A neoantigen fitness model predicts tumour response to checkpoint blockade immunotherapy

Luksza et al.
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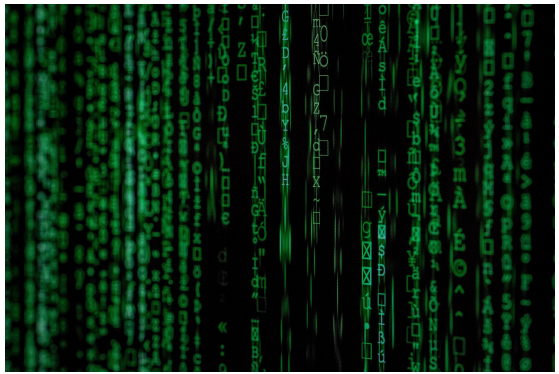
Presented by: Leah Weber

Besides, “model”, “tumor” and “predict”, what do the rest of these words even mean?

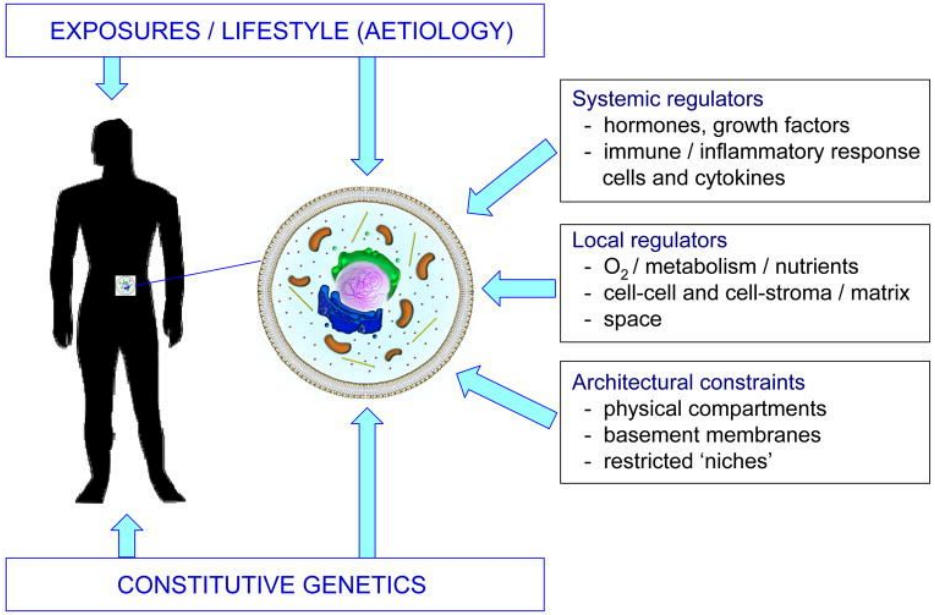
- Neoantigen?
- Fitness Model?
- Checkpoint blockade immunotherapy?

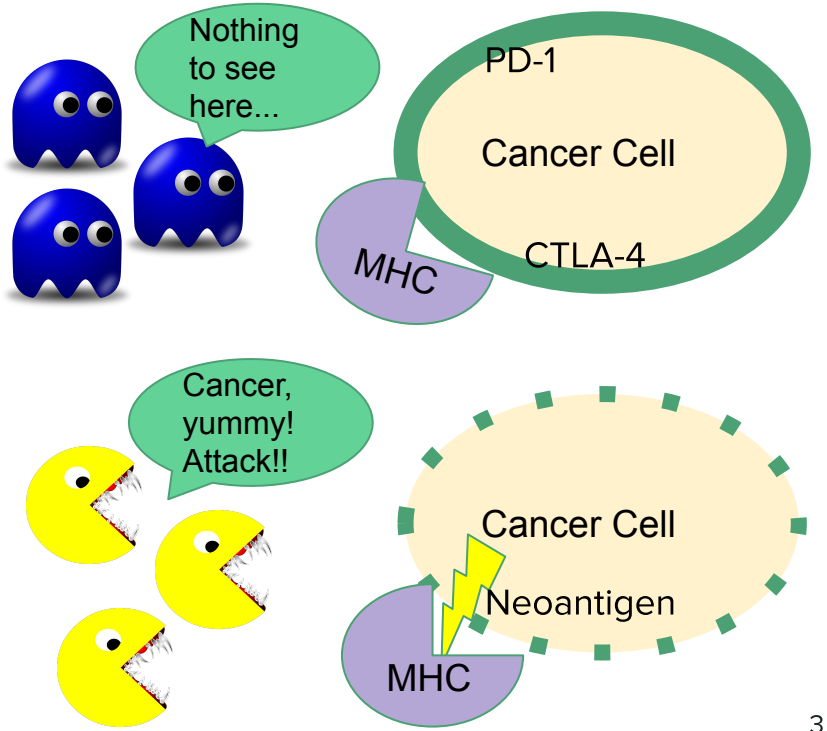
Is this yet another sequel to the Matrix?



