ADVANCES IN Cancer IMMUNOTHERAPY™

Basic Principles of Cancer Immunotherapy

Kunle Odunsi, MD PhD

ROSWELL PARK COMPREHENSIVE CANCER CENTER

AMERICAN ACADEMY OF EMERGENCY MEDICINE

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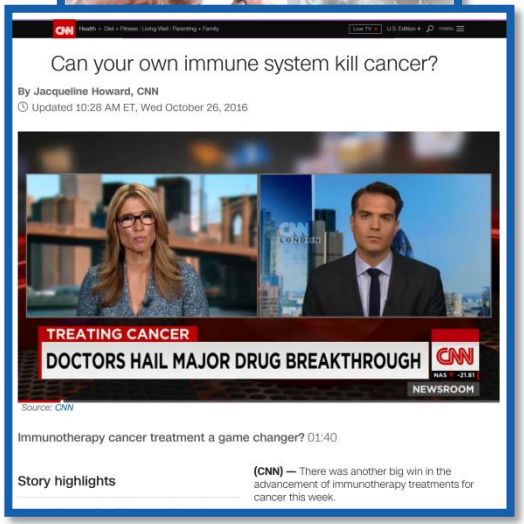
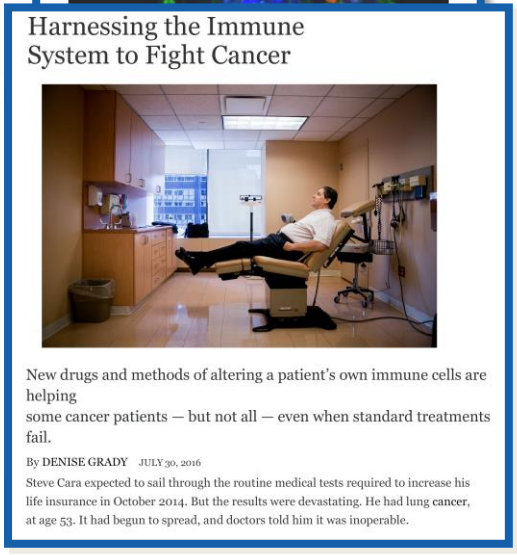
Disclosures

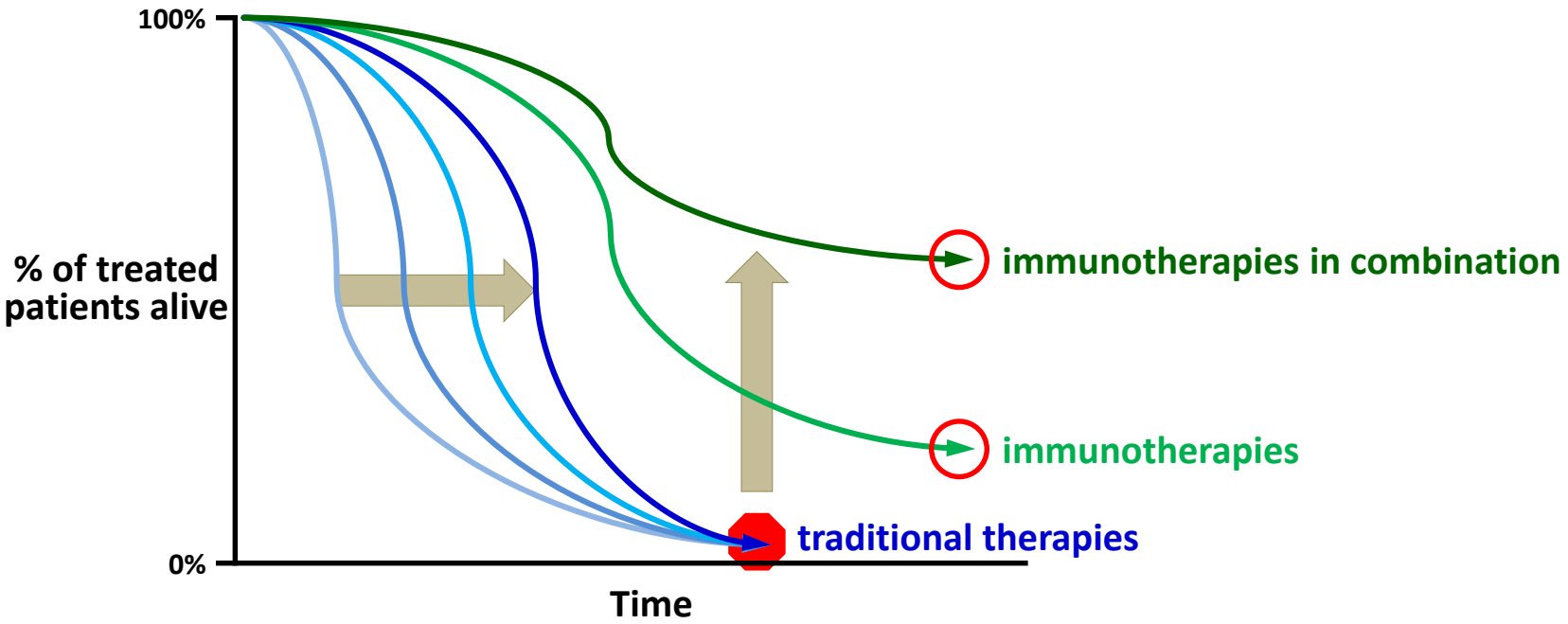
- No relevant financial relationships to disclose
- I will be discussing non-FDA approved indications during my presentation.

Immunotherapy is the new focus in oncology





Clinical outcomes of immunotherapy



Immunotherapies:

Patients with sufficient anti-cancer immunity achieve durable disease control.

Many lives are saved.

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Why does the immune system fail to eliminate cancer?

Cancer cells grow progressively
in immunocompetent hosts without evidence of
T cell exhaustion or systemic anergy.

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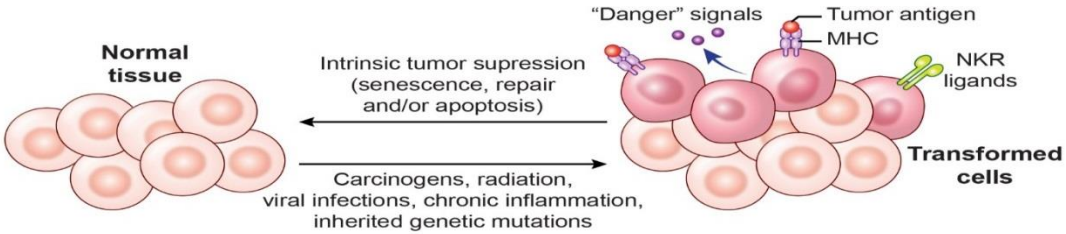
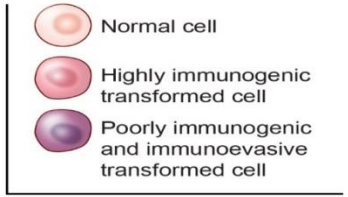
Cancer immunoediting: 3Es





