NASDC
NCI Awardee Skills Development Consortium

Translational Opportunities in Immunotherapy Research

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Disclosures

- IMVAQ therapeutics co-founder
- Advisory board immunos therapeutics
- Consulting for Pfizer, Daichii
- Inventor on a patent applications related to work on Oncolytic Viral therapy, Alpha Virus Based Vaccine, Neo Antigen Modeling, CD40, GITR, OX40, PD-1 and CTLA-4.

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- Bristol-Myers Squibb
- Surface Oncology
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- Infinity Pharmaceuticals, Inc.
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- Adaptive Biotechnologies
- Leap Therapeutics, Inc.
- Aprea.

Some key points for today's lecture

» Pre-clinical models inform mechanism based therapeutic strategies.

» Tumor immune landscape should be taken into consideration when designing immune therapy.

» The timing of the immune intervention is key.

» Real time monitoring of the tumor microenvironment should help rationally design immune intervention.

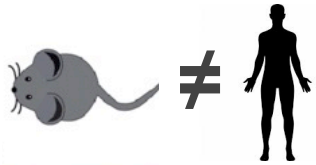
» Do not ignore a phenomena when you don't understand it.

Some key points for today's lecture

» Use appropriate models for each type of approach.

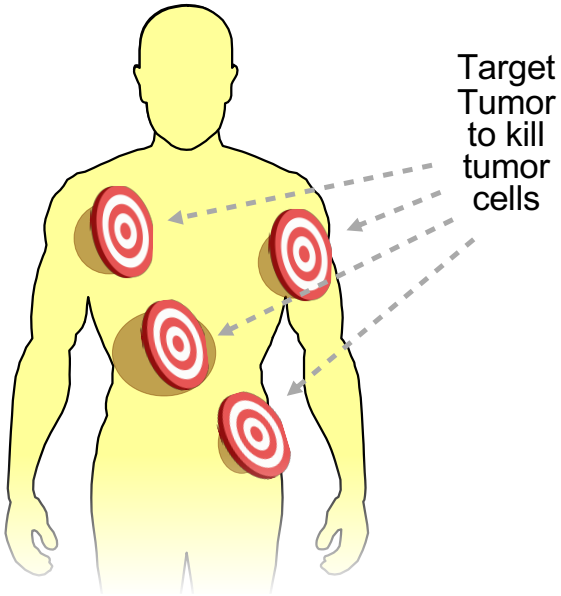
» Often time the models are not the problem. We are.

› We need to make sure that we are not over interpreting (literal translation).

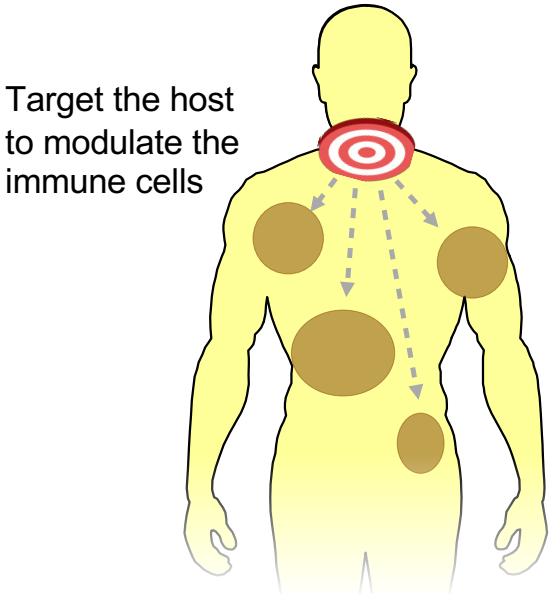


Two Main Paradigms for Advancing Cancer Therapy Melanoma: the poster child

Targeted Therapy



Immunotherapy



Melanoma Therapy — 2010

FDA Approved Therapies (USA)	Date
DTIC (chemotherapy): Helps 10% of patients for short periods of time (3 months)	1970s
High-dose interleukin-2: Helps <15% of patients for a decade or more; high toxicity	1998

There was a clear need for new and more effective therapies.

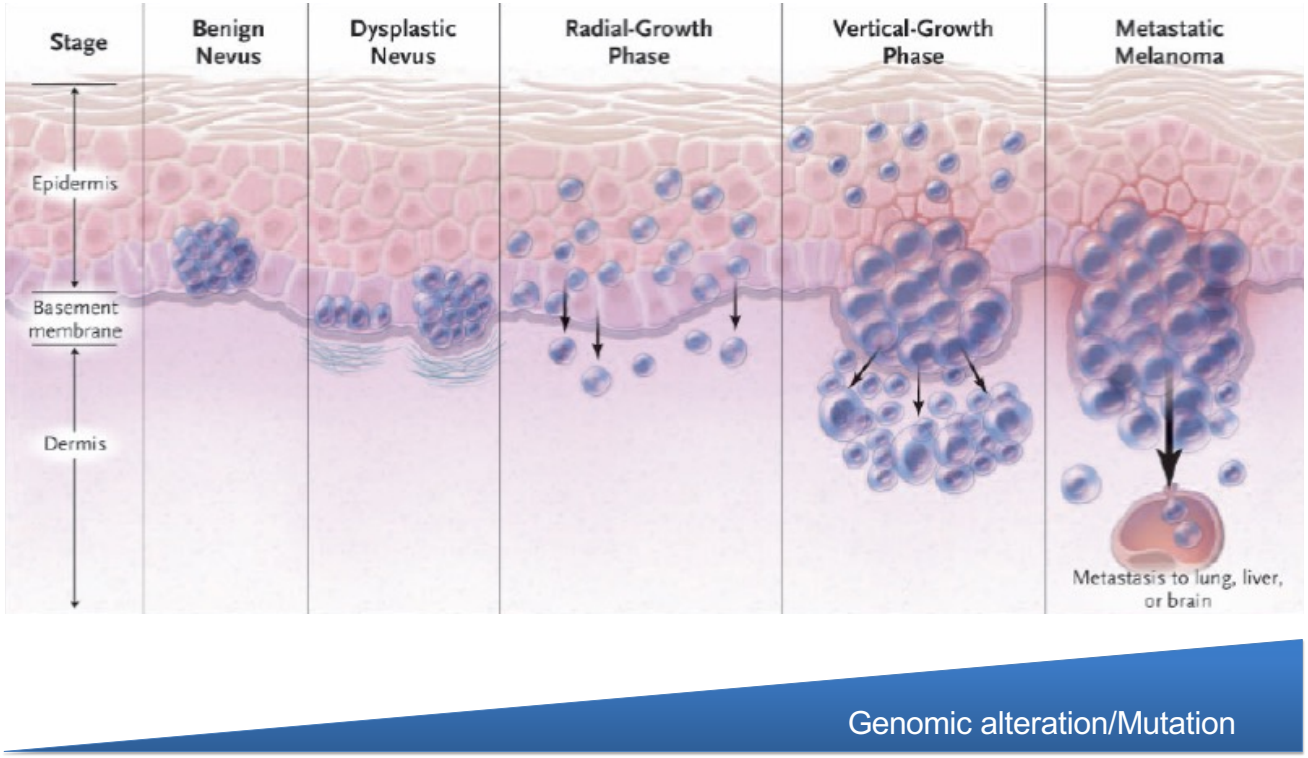
The Poster Child: Metastatic Melanoma today

FDA-approved Therapies (USA)	Date
DTIC (dacarbazine)	1970s
Interferon alfa (adjuvant)	1996
High-dose interleukin-2	1998
Ipilimumab	2011
Nivolumab	2014
Pembrolizumab	2014
Ipilimumab/Nivolumab	2015
Talimogene Laherparepvec (T-VEC)	2015
Vemurafenib	2011
Dabrafenib	2013
Trametinib	2013
Cobimetinib	2015
Encorafenib/Binimetinib	2018

NCI, cancer.gov, 2021

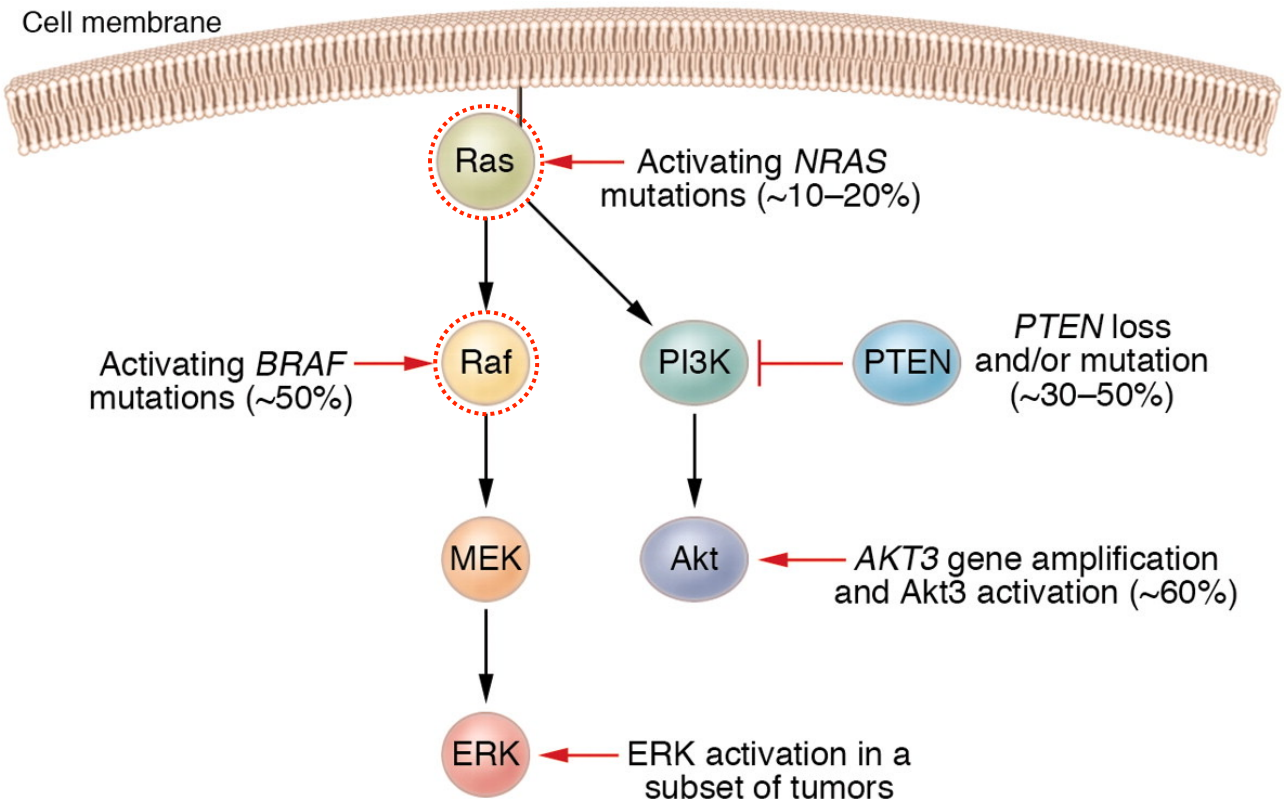
Biological Events and Molecular Changes in Melanoma Progression

- Many molecular changes occur during melanoma progression
- Oncogenes and Tumor Suppressor genes are mutated



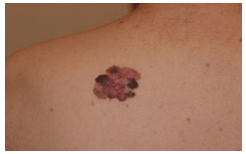
(Adapted from Miller A.R., and Merghoub T)

Genes and Pathways Involved in Melanoma Development



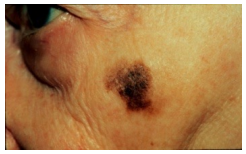
Chudnovsky Y,
JCI, 2005.

Mutations Define Distinct Melanoma Molecular Subsets

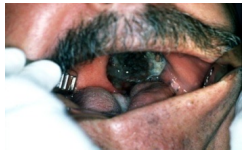


Arising from Skin Without Chronic Sun Damage → 50% BRAF, 20% NRAS — 0% KIT

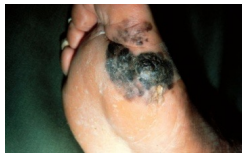
Vemurafenib



Arising from Skin With Chronic Sun Damage → 10% BRAF, 10% NRAS — 2% KIT



Arising from Mucosal Surfaces → 5% BRAF, 15% NRAS — 20% KIT

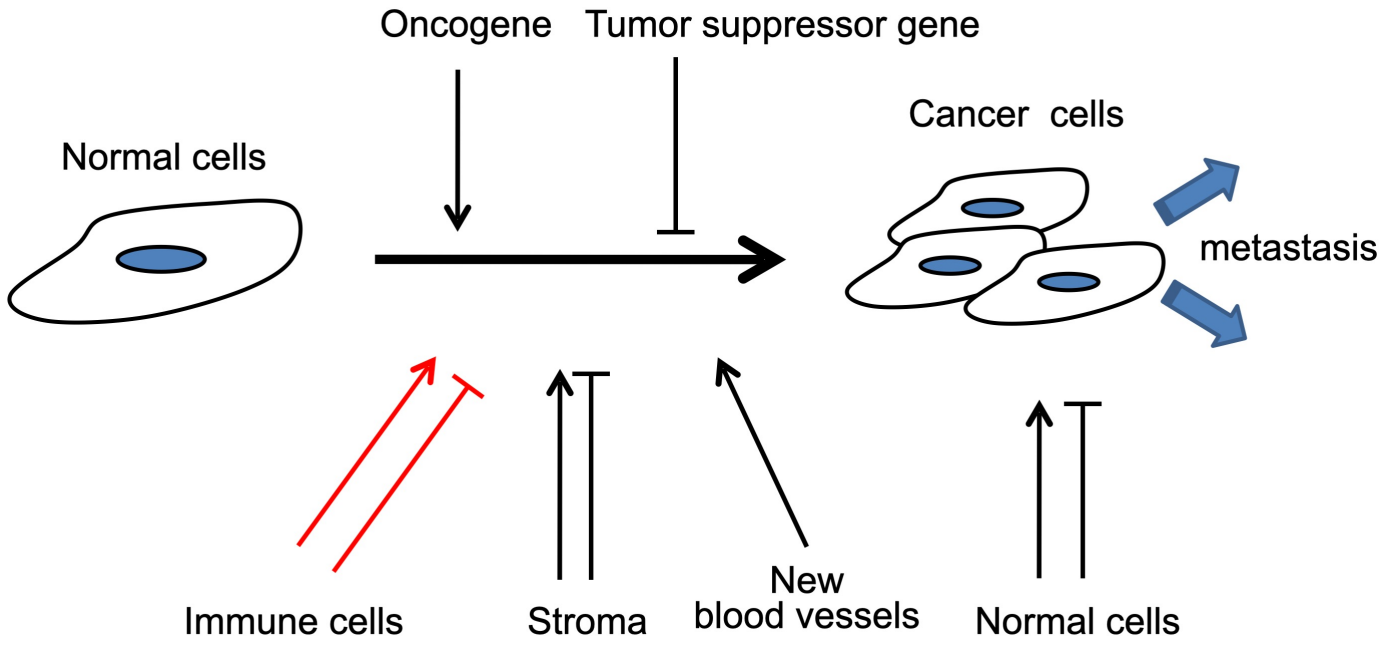


Arising from Acral Surfaces → 15% BRAF, 15% NRAS — 15% KIT

Uveal Melanoma → 25% GNAQ — 55% GNA11

Curtin et al. NEJM 2005; Curtin et al. JCO 2006; Van Raamsdonk et al., NEJM 2010

Targeting Multiple Pathways is Needed for Effective Therapy



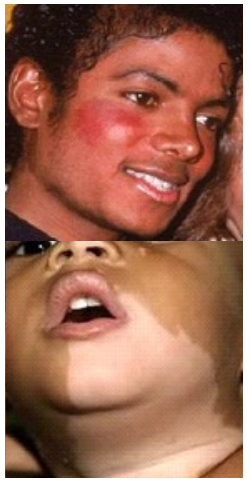
Memorial Sloan Kettering
Cancer Center

Can the immune system recognize cancer?

The immune system is designed to recognize foreign antigens

~~Non~~-self Self

What if the immune system recognizes and attacks self?