The world's shortest class in tumor immunology

Tumor immunology seeks to describe how the immune system and cancer cells interact

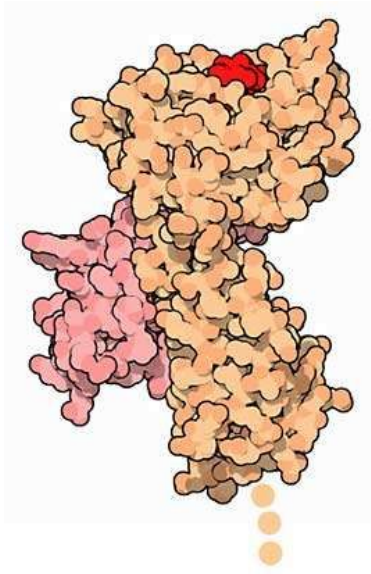




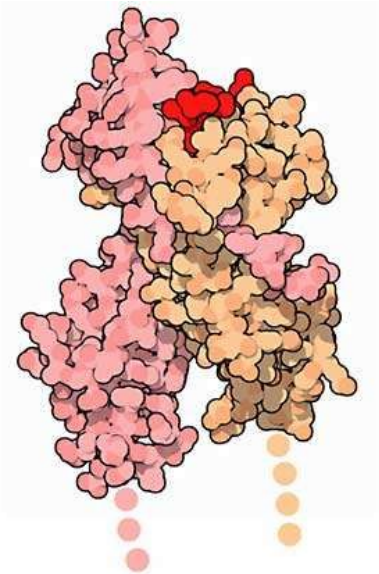
Greaves, M., & Maley, C. C. (2012). Clonal evolution in cancer. *Nature*, *481*(7381), 306–313. https://doi.org/10.1038/nature10762

Major Histocompatibility Complex (MHC)

- A gene that codes for a protein in all vertebrate organisms that can be found lurking on the surface of cells
- Purpose is to help the immune system recognize foreign substances
- In humans, MHC is referred to as the human leukocyte antigen (HLA system)
- There are a large number of HLA alleles. HLA allele determines tissue compatibility for transplants among other things (“Histo” comes from the greek for tissue)



Hansel (aka MHC I)

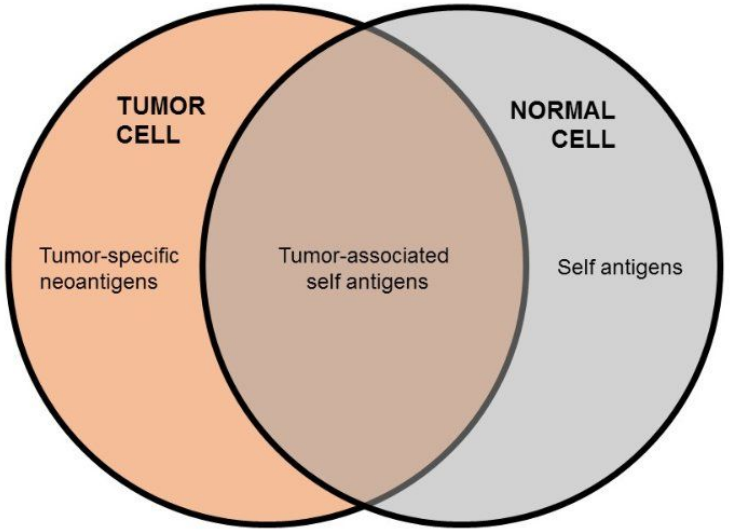


Gretel (aka MHC II)

https://www.britannica.com/science/major-histocompatibility-complex

Neoantigens

- Novel proteins found only in tumors
- Created by Non-synonomous somatic mutations that change an amino acid
- Can be presented by MHC and targeted by T-cells as non-self



https://blogs.shu.edu/cancer/2017/07/12/neo-antigen-vaccines-extend-progression-free-survival-in-melanoma/

