

# On the Path to Better Cancer Vaccines

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**BRIGHAM AND  
WOMEN'S HOSPITAL**

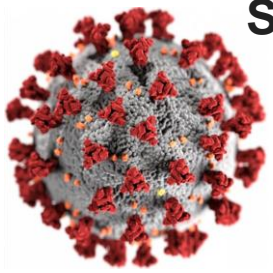


**Dana-Farber**  
Cancer Institute



**HARVARD**  
MEDICAL SCHOOL

# The world has changed...



SARS-CoV-2

## Pathogens — Prophylactic vaccines

Antibody generation  
? T cell responses

- Safe, our ticket "out"
- Major development targets of **time** and **cost** had to be achievable with the chosen technology

Biogen,  
Boston  
Feb 26 2020



The Boston Marriott Long Wharf hosted the Biogen leadership conference in February 2020. ERIN CLARK/GLOBE STAFF

Provincetown  
July 4 2021

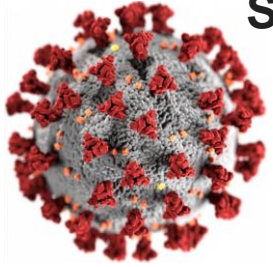


Commerce Street in Provincetown in August. CRAIG F. WALKER/GLOBE STAFF

*"Despite its magnitude, the outbreak was restricted in its onward impact in MA and the US, likely due to high vaccination rates and a robust public health response."* Siddle medRxiv 2021

# Cancer: The challenges haven't changed enough...

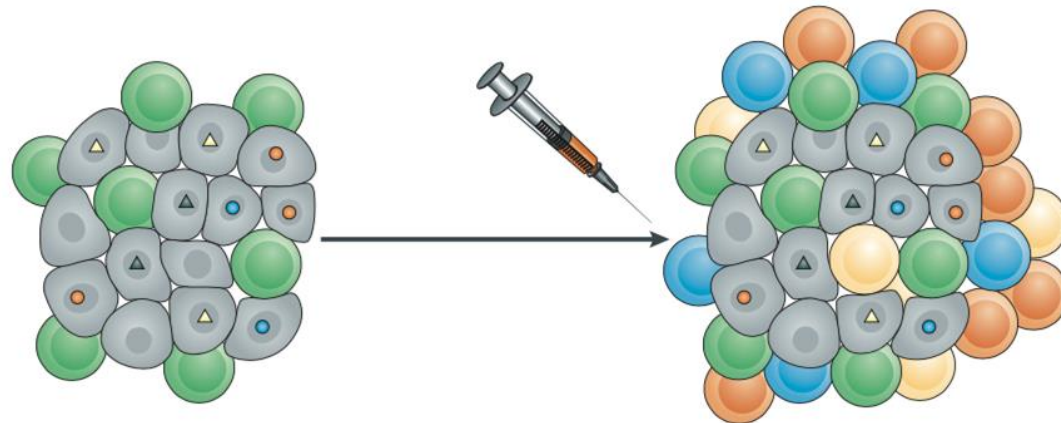
SARS-CoV-2



**Pathogens — Prophylactic vaccines**

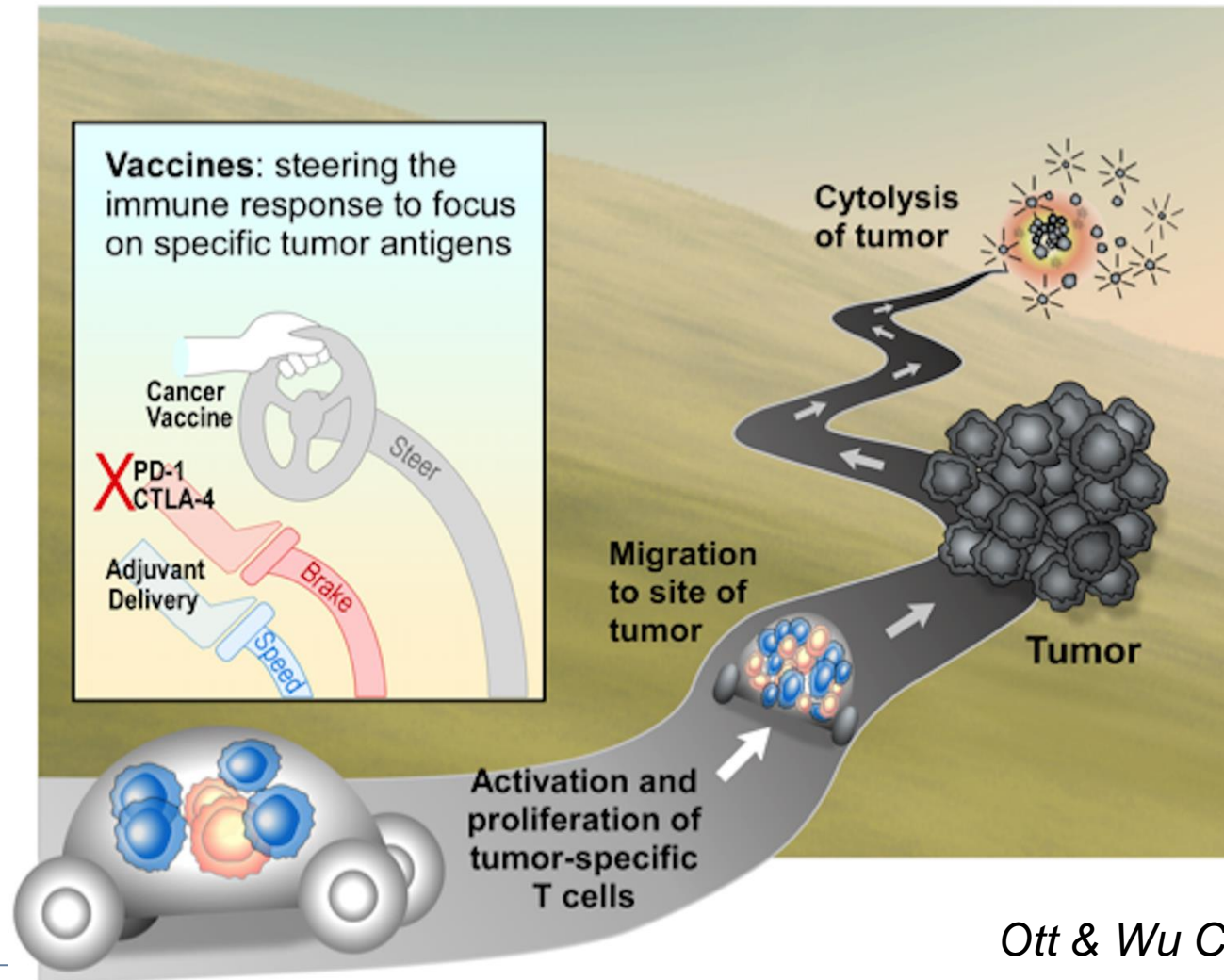
Antibody generation  
? T cell responses

