Animal models of AMR: how they inform clinical trials

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UoC
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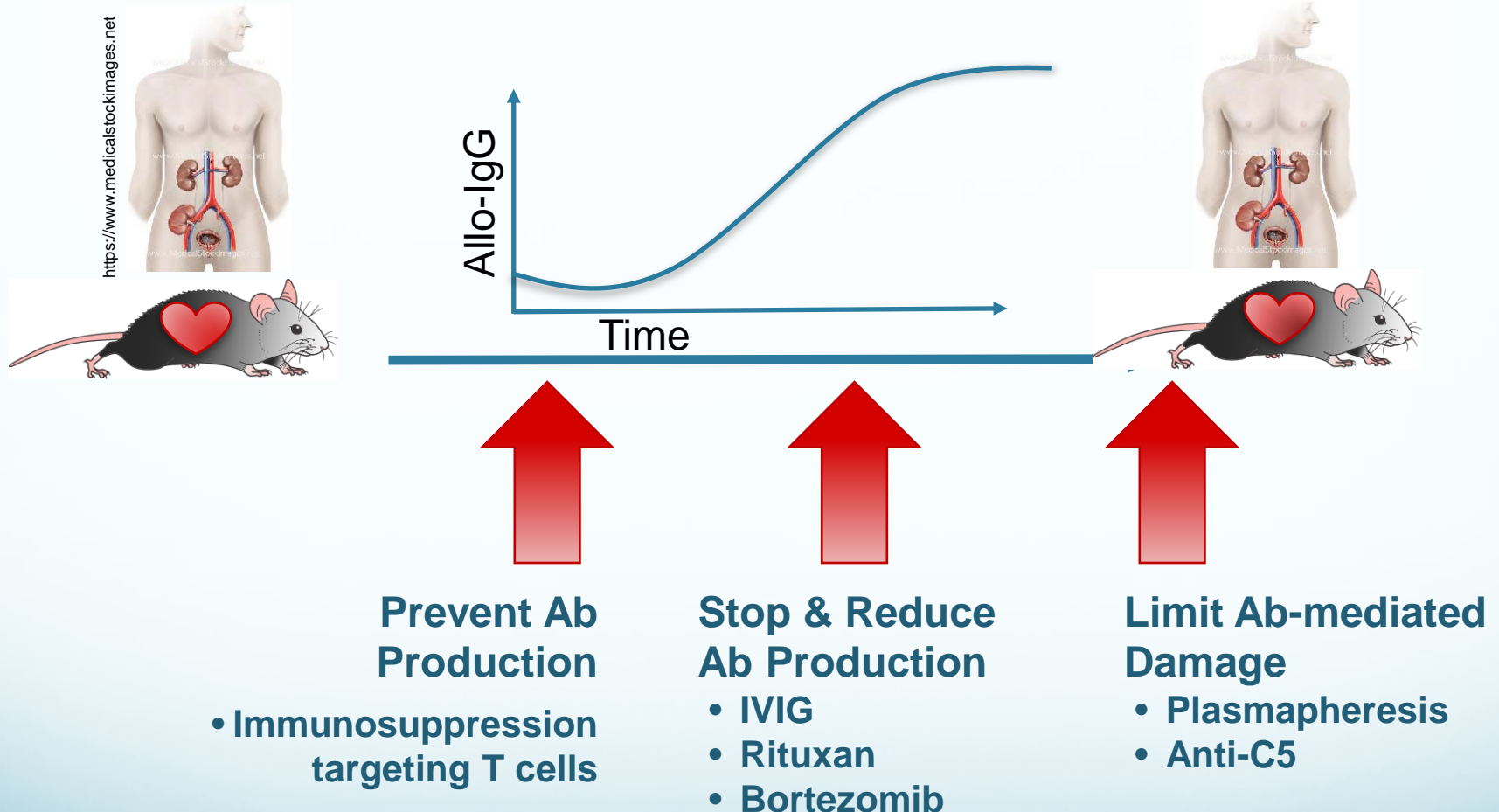
James Young
Qiang Wang
Dengping Yin

