

**“Cancer immunotherapy:  
an old idea that finally has its day!”**

**Carl June**  
**March 25, 2016**



# History of cancer immunotherapy: December 2013



## 2013 Breakthrough

■ Cancer Immunotherapy

## The Runners-Up

CRISPR

CLARITY

Human Stem Cells from Cloning

Mini-Organs

Cosmic Particle Accelerators  
Identified

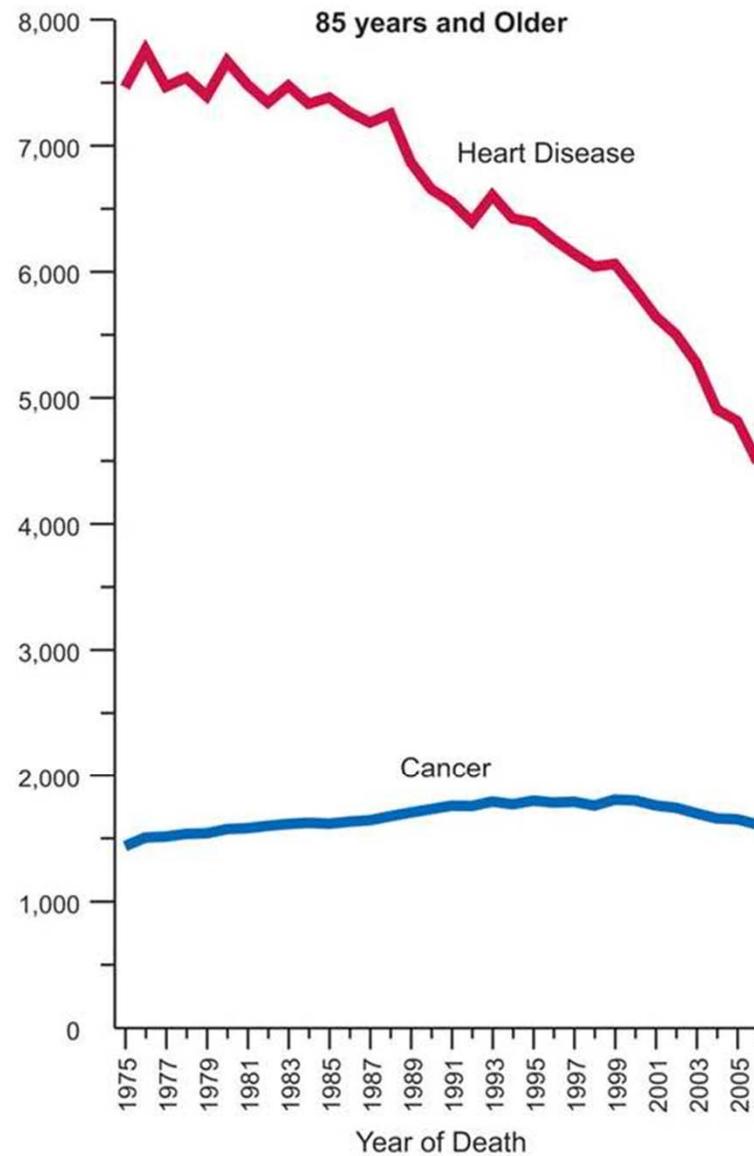
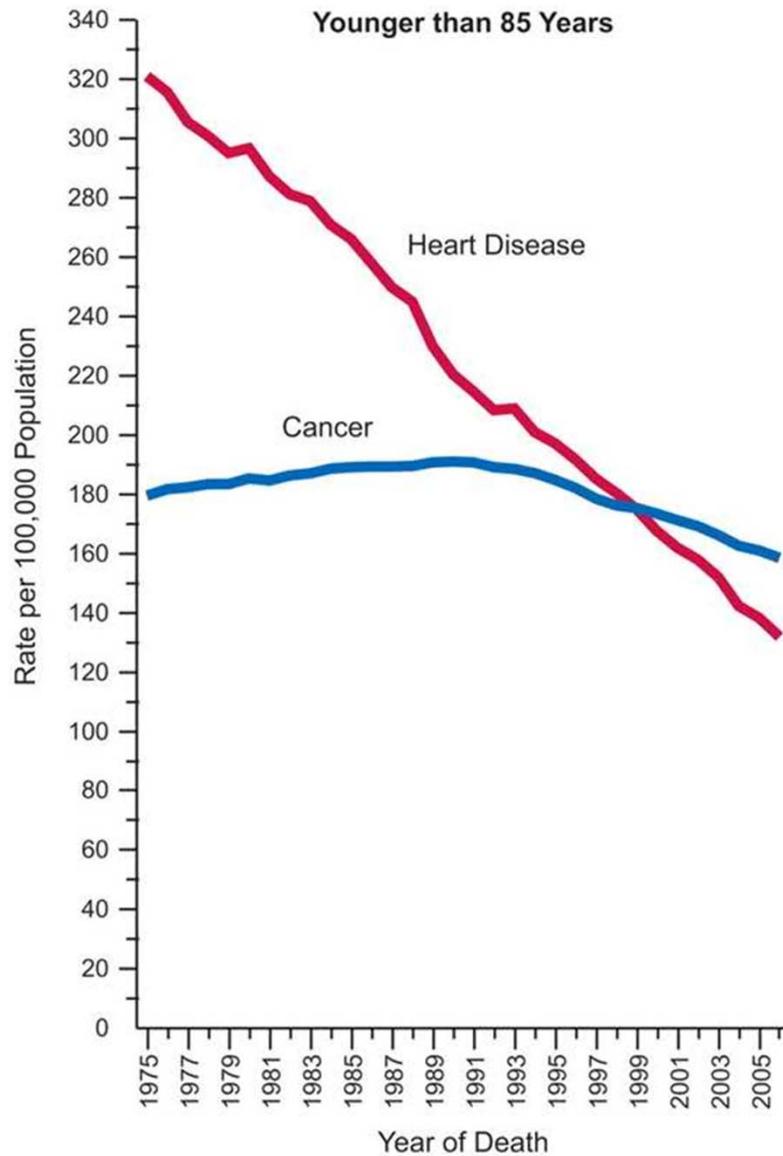
Perovskite Solar Cells

Why We Sleep

Our Microbes, Our Health

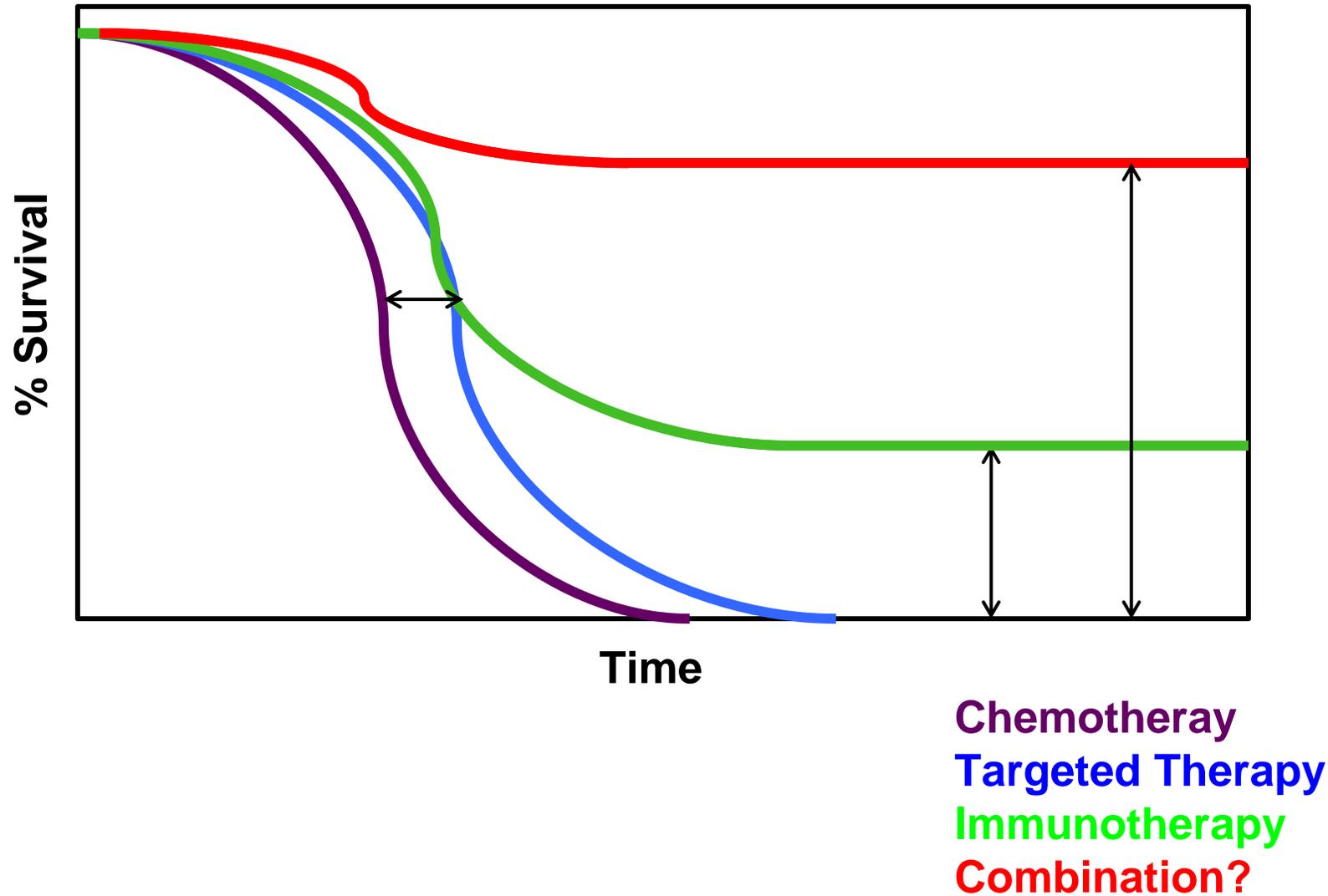
In Vaccine Design, Looks Do Matter

# Advances in Health Care: Cardiac Surpasses Cardiac Mortality



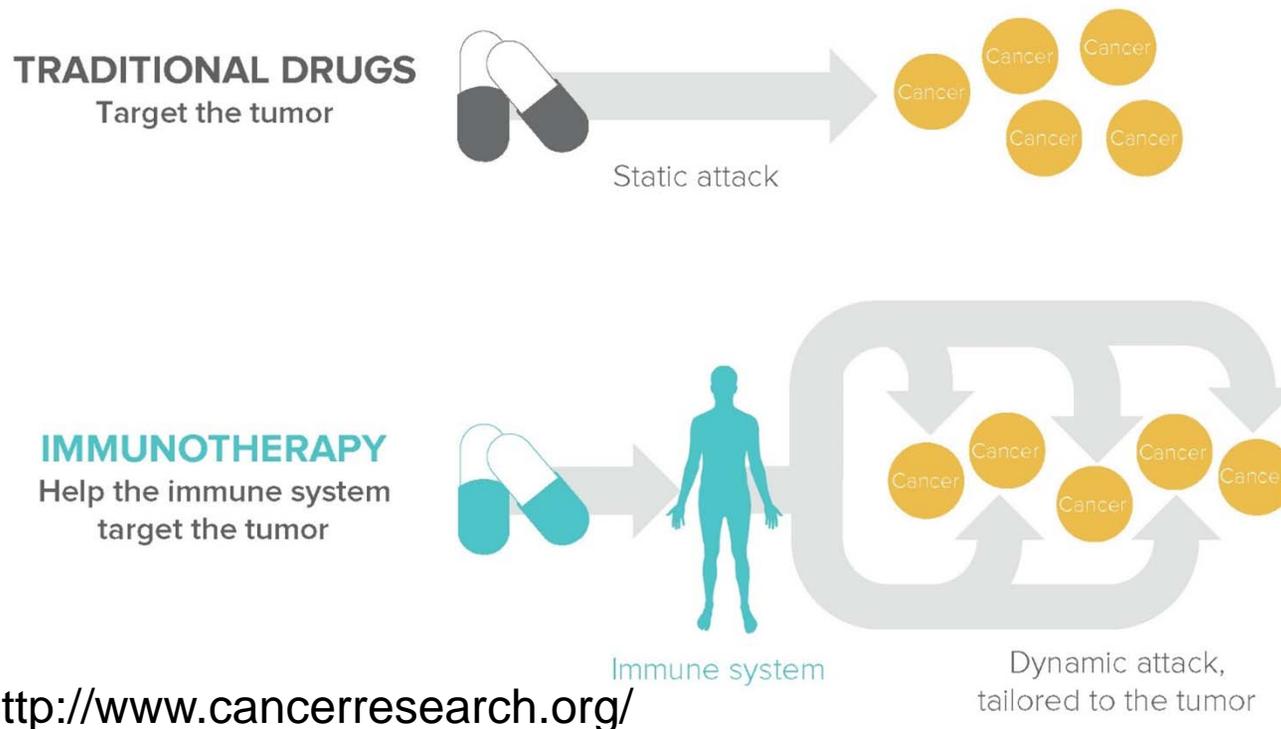
# Cancer Epidemic: The need for curative therapies

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# The Case for Immunotherapy

