T Cells Stress Response and Lupus Organ Damage

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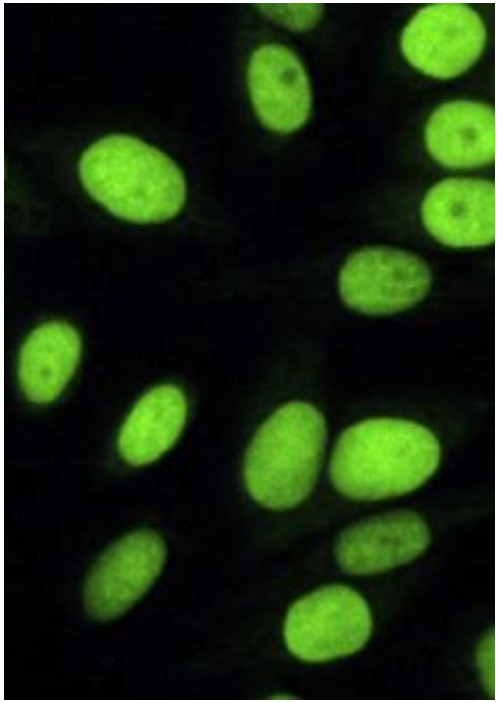
T Cells Stress Response and Lupus Organ Damage

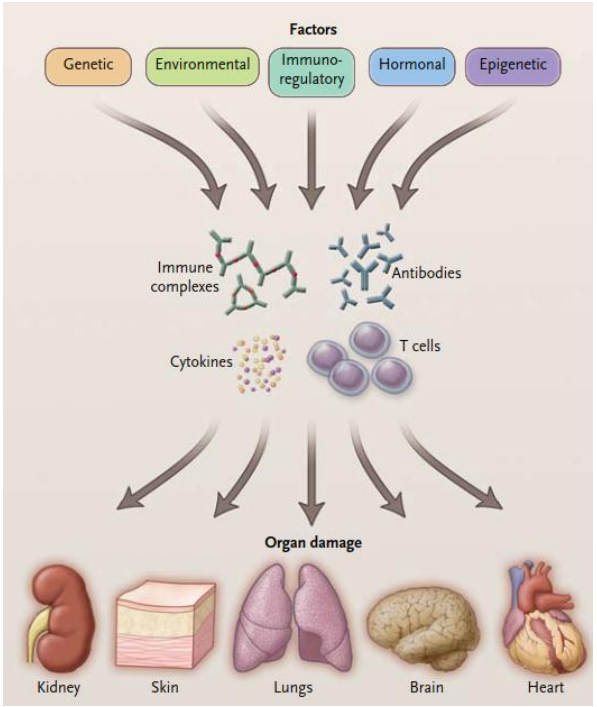
Key points

1. Two Step Pathogenesis
2. Target tissue infiltrating immune cells
3. Identify the origin of tissue infiltrating T cells
4. Stress shape the formation of stem-like T cells population
5. Selective eliminating this stem-like T cells population

Systemic lupus erythematosus

- Autoimmune disease: autoantibody production
- Organ damage initiated by complex deposition, followed by numerous immune cells infiltration
- Mainstream research on suppressing autoantibody production



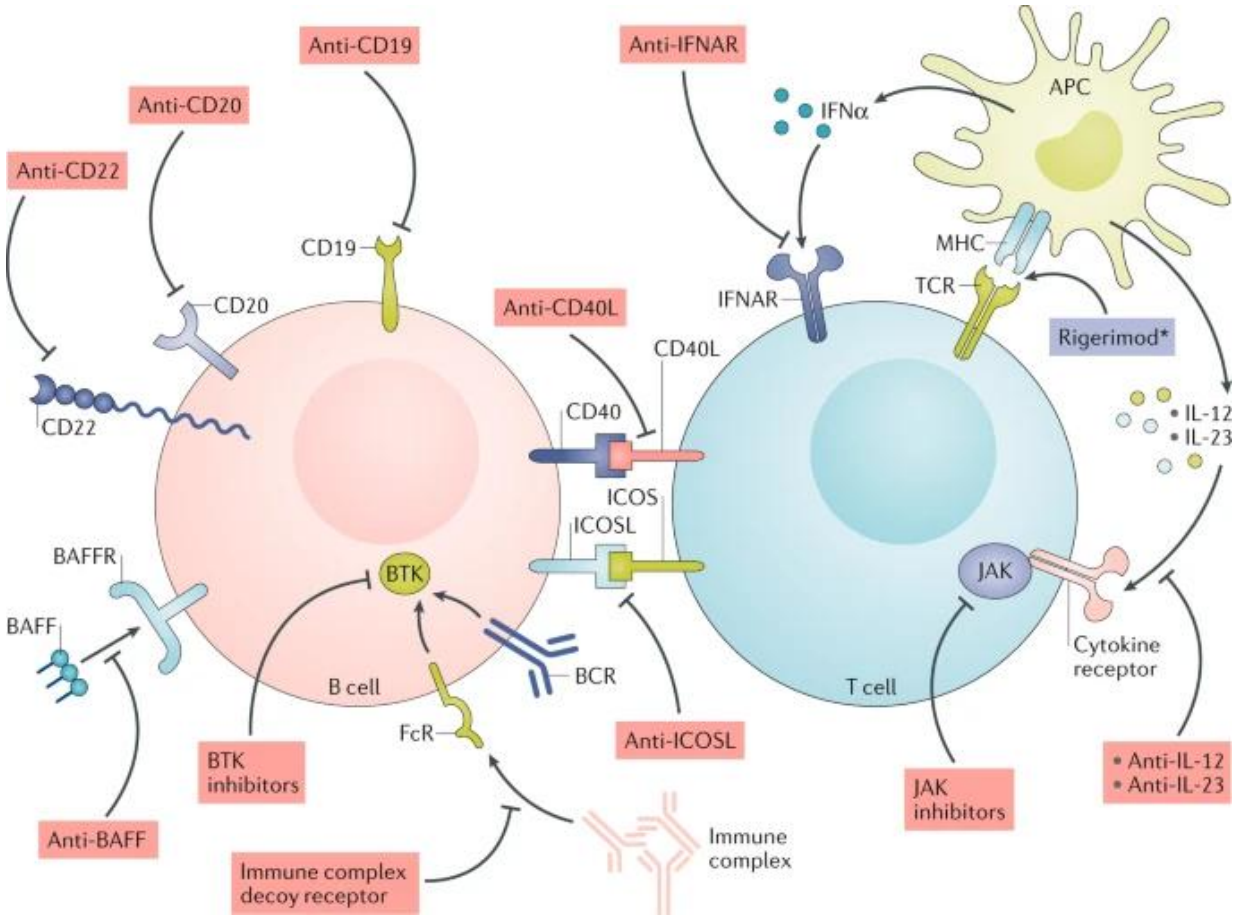


J Autoimmun 2013 Oct;46:17-24

J Am Soc Nephrol 1999 Feb;10(2):413-24.

N Engl J Med 2011; 365:2110-2121

Most Lupus Research Focuses on Autoantibody producing B cells



Nat Rev Rheumatol. 2019;15(8):509

Recent clinical trail revealed that fewer than 50% of LN patients achieve complete renal remission

Clinical trail	Target	Complete renal response (treat)	Complete renal response (placebo)
Phase 3 **Belimumab**	B lymphocyte stimulator (BLyS) /B-cell activating factor (BAFF)	67/223 (30%)	44/223 (20%)
Phase 3 **Obinutuzumab**	Humanized Anti-CD20	43%	31%

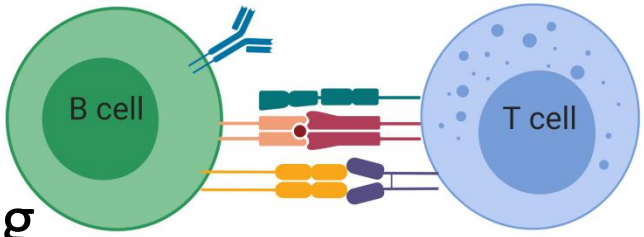
N Engl J Med . 2020 Sep 17;383(12):1117-1128.
N Engl J Med . 2025 Apr 17;392(15):1471-1483.

Two-Step Model for Disease Development in Lupus

- **Focus on tissue damage**
- **Targeting tissue Immune cells**

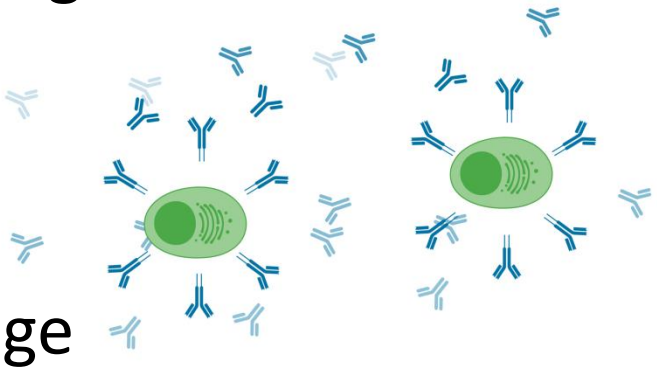
1st Step:

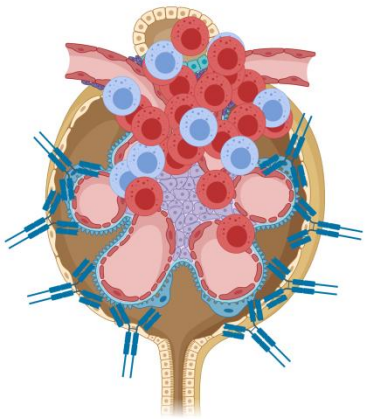
B cell priming

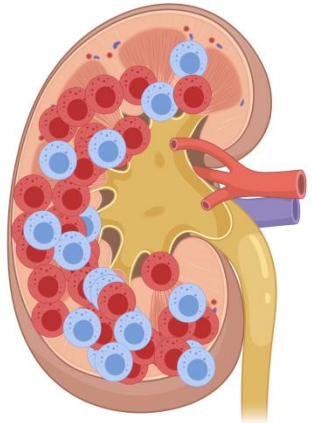


2nd Step:

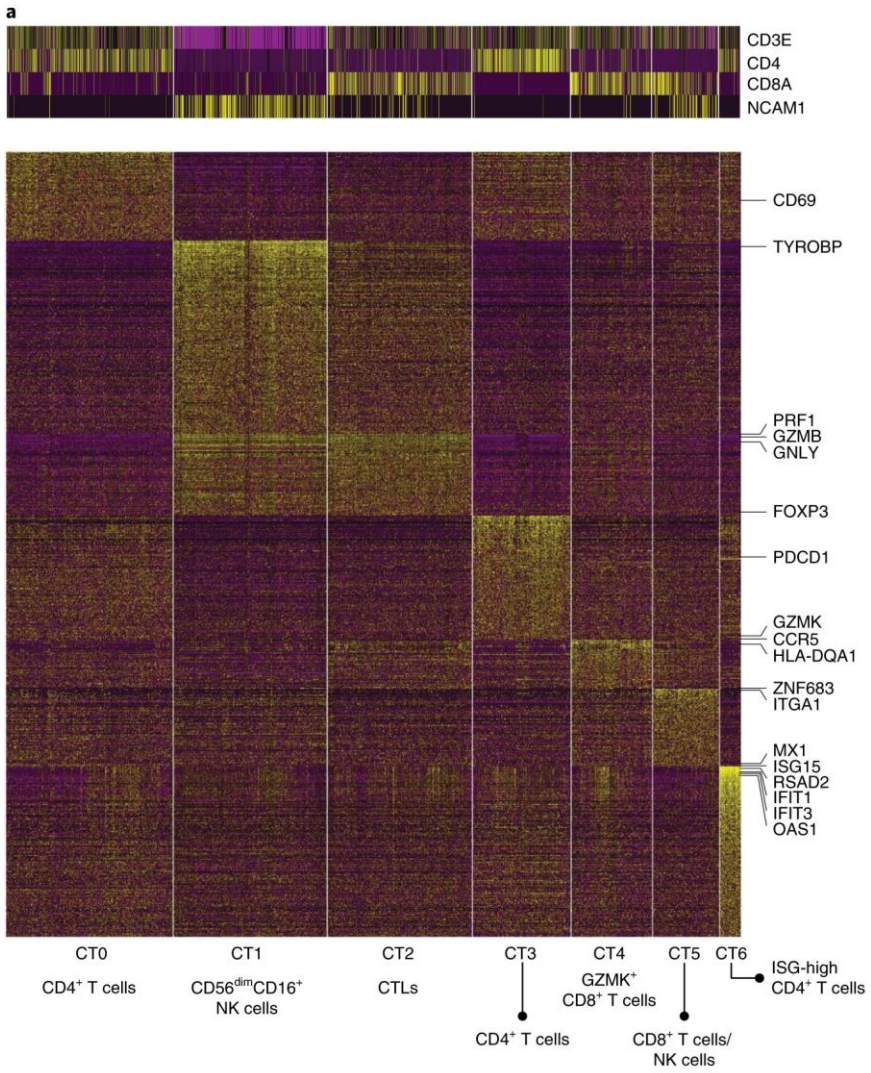
Tissue damage







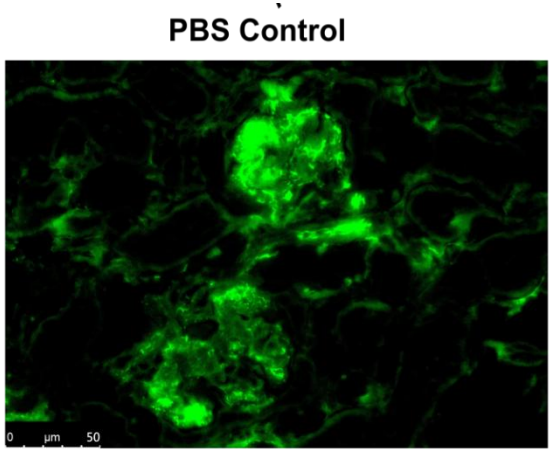
Cytotoxic Cells are dominant in human lupus nephritis samples

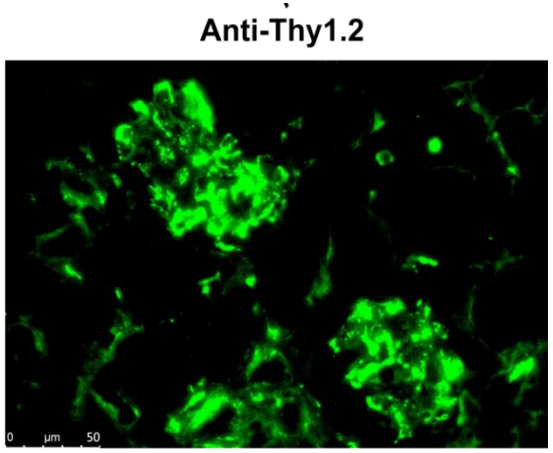


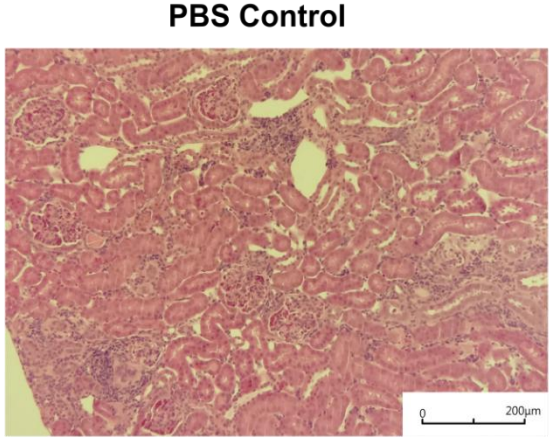
Accelerating Medicines Partnership in SLE network

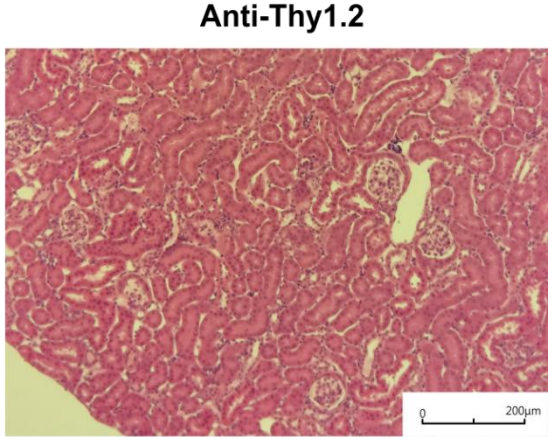
Arazi A, Hacohen N, Diamond B, et.al, Nat Immunol 2019 Jul;20(7):902-914.

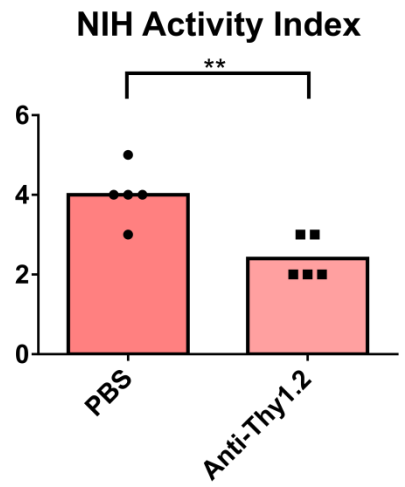
T cells are responsible for lupus organ damage

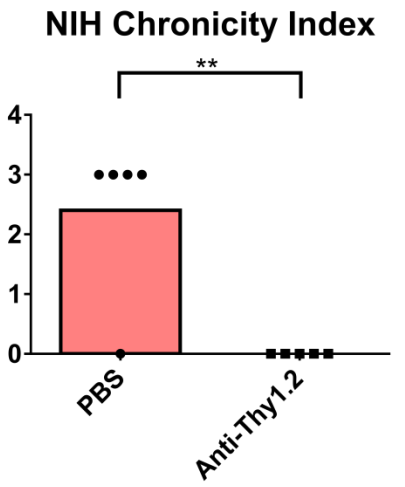








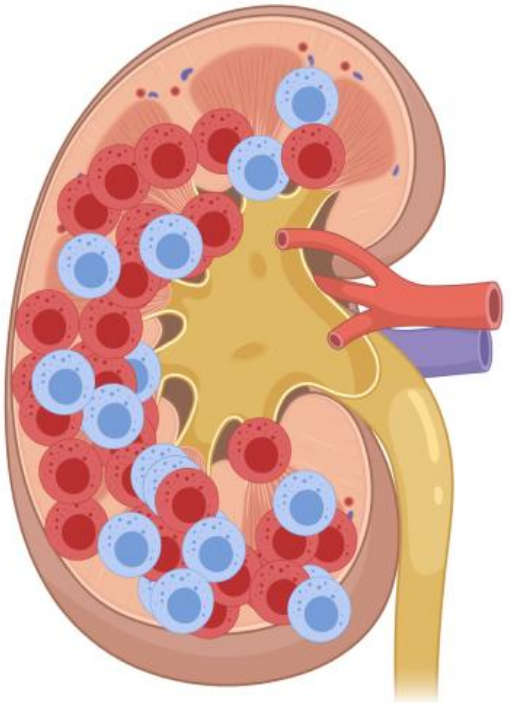


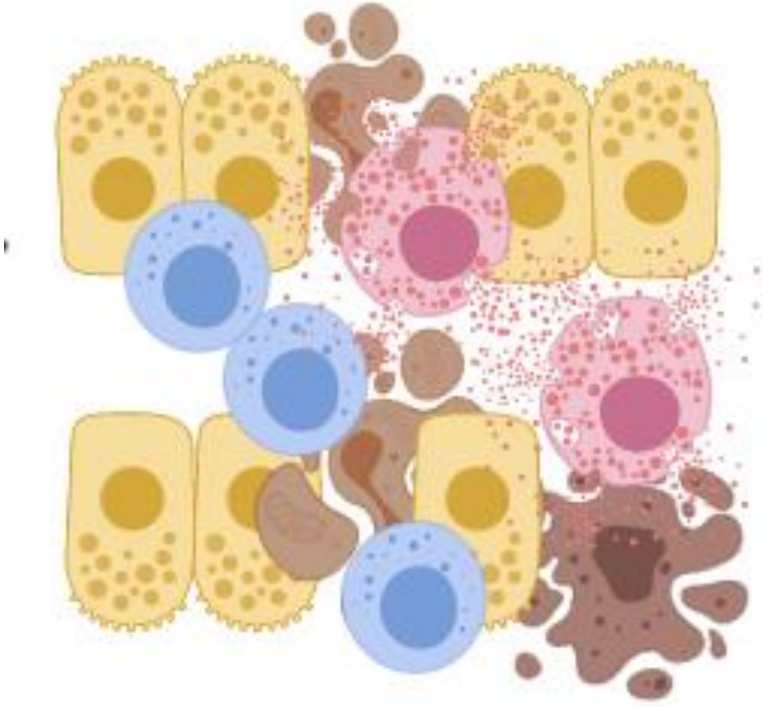


Chen PM, Craft J, et.al, Sci Transl Med 2020 Apr 8;12(538)

Possibility of targeting only the tissue infiltrating T cells?

