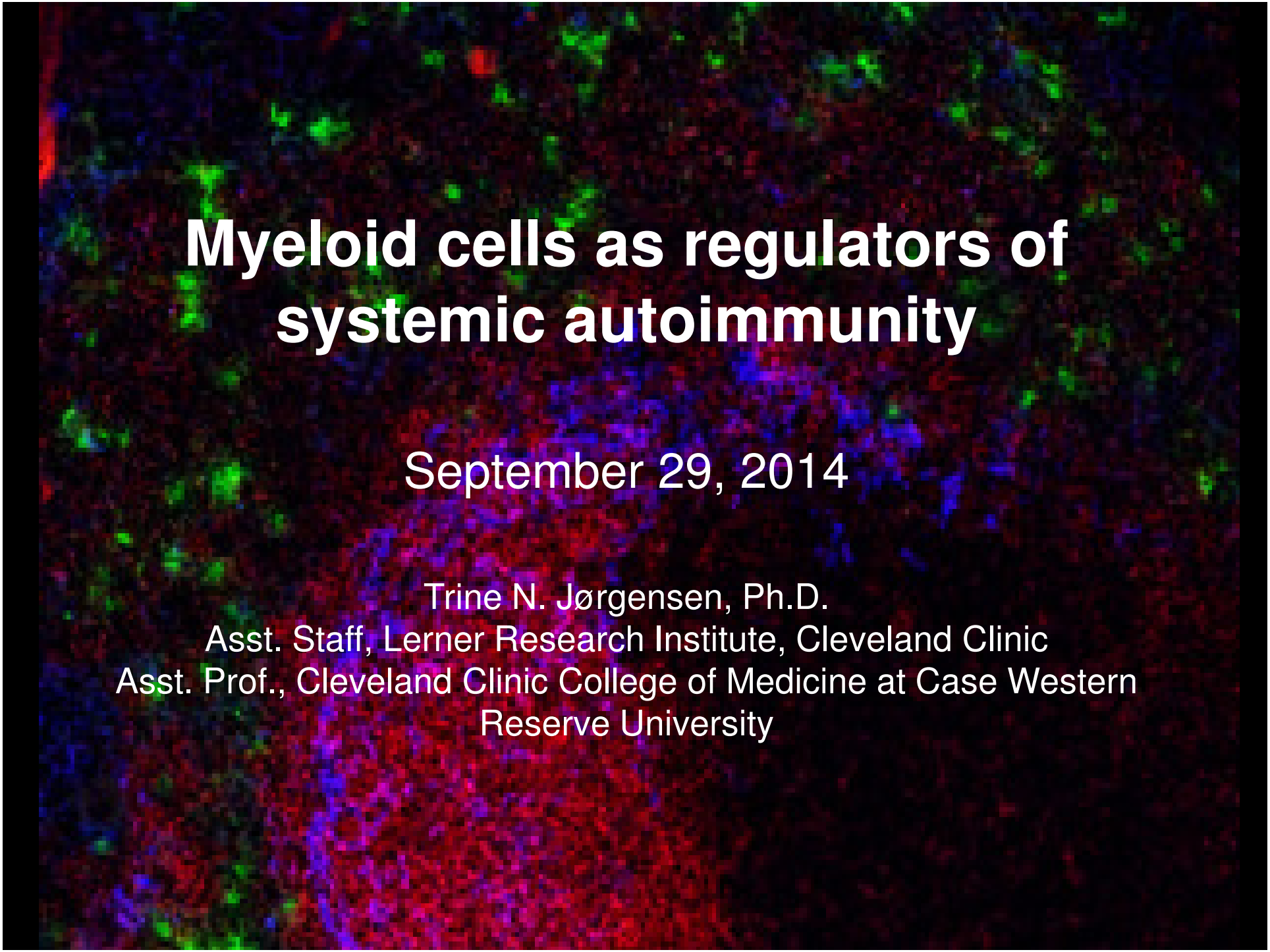

Myeloid cells as regulators of systemic autoimmunity

September 29, 2014

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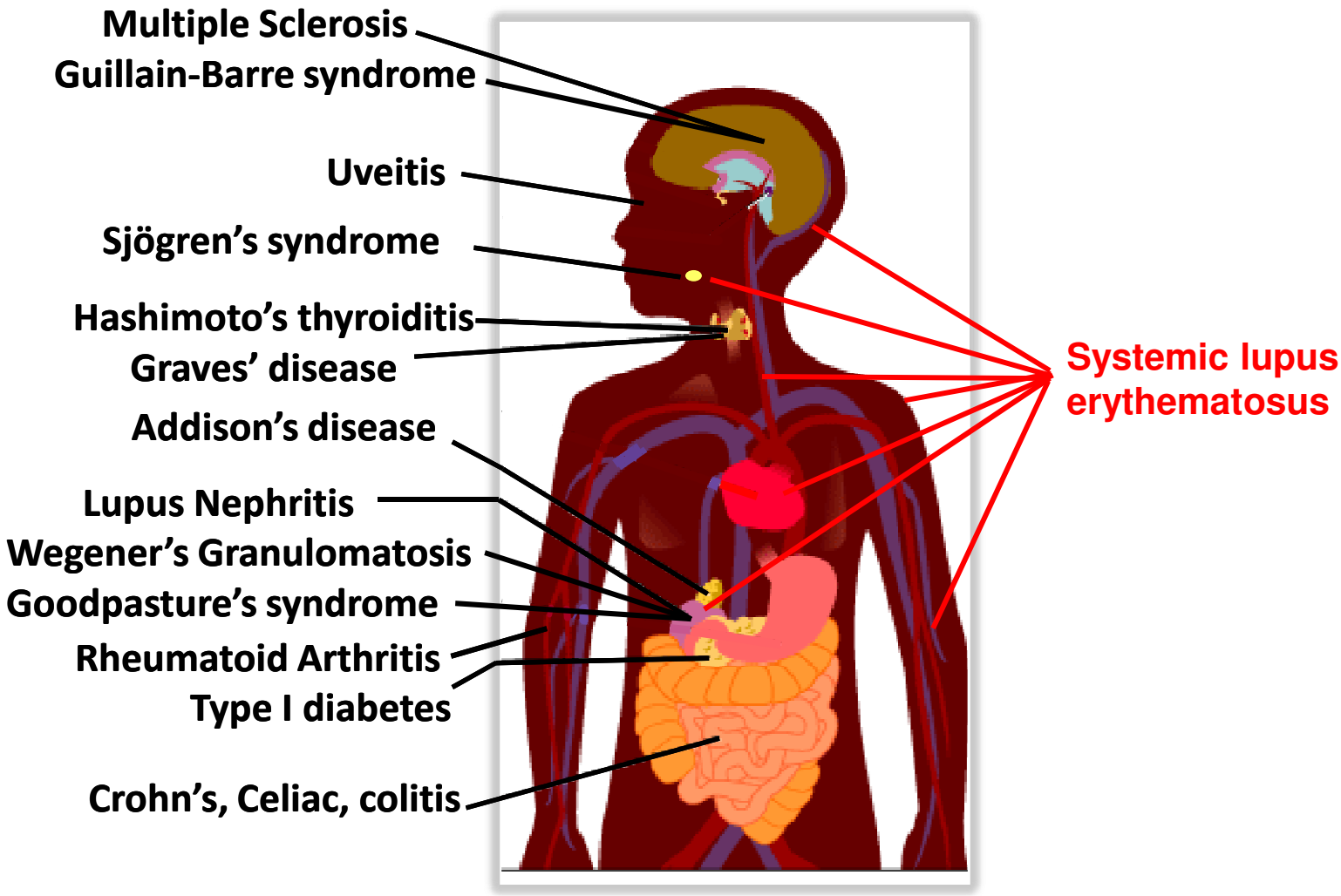
Asst. Staff, Lerner Research Institute, Cleveland Clinic
Asst. Prof., Cleveland Clinic College of Medicine at Case Western Reserve University

