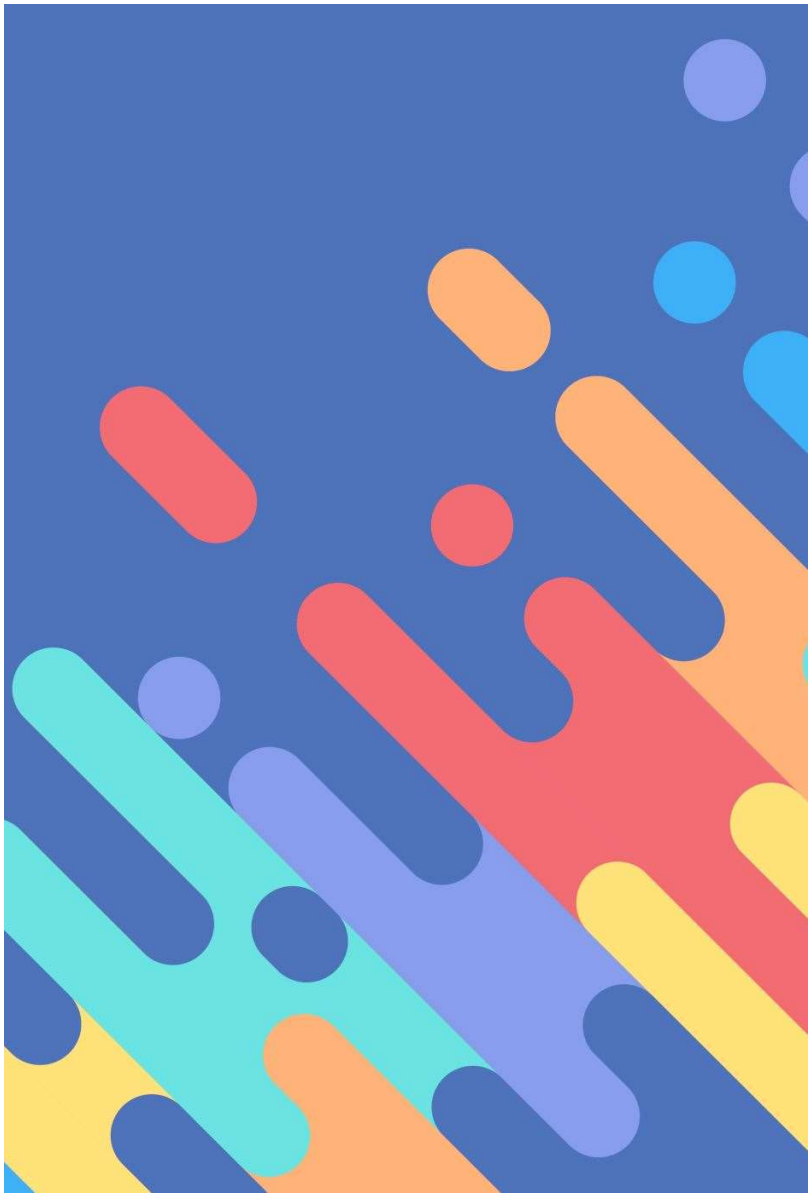
Use of an XGBoost classifier to explain tumor resistance in bulk RNA seq from scRNAseq

Marco A. Tello Palencia

CPSC-545 Final project presentation



RESEARCH ARTICLES

CANCER GENOMICS

Dissecting the multicellular ecosystem of metastatic melanoma by single-cell RNA-seq

