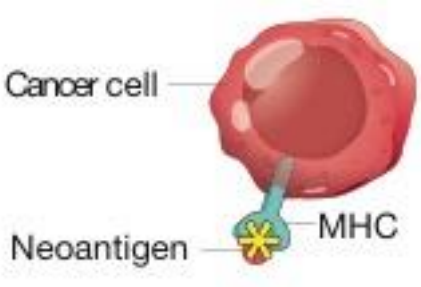
Predicting tumor evolution from immune interactions

Marta Łuksza

Icahn School of Medicine, Mount Sinai

Immune recognition of cancer cells

Neoantigen: a mutated peptide in a cancer cell, presented on its surface



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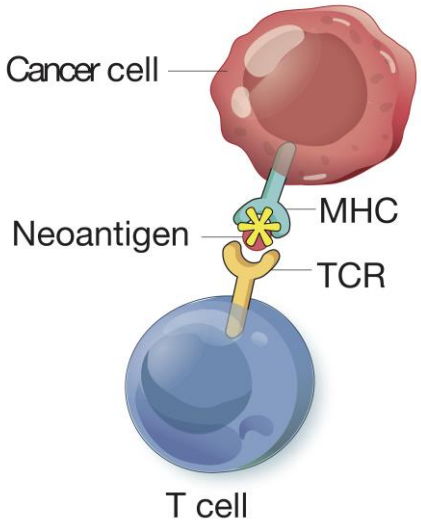

They are potentially “immunogenic” - recognized by **T-cell receptors** (TCRs)

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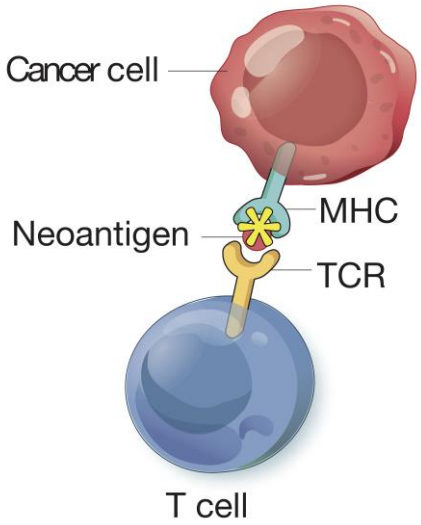

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Goal: quantify **immunogenicity of neoantigens in an evolutionary model** to predict tumor response to therapy

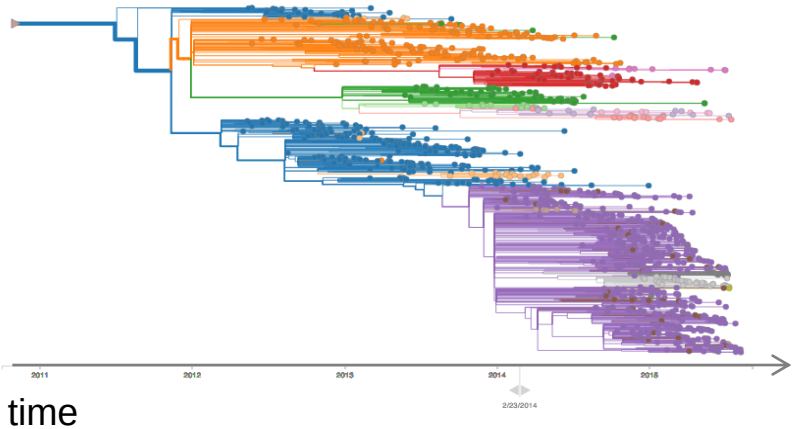
[figures adapted from Sarkizova&Hacohen, News&Views, Nature 2017]

A fitness model predicts evolution of influenza virus

– High viral population heterogeneity (inter host)

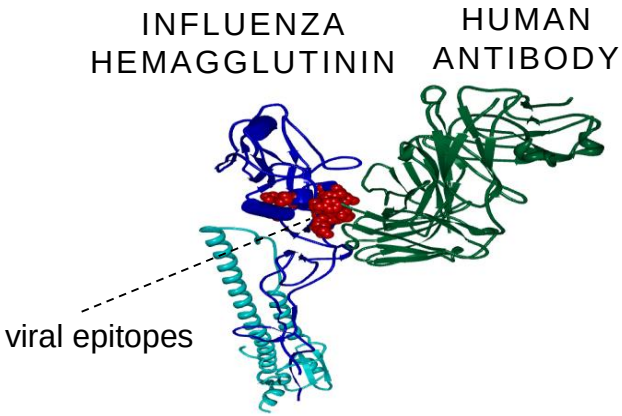
– Strong immune selection (driven by **B-cell** interactions with one surface protein)

Evolving viral population



time

Immune interactions with host antibodies



[Łuksza&Lässig, Nature 2014]

A fitness model predicts evolution of influenza virus

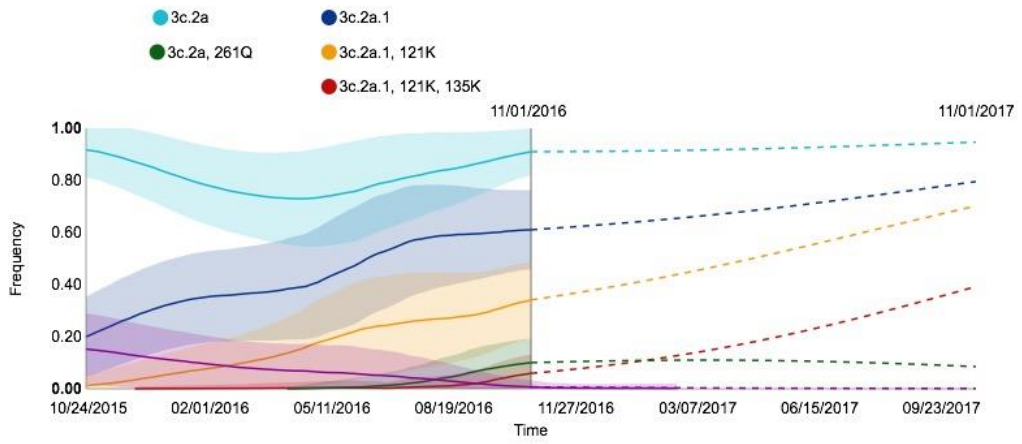
– High viral population heterogeneity (inter host)

– Strong immune selection (driven by **B-cell** interactions with one surface protein)

We use an **influenza immune-interaction based fitness model** to predict vaccine strain candidates and consult WHO vaccine selection.

Prediction of influenza A/H3N2 evolution until winter 2018

Marta Łuksza[a], William Harvey[b], Richard Reeve[b], and Michael Lässig[c]



[Łuksza&Lässig, Nature 2014]

Are models still needed?

