CANCER RESEARCH INSTITUTE

IMMUNOTHERAPY PATIENT SUMMIT

San Francisco • Chicago • New York • Houston • Tampa

San Francisco July 8, 2017

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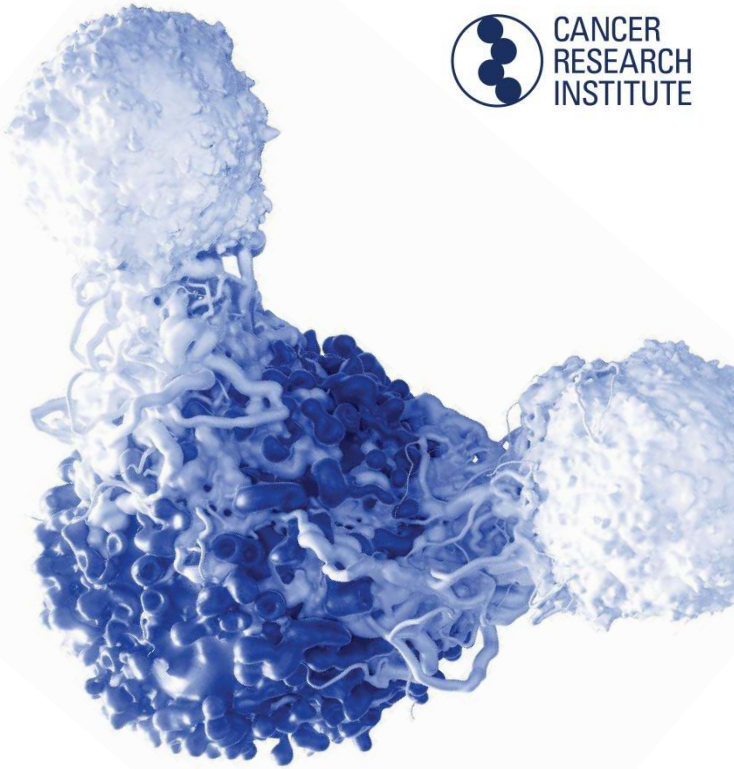

Jill O'Donnell-Tormey, Ph.D.

Cancer Research Institute

WELCOME

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IMMUNOTHERAPY PATIENT SUMMIT

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A special thank you to those who helped promote the summit

- Addario Lung Cancer Foundation
- Bay Area Cancer Connections
- Coalition for Clinical Trial Awareness
- Colon Cancer Alliance
- Cancer Support Community
- Fight Colorectal Cancer
- Focused Ultrasound Foundation
- FORCE
- GI Cancers Alliance
- Head and Neck Cancer Alliance
- Imerman Angels
- Immunotherapy Foundation
- Let Life Happen
- Parker Institute for Cancer Immunotherapy
- Patient Empowerment Network
- UCSF Helen Diller Family Comprehensive Cancer Center

Our Guest Faculty

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Scientific Experts

Ezra Cohen, M.D.
University of California San Diego

Lewis Lanier, Ph.D.
University of California San Francisco

Aaron Miller, M.D., Ph.D.
University of California San Diego

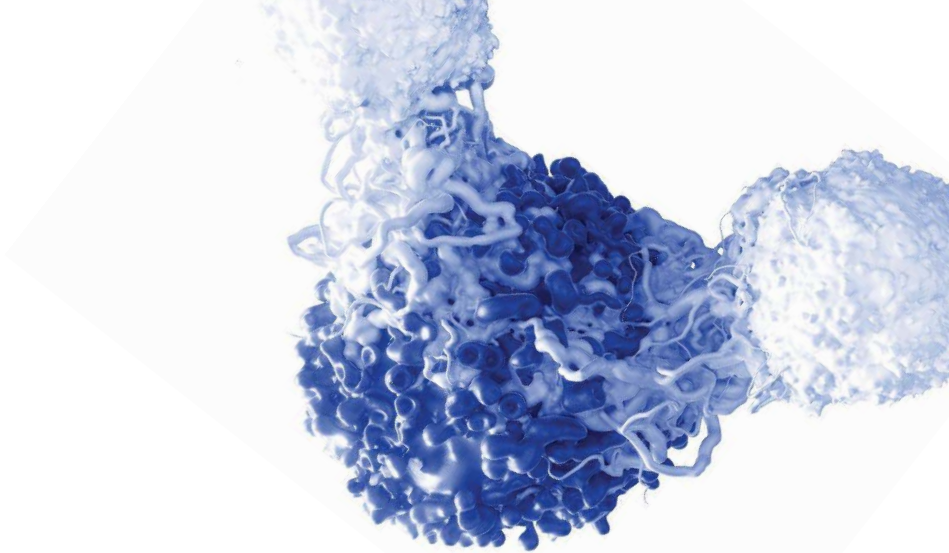
Stanley Riddell, M.D.
Fred Hutchinson Cancer Research Center

Patient & Caregiver Experts

Janie Ferling
Melanoma Survivor

Johanna Packard
Caregiver (Prostate Cancer)

Philip Prichard
Kidney Cancer Survivor



Lewis Lanier, Ph.D.

UCSF Helen Diller Family Comprehensive Cancer Center

Parker Institute for Cancer Immunotherapy

IMMUNOTHERAPY BASICS

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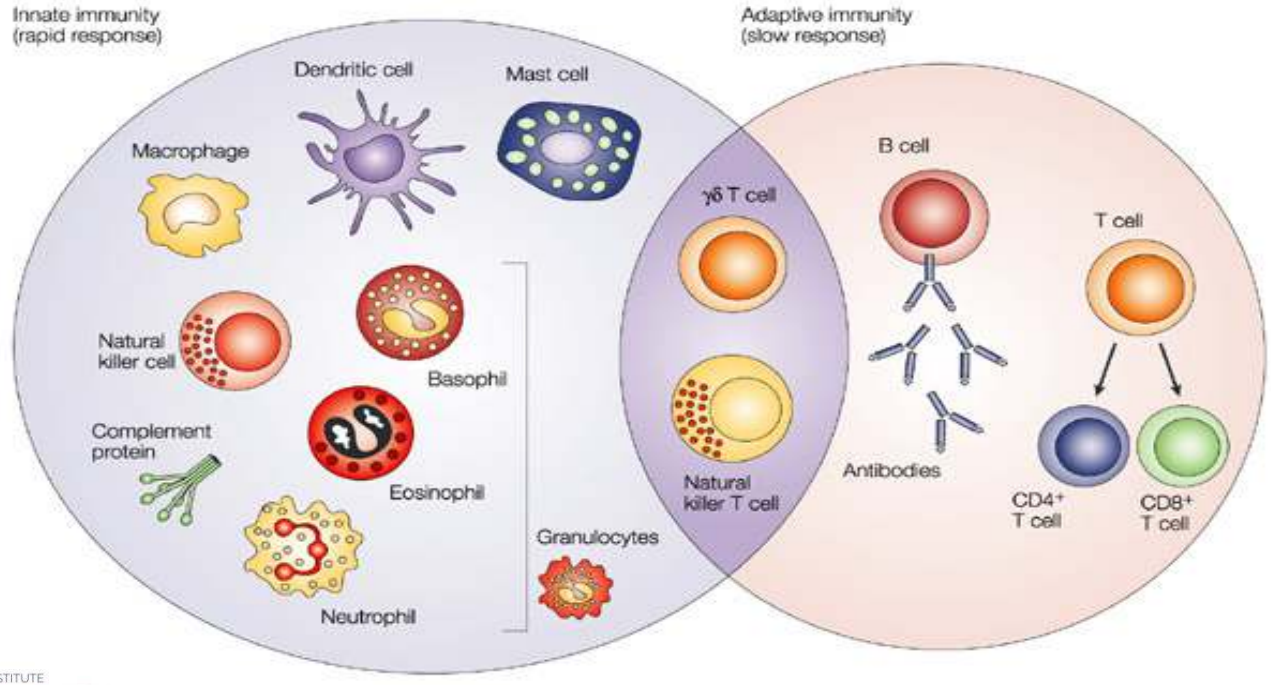
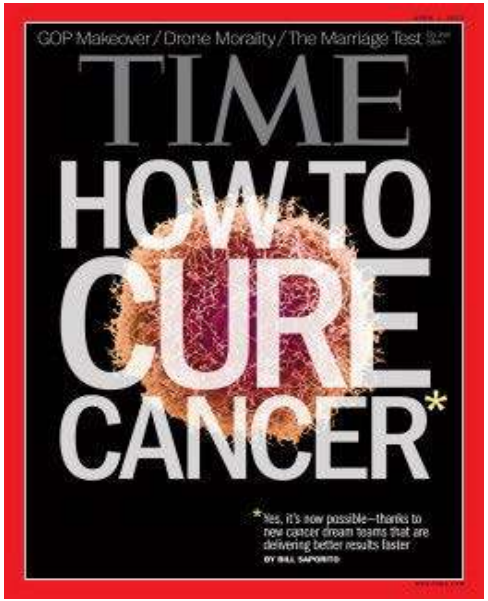
Cut 'em, Burn 'em, Poison 'em

We now have a new weapon against cancer – your immune system



Nature Reviews | Cancer



The New York Times

Patient's Cells Deployed to Attack Aggressive Cancer

The Washington Post

Health & Science

New therapies raise hope for a breakthrough in tackling cancer

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Immunological Surveillance of Cancer
Ehrlich, Burnet & Thomas

