Society for Immunotherapy of Cancer

Epigenetic reprogramming of T cell fate and antitumor immunity

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Experimental Transplantation& Immunology Branch

I have no financial interests or relationships to disclose

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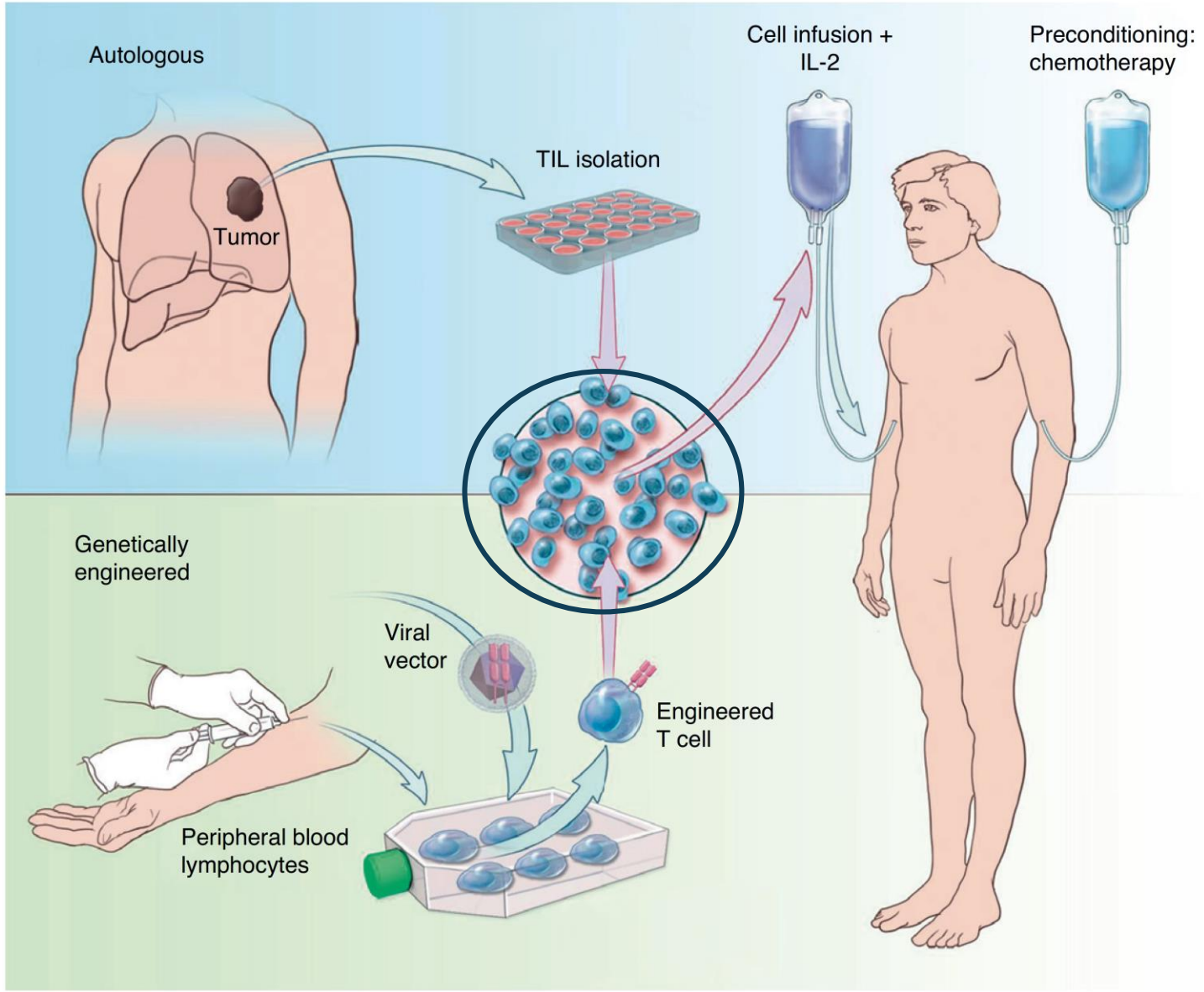
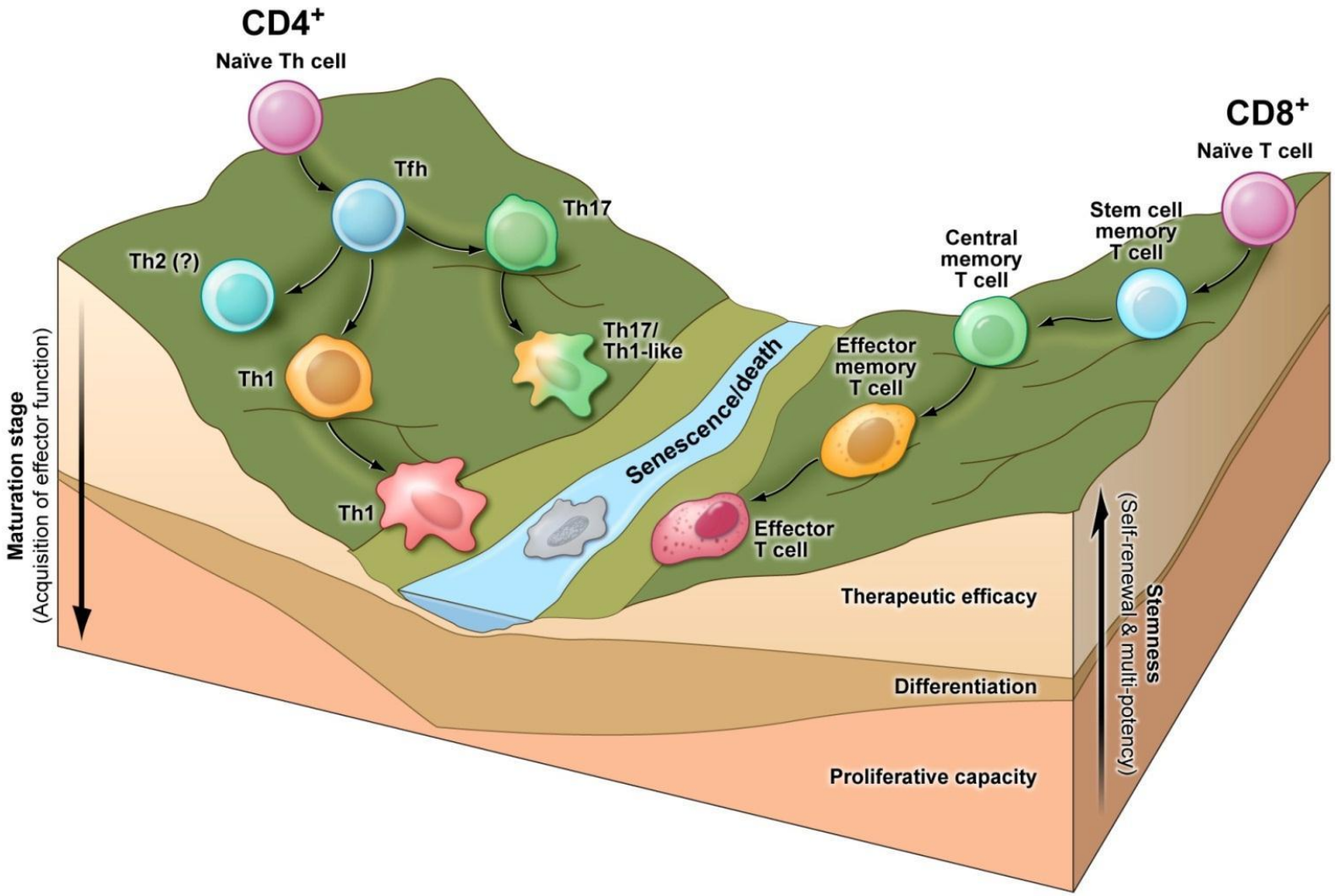
Current adoptive T cell-based immunotherapies

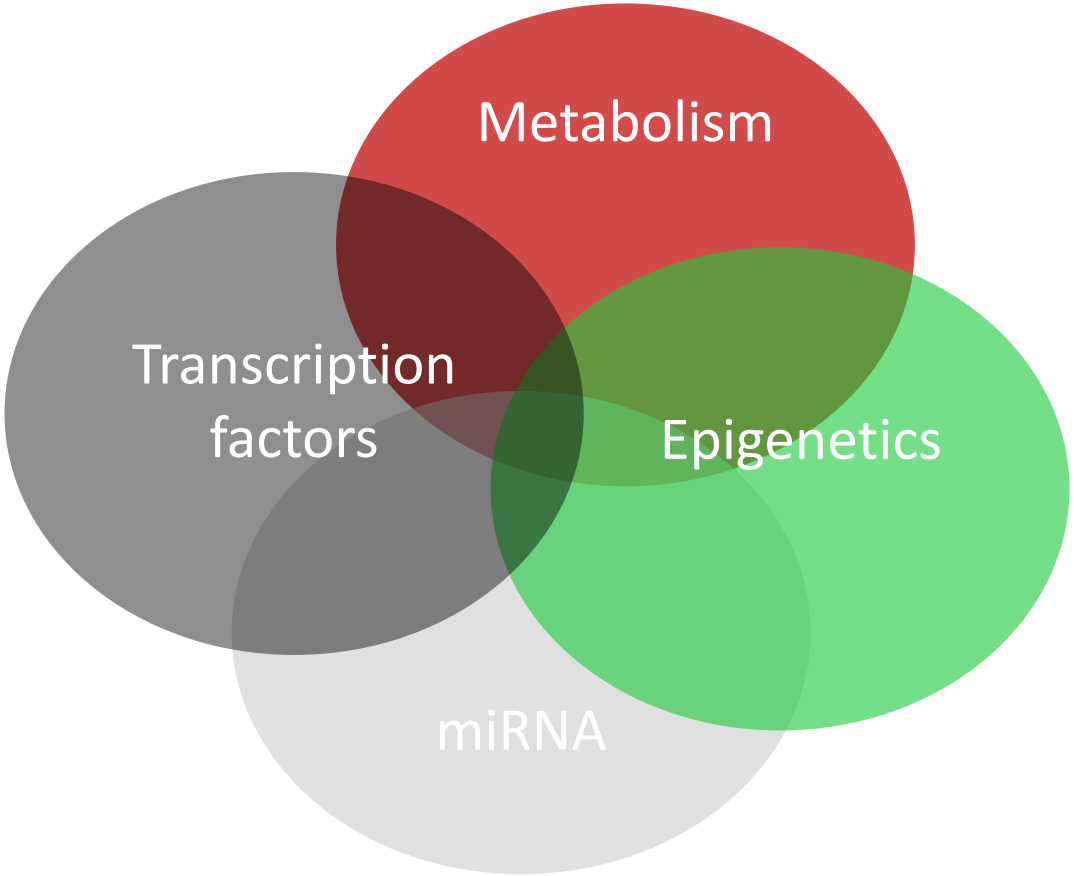


T cell differentiation is accompanied by a progressive loss of antitumor efficacy

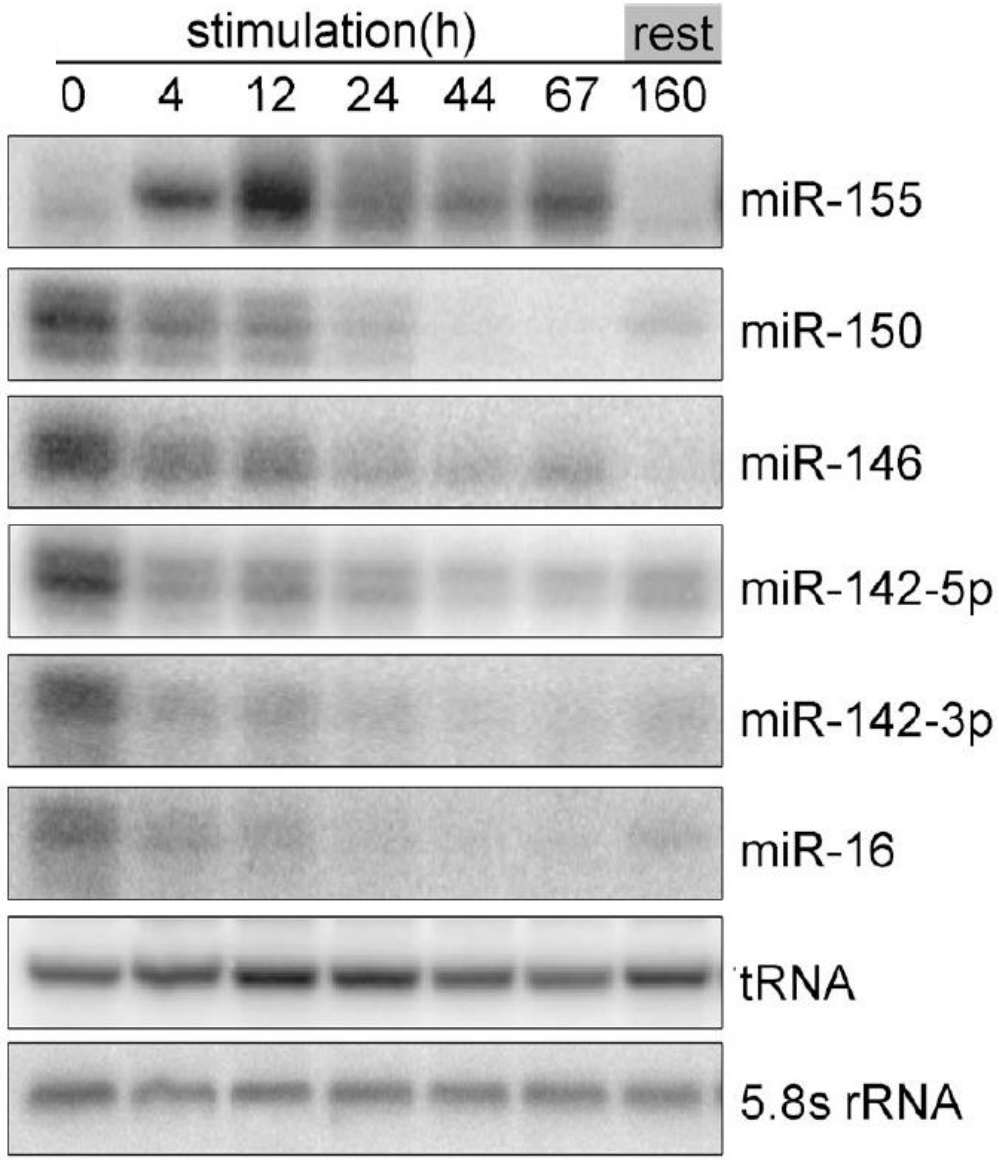


Gattinoni *et al*. *Nature Rev Immunol* 2012

Understanding the mechanisms regulating T cell differentiation

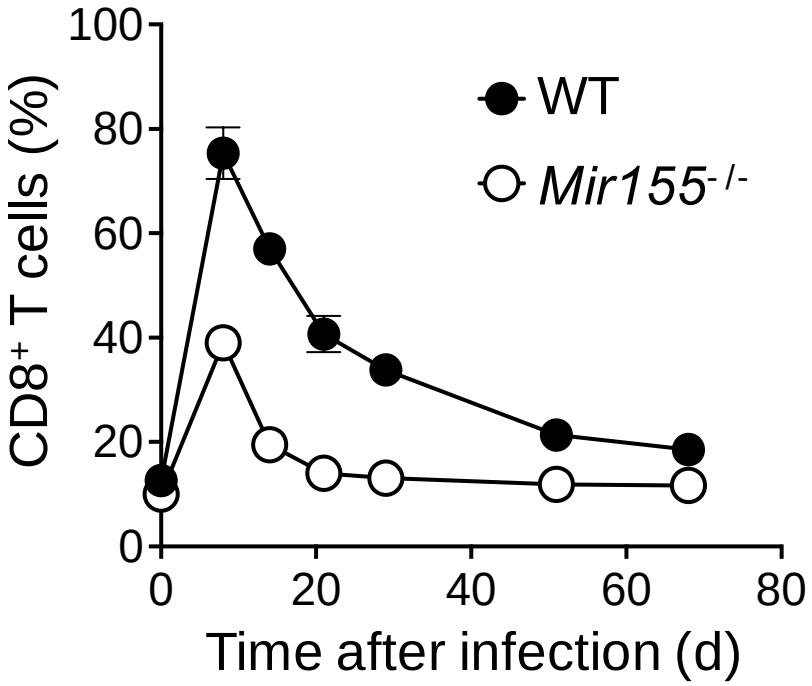


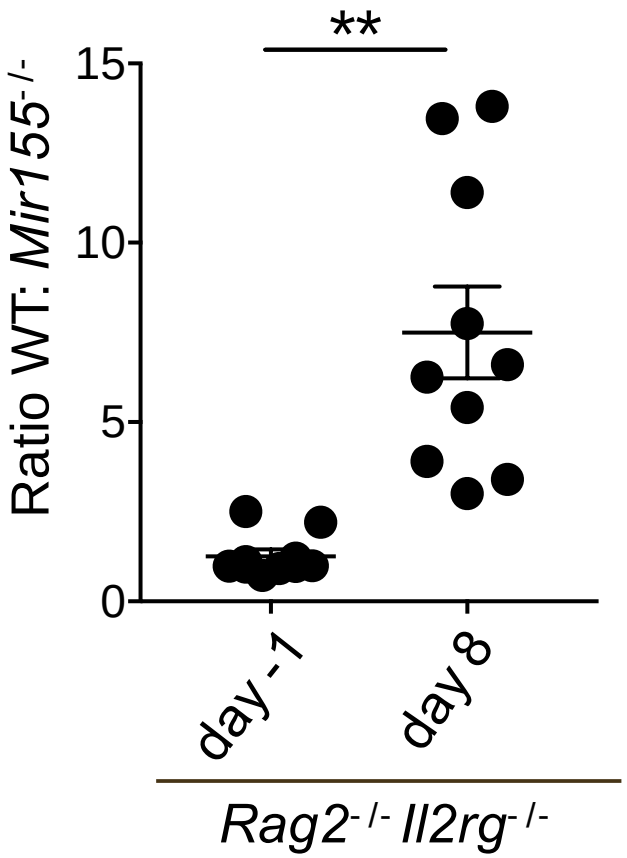
Elucidating the role of miR-155 in CD8$^+$ T cell immunity