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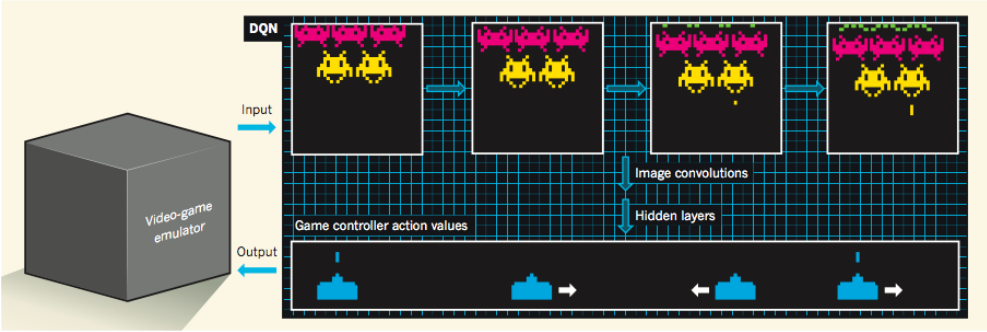
DeepMind algorithm:

– Deep reinforcement learning to play 49 vintage computer games **without a priori knowledge** of the games and rules (Mnih et al. Nature 2015)



[from Scholkopf, Nature 2015]

– AlphaGo, AlphaGo Zhero: similar algorithm trained to win GO with a human (Silver, D. et al. Nature, 2016).

Are models still needed?

*AlphaGo first studied **30 million positions** from expert games, gleaning abstract information on the state of play from board data, much as other programs categorize images from pixels. Then it played against itself **across 50 computers**, improving with each iteration, a technique known as reinforcement learning.*

– Largest tumor database has ~20000 tumors across ~30 cancers at one time point
– Evolutionary data are always incomplete, and evolutionary processes are slow

– These differences may favor mechanistic models for making evolutionary predictions.

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– Largest tumor database has ~20000 tumors across ~30 cancers at one time point
– Evolutionary data are always incomplete, and evolutionary processes are slow

– These differences may favor mechanistic models for making evolutionary predictions.

– Health care decisions need to be rationalized

Neoantigen fitness model

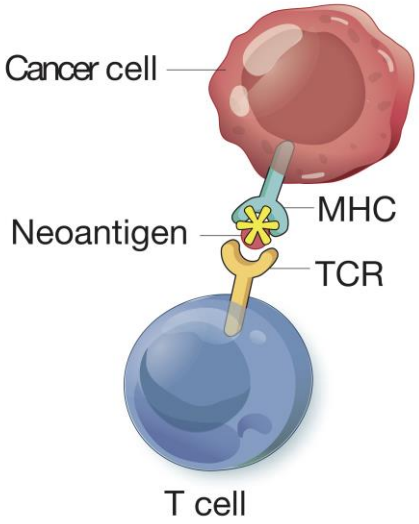
Benjamin Greenbaum
(Icahn School of Medicine, Mount Sinai)

Arnold Levine (IAS)

Vinod Balachandran,
Taha Merghoub
Timothy Chan
Steven Leach
Nadeem Riaz
Vladimir Makarov
Matthew Hellman
Jedd Wolchok
(MSKCC)

Immunogenicity of a neoantigen

When is a **neoantigen** recognized by a T-cell?



Recognition potential of peptide s:

$$P(\mathbf{s}) = A(\mathbf{s}) \times R(\mathbf{s})$$

MHC presentation
depends on peptide-MHC binding affinity

TCR recognition
depends on peptide–TCR binding affinity, for available TCRs

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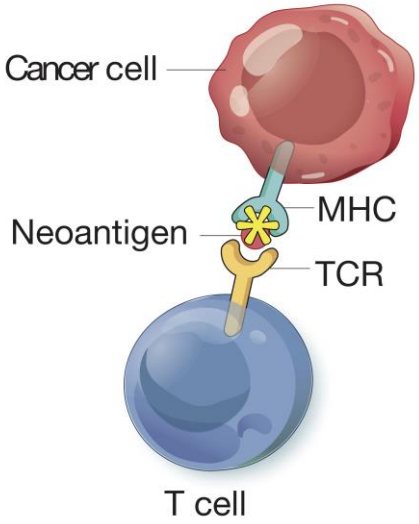

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– biophysical model based on dissociation constants predicted for peptide sequence (netMHC algorithm)

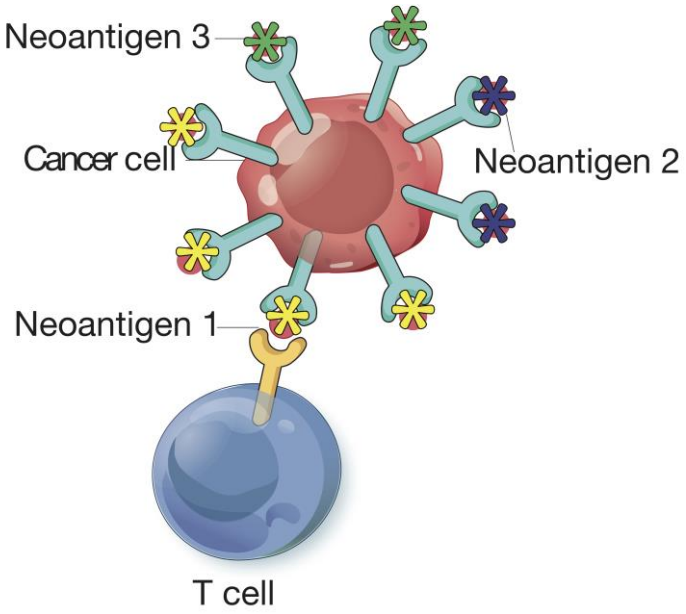
TCR recognition
depends on peptide–TCR binding affinity, for available TCRs

– is estimated from **sequence similarity** to validated T-Cell microbial epitope sequences (IEDB)

Immunogenicity of a cell

Cancer cell can have **multiple neoantigens**

Immune interactions of neoantigens affect cell's **fitness** (growth rate)



