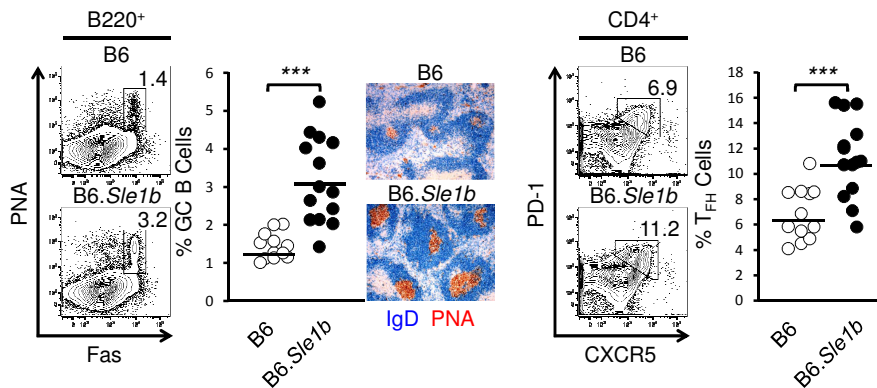


Our goal is to understand the mechanisms by which loss of B cell tolerance in the germinal centers contributes to autoantibody production and subsequent development of an autoimmune disease SLE/lupus disease