Bronevetsky *et al*. *J. Exp. Med.* 2013

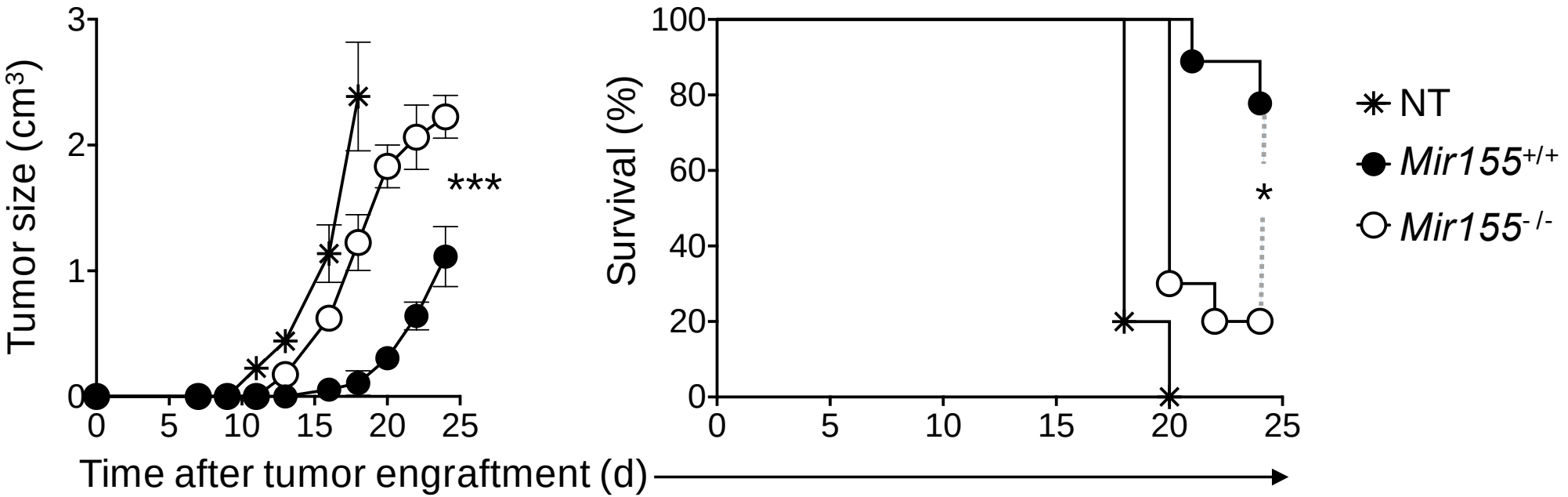
miR-155 is required to mount productive antiviral CD8$^+$ T cell responses





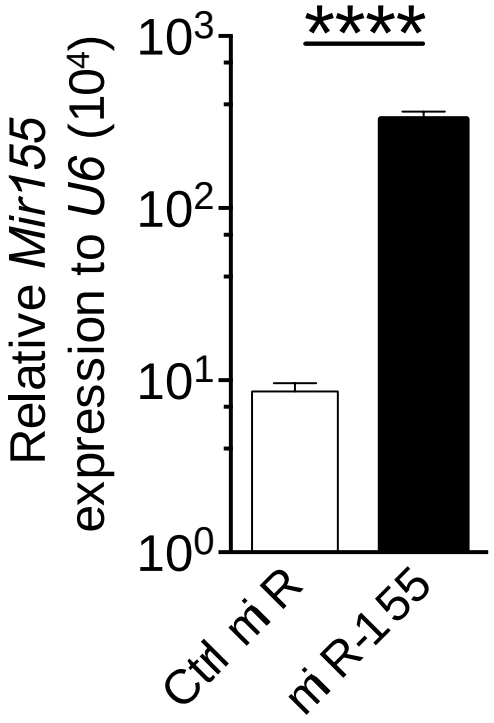
Dudda, Salaun, Ji *et al*. *Immunity 2013*

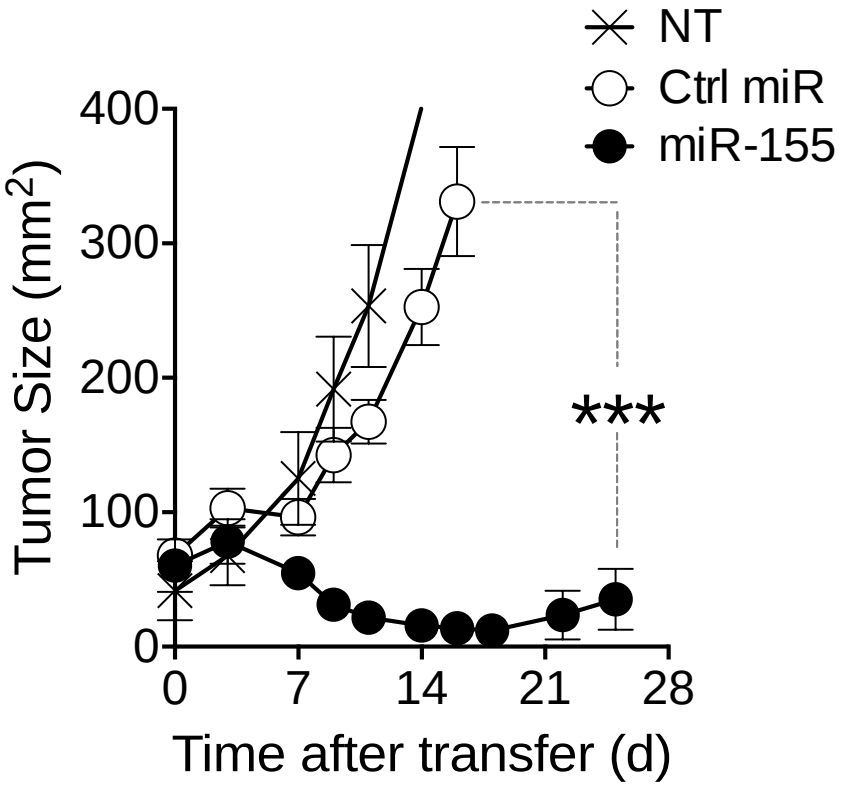
miR-155 is required to mount productive antitumor CD8$^+$ T cell responses



Dudda, Salaun, Ji *et al*. *Immunity 2013*

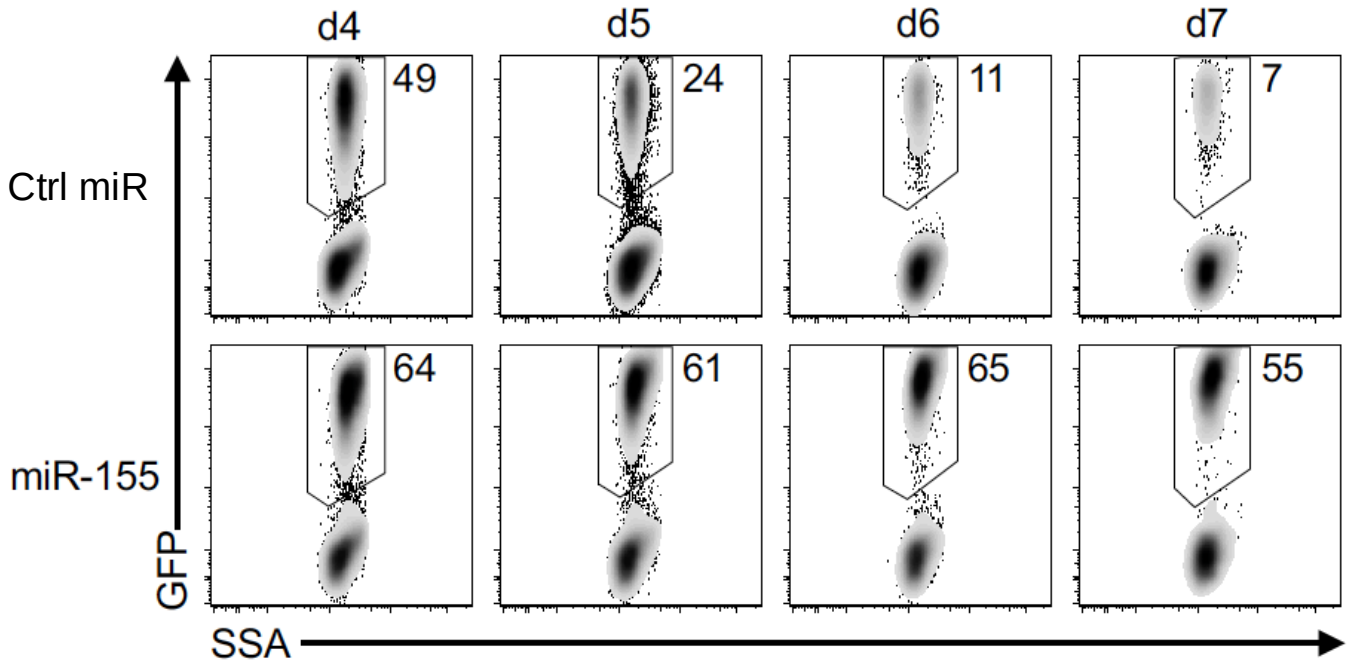
Enforced expression of miR-155 enhances T cell-based immunotherapy in lymphoreplete hosts

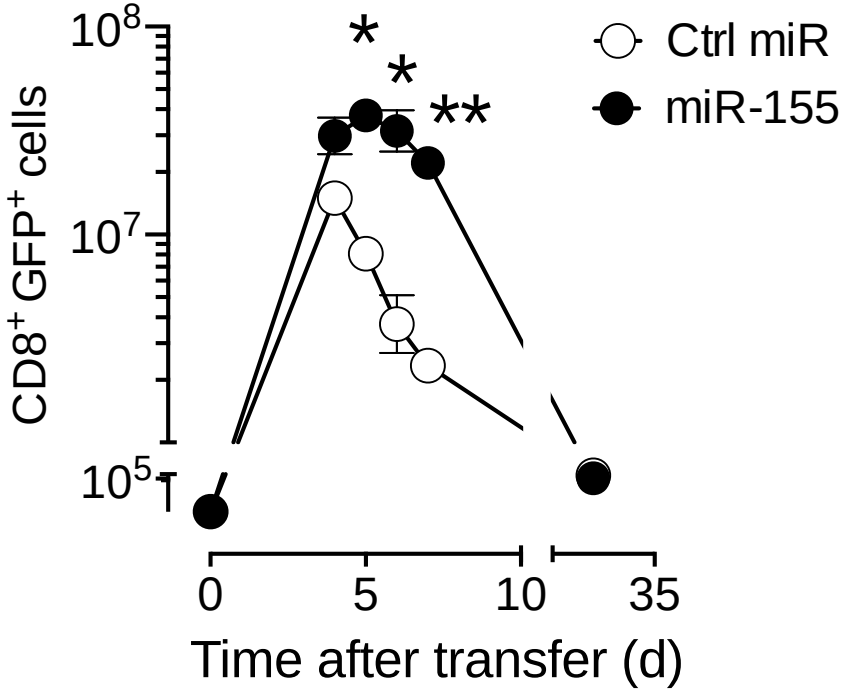




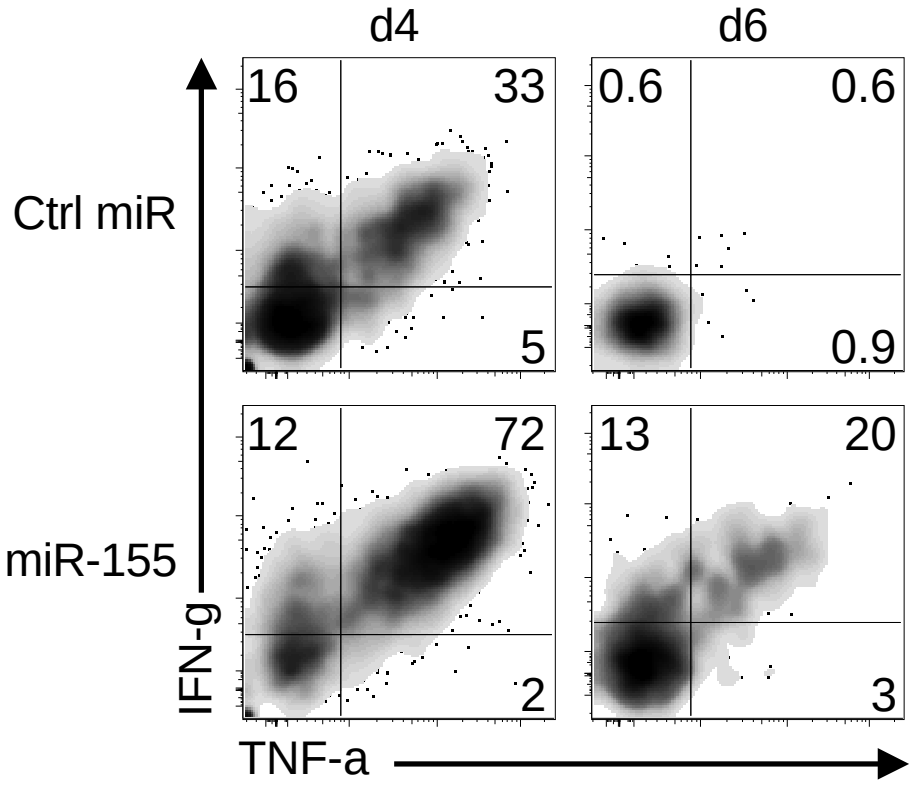
Ji *et al*. *PNAS 2015*

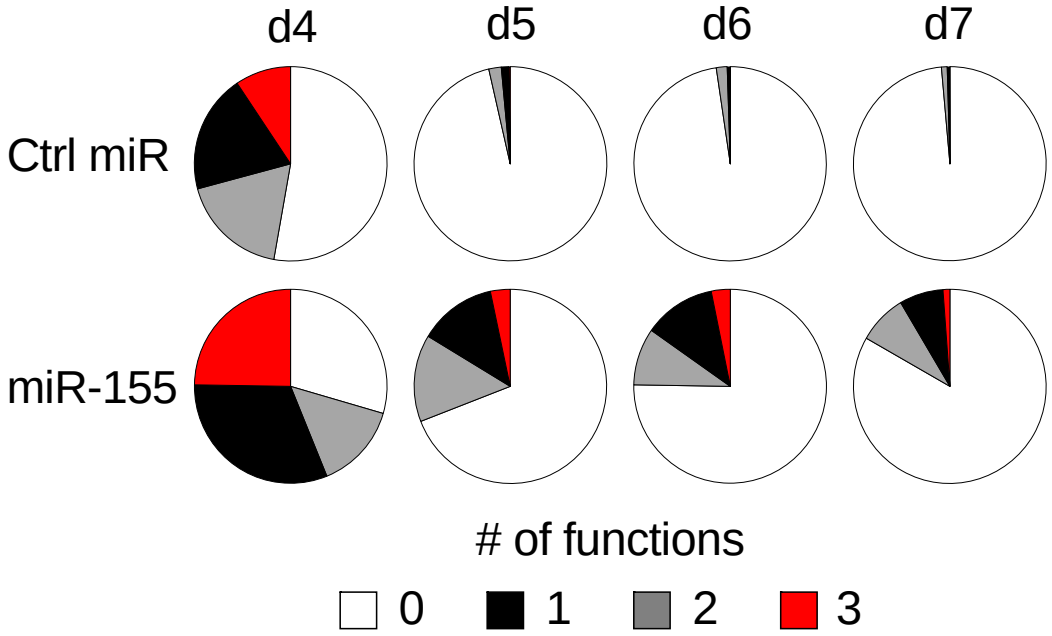
Enforced expression of miR-155 promotes T cell accumulation and persistence



