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Federation of Clinical Immunology Societies

Real Time Analysis of Immunotherapy Evasion

Shashank Patel, PhD
Asso. Vice President, R&D, Immunai

Disclosure

This work was undertaken at National Cancer Institute, NIH which is one of the US Federal Government research organizations, unless indicated on the slides.

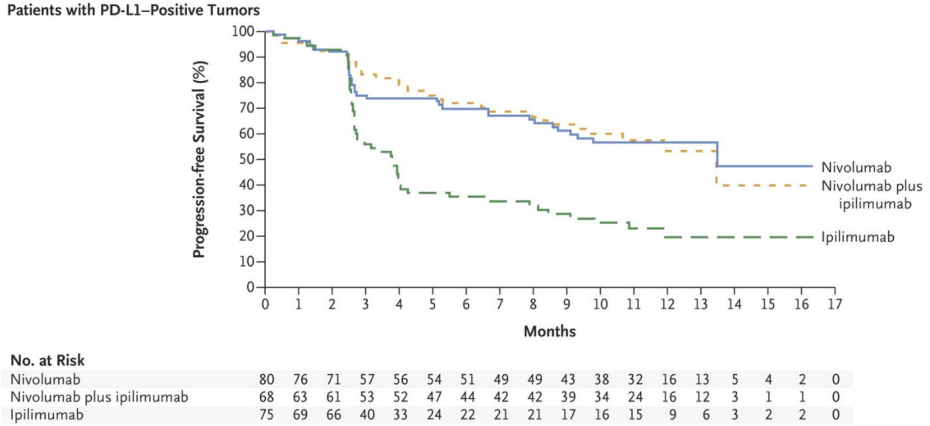
I am currently employed at Immunai USA.

Time : A key dimension and measurement

Measure of success in Clinical Oncology is **Survival - OS, PFS (time unit)**

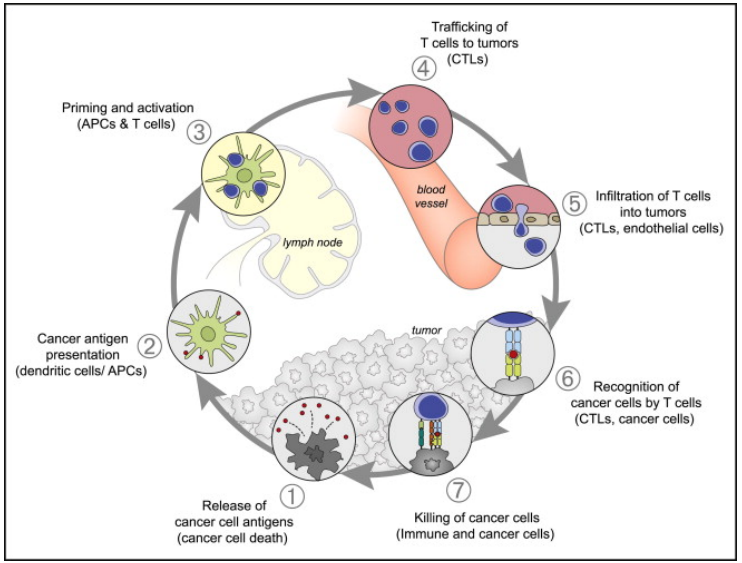
How do we gain real time understanding of tumor immune evasion for T cell killing? Inherent resistance (Unresponsiveness) - Adaptive resistance (Relapse)

https://sciencevibe.com/wp-content/uploads/2014/12/



Larkin et al. 2015 *NEJM*

Immunity cycle in cancer and how immune system kills cancer?



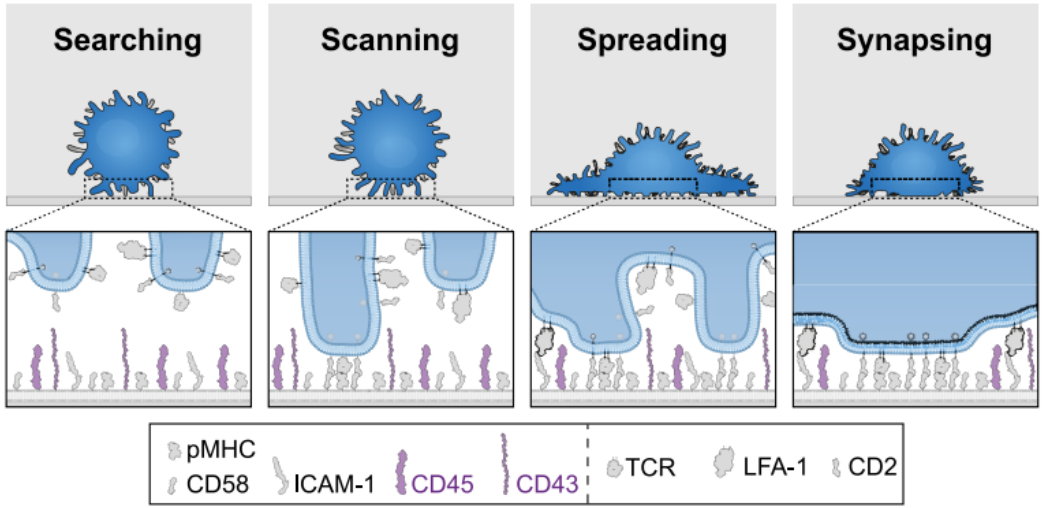
Chen and Mellman, Immunity 2013

Over decades of research, now we understand nothing is as simple in cancer!

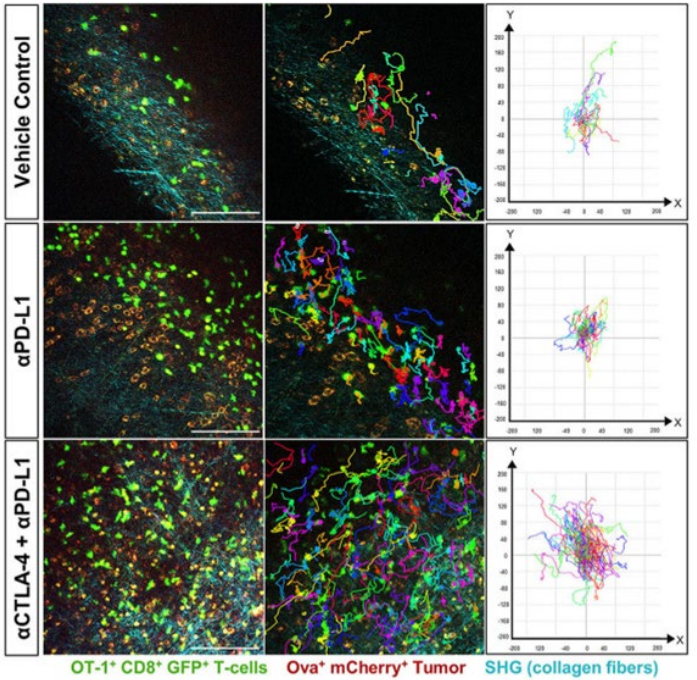
But, so far the **common denominator** of most potent anti-cancer response is:

T cell mediated killing

Dynamics (timings) of T cell interactions with cancer cells or antigen presenting cells

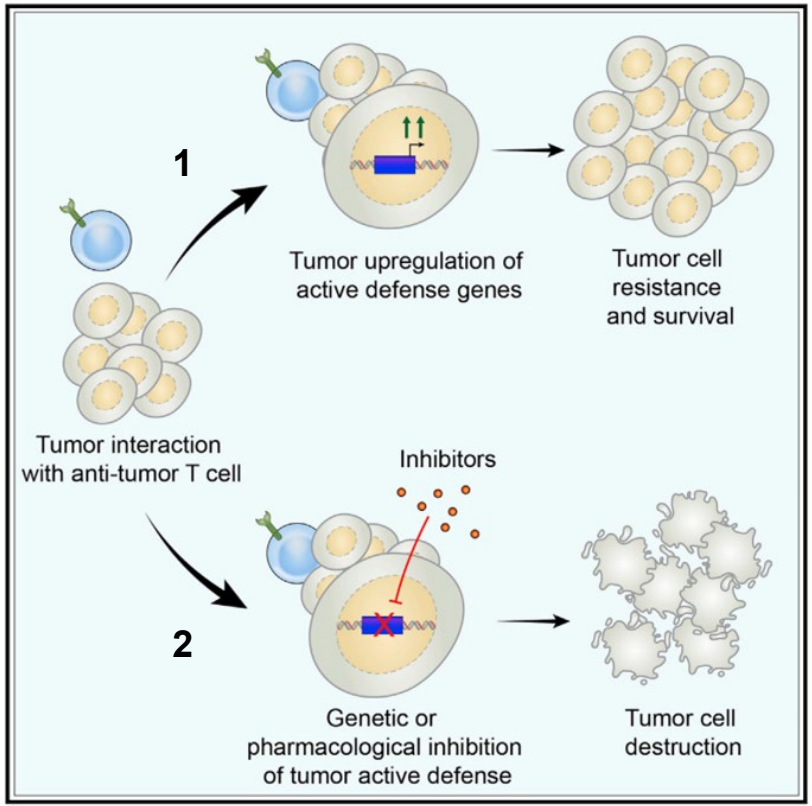


Jenkins et al. 2023 *Nat comm.*



Lau et al. 2020 *Front Imm.*

Rational approach to identify and target *Disfavored* genes against anti-cancer immunity



Correlates in The Cancer Genome Atlas

↓

Time-lapse capture of *Disfavored* genes in cancer cells

↓

Time-controlled assay systems to functionally verify the ‘true’ *disfavored* genes

