Tumor Antigens and Cancer Vaccines

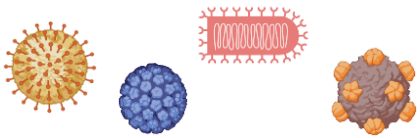
MCBO Core Lecture II

Guido Wollmann

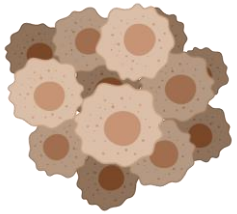
Division of Virology

History

pathogen

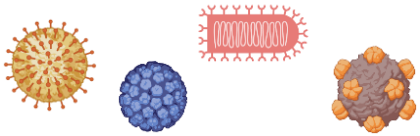


tumor

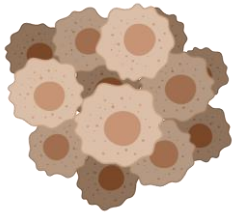


History

pathogen



tumor

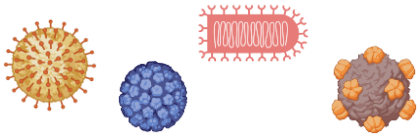


Edward Jenner

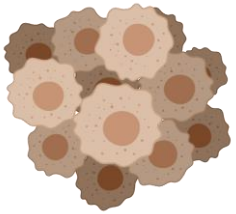
1796

History

pathogen



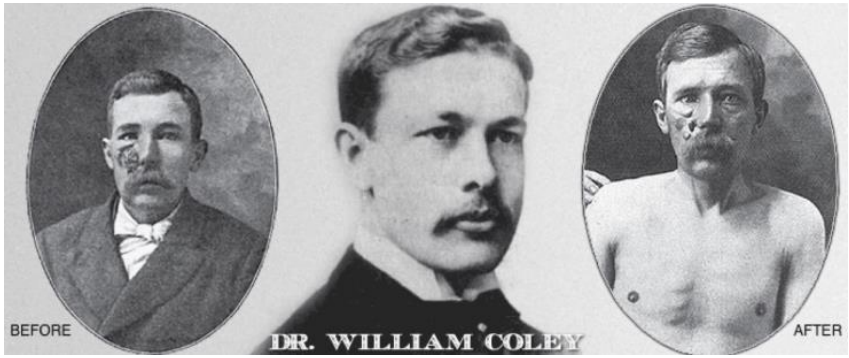
tumor



Edward Jenner

1796

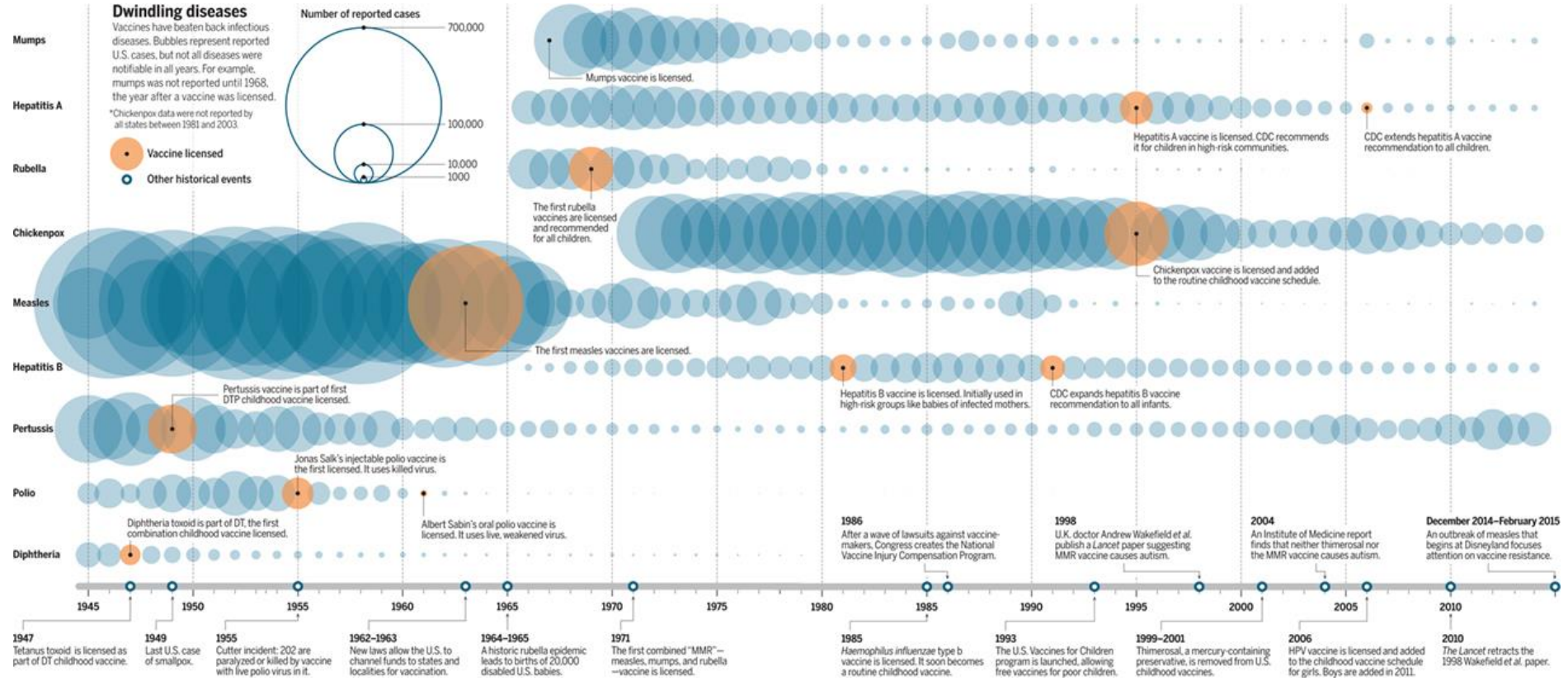
William Coley



1893

History

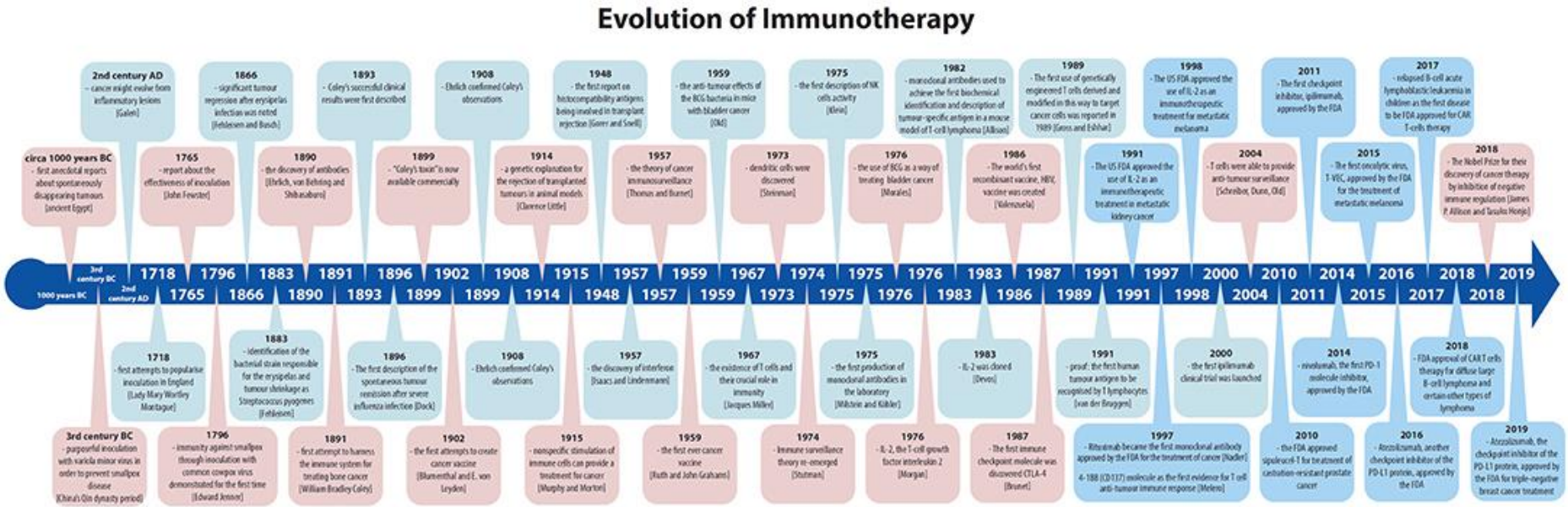
Century of vaccines!



highly successful development to fight pathogen disease burden

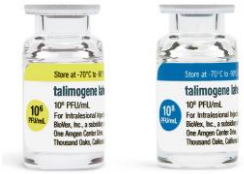
Wadman and You, Science 2017

History



Dobosz and Dzieciątkowski, Frontiers Immunol. 2019

History



Evolution of Immunotherapy

circa 1000 years BC – first anecdotal reports about spontaneously disappearing tumours (ancient Egypt)

2nd century AD – cancer might evolve from inflammatory lesions (Galen)

1718 – first attempts to popularise inoculation in England (Lady Mary Wortley Montague)

1765 – report about the effectiveness of inoculation (John Fewster)

1796 – immunity against smallpox through inoculation with common cowpox virus demonstrated for the first time (Edward Jenner)

1866 – significant tumour regression after erysipelas infection was noted (Fehleisen and Busch)

1883 – identification of the bacterial strain responsible for the erysipelas and tumour shrinkage as Streptococcus pyogenes (Fehleisen)

1890 – the discovery of antibodies (Ehrlich, von Behring and Shibasaburo)

1891 – first attempt to harness the immune system for treating bone cancer (William Bradley Coley)

1893 – Coley's successful clinical results were first described

1896 – The first description of the spontaneous tumour remission after severe influenza infection (Dock)

1899 – "Coley's toxin" is now available commercially

1902 – the first attempts to create cancer vaccine (Blumenthal and E. von Leyden)

1908 – Ehrlich confirmed Coley's observations

1914 – a genetic explanation for the rejection of transplanted tumours in animal models (Clarence Little)

1915 – nonspecific stimulation of immune cells can provide a treatment for cancer (Murphy and Morton)

1948 – the first report on histocompatibility antigens being involved in transplant rejection (Gorer and Snell)

1957 – the theory of cancer immunosurveillance (Thomas and Burnet)

1959 – the first ever cancer vaccine (Ruth and John Grahams)

1959 – the anti-tumour effects of the BCG bacteria in mice with bladder cancer (Old)

1967 – the existence of T cells and their crucial role in immunity (Jacques Miller)

1973 – dendritic cells were discovered (Steinman)

1974 – Immune surveillance theory re-emerged (Stutman)

1975 – the first description of NK cells activity (Klein)

1975 – the first production of monoclonal antibodies in the laboratory (Milstein and Kohler)

1976 – the use of BCG as a way of treating bladder cancer (Morales)

1976 – IL-2, the T-cell growth factor interleukin 2 (Morgan)

1982 – monoclonal antibodies used to achieve the first biochemical identification and description of tumour-specific antigen in a mouse model of T-cell lymphoma (Allison)

1983 – IL-2 was cloned (Devos)

1986 – The world's first recombinant vaccine, HBV, vaccine was created (Valenzuela)

1987 – The first immune checkpoint molecule was discovered (CTLA-4 (Brunet)

1989 – The first use of genetically engineered T cells derived and modified in this way to target cancer cells was reported in 1989 (Gross and Eshhar)

1991 – The US FDA approved the use of IL-2 as an immunotherapeutic treatment in metastatic kidney cancer

1991 – proof: the first human tumour antigen to be recognised by T lymphocytes (van der Bruggen)

1997 – Rituximab became the first monoclonal antibody approved by the FDA for the treatment of cancer (Nadler)

1998 – The US FDA approved the use of IL-2 as an immunotherapeutic treatment for metastatic melanoma

2000 – the first ipilimumab clinical trial was launched

2004 – T cells were able to provide anti-tumour surveillance (Schreiber, Dunn, Old)

2010 – the FDA approved sipuleucel-T for treatment of castration-resistant prostate cancer

2011 – The first checkpoint inhibitor, ipilimumab, approved by the FDA

2014 – nivolumab, the first PD-1 molecule inhibitor, approved by the FDA

2015 – The first oncolytic virus, T-VEC, approved by the FDA for the treatment of metastatic melanoma

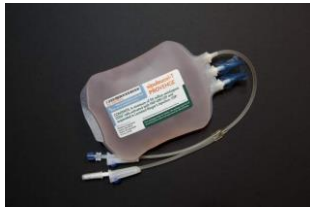
2016 – Atezolizumab, another checkpoint inhibitor of the PD-L1 protein, approved by the FDA

