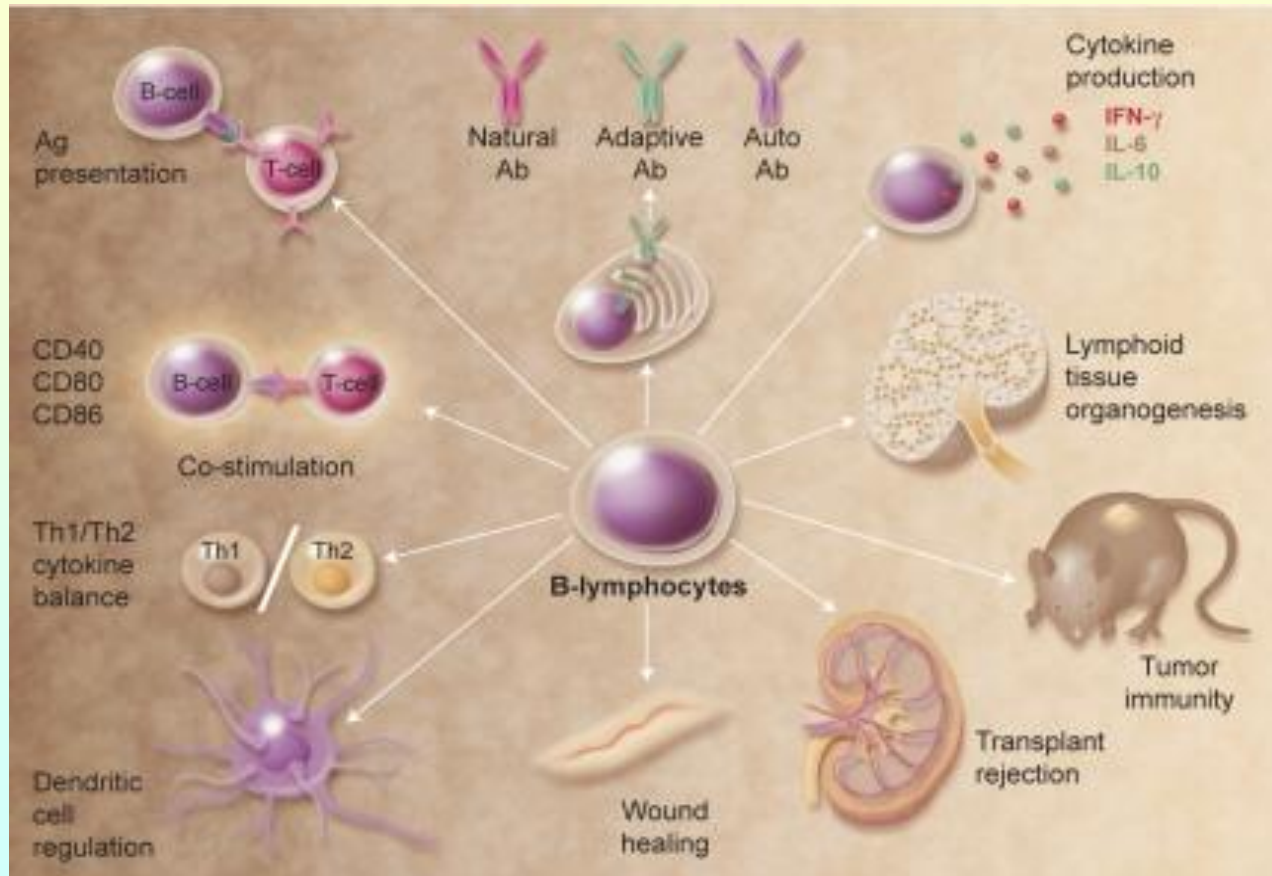


Regulatory B cells in autoimmunity

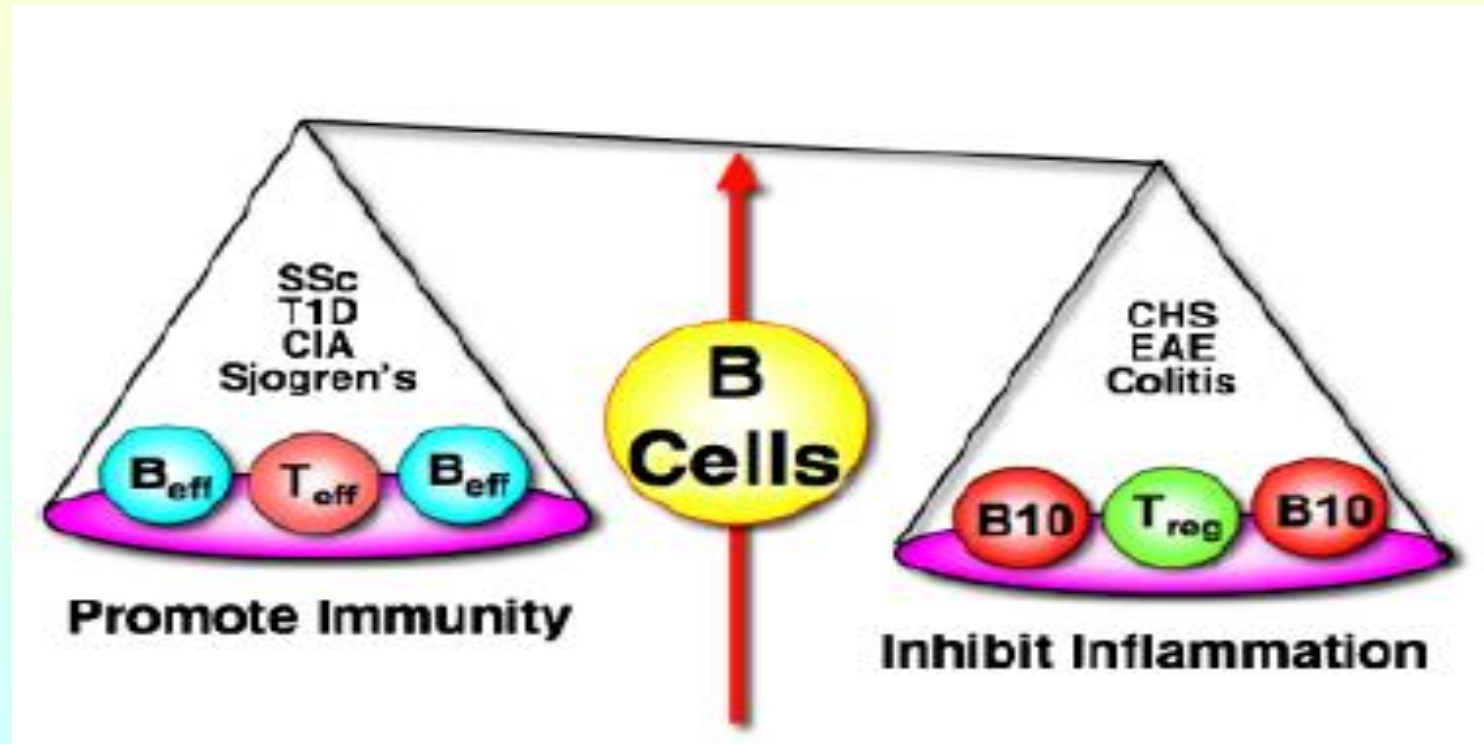
Liwei Lu
University of Hong Kong, China

Multiple functions of B cells in immunity

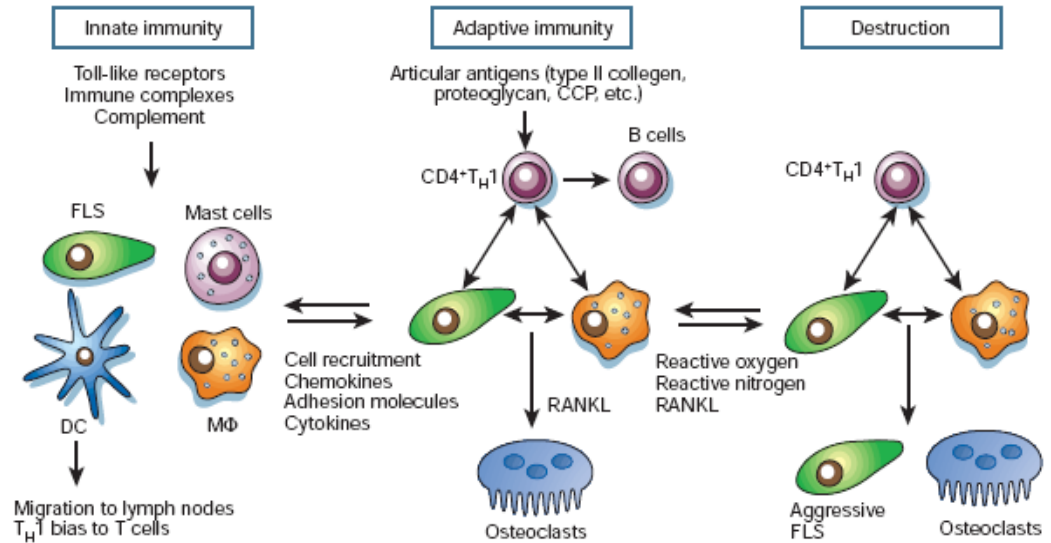


LeBien and Tedder, Blood (2008)

B cell functions in autoimmune pathogenesis



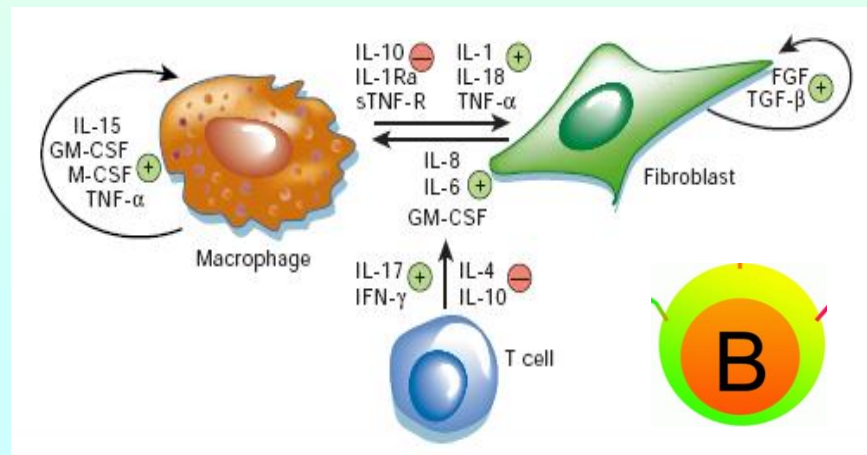
The Immunopathogenesis of Rheumatoid Arthritis



insight review articles

Evolving concepts of rheumatoid arthritis

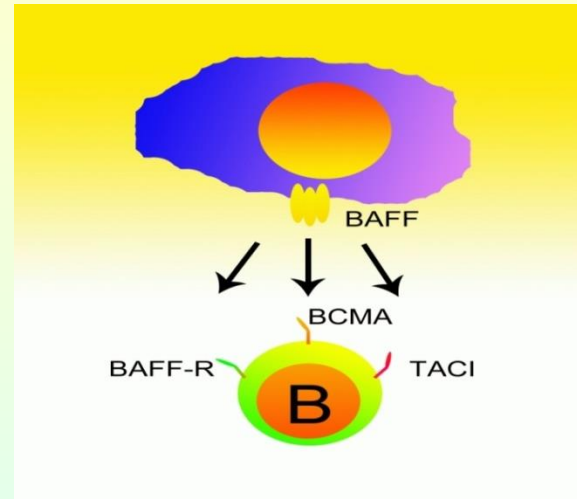
Gary S. Firestein *Nature* 423 (2003)



Role of BAFF in B cell maturation and function

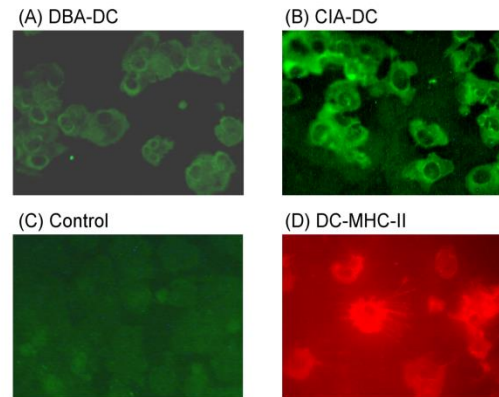
B cell activating factor (BAFF, BLyS)

