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Society for Immunotherapy of Cancer

SITC 2020
NOVEMBER 10–15
NATIONAL HARBOR, MD.

Molecular Events Regulating Solid Tumor Cell Responses to Natural Killer (NK) Cells

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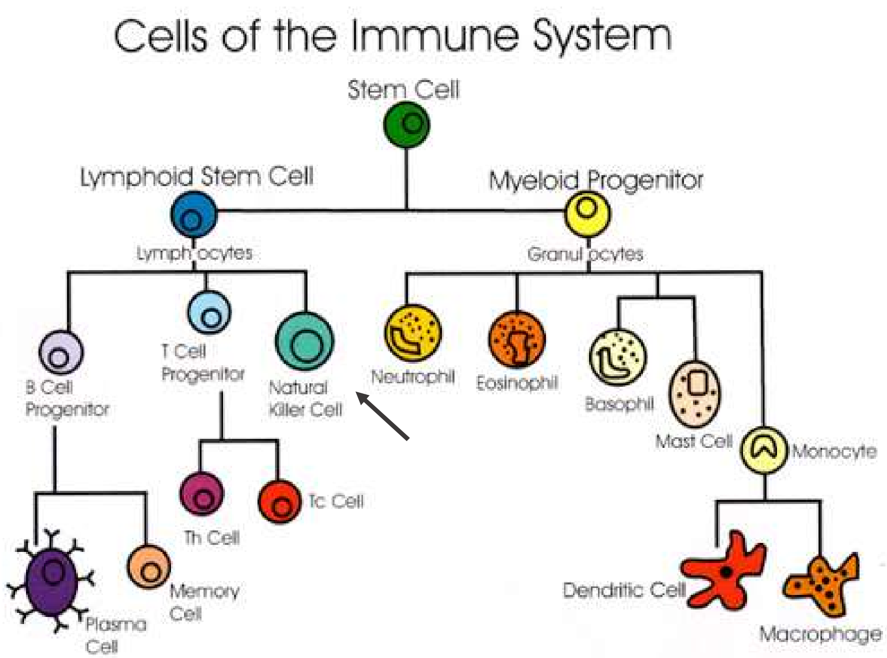
No Conflicts of Interest to Disclose

NK Cells - Overview



http://textbookofbacteriology.net/ken_todar.html

- Lymphocytes of the Innate immune system
- $CD3^-/CD56^+$
- Activated by IL2, IL15 and other cytokines
- Secrete IFNγ, TNFα
- Express many activating and inhibitory receptors
- Signaling balance - the decision to kill is based on the balance between activating and inhibitory receptors
- Killing is done through secretion of granzymes and perforins, activation of death receptors and Antibody-dependent cellular cytotoxicity (ADCC)

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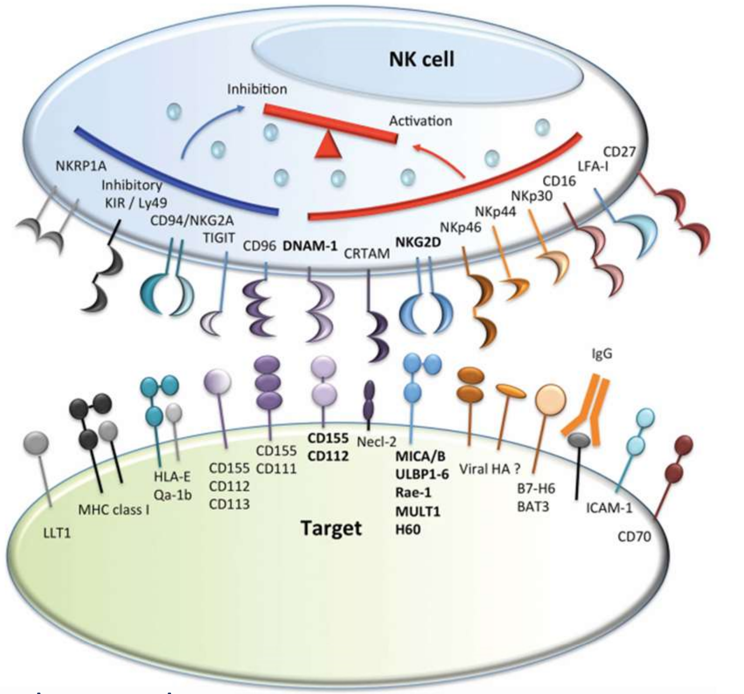

Chan et al. 2014

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Why NK Cells?