Cancer = Self

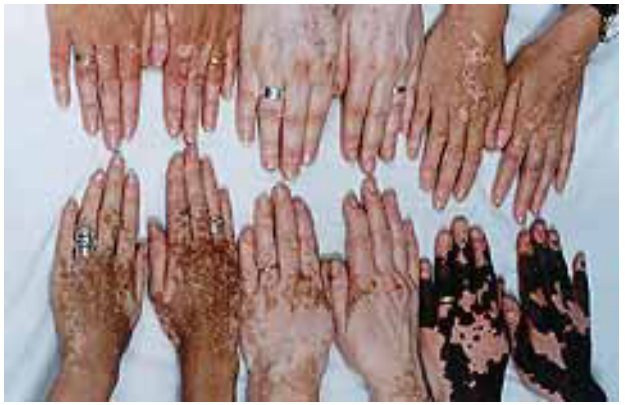
Autoimmune reaction to self / transformed self

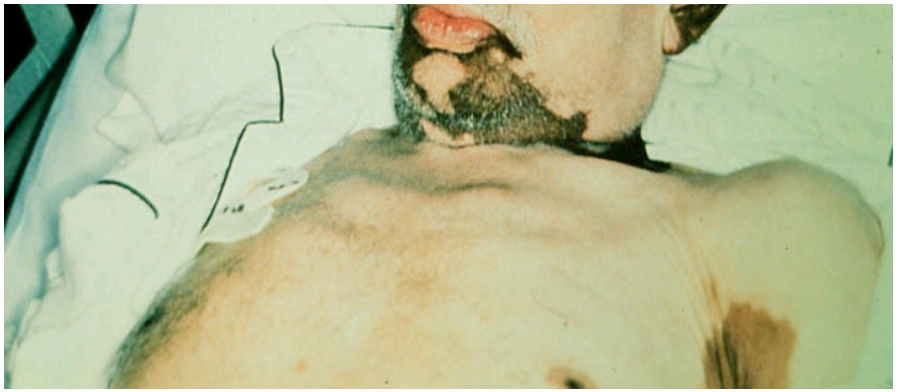
Recognizing self as non-self:
Autoimmunity/Vitiligo

Goal: Recognition of
Transformed-self/Cancer

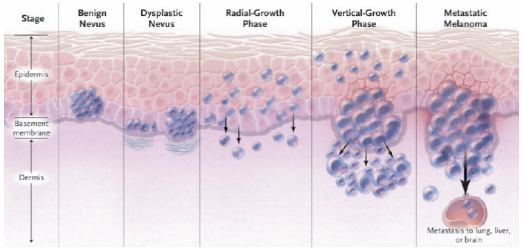
Natural response to melanoma

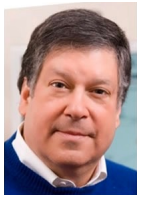
- Clinical observation that melanoma patients who develop vitiligo “do better” and that vitiligo is associated with response to chemotherapy as well as immunotherapy
- Isolation from a patient of an antibody recognizing “pigmented associated antigen”



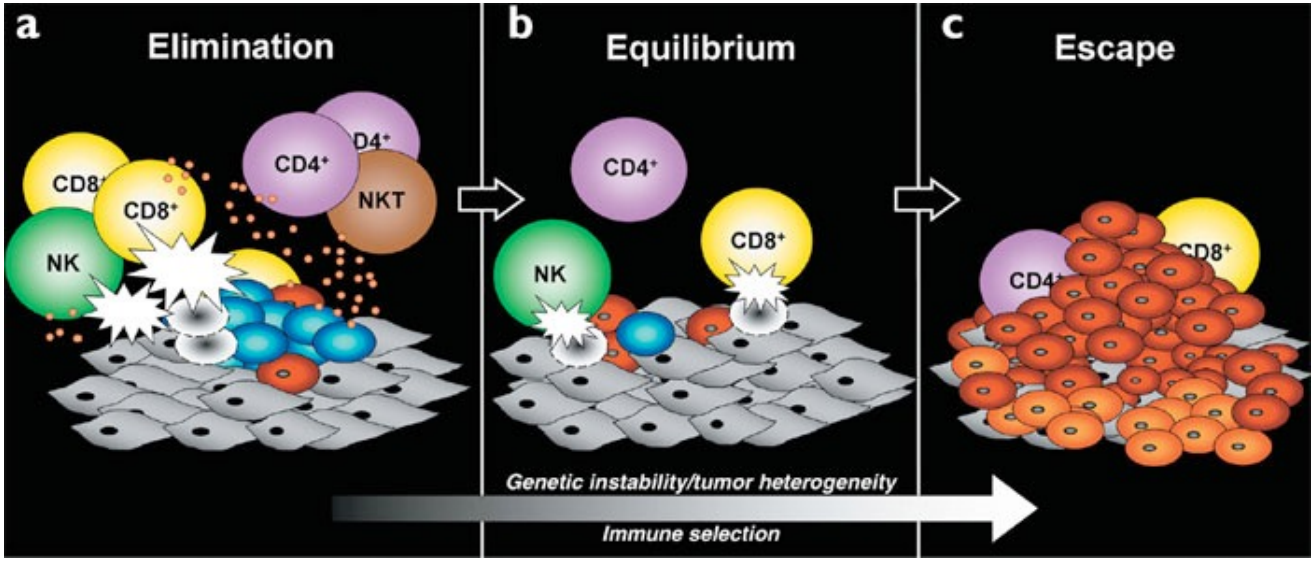


Role of the Immune System in Cancer: Immunoediting



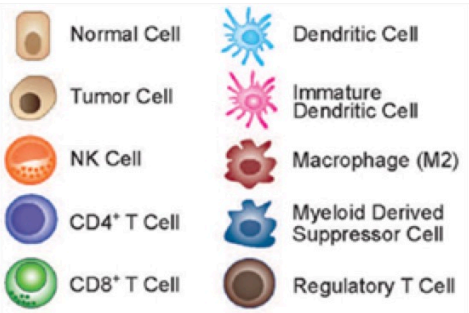


Robert D. Schreiber



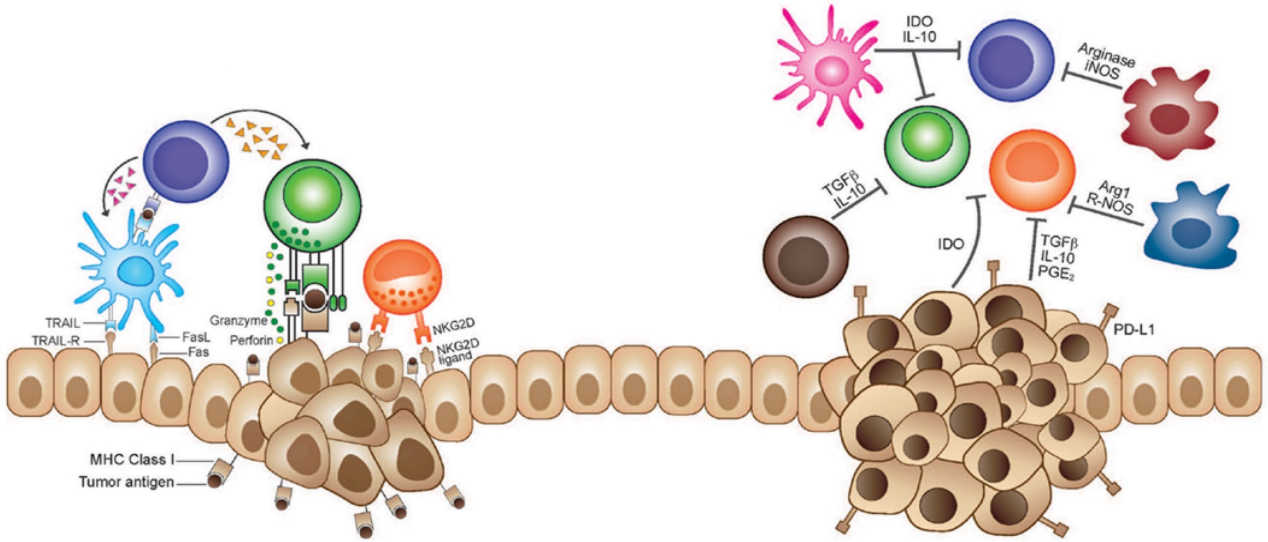
Immunoediting

Immune Suppressive Microenvironment



William J. Murphy.
Front Oncol.
2013; 3: 197.

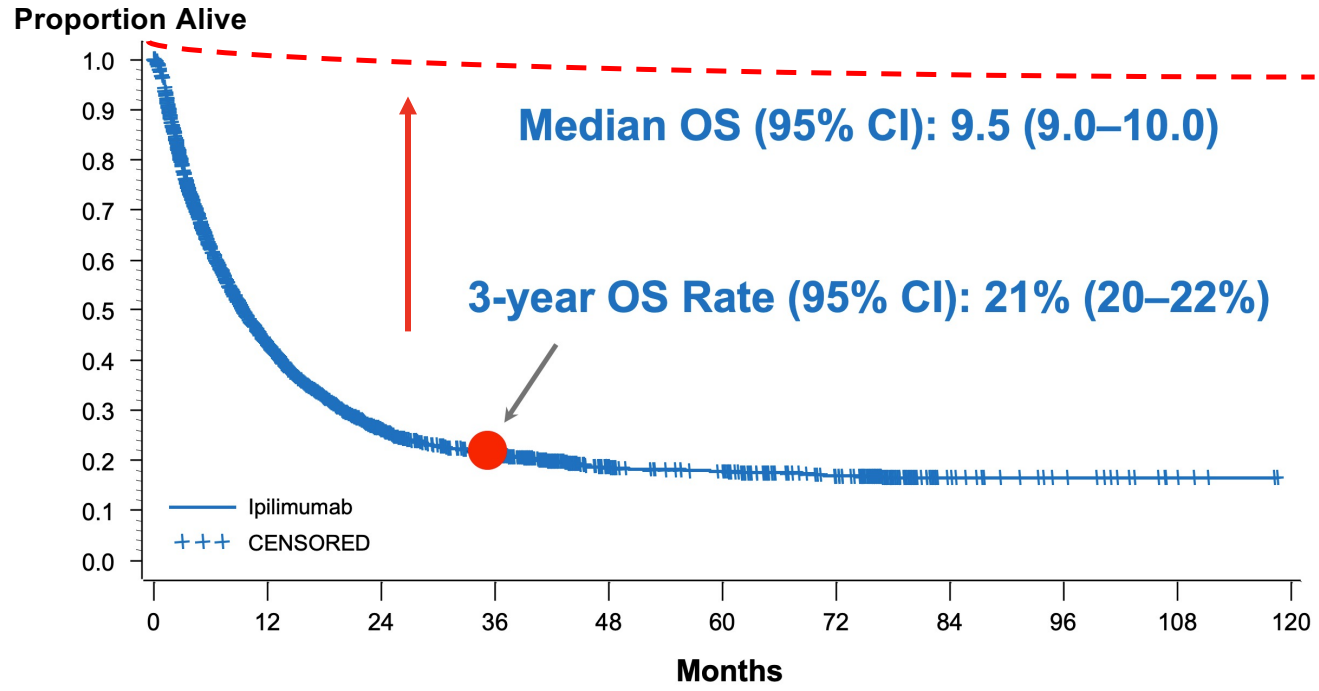
Tumor Microenvironment



Elimination

Escape

Ipilimumab Long Term Pooled Survival Analysis: 4846 Patients



Patients at Risk

Ipilimumab	4846	1786	612	392	200	170	120	26	15	5	0

Schadendorf, Hodi
Wolchok, ESMO, 2013

1. Can we predict response to immune therapy reliably?

2. Can we improve response to immune therapy?

Can we predict response to immune therapy reliably?

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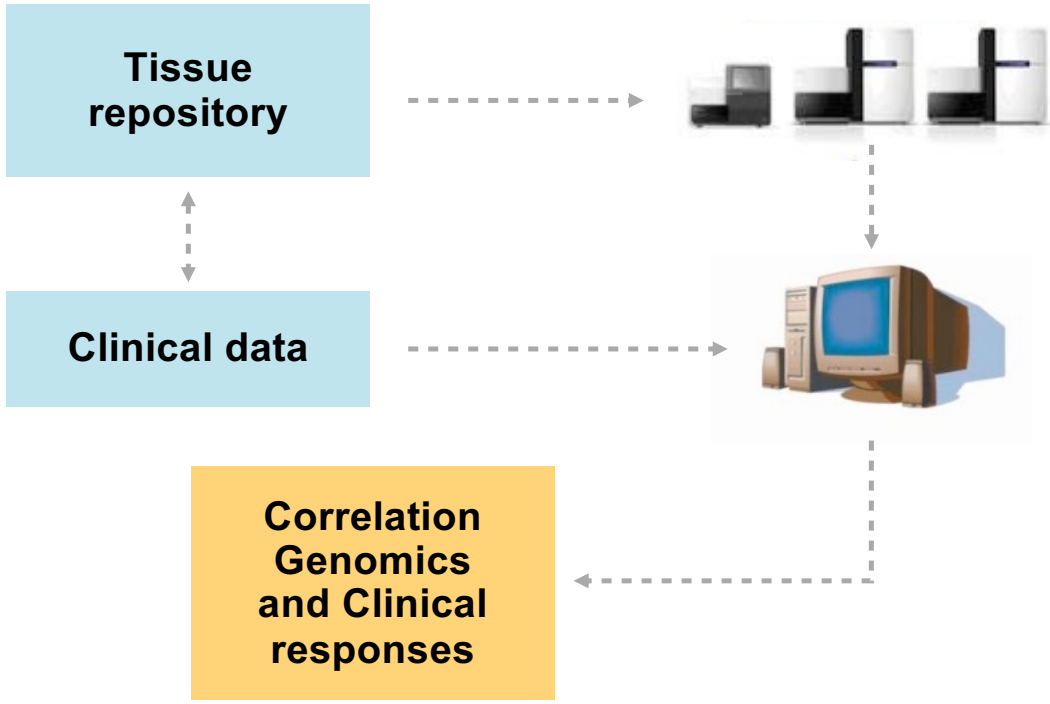
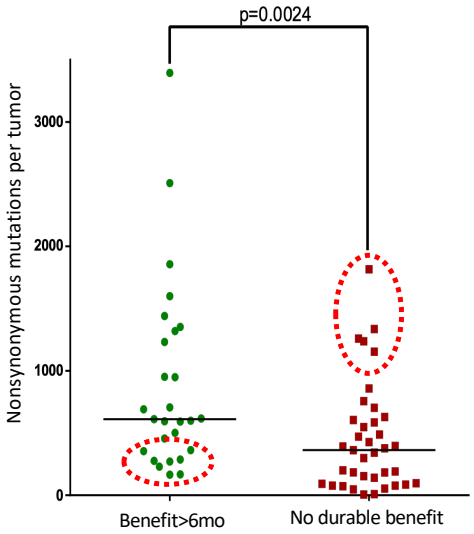
Mutations, Immunogenicity and Prediction of clinical response



Snyder Charen et al., New Engl J Med, 2014

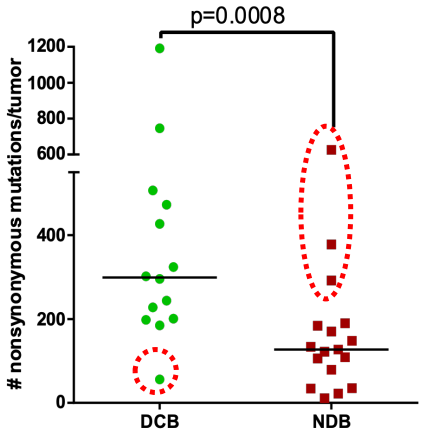
Mutational Load Correlates with Benefit from Checkpoint Blockade ….With Important Exceptions

Melanoma/anti-CTLA-4



Snyder, Makarov, Merghoub, Yuan et al NEJM 2014
Van Allen, Miao et al Science 2015, Hugo et al Cell 2016