**Cancer — Therapeutic vaccines**



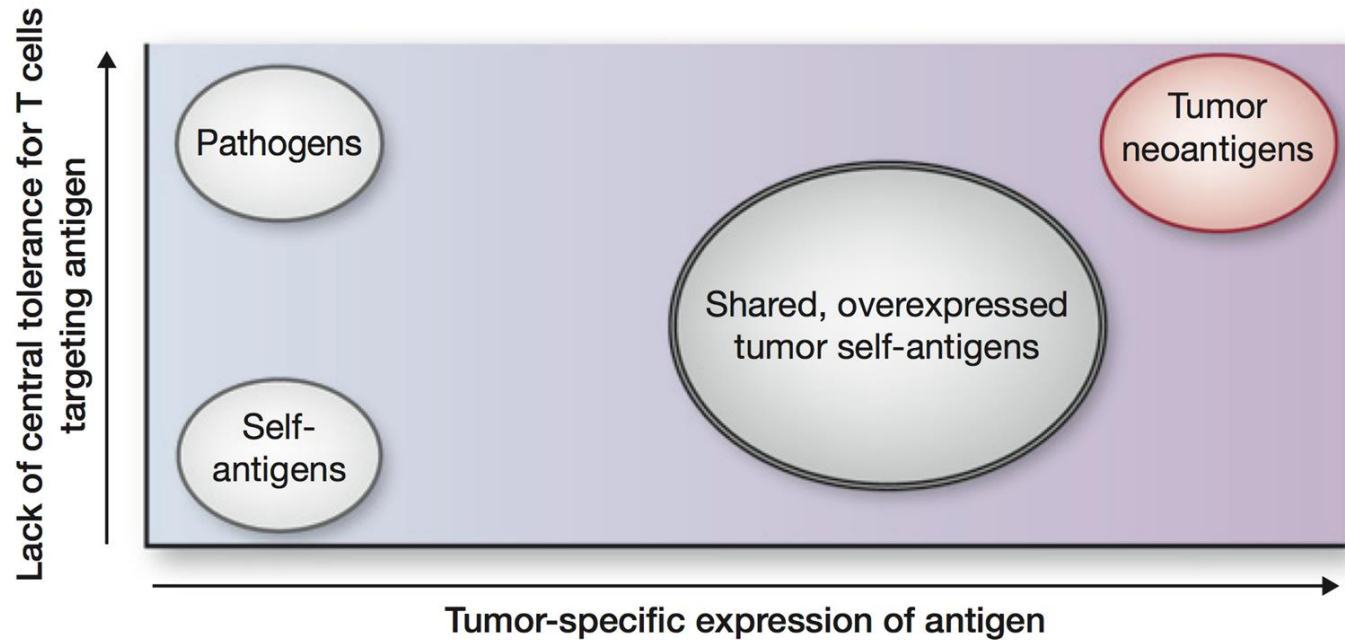
Increased breadth  
and diversity of  
tumour-specific  
T cell response

