

Background Research Experience



Yang-Hong Dai, MD
Department of Oncology
University of Oxford
St. Cross College
Supervisor: Katherine Vallis

Education, training and working experience



- Since 2021: a qualified radiation oncologist
- 25 related studies published
 - First author: 5
 - Corresponding author: 4
- International collaborative study (Cambridge University): 1
- Ongoing study: 1

National Defense Medical Center



National Central University



Tri-Service General Hospital



Medicine
2007-2014

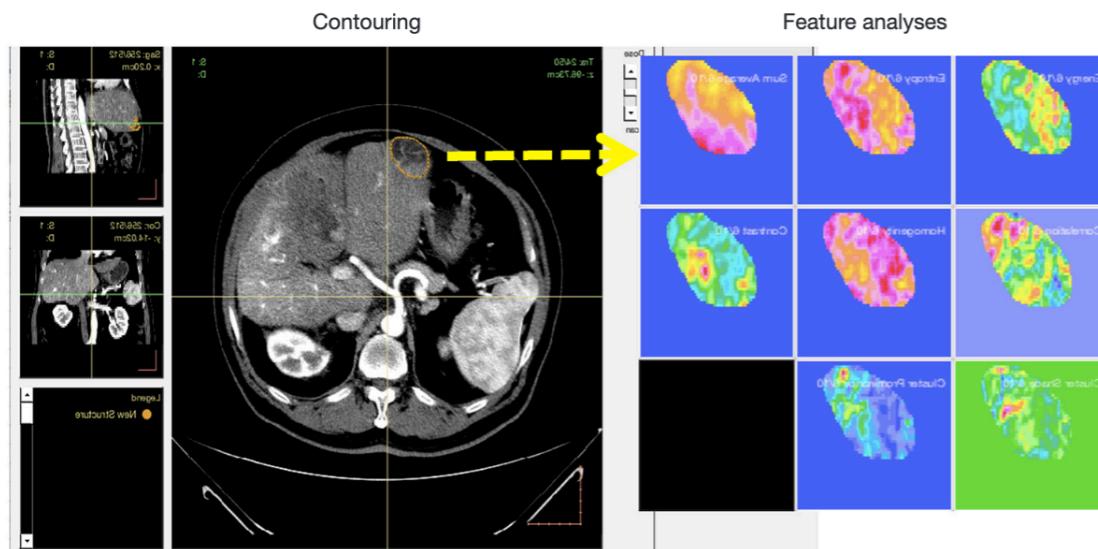
Photonics
2014-2016

Resident in radiation oncology
2017-2021

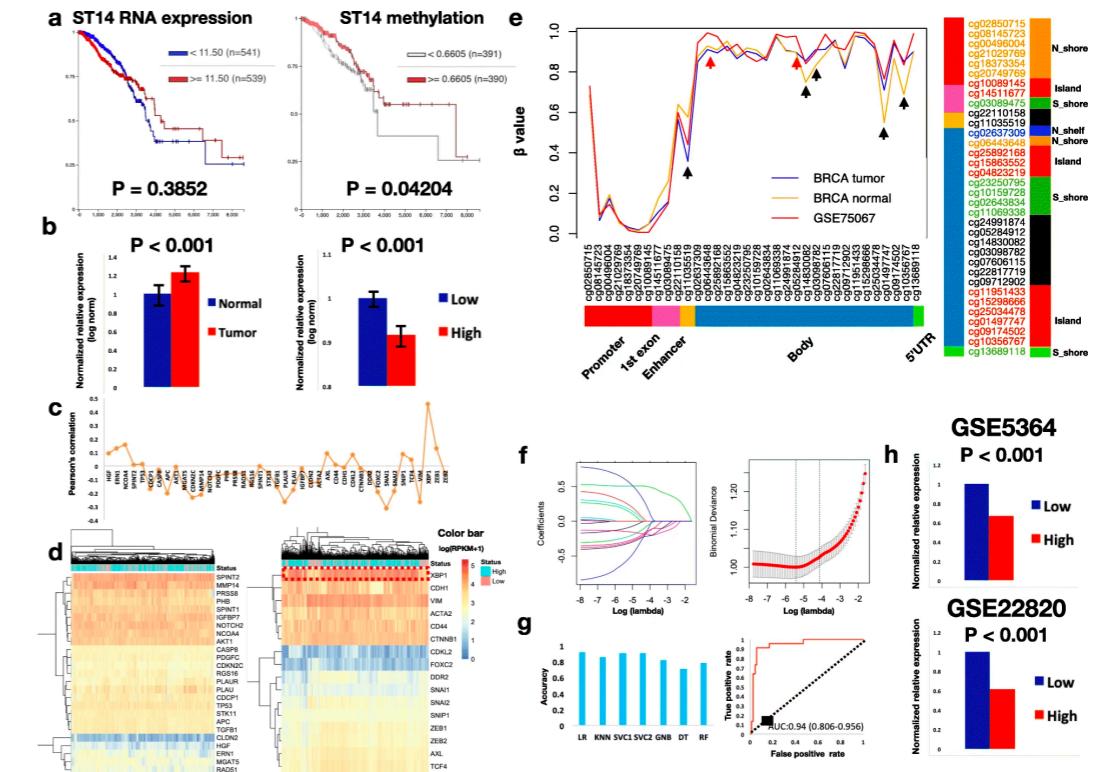
Previous research experience in oncology

- Using **radiomics** to predict local response of SBRT in **hepatocellular carcinoma** patients (**conference paper**)
- Analysing methylation profiles from TCGA in **breast cancer** (**BMC Cancer**, DOI: [10.1186/s12885-021-08645-3](https://doi.org/10.1186/s12885-021-08645-3))
- Analysing methylation/mutation profiles from TCGA in **endometrial cancer** (**Japanese Journal of Clinical Oncology**, DOI: [10.1093/jjco/hyac077](https://doi.org/10.1093/jjco/hyac077))
- Analysing transcriptomic files from GEO and TCGA and building **inflammasome**-based prediction model for **early-stage non-small cell lung cancer** (**Biomedicines**, DOI: [10.3390/biomedicines10071539](https://doi.org/10.3390/biomedicines10071539))

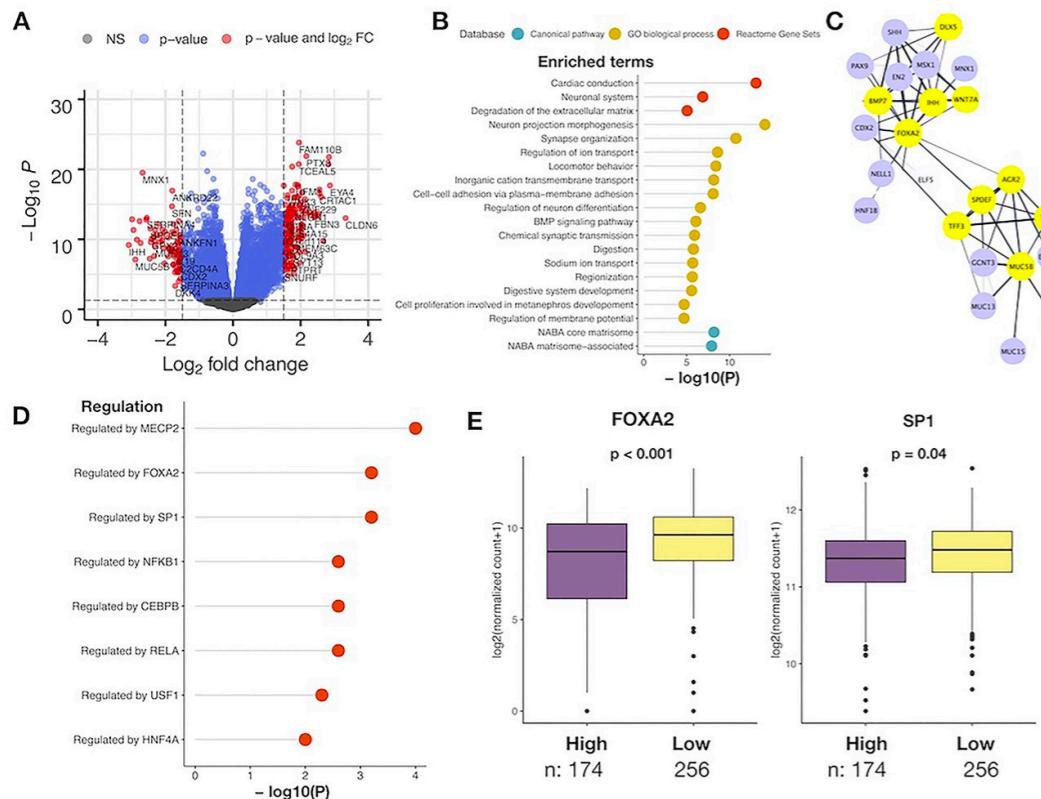
Radiomics analysis for SBRT in hepatocellular carcinoma



