SITC 2019

Gaylord National Hotel
& Convention Center

Nov. 6-10

NATIONAL HARBOR, MARYLAND

sitc

Society for Immunotherapy of Cancer

Predicting Tumor Response to Immunotherapies

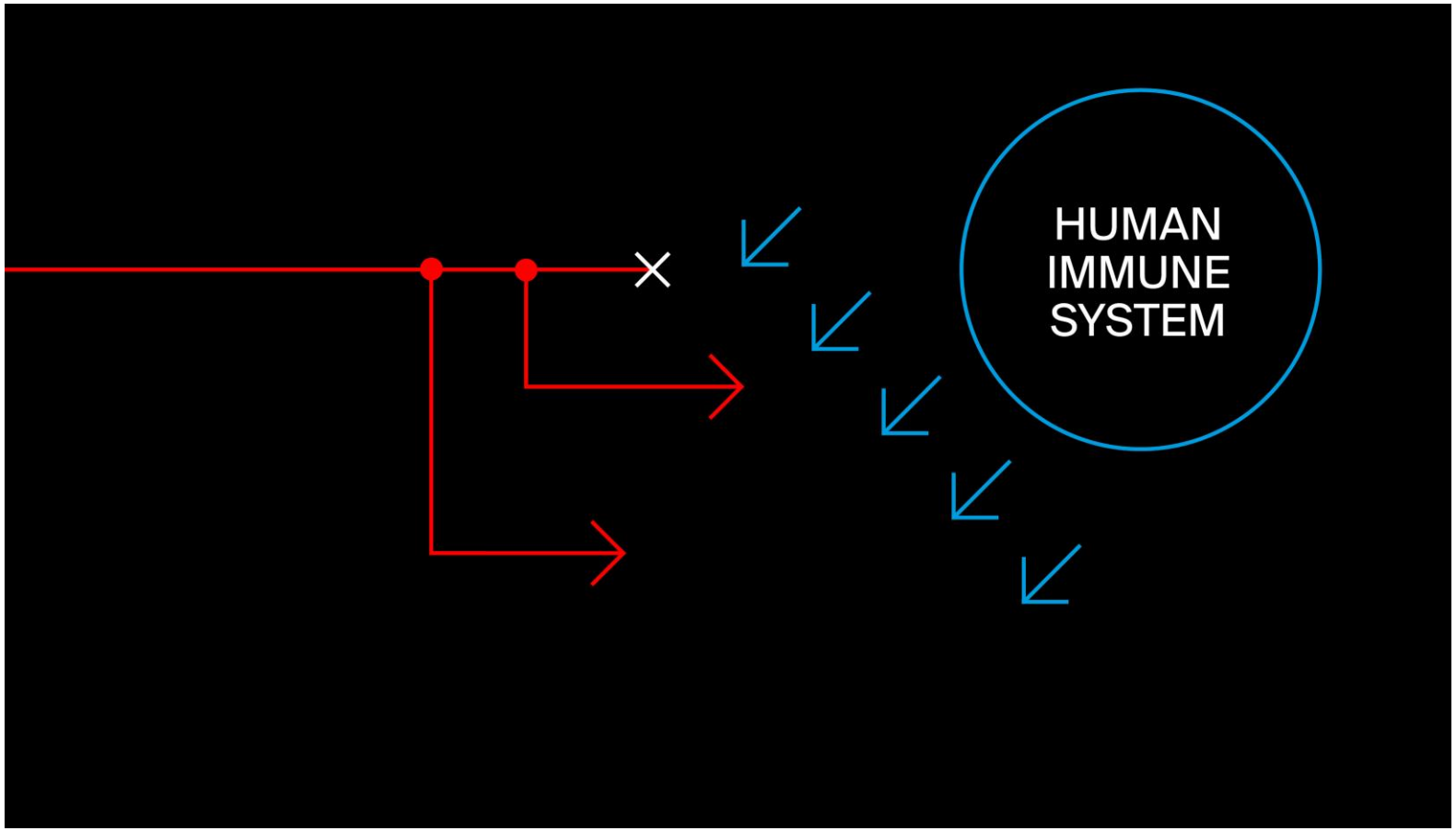
Marta Łuksza
Icahn School of Medicine, Mount Sinai, New York
SITC, November 9th 2019

Disclosure

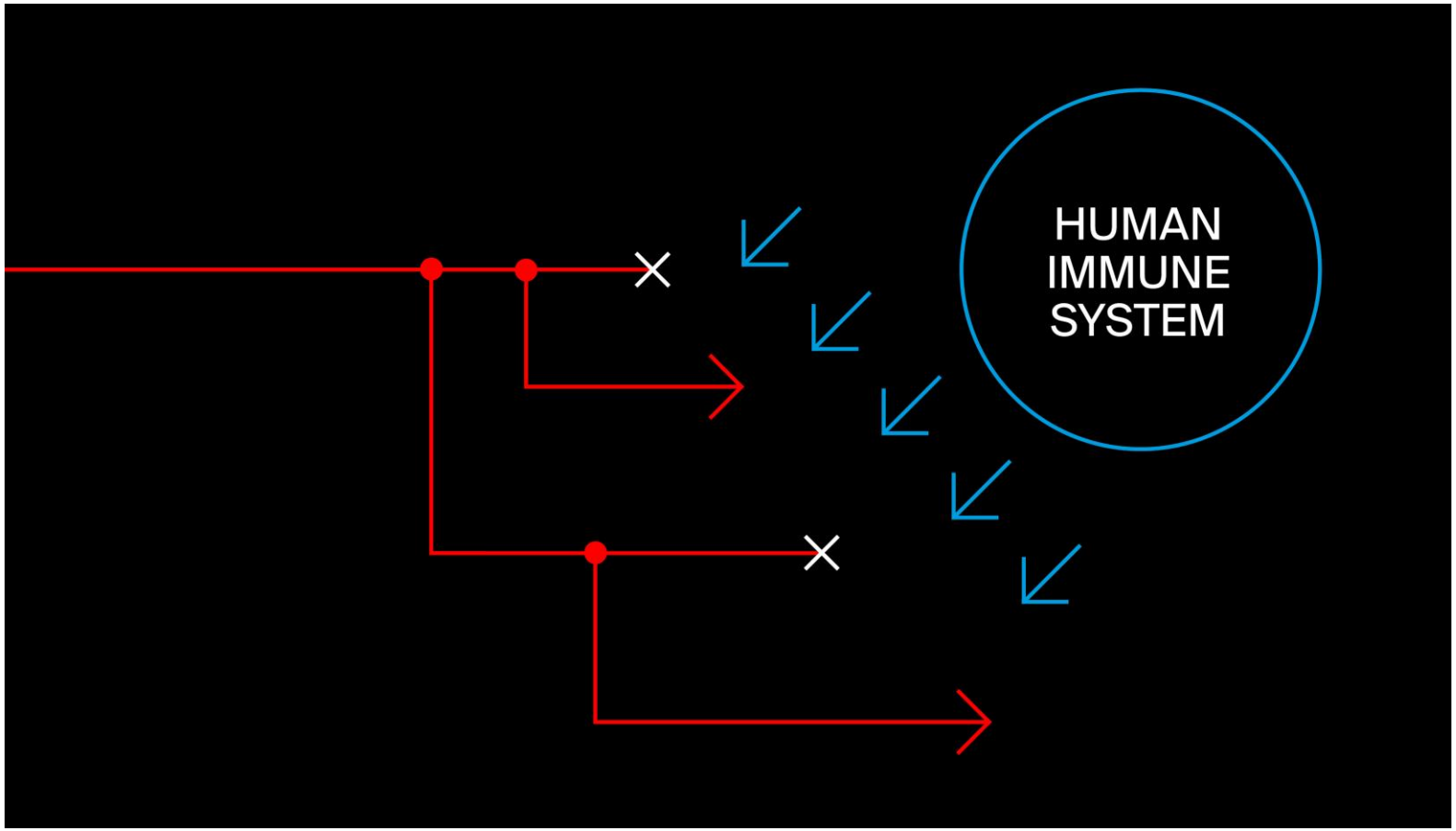
Honorarium from: Merck, Bristol-Myers Squibb