OSU
Ron Pelletier

UC Davis
Roger Sciammas

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

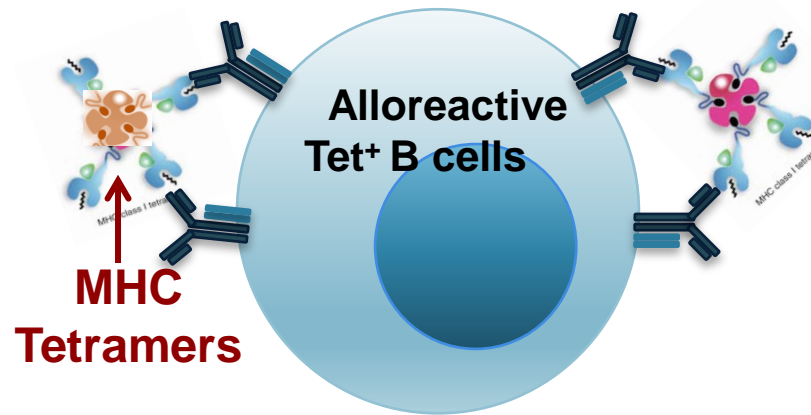# Delayed CTLA-4Ig stops ongoing antibody responses

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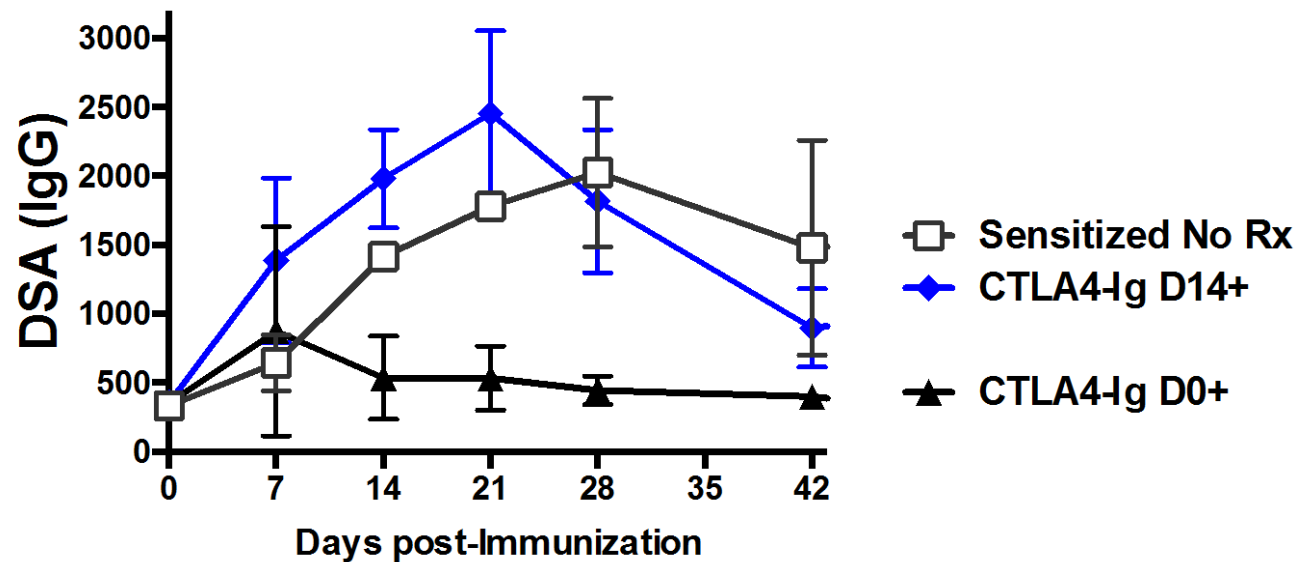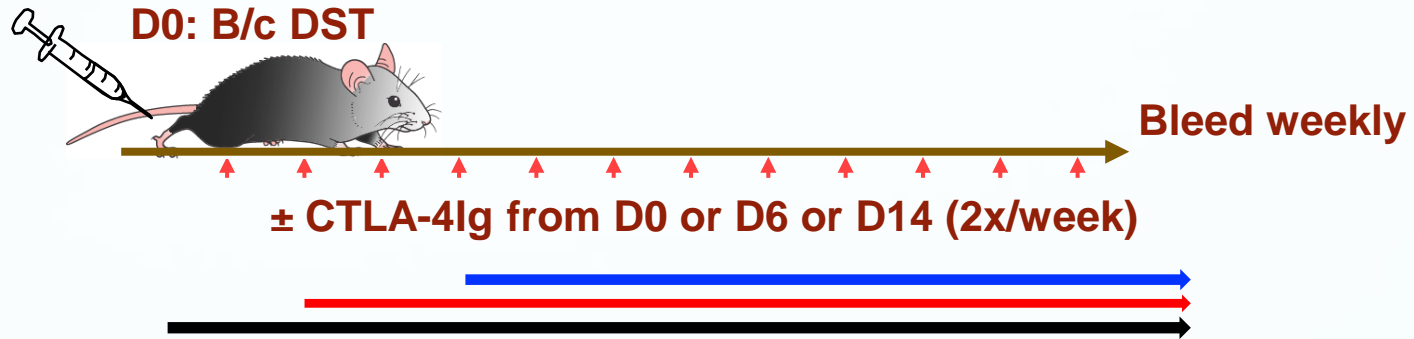
Possible Causes for delayed CTLA4-Ig treatment failure

