PD-1 Cancer Immunotherapy

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MEDICAL SCHOOL

Disclosure Information

Gordon Freeman, PhD

I have the following financial relationships to disclose:

Intellectual Property related to the PD-1 / PD-1 Ligand pathway licensed non-exclusively to:
Bristol-Myers-Squibb, Roche, Merck, Merck-Serono, Boehringer-Ingelheim, AstraZeneca, Novartis

Intellectual Property related to TIM-3 licensed to Novartis

***Consultant for*: Bristol-Myers Squibb, Novartis, Roche, Lilly, Seattle Genetics, Bethyl Labs, Xios, Quiet**

Immunology has offered hope for curing cancer for 100 years

What is different now?

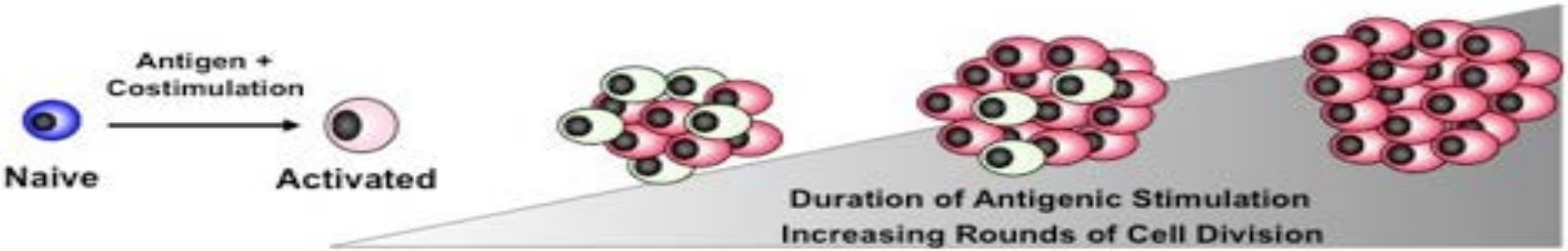
New Strategy

Blockade of pathways
used by tumors to
inhibit anti-tumor immunity

Checkpoint blockade

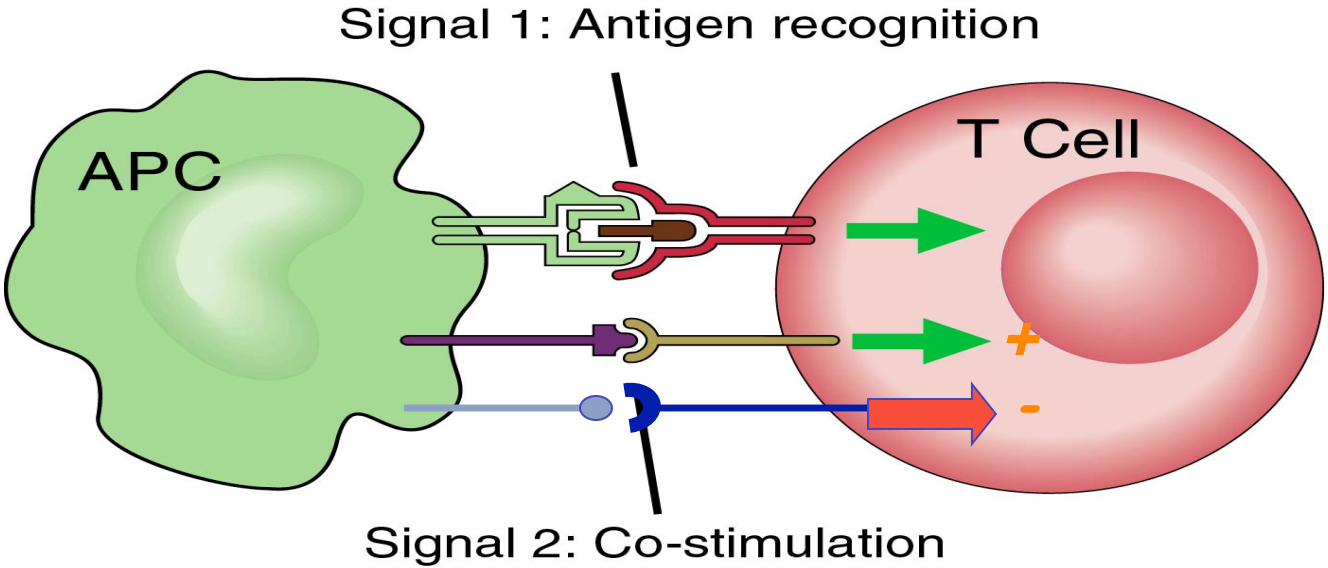
T cells are white blood cells that can kill cancer cells: more is better

T cell clonal expansion



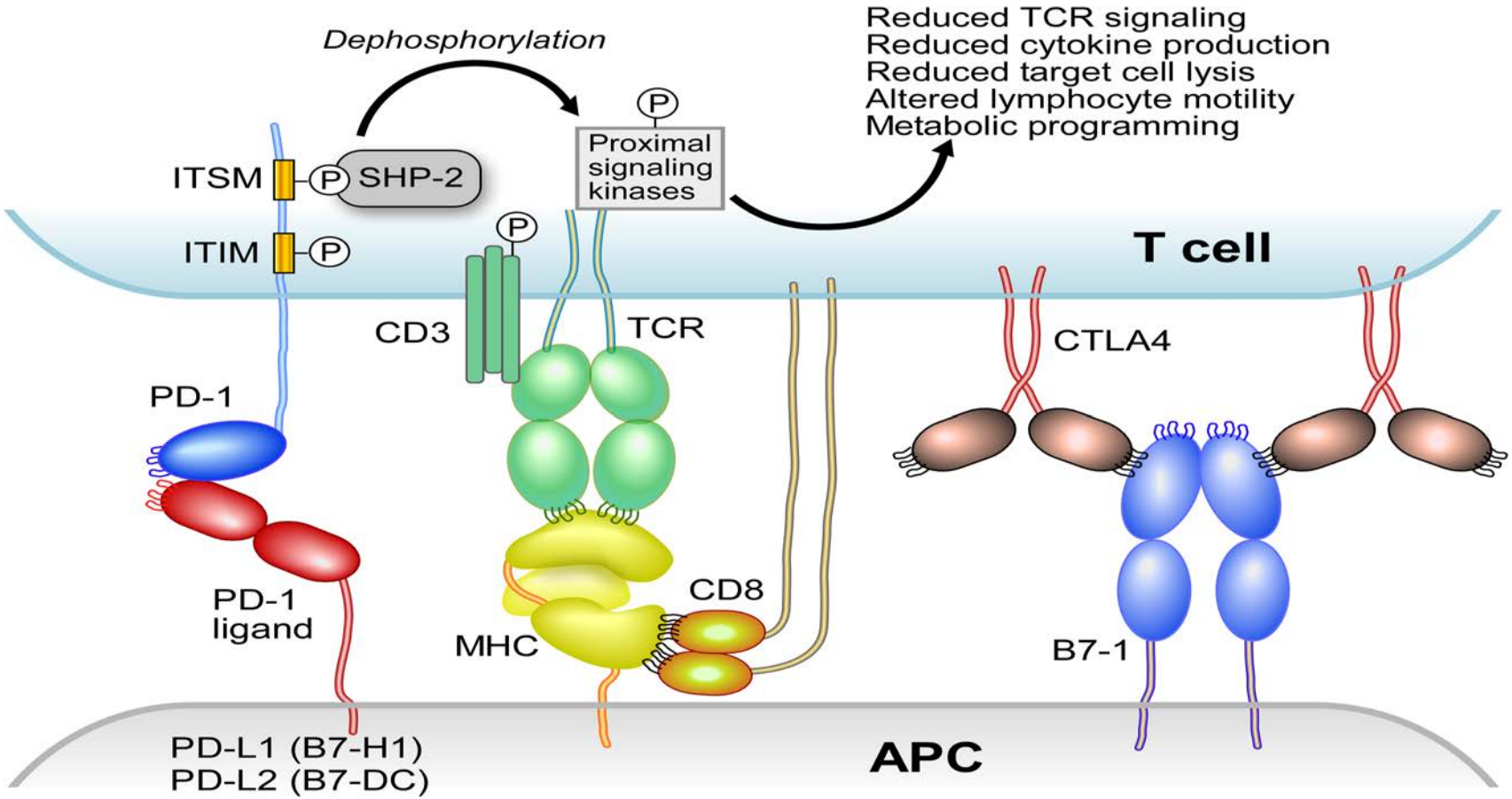
1000 T cells 18 divisions (6 days) millions of T cells

T cell activation



- **There are positive and negative second signals**

The PD-1 Pathway Inhibits T Cell Activation



Identify the drug target: block PD-1/PD-L1

Engagement of the PD-1 Immunoinhibitory Receptor by a Novel B7 Family Member Leads to Negative Regulation of Lymphocyte Activation

By Gordon J. Freeman,* Andrew J. Long,‡ Yoshiko Iwai,§ Karen Bourque,‡ Tatyana Chernova,* Hiroyuki Nishimura,§ Lori J. Fitz,‡ Nelly Malenkovich,* Taku Okazaki,§ Michael C. Byrne,‡ Heidi F. Horton,‡ Lynette Fouser,‡ Laura Carter,‡ Vincent Ling,‡ Michael R. Bowman,‡ Beatriz M. Carreno,‡ Mary Collins,‡ Clive R. Wood,‡ and Tasuku Honjo§

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Volume 192, Number 7, October 2, 2000 1027–1034

PD-1 = Programmed Death-1

- cloned from a CD3-activated T cell hybridoma undergoing activation-induced cell death (Honjo lab)

- Does not directly activate caspases and cause cell death or apoptosis; not like CD95 (Fas)

- Indirect effect on cell death by reduced cytokines, survival factors (less Bcl-xL, more BIM)

Why have negative signals like PD-1 ?

1. Maintain immune tolerance

2. Tune down the immune response after elimination of disease

3. Prevent too strong an immune response damaging tissues

Arlene Sharpe, Tasuku Honjo

PD-L2 is a second ligand for PD-1 and inhibits T cell activation

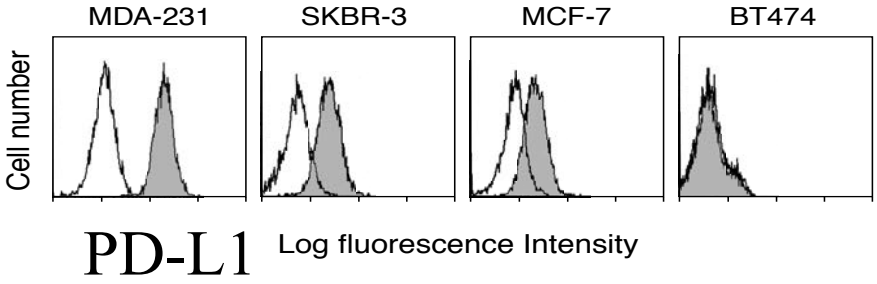
Discovery may shed light on cancer's shield against the immune system

For years, a question has tantalized cancer researchers: why is the immune system, normally so adept at unmasking and eliminating foreign invaders and abnormal cells, not always spry enough to destroy tumor cells?

A new study by Dana-Farber scientists suggests an answer.

In a paper published in the March issue of *Nature Immunology*, investigators led by Gordon Freeman, Ph.D., of Adult Oncology report that a structure

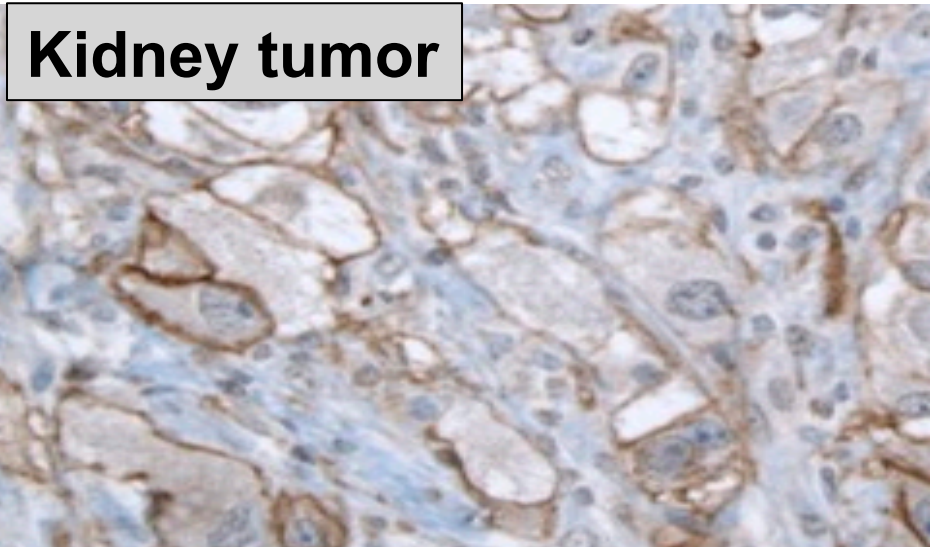
PD-L1 on Breast cancer cell lines



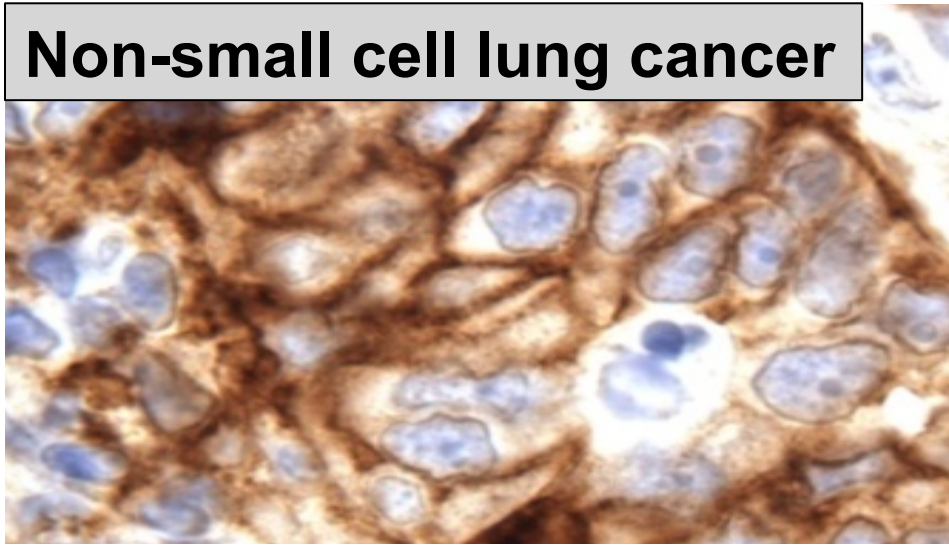
PD-L1 in Cancer

- **Expressed on cell surface of ~30% solid tumors and selected hematologic malignancies**
- **Inhibits anti-tumor immune responses**

Kidney tumor



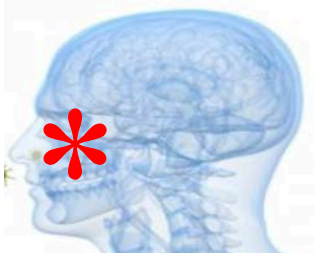
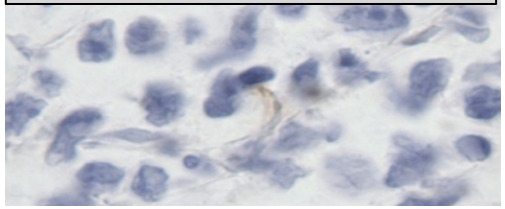
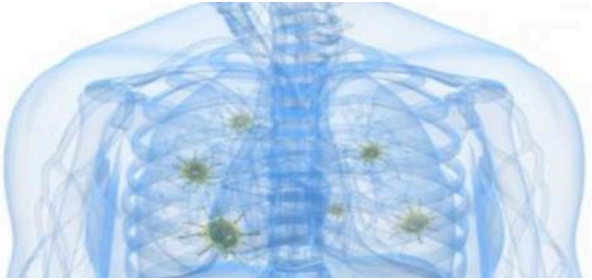
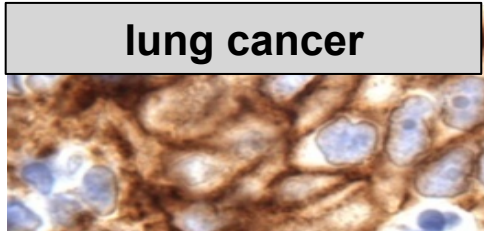
Non-small cell lung cancer



Brown = PD-L1

Rodig, Signoretti, McDermott; BWH & DFCI

In most cancer patients, only the immune response against cancer is suppressed.
The immune response against infection is OK.

