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Early Life Intervention Diminishes Manifestations of Sjögren's Syndrome in NOD.H-2^{h4} mice

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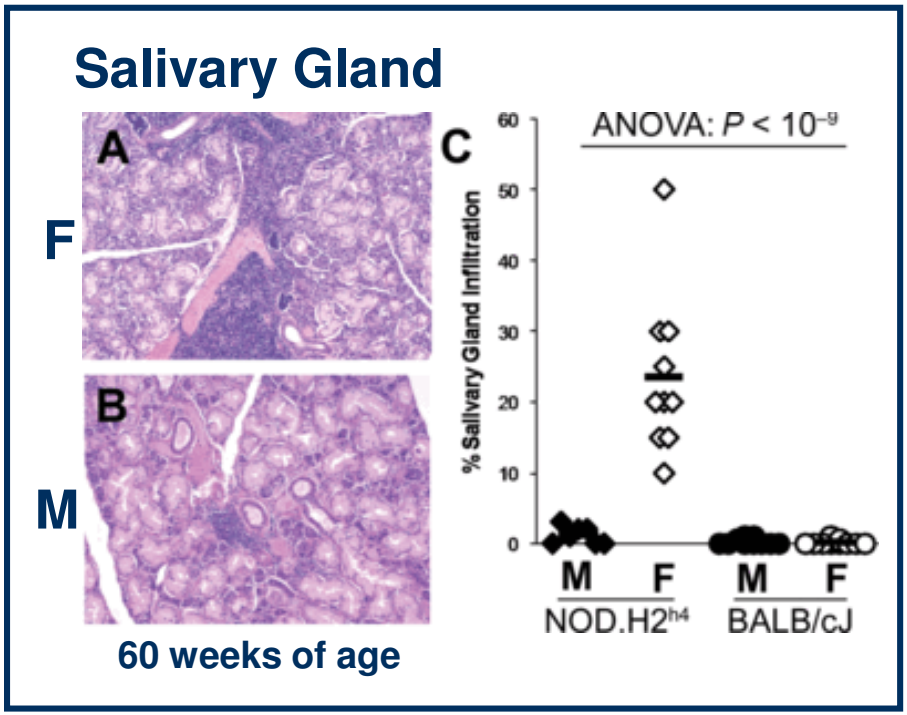
Clinical Manifestations of Sjögren's Syndrome in Humans and Mice

- Sjögren's Syndrome is the 2nd most common autoimmune rheumatic disease characterized by:
- ↑ Autoantibodies
- Ectopic lymphoid follicles in the salivary and lacrimal gland
- ↓ salivary and tear flow
- ↑ Female predisposition (9:1)
- NOD.H-2^{h4} mice recapitulate many of the human clinical presentations



Cihakova, D. et al. Contemporary Challenges in Autoimmunity. 1173:378-383 (2009).

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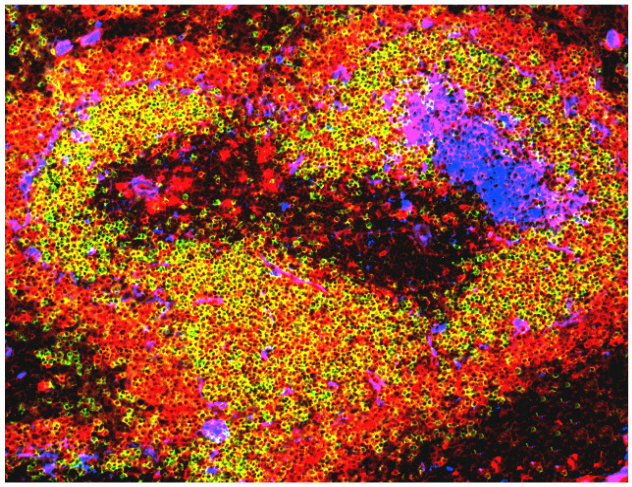
Ectopic Follicles are Organized Lymphocyte Clusters that Develop in Chronically Inflamed Tissue

