Developing neoantigen cancer vaccines for personalized immunotherapy

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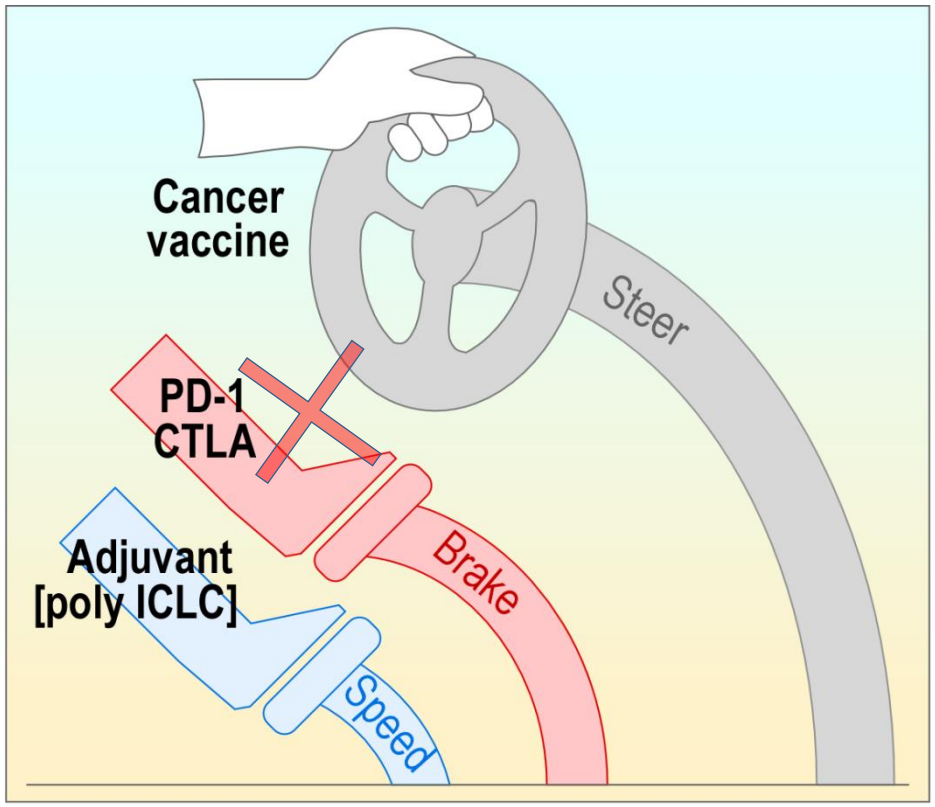
Disclosures

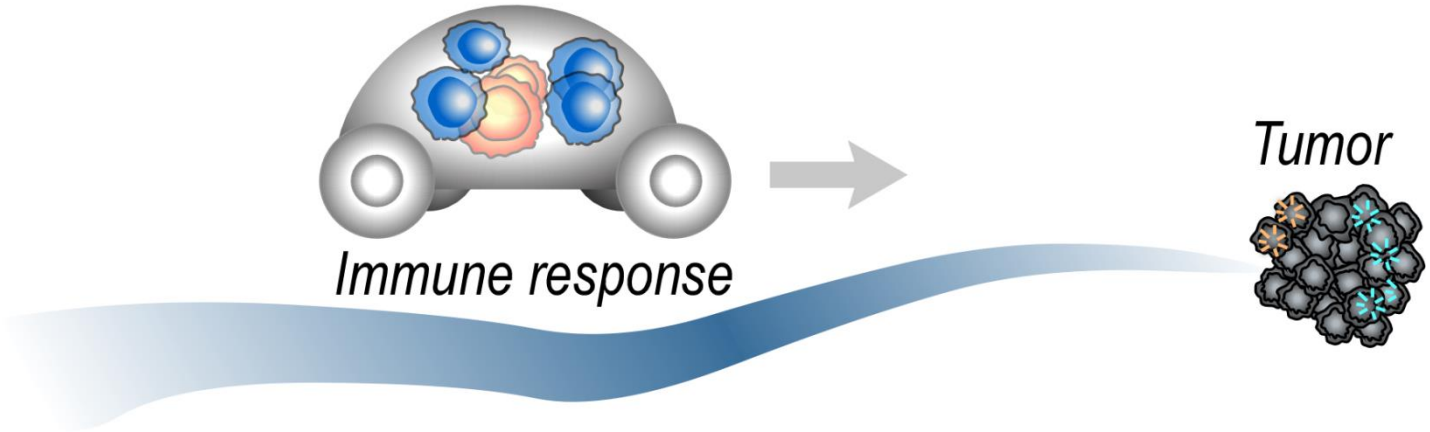
CJW is co-founder of Neon Therapeutics, Inc

2017: Critical questions to address

- How to increase fraction of patients with durable responses?
- How to minimize autoimmunity?



- Expand and broaden the T cell repertoire by inducing tumor-specific T cells
- Generate highly specific anti-tumor immunity with fewer side effects on vital tissues



nature medicine

PERSPECTIVE

Cancer immunotherapy: moving beyond current vaccines

Steven A Rosenberg, James C Yang & Nicholas P Restifo

Great progress has been made in the field of tumor immunology in the past decade, but optimism about the clinical application of currently available cancer vaccine approaches is based more on surrogate endpoints than on clinical tumor regression. In our cancer vaccine trials of 440 patients, the objective response rate was low (2.6%), and comparable to the results obtained by others. We consider here results in cancer vaccine trials and highlight alternate strategies that mediate cancer regression in preclinical and clinical models.

We now know the molecular identities of many tumor-associated antigens, and this knowledge has provided a major stimulus for the development of new immunotherapies for the treatment of patients with solid cancers[1]. In the field of cancer immunotherapy, most enthusiasm has been directed at the use of cancer vaccines—active immunizations designed to treat growing tumors. A recent review of dendritic cell vaccines mentioned 98 published studies involving over 1,000 patients[2]. A tabulation in 2003 listed 216 ongoing vaccine clinical trials in cancer patients[3]. These studies were conducted, and others are underway, despite the absence of convincing animal data that can-

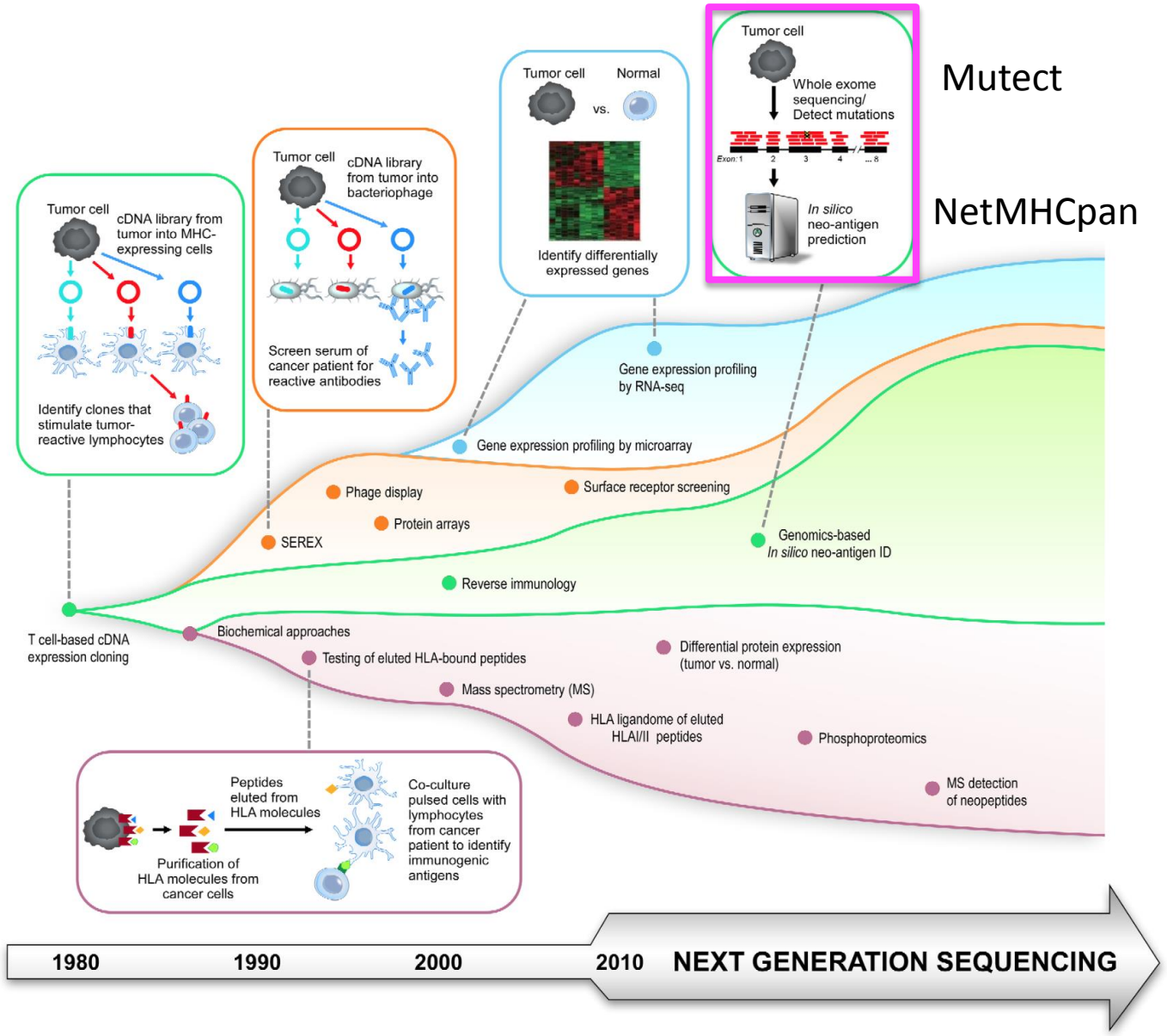
patients who achieved clinical responses, many cancer vaccine trials have been optimistically reported because surrogate or subjective endpoints were achieved. Sensitive techniques such as tetramer or ELISpot assays have been used to demonstrate the generation *in vivo* of antitumor T cells in vaccinated patients, but the scarcity of clinical responses in these patients has made it difficult to validate any of these assays as a useful surrogate of clinical response.

Analysis of trials using standard oncologic criteria

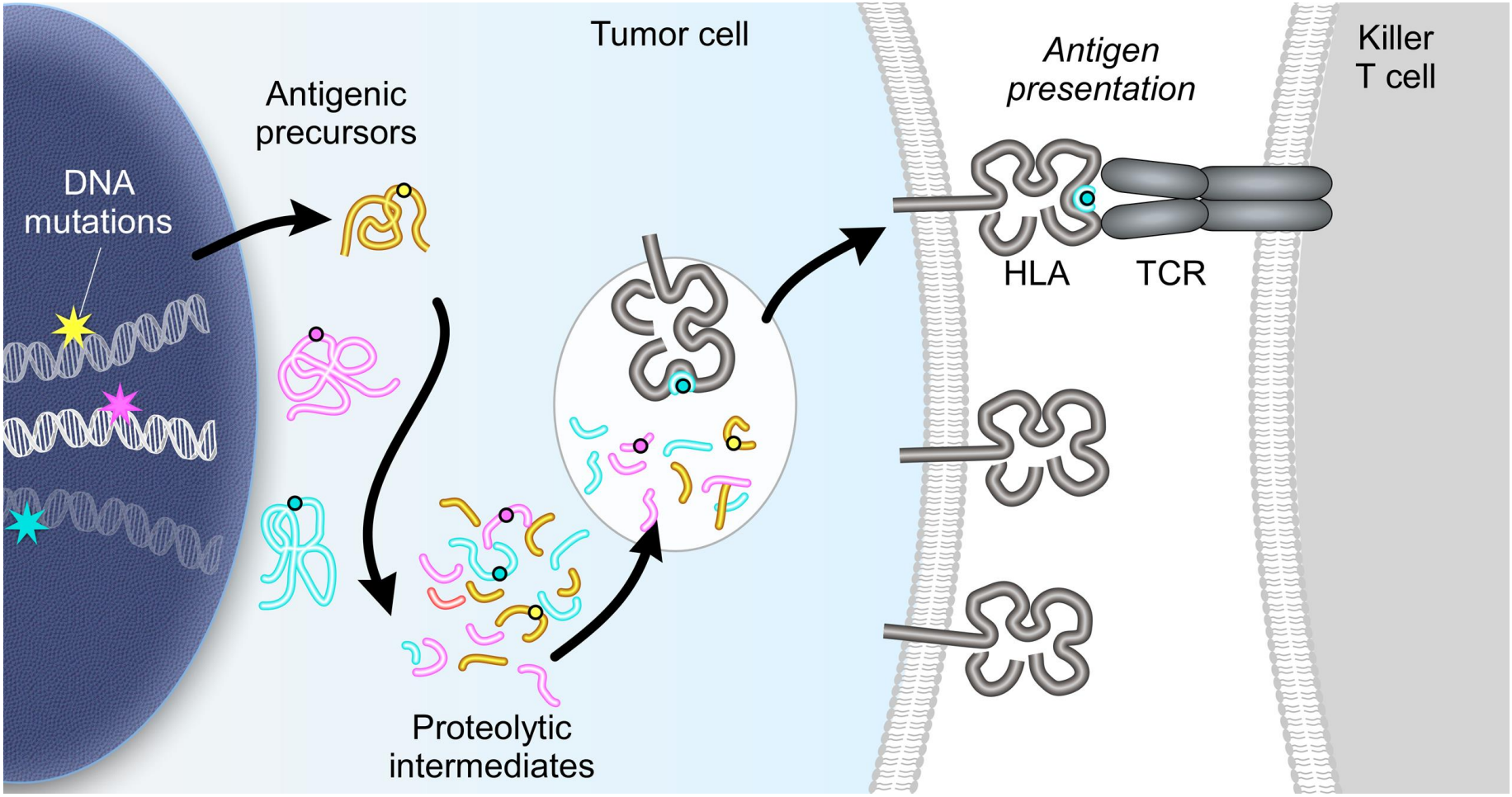
Standard oncologic criteria for evaluating and reporting objective clinical responses to treatment are well established in oncology, and adherence to these guidelines is essential in comparing the results of treatment protocols[6–8]. A set of criteria proposed recently is the Response Evaluation Criteria in Solid Tumors (RECIST): a 30% reduction in the sum of the maximum diameters of lesions to indicate a response, along with the appearance of no new or progressive lesions. The most commonly used definition of objective clinical response, however, is at least a 50% reduction in the sum of the products of the perpendicular diameters of all lesions without the 25% growth of any lesion or the appearance of new lesions. The latter definition has been used in our analysis of our own protocols as well as