# Vaccines: Steering effective immune responses

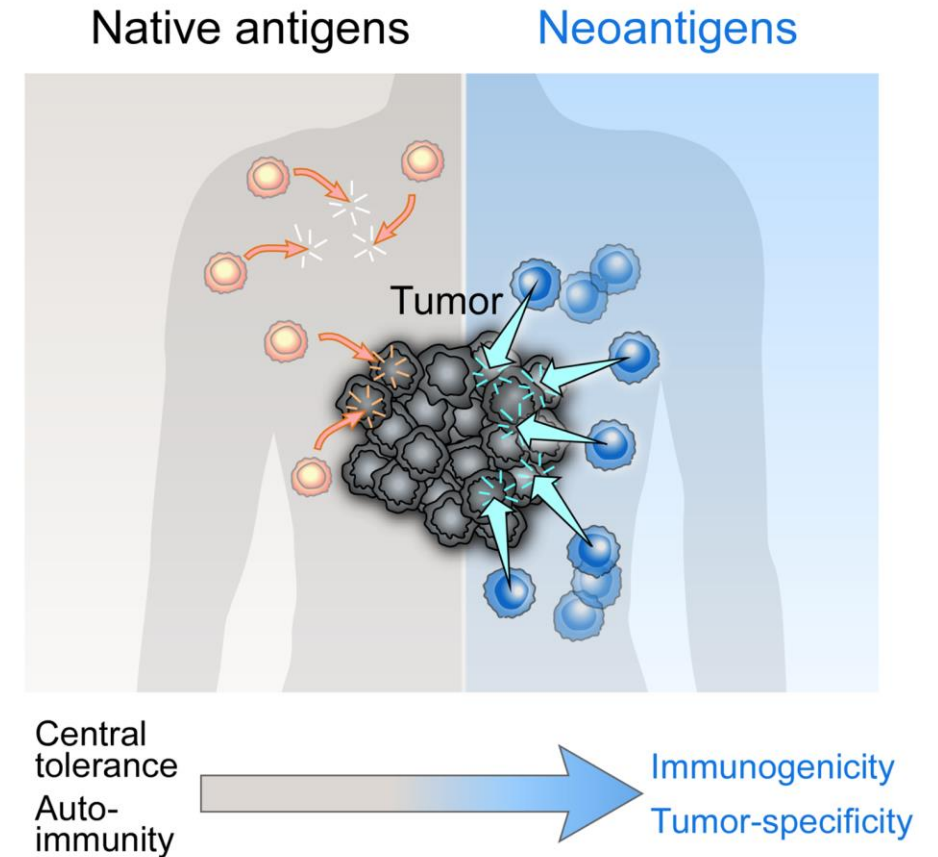


*Ott & Wu Can Discovery, 2019*

# Hitting the “sweet spot”: Towards a paradigm shift

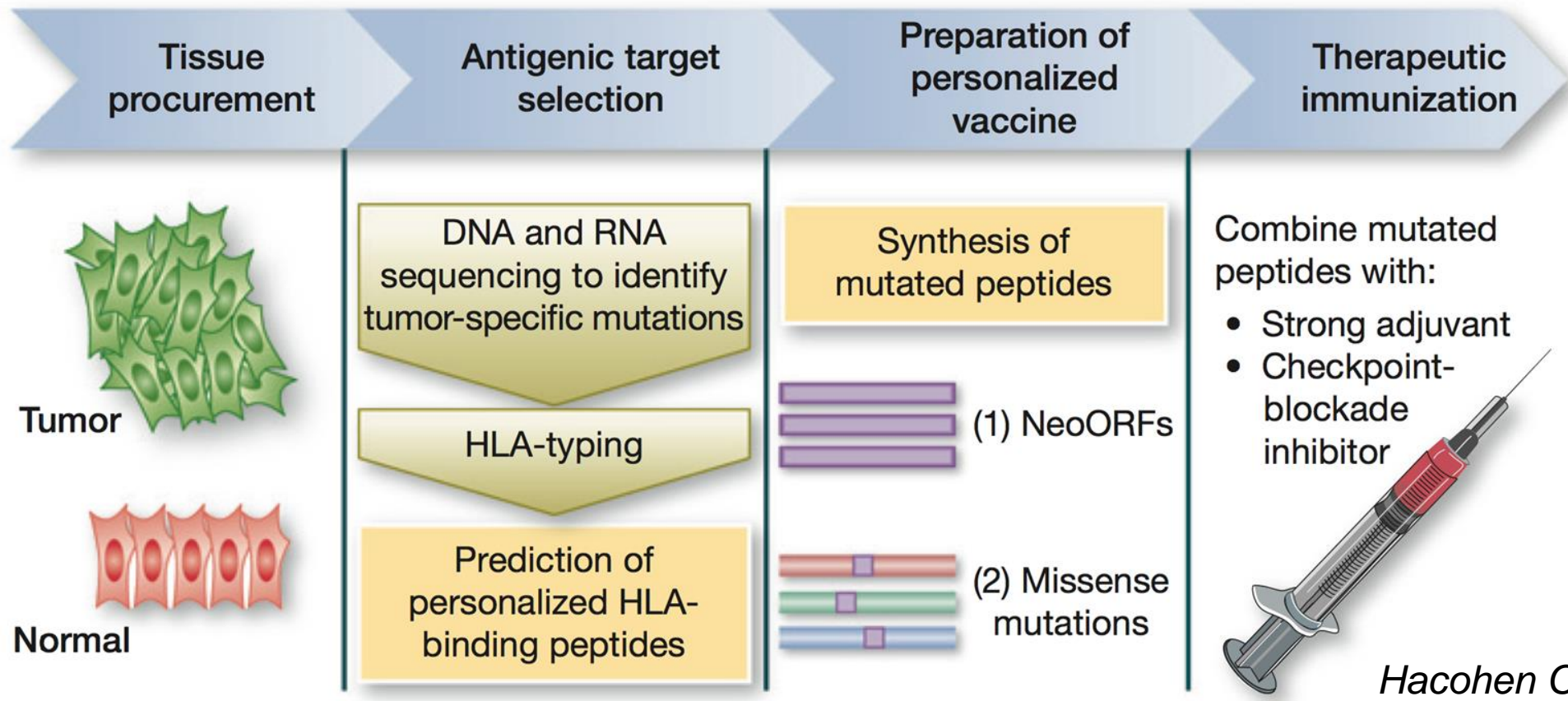


*Hacohen CIR 2013*



*Ott PA Hematol Oncol Clin North Am  
2014*





Adjuvant setting

High-risk melanoma

*Ott & Hu Nature (2017)*  
*Sahin Nature (2017)*  
*Carreno Science (2015)*

Newly diagnosed GBM

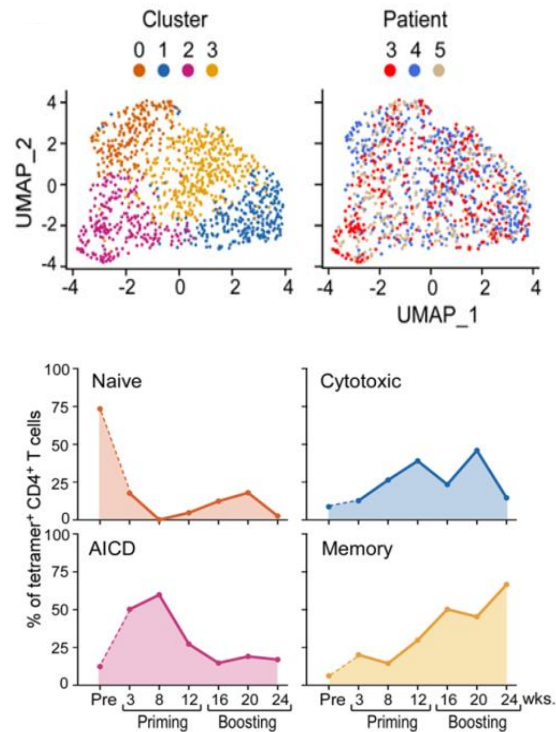
*Keskin, Nature (2019); Hilf Nature (2019)*

- Safe, feasible
- Highly immunogenic
- Expansion of neoantigen-specific T cells
- Promising results in combination with CPE

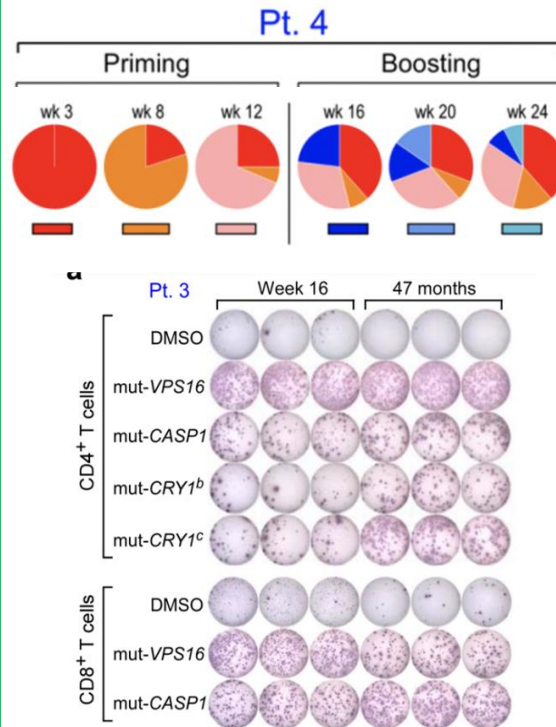
# Durable and encouraging long-term responses