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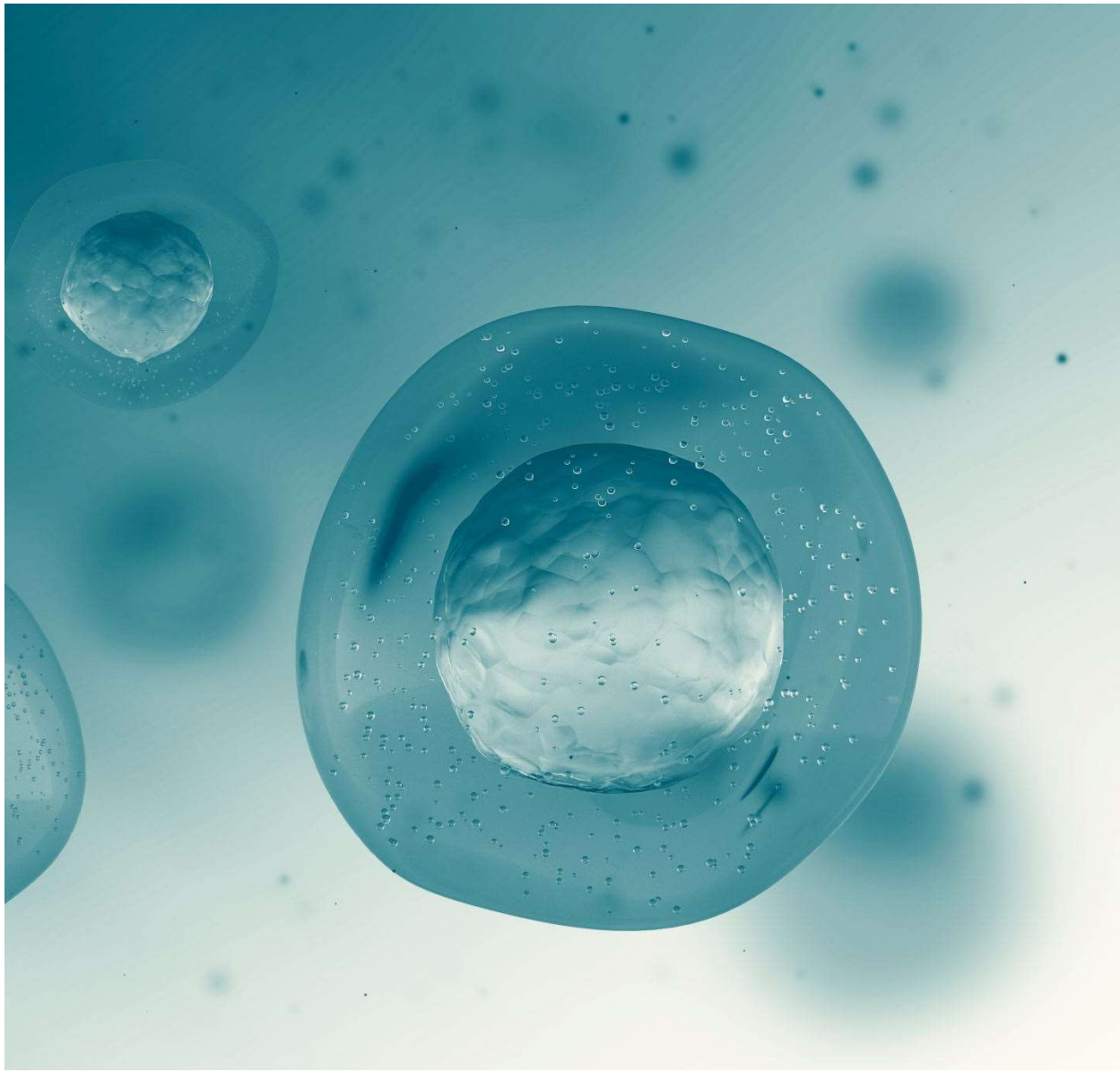
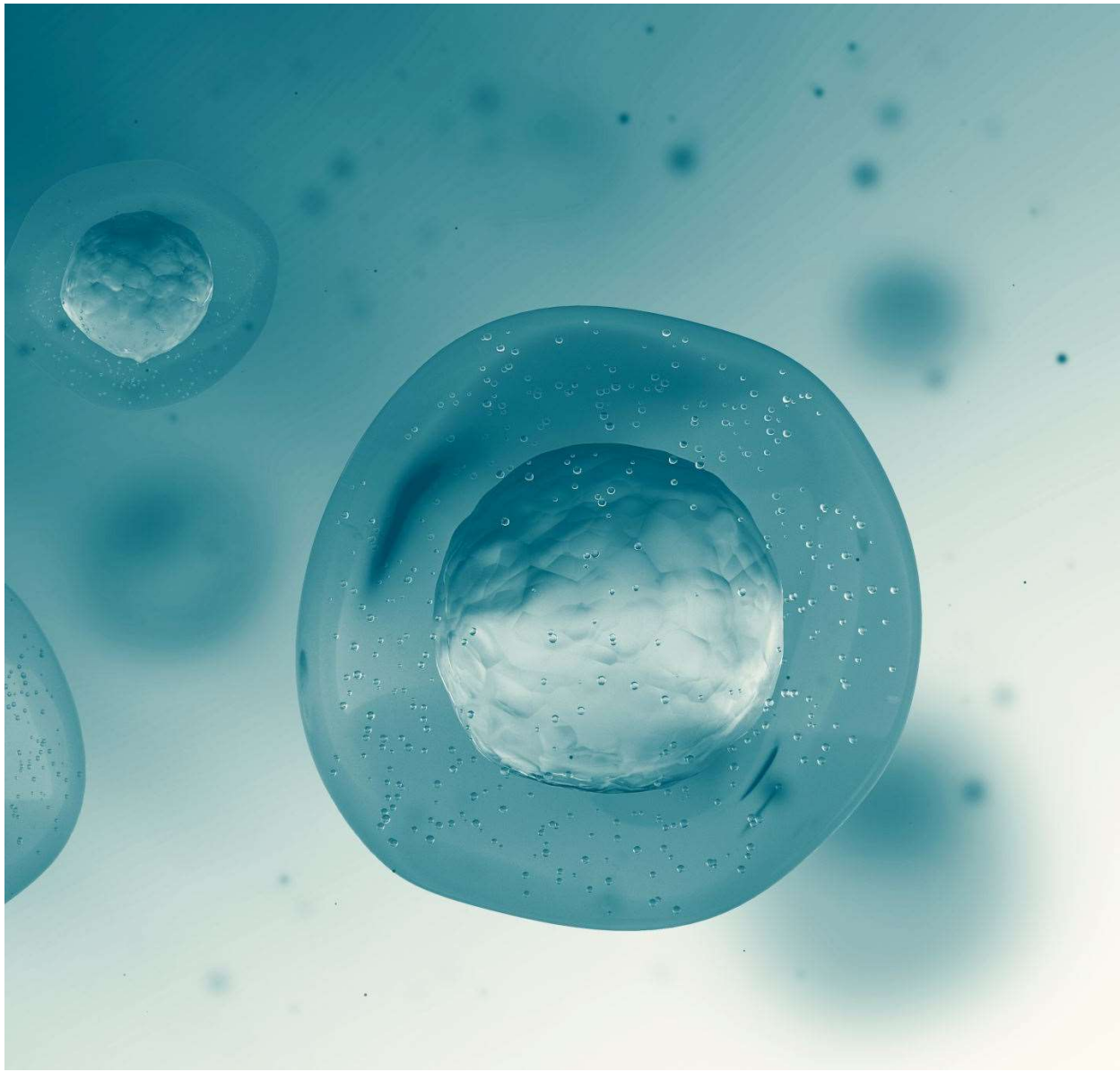
Tumors are complex ecosystems

- Tumors, intricate ecosystems shaped by diverse cell types.
- Interactions among malignant, immune, and stromal cells crucial for cancer development (1).
- Cellular composition and interplay's pivotal roles in tumor behavior (2).



Melanoma cell composition and treatment resistance

- It is possible that subsets of malignant cells and the microenvironment play essential roles in the response to treatments (3).
- Melanomas with the BRAF V600E mutation have a defined treatment however most tumors with this mutation develop resistance (4,5)



