Modeling the Fitness Costs of Neoantigens

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11.12.17

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Modeling neoantigen driven evolution

Neoantigen:

– a novel, mutated peptide
– presented by MHC I
– potentially “immunogenic” – recognized by T-cell receptors

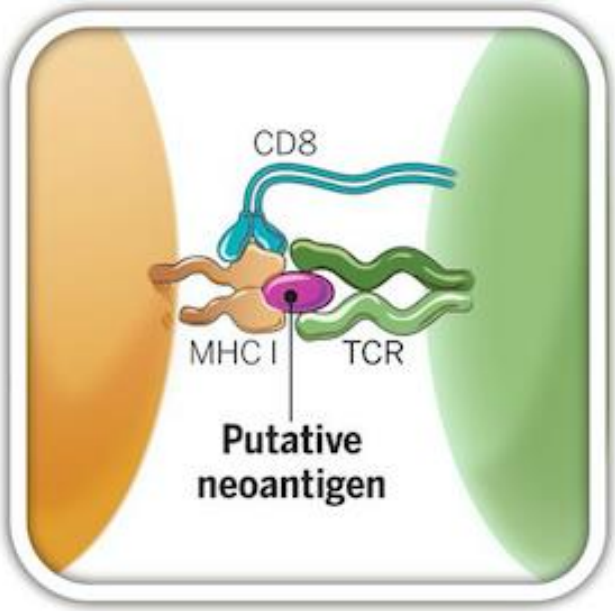


figure adapted from Schumacher & Schreiber, *Science*, 2015

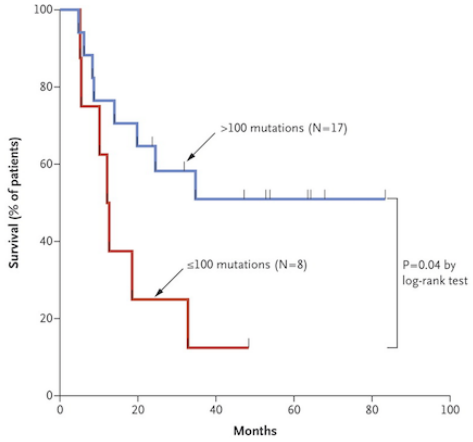
How can we (and others) help?

- These are **physical interactions** that support use of **computationally intensive biophysics**
- Physics “inspired” approaches can help – use of **statistical physics** in machine learning
- Other route (taken here) is to build **minimal (“simple”) models informed by underlying biophysical processes** and experimentally derived features to test hypotheses, make predictions, and design further experiments

Genomic correlates of response

What determines patient's response to therapy?

- Highly mutated tumors respond better [Snyder et al. 2014, Rizvi et al. 2015, Van Allen et al. 2015, Riaz et al. 2017]



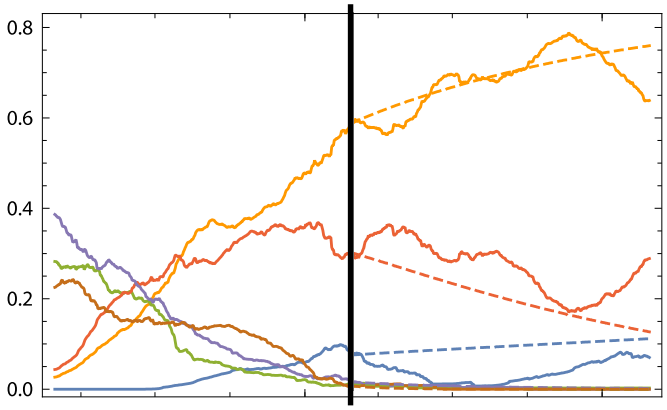
[Snyder et. al. NEJM 2014]

- Tumor heterogeneity may have negative impact on therapy success [McGranahan et al., 2016]
- Other markers such as information from the microenvironment

- **Goal: Integrative mathematical framework reflecting these features**

Fitness model predicts dominant influenza strain

- Clonal frequency predictions for WHO (example of prediction from February 2014)



