What's Next For Cancer Immunotherapy?

Dario AA Vignali, PhD

Frank Dixon Chair in Cancer Immunology, Vice Chair and Professor, Department of Immunology, University of Pittsburgh School of Medicine

Leader of the Cancer Immunology and Immunotherapy Program, Co-Director of the Tumor Microenvironment Center, Director of the Cancer Immunology Training Program, UPMC Hillman Cancer Center

Scientific Director of Fondazione Ri.MED

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Disclosures

Patents: LAG-3 (BMS), IL-35 (Tizona) and Nrp1 (Potenza), granted and pending.

Founder: Potenza Therapeutics Inc, Tizona Therapeutics Inc., TTMS Inc.

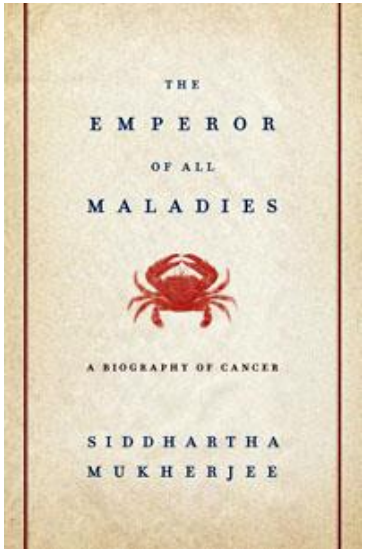
Stock Owner: Potenza Therapeutics Inc, Tizona Therapeutics Inc., TTMS Inc., Oncorus Inc.

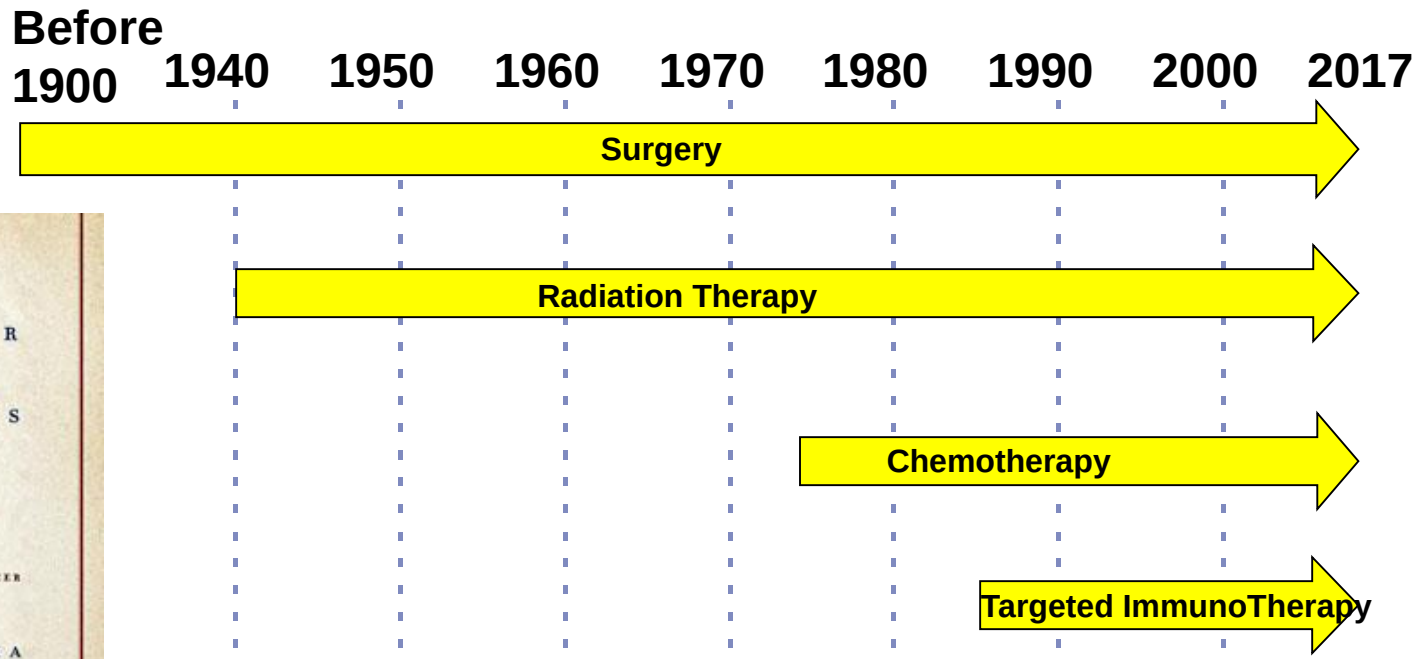
SAB: Potenza, Tizona, Oncorus, F-Star, Pieris.

Consultation: Crescendo, MPM.

I will be discussing non-FDA approved indications during my presentation.

The Evolution of Treatment for Cancer



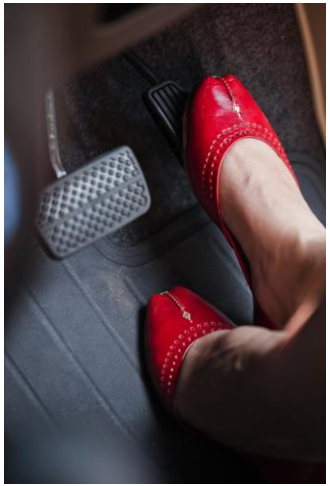


Siddhartha Mukherjee

"… taking patients to the edge of death."

Therapies to “Drive” an Immune Response

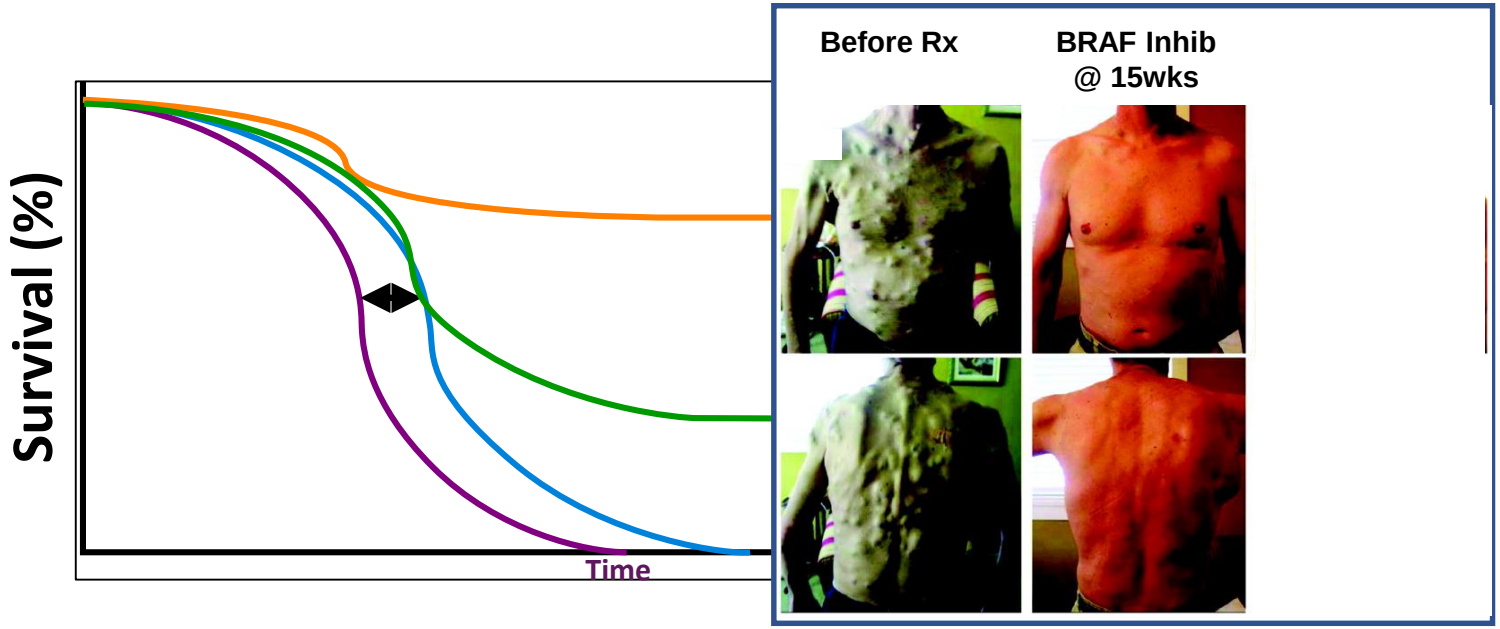
- Vaccines



- Immune effector cells
- “Go signals”

- Immune inhibitory cells
- “Stop signals”

The Promise of Immunotherapy



- Chemotherapy
- Genomically-targeted therapy
- Immune checkpoint therapy
- Combination of immune checkpoint therapy and immunotherapies, genomically-targeted agent and/or other cancer therapies

Sharma P & Allison JP. Cell 2015

Unique Kinetics of Response in Patients Treated With Ipilimumab (anti-CTLA-4)

Screening

Week 12: swelling and progression

Week 12: improved

Week 16: continued improvement

Week 72: complete remission

Week 108: complete remission

Images courtesy of Jedd D. Wolchok, MD.