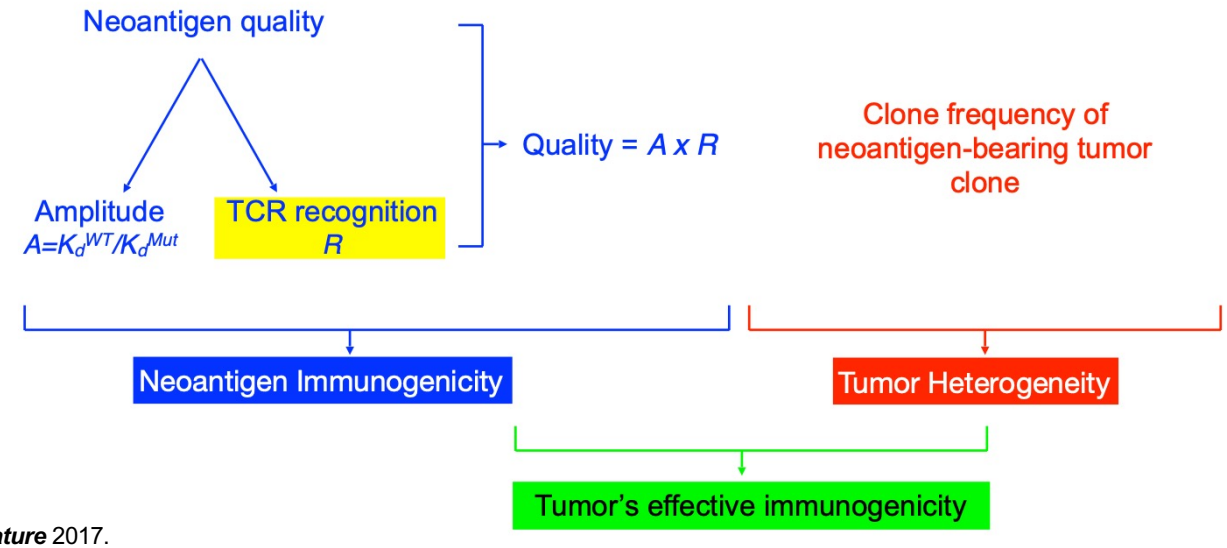
NSCLC/anti-PD-1



Le et al NEJM 2016, Rizvi , Hellmann, Snyder et al Science 2015, Rosenberg et al Lancet Oncol 2016

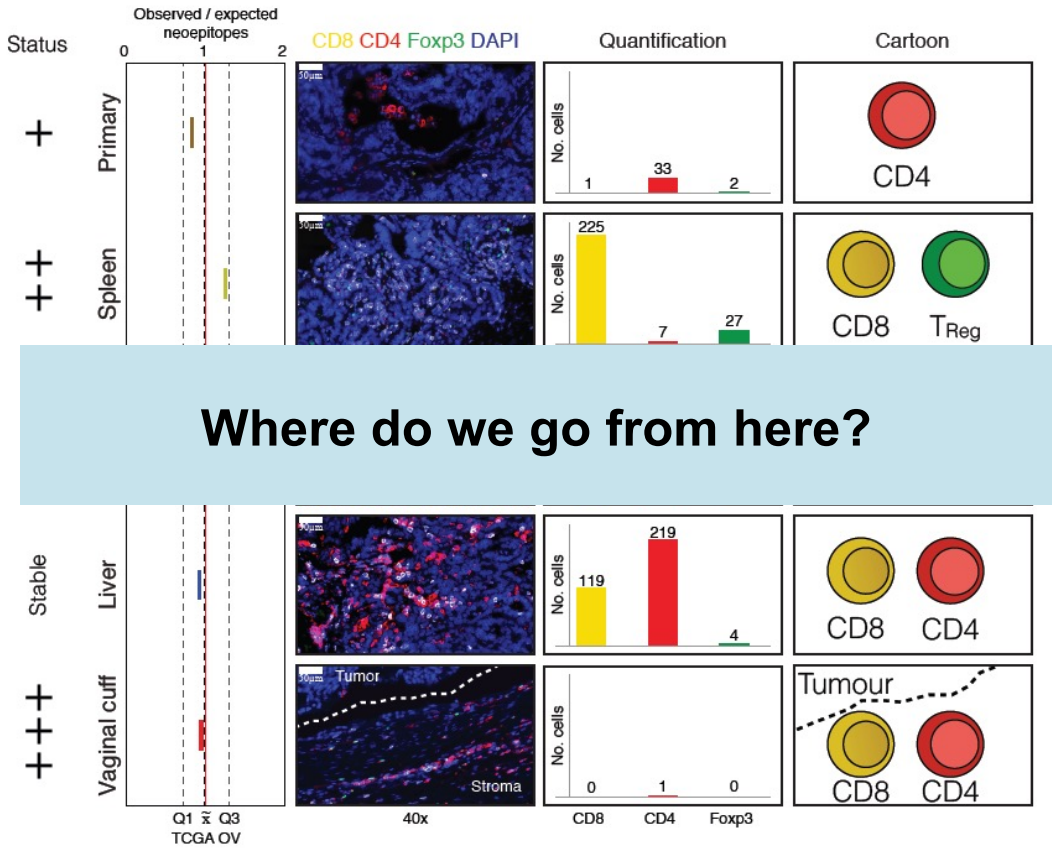
A computation model of neoantigen quality based immunogenicity

Which neoantigen(s) are the most immunogenic?



Balachandran VP, Wolchok JD, Merghoub T et al. ***Nature*** 2017.
Luksza M, Balachandran VP, Greenbaum BG et al. ***Nature*** 2017.

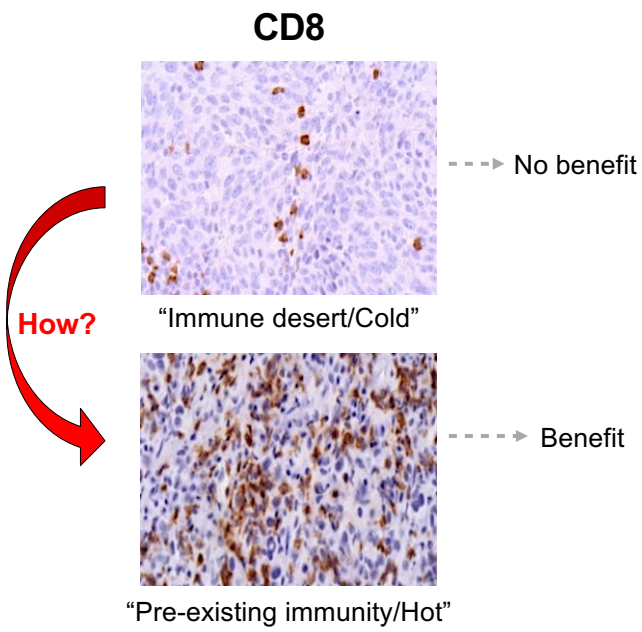
Distinct Tumor Immune TME in one Patient, Controlled for Environmental & Inherited Factors

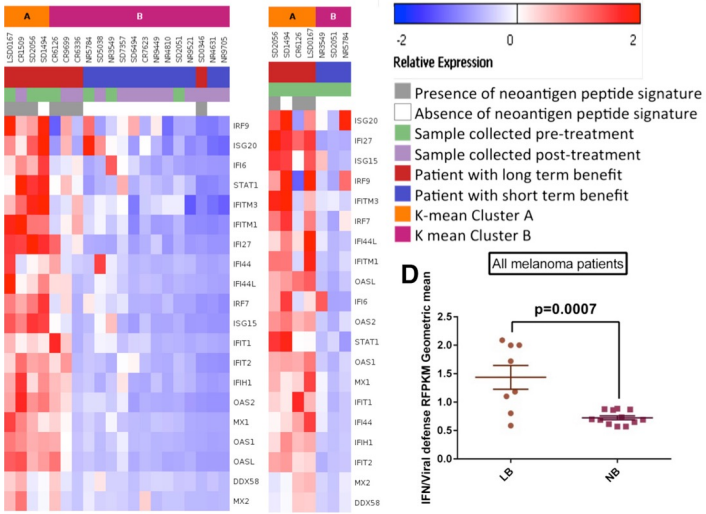


Jiménez-Sánchez A, Cell. 2017

Can we improve response to immune therapy?

Immune-active microenvironment in human cancers is associated with clinical benefit from immunotherapies





Type I IFN signature is associated with clinical benefit from CTLA-4 blockade in melanoma

“Pre-existing immunity/Hot”

↓

Immune check point is enough

“Immune desert/Cold”

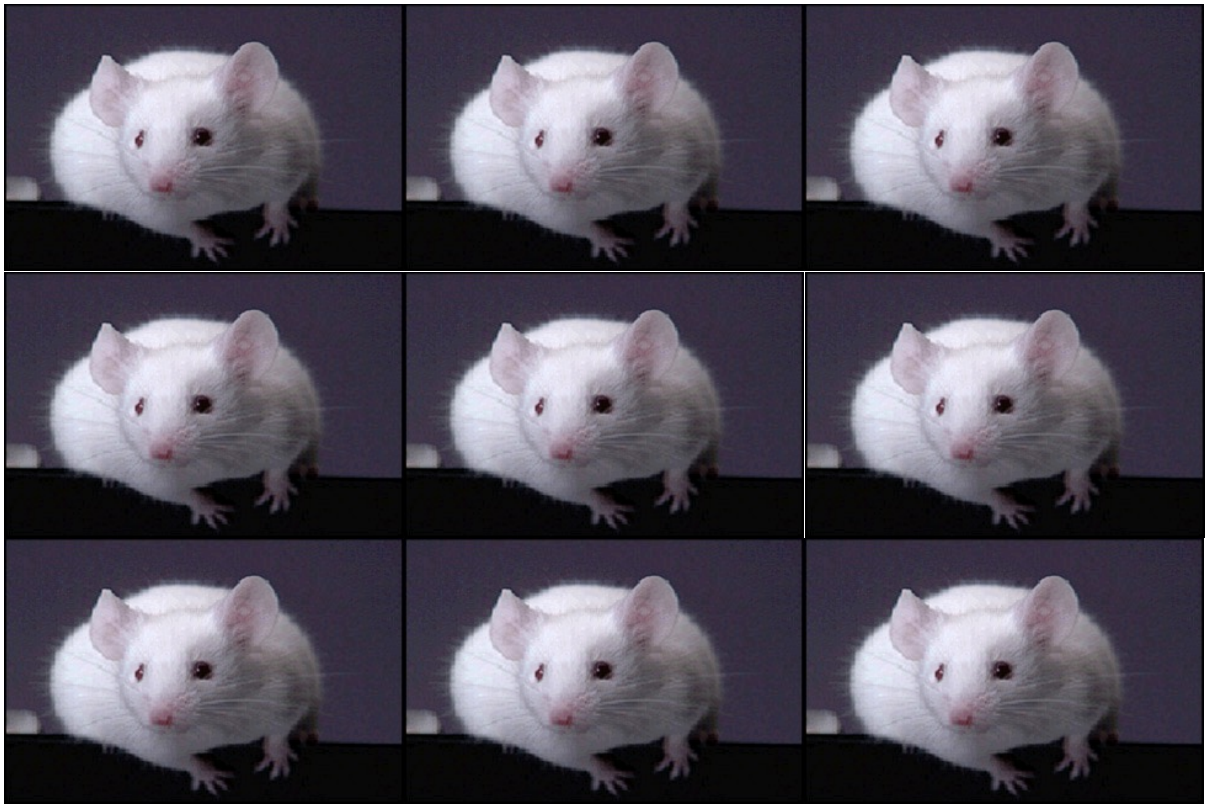
↓

Immune check point + bring immune cells to tumors

Need to go back to murine tumor models

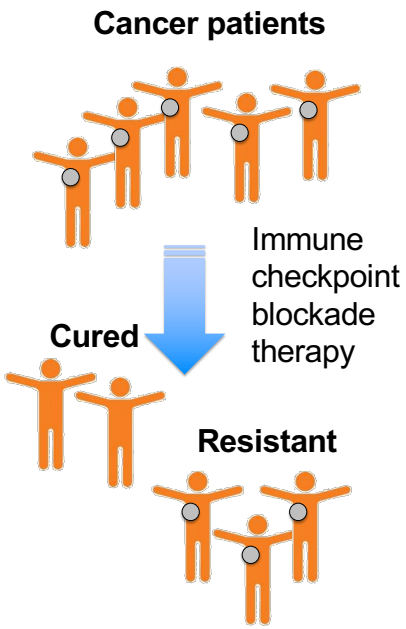
We look like identical twins!

Inbred mouse strains are a great tool



Memorial Sloan Kettering Cancer Center

Major mechanisms of resistance to anti-tumor immunity



Tumor intrinsic resistance

LETTER

doi:10.1038/nature14404

Melanoma–intrinsic β–catenin signalling prevents anti–tumour immunity

Stefani Spranger[1], Riyue Bao[2] & Thomas F. Gajewski[1,3]

Loss of IFN-γ Pathway Genes in Tumor Cells as a Mechanism of Resistance to Anti-CTLA-4 Therapy

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Genomic and Transcriptomic Features of Response to Anti-PD-1 Therapy in Metastatic Melanoma

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ESTABLISHED IN 1812 SEPTEMBER 1, 2016 VOL. 375 NO. 9

Mutations Associated with Acquired Resistance to PD-1 Blockade in Melanoma

Jesse M. Zaretsky, B.S., Angel Garcia-Diaz, Ph.D., Daniel S. Shin, M.D., Helena Escuin-Ordinas, Ph.D., Willy Hugo, Ph.D., Siwen Hu-Lieskovan, M.D., Ph.D., Davis Y. Torrejon, M.D., Gabriel Abril-Rodriguez, M.Sc., Salemiz Sandoval, Ph.D., Lucas Barthly, M.Sc., Justin Saco, B.S., Blanca Homet Moreno, M.D., Riccardo Mezzadra, M.Sc., Bartosz Chmielowski, M.D., Ph.D., Kathleen Ruchalski, M.D., I. Peter Shintaku, Ph.D., Phillip J. Sanchez, Ph.D., Cristina Puig-Saus, Ph.D., Grace Cherry, R.N., N.P., Elizabeth Seja, B.A., Xiangju Kong, M.Sc., Jia Pang, B.S., Beata Berent-Maoz, Ph.D., Begoña Comin-Anduix, Ph.D., Thomas G. Graeber, Ph.D., Paul C. Tumeh, M.D., Ton N.M. Schumacher, Ph.D., Roger S. Lo, M.D., Ph.D., and Antoni Ribas, M.D., Ph.D.

Immune-mediated resistance

ORIGINAL ARTICLE

Frequencies of circulating MDSC correlate with clinical outcome of melanoma patients treated with ipilimumab

Christiane Meyer · Laurène Cagnon · Carla M. Costa-Nunes · Petra Baumgaertner · Nicole Montandon · Loredana Leyvraz · Olivier Michielin · Emanuela Romano · Daniel E. Speiser

REVIEW ARTICLE

Tumor-associated macrophages in cancers

W. Hu[1,2,3] · X. Li[1,2,3] · C. Zhang[1] · Y. Yang[1] · J. Jiang[2,3] · C. Wu[1,2,3]

Research article

CTLA4 blockade and GM-CSF combination immunotherapy alters the intratumor balance of effector and regulatory T cells

Sergio A. Quezada, Karl S. Peggs, Michael A. Curran, and James P. Allison

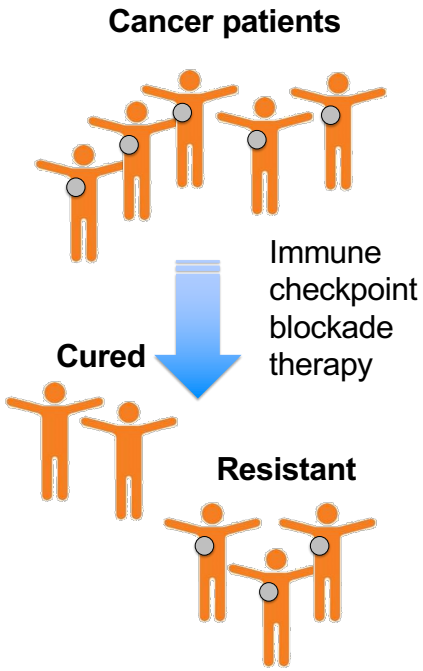
Howard Hughes Medical Institute, Department of Immunology, Memorial Sloan-Kettering Cancer Center, New York, New York, USA.

JEM Article

Indoleamine 2,3-dioxygenase is a critical resistance mechanism in antitumor T cell immunotherapy targeting CTLA-4

Rikke B. Holmgaard,[1,2] Dmitriy Zamarin,[1,2,3] David H. Munn,[4] Jedd D. Wolchok,[2,3,5,6] and James P. Allison[1,7]

1 – Better define the tumor intrinsic mechanisms of response to immune therapies



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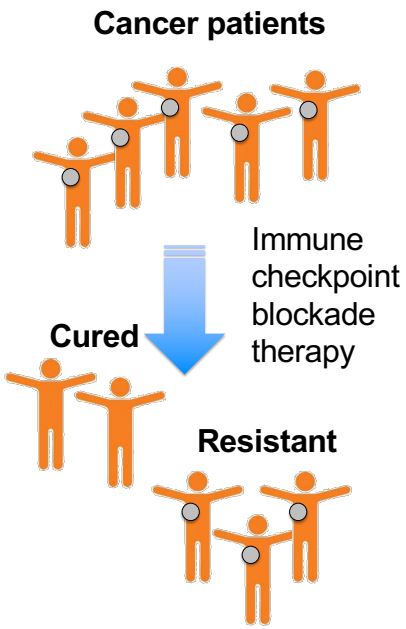
Major mechanisms of resistance to anti-tumor immunity



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Mutations Associated with Acquired Resistance to PD-1 Blockade in Melanoma

Jesse M. Zaretsky, B.S., Angel Garcia-Diaz, Ph.D., Daniel S. Shin, M.D., Helena Escuin-Ordinas, Ph.D., Willy Hugo, Ph.D., Siwen Hu-Lieskovan, M.D., Ph.D., Davis Y. Torrejon, M.D., Gabriel Abril-Rodriguez, M.Sc., Salemiz Sandoval, Ph.D., Lucas Barthly, M.Sc., Justin Saco, B.S., Blanca Homet Moreno, M.D., Riccardo Mezzadra, M.Sc., Bartosz Chmielowski, M.D., Ph.D., Kathleen Ruchalski, M.D., I. Peter Shintaku, Ph.D., Phillip J. Sanchez, Ph.D., Cristina Puig-Saus, Ph.D., Grace Cherry, R.N., N.P., Elizabeth Seja, B.A., Xiangju Kong, M.Sc., Jia Pang, B.S., Beata Berent-Maoz, Ph.D., Begoña Comin-Anduix, Ph.D., Thomas G. Graeber, Ph.D., Paul C. Tumeh, M.D., Ton N.M. Schumacher, Ph.D., Roger S. Lo, M.D., Ph.D., and Antoni Ribas, M.D., Ph.D.