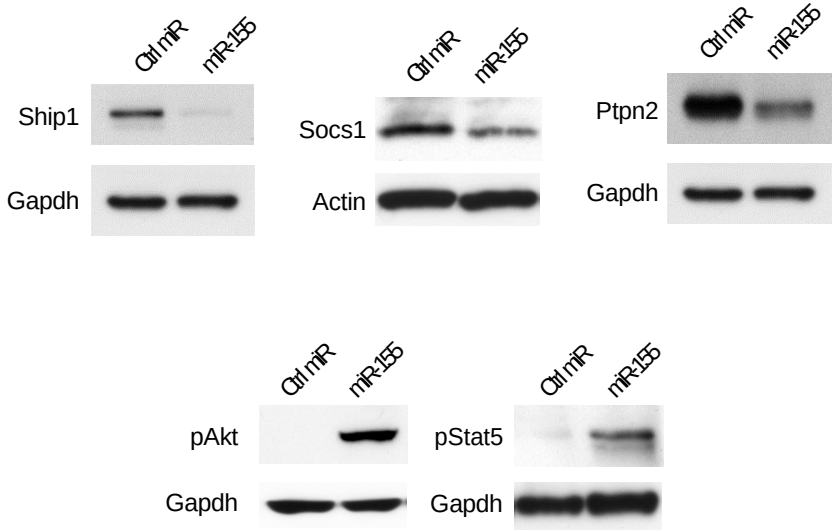


Enforced expression of miR-155 promotes sustained T cell effector function

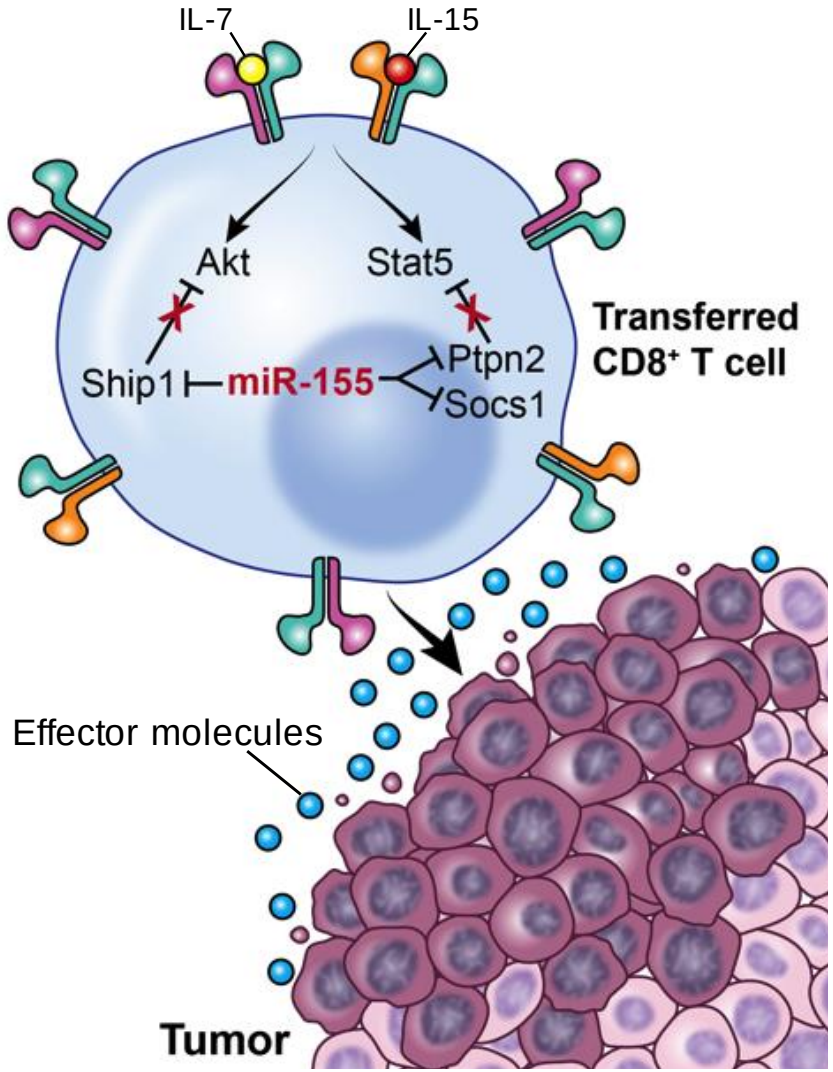




miR-155 augments CD8⁺ T cell antitumor activity by enhancing responsiveness to homeostatic cytokines



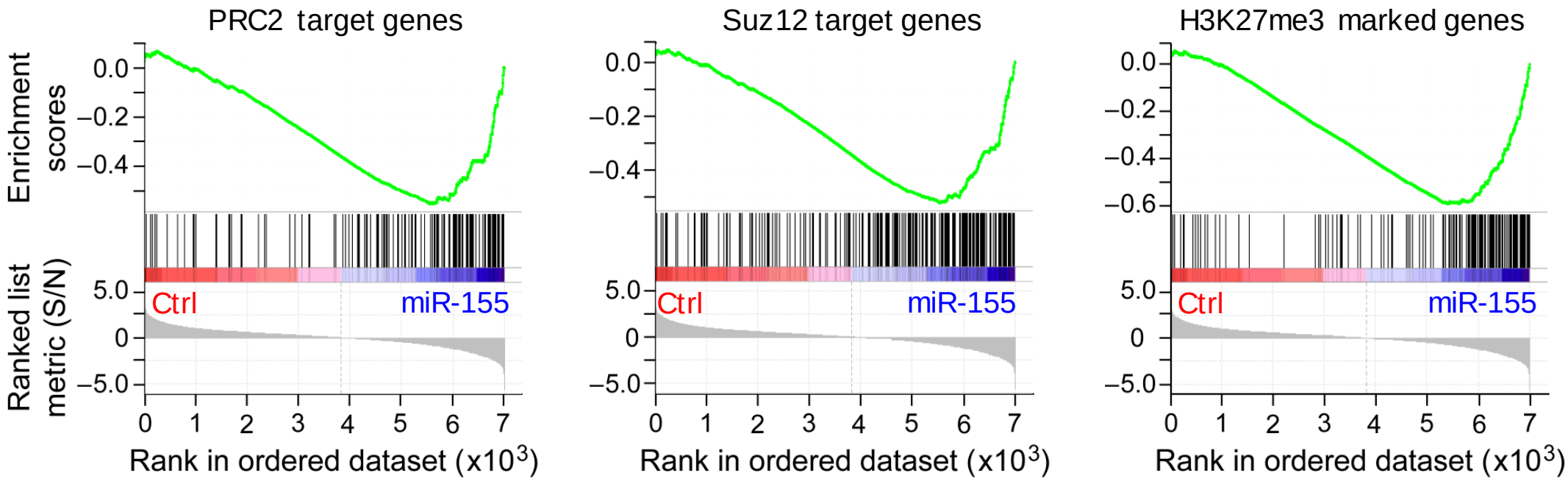
Ji et al. PNAS 2015



Adapted from Ji *et al*. *Oncoimmunology* 2015

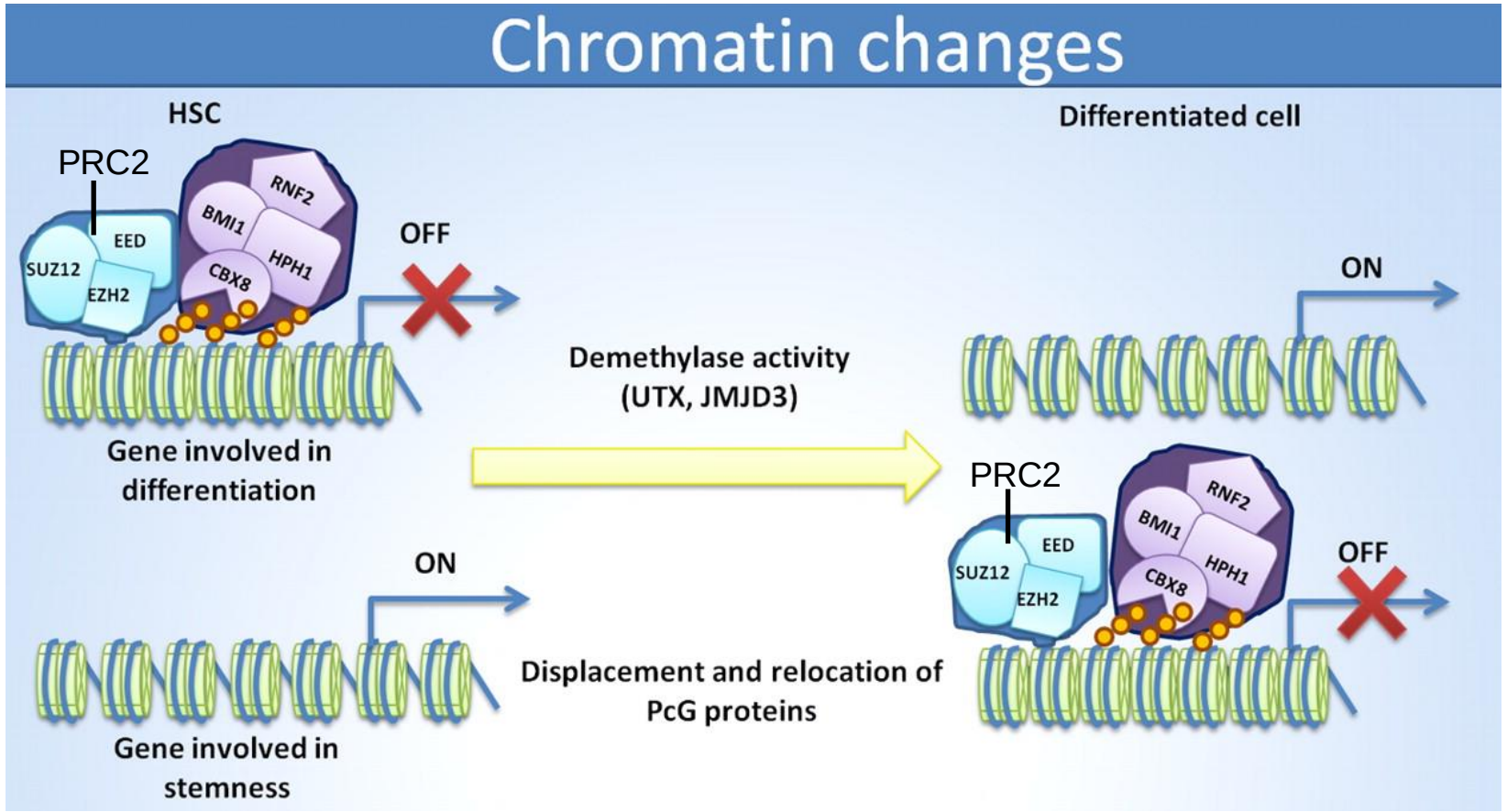
miR-155 CD8^{+} T cells have reduced expression of genes silenced by Polycomb Repressor Complex 2 (PRC2) in stem cells

- *Ex vivo* RNA-seq analysis of miR-155 and Ctrl miR engineered CD8^{+} T cells



Ji, Fioravanti, Zhu *et al*. *Nature commun 2019*

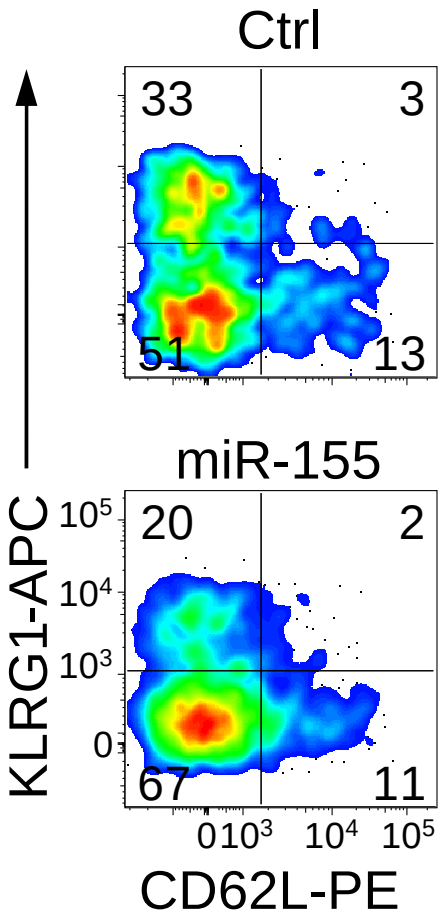
PRC2 suppresses pro-differentiating genes in stem cells and progenitor cells

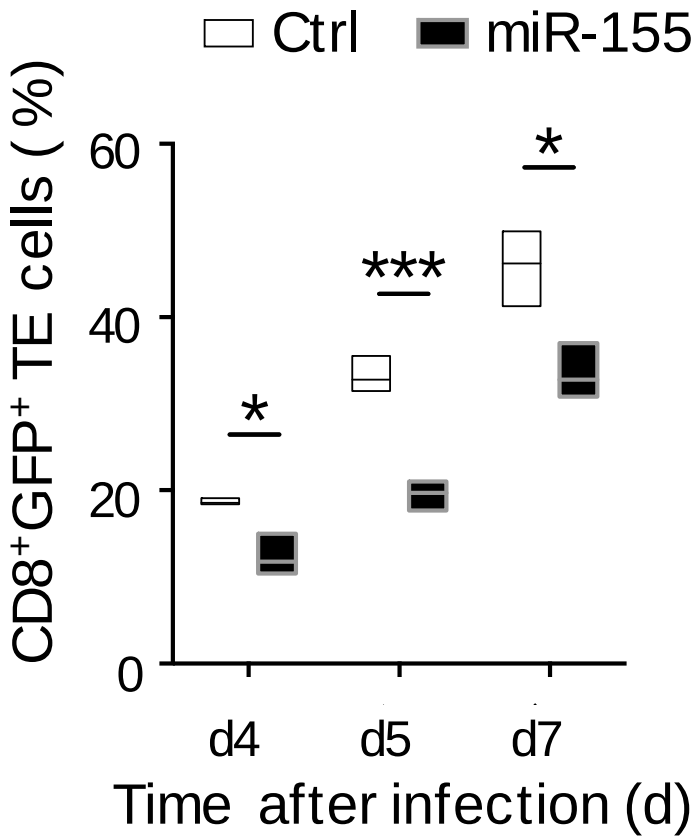


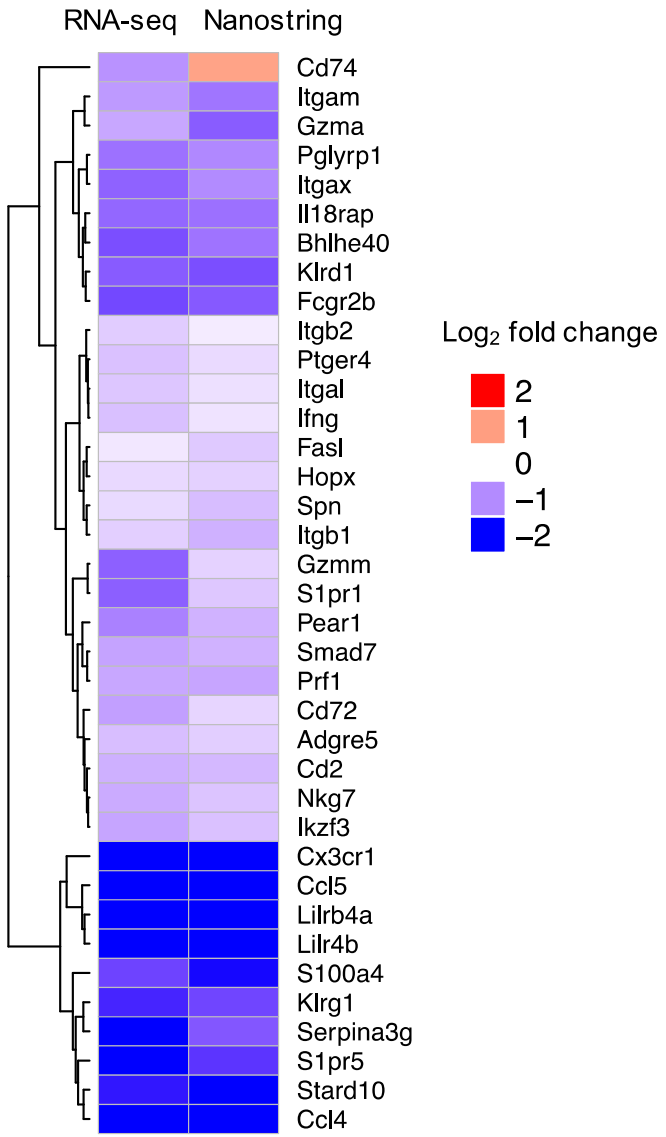
Martin-Perez D *Blood* 2010

Does miR-155 enhance PRC2 activity to limit $CD8^+$ T cell senescence and functional exhaustion?

