Memorial Sloan Kettering Cancer Center

Pre-Clinical Combination Immunotherapy

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2020 SITC Cancer
Immunotherapy Winter School

January, 2020

LUDWIG CANCER RESEARCH

PARKER INSTITUTE for CANCER IMMUNOTHERAPY

SWIM ACROSS AMERICA
MAKING WAVES TO FIGHT CANCER

Disclosures

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

Kyn Therapeutics

Infinity Pharmaceuticals, Inc.

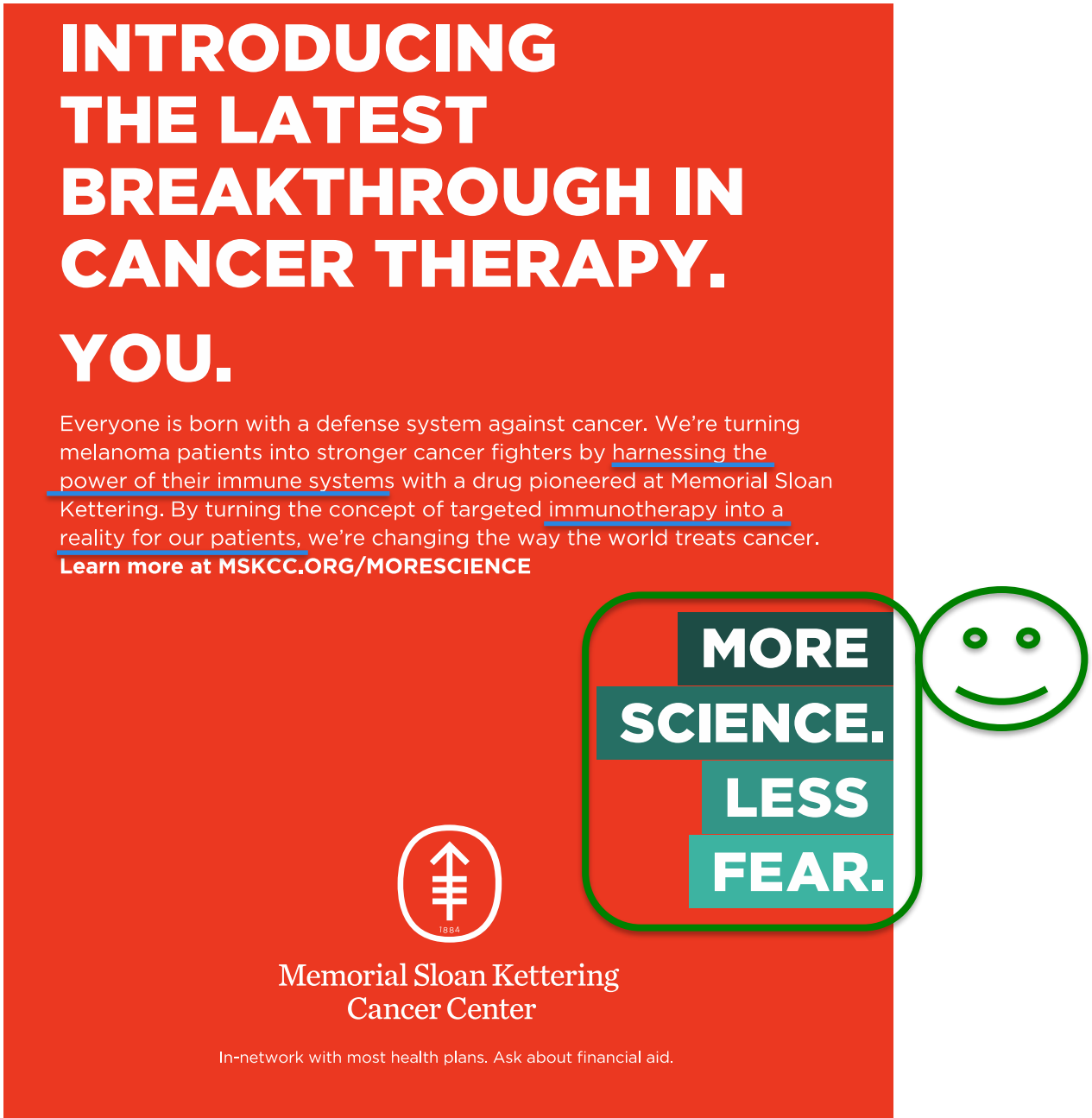
Peregrine Pharmeceuticals, Inc.

Adaptive Biotechnologies

Leap Therapeutics, Inc.

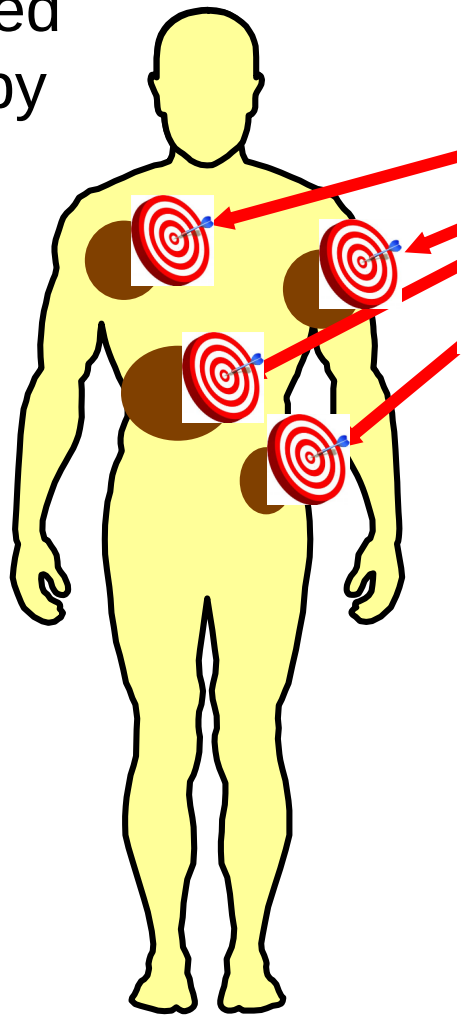
Aprea.

It's Been A Long Journey and we came a long way…..



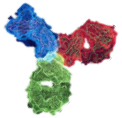
Two Main Paradigms for Advancing Cancer Therapy
Melanoma: the poster child

Targeted Therapy

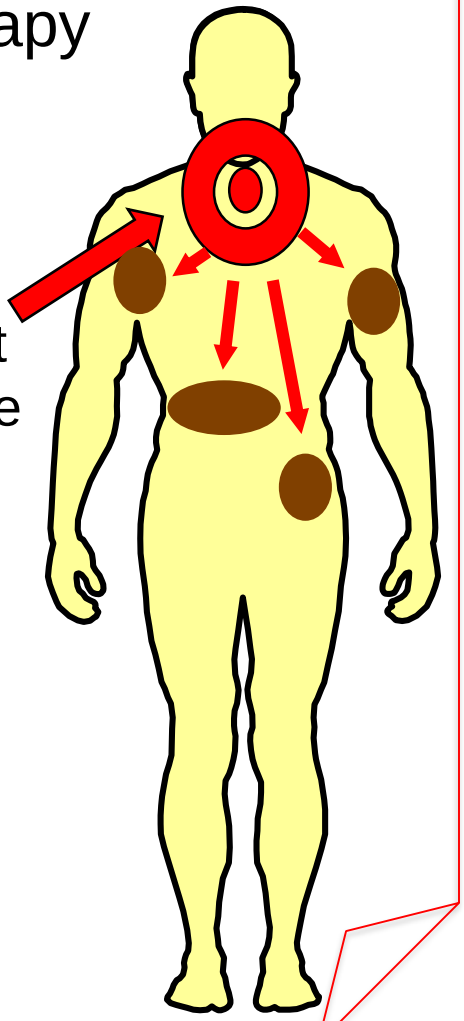


Target Tumor to kill tumor cells

Immunotherapy



Target the host to modulate the immune cells



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

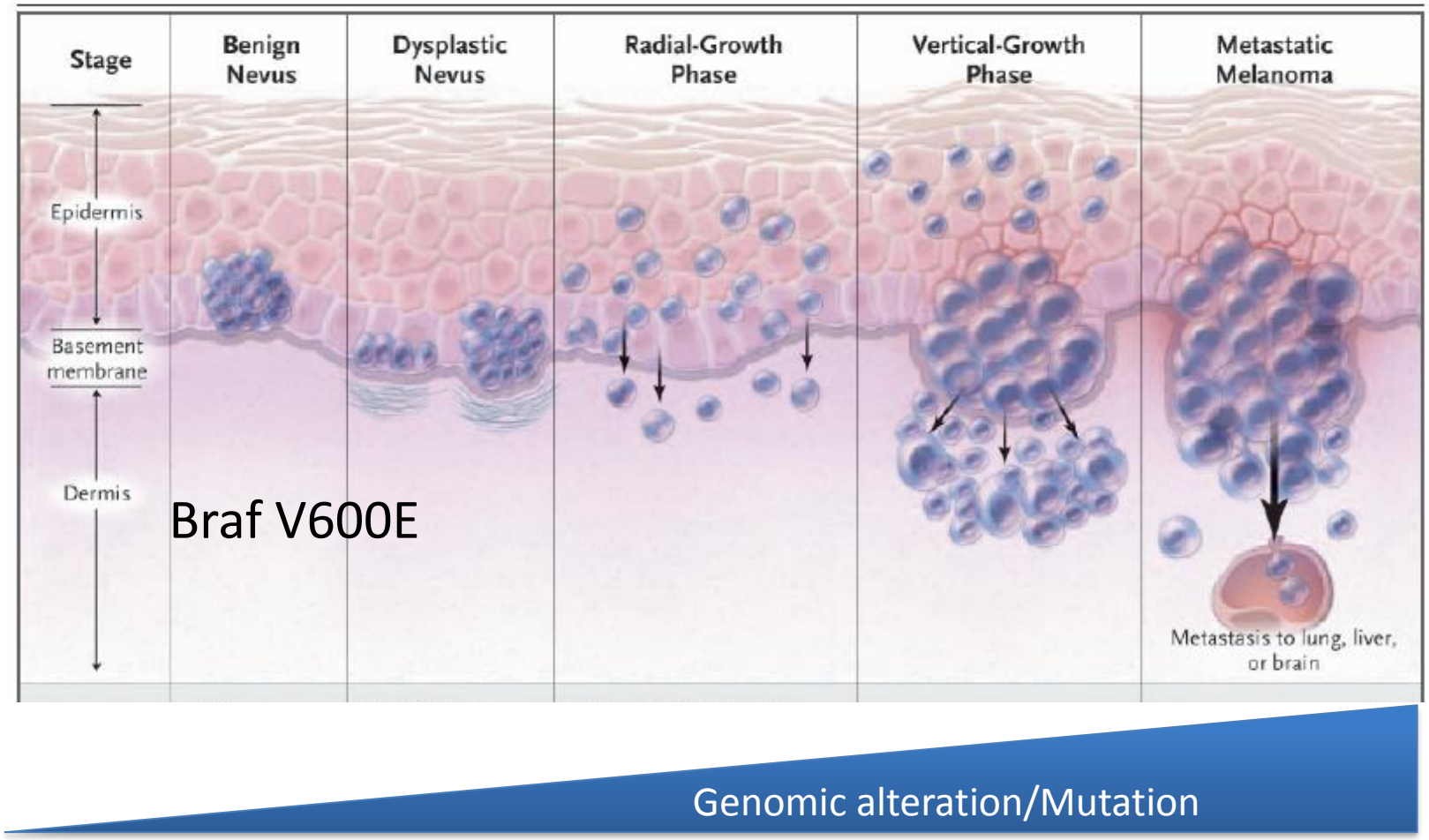
THERE WAS A CLEAR NEED FOR NEW AND MORE EFFECTIVE THERAPIES

The Poster Child: Metastatic Melanoma today

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
T-VEC	2015
Vemurafenib	2011
Dabrafenib	2013
Trametinib	2013

Immune therapy

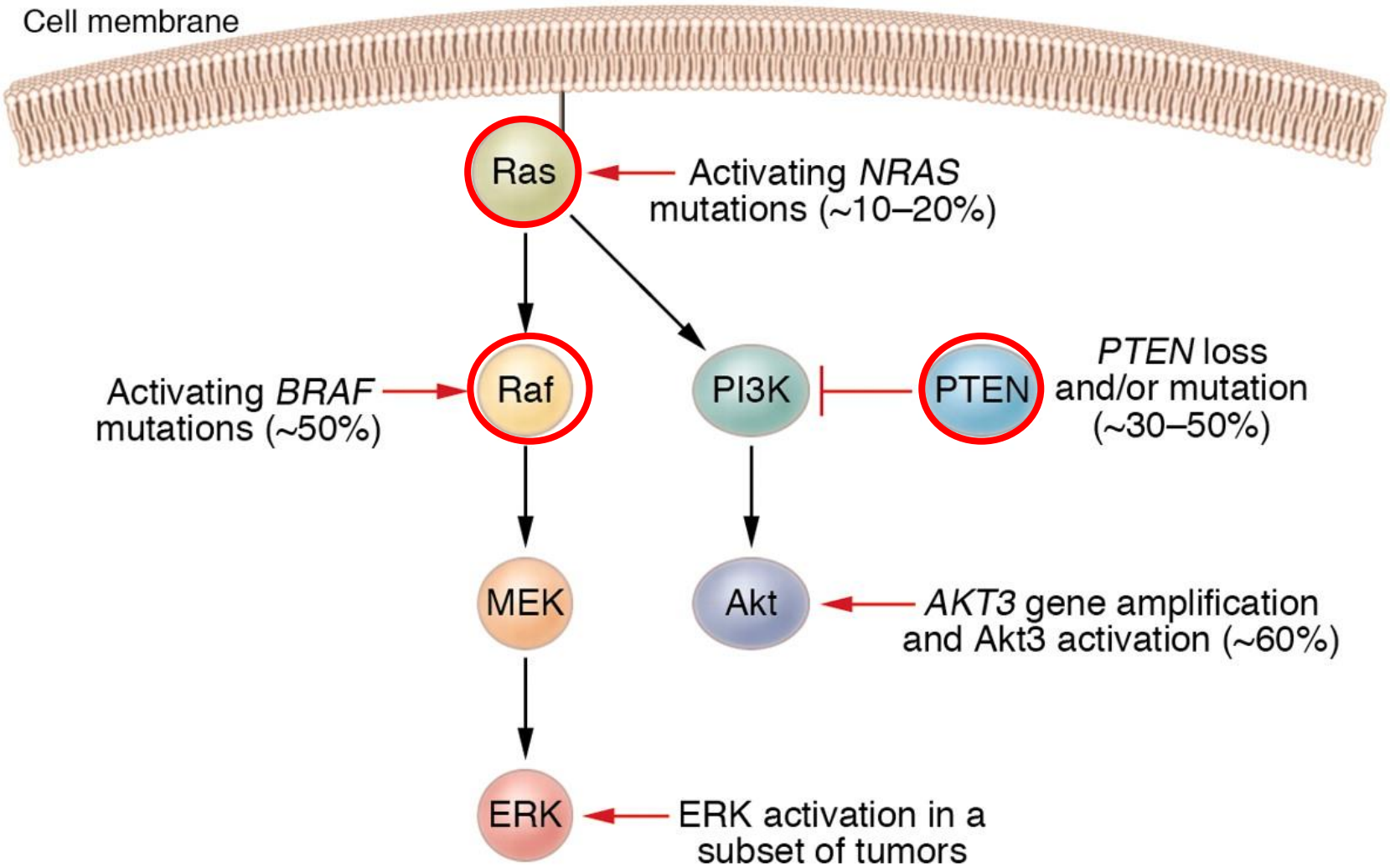
Biological Events and Molecular Changes in Melanoma Progression



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

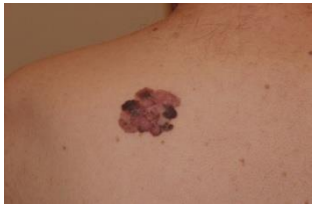
(Adapted from Miller A.R., and Merghoub T)

Genes and Pathways Involved in Melanoma Development



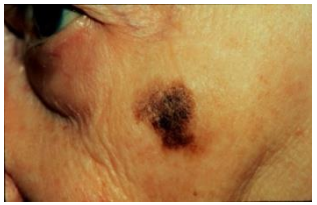
Chudnovsky Y, JCI, 2005.

Mutations Define Distinct Melanoma Molecular Subsets



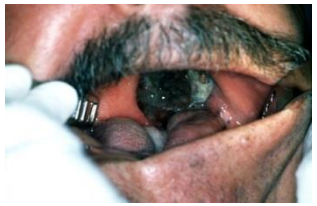
Arising from Skin Without Chronic Sun Damage

→ 50% ~~BRAF~~ (Vemurafenib) 0% KIT
20% NRAS



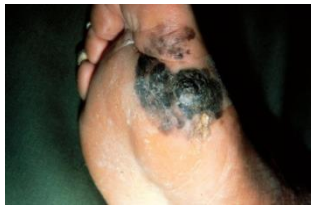
Arising from Skin With Chronic Sun Damage

→ 10% BRAF 2% KIT
10% NRAS



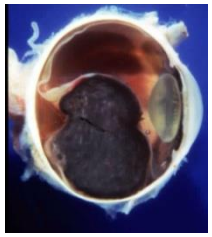
Arising from Mucosal Surfaces

→ 5% BRAF 20% KIT
15% NRAS



Arising from Acral Surfaces

→ 15% BRAF 15% KIT
15% NRAS

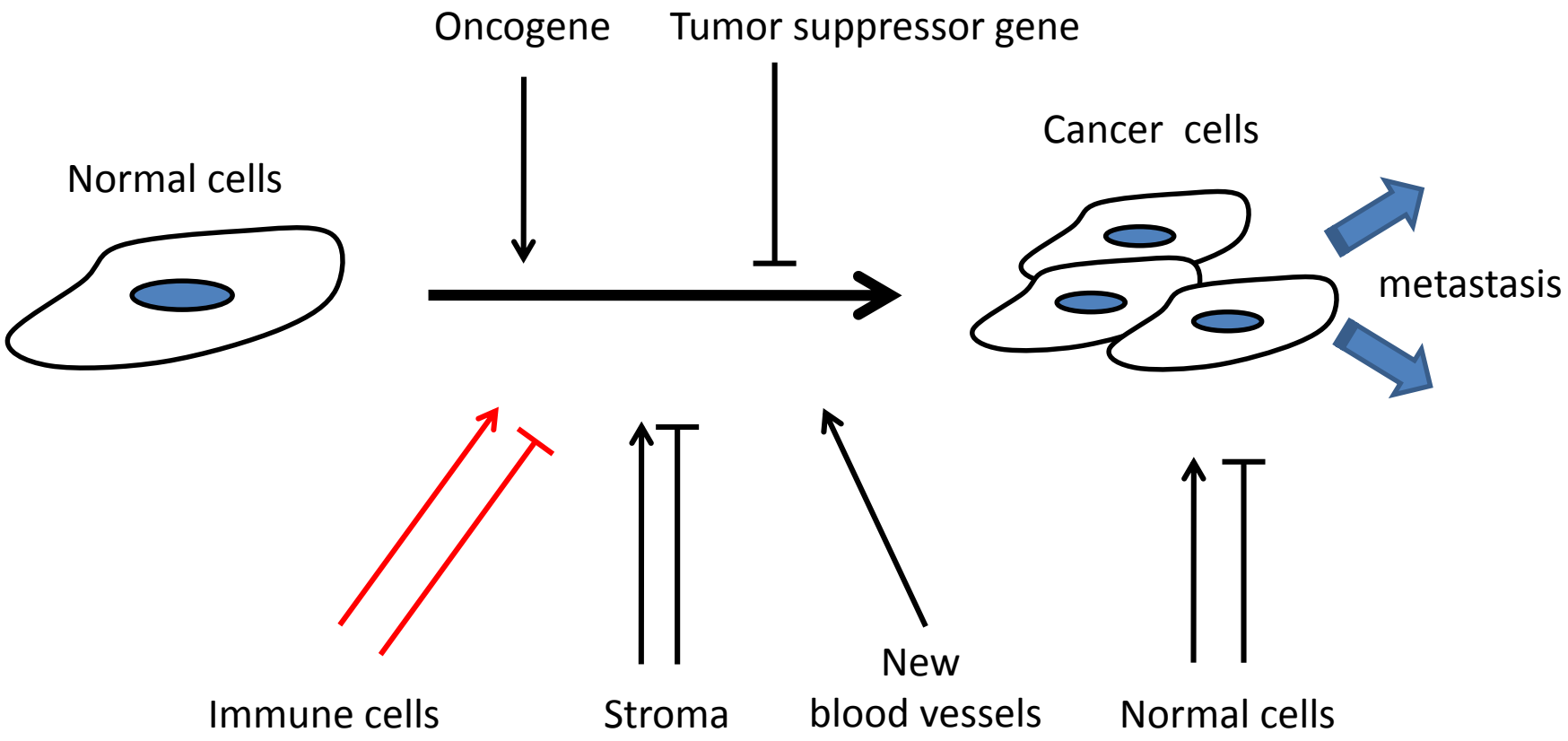


Uveal Melanoma

→ 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

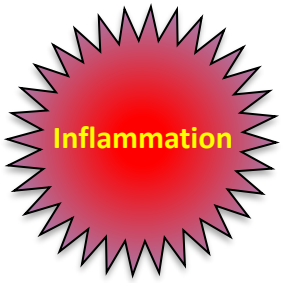
~~non self~~

self

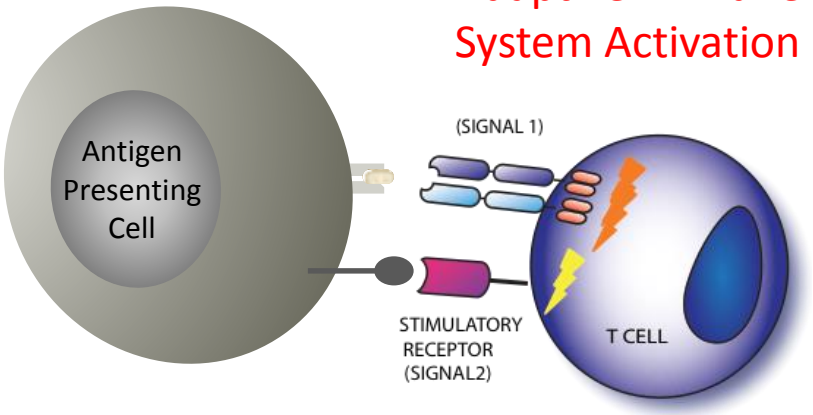
Immune Response 101

Pathogen

Danger (Innate Sensors)

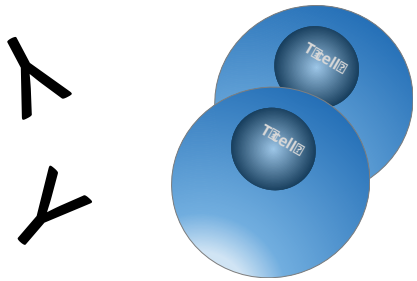


Adaptive Immune System Activation

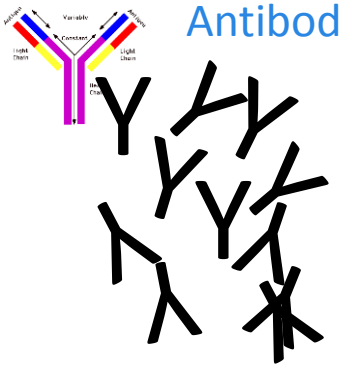


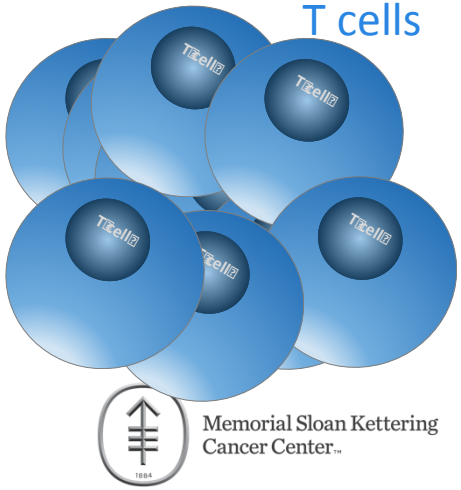
- Signal 1 = Antigen
- Signal 2 = Activation

Immunologic Memory



Elimination





The immune system is designed to recognize foreign antigens

~~non self~~

self

What if the immune system recognizes and attacks self?

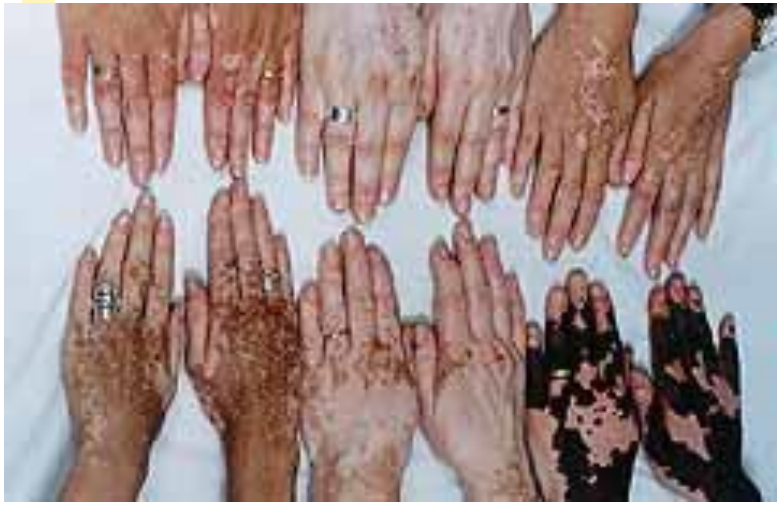
Cancer = self

Autoimmune reaction to self / transformed self

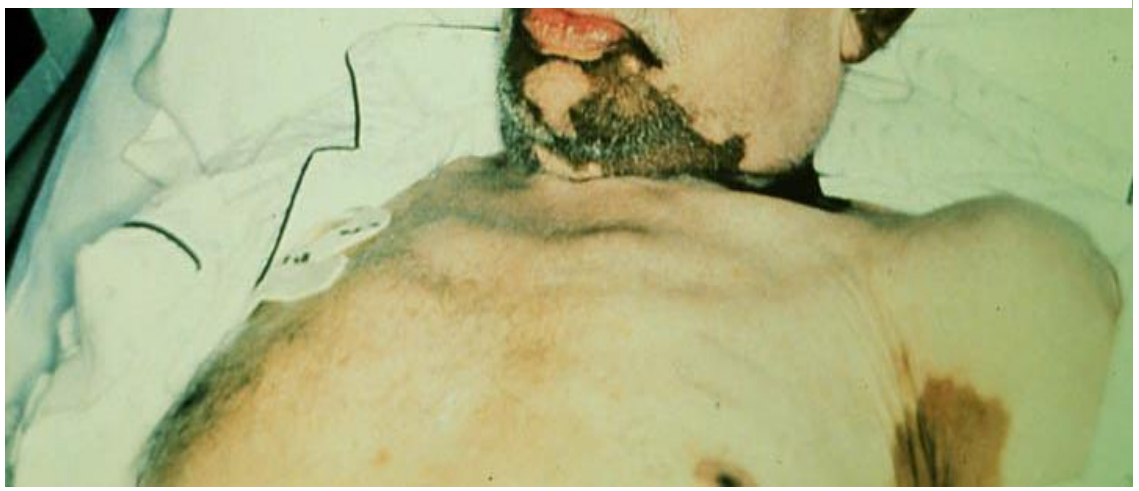
Recognizing self as non-self:
Autoimmunity/Vitiligo

Goal :
Recognition of
Transformed-self/Cancer

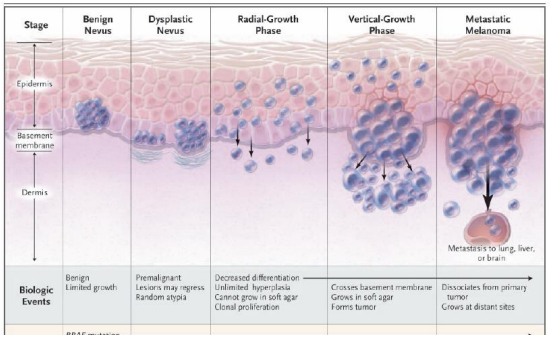
Natural response to melanoma

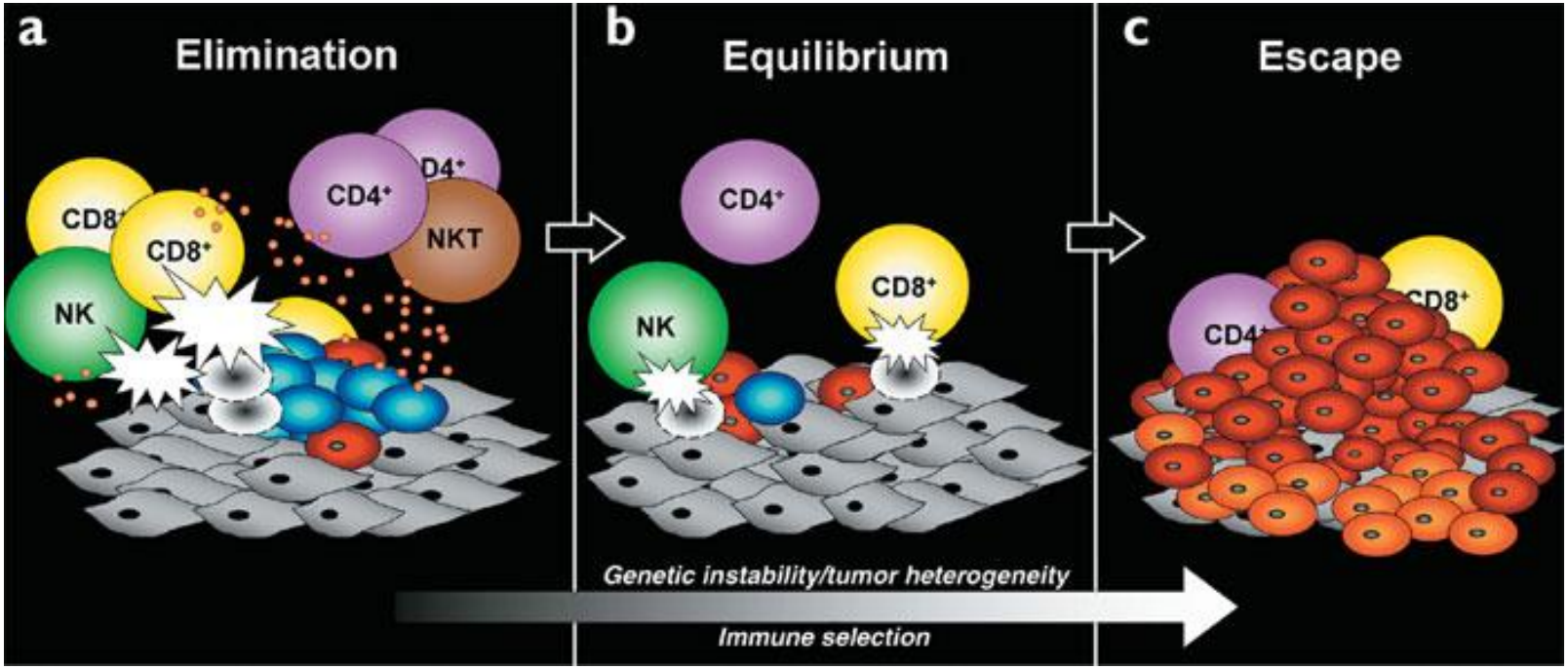


- Clinical observation that melanoma patients who develop vitiligo “do better” and that vitiligo is associated with response to chemotherapy as well as immunotherapy
- Isolation from a patient of an antibody recognizing “pigmented associated antigen”