Immune-mediated resistance

ORIGINAL ARTICLE

Frequencies of circulating MDSC correlate with clinical outcome of melanoma patients treated with ipilimumab

Christiane Meyer · Laurène Cagnon · Carla M. Costa-Nunes · Petra Baumgaertner · Nicole Montandon · Loredana Leyvraz · Olivier Michielin · Emanuela Romano · Daniel E. Speiser

REVIEW ARTICLE

Tumor-associated macrophages in cancers

W. Hu[1,2,3] · X. Li[1,2,3] · C. Zhang[1] · Y. Yang[1] · J. Jiang[2,3] · C. Wu[1,2,3]

Research article

CTLA4 blockade and GM-CSF combination immunotherapy alters the intratumor balance of effector and regulatory T cells

Sergio A. Quezada, Karl S. Peggs, Michael A. Curran, and James P. Allison

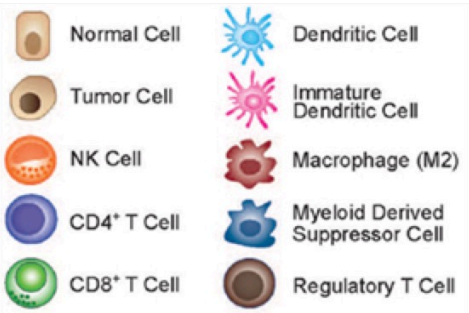
Howard Hughes Medical Institute, Department of Immunology, Memorial Sloan-Kettering Cancer Center, New York, New York, USA.

JEM Article

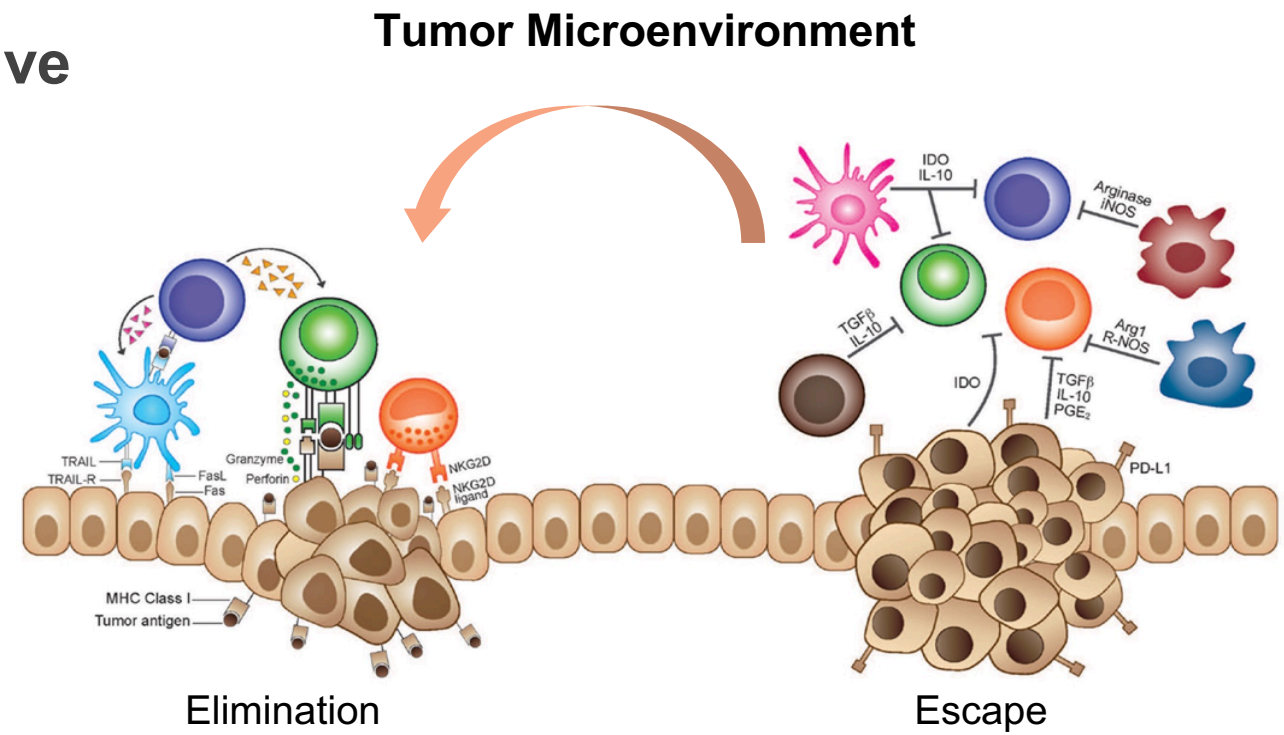
Indoleamine 2,3-dioxygenase is a critical resistance mechanism in antitumor T cell immunotherapy targeting CTLA-4

Rikke B. Holmgaard,[1,2] Dmitriy Zamarin,[1,2,3] David H. Munn,[4] Jedd D. Wolchok,[2,3,5,6] and James P. Allison[1,7]

2 – Modify the Immune Suppressive Microenvironment



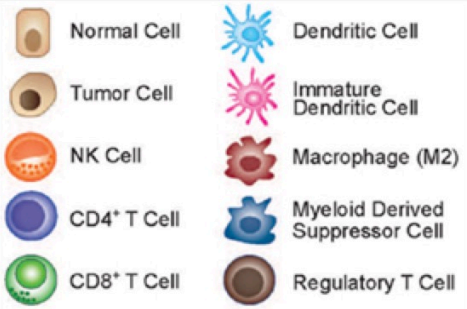
William J. Murphy.
Front Oncol.
2013; 3: 197.



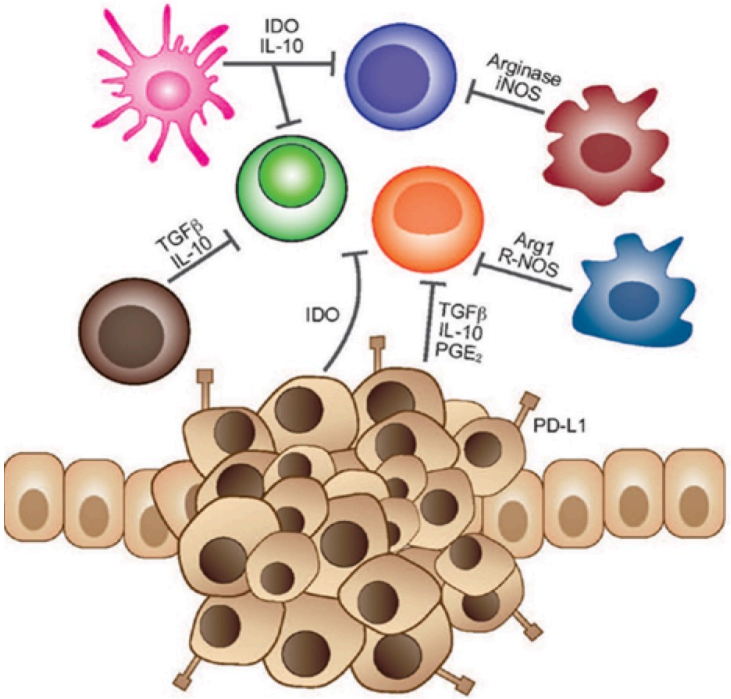
» Reverse immune suppression

» Induce anti-tumor immune response

Variants for immunogenicity study



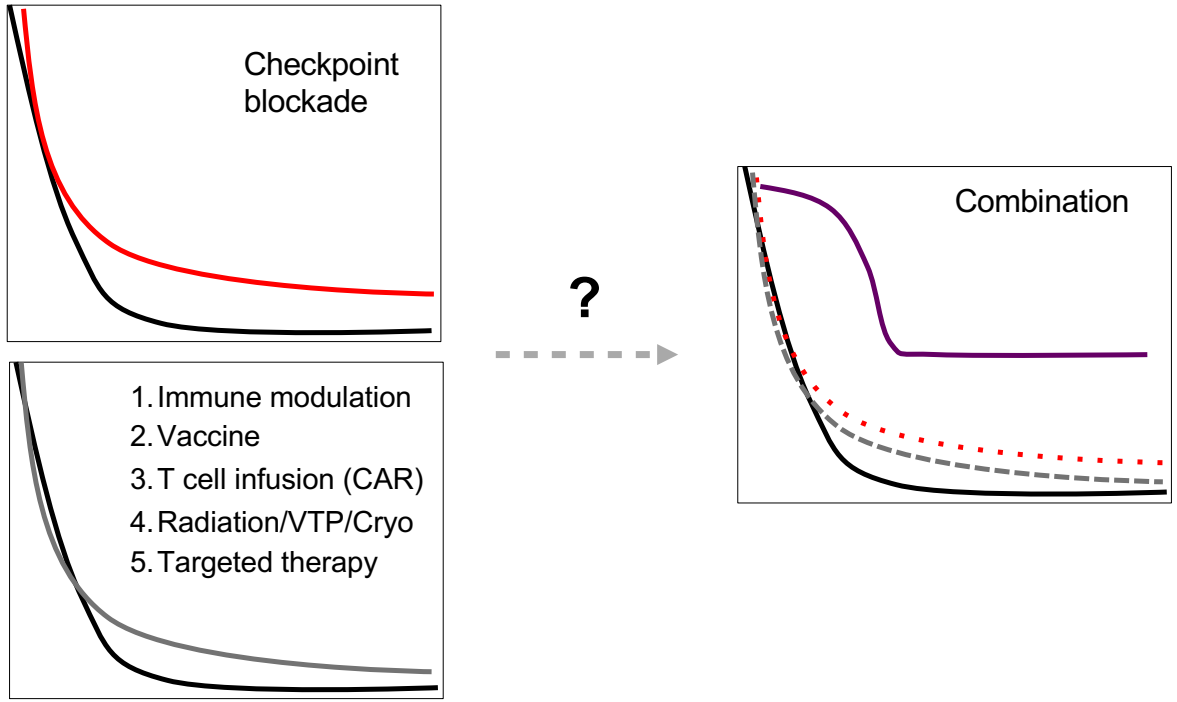
Segal et al. Cancer Res 2008
Matsushita et al. Nature 2012



Escape

Rationale for Combination with other therapies:

- Use other means to enhance tumor recognition
- Strategy to address low response rates of checkpoint blockade



Approach combining blockade of immune suppression with immunotherapy

- - - - ▸ The target cell need to be present

Modify the Immune Suppressive Microenvironment

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-020-17750-z OPEN

Blockade of the AHR restricts a Treg-macrophage suppressive axis induced by L-Kynurenine

Luis Felipe Campesato[1,2], Sadna Budhu[1,2], Jeremy Tchaicha[3], Chien-Huan Weng[1,2], Mathieu Gigoux[1,2], Ivan Jose Cohen[4], David Redmond[1,2], Levi Mangarin[1,2], Stephane Pourpe[1,2], Cailian Liu[1,2], Roberta Zappasodi[1,2], Dmitriy Zamarin[1,2], Jill Cavanaugh[3], Alfredo C. Castro[3], Mark G. Manfredi[3], Karen McGovern[3], Taha Merghoub[1,2,5✉] & Jedd D. Wolchok[1,2,5✉]

Timing of CSF-1/CSF-1R signaling blockade is critical to improving responses to CTLA-4 based immunotherapy

Rikke B. Holmgaard, Alexandra Brachfeld, Billel Gasmi, Thompson Doman, Mary Murphy, David Schaer, Jedd D. Wolchok & Taha Merghoub

To cite this article: Rikke B. Holmgaard, Alexandra Brachfeld, Billel Gasmi, Thompson Doman, Mary Murphy, David Schaer, Jedd D. Wolchok & Taha Merghoub (2016): Timing of CSF-1/CSF-1R signaling blockade is critical to improving responses to CTLA-4 based immunotherapy, OncoImmunology, DOI: 10.1080/2162402X.2016.1151595

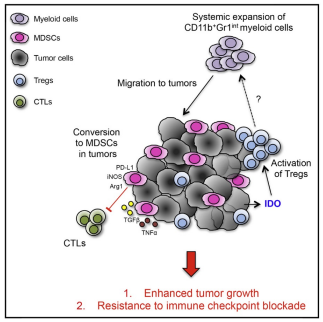
Memorial Sloan Kettering Cancer Center

Article

Cell Reports

Tumor-Expressed IDO Recruits and Activates MDSCs in a Treg-Dependent Manner

Graphical Abstract



Authors

Rikke B. Holmgaard, Dmitriy Zamarin, Yanyun Li, ..., James P. Allison, Taha Merghoub, Jedd D. Wolchok

Correspondence

wolchokj@mskcc.org

In Brief

IDO mediates immune inhibition in tumors, though the mechanisms of this are poorly understood. Holmgaard et al. demonstrate that tumor IDO is a central regulator of both local and systemic immunosuppression and resistance to immunotherapy, which is orchestrated through expansion, recruitment, and activation of MDSCs in a Treg-dependent manner.

LETTER

doi:10.1038/nature20554

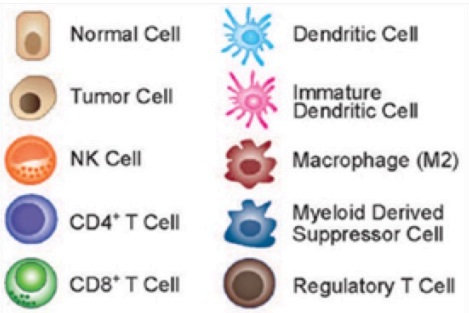
Overcoming resistance to checkpoint blockade therapy by targeting PI3Kγ in myeloid cells

Olivier De Henau[1], Matthew Rausch[2], David Winkler[2], Luis Felipe Campesato[1], Cailian Liu[1], Daniel Hirschhorn-Cymerman[1], Sadna Budhu[1], Arnab Ghosh[1], Melissa Pink[2], Jeremy Tchaicha[2], Mark Douglas[2], Thomas Tibbitts[2], Sujata Sharma[2], Jennifer Proctor[2], Nicole Kosmider[2], Kerry White[2], Howard Stern[2], John Soglia[2], Julian Adams[2], Vito J. Palombella[2], Karen McGovern[2], Jeffery L. Kutok[2], Jedd D. Wolchok[1,3]§ & Taha Merghoub[1]§

Recent clinical trials using immunotherapy have demonstrated its potential to control cancer by disinhibiting the immune system. Immune checkpoint blocking (ICB) antibodies against cytotoxic-T-lymphocyte-associated protein 4 or programmed cell death protein 1/programmed death-ligand 1 have displayed durable clinical responses in various cancers[1]. Although these new immunotherapies have had a notable effect on cancer treatment, multiple mechanisms of immune resistance exist in tumours. Among the key mechanisms, myeloid cells have a major role in

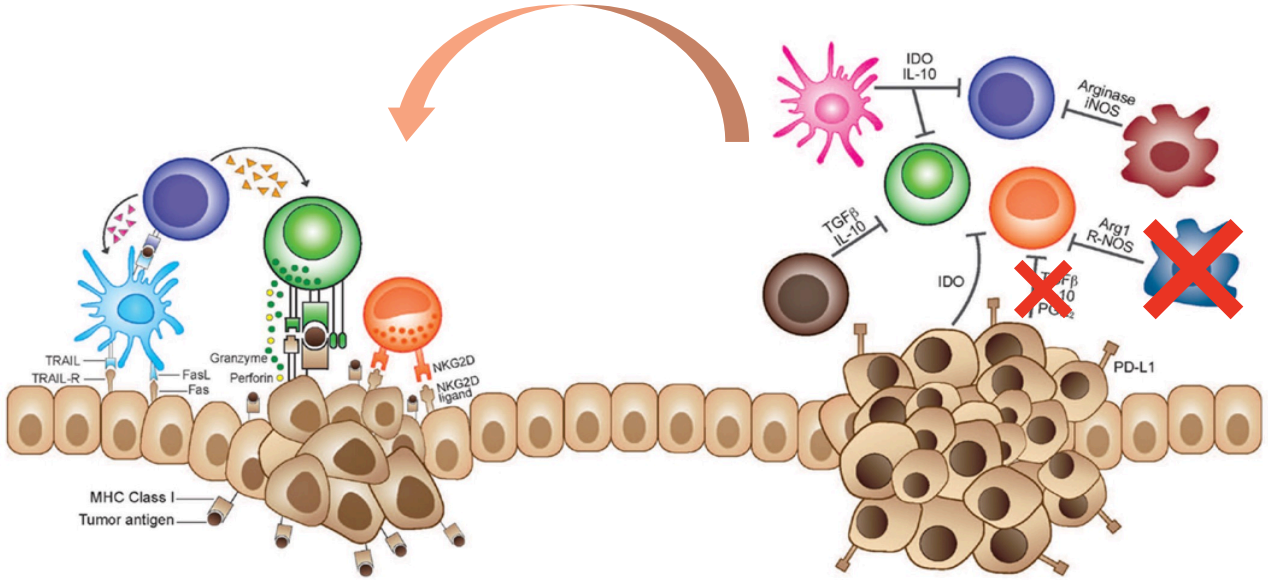
but contain more activated CD8$^+$ T cells (Fig. 1b, c). Additionally, CD8$^+$ T cells express more granzyme B in the B16-F10 model. They also express higher levels of PD-1 and CTLA4 (Fig. 1c, data not shown), which might explain their sensitivity to ICB. Furthermore, myeloid cells from 4T1 tumours or spleens suppress proliferation of T cells to a greater extent compared to myeloid cells from B16-F10 models (Fig. 1d and Extended Data Fig. 1b). These data suggest that TAMCs have varying phenotypes and are more suppressive in ICB-resistant tumours. Tumour-derived soluble factors such as granulocyte-

Immune Suppressive Microenvironment



William J. Murphy.
Front Oncol.
2013; 3: 197.