*Hu Leet & Allesoe Nat Med (2021); Ott PA Cell 2020*

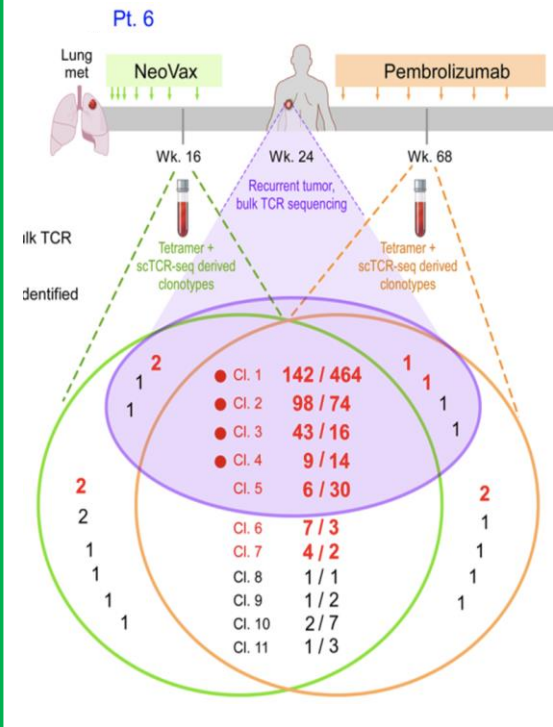
## Generation of memory response



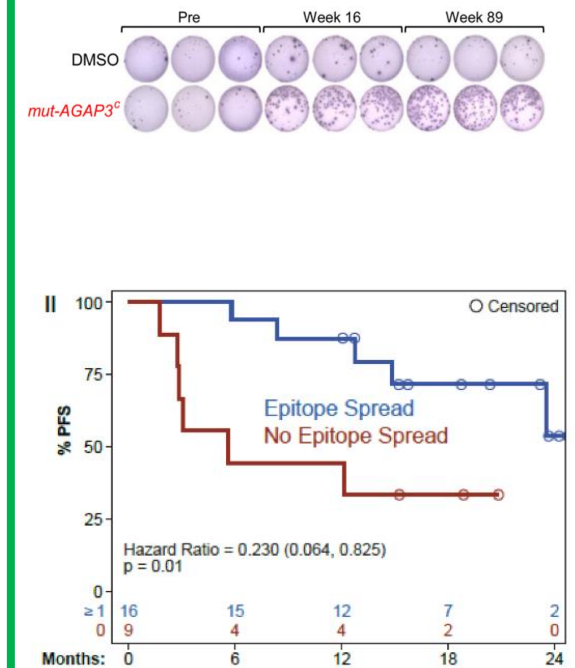
## T cell diversification & persistence



## Tracking of NeoAg T cells to the site of tumor

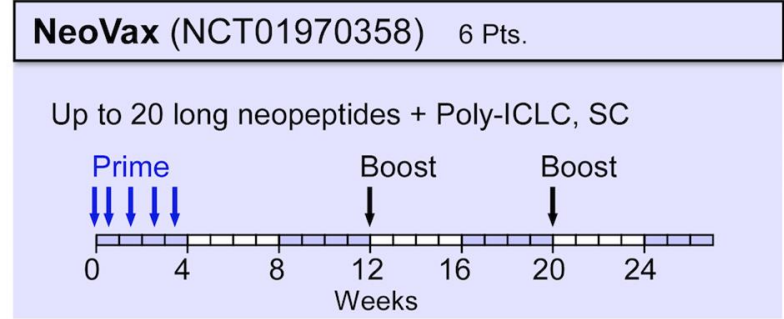


## Epitope spreading



An immunogenic personal neoantigen vaccine for patients with melanoma

Patrick A. Ott<sup>1,2,3\*</sup>, Zhuting Hu<sup>1\*</sup>, Derin B. Keskin<sup>1,3,4</sup>, Sachet A. Shukla<sup>1,4</sup>, Jing Sun<sup>1</sup>, David J. Bozym<sup>1</sup>, Wandl Zhang<sup>1</sup>, Adrienne Luoma<sup>5</sup>, Anita Giobbie-Hurder<sup>6</sup>, Lauren Peter<sup>7,8</sup>, Christina Chen<sup>1</sup>, Oriol Olive<sup>1</sup>, Todd A. Carter<sup>4</sup>, Shuqiang Li<sup>4</sup>, David J. Lieber<sup>4</sup>, Thomas Eisenhaure<sup>4</sup>, Evisa Gjini<sup>9</sup>, Jonathan Stevens<sup>10</sup>, William J. Lane<sup>10</sup>, Indu Javeri<sup>11</sup>, Kaliappanadar Nellaippan<sup>11</sup>, Andres M. Salazar<sup>12</sup>, Heather Daley<sup>1</sup>, Michael Seaman<sup>7</sup>, Elizabeth I. Buchbinder<sup>1,2,3</sup>, Charles H. Yoon<sup>3,13</sup>, Maegan Harden<sup>4</sup>, Niall Lennon<sup>4</sup>, Stacey Gabriel<sup>4</sup>, Scott J. Rodig<sup>9,10</sup>, Dan H. Barouch<sup>3,7,8</sup>, Jon C. Aster<sup>3,10</sup>, Gad Getz<sup>3,4,14</sup>, Kai Wucherpfennig<sup>3,5</sup>, Donna Neuberg<sup>6</sup>, Jerome Ritz<sup>1,2,3</sup>, Eric S. Lander<sup>3,4</sup>, Edward F. Fritsch<sup>1,4</sup>, Nir Hacohen<sup>3,4,15</sup> & Catherine J. Wu<sup>1,2,3,4</sup>



Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer

Ugur Sahin<sup>1,2,3</sup>, Evelyn Derhovanessian<sup>1</sup>, Matthias Miller<sup>1</sup>, Björn-Philipp Klocke<sup>1</sup>, Petra Simon<sup>1</sup>, Martin Löwer<sup>2</sup>, Valesca Bukur<sup>1,2</sup>, Arbel D. Tadmor<sup>2</sup>, Ulrich Luxemburger<sup>1</sup>, Barbara Schrörs<sup>2</sup>, Tana Omokoko<sup>1</sup>, Mathias Vormehr<sup>1,3</sup>, Christian Albrecht<sup>2</sup>, Anna Paruzynski<sup>1</sup>, Andreas N. Kuhn<sup>1</sup>, Janina Buck<sup>1</sup>, Sandra Heesch<sup>1</sup>, Katharina H. Schreeb<sup>1</sup>, Felicitas Müller<sup>1</sup>, Inga Ortseifer<sup>1</sup>, Isabel Vogler<sup>1</sup>, Eva Godehardt<sup>1</sup>, Sebastian Attig<sup>2,3</sup>, Richard Rae<sup>4</sup>, Andrea Breitkreuz<sup>1</sup>, Claudia Tolliver<sup>1</sup>, Martin Suchan<sup>4</sup>, Goran Maric<sup>4</sup>, Alexander Hohenberger<sup>5</sup>, Patrick Sorn<sup>6</sup>, Jan Diekmann<sup>1</sup>, Janko Glesia<sup>4</sup>, Olga Waksman<sup>1</sup>, Alexandra-Kemner Brück<sup>4</sup>, Meike Wirt<sup>1</sup>, Martina Zillgen<sup>1</sup>, Andree Rothermel<sup>1</sup>, Barbara Kasemann<sup>1</sup>, David Langer<sup>1</sup>, Stefanie Bolte<sup>1</sup>, Mustafa Diken<sup>1,2</sup>, Sebastian Kreiter<sup>1,2</sup>, Romina Nemecek<sup>2</sup>, Christoffer Gebhardt<sup>6,7</sup>, Stephan Grabbe<sup>3</sup>, Christoph Höller<sup>3</sup>, Jochen Utikal<sup>6,7</sup>, Christoph Huber<sup>1,2,3</sup>, Carmen Loquai<sup>1\*</sup> & Özlem Türeci<sup>1\*</sup>

