

# **AI-based identification of Tumor Neoantigens from NGS data**

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**Korea-Japan-China Bioinformatics Symposium 2018**

# ***BM*<sup>2</sup>: Biological and Medical Big data Mining group**



## **AI & Machine Learning Methodology and Platform**

**Drug informatics**

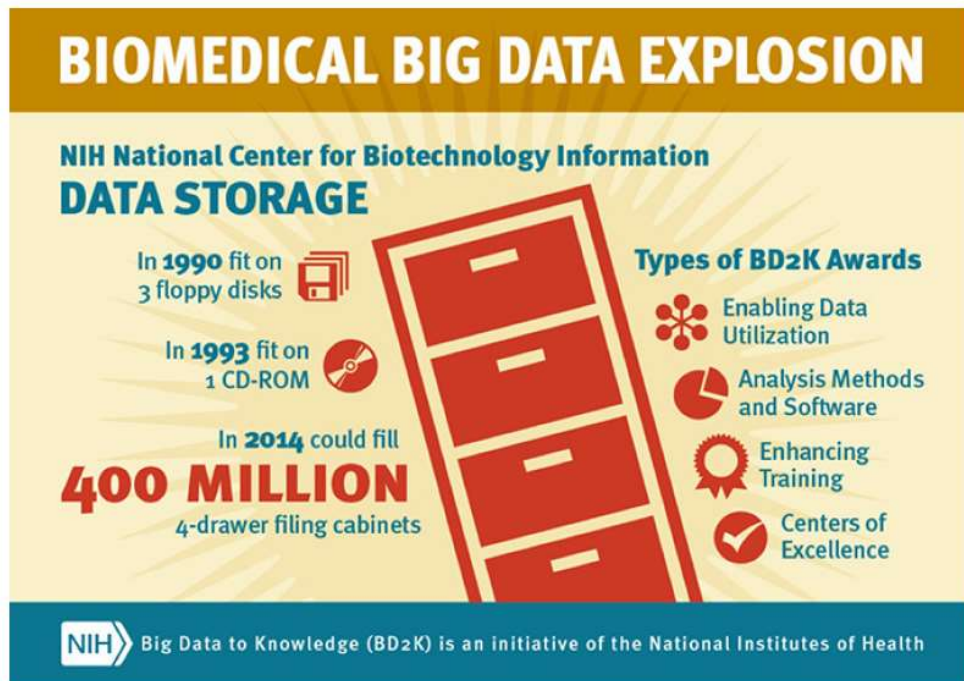
**Genome editing analysis**

**Tumor immuno-therapy data analysis**



★ biomedical big data explosion

- ▶ “..exceeds researchers’ ability to capitalize..” (NIH)



source: National Institutes of Health (NIH), IBM

★ needs for precise analysis

- ▶ BD2K initiative (\$656 mil)
- ▶ PM initiative (\$215 mil)





# AI/machine learning boom in biomedicine



The average person is likely to generate more than one million gigabytes of health-related data in their lifetime. Equivalent to 300 million books.























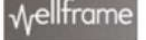






















IBM Watson Health



Google DeepMind



## DeepMind Health

<b>Medical Imaging &amp; Diagnostics</b>                	<b>Wearables</b>         	<b>Health &amp; Lifestyle Management</b>           <b>AI In Healthcare: Machine Learning and Deep Learning Startups To Watch</b> <p>Created By</p> 	<b>Emergency Room &amp; Hospital Monitoring</b>      <b>Healthcare Biotech</b>  	<b>Mental Health</b>      <b>Virtual Assistants</b>    	
<b>Insights &amp; Risk Management</b>             					
<b>Drug Discovery</b>     					<b>Nutrition</b> 

source: IBM, Google DeepMind, CBinsights



living  
cells



biologists



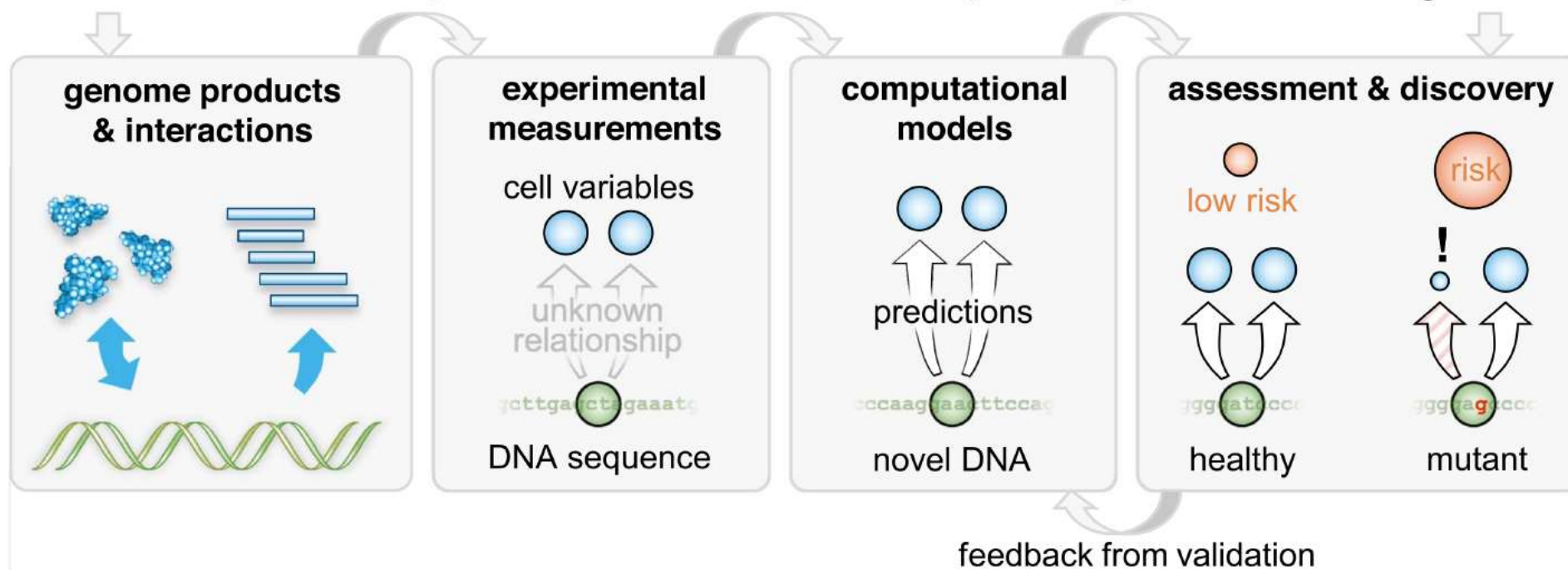
data scientists



diagnosticians,  
pharmacogeneticists

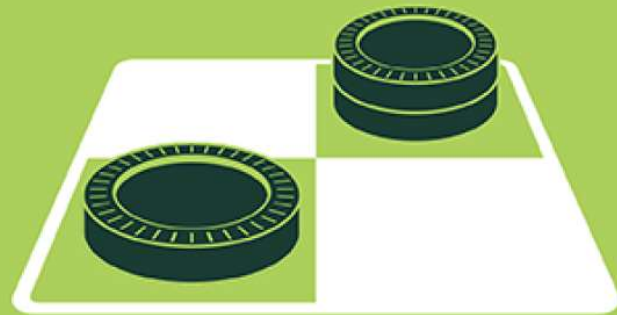


patient  
genomes



# ARTIFICIAL INTELLIGENCE

Early artificial intelligence stirs excitement.



# MACHINE LEARNING

Machine learning begins to flourish.



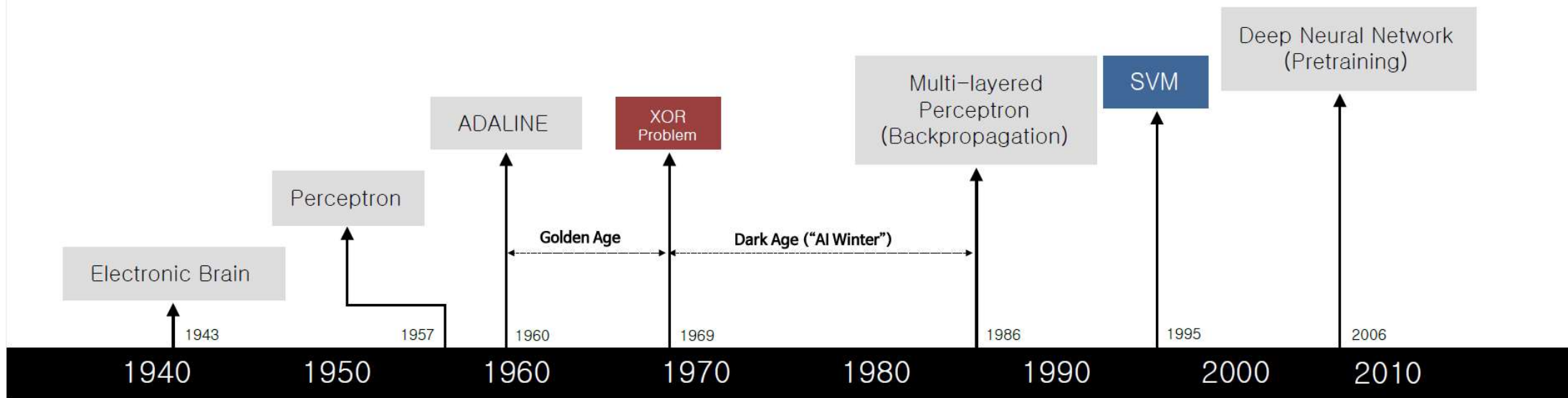
# DEEP LEARNING

Deep learning breakthroughs drive AI boom.

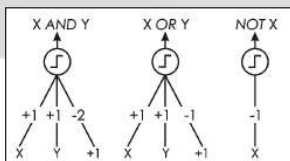


Since an early flush of optimism in the 1950s, smaller subsets of artificial intelligence – first machine learning, then deep learning, a subset of machine learning – have created ever larger disruptions.





