

Targeting microbiota-specific T cells in colorectal cancer

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SITC Tumor Immune Microenvironment Workshop

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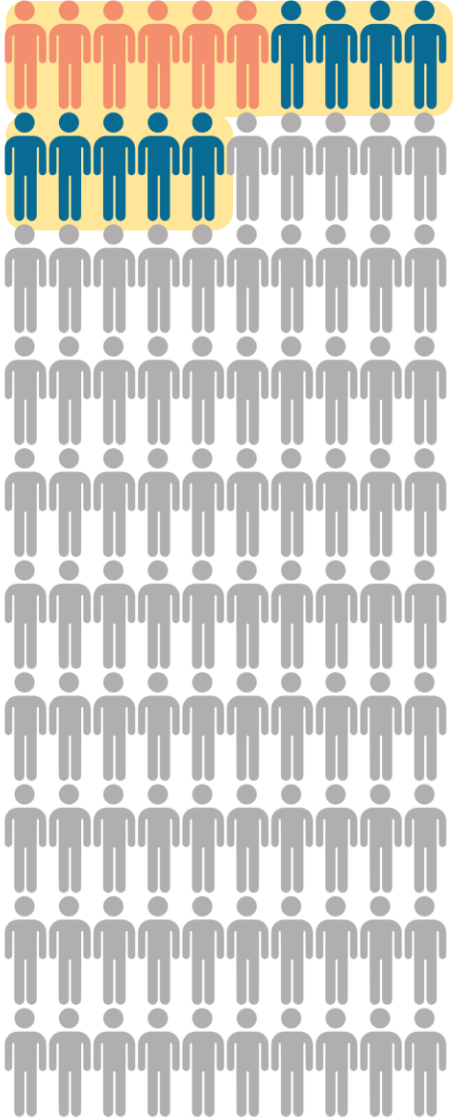
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Colon cancer is common and largely unresponsive to immunotherapy



CRC is the third most common cancer in the world and one of the most deadly/difficult to treat in advanced cases.

Very few show response to current immunotherapies like anti-PD1. Why is this?

- The microbiota (and a healthy one at that) is necessary for anti-PD1 responses in melanoma patients
- Select bacterial taxa have been associated with this response; however, the mechanism remains unclear
- Could this be applied to other cancers, especially those with direct interaction with the gut microbiome, such as CRC?

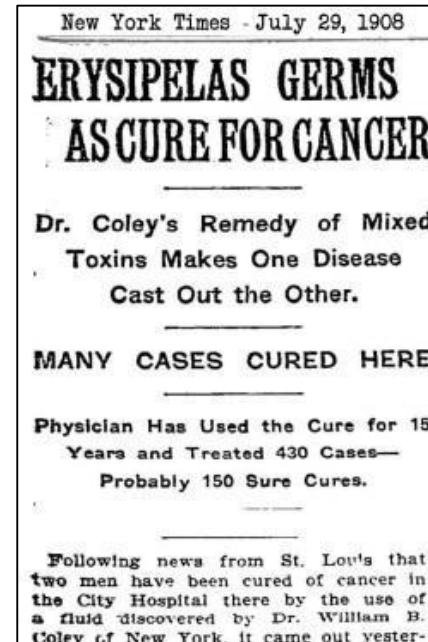


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Matson, V. et al. *Science*. 2018.
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“I think I’ve seen this one before...”

William B. Coley (1862-1936): bone surgeon and cancer researcher

- Known as the father of cancer immunotherapy for Coley’s Toxins
- A newly minted surgeon, Coley was frustrated by the current treatment options for Sarcoma patients
- Noticed that a patient in NY had an inoperable tumor miraculously disappear after a skin infection with *Streptococcus pyogenes*
- Injected heat killed ‘bacterial toxins’ into tumors which resulted in tumor reduction or cures for some
- The emergence of radiation the practice became scarce
- Helen Coley Nauts carried on his work in 1953



Can we treat CRC with microbiota modulation?



Microbiome modulation through *Helicobacter hepaticus*

- Initially found in A/JCr mice with liver tumors in the 1990s
- Gram negative microaerophilic *Proteobacteria*
- Lives in the colon and cecum (and liver), adheres to the epithelium, and can invade
- Elicits a strong *Hhep*-specific immune response that is contextual to the environment (Th1, Tfh, Treg)
- Contributes to colitis and tumors in immunodeficient mice, associated with a lack of IL-10 production