Role of the Immune System in Cancer: Immunoediting

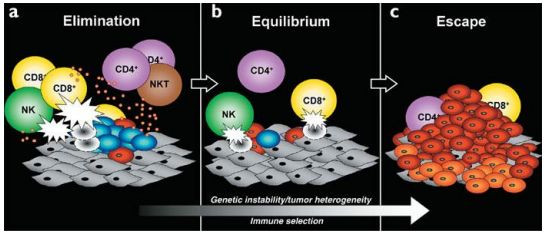


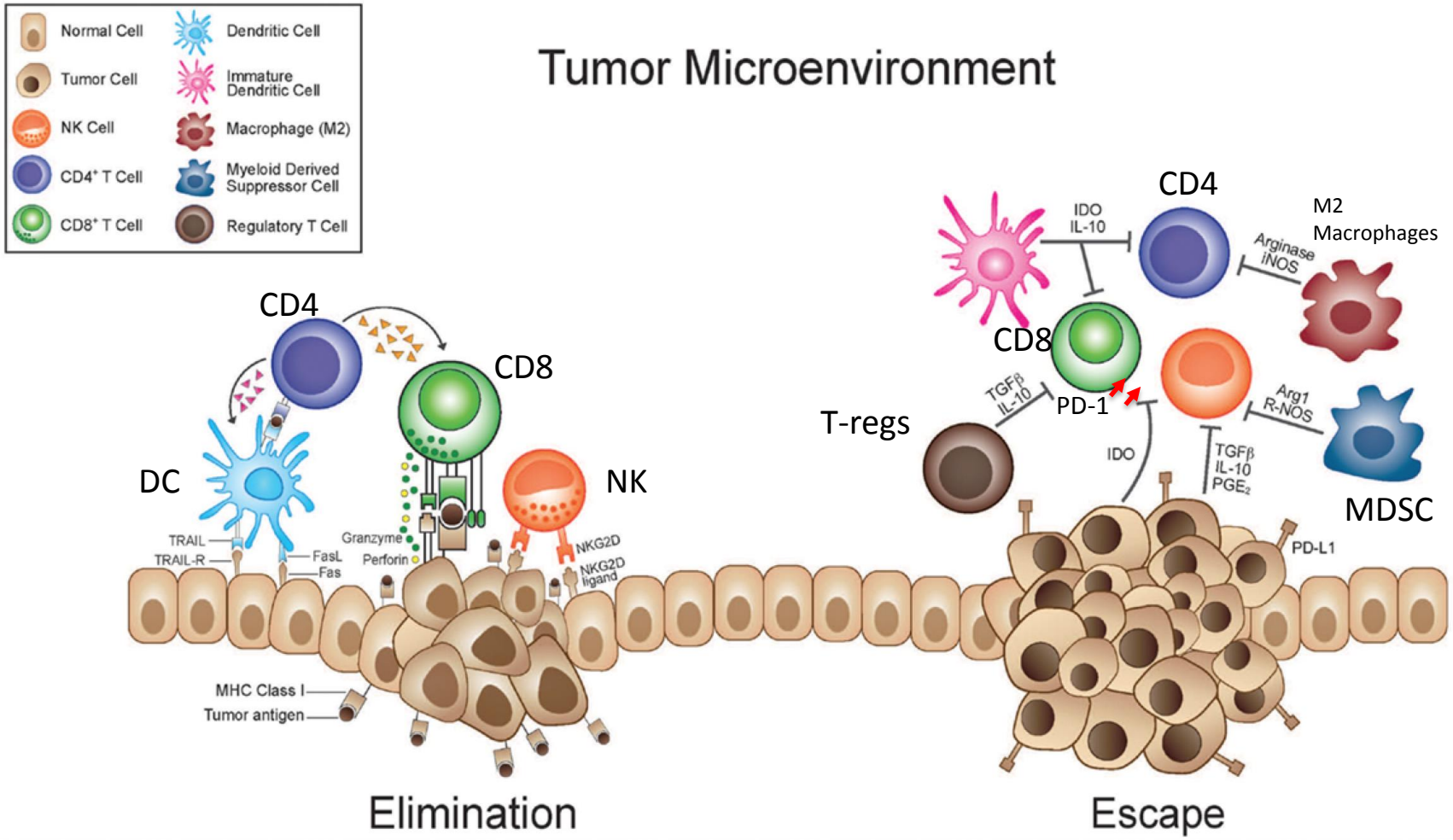


Robert D. Schreiber

Immunoediting

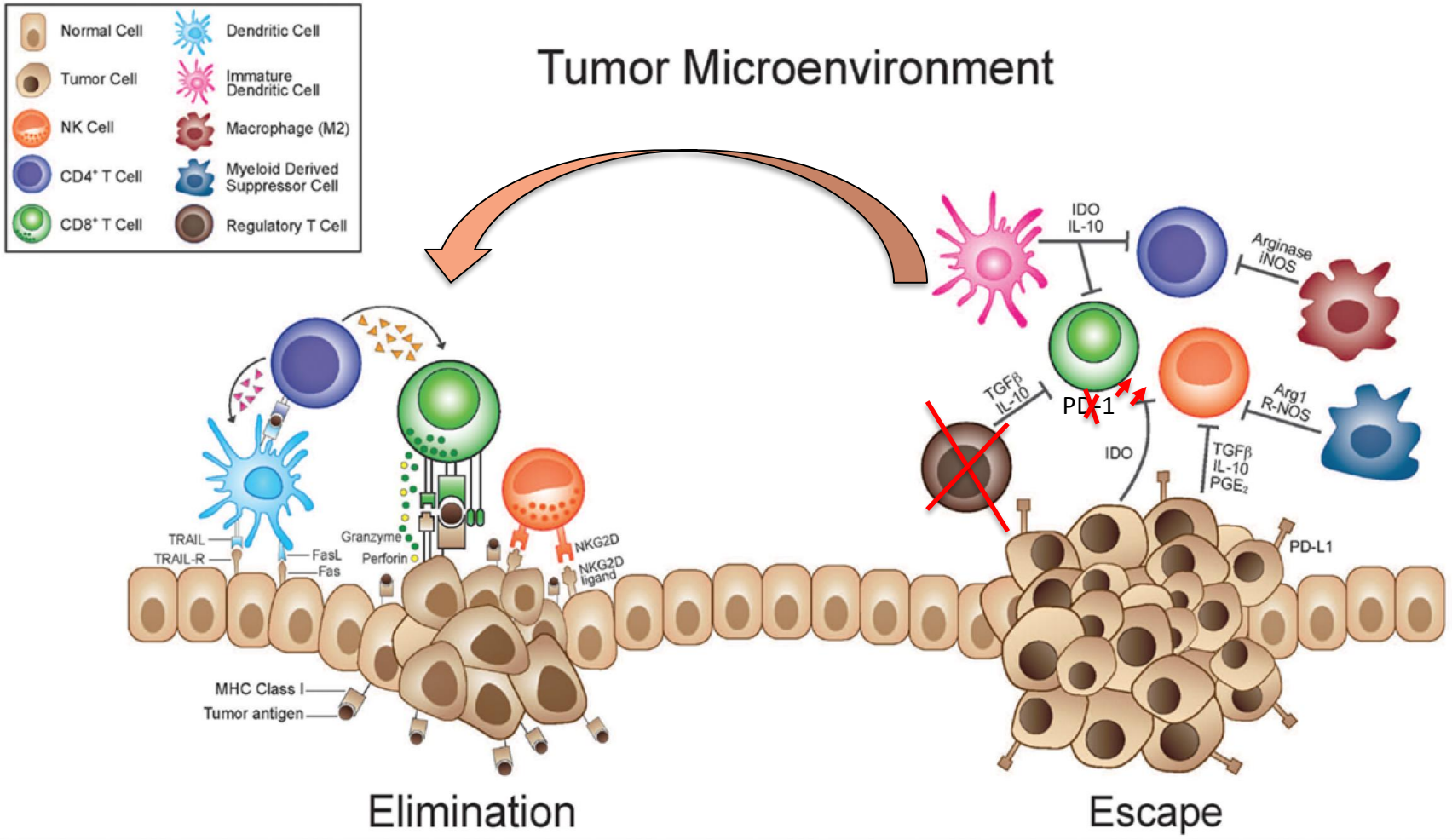
Immune Suppressive Microenvironment





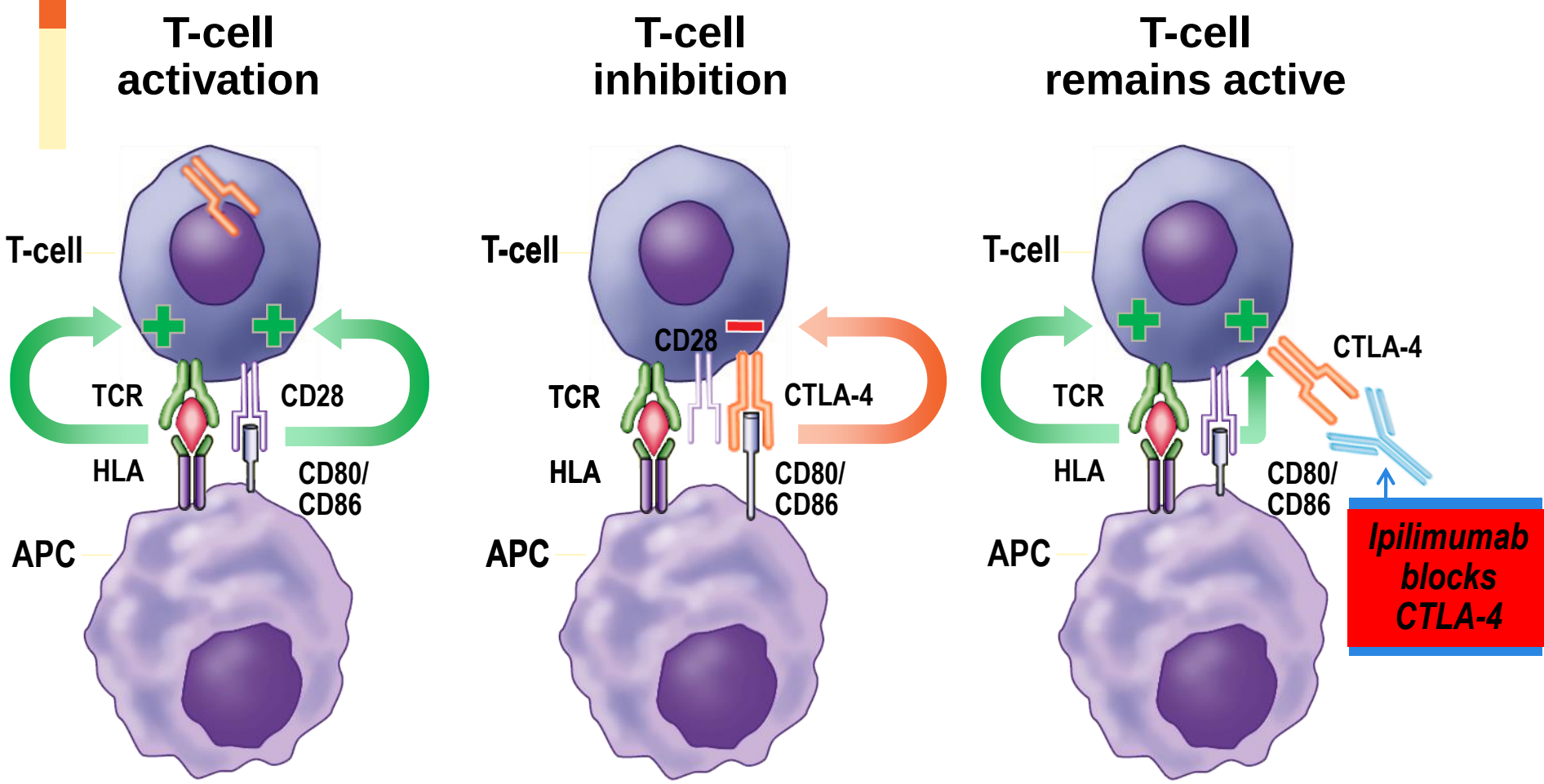
William J. Murphy. Front Oncol. 2013; 3: 197.

Immune Suppressive Microenvironment



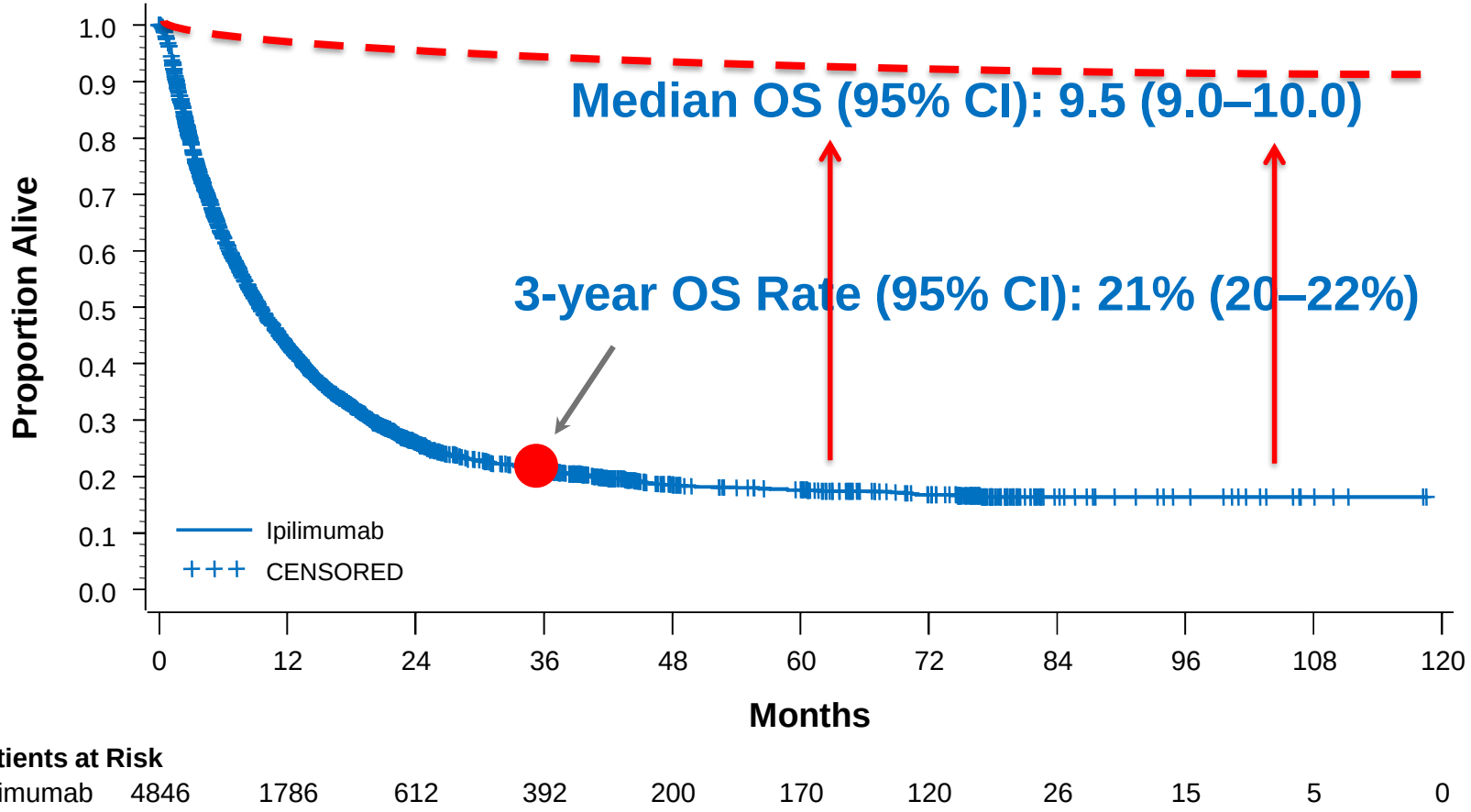
William J. Murphy. Front Oncol. 2013; 3: 197.

Ipilimumab Augments T-Cell Activation and Proliferation



Adapted from O'Day et al. Plenary session presentation, abstract #4, ASCO 2010.

Ipilimumab Long Term Pooled Survival Analysis: 4846 Patients

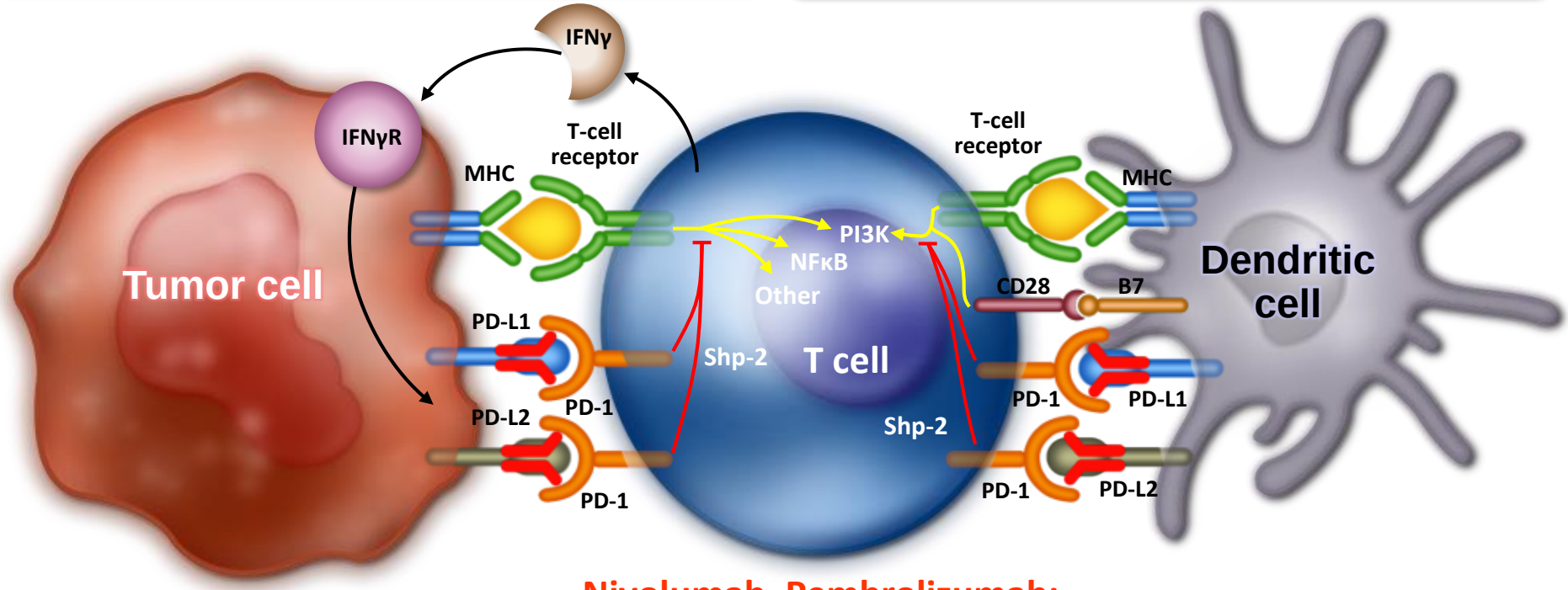


Schadendorf, Hodi Wolchok, ESMO, 2013

Role of PD-1 Pathway in Tumor Immunity

Recognition of tumor by T cell through MHC/antigen interaction mediates IFNγ release and PD-L1/2 up-regulation on tumor

Priming and activation of T cells through MHC/antigen & CD28/B7 interactions with antigen-presenting cells



Nivolumab, Pembrolizumab:
PD-1 Receptor Blocking Abs

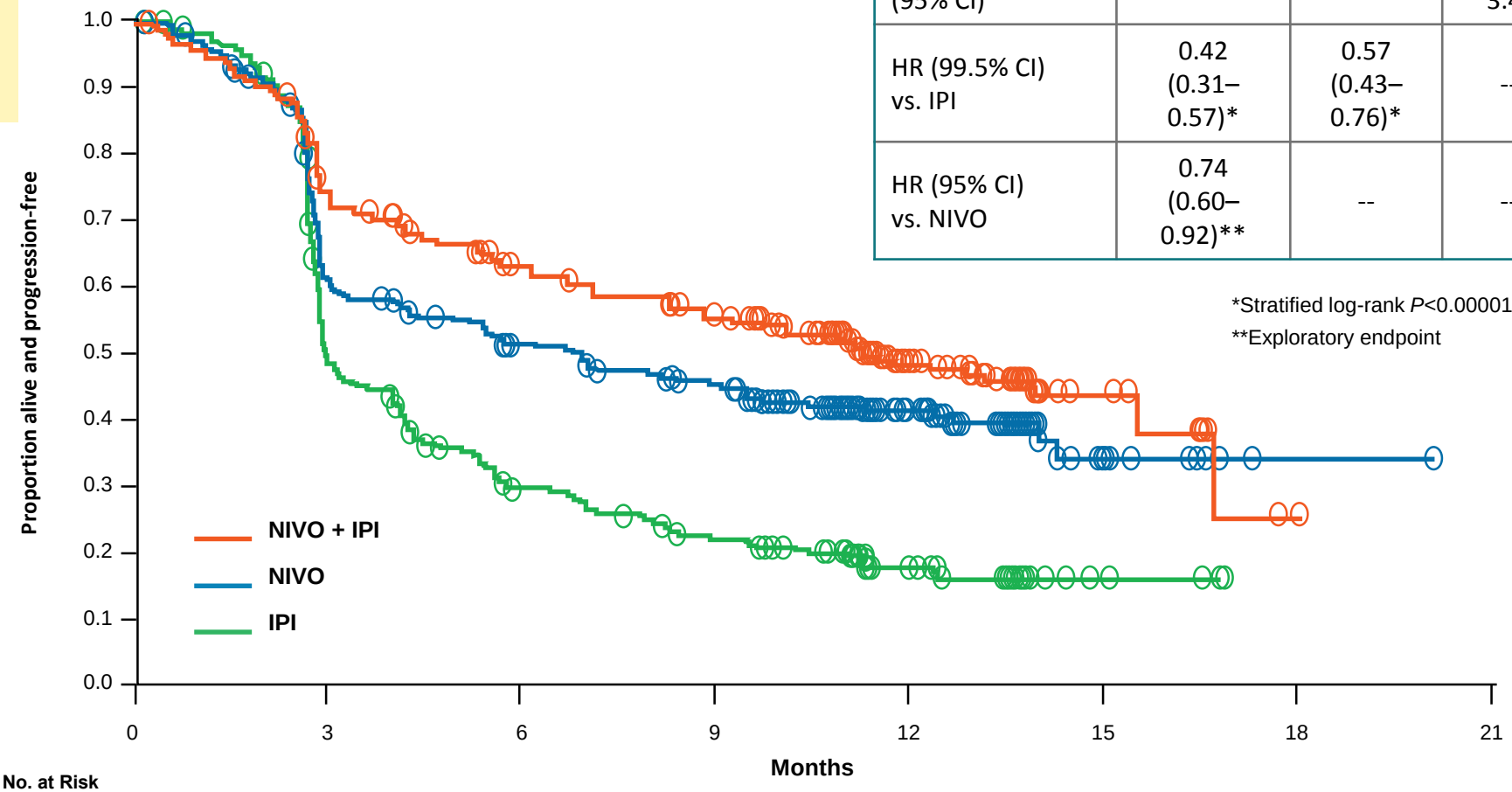
Sznol et al., ASCO, 2013

PFS (Intent-to-Treat)

	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31–0.57)*	0.57 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.74 (0.60–0.92)**	--	--

*Stratified log-rank *P*<0.00001 vs. IPI

**Exploratory endpoint



No. at Risk								
NIVO + IPI	314	219	173	151	65	11	1	0
NIVO	316	177	147	124	50	9	1	0
IPI	315	137	77	54	24	4	0	0

Larkin et al, NEJM, 2015

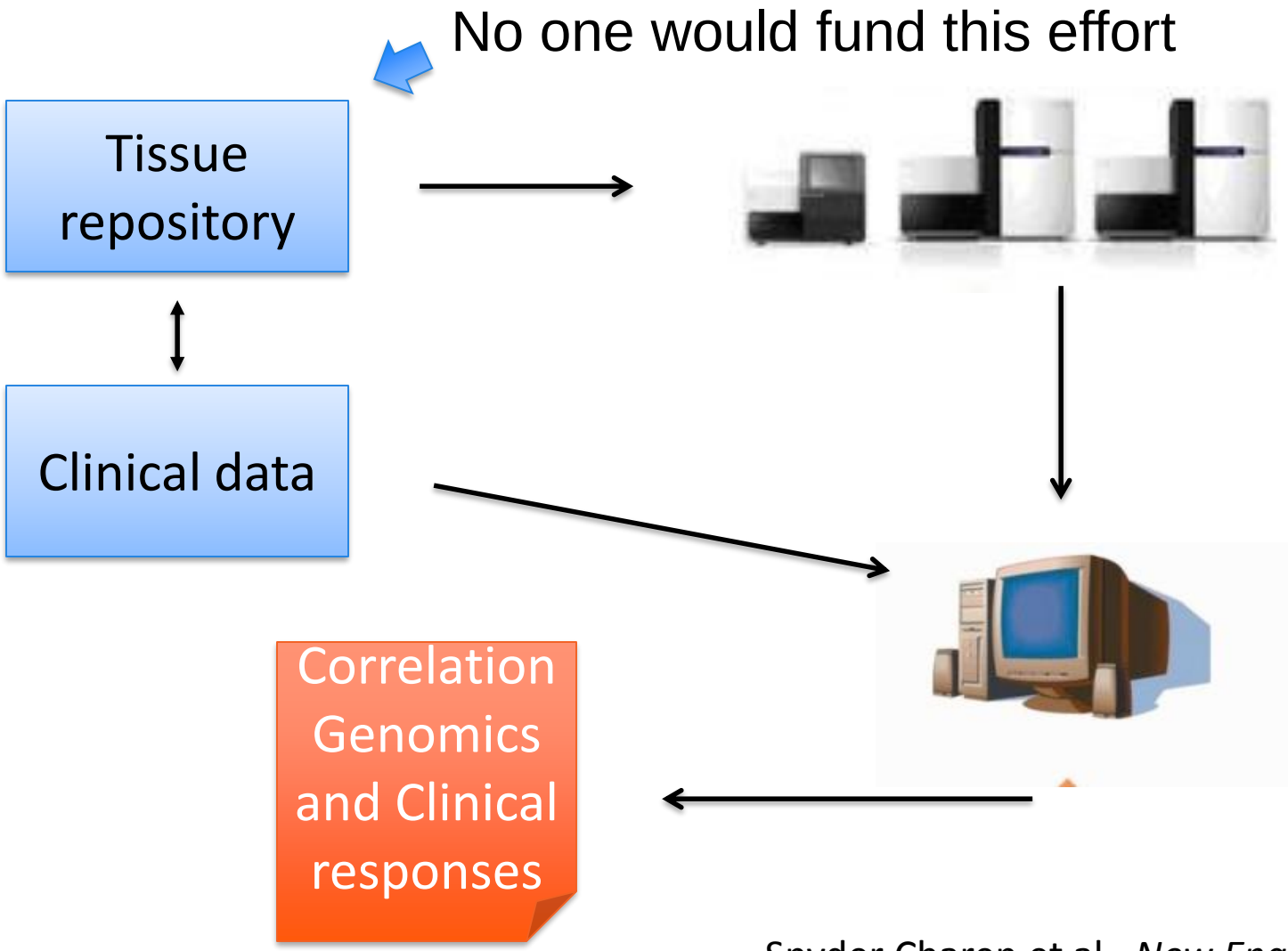
1- Can we predict response to immune therapy reliably?

2-Can we improve response to immune therapy?

Can we predict response to immune therapy reliably?