Pitfalls of the single antigen-targeting vaccine, and a one size fits all approach

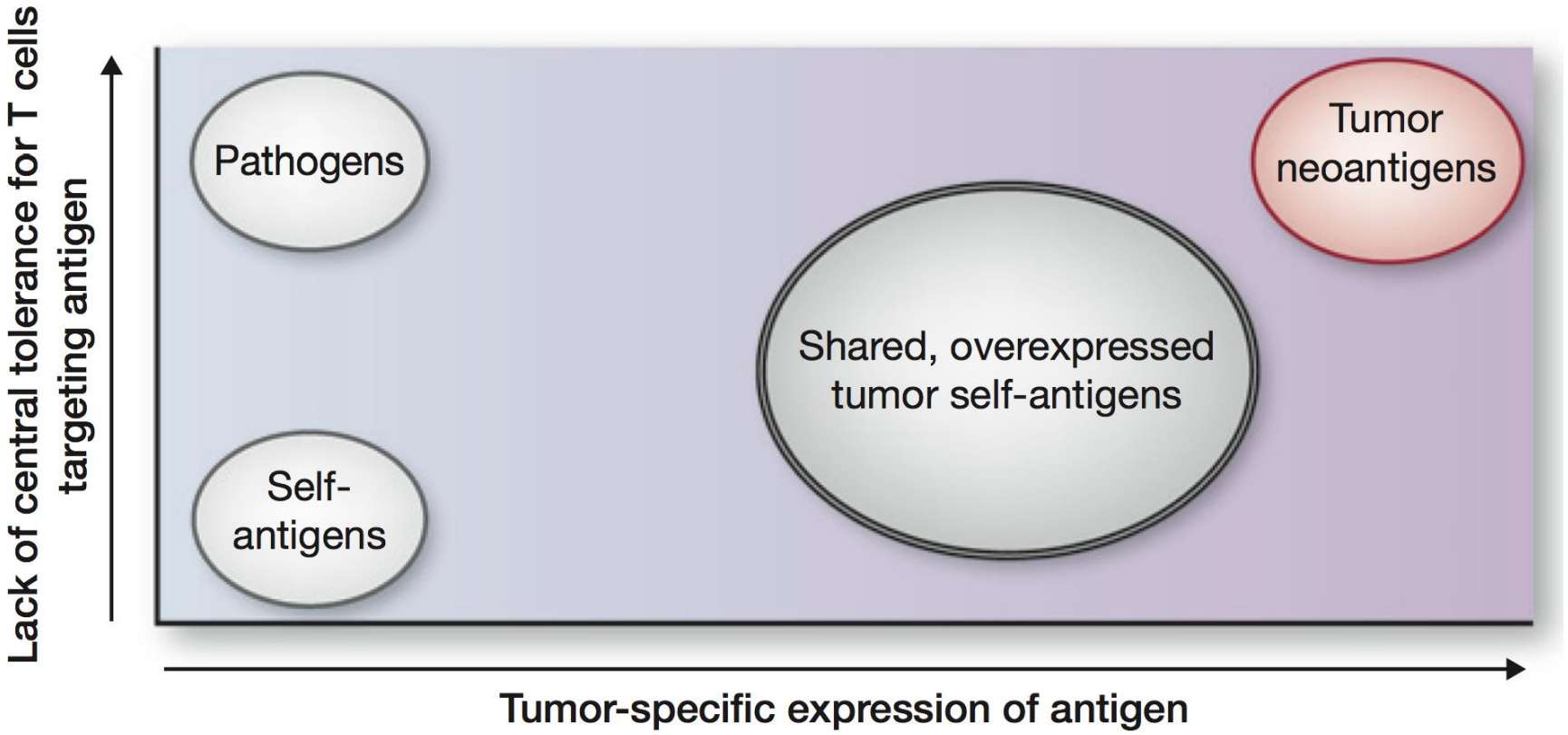
Evolution of methods for antigen discovery



Somatic mutations have the potential to generate neoantigens

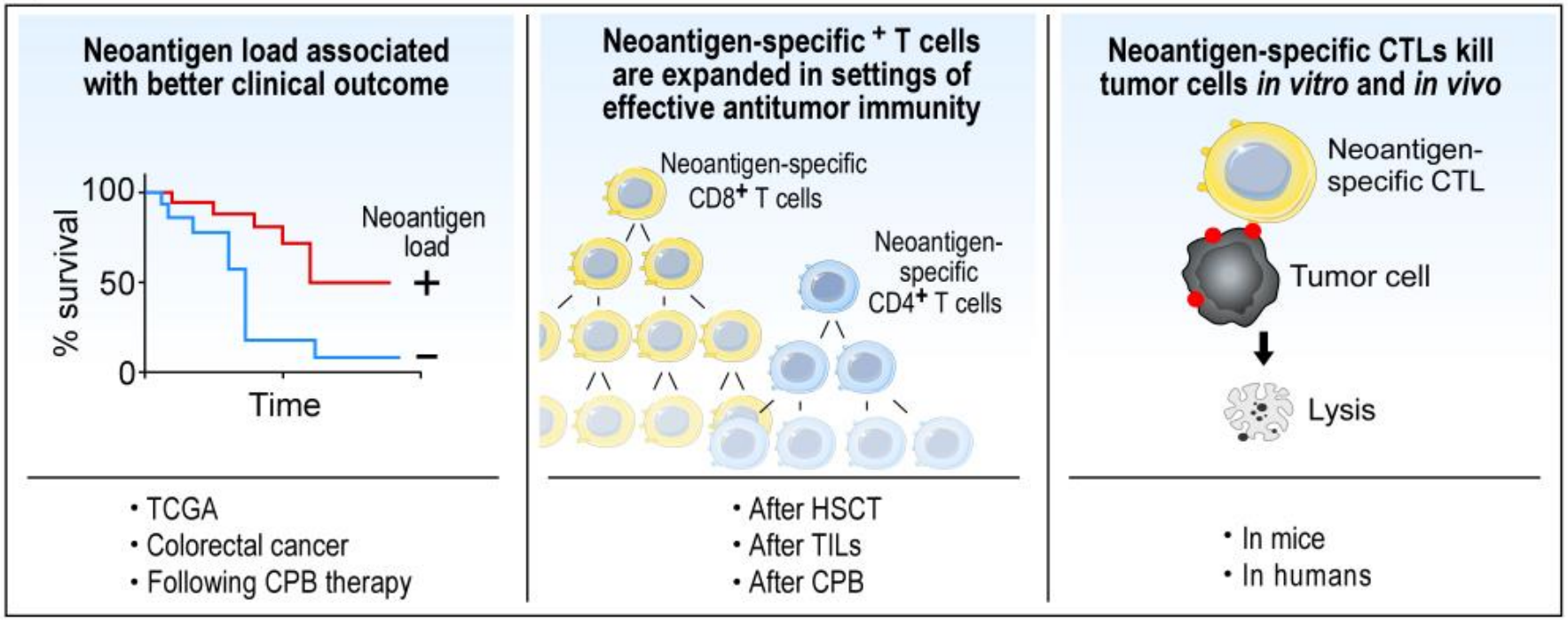


Hitting the “sweet spot”



Hacohen CIR 2013

Growing compelling evidence for neoantigens as effective tumor rejection antigens



Can a personalized cancer vaccine stimulate anti-tumor immunity in humans?