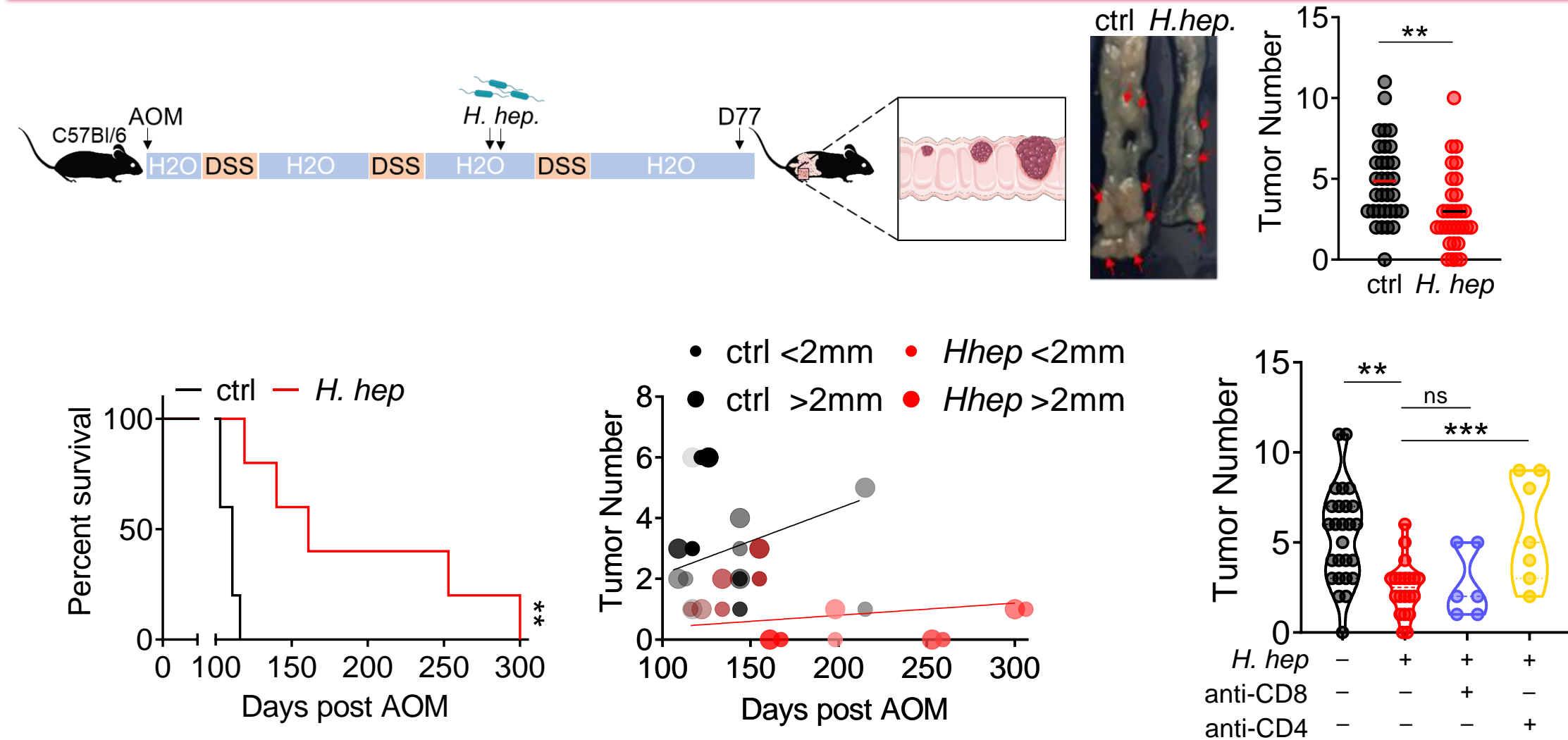


We hypothesized that addition of *Hhep* during CRC tumorigenesis would induce Tregs within the colon, causing more severe disease and possibly T cell dysfunction.

