Animal Models of Antibody Mediated Rejection

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FDA WORKSHOP: ANTIBODY MEDIATED REJECTION IN KIDNEY TRANSPLANTATION
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nhanced *De Novo* Alloantibody and Antibody-lediated Injury in Rhesus Macaques

K. Page, A. J. Page, J. Kwun, A. C. Gibby, F. Leopardi, J. B. Jenkins,
A. Strobert, M. Song, R. A. Hennigar, N. Iwakoshi, S. J. Knechtle

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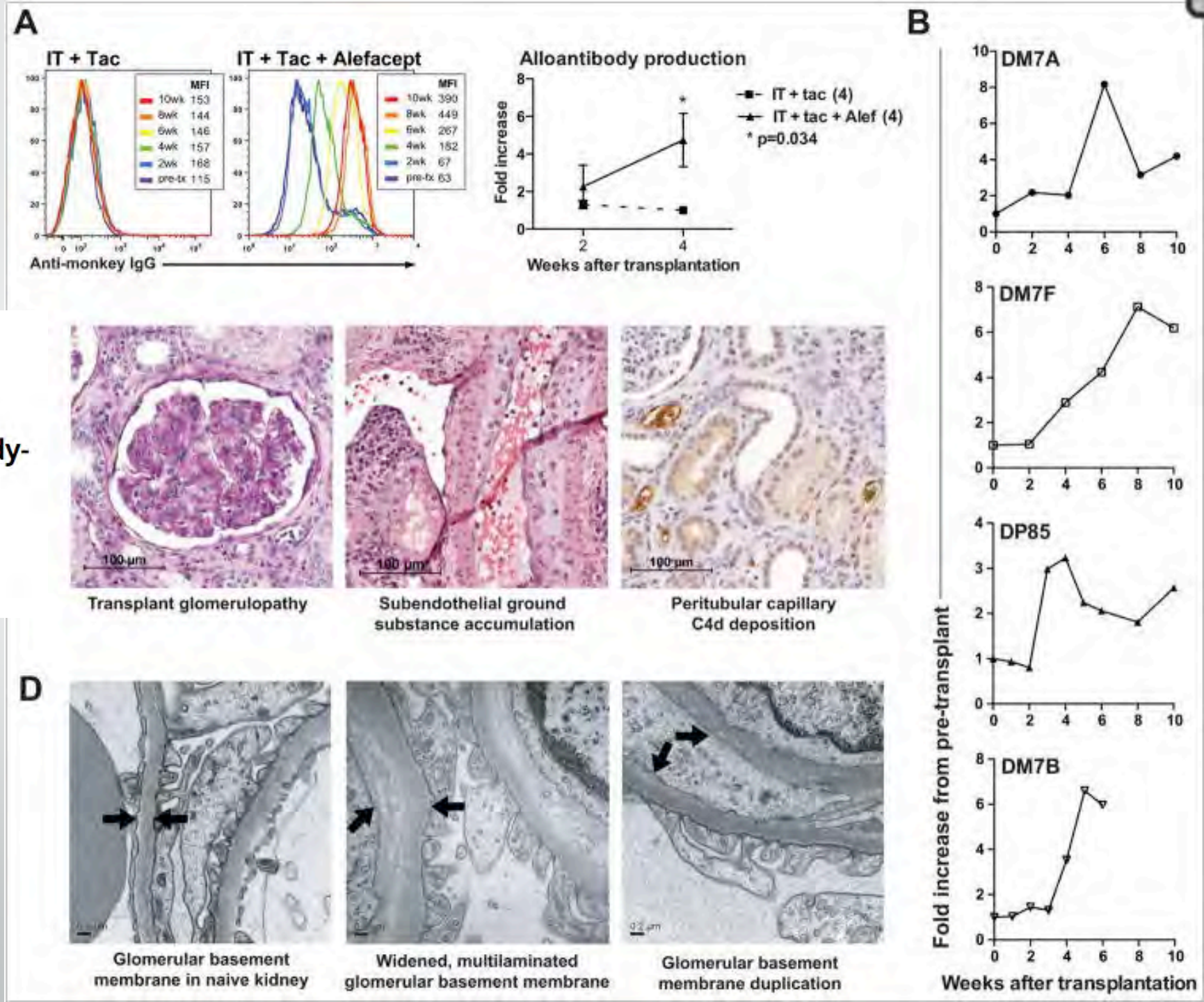