Checkpoint blockade immunotherapies are a promising treatment and can prolong survival in some patients

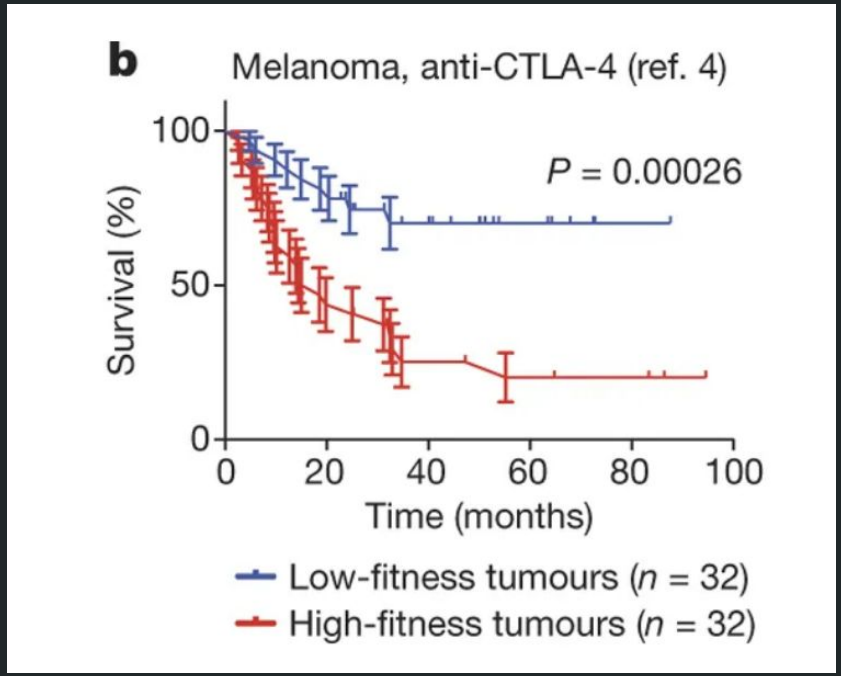
But many patients, receive little to no effects and can even experience harmful and/or painful/deadly side effects

Can we identify which patients are likely to respond to checkpoint blockade immunotherapies?

Let’s try to develop a neoantigen fitness predictive model …

- Fitness models are used to describe the dynamics of the evolutionary process
- The treatment places cancer cells under strong evolutionary pressure
- Can we predict how the system will respond to these pressures?

Spoiler Alert!



Let’s dive into the model……

The Science:

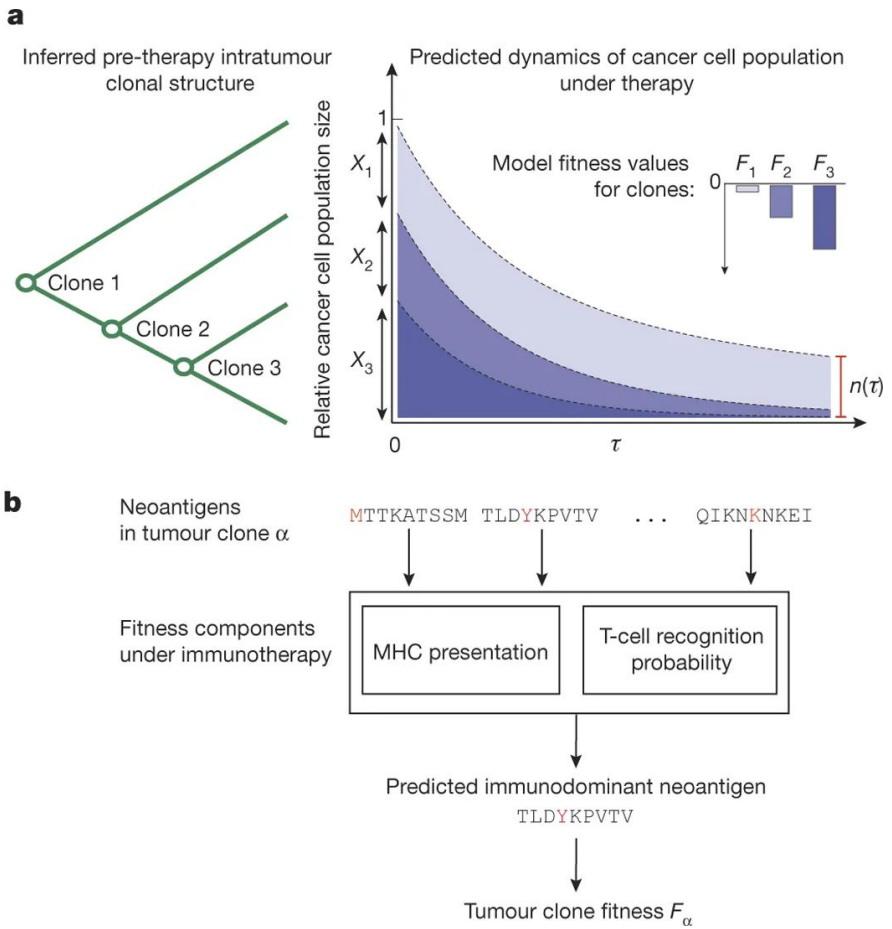
$n(\tau)$ =predicted future effective size of a cancer cell population in a tumour relative to its effective size at the start of therapy

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

τ = characteristic time scale

X_{α} = initial population size of each clone

F_{α} = the fitness value for each clone



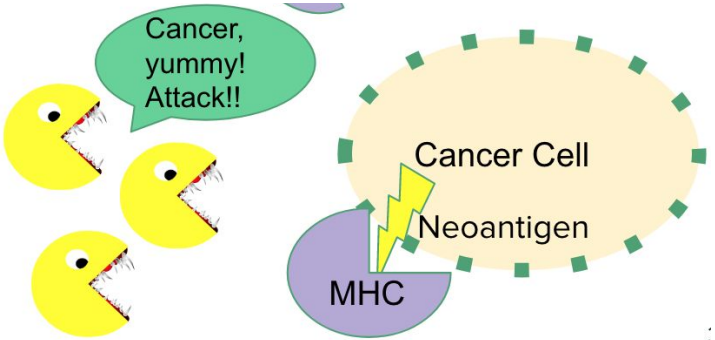
The Art:

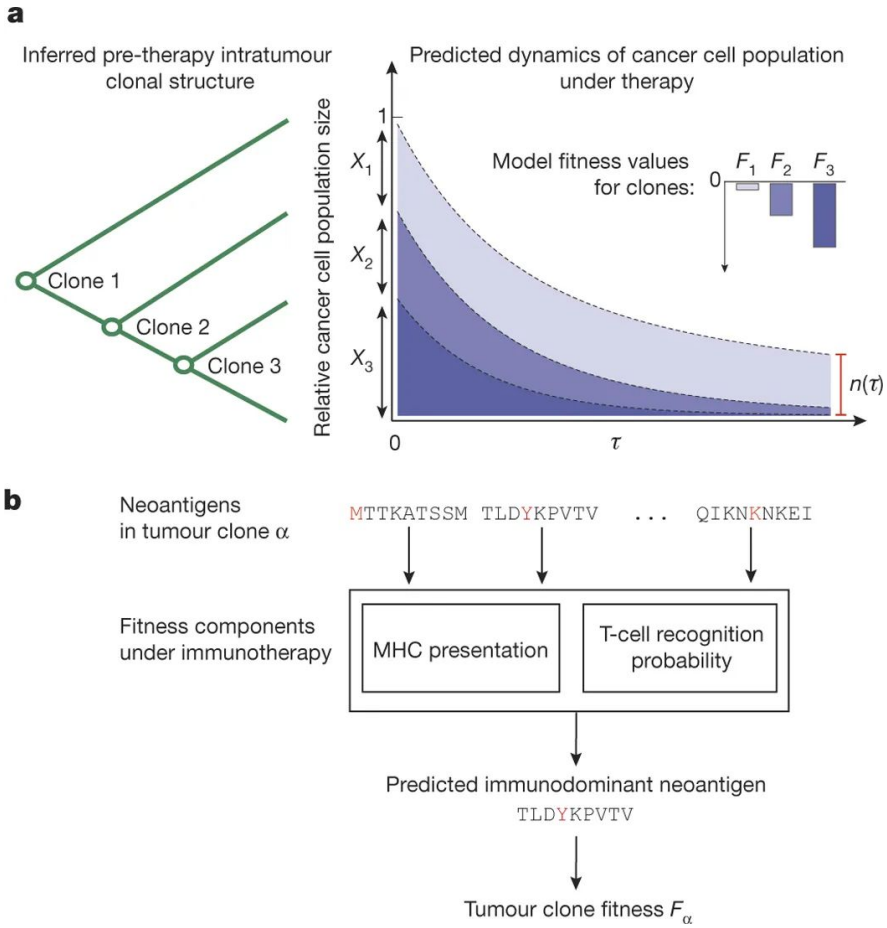
The dominant antigen approach

$$F_\alpha = - \max_{i \in \text{ clone } \alpha} (A_i \times R_i)$$

R = TCR recognition

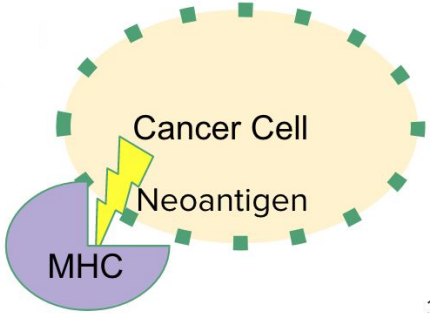
A = MHC Amplitude

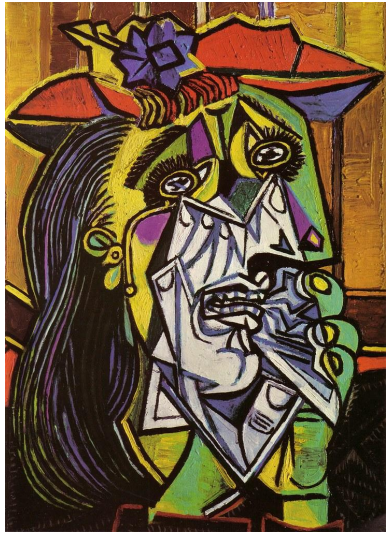




The Picasso:

MHC Amplitude





Amplitude is calculated as the product of two relative probabilities

Relative probability wild type (WT) neoantigen is not bound * relative prob mutant type class I MHC is bound to a neoantigen

$$A = (P_U^{\mathrm{WT}}/P_B^{\mathrm{WT}}) \times (P_B^{\mathrm{MT}}/P_U^{\mathrm{MT}})$$

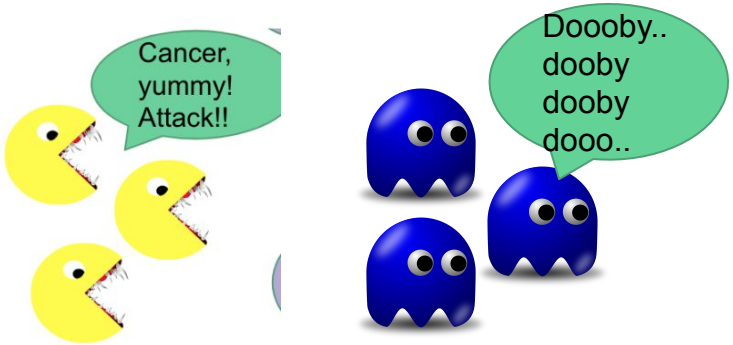
****If A is high, the immune system is good at discriminating between mutant and wild-type peptides****

$$A \approx \frac{K_{\mathrm{d}}^{\mathrm{WT}}}{K_{\mathrm{d}}^{\mathrm{MT}}} \cdot \frac{1}{1 + (\varepsilon/[L]) \cdot K_{\mathrm{d}}^{\mathrm{WT}}}$$

$K_d =$ Dissociation constant = inferred binding affinities in IC50 values

The Warhol:

TCR Recognition



R = probability that a neoantigen will be recognized by the TCR repertoire

*****Higher sequence similarity between epitopes and neoantigens implies higher probability of recognition*****

$$R = Z(k)^{-1} \sum_{e \in \mathrm{IEDB}} \exp(-k(a - |s, e|))$$

$$Z(k) = 1 + \sum_{e \in \mathrm{IEDB}} \exp(-k(a - |s, e|))$$

$|s, e|$ Alignment score

k, a Free parameters specifying shape of the logistic curve

$IEDB$ Database of input set of linear epitopes

Parameter Estimation & Model Selection

Parameter Estimation

$$\Theta = (a, k, \tau)$$

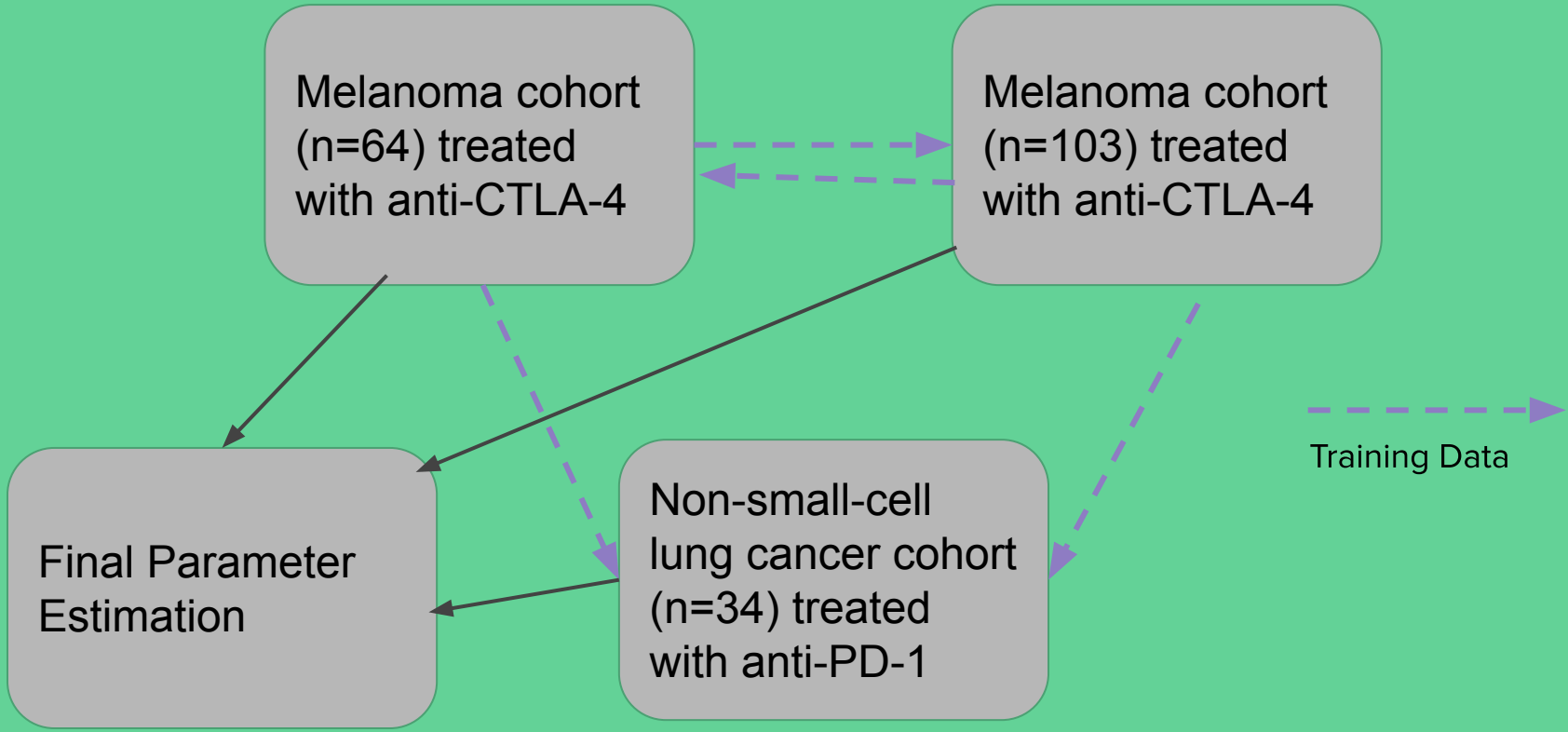
Find parameters that maximize the log-rank test scores of the survival analysis by patient cohorts

I.e. Find the parameters that maximizes the differences in how the survival curves split between low fitness and high fitness values.