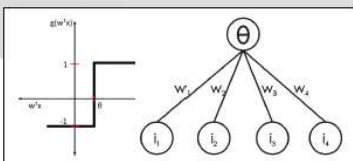
S. McCulloch – W. Pitts



- Adjustable Weights
- Weights are not Learned



F. Rosenblatt



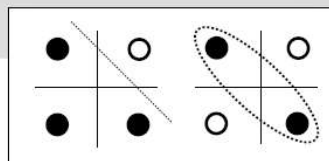
- Learnable Weights and Threshold



B. Widrow – M. Hoff



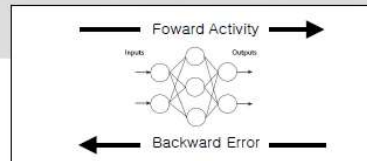
M. Minsky – S. Papert



- XOR Problem



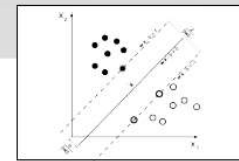
D. Rumelhart – G. Hinton – R. Williams



- Solution to nonlinearly separable problems
- Big computation, local optima and overfitting



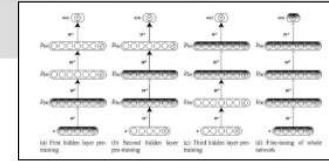
V. Vapnik – C. Cortes



- Limitations of learning prior knowledge
- Kernel function: Human Intervention



G. Hinton – S. Ruslan

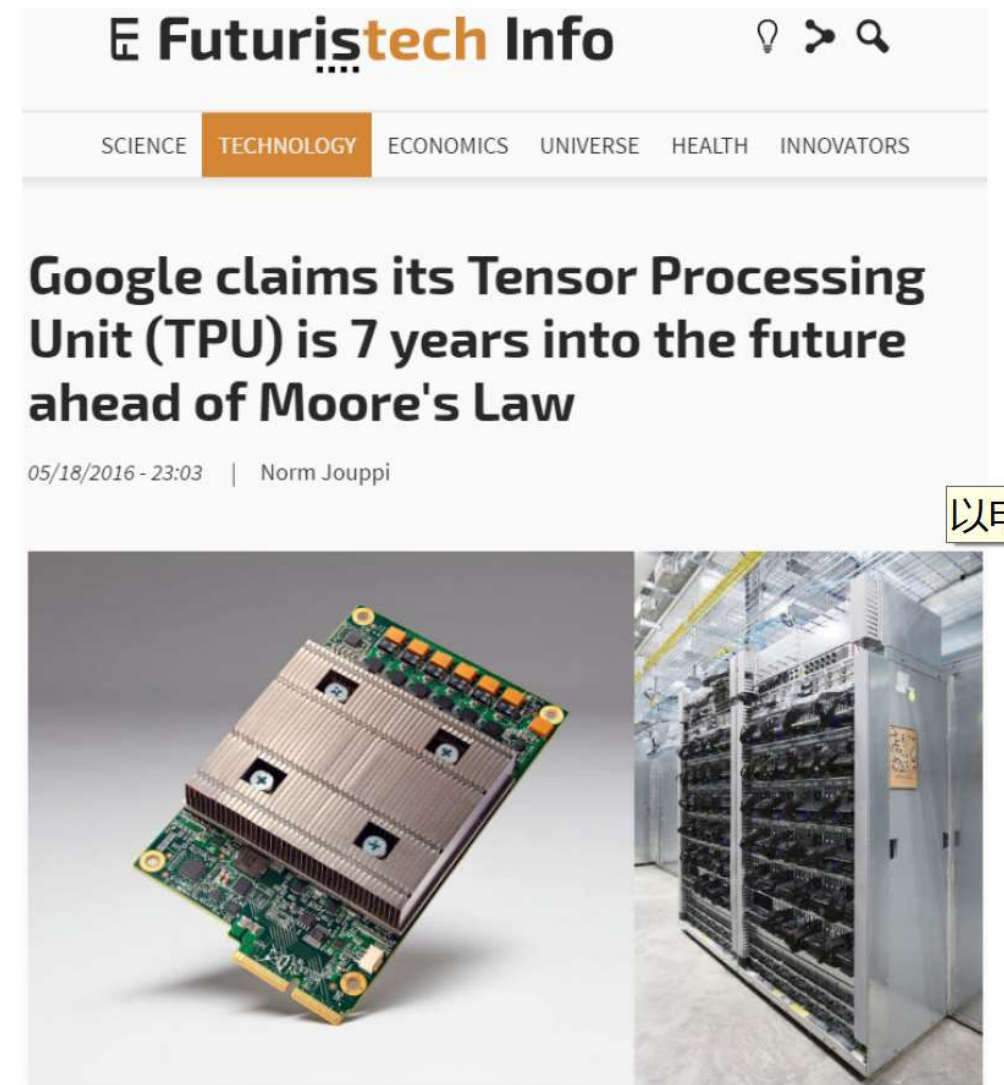


- Hierarchical feature Learning

## ★ AlphaGo (DeepMind)

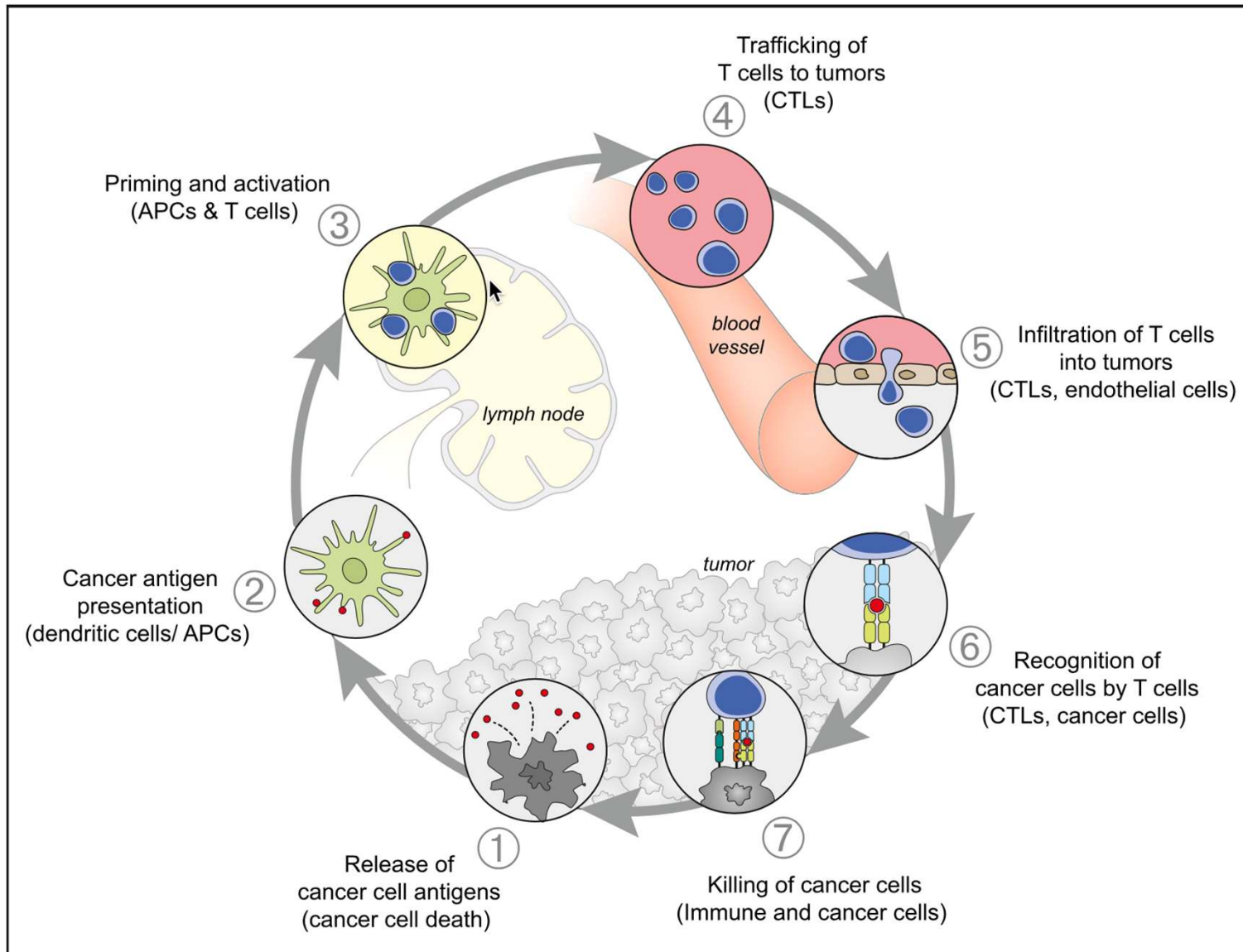


## ★ TPU (Google)



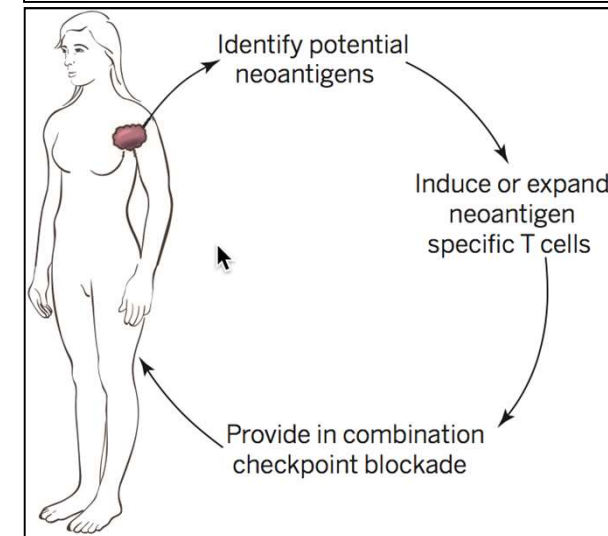
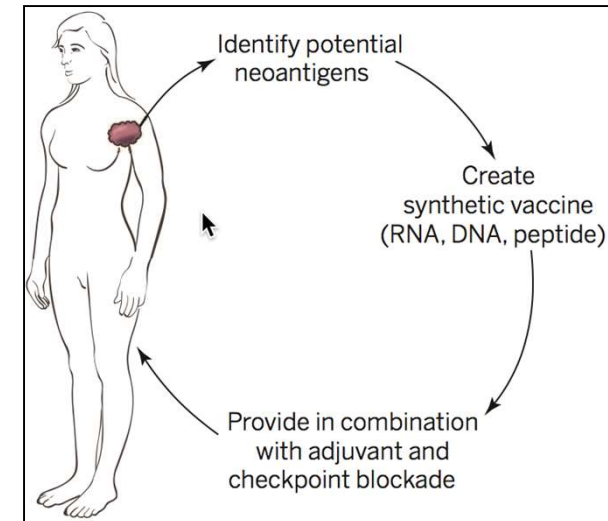
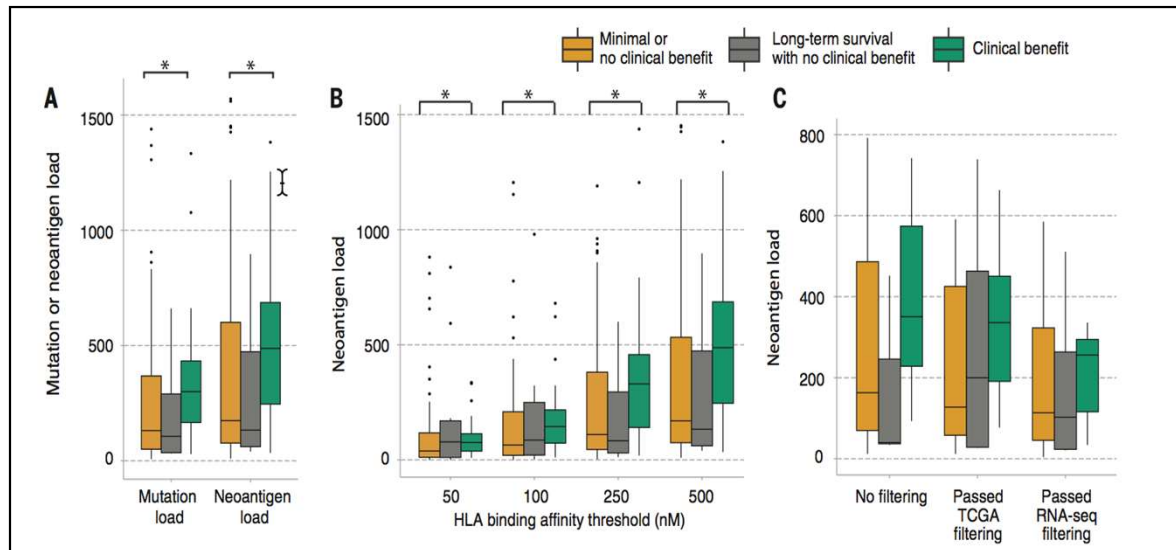


**iTunes: identification of Tumor neoantigens  
from NGS data**



# 1

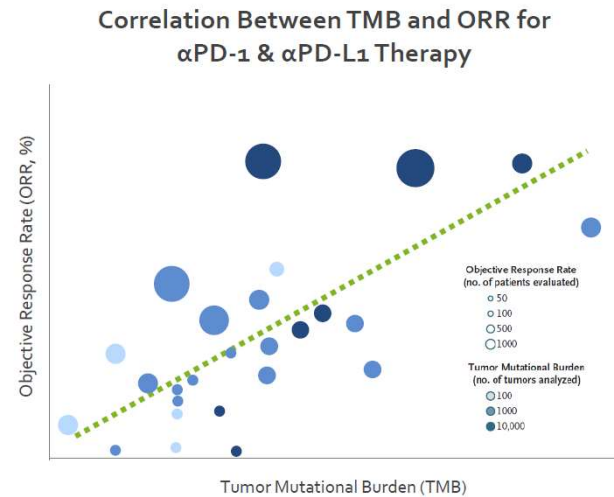
## Background and Significant







## Neoantigens Represent Ideal Tumor Targets



Adapted from Yarchoan 2017

✓ **INTIMATELY  
TUMOR-SPECIFIC**

➔ Not found on  
normal tissue

✓ **CAN BE HIGHLY  
IMMUNOGENIC**

➔ Recognized as  
non-self

✓ **BROAD APPLICABILITY  
ACROSS CANCERS**

➔ High and low  
TMB



# Cancer vaccine development

Cancer vaccine	Company	Targeted antigen & adjuvants	Disease	n	Status	Outcome
Sipuleucel-T (Provenge) Autologous cell vaccine	Dendreon Corporation, Seattle, USA	PAP GM-CSF	Metastatic, castration-resistant prostate cancer	512	Completed (2003-2009) NCT00065442 IMPACT	April 10, 2010 FDA approved
