Society for Immunotherapy of Cancer

Mutation Drivers of Immunological Responses to Cancer

Eduard Porta-Pardo

La Caixa Junior Leader Fellow

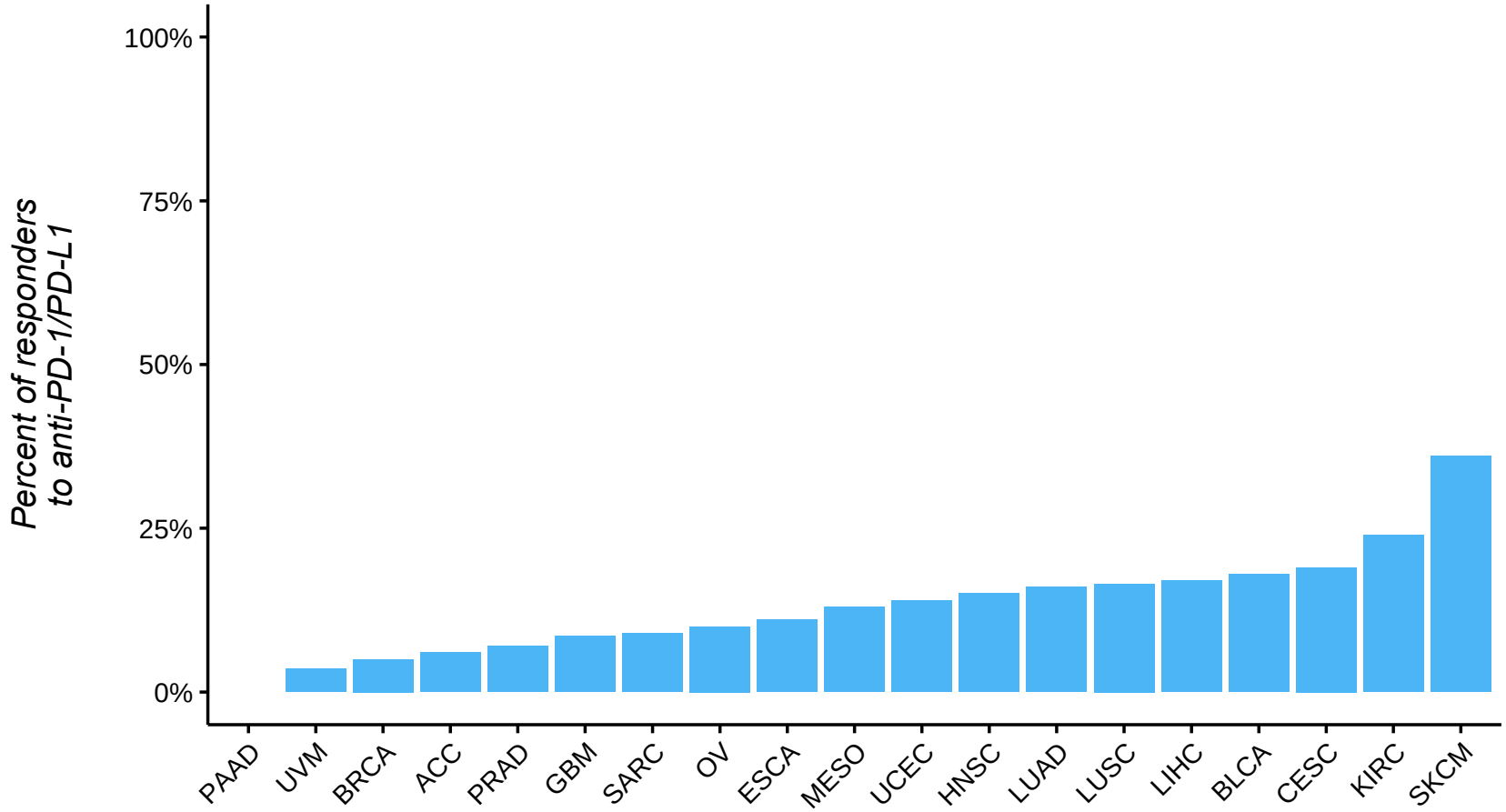
Barcelona Supercomputing Center (BSC)