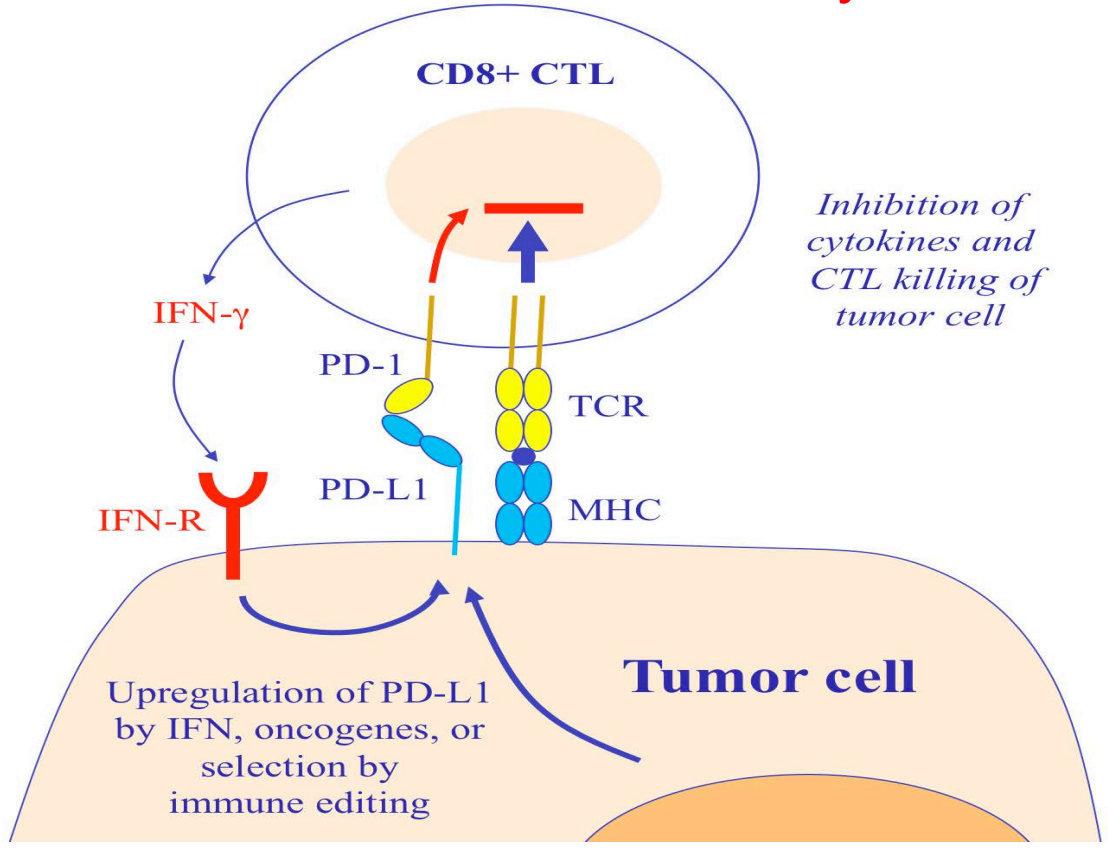
		PD-L1 expression	Immune response
Common cold		normal 	good
Lung cancer		lung cancer 	suppressed

Brown = PD-L1

Why doesn’t directly stimulating the immune response cure cancer ?

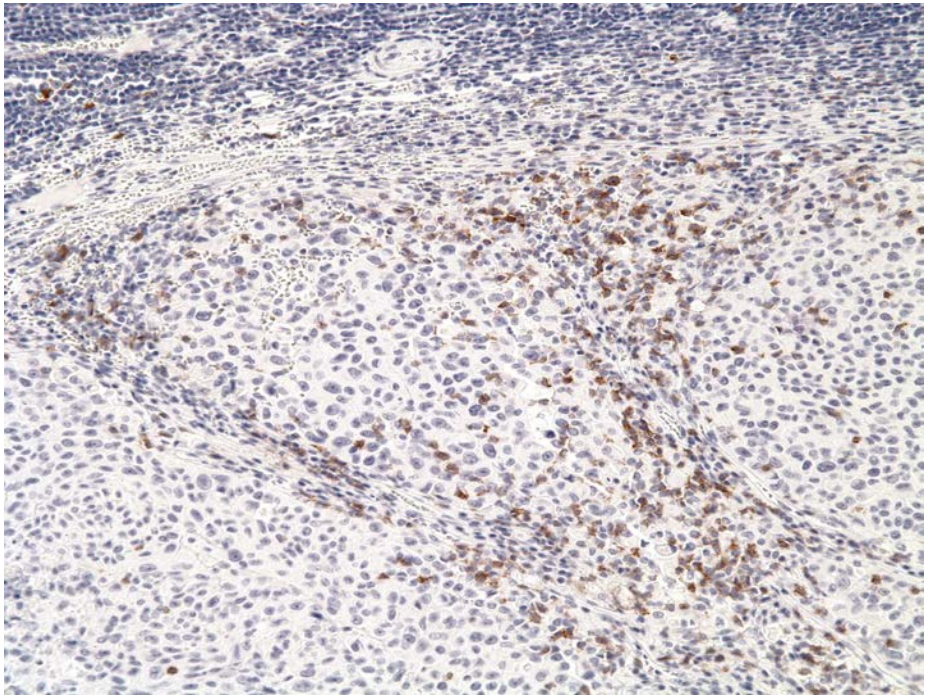
Once the tumor gets ahead and expresses PD-L1, Immuno-inhibition is dominant and maintained by a feedback loop

Taube et al:
Adaptive resistance

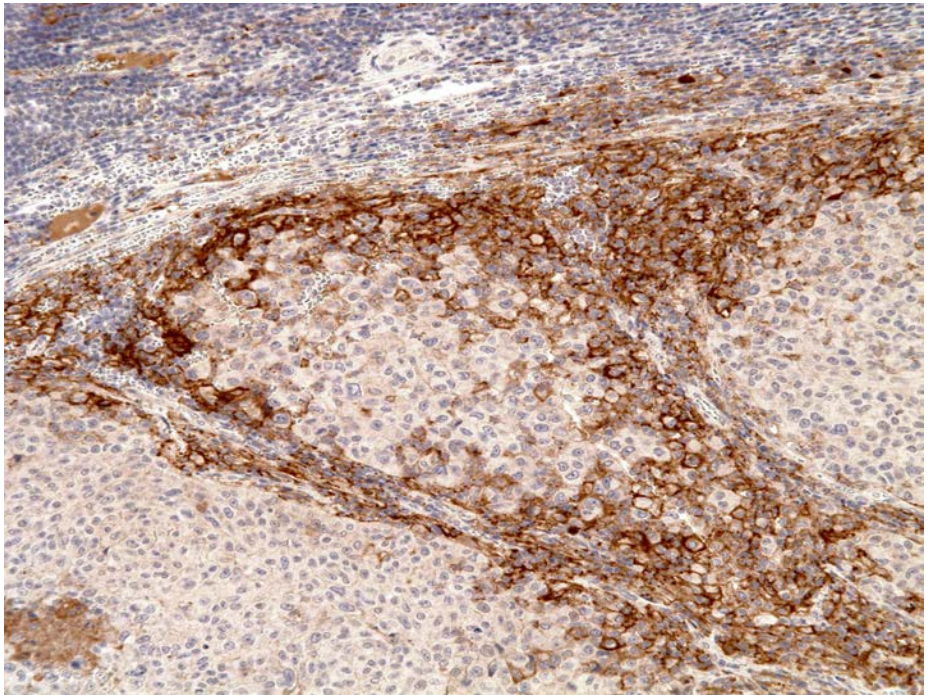


PD-1^{+} T cells at a PD-L1^{+} tumor interface

PD-1^{+} T cells

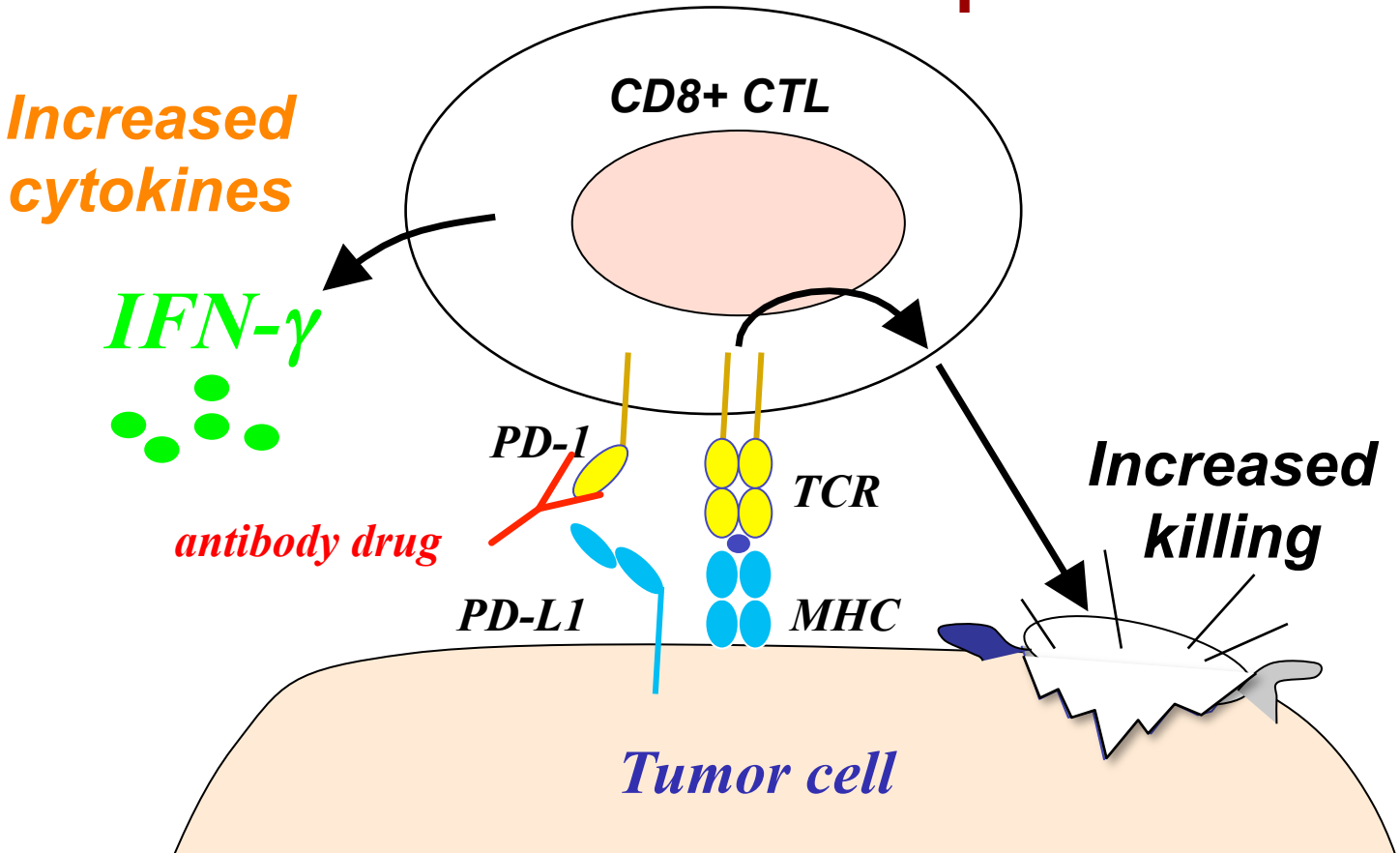


PD-L1^{+} melanoma



George Murphy, Scott Rodig, Gordon Freeman, BWH & DFCI

PD-1 or PD-L1 Blockade Stimulates anti-tumor T cell response



Antibodies in Clinical Trials

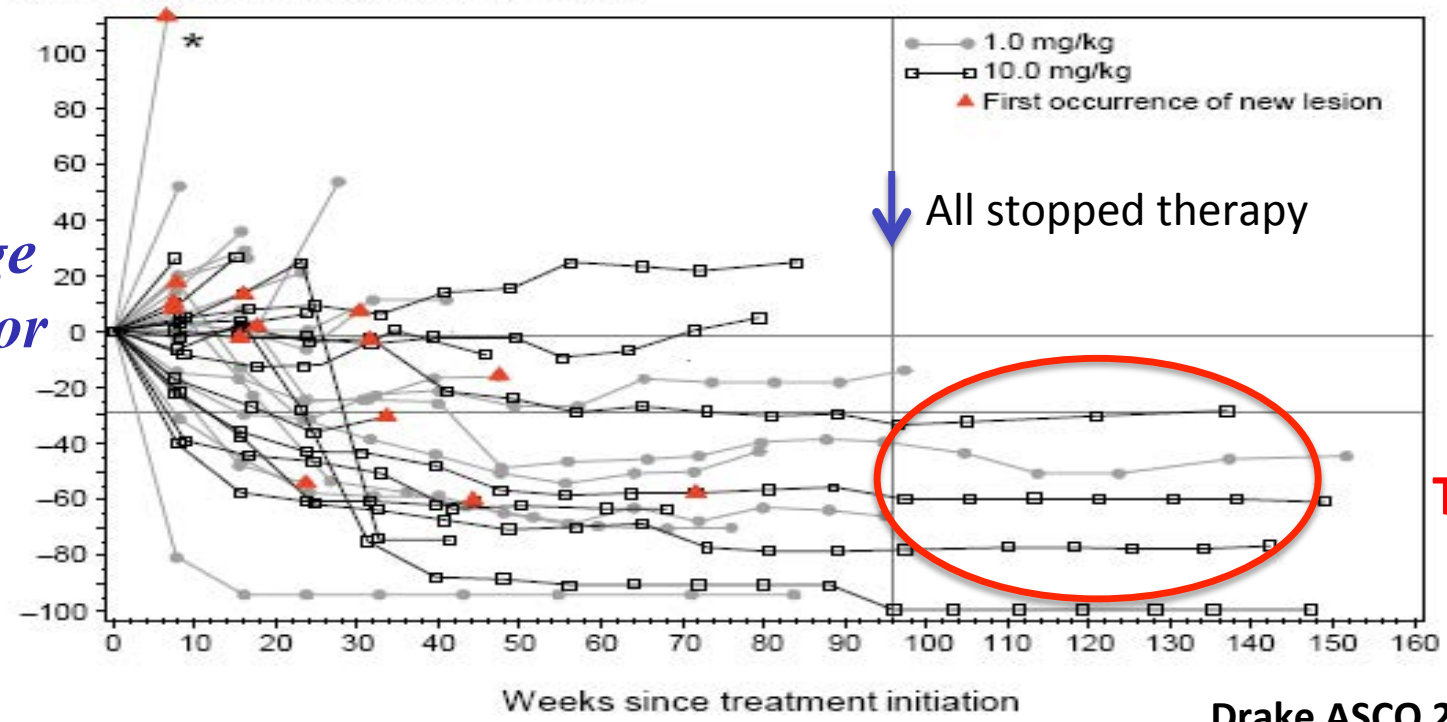
- Anti-PD-1
  - Nivolumab (BMS)
  - Pembrolizumab (Merck)
  - MEDI-0680 (AstraZeneca)
  - PDR001 (Novartis)
  - REGN2810 (Regeneron)

- Anti-PD-L1
  - Atezolimumab (Roche)
  - Durvalumab (AstraZeneca)
  - Avelumab (EMD Serono/Pfizer)
  - MDX-1105 (BMS)

