Liver Transplant Immunosuppression

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Disclosures

• No financial disclosures

• I will be discussing the off-label use of almost everything.
Objectives

• Describe the principles of immunomodulation.
• Discuss current immunosuppression medicines, their classes and indications.
• Explore the variety of possible targets for new therapies.
• Keep you awake until time for drinks!
Principles of Immunosuppression

• Prevent Rejection
• Minimize Infection
• Minimize Toxicity
Phases of Immunosuppression

- **Induction**
  - Intense therapy at the time of transplant
- **Maintenance**
  - Chronic, slowly tapering immunosuppression
- **Salvage**
  - Rescue after rejection
Abandon All Hope ye Who Enter Here
DON’T PANIC
Immune Response in 1 slide

• Signal 1
  • T-cell receptor binding

• Signal 2
  • Co-Stimulation

• Signal 3
  • Trigger for clonal expansion
  • Important growth pathway
Immune Pathways
Classes

• Calcineurin Inhibitors
• mTOR Inhibitors
• Anti-metabolites
• Steroids
• Antibodies
  • Binding
  • Depleting
• Novel/directed action
Calcineurin Inhibitors

- Calcineurin is a second messenger
  - T-cell Receptor complex to NFAT
- Pathway leads to Transcription
  - Products that promote T-cell activation
    - IL-2
- Extracted from yeast
Calcineurin Inhibitors

- **Cyclosporine**
  - First trial in 1978
  - Exceeding efficacy, opened a new era . . .
  - Dose related nephrotoxicity, neurotoxicity, diabetogenicity,
  - Increased incidence of B-cell lymphoma, and cosmetic changes

- **Tacrolimus**
  - Clinical trials in 1990
  - More efficacious than CSA
  - Similar side effect profile.
<table>
<thead>
<tr>
<th>Condition</th>
<th>CSA</th>
<th>TAC</th>
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<tbody>
<tr>
<td>Nephrotoxic</td>
<td>CSA=TAC</td>
<td></td>
</tr>
<tr>
<td>Diabetogenic</td>
<td>CSA&lt;TAC</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>CSA&gt;TAC</td>
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<tr>
<td>Lipids</td>
<td>CSA&gt;TAC</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Risk</td>
<td>CSA&gt;TAC</td>
<td></td>
</tr>
<tr>
<td>Non-Melanoma Skin Cancers</td>
<td>CSA=TAC</td>
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</tbody>
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- May even promote tumor growth
Calcinurin Inhibitors - compared

• TAC may reduce acute, steroid resistant rejection compared to CSA
• TAC results in better late graft function in renal transplant
• TAC has a better cardiovascular risk profile
• TAC is CNI of choice in abdominal transplantation.
mTOR Inhibitors

• Mammalian Target of Rapamycin
• Blocks Signal 3
• Stops signal to final common pathway of clonal expansion.
mTOR Inhibitors – pro’s

- Not as effective as primary immunosuppression
- Anti-neoplastic activities.
  - Current subject of research here at UK
- Anti-proliferative
  - The “drug” in drug eluting stents
- May reduce CMV disease
mTOR Inhibitors – con’s

- Delayed recovery of ATN
- Impaired wound healing
- Hepatic Artery Thrombosis
- Thrombocytopenia
- Hyperlipidemia
- Mouth ulcers
Three Era’s of liver Transplantation
Anti-metabolites

- 6 - Mercaptopurine
- Azathioprine
- Mycophenolic Acid
Purine Biosynthesis

Pathways of Purine Biosynthesis

DeNovo Pathway
- Ribose-5P + ATP
  - PRPP Synthetase
- 5-phosphoribosyl-1-pyrophosphate (PRPP)
- Inosine MP
  - Adenosine Deaminase (ADA)
  - Ribonucleotide Reductase
- Adenosine MP
  - Adenosine TP
  - RNA

Salvage Pathway
- Guanine
  - HGPATase (Lesch-Nyhan)
- Guanosine TP
  - IMP Dehydrogenase (IMPD)
  - Mycophenolic Acid
  - Ribonucleotide Reductase
  - Deoxyguanosine TP
    - DNA
  - Guanosine MP
    - RNA

Deoxyadenosine TP
  - DNA
Purine Biosynthesis
• WBC lack a Salvage pathway
Azathioprine

Pathways of Purine Biosynthesis

DeNovo Pathway

PRPP Synthetase

Ribose-5P + ATP

5-phosphoribosyl-1-pyrophosphate (PRPP)

Inosine MP

Adenosine Deaminase (ADA)

Adenosine MP

Ribonucleotide Reductase

Deoxyadenosine DP

DNA

IMP Dehydrogenase (IMPD)

Mycophenolic Acid

Guanosine MP

Glycoprotein

Syntees

Guanine

Deoxyguanosine TP

RNA

Salvage Pathway

Guanosine TP

Deoxyguanosine DP

Guanosine TP

DNA
Mycophenolic Acid

Pathways of Purine Biosynthesis

DeNovo Pathway

Ribose-5P + ATP

PRPP Synthetase

5-phosphoribosyl-1-pyrophosphate (PRPP)

