PARKER INSTITUTE
for CANCER IMMUNOTHERAPY

Neoantigen Selection and the TESLA Program

Fred Ramsdell

VP, Research

Our Model: Collaborate with the Best

Our Leadership

Institute Leaders

ANTONI RIBAS, MD, PhD
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JAMES ALLISON, PhD
MD Anderson Cancer Center

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President + CEO
Parker Institute for Cancer Immunotherapy

SEAN PARKER
Founder + Chairman
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Stanford Medicine

LEWIS LANIER, PhD
UCSF

LAURIE GLIMCHER, MD
Dana-Farber Cancer Institute

Scientific Steering Committee

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NYU

STEPHEN SHERWIN, MD
UCSF

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LARRY TURKA, MD
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NEA

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Broad Institute

Programmatic Collaborators

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Mount Sinai

PHIL GREENBERG, MD
Fred Hutch

ROBERT SCHREIBER, PhD
Washington University

STEPHEN FORMAN, MD
City of Hope

Our Research Teams

Best-in-Class T-cells

Opportunity:
To accelerate and broaden the use and utility of adoptive T-cell therapy.

Charge:
Uncover new pathways and factors to improve T-cell activity and, using state-of-the-art technologies, create a new generation of more effective therapies.

Checkpoint Blockade

Opportunity:
To understand why some patients do not respond to therapy and develop new combination treatments to overcome drug resistance.

Charge:
Discover new pathways and treatments to improve survival rates and broaden treatment to more cancers.

Tumor Antigen Discovery

Opportunity:
To identify new tumor markers to improve effectiveness and broaden use of novel therapeutic targets and vaccines to more cancers.

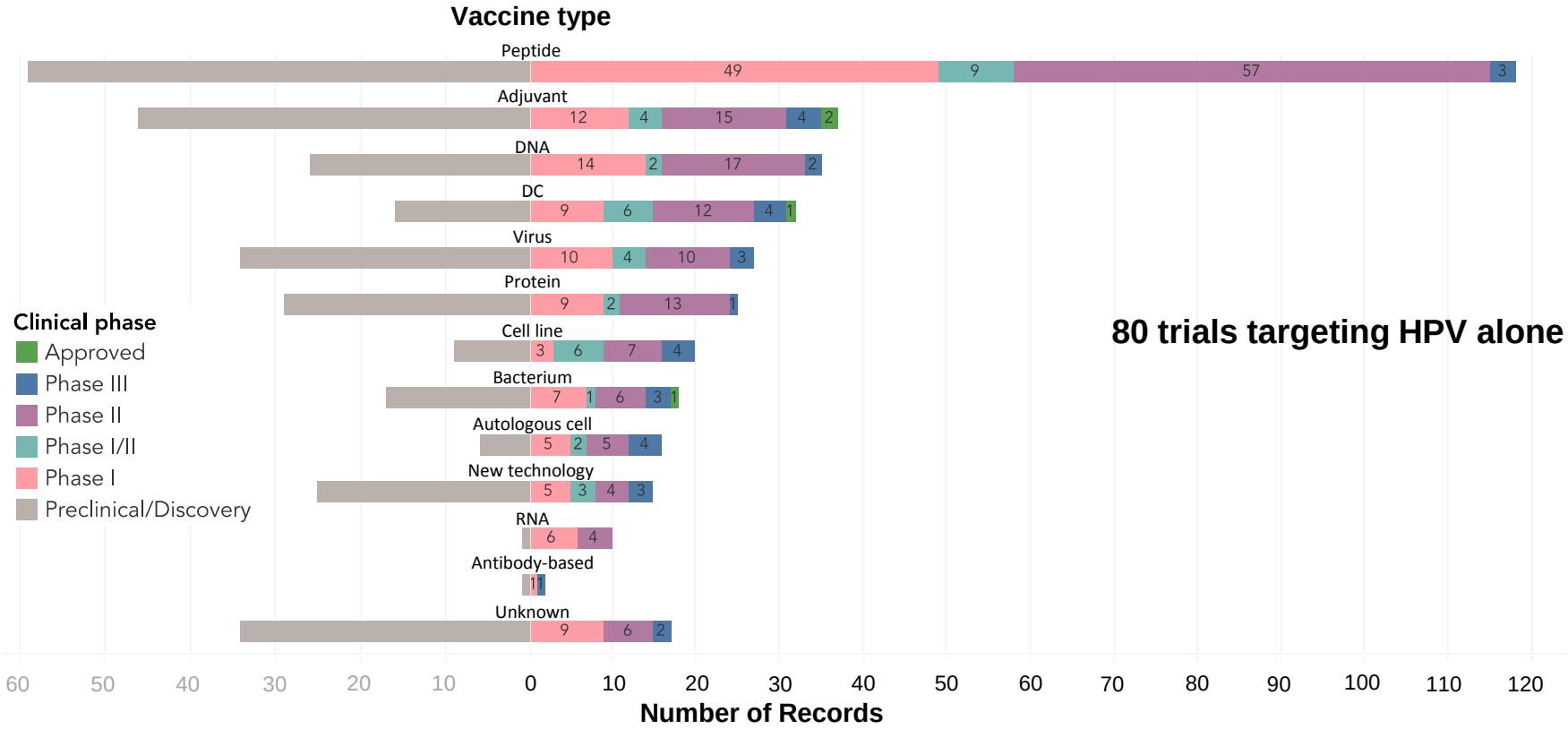
Charge:
Use DNA sequencing, proteomics and computational biology to develop targeted vaccines and other therapies.