- **Late Germinal Center B cell responses are CTLA4-Ig resistant**

- **B cells differentiated into antibody-secreting cells (ASC) that are CTLA4-Ig resistant**
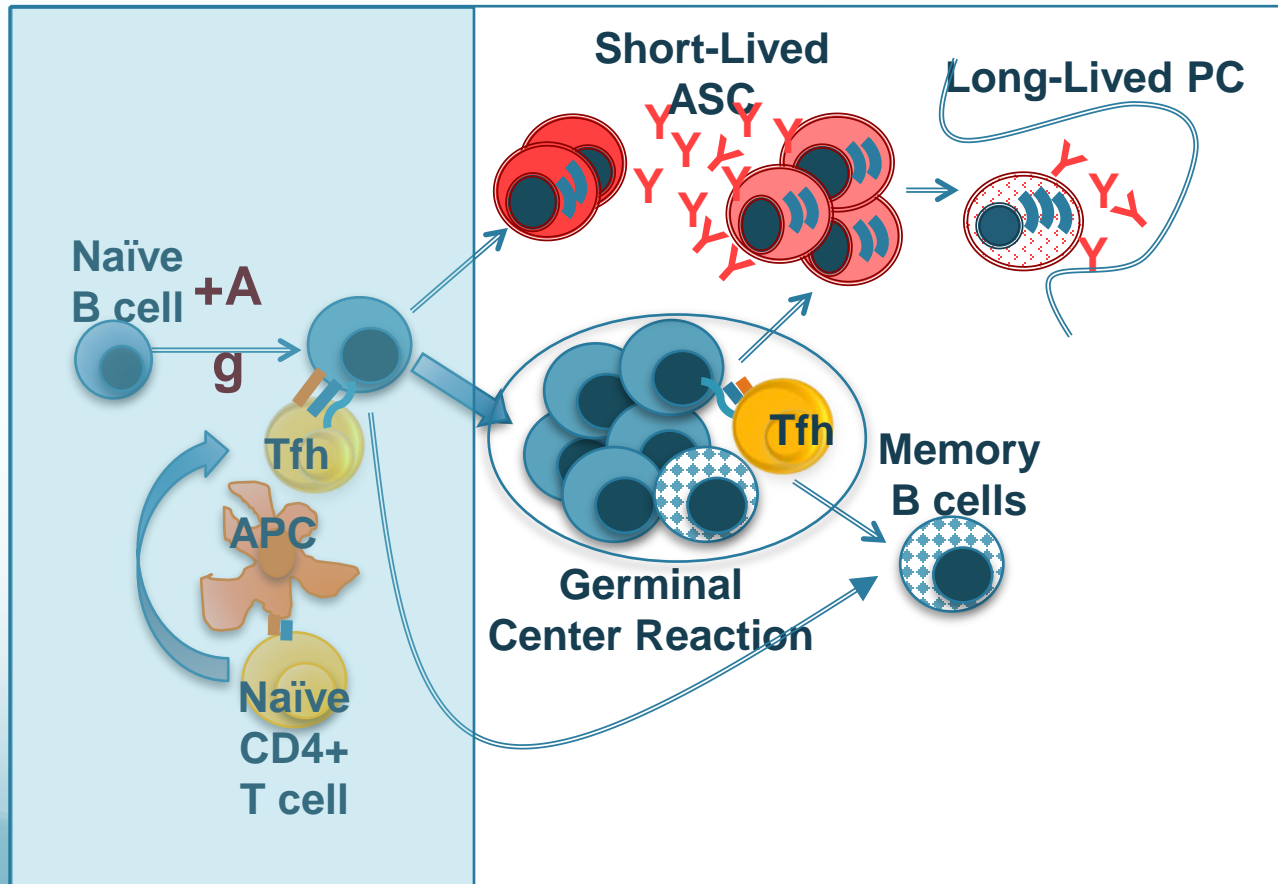