- * A member of TNF family cytokines
- * A survival factor for B cell maturation

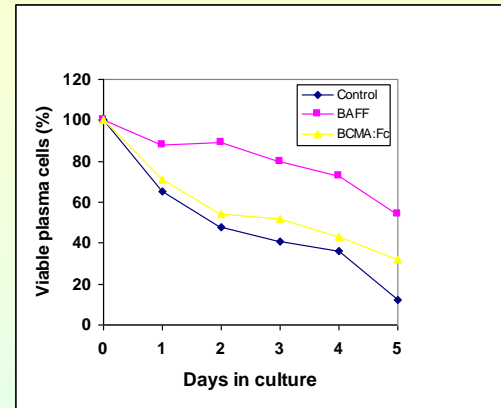
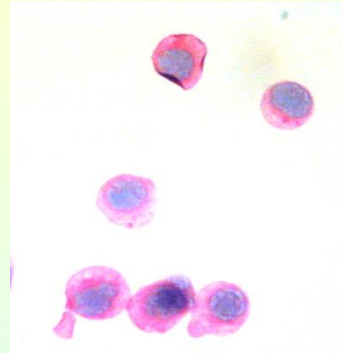
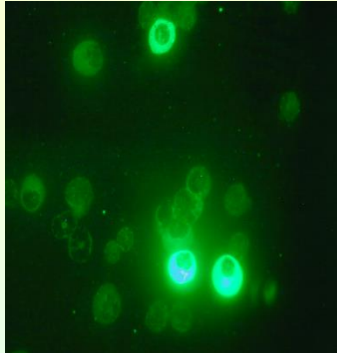


**Increased BAFF
in DC from CIA mice**

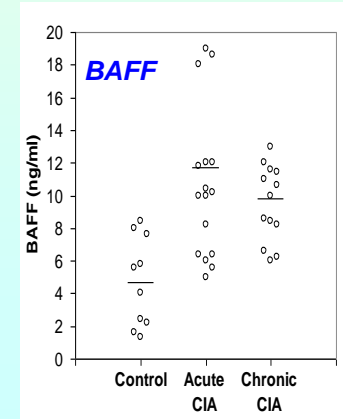
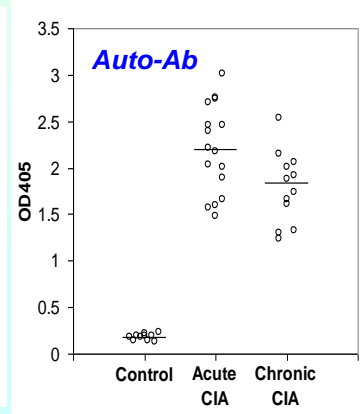
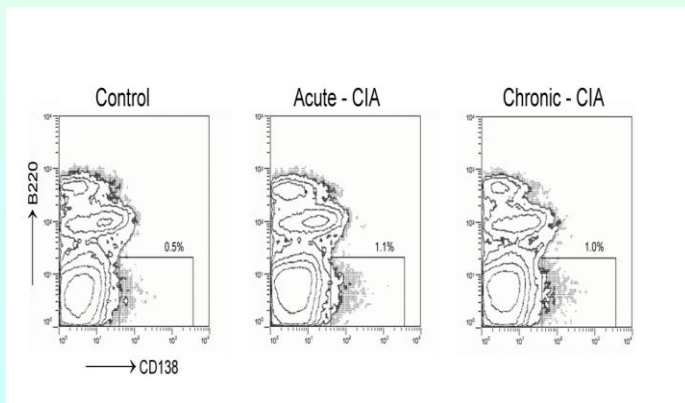
**Serum BAFF levels:
increased in SLE & RA ↑**



BAFF enhances the survival of plasma cells

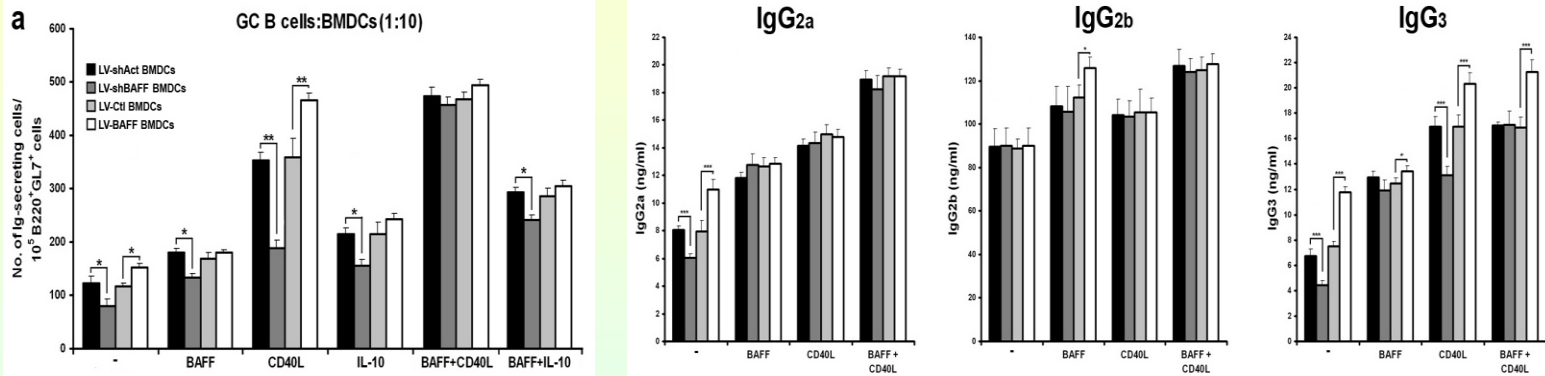


BAFF overproduction correlates with elevated autoAb in CIA

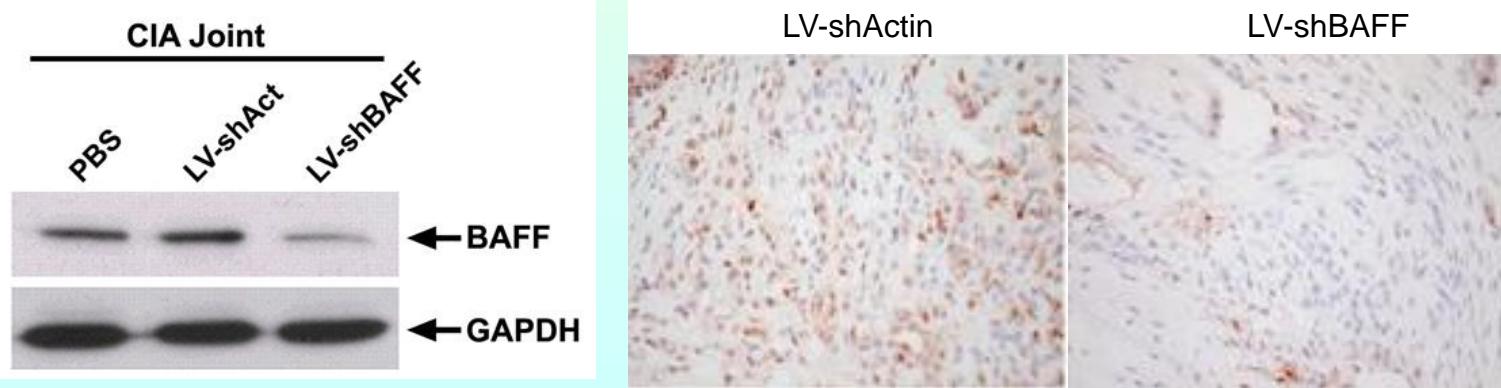


Effect of BAFF on B cell maturation and function

BAFF-silenced DCs are defective in B cell maturation and Ab production

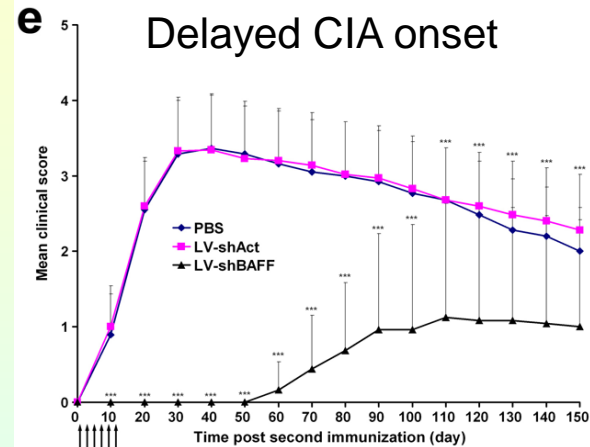
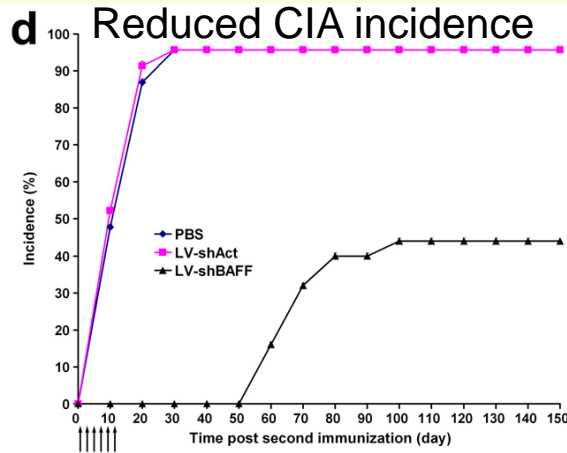


BAFF gene silencing by lentivirus expressing shRNA in joint tissue

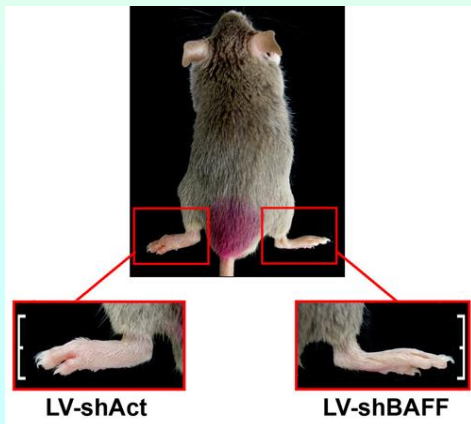


BAFF silencing suppresses CIA development

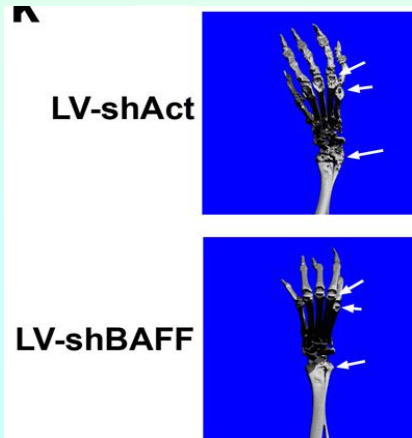
Intra-articular injection of lentivirus expressing shRNA-BAFF