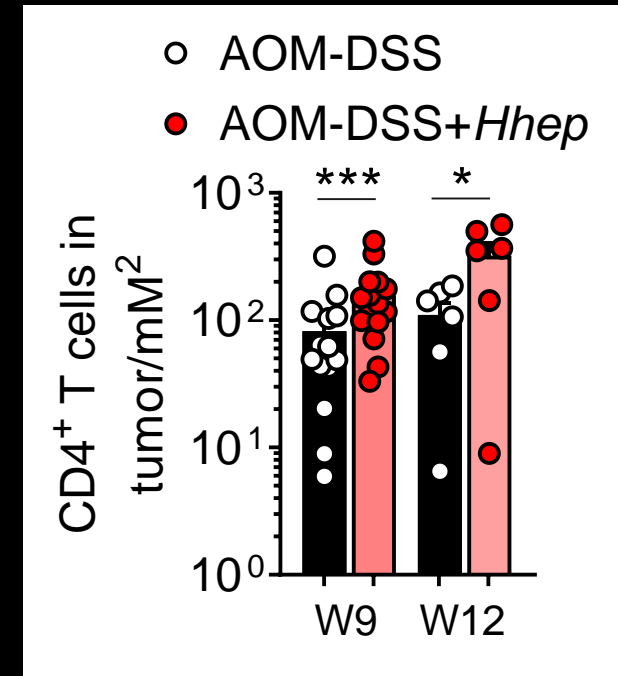
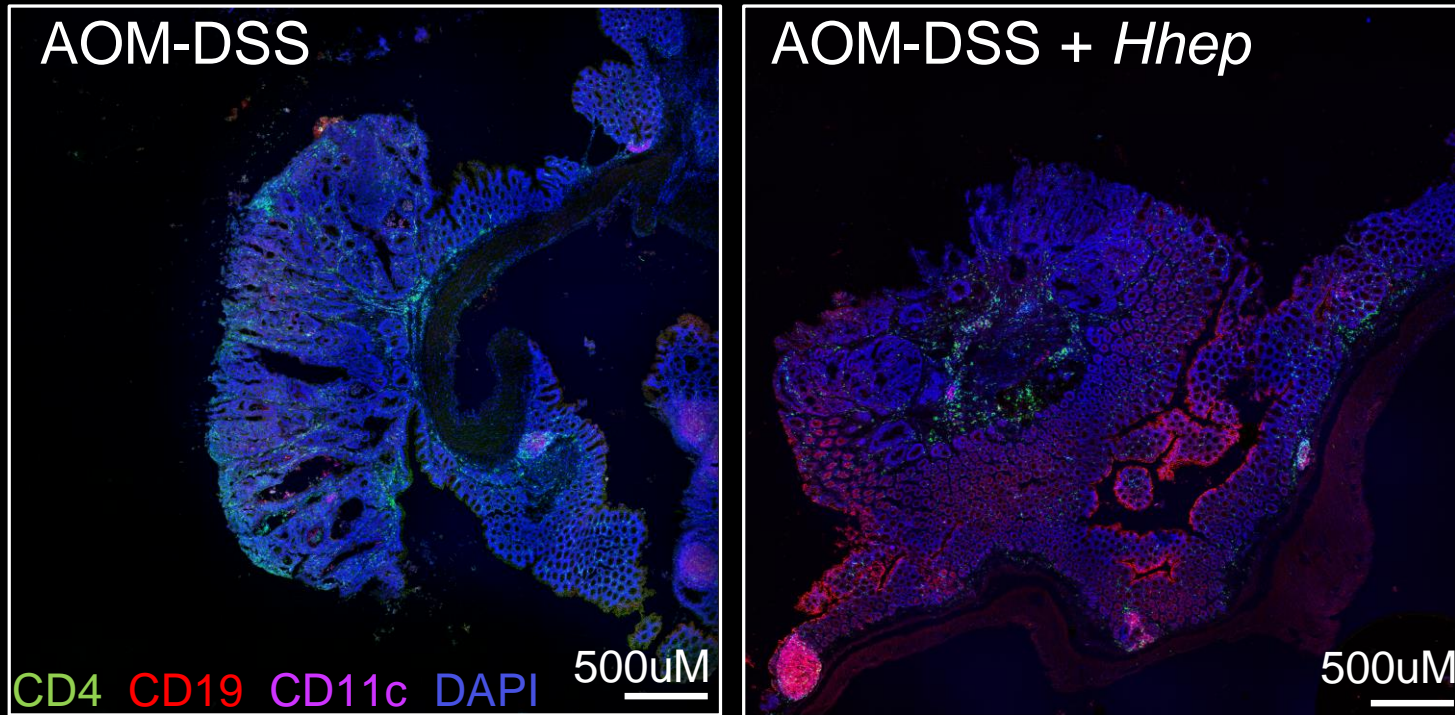
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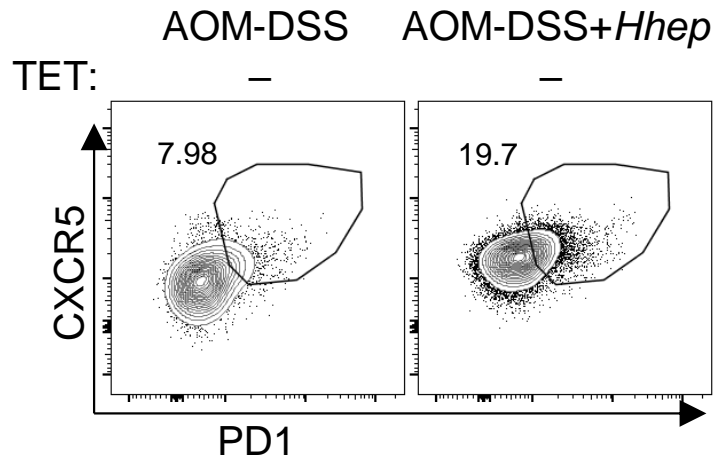
Helicobacter hepaticus reduces CRC tumor burden and is CD4⁺ T cell dependent