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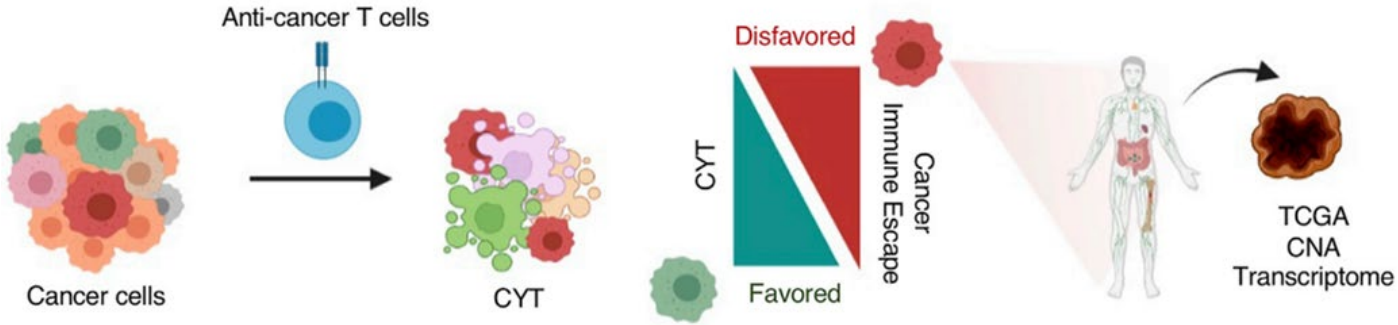
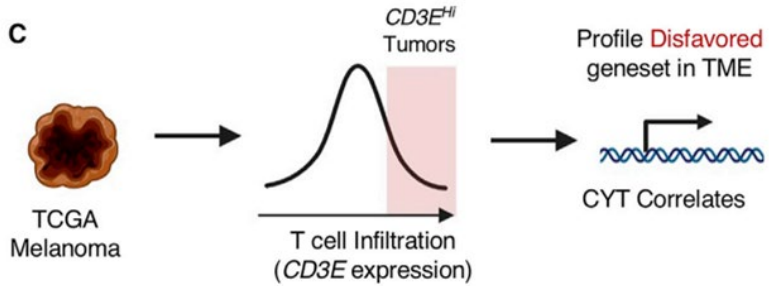
Drug based perturbations leading to discovery of immune sensitizers and underlying MOA

Rationalized drug combination for T cell therapy

The Cancer Genome Atlas (TCGA)- '*Correlates'* Hunt

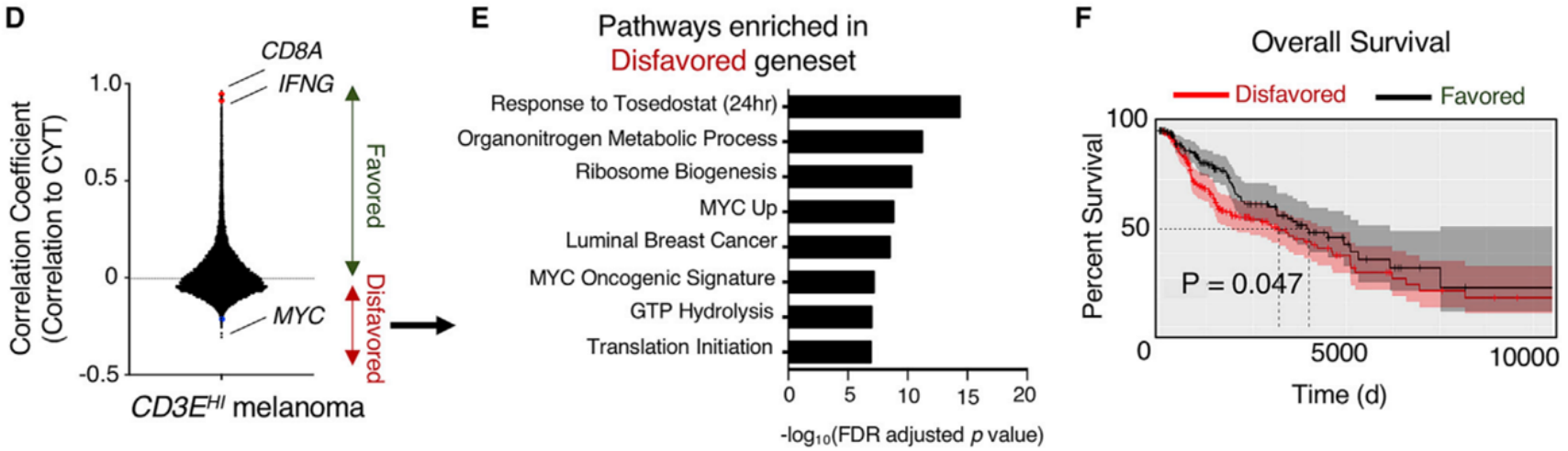




In T cell enriched melanomas (top 25% *CD3E-Hi*), search of genes and pathways associated with cytolytic activity (*PRF*, *GZM*)

Identification of correlates disfavoring T cell cytotoxicity in TCGA **melanoma** dataset

Geneset **Pathways** **Prognosis**



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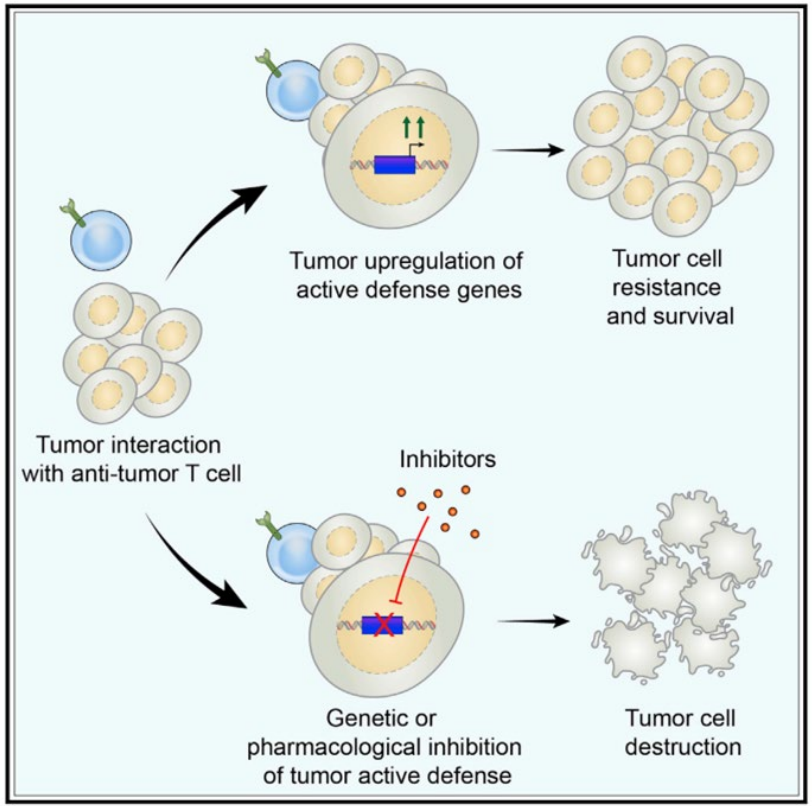

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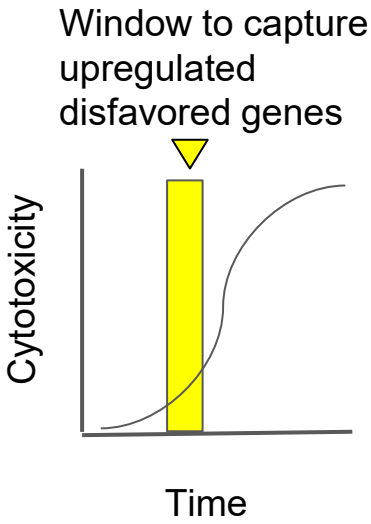

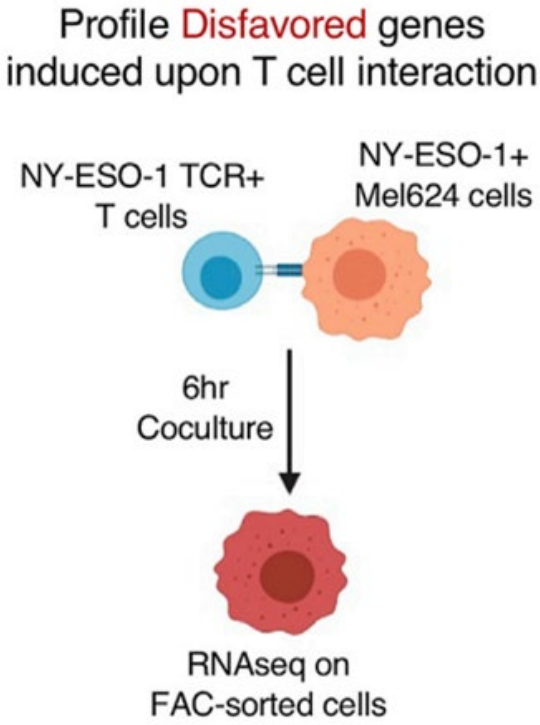

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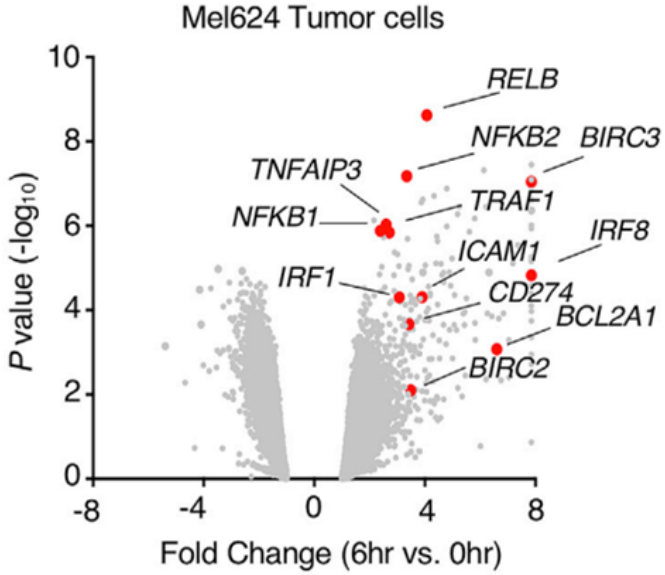