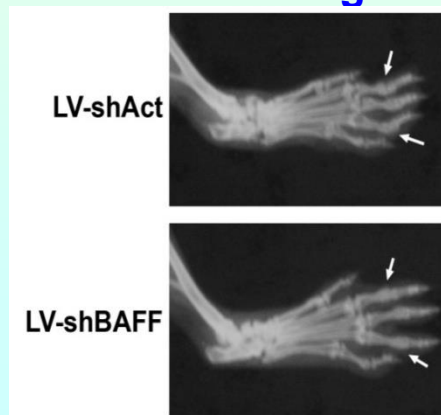
Long term, localized effect



Bone erosion

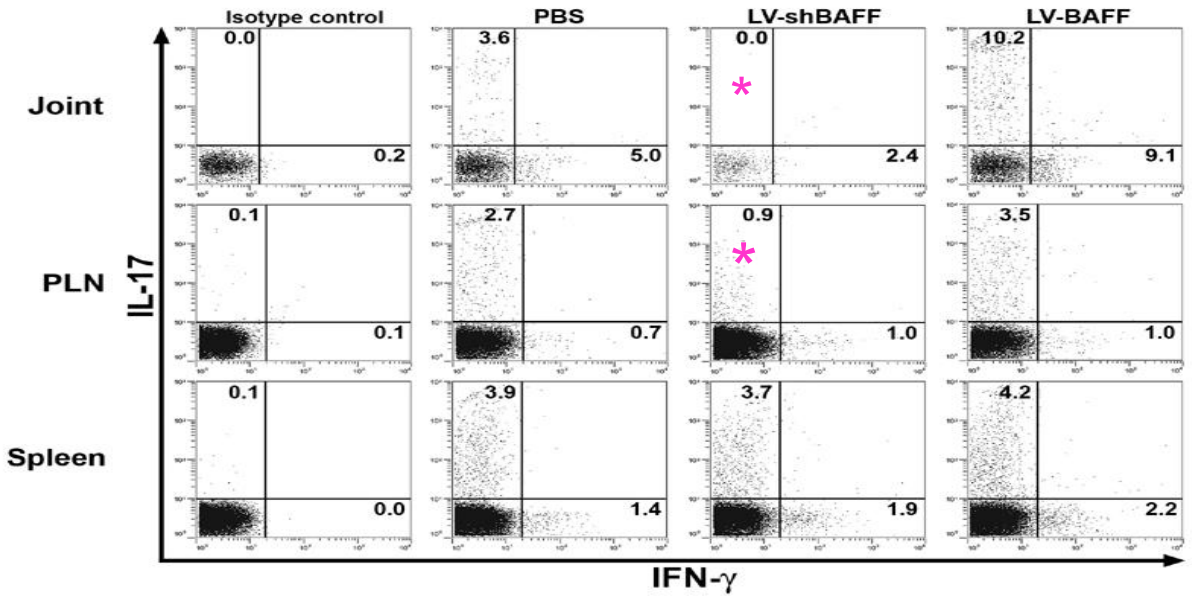
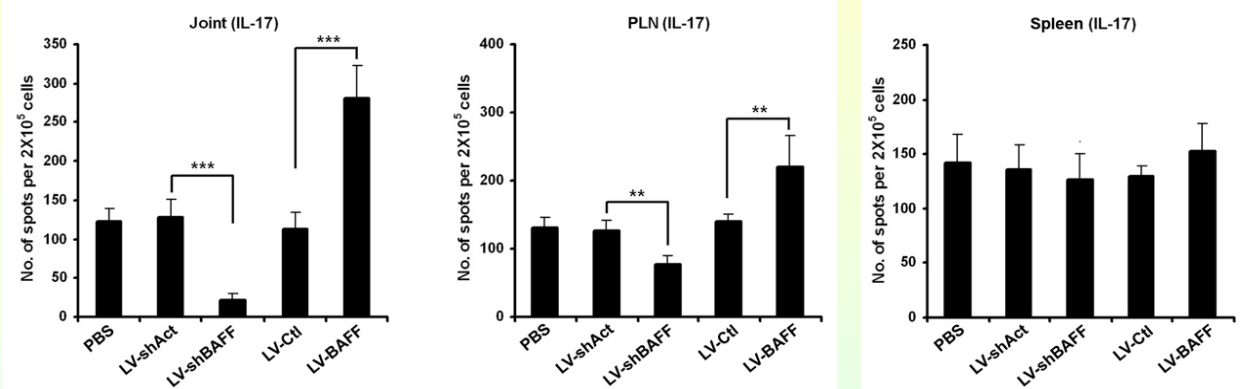


Joint damage

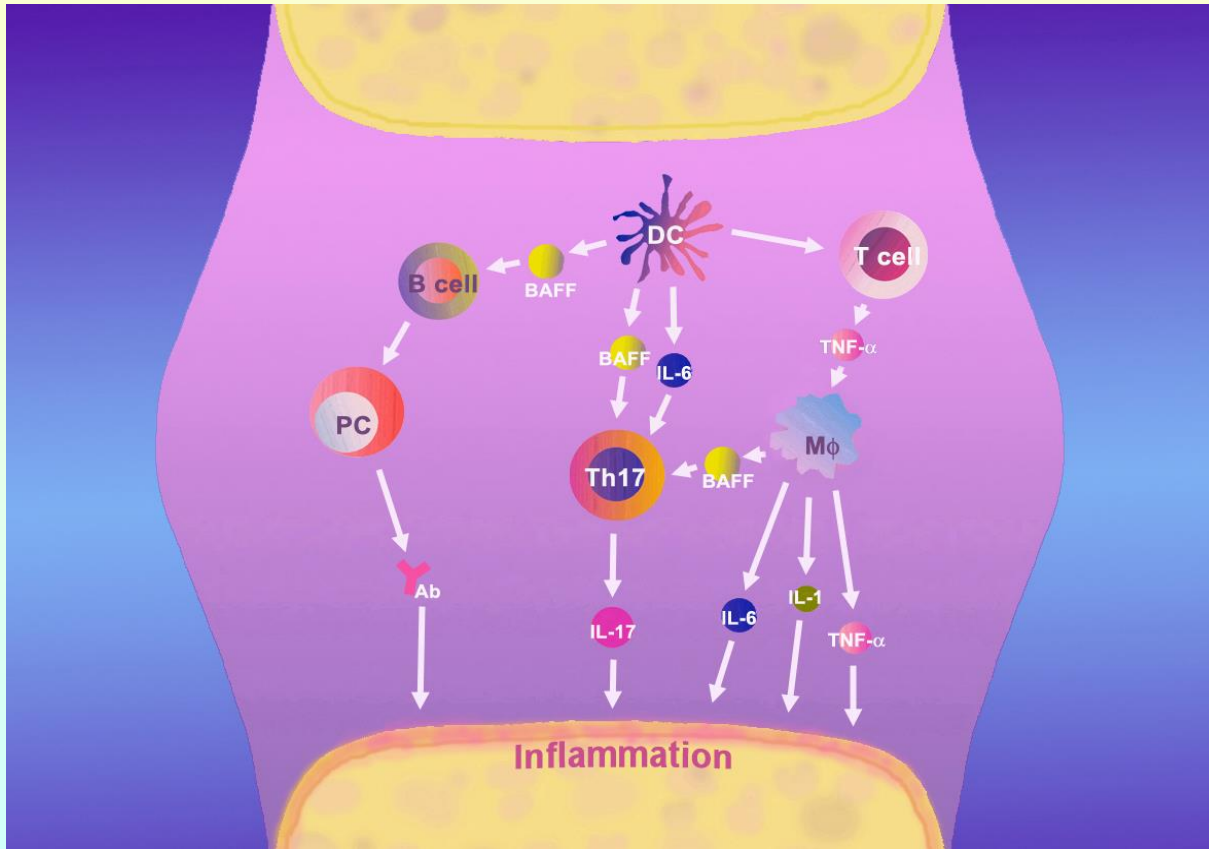


BAFF silencing inhibits Th17 cells in the joint and LN

Detection of IL-17 producing cells by ELISPOT assays



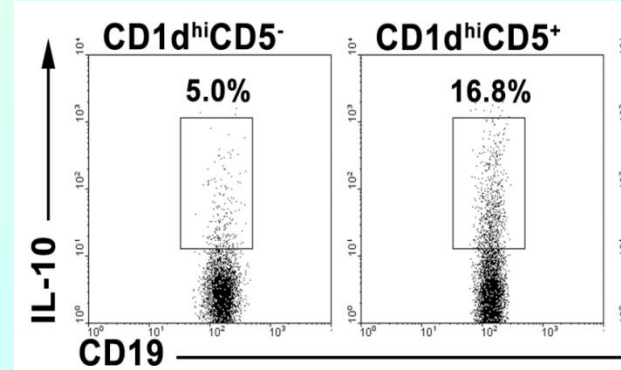
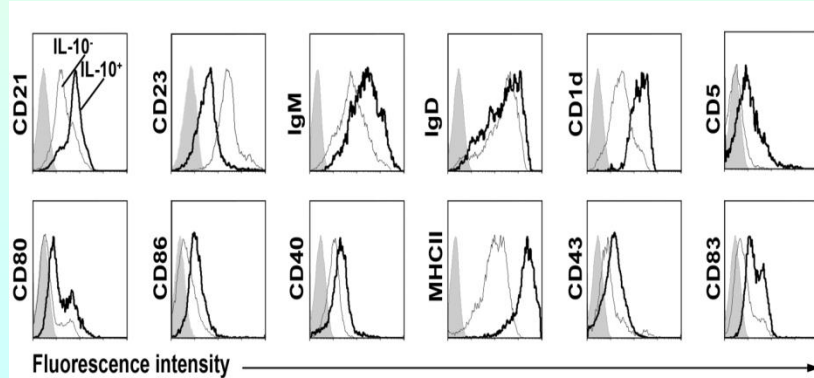
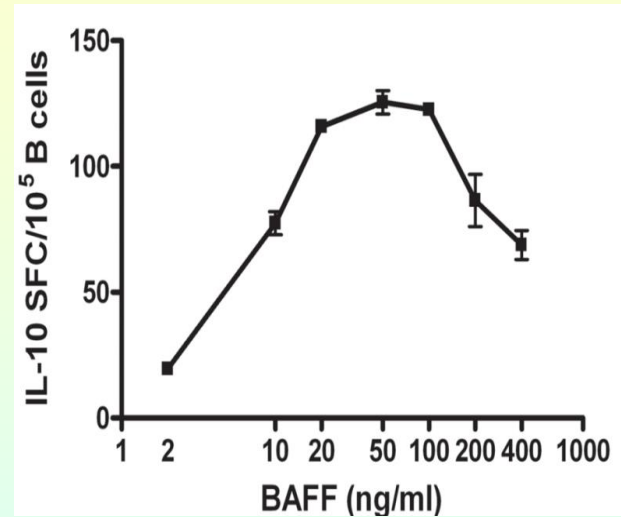
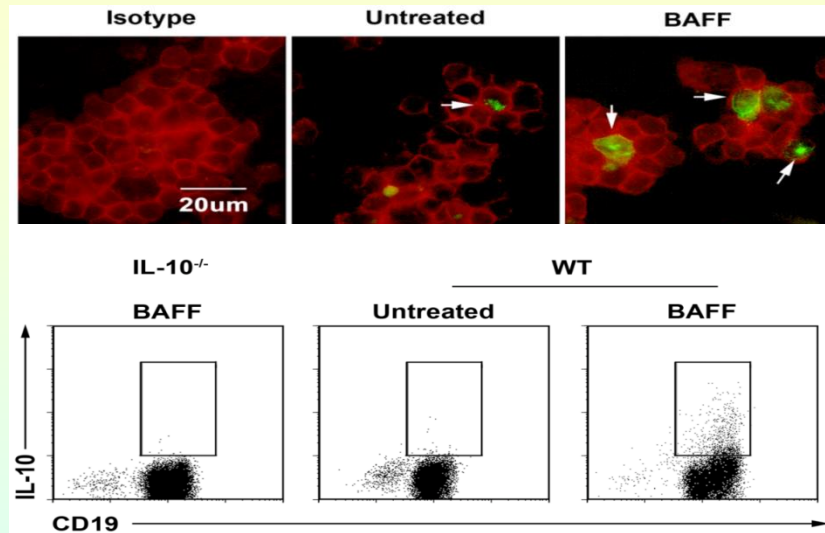
A pathogenic role of BAFF in autoimmune arthritis



Validation of BAFF as a therapeutic target in experimental arthritis

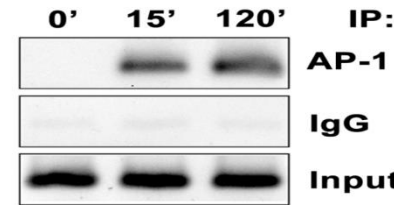
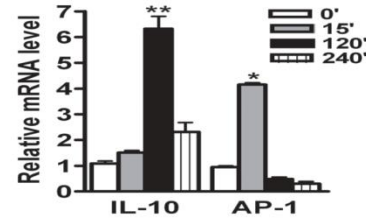
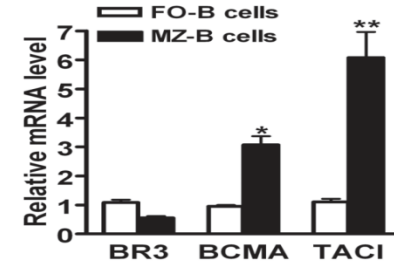
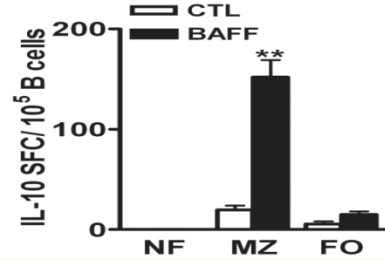
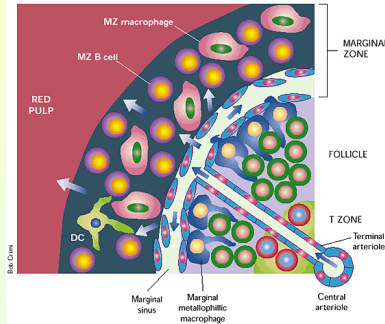
Lam Q, et al, PNAS (2010)

BAFF induces IL-10 production in B cells

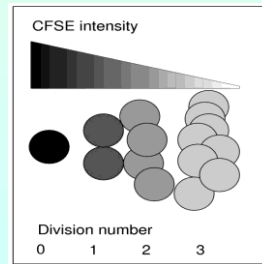
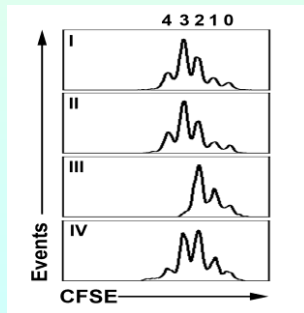


BAFF induces IL-10 production in MZ B cells

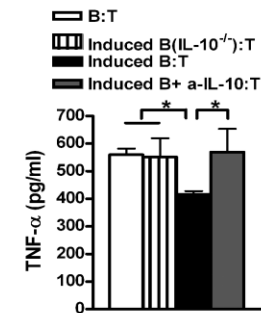
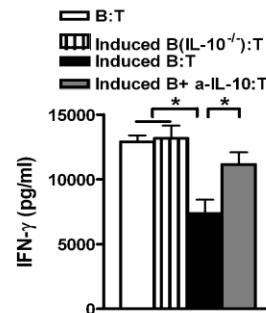
Lymphoid follicle