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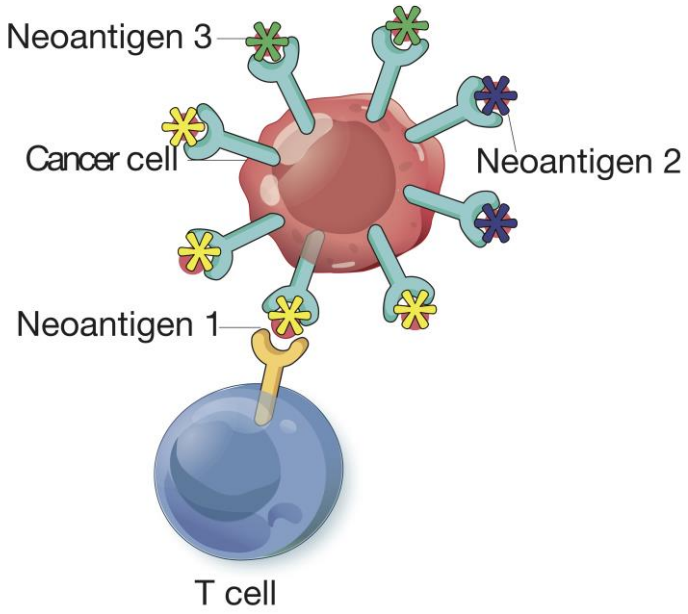


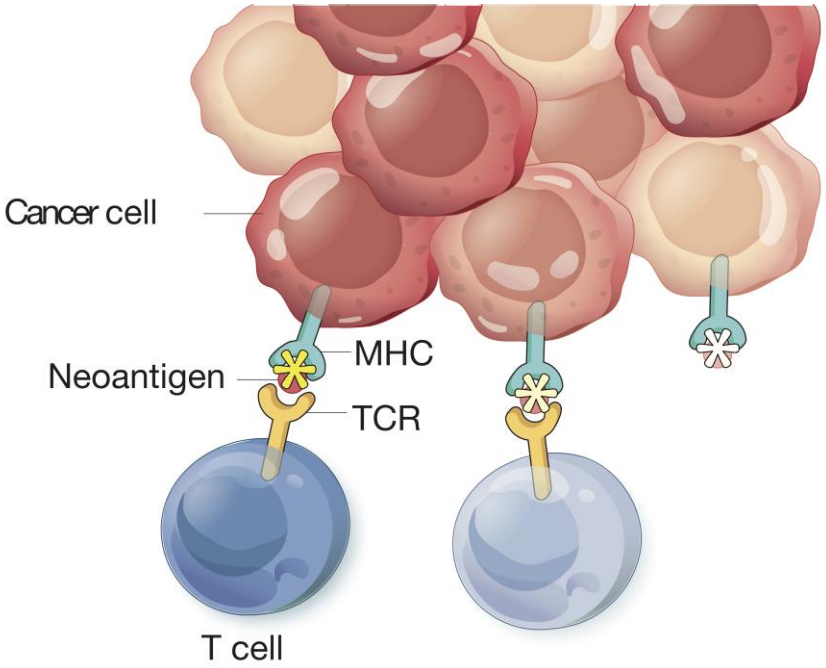
From model fitting:

Cell's fitness is determined by the **dominant** neoantigen

$$F = - \max_{i \in \text{neoantigens}} P_i$$

Tumor heterogeneity

– Tumor cells are genetically heterogeneous
– They potentially have different immune interactions



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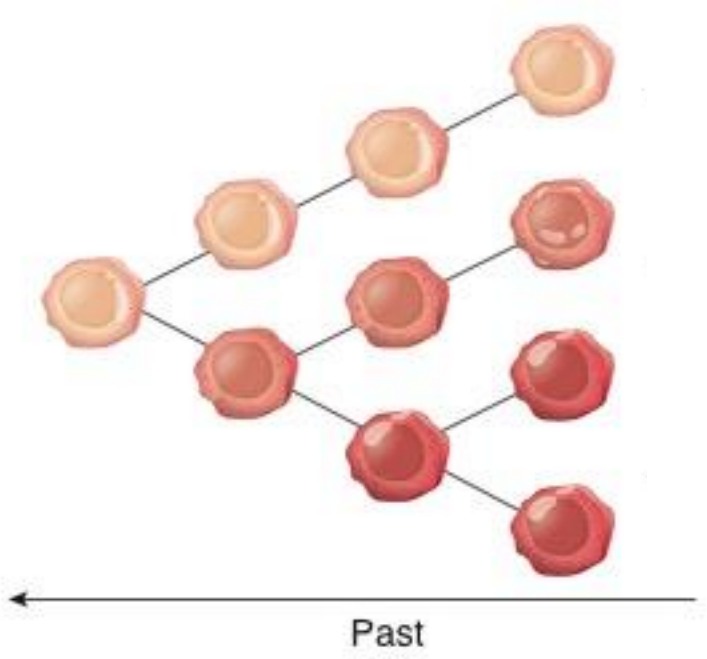
– Tumor is **an evolving population of cancer cells**



Tumor heterogeneity and evolutionary predictions

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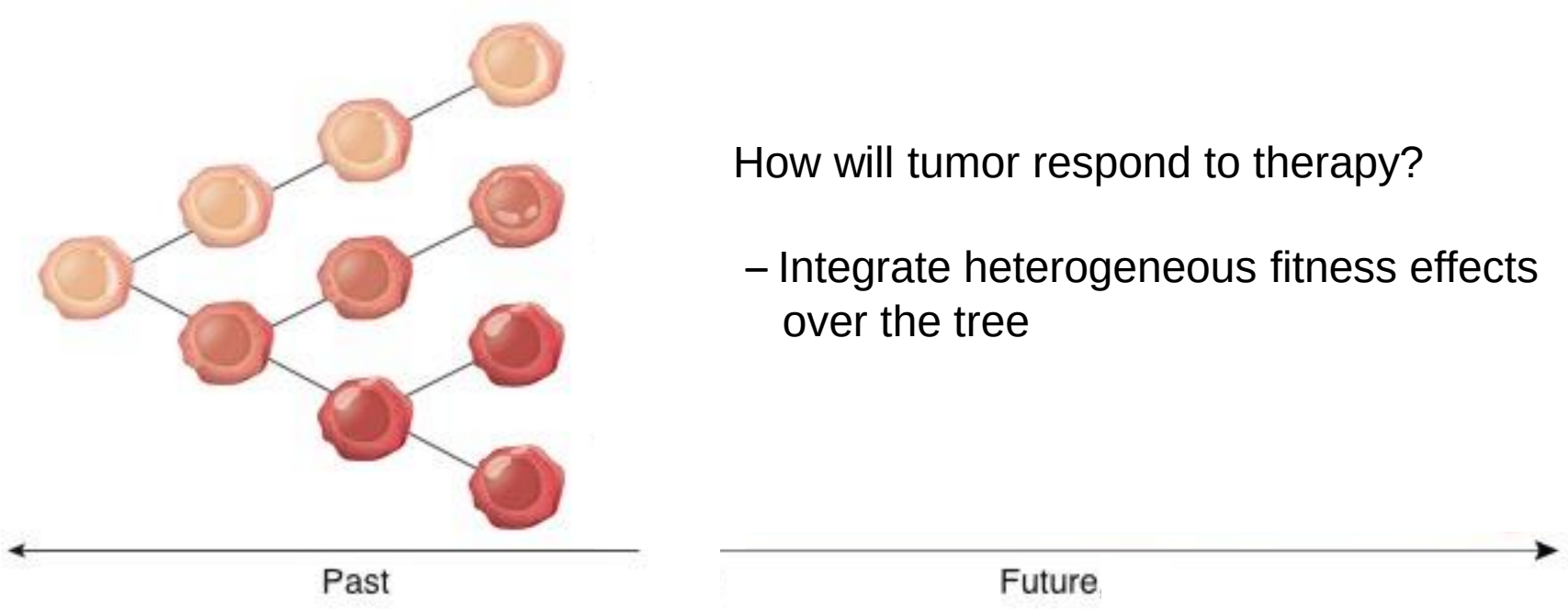

