Cancer Vaccines

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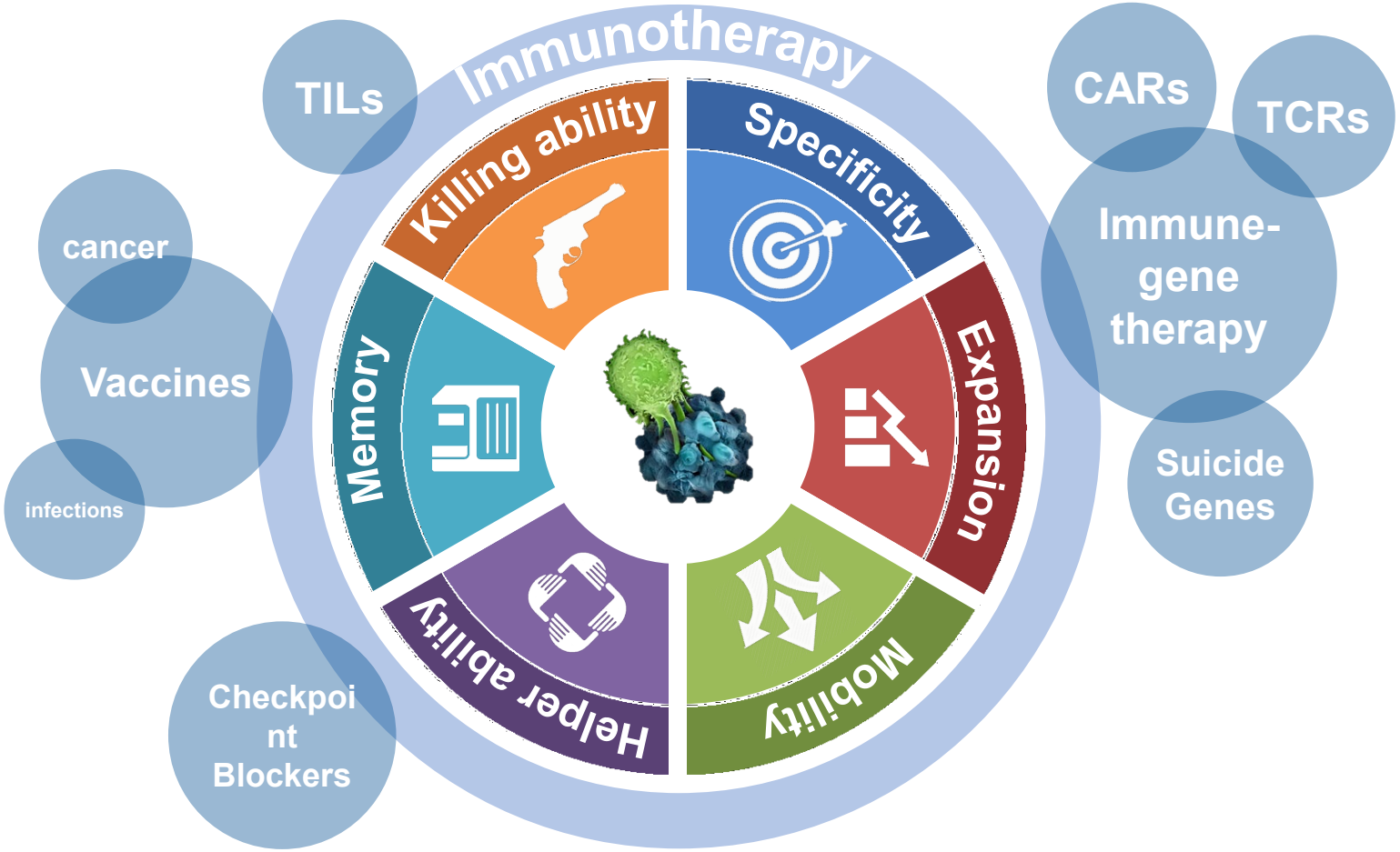
Disclosures

I hold equity in BioNTech, and receive research funding from Pharmacyclics

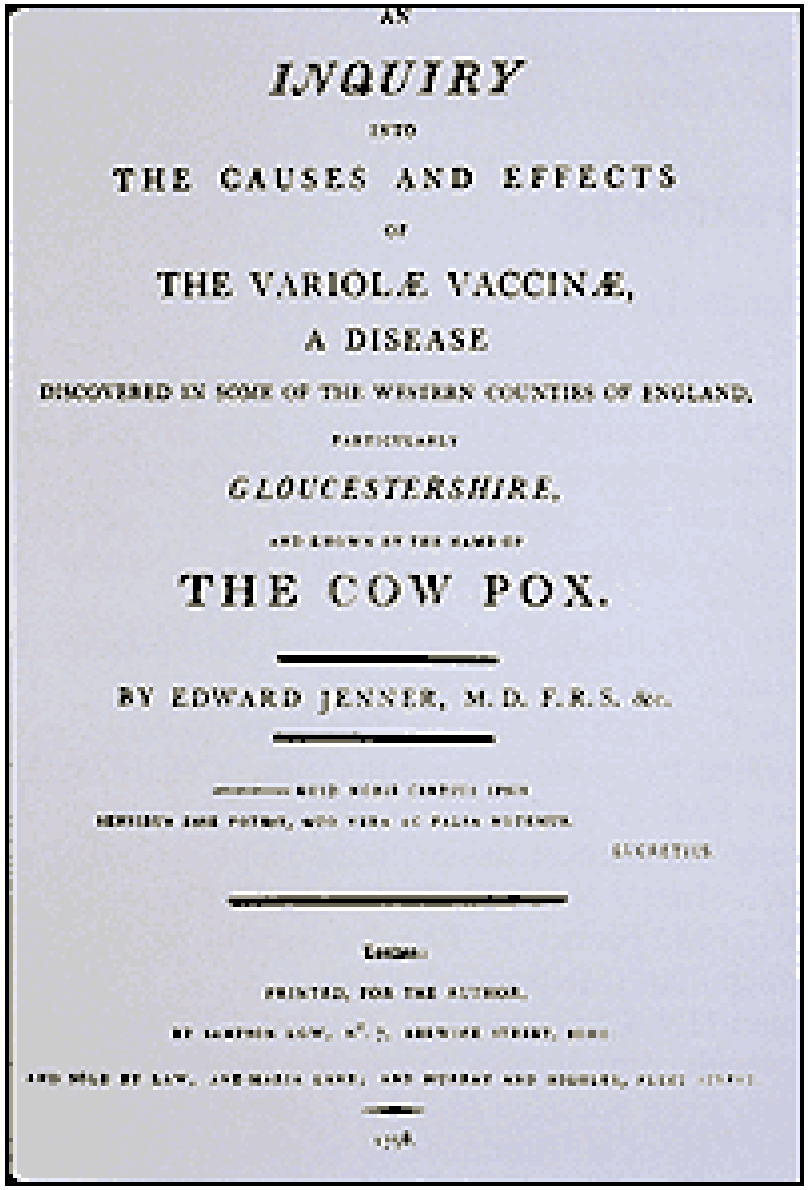
Hallmarks of T lymphocytes



Principles underlying immunotherapeutics

- ***Taking advantage of existing spontaneous T cell responses***
  - Adoptive transfer of TILs
  - Checkpoint inhibitors
  - Oncolytic viruses
  - Cancer vaccines

- ***Engineering new responses***
  - Antibody therapy
  - CAR-Ts
  - Oncolytic viruses
  - Cancer vaccines



AN

INQUIRY

INTO

THE CAUSES AND EFFECTS

OF

THE VARIOLÆ VACCINÆ,

A DISEASE

DISCOVERED IN SOME OF THE WESTERN COUNTIES OF ENGLAND,

PARTICULARLY

GLOUCESTERSHIRE,

AND KNOWN BY THE NAME OF

THE COW POX.

BY EDWARD JENNER, M.D. F.R.S. &c.

PRINTED, FOR THE AUTHOR,

1798.

Dr. Donald A. Henderson

Title page of a 1798 book by Edward Jenner, documenting his findings.

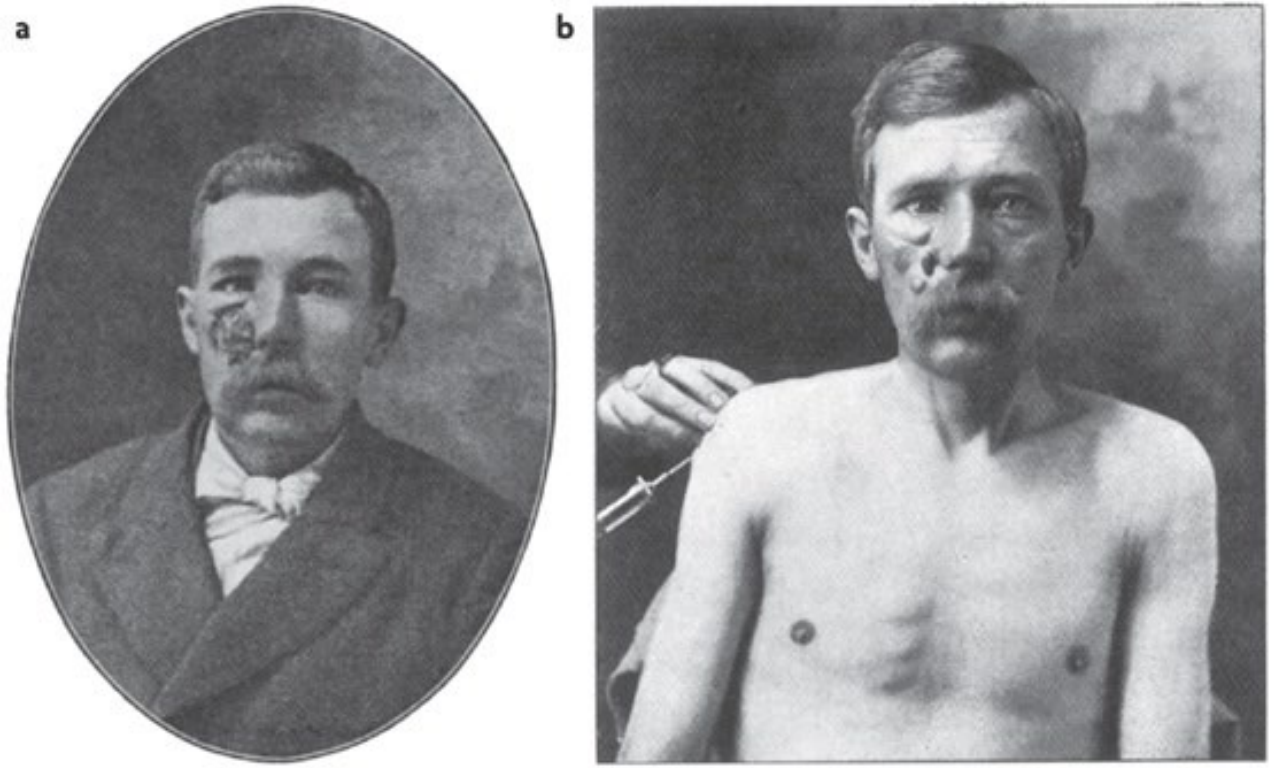
JENNER 1798

Cowpox immunization prevents smallpox

PASTEUR 1870s

Inactivated pathogen

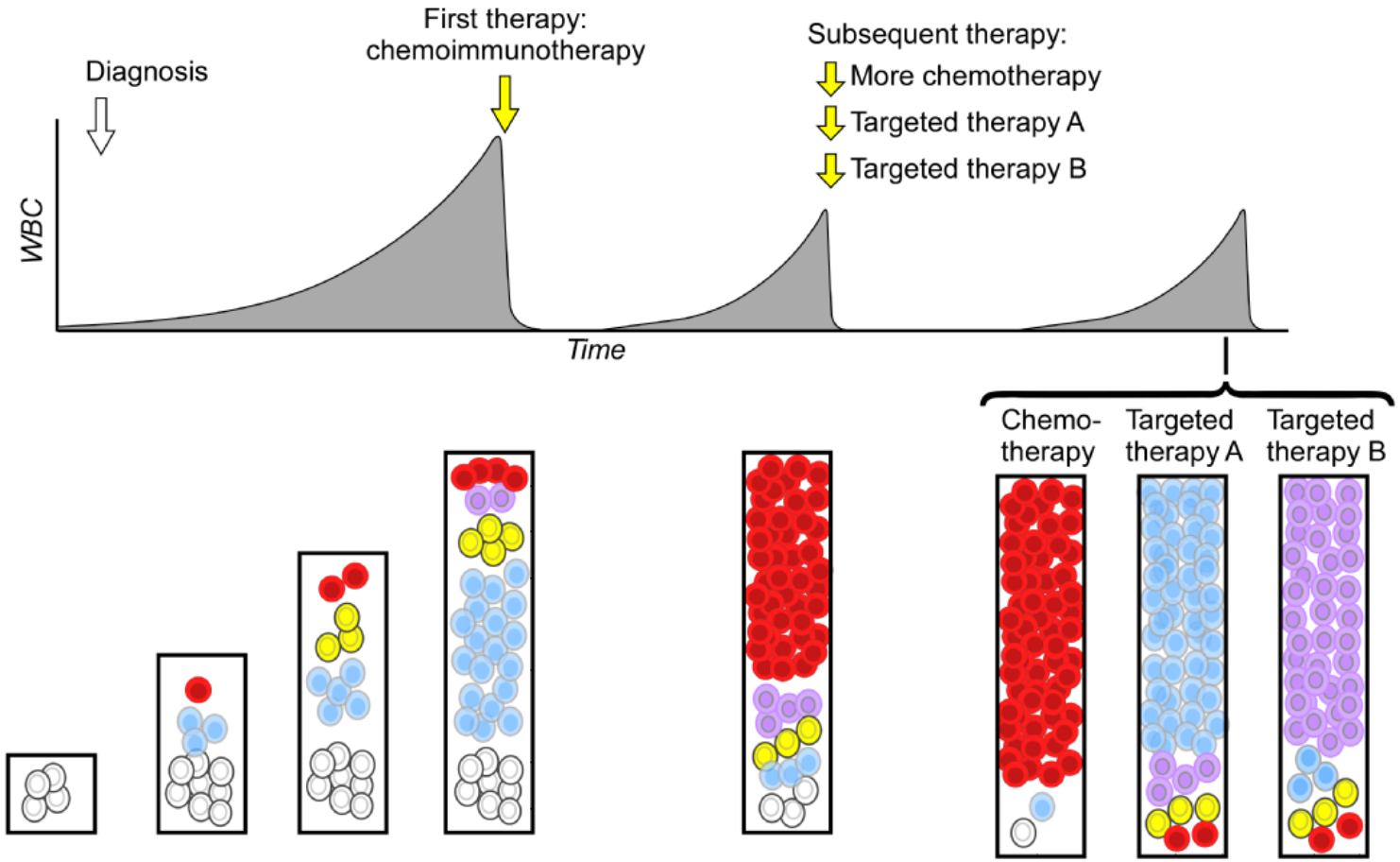
Whispers and murmurs: Coley’s toxin-- the first adjuvant



A patient with round cell sarcoma of the jaw and abdominal metastases seen by Coley in 1899. a | Photograph after 63 injections with Coley's toxins; tumour had diminished to about half its original size. b | Photograph after further treatment with Coley's toxins. In his 1910 lecture at the Royal Society of Medicine Coley reported that the patient was still alive and well. Images reproduced, with permission, from Ref. 17 © (1910) Royal Society of Medicine.