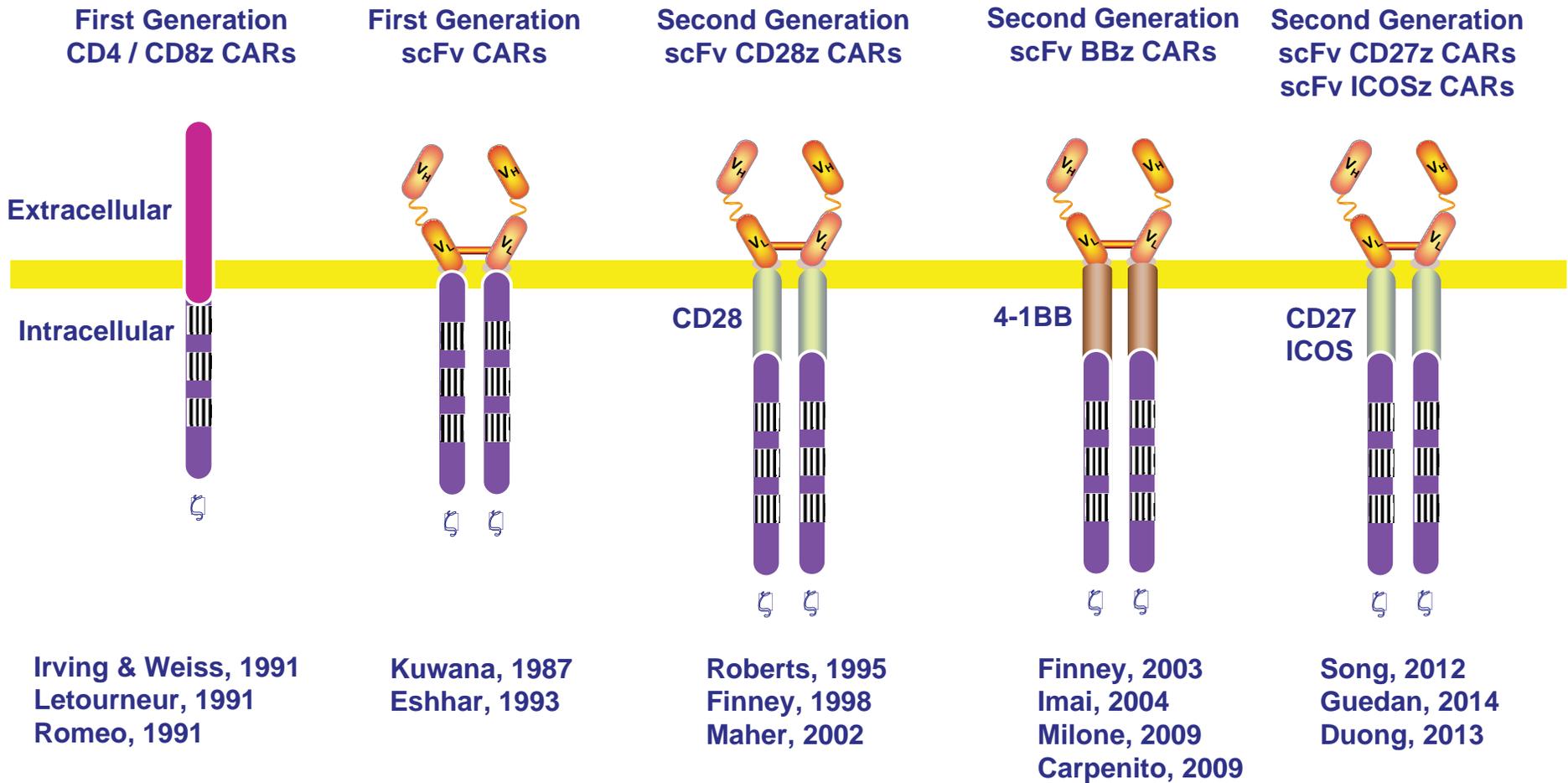
- Immunotherapy is a “living drug”
- Immune system can evolve to treat the tumor
- Immunotherapy can cure cancers





# Using Synthetic Biology to Overcome Tolerance

## Creation of Bi-specific CAR T cells



## Design of CAR T Cells

# CAR T Cell Breakthrough: Hype = Reality?

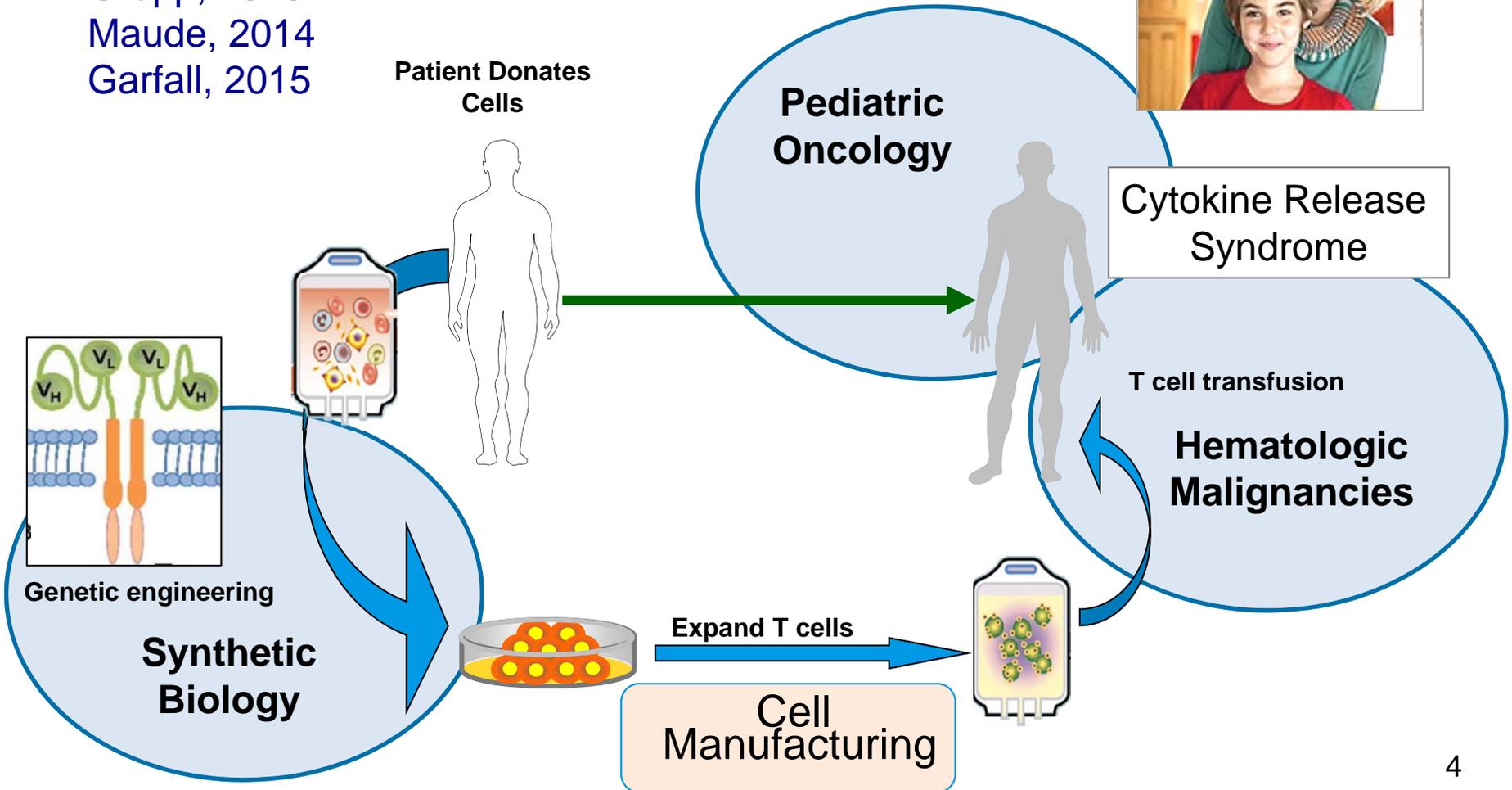


July 31, 2010  
1st CART19 Infusion

The New York Times



Porter, 2011  
Grupp, 2013  
Maude, 2014  
Garfall, 2015



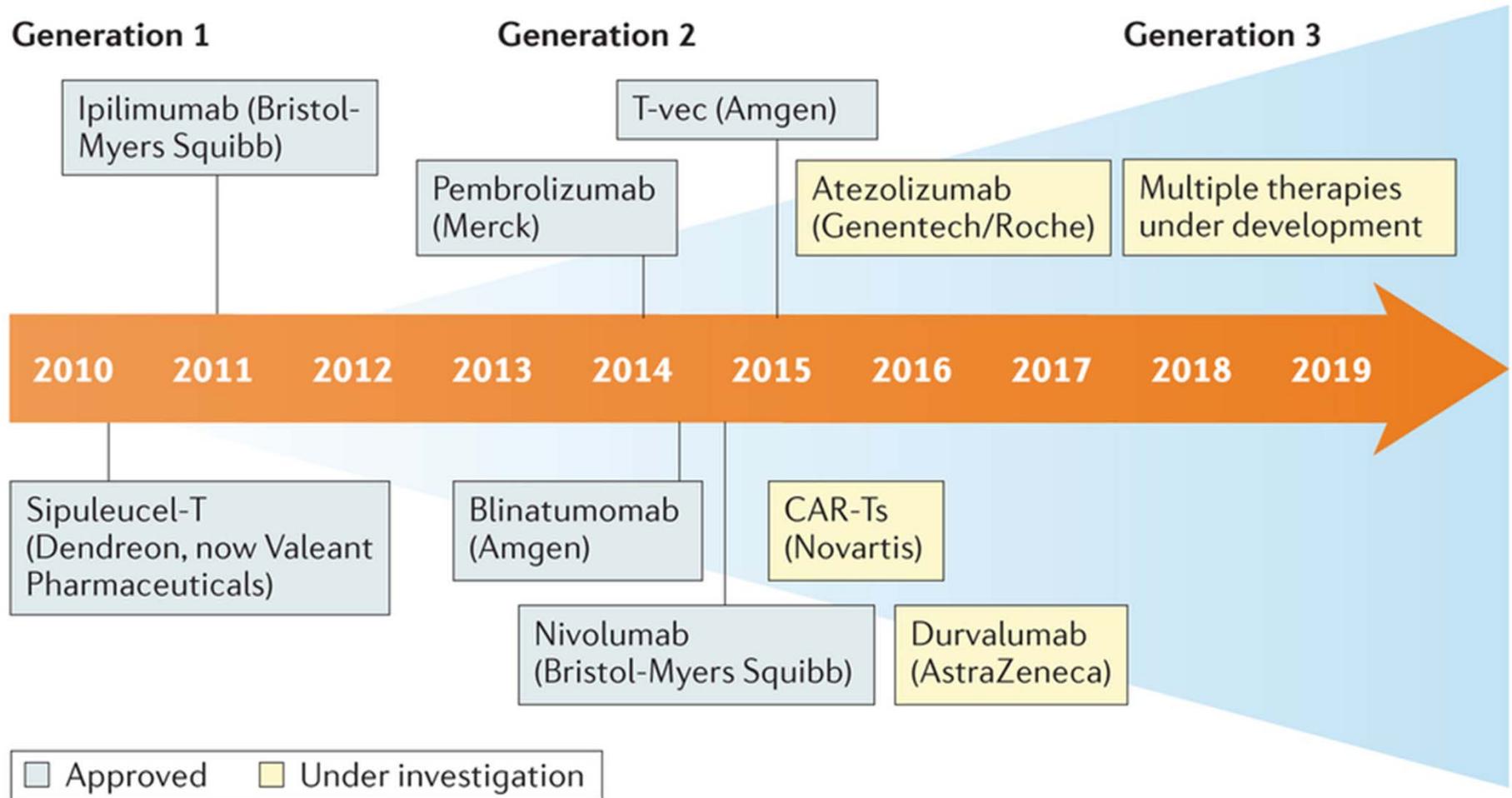
# CAR T CELL THERAPIES

- Durable responses in leukemia, lymphomas, myeloma, melanoma
- First example of “synthetic immunity”
- Immunotherapy is a “living drug”
- Immune system can evolve to treat the tumor
- Immunotherapy can “cure” cancers