Multiple other agents in development

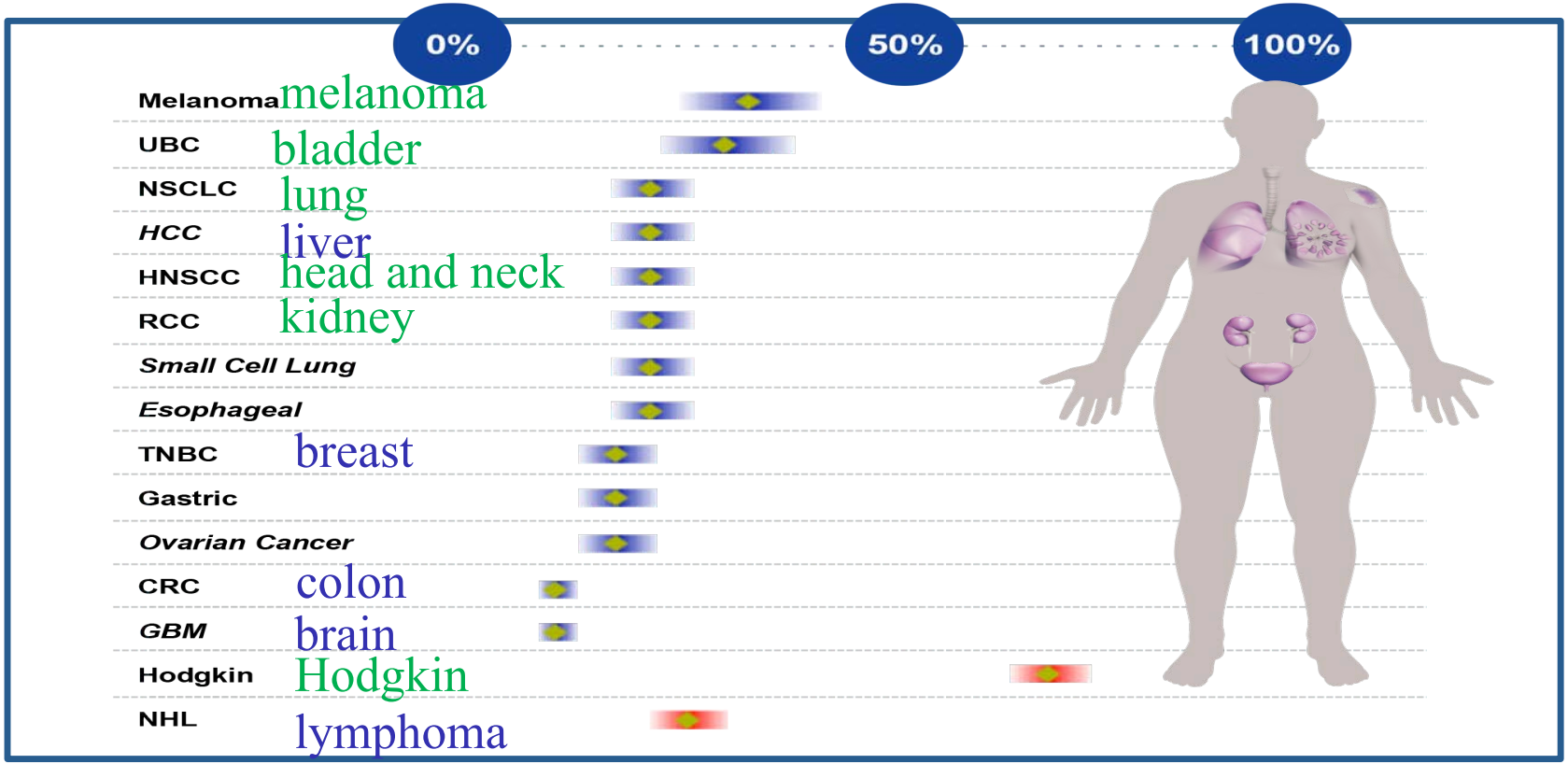
Phase I clinical trial of anti-PD-1 antibody Nivolumab: Kidney Cancer cohort (34 patients)

- Generally tolerable: fatigue, rash, pruritus, diarrhea
  - Each line follows growth or shrinkage of tumor in one patient



Drake ASCO 2013

Broad anti-tumor efficacy of anti-PD-L1/PD-1 inhibitors:
Overall Response Rates



243 clinical study reports

Modified from D. Chen, BioScience Forum, 2015

PD-1 Cancer Immunotherapy is different from chemotherapy

- Well tolerated: This is not chemotherapy or a cell poison!
  some nausea, no hair loss, no blood cell count decline.

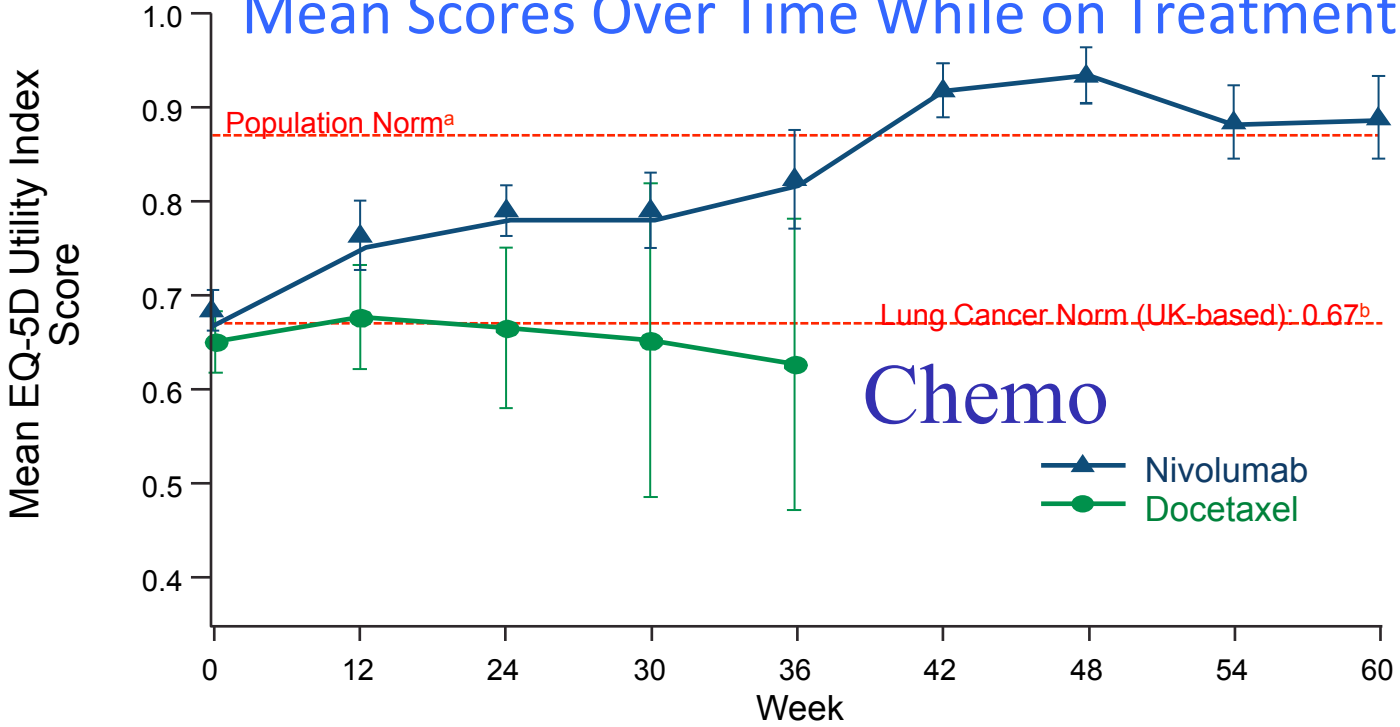
- Good safety profile

- Most serious adverse events are autoimmune-mediated, like pneumonitis, colitis. Less than 10% of patients

- Physicians will have to learn to manage a different spectrum of adverse events than those seen in chemotherapy

- This can be community hospital medicine: half-hour intravenous drug infusion.

Better Quality of life:
Squamous NSCLC : EQ-5D Utility Index
Mean Scores Over Time While on Treatment



Nivolumab (n = 97)	97	50	32	32	21	18	13	13	8
Docetaxel (n = 89)	88	32	9	5	5	4	4	2	1

Higher scores indicate better health status.
Only time points that had PRO data available for ≥5 patients in either treatment arm are plotted on the graph.

[a]Bharmal M, Thomas J 3rd. *Value Health*. 2006;9:262–71.
[b]Pickard AS, et al. *Health Qual Life Outcomes*. 2007;5:70.

Better Quality of Life

- Reck said responding patients “remaining on treatment with nivolumab returned to population health-status norm, suggesting that prolonged survival occurs with a resumption of normal life”

Checkpoint works equally well in the aged

Meta-analysis of 6 Phase III PD-1 and CTLA-4 trials

2,078 younger patients < 65-70 years

1,224 older patients > 65-70 years

Younger: Hazard Ratio, 0.73; P<0.001

Older: Hazard Ratio, 0.72; P=0.004

T Funakoshi et al., SITC 2015

90 year old with metastatic melanoma and 4 brain metastases:

Treated with PD-1 mab

Predictive biomarkers are essential for getting the right treatment to the right patient.

PD-L1 expression in tumor increases the likelihood of response to PD-1/PD-L1 blockade

Objective Response Rates

	Solid tumors Topalian NEJM 2012	Melanoma Weber JCO 2013	Melanoma Grosso ASCO 2013	Melanoma Daud AACR 2014	NSCLC Gandh AACR 2014	Head+Neck Seiwert ASCO 2014	Melanoma Ribas ASCO 2014	Solid tumors Herbst ASCO 2013	Melanoma Hamid ASCO 2013	NSCLC Soria ECC 2013	Bladder Powles ASCO 2014	Solid tumors Segal ASCO 2014
n=	42	44	34	113	129	55	411	94	30	53	65	179
unselected	21%	32%	29%	40%	19%	18%	40%	21%	29%	23%	26%	11%
PD-L1 +	36%	67%	44%	49%	37%	46%	49%	36%	27%	46%	43%	22%
PD-L1 -	0%	19%	17%	13%	11%	11%	13	13%	20%	15%	11%	4%
Treatment:	anti-PD-1 Antibody							anti-PD-L1 Antibody				
Assay:	Membranous pattern on tumor cells							Immune infiltrate				NR

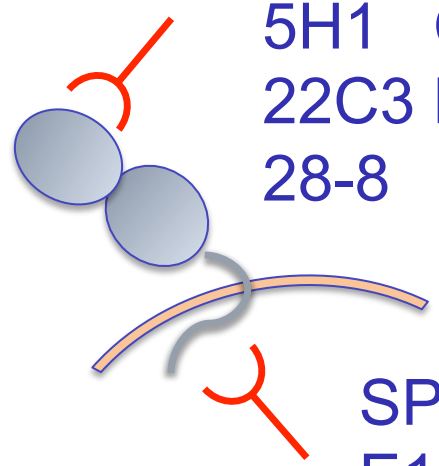
Nivolumab Pembrolizumab MPDL3280A MEDI 4736

A new era in PD-L1 immunohistochemistry

Now at least 5 good PD-L1 IHC mAbs available

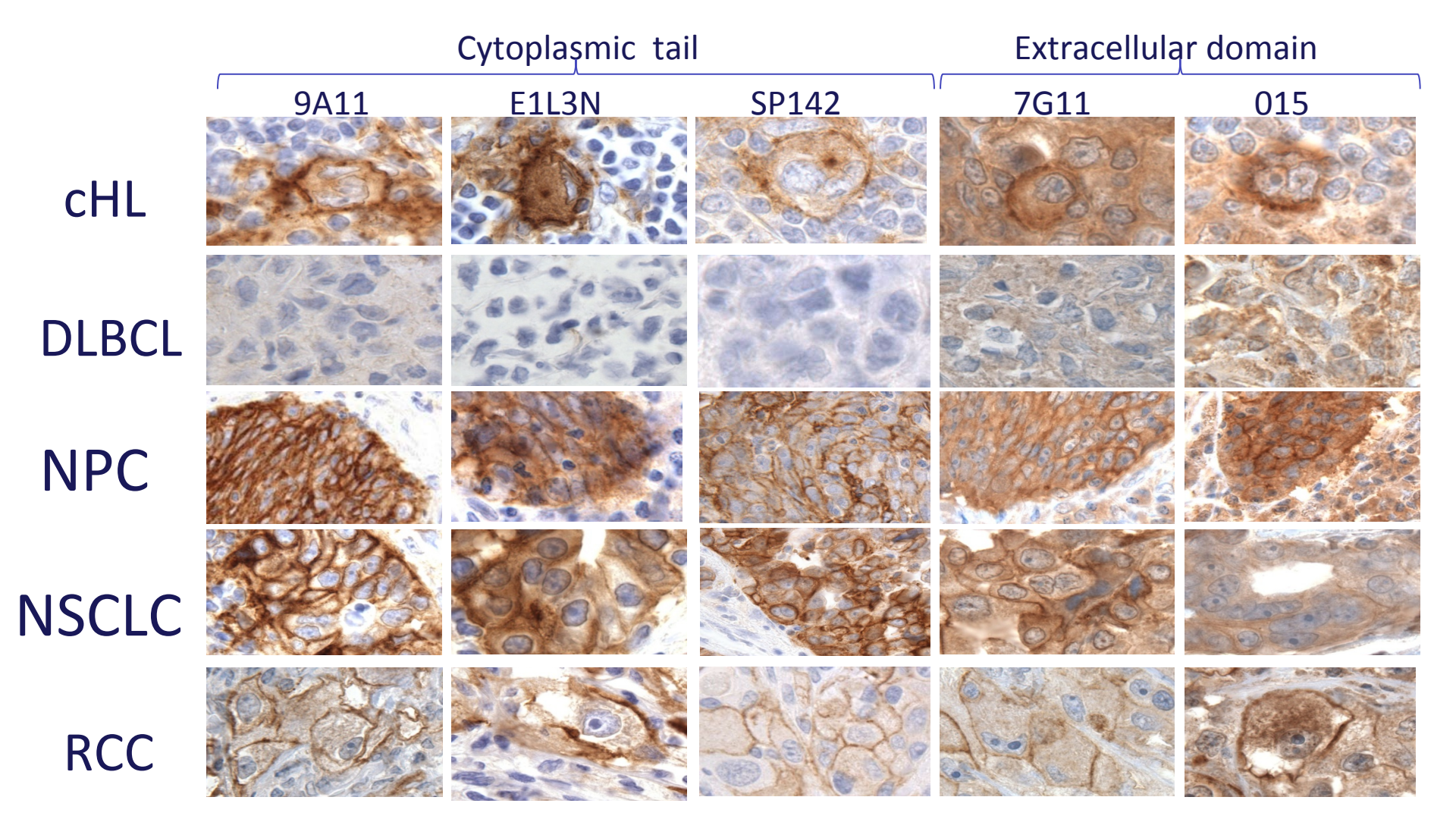
extracellular

5H1 Chen
22C3 Merck - Dako/Quest
28-8 BMS - Dako/Quest



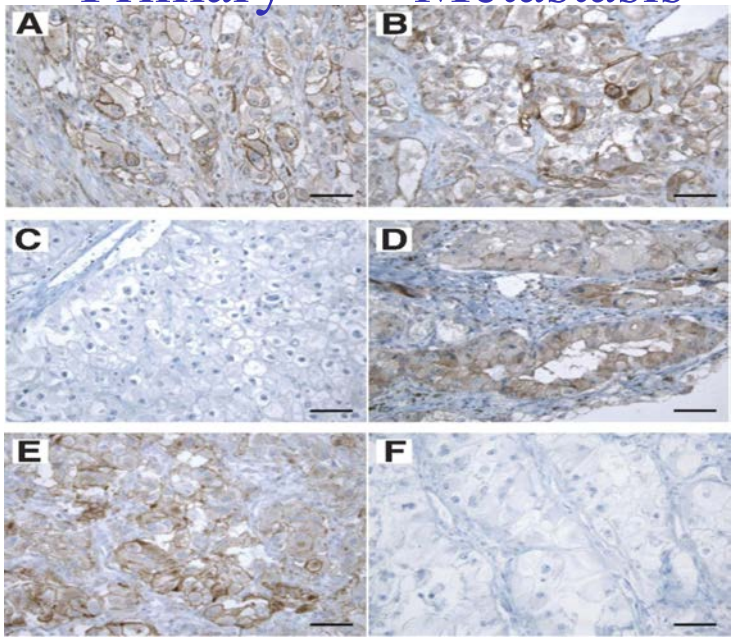
intracellular

SP142 Roche - Spring
E1L3N CST
9A11 Freeman - CST


Cytoplasmic tail
Extracellular domain
9A11
E1L3N
SP142
7G11
015
cHL
DLBCL
NPC
NSCLC
RCC

21% Discordancy between PD-L1 on Primary and Metastasis in RCC

Primary Metastasis



Callea et al. Cancer Immunol Res 2015;3:1158-1164

9

- PD-L1 positivity was heterogeneous and almost exclusively detected in high nuclear grade areas ($P < 0.001$).

3

- Assessment as a predictive biomarker for PD-1 blockade may require analysis of metastatic lesions.