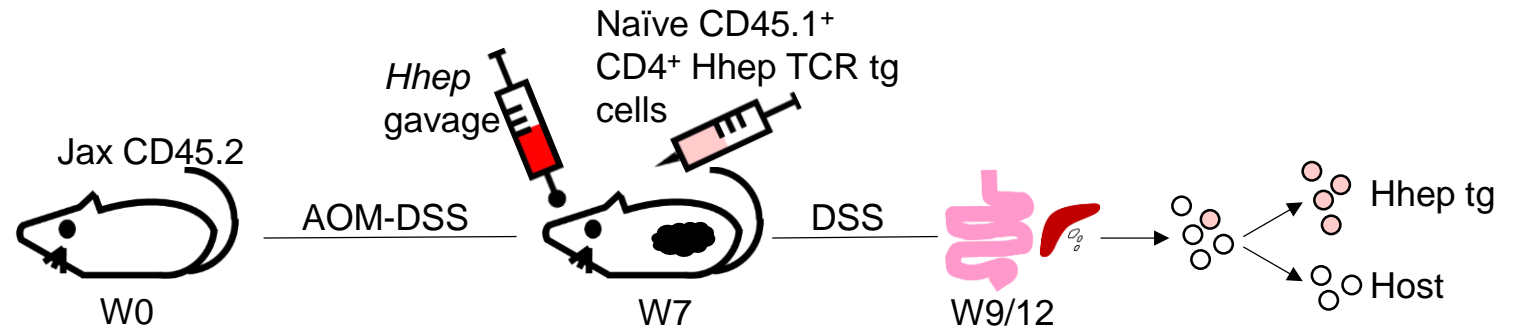
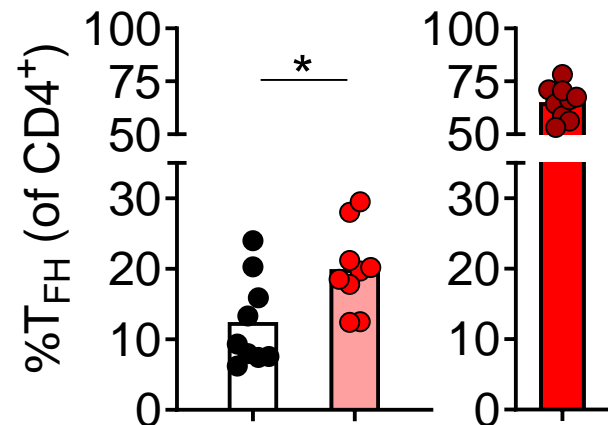
Colonization is associated with remodeling of the tumor microenvironment



Hhep induces follicular helper CD4⁺ T cell development

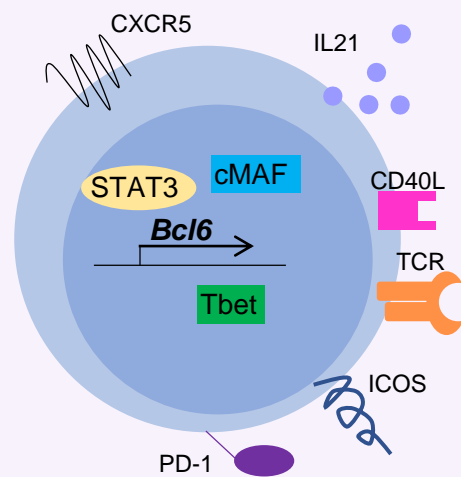


- AOM-DSS ● AOM-DSS+*Hhep*
- Tet. pos (AOM-DSS+*Hhep*)



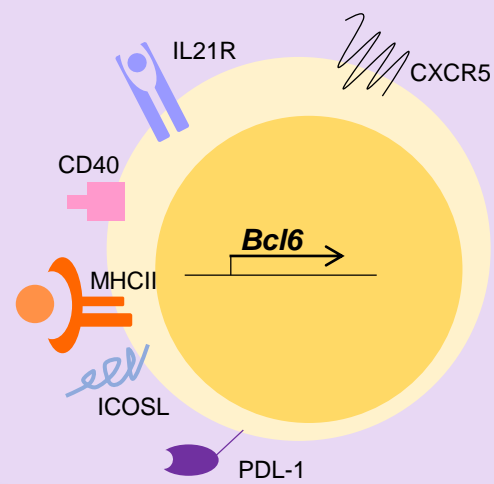
How do changes to CD4⁺ T cell development impact the surrounding tissue?