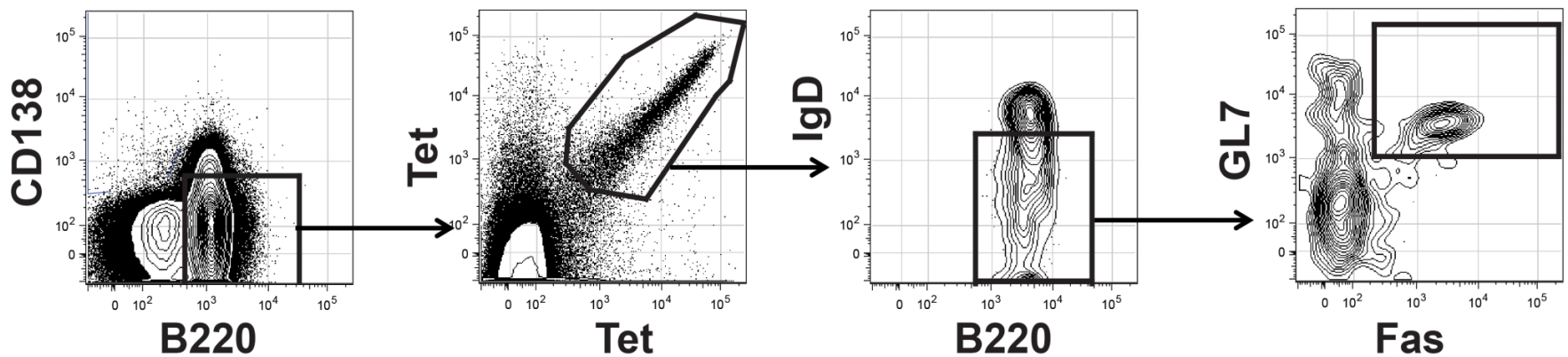# Tracking allo-specific B cells
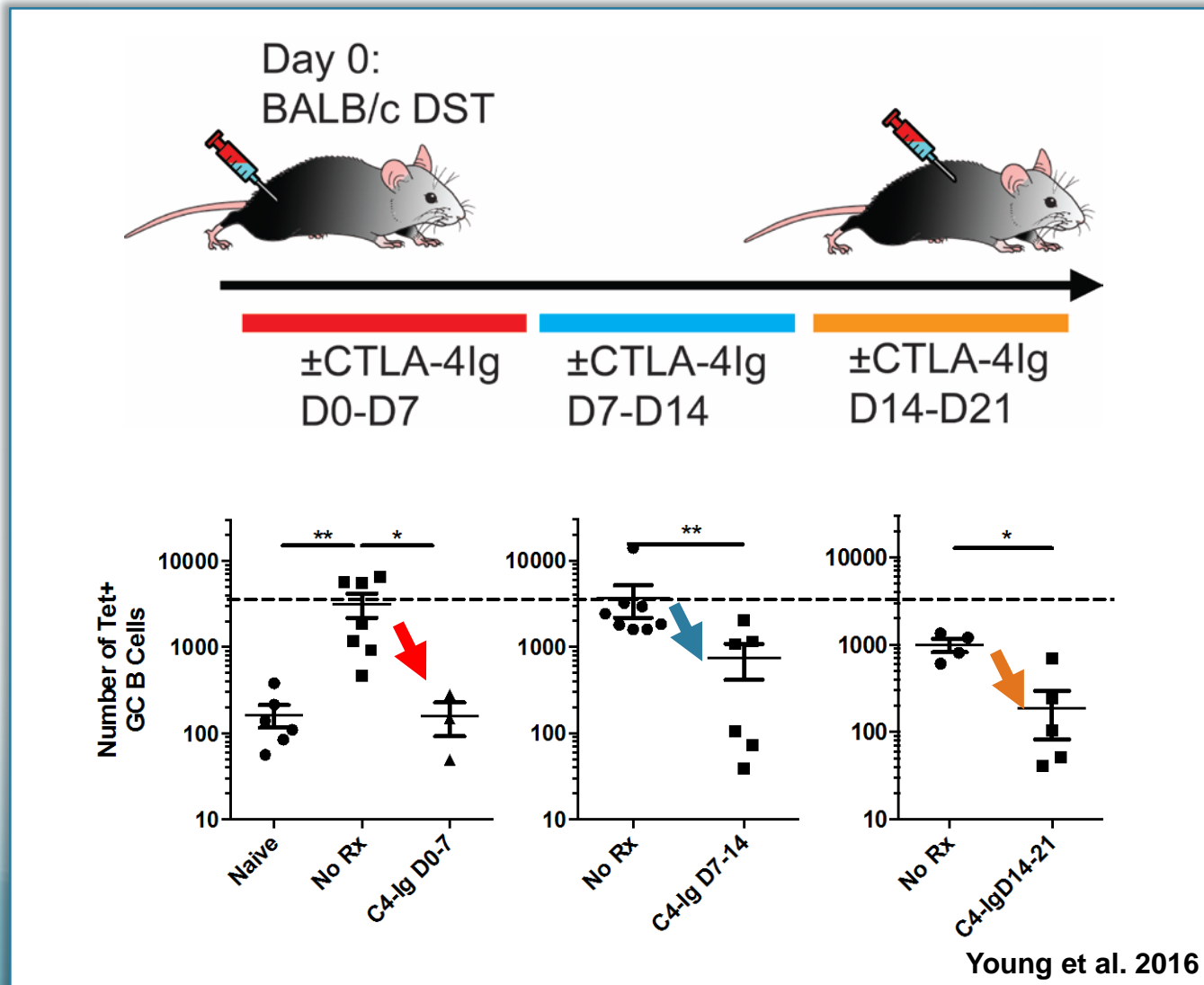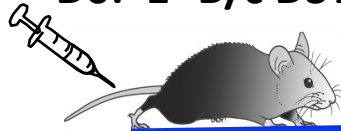# with donor Class I or Class II tetramers