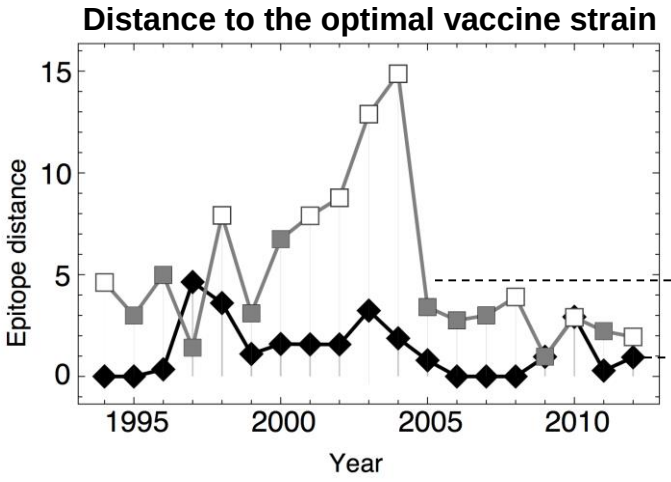
prediction start date: Feb 28th 2014

Prediction period: one year

prediction

validation

- Vaccine strain selection



WHO vaccine strains

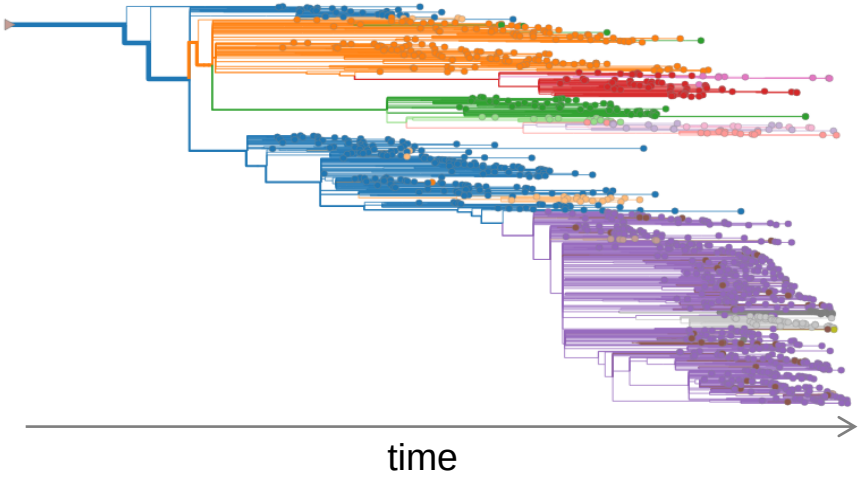
model-based vaccine strains

Łuksza, Lässig, *Nature*, 2014

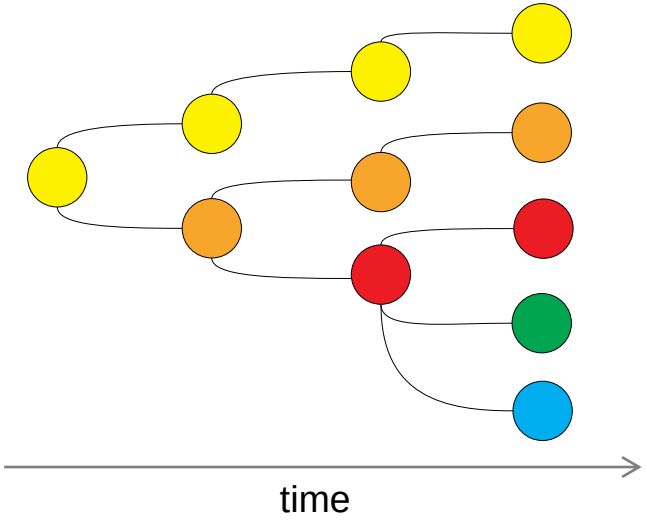
Different principles for checkpoint therapy

(with Marta Łuksza, IAS)

Influenza



Cancer

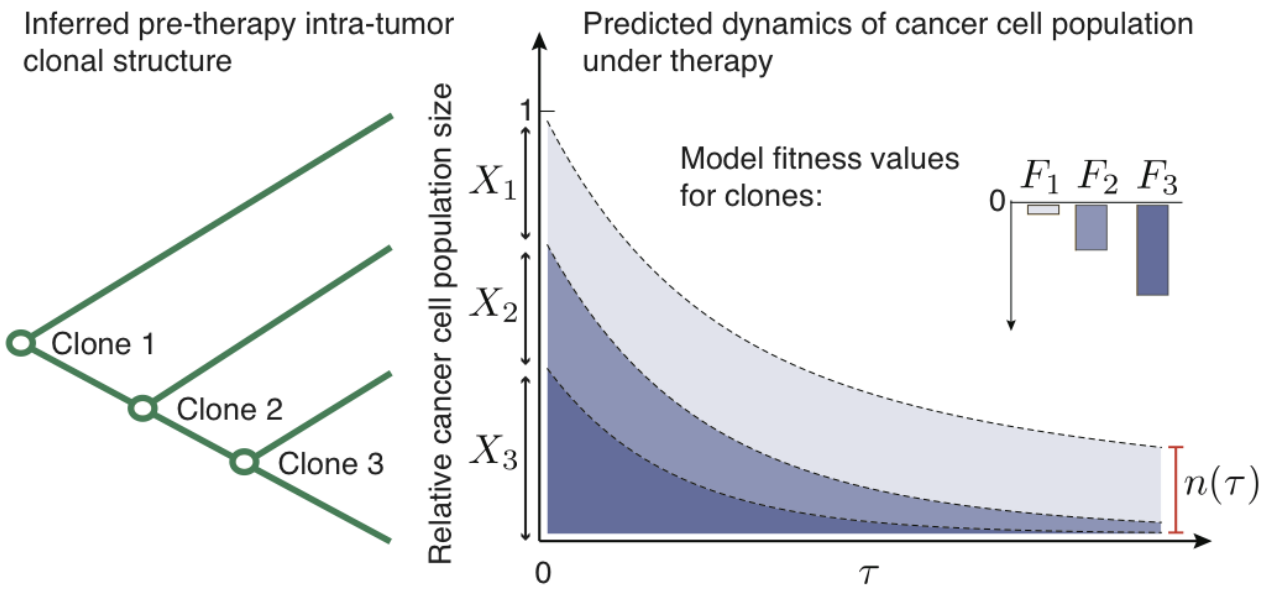


Differences:

Physical fitness interaction: B-cells with known viral epitopes versus T-cells with putative neoantigens

Distribution of fitness effects over tree: Which clone will win competition versus can all clones be suppressed?