Pathogen/cancer arms race with the immune system

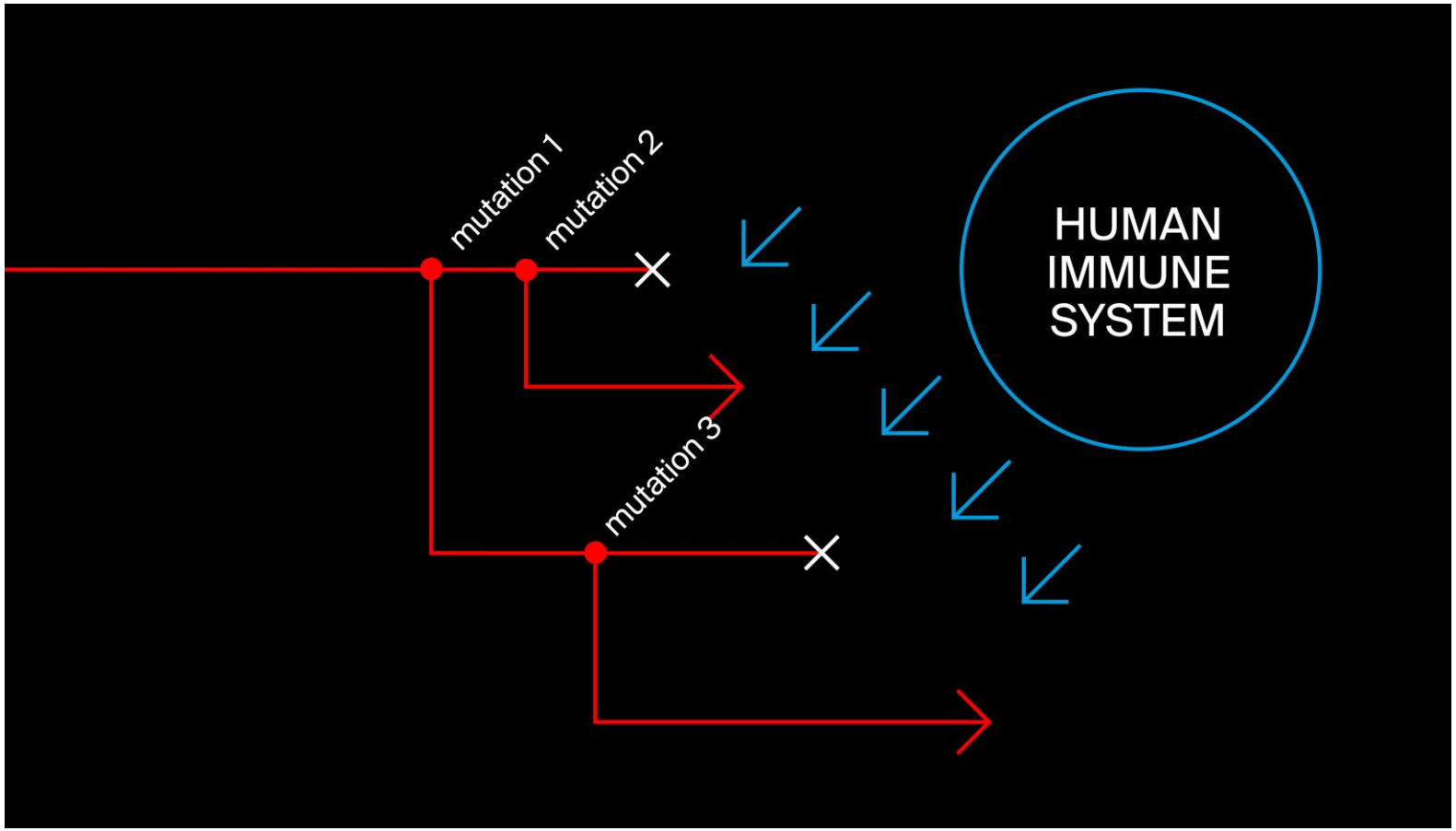
Pathogen/cancer arms race with the immune system