Memorial Sloan Kettering Cancer Center

Mutations, Immunogenicity and Prediction of clinical response

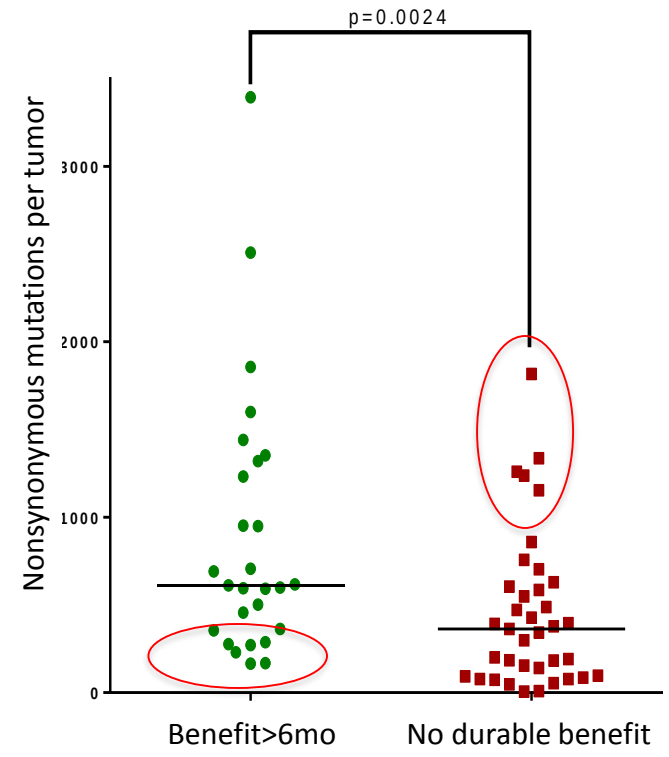


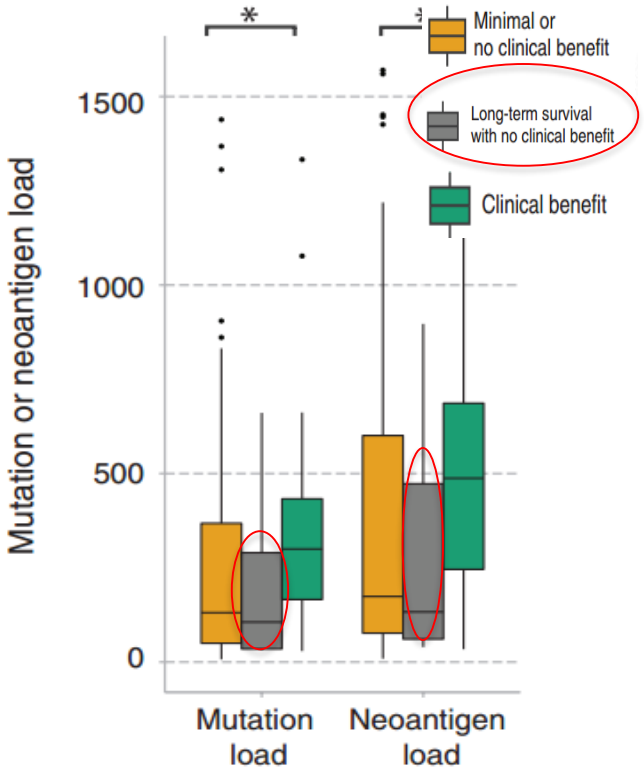
Snyder Charen et al., *New Engl J Med*, 2014

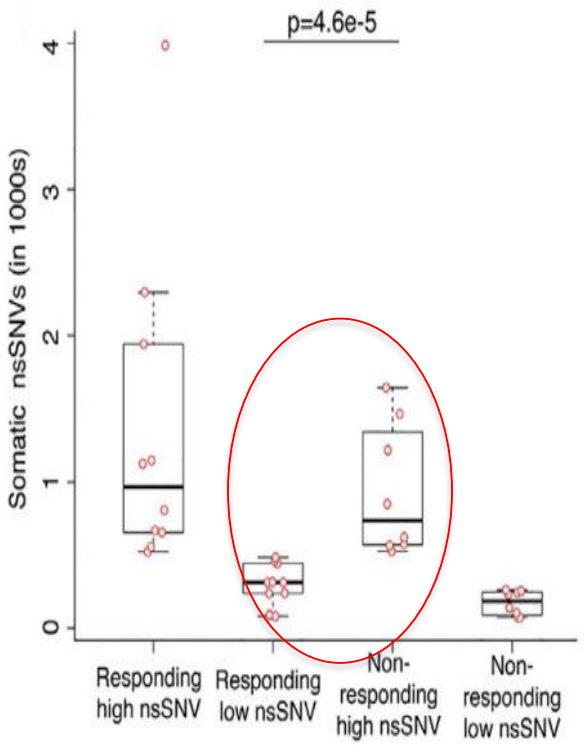
Mutational Load Correlates with Benefit from Checkpoint Blockade ….With Important Exceptions

Melanoma/anti-CTLA-4

Melanoma/anti-PD-1



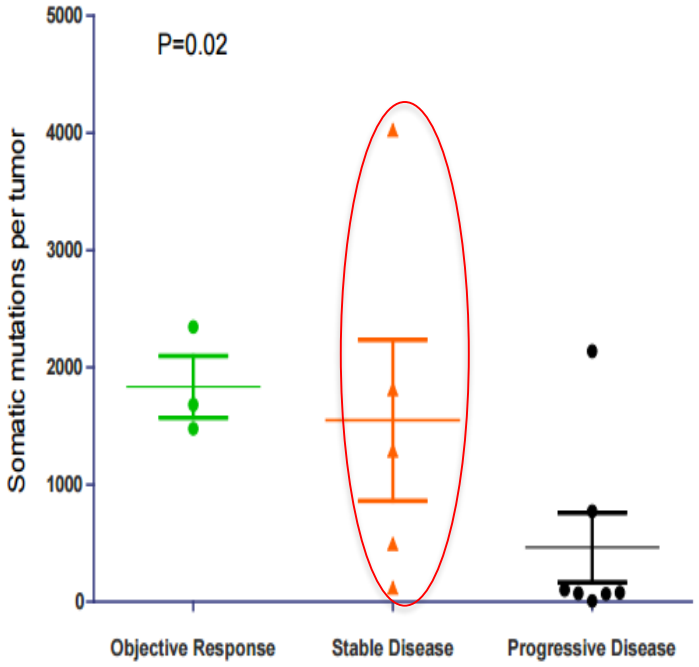




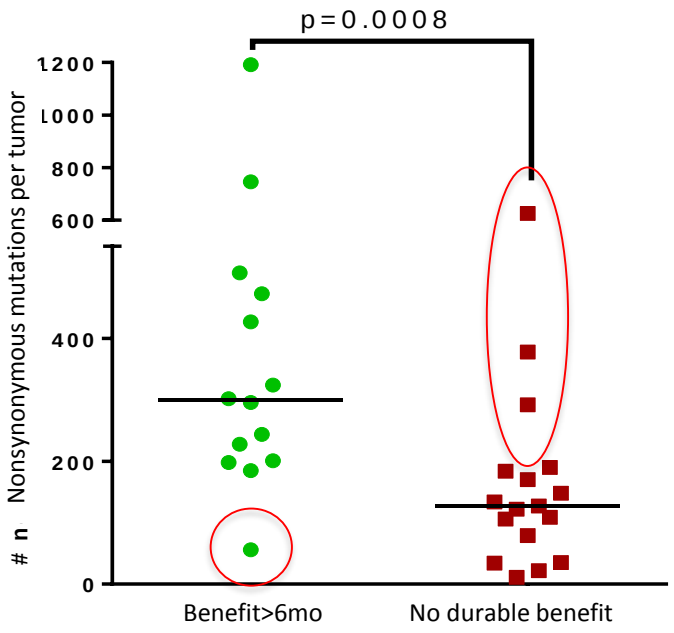
Snyder, Makarov, Merghoub, Yuan et al NEJM 2014
Van Allen, Miao et al Science 2015, Hugo et al Cell 2016

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

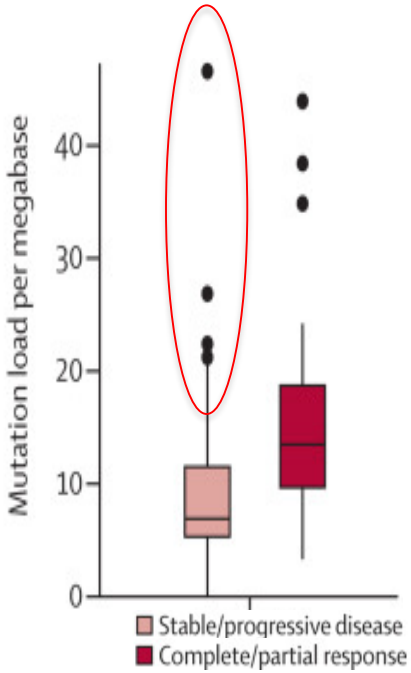
MSI-H CRC/anti-PD-1



NSCLC/anti-PD-1



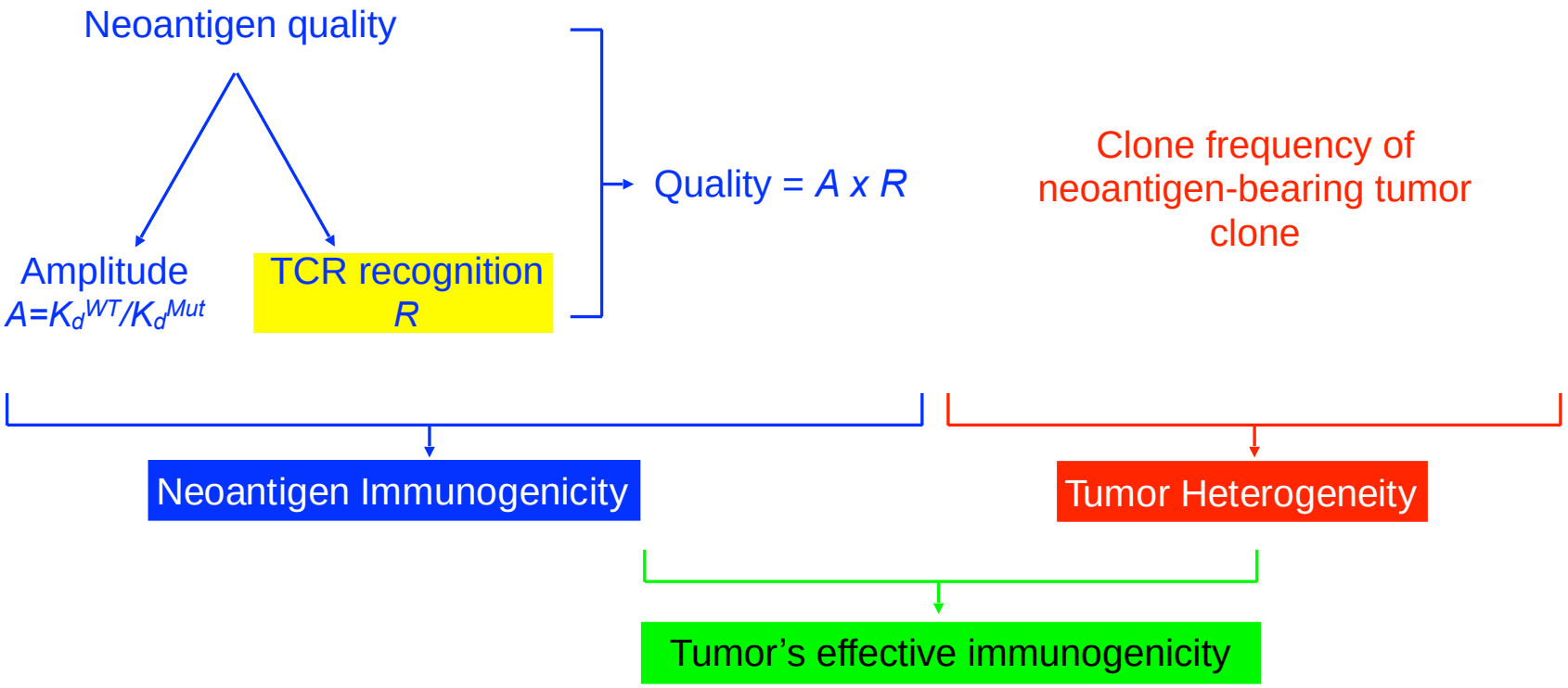
Bladder/anti-PD-L1



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

A computational model of neoantigen quality based immunogenicity

Which neoantigen(s) are the most immunogenic?



IAS

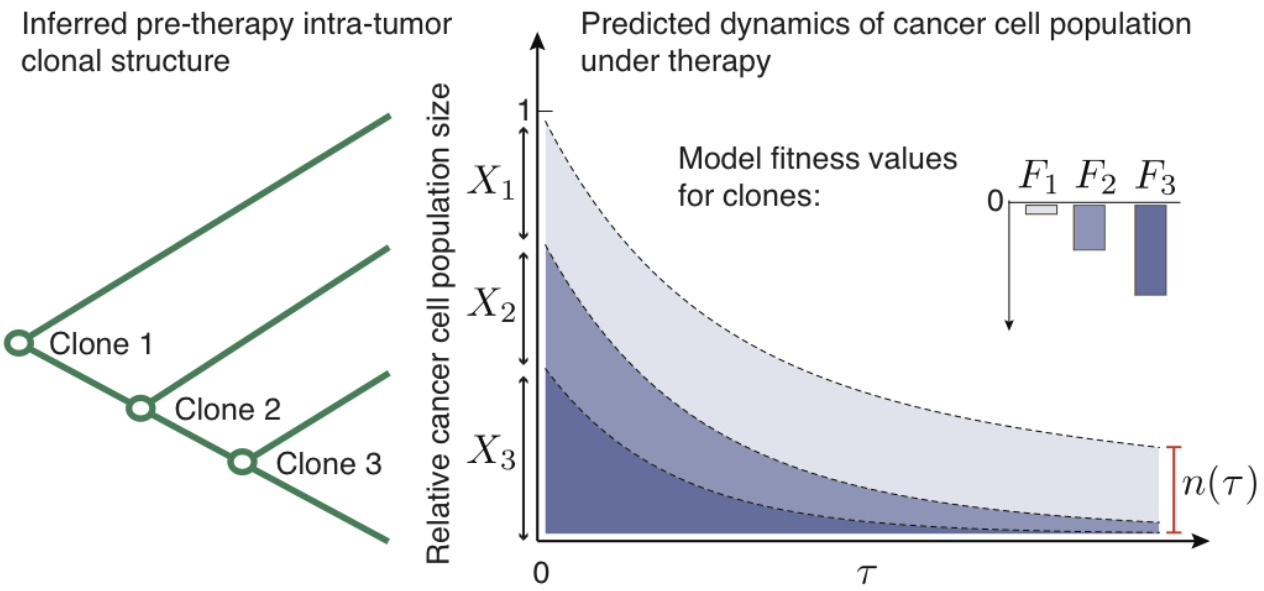
Memorial Sloan Kettering Cancer Center

Mount Sinai

Balachandran VP, Wolchok JD, Merghoub T et al. ***Nature*** 2017.

Łuksza M, Balachandran VP, Greenbaum BG et al. ***Nature*** 2017.

Neoantigen driven tumor evolutionary dynamics



$$n(\tau) = \sum_{\alpha} X_\alpha \exp[F_\alpha \tau]$$

Relative effective population size after forward evolution

Initial clone frequency (from phylogeny)

Fitness of clone (derived from model)

Łuksza et al., *Nature*, 2017

Model construction: fitness of a clone

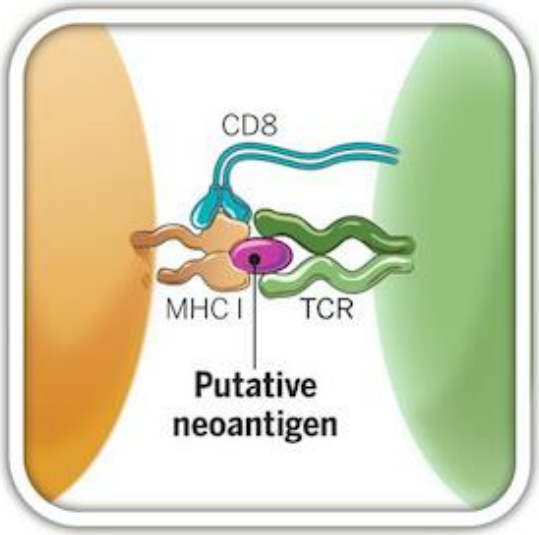
Neoantigens in a clone:

MTTKATSSM →

TLDYKPVTV →

QIKNKNKEI →

Neoantigen fitness model



Predicted dominant neoantigen:

→ TLDYKPVTV →

Tumor clone fitness:

F_α

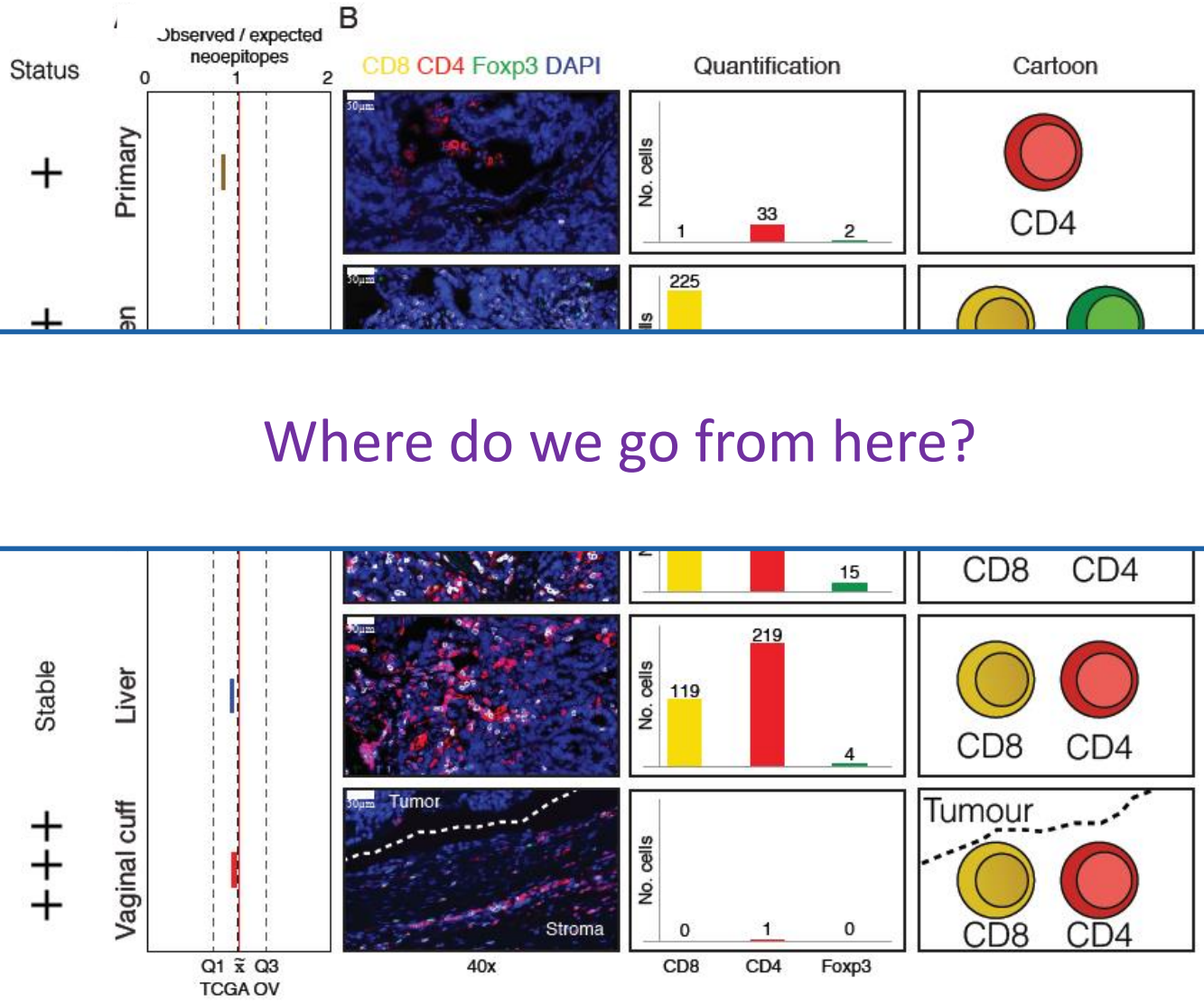
Amplitude due to MHC presentation:

- From inferred affinities of wildtype and mutant peptides
- Should relate to discrimination ability by class I HLA molecule

TCR recognition probability:

- Sequence similarity to pathogen epitopes (IEDB) as a proxy for TCR binding affinity
- Hypothesized measure of likelihood of TCR recognition

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



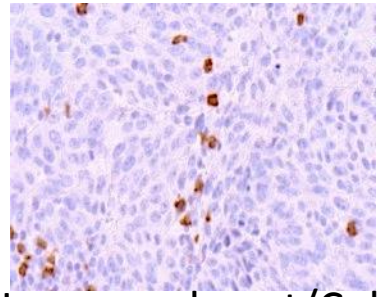
Where do we go from here?

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

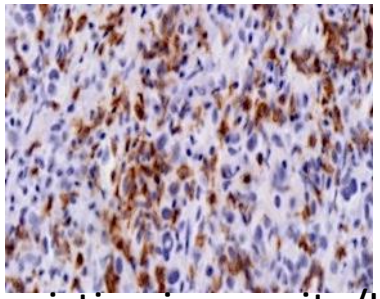
CD8



→ No benefit

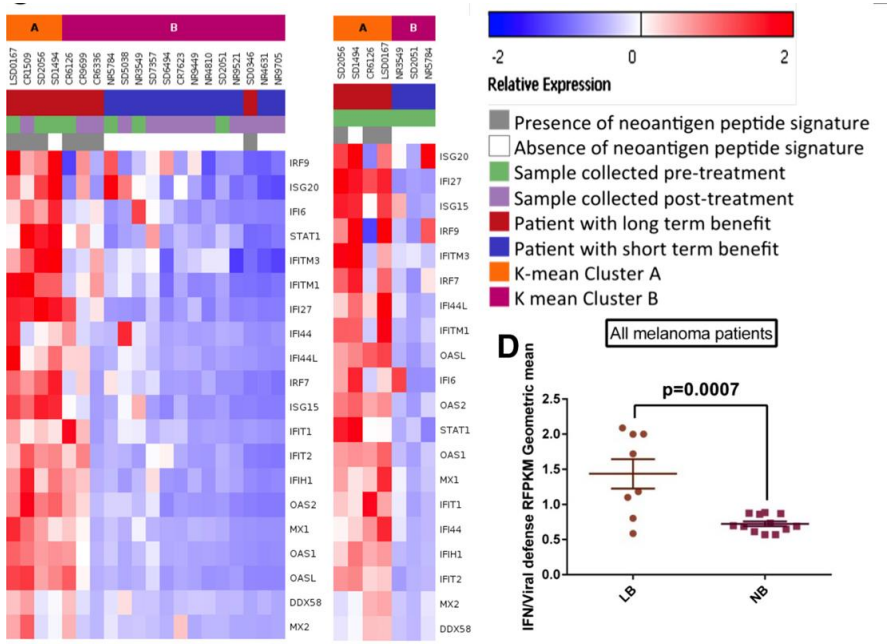
How?

"Immune desert/Cold"



→ Benefit

"Pre-existing immunity/Hot"

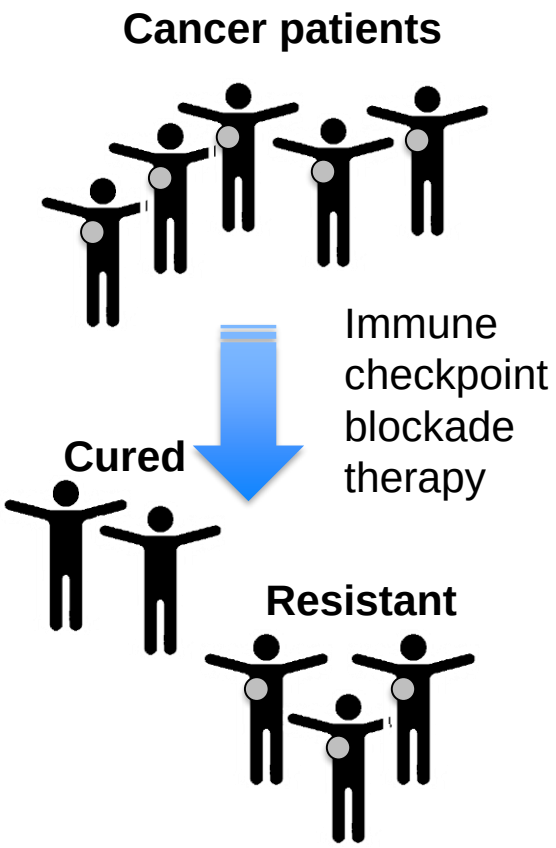


Type I IFN signature is associated with clinical benefit from CTLA-4 blockade in melanoma
Chiappinelli et al., Cell 2015

"Pre-existing immunity/Hot" → **Immune check point** is enough

"Immune desert/Cold" → **Immune check point + bring immune cells to tumors**

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]

Article Cell

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,[5] Chantale Bernatchez,[5] Scott E. Woodman,[5] Pei-Ling Chen,[5] Patrick Hwu,[5] James P. Allison,[4] Andrew Futreal,[5] Jennifer A. Wargo,[3,5] and Padmanee Sharma[1,4,7,*]

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

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The NEW ENGLAND JOURNAL of MEDICINE

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

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Immune-mediated resistance

Cancer Immunol Immunother (2014) 63:247–257
DOI 10.1007/s00262-013-1508-5

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

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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

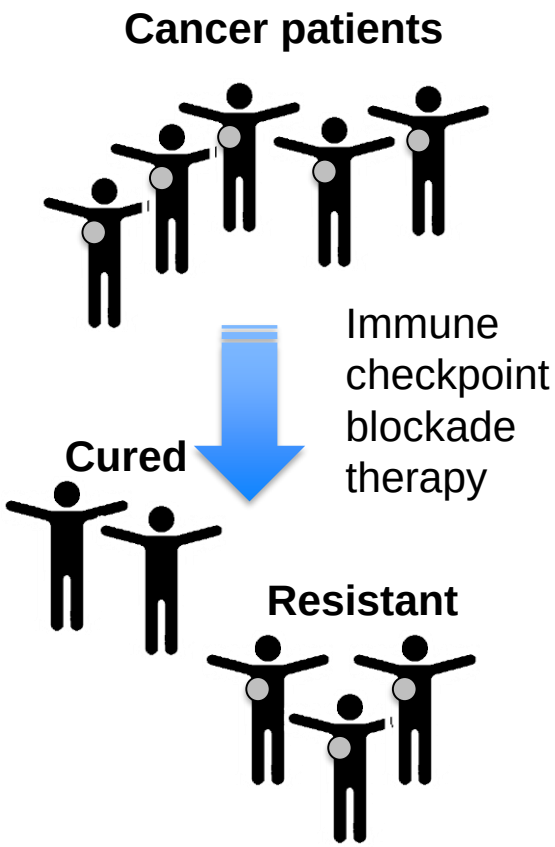
JEM Article

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]

Memorial Sloan Kettering Cancer Center

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



Tumor intrinsic resistance

LETTER

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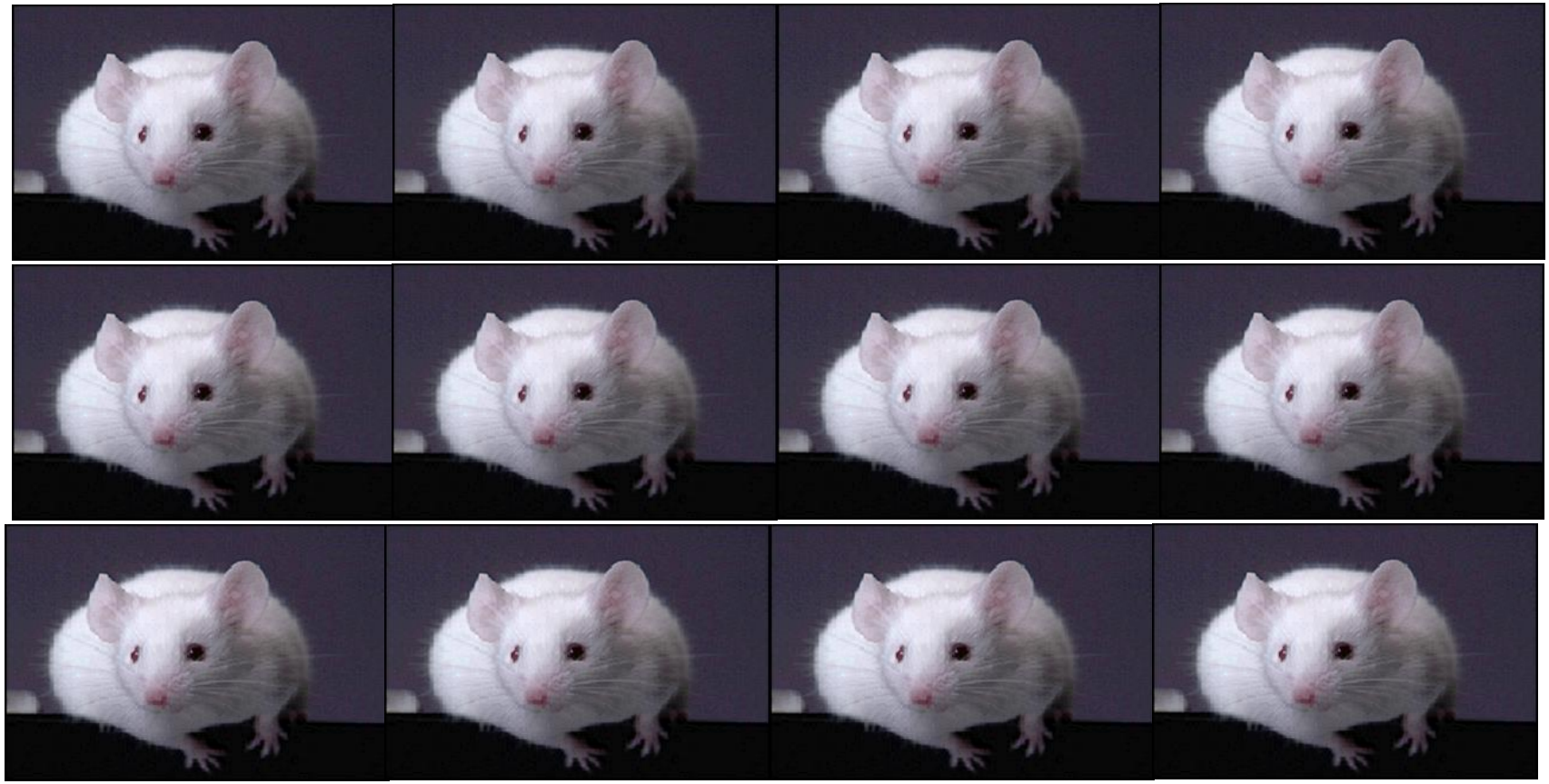
Need to go back to murine tumor models



We look like identical twins!