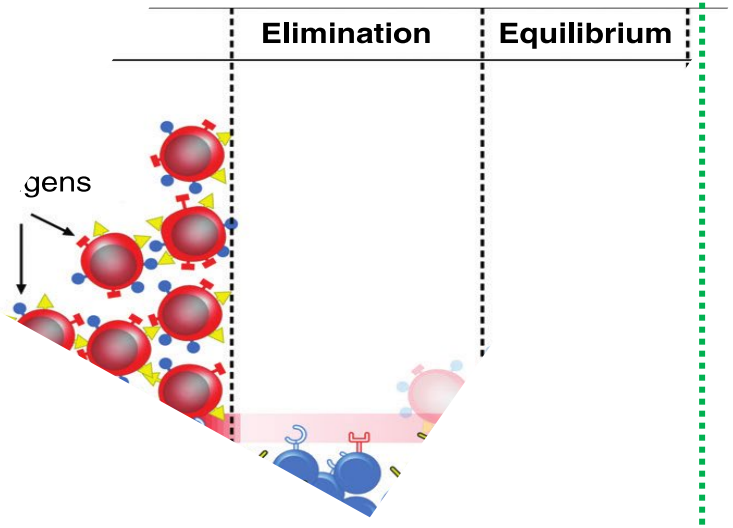
What is the challenge?

1. The evolutionary capacity of cancer: fuel for therapeutic resistance



Lazarian, Guieze & Wu 2015

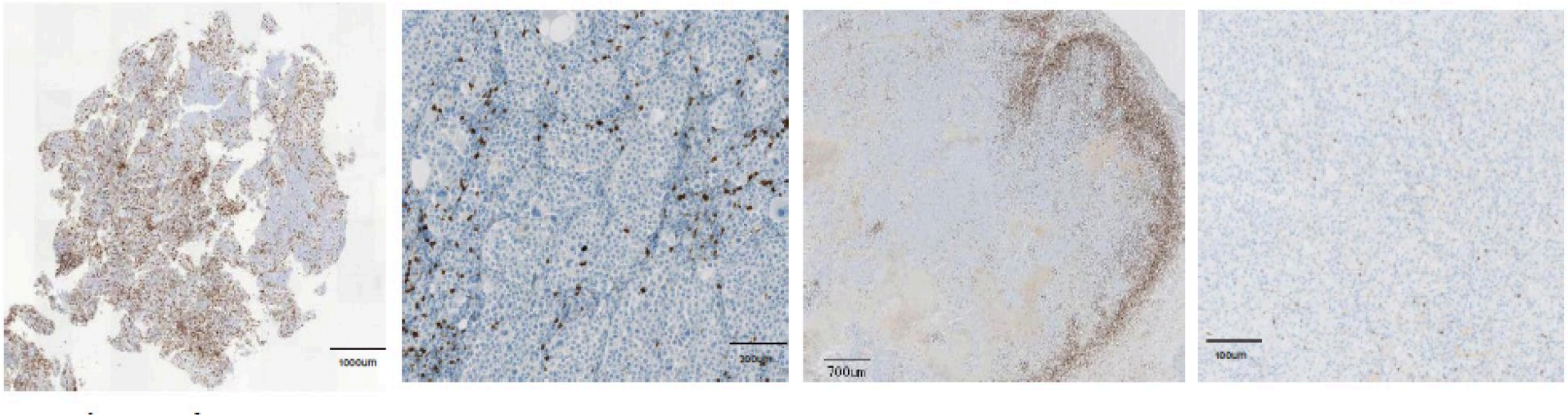
2. How do we address tumor-immune co- evolution?



Purroy N and Wu C. *Cold Spring Harb Perspect Med*. 2017

3. What about tumors without pre-existing immunity?

Pre-existing Immunity (20-30%) | **Non-functional immune response** | **Excluded infiltrate** | **Immune desert**



CD8 / IFN signature

Current immunotherapies work best for patients with a pre-existing anti-tumor immune response

***Challenge*: driving T cells/immune cells into tumors**

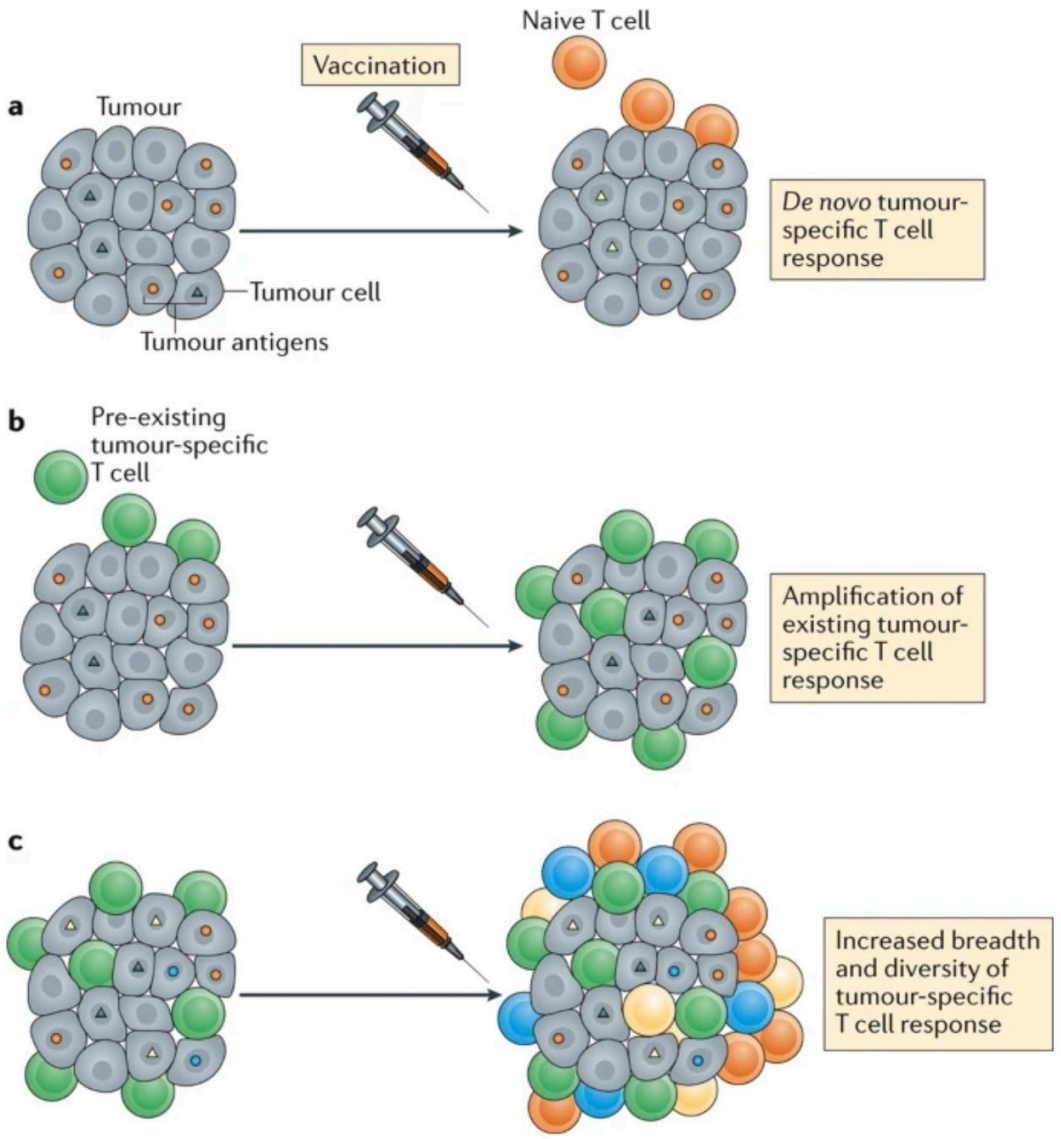
- Insufficient priming
- Absence of antigens or dysfunctional antigen presentation leading to immunologic ignorance
- Suppressive soluble factors or inhibitory immune cell populations leading to immune tolerance
- Vascular factors, chemokines or ECM conditions posing barriers to migration of T cells into tumor

What can vaccines do?

Vaccines: an opportunity to expand tumor-directed T cell responses

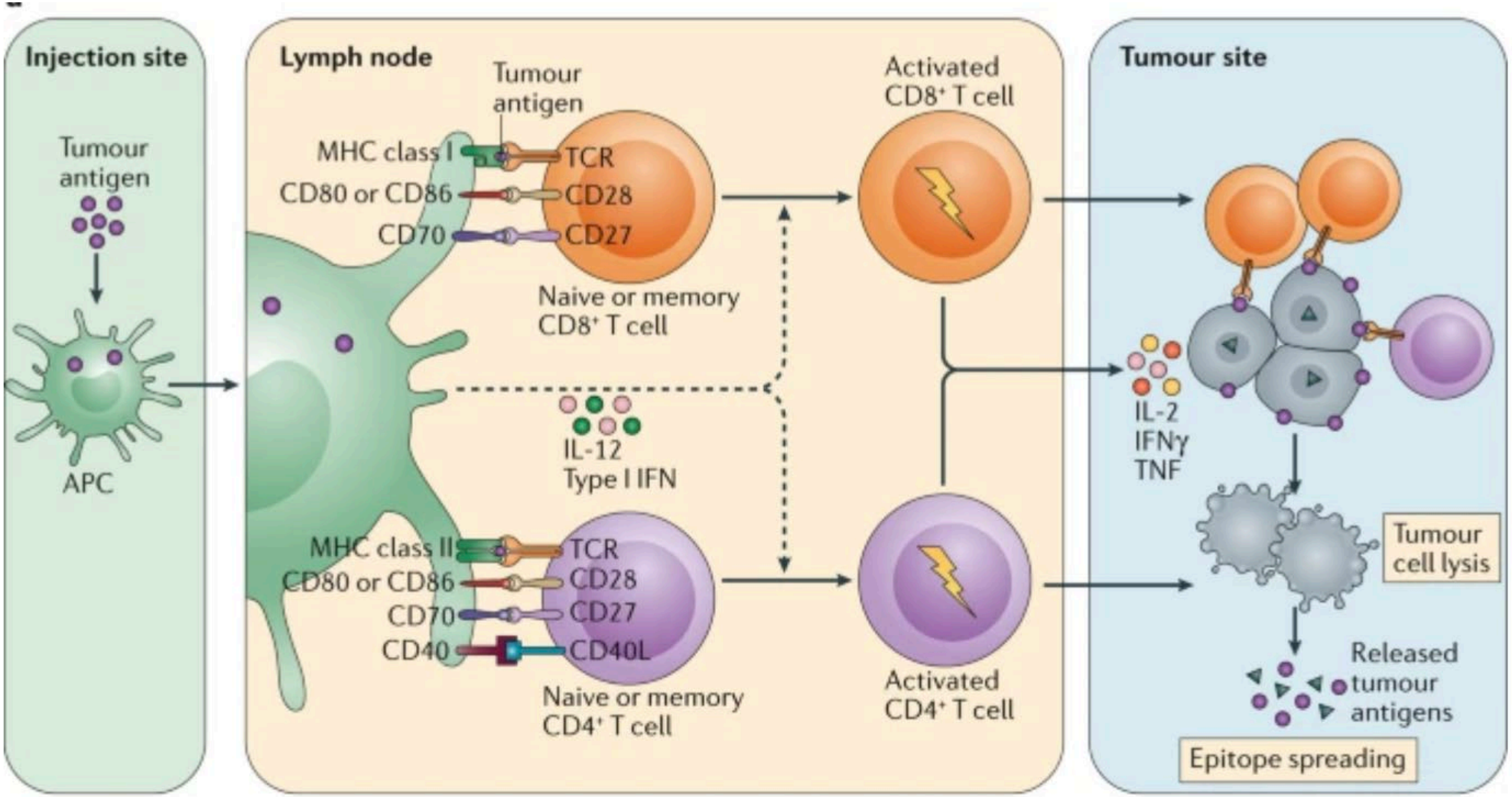
Pathogens —— **Prophylactic/Preventive vaccines**