T follicular helper cell



Germinal Center

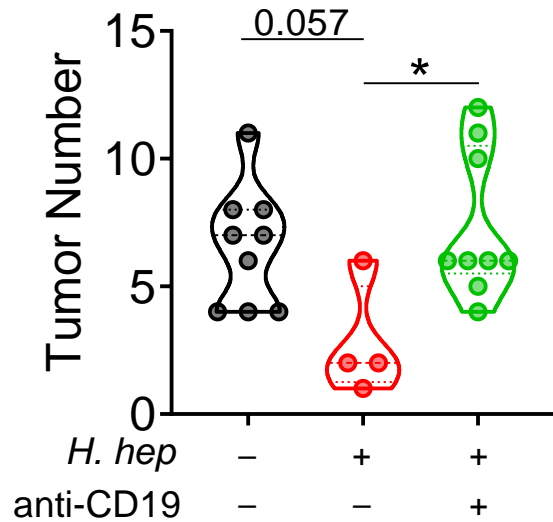
B cell



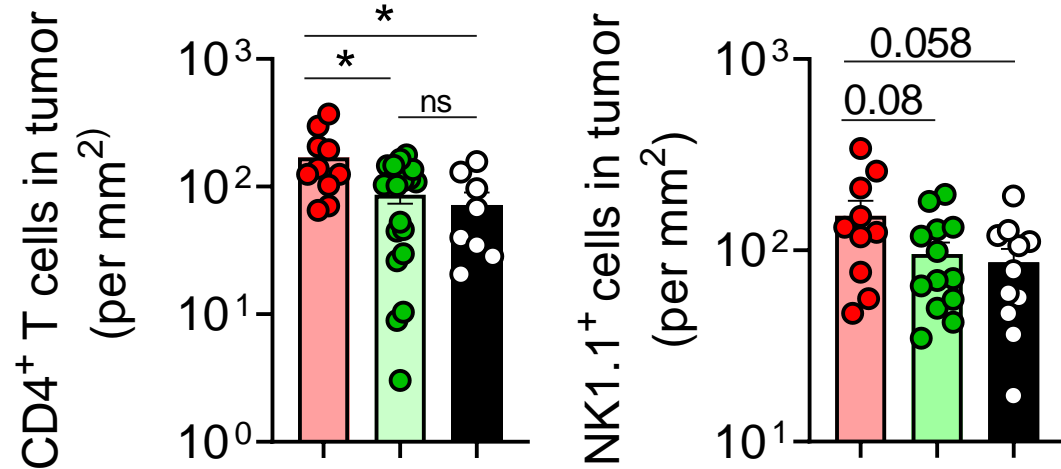
High affinity B
cells and
antibodies

LYMPHOID STRUCTURES

B cells are required for anti-tumor immunity after microbiome modulation

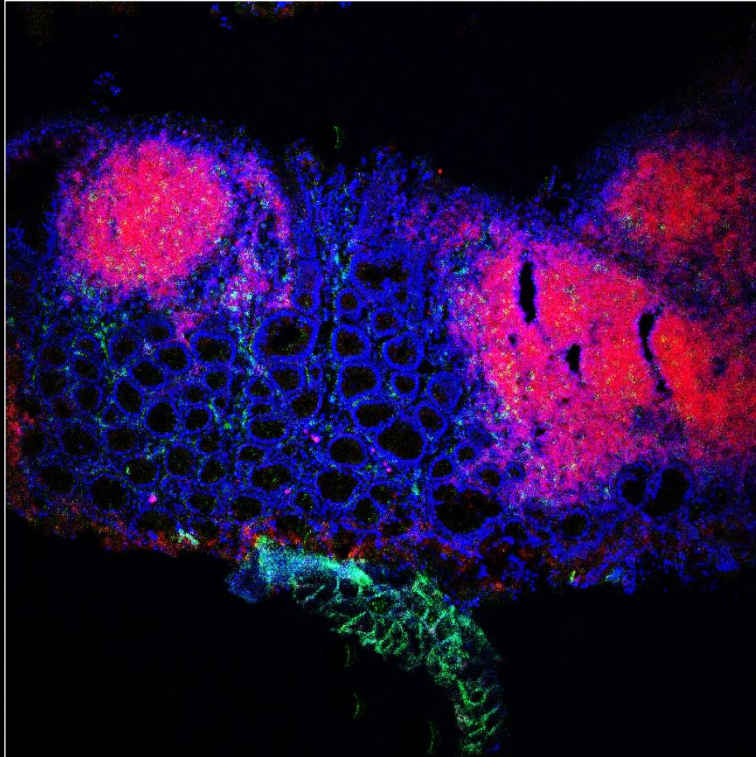