Neoantigen driven tumor evolutionary dynamics



$$n(\tau) = \sum_{\alpha} X_\alpha \exp[F_\alpha \tau]$$

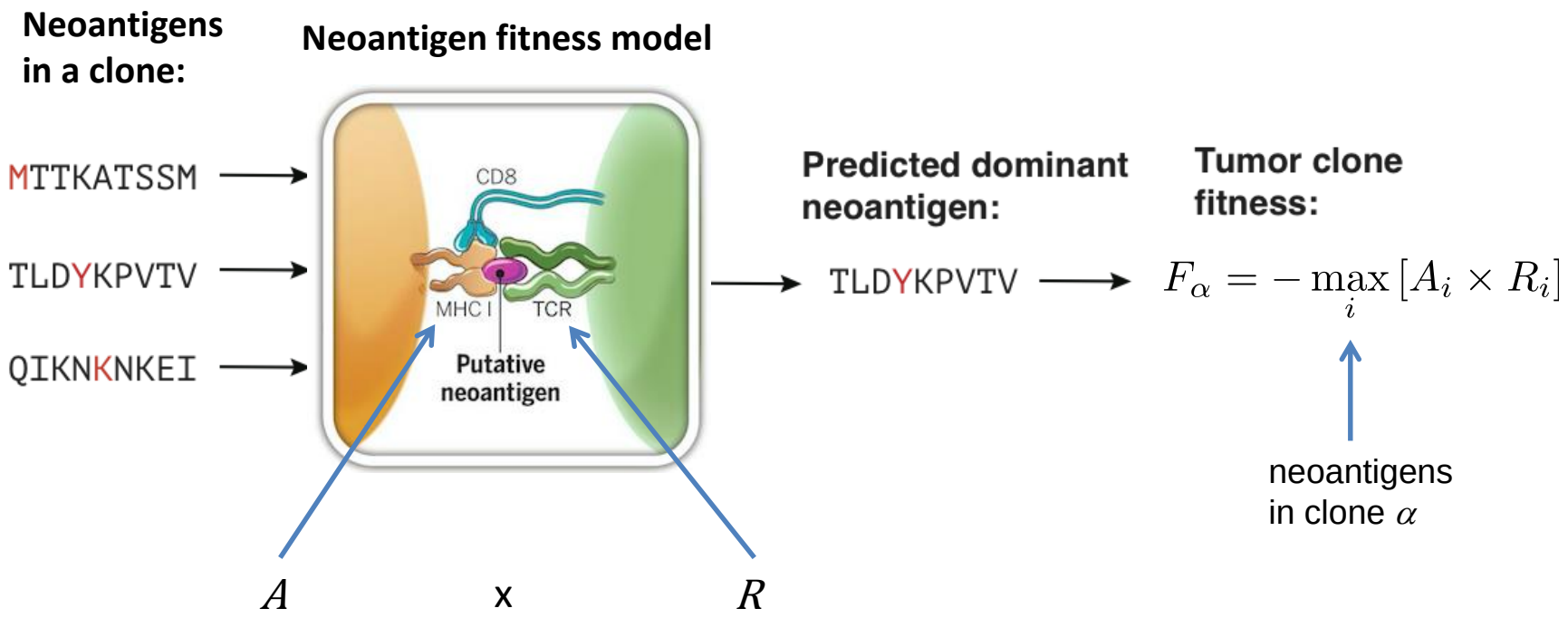
Relative effective population size after forward evolution

Initial clone frequency (from phylogeny)

Fitness of clone (derived from model)

Łuksza, et al, *Nature*, 2017

Model construction: fitness of a clone



Amplitude due to MHC presentation:

- From inferred affinities of wildtype and mutant peptides
- Should relate to discrimination energy by class I HLA molecule
- Measure of peptide “selfness”

TCR recognition probability:

- Use pathogen epitope (IEDB) alignments as proxy for biophysical interactions
- Measure of cross-reactivity with database antigen
- Measure of peptide “non-selfness”

Łuksza, et al, *Nature*, 2017

Proof of concept on current data & methods

Three immunotherapy datasets:

Van Allen, et al., *Science*, 2015: Melanoma, anti-CTLA4, 103 samples
Snyder, et al., *NEJM*, 2014: Melanoma, anti-CTLA4, 64 samples
Rizvi, et al., *Science*, 2015: Lung, anti-PD1, 34 samples

Measurements:

- Exome sequencing
- Tumor and normal tissue
- Survival times

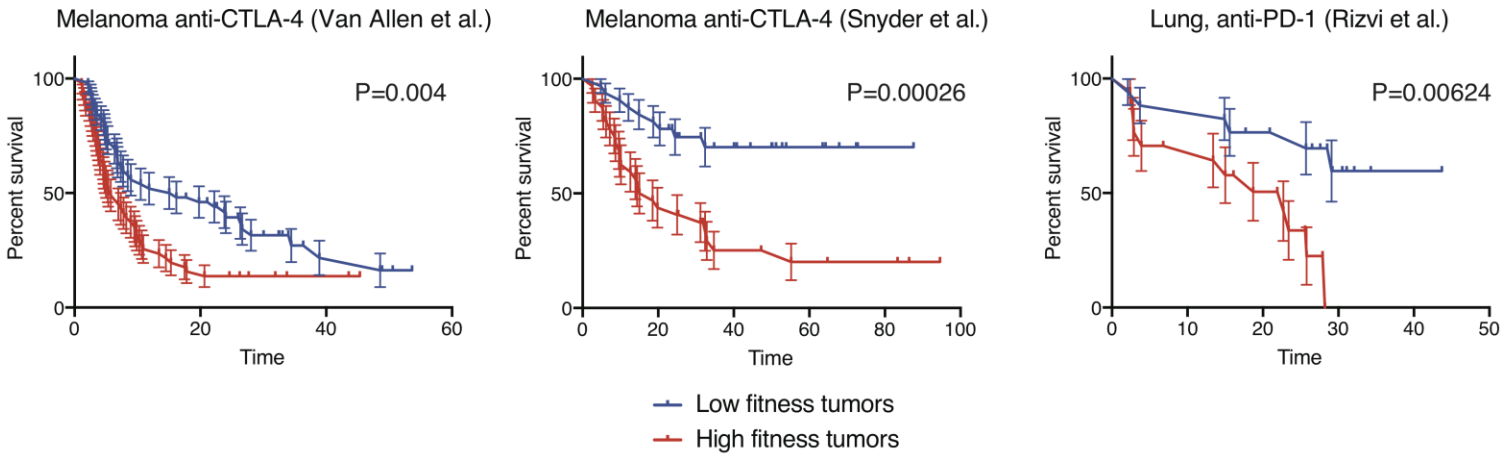
Processing:

- Somatic mutations: 4-caller variant pipeline for mutations (Chan Lab)
- Affinity prediction: NetMHC 3.4
- Nested clonal structure: Deshwar, PhyloWGS, 2015

Benchmarking on public datasets

Survival analysis:

- **Assumption**: predicted effective tumor size $n(\tau)$ anti-correlated with survival
- Split patient cohorts by median $n(\tau)$



