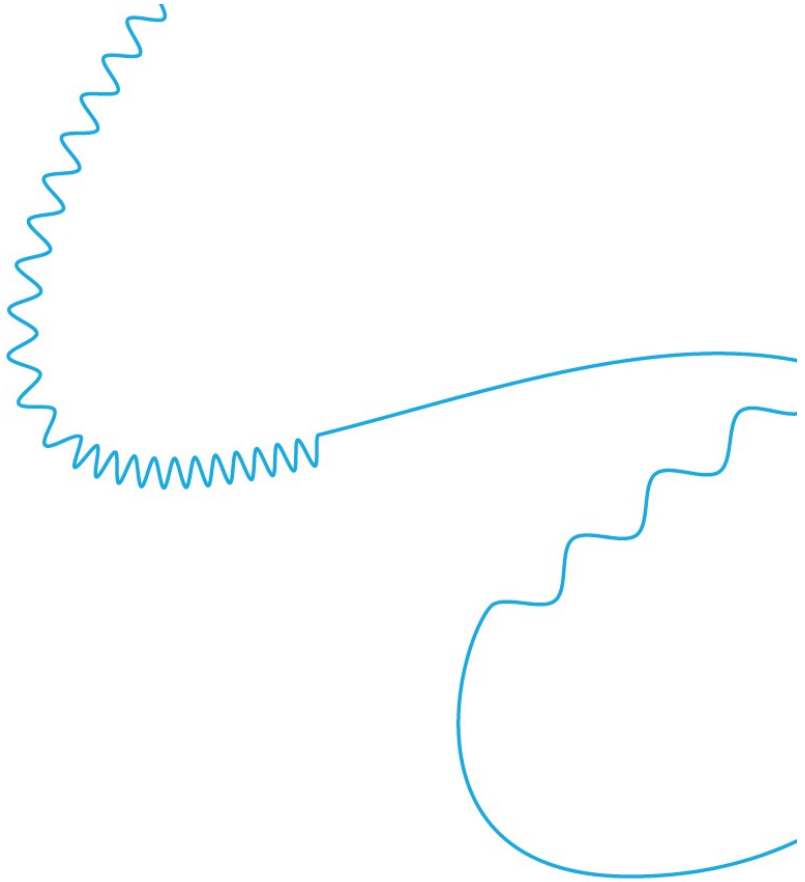
Cancer Vaccine: Identifying Druggable Targets

SITC-NCI Computational Immuno-oncology Webinar

Wei Zheng, Dec. 2023



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Outline

- **Why** **are we excited about cancer vaccines**
  - potential to be the next IO frontier
  - positive clinical signals from multiple recent trials
  - synergy with other treatment strategies
- **What** **are the different types of cancer vaccines**
  - tumor specific antigens vs. tumor associated antigens
  - neoantigens from somatic variants, unannotated ORFs, fusions, splice variants
  - antigens targeting immunosuppressive microenvironment (PDL1, IDO1, and other suppressive proteins)
- **How** **do we select antigen targets for cancer vaccines**
  - commonly used computational resources
  - methodologies
  - emerging technologies (TCR, single cell, spatial, digital path, high throughput immunogenicity assays)

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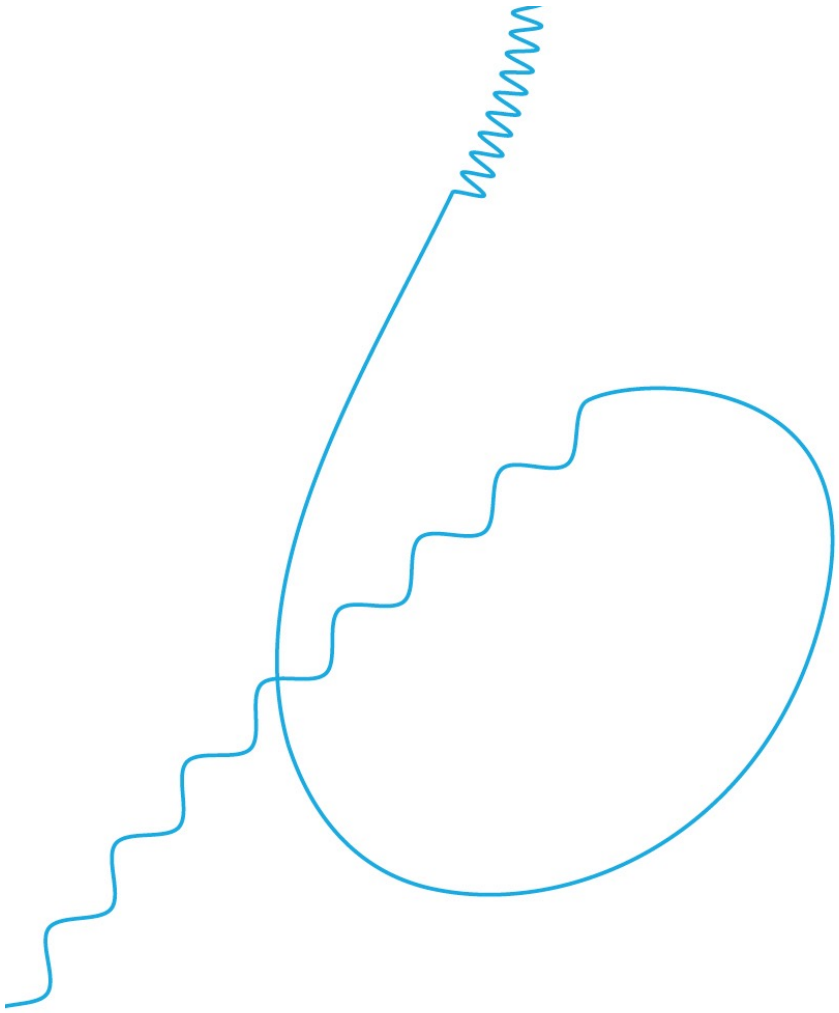