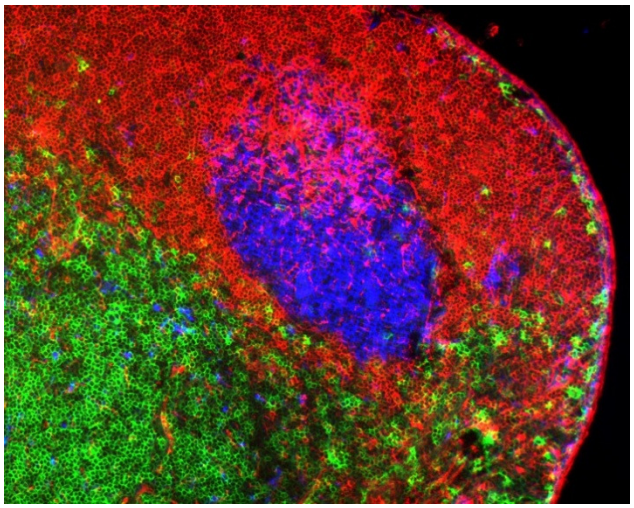
Spleen

IgM
IgD
PNA



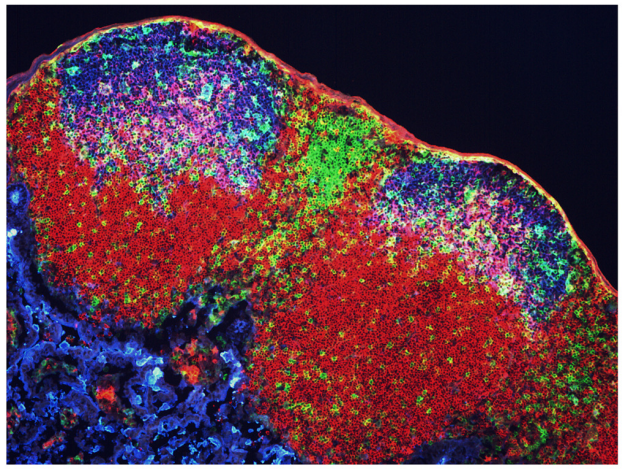
Lymph Node

IgM
CD4
PNA



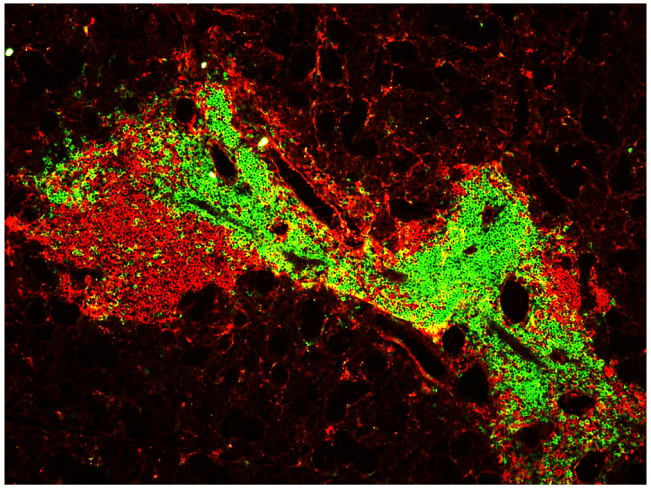
Peyer's Patch

IgM
CD4
PNA



Ectopic Follicle

B220
CD4



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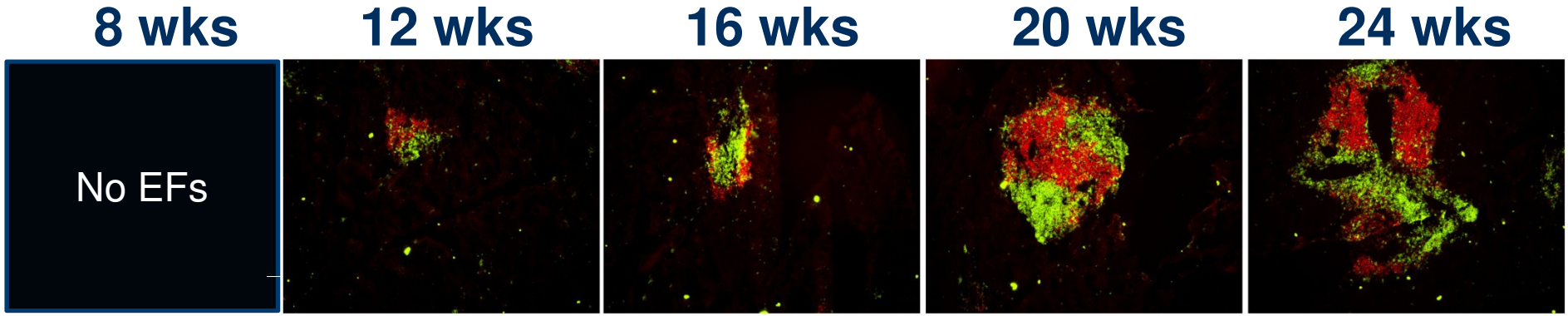
Ectopic Lymphoid Follicles in Salivary Glands Fully Develop at 20 Weeks of Age

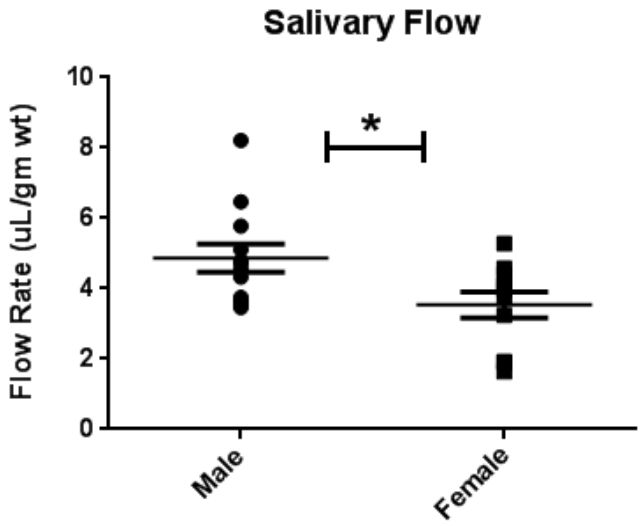
B220 / **CD3**
100X

Salivary Gland



% of mice with EFs:	0%	67%	50%	100%	100%

60 wks



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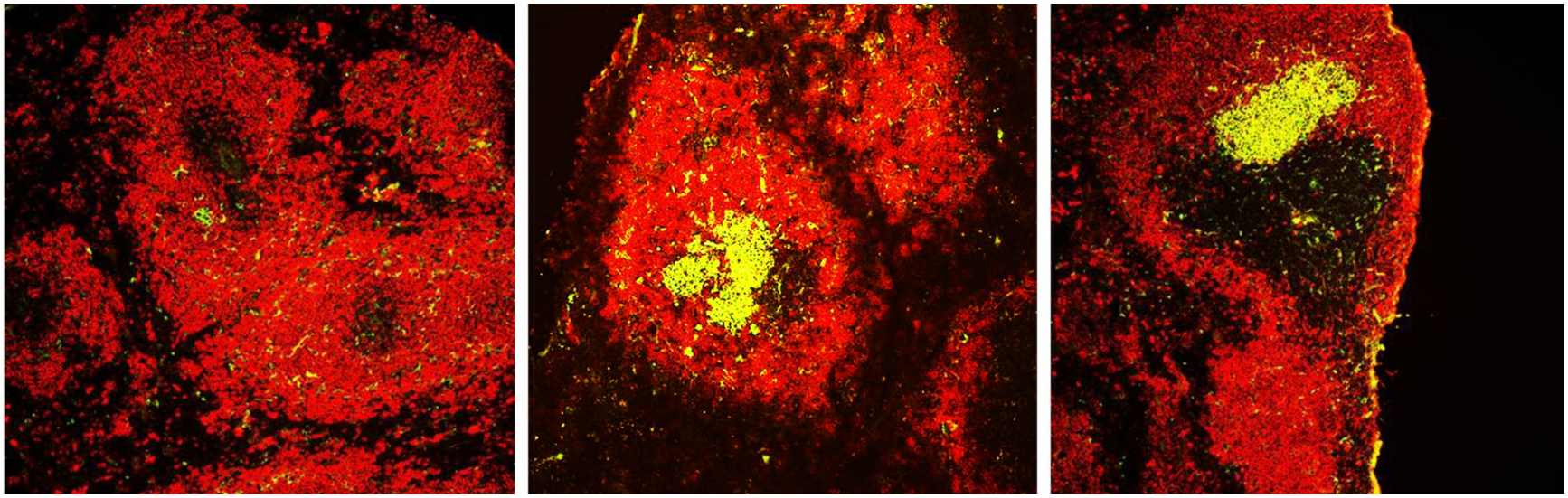
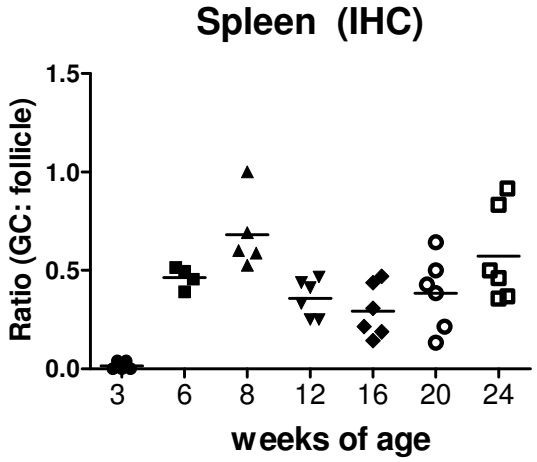
Karnell et. al, Mol. Imm. 2014

