NASDC
NCI Awardee Skills Development Consortium

Translational Opportunities in Immunotherapy Research

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Memorial Sloan Kettering Cancer Center

Weill Cornell Medicine

Disclosures

- IMVAQ therapeutics co-founder
- Advisory board immunos therapeutics
- Advisory board Normunity.
- 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.

Some of my research was supported by:

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- Surface Oncology
- Kyn Therapeutics
- Infinity Pharmaceuticals, Inc.
- Peregrine Pharmeceuticals, Inc.
- 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.

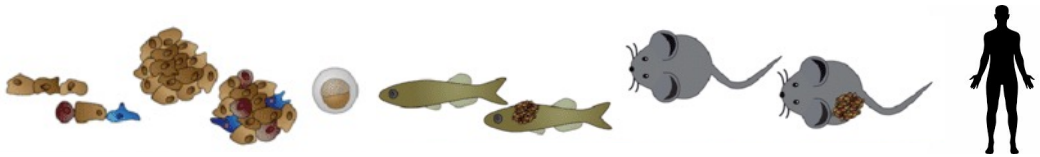
» The timing of the immune intervention is key.

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

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

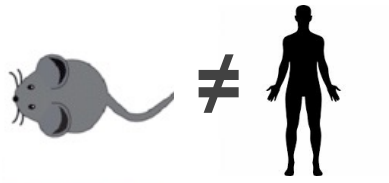
Some key points for today's lecture

» Use appropriate models for each type of approach.



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

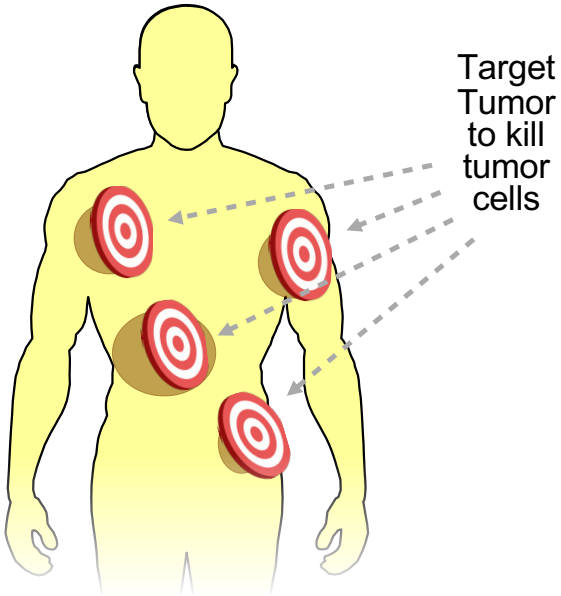
› We need to make sure that we are not over-interpreting (literal translation).



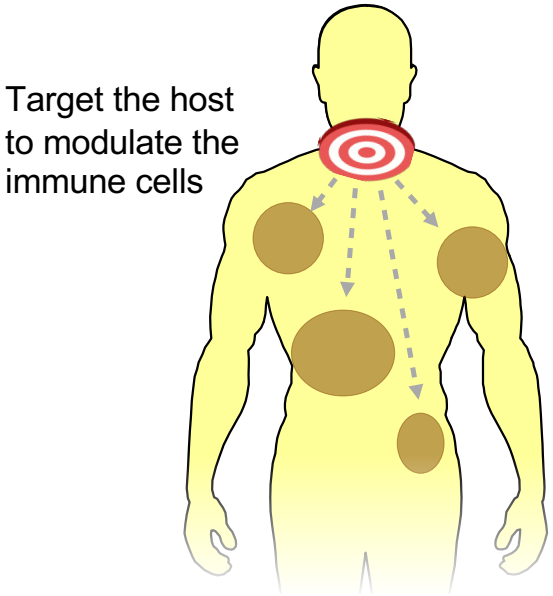
Translation gone wrong: 7 big translation fails from 2016. Richard Brooks. K International.

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

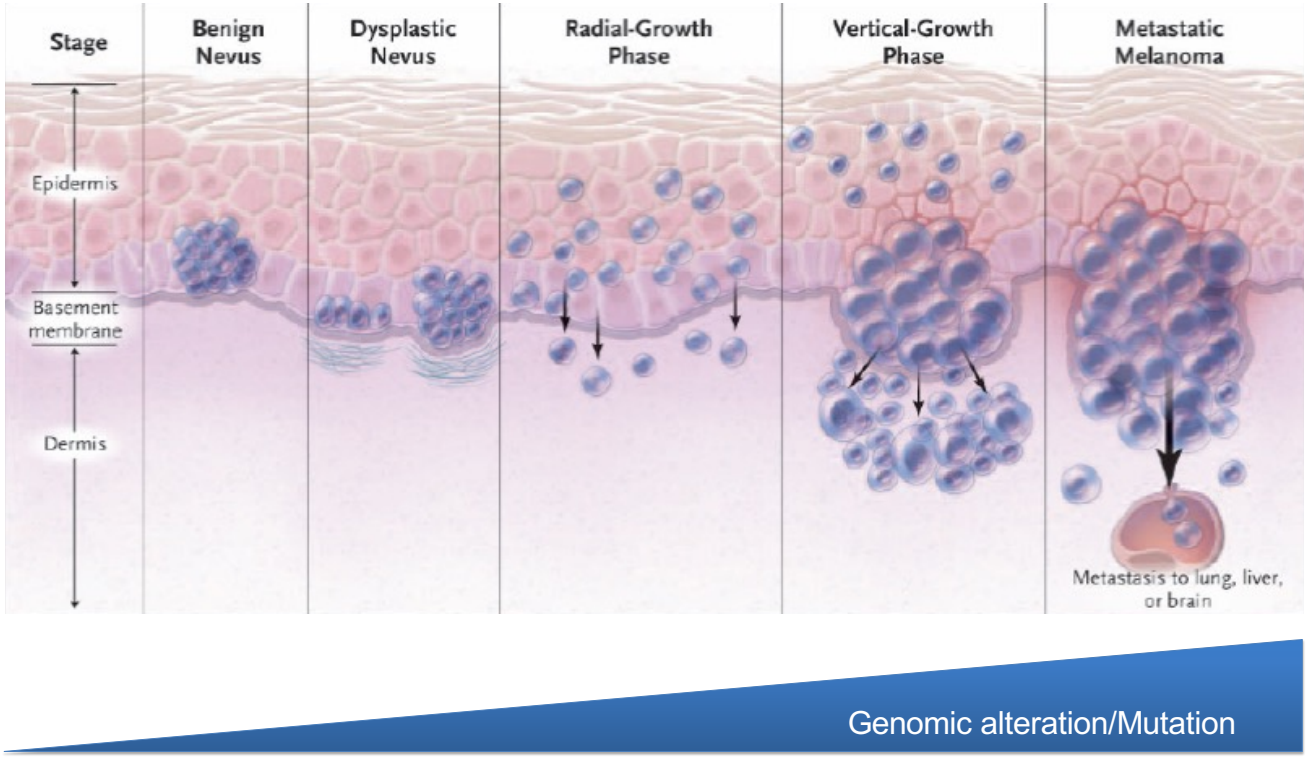
There was a clear need for new and more effective therapies.

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
Tebentafusp	2022

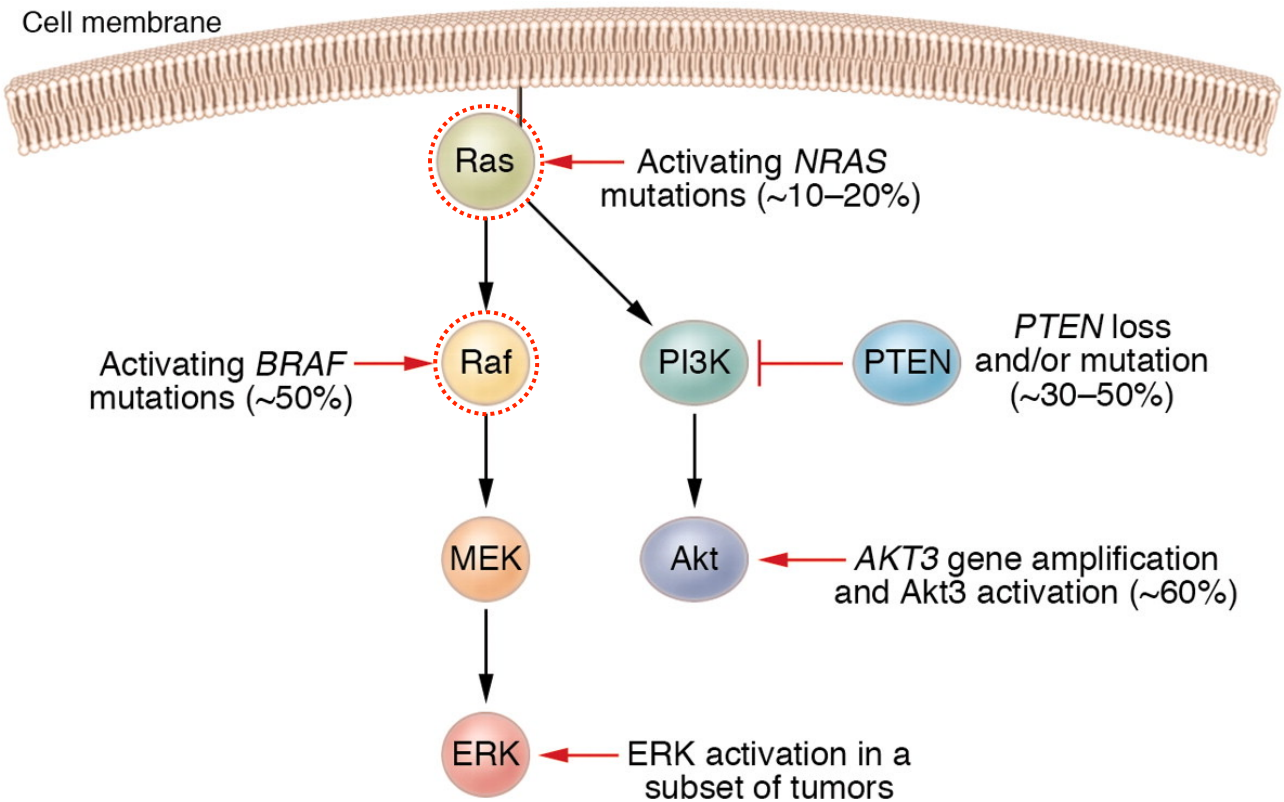
Biological Events and Molecular Changes in Melanoma Progression

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



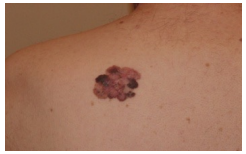
(Adapted from Miller A.R., and Merghoub T)

Genes and Pathways Involved in Melanoma Development



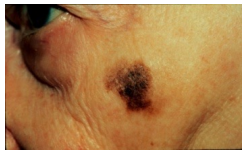
Chudnovsky Y,
JCI, 2005.

Mutations Define Distinct Melanoma Molecular Subsets

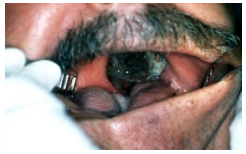


Arising from Skin Without Chronic Sun Damage → 50% BRAF, 20% NRAS — 0% KIT

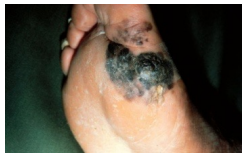
Vemurafenib



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



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

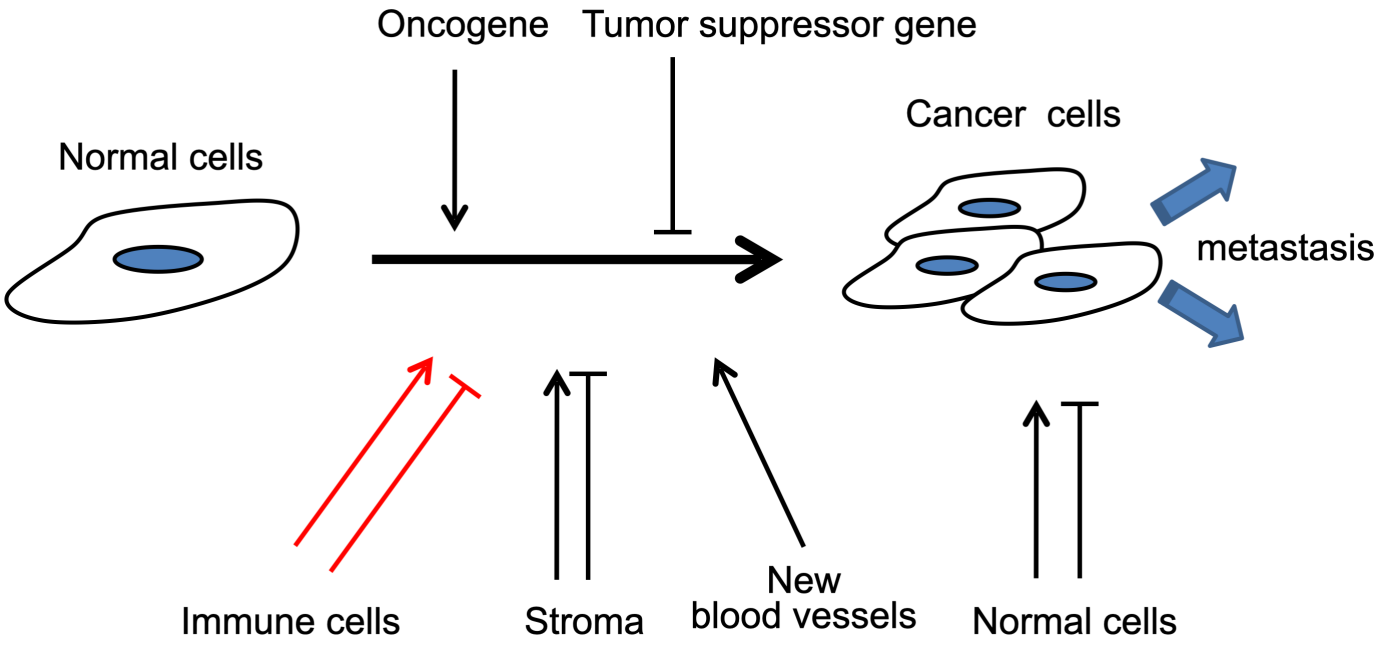


Arising from Acral Surfaces → 15% BRAF, 15% NRAS — 15% KIT

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

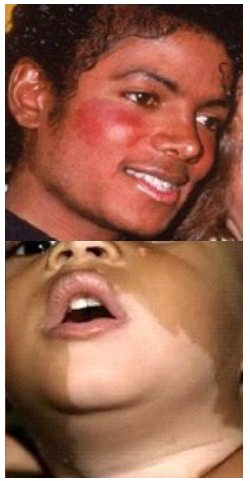


Can the immune system recognize cancer?

The immune system is designed to recognize foreign antigens

~~Non-self~~ Self

What if the immune system recognizes and attacks self?