2017 – relapsed B-cell acute lymphoblastic leukaemia in children as the first disease to be FDA approved for CAR T-cells therapy

2018 – FDA approval of CAR T cells therapy for diffuse large B-cell lymphoma and certain other types of lymphoma

2018 – The Nobel Prize for their discovery of cancer therapy by inhibition of negative immune regulation (James P. Allison and Tasuku Honjo)

2019 – Atezolizumab, the checkpoint inhibitor of the PD-L1 protein, approved by the FDA for triple-negative breast cancer treatment



challenge to apply vaccines as tumor immunotherapies

Dobosz and Dzieciątkowski, Frontiers Immunol. 2019

fundamental difference

pathogen vaccine

tumor vaccine

fundamental difference

pathogen vaccine

A pathogen is a foreign invader.
The invader or parts of it can be directly used.

tumor vaccine

A tumor is part of oneself.
The tumor cannot be directly used

fundamental difference

pathogen vaccine

A pathogen is a foreign invader.
The invader or parts of it can be directly used.

vaccine is based on MATERIAL

tumor vaccine

A tumor is part of oneself.
The tumor cannot be directly used

vaccine is based on INFORMATION

fundamental difference

pathogen vaccine

A pathogen is a foreign invader.
The invader or parts of it can be directly used.

vaccine is based on MATERIAL

vector vaccines are the <u>exception</u>

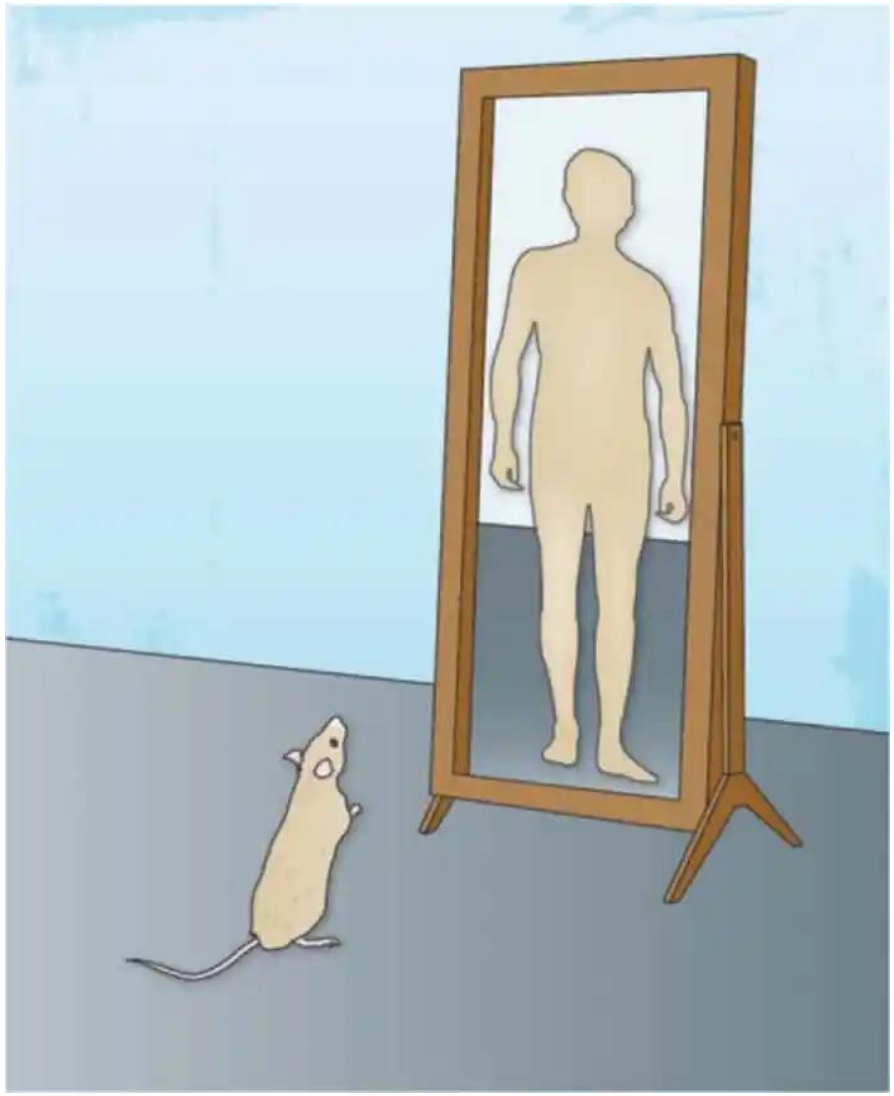
tumor vaccine

A tumor is part of oneself.
The tumor cannot be directly used

vaccine is based on INFORMATION

vector vaccines are the <u>rule</u>

When mice tell lies – and when they don‘t



https://sciwri.club/archives/4291

Cancer vaccines work! ..... in mice

nature COMMUNICATIONS

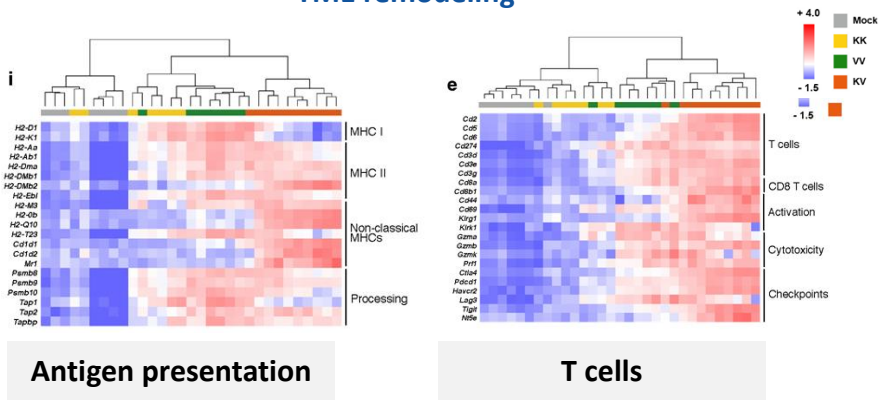
ARTICLE

https://doi.org/10.1038/s41467-021-25506-6 OPEN

A modular self-adjuvanting cancer vaccine combined with an oncolytic vaccine induces potent antitumor immunity

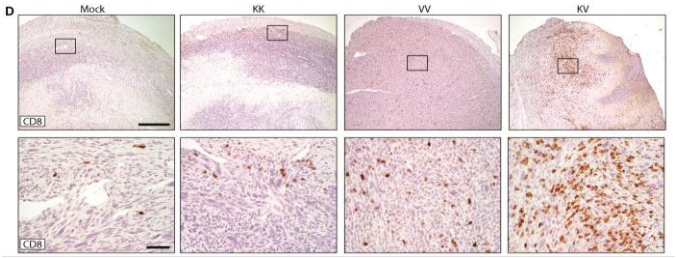
Krishna Das[1,2,8], Elodie Belnoue[3,4,8], Matteo Rossi[3,4], Tamara Hofer[1,2], Sarah Danklmaier[1,2], Tobias Nolden[4,5], Liesa-Marie Schreiber[1,2], Katharina Angerer[1,2], Janine Kimpel[2], Sandra Hoegler[6], Bart Spiesschaert[4,5], Lukas Kenner[6,7], Dorothee von Laer[2], Knut Elbers[4,5], Madiha Derouazi[3,4✉] & Guido Wollmann[1,2✉]

