Innovation In Transplantation: Improving outcomes

Thomas C. Pearson
Department of Surgery
Emory Transplant Center

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Disclosures

• Belatacept preclinical and clinical trial were supported by Bristol-Myers Squibb

• I have served on an Advisory Board for Bristol-Myers

• I will discuss studies of off-label use of belatacept
Innovation in Transplantation

improving outcomes

• Current status of clinical transplantation: how we got here

• Stimulation blockade: concept, mechanism of action and rationale design

• Belatacept: Pre-Clinical Development Pathway

• Belatacept: Lessons from Clinical Trials

• New Opportunities and Unmet Needs
Saints Cosmas and Damian

“The Miracle of the Black Leg” 348 AD
Nobel Prize in Medicine 1912

Alexis Carrell developed methods for sewing blood vessels together.
The Nobel Prize in Physiology or Medicine 1960

"for discovery of acquired immunological tolerance"

Sir Peter Medawar
Innovations in Transplantation:

- Circa 1950
  - Basic surgical techniques defined
  - Transplants are lost due to an immune response
First Kidney Transplant- Dec 1954
First Kidney Transplant - Dec 1954
The Era of Immunosuppression

Tweedledee

Sir Roy Calne

Gertrude Elion

George Hitchings

Titus

Lollipop
Evolution of transplant immunosuppression

Improved Immunosuppression Results in Reduced Rejection and Improved Graft Survival
Current Agents

- Calcineurin inhibitors
- Mycophenolate Mofetil
- Sirolimus
- Azathioprine
- Steroids
- IL-2R antagonists
- Anti-lymphocyte antibody preparations
- Alemtuzumab
- Co-stimulation blockade
- Leflunomide
Kidney Graft Survival Rates

UNOS: National Registry Data
Kaplan-Meier Analysis of 1997-2004 (Data as of 09/02/2016)
Transplants By Organ Type January 1, 1988 - June 30, 2016

Based on OPTN data as of July 29, 2016

<table>
<thead>
<tr>
<th>Organ</th>
<th>Transplants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>395,511</td>
</tr>
<tr>
<td>Liver</td>
<td>143,856</td>
</tr>
<tr>
<td>Pancreas</td>
<td>8,235</td>
</tr>
<tr>
<td>Kidney / Pancreas</td>
<td>21,727</td>
</tr>
<tr>
<td>Heart</td>
<td>64,085</td>
</tr>
<tr>
<td>Lung</td>
<td>32,224</td>
</tr>
<tr>
<td>Heart / Lung</td>
<td>1,186</td>
</tr>
<tr>
<td>Intestine</td>
<td>2,733</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>669,557</strong></td>
</tr>
</tbody>
</table>

- Kidney: 59.1%
- Liver: 21.5%
- Pancreas: 9.6%
- Kidney / Pancreas: 3.3%
- Heart: 3.3%
- Lung: 4.8%
- Heart / Lung: 0.2%
- Intestine: 0.4%
Kidney Transplants Performed

Year

0 04 06 08 10 12 14

Transplants

20000
15000
10000
5000

Living donor

Deceased donor

All

Living donor

Transplants

Deceased donor

All
Region 3 Deceased and Living Donors,
7/1/2006-6/30/2016

Waiting List Candidates by Organ Type - All States
Based on OPTN data as of February 5, 2016

<table>
<thead>
<tr>
<th>Organ</th>
<th>Candidates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>100,522</td>
</tr>
<tr>
<td>Liver</td>
<td>14,800</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1,041</td>
</tr>
<tr>
<td>Kidney / Pancreas</td>
<td>1,960</td>
</tr>
<tr>
<td>Heart</td>
<td>4,169</td>
</tr>
<tr>
<td>Lung</td>
<td>1,489</td>
</tr>
<tr>
<td>Heart / Lung</td>
<td>47</td>
</tr>
<tr>
<td>Intestine</td>
<td>279</td>
</tr>
<tr>
<td>Total</td>
<td>121,422</td>
</tr>
</tbody>
</table>
Kidney Median Time to Transplant

![Graph showing the median time to transplant for active at listing and all patients over years.

