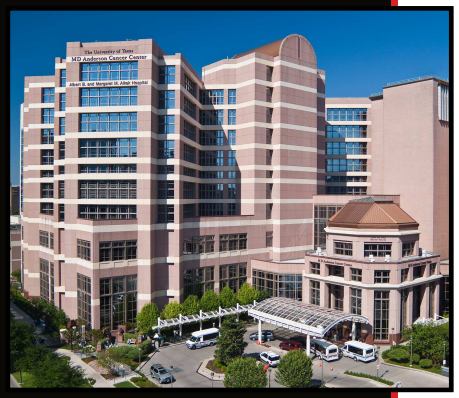


THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Casey Ager
Curran Lab
Department of Immunology

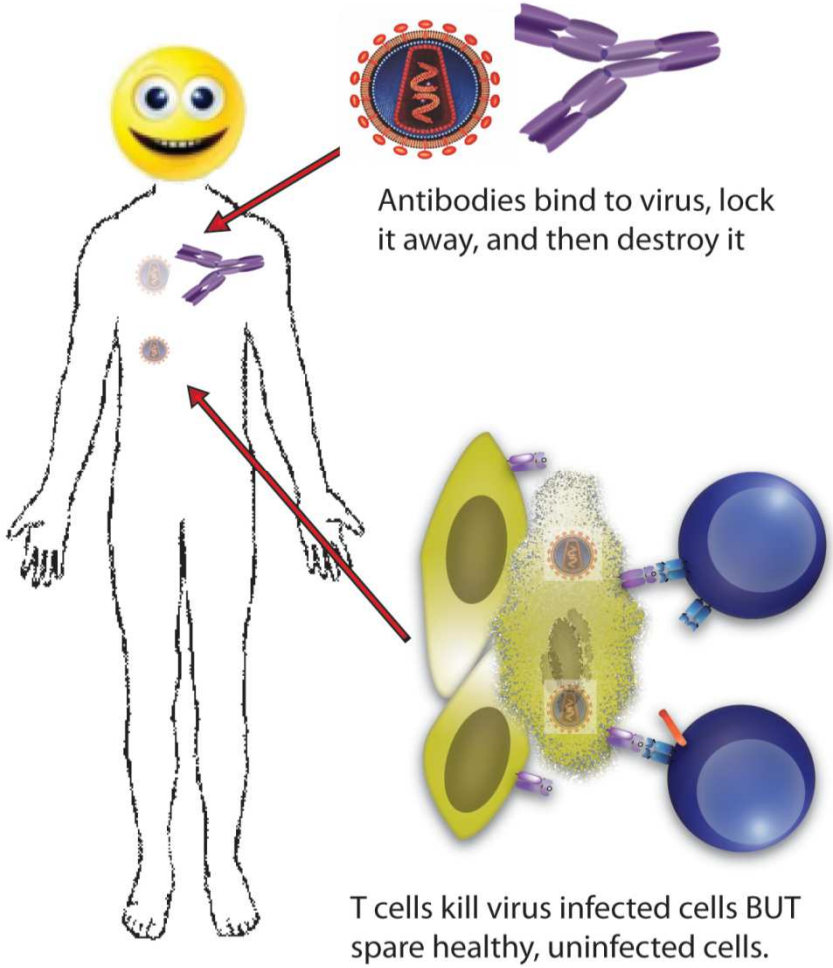
Presenter Disclosure Information

Casey Ager

I have no conflicts to disclose.

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

How does your immune system work?



THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Why does the immune system fail to eliminate cancer?

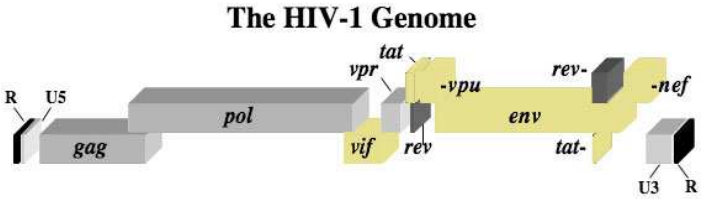
Antigenic Cancer Cells Grow Progressively in Immune Hosts without Evidence for T Cell Exhaustion or Systemic Anergy

By Maresa Wick,* Purnima Dubey,* Hartmut Koeppen,* Christopher T. Siegel,‡ Patrick E. Fields,§ Lieping Chen,‖ Jeffrey A. Bluestone,§ and Hans Schreiber*

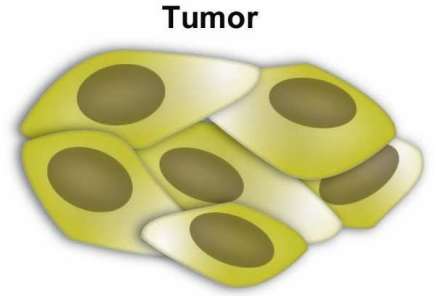
J. Exp. Med. © The Rockefeller University Press
Volume 186, Number 2, July 21, 1997 229–238

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Like pathogens, tumors deploy multigenic immune evasion programs



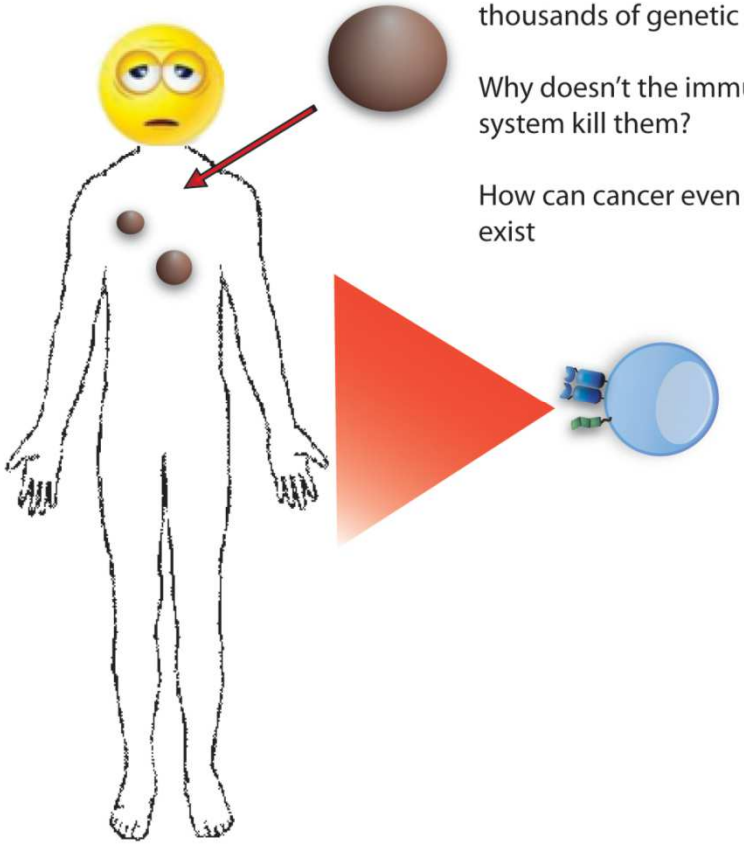
With < 9.8 kB of genome space HIV, like many other viruses devotes a large percentage of its genome to immune evasion.



Can access the entire $3x10^9$ base genome for evolutionary as well as adaptive immune evasion.

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

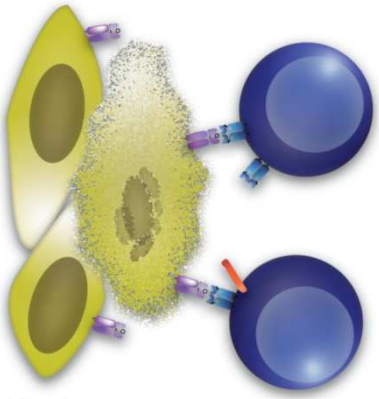
Why is there cancer?



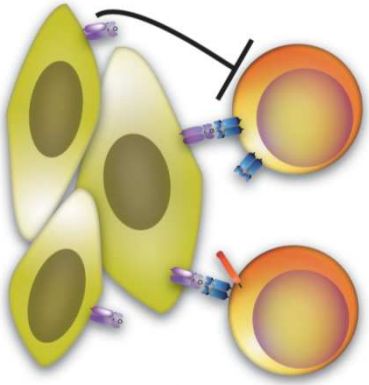
Tumors have dozens to thousands of genetic changes

Why doesn't the immune system kill them?

How can cancer even exist



The immune system has the potential to recognize and eliminate cancer, BUT...



Tumors actively cripple the immune system, creating a shield against elimination.

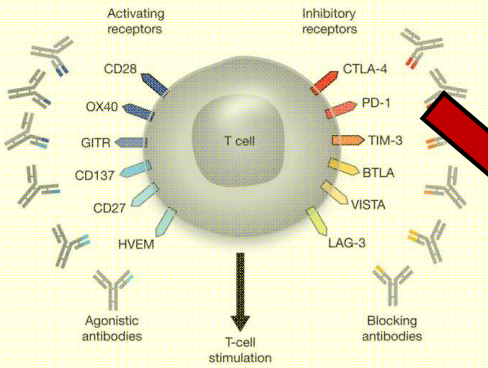
To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.

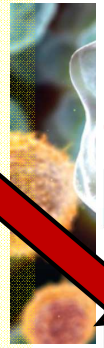
The goal of immunotherapy, then, is to restore the capacity of the immune system to recognize and reject cancer.