TME remodeling

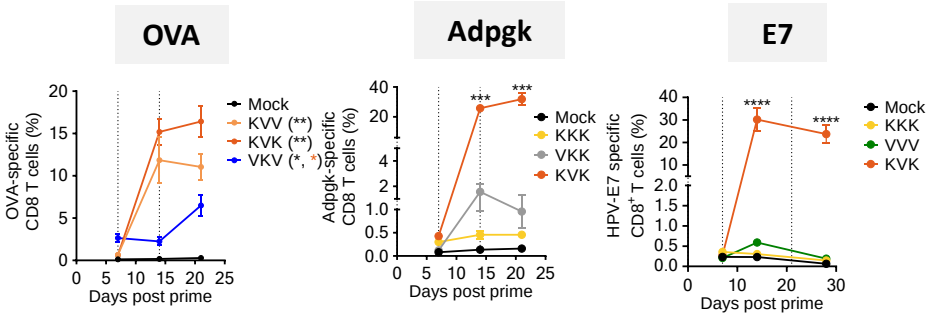


Antigen presentation **T cells**

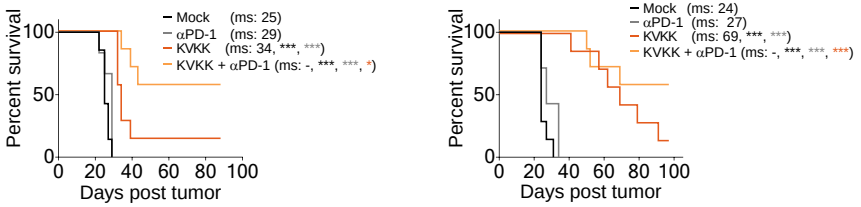
TILs infiltration



Antigen-specific T cell induction



Effect on CPI failures



Vaccine

Platform vs Target

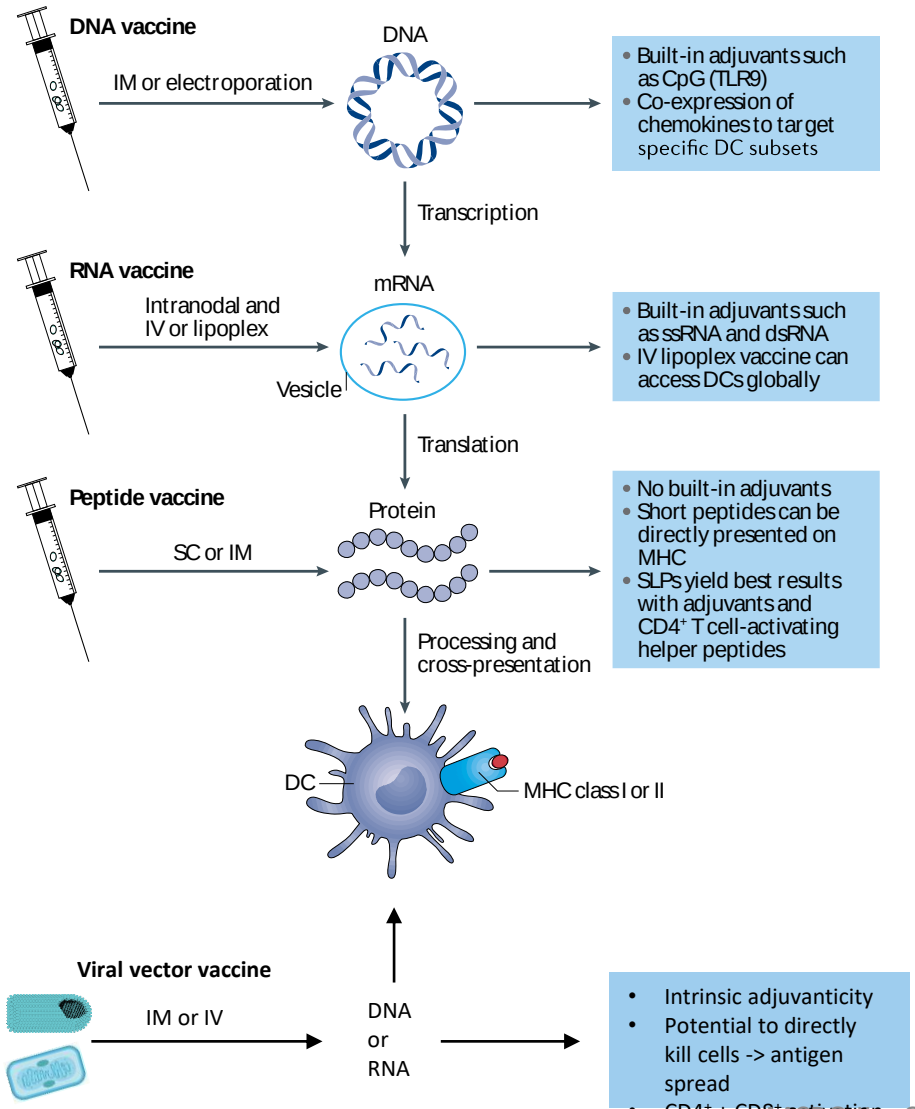
Vaccine platforms

General requirements

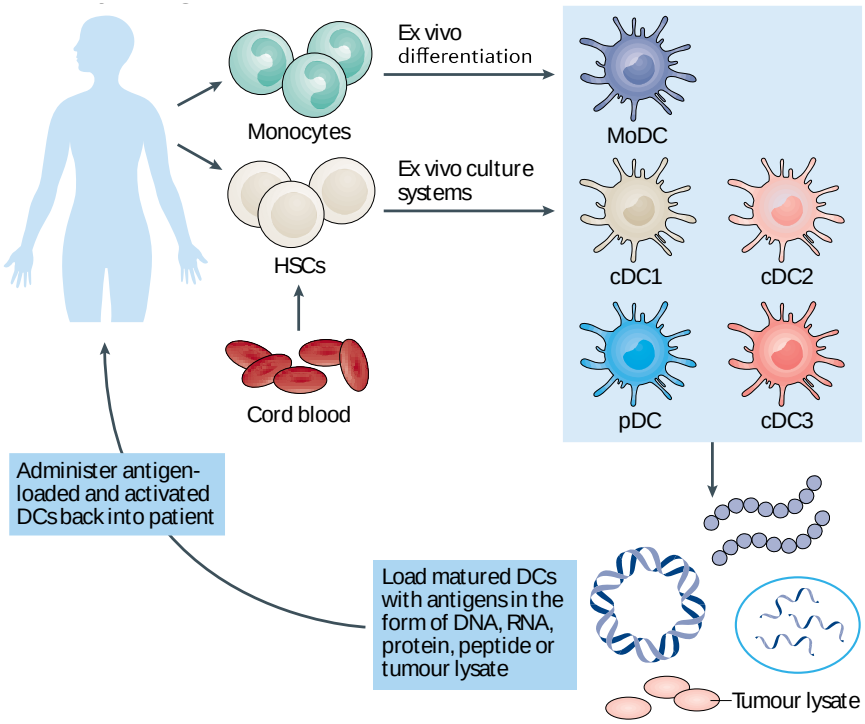
- target: antigen presenting cells (DCs)
- MHC-1 presentation = intracellular proteins
- immune adjuvanticity

Vaccine platforms

Inside the body



outside the body

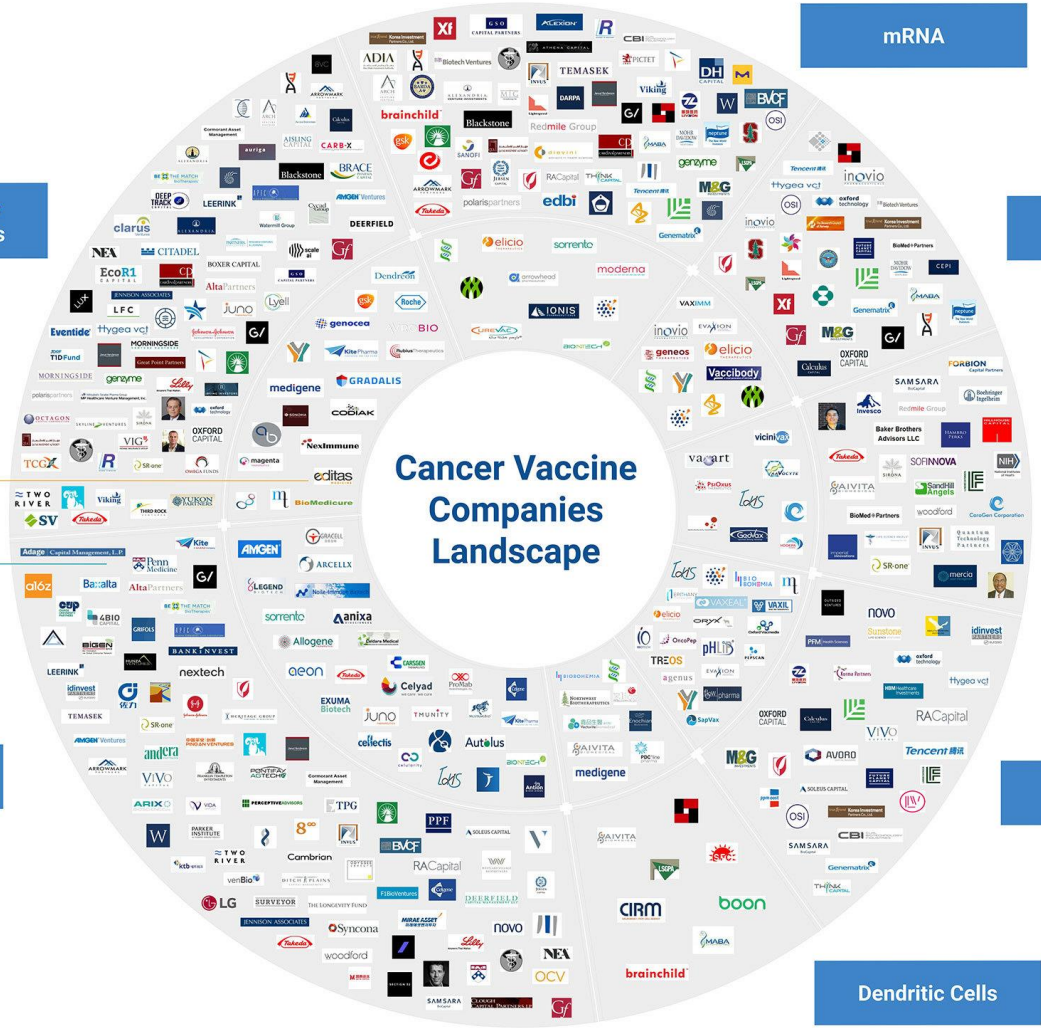


Modified: Saxena et al., Nature Rev Cancer, 2021

Vaccine platforms

Cancer Vaccines and Cell Immunotherapies by Delivery Form Q2 2021

Companies - 105
Investors - 225



DEEP PHARMA INTELLIGENCE

Vaccine platforms

We don’t have a shortage on effective vaccine platforms !!!

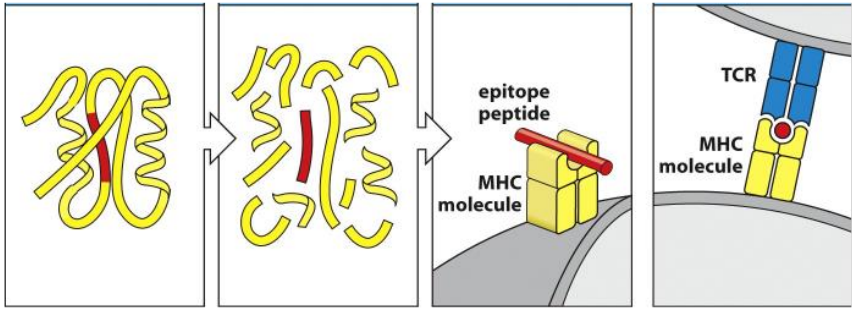
vaccine targets

=

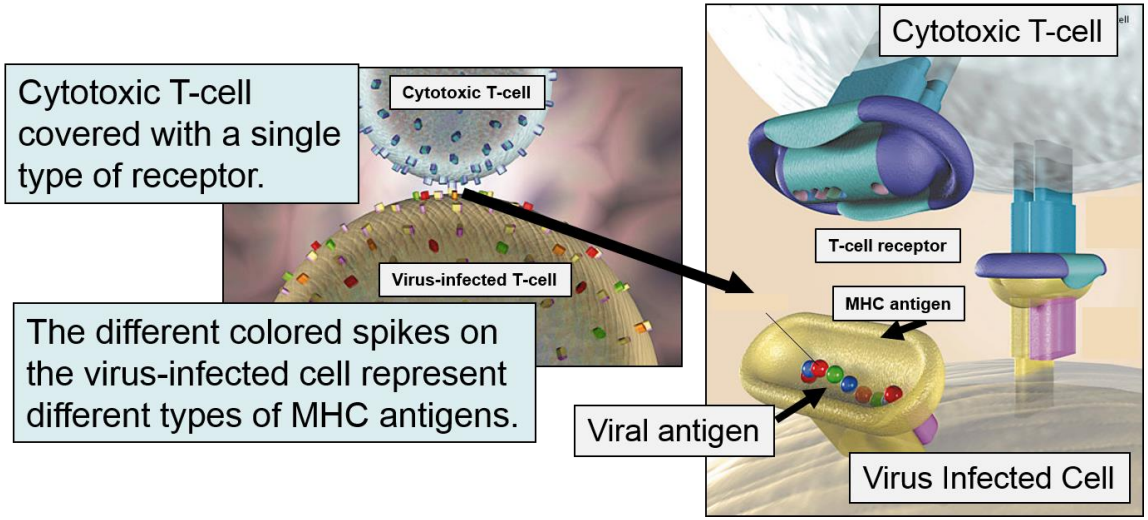
tumor antigens

Antigen presentation and recognition

antigen = only a SMALL PART of a protein



T cell recognition is HIGHLY specific for certain epitopes



Janeway Immunologie, 2018, Springer

Boston University School of Public Health

Perfect world tumor antigen

Perfect world tumor antigen

- selective expression in tumor cells

- homogenous expression in all tumor cells

- essential expression in tumor cells

- high immunogenicity

Perfect world tumor antigen

- selective exp
- homogenous
- essential exp
- high immun

Tumor antigen classes

Foreignness
Immunogenicity
Tolerance
Shared
Personalized
Cost

tumor ASSOCIATED antigen		
Cancer Testis	Overexpression	Lineage
low		
low		
high		
mostly		
rarely		
medium		

=TAA

* only few tumor entities

Tumor antigen classes

	tumor SPECIFIC antigen		tumor ASSOCIATED antigen		
	Neoantigen	Oncoviral	Cancer Testis	Overexpression	Lineage
Foreignness	high	high	low		
Immunogenicity	high	high	low		
Tolerance	low	low	high		
Shared	rarely	mostly*	mostly		
Personalized	mostly	yes (HLA)/no	rarely		
Cost	high	medium	medium		

=TSA

=TAA

* only few tumor entities

Non-personalized tumor antigens – examples

oncoviral	cancer testis (> 140 CTA)	lineage	overexpression
• HPV E6/7	• NY-ESO-1	• HER2/Neu	• MUC1
• LMP1/LMP2	• MAGE-A	• MUC1	• WT1
	• SAGE	• gp100	• EGFR
	• LY6K		
	• CDCA1		
	• PRAME		

Oncoviral tumor antigens

Antigen	Oncovirus	Associated cancer
E6, E7	HPV	cervix CA, head-neck SCC
LMP1, LMP2	EBV	Nasopharingeal CA, B cell lymphoma
Large T, small T	Merkel Polyomavirus	skin CA
Tax	HTLV1 retrovirus	T cell leukaemia

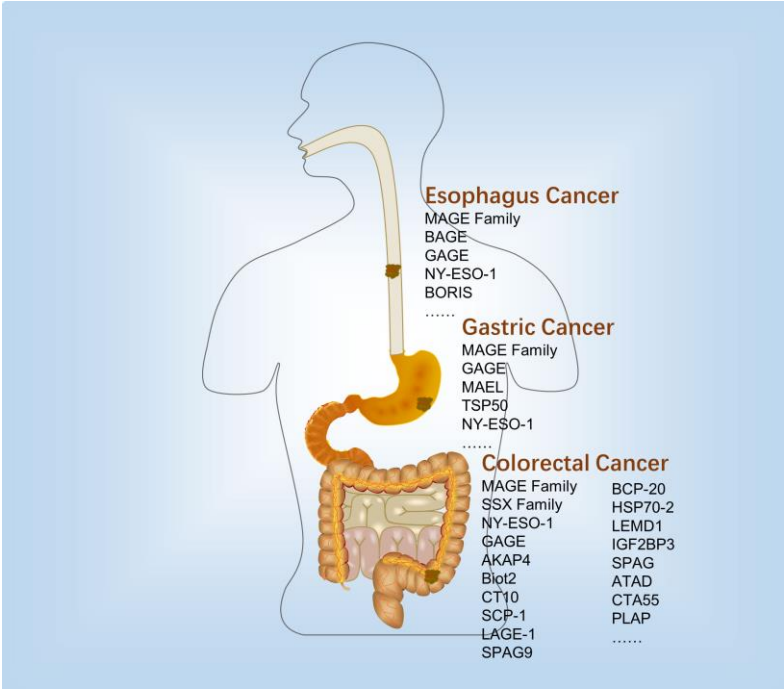
Cancer testis antigens

over 140 cancer testis antigens (CTA) known to date

CTA main examples

Antigen	Associated cancer
NY-ESO-1	melanoma
MAGE-A	melanoma, lung
BAGE	melanoma, other cancers
PRAME	melanoma, other cancers
XAGE1B	multiple cancers
WT1	multiple cancers