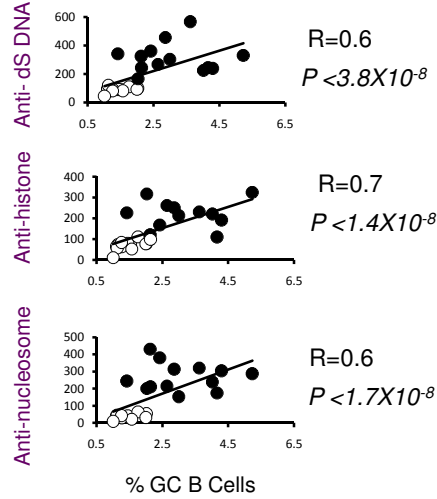
3

### Increased spontaneous GC response in aged B6.*Sle1b* mice



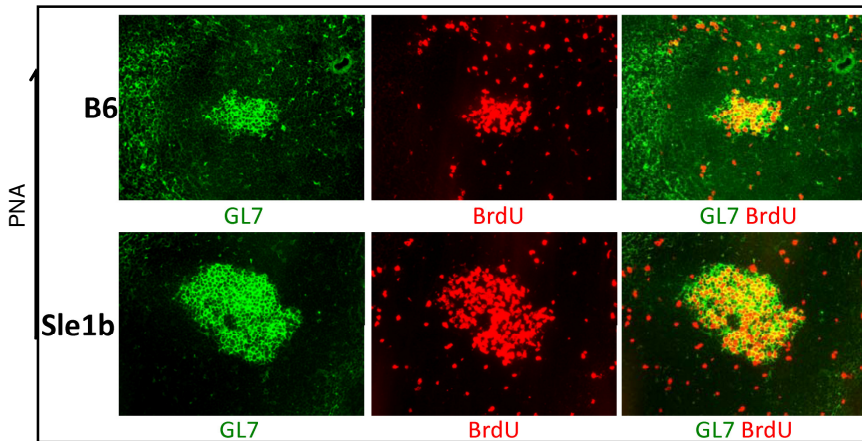
Wong et al.  
2012

% GC B cells correlates with autoantibody titers



Wong et al.  
2012

Increased spontaneous GC response in aged B6.Sle1b mice