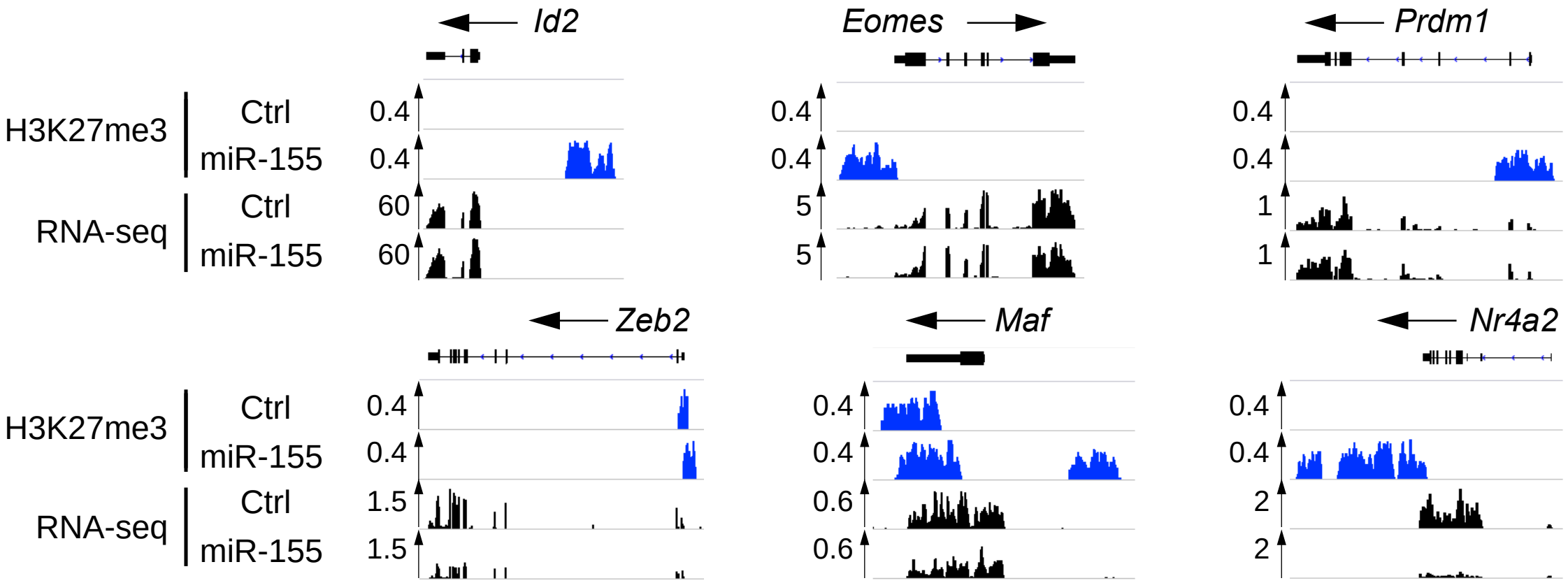
miR-155 overexpression limits CD8⁺ T cell senescence



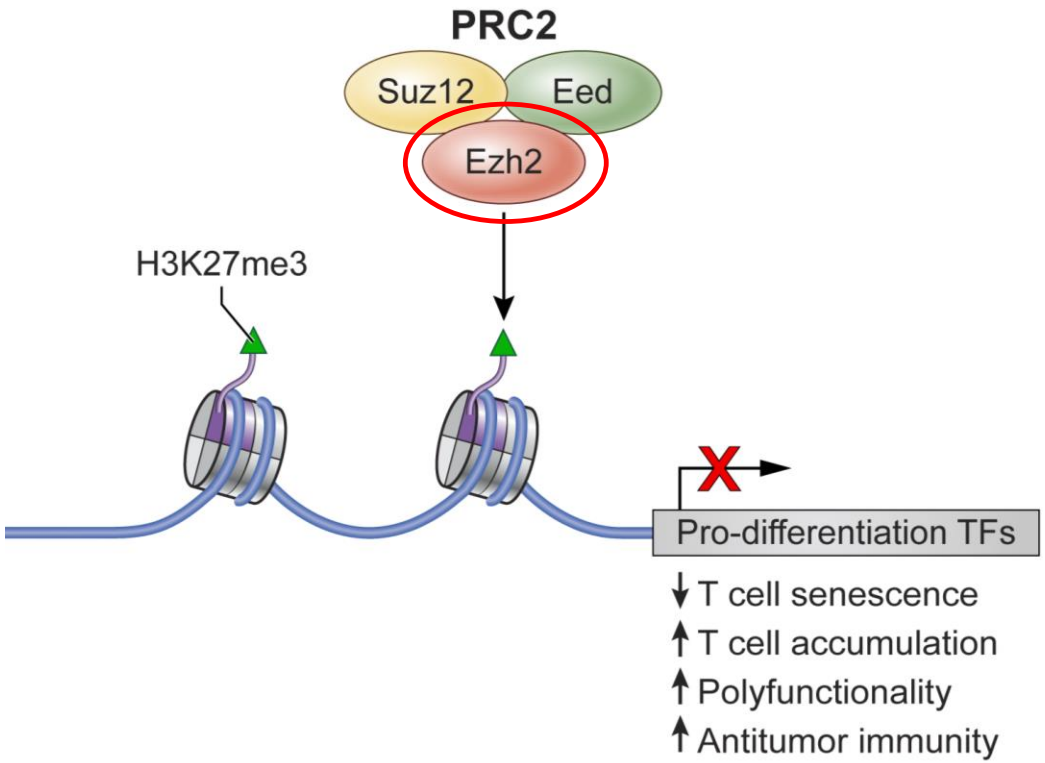




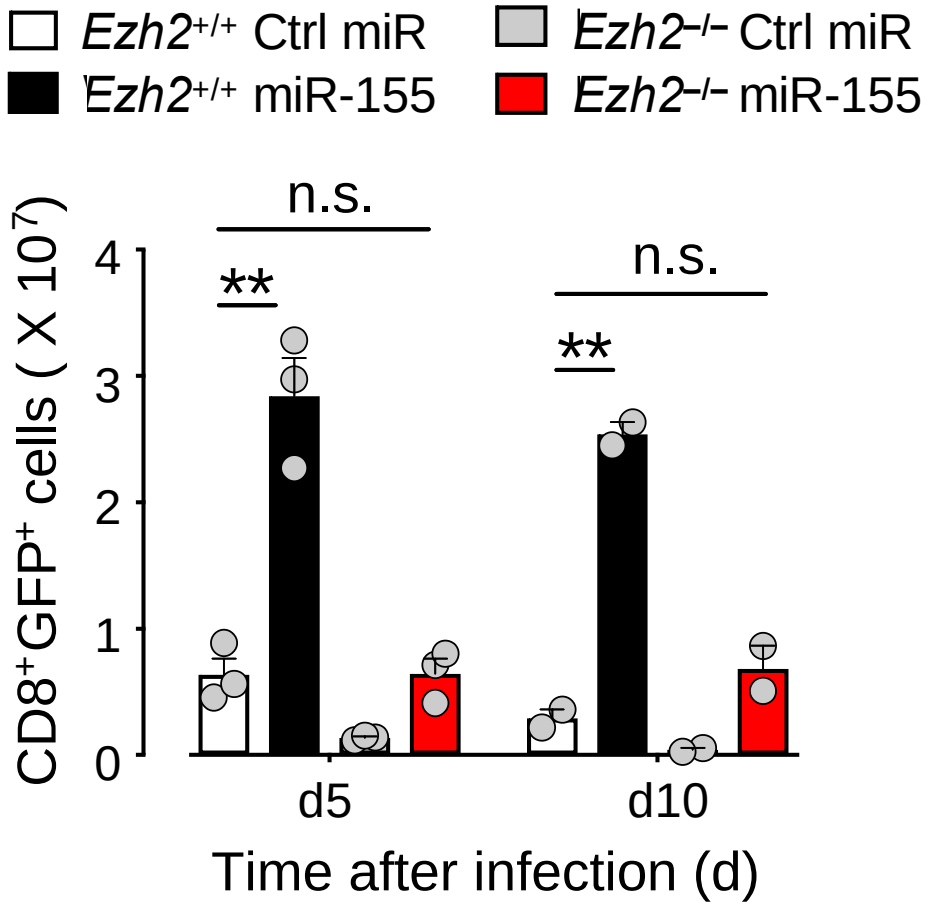
Key drivers of T cell differentiation and exhaustion are epigenetically repressed (H3K27me3) in miR-155 CD8^{+} T cells

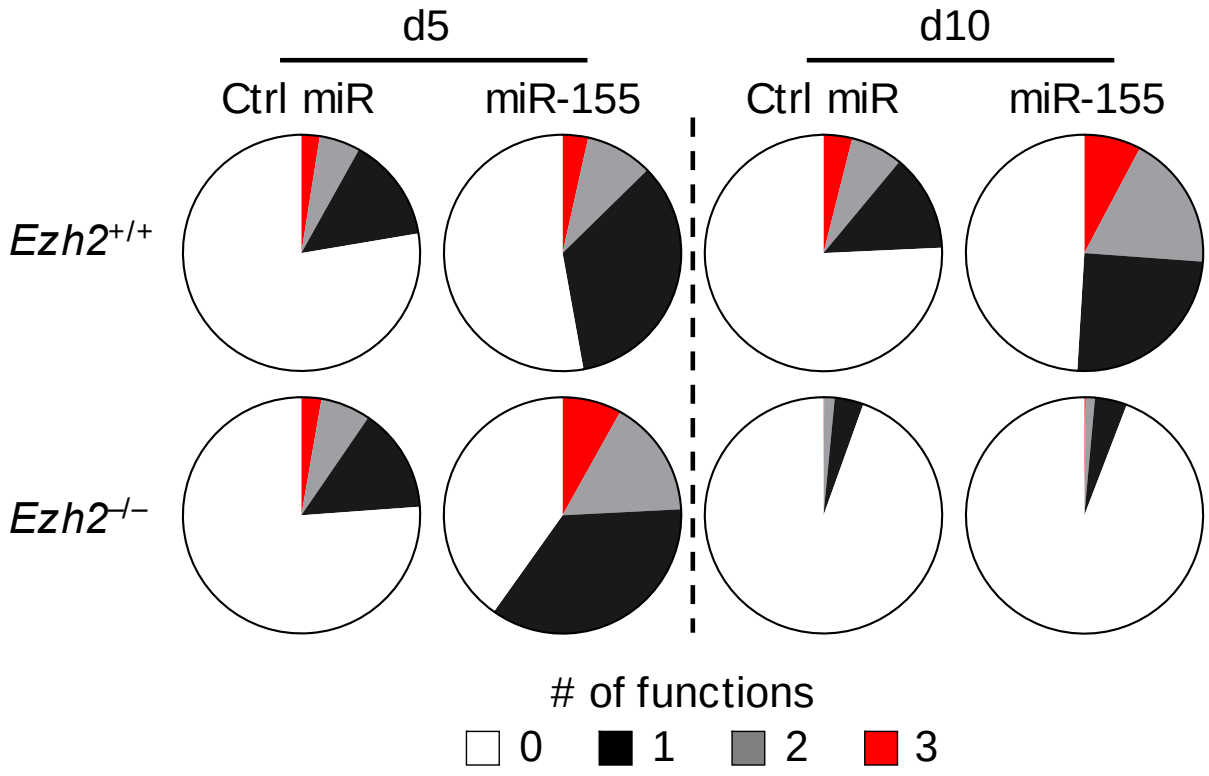


Is PRC2 essential for miR-155 activity?

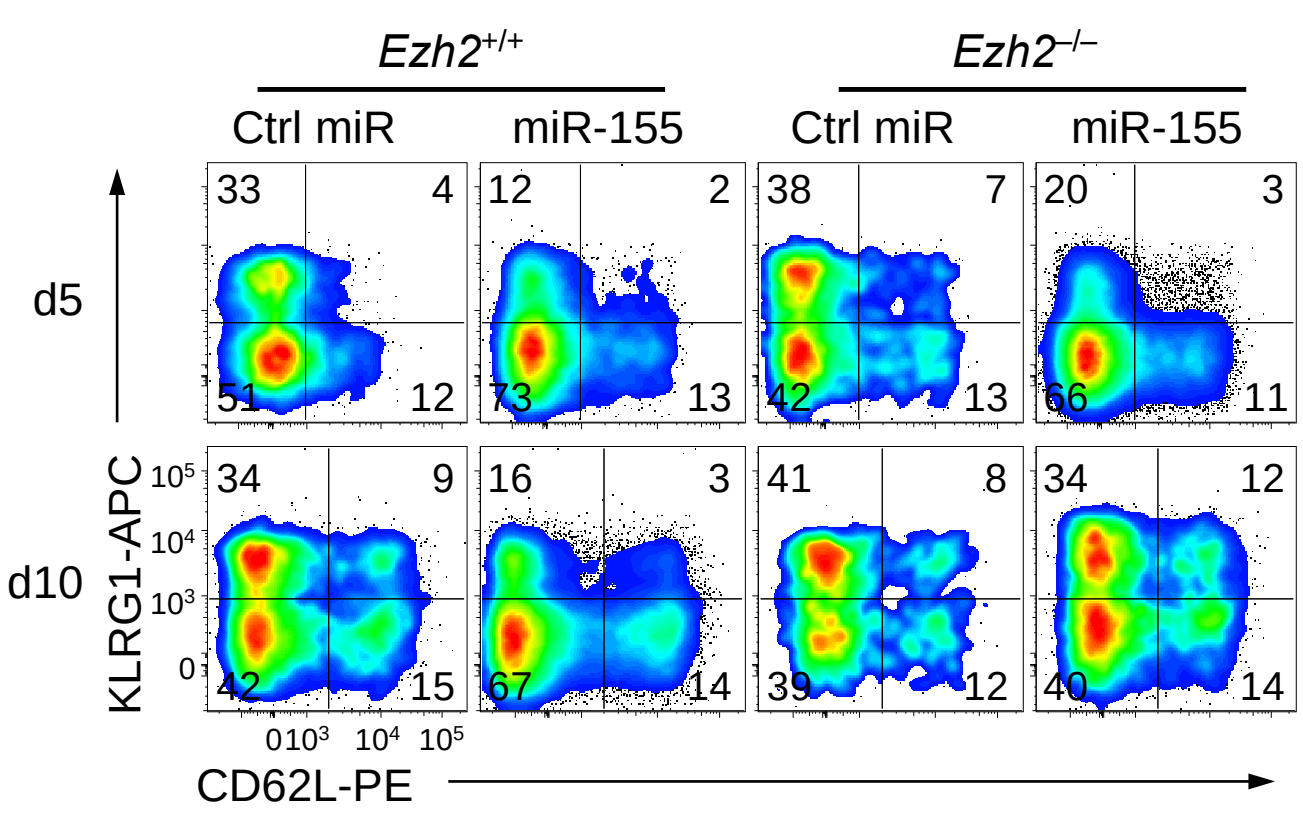


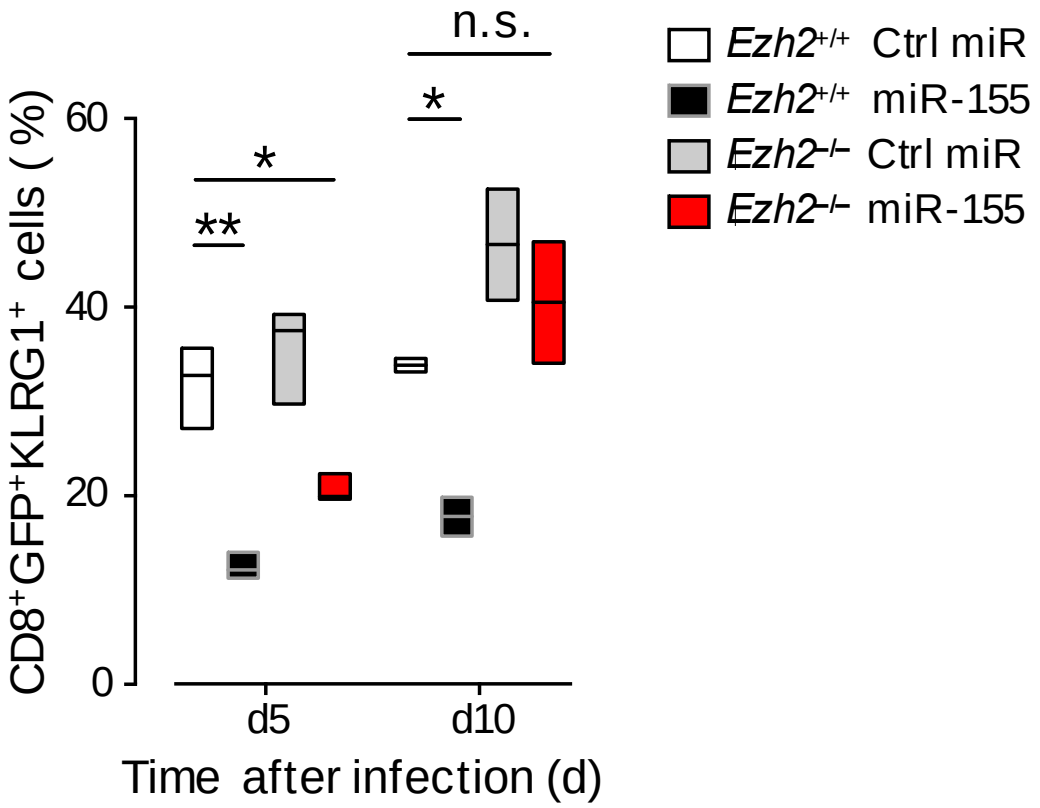
Ezh2 is essential to promote T cell expansion and sustained effector function in miR-155 T cells