How will tumor respond to therapy?

– Integrate heterogeneous fitness effects over the tree

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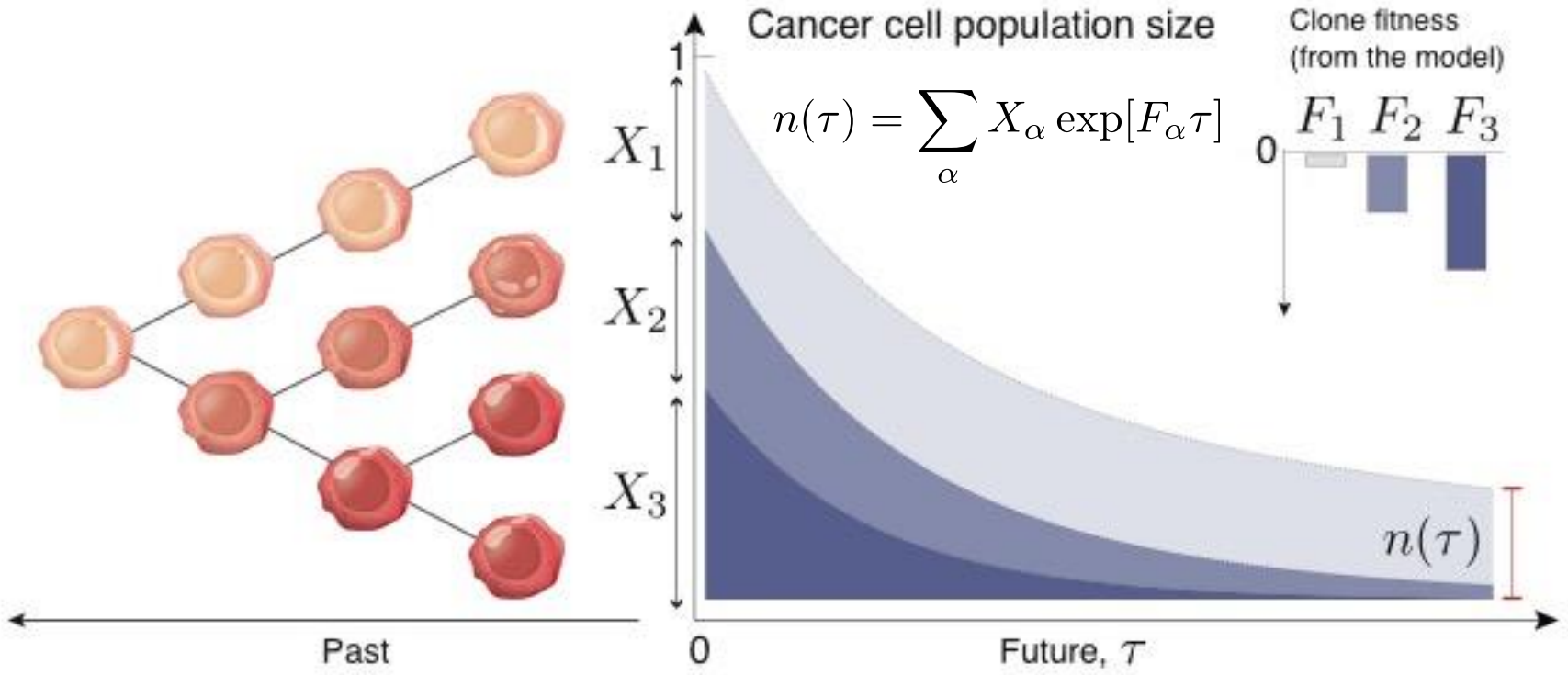
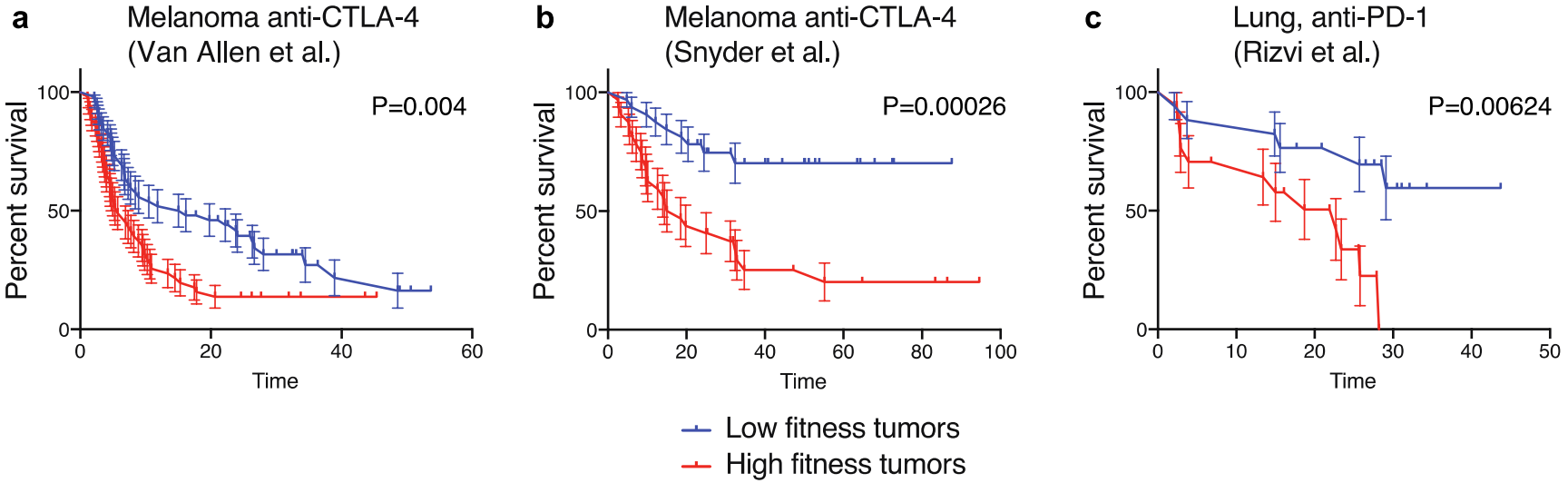