The dataset

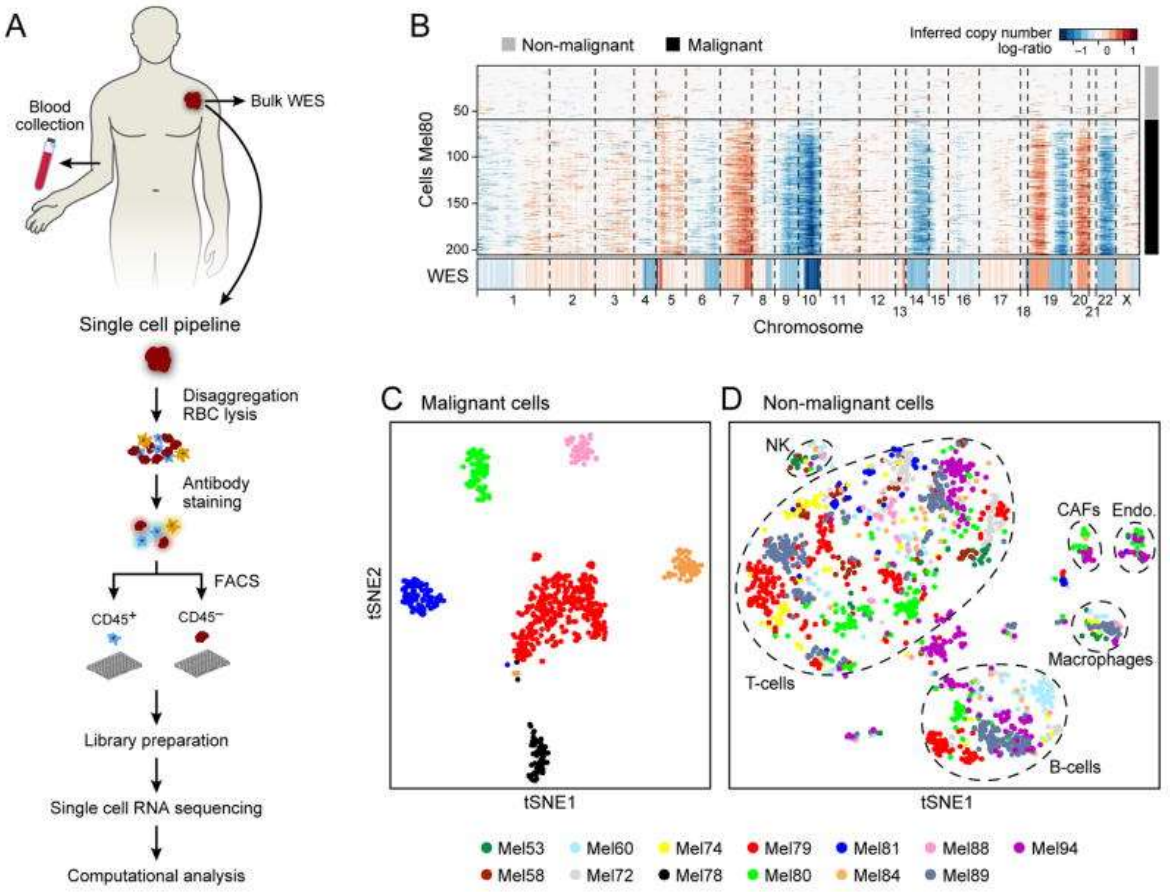
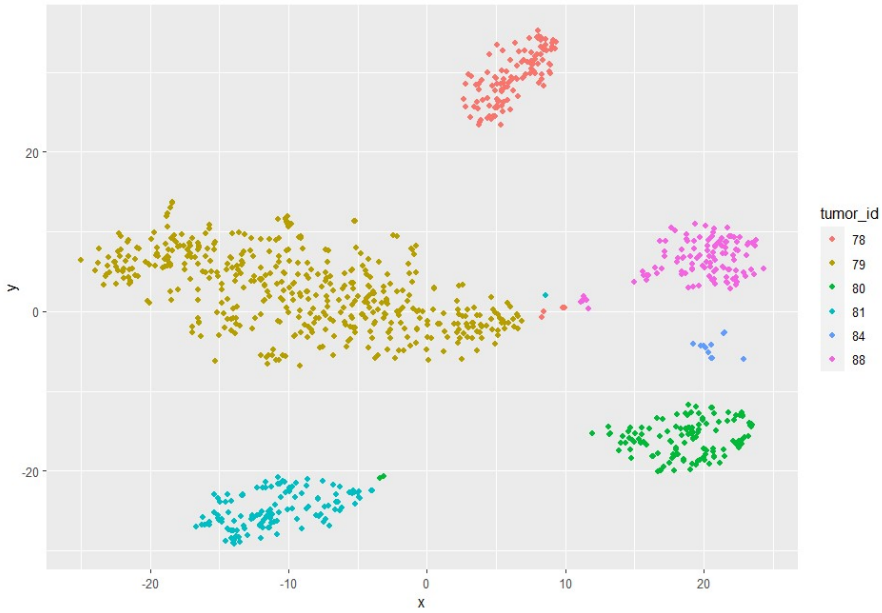
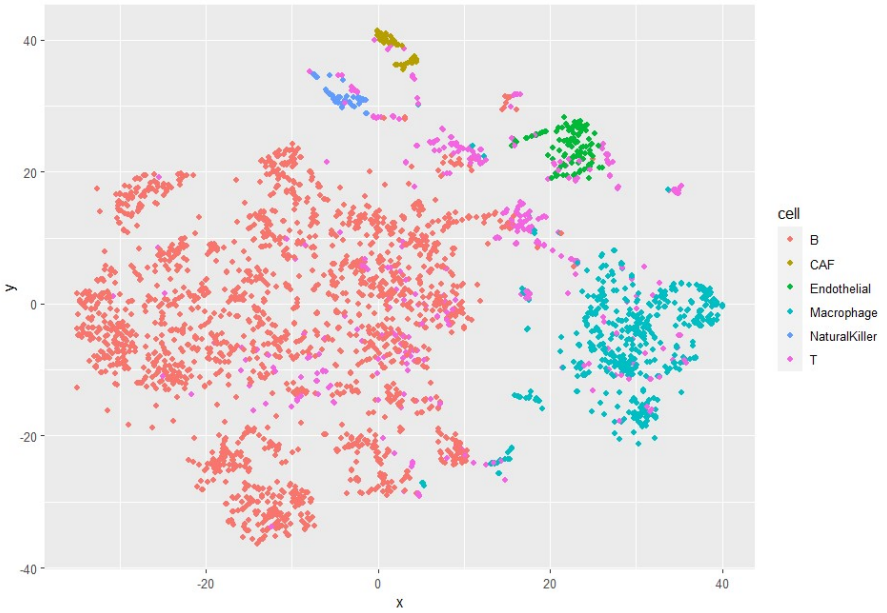


