

# Faux History of Cancer Immunotherapy

## Conceptual Advances



M

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rgery

Professor of Sur

Bioengineering

Senior Advisor, Immu

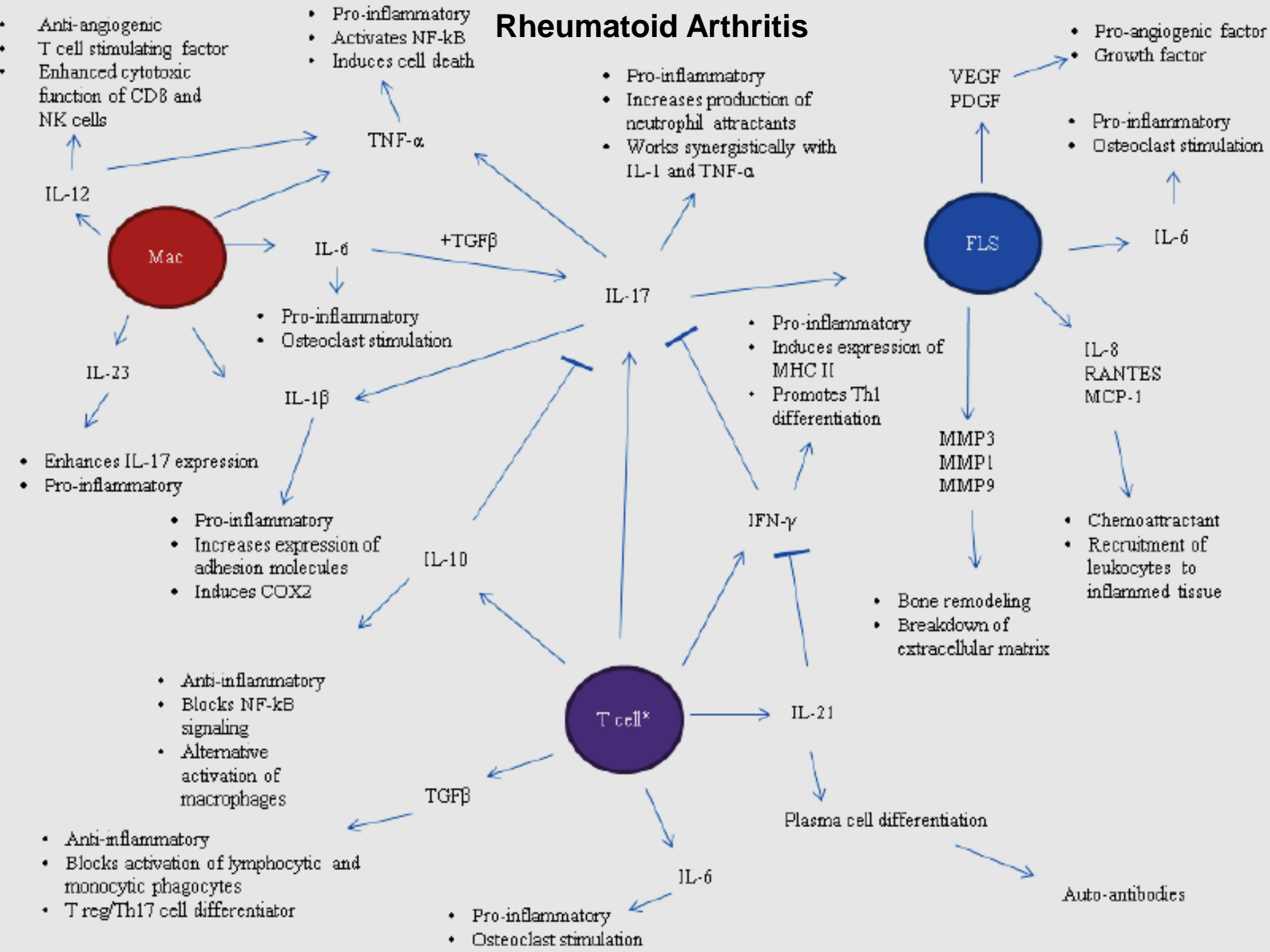
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UPM

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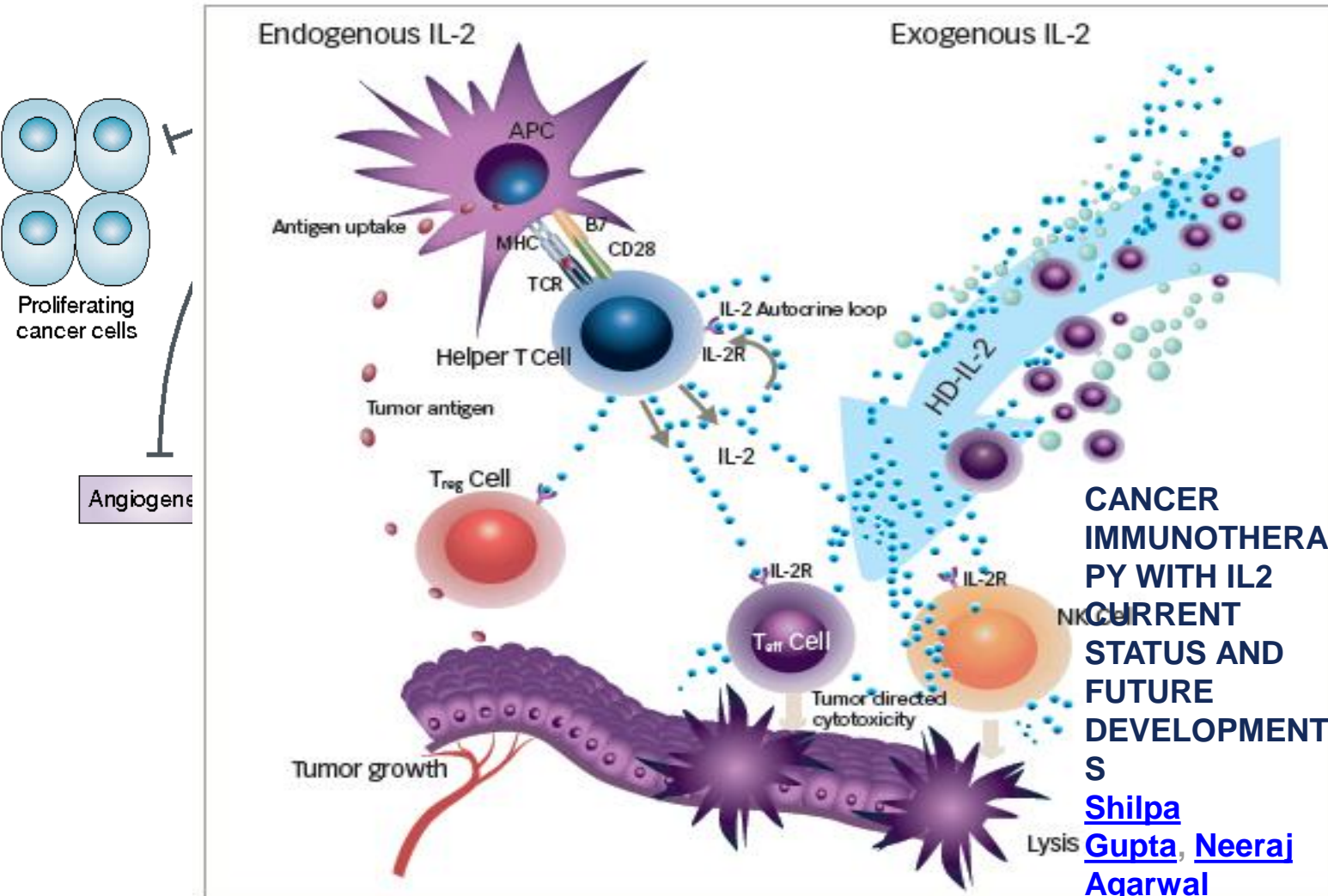
- "Do or do not. There is no try." ...
- "You must unlearn what you have learned." ...
- "Named must be your fear before banish it you can." ...
- "Fear is the path to the dark side. ...
- "That is why you fail." ...
- "The greatest teacher, failure is." ...
- "Pass on what you have learned."

# Rheumatoid Arthritis



# Cancer Immunotherapy

Figure 1: Dual mechanism of action of interleukin-2



APC = antigen-presenting cell; HD-IL-2 = high-dose interleukin; NK = natural killer cell; MHC = major histocompatibility complex. TCR = T cell receptor. Source: Prometheus Review

Nature  
Reviews  
Cancer 20  
04DOI:[10.1038/nrc1252](https://doi.org/10.1038/nrc1252)

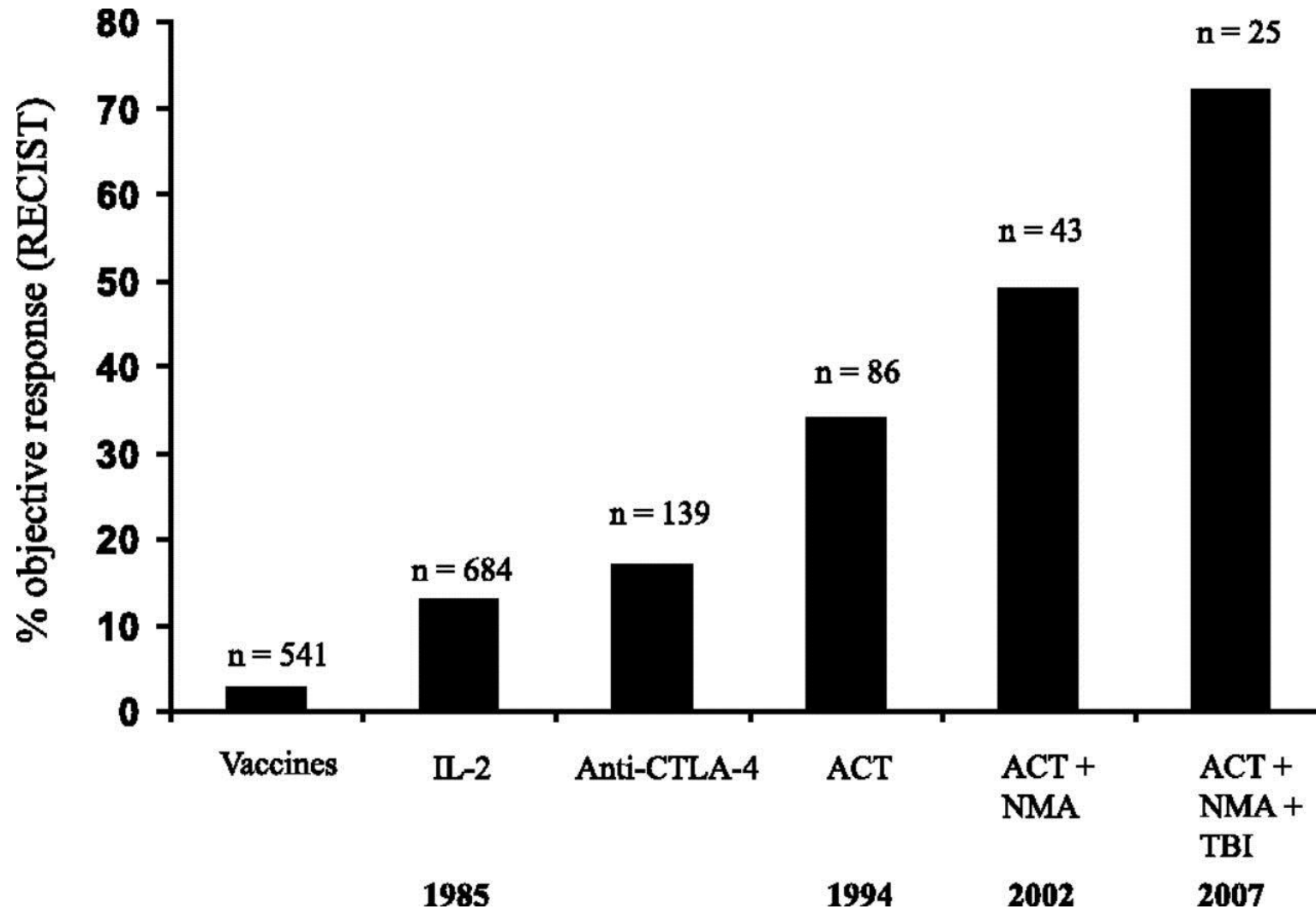
**Cytokines  
in cancer  
pathogen  
esis and  
cancer  
therapy**

• [Glenn  
Dranoff](#)

**CANCER  
IMMUNOTHERA  
PY WITH IL2  
CURRENT  
STATUS AND  
FUTURE  
DEVELOPMENT  
S**

[Shilpa  
Gupta, Neeraj  
Agarwal](#)  
Oncology &  
Hematology  
Review

## Evolution of Immune Treatments for Patients with Melanoma



## IL-2: The First Effective ImmunoRx for Human Cancer

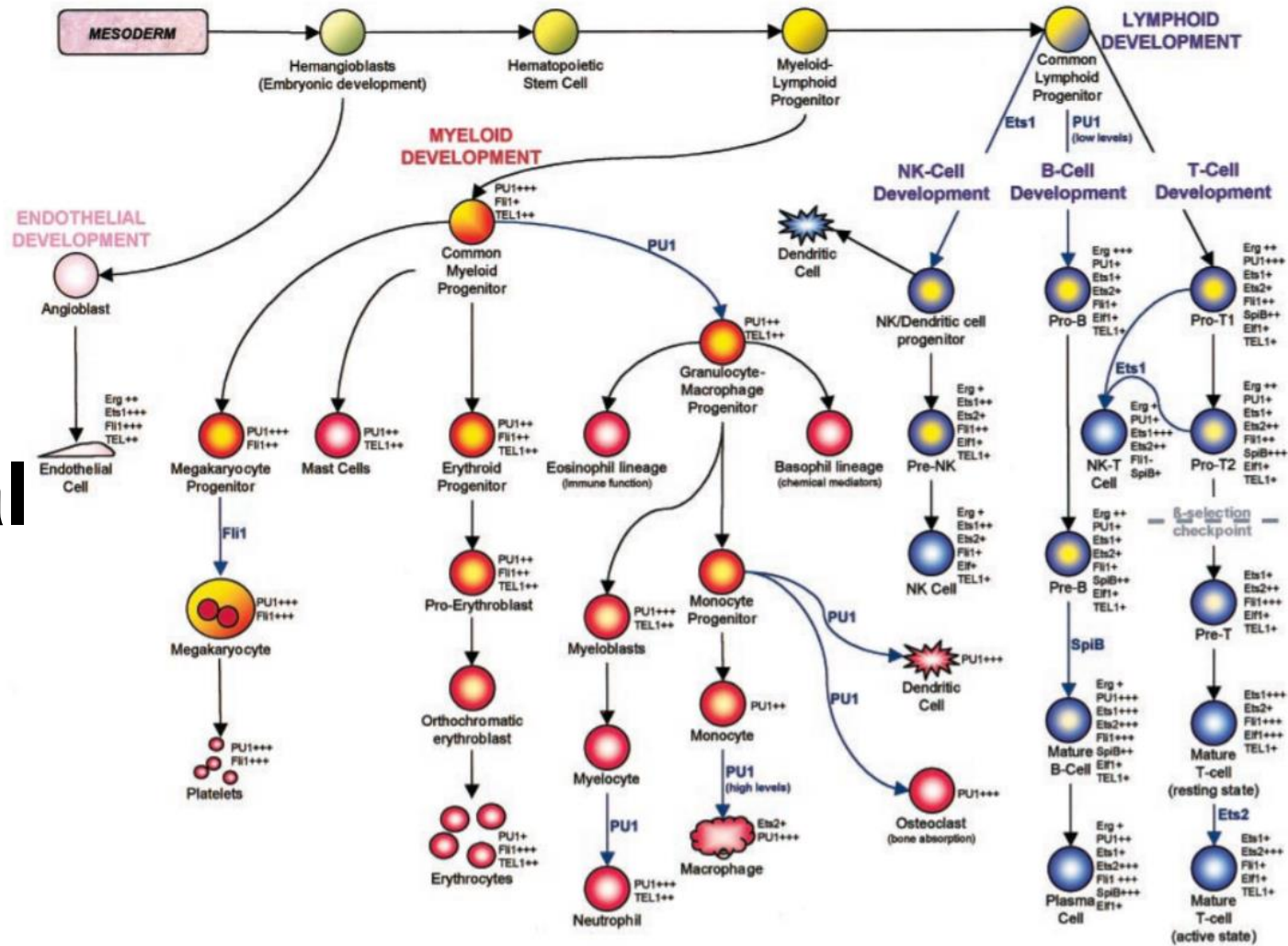
Steven A. Rosenberg  
J Immunol  
June 15,  
2014, 192:  
5451-5458

