

# Questions

- 1) How can we distinguish sex determined differences from hormonally regulated differences?
- 2) Are the important hormonal effects due to high or low levels of hormone or to cycling levels?
- 3) Are estrogen and other reproductive hormones pro-inflammatory or anti-inflammatory?
- 4) What does perimenopause do to hematopoiesis, lymphopoiesis, thymic function, lymphocyte repertoire and selection and immune response?
- 5) Do estrogen and other reproductive hormones regulate TH1/TH2 differentiation?
- 6) Do estrogen and other reproductive hormones set thresholds on the innate immune response?

**7) What is the evidence that the immune system is differently affected by sex hormones pre and post menopause. Does this apply to both the innate and adaptive immune system? If so, does this have implications for biologic processes beyond infection control?**

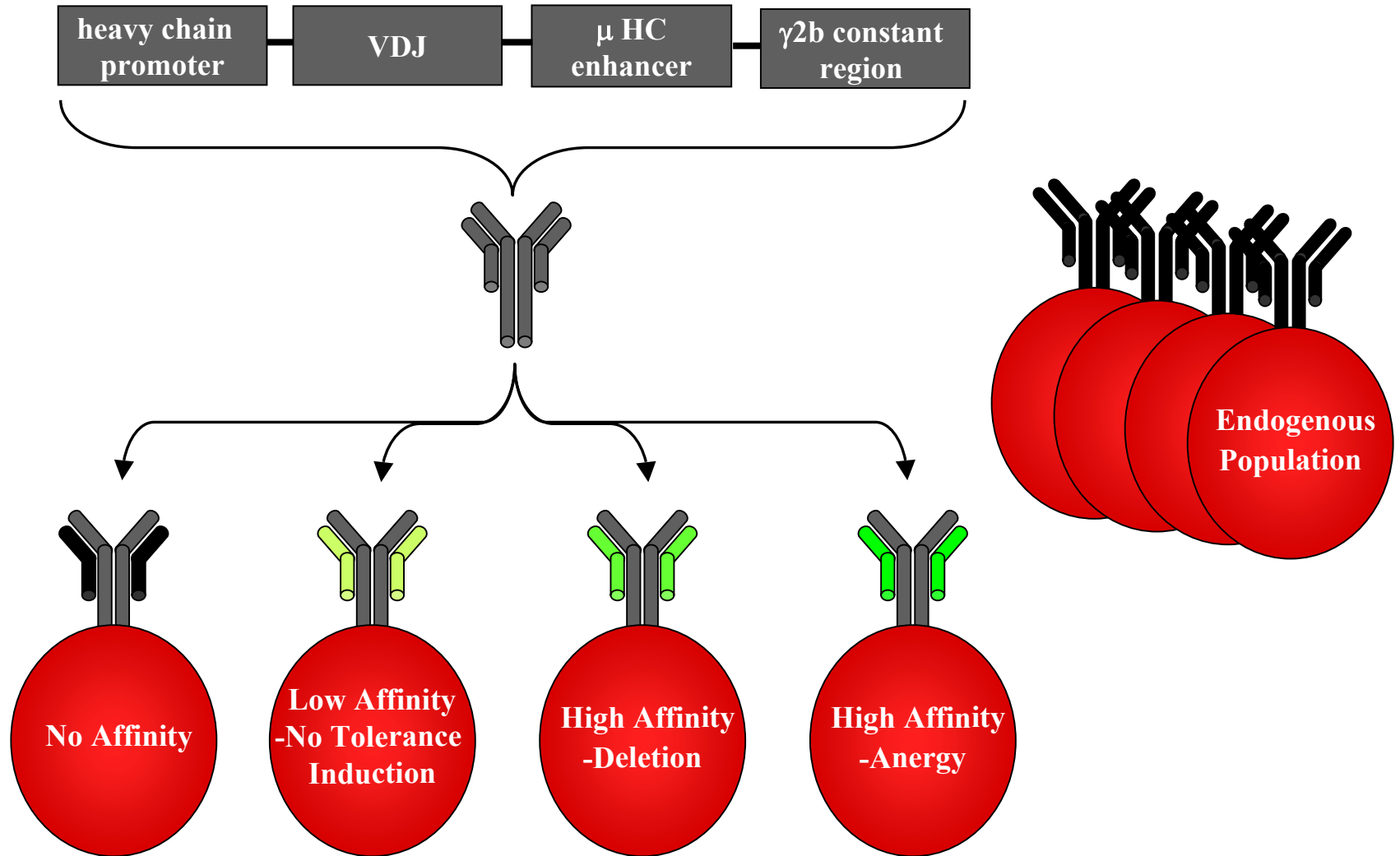
**8) What is known of underlying mechanisms of hormonal regulation of the immune response? Do these mechanisms affect different diseases differentially?**

