CD8α$^+$ dendritic cells regulate leukemia antigen-specific CD8$^+$ T cell tolerance

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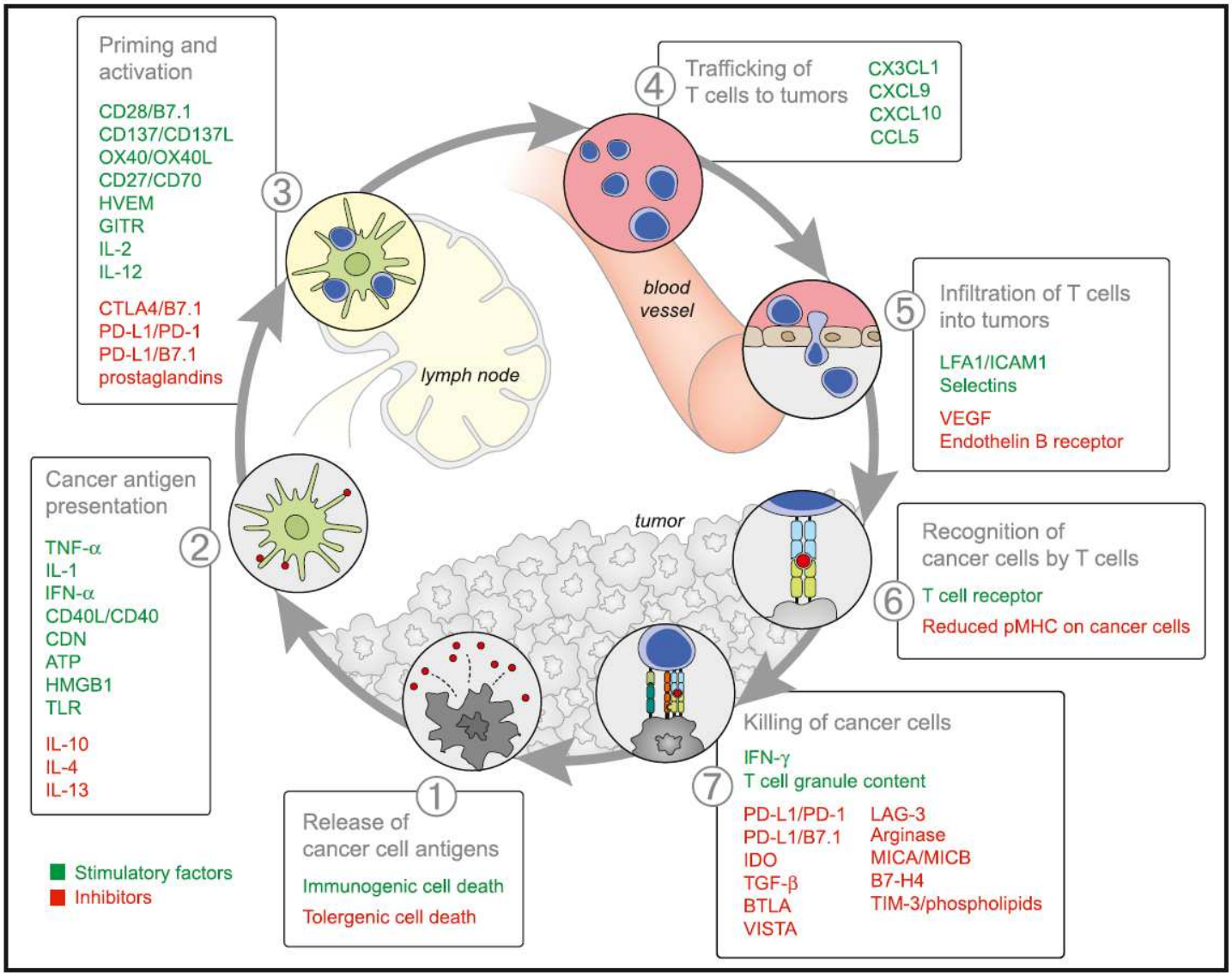
Disclosures

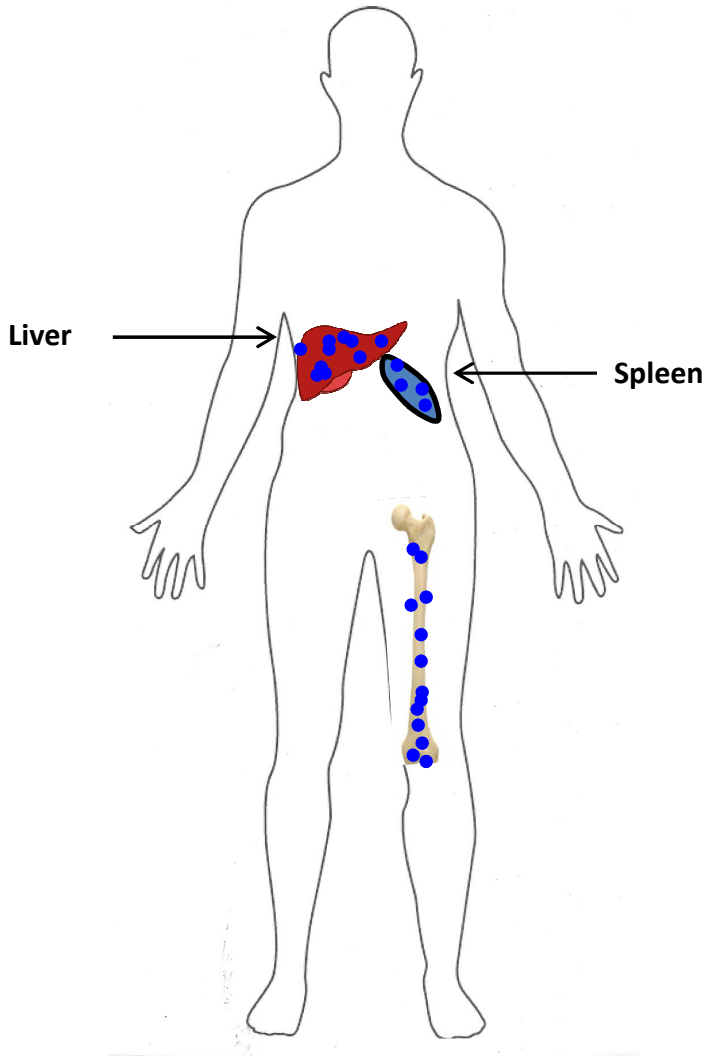
- Research support – BMS, Merck and Vasculox
- Consulting fees - Merck

Generation of spontaneous immunity to solid cancers



Chen and Mellman, Immunity 2013

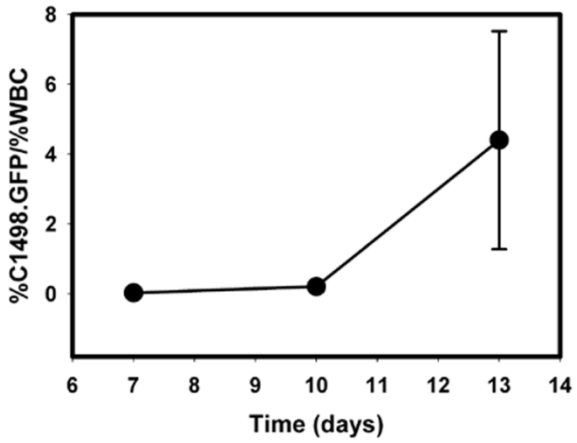
Progression of AML



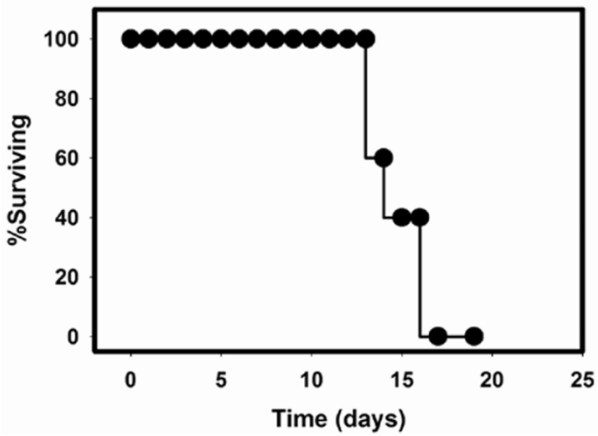
- Rapid development
- Systemic disease
- No classical tumor-draining LN
- These factors may be important when considering differences between anti-tumor immunity in patients with “solid vs liquid” cancers

C1498 AML cells infiltrate the blood, marrow and liver and are lethal in C57BL/6 mice