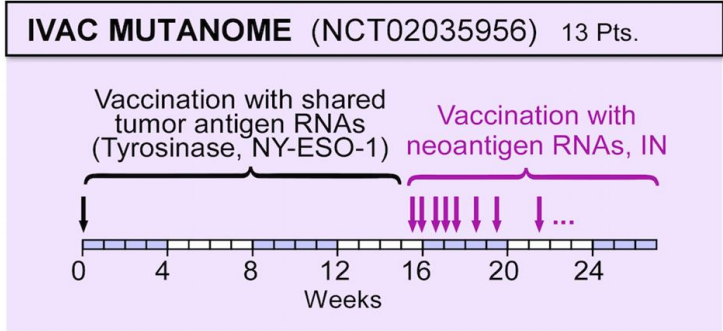


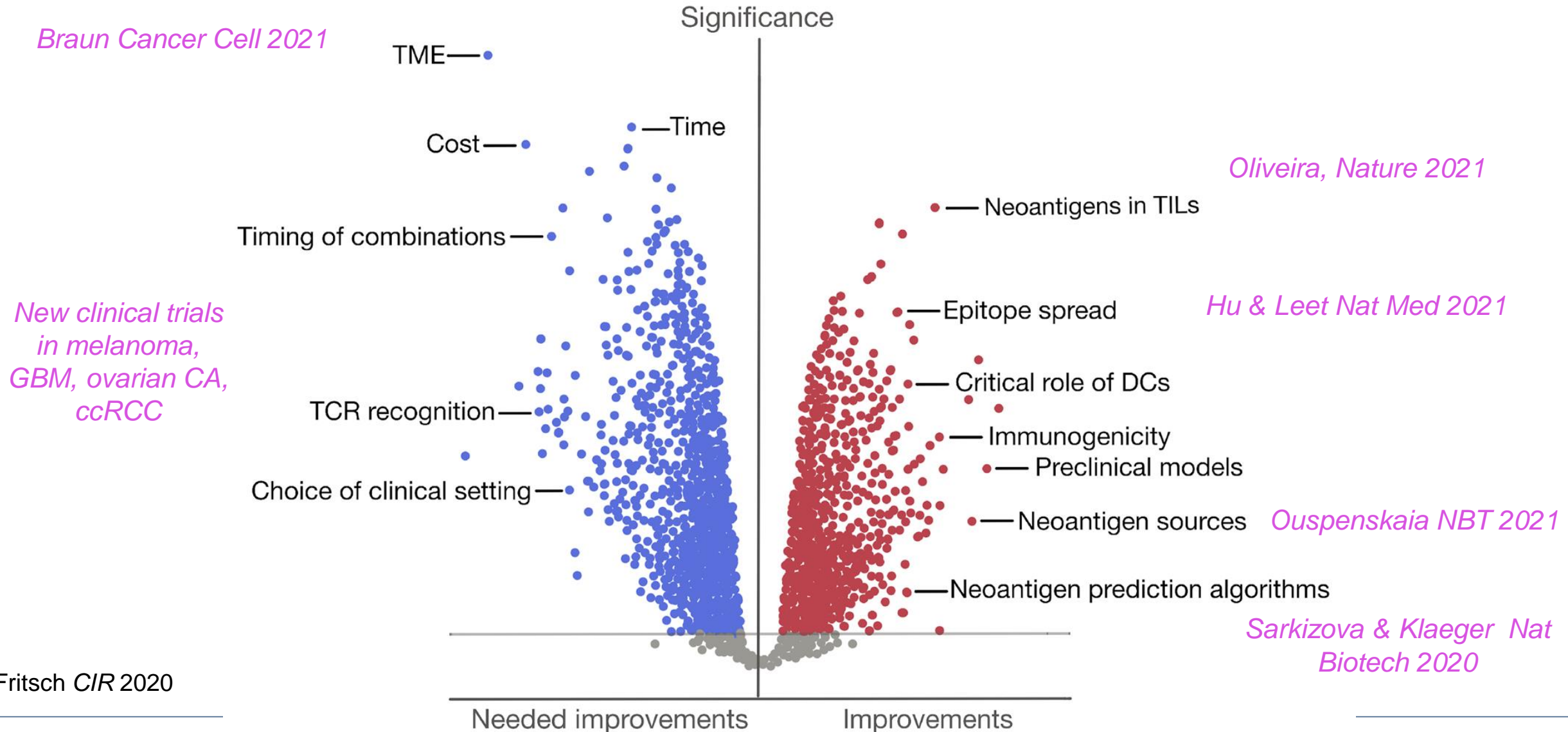
Table 1. Summary of Neoantigen Vaccines

	Ott <i>et al.</i> [4]	Sahin <i>et al.</i> [3]
No. of patients	6	13
Vaccine	Synthetic peptide+ poly IC:LC	RNA
Administration route	Subcutaneous	Intranodal
Epitope length	15–30 aa	27 aa
No. of epitopes/patient	13–20	10
No. of doses	7	8–20
Immunogenicity (total no. peptides tested)	91 peptides	125 epitopes
CD8 <sup>+</sup> T cell response rate <sup>b</sup>	16%	25%
CD4 <sup>+</sup> T cell response rate <sup>b</sup>	60%	66%

<sup>a</sup>Ex vivo manufactured and pulsed with synthetic peptides.  
<sup>b</sup>Immune response rate to MHC class I or class II epitopes (per vaccine trial).

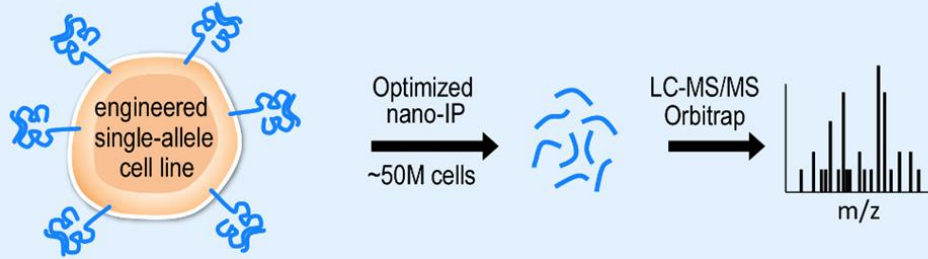


# Where next?



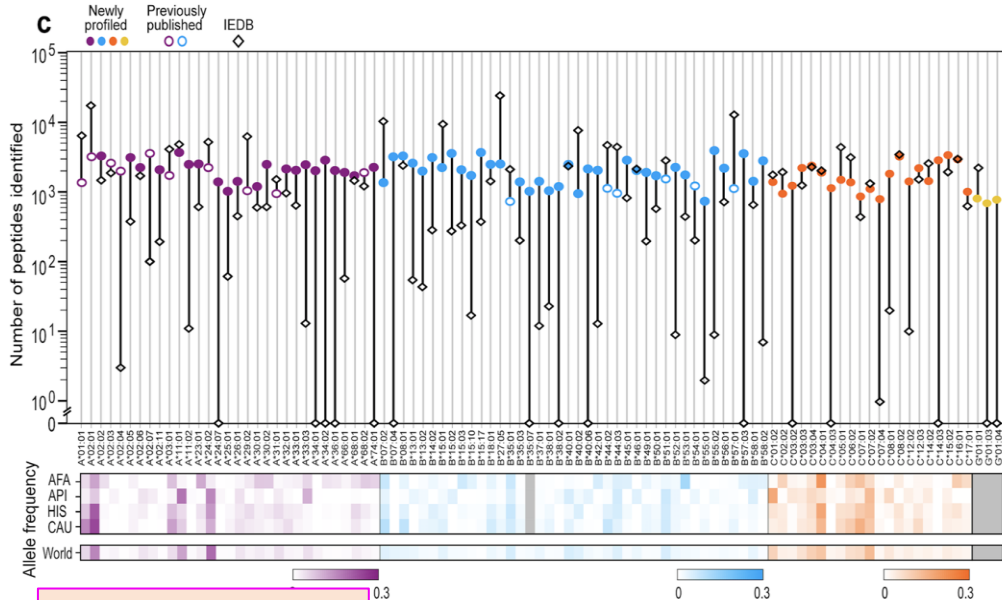
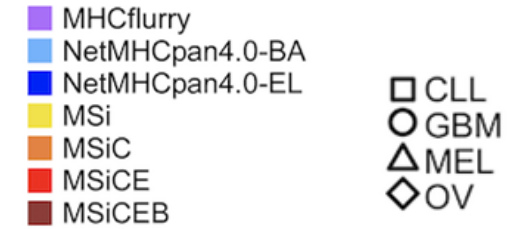
# (1) Can do better at prediction?