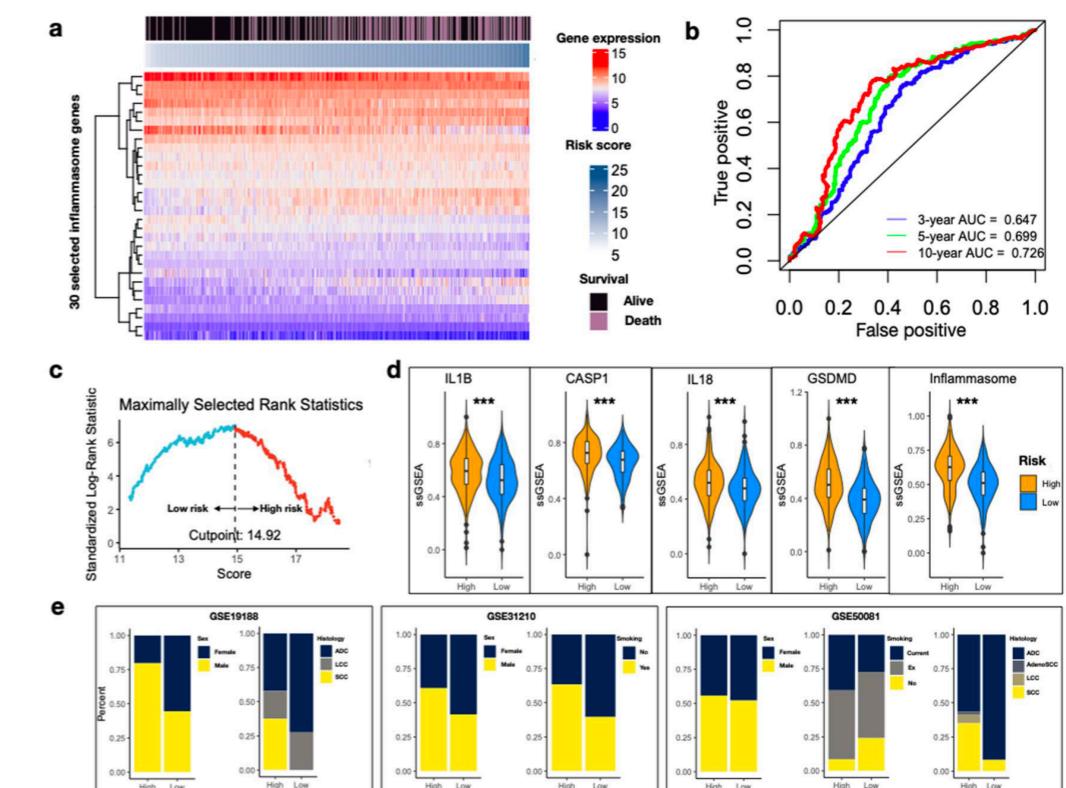
ST14 DNA methylation in breast cancer



DNA methylation risk score for endometrial cancer

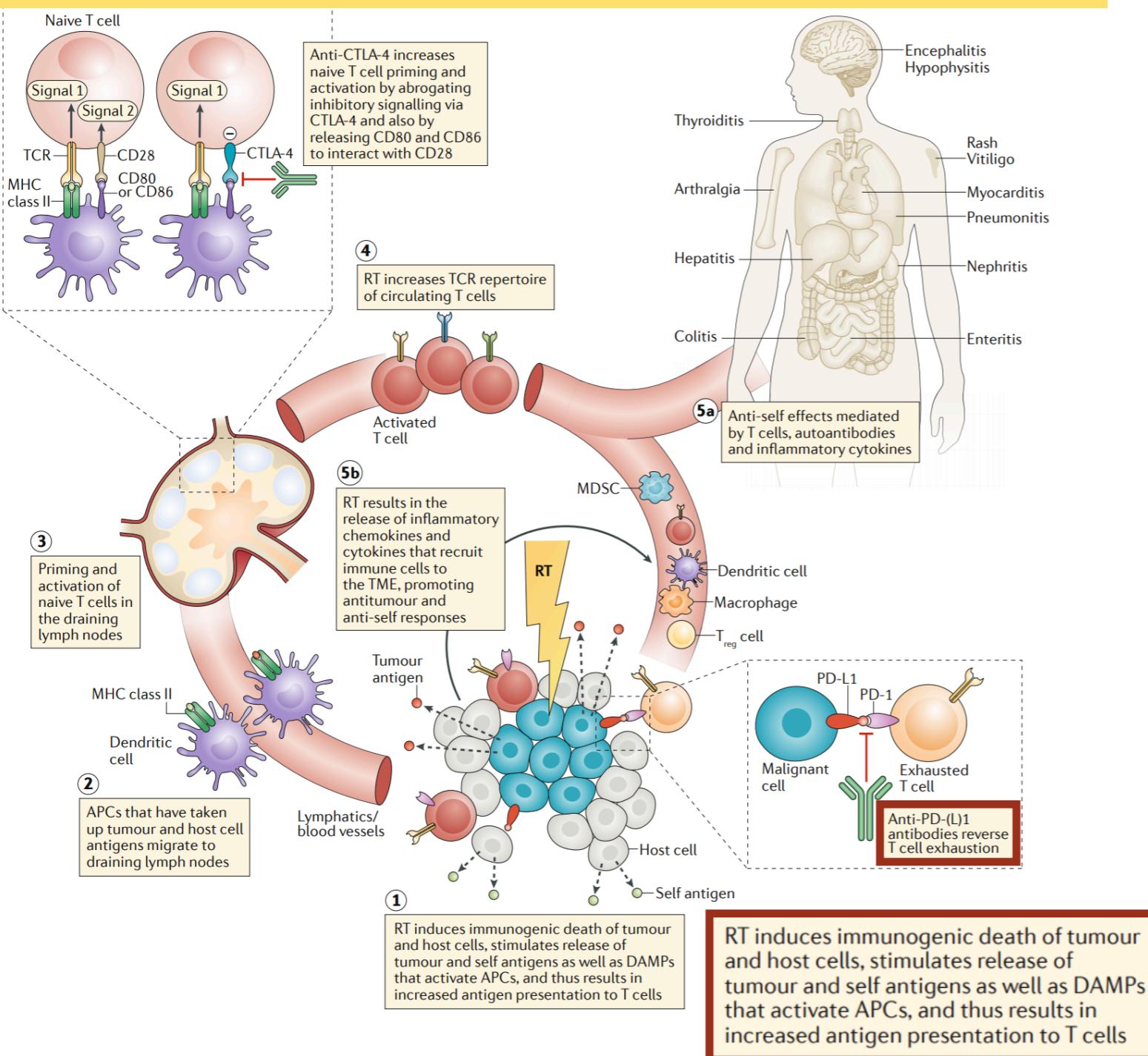


Inflammasome-risk score for lung cancer



Study in radiotherapy: Research background

Radiation can induce release of tumour antigens and antigen presentation to T cells



Hypothesis

- Tumour radiosensitivity may be related to immune activation and response to immunotherapy**

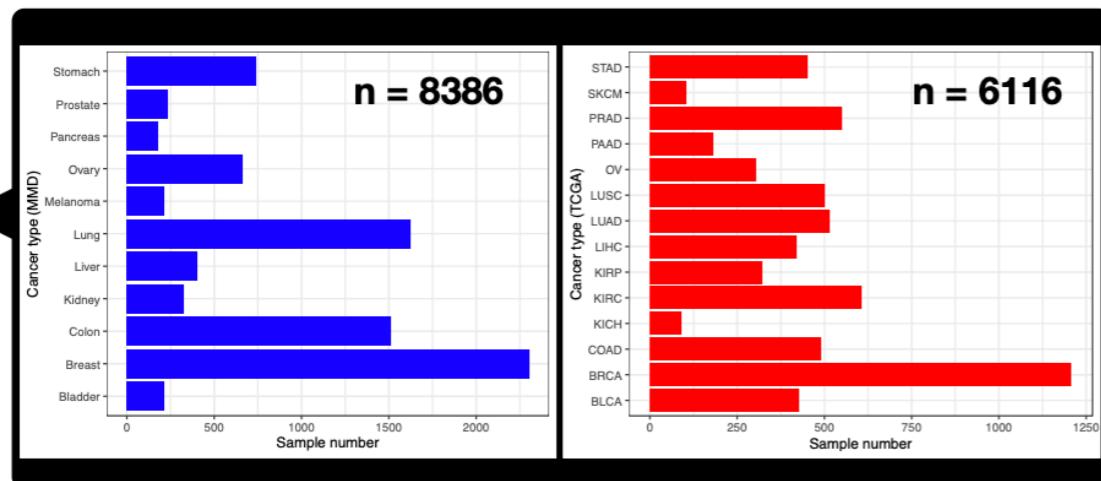
Aims

- Application of a radiosensitivity index that represents radiosensitivity and a gene signature that predicts response to immunotherapy**
- Investigate their potential as biomarkers**

Study samples

11 cancer types

DNA microarray
GEO



Radiosensitivity index

CANCER RESEARCH

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Molecular Biology, Pathobiology and Genetics

Prediction of Radiation Sensitivity Using a Gene Expression Classifier

Javier F. Torres-Roca, Steven Eschrich, Haiyan Zhao, Gregory Bloom, Jimmy Sung, Susan McCarthy, Alan B. Cantor, Anna Scuto, Changgong Li, Suming Zhang, Richard Jove, and Timothy Yeatman

$$\text{RSI} = -0.0098009 * \text{AR} + 0.0128283 * \text{cJun} + 0.0254552 * \text{STAT1} - 0.0017589 * \text{PKC} - 0.0038171 * \text{RelA} + 0.1070213 * \text{cABL} - 0.0002509 * \text{SUMO1} - 0.0092431 * \text{CDK1} - 0.0204469 * \text{HDAC} - 0.0441683 * \text{IRF1}$$

Radiosensitivity ↑ ▶ Radiosensitivity index ↓

Defining the gene signature (T-cell inflamed activity)



The Journal of Clinical Investigation

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Research Article Immunology Oncology Free access | 10.1172/JCI91190

IFN- γ -related mRNA profile predicts clinical response to PD-1 blockade

Mark Ayers,¹ Jared Lunceford,¹ Michael Nebozhyn,¹ Erin Murphy,¹ Andrey Loboda,¹ David R. Kaufman,¹ Andrew Albright,¹ Jonathan D. Cheng,¹ S. Peter Kang,¹ Veena Shankaran,² Sarina A. Piha-Paul,³ Jennifer Yearley,¹ Tanguy Y. Seiwert,⁴ Antoni Ribas,⁵ and Terrill K. McClanahan¹

18 genes → estimated by Gene set variation analysis

<i>CD3D</i>	<i>IL2RG</i>
<i>IDO1</i>	<i>NKG7</i>
<i>CIITA</i>	<i>HLA-E</i>
<i>CD3E</i>	<i>CXCR6</i>
<i>CCL5</i>	<i>LAG3</i>
<i>GZMK</i>	<i>TAGAP</i>
<i>CD2</i>	<i>CXCL10</i>
<i>HLA-DRA</i>	<i>STAT1</i>
<i>CXCL13</i>	<i>GZMB</i>

Tumours with higher radiosensitivity are associated with specific molecular subtypes and various immune statuses