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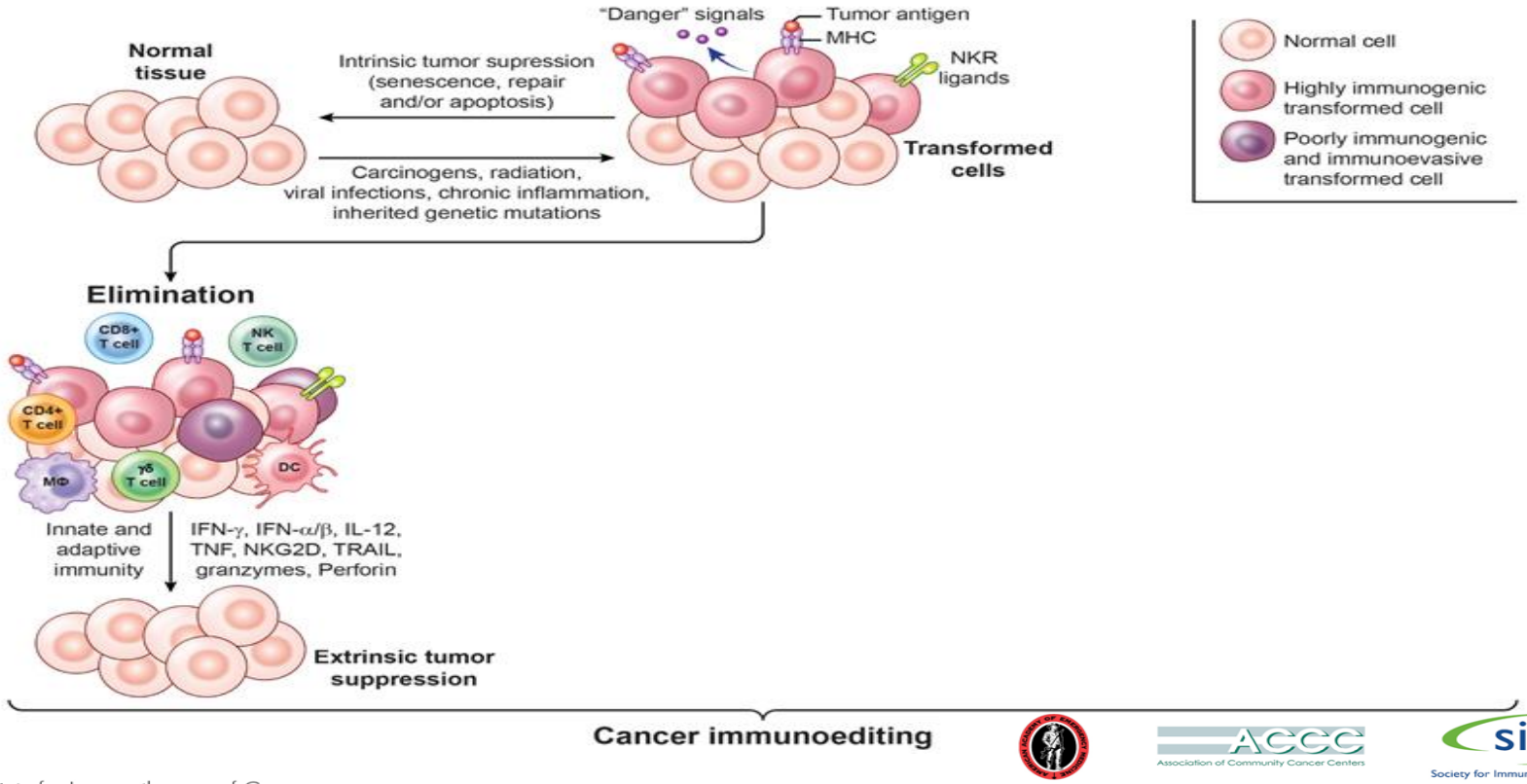
Cancer immunoediting



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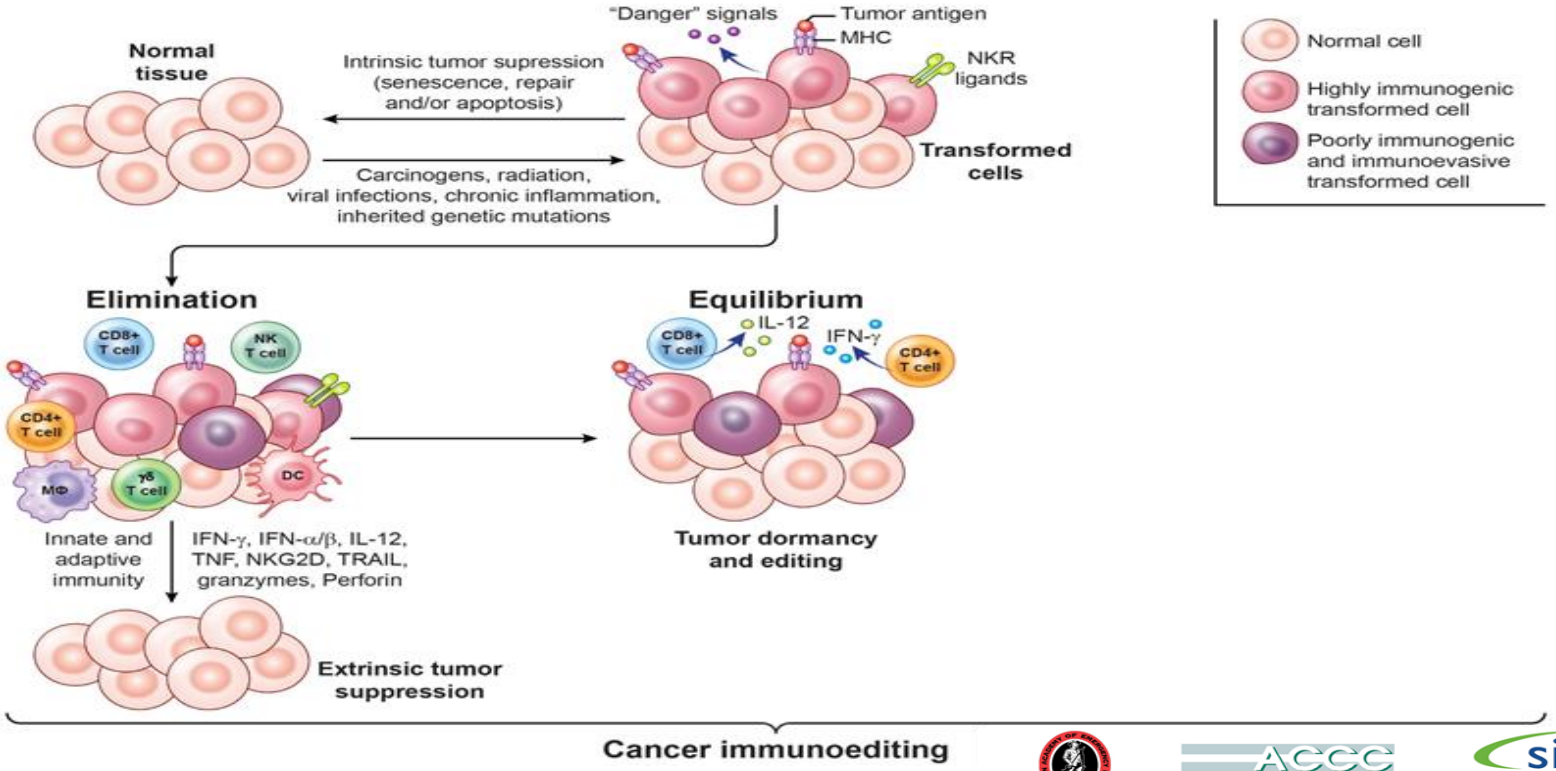
Cancer immunoediting



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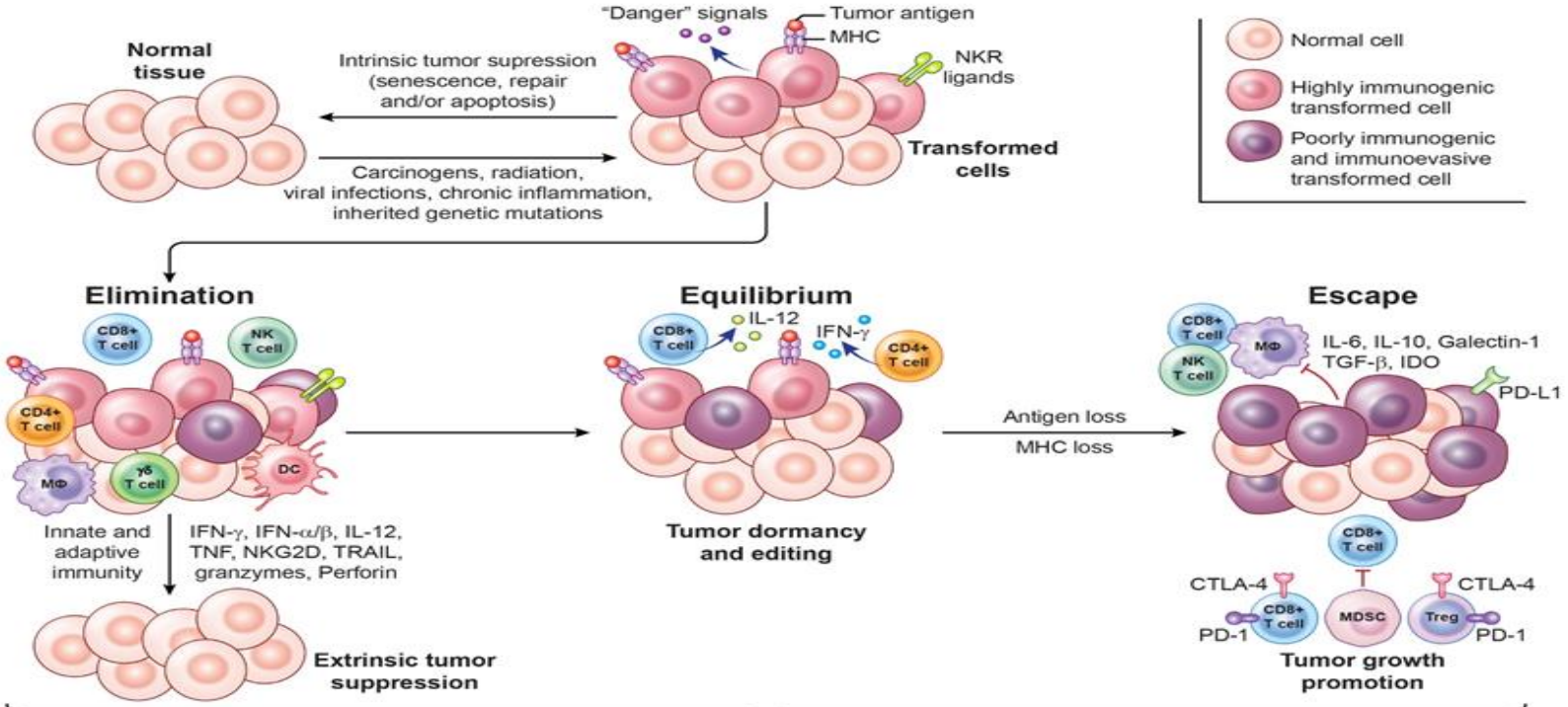
Cancer immunoediting



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To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.