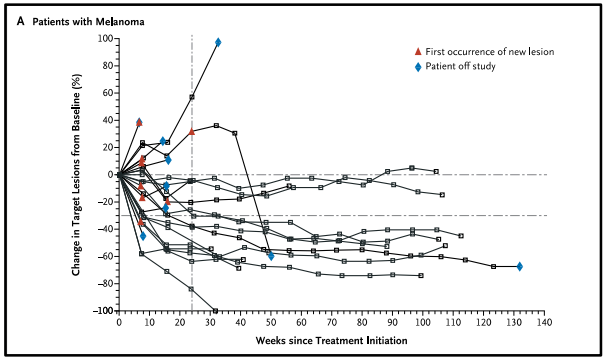
Inhibitory Receptor Targeted Immunotherapy

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 28, 2012 VOL. 366 NO. 26

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

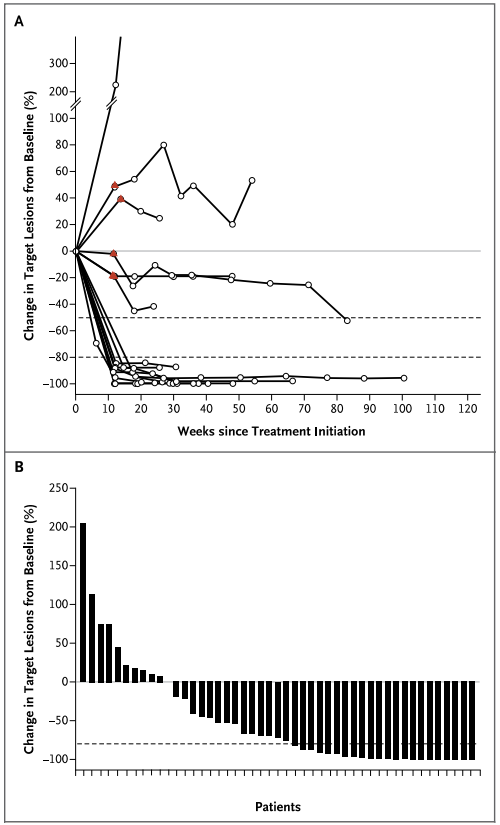


The NEW ENGLAND JOURNAL of MEDICINE

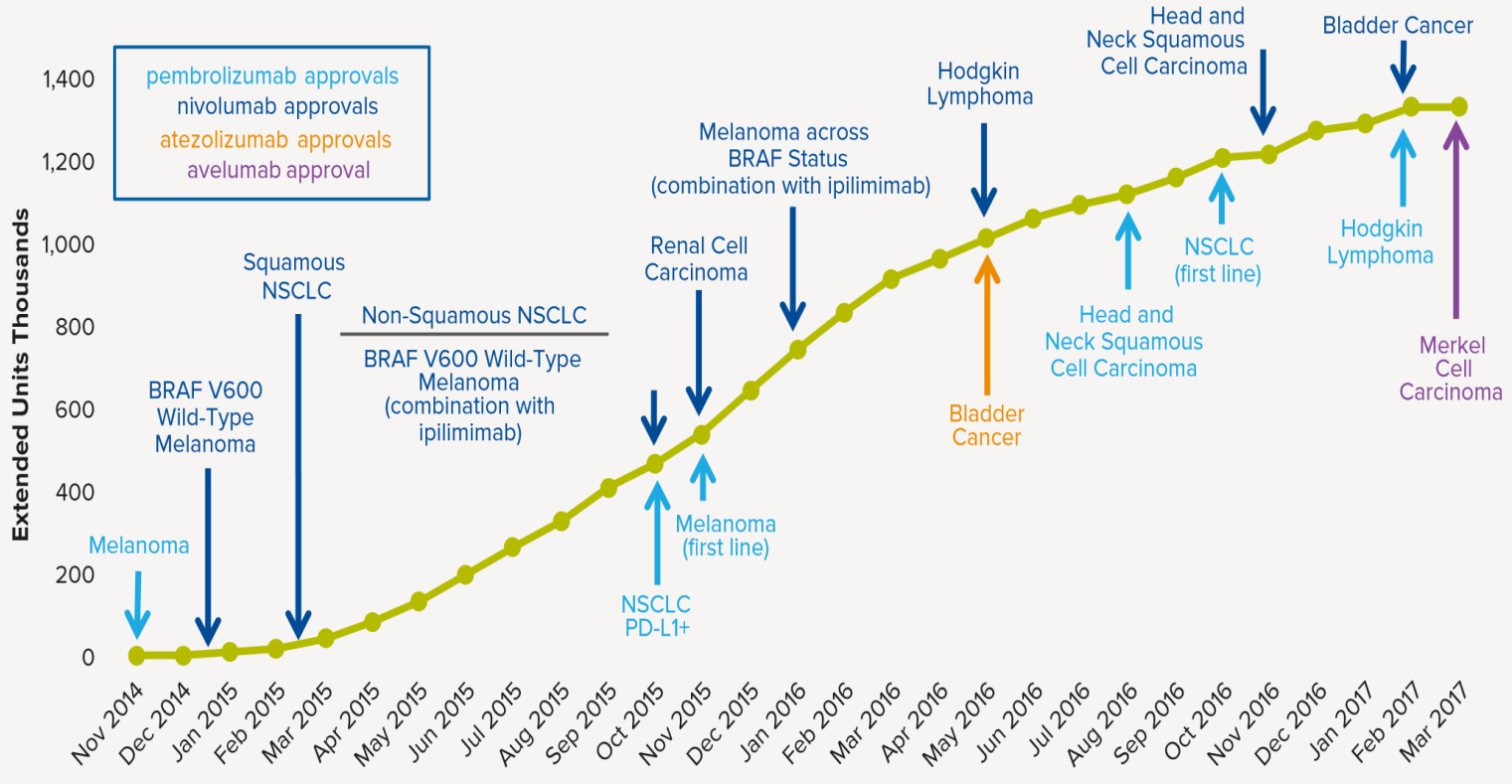
ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Advanced Melanoma

Jedd D. Wolchok, M.D., Ph.D., Harriet Kluger, M.D., Margaret K. Callahan, M.D., Ph.D., Michael A. Postow, M.D., Naiyer A. Rizvi, M.D., Alexander M. Lesokhin, M.D., Neil H. Segal, M.D., Ph.D., Charlotte E. Ariyan, M.D., Ph.D., Ruth-Ann Gordon, B.S.N., Kathleen Reed, M.S., Matthew M. Burke, M.B.A., M.S.N., Anne Caldwell, B.S.N., Stephanie A. Kronenberg, B.A., Blessing U. Agunwamba, B.A., Xiaoling Zhang, Ph.D., Israel Lowy, M.D., Ph.D., Hector David Inzunza, M.D., William Feely, M.S., Christine E. Horak, Ph.D., Quan Hong, Ph.D., Alan J. Korman, Ph.D., Jon M. Wigginton, M.D., Ashok Gupta, M.D., Ph.D., and Mario Sznol, M.D.