Cancer = Self

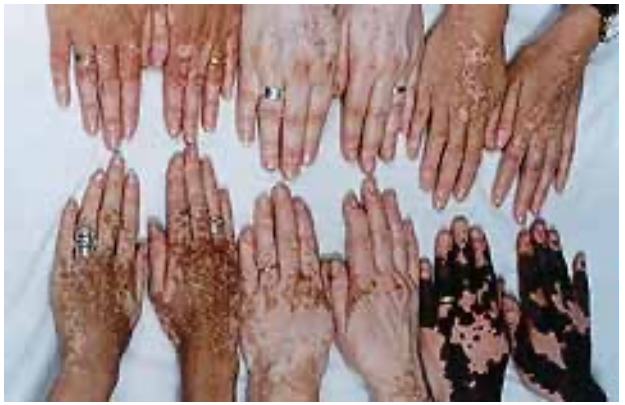
Autoimmune Reaction to Self / Transformed Self

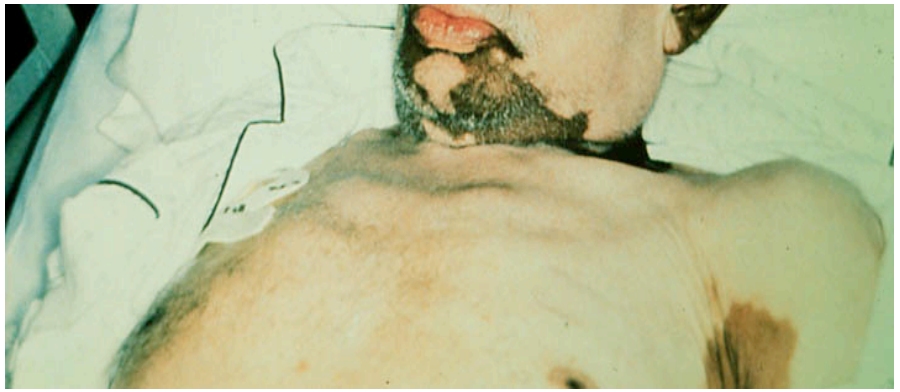
Recognizing self as non-self:
Autoimmunity/Vitiligo

Goal: Recognition of
Transformed-self/Cancer

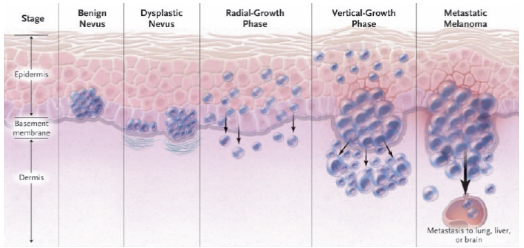
Natural Response to Melanoma

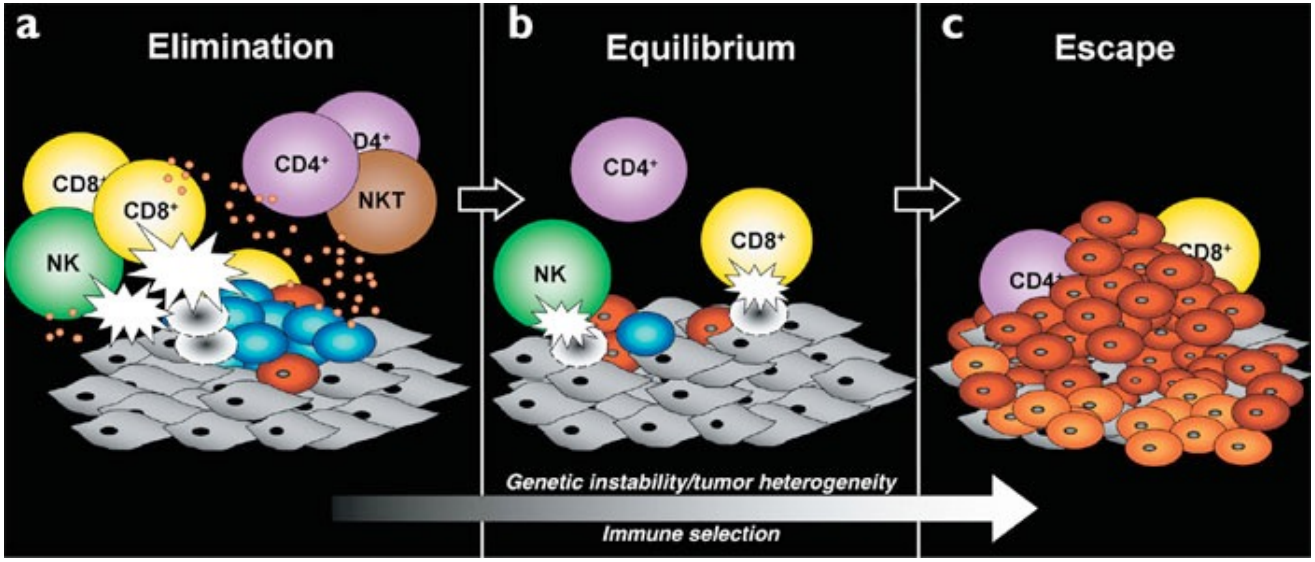
- Clinical observation that melanoma patients who develop vitiligo “do better” and that vitiligo is associated with response to chemotherapy as well as immunotherapy
- Isolation from a patient of an antibody recognizing “pigmented associated antigen”





Role of the Immune System in Cancer: Immunoediting

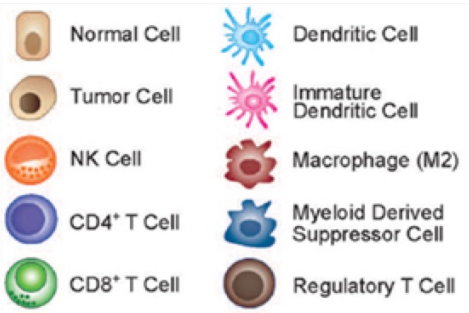




Robert D. Schreiber

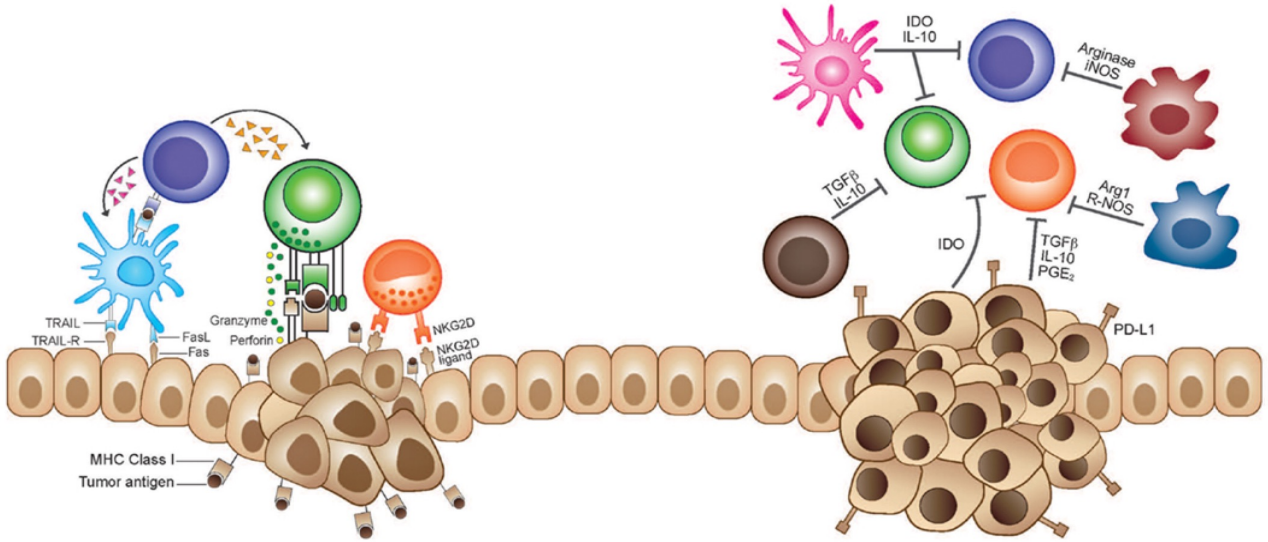
Immunoediting

Immune Suppressive Microenvironment



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

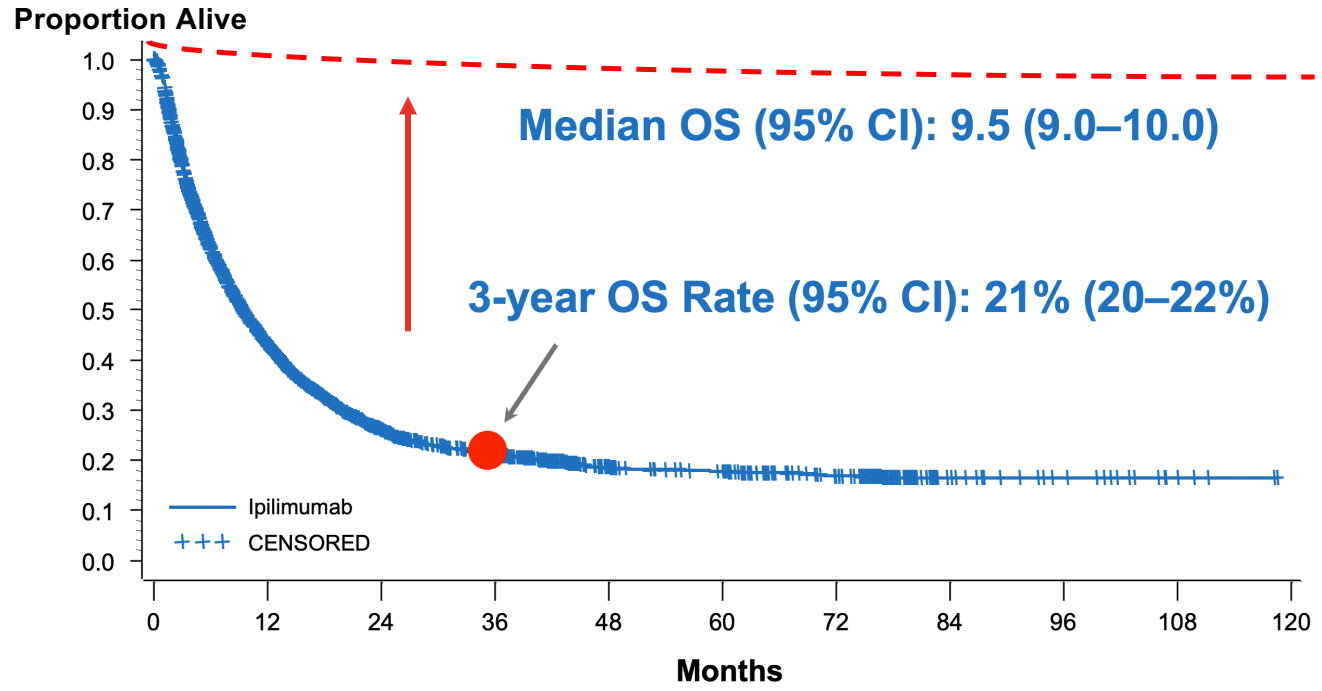
Tumor Microenvironment



Elimination

Escape

Ipilimumab Long Term Pooled Survival Analysis: 4846 Patients



Patients at Risk

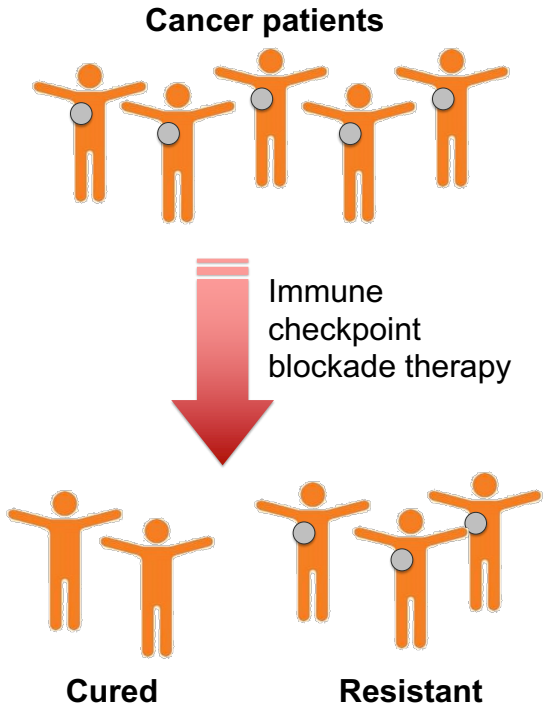
Ipilimumab	4846	1786	612	392	200	170	120	26	15	5	0

Schadendorf, Hodi
Wolchok, ESMO, 2013

Many Approved Immune Based Therapies

Table 1. FDA-approved immune checkpoint inhibitors

Drug	Target	Approval
Ipilimumab	CTLA-4	2011
Nivolumab	PD-1	2014
Pembrolizumab	PD-1	2014
Atezolizumab	PD-L1	2016
Durvalumab	PD-L1	2017
Avelumab	PD-L1	2017
Cemiplimab	PD-1	2019

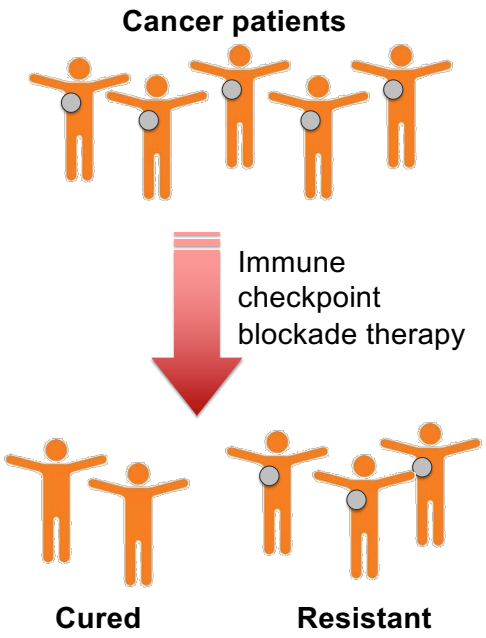


J Clin Invest DOI: 10.1172/JCI145186

Can we predict response to immune therapy reliably?

Can we improve response to immune therapy?

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

Jianjun Gao,[1,6] Lewis Zhichang Shi,[1,6] Hao Zhao,[4,6] Jianfeng Chen,[1] Liangwen Xiong,[1] Qiuming He,[1] Tenghui Chen,[4] Jason Roszik,[2] Chantale Bernatchez,[2] Scott E. Woodman,[2] Pei-Ling Chen,[5] Patrick Hwu,[2] James P. Allison,[4] Andrew Futreal,[3] Jennifer A. Wargo,[2,3] and Padmanee Sharma[1,4,7,*]

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

Willy Hugo,[1,6,9] Jesse M. Zaretsky,[2,6,9] Lu Sun,[1,6] Chunying Song,[1,6] Blanca Homet Moreno,[2] Siwen Hu-Lieskovan,[3] Beata Berent-Maoz,[2] Jia Pang,[2] Bartosz Chmielowski,[1] Grace Cherry,[2] Elizabeth Seja,[2] Shirley Lomeli,[1,6] Xiangju Kong,[1,6] Mark C. Kelley,[7] Jeffrey A. Sosman,[8] Douglas B. Johnson,[8] Antoni Ribas,[2,3,4,5,6] and Roger S. Lo[1,2,5,6,*]

The NEW ENGLAND JOURNAL of MEDICINE

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

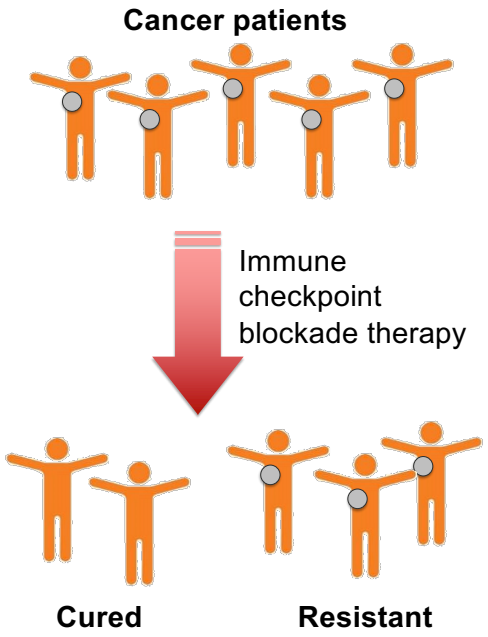
Howard Hughes Medical Institute, Department of Immunology, Memorial Sloan-Kettering Cancer Center, New York, New York, USA.

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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Can we predict response to immune therapy reliably?

Memorial Sloan Kettering
Cancer Center

Further understand the mechanisms underlying resistance to check point blockade & define potential immunogenic antigens.

» Paul Ehrlich, Lewis Thomas…

» **Macfarlane Burnet,** 1957: “It is by no means inconceivable that small accumulations of tumour cells may develop and, because of their possession of new antigenic potentialities, provoke an effective immunological reaction with regression of the tumour and no clinical hint of its existence.”