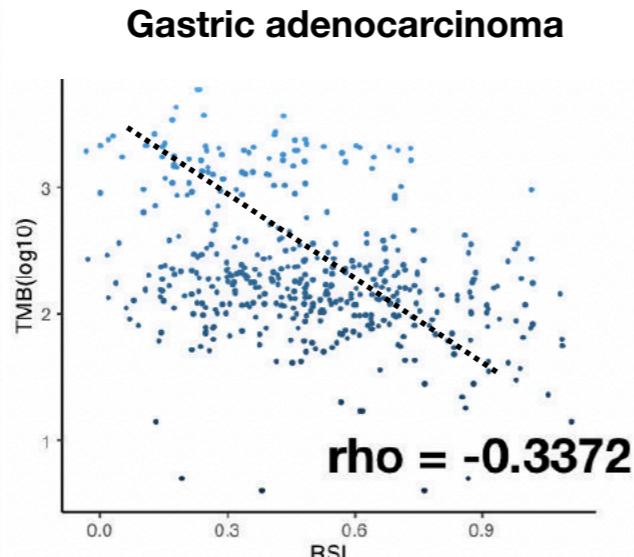
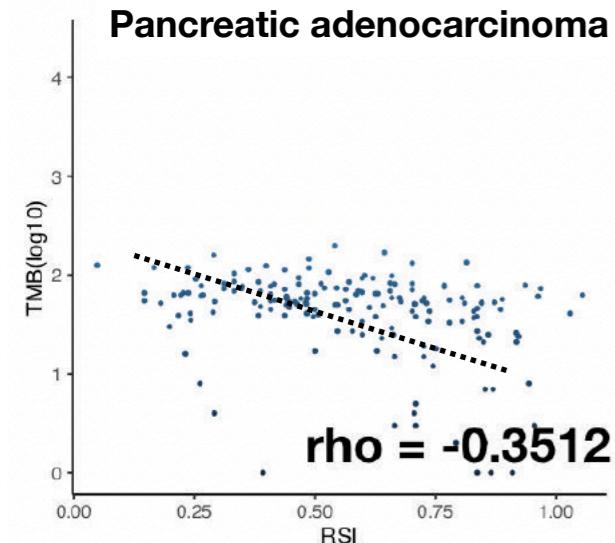
Specific molecular subtypes

Basal-like subtype in breast cancer

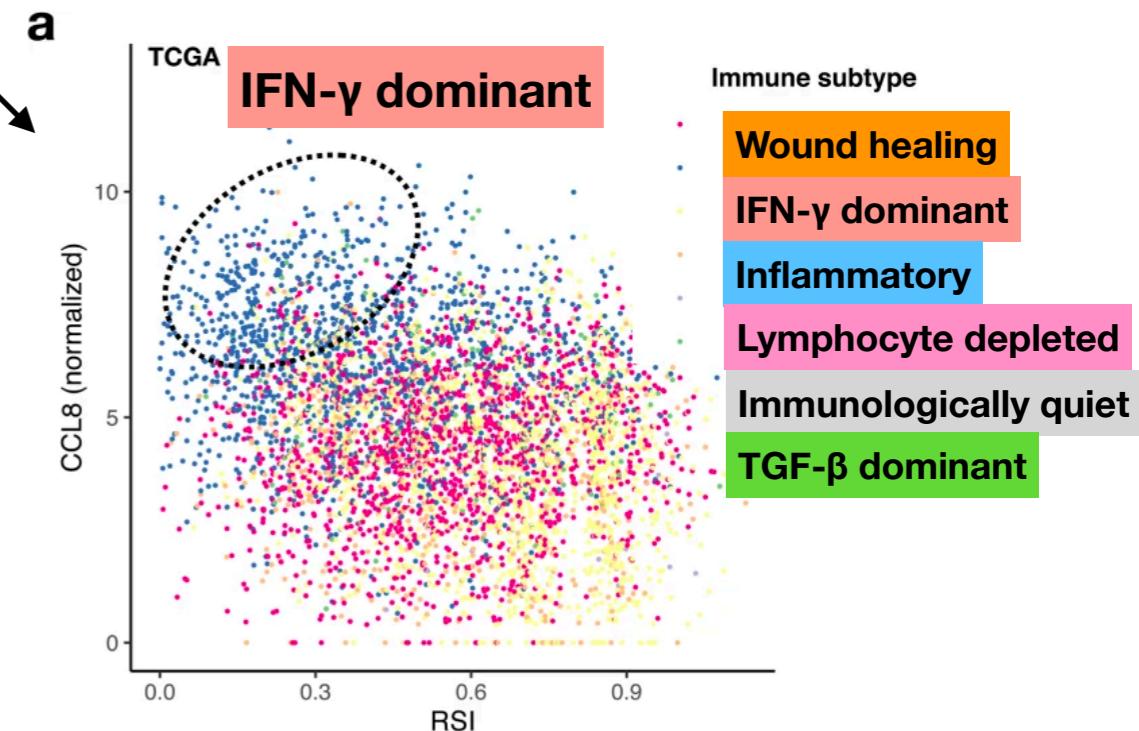
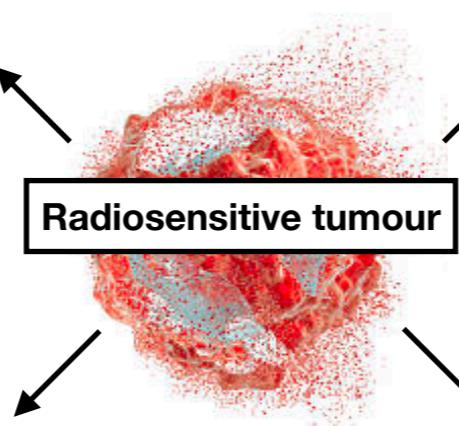
EBV-associated subtype in gastric cancer

HPV-associated subtype in oropharyngeal cancer

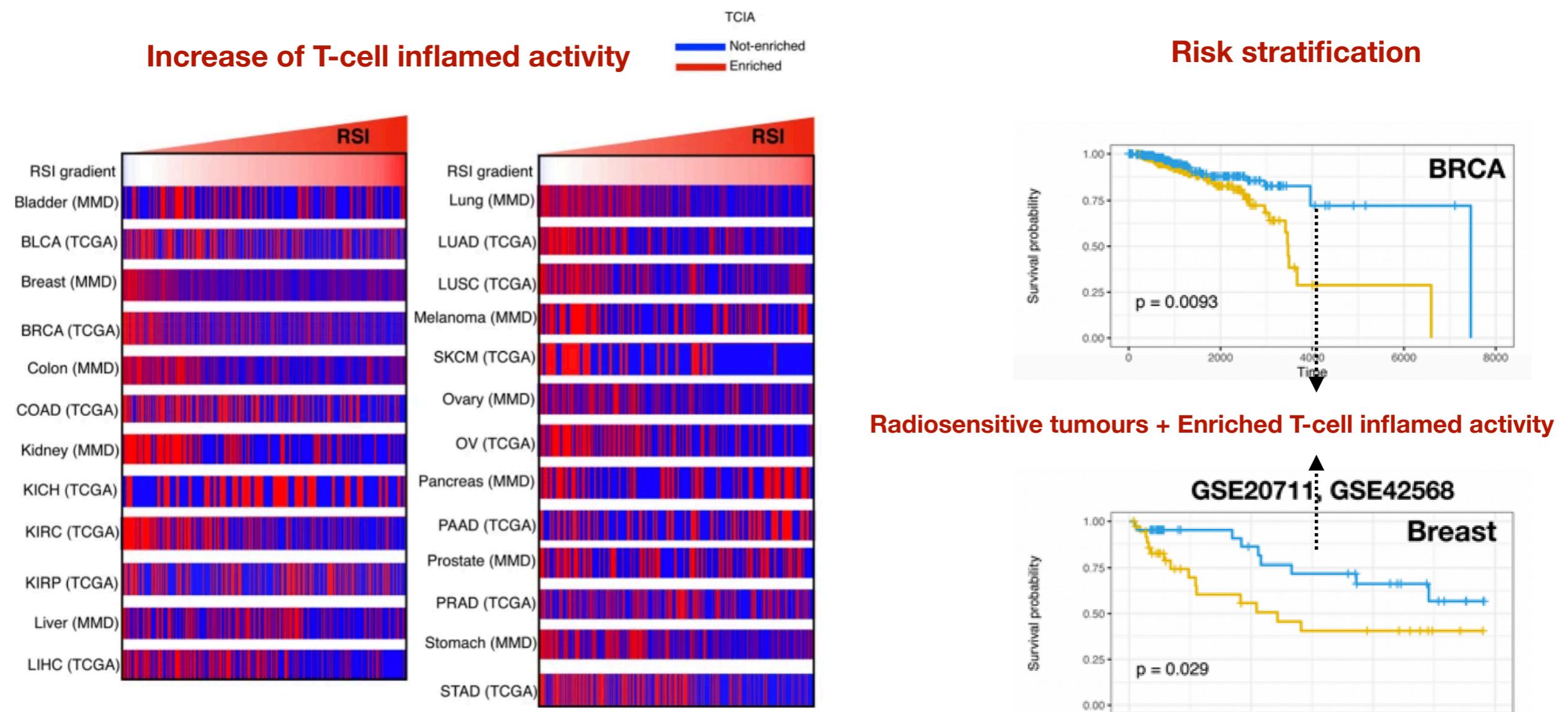
Higher mutational burden



Higher proportion of M1 macrophages (pro-inflammatory)



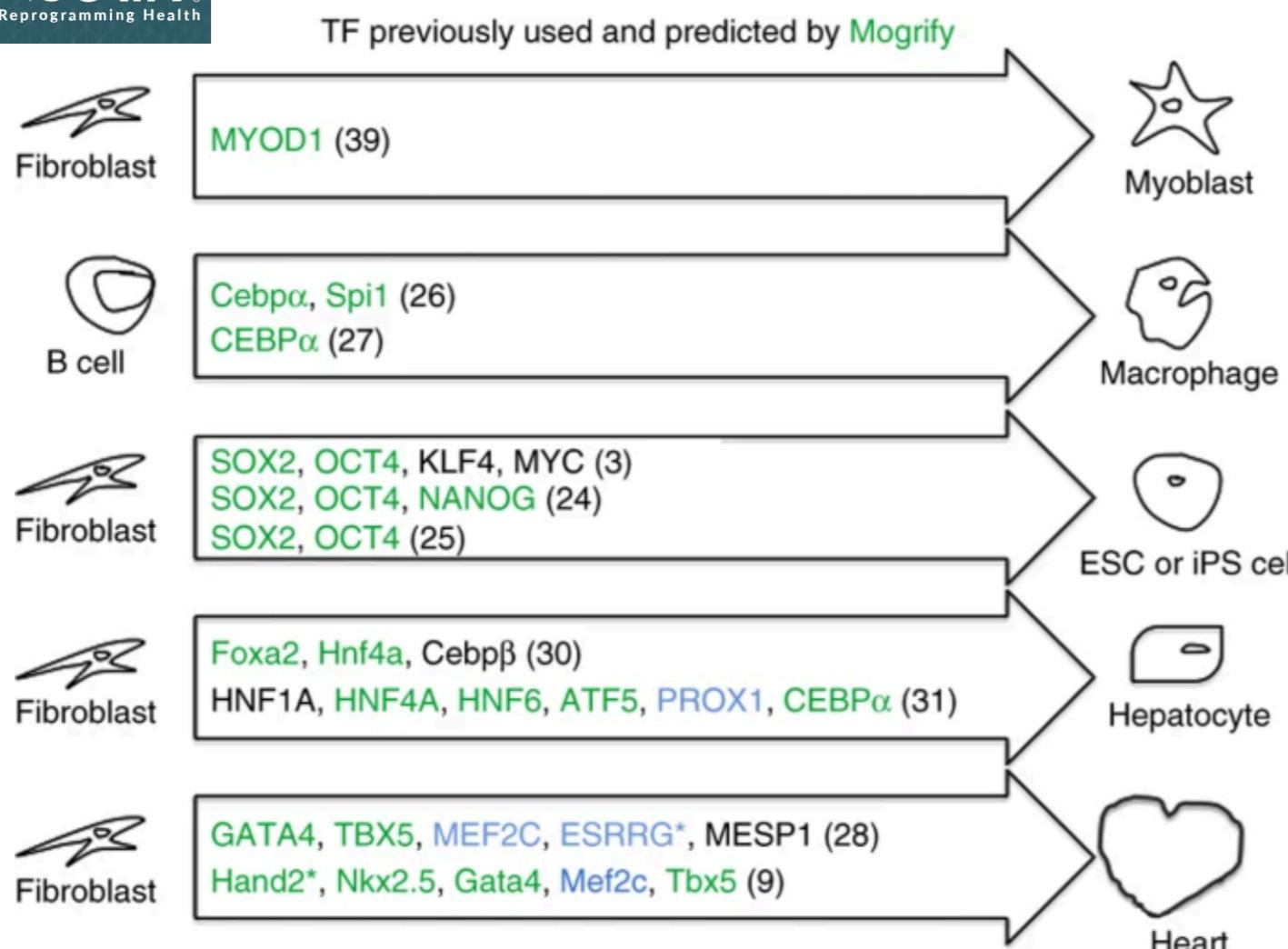
Tumours with higher radiosensitivity are associated with higher T-cell inflamed activity