Autoimmune Disorders



Systemic Lupus Erythematosus

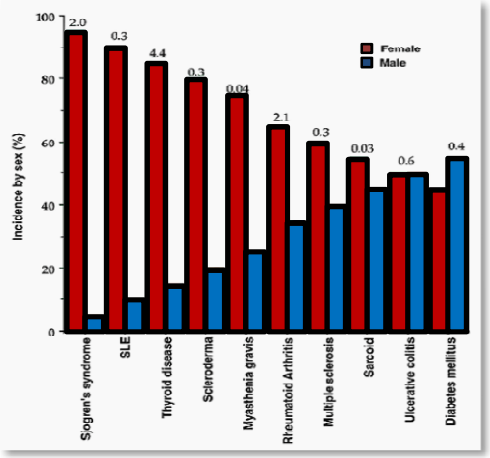
Estimated 1.5 million patients in USA

Diagnosis occur most often between the ages of 15 and 45.

Diagnosis based on multiple criteria

Much more prevalent in women than in men

Etiology unknown, but dependent on both genetic, environmental and hormonal factors



Whitacre et al, 2001

Immunosuppressive neutrophil-like cells protect male lupus-prone mice from disease development

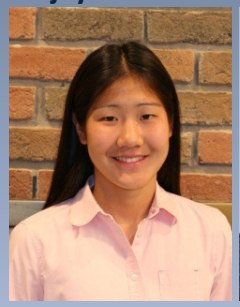

Abhishek Trigunaite

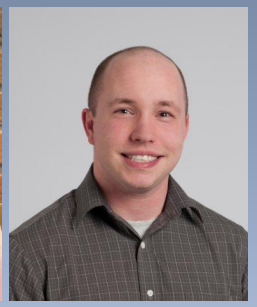

Evan Der

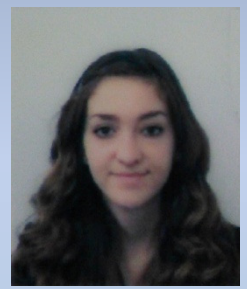

Ayesha Khan


Sanjay Varikuti


Elena Gonzalez

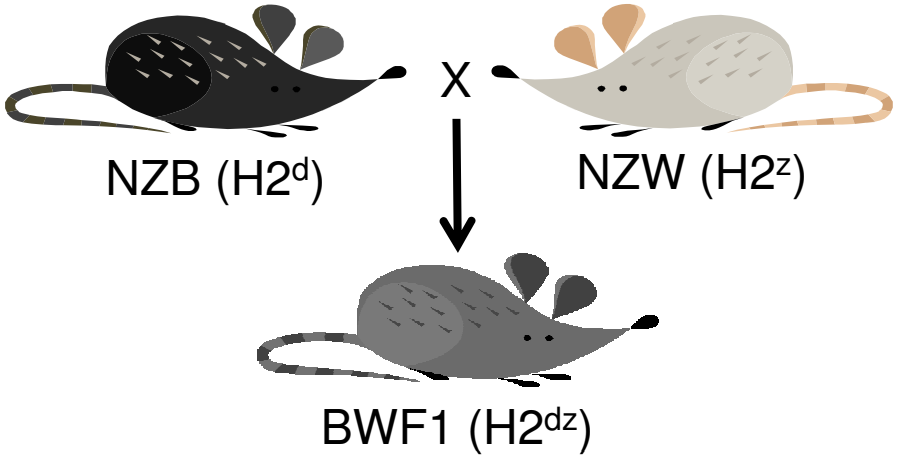

Anne Song


Justin Jones

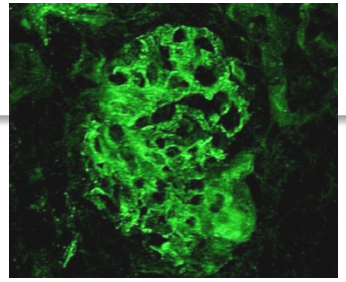

Joana Dimo

Cleveland Clinic

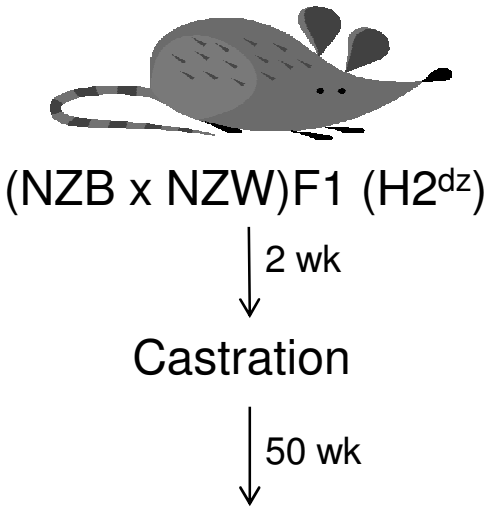