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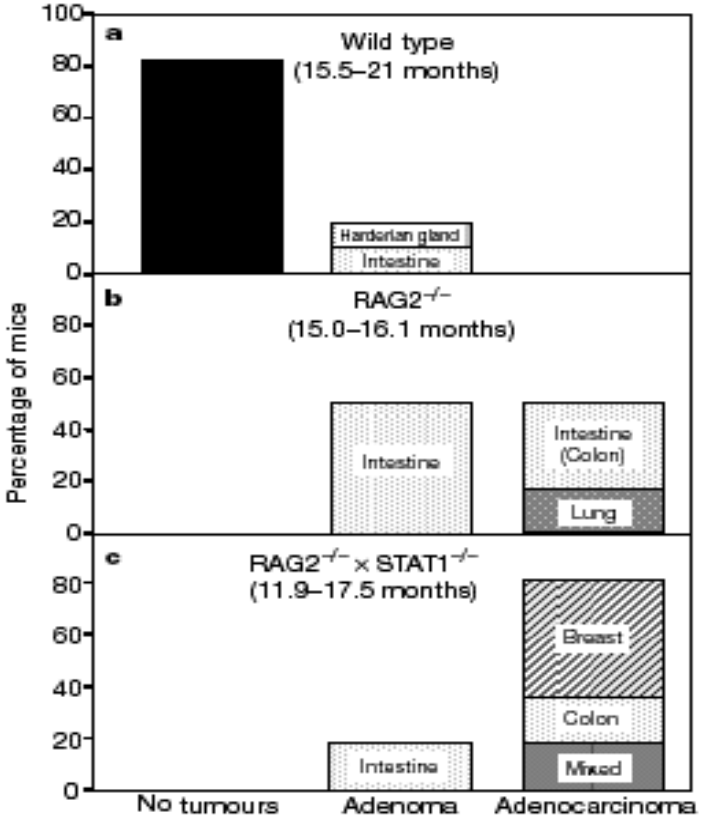
Paul Ehrlich (1909) Concept of cancer immunosurveillance. Predicted that cancer would occur at "incredible frequency" if host defenses did not prevent the outgrowth of continuously arising cancer cells

Lewis Thomas (1957) "primary function of cellular immunity….is to protect from neoplastic disease"

Macfarland Burnet (1957) "It is by no means inconceivable that small accumulations of tumour cells may develop and because of their possession of new antigenic potentialities provide an effective immunological reaction with regression of this tumor and no clinical hint of its existence"

Spontaneous Tumors in Immunocompetent and Immunodeficient Mice



Mice without T and B cells

Mice without T and B cells and unable to respond to interferons

Cancer Immunotherapy

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In the beginning….Dr. William Coley 1890s

Treating cancer with bacterial products to stimulate the patient's immune system

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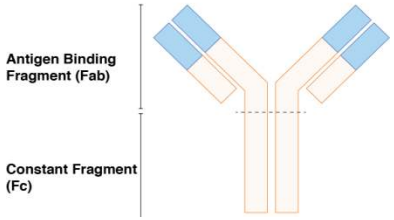
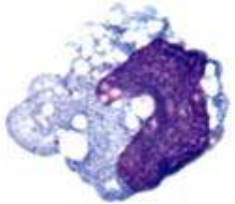
Immunity to Cancer – The Players



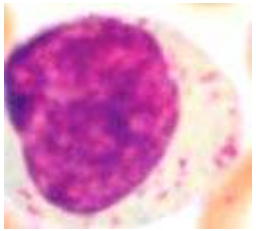
Antibodies

- made by your B cells or given as drugs



Myeloid cells

- good ones stimulate the immune system (dendritic cell) and kill tumors (macrophages)
- bad ones suppress immune responses



T cells and Natural Killer cells

- good ones kill tumors (cytotoxic and helper T, NK)
- bad ones suppress immune responses (Treg)

Using Antibodies to Boost the Immune Response to Cancer

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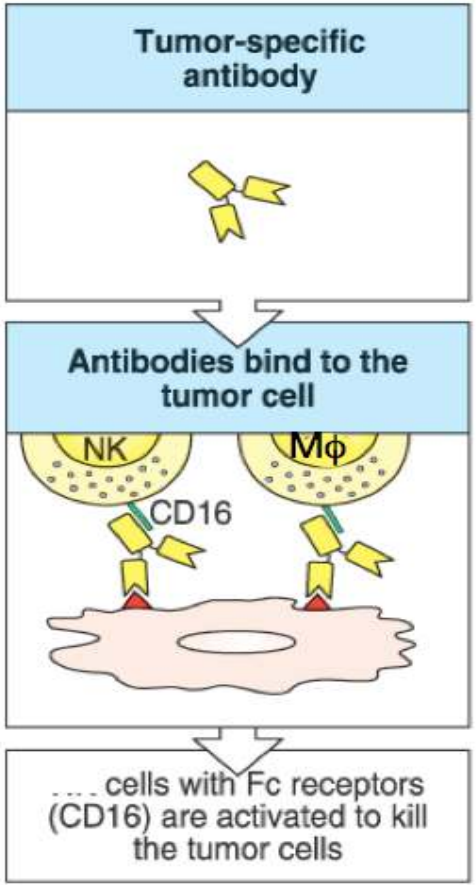
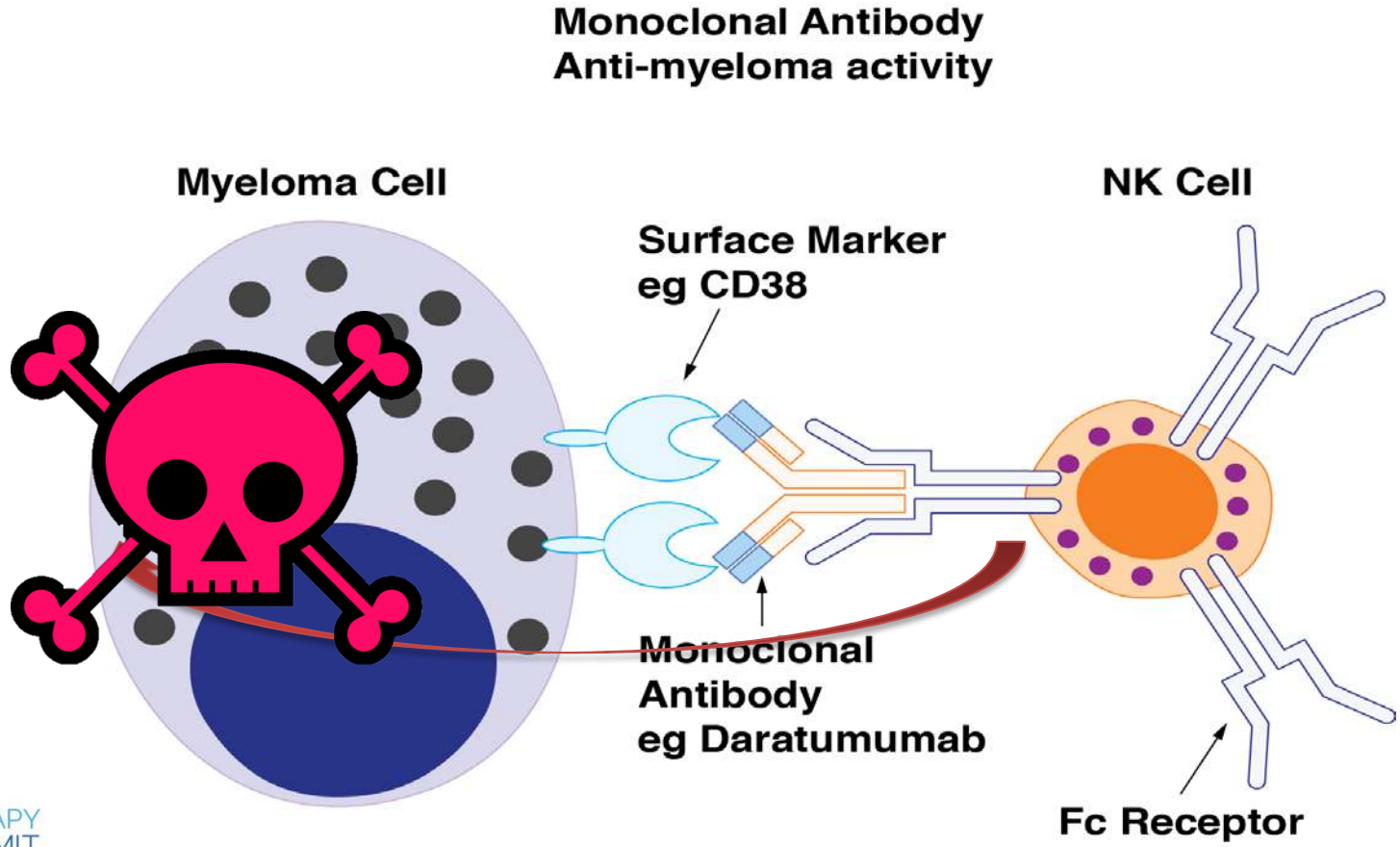


Monoclonal antibody coats tumor cells

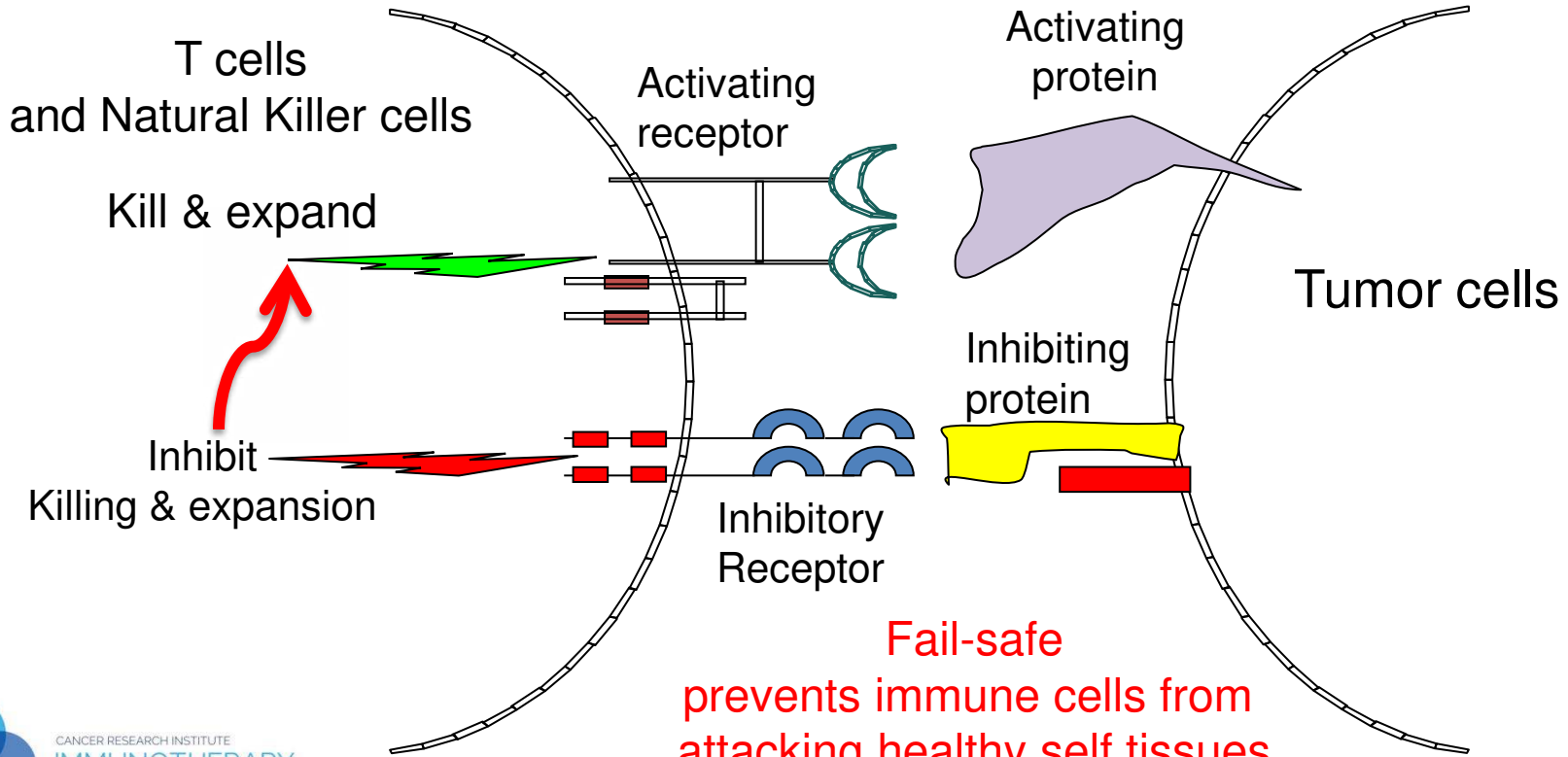
Natural Killer cells and macrophages with Fc receptors bind to the tail (Fc) of the antibody and kill the tumor