Why are we excited about cancer vaccine

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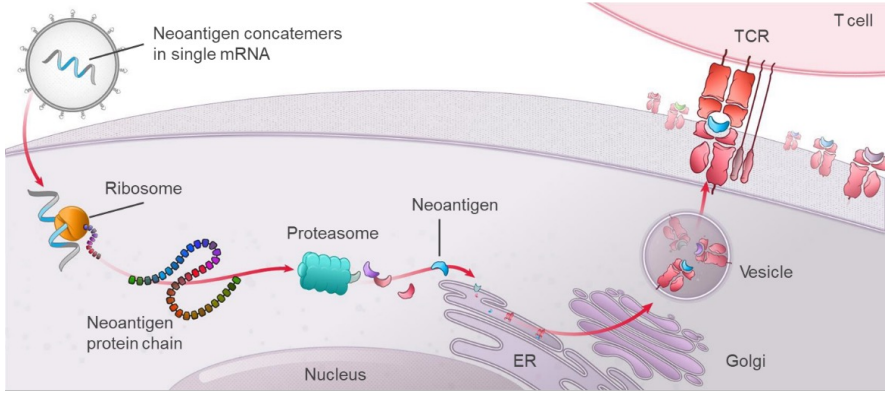
Cancer vaccine leverages our own immune system to fight cancer

It is called a "vaccine" but it functions as a therapy

- **Vaccines against certain viruses (HPV, HCV, EBV) are protecting people from certain cancers.**
- **We will focus on therapeutic cancer vaccine today.**
- **Mechanism of action: cancer antigen induced T cell immunogenicity**
- **A great introductory podcast: Two Scientists Walk into a Bar - Cancer Vaccine**



Moderna's personalize cancer vaccine, aka. individualized neoantigen therapy

Abbreviations: mRNA = messenger ribonucleic acid; ER = endoplasmic reticulum; TCR = T-cell receptor

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Cancer vaccine has potential to be the next IO frontier

"It has been decades and decades…The hallways of science are littered with failures here." -- Wellington

- This visionary review Lin..Brody (2022) Nat Cancer, published on 08/23/2022, has garnered considerable attention, with 137 citations as of November 30, 2023.

- Why so much enthusiasm?

  - Relevance to current events: "The rapid development and success of RNA-based vaccines against SARS-CoV-2 in response to the COVID-19 pandemic have brought cancer vaccines back into focus." (Vishweshwaraiah .. Dokholyan Front Immunol. 2022)

  - Clinical and translational successes: recent clinical trial successes and solid translational data demonstrated great potential

  - Technological advances: could dramatically improve target ID accuracy and reduce development and manufacturing cost

nature cancer

REVIEW ARTICLE

https://doi.org/10.1038/s43018-022-00418-6

Check for updates

Cancer vaccines: the next immunotherapy frontier

Matthew J. Lin[1,2,3,4], Judit Svensson-Arvelund[1,2,3,5], Gabrielle S. Lubitz[1,2,3], Aurélien Marabelle[6], Ignacio Melero[7], Brian D. Brown[2] and Joshua D. Brody[1,2,3]

After several decades, therapeutic cancer vaccines now show signs of efficacy and potential to help patients resistant to other standard-of-care immunotherapies, but they have yet to realize their full potential and expand the oncologic armamentarium. Here, we classify cancer vaccines by what is known of the included antigens, which tumors express those antigens and where the antigens colocalize with antigen-presenting cells, thus delineating predefined vaccines (shared or personalized) and anonymous vaccines (ex vivo or in situ). To expedite clinical development, we highlight the need for accurate immune monitoring of early trials to acknowledge failures and advance the most promising vaccines.