DOI:

<https://doi.org/10.4049/jimmunol.1490019>

# The Immune System is the Best Doctor

Human  
Army:

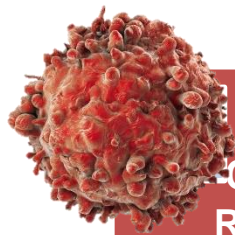


Maroulakou & Bowe © 2000,  
*Oncogene*

Endothelial  
Platelet,  
Myeloid,  
Lymphoid  
Cell Dev't

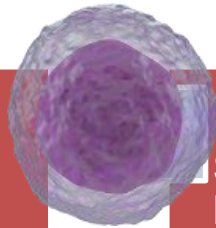


# Foundations of Cancer Therapy



Surgery  
ChemoRx  
Radiation

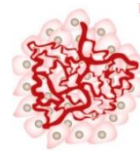
- **Other Targets:**
- Signal Transduction
- Autophagy
- Oncogenes
- Tumor Suppressor Genes



T Cells

Immune Stimulants  
IL2-1<sup>st</sup> ICI

- Checkpoint Inhibition-CTLA4, PD1, PDL1
- Adoptive Cell Therapy (CARTs, TIL, TCRs)
- DC, Other Vaccines



Anti-VEGF

- Chloroquine
- Platelet Derived Growth Factor (PDGF)
- Fibroblast Growth Factor (FGF)
- Tie 2 Kinase stabilization
- $\beta$ -phosphatase inhibitors

Disturbance of function (*functio laesa*): the legendary 5<sup>th</sup> cardinal sign of inflammation, added by Galen to the four cardinal signs of Celsus=Autophagy.

---

Rather LJ. Bull N Y Acad Med. 1971.

*Calor* (warmth), *dolor* (pain), *tumor* (swelling) and *rubor* (redness), and (later) loss of function Celsus,

*De Medicina*

Cancer is the endstage of chronic inflammation in adults



*De Medicina* is a 1st-century medical treatise by Aulus Cornelius Celsus, a Roman encyclopedist and possibly practicing physician.

# Evolution of Cancer Treatments: Surgery (ACS)



Ancient physicians and surgeons knew that cancer would usually come back after it was surgically removed. The Roman physician Celsus wrote, "After excision, even when a scar has formed, none the less the disease has returned."

**Successful Surgical Excision is Immunotherapy**  
**Successful Radiation Therapy is Immunotherapy**  
**Successful Hormonal Therapy is Immunotherapy**  
**Successful Chemotherapy is Immunotherapy**



A Decade in the Life of Tumor Immunology 1990-2000

**Olivera J. Finn<sup>1</sup> and Michael T. Lotze**  
University of Pittsburgh Cancer Institute, University of Pittsburgh  
School of Medicine, Pittsburgh, Pennsylvania 15261 [O. J. F.],  
GlaxoSmithKline Pharmaceuticals, King of Prussia,  
Pennsylvania 19406

The role of the immune system in the recognition and prevention or therapy of cancer remains a fascinating and important topic of research. The first in the series of Keystone Symposia on Cellular Immunity and Immunotherapy of Cancer was held in 1990 in Park City, Utah (1). Progress in tumor immunology and new developments in immunology that could impact on this field have been featured and appraised in these meetings at 3- or 4-year intervals (2, 3). The fourth meeting in this series was held in January 2000 in Santa Fe, NM. This special issue of Clinical Cancer Research is devoted to the major topics discussed at the meeting. It features original articles by the meeting participants and reviews of recent progress in cancer immunology.

cytokine-activated T cells that were not antigen specific but could kill tumor cells, the identification of tumor antigens focused the field on specificity. Years of experiments with tumors in mice taught two important lessons: antitumor immune responses can be tumor specific, and tumor growth can be prevented by immunization. Identification of tumor antigens in human tumors foreshadowed the future of tumor-specific immunization in people. This goal was very appealing and every newly identified tumor peptide brought that goal closer to reality. Already by the time of the second Symposium, Phase I clinical trials in peptide-based cancer vaccines occupied a large portion of the meeting agenda. Progress in identification of new tumor antigens and their use in cancer immunotherapy continues to generate excitement in the field, and papers by Kao *et al.*, Geiger, *et al.*, Beatty *et al.*, Santin *et al.*, Rudolf *et al.*, Gajewski *et al.*, Meaker *et al.*, Zier *et al.*, Pittet *et al.*, and Romero *et al.* featured in this

models where



**Cancer vaccine tested**

PITTSBURGH (AP) — Doctors are testing a vaccine that could trigger immunity to three forms of cancer and eventually prevent the disease.

A 50-year-old man with colon cancer was injected with the vaccine yesterday at the Pittsburgh Cancer Institute. He was the second of 30 patients to undergo treatment for cases of colon, breast or pancreatic cancer now considered incurable.

"We want to know if we can induce immunity," said Dr. Olivera J. Finn, director of the center's immunology program. "If this is eventually successful, clearly I see it as the first therapy that a patient would receive following surgery or following diagnosis."

The patients will continue to receive shots for six weeks and doctors will be able to evaluate the success of the treatment after a year, Finn said.

The vaccine is developed from an abnormal form of a complex of protein and sugars called mucin, a molecule found on the surface of cells in the breast, colon and pancreas. Other cancer vaccines are made from whole proteins and from tumor cells.

"We're shining a light, a beacon, on this abnormal mucin," said Dr. Michael T. Lotze. "We're identifying a target for the vaccine."

If the vaccine produces immunity, it could be administered to patients after surgery to help prevent a recurrence of cancer, he said.

"That's the ideal time to consider a vaccine," said Dr. Philip Livingston of Memorial Sloan-Kettering Cancer Center in New York. "If that proves to be effective in that setting, then you can of course consider using it in patients with high-risk factors."

Lotze said Pittsburgh researchers hope someday to inject people at risk for developing cancer as a preventative.

The vaccine can cause slight side effects such as fever, chills and swelling, Lotze said.

The Pittsburgh Cancer Institute received U.S. Food and Drug Administration approval for vaccine testing on Dec. 18.

Finn said.



While in her lab at the University of Pittsburgh Medical Center yesterday, Olivera J. Finn tells how the cancer vaccine she helped develop works.

DECEMBER 29, 1993

True History 1990-2020  
Three Decades in the  
Life of Immunotherapy:  
Looking Back and  
Looking Forward to  
Immunotherapy of  
Cancer Coming of Age

Michael T. Lotze, MD  
Professor of Surgery, Immunology, and Bioengineering  
Vice Chair Research, Dept. of Surgery  
Director, Center for Damage Associated Molecular Pattern Molecule Laboratories  
UPMC Hillman Cancer Center  
Senior Advisor UPMCE-ITTC  
Email: [lotzemt@upmc.edu](mailto:lotzemt@upmc.edu)  
Phone: 412-623-6790  
Cell: 412-478-3316





THE UNIVERSITY OF TEXAS

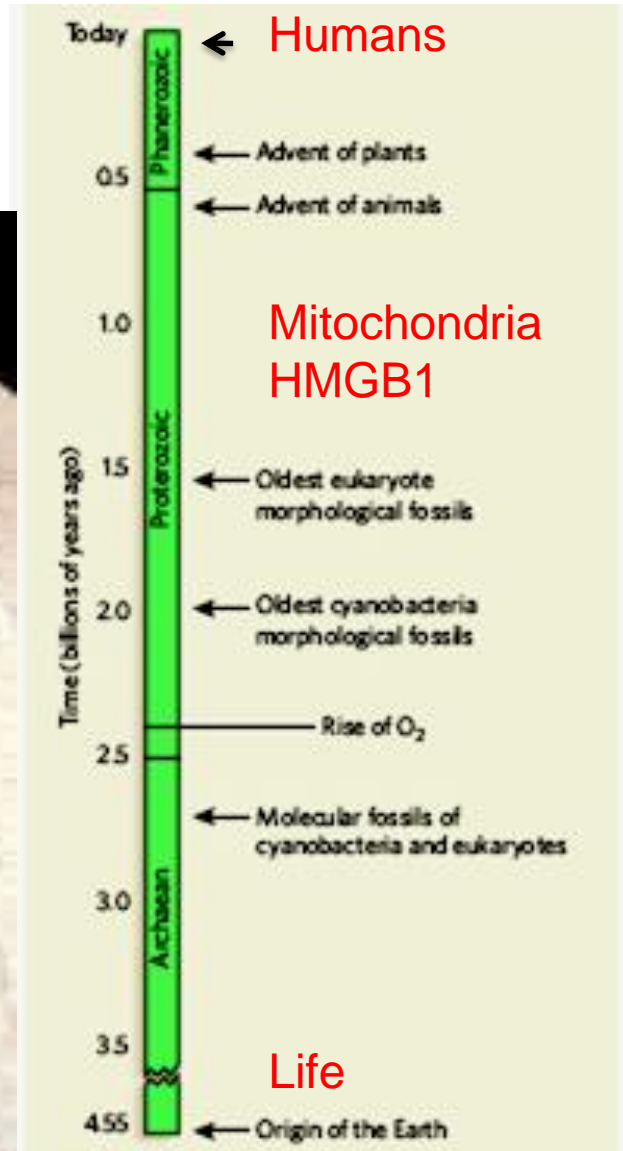
MD Anderson  
~~Cancer~~ Center



# History of Life

- $13.75 \pm 0.11$  b Universe

• 4.5 b Planet Earth



# SIGNAL 0 – PAMPS AND DAMPS

## PATHOGEN AND DAMAGE ASSOCIATED MOLECULAR PATTERN MOLECULES

**Innate immunity** in single cell organisms (4byrs) evolved:

0) TLRs, NLRs, ALRs, RLRs, STING/cGAS (**STRANGER-Janeway**)

1) engulf organisms by

'adaptive' immunity  
SPR/Cas9;

olites (yeast:

: salicylic acid

acid) that limit

pathogens;

4) SIRP $\alpha$ /CD47

5) PIR's

NK cells and MHC-like molecules

(Maternal/Fetal

interface): *Botryllus*

*schlosseri*

investigates

(Ur

2000 100.022 1.

**DANGER-**

**Matzinger**

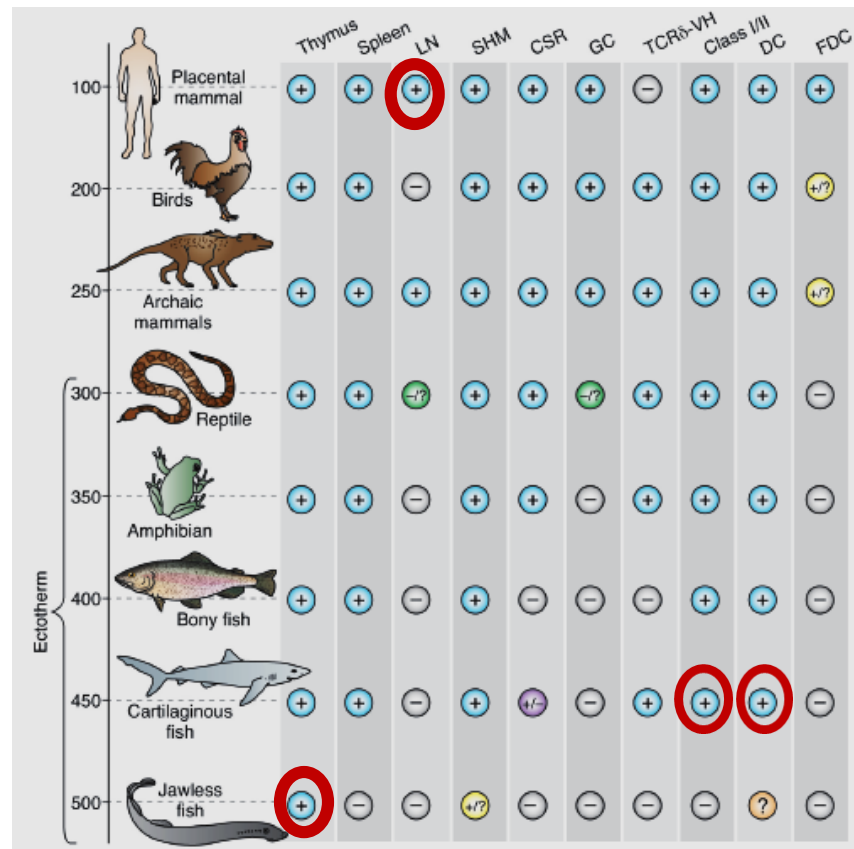
**(HMGB1, ATP, DNA, ...)**



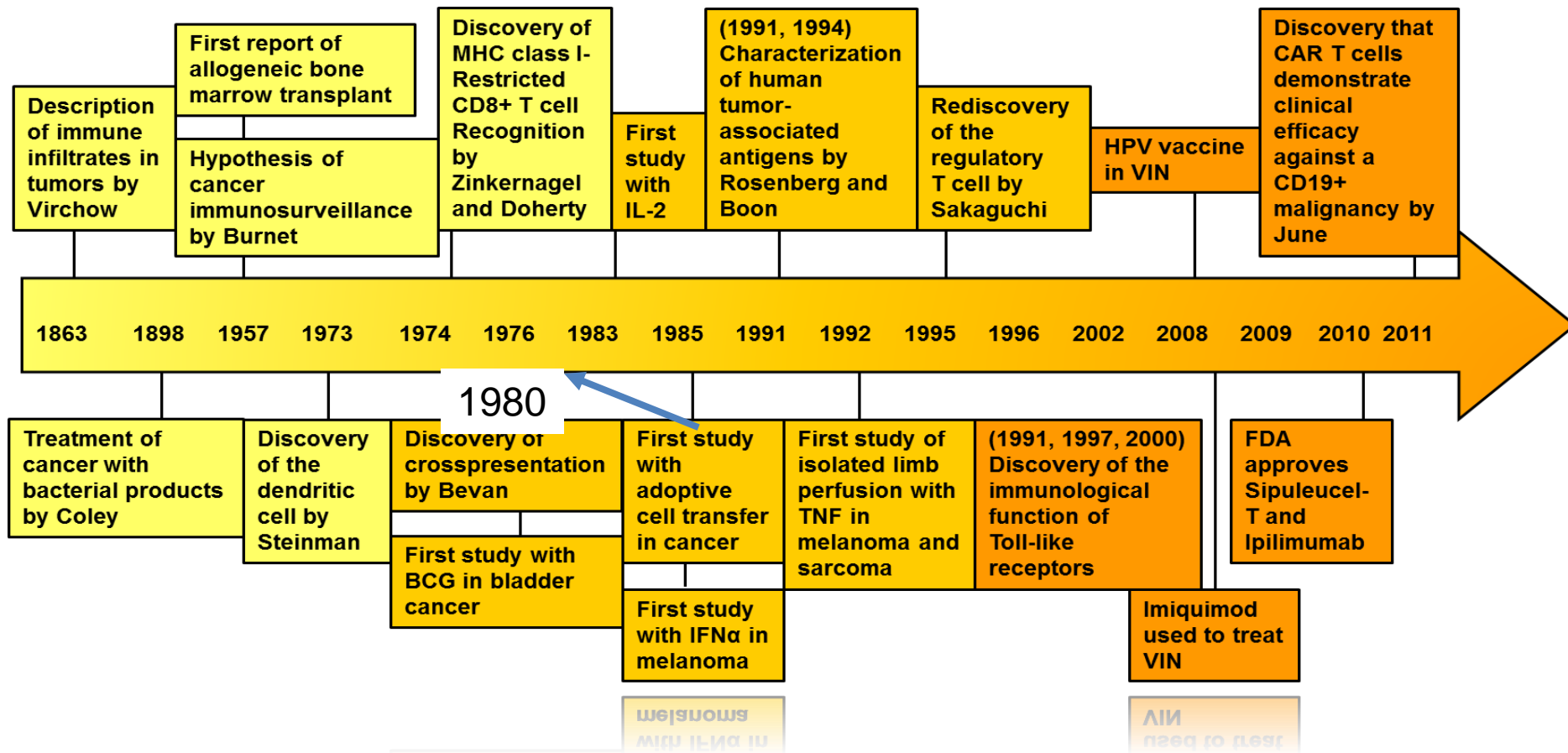
# A cold-blooded view of adaptive immunity