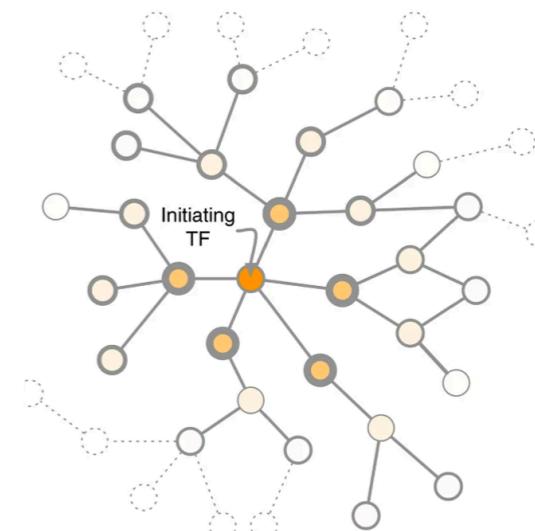
Summary

- Tumour's radiosensitivity is associated with specific immune status in various cancer types
- This association may be exploited to optimise radiotherapy-immunotherapy combination

Collaborative study: Research background



A predictive computational framework for direct reprogramming between human cell types. *nature genetics*. 2016

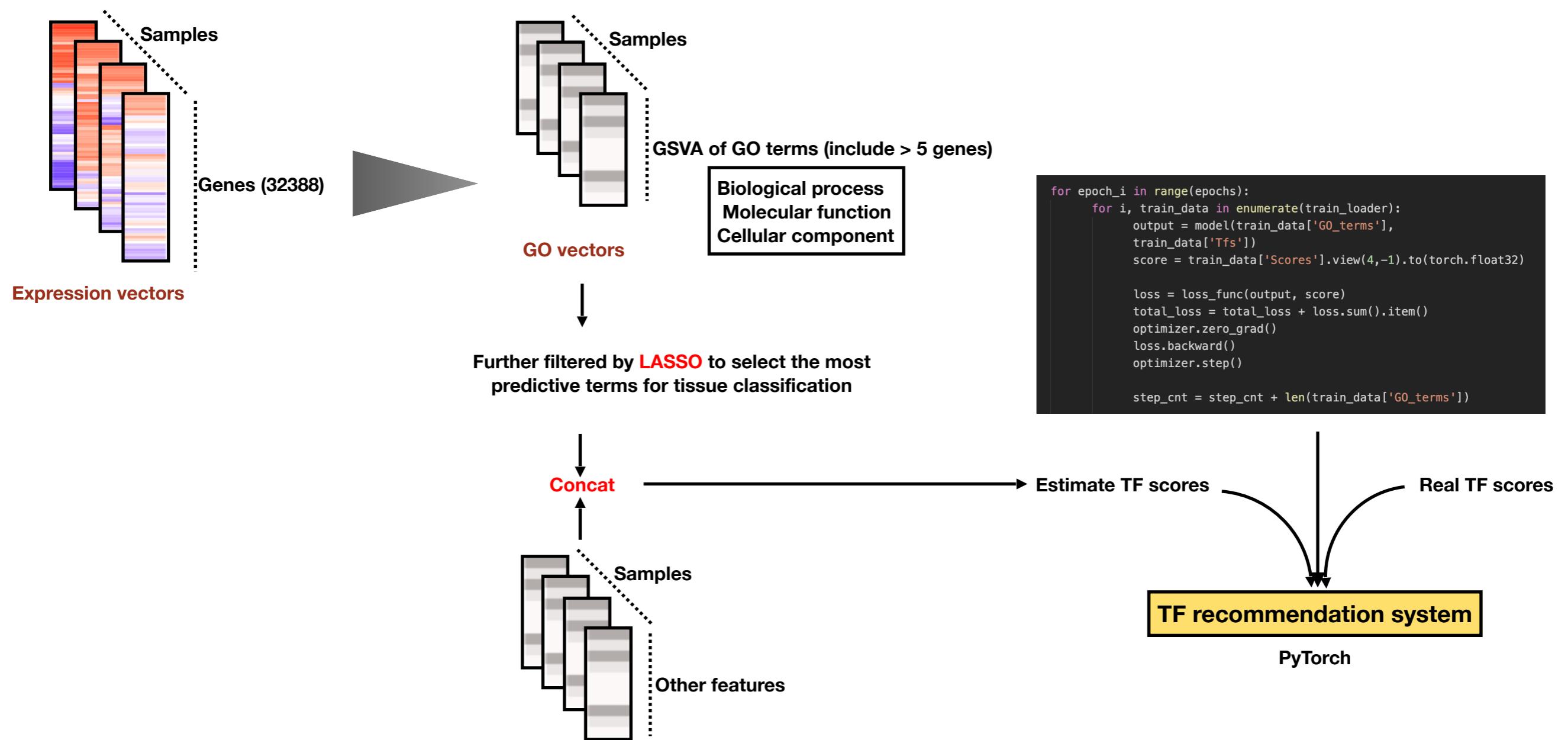
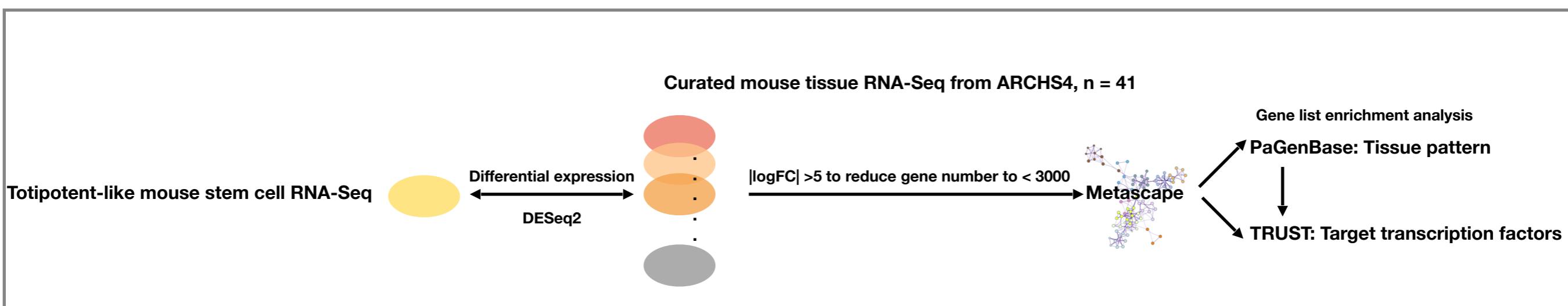


- Current identification of transcription factors for cell differentiation: **bioinformatic analyses**
- No deep learning model has been constructed

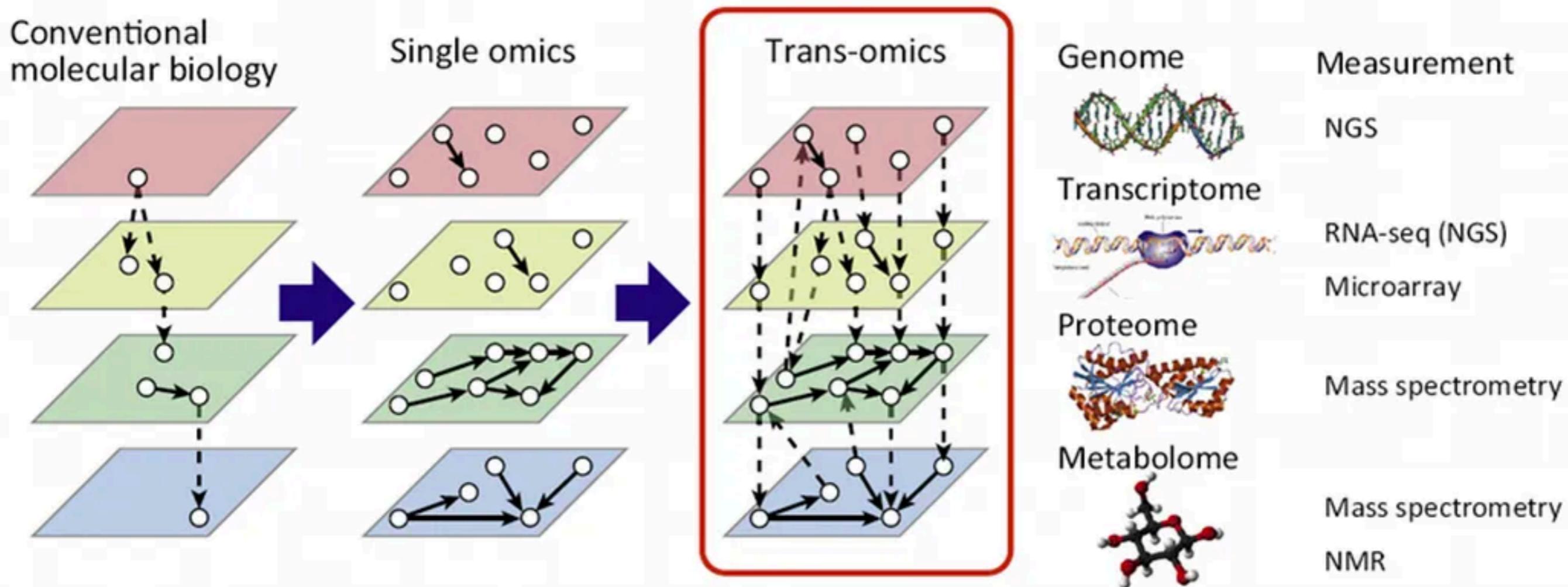
Aim

- Deep learning model can be applied to predict transcription factors

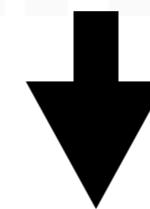
- What I am in charge: Study design Data preprocessing Construction of deep learning model