Cancer —— **Therapeutic vaccines**

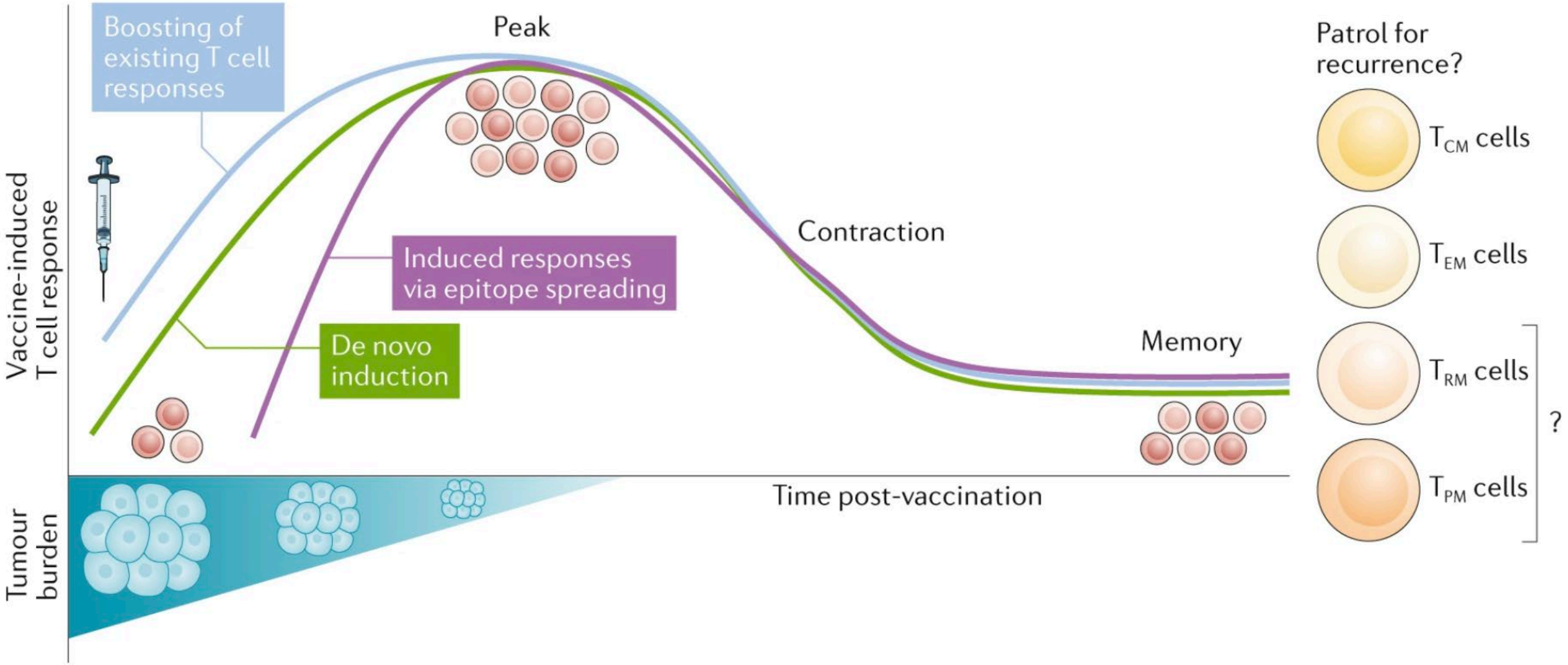


Hu Ott Wu *Nature Reviews Immunology* 2018

Vaccines: an opportunity to expand tumor-directed T cell responses



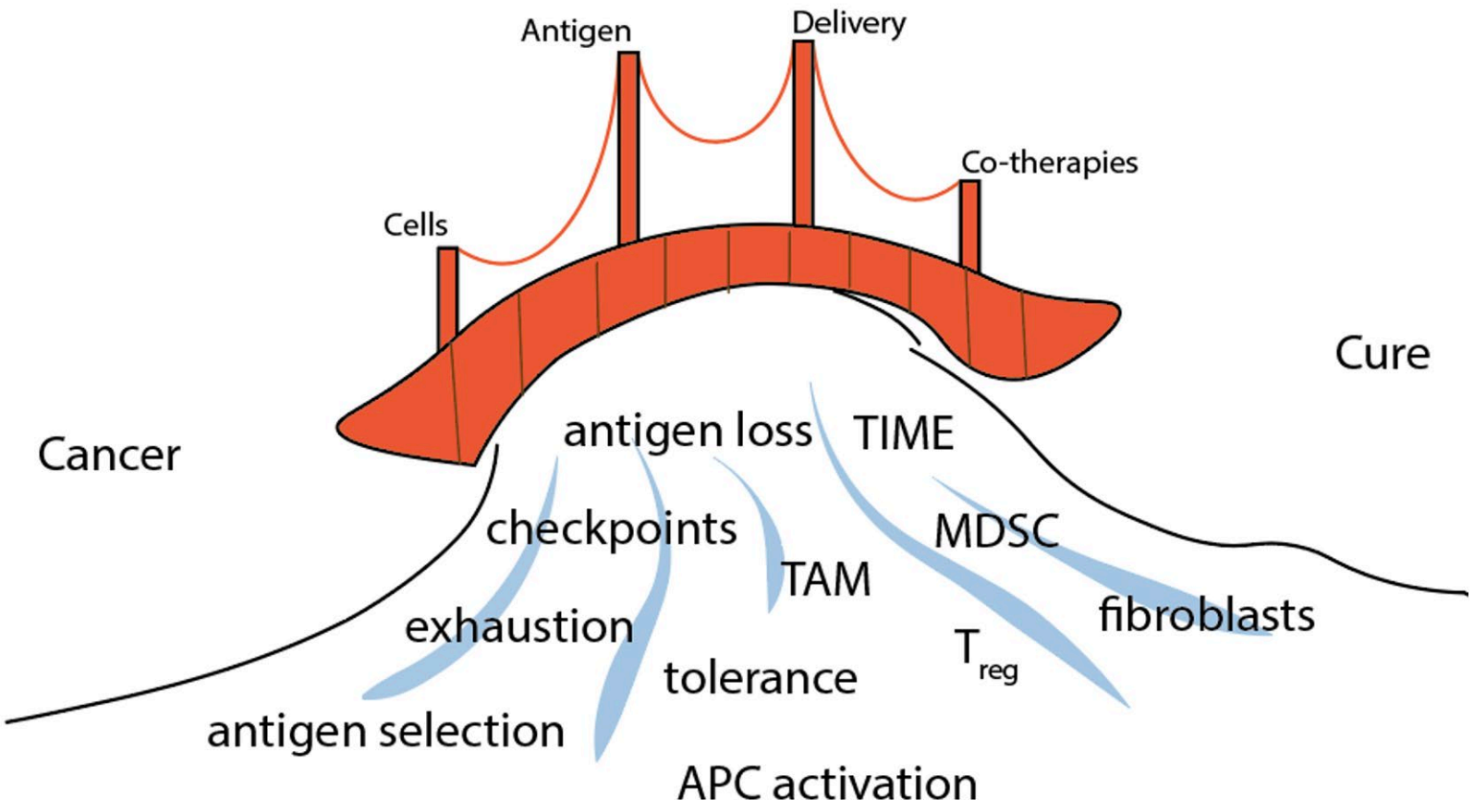
Hu Ott Wu *Nature Reviews Immunology* 2018



Blass, Ott *Nature Rev Clin Oncol*, 2021

What are the critical components of a vaccine?

Vaccines: a bridge to cure….?



Diverse choices

Antigen

Tumor-associated

- Cancer-testis
- Oncofetal
- Tissue differentiation
- Overexpressed
- Oncogenic viral

Tumor-specific

- Neoantigens

Adjuvant

Cytokines

- GM-CSF
- IL-2

TLR agonists

- Poly ICLC
- MPL
- CpG ODN

STING ligands

DC-targeted mAb

- DC205
- Agonistic αCD40

Tetanus/diphtheria toxoid

Formulation and delivery

Peptide/protein

Nucleic acid-based

- DNA
- mRNA

Cell-based

- Whole tumor cell
- Ag-loaded DC
- DC-targeting antibody

HSP-based

Vector-based

- Viral
- Bacterial

Emulsions

- Montanide ISA 51, 720

Saponin-based

- ISCOMATRIX
- QS-21

Liposomes

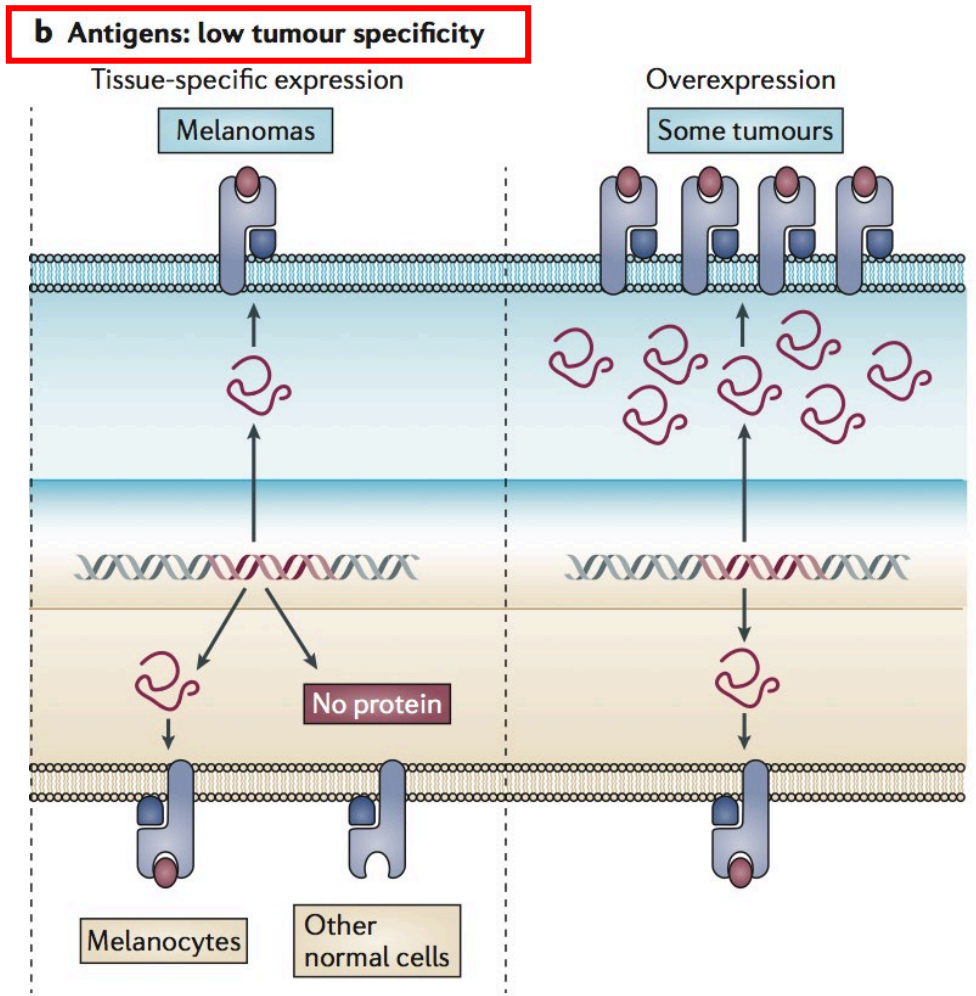
Virosomes

Nanoparticles


So many choices
So little time!