## Nature Review Immunology (2018)

*Martin F. Flajnik* Department of Microbiology and Immunology  
University of Maryland Baltimore



# History of Immunotherapy



Abramson Cancer Center



Penn Medicine

Adapted from: Lesterhuis et al., *Nature Reviews*, 2011

Fraietta, Joseph A <jfrai@upenn.edu>



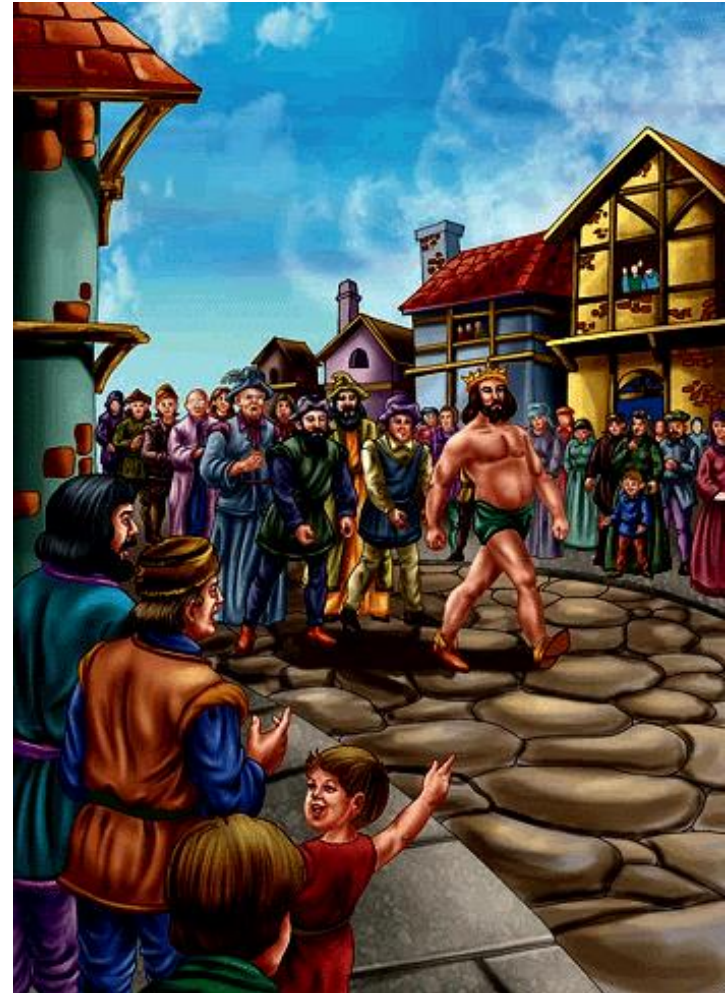
THE  
EMPEROR  
OF ALL  
MALADIES



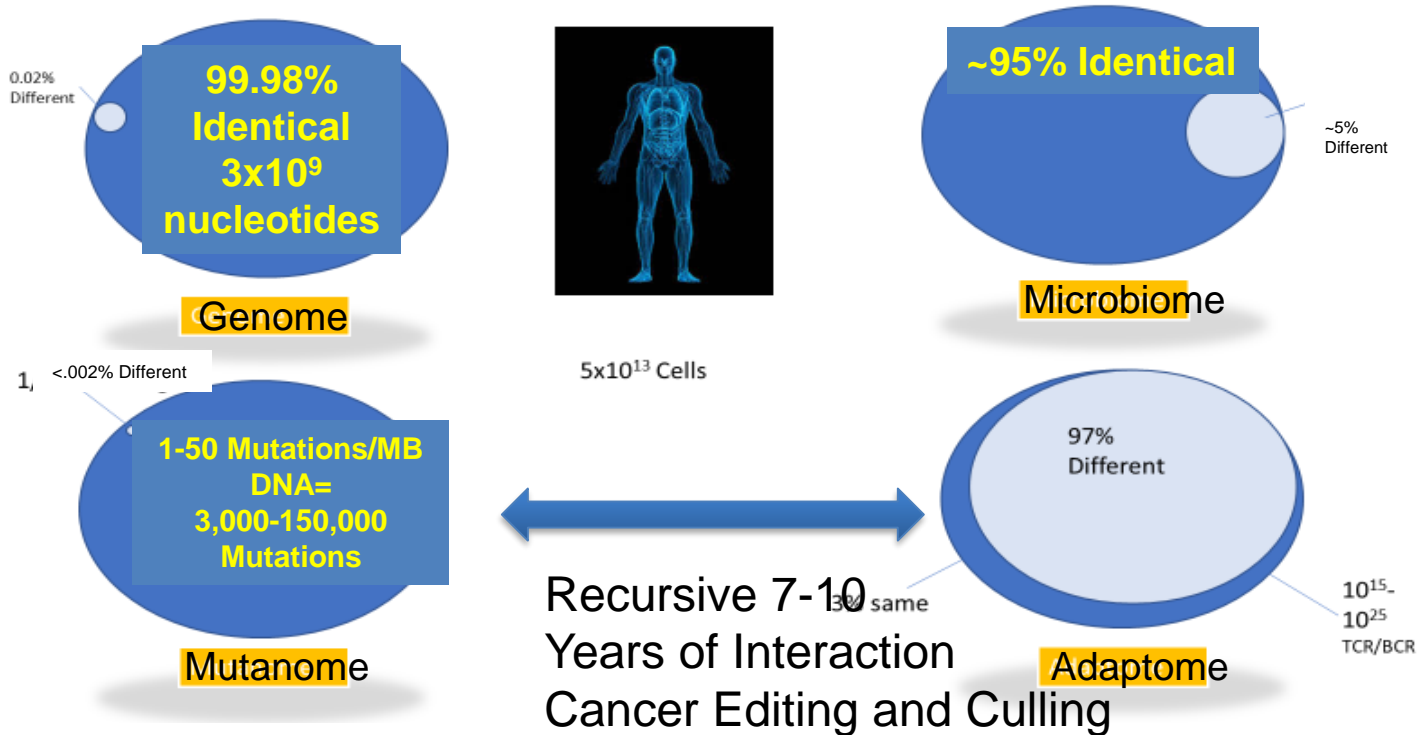
A BIOGRAPHY OF CANCER

SIDDHARTHA  
MUKHERJEE

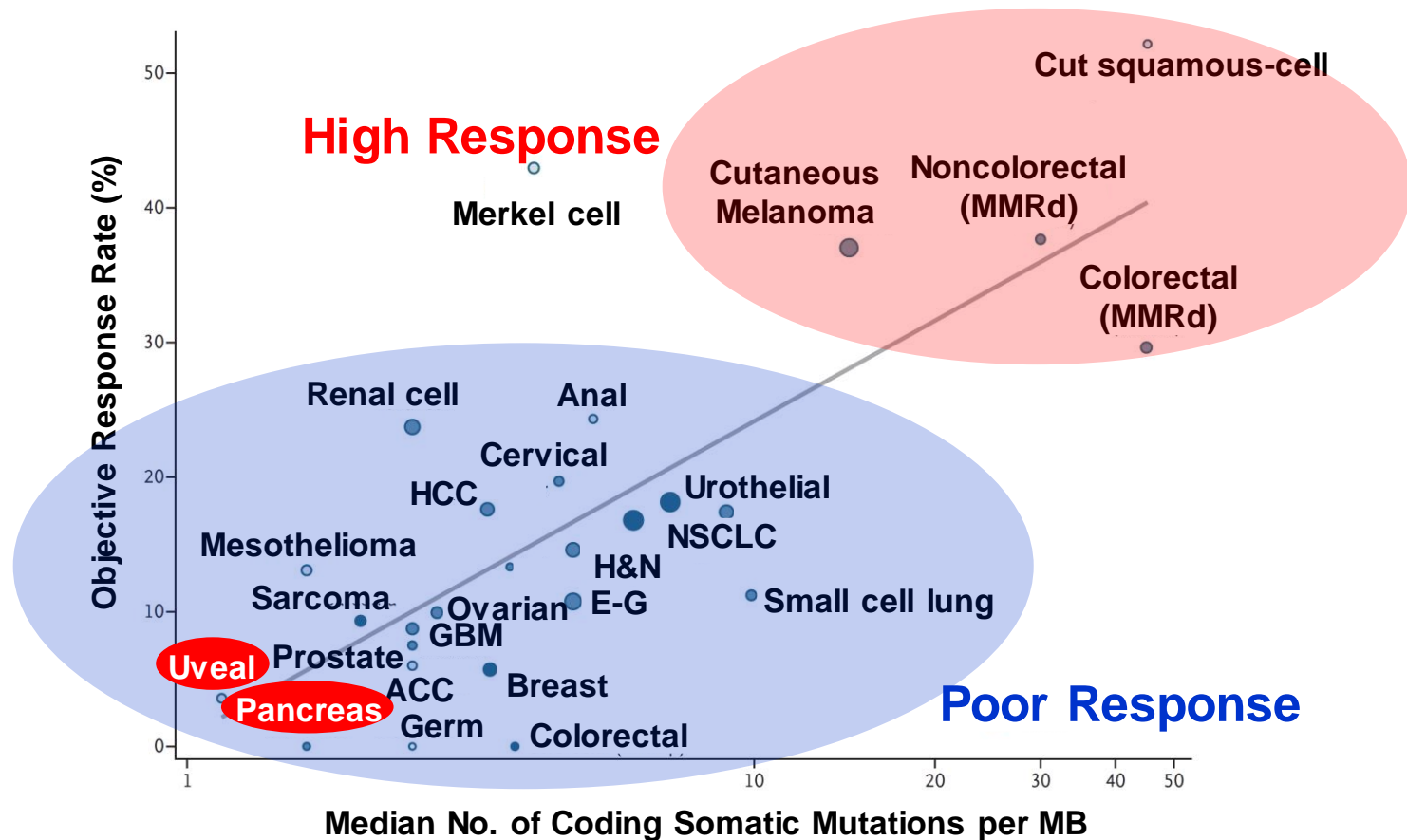
# Emperors



# How does Genomic Instability Interface with Host Response?



# The Critical Need for More Effective Immunotherapies for Solid Tumors



Adapted from NEJM Dec 21 2017



# The lymphocyte as a factor in natural and induced resistance to transplanted cancer.

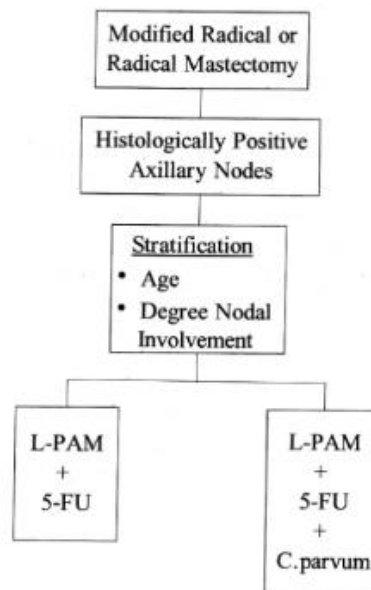
Proc Natl Acad Sci U S A 1:435–437; 1915

Hence, it would seem fair to conclude that the lymphocyte is a necessary factor in cancer immunity – James B. Murphy and John J. Morton (Murphy and Morton 1915)



**Abstract**

The aim of this study was to test the hypothesis that surgery with L-PAM + 5-FU + C. parvum + hydrocortisone (PF + CP) is more effective than surgery with L-PAM + 5-FU (PF) alone in prolonging disease-free survival and survival.



Ber  
Dies

Accrual began on May 1, 1977, and terminated on May 31, 1981. During that time, 265 patients were entered, 11 of whom were declared ineligible. Toxicity was discussed in the August 1995 NSABP Progress Report. An analysis of disease-free survival and survival as of December 31, 1994, was presented in the same report. At that time the average time on study was 193 months, and results were summarized through 12 years of follow-up. The results failed to indicate any benefit from the addition of C. parvum to PF. In fact, the use of the immunomodulator resulted in a poorer, though not statistically significant, outcome.

**Publication:**

Fisher B, Brown A, Wolmark N, et al. Evaluation of the Worth of Corynebacterium parvum in Conjunction With Chemotherapy as Adjuvant Treatment for Primary Breast Cancer. *Cancer* 66:220-227, 1990.



# NIELS K. JERNE, M.D.

Professor and Chairman, Department of Microbiology, 1962-1966

*Winner of the  
1984 Nobel Prize in Physiology or Medicine  
for his contributions to the understanding of the immune*

"Foreign"  
stimulus

**Eigen-behaviour of the immune system following Niels Jerne**

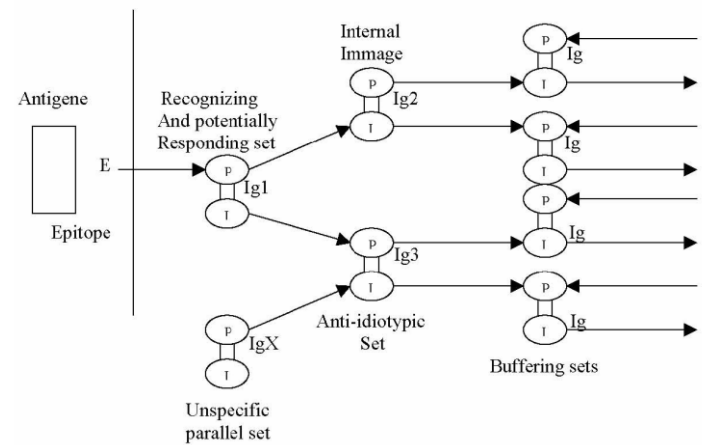
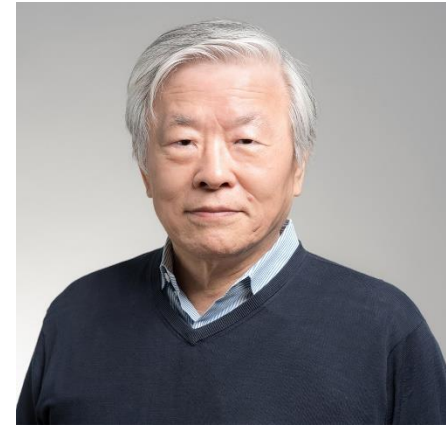


Fig. 1. A model of Niels Jerne's immunological networks modified from (1). For each Ig molecule (p) and an idiotypic (I)



# Rearranged Receptors in B and T Cells

Susumu Tonegawa Professor, Nobel Laureate  
(1987 Nobel Prize In Physiology or Medicine)  
Massachusetts Institute of Technology  
Massachusetts, US



Davis MM, Chien YH, Gascoigne NR, Hedrick SM. A murine T cell receptor gene complex: isolation, structure and rearrangement. *Immunol Rev* 1984;81:235-58.

