Mechanisms of immunoevasion in acute lymphoblastic leukemia

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Disclosure of Conflicts of Interest

- None

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Learning Objectives

Within the setting of acute lymphoblastic leukemia, this presentation will:

- Survey the evidence linking T-cell exhaustion with subsequent relapse

- Describe mechanisms by which immune checkpoint blockade can prolong survival in murine models

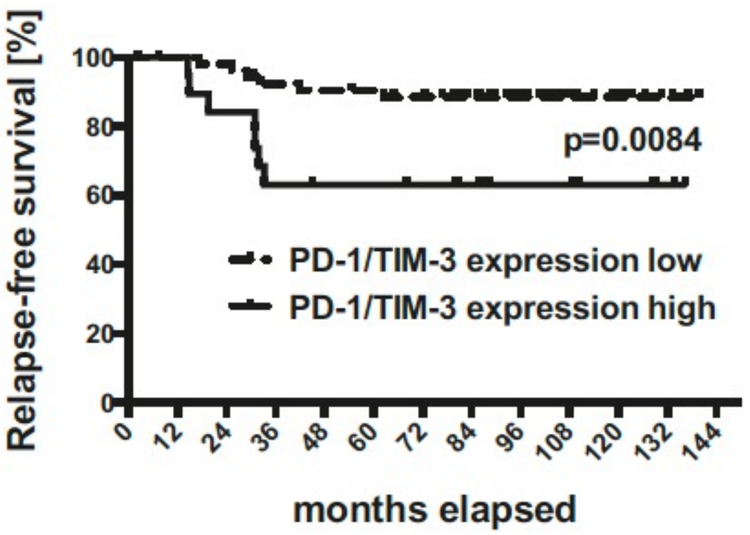
- Highlight promising clinical trial strategies to counter T-cell exhaustion

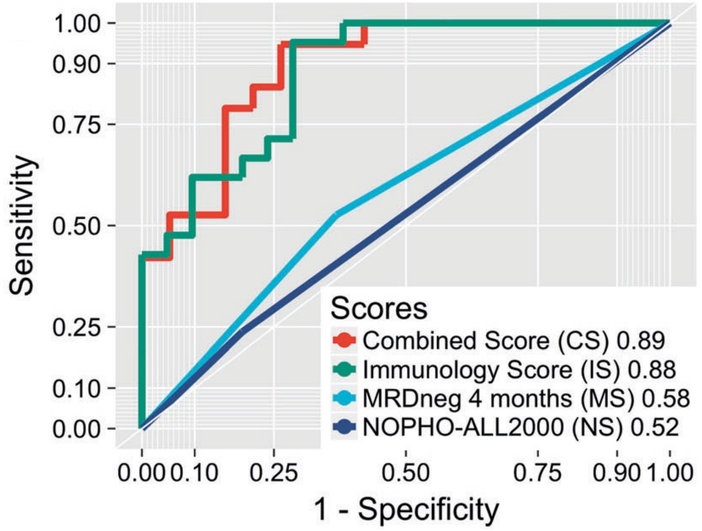
T-cell exhaustion in acute lymphoblastic leukemia

- T-cell exhaustion is associated with treatment failure following chimeric antigen receptor T-cells (CART), bi specific T-cell engagers (BiTEs), and allogeneic hematopoietic cell transplantation

- Leukemic relapse risk is also increased in the setting of endogenous CD4+ T-cell exhaustion

- Understanding of the mechanisms governing the induction of T-cell exhaustion and its contribution to relapse remains inadequate





<u>Research Questions:</u>

1. **What are the mechanisms linking CD4+ T-cell exhaustion and relapse in ALL?**

2. **Why do some patients present with T-cell exhaustion while most do not?**

3. **How can we recruit the endogenous immune system to eradicate residual disease?**

[1]Blaeschke et al Leukemia March 2020
[2]Hohtari et al Leukemia 33 (2019) 1570–1582
[3]Liu et al Clinical Immunology 190 (2018) 32