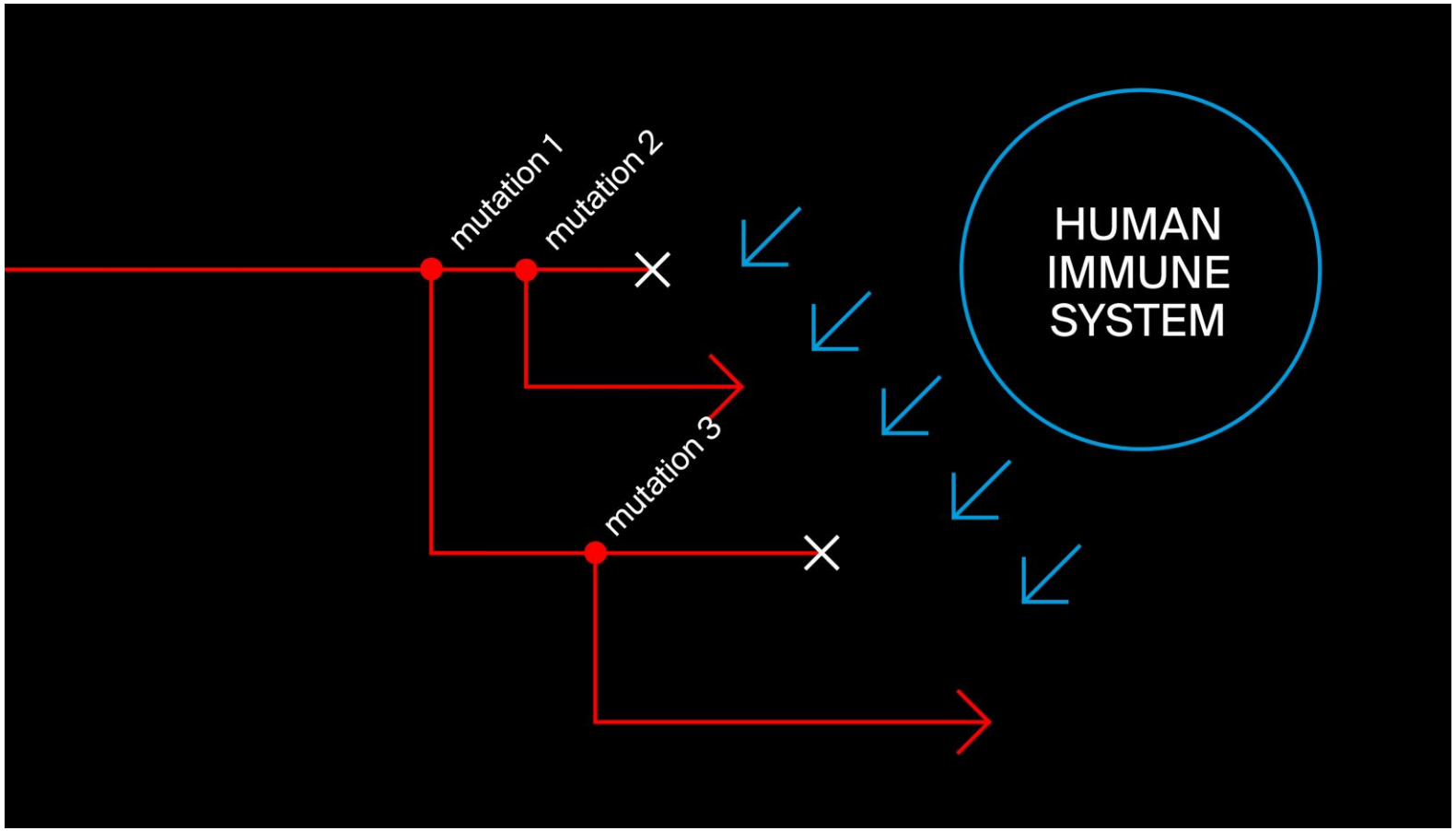
Pathogen/cancer arms race with the immune system



Pathogen/cancer arms race with the immune system



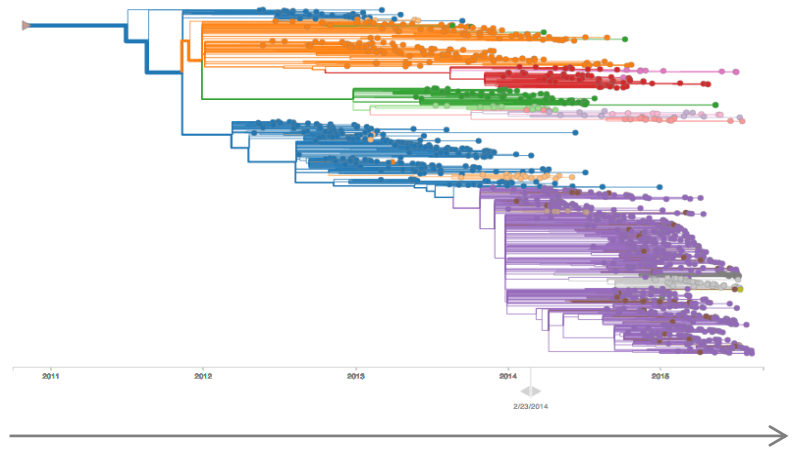
Pathogen/cancer arms race with the immune system



Can we quantify the immune interactions to predict the evolution?

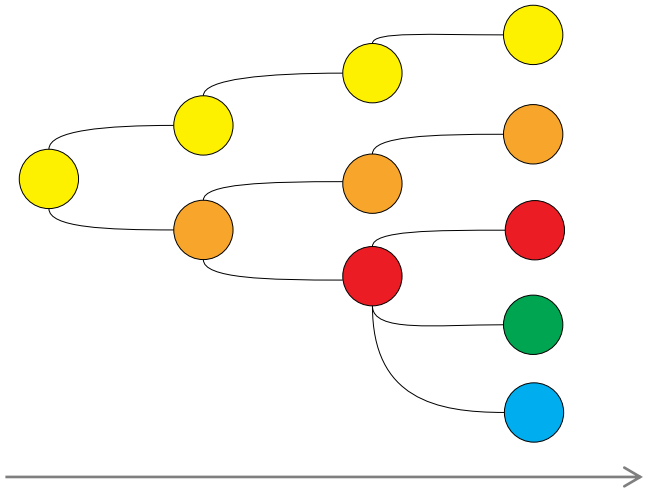
Immune-fitness models for evolutionary predictions

Influenza



time

Cancer + immunotherapy

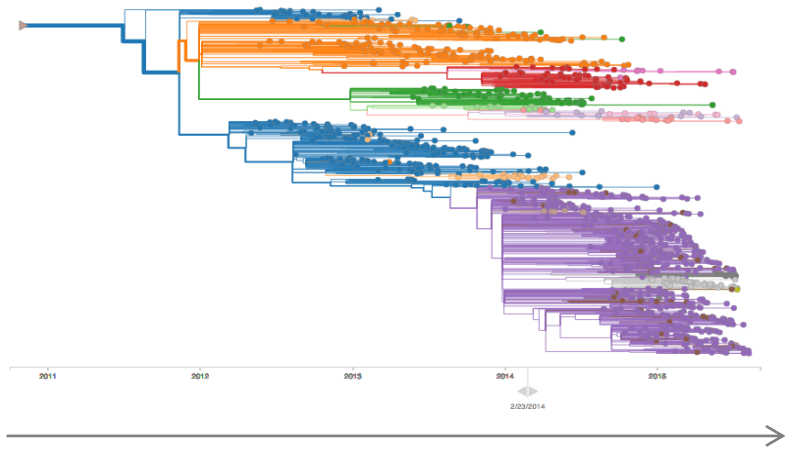


time

– High population heterogeneity
– Strong **immune** selection

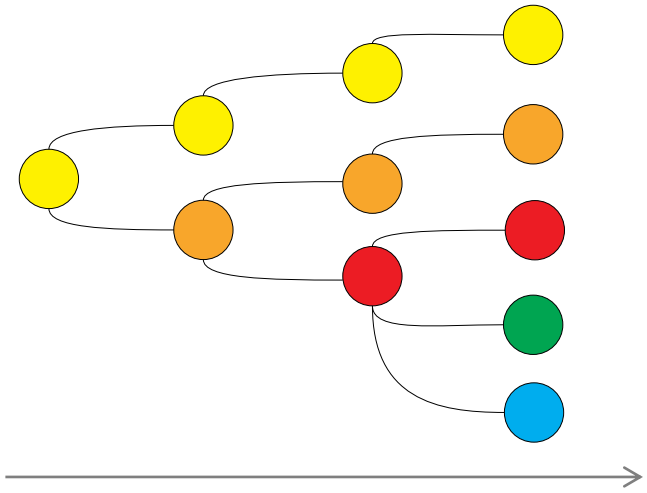
Immune-fitness models for evolutionary predictions

Influenza



time

Cancer + immunotherapy



time

[Łuksza&Lässig, Nature 2014]

Evolutionary predictions based on a **fitness model** are currently used to support the influenza vaccine selection by the WHO.