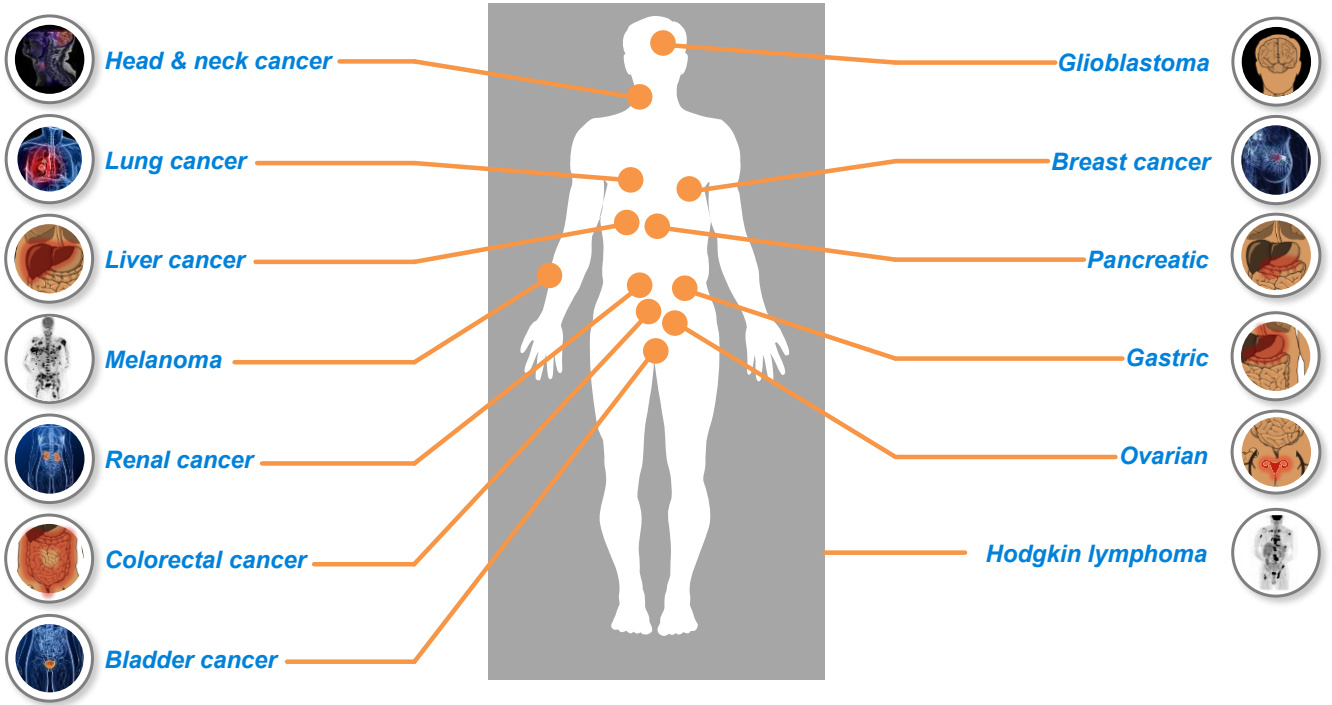


Growing Prevalence of Immuno-Oncology Drugs



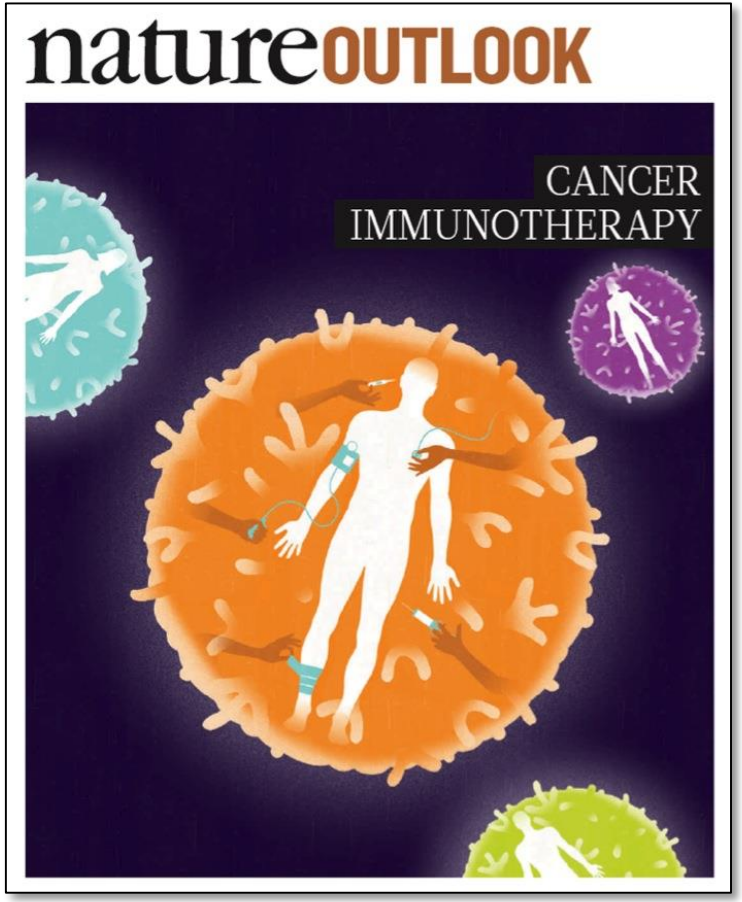
Source: U.S. FDA, QuintilesIMS, National Sales Perspectives, Feb 2017; QuintilesIMS Institute, Apr 2017

Broad Activity of Immunotherapeutic Drugs



Only a subset of patients (~10-30%) exhibit substantive benefit from immunotherapy

Cancer Immunotherapy: What's Next?



Cancer Immunotherapy: Overcoming PD1 Resistance

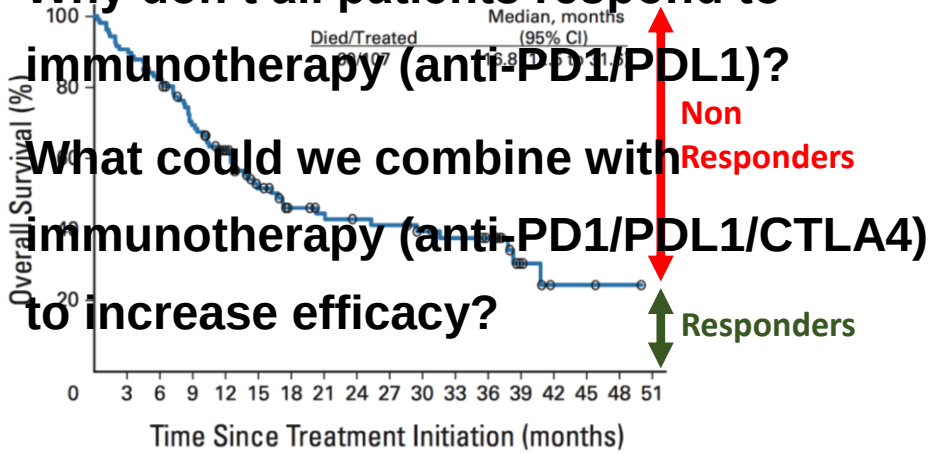
VOLUME 32 · NUMBER 10 · APRIL 1 2014
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Survival, Durable Tumor Remission, and Long-Term Safety in Patients With Advanced Melanoma Receiving Nivolumab