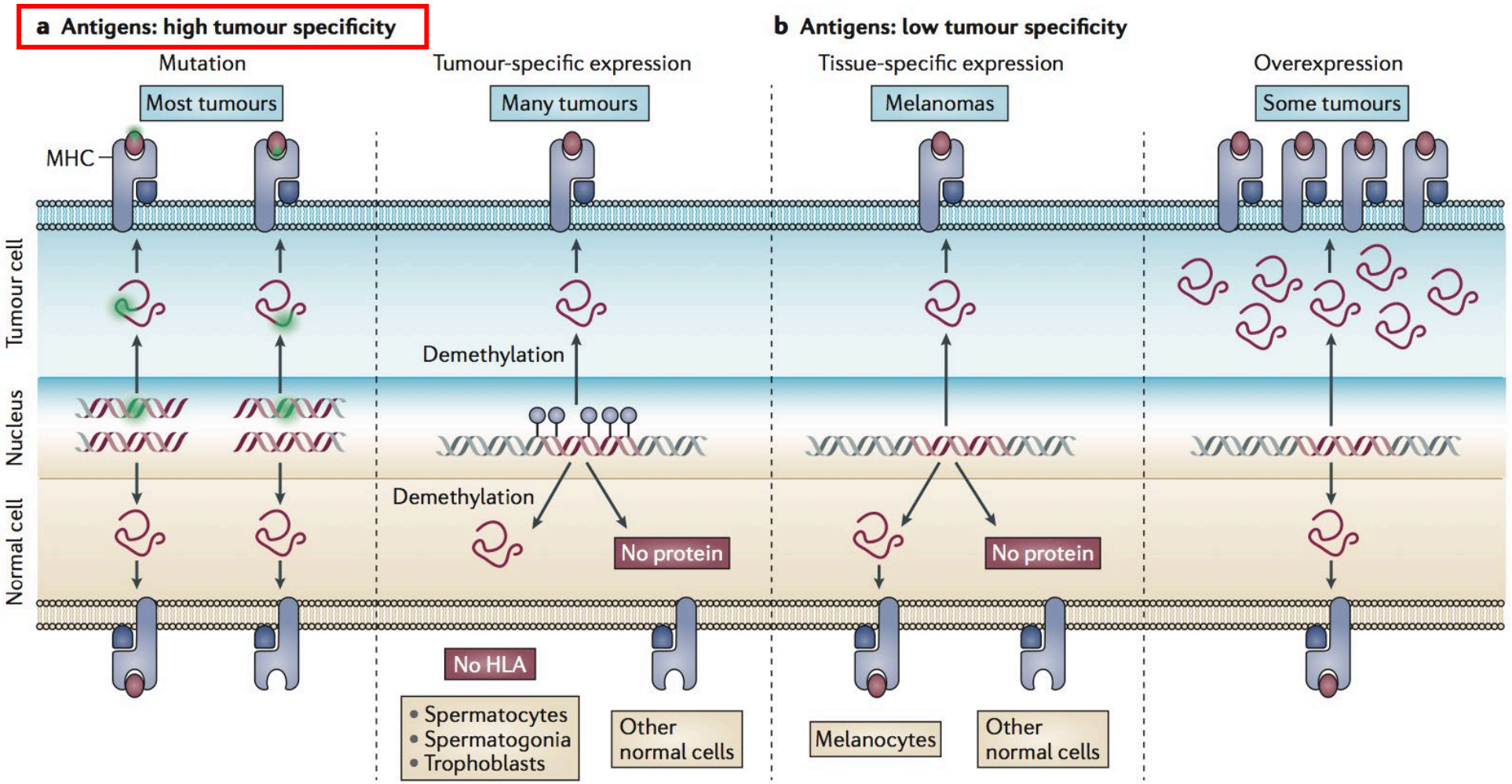
Classes of tumor antigens

Overexpressed Ag, shared

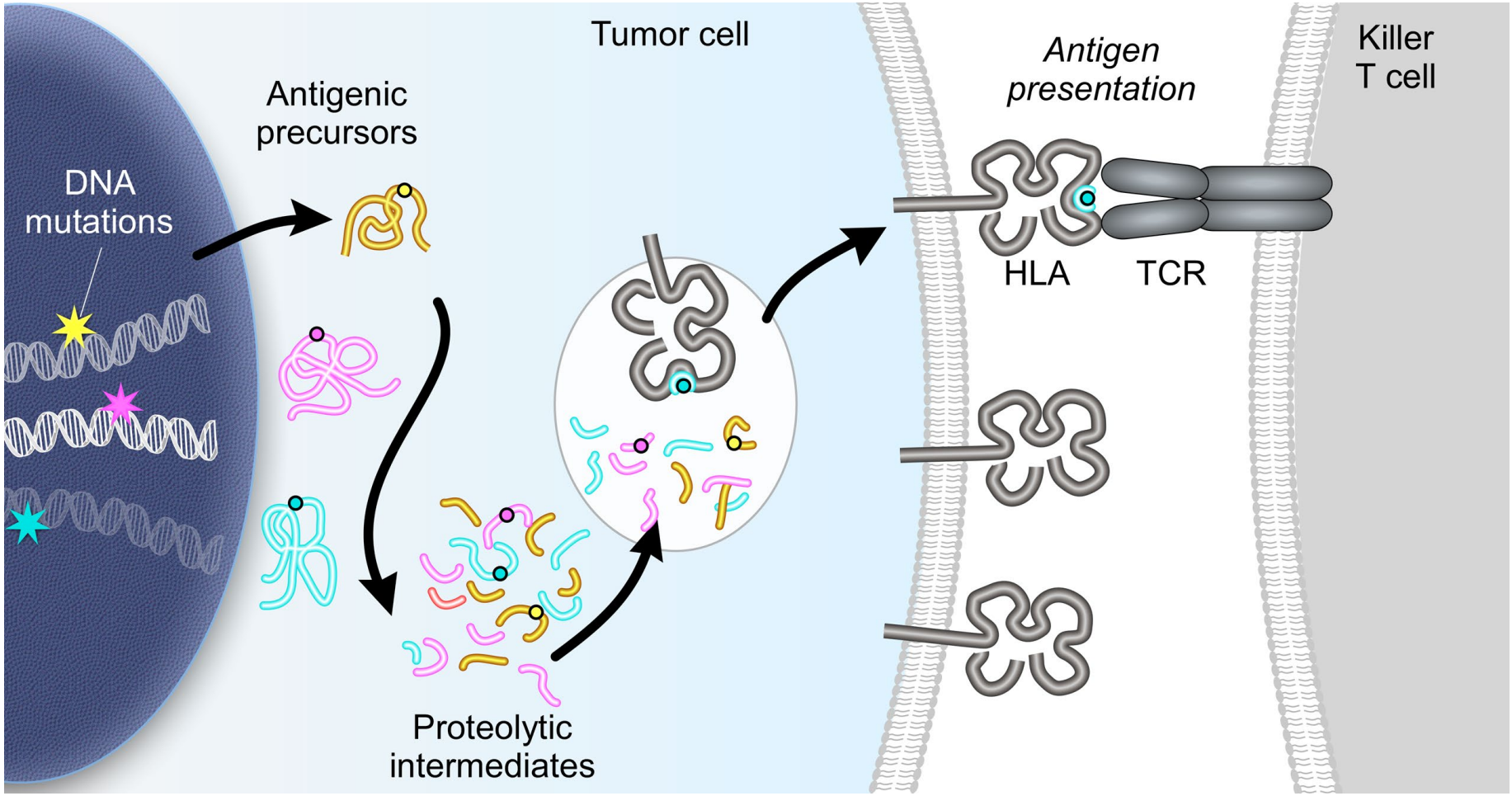


Classes of tumor antigens

Neoantigens **CT antigens** **Overexpressed Ag, shared**



Somatic mutations have the potential to generate neoantigens



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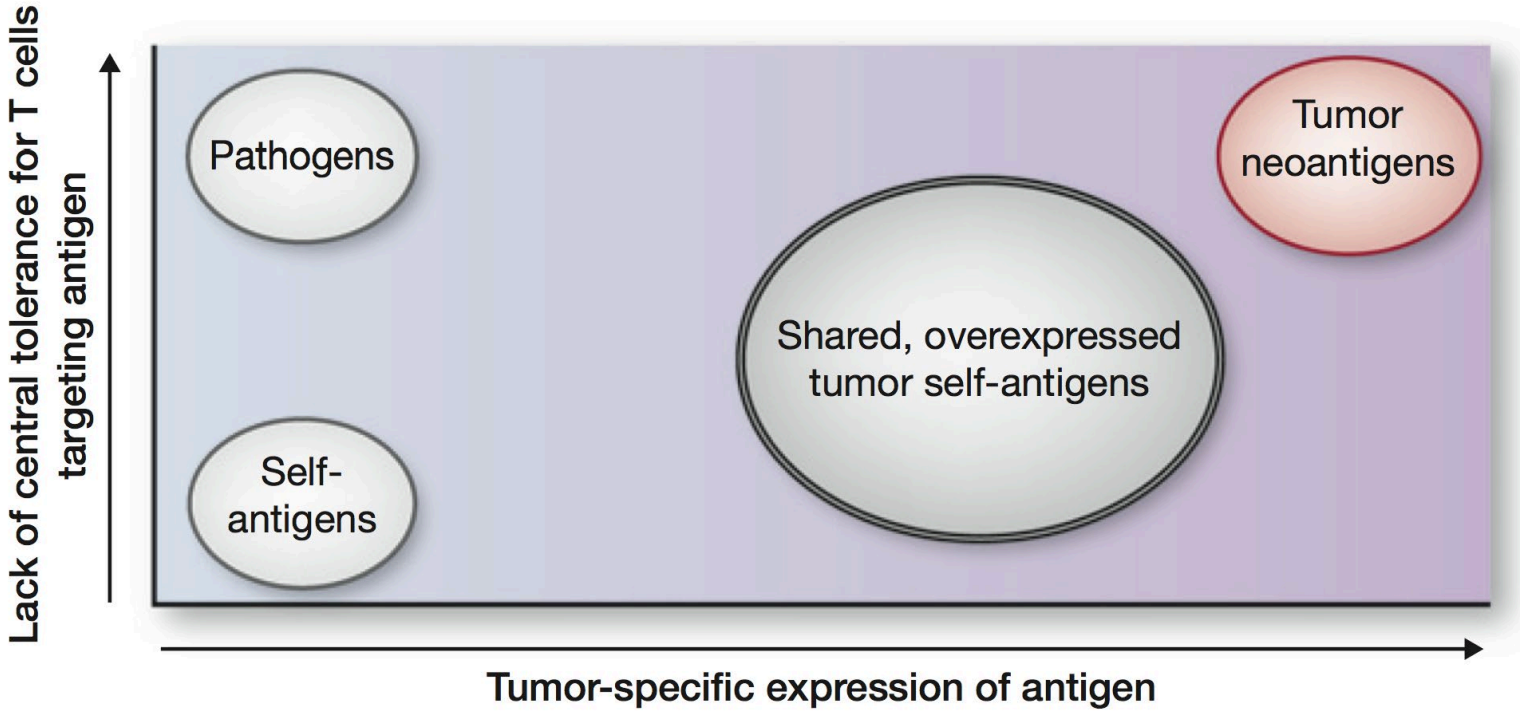
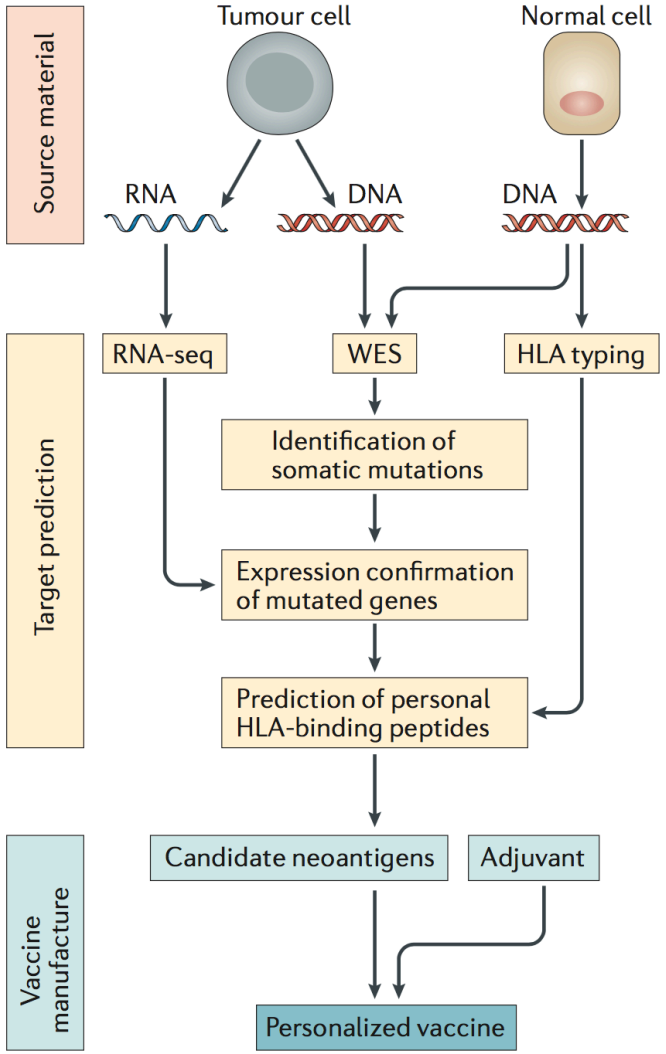
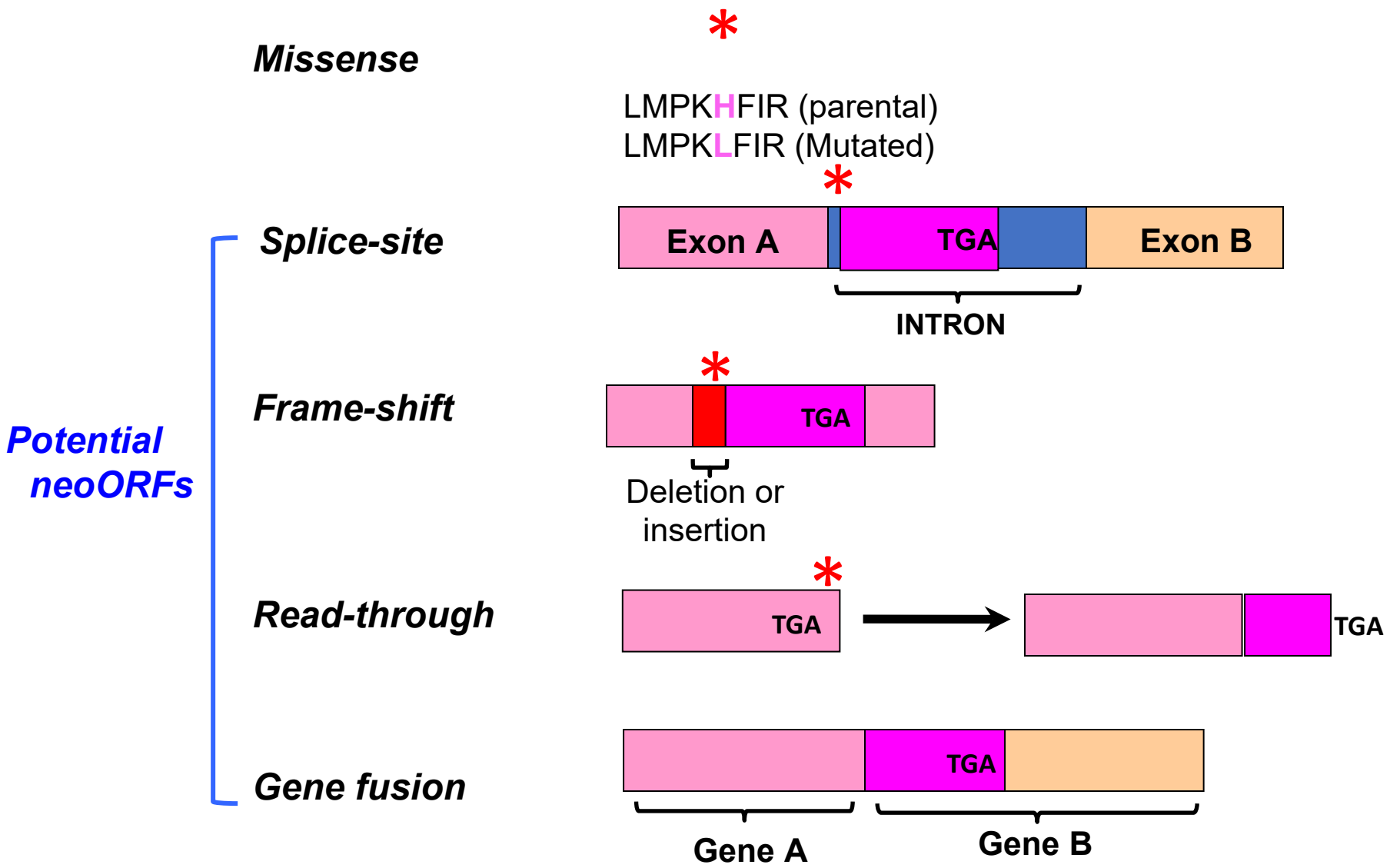
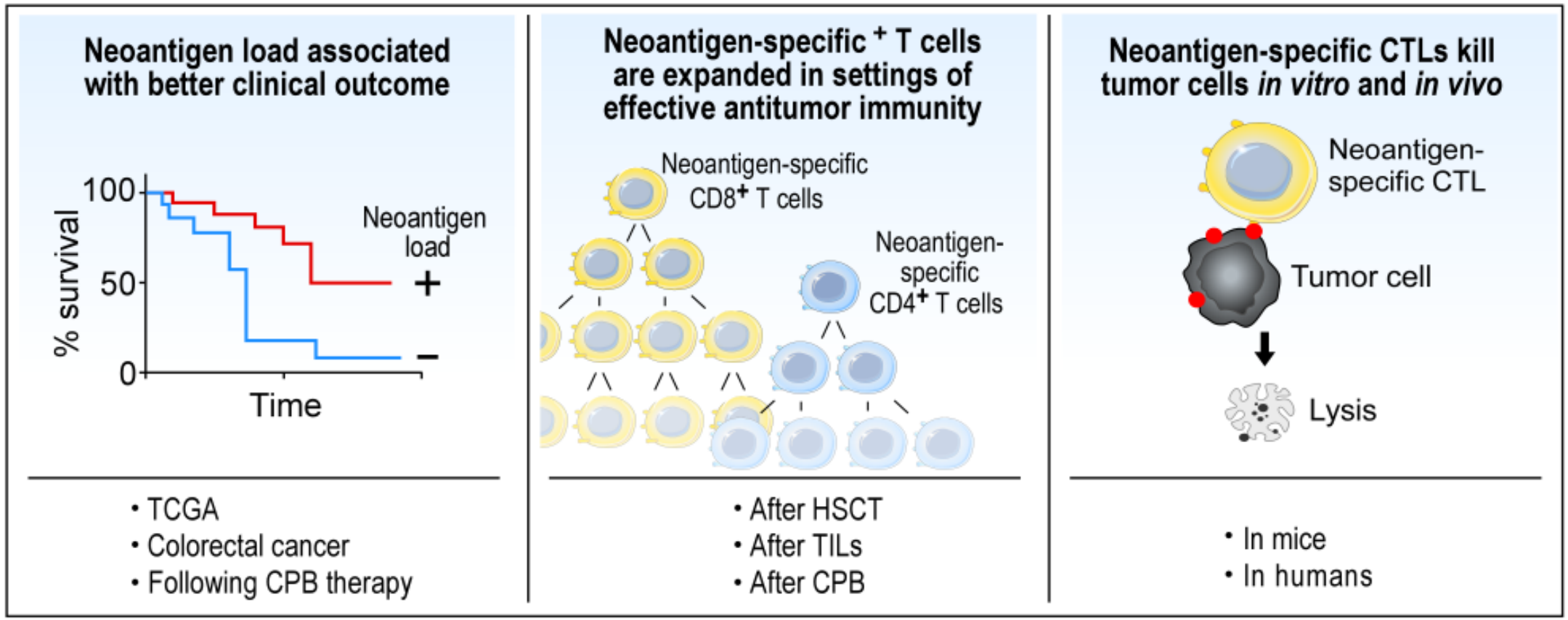




