Animal models of AMR: how they inform clinical trials

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Targeting AMR in 3 Phases

Prevent Ab Production
- Immunosuppression targeting T cells

Stop & Reduce Ab Production
- IVIG
- Rituxan
- Bortezomib

Limit Ab-mediated Damage
- Plasmapheresis
- Anti-C5

Stop ongoing B cell & PC responses rapidly and long-term
Delayed CTLA-4Ig stops ongoing antibody responses

D0: B/c DST
± CTLA-4Ig from D0 or D6 or D14 (2x/week)

Bleed weekly

Young et al. 2016
Possible Causes for delayed CTLA4-Ig treatment failure

- Late Germinal Center B cell responses are CTLA4-Ig resistant
- B cells differentiated into antibody-secreting cells (ASC) that are CTLA4-Ig resistant
Tracking allo-specific B cells with donor Class I or Class II tetramers

Phenotype of alloreactive B cells

MHC Tet+ Activated IgDlo Germinal Center

Young et al. 2016
Delayed CTLA-4Ig collapses established germinal center B cell responses
Delayed CTLA4-Ig treatment inhibits alloreactive memory B cell generation

AID-Cre x Rosa29-loxP-EYFP

D0: 1° B/c DST

+ CTLA4-Ig (D6-43; 2x/wk)

+ CTLA4-Ig (D14-43; 2x/wk)

Sac on D43

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**Table:**

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<th>Naïve</th>
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<td>CTLA4-Ig</td>
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Yang et al. Transplantation 2016
CTLA-4Ig inhibits memory B cell and recall DSA responses in sensitized recipients

Chen et al. JI 2015
Rapid reversal of DSA responses with delayed CTLA4-Ig and Bortezomib (Btz)

1° B/c Immunization

± CTLA4-Ig (250 µg/mse; D14->28; 2x/week) ± Btz D14 & 16 (0.5 mg/kg)

Young et al. unpublished
Inhibiting acute AMR in the clinic with Belatacept and Velcade

Ronald Pelletier, MD
Transplant Surgeon
Ohio State University
Human Data
Animal models can inform clinical trials

**Germinal Center Reaction**

- Naïve B cell +Ag → Germinal Center Reaction
- Bortezomib

**Short-Lived ASC**

- Tfh + Ag
- Long-Lived PC

**Memory B cells +Ag**

- D6+ CTLA-4Ig: Collapses GC response
- Inhibiting memory B cell recall IgG responses with CTLA-4Ig


Chen et al. 2016