CTA examples gastro-intestinal tumors



Ai et al., Frontiers Immunology, 2023

Cancer testis antigens

Tumor-associated antigen clinical trials in lung cancer

Platform	Name	TAA	Phase	Patients		Signs of efficacy
cellular vaccine	GVAX	Autol. tumor cells	I/II	86	NCT00074295	negative
	Belagenpumatucel- L	Allogenic NSCLC	III	532	NCT00676507	negative
	1650-G	Allogenic NSCLC	II	12	NCT00654030	n.a.
peptide	MAGE-A3	MAGE-A3	III	2312	MAGRIT, NCT00480025	negative
	CIMAvax-EGF	EGF	III	579		negative
	Racotumomab-alum	NeuGcGM3	III	1082	NCT01460472	low
	Tecemotide (L-BLP25)	MUC-1	III	1513	NCT00409188	negative
	PRAME	PRAME	I	60	NCT01159964	negative
virus	TG4010	MUC-1	II	65	NCT00415818	positive
	LV305	NY-ESO-1	I	47	NCT02122861	positive
DNA	V934/935	hTERT	I		NCT00753415	
RNA	CV9201	NY-ESO-1, MAGE-C1,2, Survivin, 5T4, MUC	I/II	46	NCT00923312	immunogenicity
	CV9202	NY-ESO-1, MAGE-C1,2, Survivin, 5T4, MUC	I	26		immunogenicity
	mRNA-5671/V941	KRAS (G12D, G12V, G13D, G12C)	I	100	NCT03948763	

=> few signs of efficacy

= vector based gene transfer

Cancer testis antigens

THE LANCET
Oncology

ARTICLES | VOLUME 17, ISSUE 6, P822-835, JUNE 01, 2016

Efficacy of the MAGE-A3 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive non-small-cell lung cancer (MAGRIT): a randomised, double-blind, placebo-controlled, phase 3 trial

Prof Dr Johan F Vansteenkiste, MD • Byoung Chul Cho, MD • Tonu Vanakesa, MD • Tommaso De Pas, MD • Prof Marcin Zielinski, MD • Moon Soo Kim, MD • Prof Jacek Jassem, MD • Masahiro Yoshimura, MD • Jubrail Dahabreh, MD • Haruhiku Nakayama, MD • Libor Havel, MD • Haruhiko Kondo, MD • Prof Tetsuya Mitsudomi, MD • Prof Konstantinos Zarogoulidis, MD • Oleg A Gladkov, MD • Katalin Udud, MD • Hirohito Tada, MD • Prof Hans Hoffman, MD • Anders Bugge, MD • Paul Taylor, MD • Prof Emilio Esteban Gonzalez, MD • Prof Mei Lin Liao, MD • Jianxing He, MD • Prof Jean-Louis Pujol, MD • Jamila Louahed, PhD • Muriel Debois, MSc • Vincent Brichard, MD • Channa Debruyne, MD • Patrick Therasse, MD • Nasser Altorki, MD • Show less

Published: April 27, 2016 • DOI: https://doi.org/10.1016/S1470-2045(16)00099-1 • Check for updates

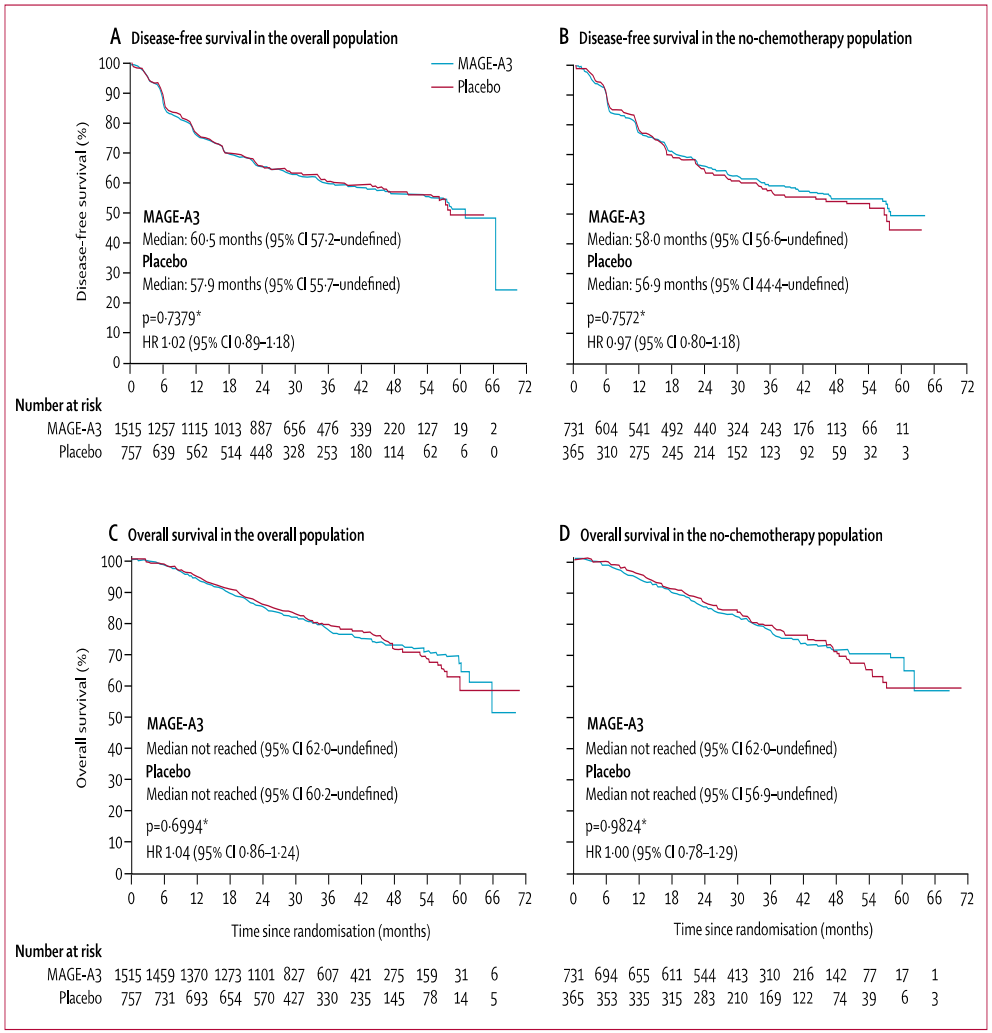


Figure 2: Disease-free survival and overall survival in the overall population and in the population that did not receive adjuvant chemotherapy

=> no signs of efficacy

Lineage / differentiation antigens

main examples

Antigen	Associated cancer
mesothelin	multiple CA
gp100	melanoma
tyrosinase	melanoma
PSA/ PSMA	prostate CA
MUC1	multiple cancers
CA125	ovarian CA

Overexpression antigens

main examples

Antigen	Associated cancer
MUC1	multiple CA
WT1	multiple CA
EGFR	multiple CA
PSA/ PSMA	prostate CA
MUC1	multiple cancers

TAA combinations

NY-ESO-1, MAGE-C1, MAGE-C2, survivin, 5T4, and MUC-1

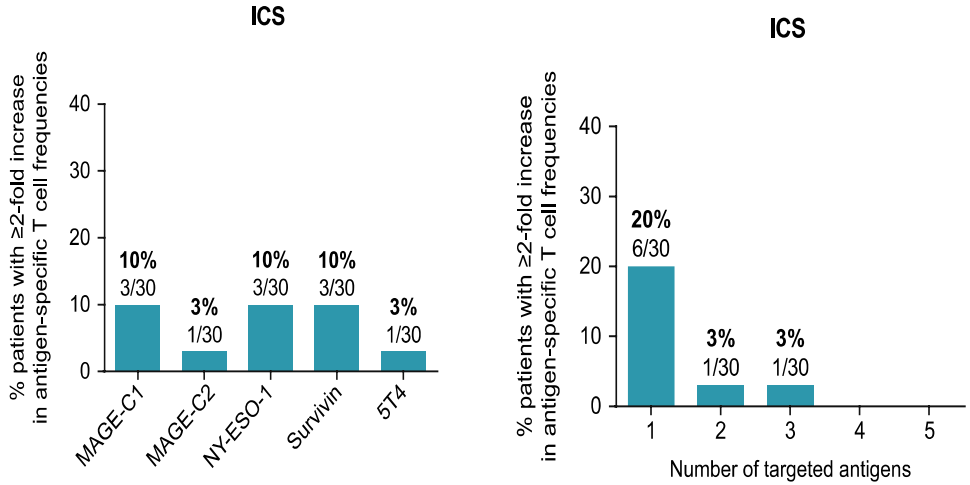
Cancer Immunology, Immunotherapy (2019) 68:799–812
https://doi.org/10.1007/s00262-019-02315-x

CLINICAL TRIAL REPORT

Check for updates

A phase I/IIa study of the mRNA-based cancer immunotherapy CV9201 in patients with stage IIIB/IV non-small cell lung cancer

Martin Sebastian[1,13] · Andreas Schröder[2,14] · Birgit Scheel[2] · Henoch S. Hong[2,14] · Anke Muth[2] · Lotta von Boehmer[3,15] · Alfred Zippelius[4] · Frank Mayer[5,16] · Martin Reck[6] · Djordje Atanackovic[7,17] · Michael Thomas[8] · Folker Schneller[9] · Jan Stöhlmacher[10,18] · Helga Bernhard[11] · Andreas Gröschel[12,19] · Thomas Lander[2] · Jochen Probst[2,20] · Tanja Strack[2] · Volker Wiegand[2] · Ulrike Gnad-Vogt[2] · Karl-Josef Kallen[2,21] · Ingmar Hoerr[2] · Florian von der Muelbe[2] · Mariola Fotin-Mleczek[2] · Alexander Knuth[3,22] · Sven D. Koch[2,23]



=> limited immunogenicity

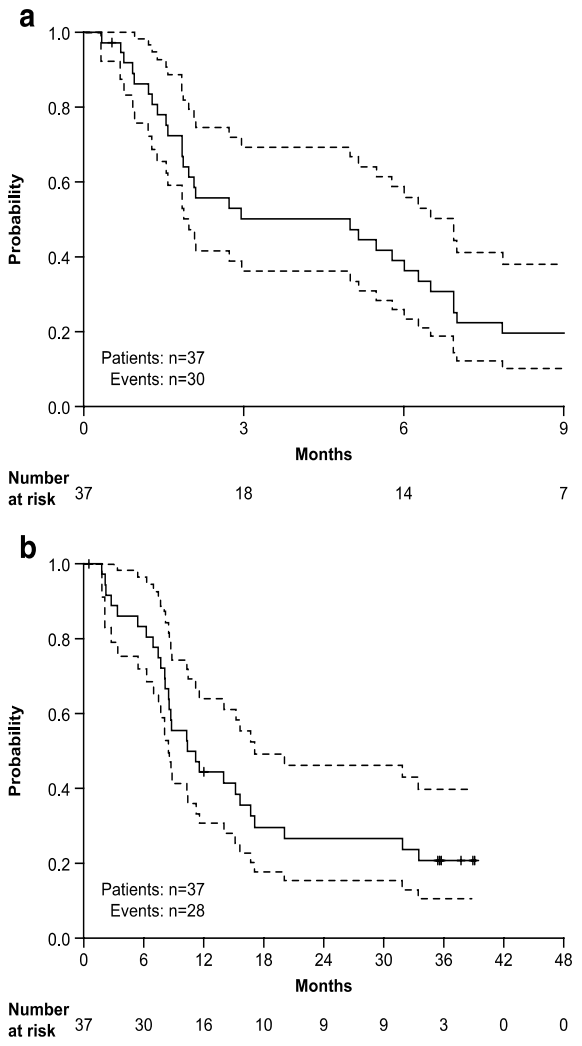


Fig. 4 Kaplan–Meier **a** PFS and **b** overall survival (OS) curves from initiation of treatment for the phase IIa cohort ($N=37$; 86% with stage IV disease). Dashed lines represent 95% CI. Median PFS was 5.0 months (95% CI 1.8–6.3 months) and the 6- and 12-month PFS rates were 38.9% and 16.7%, respectively. Median OS was 10.8 months (95% CI 8.1–16.7 months) and survival rates at 1, 2, and 3 years were 44.4%, 26.7%, and 20.7%, respectively

TAA cancer vaccine clinical development

Meta-analysis

Breast CA

- 46 studies, 1698 patients: ORR* only 9%

Ovarian CA

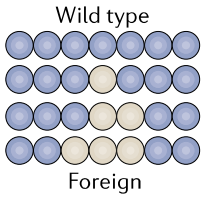
- 32 studies, 426 patients: ORR* only 4%