Kavaler J, Davis MM, Chien Y. Localization of a T-cell receptor diversity-region element. *Nature* 1984;310:421-3.

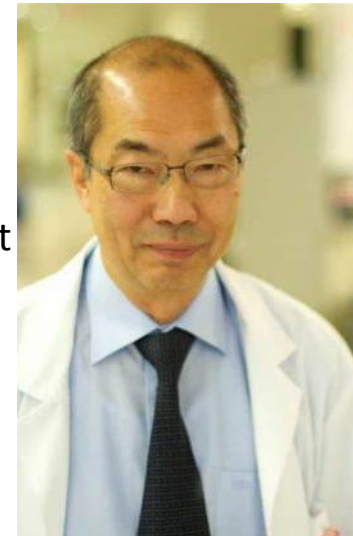
Robertson M. Receptor gene rearrangement and ontogeny of T lymphocytes. *Nature* 1984;311:305-6.

Royer HD, Acuto O, Fabbi M, et al. Genes encoding the Ti beta subunit of the antigen/MHC receptor undergo rearrangement during intrathymic ontogeny prior to surface T3-Ti expression. *Cell* 1984;39:261-6.

Siu G, Kronenberg M, Strauss E, Haars R, Mak TW, Hood L. The structure, rearrangement and expression of D beta gene segments of the murine T-cell antigen receptor. *Nature* 1984;311:344-50.

Hayday AC, Saito H, Gillies SD, et al. Structure, organization, and somatic rearrangement of T cell gamma genes. *Cell* 1985;40:259-69.

Lefranc MP, Rabbitts TH. Two tandemly organized human genes encoding the T-cell gamma constant-region sequences show multiple rearrangement in different T-cell types. *Nature* 1985;316:464-6.



# The Immunologic Big Bang

Pillars of Immunology

The Journal  
of Immunology

## **A Convergent Immunological Holy Trinity of Adaptive Immunity in Lampreys: Discovery of the Variable Lymphocyte Receptors**

Martin F. Flajnik

doi: 10.4049/jimmunol.1800965  
*J Immunol* 2018; 201:1331-1335



# Zeev Pancer and Max Cooper With a Larval Lamprey at UAB.

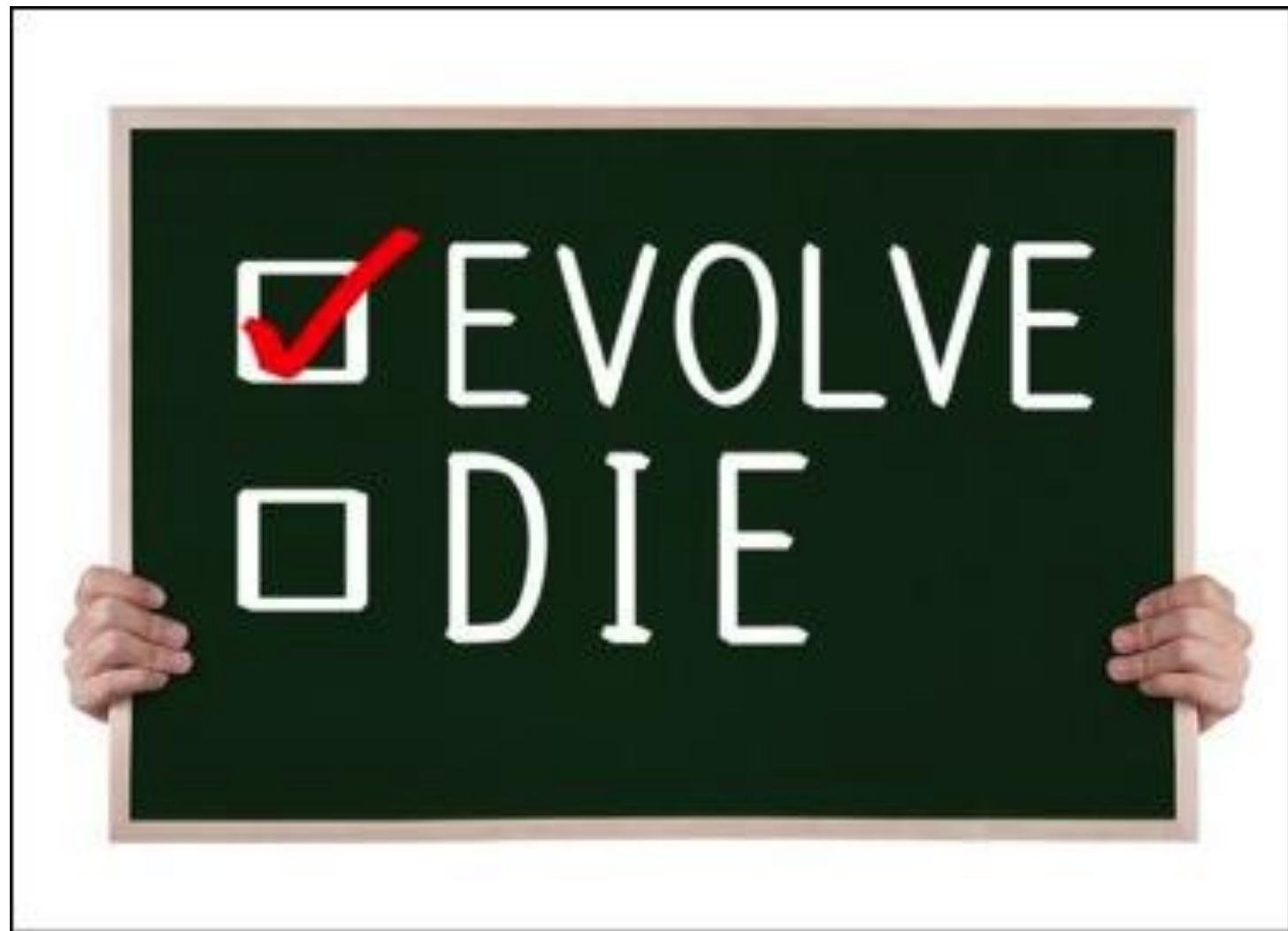




>500 Million Years of Adaptive Immunity-Wu Xing  
The Immunologic Big Bang

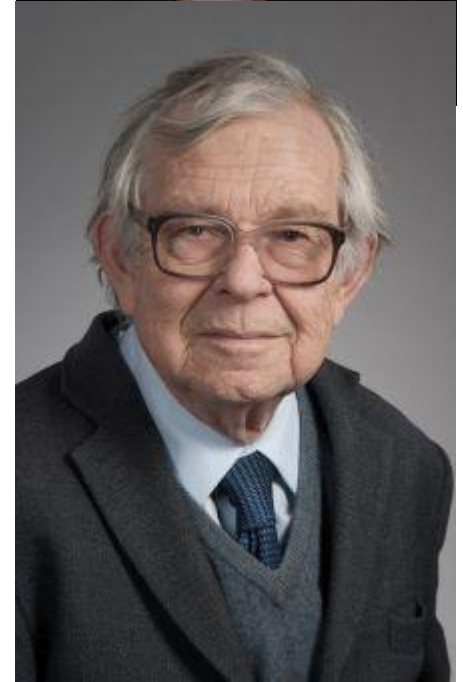


"Wǔ zhǒng liúxíng zhī qì" (五種流行之氣) or "the five types of chi dominating at different times".



# The Hellström Paradox

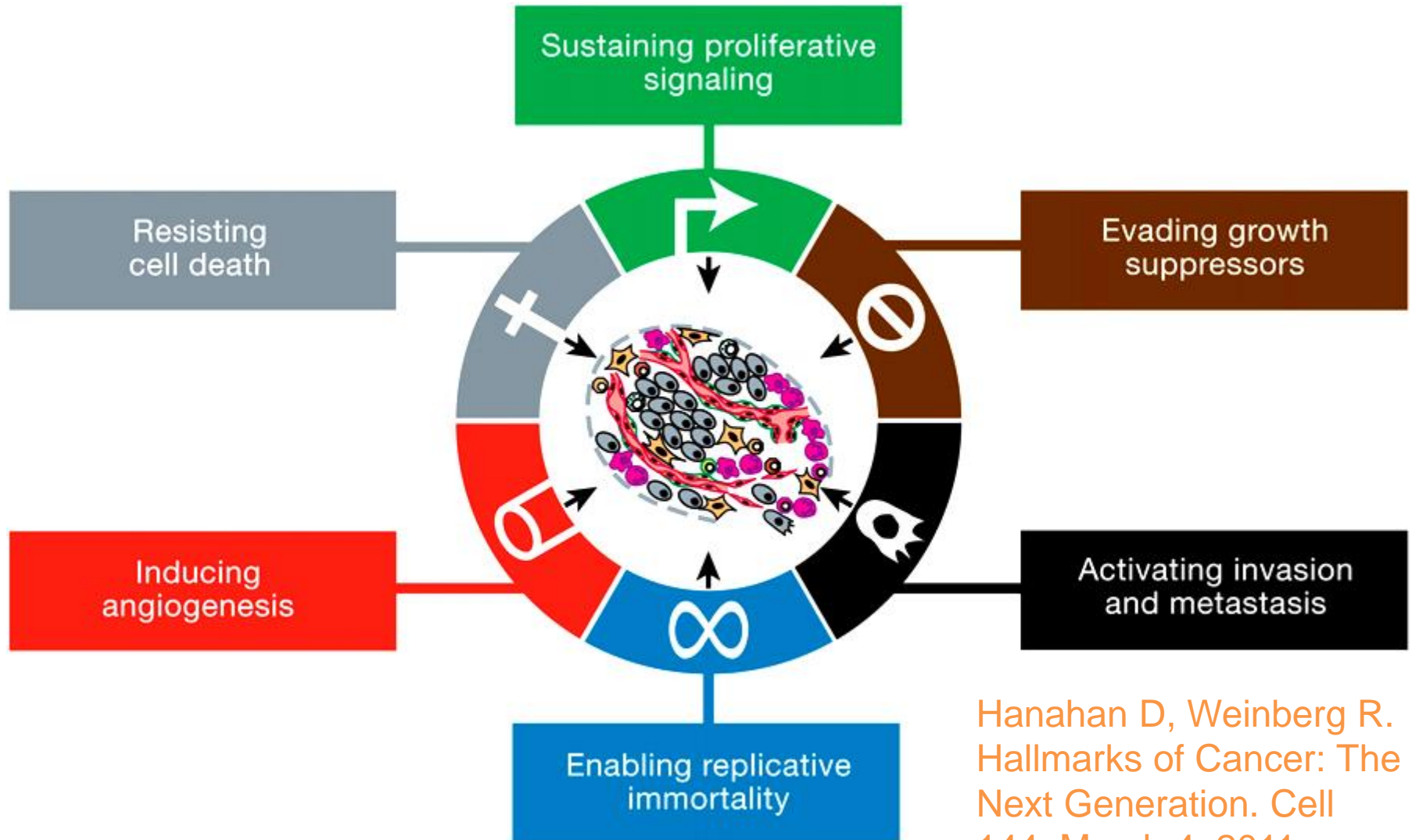
- A paradox lies at the heart of cancer.
- Coursing through many tumors are legions of immune cells, including the T cells that should be fighting the cancer.
- Yet these T cells are typically dysfunctional — they stop working and let the tumor grow with abandon.
- Ingegerd and Karl Hellström, the immunologists first drew attention to it more than 50



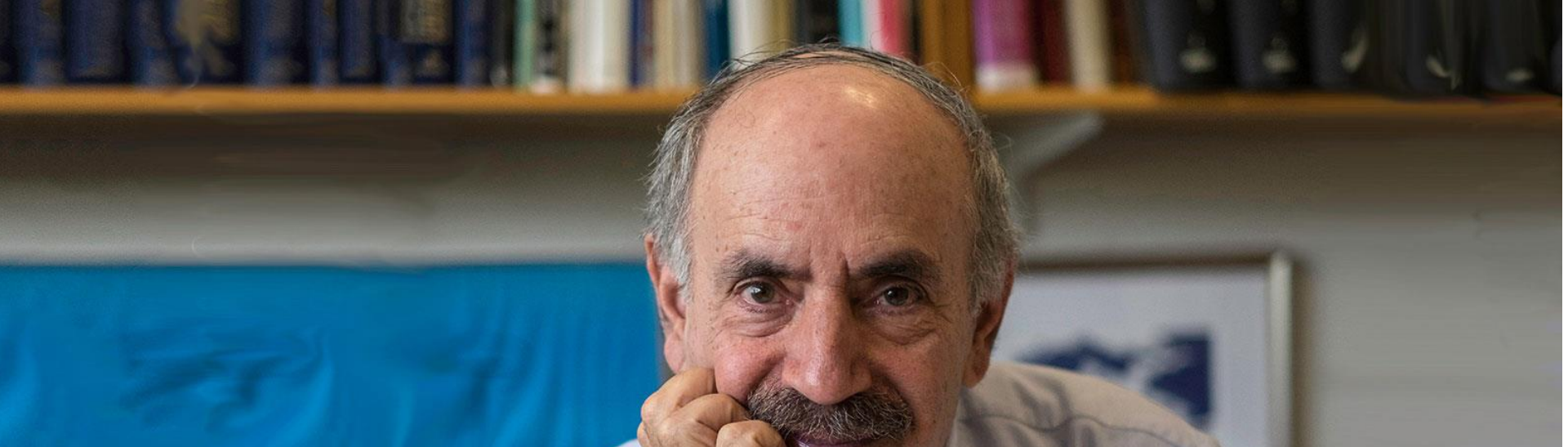


# Original Hallmarks of Cancer

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Hanahan D, Weinberg R.  
Hallmarks of Cancer: The  
Next Generation. Cell  
144, March 4, 2011