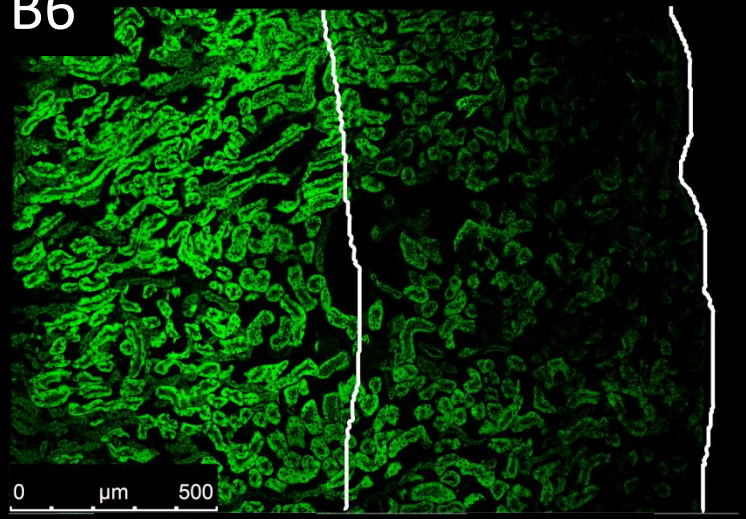
Microenvironment cues define specific Immune cell phenotype



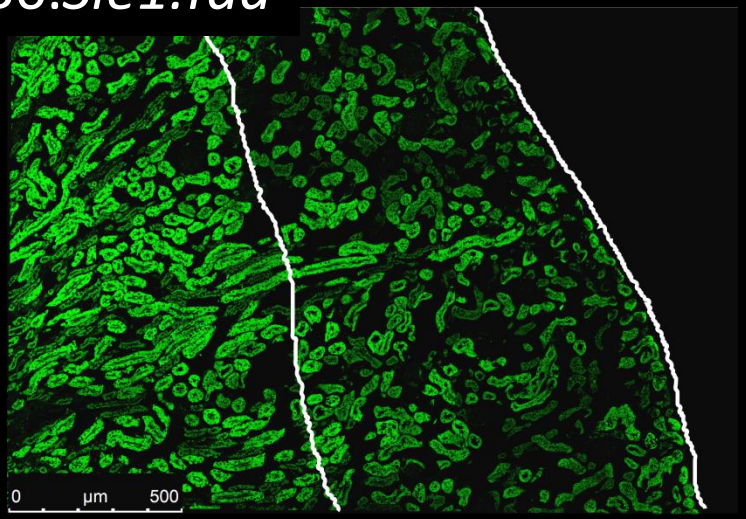


Extensive tissue hypoxia after IC deposition

B6

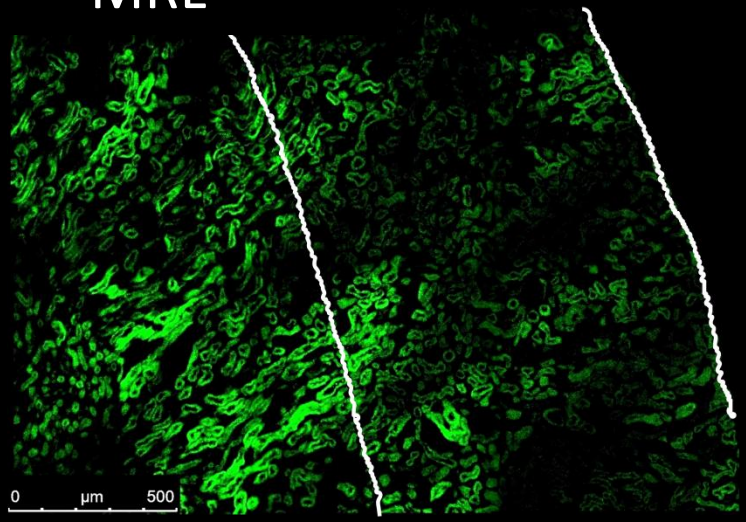


B6.*Sle1.Yaa*

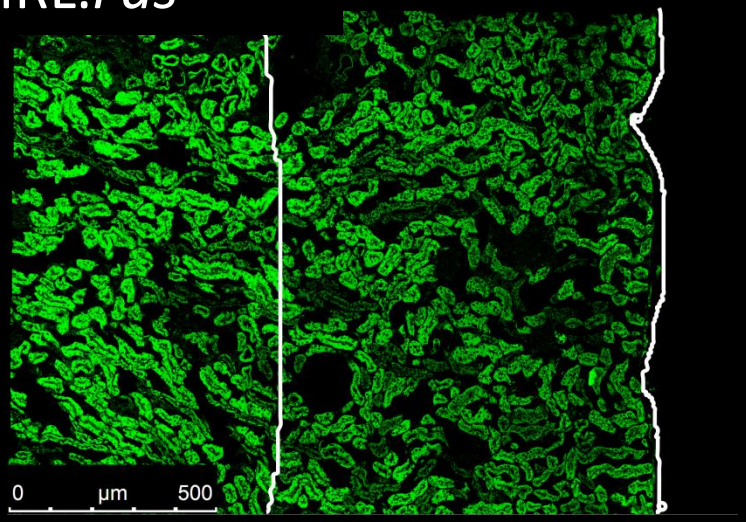


Medulla Cortex

MRL $^{+/+}$

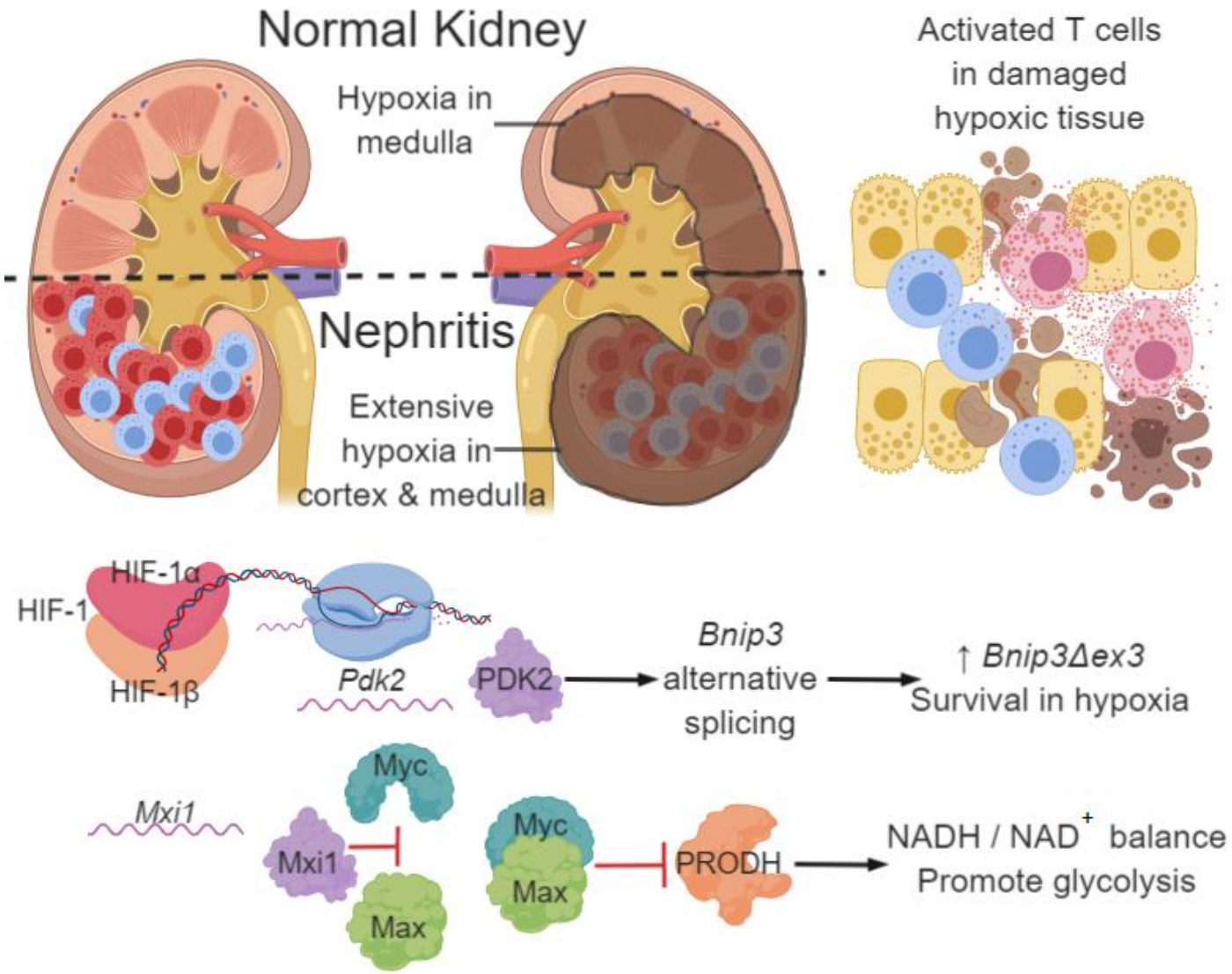


MRL.*Fas* $^{lpr/lpr}$



Chen PM, Craft J, et.al, Sci Transl Med 2020 Apr 8;12(538)