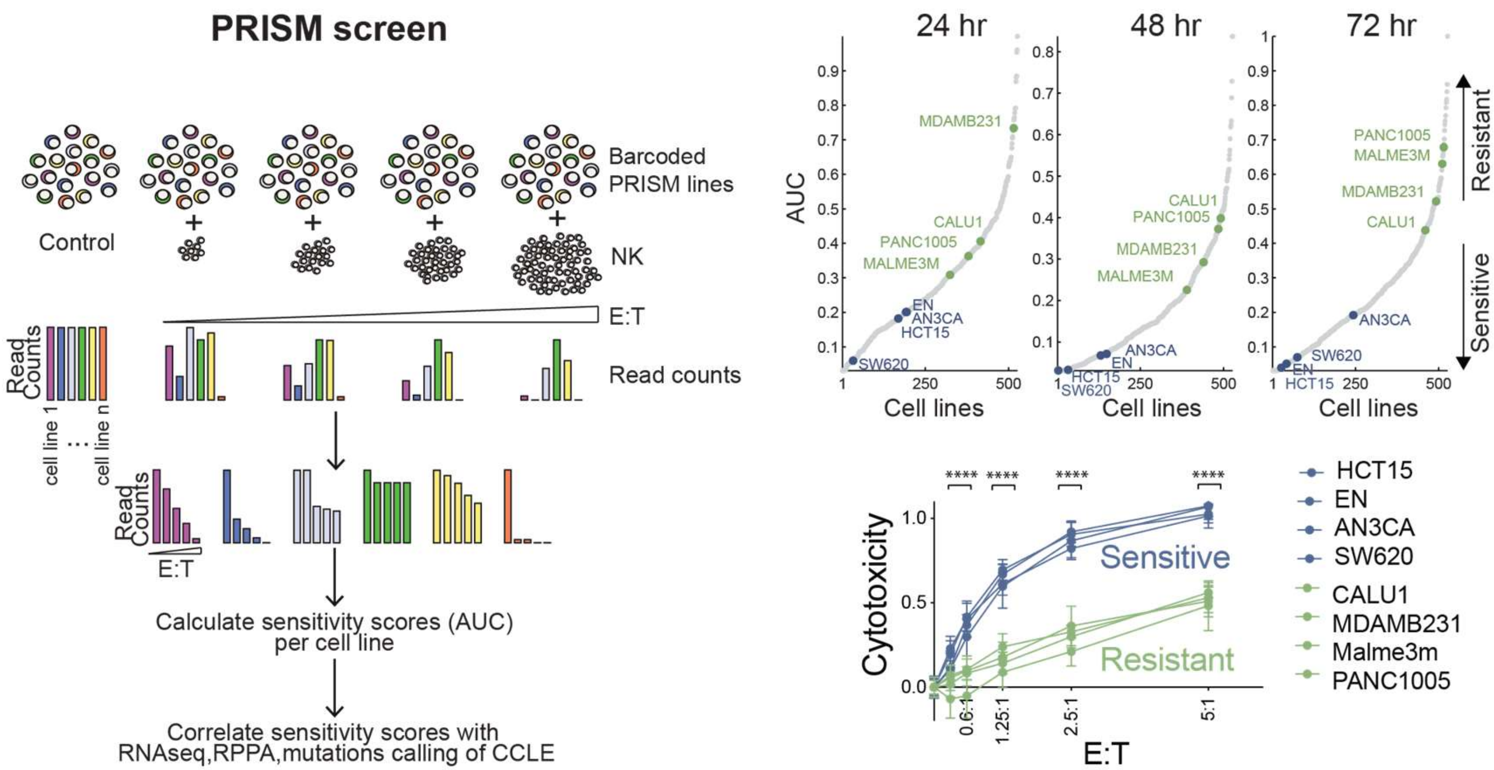
- Potent killers of tumor cells
- Do not kill healthy cells
- Operate across HLA barriers – can be isolated from any healthy donors
- Promising results from clinical trials
- Can be used to treat other types of diseases
- Easy to expand