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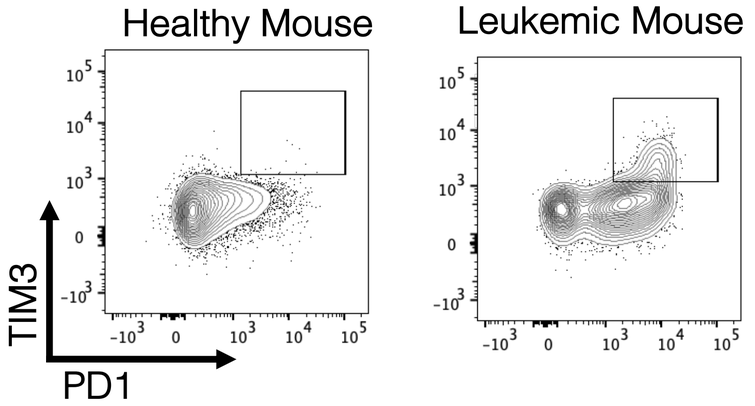
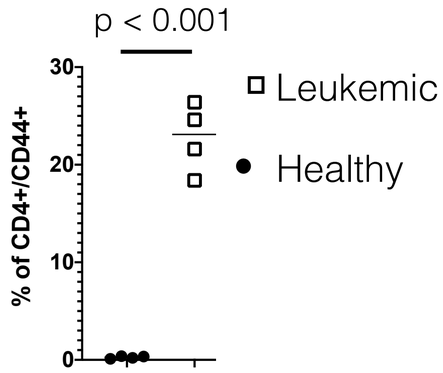
Murine models of ALL recapitulate T-cell exhaustion

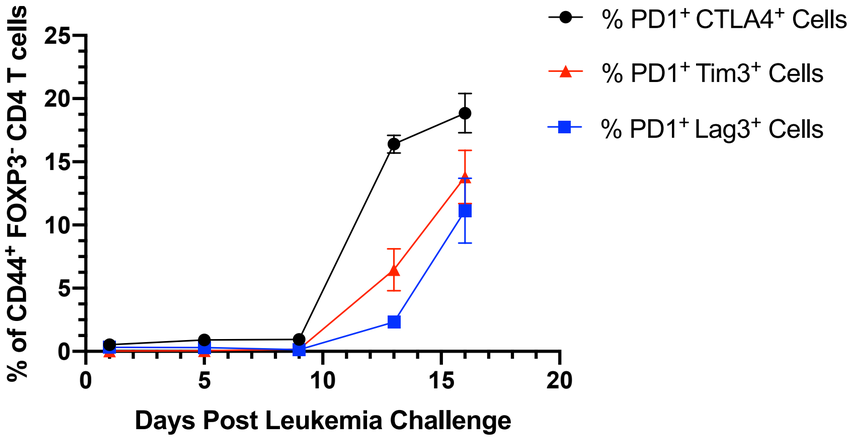
Ph+ALL cell line "LM138"