Benchmarking on public datasets

Survival analysis: rank patients by their predicted cancer population size $n(\tau)$

– **Assumption:** tumor size decrease is related to prolonged survival



[Łuksza et al, Nature 2017]

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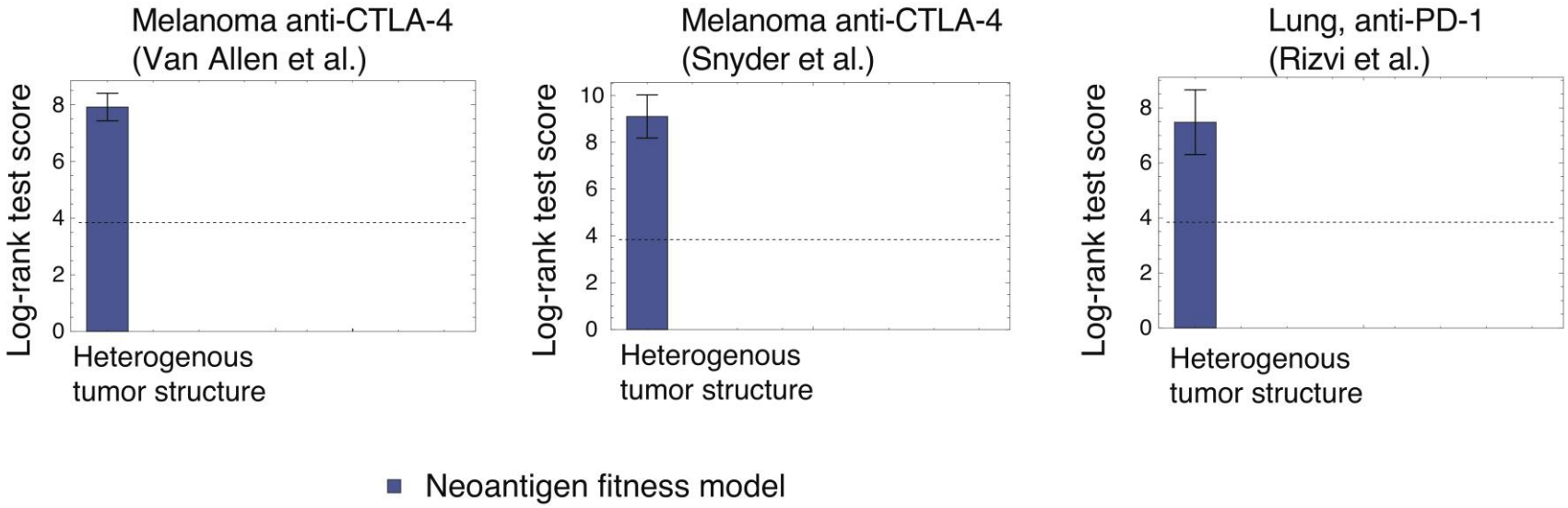
Log-rank test score:



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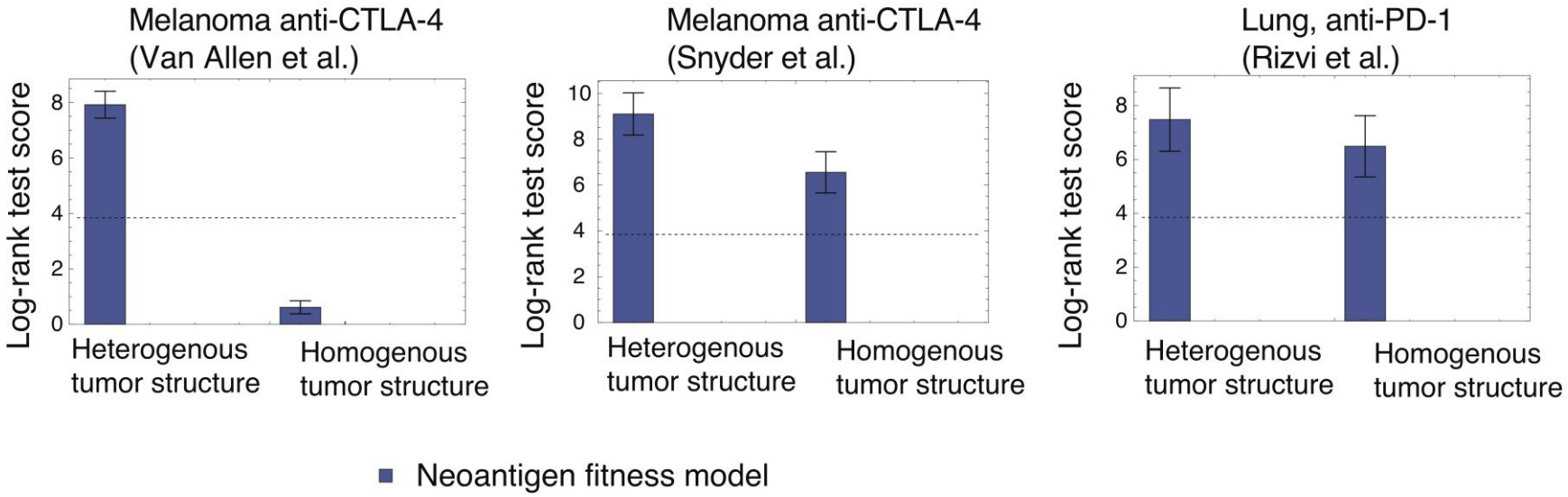
Tumor heterogeneity is important for predictions:



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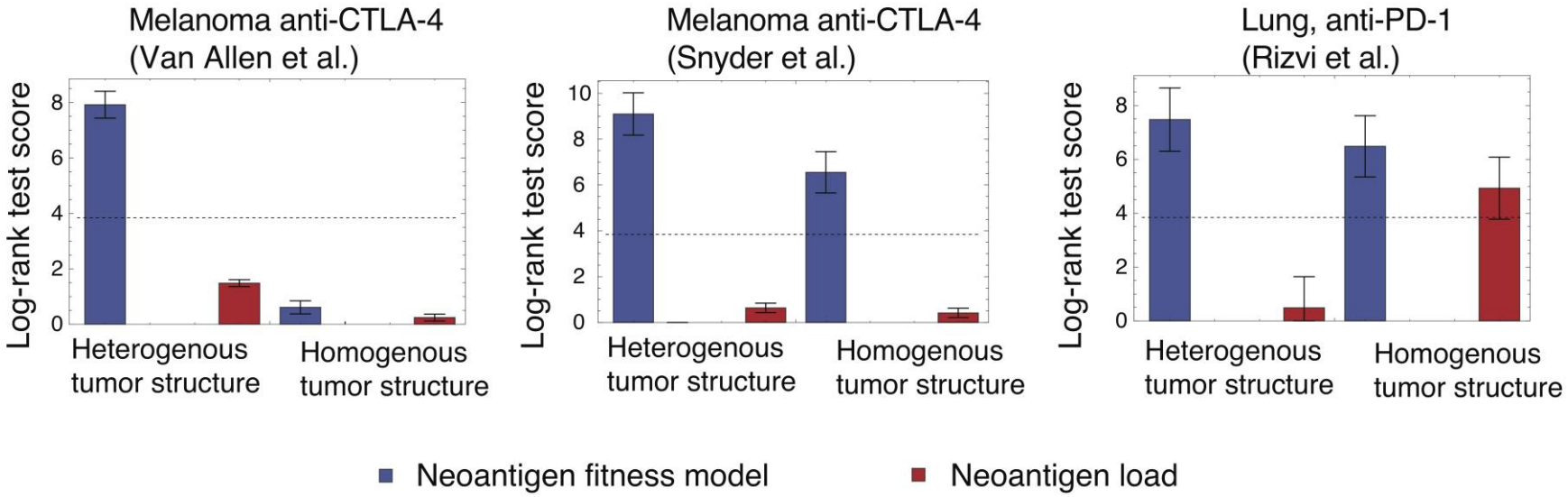
Neoantigen fitness model outperforms neoantigen load



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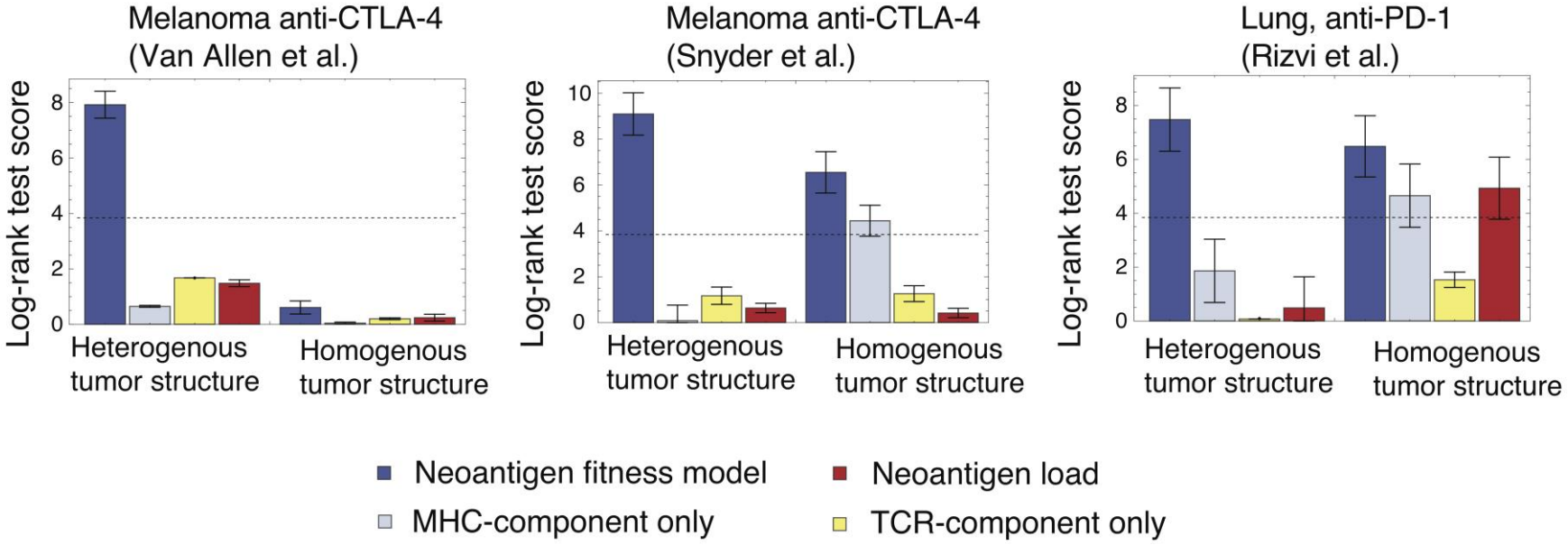
All model components are informative:



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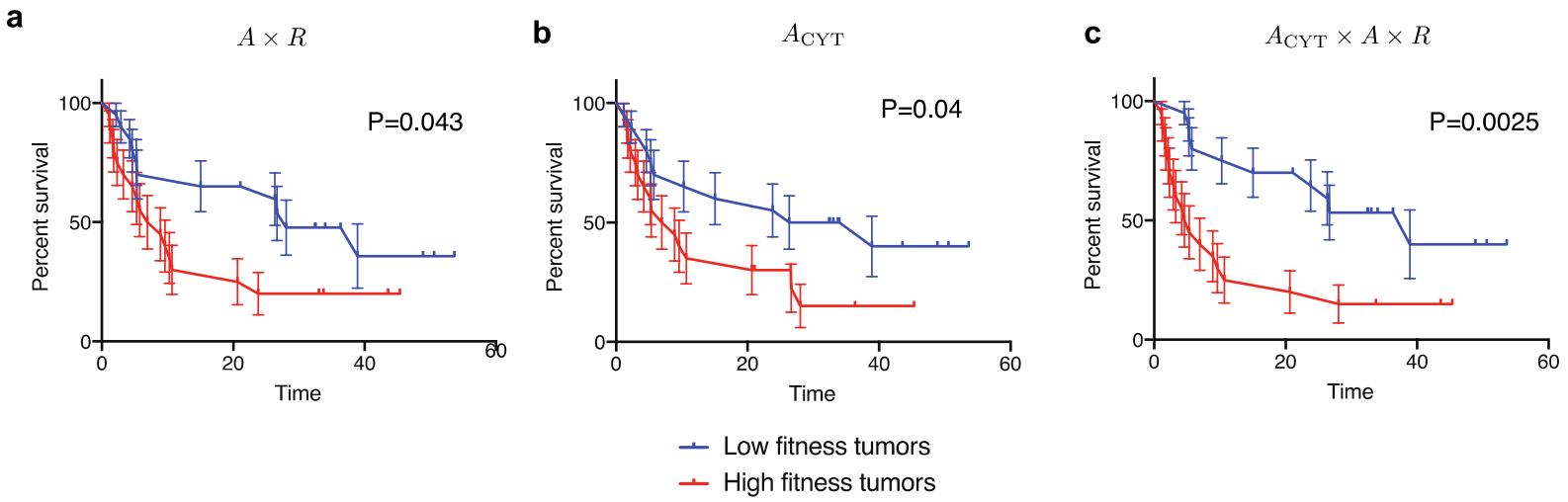
Other fitness effects