Spontaneous Germinal Centers Develop in the Spleens of Female but not Male Mice Early in Life

Age 3 weeks 3.5 weeks 6 weeks



IgM PNA
100X



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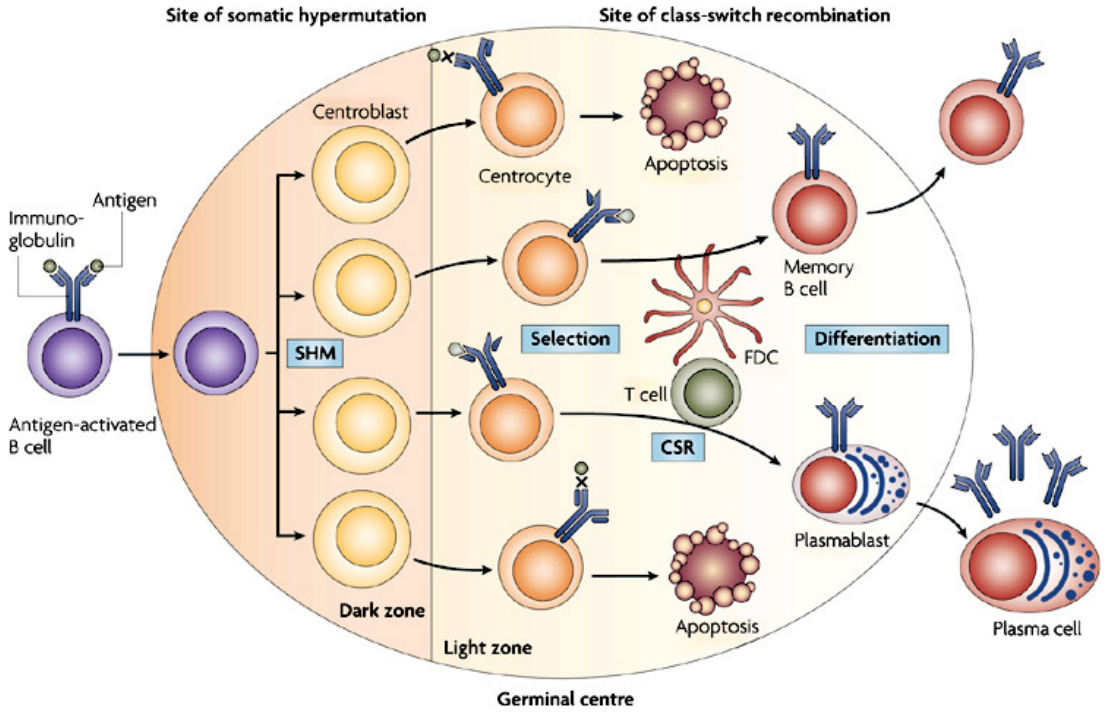
Karnell et. al, Mol. Imm. 2014

Activated B Cells undergo Affinity Maturation and Class Switch Recombination in Germinal Centers



Klein et al. 2008
Nature Reviews | Immunology

GC in autoimmune mice are likely to be the sites where mutated, self-reactive autoantibodies are generated

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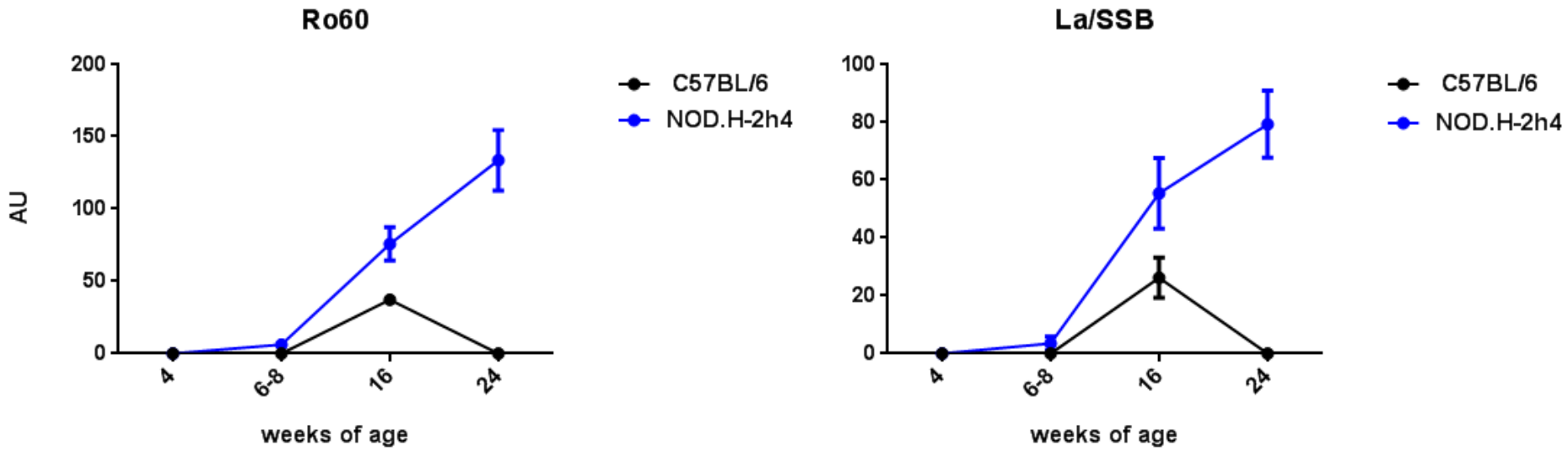
Detection of α Ro/La Autoantibodies Following the Emergence of Spontaneous Germinal Centers