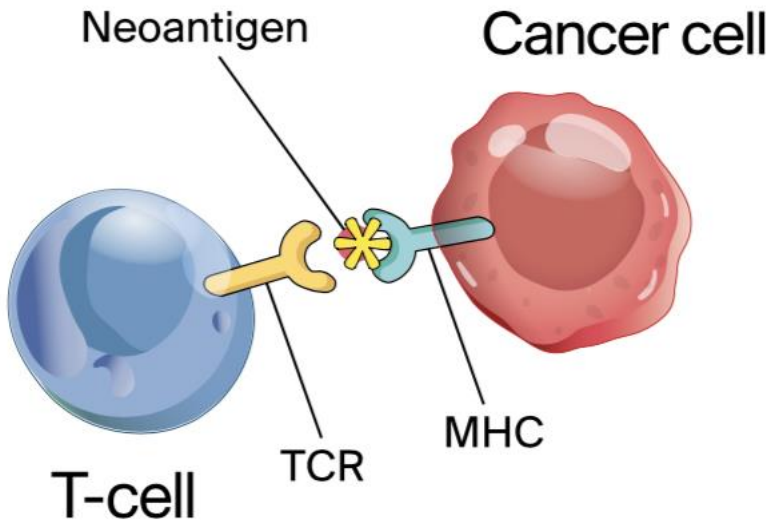
Neoantigen fitness model for tumors

The learning problem:

Predict tumor response to immunotherapy from genetic data

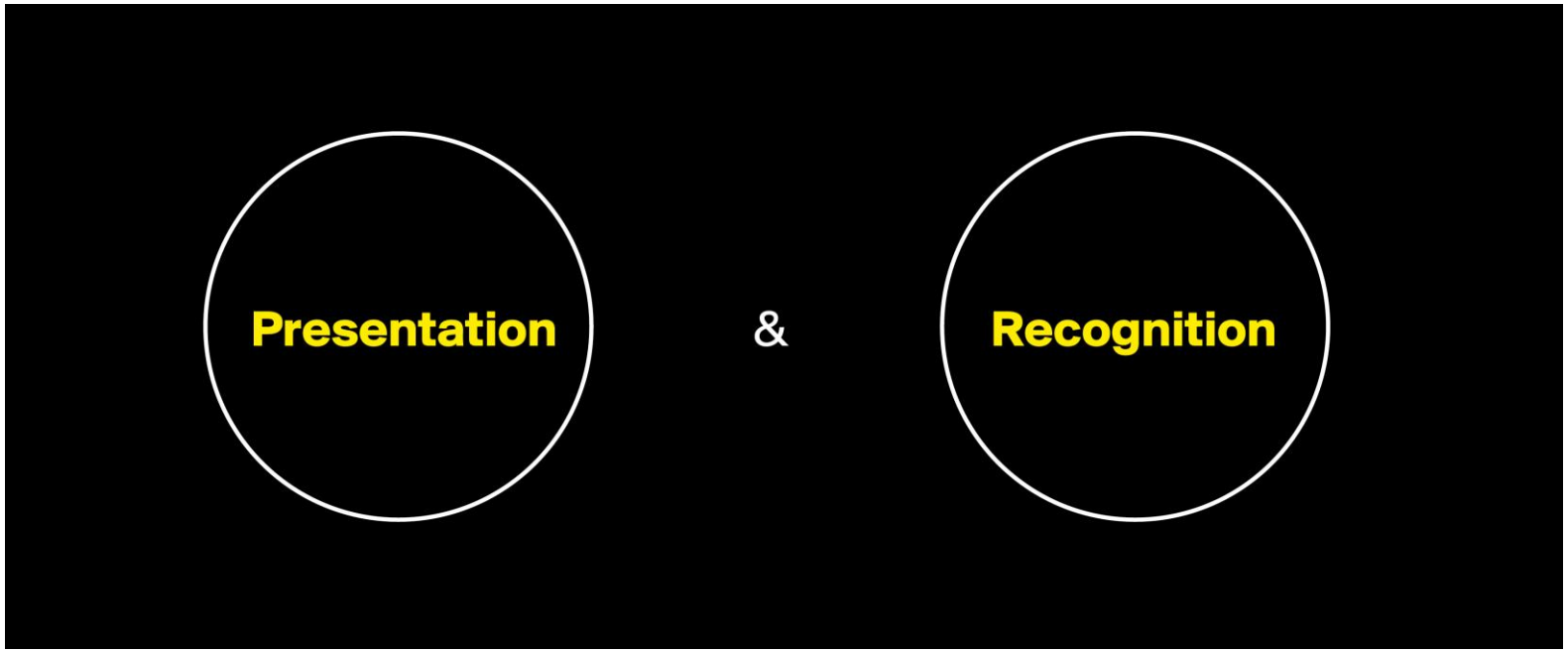
Learning problem challenge 1: molecular complexity

MHC-presented neoantigens are potentially **immunogenic:**
recognized by the host's T-cells