**9) Is there an interplay of hormones with genetic background or non genetic modulators of the immune system?**

**10) Why does autoimmune disease has much higher incidence in women, especially premenopausal, as compared to men, i.e. lupus, rheumatoid arthritis, thyroid disease, etc.**

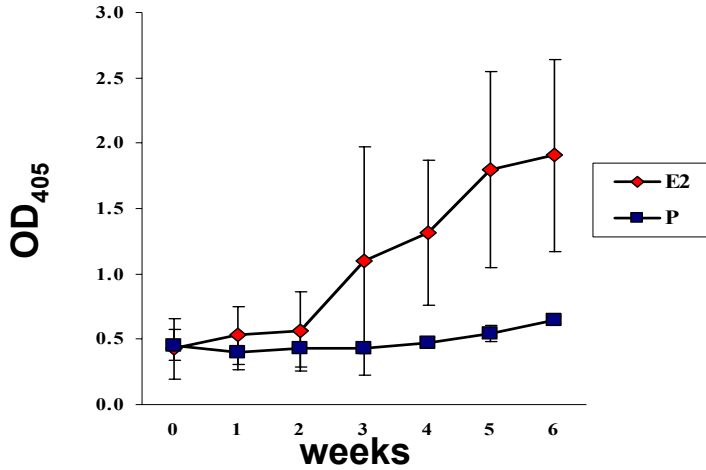
**11) What do we still need to learn about?**