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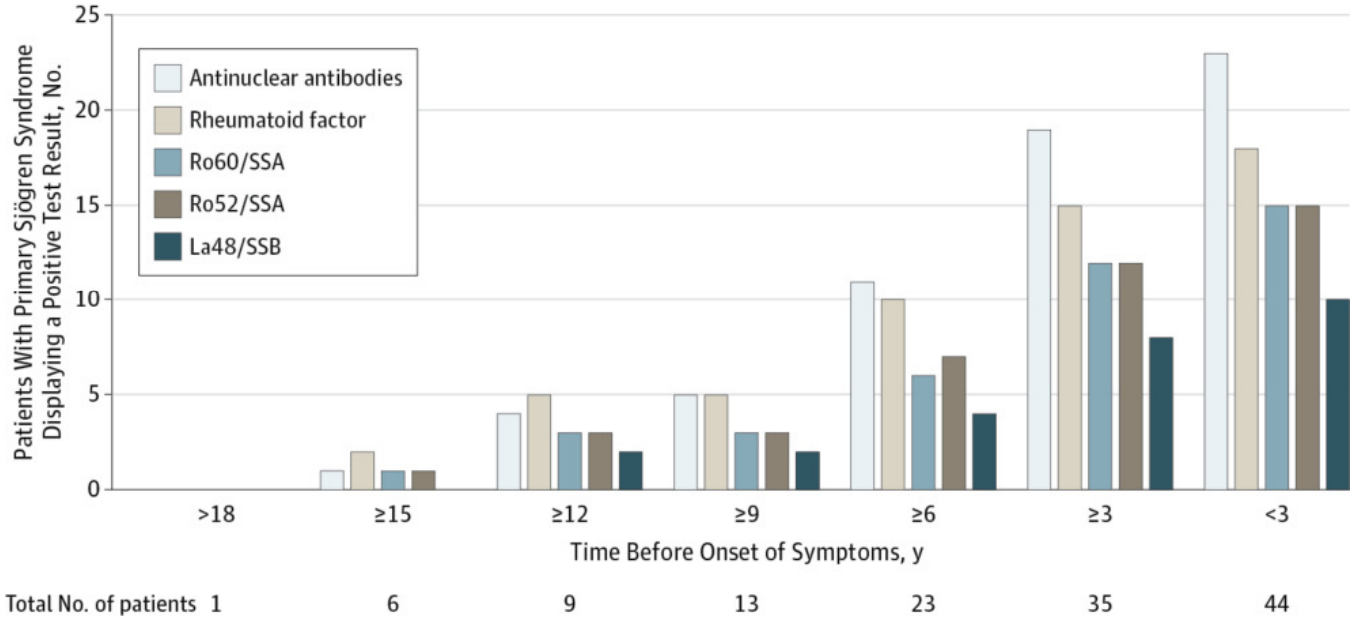
Autoantibodies Present Before Symptom Onset in Primary Sjögren Syndrome



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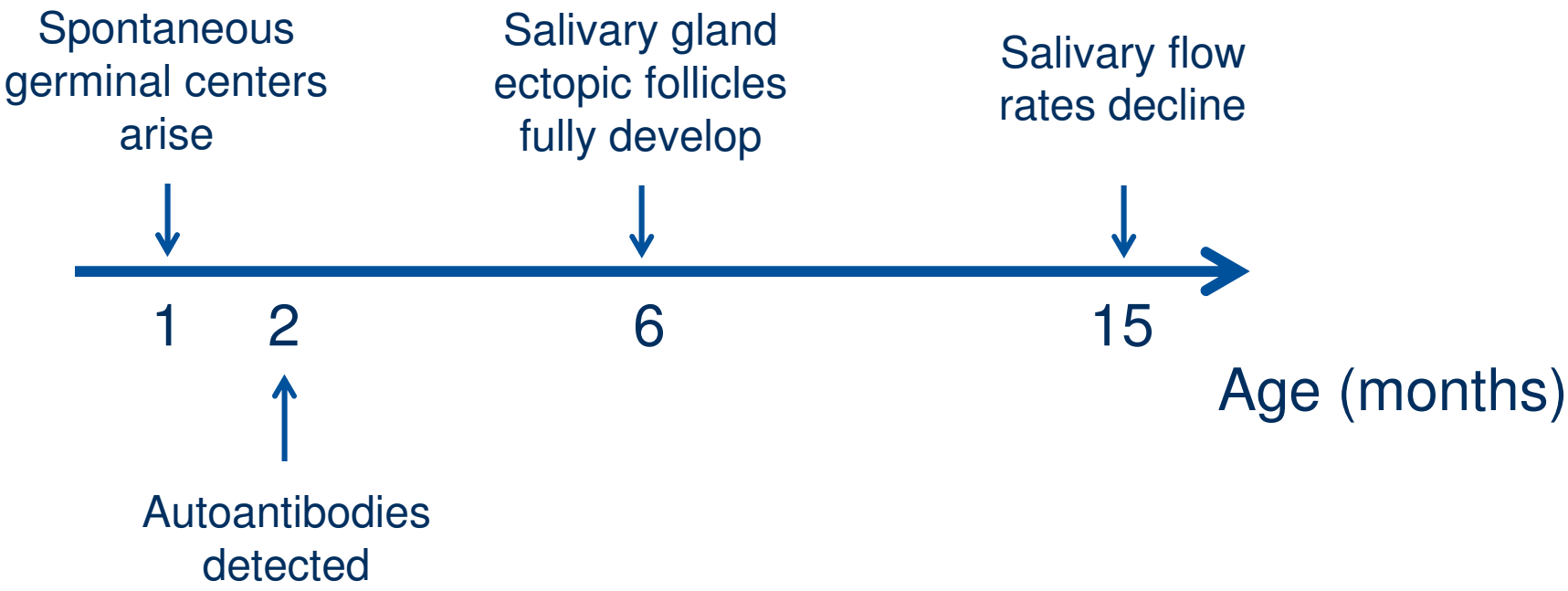
JAMA. 2013;310(17):1854-1855. doi:10.1001/jama.2013.278448