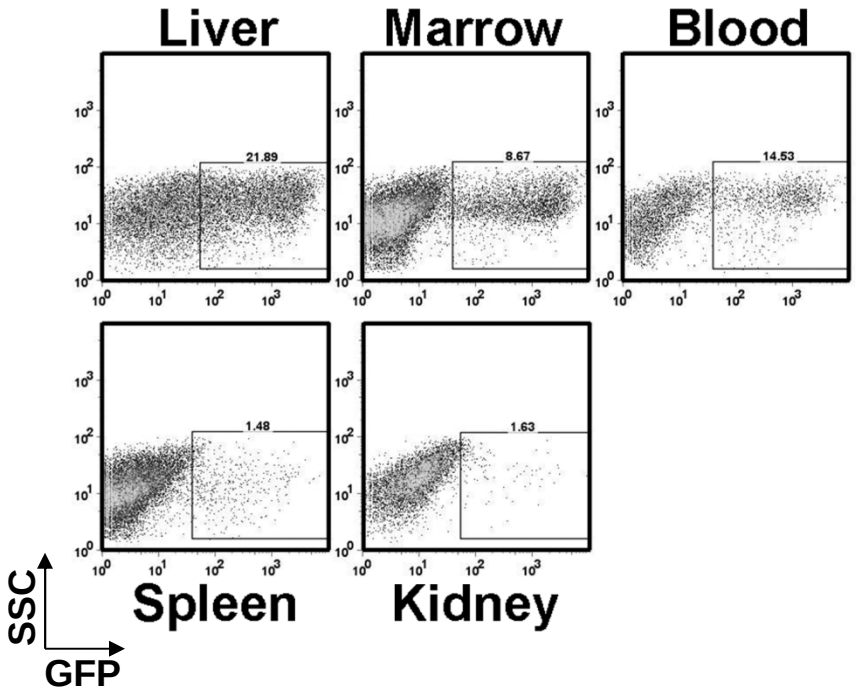
A. Growth kinetics - blood



C. Survival in C57BL/6 mice

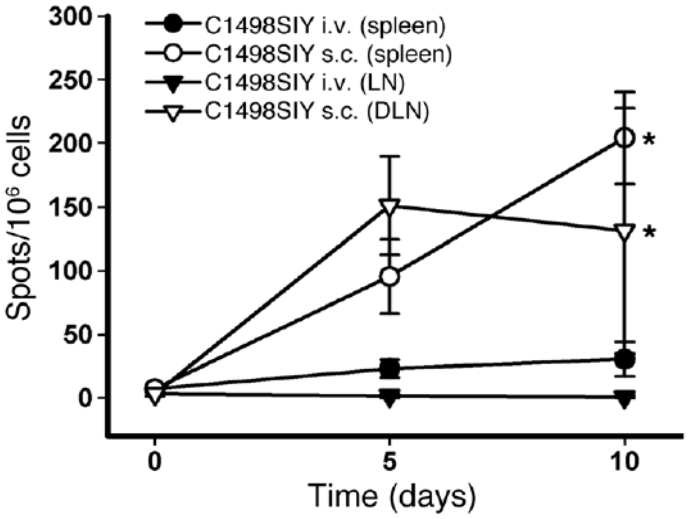


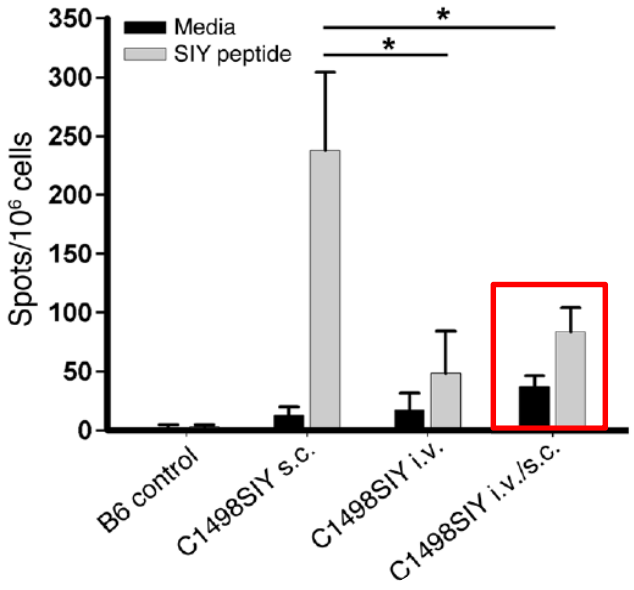
B. End-organ involvement

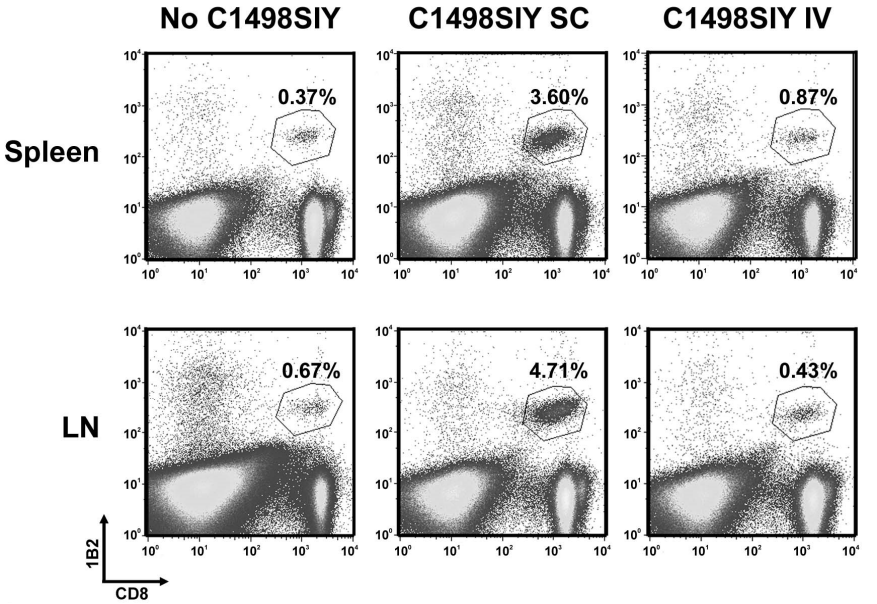


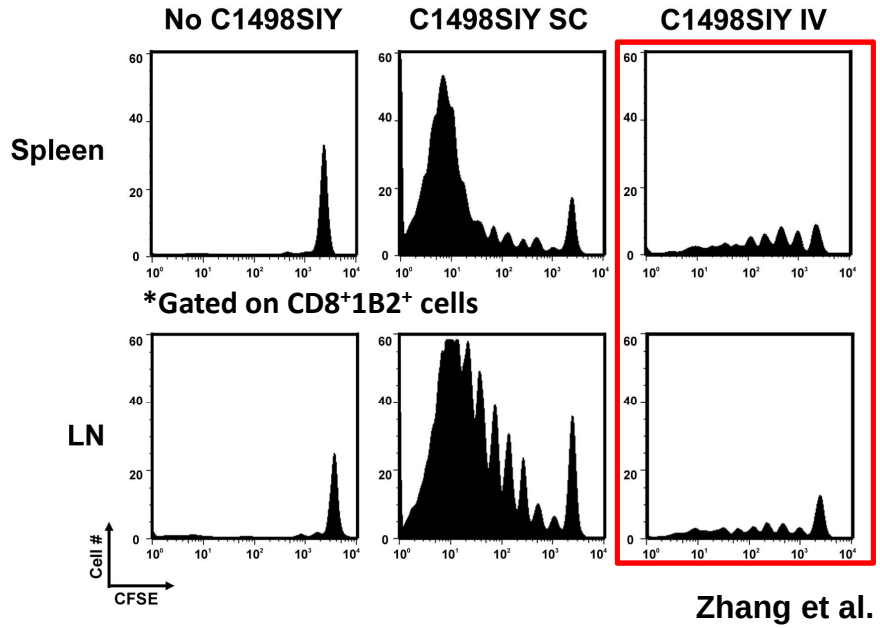
Zhang et al. Blood 2009

Systemic AML induces CD8$^+$ T cell tolerance



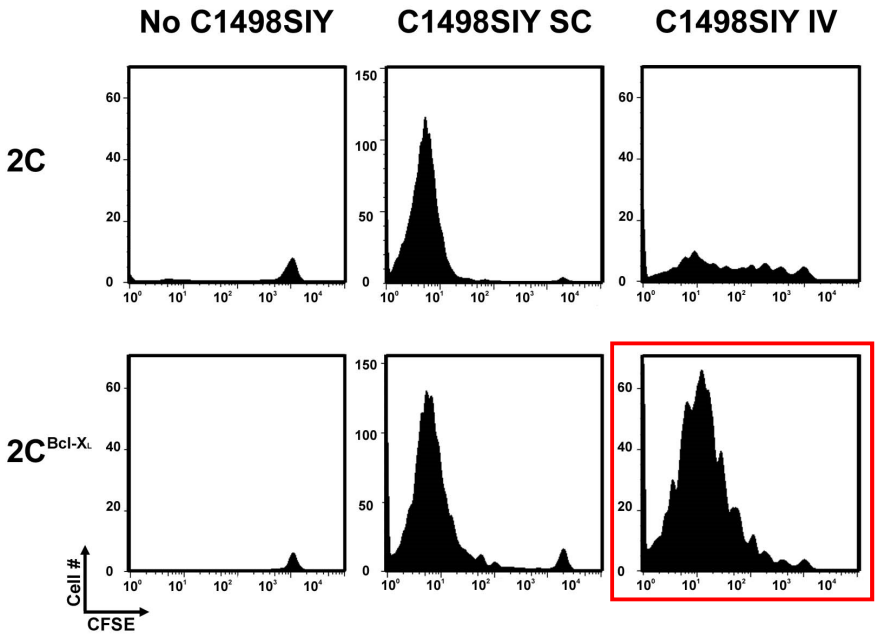


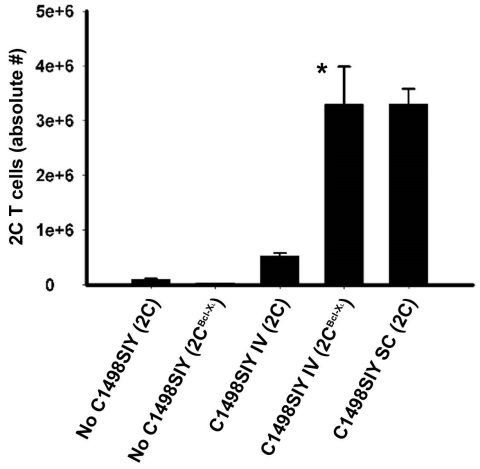


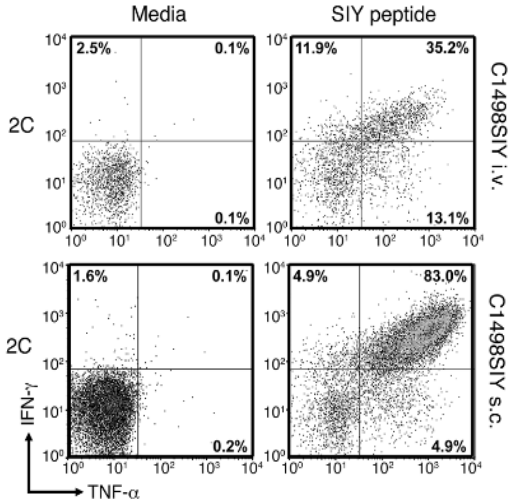


Zhang et al. JCI 2013

Leukemia-specific CD8^{+} T cells are deleted in mice with systemic AML