Financial conflicts of interest

None

Society for Immunotherapy of Cancer

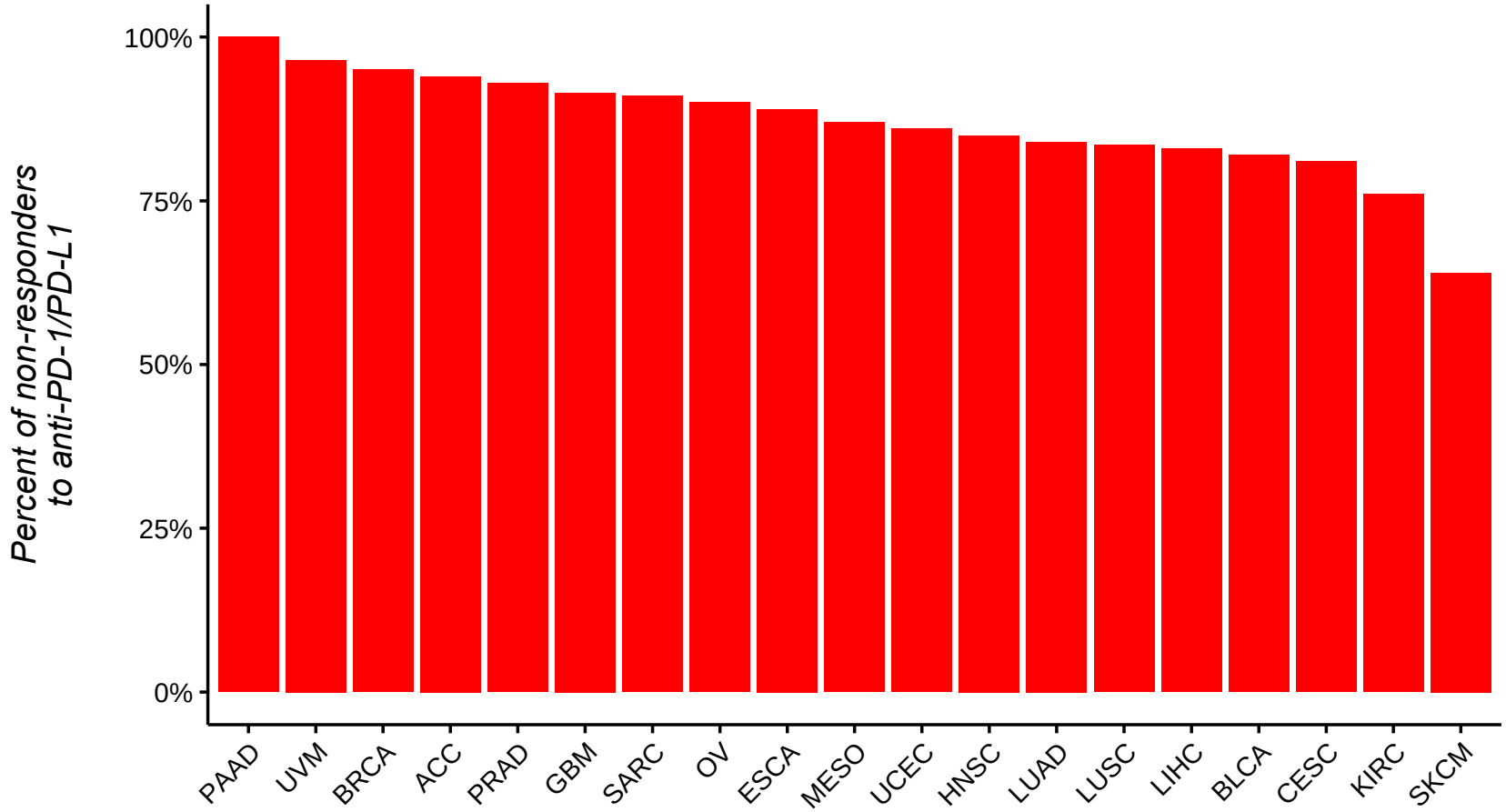
Exciting times in cancer immunology



sitc
Society for Immunotherapy of Cancer

Data from Joo Sang Lee and Eytan Ruppin, Jama Oncology, 2019

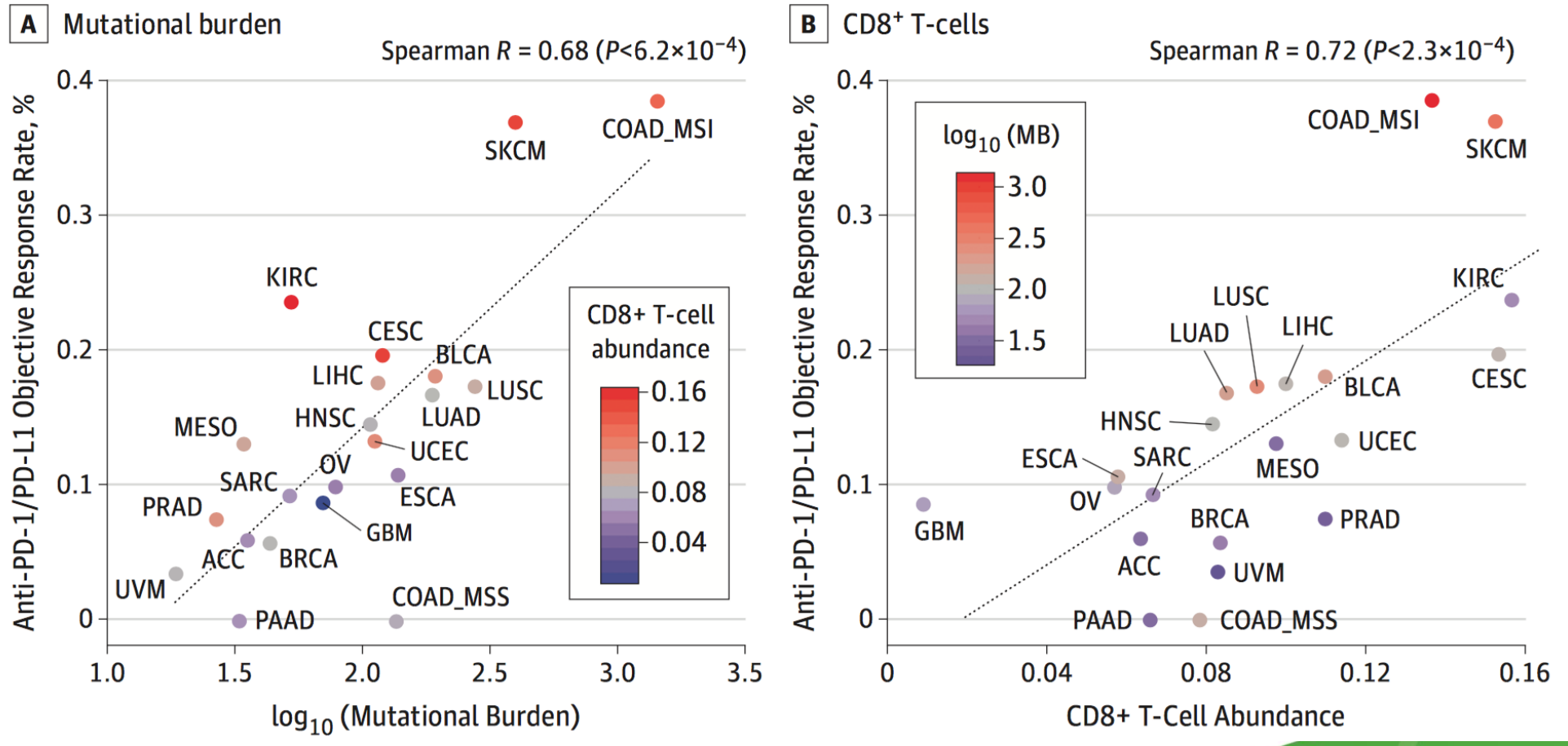
… but there's still a lot to do!



sitc
Society for Immunotherapy of Cancer

Data from Joo Sang Lee and Eytan Ruppin, Jama Oncology, 2019

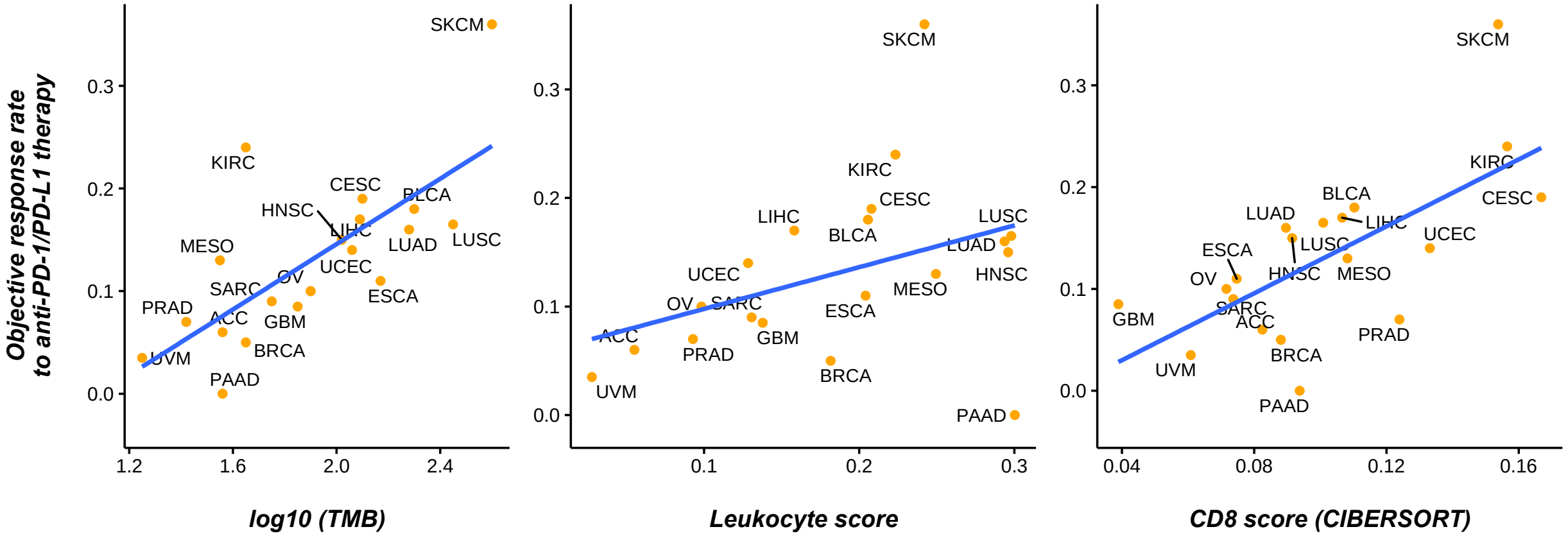
Predicting success of immune-based therapies