The goal of immunotherapy, then, is to restore the capacity of the immune system to recognize and reject cancer.

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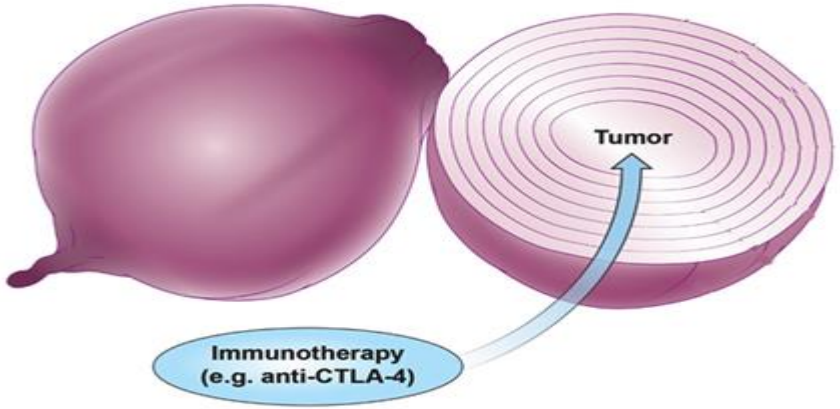
Multi-layered immunosuppression

- Tumors insulate themselves with dense layers of **immunosuppressive** stroma
- Overcoming the many layers of **interconnected and often functionally redundant immune suppressive mechanisms** represents a daunting challenge for tumor-specific T cells
- Immunotherapy can “peel back” the layers of local immune suppression, thereby **restoring the capacity of T cells** to eradicate the tumor



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Types of Immunotherapy

monoclonal antibodies

oncolytic virus

checkpoint blockade

adoptive T cell transfer

cancer vaccine

cytokine/immunomodulator

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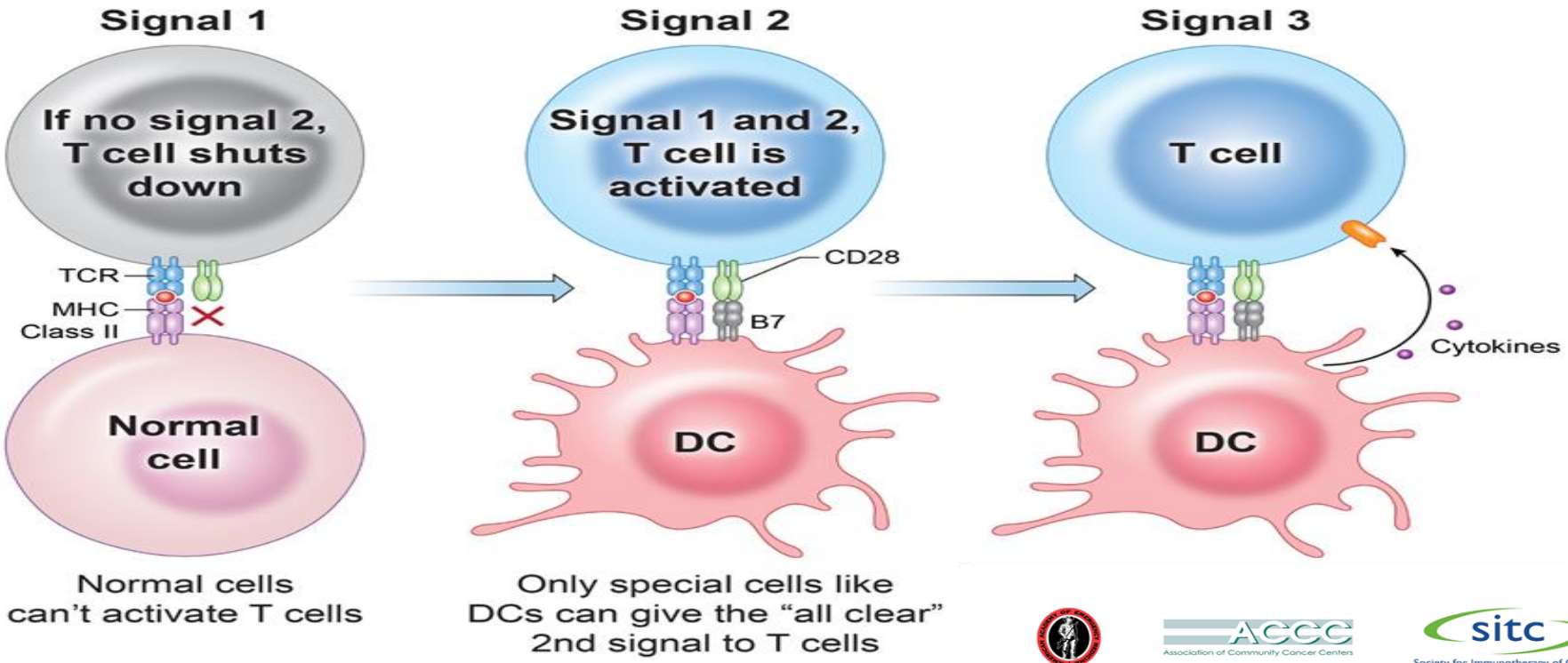
Signals for T cell activation



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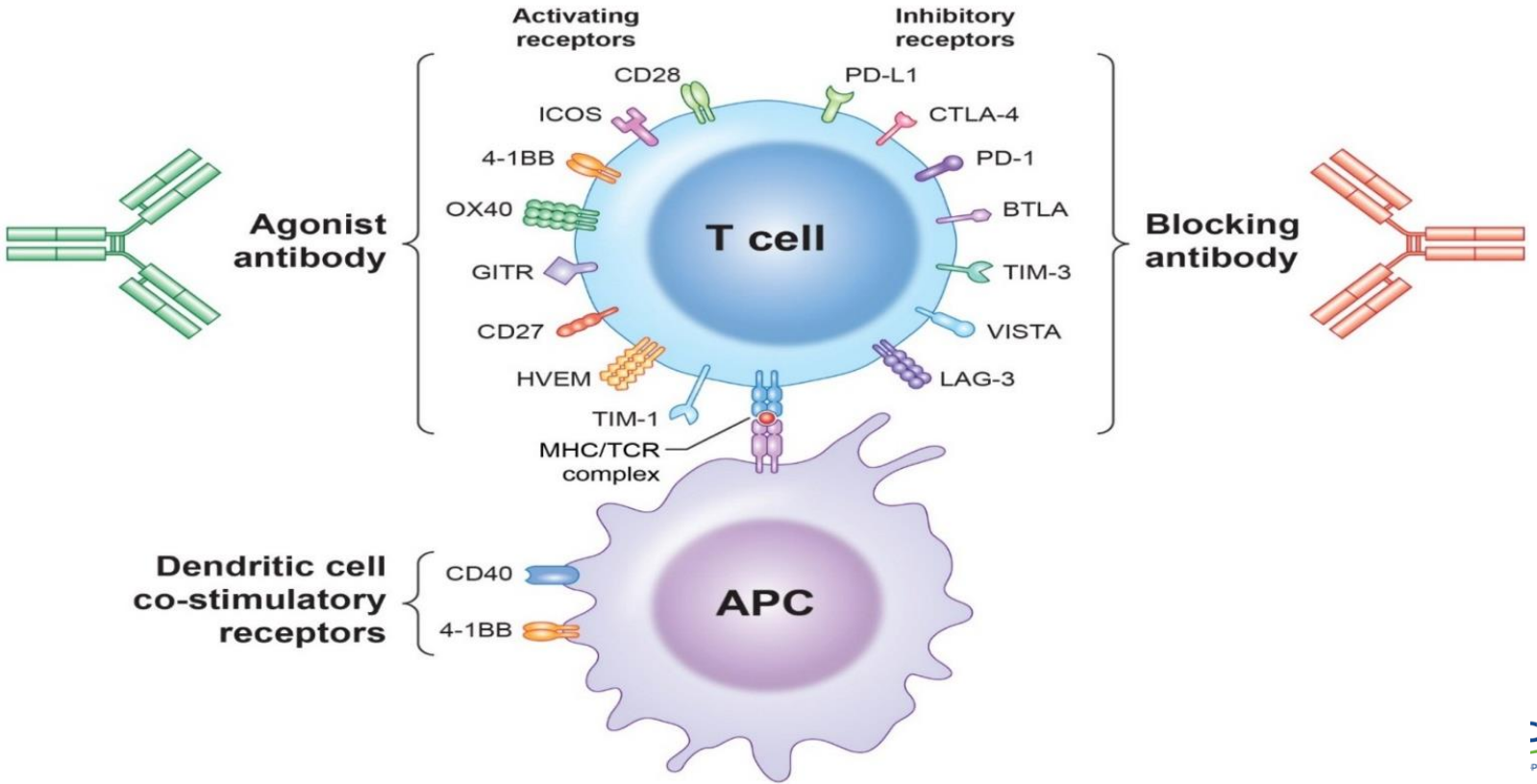
Checkpoint modulation