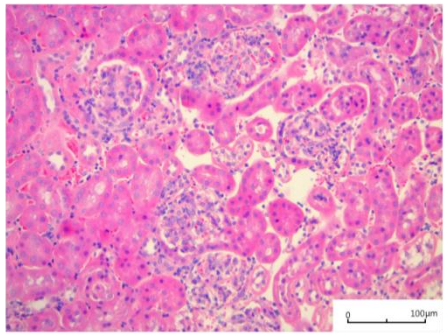
Hypoxia in inflamed tissue dictates T cell functionality



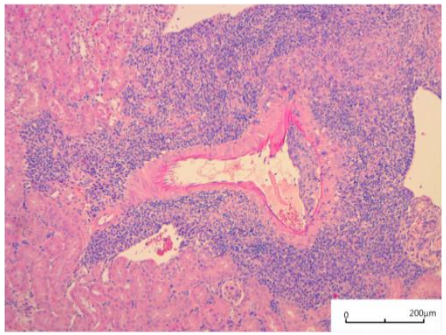
Chen PM, Craft J, et.al, Sci Transl Med 2020 Apr 8;12(538)

Targeting hypoxic response by T cells reverse tissue damage

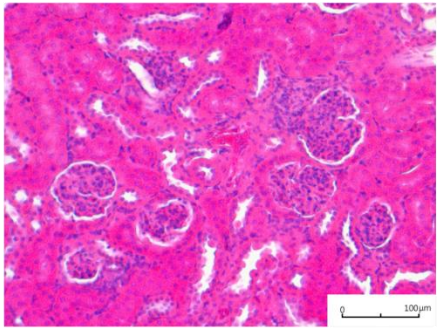
PBS Glomeruli



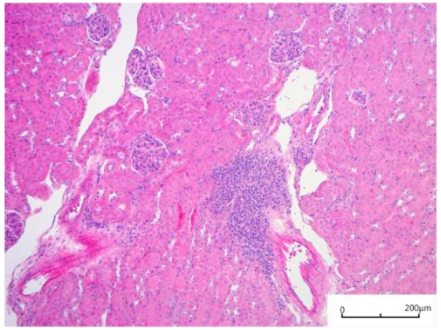
PBS Perivascular Region



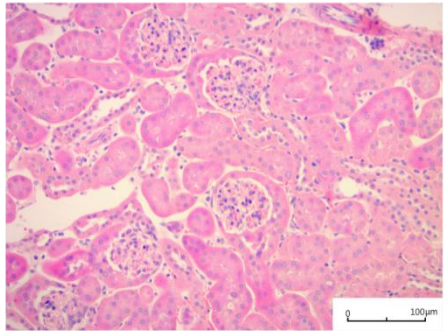
CD4^{WT}*Hif1a*$^{f/f}$ Glomeruli



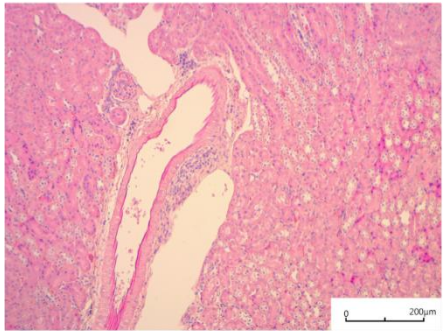
CD4^{WT}*Hif1a*$^{f/f}$ Perivascular Region



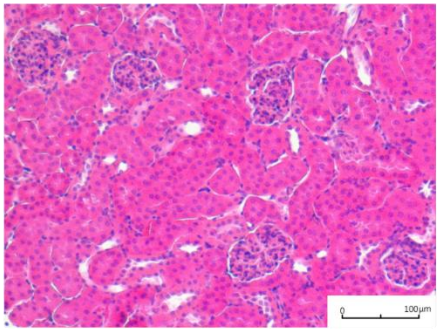
PX-478 Glomeruli



PX-478 Perivascular Region



CD4^{Cre}*Hif1a*$^{f/f}$ Glomeruli



CD4^{Cre}*Hif1a*$^{f/f}$ Perivascular Region

Chen PM, Craft J, et.al, Sci Transl Med 2020 Apr 8;12(538)

Summary

- HIF signature: tissue hypoxia + stress

  T cell stress response
- Maladaptive stress sensing → T cell activation → persistence of tissue damage

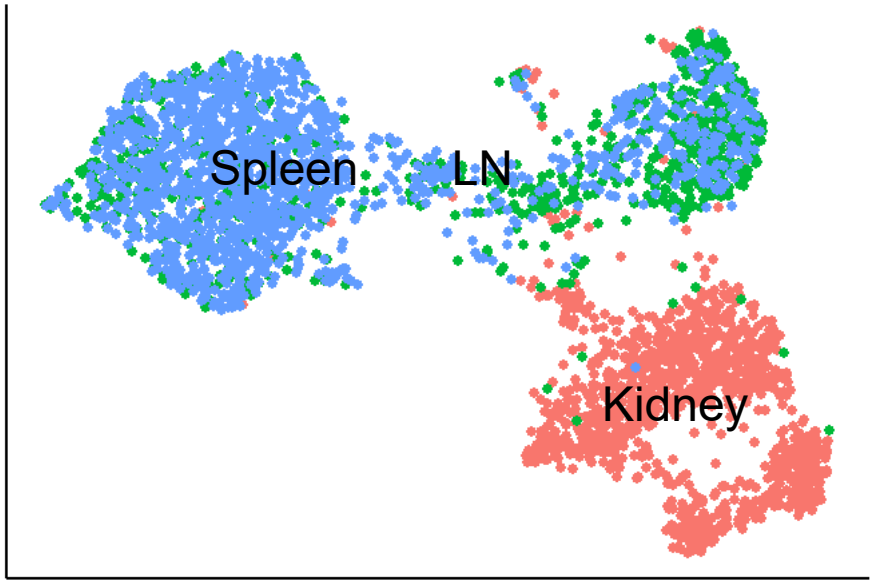
- Critics: HIF-1 blockade feared for its adverse effects
- Another more targeted approach?

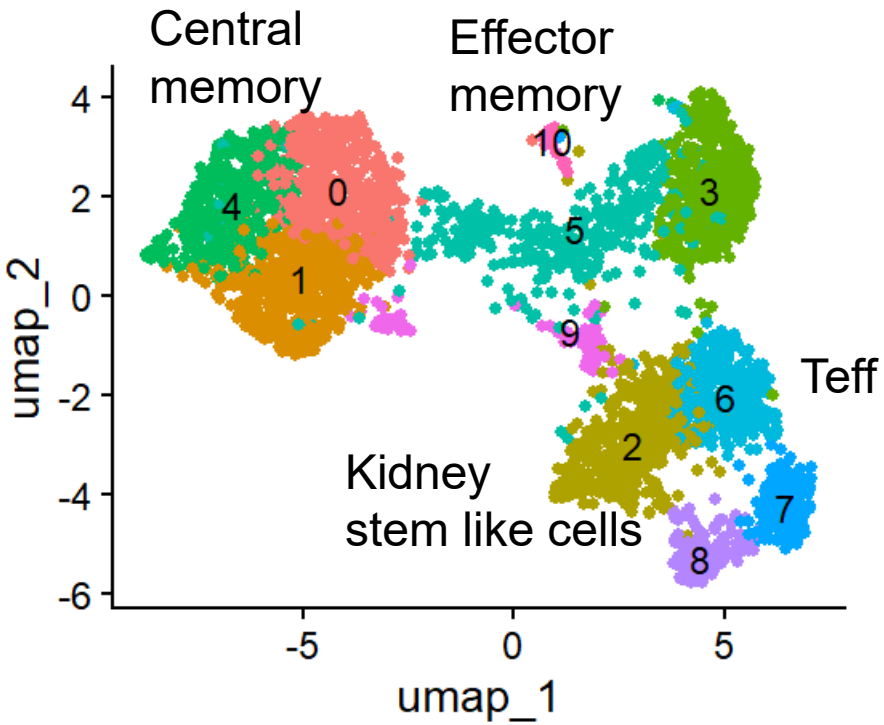
Questions remain to be addressed

- The origin of tissue effector T cells
- Chick and egg question
  - Sensing stress signal before T cell migration
  - Simply T cell adaptation to the stress environment

- Unpublished data coming. Please refrain from taking photos

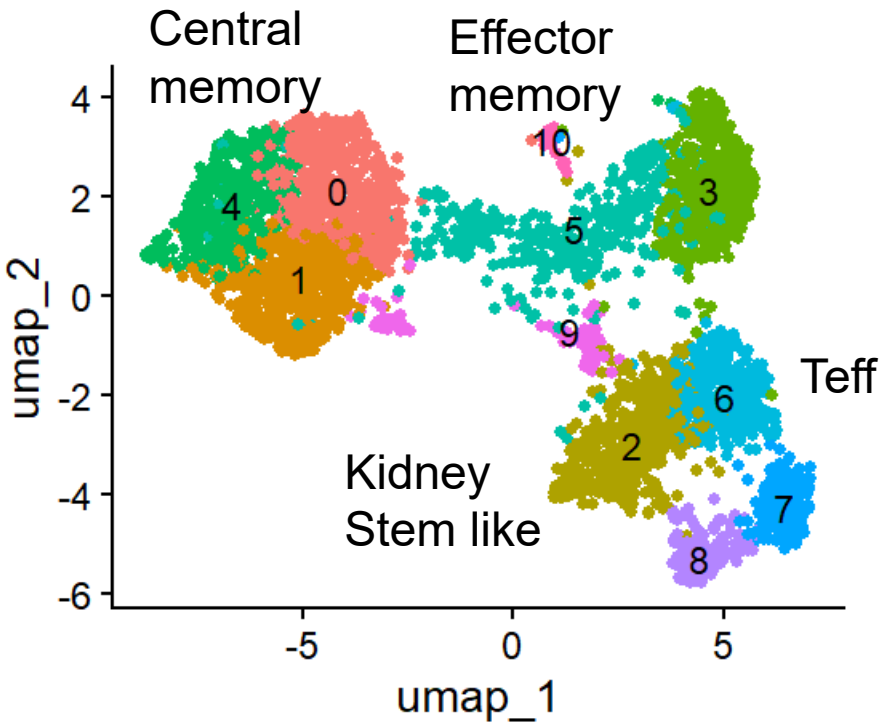
Origin of tissue effector T cells addressed by scRNAseq