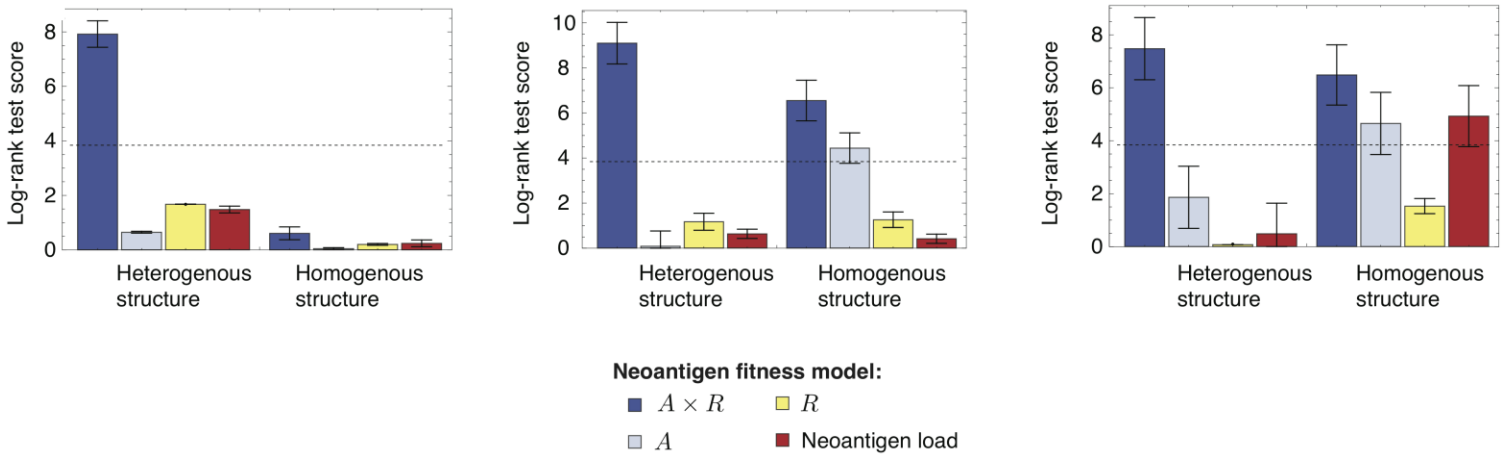
Łuksza, et al, *Nature*, 2017

Benchmarking on public datasets

Survival analysis:

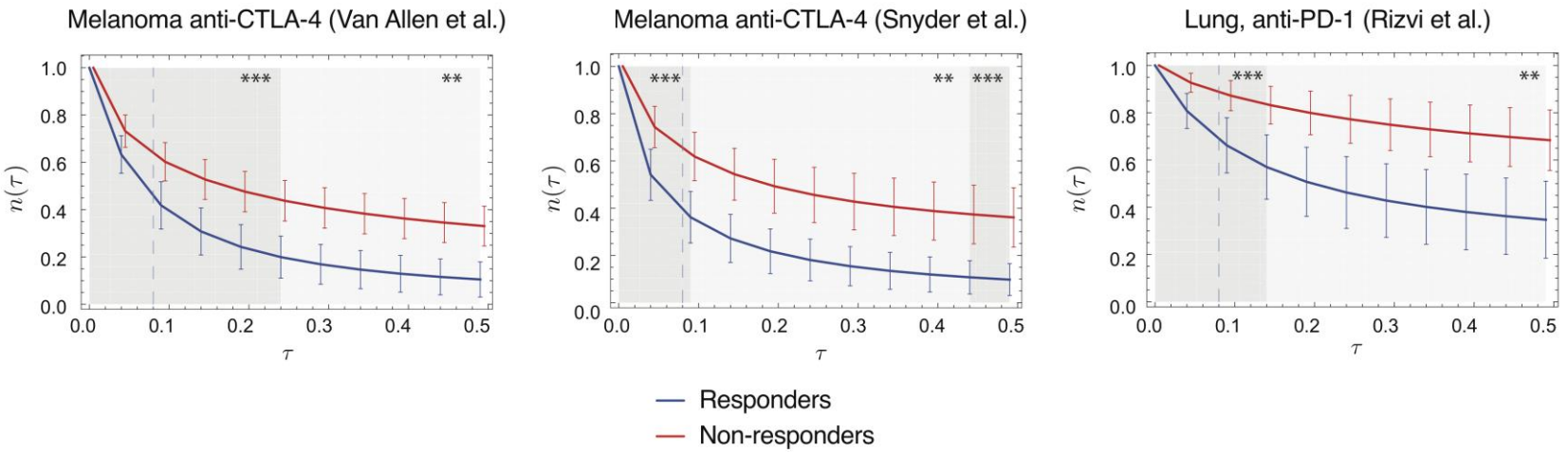
- **Assumption**: predicted effective tumor size $n(\tau)$ anti-correlated with survival
- Split patient cohorts by median $n(\tau)$

All model components **are informative and necessary** for predictions:



Łuksza, et al, *Nature*, 2017

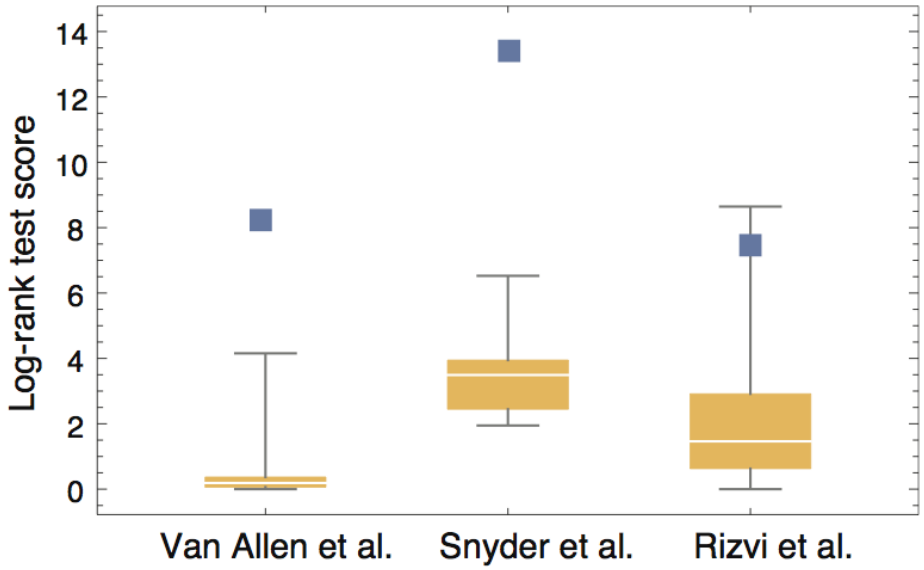
Predictions for responders and non-responders