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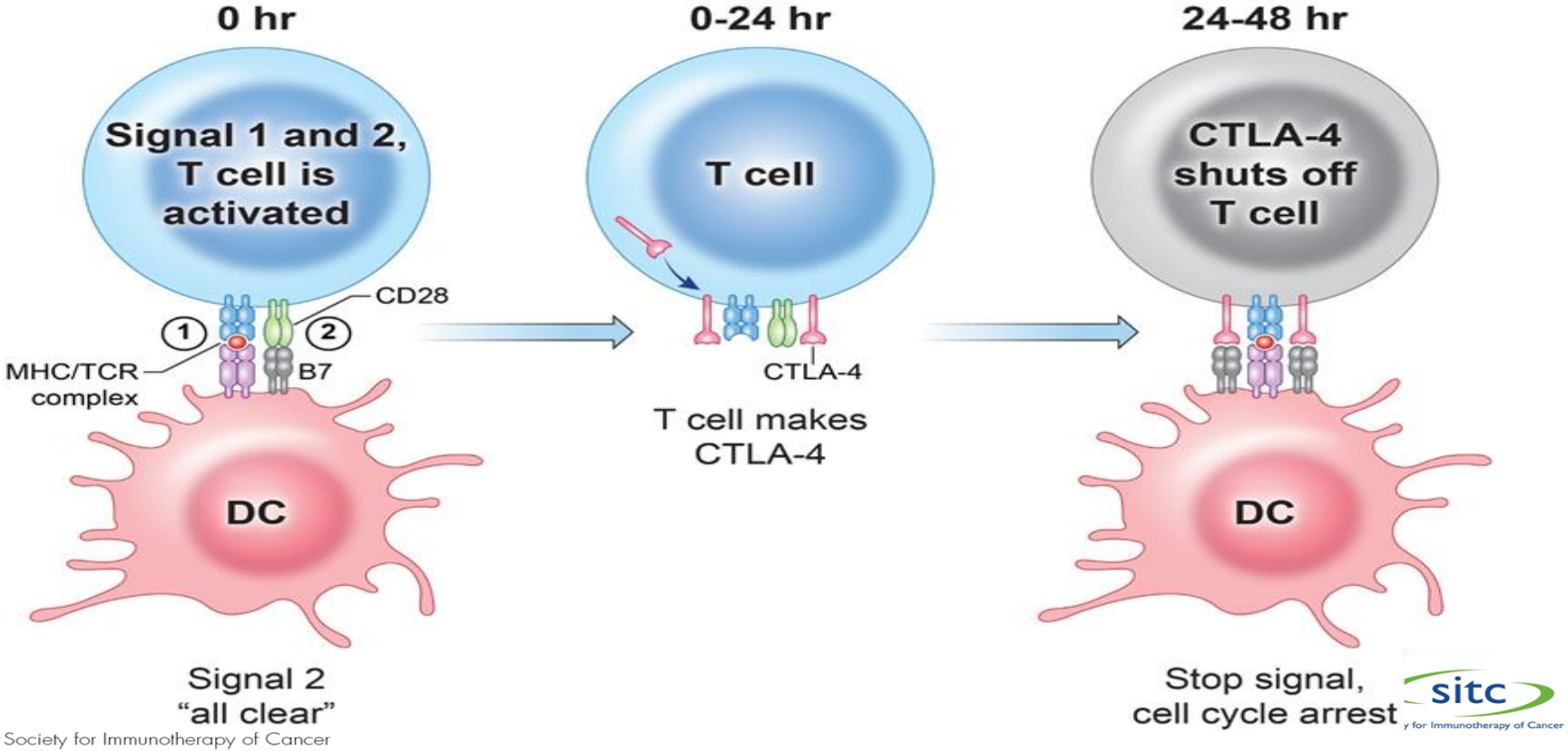
CTLA-4 limits the function of T cells



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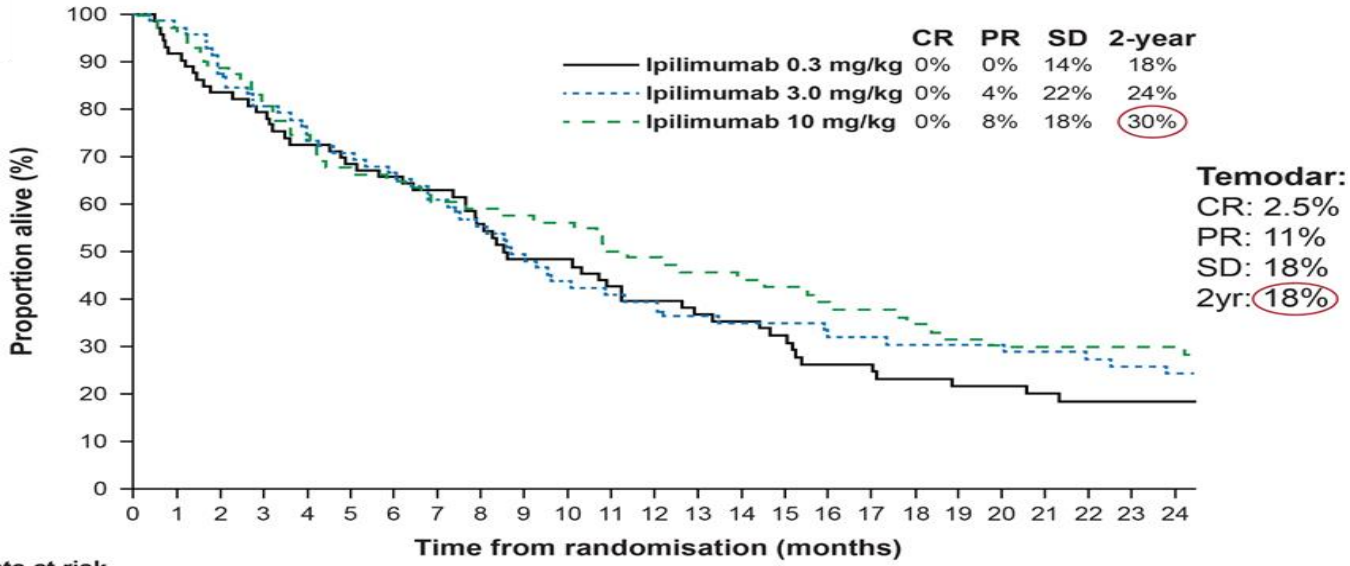
Ipilimumab (anti-CTLA-4) was approved for metastatic melanoma by FDA in 2010



Wolchok et al. 2010. Lancet Oncol.