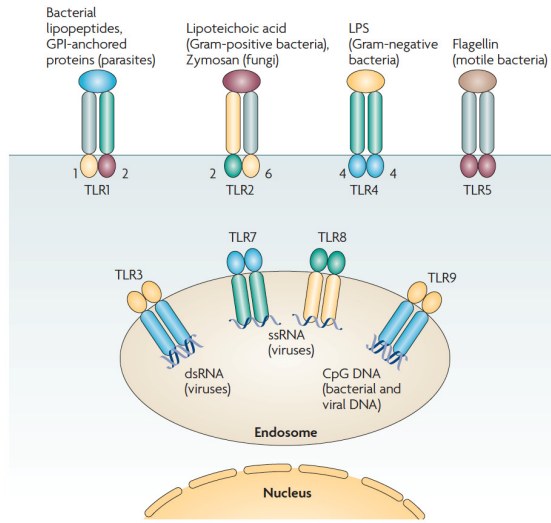


Wong et al.  
2012

**Toll Like receptors (TLRs)**

**Stimulated by:**

- exogenous viral and bacterial components
- endogenous viral and self nucleic acids (ssRNA, unmethylated CpG) DNA

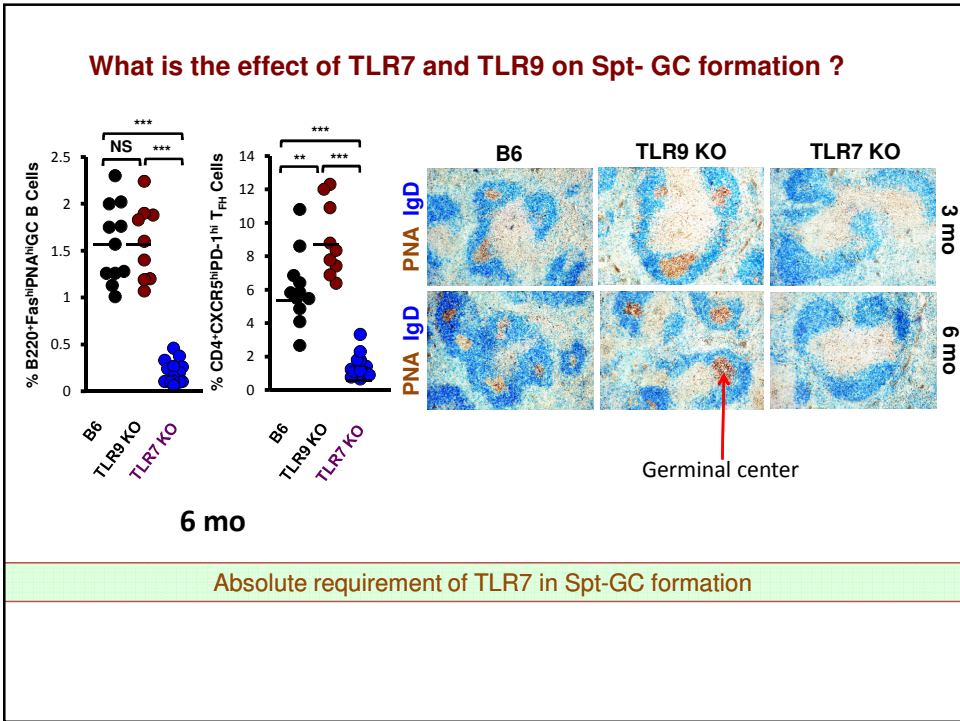
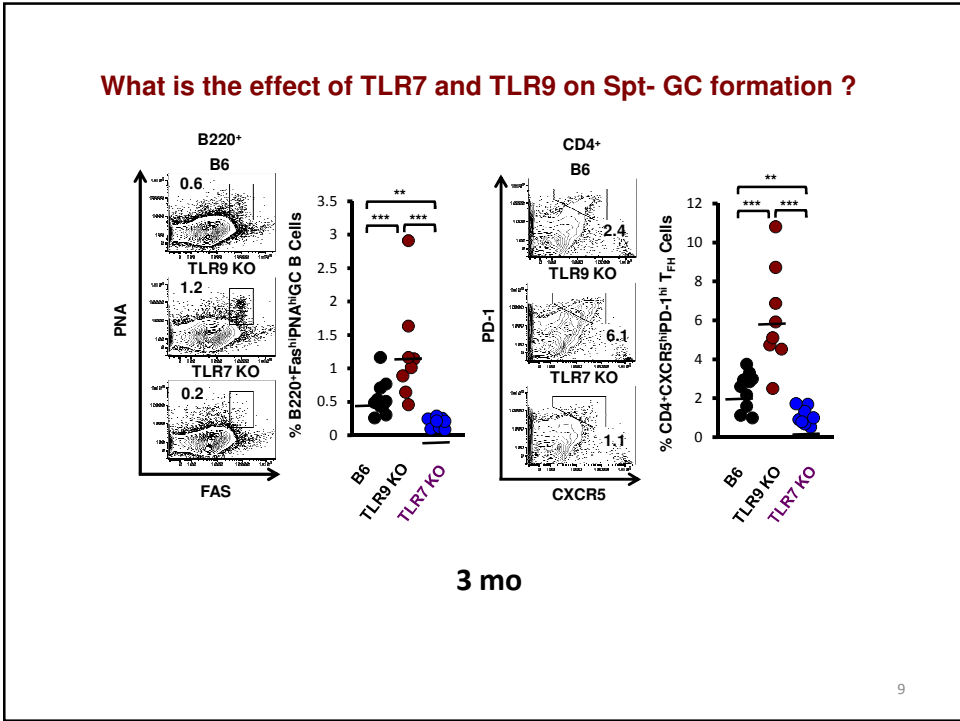