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

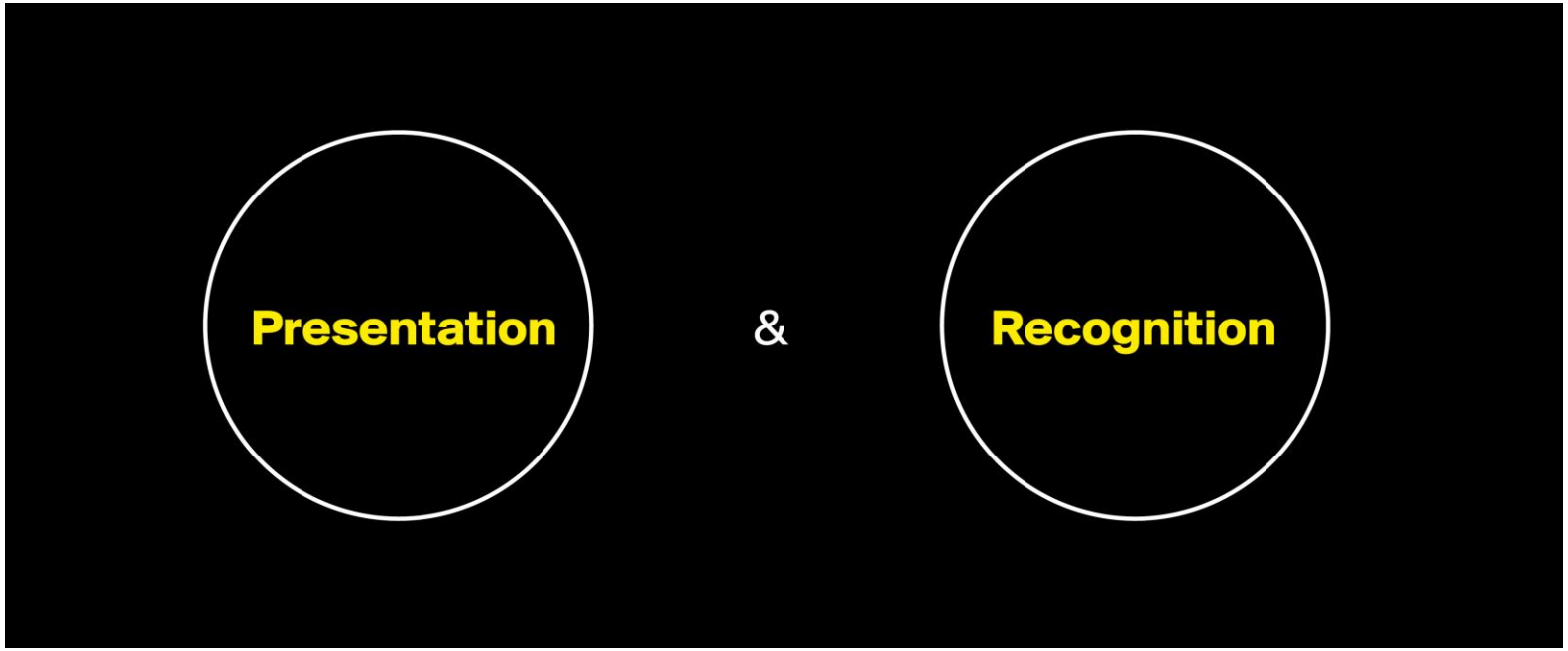
Learning problem challenge 1: molecular complexity



Fitness of a cancer cell is decreased due to recognition of presented neoantigens.

Goal: quantify the likelihood of these events **using genomics patient data**

Learning problem challenge 1: molecular complexity



- **Likelihood of presentation** based on binding affinities inferred with the netMHC algorithm, trained on (abundant) MHC assay data

[netMHC, Nielsen et al, Protein Sci,2003]

Probability of neoantigen TCR-recognition

Our solution: let's copy how others do it:
Compare tumor neoantigens to pathogens

Tumor neoantigen:	PPSARRGPL
Human Herpes Virus (HHV)-8:	PPSGQRGPV

- Positive examples from the IEDB database of validated T-cell assays for microbial epitopes

[Łuksza et al, Nature 2017]

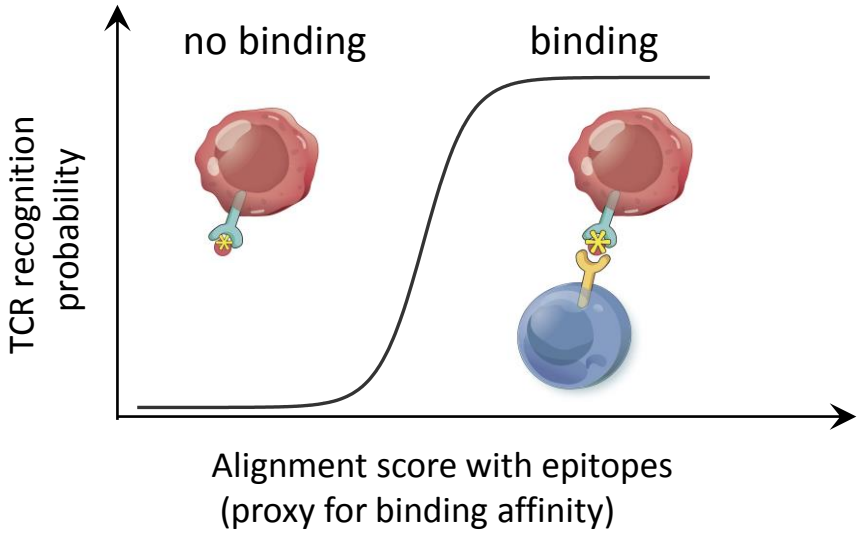
Probability of neoantigen TCR-recognition

Our solution: let's copy how others do it:
Compare tumor neoantigens to pathogens

Tumor neoantigen:	PPSARRGPL
Human Herpes Virus (HHV)-8:	PPSGQRGPV

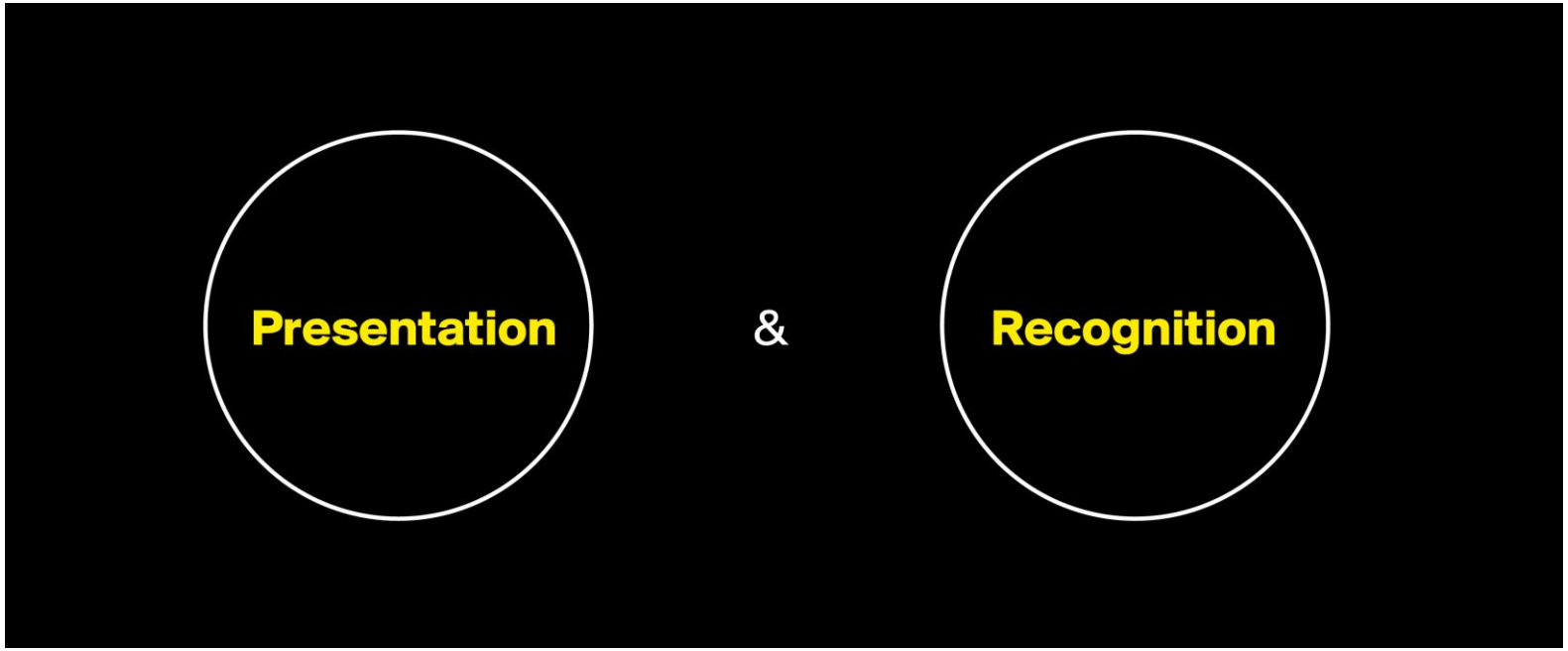
– Positive examples from the IEDB database of validated T-cell assays for microbial epitopes