Inducing  
angiogenesis

Activating  
invasion &  
metastasis

Selective anti-  
inflammatory drugs

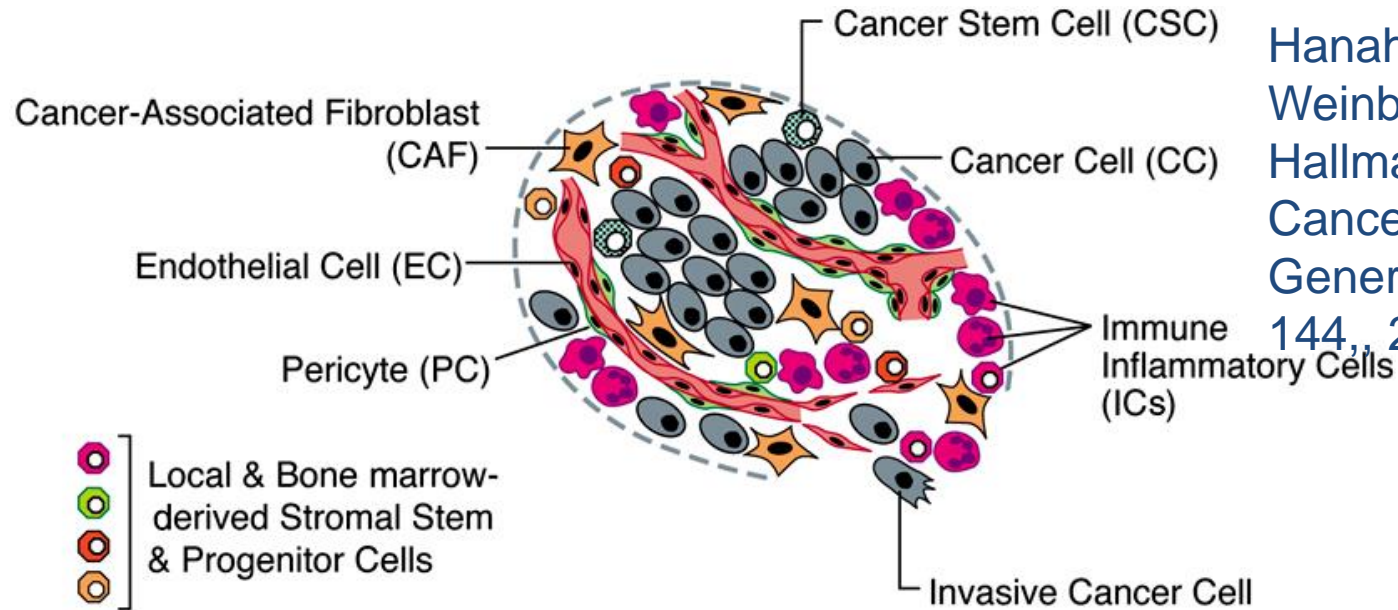
↑  
Inhibitors of  
signaling

↑  
Inhibitors of  
HGF/c-Met

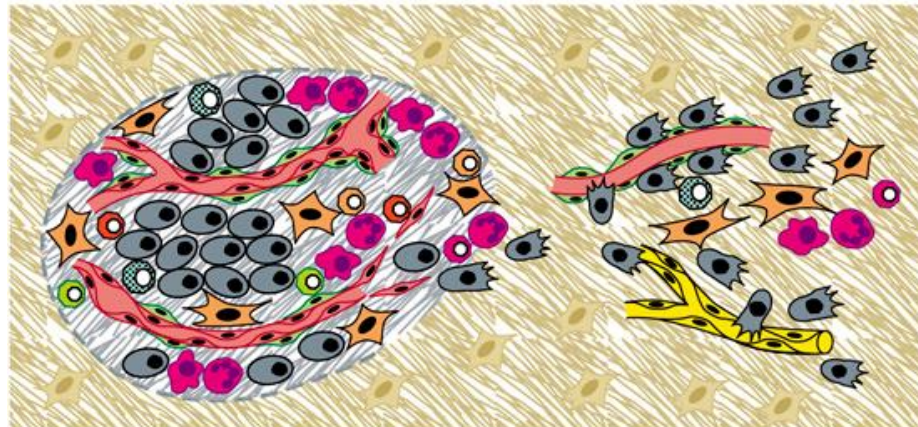
Hanahan D, Weinberg R. Hallmarks of Cancer: The Next Generation. Cell 144, March 4, 2011



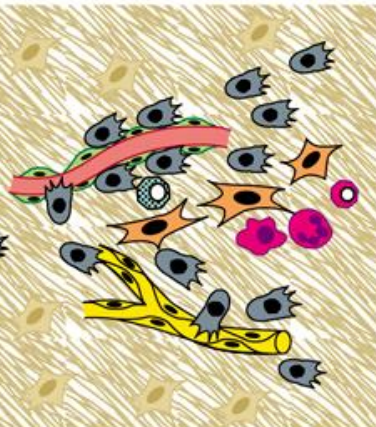
# The Cells of the Tumor Microenvironment



Hanahan D,  
Weinberg R.  
Hallmarks of  
Cancer: The Next  
Generation. Cell  
144, 2011



Core of Primary Tumor  
microenvironment



Invasive Tumor  
microenvironment



Metastatic Tumor  
microenvironment



Look!  
Stem cells!

Art by Mike Fishers

BIZARROCOMICS.COM Facebook.com/BizarroComics

P. RARO.  
1.11.13

# The Beginning of Molecular Therapeutics - 1978

PEOPLE.COM • ARCHIVE

## Will Interferon Kill Cancer? Finnish Dr. Kari Cantell Is Helping the World Find Out

But Cantell and the Finnish Red Cross, now producing 250 billion units (5,285 quarts) a year, have provided the great bulk of pure interferon used for clinical studies on humans, including a \$2 million batch bought last year by the American Cancer Society. “Production is the bottleneck,” says Cantell, who finds it “stupid and irritating” that until recently nobody else has tried to produce the substance in large-scale volume.



# History of SITC

- 1980-1984 NCI Frederick Biologic Response Modifiers (nonspecific immunotherapies) - Journal of Biologic Response Modifiers (1982); Society for Biologic Therapy (1984)
- 1985 Cytokine Therapeutics – 1<sup>st</sup> Annual Meeting of SBT (1986) in Williamsburg
- 1990's Antibody (Her2, CD20, VEGF, etc.) Therapeutics – First Primer on Tumor Immunology (1998, Pittsburgh)
- 2000's Cancer Vaccines - iSBTc (2002); SITC (2010)
- 2010's Cell Therapies (TIL, CART, DC, NK/NKT, etc.) - Journal for ImmunoTherapy of Cancer (2013)
- 2015 Checkpoint Inhibitors; Oncolytic Viruses/Cytokines
- 2020+ The Future Just Ain't What it Used to be (Yogi Berra) – 1<sup>st</sup> Cancer Immunotherapy Winter School (2019); 34<sup>th</sup> Annual Meeting (2019)-OJF







# Cancer Immunotherapy



2013



2014

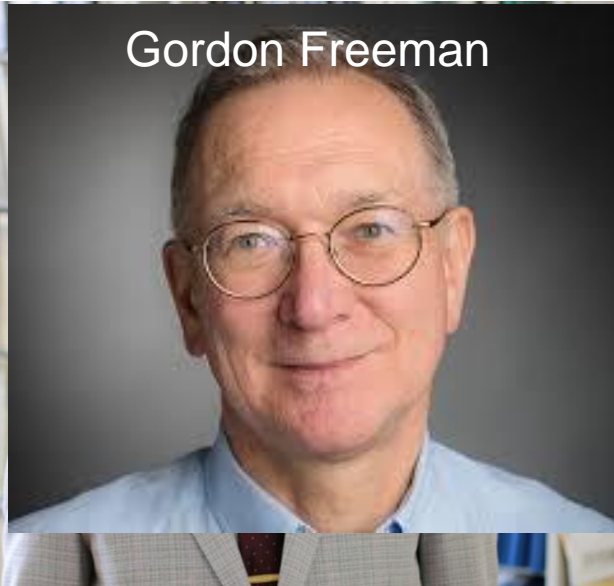




**James Allison**  
**Immunotherapy**  
**Nobel Prize 2018**



**Yoshinori Ohsumi**  
**Autophagy**  
**Nobel Prize 2016**

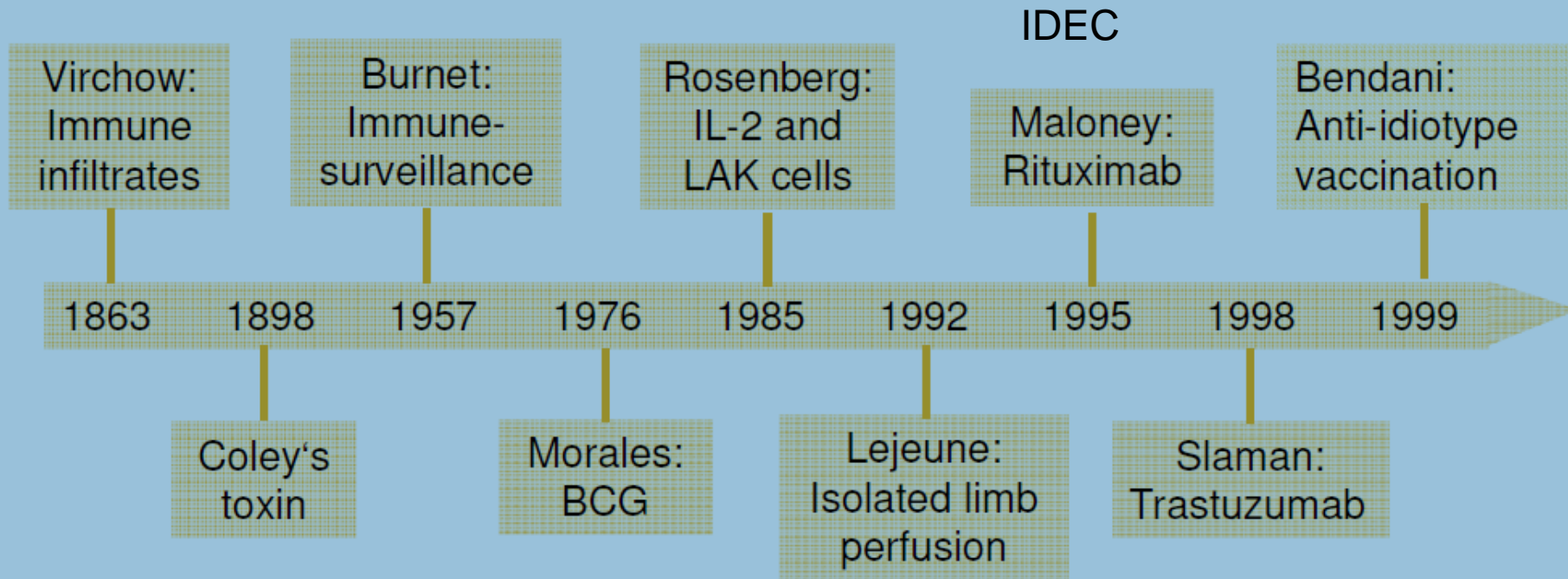


**Tasuku Honjo**  
**Immunotherapy**  
**Nobel Prize 2018**

**Dana-Farber scores legal win on immunotherapy patents likely worth billions: 6 things to know Alia Paavola, May 20th, 2019**

**In a major win for Boston-based Dana-Farber Cancer Institute, a federal court ruled that one of its researchers should be listed as an inventor on six patents that are believed to be worth billions of dollars.**

# Before There were Checkpoints





# Coley's Toxins, 1893



Fig. 2. Patient as he first appeared to Coley in 1891, 7 years after the accidental erysipelas-induced regression of inoperable sarcoma (Coley, 1893a).

W. Busch.  
Einfluß von  
Erysipel.  
Berliner  
Klin Wschr  
1866. 3:  
245–246.

Complete remission of a sarcoma in  
a patient after 2 episodes of  
erysipelas caused by  
streptococcus pyogenes

*William Coley, 1893*

# First 40 Yrs of Cancer Immunotherapy



Steven A.  
Rosenberg



Michael T.  
Lotze



Suzanne  
Topalian



Yutaka  
Kawakami



Michael  
Atkins



Hideaki  
Tahara



Olja  
Finn



Daolin  
Tang

IL-2 Activate  
NK/LAK  
Cells  
Infused

IL-2 Given to  
Patients- The  
First  
Checkpoint  
Inhibitor

Tumor  
Infiltrating  
Lymphocytes  
(TILs)  
And gene  
therapy (PD-  
1/PD-L1)

IL-4 given to  
patients;  
MART-  
1/Melan A

IL-12 given  
to patients

IL12  
Gene  
Therapy

Dendritic  
Cells  
Given To  
Patients

HMGB1 as  
the Ur-  
Cytokine;  
regulates  
autophagy  
and  
apoptosis

1980

1985

1987

1989

1995

1996

1997

2017

T-cells & TCGF/IL2

Dendritic Cells/Tumor Vaccines

CART/TIL  
Checkpoints

Pubmed: > 357,762 articles about Tumor Immunology  
1.5.20

2014  
PD-1

# Cytokines are medically relevant endogenous small (~15kDa) proteins

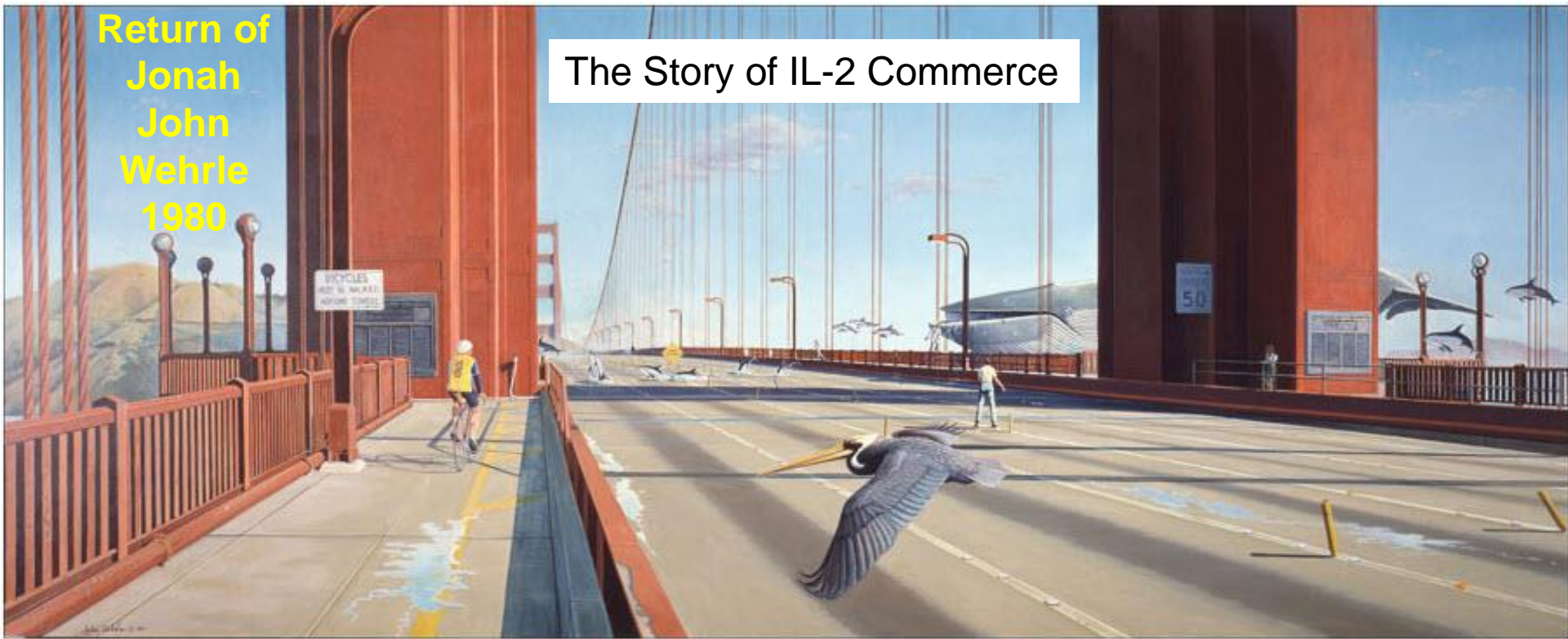
## Cytokine-based therapies in human disease

Cytokine	Brand name	Status	Indication	Year of 1 <sup>st</sup> FDA Approval
IL-2	Proleukin	Approved	Cancer	1992
IL-11	Neumega	Approved	Thrombocytopenia	1994
EPO	Epogen	Approved	Anemia	1989
G-CSF	Neupogen	Approved	Myelosuppression from chemo	1991
GM-CSF	Leukine	Approved	Myelosuppression from chemo	1991
IFN- $\alpha$	Intron-A	Approved	Hepatitis, Cancer	1991
IFN- $\beta$	Betaseron	Approved	Multiple sclerosis	1993
IFN- $\gamma$	Actimmune	Approved	Granulomatosis	1990
IL-7		Clin dev	Cancer, anti-viral	
IL-10		Clin Dev	Cancer, anti-inflammatory	
IL-12		Clin dev	Cancer, anti-viral	
IL-15		Clin dev	Cancer	
IL-21		Clin dev	Cancer	



Return of  
Jonah  
John  
Wehrle  
1980

## The Story of IL-2 Commerce



Dupont 1983  
Taniguchi, T 1983  
Roche 9/84  
Cetus-PEG  
Chiron 1990  
Novartis  
Prometheus  
Nestle  
Clinigen