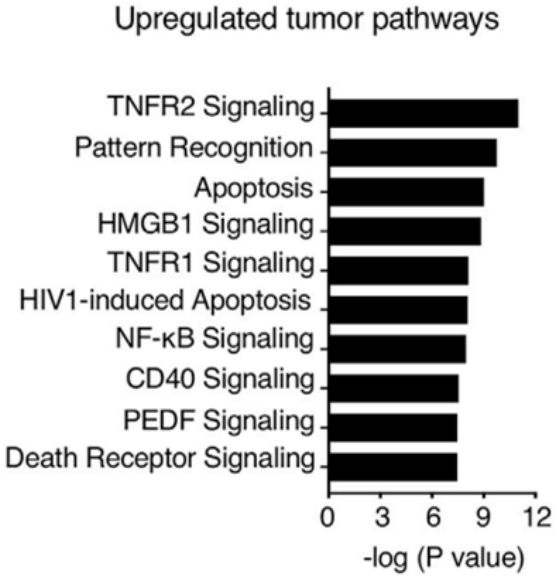

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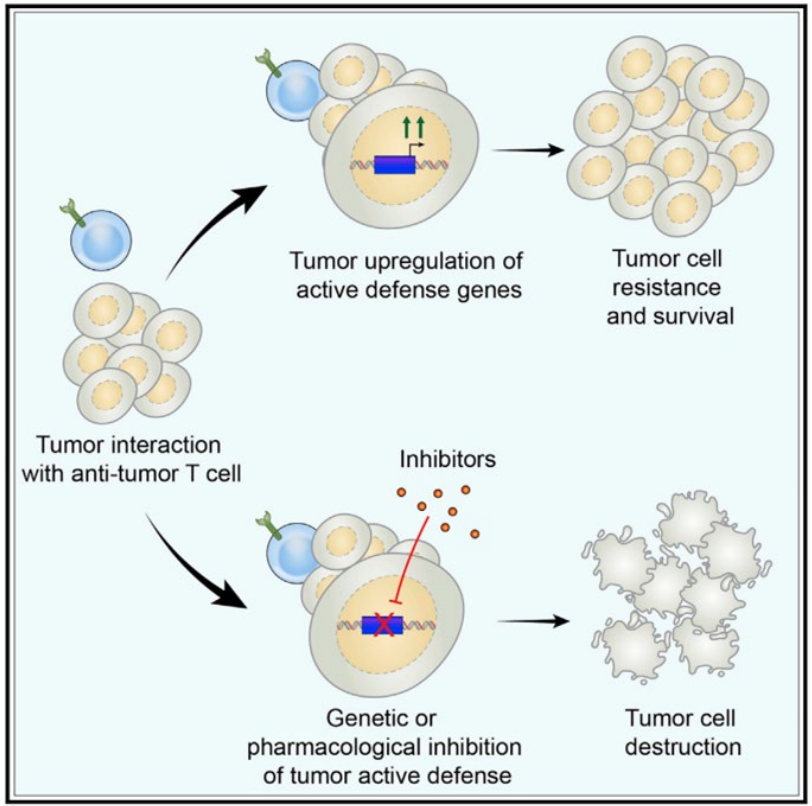

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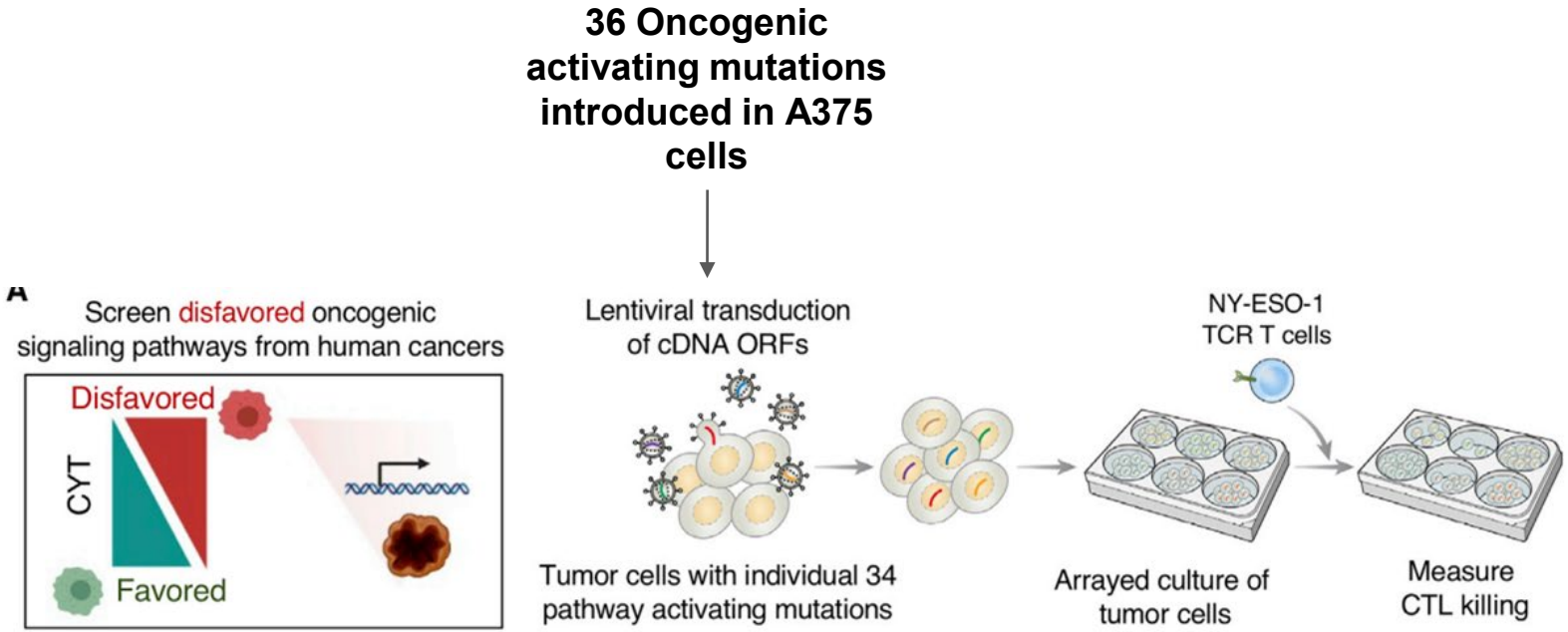
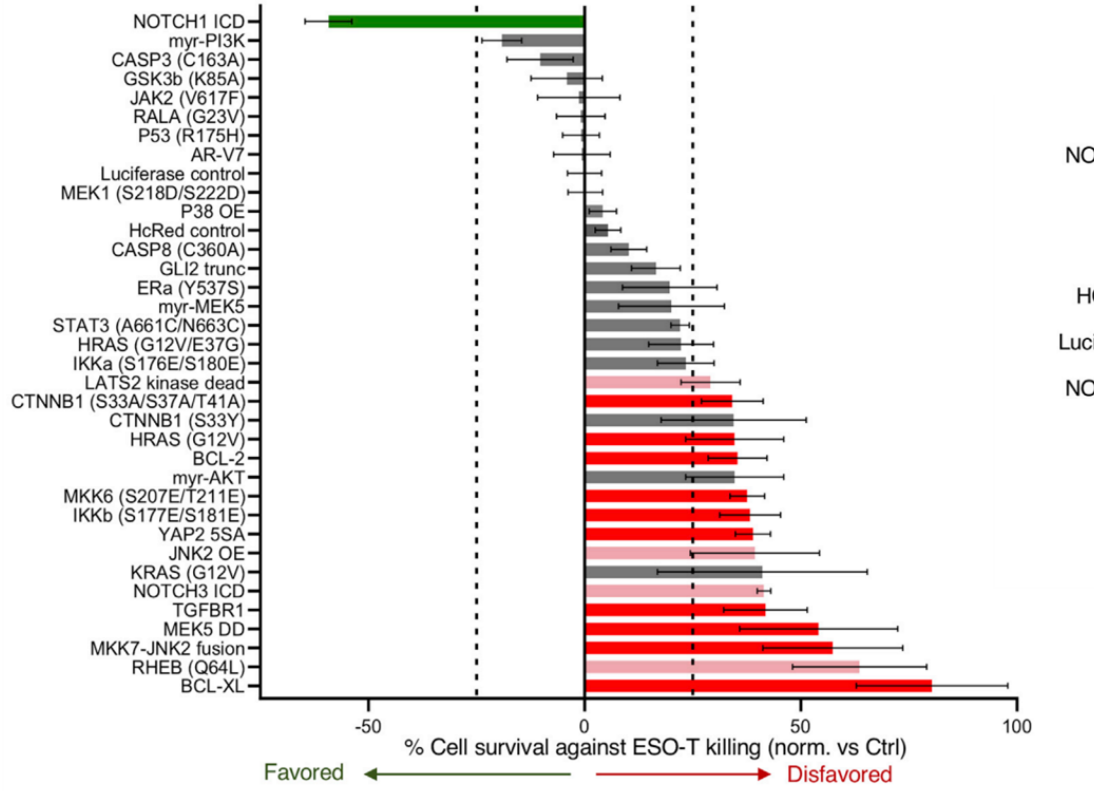
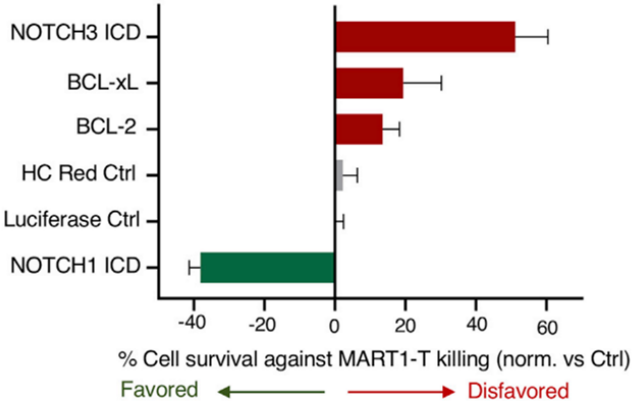
Oncogenic pathways- ORF library