Alternative Fitness Models

- The dominant neoantigen approach is one of many possible approaches
  - Decomposition into only A and R
  - Variations of models for R
  - Sum of clones
  - Constant fitness for each clone
  - Homogenous clonal structure

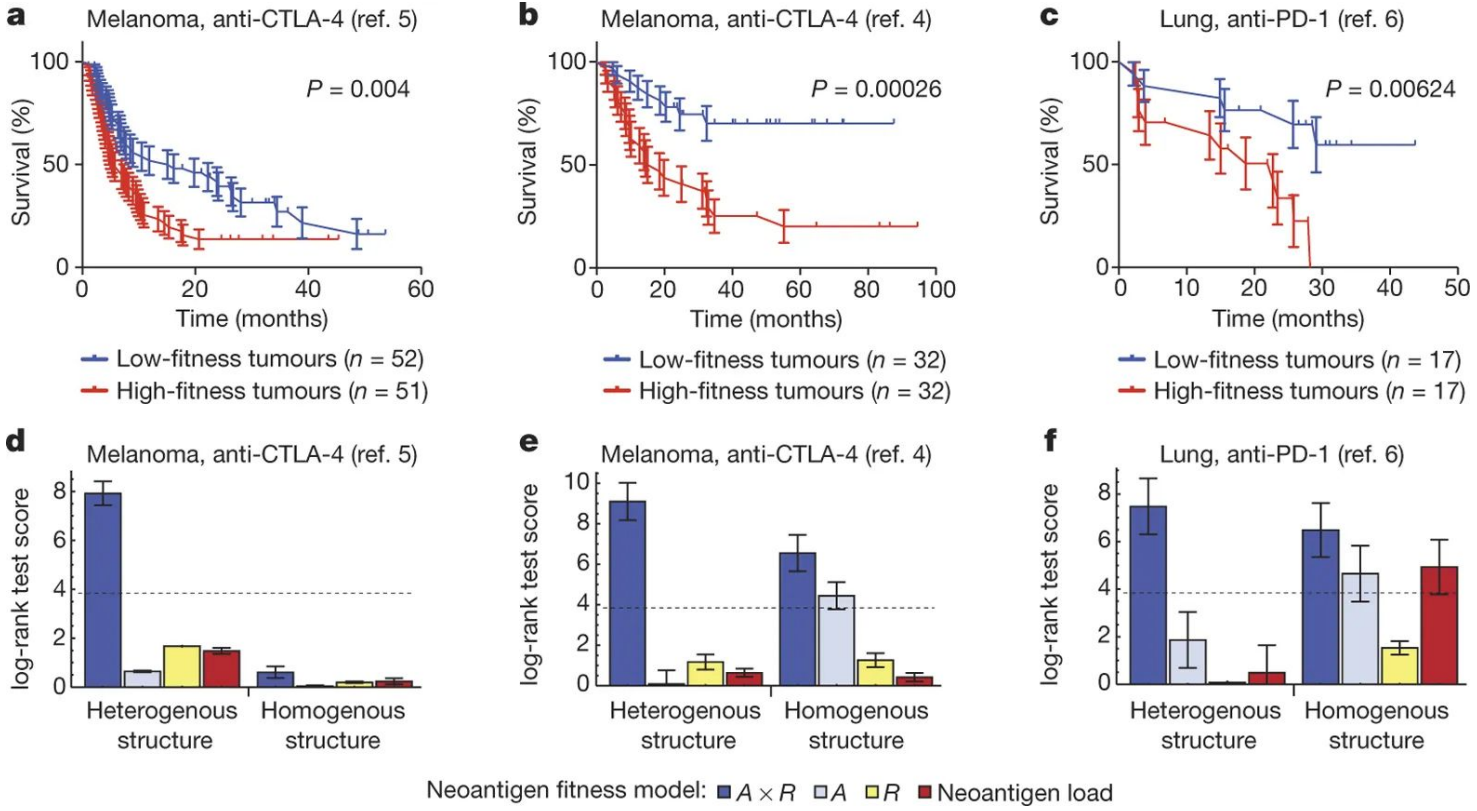
Evaluation Metric = Survival



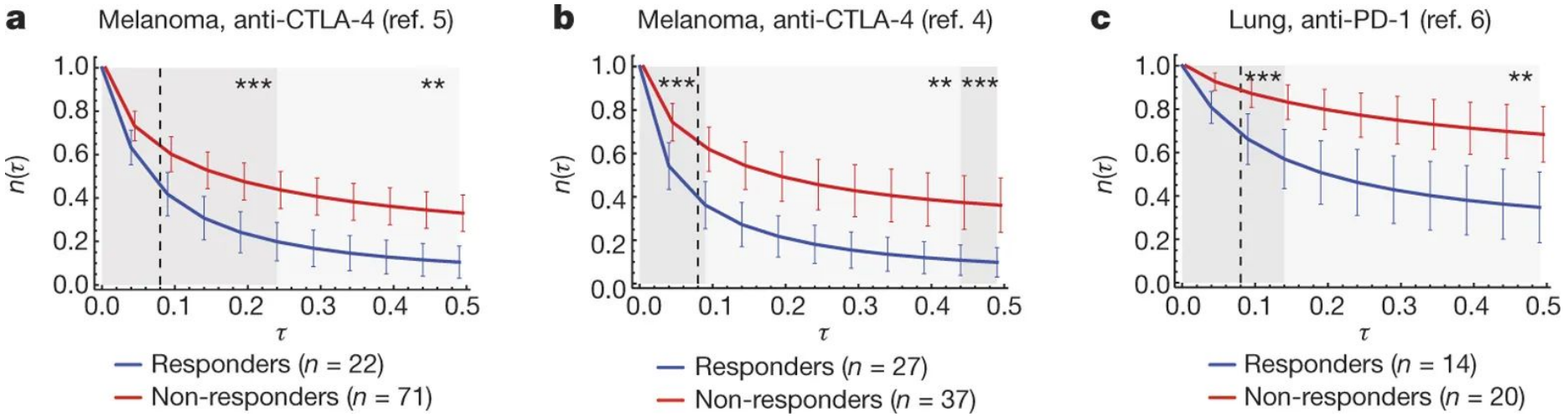
Key Assumptions

- We can identify the correct cancer phylogenetic tree (PhyloWGS is used)
- Subclones have the same or lower fitness than ancestors because they have to acquire new dominant neoantigens
- There are similar concentrations for mutant and wild-type peptides (impacts estimation of A)
- Neoantigen predicted to cross-react with selected immunogenic epitopes in the IEDB are more likely to be immunogenic themselves (impacts estimation of R)

Results


a
Melanoma, anti-CTLA-4 (ref. 5)
P = 0.004
Survival (%)
Time (months)
Low-fitness tumours (n = 52)
High-fitness tumours (n = 51)
b
Melanoma, anti-CTLA-4 (ref. 4)
P = 0.00026
Survival (%)
Time (months)
Low-fitness tumours (n = 32)
High-fitness tumours (n = 32)
c
Lung, anti-PD-1 (ref. 6)
P = 0.00624
Survival (%)
Time (months)
Low-fitness tumours (n = 17)
High-fitness tumours (n = 17)
d
Melanoma, anti-CTLA-4 (ref. 5)
log-rank test score
Heterogenous structure
Homogenous structure
e
Melanoma, anti-CTLA-4 (ref. 4)
log-rank test score
Heterogenous structure
Homogenous structure
f
Lung, anti-PD-1 (ref. 6)
log-rank test score
Heterogenous structure
Homogenous structure
Neoantigen fitness model: A × R A R Neoantigen load

Prediction of Evolutionary Dynamics



Take Home Messages

FYI, I believe if I include an adorable puppy, you will better recall everything on this slide.

- Model quantifies how the immune system will respond to neoantigens (aka level of non-self)
- Because it is a mechanistic model, it could be useful for better understanding acquired resistance to therapy
- A useful step towards therapeutic targets of tumor vaccines

Future Directions

- Use a machine learning approach to predict survival and compare results to mechanistic model
- Incorporate features of the microbiome into fitness model
- Use a similar fitness approach to model acquisition of driver mutations
- Study the impact of phylogenetic tree inference on fitness estimation (how sensitive is the model to the input)