Cancer Biology (PATH4500), November 19, 2025
Cancer Immunotherapy: vaccination, antibody and cellular therapies

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Columbia Center for Translational Immunology
Herbert Irving Comprehensive Cancer Center

Learning objectives

1. Concept of tumor neoantigens and recognition of non-self
2. Pros and cons of different vaccination strategies
3. Immune checkpoint blockade and mechanisms of resistance
4. TIL therapy vs. CAR-T therapy

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A brief glimpse at the historical roots of cancer immunotherapy

Basics of cancer immunology

Conventional and modern cancer vaccines

Cellular cancer immunotherapies

We are standing on the shoulders of giants

Dr. William B. Coley (1862-1936)

In **1890** treated a patient (Fred Stein) with metastatic sarcoma, but patient developed recurring disease

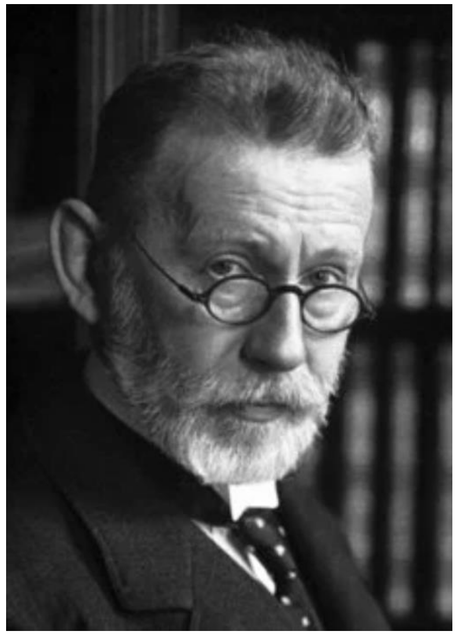
F.S. then developed a skin infection (erysipelas) from *Streptococcus pyogenes* and experience a dramatic resolution of his cancer.

In **1891** treated 10 patients with a variety of cancers by injecting *S. pyogenes* into the tumor, with reportedly some responses, but also two deaths.

Refined the strategy by mixing *S. pyogenes* and *Serratia marcescens* (**Coley's toxin**) which he heat-inactivated before injection.

With the development of radiation and chemotherapy, fell out of favor, but to date, is used in some parts of the world (including in the US!)

We are standing on the shoulders of giants



Dr. Paul Ehrlich (1854-1915)

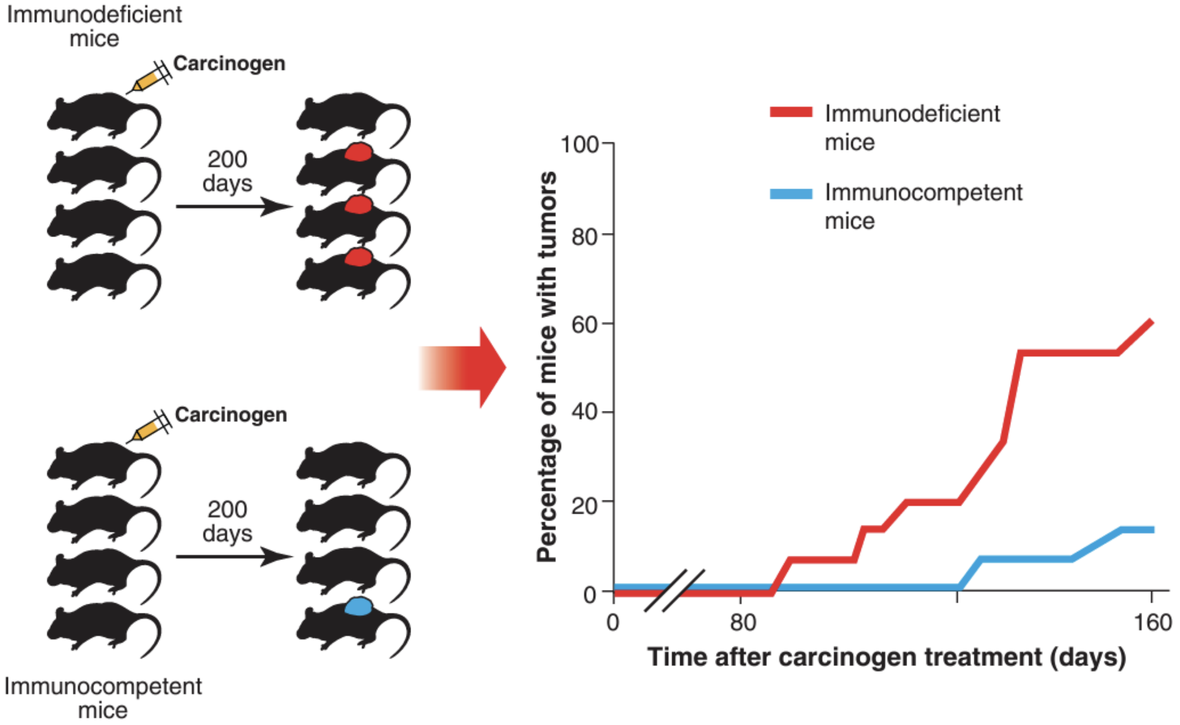
— 124 —

diejenige Beachtung gefunden hat, die ihr unzweifelhaft zukommt.

Ein derartiges Zusammen- oder richtiger Gegeneinanderwirken der Proliferationskraft der Tumorzellen einerseits und der Resistenz des Wirtstieres andererseits, tritt bei der natürlichen Geschwulstimmunität klar zutage, über die bereits zahlreiche Angaben vorliegen. Wenn es Geschwulststämme gibt, bei denen die Impfausbeute über Jahre hinaus eine ungefähr konstante Größe von 25, 50 oder 60 Prozent darstellt, so heißt das nichts weiter, als daß Virulenz der Tumorzelle und Resistenz des Organismus so aufeinander eingestellt sind, daß das Überwiegen der einen Kraft über die andere in einem für jeden Stamm annähernd gleichen Prozentsatz

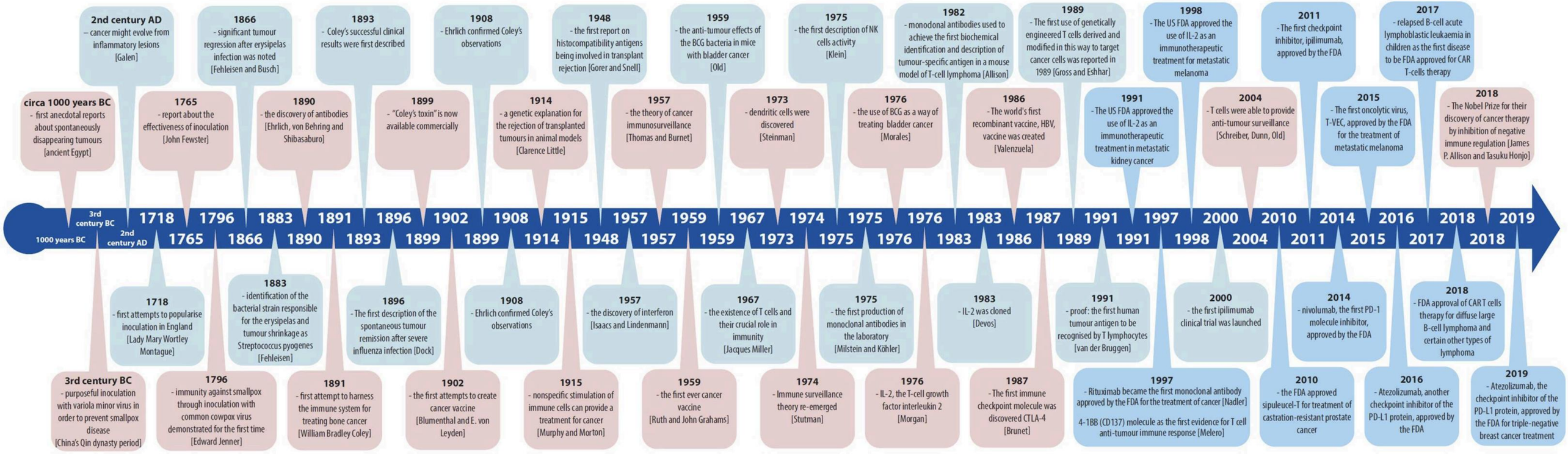
ferential unter gewissen Bedingungen auch bei der Verimpfung hochvirulenter Tumoren erkennbar ist. Zunächst ist mir, mit Ausnahme unseres Chondroms, bei dem so gut wie nie eine Fehlimpfung beobachtet wird, noch keine Geschwulst begegnet, gegen die nicht gelegentlich

Über den jetzigen Stand der Karzinomforschung, 1908
(A lecture given to students in Amsterdam, Netherlands)



Robert D. Schreiber, Lloyd J. Old, Mark J. Smyth, Science, 2011

A short history of immunotherapy…



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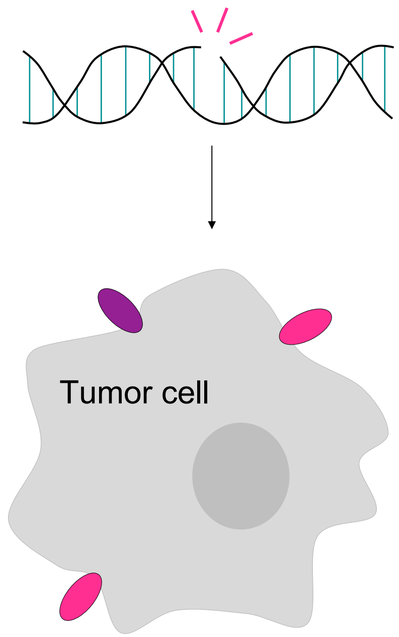
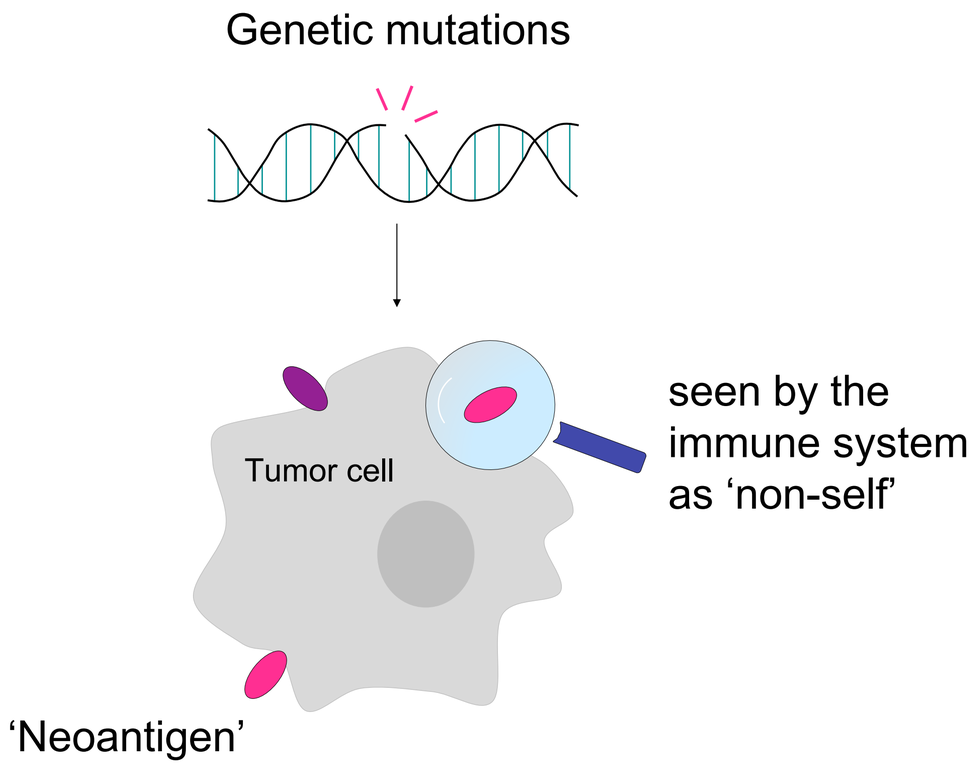
Neoantigens: how T cells “see” cancer

Genetic mutations



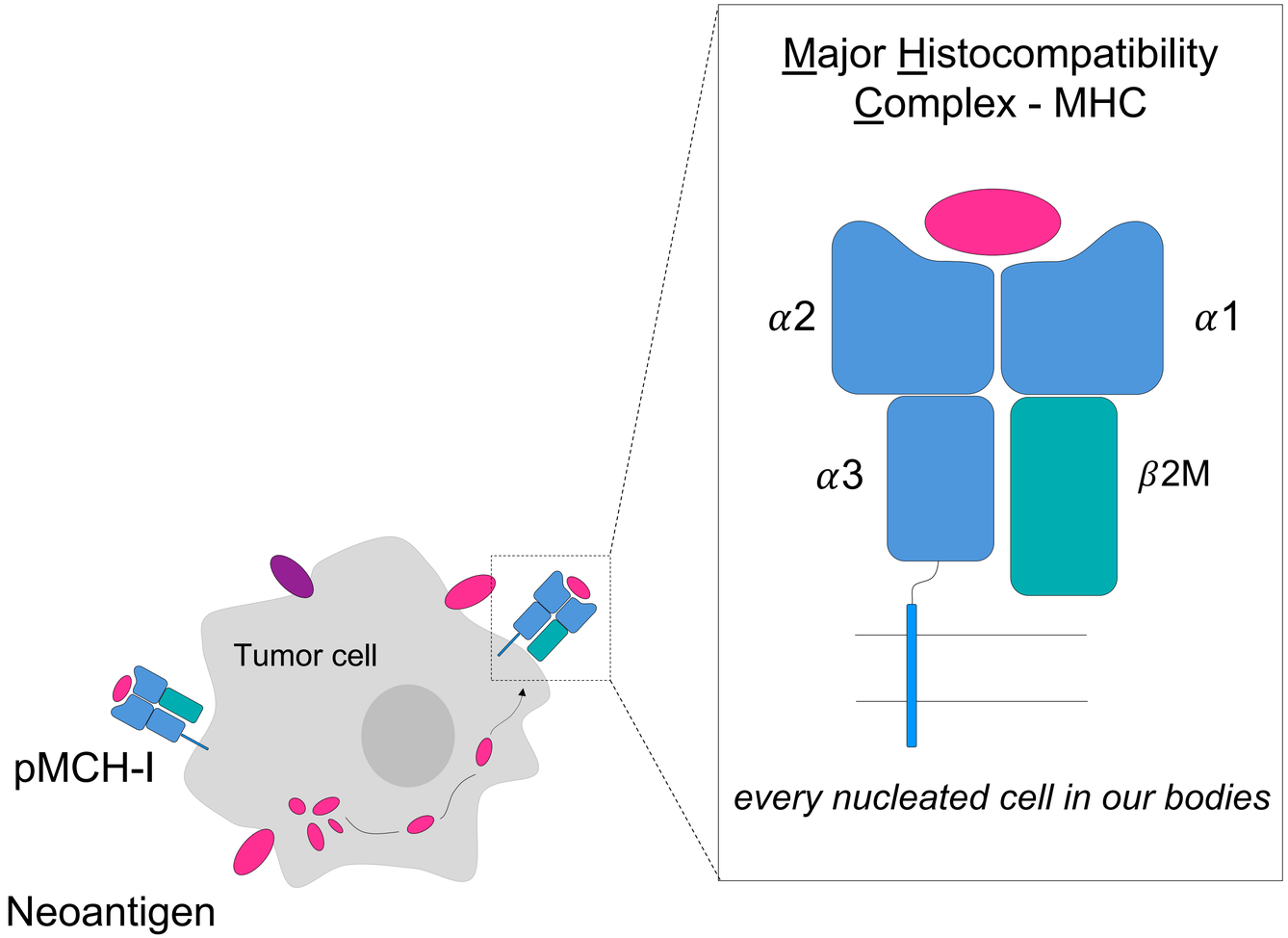
Slide: Courtesy of Dr. Nic Aparia and Dr. Tal Danino