Ernest C. Borden et al., Nature Reviews Drug Discovery, 2007



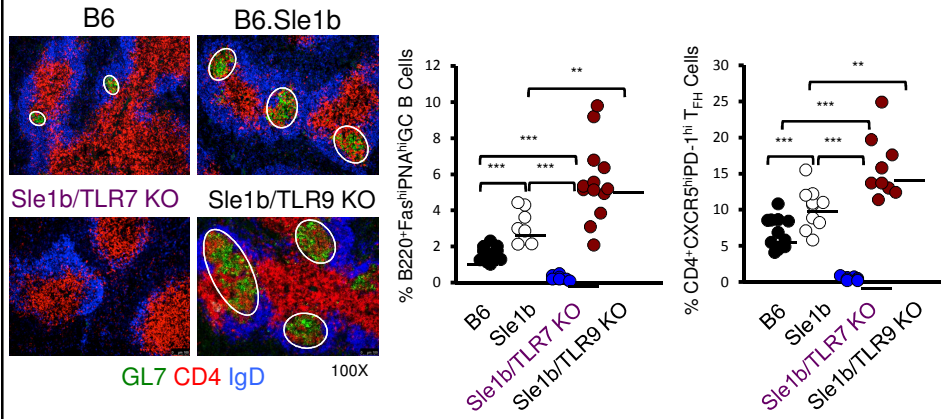
**Mouse Strains GCs (Spontaneously formed)**

|        |   |
|--------|---|
| B6     | + |
| TLR2KO | + |
| TLR3KO | + |
| TLR4KO | + |
| TLR7KO |   |
| TLR9KO |   |



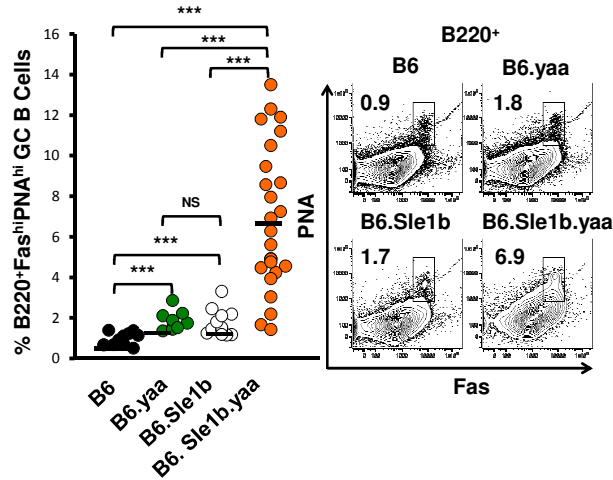
**What is the role of TLR7 and TLR9 in Spt-GC response in B6.Sle1b mice?**