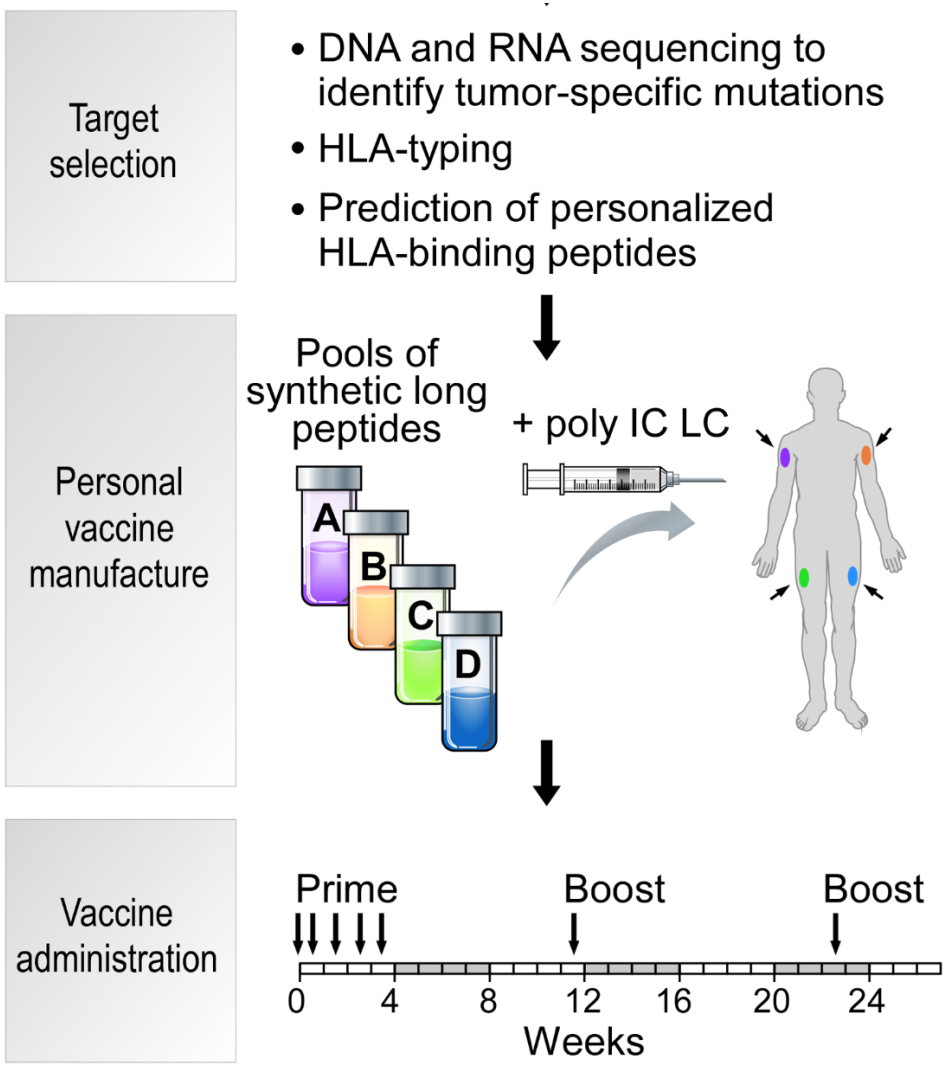
Disease: melanoma

- stage III/resectable

– stage IV

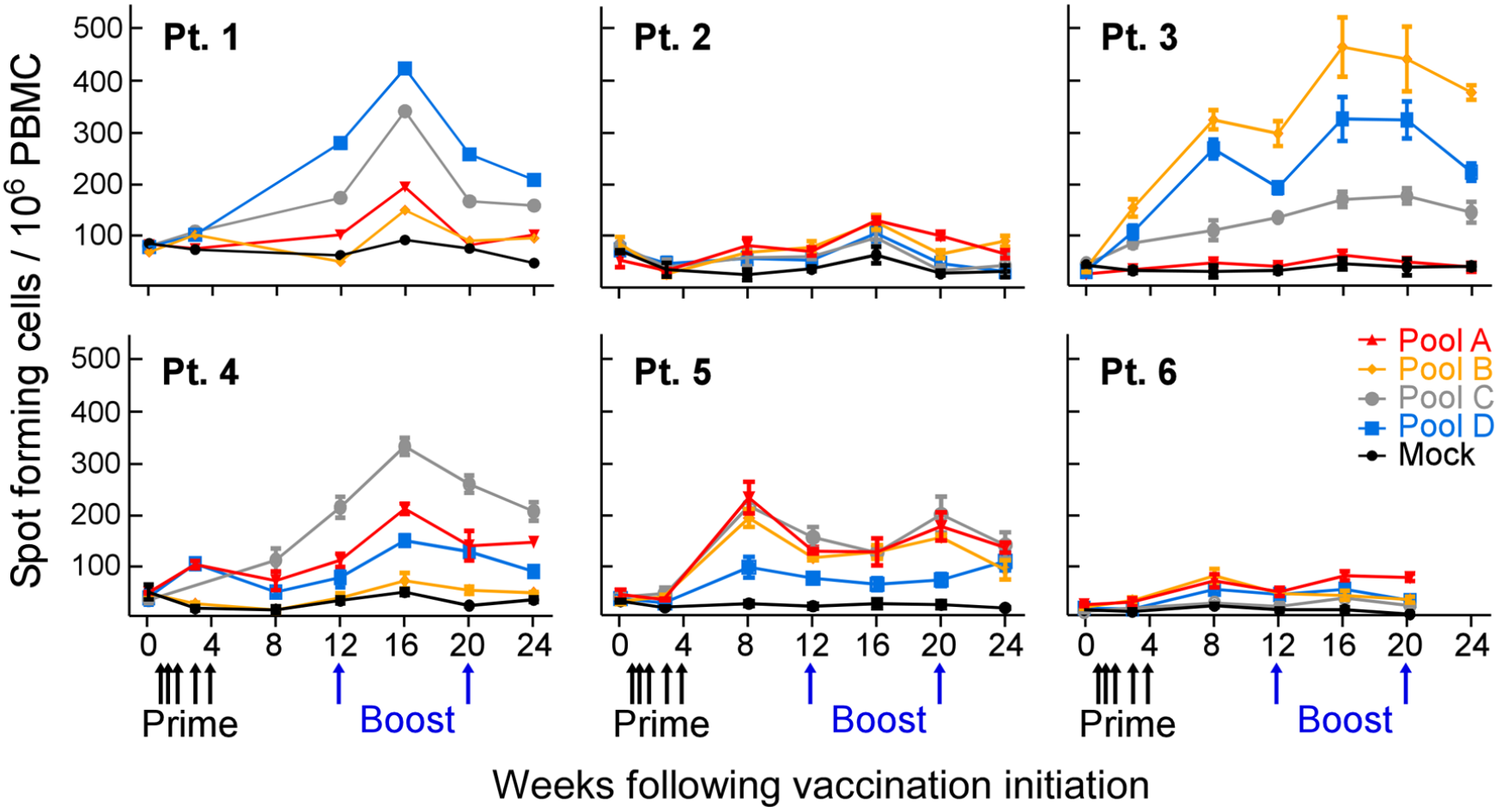
Ott & Hu Nature (2017)

Vaccine: up to 20 personalized neoantigens as SLPs with adjuvant (polyICLC)



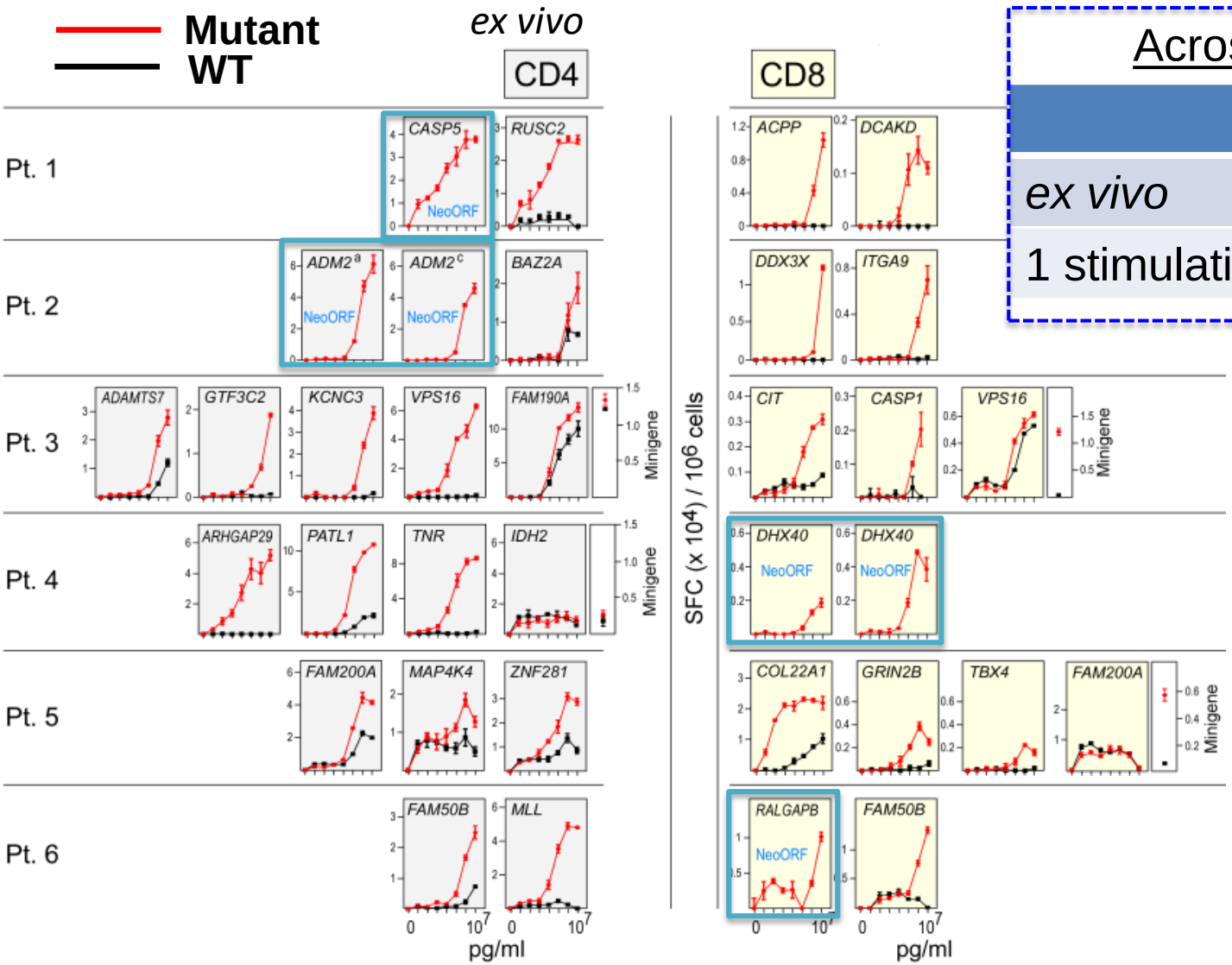
- 11 enrolled
- 8 vaccines generated
- **6 dosed**

The vaccine induces T cells against almost all pools



20% of selected neoantigens induced CD8 T cell responses
>30% of selected neoantigens induced CD4 T cell responses

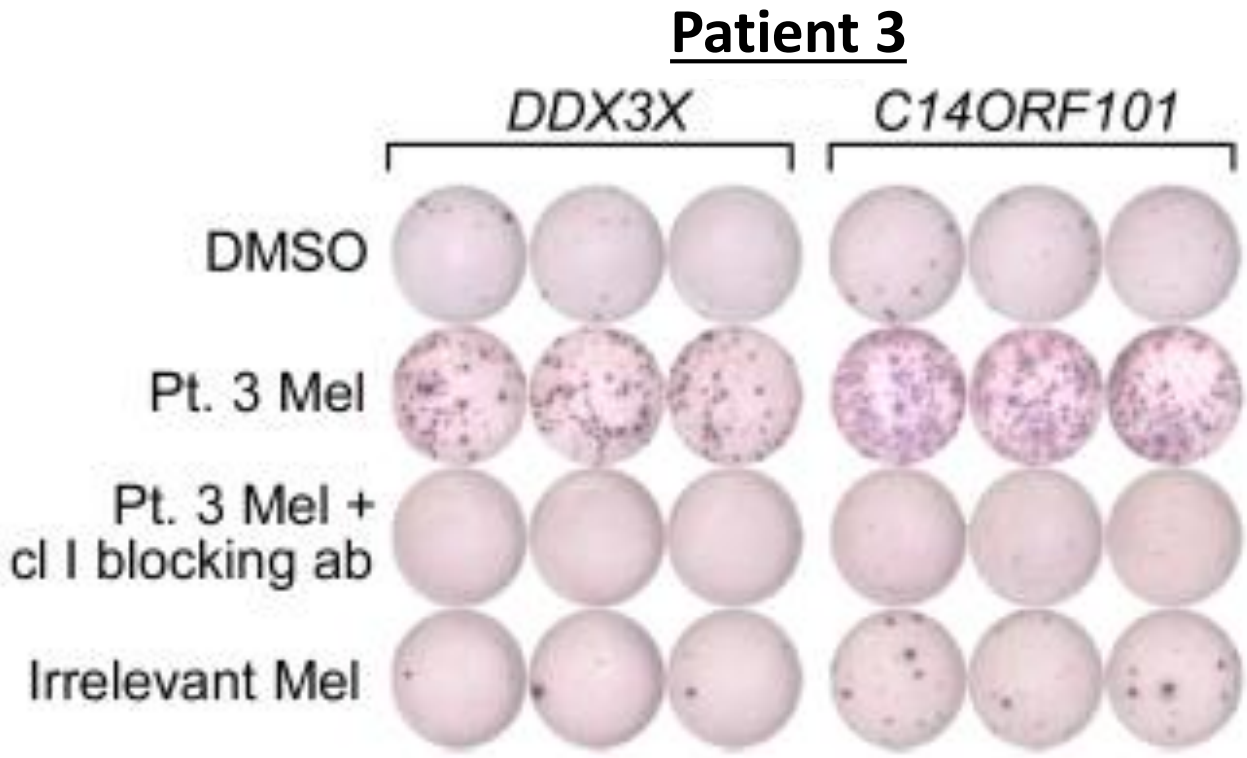
Neoepitope-specific T cell responses are largely restricted to mutated epitopes