Neoantigens: how T cells “see” cancer



Slide: Courtesy of Dr. Nic Aparia and Dr. Tal Danino

Neoantigens and MHC: how T cells “see” cancer



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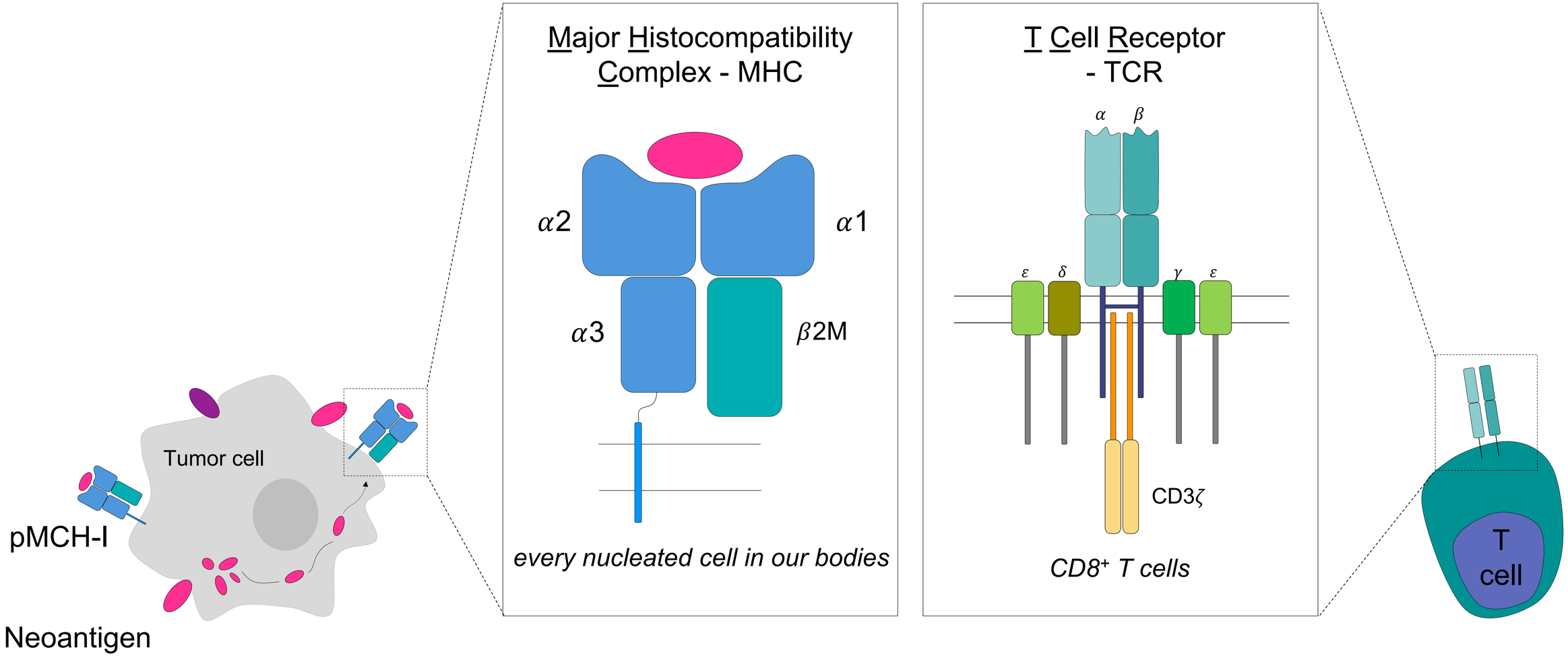
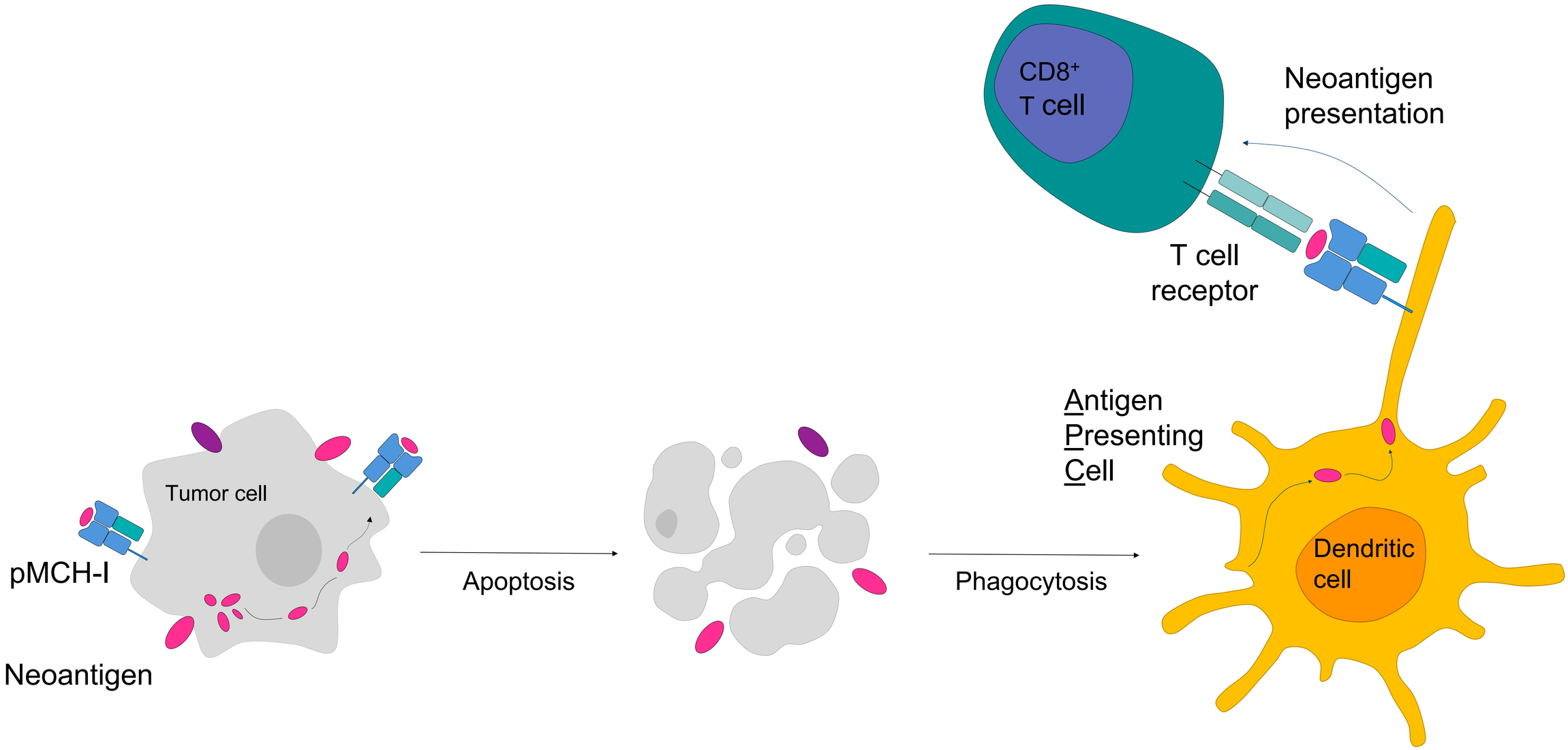


Slide: Courtesy of Dr. Nic Aparia and Dr. Tal Danino

Antigen presentation: how T cells “see” cancer



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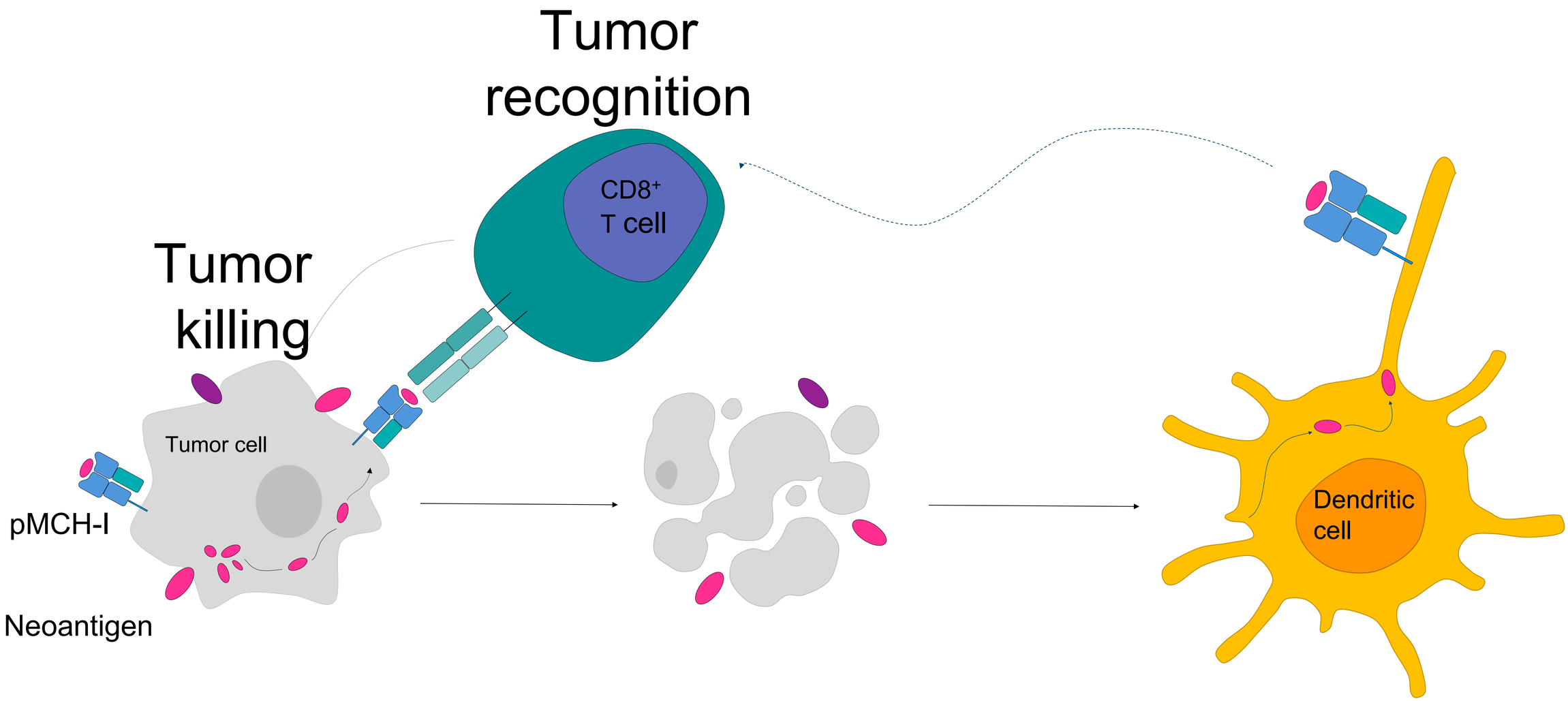
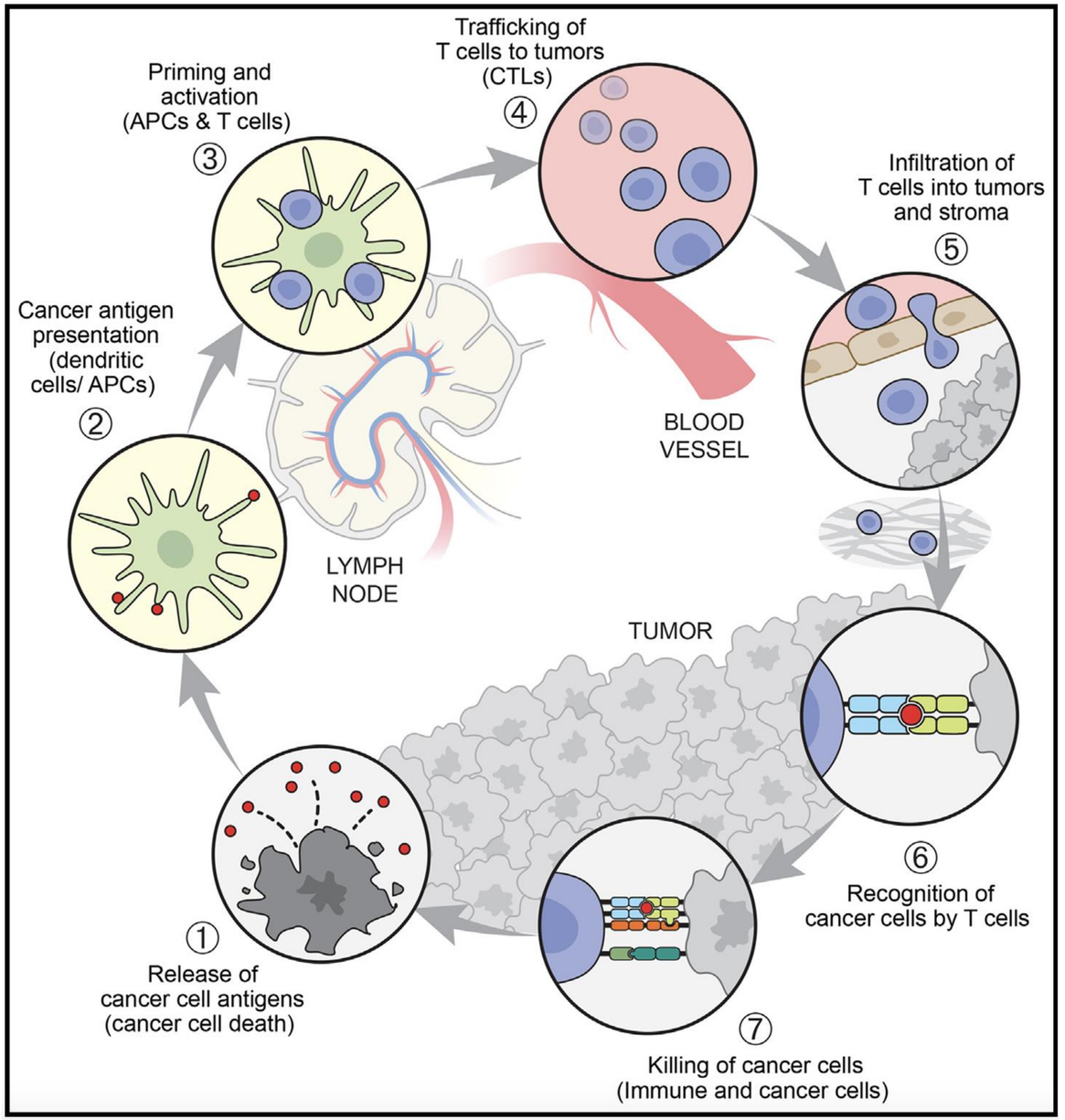
Antigen presentation: how T cells “see” cancer



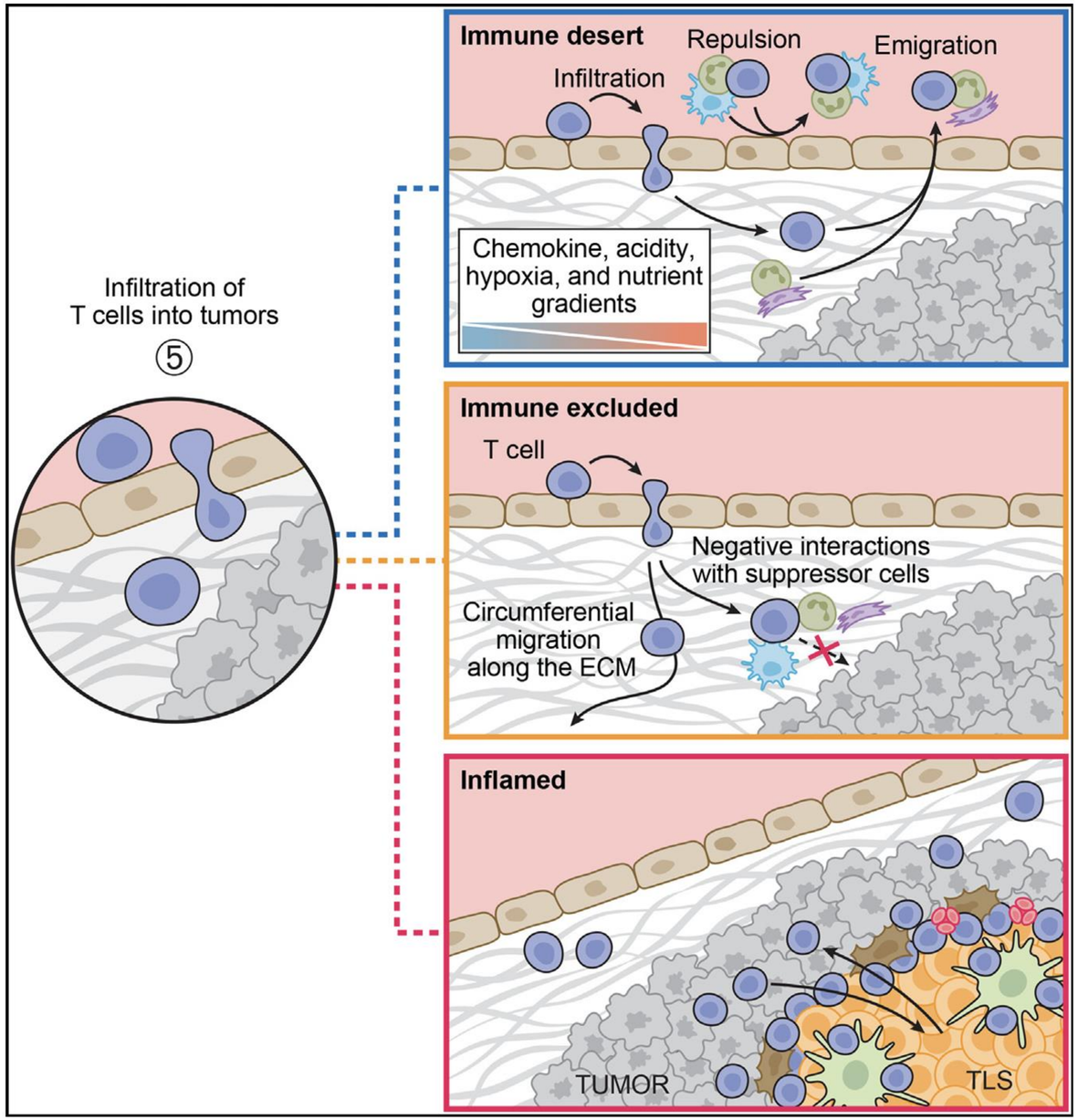
Slide: Courtesy of Dr. Nic Aparia and Dr. Tal Danino