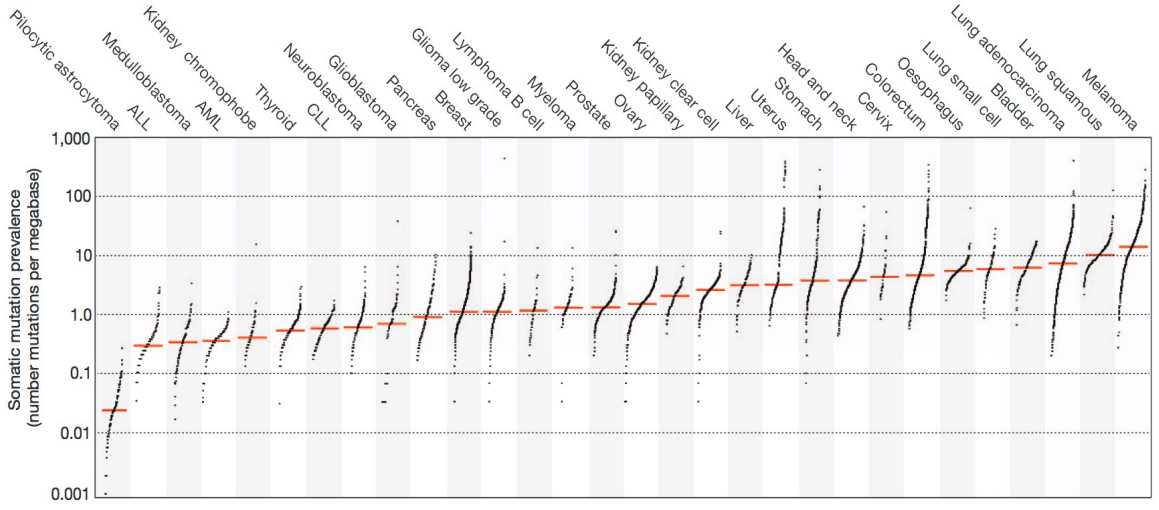
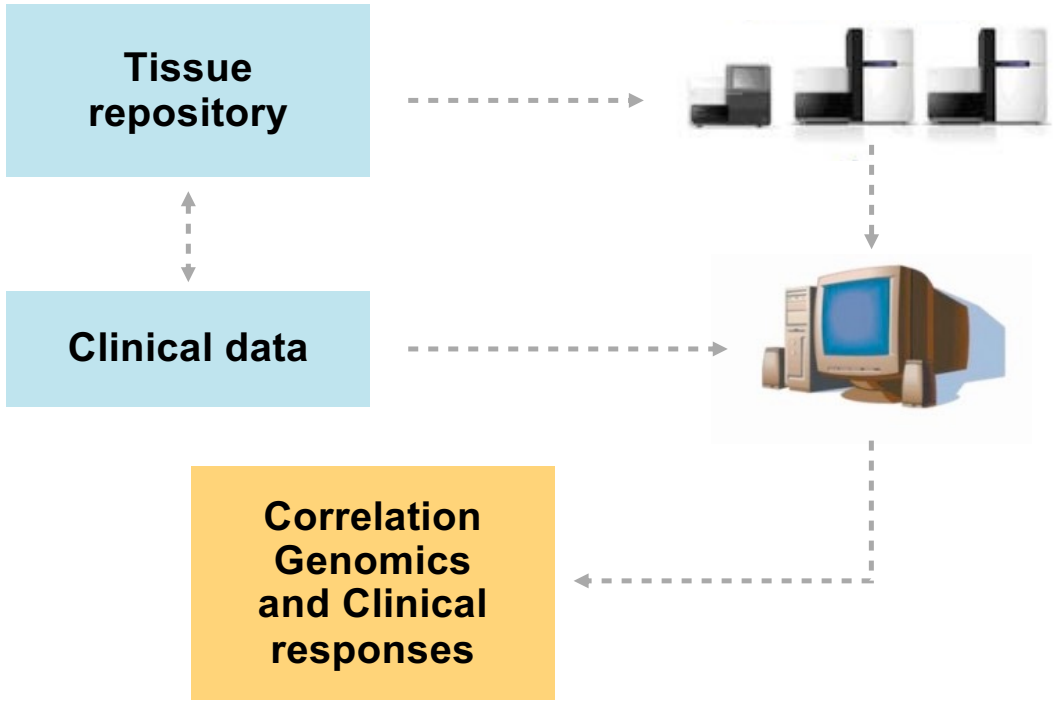


Figure 1 | The prevalence of somatic mutations across human cancer types. cancer types are ordered on the horizontal axis based on their median numbers

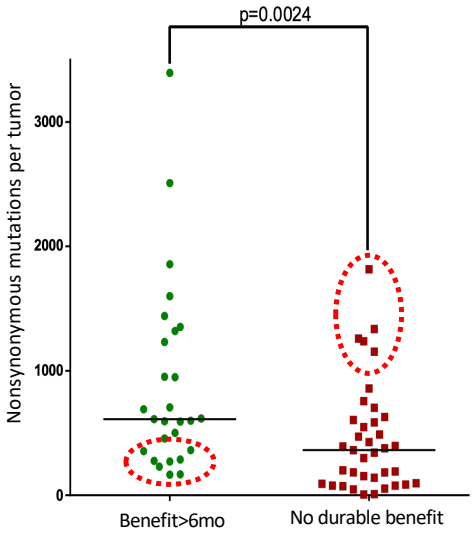
Mutations, Immunogenicity and Prediction of clinical response



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

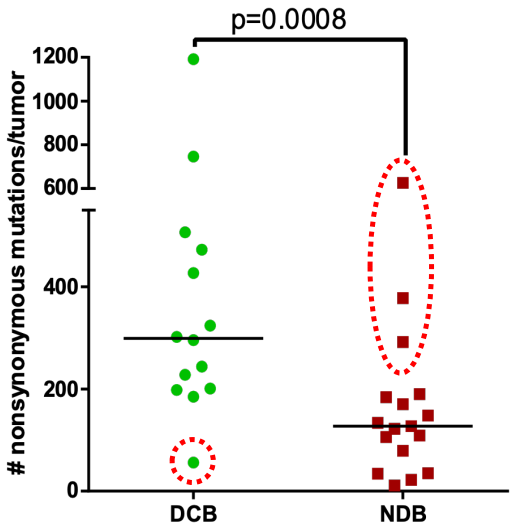
Mutational Load Correlates with Benefit from Checkpoint Blockade ….With Important Exceptions

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

Mutations are not all equal?

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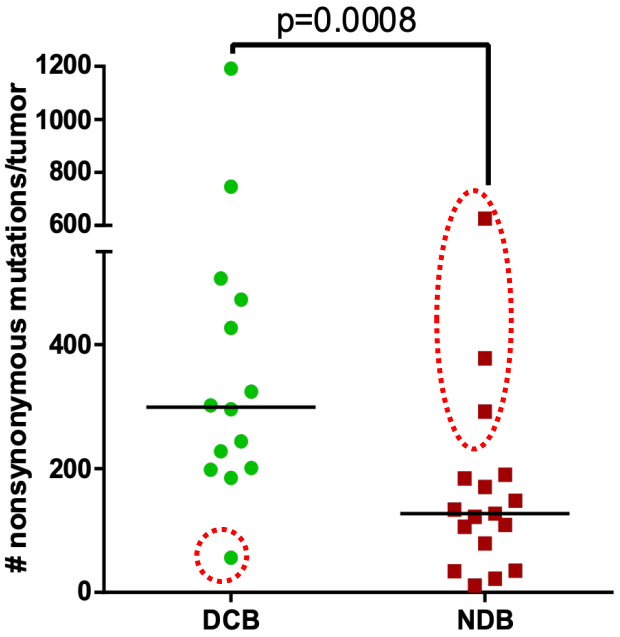
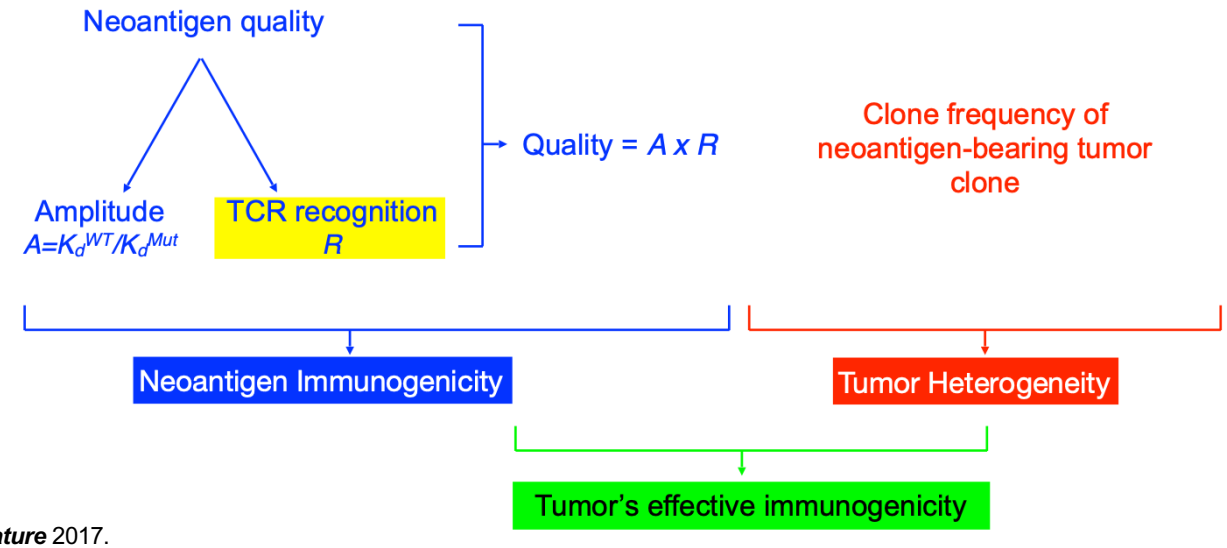
Medicine

Having an immunogenic mutation is like drawing the lucky number



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.

Do hotspot mutations offer a selective advantage?

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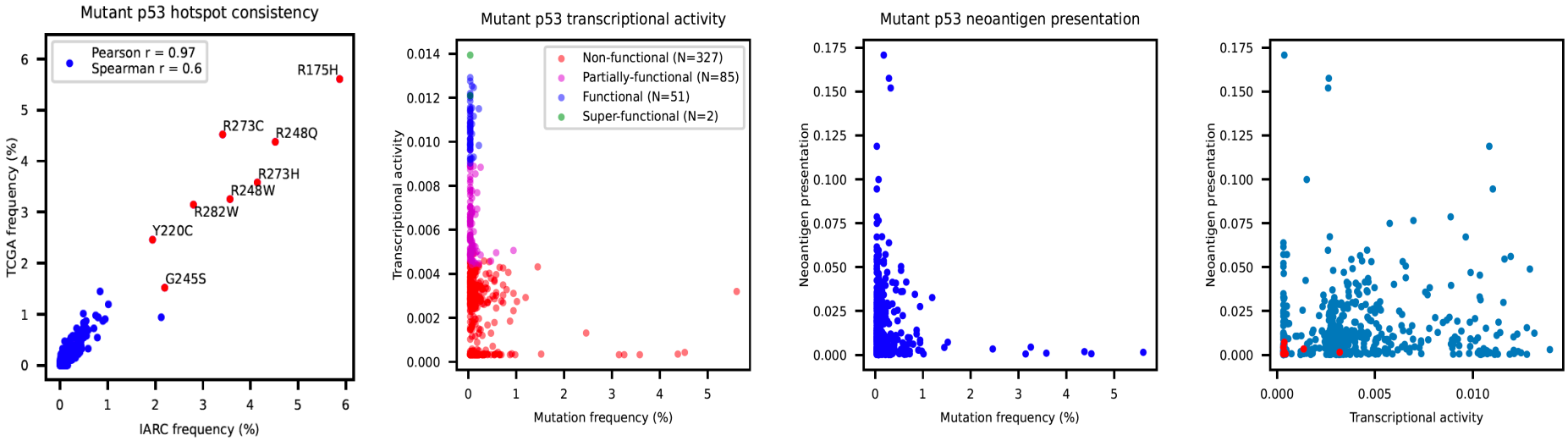
Medicine

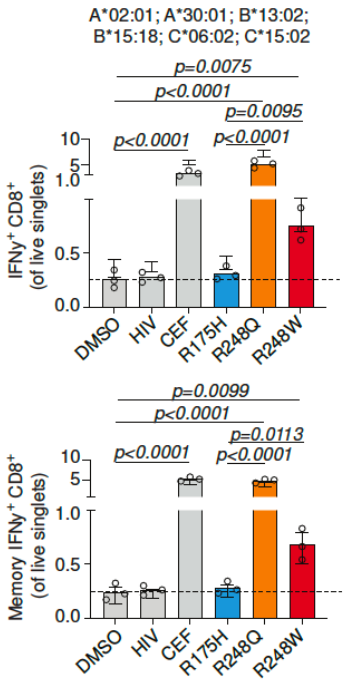
Highly conserved hotspot avoid neoantigen presentation



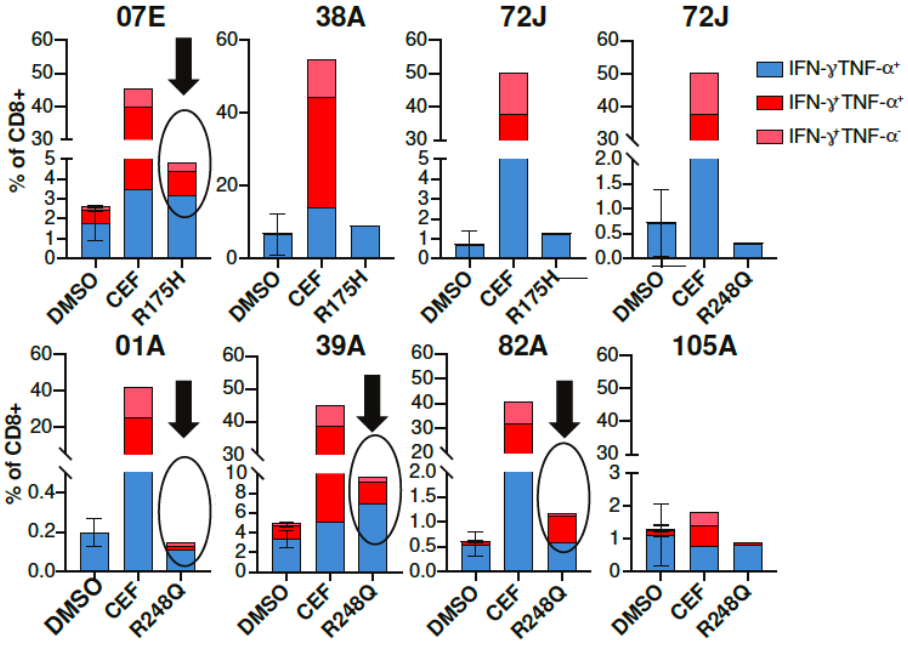
With Hoyos D, Zappasodi R, Levine A, Łuksza M, Greenbaum B
Hoyos D et al, Nature. 2022 May 11

Differential reactivity to mutant p53 neoepitopes in cancer patients and healthy donors.