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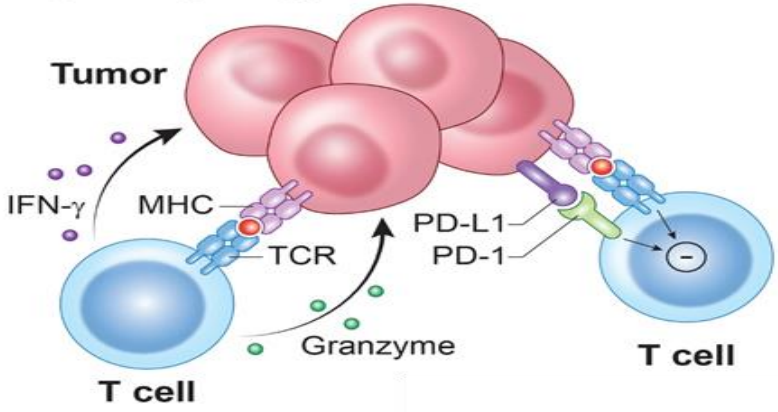
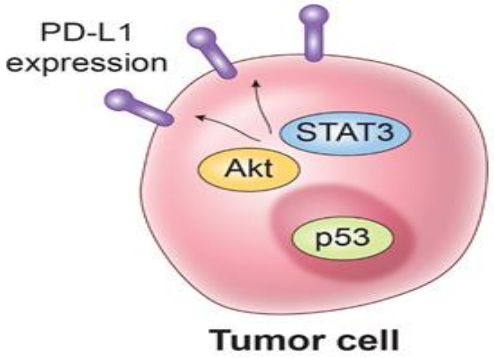
PD-1: PD-L1 inhibitory pathway

- PD-1 signaling promotes T cell tolerization by inhibiting downstream activation signals
- PD-1 expression is upregulated by activated and exhausted T cell populations
- T cell surface PD-1 receptor binds to and is activated by PD-L1 and PD-L2
- Many cells within the tumor microenvironment express PD-L1/PD-L2 allowing for the suppression of T cell activation
- Tumor PD-L1 expression is regulated via two general mechanisms:
  1. TIL production of IFN-γ
  2. Oncogenic signaling pathways





Francisco, L. et al. *Immunol Rev.* 2010. 236: 219.
Pardoll, D.M. *Nat Rev Cancer.* 2012. 12: 252.

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To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.

The goal of T cell checkpoint blockade is to make T cell “off-switches” inaccessible to tumor cells, thus restoring tumor-specific immunity.

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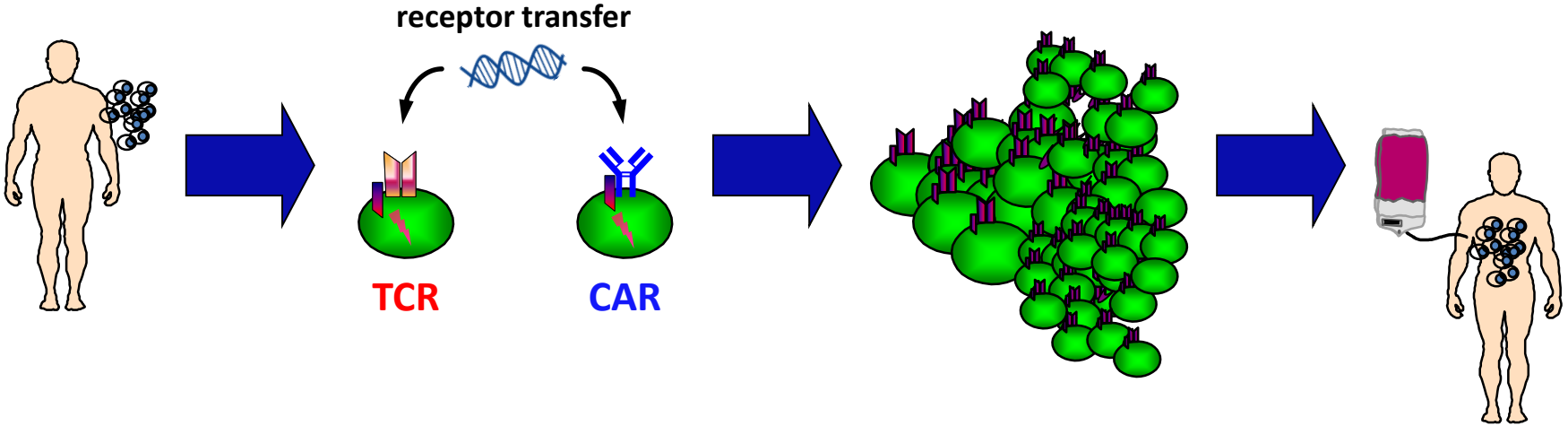
Generating T cells for adoptive transfer

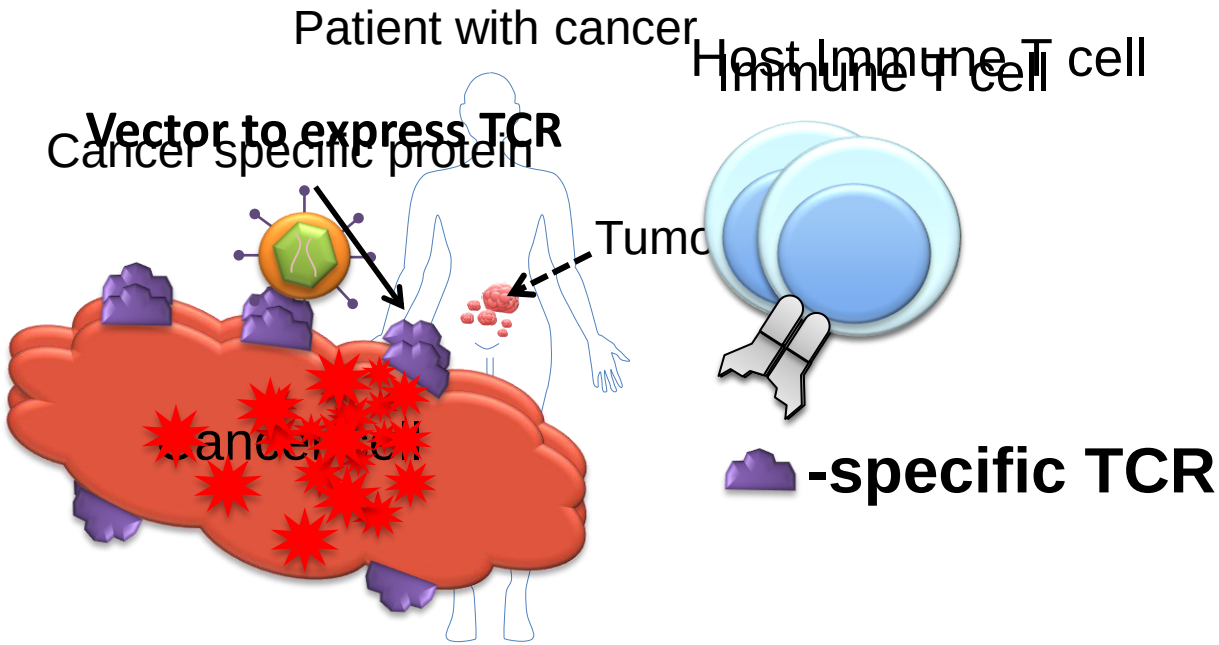


TCR = T cell receptor

CAR = chimeric antigen receptor

} recognize and destroy tumor cells

How do engineered T cells destroy tumors?



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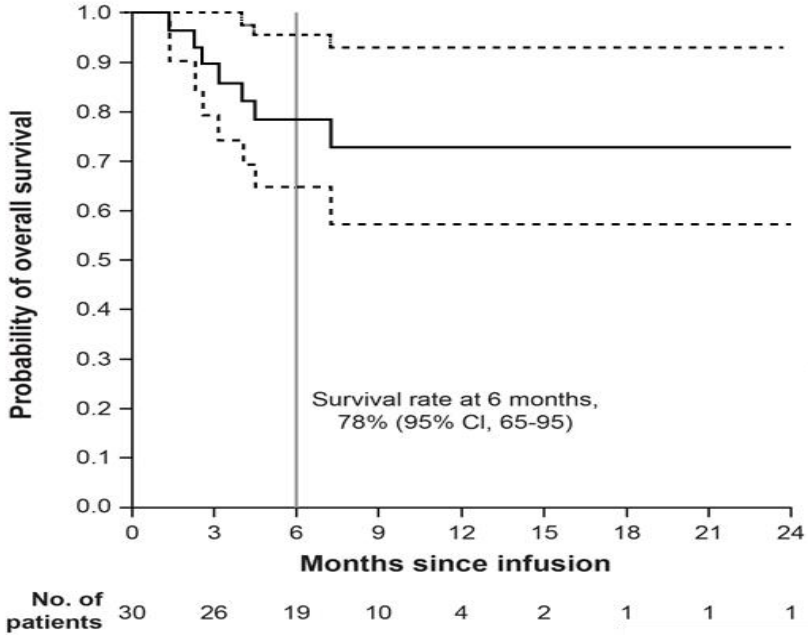
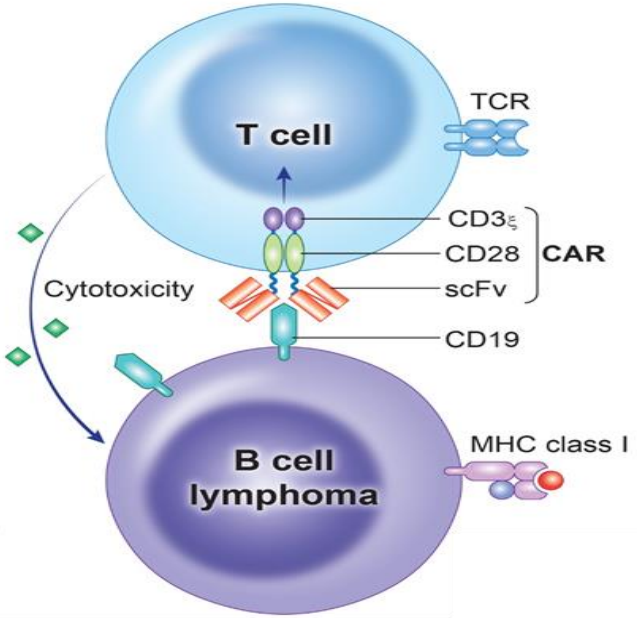
Effective treatment of relapsed B cell ALL with CD19 CAR T cell therapy