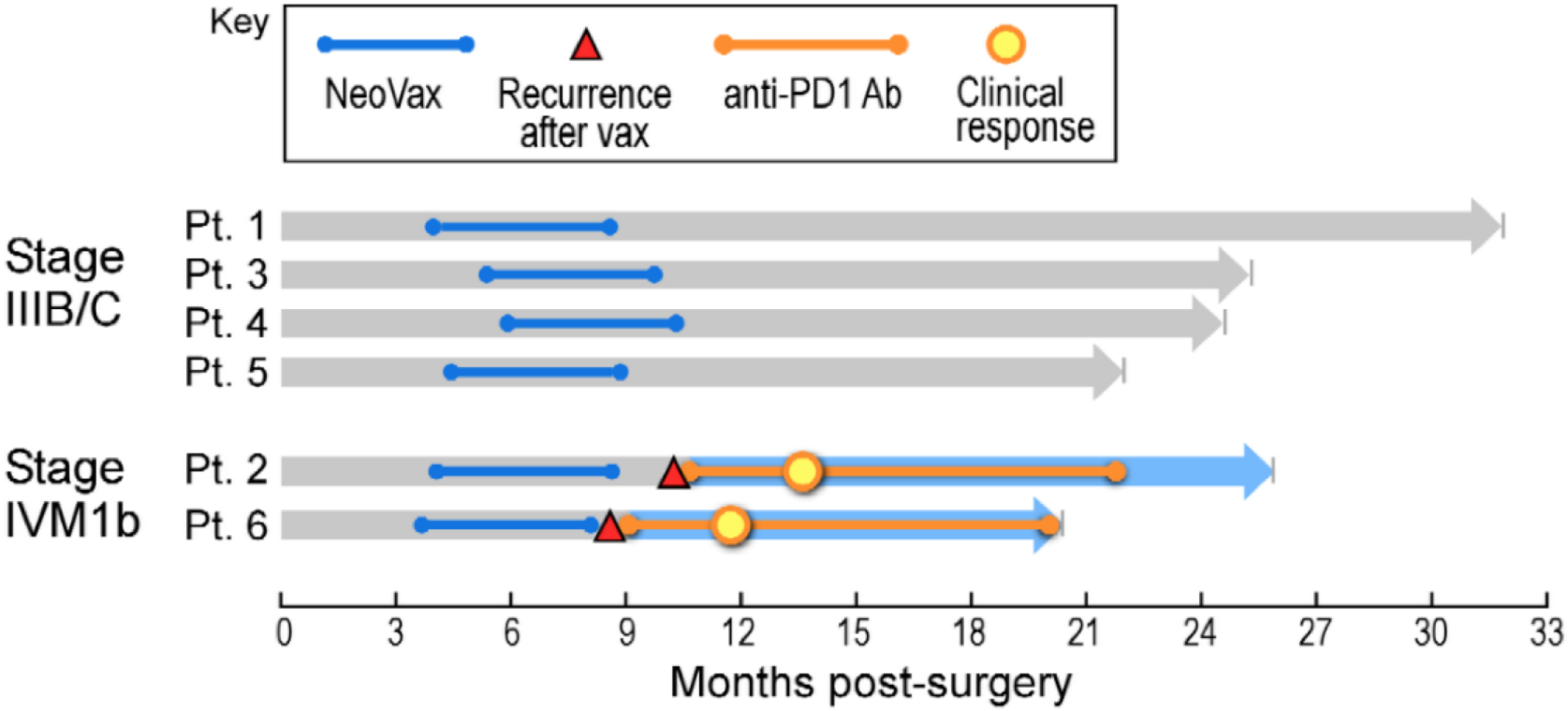
Across 6 patients

	CD4	CD8
ex vivo	18%	0%
1 stimulation	60%	19%

T cells recognize autologous melanoma cells

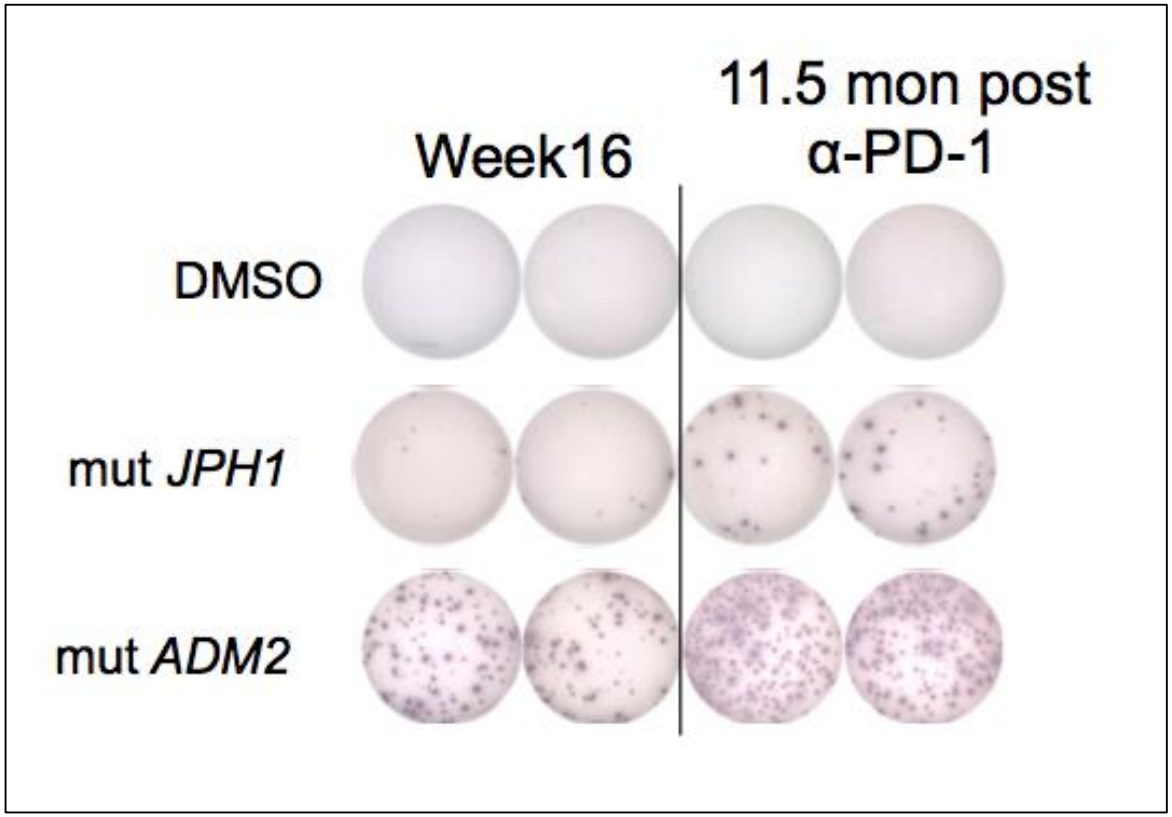


Complete responses with α-PD-1 treatment for 2 patients with progression after Neovax



**The overall response rate in patients with metastatic melanoma is 35-40%; CR rate is 5%.

Enhanced breadth of neoepitope-specific T cell responses after Neovax and α-PD-1 treatment



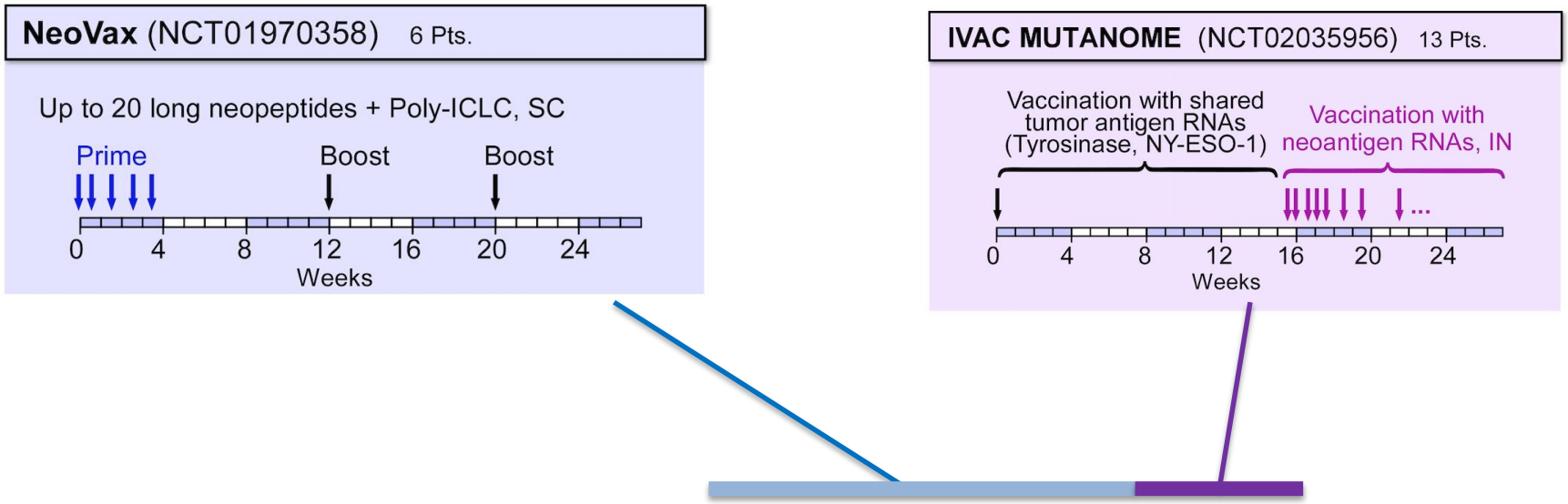


Table 1. Summary of Neoantigen Vaccines

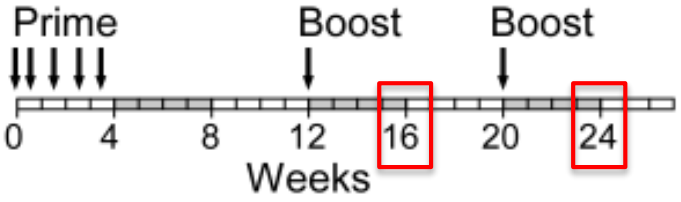
	Ott *et al.* [4]	Sahin *et al.* [3]
No. of patients	6	13
Vaccine	Synthetic peptide+ poly IC:LC	RNA
Administration route	Subcutaneous	Intranodal
Epitope length	15–30 aa	27 aa
No. of epitopes/patient	13–20	10
No. of doses	7	8–20
Immunogenicity (total no. peptides tested)	91 peptides	125 epitopes
$CD8^+$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

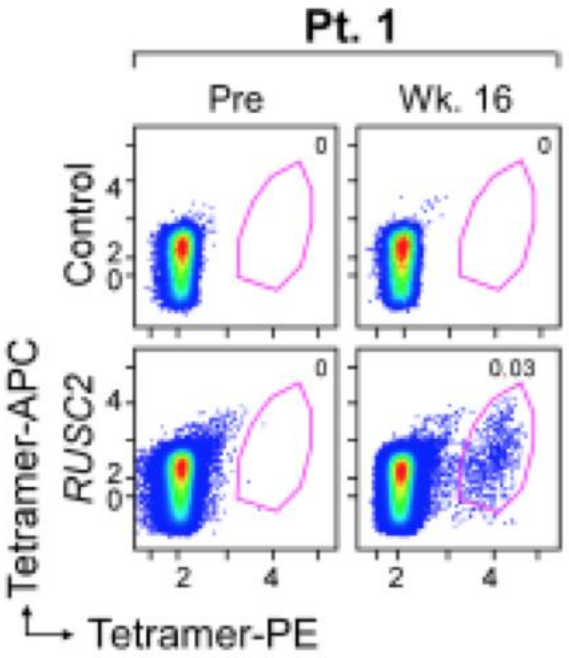
Linette & Carreno Trends in Molecular Medicine (2017)

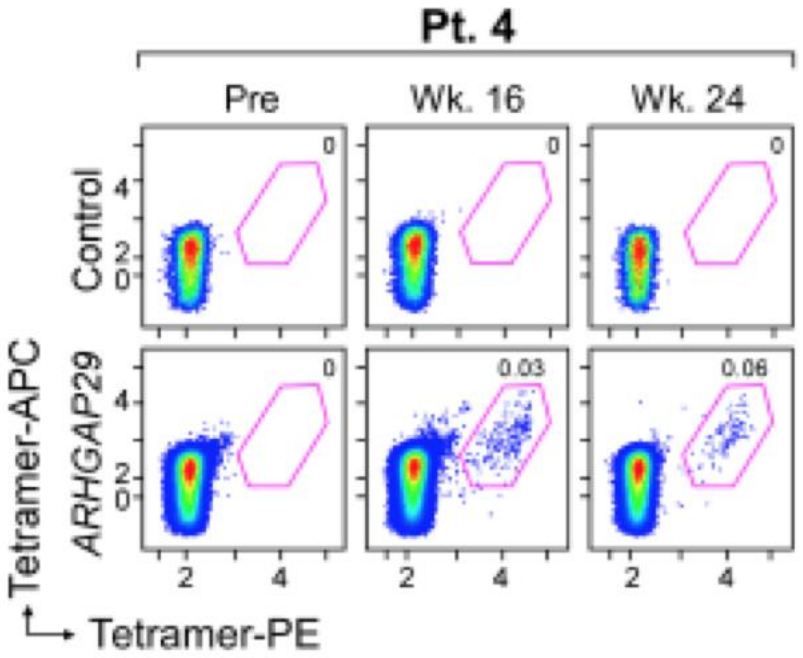
Do neoantigen-specific CD4+ T cells change their state with vaccination?

scRNAseq of neoantigen-specific CD4+ T cells



- Single cells sorted into 384 well plates
  - Pre: CD4+ cells
  - Post: Class II tetramer+ cells
- CELseq2 for scRNAseq