Joo Sang Lee and Eytan Ruppin, Jama Oncology, 2019

Society for Immunotherapy of Cancer

This is also true with other immune scores



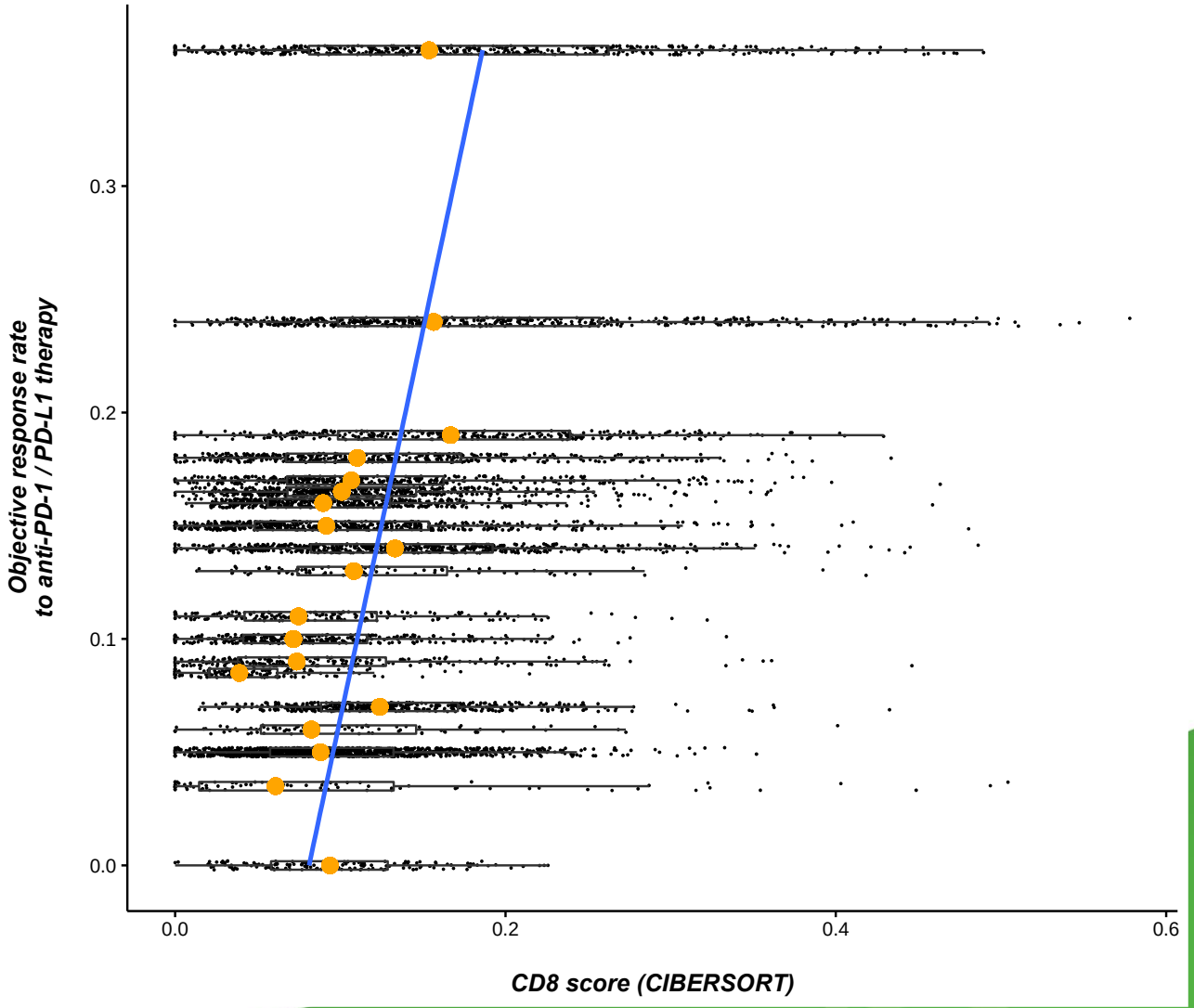
Society for Immunotherapy of Cancer

Data from Thorsson *et. al.* 2018 and Sang Lee and Ruppin 2019

Medians hide an immense variability

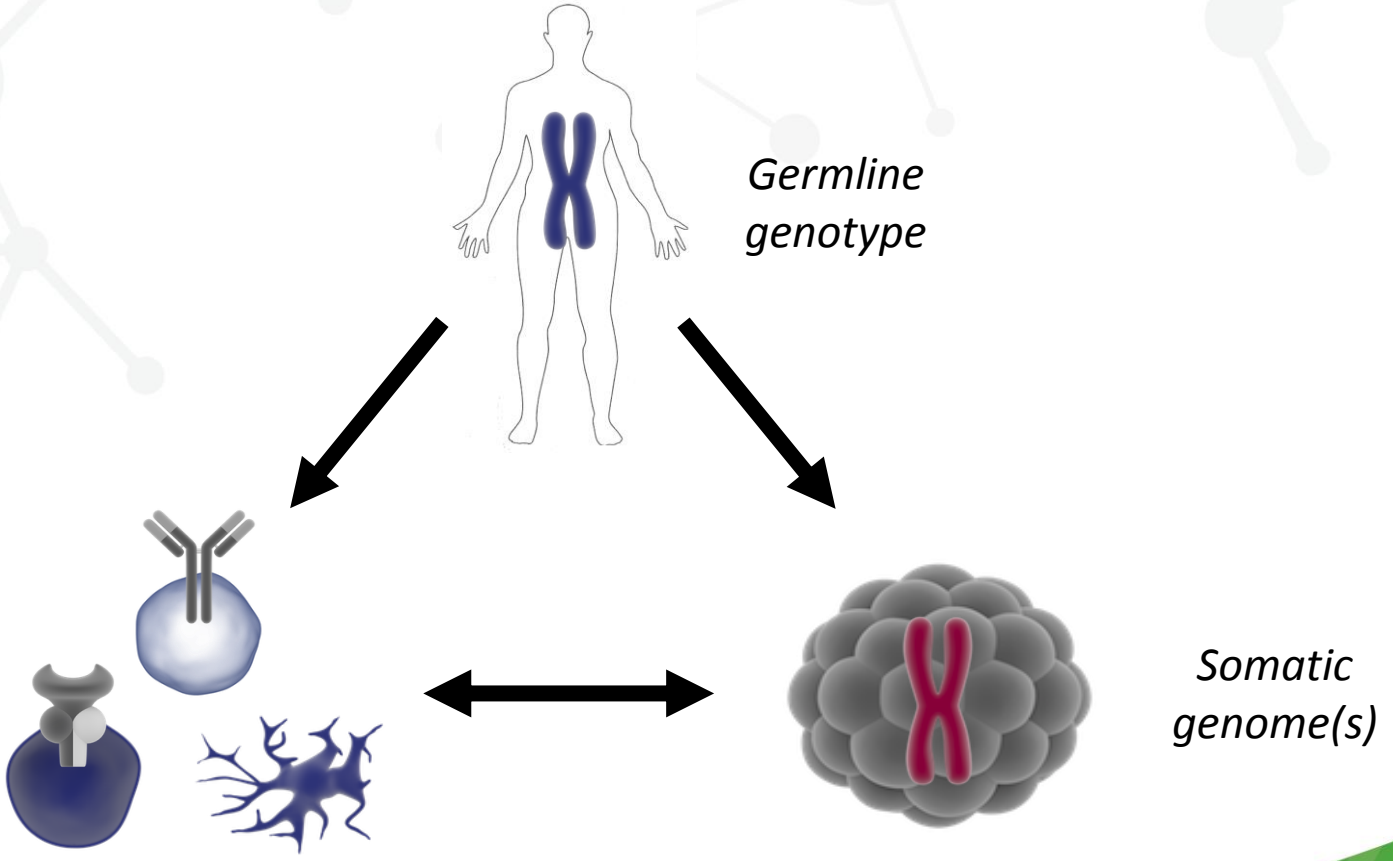
Each black dot is a TCGA sample.