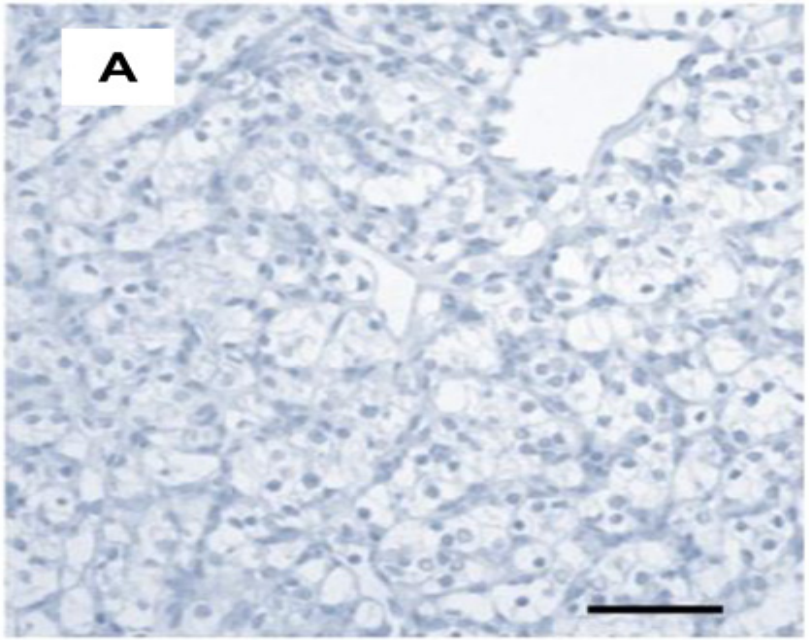
8

- Pathologists should select high grade tumor areas for PD-L1 IHC analysis to avoid false negatives.

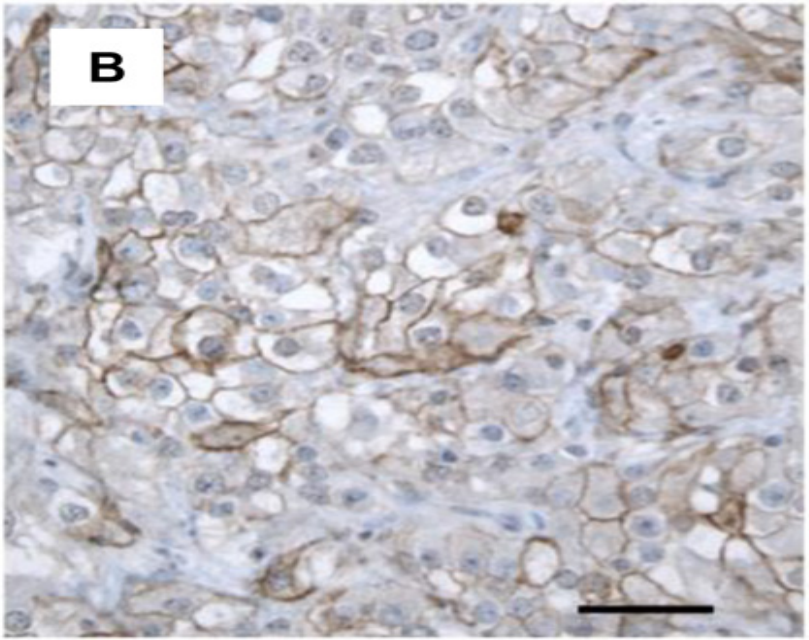
20 positive
33 negative in primary & met
53 cases

PD-L1 expression was heterogeneous even within individual RCC lesions

Low grade area



High grade area



Callea et al. Cancer Immunol Res 2015;3:1158-1164

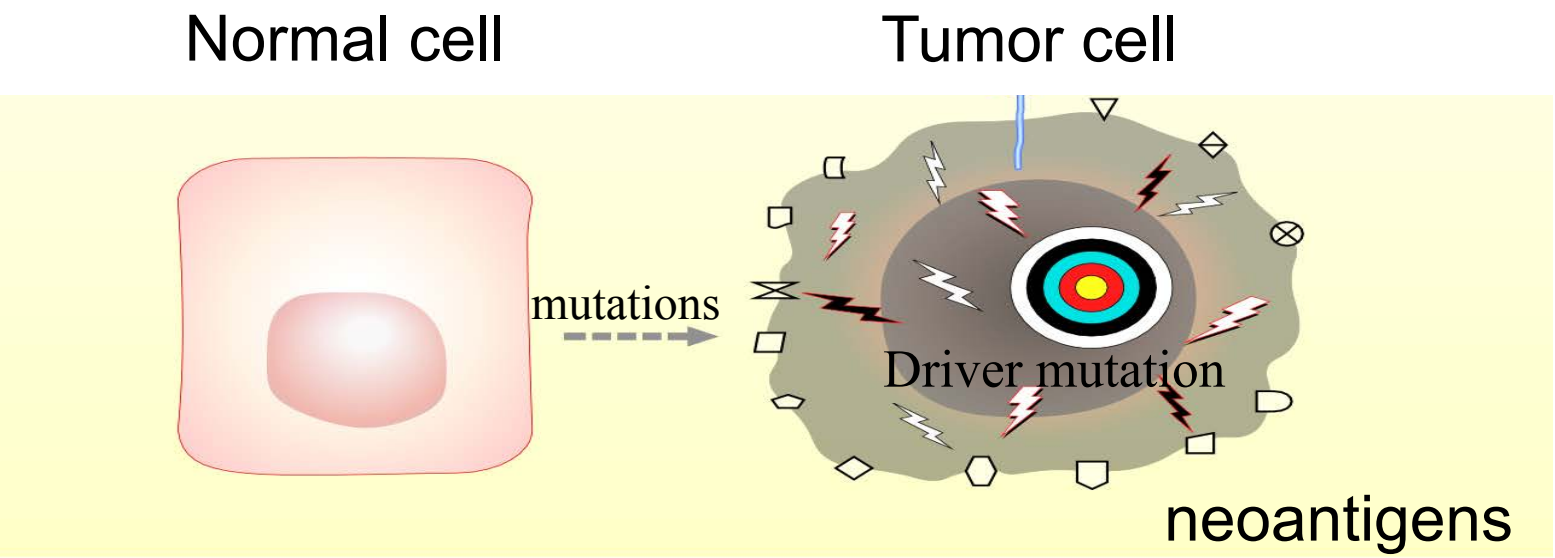
PD-L1 was almost exclusively detected **in high nuclear grade areas** ($P < 0.001$)

- PD-L1 expression on the tumor is not a good enough biomarker.

- Further analysis is needed to identify what biomarkers correlate with responsiveness to immunotherapy.

What does the immune system see in a tumor to attack ?

The immune system recognizes protein coding changes in the tumor cell, called tumor neoantigens.



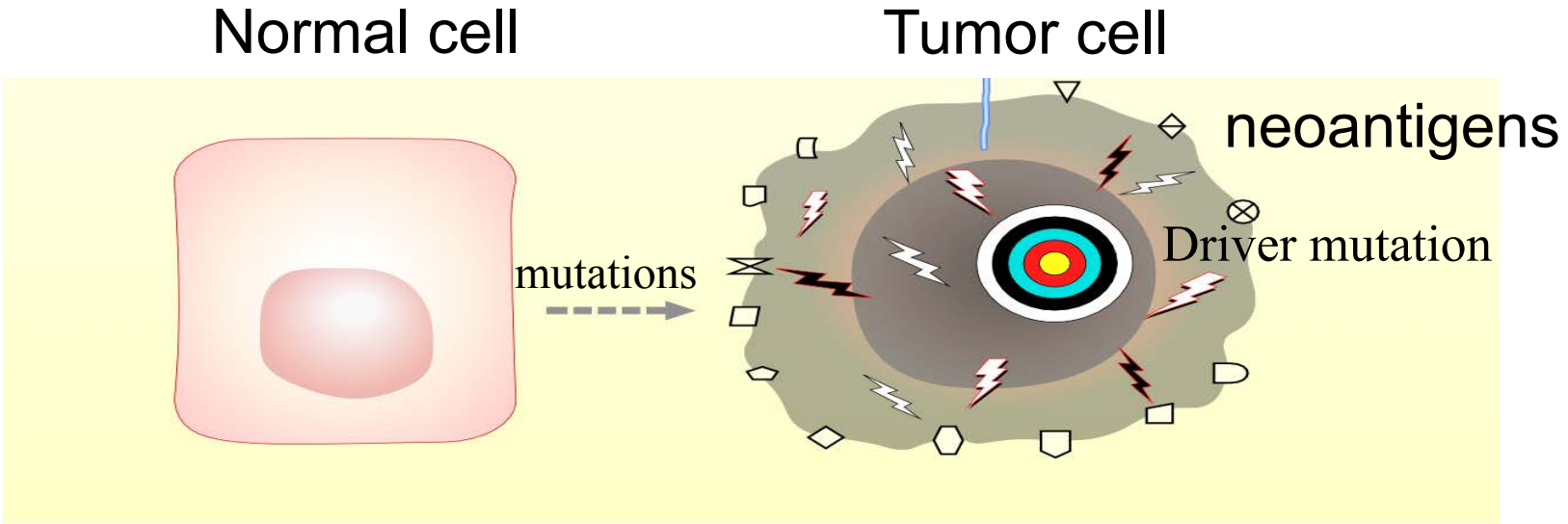
Two evolutionary processes in cancer:

1. **DNA mutation**

   Rare driver mutations

   many passenger mutations

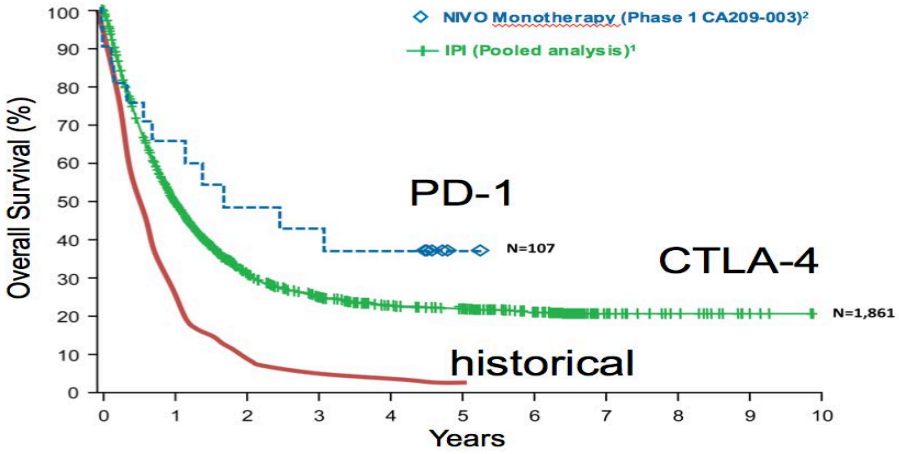
2. **Immune evasion: PD-L1, IDO, TGF-β, IL-10, loss of MHC, others**



Understanding immunology and genetics has identified groups that respond well to PD-1/PD-L1 therapy

- Highly mutated tumors (MSI, defects in DNA repair) : 62%
- Genetically amplified PD-L1 and PD-L2 (Hodgkin) : 87%
- With Viral antigens (HPV, Head and neck; Merkel)
- What other cancer types might respond well ?

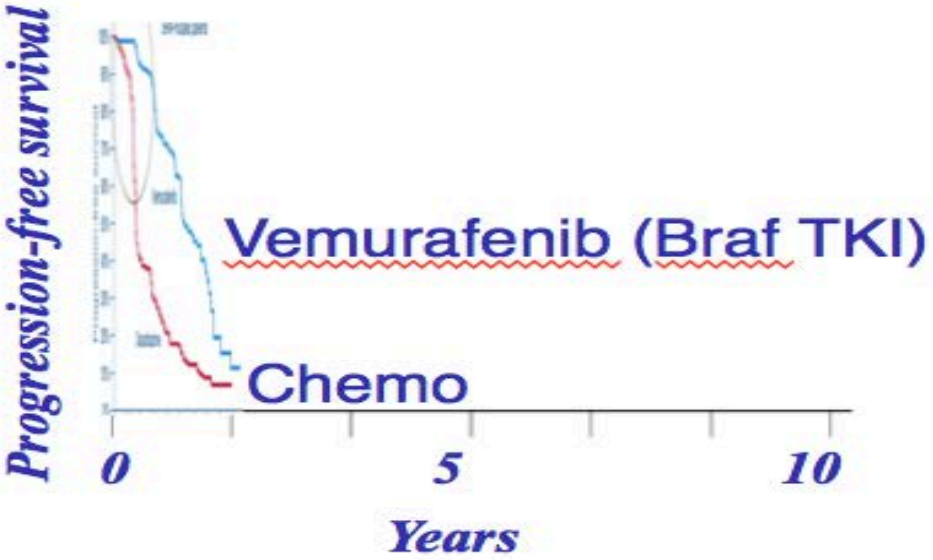
Why the enthusiasm for immunotherapy?