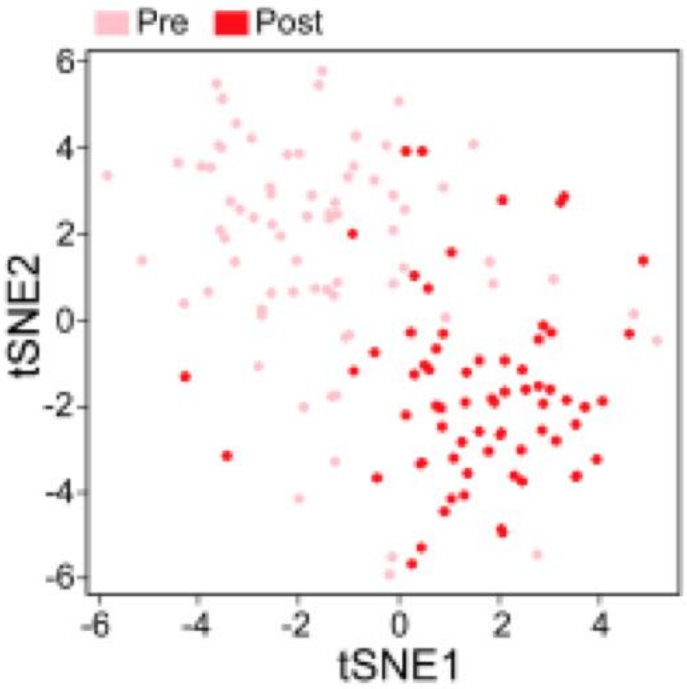


Adrienne Luoma
Kai Wucherfennig

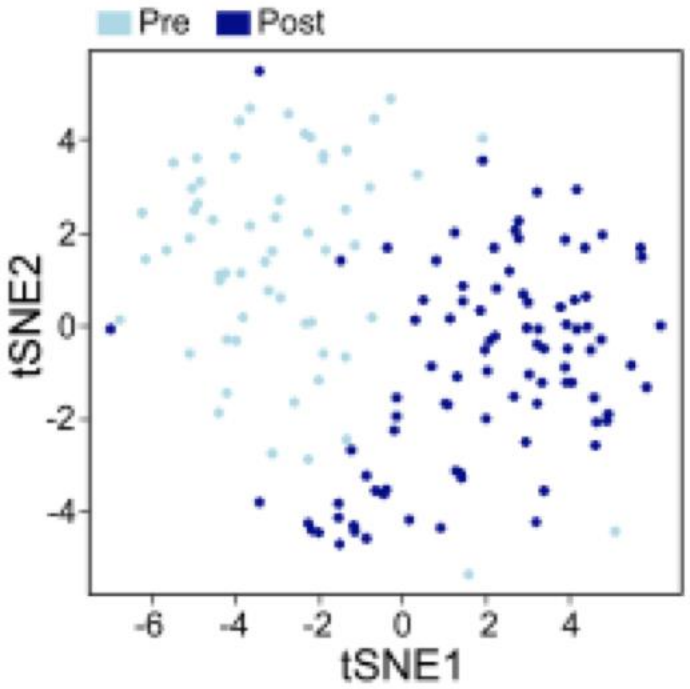
Major shifts in gene expression post-vax

- Shutting off of genes that promote naïve T cell homeostatic survival (*IL7R*) and fate (*FOXP1*)
- Upregulated: genes involved in energy metabolism needed for cell proliferation and growth (*SLC2A3*)

Patient 1

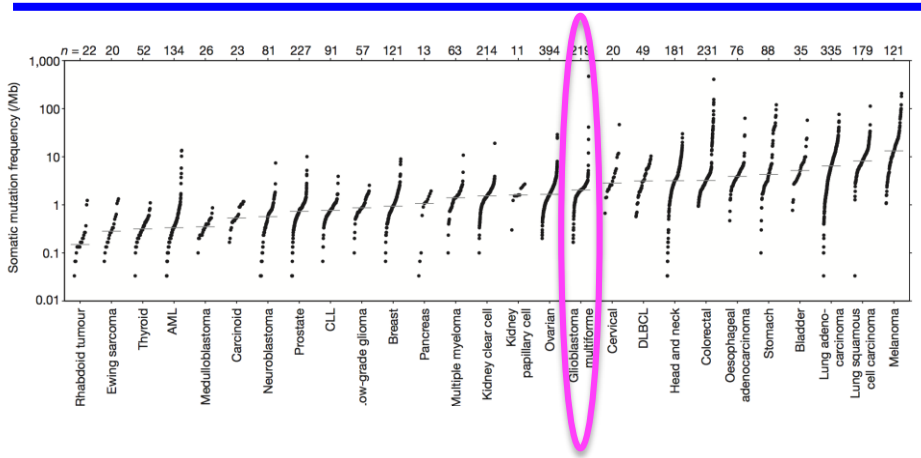


Patient 4

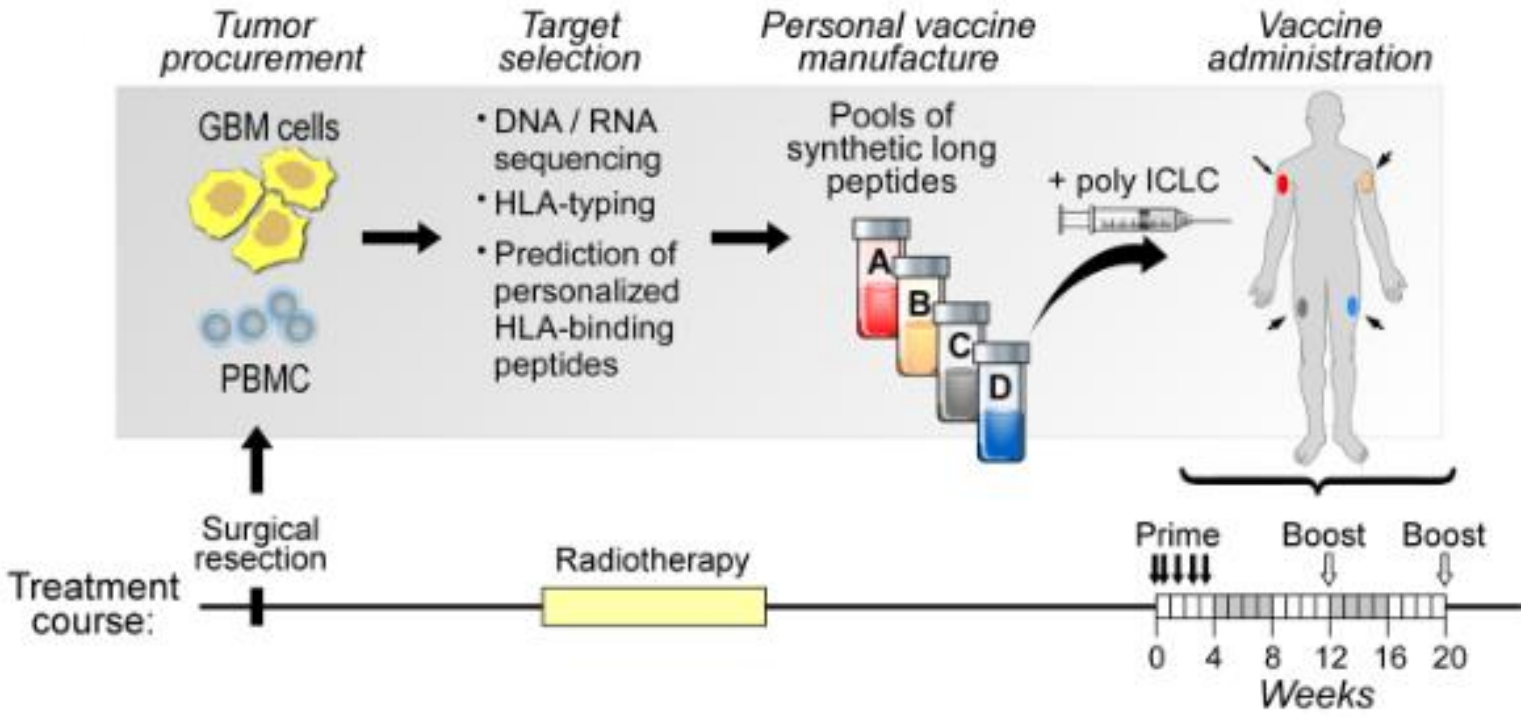


Can such a vaccination approach be tested in lower mutation rate tumors?

Testing Neovax in a lower mutation rate tumor and within context of SOC therapy: GBM

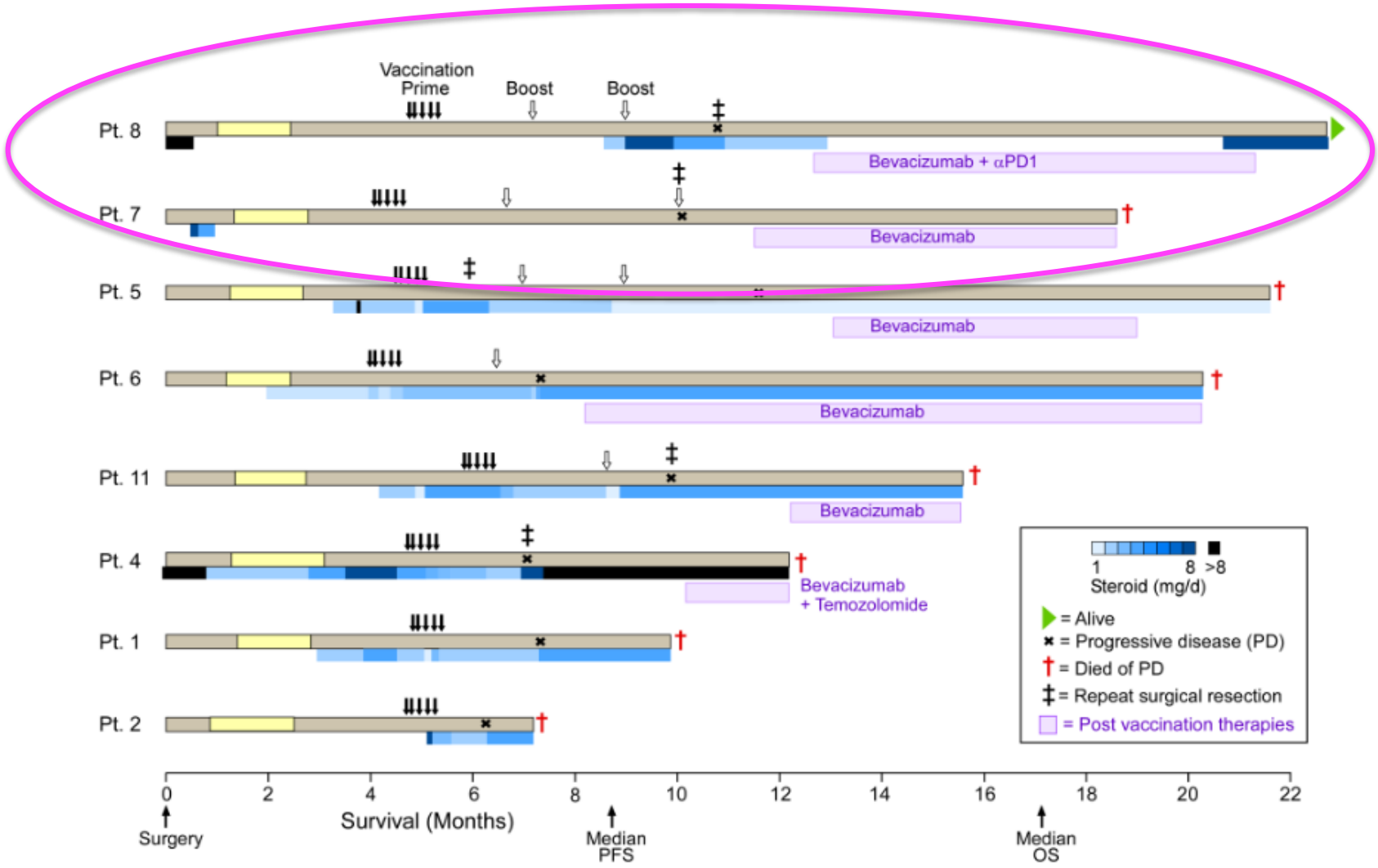


Lawrence , Getz Nature 2013

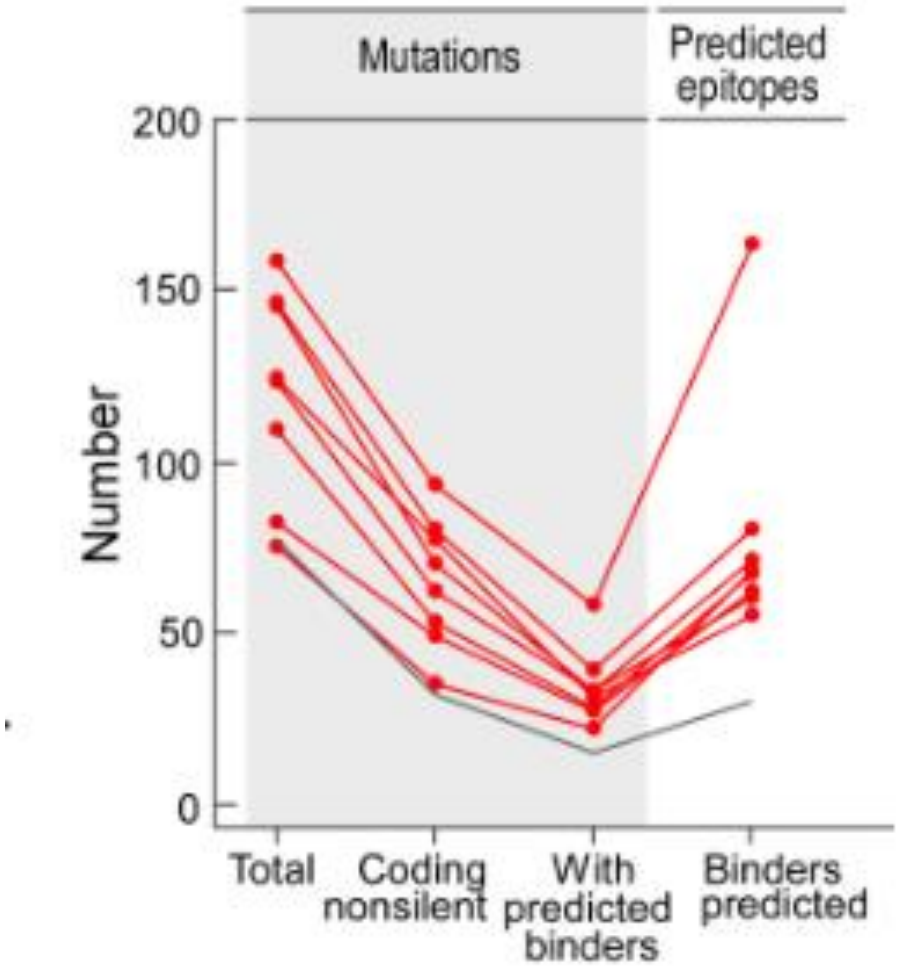


A more challenging study cohort….