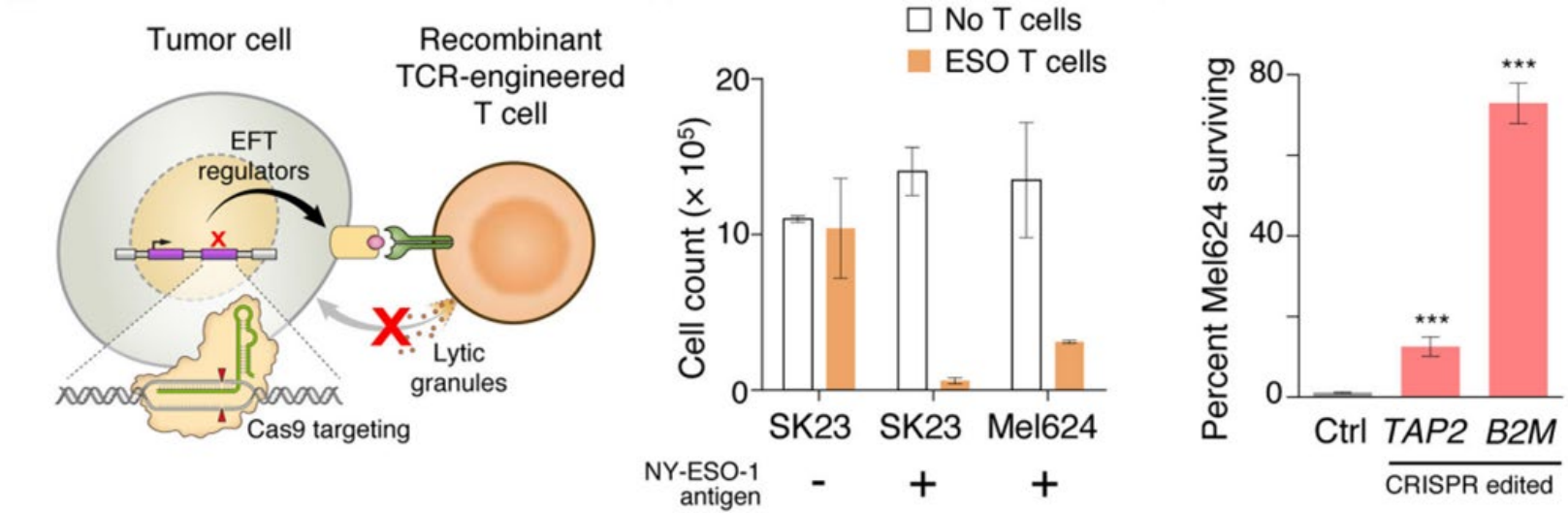


Oncogenic pathways resisting T cell responses

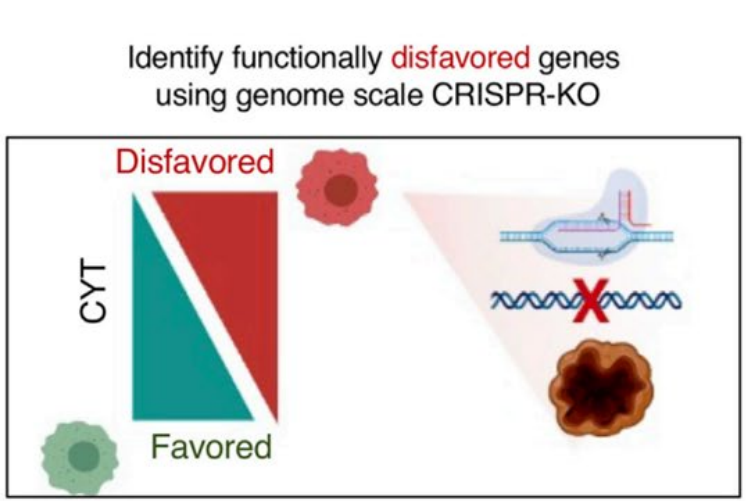


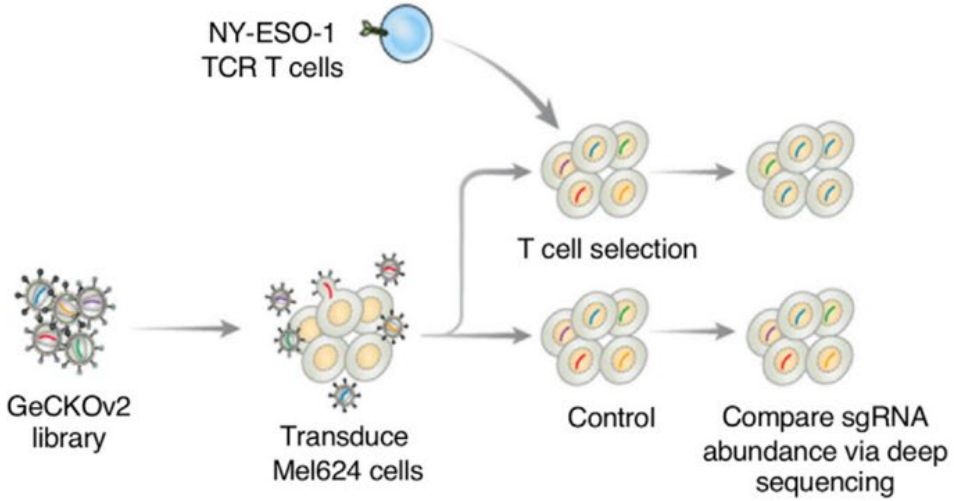


CRISPR-based genetic deletion in T cell:Cancer cell coculture systems



Unbiased genome-scale CRISPR screens to search for disfavored genes





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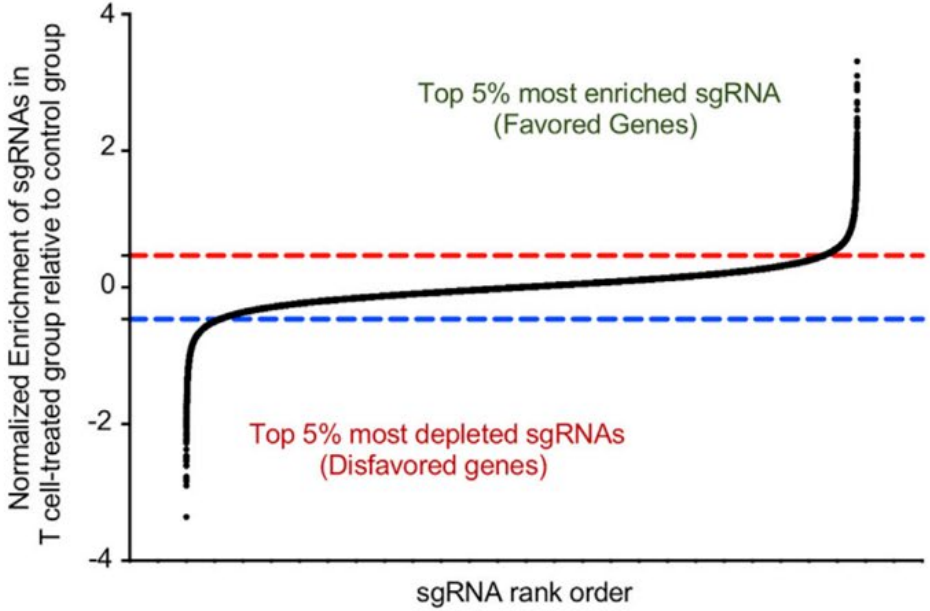