melanoma

Data from *Hodi et al., AACR 2016; Schadendorf et al. J Clin Oncol 2015*

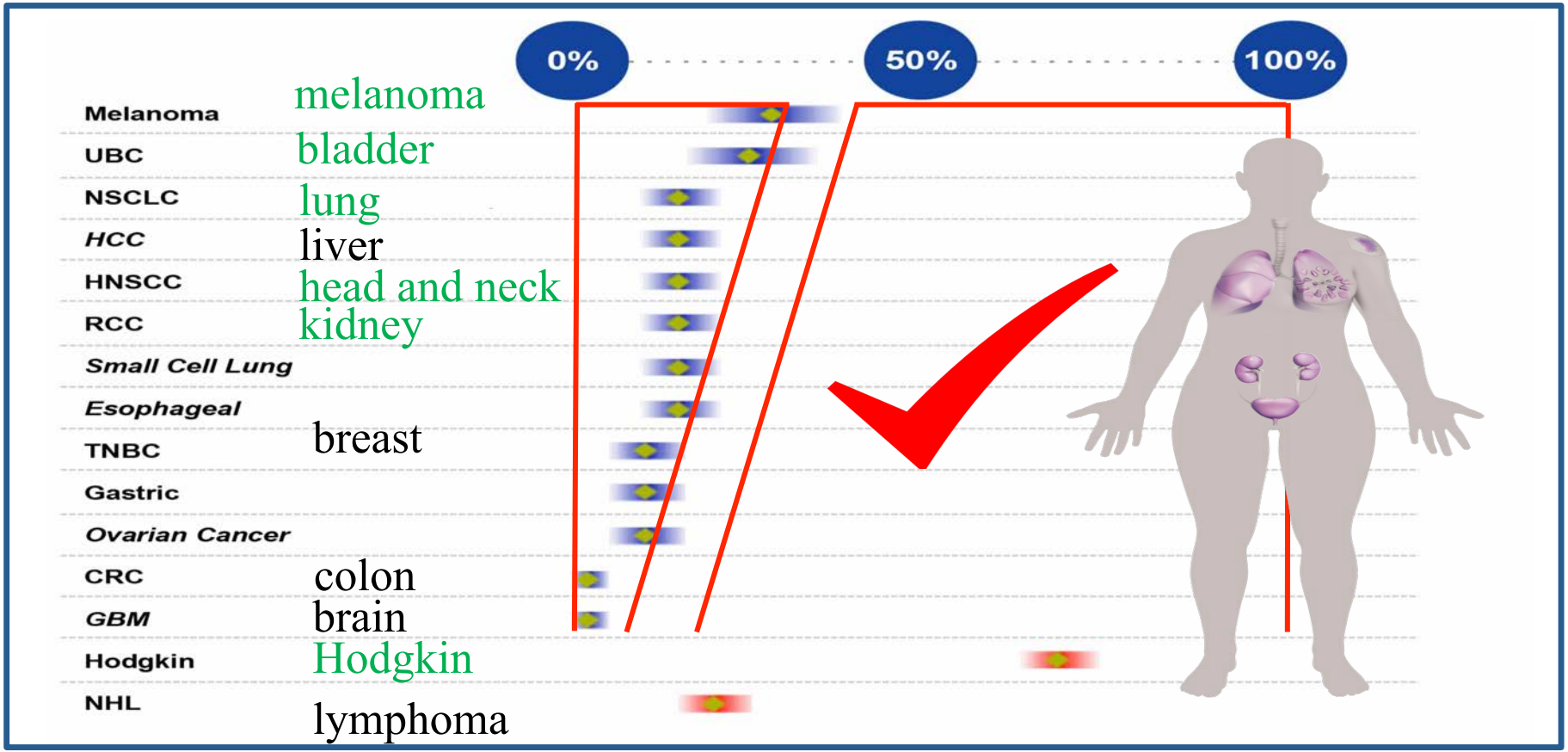
Moderate percentage but long-term



Chapman NEJM 2011

High percentage but short-term

Broad anti-tumor efficacy of anti-PD-L1/PD-1 inhibitors:
Overall Response Rates

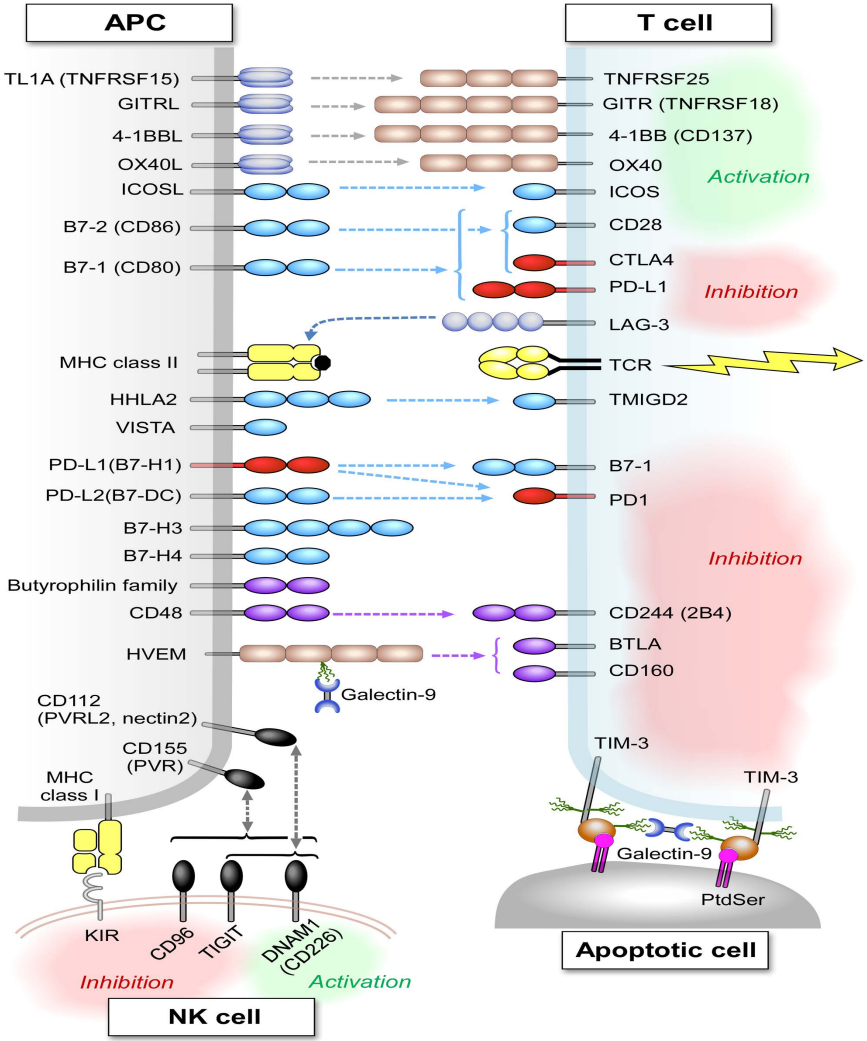


Why did T cells need PD-1 blockade to attack the tumor ?

Anti-tumor immune response is a years long struggle.

The T cells had tried, failed, upregulated expression of inhibitory receptors and become “exhausted”

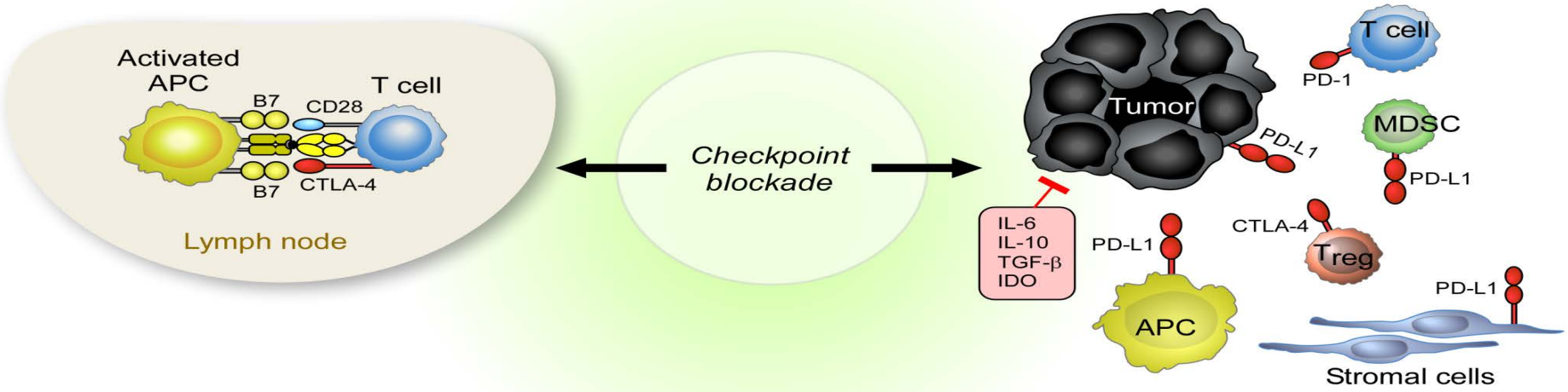
T cell exhaustion is more than PD-1



Exhausted tumor infiltrating lymphocytes express multiple immunoinhibitory receptors:

These are druggable targets for tumor immunotherapy

Where does checkpoint blockade function?



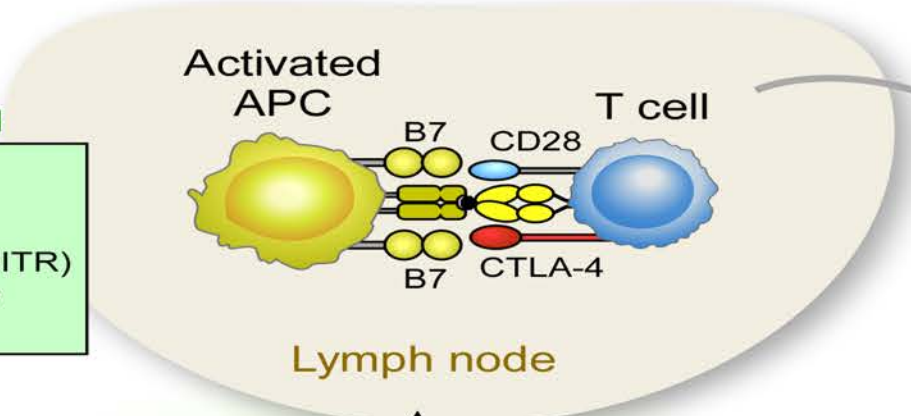
CTLA-4 in the lymph node

PD-1 in the tumor

The Future is Combination Therapy

T cell priming & activation

DEFICIT	THERAPEUTIC APPROACH
Insufficient priming/activation naïve T cells	• Block multiple checkpoints (CTLA-4, PD-1, LAG-3, TIM-3) • Activate stimulatory pathways (CD137, OX-40, CD27, ICOS, GITR) • Administer stimulatory cytokines (IL-2, IL-12)

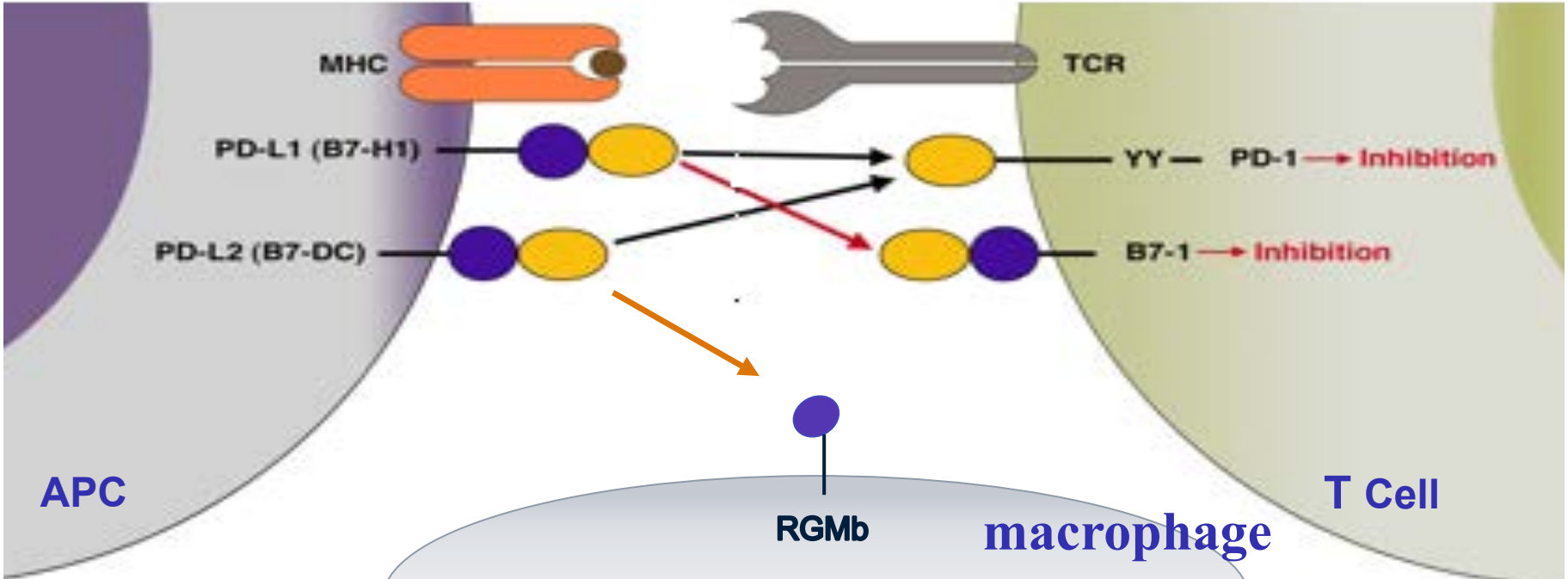


- **PD blockade + other immunoinhibitor blockade:**
  CTLA-4

PD-1 mAb doesn't block all immunoinhibitory possibilities

PD-L1 : B7-1

PD-L2 : Repulsive Guidance Molecule b (RGMb)

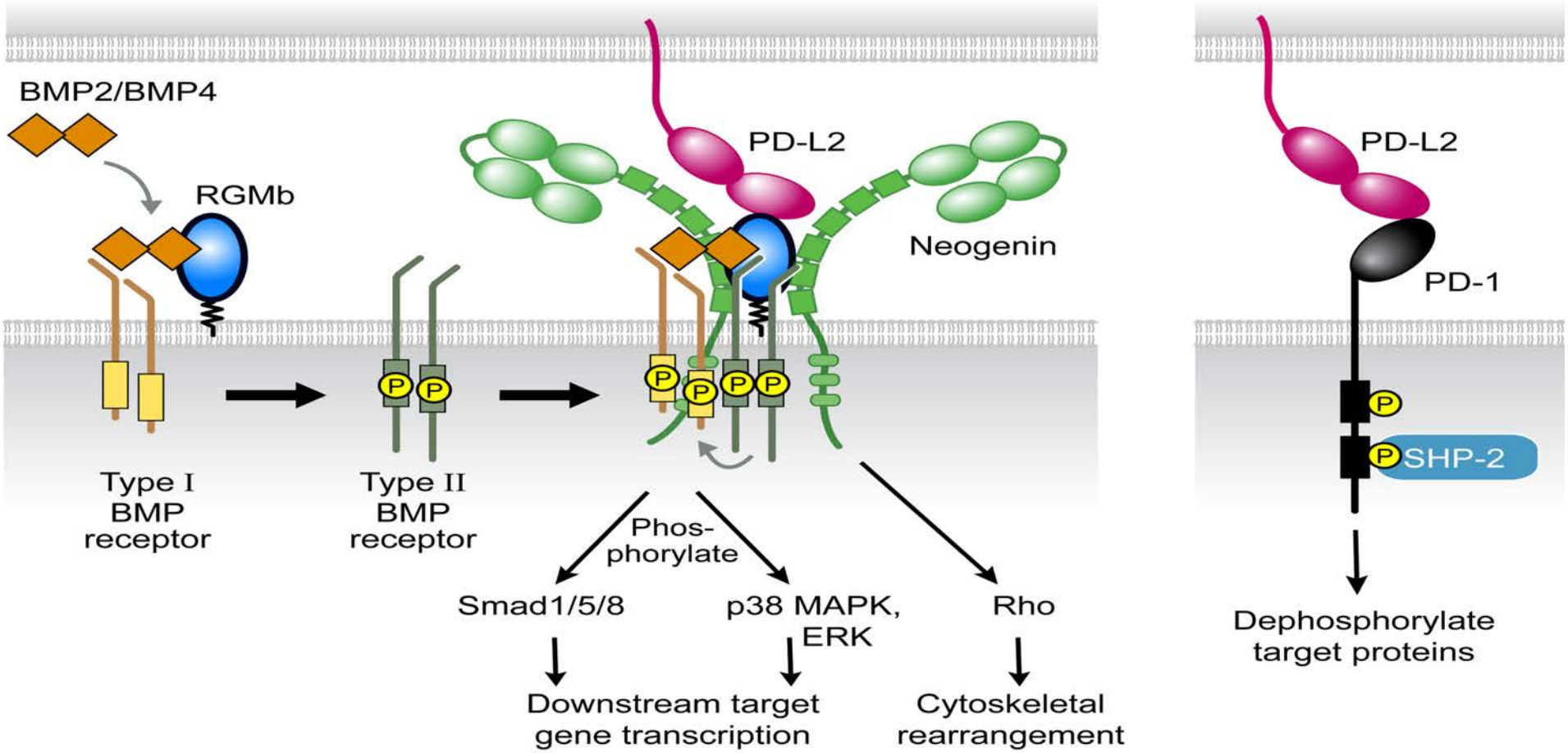


Summary of recent RGMb work

- **RGMb is a novel binding partner for PD-L2**
- **RGMb originally identified in the nervous system and has immune function in macrophages**
- **RGMb and PD-L2 interaction promotes respiratory tolerance**
- **Targeting this interaction may provide therapeutic approaches for cancer, asthma and other immune disorders**