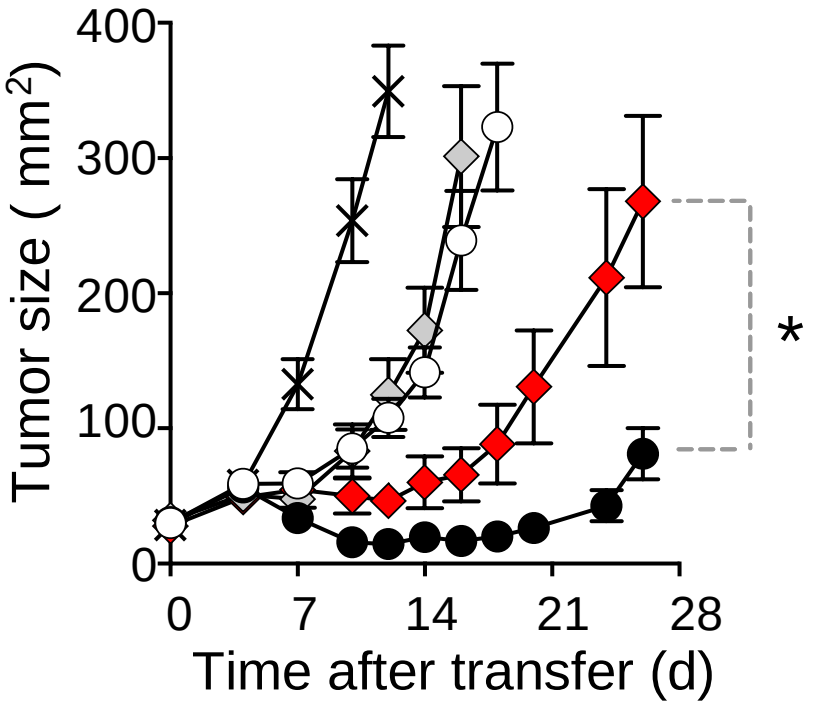


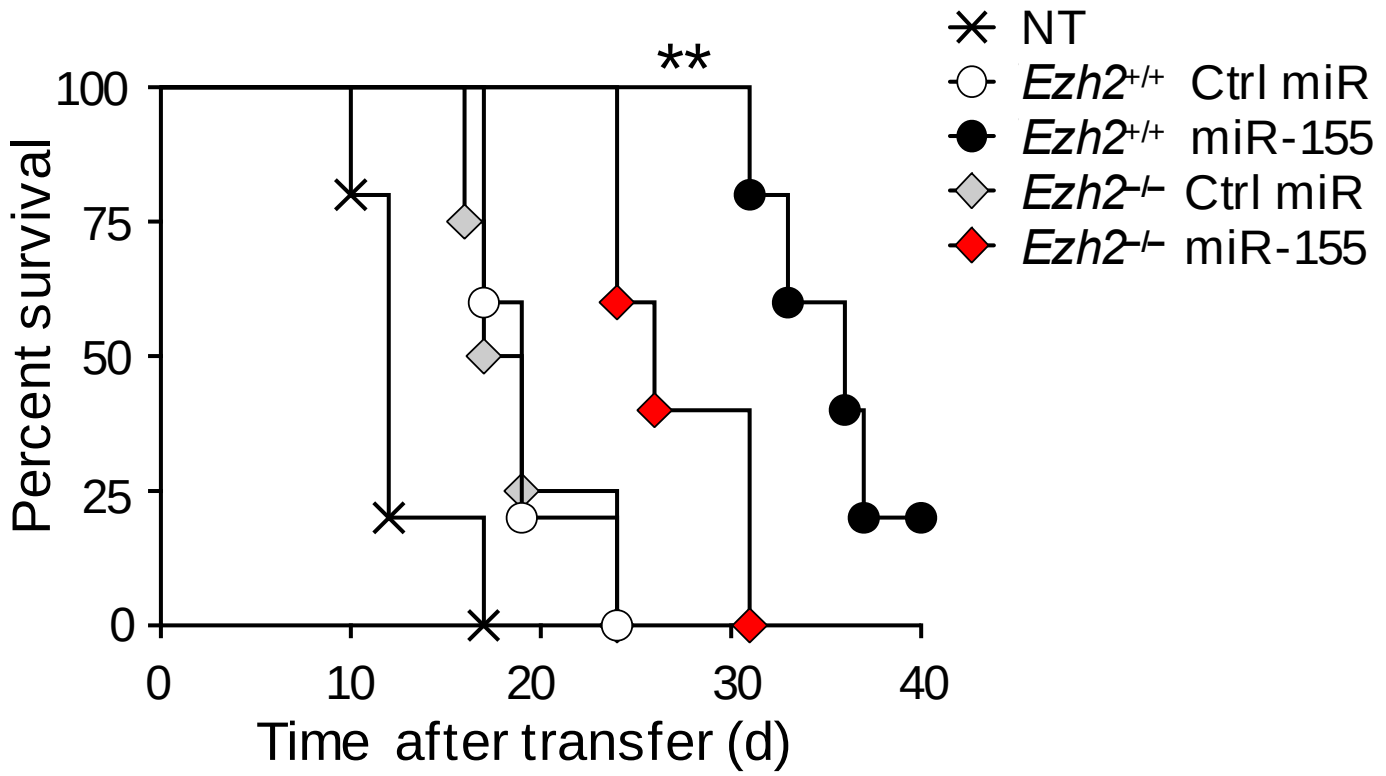
Ezh2 is required to restrain CD8⁺ T cell senescence in miR-155 T cells



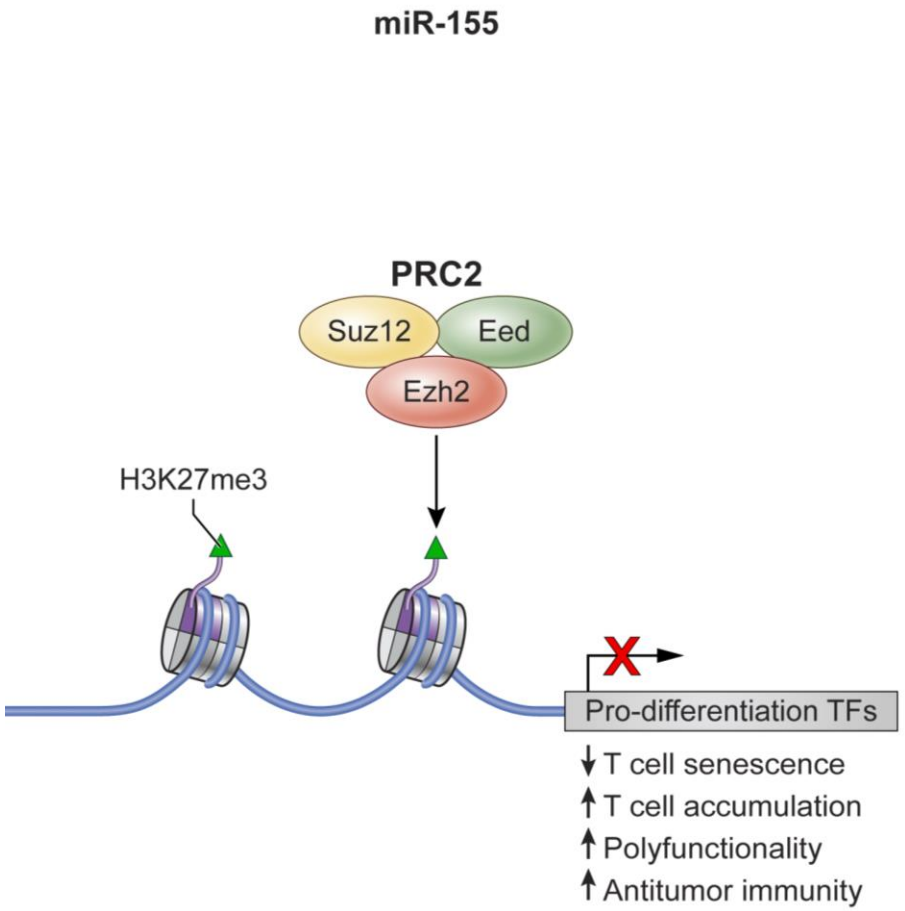


Productive antitumor responses mediated by miR-155 CD8$^+$ T cells require Ezh2





How does miR-155 enhance PRC2 activity?



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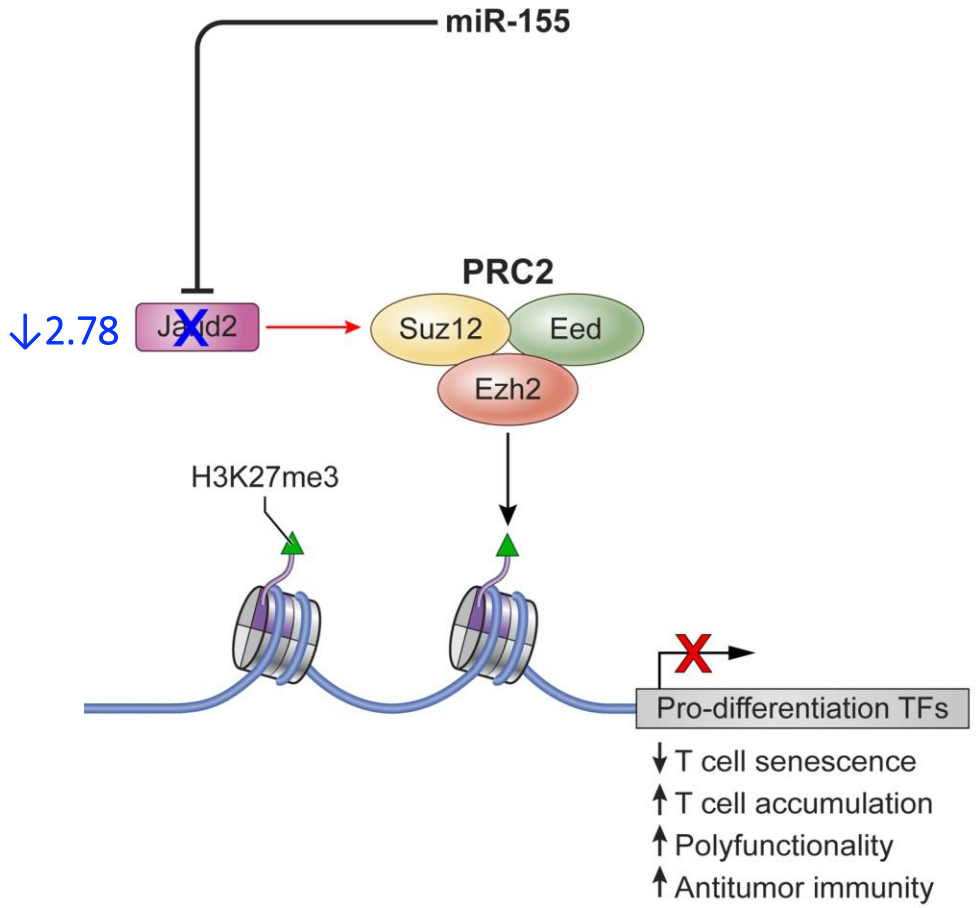