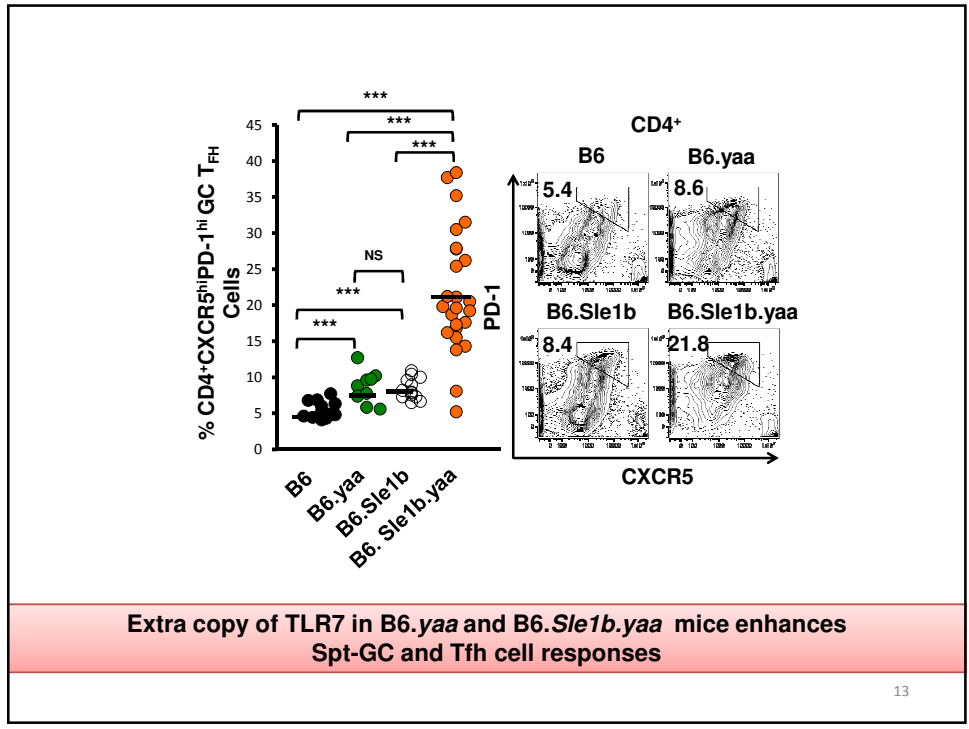
6 mo old naïve mice



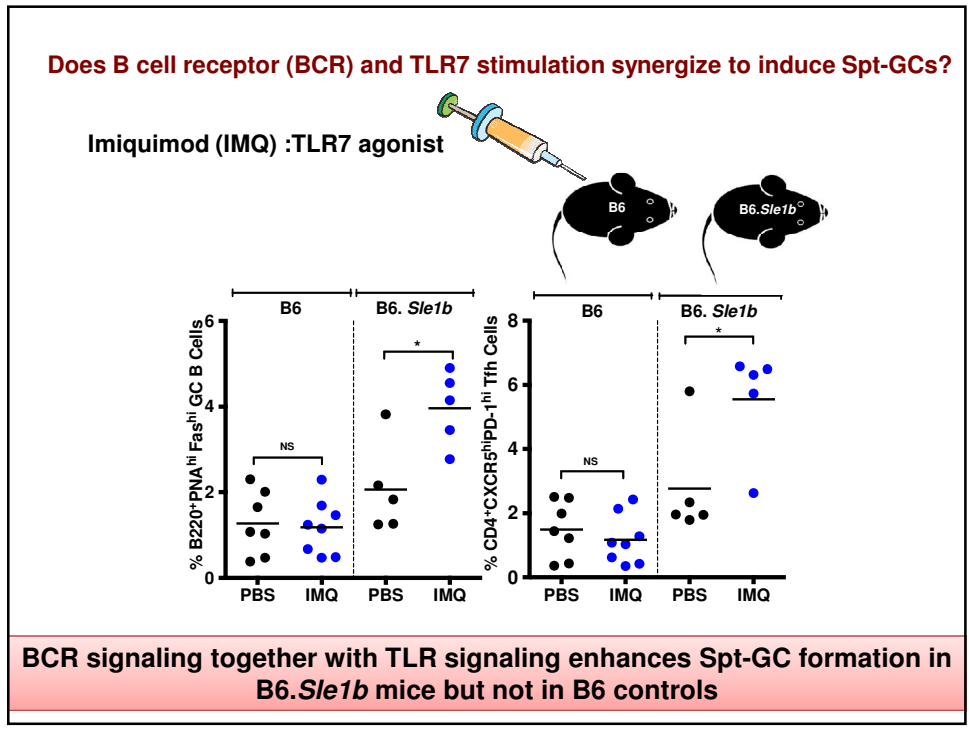
**TLR7 promotes while TLR9 downregulates Spt-GCs in B6.Sle1b mice**