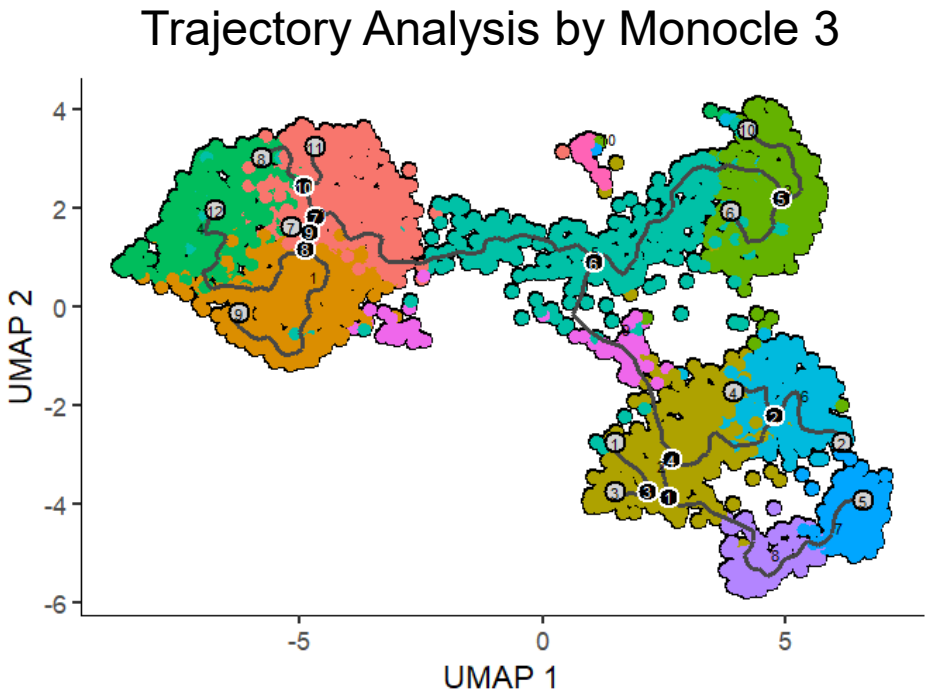




Al Souz J, Chen PM, Craft J, et.al, manuscript submitted

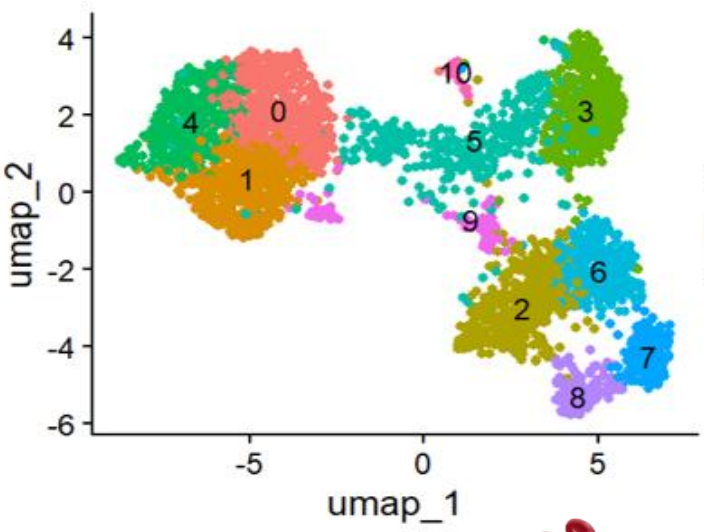
More Teff in the tissue originate from tissue stem-like memory T cells

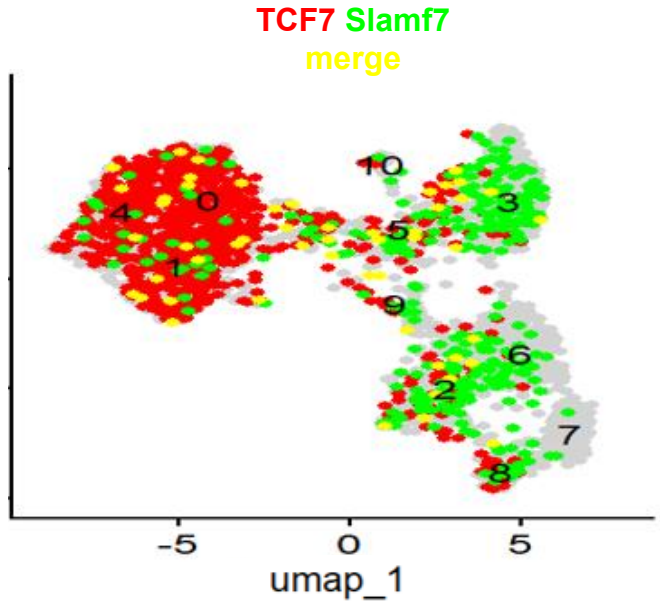


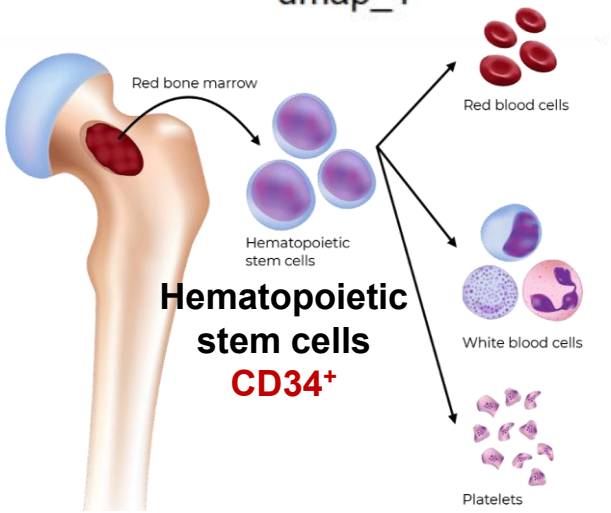


Al Souz J, Chen PM, Craft J, et.al, manuscript submitted

Stem-like Precursor CD8⁺ T Cells identified by Transcriptome





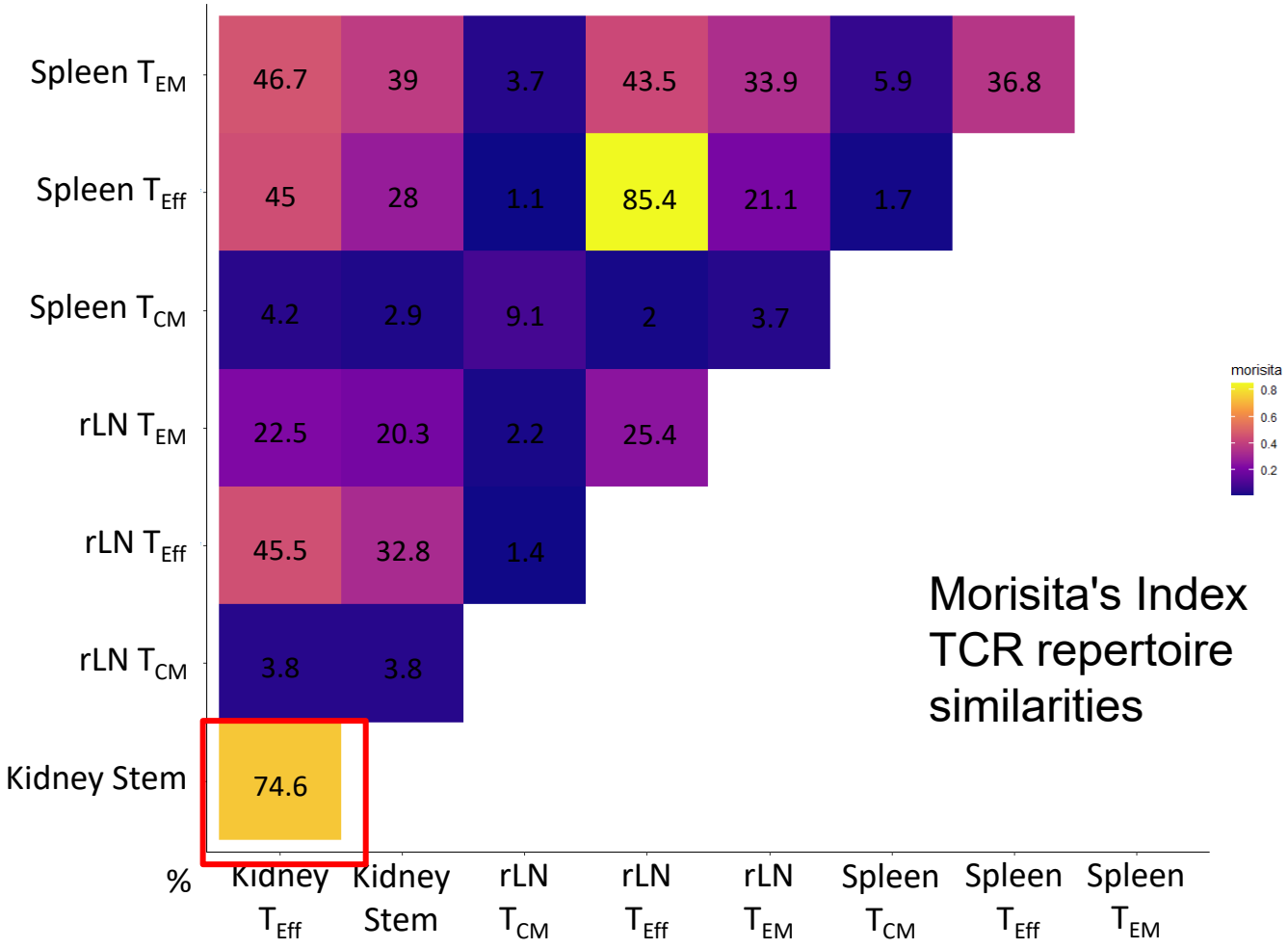


OPEN ACCESS Freely available online PLoS GENETICS

Tcf7 Is an Important Regulator of the Switch of Self-Renewal and Differentiation in a Multipotential Hematopoietic Cell Line