# R4A- $\gamma$ 2b BALB/c Transgenic Mouse Model

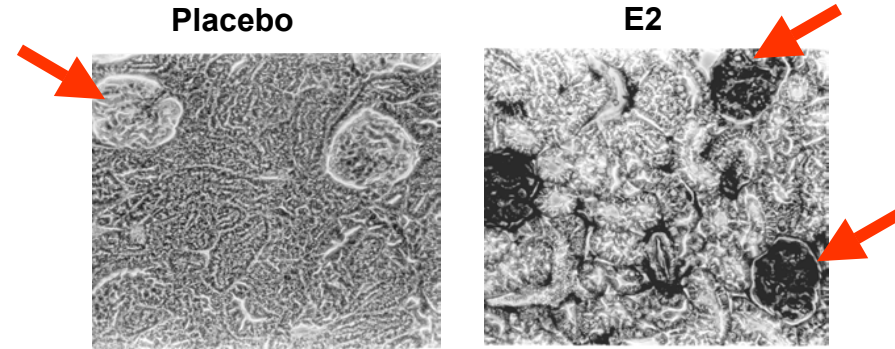


# Maturation and Activation of Anti-DNA B Cells in Estrogen Treated Mice

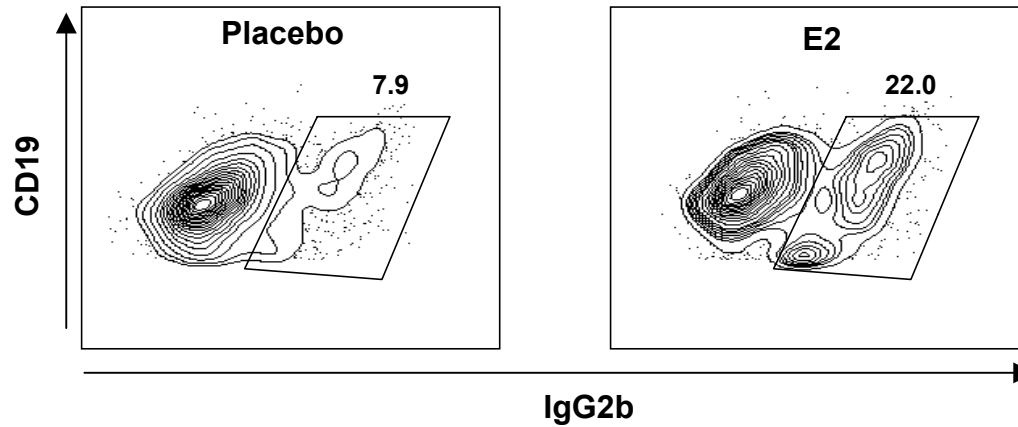
Anti-DNA antibody levels



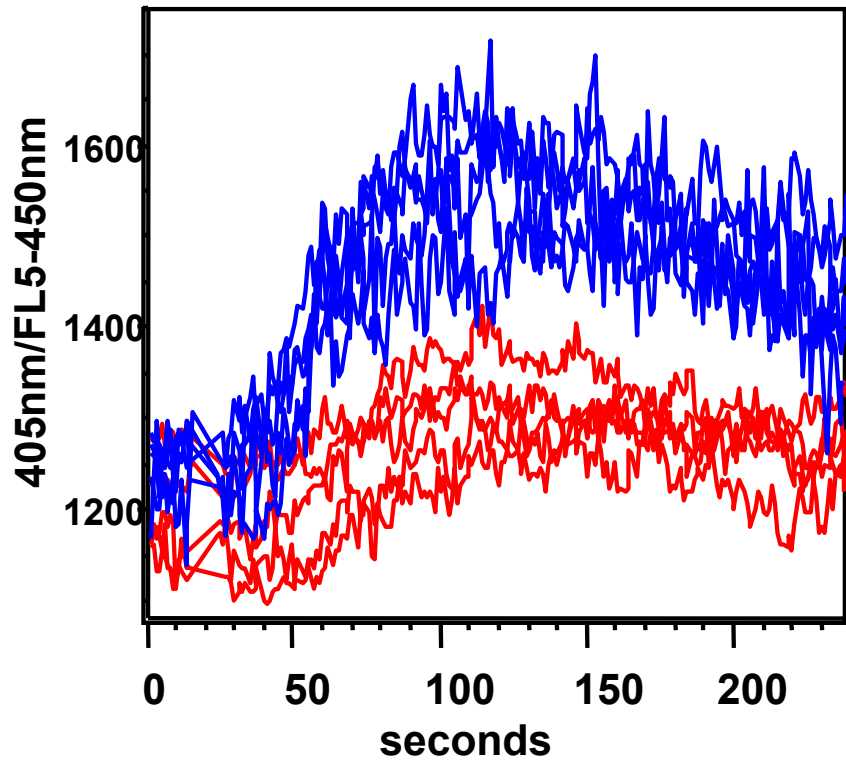
Glomerular immunoglobulin deposition



Expansion of Tg<sup>+</sup> B cells



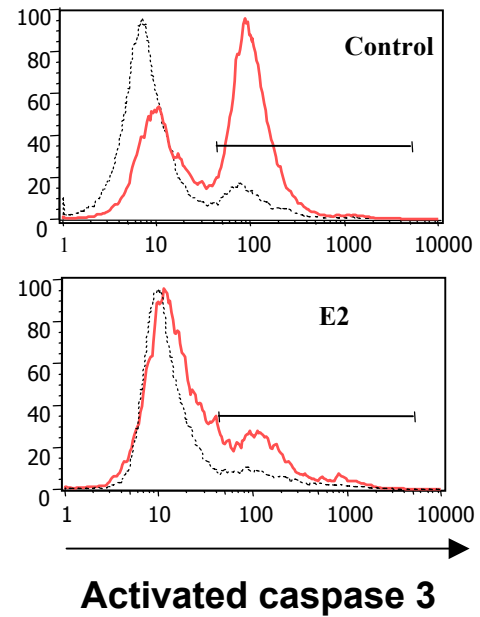
## Strength of the BCR in MZ B cells of BALB/c mice treated with E2