*ORR = overall response rate (incl. stable disease, partial response, complete response)

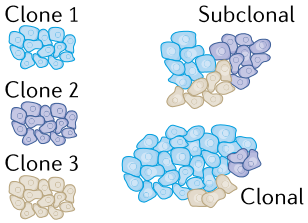
Neoantigens

Qualities of neoantigens

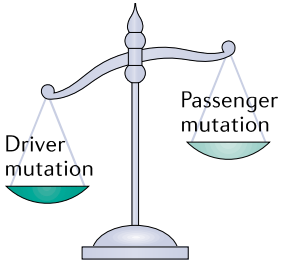
Foreignness
The greater the similarity to the wild-type amino acid sequence, the higher the probability of the responding T cells to be deleted during thymic selection



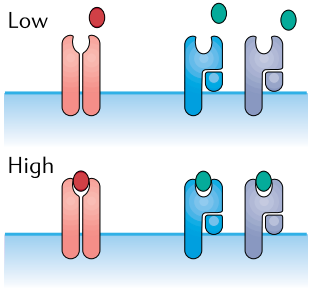
Clonal distribution
Subclonal mutations are present in a small percentage of tumour cells and have high chance of losing expression either spontaneously or after ICI



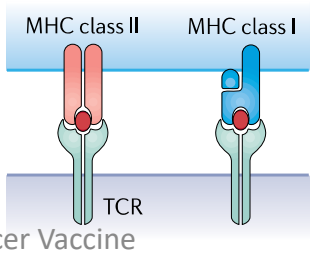
Driver vs passenger mutation
Passenger mutations are subject to loss of expression through tumour evolution or immune resistance. Driver mutations are more conserved as these serve critical survival functions



MHC presentation
Neoantigen presentation on MHC class I and/or MHC class II molecules and expression in tumours with higher HLA heterozygosity in HLA class I loci is more likely to induce T cell infiltration and increase survival in response to ICI

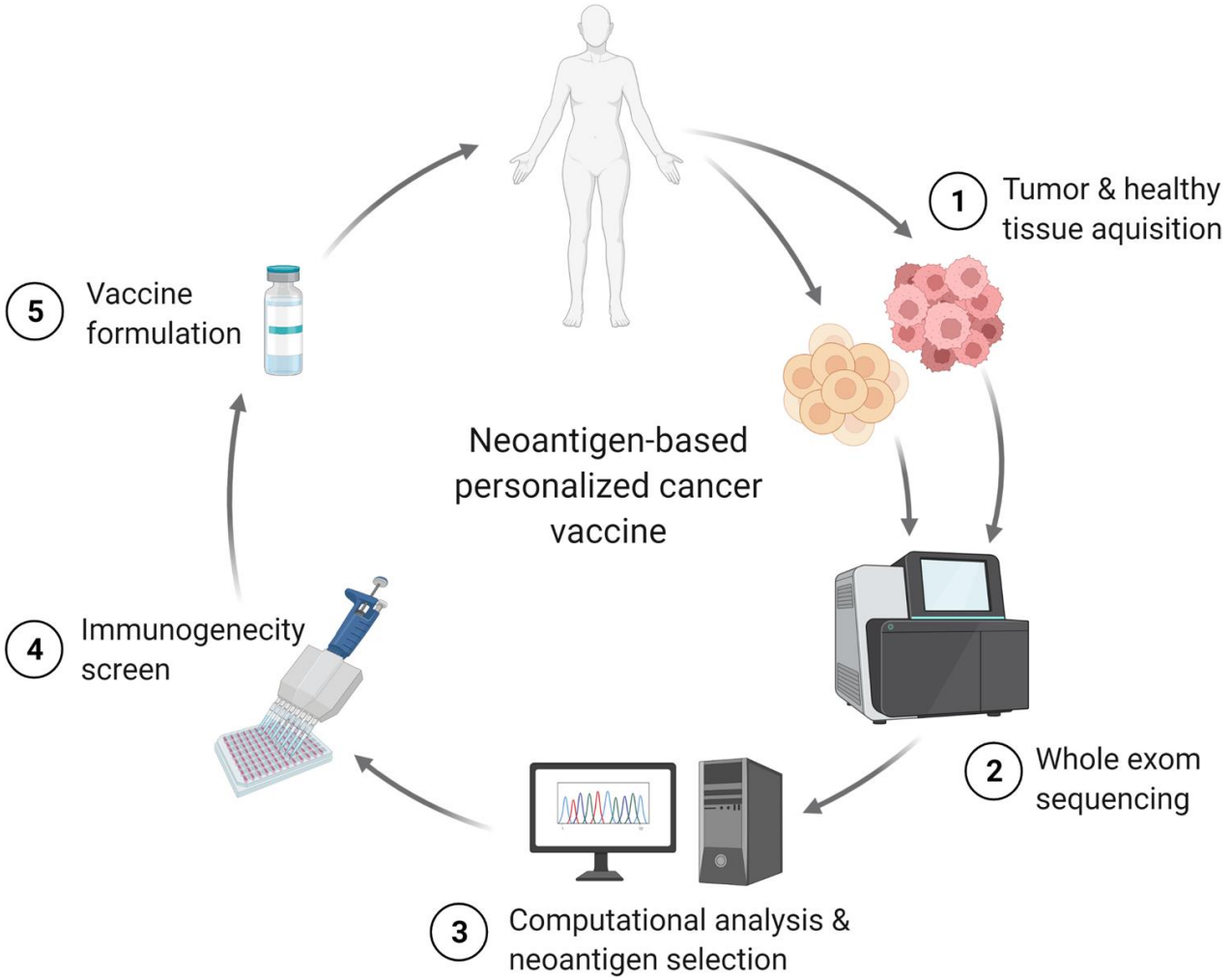


TCR avidity
- High TCR avidity of neoantigens induces a strong CTL-driven response to treatment
- Hard to predict



Saxena et al., Nature Rev Cancer, 2021

Personalized neoantigen vaccine – the simplified view



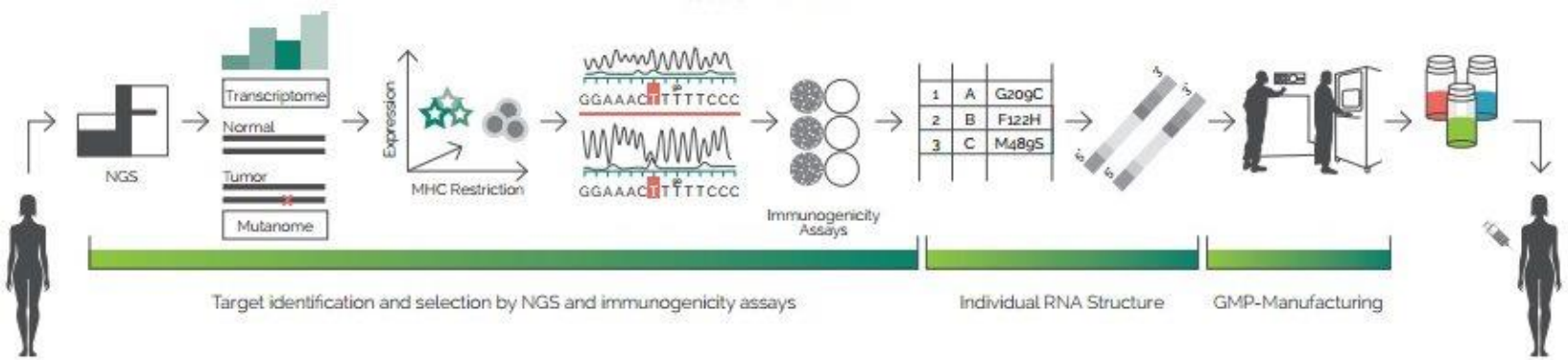
Grimmett et al., 2022,Discover Oncology

Personalized neoantigen vaccine – CHALLENGES

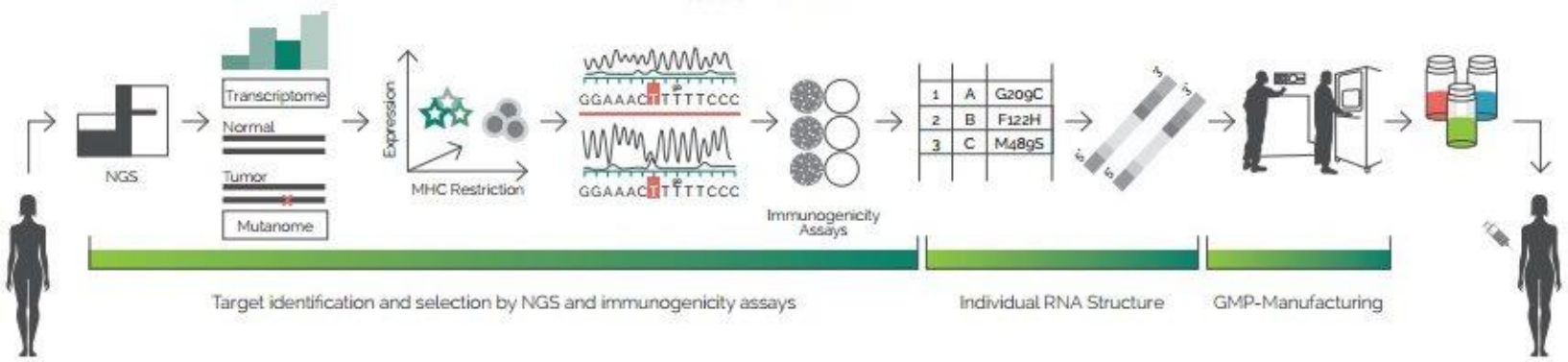
Challenges with personalized neoantigen vaccines:

- Speed
- Metastatic heterogeneity
- TMB (tumor mutational burden)
- Prediction
- HLA dependence

Challenge I - speed



Challenge I - speed



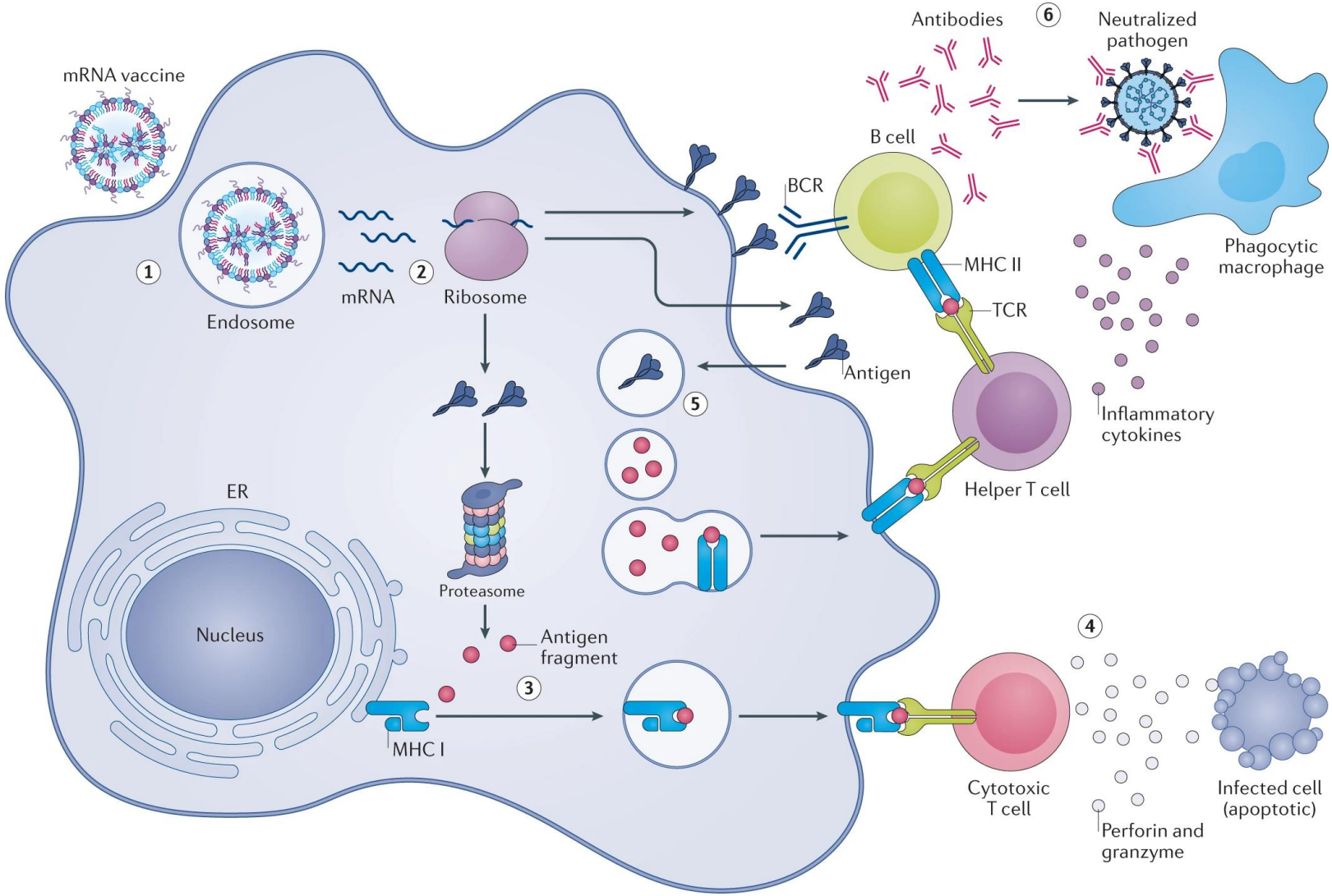
Turn around time from tumor biopsy to GMP-grade production and treatment*:

< 1 month!!!