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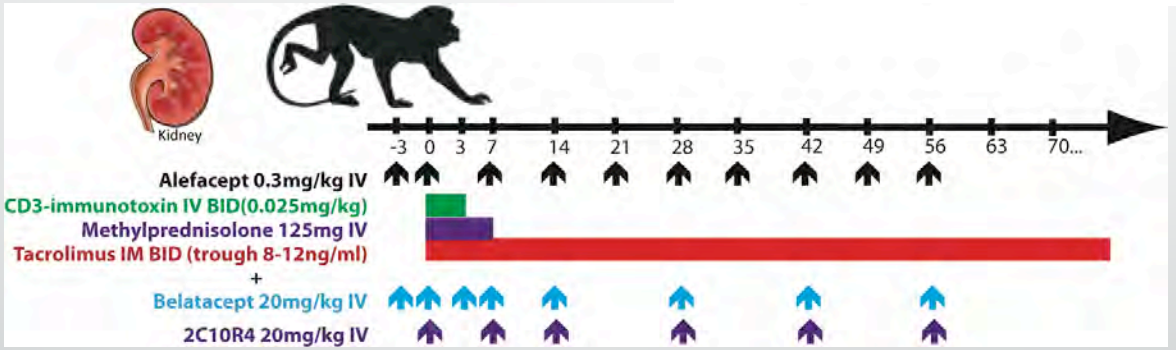
Costimulation Blockade Alters Germinal Center Responses and Prevents Antibody-Mediated Rejection

E. J. Kim[1,†], J. Kwun[1,†], A. C. Gibby[1], J. J. Hong[2,3], A. B. Farris III[2], N. N. Iwakoshi[1], F. Villinger[2,3], A. D. Kirk[1] and S. J. Knechtle[1,*]



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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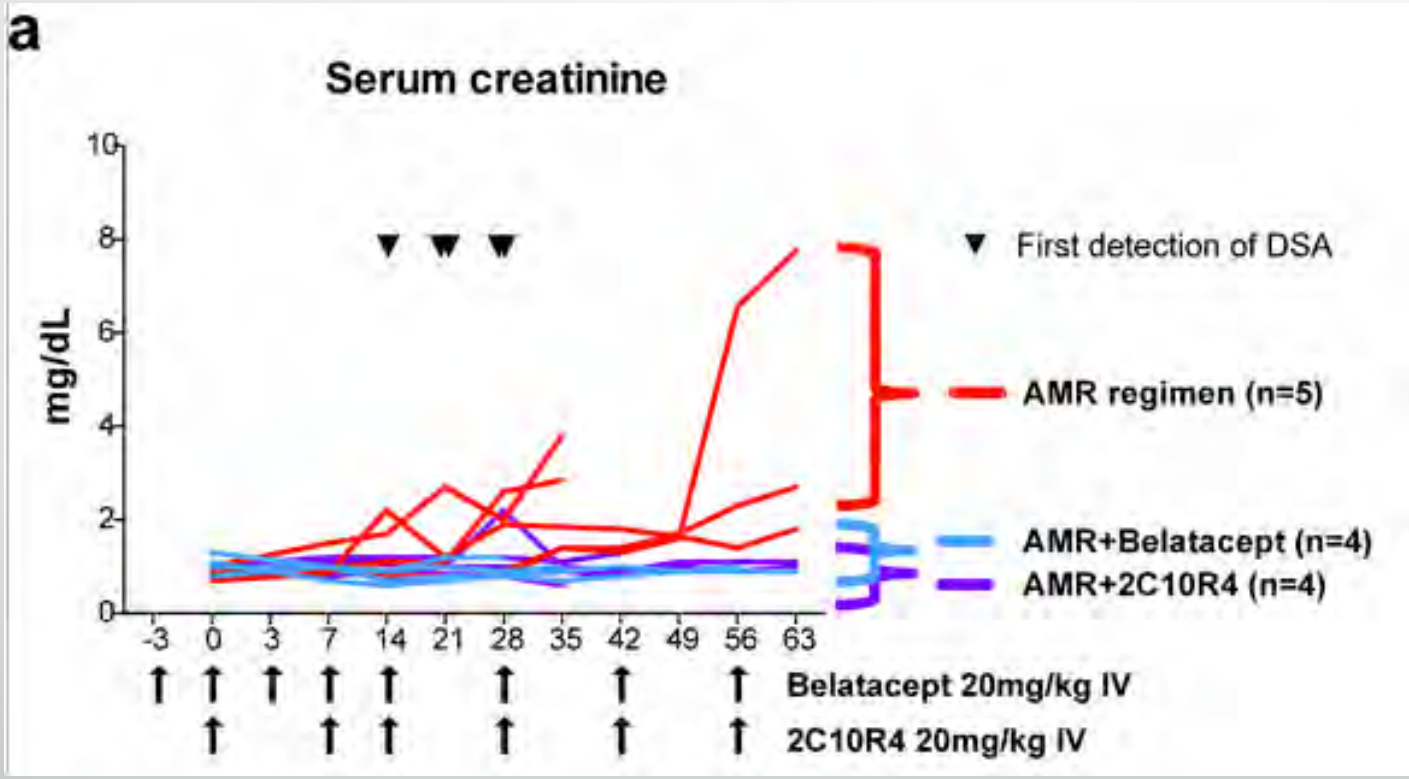