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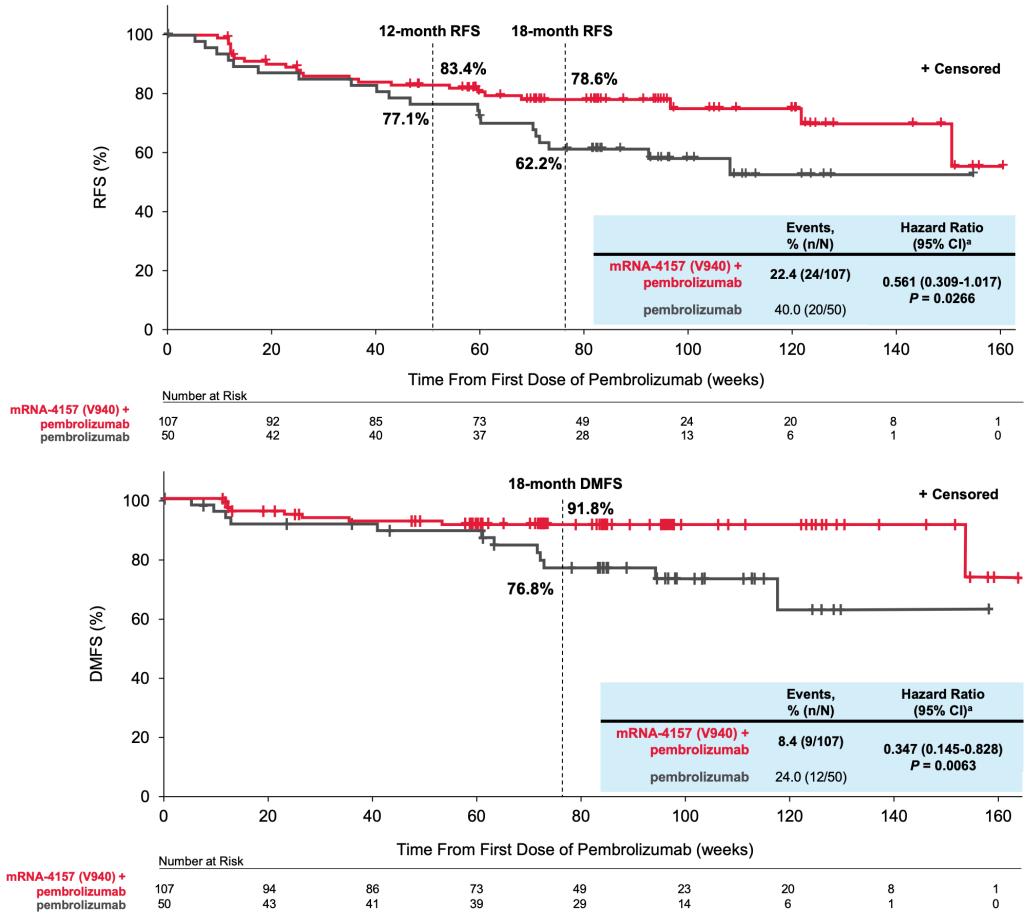
Moderna's mRNA-4157 in combination with Merck's Keytruda met primary and secondary efficacy endpoints in Phase 2 study

Interim Analysis Data (Nov 2022 cut) presented at AACR and ASCO in 2023



- mRNA-4157 (V940) and pembrolizumab demonstrated a clinically significant improvement in RFS and DMFS compared to standard of care pembrolizumab in high-risk resected melanoma, with a 44% reduction in the risk of recurrence or death and a 65% reduction in the risk of distant metastasis or death with a median of 2 years of follow-up
- mRNA-4157 (V940) in combination with pembrolizumab was well-tolerated without an increase in immune-mediated AEs compared with pembrolizumab monotherapy
- mRNA-4157 (V940) in combination with pembrolizumab received Breakthrough Therapy Designation from FDA in February 2023 and PRIME Designation from EMA in April 2023
- *Updated results (Nov 2023 data cut) announced Dec 14, 2023: at a median planned follow-up of approximately three years, mRNA-4157 (V940) in combination with KEYTRUDA reduced the risk of recurrence or death by 49% (HR=0.510 [95% CI, 0.288-0.906]; one-sided nominal p=0.0095) and the risk of distant metastasis or death by 62% (HR=0.384 [95% CI, 0.172-0.858]; one-sided nominal p= 0.0077) compared to KEYTRUDA alone in stage III/IV melanoma patients with high risk of recurrence following complete resection*

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BioNTech's BNT122 induces immune responses in PDAC in Phase 1 study and Phase 2 study started in Q4 2023

BioNTech Innovation Series 11/14/2023

Autogene Cevumeran/BNT122[1] Induces Immune Responses in Adjuvant Pancreatic Cancer

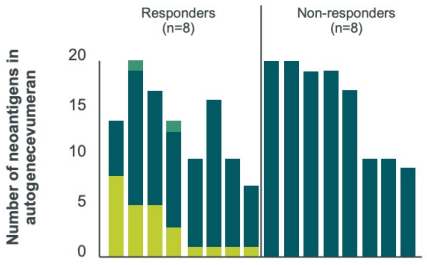
BNT122 induces functional neoantigen-specific T cells

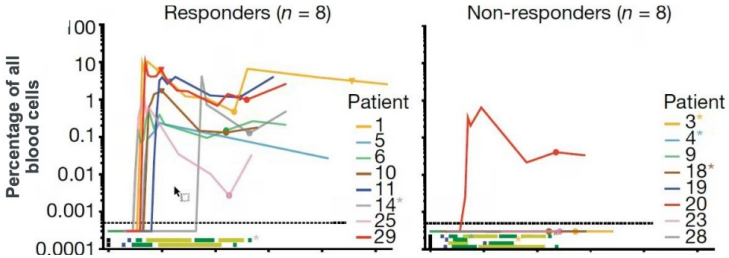
Rojas et al. Nature. 2023

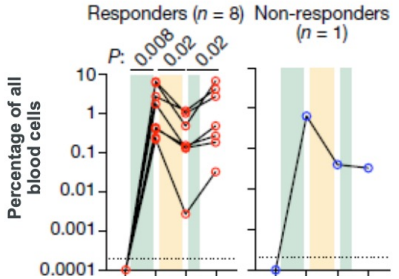
Half of all the patients who received the vaccine mount neoantigen-specific *de novo* T cell responses against at least one vaccine neoantigen

Vaccine-expanded T cells are durable and persist for up to 2 years

Vaccine-expanded T cells persist despite mFOLFIRINOX treatment







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Cancer vaccine (CV) is a promising pillar in combination immunotherapy strategies