PROSTVAC-VF Viral vector vaccine	Bavarian Nordic, Kvistgaard, Denmark	PSA GM-CSF	Metastatic, castration-resistant prostate cancer	1298	2011-2018 NCT01322490 PROSPECT	Futile, based on IDMC's interim analysis
GVAX Allogeneic tumour cell vaccine	Cell Genesys, CA, USA	Tumor cell GM-CSF	Castration-resistant prostate cancer	626	Completed (2004-2008) NCT00089856 VITAL-1	Futile, <30% chance of meeting primary endpoint
GVAX Allogeneic tumour cell vaccine	Cell Genesys, CA, USA	Tumor cell GM-CSF	Castration-resistant prostate cancer	408	Completed (2005-2009) NCT00133224 VITAL-2	Terminated, increased mortality
Neuvax Peptide vaccine	Galena Biopharma, CA, USA	HER2 GM-CSF	Breast cancer, low to intermediate HER2 Expression	758	Completed (2011-2016) NCT01479244 PRESENT	Futile, based on IDMC's interim analysis
Theratope Peptide vaccine	Biomira, Inc, Edmonton, Canada	Sialyl-Tn KLH	Metastatic breast cancer, in remission after first-line chemotherapy	1028	Completed (1999-2008) NCT00003638	No improvement in time to disease progression or overall survival
Tecemotide (L-BLP25) Peptide vaccine	EMD Serono, Merck KGaA	MUC1 cyclophosphamide	Unresectable stage III NSCLC	1513	Completed (2007-2015) NCT00409188 START	No improvement in overall survival
Tecemotide Peptide vaccine	Merck KGaA	MUC1 cyclophosphamide	Asian subjects with unresectable stage III NSCLC	285	Terminated (2009-2015) NCT01015443 INSPIRE	Terminated, the sponsor decided to discontinue program with Tecemotide in NSCLC
Tecemotide Peptide vaccine	EMD Serono	MUC1 cyclophosphamide	Unresectable stage III NSCLC	35	Terminated (2014-2015) NCT02049151 START2	Terminated, the sponsor decided to discontinue program with Tecemotide in NSCLC



## HHS Public Access

Author manuscript

*Nature*. Author manuscript; available in PMC 2018 January 13.



Published in final edited form as:

*Nature*. 2017 July 13; 547(7662): 217–221. doi:10.1038/nature22991.