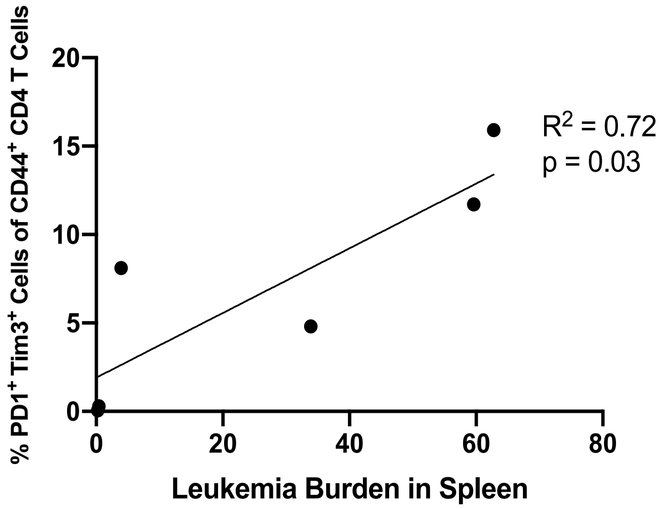
Day 16

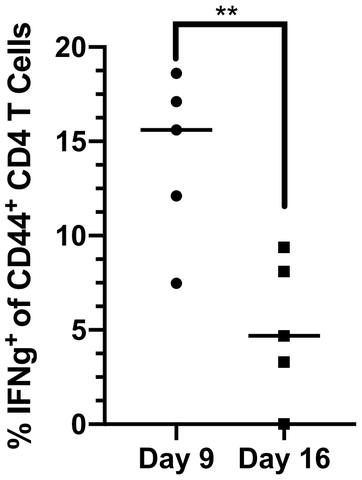
Foxp3- CD44+ CD4+ T-cells











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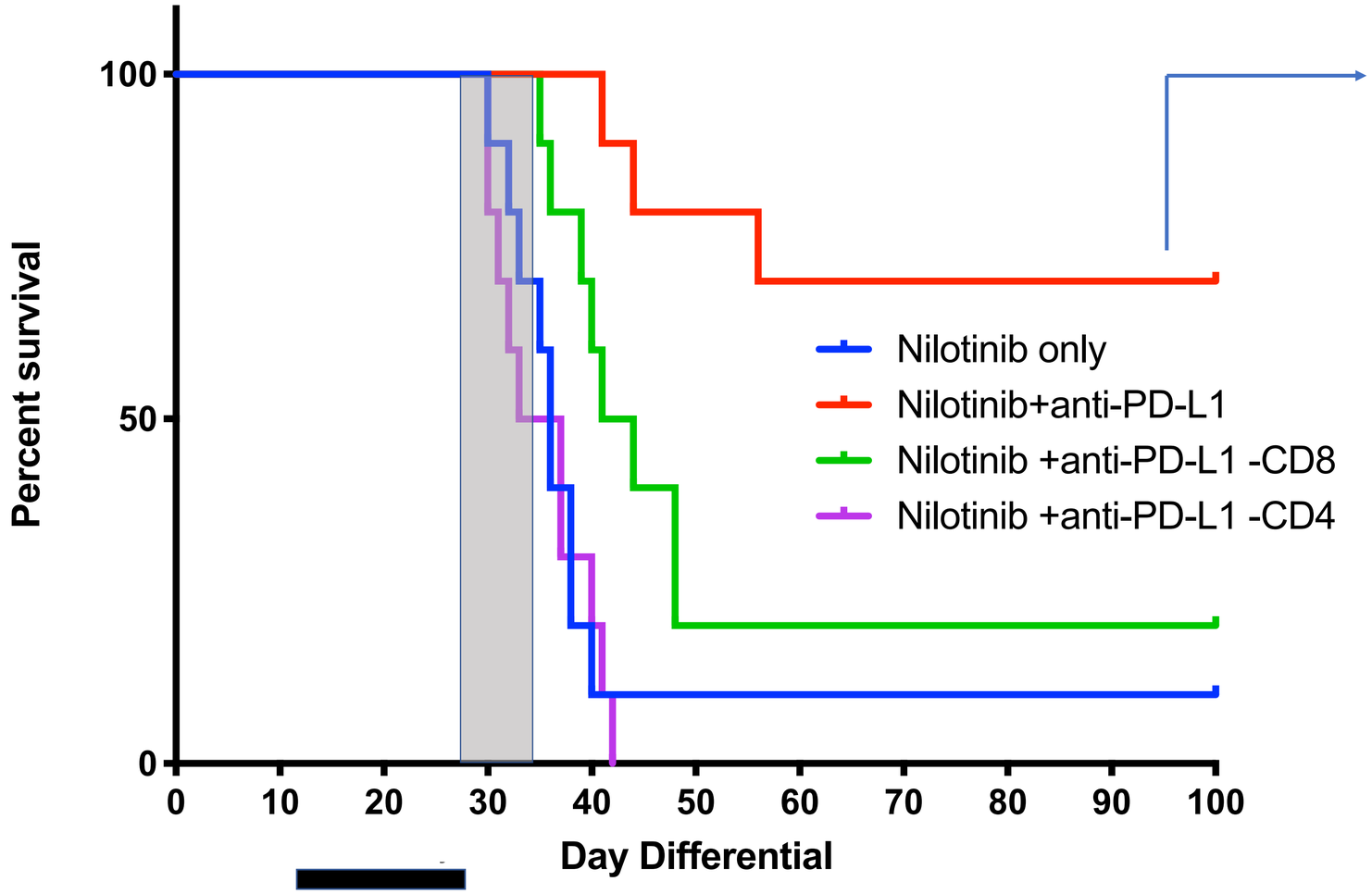
PD-L1 ICB leads to eradication of residual leukemia