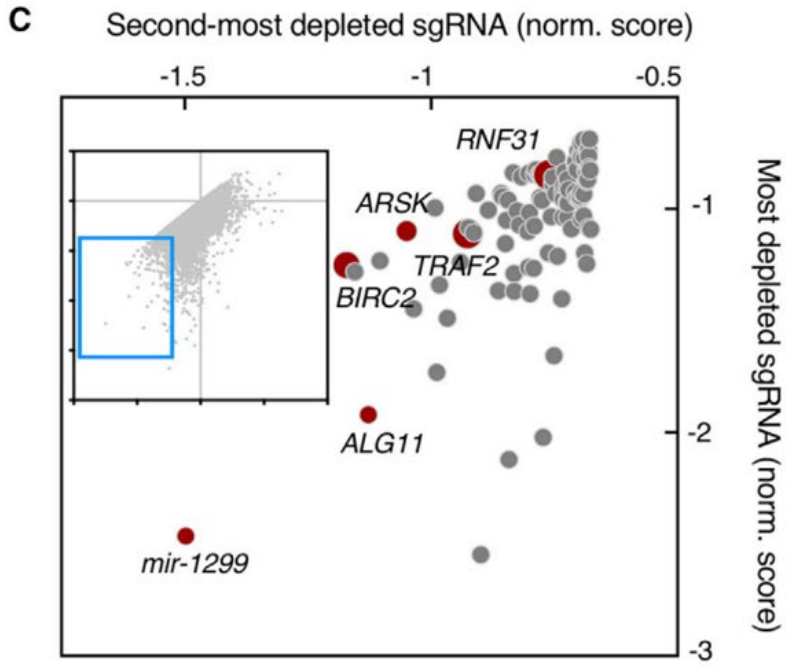
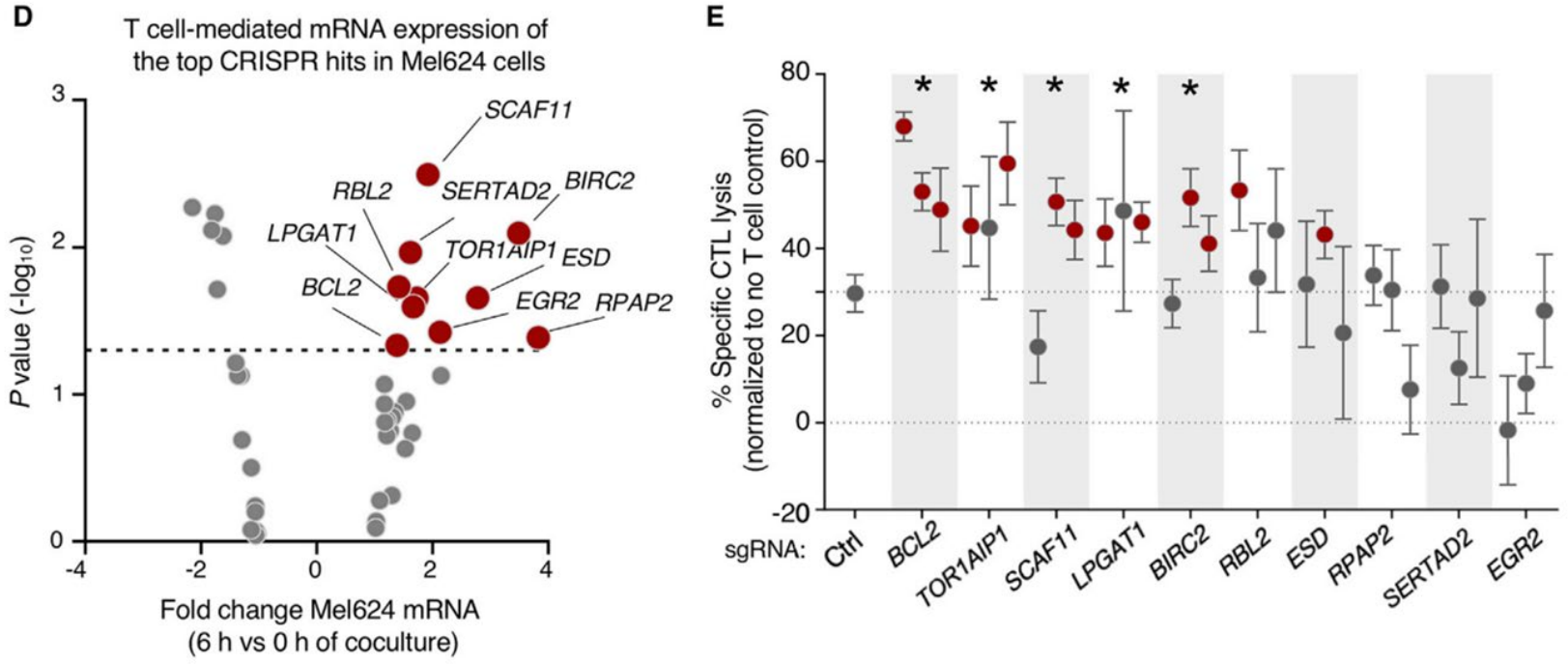




Validated disfavored genes are rapidly induced in cancer cells upon T cell contact



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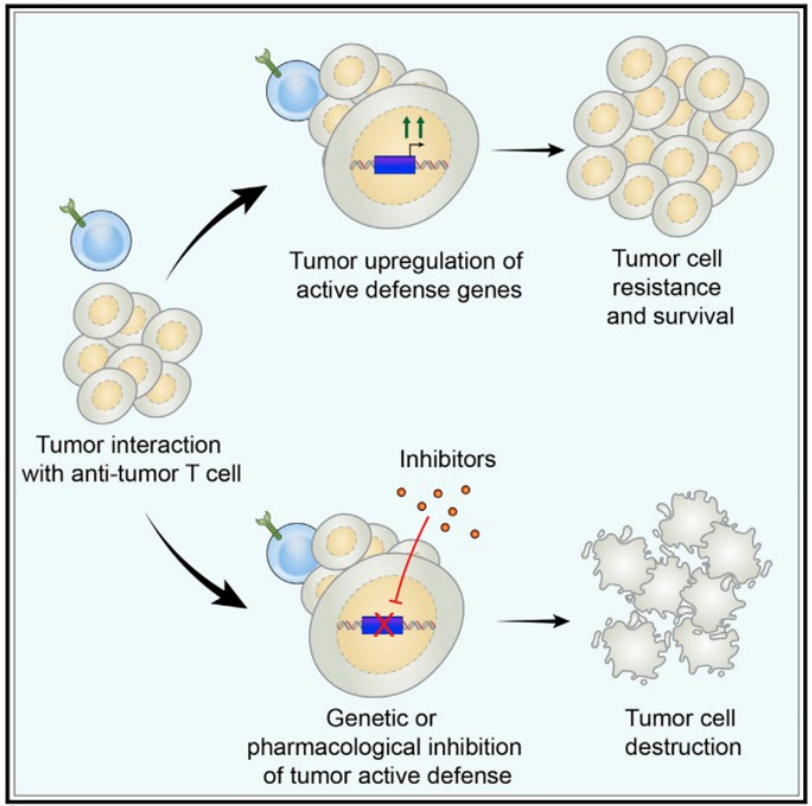

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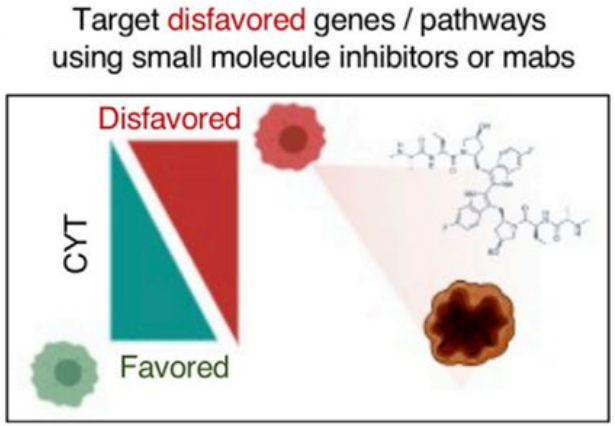
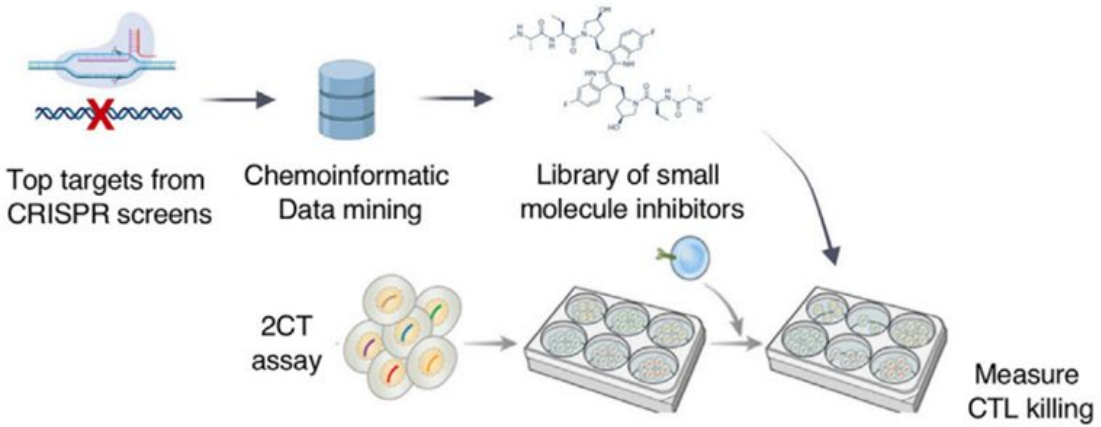
Rationalized drug combination for T cell therapy