And use a biophysical model:



[Łuksza et al, Nature 2017]

Learning problem challenge 1: molecular complexity



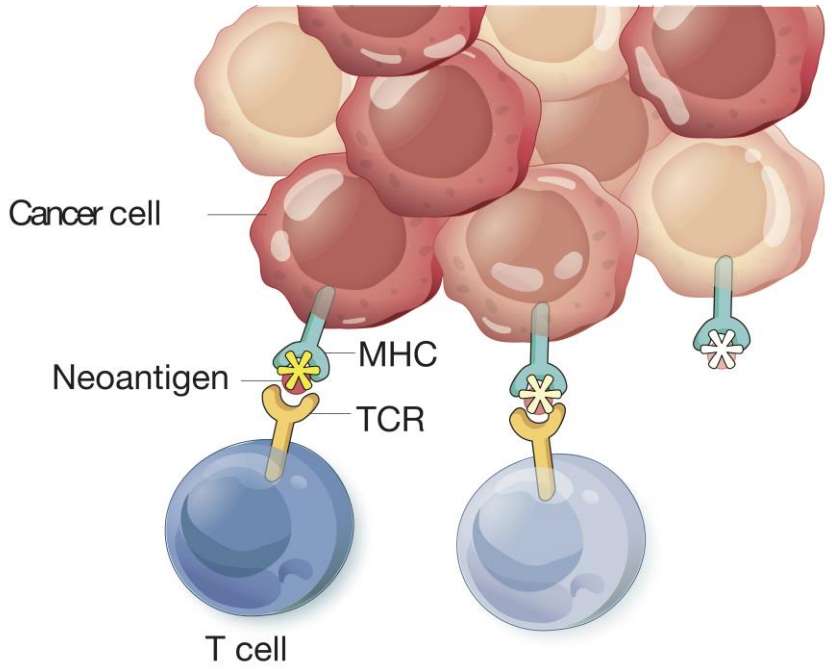
Fitness of a cancer cell is decreased due to recognition of presented neoantigens:

$$F = F_0 - (\text{MHC presentation probability} \times \text{TCR recognition probability})$$

[Łuksza et al, Nature 2017]

Learning problem challenge 2: Tumor heterogeneity

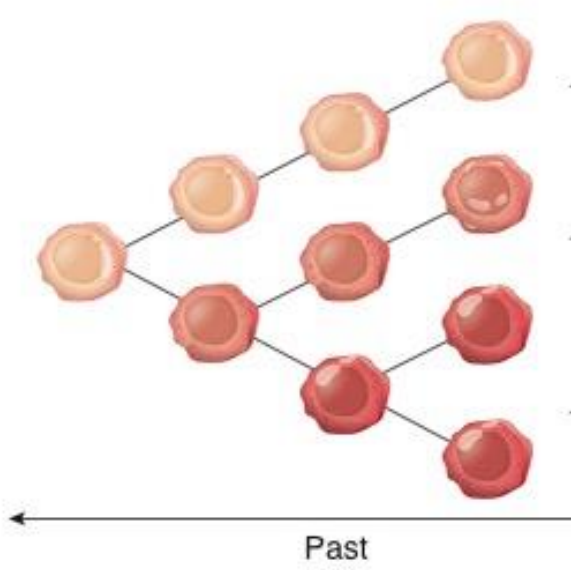
- Tumor cells are genetically heterogeneous
- They potentially have different immune interactions



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

Learning problem challenge 2: Tumor heterogeneity

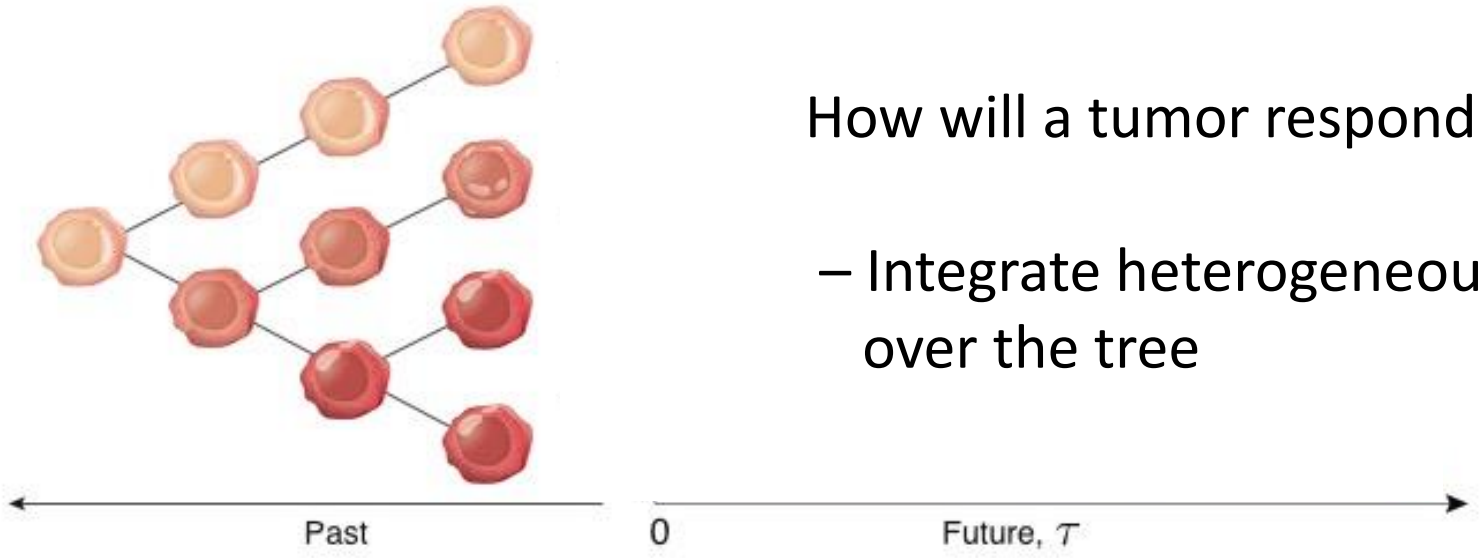
Tumor is **an evolving population of cancer cells**