New Zealand Hybrid Mice

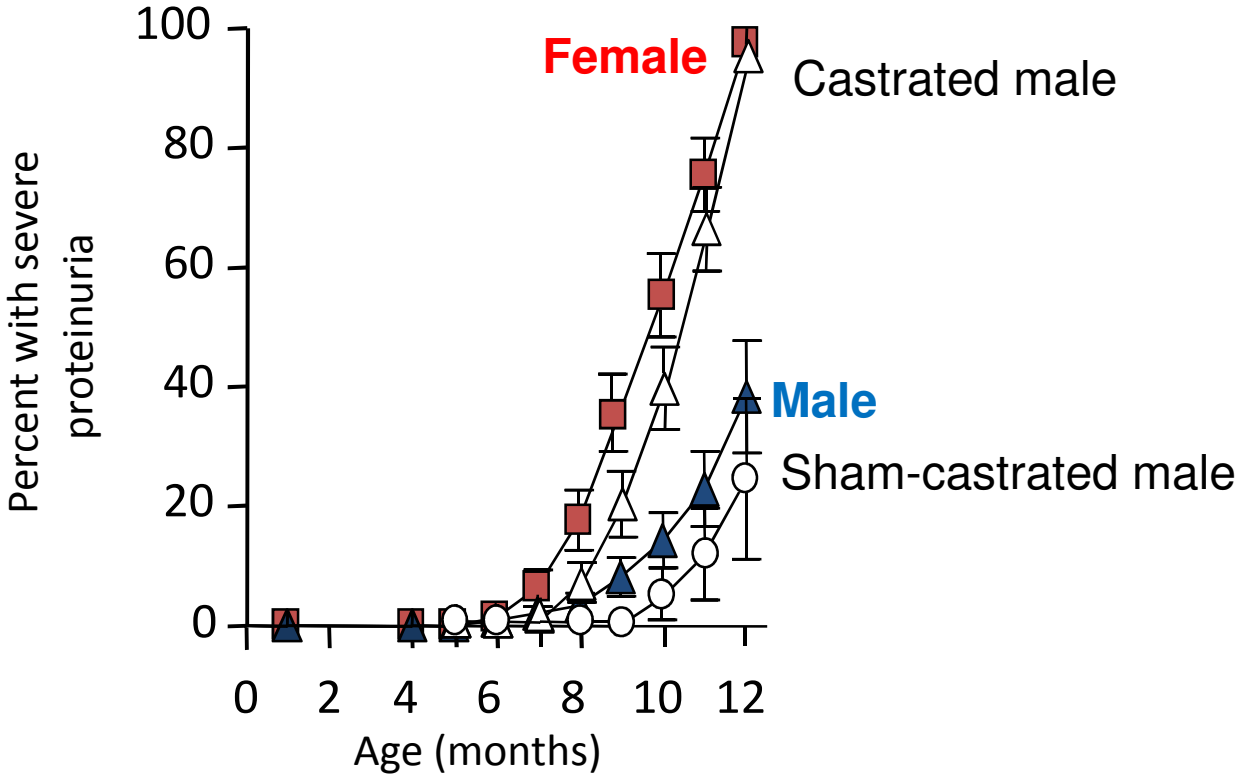


New Zealand Hybrid mice (NZB x NZW)F1 are characterized by the spontaneous development of lupus-like disease including lymphadenopathy and splenomegaly, spontaneous presence of hyperactive B cells, elevated levels of anti-nuclear autoantibodies, immune complex formation, glomerulonephritis and death from kidney failure.



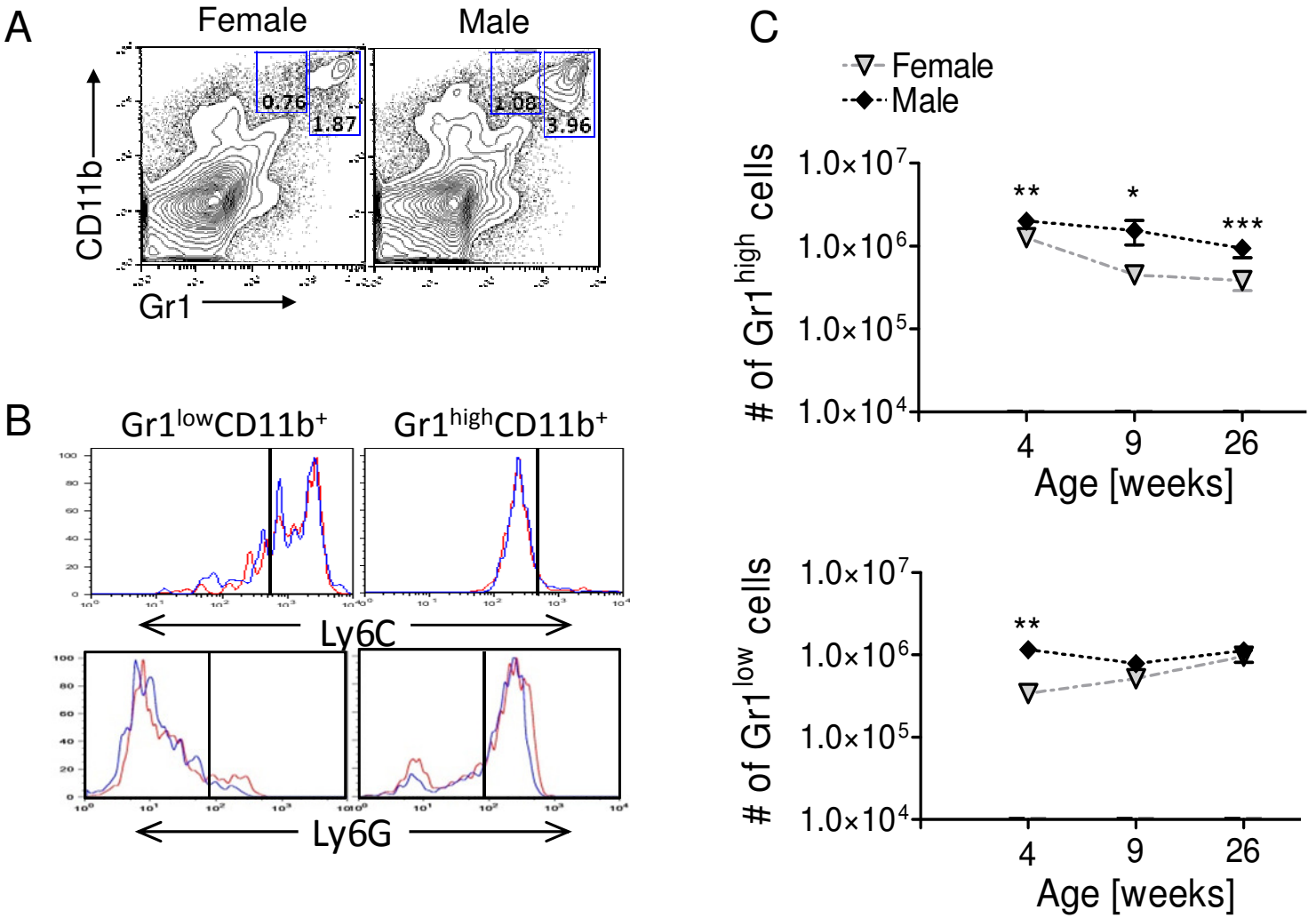
Male BWF1 mice develop disease with a delayed onset and reduced incidence





Gubbels Bupp et al, Genes Immun., 2008

Neutrophil-like cells are elevated in protected lupus-prone male (NZB x NZW)F1 mice



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Trigunaite et al, Arthritis Rheum. 2013

Neutrophil-like Gr1^{+} cells are regulated by Testosterone *in vivo*

(NZB x NZW)F1 (H2^{dz})