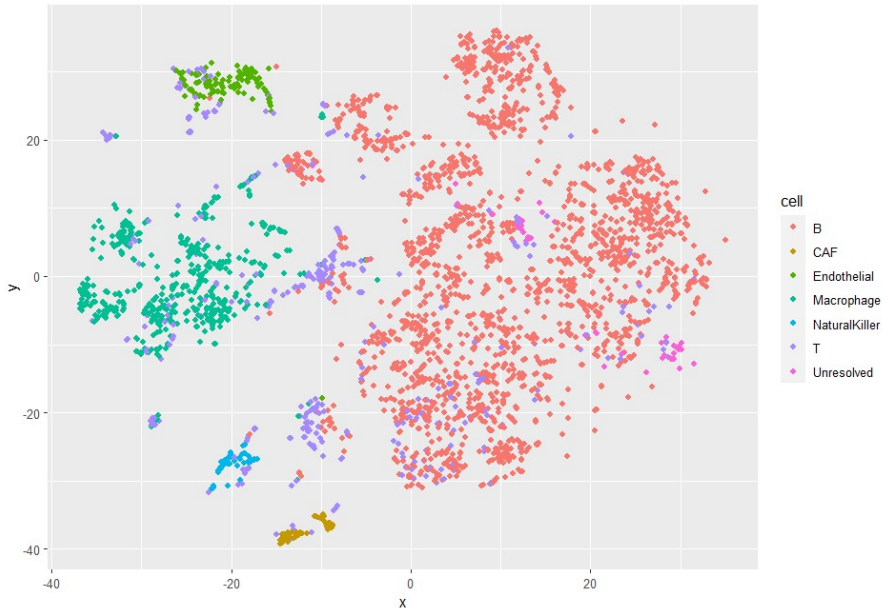
Figure 1. Tirosh, et al 2016

Exploratory data analysis – reproduce plots

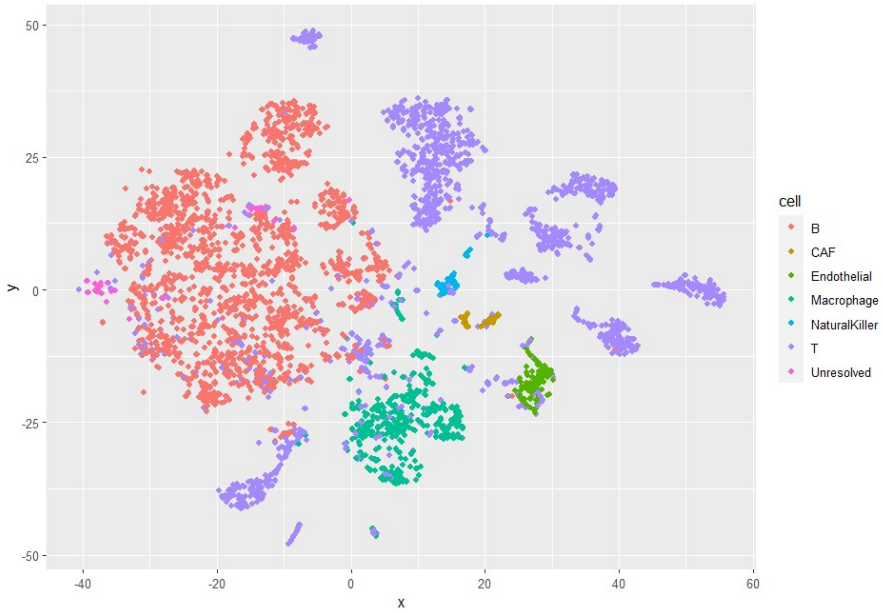


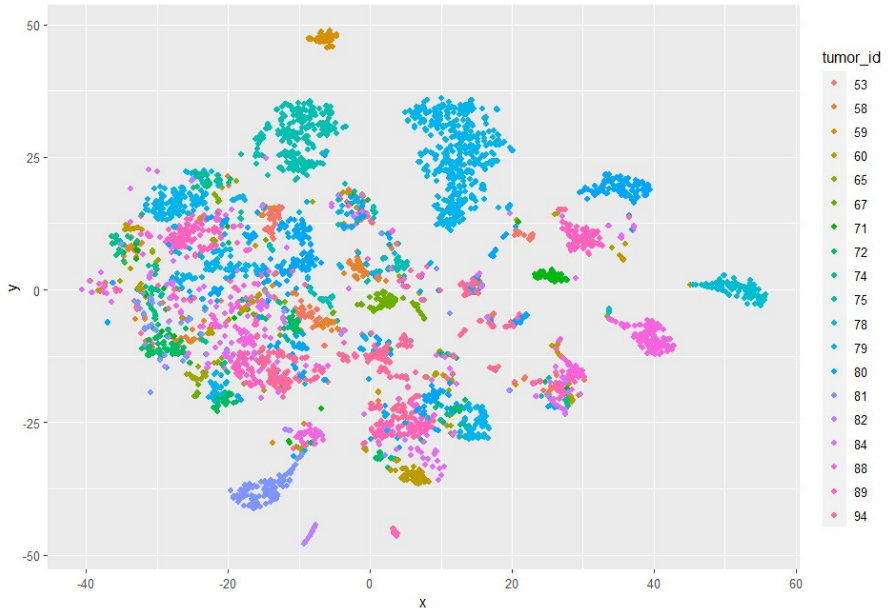


Exploratory data analysis – using the full data

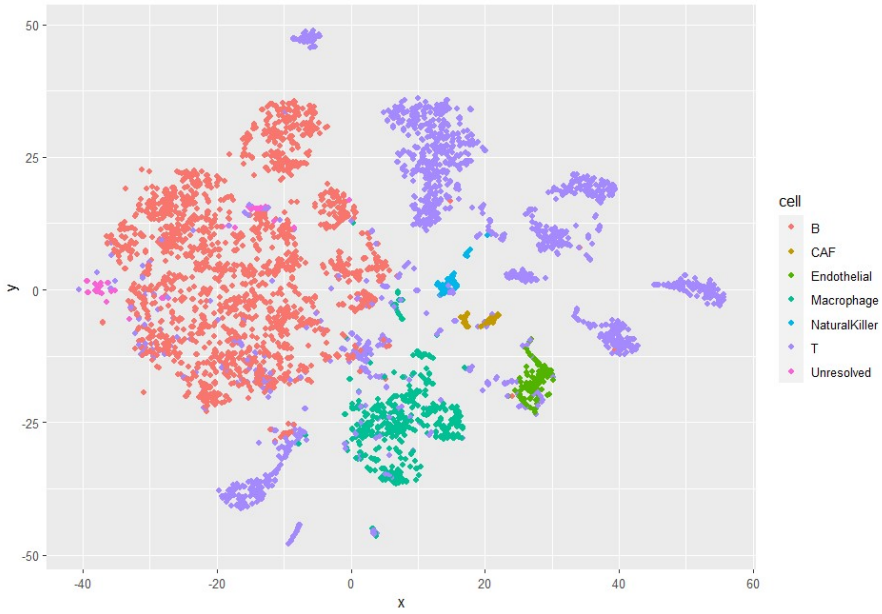


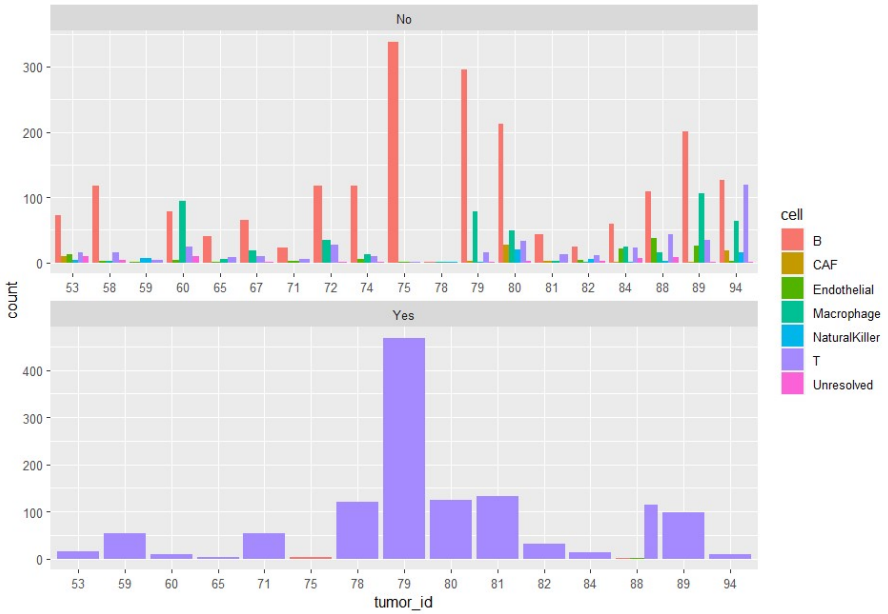