AIMS

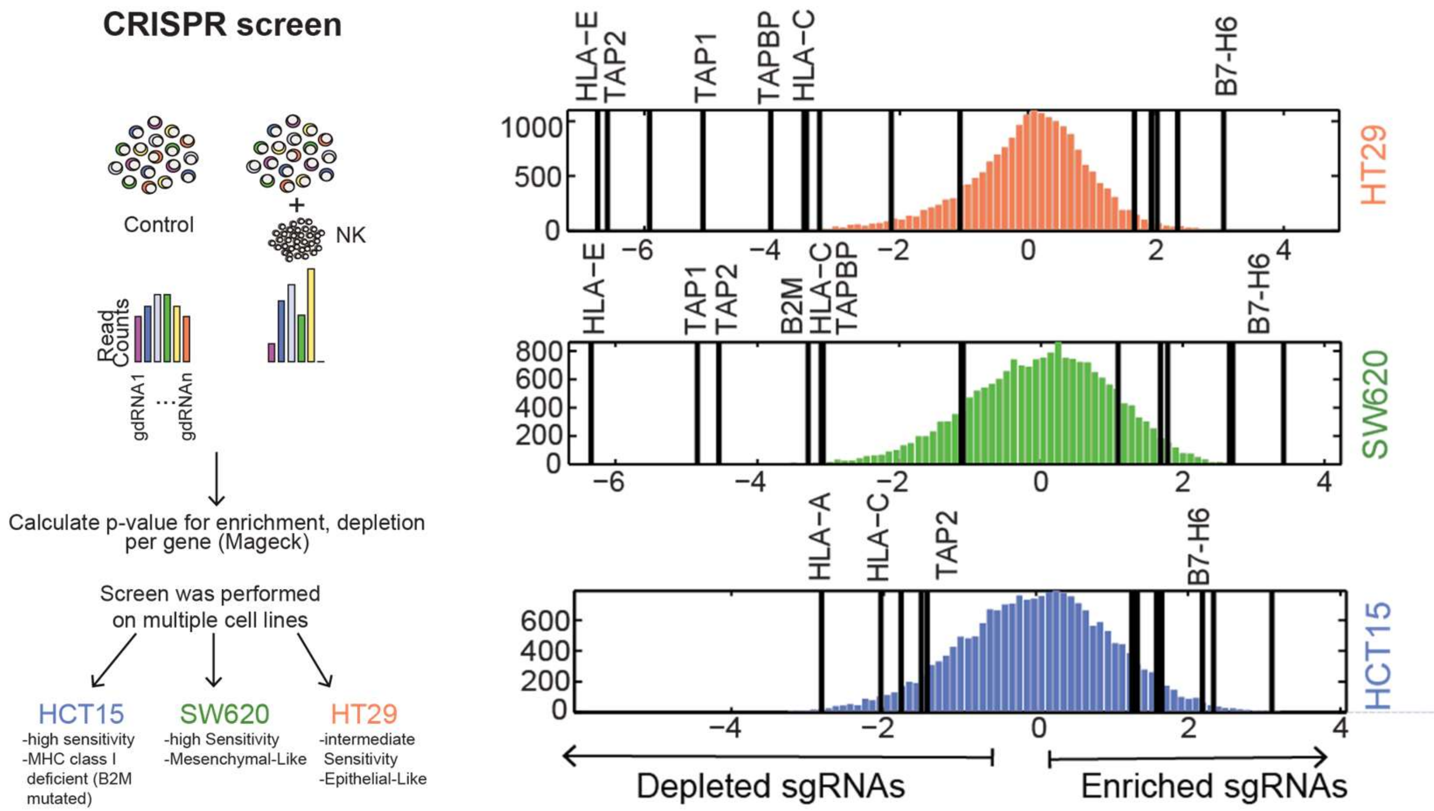
Find Novel regulators of responses to NK cells using high-throughput unbiased approaches in order to:

- better understand mechanisms of immune evasion
- enhance NK immunotherapy

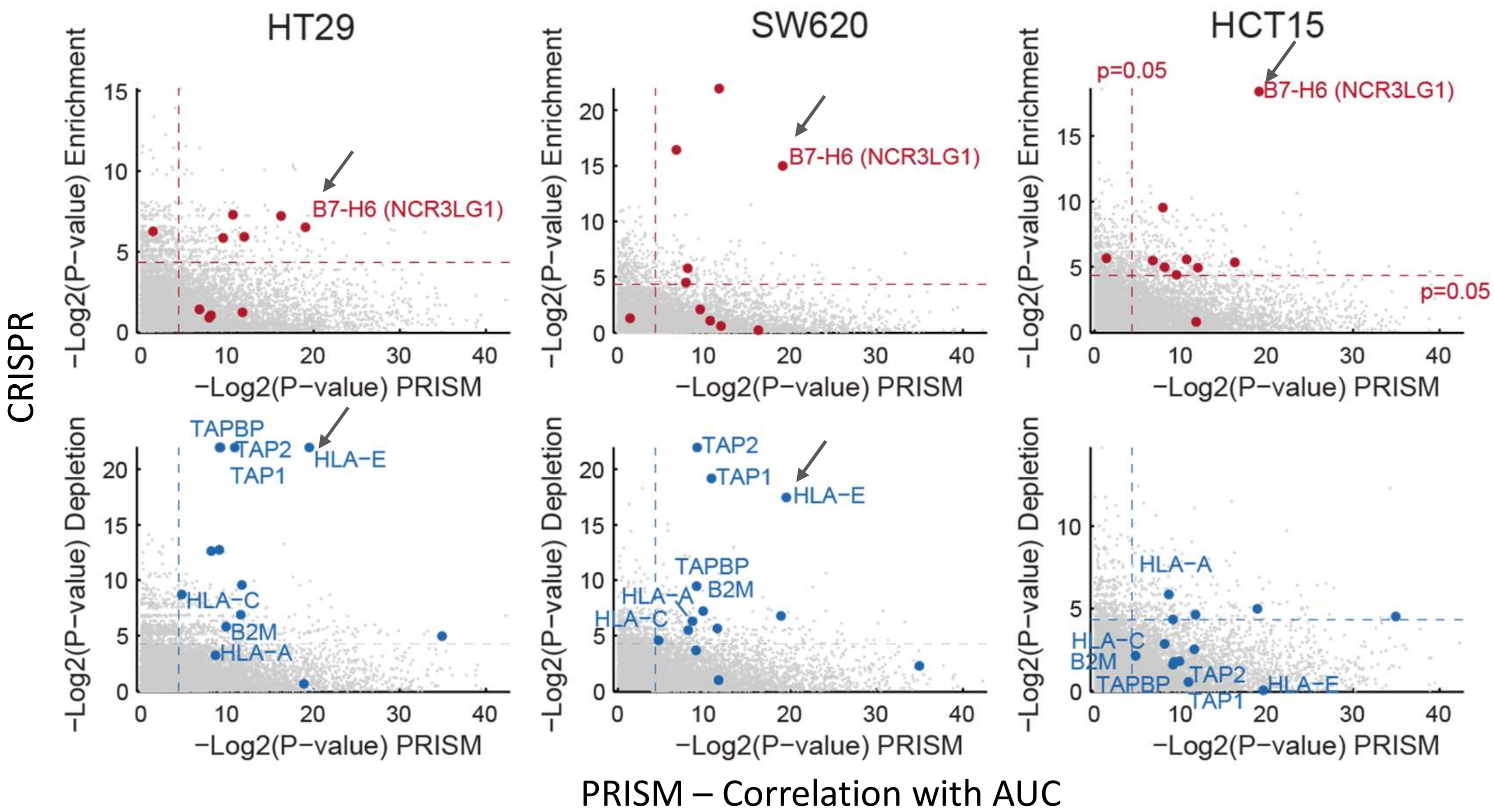
Cytotoxic Assays for Pooled Barcoded Cell-lines (n=568)