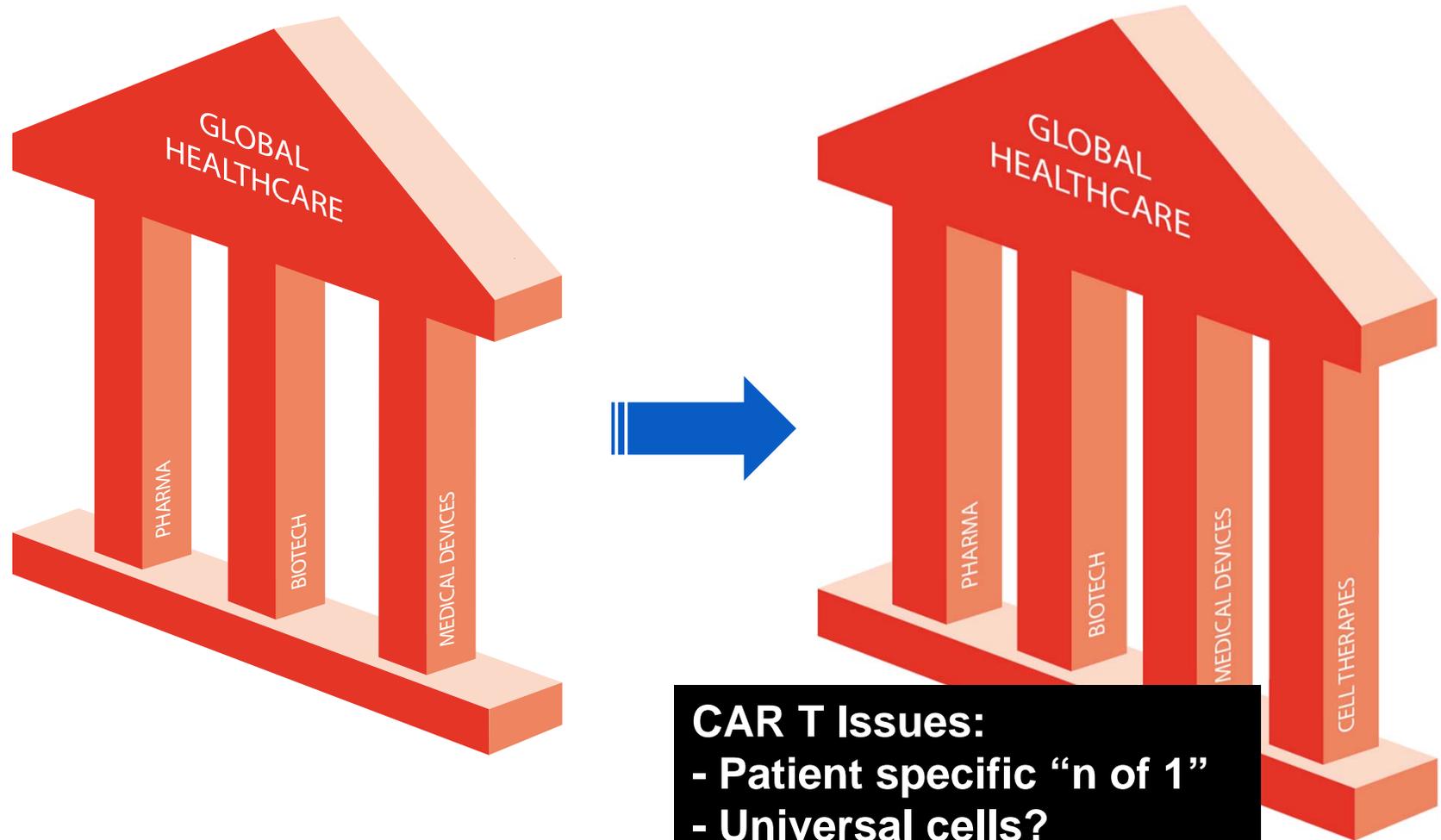
Jan 31, 2015

# Deep Pipeline of Immunotherapies



Nature Reviews Drug  
Discovery (2016) doi:10.1038/nrd.2015.35

# Health Care Challenges: New Cell Therapy Industry

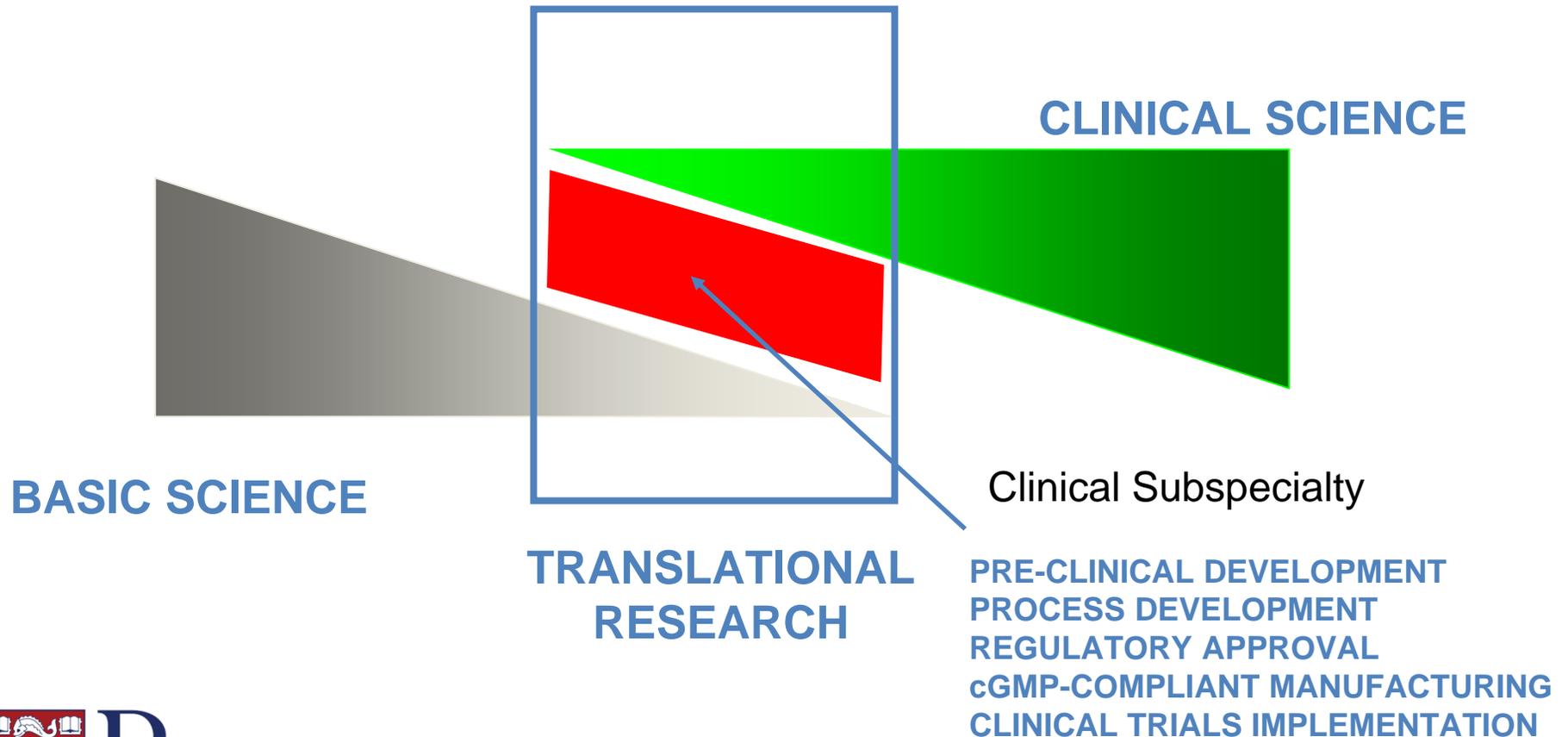


Chris Mason et al, Regen Med. 2011  
Levine and June, Nature. 2013

## CAR T Issues:

- Patient specific “n of 1”
- Universal cells?
- Reimbursement models?

# EVOLVING CELLULAR AND BIOLOGIC THERAPEUTICS IN ONCOLOGY



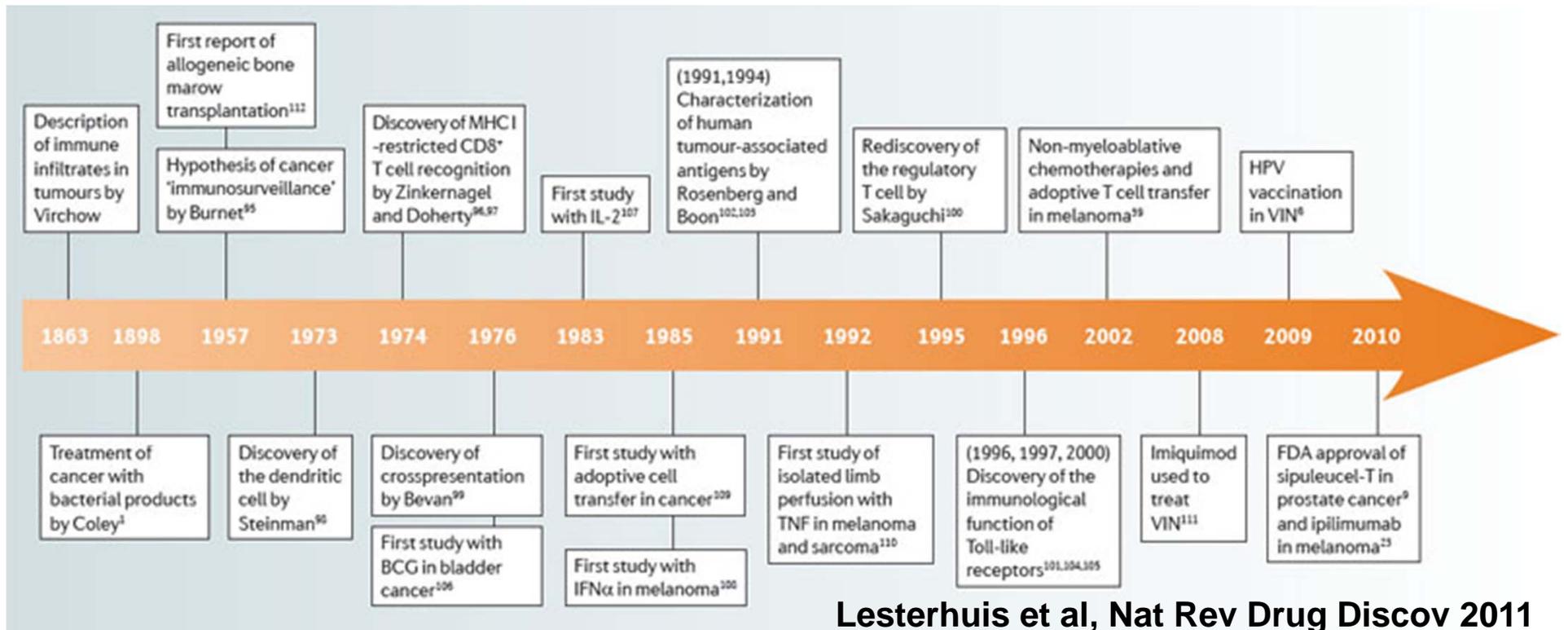
# Summary: Cancer immunotherapy



- **Synthetic biology is adding to the “toolbox” for cancer therapies:**
  - **Engineered herpesvirus (Amgen)**
  - **CAR T cell pivotal trials underway (Novartis, others)**
- **Combinatorial trials with other targeted therapies will be synergistic: thousands of combinations need to be tested**
- **Moonshot initiative may accelerate the “cure” of cancer**