Initial plan – Predict malignancy using cell type expression profiles





The problem… malignancy and cell type are associated





Complementary data from bulk-RNAseq

Samples from donors before and after development of resistance

Identified transcriptomic profiles associated with this change

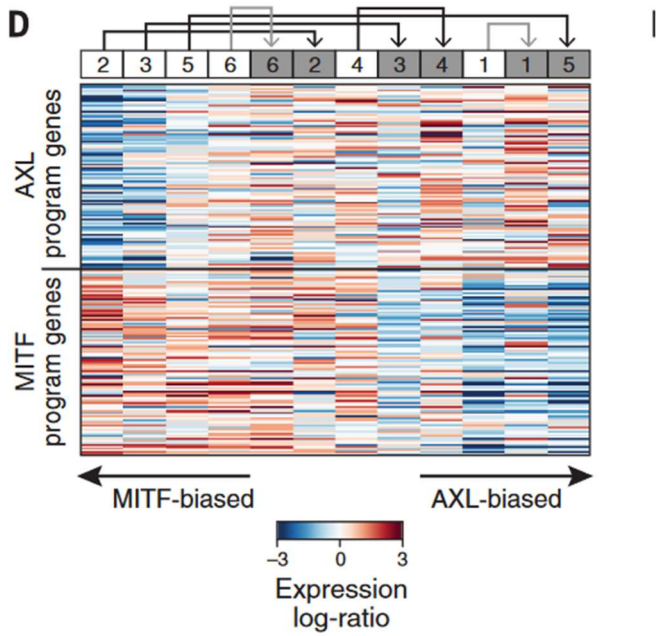
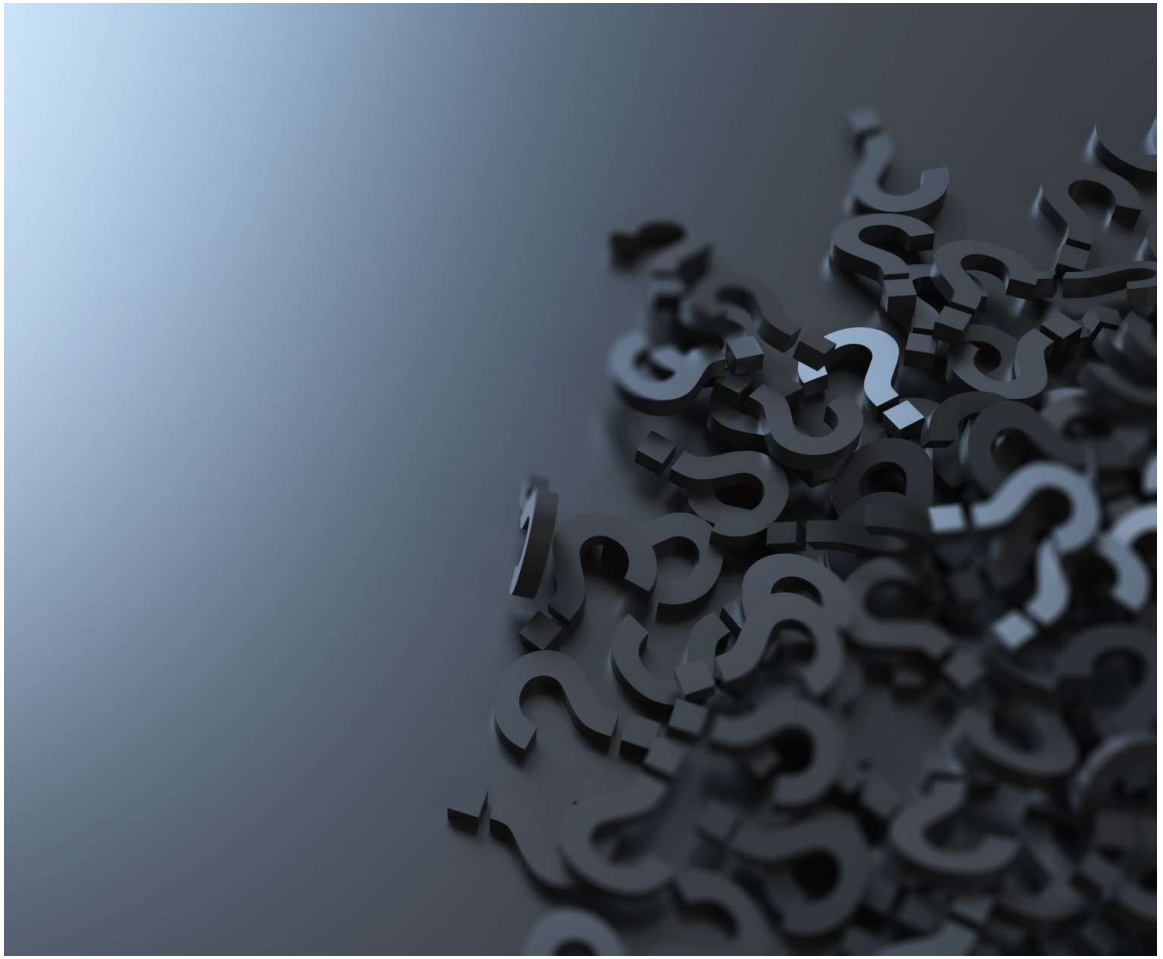