Delayed CTLA-4Ig collapses established germinal center B cell responses

Young et al. 2016

Delayed CTLA4-Ig treatment inhibits alloreactive memory B cell generation
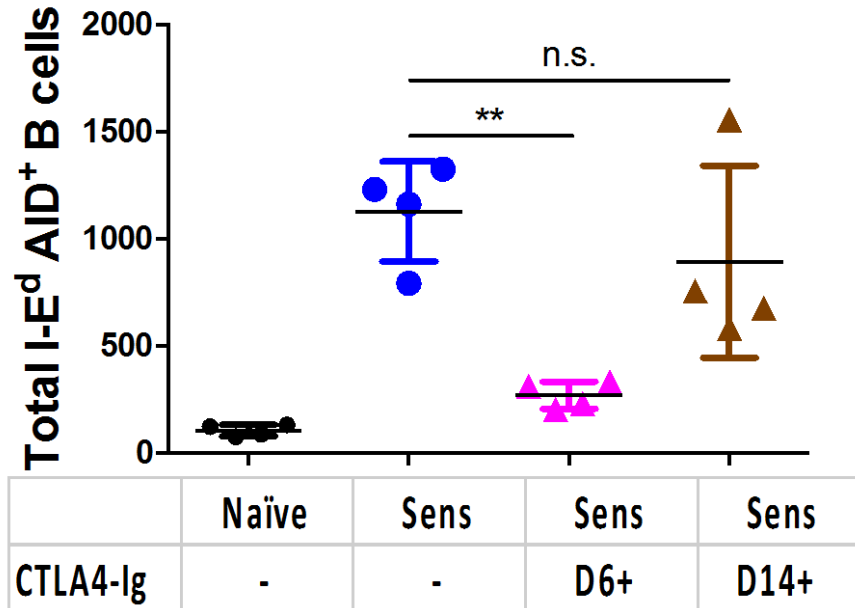