# Abridged history of cancer immunotherapy: Disappointing until recently

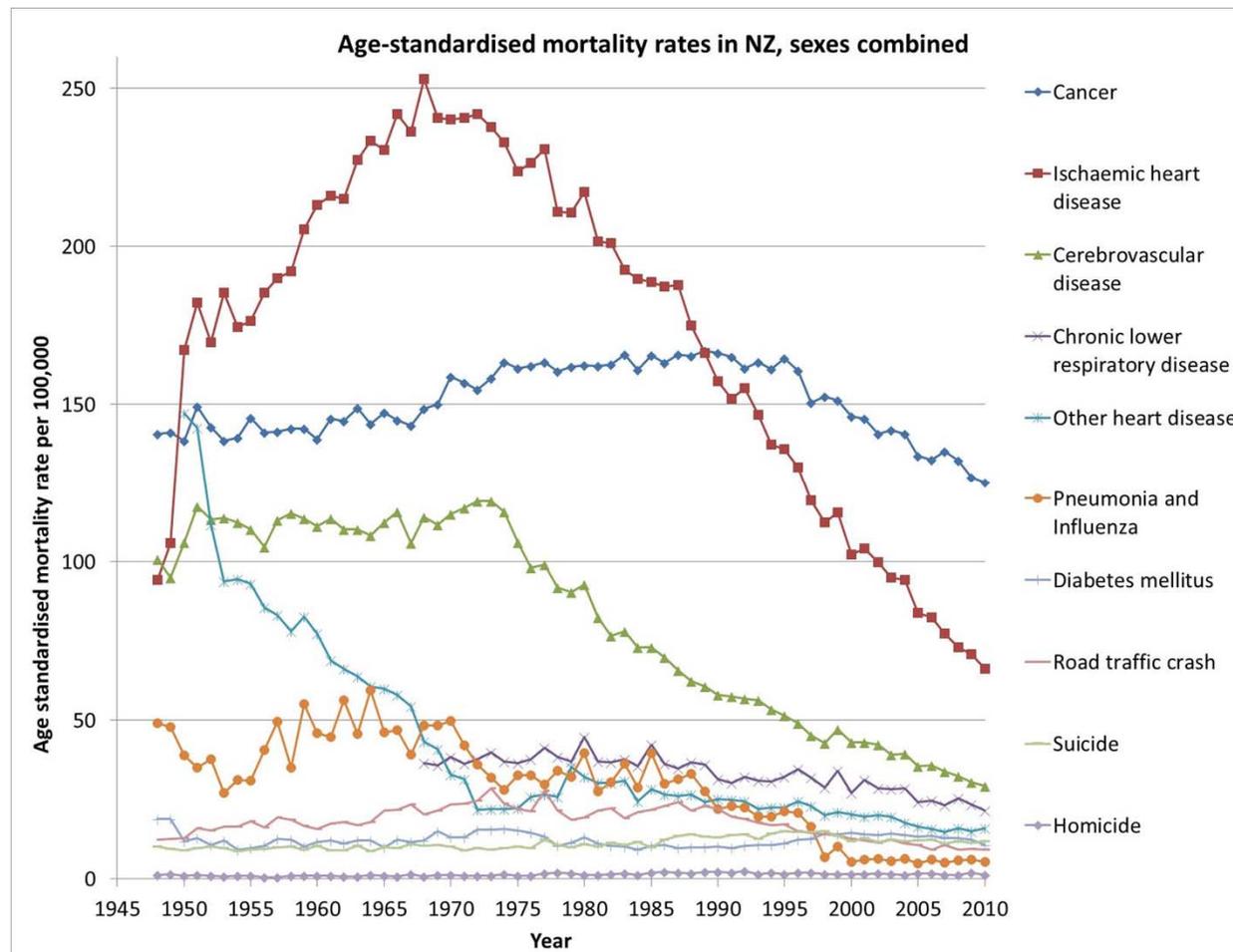


**2011: Ipilimumab shows overall survival benefit in melanoma**

**2012-2014: PD1 and PD-L1 blockade has benefit in melanoma and lung cancer**

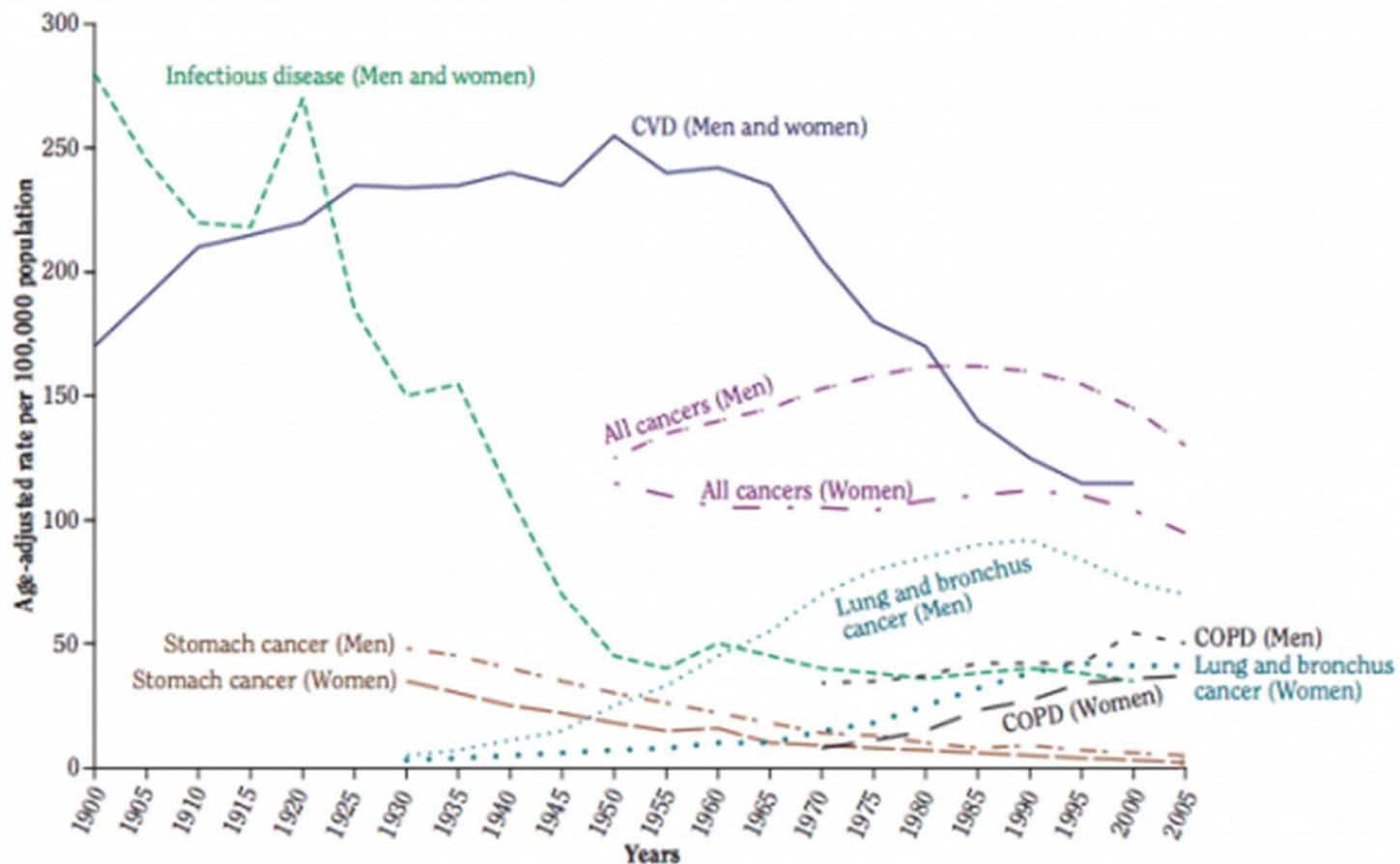
**2011-2014: CAR-modified T cells show durable remissions in leukemia**

# Advances in Health Care: Cardiac Mortality vs Cancer Mortality



# Advances in Health Care: Cardiac Mortality vs Cancer Mortality

Figure 4.1 Mortality rates for major diseases in the United States, 1900–2005



Source: Infectious disease and CVD rates from Cutler et al. 2006. Age-adjusted rates for stomach, lung, and bronchus cancer from American Cancer Society 2009. Age-standardized rate for all cancers from World Health Organization Mortality Database 2012.

# The Case for Cancer Immunotherapy

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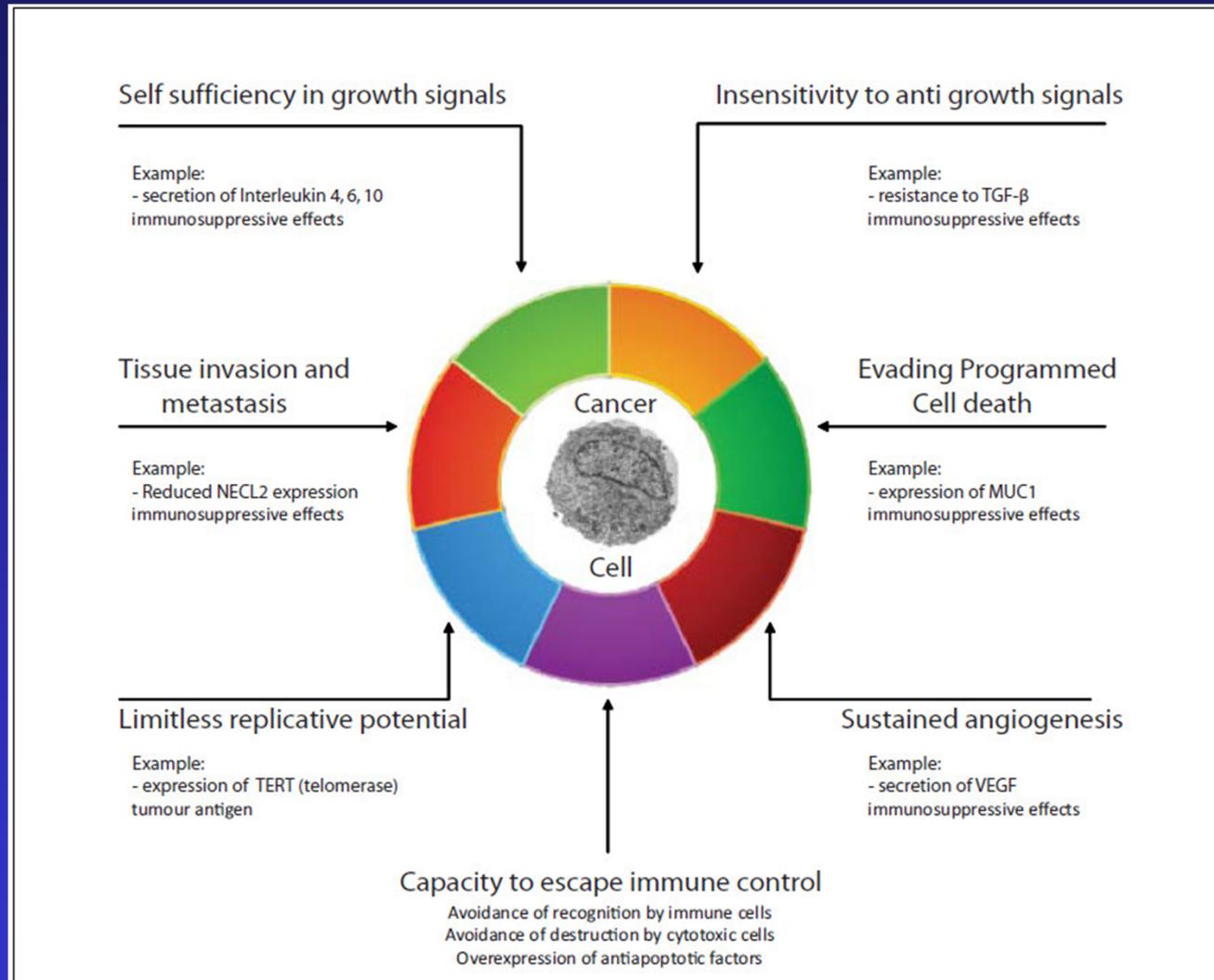
- No new truly curative anticancer cytotoxic drugs or targeted therapies developed in the last 20 yrs
  - Too many escape routes?
- The immune response is designed to identify and disable “escape routes” that cancers employ
- Immunotherapy can cure cancers

News » Breakthrough of the Year 2013

# Breakthrough of the Year 2013



# Hallmarks of Cancer: Immune Escape and Tolerance

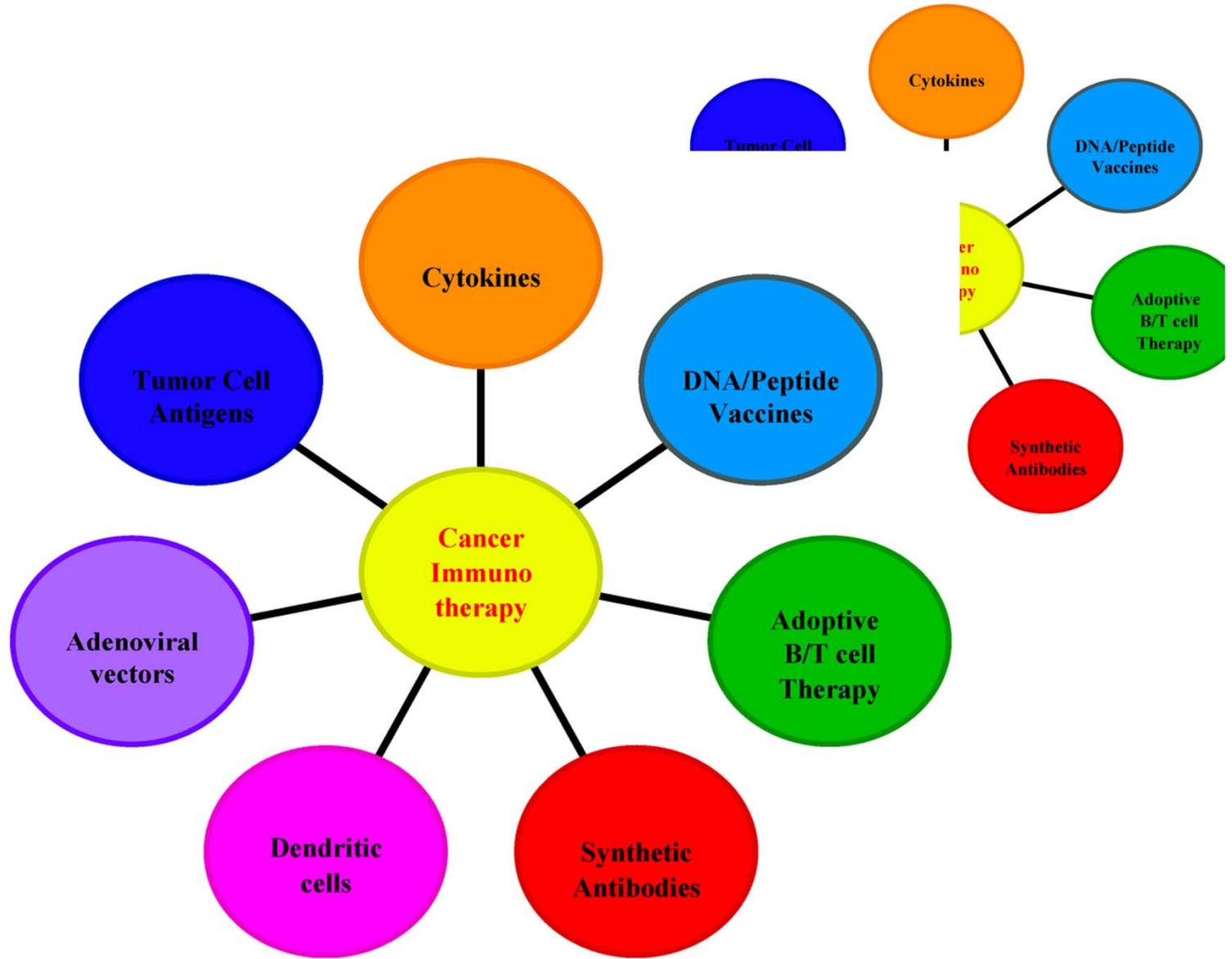


Tesniere, et al. *Discovery Med* (2009)  
Hannahan and Weinberg. *Cell* (2000)