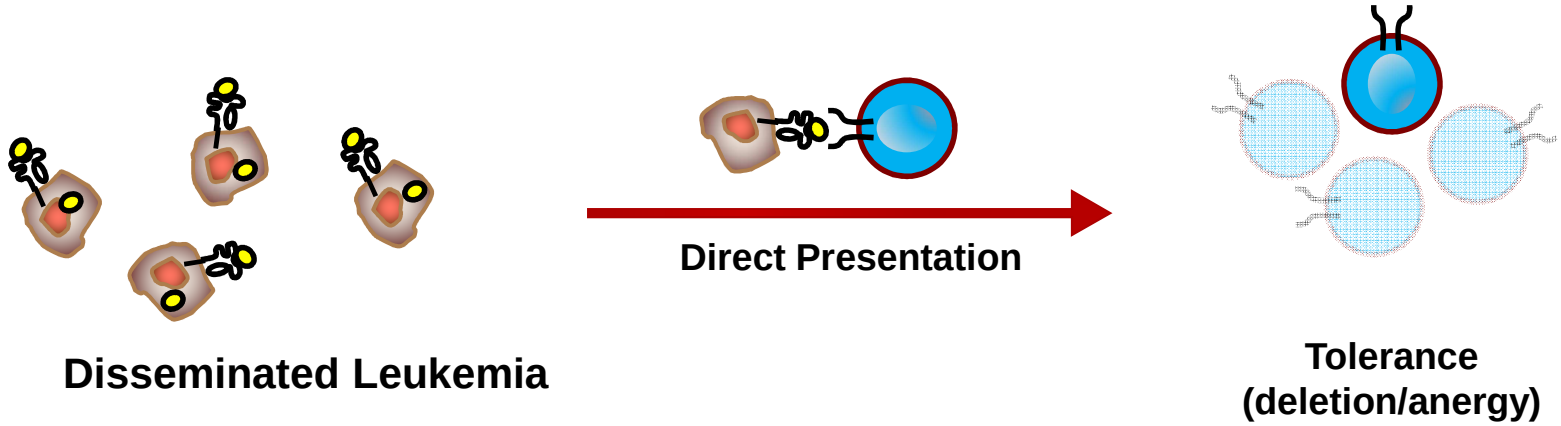


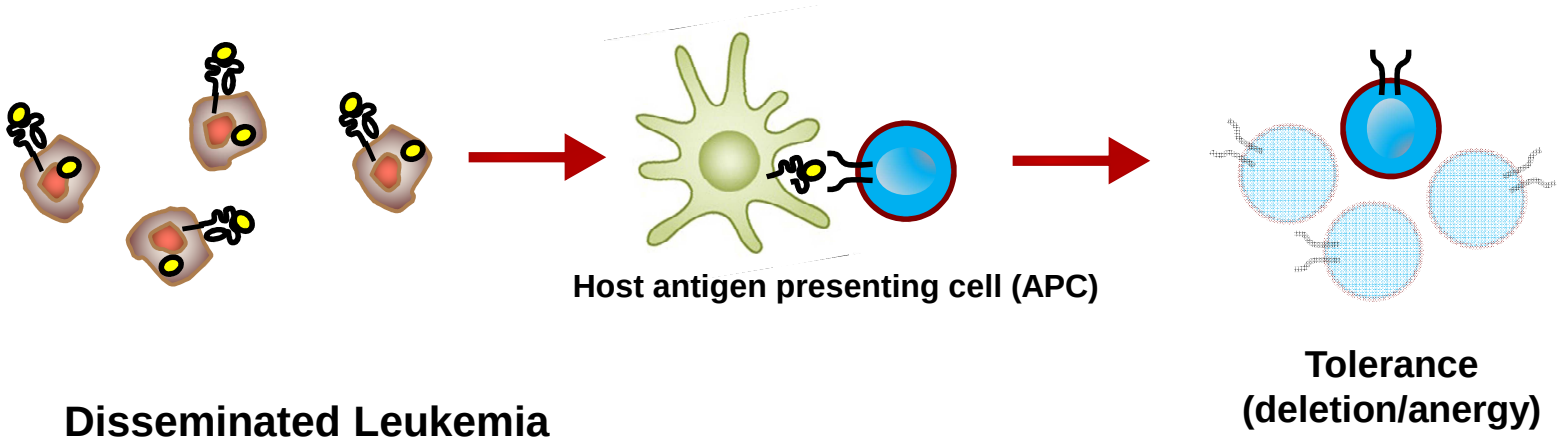




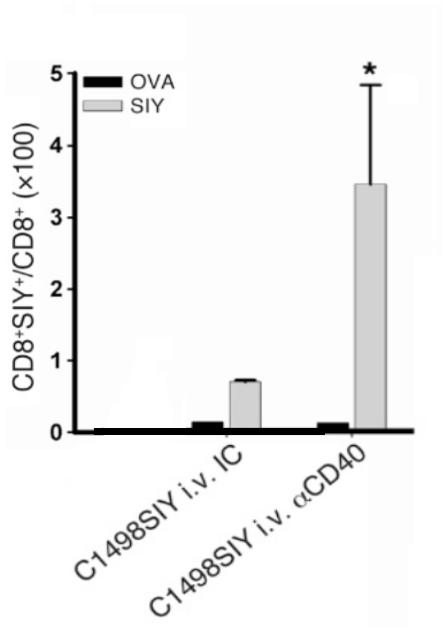
Zhang et al. JCI 2013

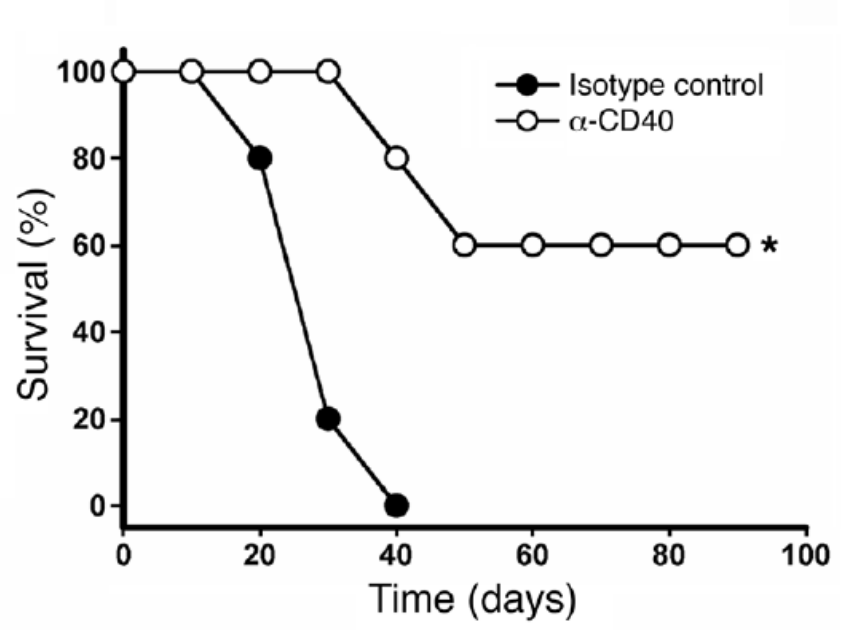
Identification of cellular mediators of T cell tolerance in mice with systemic AML





Systemic maturation of host APCs prevents T cell tolerance in leukemia-bearing mice



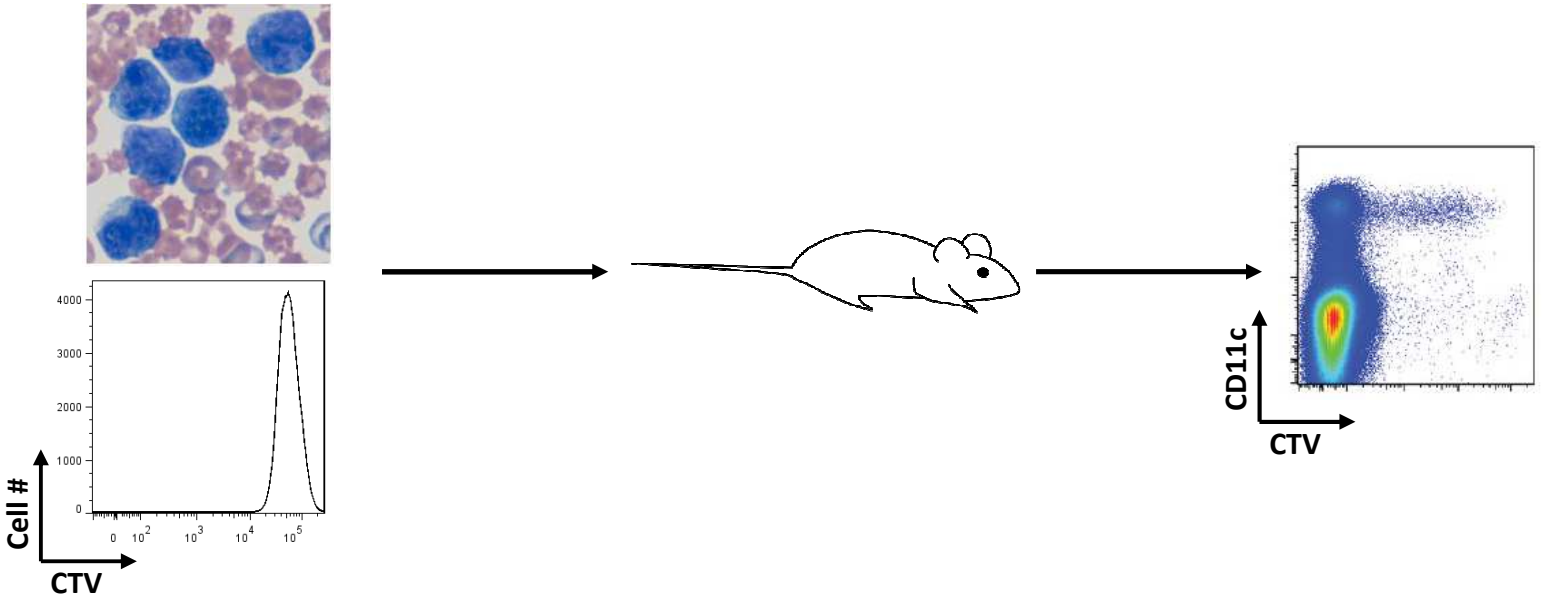


Zhang et al. JCI 2013

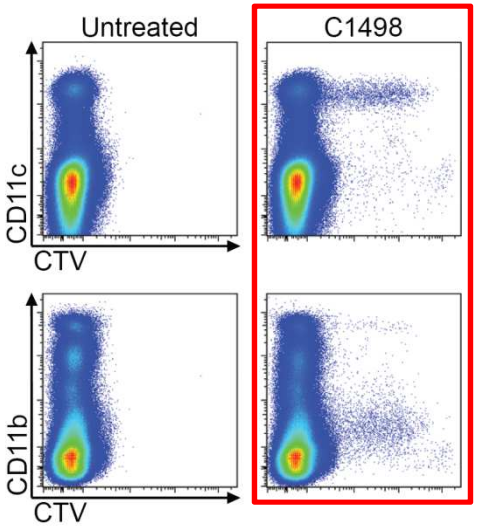
Do APCs engulf circulating AML cellular material?