» Trade-off between oncogenic potential and neoantigen immunogenicity



Health Donors



Cancer Patients

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

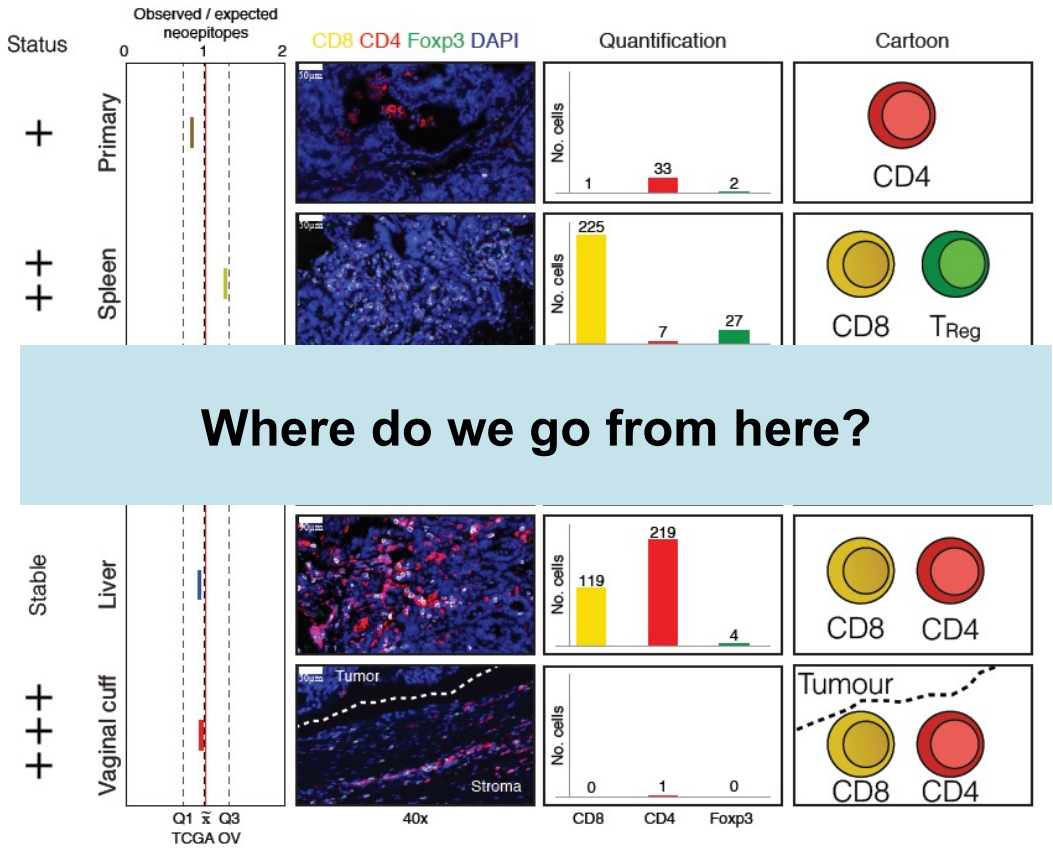
CANCER

Calreticulin mutant myeloproliferative neoplasms induce MHC-I skewing, which can be overcome by an optimized peptide cancer vaccine

AQ1 Mathieu Gigoux[1,2]*, Morten O. Holmström[3,4]†, Roberta Zappasodi[1,2,5,6]†, Joseph J. Park[1,7], Cansu Cimen Bozkus[8], Levi M. B. Mangarin[1,2], David Redmond[1,9], Svena Verma[1,2,7], Sara Schad[1,2,7], Mariam George[1,2], Divya Venkatesh[1,2], Arnab Ghosh[1,2,10], David Hoyos[11], Zaki Molvi[12,13], Baransel Kamaz[14], Anna E. Marneth[14], William Duke[14], Matthew J. Leventhal[15], Max Jan[16], Vincent Ho[17], Gabriela S. Hobbs[18], Trine Alma Knudsen[19], Vibe Skov[19], Lasse Kjær[19], Thomas Stauffer Larsen[20], Dennis Lund Hansen[20], R. Coleman Lindsley[17], Hans Hasselbalch[19], Jacob H. Grauslund[3,4], Thomas L. Lisle[3,4], Özcan Met[3,4], Patrick Wilkinson[21], Benjamin Greenbaum[11,22], Manuel A. Sepulveda[21], Timothy Chan[7,23], Raajit Rampal[24], Mads H. Andersen[3,4], Omar Abdel-Wahab[24], Nina Bhardwaj[25], Jedd D. Wolchok[1,2,5,7]‡, AQ2 Ann Mullally[14,17,15]‡, Taha Merghoub[1,2,5,7]*

Sci Transl Med. 2022 Jun 15

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



Jiménez-Sánchez A, Cell. 2017

Can we improve existing immune therapies?

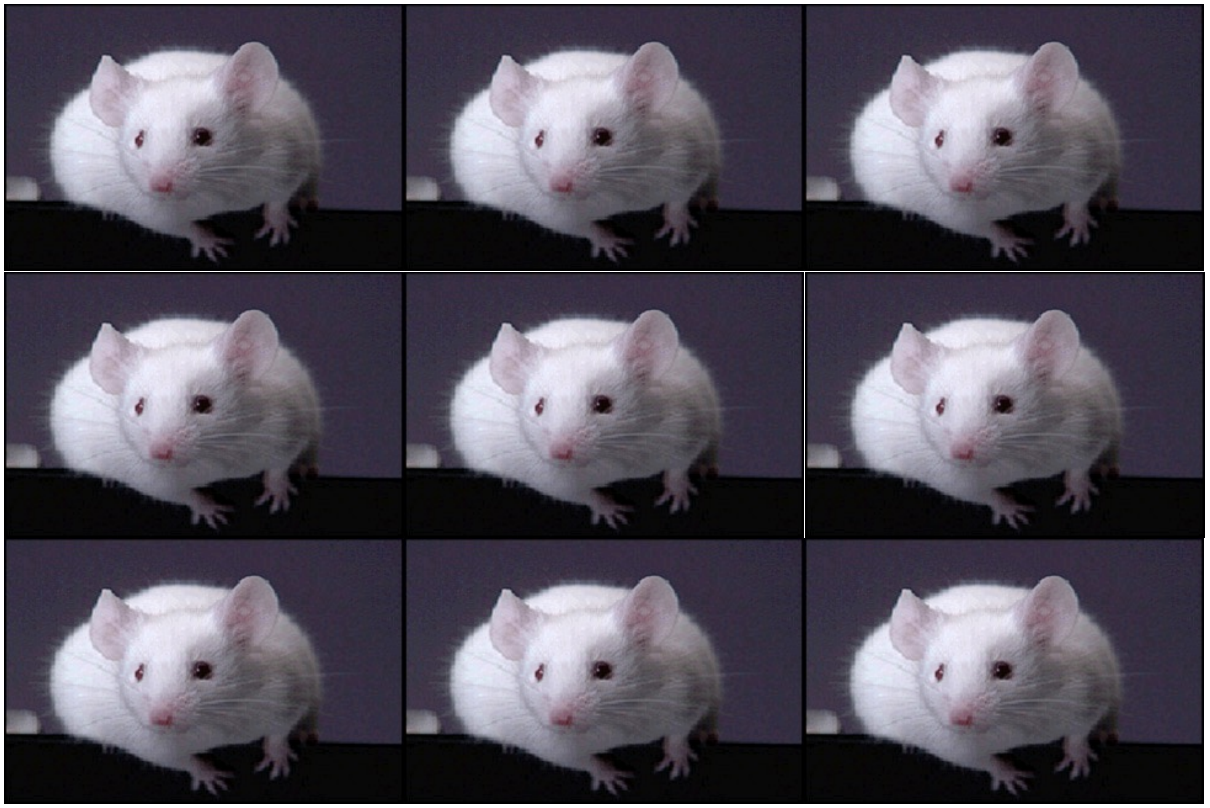
Memorial Sloan Kettering Cancer Center

Weill Cornell Medicine

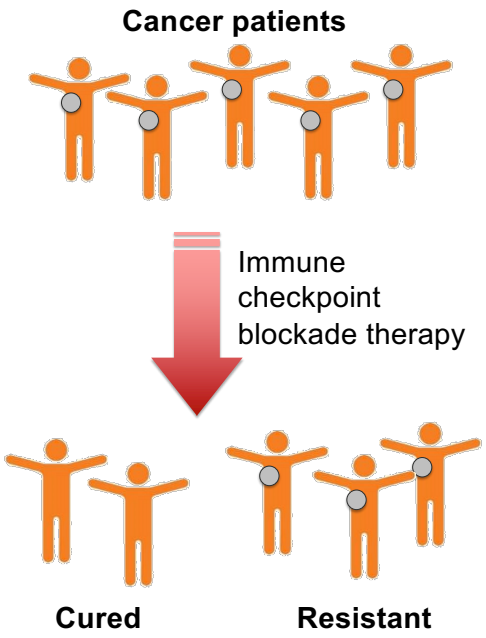
Need to go back to murine tumor models

We look like identical twins!

Inbred mouse strains are a great tool



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

Jianjun Gao,[1,6] Lewis Zhichang Shi,[1,6] Hao Zhao,[4,6] Jianfeng Chen,[1] Liangwen Xiong,[1] Qiuming He,[1] Tenghui Chen,[4] Jason Roszik,[2] Chantale Bernatchez,[2] Scott E. Woodman,[2] Pei-Ling Chen,[5] Patrick Hwu,[2] James P. Allison,[4] Andrew Futreal,[3] Jennifer A. Wargo,[2,3] and Padmanee Sharma[1,4,7,*]

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

Willy Hugo,[1,6,9] Jesse M. Zaretsky,[2,6,9] Lu Sun,[1,6] Chunying Song,[1,6] Blanca Homet Moreno,[2] Siwen Hu-Lieskovan,[3] Beata Berent-Maoz,[2] Jia Pang,[2] Bartosz Chmielowski,[3] Grace Cherry,[2] Elizabeth Seja,[2] Shirley Lomeli,[1,6] Xiangju Kong,[1,6] Mark C. Kelley,[7] Jeffrey A. Sosman,[8] Douglas B. Johnson,[8] Antoni Ribas,[2,3,4,5,6] and Roger S. Lo[1,2,5,6,*]

The NEW ENGLAND JOURNAL of MEDICINE

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, Kari S. Peggs, Michael A. Curran, and James P. Allison

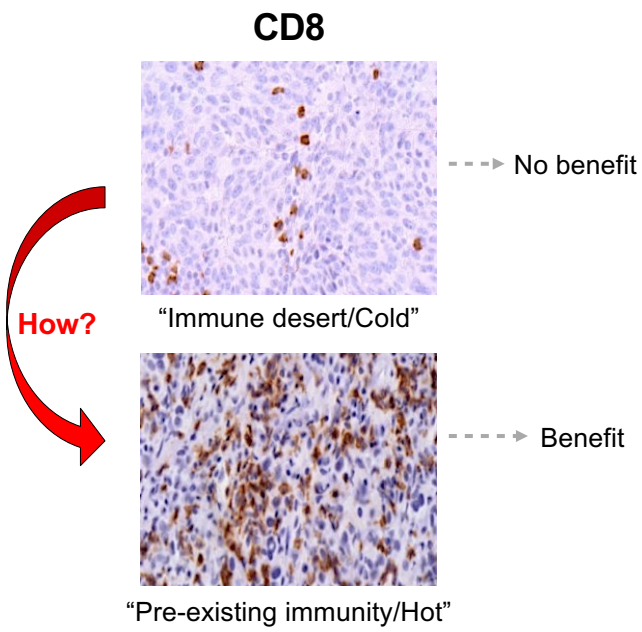
Howard Hughes Medical Institute, Department of Immunology, Memorial Sloan-Kettering Cancer Center, New York, New York, USA.

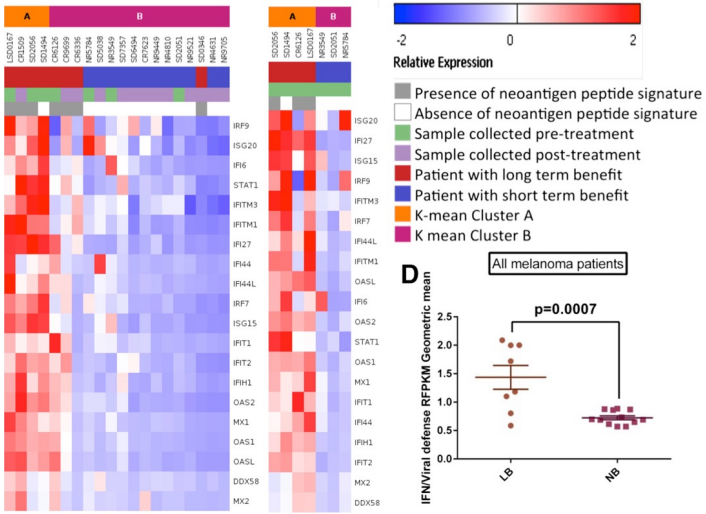
JEM Article

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]

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”

↓

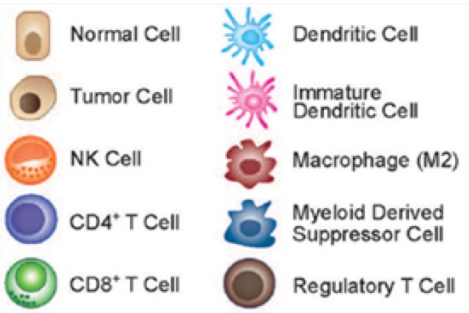
Immune check point is enough

“Immune desert/Cold”

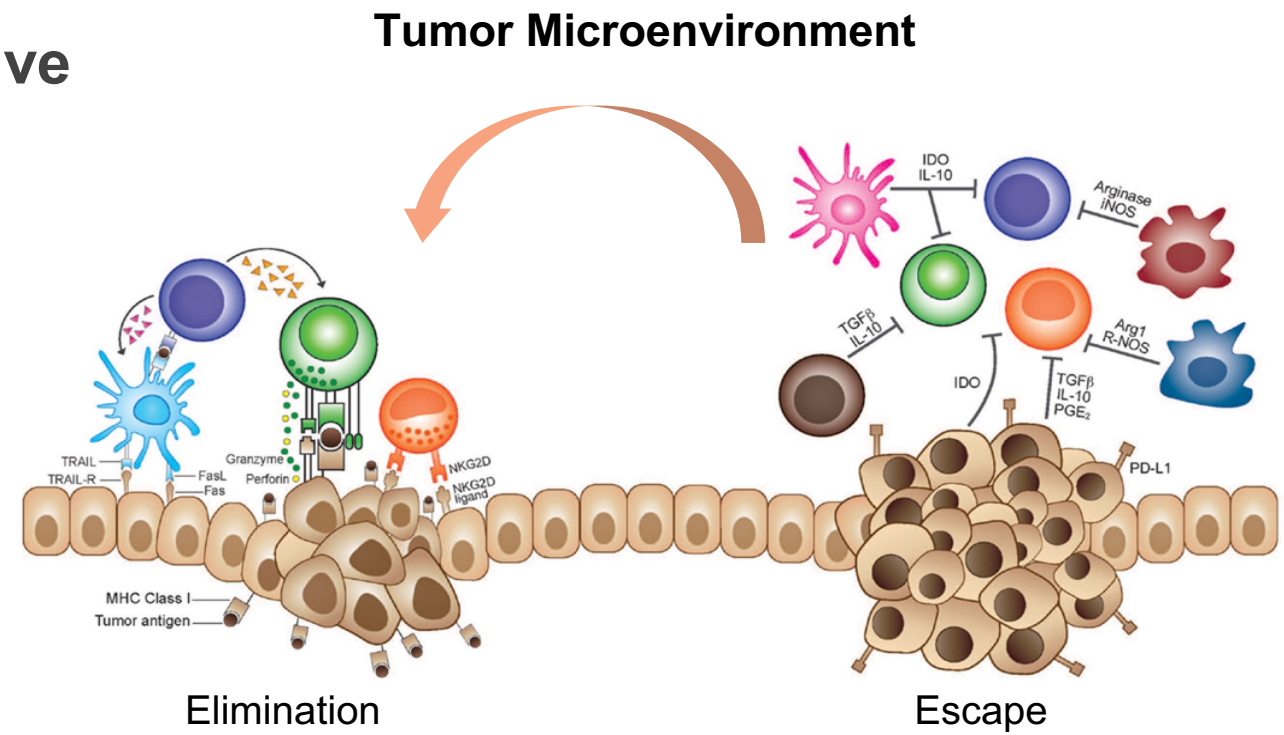
↓

Immune check point + bring immune cells to tumors

2 – Modify the Immune Suppressive Microenvironment



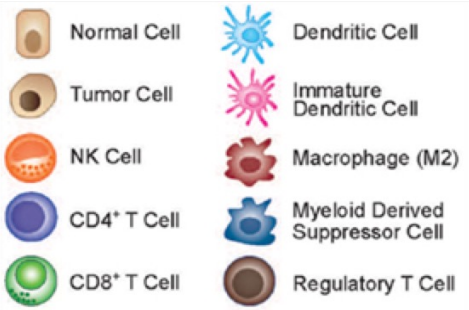
William J. Murphy.
Front Oncol.
2013; 3: 197.



