

Adjuvant-Enhanced Antibody Responses in the Absence of Toll-Like Receptor Signaling

Amanda L. Gavin,¹ Kasper Hoebe,¹ Bao Duong,^{1,2} Takayuki Ota,¹ Christopher Martin,^{1,2}
Bruce Beutler,¹ David Nemazee^{1*}

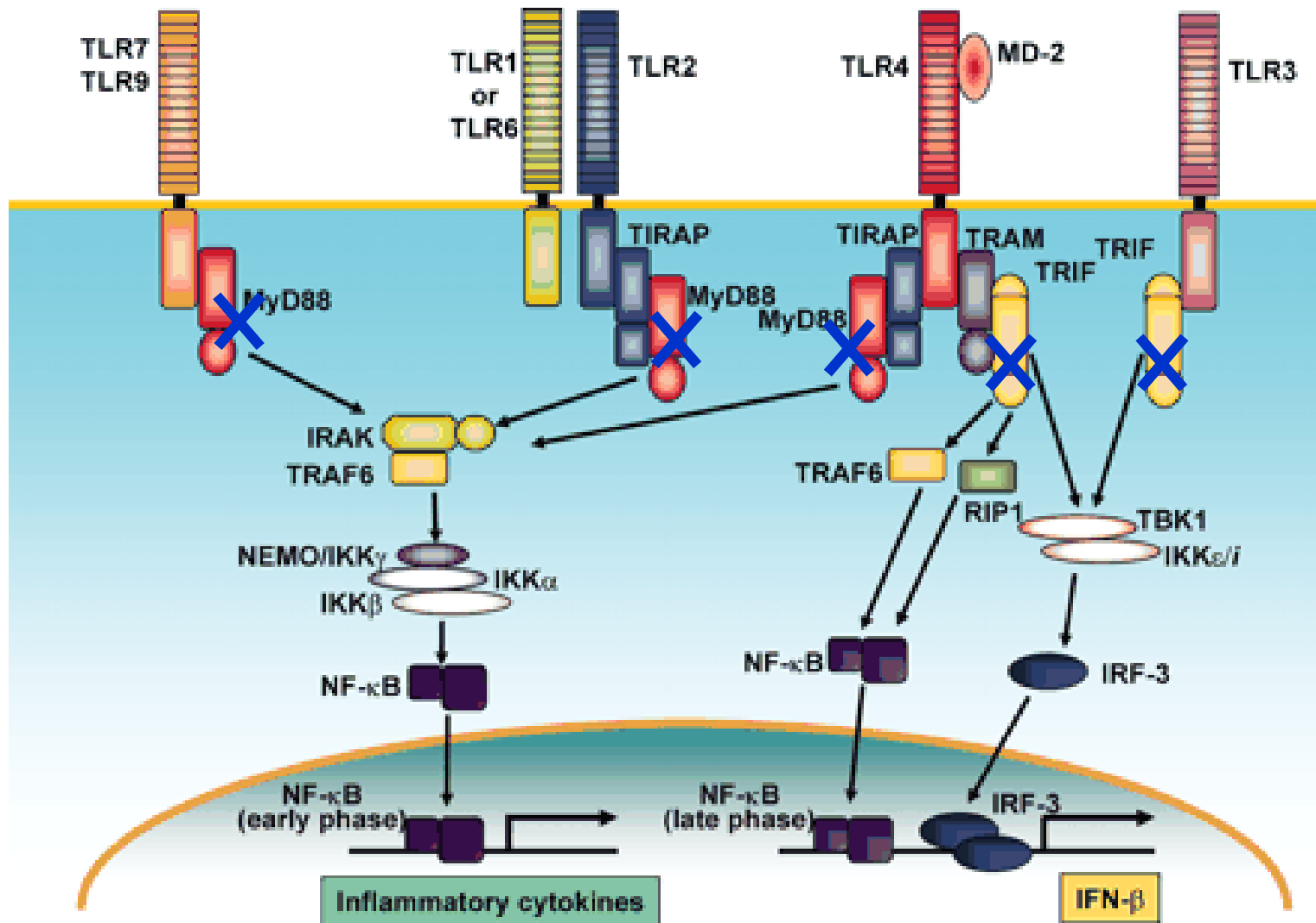
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Implications for vaccine design and self/non-self discrimination