The Cancer-Immunity cycle



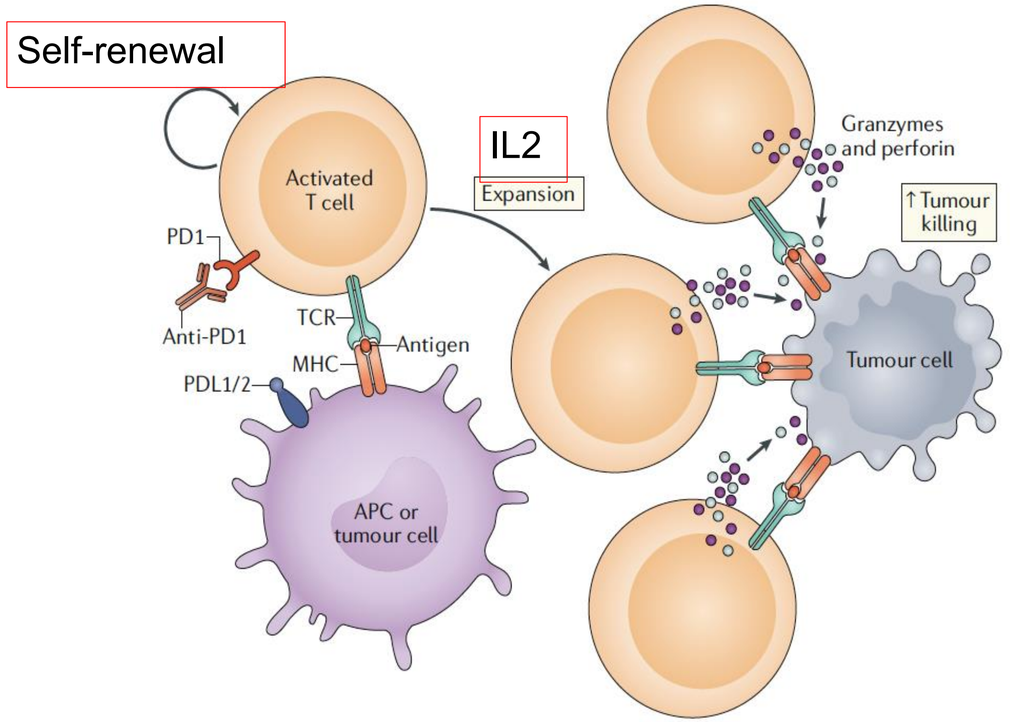
Mellman et al., Immunity, 2023

Immunotypes



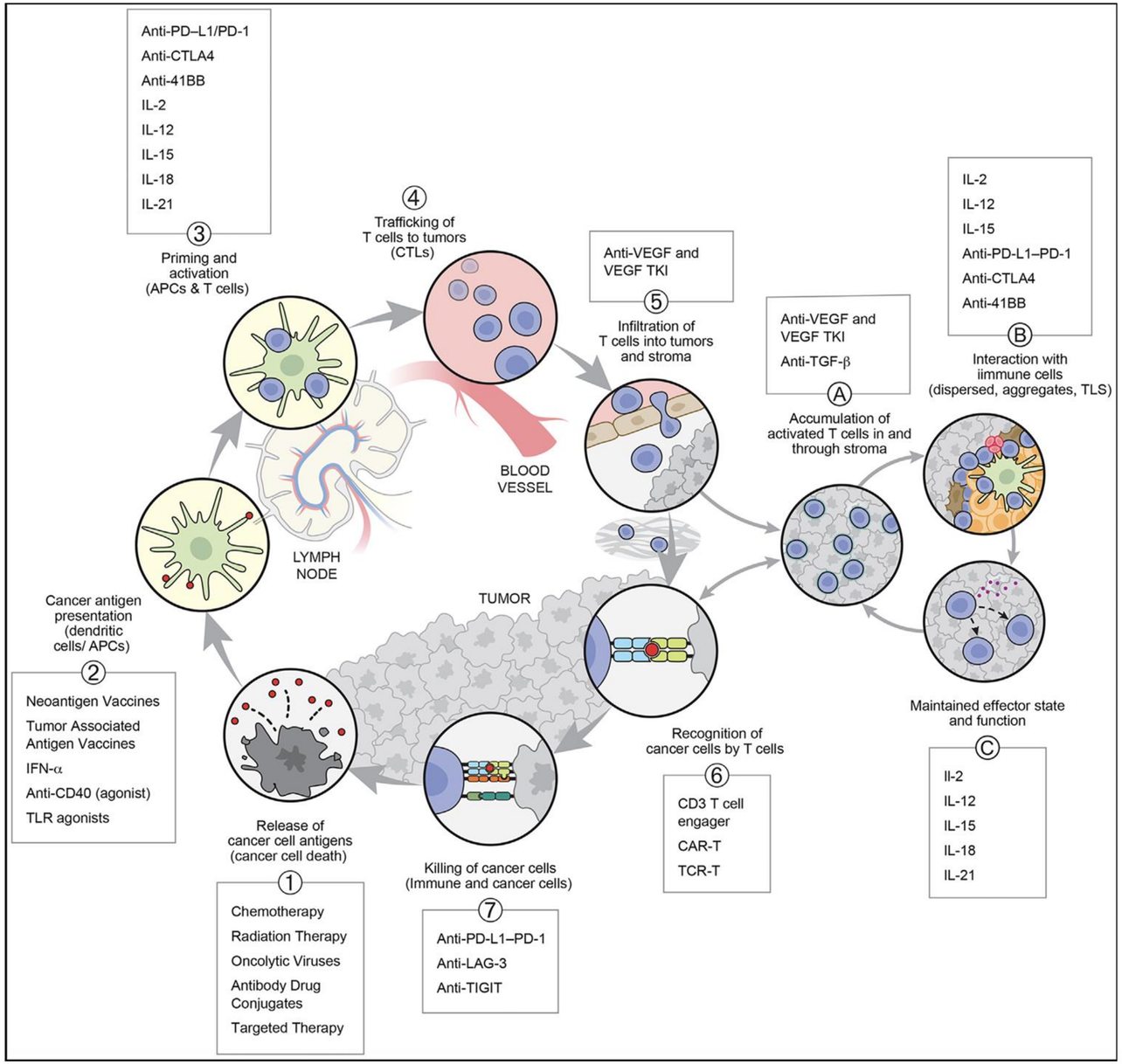
Mellman et al., Immunity, 2023

Self-renewal vs. exhaustion



Mellman et al., Immunity, 2023

From biological concepts to therapies



Mellman et al., Immunity, 2023

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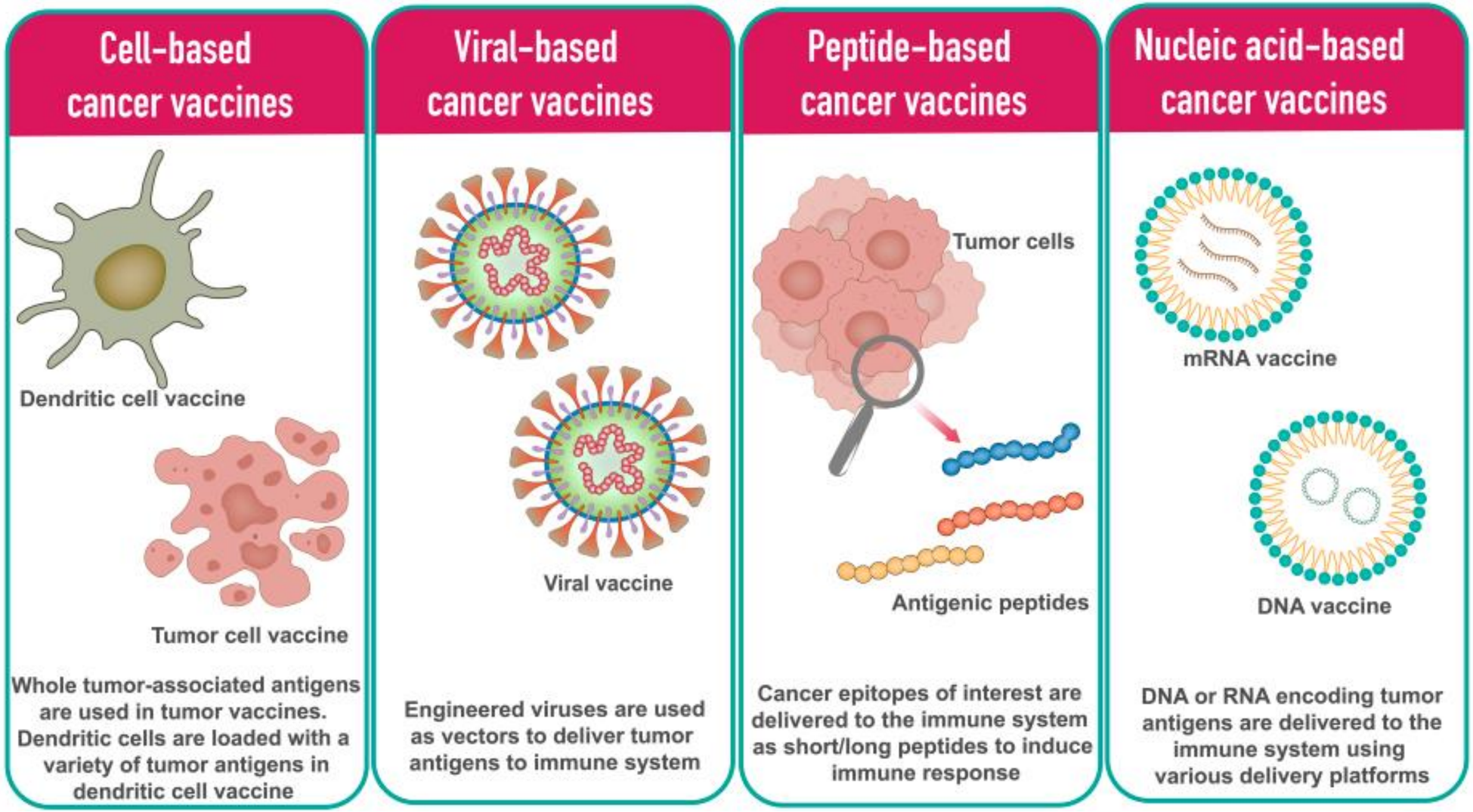
Goal: elicit a strong, durable and specific immune response against emerging or existing cancer tumor antigens. Ideally, easily produced and delivered, stable, and broadly applicable.

Overview of types of cancer vaccines



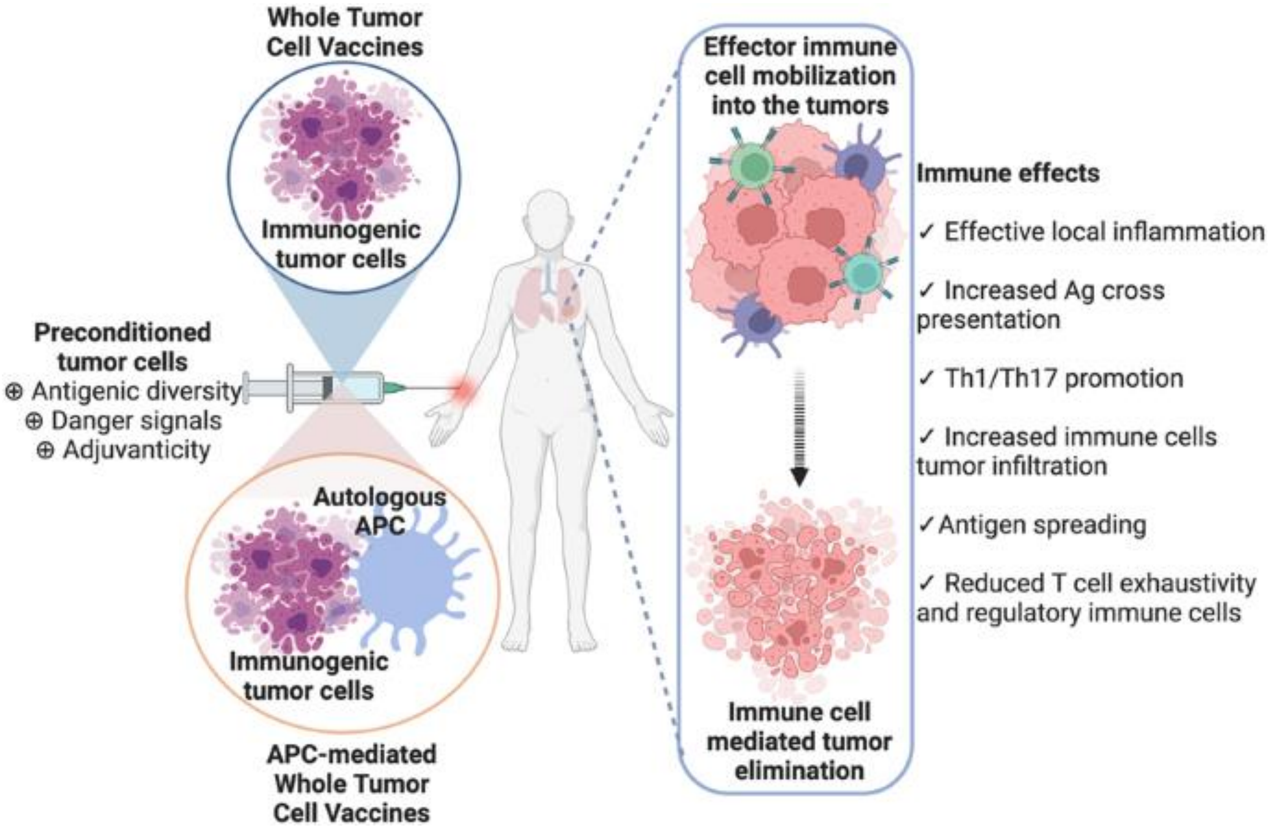
Cell-based vaccines

Rationale: deliver a comprehensive set of autologous/allogenic antigen that increases the chances for eliciting a specific immune response.