IL-10-producing B cells suppress T cell function



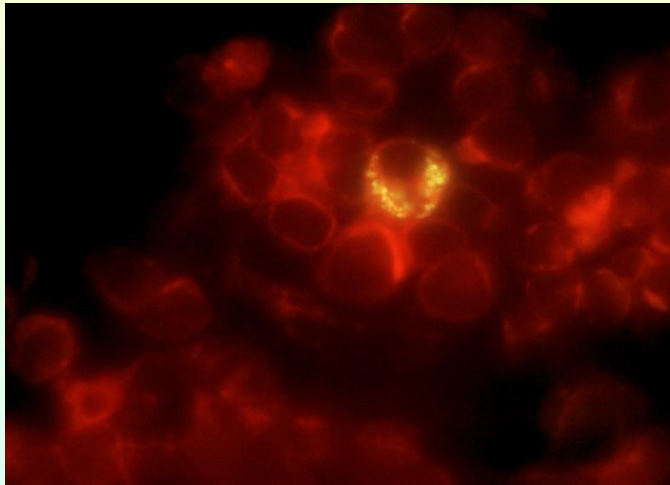
- I: B:T
- II: Induced B (IL-10^{-/-}):T
- III: Induced B:T
- IV: Induced B+a-IL-10:T



Yang M, et al, *J Immunol* (2010)

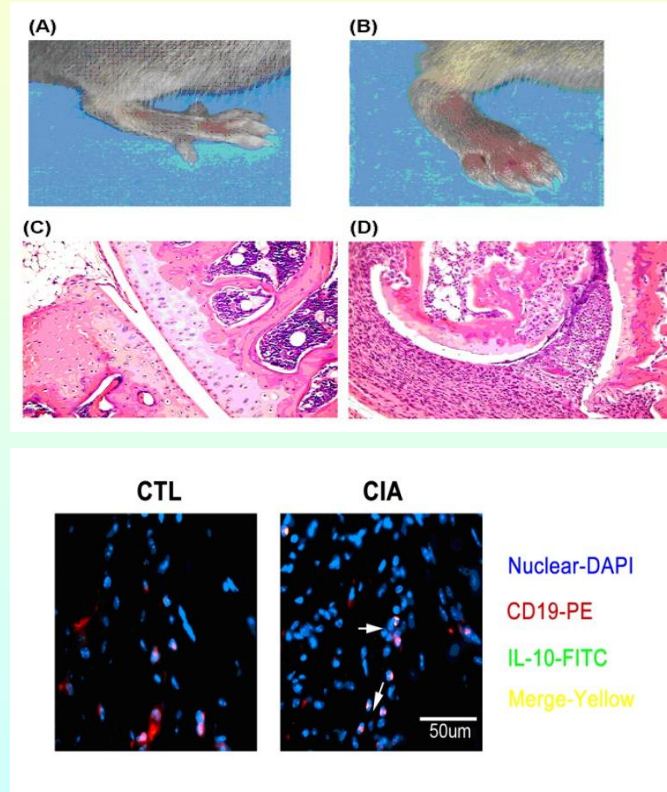
Existence of IL-10-producing B cells *in vivo*

Spleen

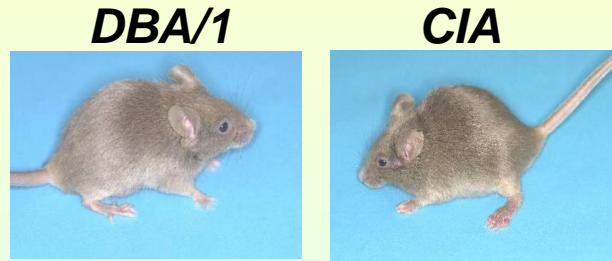


IL-10-producing B cells

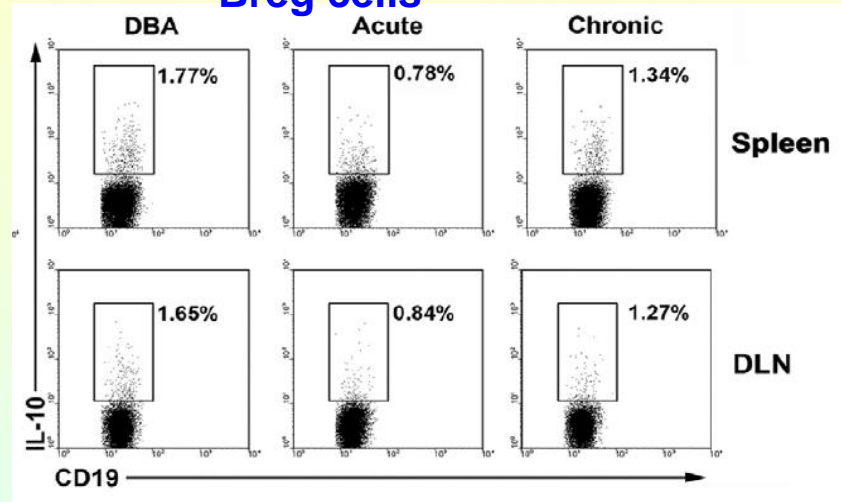
CIA Joint tissue



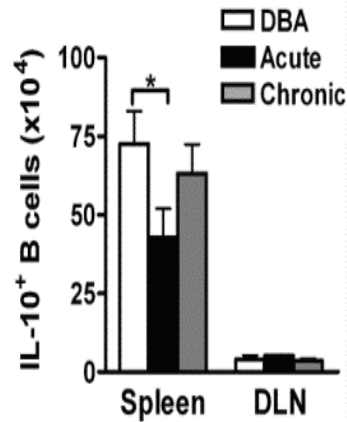
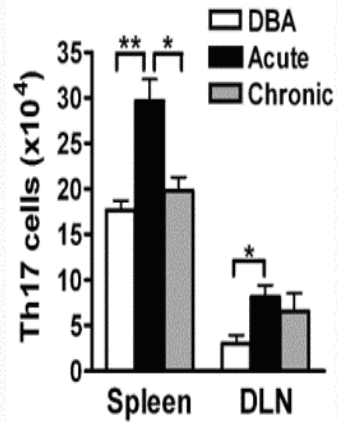
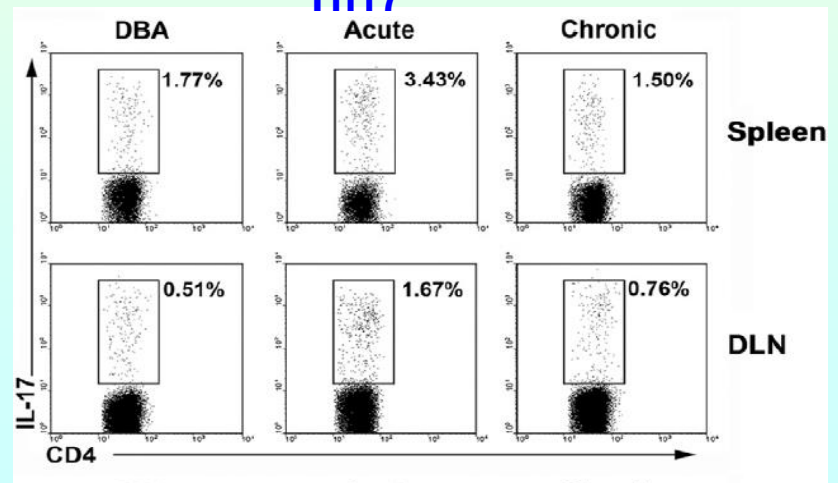
Kinetic changes of Breg and Th17 cells during CIA induction



Breg cells

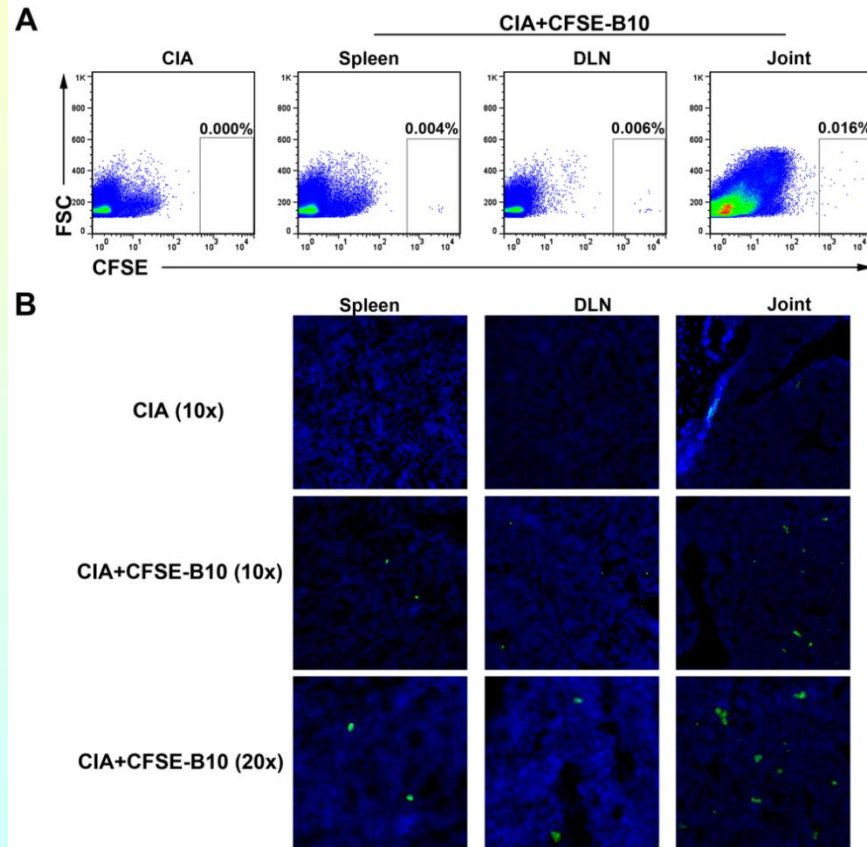
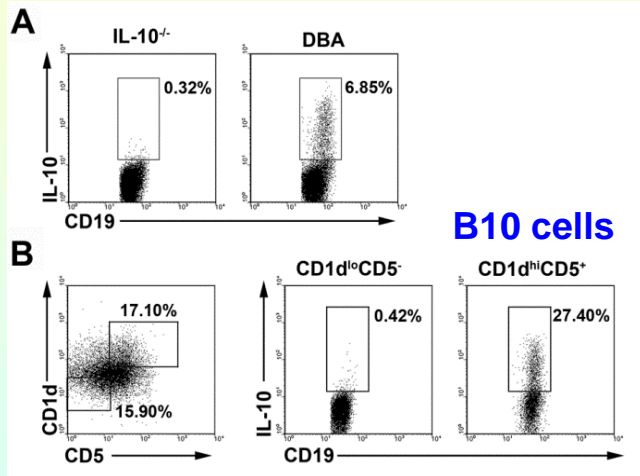


Th17

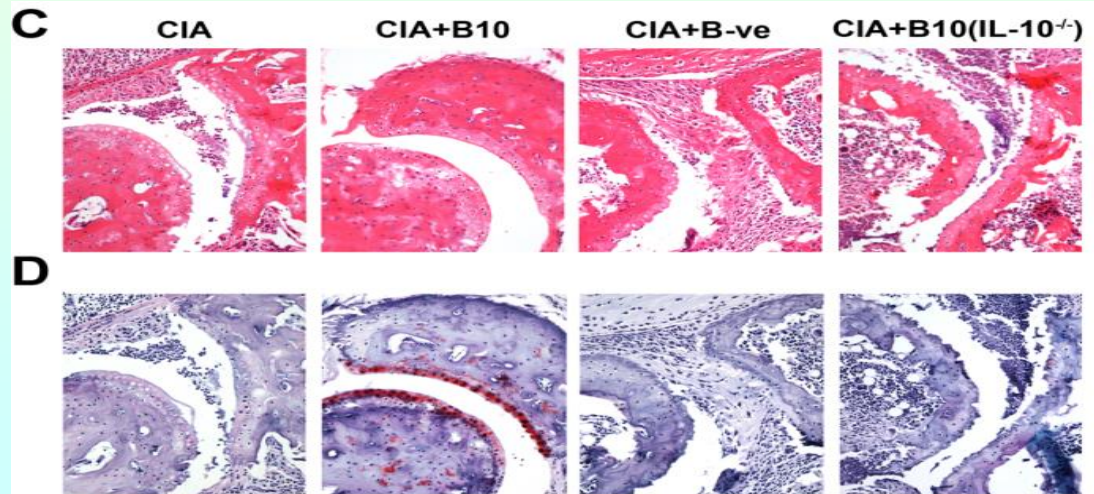
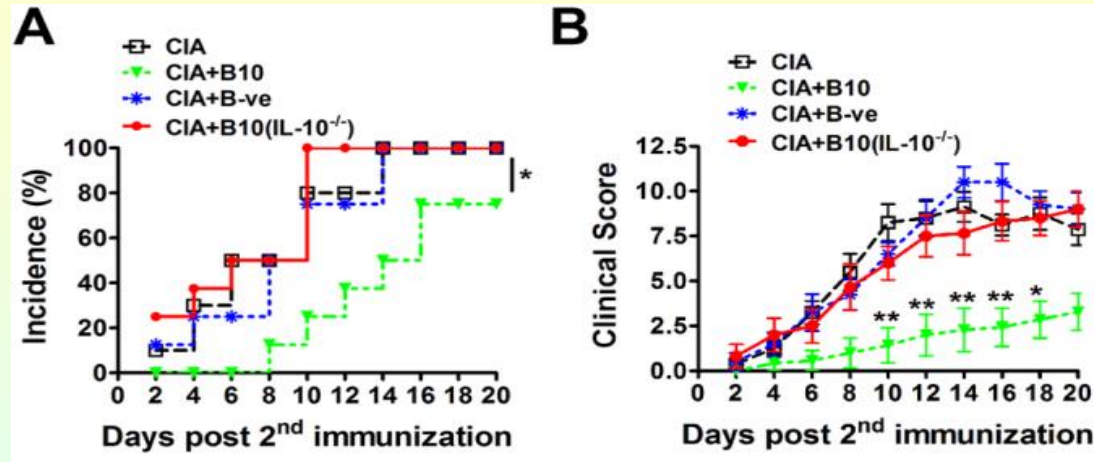