## An Immunogenic Personal Neoantigen Vaccine for Melanoma Patients



**Catherine Wu, MD**

*Nature*, 2017

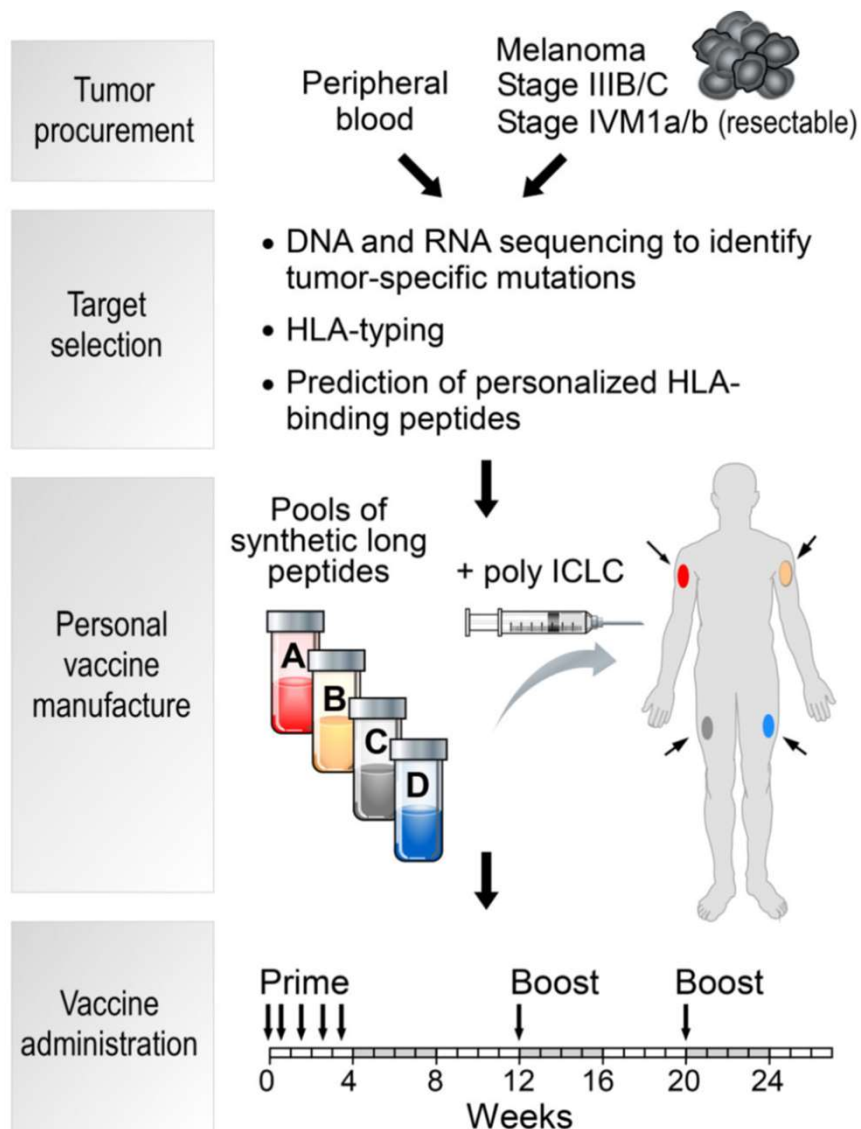


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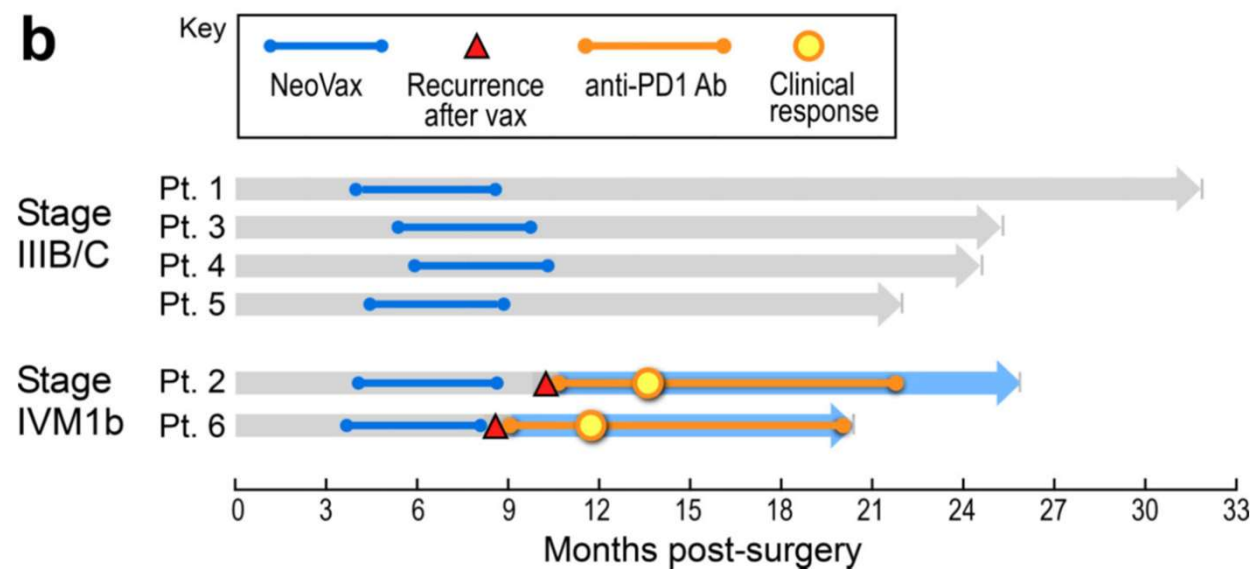
## Background and Significant