Ongoing study: Research background

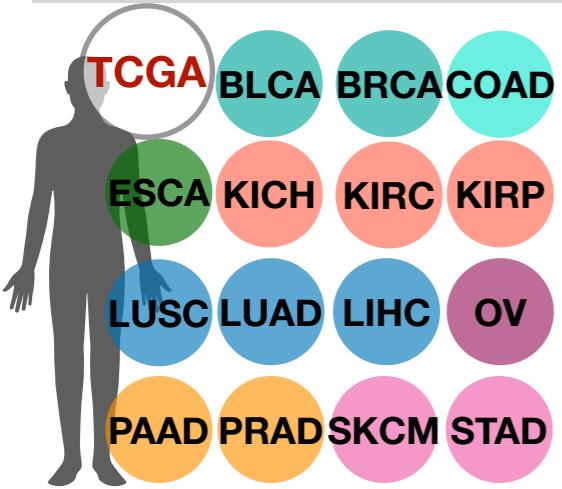


Trends Biotechnol. 2016 Apr;34(4):276–290

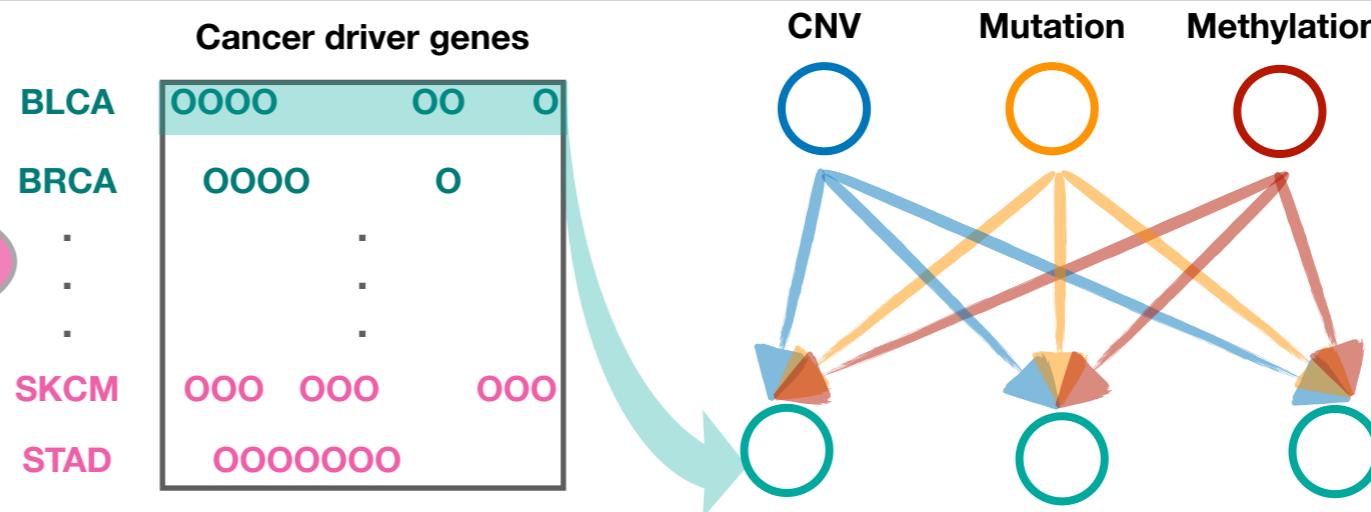


Integrate multi-omics information for precise prediction of biological events

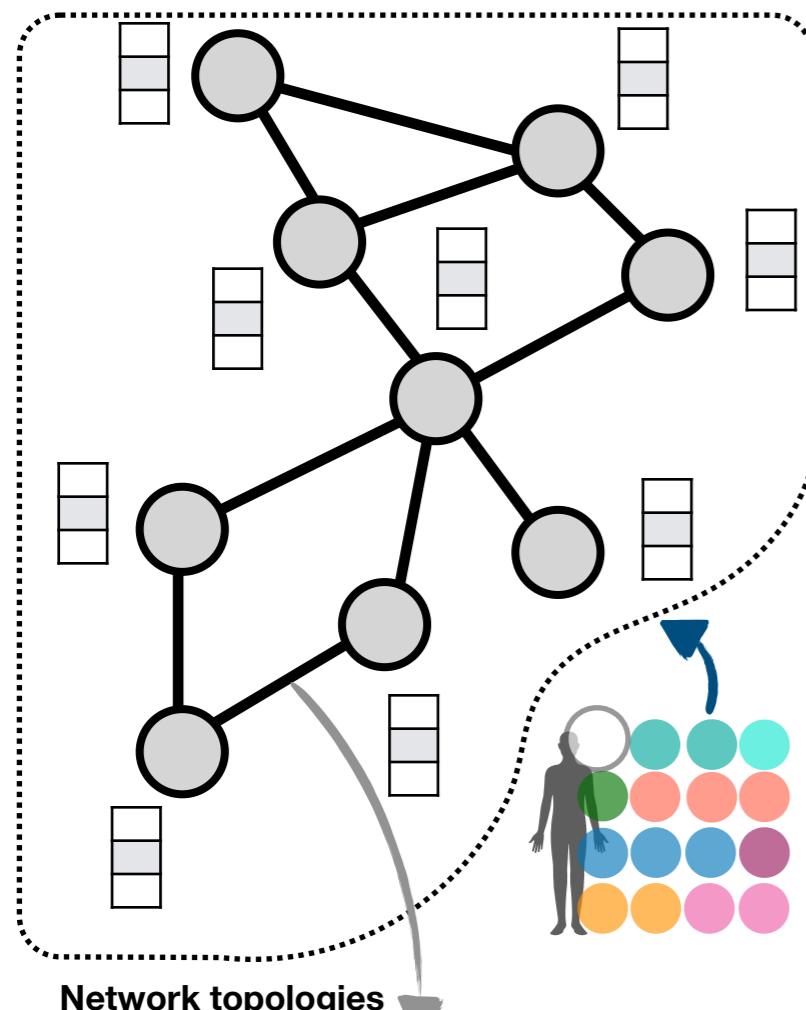
Sample collection



Incorporation of multi-omics data into driver genes



Network construction



Target labelling

Clinical labeling

Stage

Survival

Molecular labeling

HRD/Stemness