* “needle-to-needle”

mRNA vaccine platform

Mode of action



Chaudhary et al., 2021, Nature Rev Drug Discovery

mRNA vaccine platform

Challenge of using mRNA vectors

1.
2.
3.

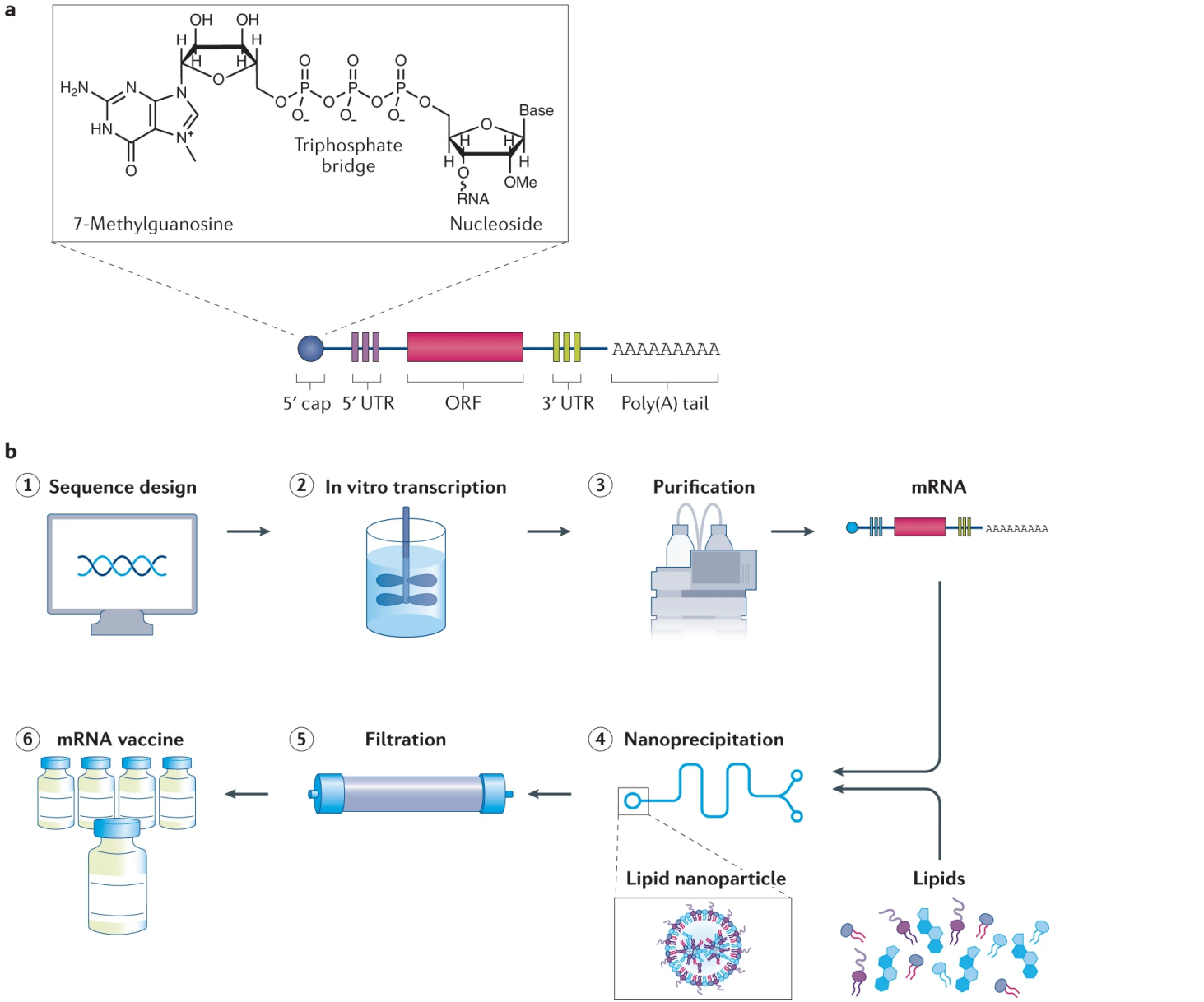
mRNA vaccine platform

Challenge of using mRNA vectors

1. **mRNA stability**
2. **mRNA delivery**
3. **mRNA reactogenicity**

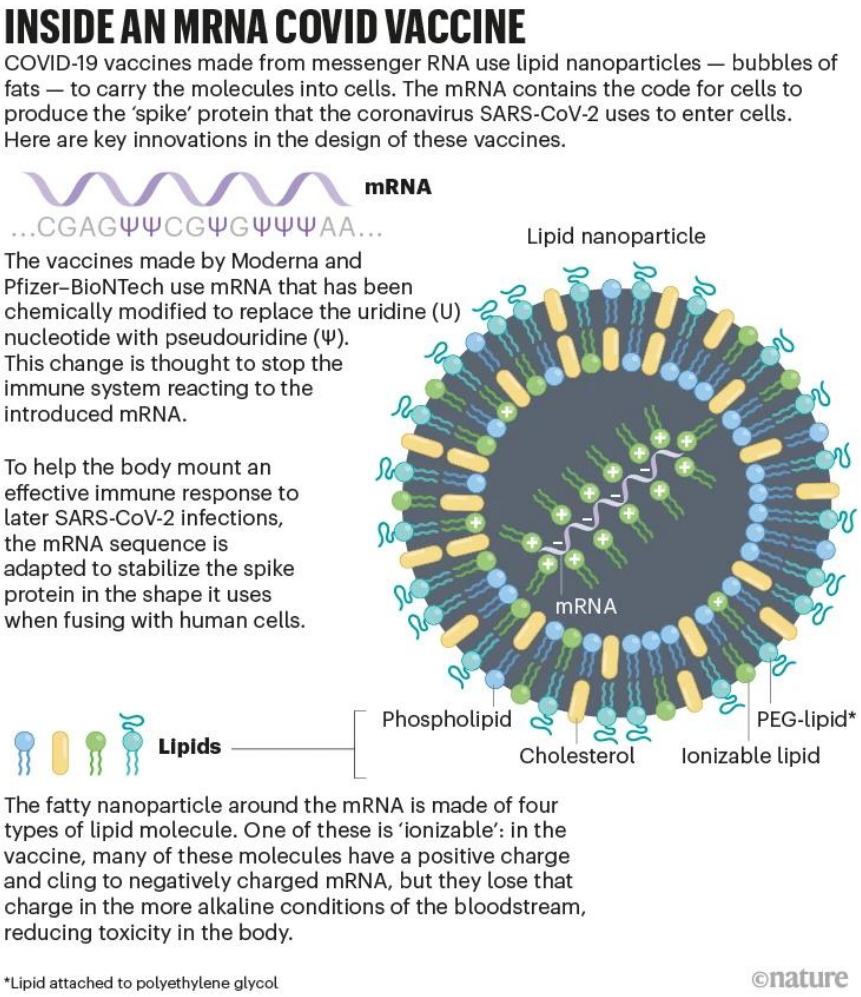
mRNA vaccine platform

Manufacturing mRNA - LNP vaccines



Chaudhary et al., 2021, Nature Rev Drug Discovery

mRNA vaccine platform



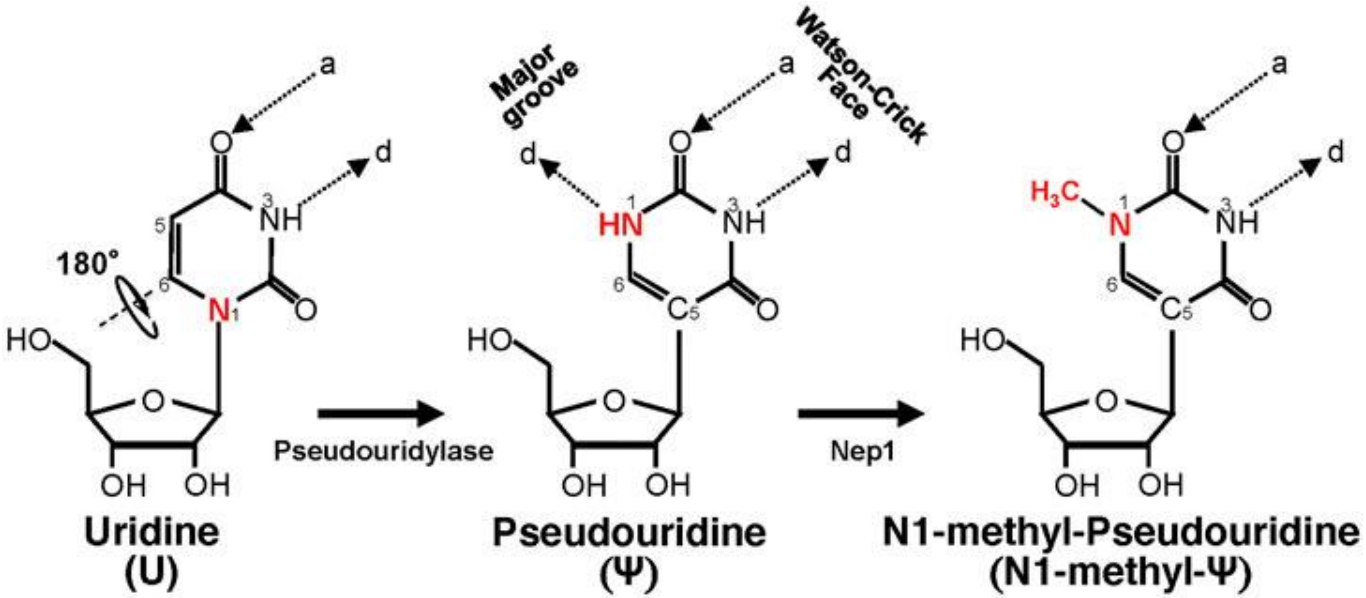
mRNA vaccines allow for a rapid turnover from design to clinical grade production:

- information input does not change biology/chemistry of compound
- stable pharmacokinetics (PK) and pharmacodynamics (PD)

Dolgin , 2021 Nature

mRNA vaccine platform

mRNA modification

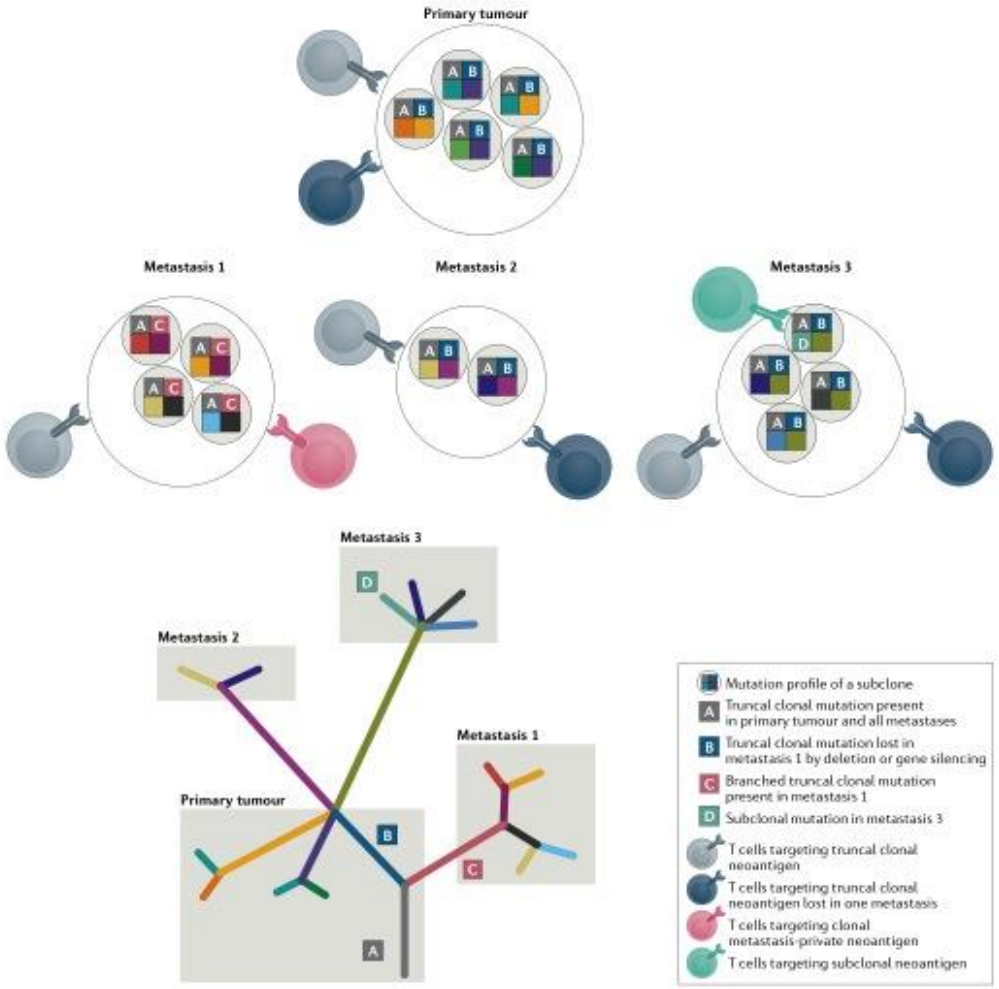


mRNA modifications reduce the cellular defense mechanisms against exogenous mRNA:

- much higher antigen production inside the cell
- superior antibody responses
- role of mRNA modification on T cell immunity unclear

Challenge II – heterogeneity of neoantigen landscape

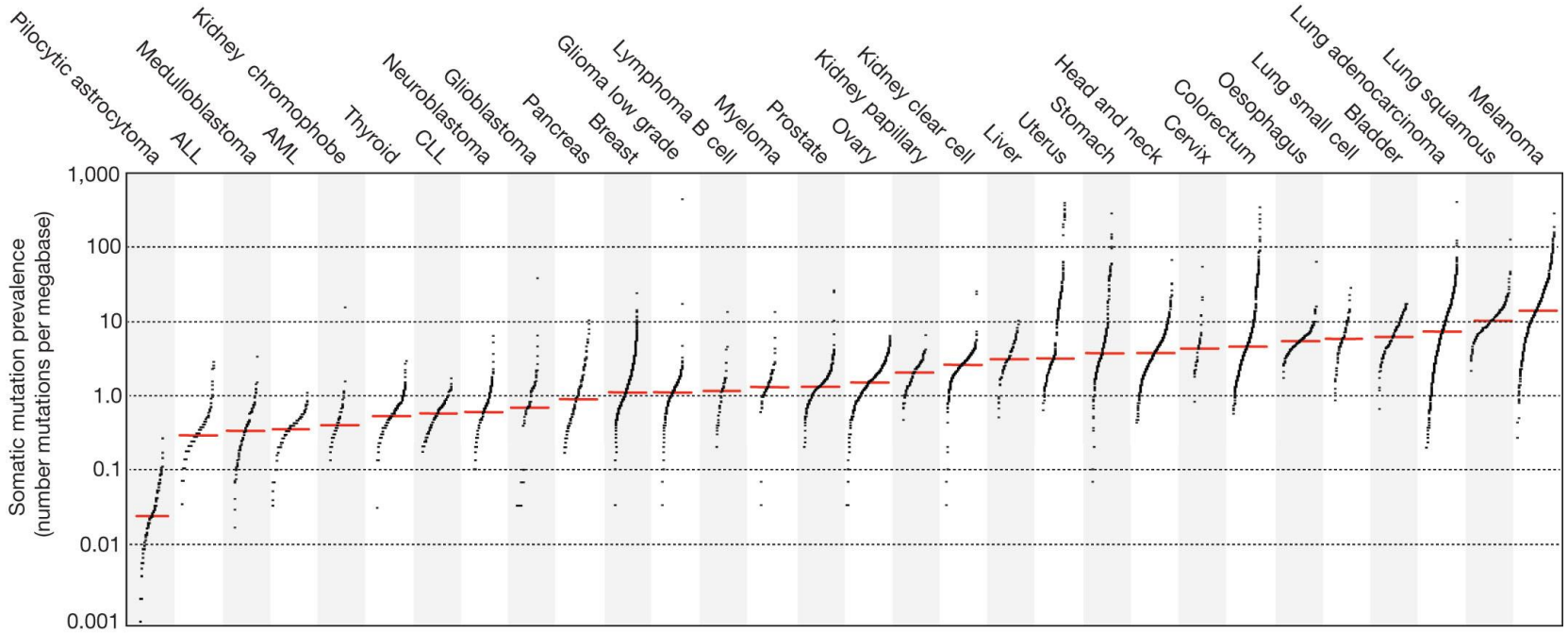
Neoantigens often differ between primary and secondary tumor sites!



Lang et al., Nature Reviews Drug Discovery, 2022

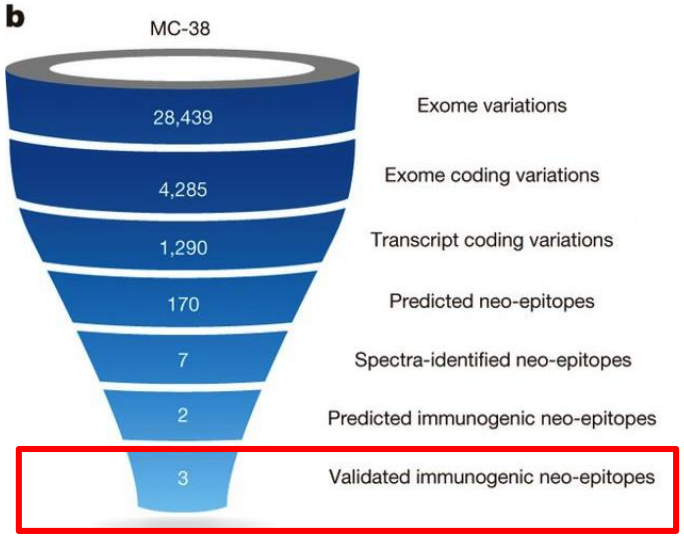
Challenge III – dependence on tumor mutational burden (TMB)