Orange dots represent the median of CD8 score for each cancer type



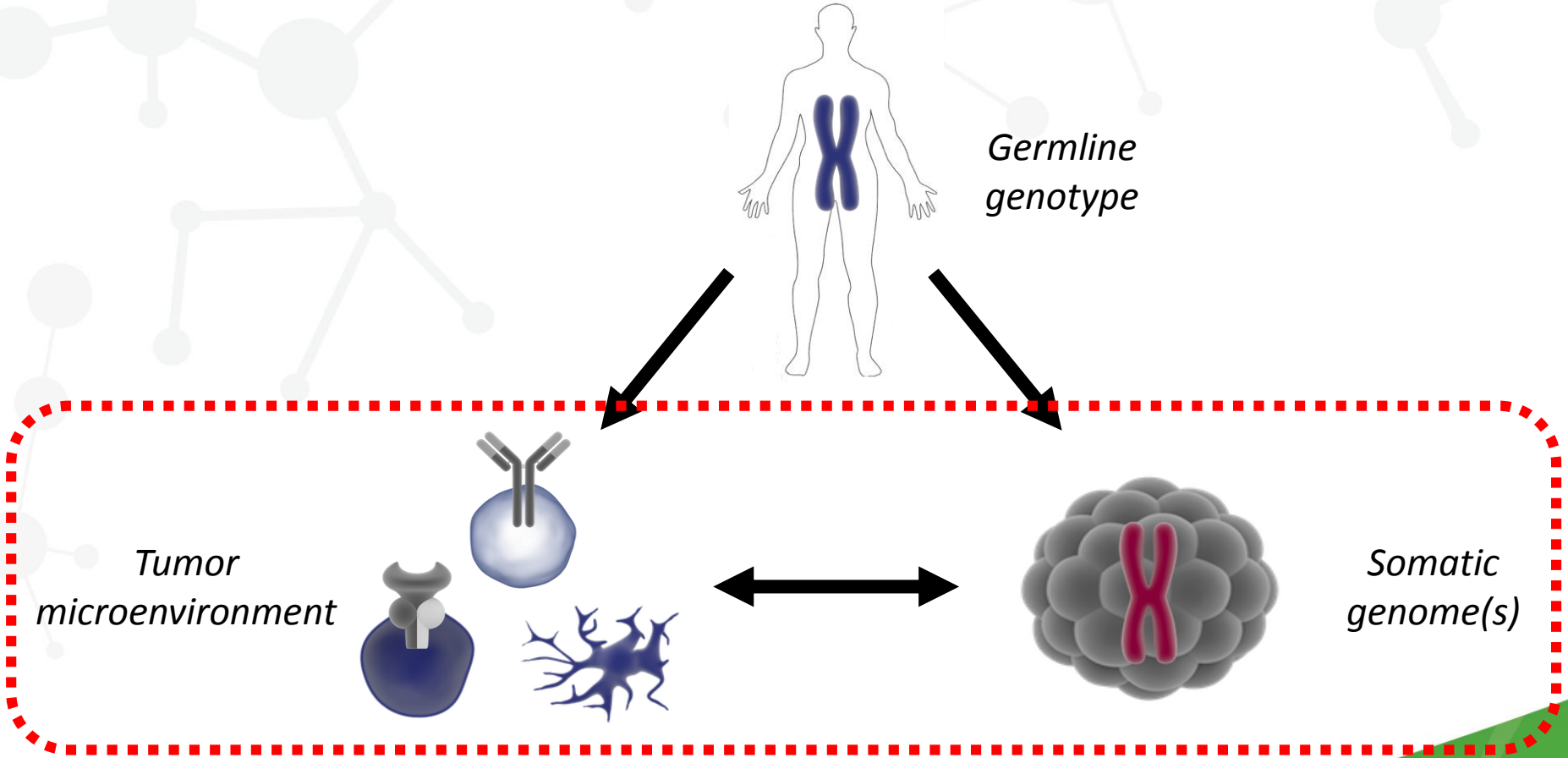
sitc
Society for Immunotherapy of Cancer

This variability stems from the “trialogue”



Society for Immunotherapy of Cancer

This variability stems from the “trialogue”

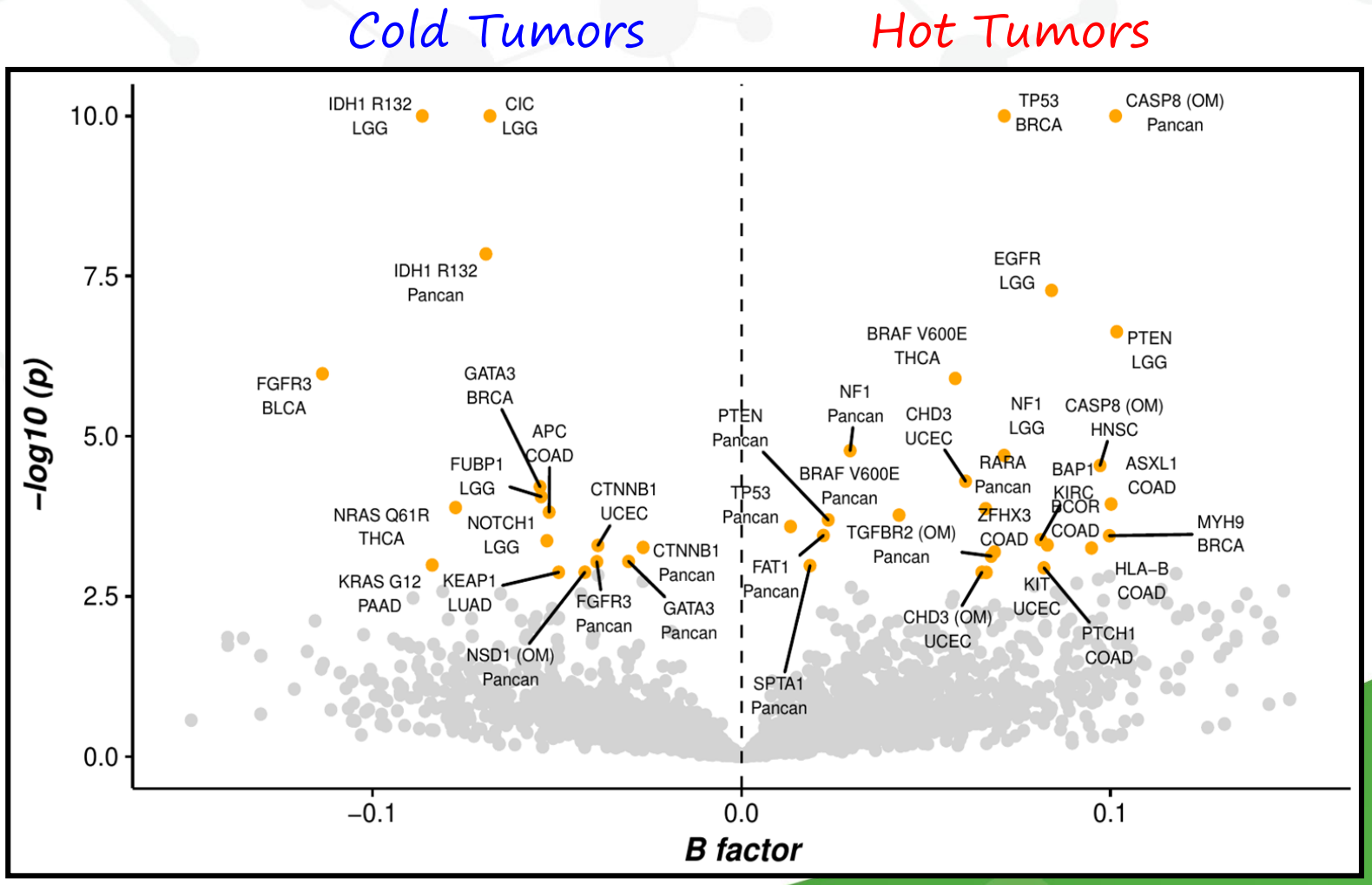


sitc
Society for Immunotherapy of Cancer

Known driver – TME interactions

Correlation between the presence of driver mutations in TCGA samples and the leukocyte score (methylation)

Positive B values indicate more leukocytes and viceversa



Rooney *et al.*, Cell, 2015
Tamborero *et. al.*, Clin Can Res, 2018
Thorsson *et. al.*, Immunity, 2018

Society for Immunotherapy of Cancer

Open questions

Victoria Ruiz-Serra

1 – Do mutations in cancer driver genes always correlate in the same direction?