Rituximab– targets CD20 on B cell tumors
Trastuzumab – targets her2 on breast cancer
Daratumumab – targets CD38 on myeloma
CetuximAb – targets EGFR on colon cancer

Using Antibodies to Boost the Immune Response to Cancer



Immune Cells Are Controlled by a Balance of Activating and Inhibitory Signals



Fail-safe
prevents immune cells from
attacking healthy self tissues
(autoimmunity)

"Checkpoint Blockade" - Use Antibodies to Block the Inhibitory Receptors to Boost the Immune Response

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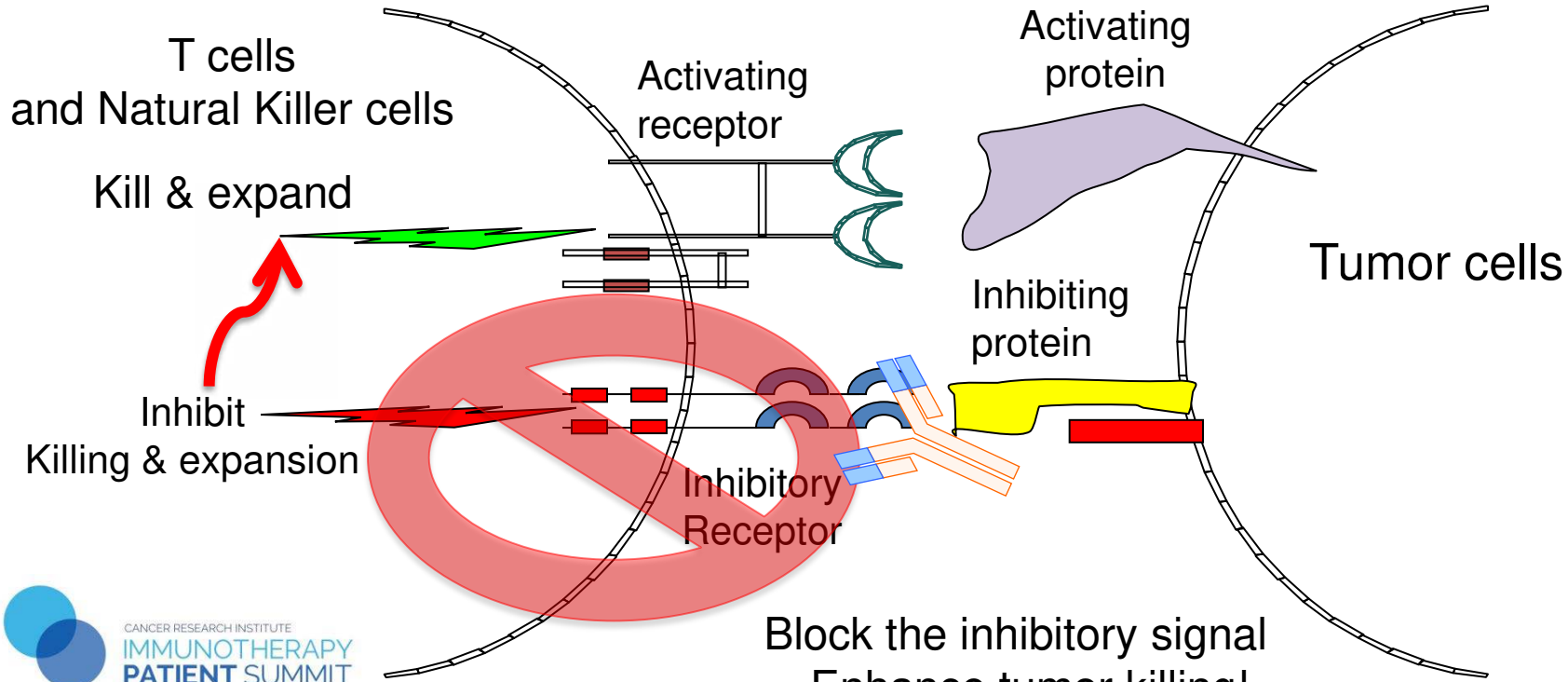

Block the inhibitory signal
- Enhance tumor killing!

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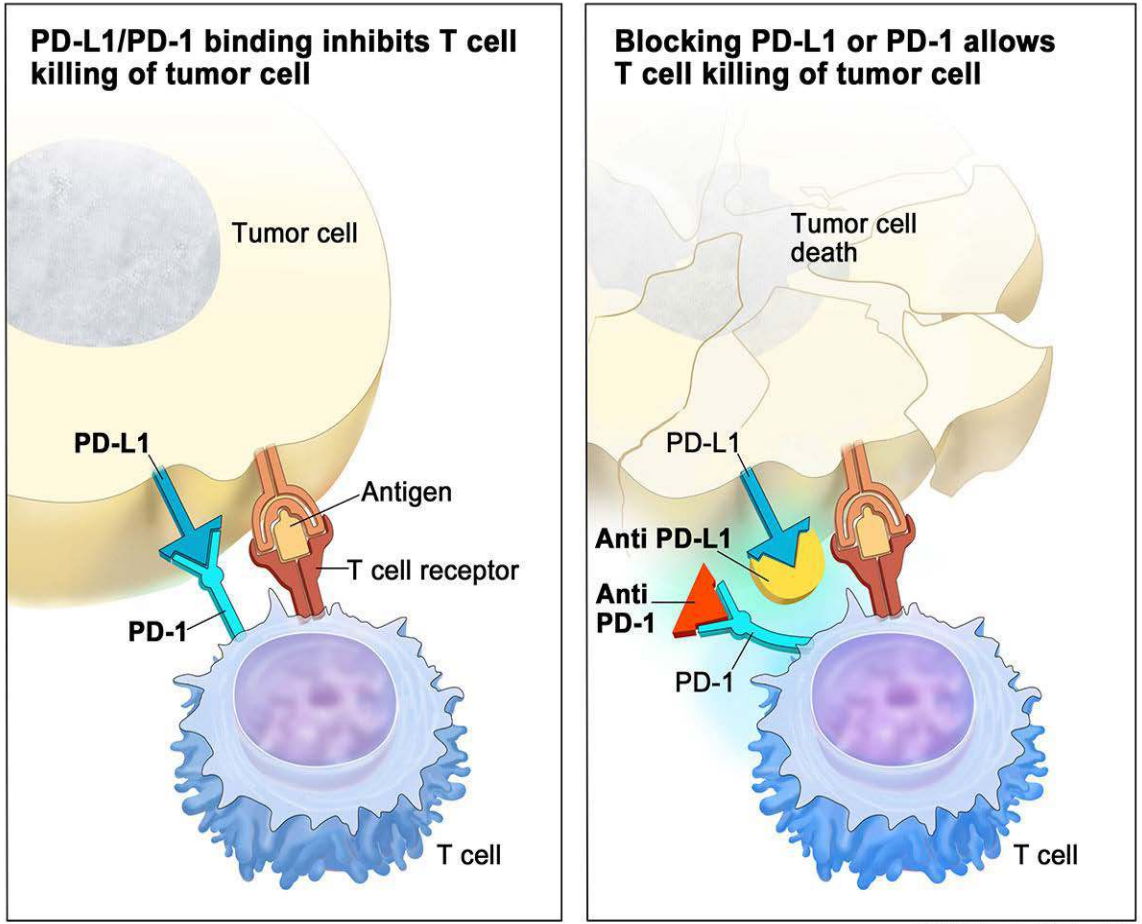
Checkpoint Inhibitors – Antibodies to Inhibitory PD-1 Receptor



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CTLA-4 Blockade: Anti-Tumor Immunity, but Autoimmunity