Figure 3D. Tirosh, et al 2016

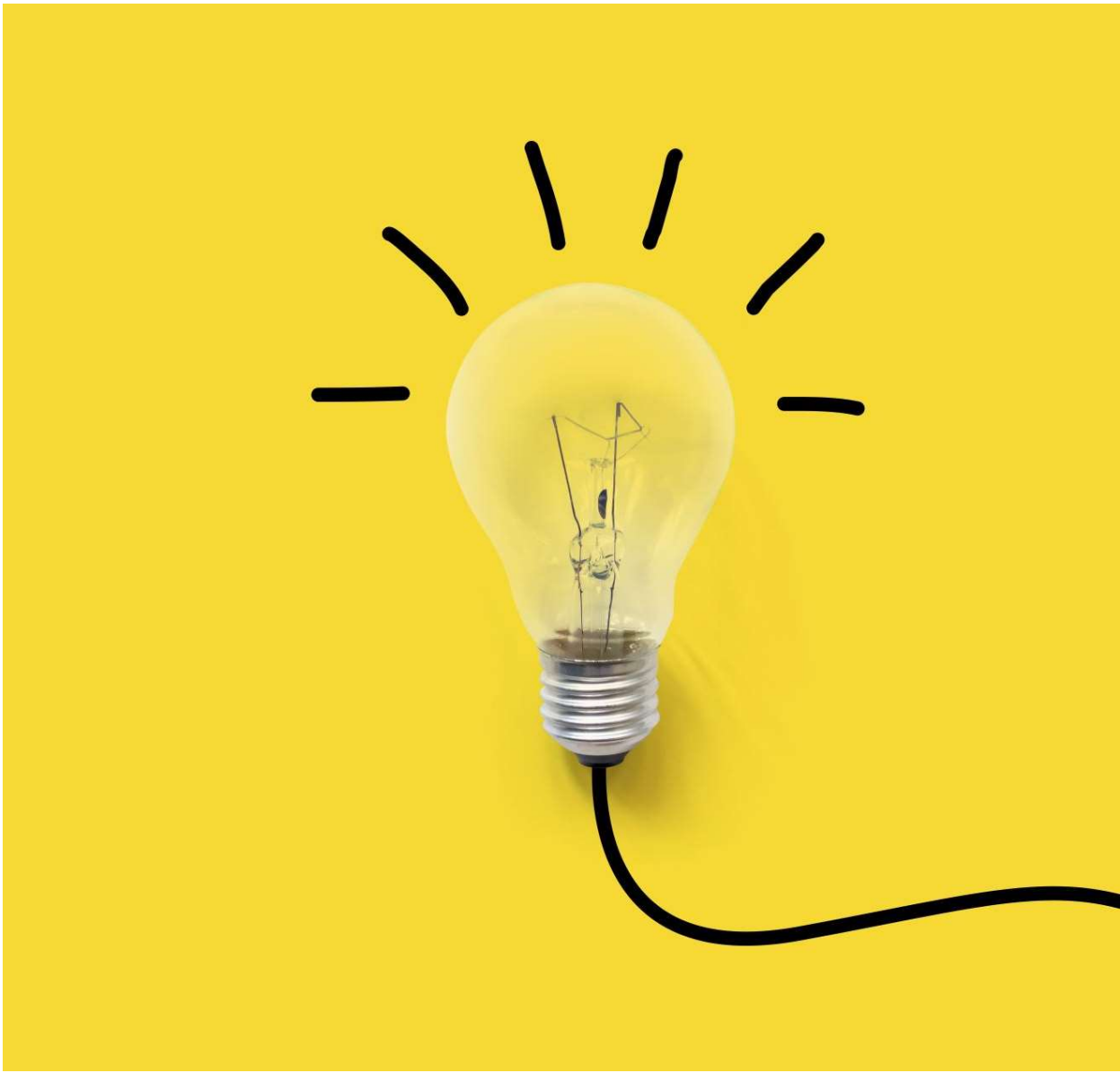
Change of question…

- Is it possible that these differences can be captured in the scRNAseq?
- If so, is it possible to transfer the knowledge from sc-RNAseq to bulk samples?
    - Predict tumor resistance on bulk based on scRNA-seq profiles



New plan

- Use an XGBoost classifier trained on sc-RNAseq to predict resistance.
- Use local interpretability of Shapley Additive explanations (SHAP) to explain what genes contribute most to predict resistance



