K30 Research Update

Transplant Immunomodulation by Allochimeric Molecules

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Background-Transplant-Related Morbidity and Mortality

- Technical Expertise
- Perioperative care
- Immunoprophylaxis
- Complications
  - infection
  - rejection
Increasing Demand for Organs

- **Waiting List**: 15 fold increase
- **Transplants**: 2.4 fold increase
- **Donors**: 2.4 fold increase
- **Deaths**: 5 fold increase

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Background

Effect of HLA Matching on Renal Allograft Survival

![Graph showing percent graft survival over years posttransplant for different HLA matching categories.](image)
Antigenic Topography of Class I Molecules

Background

1. accelerated allograft rejection
2. alloantibody production
3. increase fTc

dominant immunogenic epitopes
RT1.A^a, RT1.A^u, RT1.A^l
Rat Major Histocompatibility Complex

RT1

\[ \text{RT1.A}^a \]

<table>
<thead>
<tr>
<th>( \alpha_1^a )</th>
<th>( \alpha_2^a )</th>
<th>( \alpha_3 )</th>
<th>TM</th>
<th>CYT</th>
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<tr>
<td>1</td>
<td>90</td>
<td>182</td>
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</table>

Background
Background

Allochimeric Class I MHC Molecules
Experimental Tolerance Model

Chimeric Alloantigen

ACI (RT1.A^a)

LEW (RT1.A^l)
or
WF (RT1.A^u)

1mg / p. v.

CsA
orally
3 days (0-2)
10mg/kg
Preliminary Data

Long-Term Survival of WF Allografts Induced by Perioperative Allochimeric Administration

- WF $\rightarrow$ ACI
- WF $\rightarrow$ ACI CsA only
- WF $\rightarrow$ ACI + $\alpha_{1h}^{u/l}$-RT1.A$^a$ + CsA

Days

% graft survival
Long-term Survival of LEW Allografts Induced by Allochimeric Molecule

Preliminary Data

Days

% graft survival

LEW → ACI
LEW → ACI CsA only
LEW → ACI + α_{1h}^{u/l}-RT1.A^{a} + CsA
Preliminary Data

Tolerance Induction by Allochimeric Molecules

Accepted donor-type allograft

Rejected third-party allograft
<table>
<thead>
<tr>
<th>DAY 120</th>
<th>SYNGENEIC</th>
<th>ALLOCHIMERIC PROTEIN</th>
<th>CsA High Dose</th>
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<td>Islet Donor</td>
<td>Recipient</td>
<td>CsA</td>
<td>$[\alpha_{1h}^{1/u}]$-RT1.A&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
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<tr>
<td>WF</td>
<td>ACI</td>
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<tr>
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<td>ACI</td>
<td>+</td>
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Proposal

Specific Aim I
- To document the induction of tolerance to pancreatic islets by allochimeric molecules

Hypothesis: Rat allochimeric molecules induce tolerance to islet allografts in allogeneic hosts
Specific Aim II

- To dissect the mechanisms of tolerance induction by allochimeric molecules

Hypothesis: Regulatory T cells that are critical for tolerance acquisition can transfer the tolerant state to naïve recipients in an “infectious” manner
  - Determine the contribution of distinct cytokine networks
  - Determine the role of T Cell anergy
Proposal

Specific Aim III

• To further determine sites of amino acids that are critical for tolerance induction

Hypothesis: Allochimeric determinants, that are critical for tolerance induction, are located on the polymorphic regions of class I MHC molecules
Translation to Clinic

• IRB
• Timing of pre-transplant treatment regimen
• Sensitivity of indicators of tolerance
  • Graft survival
  • Freedom from rejection
  • Donor-specific antibodies
Acknowledgments

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• F Gao, Ph.D.