobiology. T lymphocyte control of alloimmunity, allo- and xeno- immune mediated acute and chronic graft arterial

injury, chronic rejection, specific manipulations to effect long term allograft acceptance, and the role of immunologic monitoring in human organ transplantation represent areas of particular interest. Recent work has focused on the study of arterial injury in acute and chronic allograft rejection. The project builds upon a small animal model that has become a successful strategy for studying human allograft responses. This work, in collaboration with Dr. Jordan Pober from the Department of Pathology and the Boyer Center for Molecular Medicine and Dr. George Tellides of the Section of Cardiothoracic Surgery, demonstrated acute rejection of human allograft skin and vascular grafts in the severe combined immuno-deficient (SCID) mouse after reconstitution with human peripheral blood mononuclear cell or human splenocytes. Temporal events, expression of endothelial activation markers, cytokine profiles, etc. leading to allo- immune arterial injury will be characterized in greater detail than would otherwise be feasible in the clinical biopsy project. Adoptive transfer experiments using well defined lines of T lymphocyte clones, and possibly other immunologically relevant cell populations will be used both to investigate the possible role of various subsets in the chronic rejection process, as well as in developing therapeutic strategies for clinical intervention. Finally, investigation into the impact of various pharmacologic agents in preventing or ameliorating the chronic rejection process continues.

Our project investigating extracorporeal photo-chemotherapy using ultraviolet irradiation as a strategy leading to long term acceptance of allo-transplants in animals and eventually in humans is now well underway. This multi- departmental collaborative project led by members of the Section of Organ Transplantation and Immunology (Drs. Lorber and Geiselhart), including Drs. Richard Edelson and Michael Girardi (Dermatology), and Dr. Jordan Pober (Pathology) is the subject of a recently submitted grant application.

Clinical investigation continues to focus on evaluation of new immunosuppressive agents designed to prevent allograft rejection, the infectious disease consequences associated with chronic immunosuppressive therapy, and immunologic monitoring as an approach to develop optimal immunosuppressive strategies in renal and pancreatic transplant recipients. Active clinical investigation has been ongoing in these areas.

Notable Achievements 2002-2003

American Society of Transplant Surgeons; Immediate Past President
American Society of Transplant Surgeons Foundation; President
United Network for Organ Sharing; Secretary
American Society of Transplantation/ American Society of Transplant Surgeons Joint Executive Council
American Journal of Transplantation
American Society of Transplant Surgeons/ American Society of Transplantation - Journal Oversight Committee
Editorial Boards - Graft, Journal of Surgical Research, Transplantation, Transplantation Proceedings, Transplantation and Immunology Letter
New England Organ Bank - Executive Committee; Board of Trustees

Dr. Amy L. Friedman focuses her research on the application of high quality clinical transplantation and renal replacement therapy in an increasingly cost restricted environment. In response to increasing awareness of unreported deaths and catastrophic complications of live kidney donors (at other American transplant centers) and in collaboration with the American Society of Transplant Surgeons, a survey of transplant surgeons is in development to investigate current rates of life threatening consequences of specific techniques of vascular stump closure, with the expectation that a national standard of care will be defined.

During the development of the Laparoscopic Kidney Donor Program, the relationship between informed consent and the “learning curve” was investigated - a previously unreported subject. Through careful patient selection and collaborative mentoring, a complication-free learning curve was established.

Investigation of the issues of obesity, weight gain and new onset diabetes in renal transplant recipients has led to a clinical focus on the feasibility of patient compliance with the principles of exercise, healthy diet and fitness after transplantation.

A retrospective multivariate analysis of donor and recipient factors associated the development of ureteral complications and lymphocoele formation following renal transplantation is in progress in collaboration with Dr. Julie Ann Sosa and will serve as the thesis subject for a Yale medical student.

Notable achievements 2002 – 2003

Appointed to the 2003 Board of Examiners for the Malcolm Baldrige National Quality Award

Assistant Medical Director of the New England Organ Bank

Maturation of Laparoscopic Kidney Donor Program with complication free “Learning Curve”

Top 100 Minimally Invasive Surgeons, New York Magazine

American Society of Transplant Surgeons; Awards Committee

Dr. Lisa Geiselhart is interested in Transplant Immunology, Anergy and Tolerance, Immunogenetics, Immunotherapy, Autoimmunity, and Apoptosis. Her specific focus relates to modulation of T lymphocyte activation and function; she is working to elucidate the mechanisms involved in T cell activation. Her long- range goals are to establish and implement applications of relevance to clinical immunology and transplantation. Specific research into various immunomodulatory agents and molecules, with respect to their effect on T lymphocytes is ongoing. T lymphocyte activation and function is affected by a diverse repertoire of agents and molecules, including immunotoxins, immunosuppressive drugs, transplanted organs and cancer cells. Increasing the fundamental understanding of normal T cell activation aids in the development of practical applications designed at modulating immune function with regards to the recognition of self versus non self, especially as it pertains to such areas as allorecognition, transplantation, graft rejection and autoimmunity. Efforts to control the acute rejection response have been highly successful, but the consequences of ongoing, low level immune attack, termed chronic rejection, remain unresolved. It is anticipated that important insights will be derived from improved understanding of molecular events in allorecognition, for example identifying “allowable” versus “non-allowable” mismatches, the induction of specific tolerance, and the amelioration of chronic graft rejection.