Maude S, Frey N, Shaw P, Aplenc R, Barrett D, Bunin N, Chew A, Gonzalez V, Zheng Z, Lacey S, et al. 2014. Chimeric antigen receptor T cells for sustained remissions in leukemia. The New England Journal of Medicine. 374(10): 998.



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Recent FDA approval for first engineered T cell

PARKER INSTITUTE
for CANCER IMMUNOTHERAPY

Novartis' Kymriah Wins FDA Approval as First CAR-T Cancer Therapy

Alex Philippidis
on August 30, 2017

The FDA today approved Novartis' Kymriah (tisagenlecleucel), with the agency hailing the chimeric antigen receptor T-cell (CAR-T) treatment as the first gene therapy to be available in the U.S.

BUSINESS INSIDER

A cancer treatment that one expert called the 'most exciting thing I've seen in my lifetime' just got approved

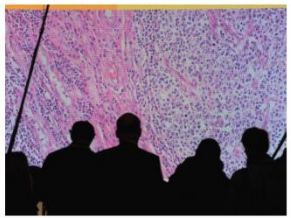
LYDIA RAMSEY
AUG. 30, 2017, 11:07 AM

The US Food and Drug Administration just approved a cutting-edge cancer therapy.

On Wednesday, the FDA approved Novartis' Kymriah, also known as tisagenlecleucel, a treatment for pediatric acute lymphoblastic leukemia.

"I think this is the most exciting thing I've seen in my lifetime," said Dr. Tim Cripe, an oncologist who was part of the FDA advisory committee panel that voted in July to recommend the drug's approval.

The highly personalized treatment is called CAR T-cell therapy (CAR is short for chimeric antigen receptor). It's a type of cancer immunotherapy, which harnesses the body's immune system to take



Cancer cells are seen on a large screen connected to a microscope.

Reuters

The New York Times

F.D.A. Approves First Gene-Altering Leukemia Treatment, Costing $475,000

By DENISE GRADY AUG. 30, 2017

RELATED COVERAGE

Setting the Body's 'Serial Killers' Loose on Cancer AUG. 1, 2017

Immune System, Loaded With Remade T-

SCIENTIFIC AMERICAN.

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BIOTECH

FDA Green-Lights First CAR-T Cancer Drug

The leukemia treatment approval opens up a new front for gene therapies in the U.S.

By Damian Garde, STAT on August 30, 2017

The Food and Drug Administration on Wednesday approved a futuristic new approach to treating cancer, clearing a Novartis therapy that has produced unprecedented results in patients with a rare and deadly cancer.

The treatment, called a CAR-T, is made by harvesting patients' white blood cells and rewiring them to home in on tumors. Novartis's product is the first CAR-T therapy to come before the FDA, leading a pack of novel treatments that promise to change the standard of care for certain aggressive blood cancers.

Novartis's therapy is approved to treat children and young adults with relapsed acute lymphoblastic leukemia. It will be marketed as Kymriah.

The Washington Times

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FDA approves first-ever gene therapy in U.S.

Drug uses body's own cells to attack childhood cancer

CANCER RESEARCH INSTITUTE

FDA Approves First-In-Class CAR T Cell Immunotherapy for Leukemia

August 30, 2017
Arthur N. Brodsky, Ph.D.

Today, August 30, 2017, the U.S. Food and Drug Administration approved a revolutionary, first-in-class cancer immunotherapy for children and young adults with relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL). Referred to as a "living drug," tisagenlecleucel (Kymriah™, Novartis) uses a patient's own T cells. After extracting them and enabling them—through genetic modification—to more effectively eliminate cancer cells, the enhanced T cells are then re-infused back into the patient. In this case, the young patients' T cells are equipped with CARs (chimeric antigen receptors) that target the CD19 protein found on cancerous B cells.

The CAR T cell immunotherapy's approval comes a month and a half after the treatment was unanimously backed by the FDA's Oncologic Drugs Advisory Committee, bolstered by an 83% overall remission rate in the pivotal phase II ELIANA study (NCT02435849). In other words, 83% of the patients experienced a complete response that eliminated all signs of their disease, although some patients exhibited an incomplete blood count recovery. All of these responses occurred within three months of treatment and, importantly, none of these patients showed evidence of minimal residual disease (MRD), a potential indicator of future relapse.

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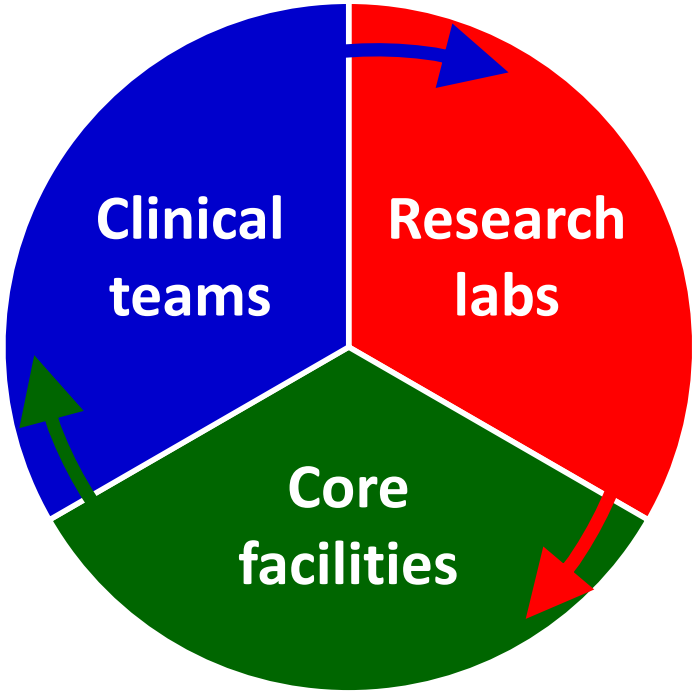
To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.

The goal of T cell adoptive transfer is to win the numbers game and overwhelm the tumor with a higher frequency of tumor-specific T cells than it is capable of suppressing.

Center for Immunotherapy at Roswell Park

Kunle Odunsi, MD PhD
Executive Director

Richard Koya, MD PhD
Associate Director



Foundation Partners

LUDWIG INSTITUTE FOR CANCER RESEARCH

CANCER RESEARCH INSTITUTE

PARKER INSTITUTE for CANCER IMMUNOTHERAPY

HUMAN VACCINES PROJECT

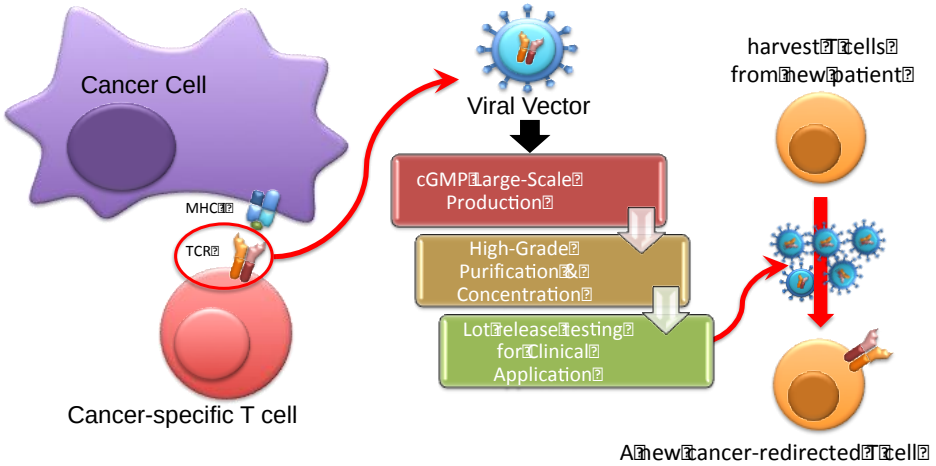
Familial Ovarian CANCER REGISTRY

cancer immunotherapy trials network

Vector Development and Production Facility

viral vector development for basic research and clinical trials

- Clinical-grade viral vector production
- cGMP optimization and scale-up
- QC Testing, viral batch/lot release
- IND Preparation and SOP development