Localization of transferred Breg cells In vivo

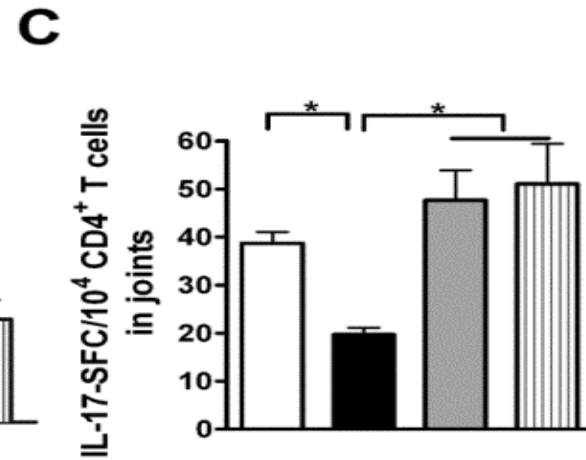
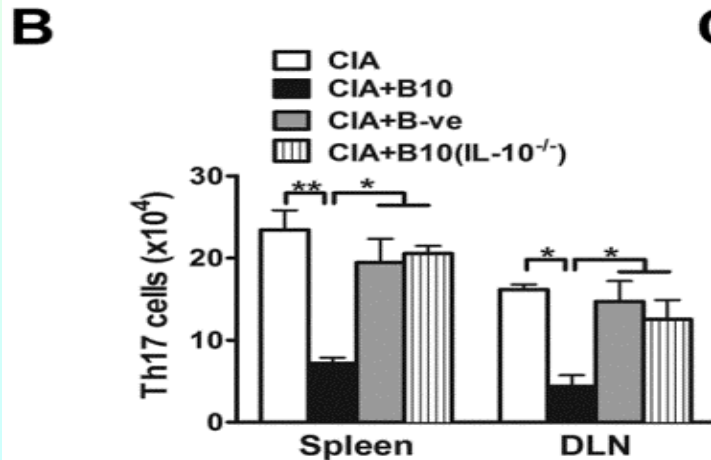
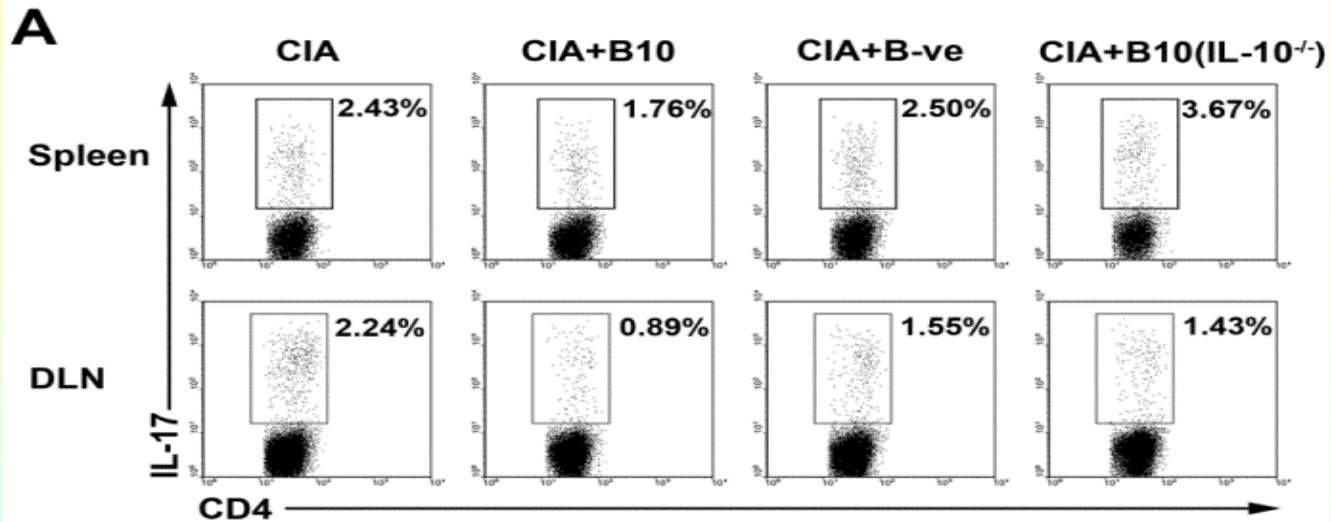
In vitro expansion of Breg cells



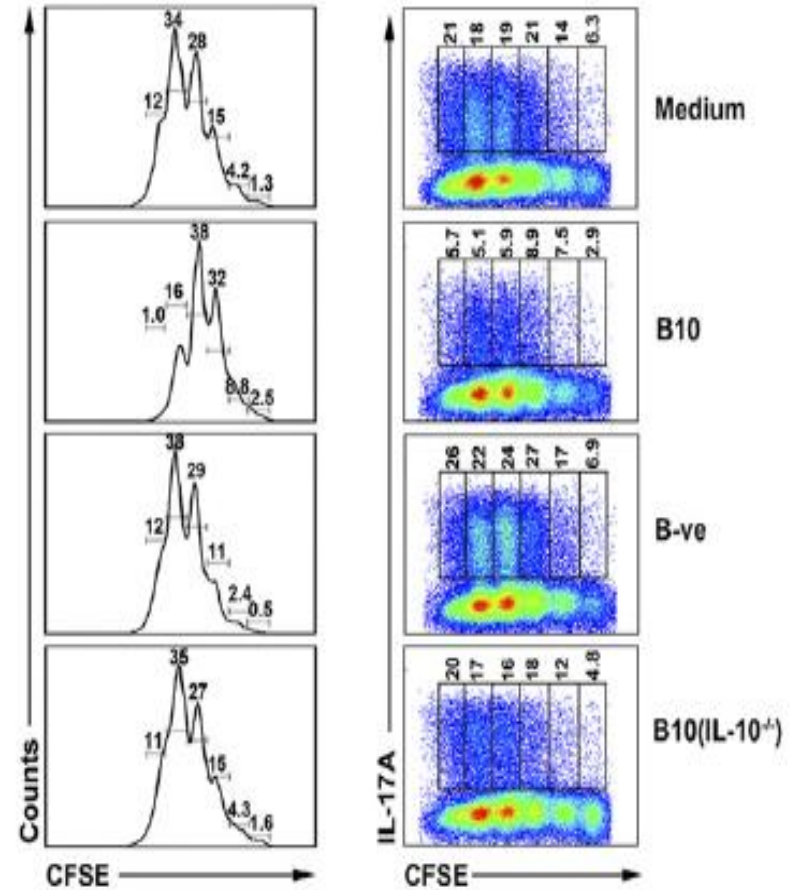
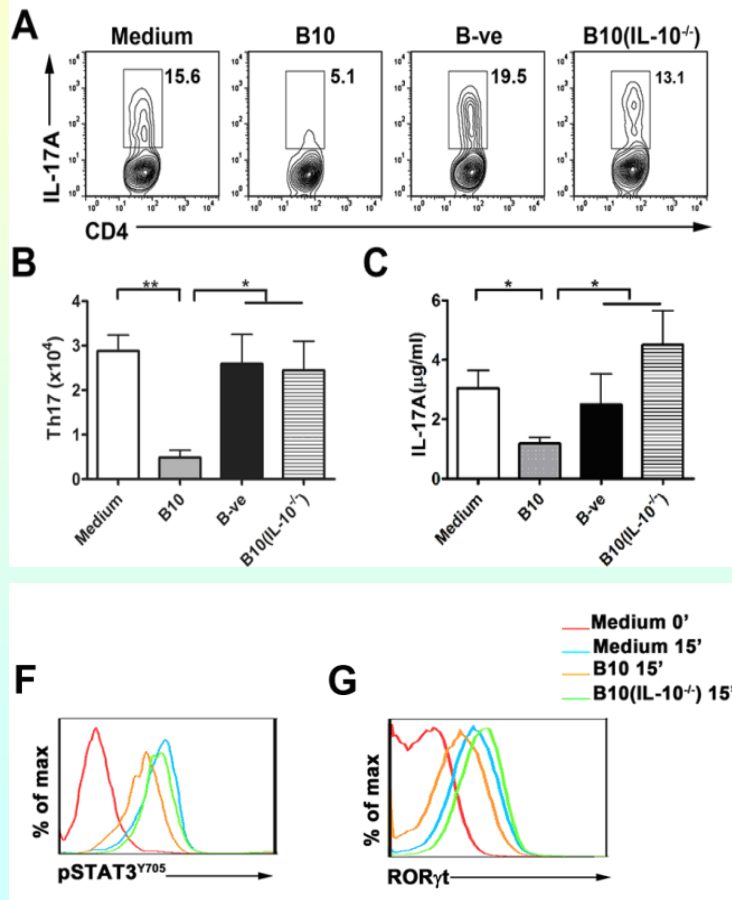
Transfer of Breg cells suppresses CIA development



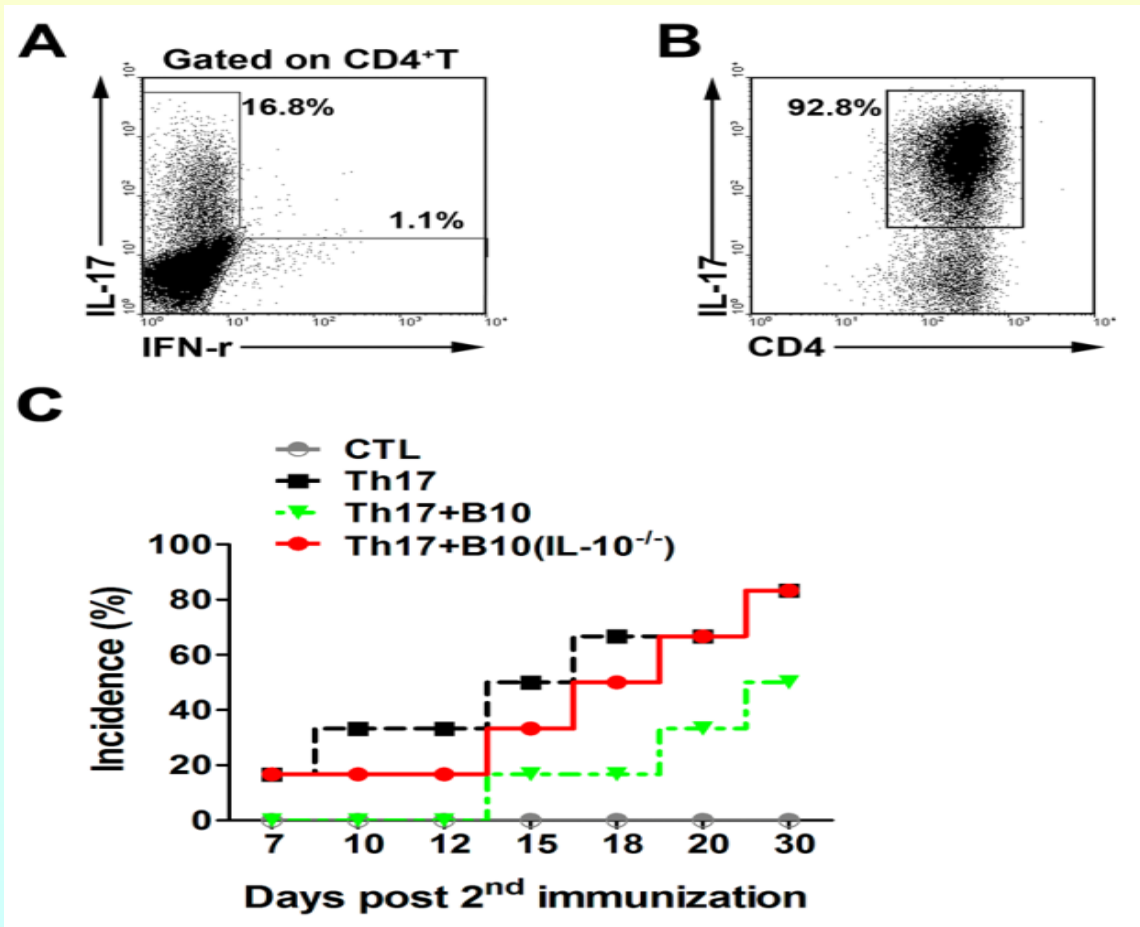
Transfer of Breg cells inhibits Th17 response in vivo