Timeline of Clinical Manifestations



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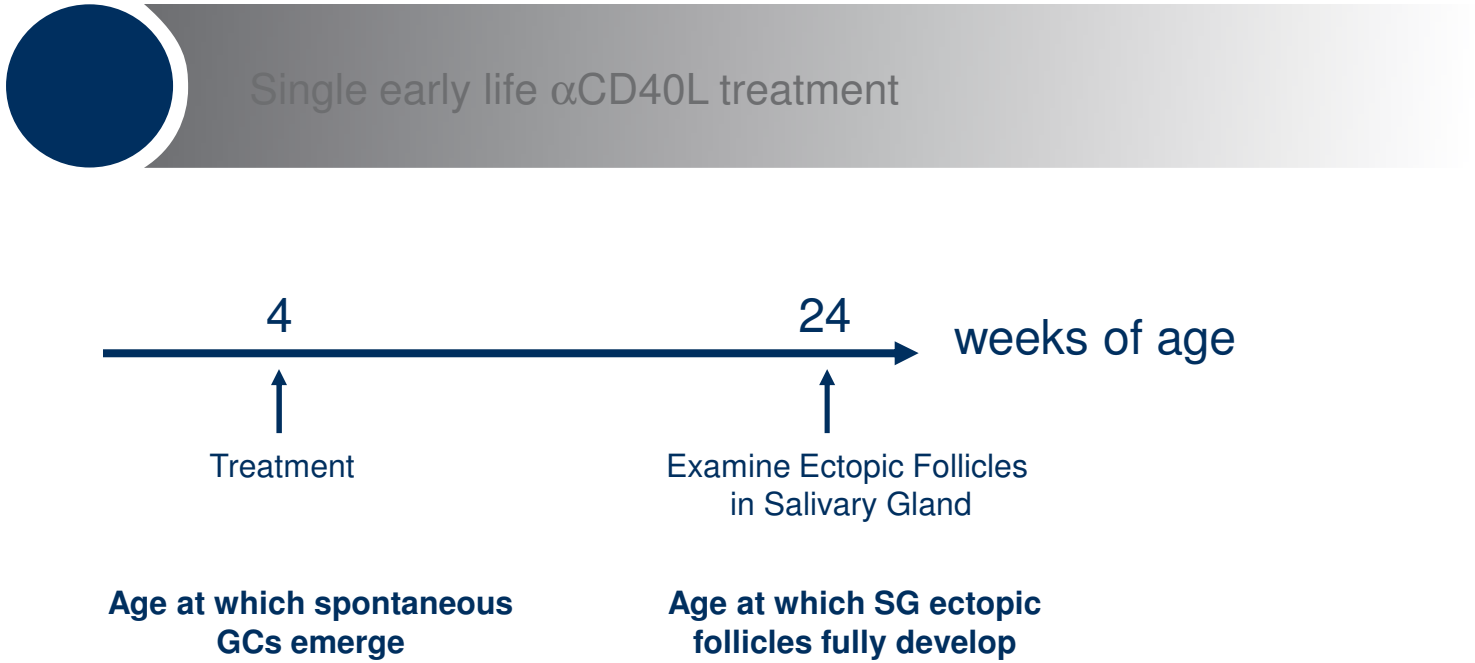
Approach: Investigate the Long-Term Effect of Germinal Center Disruption in Early Life



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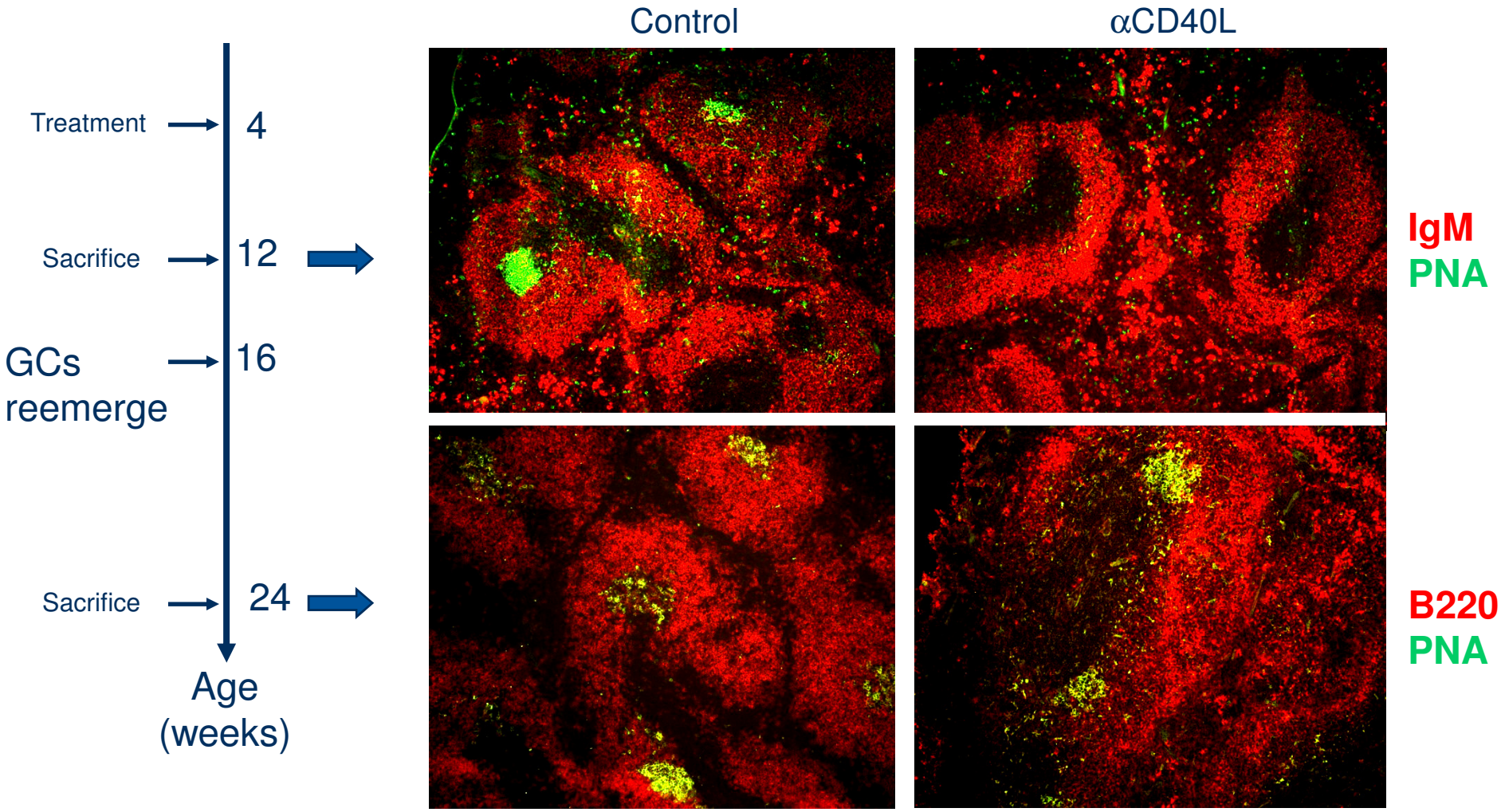
Transient Disruption of Splenic Germinal Centers Post αCD40L Treatment