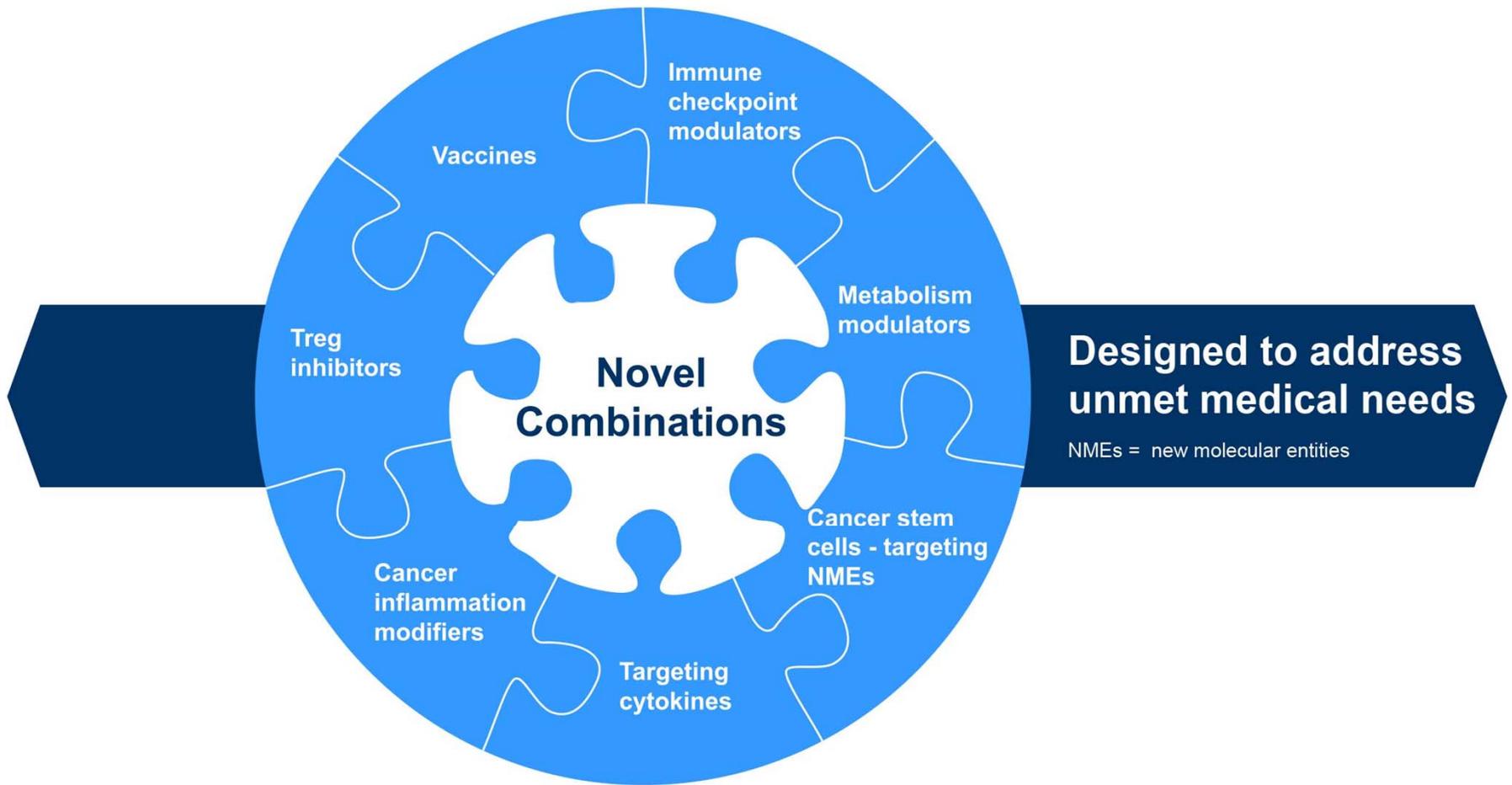
# HISTORY OF CANCER TREATMENT MODALITIES

	<b>SURGERY</b>	<b>RADIATION</b>	<b>CHEMO-THERAPY</b>	<b>TARGETED DRUGS</b>	<b>IMMUNO-THERAPY</b>
<b>APPROACH</b>	Cut out accessible tumor cells to stop growth and prevent their spread	Use highly concentrated X-rays or radioactive isotopes to kill cancerous cells	Use cytotoxic drugs to kill or inhibit cancer cells	Interfere with a mechanism required for, or that supports tumor growth	Support the immune system's innate ability to recognize and eliminate tumor cells
<b>SINCE</b>	1800s	early 1900s	late 1940s	2000s	2010s
<b>LIMITATIONS</b>	Many inaccessible tumors ineligible; limited effectiveness if tumor has already begun to spread	Limited effectiveness if tumor has already begun to spread; potentially dangerous for tumors near vital organs	High toxicity and often does not destroy the whole tumor, leading to high rates of recurrence	Limited tumor types eligible; high efficiency but short durability driving high rates of recurrence	Applicable to all tumors at all stages of disease including metastatic tumors; responses are highly durable; potential for lower toxicity profiles; synergistic with other treatments