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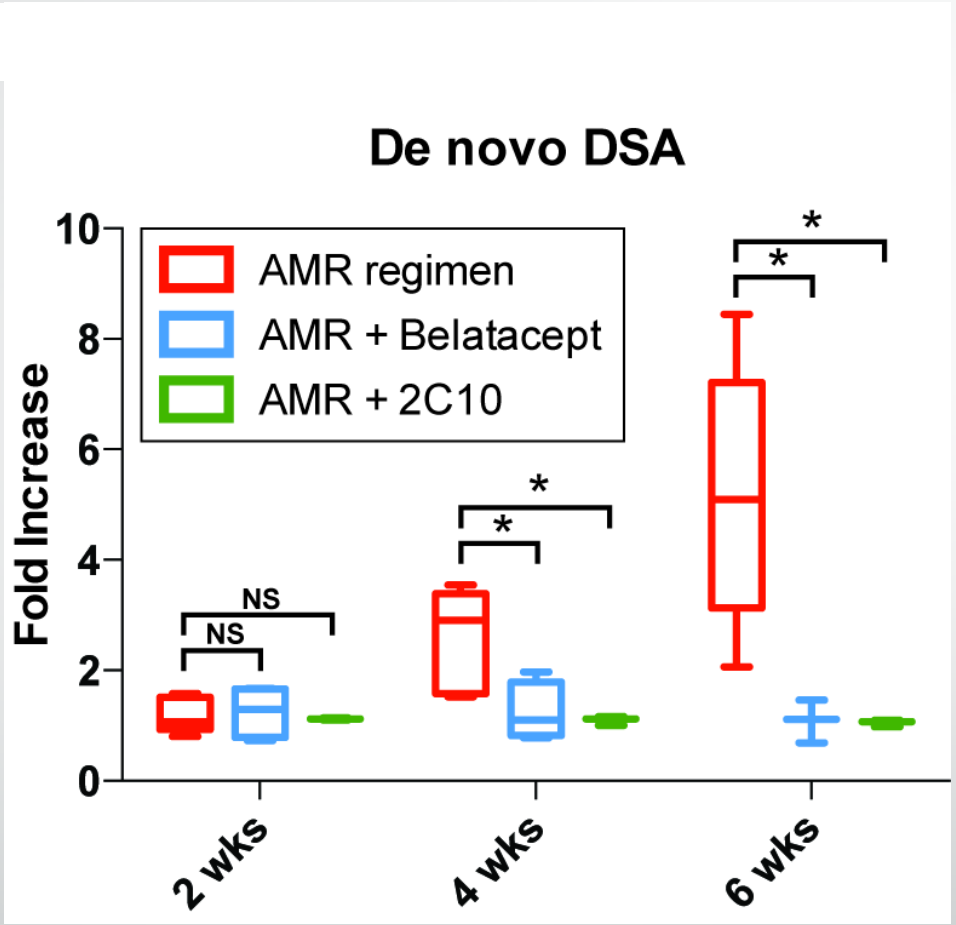
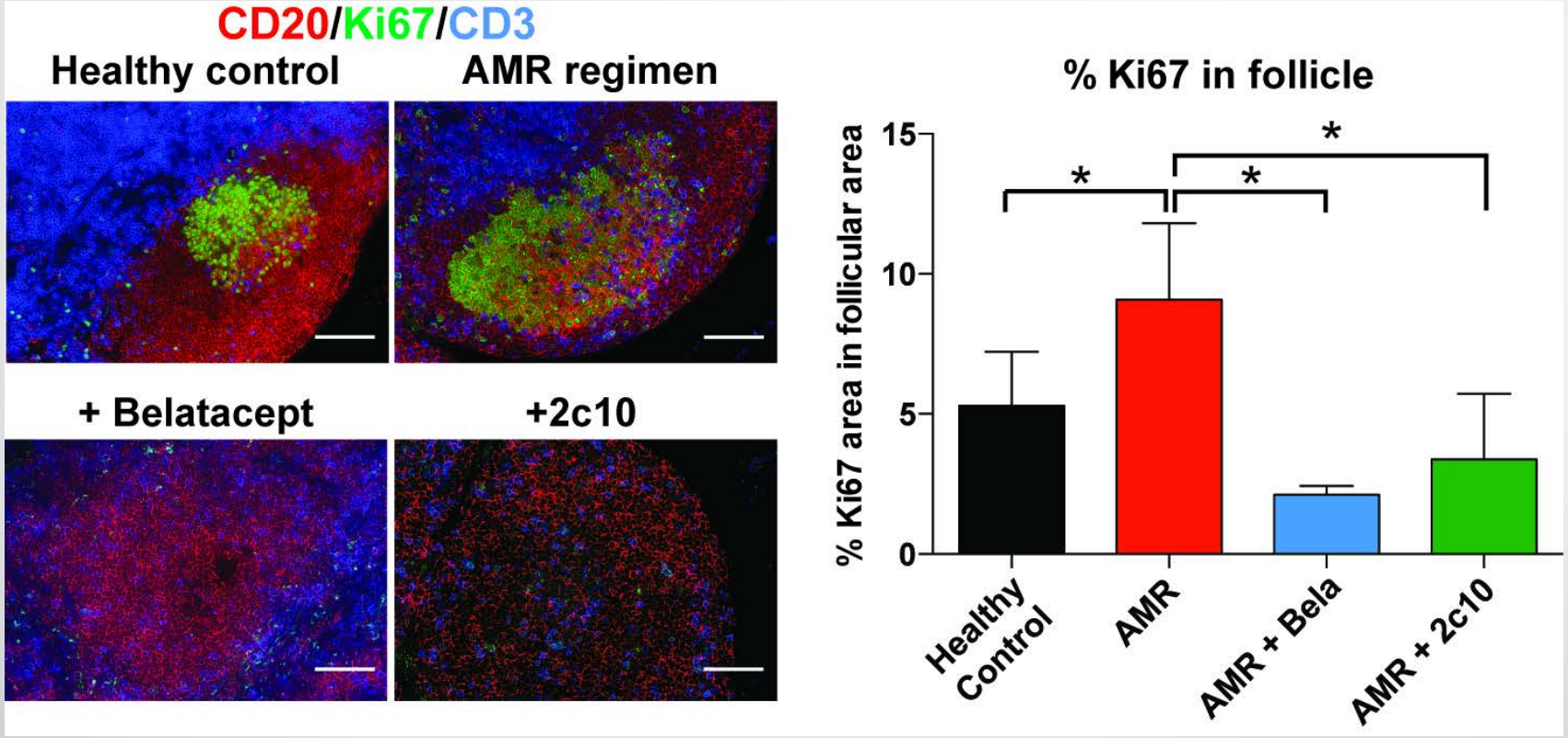
Donor Specific Antibody (DSA) production