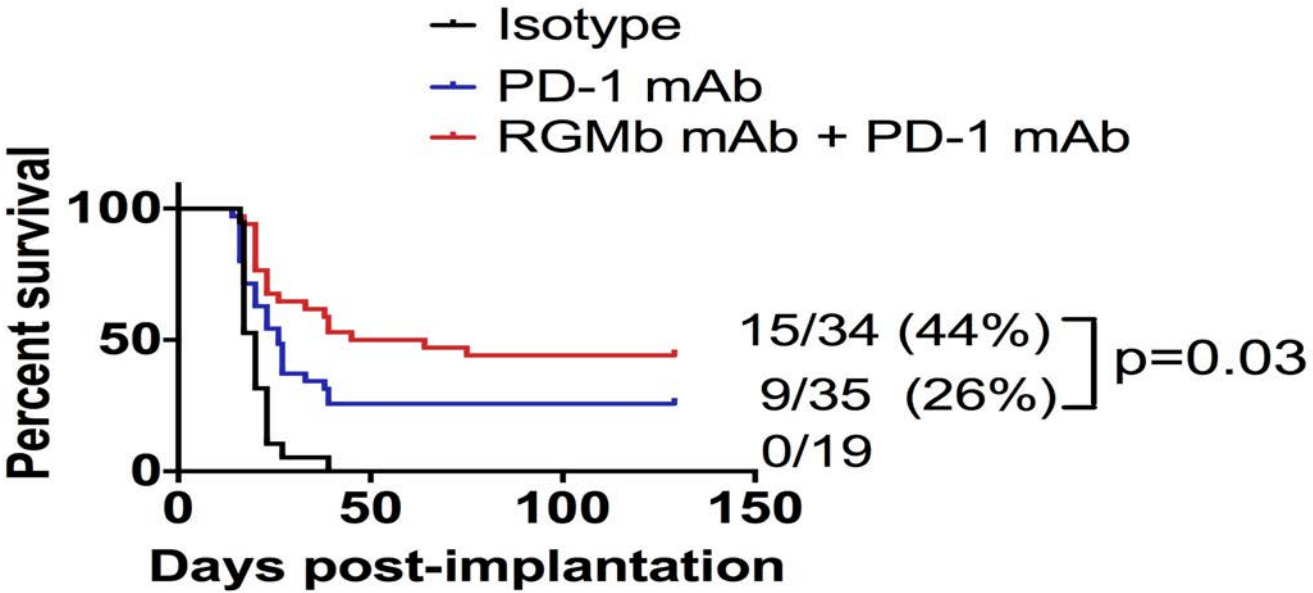
Xiao et al., J Exp Med, 2014

Model for RGMb-PD-L2 signaling: BBRN supercomplex



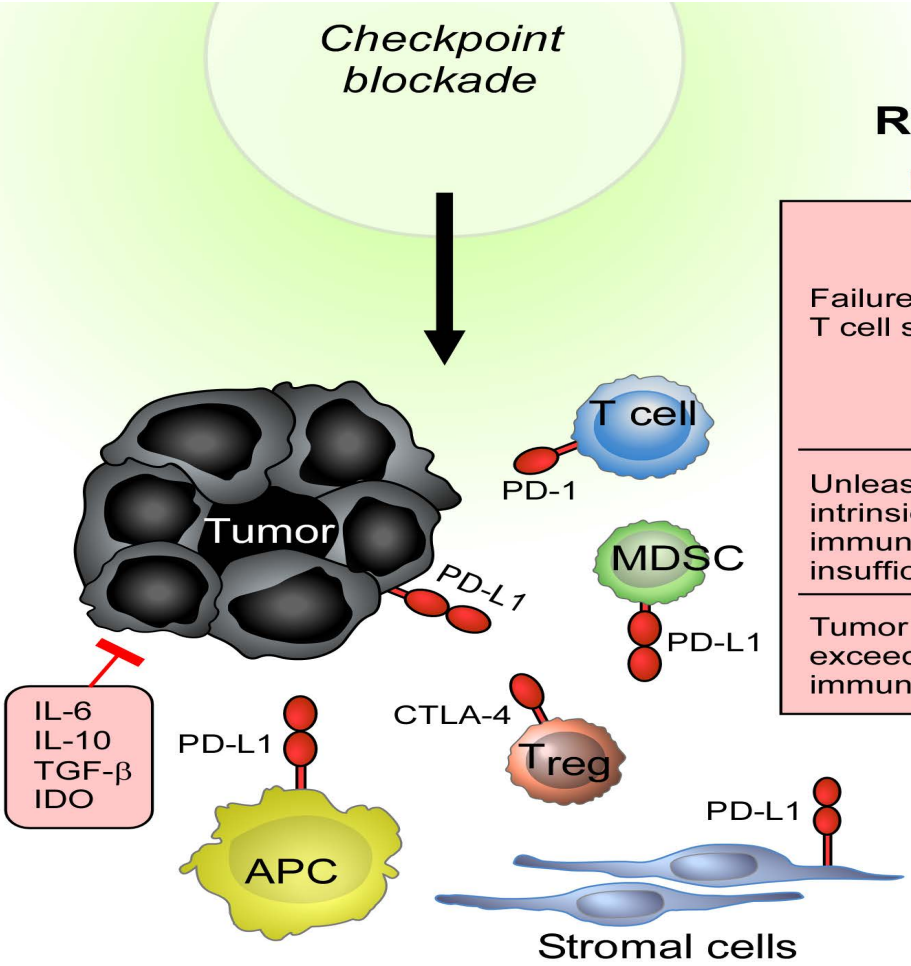
Targeting RGMb in CT26 colorectal cancer immunotherapy

RGMb and PD-1 combination blockade increases mouse survival



Kaplan-Meier survival analysis

Yanping Xiao



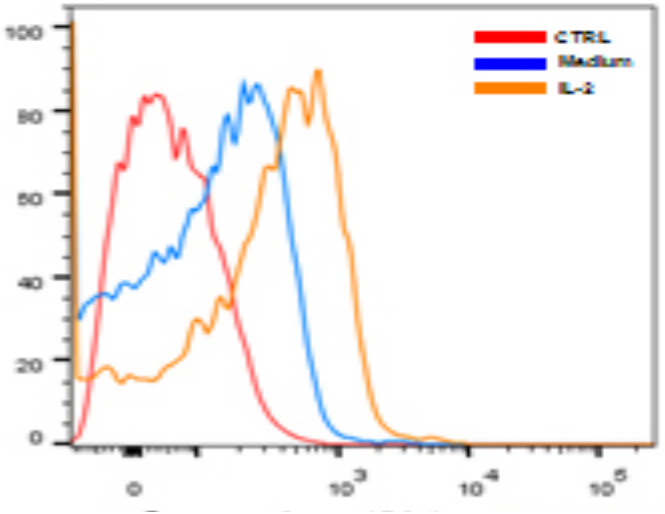
Recognition & killing of cancer cells

DEFICIT	THERAPEUTIC APPROACH
Failure to overcome T cell suppression	• Block multiple checkpoints (PD-1, PD-L1, LAG-3, TIM-3, CTLA-4) • Activate stimulatory pathways (CD137, OX40, CD27, ICOS, GITR) • Deplete/target immunsuppressive cells (Treg, MDSCs, M2) • Target other suppressive mechanisms in microenvironment (IDO, TGF-β)
Unleashing intrinsic T cell immunity is insufficient	• Induce/Provide other anti-tumor immune cells (CARs, TCR-engineered T cells, NK cells)
Tumor burden/growth exceeds capacity for immune clearance	• Reduction of tumor burden (Surgery, Radiation, Chemo-therapy, Targeted therapy)

Can PD-L1 mAb help NK cells?

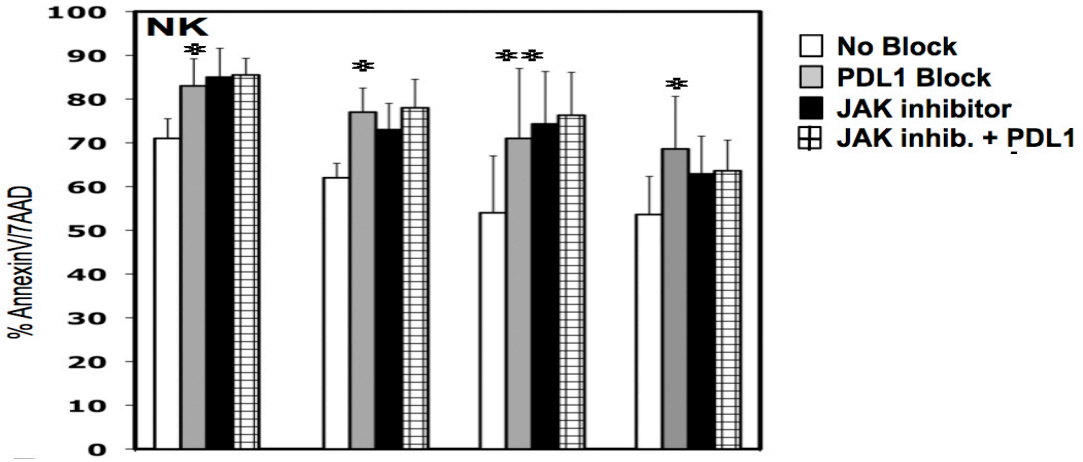
Human NK cell lysis of tumor cells is increased by PD-L1 blockade

NK express PD-1



PD-1 →

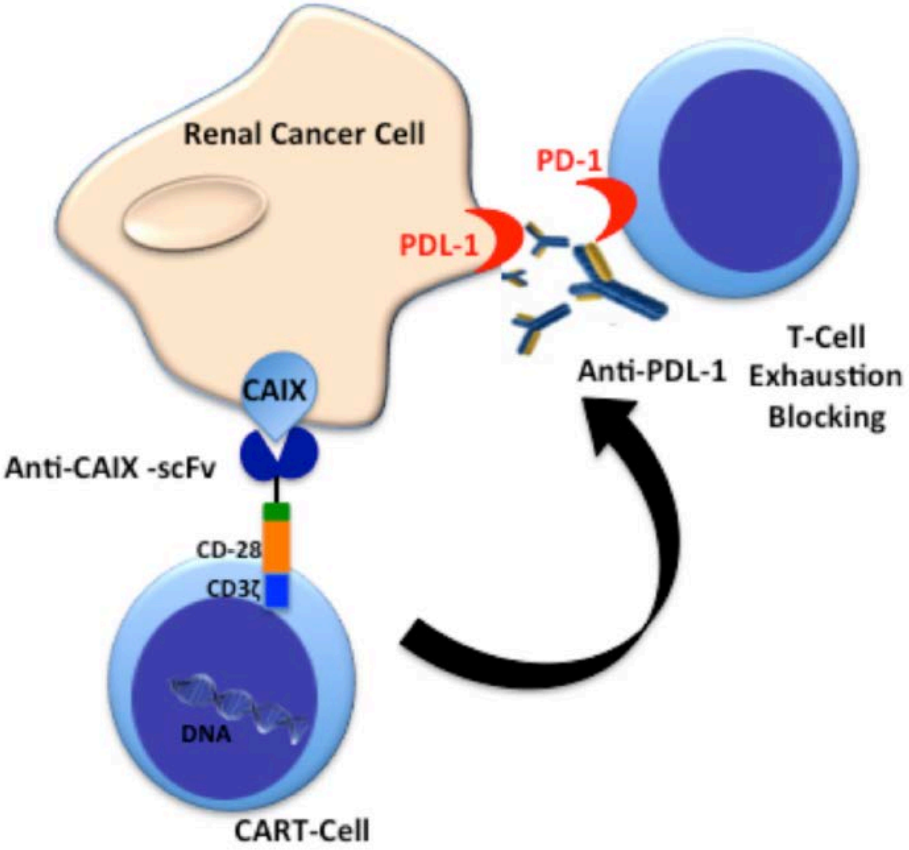
% dead tumor cells



U937 AML MM ALL

Roberto Belluci and Jerry Ritz

Can PD-L1 mAb help CAR-T?



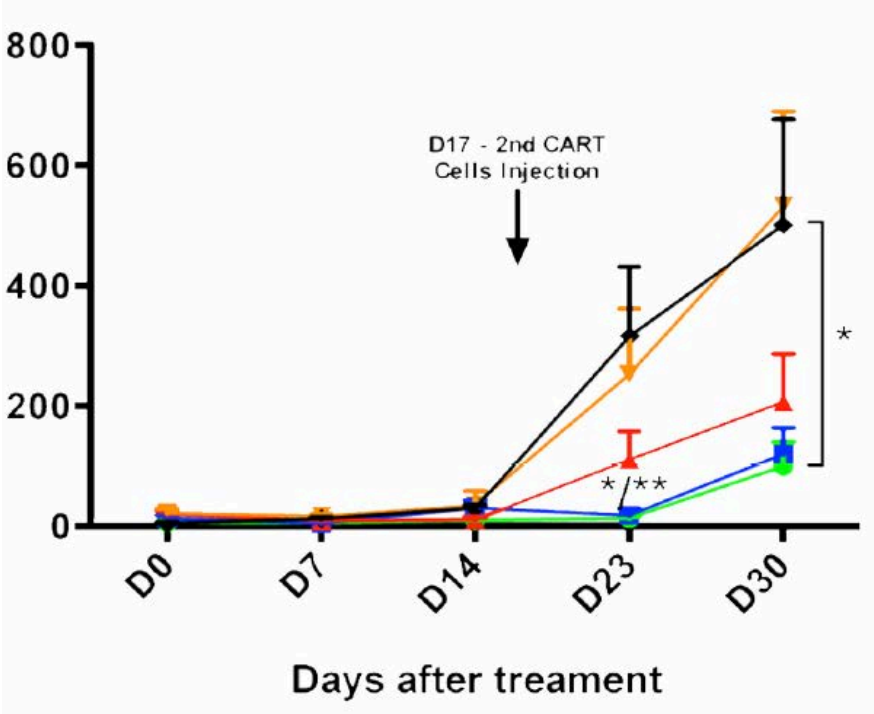
CAR-T cells with bicistronic lentiviral vector expressing:

- anti-carbonic anhydrase IX (CAIX) chimeric antigen receptor (CAR)
- secreting PD-L1 antibody locally at the tumor site.

Eloah Suarez
Wayne Marasco

PD-L1 mAb in the CAR-T vector improves treatment efficacy

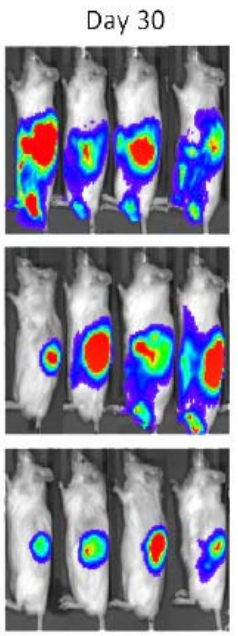
RCC tumor size (flux x 10^9)



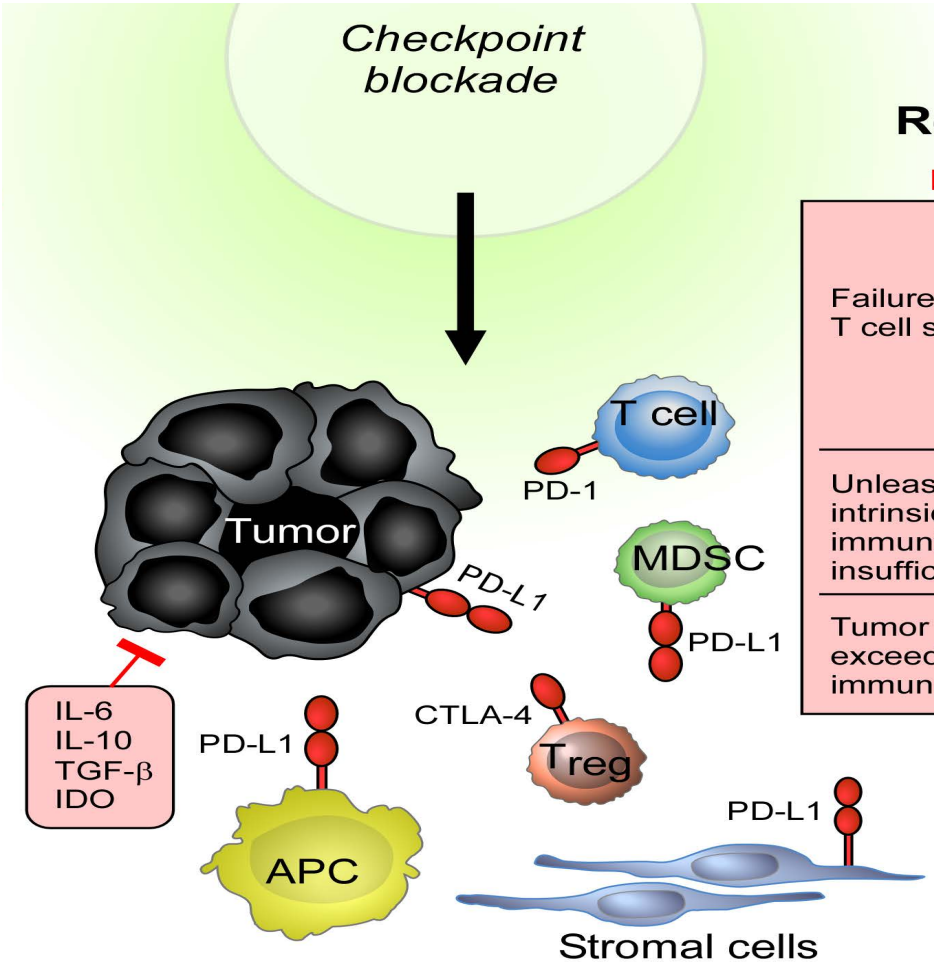
control

CAR-T

CAR-T expressing PD-L1 mAb



Other combinations



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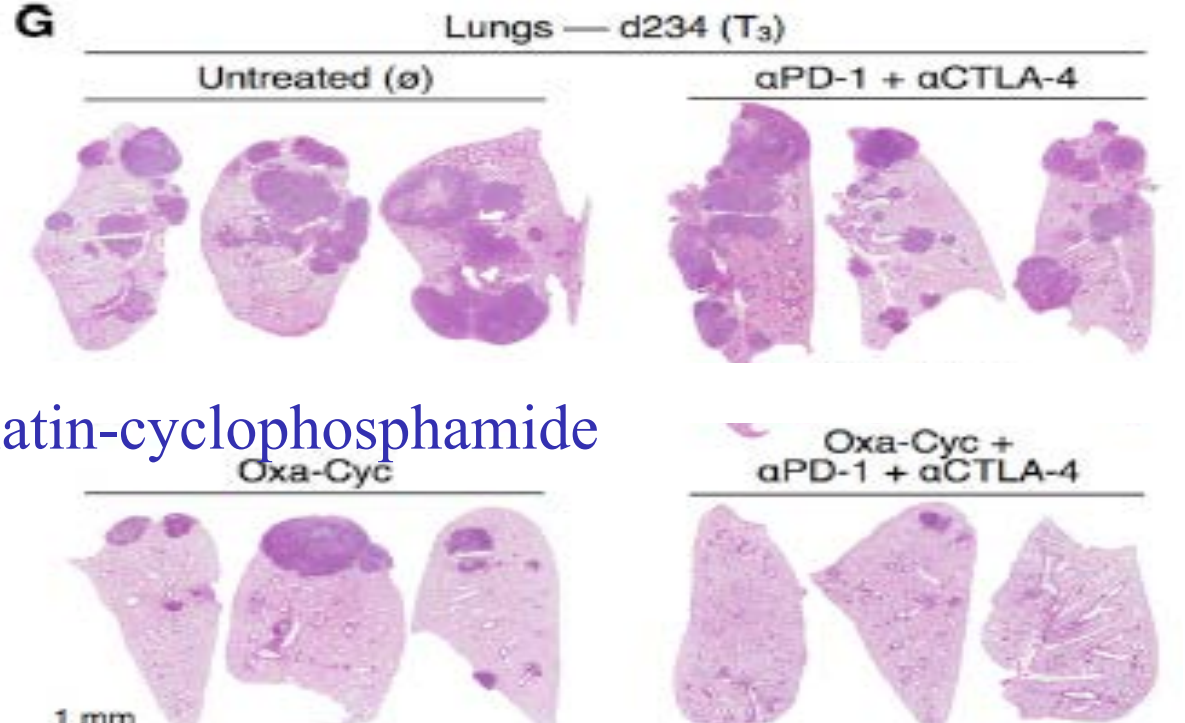
Immunity
Article