Richard Koya, MD PhD
Director – VDPF

Therapeutic Cell Production Facility

cGMP-certified therapeutic cell manufacturing for clinical trials

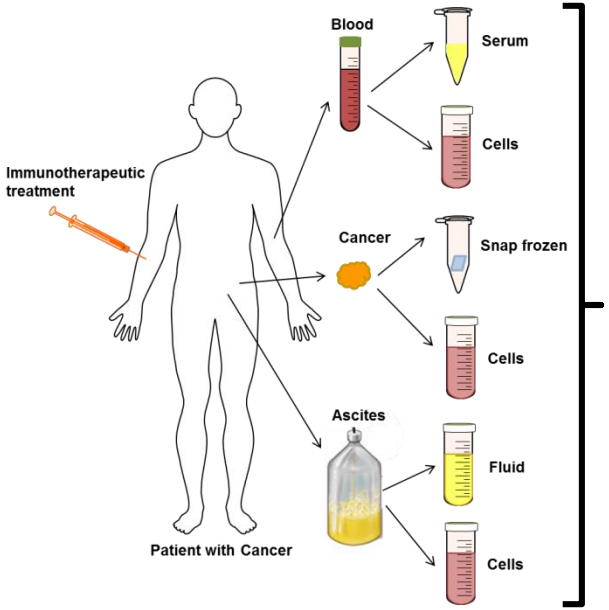
- Cell manufacturing
- Product and process development
- Optimization and scale-up
- IND preparation & SOP development
- Cell banking

Chris Choi, PhD
Director – TCPF

Thinle Chodon, MD PhD
Director – Translational Research Operations

Immune Analysis Facility

state-of-the-art immune monitoring for basic and clinical research



- Biospecimen cryopreservation
- ELISA and ELISPOT
- Immune cell phenotyping
- Intracellular cytokine staining
- Cell sorting
- Tetramer staining and cytotoxicity
- Multiplex cytokine arrays
- TCR Vβ repertoire analysis
- HLA typing
- Metabolic analysis

Junko Matsuzaki, PhD
Director – IAF

Specialized Program of Research Excellence in Ovarian

TRP Translational Research Program

"To support investigator-initiated translational research that will contribute to improved prevention, early detection, diagnosis, and treatment of an organ-specific cancer."

6 year $12M grant

1 of 3 nationwide devoted to ovarian cancer

Clinical studies supported by SPORE award

ROSWELL PARK CANCER INSTITUTE

University of Pittsburgh Cancer Institute

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

MAYO CLINIC

1. Vaccine ± immune modulation (Phase I/II)
2. ACT + immune modulation (Phase I)
3. ACT + vaccine (Phase I)
4. Immune cell genetics (population study)

Harnessing durability of stem cells for ACT

4 year

$11M grant

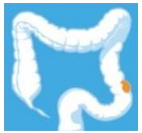
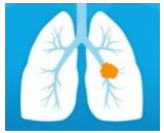
Consortium partners

The Jackson Laboratory

University at Buffalo
The State University of New York

OBJECTIVE Re-engineer adult hematopoietic stem cells with tumor-specific TCR to generate durable anti-tumor immune responses

Selection of trials conducted by CFI

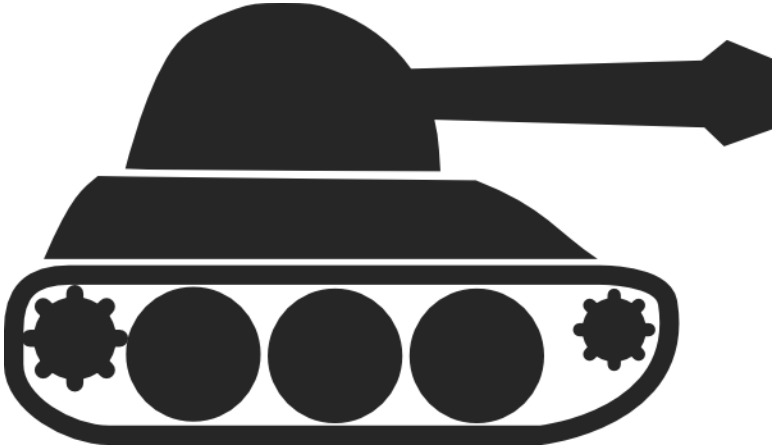
	breast cancer	colon cancer	leukemia lymphoma	lung cancer	melanoma	ovarian cancer	prostate cancer
							
checkpoint blockade	I 291016 PH 253914	I 291016 I 274515	PH 236713 PH 281816	I 291016 PH 269015	I 291016 PH 227012	I 291016 I 270715 I 288216	I 291016 PH 283216
adoptive transfer	I 258514 P 63818 P 35216	I 258514 P 54617 P 35216	PH 251514 I 210611 PH 268215	I 258514 P 54617 P 35216	I 258514 P 54617 P 54117	I 258514 I 287616 I 283616 P 54617	I 258514 I 223912 P 63818
cancer vaccines	I 191511	I 191511	I 227712	I 191511	I 215912	I 248613 I 277115 I 288216 I 60417	I 250113
oncolytic virus		P 39716			P 39716	P 39716	NCT02879760

Developing next-gen engineered T cells

current generation

- attack tumor cells
- limited defense against tumor counter-attack

next generation



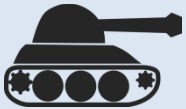
- attack tumor cells
- resist tumor counter-attack

Next-gen engineered T cell trials at RPCI

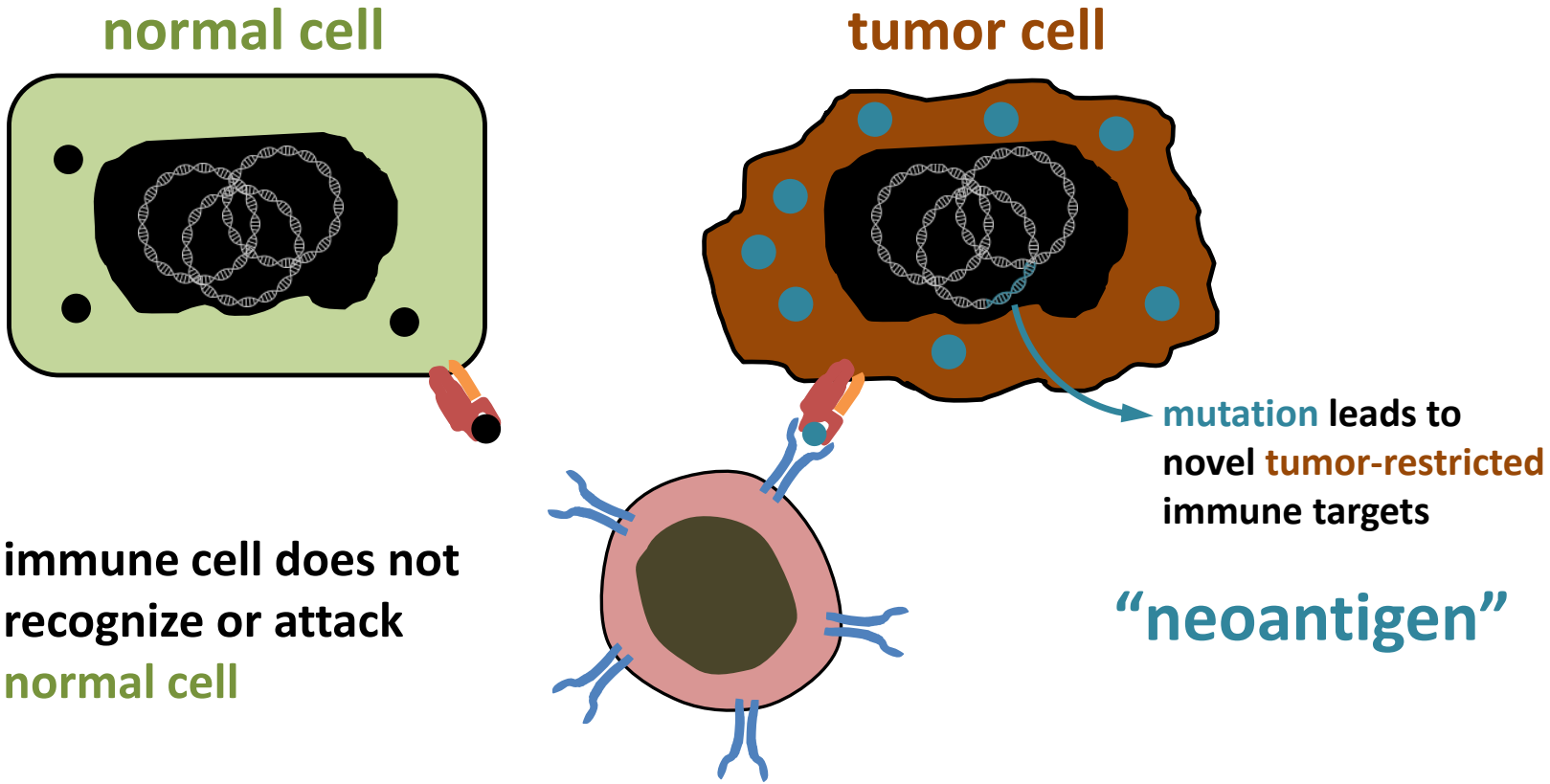
ROSWELL PARK CANCER INSTITUTE
Alliance Foundation