Drug perturbations to find rationalized combination for T cell therapy





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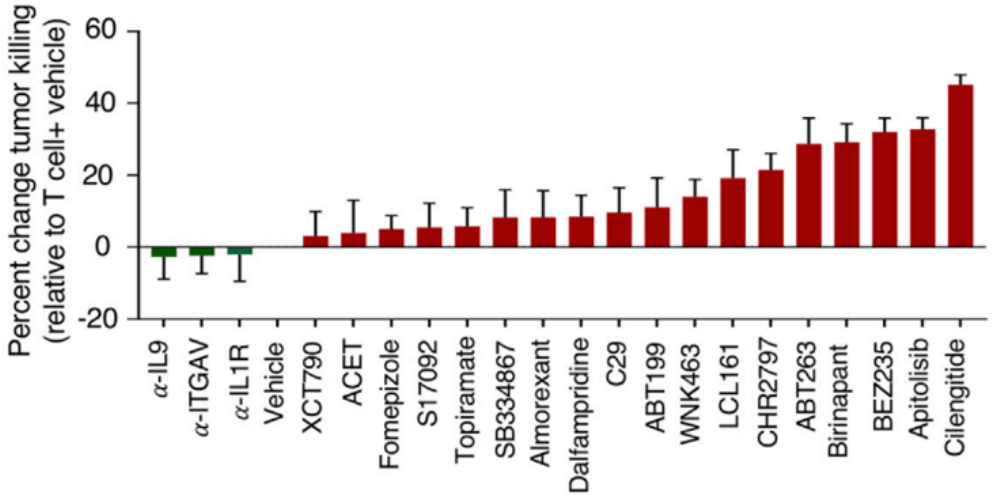
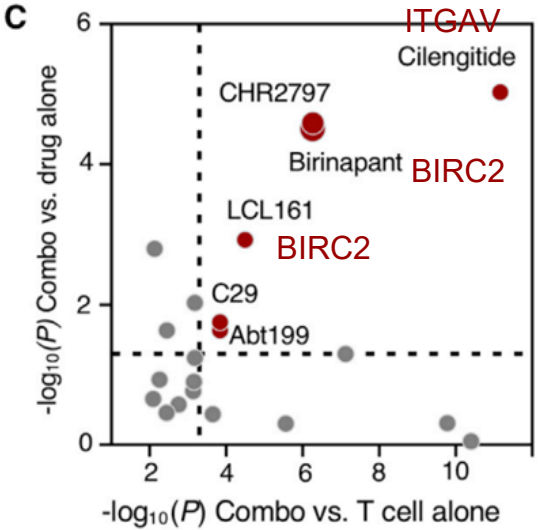
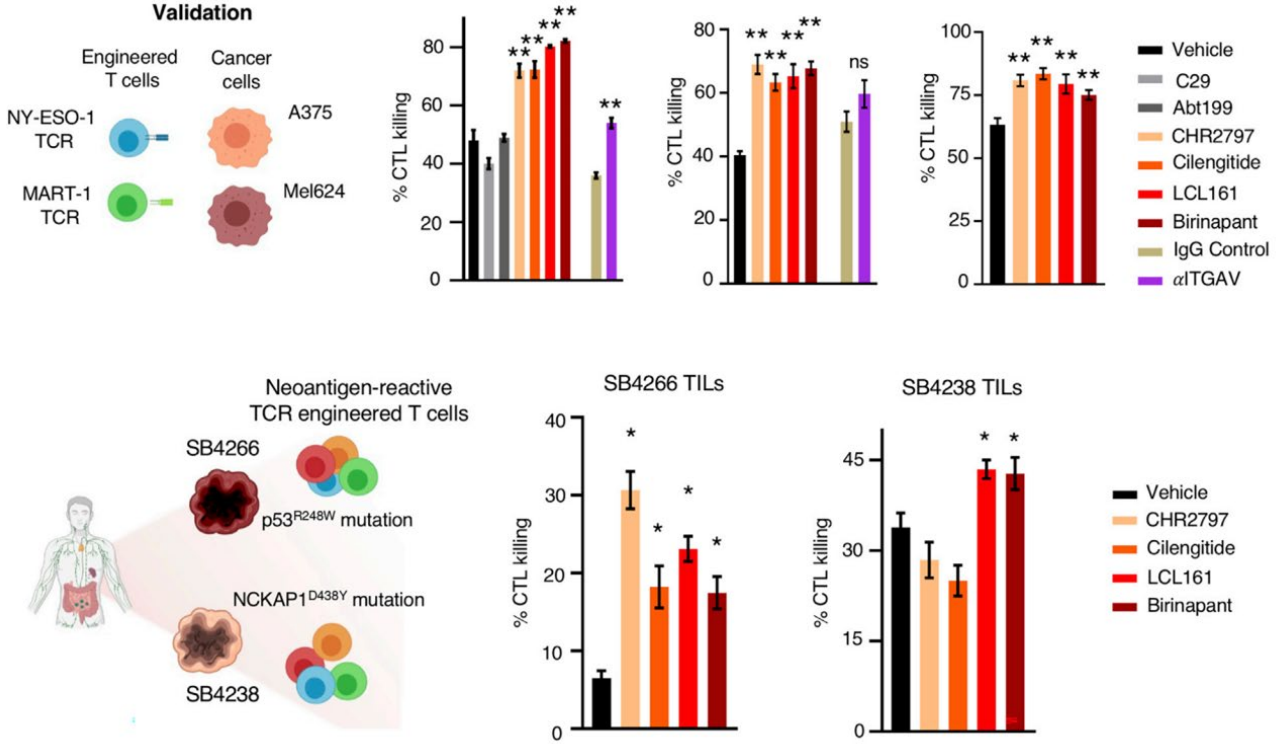




Rigorous validation of drug hits across different cell systems

Melanoma cell lines and TCR antigens



Biology of top validated gene

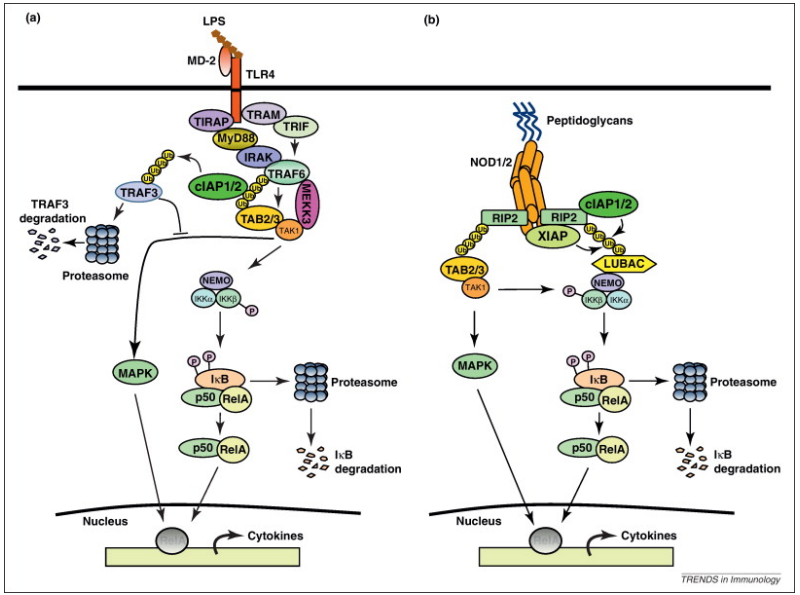
BIRC2 (cIAP1)

Amplified in cancers, e.g. head and neck

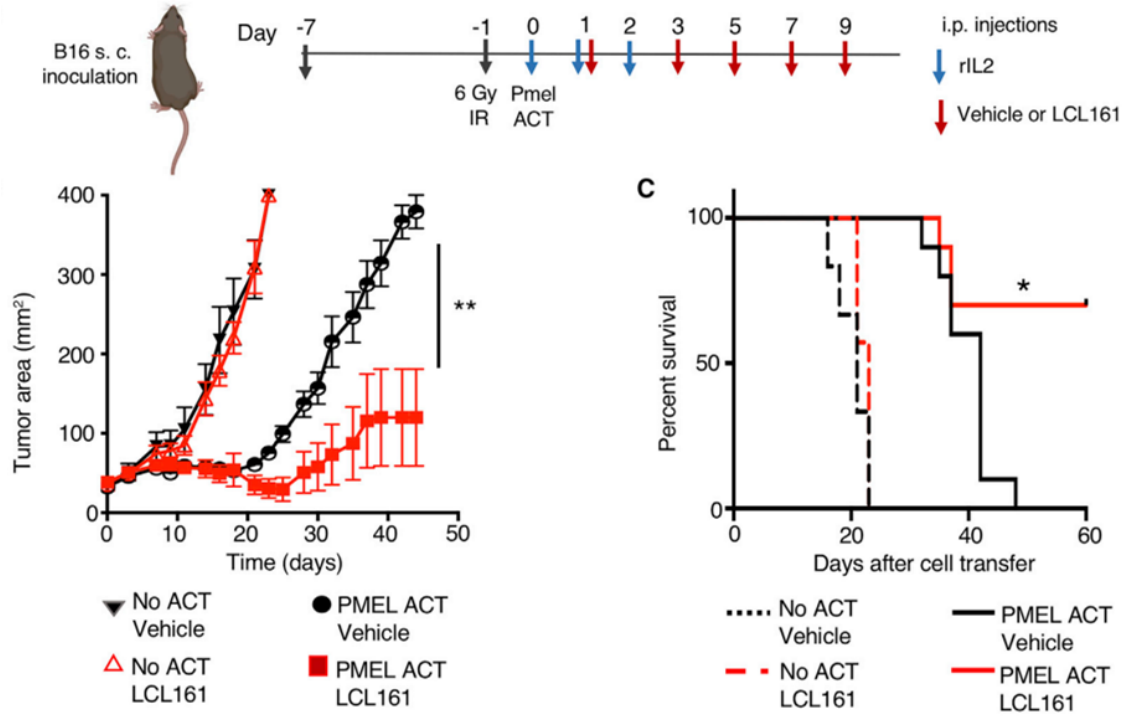
BIRC2 is an E3 ubiquitin-protein ligase that regulates nuclear factor κB (NF-κB) signaling and inhibits apoptosis

In immune cells, it can regulate antibacterial response via RIP2 and TRAF3 pathways