Paging Dr. Crick  
John Wehrle



CANCER, DEALS

# As drugmakers seek ways to elude IL-2 flaws, Clinigen secures the full rights to original troubled IL-2 drug Proleukin



by **NATALIE GROVER**  — on February 13, 2019 07:15 AM EST

Updated: 11:58 AM

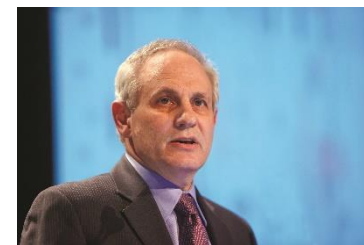
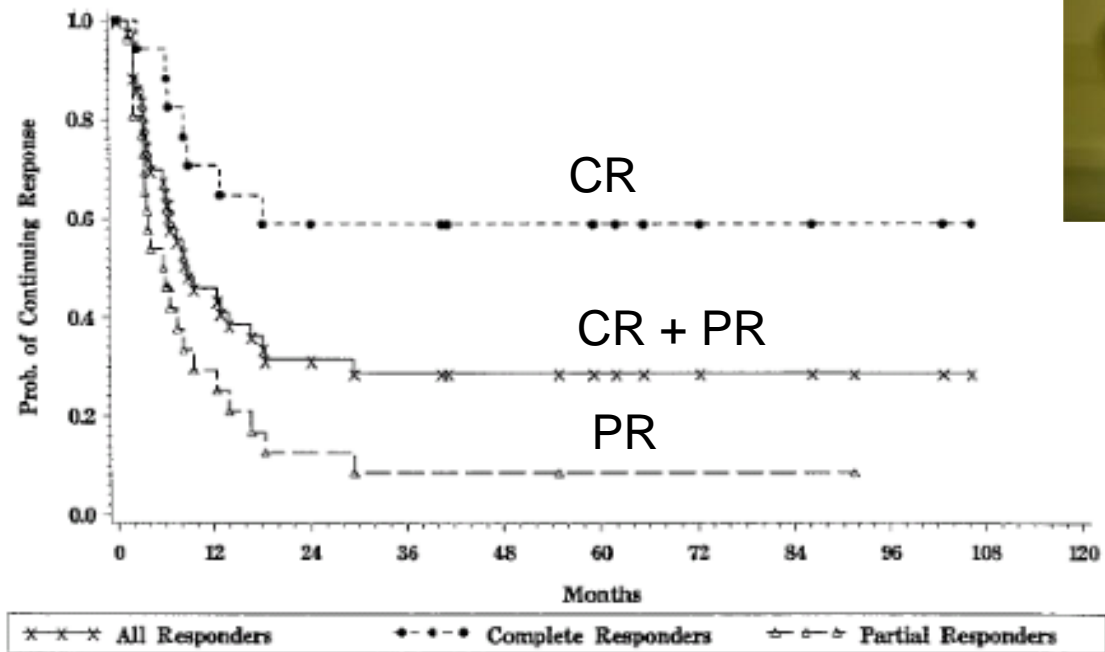
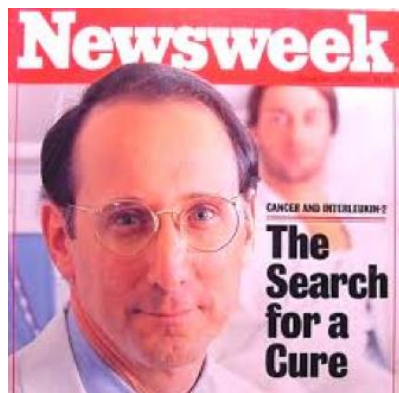


Proleukin, the troubled IL-2 cancer drug sold by Novartis, has found a new home at Clinigen, while **others** in the field of immuno-oncology seek ways to create an **improved version** of the class of drugs sans the toxicity that has stymied the use of the original IL-2.

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The best pla  
**POINTS NE**  
Comprehensive

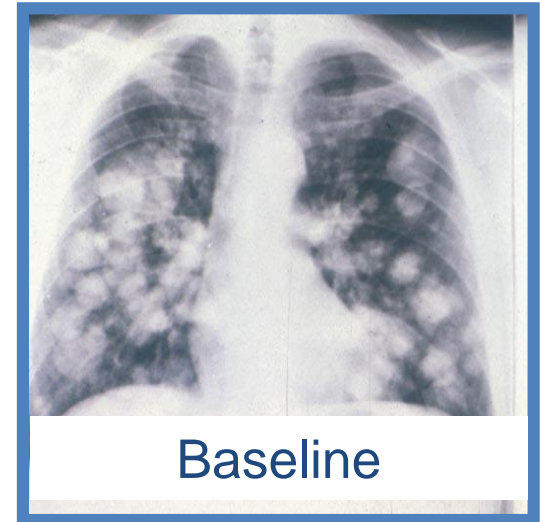
# Proof of Principle: Deep responses produce remissions



Atkins, Lotze et al. J Clin Oncol. 1999

# High Dose IL-2 Immunotherapy

- Approved in patients with melanoma and kidney cancer.
- Significant 'toxicity'.
- Associated with 'cytokine storm'.
- iNOS blockers, sTNF-R or IL-1Ra have yielded limited reduction in side effects.
- IL-2 treatment is associated with a '**systemic autophagic syndrome**' and temporally limited tissue dysfunction.



*AR. Chavez, X Liang, MT Lotze.  
Ann. N.Y.Acad.Sci.1182:14-27 (2009)*



# Cytokine Working Group

## CWG: The Abbreviated History (SITC 2018)

David McDermott, MD

Beth Israel Deaconess Medical Center

Dana Farber/Harvard Cancer Center

Harvard Medical School



Beth Israel Deaconess  
Medical Center



HARVARD MEDICAL SCHOOL  
TEACHING HOSPITAL



*A founding member of*  
**Dana-Farber/Harvard  
Cancer Center**

# Second Randomized Treatment with Interleukin 2 as Immunotherapy for Cancer

VOLUME 23 • N

JOURNAL OF

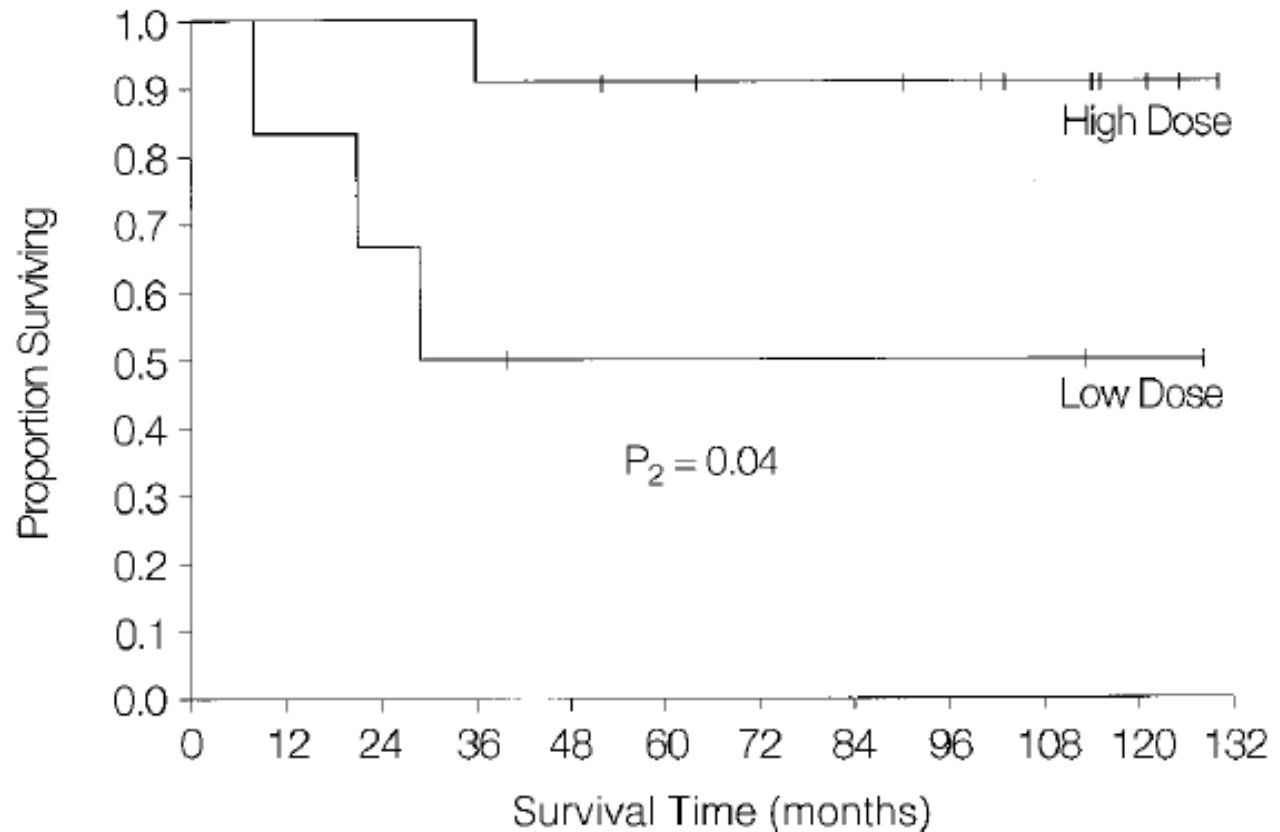


Fig 2. Survival of patients completely responding to high-dose versus low-dose intravenous interleukin-2.

J Clin Oncol 2005; 23:133-

***J Clin Oncol 21:3127-3132. © 2003 by American Society of Clinical Oncology.***

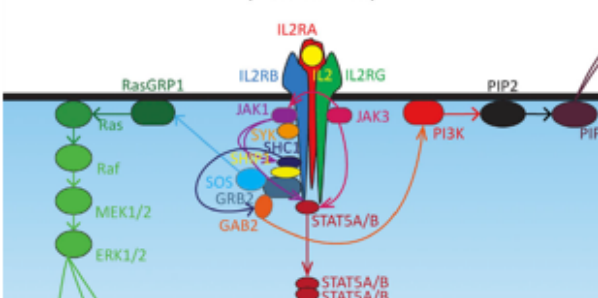
Taniguchi T, Matsui H, Fujita T, Takaoka Y, Yoshimoto R, Hamuro J. Structure and cloned cDNA for human interleukin-2. *Nature* Mar 24-30;302:305-10.

#### REVIEW

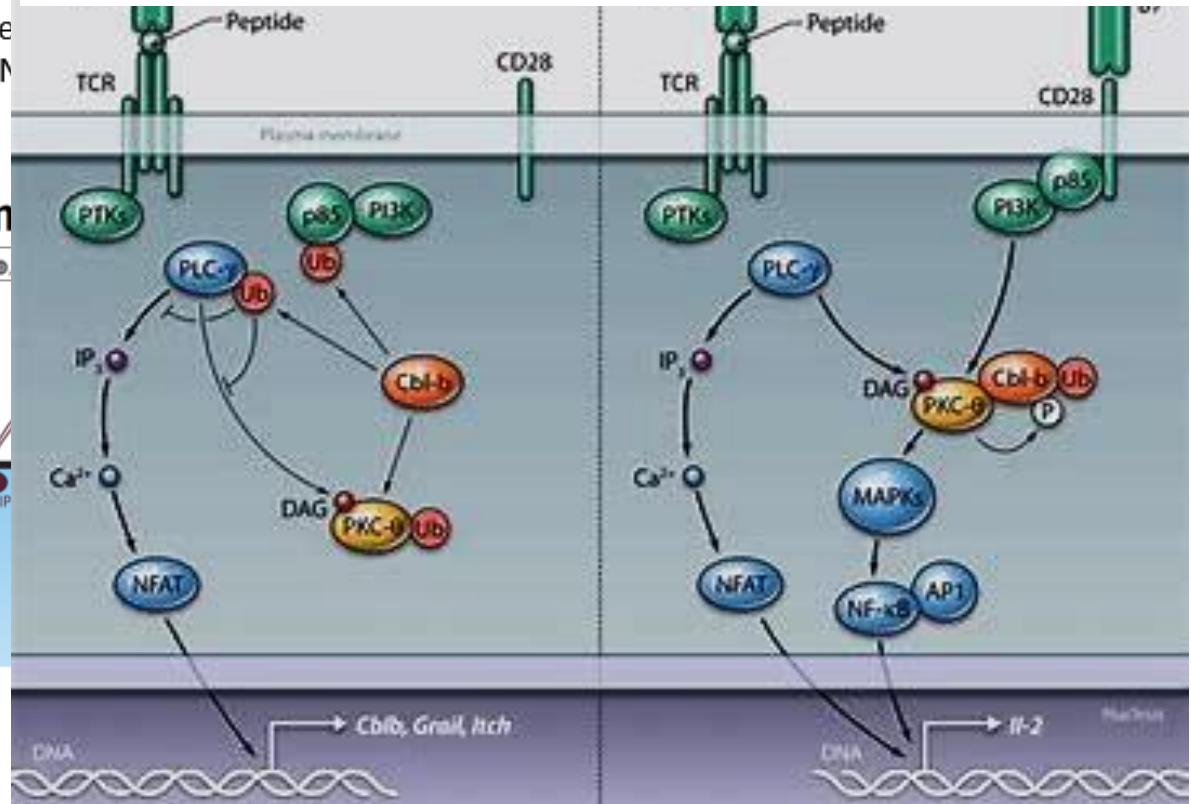
## Effects of interleukin-2 in immunosuppression

Jonathan G. Pollard

High-affinity IL2R (cis conformation)



## Repeal and Replace (or add to Interleukin 2) Cbl-Bi





# ULD IL-2 for GVHD Prophylaxis: ↑Tregs (S. Ito, J. Ritz)

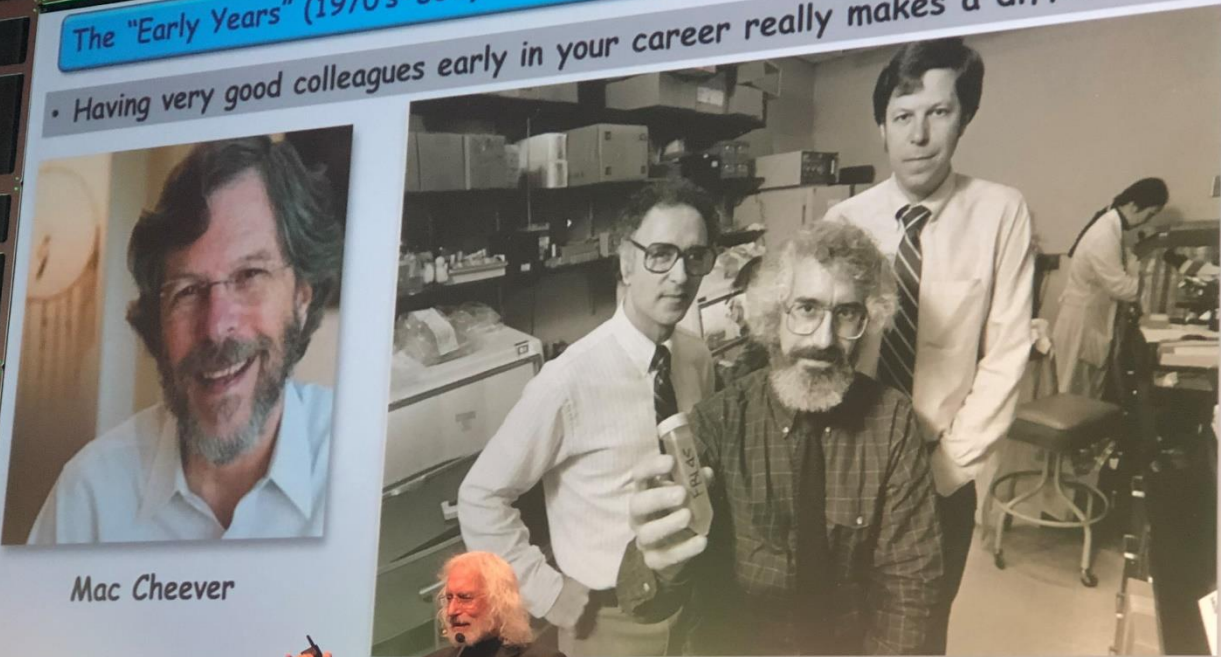
- **Ultra low dose IL-2**
  - Expands T<sub>regs</sub> and NK cells
  - Effective for steroid refractory GVHD
  - Has been used for GVHD prophylaxis in matched donor SCT
- Quality and quantity of **regulatory T<sub>reg</sub> and NK cells** impact haplo-SCT outcomes

