A Tolerance Approach to the Transplantation of Vascularized Tissues

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Overcoming the Immune Response to Transplants

- Matching
- Non-specific immunosuppressive medications
- Tolerance
What Patient’s Take in One Day to Prevent Organ Rejection
Late onset renal allograft rejection after cessation of immunosuppression
TOLERANCE

Definition: The specific absence of a destructive immune response to a transplanted tissue
Mechanisms of Tolerance

Central Tolerance: Generated by intrathymic deletion of immature T cells

Peripheral Tolerance: Affects cells which already matured in the thymus (anergy, regulation, linked suppression)
MIXED CHIMERAS

Irradiate and Reconstitute
A(-T) + B(-T)
Mixed Bone Marrow
MIXED CHIMERAS

1) Day -6 or -1: mAbs (anti-CD4,CD8)

2) Day 0: 3 Gy TBI

7 Gy Thymic Irrad

3) Infuse Allogeneic BM (1.5x10^7 cells)
NON-MYELOABLATIVE PROTOCOL FOR INDUCTION OF TOLERANCE IN CYNOMOLGUS MONKEYS

1. WBI 300R (or 150x2)
2. TI 700R
3. Kidney Tx
   Native nephrectomy
   Splenectomy
4. Donor Bone Marrow
5. ATG
6. Cyclosporine A
Chimerism in PBL Subpopulations

Day 19

Day 27

Relative cell numbers

Granulocytes  Monocytes  Lymphocytes

Relative fluorescence

(GSP5.3)
<table>
<thead>
<tr>
<th>(n=)</th>
<th>Host Conditioning</th>
<th>Multilineage Chimerism</th>
<th>Graft Survival (days)</th>
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</thead>
<tbody>
<tr>
<td>3</td>
<td>Ab: ATG, TBI: 300, TI: 700, CSA: +, DBM: +</td>
<td>Yes (1/3)</td>
<td>14, 175, 834^*</td>
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<tr>
<td>1</td>
<td>Ab: ATG, TBI: 150x2, TI: —, CSA: +, DBM: +</td>
<td>Yes</td>
<td>&gt;165</td>
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</table>
Biopsy of M1693 -- 10 years post Transplant
IMMUNE TOLERANCE NETWORK (NIH) PROTOCOL - NKD03

RENAL ALLOGRAFT TOLERANCE THROUGH MIXED CHIMERISM

RESULTS TO DATE:

• 5 patients treated (2 – 6 years)
• HLA one-haplotype mismatched bone marrow
• 4 off all immunosuppression
HLA-Mismatched Renal Transplantation without Maintenance Immunosuppression

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ITN Protocol NKD03
(HLA-mismatched)

Cyclosporine A

MEDI507 0.1 mg/kg, first dose, then 0.6 mg/kg/day x 3 doses

Cyclophosphamide, 60 mg/kg followed 14 hours later by hemodialysis

T1 700 cGy

Bone marrow infusion and renal transplant

Days pre and post-transplant

ITN Protocol NKDO3
D.H. Sachs and A.B. Cosimi
Mass. General Hospital
Protocol: Renal allograft recipients (n=5)

- 1 female 22 yo (Tx: 9/17/2002)
- 1 male 22 yo (Tx: 6/6/2003)
- 1 male 39 yo (Tx: 10/28/2003)
- 1 male 25 yo (Tx: 2/15/2005)
- 1 male 46 yo (Tx: 1/24/2006)

- End-stage renal disease (ESRD)
- No malignancy, no HLA-identical donor
<table>
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<tr>
<th>#</th>
<th>Age</th>
<th>Sex</th>
<th>Date of Tx</th>
<th>Original Disease</th>
<th>Donor</th>
<th>Reasons for enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>22</td>
<td>F</td>
<td>9/02</td>
<td>Alport</td>
<td>Mother</td>
<td>severe HPV infection</td>
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<tr>
<td>#2</td>
<td>22</td>
<td>M</td>
<td>6/03</td>
<td>MPGN</td>
<td>Father</td>
<td>history of noncompliance</td>
</tr>
<tr>
<td>#4</td>
<td>25</td>
<td>M</td>
<td>2/05</td>
<td>Alport</td>
<td>Mother</td>
<td>strong desire not to use chronic immunosuppression</td>
</tr>
<tr>
<td>#5</td>
<td>46</td>
<td>M</td>
<td>1/06</td>
<td>PCKD</td>
<td>Sister</td>
<td>strong desire not to use chronic immunosuppression</td>
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Non-Myeloablative Regimen for Clinical HLA Mismatched Kidney Transplantation

-7 -5 -4

Cyclophosphamide
60 mg/kg X 2

Thymic Irradiation
7 Gy

-2 -1 0 1 day

Kidney Tx
Donor Bone Marrow Tx

Rituximab
(anti-B cell)

Anti-CD2 mAb

steroids

CYA

9-12 months
Clinical Course of Patients Weaned from Immunosuppression

Patient 1

Patient 2

Patient 4

Patient 5

Days post-transplant

Serum Creatinine

- CYA
- Tacrolimus
- Pred
- MMF
- Mycophenolate mofetil

↑ biopsies

= days post-transplant
Recent Biopsies in Four Patients off all Immunosuppression
NKD03 - First Renal allograft recipient

- Female 22 yo  (Tx: 9/17/02)
- Full one-haplotype HLA mismatch from mother
- First transplant from father in 1994 for ESRD due to Alport’s Syndrome (standard IS)
- Severe warts as complication of IS
- 2nd transplant due to progressive chronic rejection (Creatinine 6.0 mg% by 2002)
### Comparisons of Tolerance vs. Stable on IS

#### Annual Maintenance Cost

<table>
<thead>
<tr>
<th>Drug</th>
<th>TOL</th>
<th>Stable on IS</th>
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<tbody>
<tr>
<td>Prograf (4mg/day)</td>
<td>0</td>
<td>$5,342</td>
</tr>
<tr>
<td>MMF (1.5g/day)</td>
<td>0</td>
<td>$6,048</td>
</tr>
<tr>
<td>Prednisone (5mg/day)</td>
<td>0</td>
<td>$120</td>
</tr>
<tr>
<td>Nexium (20mg/day)</td>
<td>0</td>
<td>$1,836</td>
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<tr>
<td>Lipitor (10mg/day)</td>
<td>0</td>
<td>$983</td>
</tr>
<tr>
<td>Atenolol (50mg/day)</td>
<td>0</td>
<td>$56</td>
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<td>Annual maintenance Cost</td>
<td>0</td>
<td>$14,385 /patient/year</td>
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</table>
ACKNOWLEDGEMENTS

MGH
- BMT Unit (Spitzer, McAfee, Dey, Ballen, et al.)
- Transplant Unit (Cosimi, Kawai, Delmonico, Ko, Hertl, et al.)
- TBRC (Sachs, Sykes, Yamada, Huang, et al.)
- Pathology (Colvin, Shimizu, Saidman, et al.)
- Infectious Disease (Fishman, et al.)
- Renal (Rubin, Williams, Goes, Wong, et al.)

OUTSIDE
- ITN (NIH)
- Biotransplant/Novartis
- Medimmune