Breg cells inhibit Th17 expansion in vitro

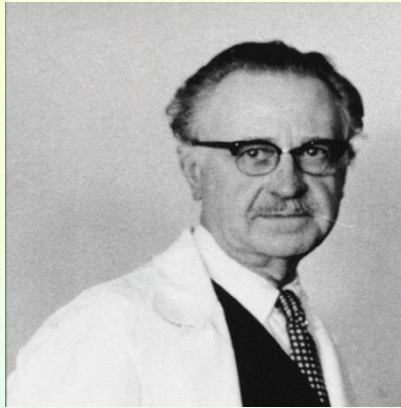


Breg cells inhibit Th17-mediated CIA in IL-17^{-/-} mice



Yang M et al. *A J Pathol* (2012)

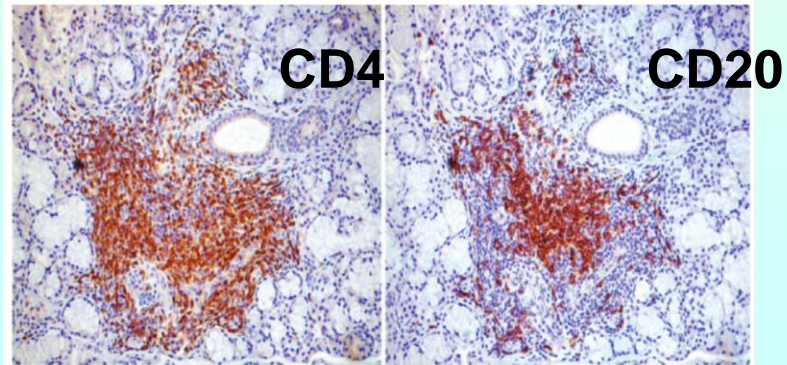
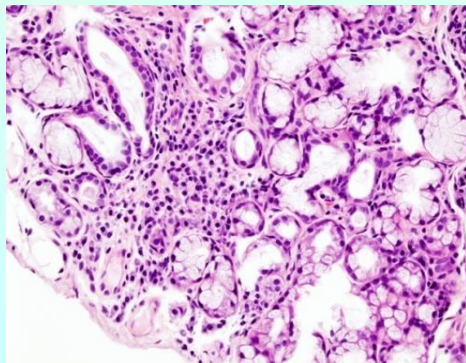
Role of Breg cells in Sjögren Syndrome



Henrik Sjögren
(1899-1986)



Dry eyes / dry mouth



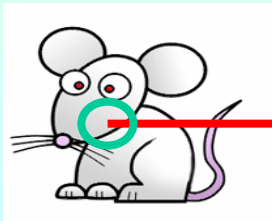
Adamson TC et al. J Immunol (1983)

Available mouse models for Sjögren Syndrome

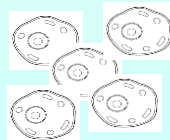
- **Spontaneous SS models:**
NOD, Fas(lpr), (NZB+NZW)F1
- **Gene-modified animal models:**
IL-12-Tg, BAFF-Tg, Id3-KO, IL-14 α -Tg

Induction of Experimental Sjögren Syndrome in normal mice

C57BL/6



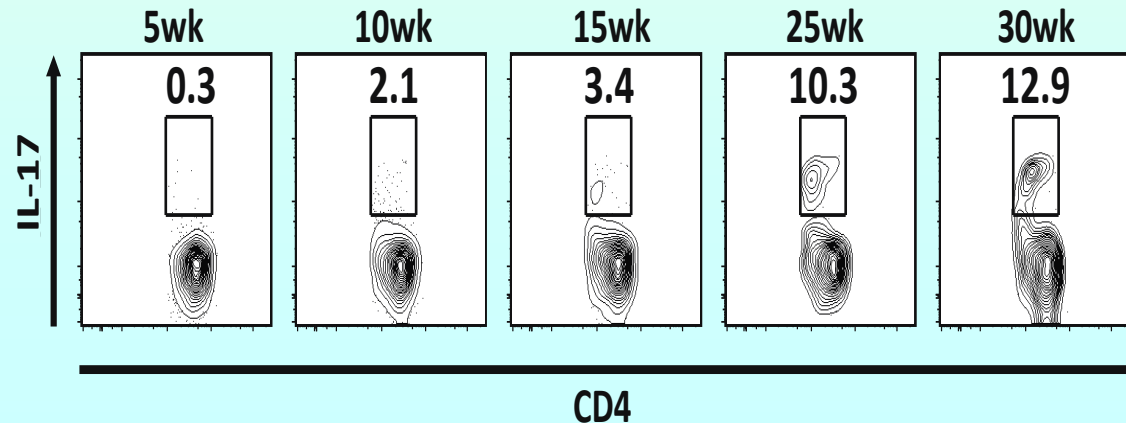
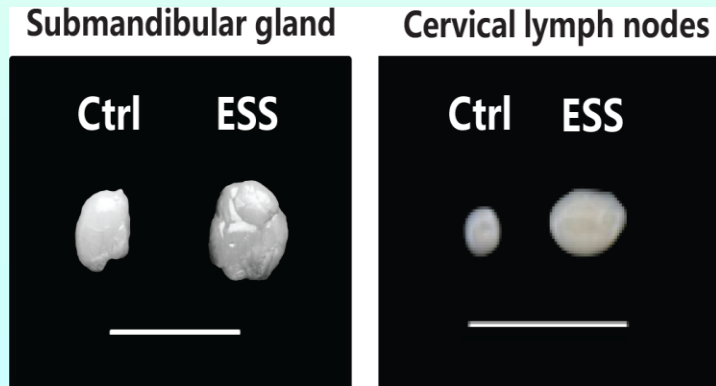
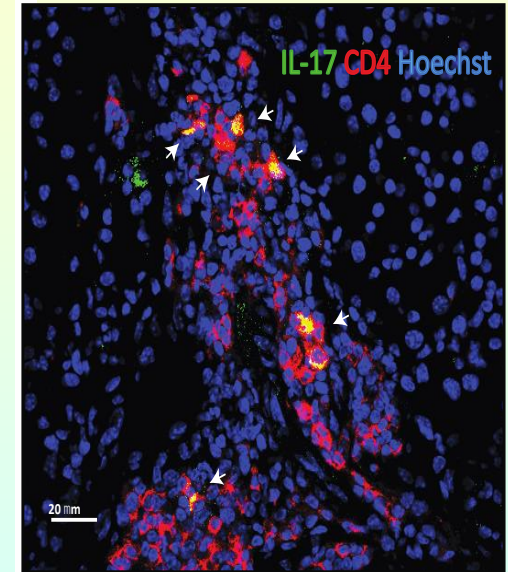
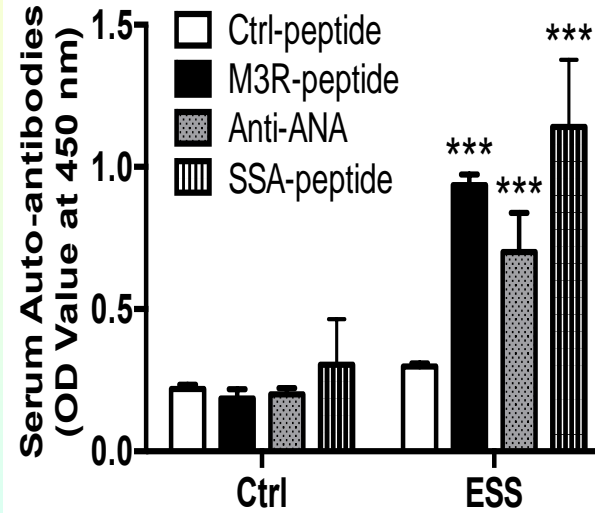
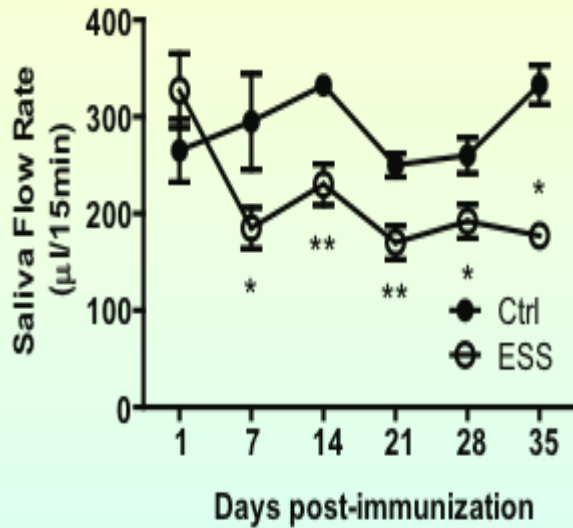
SG protein



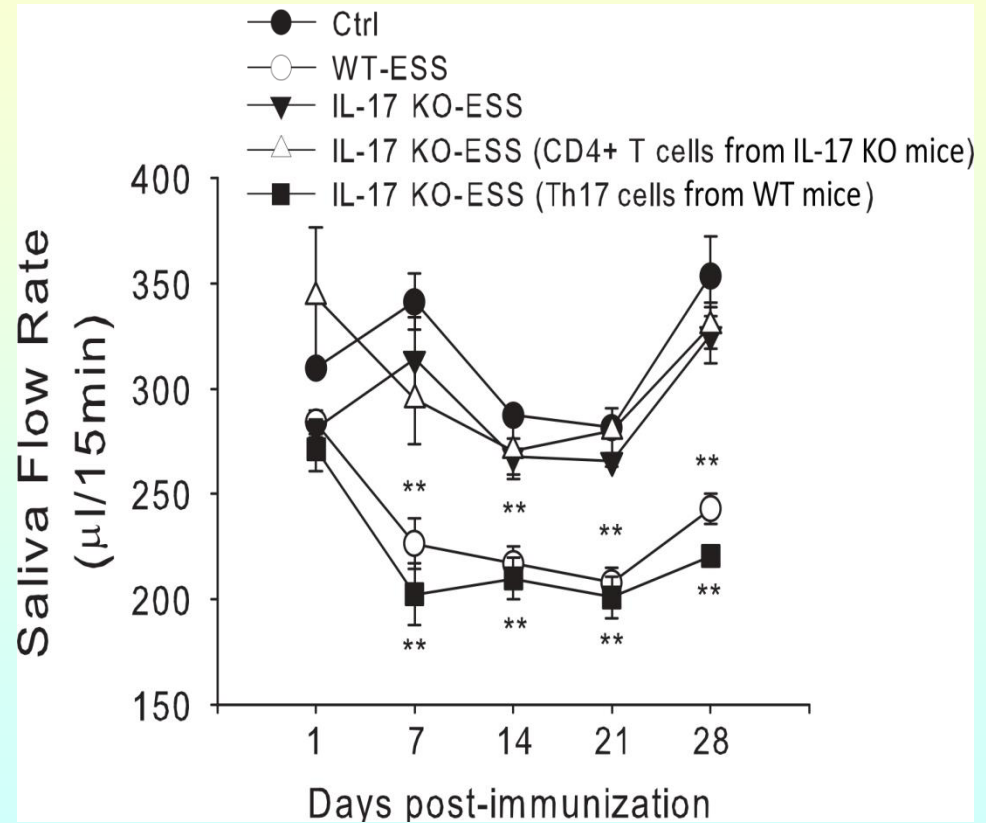
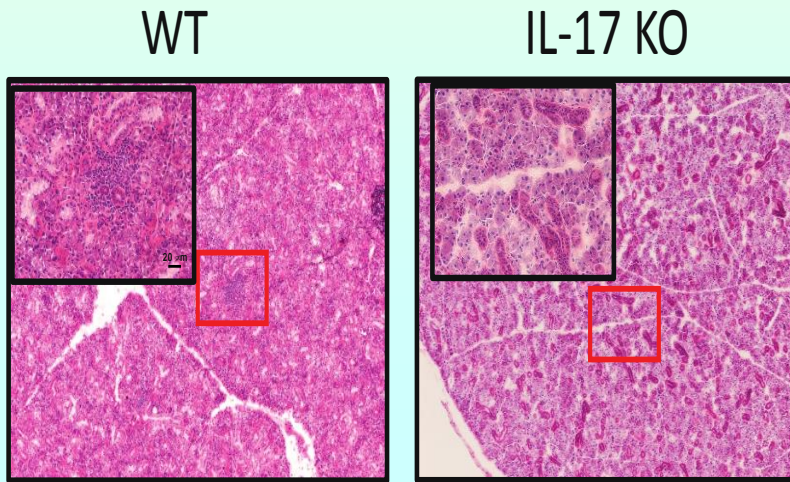
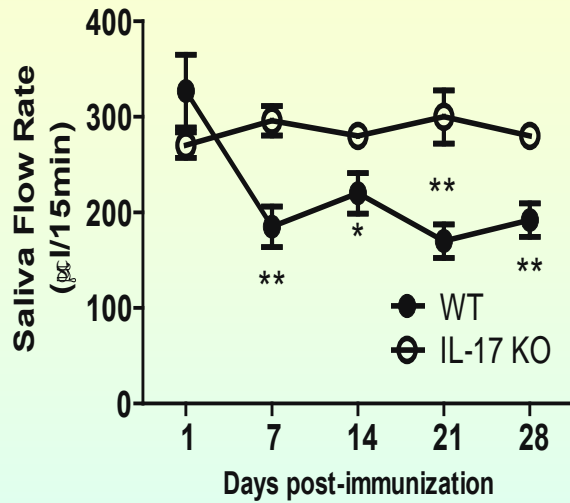
Immunization