AID-Cre x Rosa29-loxP-EYFP

D0: 1° B/c DST
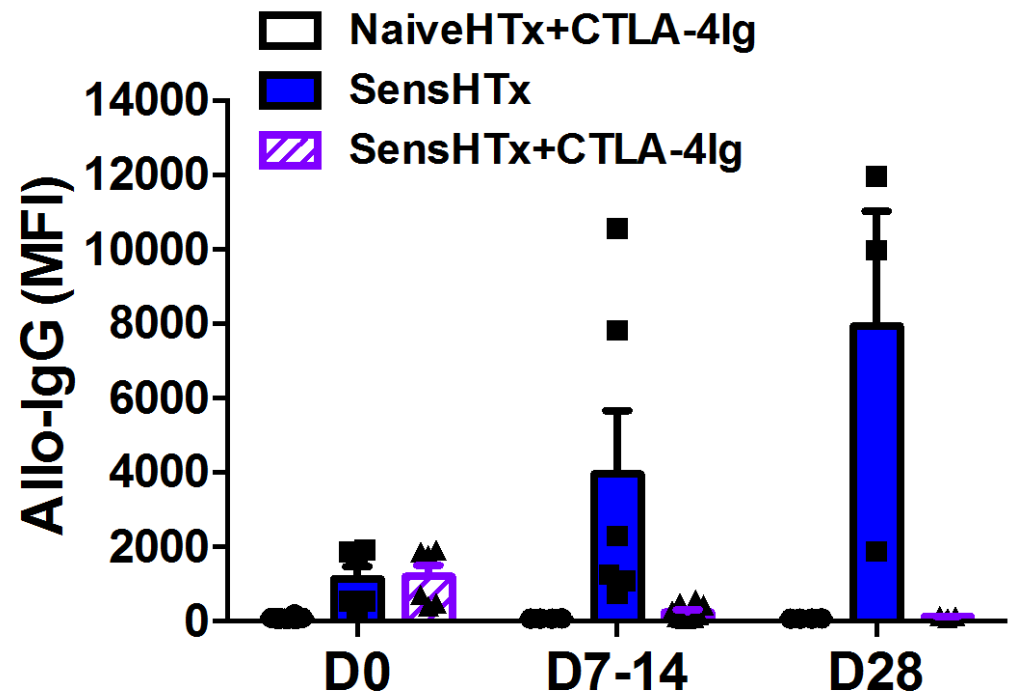
+ CTLA4-Ig (D6-43; 2x/wk)
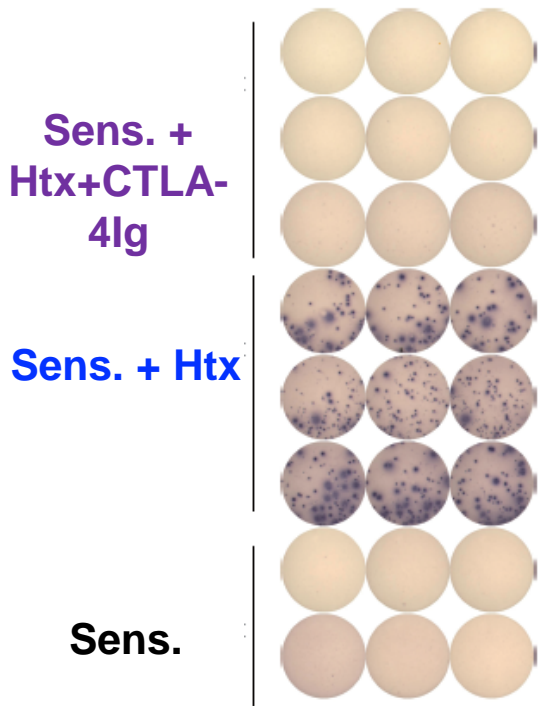
+ CTLA4-Ig (D14-43; 2x/wk)

Sac on D43

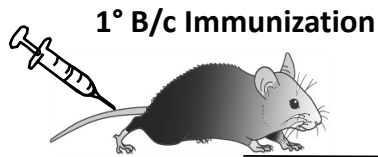|	Naïve	Sens	Sens	Sens
CTLA4-Ig	-	-	D6+	D14+

CTLA-4Ig inhibits memory B cell and recall DSA responses in sensitized recipients