**Amanda
Gavin**



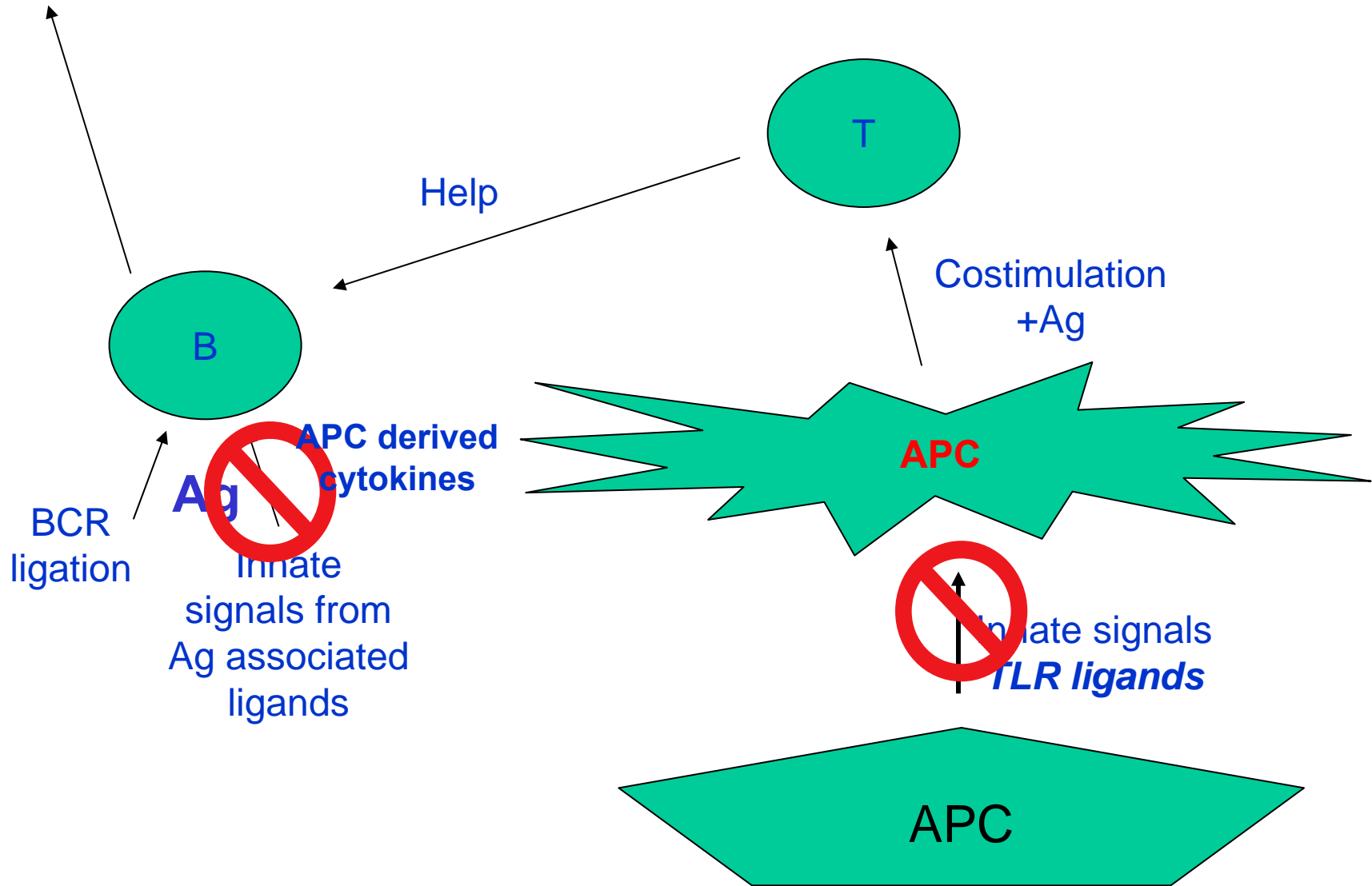
Analysis of MyD88^{-/-}; TRIF^{Lps2/Lps2} mice