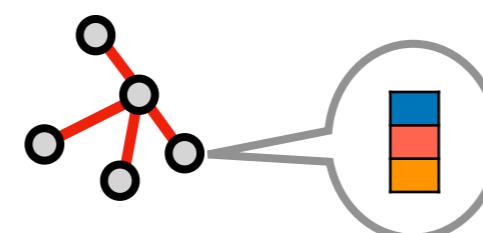
IM

Group 1

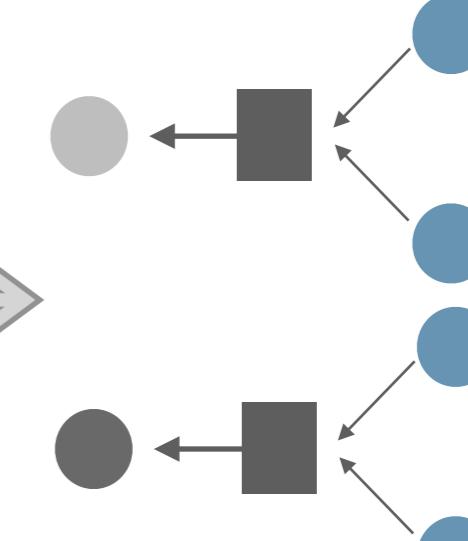
Group 2

GNN explanation

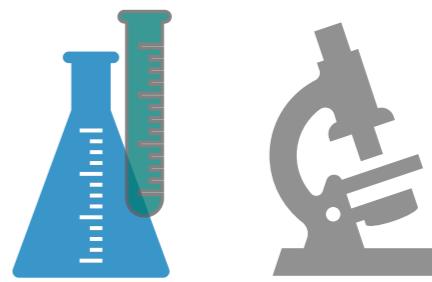
Important edges Important features

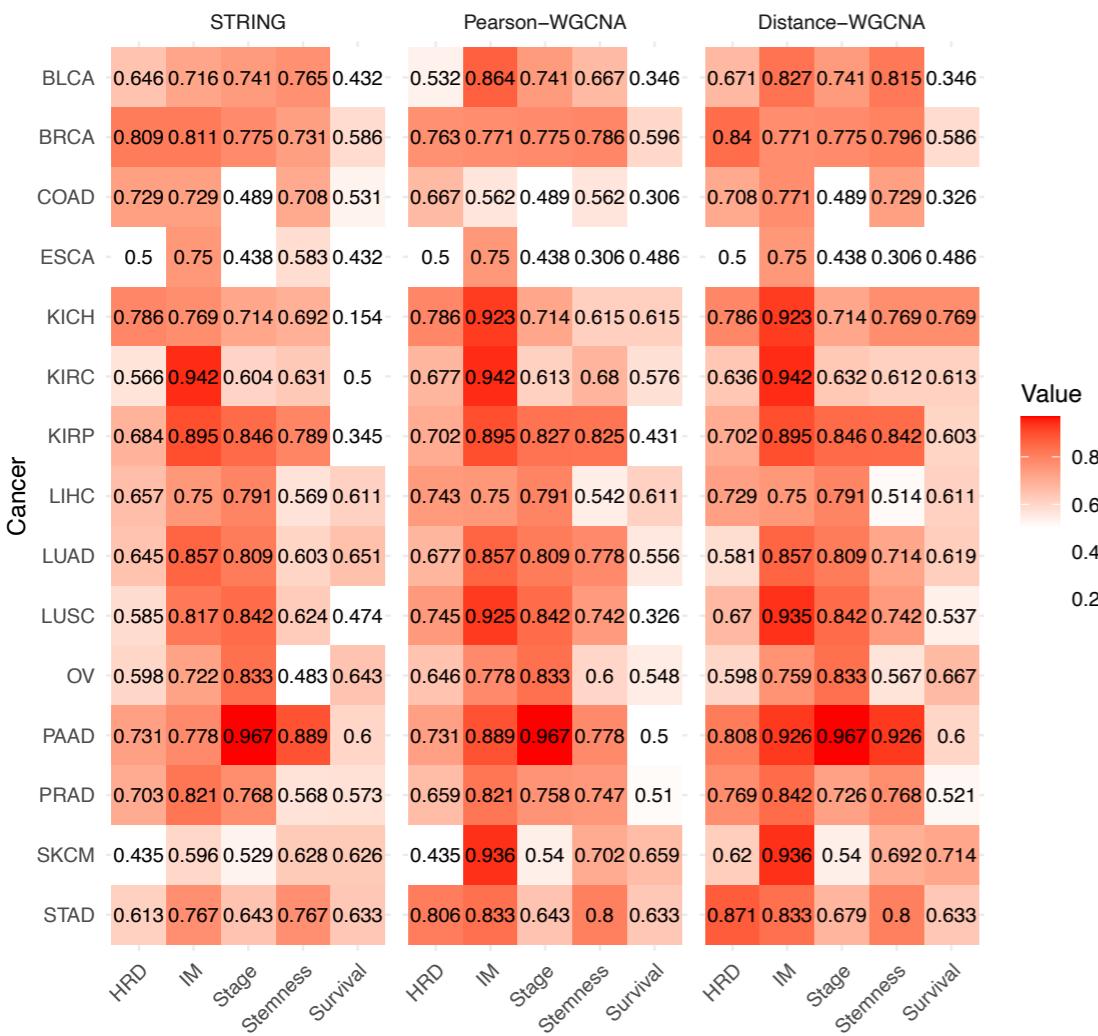
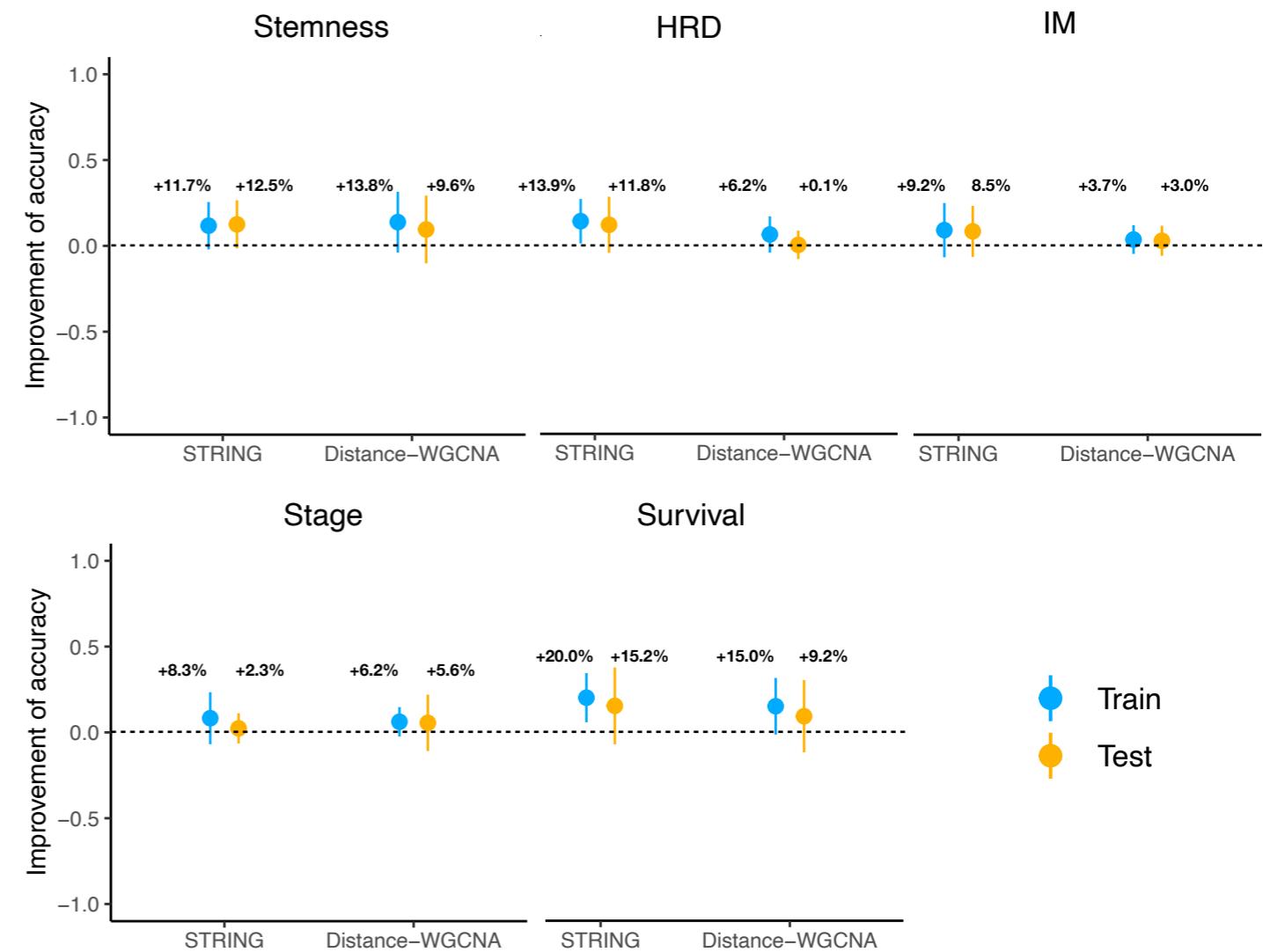


GNN model



Validation

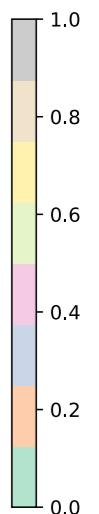
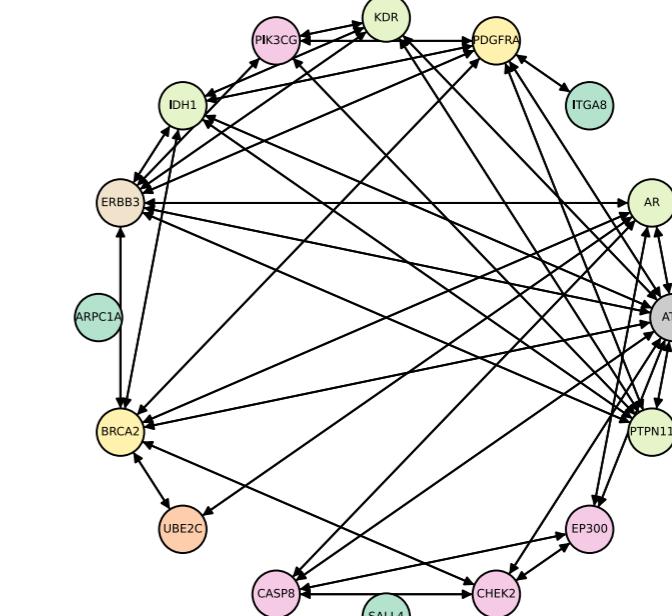
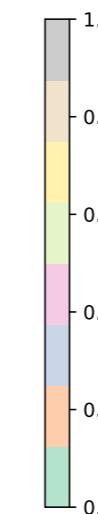
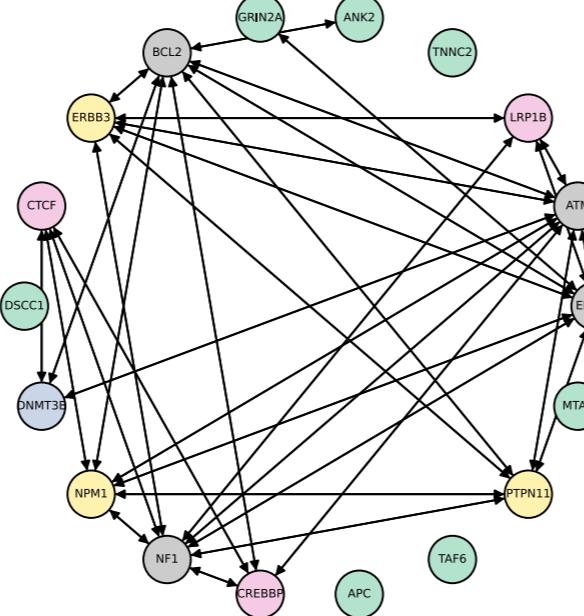
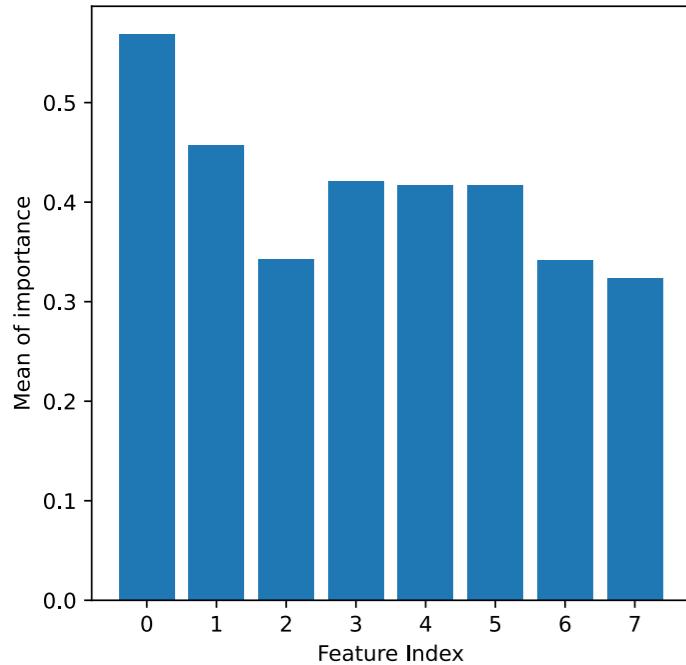