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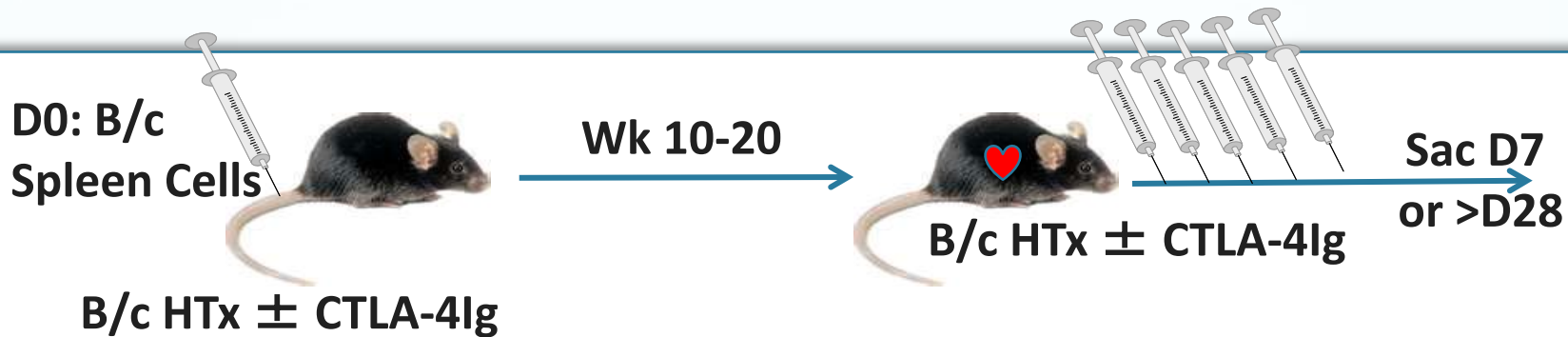
Rapid reversal of DSA responses with delayed CTLA4-Ig and Bortezomib (Btz)

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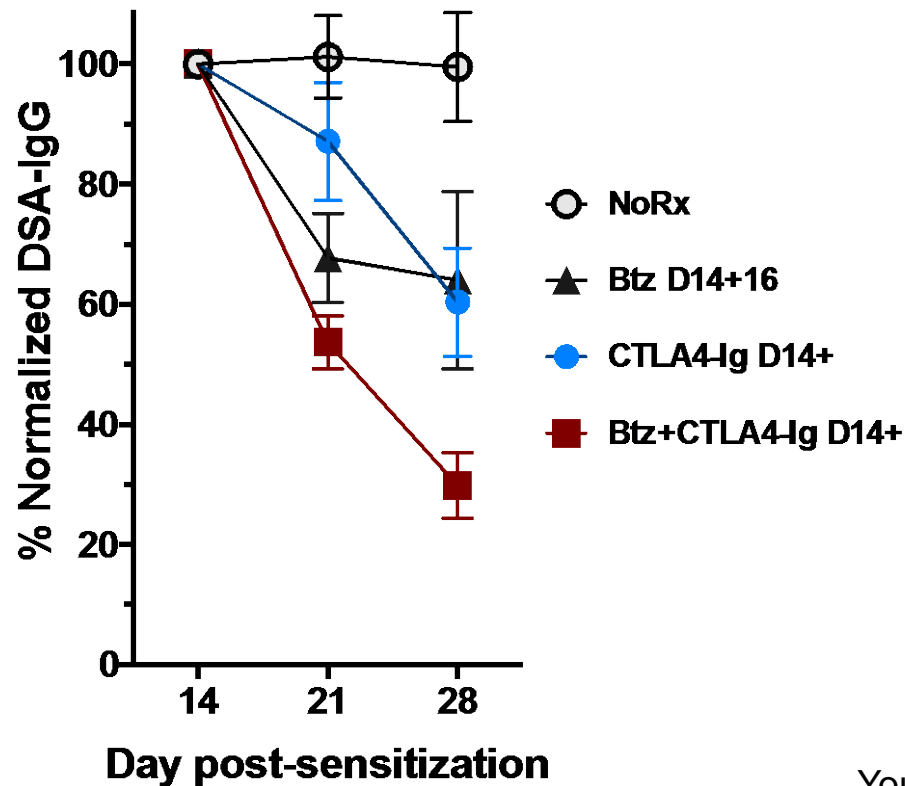
Inhibiting acute AMR in the clinic with Belatacept and Velcade

Ronald Pelletier, MD
Transplant Surgeon
Ohio State University

Human Data

Animal models can inform clinical trials

Short-Lived ASC

Long-Lived PC

Bortezomib

Naïve B cell +Ag

Germinal Center Reaction

Tfh

Tfh

Memory B cells +Ag

D6+ CTLA-4Ig:
Collapses GC response
Chen et al. 2015, Young et al. 2016; Yang et al. 2016

Inhibiting memory B cell recall
IgG responses with CTLA-4Ig
Chen et al. 2016