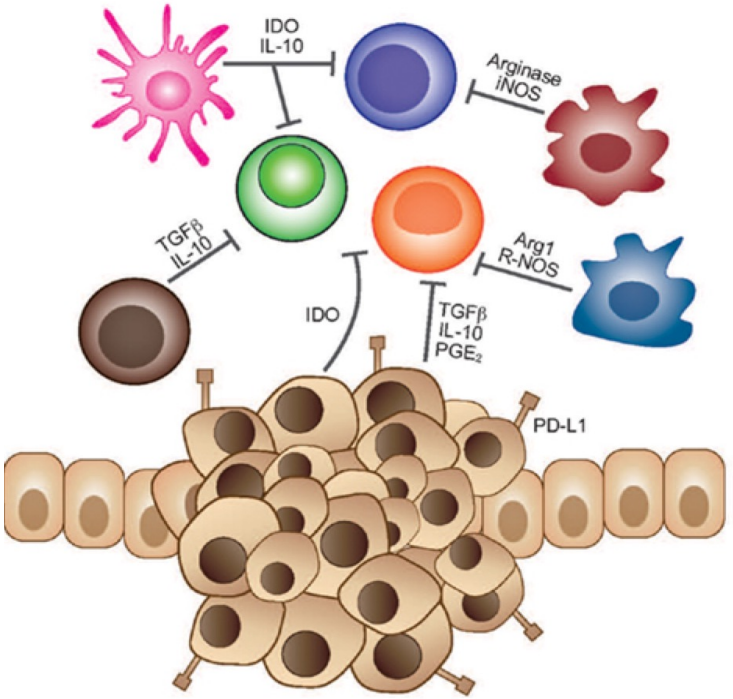
» Reverse immune suppression

» Induce anti-tumor immune response

Variants for immunogenicity study



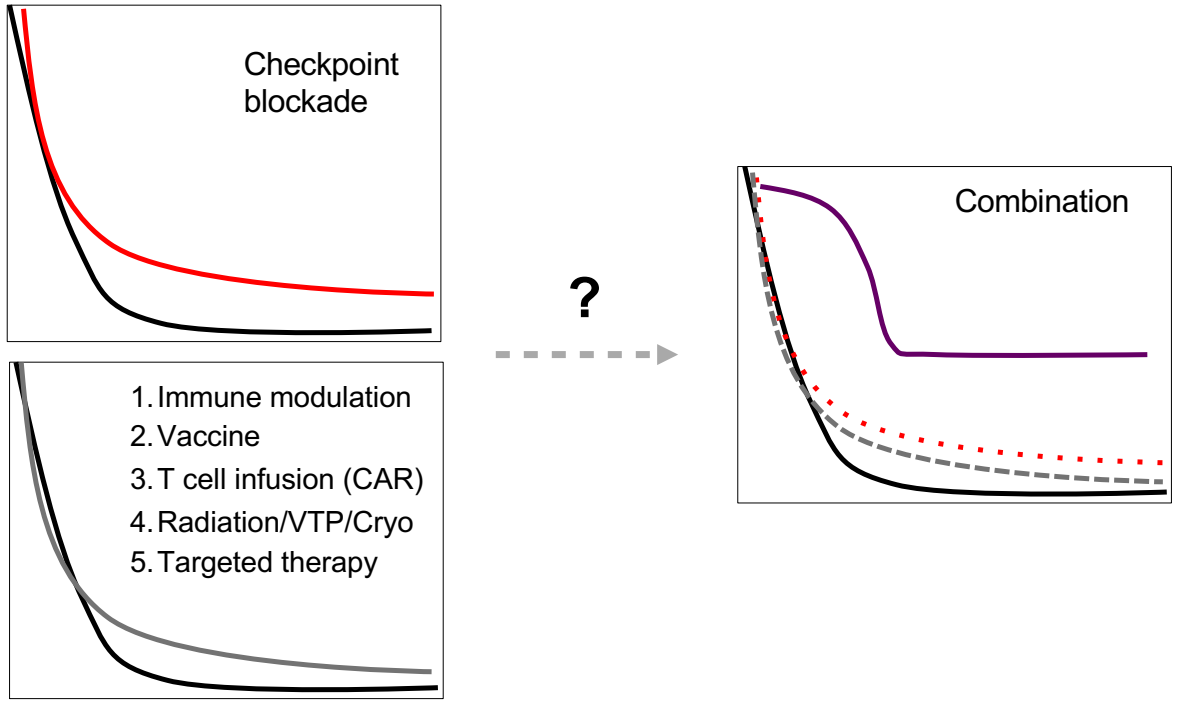
Segal et al. Cancer Res 2008
Matsushita et al. Nature 2012



Escape

Rationale for Combination with other therapies:

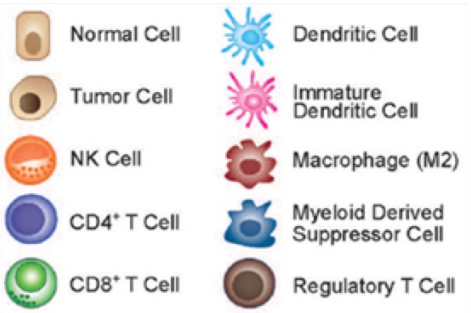
- Use other means to enhance tumor recognition
- Strategy to address low response rates of checkpoint blockade



Approach combining blockade of immune suppression with immunotherapy

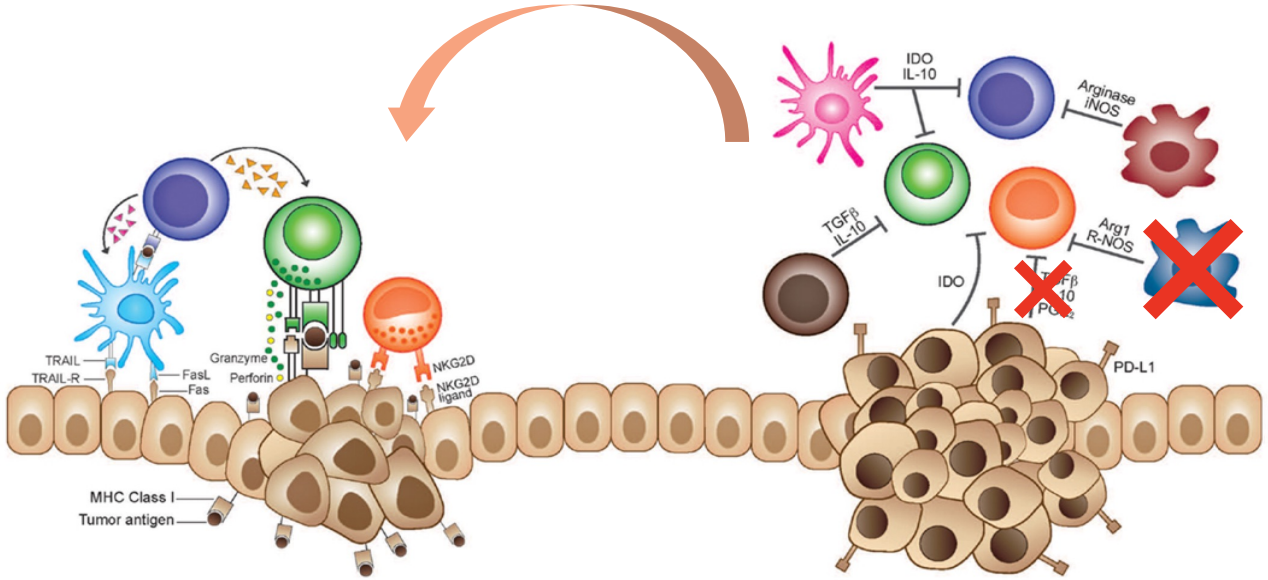
- - - - ▸ The target cell need to be present

Immune Suppressive Microenvironment



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

Tumor Microenvironment



Elimination

Escape

Modify the Immune Suppressive Microenvironment

Memorial Sloan Kettering Cancer Center

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

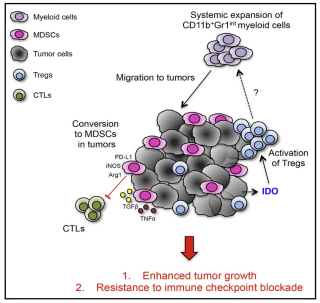
Rikke B. Holmgaard, Alexandra Brachfeld, Billel Gasmi, Thompson Doman, Mary Murphy, David Schaer, Jedd D. Wolchok & Taha Merghoub

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

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.

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[3], Jeffery L. Kutok[2], Jedd D. Wolchok[1,3]§ & Taha Merghoub[1]§

ONCOIMMUNOLOGY
2019, VOL. 8, NO. 6, e1581528 (10 pages)
https://doi.org/10.1080/2162402X.2019.1581528

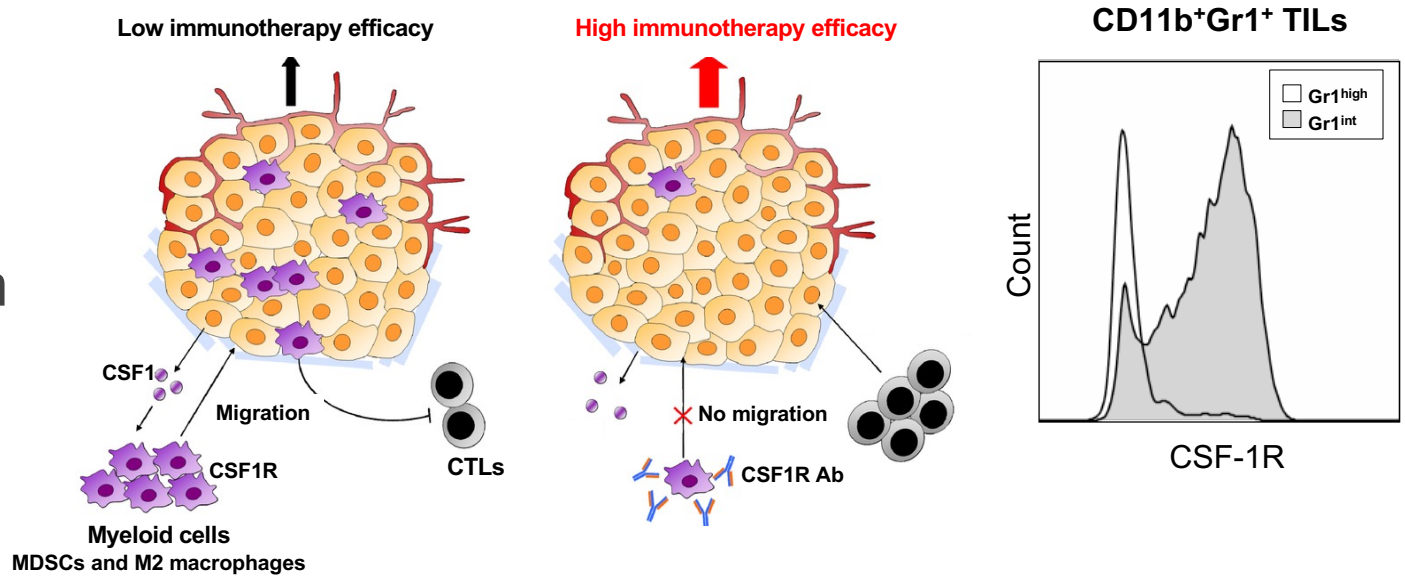
Taylor & Francis
Taylor & Francis Group

ORIGINAL RESEARCH

Potentiating vascular-targeted photodynamic therapy through CSF-1R modulation of myeloid cells in a preclinical model of prostate cancer

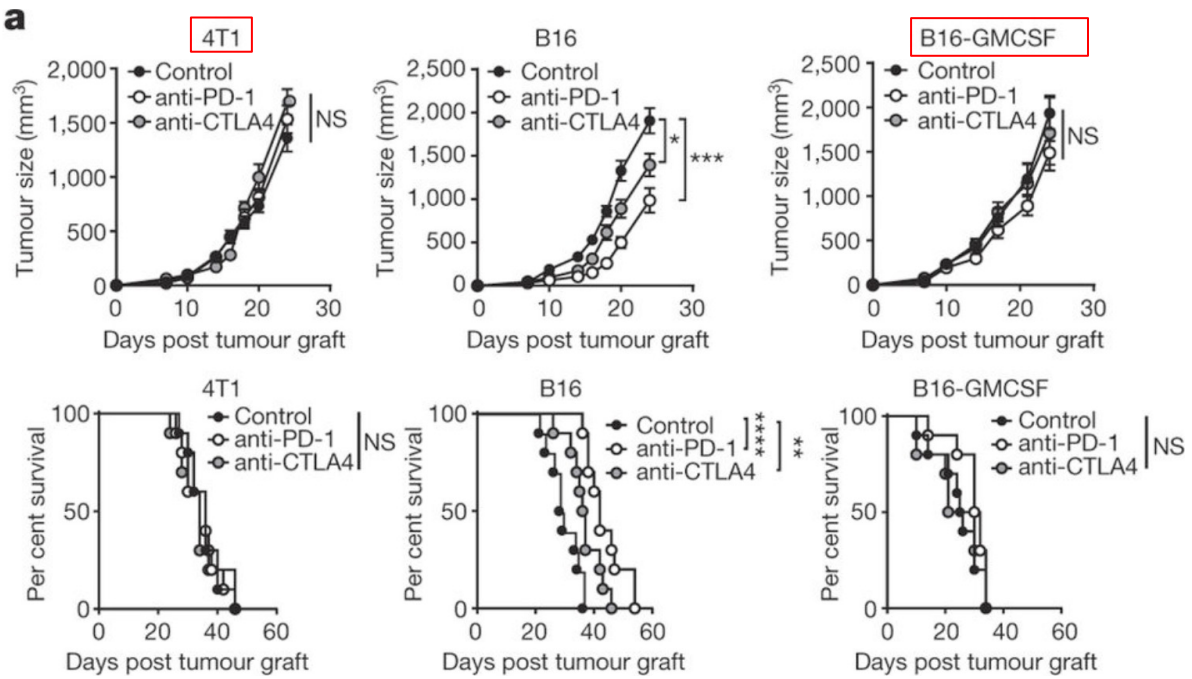
Souhil Lebdai[a,b,c], Mathieu Gigoux[a,d,e], Ricardo Alvim[a], Alexander Somma[a], Karan Nagar[a], Abdel Rahmene Azzouzi[c], Olivier Cussenot[b], Taha Merghoub[a,d,e], Jedd D. Wolchok[a,d,e,f,g], Avigdor Scherz[h], Kwanghee Kim[a], and Jonathan Coleman[a,f]

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)

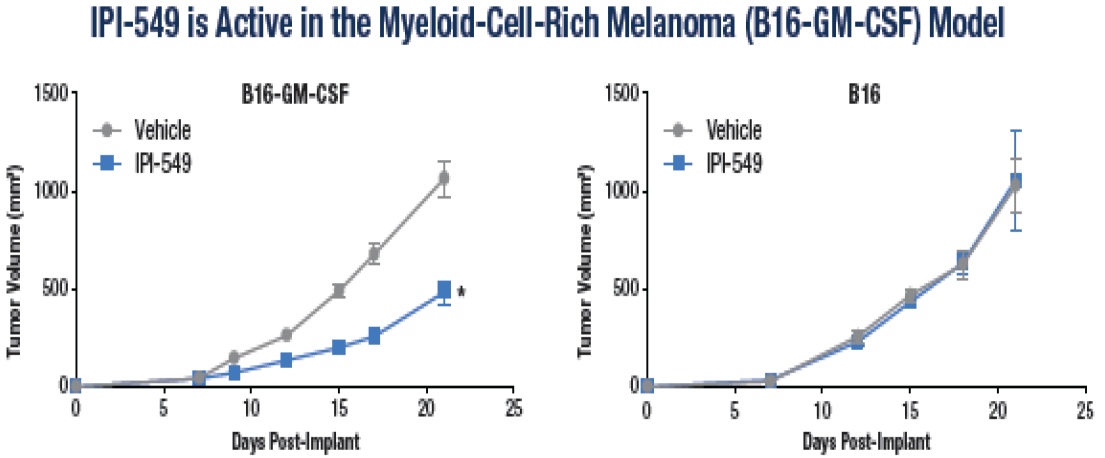
Melanoma Model (Rich in myeloid cells)

O De Henau et al. Nature (2016)