The feature table design

To reduce high-dimensionality

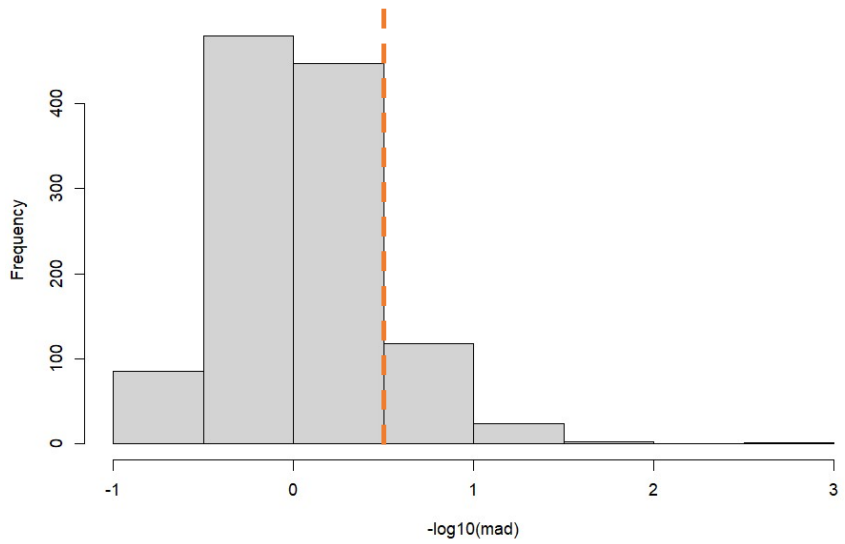
- Conserve top 10% most variable genes in single cell (median absolute deviation)

Genes shared with validation dataset.

- Final subset of 558 genes

Expression standardized within cells

- Capture relative variability within cell
- Reduce impact of cell-cell variability



Supervised XGBoost model results

- Classification of cells into resistant or not (16% of cells positive)
- Train split: 70% of cells
- 10-fold CV for hyper-parameter tunning in train split
  - Optimized for average precision
  - Random search 500 iterations

- 10-fold evaluation in test split:
  - F1 Score: 0.945 (±0.07)
  - AUROC: 0.98 (±0.05)
  - AUPR: 0.97 (±0.07)

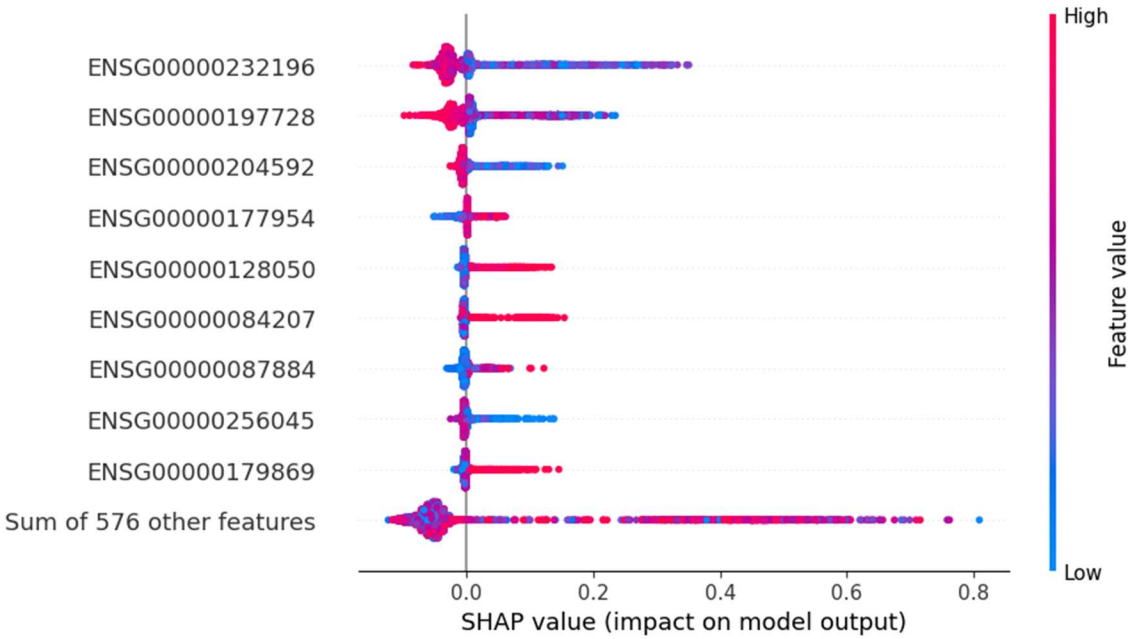
Results from the validation dataset

- Two donors out of five were accurately classified.
- Influenced by the imbalanced training dataset
- What genes primarily influenced the model prediction for these samples?

Donor	Time	Prob(No)	Pro(Yes)	Resistant
1	Pre	0.899	0.101	No
1	Post	0.947	0.053	Yes
2	Pre	0.91	0.09	No
2	Post	0.919	0.081	Yes
3	Pre	0.747	0.253	No
3	Post	0.403	0.597	Yes
4	Pre	0.952	0.048	No
4	Post	0.945	0.055	No
5	Pre	0.825	0.175	No
5	Post	0.969	0.031	Yes