Classes of mutations that can generate potential tumor neoepitopes



Support for neoantigens as effective tumor rejection antigens



Castle Can Res 2012; Brown Gen Res 2014; Snyder NEJM 2014; Rivzi Science 2015; Cai Clin Can Res 2012; Rajasagi 2014; Robbins Nat Med 2013; van Rooij JCO 2013; Rooney Cell 2015; Rivzi Science 2015; Tran Science 2014; Gubin Nat 2014; Yadav 2014

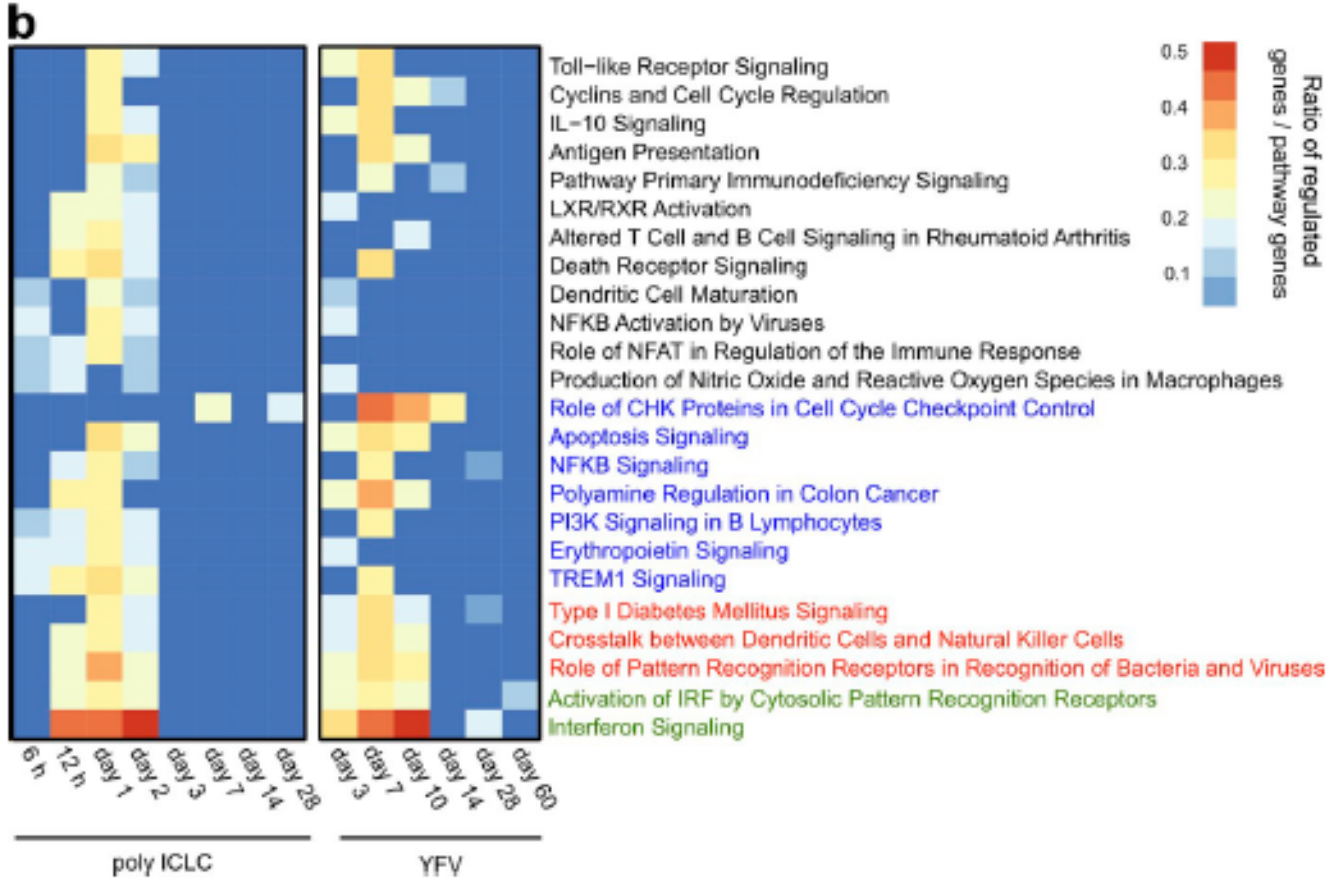
Adjuvants: an immune ‘kick in the pants’

- Enhance the magnitude, breadth and durability of the immune response
  - Alum (1920s)→ incorporated in hep B, diptheria, tetanus pertussis and HPV vaccines
  - Since 1990s 4 others with licensure
- Modulation of the innate immune system to activate adaptive immunity
  - Through pattern recognition receptors (PRRs)
    - 1990s: TLRs, via pathogen-associated molecular patterns (PAMPs)-> activation of DCs
    - Other innate PRRs RIG-I/other RNA sensors, DNA sensors (i.e. STING), C-type lectins, NOD-like receptors (NLRs) and cytosolic receptors (NLRP3-activates the inflammasome)
  - DCs can be also activated through stress signals: pathways of tissue damage, different forms of cell death, and metabolic and nutrient sensors → Release of damage-associated molecular patterns (DAMPs)
- Induction of effective CD8+ T cell responses in humans: requires the optimal adjuvant signaling & sustained presence of antigen

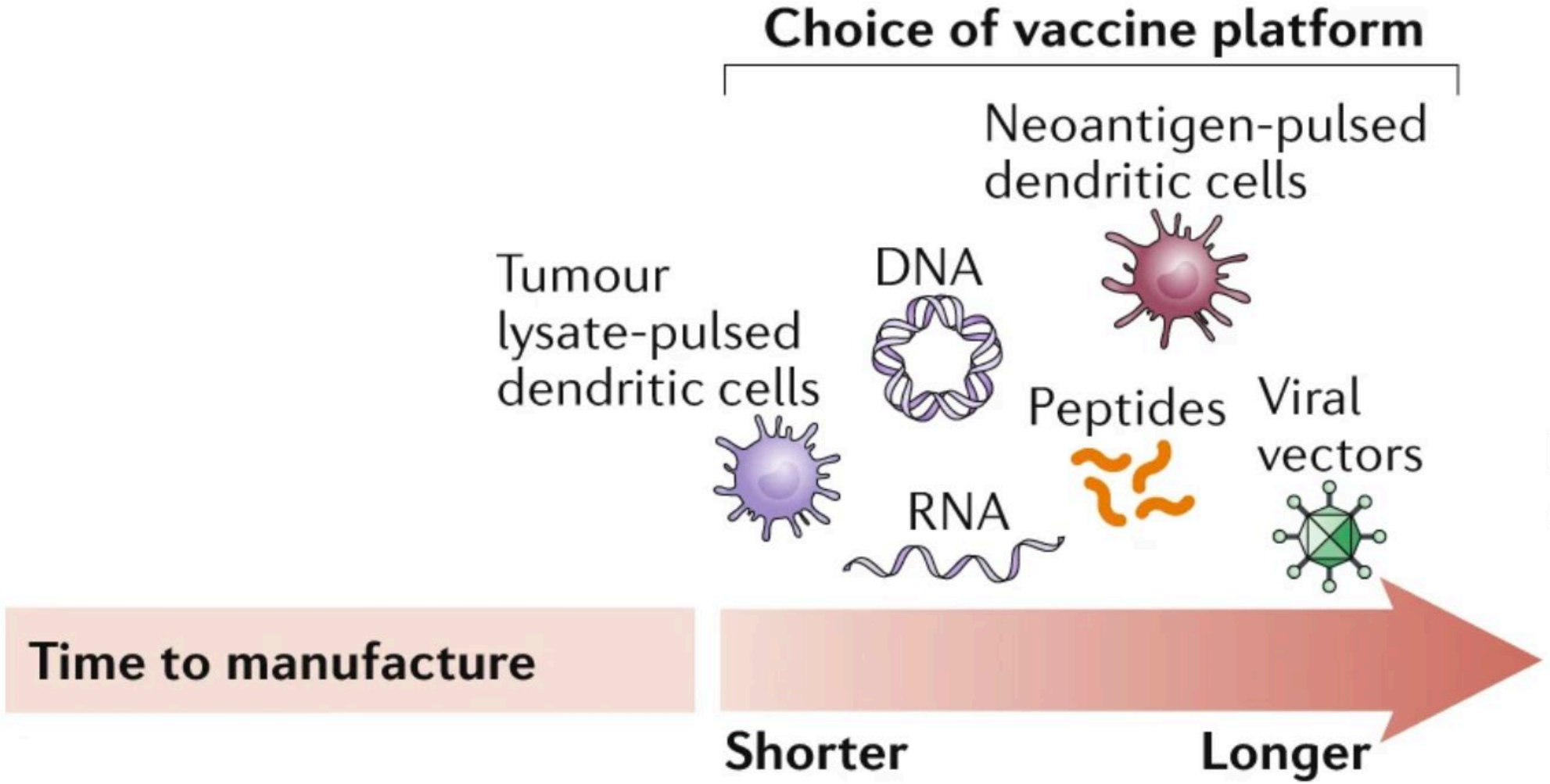
Poly ICLC is a highly effective vaccine adjuvant

- Nucleic acid ligands of TLR/RLRs are effective adjuvants
  - CpG DNA is difficult to obtain for trials
  - dsRNA stimulates several key pathogen sensors

- Stabilization of pIC in a complex with carboxymethylcellulose, poly-lysine and pIC



Caskey M J Exp Med. 2011


Choice of vaccine platform
Neoantigen-pulsed dendritic cells
Tumour lysate-pulsed dendritic cells
DNA
Peptides
Viral vectors
RNA
Time to manufacture
Shorter
Longer

What studies of cancer vaccines in patients are there?

nature medicine

PERSPECTIVE

Cancer immunotherapy: moving beyond current vaccines

Steven A Rosenberg, James C Yang & Nicholas P Restifo

Great progress has been made in the field of tumor immunology in the past decade, but optimism about the clinical application of currently available cancer vaccine approaches is based more on surrogate endpoints than on clinical tumor regression. In our cancer vaccine trials of 440 patients, the objective response rate was low (2.6%), and comparable to the results obtained by others. We consider here results in cancer vaccine trials and highlight alternate strategies that mediate cancer regression in preclinical and clinical models.

We now know the molecular identities of many tumor-associated antigens, and this knowledge has provided a major stimulus for the development of new immunotherapies for the treatment of patients with solid cancers[1]. In the field of cancer immunotherapy, most enthusiasm has been directed at the use of cancer vaccines—active immunizations designed to treat growing tumors. A recent review of dendritic cell vaccines mentioned 98 published studies involving over 1,000 patients[2]. A tabulation in 2003 listed 216 ongoing vaccine clinical trials in cancer patients[3]. These studies were conducted, and others are underway, despite the absence of convincing animal data that can-

patients who achieved clinical responses, many cancer vaccine trials have been optimistically reported because surrogate or subjective endpoints were achieved. Sensitive techniques such as tetramer or ELISpot assays have been used to demonstrate the generation *in vivo* of antitumor T cells in vaccinated patients, but the scarcity of clinical responses in these patients has made it difficult to validate any of these assays as a useful surrogate of clinical response.

Analysis of trials using standard oncologic criteria

Standard oncologic criteria for evaluating and reporting objective clinical responses to treatment are well established in oncology, and adherence to these guidelines is essential in comparing the results of treatment protocols[6–8]. A set of criteria proposed recently is the Response Evaluation Criteria in Solid Tumors (RECIST): a 30% reduction in the sum of the maximum diameters of lesions to indicate a response, along with the appearance of no new or progressive lesions. The most commonly used definition of objective clinical response, however, is at least a 50% reduction in the sum of the products of the perpendicular diameters of all lesions without the 25% growth of any lesion or the appearance of new lesions. The latter definition has been used in our analysis of our own protocols as well as

Pitfalls of the single antigen-targeting vaccine

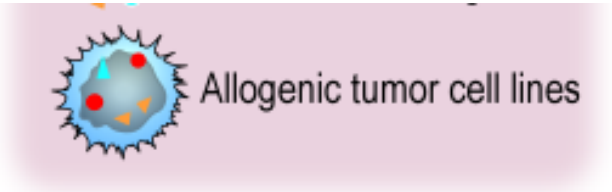
Selection and delivery of antigen

Antigen-specific vaccination: the opportunity to focus the response and broaden the T cell repertoire

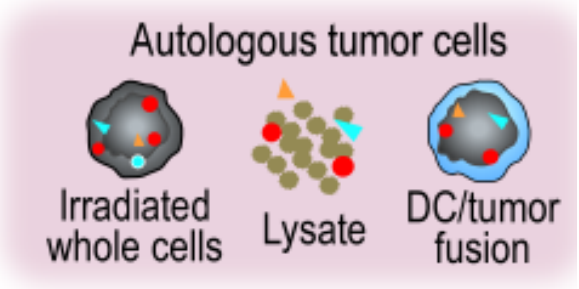
- Less impressive….
  - Single immunogen vaccine studies

- Glimmers of success!
  - Whole tumor cell vaccines
  - Improved delivery
    - Long peptides (HPV)
    - Dendritic cell-based vaccines (DC fusion, Provenge)

Whole tumor cell vaccines



- *Complex* vaccines-many antigens available to stimulate B and T cell responses
- Potential to be a ‘personal’ vaccine