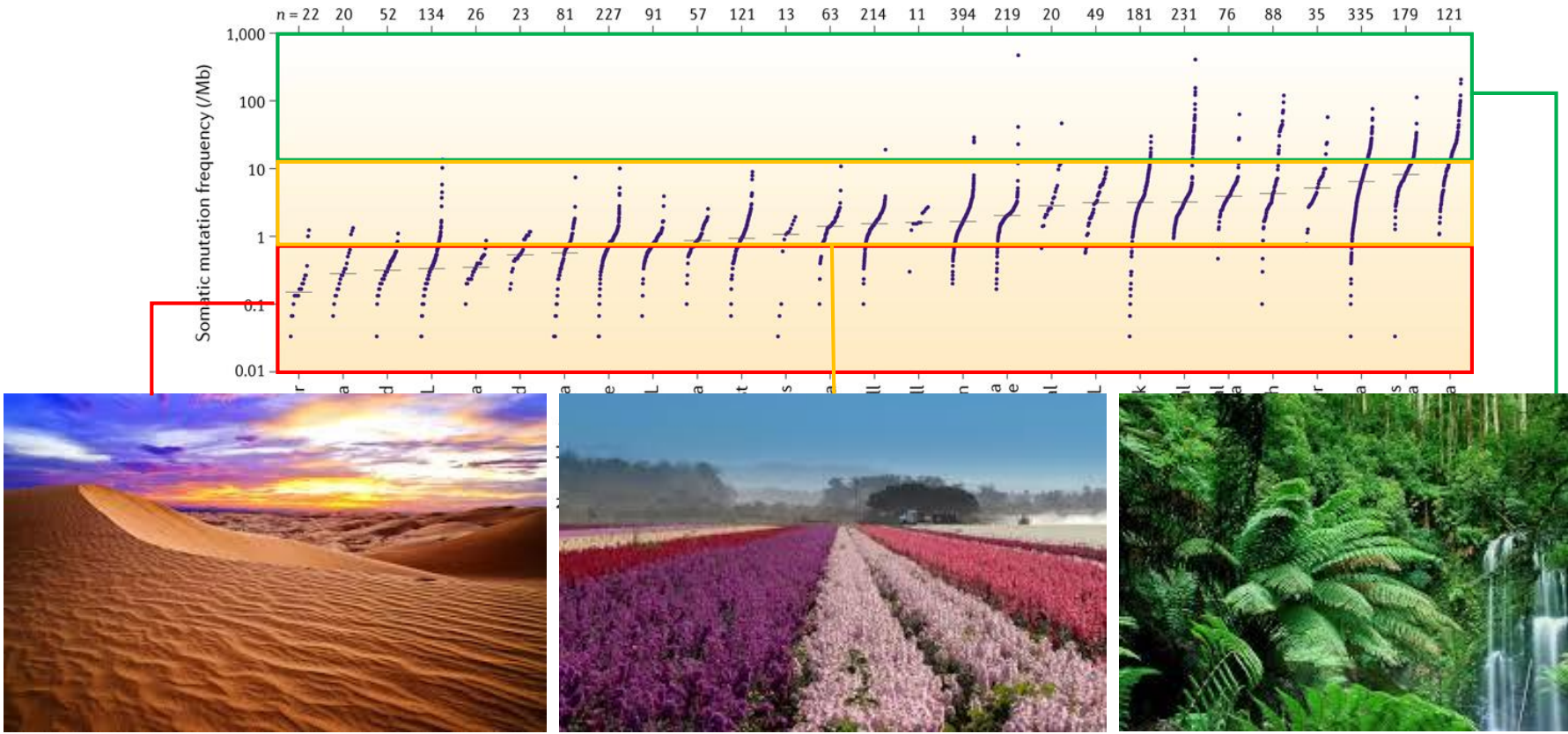
Suzanne L. Topalian, Mario Sznol, David F. McDermott, Harriet M. Kluger, Richard D. Carvajal, William H. Sharfman, Julie R. Brahmer, Donald P. Lawrence, Michael B. Atkins, John D. Powderly, Philip D. Leming, Evan J. Lipson, Igor Puzanov, David C. Smith, Janis M. Taube, Jon M. Wigginton, Georgia D. Kollia, Ashok Gupta, Drew M. Pardoll, Jeffrey A. Sosman, and F. Stephen Hodi

Two key questions:

- **Why don't all patients respond to immunotherapy (anti-PD1/PDL1)?**
- **What could we combine with immunotherapy (anti-PD1/PDL1/CTLA4) to increase efficacy?**



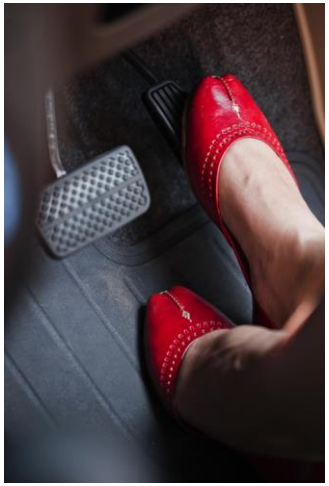
Cancer mutations and response to immunotherapy



From Lawrence, M. S. *et al*. *Nature* **499**, 214 (2013)

Overcoming “resistance” to immunotherapy

- Vaccines
- Adoptive T-cell therapies
  - CAR-T
  - TIL therapy



- Cytokines
- TLR agonists
- Agonist antibodies (4-1BB, OX-40, etc)

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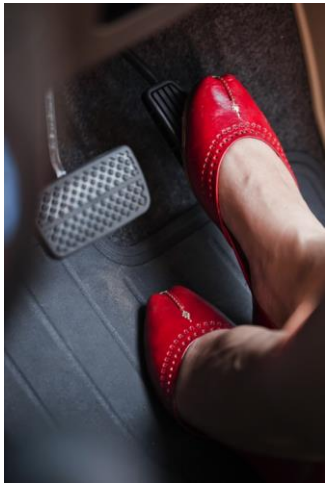

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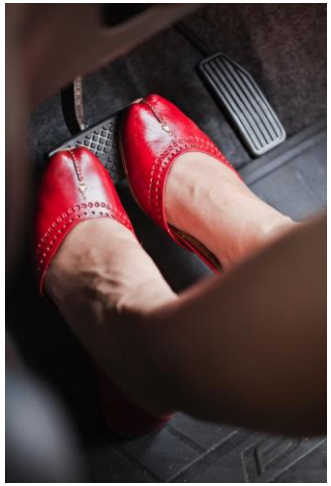

Overcoming “resistance” to immunotherapy

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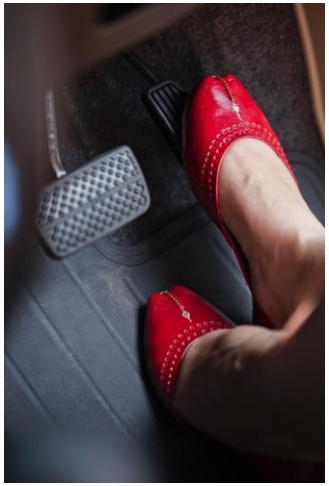

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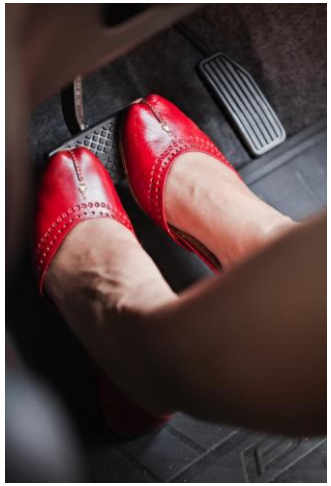


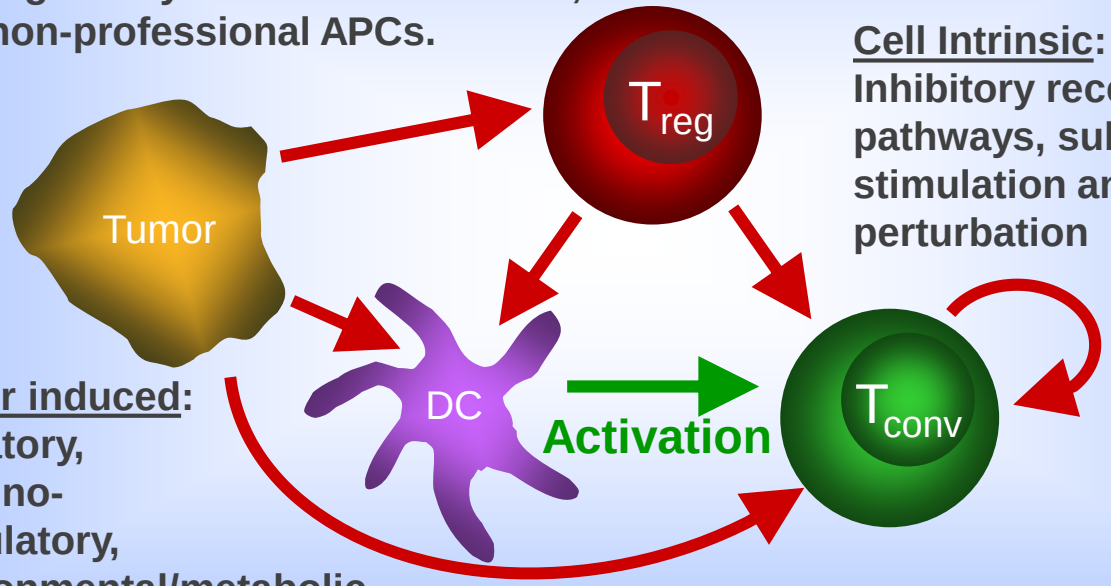
- Checkpoint blockade (Abs blocking CTLA4, PD-1/PD-L1, LAG3, TIGIT, TIM-3, etc)

- Manipulating the tumor environment

Checkpoints in Anti-Tumor Immunity

Cell Extrinsic:
Cytokines (IL-10, TGFβ), regulatory T cells (T_{regs}), MDSCs, TAMs, regulatory DCs and fibroblasts, non-professional APCs.