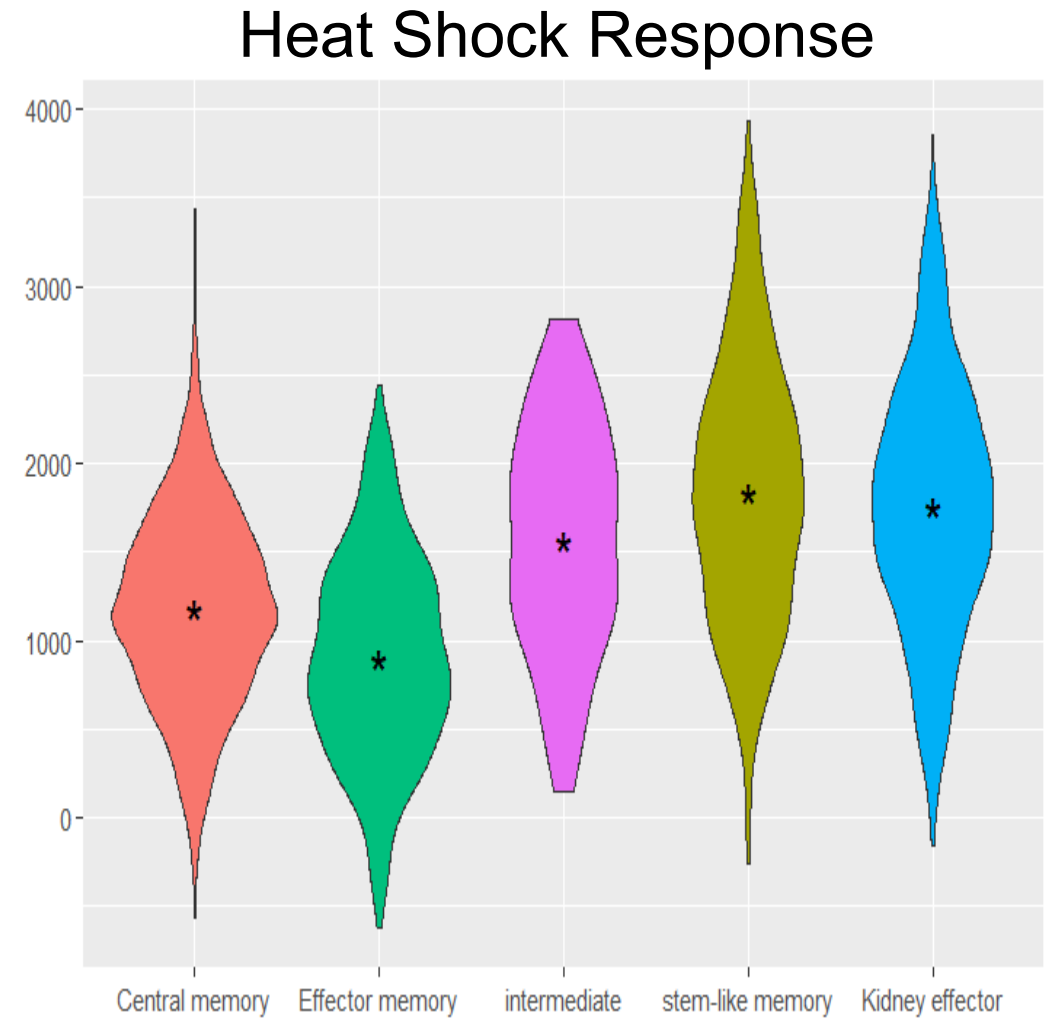
PLoS Genet . 2012;8(3):e1002565.

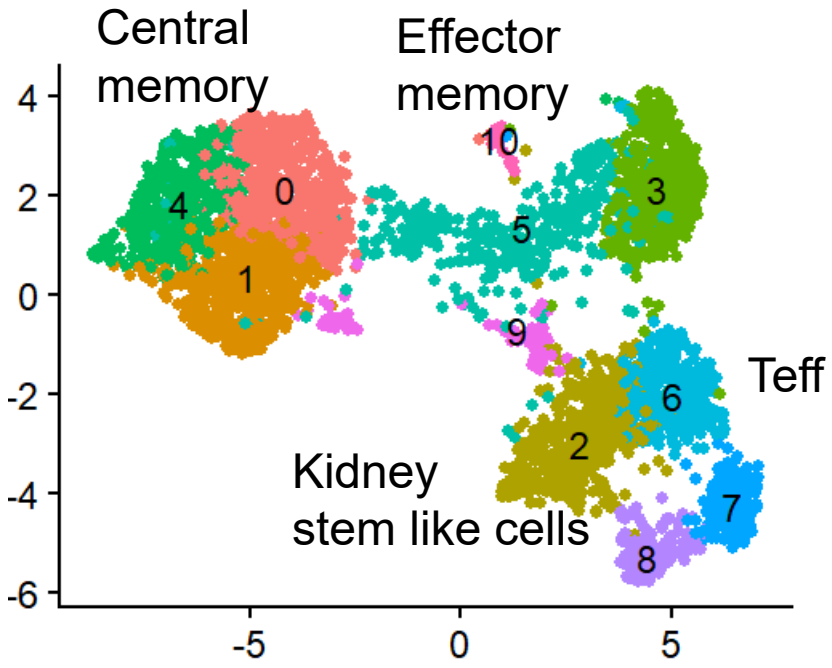
More Teff in the tissue originate from tissue stem-like memory T cells



Al Souz J, Chen PM, Craft J, et.al, manuscript submitted

Heat shock response is the earliest sensed stress for T cells





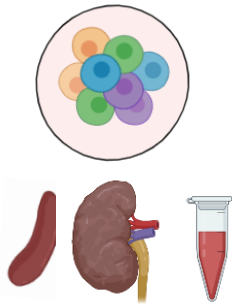
Chen H, Chen PM et.al, unpublished work

HSP found in Stem like T cells

TCF7-GFP MRL/lpr

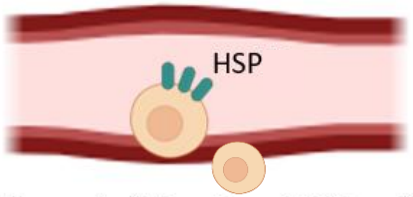
BV711-CD45.1

5 min



Kidney-migratory CD8 cells

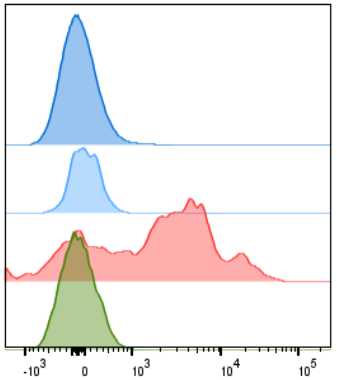
BV711-CD45.1+



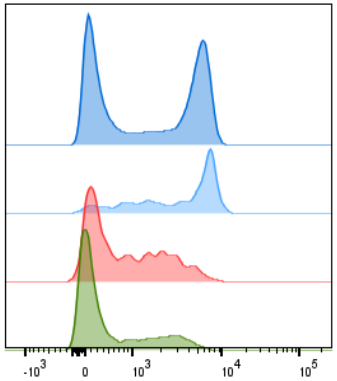
Kidney-infiltrating CD8 cells

BV711-CD45.1-

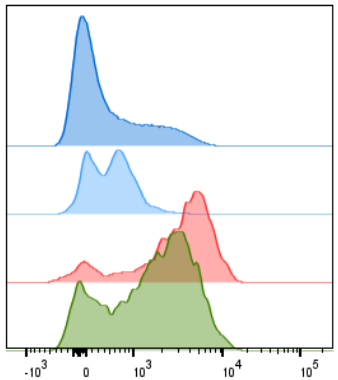
- Splenic CD8
- Blood
- Kidney-migratory CD8 cells (antibody labeled)
- Kidney-infiltrating CD8 cells (not antibody labeled)