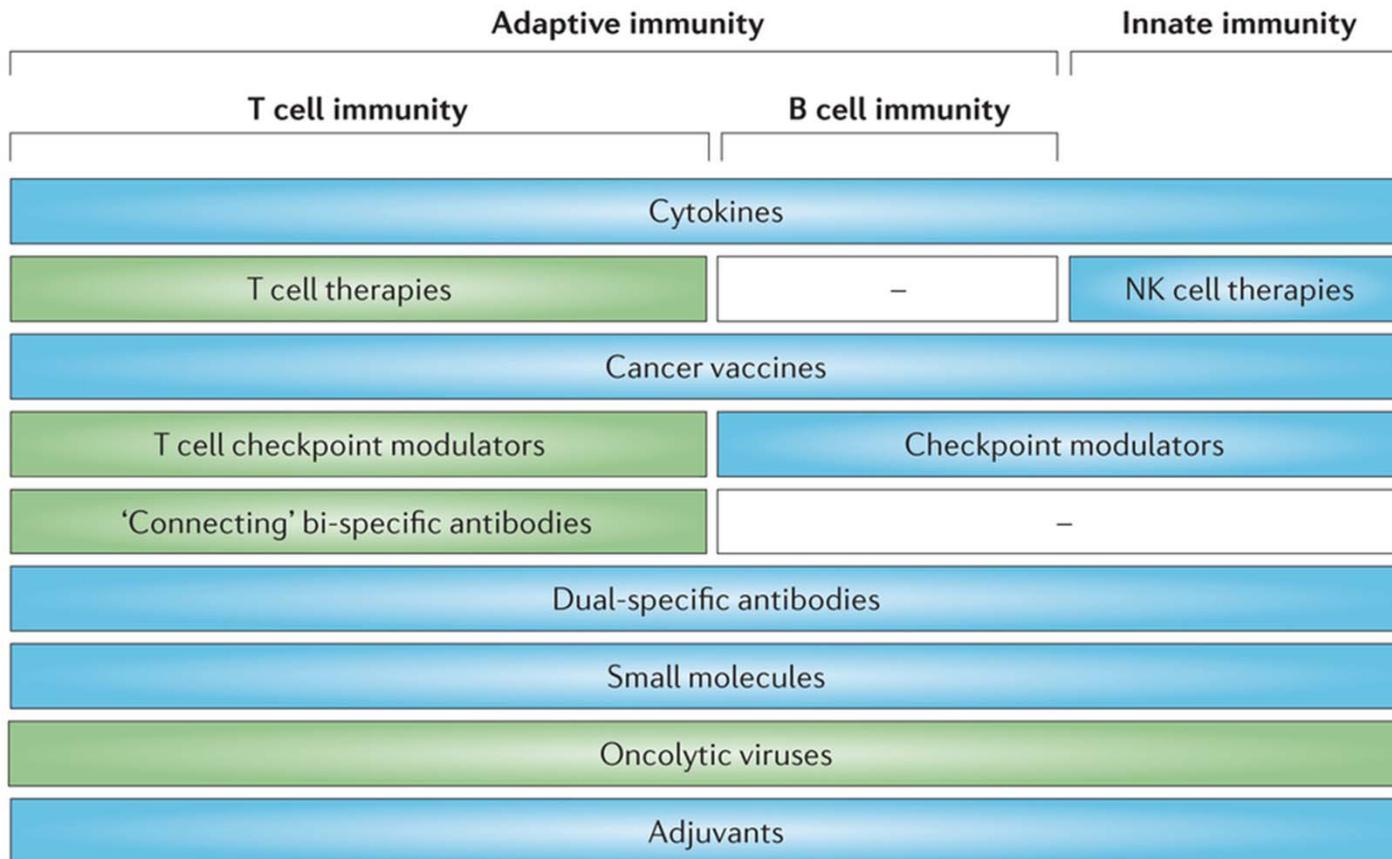
# Personalized Medicine



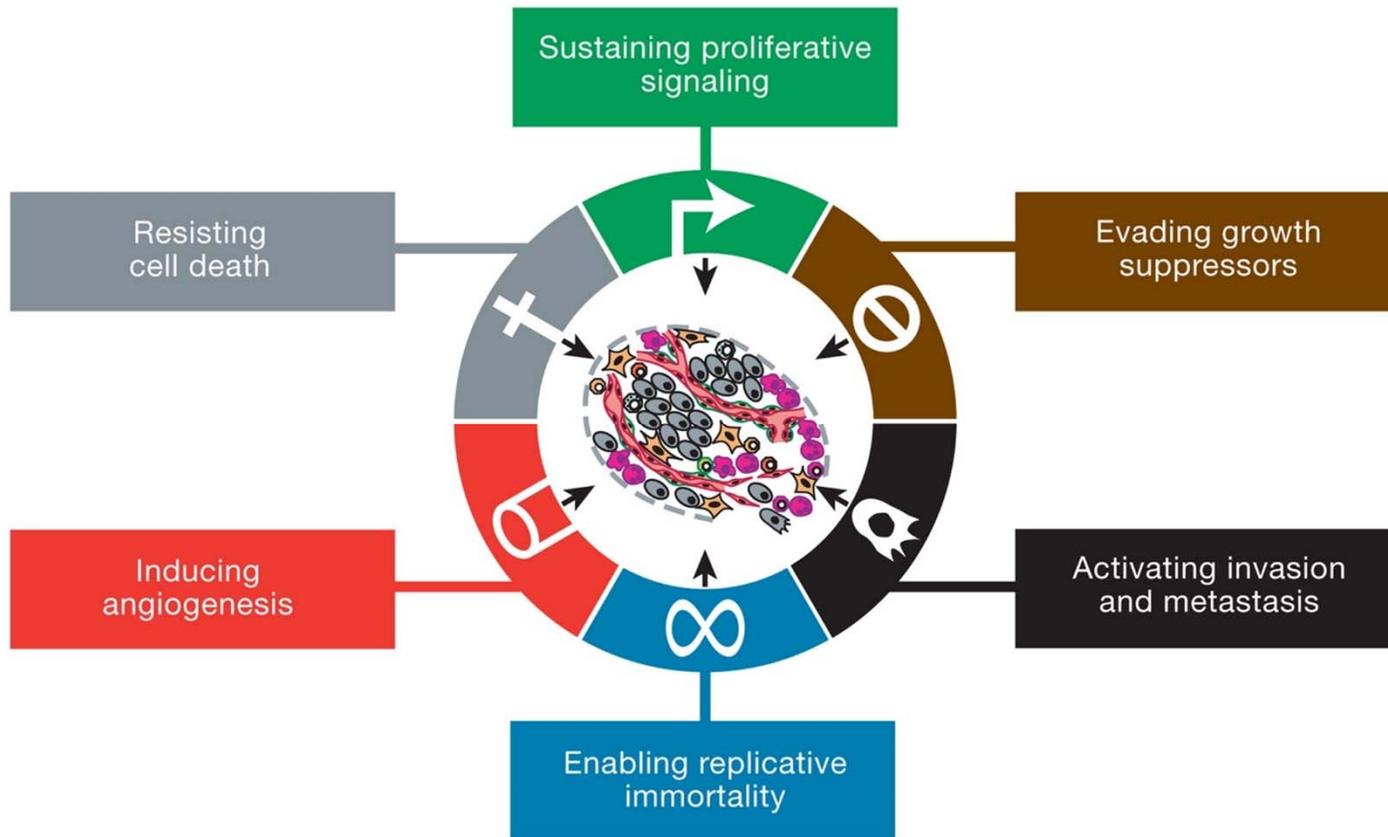


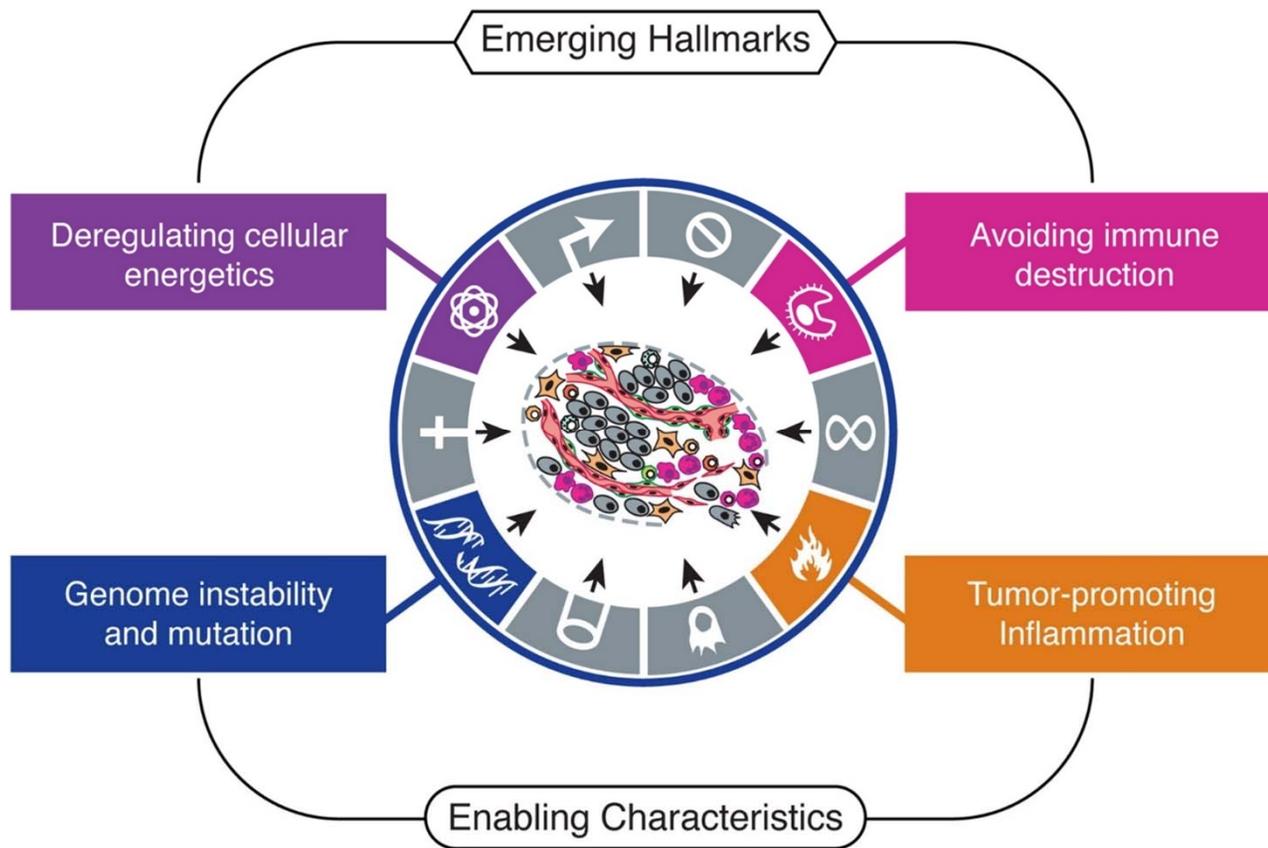


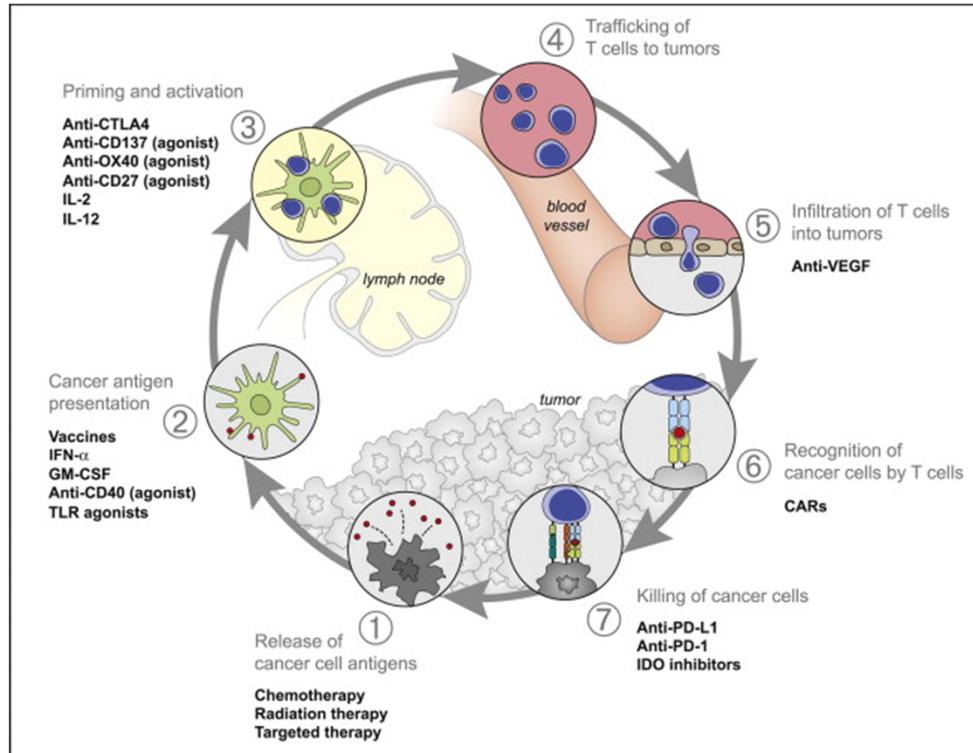
<http://www.ionc.com/mashup/>

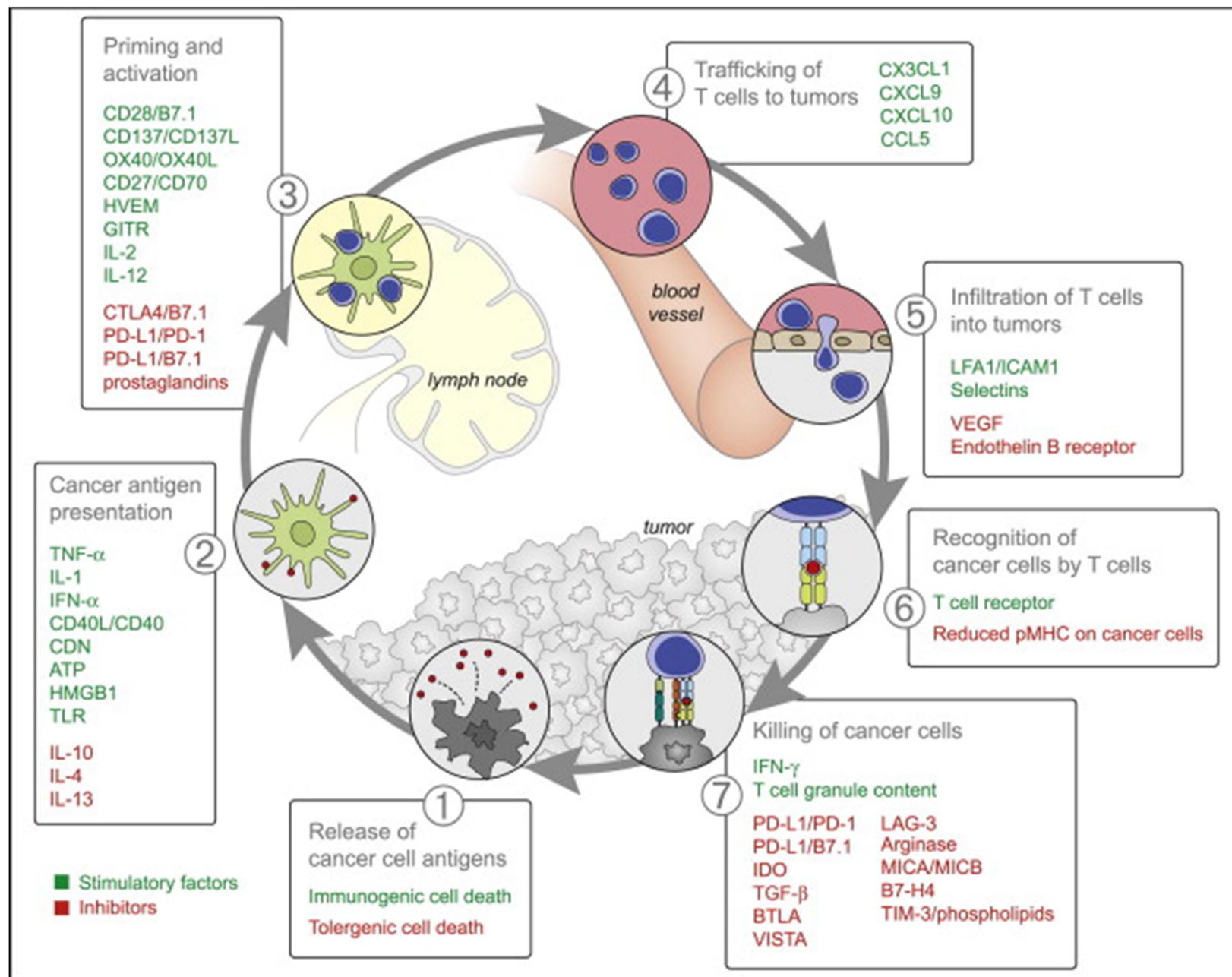


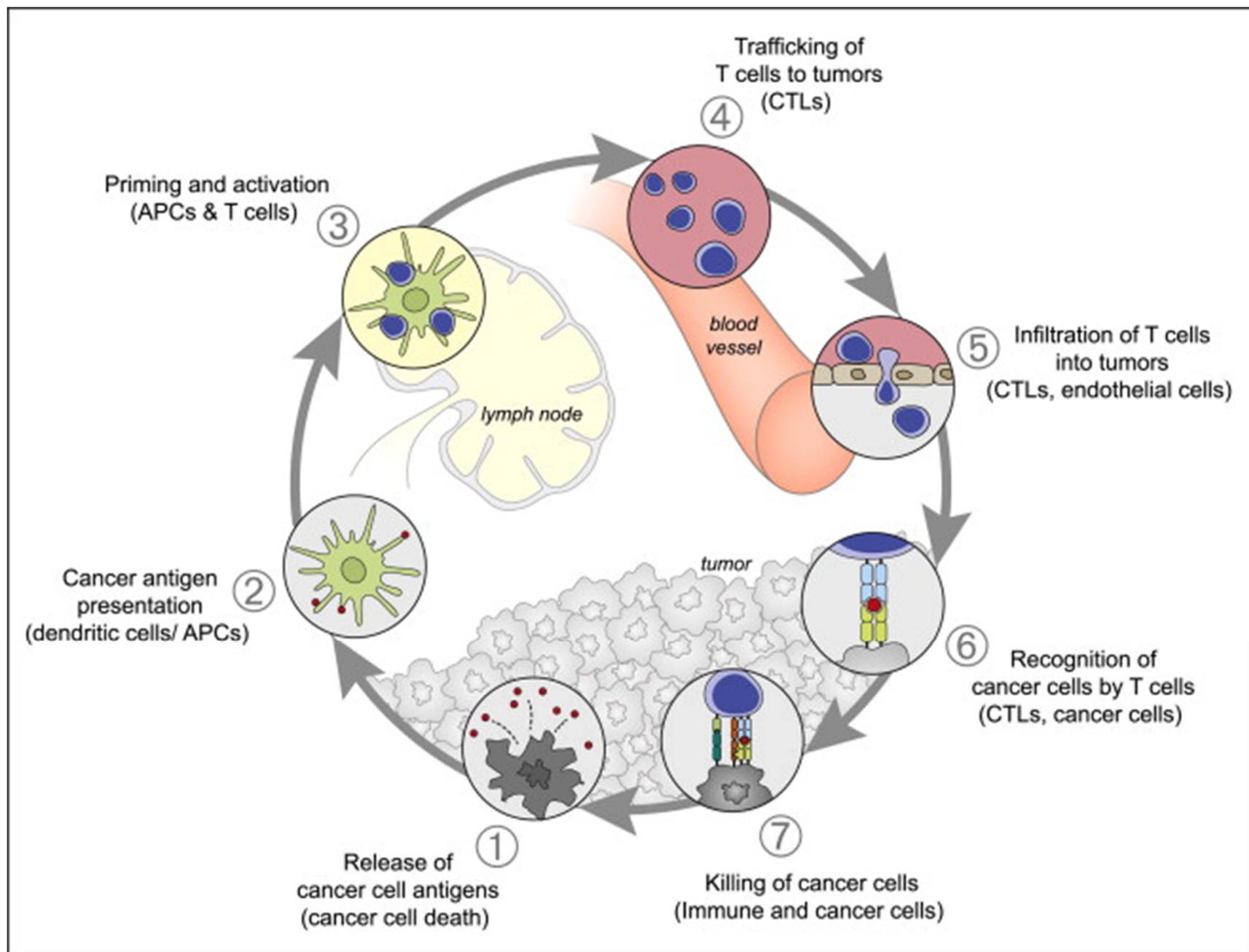
■ Clinically validated modalities through approved therapies  
■ Modalities under investigation











# The Flexner Report [1910]

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*"...The curse of medical education is the excessive number of schools. The situation can improve only as weaker and superfluous schools are extinguished." Abraham Flexner, 1910*

In a muckraking style, Flexner revealed the discrepancies between school catalogue descriptions of courses and clinical opportunities and the realities of medical training in schools throughout the nation. Flexner argued strongly for placement of medical education within the structure of American universities, away from strict control of practitioners, and he emphasized the need to close substandard schools. For Flexner, the desired ideal was truly academic training, with clinical teaching in close geographical association with university science departments.