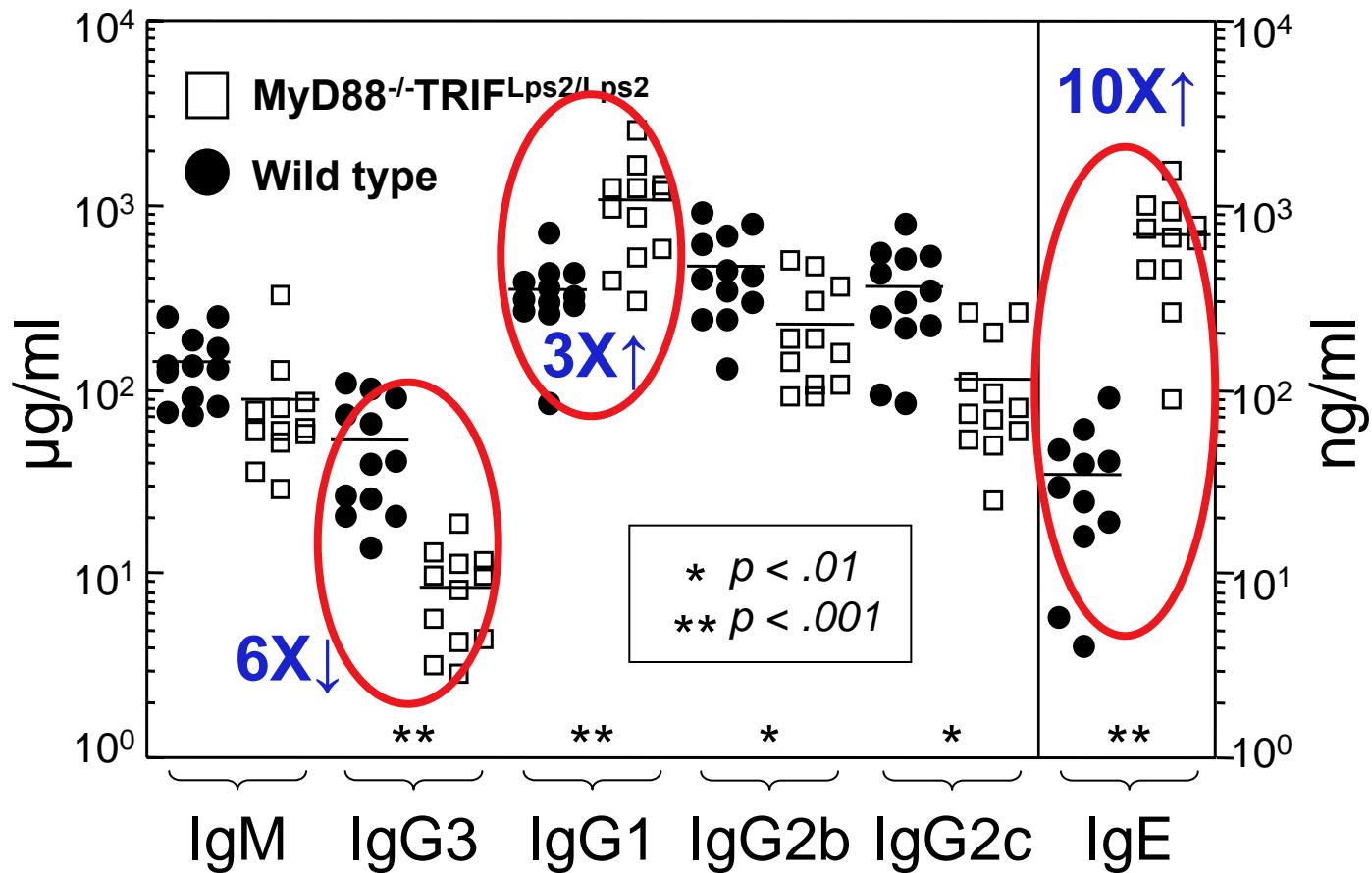
From Takeda and Akira 2005

Standard Model for the Immune Response

Ab



Abundant serum Igs and altered isotype distribution in MyD88/TRIF double KOs



Comparison of adjuvants

100µg model antigen (TNP-KLH)