Role of Myeloid Cells in IPI-549 Antitumor Activity

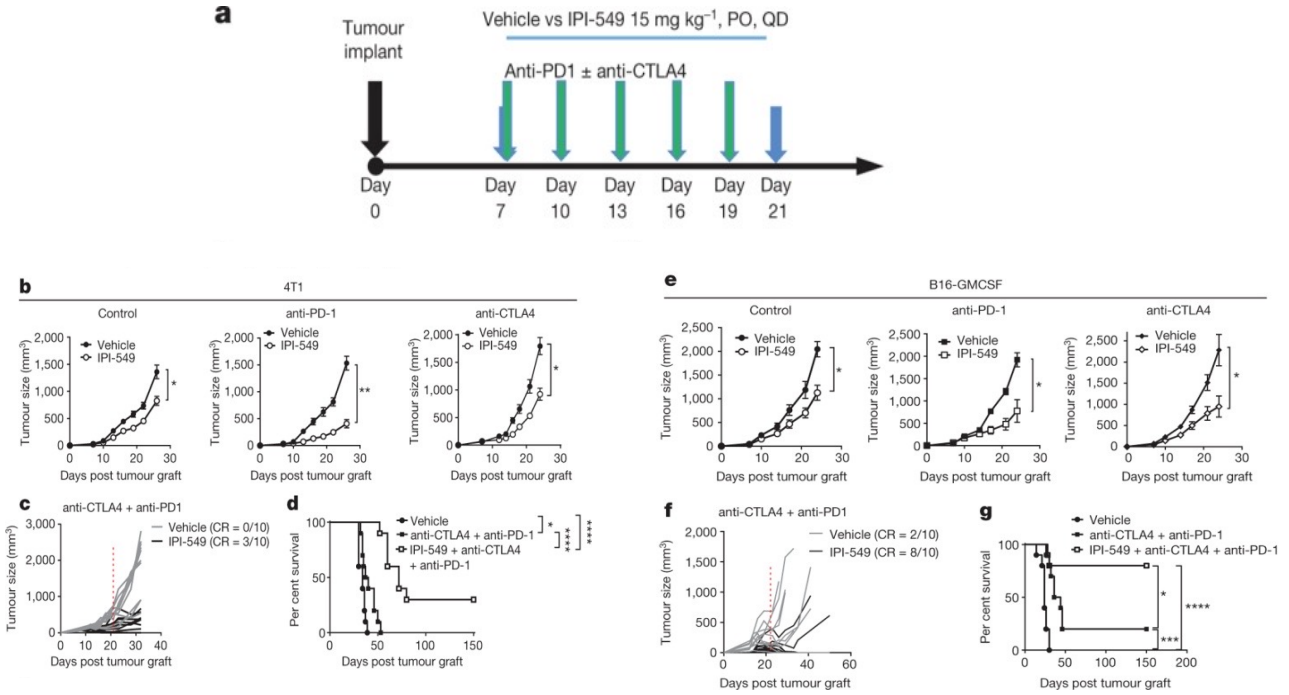
- PI3 kinase gamma is preferentially expressed in MDSCs
- IPI-549 is a PI3 kinase gamma inhibitor.
- IPI-549 is only active in myeloid MDSC dependent tumors.

O De Henau et al. Nature (2016)



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).

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



Mammary Carcinoma Model

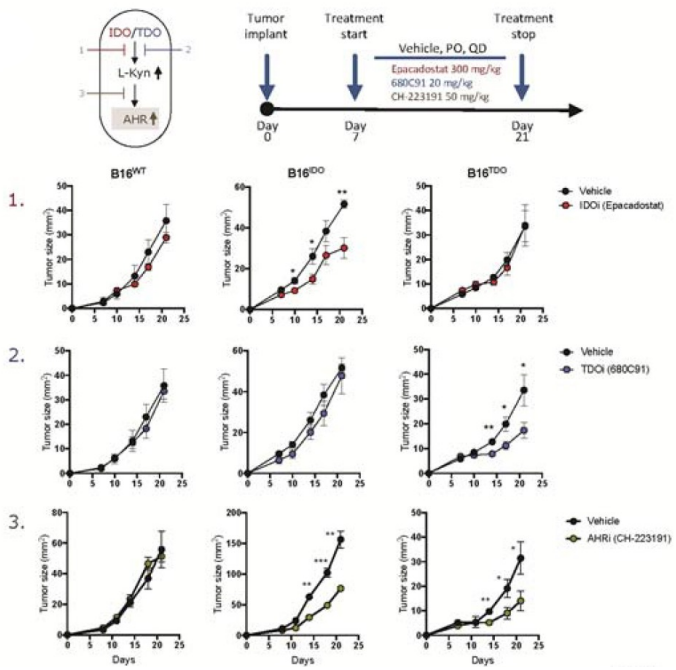
Melanoma Model

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

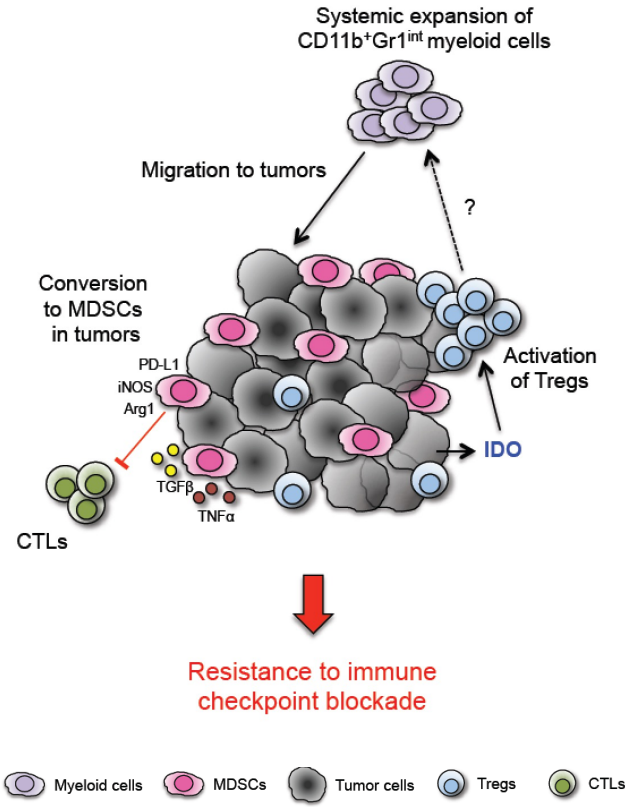
Blocking Suppressive Mechanisms

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

IDO inhibition, Kyn, AHR



AHRi delays tumor regression of IDO and TDO expressing tumors

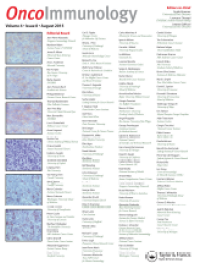


Campesato, et al, Nat Commun, 2020
Hoolmgard et al, Cell Report,2015

Approach combining blockade of immune suppression with checkpoint blockade

- The target cell need to be present
  Timing is key

Memorial Sloan Kettering Cancer Center



OncoImmunology

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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

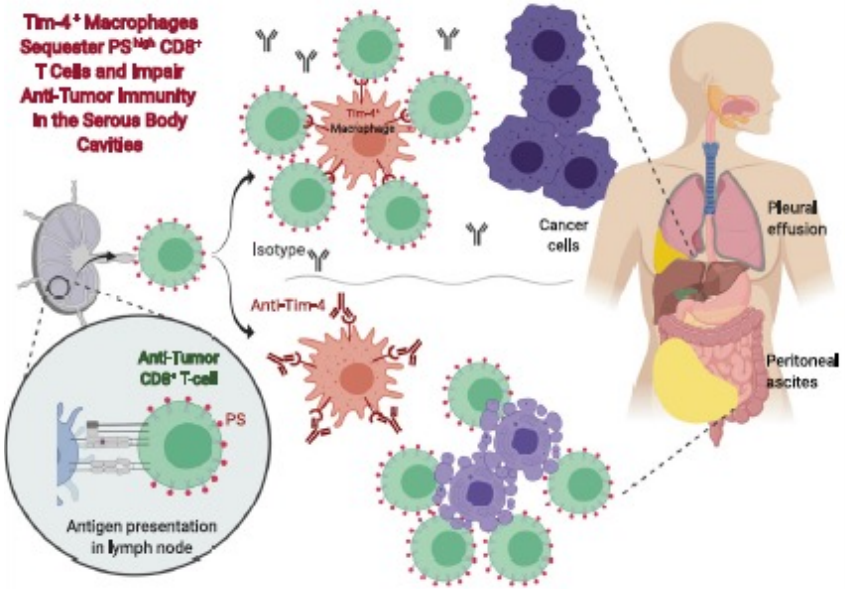
Weill Cornell Medicine

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



Authors

Andrew Chow, Sara Schad

Michael D. Green, …, Jedd D. Wolchok

Charles M. Rudin, Taha Merghoub

Correspondence

rudinc@mskcc.org (C.M.R.),

merghoubt@mskcc.org (T.M.)

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

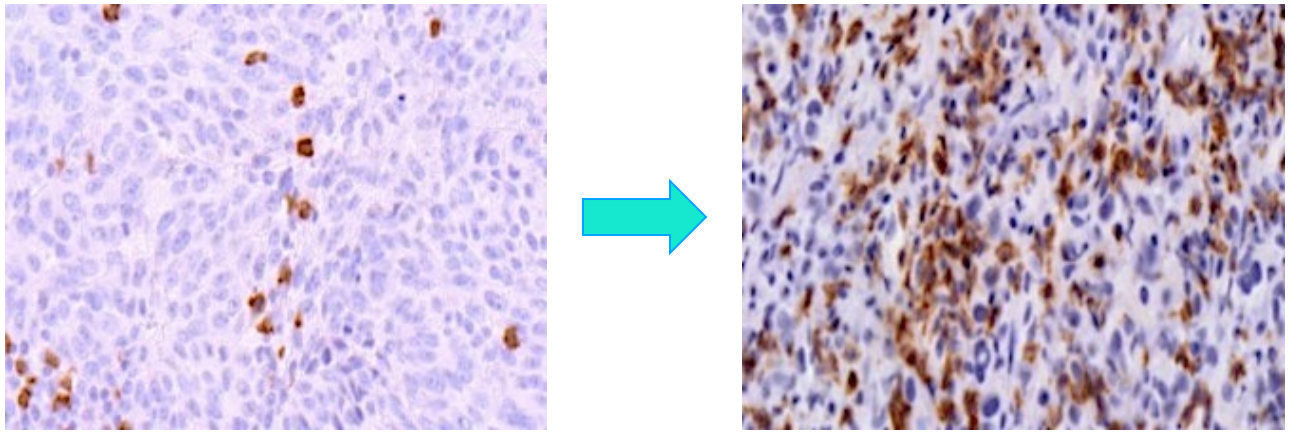
- Antitumor immune response is needed in situ vaccine

Approach

Induce Tumor Antigen Response

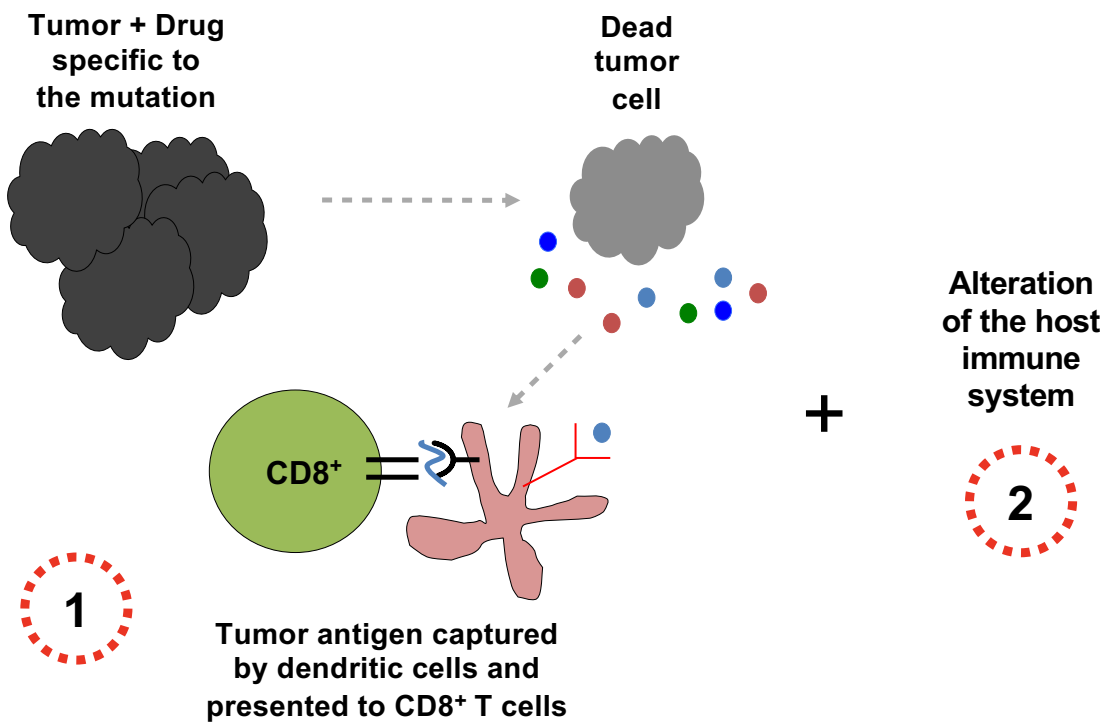
- » Killing the tumors with targeted therapies
- » Oncolytic viral therapy
- » Chemotherapy
- » Radiation therapy
- » VTP
- » Other means…

Increase the Number of Immune Infiltrating Immune Cells

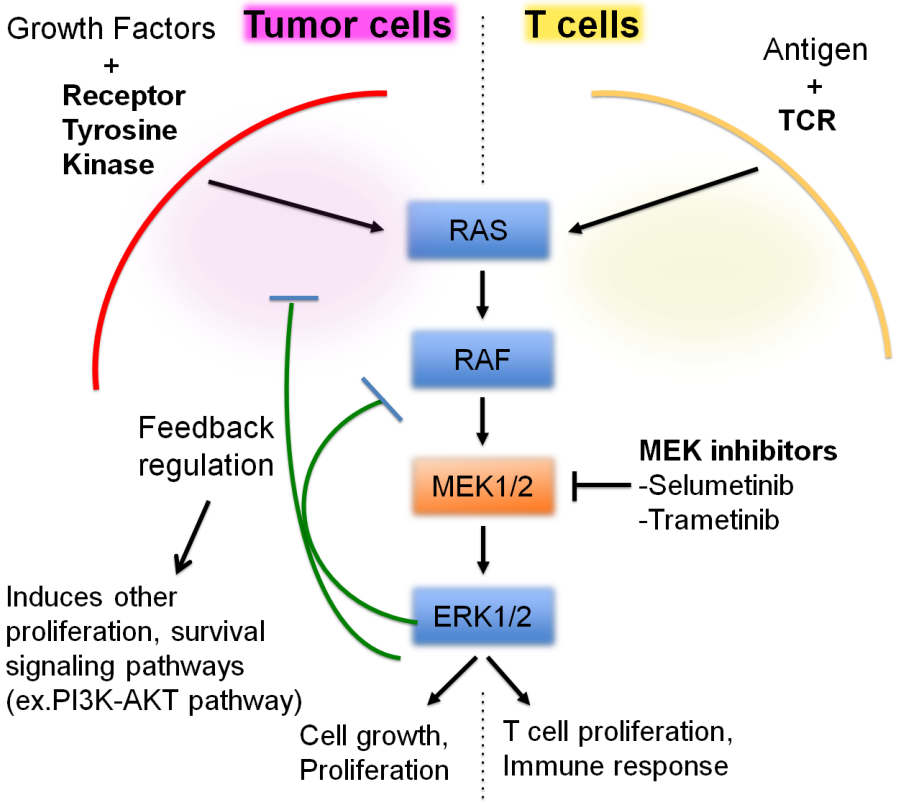


Segal et al. Cancer Res 2008
Matsushita et al. Nature 2012

Targeting tumor cells should induce a tumor-specific immune response



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

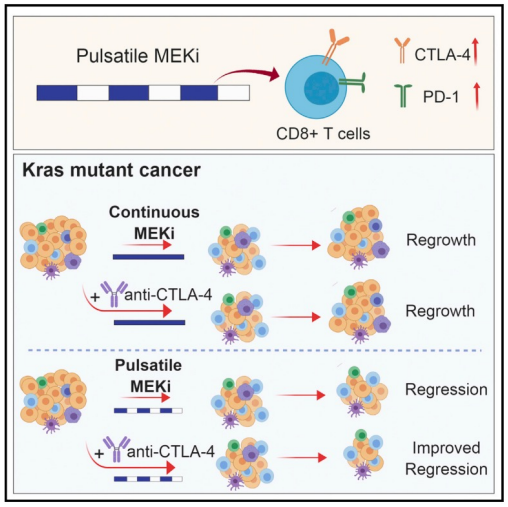


Article

Cell Reports

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

Correspondence

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

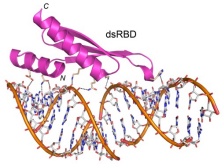
In Brief

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.