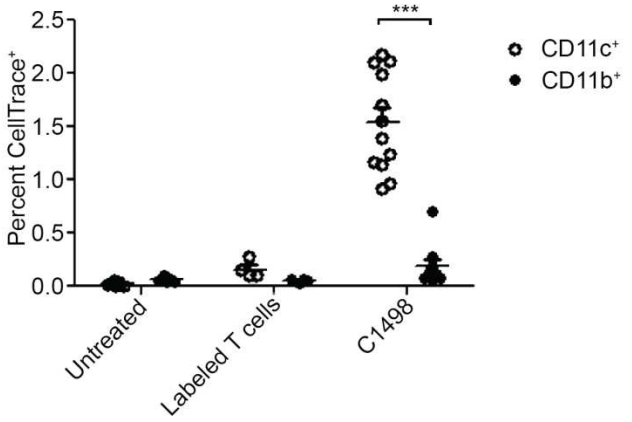
CellTrace Violet (CTV) label C1498 cells
Inject 4 x 10^6 C1498 cells IV

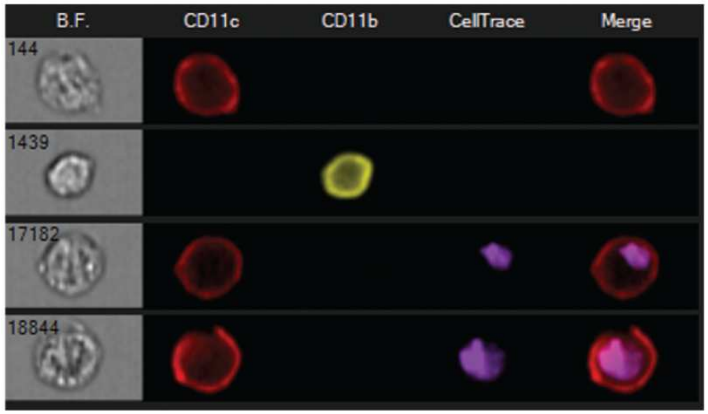
Analyze for CTV fluorescence among known phagocytic cell populations



CD11c⁺ cells engulf circulating AML cellular material







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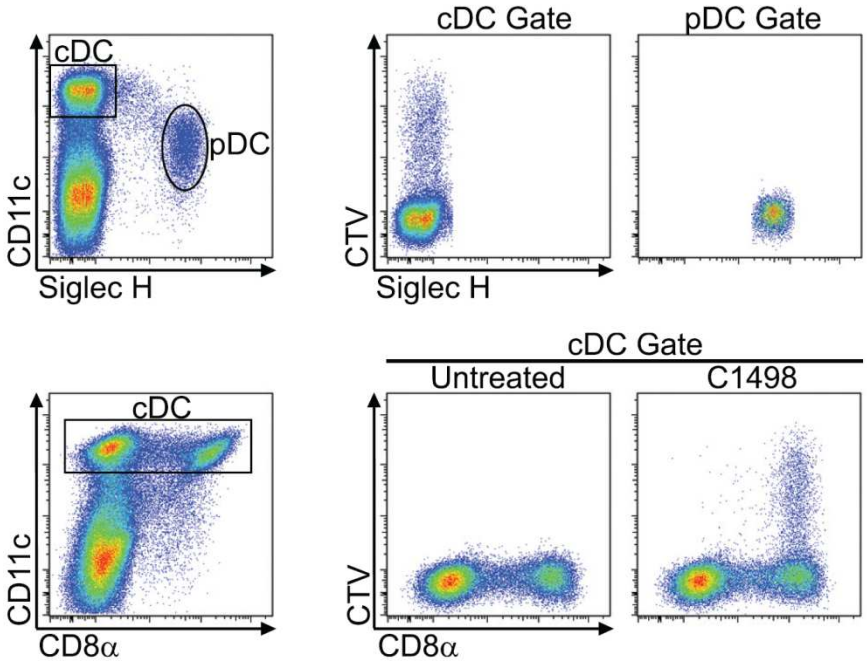
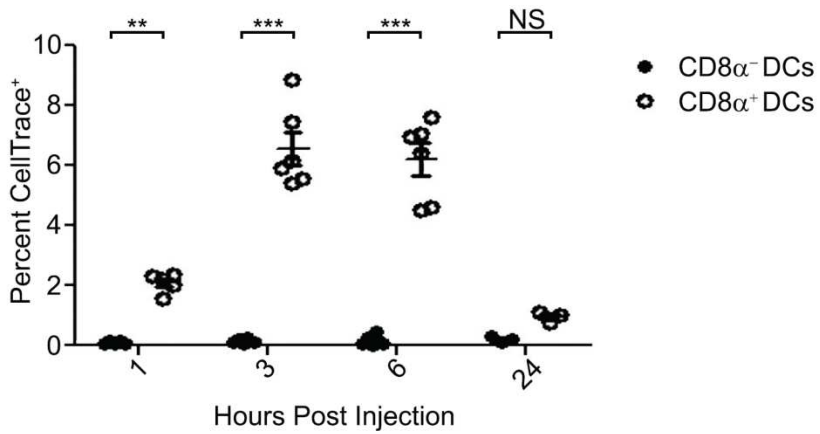
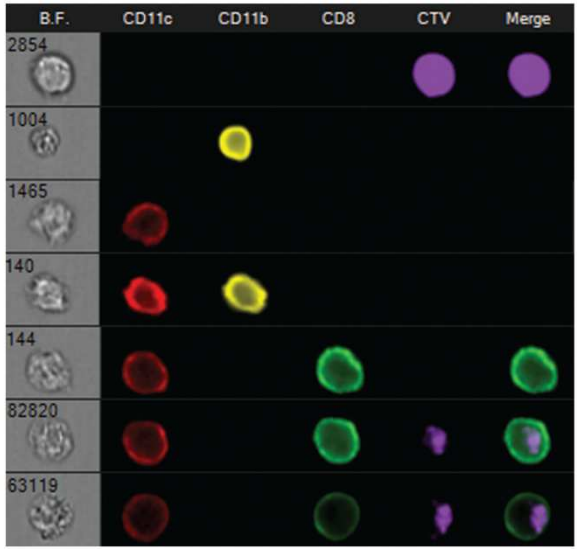
CD8α⁺ DCs selectively acquire AML cellular material







C1498

CD11b⁺

CD11c⁺

CD11c⁺CD11b⁺

CD11c⁺CD8α⁺

CD11c⁺CD8α⁺ CTV⁺

CD11c⁺CD8α⁺ CTV⁺

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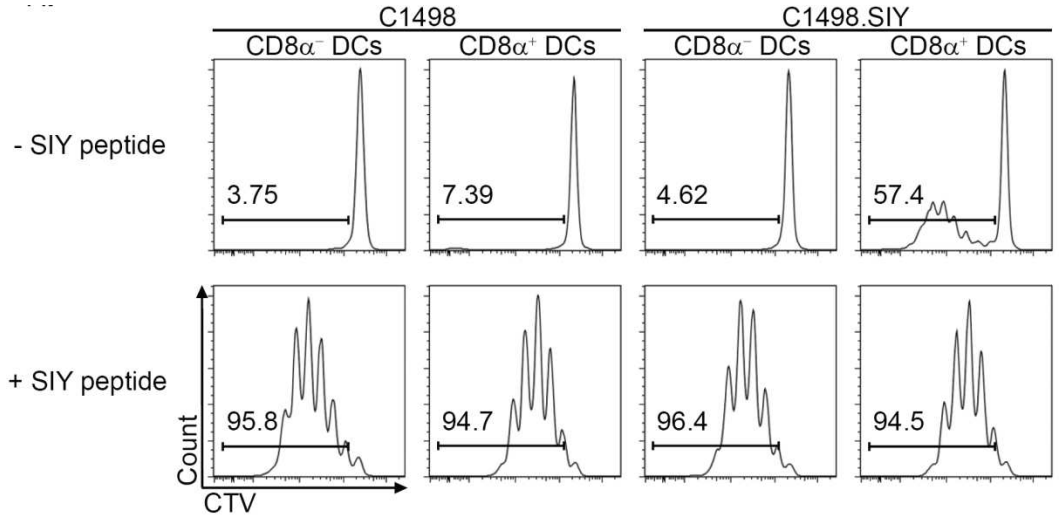
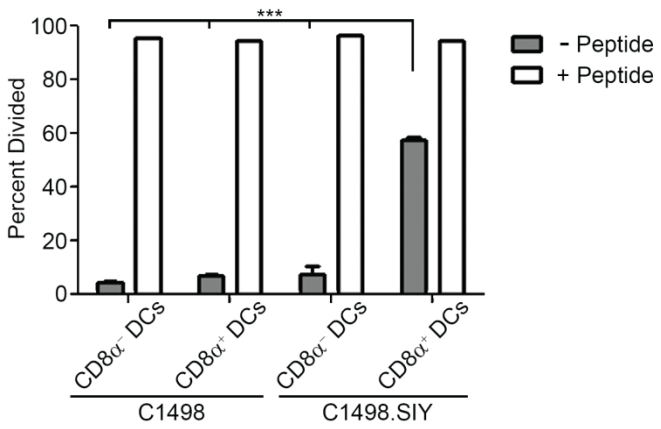
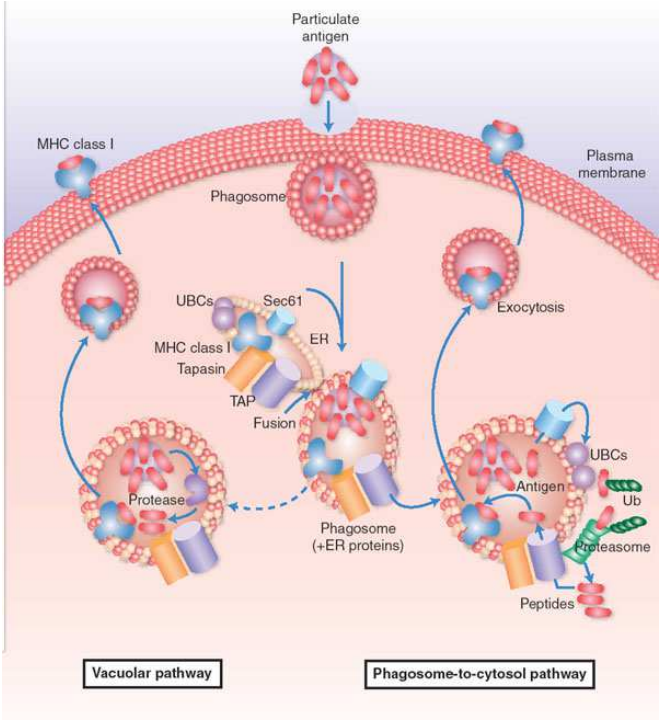
CD8α⁺ DCs cross-present leukemia antigens