Tumor Microenvironment

Opportunity:
To characterize the solid tumor microenvironment as an ecological entity, including the interactions that affect the immune response and tumor growth.

Charge:
Develop approaches to overcome local immune suppression and resistance.

675 ACTIVE CANCER VACCINES AND 372 IN CLINICAL DEVELOPMENT



CANCER VACCINES/ADJUVANTS FAILED AT PHASE III

Failed P3 trials

Vaccine name	Vaccine type	Target	Condition	NCT Number	Last Verified
PROSTVAC + GM-CSF	Viral vaccine	PSA	Prostate cancer	NCT01322490	Aug-17
BVNSCLC-001	Protein vaccine	EGF	NSCLC	NCT01444118	Jul-15
Imprime PGG + cetuximab	Adjuvant	CD11b; CD32	Colorectal cancer	NCT01309126	Jul-17
Tecemotide + low-dose cyclophosphamide	Peptide vaccine	MUC1	NSCLC	NCT01015443	Sep-16
Tecemotide + low-dose cyclophosphamide	Peptide vaccine	MUC1	Breast cancer	NCT00925548	Jul-14
BCG	Bacterium vaccine	N/A	Bladder cancer	NCT00974818	Oct-15
BVNSCLC-001 + low-dose cyclophosphamide	Protein vaccine	EGF	NSCLC	NCT00516685	Sep-11
Abagovomab	Antibody vaccine	MUC16	Ovarian cancer	NCT00418574	Nov-11
BCG + gefitinib	Bacterium vaccine	N/A	Bladder cancer	NCT00352079	Dec-12
GVAX	Cell line vaccine	TAA	Prostate cancer	NCT00133224	Sep-08
HSPPC-96	Autologous protein vaccine	HSP90	Kidney cancer	NCT00126178	Sep-12
GVAX	Cell line vaccine	TAA	Prostate cancer	NCT00089856	Nov-08
MyVax	Protein vaccine	N/A	Non-Hodgkin's lymphoma	NCT00089115	Feb-06
Melanoma peptide vaccine	Peptide vaccine	MAGE; NY-ESO-1	Ocular melanoma	NCT00036816	Sep-12
MyVax	Protein vaccine	N/A	Diffuse large B-cell lymphoma	NCT00324831	Mar-07