6/7 mice survived leukemia rechallenge

Isotype + Nilotinib
T315I, I403V
E255K
T315I
CD4 depletion + Nilotinib + PDL1
E255K
E255K
E255K

Nilotinib:

Depletion:

PD-L1 blockade

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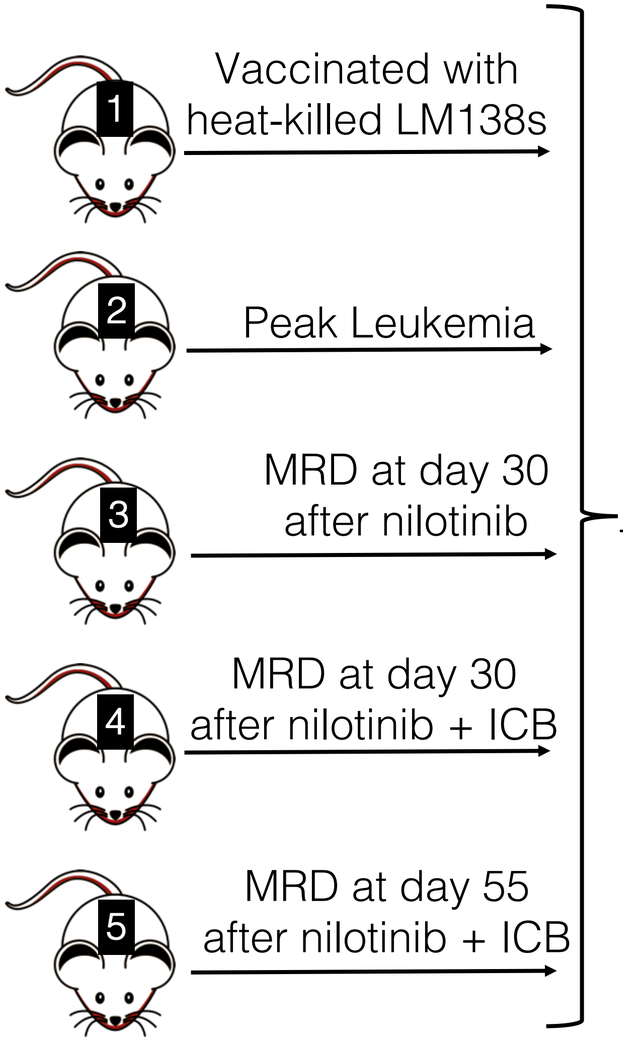
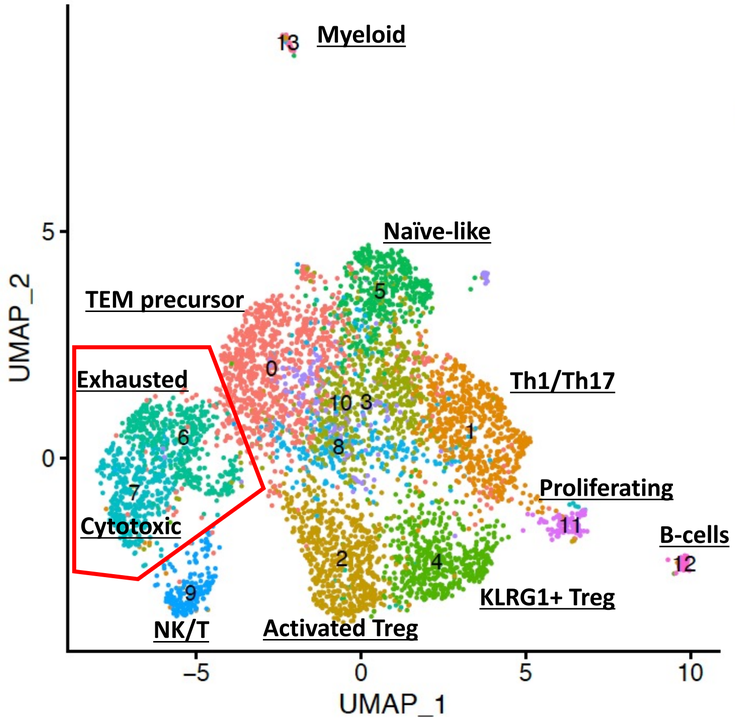
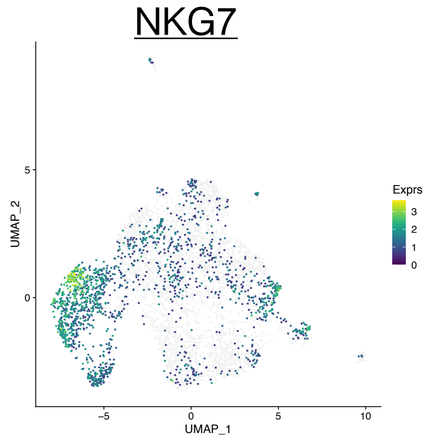
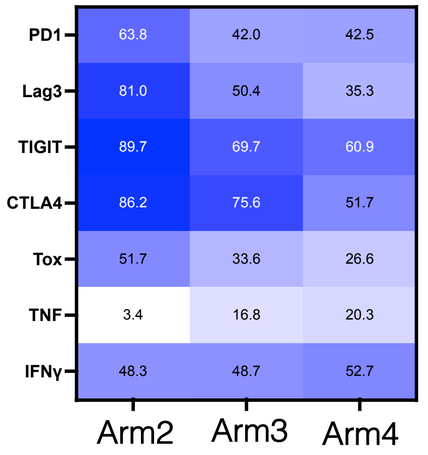
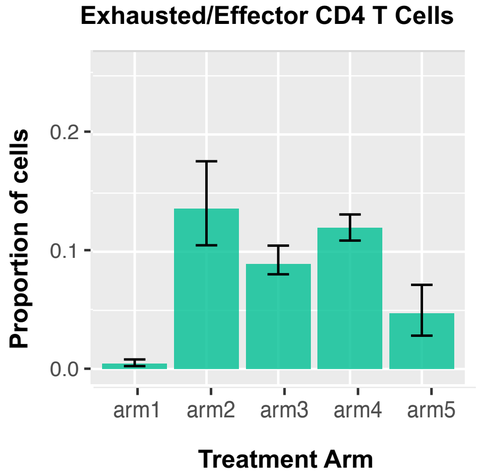
scRNA-seq reveals that PD-L1 ICB rescues an NKG7+ cytotoxic subset from exhaustion