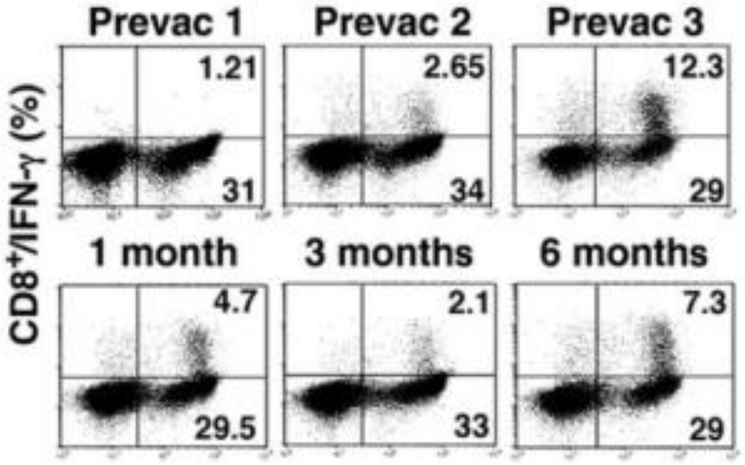
TABLE 4.—*Persistence of isologous immunity in later tumor transplant generations*

Tumor no.	Strain	Sex	Transplant generation of immunizing tumor	Transplant generation of challenge tumor	Growth of challenge tumors					
					Immunized mice			Controls		
					No. tumors	No. mice	Percent	No. tumors	No. mice	Percent
H	BALB/cAn	♂	1 2 3	2 3 4	0 1 0	39 36 44	00 3 00	6 30 32	38 40 44	16 75 73
A	C3Hf/He	♀	1 4	2 5	3 1	18 21	17 5	18 18	21 19	86 95
G	BALB/cAn	♂	1 3 4 4 5 6	2 4 5 5 6 7	5 1 18 19 24 15	27 20 40 29 32 16	19 5 45 66 75 94	33 24 21 25 18 22	37 24 21 31 18 22	89 100 100 81 100 100
K	DBA/2	♂	1 3	2 4	2 2	8 27	25 6	5 24	6 24	83 100
L	DBA/2	♂	1 3	2 4	0 0	7 32	00 00	6 24	8 24	75 100

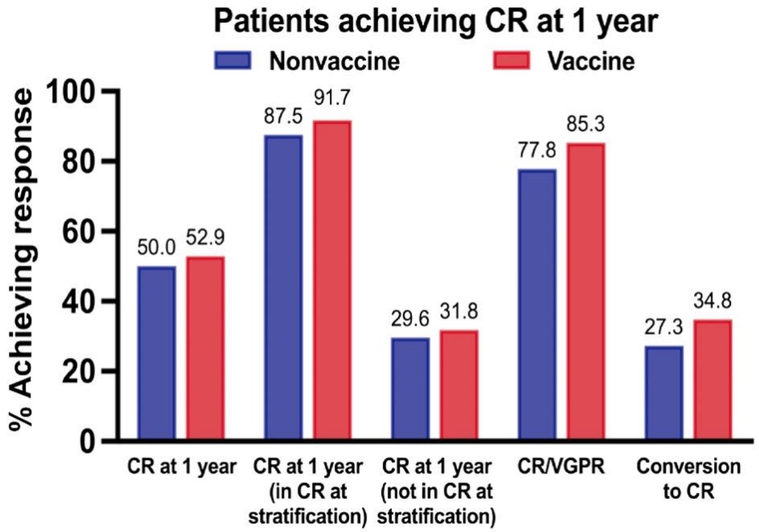
Prehn and Main, *JNCI*, 1957



Cell-based vaccines



Rosenblatt et al., *STM*, 2016



Chung et al., *CCR*, 2023

Pros

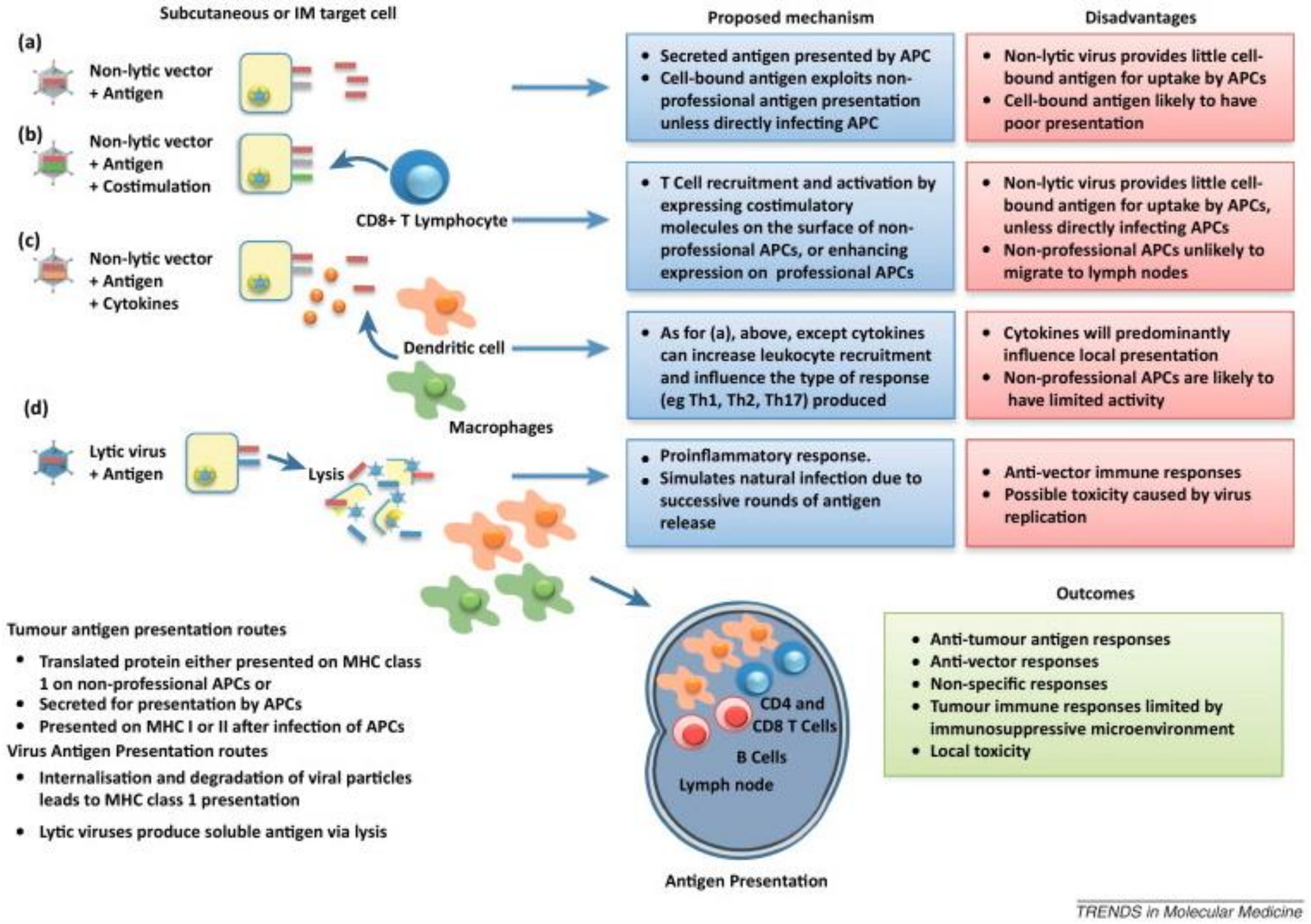
- potentially broad antigen presentation
- no need to prospectively specify antigen

Challenges;

- uniform production is challenging
- many production questions (whole-tumor, cells, selection, tissue heterogeneity etc)
- Lack of antigen in the product
- Cell viability
- Dosing

… so far not realized its full potential

Cell-based vaccines



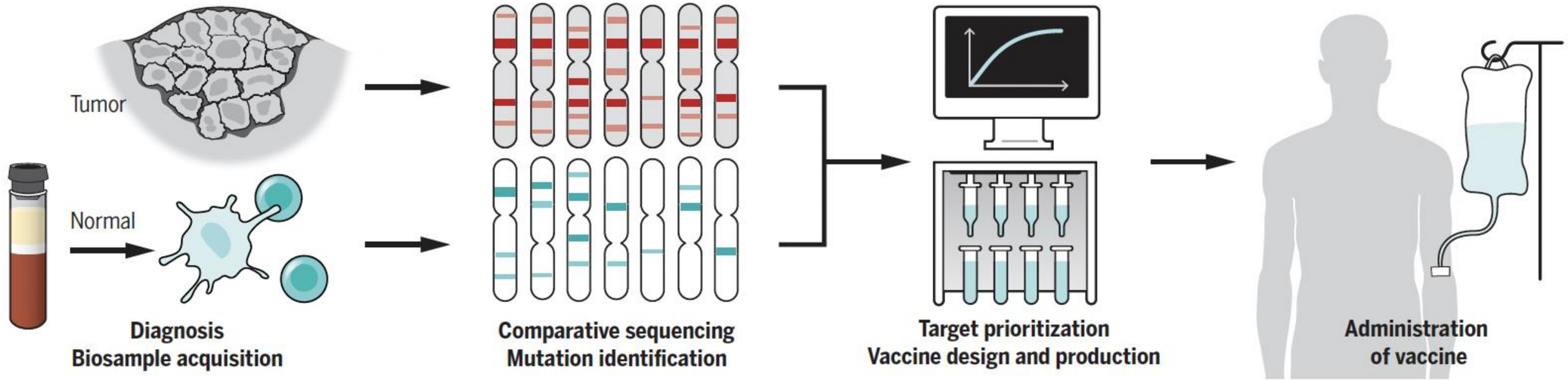
Cawood et al., *Trends in Molecular Medicine*, 2012

Therapeutic cancer vaccination approaches

REVIEW

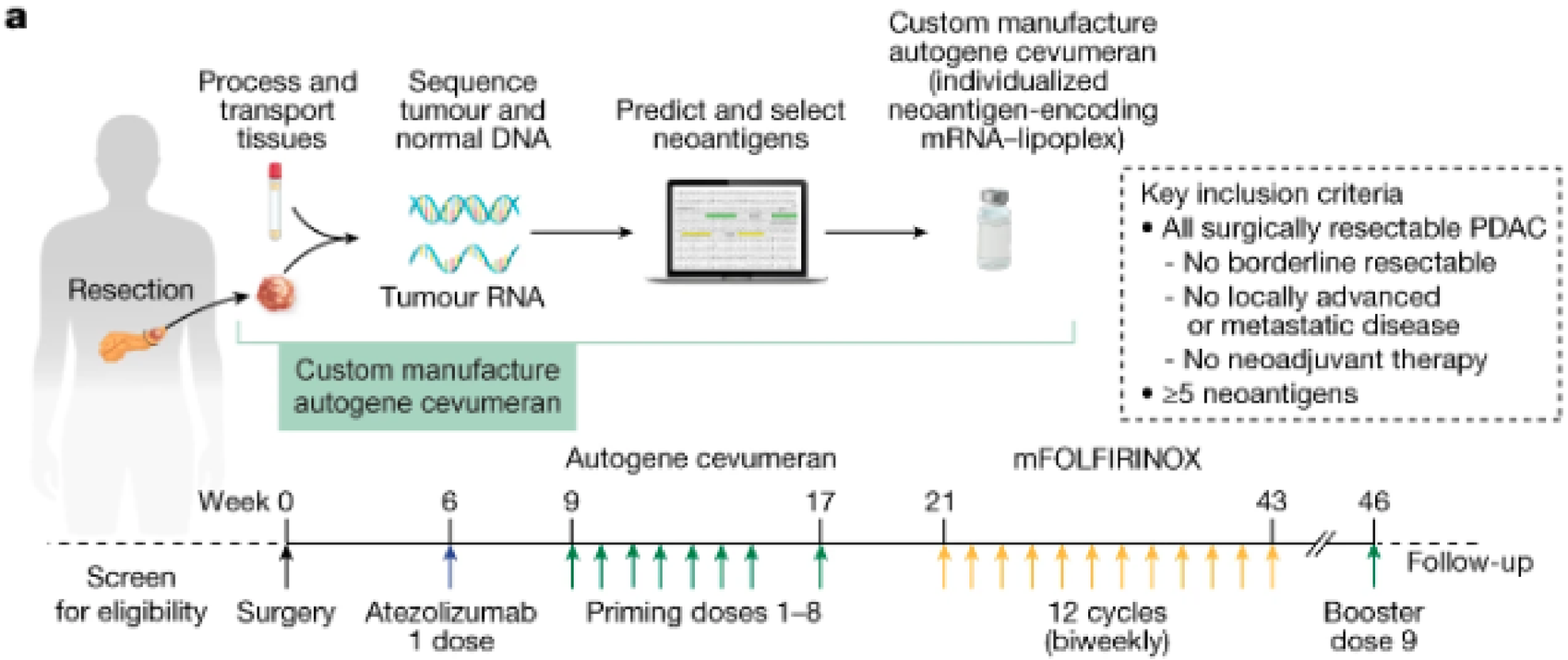
Personalized vaccines for cancer immunotherapy

Ugur Sahin[1,2,3]* and Özlem Türeci[4]

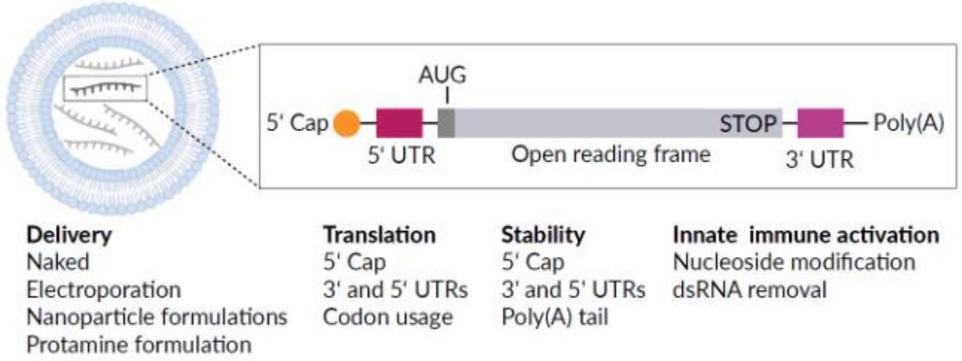


Science (2018)

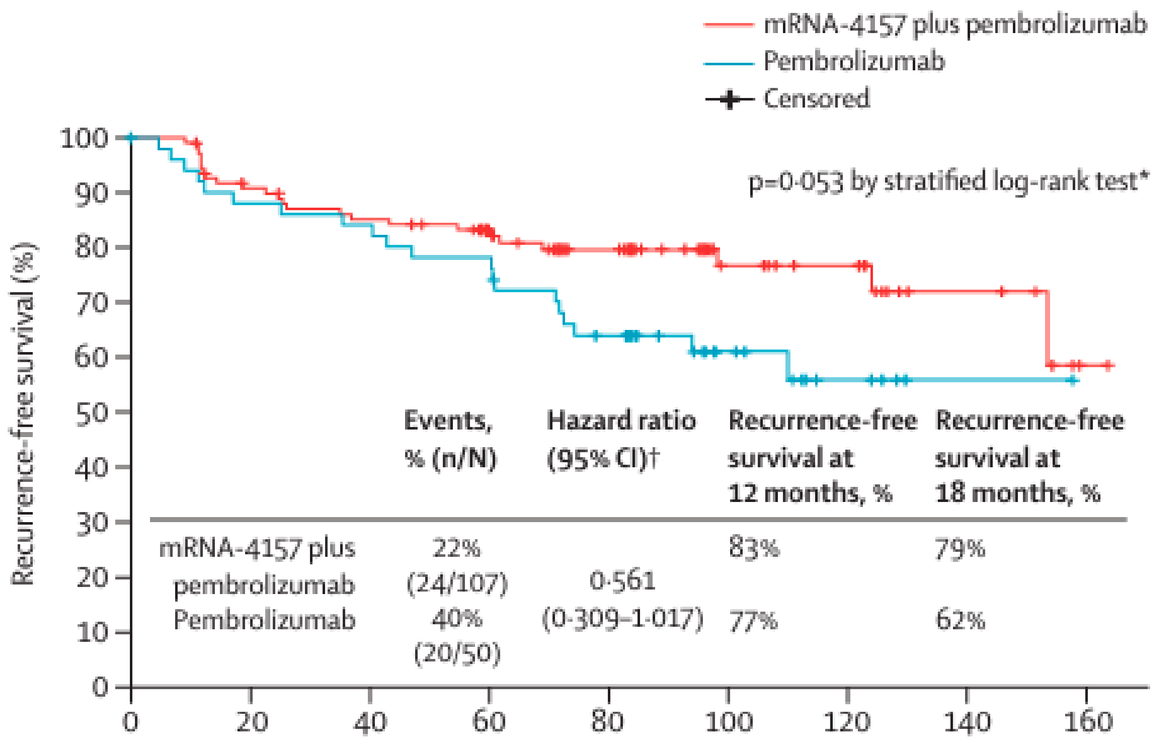
Personalized mRNA vaccines in clinical reality



Rojas et al., *Nature*, 2023



Clinical efficacy in patients with melanoma



Webber et al., Lancet, 2023

Pros and cons of personalized (mRNA—based) vaccines

Pros

- highly specific to a tumor neo-antigen (high specificity and no off-target activity)
- Rationale combination with other therapies (e.g., checkpoint inhibitors)
- mRNA production rapid, feasible, and scalable (see COVID-19!)
- already progressed in clinic and shows promising activity

Challenges;

- highly specific, but significant tumor heterogeneity
- Cumbersome process of profiling, identification of neo-antigens etc
- Prioritization of neo-epitopes
- cold chain requirement (e.g., mRNA stability)

A brief overview of pros and cons of different vaccine approaches

Type of Vaccine	Description	Examples	Pros	Cons
Preventive Vaccines	Target viruses associated with cancer to prevent its onset.	HPV (Gardasil, Cervarix), HBV	Highly effective at preventing virus-related cancers. Long-lasting immunity.	Limited to virus-associated cancers. No effect on existing cancers.
Tumor Antigen Vaccines	Use specific antigens found on cancer cells to trigger an immune response.	MAGE-A3, HER2, NY-ESO-1	Broad applicability. Easy to design for known tumor antigens.	Weak response if antigens are shared with normal tissues. Tumor heterogeneity limits efficacy.
Dendritic Cell Vaccines	Utilize dendritic cells loaded with tumor antigens to stimulate immune activation.	Sipuleucel-T (Provenge)	Proven success in prostate cancer. Targets immune activation directly.	Time-consuming and expensive to produce. Limited success in solid tumors.
Neoantigen Vaccines	Personalized vaccines targeting unique tumor mutations specific to an individual’s cancer.	Clinical trials (mRNA, DNA)	Highly specific. Reduced off-target effects. Tailored to individual patients.	Complex and costly to produce. Requires extensive tumor profiling.
DNA/RNA/Peptide Vaccines	Use genetic material or protein fragments to induce an immune response against cancer cells.	mRNA-based vaccines (under development)	Stable, easy to manufacture. Can target multiple antigens simultaneously.	Limited immune response without adjuvants. Delivery methods require optimization.
Whole-Cell Vaccines	Use entire tumor cells (autologous or allogeneic) to present a wide range of tumor antigens.	GVAX (GM-CSF-modified vaccines)	Broad antigen coverage. Can stimulate diverse immune responses.	Risk of targeting normal cells. Requires tumor tissue availability.