Mutational burden in different tumor types

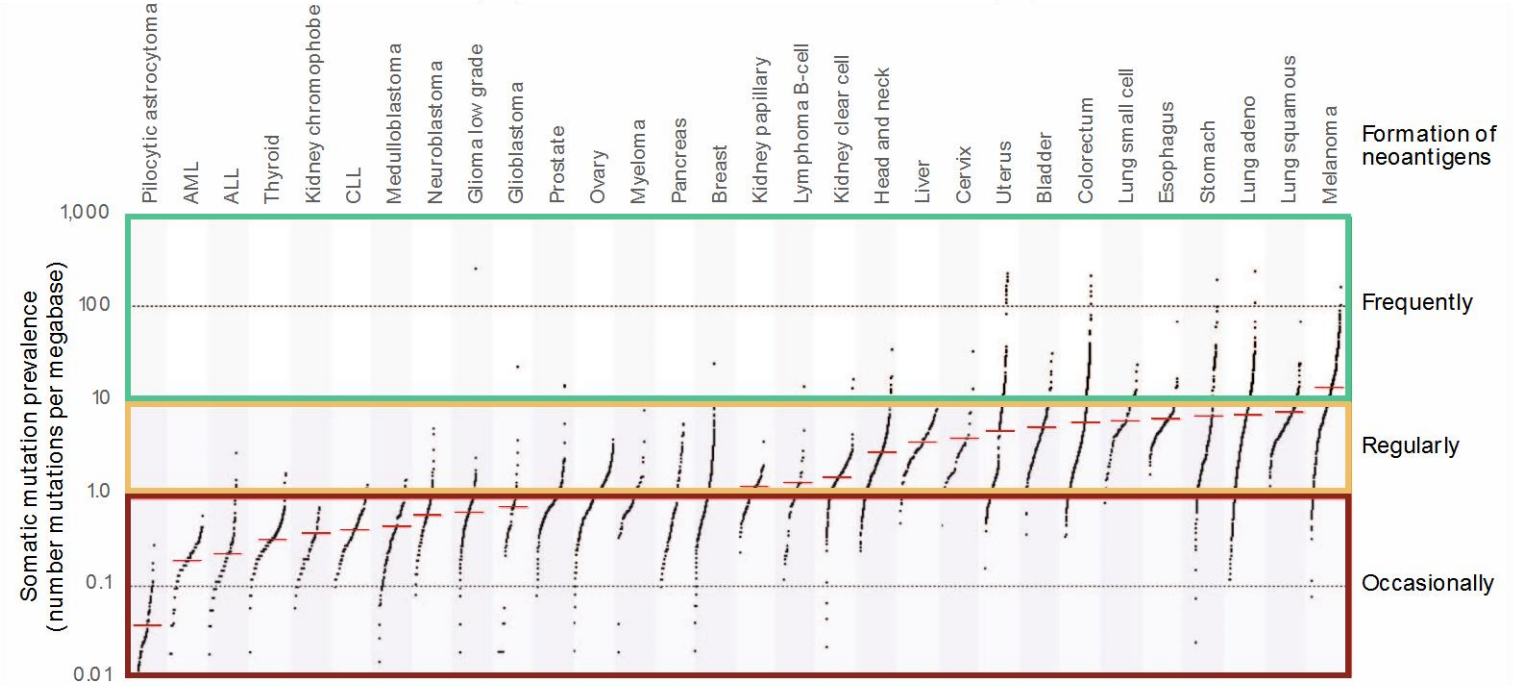
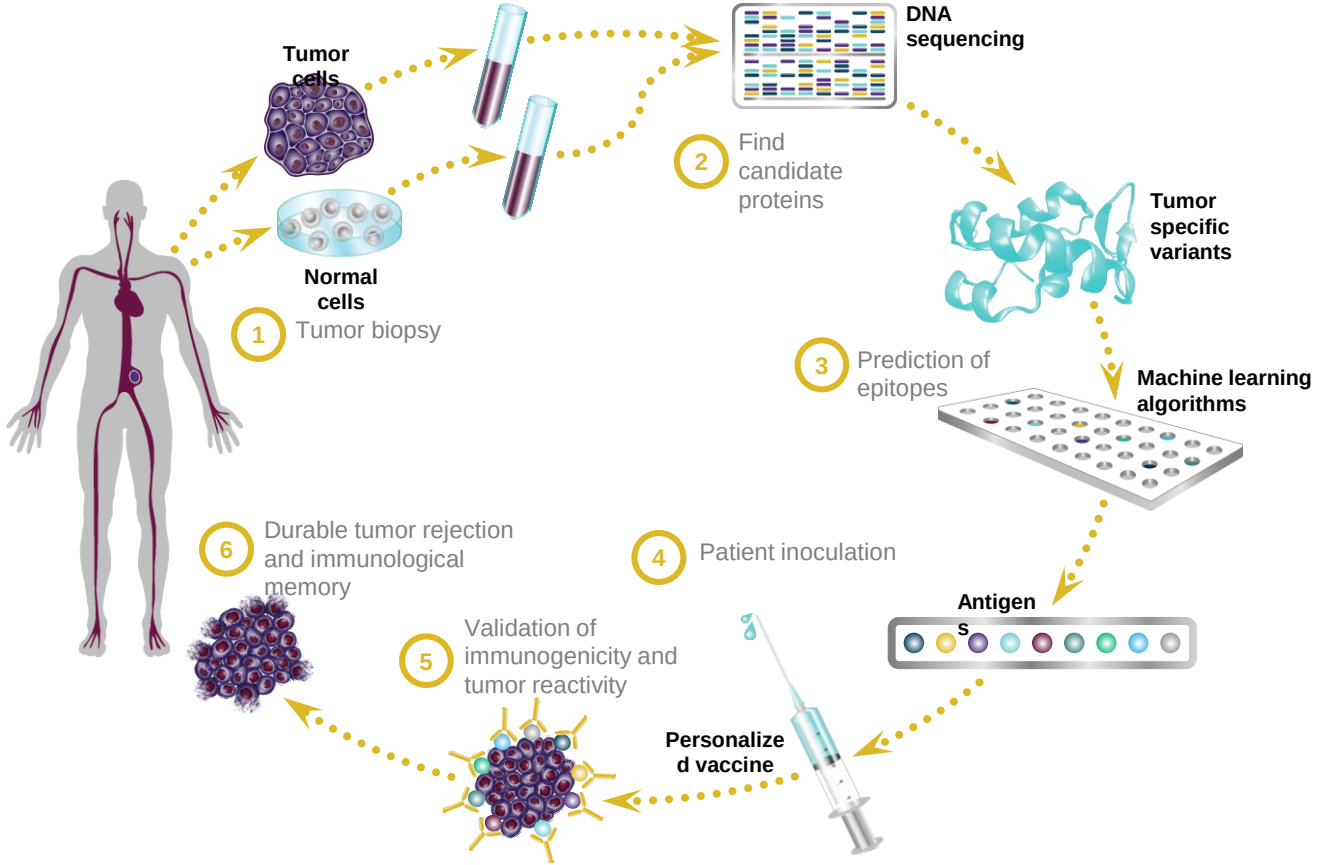


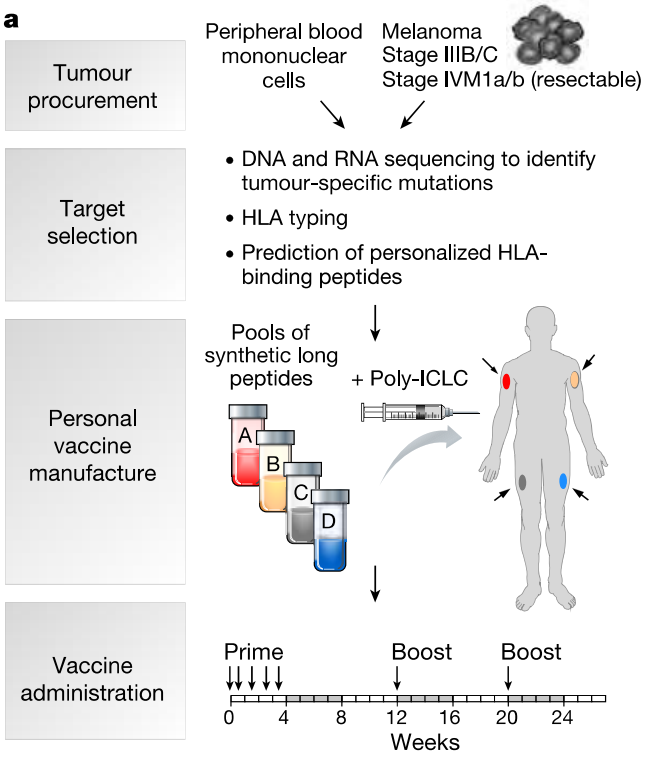
Fig. 2. Estimate of the neoantigen repertoire in human cancer. Data depict the number of somatic mutations in individual tumors. Categories on the right indicate current estimates of the likelihood of neoantigen formation in different tumor types. Adapted from (50). It is possible that the immune system in melanoma patients picks up on only a fraction of the available neoantigen repertoire, in which case the current analysis will be an underestimate. A value of 10 somatic mutations per Mb of coding DNA corresponds to ~150 nonsynonymous mutations within expressed genes.