Łuksza, et al, *Nature*, 2017

Consistency with underlying processes

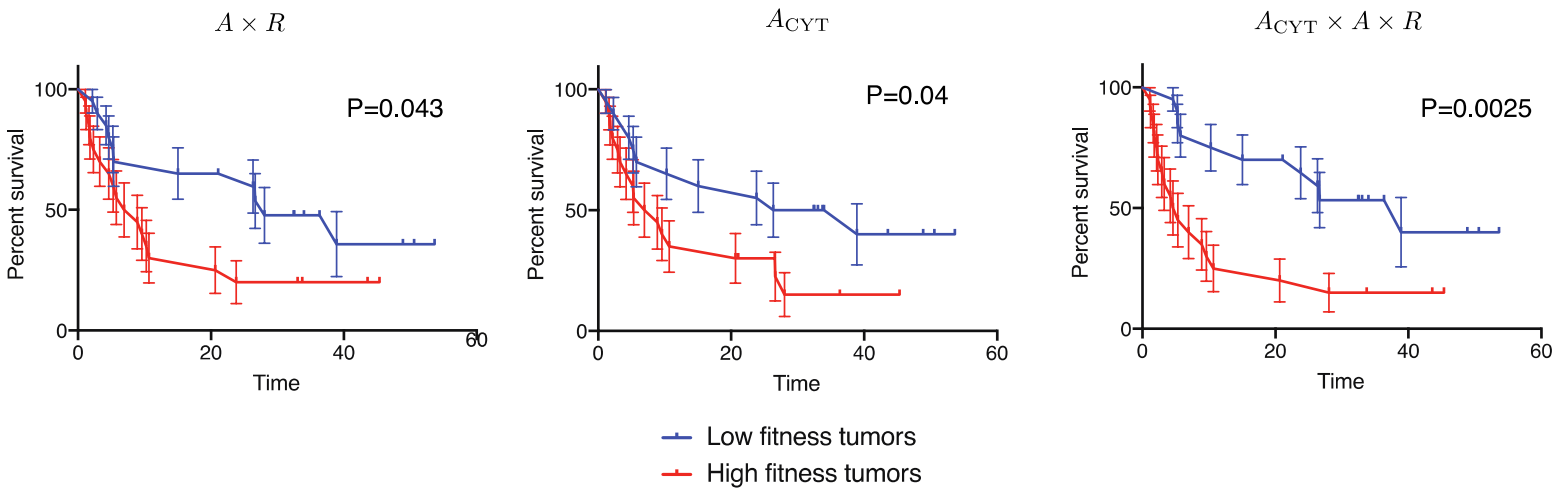
Results do not survive shuffling patient HLA type



Typical discrimination length ~ TCR repertoire discrimination length

Łuksza, et al, *Nature*, 2017

Expandable framework can incorporate microenvironment



Other variables can be incorporated as well

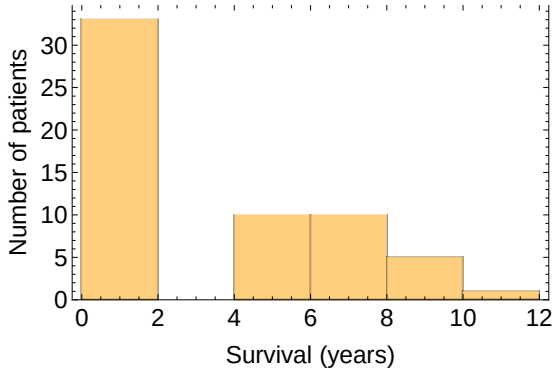
Łuksza, et al, *Nature*, 2017

Can we apply this framework in the nontherapy setting?

Pancreatic cancer study: beyond immunotherapies

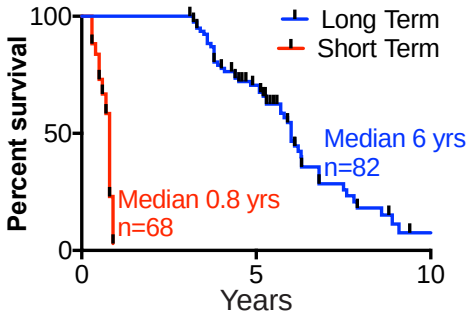
Less than 7% of PDAC patients survive 5 years after diagnosis