MEDICAL EDUCATION  
IN THE  
UNITED STATES AND CANADA

A REPORT TO  
THE CARNEGIE FOUNDATION  
FOR THE ADVANCEMENT OF TEACHING

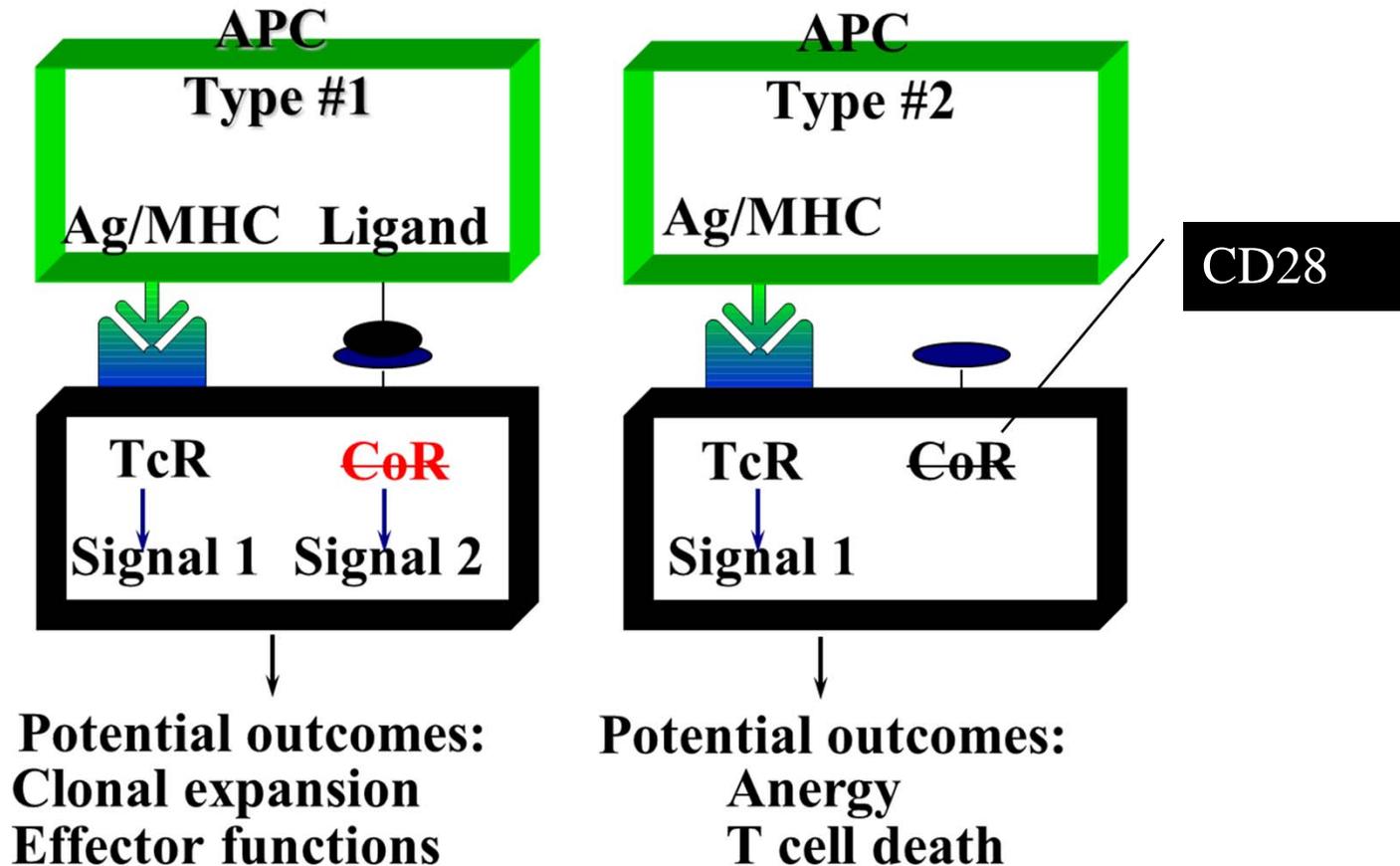
BY  
ABRAHAM FLEXNER

WITH AN INTRODUCTION BY  
HENRY S. PRITCHETT  
PRESIDENT OF THE FOUNDATION

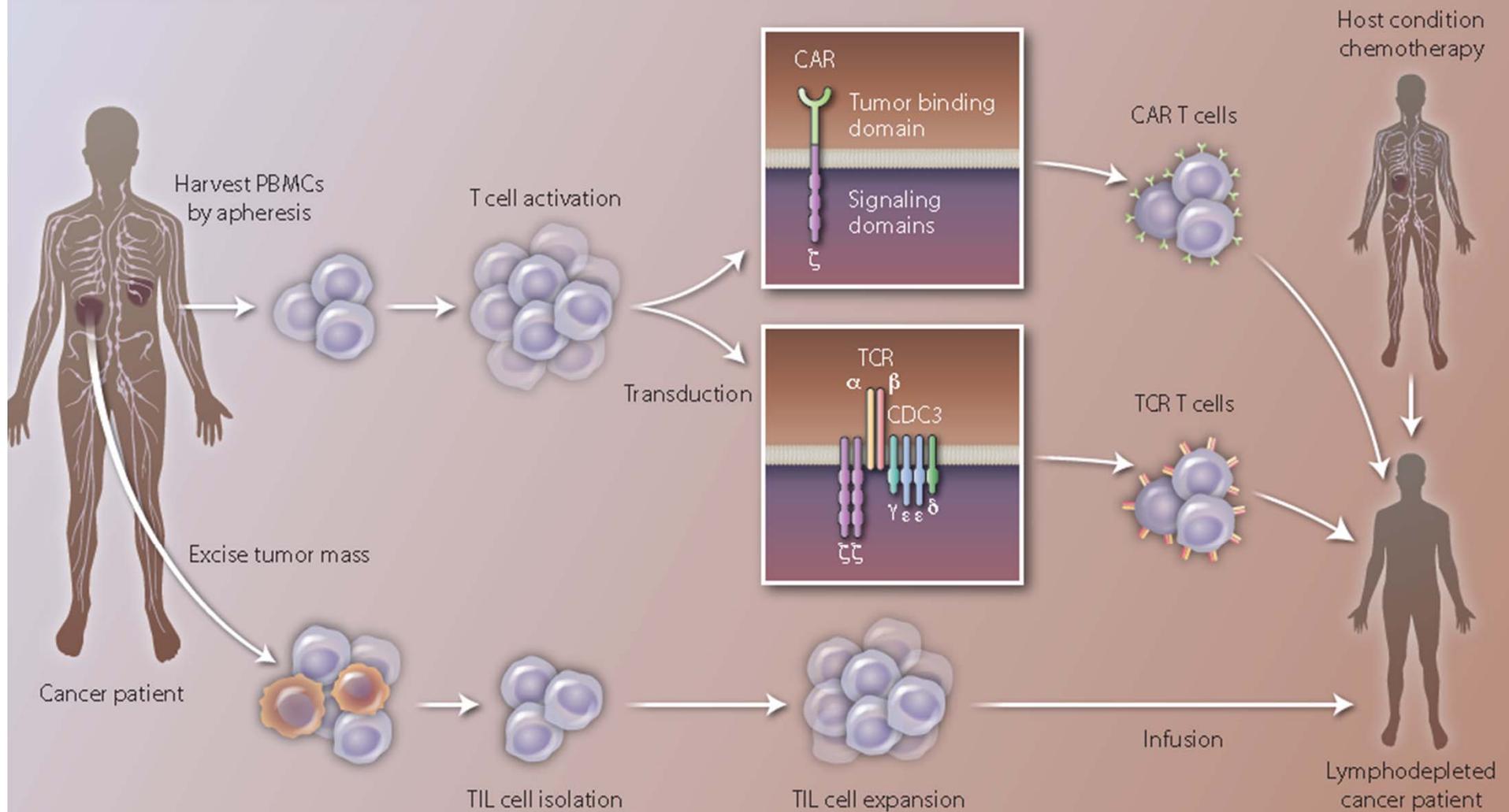
BULLETIN NUMBER FOUR

576 FIFTH AVENUE  
NEW YORK CITY

# CD28 Family of Receptors Control Immunologic Tolerance: 1995



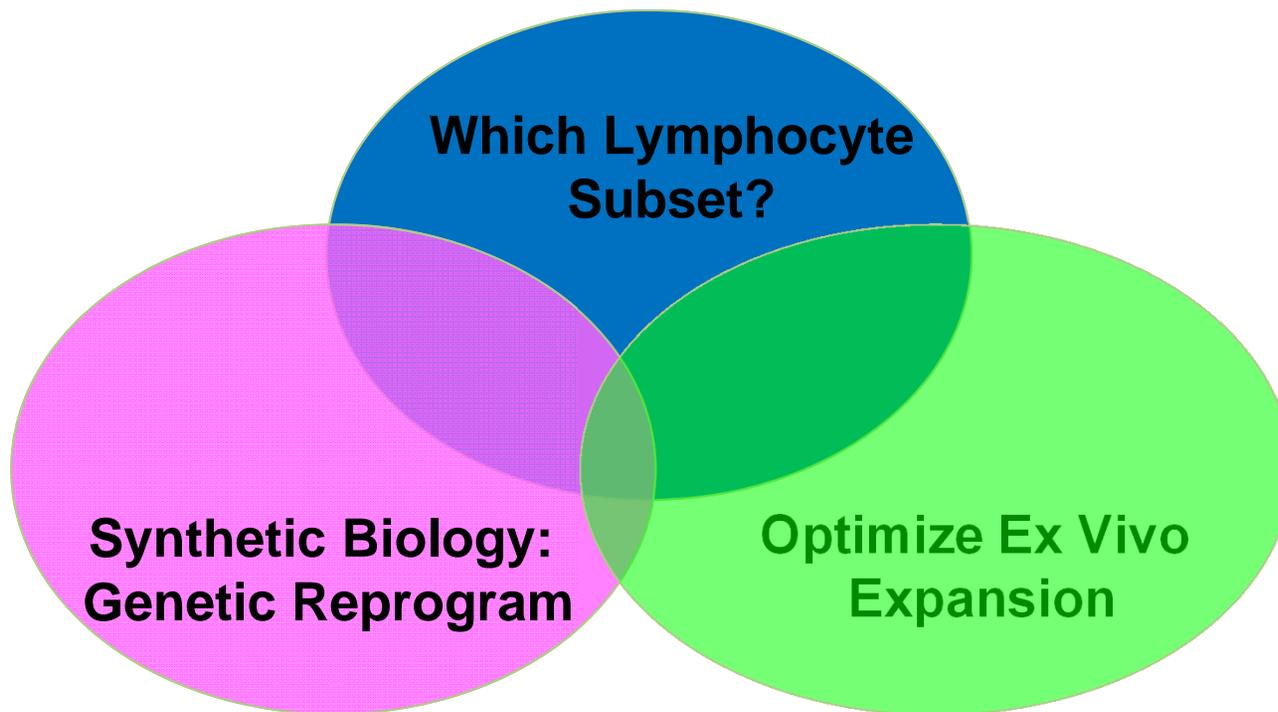
# Adoptive Cell Therapy: 3 Approaches in Advanced Development



Science Trans Med, 2015

# Essential factors for augmenting adoptive immunotherapy

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# Synthetic biology: “putting the immune system on steroids”

- ◆ An emerging interdisciplinary field with the common approach of **manipulating or engineering properties of biological systems** from biological ‘parts’ or synthetic components **to create functions or systems not found in nature.**
- ◆ **For the Biomedical researcher:**  
An approach and set of tools to improve our knowledge of biological systems and engineer novel therapies.
- ◆ Examples:
  - “artificial life (Craig Ventner),
  - bacteria producing biofuels,
  - CAR T cells!

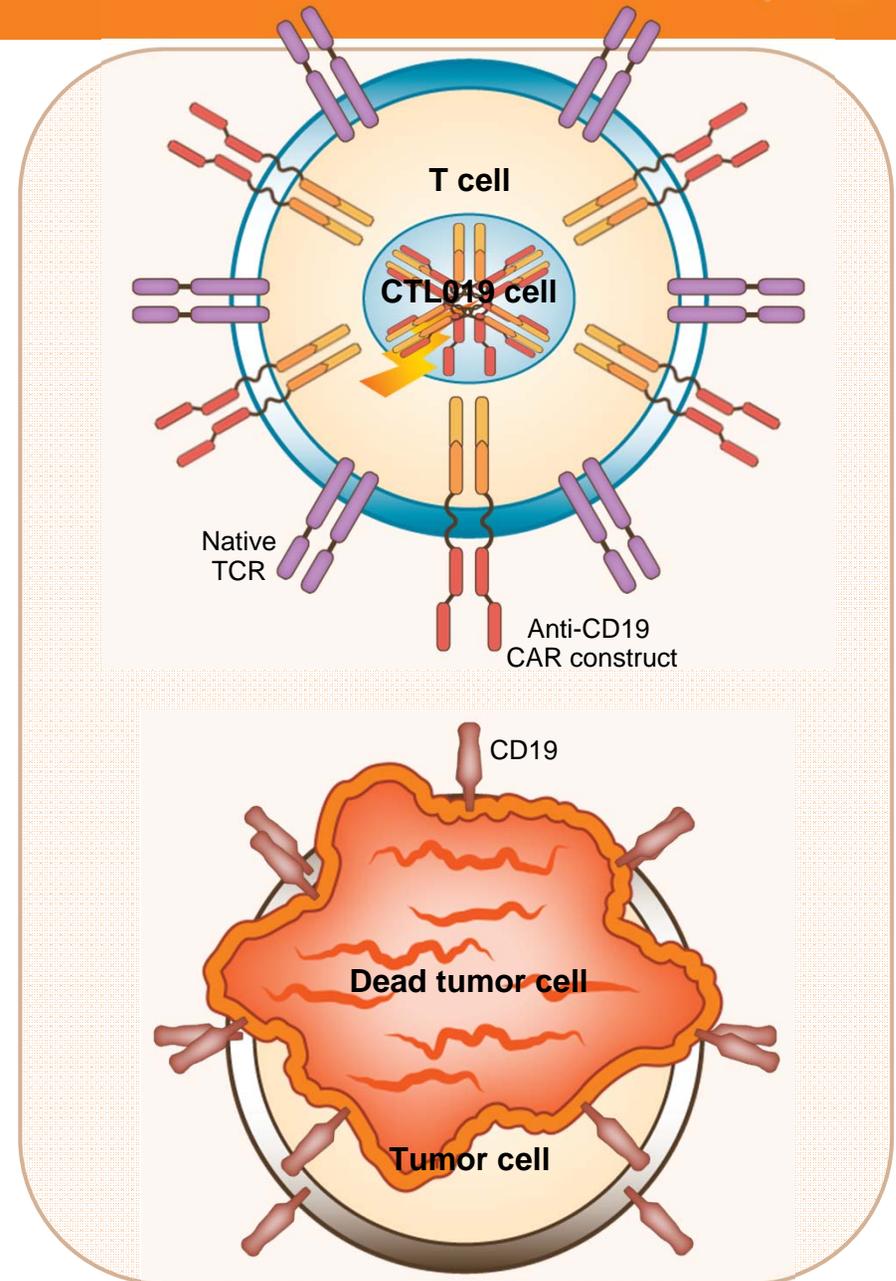


*Pigs Might Fly*

– Damien Hirst

# CAR T cells: personalized “serial killer” cells

- Gene transfer technology is used to stably express CARs on T cells, conferring novel antigen specificity<sup>1,2</sup>
- CART19 therapy takes advantage of the cytotoxic potential of T cells thereby killing tumor cells in an antigen-dependent manner<sup>1,3</sup>
- Persistent CART19 cells consist of both effector (cytotoxic) and central memory T cells<sup>3</sup>
- T cells are non-cross resistant to chemotherapy
- Responses are cytolytic: no swelling!