Memorial Sloan Kettering Cancer Center

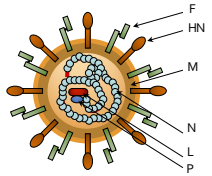
Weill Cornell Medicine

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

Memorial Sloan Kettering Cancer Center

Weill Cornell Medicine

Alter Host Immune System: Rationale Combination with Immune modulation

Receptor and ligands	Mechanism of action	Current status	Examples of agents
Co-inhibitory receptors			
	Limits initial T cell activation and proliferation	FDA-approved	Ipilimumab, tremelimumab
	Inhibits the activity of effector T cells	FDA-approved	Nivolumab, pembrolizumab, durvalumab, atezolizumab
	Inhibits the activity of effector T cells via the KIEELE motif, which is functionally linked with T_{reg} cell-mediated immunosuppression	Phase III trial ongoing	Relatlimab
	Triggers $CD8^+$ T cell apoptosis and/or exhaustion	Phase II trials ongoing	Cobolimab, sabatolimab
	Downregulation of T cell and NK cell function	Phase II trials ongoing	Tiragolumab
	Suppression of downstream activation of TCR signalling via SH2	Phase I trials ongoing	Icatolimab
Co-stimulatory receptors			
	Promotes activation and proliferation of effector T cells and a reduction in T_{reg} cells	Phase II trials ongoing	TRX518, BMS-986156
	Promotes survival, but not priming, of both effector and memory T cells	Phase II trials ongoing	GSK3174998, MEDI6469, PF-04518600
	Promotes T cell proliferation and mitochondrial function and biogenesis	Phase I trials ongoing	Utomilumab, urelumab
	Promotes TCR co-stimulation and T_{reg} cell stimulation	Phase I trials ongoing	Vopratelimab, KY1044, GSK3359609

Kraehenbuehl L, Weng CH, Eghbali S, Wolchok JD, Merghoub T. Nat Rev Clin Oncol. 2022

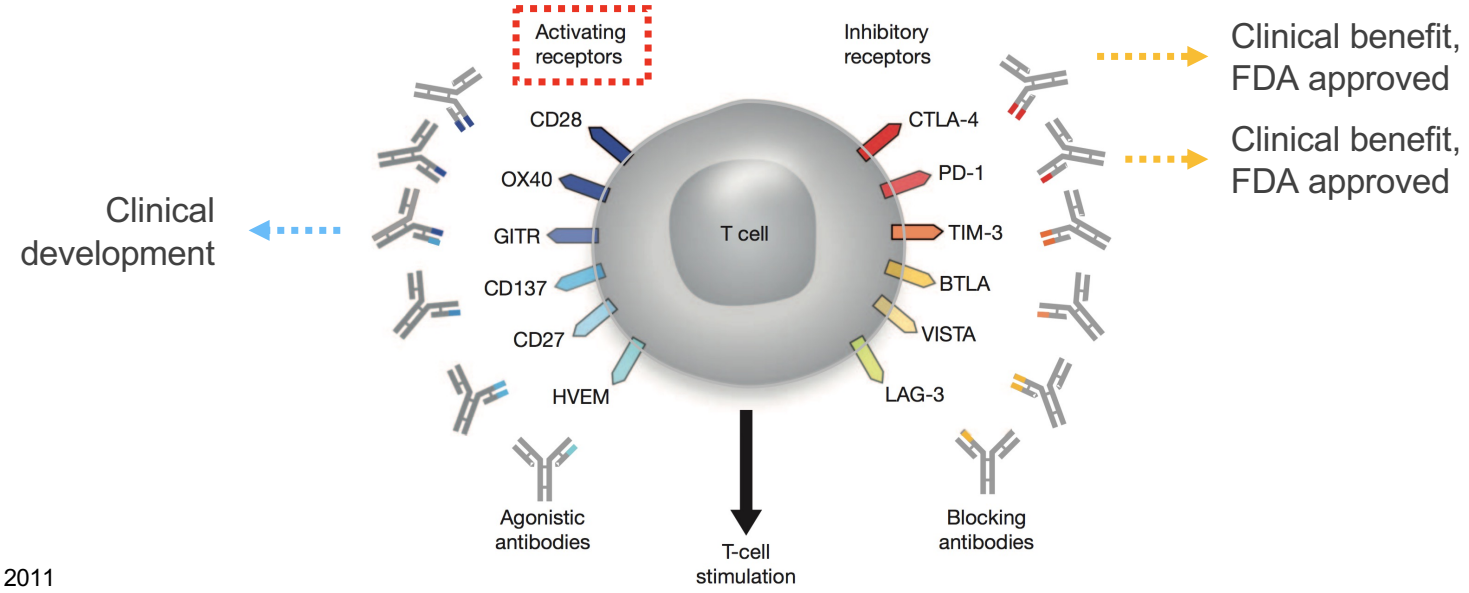
Approach:

Combining Other immune modulatory antibodies beyond checkpoint blockade

Memorial Sloan Kettering Cancer Center

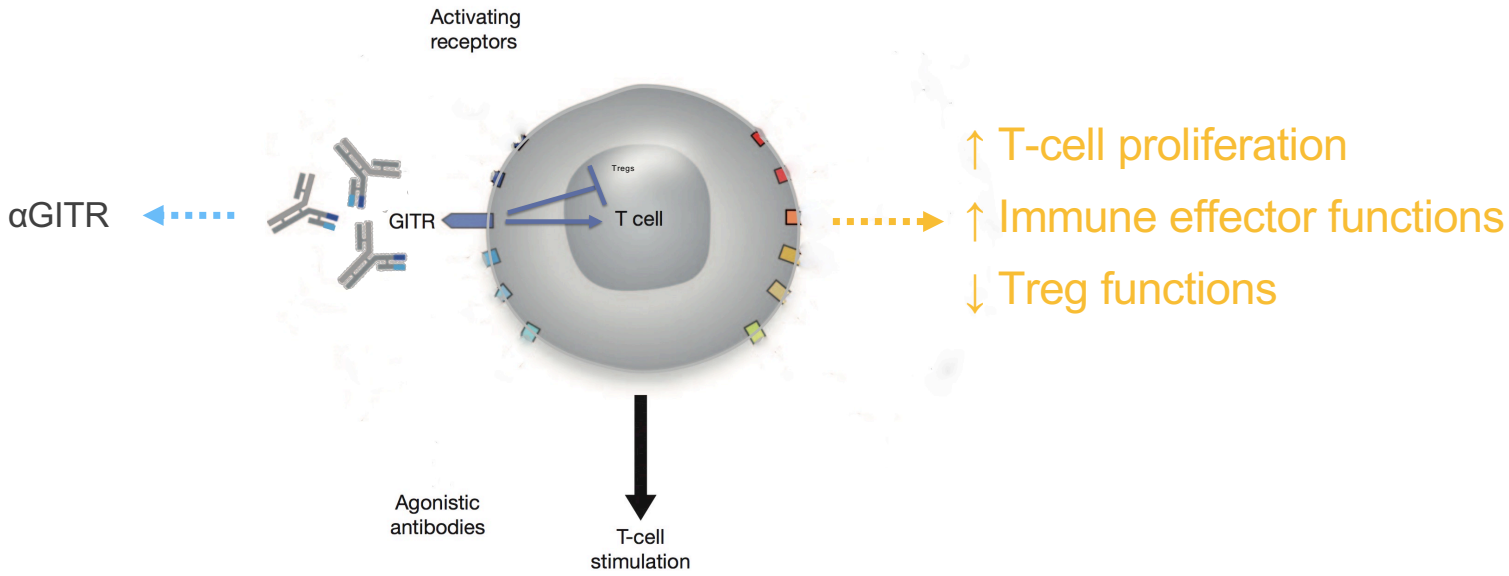
Weill Cornell Medicine

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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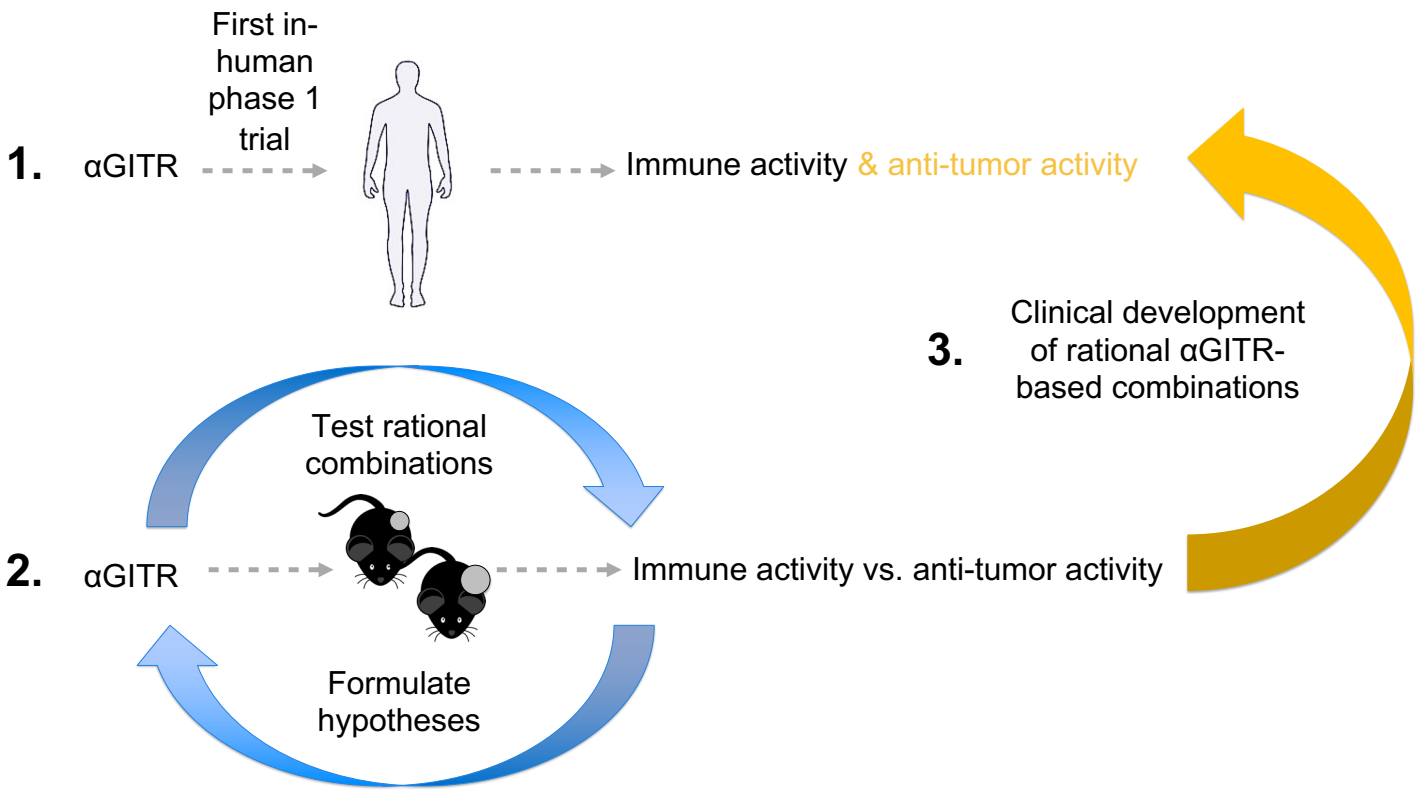
Study Design



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

Rational design of anti-GITR-based combination immunotherapy

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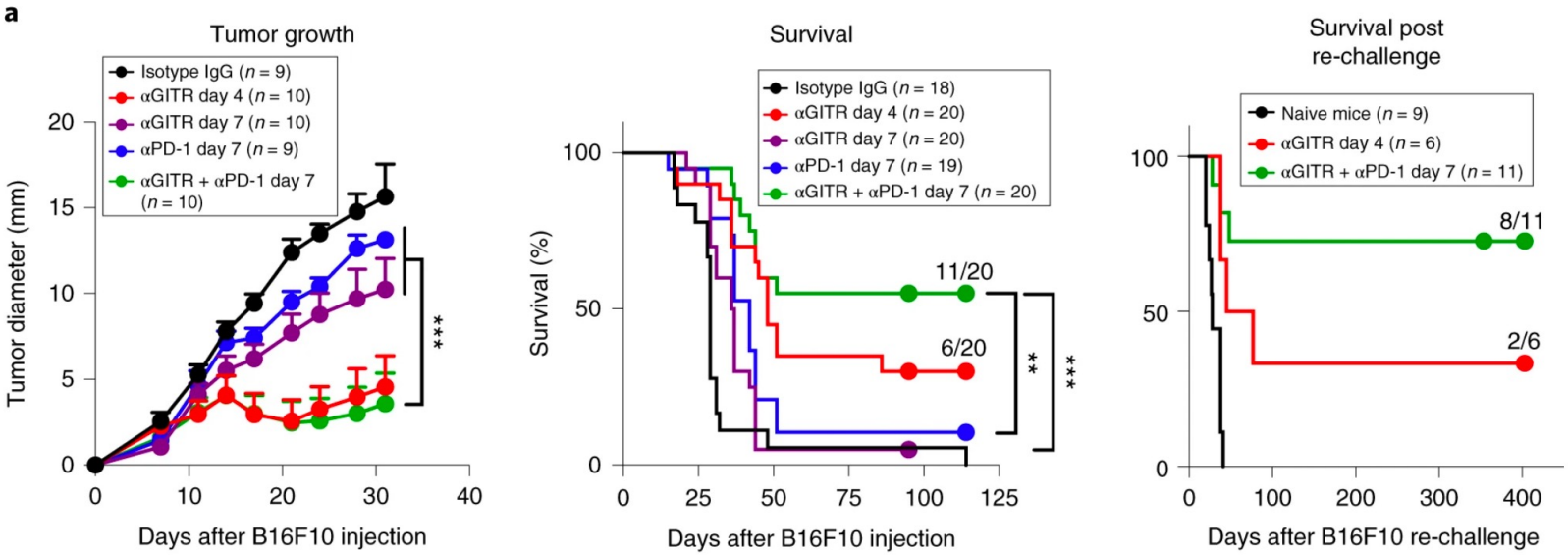
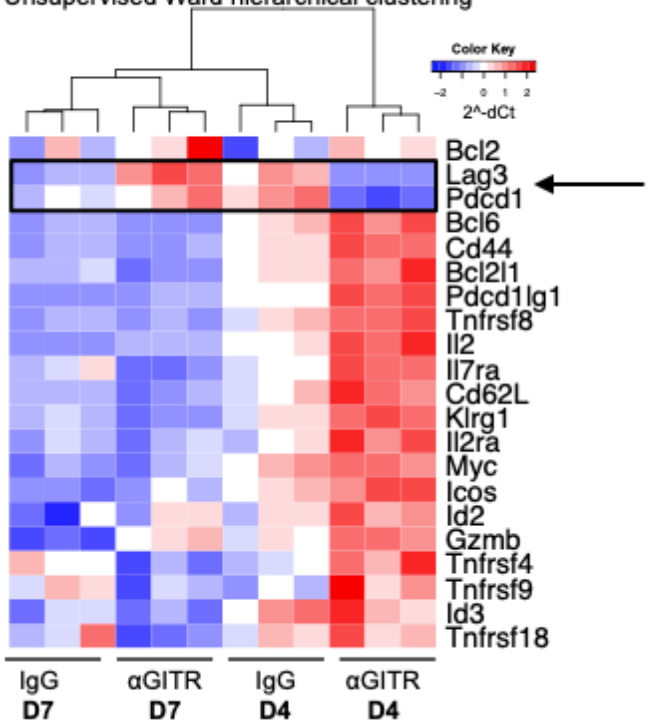