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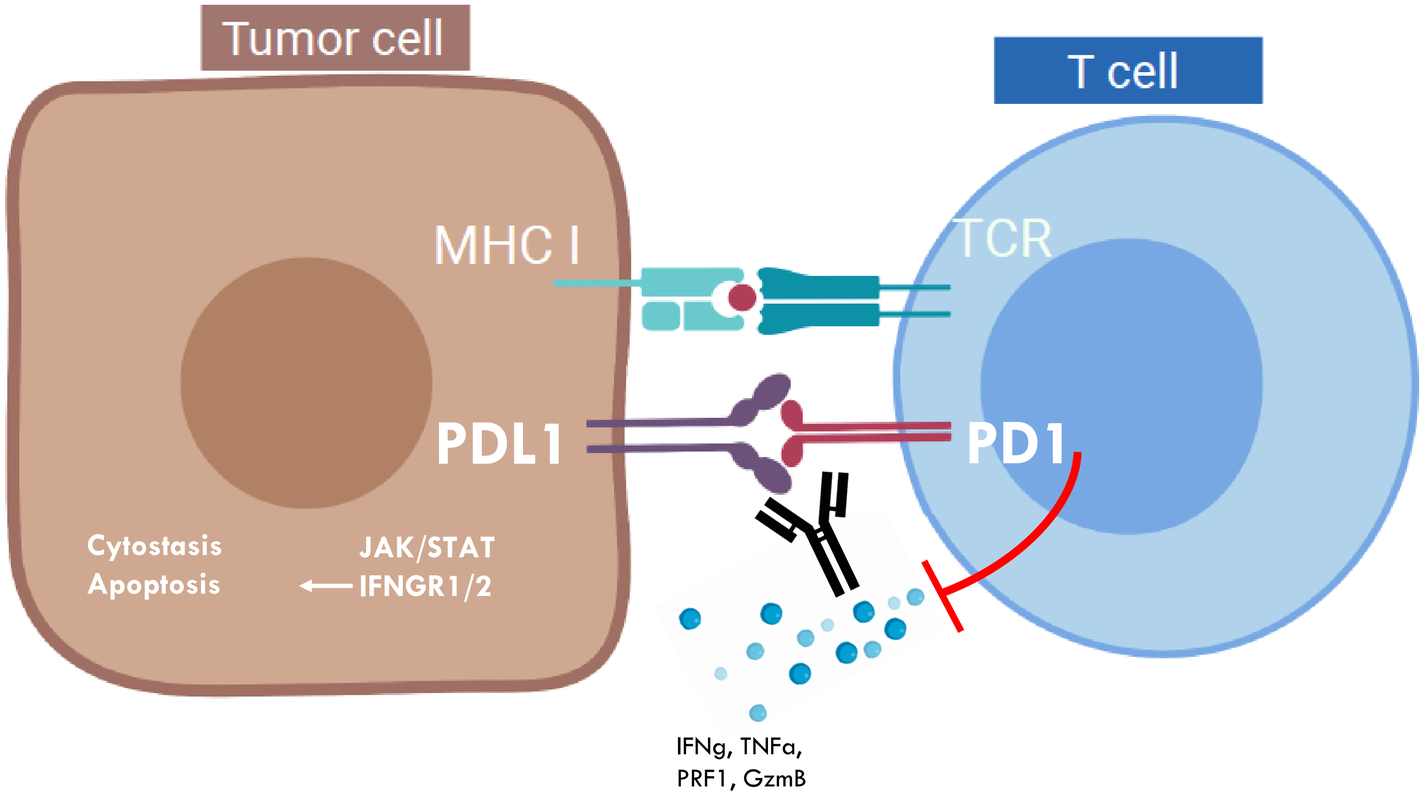
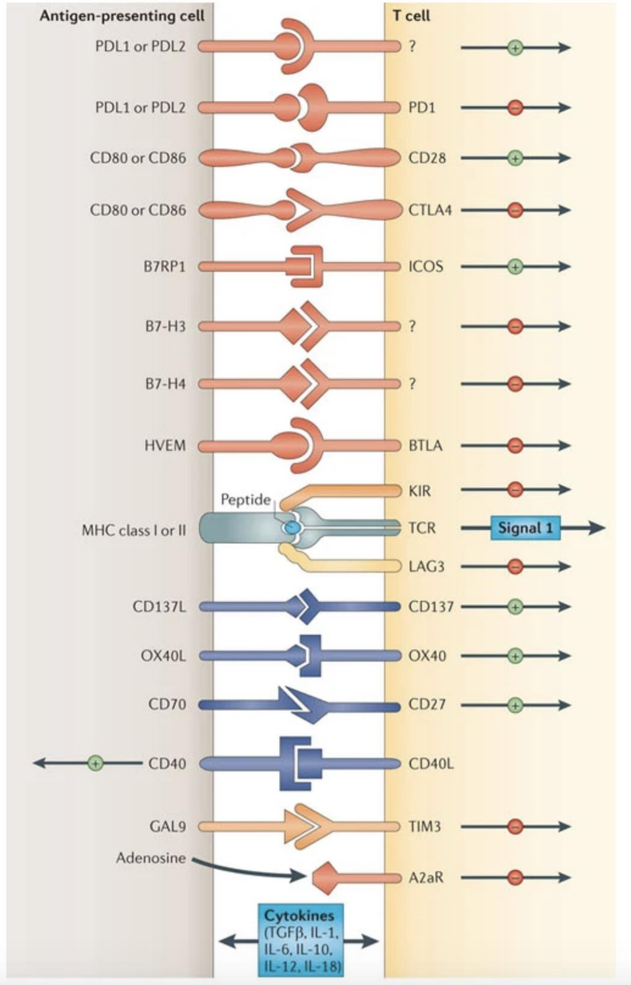
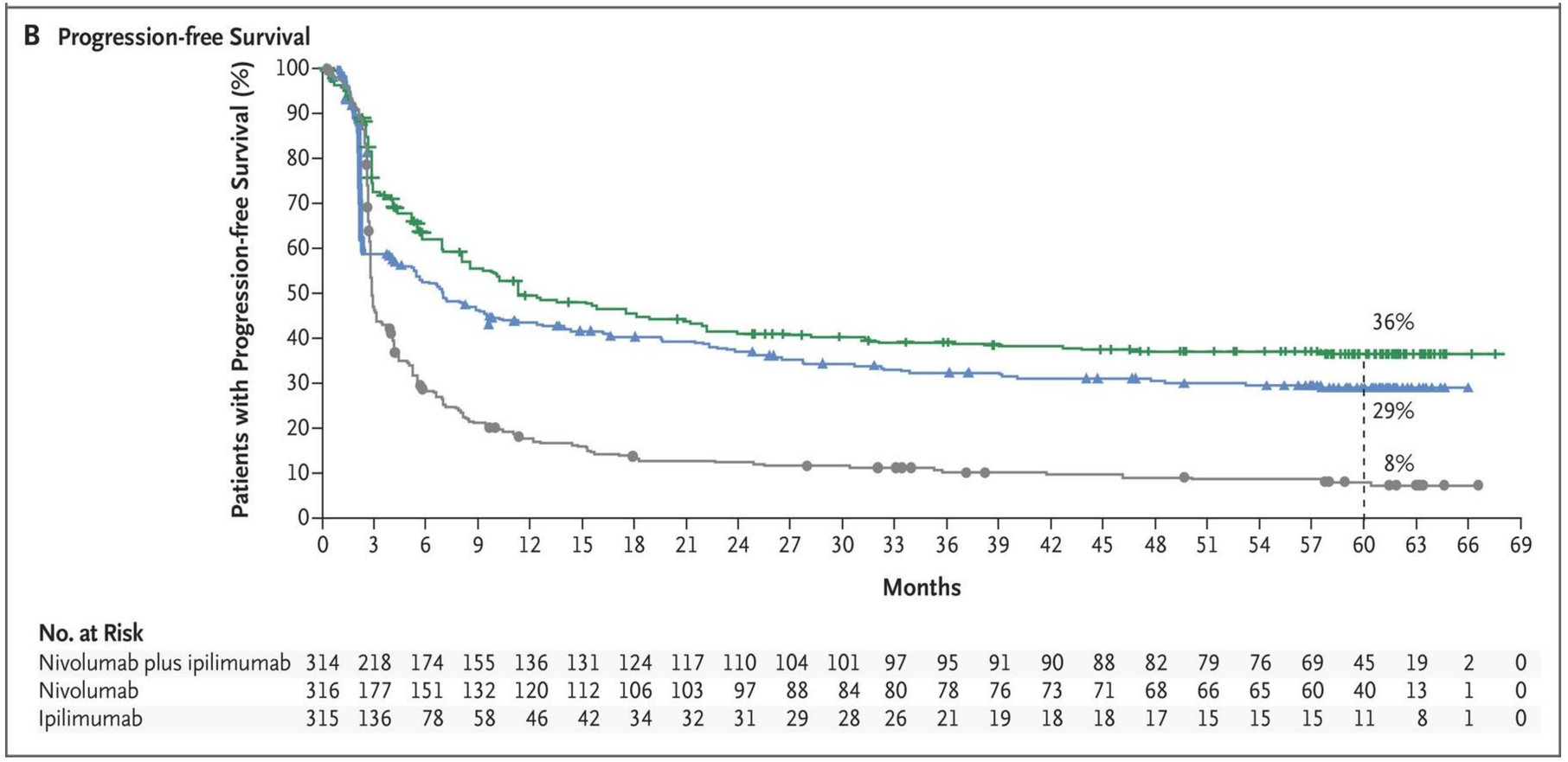
Co-inhibitory Immune checkpoints





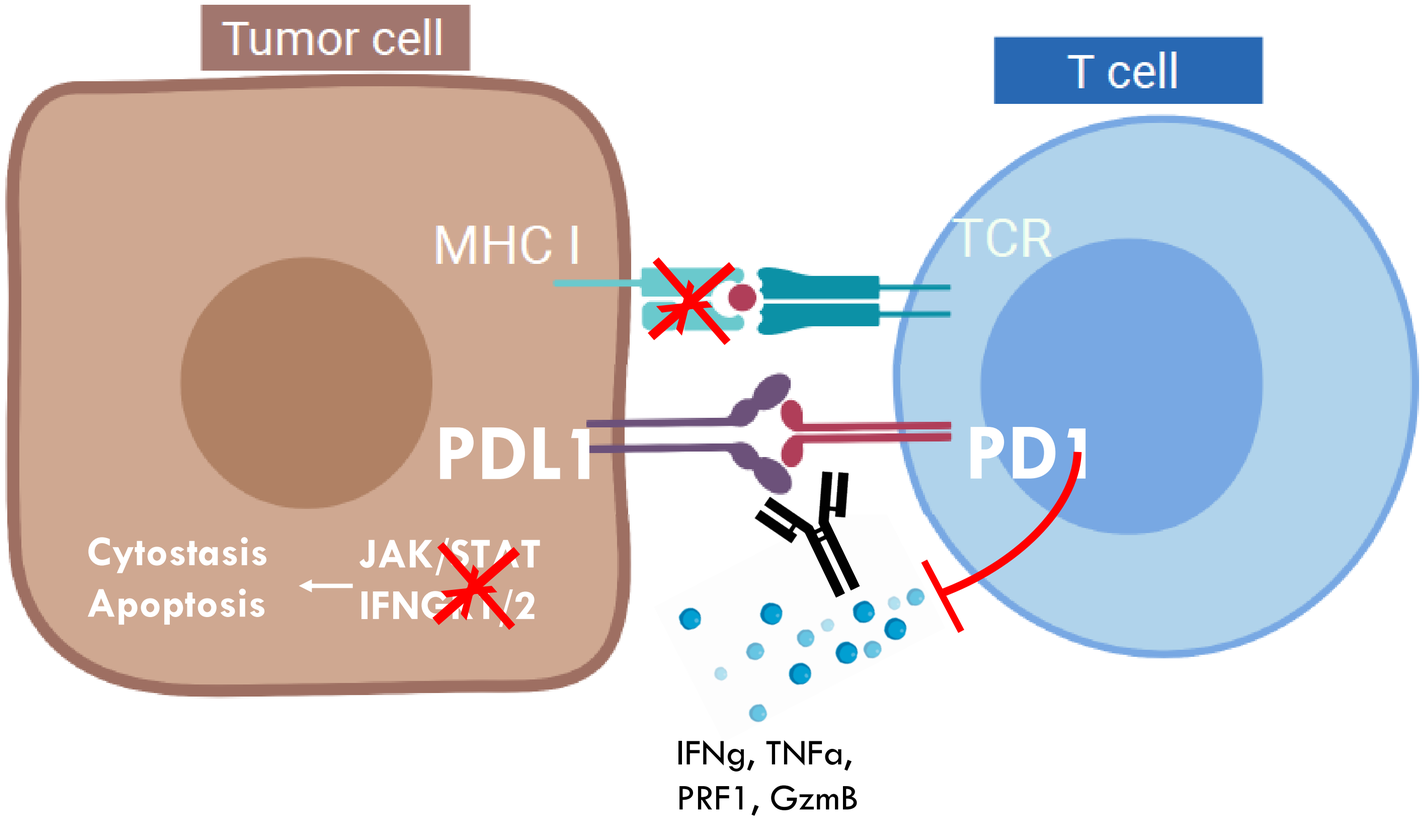
Pardoll, Nat Rev Cancer, 2012

Immune checkpoint blockade – clinical impact

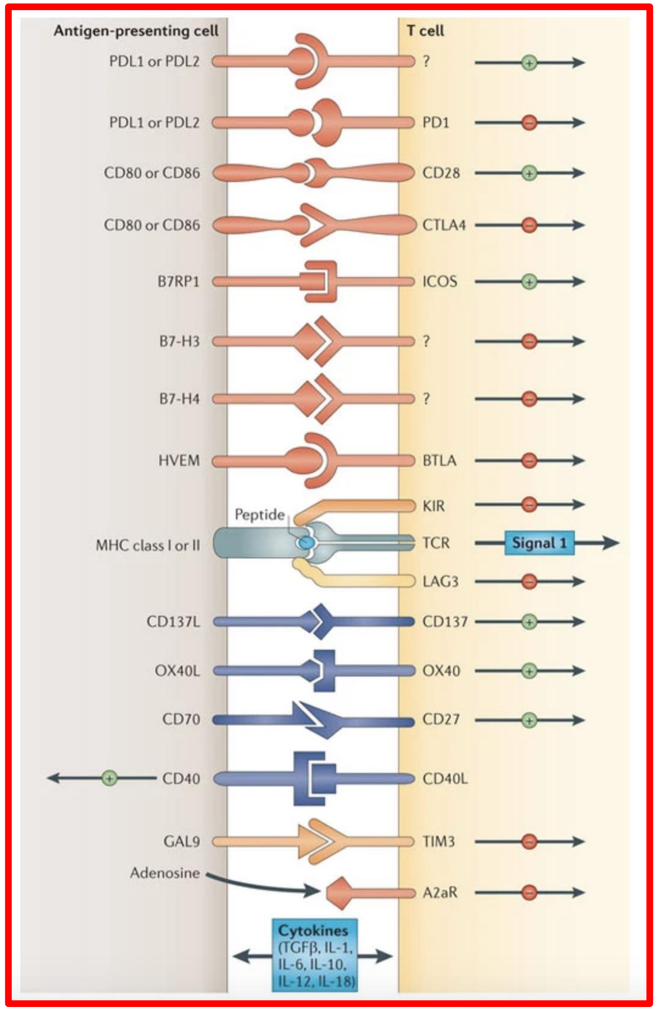


Larkin, NEJM, 2019

ICB resistance

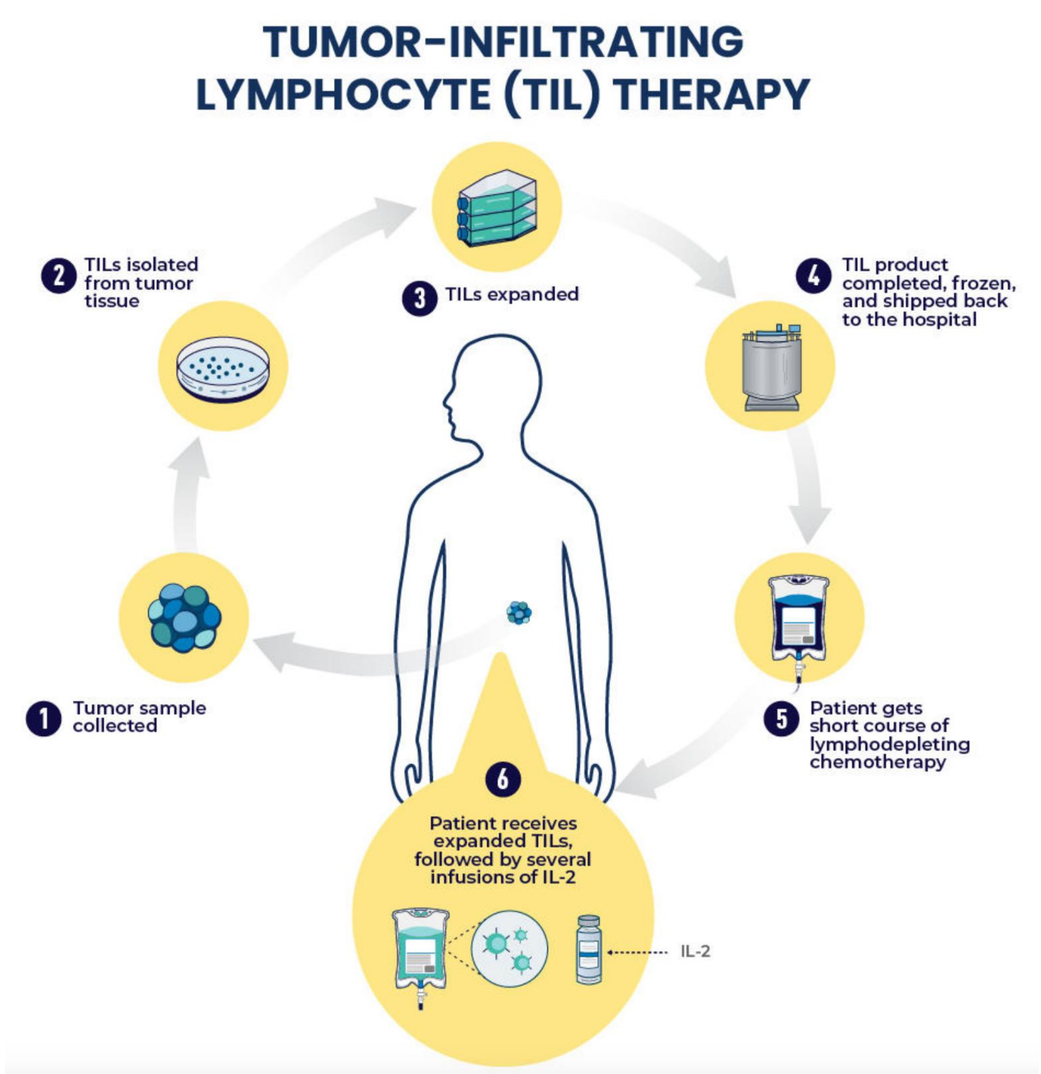


- Mutations in IFNg-JAK/STAT pathway
- Mutations of antigen presentation machinery
- Downregulation of antigen presentation
- Alternative checkpoint regulation…