Cell Intrinsic:
Inhibitory receptors and pathways, sub-optimal co-stimulation and metabolic perturbation

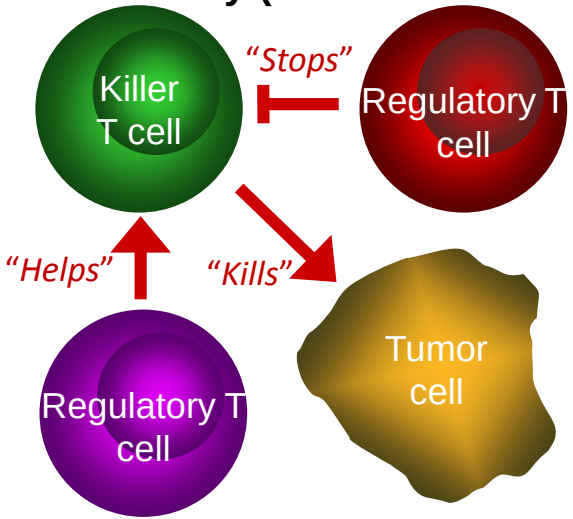


Tumor induced:
Migratory, immuno-modulatory, environmental/metabolic.

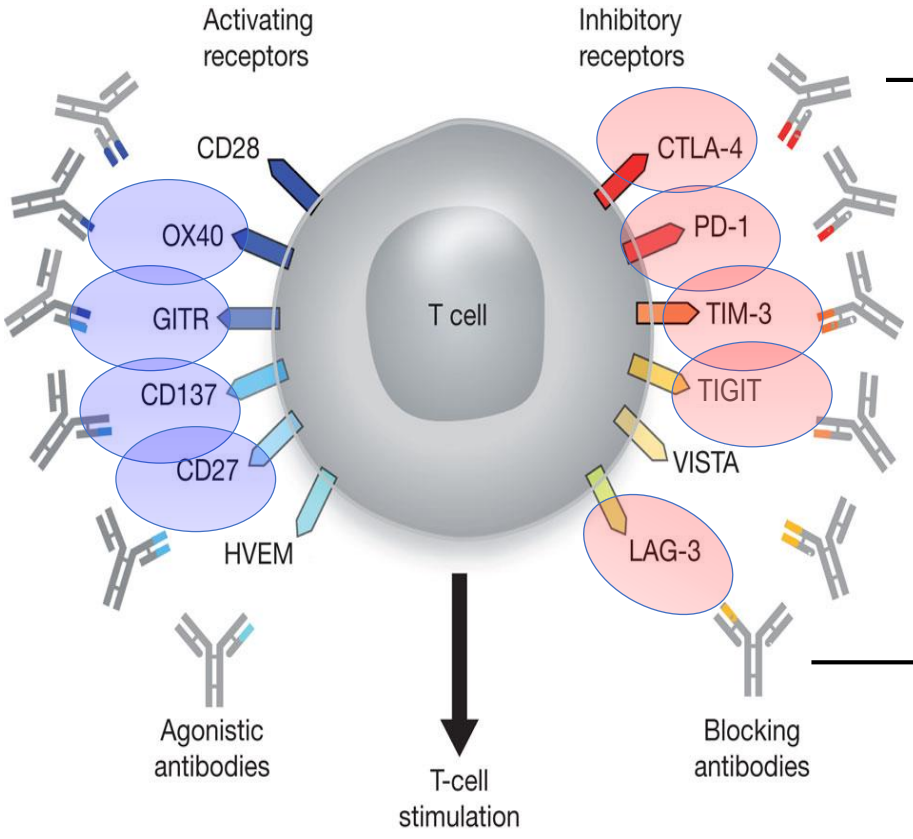
Immunity (2004) 21:503; *JI-CE* (2002) 169:5392; *JI* (2005) 174:688; *EMBOJ* (2007) 26:494; *Nature* (2007) 450:566; *JI* (2009) 182:6121; *Nature Immunology* (2010) 11:1093; *Nature Immunology* (2012) 13:290; *Immunity* (2012) 36:717; *Nature* (2013) 501:252; *Immunity* 44:316 (2016), *Science Immunology* 2:eaah4569 (2017), *Cell* 169:1130 (2017).

Developing Cancer Immunotherapies

- Regulatory T cells are potent suppressive cells that prevent autoimmune and inflammatory disease.
- However, they can also be a major barrier to anti-tumor immunity.
- How can we selectively target them for therapeutic efficacy in cancer?
- Vignali lab has previously shown that a molecule called Neuropilin-1 in required for regulatory T cells to work in tumors but is dispensable elsewhere in the body (*Nature 501:252, 2013*, *Cell 169:1130, 2017*).
- Neuropilin-1 is not expressed by regulatory T cells in healthy subjects.
- However, a high proportion of regulatory T cells in cancer patients express neuropilin-1 and this correlates with a poor survival outcome (*Cell 169:1130, 2017*).
- Biotech start-up founded in 2014 to develop a drug that targets Neuropilin-1. Clinical trial was started in August 2018.



LAG3 is the third checkpoint target to enter the clinic



Clinical Trials Accuring: >60

- Ipilimumab
- Tremelimumab
- AGEN-1884

1000s!

