Animal Models of Antibody Mediated Rejection

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FDA WORKSHOP: ANTIBODY MEDIATED REJECTION IN KIDNEY TRANSPLANTATION
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Enhanced De Novo Alloantibody and Antibody-Mediated Injury in Rhesus Macaques


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Five control animals were treated with CD3-Immunotoxin/alefacept/tacrolimus, inducing AMR.

Four animals received 20mg/kg Belatacept or 20mg/kg 2C10R4 in addition to the AMR inducing regimen.
Costimulation blockade alters germinal center responses and prevents antibody-mediated rejection

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Production of early de novo DSA was completely attenuated for both bela- and 2c10 treated groups at 4 and 6wks post transplantation.
Proliferating (Ki67+) B cells in GC decreased in bela- and 2c10-treated animals
Summary

• In a *de novo* AMR NHP model treated with IT/tac/alefacept, costimulation blockade prevented:
  • AMR clinically and by histology
  • de novo alloantibody production, B cell isotype switching (IgM → IgG), GC reconstruction, Tfh cells in GC

• Kirk et al. Renal transplantation with alemtuzumab, sirolimus, belatacept (FDA sponsored trial)
Rationale for a sensitized Non-human primate model

- Current desensitization strategies mostly address antibody and B cells, but not memory cells and plasma cells
- Efficacy is limited, especially long term
Methods II: Desensitization

Triple therapy
Bortezomib 1.3 mg/m²
Belatacept 20 mg/kg
2C10 20 mg/kg
twice weekly
Synergy of Costimulation blockade and Bortezomib in reduction of DSA

Skin graft
No Immunosuppression

Desensitization
Bortezomib alone
Belatacept+2C10
Triple (BTZ+Bela+2C10)

BM plasma cell CD19+38+20-IgD-

% change to pretreatment

p<0.05

p<0.01
Methods III: Transplantation

Skin graft
No immuno-suppression

Triple therapy
n=5

No desensitization
n=6

Kidney transplant
Immunosuppression
anti-CD4, -CD8
Tacrolimus
MMF
Methylprednisolone

DSA peak
Desensitization results: renal allograft survival

Survival: Triple vs. non desensitized

- Serum creatinine 0.9mg/dl
- Serum creatinine 1.1mg/dl
- Serum creatinine 0.55mg/dl
- Serum creatinine 1.2mg/dl (ongoing)

Percent survival

- Red line: triple therapy (n=5)
- Orange line: not desensitized (n=6)

\[ p = 0.073 \]
Humoral Compensation after Bortezomib Treatment of Allosensitized Recipients

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Conclusions

• NHP provide an invaluable tool for developing better immunosuppressive strategies, drugs for transplantation
• Responsible use of NHP for research provides a precious national resource to understand transplant biology better
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