Multiple clinical studies are ongoing with following combinations:

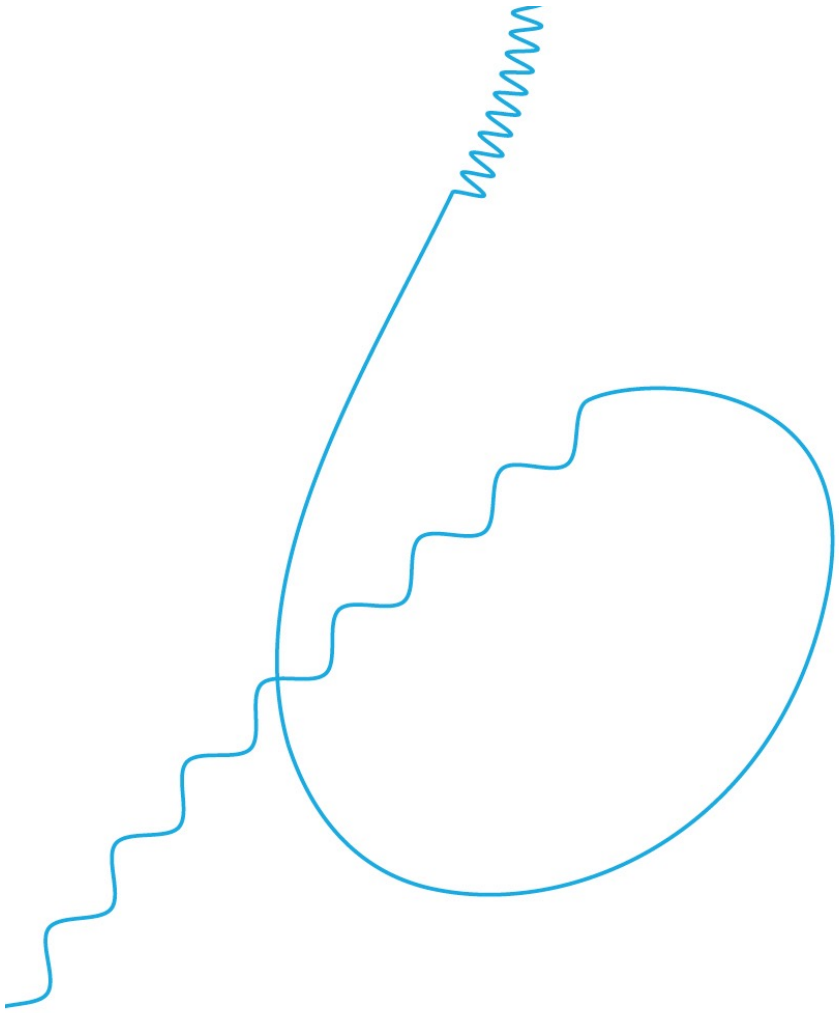
- **monotherapy**
- **CV + ICI**
- **CV + chem**
- **CV + ICI + chem**
- **CV + ICI + chem + radio**

Synergy between CV and TCR-T/CAR-T are also being actively explored preclinically:

- **CV + cell Tx**

A great review on neoantigen therapy clinical trial progresses:
[Xie..Fu (2023) Signal Transduct Target Ther]

Figure from Zhu..Pan (2021) J Hematol Oncol



What are the different types of targets in cancer vaccines

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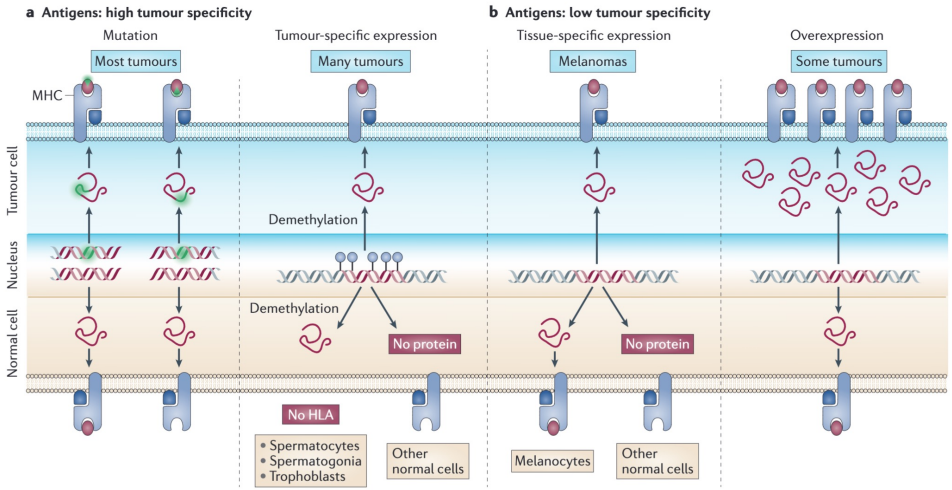
Tumor specific antigens (TSA) vs. tumor associated antigens (TAA)



Colie..Boon (2014) Nat Rev Cancer

- **TSAs**

Neoantigens

Viral oncoproteins (HPV, EBV)

- **TAAs**

Cancer germline antigens (MAGE, NY-ESO-1)

Tissue differentiation antigens (MART1, tyrosinase)

Overexpressed antigens (HER2, CEA)

Human endogenous retroviruses (HERV)

Oliveria..Wu (2023) Nat Rev Cancer

Both TSAs and TAAs have been considered as cancer vaccine targets, and the current classification helps us understand their specific properties and potential application scenarios.