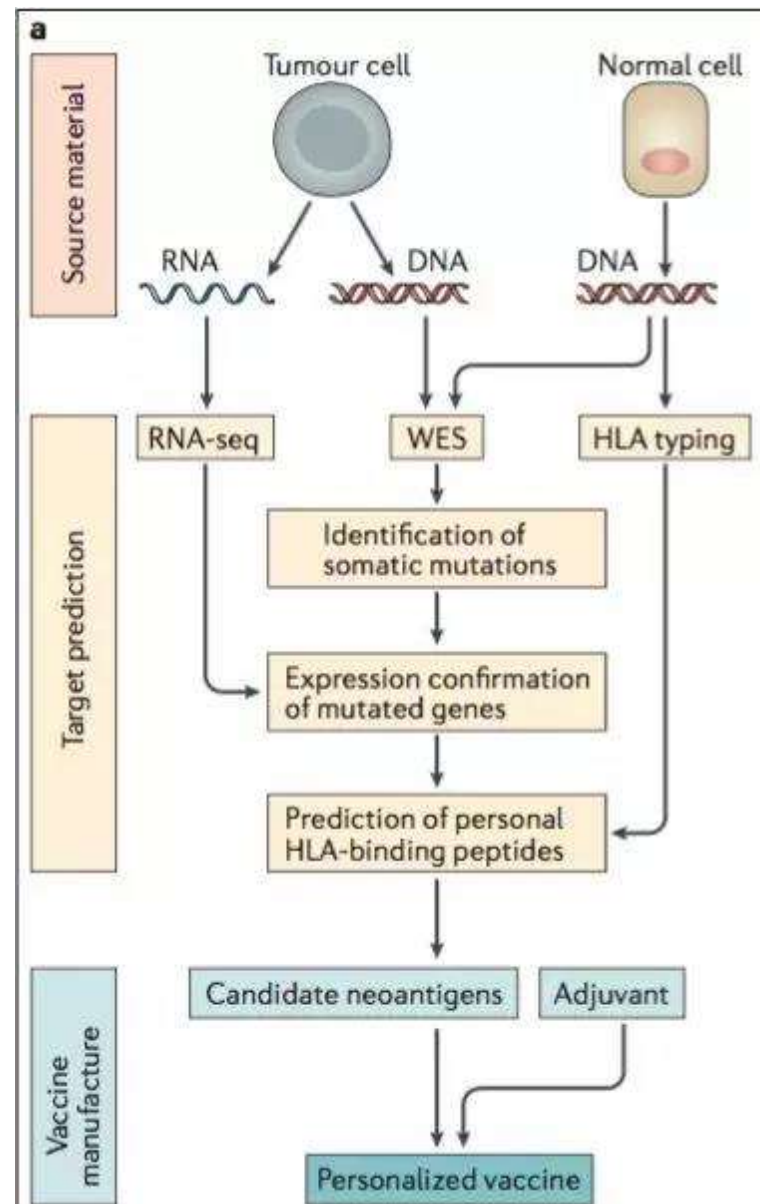
a



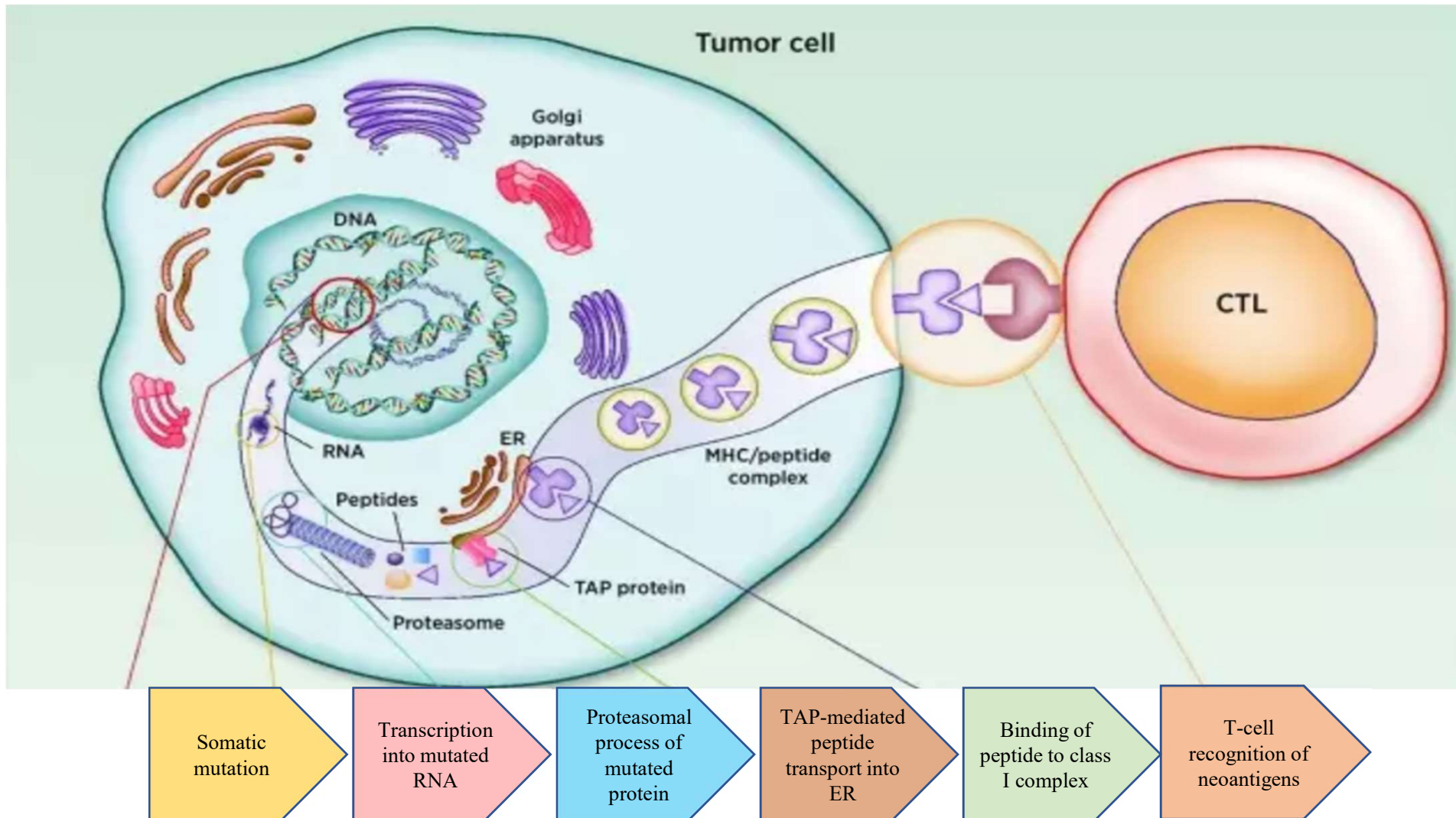
b



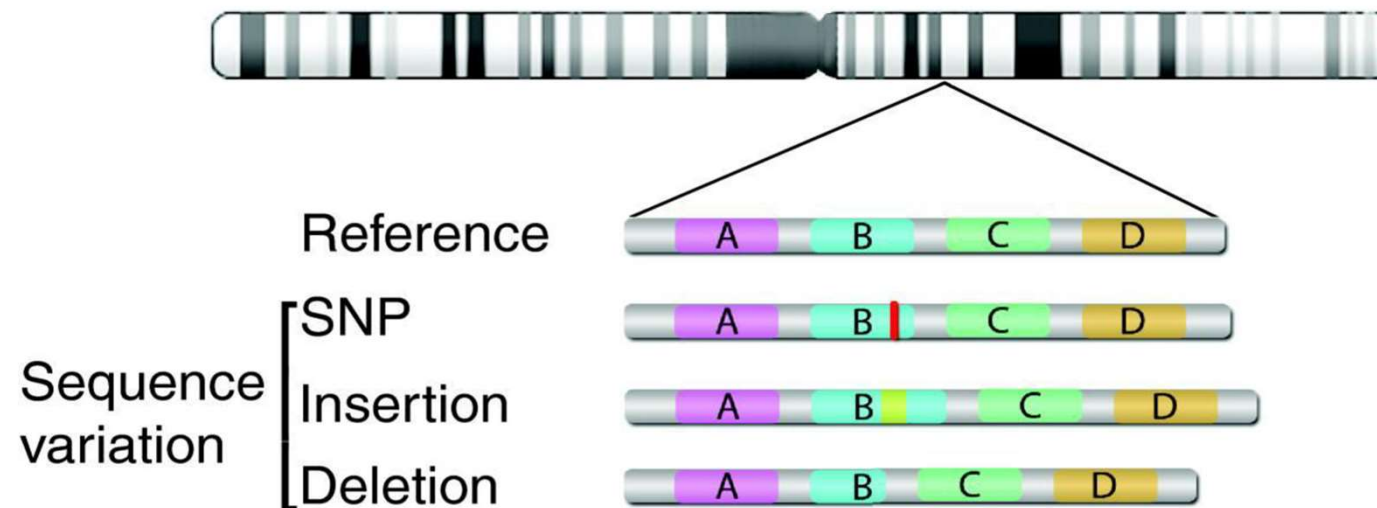
Nature, 2017



# Big picture



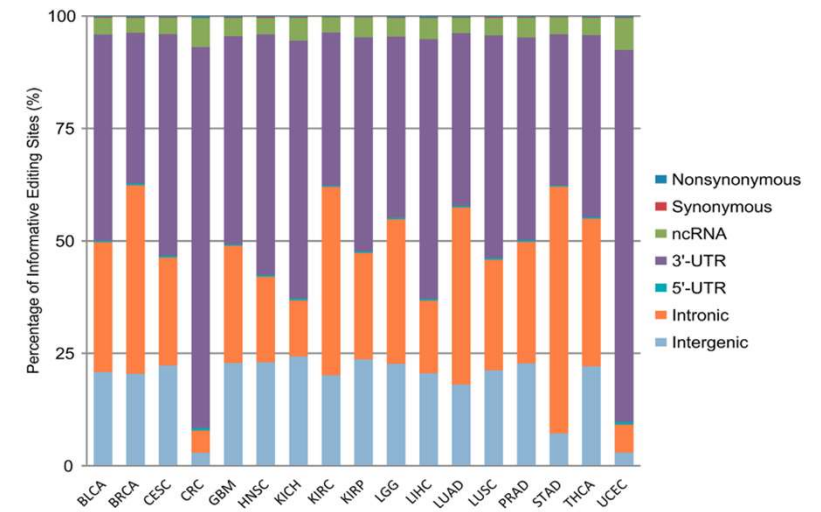
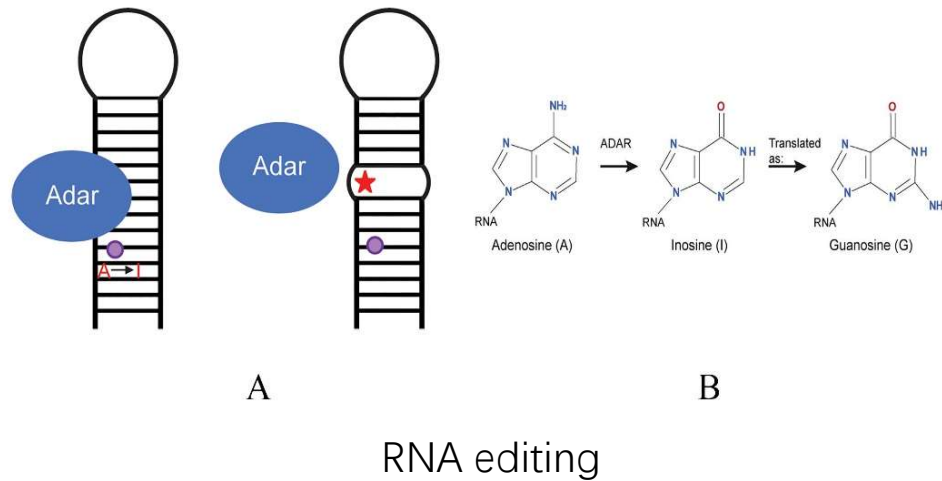




Neoantigen sources: Mutations

## 2

## Materials and Methods



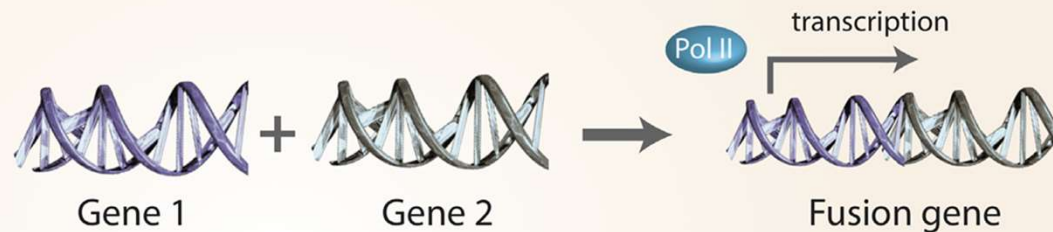
RNA editing distribution

Neoantigen sources: Transcriptome modification

## Gene fusion formation

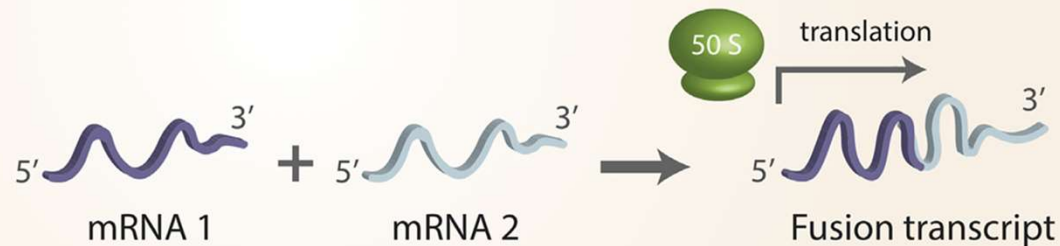
### A Fusion by structural rearrangements