- Production of early de novo DSA was completely attenuated for both bela- and 2c10 treated groups at 4 and 6wks post transplantation.

Clonal B cell expansion (Ki67+CD20+) in GC



- Proliferating (Ki67+) B cells in GC decreased in bela- and 2c10-treated animals

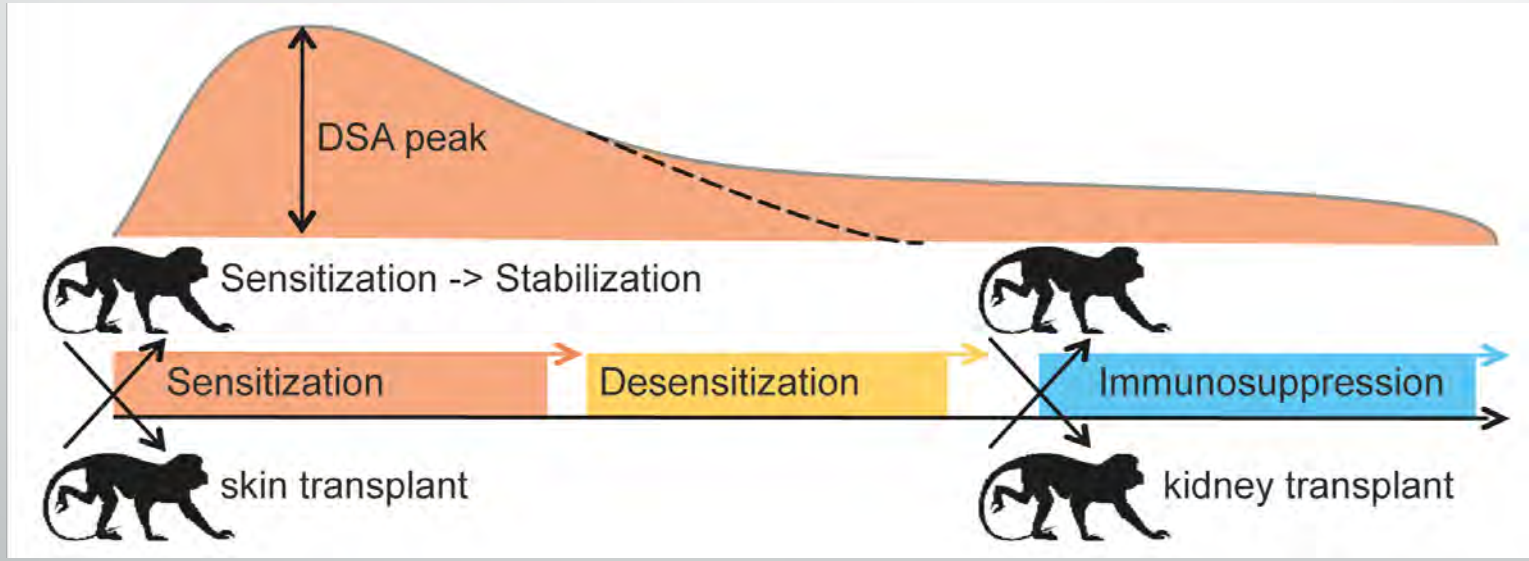
Summary

- 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

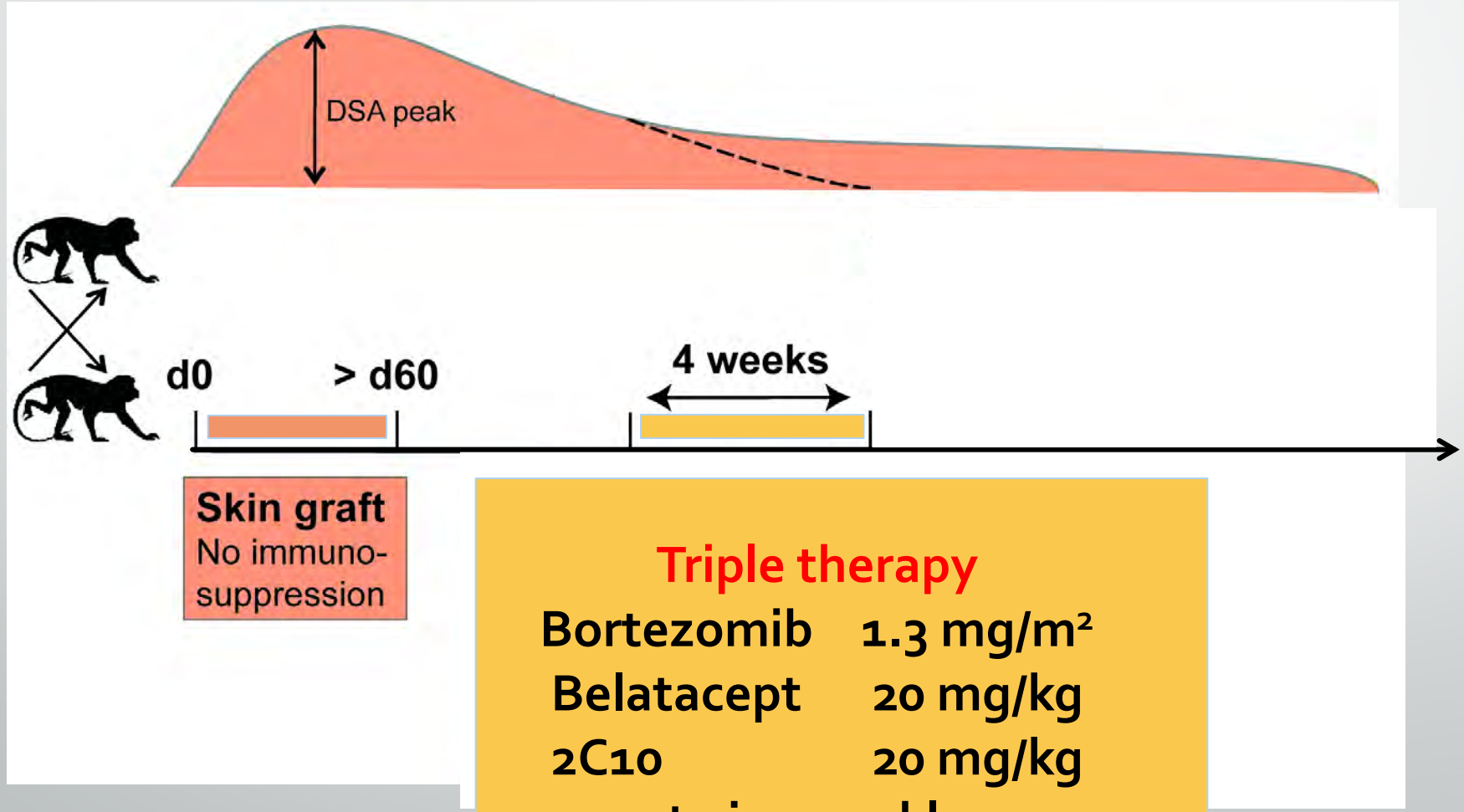
- Kirk et al. Renal transplantation with alemtuzumab, sirolimus, belatacept (FDA sponsored trial)