6 mo old naïve mice





13



### We also observed that:

- ❑ TLR7 is essential for the generation of anti-dsDNA, anti-histone, anti-nucleosome, anti-Sm/RNP, and anti-cardiolipin antibodies.
- ❑ TLR9 is essential for the formation of anti-dsDNA, anti-histone and anti-nucleosome antibodies but NOT anti-Sm/RNP and anti-cardiolipin antibodies
- ❑ Both TLR7 and TLR9 are essential for Glomerular complement deposition and progressive kidney pathology

15

### Does TLR7 expression in myeloid cells contribute to Spt-GC formation?



#### Mouse strain

#### Spt-GC at 3 mo

CD11c-Cre<sup>+/-</sup>-MyD88<sup>fl/fl</sup>

✓

LysM-Cre<sup>+/-</sup>-MyD88<sup>fl/fl</sup>

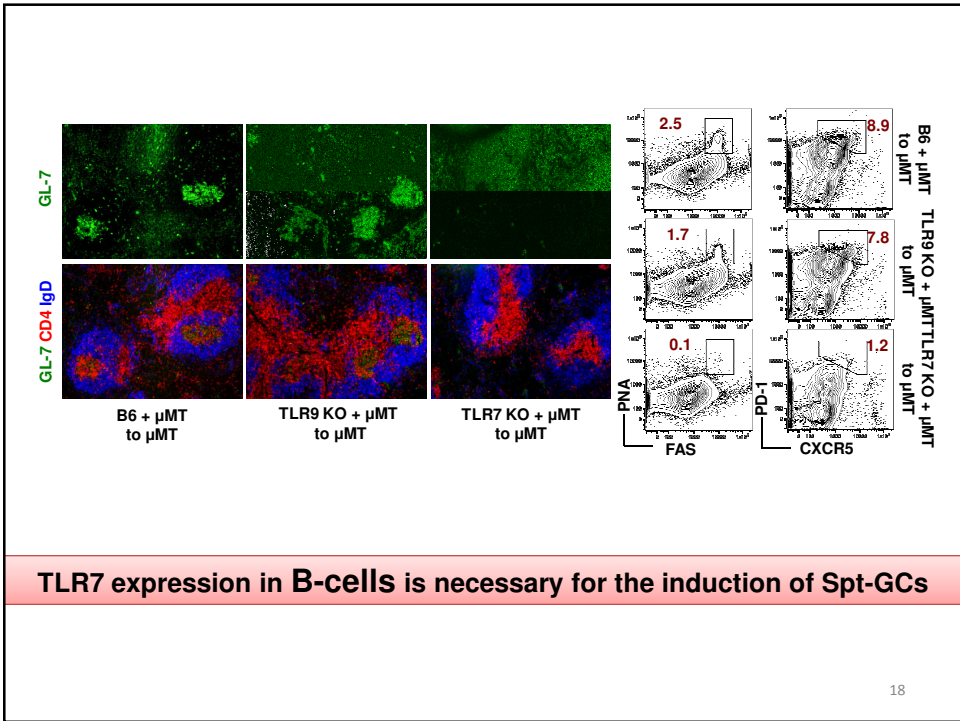
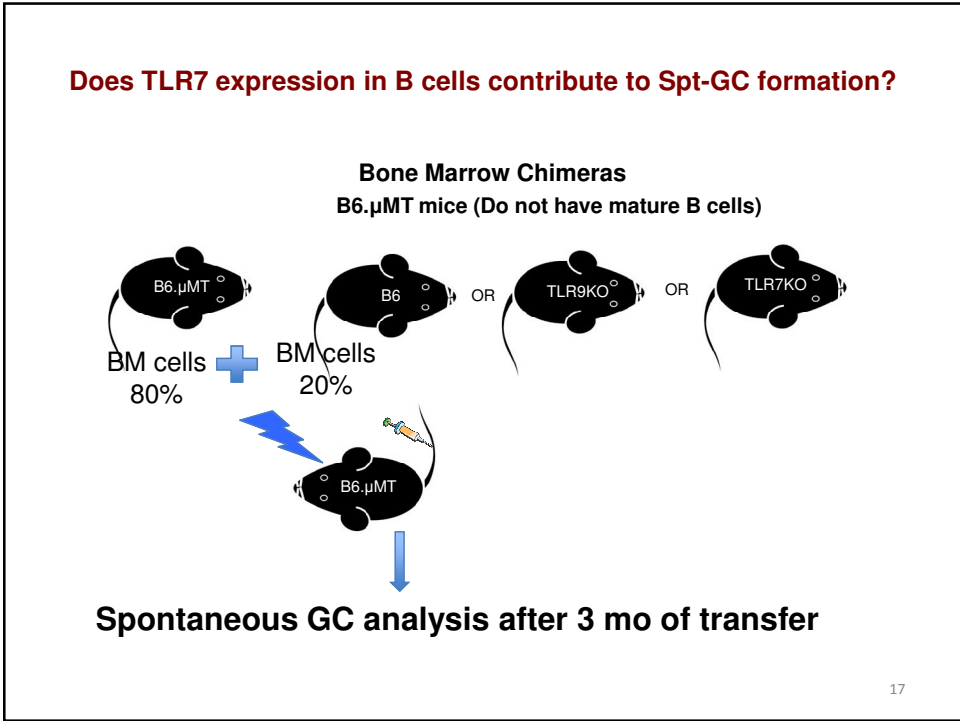
✓