PBS

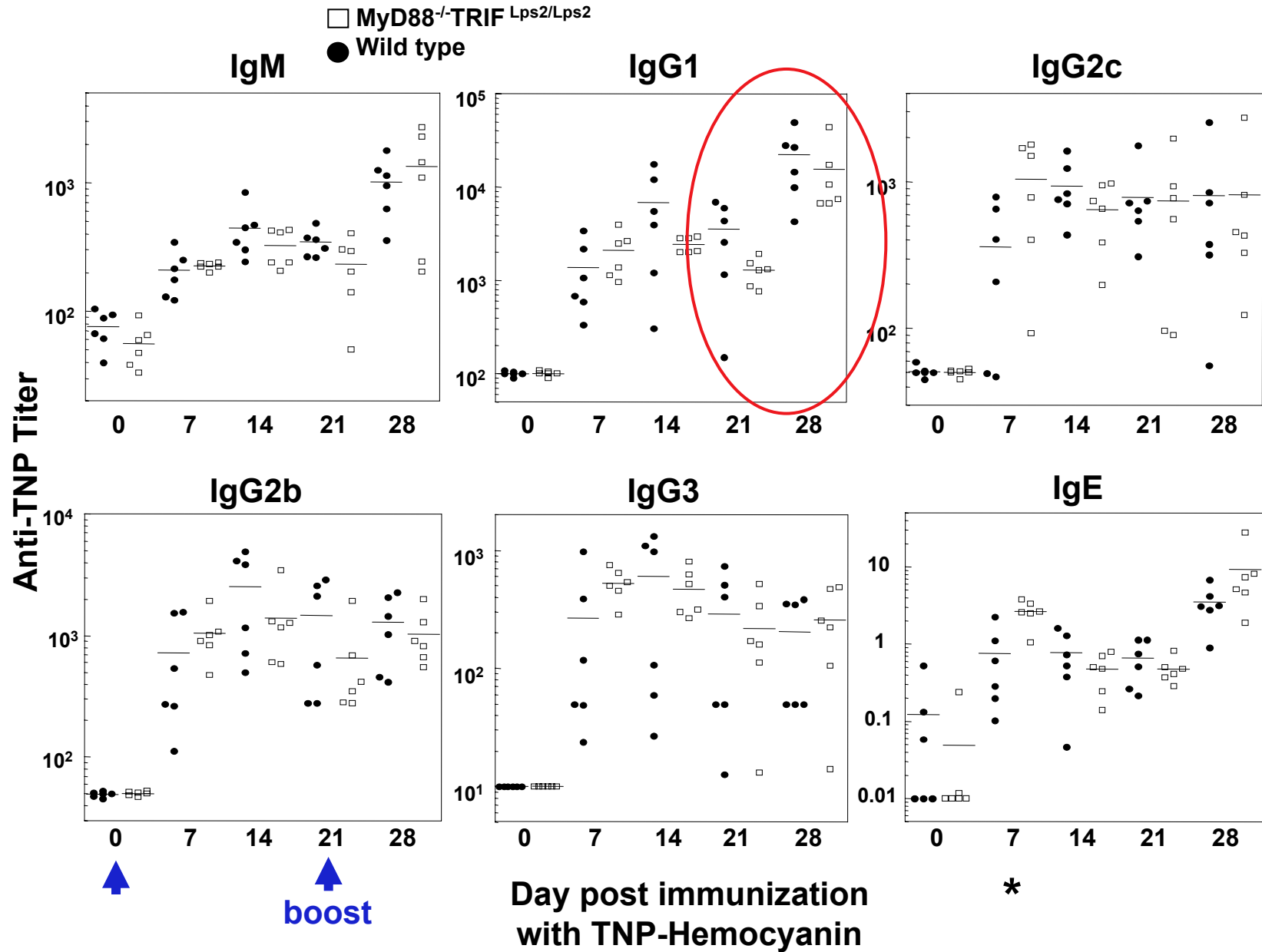
IFA

CFA (IFA + *Mycobacterium Tuberculosis*)

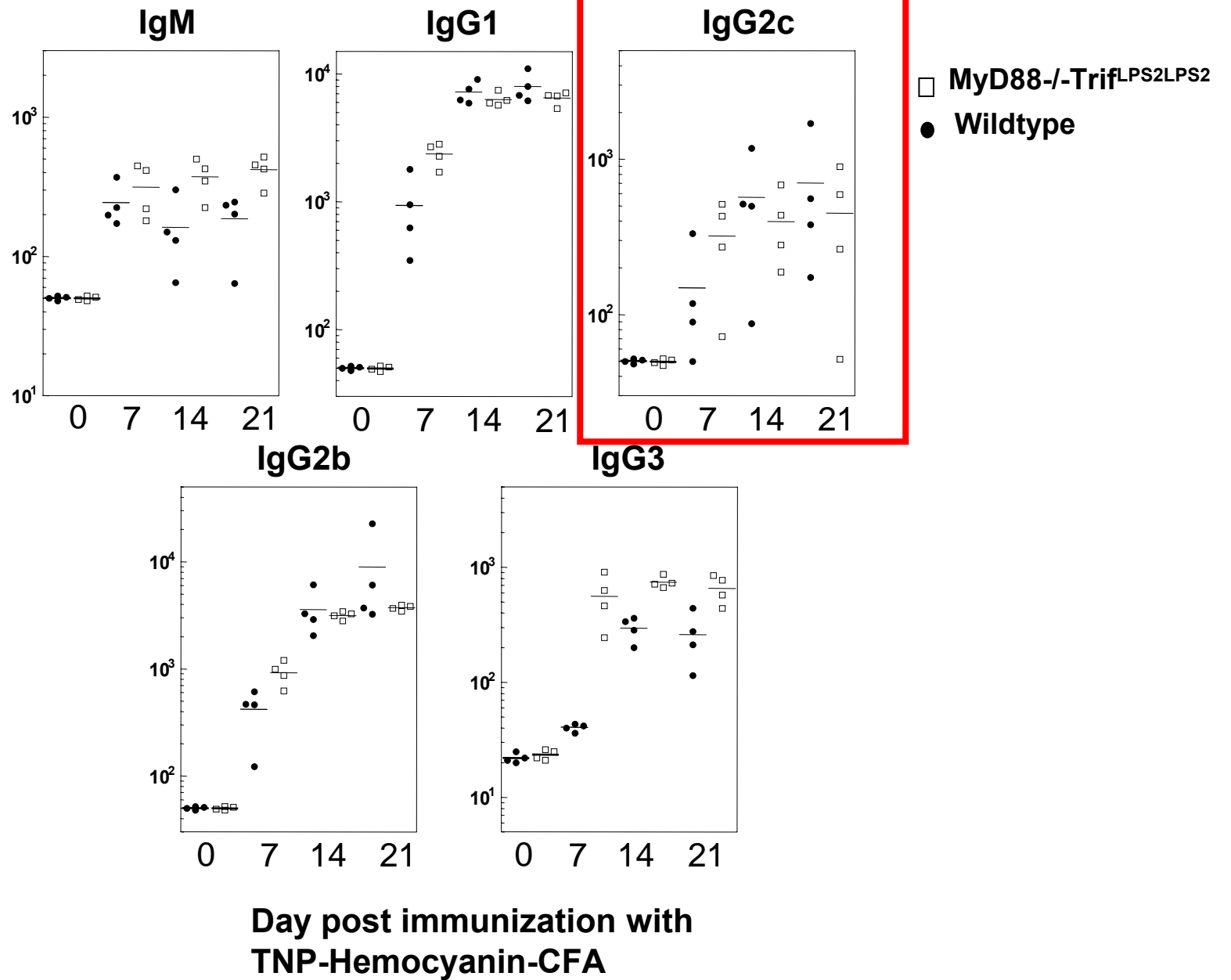
Ribi (MPL + Trehalose TDCM)