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

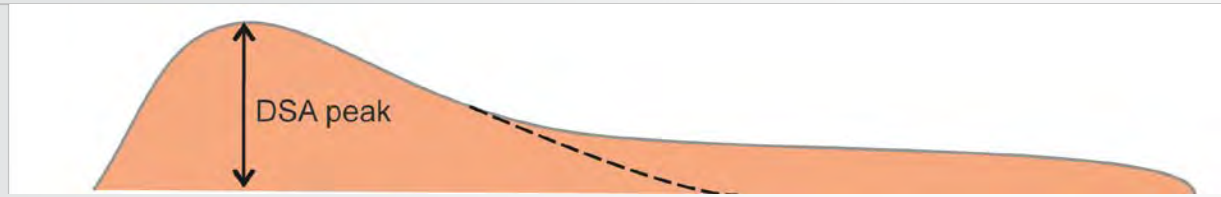


Triple therapy

Bortezomib	**1.3 mg/m²**
Belatacept	**20 mg/kg**
2C10	**20 mg/kg**

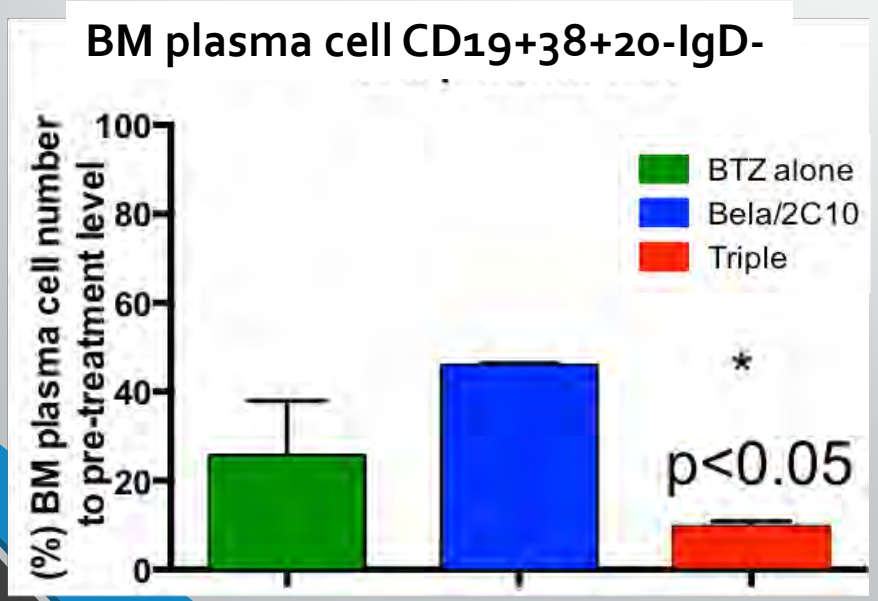
twice weekly

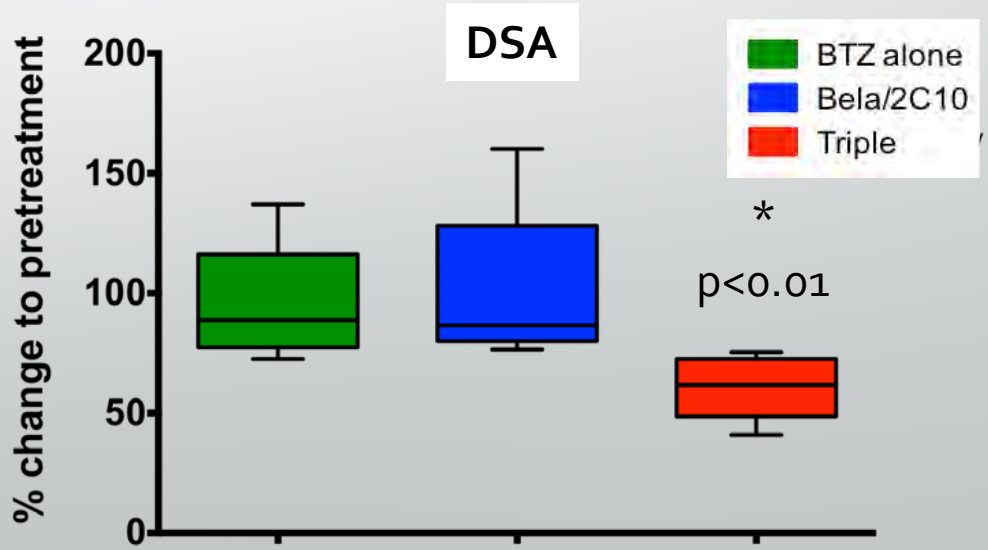
Synergy of Costimulation blockade and Bortezomib in reduction of DSA