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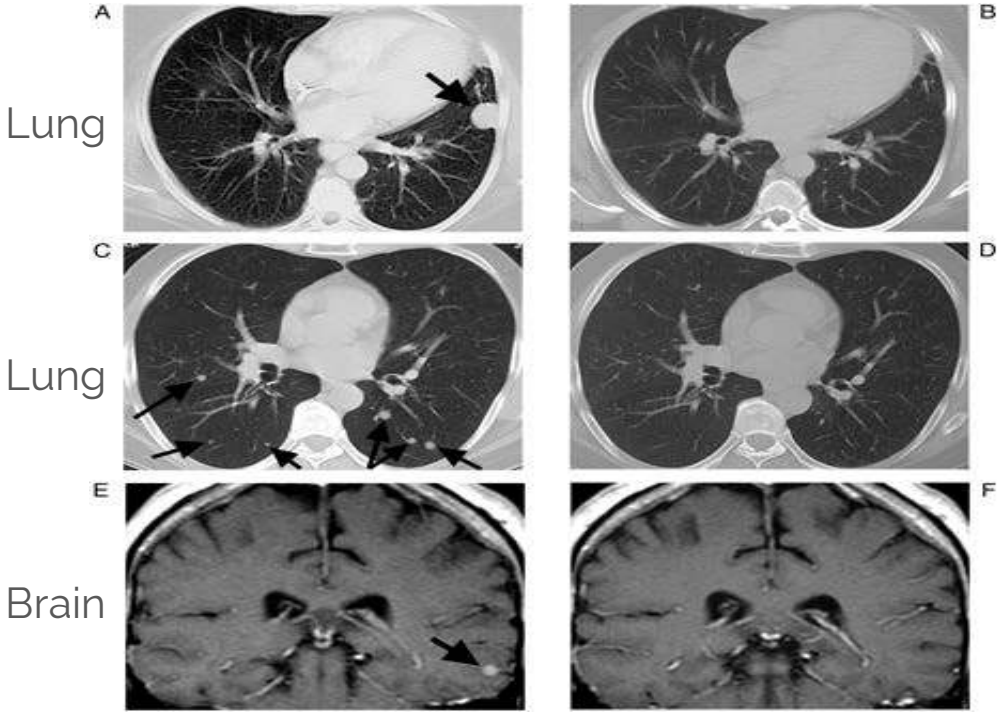
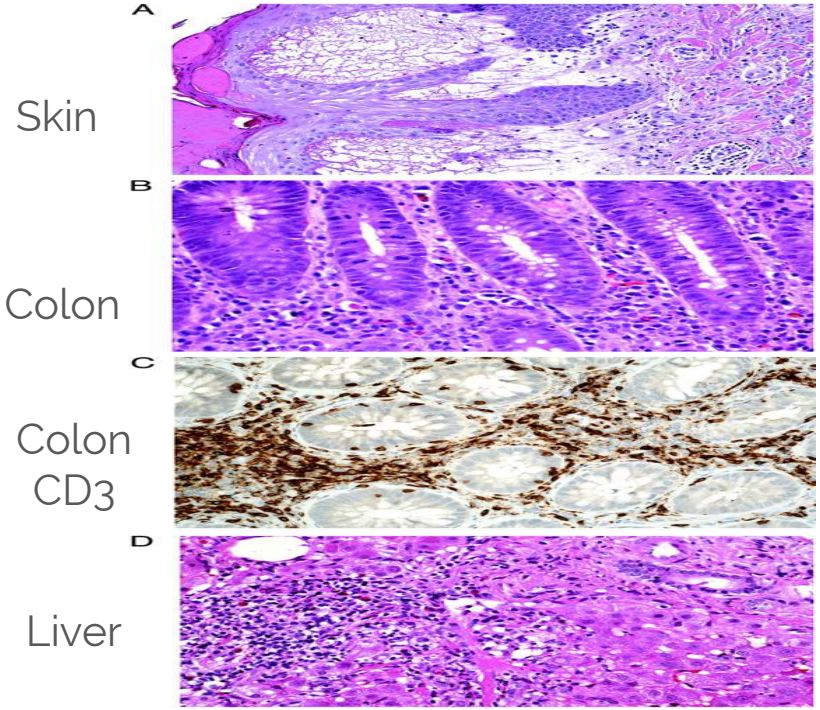
The good news….



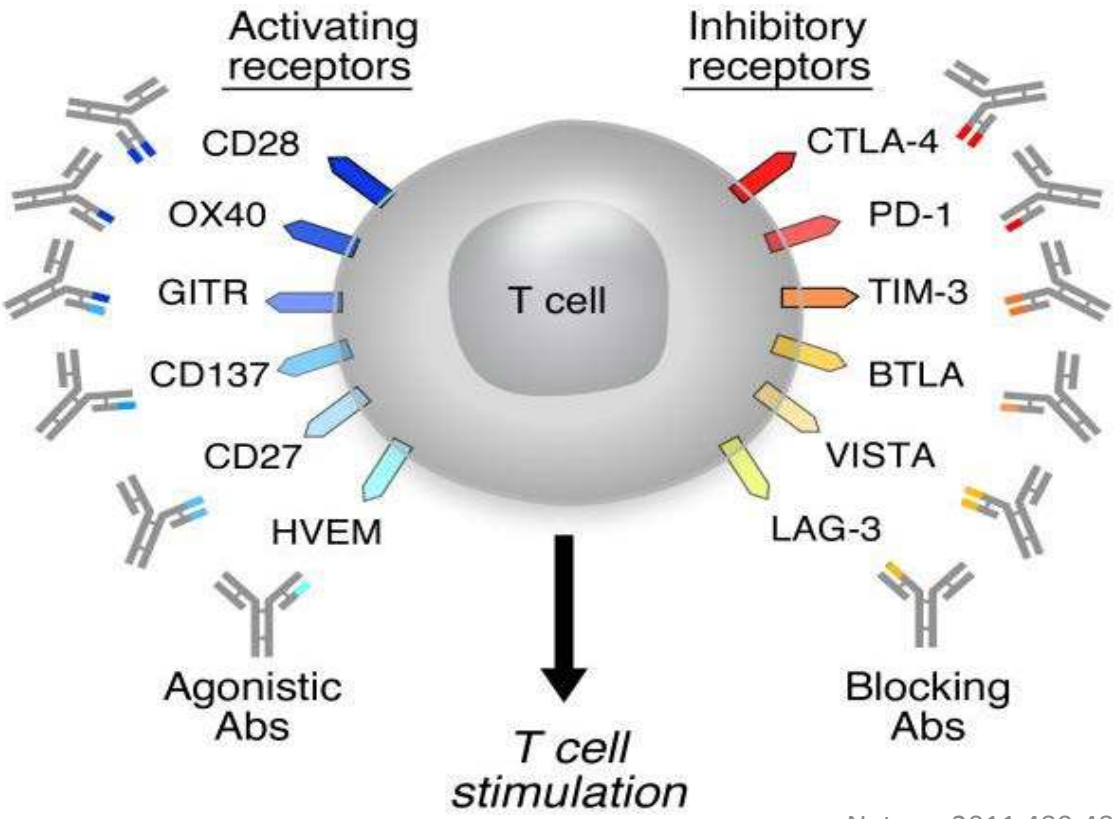
The bad news….



Phan et al. PNAS (2003) 100:8372

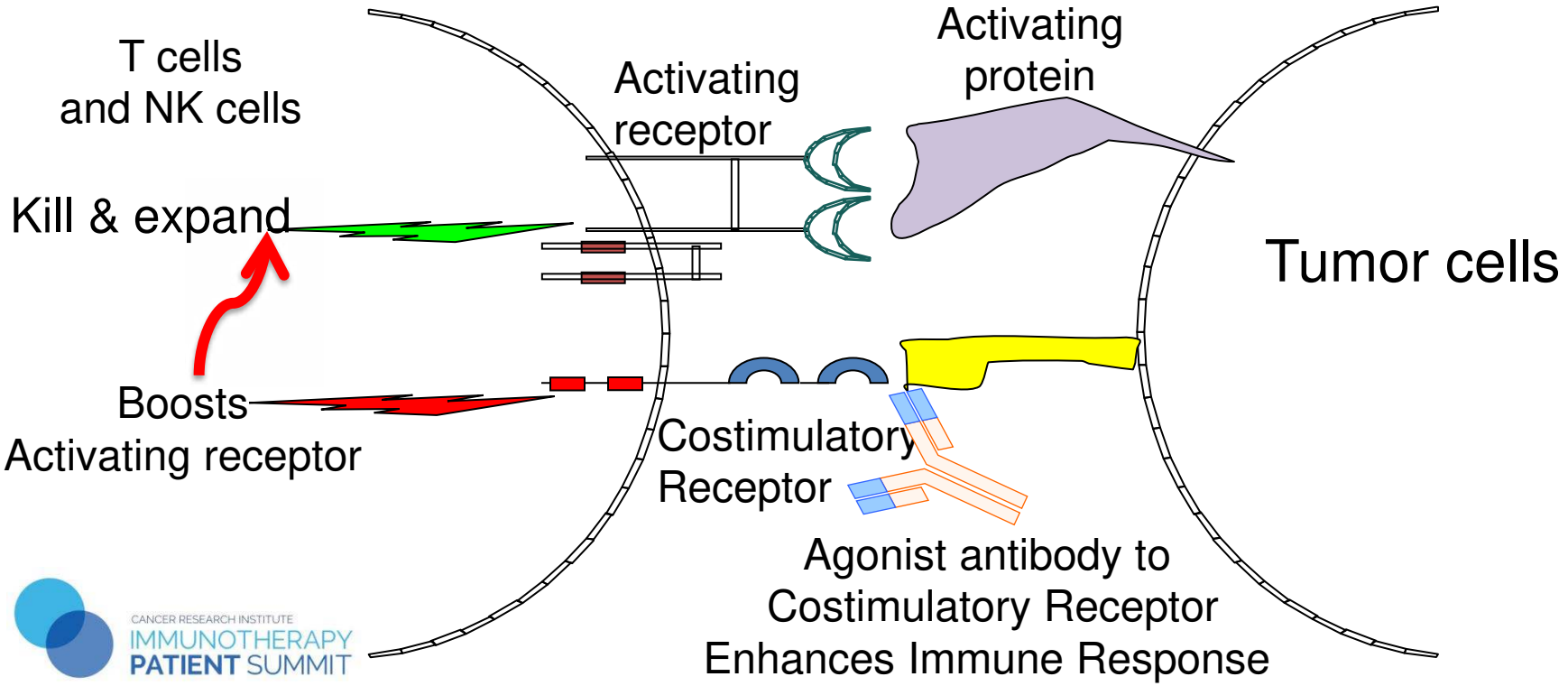
Checkpoint Blockade Success!