Prevailing view would be that TLR signaling mediates adjuvant effects of CFA and Ribi responses

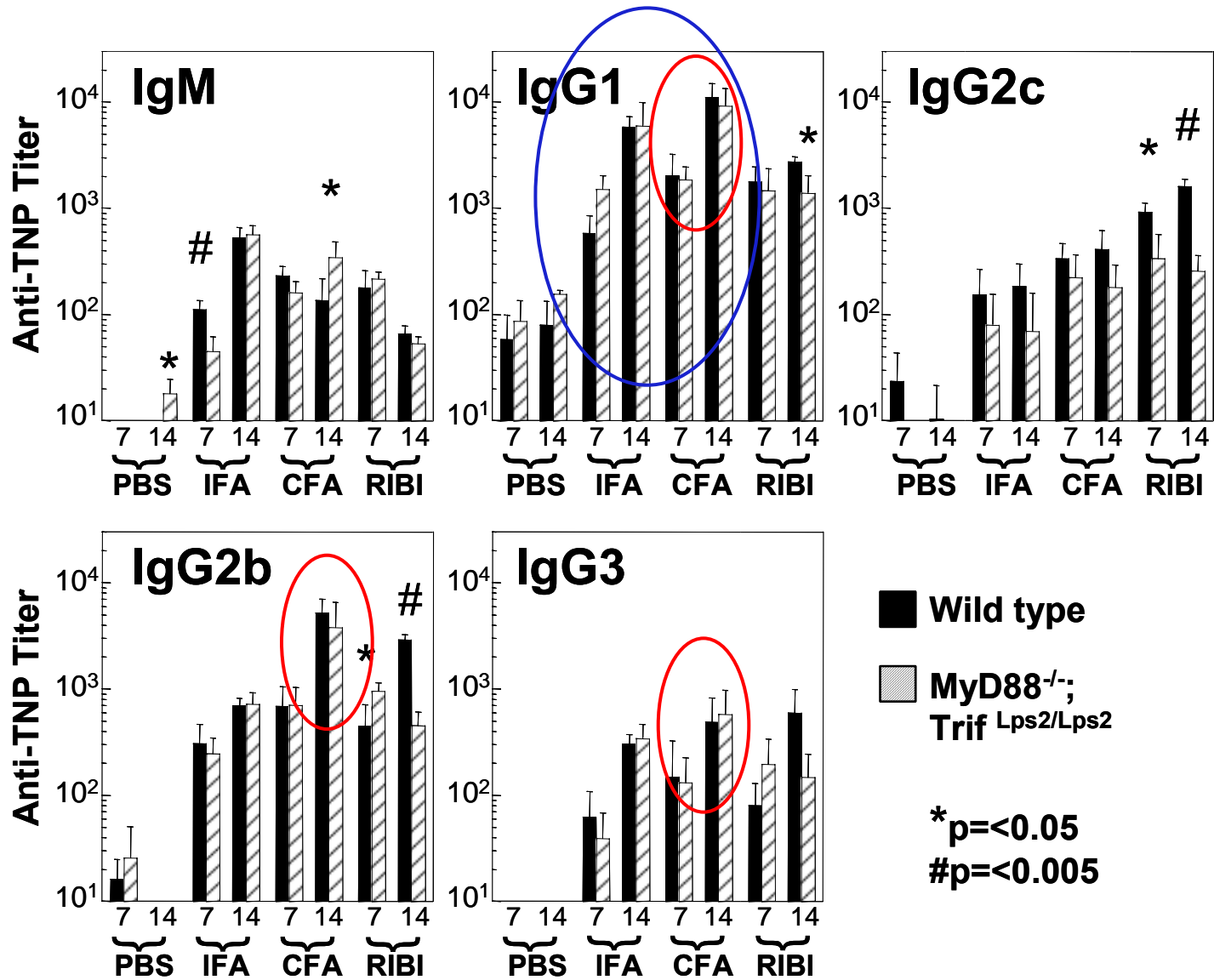
Normal T cell dependent antibody response to TNP-Hy in alum