Translocations, inversions, deletions and insertions



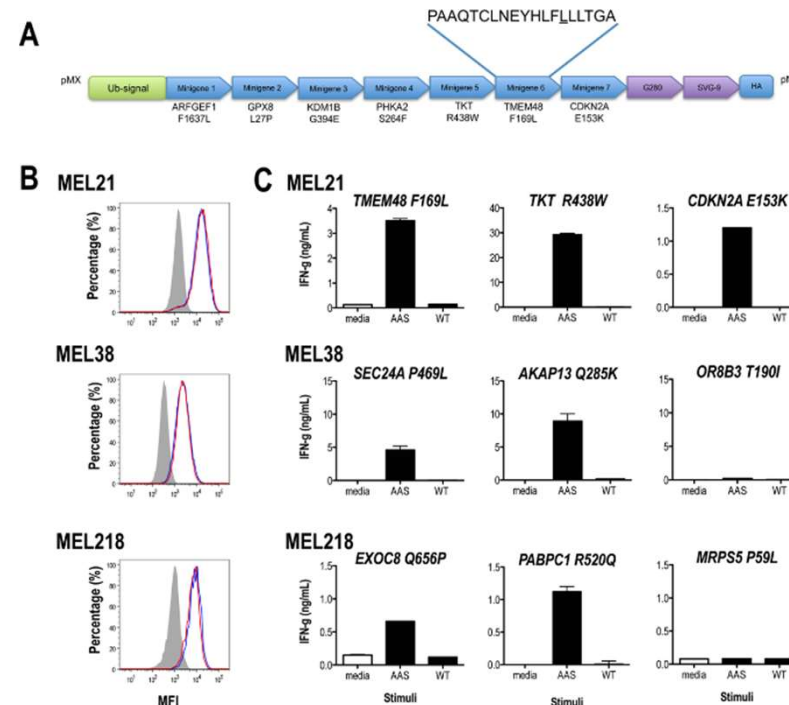
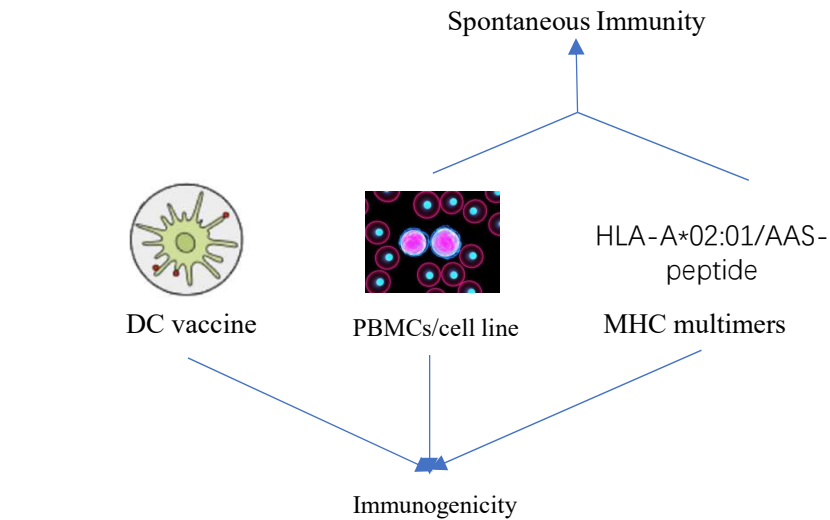
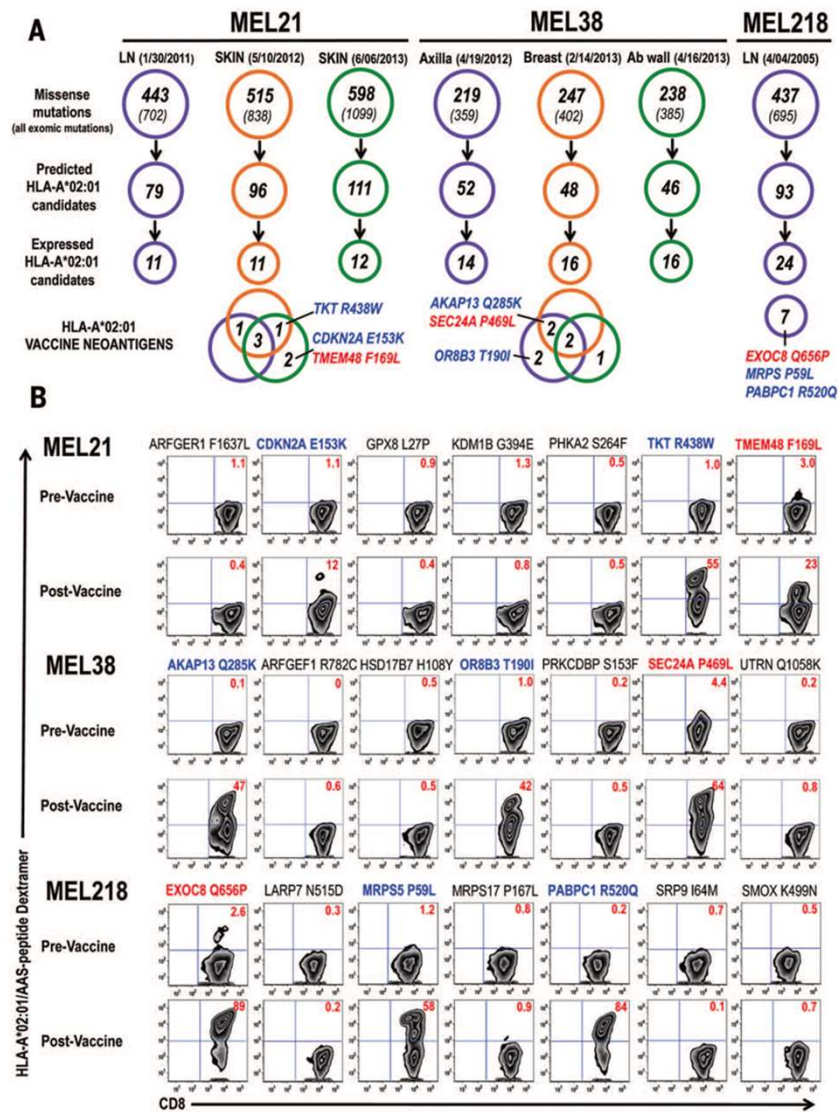
### B Fusion by transcription or splicing