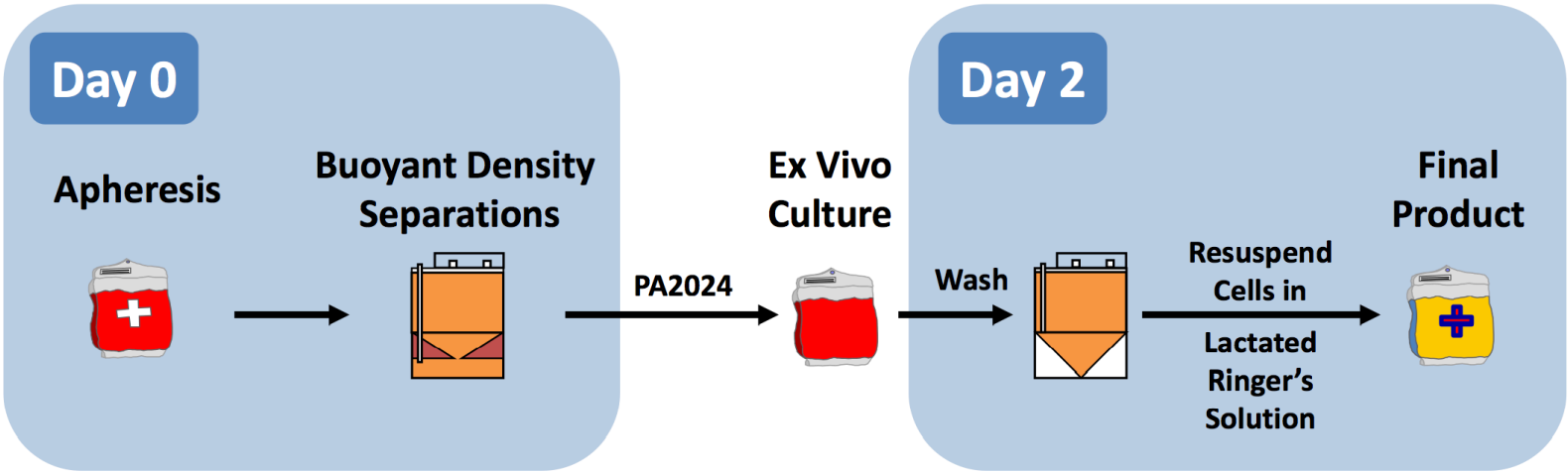


+GM-CSF

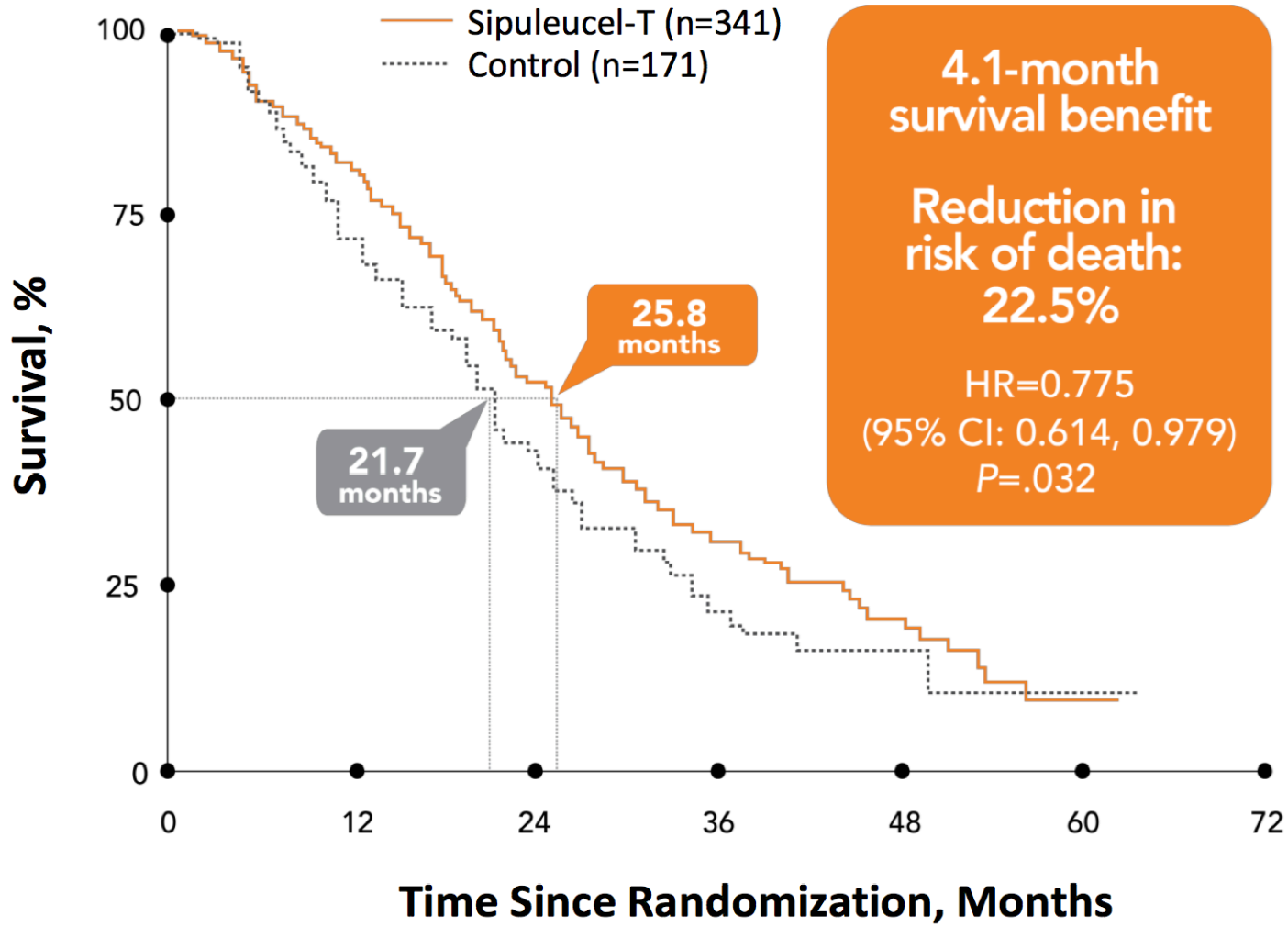
- Potentially poorer expression of any one ag
- Low-ish activity

Sipuleucel: “DC-based” vaccine

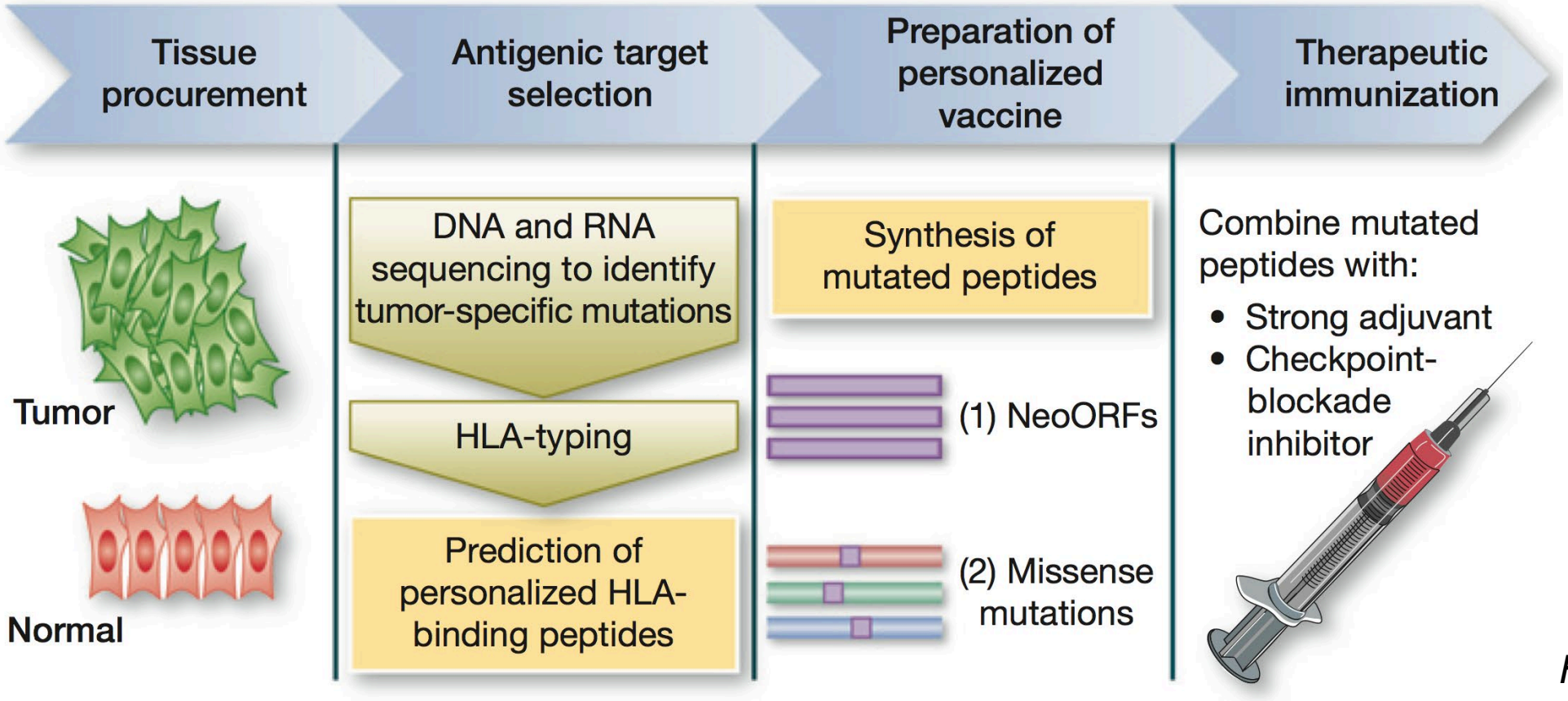
Final product cell composition reflects the major components of the immune system



Patient cells are incubated with PA2024, a fusion protein of prostatic acid phosphatase (PAP) and GM-CSF



Kantoff PW, et al. *N Engl J Med*. 2010;363:411-422.



- SLPs
- Poly-ICLC
- Up to 20 targets, separate pools

Hacohen CIR (2013)

Adjuvant setting

- High-risk melanoma
  - *Ott & Hu Nature (2017)*
  - *Sahin Nature (2017)*
  - *Carreno Science (2015)*
- Newly diagnosed GBM
  - *Keskin, Nature (2019); Hilf Nature (2019)*

- Safe, feasible
- Highly immunogenic
- Promising combination with CPB

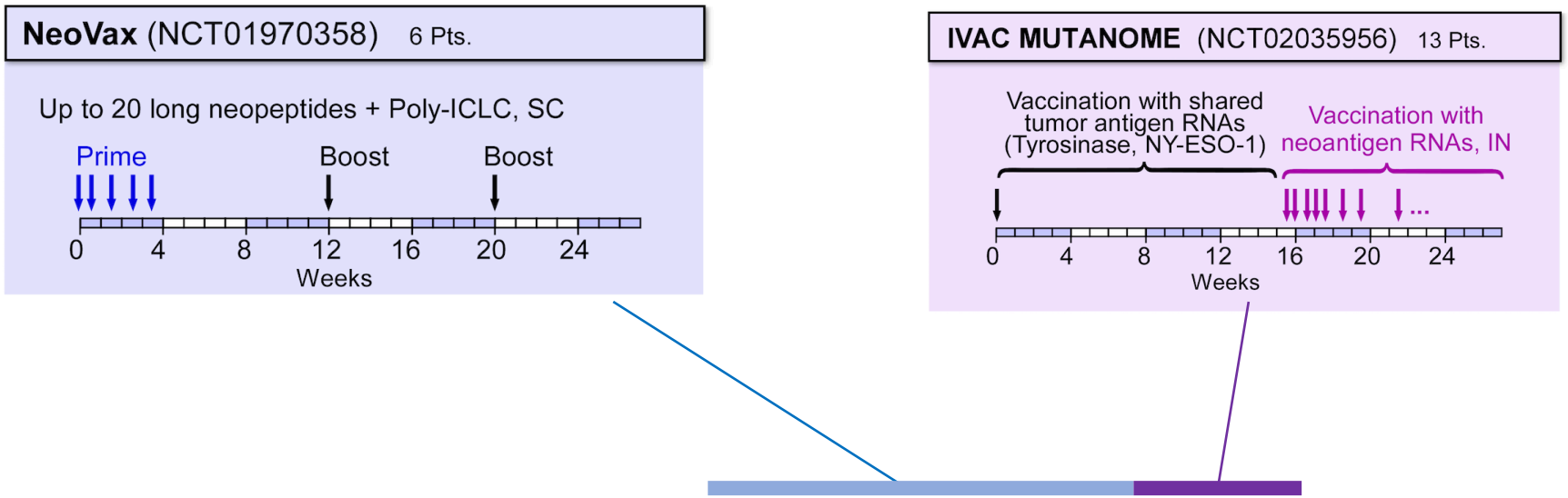


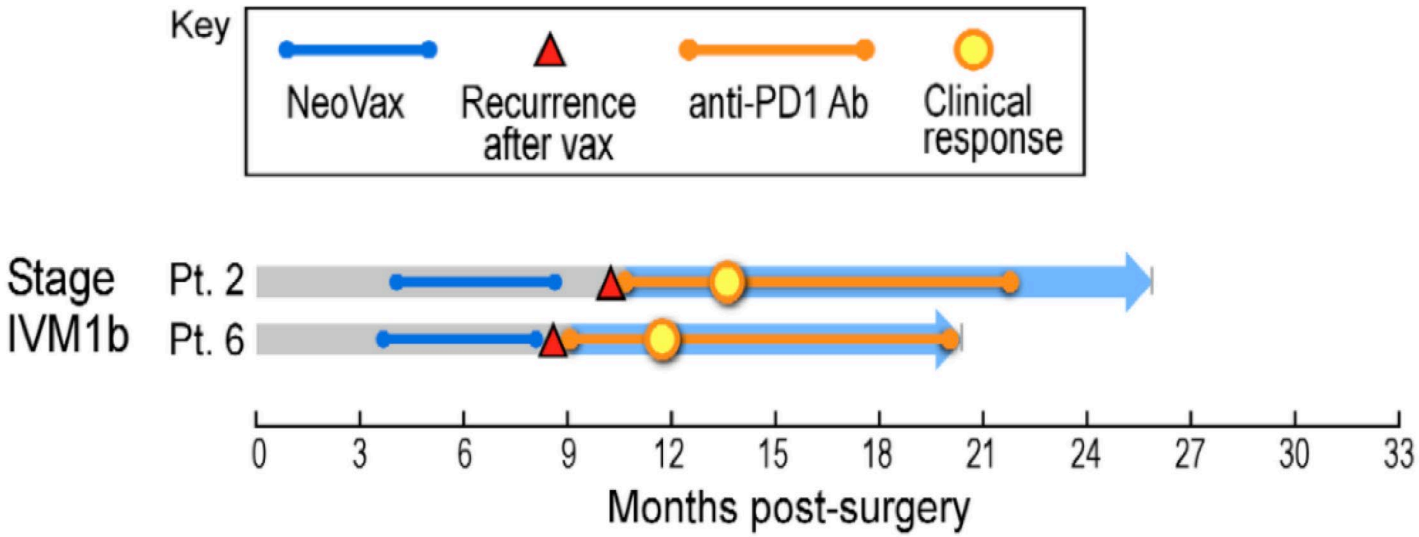
Table 1. Summary of Neoantigen Vaccines

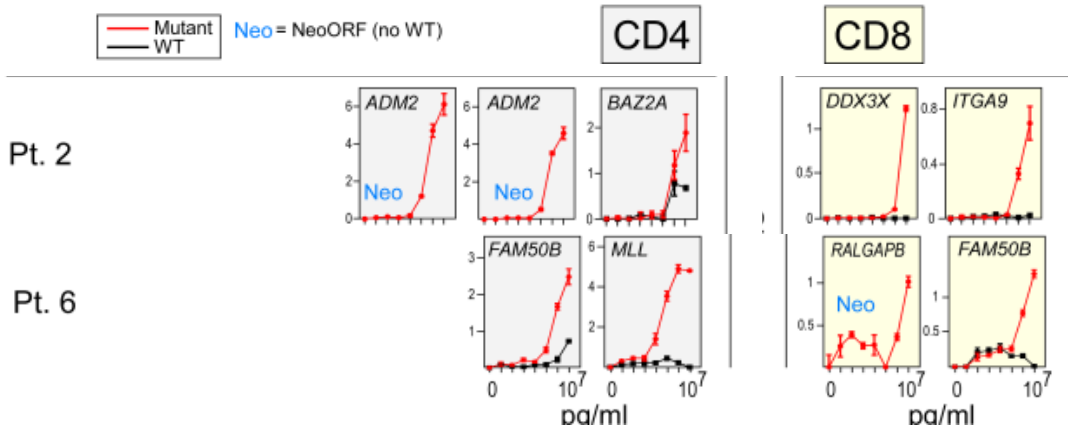
	Ott *et al.* [4]	Sahin *et al.* [3]
No. of patients	6	13
Vaccine	Synthetic peptide+ poly IC:LC	RNA
Administration route	Subcutaneous	Intranodal
Epitope length	15–30 aa	27 aa
No. of epitopes/patient	13–20	10
No. of doses	7	8–20
Immunogenicity (total no. peptides tested)	91 peptides	125 epitopes
$CD8^+$ T cell response rate[b]	16%	25%
$CD4^+$ T cell response rate[b]	60%	66%