- AOM-DSS+*Hhep* ○ AOM-DSS
- AOM-DSS+*Hhep*+anti-CD19

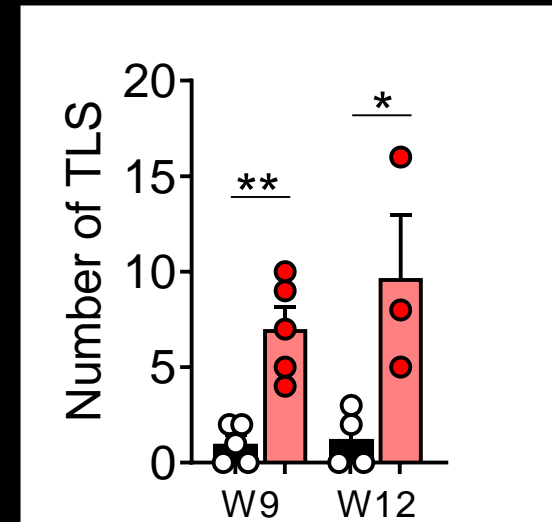
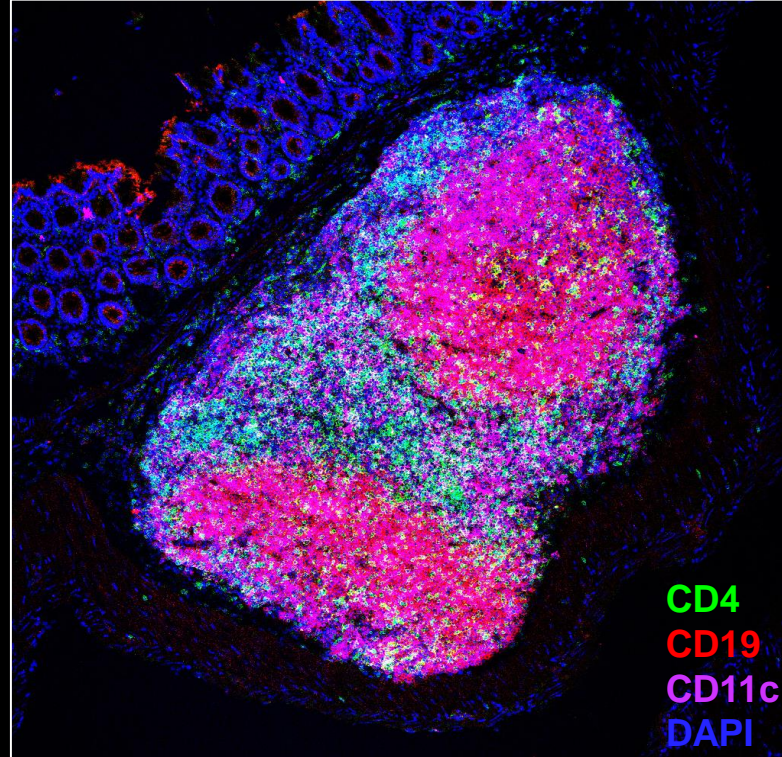


Mature TLS form in response to *Hhep*

AOM-DSS

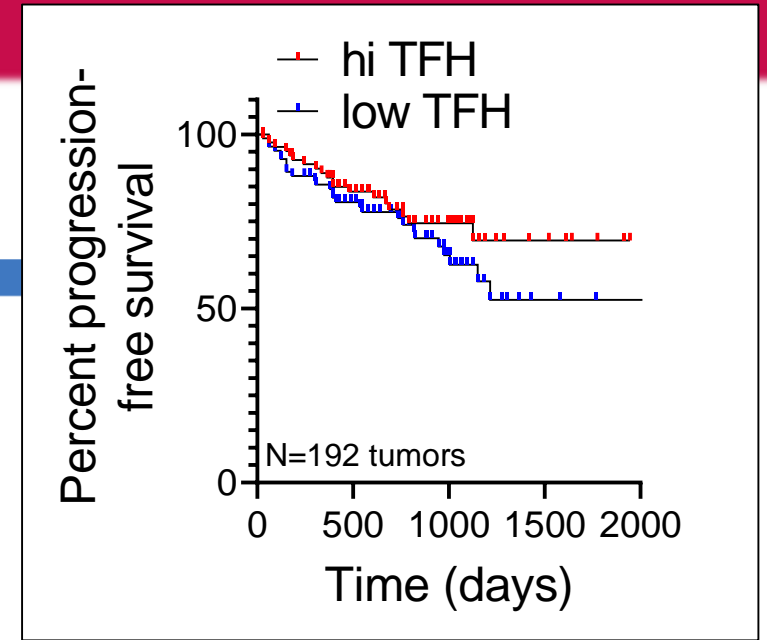
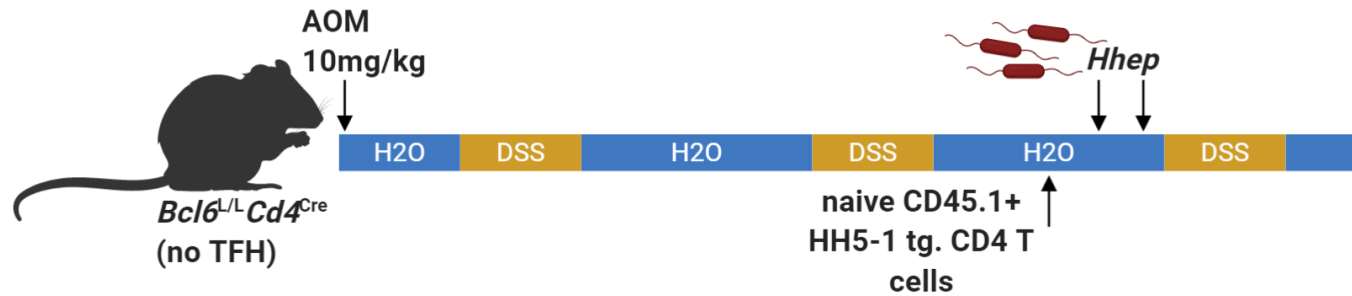