↓ 3 wk

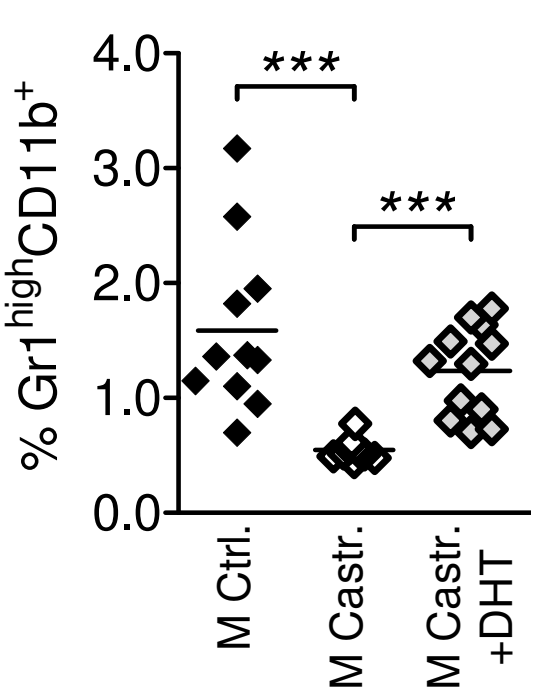
Castration

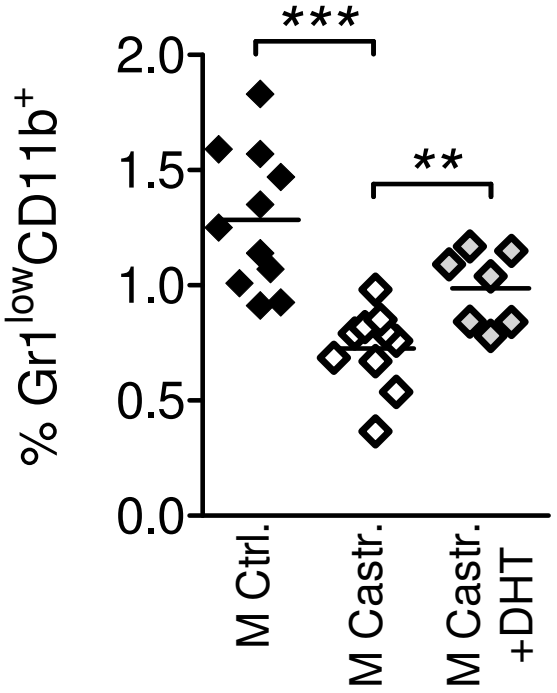
↓ 10 days

Sham or DHT-implant

↓ 5 wk

Gr1^{+} cell analyses

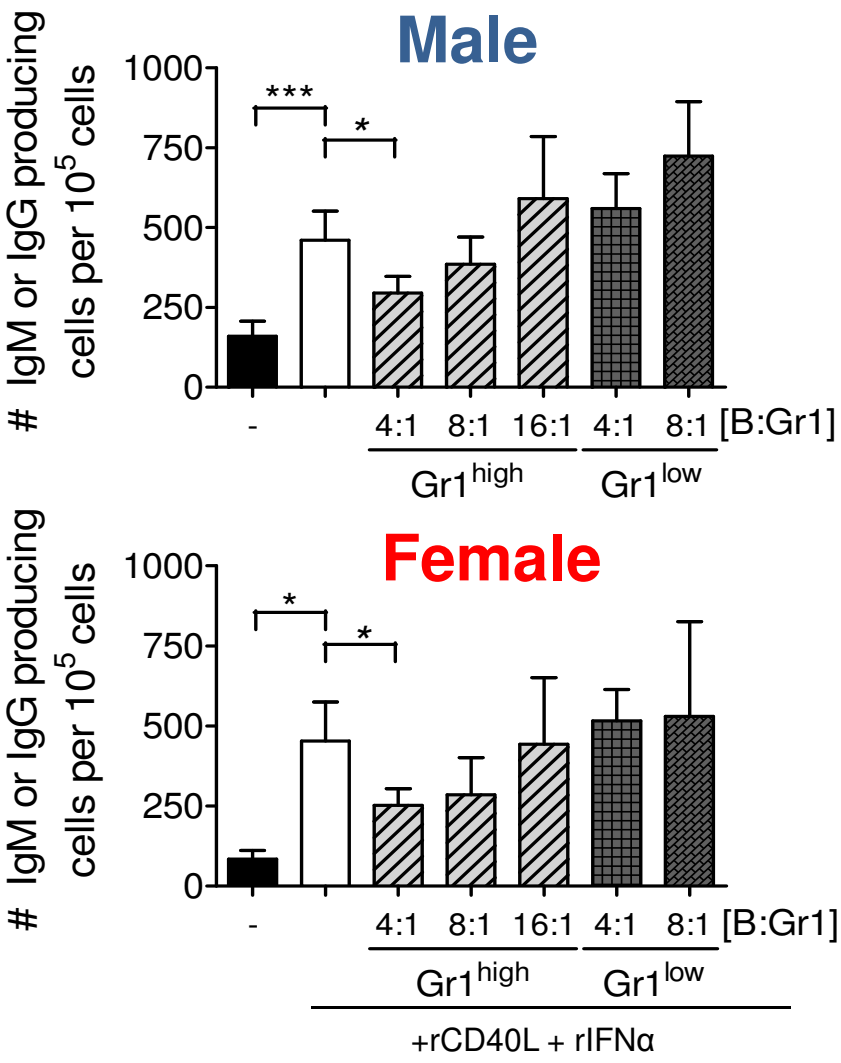




Trigunaite et al, Arthritis Rheum. 2013 and unpublished results

Are neutrophil-like cells in male lupus-prone (NZB x NZW)F1 mice immunosuppressive?

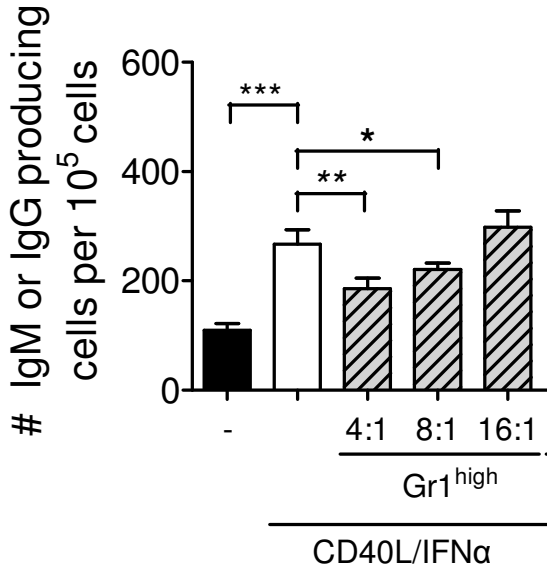
Gr1^{+} cell subsets suppress B and T cell activation and differentiation *in vitro*



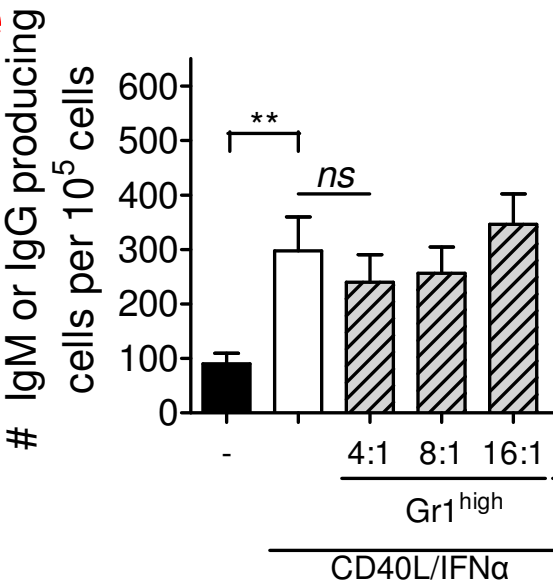
Trigunaite et al, Arthritis Rheum. 2013, Der et al, J. Immunol. 2014.