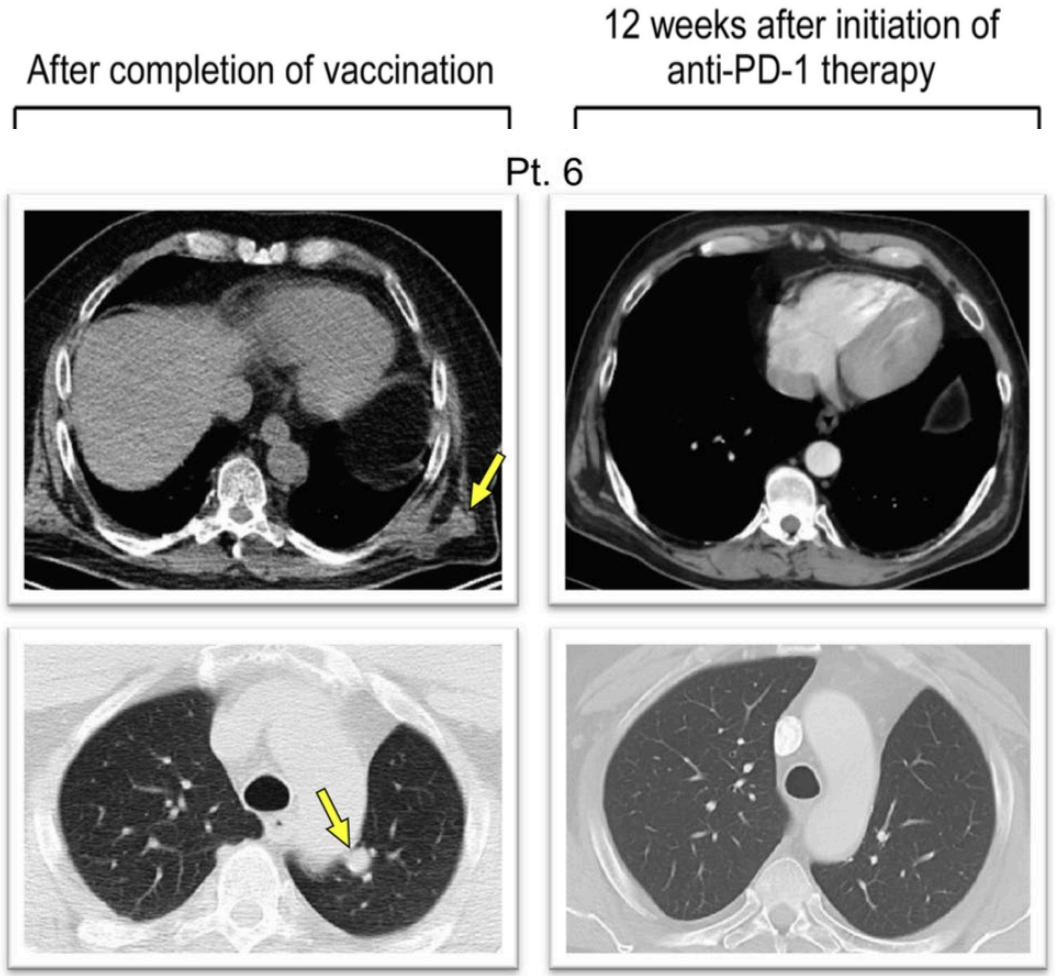
[a] *Ex vivo* manufactured and pulsed with synthetic peptides.
[b] Immune response rate to MHC class I or class II epitopes (per vaccine trial).

Linette & Carreno Trends in Molecular Medicine (2017)

Melanoma Neovax: Enduring CRs after Neovax + α-PD-1





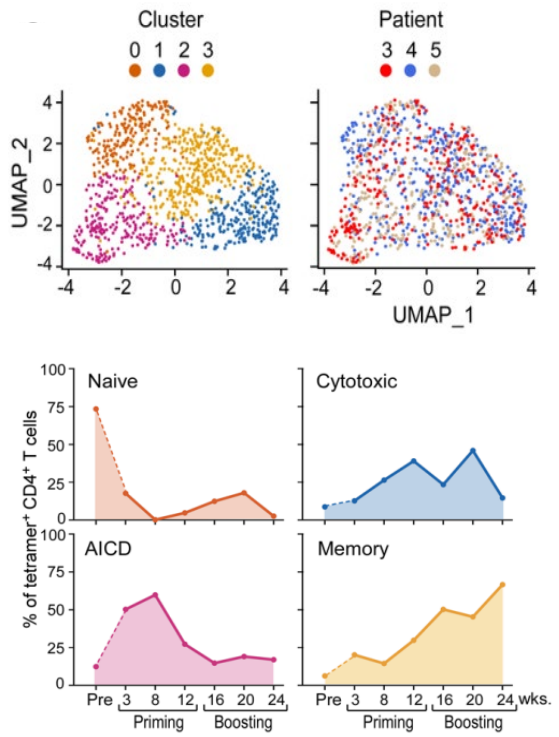


Ott & Hu Nature (2017)

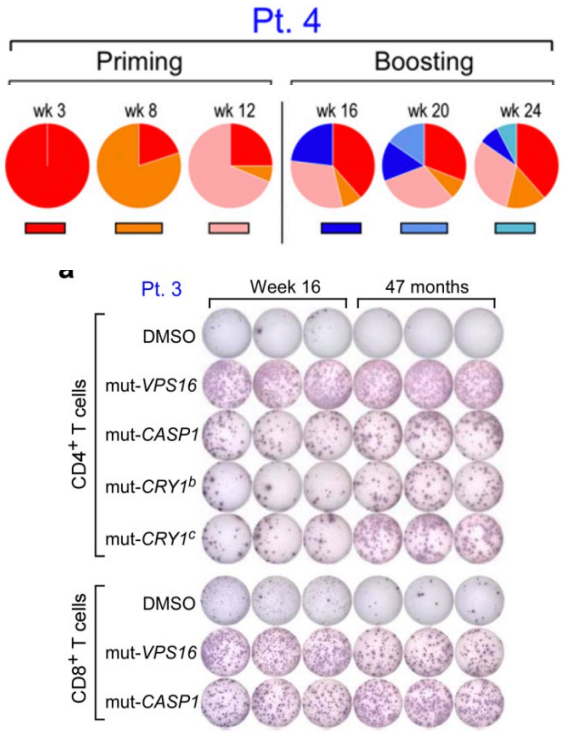
Durable and encouraging long-term responses

Hu Leet & Allesoe Nat Med (2021); Ott PA Cell 2020

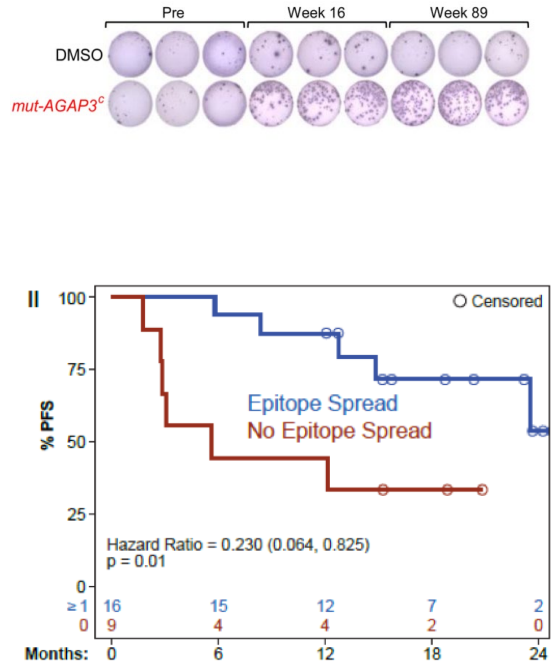
Generation of memory response



T cell diversification & persistence



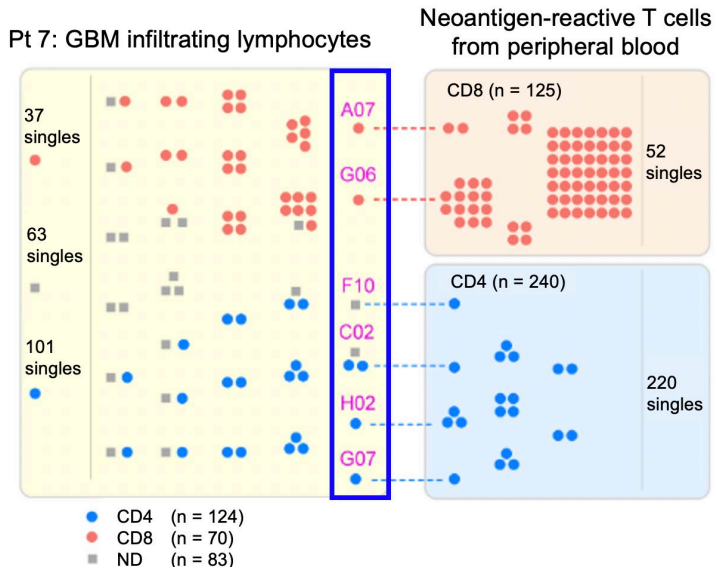
Epitope spreading



Tracking of NeoAg T cells to the site of tumor after vax

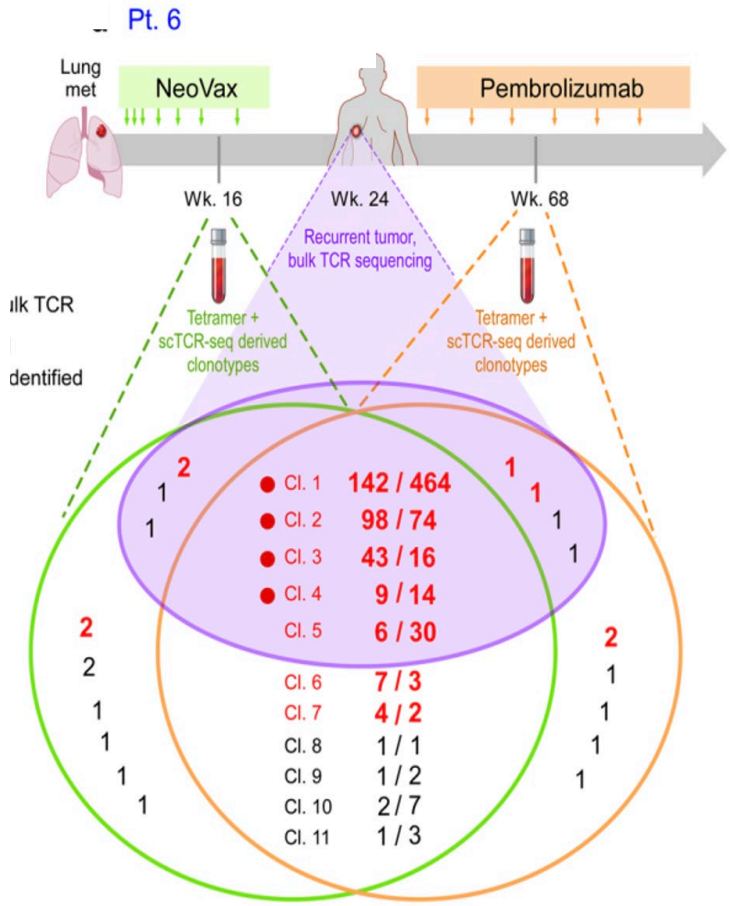
GBM

Keskin et al Nature (2019)



Met melanoma

Hu Leet & Allesoe Nat Med (2021)



Ongoing Clinical Trials Testing Neoantigen Targeted Vaccines

Vaccine (format)	Number of neoantigens included	Neoantigen discovery platform	Adjuvant and/or delivery system	Study phase	Tumour types	Treatment approach	ClinicalTrials.gov identifier (Ref.)[a]
NeoVax (SLP)	7–20	Broad Institute/DFCI pipeline[45,48,142]	Poly-ICLC	Pilot	Completely resected advanced-stage RCC	NeoVax plus locally administered ipilimumab (anti-CTLA4 antibody)	NCT02950766
				Phase Ib	Advanced-stage melanoma	NeoVax plus nivolumab (anti-PD-1 antibody) and locally administered ipilimumab	NCT03929029
GEN-009 (SLP)	4–20	ATLAS[133]	Poly-ICLC	Phase I/IIa	Melanoma, NSCLC, HNSCC, RCC or urothelial carcinoma	GEN-009 alone for patients who have no evidence of disease after completion of curative-intent treatments and with nivolumab or pembrolizumab (anti-PD-1 antibody) for those with unresectable advanced-stage tumours	NCT03633110 (REF.[136])
PGV001 (SLP)	Up to 10	Personalized genomic vaccine pipeline (Openvax)[144]	Poly-ICLC	Phase I	Advanced-stage solid tumours	PGV001 alone	NCT02721043 (REF.[145])
AutoSynVax (ASV), also known as AGEN2003 (SLP with recombinant HSP70)	Up to 24	AIM	QS-21 Stimulon	Phase Ia	Advanced-stage solid tumours	AutoSynVax alone	NCT02992977 (REF.[146])
RO7198457, also known as iNeST (RNA–lipoplex)	Up to 20	Not disclosed	NA	Phase Ib	Advanced-stage solid tumours, most commonly NSCLC, TNBC, melanoma and CRC	RO7198457 alone or with atezolizumab (anti-PD-L1 antibody)	NCT03289962 (REF.[117])
				Randomized phase II	ctDNA-positive resected stage III NSCLC	RO7198457 plus atezolizumab vs atezolizumab alone, after adjuvant chemoradiotherapy	NCT04267237
				Randomized phase II	Advanced-stage melanoma (treatment-naive)	RO7198457 plus pembrolizumab vs pembrolizumab alone	NCT03815058
VB10.NEO (plasmid DNA)	Up to 20	NeoSELECT	PharmaJet Stratis injection system	Phase I/IIa	Advanced-stage RCC, HNSCC, melanoma or NSCLC without a complete response to SoC immune-checkpoint inhibitor therapy	VB10.NEO plus bempegaldesleukin (pegylated IL-2, a CD122-preferential IL-2 pathway agonist)	NCT03548467 (REF.[148])
GNOS-PV02 (plasmid DNA)	>50	Not disclosed	INO-9012 (plasmid encoding IL-12); CELLECTRA delivery device (in vivo electroporation)	Phase I	Newly diagnosed *MGMT* promoter-unmethylated glioblastoma	GNOS-PV02 alone following SoC surgery and/or radiotherapy	NCT04015700
				Phase I/II	Advanced-stage hepatocellular carcinoma	GNOS-PV02 plus pembrolizumab, folllowing disease progression or intolerance of SoC TKI therapy	NCT04251117
Granite (GRT-C901 adenovirus-based prime plus GRT-R902 RNA-based booster)	Up to 20	Edge	NA	Phase I/II	NSCLC, CRC (MSS), gastroesophageal adenocarcinoma, urothelial carcinoma or PDAC	Granite alone	NCT03794128
				Phase I/II	NSCLC, CRC (MSS), gastroesophageal adenocarcinoma or urothelial carcinoma	Granite plus nivolumab and ipilimumab	NCT03639714
mRNA-4157 (lipid encapsulated RNA)	Up to 20	Proprietary algorithm	NA	Phase I	Advanced-stage solid tumours	mRNA-4157 alone for patients with resected tumours or with pembrolizumab for those with unresectable tumours	NCT03313778 (REF.[118])
				Phase I	Resected high-risk melanoma (stage III)	mRNA-4157 plus pembrolizumab	NCT03897881
Not specified (DNA)	Not specified	Not disclosed	Intramuscular TriGrid Delivery System (TDS-IM)	Randomized phase I	Stage II or III TNBC	Vaccine vs vaccine plus durvalumab (anti-PD-L1 antibody), following SoC therapy	NCT03199040
			TDS-IM	Phase I	Resectable PDAC	Vaccine alone, following surgery and adjuvant chemotherapy	NCT03122106