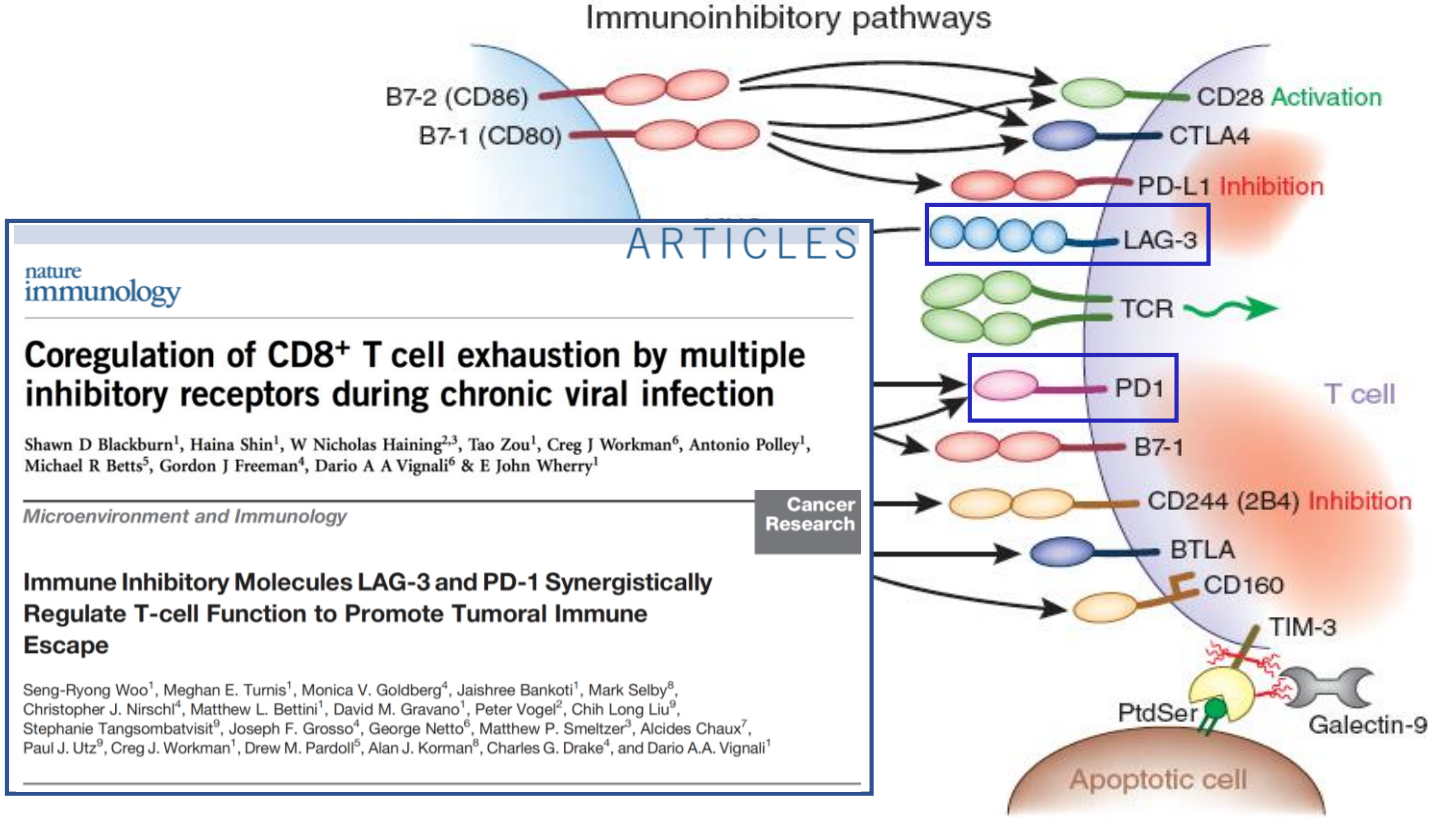
- Pembrolizumab
- Nivolumab
- Durvalumab
- Atezolizumab
- Pidilizumab
- REGN2810
- TSR-042, Others?

~30

- Relatlimab (BMS-986016)
- LAG525
- MK-4280
- REGN3767
- TSR-033
- Sym022
- INCAGN02385
- MGD013 (LAG3-PD1 bispecific)
- FS118 (LAG3-PDL1 bispecific)
- IMP321 (LAG3-Ig)
- Others?

Mellman et al. *Nature*. 2011;480:480-489.

Multiple Immuno-Inhibitory Pathways Regulate T cell Tolerance and T cell Exhaustion



ARTICLES

nature immunology

Coregulation of CD8+ T cell exhaustion by multiple inhibitory receptors during chronic viral infection

Shawn D Blackburn[1], Haina Shin[1], W Nicholas Haining[2,3], Tao Zou[1], Creg J Workman[6], Antonio Polley[1], Michael R Betts[5], Gordon J Freeman[4], Dario A A Vignali[6] & E John Wherry[1]

Microenvironment and Immunology

Cancer Research

Immune Inhibitory Molecules LAG-3 and PD-1 Synergistically Regulate T-cell Function to Promote Tumoral Immune Escape

Seng-Ryong Woo[1], Meghan E. Turnis[1], Monica V. Goldberg[4], Jaishree Bankoti[1], Mark Selby[8], Christopher J. Nirschl[4], Matthew L. Bettini[1], David M. Gravano[1], Peter Vogel[2], Chih Long Liu[9], Stephanie Tangsombatvisit[9], Joseph F. Grosso[4], George Netto[6], Matthew P. Smeltzer[3], Alcides Chaux[7], Paul J. Utz[9], Creg J. Workman[1], Drew M. Pardoll[5], Alan J. Korman[8], Charles G. Drake[4], and Dario A.A. Vignali[1]

Sharpe and Freeman, Nature Immunology 13:113 (2012)

Tumor clearance with combinatorial anti-LAG-3 / anti-PD-1 treatment

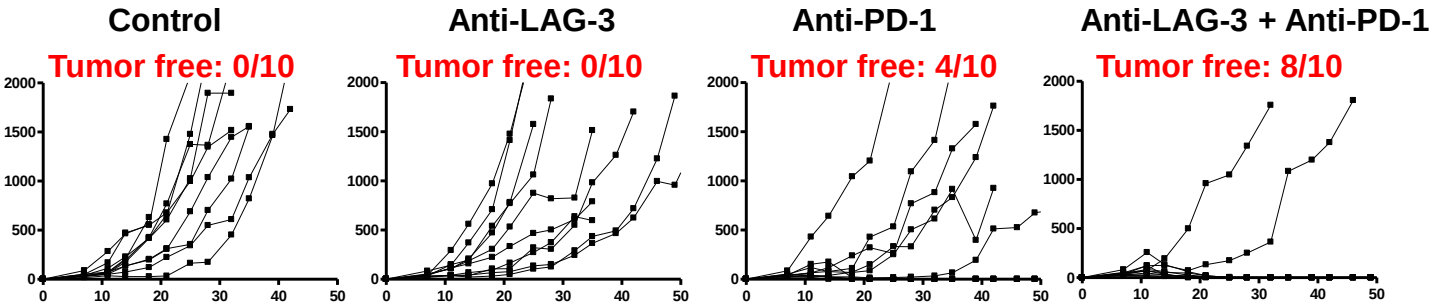
Sa1N Fibrosarcoma - A/J mice (Ab treatment = 10mg/kg at day 8, 11, 14)

How can one predict which patients will respond to combinatorial PD1/LAG3 immunotherapy?

What is the mechanistic basis of PD1/LAG3 synergistic activity?

Time after inoculation (d)

MC38 Adenocarcinoma – C57BL/6 mice (Ab treatment = 10mg/kg at day 8, 11, 14)