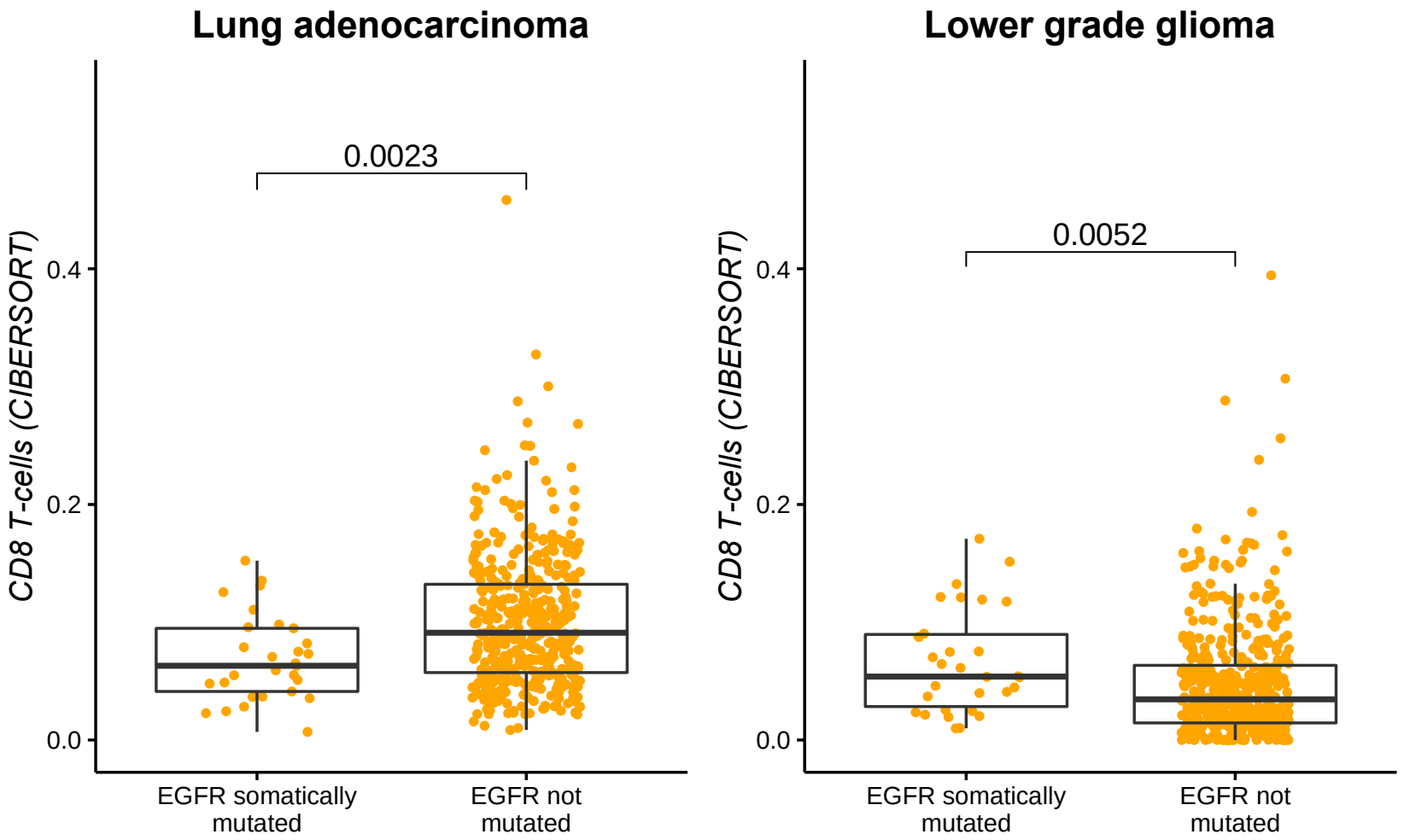
2 - Do all mutations in cancer driver genes correlate similarly with the immune component of the TME?

3 – Do different mutations interact with each other?

sitc
Society for Immunotherapy of Cancer

Correlations might depend on the tissue

Victoria Ruiz-Serra



Society for Immunotherapy of Cancer

Open questions

Victoria Ruiz-Serra

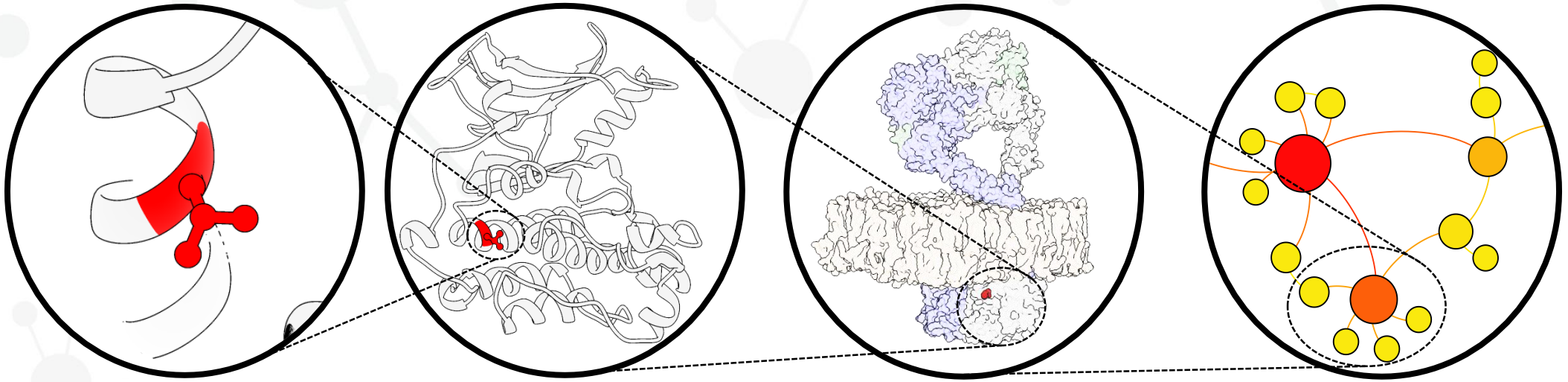
1 – Do mutations in cancer driver genes always correlate in the same direction? **They might!**

2 - Do all mutations in cancer driver genes correlate similarly with the immune component of the TME?

