Overview of Transplantation Immunology Research at the Starzl Transplantation Institute for Incoming Students

Starzl Transplantation Institute & Departments of Surgery and Immunology, University of Pittsburgh School of Medicine
The appeal of transplantation research

“Spare-parts’ surgery, a fantasy for centuries, has progressed from the impossible to commonplace, prolonging the lives of patients with end-stage kidney, liver, heart, or lung disease.

**Transplantation science** has also revolutionized basic science, transcending boundaries between immunology, genetics, cellular and molecular biology, pharmacology and microbiology.

**Transplantation immunology** provides the basis for design of safer/more effective means to control rejection, alleviate patients’ dependence on anti-rejection drugs and promote transplant tolerance.
Evolution of transplantation

First successful transplant

Commonest transplant

“Quality of life ”transplant

Live donor transplant
Transplant tolerance can be *induced easily in rodents*

- Injection of *neonatal* mice with allogeneic hematopoietic cells

  Billingham, Brent & *Medawar*, *Nature* 1953

*Many drugs & biologics can induce robust transplant tolerance*

*But not in humans*

*Tolerance occurs rarely in transplant patients (liver and kidney), but cannot be induced routinely or predicted*
Generation of T cell responses to an organ graft

Halloran PF, NEJM 2004:351;2715
T cell activation signals serve as targets for immunosuppressive drugs

Halloran PF, *NEJM* 2004:351;2715
Acute rejection is readily controlled but transplant patients suffer chronic rejection.
Chronic graft rejection

Renal allograft

Heart allograft
The Current Problem

Immunosuppressive drugs lack immunologic or Ag specificity

- Increased risk of opportunistic infections and cancer
- Fail to induce IS drug-free tolerance

• Long-term use of drug therapy results in non-immunologic side effects

There is clearly an unmet clinical need
Current goal

• To develop of novel, safe approaches that will promote sustained, *donor-specific immune hyporesponsiveness*, while lowering the incidence and severity of acute and chronic rejection and reduce patients’ dependence on anti-rejection drugs

• *Is tolerance* essential/achievable in humans?
What is tolerance?

Specific unresponsiveness to tissue antigens in the absence of graft pathology and (sustained) immunosuppressive therapy
New agents that block costimulation, - a pathway to tolerance?

Co-stimulatory pathways that might modulate memory T-cell responses in transplantation and autoimmunity
New Approaches to Preventing Transplant Rejection/Promoting Tolerance

<table>
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<tr>
<th>Category</th>
<th>Therapy</th>
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<tbody>
<tr>
<td>Reducing inflammatory cytokines</td>
<td>Anti-IL-6R</td>
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<td></td>
<td>Anti-IL-17A mAb</td>
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<td>Altering immune cell trafficking</td>
<td>CCR5 inhibitor</td>
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<td>Inhibition of T and B cell signaling</td>
<td>JAK 1/2 inhibitor</td>
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<td>B cell depletion</td>
<td>Anti-CD20</td>
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<tr>
<td>In vivo Treg expansion</td>
<td>mTOR inhibition (+ IL-2)</td>
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<tr>
<td>Cell therapies</td>
<td>Tregs</td>
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<td>DCregs</td>
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<td>MSCs</td>
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<td>Inhibition of co-stimulation</td>
<td>CTLA4-Ig</td>
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<td></td>
<td>Single chain anti-CD28 mAb</td>
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<tr>
<td>Blocking germinal center formation</td>
<td>Bcl-6 small molecule inhibitor</td>
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</tbody>
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From drugs and biologics to cell therapy: Treg infusion in transplantation

Riley JL, *Immunity* 2009:30;656
Important questions regarding regulatory immune cell (Treg) therapy

The source, number, timing and frequency of cells infused

Choice of immunosuppressive agents

In vivo fate, stability and longevity of the cells
Immunology Research Topics at the Starzl Transplantation Institute

stiresearch.health.pitt.edu
Innate Immunity

• Mechanisms of innate allore cognition
• Role of the innate immune system in acute and chronic rejection

Innate and adaptive mechanisms of allograft rejection


How do dendritic cells regulate rejection versus transplant tolerance?

Dendritic cells as a potential cellular therapy for tolerance induction
Dendritic cells, microvesicles, transplant rejection and tolerance


Roles of dendritic cells and T cells in immune regulation and the promotion of transplant tolerance


Adaptive Immunity and its Regulation
B cells, alloimmunity and pathogenesis of rejection

**Research Area(s):**
- Adaptive Immunity
- Clinical Research
- Human Immunology
- Immunological Tolerance
- Innate Immunity


Immunological Tolerance

- Innovative strategies to promote tolerance
- Regulatory immune cell therapy
- Mechanisms of transplantation tolerance
- Roles of regulatory immune cells
Regulation of the immune system and tolerance induction


Research Area(s):
Adaptive Immunity
Cell Transplantation
Clinical Research
Human Immunology
Immunological Tolerance
Innate Immunity
Cytokine and dendritic cell immunobiology in transplantation


Liver transplant research in the lab and clinic

Immunosuppression can be safely withdrawn in about 20% of stable transplant patients

Livers are accepted across MHC barriers without immunosuppression in mice

Tolerogenic function of liver APCs?

Role of Tregs?

Intrahepatic T cell apoptosis?
Human Transplant Immunology

- Immunological monitoring of the transplant recipient
- Mechanisms of rejection in humans
- Mechanisms of graft acceptance (tolerance) in humans
- Immunogenetics
- Viral infections in transplantation
Diana M. Metes MD

Human immunology, transplantation, EBV, T cell memory, dendritic cells


Xenotransplantation

- Identification of novel xeno-antigens
- Humoral and cellular mechanisms of xenograft rejection
- Genetic engineering of (donor) pigs for xenotransplantation
- Pre-clinical, non-human primate studies (heart, kidney and pancreatic islets)
The potential of cross-species organ transplantation (xenotransplantation)


Recent Graduate Student Trainees in Transplantation Immunology
Sherri Devito, MD PhD

NIH Training Fellowship

Thesis: The role of tolerogenic dendritic cells in islet-cell allograft transplantation

Now: Harvard University/MGH
Ben Matta, PhD

NIH Training Fellowships

**Thesis:** Regulation of T cell function by liver plasmacytoid dendritic cells

**Now:** Postdoctoral Research Fellowship, STI (Turnquist Lab) AST Fellowship
Dawn Reichenbach, PhD

NIH Training Fellowship


Now: Postdoctoral Fellow, Blazar Lab, University of Minnesota
Brian Rosborough, MD PhD

AHA and NIH Training Fellowships
**Thesis:** Regulation of alloimmunity by mTOR inhibition
**Now:** Harvard University/MGH
Jeff Walch, MD PhD

Principal Mentor: NIH Training Fellowship
Thesis: Migration of T cells to vascularized allografts
Now: Johns Hopkins University School of Medicine
NIH T32 fellowships
Interdisciplinary Training in Transplantation Biology

A unique, NIH-supported interdisciplinary training program in transplantation biology to train future leaders in transplantation research. Training positions for pre-doctoral graduate students (PhD or MD/PhD candidates) and for post-doctoral fellows (PhDs, MDs, MD/PhDs and VDMs) are available. Candidates for support from the institutional NIH T32 training grant must be US citizens or permanent residents.