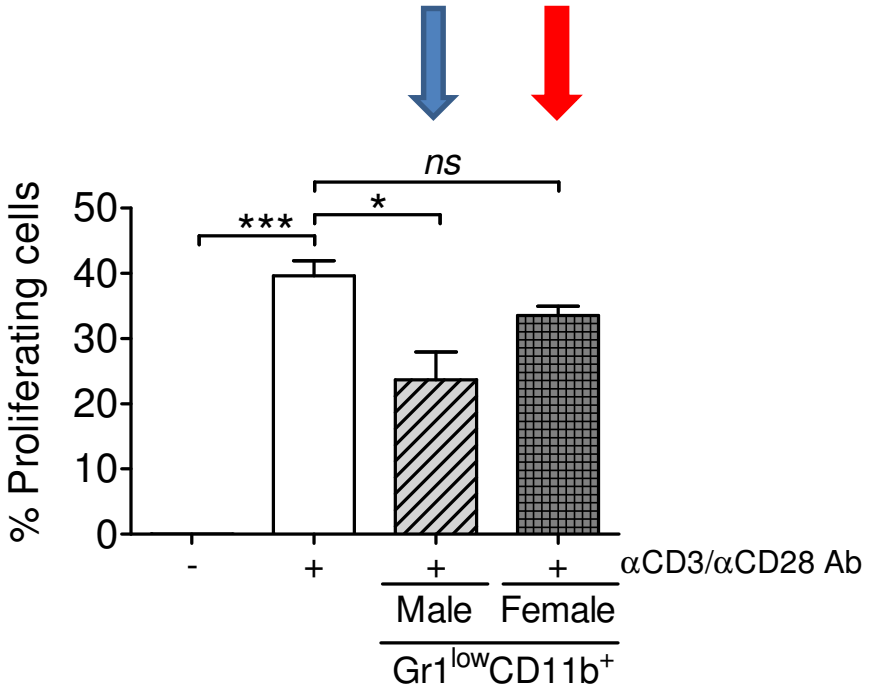
As the mice age, female Gr1+ cell subsets lose their suppressive capacity

Male



Female





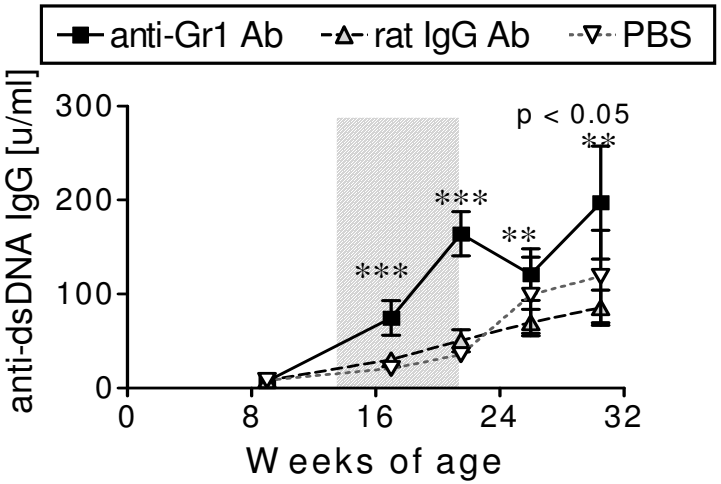
Trigunaite et al, Arthritis Rheum. 2013, Der et al, J. Immunol. 2014.

What is the function of Gr1+ cells *in vivo* in (NZB x NZW)F1 mice?

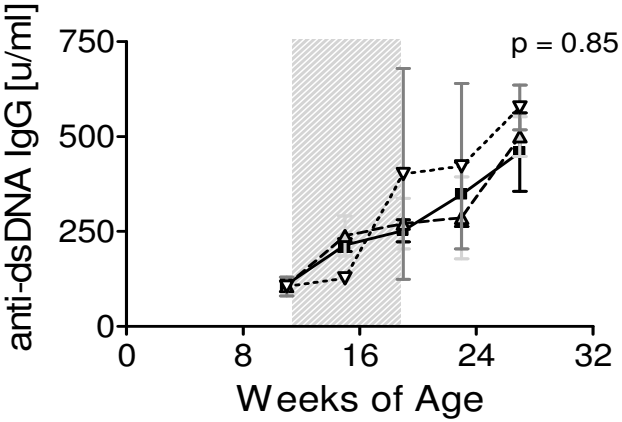
Gr1-expressing cell subsets suppress spontaneous and induced antibody-production *in vivo*