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Research/clinical progress on TSA vs. TAA cancer vaccines

TSA highlights:

✓ No central tolerance → no toxicity, high immunogenicity

! Finding a needle in a haystack, only <5% of predicted neoantigens elicit anti-tumor T cell responses

! Usually unique to each tumor → individualized therapy

- Nonsynonymous somatic variants (SNV, short INDEL's, and frameshift) can leverage cost-effective WES + RNASeq and has most established computational workflow
- Mutations in unannotated translated ORF's (nuORFs) are a new source of neoantigens, requires RiboSeq + immunopeptidomics Ouspenskaia..Regev (2022) Nat Biotech
- Fusions and other structural variants
- An excellent webinar on neoantigen discovery, especially on RNA dysregulation derived neoantigens, is covered in this series by Dr. Yi Xing in 2021

TAA highlights:

✓ Present across patients → ideal for off-the-shelf vaccine

! Low avidity TCR → low immunogenicity

! Central tolerance → toxicity concerns

- Cancer-testis antigens are more actively pursued due to higher tumor specificity
- TAA epitope selection can also take cross-HLA presentation into consideration, while needing multiple orthogonal validation approaches Yarmarkovich..Maris (2023) Nat
- Vaccines target PDL1, IDO1, and other suppressive proteins has phase 1/2 trial published in Kjeldsen..Svane (2021) Nat Med, combo with ICI currently in Phase 3 study for advanced melanoma

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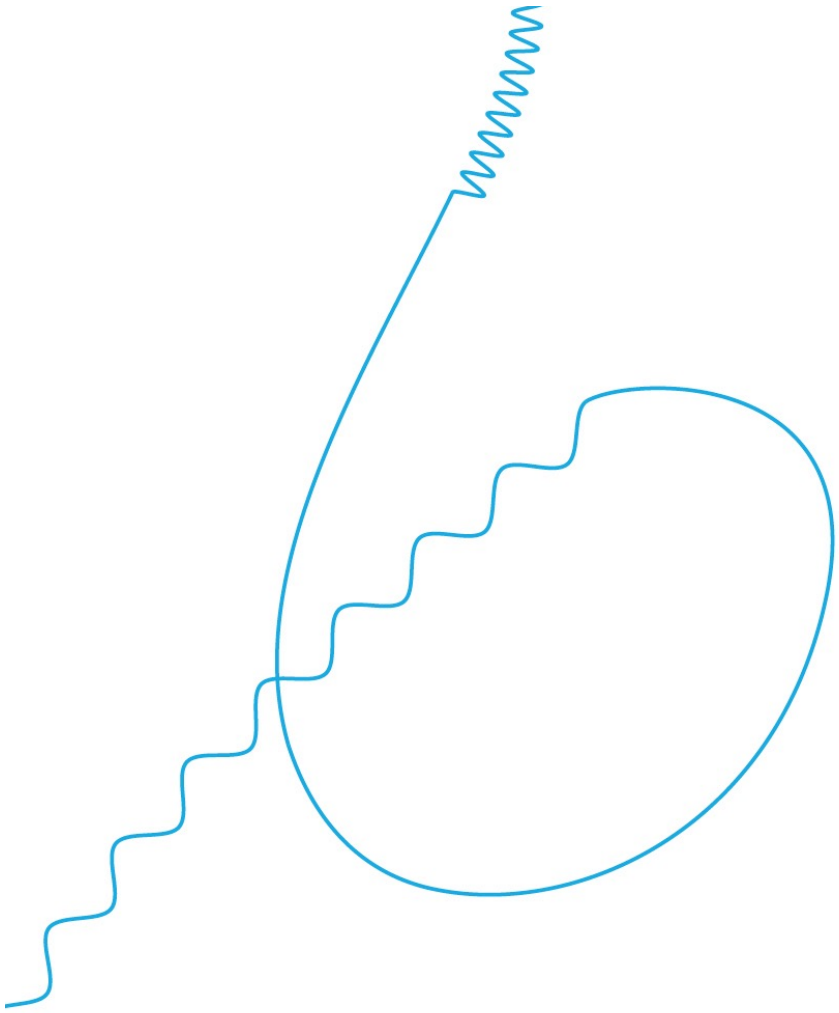