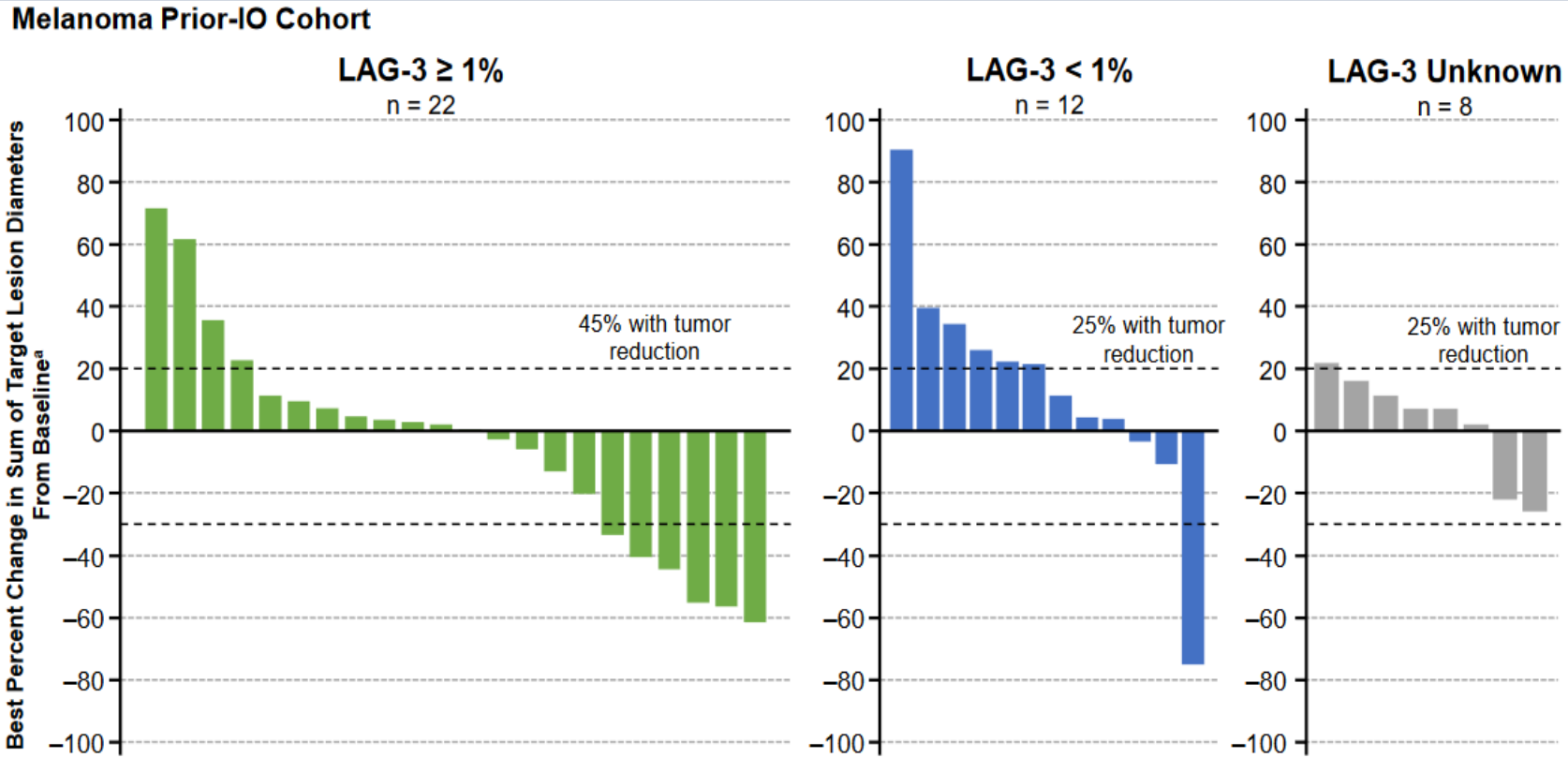


Time after inoculation (d)

Meghan Turnis, Mark Selby (*BMS*), Alan Korman (*BMS*), Chuck Drake (JHU)

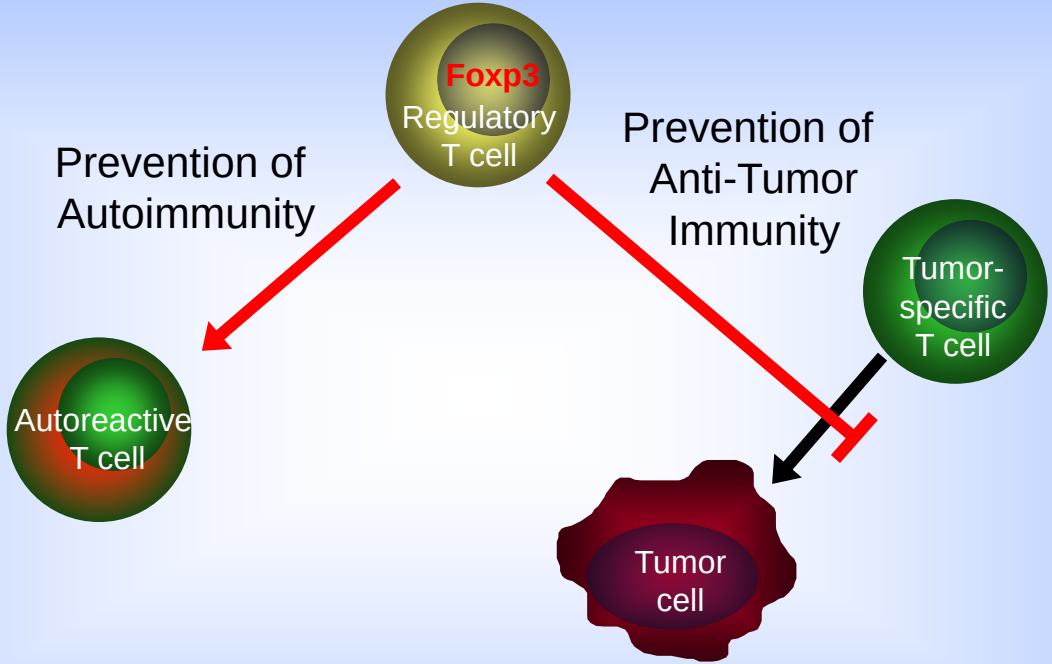
Cancer Research 72:917 (2012)

Overall response rate to Relatlimab in IO-unresponsive melanoma patients is 13% (20% in LAG3 ≥1%)



Ascierto et al. 2017. "Initial efficacy of anti-lymphocyte activation gene-3 (anti–LAG-3; BMS-986016) in combination with nivolumab (nivo) in pts with melanoma (MEL) previously treated with anti–PD-1/PD-L1 therapy." ASCO Poster #9520.

Regulatory T cells - The Master Controller

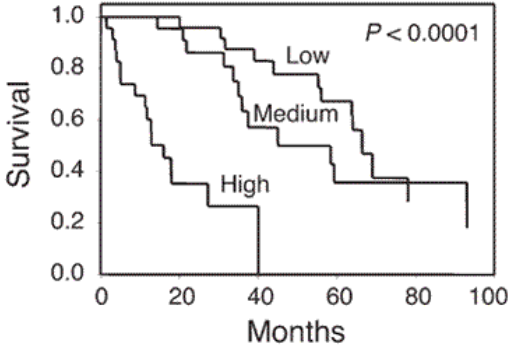


What is the impact of T_{reg} on cancer prognosis?

Would targeting T_{regs} have a therapeutic benefit in cancer?

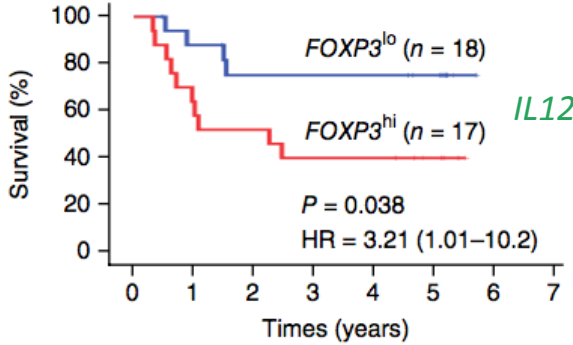
Significance of regulatory T cells in human cancer