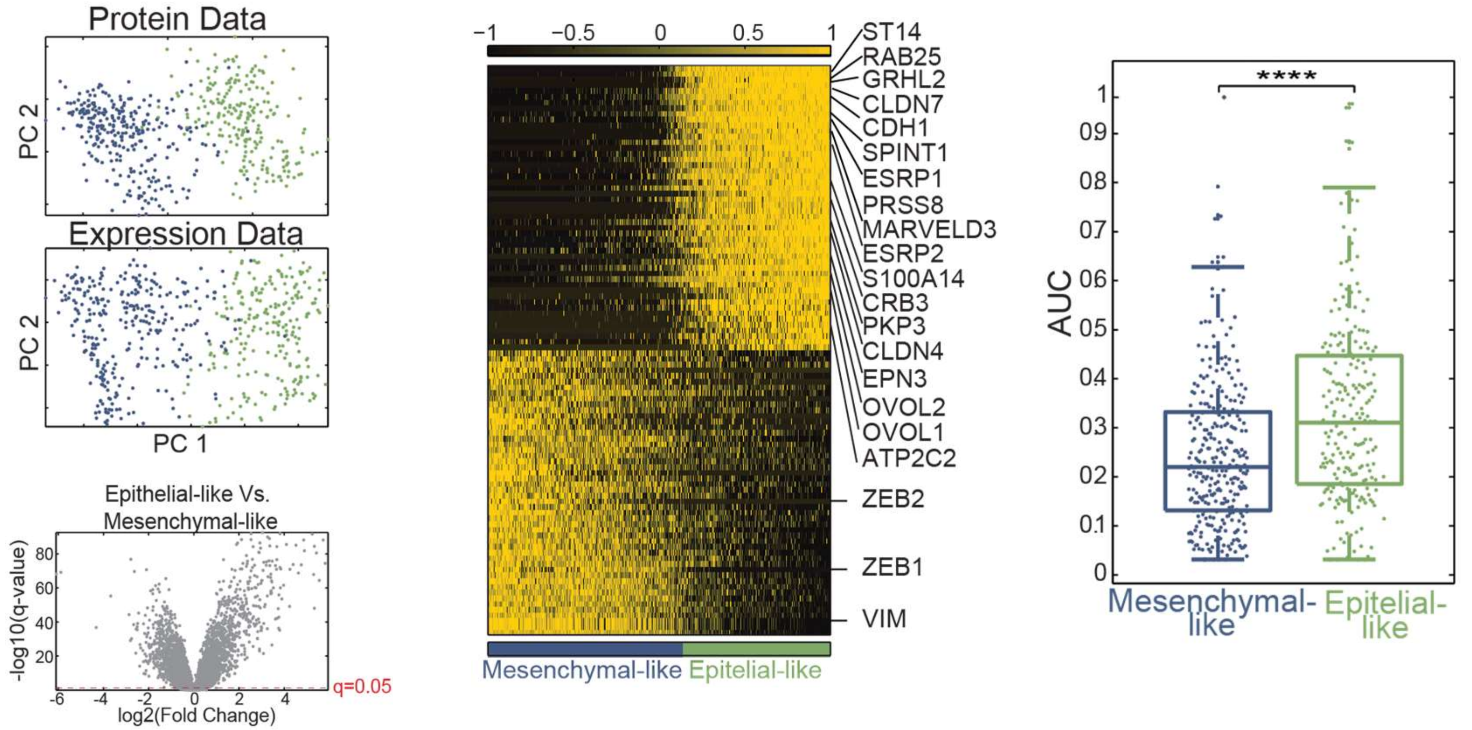
Whole Genome CRISPR Screens



Combined Analysis for CRISPR and PRISM



Mesenchymal-like Tumor Cells are More Sensitive to NK Cell Cytotoxicity