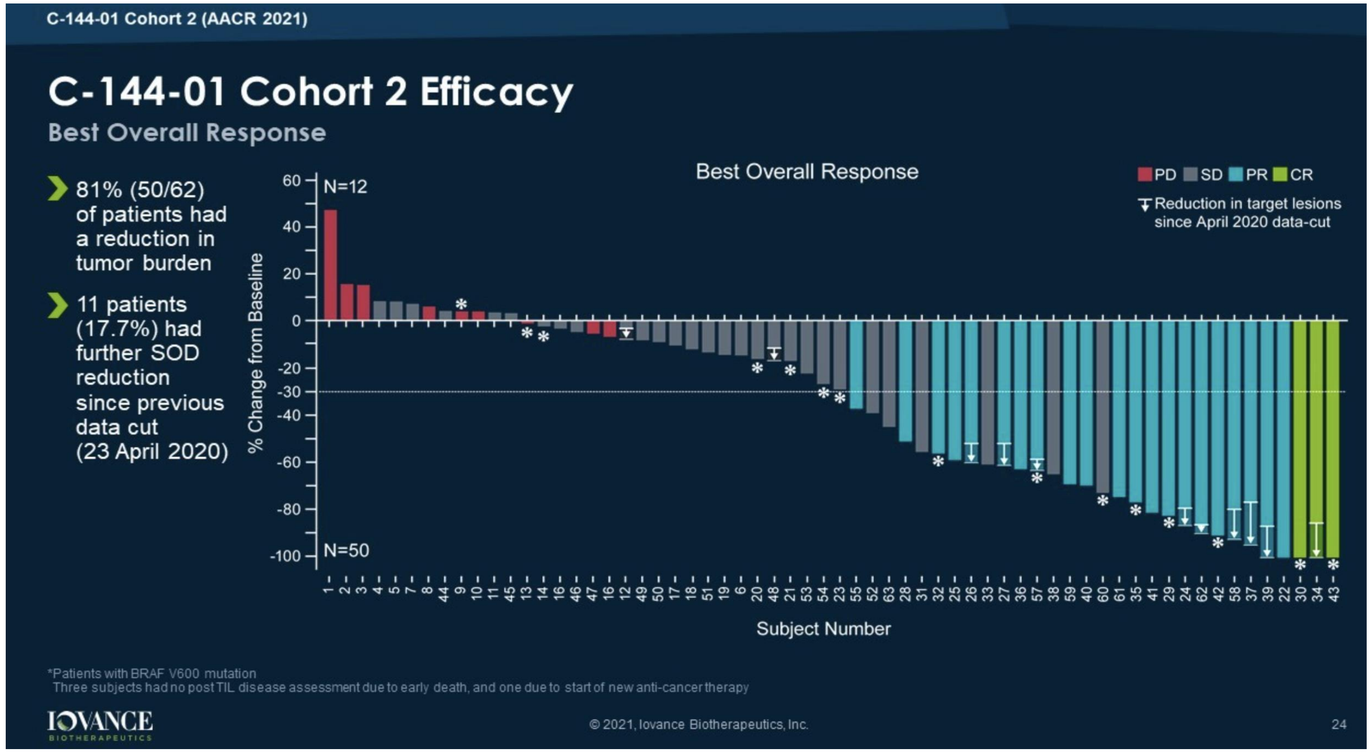


Pardoll, Nat Rev Cancer, 2012

Adoptive TIL transfer in patients

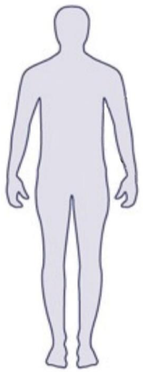


www.cancer.gov

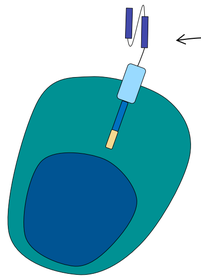


Prior lines of therapy > 3

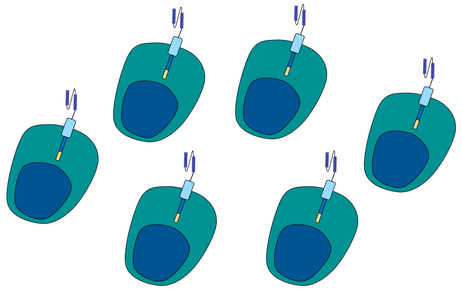
Autologous CAR-T cell therapy



Isolate T cells from patient

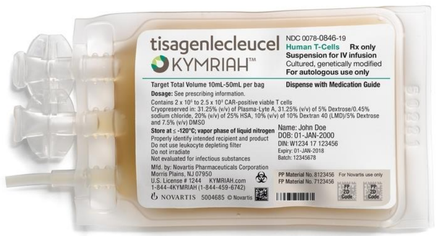


CAR receptor

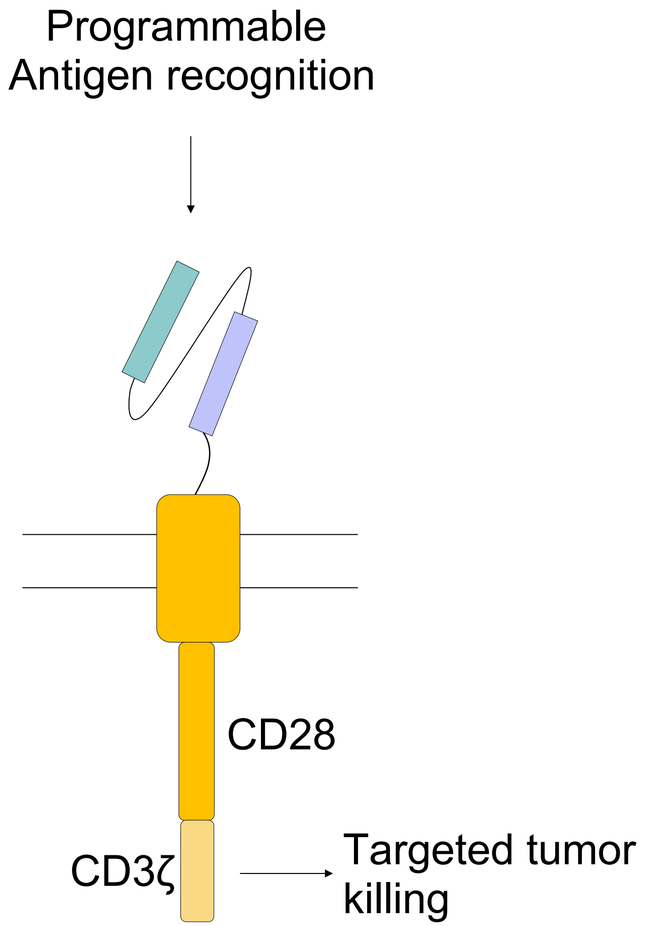


Expand *ex vivo*

Deliver back into patient

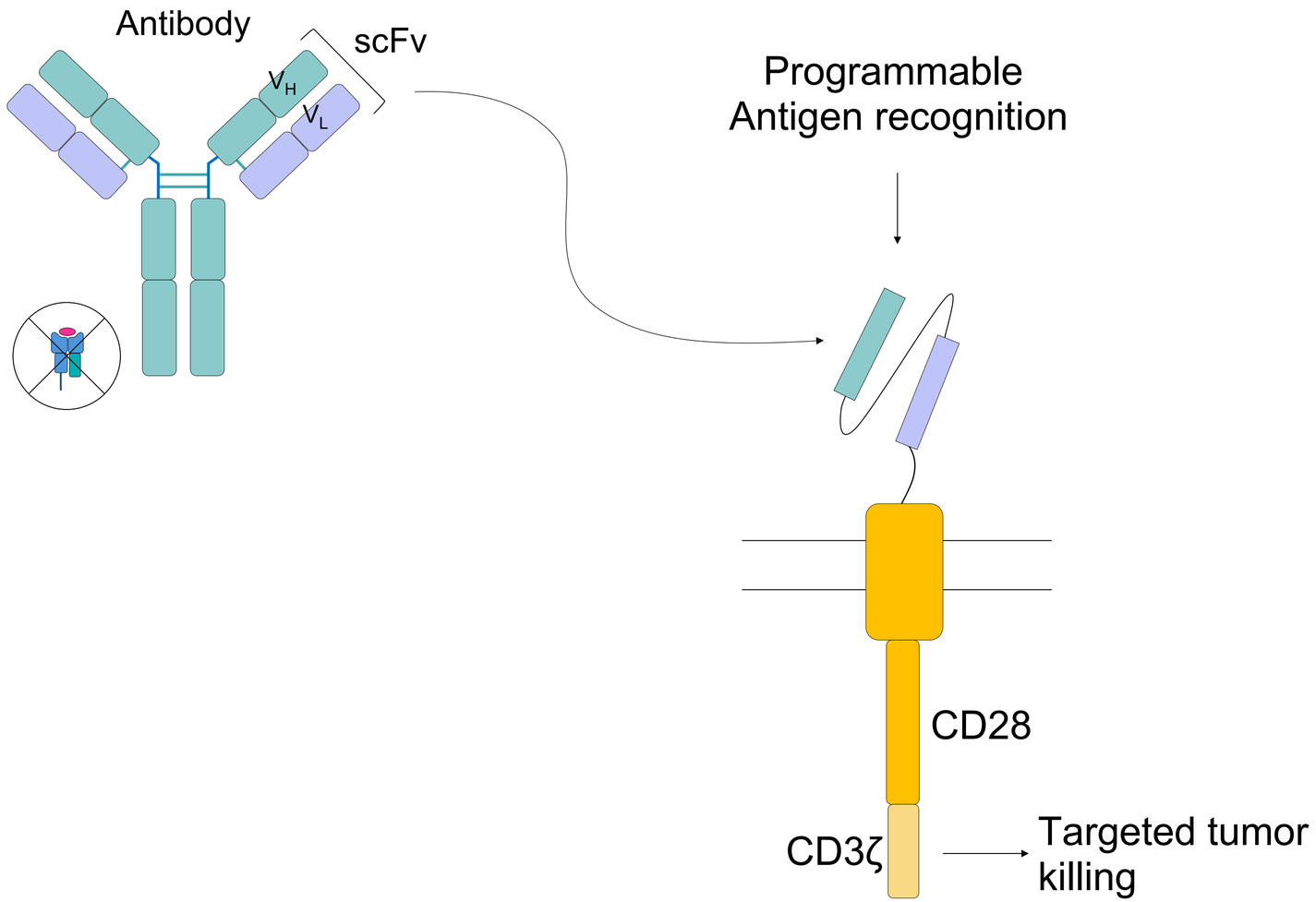


Chimeric Antigen Receptors (CAR) T cells



Slide: Courtesy of Dr. Nic Aparia and Dr. Tal Danino

Solution: Chimeric Antigen Receptors (CAR)



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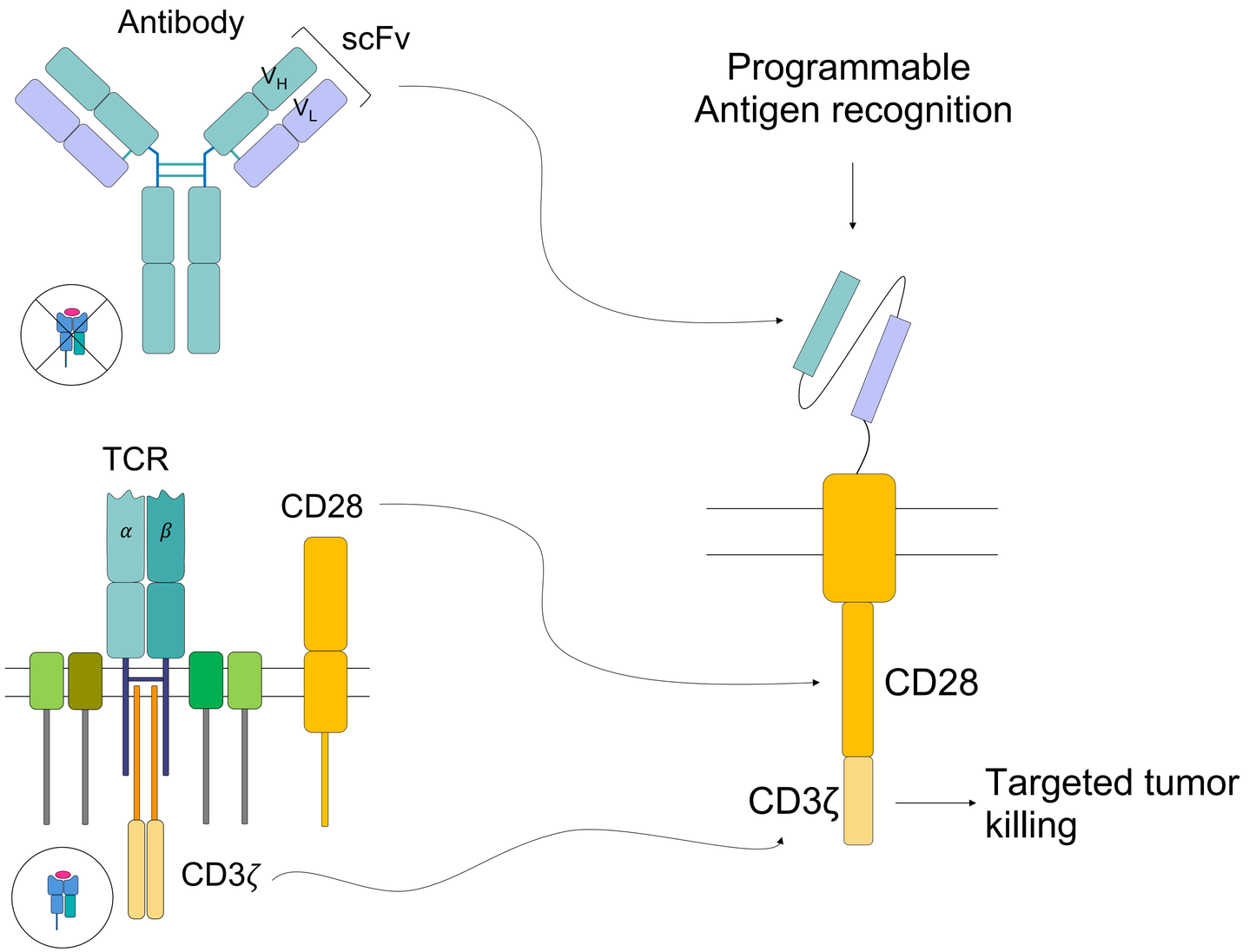