Rock KL. Nat Immunol 2013

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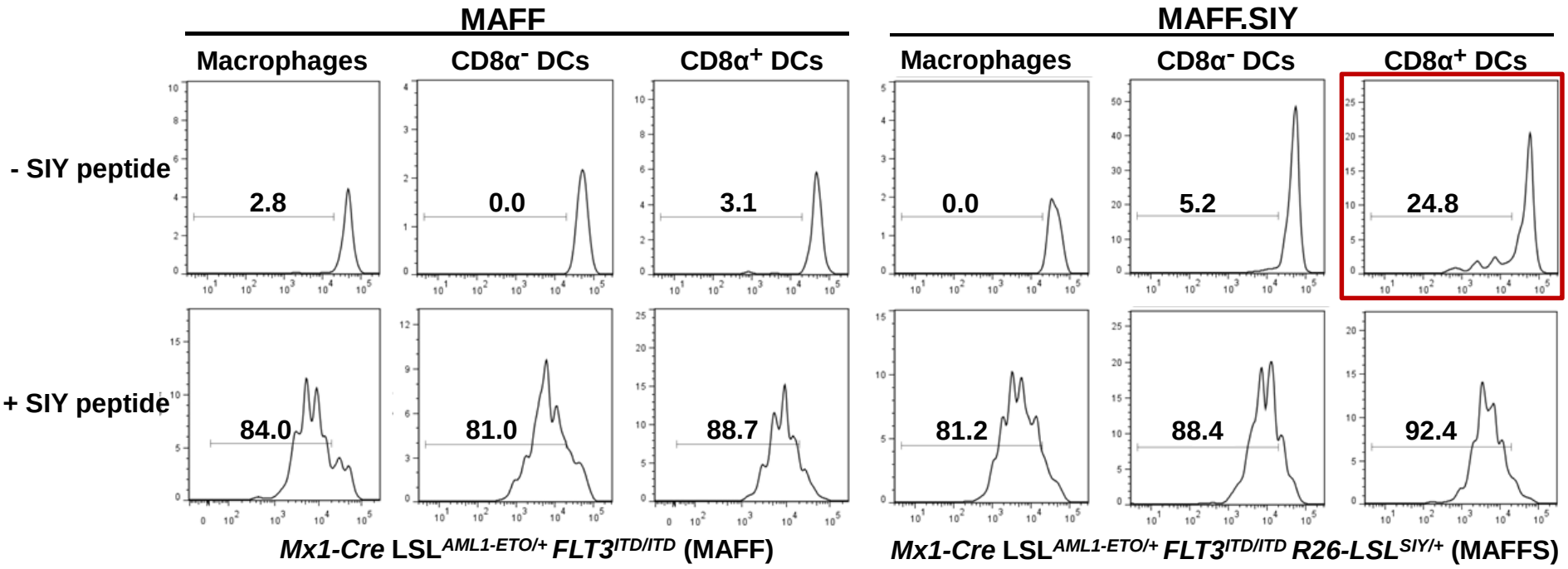
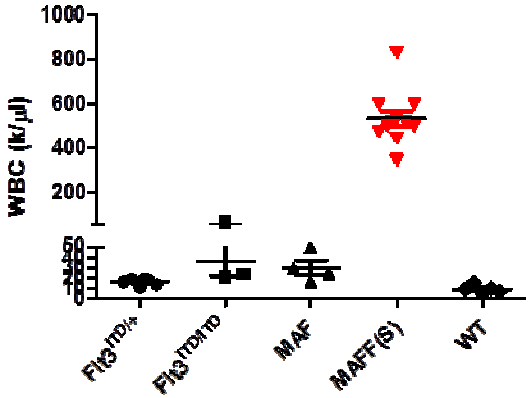
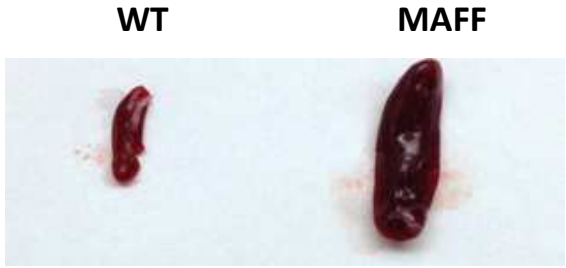
CD8α⁺ DCs cross-present leukemia antigens

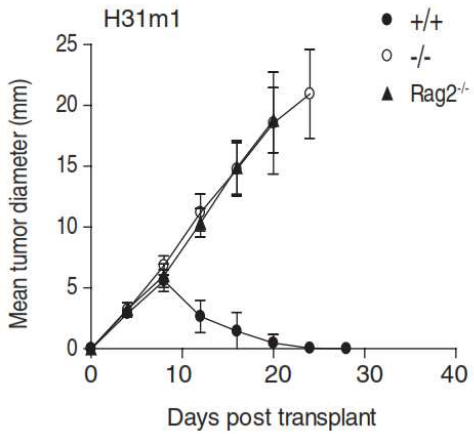


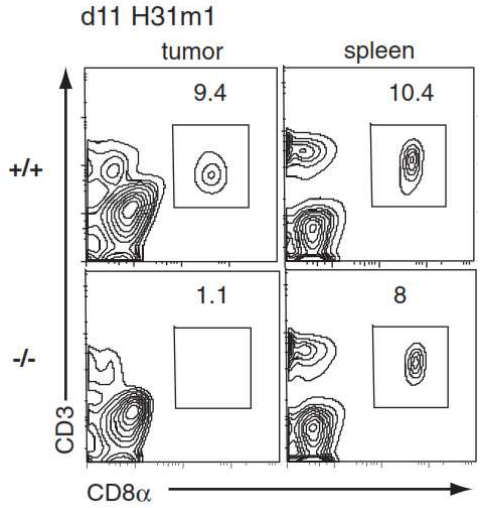




Xiufen Chen

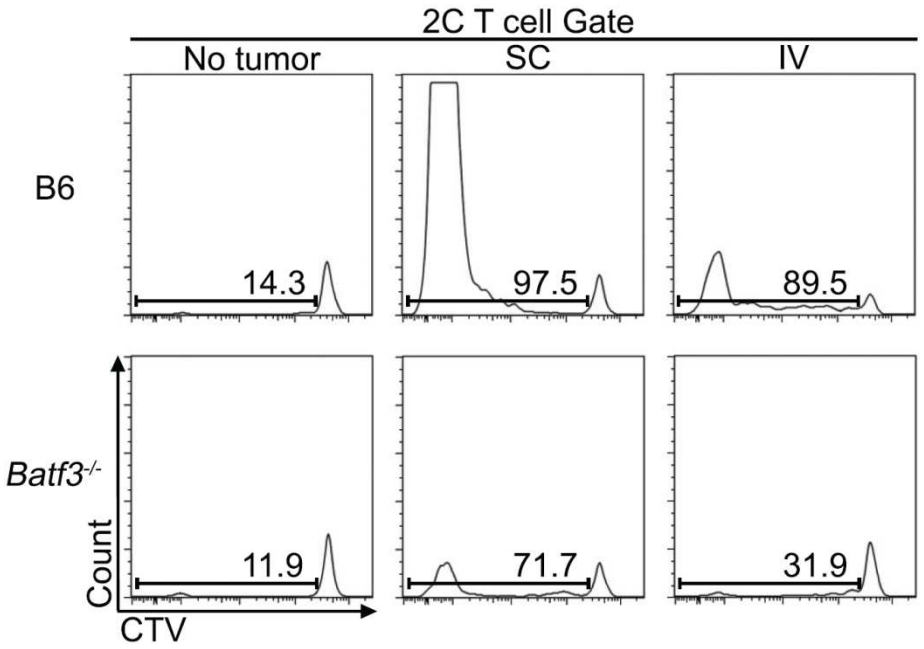
Batf3-lineage DCs are required for CD8$^+$ T cell priming against solid tumor antigens