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Types of Immunotherapy

T Cell Checkpoint Modulation





Jimmy Carter says he no longer needs cancer drug treatment

AP By KATHLEEN FOODY
March 6, 2016 6:47 PM

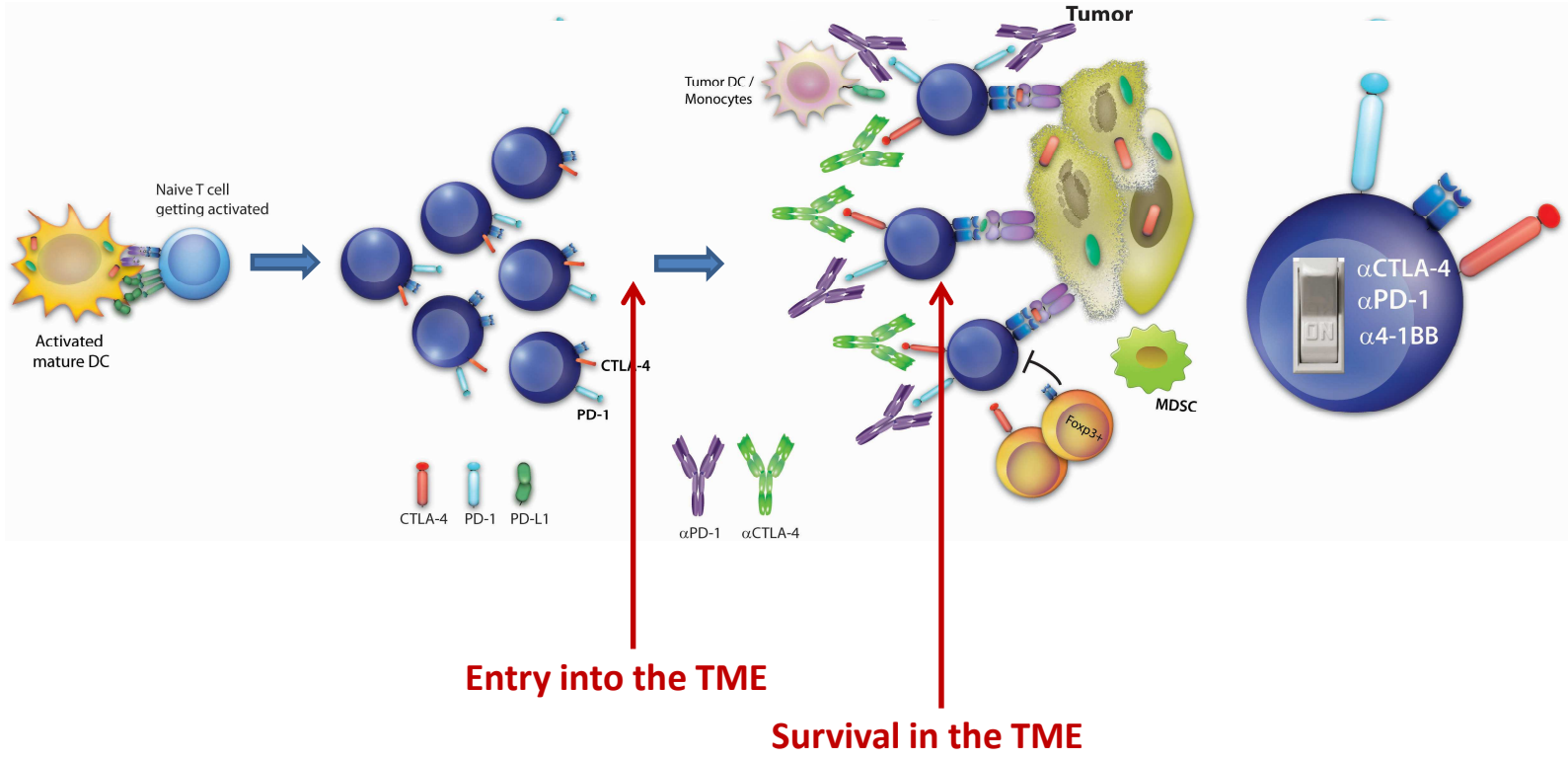
Therapeutic Cancer Vaccines

Me

DCs

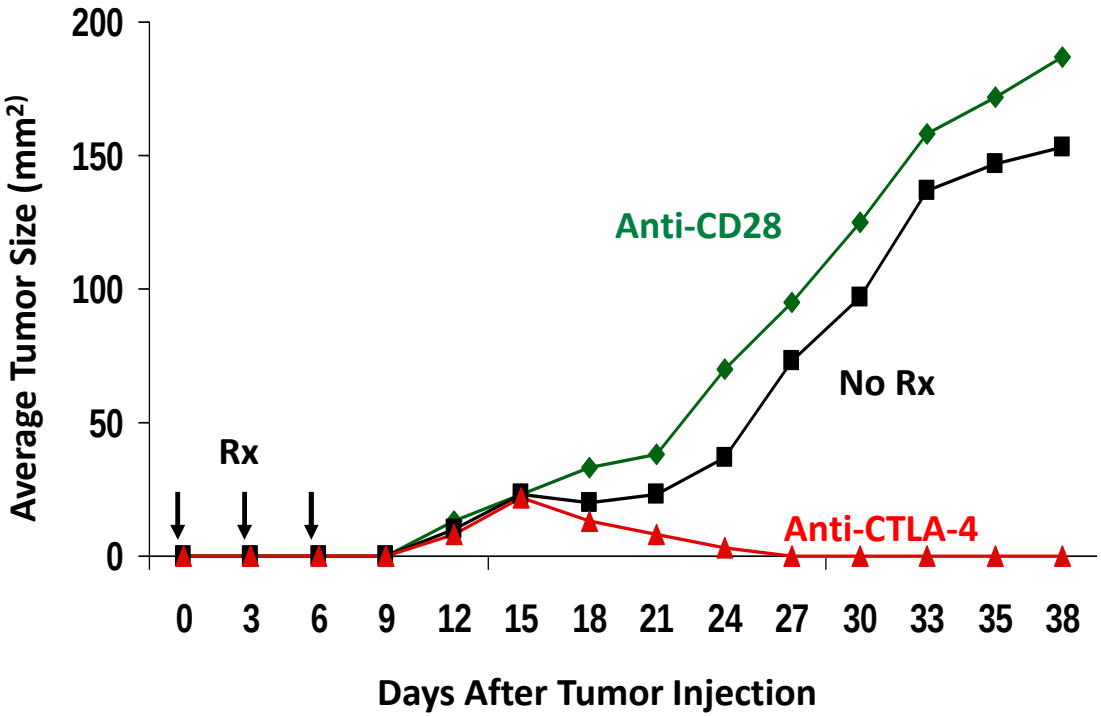
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

How do "immune checkpoint" antibodies like αCTLA-4 (Yervoy) and αPD-1 (Opdivo/Keytruda) treat cancer?



THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Antibodies that block immune checkpoints can cure murine tumors



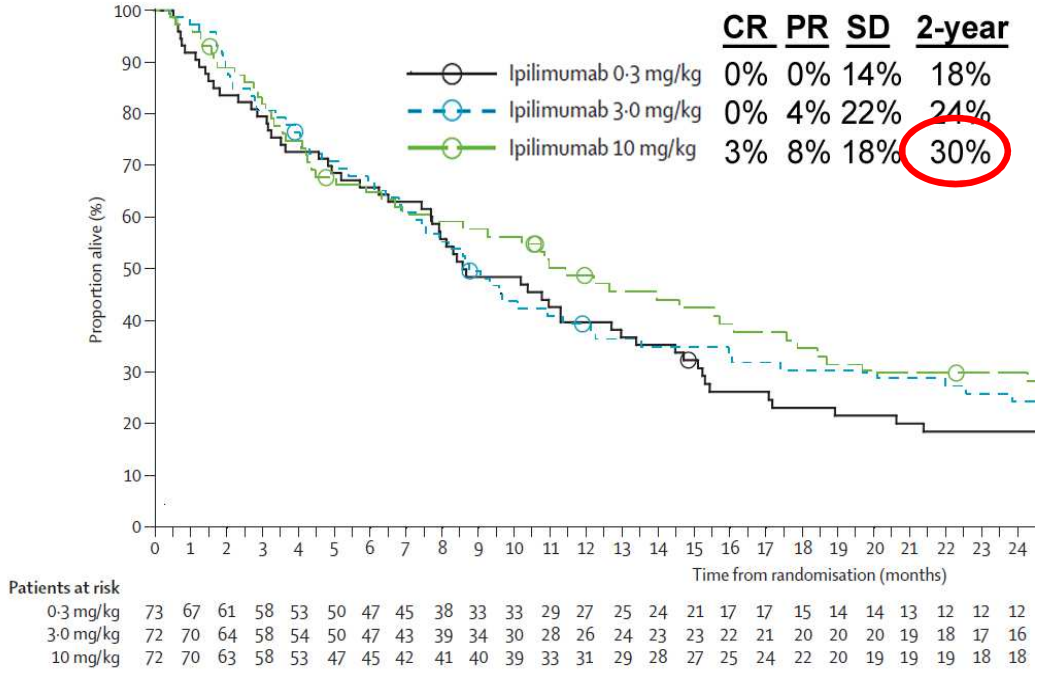
Science. 1996 Mar 22;271(5256):1734-6.

Enhancement of antitumor immunity by CTLA-4 blockade.

Leach DR[1], Krummel MF, Allison JP.

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Ipilimumab (αCTLA-4) was approved for the treatment of melanoma by the FDA in 2010



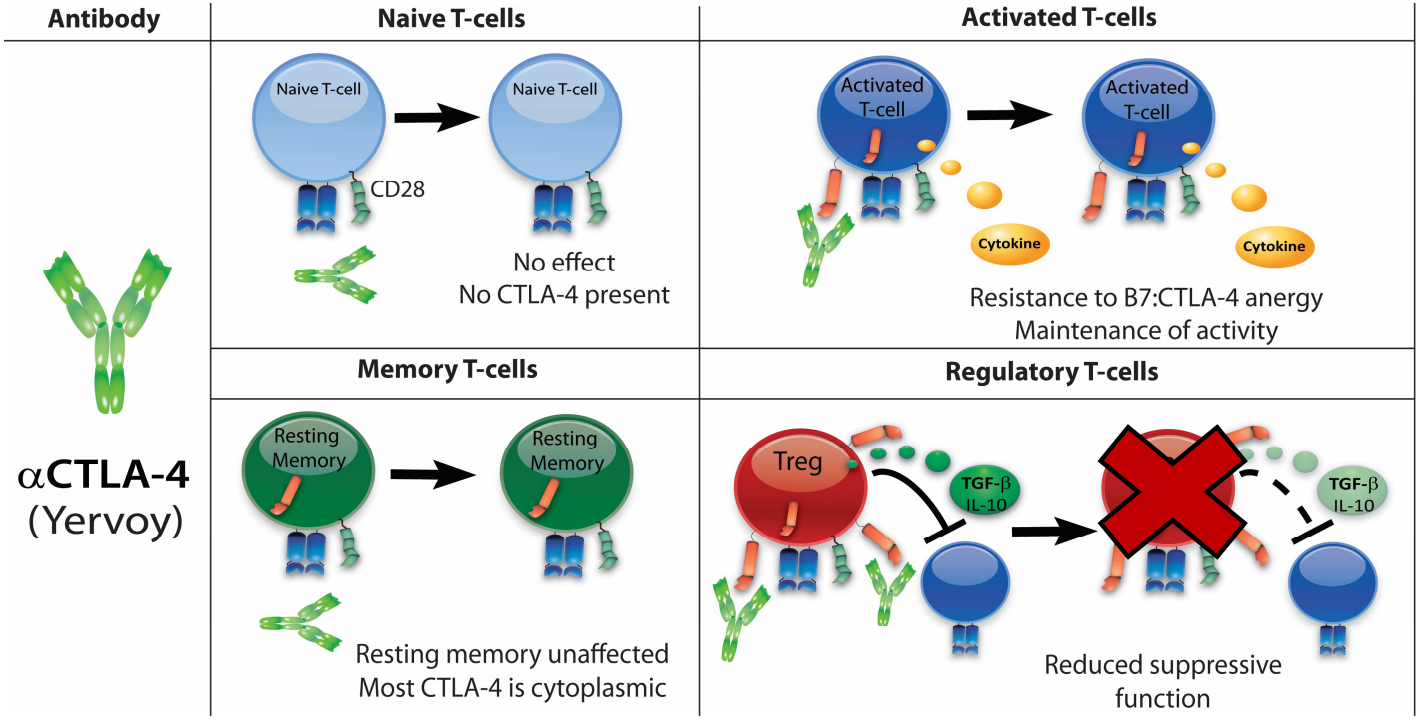
Wolchok et al, *Lancet Oncol*, 2010

Temodar:
CR: 2.5%
PR: 11%
SD: 18%
2yr: 18%

Middleton et.al, *J Clin Oncol*, 2000

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Which T-cells are affected by Ipilimumab(αCTLA-4)?