This model can be further extended:

Cytolytic score - measure of T-cell infiltration inferred from gene expression

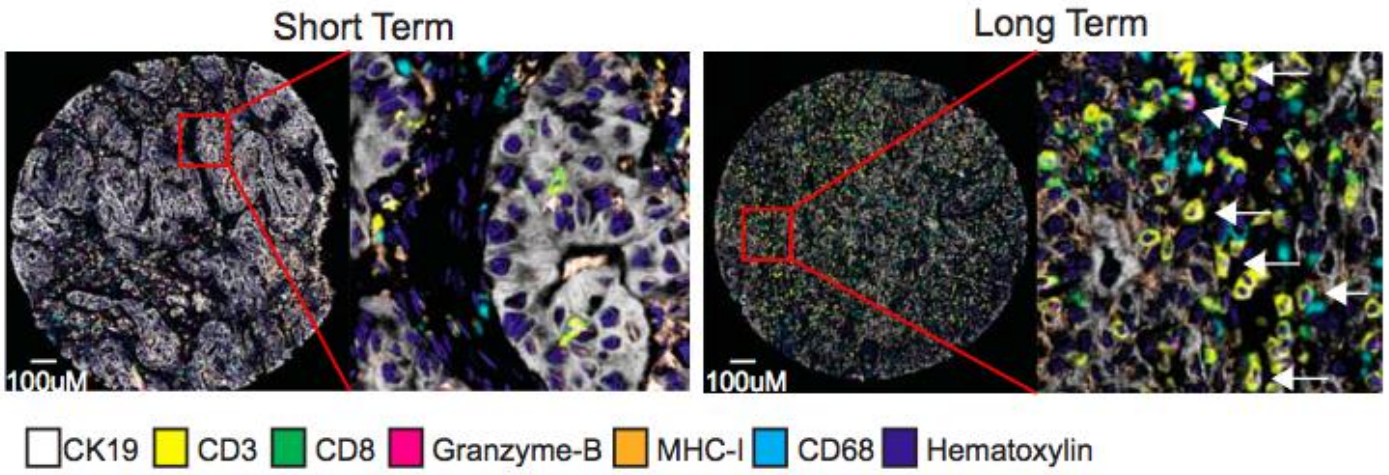
[Rooney et al., Cell 2015]



Pancreatic cancer study: beyond immunotherapies

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

Role of the immune system:
Long-term survivors show increased T-cell infiltration of tumors



[imaging by R. Remark, M. Merad and S. Gnjatic, Mount Sinai]

[Balachandran, et al., Nature 2017]

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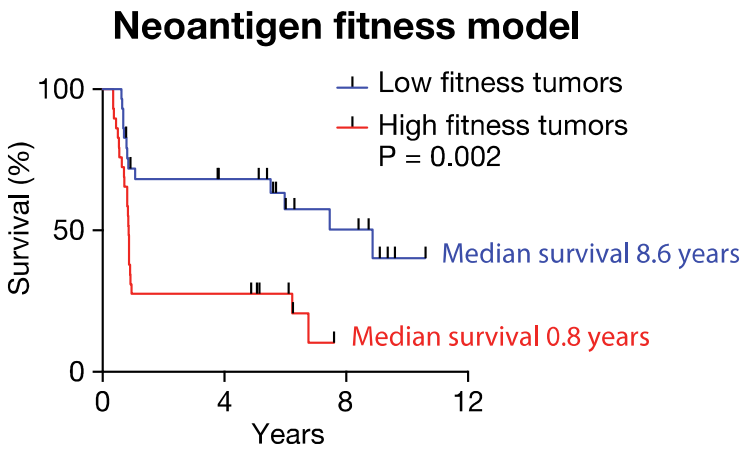
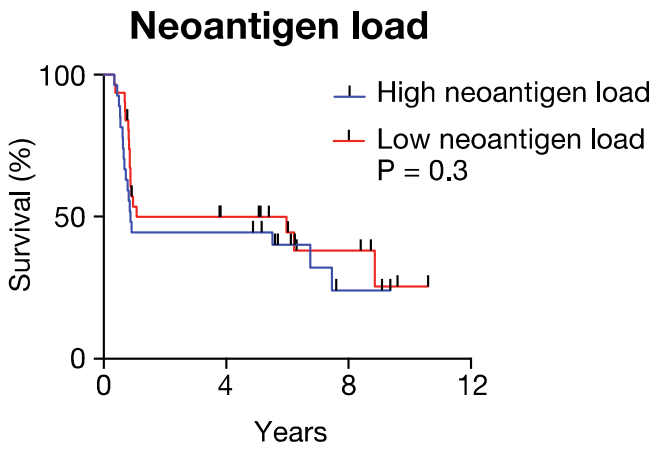
Neoantigen fitness model separates short and long-term survivors:





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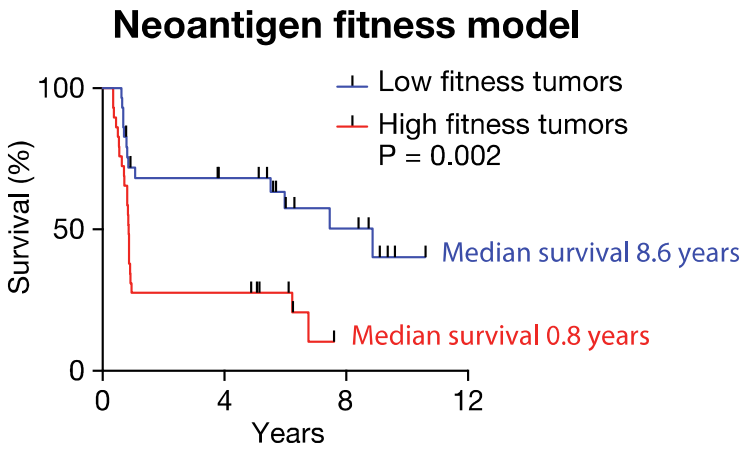