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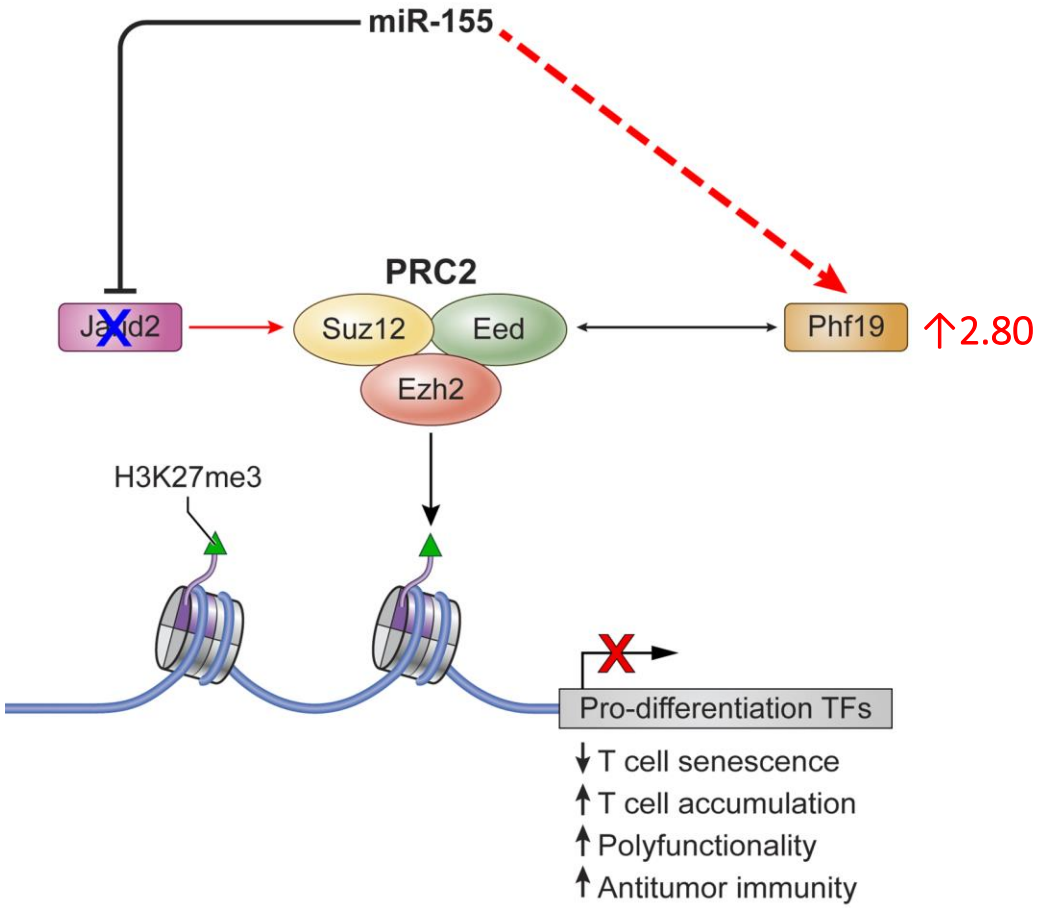
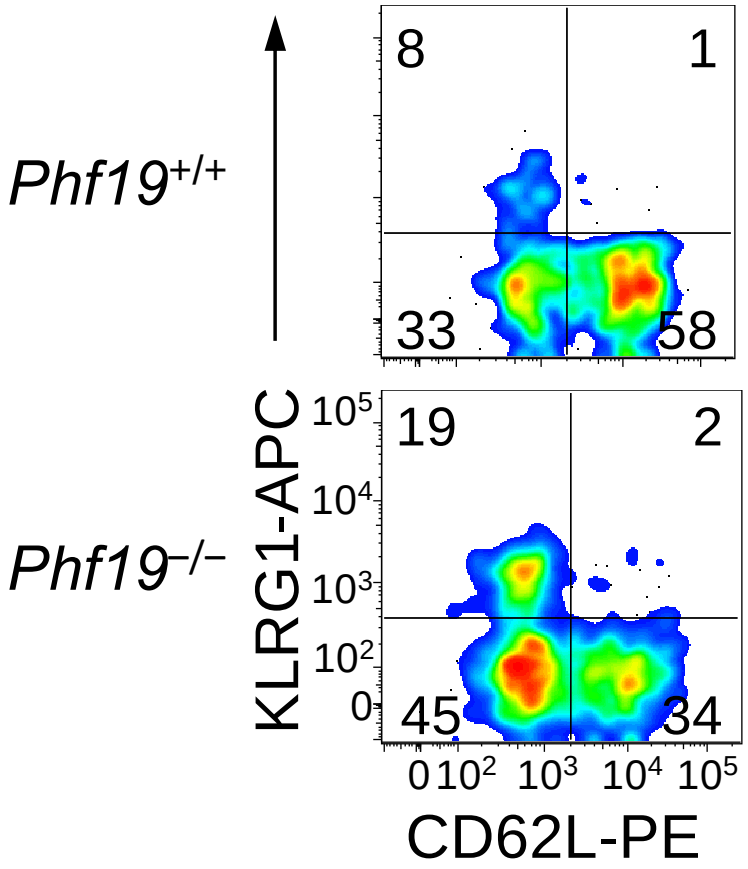
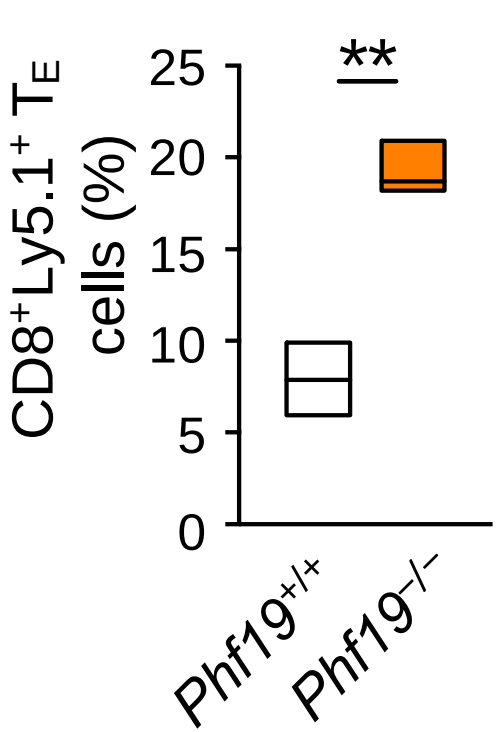
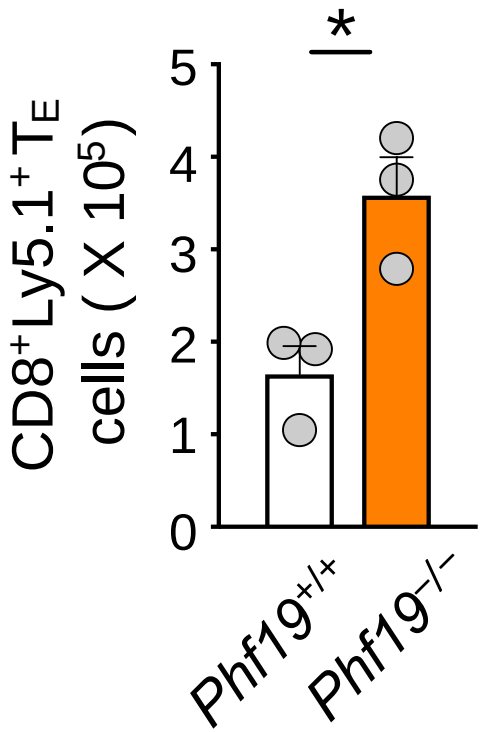


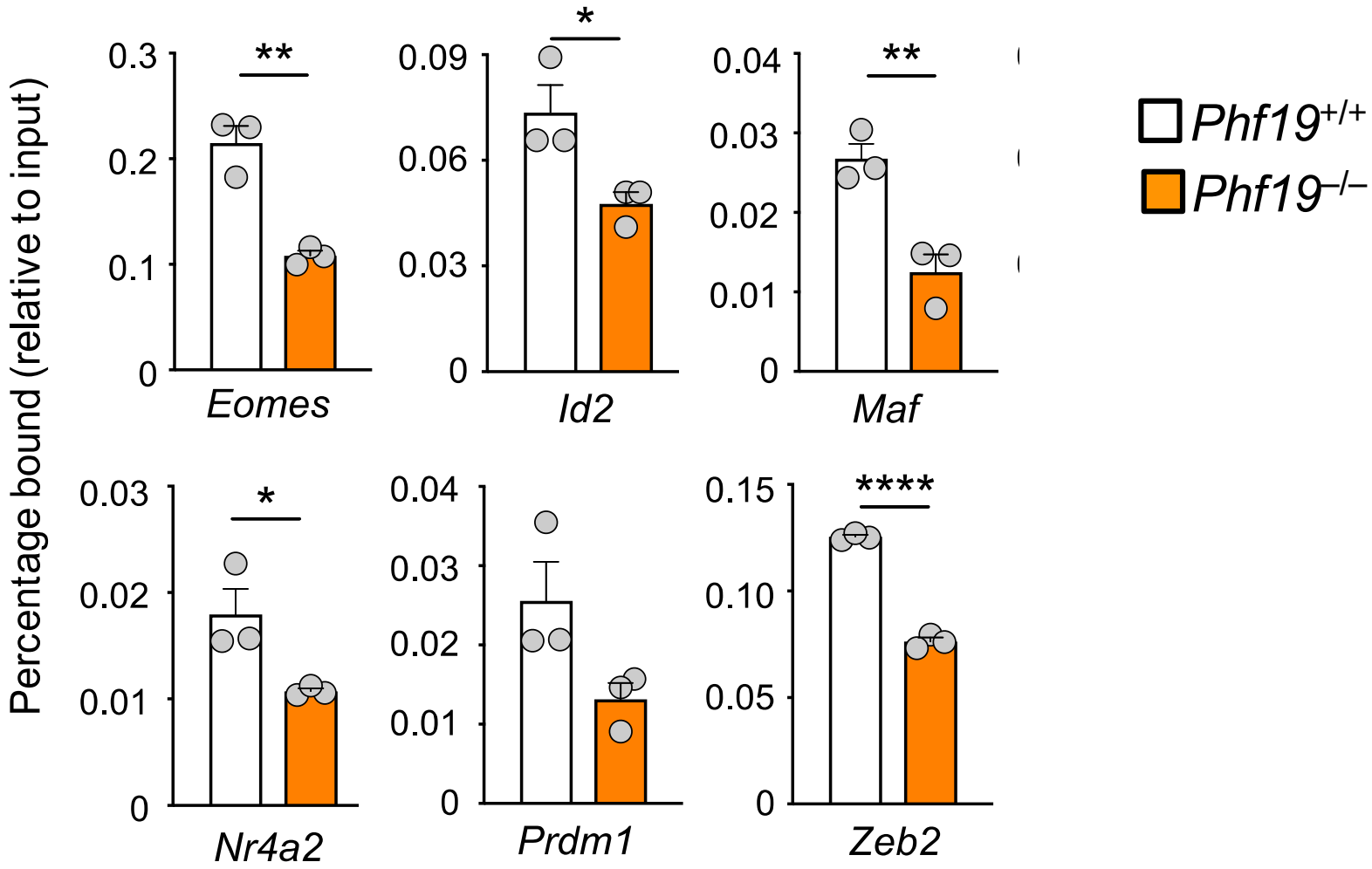
Phf19 restrains CD8⁺ T cell senescence



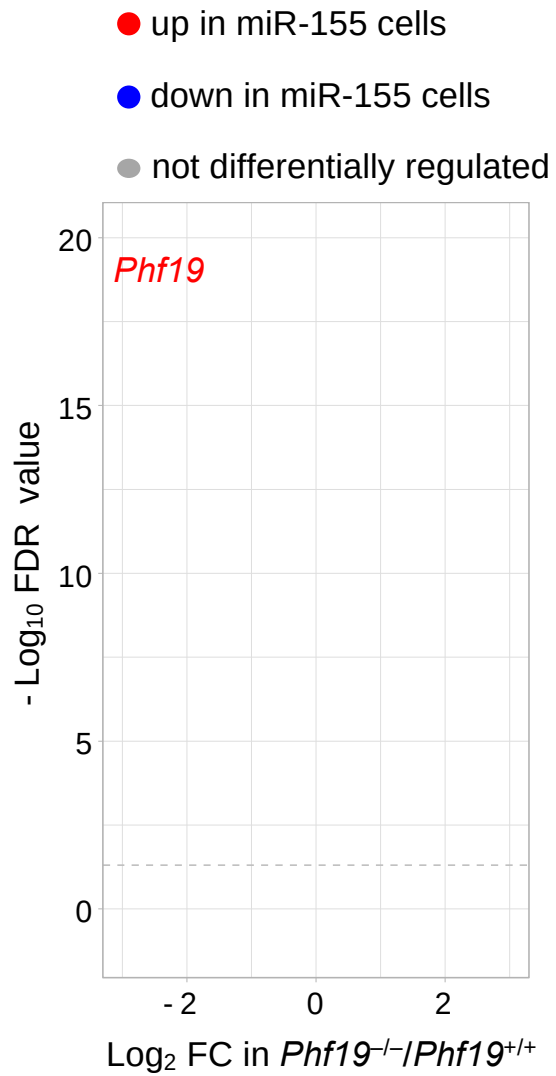


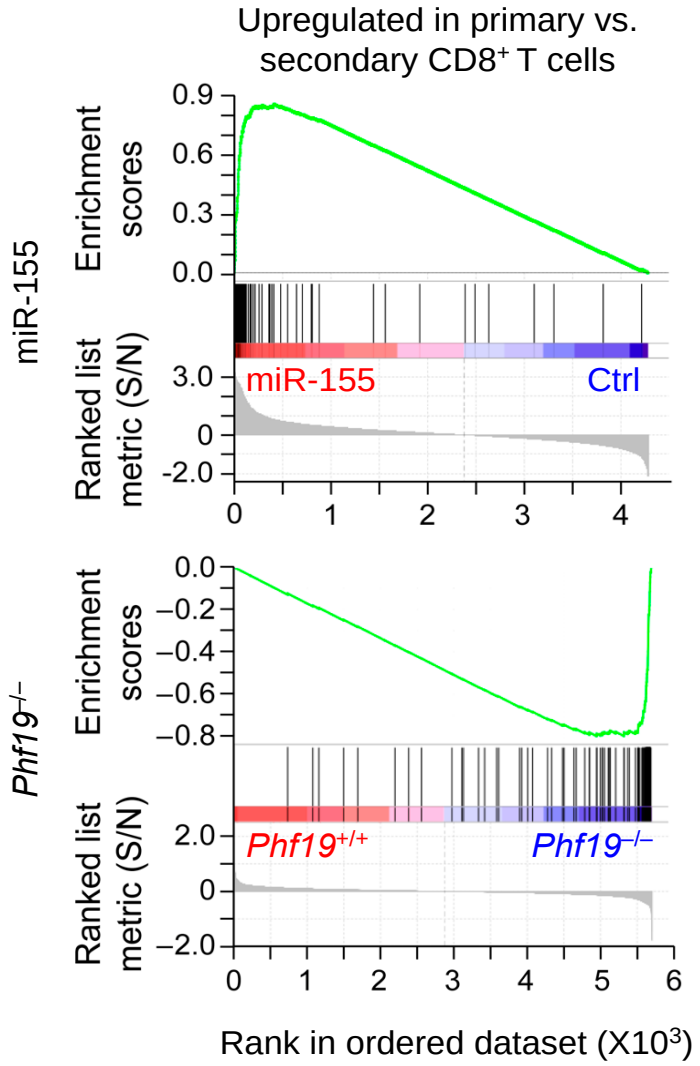


H3K27me3 deposition at key drivers of T cell differentiation and exhaustion is reduced in the absence of Phf19