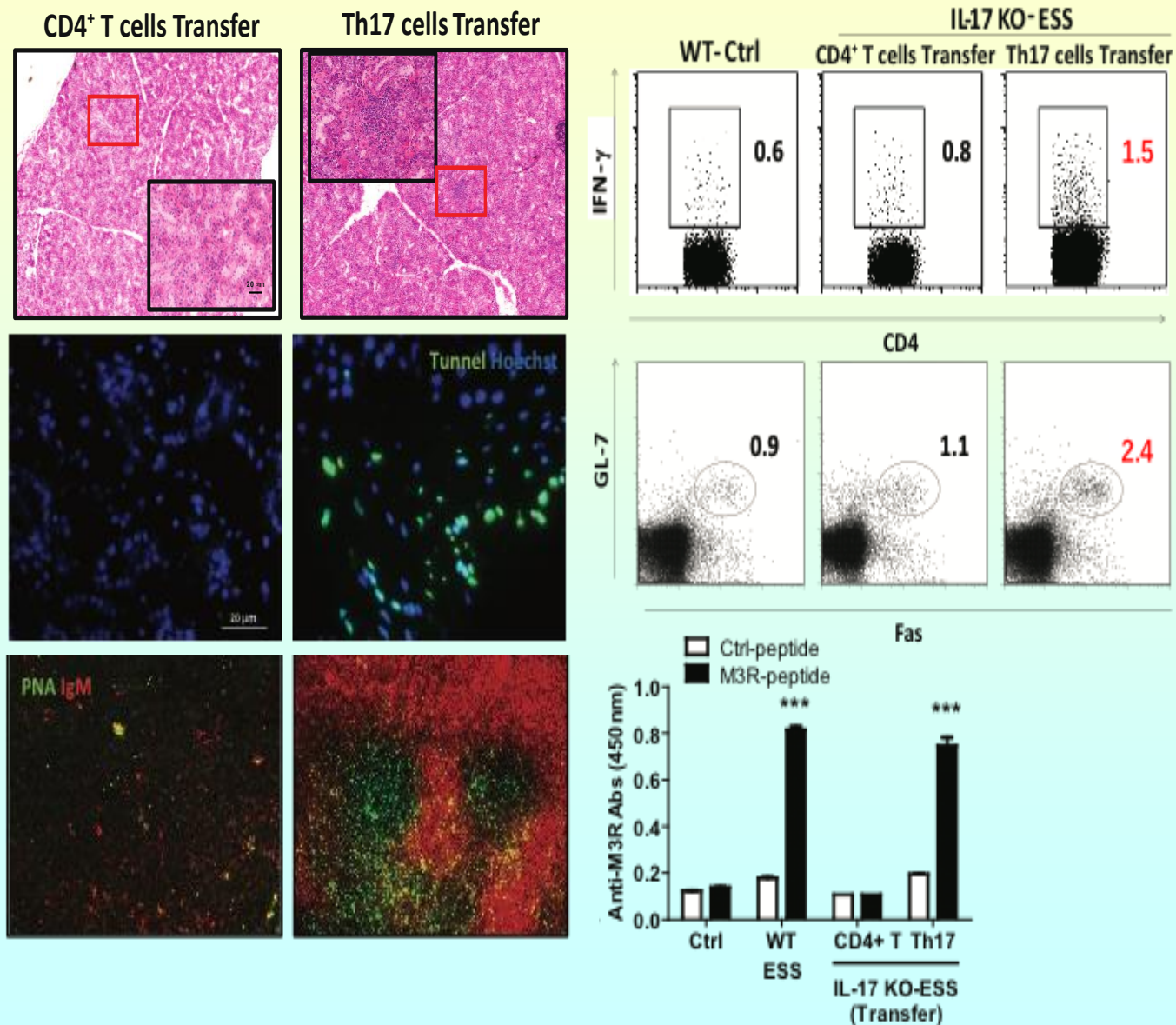
Enhanced Th17 responses during ESS development



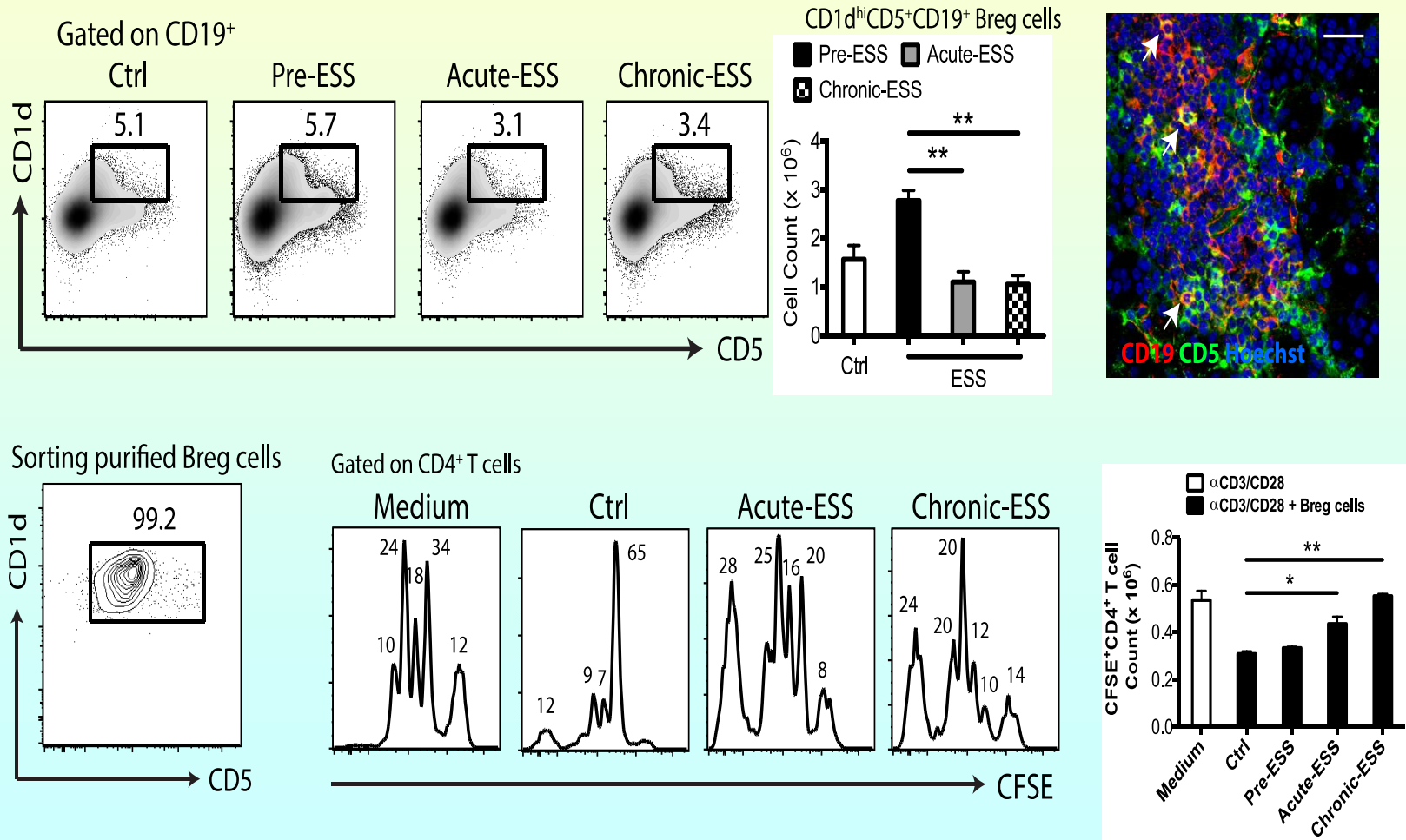
IL-17KO mice are resistant to ESS induction



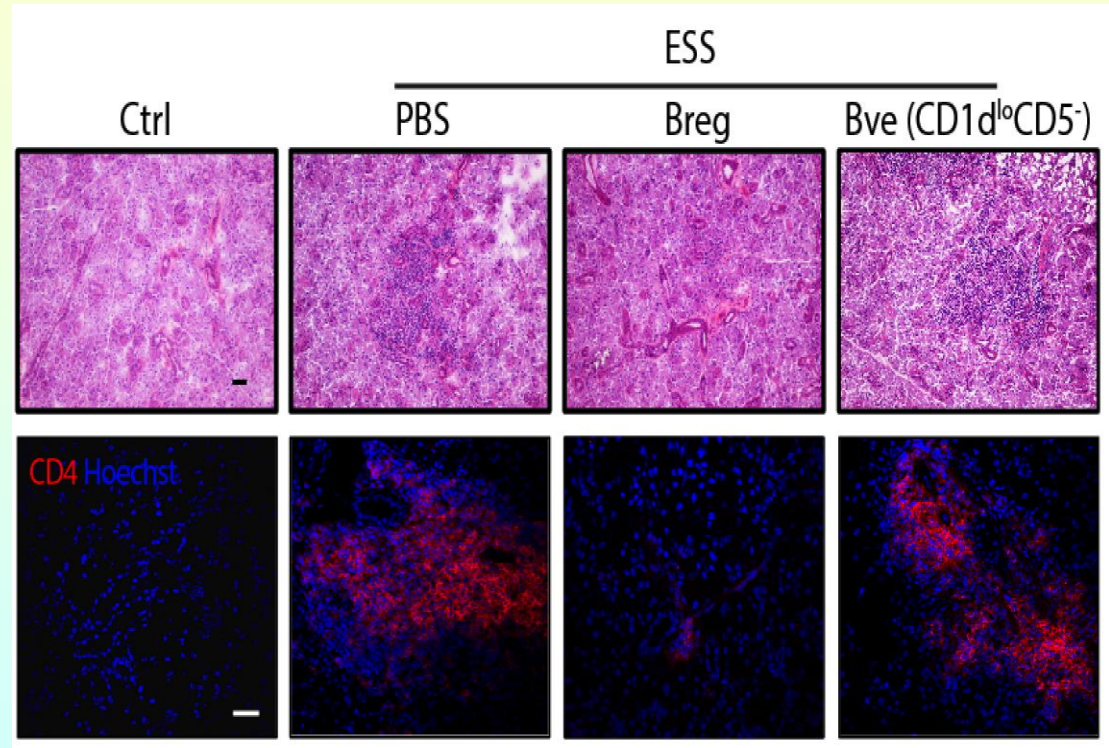
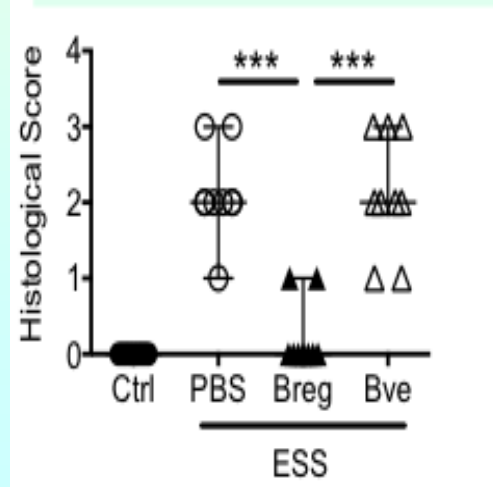
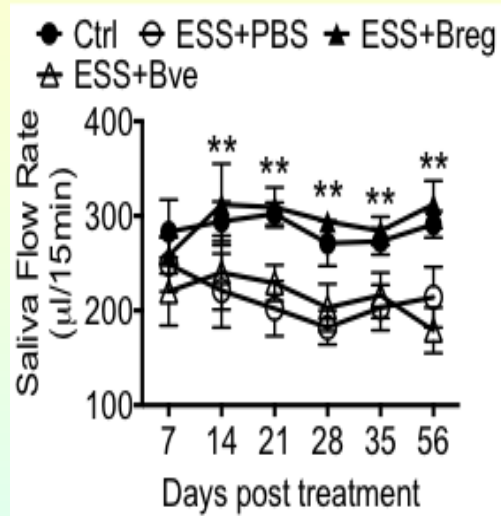
Th17 cell transfer restores disease pathology in IL-17KO mice