single-allele approach



**Unambiguous**  
allele  
assignment;  
creation of **de-novo**  
predictors

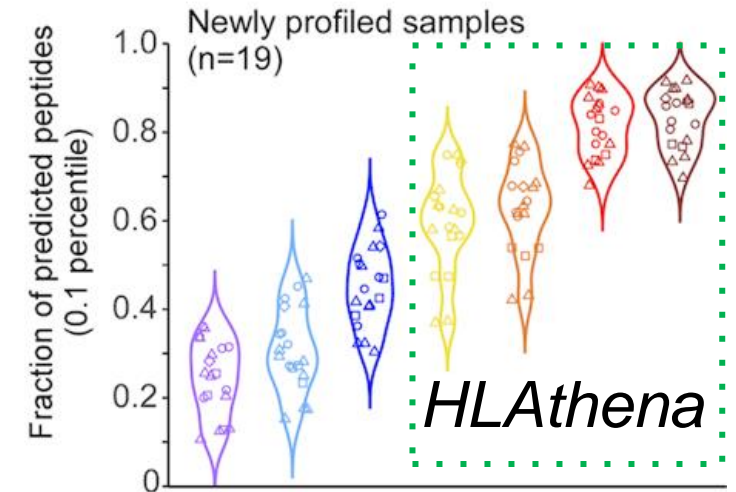
Abelin Keskin & Sarkizova  
Immunity 2017



Generation of:

- Allele-and-length specific models
- Pan-allele-pan-length models

95 HLA lines

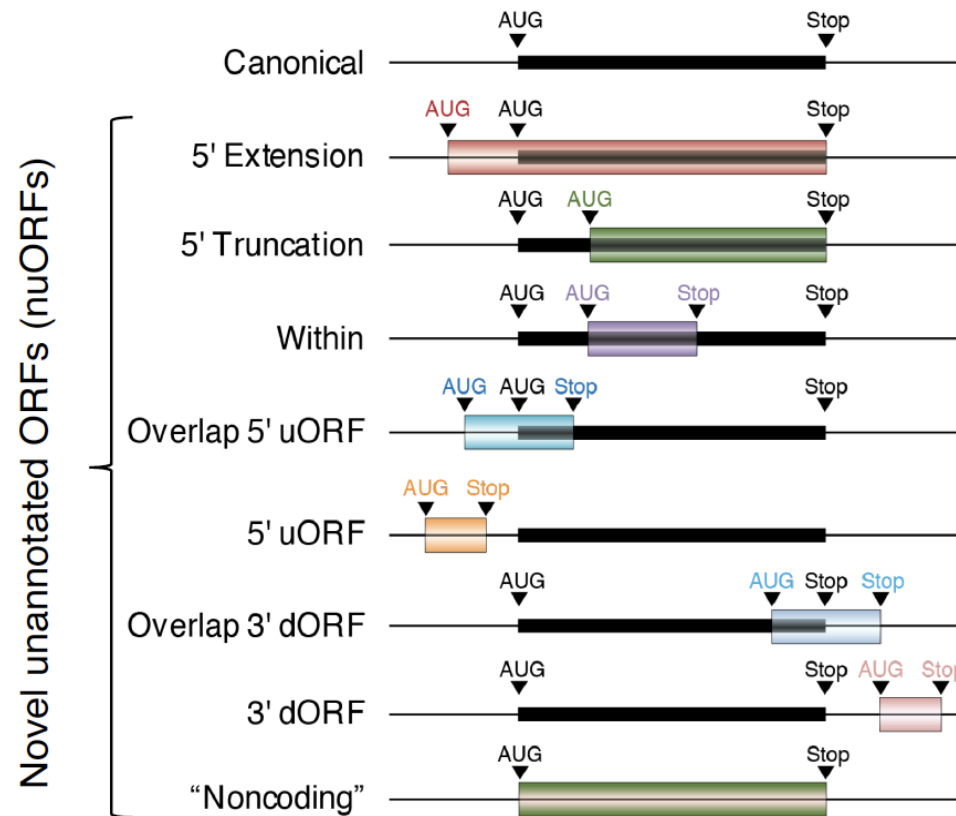


9-38% increase in peptide identifications with MSEC

Sarkizova & Klaeger Nat Biotech 2020

## (2) Can we find new classes of targets?

Ribo-seq predicts translated *unannotated* open reading frames

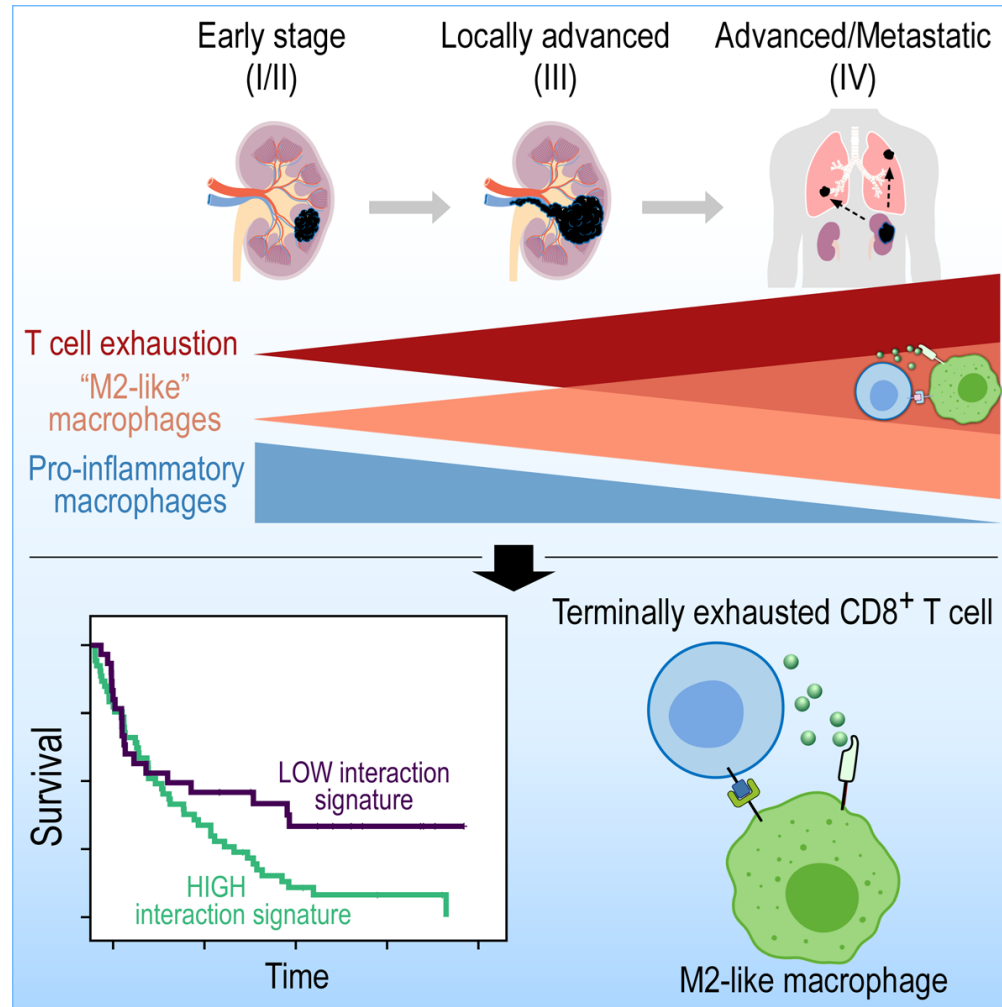


Ouspenskaia *Nat Biotech*  
2021

- Even more sources need exploration: Splice variants, gene fusions, A-to-I editing, etc

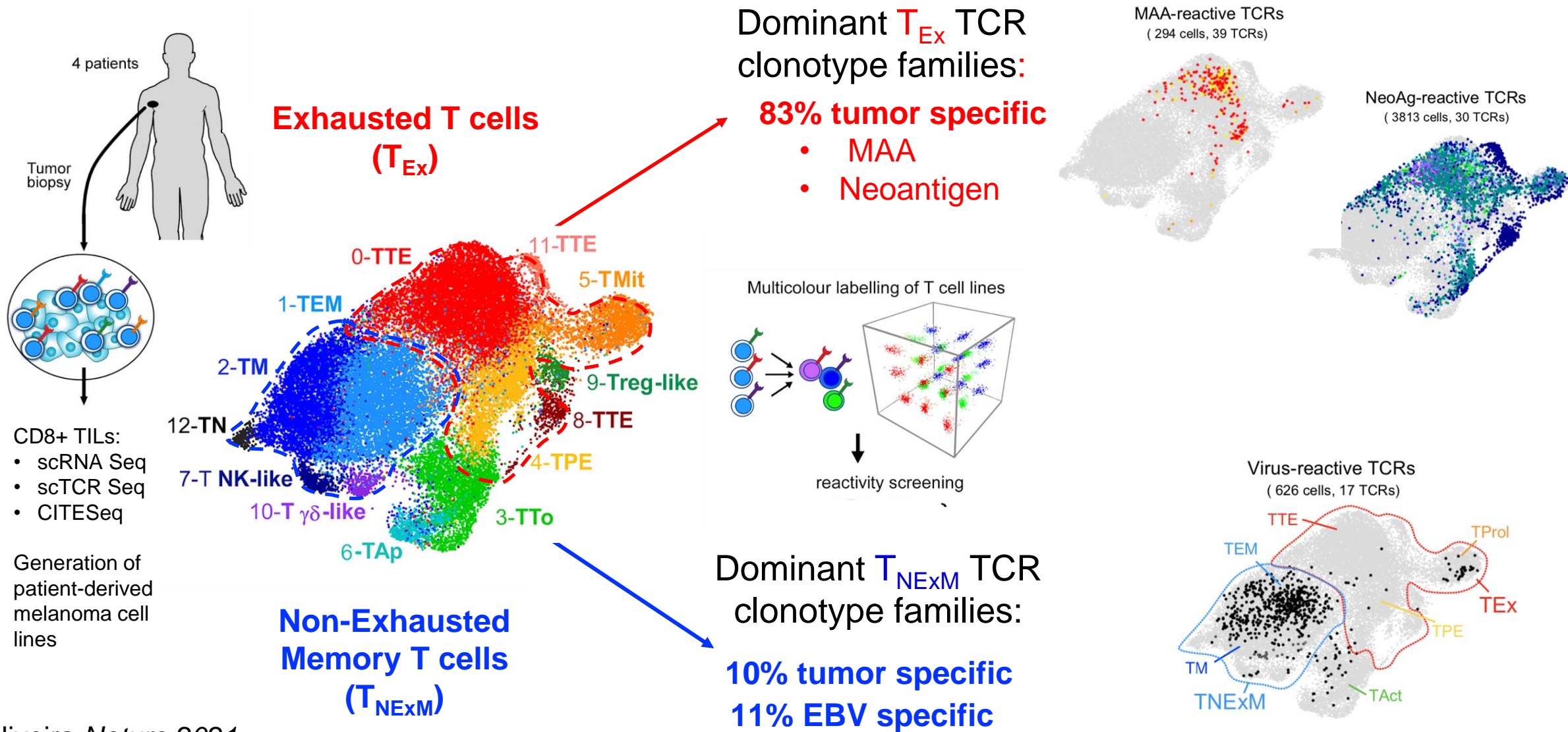
### (3) Can we understand cell states involved in natural disease progression and response