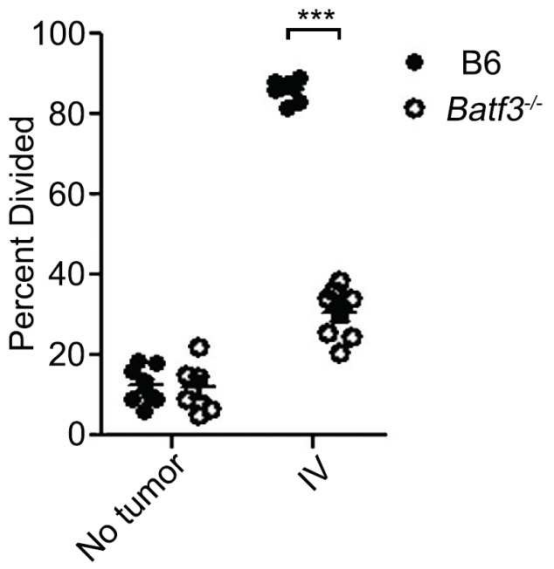




Hildner et al. Science 2008

CD8α⁺ DCs mediate T cell recognition of AML antigens





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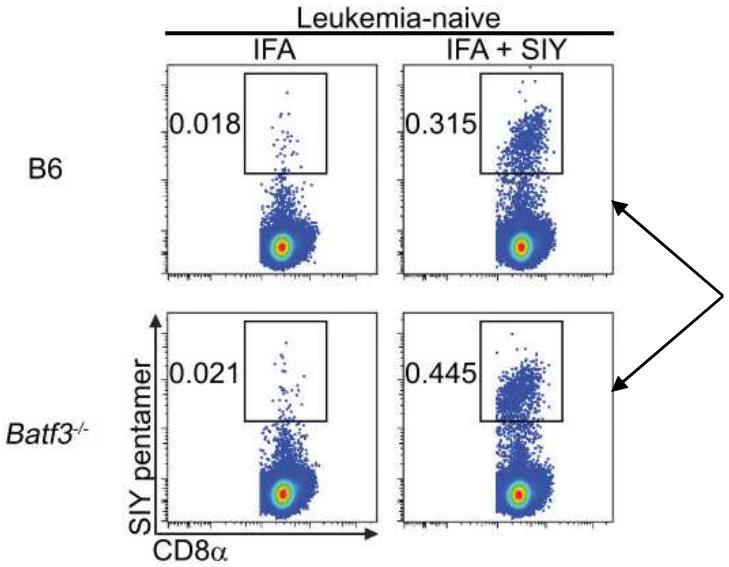
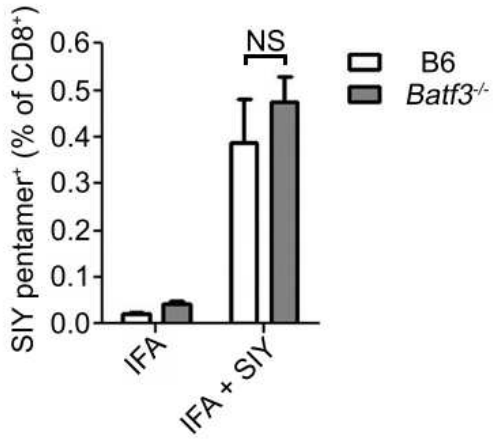
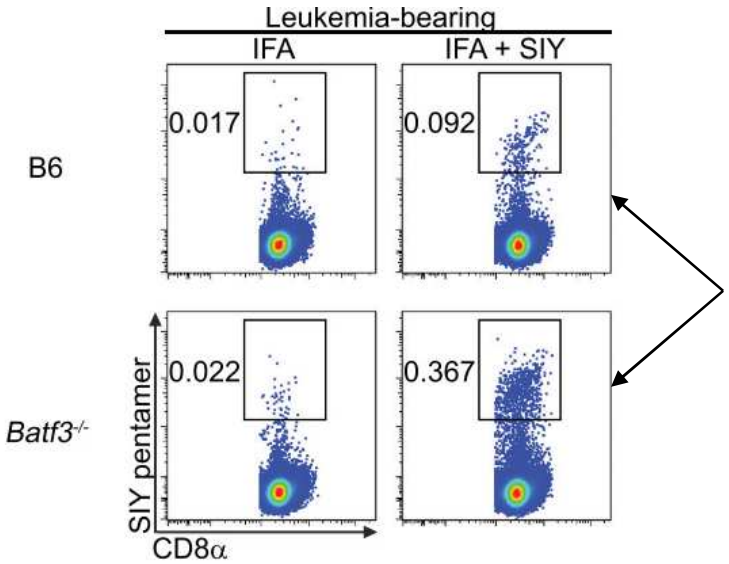
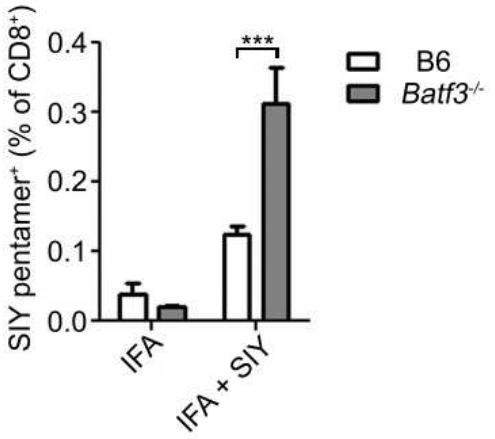
CD8α⁺ DCs induce leukemia-specific T cell tolerance









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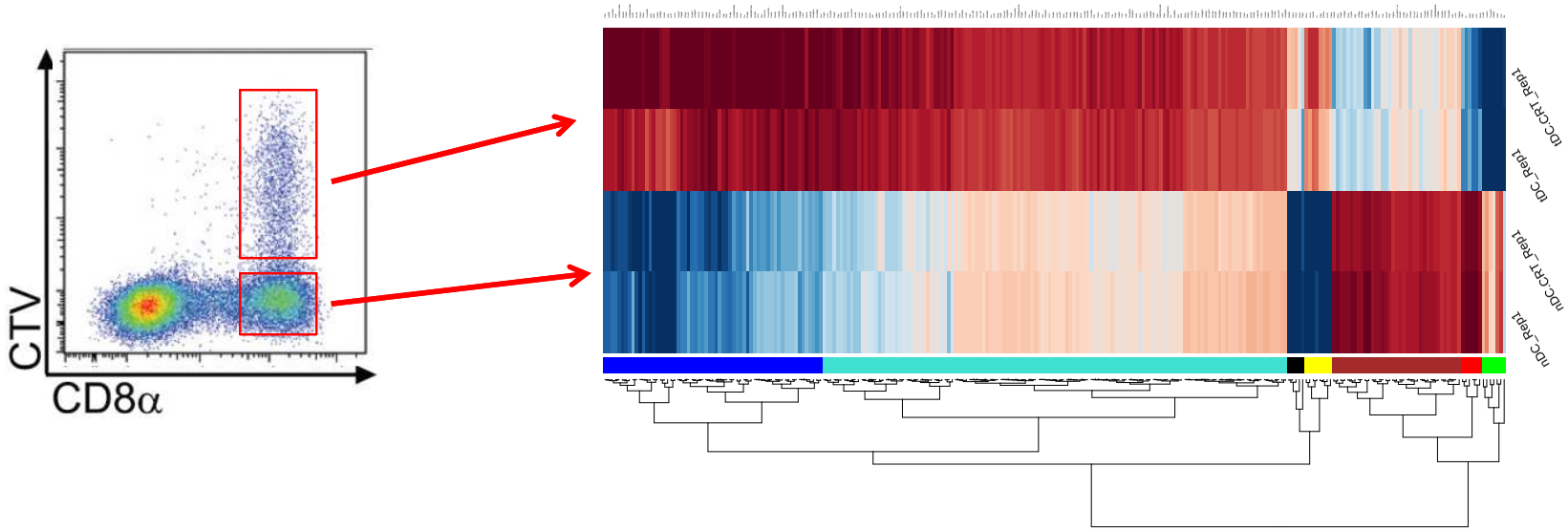
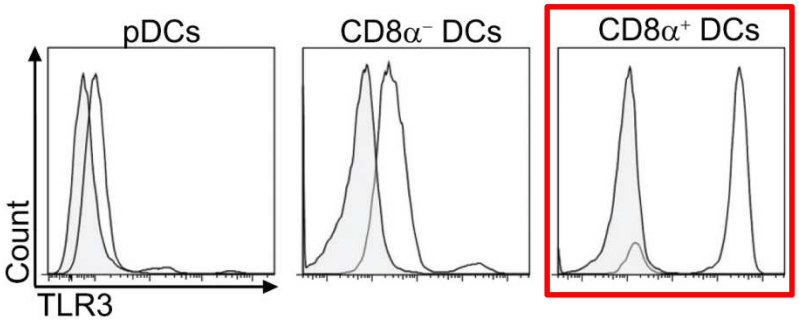
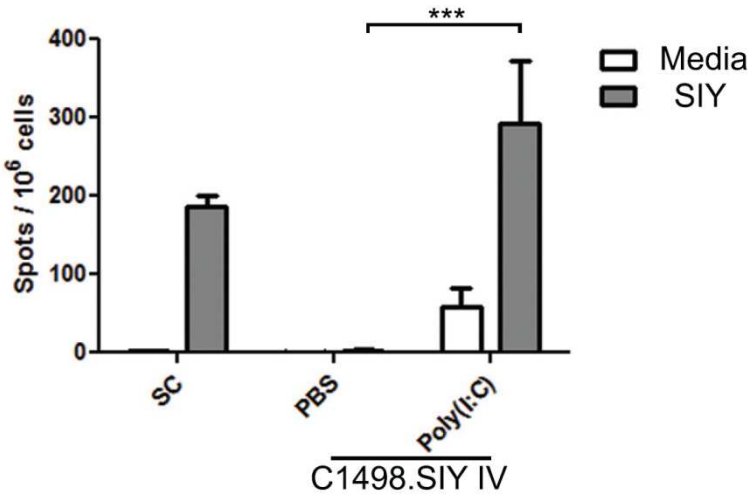
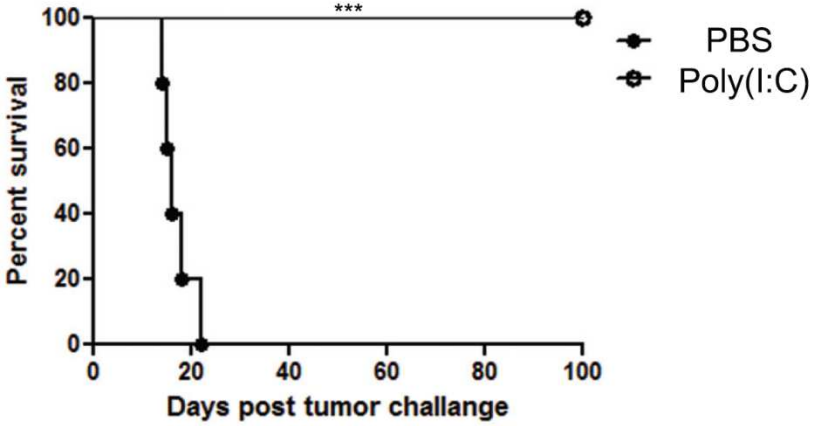
Leukemia cell engulfment is associated with a unique gene expression program in CD8α⁺ DCs