Inbred mouse strains are a great tool

Transplantable lung tumor model from KP mice derived cells

KP mice

Kras$^{G12D/+}$ p53$^{flox/flox}$

HKP1

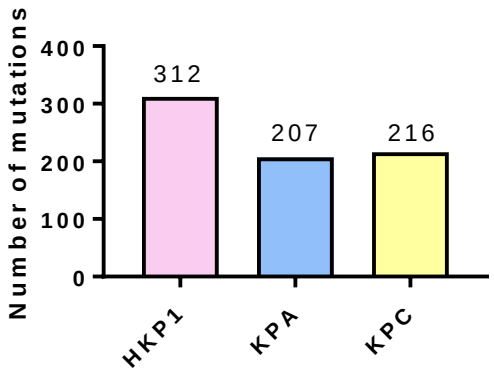
KPA

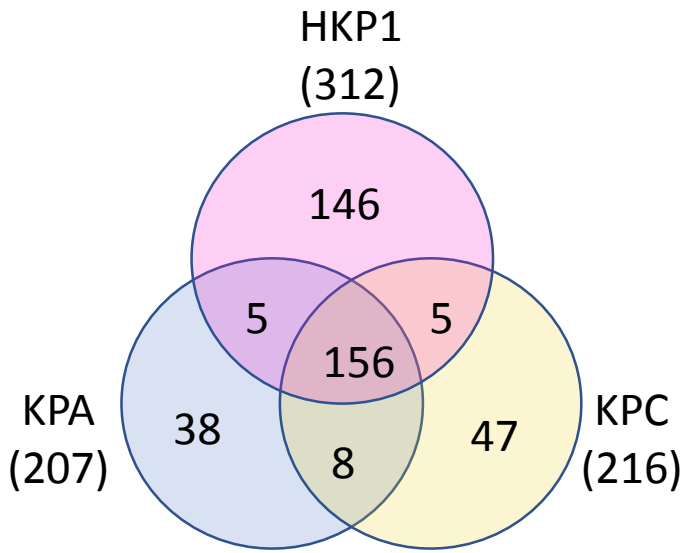
KPC

Variants for immunogenicity study

No dbSNP filtration

Only missense mutation



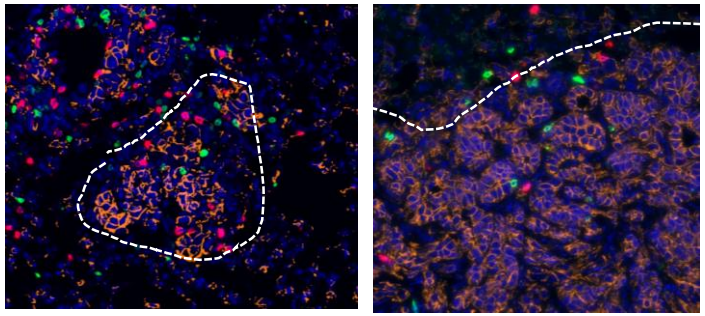


KPA and KPC cells from Kwok-kin Wong's lab

T cell infiltration in Kras mutant lung cancer models

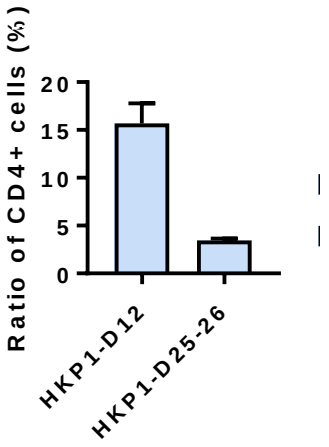
HKP1 model

DAPI/CD4/CD8/Ecad

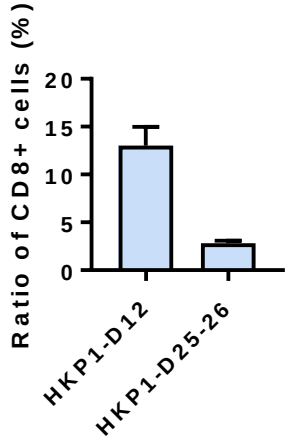


day 12 day 26

CD4+ cells

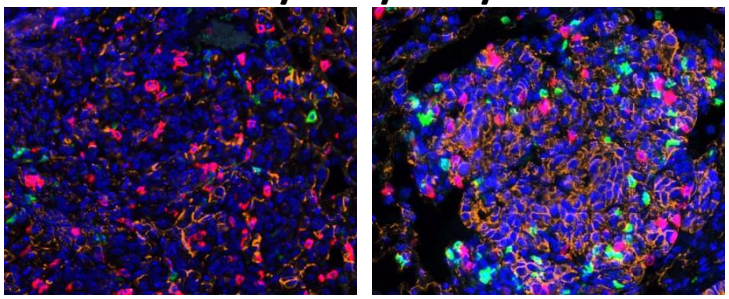


CD8+ cells



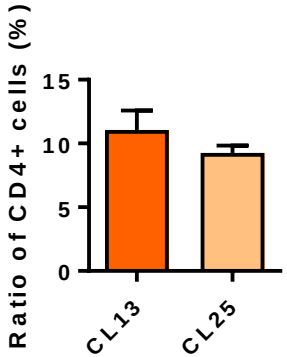
CL13 CL25 model

DAPI/CD4/CD8/Ecad

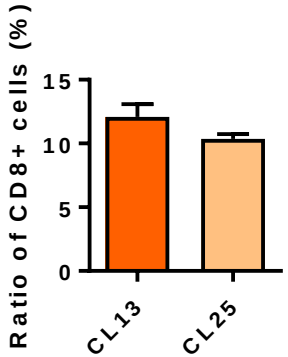


CL13 CL25

CD4+ cells



CD8+ cells



CL13: day 28
CL25 : day 20

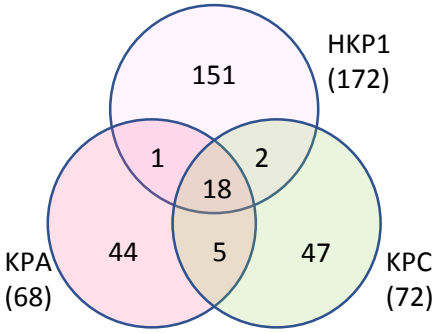
How are neoantigens edited in vivo?

= Is there a rule to eliminate certain neoantigens in tumor?

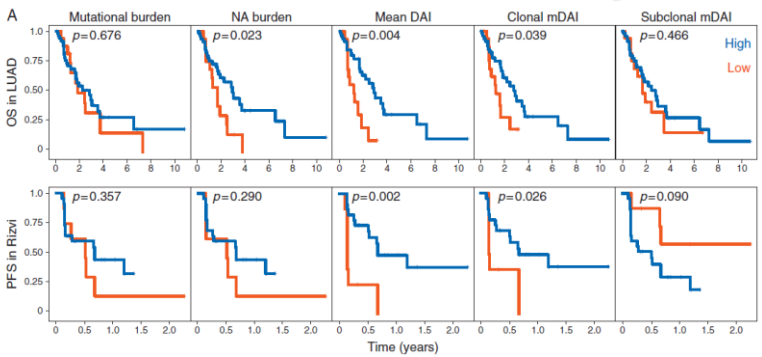
Neoantigen quality matters?

1. Clonal vs branch mutations in tumors

Clonal mutations are associated with response to immune checkpoint blockade.



2. High affinity vs low affinity to MHC?



High DAI (MHC I affinity, WT_A-M_A) is associated with better prognosis.

Neoantigen quantity matters?

1. Abundant vs rare

McGranahan et al., 2017
Ghorani et al., 2018

How are neoantigens edited in vivo?

Question

✔☐ What clones (clonal/subclonal or high/log MHC binder) are eliminated by immune system?

HKP1
KPA
KPC

WES

RAG-/-

Tumor cells injection

WES

B6

Tumor cells injection

WES

Tumor collection

How are neoantigens edited in vivo?

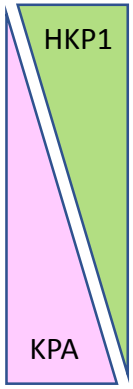
Question

✔☐ Will abundant or rare clones be eliminated in an equal way or unequally by immune system?
(= are they subject to the same degree of T cell attack?)

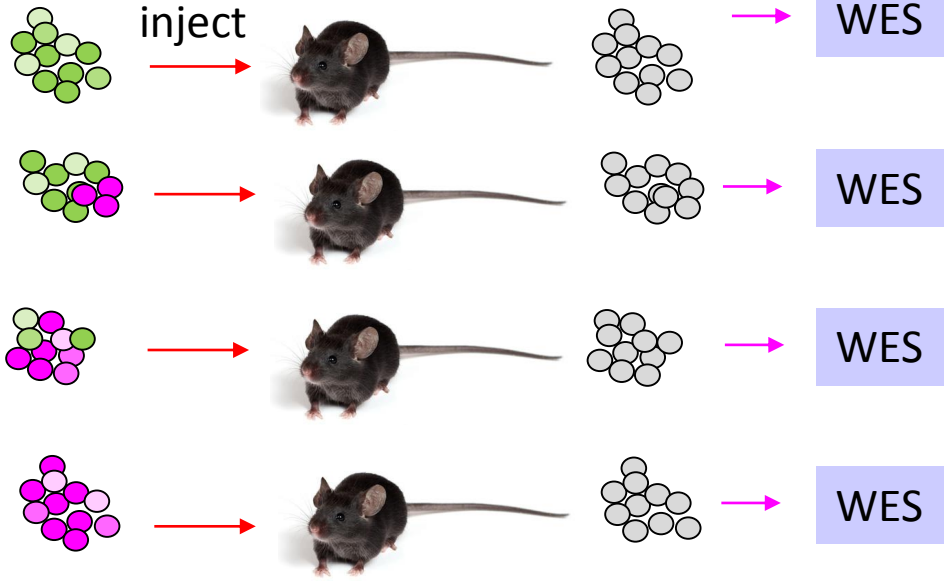
HKP1
KPA
KPC

WES

Mix cells in diverse ratio



HKP1	KPA
100 %	0 %
70 %	30 %
30 %	70 %
0 %	100 %



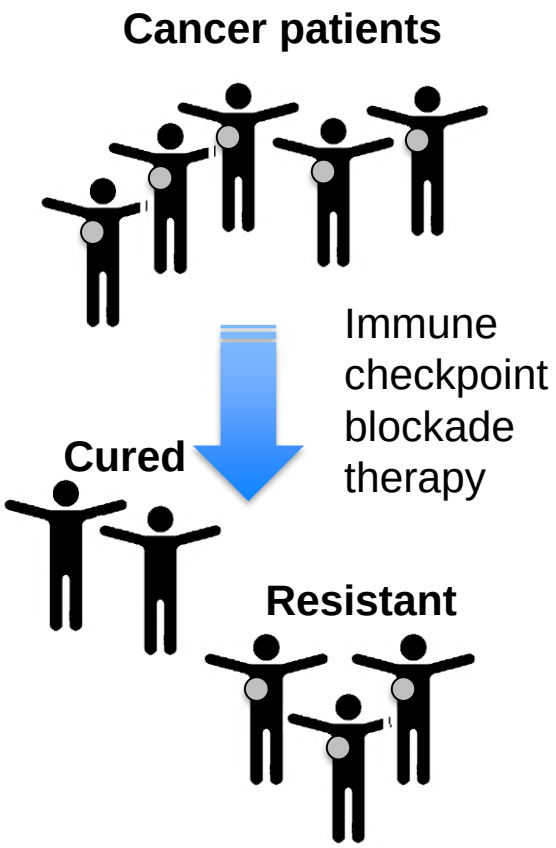
Summary and Future plan

1. **Transplantable Kras lung cancer model for neoantigen study and targeting** was developed.

2. The model will be used to address questions about in vivo **cancer immune editing pattern** to understand how tumor heterogeneity is shaped.

3. Diverse strategies of **targeting neoantigens** in Kras lung cancer will be investigated for best efficacy of cancer vaccine.

Major mechanisms of resistance to anti-tumor immunity



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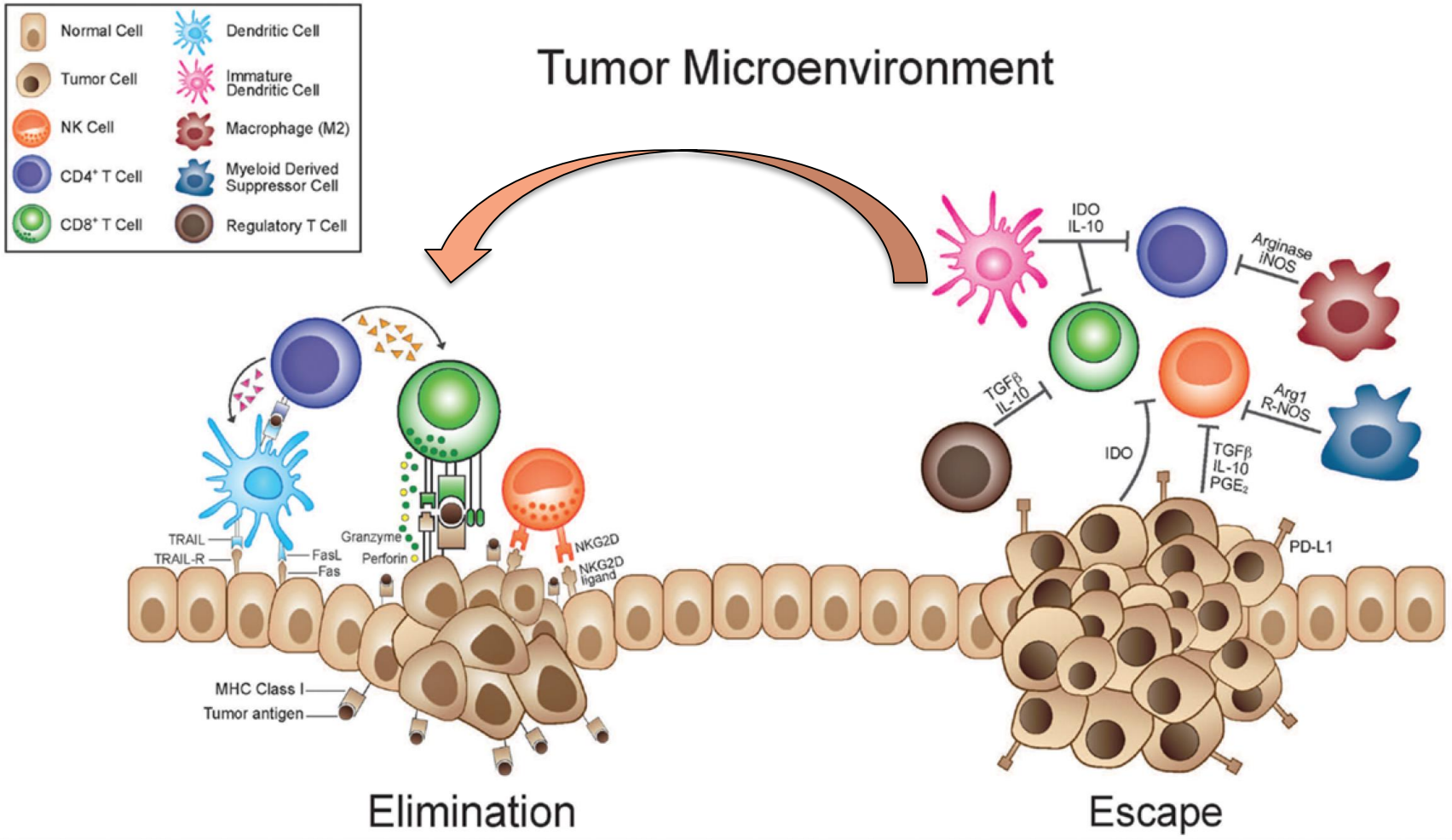
Memorial Sloan Kettering Cancer Center

2 Modify the Immune Suppressive Microenvironment



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

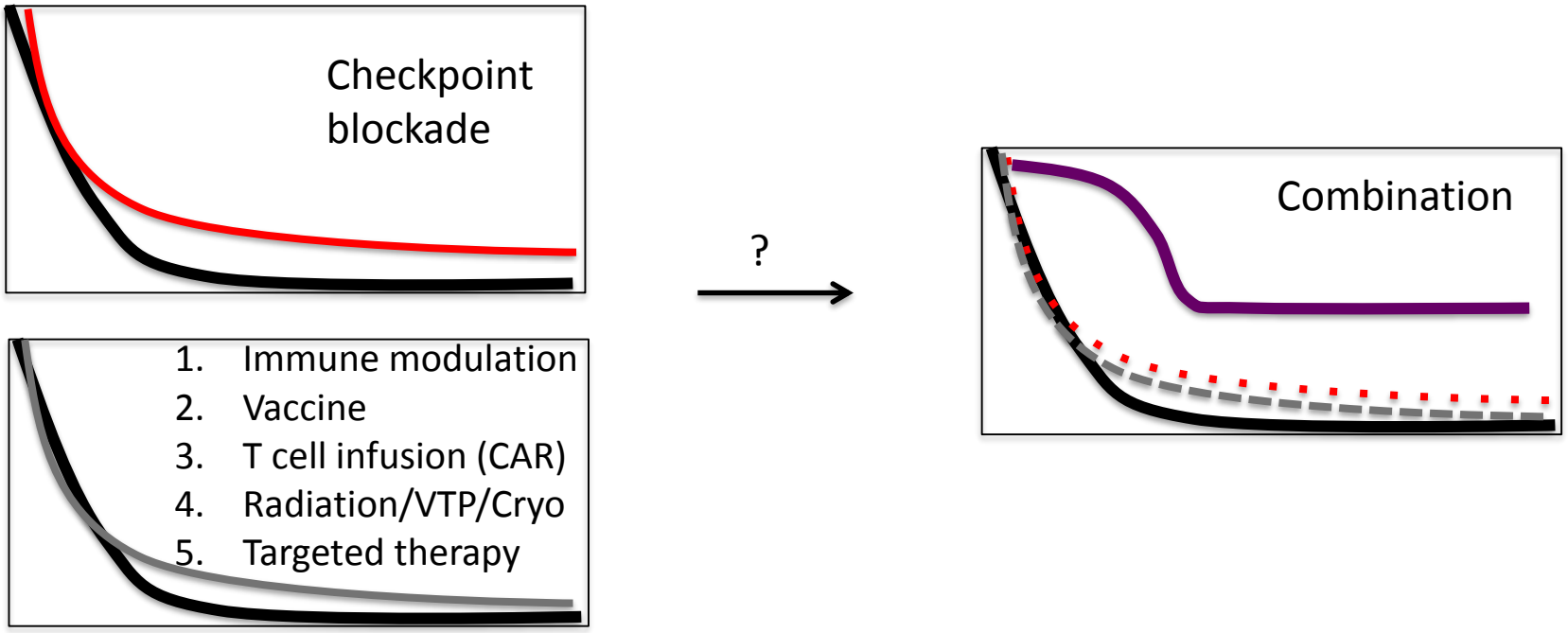
- Reverse immune suppression

- Induce anti-tumor immune response

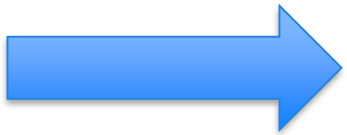
Depends on the immune landscape

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



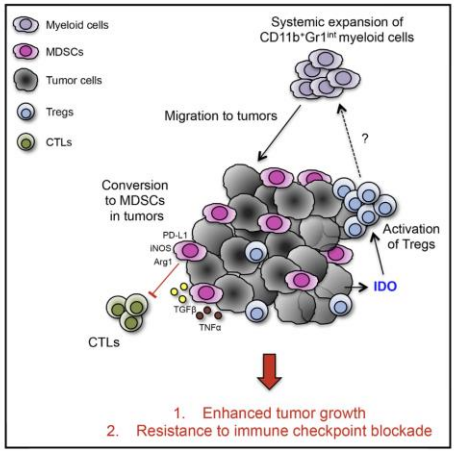
The target cell need to be present

Modify the Immune Suppressive Microenvironment

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 immunother through exp activation of 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 limiting effective tumour immunity[2–4]. Growing evidence suggests

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-macrophage colony-stimulating factor (GM-CSF) help shape the

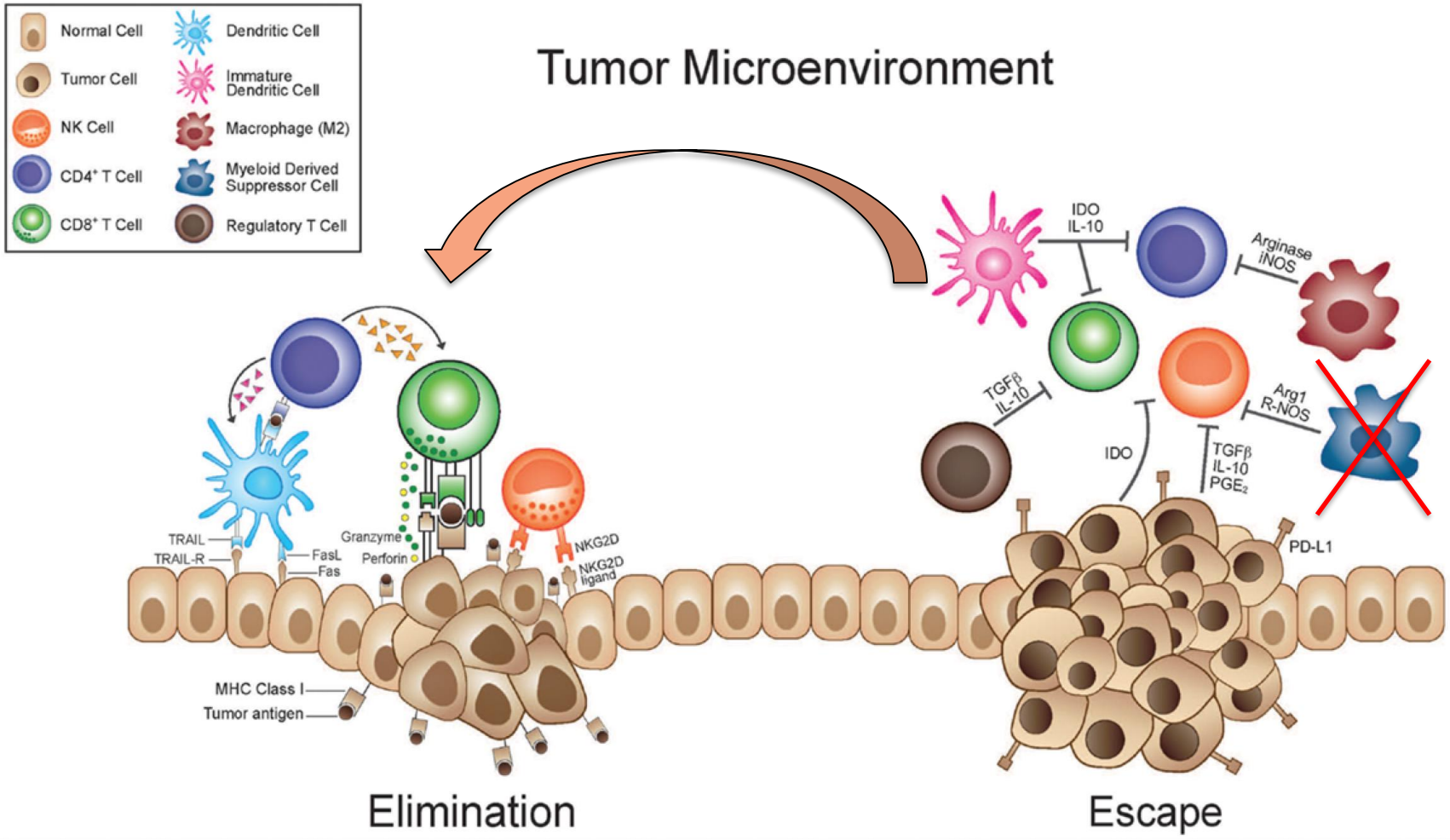
Timing of CSF-1/CSF-1R signaling blockade is critical to improving responses to CTLA-4 based immunotherapy

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

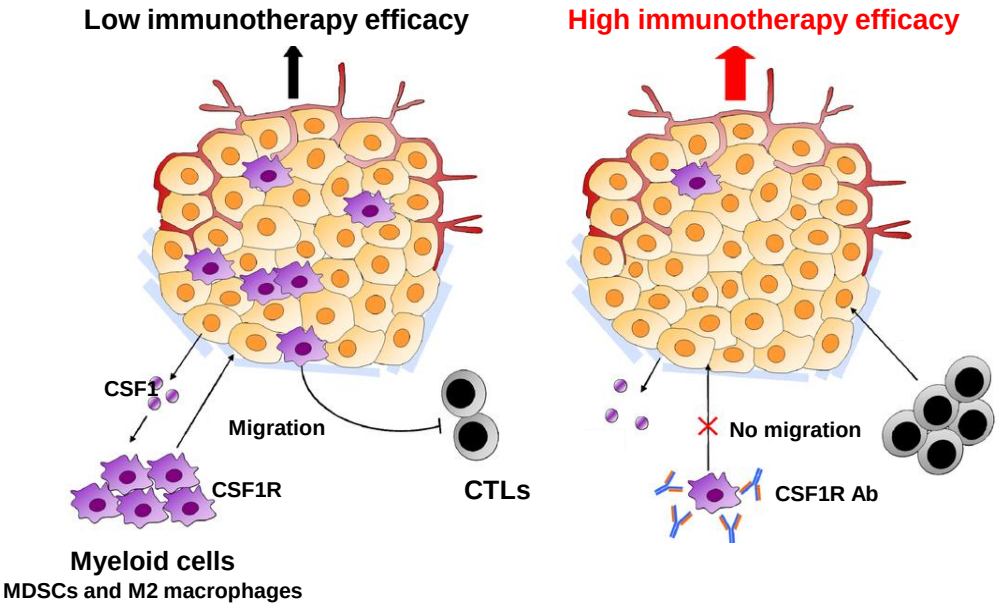
To link to this article: http://dx.doi.org/10.1080/2162402X.2016.1151595

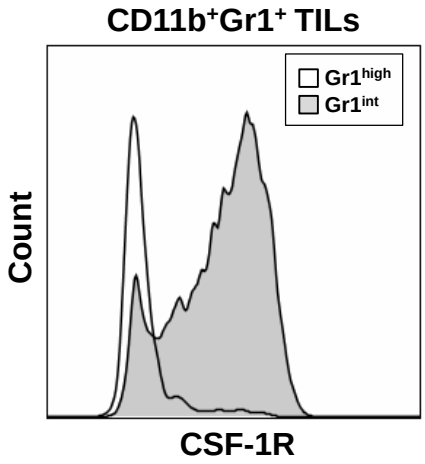
Immune Suppressive Microenvironment



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

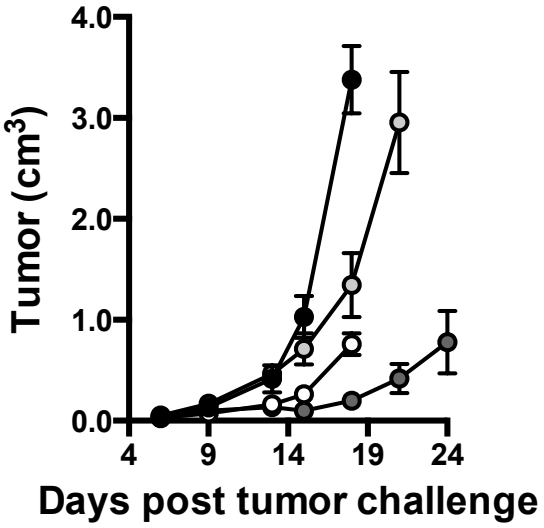
Therapeutic targeting of suppressive MDSCs: Suppressive MDSCs show high expression of CSF-1R

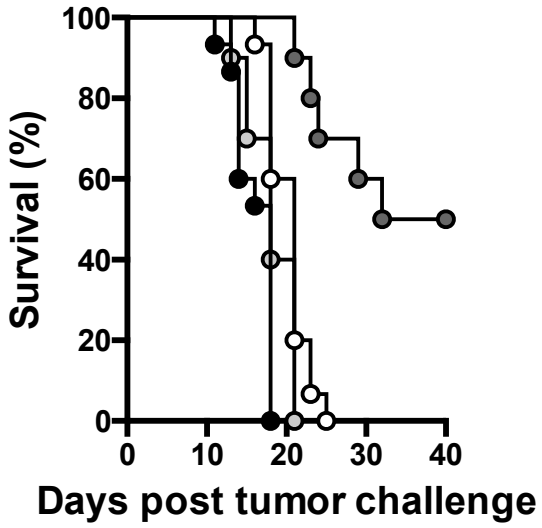


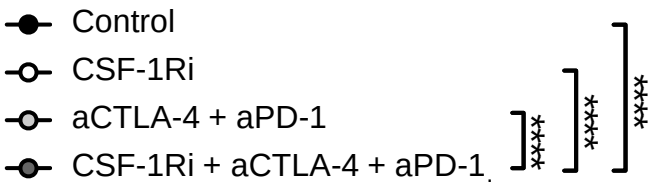


Castells et al. 2012, Int J Mol Sci.

CSF-1Ri potentiates the anti-tumor efficacy of T cell checkpoint immunotherapy







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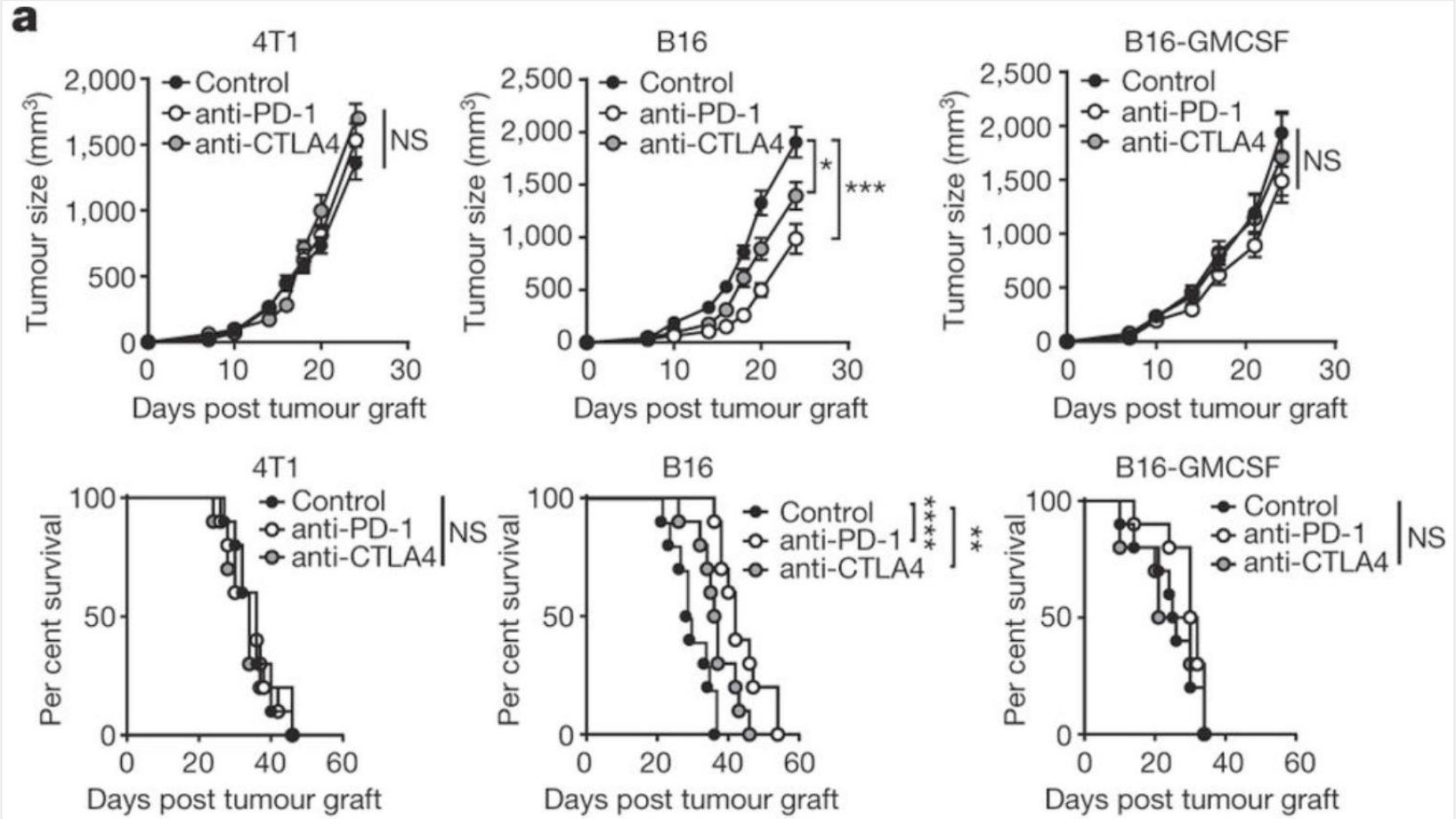
Resistance to checkpoint blockade is associated with suppressive myeloid cells infiltration in tumor microenvironment



Mammary Carcinoma Model
(Rich in myeloid cells)

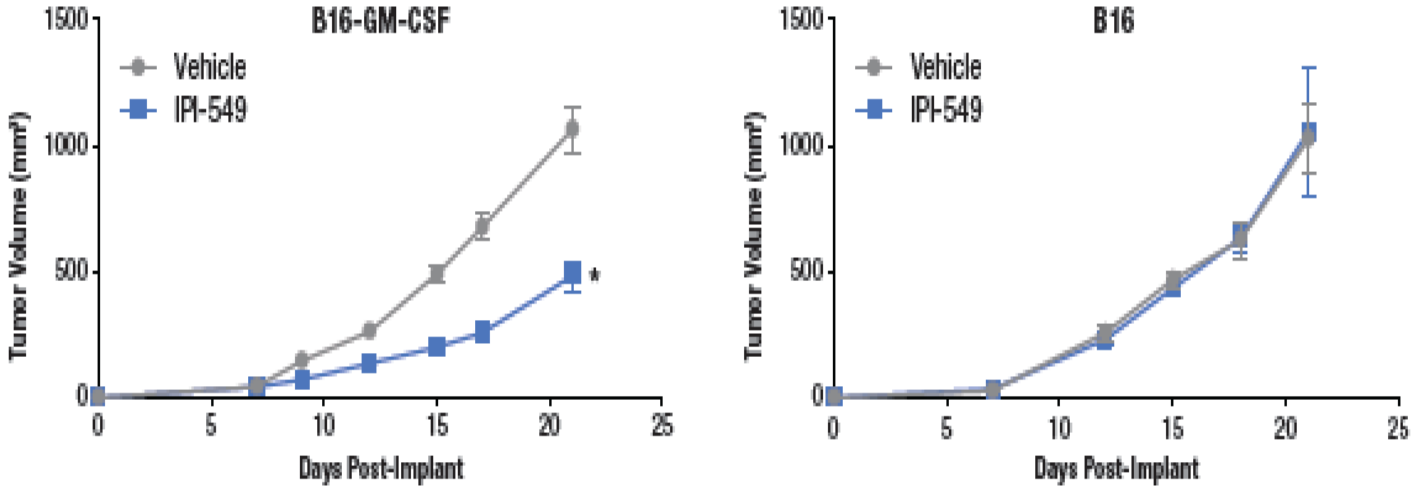
Melanoma Model
(Poor myeloid cells)

Melanoma Model
(Rich in myeloid cells)

O De Henau *et al. Nature* (2016)

Role of Myeloid Cells in IPI-549 Antitumor Activity

IPI-549 is Active in the Myeloid-Cell-Rich Melanoma (B16-GM-CSF) Model



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).