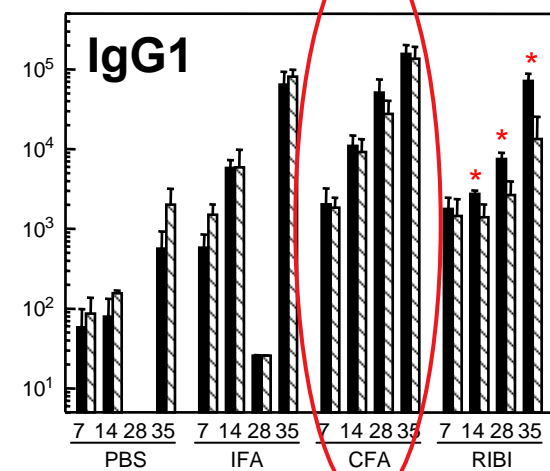
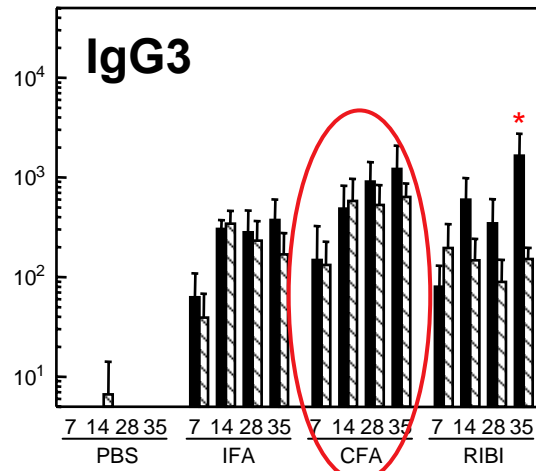
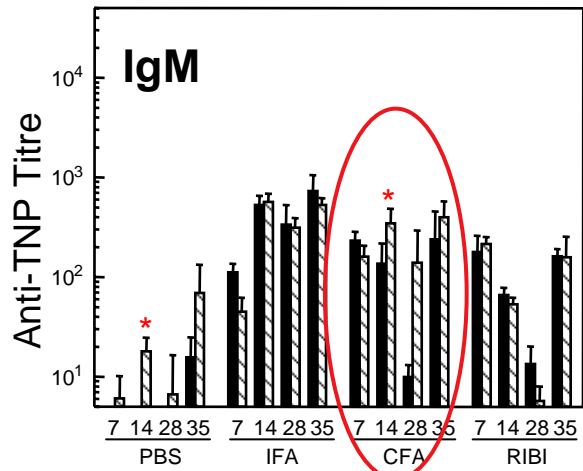
TNP-Hy in Complete Freund's Adjuvant (CFA)



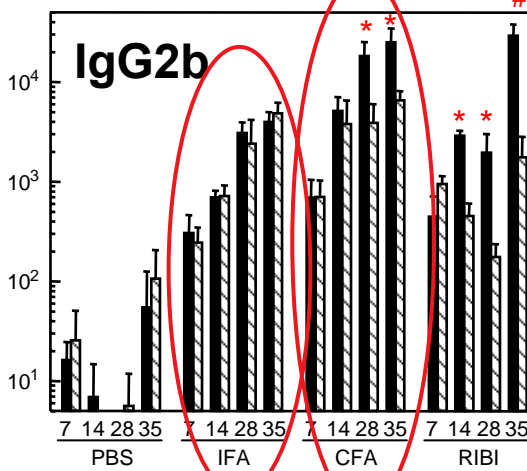
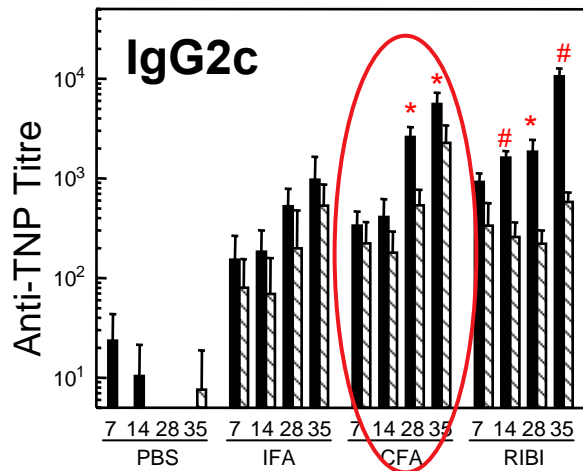
Adjuvant effect of Complete Freund's Adjuvant is mainly TLR independent