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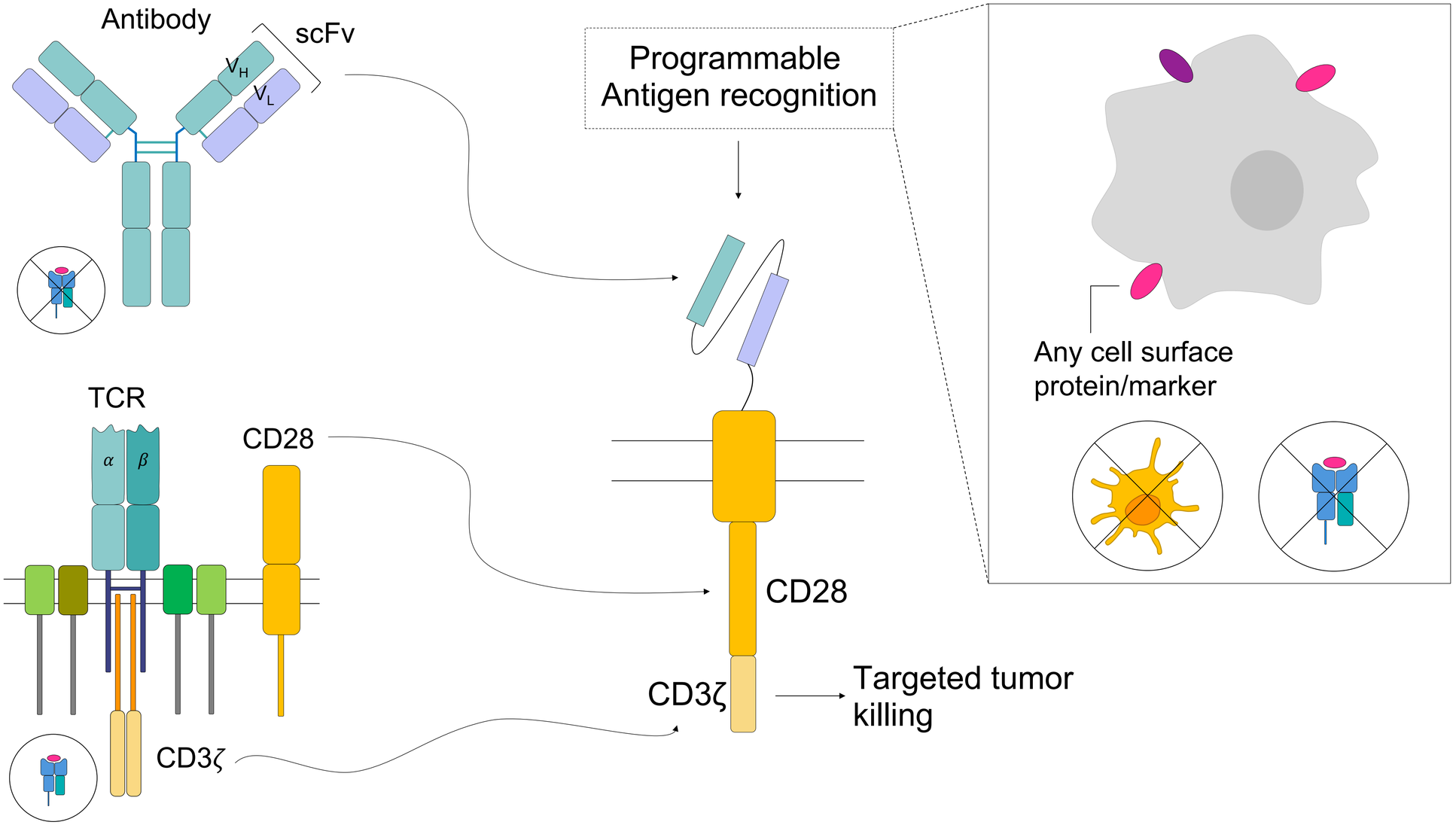
Solution: Chimeric Antigen Receptors (CAR)



Slide: Courtesy of Dr. Nic Aparia and Dr. Tal Danino

CAR-T Cell Therapy: Hematological malignancies

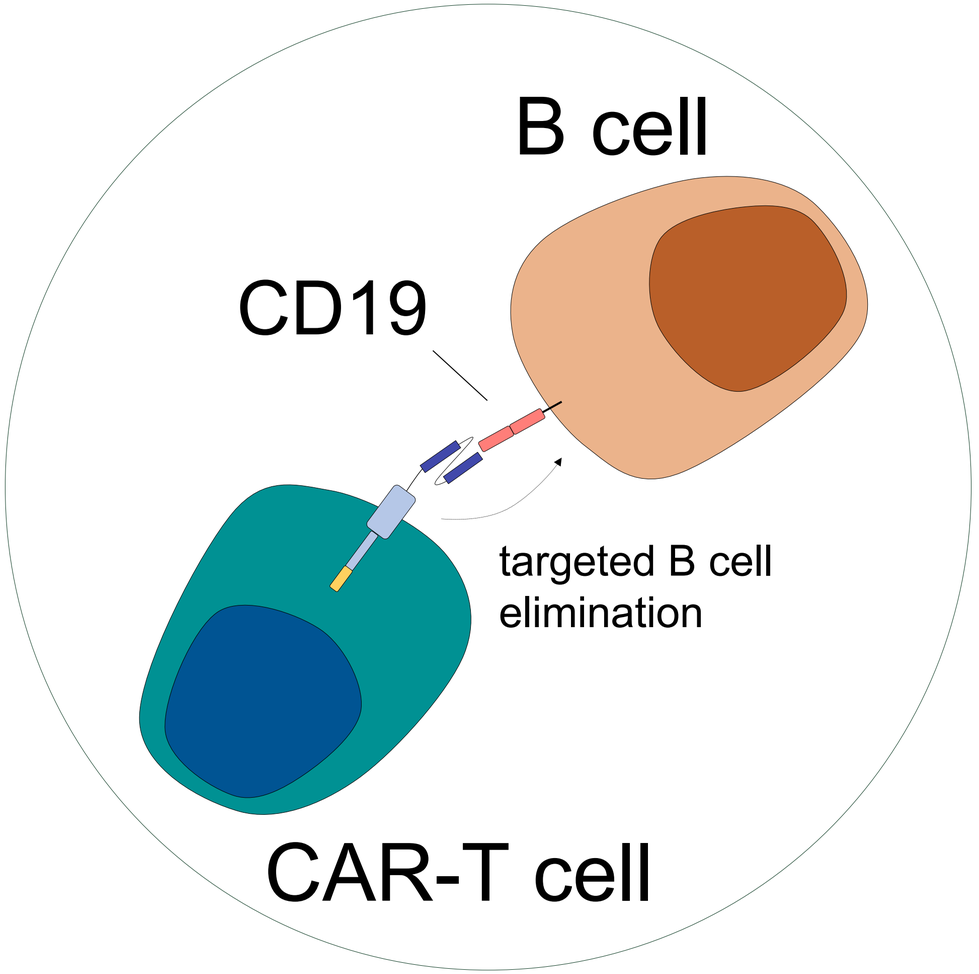
FDA Approvals: **CD19**

2017: Kymriah – Novartis

2017: Yescarta – Gilead

2020: Tecartus – Gilead

2021: Breyanzi – BMS



FDA Approvals: **BCMA**

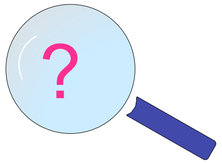
2021: Abecma – BMS

2021: Carvykti – Janssen Biotech

CAR-T Cell Therapy: Limitations in Solid tumors

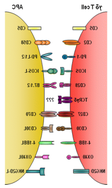
Antigen loss, tumor escape

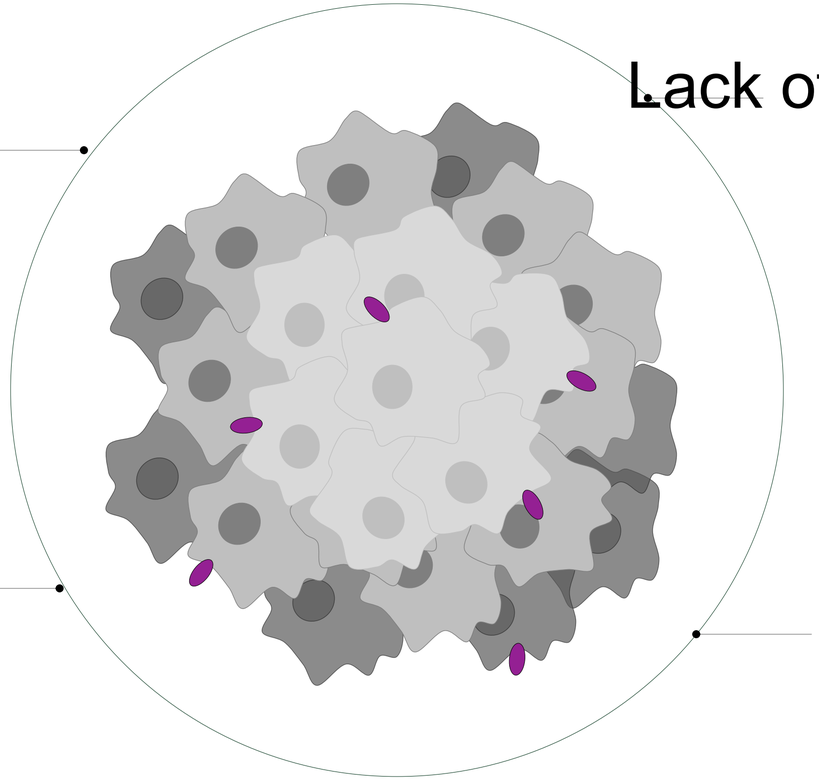
Majzner & Mackall, *Cancer Discovery* (2018)
Choi *et al., Nat. Biotech.* (2019)



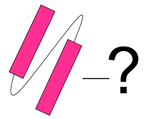
Impaired co-stimulation

Ho et al., Cancer Cell, 2023



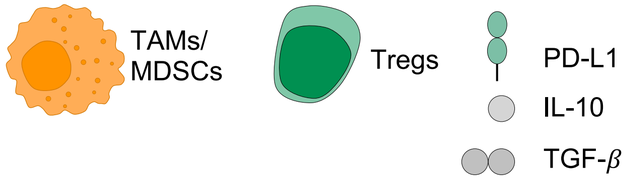


Lack of safe and effective targets



June & Sadelain, *New England J. of Med.* (2018)
Richmanet *et al., Cancer Immunol Res* (2018)

Dysfunction in the immunosuppressive TME



Hyrenius-Wittsten & Roybal, *Nat. Rev. Drug Discov.* (2019)

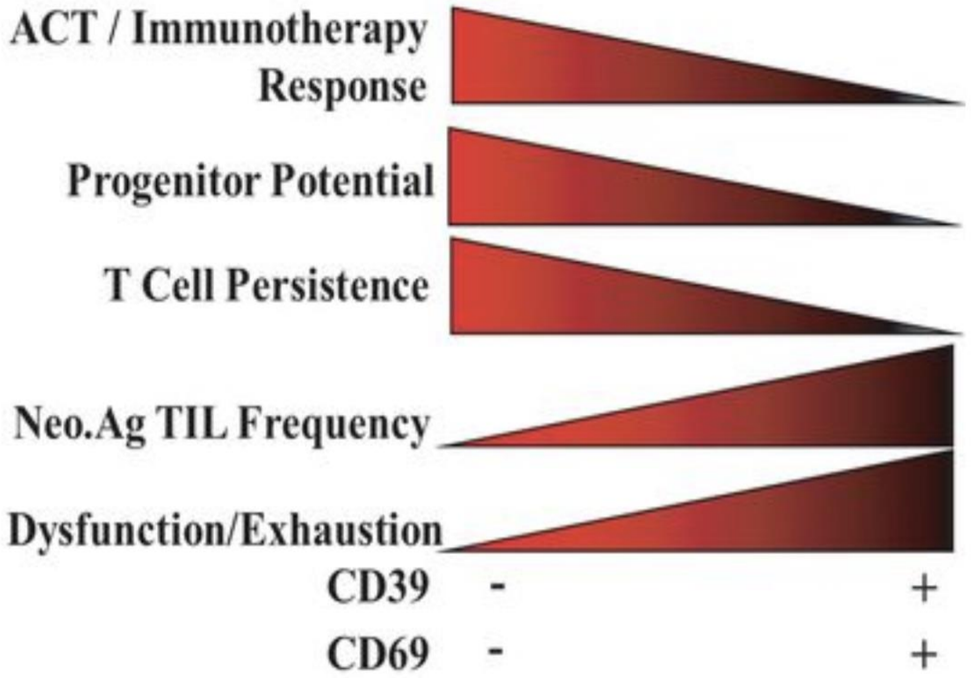
Modified Slide: Courtesy of Dr. Nic Aparia and Dr. Tal Danino

Learning objectives

1. Concept of tumor neoantigens and recognition of non-self
2. Pros and cons of different vaccination strategies
3. Immune checkpoint blockade and mechanisms of resistance
4. TIL therapy vs. CAR-T therapy

What can we learn from nature?

T cell features linked to response

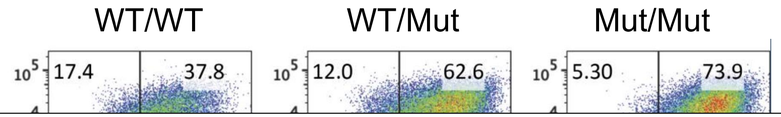


Krishna et al; *Science*, 2020

Rationale for minimalistic cell engineering approach

TSC2 S1365A mutation potently regulates CD8+ T cell function and differentiation and improves adoptive cellular cancer therapy

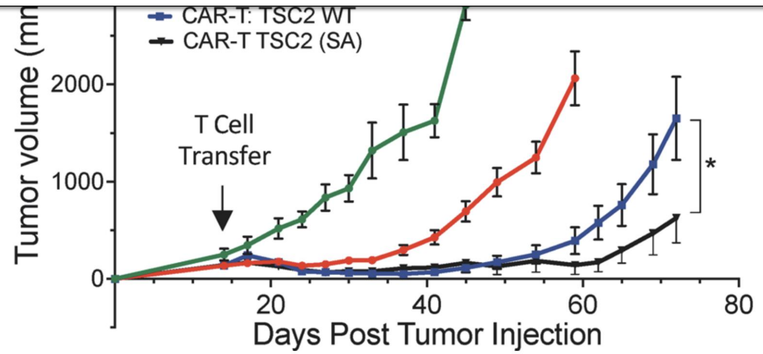
Chirag H. Patel,[1] Yi Dong,[1] Navid Koleini,[2] Xiaoxu Wang,[1] Brittany L. Dunkerly-Eyring,[2] Jiayu Wen,[1] Mark J. Ranek,[2,3] Laura M. Bartle,[4] Daniel B. Henderson,[4] Jason Sagert,[4] David A. Kass,[2,3] and Jonathan D. Powell[1]

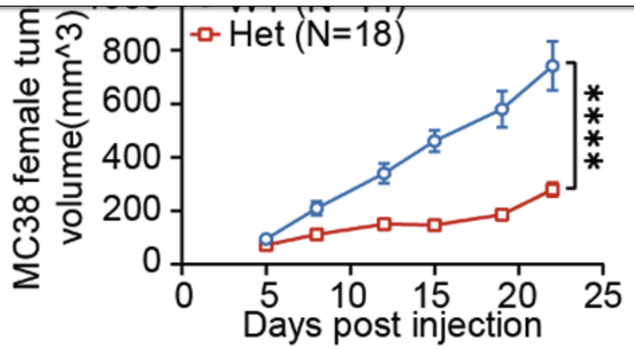


Somatic *TYK2* activating mutations in tumor-infiltrating T cells promote anti-cancer immunity

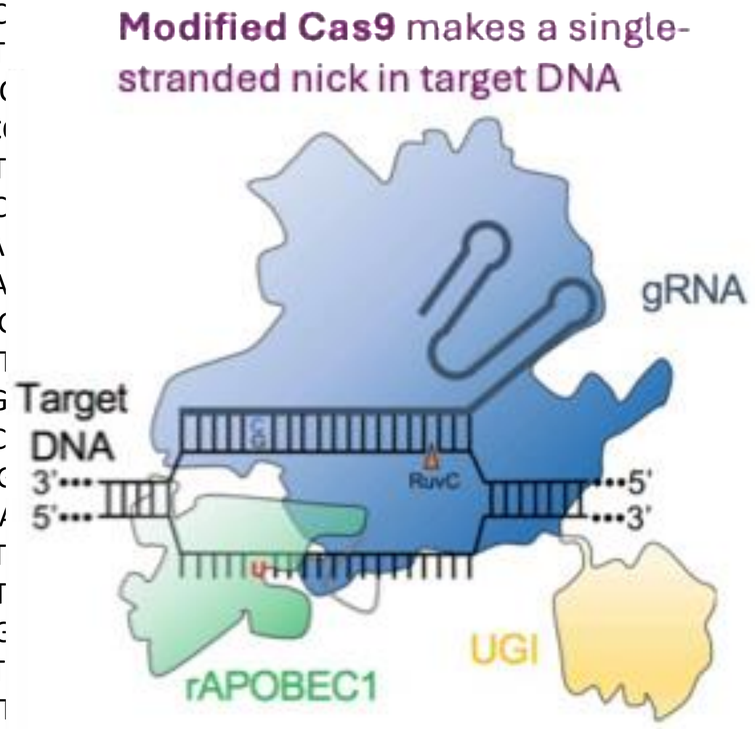
Authors: Zhijie Li[1], Meng-Hsiung Hsieh[1], Alisa Arutyunova[3], John Evans[3], Tao Liu[3], Andrew R.J. Lawson[4], Pantelis A. Nicola[4], Gerda Kildisiute[3], Heather E. Machado[3], Ahmad Al Kawam[3], Rui Wang[3], Qiyu Zeng[1], Nisi Jiang[1], Xun Wang[1], Gregory Mannino[1], Xiongzhao Ren[1], Xiangyi Fang[1], Tripti Sharma[1], Suman Komjeti[1], David Hsiehchen[4], Scott Hayton[3], Simon Brunner[3], Iñigo Martincorena[3,4], Peter J. Campbell[3], and Hao Zhu[1]