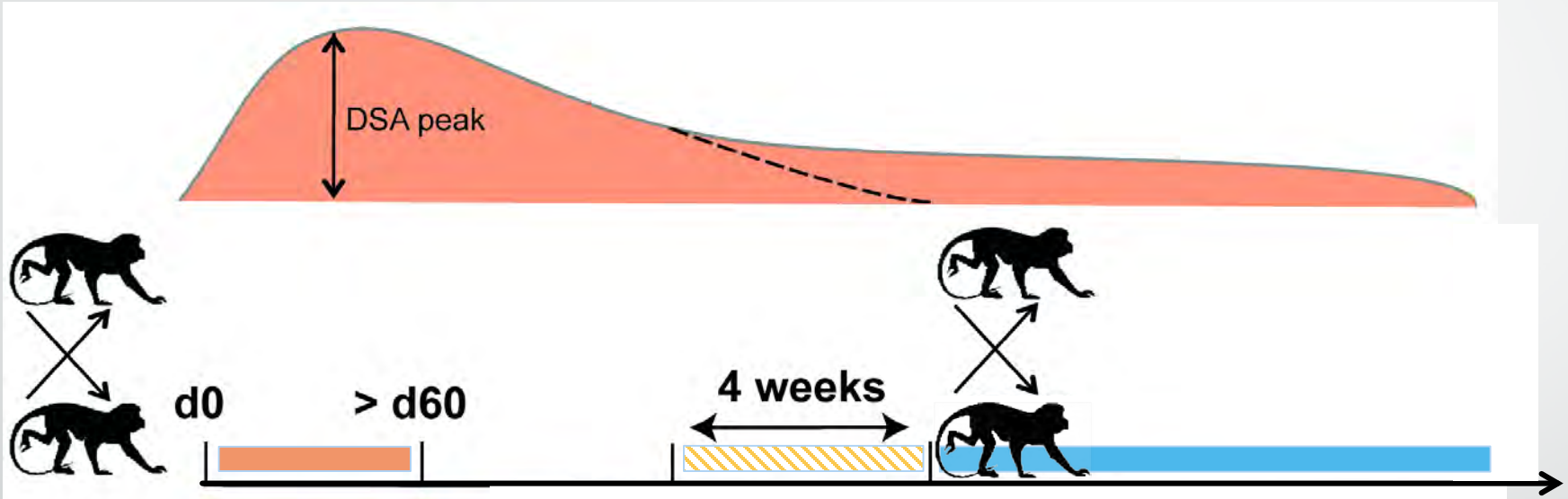
Skin graft
No Immuno-suppression

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





Methods III: Transplantation



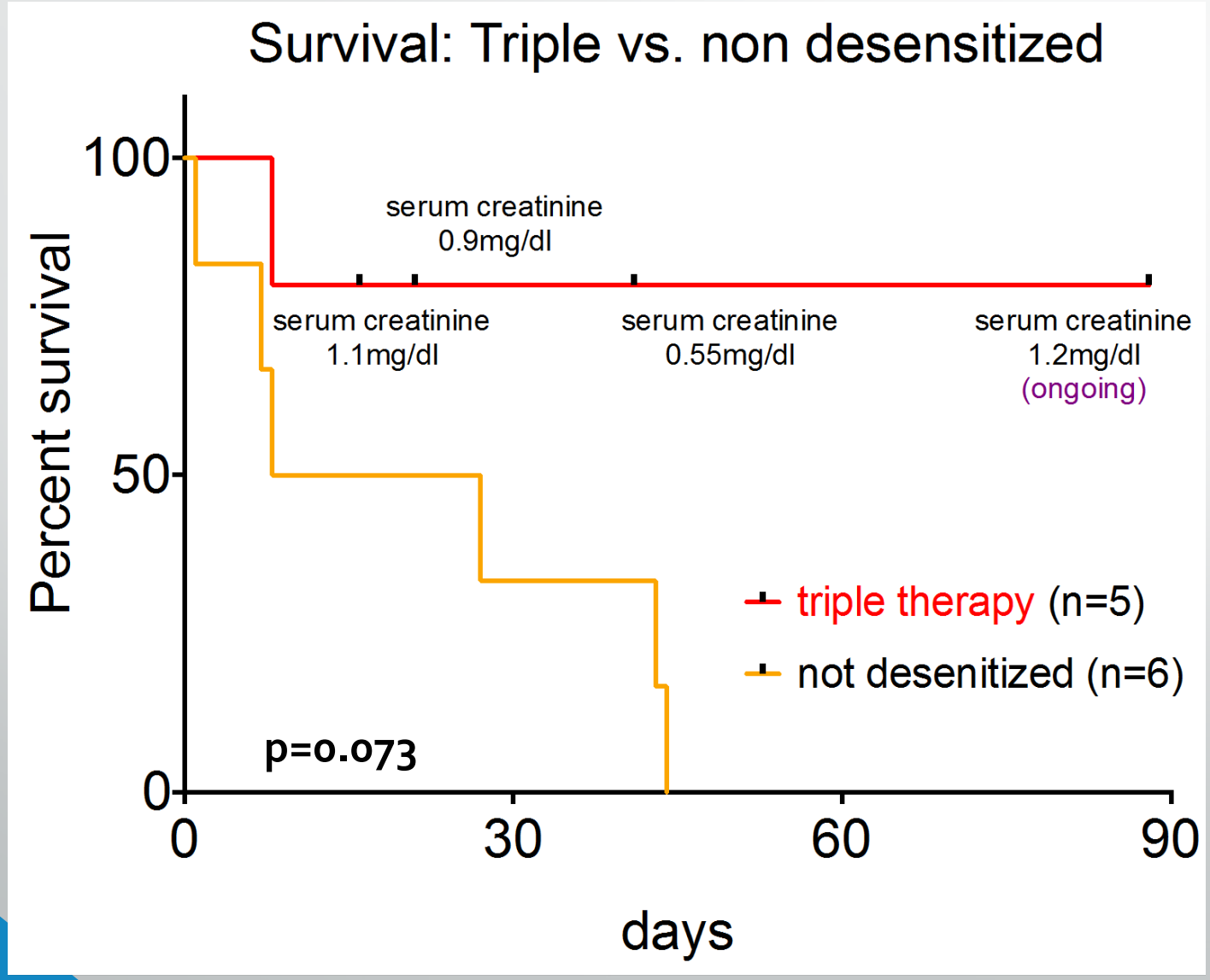
Skin graft
No immuno-suppression

Triple therapy
n=5

No desensitization
n=6

Kidney transplant
Immunosuppression
anti-CD_4, -CD8
Tacrolimus
MMF
Methylprednisolone

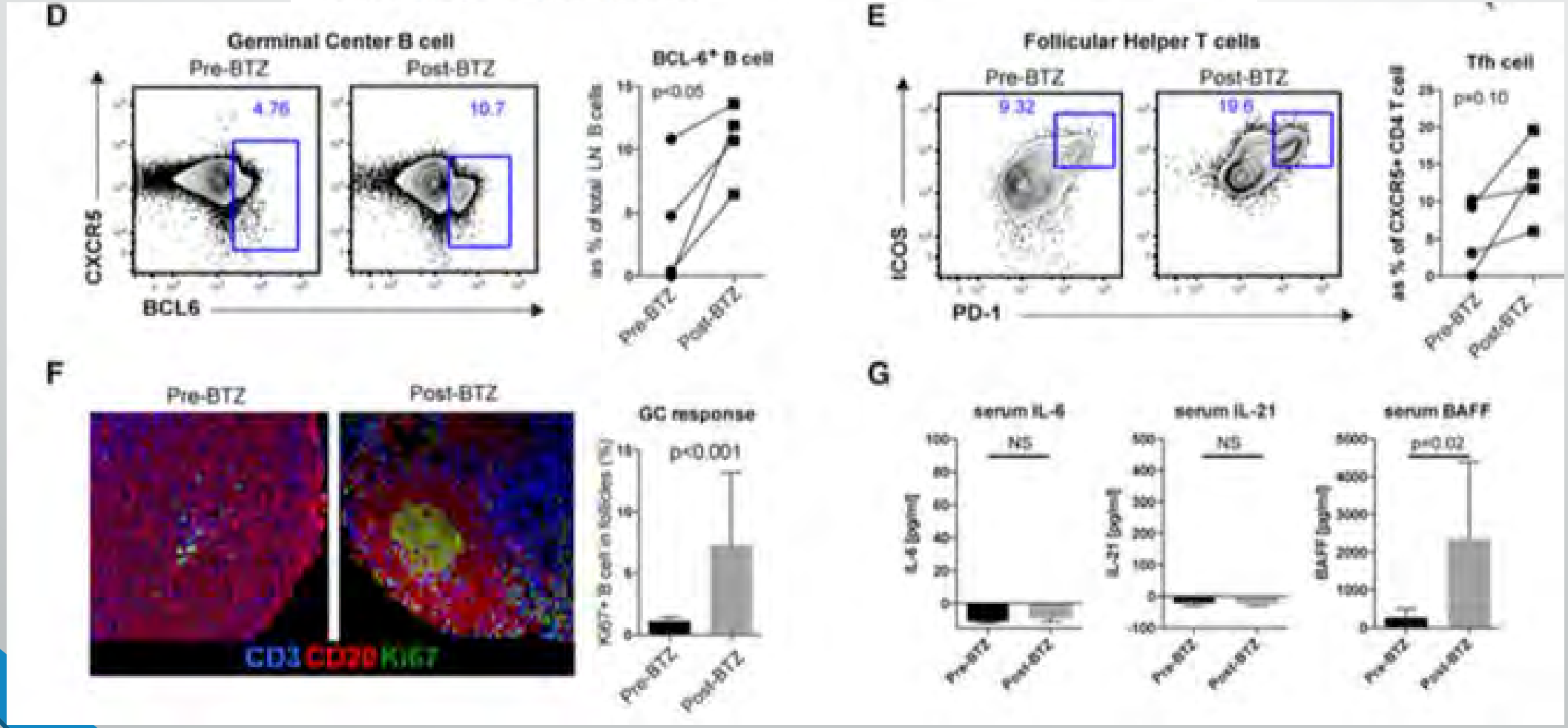
Desensitization results: renal allograft survival



BRIEF COMMUNICATION www.jasn.org

Humoral Compensation after Bortezomib Treatment of Allosensitized Recipients

Jean Kwun,*† Christopher Burghuber,†‡ Miriam Manook,* Neal Iwakoshi,† Adriana Gibby,† Jung Joo Hong,§ and Stuart Knechtle*†



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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