3 – Do different mutations interact with each other?

sitc
Society for Immunotherapy of Cancer

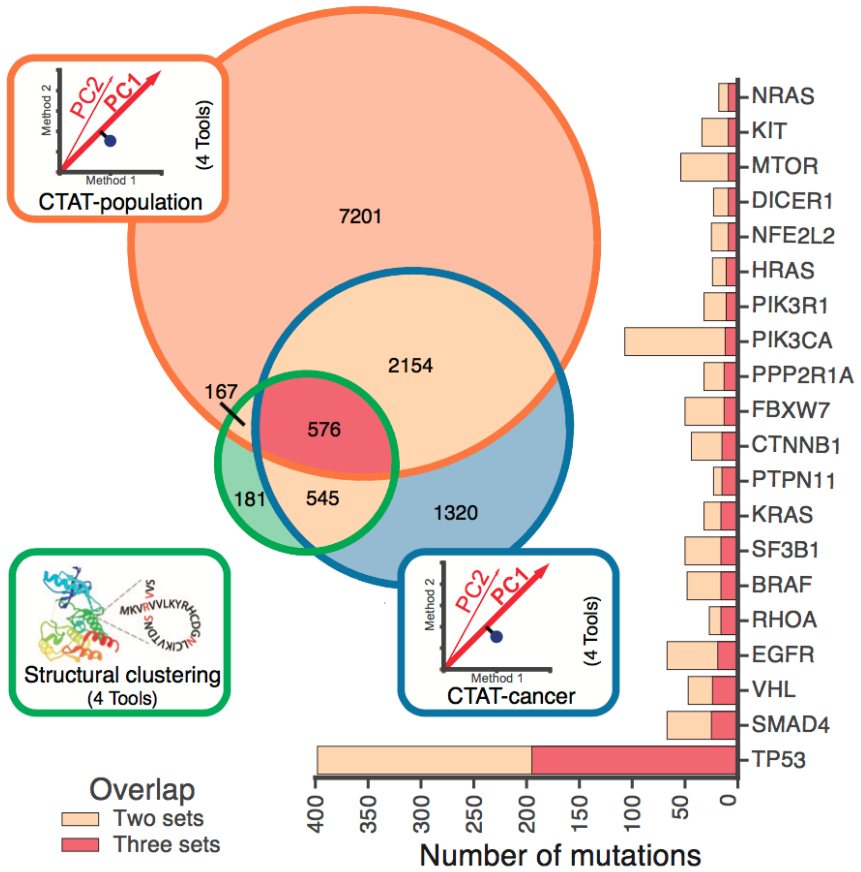
Perspective is important

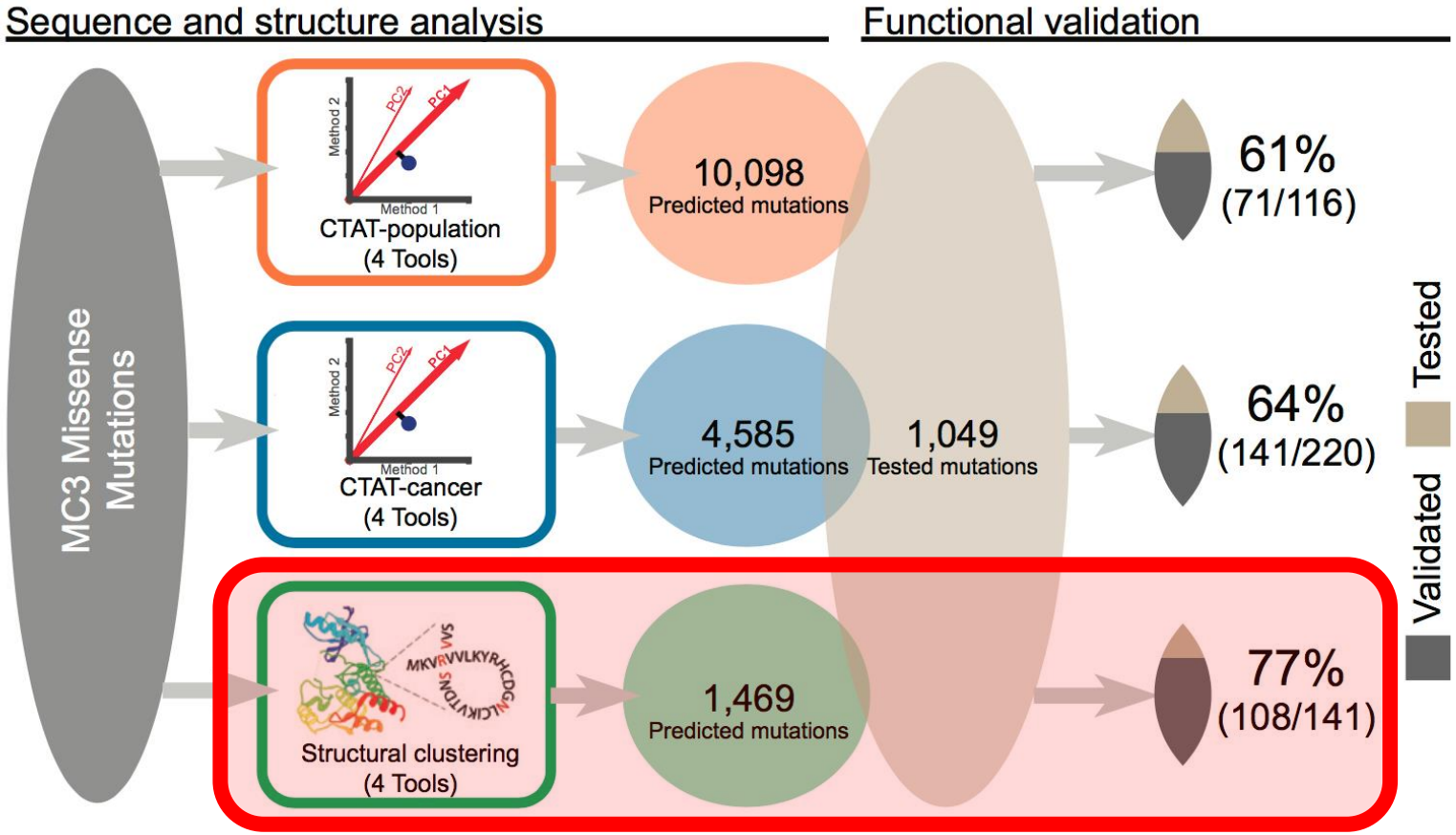


Society for Immunotherapy of Cancer

Bailey*, Tokheim*, Porta-Pardo* *et. al.,* Cell, 2019

Not all driver mutations are equal





Society for Immunotherapy of Cancer