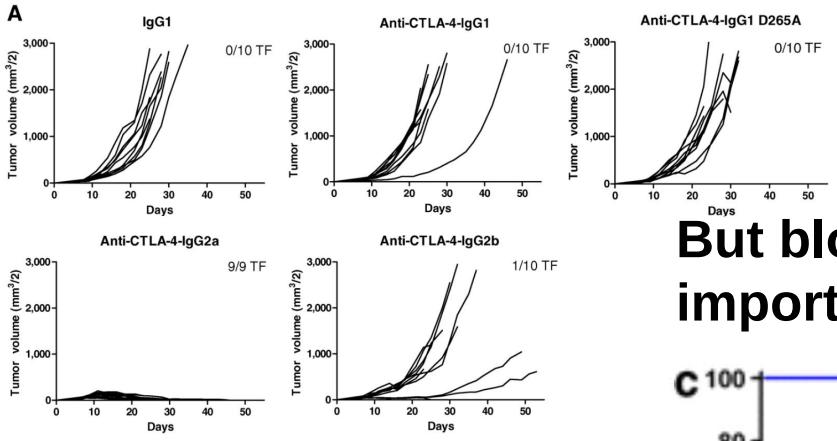


The greater the percentage of active T-cells in a patient targeting the tumor when αCTLA-4 is initiated, the greater the efficacy and selectivity should be.

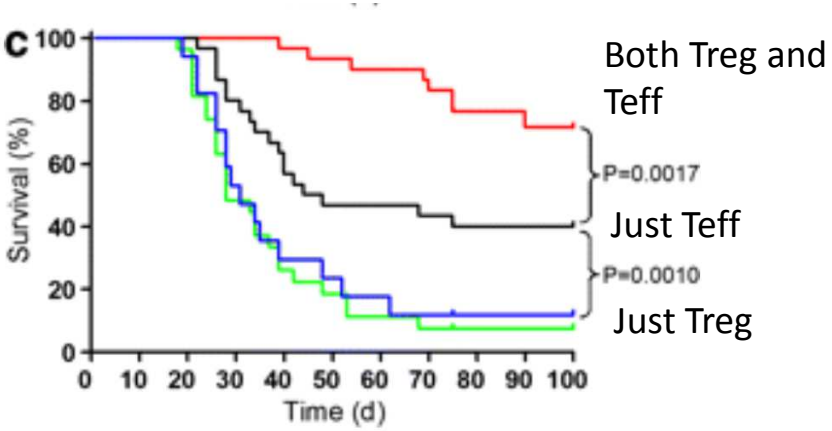
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

How do CTLA-4 antibodies potentiate tumor immunity?

Treg depletion is critical

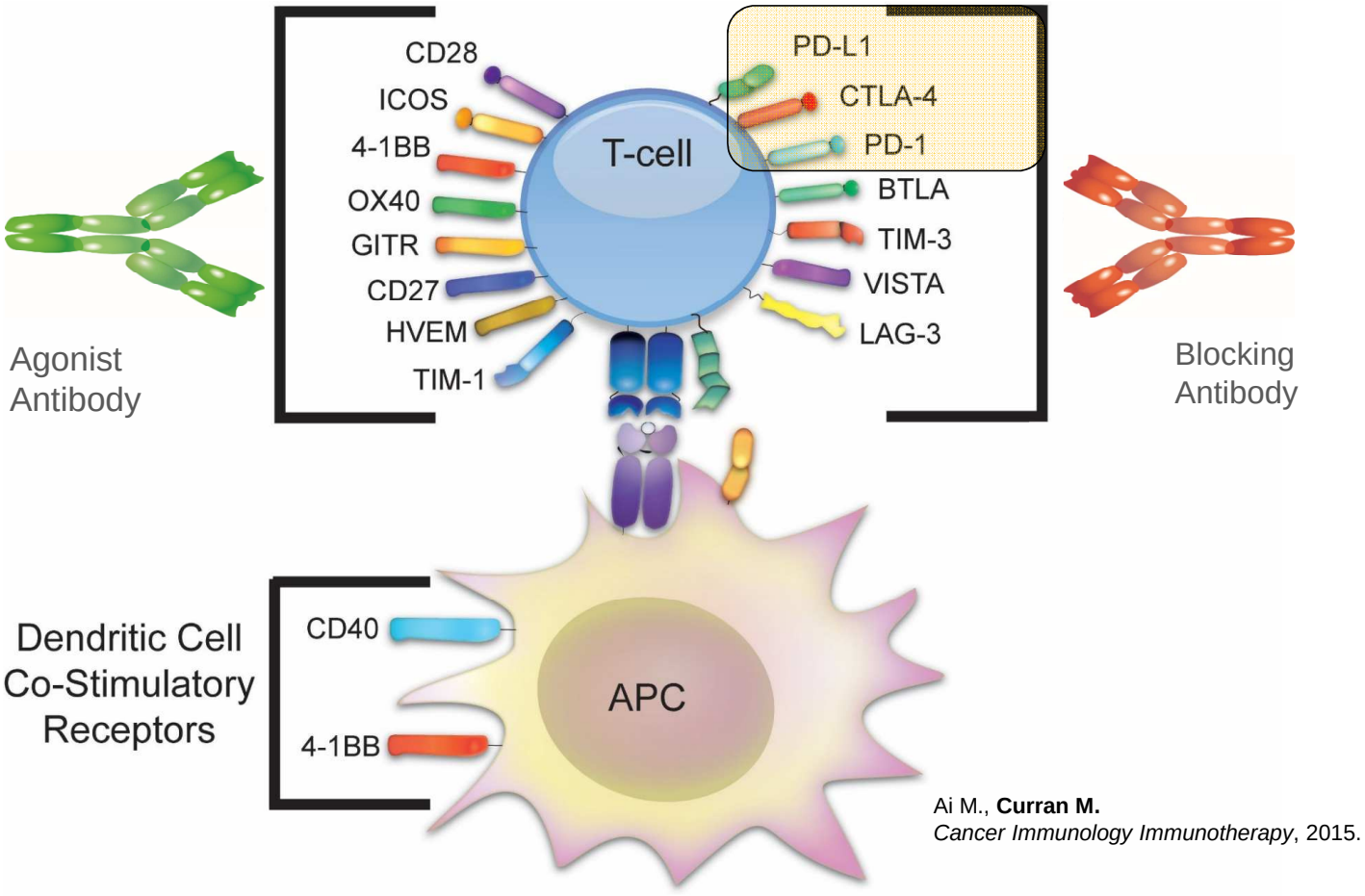


But blockade is also important



THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

T cell co-stimulatory and co-inhibitory receptors

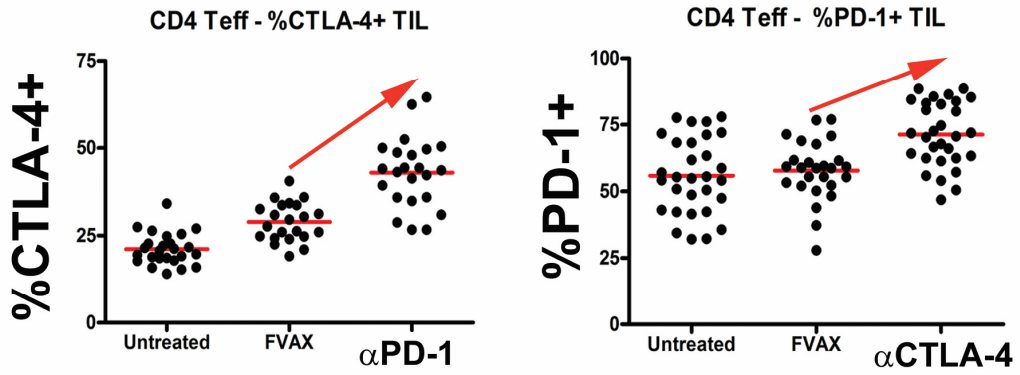


Ai M., **Curran M.**
Cancer Immunology Immunotherapy, 2015.

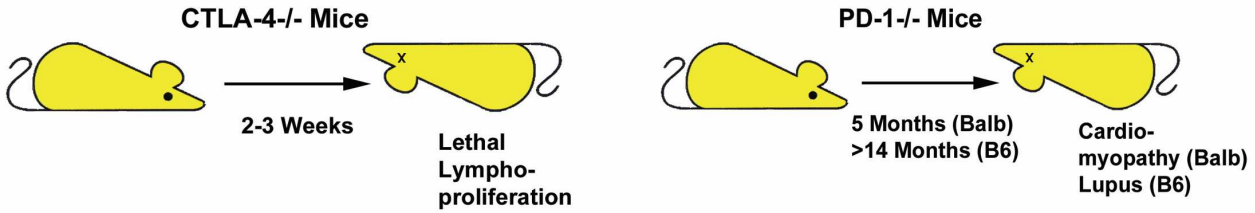
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Why choose to block the PD-1 pathway in addition to CTLA-4?