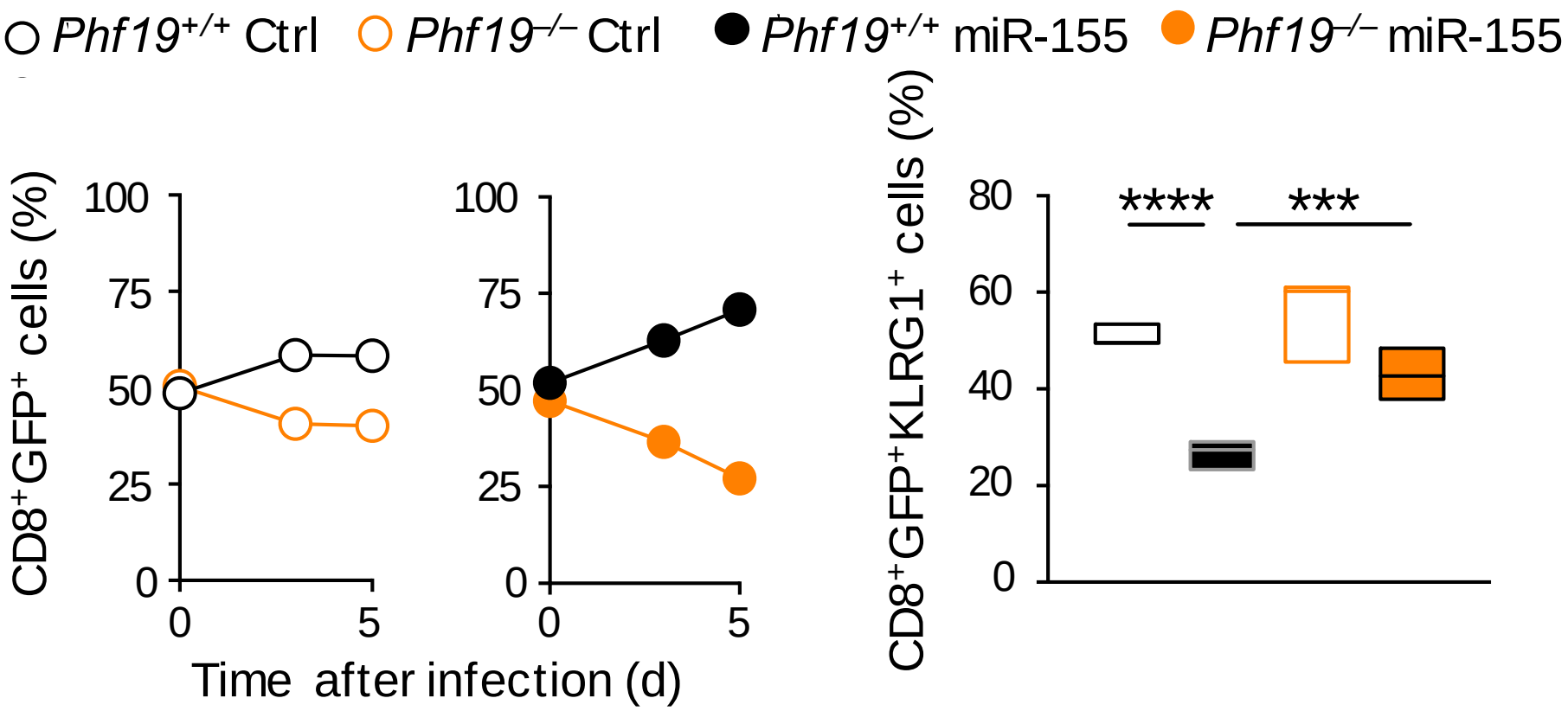


Phf19 orchestrates a shared transcriptional program with miR-155

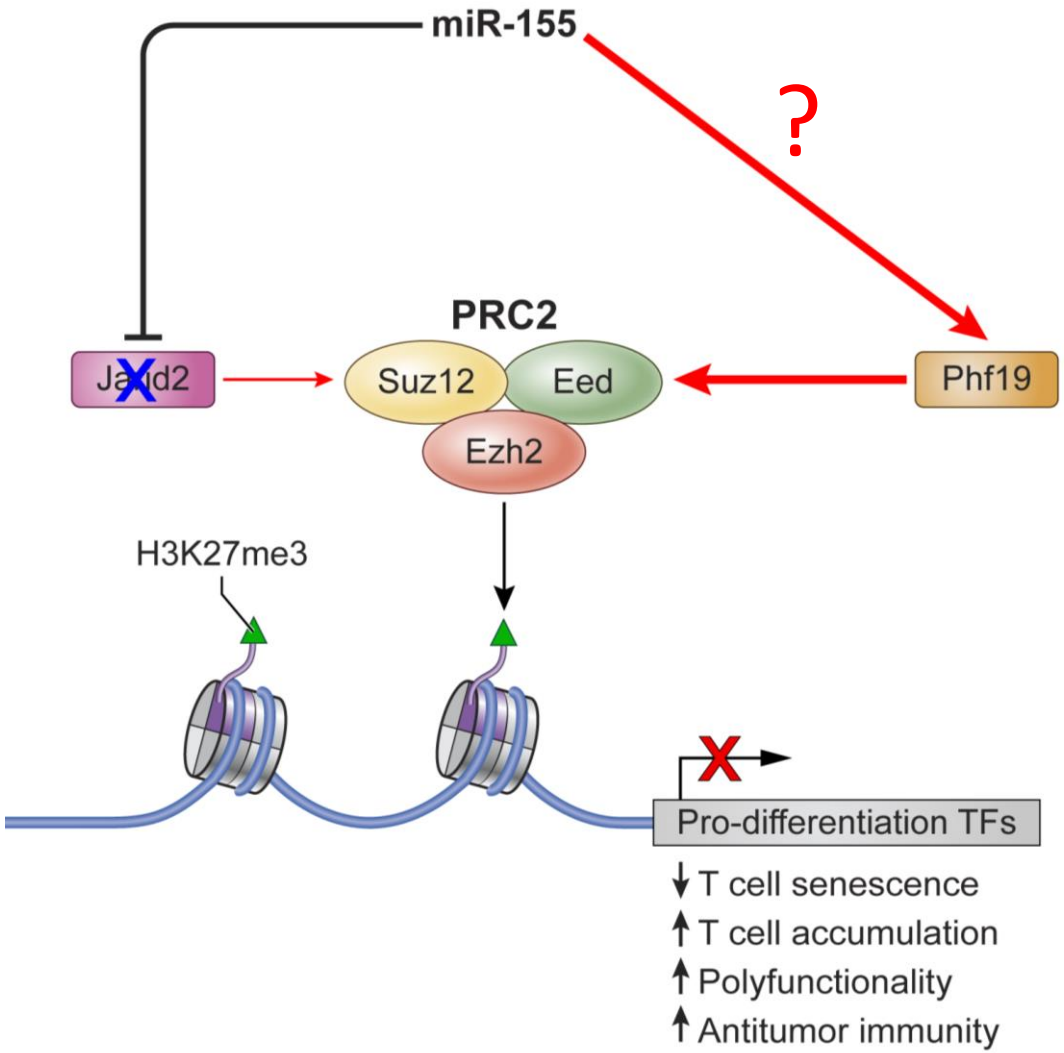




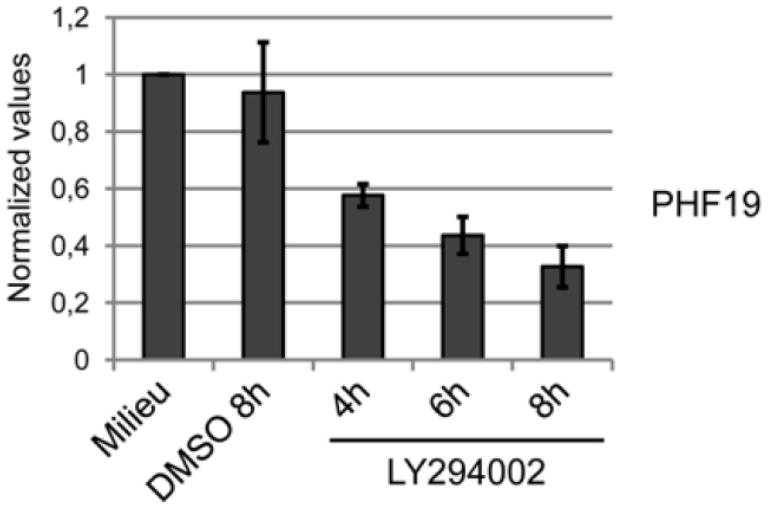
Phf19 is required to promote T cell expansion and restrain differentiation in miR-155 T cells



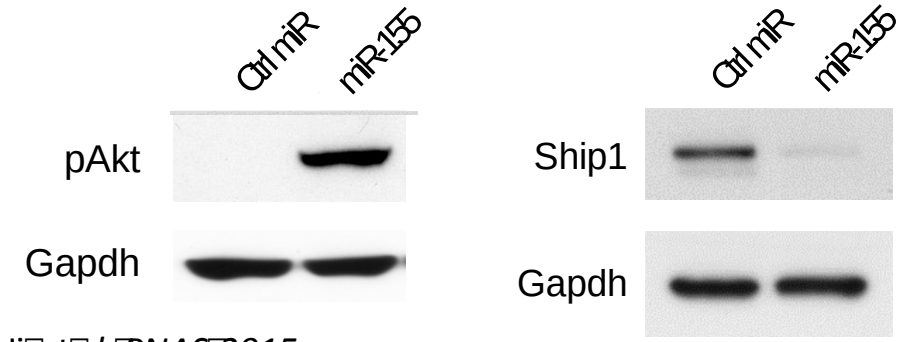
Phf19 acts downstream of miR-155 to regulate PRC2 function



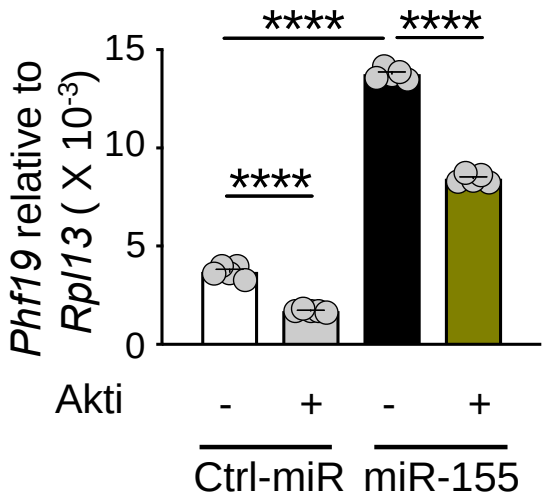
miR-155 promotes Phf19 expression by enhancing Akt signaling

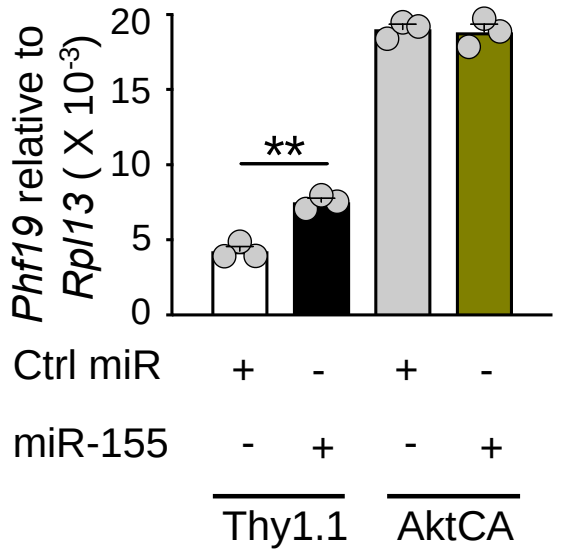


Ghislin S. et. al. *Cell Cycle* 2012

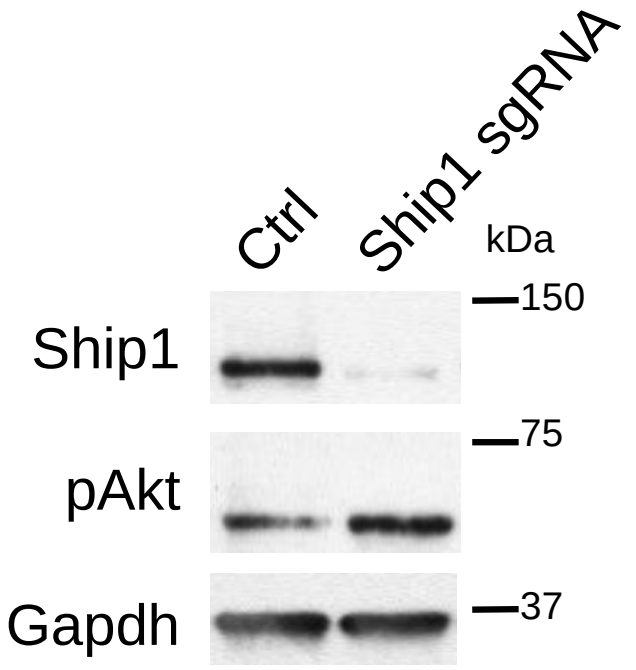


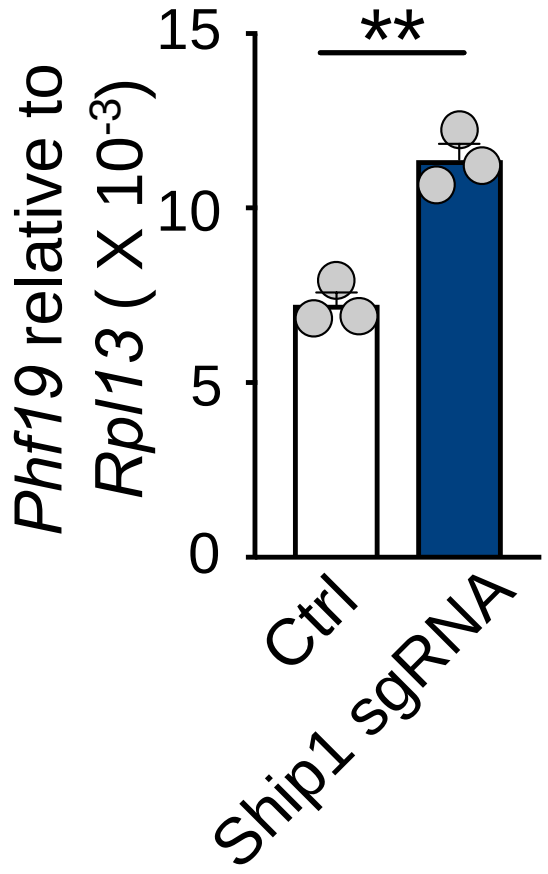
Ji et al. PNAS 2015



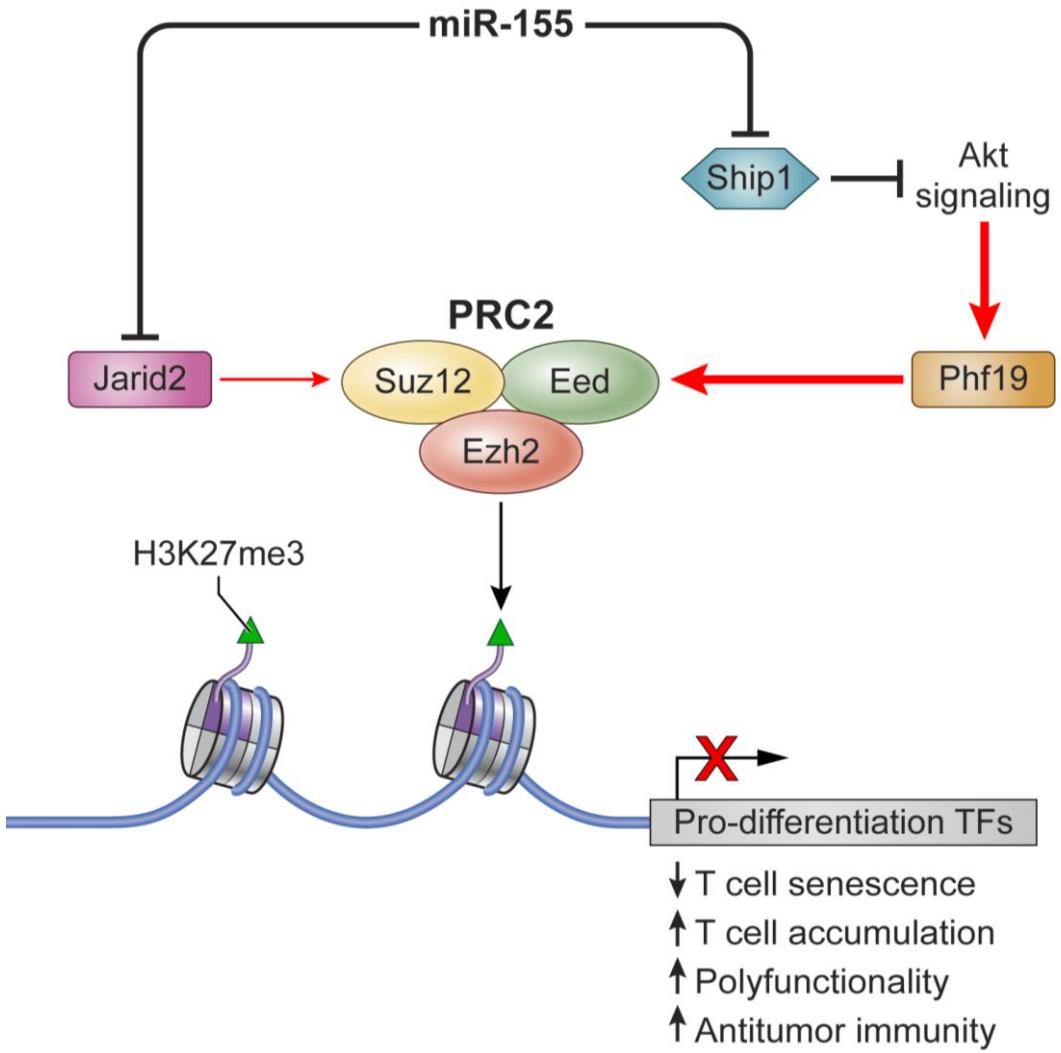


Ship1 knockdown enhances pAkt and upregulates *Phf19*

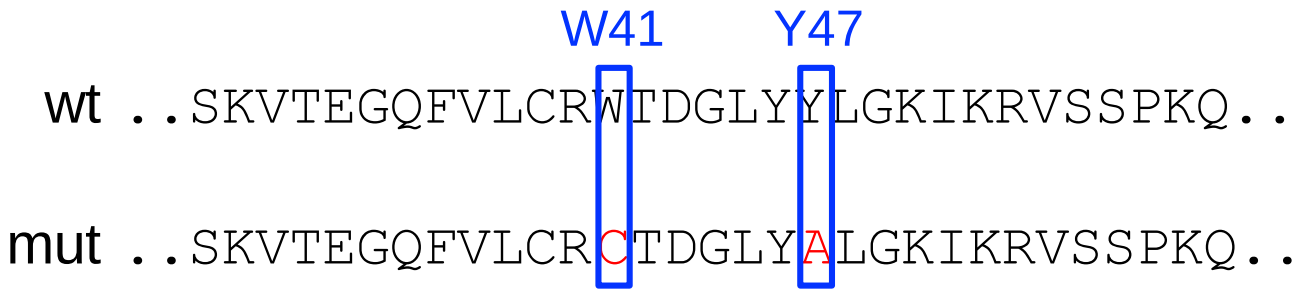


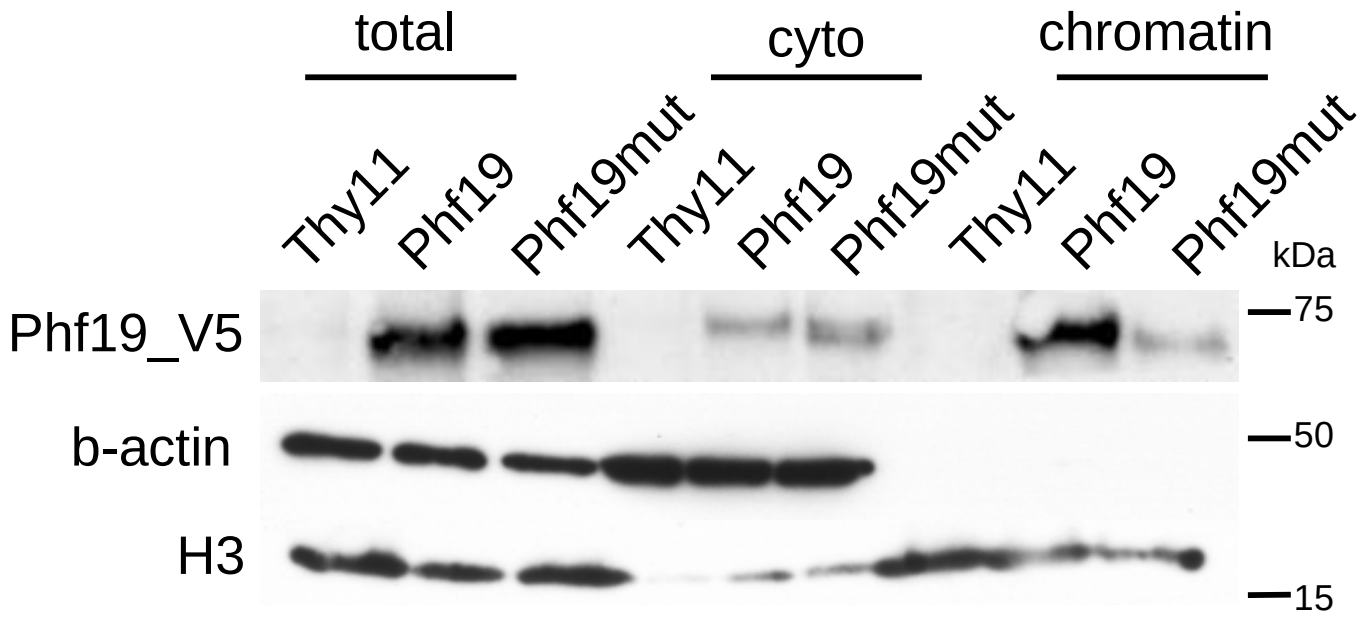


miR-155 promotes Phf19 expression by enhancing Akt signaling *via* downregulation of Ship1