How do we select targets for cancer vaccines

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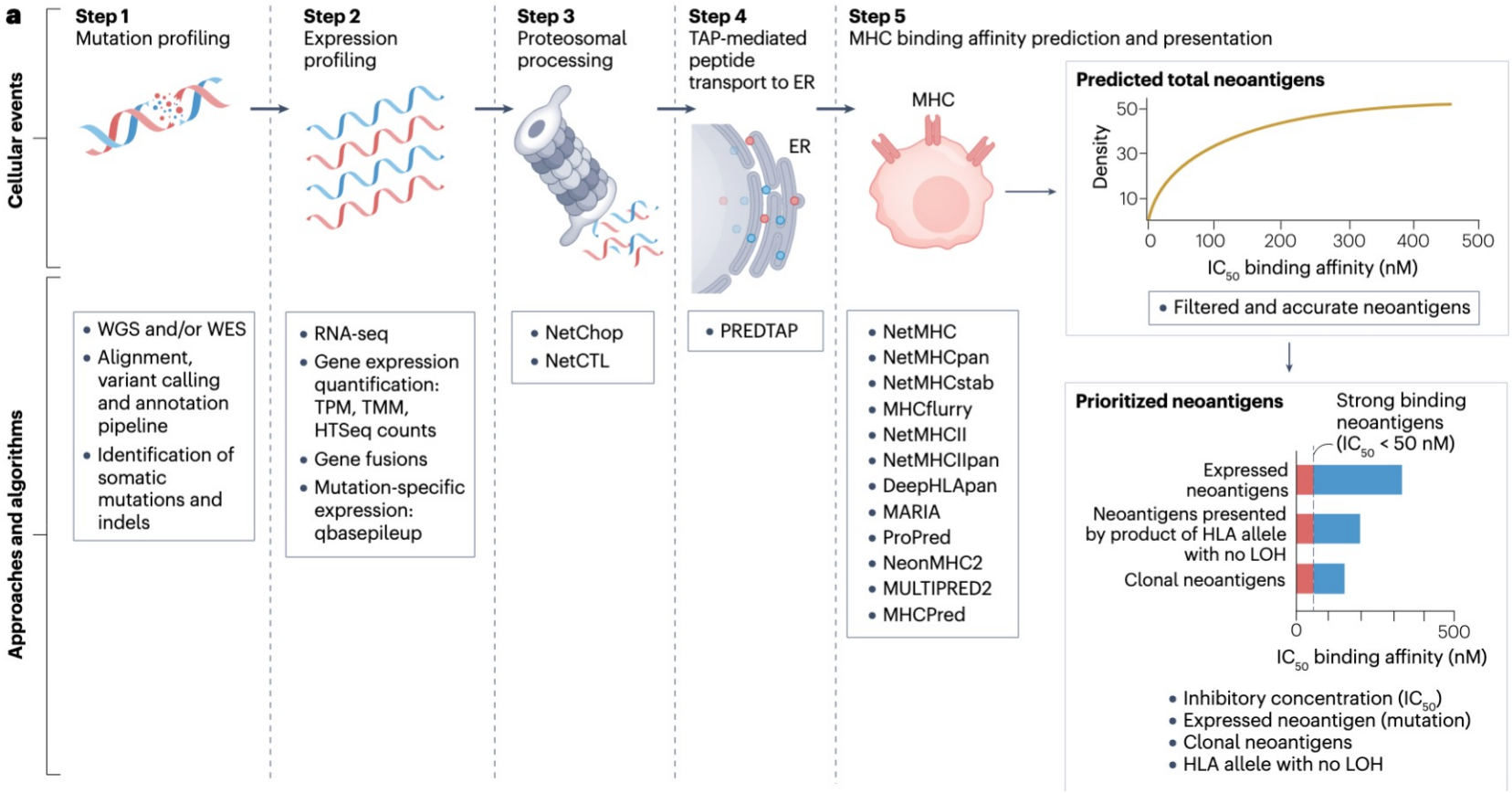
Neoantigen identification computational workflow



Addala ..Waddell (2023) Nat Rev Clin Onc

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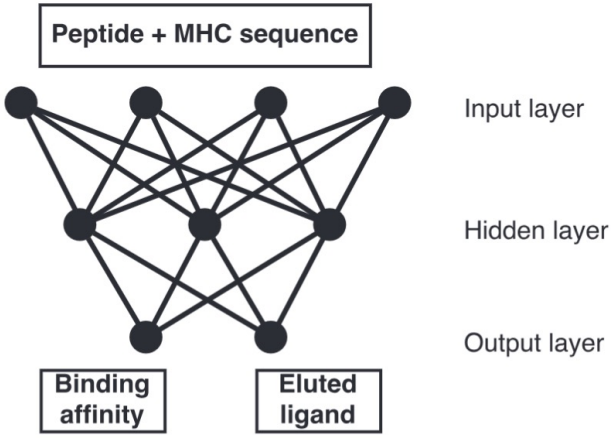
State-of-the-art peptide MHC binding prediction models

Ensemble of artificial neural networks are the mainstream with room for improvement

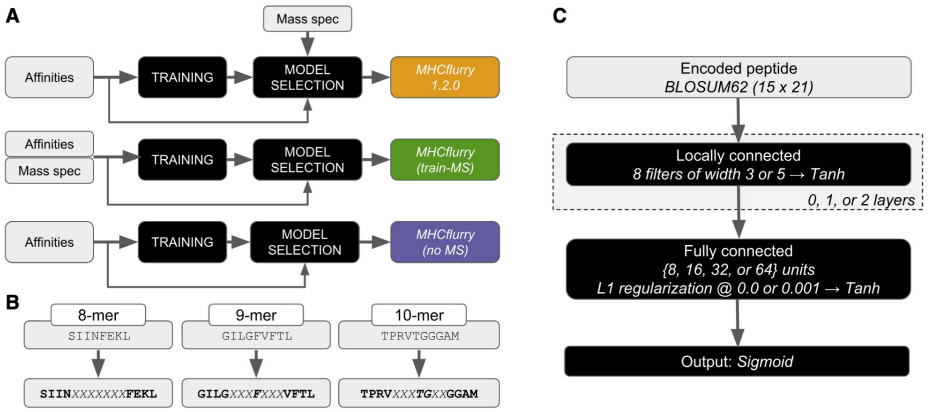
- **Representative algorithms: NetMHCpan, MHCflurry**
- **Key features to improve predictive power:**

  integrated training with both BA and EL data

  multi-allelic data deconvolution by simultaneous align/clustering or pseudolabeling (GibbsCluster, NNAlign_MA)