Blocking one co-inhibitory receptor leads to reciprocal upregulation of the other



CTLA-4 and PD-1 inhibitory signals are non-redundant



Curran M A et al. PNAS 2010; 107(9):4275-80.

THE UNIVERSITY OF TEX
MD Ande
Cancer C
Making Cancer History

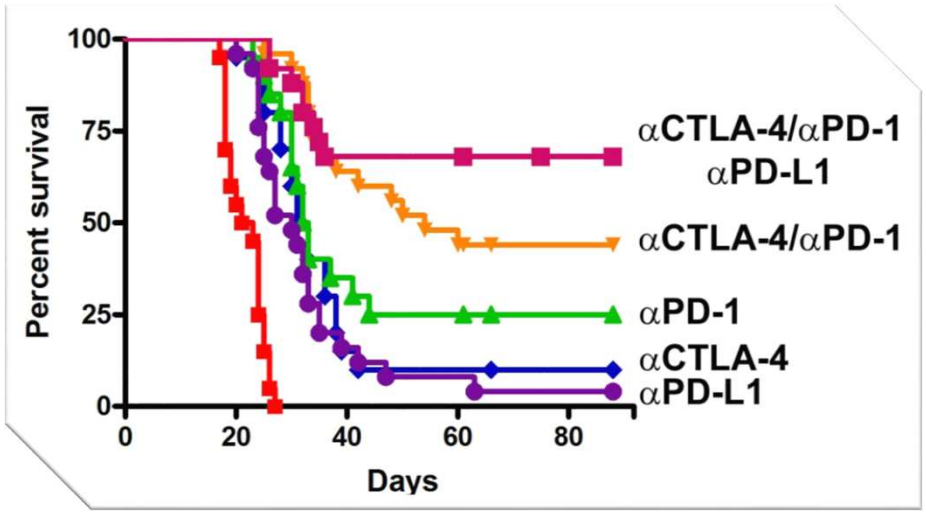
PNAS

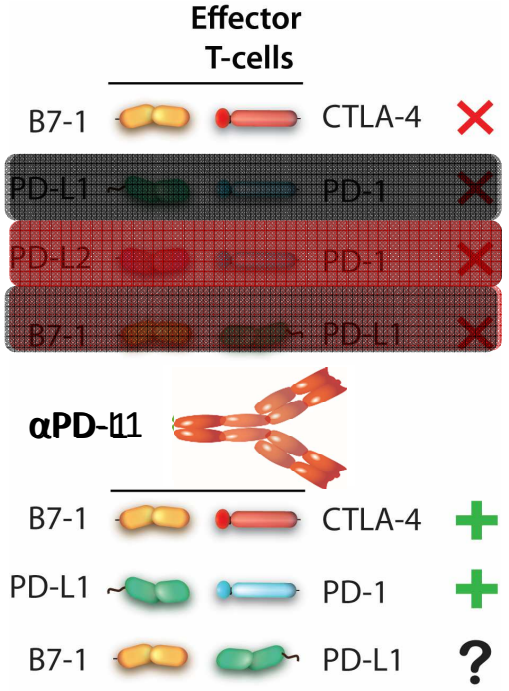
PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors

Michael A. Curran[a], Welby Montalvo[a], Hideo Yagita[b], and James P. Allison[a,1]

[a]Howard Hughes Medical Institute, Department of Immunology, Memorial Sloan-Kettering Cancer Center, New York, NY 10065; and [b]Department of Immunology, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan

Contributed by James P. Allison, January 19, 2010 (sent for review December 17, 2009)

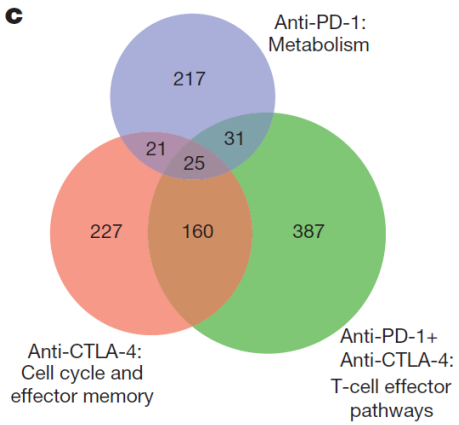


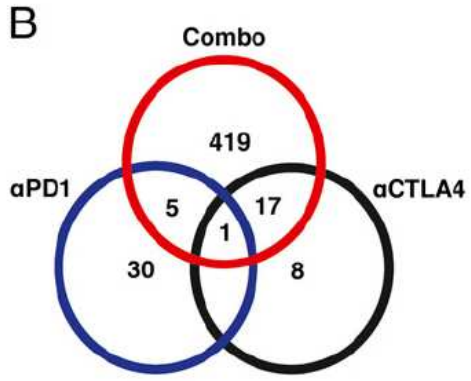


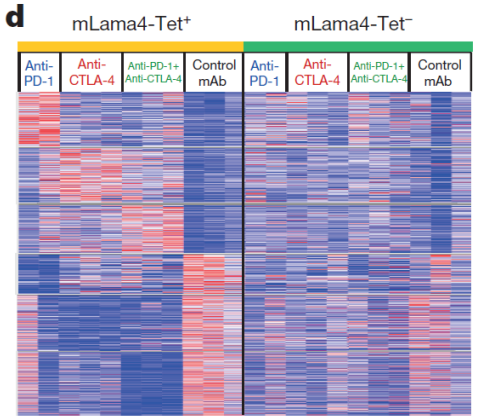
Curran M A et al. PNAS 2010; 107(9):4275-80.

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Combination checkpoint blockade = More than the sum of the parts







doi:10.1038/nature13988

Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens

Matthew M. Gubin[1], Xiuli Zhang[2], Heiko Schuster[3], Etienne Caron[4], Jeffrey P. Ward[1,5], Takuro Noguchi[1], Yulia Ivanova[1], Jasreet Hundal[6], Cora D. Arthur[1], Willem-Jan Krebber[7], Gwenn E. Mulder[7], Mireille Toebes[8], Matthew D. Vesely[1], Samuel S. K. Lam[1], Alan J. Korman[9], James P. Allison[10], Gordon J. Freeman[11], Arlene H. Sharpe[12], Erika L. Pearce[1], Ton N. Schumacher[8], Ruedi Aebersold[4,13], Hans-Georg Rammensee[3], Cornelis J. M. Melief[7,14], Elaine R. Mardis[6,15], William E. Gillanders[5], Maxim N. Artyomov[1] & Robert D. Schreiber[1]

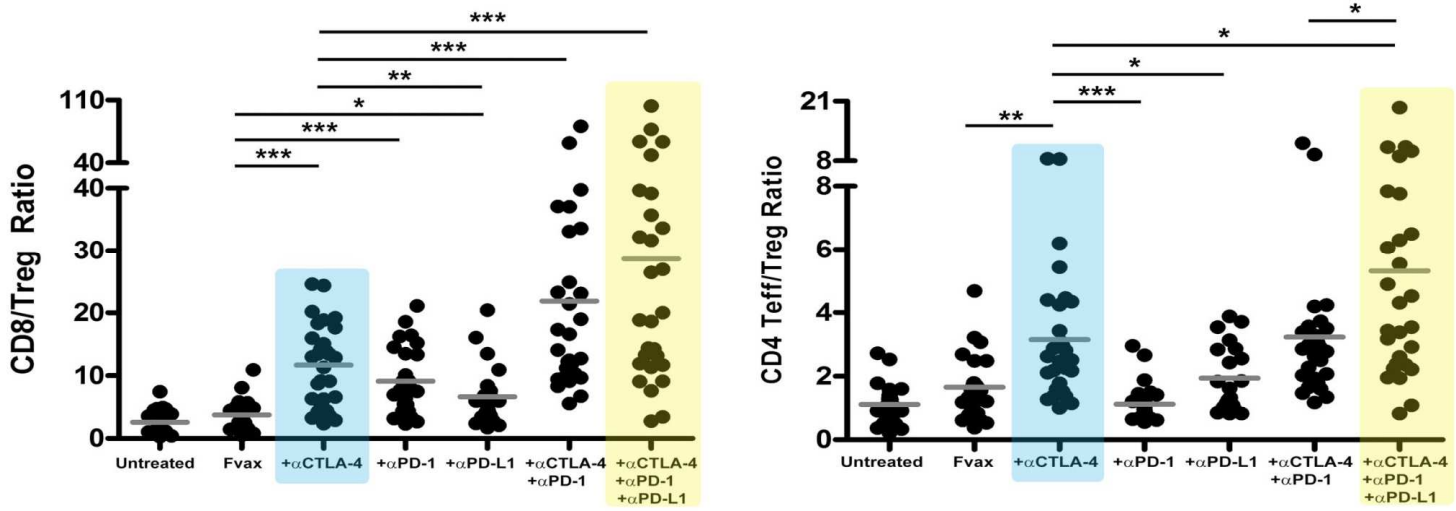
The Journal of Immunology

Combination Therapy with Anti–CTLA-4 and Anti–PD-1 Leads to Distinct Immunologic Changes In Vivo

Rituparna Das, Rakesh Verma, Mario Sznol, Chandra Sekhar Boddupalli, Scott N. Gettinger, Harriet Kluger, Margaret Callahan, Jedd D. Wolchok, Ruth Halaban, Madhav V. Dhodapkar and Kavita M. Dhodapkar

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

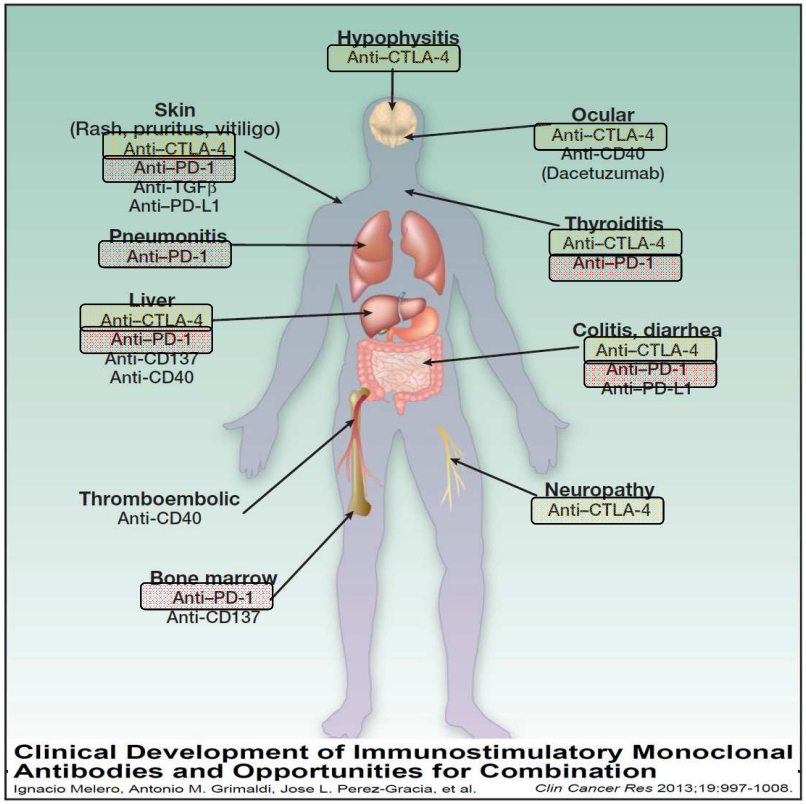
Conversion of the tumor micro-environment from suppressive to inflammatory



Curran M A et al. PNAS 2010; 107(9):4275-80.