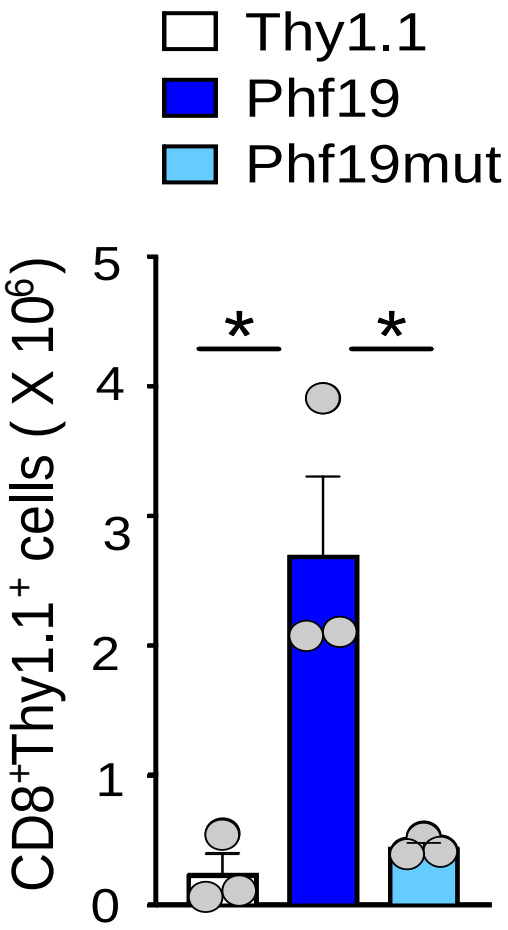


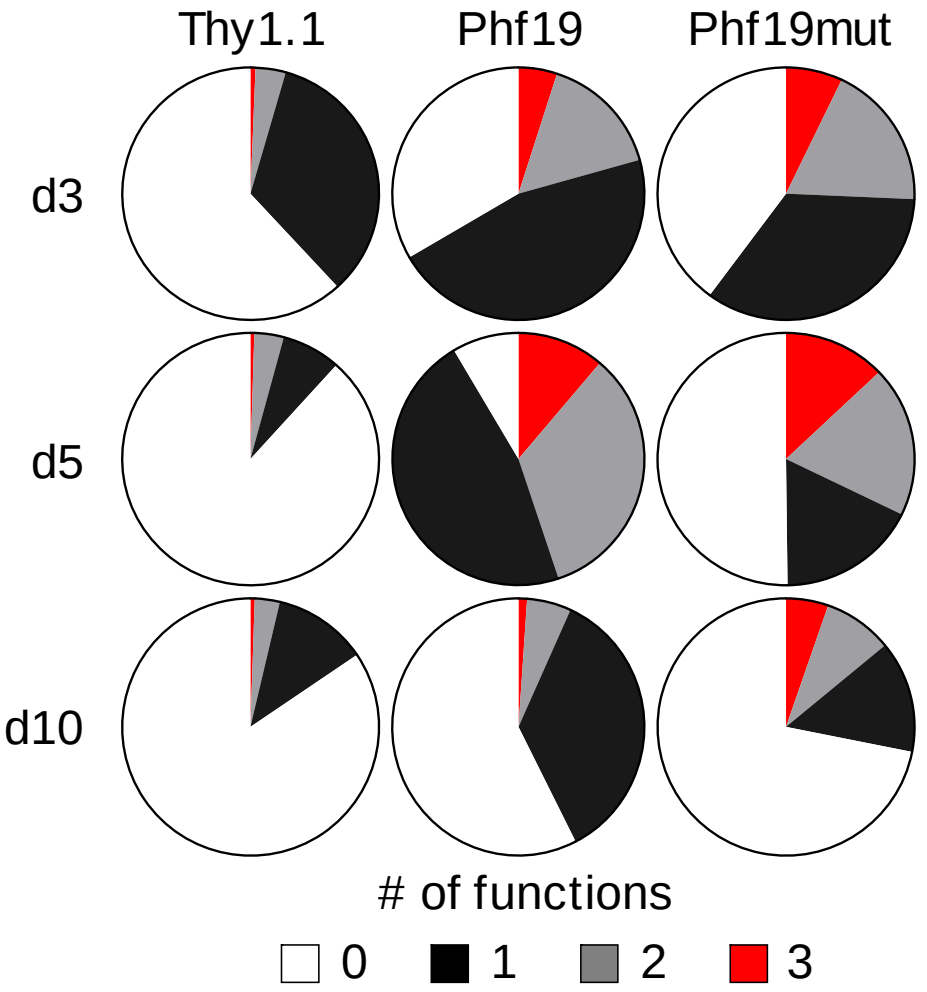
Harnessing Phf19 to epigenetically modulate T cell differentiation and antitumor function



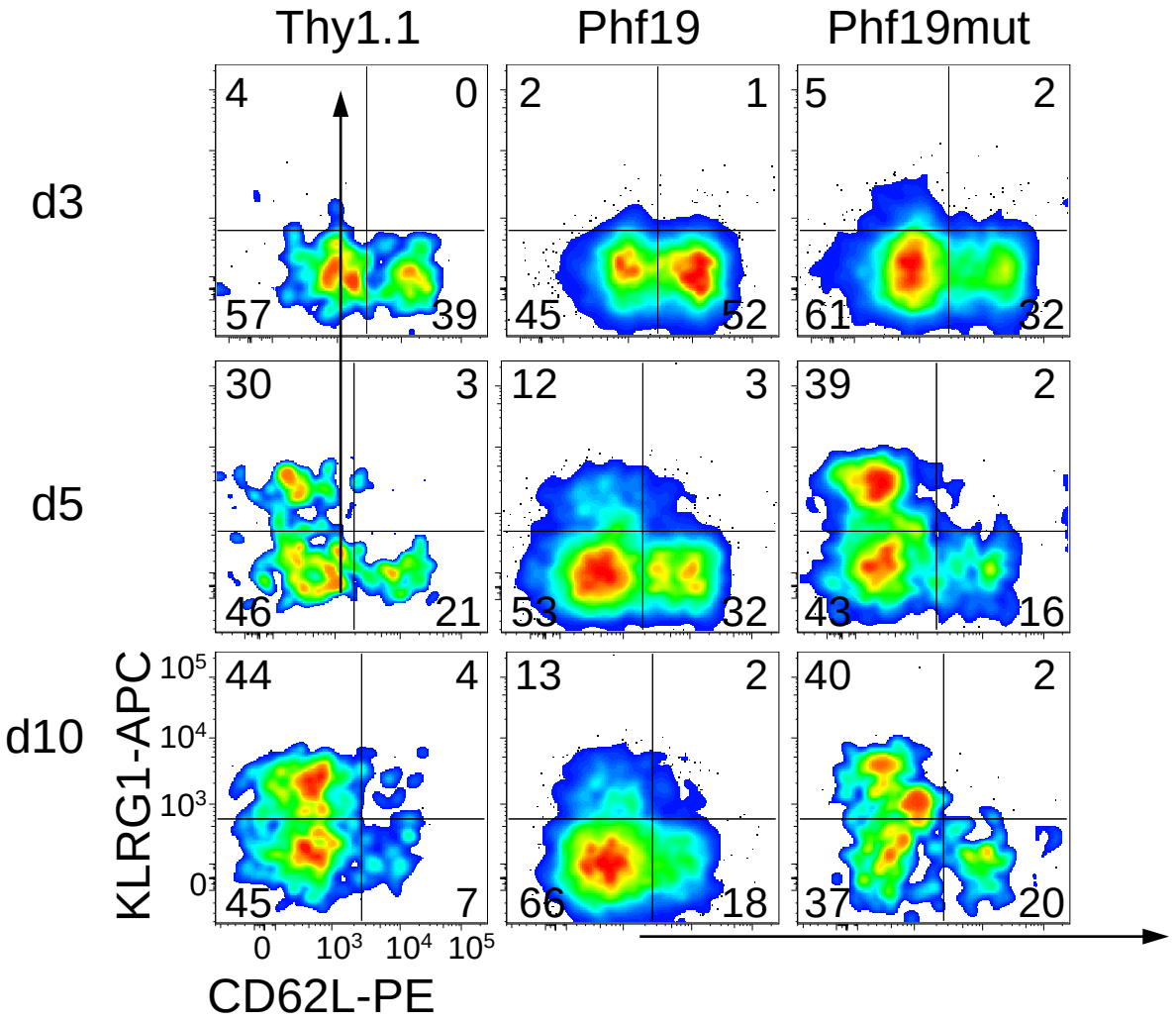


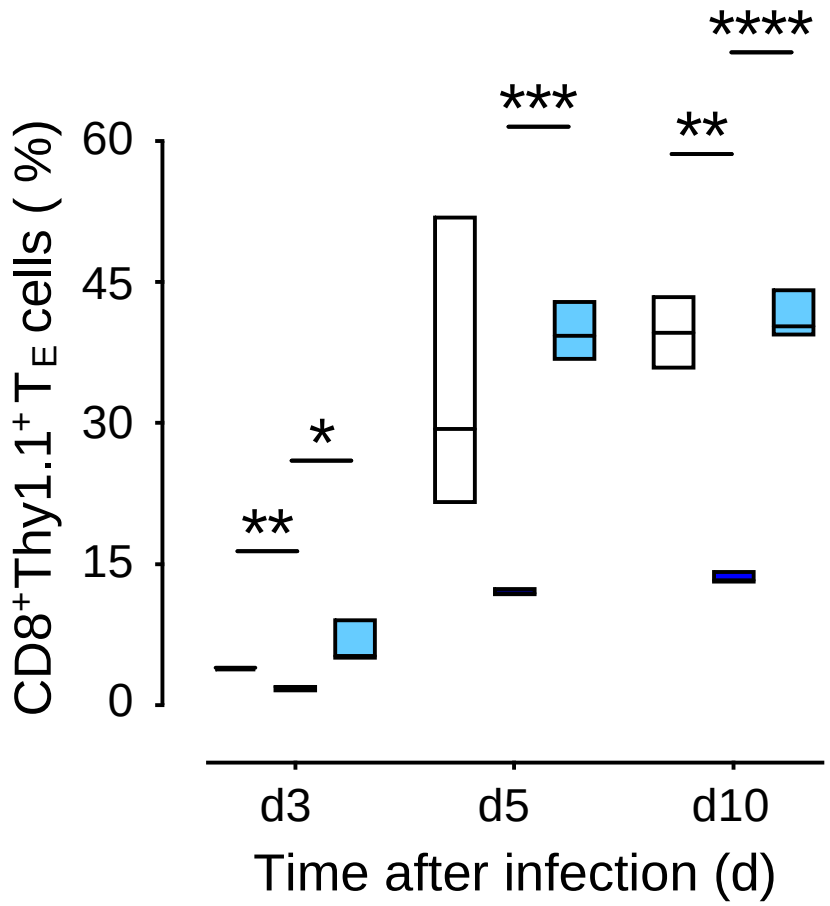
Enforced expression of Phf19 promotes T cell accumulation and sustained effector functions



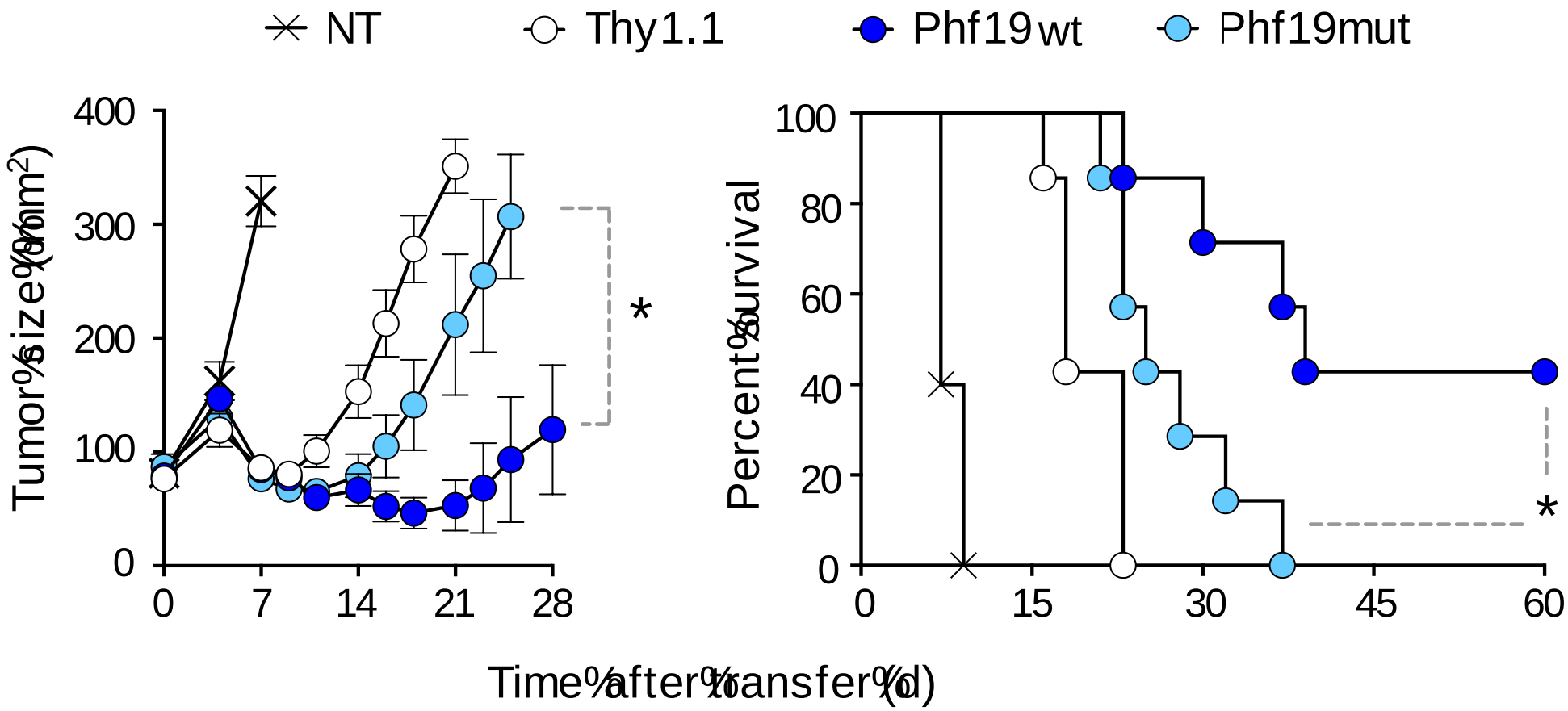


Enforced expression of Phf19 limits CD8⁺ T cell senescence





Enforced expression of Phf19 enhances T-cell based immunotherapies



Take home messages

- miR-155 is required for $CD8^+$ T cell responses to virus infection and cancer
- miR-155 can be harnessed to potentiate T cell-based therapies without the requirement of life-threatening preconditioning maneuvers
- miR-155 enhances $CD8^+$ T cell responsiveness to homeostatic cytokines
- miR-155 indirectly promotes PRC2 activity to restrain T cell terminal differentiation and sustain antitumor immunity
- Phf19 acts downstream of miR-155 to enhance cell expansion and limit terminal differentiation
- Phf19 can be harnessed to epigenetically modulate $CD8^+$ T cell differentiation and enhance $CD8^+$ T cell antitumor immunity

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Society for Immunotherapy of Cancer

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Temple University
Yi Zhang
He Shan

NIAMS
Vittorio Sartorelli
Hongjun Wang

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