AOM-DSS + *Hhep*

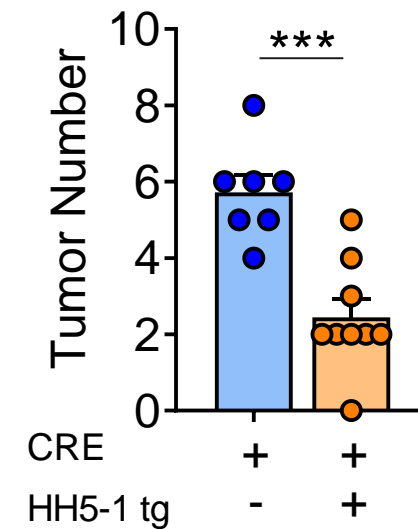
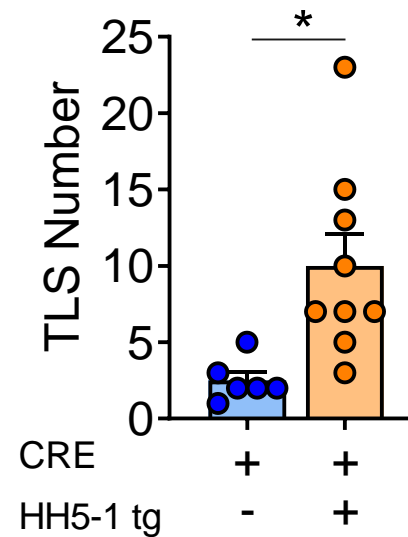
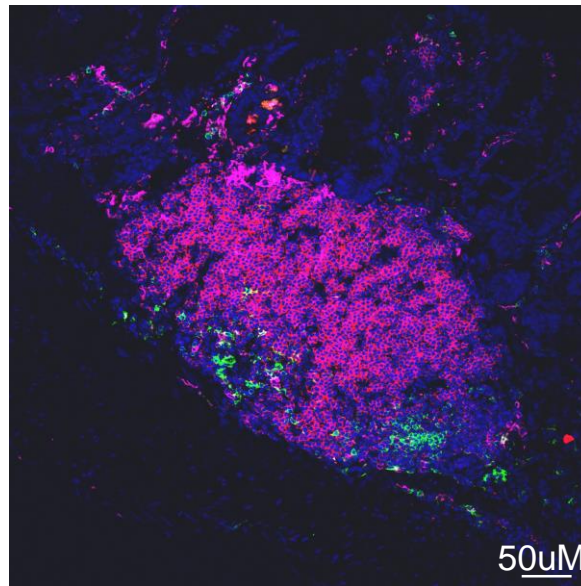
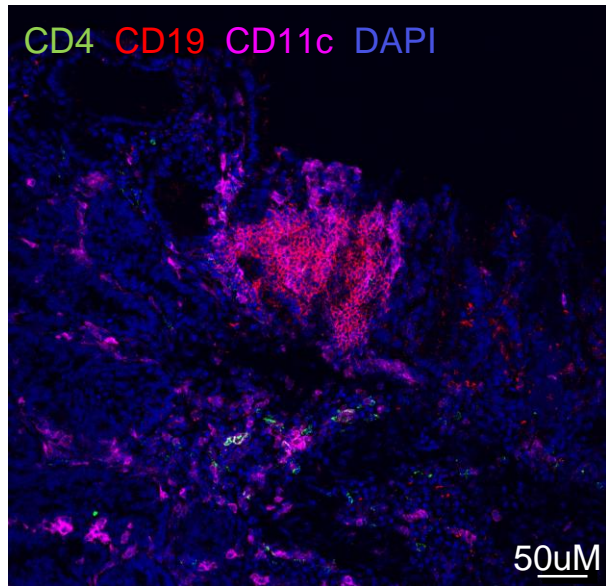