HSP



TCF7-GFP



CXCR6

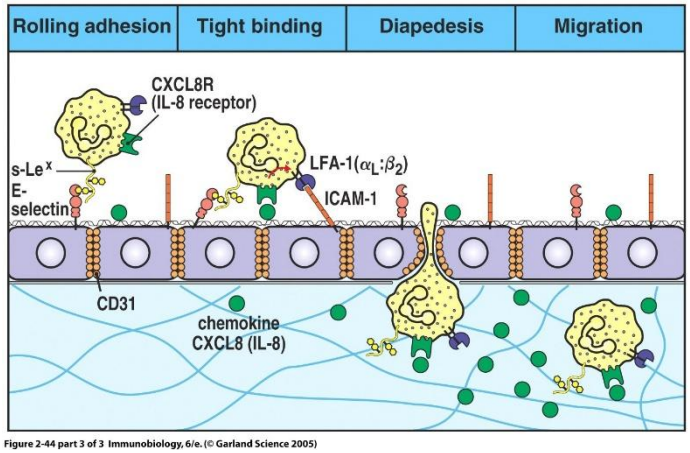
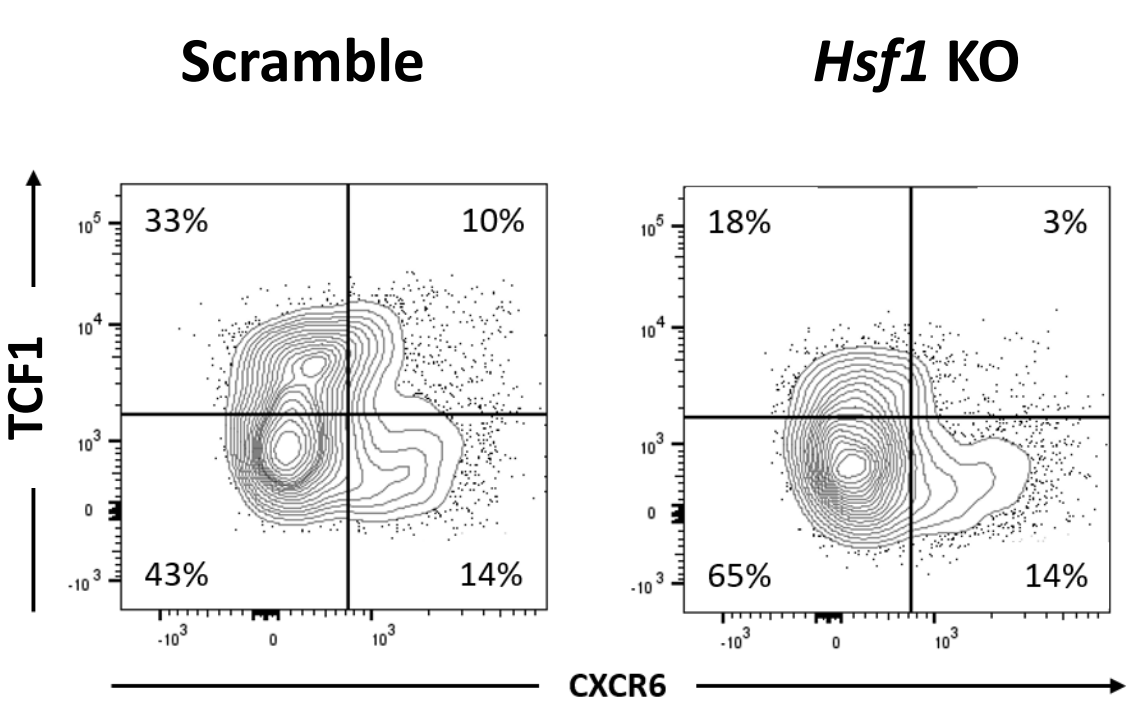
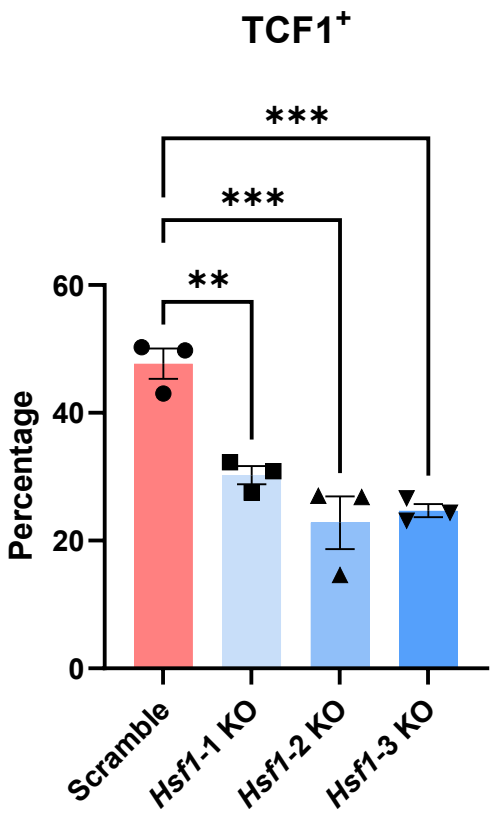


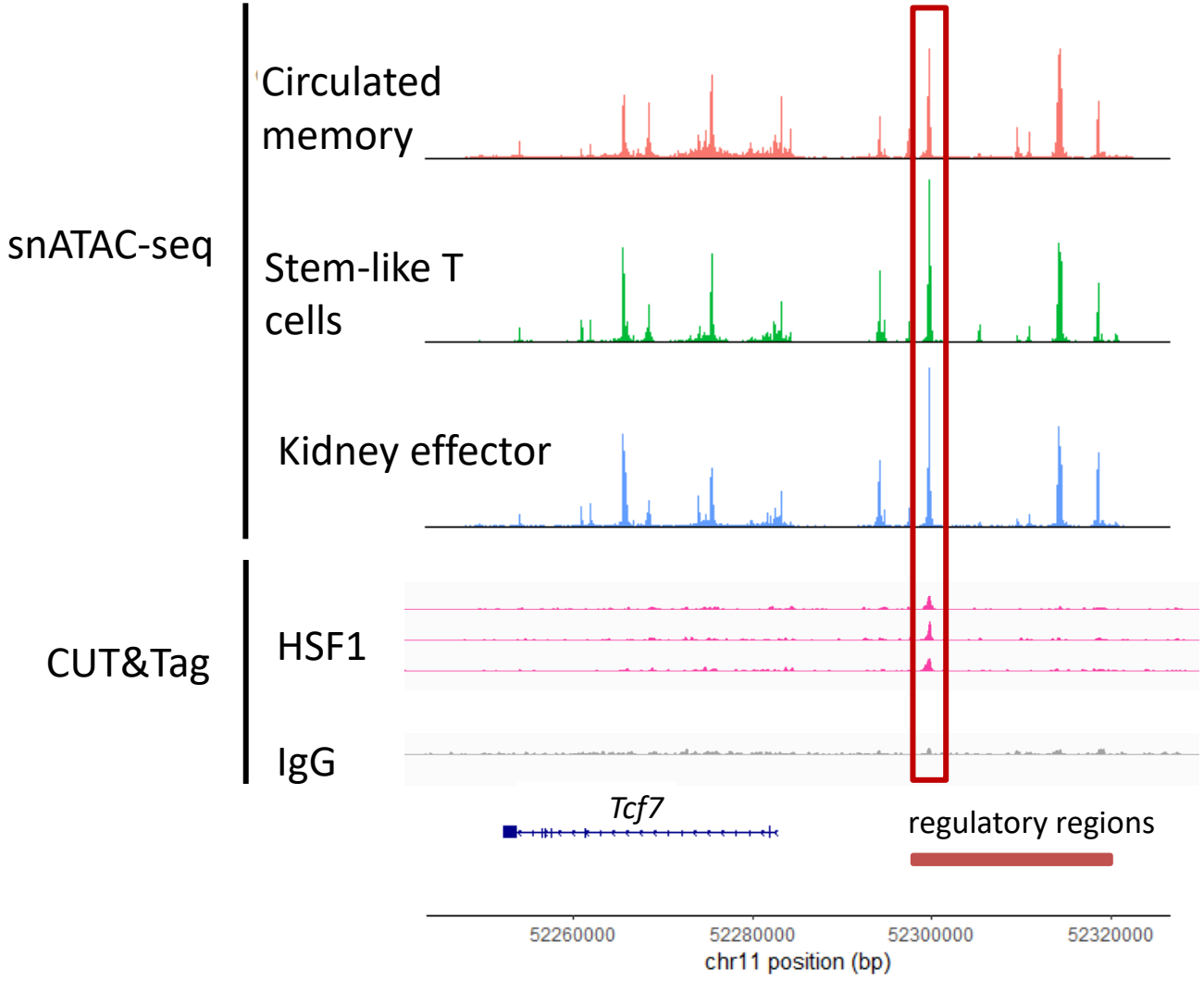
Figure 2-44 part 3 of 3 Immunobiology, 6/e. (© Garland Science 2005)

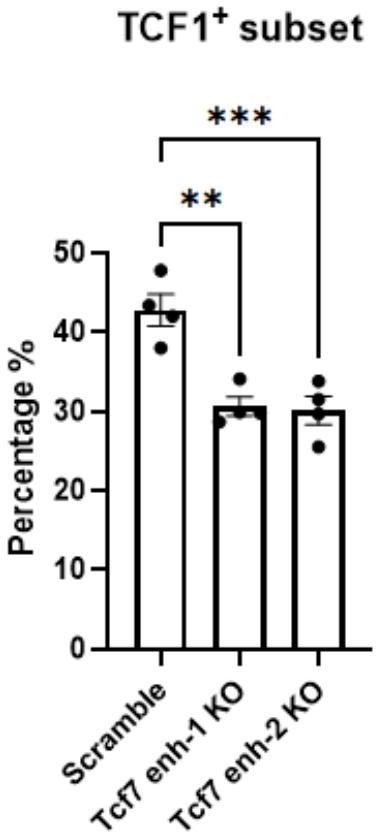
CRISPR knockout of *Hsf1* reduces Stem-like T cells