Peptid

eRNA

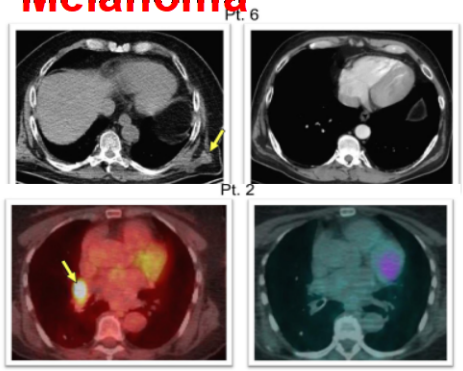
DNA

Viral

Blass, Ott *Nature Rev Clin Oncol*, 2021

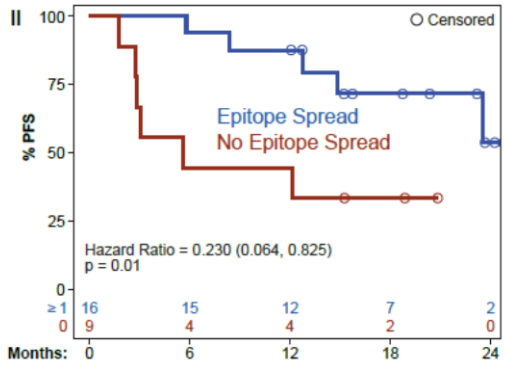
Composite results across studies….

CRs with α-PD-1 post long peptide Vax in Melanoma



Ott & Hu, *Nature* 2017

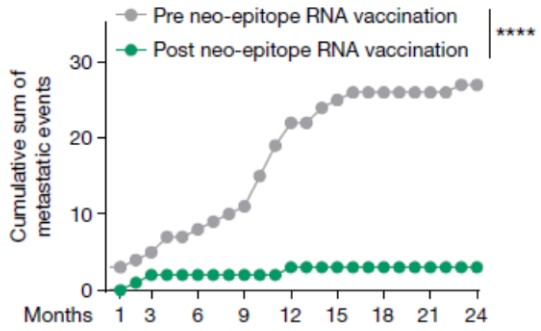
Epitope Spreading post long-peptide Vax in mel, NSCLC, bladder Ca



Ott, *Cell* 2020

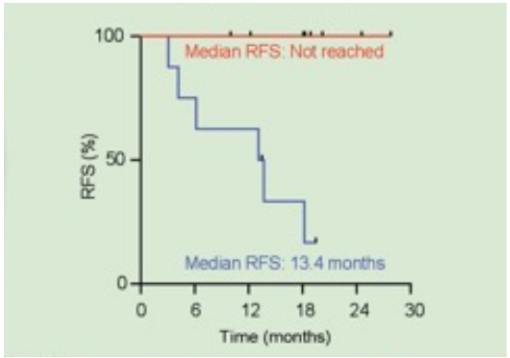
Tracking of T cells to site of tumor

Decreased Recurrences post RNA Vax in Melanoma



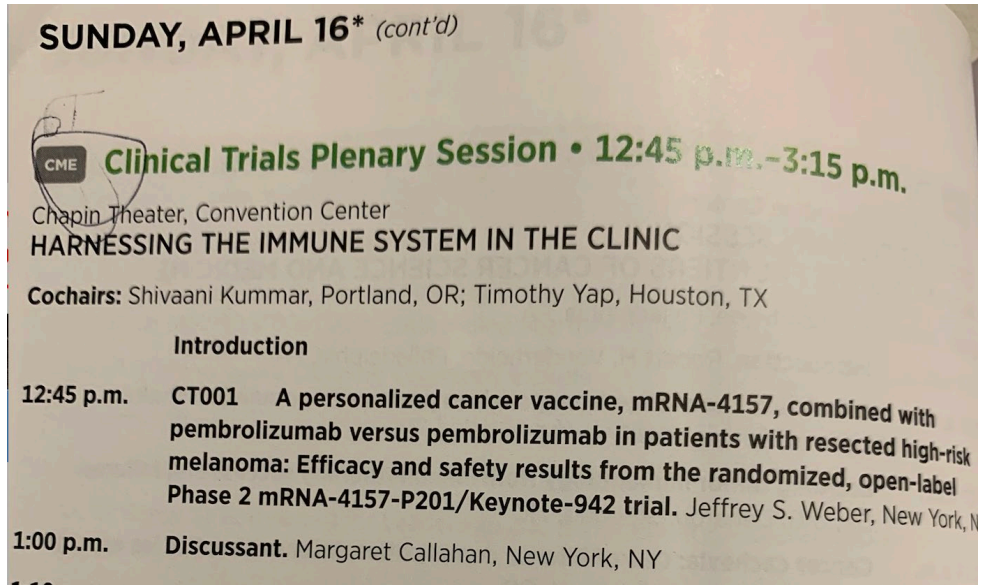
Sahin, *Nature* 2017

No recurrences post RNA Vax in PDAC



Balachandran, *ASCO* 2022

Randomized open label phase 2



SUNDAY, APRIL 16* *(cont'd)*

CME **Clinical Trials Plenary Session • 12:45 p.m.–3:15 p.m.**

Chapin Theater, Convention Center

HARNESSING THE IMMUNE SYSTEM IN THE CLINIC

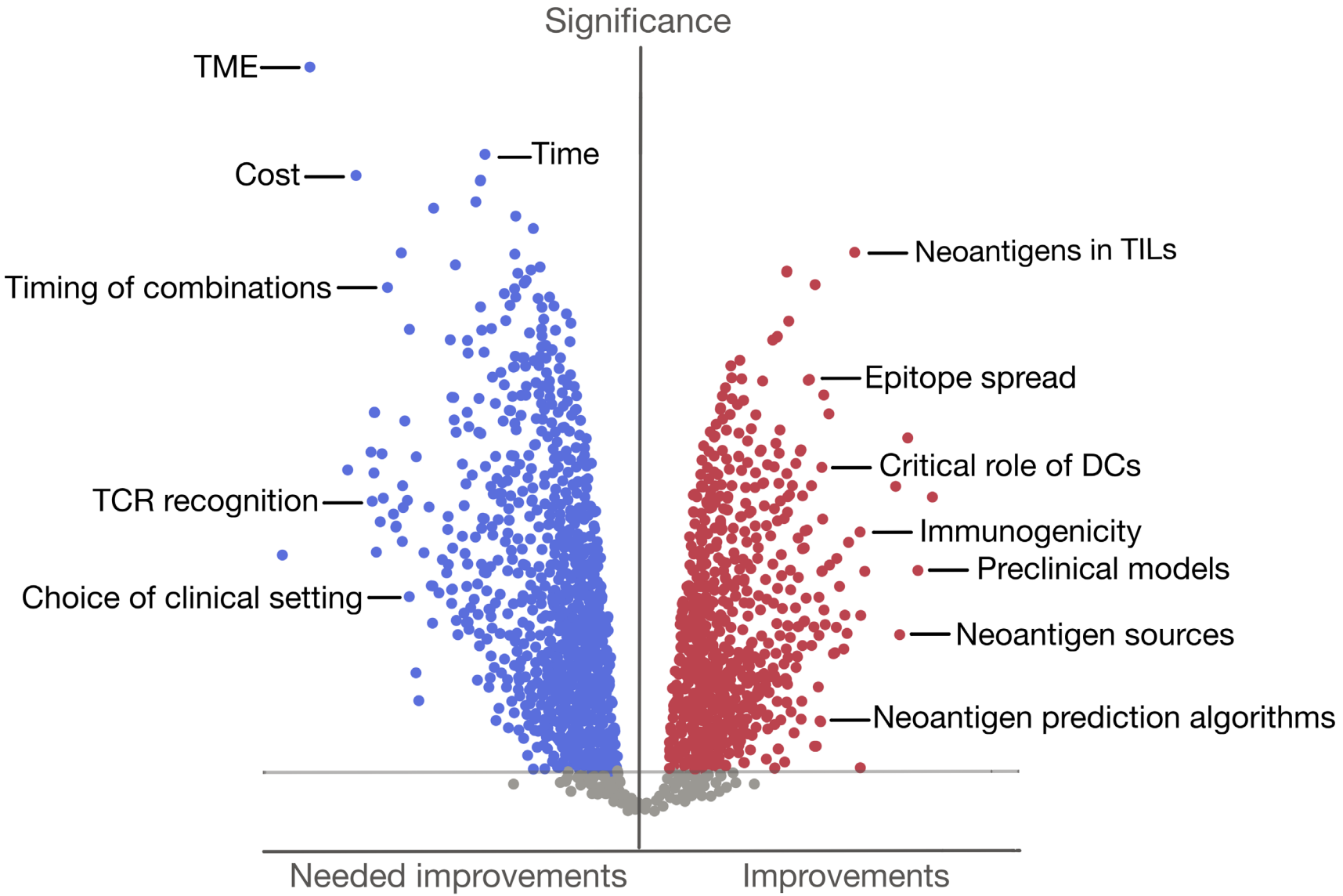
Cochairs: Shivaani Kummar, Portland, OR; Timothy Yap, Houston, TX

Introduction

12:45 p.m. **CT001 A personalized cancer vaccine, mRNA-4157, combined with pembrolizumab versus pembrolizumab in patients with resected high-risk melanoma: Efficacy and safety results from the randomized, open-label Phase 2 mRNA-4157-P201/Keynote-942 trial.** Jeffrey S. Weber, New York, N

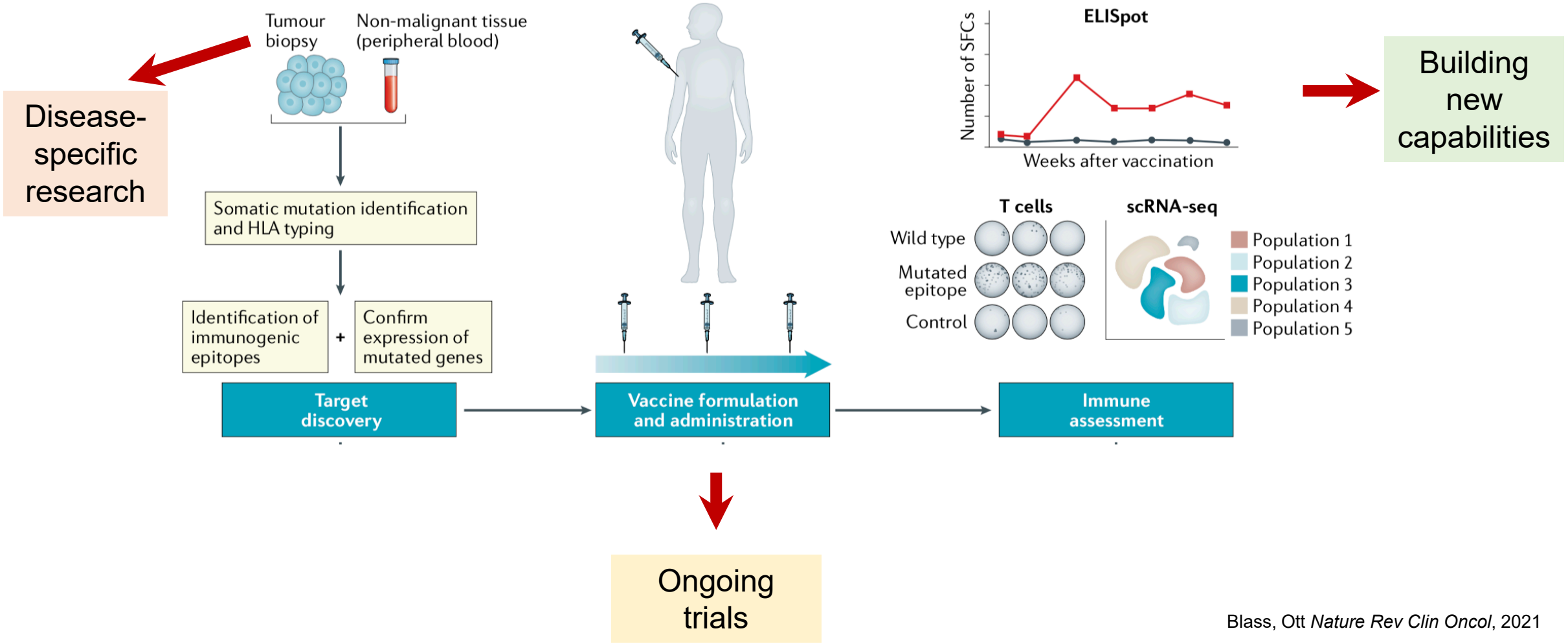
1:00 p.m. **Discussant.** Margaret Callahan, New York, NY

Where next?



Fritsch *CIR* 2020

Ongoing bedside to bench and back again efforts



Blass, Ott *Nature Rev Clin Oncol*, 2021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