a**b**

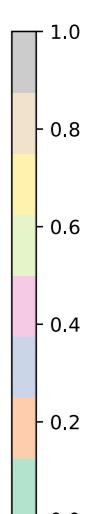
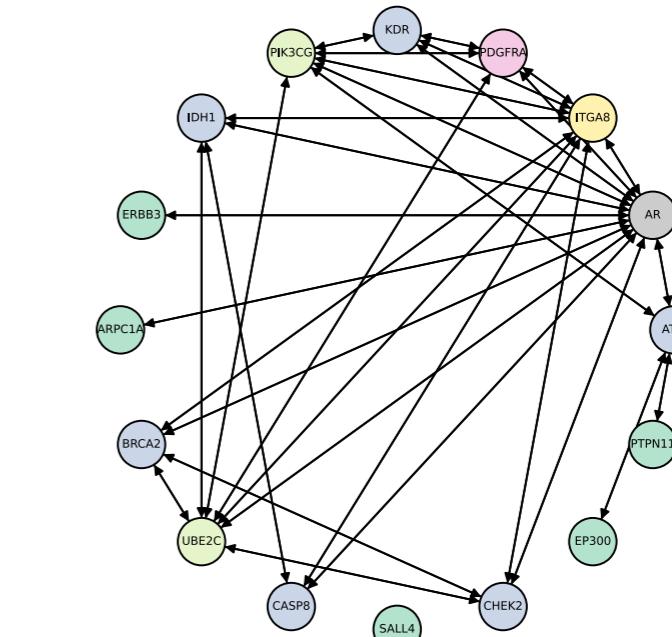
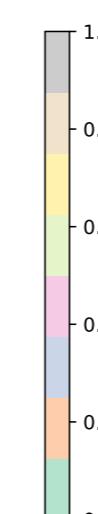
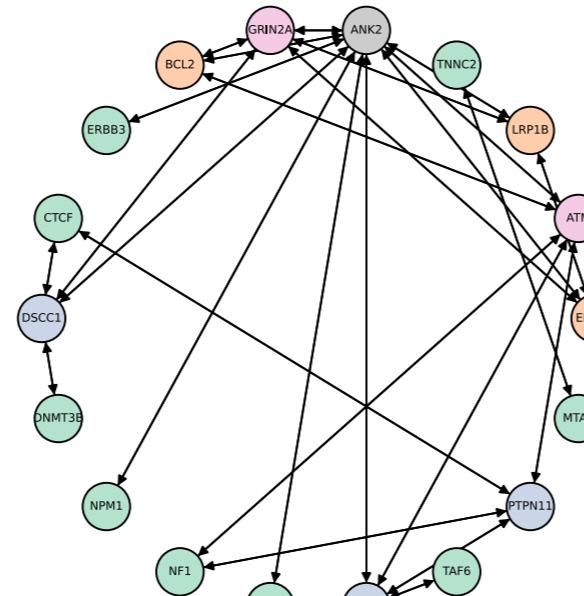
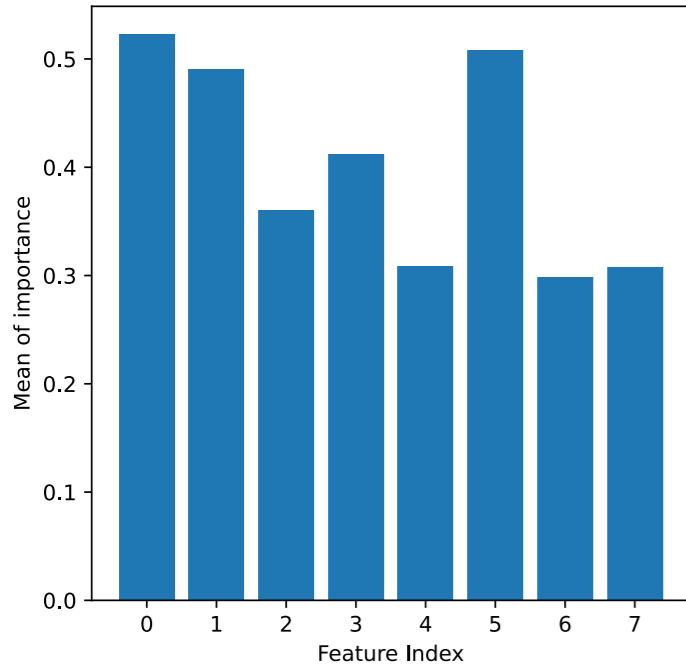
Training of over 200 models

Specialised gene regulatory structure (**distance WGCNA**) has the highest accuracy in predicting the phenotypes of cancer

STAD-HRD-STRING



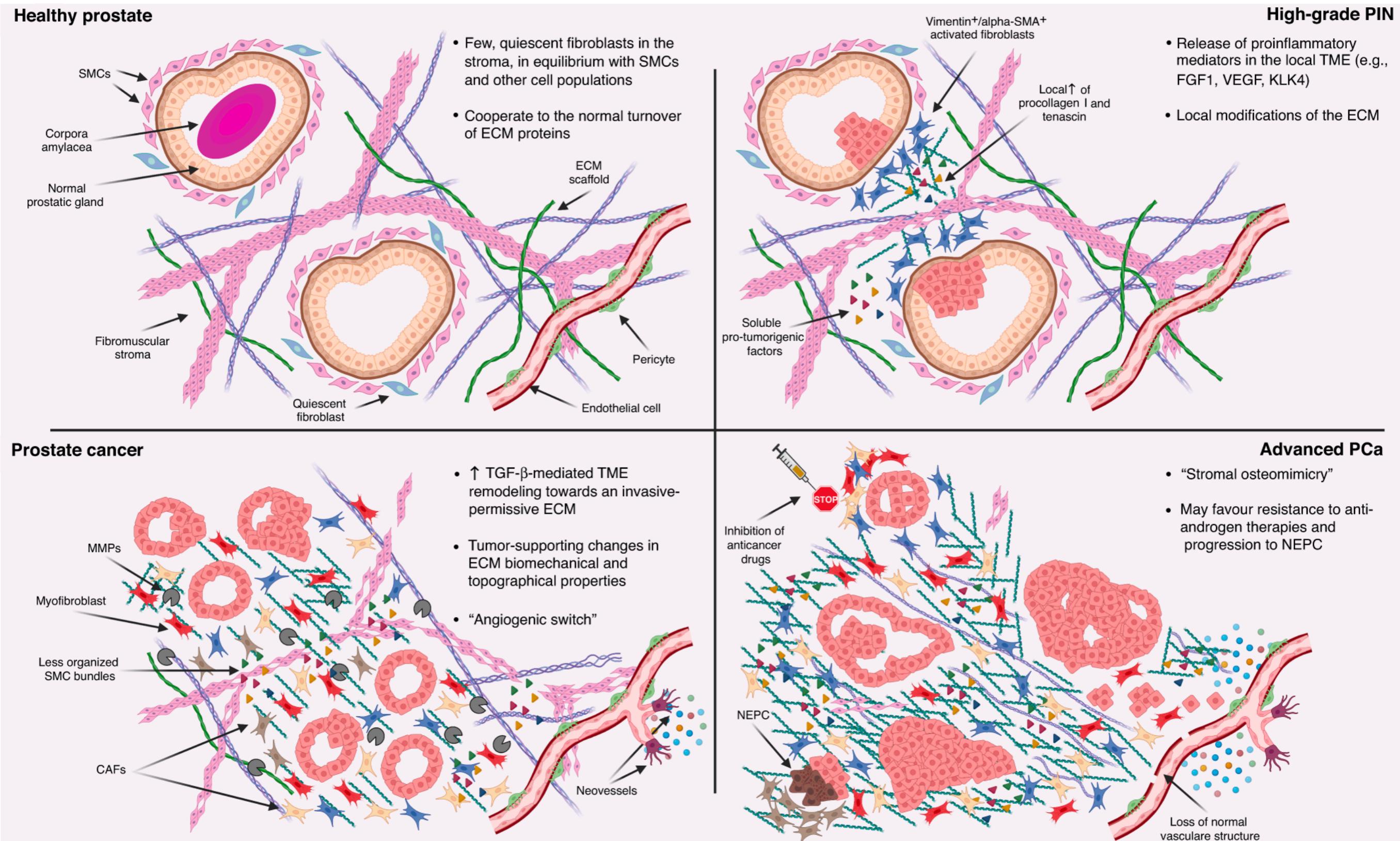
STAD-HRD-WGCNA



Current project

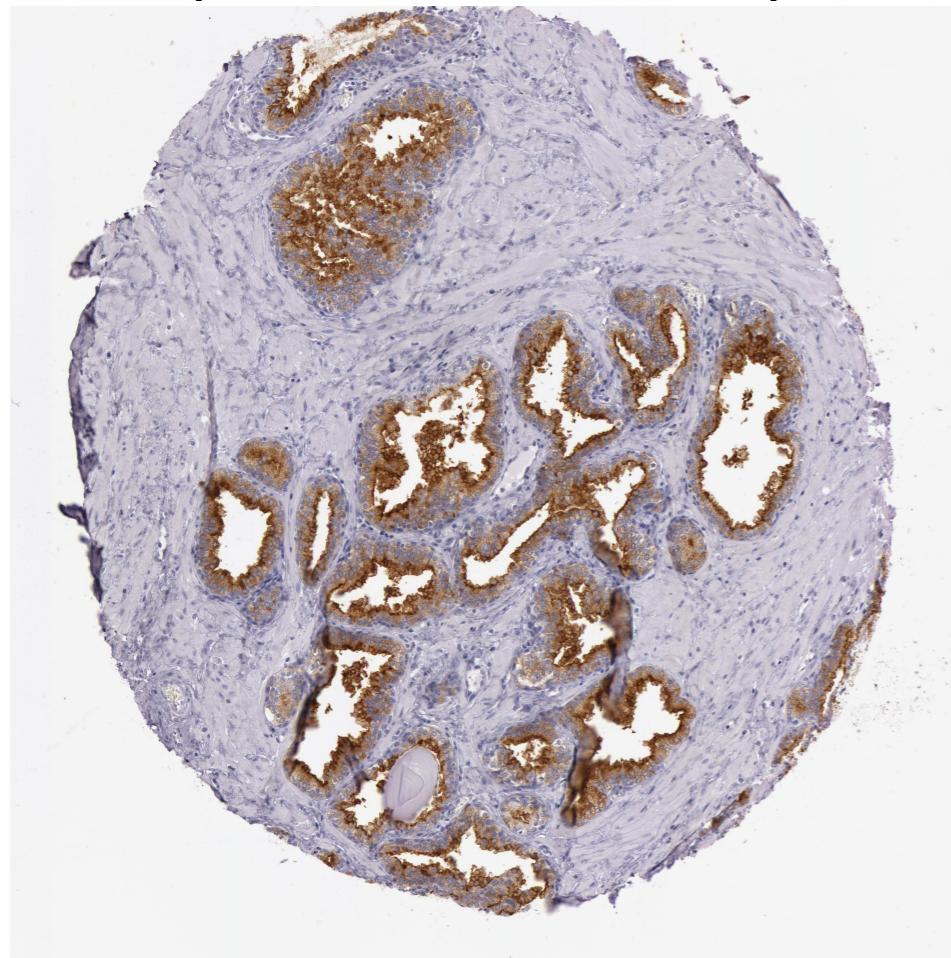
Using single cell RNA sequencing to explore the dynamics of transcriptional landscapes in prostate cancer after external beam radiotherapy and Lu-177-PSMA targeted radionuclide therapy