mutation frequency varies between tumor types



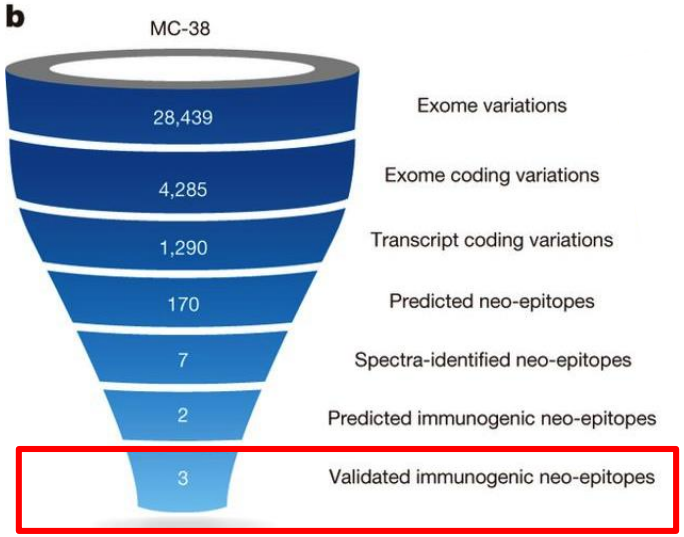
Alexandrov et al. Nature, 2013

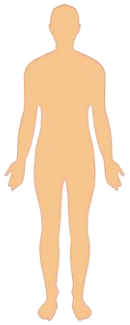
Challenge IV – computational prediction

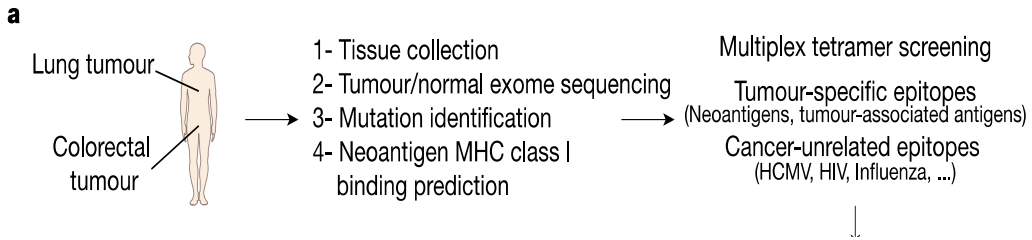


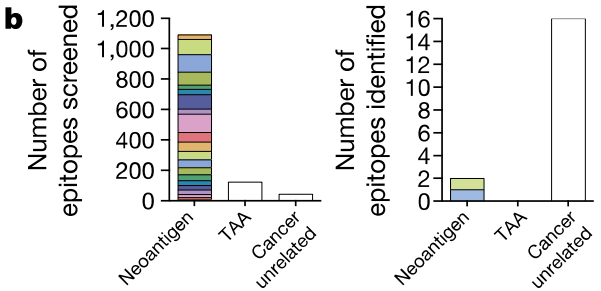
Yadav et al., Nature 2014

Challenge IV – computational prediction









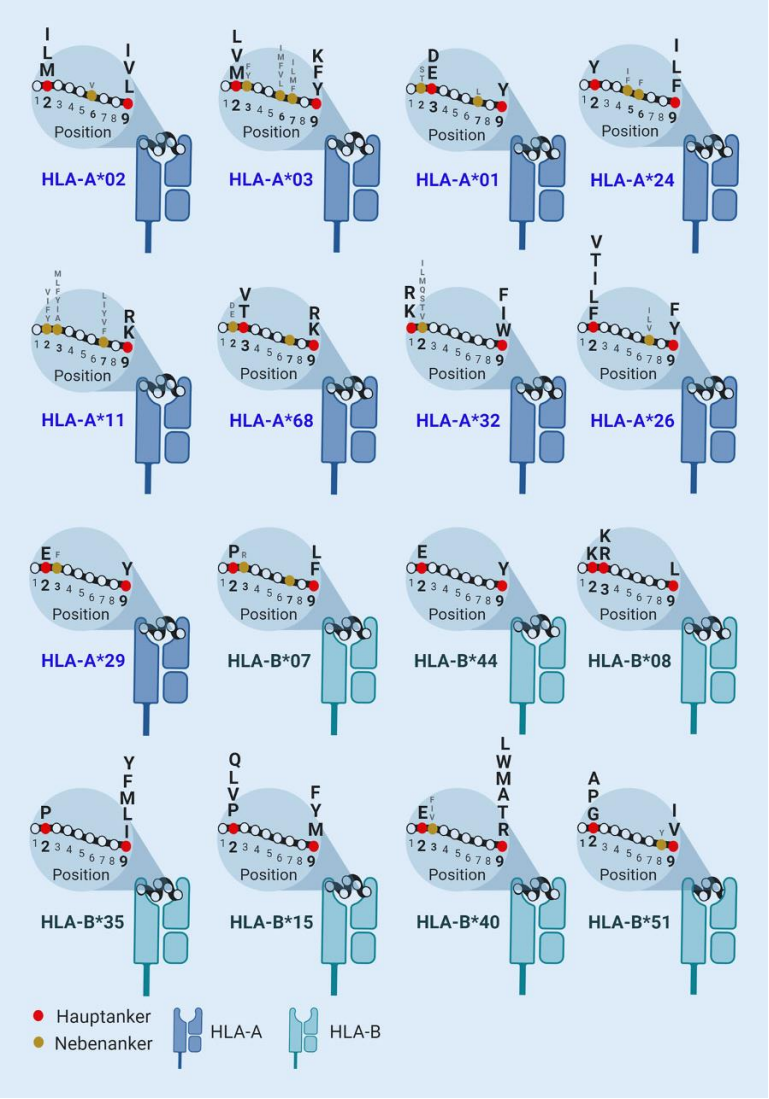
1000 vs 2

Yadav et al., Nature 2014

Simoni et al., Nature 2018

Challenge V – HLA dependency

HLA Variability



Epitope prediction depends on **common** HLA types

Rammensee and Löffler, 2020, Bundesgesundheitsblatt

Personalized neoantigen vaccine – clinical trials

Table 2 | Published clinical trials utilizing neoantigens as targets

Year of publication	Investigator /sponsor	Clinicaltrials.gov identifier, phase	Indication	Platform /treatment	Key results	Ref.
2014	NIH	NCT01174121, 1	Metastatic cholangiocarcinoma	Adoptive transfer of neoantigen-specific (ERBB2IP E805G) $CD4^+$ T cells isolated from tumor	Decrease in target lesions with stabilization of disease, reinjection led to tumor regression, single patient report	9
2015	Washington University	NCT00683670, 1	Stage III or IV melanoma	Intravenous application of neoepitope peptide-loaded DC vaccine	$CD8^+$ T cell responses and broadened antigenic breadth as well as clonal diversity	188,189
2016	NIH	NCT01174121, 2	Metastatic colorectal cancer	Adoptive transfer of neoantigen-specific (KRAS G12D) $CD8^+$ T cells isolated from tumor	Regression of multiple lung metastases upon infusion of four different T cell clonotypes	8
2017	BioNTech	NCT02035956, 1	Stage III or IV melanoma	Intranodal application of naked mRNA vaccine encoding for multiple neoepitopes	$CD8^+$ and especially $CD4^+$ T cell responses against multiple neoantigens, significant reduction of cumulative rate of metastatic events after vaccination	173
2017	Dana-Farber Cancer Institute	NCT01970358, 1	Stage III or IV melanoma	Subcutaneous application of peptide vaccine consisting of pooled mutated epitopes	Polyfunctional $CD8^+$ and especially $CD4^+$ T cell responses with durable memory response, recognition of autologous tumor, combination with anti-PD-1 therapy beneficial for clinical outcome	172,190
2019	Immatics	NCT02149225, 1	Glioblastoma	Intradermal application of peptide vaccine consisting of shared and mutated epitopes	$CD8^+$ and $CD4^+$ T cell responses against multiple shared and mutated epitopes	191
2019	Dana-Farber Cancer Institute	NCT02287428, 1/1b	Glioblastoma	Subcutaneous application of peptide vaccine consisting of pooled mutated epitopes	Polyfunctional $CD8^+$ and $CD4^+$ T cell responses with enriched memory phenotype and augmented T cell infiltration to the tumor	192
2020	Dana-Farber Cancer Institute /Neon Therapeutics / BioNTech US	NCT02897765, 1	Advanced melanoma, NSCLC, bladder cancer	Subcutaneous application of peptide vaccine consisting of pooled mutated epitopes combined with PD-1 blockade	Durable $CD8^+$ and especially $CD4^+$ T cell responses with cytotoxic potential, observation of epitope spreading upon vaccination	193
2020	NIH/Moderna	NCT03480152, 1	Metastatic gastrointestinal cancer	Intramuscular application of LNP-formulated mRNA vaccine encoding for multiple neoepitopes	$CD8^+$ and $CD4^+$ T cell responses against multiple mutated epitopes, small patient group ($n=4$), no objective clinical response	194
2021	NCT/ University of Heidelberg	NCT02454634, 1	Newly diagnosed glioma	Subcutaneous application of a single IDH1 (R132H) peptide vaccine	Vaccine-induced $CD4^+$ T cell responses across multiple MHC alleles in over 90% of the patients	174

= vector based gene transfer

Peri et al., Nature Cancer, 2023

Personalized neoantigen vaccine – clinical trials

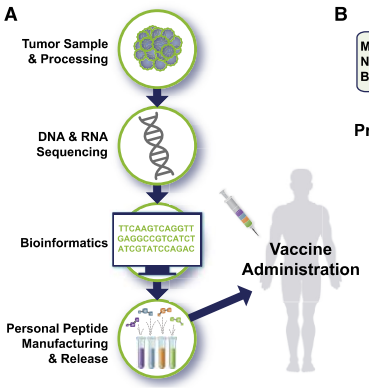
Cell

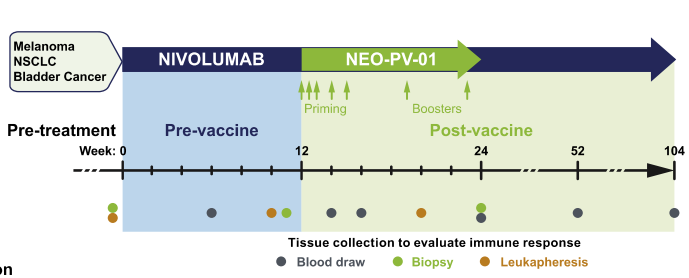
Volume 183, Issue 2, 15 October 2020, Pages 347-362.e24

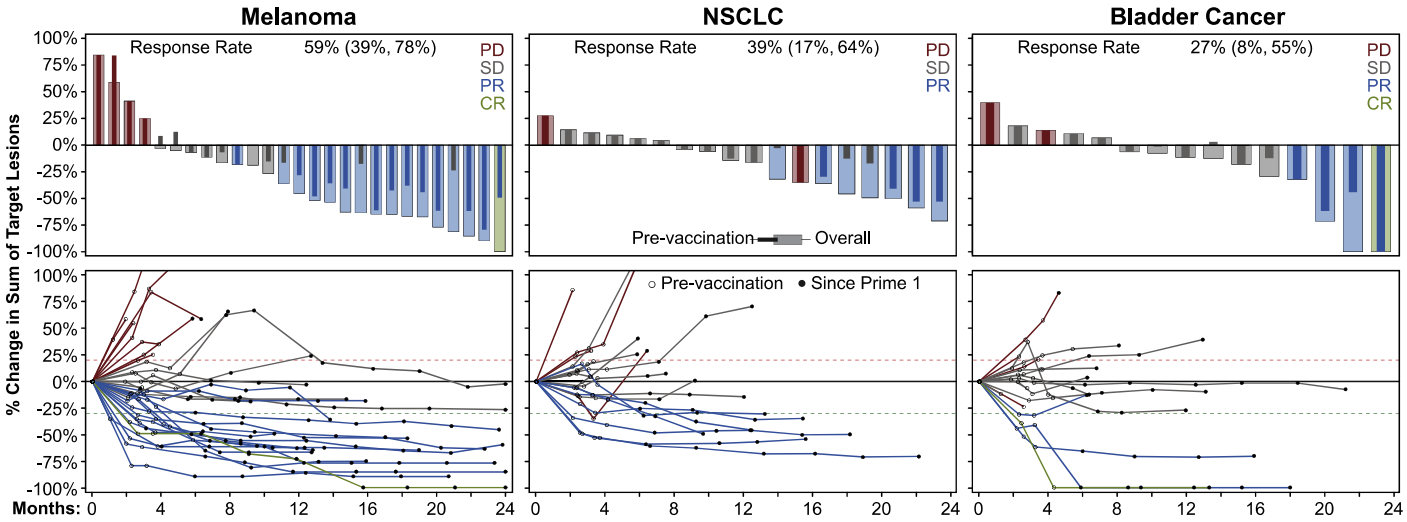
Article

A Phase Ib Trial of Personalized Neoantigen Therapy Plus Anti-PD-1 in Patients with Advanced Melanoma, Non-small Cell Lung Cancer, or Bladder Cancer

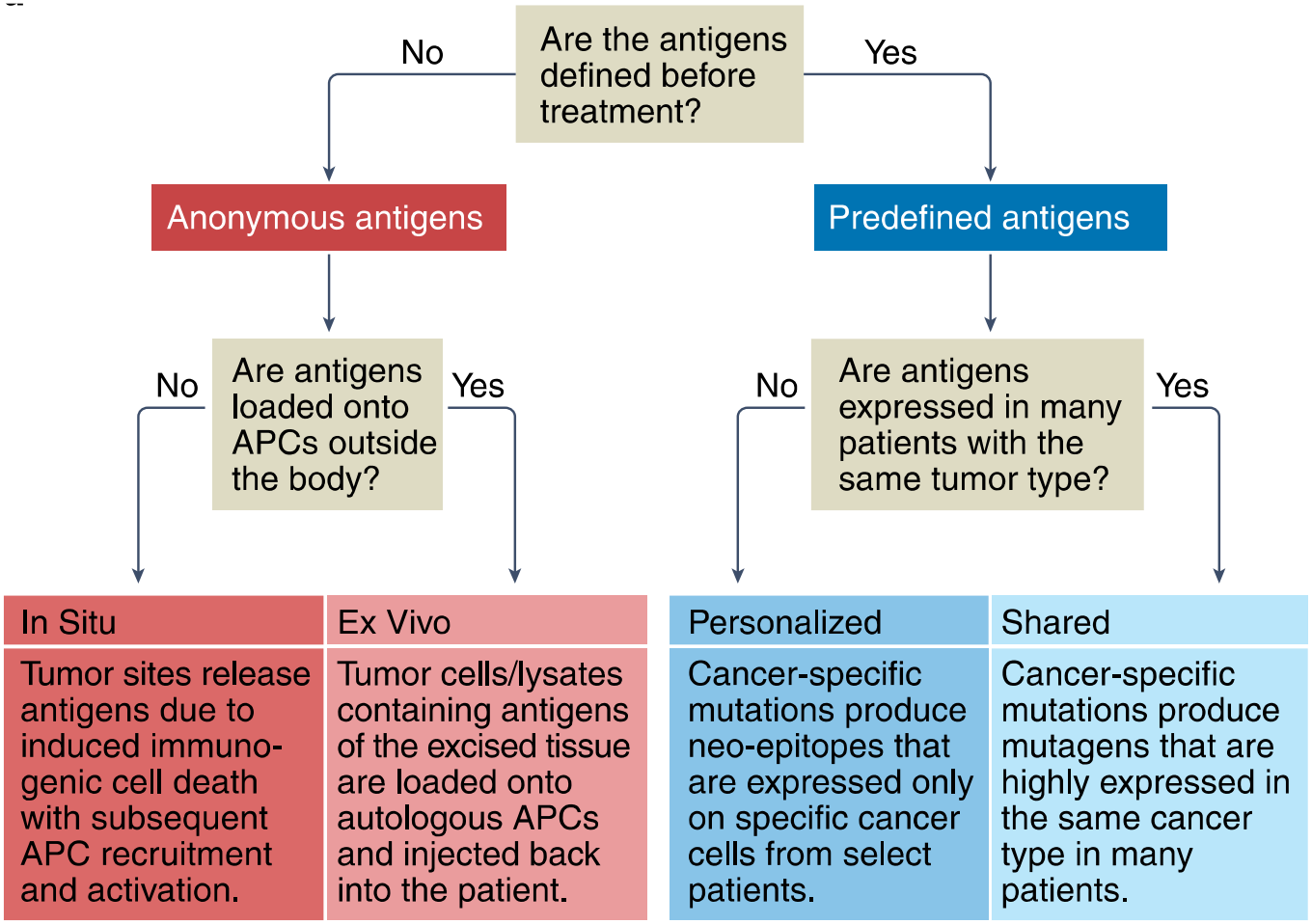
Patrick A. Ott [1], Siwen Hu-Lieskovan [2], Bartosz Chmielowski [2], Ramaswamy Govindan [3], Aung Naing [4], Nina Bhardwaj [5], Kim Margolin [6], Mark M. Awad [1], Matthew D. Hellmann [7], Jessica J. Lin [8], Terence Friedlander [9], Meghan E. Bushway [10], Kristen N. Balogh [10], Tracey E. Sciuto [10], Victoria Kohler [10], Samantha J. Turnbull [10], Rana Besada [10], Riley R. Curran [10] ... Lakshmi Srinivasan [10, 11]







Tumor antigens – quo vadis?



Lin et al., Nature Cancer 2022

Tumor antigens – anything else?

Private neoantigens

Shared tumor-associated antigens

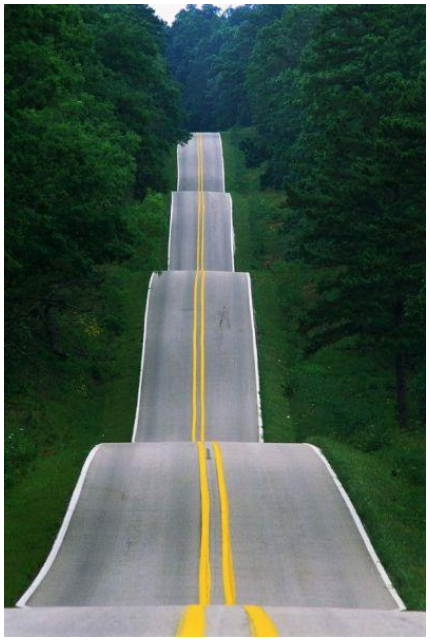
Black box

Tumor antigens – anything else?

Private neoantigens

Shared tumor-associated antigens

The road ahead



Shared neoantigens

1. driver mutations (e.g. KRAS, p53)
2. NON-coding regions
3. splicing variants
4. cryptic peptides

Questions???