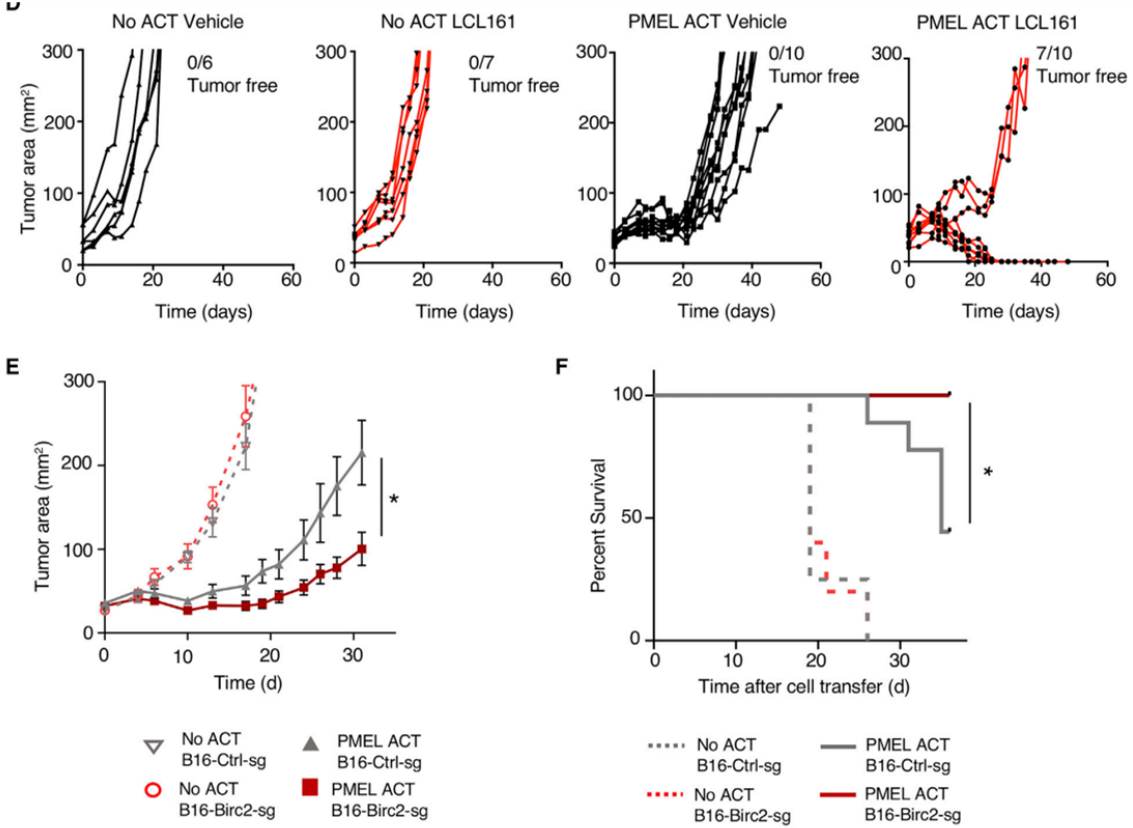
However the role in cancer : T cell responses is unexplored



BIRC2 inhibition via LCL161 emerges as rational combination for ACT / T cell immunotherapy



BIRC2 deletion improves anti-tumor T cell response in cancer model



What is the underlying MOA of BIRC2i antitumor effect?

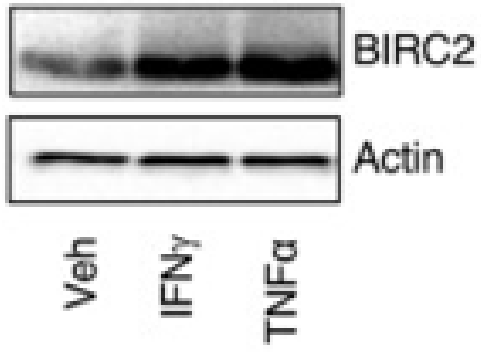
Is it just ‘inhibition of apoptosis’?

Is it more to this story?

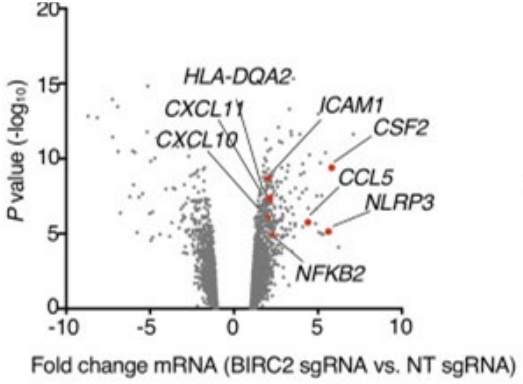
Induction of BIRC2 in cancer cells upon T cell encounter

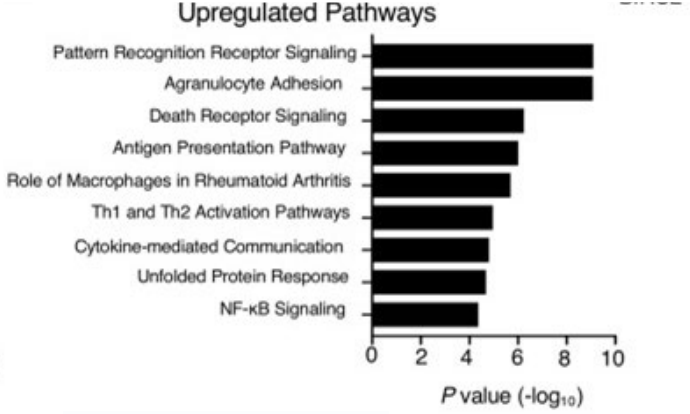
IFNg and TNFa are key effector cytokines released upon TCR activation

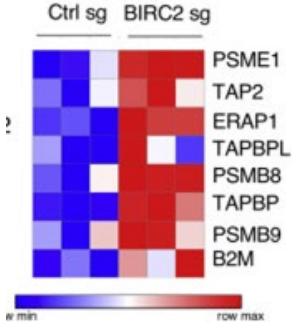
These cytokines rapidly induce BIRC2 expression



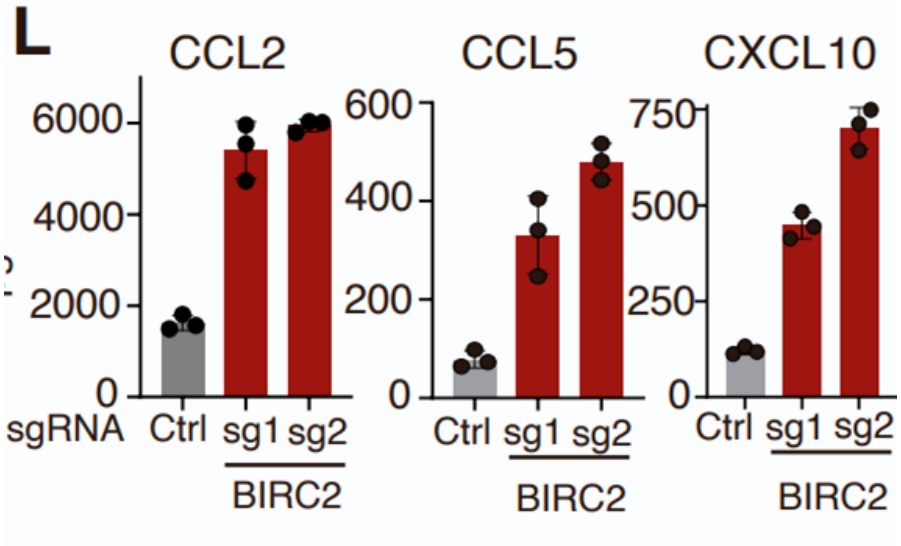
BIRC2 depletion upregulates antigen presentation and T cell chemoattractant genes

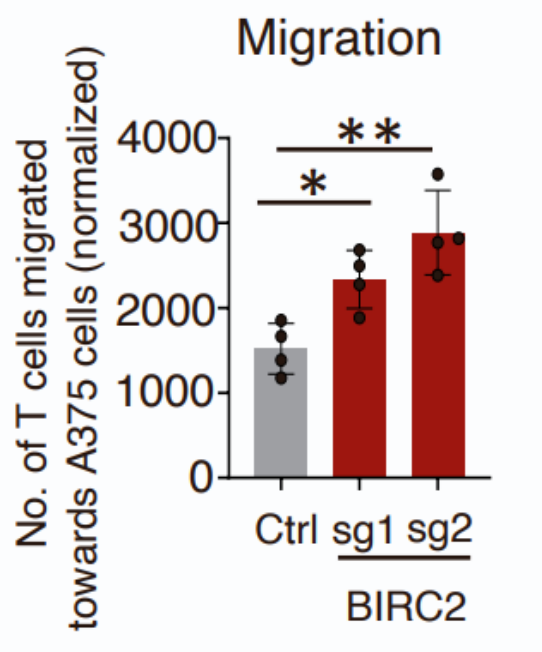






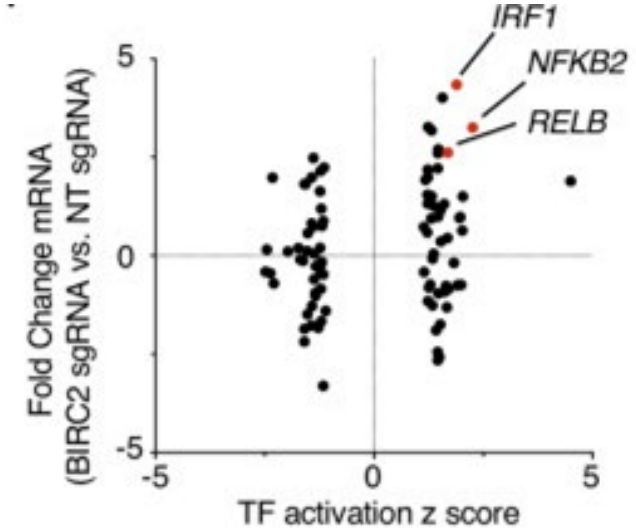
BIRC2 perturbation augments chemotactic migration of T cells