- Median years to transplant:
  - 0 to 8

- Year of listing:
  - 2004 to 2014

- Lines:
  - Teal: Active at listing
  - Brown: All

American Journal of Transplantation
pages 11-46, 11 JAN 2016 DOI: 10.1111/ajt.13666
Immunosuppression for Renal Transplantation

- Basiliximab
- Thymoglobulin
- Calcineurin Inhibitor
- Mycophenolate
- Steroids

Time
Deceased (n=164,480) and Living (n=88,430) donor kidney transplant half-lives in the US

Adapted from: Lamb et.al. AJT early online 25 OCT 2010

Lodhi and Meier-Kriesche, 2011
Improving long-term outcomes and healthspan: a daunting but worthy goal

Meier-Kriesche AJT 2004; 4: 1289

Highly complex regimens
Demanding follow-up
Mechanism-based toxicity
High blood pressure
Diabetes
Nephrotoxicity
Risk of DSA
Non-adherence
Causes of Graft Loss

Causes of Graft Loss >6 Months

- Chronic rejection 36%
- Death with function 50%
- Glomerulonephritis 6%
- Other 5%

Causes of Death with a Functioning Graft

- CV Disease: 30%
- Infection: 21%
- Unknown: 17%
- Other: 23%
- Malignancy: 9%

USRDS 2009 Adult Renal Transplants 2003–2007
Why is it so hard to improve long-term survival and *healthspan*?

- Long-term trials are logistically and financially impractical.
- SRTR, CMS and Centers of Excellence drive improvement in short-term outcomes.
- Pressures to reduce acute care cost can compete with strategies to improve long-term outcomes.
- Much (most) of long care is given outside of transplant centers.
- And yet, we the transplant community must design and deliver the solutions.
Innovations in Transplantation:

- Circa 2000
  - Short-term results are very good
  - Long-term results not improving
  - The wait list is long and getting longer
Immunosuppression: Goals

Maintain efficacy
- acute rejection

Improve toxicity profile

Improved long-term outcomes
Transplant Immunology 101

- T cells play a central role in graft rejection

- Co-stimulation pathways critical for T cell function
CD28 a Critical Costimulatory Pathway

Enhanced T cell survival
Activate bioenergetics
Cytokine synthesis

B7-1 (CD80)
B7-2 (CD86)
CD28
CTLA4
MHC
TCR
MIGRATION OF DENDRITIC LEUKOCYTES FROM CARDIAC ALLOGRAFTS INTO HOST SPLEENS
A Novel Pathway for Initiation of Rejection

By Christian P. Larsen, Peter J. Morris, and Jonathan M. Austyn

From The Nuffield Department of Surgery, University of Oxford, John Radcliffe Hospital, Headington, Oxford OX3 9DU, United Kingdom

The Journal of Experimental Medicine

Induction of transplantation tolerance in adults using donor antigen and anti-CD4 monoclonal antibody

Thomas C. Pearson, Joren C. Madsen, Christian P. Larsen, Peter J. Morris, and Kathryn J. Wood

Nuffield Department of Surgery, University of Oxford John Radcliffe Hospital, Headington, Oxford OX3 9DU, England
“Maturation” renders DC 100-fold more potent T cell activators

Nobel Prize in Medicine, 2011
Development of CTLA4-Ig

CTLA-4 Is a Second Receptor for the B Cell Activation Antigen B7
By Peter S. Linsley, William Brady, Mark Urnes, Laura S. Grosmaire, Nitin K. Damle, and Jeffrey A. Ledbetter

From the Oncogen Division, Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, Washington 98121

Structure and Function of B7, CD28, and CLTA4 begin to be elucidated

Peter Linsley
Ed Clark
Craig Thompson
Jeff Bluestone

CLTA4-Ig in born
Development of a CTLA-4 Fusion Protein to Block CD28 Costimulation
"Costimulation" moves from biology to therapeutic target

Transplantation®
RAPID COMMUNICATION

TRANSPLANTATION TOLERANCE INDUCED BY CTLA4-Ig

THOMAS C. PEARSON, D. DIANE Z. ALEXANDER, KEVIN J. WINN, PETER S. LINSLEY, ROBIN P. LOWRY, AND CHRISTIAN P. LAUSEN

Departments of Surgery, Pathology, and Medicine, Emory University School of Medicine, Atlanta, Georgia 30322; and Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, Washington 98121