*Koreth et al. N Engl J Med 2011; 365: 2055, Koreth et al. Blood 2016; 128: 130  
Kennedy-Nasser, Ito S et al. Clin Cancer Res 2014; 20: 2215*

# Cheever, Greenberg, Fefer

The "Early Years" (1970's-80's): Developing T cell therapy in mouse models

- Having very good colleagues early in your career really makes a difference

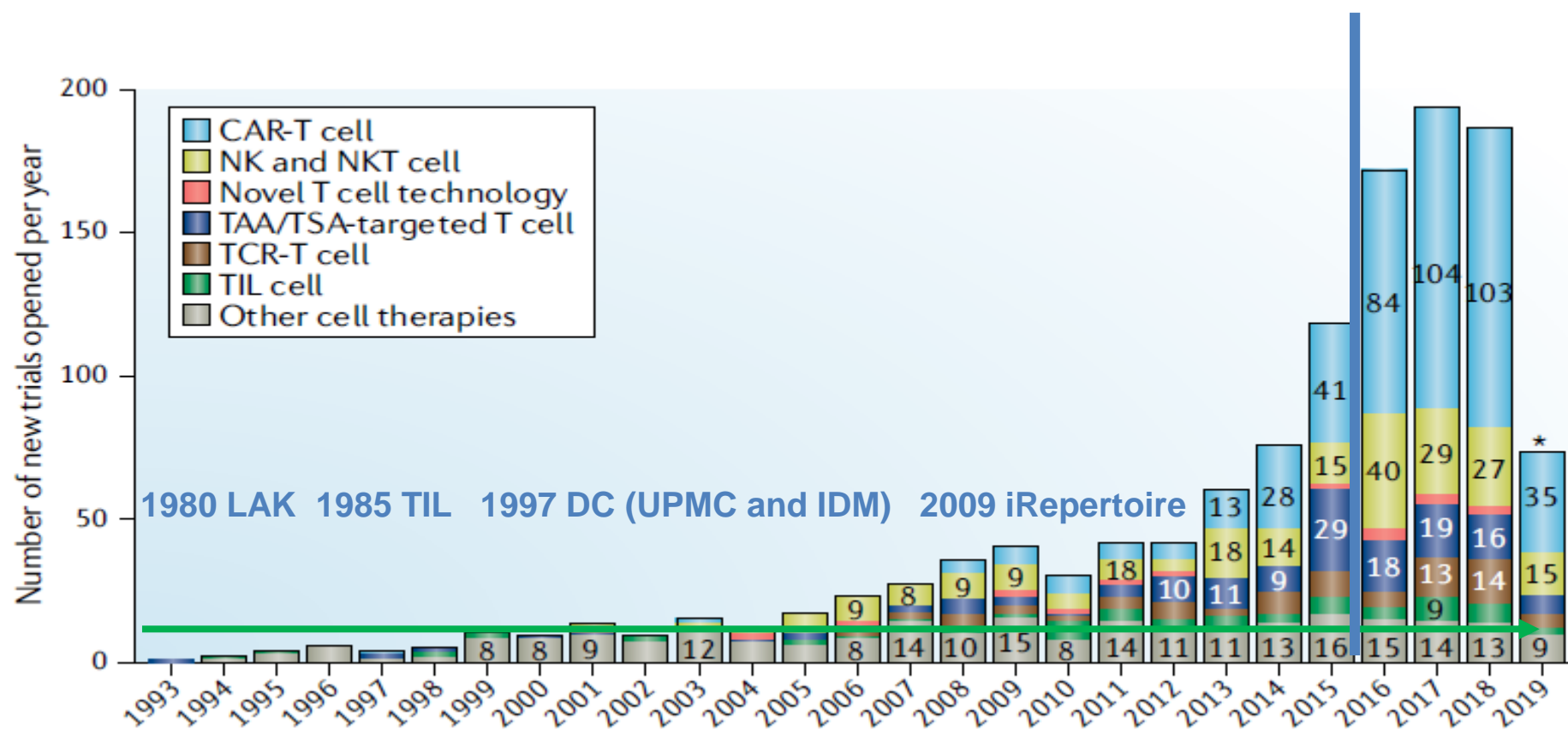


Mac Cheever

SITC 2018

The image shows a presentation slide with a blue header and a grey bullet point. Below the text are two photographs. The left photo is a portrait of a man with a beard and glasses, identified as Mac Cheever. The right photo is a group of three men in a laboratory setting; the man in the center is holding a vial labeled 'T-RAE'. In the foreground, a man with white hair and glasses is speaking at a podium that has 'SITC 2018' on it. The background of the slide is decorated with a green and black geometric pattern.

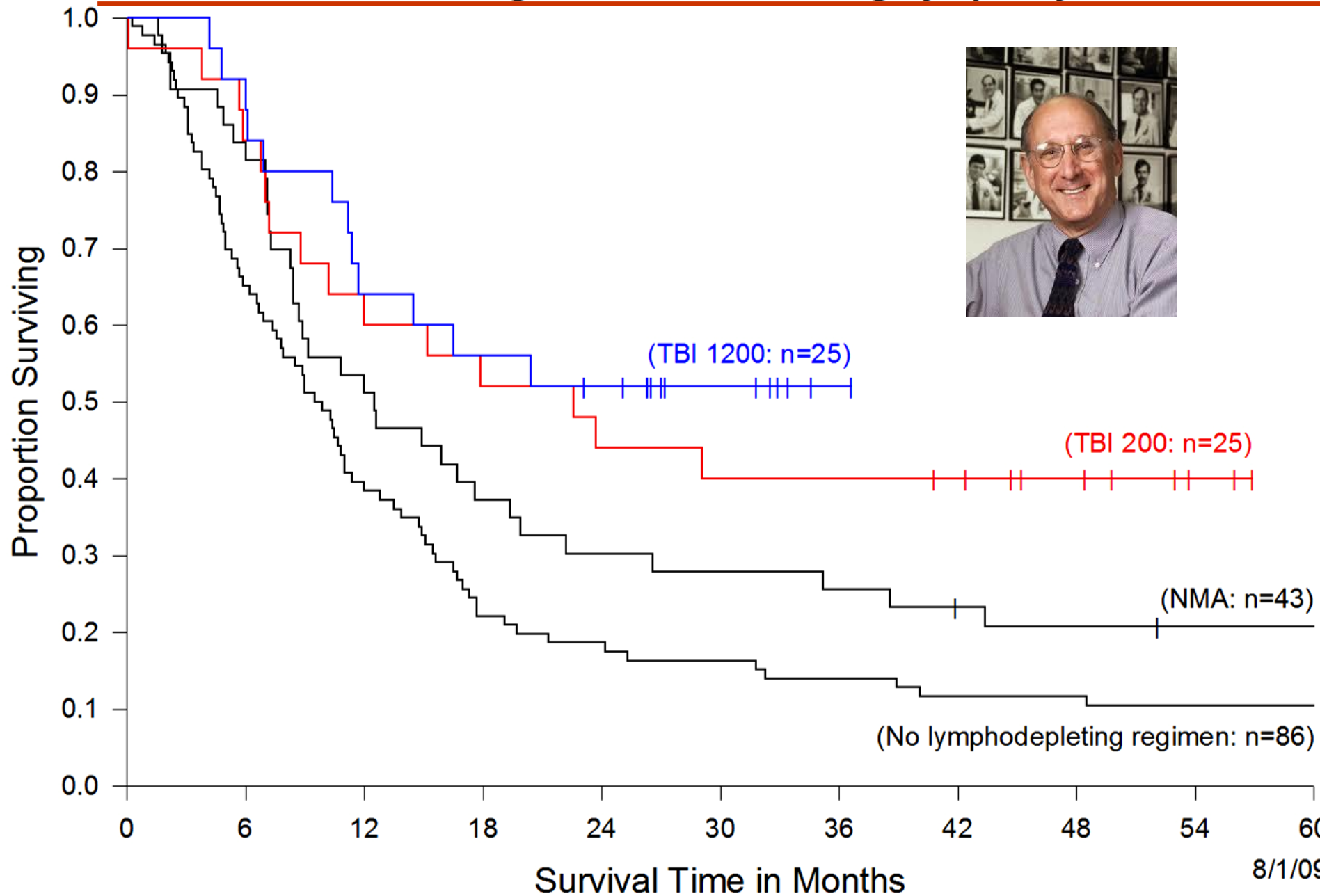
## Growth of Cell Therapy Last 25 Years



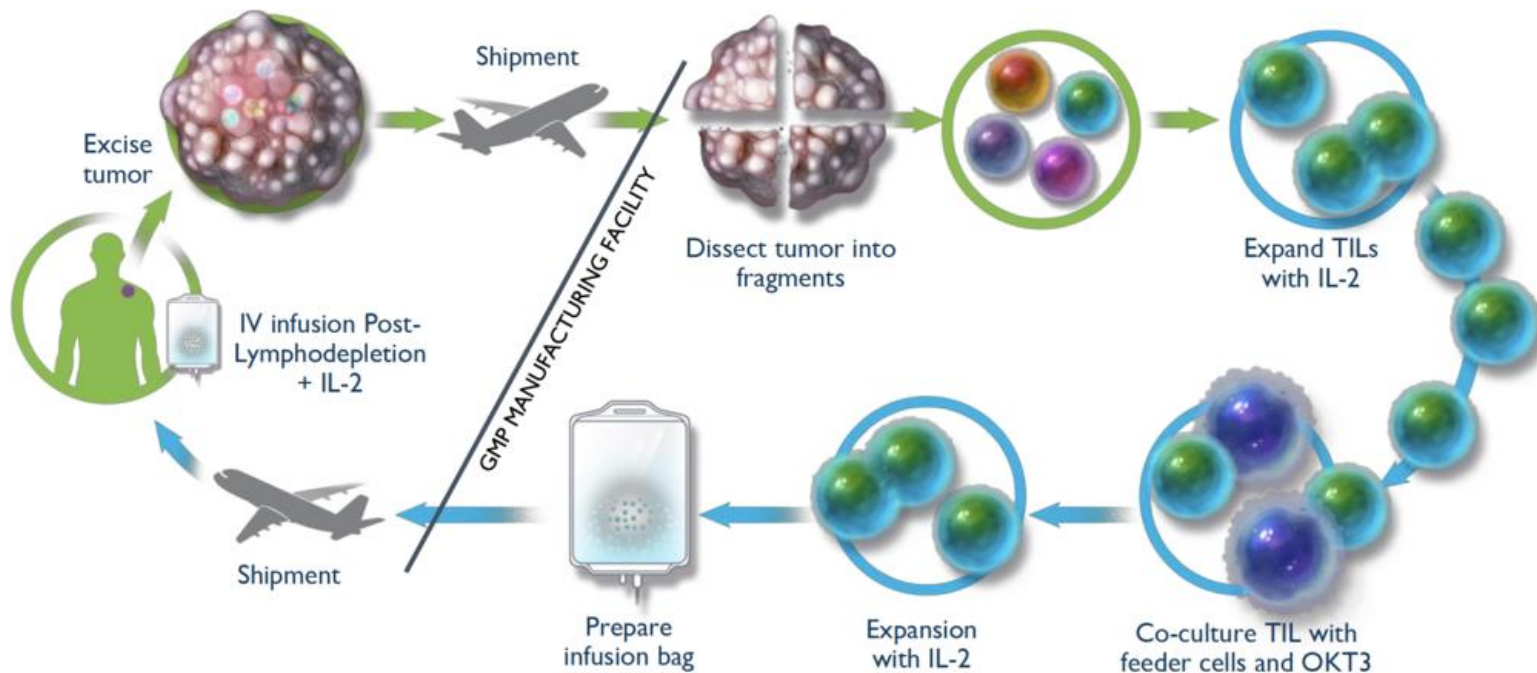




# Survival of Patients with Metastatic Melanoma Treated with Autologous Tumor Infiltrating Lymphocytes and IL-2



# Tumor Infiltrating Lymphocyte (TIL) Therapy – Iovance (Instil, Myst, NxACT-Nurix, Achilles...)



**Lotze, US Patent 20190083539 2018**





Bruce Levine  
@BLLPHD

Selfie with [@ladygaga](#) after talking about T cells



Kershaw M  
DE, Wunde  
SA, Hwu P.  
for ovarian c  
17062687;

Kochende  
Stevenson  
BJ, Morga  
and regro  
autologo  
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antigen  
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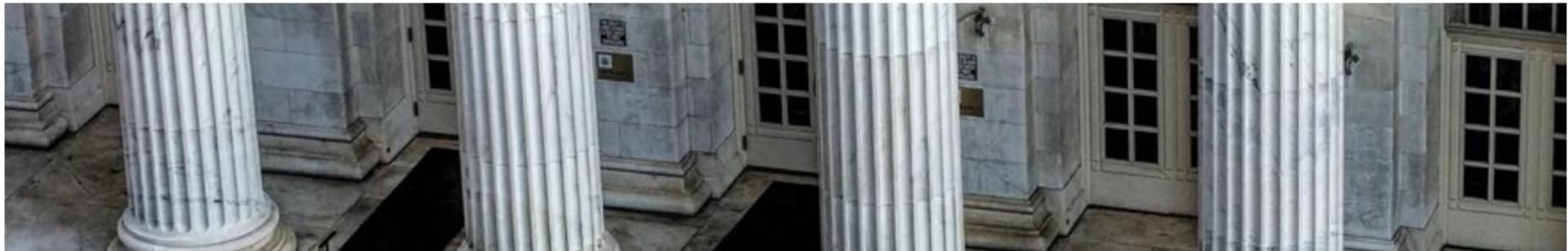
**Attend the FiercePharma Executive Breakfast at JPM**

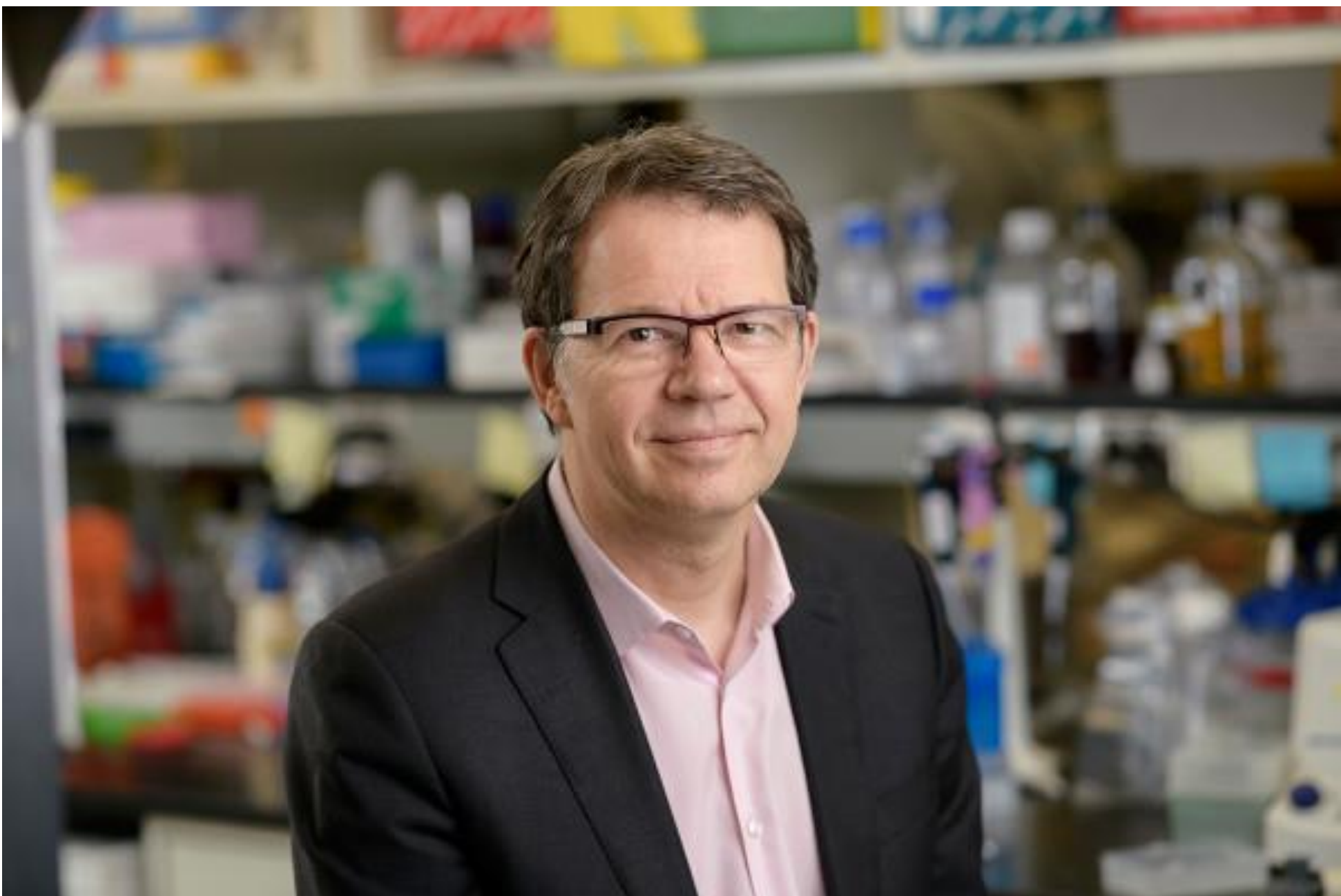
Join us on January 14th at the Fairmont San Francisco. Reserve your seat today.