Ovarian cancer



Curiel et al, Nat Med 2004

Colorectal cancer

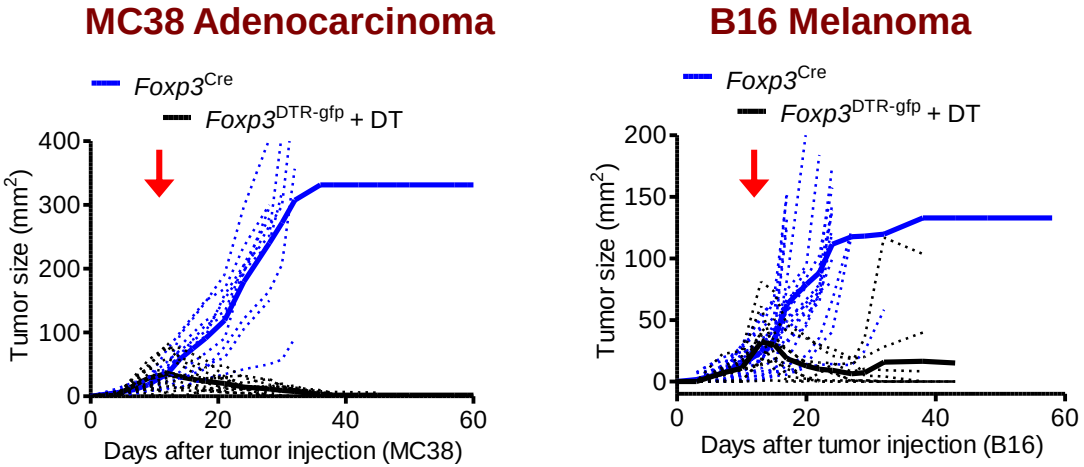


IL12A^{lo}TGFB^{lo} CRC

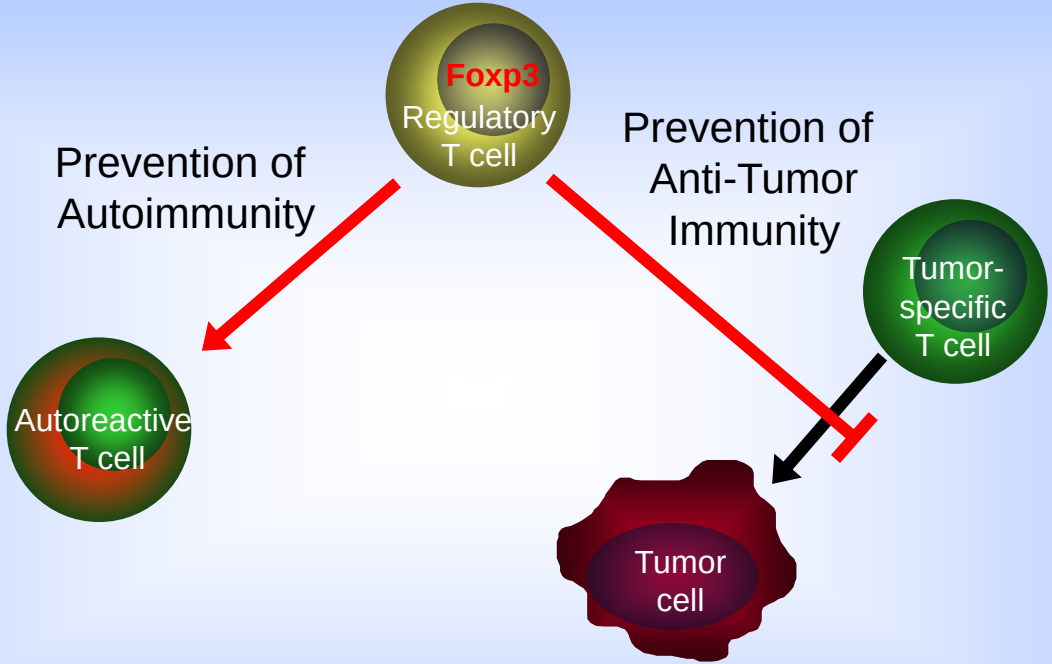
Saito et al, Nat Med 2016

- **T_{regs} are elevated in the peripheral blood of cancer patients and infiltrate tumor tissue.**
- **Increased intratumoral T_{reg} frequency correlates with reduced survival in multiple solid tumors.**

The impact of T_{regs} on tumor growth



Regulatory T cells - The Master Controller



Is it possible to limit the activity of T_{regs} in tumors without inducing systemic autoimmune or inflammatory reactions?

Targeting T_{reg} in Tumors: What is the optimal approach?

- Intratumoral T_{reg} depletion (eg: cytolytic mAbs to CTLA4, GITR, TIGIT):
  - Advantage: May have a bigger therapeutic index
  - Disadvantage: This may be accompanied by significant grade 3-5 AEs
- Target features that are selectively utilized or expressed in the by T_{regs} tumor microenvironment:
  - Migration (eg: CCR4)
  - Suppressive mechanisms (eg: CTLA4, GITR, TIGIT, CD39/73, IL35)
  - Stability/survival (eg: NRP1)
  - Metabolism (eg: ?)

Cancer Immunology and Immunotherapy Program (CIIP)

Dario A. A. Vignali, PhD

Frank Dixon Chair of Cancer Immunology, Vice Chair and Professor, Dept. of Immunology;
Co-Director of the Tumor Microenvironment Center, & Leader of CIIP

University of Pittsburgh

NCI CCC A Comprehensive Cancer Center Designated by the National Cancer Institute

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Research Mission and Themes

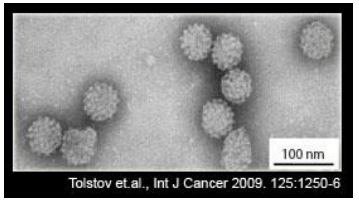
The mission of the Cancer Immunology and Immunotherapy Program (CIIP) is to reduce the burden of cancer by elucidating the basic mechanisms of interactions between the immune system and cancer, thus providing a scientific rationale for the design of new and more effective approaches for cancer treatment and prevention.

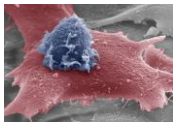
Inhibitory Mechanisms in the TME	Stimulatory Mechanisms in the TME	Cancer Immunotherapy
• Inhibitory receptors • Regulatory T cells (T_{regs}) • Suppressive macrophages, DCs, fibroblasts, etc. • Metabolic dysfunction	• Costimulatory molecules • Optimizing tumor-infiltrating lymphocytes (TIL) • Cell Engineering: CAR-T, T cell receptor (TCR) cloning, etc. • Vaccine development	• Pre-clinical mouse studies • Pre-clinical human studies • Immunotherapy trials • Prevention trials

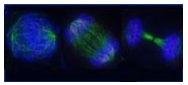
Top Six Cancers in Catchment Area

Top Six Cancers

Incidence	Mortality
Breast	Lung
Prostate	Breast
Lung	Prostate
Colon	Colon
Thyroid	Pancreas
Bladder	Ovary

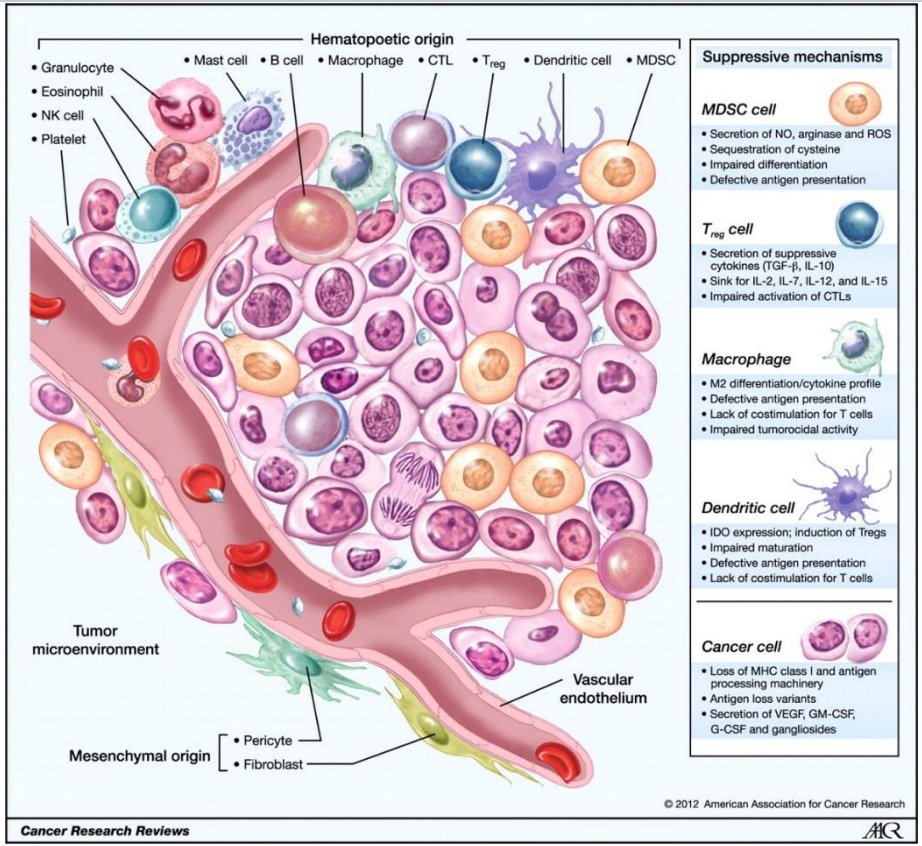






UPMC | HILLMAN CANCER CENTER

Tumor Microenvironment Center



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&

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Man-Tzu Wang, PhD

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Vignali Lab

Creg Workman
Tullia Bruno
Kate Vignali
Gracie (Chang) Liu
Lawrence Andrews
Tony Cillo
Angela Gocher

Present

Jessie Moskovitz
Ashwin Somasundaram
Richard Wu
Maggie (Mengting) Liao
Abby Overacre-Delgoffe
Hiroshi Yano

Rebekah (Becky) Dadey
Chris Chuckran
Stephanie Grebinoski
Ayana Ruffin
Feng Shen
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Sheryl Kunning

Past

Greg Delgoffe
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Deepali Sawant
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Thank you for listening

VIGNALI LAB - Present

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Gracie (Chang) Liu
Lawrence Andrews

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