Control

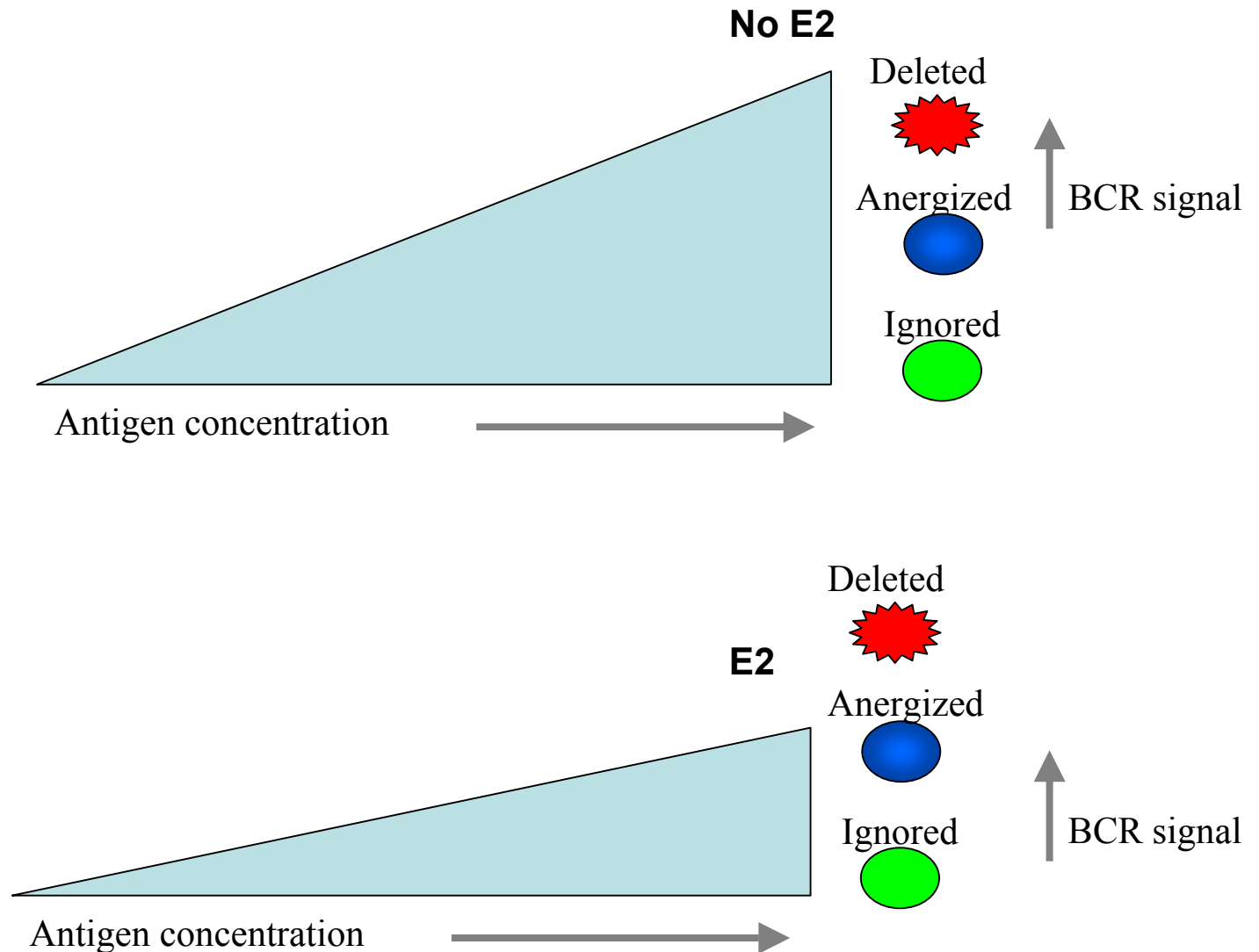
E2

## Apoptosis of Transitional B cells

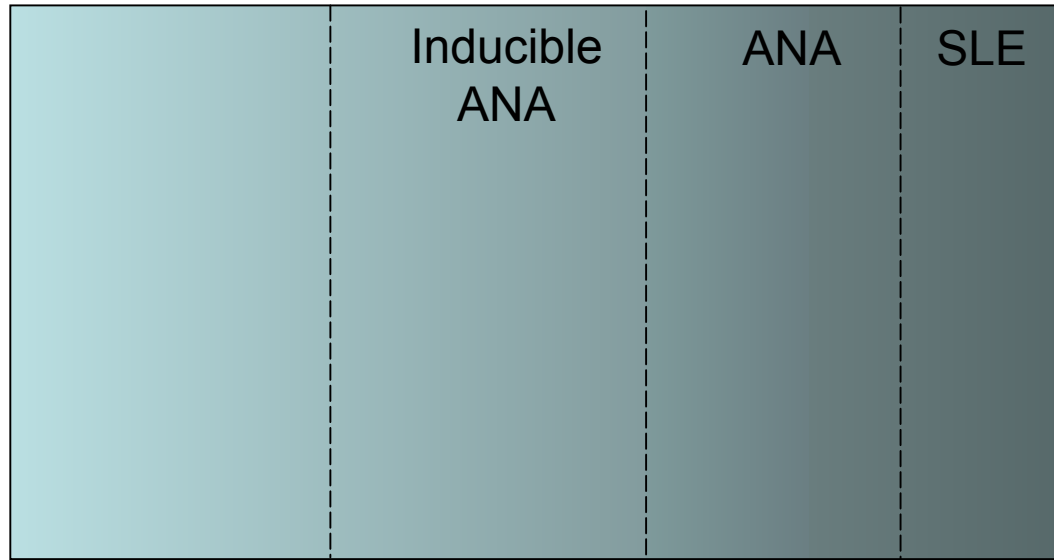


Activated caspase 3

# Estrogen leads to the survival of autoreactive B cells



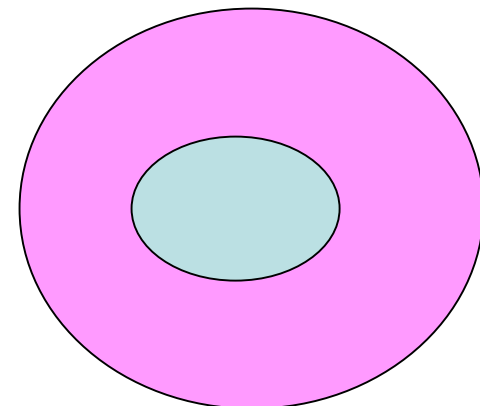
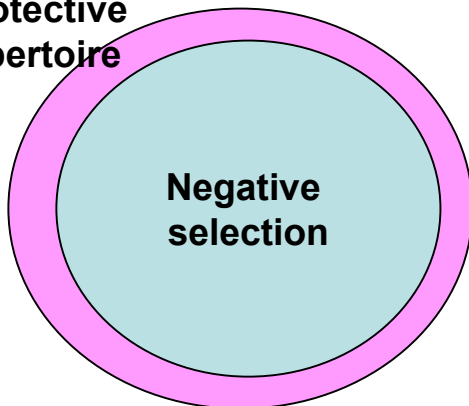
# Stringency of lymphocyte selection and predisposition to autoimmunity



Leakiness in Negative Selection



Protective repertoire



# Estrogen does not induce autoantibodies in C57BL/6 mice