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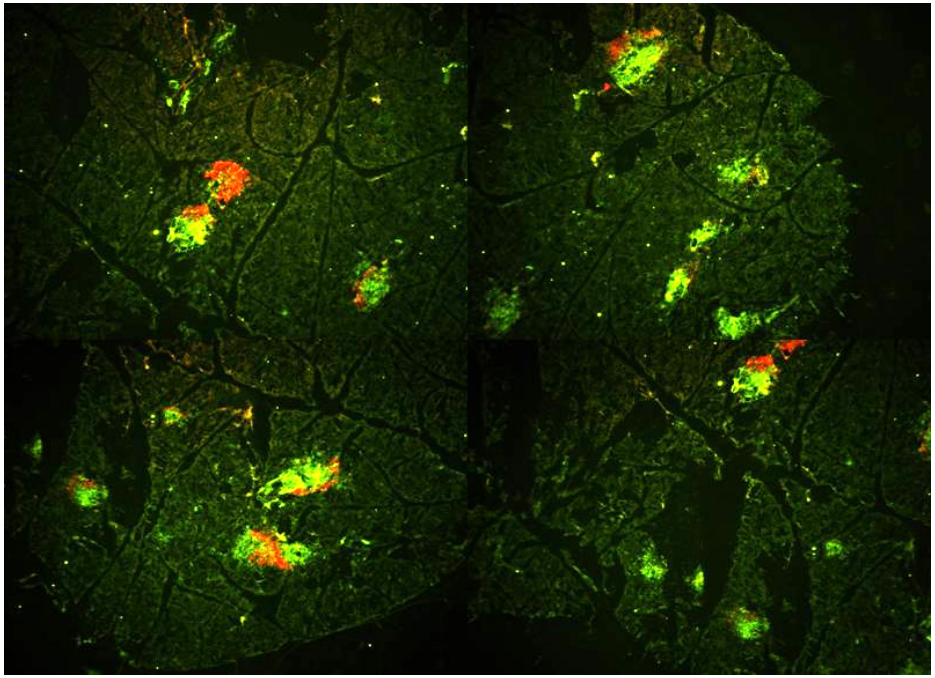
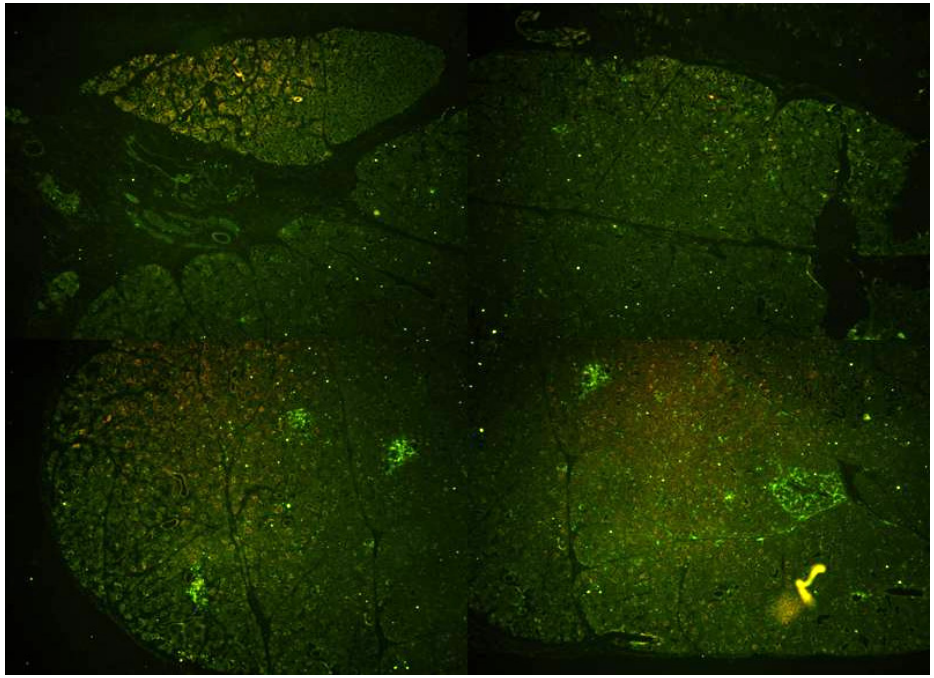
Spleen (100X)

Single Early Life Treatment with αCD40L Abolished Salivary Gland Ectopic Follicles in Aged Mice