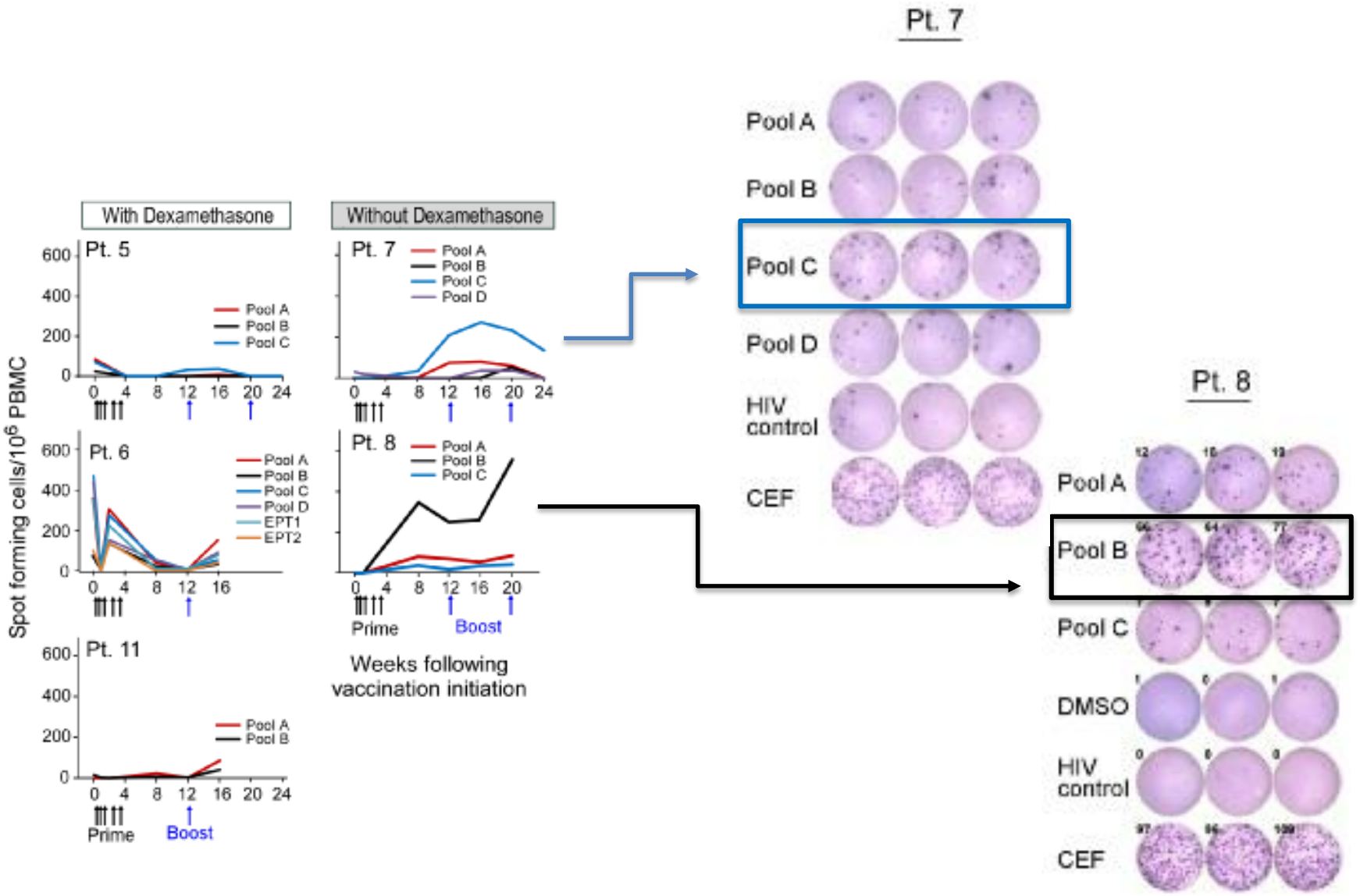
- 11 enrolled; 8 vaccines generated and dosed



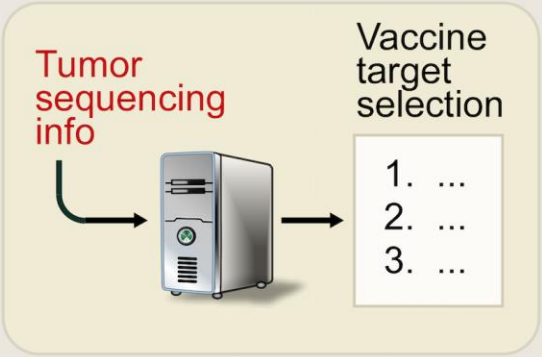
With fewer neoantigen targets….



But circulating neoantigen-specific responses still detected

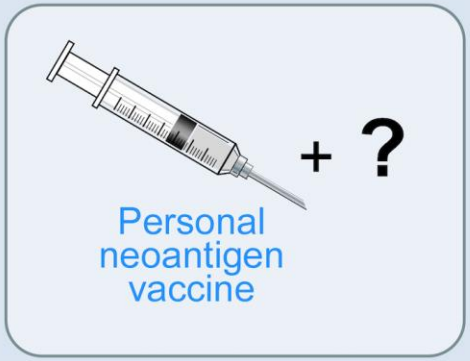


Improving antigen prediction



- Mass spectrometric detection of presented antigens on tumor
- Improved MHC class I/II epitope prediction
- Understanding antigen processing
- Identifying additional classes of somatic alteration

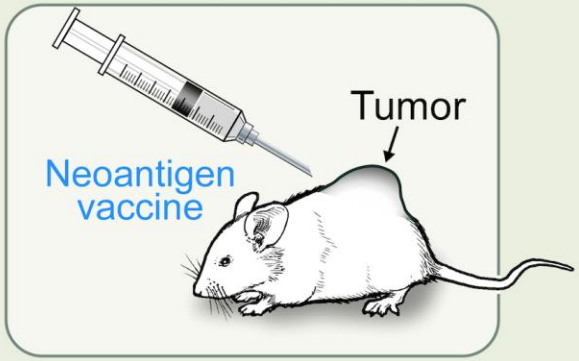
Developing combination therapy



With

- CPB
- Agonistic antibody
- Radiotherapy
- Chemotherapy
- Targeted inhibitors

Developing and using pre-clinical models



To re-evaluate

- Formulation
- Adjuvant
- Delivery
- Dose
- Schedule
- Route

Can we improve prediction of cancer neoantigen targets?