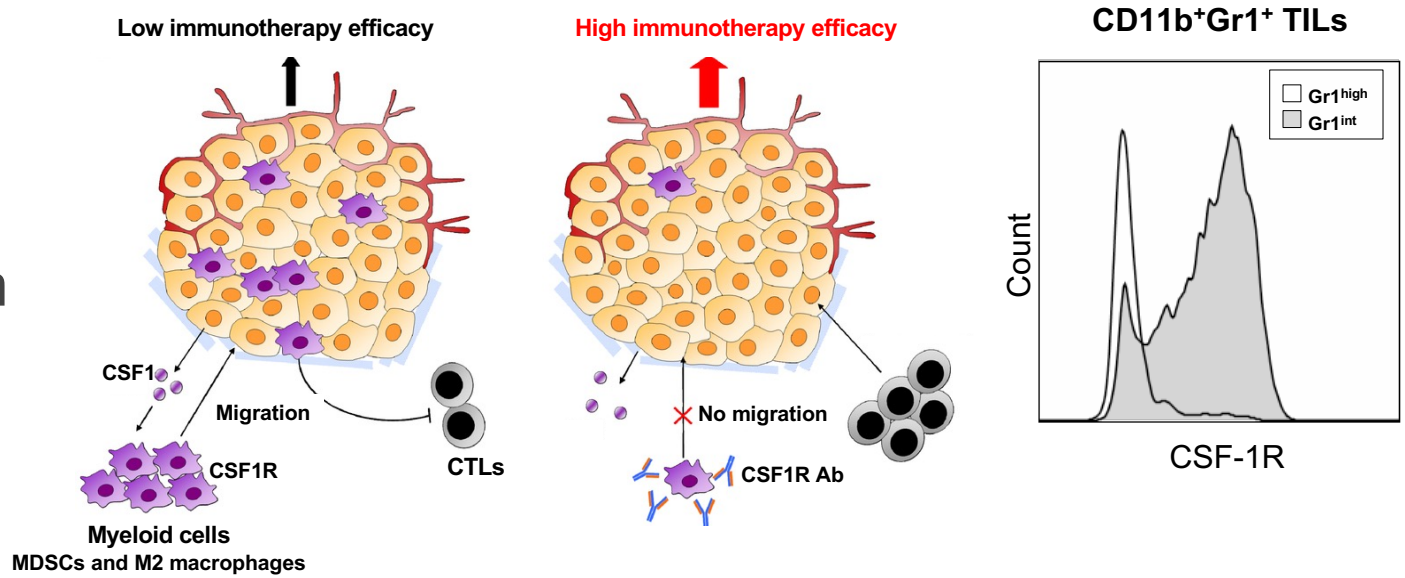
Tumor Microenvironment



Elimination

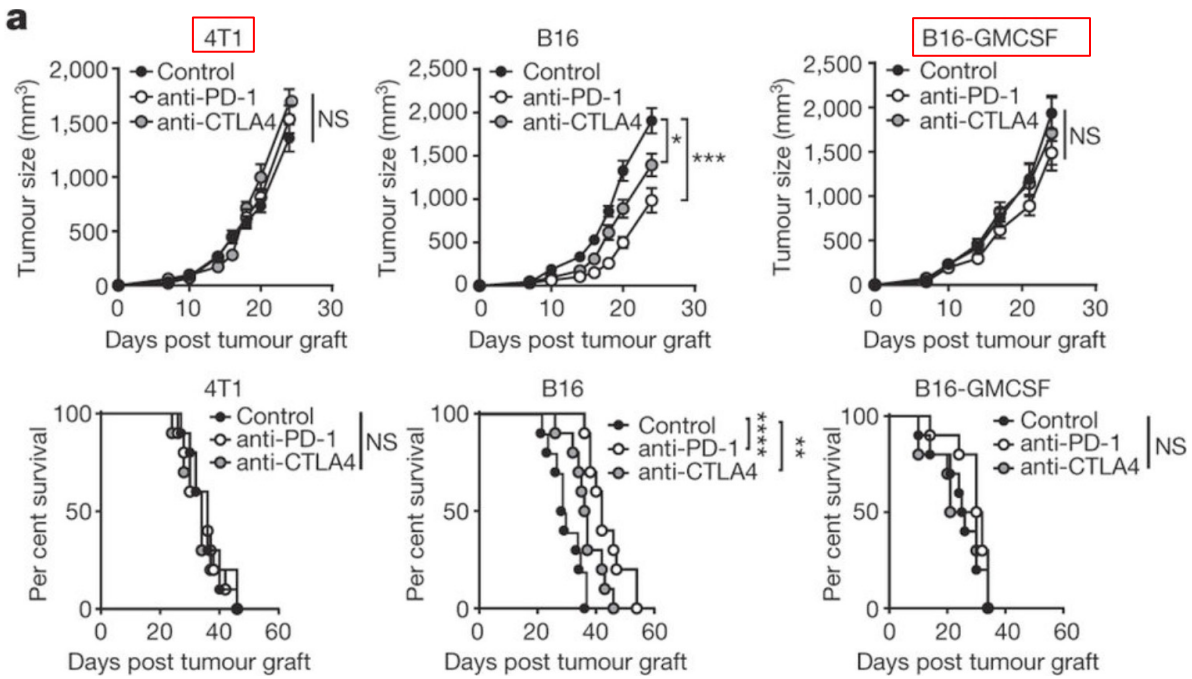
Escape

Therapeutic targeting of suppressive MDSCs: Suppressive MDSCs show high expression of CSF-1R



Castells et al. 2012, Int J Mol Sci.

Resistance to checkpoint blockade is associated with suppressive myeloid cells infiltration in tumor microenvironment



Mammary Carcinoma Model (Rich in myeloid cells)

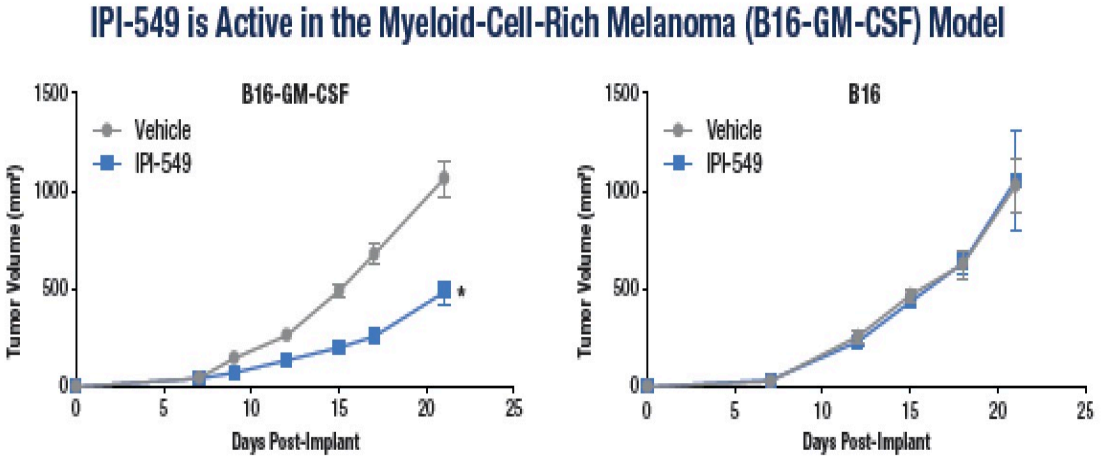
Melanoma Model (Poor myeloid cells)

Melanoma Model (Rich in myeloid cells)

O De Henau et al. Nature (2016)

Role of Myeloid Cells in IPI-549 Antitumor Activity

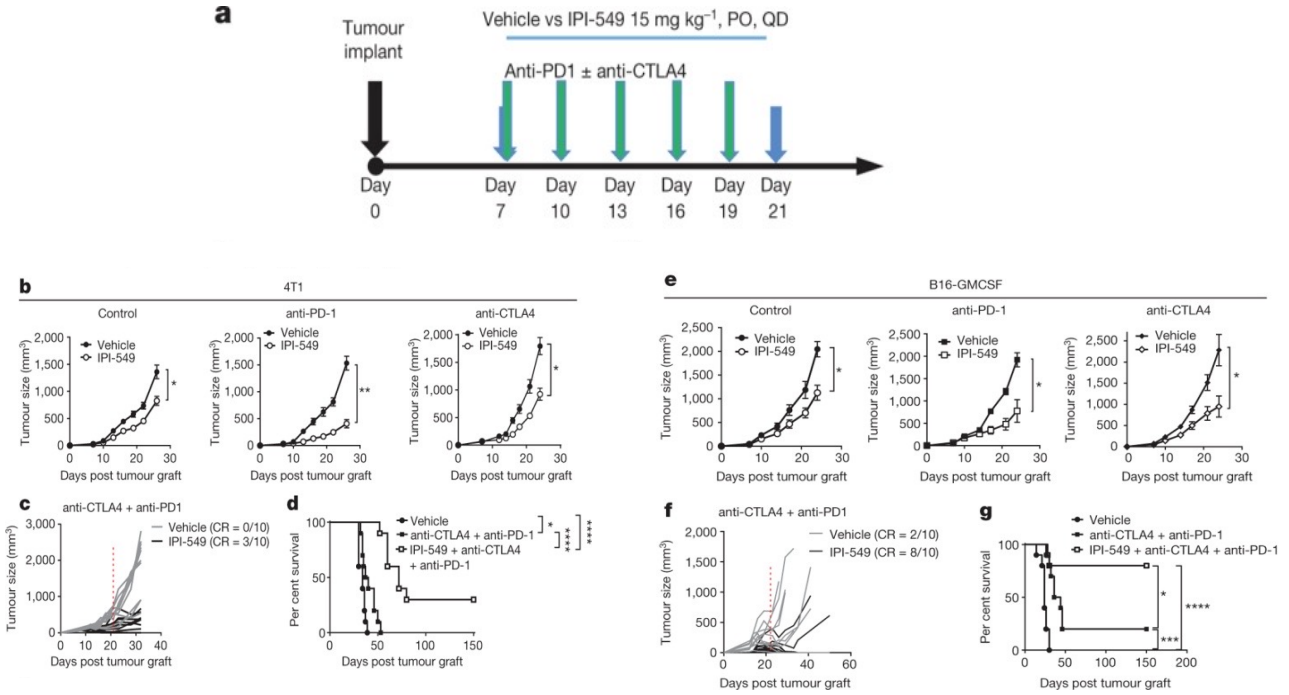
- PI3 kinase gamma is preferentially expressed in MDSCs
- IPI-549 is a PI3 kinase gamma inhibitor.
- IPI-549 is only active in myeloid MDSC dependent tumors.



Administration of IPI-549 15 mg/kg orally, daily to C57Bl6 mice bearing GM-CSF transduced B16 tumors resulted in a significant inhibition of tumor growth (*$p < 0.0001$), while IPI-549 had no impact on B16 tumors without GM-CSF ($p = 0.1852$) ($n = 5$-6 mice/group).

O De Henau et al. Nature (2016)

Resistance to checkpoint blockade therapy is overcome when combined with selective PI3Kγ inhibition



Mammary Carcinoma Model

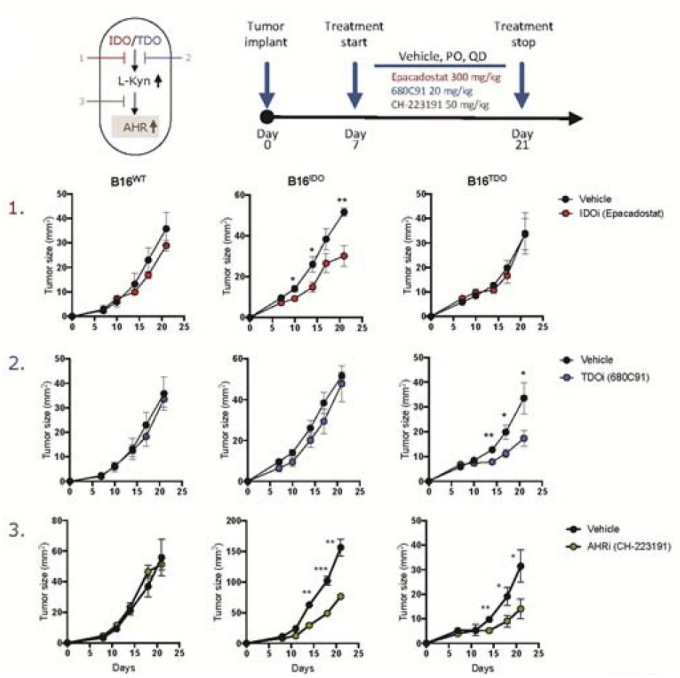
Melanoma Model

O De Henau et al. Nature 1–4 (2016) doi:10.1038/nature20554

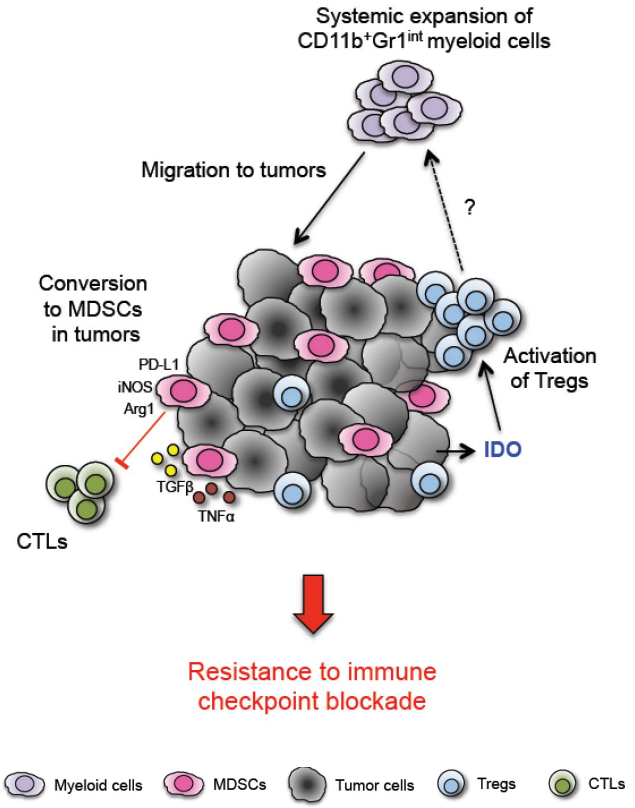
Blocking Suppressive Mechanisms

MDSCs Inhibition (CSF1R blockade, PI3 Kinase…..)