Using Antibodies to Block Inhibitory Receptors or Stimulate Activating Receptors Boosts Immune Responses



Nature. 2011 480:480-9

Activating and Co-Stimulatory Receptors



Combined PD-1 and CTLA-4 Blockade in Melanoma Pts

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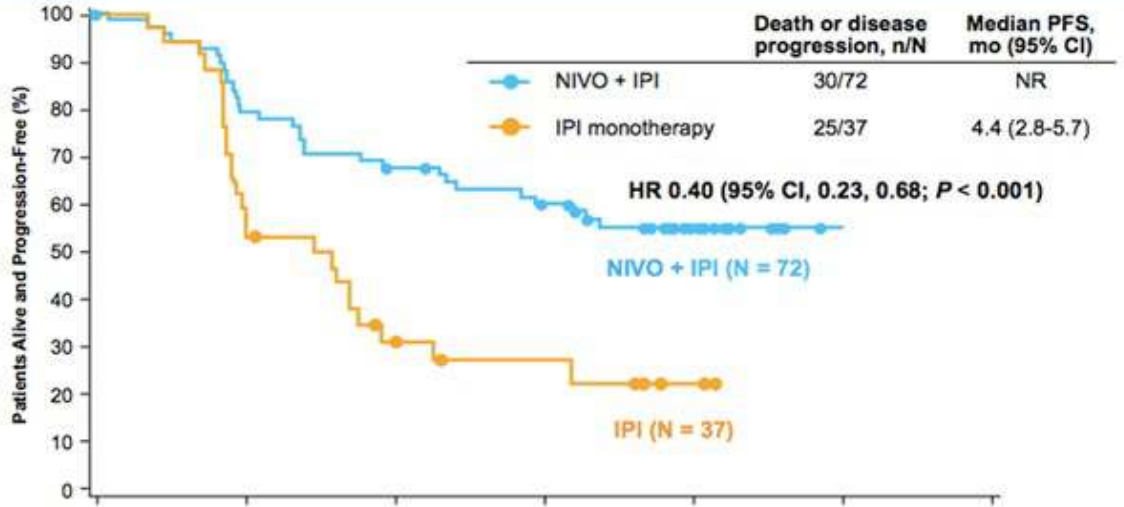
PFS Among BRAF WT Patients



- PFS among BRAF MT patients (8.5 mo for NIVO + IPI, 2.7 mo for IPI monotherapy) was similar to that observed among BRAF WT patients

HR = hazard ratio

Database lock: January 30, 2015

Combination Therapies in Trials

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Table 3 Clinical trials of combination therapies with molecularly targeted drugs

PD-1/PD-L1mAb	Combination	Tumor	Reference
PD-1 mAb (Nivolumab)	LAG3 (BMS-986016)	Solid Tumors	NCT01968109
PD-1 mAb (Nivolumab)	B7-H3 (Enoblituzumab)	Solid Tumors	NCT02817633
PD-1 mAb (Pembrolizumab)	B7-H3 (Enoblituzumab)	Solid Tumors	NCT02475213
PD-1 mAb (Nivolumab)	KIR (Lirilumab)	Solid Tumors	NCT01714739
PD-L1 mAb (MEDI4736)	OX40 (MEDI6383)	Solid Tumors	NCT02221960
PD-1 mAb (Nivolumab)	4-1BB (Urelumab)	Solid tumors and B-cell non-Hodgkin lymphoma	NCT02253992
PD-1 mAb (Nivolumab)	ICOS (JTX-2011)	Solid Tumors	NCT02904226
Pd-1 mAb (PDR001)	GITR (GWN323)	Solid Tumors and Lymphomas	NCT02740270
PD-1 mAb (Nivolumab)	CD27 (Varlilumab)	Solid Tumors	NCT02335918
PD-L1 mAb (Atezolizumab)	CD27 (Varlilumab)	Solid Tumors	NCT02543645
PD-1 mAb (Nivolumab)	GM.CD40L (vaccine for NSCLC)	Lung (NSCLC)	NCT02466568
PD-L1 mAb (Atezolizumab)	VEGF inhibitors (Bevacizumab cediranib)	Ovarian Cancer	NCT02659384
PD-L1 mAb (MEDI4736)	PARP inhibitors (Olaparib)	S tumors	NCT02484404
PD-L1 mAb (MEDI4736)	Multi-kinase inhibitor (Sunitinib)	Solid tumors	NCT02484404
PD-1 mAb (Pembrolizumab) with SBRT	Multi-kinase inhibitor (Sunitinib)	TKI refractory mRCC[a]	NCT02599779
PD-L1 mAb (Durvalumab)	EGFR inhibitor (Osimertinib)	Lung (NSCLC)	reference [70]

[a] Tyrosine kinase inhibitor refractory metastatic recal cell cancer

Iwai J. Biomed Sci. 2017

Autoimmunity Caused by Checkpoint Blockade - combinations can increase toxicity

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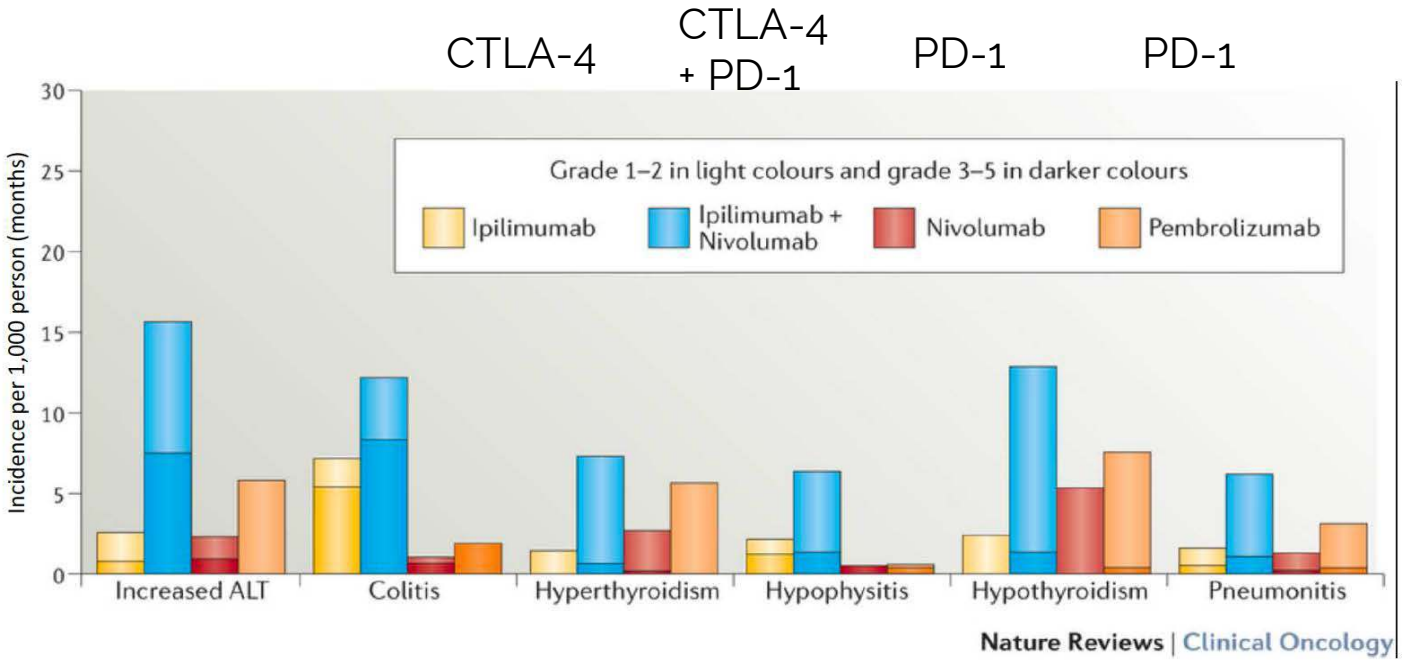

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Boutros et al., Nature Reviews Clinical Oncology, 2016

Tumor Antigens - What the Immune System Recognizes

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Tumor-specific "neo-antigens"

- Expressed ONLY by tumors due to genetic mutations

Tumor-associated antigens

- Preferentially expressed by tumors (overexpressed normal proteins due to gene amplification or epigenetics)

Oncofetal antigens

- Expressed by tumors in adult, but also expressed by fetal (not adult) tissues

Viral antigens

- Expressed by oncogenic viruses (HPV, EBV, KSV)

Genetic Mutations Are Frequent in Some Tumors (Melanoma, Lung, etc.) – Rare in Others

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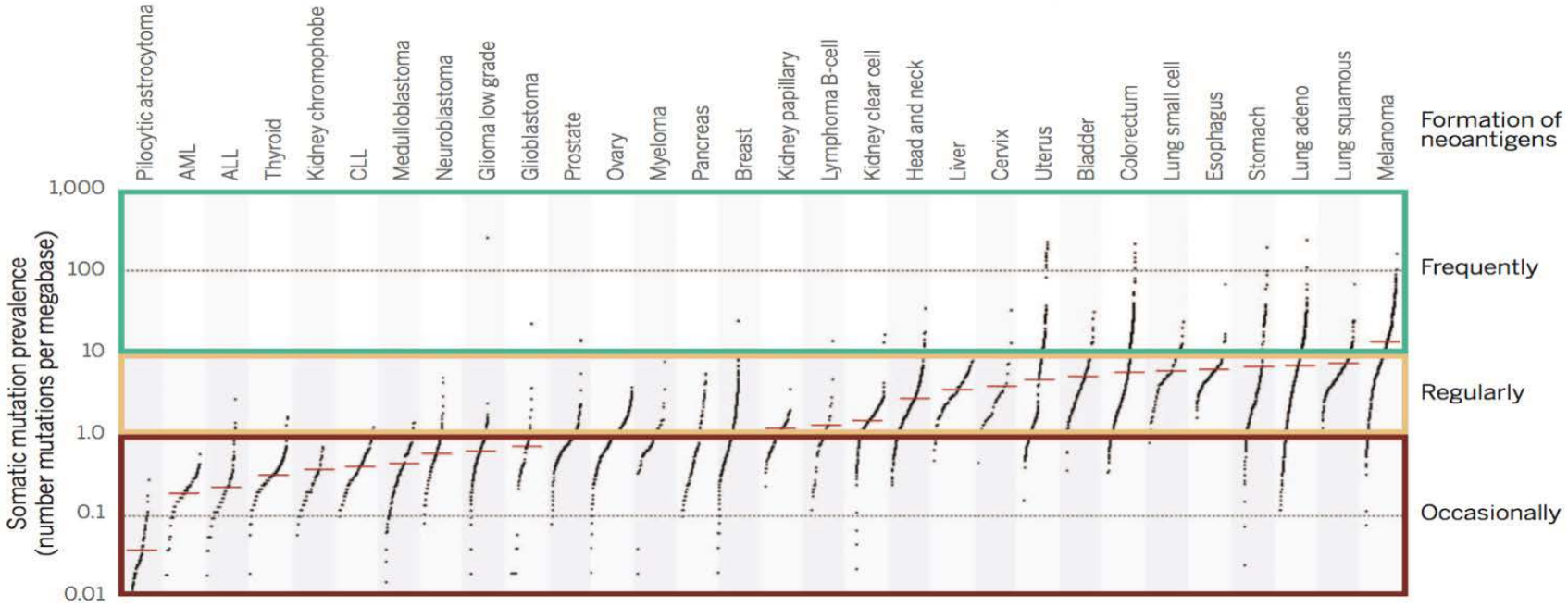