Inosine MP

Adenosine Deaminase (ADA)

Adenosine TP

Adenosine MP

Deoxyadenosine DP

Deoxyadenosine TP

DNA

RNA

Guanosine TP

Guanosine MP

Glycoprotein

Synthesis

Deoxyguanosine TP

Deoxyguanosine DP

Salvage Pathway

ATase

PRPP Kinase

Ribonucleotide Reductase

Mycophenolic Acid

(Uracil DNA)
Mycophenolic Acid

• Pro’s
  • Use without monitoring
  • Effective in combination
  • No organ toxicity

• Con’s
  • GI
    • diarrhea
  • Hematologic
    • Anemia, Neutropenia
Steroids

- Improved skin-graft survival
- Mechanism is a “black box”
  - Non-specific
  - Glucocorticoid receptors within the nucleus
  - Transcriptional modulation
- Many side effects
Antibodies

• Binding
  • Activate (or prevent activation)

• Depleting
  • Mechanism of action is mediating cell death
    • ADCC
    • Compliment activation

Kohler & Milstein – 1975
Antibodies

• Anti-Thymocyte Globulin – Polyclonal antibodies to T-lymphocytes generated by injecting them into a rabbit or horse
  • “Minnesota ALG” - Widely variable preparation and potency made trials of this drug impossible

• OKT3 – Depleting monoclonal Ab against CD3
  • Very effective
  • Very dangerous
Other antibodies

• Basiliximab – IL-2 receptor antagonist
  • Blocks IL-2 signaling

• Alemtuzumab – Depleting Ab against CD52
  • Present on “all” lymphocytes (B and T)

• Rituximab – Depleting Ab against CD20
  • Present on “all” B-cell’s (not plasma cells)

• Belatacept – humanized CTLA-4 analog
  • Competitive inhibitor CD80,86
• Eculizumab – Inhibits assembly of MAC  
  • Binds Compliment C5  
• Alafecept – Humanized LFA-3 analog  
  • Inhibitor of LFA3/CD2 costimulation  
• Bortezomib – Inhibitor of 26S Proteosome  
  • Disrupts homeostasis and leads to apoptosis  
• Tocilizumab – blocks the IL-6 receptor
Etc. . .
Ongoing Research in the Transplant Center

The Role of PI3K/mTOR Inhibition in Combination with Sorafenib in Hepatocellular Carcinoma Treatment

ROBERTO GEDALY¹, PAUL ANGULO², CHANGGUO CHEN¹, KATE TOWNSEND CREASY³,⁴, BRET T. SPEAR³,⁴, JONATHAN HUNDLEY¹, MICHAEL F. DAILY¹, MALAY SHAH¹ and B. MARK EVERS¹,⁴

Departments of ¹Surgery, ²Internal Medicine, ³Immunology and ⁴Markey Cancer Center, University of Kentucky, College of Medicine, Lexington, KY, U.S.A.

Figure 2. Growth curves of tumor xenografts. Mice were treated with sorafenib and PI-103 as single agents or in combination. *Control significantly different from mono-drug or drug-combination treatments (p<0.05); **drug-combination treatment significantly different from mono-drug treatments (p<0.032).
Evidence of the immunomodulatory role of dual PI3K/mTOR inhibitors in transplantation: an experimental study in mice

Valery Vilchez¹,†, Lilia Turcios¹, David A. Butterfield²,³, Mihail I. Mitov², Cristin L. Coquillard¹, Ja Anthony Brandon⁴, Virgilius Cornea⁵, Roberto Gedaly¹ & Francesc Marti¹

SUMMARY
The PI3K/mTOR signaling cascade is fundamental in T-cell activation and fate decisions. We showed the distinct regulation of PI3K/mTOR in regulatory and effector T-cells and proposed the potential therapeutic benefit of dual inhibition.
Unbalanced Treg function: Pathological outcomes

Low level of Tregs → High effector T cell activity

- Autoimmune disease
- Inflammatory disease
  - Allergy
  - Asthma
  - IBD
- Graft rejection
- GVHD

Over-reaction

High level of Tregs → Low effector T cell activity

- Cancer
- Infectious Diseases (Opportunistic)
  - CMV, HSV
  - Mycobacteria
  - Leishmania
  - Pneumonia

Immunosuppression
Treg-based adoptive Immunotherapy

I. Isolation and culture of allograft-recipient Treg cells

Blood extraction

Ficoll Centrifugation

Magnetic Selection

Regulatory T cells (Tregs)

Treg cell culture
Treg-based adoptive Immunotherapy

II. *Ex vivo* expansion and re-infusion of autologous Treg cells

1-5x10^6

15-25 days

300x10^6

Testing Treg cell potency:
- Phenotype
- Suppressive function
- Stability

Re-infusion of autologous Treg cells to allograft recipient
Pearls

• Sirolimus requires caution:
  • Avoid in ATN
  • Hold for surgery

• Consider immunosuppression drugs in atypical patient presentations.

• Research into immune function uncovers new targets all the time.
QUESTIONS?