Hypothesis: Naturally occurring or synthetic protein variants may enhance human T cell function and enable production of more effective cell therapies.x

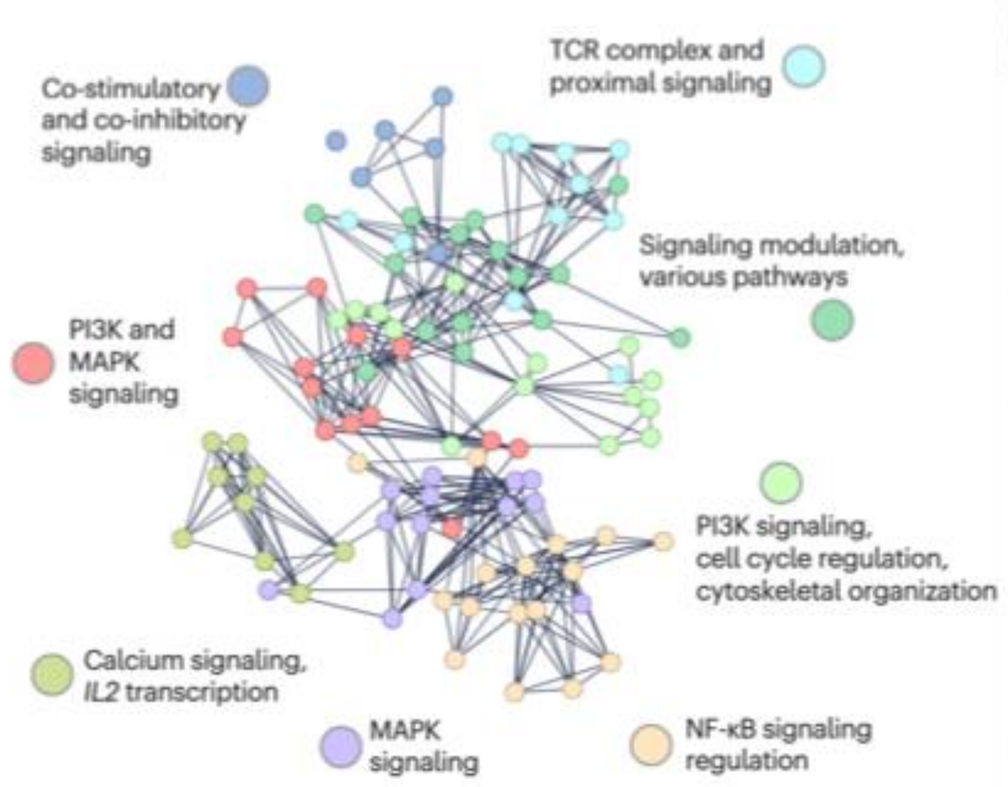




How and what to engineer?

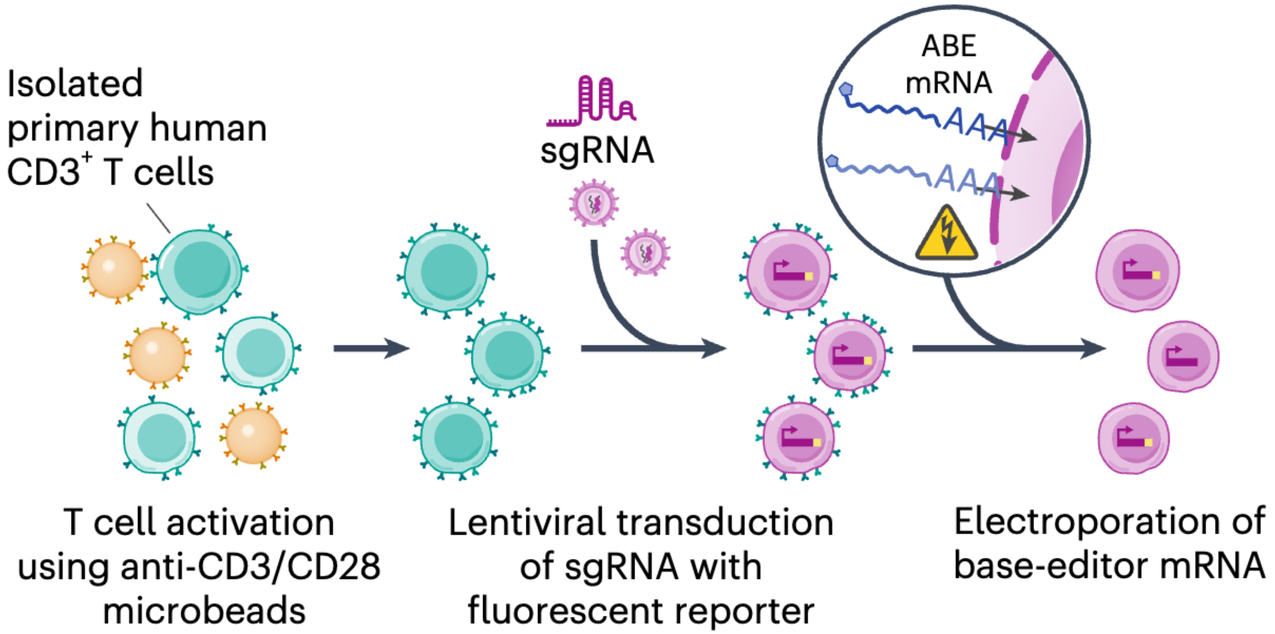


Webber et al., ***Nature Communications****, 2019*



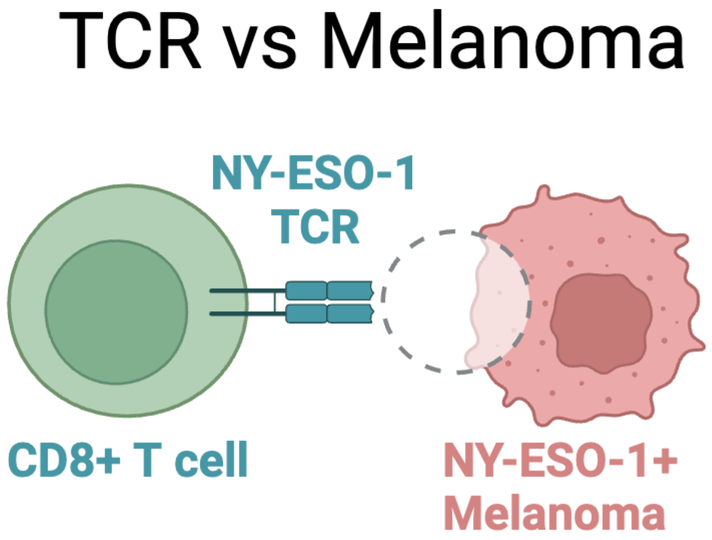
Walsh, Shah*, et al.,* ***Nature Biotechnology,*** *2024*
Walsh et al., ***Cell****, 2025*

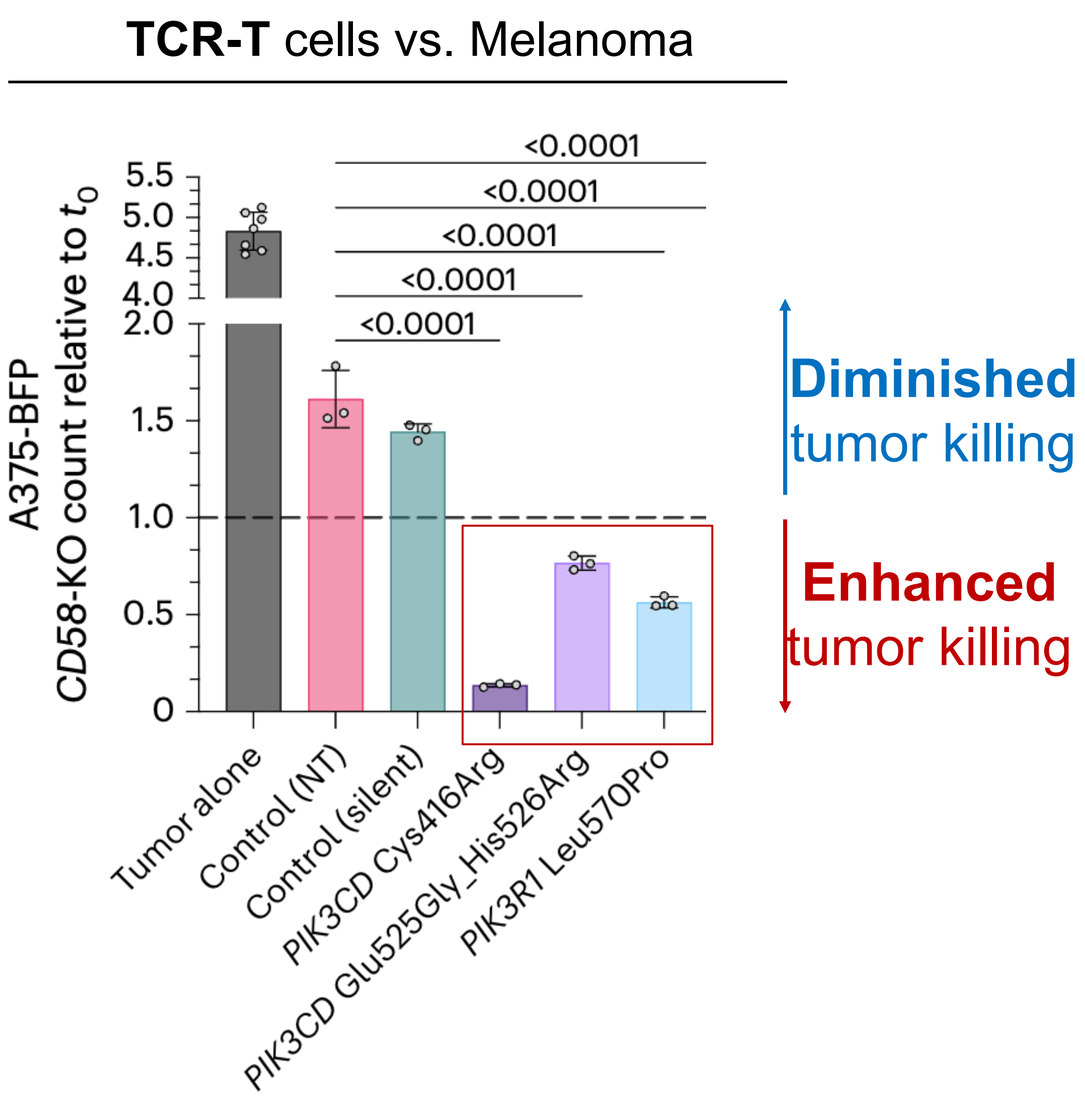
Mapping variant effects to hallmarks of T cell-mediated immunity



Walsh, Shah*, et al.,* ***Nature Biotechnology,*** *2024*

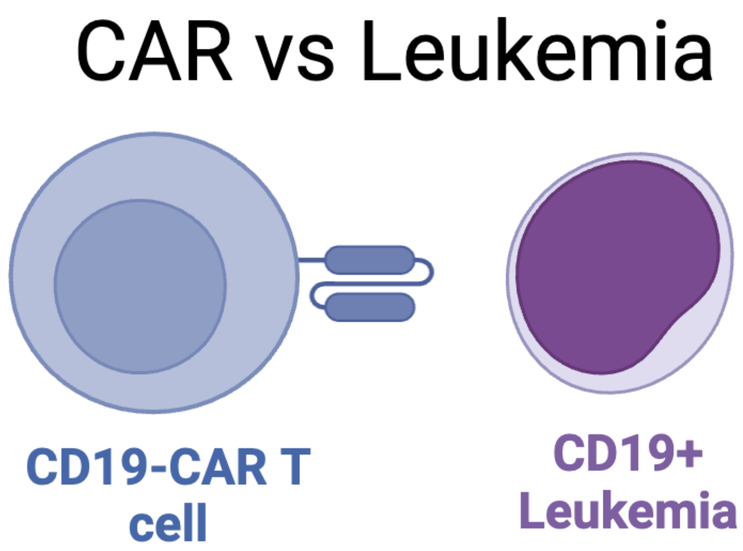
Can we harness these variants for cell therapies?

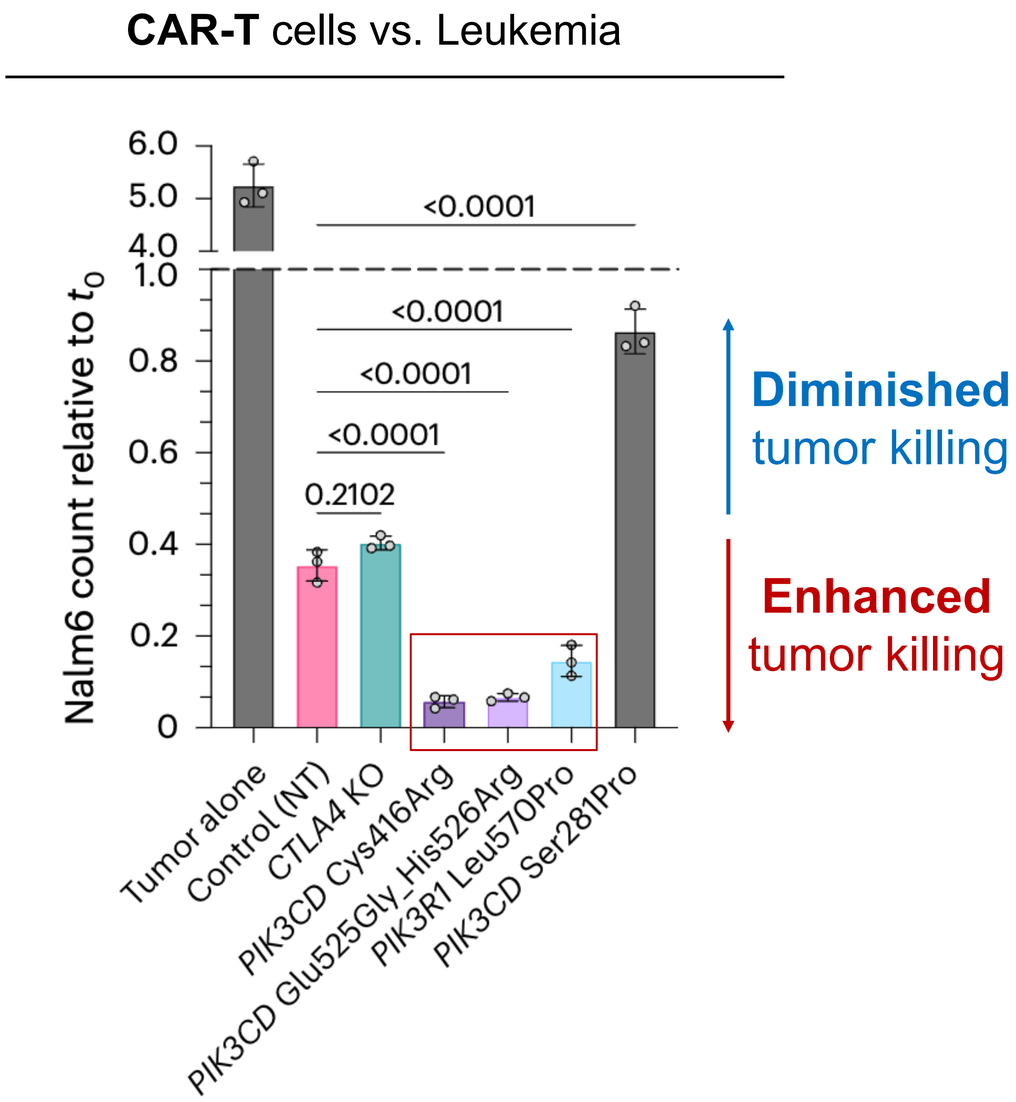




Walsh, Shah*, et al.,* ***Nature Biotechnology,*** *2024*

Can we harness these variants for cell therapies?





Walsh, Shah*, et al.,* ***Nature Biotechnology,*** *2024*

Questions?