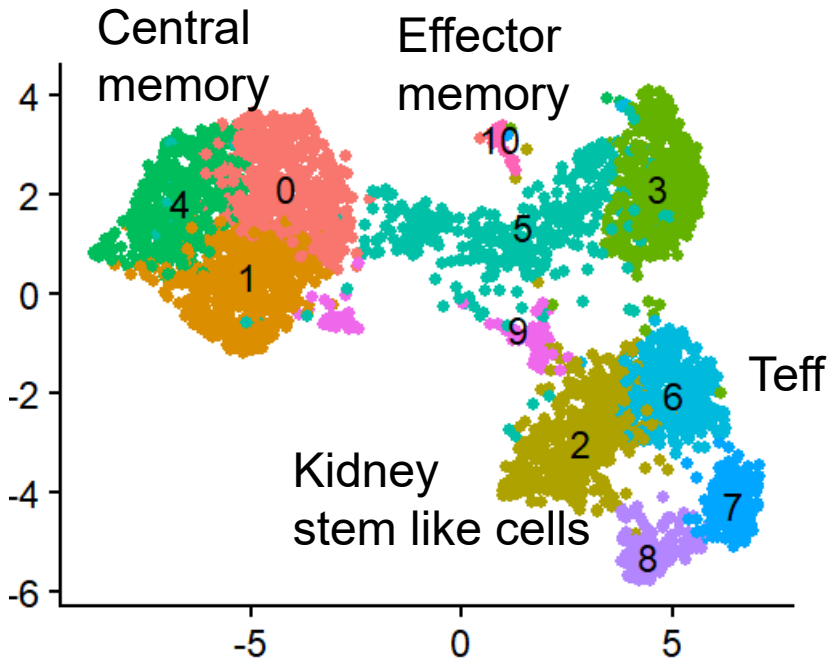


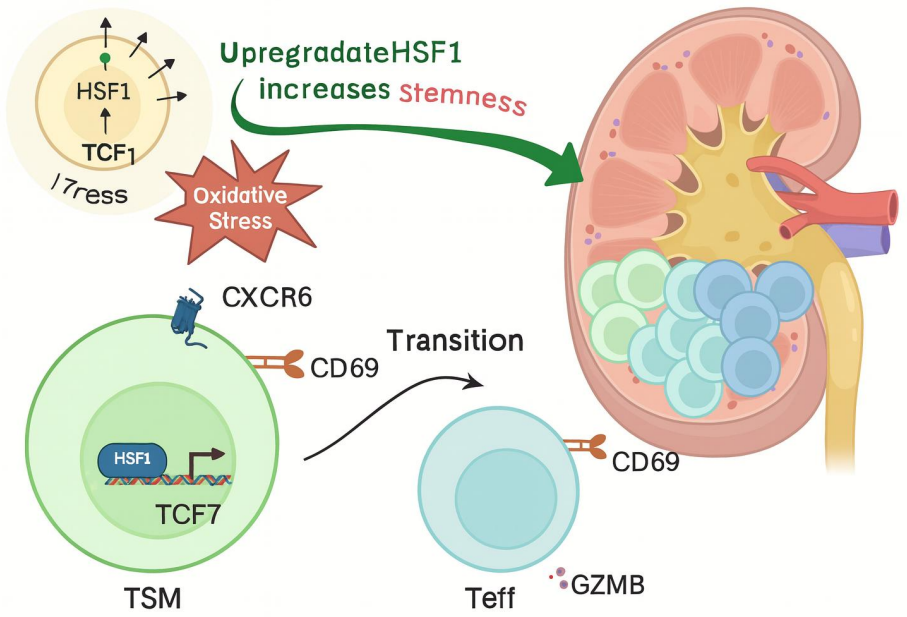
HSF1 regulates a *Tcf7* upstream super-enhancer





Heat shock response shaped the stem like phenotype of T cells



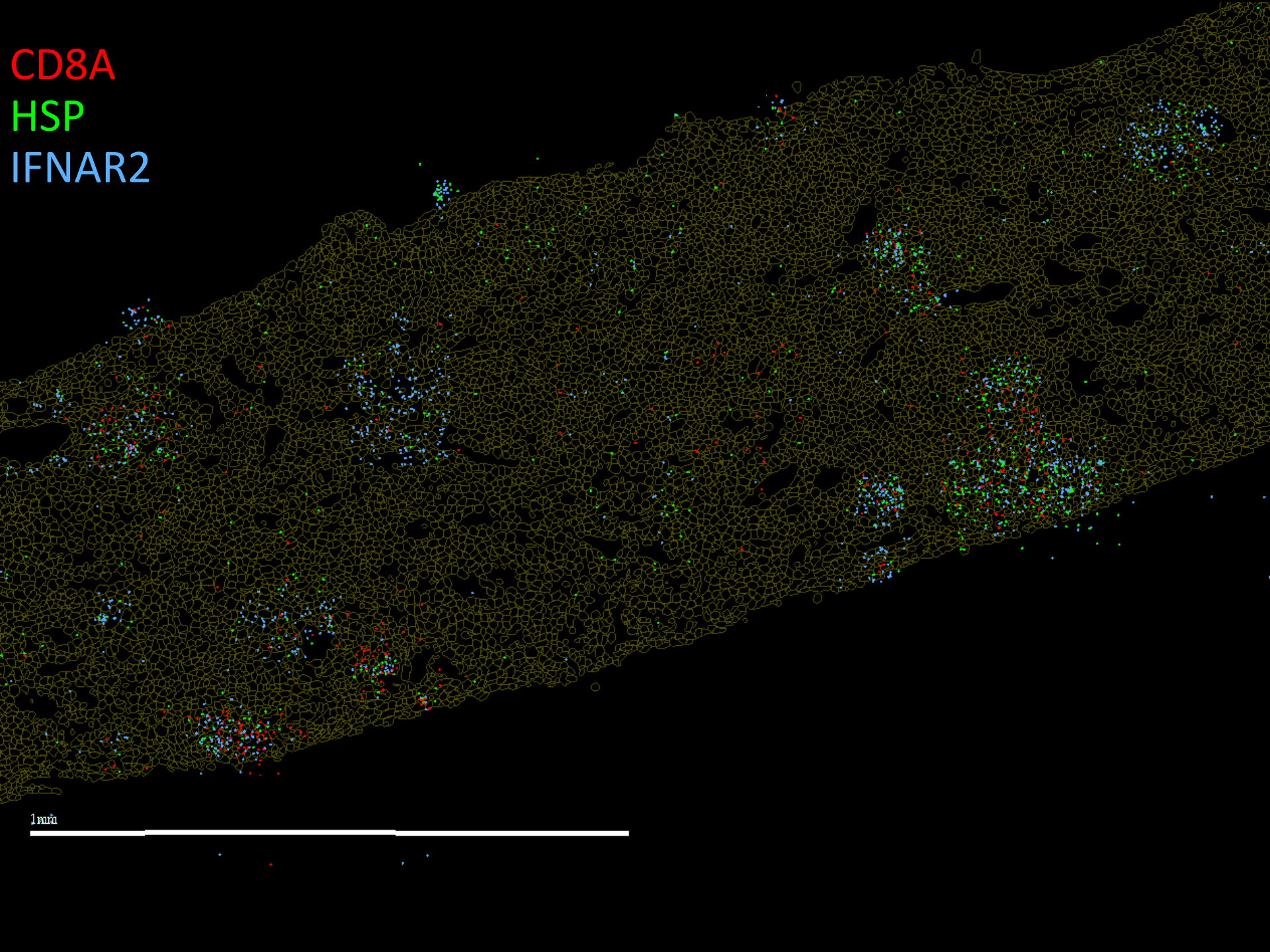


Chen H, Chen PM et.al, unpublished work

Inclusion criteria for analyzed samples

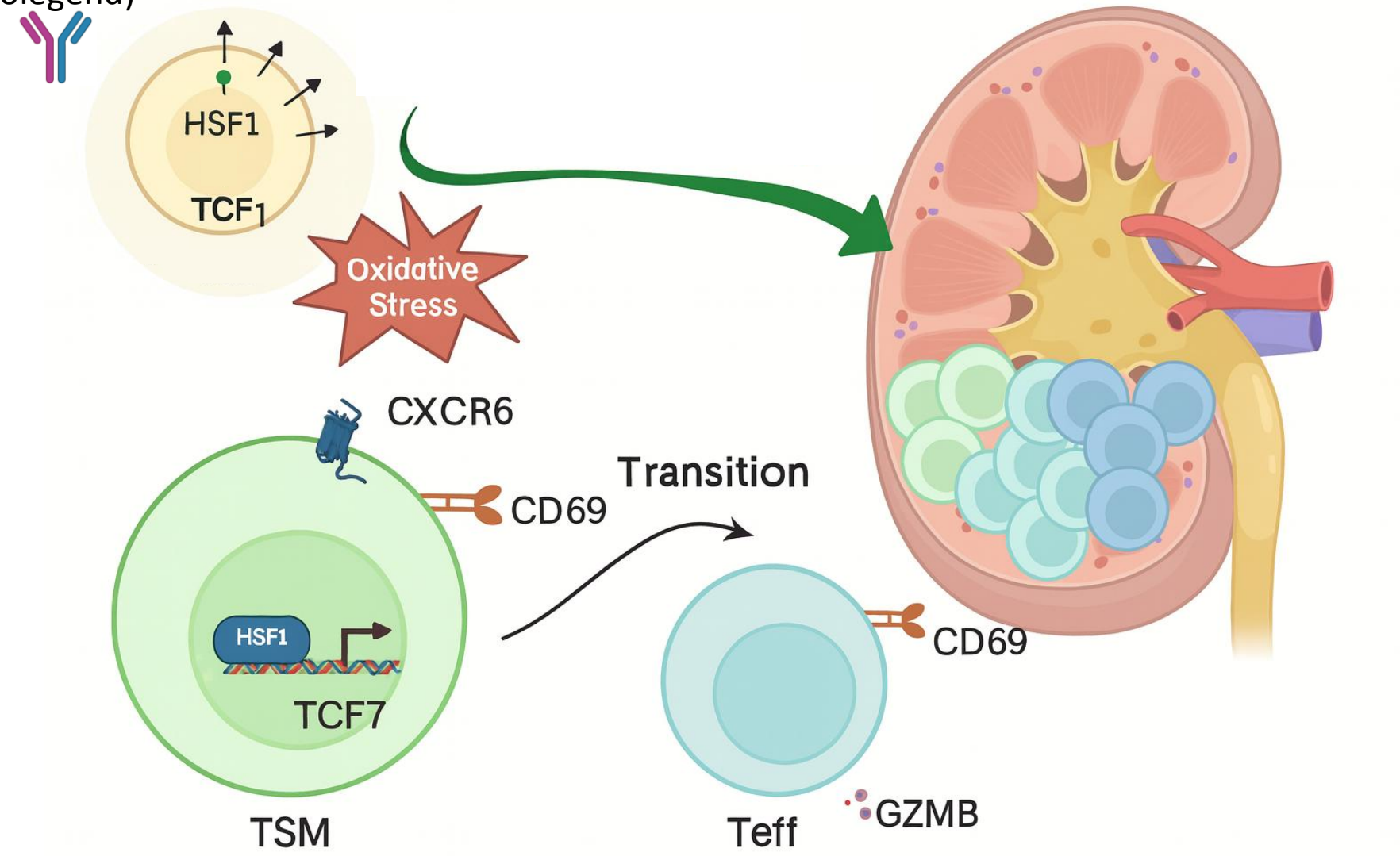
- 2014-2025 NTUH biopsy case
- Class IV Lupus nephritis with NIH Activity Index >= 10
- Serum creatinine > 1.5 at the time of biopsy
  - Cases with complete recovery of renal function
  - Cases with progression

- MERSCOPE with customed 950 genes panel


CD8A
HSP
IFNAR2
1 mm

Summary

Targeted Stem like cell depletion (Biolegend)



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