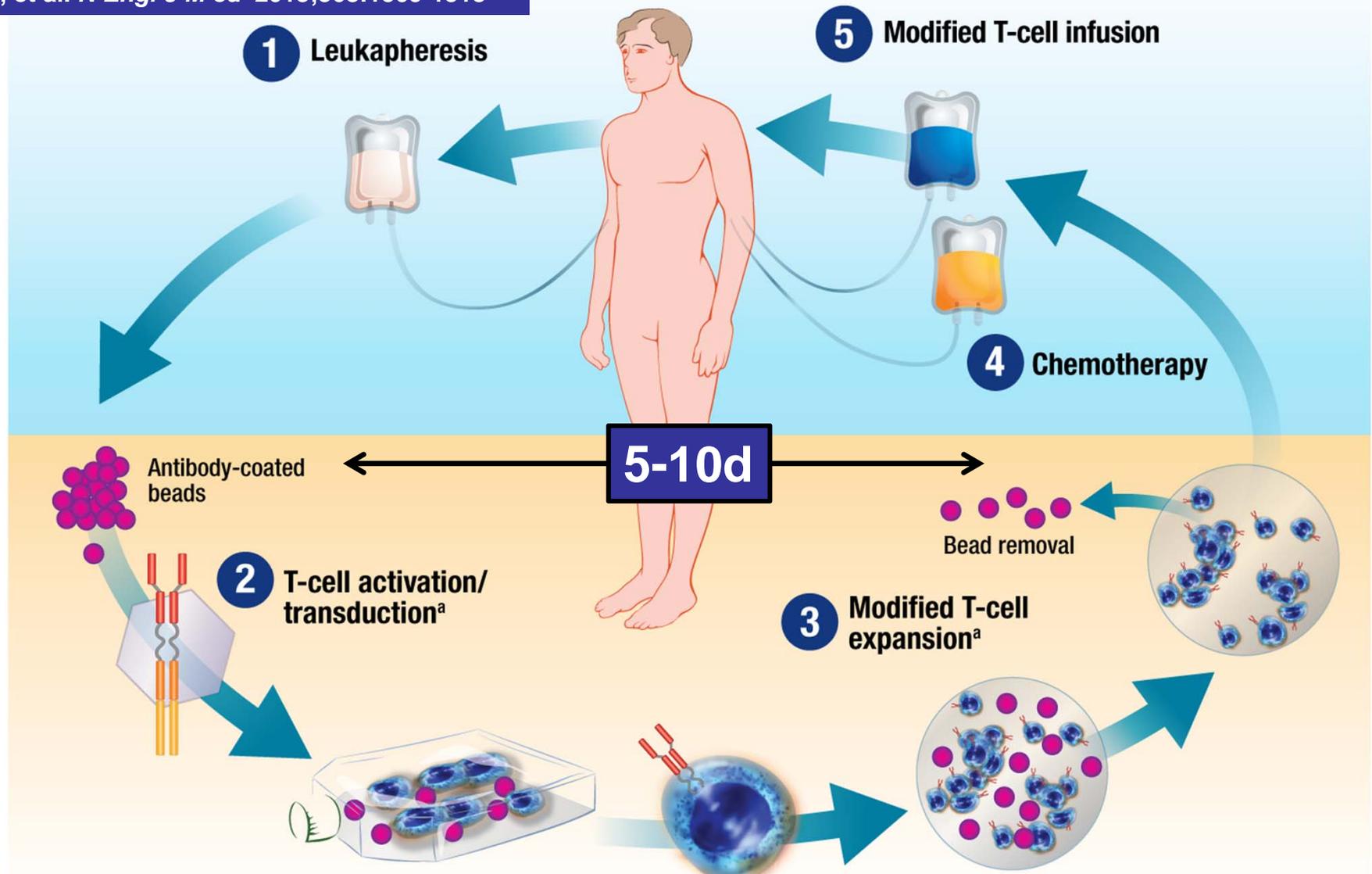
1. Milone MC, et al. *Mol Ther.* 2009;17:1453-1464.
2. Hollyman D, et al. *J Immunother.* 2009;32:169-180.
3. Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73.

# Adult Chronic Leukemia Study Overview\*

Porter DL, et al. *N Engl J Med.* 2011;365(8):725-733

Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73

Grupp S, et al. *N Engl J Med.* 2013;368:1509-1518

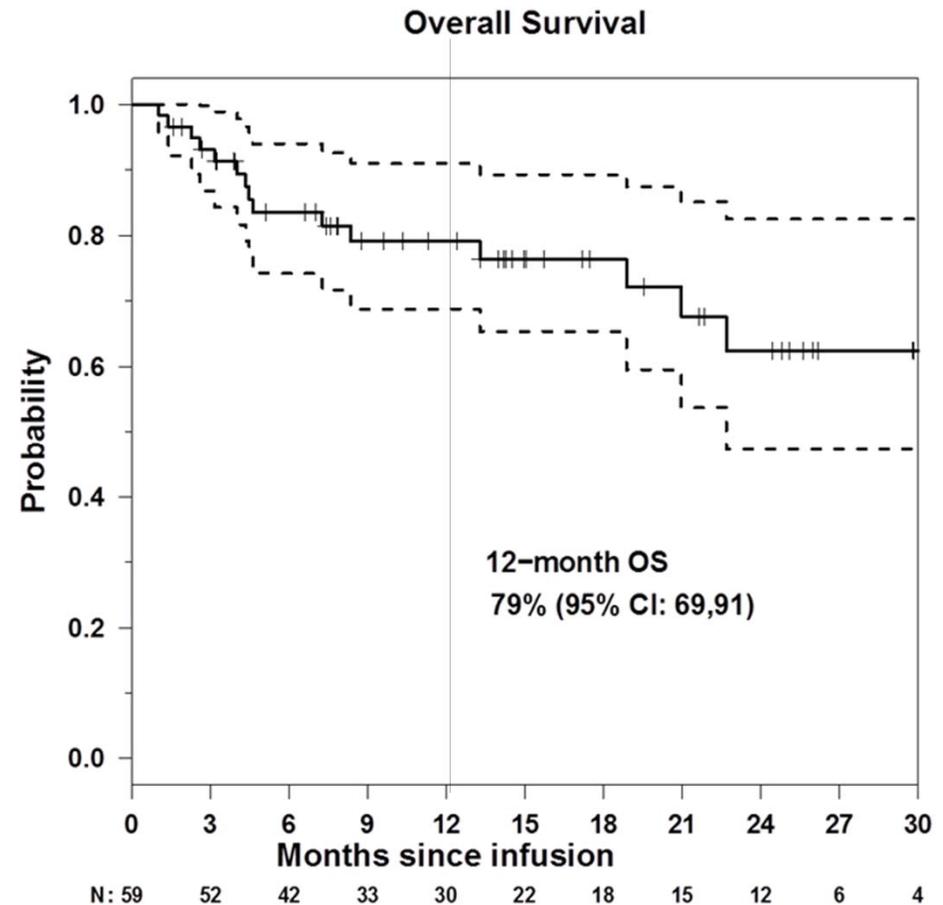


\* [ClinicalTrials.gov #NCT01029366](https://clinicaltrials.gov/ct2/show/study/NCT01029366)

# 93% CR rate for r/r ALL after CTL019

>200 patients with CLL, ALL, NHL, MM have gotten CTL019

- 59 r/r pediatric ALL pts:  
55 in CR at 1 mo (93%)
- 6 went to subsequent transplant
- 6-month RFS: 76%
- No relapses past 1 year
- 13 patients in remission beyond 1 year,  
10 without further therapy





Please excuse  
Emily from  
school — she was  
with me!

A handwritten signature in black ink, which appears to be "Barack Obama", written in a cursive style.

THE PRESIDENT

# Some of Dr Grupp's Pediatric Leukemia Patients



# Feb 2016

“The goal of this initiative — this ‘Moonshot’ — is to seize this moment. To accelerate our efforts to progress towards a cure, and to unleash new discoveries and breakthroughs for other deadly diseases.” Vice President Biden



Vice President Biden listens to Penn president Amy Gutmann at the Abramson Cancer Center. Looking on are doctors Bruce L. Levine (center, left) and Carl H. June. JOSEPH KACZMAREK / AP, Pool

## At Penn, Biden sets cancer ‘moonshot’

By Don Sapatkin  
STAFF WRITER

Vice President Biden met with scientists at the University of Pennsylvania’s Abramson Cancer Center Friday afternoon, officially launching his “moonshot” quest to cure cancer.

“We’re on the cusp of phenomenal breakthroughs,” Biden said, adding that President Obama would be issuing an executive order that would get every federal agency involved in the effort.

Biden asked the researchers to educate him on the challenges and possibilities of genome-based discoveries of the last several years, particularly a type of immunotherapy that has been pioneered by Penn researcher Carl H. June.

Just last month, researchers from Penn and Children’s Hospital of Philadelphia, led by June, announced that an experimental cell therapy that boosts the immune system continues to produce  
See **CANCER** on A2

### In Sunday’s Health Section

Precision medicine, such as the immunotherapy innovations Vice President Biden discussed at Penn on Friday, is transforming cancer diagnosis and treatment. Find out how these discoveries are already helping patients, and where their promise lies.

# Determine Efficacy and Safety of CTL019 in Pediatric Patients With Relapsed and Refractory B-cell ALL (ELIANA)

Stephan Grupp, Children's Hospital of Philadelphia

Stella Davies, Cincinnati Children's Hospital

Christian Capitini, University of Wisconsin

Ted Laetsch, Children's Medical Center of Dallas

Doug Myers, Children's Mercy Kansas University

Enelda Nemecek, Oregon Health & Science University

Krysta Schlis, Stanford University

Michael Verneris, University of Minnesota

Alan Wayne, Children's Hospital Los Angeles

Gary Yanik, University of Michigan

Paul Martin, Duke University

Francoise Mechinaud, Royal Children's Hospital (Australia)

Henrique Bettencourt, Hospital St. Justine (Canada)

# Lessons Learned

long term attention span

incorporate new technologies

stubbornness: do what you believe!

patients accept “on target” toxicity

details matter: small changes in experimental  
approach can lead to large changes in  
outcome

Sometimes luck is a major component of  
success

Study patient outliers

You can have a career in Immuno-Oncology!

# Pharma and Biotech Take on CAR T cells

- Penn-Novartis Alliance for CAR T cells. August 2012
- Joe Jiminez CEO: "I've told the team that resources are not an issue. Speed is the issue". May 2014
- FDA awards "breakthrough designation" to UPENN for CART19. July 2014



# CAR's in Clinical Development



**Commercial CARs: Autolus/UCL, Bellicum, BioNTech, CBMG, Cardio3→Celyad, CARSGen, Celgene/Bluebird, Collectis/Servier/Pfizer, Cellular Therapeutics Ltd, Juno/Opus, Kite/Amgen, Mustang/COH, Novartis, Sorrento/Conkwest, Takara, Transposagen/J&J/Janssen, TheraVectys, Unum, Intrexon/Ziopharm . . .**

<b>Academic Institute (US)</b>	<b>Target(s)</b>
Baylor College of Medicine	CD19, GD-2, Her2, CD30, kappa Ig
FHCRC	CD19, CD20, ROR1
MD Anderson Cancer Center (MDACC)	CD19
Memorial Sloan Kettering)	CEA, mesothelin, PSMA
National Cancer Institute (NCI)	CD19, CD22, CSP4, GD-2, EGFRvIII , mesothelin, VEGFR2
University of Pennsylvania	CD19, CD123, BCMA, mesothelin, cMet, EGFRvIII
<b>Academic Institute (non-US)</b>	<b>Target(s)</b>
Chinese PLA General Hospital	CD19, CD20, CD33, CD138, HER2
Christie Hospital NHS Foundation Trust	CD19
Peter MacCallum Cancer Centre, Australia	LewisY
University of Zurich	FAP

# CAR Trials: A special thanks

## CVPF

Bruce Levine

Zoe Zheng

Alexey Bersenev

Andrea Brennan

Julio Cotte

Elisabetta Cribioli

Chris Nowaczyk

Hima Patel

Suzanne Pavluk

Tamara Tripic

## TCSL

Jos Melenhorst

Simon Lacey

## PENN Medicine

David Porter

Noelle Frye

Marcela Maus

Stephen Schuster

Edward Stadtmauer

Alison Loren

Lynn Schuchter

Martin Carroll

Robert Vonderheide

Don Siegel

Saar Gill

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 The Children's Hospital  
of Philadelphia®

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Children's Hospital of  
Philadelphia

Stephan Grupp

David Barrett

Shannon Maude

**Patients and  
Families**



**The Leukemia &  
Lymphoma Society®**

*Fighting Blood Cancers*



Center for Cellular Immunotherapies



**NOVARTIS**