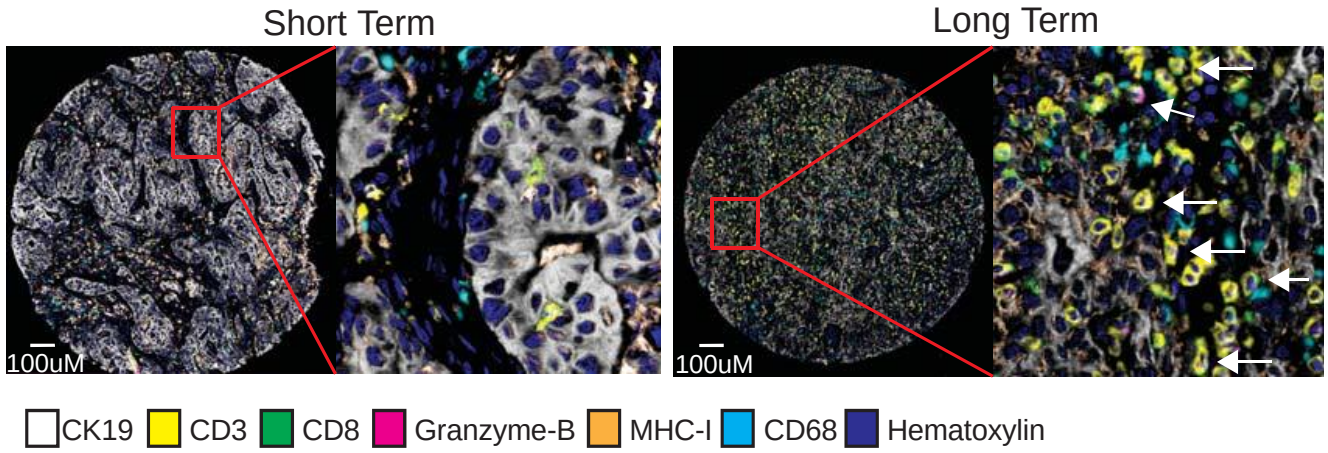
This study: A unique cohort of pancreatic cancer patients with **extreme long-term survivors**.



Balachandran, et al, *Nature*, 2017

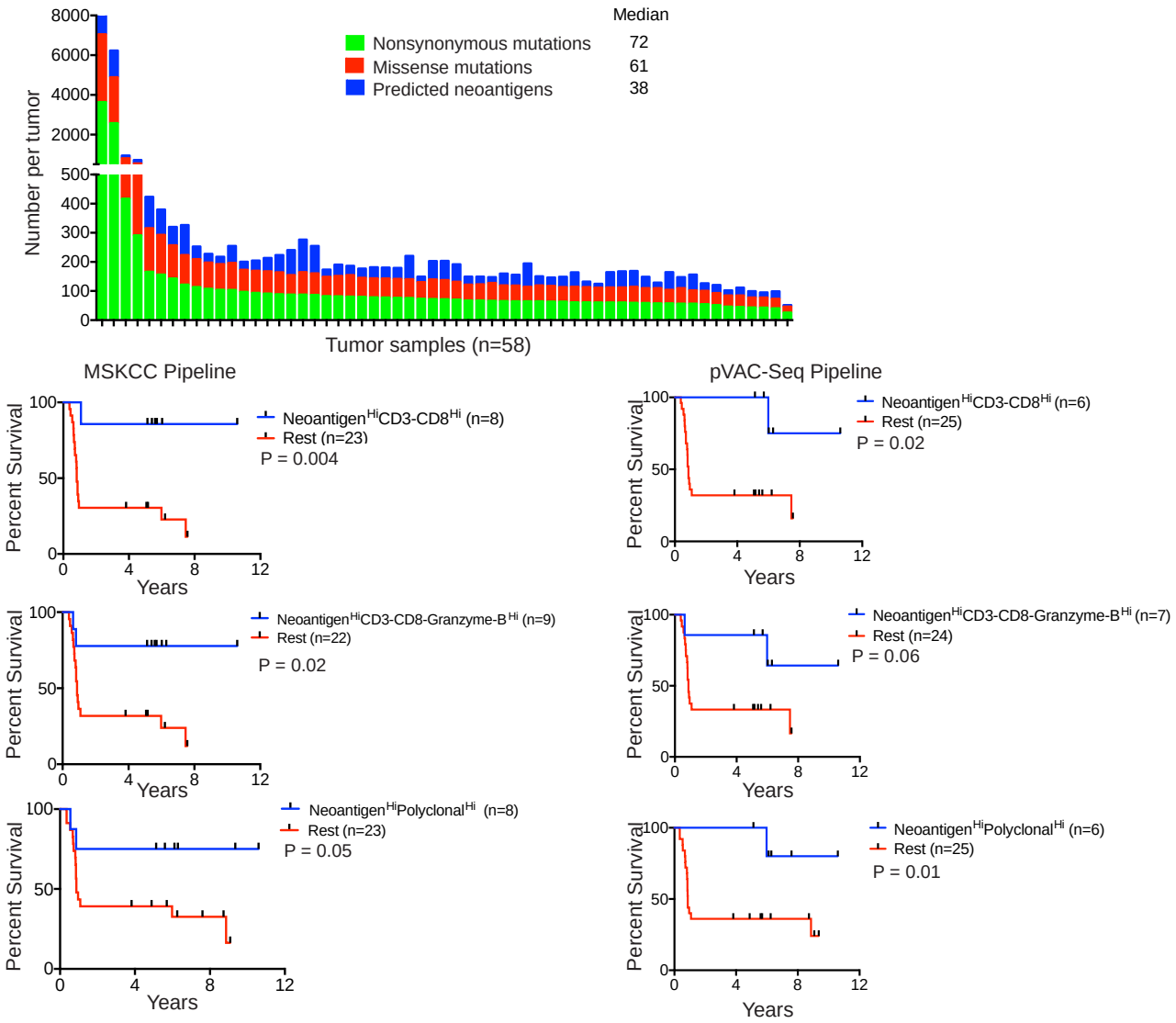
Immune monitoring indicates T-cell infiltration associates with response





Balachandran, et al, *Nature*, 2017

Mutational burden + high T-cell is predictive



Balachandran, et al, *Nature*, 2017

Quality model recapitulates survival & monitoring

Quality Score

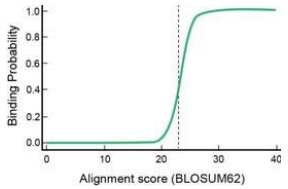
a) Assess sequence similarity of neoantigen to pathogen

Wild type epitope: PPSARGGPL
Tumor neoepitope: PPSARRGPL
Human Herpes Virus (HHV)-8: PPSGQRGPVAFRTRV

