Cancer Vaccine: Identifying Druggable Targets
SITC-NCI Computational Immunology Webinar

Wei Zheng, Dec. 2023
I 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)
Why are we excited about cancer vaccine
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

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

Abbreviations: mRNA = messenger ribonucleic acid; ER = endoplasmic reticulum; TCR = T-cell receptor
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
Modernia’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.
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 \textit{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 mFOLSIRINOX treatment

![Graphs showing immune responses and T cell responses over time](image)
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
What are the different types of targets in cancer vaccines
Tumor specific antigens (TSA) vs. tumor associated antigens (TAA)

- **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)

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.
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
How do we select targets for cancer vaccines
Neoantigen identification computational workflow

**Step 1: Mutation Profiling**
- WGS and/or WES
- Alignment, variant calling and annotation pipeline
- Identification of somatic mutations and indels

**Step 2: Expression Profiling**
- RNA-seq
- Gene expression quantification: TPM, TMM, HTSeq counts
- Gene fusions
- Mutation-specific expression: gbasepileup

**Step 3: Proteasomal Processing**
- NetChop
- NetCTL

**Step 4: TAP-mediated Peptide Transport to ER**
- PREDTAP

**Step 5: MHC Binding Affinity Prediction and Presentation**
- NetMHC
- NetMHCPan
- NetMHCstab
- MHCflurry
- NetMHCII
- NetMHCIIpan
- DeepHLA
- MARIA
- ProPred
- NeonMHC2
- MULTIPRED2
- MHCPred

**Predicted Total Neoantigens**
- Filtered and accurate neoantigens

**Prioritized Neoantigens**
- Strong binding neoantigens ($IC_{50} < 50$ nM)
- Expressed neoantigens
- Neoantigens presented by product of HLA allele with no LOH
- Clonal neoantigens
- Inhibitory concentration ($IC_{50}$)
- Expressed neoantigen (mutation)
- Clonal neoantigens
- HLA allele with no LOH

_Addala .. Waddell (2023) Nat Rev Clin Onc_
**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**:
  1. integrated training with both BA and EL data
  2. multi-allelic data deconvolution by simultaneous align/clustering or pseudolabeling (GibbsCluster, NNAlign_MA)

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![Diagram of artificial neural network]


Important databases and computational resources

**IEDB**

- PubMed / PDB
  - Complex query
  - Bi-weekly
  - 240K retrieved

- Classifier
  - Content based categories
  - Retrained annually
  - 151K epitope related

- Abstract Review
  - Manual scan
  - Confirmation of classification
  - 44K likely curatable

- Manual Curation
  - Assigned to curators
  - Peer review
  - 24K curated

**CEDAR**

- Utilizing the IEDB curation process:
  - Published / PDB
  - Classifier
  - Manual curation
  - Published 2023: 85% 57
  - Published 2022: 97% 110
  - Published 2021: 97% 83
  - Published 2020: 95% 109
  - Published 2019: 83% 92

**Breakdown of Classified and Curatable References**

- Infectious Disease: 39%
- Allergy: 6%
- Autoimmune: 16%
- Transplant: 3%
- Other: 14%
- HIV: 9%
- Other: 13%

**Growth of IEDB Curated References**

- 0
- 5,000
- 10,000
- 15,000
- 20,000
- 25,000

- Year

**Categorical Breakdown of Curated References**

- Infectious Disease: 53%
- Allergy: 8%
- Autoimmunity: 10%
- Transplant: 25%
- Others: 2%

**IEDB workshop 2023**, classical tools (e.g. NetMHC suite) and new ones [https://nextgen-tools.iedb.org/](https://nextgen-tools.iedb.org/)
Immunepeptidomics plays a critical role in neoantigen therapies

- A fantastic webinar on immunepeptidomics is covered in this series by Dr. Bing Zhang in 2021.
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
Thank you