Schumacher and Schreiber, Science 2015

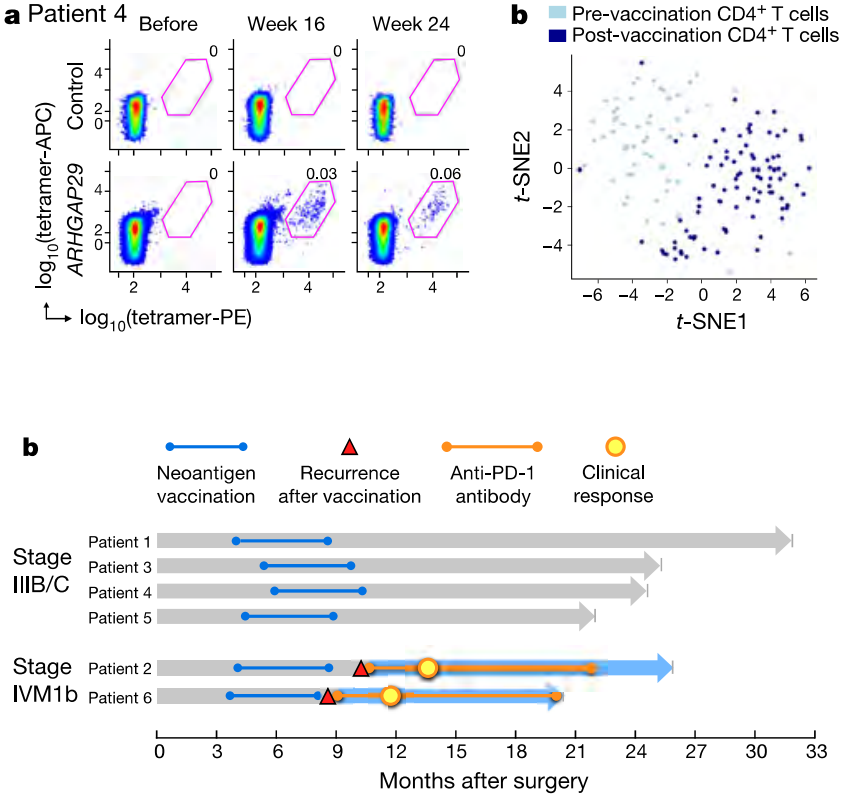
Tumor Antigen Discovery



Pipeline for neoepitope (personalized) vaccines



Ott, et.al., Nature 2017



3 REPRESENTATIVE TRIALS WITH NEO-ANTIGEN VACCINES

2 out 3 vaccines are peptide-based

Table 1. Summary of Neoantigen Vaccines

	Carreno et al. [5]	Ott et al. [4]	Sahin et al. [3]
No. of patients	3	6	13
Vaccine	Mature dendritic cells[a]	Synthetic peptide+ poly IC:LC	RNA
Administration route	Intravenous	Subcutaneous	Intranodal
Epitope length	9 aa	15–30 aa	27 aa
No. of epitopes/patient	7	13–20	10
No. of doses	3	7	8–20
Immunogenicity (total no. peptides tested)	21 peptides	91 peptides	125 epitopes
$CD8^+$ T cell response rate[b]	43%	16%	25%
$CD4^+$ T cell response rate[b]	NT	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 et al, 2017, Trends Mo Med

Why TESLA?

EDITORIAL

nature biotechnology

The problem with neoantigen prediction

Personalized immunotherapy is all the rage, but neoantigen discovery and validation remains a daunting problem.

Today, a raft of software tools for predicting MHC binders are now available (http://cancerimmunity.org/resources/webtools/). But each of these packages has its own idiosyncrasies, strengths and weaknesses. What's more, it has proven difficult to benchmark which tools and combinations of tools work best for particular contexts.

TESLA program goals

The consortium aims to support the field's efforts to develop safe and efficacious neo-antigen vaccines for cancer, by:

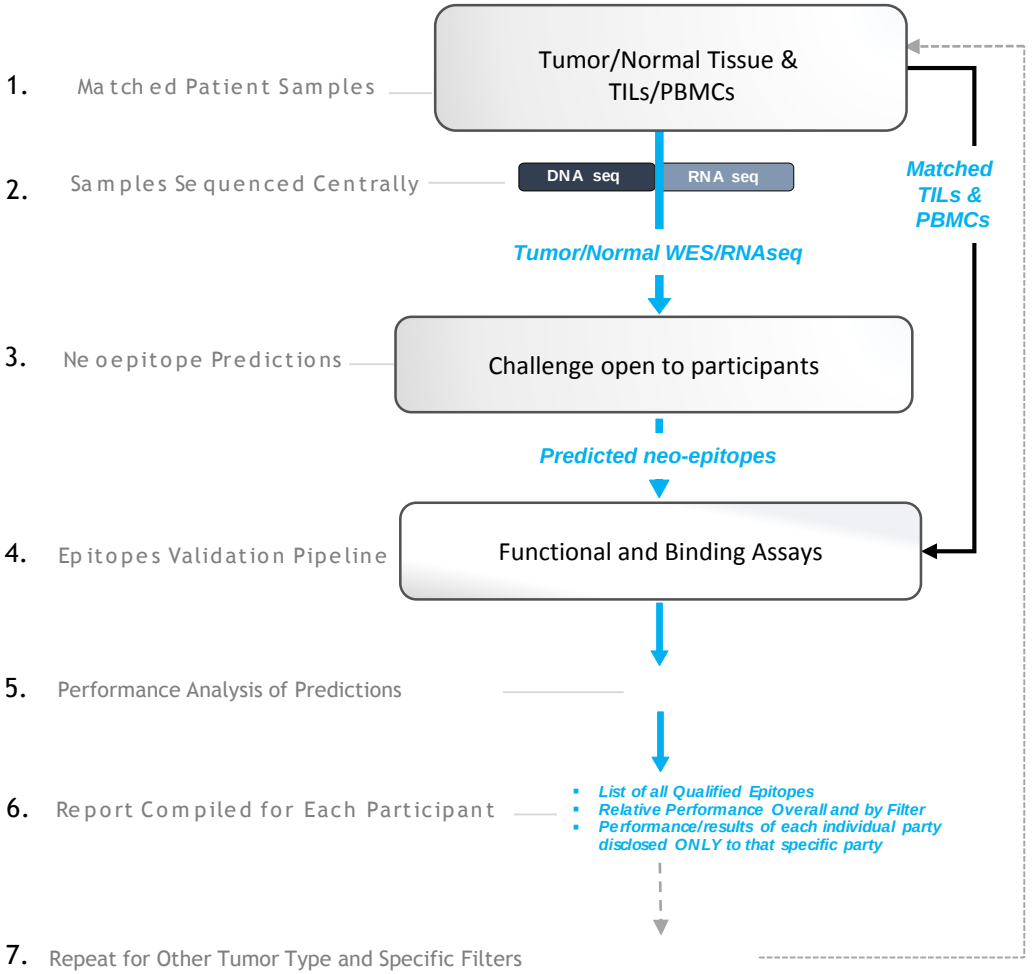
- Delineating the variation of neoepitope predictions in existing computational pipelines
- Generating high quality epitope validation sets that provide a basis to assess and improve prediction pipelines
- **Elucidate the key factors for accurate neo-epitope prediction**

Project workflow

PARKER INSTITUTE for CANCER IMMUNOTHERAPY

CANCER RESEARCH INSTITUTE

Sage BIONETWORKS



TESLA Participating Groups and Contributors

- 24 Academia/Non-Profits
- 18 Pharma/Biotech

Operational Mechanics of the TESLA program

- For each sample, participants download:
  - FASTQ files of tumor whole-exome sequence
  - FASTQ files for germline whole-exome sequence
  - FASTQ files for RNA-seq on tumor sample
  - Pre-called variants identified by Washington University
  - Data is downloaded from Synapse – the data hosting/sharing platform hosted by Sage Bionetworks.

- Participants run their neoantigen algorithm on that data in two ways:
  - Participants identify their own somatic variants and in turn generate a ranked list of possible neoantigens
  - Participants generate a ranked list of neoantigens from the pre-called variants.
  - In each case, what we require for submission is a ranked list of neoantigen + HLA allele pairs

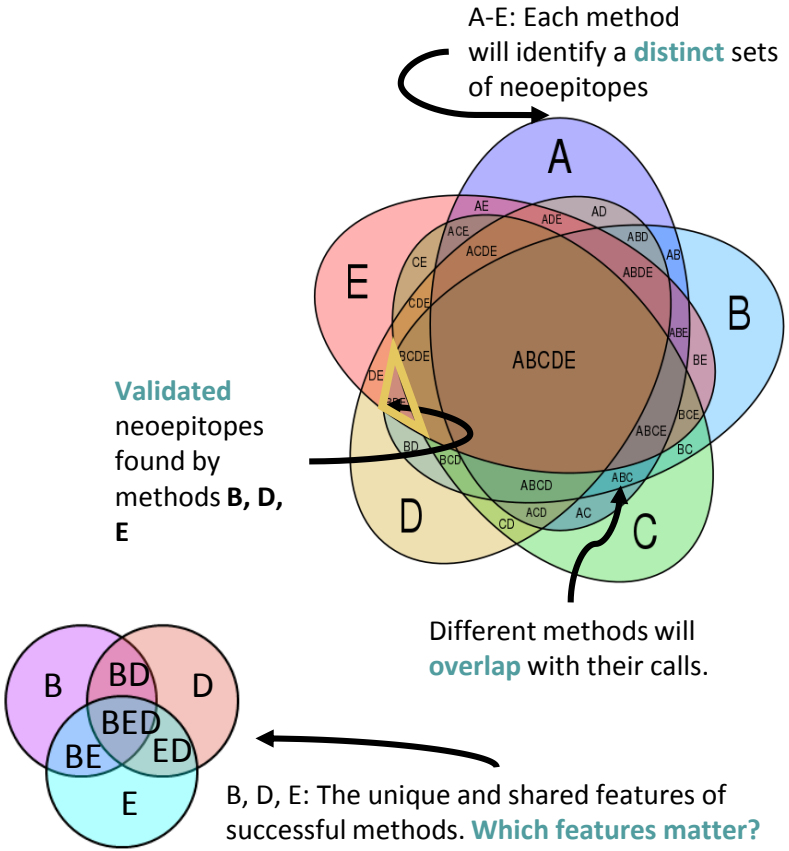
- From these submitted lists, we generate a list of peptides that we will validate with at least 2 of the four methods we are using.
  - Every participant will get their top 4 or 5 peptides validated with two methods
  - With remaining validation capacity, we select peptides that are recurrently identified in the top 50 peptides by a large number of groups, or peptides that are unique in other ways.
  - Goal: validate 100 peptides/sample with at least 2 independent methods.