Jenn Abelin

Derin Keskin

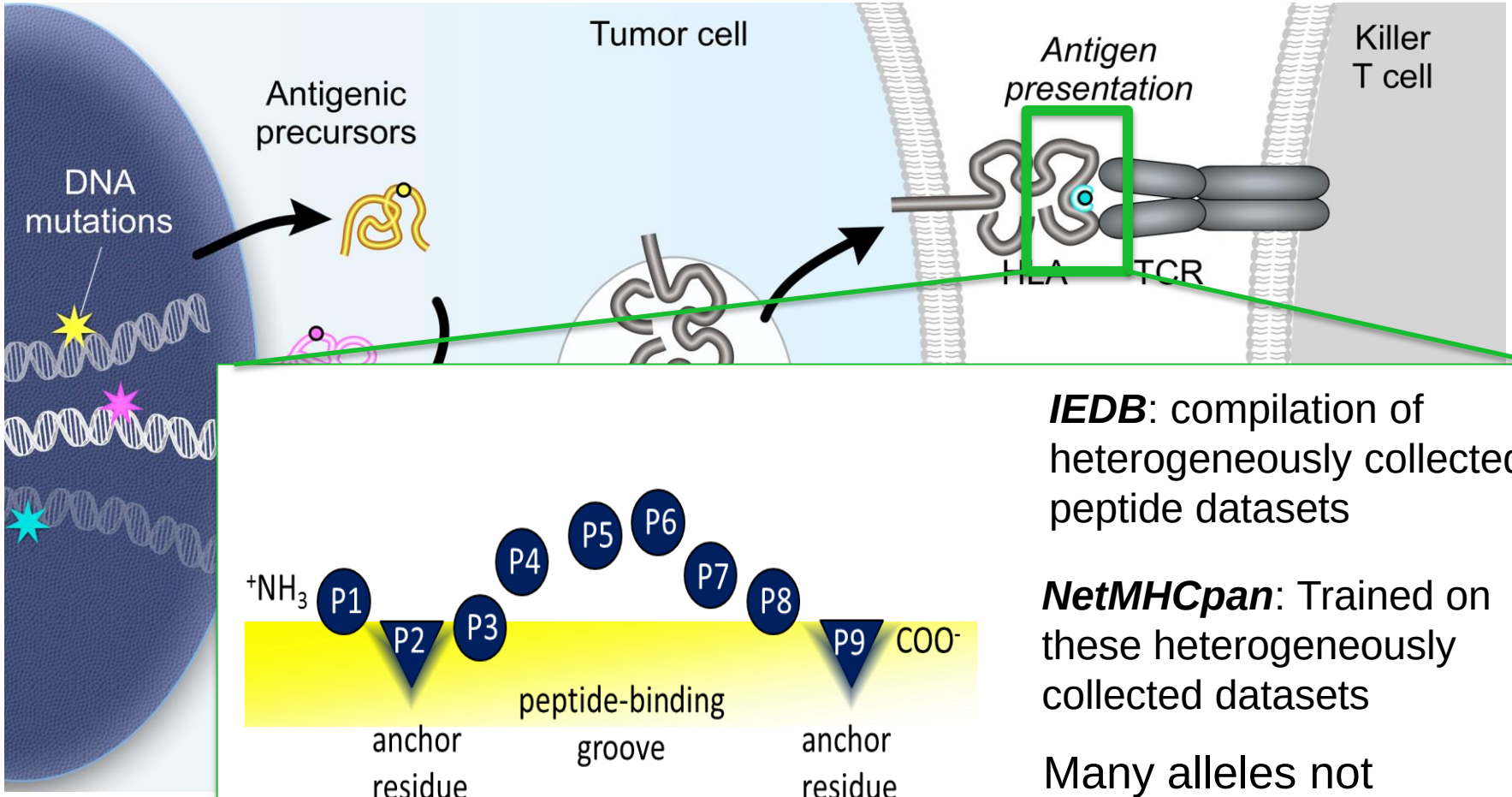
Sisi Sarkizova

Steve Carr

Nir Hacohen

Mike Rooney

Somatic mutations have the potential to generate neoantigens

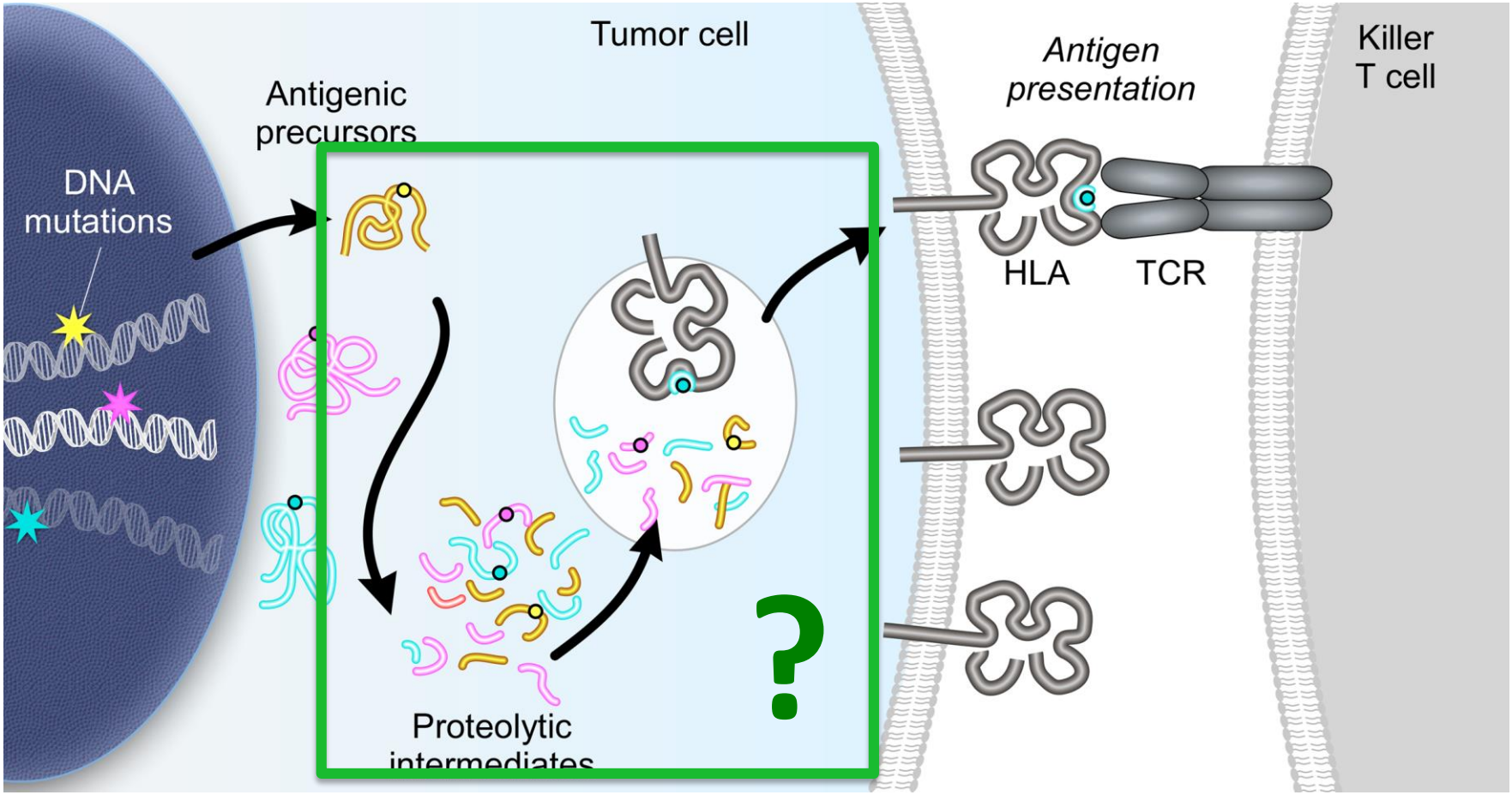


IEDB: compilation of heterogeneously collected peptide datasets

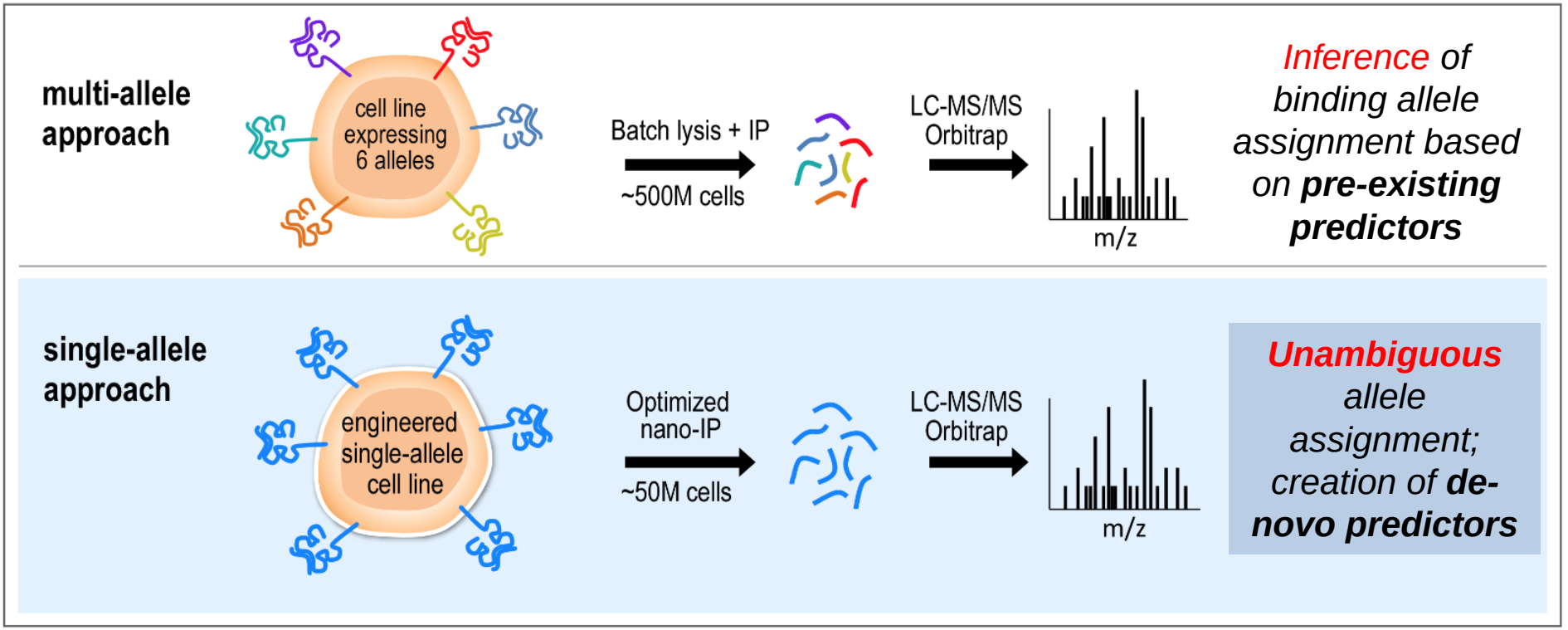
NetMHCpan: Trained on these heterogeneously collected datasets

Many alleles not covered

Somatic mutations have the potential to generate neoantigens



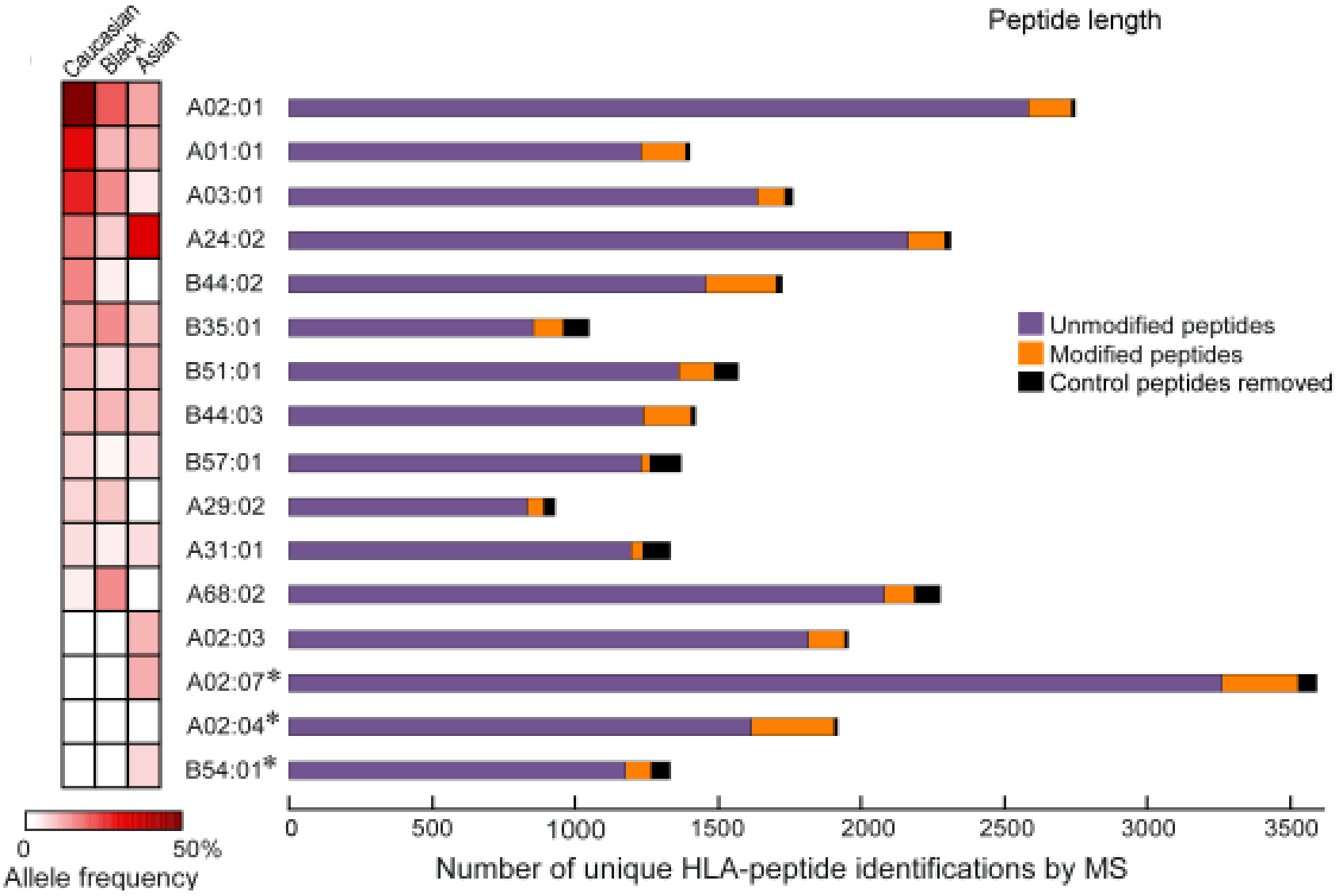
Single- vs *multi-* allele HLA peptide sequencing by MS



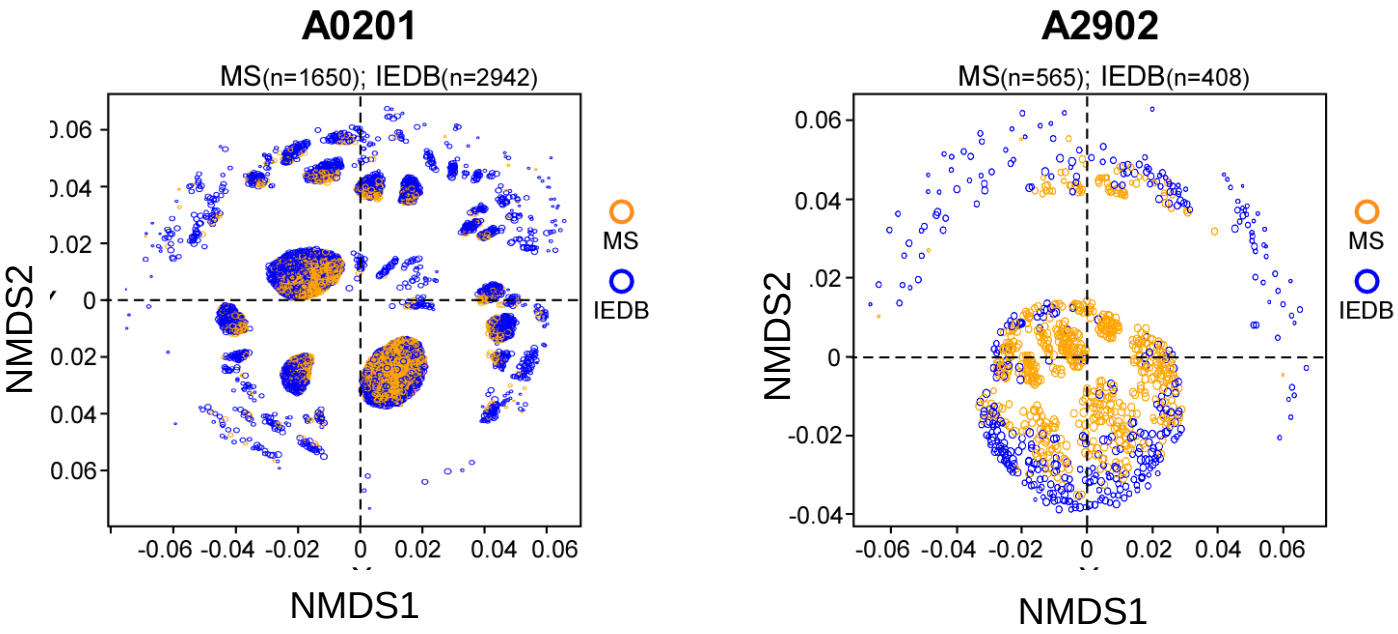
- Single HLA allele
- 10x lower sample input
- Advances in instrumentation
- Improved search strategies