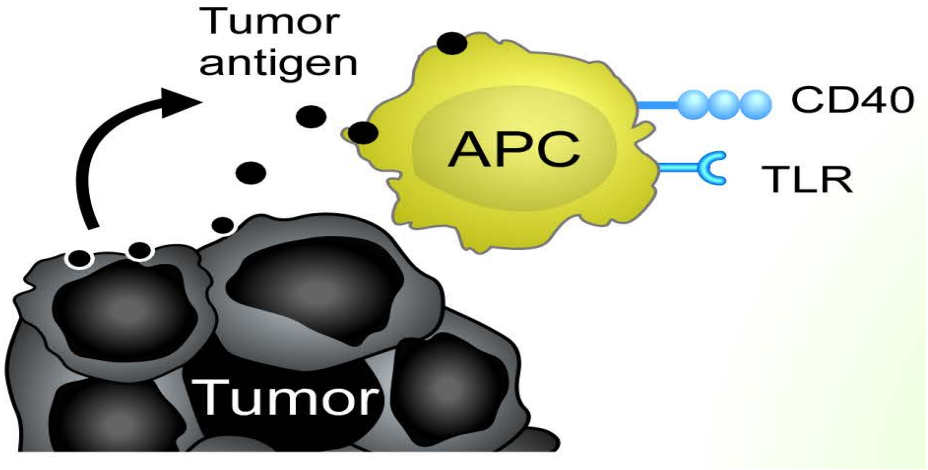
Immunogenic Chemotherapy Sensitizes Tumors to Checkpoint Blockade Therapy

Christina Pfirschke,[1,7] Camilla Engblom,[1,2,7] Steffen Rickelt,[3] Virna Cortez-Retamozo,[1] Christopher Garris,[1,2] Ferdinando Pucci,[1] Takahiro Yamazaki,[4] Vichnou Poirier-Colame,[4] Andita Newton,[1] Younes Redouane,[1] Yi-Jang Lin,[1] Gregory Wojtkiewicz,[1] Yoshiko Iwamoto,[1] Mari Mino-Kenudson,[5] Tiffany G. Huynh,[5] Richard O. Hynes,[3] Gordon J. Freeman,[6] Guido Kroemer,[4] Laurence Zitvogel,[4] Ralph Weissleder,[1] and Mikael J. Pittet[1,*]



oxaliplatin-cyclophosphamide

More combinations



Cancer antigen release, uptake & processing

DEFICIT	THERAPEUTIC APPROACH
Non-immunogenic cell death or insufficient neoantigens	• Oncolytic viruses • Chemotherapy • Radiation therapy • Cryotherapy • Targeted therapy • Epigenetic modifiers • Blockade of phos-phatidylserine
Insufficient antigen processing/DC maturation	• Vaccines • TLR agonists/STING • GM-CSF • IFN-α • CD40 agonists

What happens
when tumors respond to PD-1
immunotherapy
but then develop resistance ?

nature COMMUNICATIONS

ARTICLE

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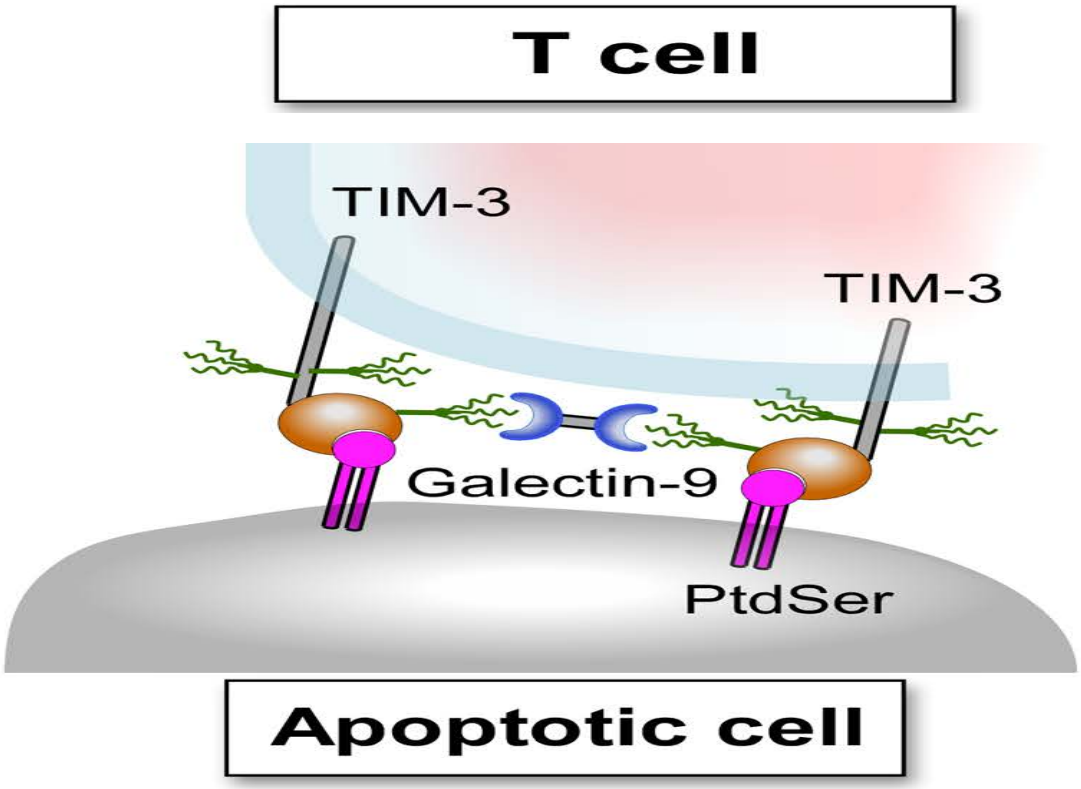
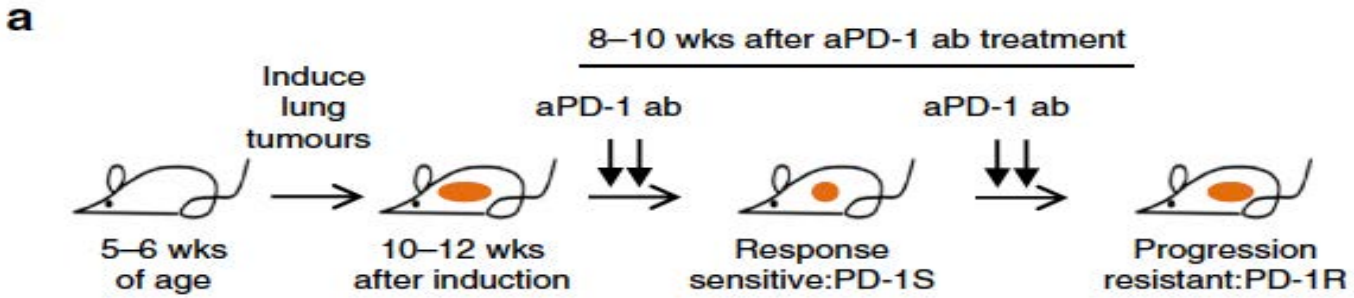
Adaptive resistance to therapeutic PD-1 blockade is associated with upregulation of alternative immune checkpoints

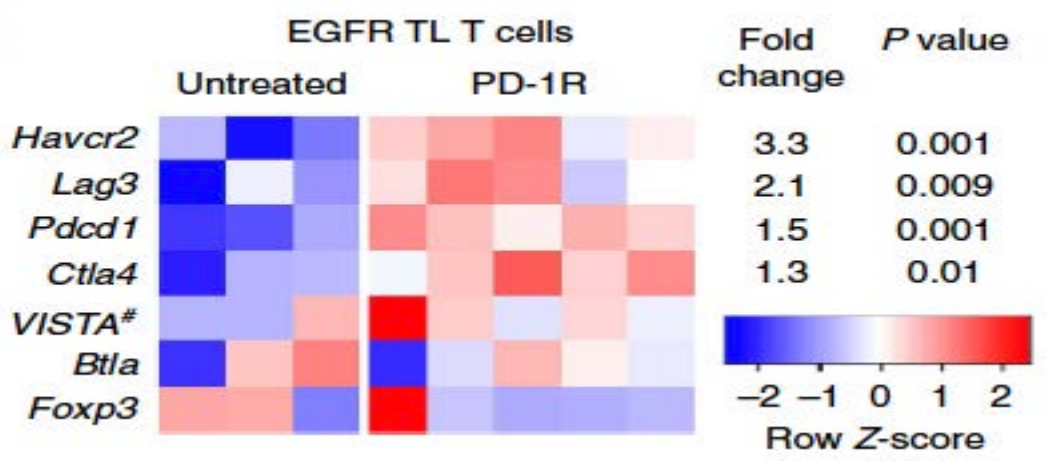
Shohei Koyama[1,2,*], Esra A. Akbay[2,3,*], Yvonne Y. Li[2,3,*], Grit S. Herter-Sprie[2,3], Kevin A. Buczkowski[3], William G. Richards[4], Leena Gandhi[3], Amanda J. Redig[3], Scott J. Rodig[5], Hajime Asahina[2,3], Robert E. Jones[6], Meghana M. Kulkarni[6], Mari Kuraguchi[6], Sangeetha Palakurthi[6], Peter E. Fecci[7], Bruce E. Johnson[2,3], Pasi A. Janne[2,3], Jeffrey A. Engelman[8], Sidharta P. Gangadharan[9], Daniel B. Costa[9], Gordon J. Freeman[1,2], Raphael Bueno[4], F. Stephen Hodi[2,3], Glenn Dranoff[1,2], Kwok-Kin Wong[2,3,6] & Peter S. Hammerman[2,3,10]