Transcription read-through, mRNA *trans*-splicing or *cis*-splicing



Neoantigen sources: Gene fusion



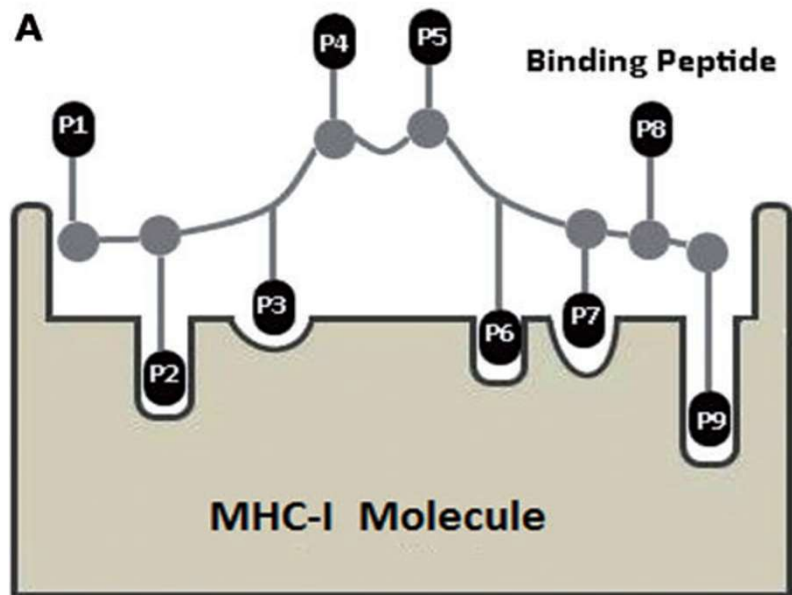


Proteasome cleavage & TAP transport

Science, 2015

## 2

## Materials and Methods



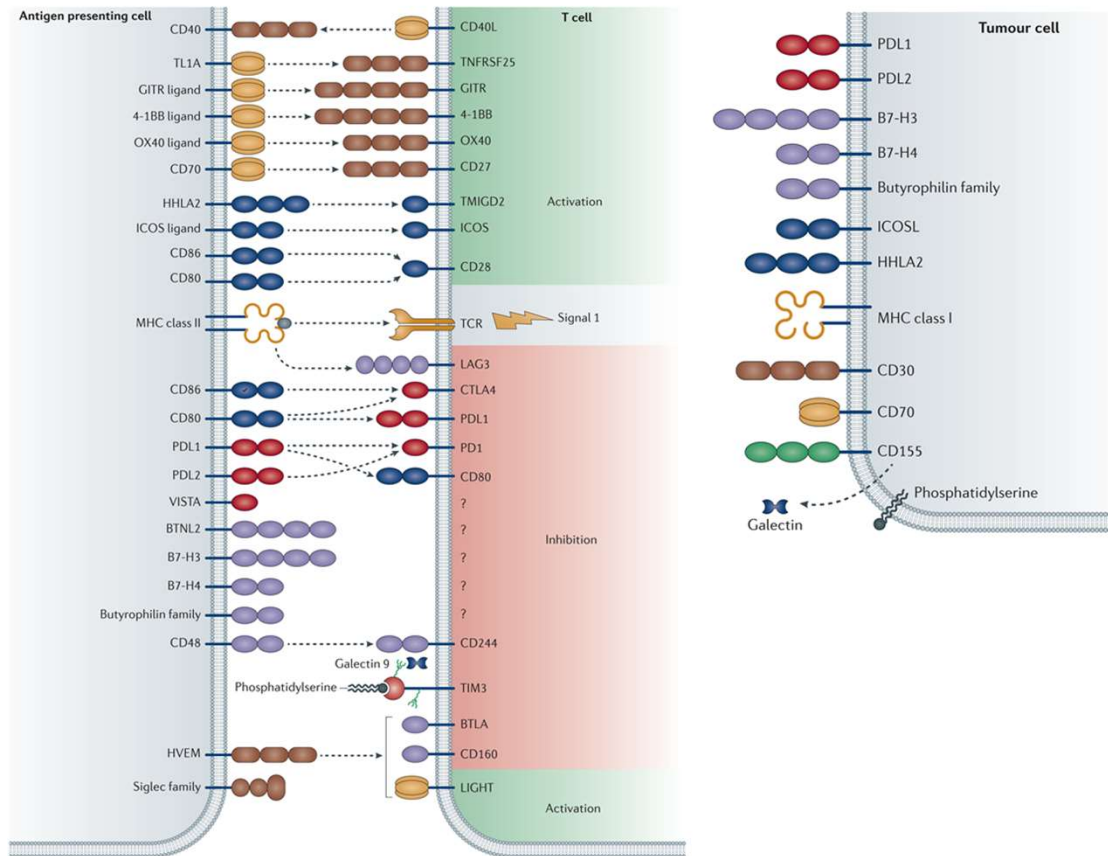
Peptide :8-11bp

MHC-I type

Similarity between mutant peptides and normal peptides

Peptide\_MHC-I binding affinity

## 2 Materials and Methods



pMHC-T cell recognition

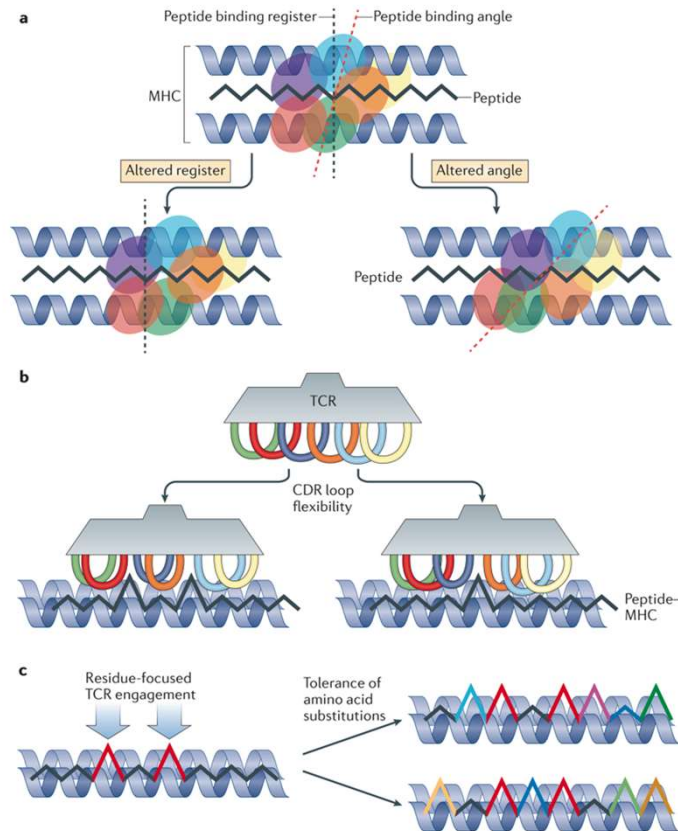
1. Many co-receptors

2. Lower binding affinity

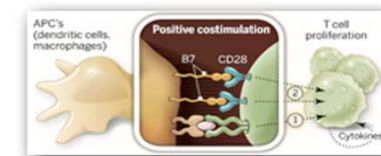
3. Long TCR sequence

## 2

## Materials and Methods



sequence similarity

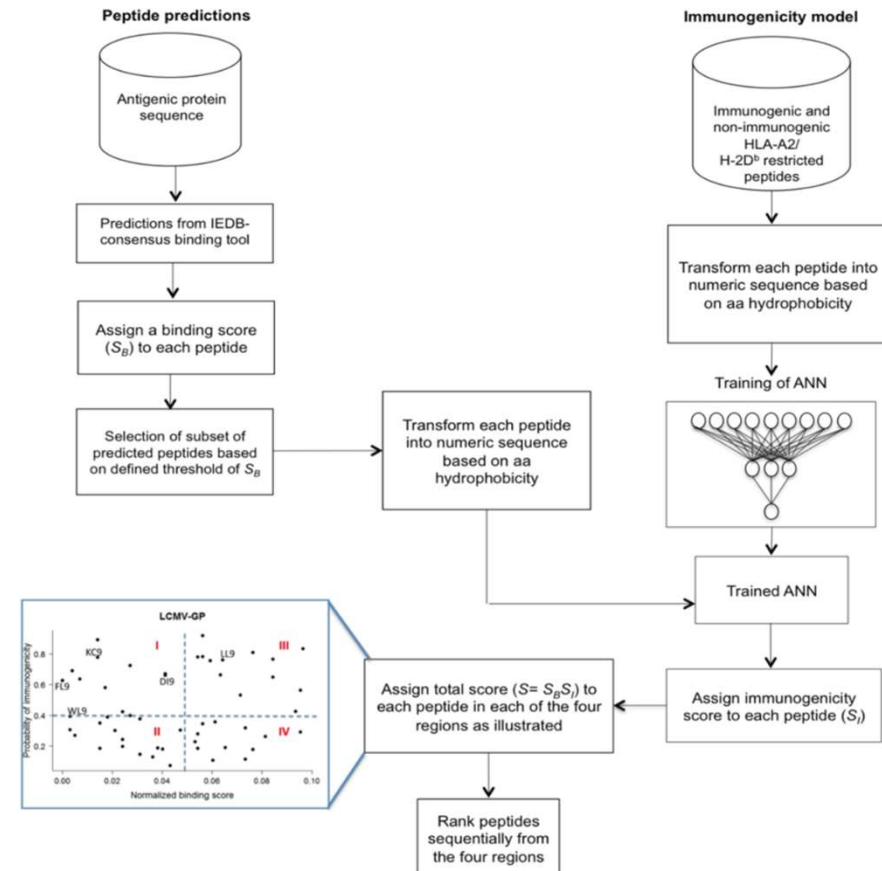
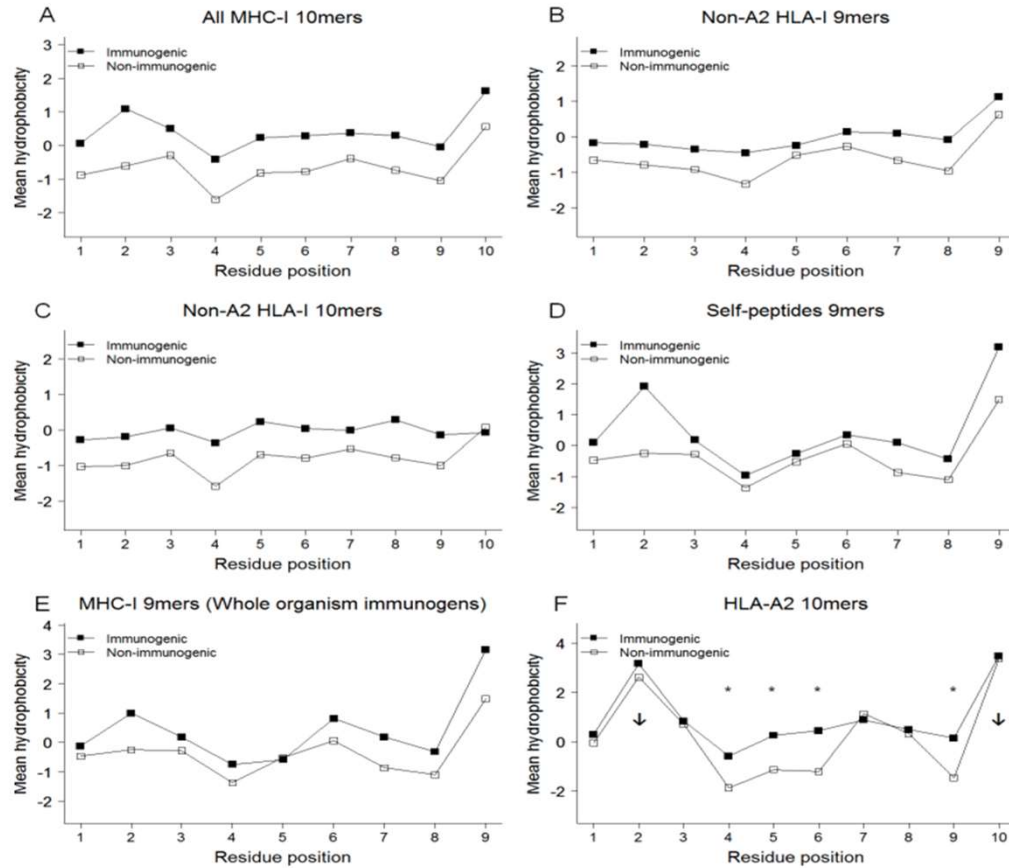


similar immunogenicity

Sequence similarity-based T cell recognition probability

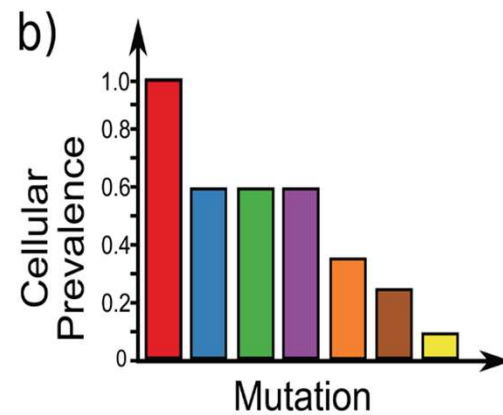
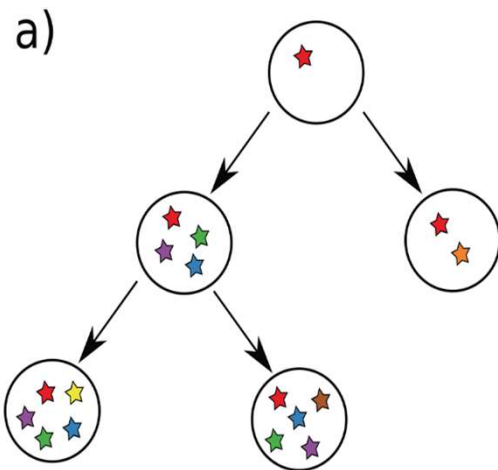