- 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)

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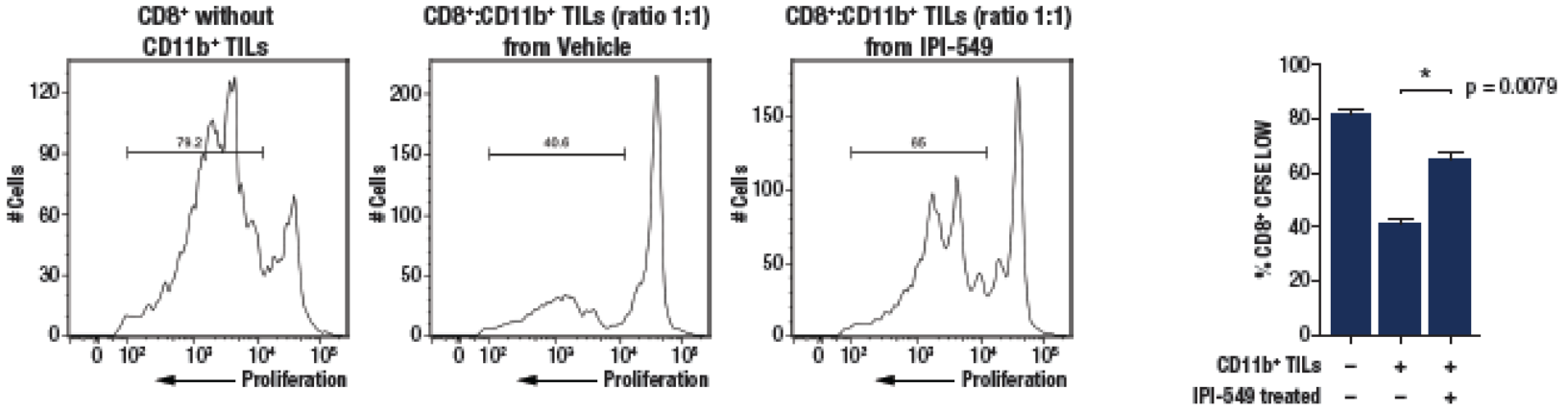
IPI-549 reverses tumor-associated MDSC supression



CD11b+ tumor-infiltrating leukocytes (TILs) were isolated from 4T1 mammary carcinoma tumors from vehicle- or IPI-549-treated (15 mg/kg orally, daily) animals. CD8+ T cells, isolated from spleens of naïve animals and preloaded with carboxyfluorescein succinimidyl ester (CFSE) dye, were activated with coated CD3/CD28; proliferation was measured 48 hours after incubation ± CD11b+ TILs at a 1:1 ratio.

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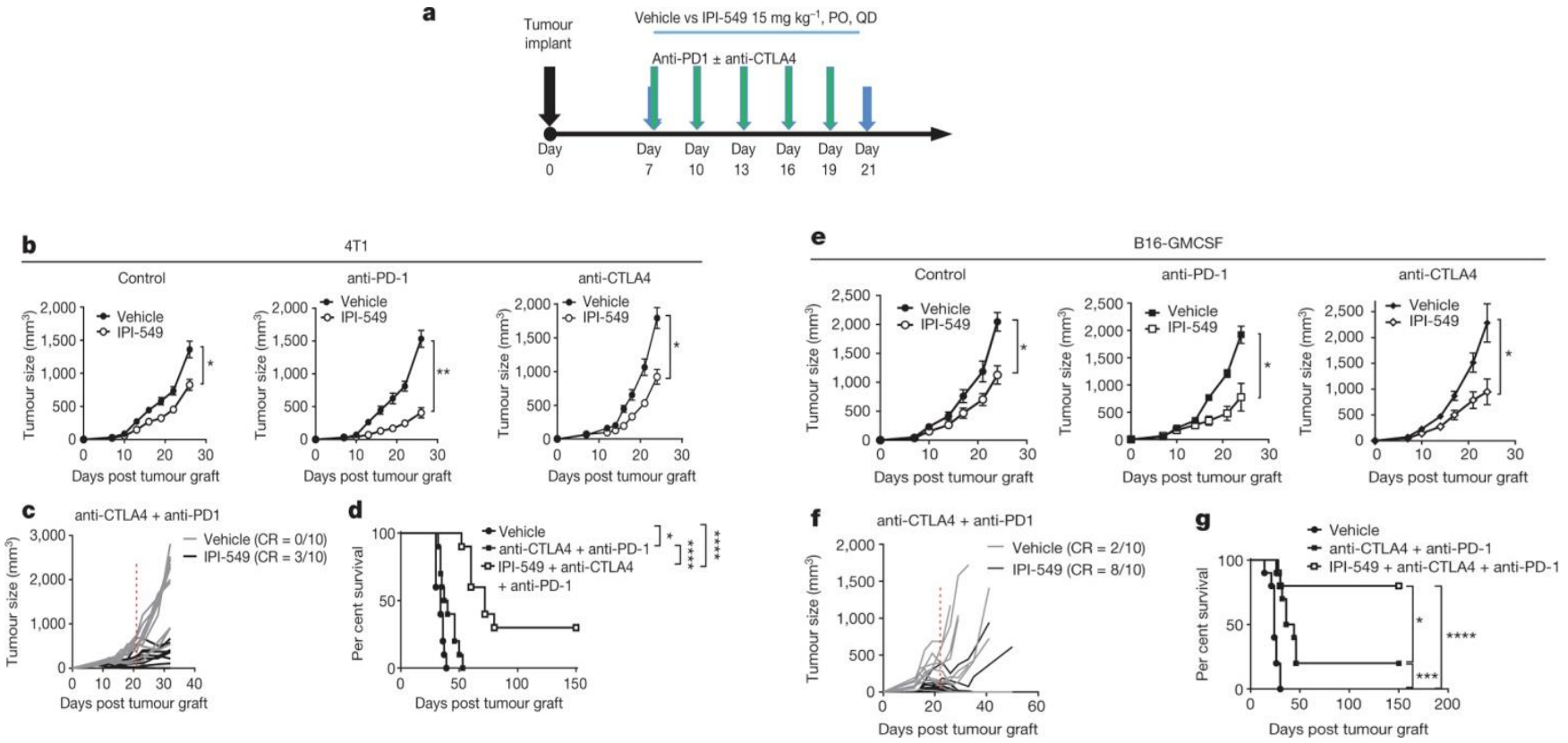
Resistance to checkpoint blockade therapy is overcome when combined with selective PI3Kγ inhibition



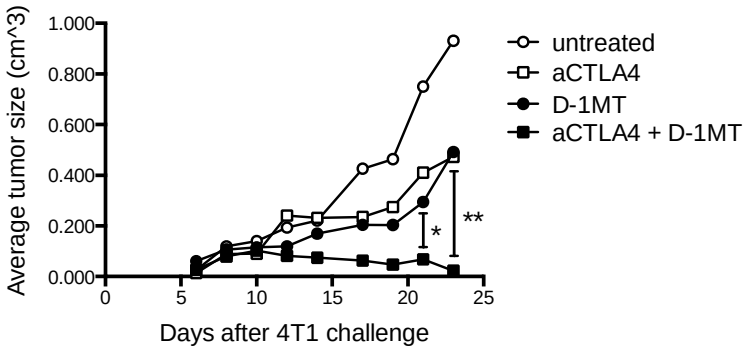
Mammary Carcinoma Model

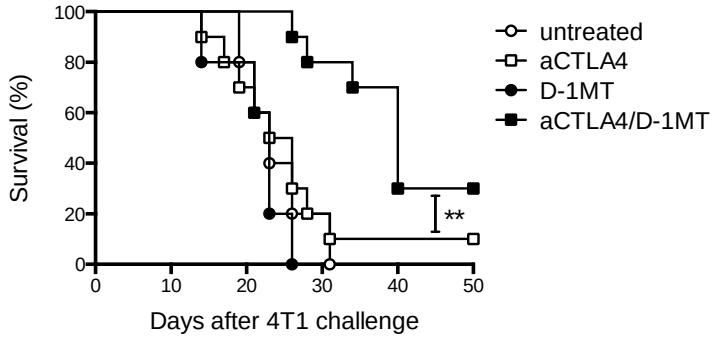
Melanoma Model

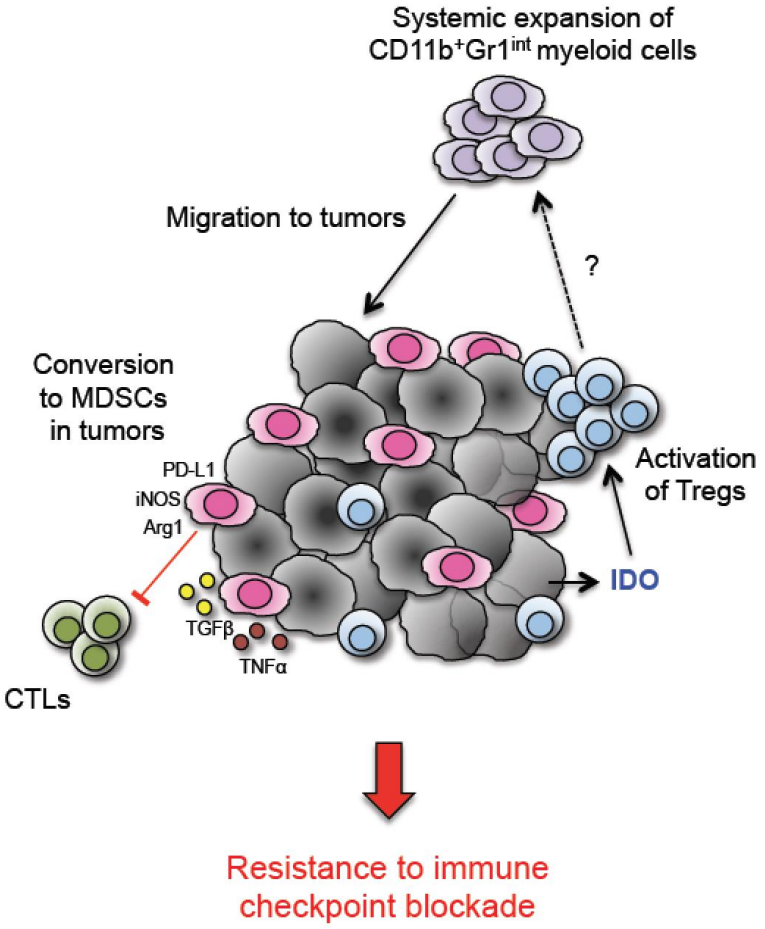
O De Henau *et al. Nature* 1–4 (2016) doi:10.1038/nature20554

Blocking Suppressive Mechanisms

MDSCs Inhibition (CSF1R blockade, PI3 Kinase.....)
IDO inhibition







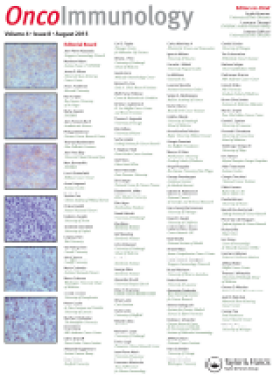
Anti-CTLA4/1MT induces regression of established 4T1 breast tumors

Hoolmgard et al, Cell Report,2015

Memorial Sloan Kettering Cancer Center

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

To link to this article: http://dx.doi.org/10.1080/2162402X.2016.1151595

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

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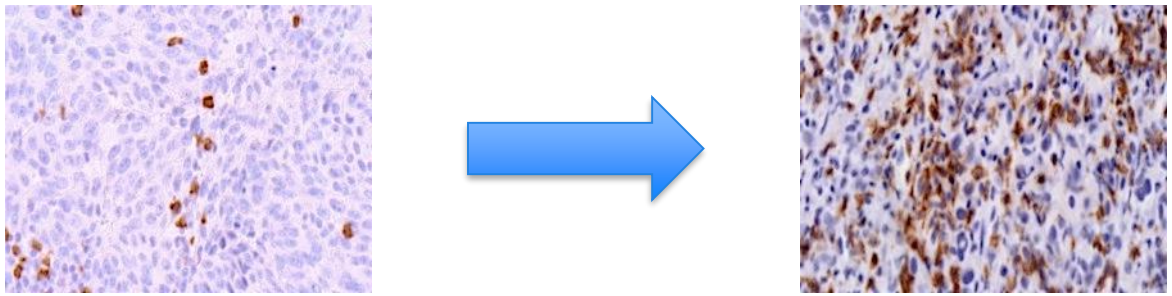
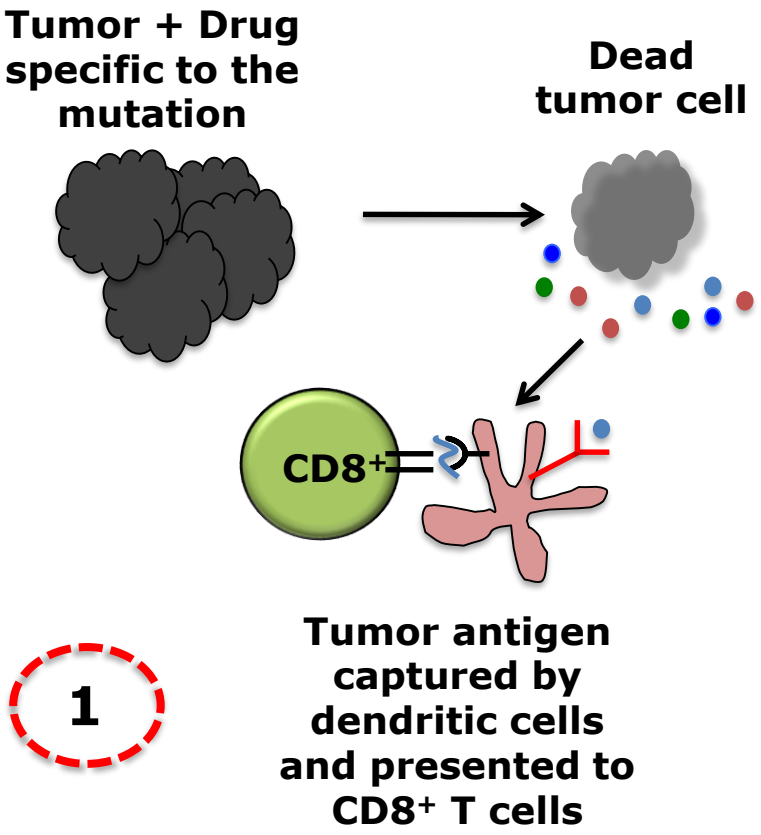
Approach:
Induce Tumor Antigen Response

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

Increase the Number of Immune Infiltrating Immune Cells



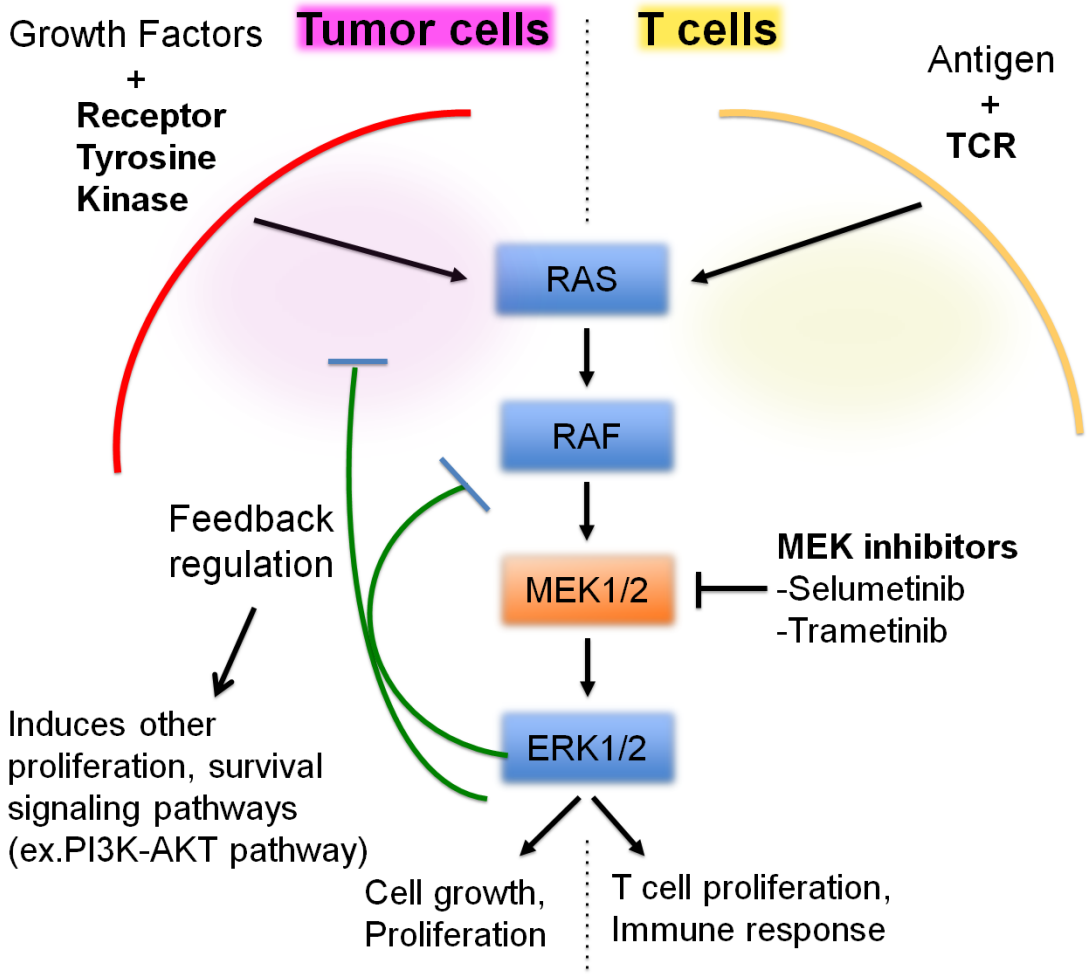
Targeting tumor cells should induce a tumor-specific immune response



+ Alteration of the host immune system

2

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

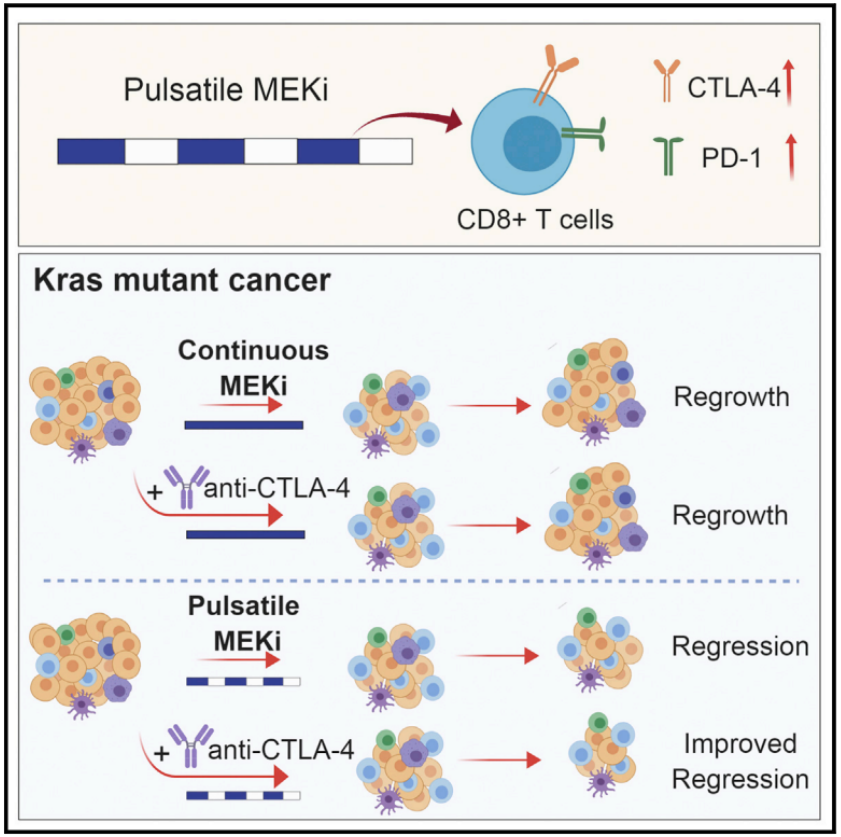


Article

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

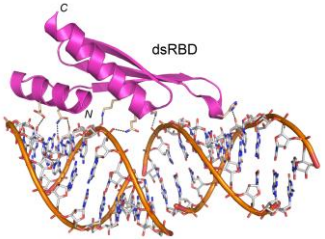
merghout@mskcc.org (T.M.), kwok-kin.wong@nyumc.org (K.-K.W.), wolchokj@mskcc.org (J.D.W.)

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.

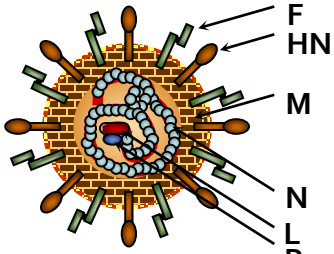
Induction of antitumor immunity with oncolytic viruses : ΔE3L vaccinia virus or Newcastle disease virus (NDV)

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

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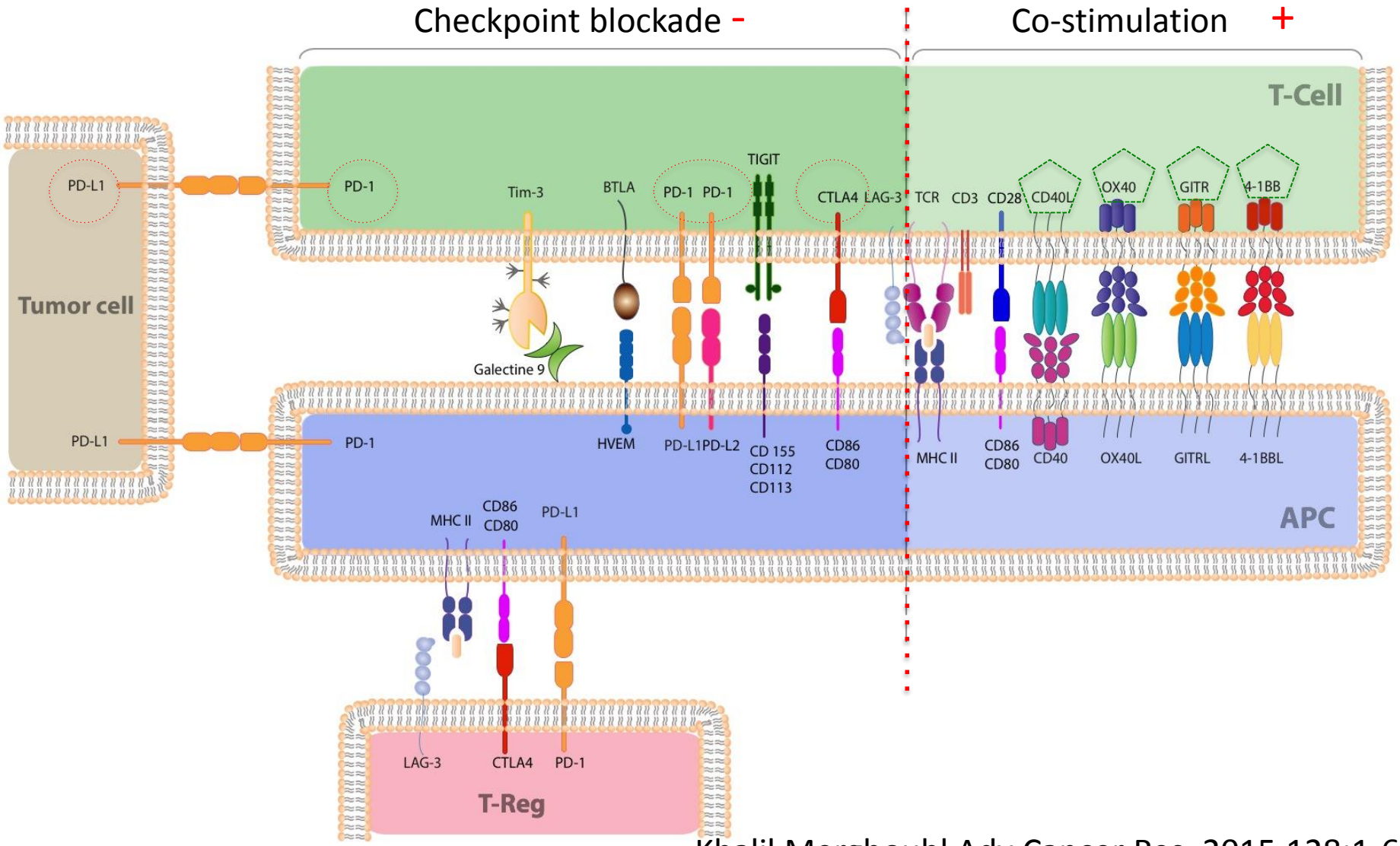
Cancer Center

Approach:

Combining Other immune modulatory antibodies

Alter Host Immune System:
Rationale Combination with Immune modulation



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

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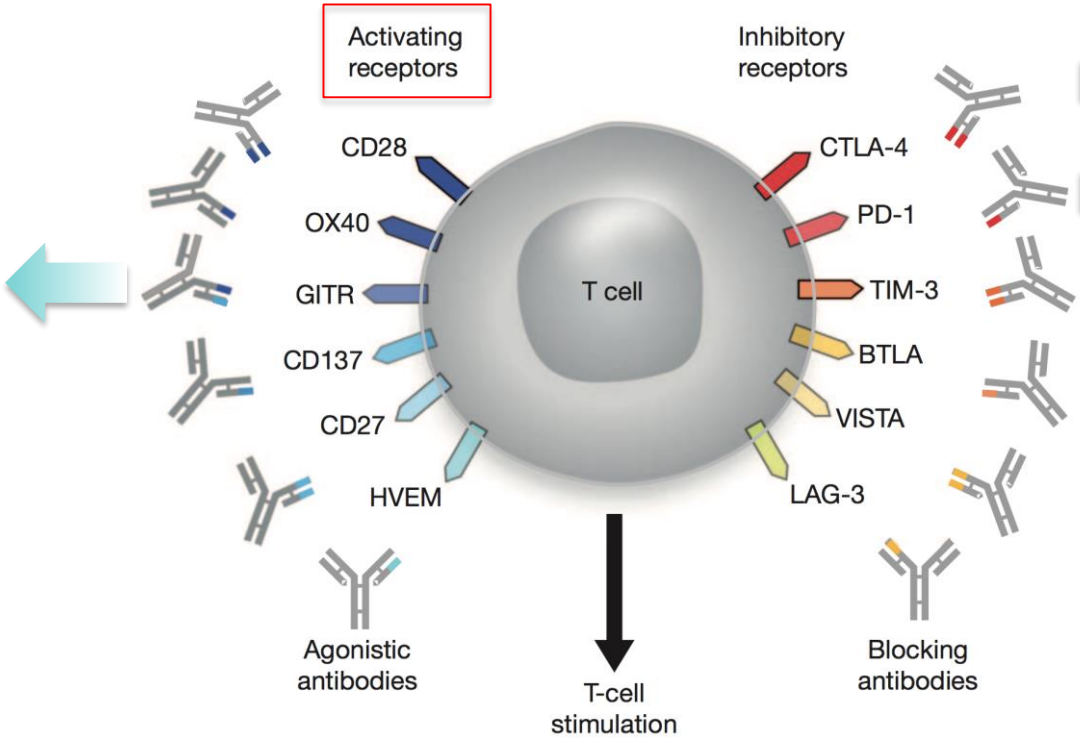
Approach:

Combining Other immune modulatory antibodies beyond checkpoint blockade

Maslow's hierarchy of needs

Immunomodulatory Abs for cancer therapy: beyond immune checkpoint blockade

Clinical development

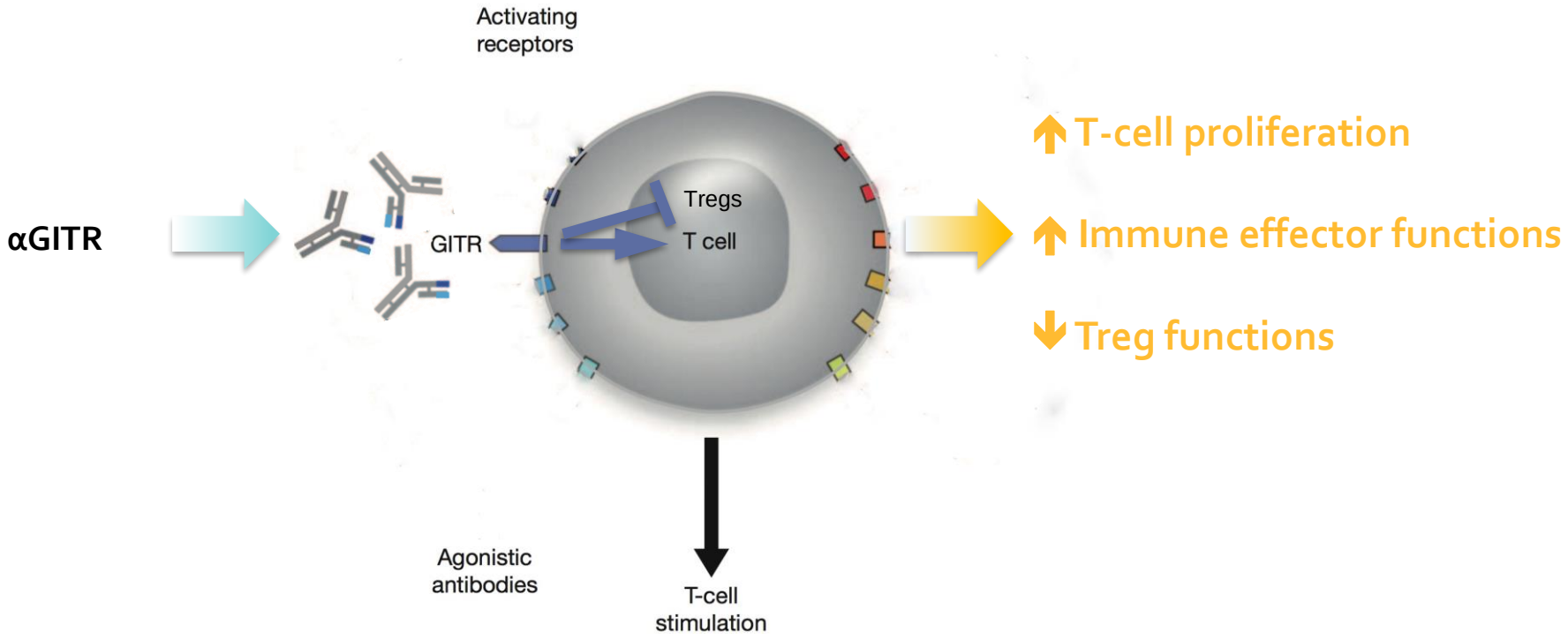


Clinical benefit, FDA approved

Clinical benefit, FDA approved

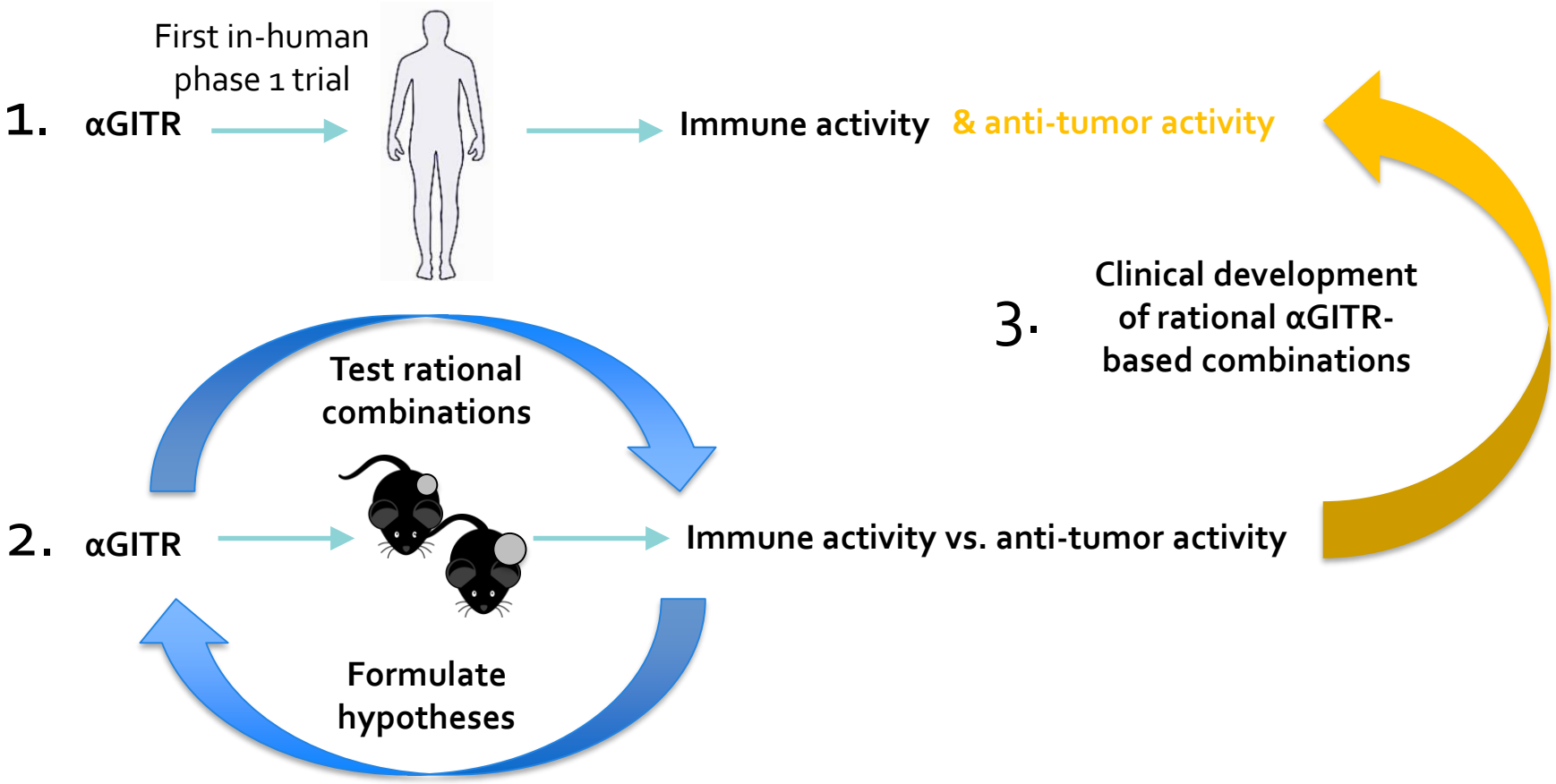
Adapted from Mellman, Nature 2011

Immunomodulatory Abs for cancer therapy: beyond immune checkpoint blockade



Adapted from Mellman, Nature 2011

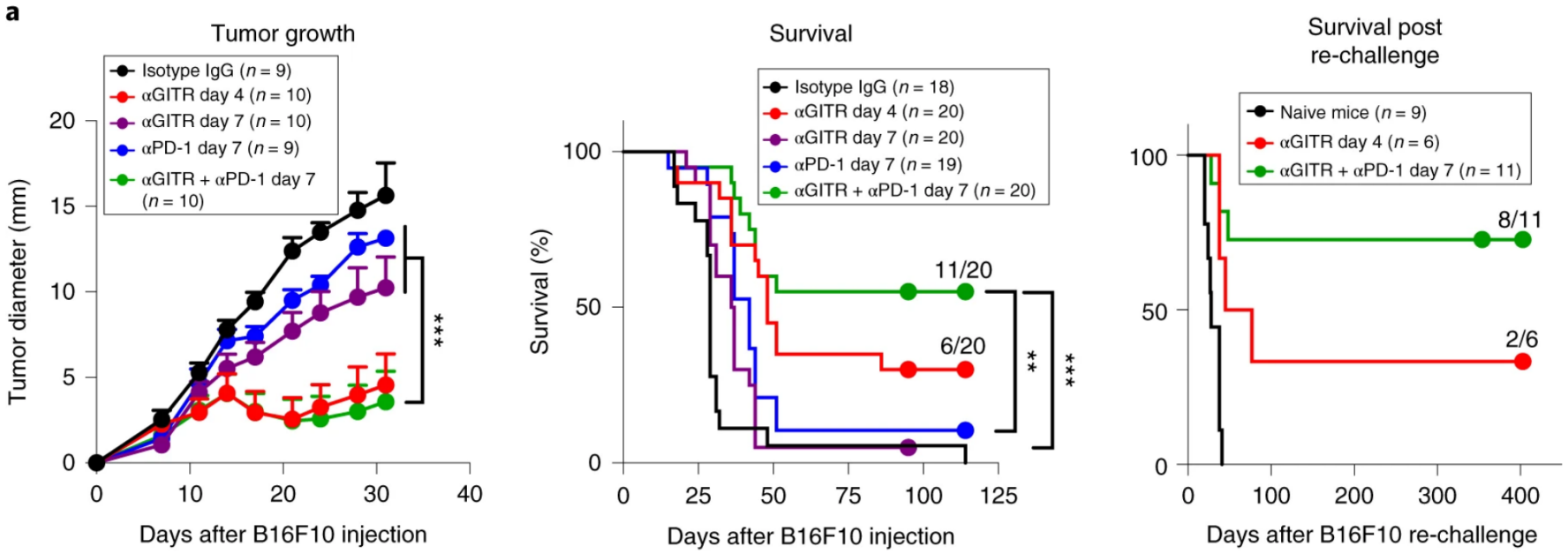
Study Design



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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Approach:

Combining Other immune modulatory antibodies beyond checkpoint blockade

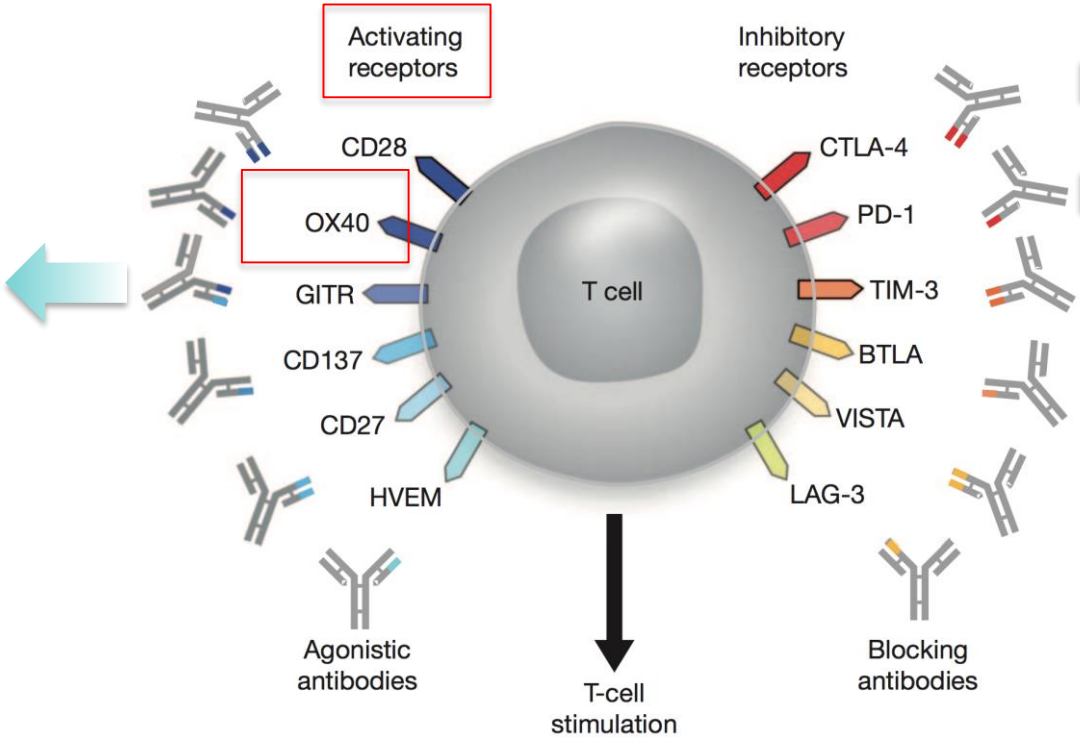
Is is all T cell dependent?

"I suppose it is tempting, if the only tool you have is a **hammer**, to treat **everything** as if it were a **nail**."

Maslow's hierarchy of needs

Immunomodulatory Abs for cancer therapy: beyond immune checkpoint blockade

Clinical development

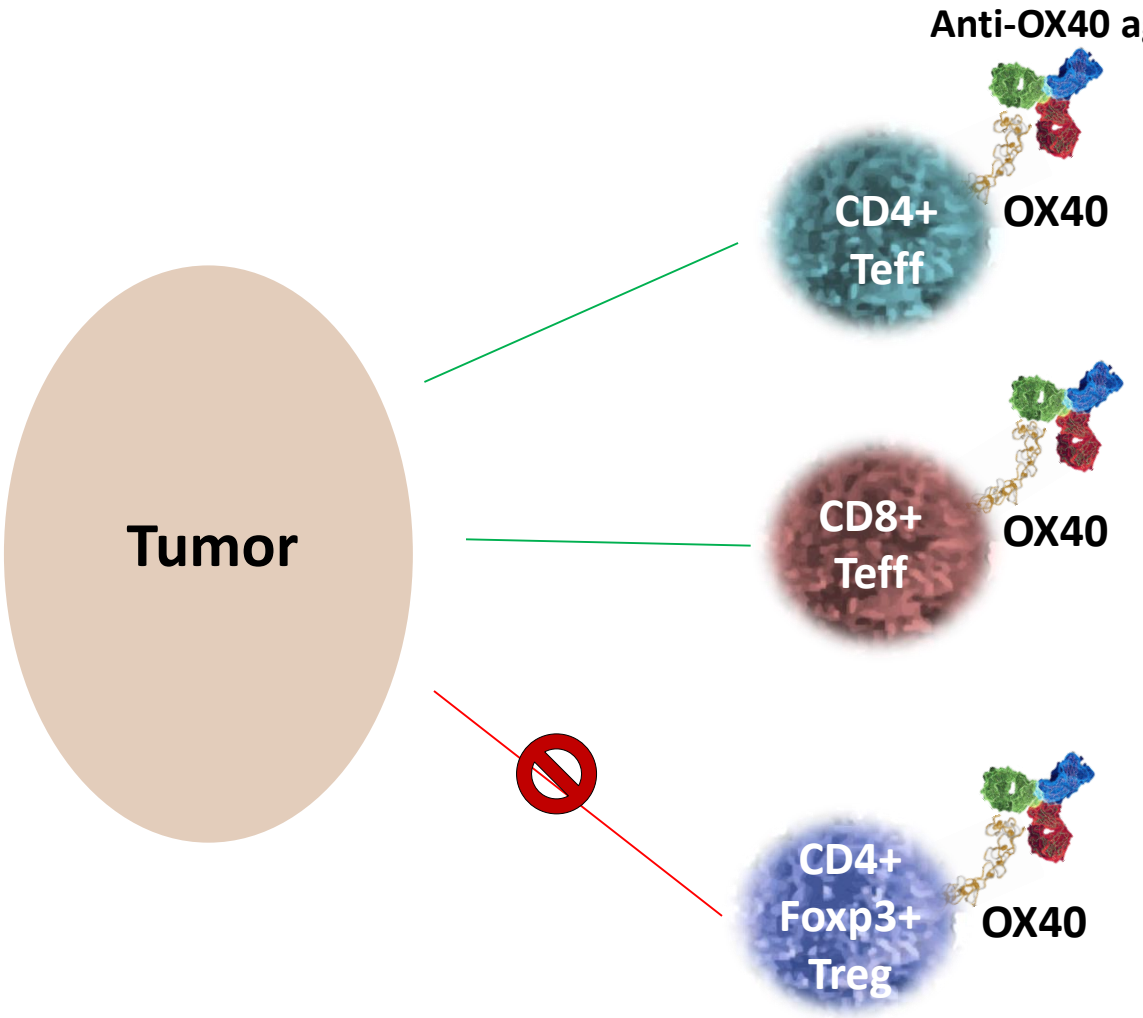


Clinical benefit, FDA approved

Clinical benefit, FDA approved

Adapted from Mellman, Nature 2011

OX40 engagement as an effective tumor immunotherapy



- Increase proliferation
- Clonal expansion
- Increase cytokine production
- Promote memory

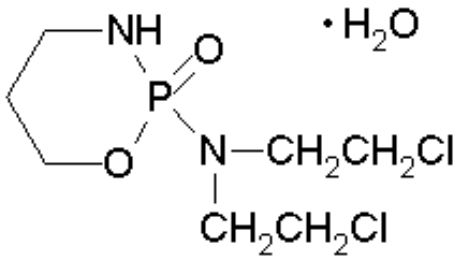
- Increase proliferation
- Clonal expansion
- Increase cytokine production
- Promote memory
- Reverse anergy

- Deactivate suppressive function
- Eliminate by AICD
- Eliminate through Fc receptors

OX40 engagement as a monotherapy ineffective treating established poorly immunogenic tumors such as B16 melanoma

Cyclophosphamide (CTX) as an adjuvant

Common chemotherapeutic with direct anti-tumor effects



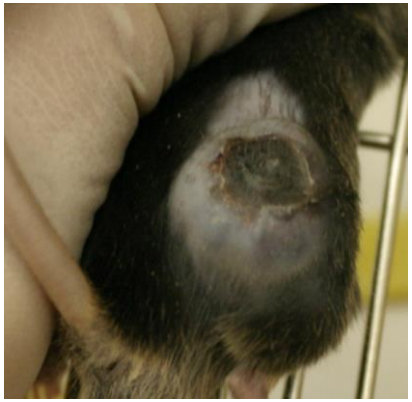
Immunologic properties of CTX:

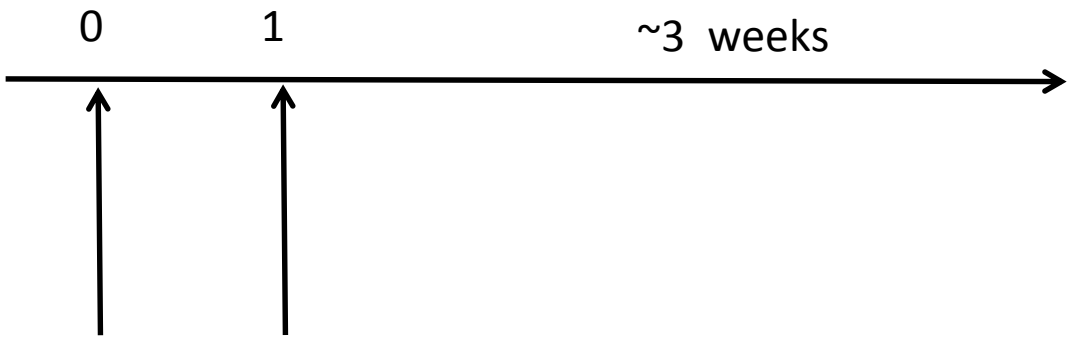
- Causes immunogenic cell death releasing tumor antigens and TLR agonists
- Homeostatic proliferation can expand tumor reactive T cells
- Depletes and functionally inhibits CD4+ Foxp3+ Tregs

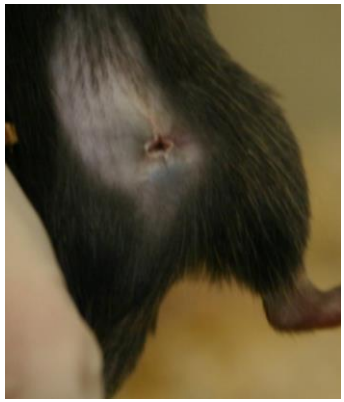
Ercolini. *JEM* 2005; Green. *Nat Rev Immunol* 2009; Zitvogel. *JCI* 2008; Lutsiak. *Blood* 2005

Melanoma-specific CD4+ T cells significantly enhances the potency of anti-OX40 Ab

21 day B16 tumor







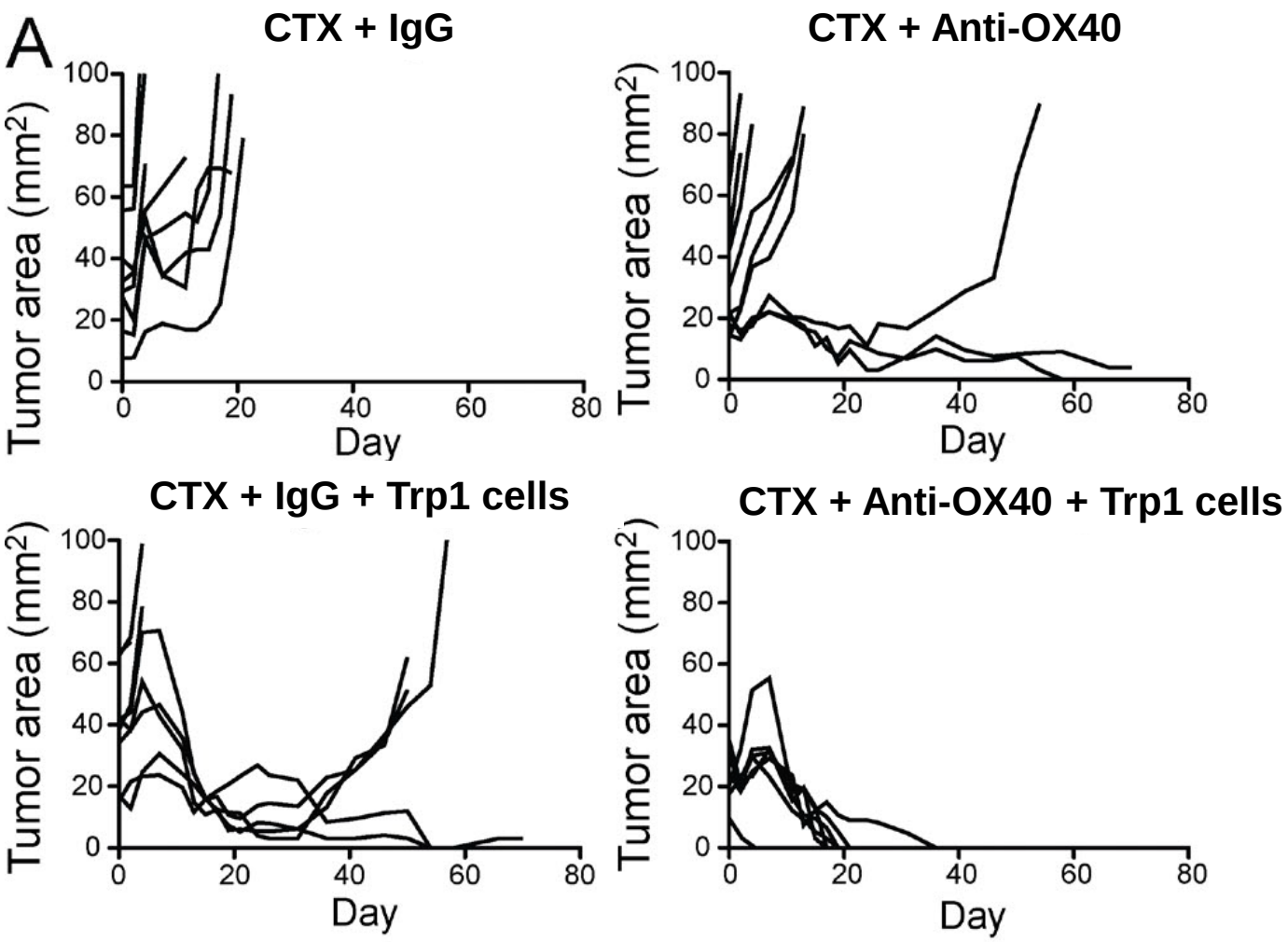
Cyclophosphamide (CTX)

Anti-OX40 + Trp1 CD4+ T cells (Melanoma antigen specific T cells)

Trp1 CD4+ T cells are purified from a TCR transgenic mouse (Muranski, *Blood*)

Hirschhorn-Cymerman, *JEM*, 2012

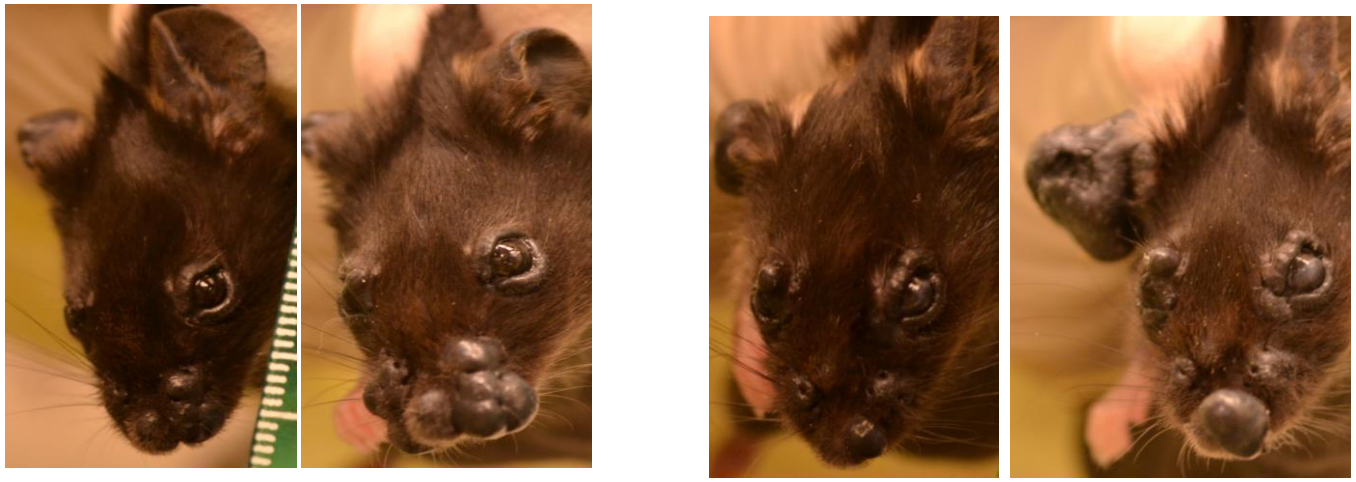
Melanoma-specific CD4+ T cells significantly enhances the potency of CTX + Anti-OX40 combination therapy



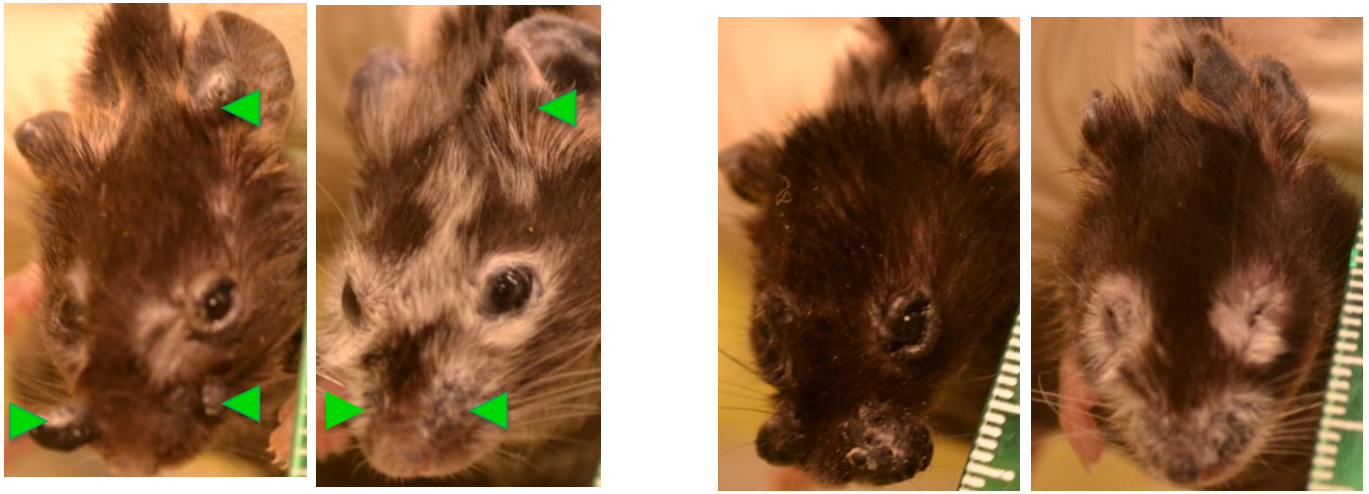
Hirschhorn-Cymerman. JEM 2012

Triple combination therapy eradicate large established tumors: Spontaneous melanoma model (TG3)

Day 0 43 0 43



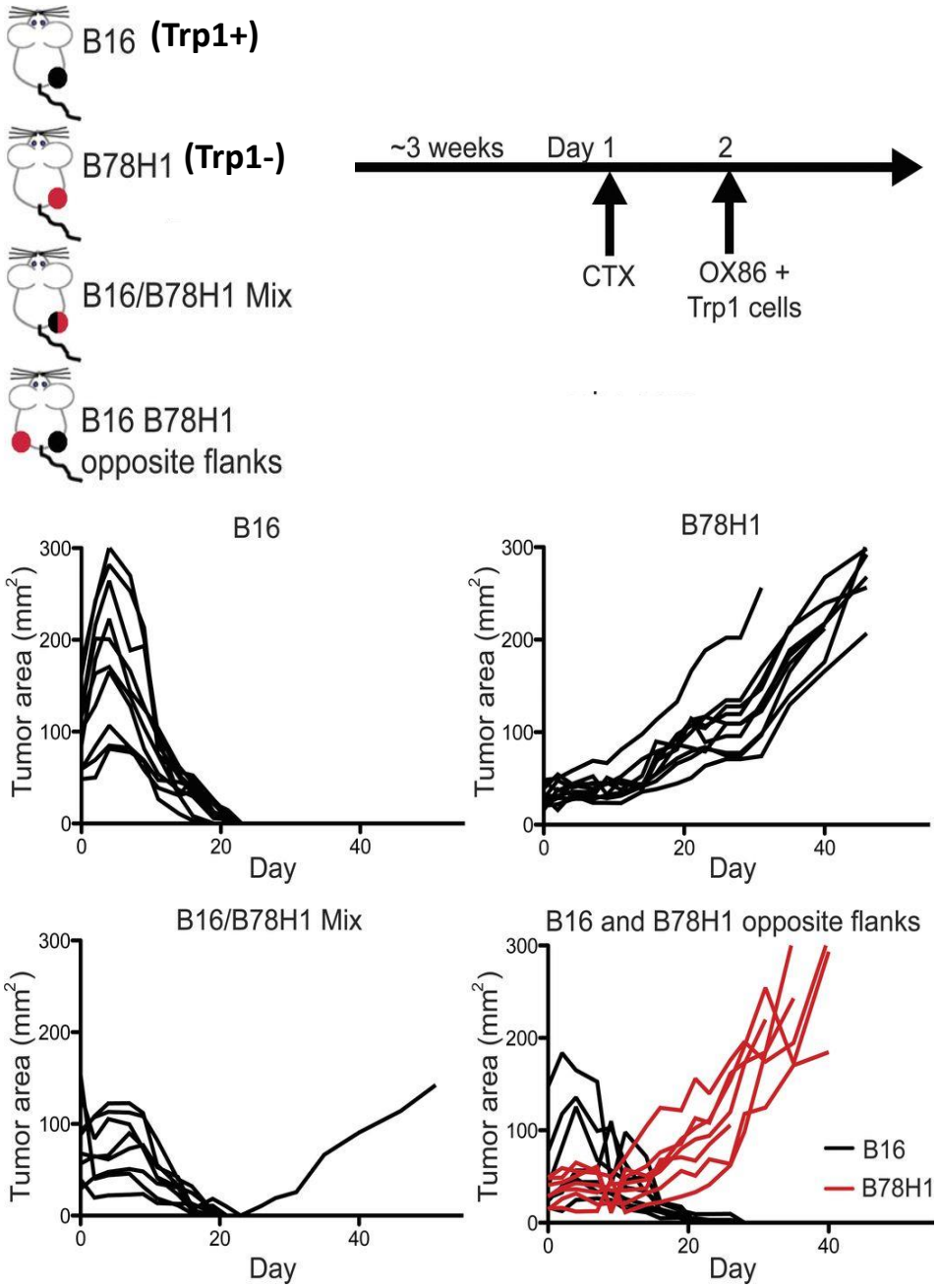
Untreated



Combination therapy

Suzie Chen

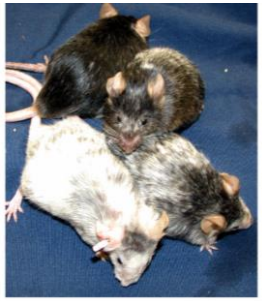
Triple combination therapy promotes bystander tumour killing of antigen loss variants