Jurtz..Nielsen (2017) J Immunol



O'Donnell..Hammerbacher (2018) Cell Systems

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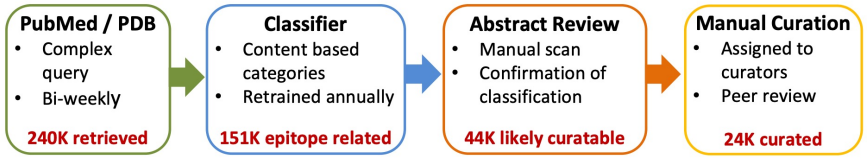
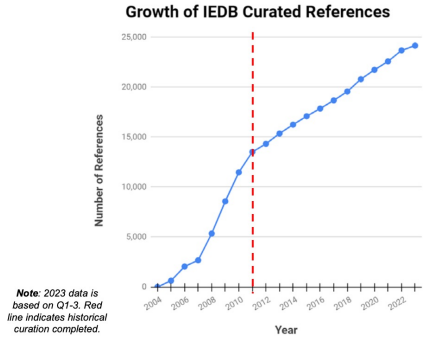
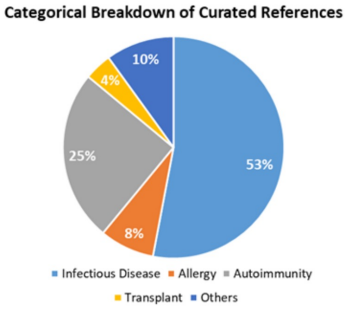
Important databases and computational resources

IEDB

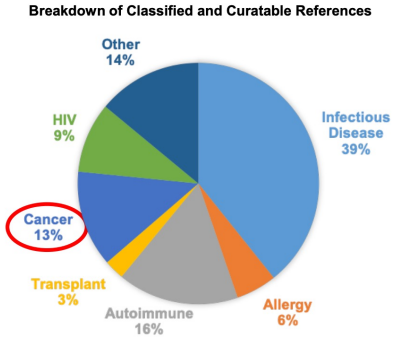


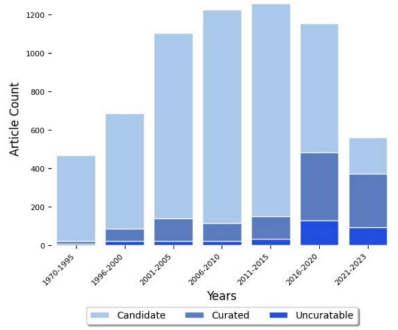




CEDAR

Cancer Curated Category	% Complete	No. of Papers
Prostate Cancer	99%	235
Neoepitope category	96%	450
Published papers in 2023	85%	57
Published papers in 2022	97%	110
Published papers in 2021	97%	83
Published papers in 2020	95%	109
Published papers in 2019	83%	92





[IEDB workshop 2023](), classical tools (e.g. NetMHC suite) and new ones [https://nextgen-tools.iedb.org/]()

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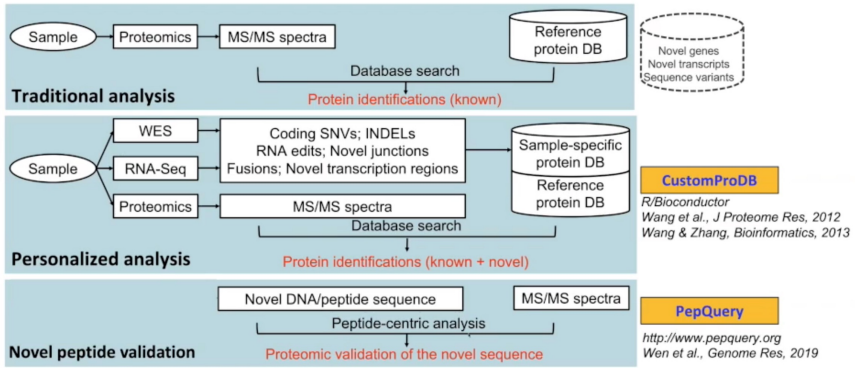
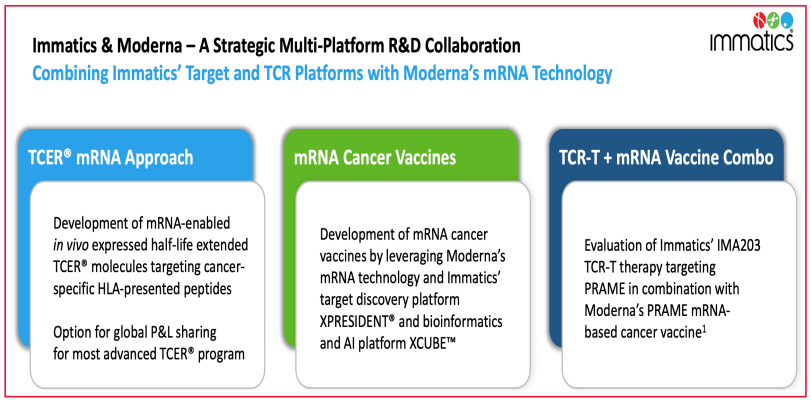
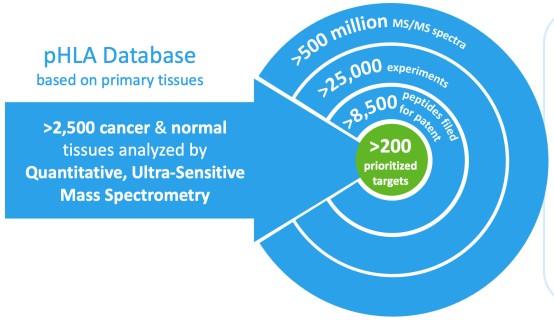
Immunopeptidomics plays a critical role in neoantigen therapies