IDO inhibition, Kyn, AHR



AHRi delays tumor regression of IDO and TDO expressing tumors



Campesato, et al, Nat Commun, 2020
Hoolmgard et al, Cell Report,2015

Approach combining blockade of immune suppression with checkpoint blockade

- The target cell need to be present
  Timing is key

OncoImmunology

Taylor & Francis
Taylor & Francis Group

ISSN: (Print) 2162-402X (Online) Journal homepage: http://www.tandfonline.com/loi/koni20

Timing of CSF-1/CSF-1R signaling blockade is critical to improving responses to CTLA-4 based immunotherapy

Rikke B. Holmgaard, Alexandra Brachfeld, Billel Gasmi, Thompson Doman, Mary Murphy, David Schaer, Jedd D. Wolchok & Taha Merghoub

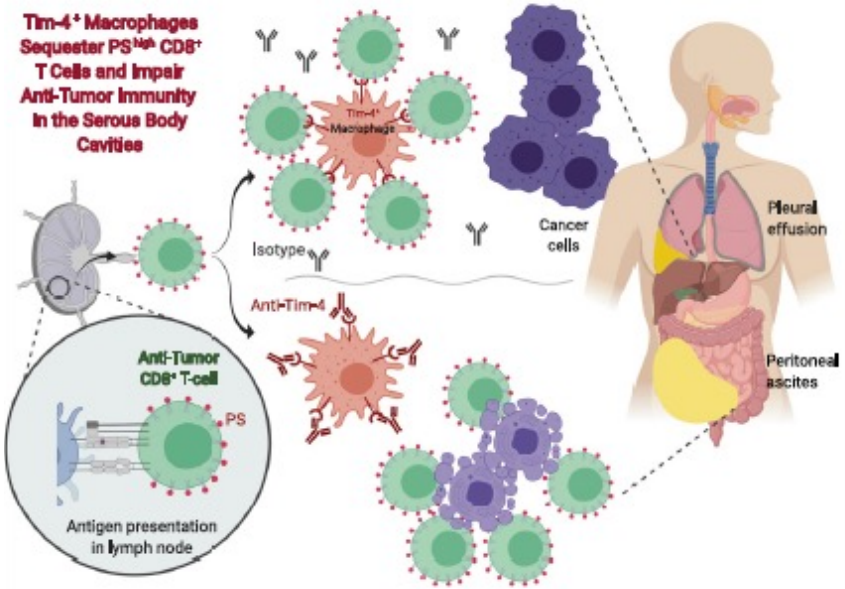
To cite this article: Rikke B. Holmgaard, Alexandra Brachfeld, Billel Gasmi, Thompson Doman, Mary Murphy, David Schaer, Jedd D. Wolchok & Taha Merghoub (2016): Timing of CSF-1/CSF-1R signaling blockade is critical to improving responses to CTLA-4 based immunotherapy, OncoImmunology, DOI: 10.1080/2162402X.2016.1151595

Approach combining blockade of immune suppression with checkpoint blockade

⇢ Location is important

Cancer Cell

Tim-4^{+} cavity-resident macrophages impair anti-tumor CD8^{+} T cell immunity



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In brief

Chow et al. demonstrate that metastatic involvement of the pleural and the peritoneal cavities is associated with poor ICB efficacy in patients with cancer. Tim-4+ cavity-resident macrophages directly impair CD8 T cell function, and Tim-4 blockade enhances the efficacy of ICB and adoptive T cells therapy in mice.

Approach of combining check point blockade with the induction of antigen response

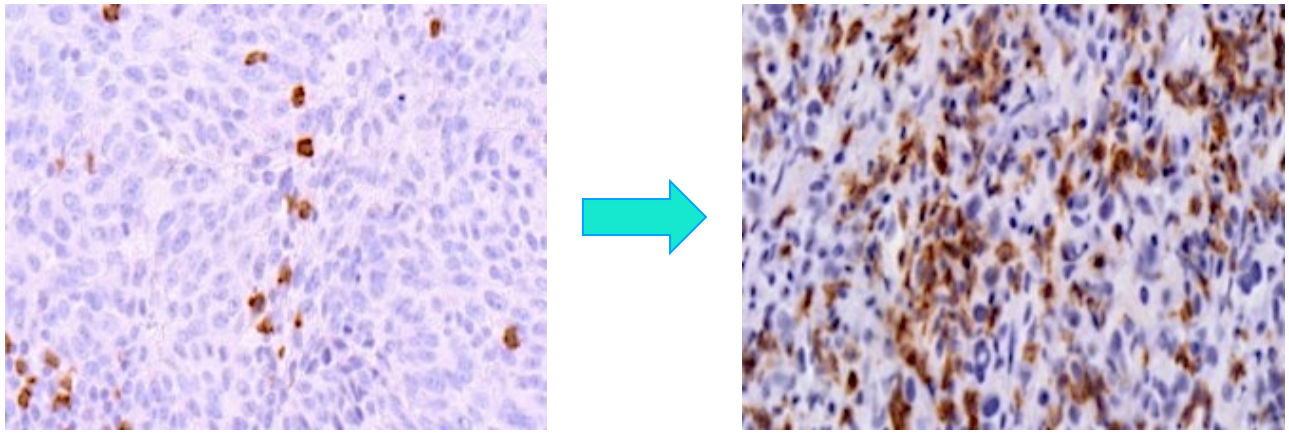
- Antitumor immune response is needed in situ vaccine

Approach

Induce Tumor Antigen Response

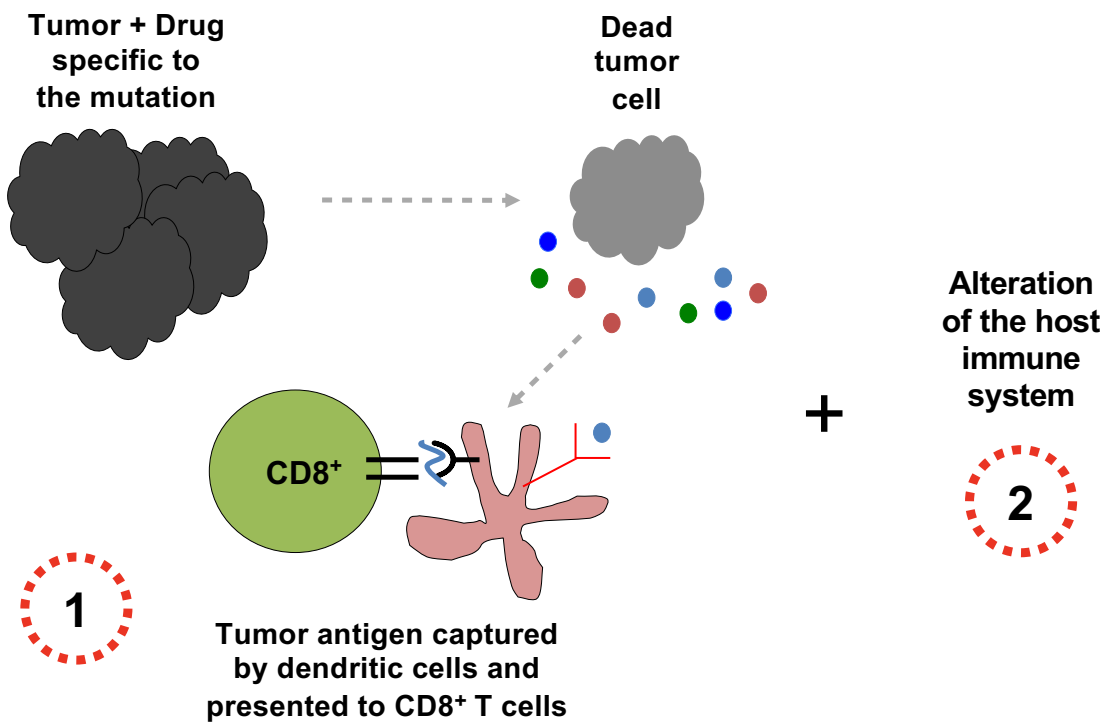
- » Killing the tumors with targeted therapies
- » Oncolytic viral therapy
- » Chemotherapy
- » Radiation therapy
- » VTP
- » Other means…

Increase the Number of Immune Infiltrating Immune Cells

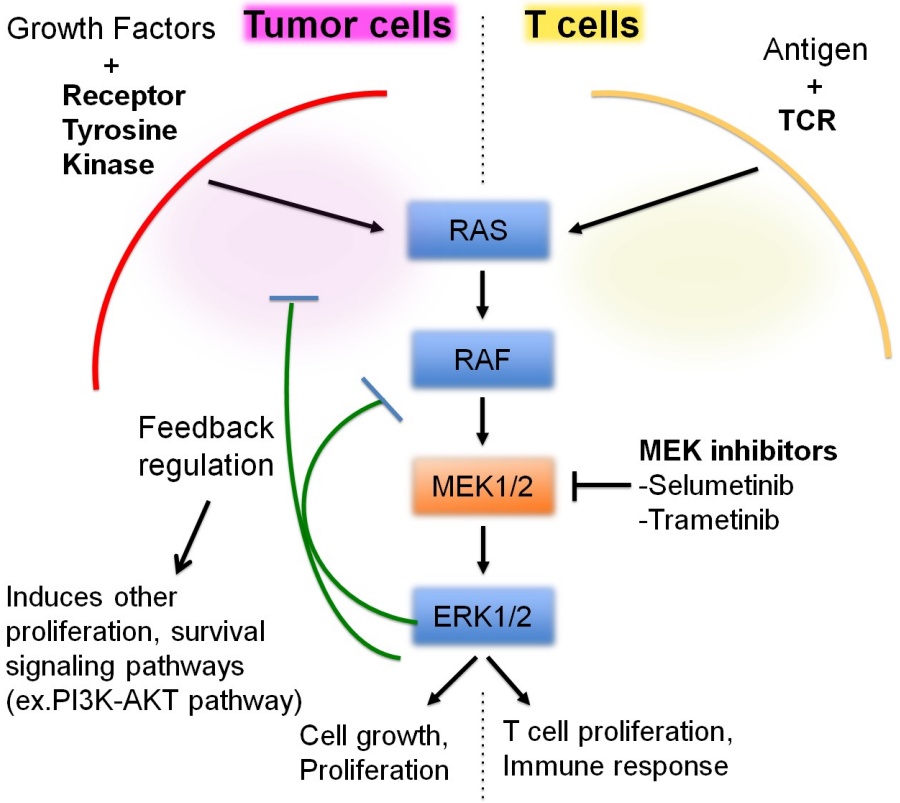


Segal et al. Cancer Res 2008
Matsushita et al. Nature 2012

Targeting tumor cells should induce a tumor-specific immune response



MEK signaling is important to the tumor cells and immune cells both

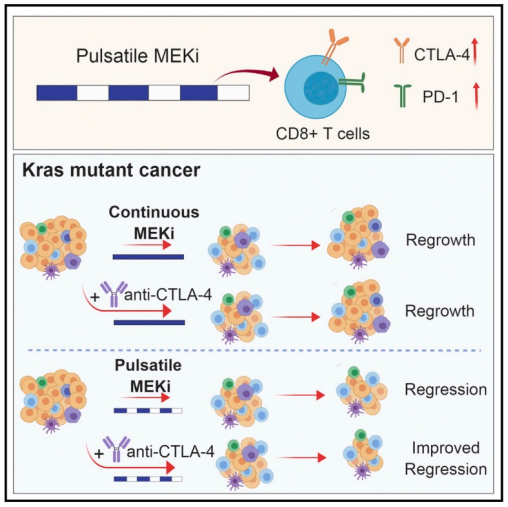


Cell Reports

Article

Pulsatile MEK Inhibition Improves Anti-tumor Immunity and T Cell Function in Murine Kras Mutant Lung Cancer

Graphical Abstract



Authors

Hyejin Choi, Jiehui Deng, Shuai Li, ..., Taha Merghoub, Kwok-Kin Wong, Jedd D. Wolchok

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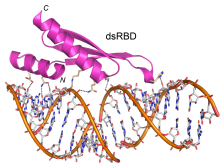
merghout@mskcc.org (T.M.), kwok-kin.wong@nyumc.org (K.-K.W.), wolchokj@mskcc.org (J.D.W.)

In Brief

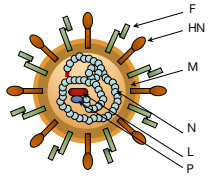
KRAS mutant non-small-cell lung cancer (NSCLC) remains refractory to targeted therapeutics. Choi et al. show that pulsatile, rather than continuous, treatment with MEK inhibitors can maintain T cell activity better and prolong survival in mice with Kras mutant cancer. This effect is further enhanced when combined with CTLA-4 blockade.

Induction of antitumor immunity with oncolytic viruses : ΔE3L vaccinia virus or Newcastle disease virus (NDV)



ΔE3L vaccinia

- Antagonist of intracellular innate immune signaling
- A mutant vaccinia virus lacking the E3L gene (ΔE3L):
  - has a restricted host-range
  - is highly sensitive to IFN
  - has greatly reduced virulence in animal models
- Both the N-terminal Z-DNA BD and C-terminal dsRNA BD are required for full pathogenesis of the virus in vivo.



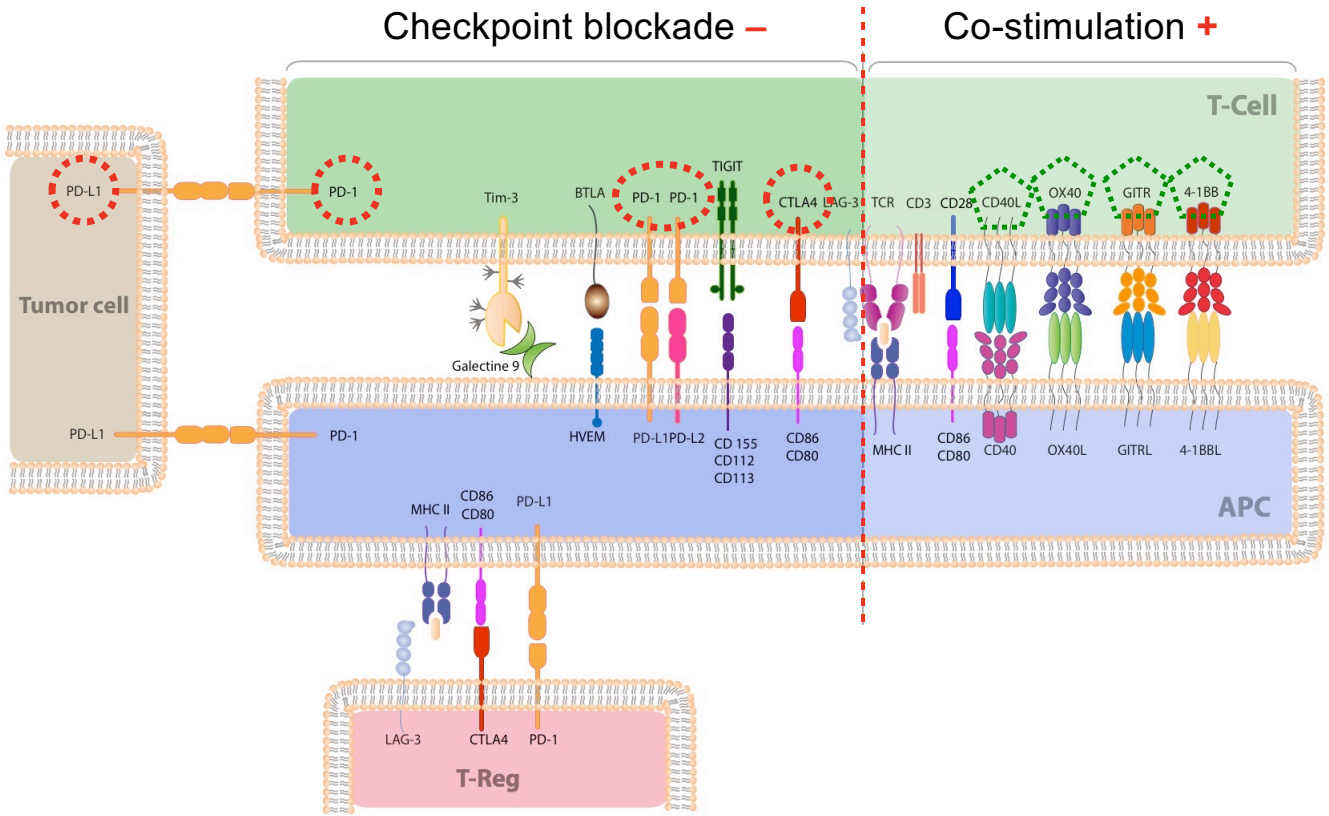
NDV

- Member of Paramyxoviridae family
- Birds are a natural host
- Strong inducer of type I IFN
- Readily infects the majority of cancer cells due to
- ubiquity of the receptor (sialic acid)
- Specificity for cancer cells is mediated by selective viral replication in cells with deficient innate immune responses and cells resistant to apoptosis
- Clinical trials with systemically-administered NDV in humans demonstrated safety and durable clinical benefit