Control



αCD40L



CD3 B220

Salivary gland 40X

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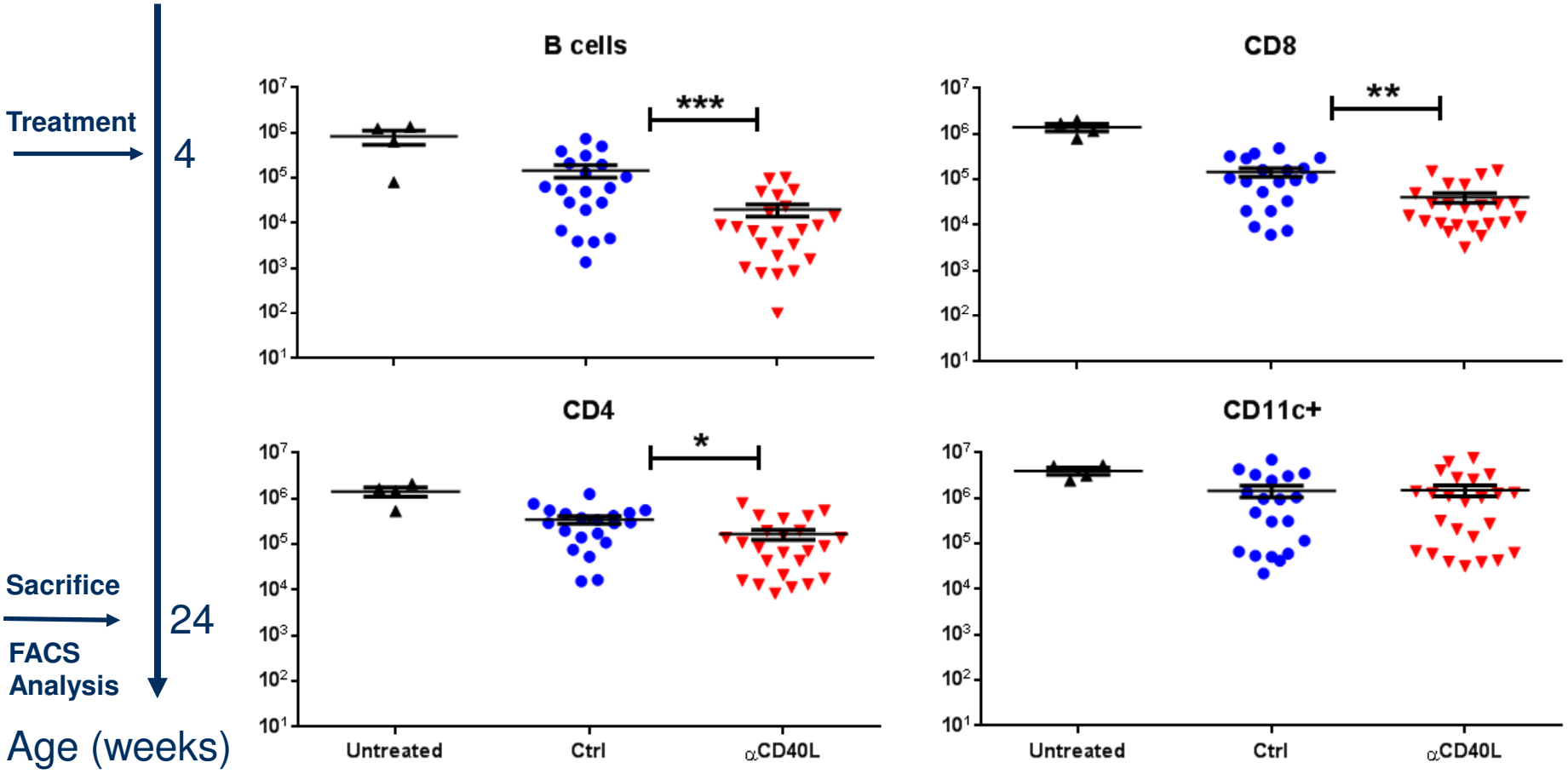
Single Early Life Treatment with αCD40L Decreased Salivary Gland B and T cells in Aged Mice



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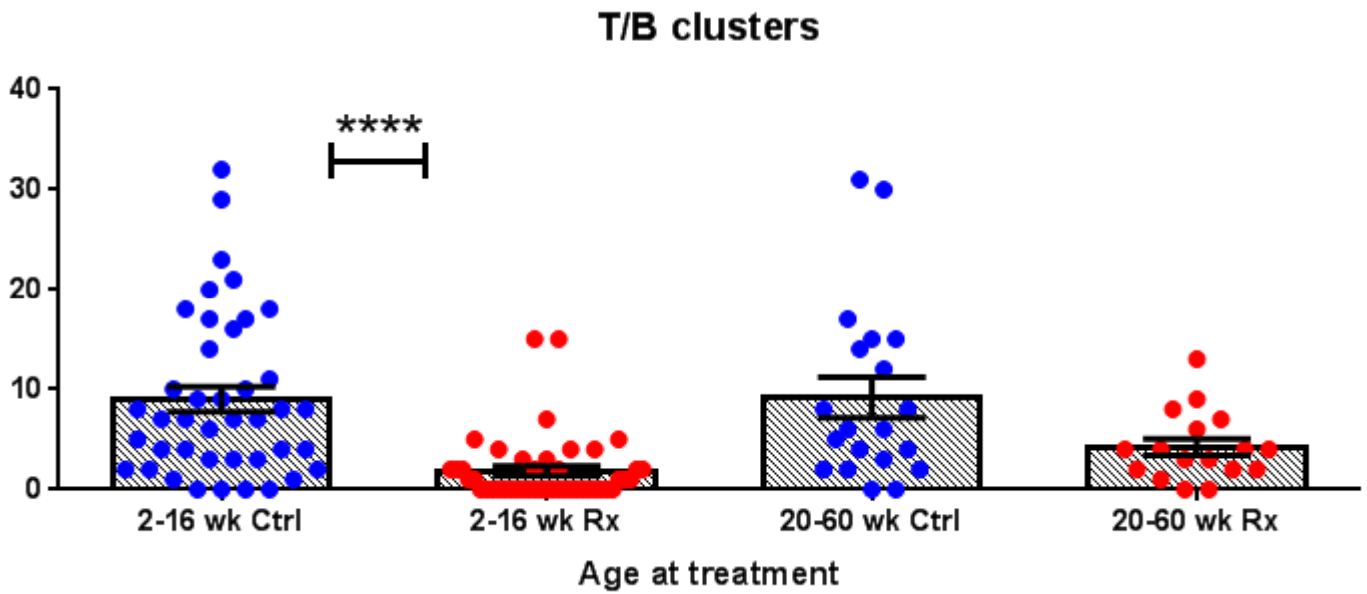
αCD40L Significantly Reduced T/B Clusters in the Salivary Gland