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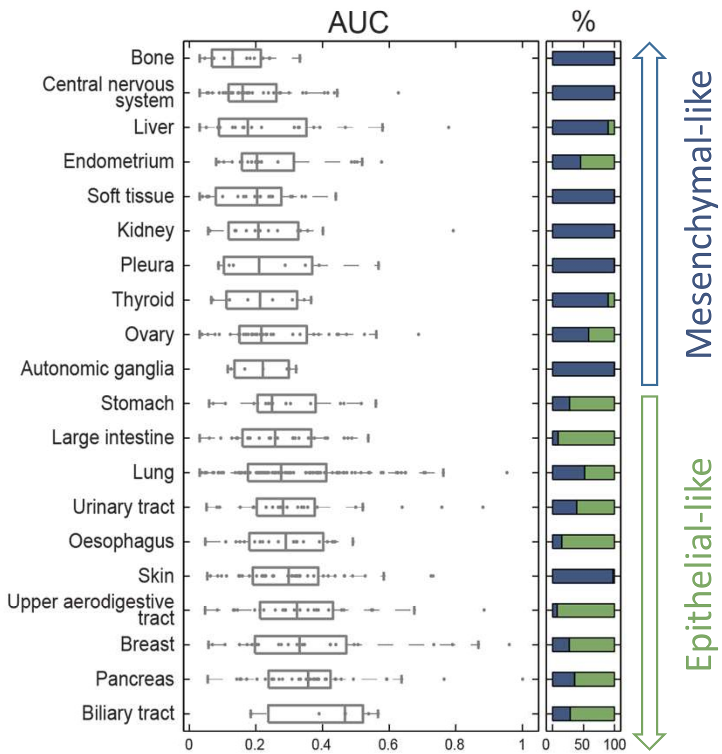
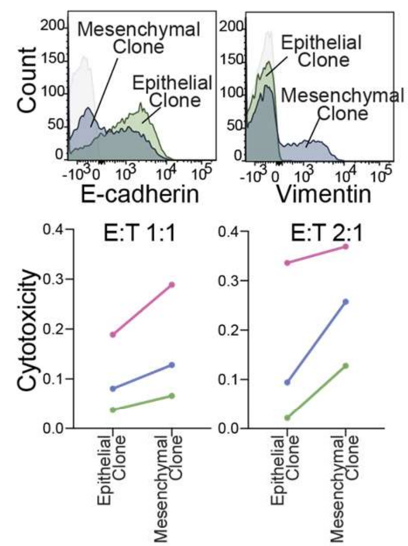
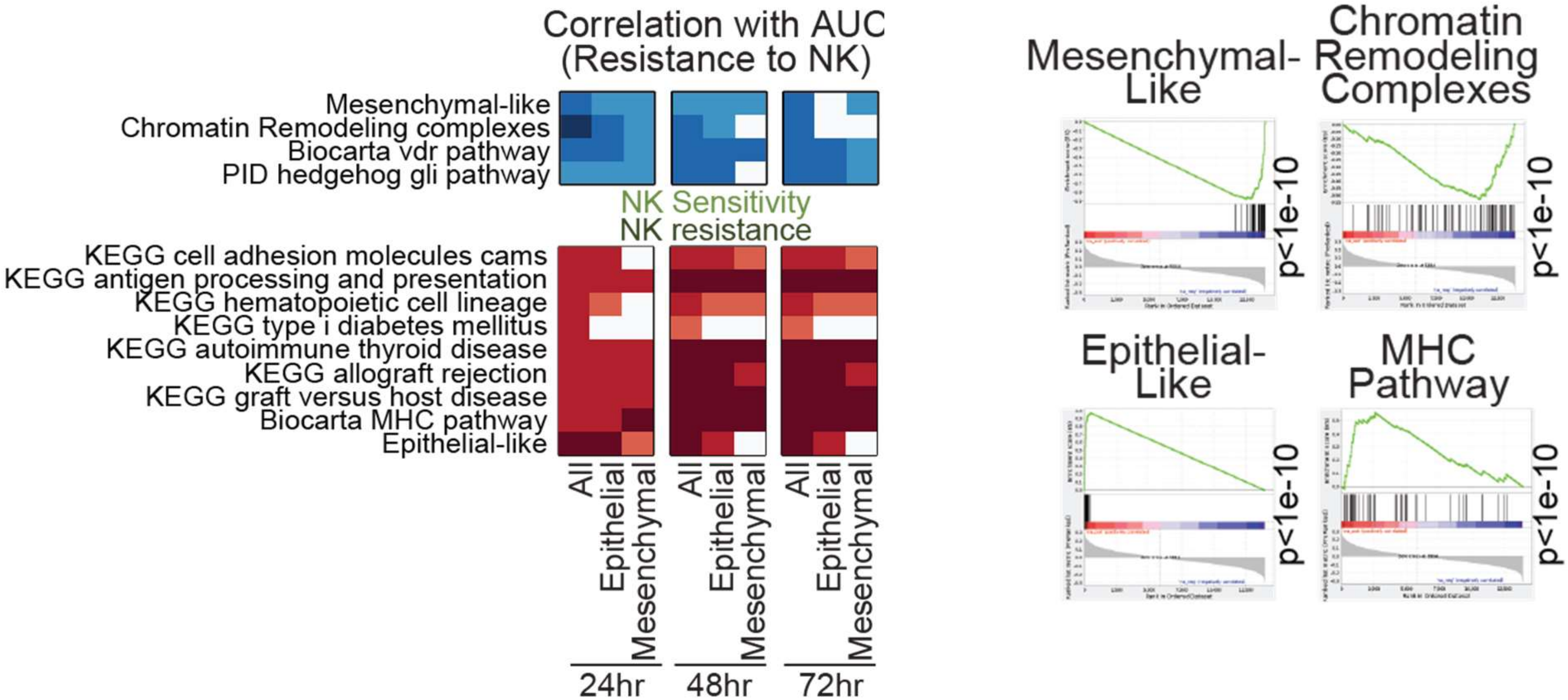