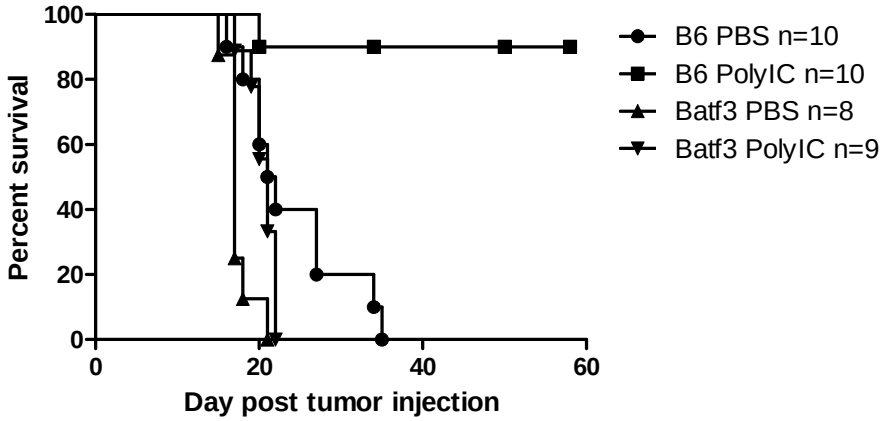


TLR3 – induced CD8α+ DC activation breaks AML-induced T cell tolerance









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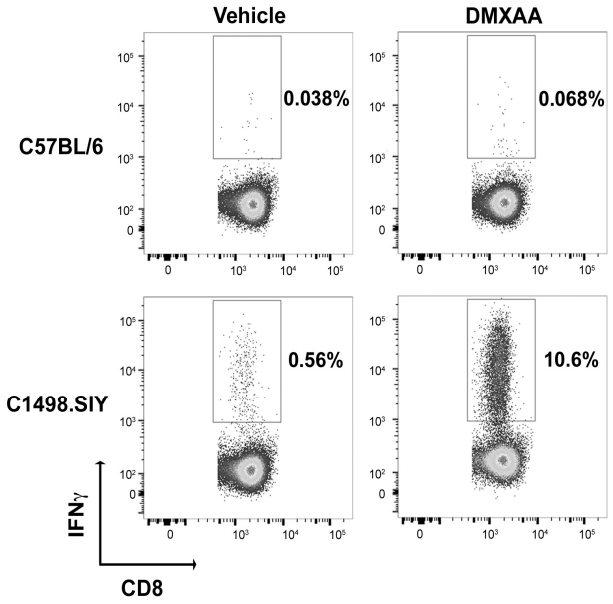
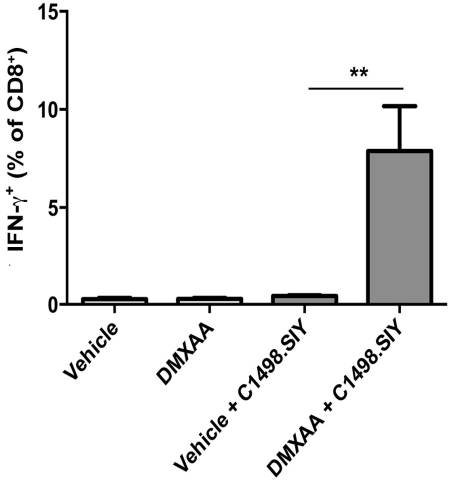
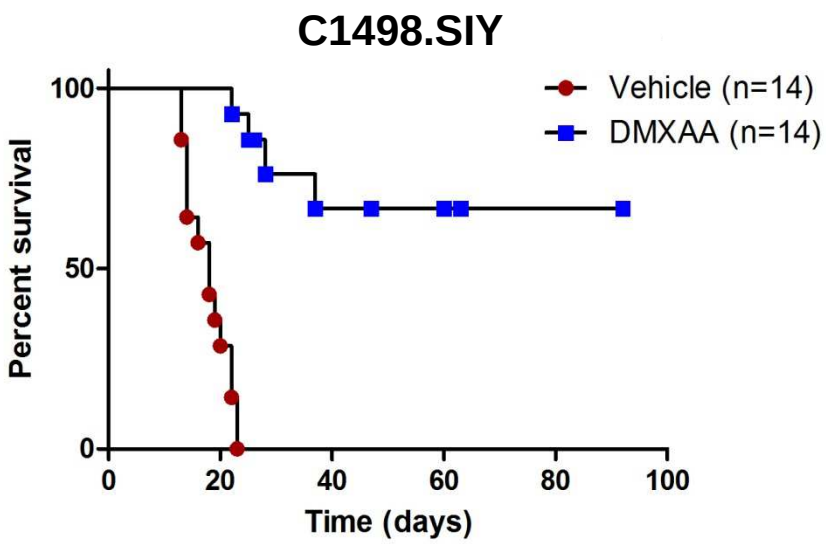
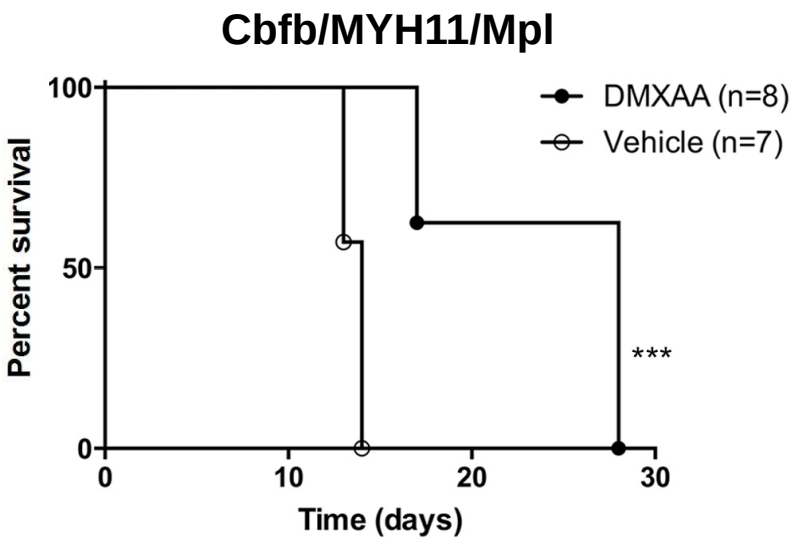
STING activation induces potent immunity against AML