Anti-Gr1 Ab treatment
every 3 days starting
at 12-14 weeks of age

Male

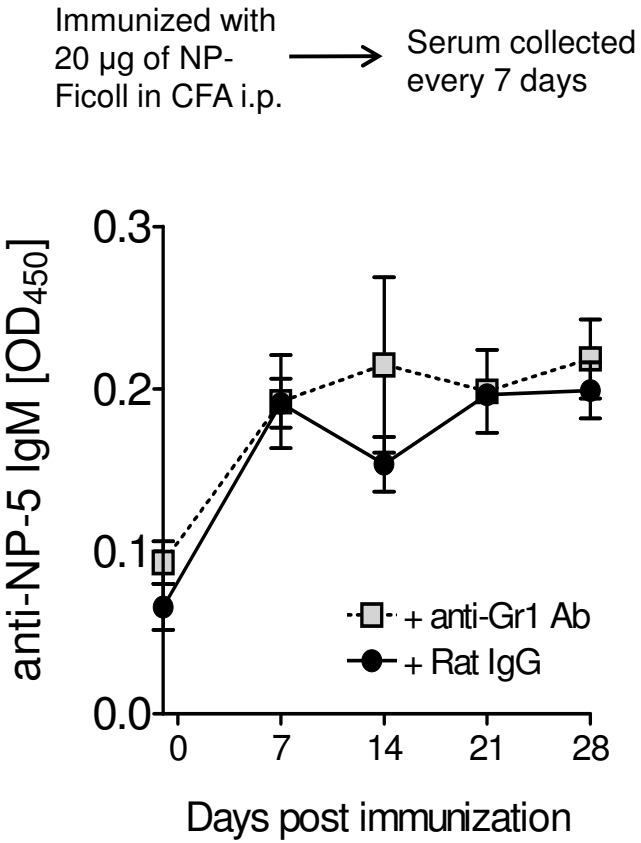


Female



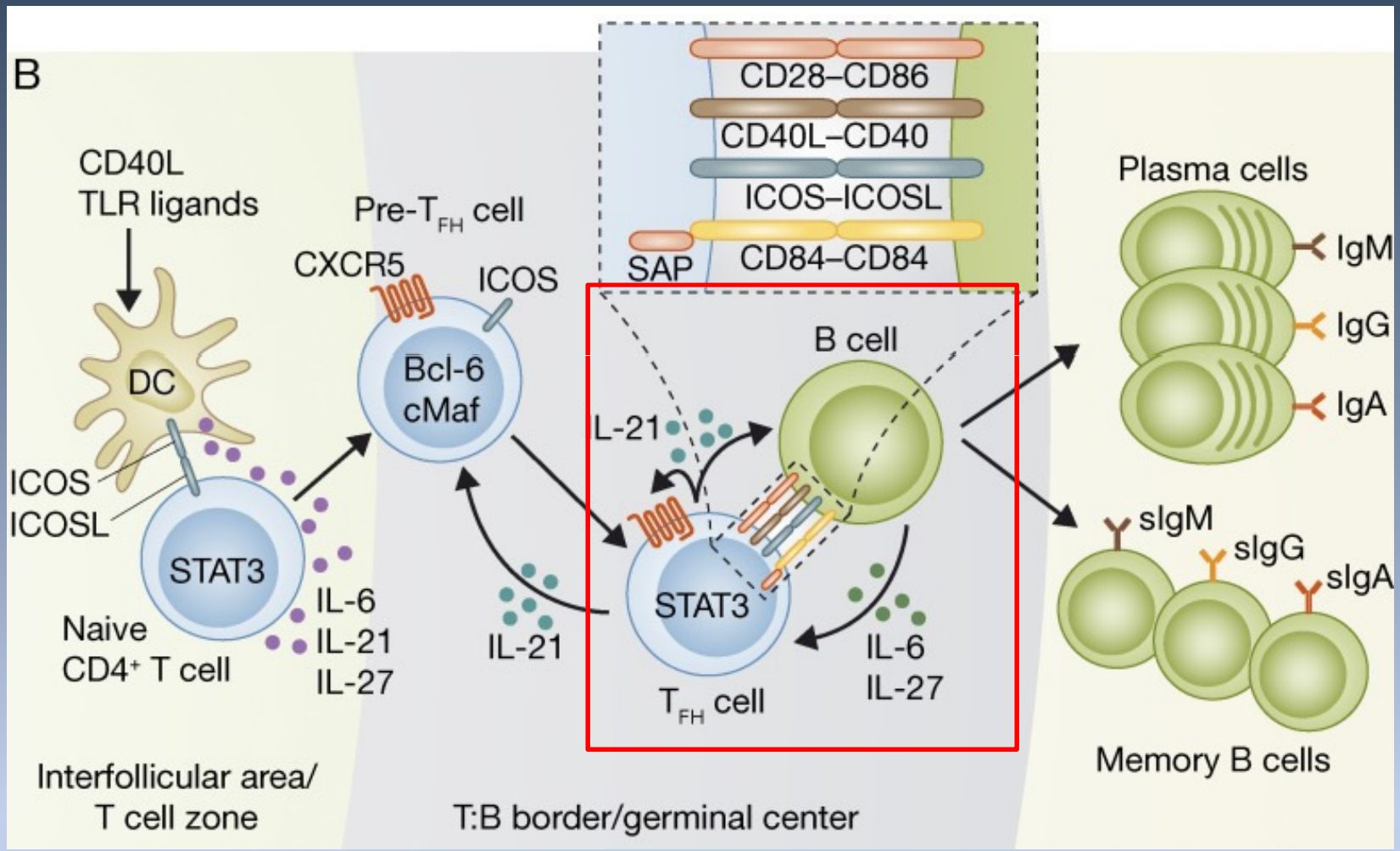
Trigunaite et al, Arthritis Rheum. 2013, Der et al, J. Immunol. 2014.

Gr1-expressing cell subsets fail to suppress TI-antibody responses *in vivo*



Der et al, J. Immunol. 2014.

Germinal center formation and the regulation of T-dependent immune responses



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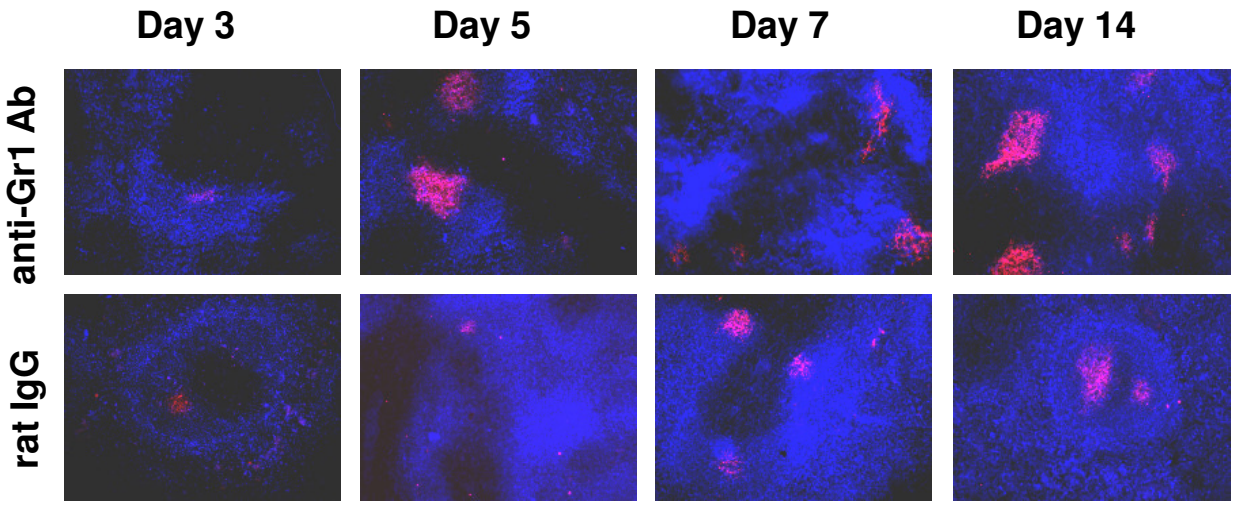
Ma et al. JEM 2012

Gr1-expressing cells suppress T_{FH} cell differentiation and germinal center formation

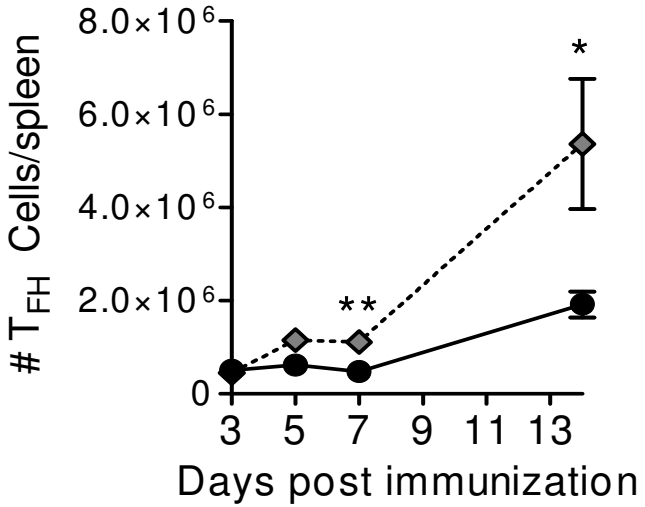
Immunized with 20 µg of NP-CGG in CFA i.p.