Clones isolated from the same ovarian tumor show different responses to NK cells



Chromatin Remodeling Genes are Associated With Response to NK Cells



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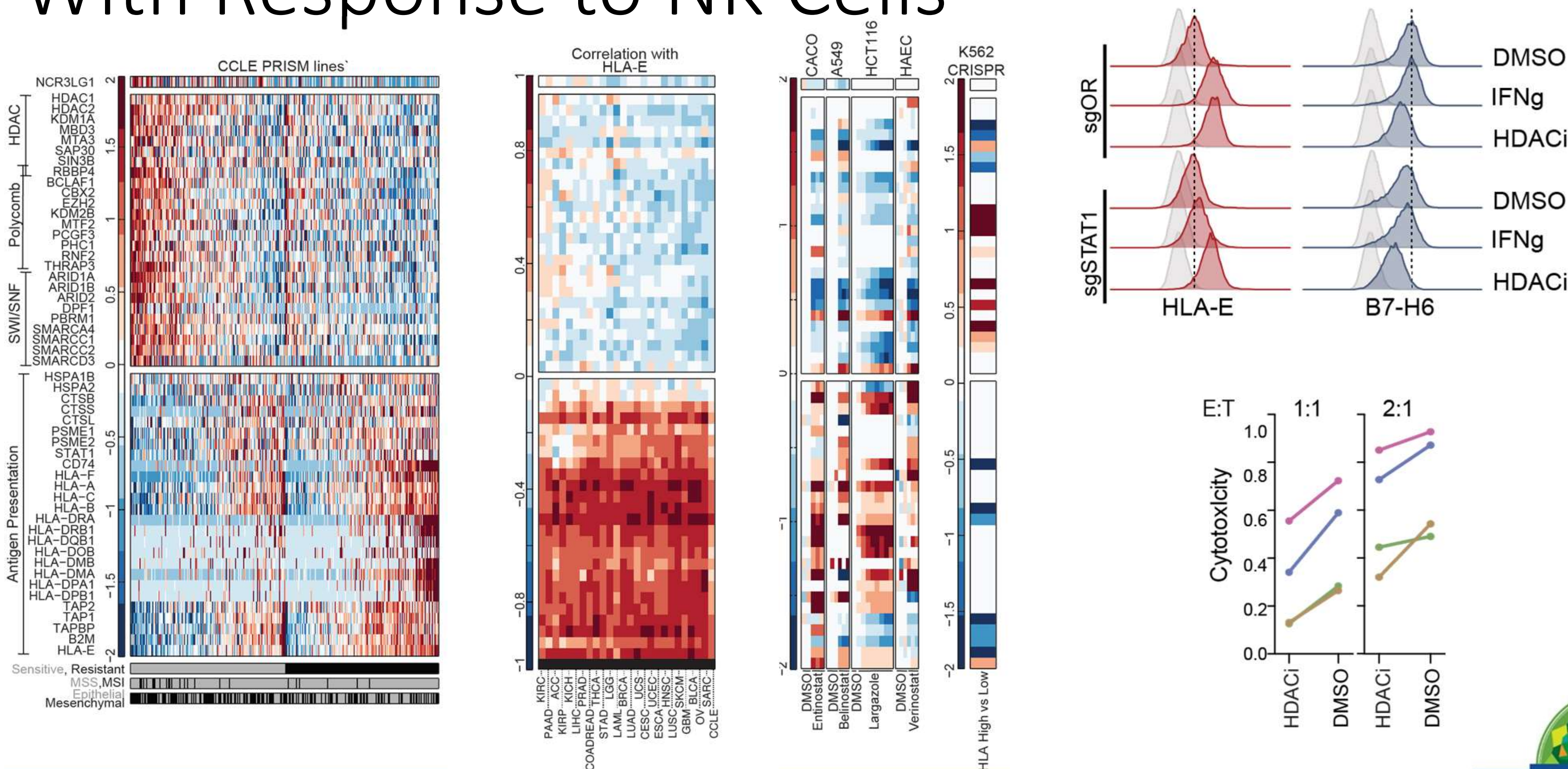
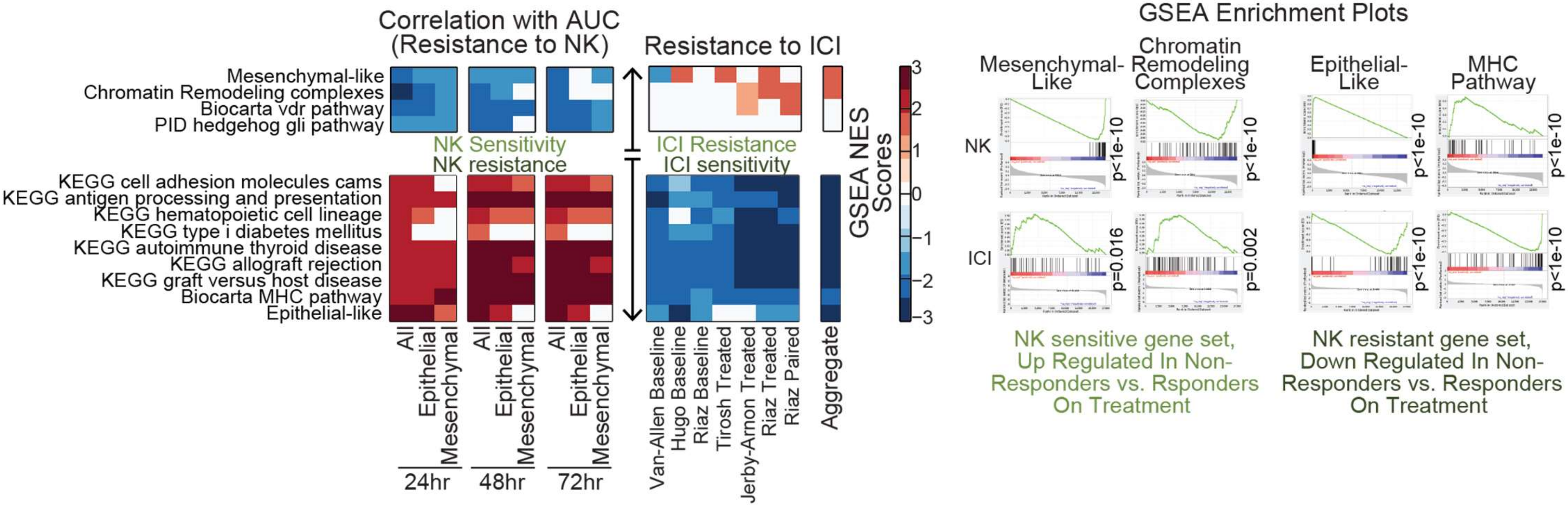