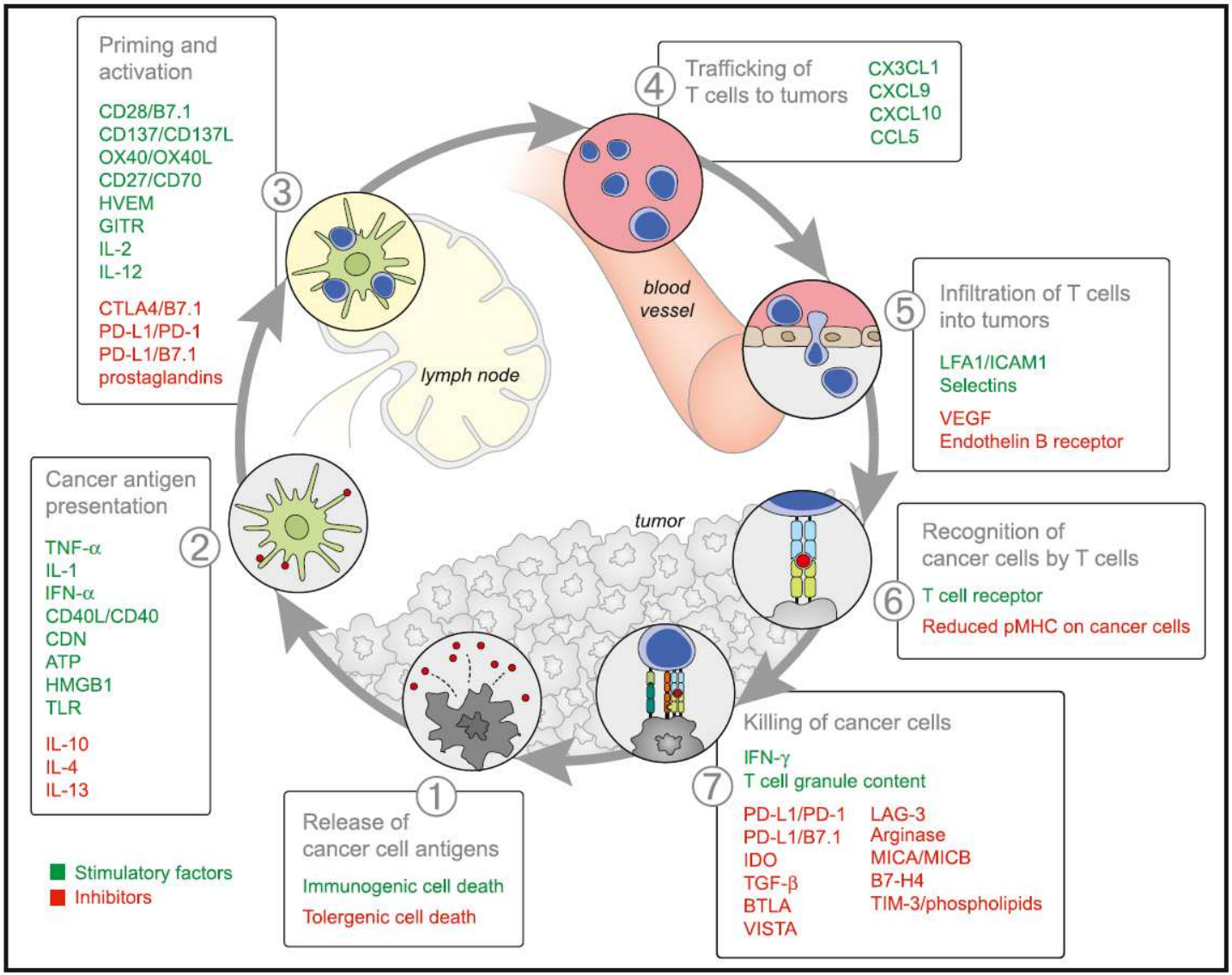


Curran et al. Cell Reports 2016

Conclusions

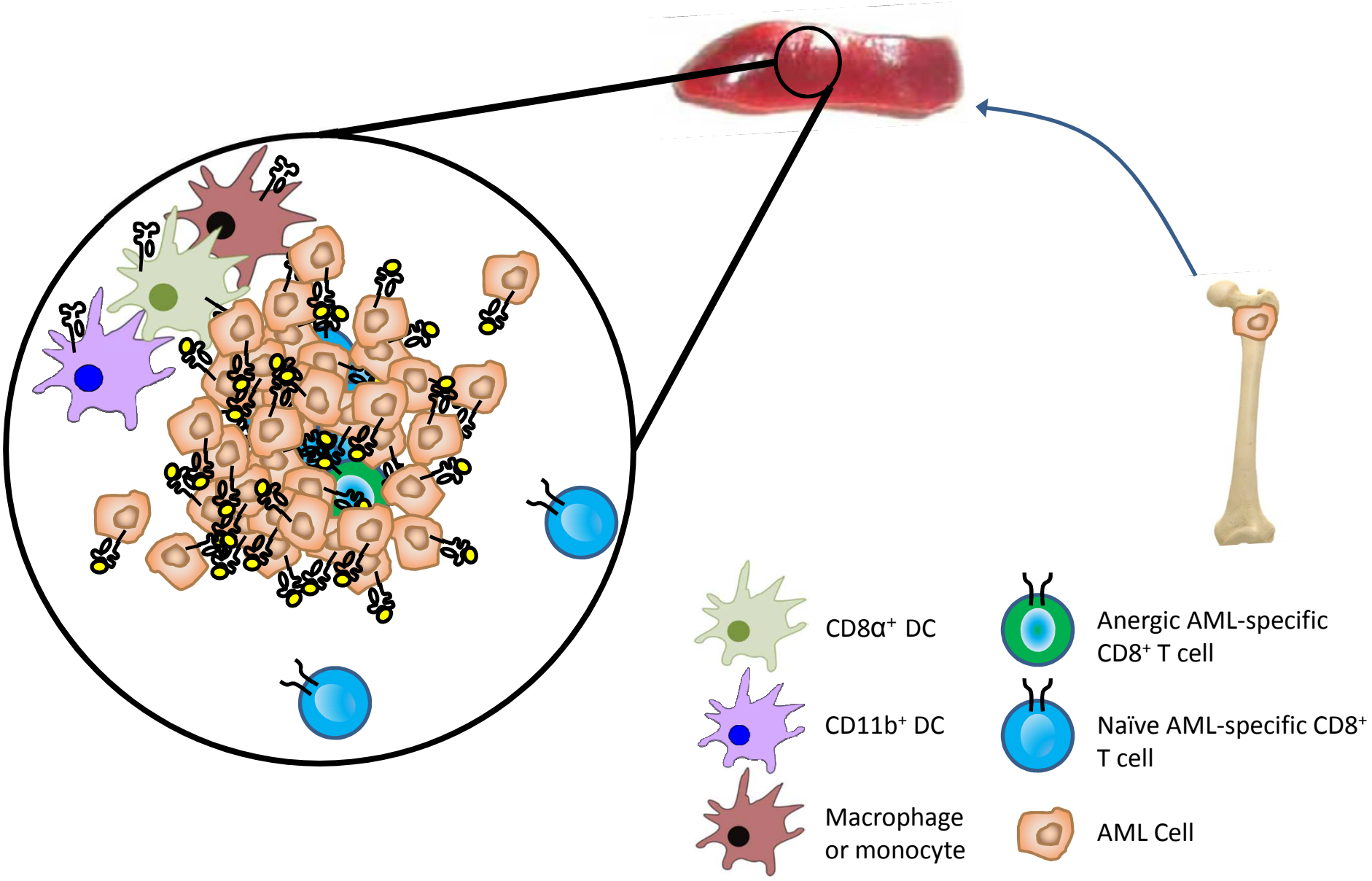
- A unique $CD8^+$ T cell tolerant state exists in mice with systemic AML
- $CD8\alpha^+$ DCs exclusively acquire leukemia cellular material and cross-present leukemia-derived antigens to $CD8^+$ T cells
- $CD8\alpha^+$ DCs dictate AML-specific immune responses
  - In the steady state, $CD8\alpha^+$ DCs rapidly induce $CD8^+$ T cell tolerance
  - In the absence of $CD8\alpha^+$ DCs, host $CD8^+$ T cells remain largely ignorant of a progressing leukemia
  - Activation of $CD8\alpha^+$ DCs facilitates their ability to prime functional AML-specific T cell responses
- Whereas Batf3-dependent DCs are required for productive $CD8^+$ T cell priming against solid tumors, our results reveal that the identical DC subset paradoxically drives T cell tolerance in animals with disseminated leukemia.
- Targeting the innate immune system may be required to generate effective adaptive immunity against AML

The (solid) cancer immunity lifecycle

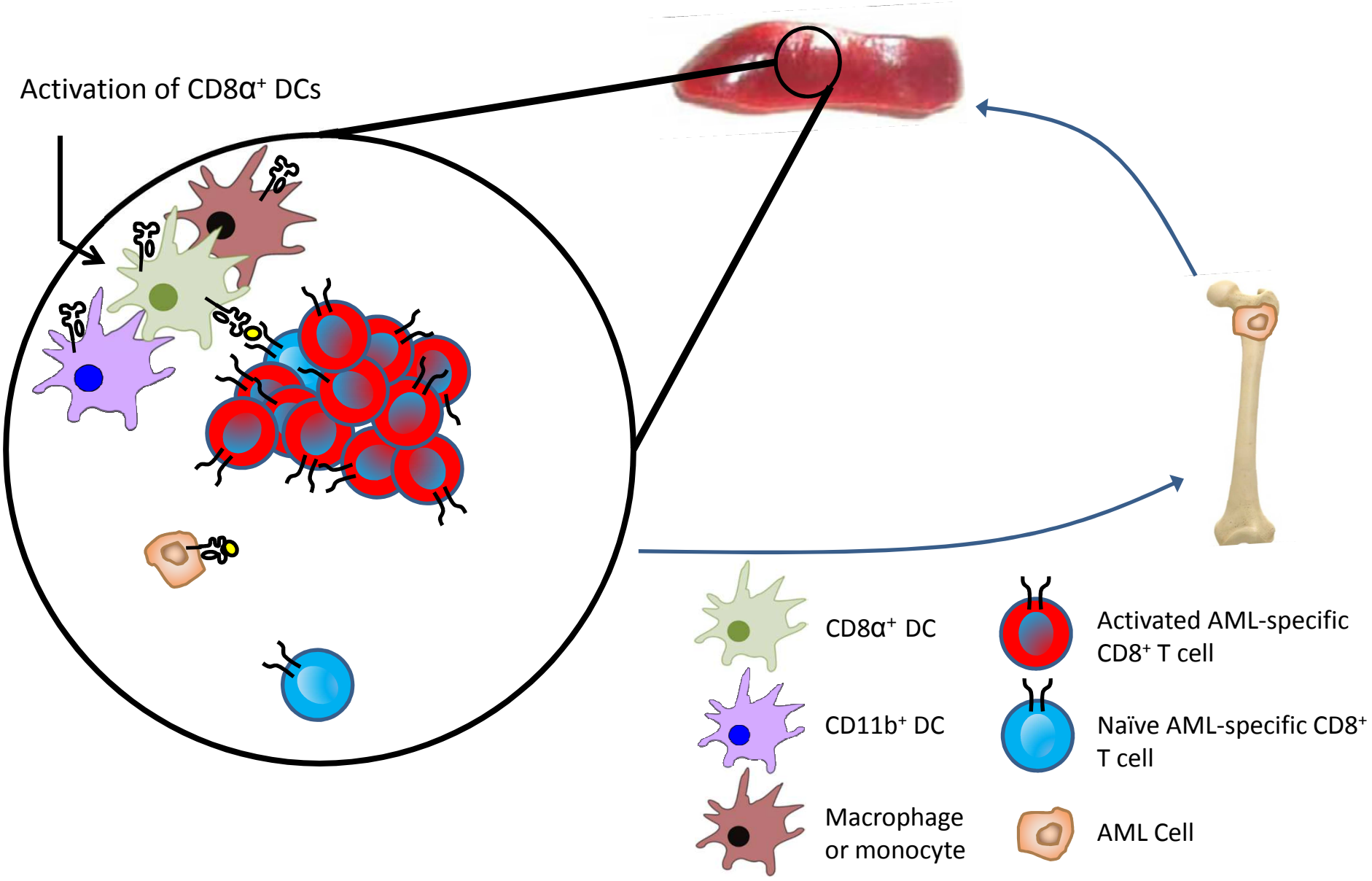


Chen and Mellman, Immunity 2013

The AML immunity lifecycle



The AML immunity lifecycle



Acknowledgments

- Kline lab
  - **Douglas Kline**
  - **Xiufen Chen**
  - **Emily Curran**
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