NATIONAL® CANCER INSTITUTE

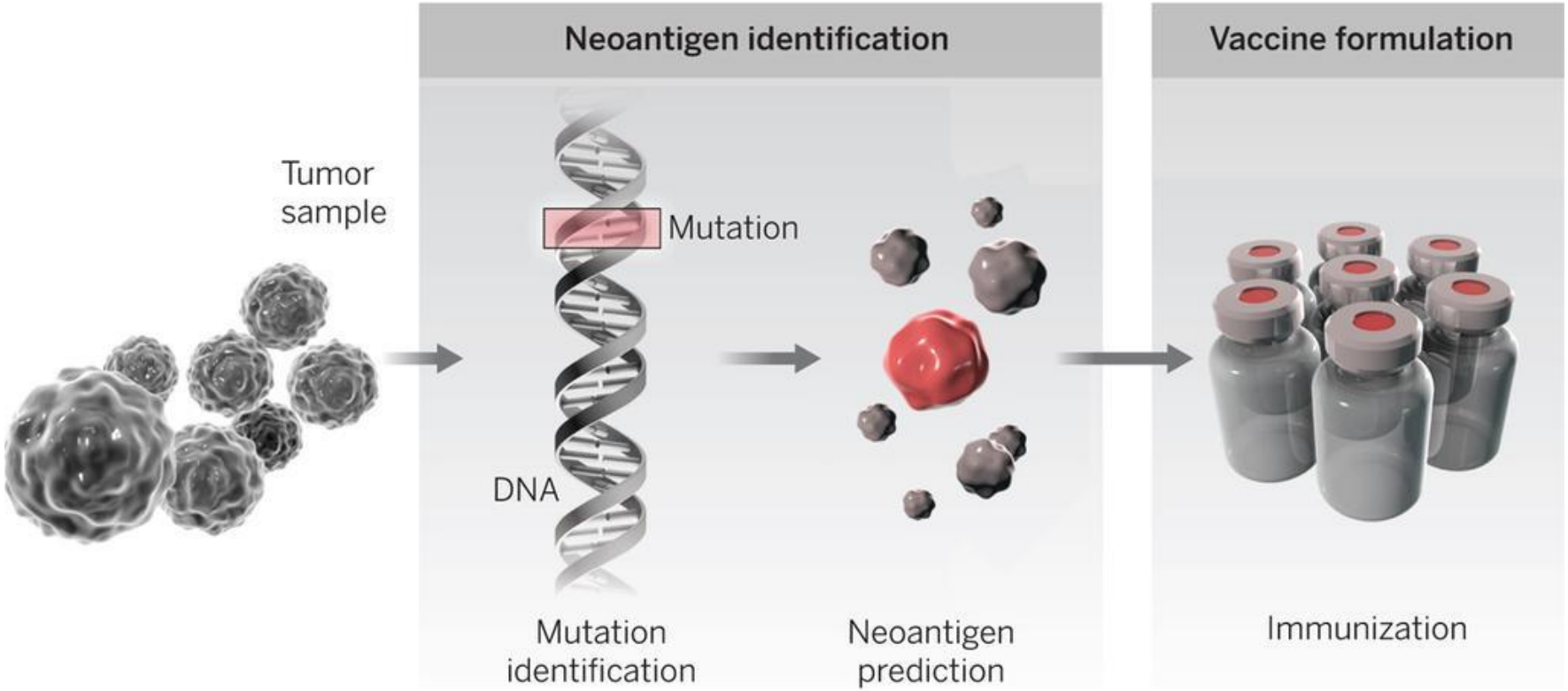
NYSTEM
NEW YORK STATE STEM CELL SCIENCE

RPCI trial number	I 258514	I 287616
tumor target	NY-ESO-1	NY-ESO-1
patient population	all solid tumor	ovarian cancer
 **modification**	resist hostile milieu (decoy receptor)	long persistence (stem cell)
status	**active**	*Jul/Aug 2018*
sponsor	NCI & RPAF	NYSTEM & RPAF

Neoantigens: potent tumor-restricted targets



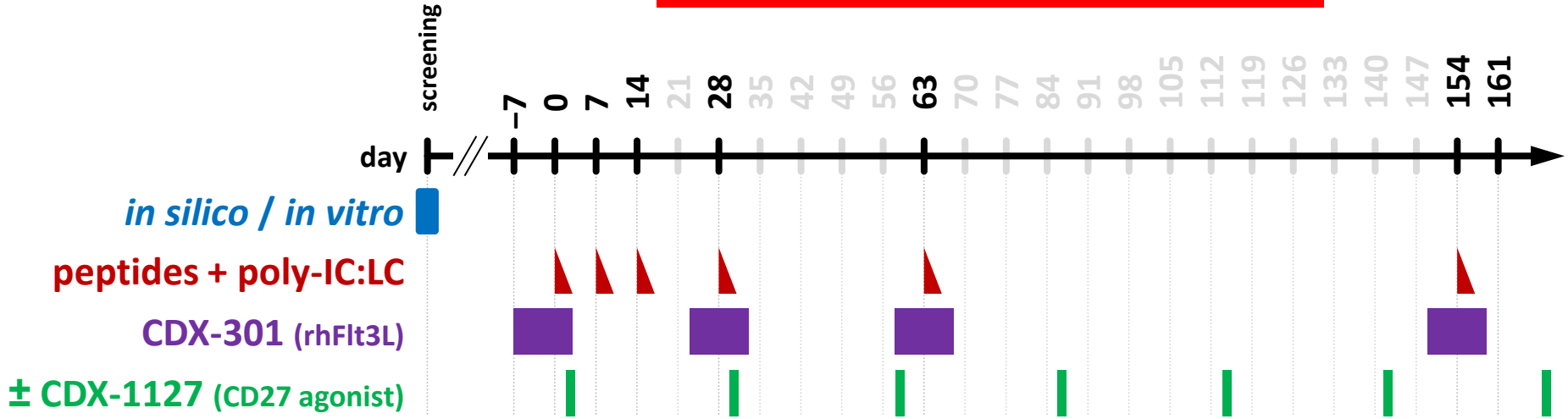
Mutations for personalized cancer vaccines



Delmarre *et al* Science 2014

Planned neoantigen vaccine trial

open to all advanced solid tumors



peptide
5-7 peptides, potentially more
400 μg / peptide / administration
in vitro validated and non-reactive epitopes

poly-IC:LC
2 mg / administration
day of and after vaccine

CDX-301
25 μg/kg
9 consecutive days

CDX-1127
3 mg/kg
Q4W

Conclusions: Benefits of cancer immunotherapy

Power to target cancer in a specific way

Ability to work on many types of cancer

even those that do not respond to chemo or radiation

Potential for reduced side effects
commonly associated with chemotherapy

e.g. nausea, vomiting, hair loss

Possibility for long-term remissions

Center for Immunotherapy faculty

Kunle Odunsi, MD PhD

Richard Koya, MD PhD

Sebastiano Battaglia, PhD

Thinle Chodon, MD PhD

Fumito Ito, MD PhD

Chris Choi, PhD

Junko Matsuzaki, PhD

Takemasa Tsuji, PhD

Emese Zsiros, MD PhD