NK Cell Sensitivity is Associated with Resistance to Immune Check-point Inhibition (ICI)



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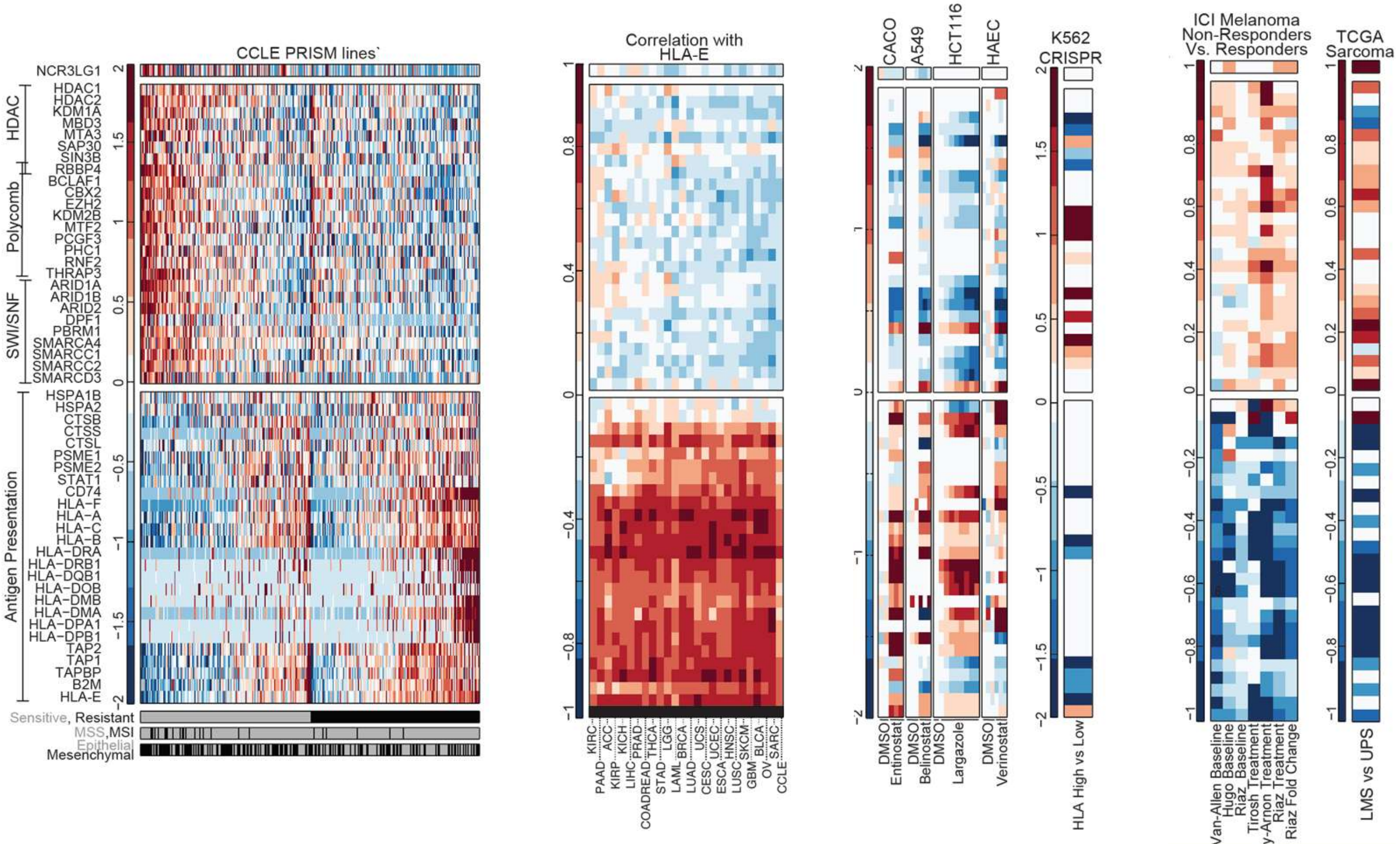
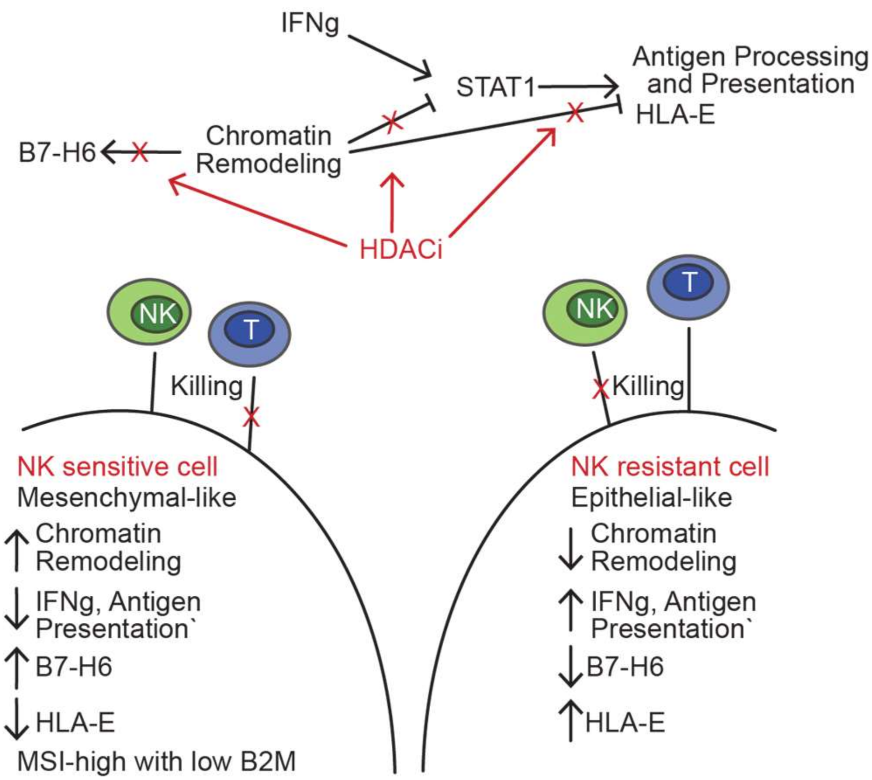


Targeting the Tumor Cells: NK- vs. T-cell



Summary

- The use of complementary high-throughput platforms - PRISM, CRISPR to identify novel and known regulators of response to NK cells
- B7-H6 and HLA-E are major regulatory ligands
- Mesenchymal-like tumors exhibit higher sensitivity to NK cells
- HDAC inhibitors induce resistance to NK cells through up-regulation of the HLA machinery
- Molecular signatures of NK sensitivity are associated with immune check-point inhibition

⇨ cancer patients may benefit from a combination of NK immunotherapy and ICI

Thank You!

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