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Risk/Benefit: αPD-1 monotherapy IrAE were less severe but largely overlapping with αCTLA-4



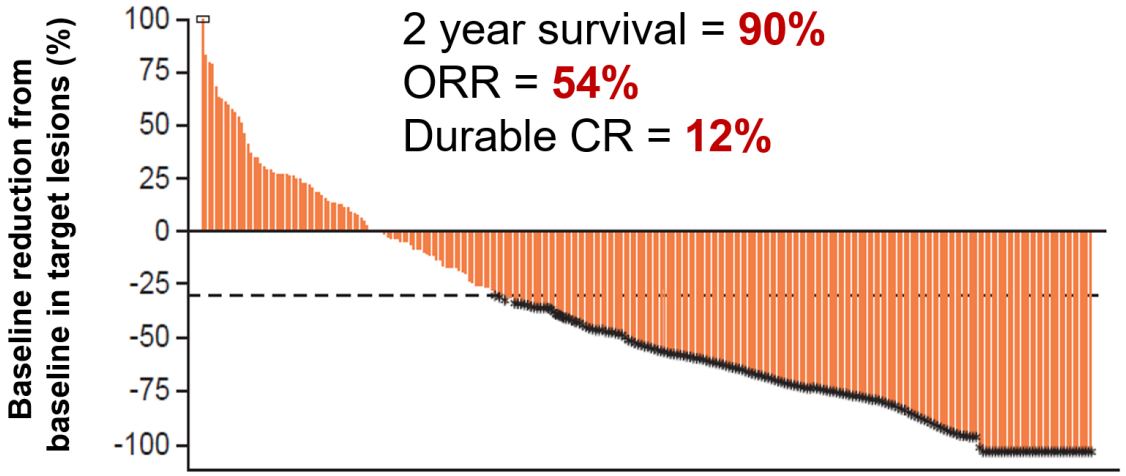
Clinical Development of Immunostimulatory Monoclonal Antibodies and Opportunities for Combination

Ignacio Melero, Antonio M. Grimaldi, Jose L. Perez-Gracia, et al. *Clin Cancer Res* 2013;19:997-1008.

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Transformative outcomes with Ipilimumab/ Nivolumab in metastatic melanoma and NSCLC

Metastatic Melanoma



Wolchok et al. ASCO 2015 and NEJM

Non-Small Cell Lung Cancer

Outcome	NIVO 1 + IPI 1 q3w	NIVO 1 q2w + IPI 1 q6w	NIVO 3 q2w + IPI 1 q12w	NIVO 3 q2w + IPI 1 q6w
Treatment-related AEs leading to discontinuation, any grade, %	13	8	5	10
Treatment-related AEs leading to discontinuation, grade 3–4, %	10	8	3	10
Confirmed overall response, %	13	25	39	31
Median PFS, months	10.6	4.9	8.0	8.3

Rizvi et al. J Thorac Oncol 2015; 10 (suppl 2): ORAL02.05

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

The first FDA approved immunotherapy combination

FDA approves nivolumab plus ipilimumab for BRAF wild-type melanoma

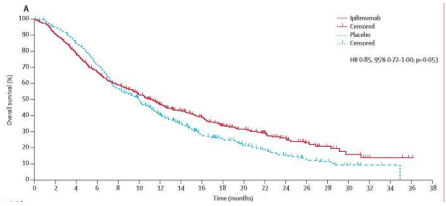
01 Oct 2015

The Melanoma Research Alliance (MRA) welcomes the U.S. Food and Drug Administration (FDA) decision to approve the use of Bristol-Myers Squibb's (BMS) nivolumab and ipilimumab in combination as a treatment for patients with unresectable or metastatic melanoma without a BRAF mutation, known as BRAF wild-type melanoma.

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

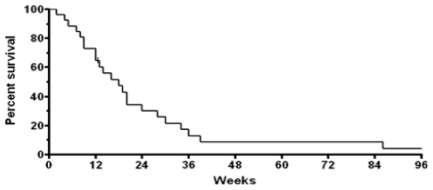
Many solid tumors fail to respond to immune checkpoint blockade

Castration-Resistant Prostate Cancer
(no significant benefit αCTLA-4 or αPD-1)



Lancet Oncol 2014; 15: 700–12

Pancreatic Ductal Adenocarcinoma
(no significant benefit αCTLA-4 or αPD-L1)

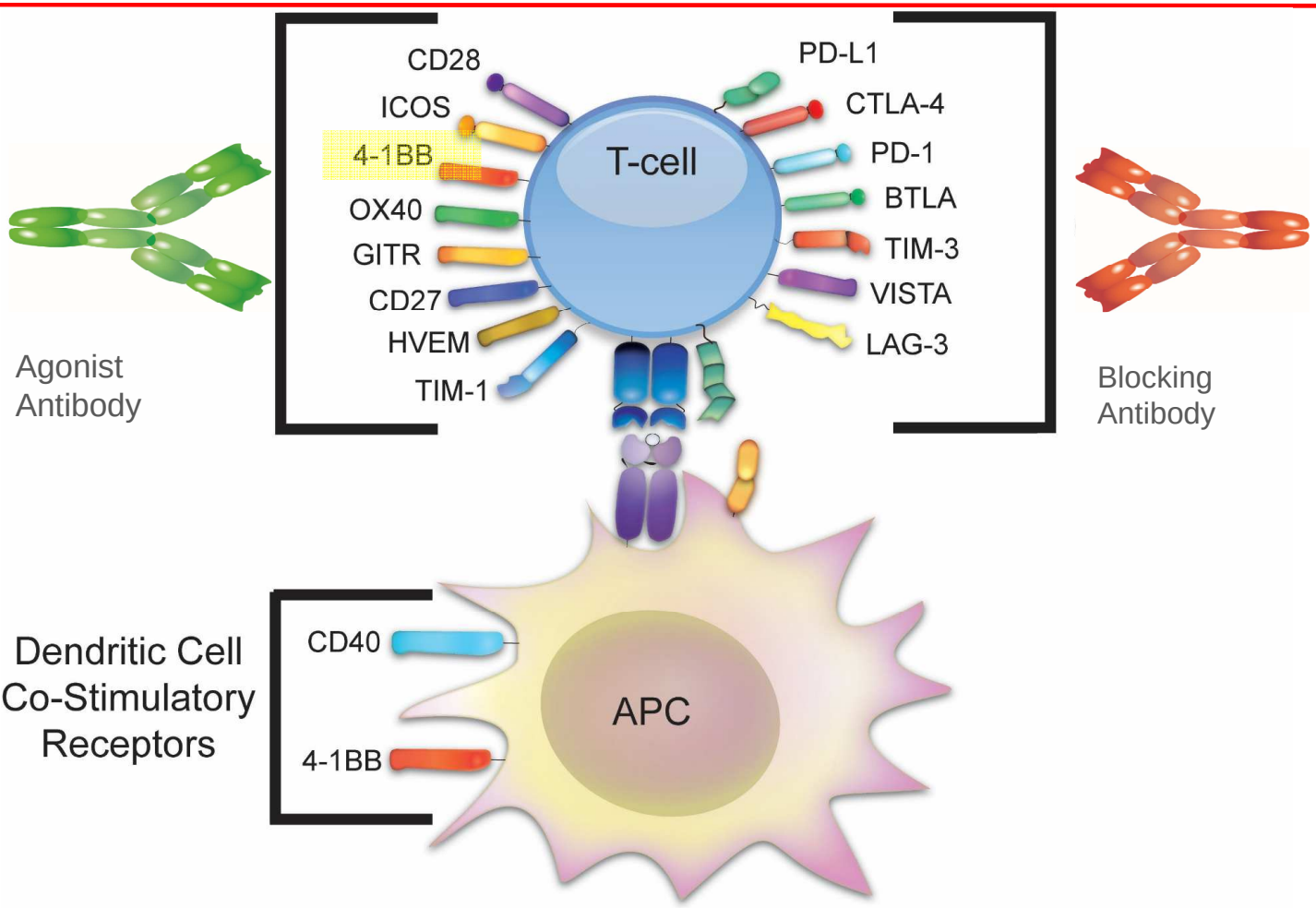


J Immunother • Volume 33, Number 8, October 2010

MSI-low Colorectal Cancer
(no significant benefit αCTLA-4 or αPD-L1)

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

T cell Checkpoint Modulation



THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

4-1BB : Favorable expression profile for immunotherapy

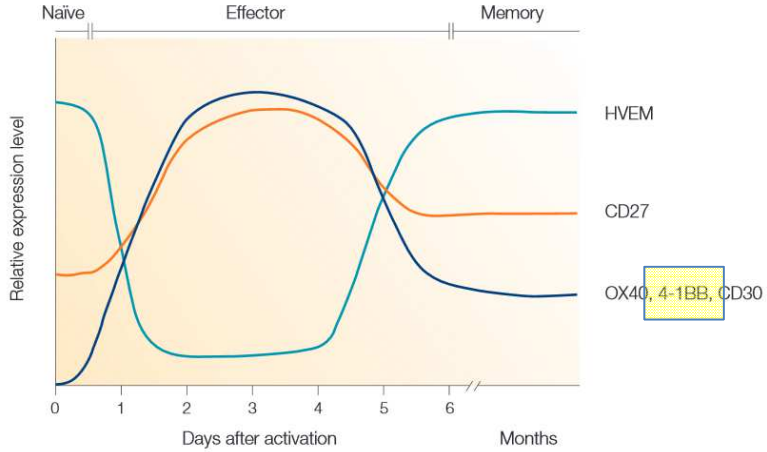


Figure 2 | **Generalized time course of expression of co-stimulatory TNFR-family members.**

Table 1 | **Expression characteristics of TNFR and TNF molecules by T cells and APCs**

Molecule	T cells			APCs	
	Naïve	*Effector*	*Memory*	*Resting*	*Activated*
CD27	++	+++	++/–	–	B*
CD70	–	+++*	–	–	B, DC, MØ
HVEM	+++	+	+++	B, DC*	B, MØ*
LIGHT	–	+++	–	DC	–
OX40	–	+++	+/–	–	B, DC*
OX40L	–	+++*	–	–	B, DC, MØ
4-1BB	–	+++	+/–	–	B, DC*
4-1BBL	–	+++*	–	–	B, DC, MØ
CD30	–	+++	+/–	–	–
CD30L	–	+++*	–	–	B, MØ

Nature Reviews Immunology **3**, 609-620 (August 2003) | doi:10.1038/nri1148

Co-stimulatory members of the TNFR family: keys to effective T-cell immunity?