↓

Mice sacrificed at days 3, 5, 7 and 14



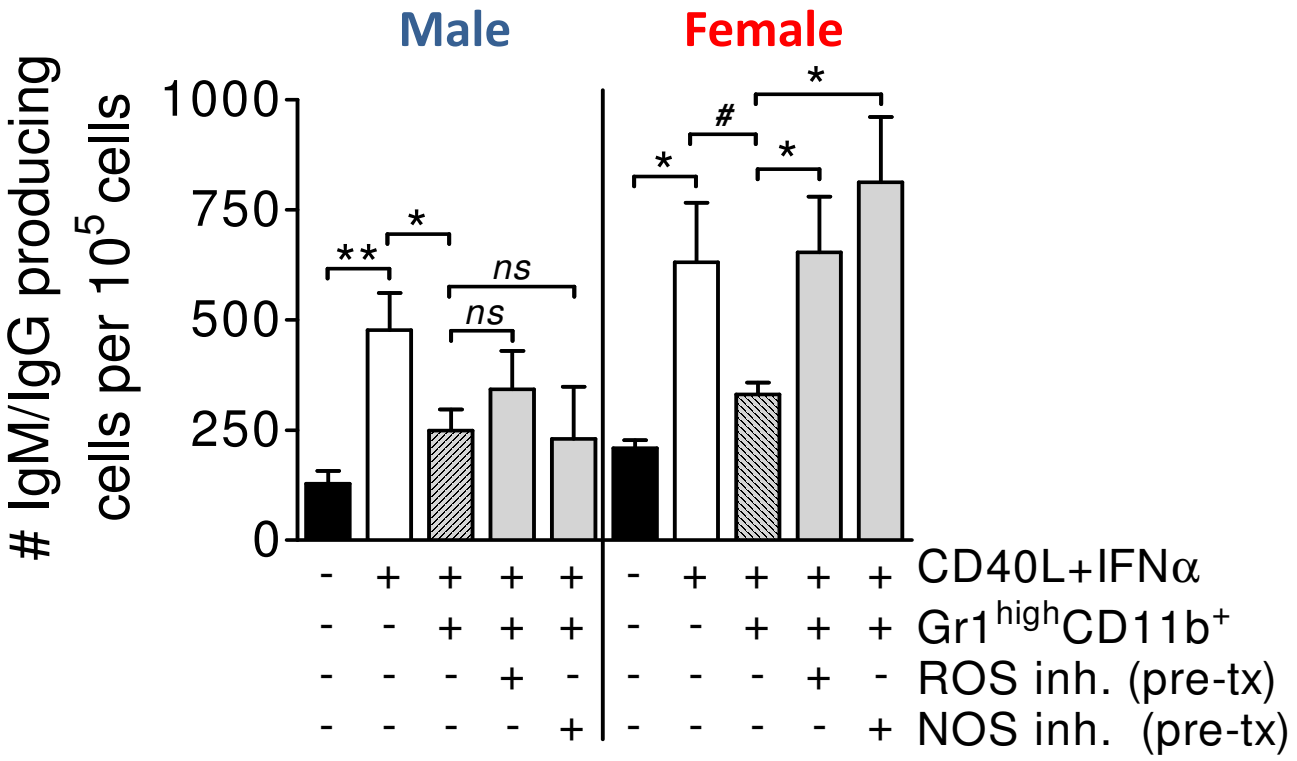
Red: GL7⁺; Blue: B220⁺



Der et al, J. Immunol. 2014.

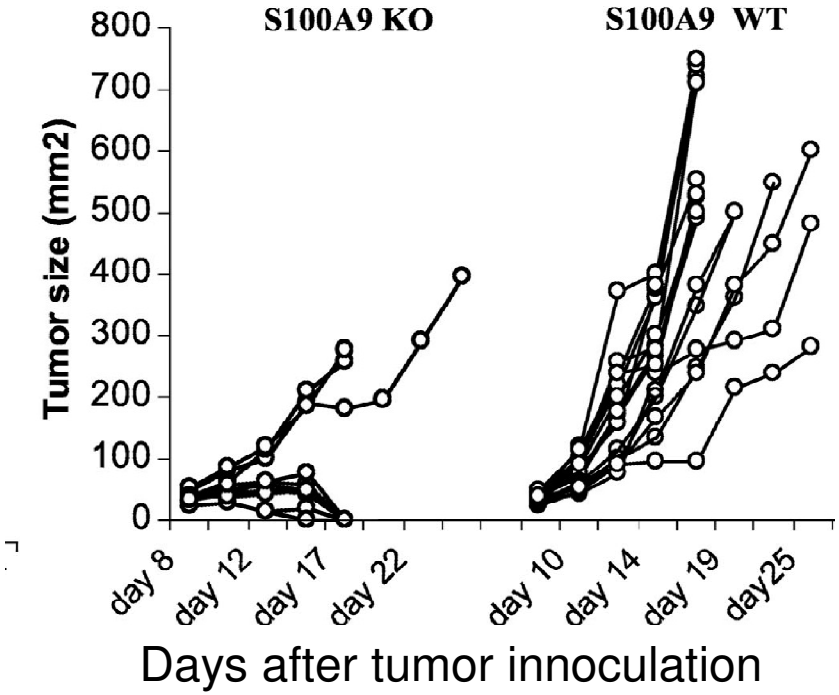
What effector functions do neutrophil-like cells utilize to suppress antibody production in male lupus-prone (NZB x NZW)F1 mice?

Female Gr1^{hi}CD11b^{+} cells use NO/ROS to suppress B cell differentiation



Trigunaite et al, Arthritis Rheum. 2013

Calgranulin B (S100a9) can act as an immunosuppressive molecule in cancer – and is overexpressed by male Gr1^{+} cells