Notable achievements 2002-2003

Passed Director Certification Examination, American Board of Histocompatibility and Immunogenetics

Promotion to Assistant Director, Yale Histocompatibility and Immune Evaluation Laboratory

United Network for Organ Sharing (UNOS) Histocompatibility Committee

Membership, American Association of Immunologists

Membership, American Society of Transplant Surgeons

Invited Lectures: “Antibody Screening and Crossmatches”; “Transplantation Immunology”; “Implementation of the Luminex Technology in the HLA Lab”

Yale Histocompatibility and Immune Evaluation Laboratory

- Validated and implemented the flow cytometric crossmatch. This crossmatch allows us to assess donor specific reactivity in a much more sensitive and specific manner.
- Implemented the LabScreen, Luminex antibody-screening assay. Our lab is one of the leading HLA labs in this new field.
- Initiated a study of cytokine promoter polymorphisms with regards to solid organ transplantation.
- Begun experiments aimed at investigating tolerance induction for solid organ transplants. We have performed experiments to determine whether extracorporeal photo-chemotherapy using ultraviolet irradiation can lead to long-term tolerance of allograft transplants in mice, and eventually humans.
- Initiated a study of KIR gene polymorphisms. KIR gene polymorphisms have been shown to be clinically relevant to bone marrow transplantation outcome, but their impact on solid organ transplant success has not yet been assessed.

Active Extramural Funding, 2002 - 2003

Clinical Research

An Open Label, concentration controlled, randomized, 12-month study of tacrolimus, sirolimus and corticosteroids vs. cyclosporine, sirolimus & corticosteroids in high-risk renal allograft recipients.

Principal Investigator **Marc I. Lorber**
 Co Investigators **AL. Friedman, MJ. Bia, AS. Kliger**
 Sponsor: Wyeth-Ayerst Pharmaceuticals

A randomized, open label, comparative evaluation of conversion from calcineurin inhibitors to sirolimus vs. continued use of calcineurin inhibitors in renal allograft recipients

Principal Investigator **Marc I. Lorber**
 Co Investigators **AL. Friedman, MJ. Bia, AS. Kliger**
 Sponsor: Wyeth-Ayerst Research

A one-year Multicenter, Randomized, open label, parallel group study of the safety, tolerability and efficacy of 2 doses (1.5 And 3 Mg/Day) of Everolimus with Basiliximab, Corticosteroids and Optimized Administration of Cyclosporine (Neoral®) in *de novo* Renal Transplant Recipients

Principal Investigator **Marc I. Lorber**
 Co Investigators **AL. Friedman, MJ. Bia, AS. Kliger**
 Sponsor: Novartis Pharmaceuticals

A one-year multi-center, prospective, open-label study of the safety, tolerability, and preliminary efficacy of oral FTY20 and RAD001 in *de novo* adult renal transplant recipients at increased risk of delayed graft function

Principal Investigator **Marc I. Lorber**
 Co Investigators **AL. Friedman, MJ. Bia, AS. Kliger**
 Sponsor: Novartis Pharmaceuticals Corporation

A three-year Randomized, Multicenter, Double-Blind, Parallel Group Study of the Efficacy and Safety of SDZ RAD Tablets Versus Mycophenolate Mofetil as Part of Triple Immunosuppressive Therapy in De Novo Renal Transplant Recipients (RADB 251)

Principal Investigator **Marc I. Lorber**
 Co Investigators **AL. Friedman, MJ. Bia, AS. Kliger**
 Sponsor: Novartis Pharmaceuticals Corporation

An open label study to evaluate the safety of steroid withdrawal in *de novo* renal allograft recipients treated with basiliximab induction and tacrolimus in combination with sirolimus (RAPA 505).

Principal Investigator **Marc I. Lorber**
 Co Investigators **AL. Friedman, MJ. Bia, R. Formica, JD. Smith**
 Sponsor: Wyeth-Ayerst Research

A one-year Multicenter, Randomized, Open Label, Parallel Group Study of the Safety, Tolerability and Efficacy of Two Doses of Everolimus with Basiliximab, Corticosteroids and Optimized Administration of Cyclosporine In *de novo* Renal Transplant Recipients

Principal Investigator

Marc I. Lorber

Co Investigators

AL. Friedman, MJ. Bia, R. Formica, JD. Smith

Sponsor:

Novartis Pharmaceuticals

Laboratory Research

Human CTL Mediated Injury of Graft Endothelial Cells

Sponsor:

NIH RO1 (HL 62188)

Principal Investigator

Jordan S. Pober

Co-Investigator

Marc I. Lorber

Chronic DTH and IFN γ in Human Graft Arteriosclerosis

Sponsor:

NIH PO-1

Principal Investigator

Jordan S. Pober

Co- Project Leaders

Jordan S. Pober, **Marc I. Lorber**

Co- Investigator

Lisa Geiselhart

Publications:

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