Approach:

Combining Other immune modulatory antibodies

Alter Host Immune System: Rationale Combination with Immune modulation



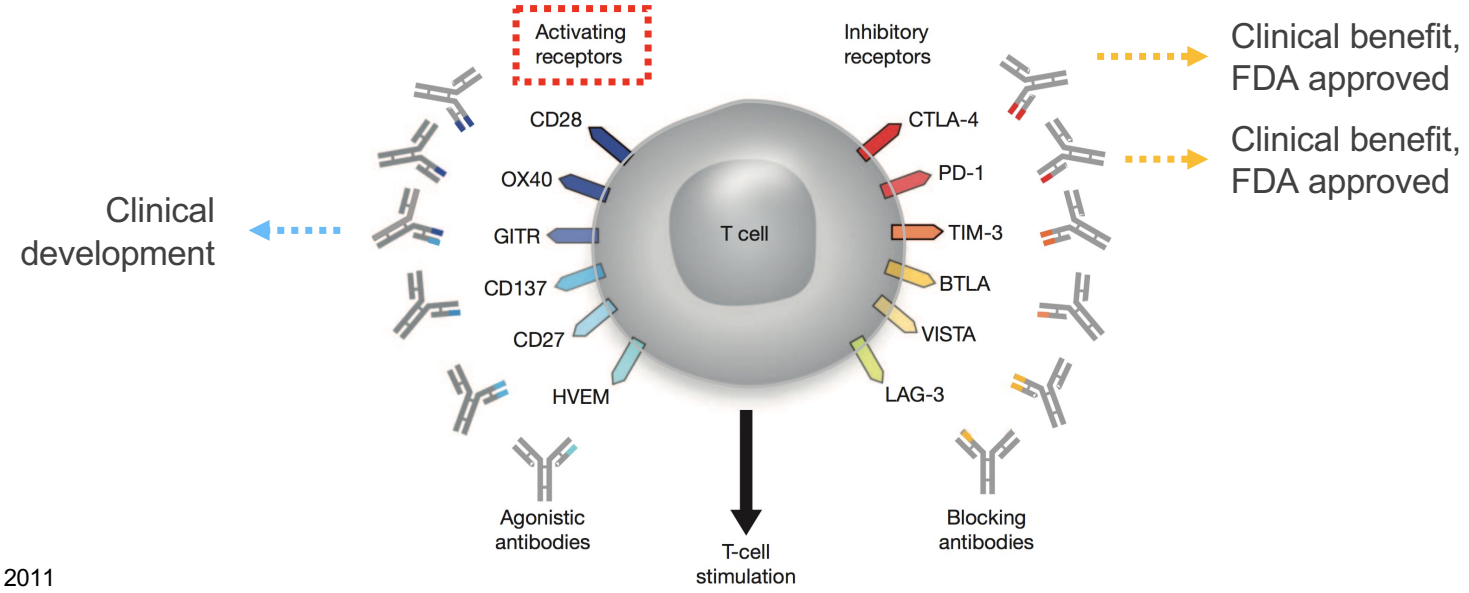
Khalil Merghoubl
Adv Cancer Res.
2015;128:1-68.

Approach:

Combining Other immune modulatory antibodies beyond checkpoint blockade

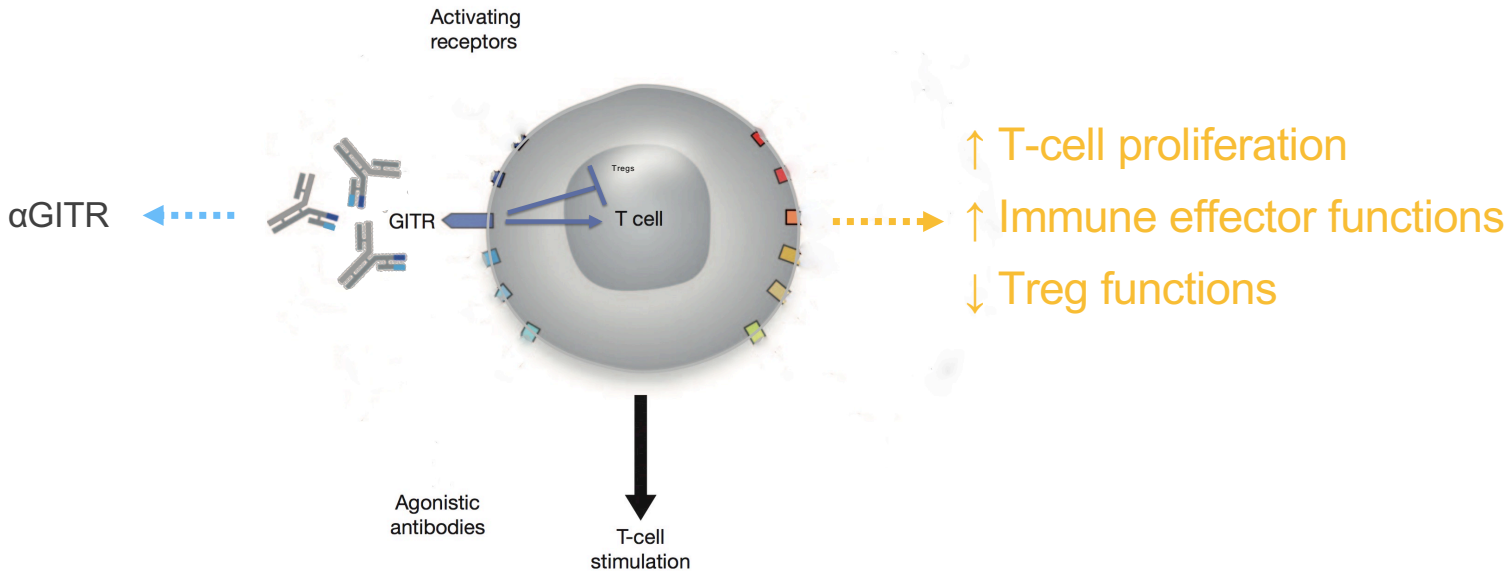
Memorial Sloan Kettering
Cancer Center

Immunomodulatory Abs for cancer therapy: beyond immune checkpoint blockade



Adapted from
Mellman, Nature 2011

Immunomodulatory Abs for cancer therapy: beyond immune checkpoint blockade



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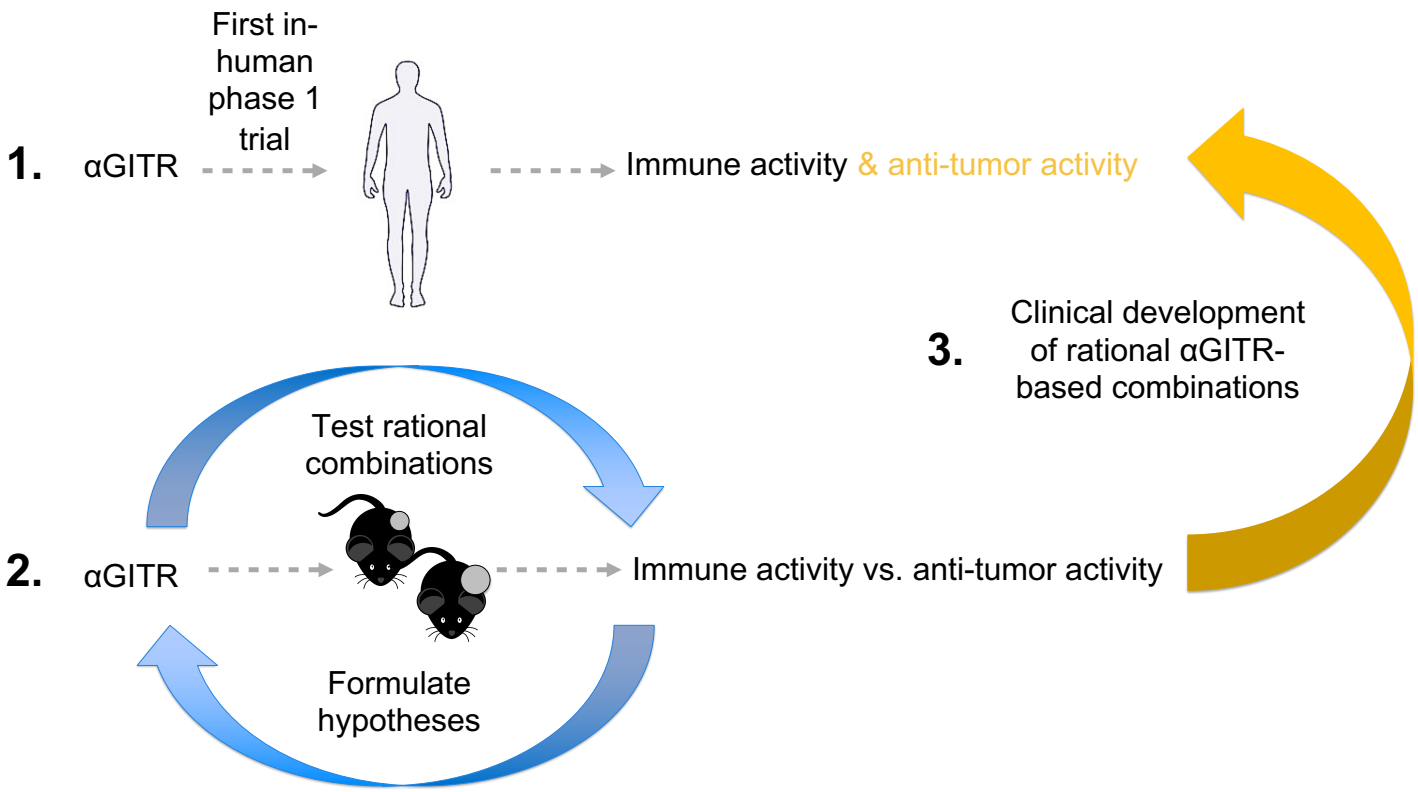
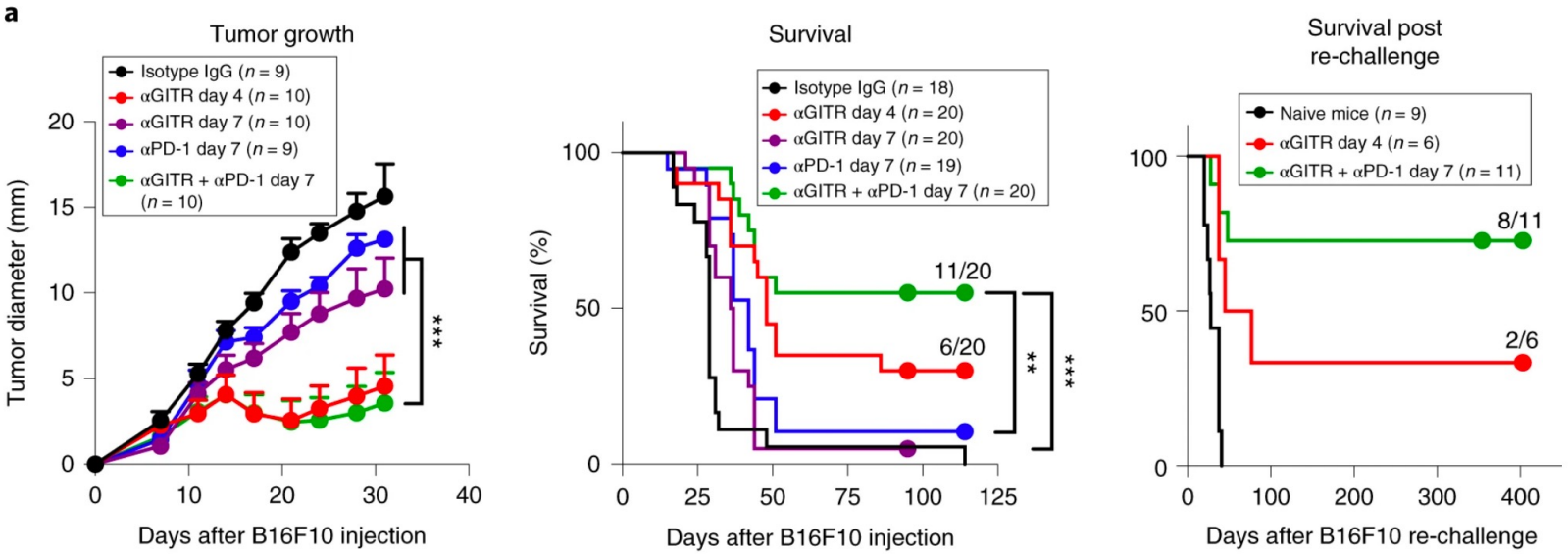
Study Design

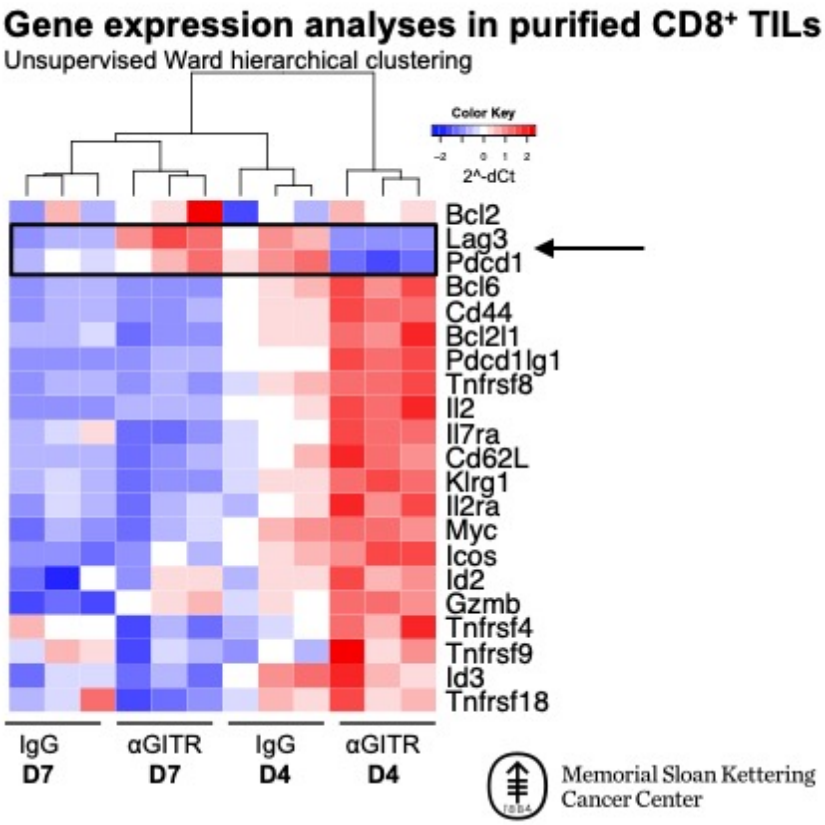


nature medicine
LETTERS
https://doi.org/10.1038/s41591-019-0420-8

Rational design of anti-GITR-based combination immunotherapy

Roberta Zappasodi[1,2], Cynthia Sirard[3], Yanyun Li[1,2], Sadna Budhu[1], Mohsen Abu-Akeel[1], Cailian Liu[1], Xia Yang[1], Hong Zhong[1], Walter Newman[3], Jingjing Qi[2,4], Phillip Wong[2,4], David Schaer[1], Henry Koon[5], Vamsidhar Velcheti[6], Matthew D. Hellmann[2,7,8], Michael A. Postow[7,8], Margaret K. Callahan[2,7,8], Jedd D. Wolchok[1,2,7,8,9*] and Taha Merghoub[1,2,7,9*]