**TLR7 and 9 in myeloid cells do not play a direct role in Spt-GC formation**

16

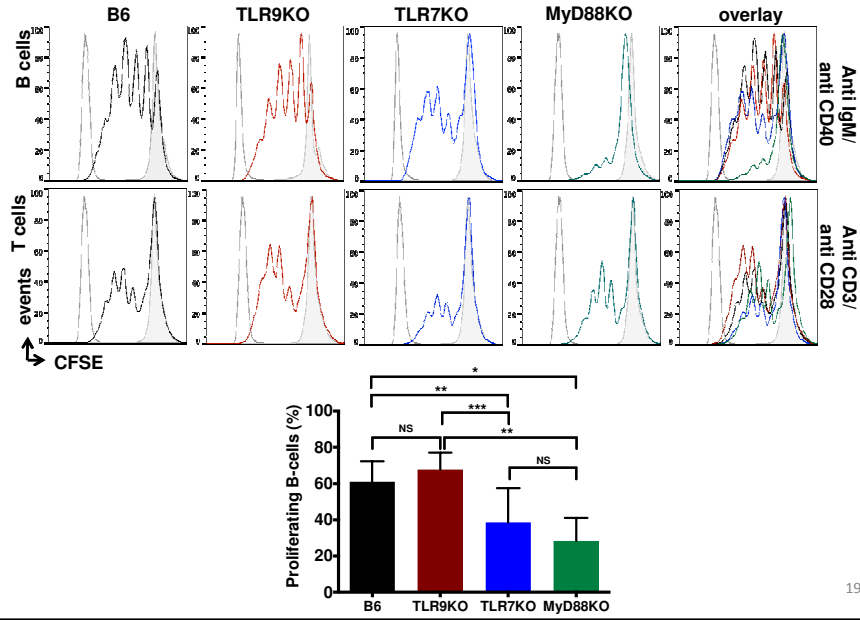


**Does TLR7 expression in B cells contribute to Spt-GC formation?**



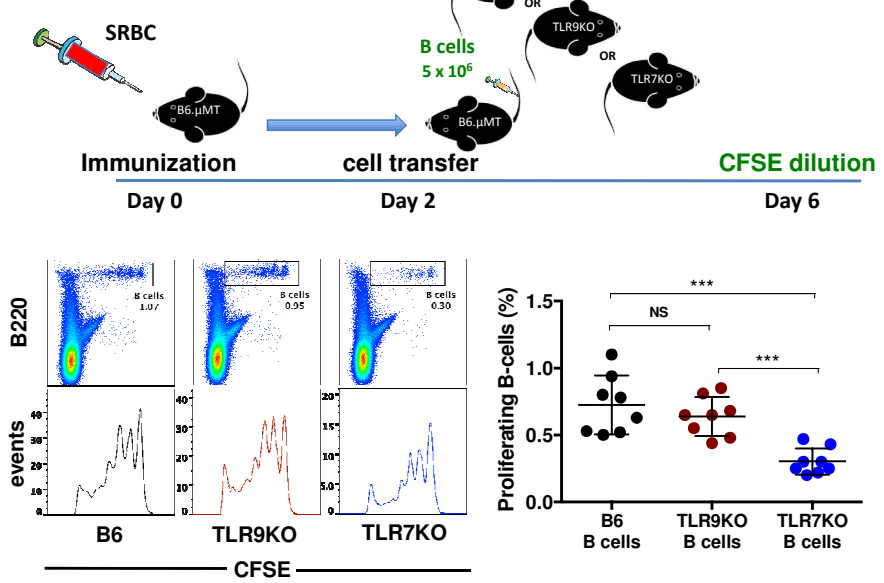
**2. What is the effect of TLR7 and 9 on B cell proliferation?**