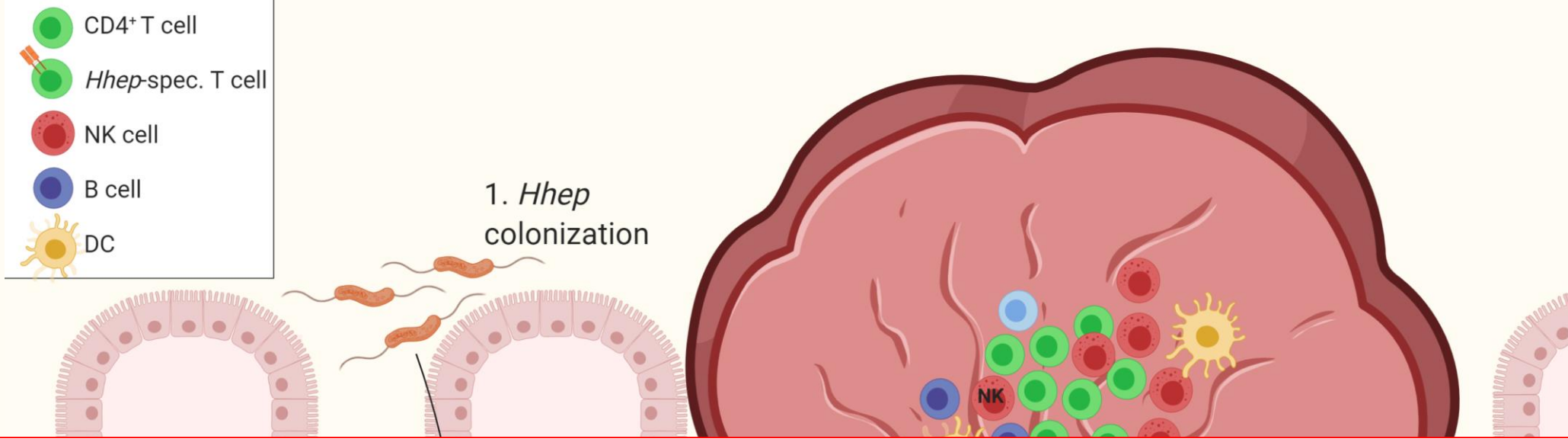
TLS (tertiary lymphoid structure): clear T cell and B cell zones, flanked by DCs

Hhep-specific T_{FH} are necessary and sufficient to drive TLS formation and limit tumor burden

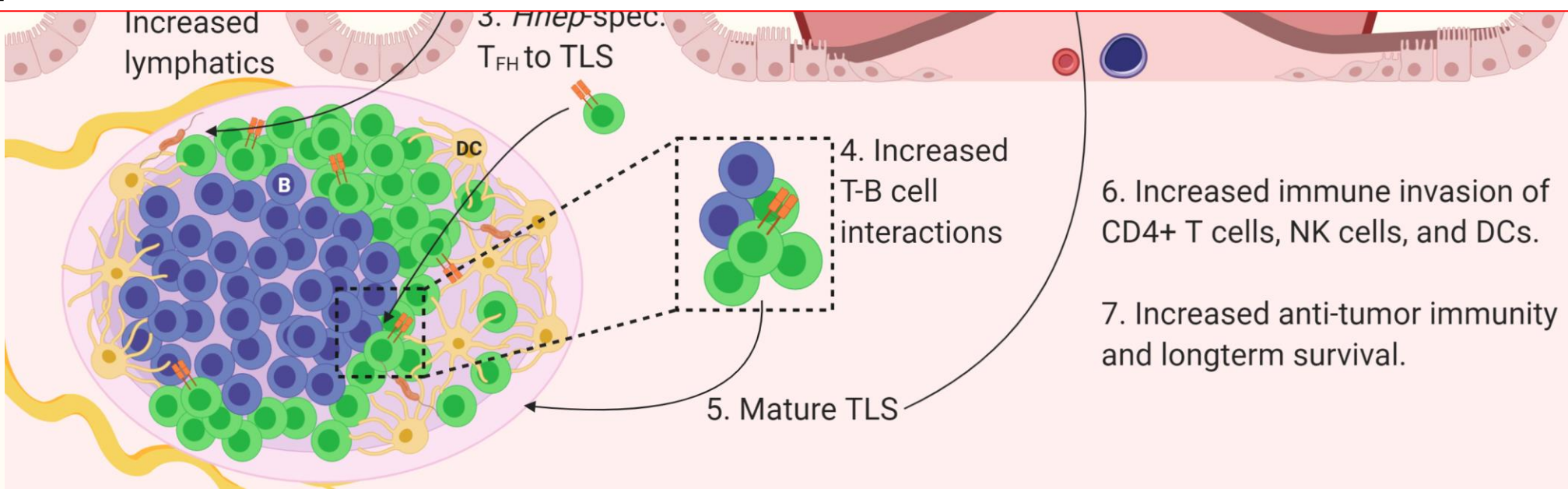


Bcl6^{L/L} CD4^{Cre} + CD45.1+ HH5-1tg T cells





Microbiota-specific T cells positively impact anti-tumor immunity and may represent a unique immunotherapeutic target to turn resistant tumors into responsive tumors.



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