Michael Croft[1] About the author

Table 1 | **Co-stimulatory and co-inhibitory receptor function in stages of T cell differentiation**

Receptor	T cell type	Priming	Cell growth	T_H cell differentiation	Effector function	Survival	Memory
4-1BB	$CD4^+$	ND	(+)	ThEO	(+)	(+)	(+)
	$CD8^+$	ND	(+)	TcEO	(+)	(+)	(+)

Adapted from: **Molecular mechanisms of T cell co-stimulation and co-inhibition**
Lieping Chen & Dallas B. Flies *Nature Reviews Immunology* **13**, 227-242 (April 2013)

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

4-1BB targets multiple arms of the immune system

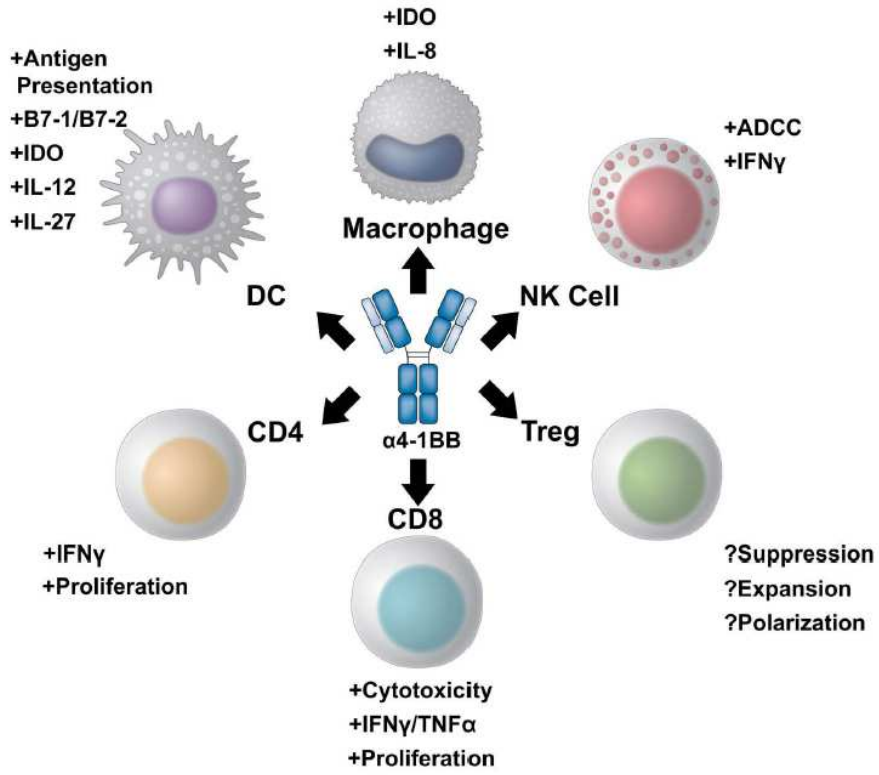


FIGURE 1 | A multi-potent role for 4-1BB targeted immunotherapy.

4-1BB Agonists: Multi-Potent Potentiators of Tumor Immunity.

Bartkowiak T, **Curran** MA.

Front Oncol. 2015 Jun 8;5:117. doi: 10.3389/fonc.2015.00117. eCollection 2015. Review.

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

4-1BB antibodies cure murine cancers

Monoclonal antibodies against the 4-1BB T-cell activation molecule eradicate established tumors

IGNACIO MELERO, WALTER W. SHUFORD, STEPHANIE ASHE NEWBY, ALEJANDRO ARUFFO, JEFFREY A. LEDBETTER, KARL ERIK HELLSTRÖM, ROBERT S. MITTLER & LIEPING CHEN

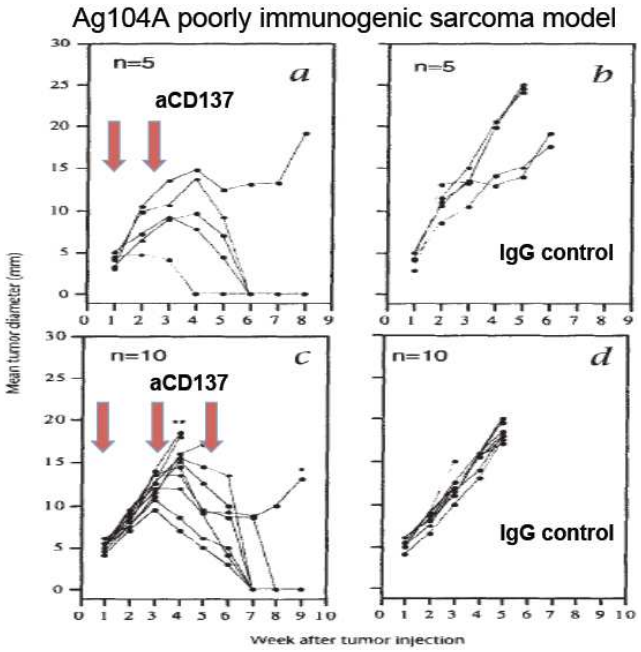


Table 1. Suppression of various tumors by targeting the 4-1BB–4-1BBL pathway

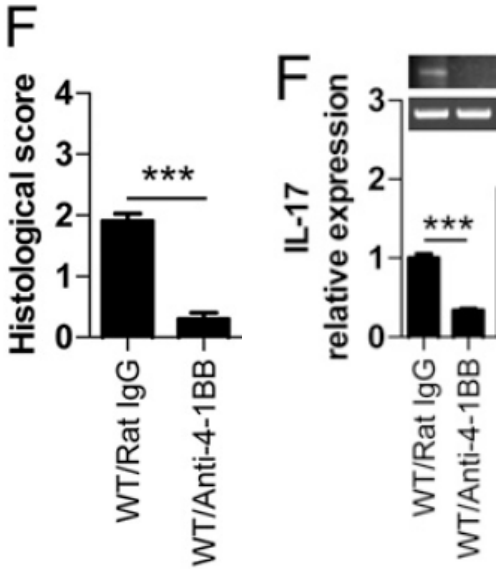
Agent	Cancer type suppressed
Anti-4-1BB mAb	Ag104A sarcoma
	MCA205, GL261 glioma
	C3 tumors, TC1 carcinoma
	J558 tumors
	A549 tumors
Variants of anti-4-1BB	K1735 melanoma
	M108 tumors
	K562 erythroleukemia
	FRα tumors
Anti-4-1BB combination therapy	B16 melanoma
	Renal cell carcinoma
	K1735 melanoma
	CT26 colon carcinoma
	MCA205 tumors
	MC38 tumors
	M109, EMT6 tumors
4-1BBL and its variants	Liver metastases
	Cholangiosarcoma
	Neuroblastoma
	AML, Wilms tumor 1
	Colon 2A and 26 tumors
	P815 plasmacytoma
	K562/AO2 tumors
	Mouse forestomach carcinoma

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

4-1BB antibodies can suppress autoimmune disease

4-1BB Triggering Ameliorates Experimental Autoimmune Encephalomyelitis by Modulating the Balance between Th17 and Regulatory T Cells *The Journal of Immunology*, 2011, 187: 1120–1128.

Young H. Kim,* Beom K. Choi,* Su M. Shin,* Chang H. Kim,* Ho S. Oh,* Sang H. Park,* Don G. Lee,* Myoung J. Lee,* Kwang H. Kim,* Dass S. Vinay,† and Byoung S. Kwon*,†

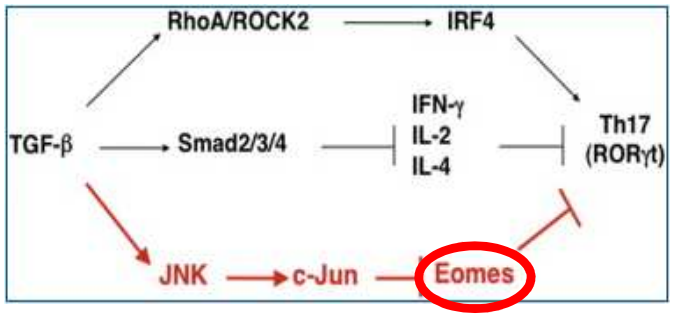


Published April 1, 2013
JEM

Article

Systemic 4-1BB activation induces a novel T cell phenotype driven by high expression of Eomesodermin

Michael A. Curran,[1] Theresa L. Geiger,[2] Welby Montalvo,[2] Myoungjoo Kim,[2] Steven L. Reiner,[3,4] Aymen Al-Shamkhani,[5] Joseph C. Sun,[2] and James P. Allison[1,2]



IL-27

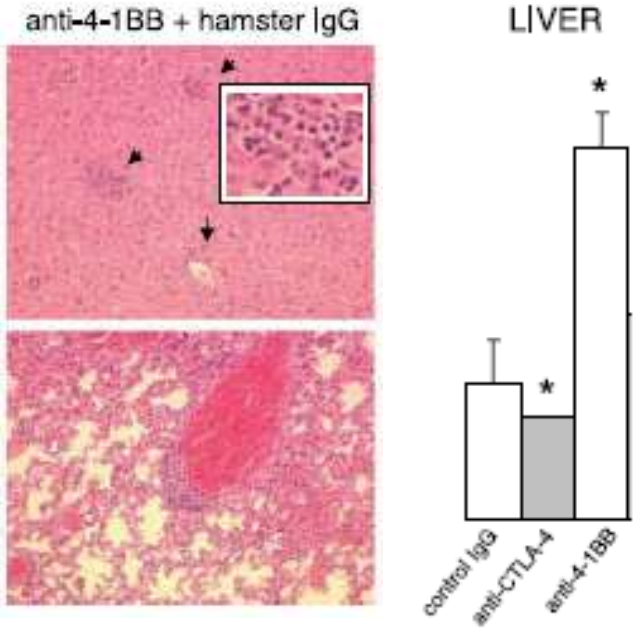
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

4-1BB agonist antibodies cause liver inflammation

Cancer Res. 2006 Jul 15;66(14):7276-84.