Antibody responses to antigen in adjuvants in TLR signaling-deficient animals at later times including recall



prime d0
boost d28



*p < 0.05

p < 0.001



C57BL/6



MyD88^{-/-}TRIF^{LPS2/LPS2}

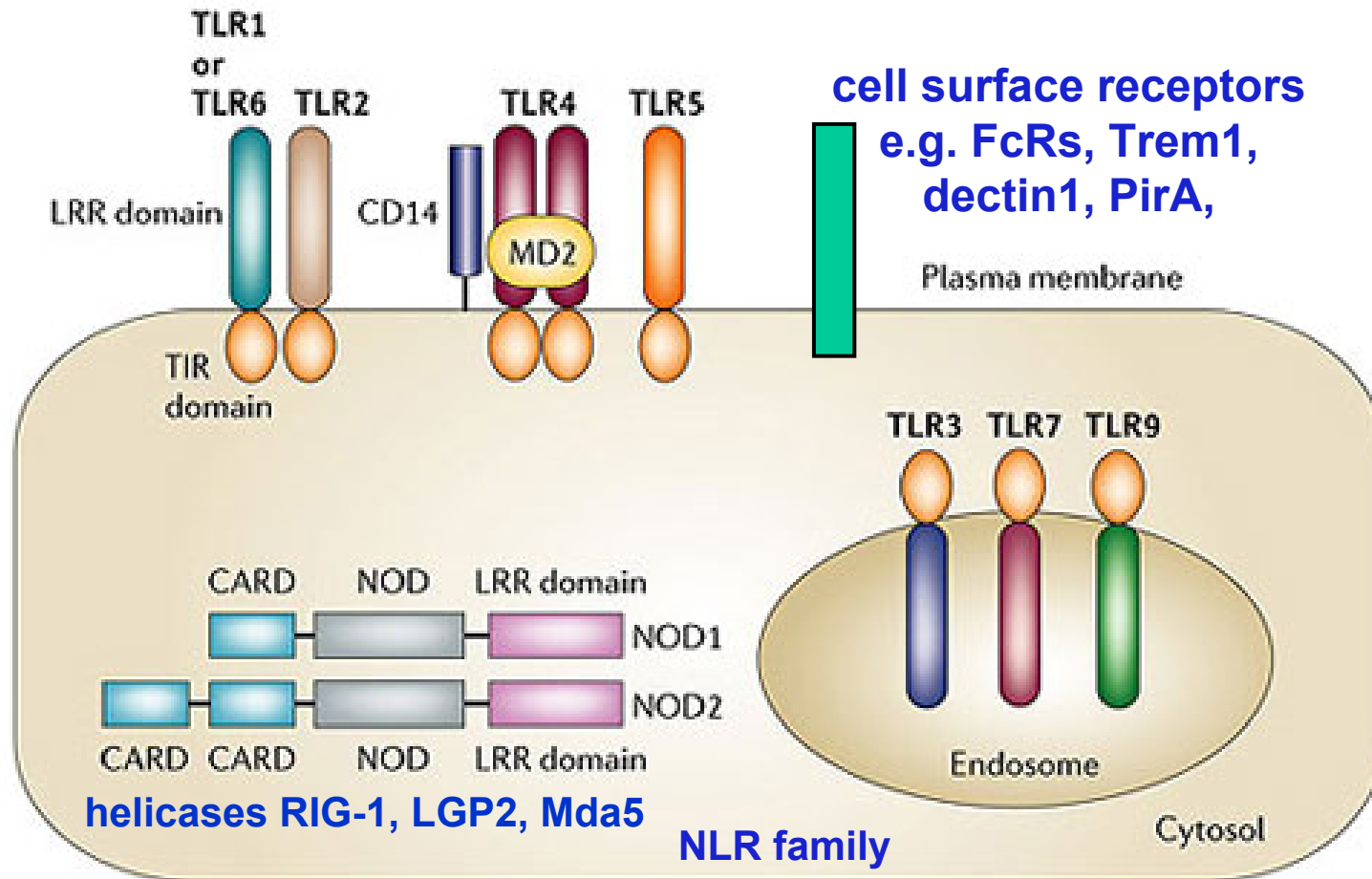
Boost Day 28 in PBS

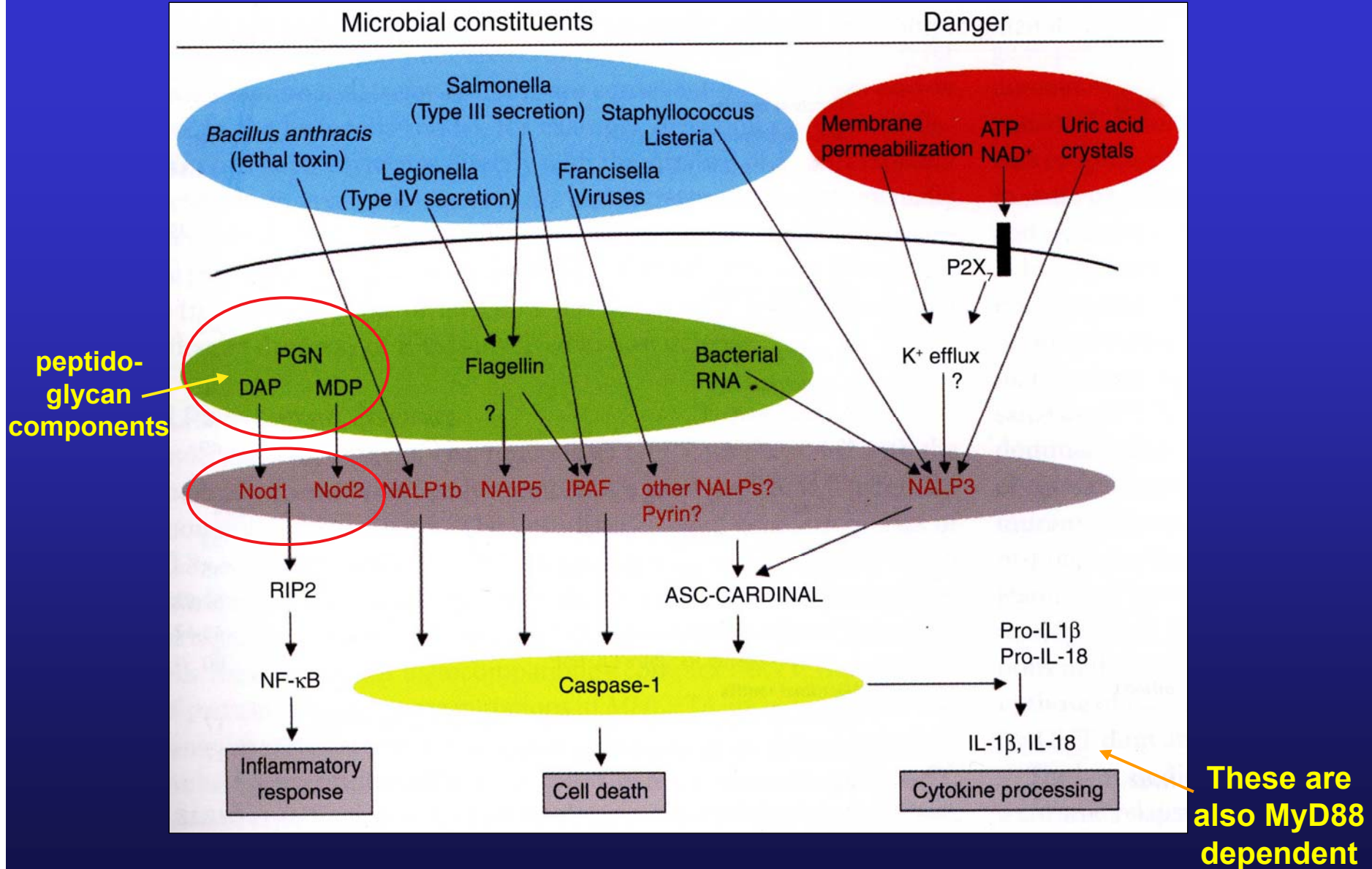
Conclusions and Interpretations

- Overall antibody responses in MyD88^{-/-};Trif^{lps2/lps2} mice were strong.
- Adjuvant effects were almost indistinguishable for Alum, CFA and IFA.
- Ribi was only slightly less effective in MyD88^{-/-};Trif^{lps2/lps2} mice, despite containing a strong TLR4 ligand.
- Deficits in MyD88^{-/-};Trif^{lps2/lps2} mice tended to appear late in the response, not early.
- Since CFA was more potent than IFA in MyD88^{-/-};Trif^{Lps2/Lps2} mice, the mycobacterial component of CFA is augmenting their responses, presumably through other innate receptors.

Implications: Other pathways besides TLR are dominant in the adjuvant effect. Alternatively, the primary effects of adjuvant are the "depot" effect and inclusion of additional antigens that promote bystander effects.

Candidate innate immune sensors of adjuvant





Review: Nod like proteins in immunity, inflammation and disease: Fritz et al., 2006 Nature Immunology

Objections to our findings

Objection

- amount of antigen too high
- Ag form too artificial or multivalent
- affinity of DKO Ab response might have been poorer
- didn't look at memory resp.
- developmental compensation
- alteration in development of myeloid/DC subsets
- residual TLR signaling
- residual TLR function independent of signaling
- Should use TLR ligands

Response

- we used an adjuvant-dependent dose
- similar results seen in MyD88^{-/-} mice (except for IgG2 responses)
- unlikely, but testable
- we saw little difference upon Ag recall
- unlikely, testable
- not ruled out, testable
- no evidence, not ruled out
(can make MyD88^{-/-};Trif^{-/-};Tram^{-/-};Tirap^{-/-} mice)
- not ruled out, but unlikely
- we did, Ribi

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Amanda Gavin
Bao Duong
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