Hirschhorn-Cymerman, *JEM*, 2012

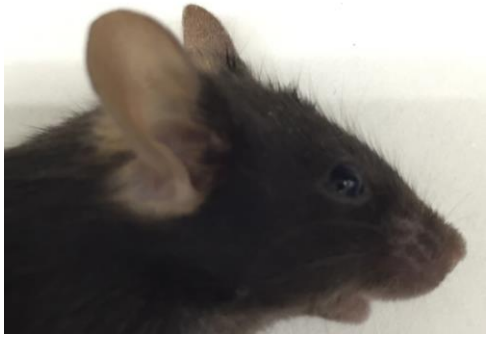
B78H1 is a B16 variant that does NOT express Trp1

Unusual immune-related adverse events of the combination therapy

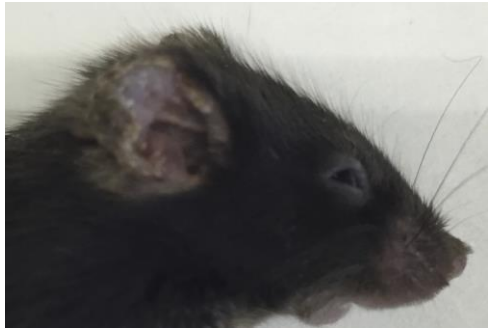


Autoimmune depigmentation is typical of anti-melanoma immune therapies

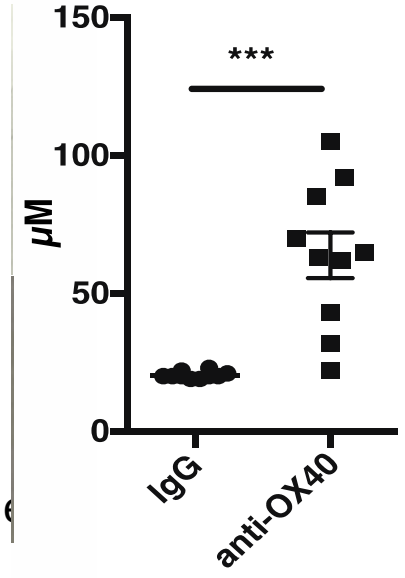
CTX + IgG + Trp1 cells



CTX + anti-OX40 + Trp1 cells

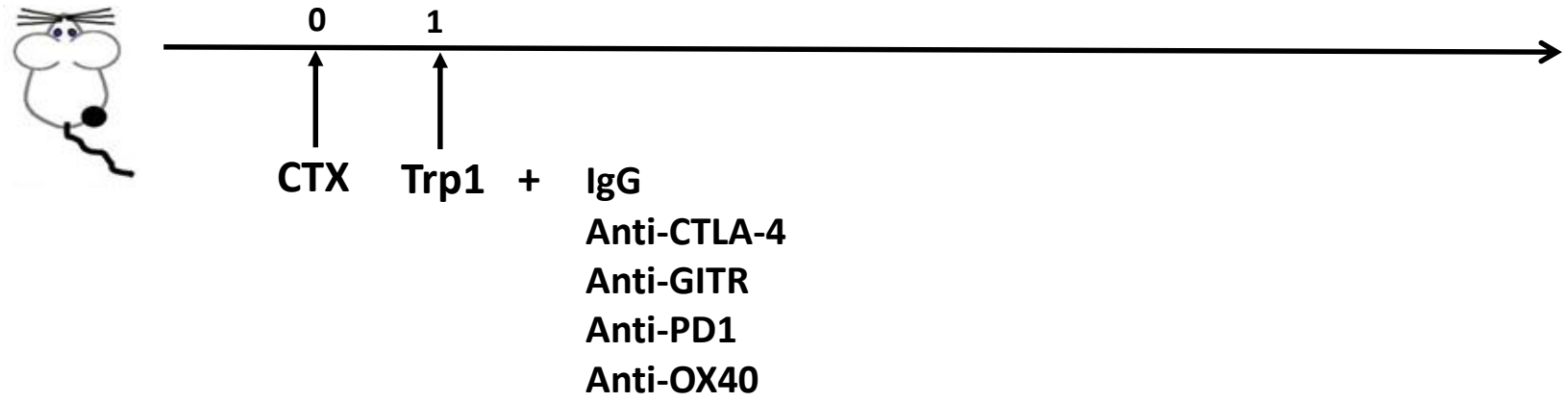


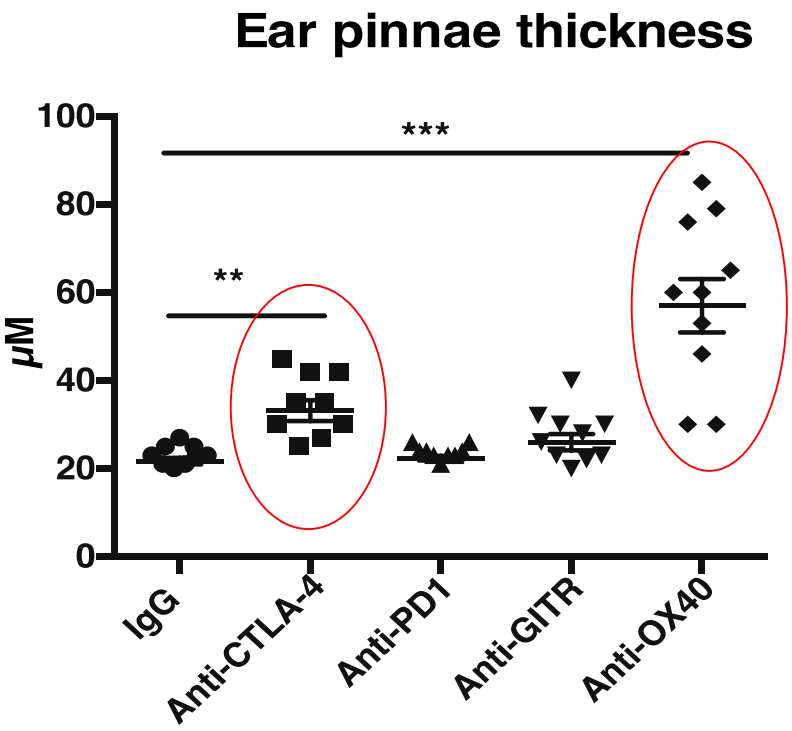
Ear pinnae thickness

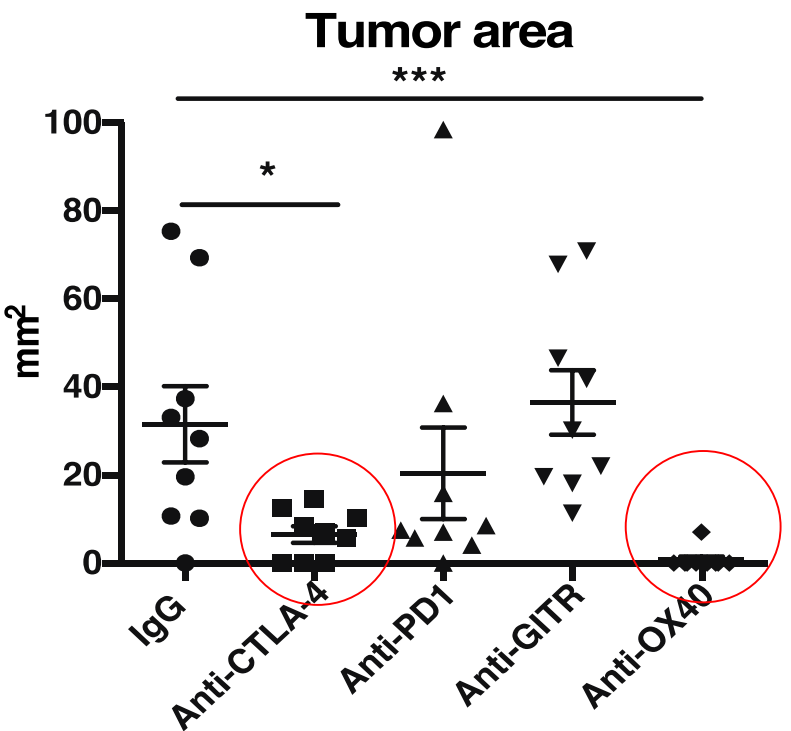


Swelling and destruction of tissues infiltrated with melanocytes such as the ears, tail, and snout (non hairy skin) ~ **3 weeks** after treatment

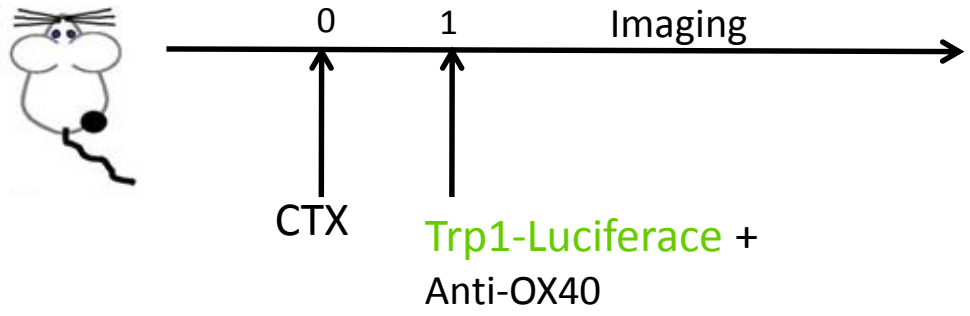
Inverse correlation of irAE and anti-tumor immunity suggest an equivalent underlying mechanism

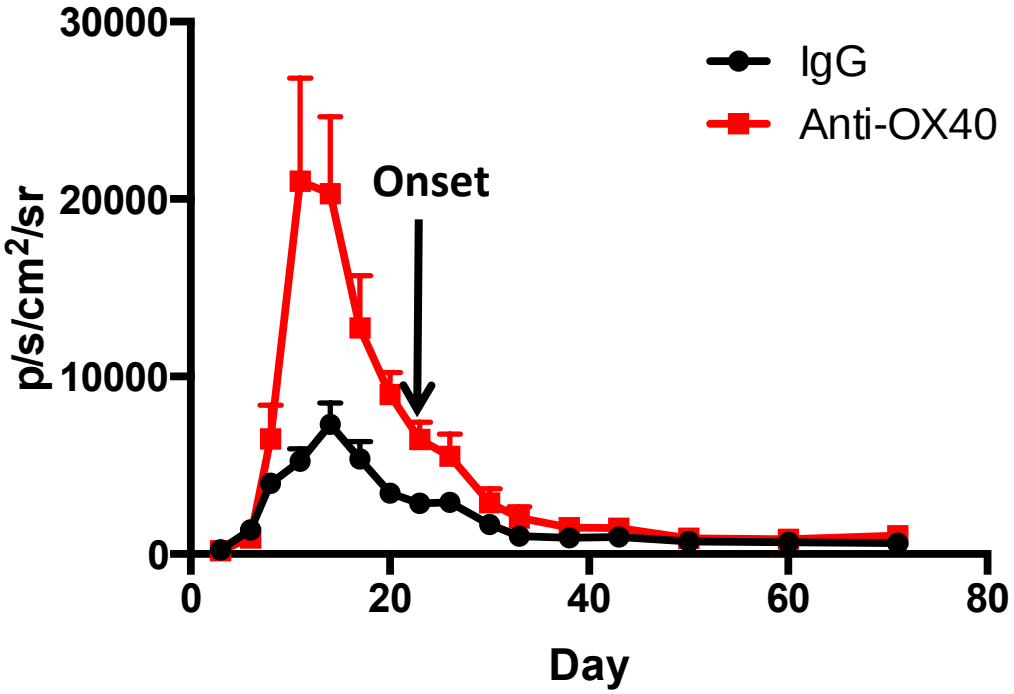


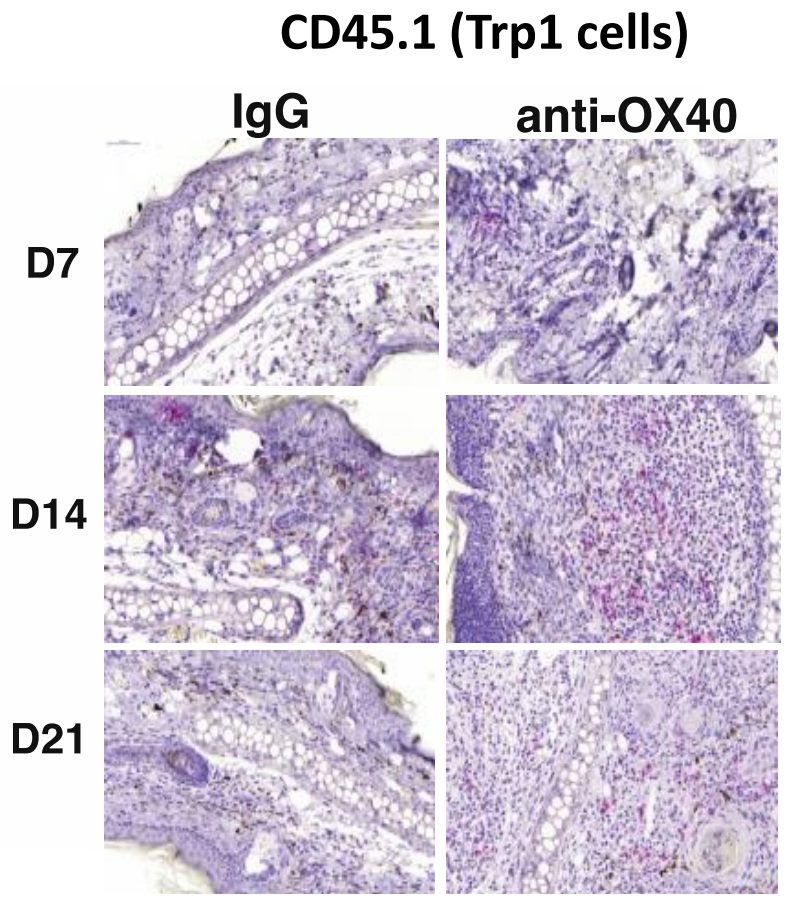




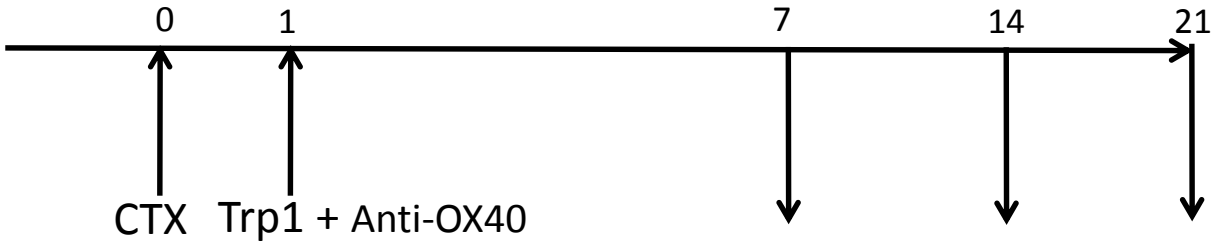
Trp1 cell infiltration does not correlate with ear pinnae inflammation onset





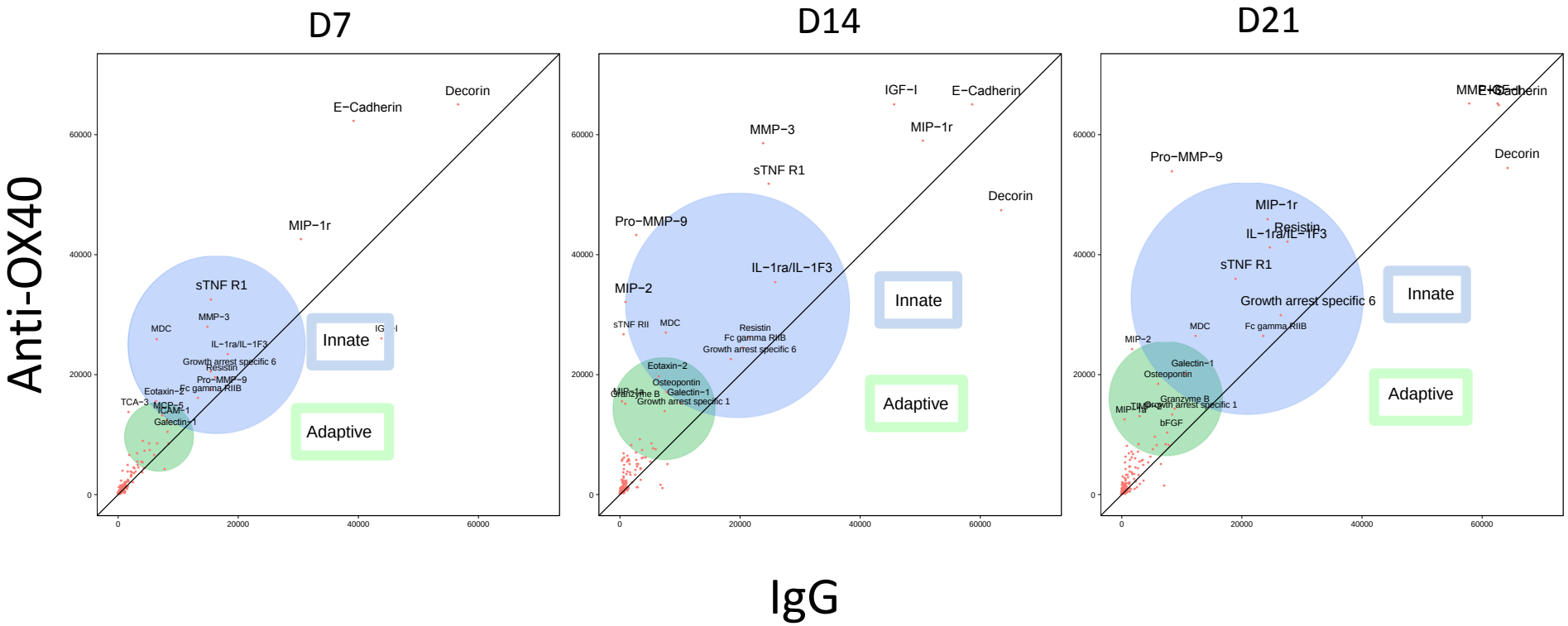


Protein extracts from ear pinnae of treated mice reveal a progressive innate immunity signature



B16

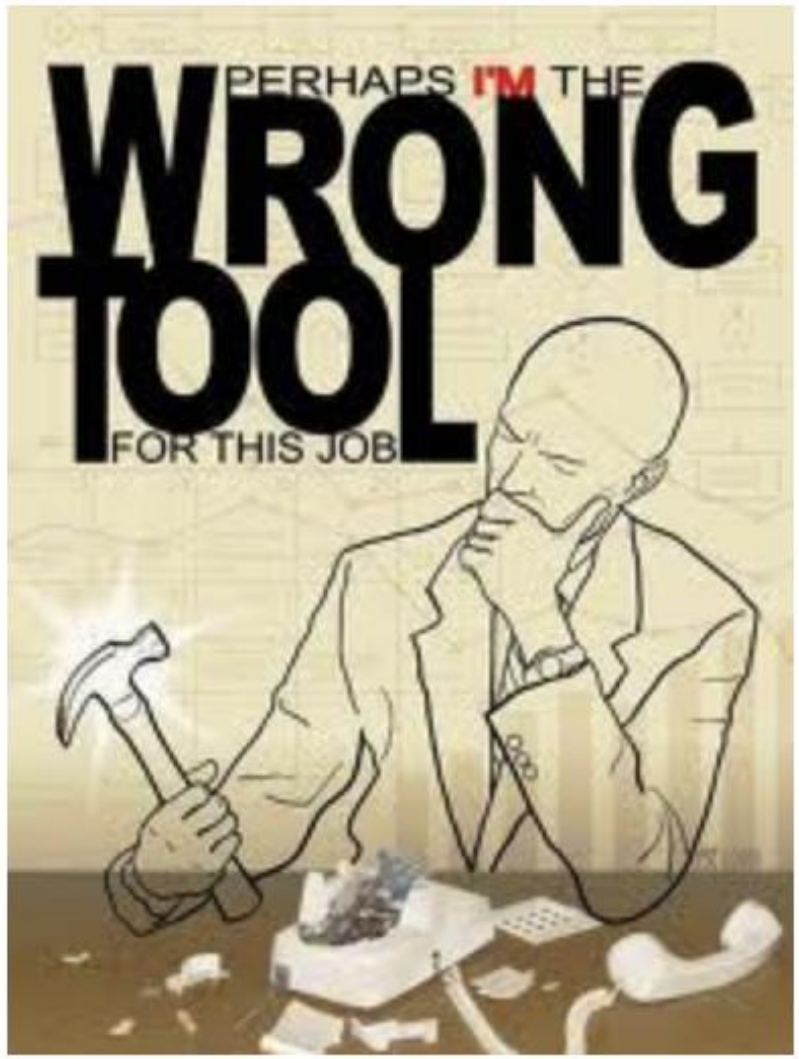
Protein extracts from ear pinnae
144 cytokine/chemokine array



Protein extracts from ear pinnae of treated mice reveal a progressive innate immunity signature

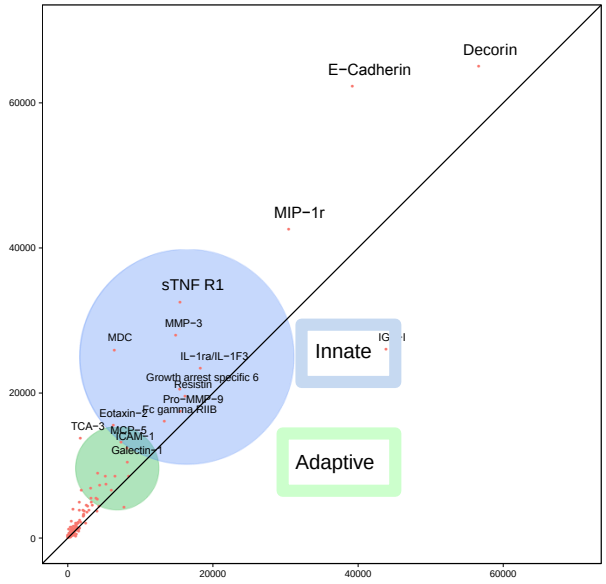
nae

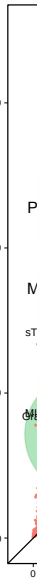
ay

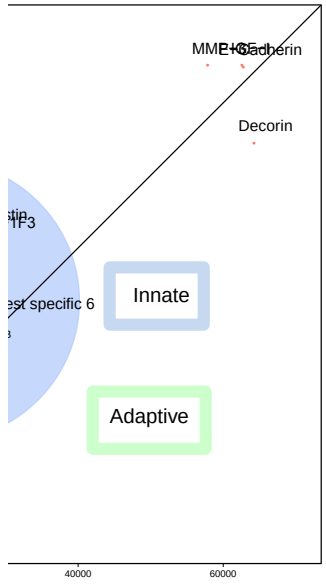


D7

Anti-OX40

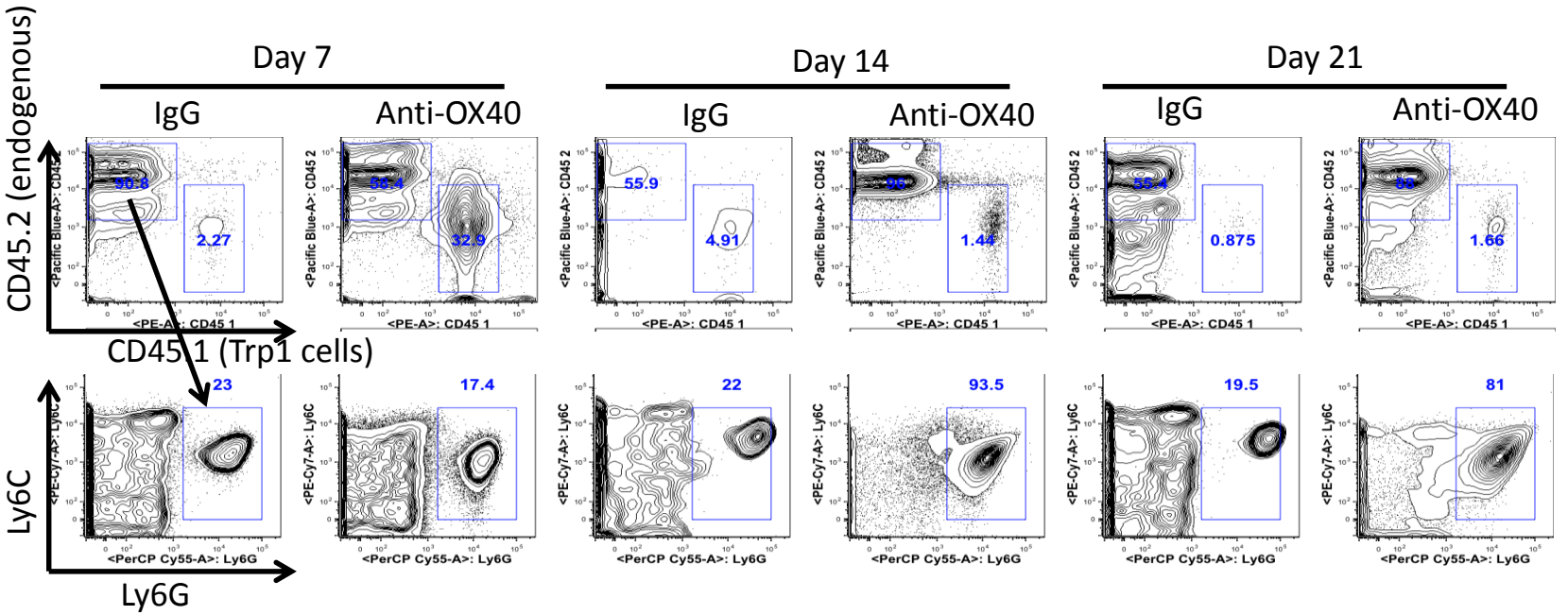




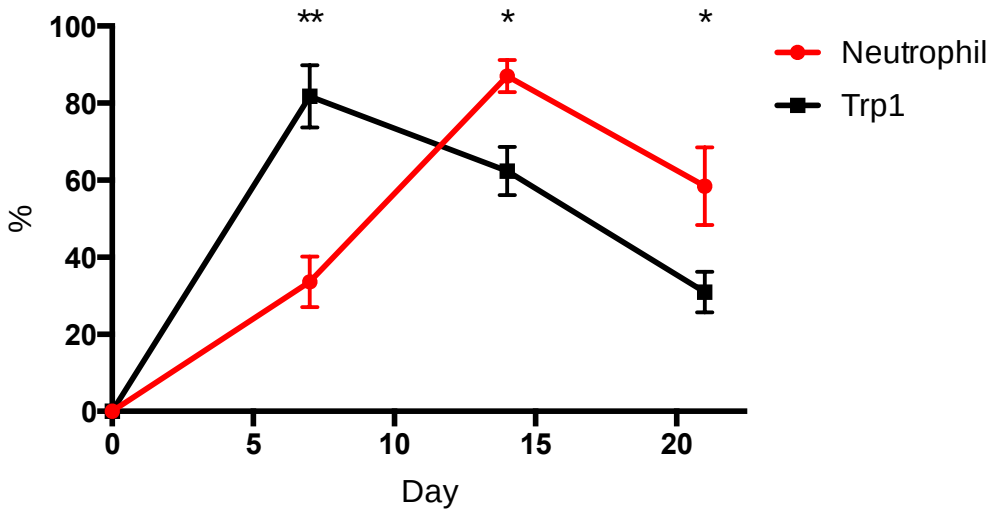


IgG

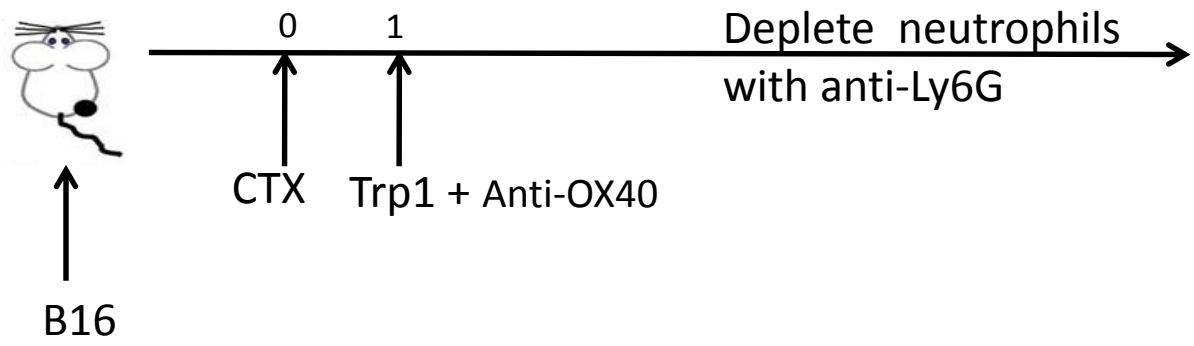
Neutrophil infiltration in the ear pinnae followed Trp1 cells

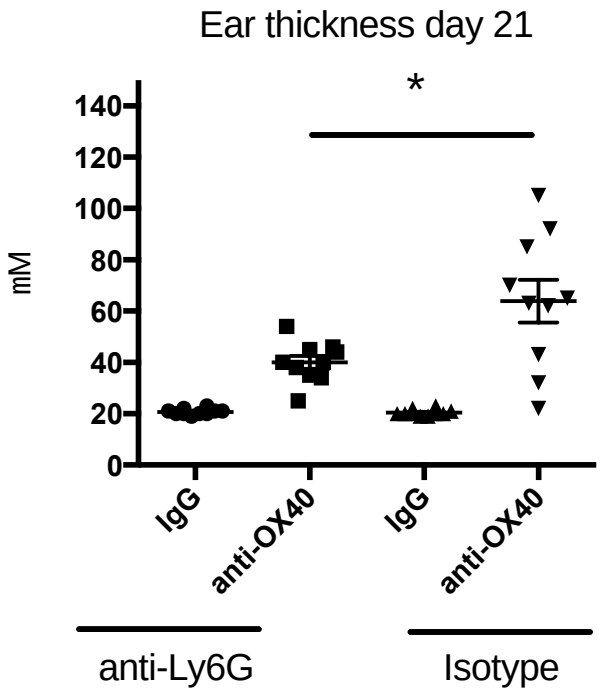


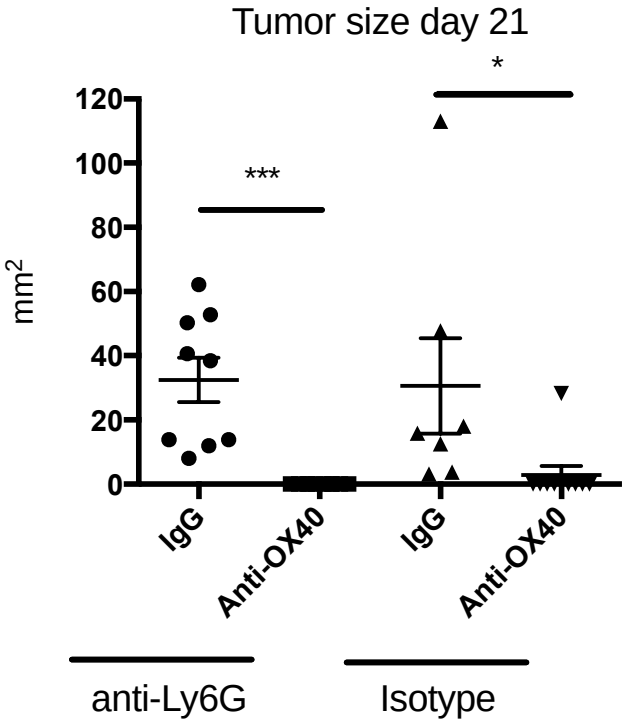
% infiltration in the ear pinnae with anti-OX40