(Anticipated) Learnings

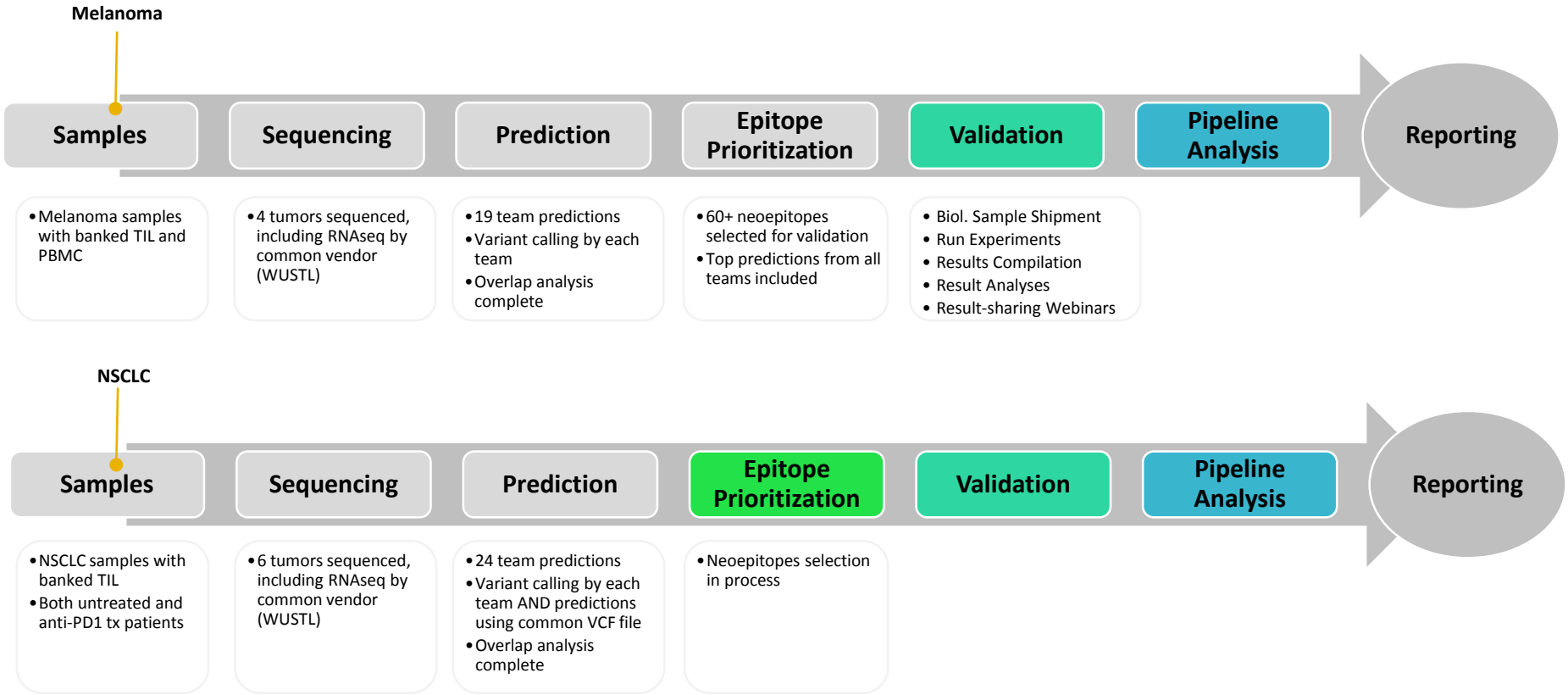
1. How similar/distinct are different methods and sets of neoepitopes?