Combination therapy with anti-CTL antigen-4 and anti-4-1BB antibodies enhances cancer immunity and reduces autoimmunity.

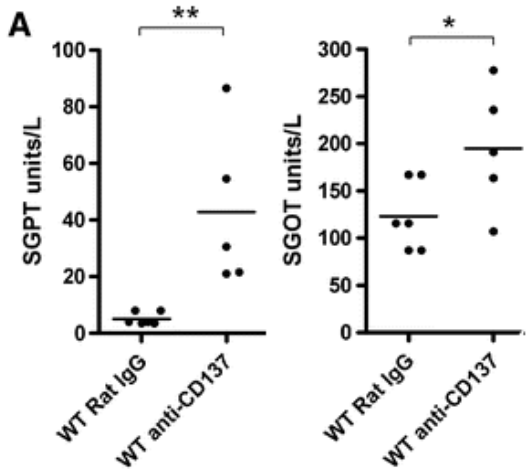
Kocak E[1], Lute K, Chang X, May KF Jr, Exten KR, Zhang H, Abdessalam SF, Lehman AM, Jarjoura D, Zheng P, Liu Y.



Cancer Immunol Immunother. 2010 Aug;59(8):1223-33. doi: 10.1007/s00262-010-0846-9. Epub 2010 Mar 25.

Treatment with anti-CD137 mAbs causes intense accumulations of liver T cells without selective antitumor immunotherapeutic effects in this organ.

Dubrot J[1], Milheiro F, Alfaro C, Palazón A, Martinez-Forero I, Perez-Gracia JL, Morales-Kastresana A, Romero-Trevejo JL, Ochoa MC, Hervás-Stubbs S, Prieto J, Jure-Kunkel M, Chen L, Melero I.



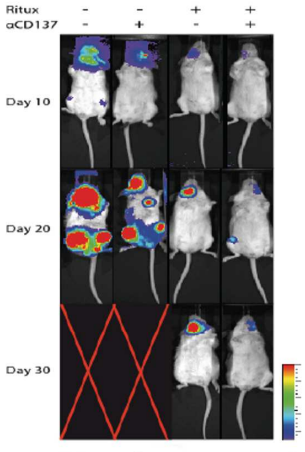
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

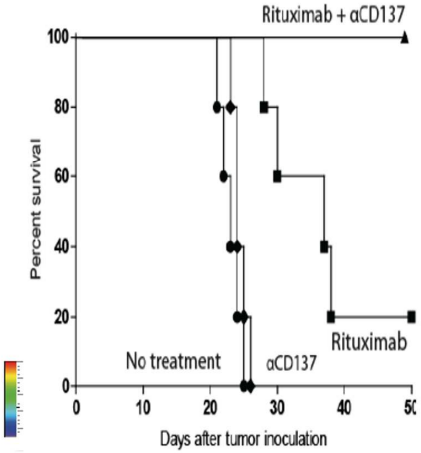
Urelumab (BMS): a potent clinical 4-1BB agonist limited by liver toxicity

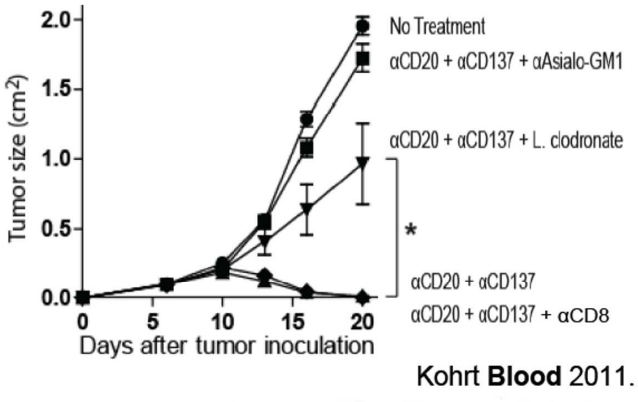
1. In an open label, dose escalation study, achieved monotherapy Recist PR in melanoma (~10%) and SD >6m in 17% of melanoma and 14% of RCC (2005).

2. During a Phase II follow-up trial in melanoma, multiple instances of Grade 4/5 liver toxicity led to an FDA hold (2009).

3. Urelumab trials resumed in 2011 at lower doses as a companion antibody to enhance the efficacy of ADCC-based antibody therapeutics such as Rituximab.







Kohrt **Blood** 2011.

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Utomilumab (Pfizer): A new 4-1BB agonist without significant liver toxicity

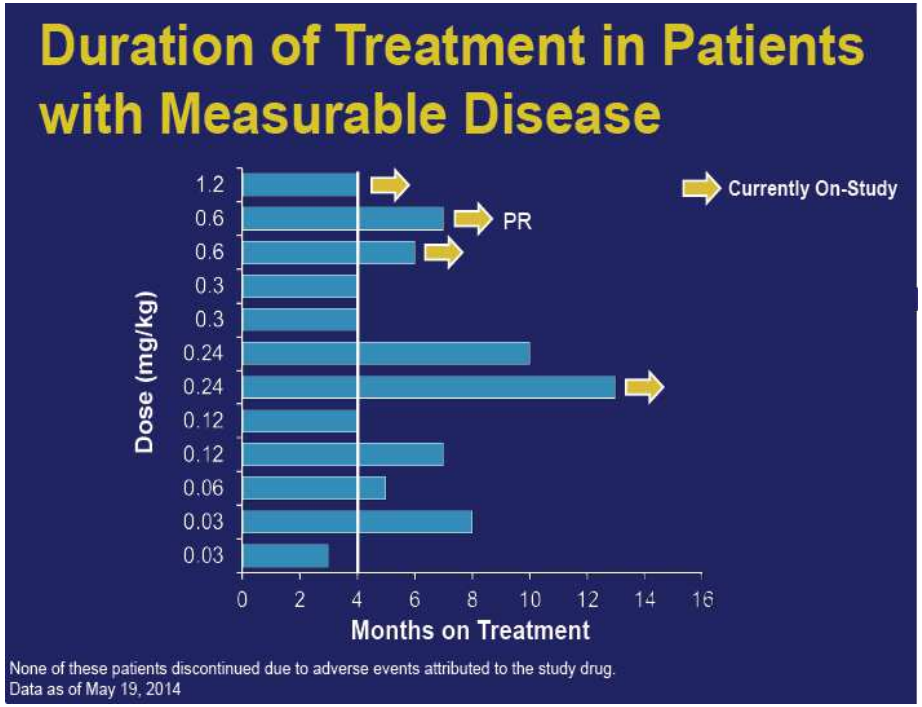
Utomilumab, Anti-CD137, Fully human, IgG2, Agonist

No liver toxicity > Grade 2
Can be safely dosed to 10mg/kg

Efficacy as monotherapy in Merkel Cell, but less than Urelumab in metastatic melanoma

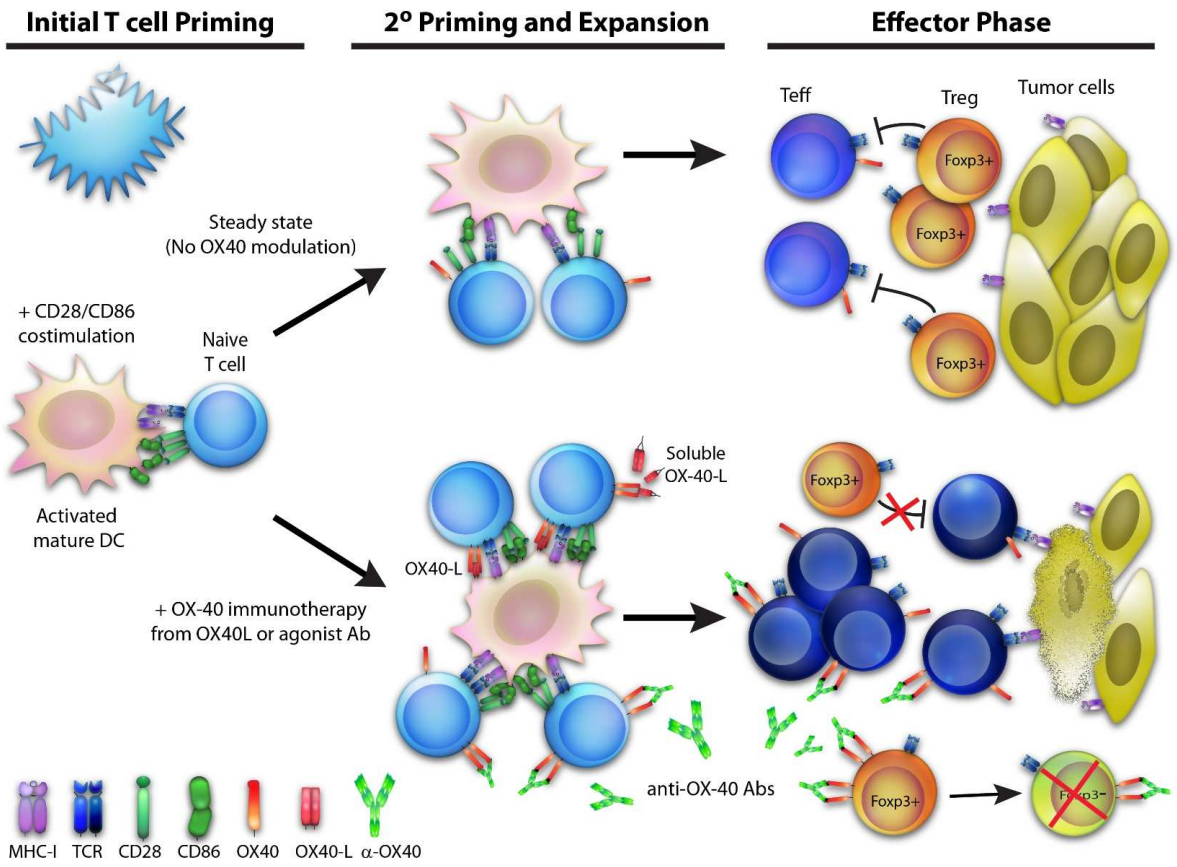
Currently being tested with αPD-1, αPD-L1, and αOX-40 in checkpoint combination trials.