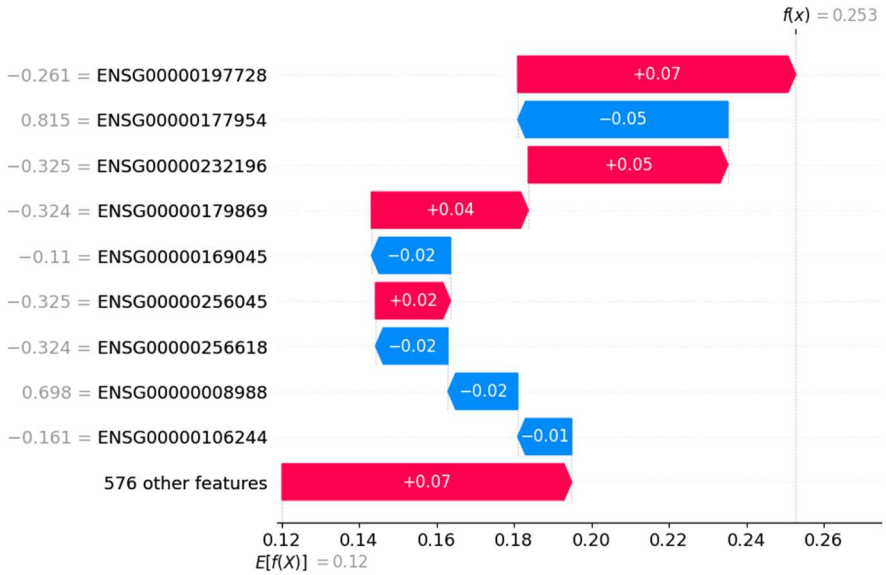
Overview of SHAP results – Full model

- **MTRNR2L4**
  - Antiapoptopic
  - Predicted to be extracellular
- **RPS26**
  - Ribosomal protein
- **HLA-E**
  - Involved in immune self-nonself discrimination
- **RPS27**
  - Ribosomal protein

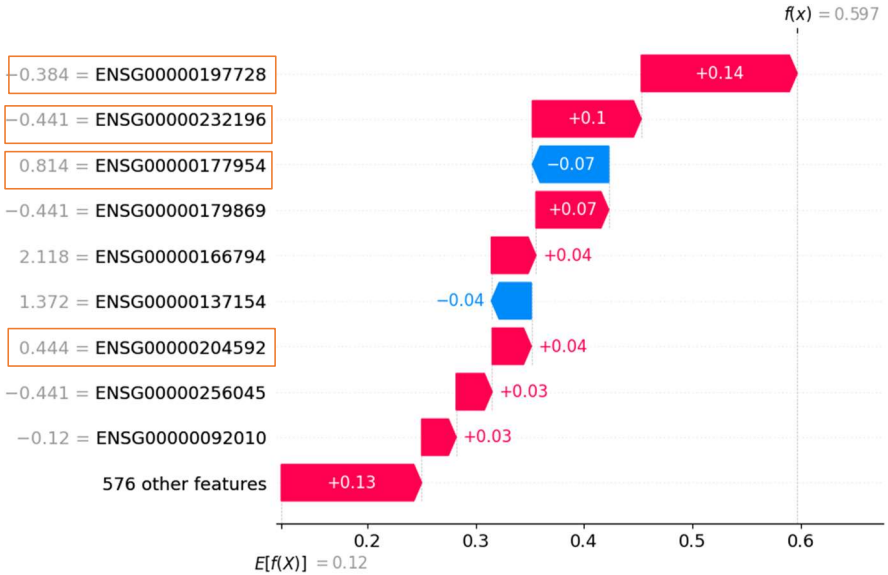


Donor which transcriptomic profile changed when developed a resistance

Before treatment



After treatment



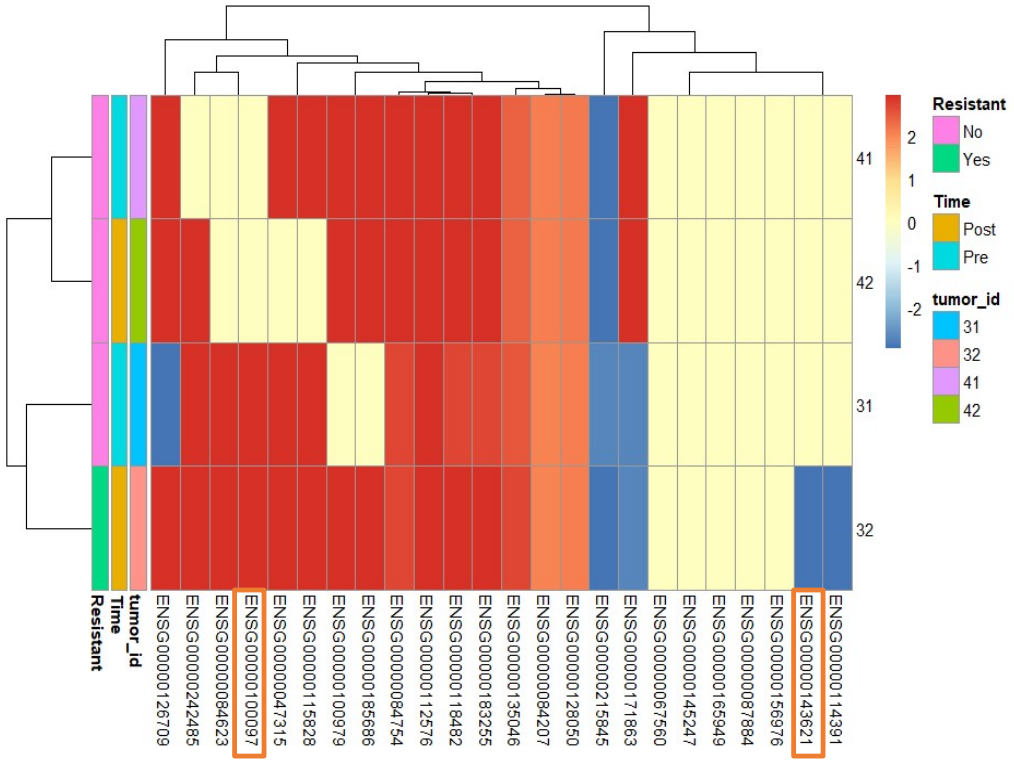
Comparison of model relevance for samples accurately predicted

ENSG00000143621 (ILF2)

Transcription factor required for T-cell expression of the interleukin 2 gene

ENSG00000100097 (Galectin)

Extracellular matrix, regulating cell proliferation.



Conclusions

- Identified several genes which were relevant for the prediction of resistance in sc-RNAseq
- Translation of knowledge from scRNAseq to bulk is probably influenced by the imbalanced dataset.
- Recovered many genes in bulk that drove predictions in scRNA-seq
- Identified new genes with a differential contribution to prediction of resistance in bulk-RNAseq

References

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2. C. E. Meacham, S. J. Morrison, Nature 501, 328–337 (2013).
3. A. Snyder et al., N. Engl. J. Med. 371, 2189–2199 (2014).
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5. E. M. Van Allen et al., Cancer Discov. 4,94–109 (2014).