2. Which methods generate the most validated neoepitopes?

3. What features of the validated epitopes, and their identifying algorithms, can be used to make new, better methods?

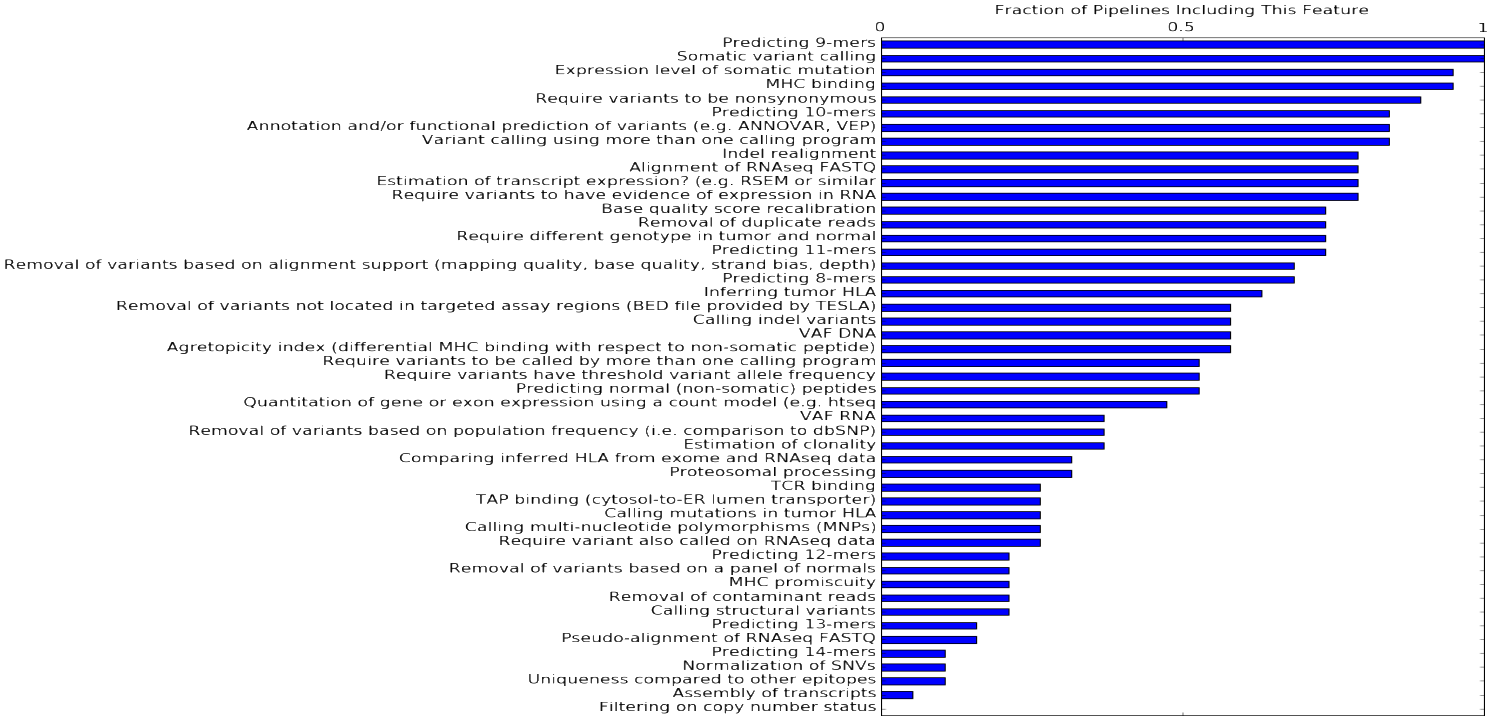


TESLA: Initial tumor analyses



TESLA: Initial tumor analyses
Most teams use 20-25 features for predictions

Samples | Sequencing | Prediction | Epitope Prioritization | Validation | Pipeline Analysis | Reporting

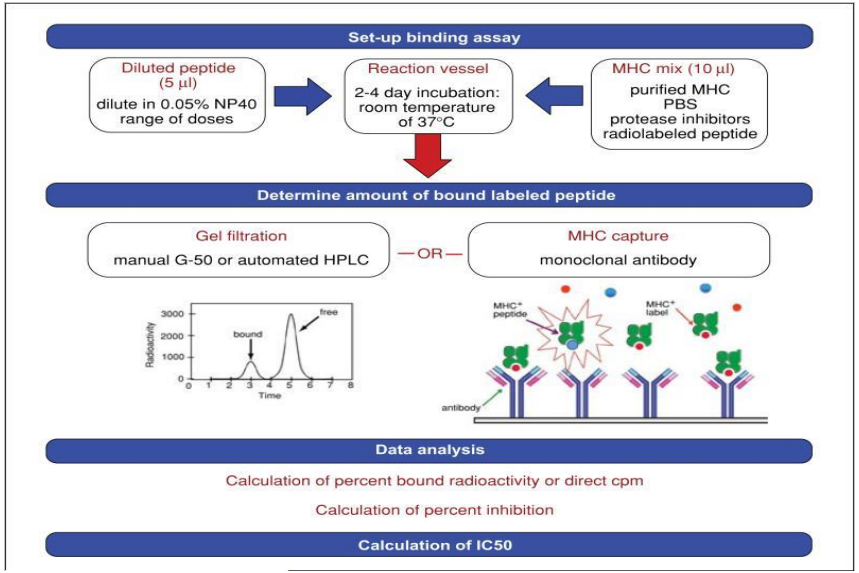


TESLA: Initial tumor analyses
Little correlation/clustering between features

Samples | Sequencing | Prediction | Epitope Prioritization | Validation | Pipeline Analysis | Reporting

TESLA functional validation methods

1. Peptide:MHC Binding

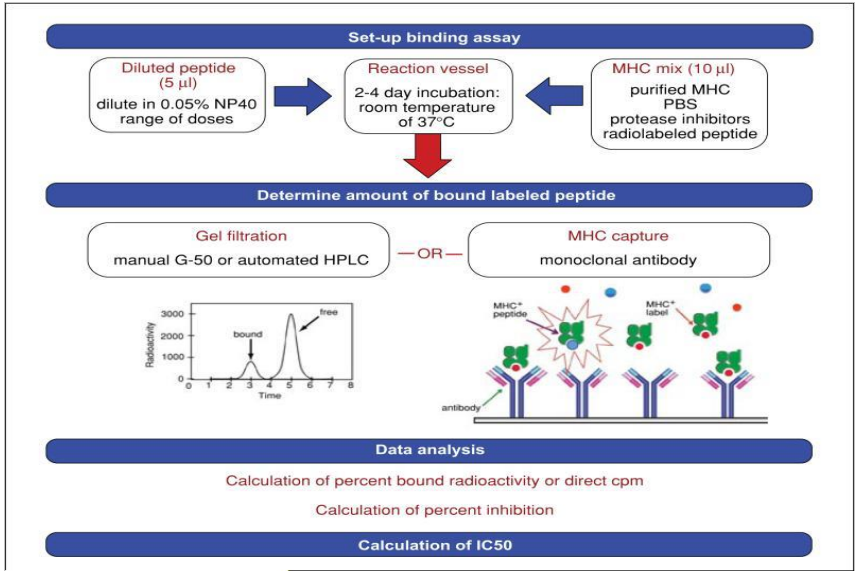


A schematic overview of the steps involved in performing an MHC-peptide binding assay.