- **A fantastic webinar on immunopeptidomics is covered [in this series by Dr. Bing Zhang in 2021.]**



[Immatics Corporate Update Nov 2023]

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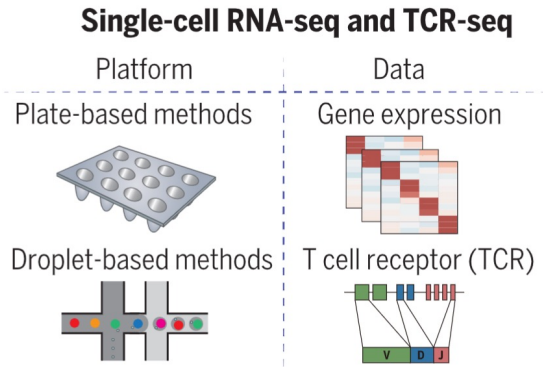
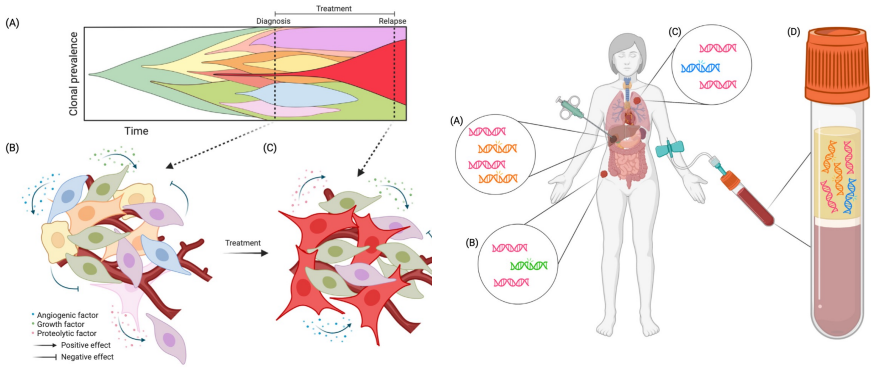
Genomic technology advances accelerate target selection and vaccine development

- **Single-cell RNA-seq and TCR-seq in combination enables the rapid and precise identification of neoantigen-specific TCRs from peripheral blood and tumor infiltrating T cells.**
- **Ultra-deep genomic profiling from liquid biopsy or multiple tissue biopsies may overcome intra/inter-tumoral heterogeneity and help identify better neoantigen targets.**
- **Digital pathology serves as orthogonal metric to validate tumor cell content and characterize TME**



Zheng..Zhang (2021) Science



Goyette.. Polyak (2021) Science

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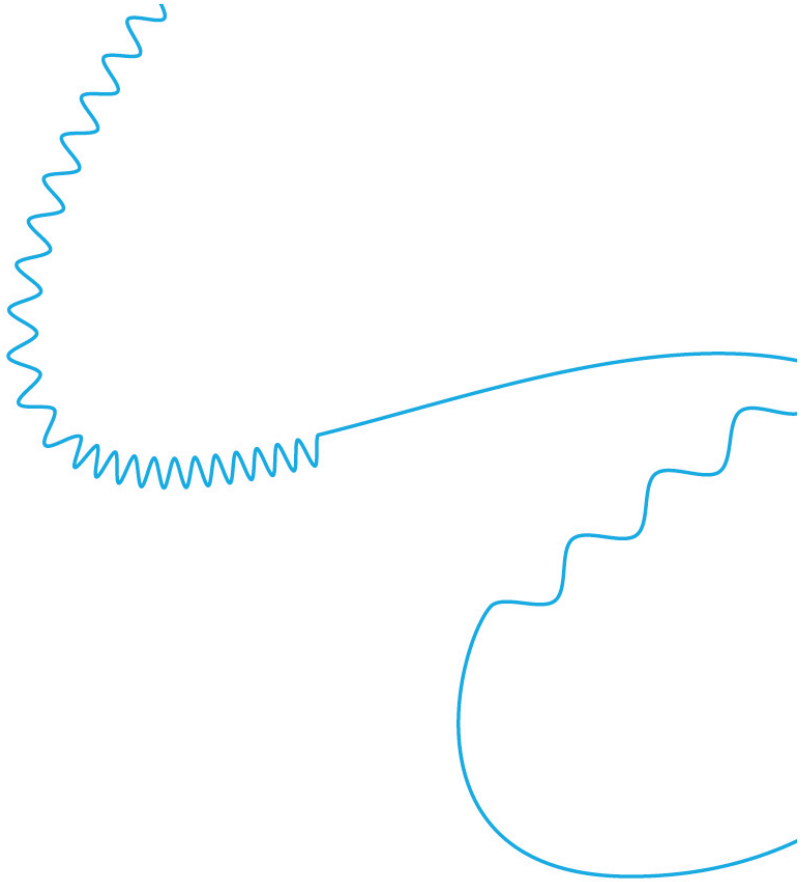
Thank you



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