Jason Gaglia
Chen Zhu
Vijay Kuchroo
Xia Bu
Rosemarie DeKruyff

T cells in PD-1 resistant lung cancer

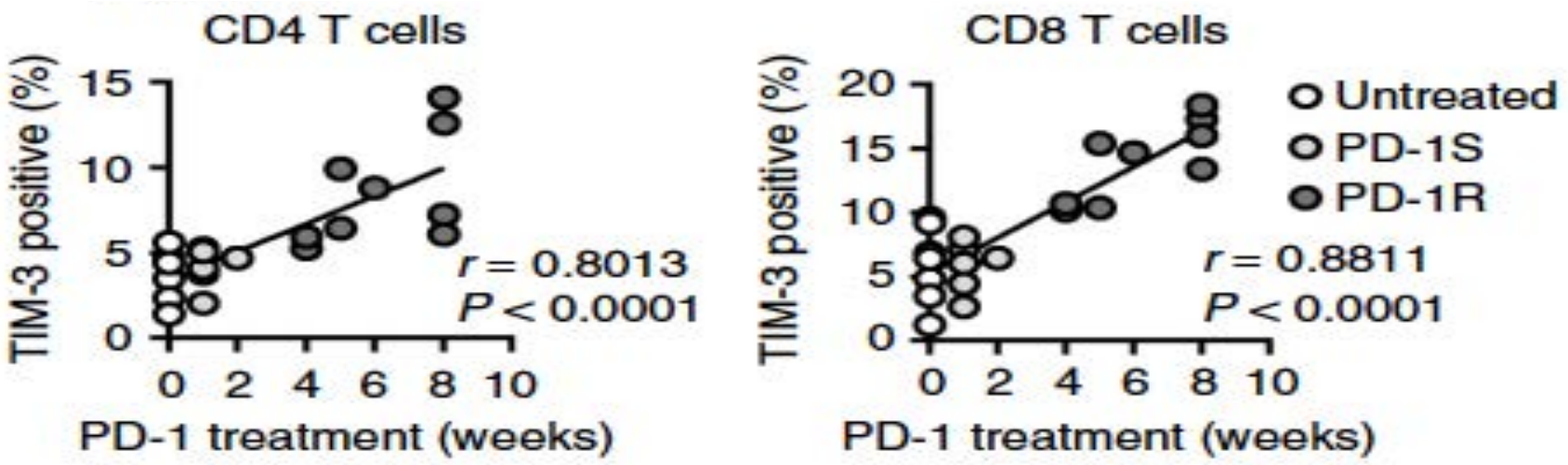




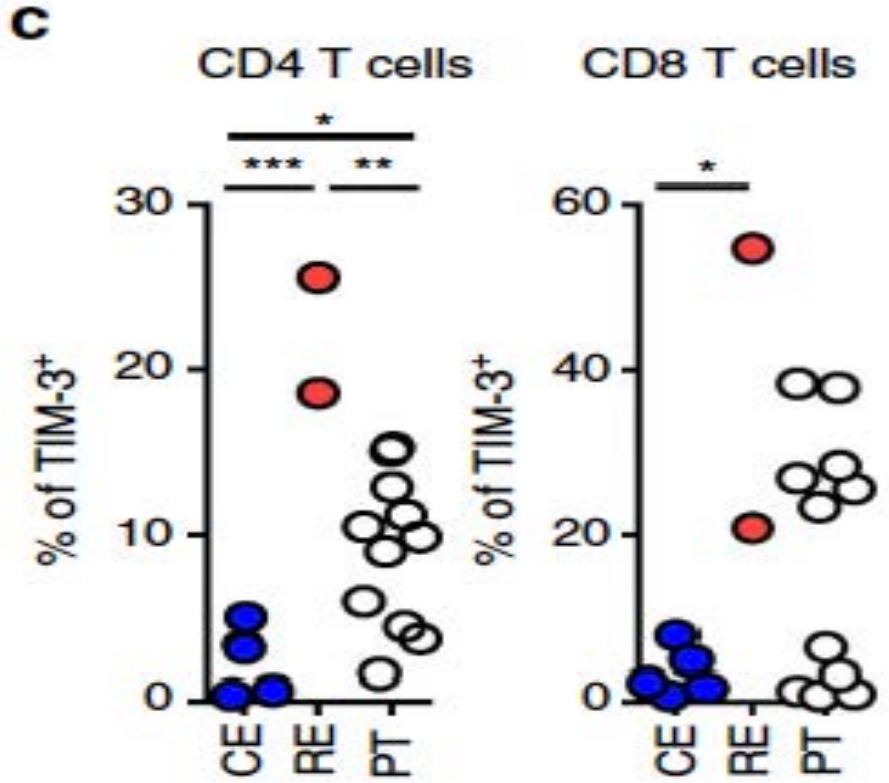
TIM-3

Shohei Koyama
Esra Akbay

Increased TIM-3^{+} T cells in PD-1 resistant mouse lung cancer

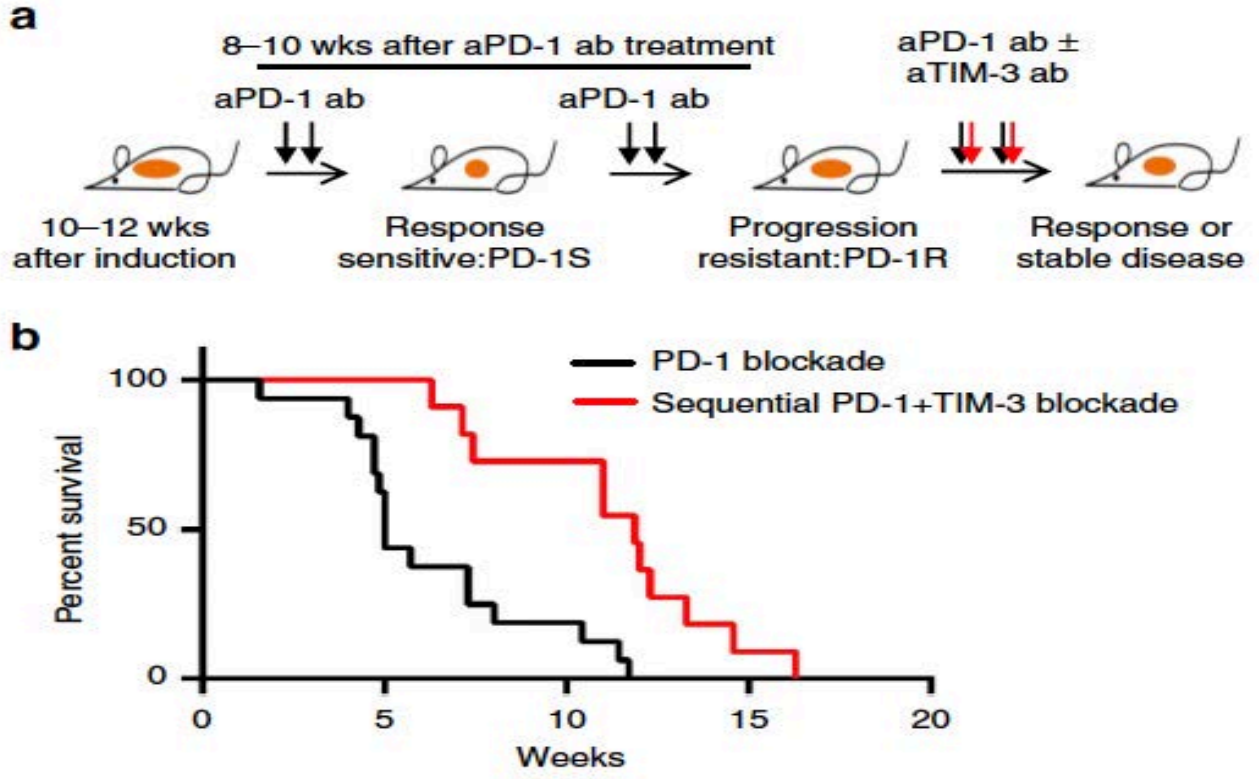


Lung cancer patients that develop resistance to PD-1 therapy express higher levels of TIM-3



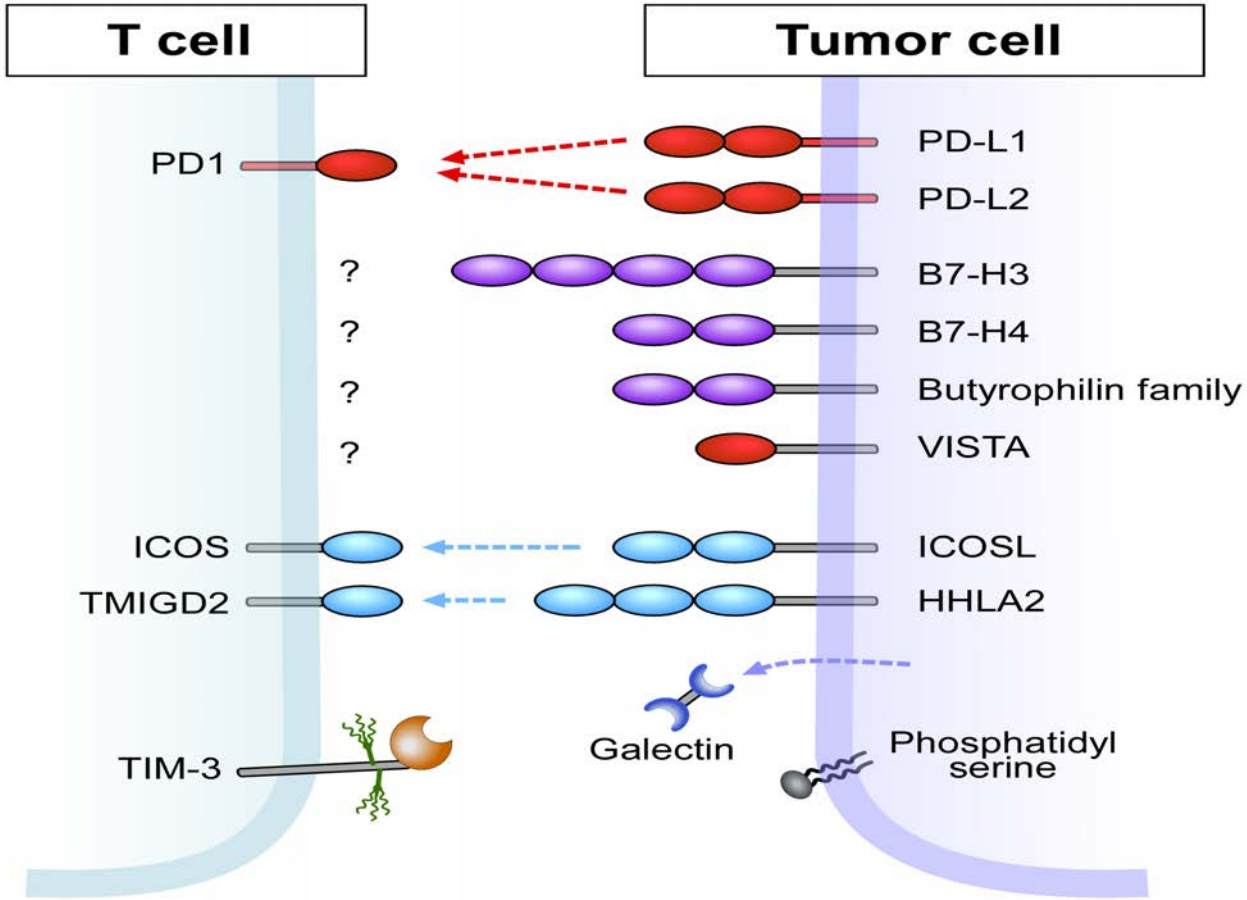
CE = control effusion
RE = resistant effusion
PT = primary tumor

Mice that develop PD-1 resistance can benefit from PD-1 + TIM-3

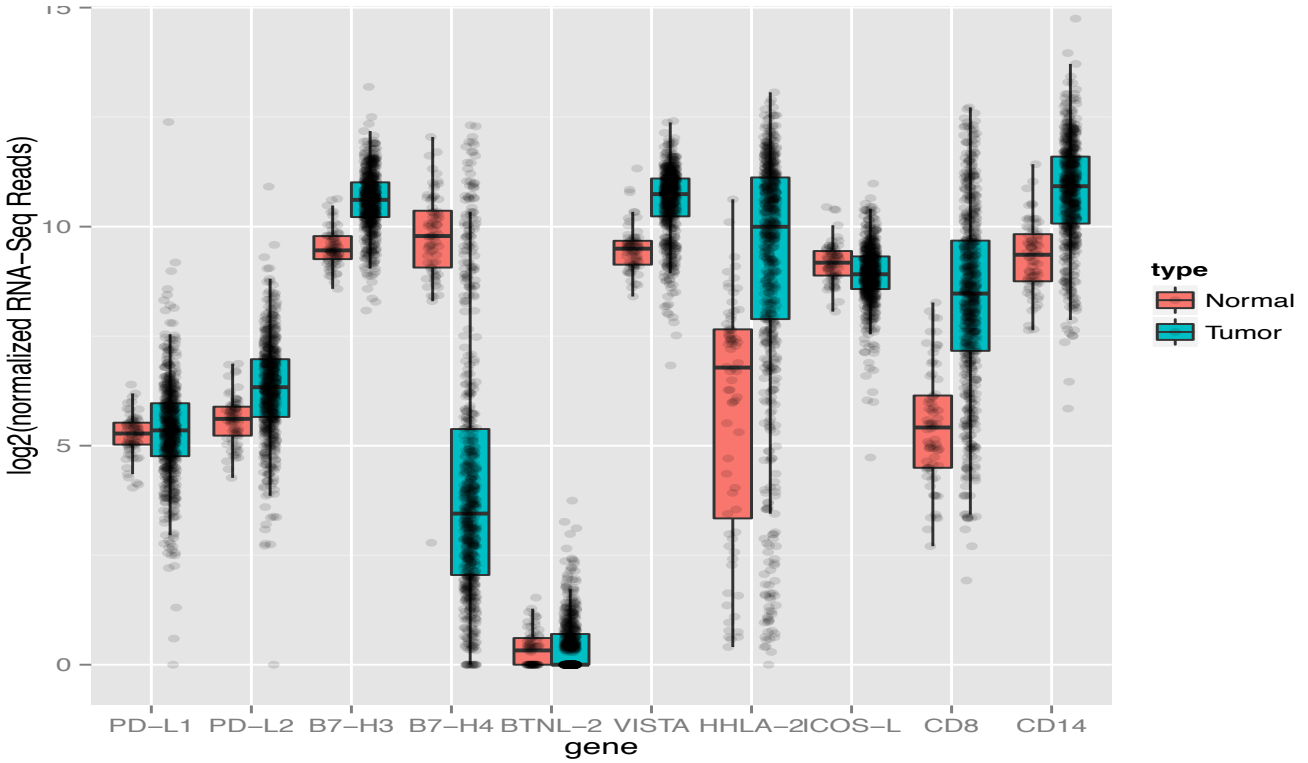


Can we use TCGA mRNA expression data of tumor and normal tissue to guide immunotherapy development ?

Immunoinhibitory B7s that can be expressed by tumors



Normal kidney vs ccRCC



ccRCC is extraordinary !

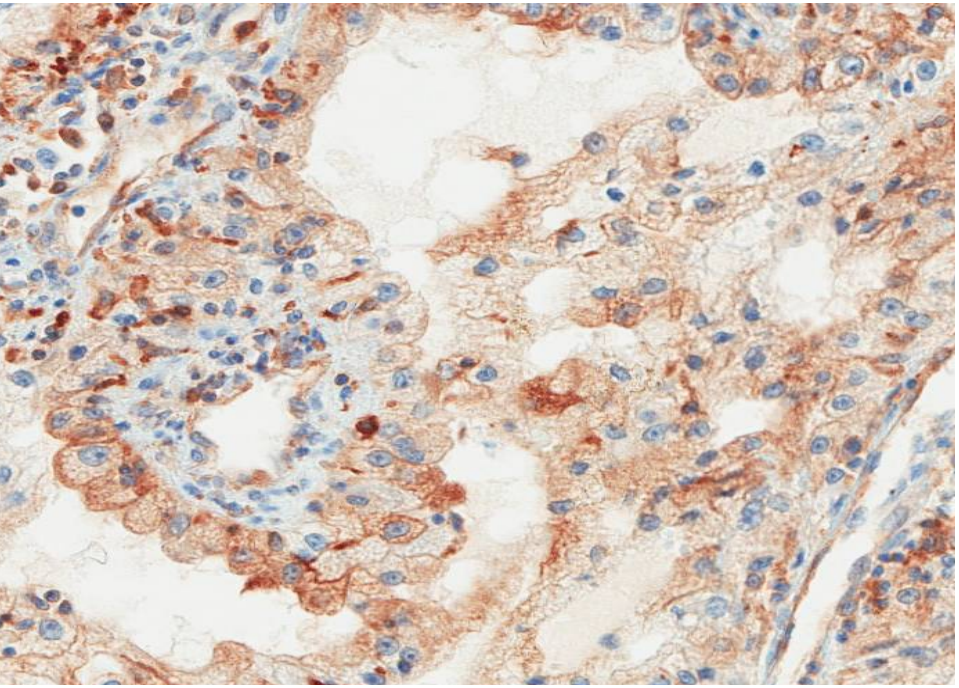
Highly inflamed

More PD-L2
More B7-H3
Less B7-H4
More VISTA
More HHLA2

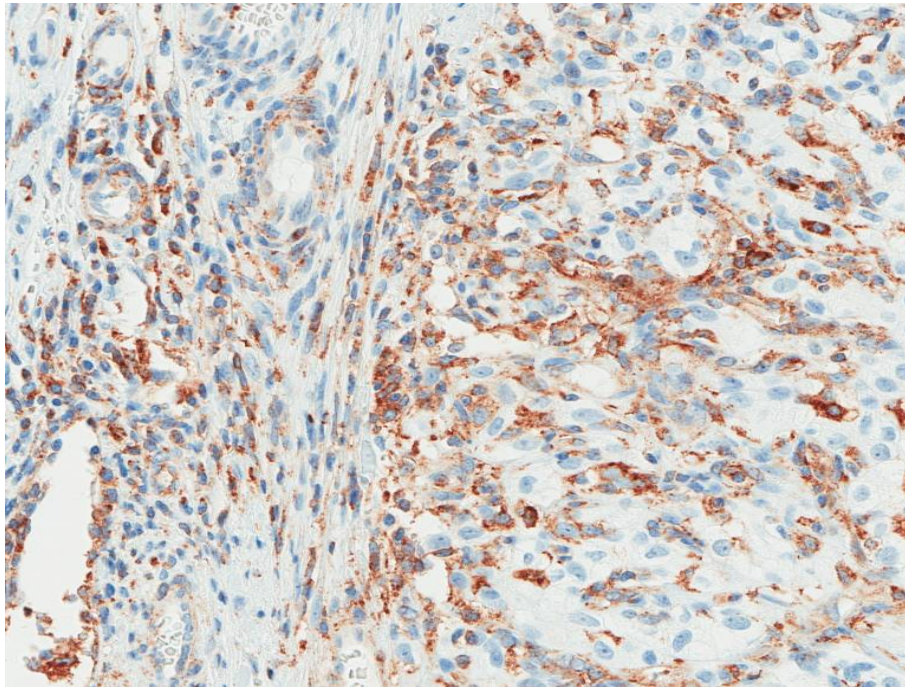
Sam Freeman

Expression of VISTA in Renal Cell Cancer

VISTA on tumor
and cells in microenvironment



VISTA on
cells in microenvironment



20x

Jessie Novak, Ping Hua, Sabina Signoretti

It's a great time to be an oncologist or researcher

- **PD-1/PD-L1 works on a wide range of tumors with**
  - **moderate percentage of responders**
  - **good safety profile**
- **PD-1/PD-L1 gives us a foundation to build on**
- **With this success, human creativity has been unleashed and we're learning to do better**

To be done

- **How do we identify who will respond to PD-1 blockade ?**
- **What are mechanisms of primary failure to respond ?**
  - **Other immunoinhibitors ?**
  - **Failure of immune cells to infiltrate tumor ?**
  - **No good neoantigens ?**
- **What are mechanisms of secondary failure to respond ?**
  - **Expression of other immunoinhibitory receptors ?**
  - **Loss of MHC ?**

Future of cancer therapy decisions

- **Tumor Genome sequencing:**

  PD-L1/2 amplification, MSI, viral genomes ➔ PD-1 therapy

  Identify which oncogenes are drug targets ?

  Identify neoantigens

- **Tumor Immunoevasion Score:**

  How much PD-L1, PD-L2, IDO, Galectin-1, Galectin-9, B7-H3, B7-H4, VISTA, HHLA2, Arginase, NKG2D-Ligands ?

  Choose best immunotherapy

  Combine immunotherapy with best targeted therapy/vaccine

Freeman lab

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- Yanping Xiao
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- Apoorvi Chaudhri
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- Yahui Hao
- Lilly Cai

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