A. Sette, LIAI

TESLA functional validation methods

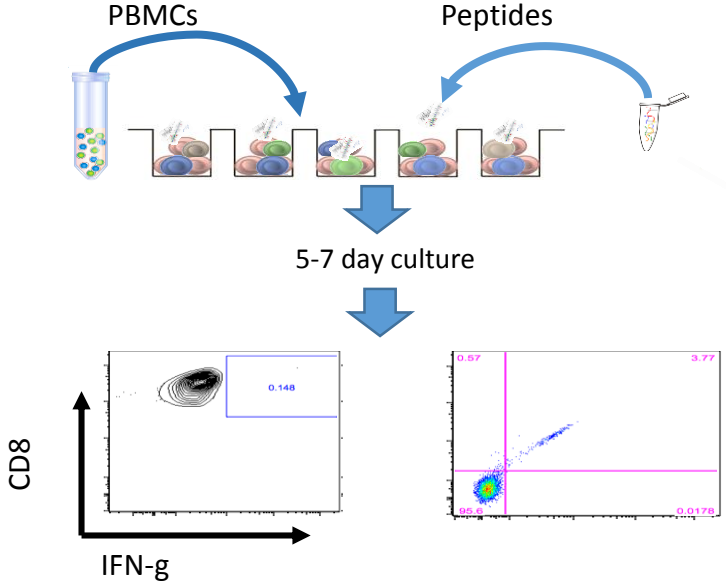
1. Peptide:MHC Binding



A schematic overview of the steps involved in performing an MHC-peptide binding assay.

A. Sette, LIAI

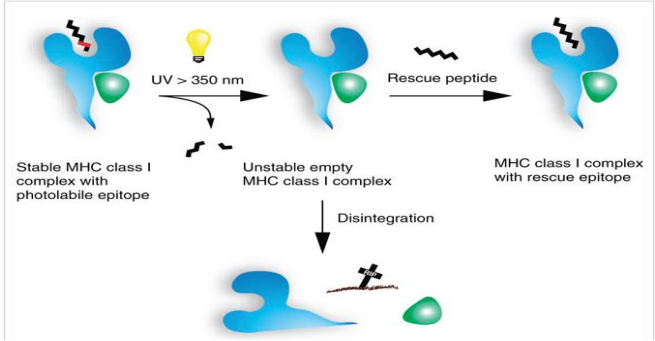
2. *ex vivo* stimulation



N. Bhardwaj, Mt Sinai

TESLA functional validation methods

3. Tetramer detection (FACS)



R. Schreiber, WUSTL
P. Kvistborg, NKI

TESLA functional validation methods

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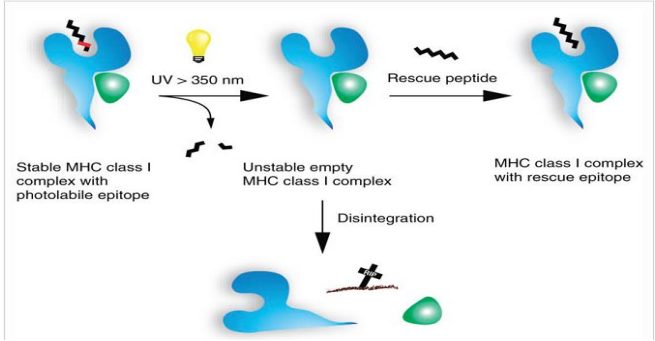

R. Schreiber, WUSTL
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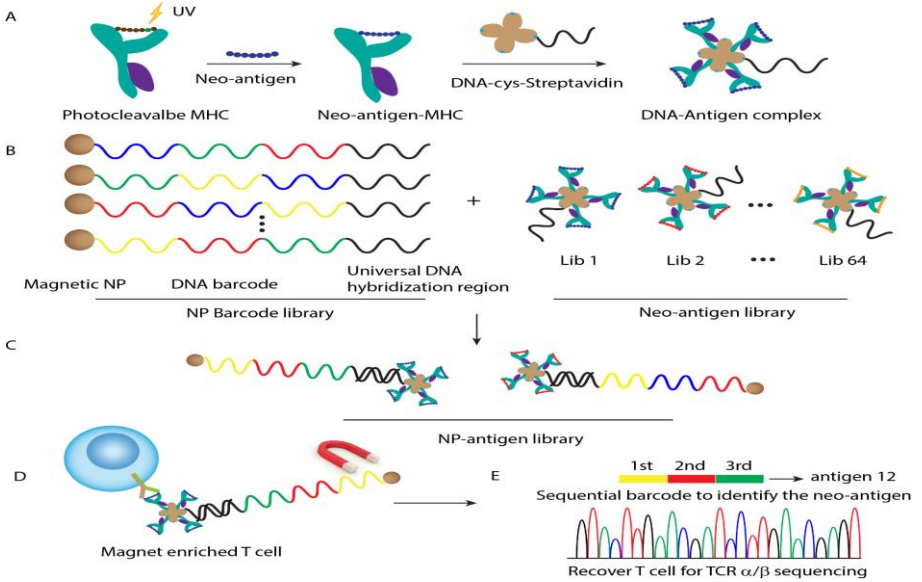
4. NP-tetramer isolation



J. Heath, Caltech/ISB

Thank you!

Nadine Defranoux (PICI)

Danny Wells (PICI)

Kristen Dang (SAGE)

SAGE Bionetworks
Justin Guinney
Michael Mason

Cancer Research Institute
Vanessa Lucey


“WHAT IF TOP RESEARCHERS
WORKED TOGETHER AND
HAD EVERY RESOURCE THEY
NEED TO PURSUE THEIR
BOLDEST RESEARCH?”