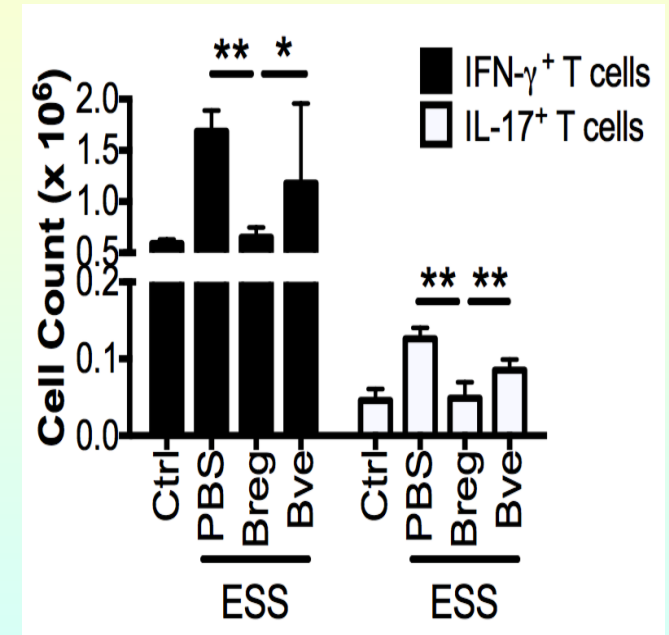
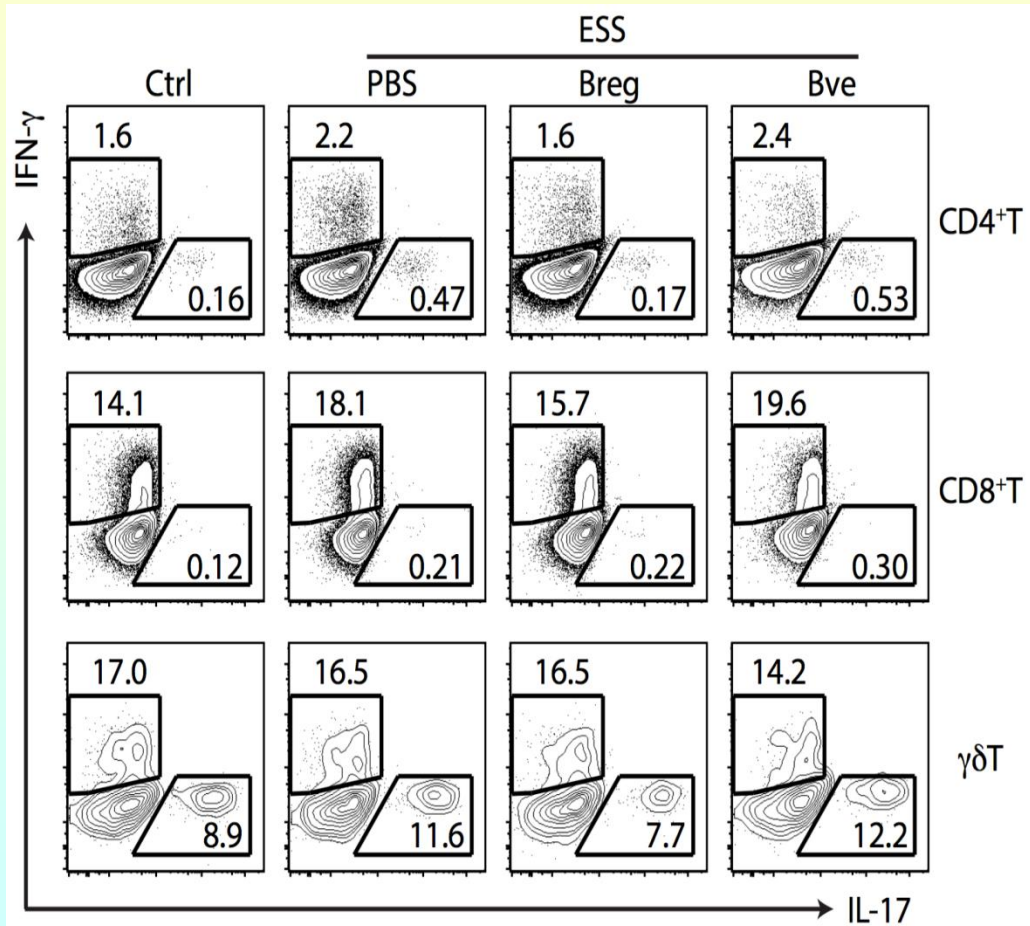
Functional defects of Breg cells in ESS development



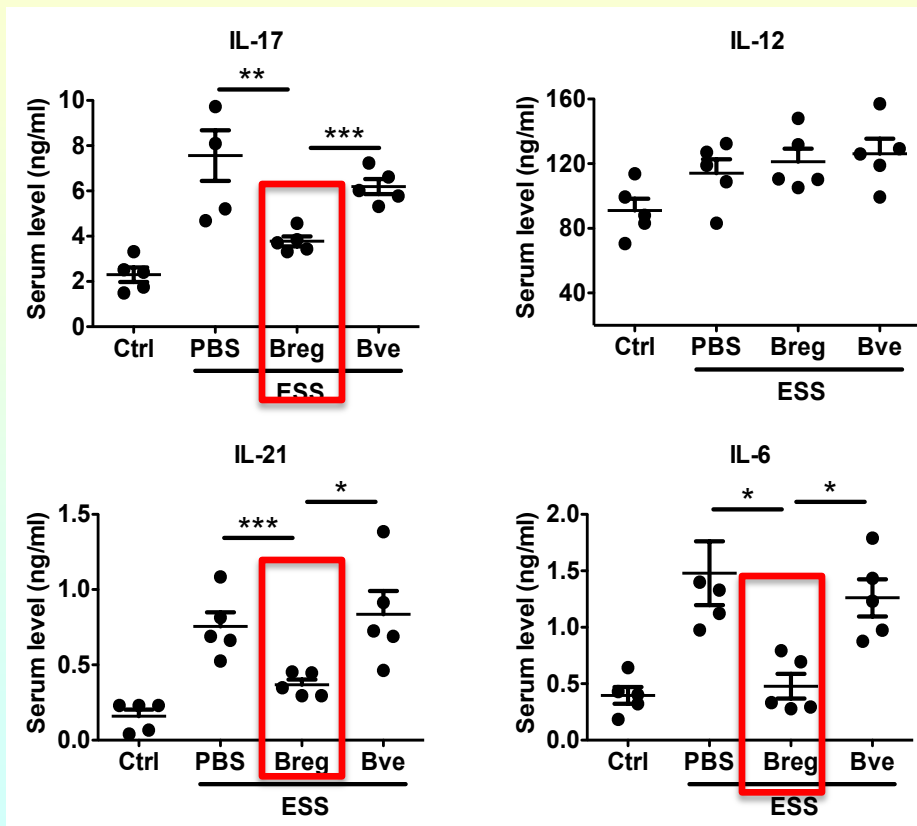
Transfer of Breg cells suppresses ESS progression



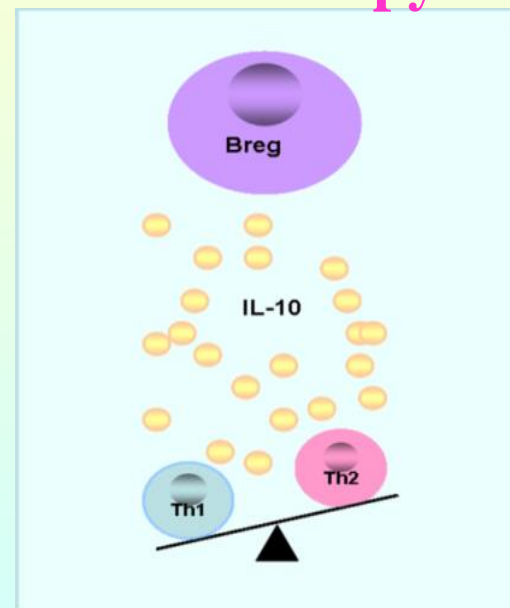
Breg transfer suppresses Th1/Th17 cells in ESS mice



Breg transfer suppresses inflammatory cytokine production

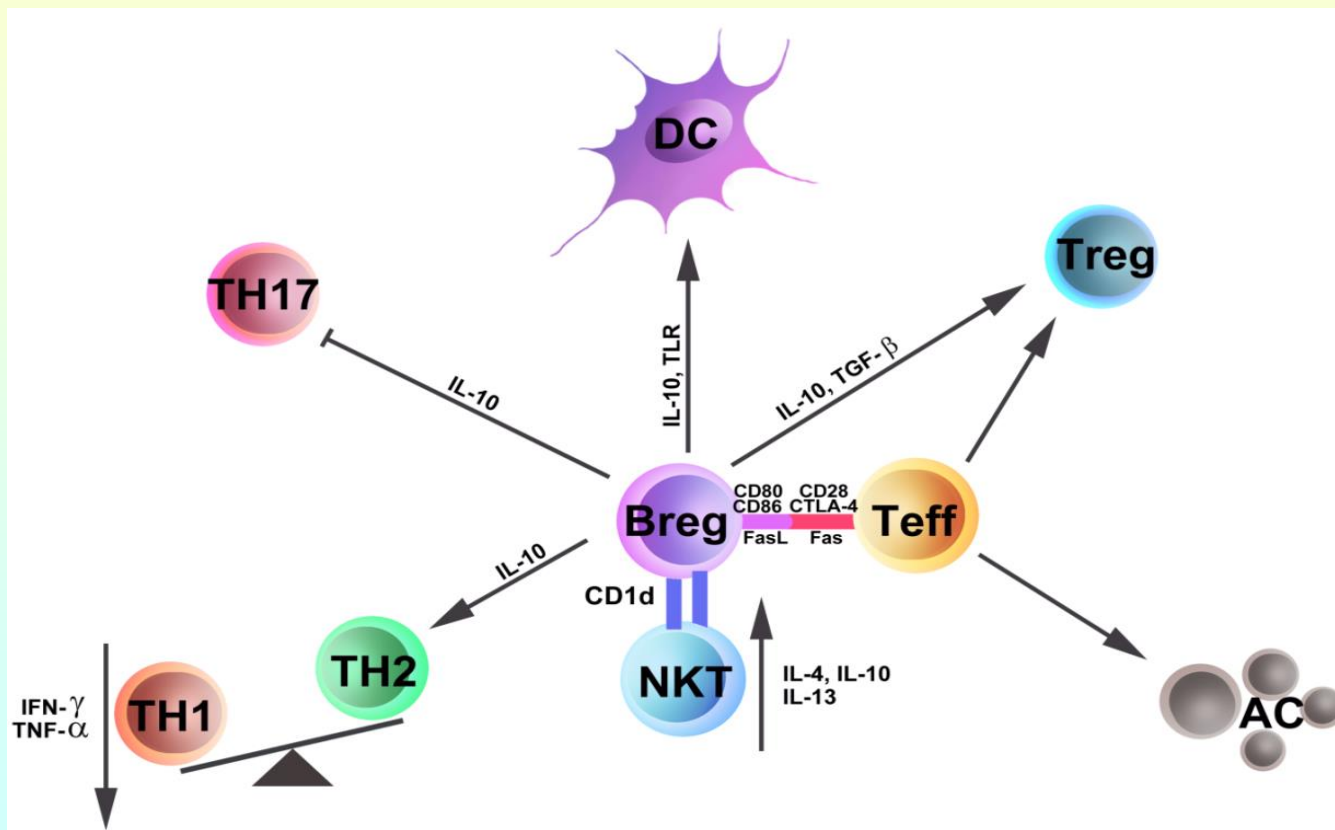


Cell therapy?



(Manuscript in preparation)

Mechanisms of action for Bregs in immune responses



Yang M et al, Cell Mol Immunol (2014)

Acknowledgements

Queenie Lam
Min Yang
Jun Deng
Xiang Lin
Xiaohui Wang
Qian Chen
Kongyang Ma
Otis Ko



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BAFF in regulating B cell maturation and function