Also being tested with Rituximab and cetuximab in ADCC combination trials.



THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

OX-40 antibody boosts effector T cells, can kill Tregs, and has a very favorable safety profile



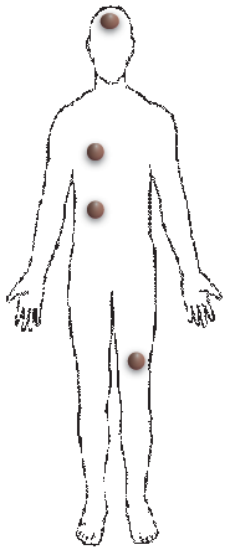
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

OX-40 Agonist Pros and Cons

- In mouse OX-40 antibodies target only CD4 T cells but in humans both CD4s and CD8s can be activated
- OX-40 agonists have a very mild safety profile making them attractive for combination regimens as well as adjuvant therapy
- Unlike 4-1BB antibodies, OX-40 activation does not augment APC function or strongly augment T / NK cell cytotoxicity

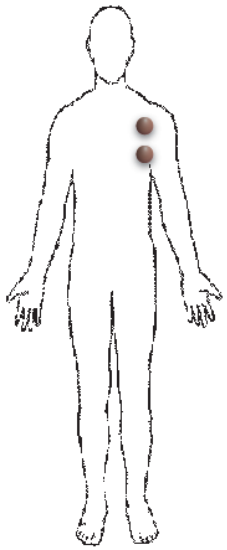
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

One (combination) shoe doesn't fit all



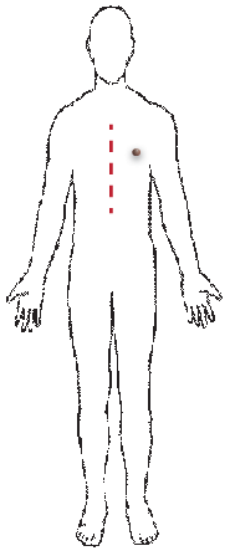
Advanced Metastatic disease

αCTLA-4/αPD-1
+Rad or drug or
Anti-stromal therapy
or STING



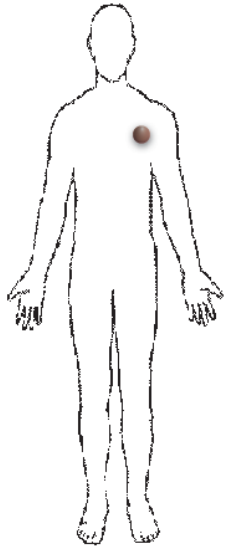
Locally advanced disease

αPD-1 or αPD-L1
+Rad or drug or
Anti-stromal therapy
or STING



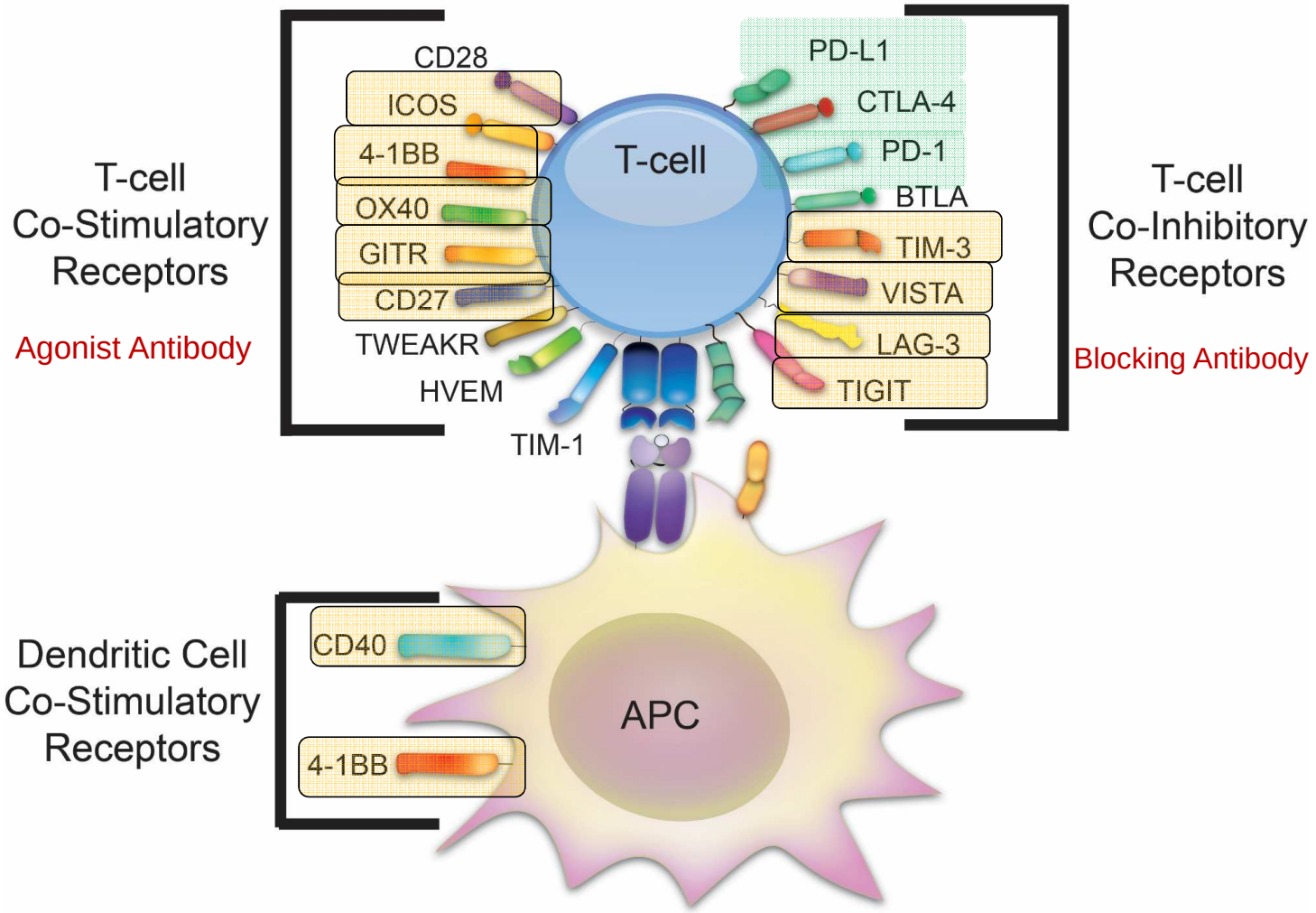
MRD post-surgery

αOX40/αPD-L1
or
αOX40/αMDSC
or
αOX-40/TLR



Localized, accessible disease

Local αCTLA-4,
α4-1BB or αCD40
or
Local STING/TLR



Ai M., **Curran M.A.** Immune checkpoint combinations from mouse to man. *Cancer Immunology Immunotherapy*, 2015.

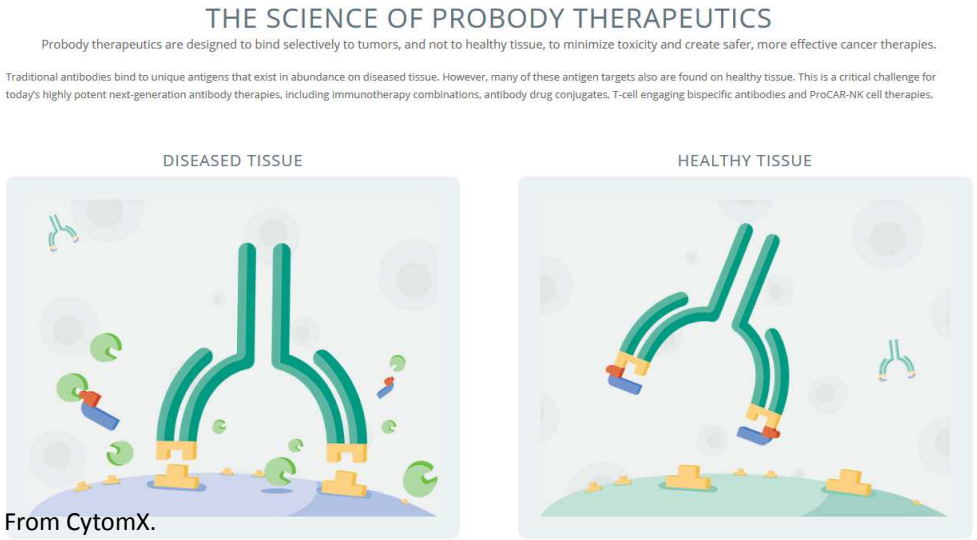
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Future checkpoint antibodies with reduced toxicity will be well-suited for multi-drug therapy

1. Current CTLA-4. 4-1BB, CD40 and possible PD-1 antibodies are under dosed and sub-optimally engineered relative to their murine counterparts to achieve tolerability.

2. Combinations of checkpoint antibodies are toxicity-limited in terms of dosing and complexity (e.g. 1I Q12W + 3N Q2W dosing for Ipilimumab/Nivolumab).

3. Emerging technologies which reduce off-target immune-related adverse events by selectively targeting checkpoint receptors in the tumor microenvironment will enable higher potency monotherapy dosing and high order combinations of multiple drugs.



From CytomX.

To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.

The goal of T cell checkpoint blockade is block the switches on T cells being engaged by the tumor to shut them down and in so doing to restore tumor-specific immunity.

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Lessons and Take Home Messages

- The immune system has the potential to recognize and reject most cancers, but tumors locally suppress immunity.
- Antibodies which block T cell immune checkpoint receptors protect these cells from being attenuated in the tumor microenvironment allowing them to regress tumors.
- Antibodies which activate (agonists) T cell co-stimulatory receptors can expand, protect, and increase the per cell effector function of tumor-specific T cells.
- Optimal combinations will be those which 1) activate non-redundant pathways, 2) target multiple cell types within the tumor microenvironment, 3) do not worsen the severity of immune related adverse events.
- The field is moving toward more effective and less toxic checkpoint modulating antibodies which can be used in double or triple combinations or rationally sequenced.