#### Renal cell Carcinoma

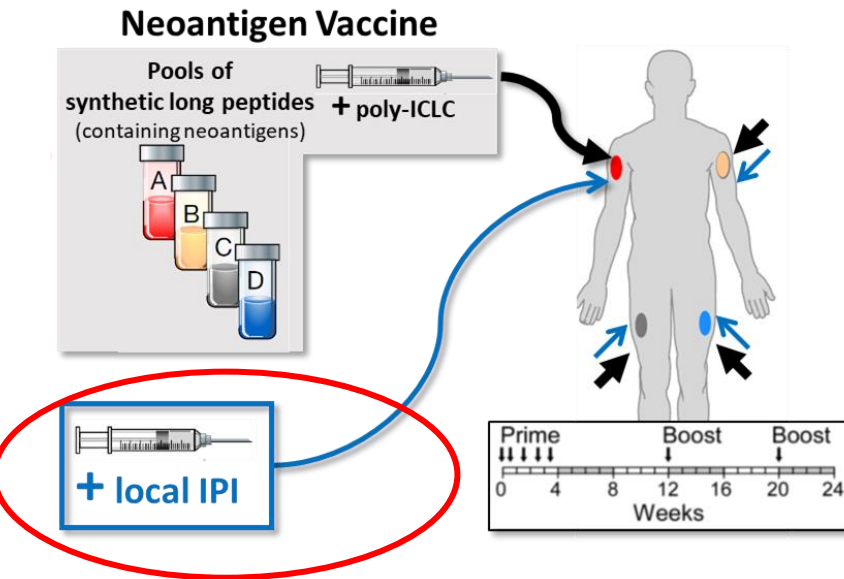




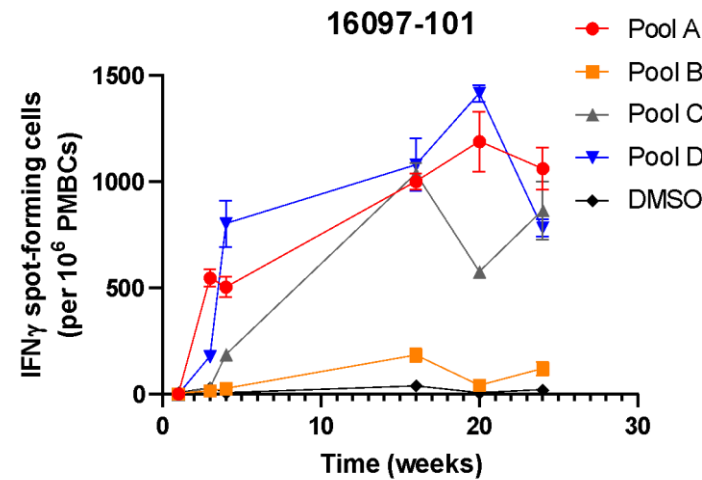
# (4) Can we link antigen specificity, phenotype and T cell clonotype information?



# (5) Can we enhance immunogenicity?

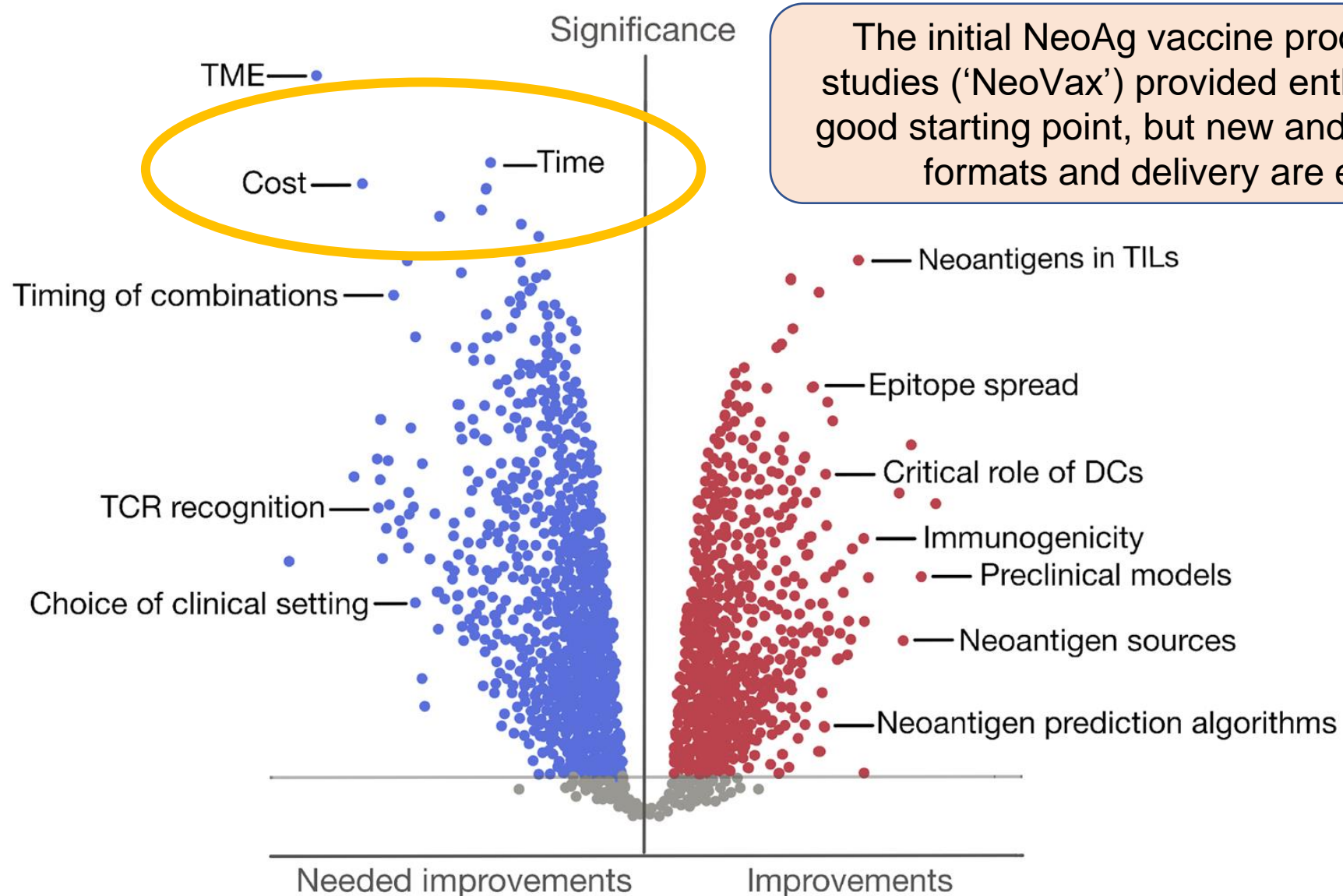


Monitor induction of neoantigen-specific T cell responses



Understand vaccine uptake by APCs in skin

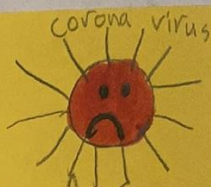
# Getting to 'Nextvax'...





Dear Cathy,

antibodys



I think I have a cure for cancer. so, do you know how the corona virus gets inside the cells? If you could somehow make a nice germ that can get inside the cells, change back the DNA, and get back out safely, then you would have a cure.

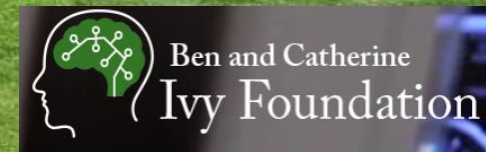
I also think that you should get it in throu a shot. Love, Eleanor



# Applying lessons from the COVID pandemic to the cancer endemic

- Operation WarpSpeed: Demonstration of the impact of laser focus and resources
  - Making the best choices and MOVING
- Justification for heightened focus/resources/cooperation
- How do we approach true prevention?
  - Focus on early disease in cancer or following 'consolidative' therapy
  - Early diagnosis
- Accelerate a team approach
  - Cooperation with regulatory authorities
  - Communication with developers
- Strong cooperation with motivated patients









ARTHUR AND SANDRA IRVING  
**CANCER IMMUNOLOGY  
SYMPOSIUM**

# Mentoring the next generation of cancer immunologists

**JULY 18-22, 2022 | BOSTON, MA**

**[IrvingCancerImmunologySymposium.com](http://IrvingCancerImmunologySymposium.com)**

This working symposium will focus on advancing the careers of young scientists doing research in cancer immunology. ~15 accomplished faculty mentors will share their research career experience in cancer immunology with ~45 promising young scientists (post-docs and starting faculty).

Applicants will be selected by a committee based on the applicant's research achievements and plans and recommendations by their mentors.

**APPLICATION DEADLINE: MONDAY, DECEMBER 20, 2021**

**[irvingcancerimmunologysymposium.com](http://irvingcancerimmunologysymposium.com)**