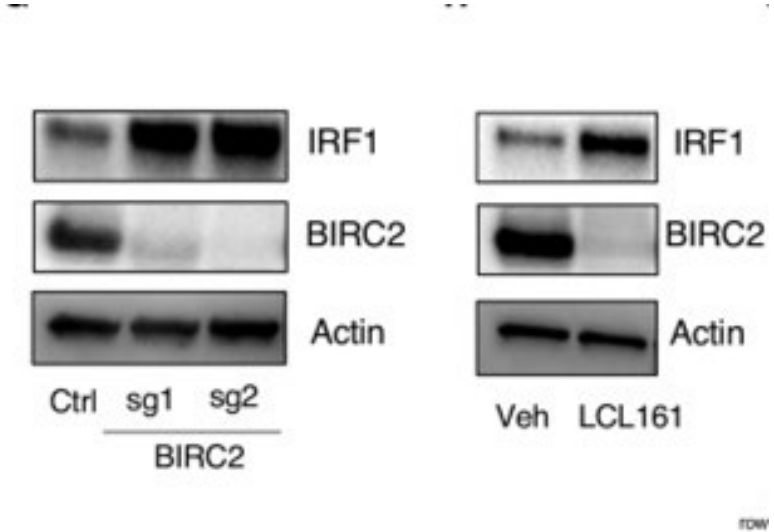


BIRC2 depletion enhances antigen presentation via IRF1

mRNA Signature



Protein levels



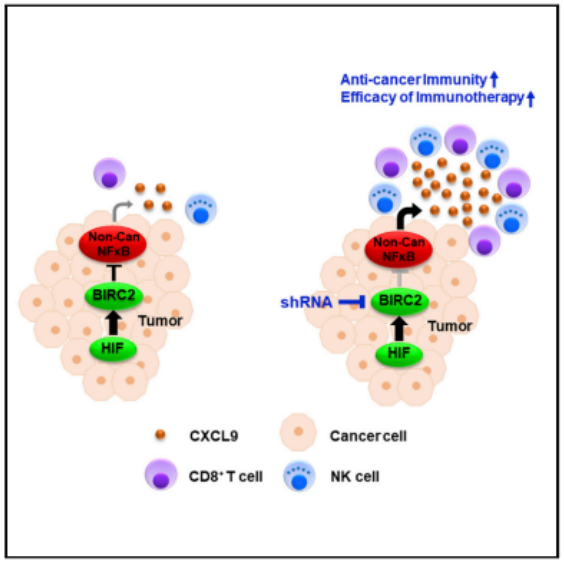
BIRC2 knockdown in Immune checkpoint responses

Article

Cell Reports

BIRC2 Expression Impairs Anti-Cancer Immunity and Immunotherapy Efficacy

Graphical Abstract



Authors

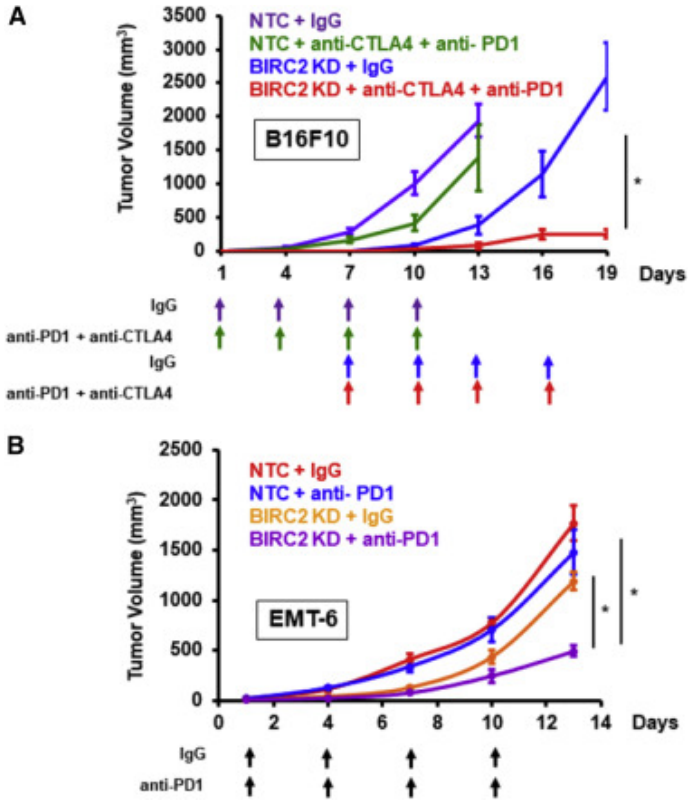
Debangshu Samanta, Tina Yi-Ting Huang, Rima Shah, Yongkang Yang, Fan Pan, Gregg L. Semenza

Correspondence

gsemenza@jhmi.edu

In Brief

Immune checkpoint blockade has led to therapeutic responses, but for most cancer patients, immunotherapy is ineffective due to cancer-cell-intrinsic resistance mechanisms. Samanta et al. report that BIRC2 knockdown in melanoma or breast cancer cells dramatically alters the immune cell tumor microenvironment and increases sensitivity to anti-CTLA4 and/or anti-PD1 therapy.



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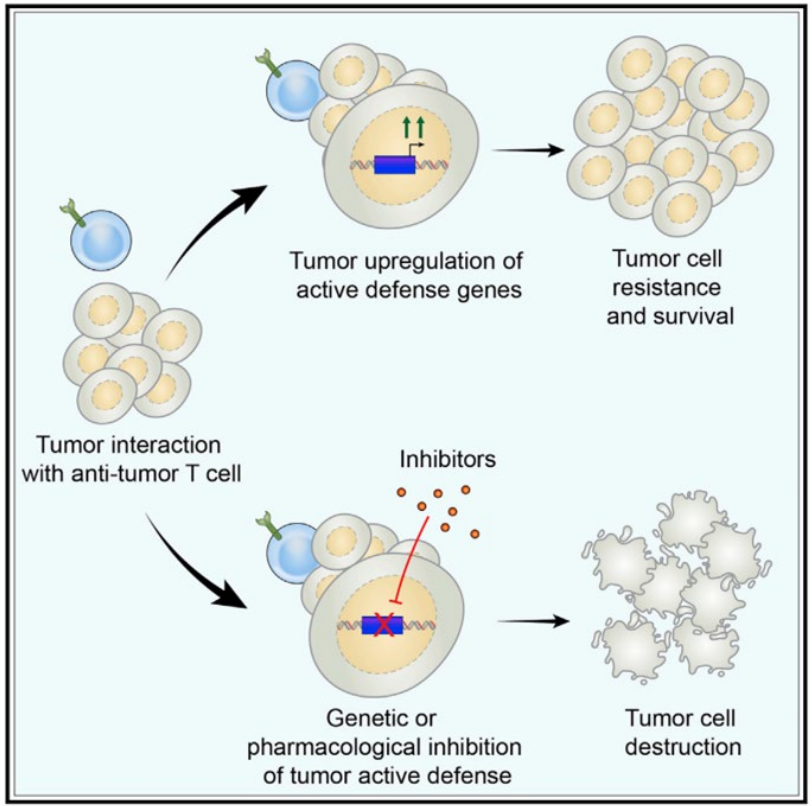

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Key learnings

Cancers find multiple routes and subroutes of evading immune attack. We can select one of these routes and interrogate the underlying principles using systems approach to find the rational combinations for drug treatments that may aid development of next generation of combinatorial treatments.

Systems approach includes utilization of public datasets to obtain patient centric insights into disease biology, development of cellular systems to generate large datasets and finally honing deeply into systematic perturbation and mechanistic studies.

It’s very important to understand limitations of systems and models used in immune interrogation.

Credits

Identification of essential genes for cancer immunotherapy

Shashank J. Patel[1,2,†,*], Neville E. Sanjana[3,4,†,*], Rigel J. Kishton[1], Arash Eidizadeh[1], Suman K. Vodnala[1], Maggie Cam[1], Jared J. Gartner[1], Li Jia[1], Seth M. Steinberg[1], Tori N. Yamamoto[1,5], Anand S. Merchant[1], Gautam U. Mehta[1], Anna Chichura[1], Ophir Shalem[6], Eric Tran[1], Robert Eil[1], Madhusudhanan Sukumar[1], Eva Perez Guijarro[1], Chi-Ping Day[1], Paul Robbins[1], Steve Feldman[1], Glenn Merlino[1], Feng Zhang[7,8], and Nicholas P. Restifo[1,9],

Cancer genes disfavoring T cell immunity identified via integrated systems approach

Rigel J. Kishton,[1,2,9,10,11,*] Shashank J. Patel,[1,2,10] Amy E. Decker,[3] Suman K. Vodnala,[1,2,9] Maggie Cam,[4] Tori N. Yamamoto,[1,2,5] Yogin Patel,[1,2,9] Madhusudhanan Sukumar,[1,2] Zhiya Yu,[1,2] Michelle Ji,[1,2] Amanda N. Henning,[1,2] Devikala Gurusamy,[1,2] Douglas C. Palmer,[1,2] Roxana A. Stefanescu,[6] Andrew T. Girvin,[6] Winifred Lo,[1] Anna Pasetto,[1] Parisa Malekzadeh,[1] Drew C. Deniger,[1] Kris C. Wood,[3] Neville E. Sanjana,[7,8] and Nicholas P. Restifo[1,2,9,*]