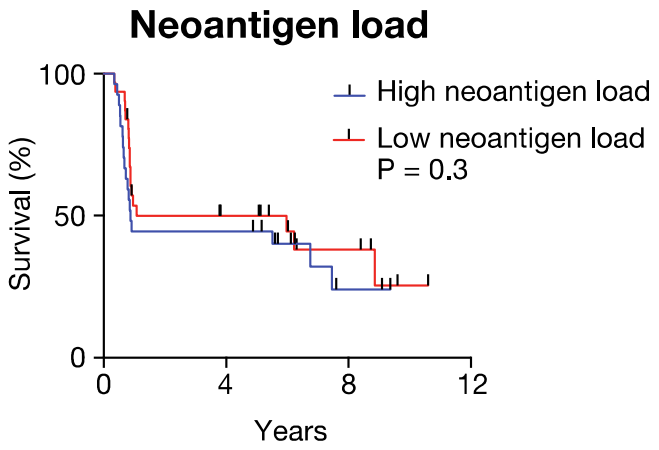

Reactive neoantigen predictions validated in 7 long-term survivors:
– The patients generally showed significant responses

[Balachandran, et al., Nature 2017]

Mechanistic models

- Based on **biophysical immune interactions**
  - MHC class I antigen presentation and TCR recognition in tumors
  - B-cell recognition in influenza
- These models utilize **prior knowledge about evolutionary dynamics**
- The combination of these insights from evolution and biophysics can significantly **reduce the complexity of the learning**
- Other machine learning approaches are / can be used for **sub-problems:**
  - Prediction of affinities between peptides and MHC (netMHC)
  - Prediction of binding between peptides and TCRs
  - Inference of TCR distribution
  - Characterizing peptide-nonselfness

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Cancer and immune system

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Simone Pompei
Mara Villa

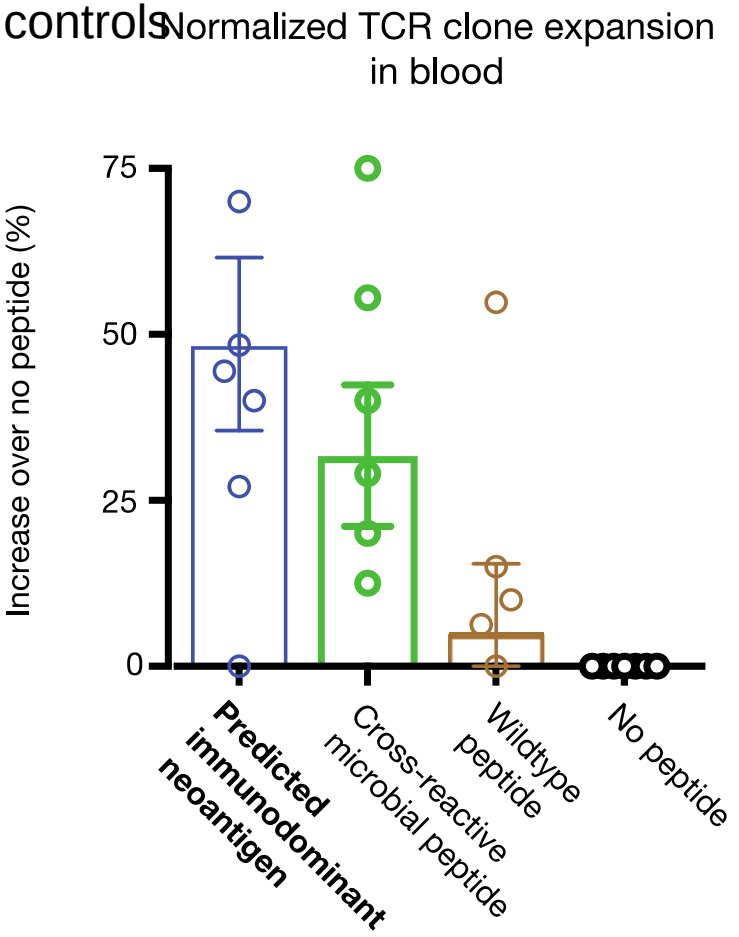
Francis Crick Worldwide Influenza Centre, WHO
John McCauley
Rodney Daniels

University of Glasgow
Richard Reeve (University of Glasgow)
William Harvey (University of Glasgow)

Experimental validation of neoantigen predictions

Reactive neoantigen predictions validated in 7 long-term survivors:

TCR clones expanding in patient's peripheral blood in presence of **the predicted immunodominant peptide**, most similar **microbial epitope** and controls



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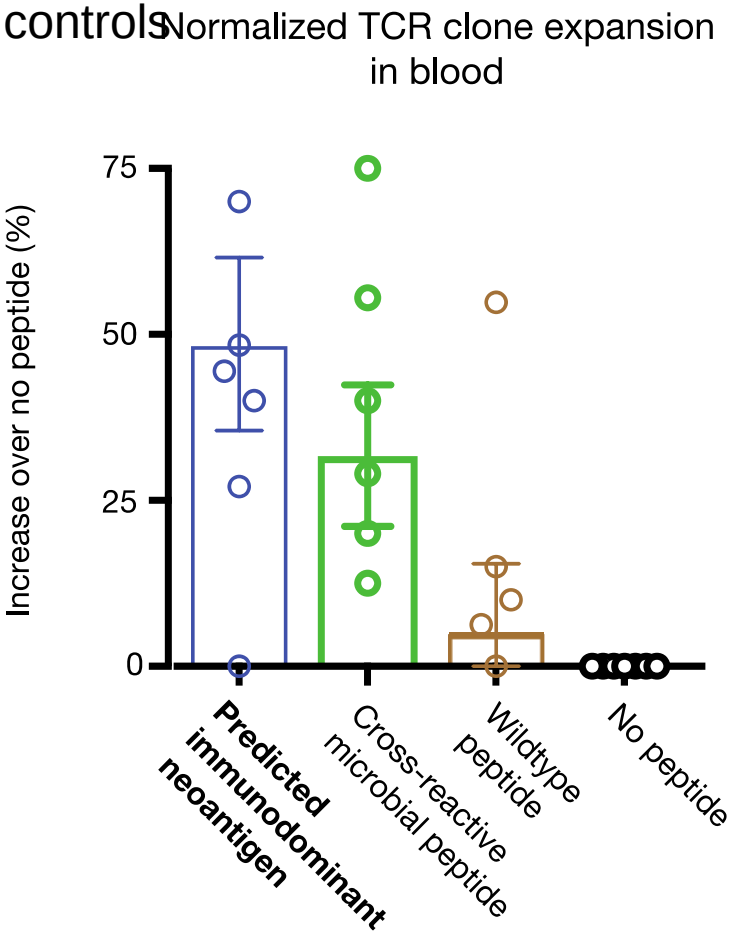

The patients generally showed significant responses to the neoantigens pointed by our model.

[Balachandran, Łuksza, et al., Nature 2017]