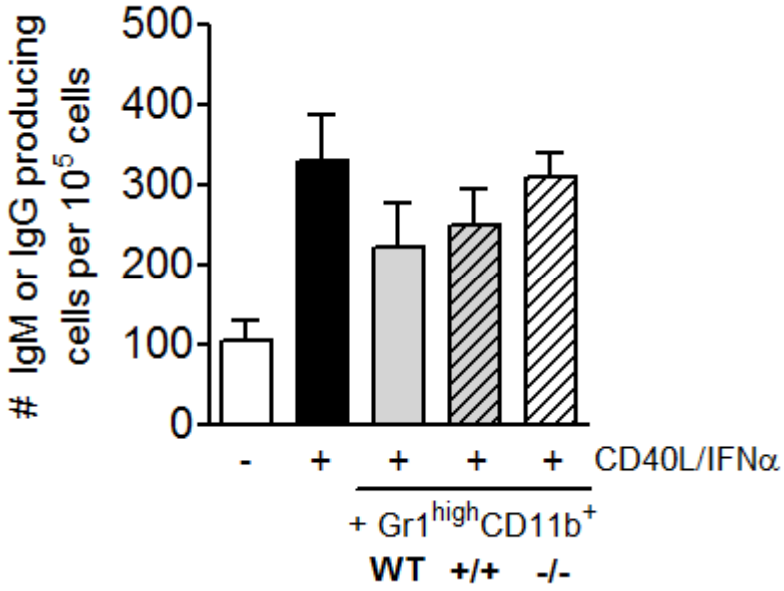


Cheng et al, JEM. 2008

Nodoka Sakurai, unpublished result

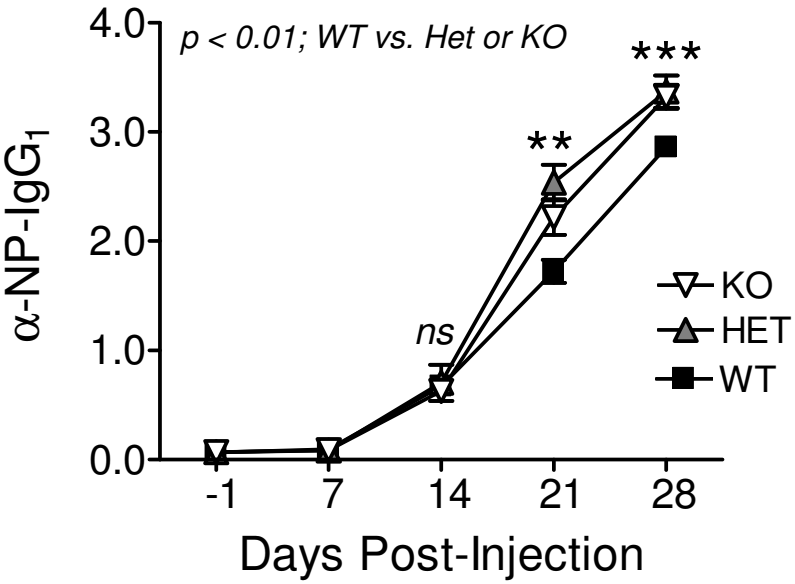
S100a9-deficient Gr1^{high}CD11b^{+} cells cannot suppress B cell differentiation *in vitro* and *in vivo*

Male



Male

Immunized with 20 µg of NP-CGG in CFA i.p. → Serum collected every 7 days

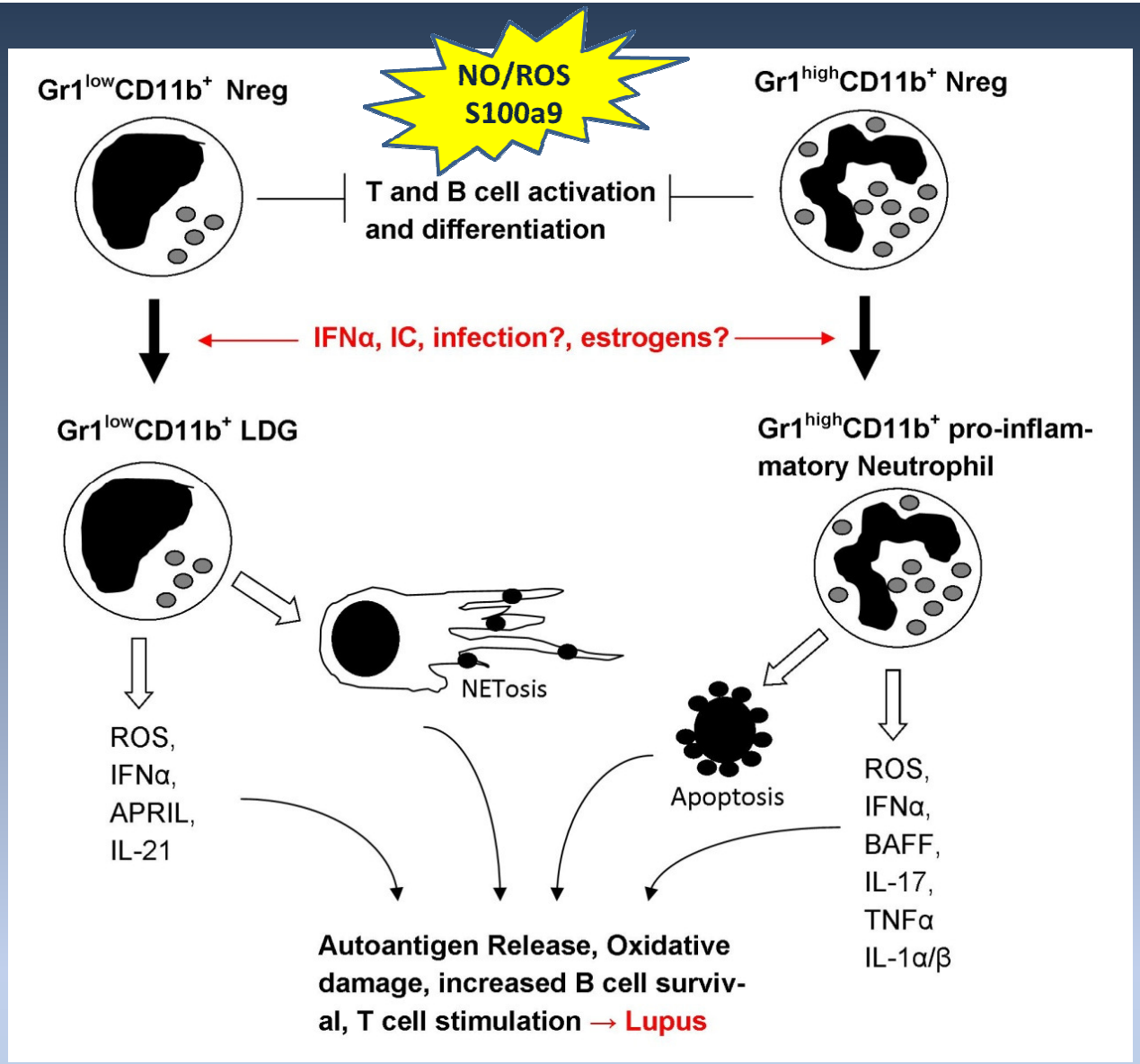


Preliminary results

Summary 1

1. $Gr1^{+}$ cells are elevated in male mice
2. $Gr1^{+}$ cells are regulated by testosterone
3. $Gr1^{high}CD11b^{+}$ cells suppress B cell differentiation
4. $Gr1^{low}CD11b^{+}$ cells suppress T cell proliferation/differentiation
5. Depletion of $Gr1^{+}$ cells results in elevated AAb production in male, but not female, lupus-prone mice
6. Female $Gr1^{high}CD11b^{+}$ cells use ROS/NO to suppress B cell differentiation *in vitro*
7. Male $Gr1^{high}CD11b^{+}$ cells appear to use S100a9 as their mechanism of suppression *in vitro*
8. $S100a9^{-/-}$ lupus-prone male mice produce increased levels of Ab *in vivo*

Working Model



Cleveland Clinic

Der et al, JCCI 2014

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The Official Lab T-shirt

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