Bailey*, Tokheim*, Porta-Pardo* *et. al.*, Cell, 2019

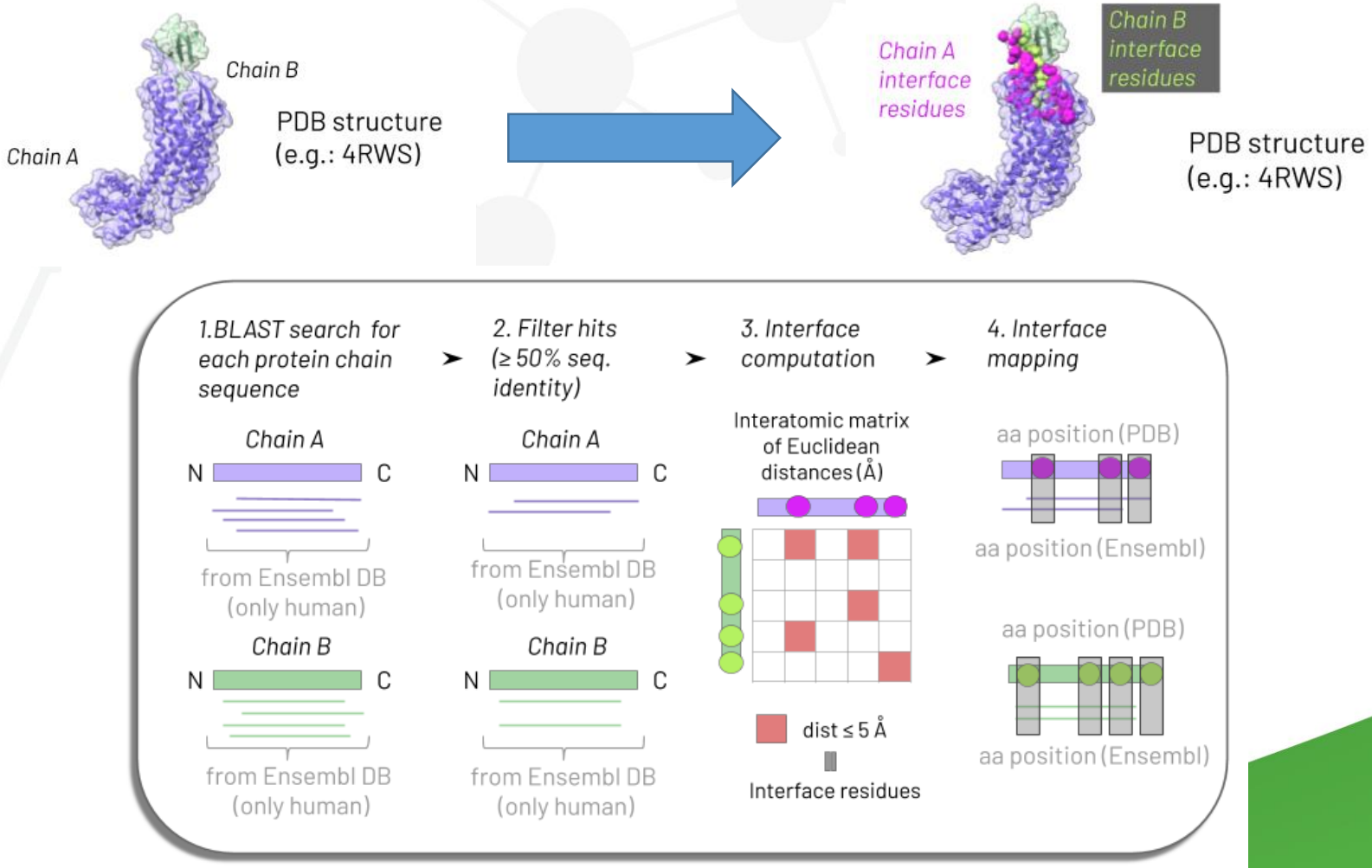
Structure – guided analysis

Victoria Ruiz-Serra

>200.000 PDB files analyzed

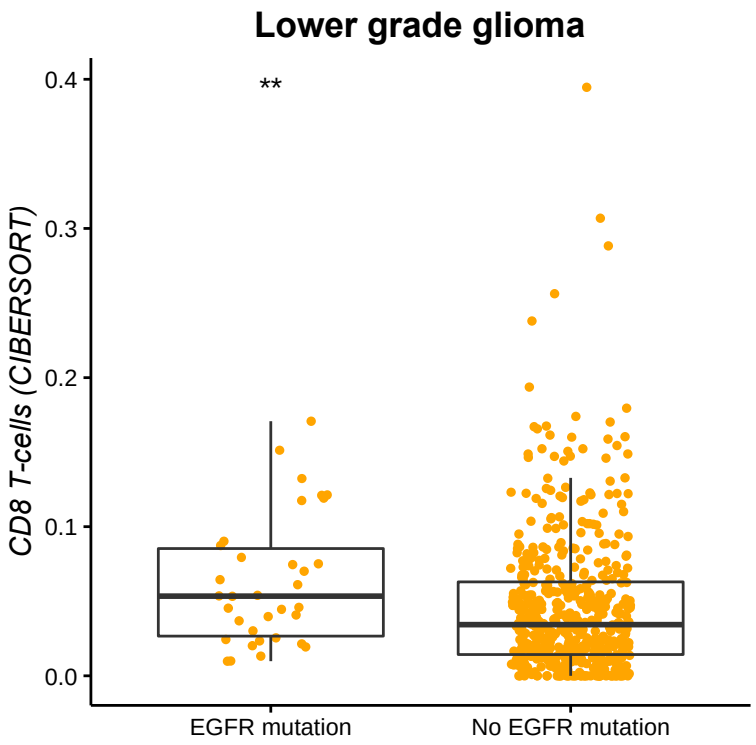
~100.000 have >50% sequence identity with human protein AND potential interface

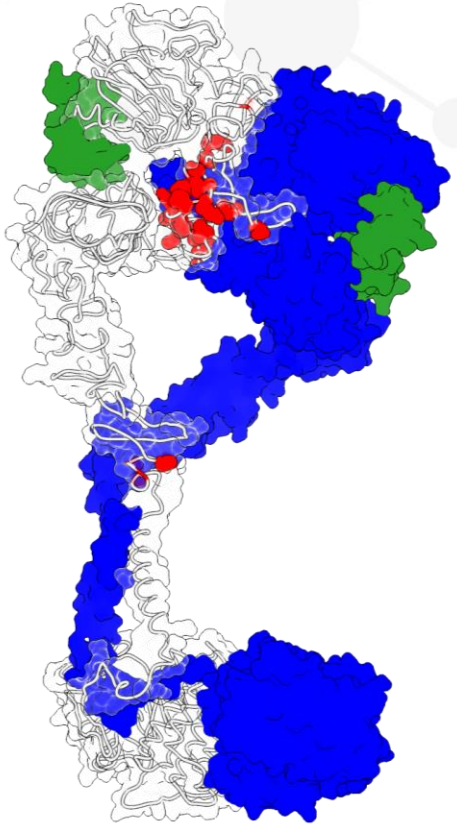
Catalogue with ~150.000 interfaces (protein, ligands or nucleic acids)