**In-vitro Proliferation**

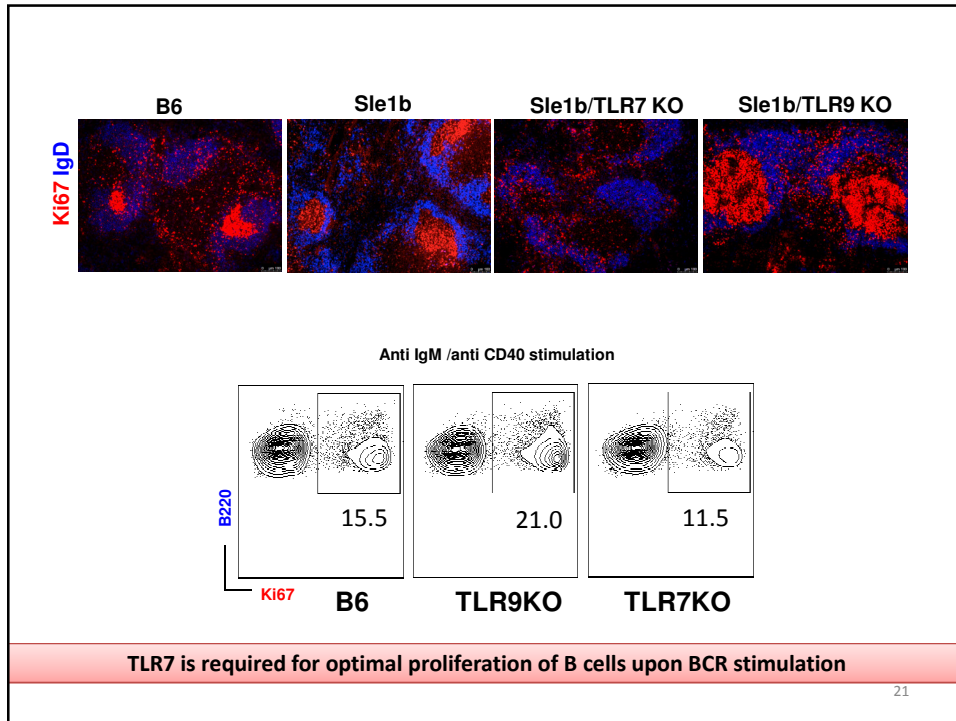


19

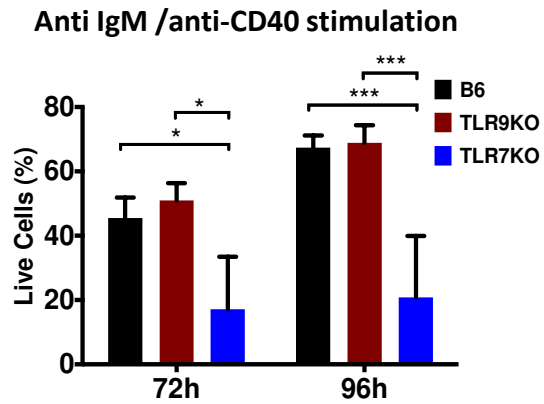
**In-vivo Proliferation**

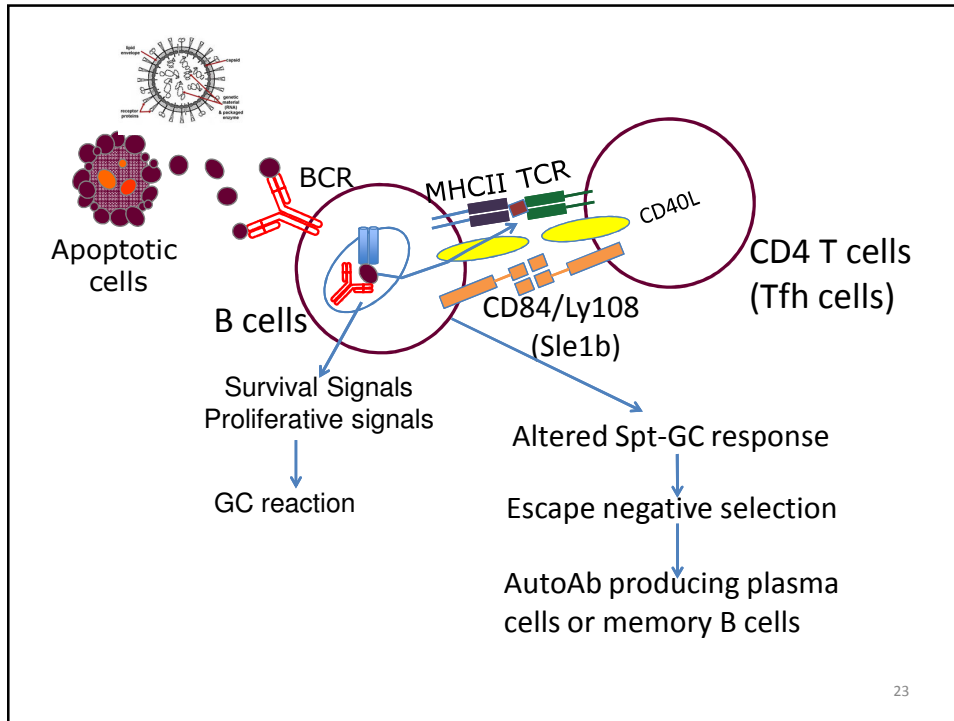


20



**3. What is the effect of TLR7 and 9 on B cell survival?**





23

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UNITED STATES OF AMERICA