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Science 2015 – Schumacher & Schreiber

Adoptive T Cell Therapy

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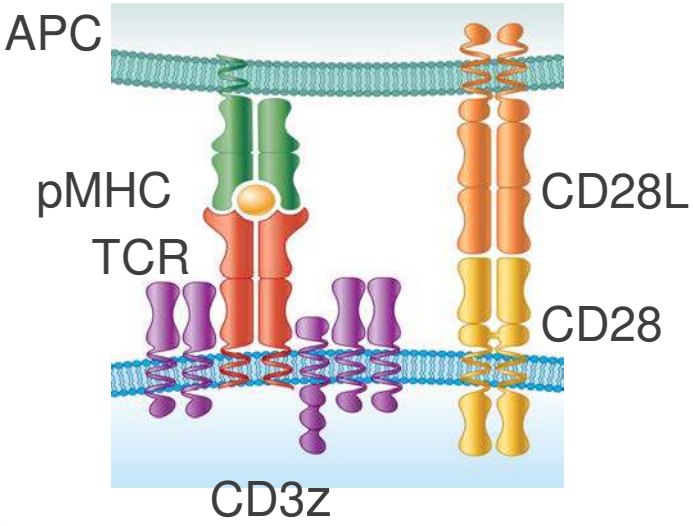
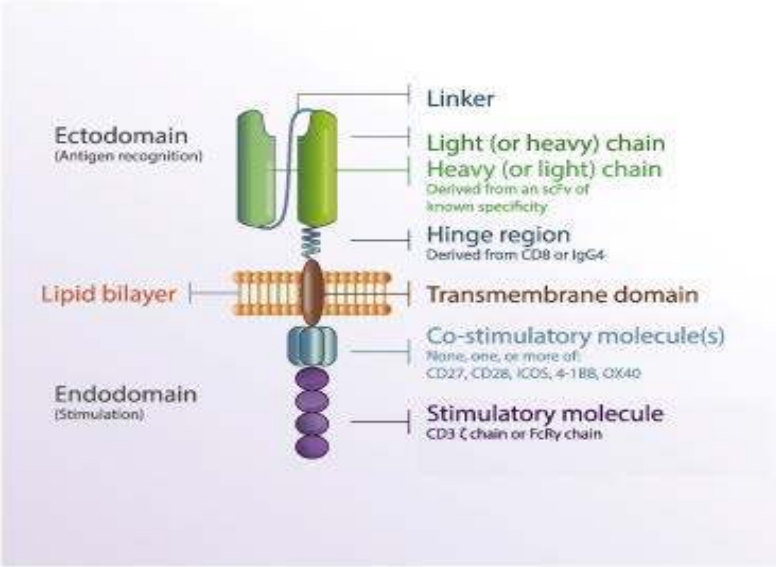
T cell
with tumor-specific
T cell receptor



T cell with engineered
Chimeric Antigen Receptor (CAR)



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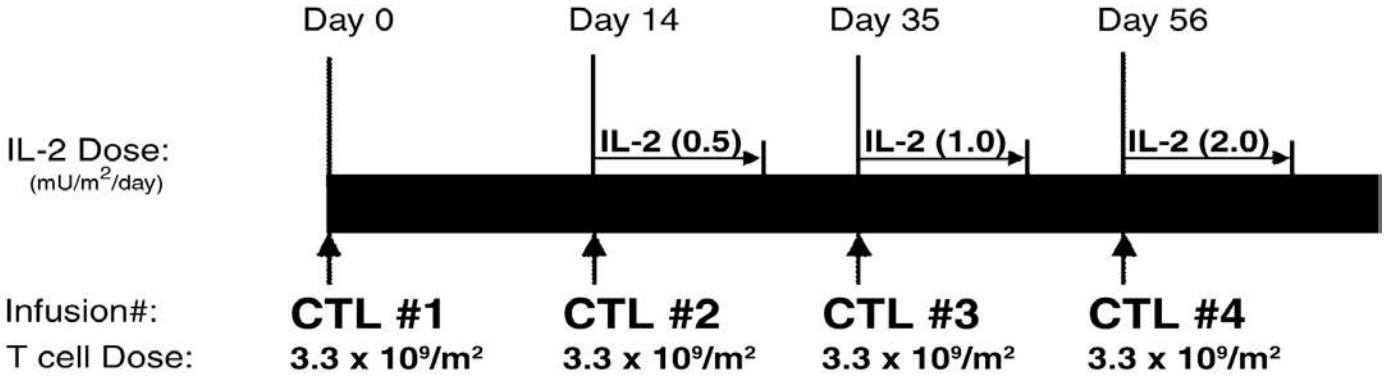
Adoptive T cell therapy using antigen-specific CD8$^+$ T cell clones for the treatment of patients with metastatic melanoma: *In vivo* persistence, migration, and antitumor effect of transferred T cells

C. Yee*,†, J. A. Thompson*, D. Byrd*, S. R. Riddell*, P. Roche‡, E. Celis‡, and P. D. Greenberg*



PNAS 99:16168, 2002

Adoptive "CAR" T cell therapy

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ORIGINAL ARTICLE

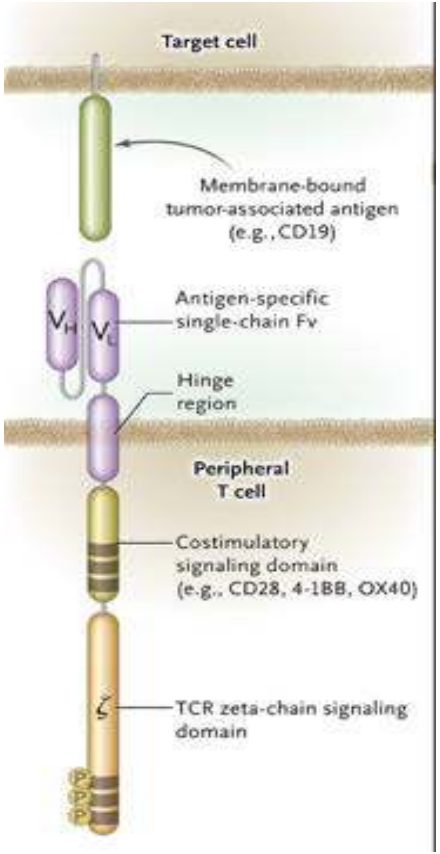
BRIEF REPORT

Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.

N Engl J Med 2011; 365:725-733 | August 25, 2011

- Isolate patient's peripheral blood T cells
- Lentivirus transduced with "CAR" (chimeric antigen receptor)
- CAR – anti-CD19 antibody fragment fused to intracellular domains of potent T cell signaling subunits
- Re-infuse "CAR"-modified T cells into patient
- Successful for treating children with B cell malignancies (toxicity – loss of normal B cells – forever?; cytokine storm)



The New York Times

HEALTH

In Girl's Last Hope, Altered Immune Cells Beat Leukemia

By DENISE GRADY DEC. 9, 2012

Emma Whitehead, with her mother, Kari. Last spring, Emma was near death from acute lymphoblastic leukemia but is now in remission after an experimental treatment at the Children's Hospital of Philadelphia.
Jeff Swensen for The New York Times

The NEW ENGLAND JOURNAL of MEDICINE

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ORIGINAL ARTICLE

Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia

Shannon L. Maude, M.D., Ph.D., Noelle Frey, M.D., Pamela A. Shaw, Ph.D., Richard Aplenc, M.D., Ph.D., David M. Barrett, M.D., Ph.D., Nancy J. Bunin, M.D., Anne Chew, Ph.D., Vanessa E. Gonzalez, M.B.A., Zhaohui Zheng, M.S., Simon F. Lacey, Ph.D., Yolanda D. Mahnke, Ph.D., Jan J. Melenhorst, Ph.D., Susan R. Rheingold, M.D., Angela Shen, M.D., David T. Teachey, M.D., Bruce L. Levine, Ph.D., Carl H. June, M.D., David L. Porter, M.D., and Stephan A. Grupp, M.D., Ph.D.

- 0.76 x 10^6 to 20.6 x 10^6 CTL019 cells/kg IV
- 27/30 (90%) children and adults with relapsed ALL achieved complete remission
- All patients developed a cytokine release syndrome
- 73% with relapse-free B cell aplasia.