## 2 Materials and Methods

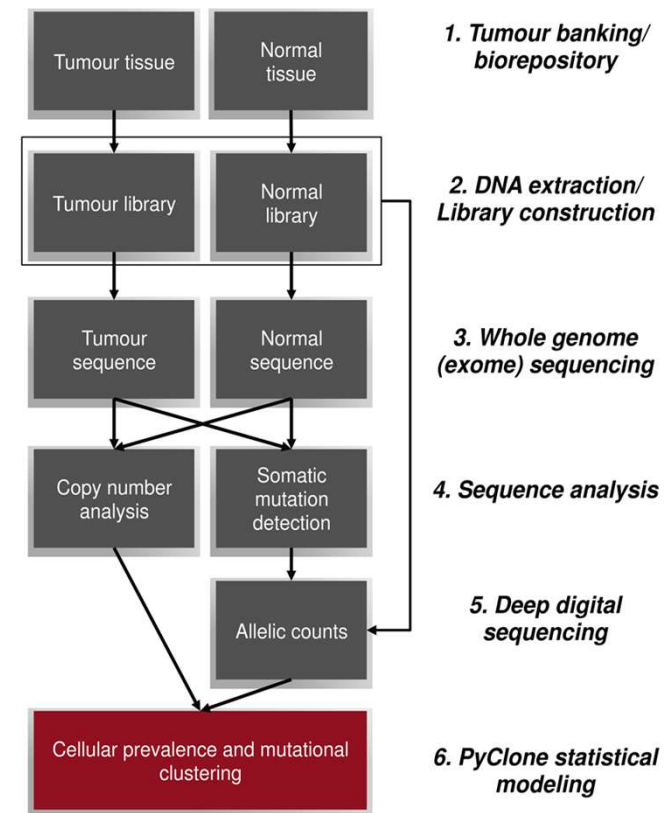


Hydrophobicity

## 2 Materials and Methods



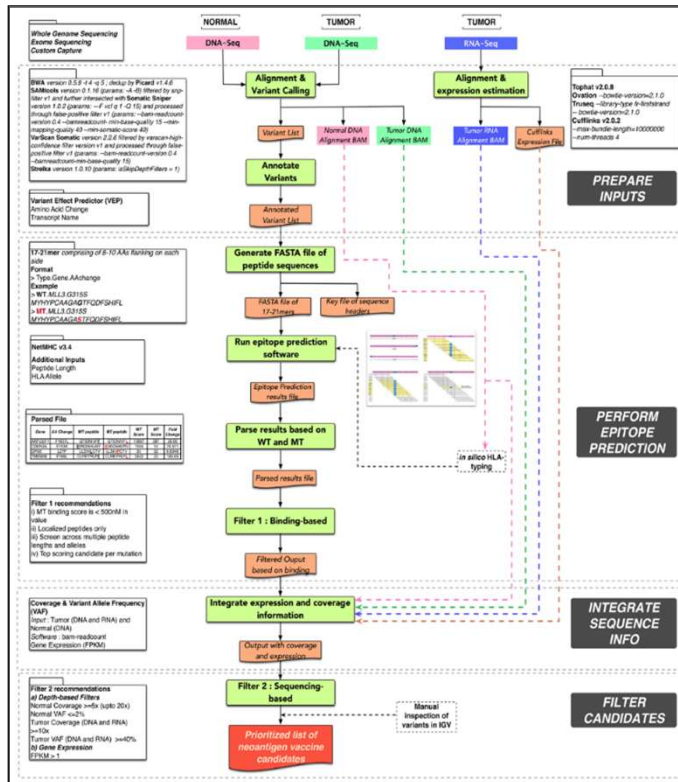
Cellular prevalence



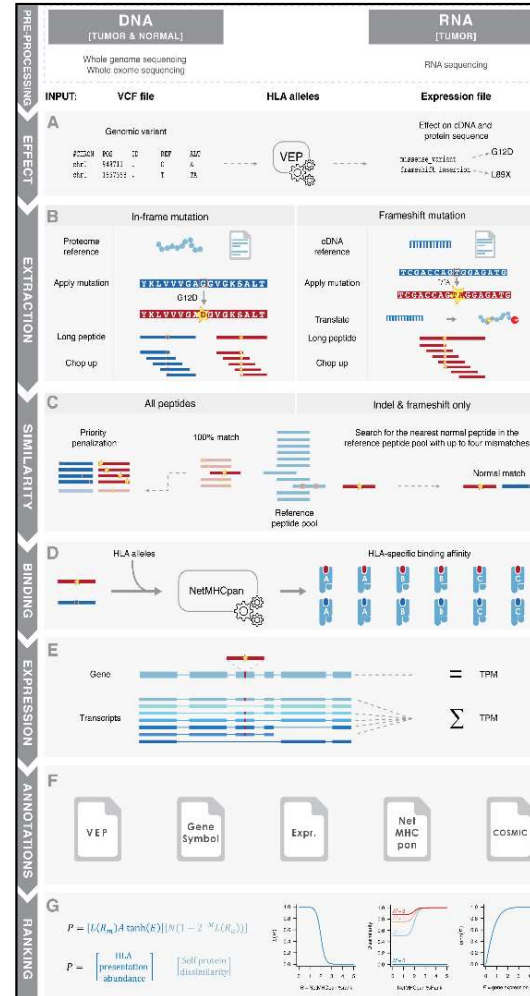
2

## Materials and Methods

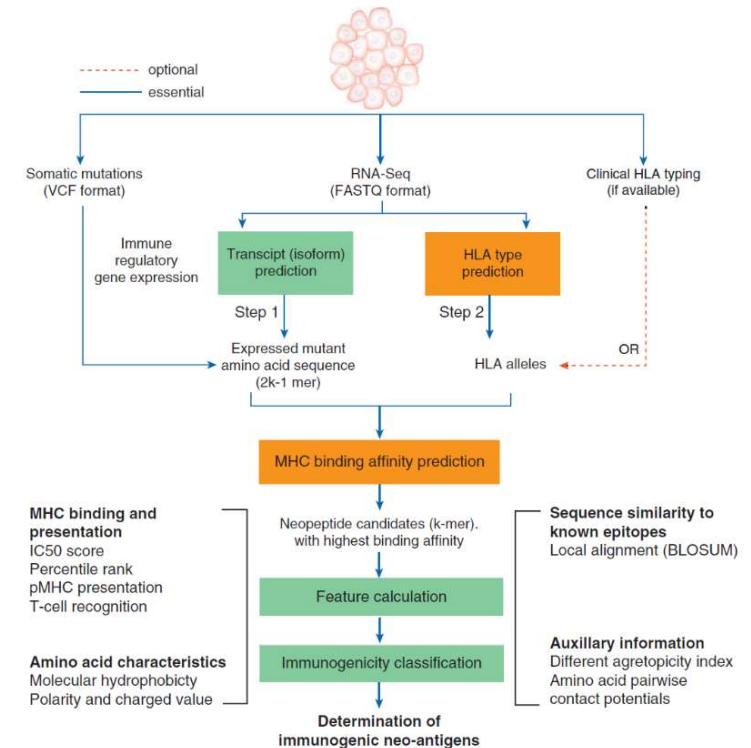
## Available tools

*pvac-seq*

Genome Medicine, 2016

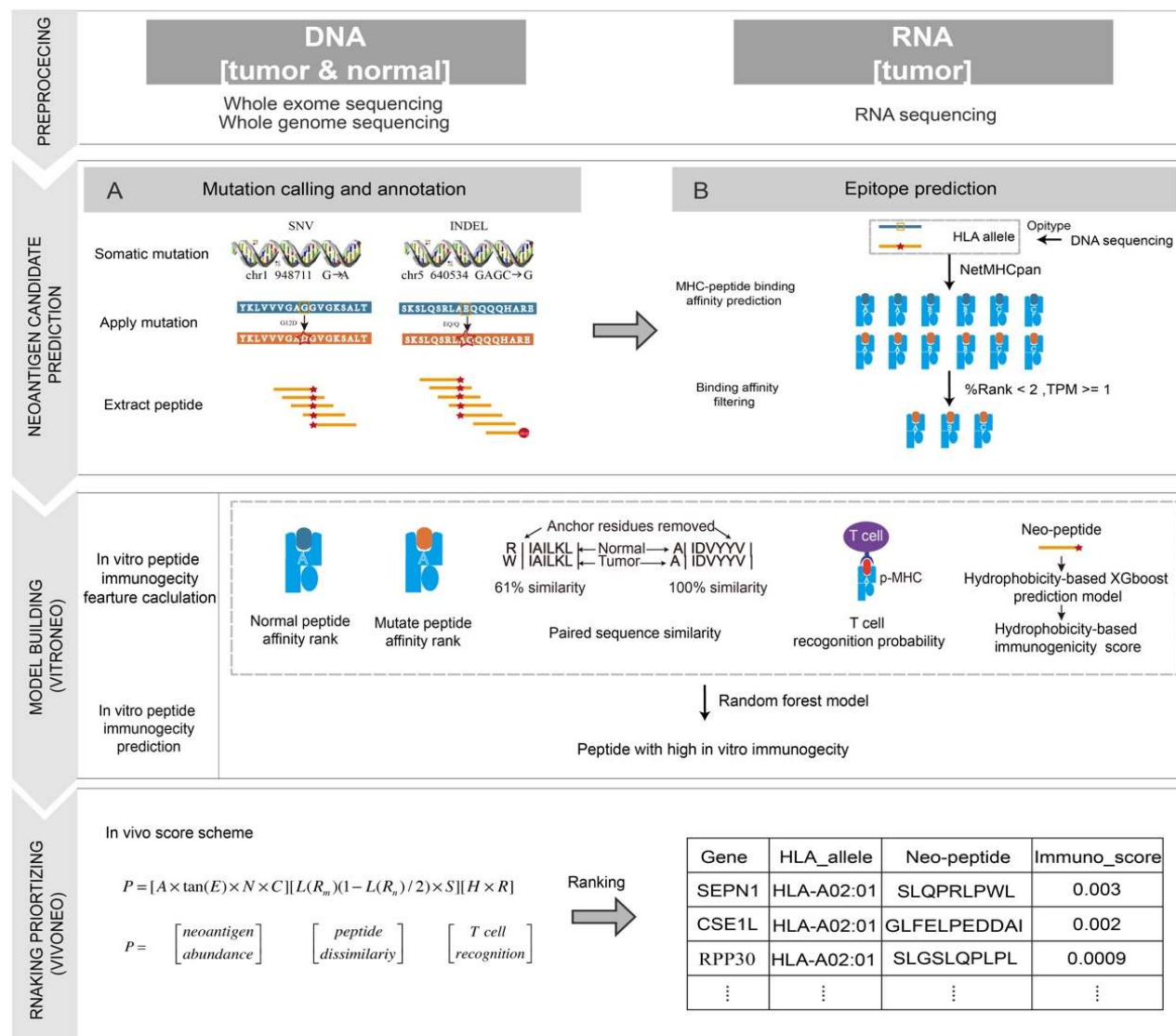
*MuPeXI*

Cancer Immunology Immunotherapy, 2017

*NeoPePsee*

Annals of Oncology, 2018

## iTunes



谢绝拍照

Unpublished



# Acknowledgement



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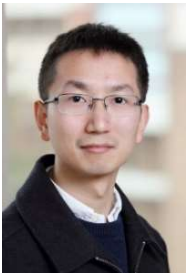
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**Prof. Quan Quan Gu  
@University of Virginia**



**Prof. Philip.S. Yu  
@UIC**



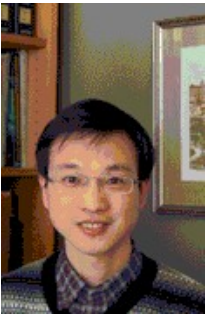
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**Dr. Hanhui Ma  
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**Prof. Zhixi Su  
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HENG RUI PHARMACEUTICALS



上海市第十人民医院



国家重点研发计划慢病专项 2016

国家重点研发计划精准医学专项 2017

# **From Data to Therapy, A Long but Prospective Way to Go**