CTLA4-Ig
Drug candidate
"Costimulation blocker"

Graph: Percent survival over time with different treatments.
Rhesus Kidney Transplant Model

Yerkes Primate Research Center
CD28 Blockade: Pre-clinical model

- CTLA4-Ig minimal effect on survival
Effective for treatment of rheumatoid arthritis
- T cell-mediated autoimmune disorder
Large safety experience with long-term administration
Belatacept: Rational Design

- High affinity CTLA4-Ig variant
- Increased biologic potency

Larsen, Pearson et al AJT 2005
Rational Development of LEA29Y (belatacept), a High-Affinity Variant of CTLA4-Ig with Potent Immunosuppressive Properties

10-fold greater inhibition of T cell responses in vitro

Larsen et al Am J Trans 2005

Prolonged Transplant survival in CNI-inhibitor-free regimens

Basiliximab

Belatacept

Treatment ends
Belatacept Core Development Program

Renal Transplant (N = 1427)

Phase II
- IM103100 (N=218) Proof of concept
- Potential alternative to CNI

Phase III
- IM103008 “BENEFIT” (N=666) Standard criteria donors
- IM103027 “BENEFIT-EXT” (N=543) Extended criteria donors

>900 renal transplant recipients received belatacept
BENEFIT and BENFIT-EXT Study Design

- De Novo therapy in Kidney Transplant recipients
- Prospective, randomized, international, multi-center
- Superior renal function, non-inferior rejection control

Randomization

Primary endpoint

Secondary endpoints

Belatacept MI

10 mg/kg

5 mg/kg every 4 weeks

DAY 1 5 14 28 42 56 70 84 112 140 168

Belatacept LI

10 mg/kg

5 mg/kg every 4 weeks

DAY 1 5 14 28 56 84 112

Cyclosporine

150–300 ng/ml

DAY 1 28

- All patients received basiliximab induction, mycophenolate mofetil, and corticosteroids
- Only CsA patients: T-cell depleting agents permitted for anticipated DGF
Belatacept Maintains Superior Renal Function

BENEFIT: cGFR

ITT analysis w/ imputation. Patients with death or graft loss imputed as cGFR = 0.
Belatacept Improves Cardiovascular & Metabolic Profiles

- Lower Blood Pressure with fewer medications
- Favorable lipid profiles with fewer medications
- New Onset Diabetes lower at 12 mo, not significant at 24 or 36 months
Allograft Rejection and its consequences
## Acute Rejection by Year 3

<table>
<thead>
<tr>
<th></th>
<th>Belatacept MI</th>
<th>Belatacept LI</th>
<th>CsA</th>
</tr>
</thead>
<tbody>
<tr>
<td>BENEFIT</td>
<td>24%</td>
<td>17%</td>
<td>10%</td>
</tr>
<tr>
<td>BENEFIT-EXT</td>
<td>18%</td>
<td>19%</td>
<td>16%</td>
</tr>
</tbody>
</table>
Comprehensive Benefit-Risk Assessment
Absolute Difference between Belatacept LI and CsA (%)

Death/Graft Loss
Death
Rejection
Rejection w/CKD 4/5
CKD Stage 4/5
NODAT
Uncontrolled HTN
Uncontrolled Dyslipidemia
Serious Infections
Malignancy
PTLD (EBV+)

Pooled Core Studies
Belatacept: path to approval

**Concept:** Belatacept evaluated as alternative to cyclosporine

**Program Objectives**
- Maintain short-term survival
- Non-inferior for control of rejection
- Superiority for renal function

- **Phase II Transplant Trial 2001**
- **Phase III Trials begin 2005**
- **FDA Panel Review 2009**
- **Belatacept FDA Approval June 15, 2011**
- **First Recipient receives Belatacept standard of care July 26, 2011**
Belatacept 1.0/1.1 Protocol (2011)

- **Belatacept**
- **Mycophenolate**
- **Prednisone (5)**
- **Basiliximab**

*Intensity of Exposure*

- **Maintenance**
- **Induction**

*Time*
Belatacept 1.0 – We have a problem!
eGFR of Tac and Bela 1.0/1.1 Intent-to-Treat Patients