H & E paraffin sections

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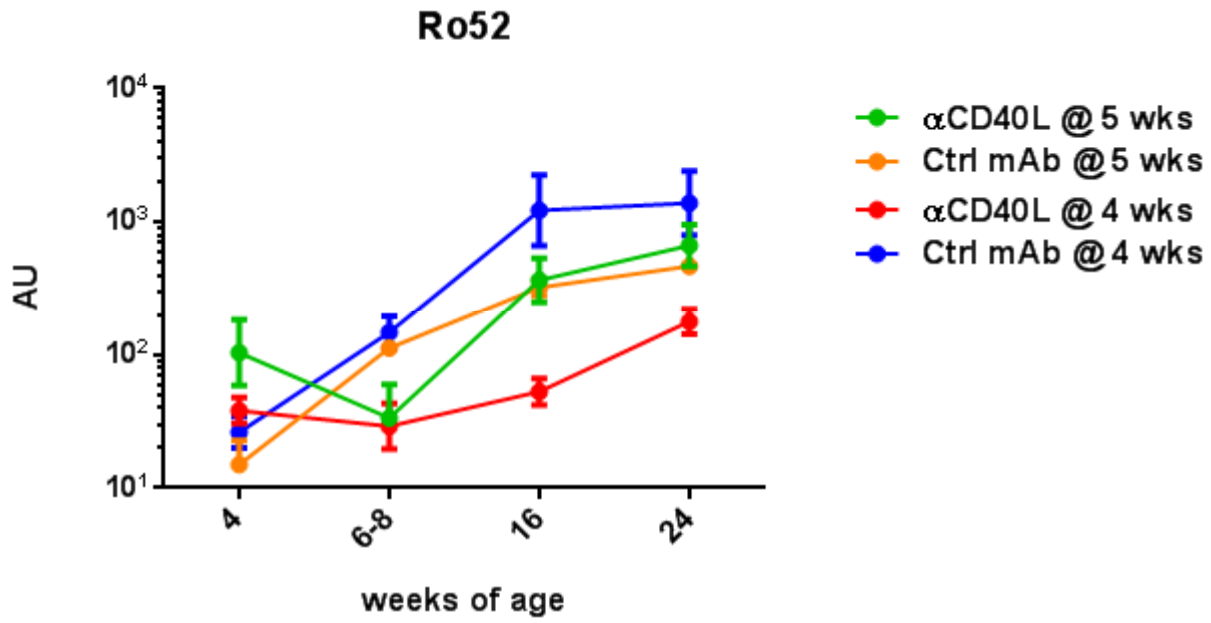
αCD40L Decreases αRo52 Autoantibodies



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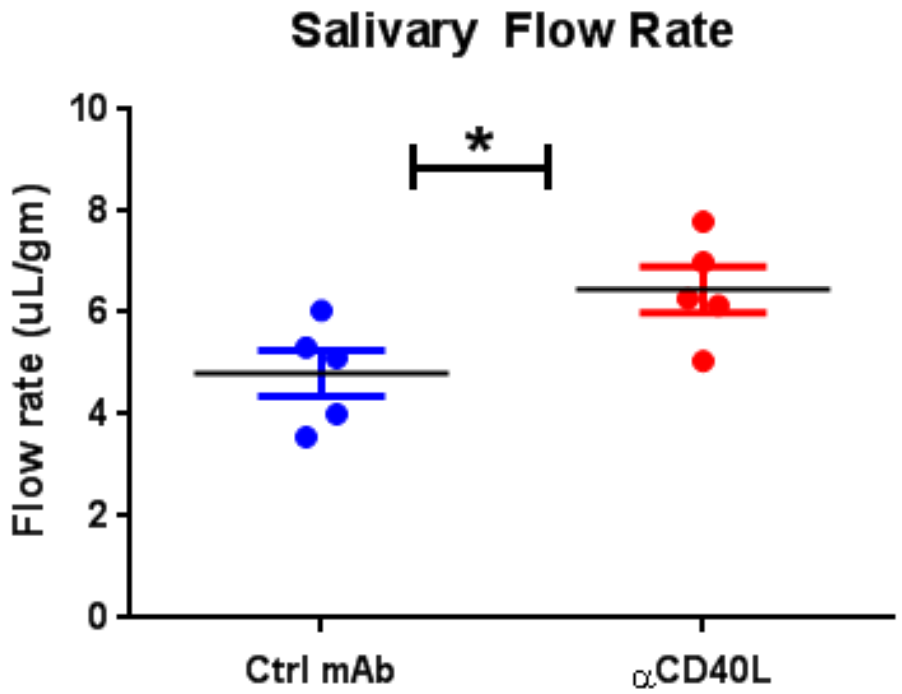
Early Life Treatment with αCD40L Improves Salivary Flow



32 week old mice

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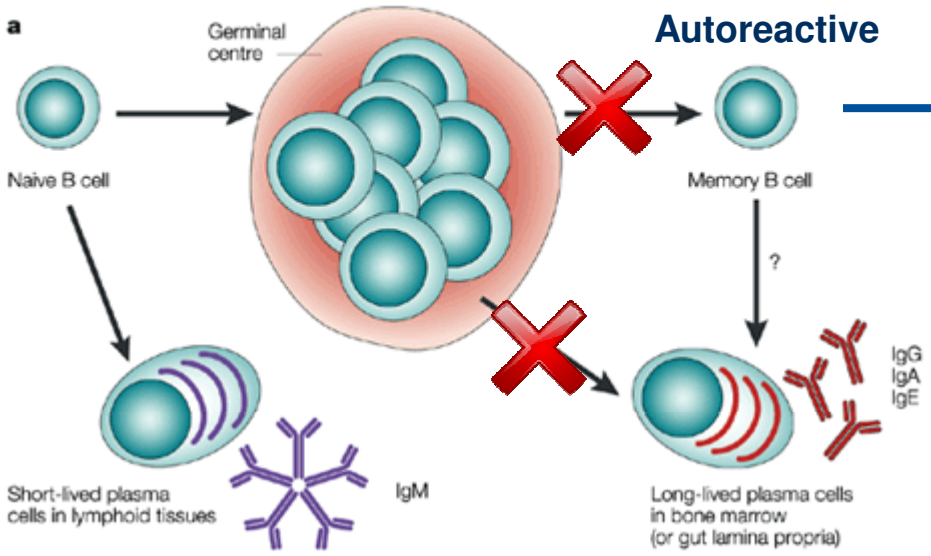
Conclusions

- NOD.H2h4 mice develop spontaneous germinal centers at 3.5 weeks of age, followed by the emergence of salivary gland lymphoid follicles starting at 12 weeks of age
- Early life blockade of CD40-CD40L interactions in mice:
  - Inhibits splenic GC reactions for at least 8 weeks
  - Significantly reduces SG lymphoid follicles in aged mice
  - Significantly reduces B cells and CD8 T cells in SG infiltrates
  - Lowers serum levels of SS-associated autoantibodies in an age-specific manner in this mouse model
  - Improves salivary flow in aged mice

Model

αCD40L



Salivary Gland Infiltration

LTβ

Ectopic Follicle Neogenesis

Elevated Autoantibodies → Reduced Salivary Flow

Acknowledgements

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