Maude, NEJM 2014

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Active Immunotherapy Vaccination

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A decade on, vaccine has halved cervical cancer rate

29 August 2016 | Australia

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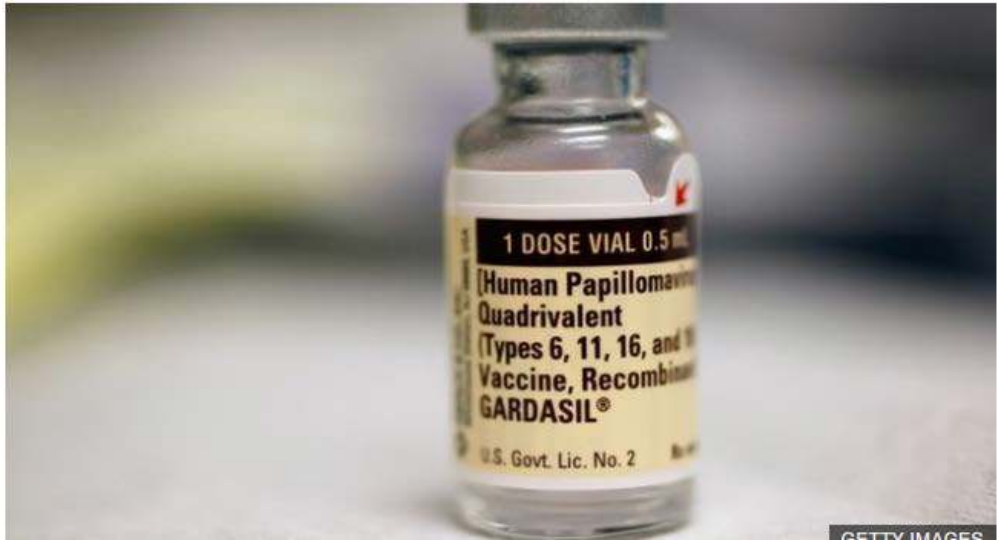

GETTY IMAGES

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Successful Active Vaccination Against Virus-Induced Cancers

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- Vaccine to feline leukemia virus for cats
- Vaccine to herpes virus (Marek's virus) in chickens
- Vaccine to hepatitis B in humans to prevent liver carcinoma
- Vaccination to HPV prevents cervical cancer

How Tumors Escape the Immune System

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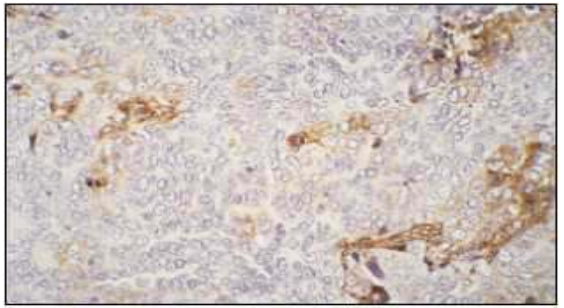
- Loss of MHC or TAP
- Antigenic variation
- Upregulate inhibitory receptor ligands (e.g. PD-1L)
- Secretion of immunosuppressive factors
  - e.g. TGF-b, IL-10
- T cells don't penetrate solid tumors efficiently
- Exhaustion of T cells
- T regulatory cells suppress anti-tumor responses



Additional Information

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Useful resources about cancer immunotherapy

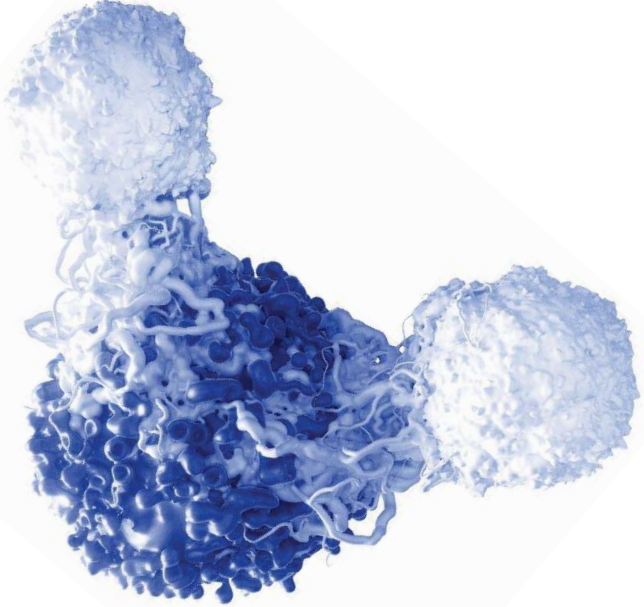
https://www.cancerresearch.org/we-are-cri/what-is-immunotherapy

https://www.mskcc.org/immunotherapy-msk

https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy.html

https://www.mdanderson.org/treatment-options/immunotherapy.html

http://www.fredhutch.org/en/treatment/treatment-research/immunotherapy.html



Panel Discussion

LATEST RESEARCH UPDATE

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Scientific Panel

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Moderator

Lewis Lanier, Ph.D.

Panel

Ezra Cohen, M.D.
Head and Neck Cancers

Aaron Miller, M.D., Ph.D.
Colorectal Cancer

Stanley Riddell, M.D.
Blood Cancer

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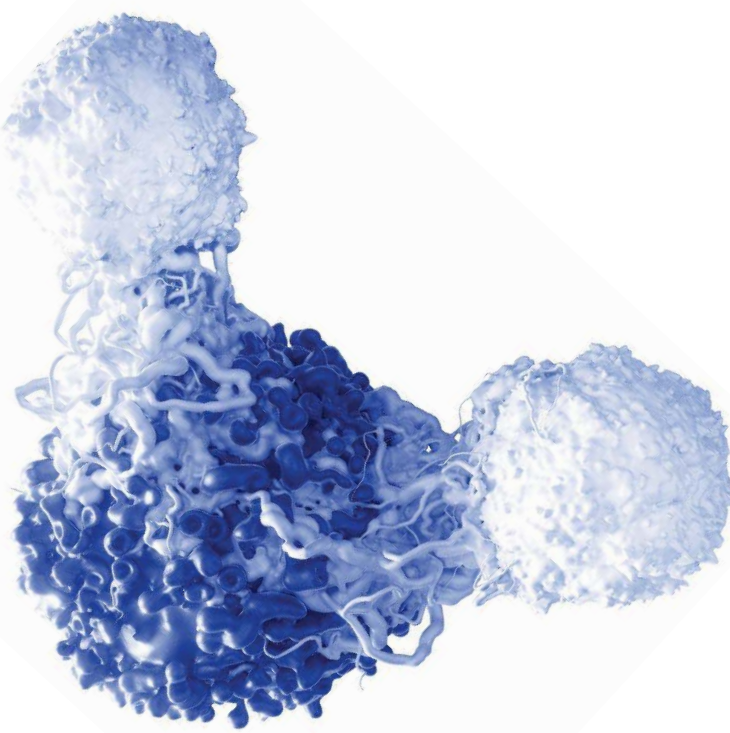

Janie Ferling

Melanoma Survivor

PATIENT PERSPECTIVE

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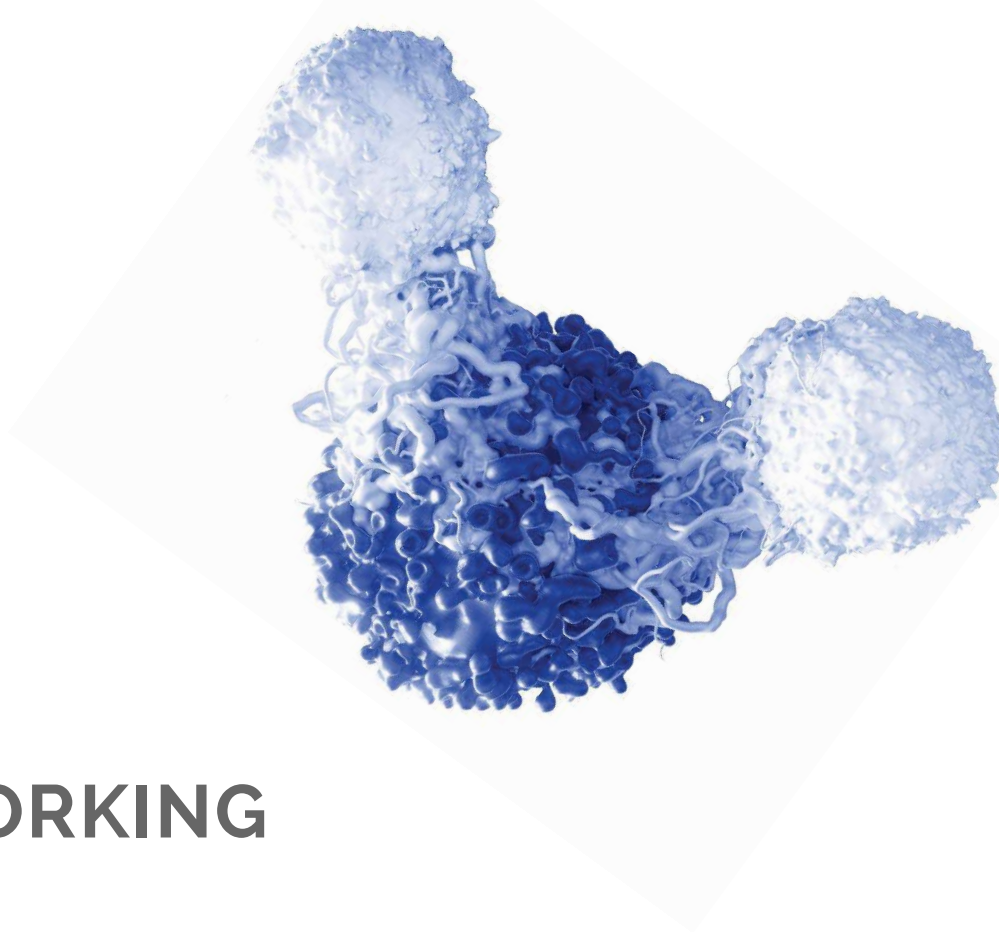

Floor 3 - Gallery

LUNCH AND NETWORKING

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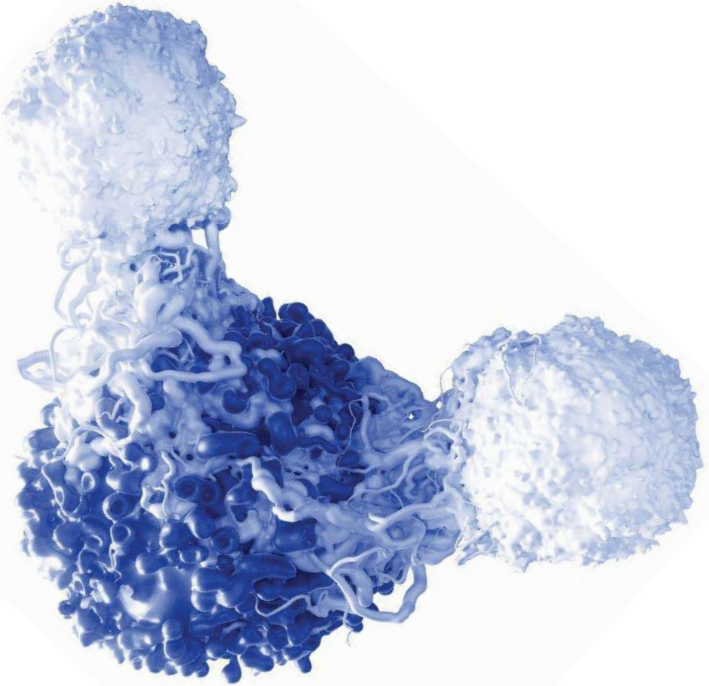

Brian Brewer

Cancer Research Institute

DEMYSTIFYING CLINICAL TRIALS

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What Are Clinical Trials?