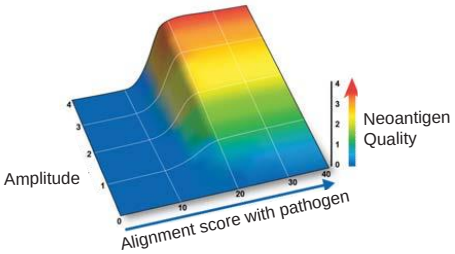
→ Calculate Alignment score (BLOSUM62)

b) Scale alignment score to binding probability of a TCR to the cross reacting antigen

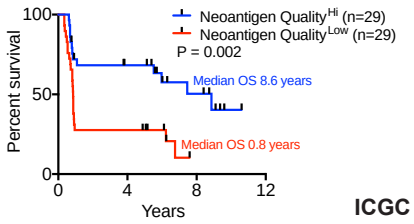
TCR binding probability is a sigmoid function of alignment score

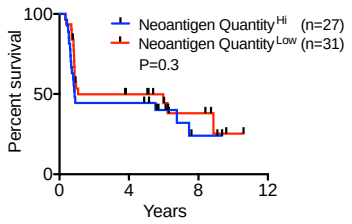


c) Neoantigen cross reactivity for a given neoantigen is a function of alignment score and amplitude (K_d^{WT}/K_d^{Mutant})



MSKCC





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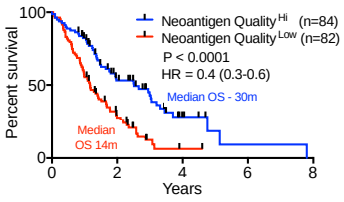
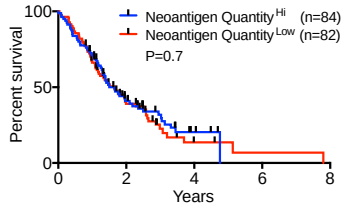
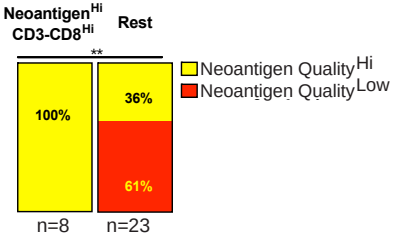
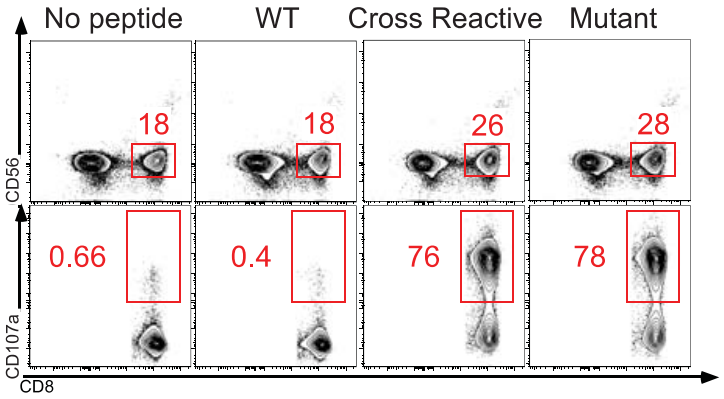