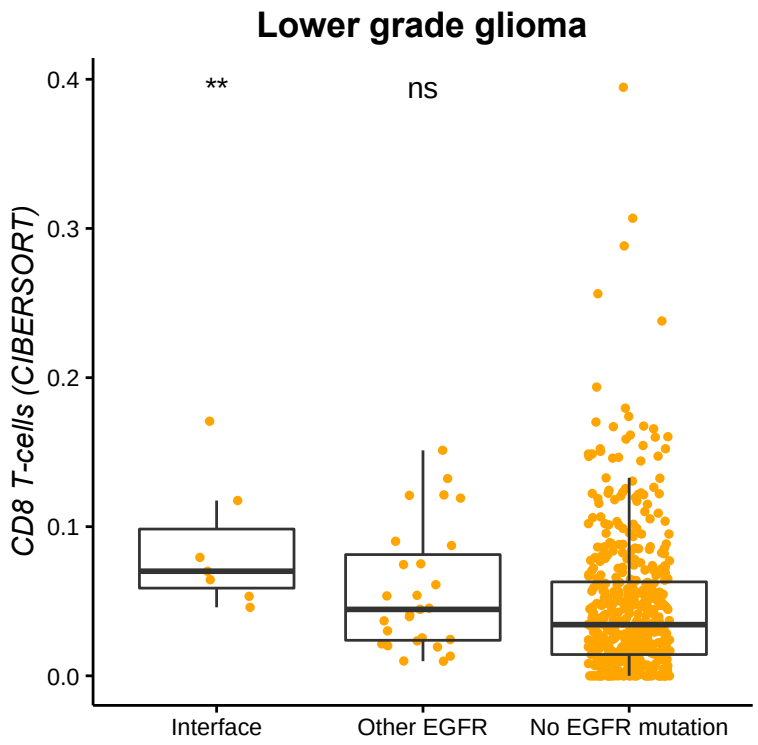


Society for Immunotherapy of Cancer

Structure analysis of EGFR - LGG







sitc
Society for Immunotherapy of Cancer

Open questions

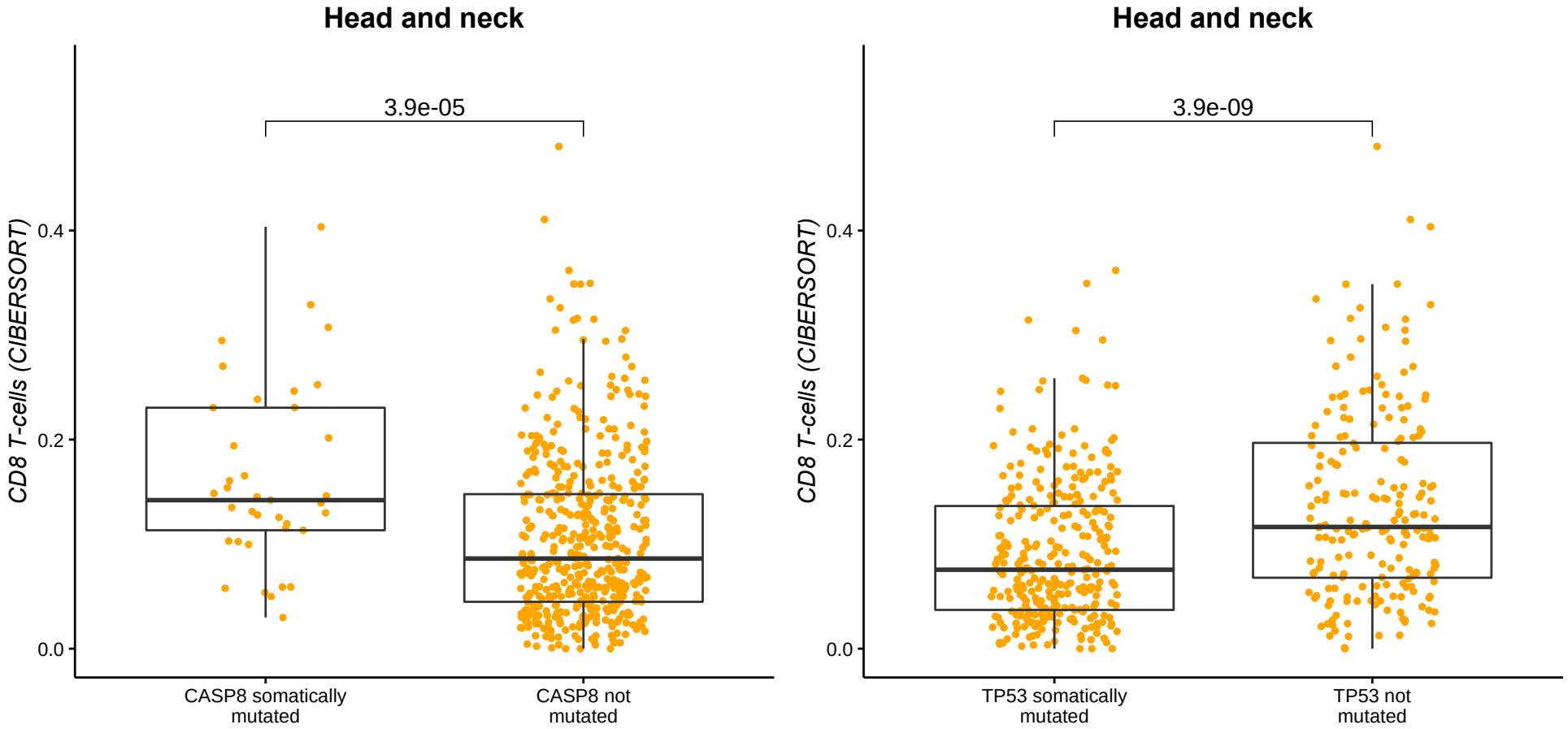
1 – Do mutations in cancer driver genes always correlate in the same direction? **They might!**

2 - Do all mutations in cancer driver genes correlate similarly with the immune component of the TME? **No!**

3 – How do different mutations interact with each other?

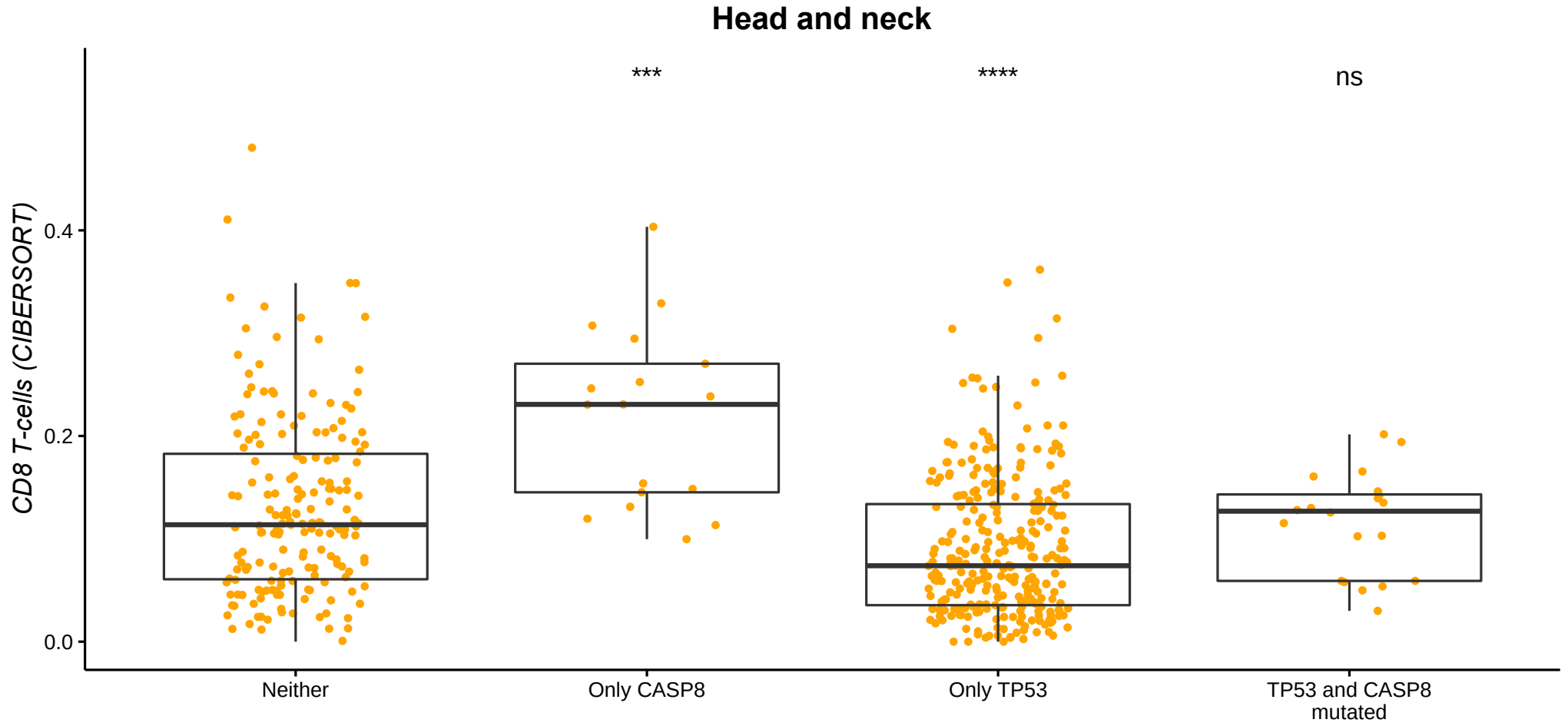
sitc
Society for Immunotherapy of Cancer

Different drivers can have different effects...



sitc
Society for Immunotherapy of Cancer

...and they can interact with each other!



Society for Immunotherapy of Cancer

Open questions

Victoria Ruiz-Serra

1 – Do mutations in cancer driver genes always correlate in the same direction? **They might!**

2 - Do all mutations in cancer driver genes correlate similarly with the immune component of the TME? **No!**

3 – Do different mutations interact with each other? **They can!**

sitc
Society for Immunotherapy of Cancer

Thank you!

Collaborators

Barcelona Supercomputing Center
Centro Nacional de Supercomputación

Victoria Ruiz-Serra
Alfonso Valencia
Carlos Garcia-Prieto

Valencia's lab

Davide Bedognetti
Farshad Farshidfar
Elad Ziv
Rosalyn Samayan
Vesteinn Thorsson
Adam Godzik

Germline Immune working group

Funding Agencies

Obra Social "la Caixa"

AGAUR Agència de Gestió d'Ajuts Universitaris i de Recerca

sitc
Society for Immunotherapy of Cancer