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- Clinical trials are research studies that involve people
- Studies are designed to answer questions about new treatments or ways of using existing treatments better
- Researchers design cancer clinical trials to test new ways to:
  - Treat cancer
  - Find and diagnose cancer
  - Prevent cancer
  - Manage symptoms of cancer and side effects from its treatment
- Through clinical trials, doctors find new ways to improve treatments and the quality of life for people with disease

National Cancer Institute. (October 2016).
Taking part in cancer treatment research studies. (NIH Publication No. 16-6249)

Why Are Clinical Trials Important?

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- Many treatments today are the results of past clinical trials
- Clinical trials determine whether new treatments are safe and effective and are better than current treatments
- Participating in a clinical trial adds to our knowledge of cancer and helps improve cancer treatment for future patients
- Clinical trials are key to making progress against cancer

National Cancer Institute. (October 2016).
Taking part in cancer treatment research studies. (NIH Publication No. 16-6249)

What Are Clinical Trial Phases?

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Phase 1	Phase 2	Phase 3
Is the treatment safe?	Does it work?	Does it work better?
Purpose: • To find a safe dose • To decide how the new treatment should be given • To see how the new treatment affects the human body and fights cancer Number of people: 15-30	Purpose: • To determine if the new treatment has an effect on a certain cancer • To see how the new treatment affects the human body and fights cancer Number of people: <100	Purpose: • To compare the new treatment (or new use of a treatment) with the current standard treatment Number of people: 100-2k +

National Cancer Institute. (October 2016). *Taking part in cancer treatment research studies.* (NIH Publication No. 16-6249)

Who Can Participate in a Clinical Trial?

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- Clinical trials follow strict guidelines that determine who will be able to join the study
- The clinical trial protocol explains what the trial will do, how it will be conducted, and the criteria of who can join
- Common criteria for entering a trial include:
  - Having a certain type or stage of cancer
  - Having received (or not having received) a certain type of therapy in the past
  - Having specific genetic changes in your tumor
  - Being in a certain age group
  - Medical history, current health status

National Cancer Institute. (October 2016).
Taking part in cancer treatment research studies. (NIH Publication No. 16-6249)

How Can I Find a Clinical Trial?

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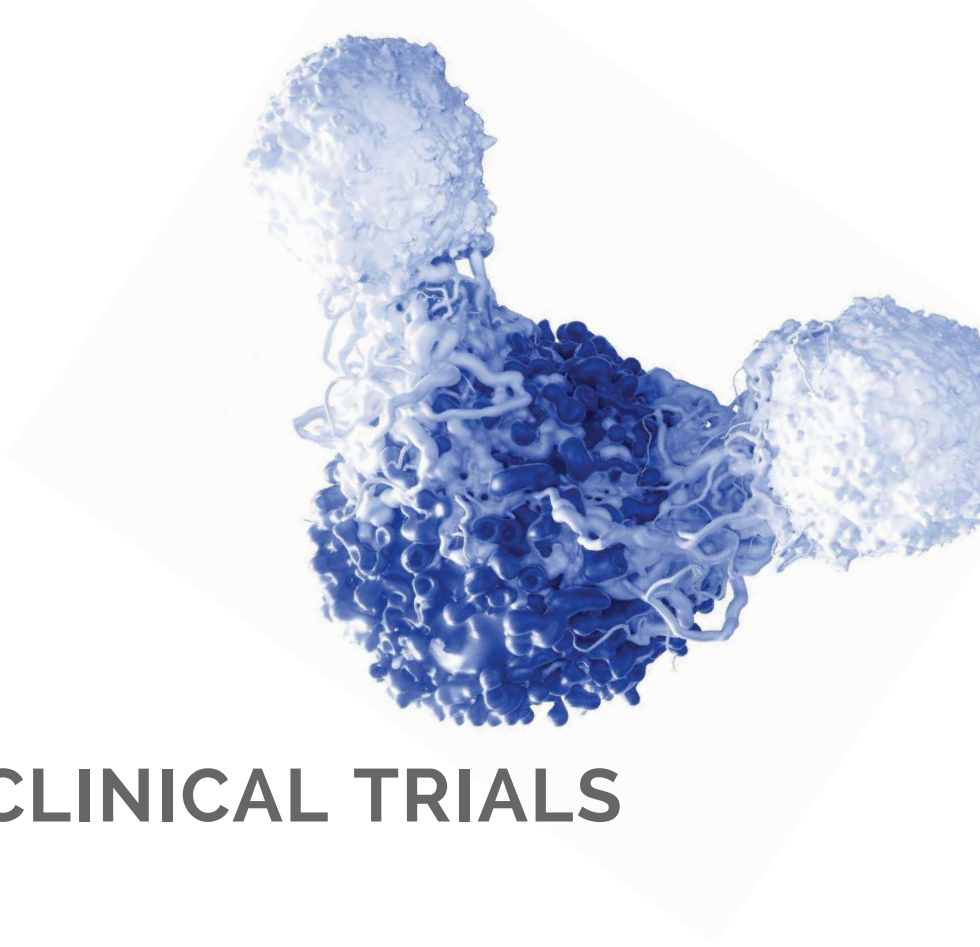
- Ask your doctor
- Ask another doctor if necessary…
- Contact a patient advocacy organization
  - Seek assistance from a clinical trial navigator, if offered
  - CRI Clinical Trial Finder: 1 (855) 216-0127
- Search online
  - https://www.cancerresearch.org/patients/clinical-trials
  - https://clinicaltrials.gov/



Panel Discussion

IMMUNOTHERAPY CLINICAL TRIALS

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PATIENT SUMMIT

Patient and Caregiver Panel

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Moderator

Brian Brewer

Panel

Janie Ferling
Melanoma

Johanna Packard
Caregiver (Prostate Cancer)

Philip Prichard
Kidney Cancer

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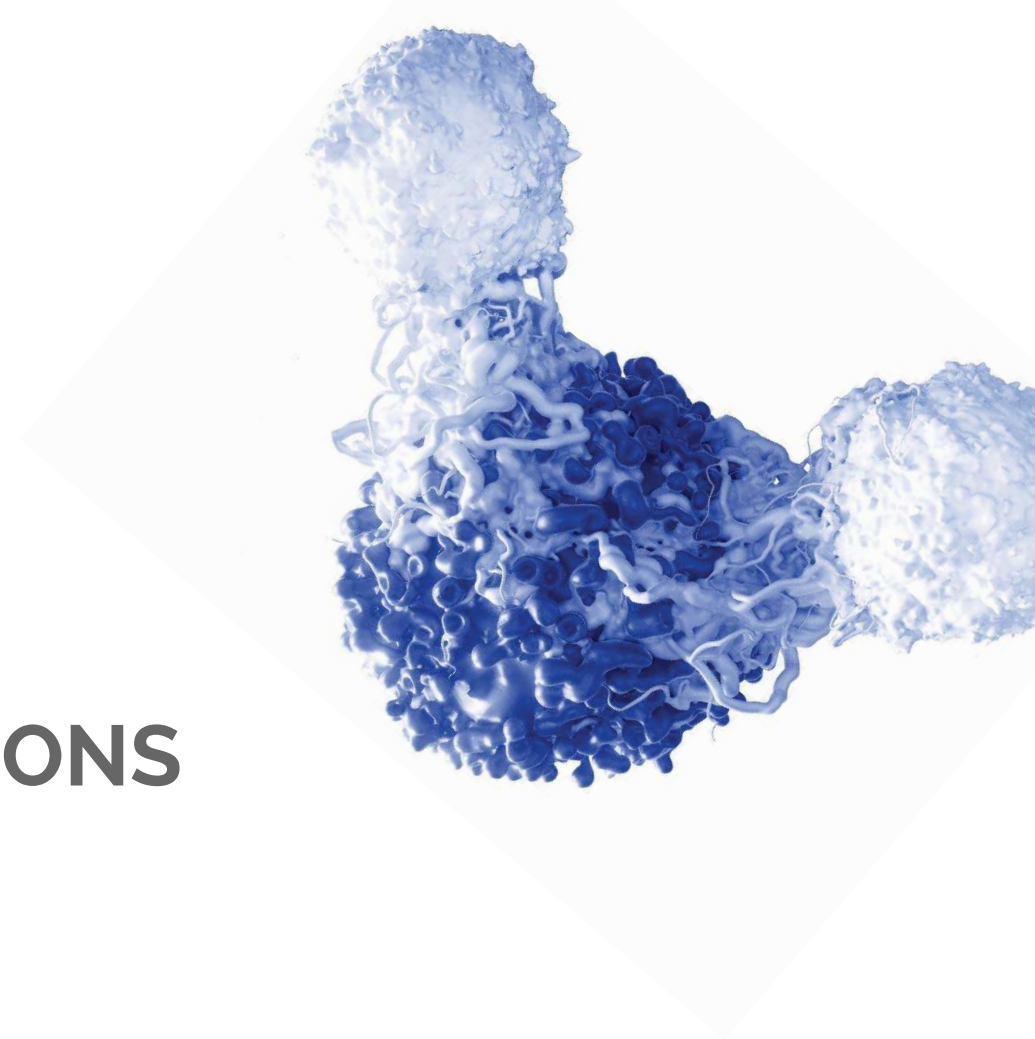

BREAKOUT SESSIONS

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Breakout Rooms

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Blood Cancers Stanley Riddell, M.D.	**Skyline A, Floor 21**
Colorectal Cancer Aaron Miller, M.D., Ph.D.	**Skyline B, Floor 21**
Head and Neck Cancer Ezra Cohen, M.D.	**Skyline C, Floor 21**
General Networking Jill O'Donnell-Tormey, Ph.D.	**Ballroom (here)**

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A special thank you to those who helped promote the summit

- Addario Lung Cancer Foundation
- Bay Area Cancer Connections
- Coalition for Clinical Trial Awareness
- Colon Cancer Alliance
- Cancer Support Community
- Fight Colorectal Cancer
- Focused Ultrasound Foundation
- FORCE
- GI Cancers Alliance
- Head and Neck Cancer Alliance
- Imerman Angels
- Immunotherapy Foundation
- Let Life Happen
- Parker Institute for Cancer Immunotherapy
- Patient Empowerment Network
- UCSF Helen Diller Family Comprehensive Cancer Center

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