## Pharma

# Jury orders Gilead's Kite Pharma to pay \$752M for CAR-T patent infringement

by [Eric Sagonowsky](#) | Dec 13, 2019 2:56pm







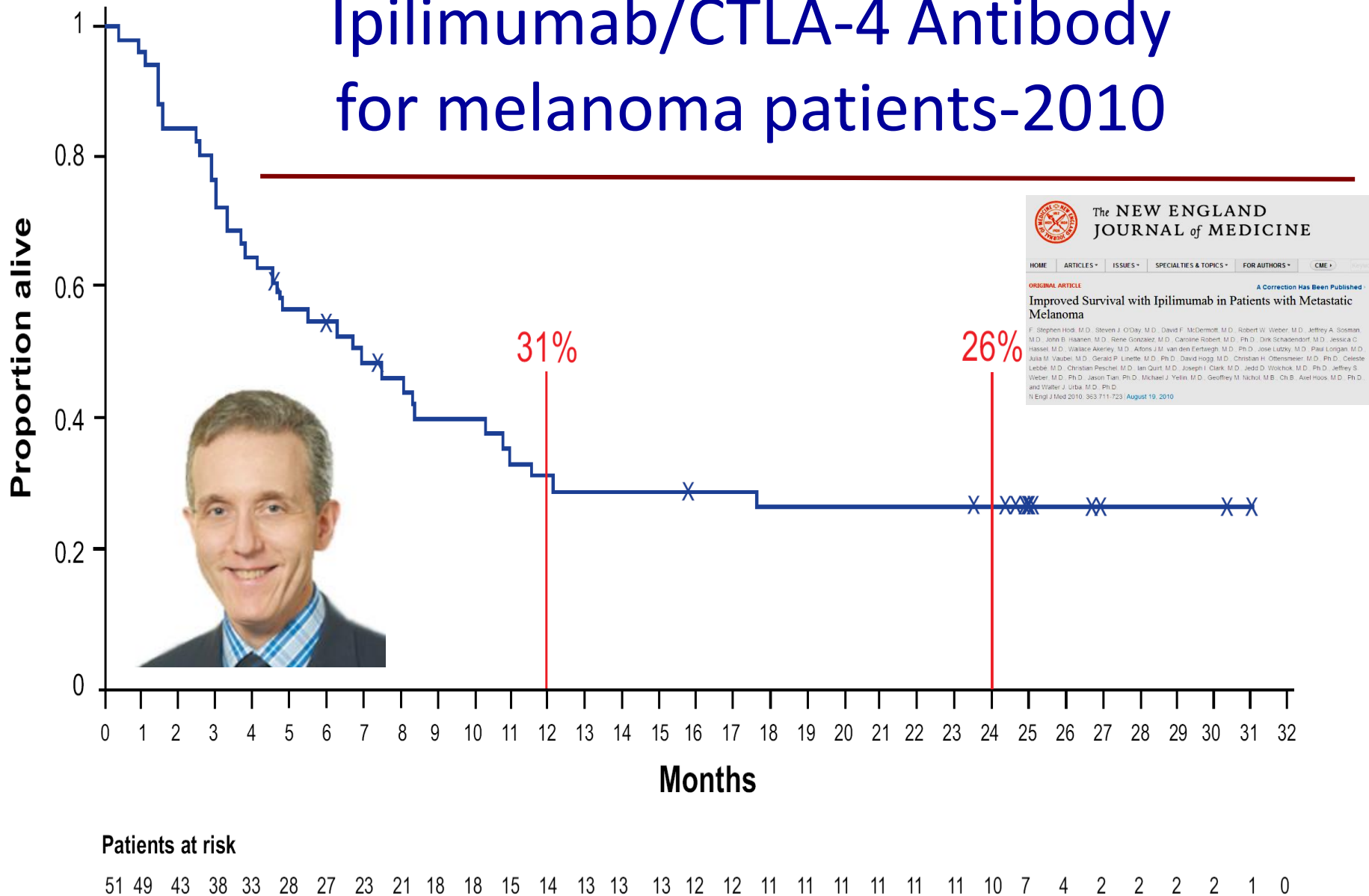
# Harvard, MIT spearhead \$50M manufacturing center to speed cell, gene therapy R&D

by [Amirah Al Idrus](#) |  
Nov 25, 2019 10:05am



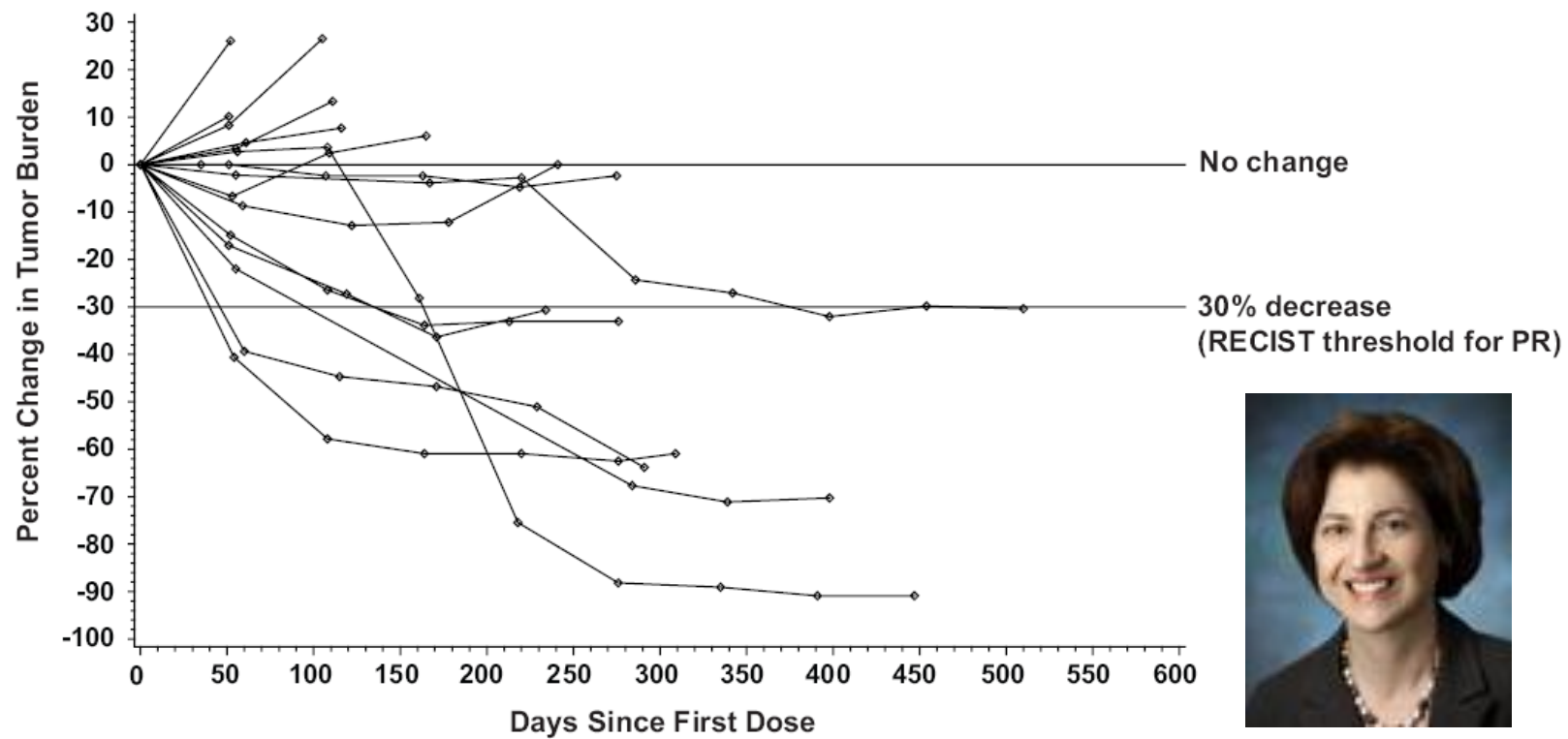


# Ipilimumab/CTLA-4 Antibody for melanoma patients-2010



x = censored data

# PD1 AB RESULTS: RCC PATIENTS



\*Patients treated at the 10 mg/kg dose



# ***Immunotherapy Drugs Slow Skin Cancer That Has Spread to the Brain***

NYT August 22, 2018



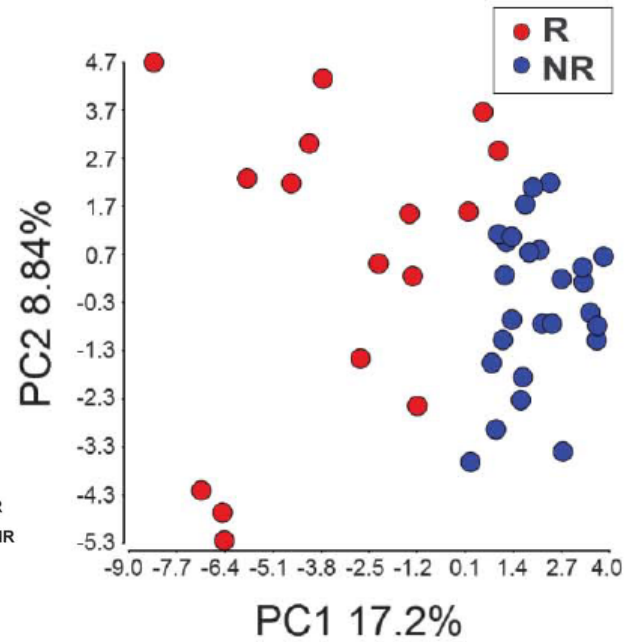
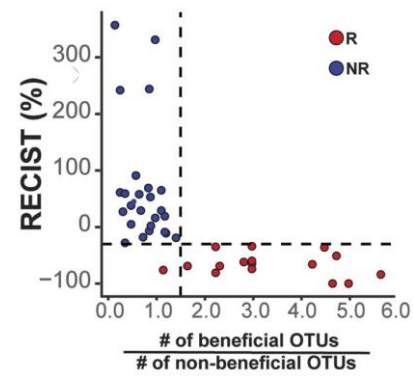
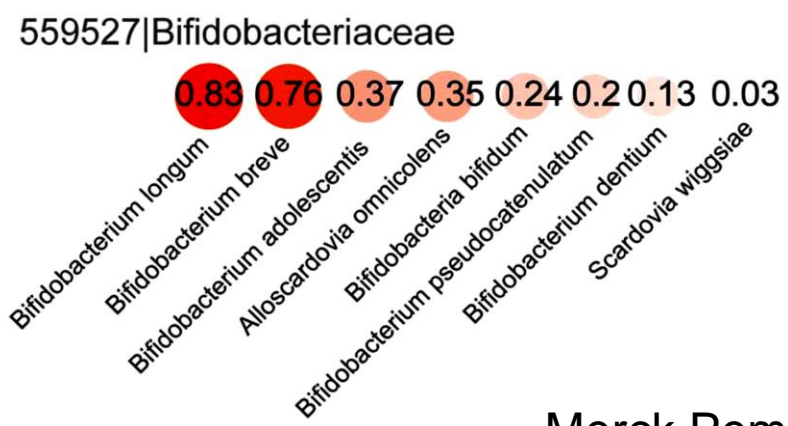




CANCER IMMUNOTHERAPY

# The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients

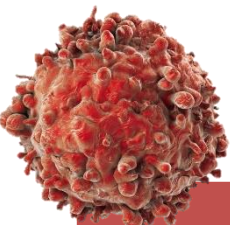
Vyara Matson,<sup>1\*</sup> Jessica Fessler,<sup>1\*</sup> Riyue Bao,<sup>2,3\*</sup> Tara Chongsuwat,<sup>4</sup> Yuanyuan Zha,<sup>4</sup> Maria-Luisa Alegre,<sup>4</sup> Jason J. Luke,<sup>4</sup> Thomas F. Gajewski<sup>1,4,†</sup>



Operational  
Taxonomic  
Units

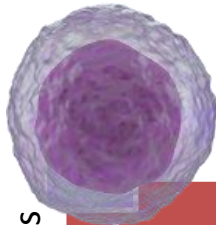
Merck Pembro Anti-PD1 + *Bifidobacterium longum*

# Foundations of Cancer Therapy (WuXing Again)



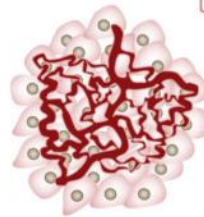
Tumor

- Surgery
- ChemoRx
- Radiation
- Other Targets:
- Signal Transduction
- Autophagy
- Oncogenes (BRAF, RAS)
- Tumor MAPK pathways
- Kinases-BTK



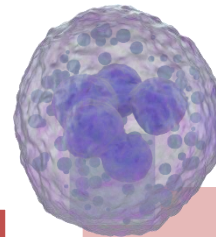
T Cells

- Immune Stimulants
- Checkpoint Inhibition
- Adoptive Cell Therapy (CARs, TIL)
- DC AND Vaccines



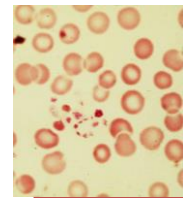
Endothelium

- Anti-VEGF
- Chloroquine
- Platelet Derived Growth Factor (PDGF)
- Fibroblast Growth Factor (FGF)
- TKI's (Sorafenib, Axitinib, Pazopanib)



Stroma and Myeloid Cells

- Stromal Component
- Tumor Associated Macrophages
- VISTA
- MDSCs
- Neutrophils



Platelets and RBC

- Erythropoietin
- Thrombopoietin
- Interleukin 11
- Red Cells
- Platelet Derived Growth Factor (PDGF)



Why science teachers  
should not be given  
playground duty.