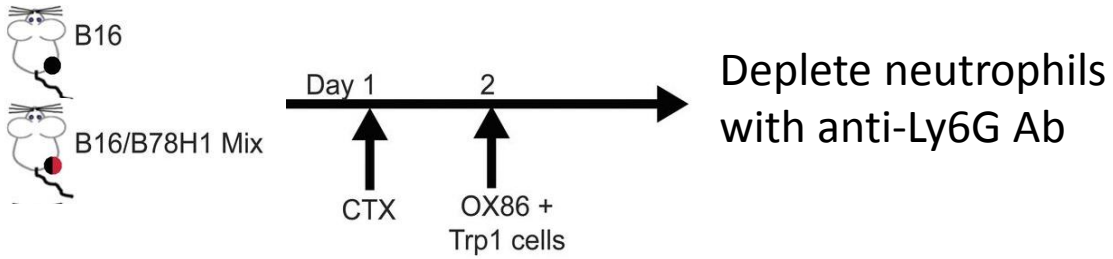
Anti-Ly6G depletion ameliorates irAE and has no effect on tumor regression

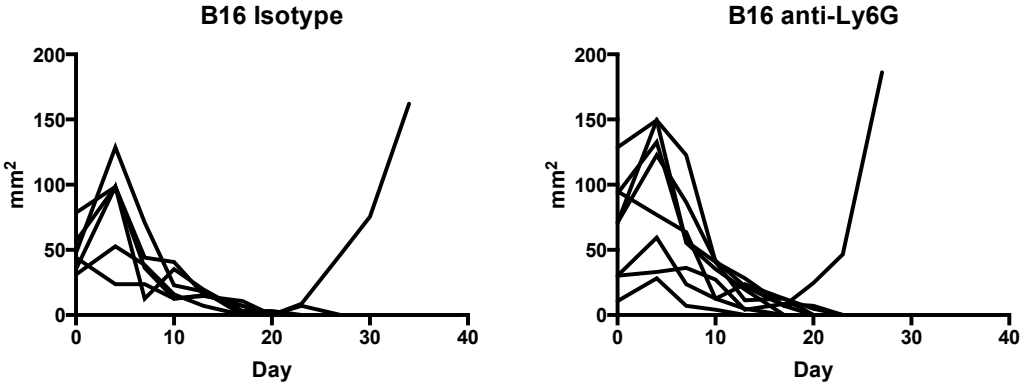


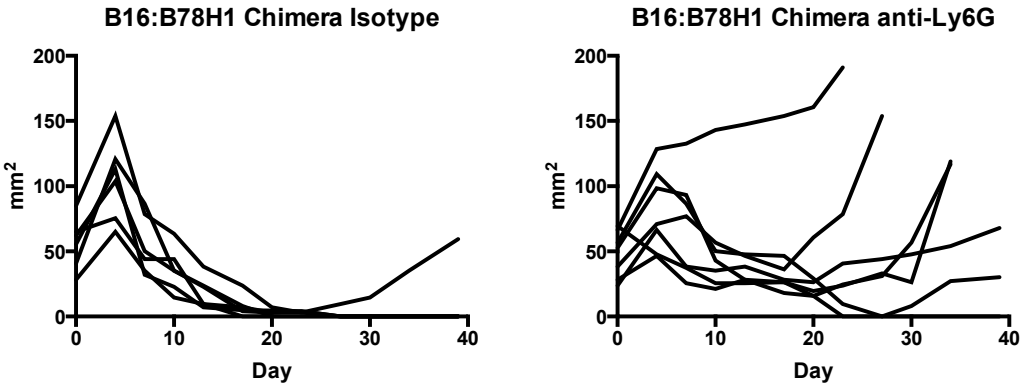




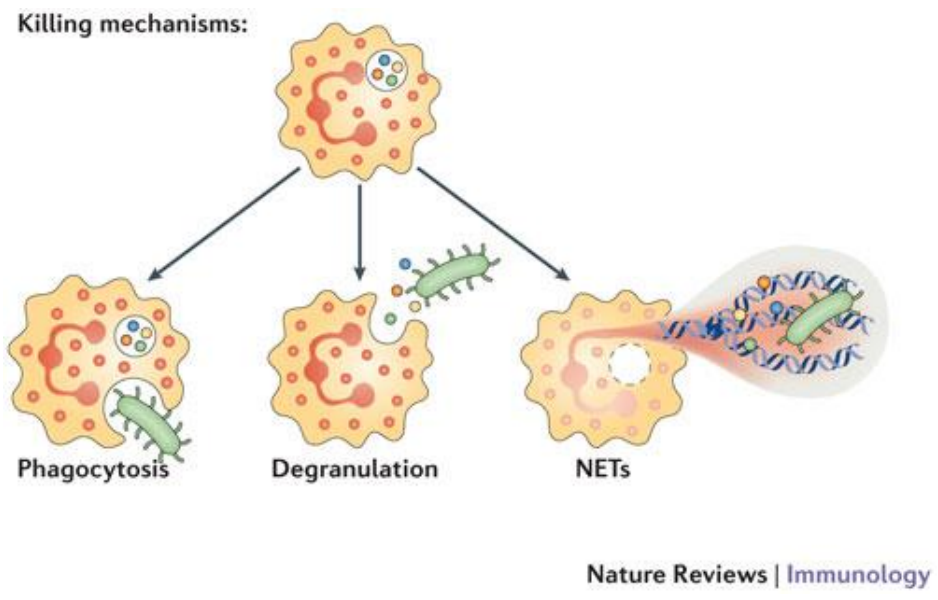
Neutrophils depletion prevents elimination of antigen loss variant chimeric tumors

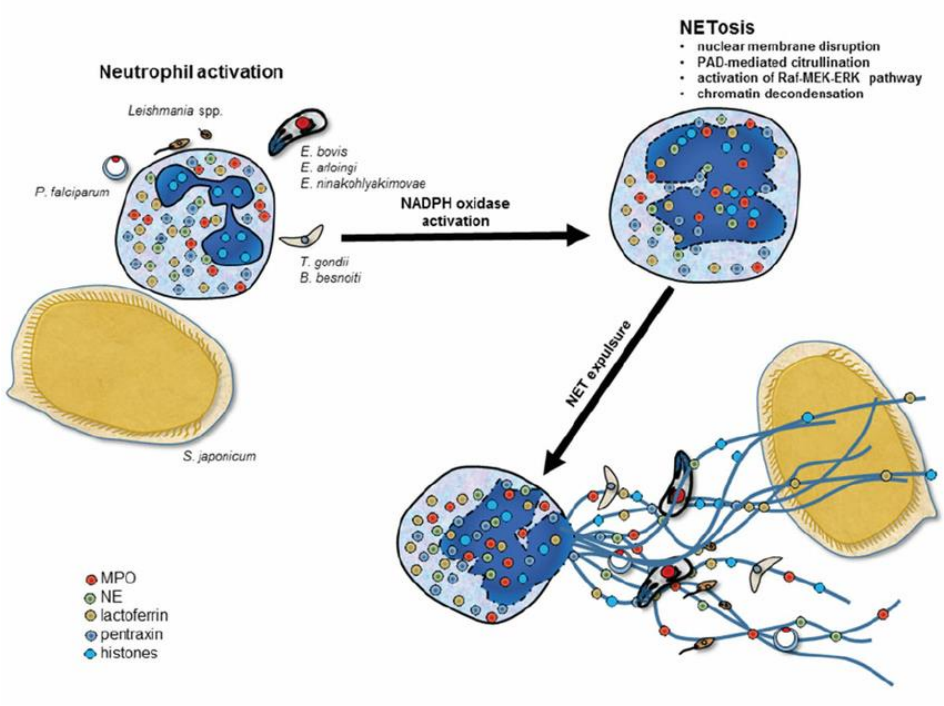






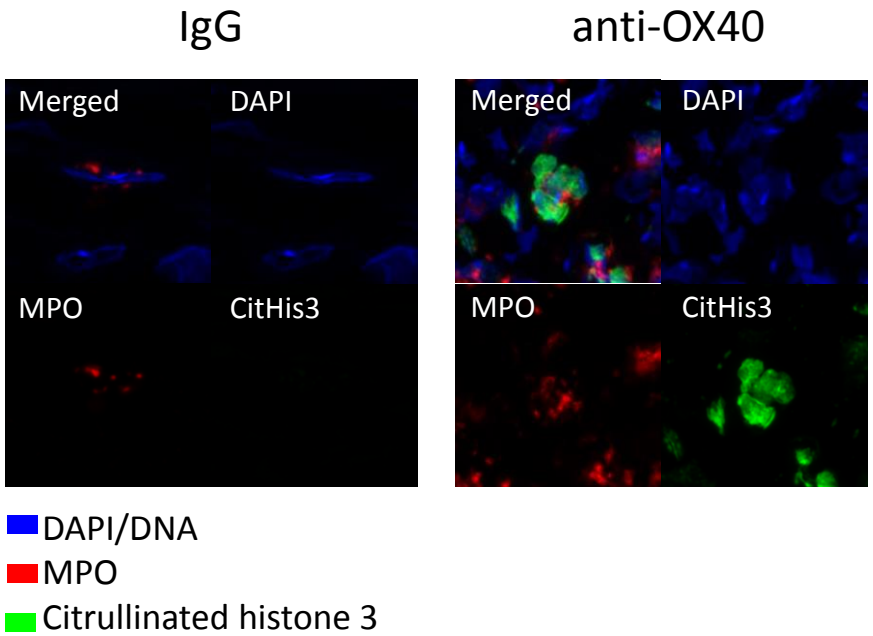
Neutrophil extracellular traps (NETs) as a mechanism for pathogen elimination

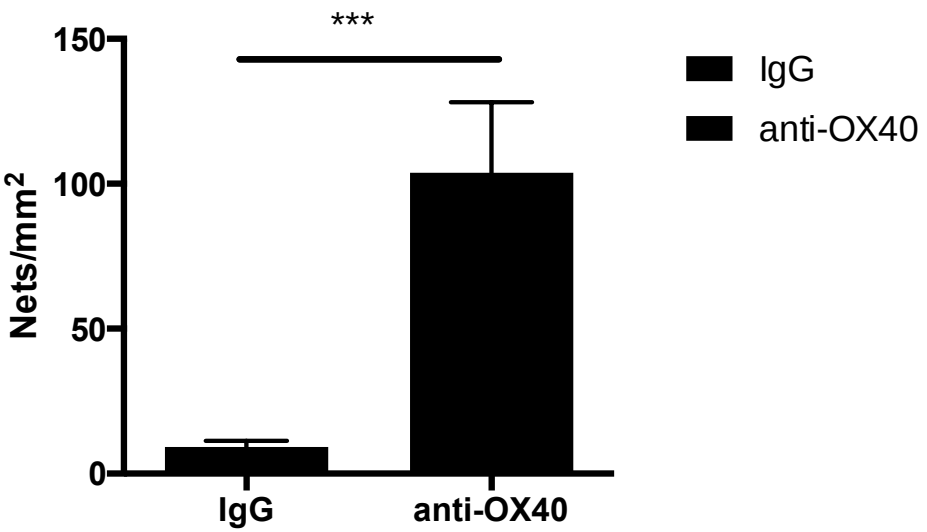




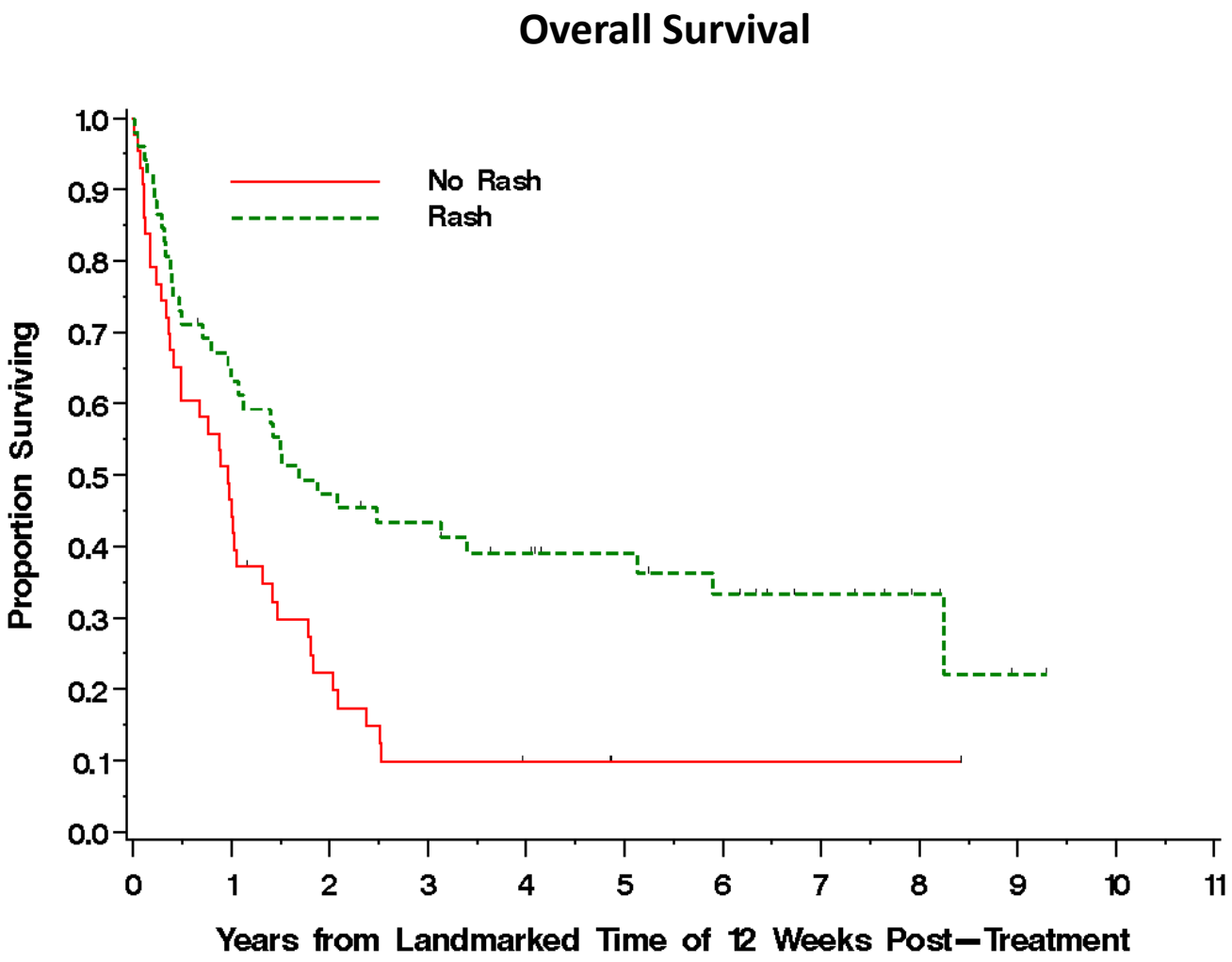
Kolaczkowska, *Nature Reviews Immunology*, 2013. Hermosilla, *Parasitology*, 2014

Ear pinnae of treated mice show extensive NETosis

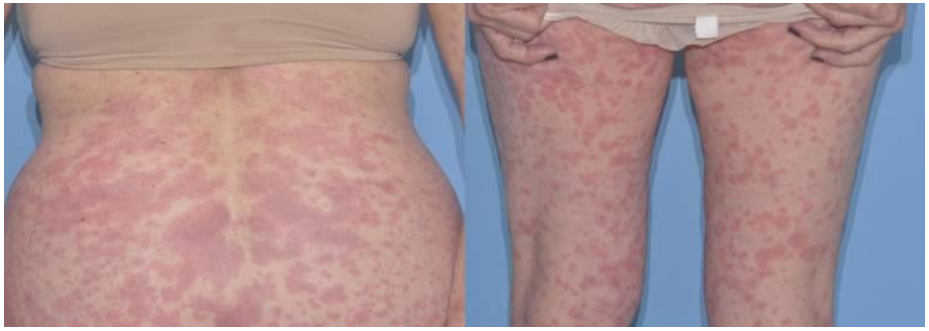


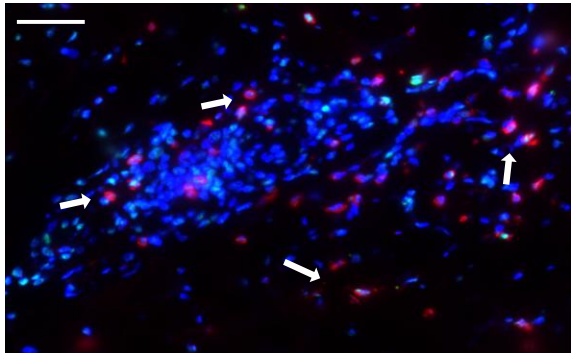


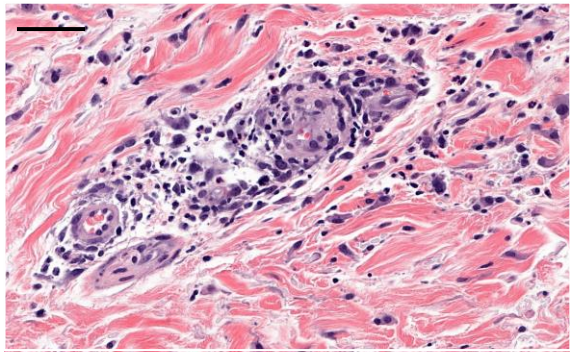
Immunotherapy-induced cutaneous rashes correlate with improved survival in melanoma patients treated with Ipilimumab (anti-CTLA-4)



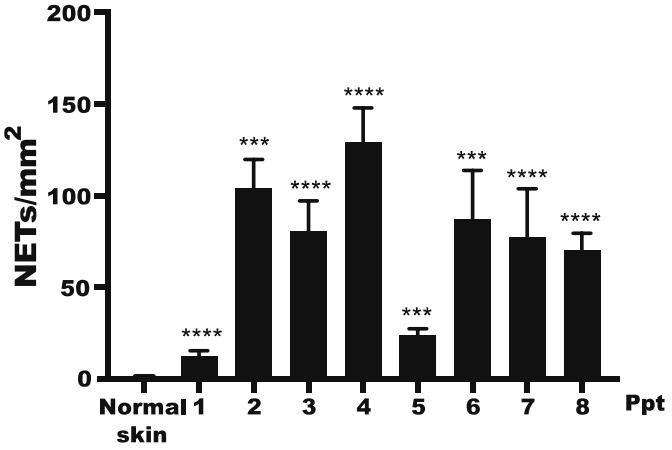
Skin rashes from melanoma patients receiving immunotherapy (ICB) exhibit extensive NETosis





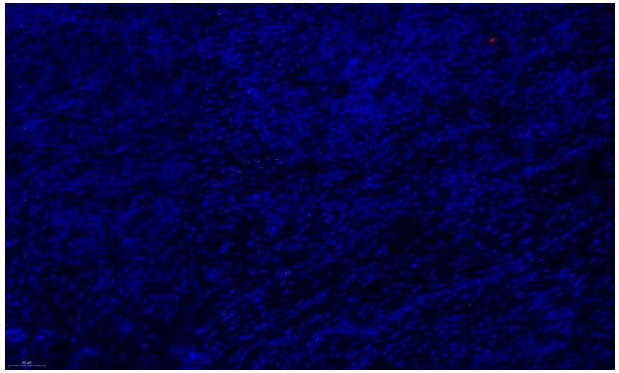


DAPI/DNA
MPO
Citrullinated histone 3

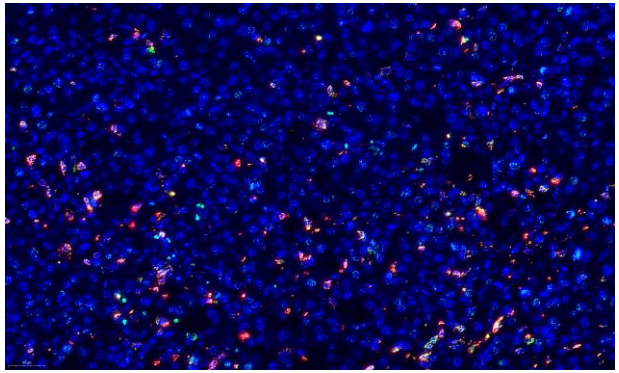


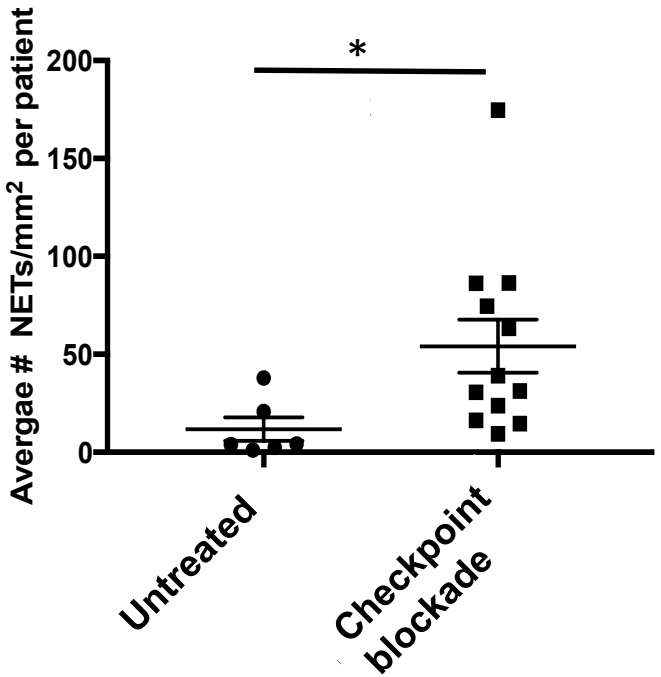
Increased NETosis in biopsies of tumors from patients receiving checkpoint blockade (Anti-CTLA-4 and/or Anti-PD-1)

No immunotherapy



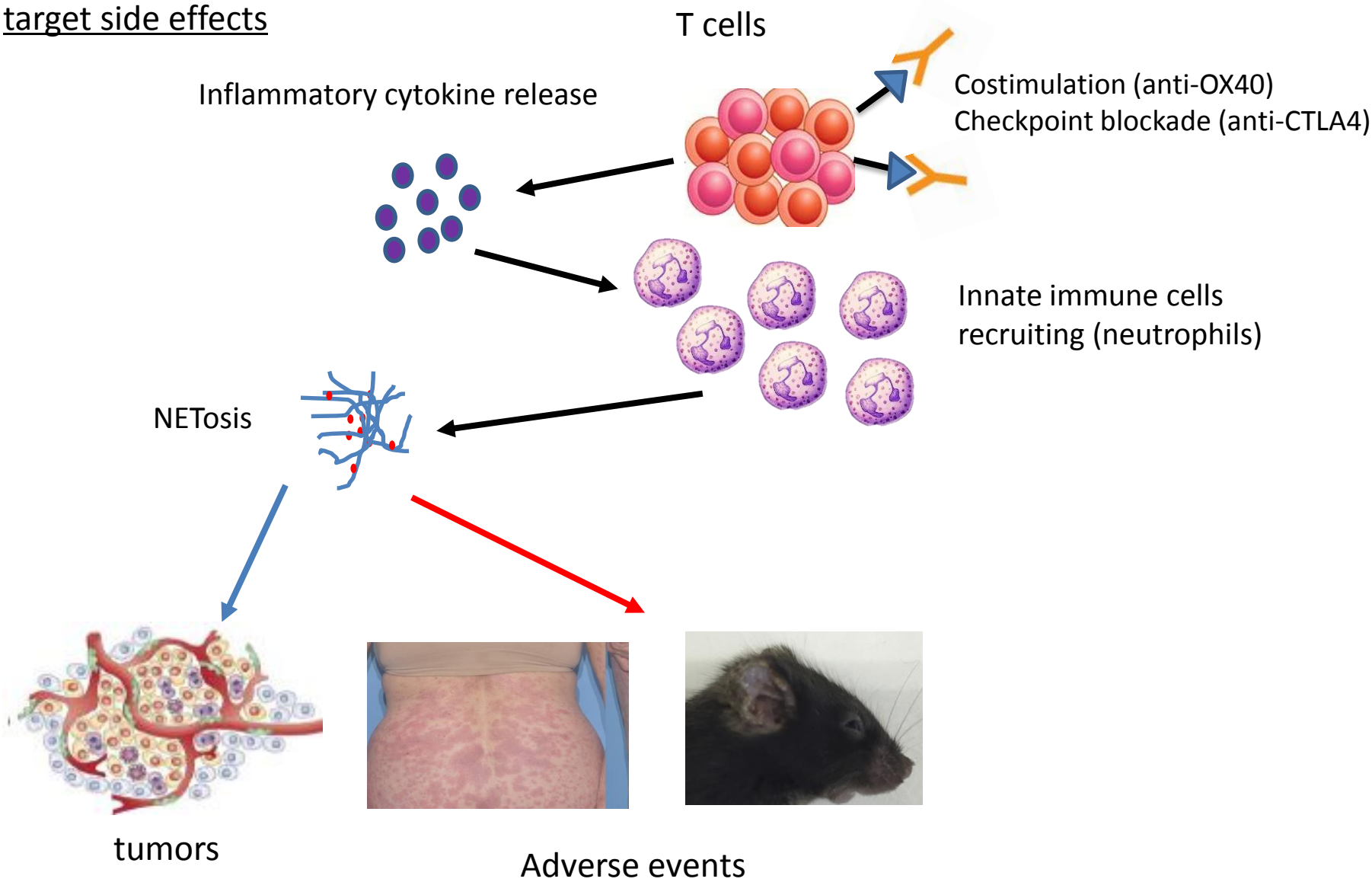
Checkpoint blockade





Model for the potency of the combination therapy and irAE

Adaptive immunity mobilize innate cells clear tumor (effectors) and promote off-target side effects



Some key points

- 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.

- The same patient may have multiple lesions that respond differently.

Some key points

- 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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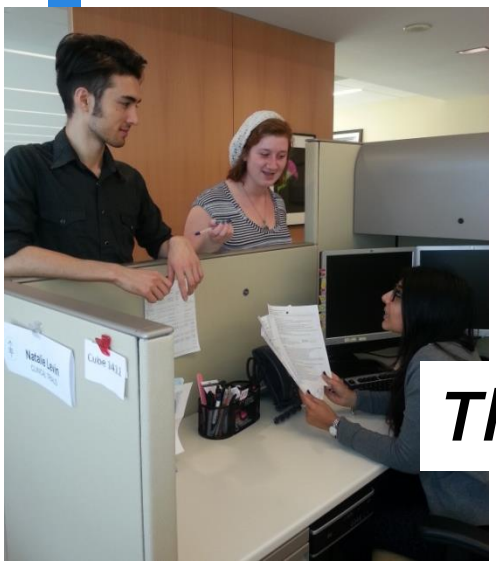

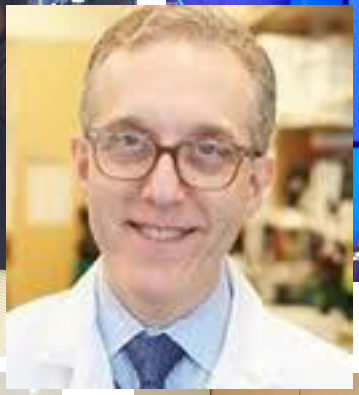

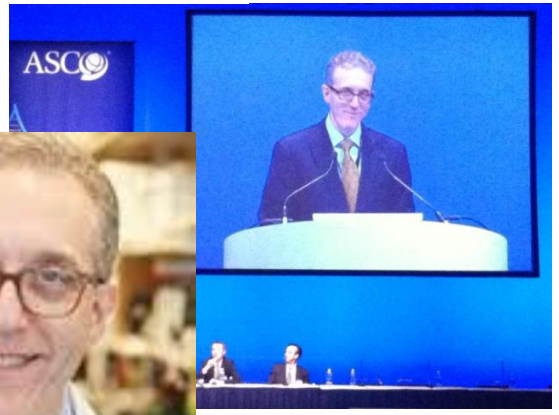

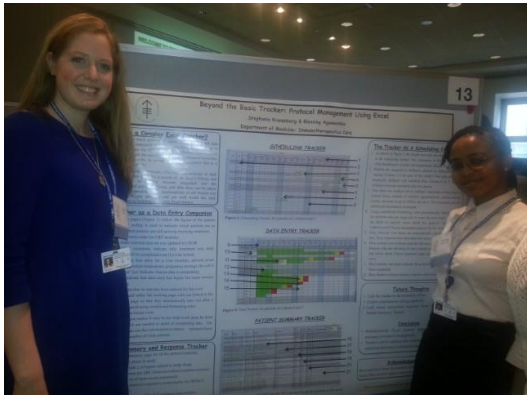

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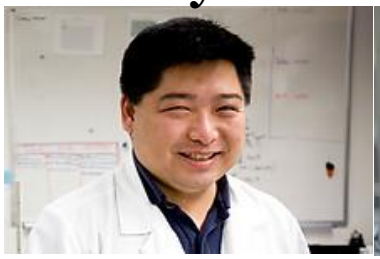
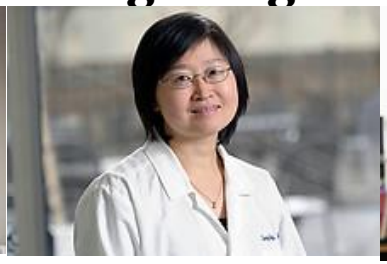
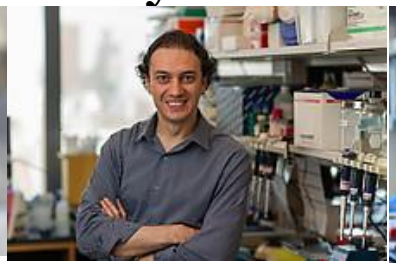


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