[PhyloWGS algorithm for bulk sequencing data, Deshwar et al, 2015]

Learning problem challenge 2: Tumor heterogeneity

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

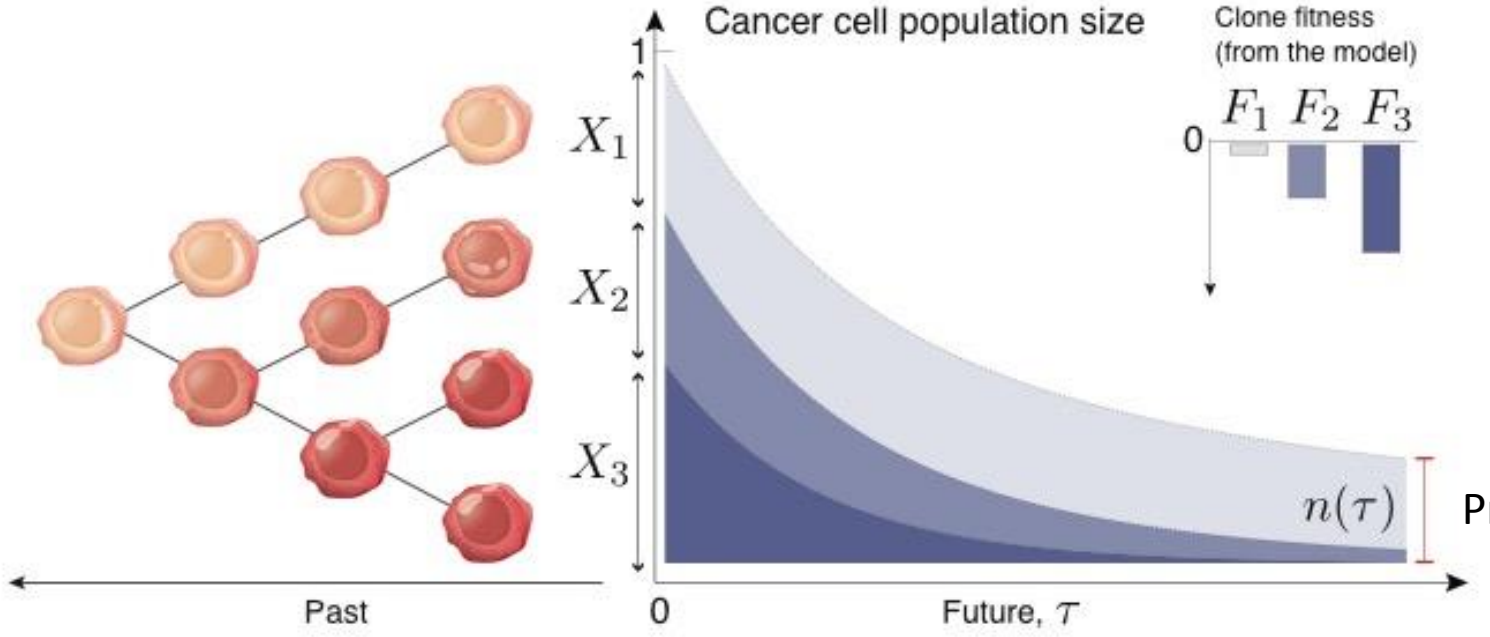


How will a tumor respond to therapy?

– Integrate heterogeneous fitness effects over the tree

Learning problem challenge 2: Tumor heterogeneity

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



Predicted size after therapy

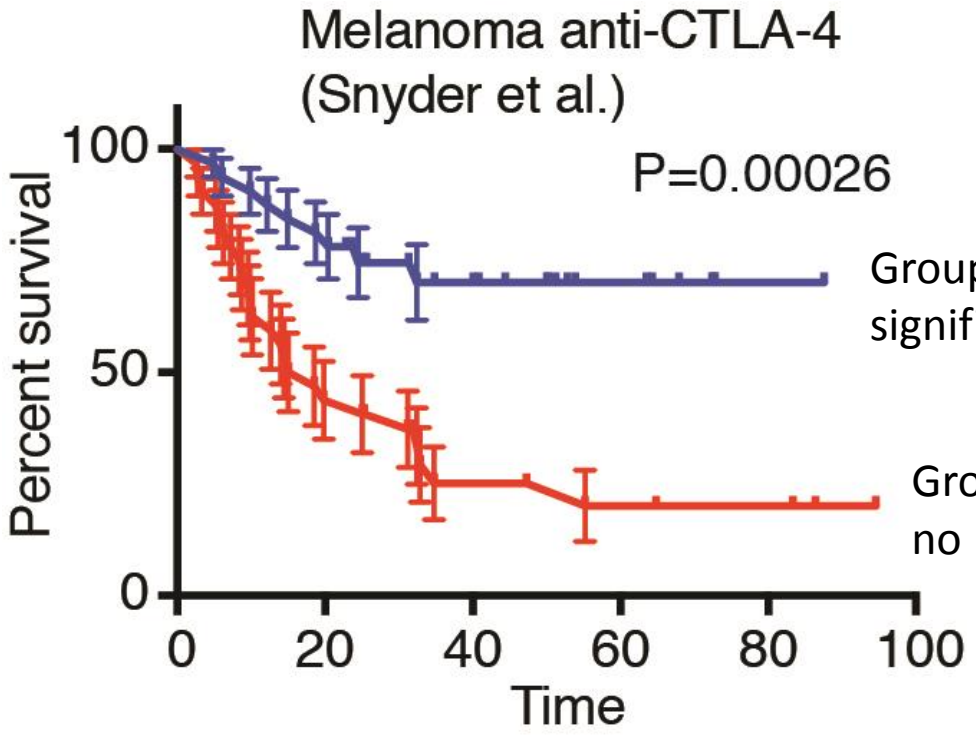
$$n(\tau) = \sum_{\alpha} X_\alpha \exp[F_\alpha \tau]$$

Initial clone frequency (from phylogeny)

Fitness of clone (derived from model)