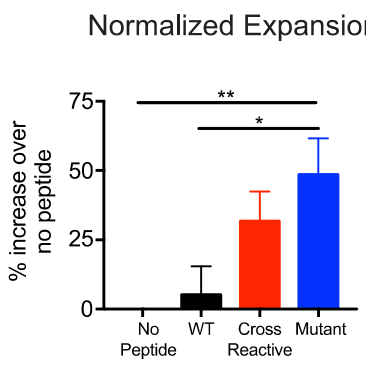


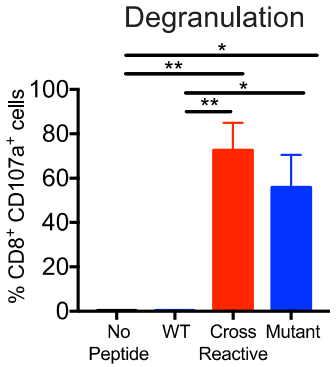


Balachandran, et al, *Nature*, 2017

Test in long-term cohort

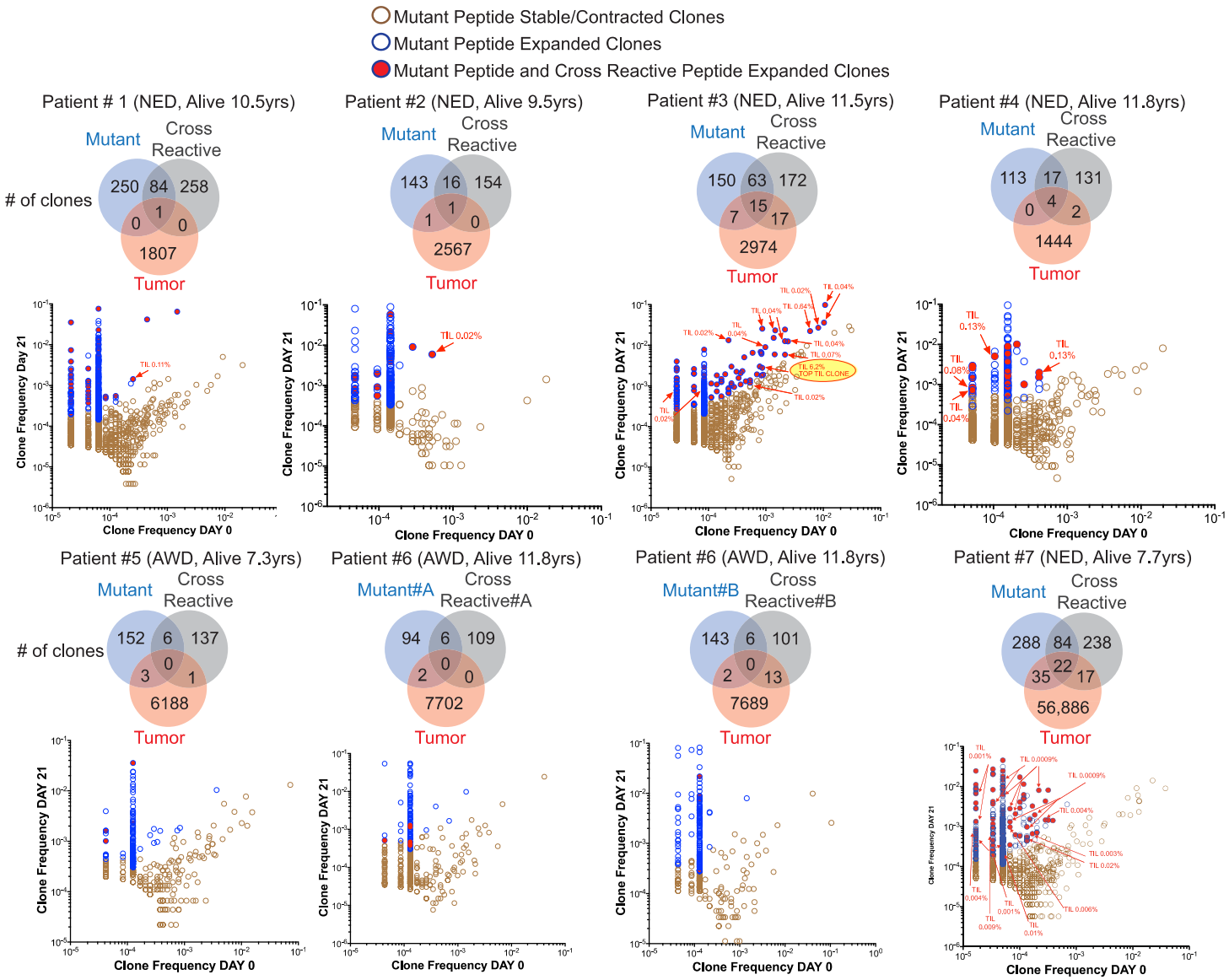






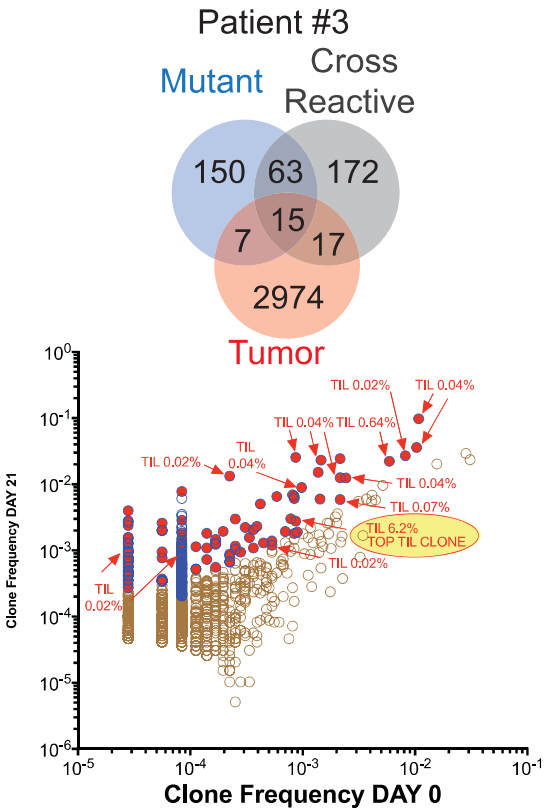
Balachandran, et al, *Nature*, 2017

Can we find TCRs?



Balachandran, et al, *Nature*, 2017

Particularly striking case:



Balachandran, et al, *Nature*, 2017

Summary

- Approaches from virus vaccine prediction may be relevant in predicting response to checkpoint blockade immunotherapy

- **All neoantigen fitness model components are informative**:
  - Tumor heterogeneity
  - MHC presentation of neoantigens
  - TCR recognition of neoantigens

- The **fitness model can be easily extended** to capture other meaningful effects such as information about the tumor microenvironment

LETTER

doi:10.1038/nature24473

A neoantigen fitness model predicts tumour response to checkpoint blockade immunotherapy

Marta Łuksza[1], Nadeem Riaz[2,3], Vladimir Makarov[3,4], Vinod P. Balachandran[5,6,7], Matthew D. Hellmann[7,8,9], Alexander Solovyov[10,11,12,13], Naiyer A. Rizvi[14], Taha Merghoub[7,15,16], Arnold J. Levine[1], Timothy A. Chan[2,3,4,7], Jedd D. Wolchok[7,8,15,16] & Benjamin D. Greenbaum[10,11,12,13]

LETTER

doi:10.1038/nature24462

Identification of unique neoantigen qualities in long-term survivors of pancreatic cancer

Vinod P. Balachandran[1,2,3], Marta Łuksza[4], Julia N. Zhao[1,2,3], Vladimir Makarov[5,6], John Alec Moral[1,2,3], Romain Remark[7], Brian Herbst[2], Gokce Askan[2,8], Umesh Bhanot[8], Yasin Senbabaoglu[9], Daniel K. Wells[10], Charles Ian Ormsby Cary[10], Olivera Grbovic-Huezo[2], Marc Attiyeh[1,2], Benjamin Medina[1], Jennifer Zhang[1], Jennifer Loo[1], Joseph Saglimbeni[2], Mohsen Abu-Akeel[9], Roberta Zappasodi[9], Nadeem Riaz[6,11], Martin Smoragiewicz[12], Z. Larkin Kelley[13,14], Olca Basturk[8], Australian Pancreatic Cancer Genome Initiative*, Mithat Gönen[15], Arnold J. Levine[4], Peter J. Allen[1,2], Douglas T. Fearon[13,14], Miriam Merad[7], Sacha Gnjatic[7], Christine A. Iacobuzio-Donahue[2,5,8], Jedd D. Wolchok[3,9,16,17,18], Ronald P. DeMatteo[1,2], Timothy A. Chan[3,5,6,11], Benjamin D. Greenbaum[19], Taha Merghoub[3,9,18]§ & Steven D. Leach[1,2,5,20]§

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Please inquire about positions!

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