Abelin Keskin & Sarkizova
Immunity 2017

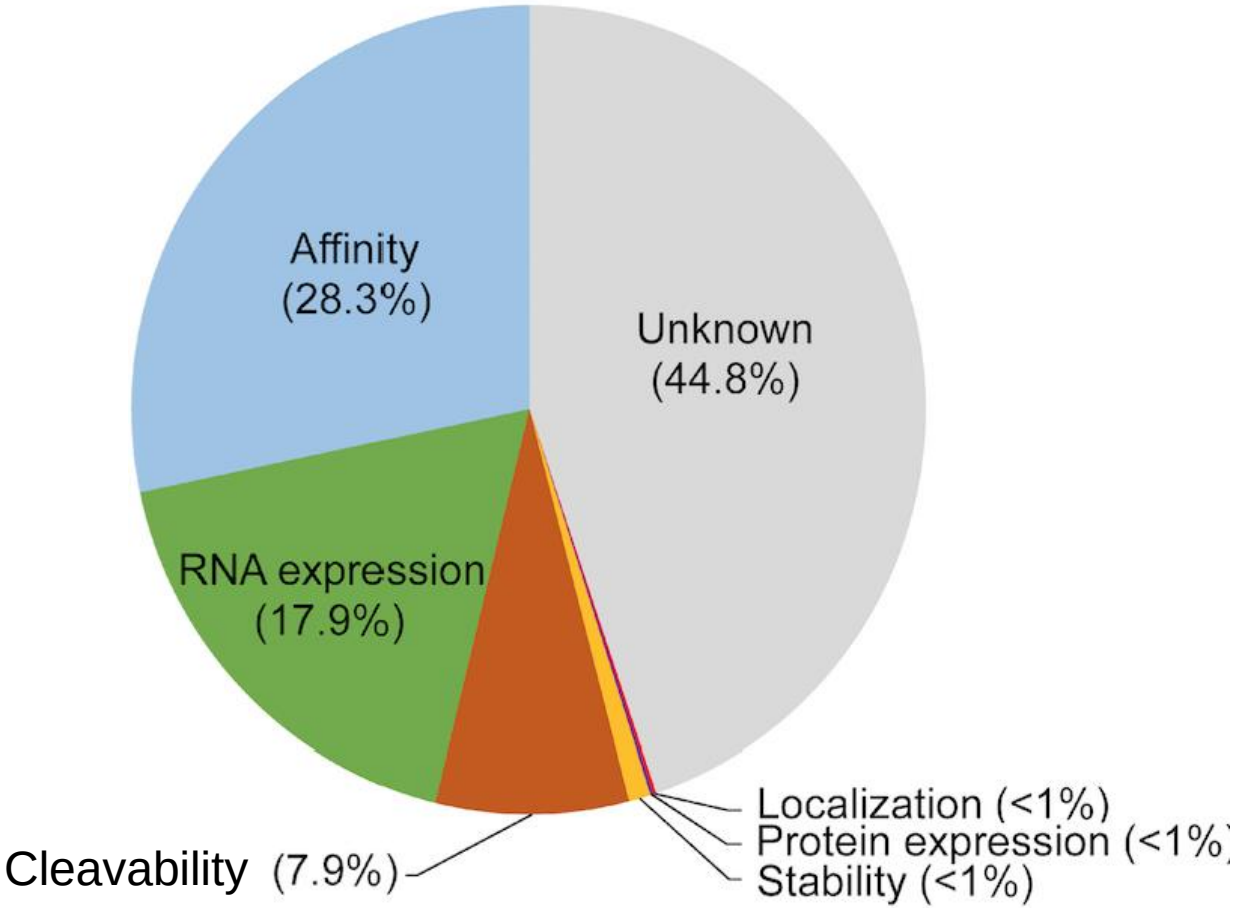
>24,000 HLA-associated peptides identified for 16 alleles



Identification of new peptide motifs

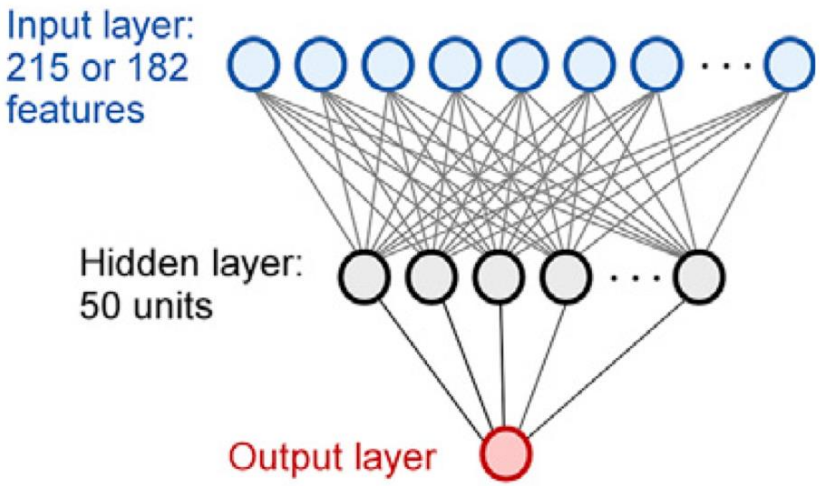


Quantitative contributions of expression, localization, cleavage



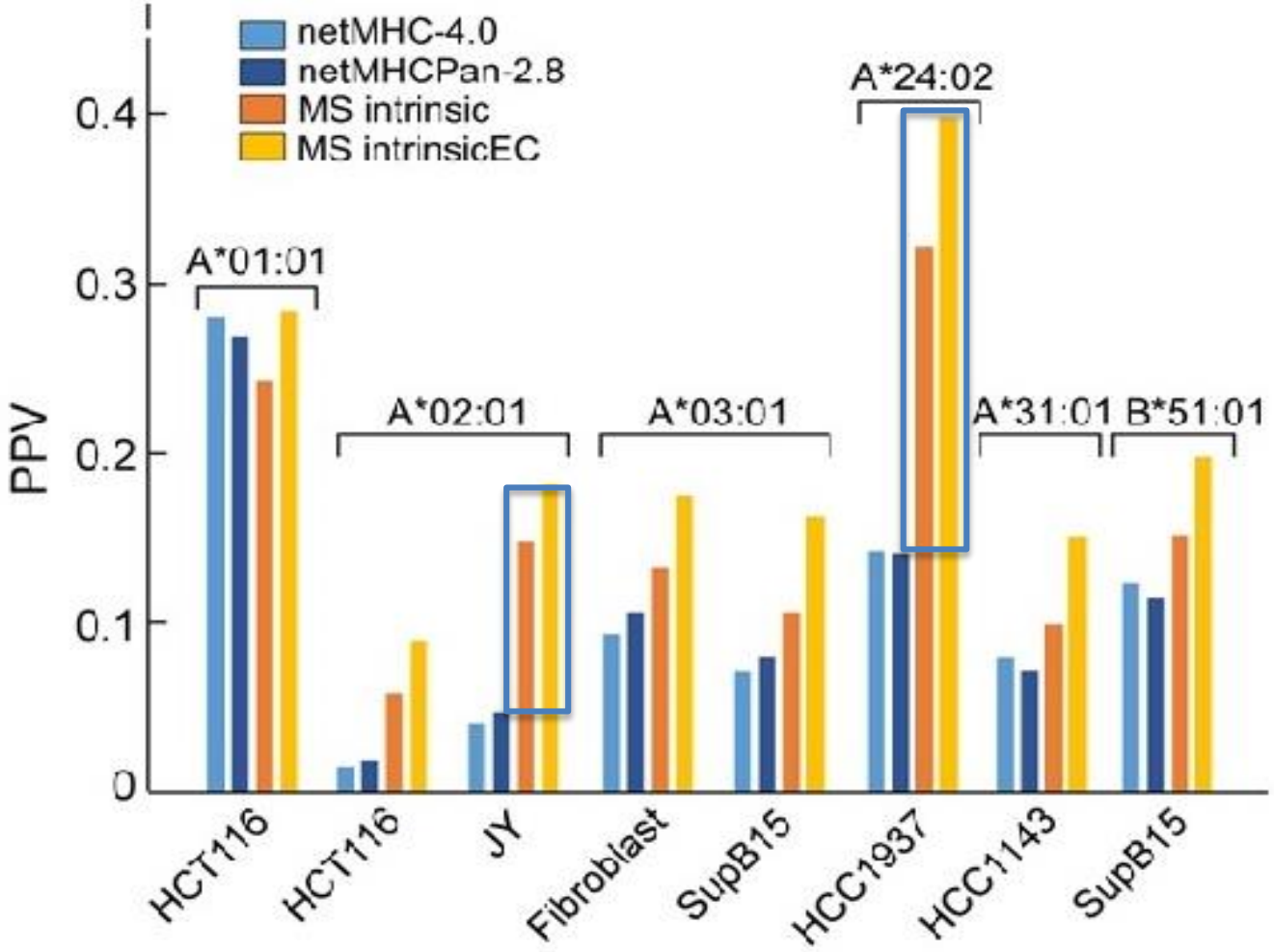
Building a new predictor

- Neural network models

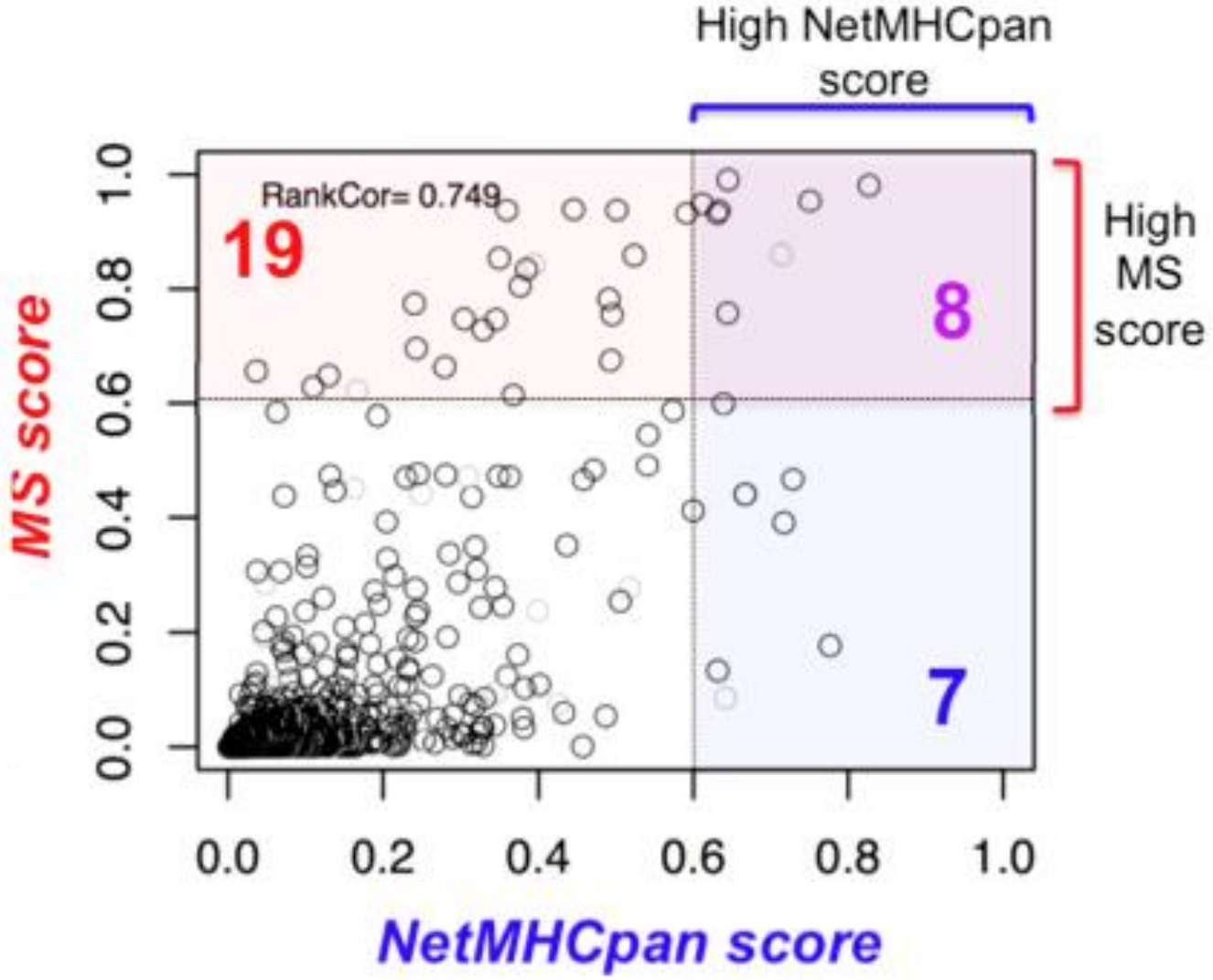


- 2 types of ensemble models –
  - Peptide intrinsic features only
  - Peptide intrinsic + extrinsic features (expression and cleavability)

Novel predictors based on single-allele MS data outperform NetMHC on external datasets



Patient 1


High NetMHCpan score
High MS score
RankCor= 0.749
19
8
7
MS score
NetMHCpan score
0.0
0.2
0.4
0.6
0.8
1.0

Summary

- Next-generation sequencing capabilities now enable systematic mining of the genome for potential neoantigens as well as characterization of the immune context
- Tumor neoantigens appear to be an important class of immunologic targets against which tumor-specific responses can be generated
- Phase I clinical trial: safe, feasible and capable of eliciting strong T cell responses in a clinical setting unconfounded by prior or intercurrent therapy
- On the horizon: combination with CPB and improved prediction algorithms

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