<table>
<thead>
<tr>
<th>Month</th>
<th>Bela (N=97)</th>
<th>Tac (N=205)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mo</td>
<td>96</td>
<td>205</td>
</tr>
<tr>
<td>2 mo</td>
<td>97</td>
<td>205</td>
</tr>
<tr>
<td>3 mo</td>
<td>97</td>
<td>204</td>
</tr>
<tr>
<td>6 mo</td>
<td>96</td>
<td>203</td>
</tr>
<tr>
<td>9 mo</td>
<td>95</td>
<td>202</td>
</tr>
<tr>
<td>12 mo</td>
<td>94</td>
<td>201</td>
</tr>
<tr>
<td>24 mo</td>
<td>95</td>
<td>196</td>
</tr>
<tr>
<td>36 mo</td>
<td>94</td>
<td>190</td>
</tr>
<tr>
<td>48 mo</td>
<td>53</td>
<td>175</td>
</tr>
</tbody>
</table>
Continuous improvement cycle
Belatacept 2.0-2.5

Protocol Design

Implement

Monitor

Adjust

50-100 patient cycles
Risk of Rejection

3 6 12 24 months post-transplant

“Tacrolimus Induction”

Patients at risk of early post-transplant rejection

Belatacept
Freedom from Rejection

Belatacept

Belatacept/Tac short

Belatacept/Tac extended
Belatacept vs Tacrolimus: All Patients

Graft Survival

Renal Function (eGFR)

Years

Months

0 365 730 1095

0 1 2 3

0 12 24 36 48

Bela (N=518)

Tac (N=205)

Bela (N=518)

Tac (N=205)
Belatacept associated with lower rates donor-specific Antibody

*p=0.002

% Freedom from DSA

Months

Belatacept 1.0-2.4

Tacrolimus
Belatacept and Long-Term Outcomes in Kidney Transplantation

Flavio Vincenti, M.D., Lionel Rostaing, M.D., Ph.D., Joseph Grinyo, M.D., Ph.D., Kim Rice, M.D., Steven Steinberg, M.D., Luis Gaite, M.D., Marie-Christine Moal, M.D., Guillermo A. Mondragon-Ramirez, M.D., Jatin Kothari, M.D., Martin S. Polinsky, M.D., Herwig-Ulf Meier-Kriesche, M.D., Stephane Munier, M.Sc., and Christian P. Larsen, M.D., Ph.D.

January 28, 2016
Rates of Death or Graft Loss

Belatacept MI vs. cyclosporine: hazard ratio for death or graft loss,
0.57 (95% CI, 0.35–0.95); P=0.02

Belatacept LI vs. cyclosporine: hazard ratio for death or graft loss,
0.57 (95% CI, 0.35–0.94); P=0.02

<table>
<thead>
<tr>
<th>Months since Transplantation</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belatacept MI</td>
<td>219 212 208 206 204 202 199 153 151 149 146 142 135 131 128</td>
</tr>
<tr>
<td>Belatacept LI</td>
<td>226 220 218 216 213 209 204 165 161 159 152 151 142 139 137</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>221 208 206 202 199 197 186 137 123 117 112 107 102 100 92</td>
</tr>
</tbody>
</table>
Kidney Graft Function

Figure 3. Glomerular Filtration Rate over the Period from Month 1 to Month 84.

The estimated glomerular filtration rate (eGFR) was determined by repeated-measures modeling, with time as a categorical variable. Error bars indicate 95% confidence intervals.
Innovation in transplantation: Circa 2016

- Better safety profile
- Improved renal function

- Higher acute rejection rate
- More severe rejection pathology
Belatacept On Going Clinical Trials

- Conversion Trial
- Thymoglobulin Induction
Moving forward: The next generation of costimulation blockers

How can we optimize CD28-based costimulation blockade?

• Improve upon current CD28 costimulation blockade reagents

• Combine current CD28 blockers with novel therapeutics to improve efficacy
Genetically Engineered Donor Organs

- Normally organs from other species are promptly rejected due to key protein differences
- Making Pig Organs more human-like by "Knocking Out" key rejection molecules
- Previous reports average time to rejection 2-3 weeks
- Emory Xeno-Kidney Project- >300 days, longest ever reported
Double Knockout Donor Pig
Gal -/-, β4Gal -/-