[Łuksza et al, Nature 2017]

Model based analysis is predictive of survival

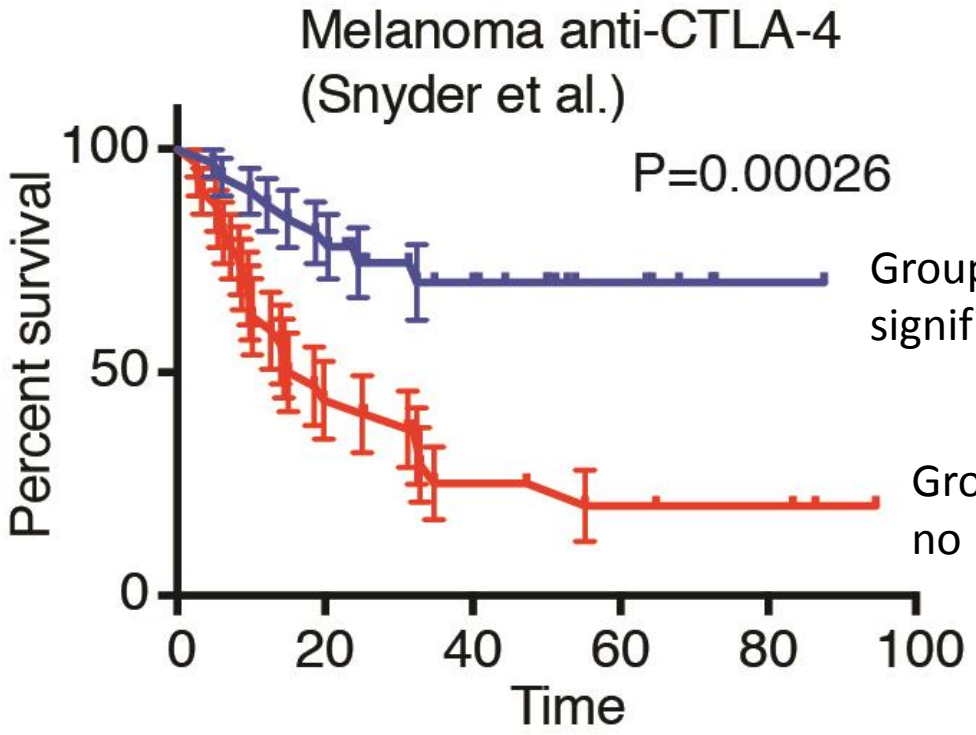


Group with **positive** prediction:
significant reduction of tumor size

Group with **negative** prediction:
no reduction of tumor size

[Łuksza et al, Nature 2017]

Model based analysis is predictive of survival



Group with **positive** prediction:
significant reduction of tumor size

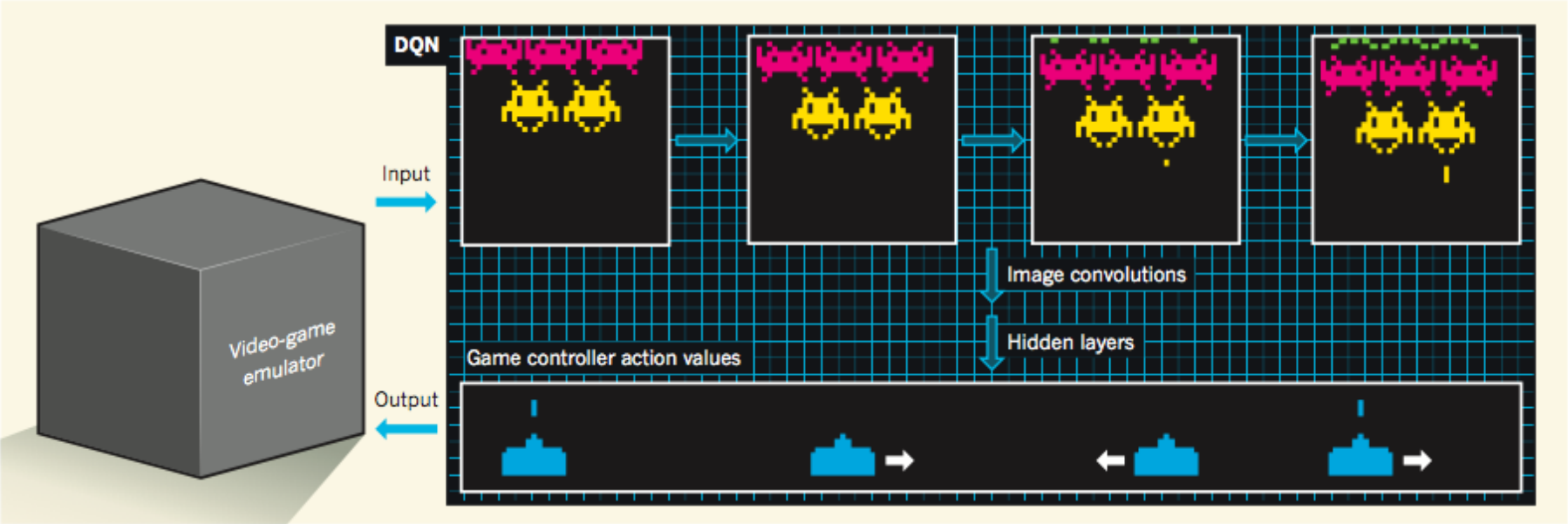
Group with **negative** prediction:
no reduction of tumor size

Validated on two anti-CTLA4 melanoma cohorts, anti-PD1 lung cohort,
and (unpublished): NSLCC cohort, metastatic pancreatic cancer cohort.

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

Are models still needed?

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



Go: Silver et al Nature 2017, Go & chess, Silver et al Science 2018:

Are models still needed?

Silver, D. et al. Nature, 2016:

*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.*

- Patient cohorts are not big data
- High molecular & population complexity
- These differences favor constrained **mechanism-informed models** for making evolutionary predictions.

Summary

- We develop **biophysically motivated models of immune interactions**
- Such models allow us to **predict the evolution** of cancer and viral pathogens
- Such predictions can **inform treatment strategies**

Acknowledgments

Cancer and immune system

Mount Sinai, New York:
Benjamin Greenbaum
David Hoyos
Alexander Solovyov
Princeton
Arnold Levine (IAS)
Curtis Callan (PU)
Victor Mikhaylov (IAS)
MSKCC, New York
Vinod Balachandran , Taha Merghoub
Steven Leach , Timothy Chan
Jedd Wolchok
Matthew Hellman, Yuval Elhanati
Zachary Sethna

Viral evolution

Cologne University, Germany:
Michael Lässig
Simone Pompei
Denis Ruchnewitz
Matthijs Meijers
University of Glasgow, UK
Richard Reeve , William Harvey
Francis Crick Institute, London, UK
John McCauley, Rodney Daniels