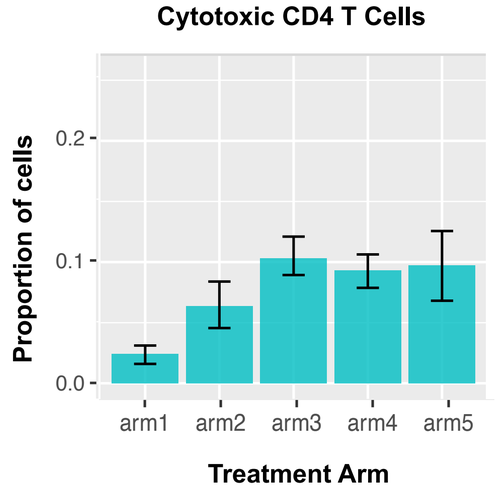












Conclusions and Future Directions

- CD4+ T-cell exhaustion is associated with inferior outcomes in B-cell ALL
- Murine models recapitulate key features of ALL-induced T-cell exhaustion
- PD-L1 immune checkpoint blockade counters CD4+ T-cell exhaustion and is able to eradicate minimal residual disease
- B-cell ALL induces exhaustion of an NKG7+ cytotoxic CD4+ T-cell subset
- Ongoing research is being conducted on patient-derived bone marrow specimens to identify immunological correlates of responsiveness to immune checkpoint blockade
- Immune checkpoint blockade is being explored following allogeneic HCT (NCT03286114), and in combination with blinatumomab (NCT04546399), (NCT02879695).