Gene expression analyses in purified CD8⁺ TILs

Unsupervised Ward hierarchical clustering



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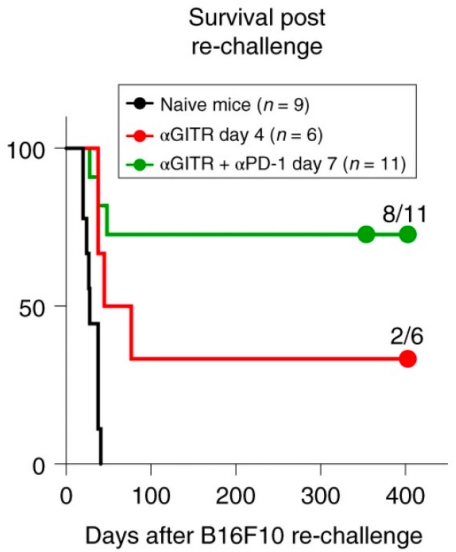
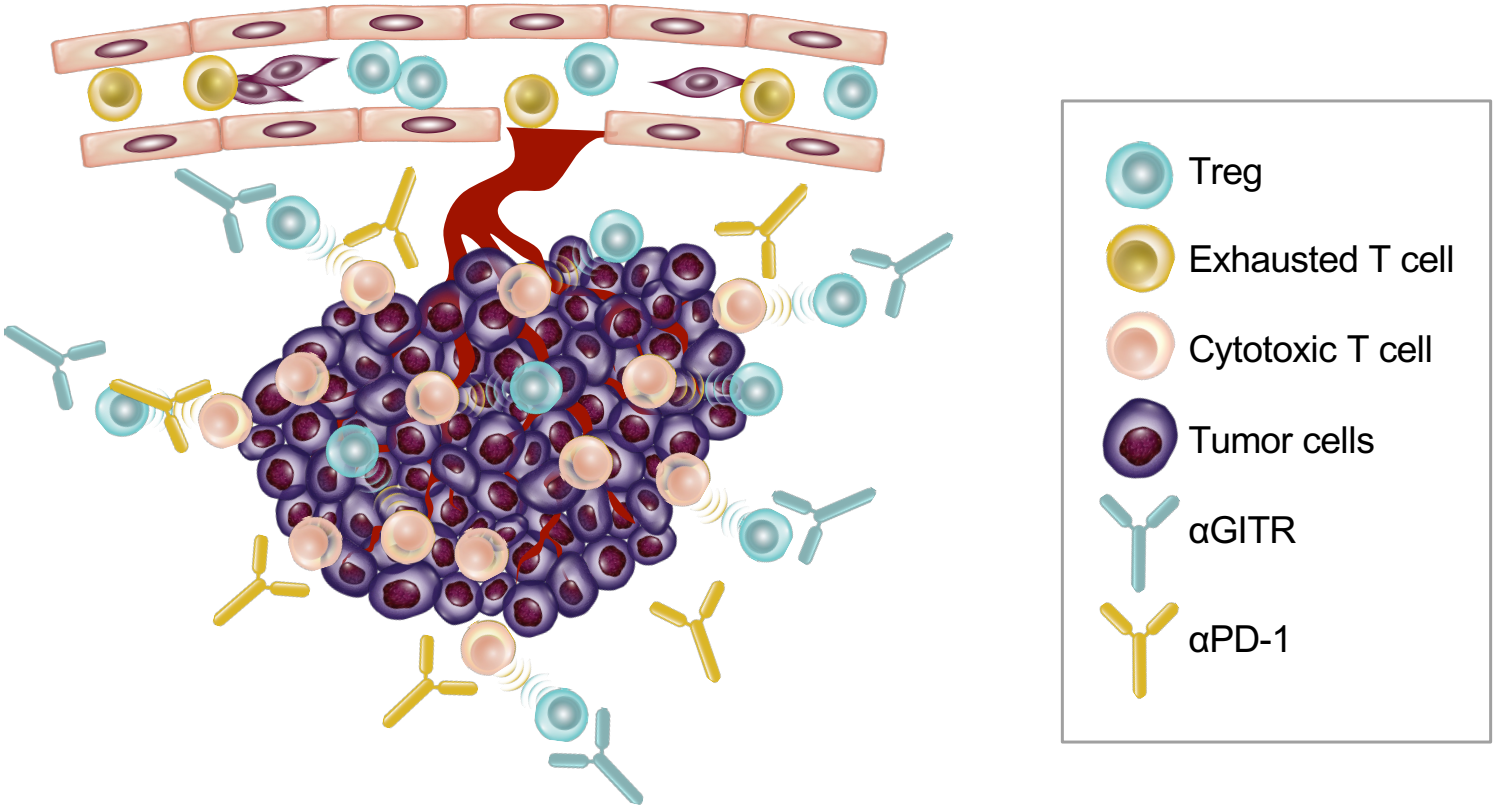


Model


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

Finally:

Don’t ignore the biology you don’t know

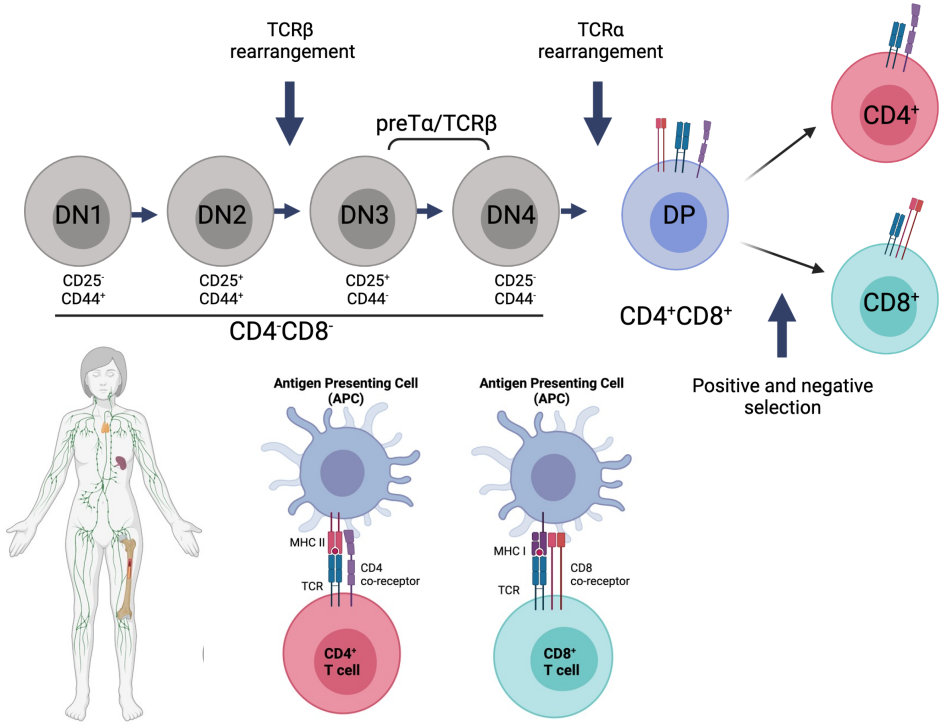
Memorial Sloan Kettering Cancer Center

Weill Cornell Medicine

T cell development and commitment to single positive fates

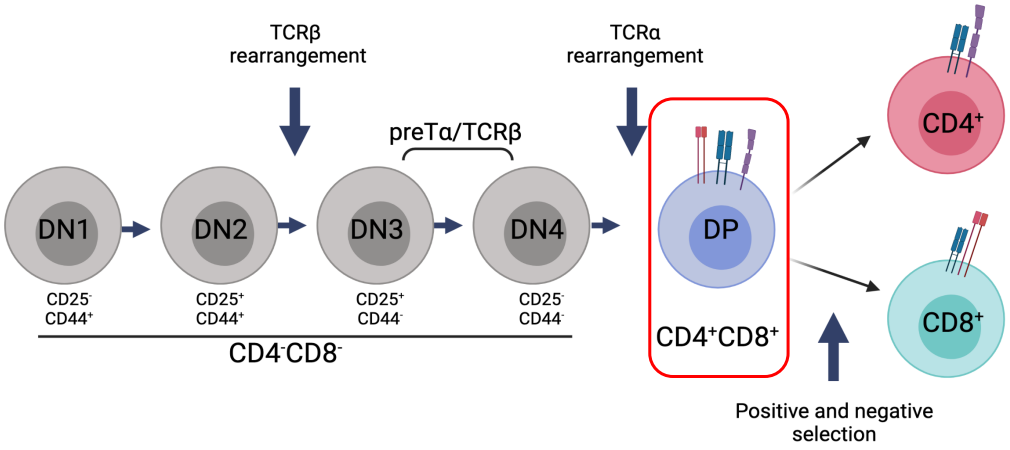
T cells originate from hematopoietic stem cells in the bone marrow and migrate to the thymus for development

- 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

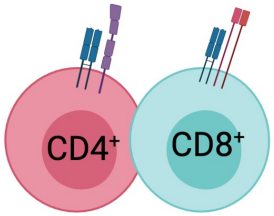


Previous understanding of $CD4^+CD8^+$ T cells

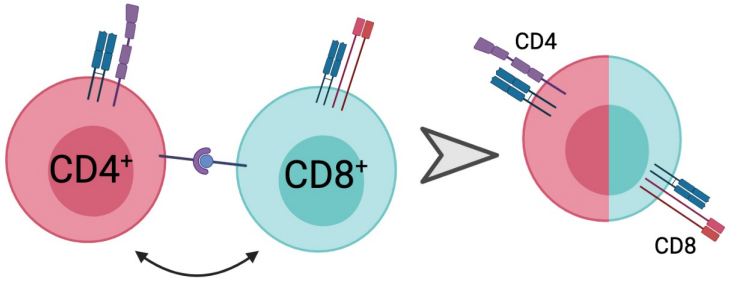
» Developmental stage



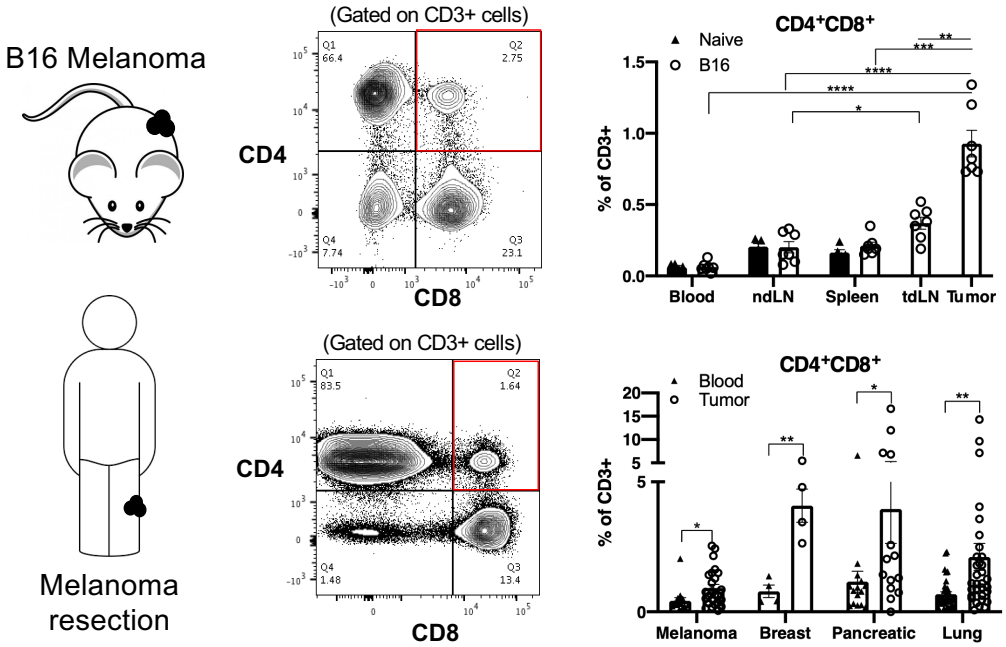
» Cell doublet

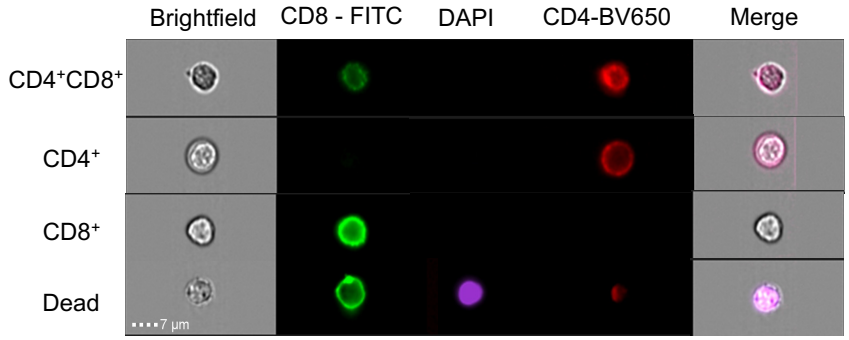


» Trogocytosis (membrane exchange)



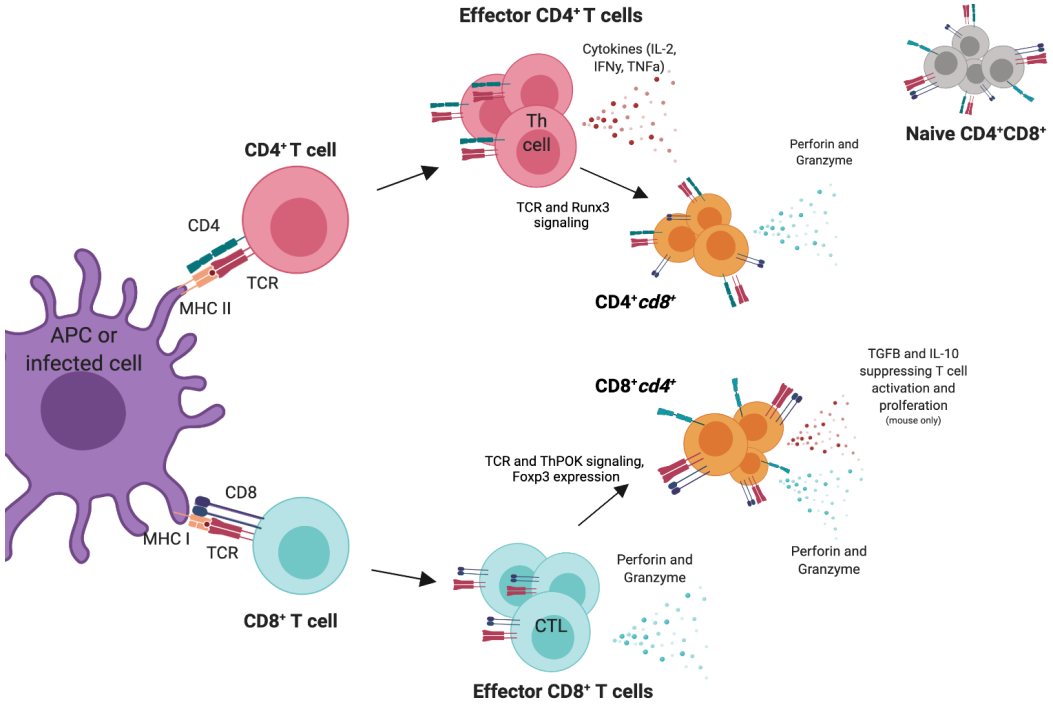
Heterogenous CD4+CD8+ T cells accumulate in murine and human melanoma tumors





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.

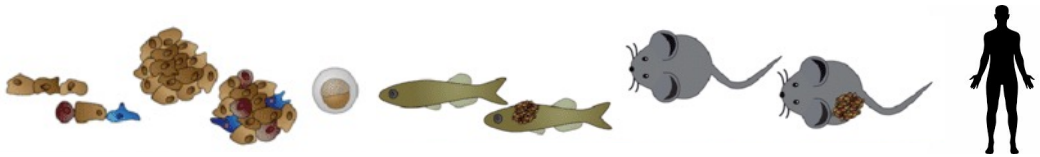
» The timing of the immune intervention is key.

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

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

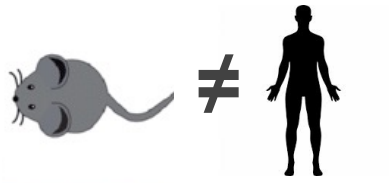
Some key points for today's lecture

» 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).



Translation gone wrong: 7 big translation fails from 2016. Richard Brooks. K International.

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Adaptive resistance mechanism to SARS-CoV-2 = Zoom

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NASDC
NCI Awardee Skills Development Consortium

Translational Opportunities in Immunotherapy Research

Questions