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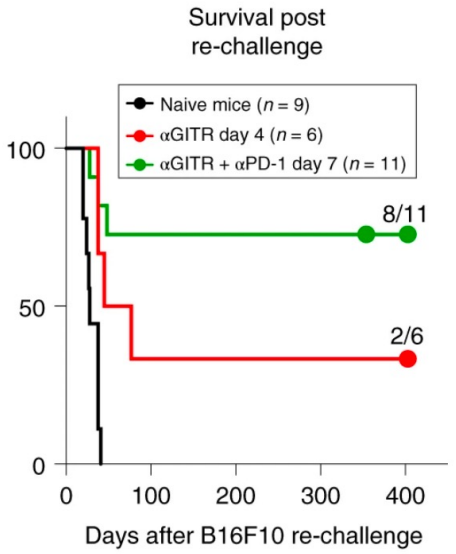
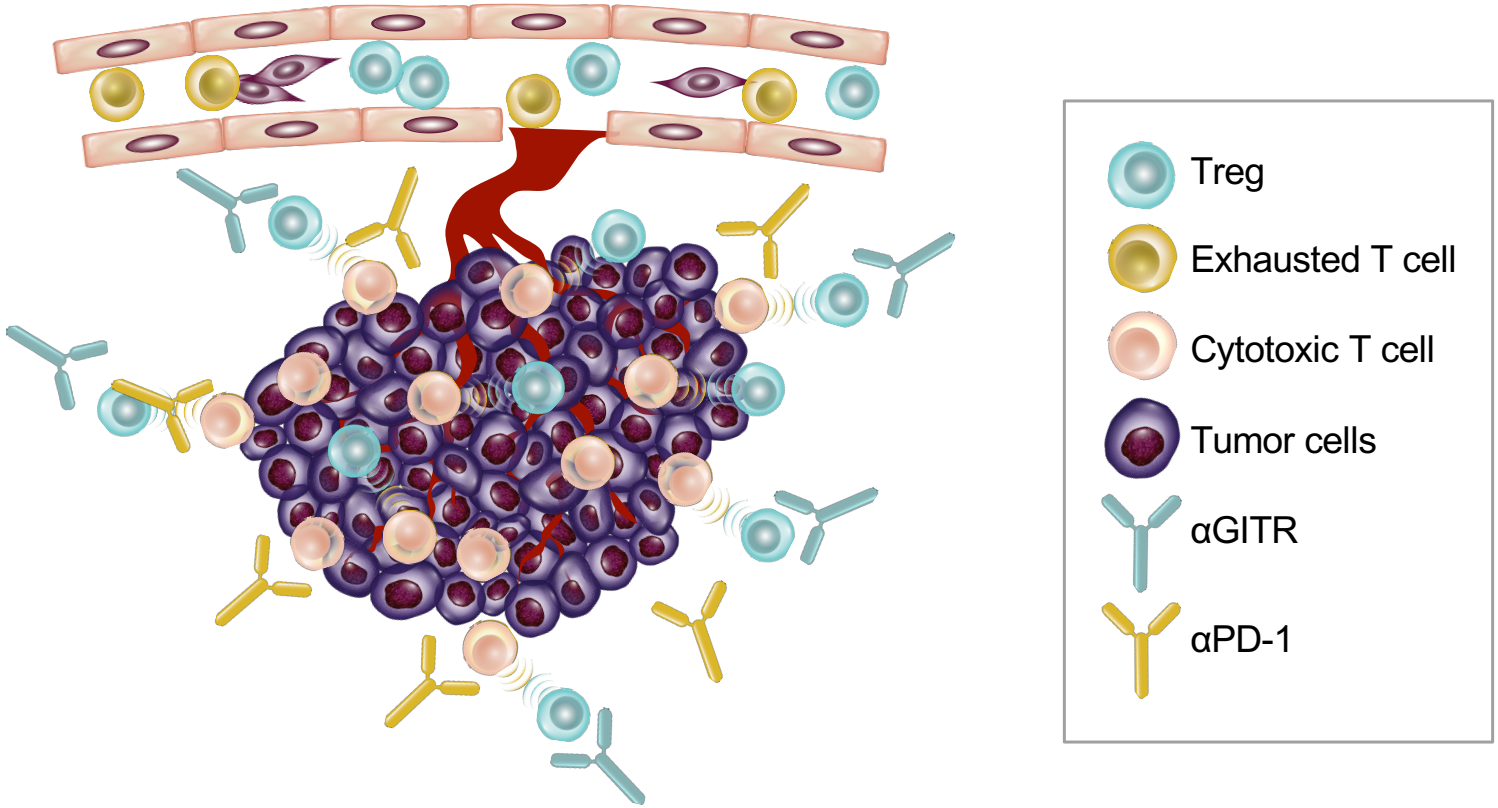


Model


Treg
Exhausted T cell
Cytotoxic T cell
Tumor cells
αGITR
αPD-1

Finally:

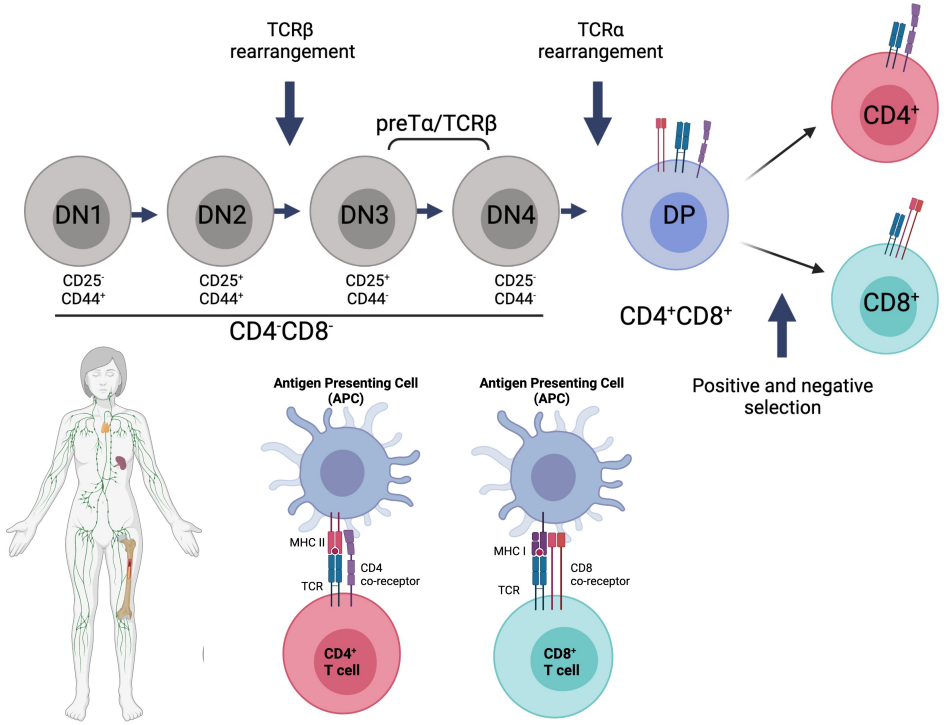
Don’t ignore the biology you don’t know

Memorial Sloan Kettering
Cancer Center

T cell development and commitment to single positive fates

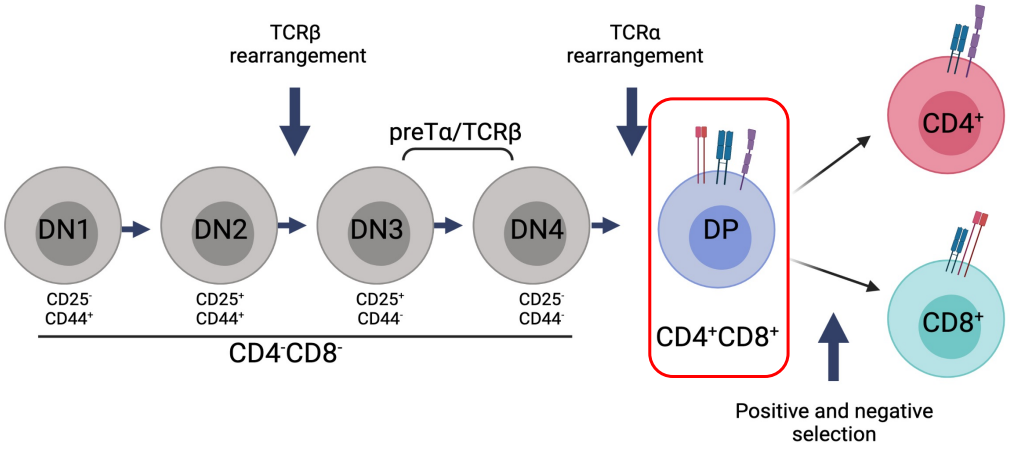
T cells originate from hematopoietic stem cells in the bone marrow and migrate to the thymus for development

- TCRs undergo rearrangement to produce millions of unique variations
- Successfully rearranged TCRs are tested for reactivity with peptide:MHC complexes
  - Strong interactions (self-reactive TCRs) induce cell death
  - Weak interactions **survive**
  - No interaction induces cell death
- Select TCRs enter the periphery as mature single positive T cells

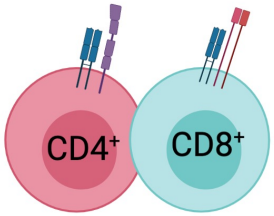


Previous understanding of $CD4^+CD8^+$ T cells

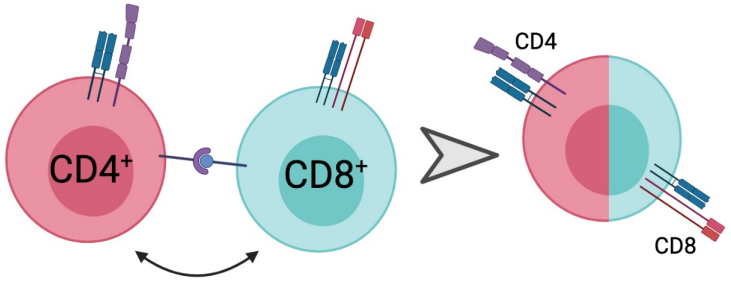
» Developmental stage



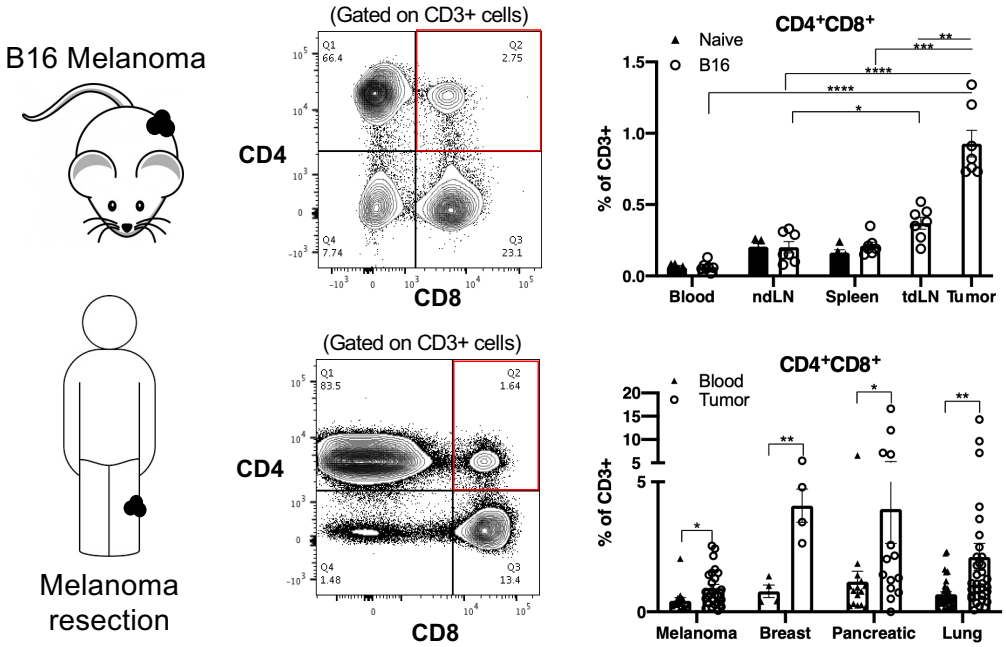
» Cell doublet

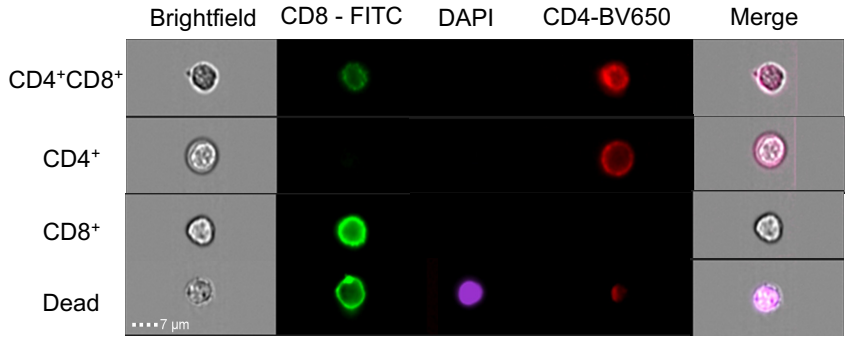


» Trogocytosis (membrane exchange)



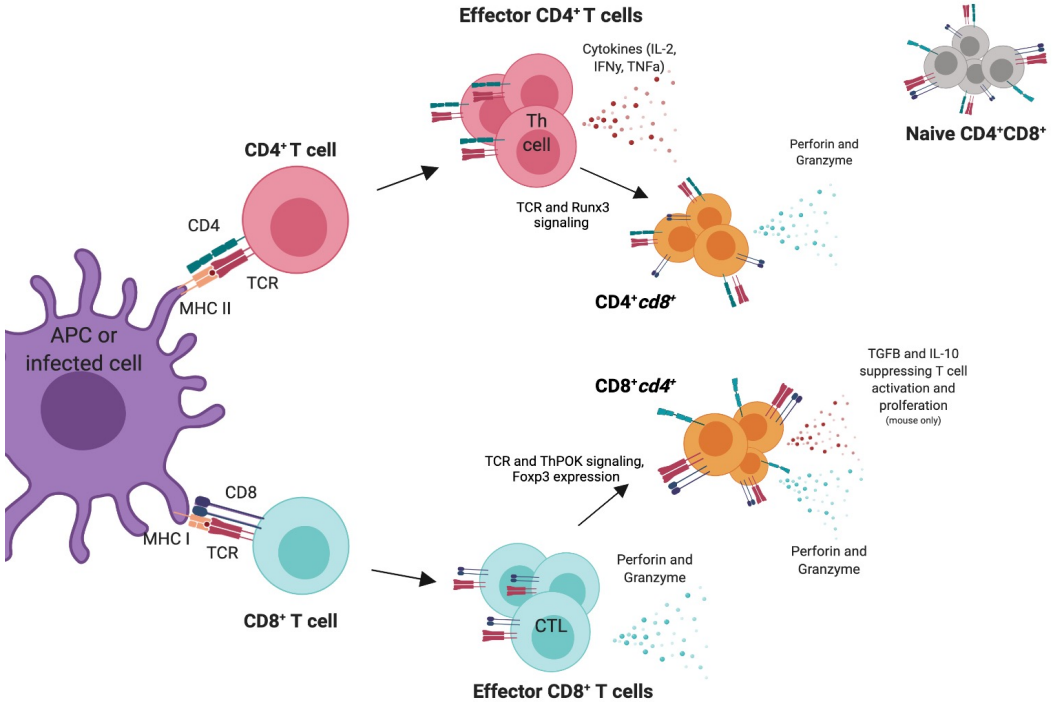
Heterogenous CD4+CD8+ T cells accumulate in murine and human melanoma tumors





CD4+CD8+ T cells are heterogenous and polyfunctional

- TCR signaling induces co-receptor re-expression
- $CD4^+CD8^+$ T cells are polyfunctional and clonally expanded:
  - Cytotoxic CD4 derived $CD4^+cd8^+$ T cells (mouse and human)
  - Suppressive (mouse only) and cytotoxic CD8 derived $CD8^+cd4^+$ T cells (mouse and human)
- "Activated" $CD4^+CD8^+$ T cells may have enriched antigen specificity
- Naïve, non-clonally expanded $CD4^+CD8^+$ T cells exist



Some key points for today's lecture

» Pre-clinical models inform mechanism based therapeutic strategies.

» Tumor immune landscape should be taken into consideration when designing immune therapy.

» The timing of the immune intervention is key.

» Real time monitoring of the tumor microenvironment should help rationally design immune intervention.

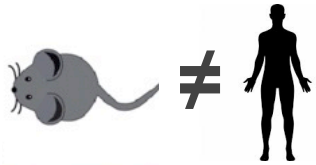
» Do not ignore a phenomena when you don't understand it.

Some key points for today's lecture

» Use appropriate models for each type of approach.

» Often time the models are not the problem. We are.

› We need to make sure that we are not over interpreting (literal translation).



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Adaptive resistance mechanism to SARS-CoV-2 = Zoom

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Translational Opportunities in Immunotherapy Research

Questions