Complex tumour-stoma interaction in prostate cancer

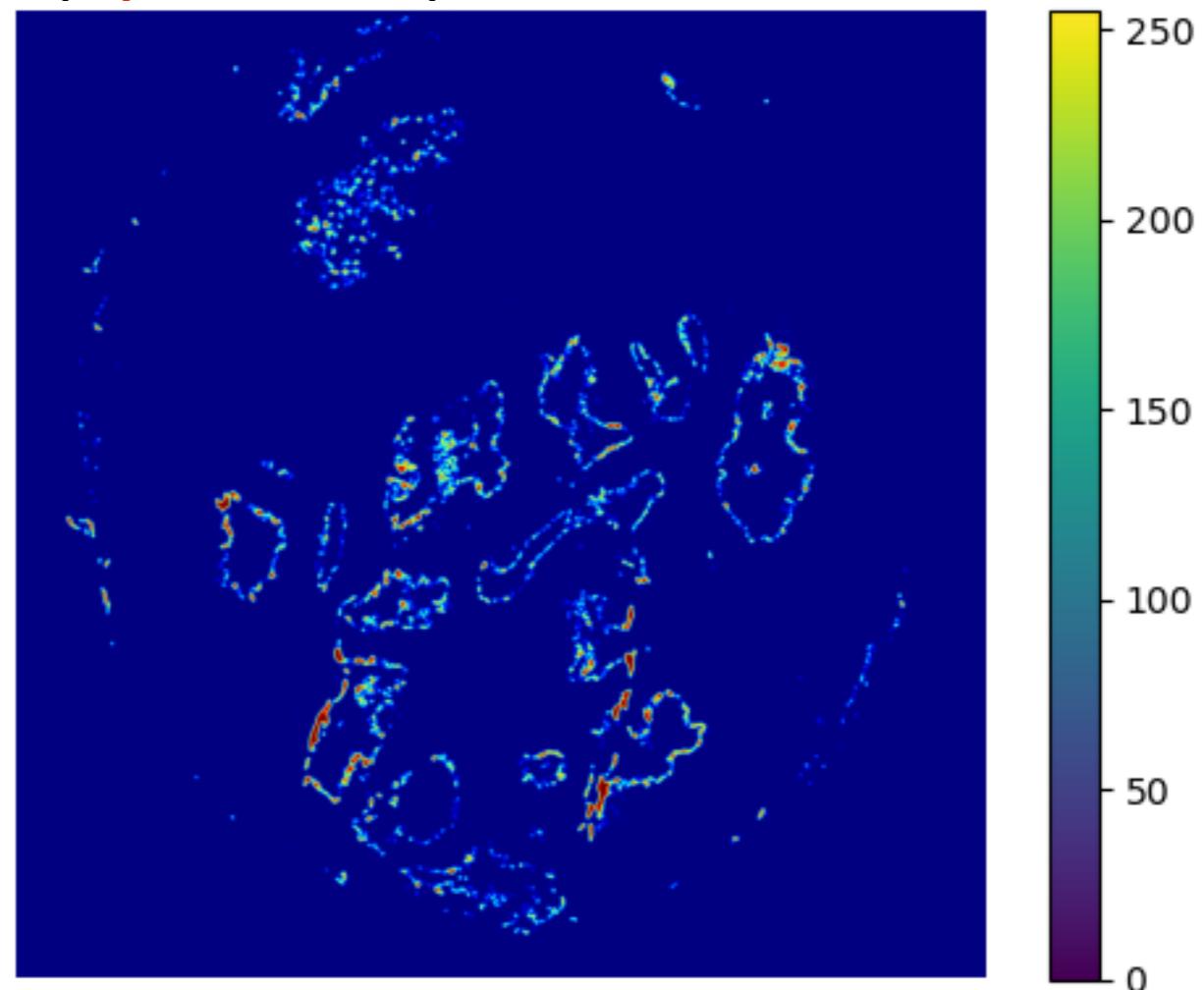


Prostate cancer-TMA-PSMA expression

Prostate cancer patient from TCGA cohort
(The Human Protein Atlas)



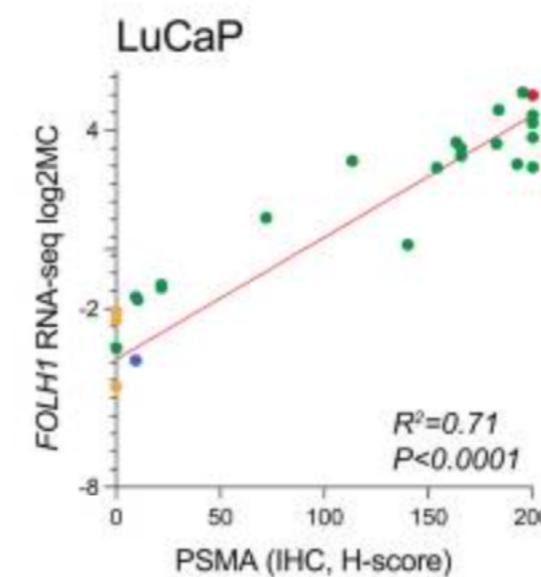
Heterogeneous spatial and **intensity**
(expression level) distribution of PSMA

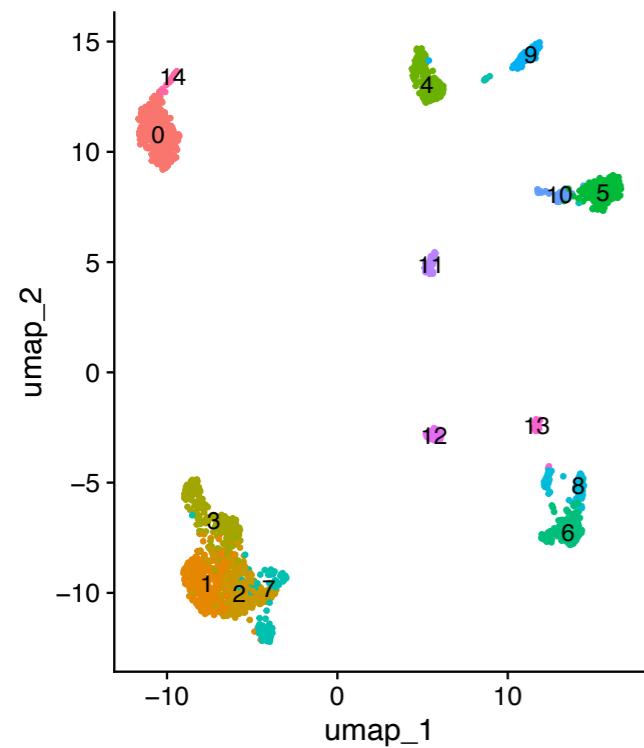
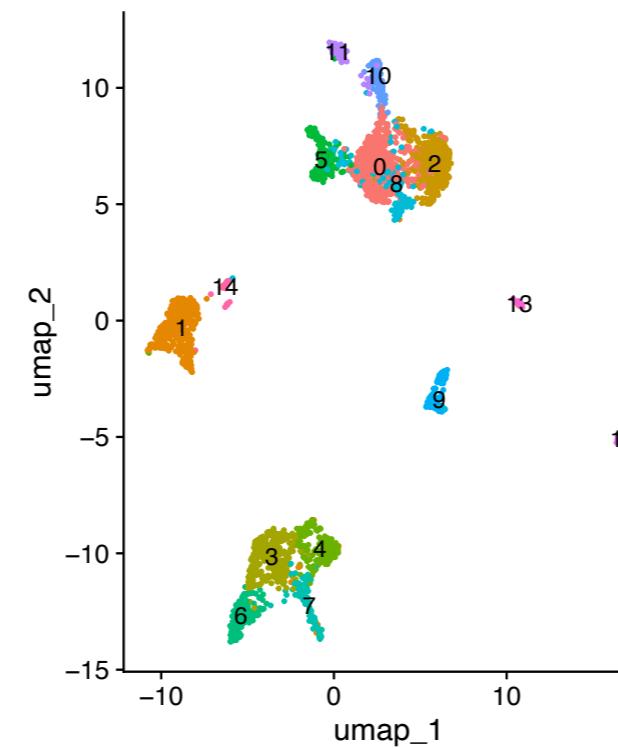
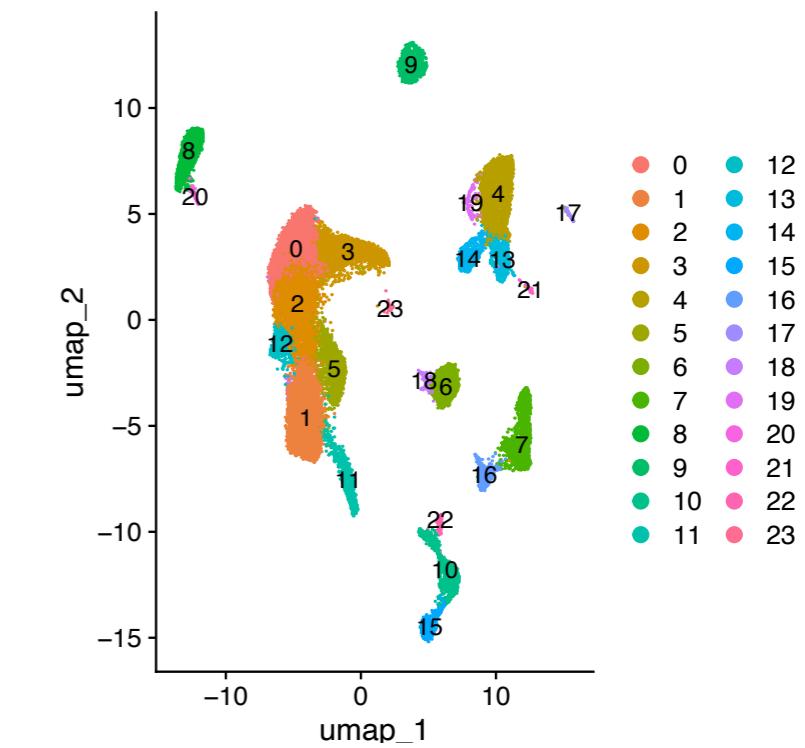
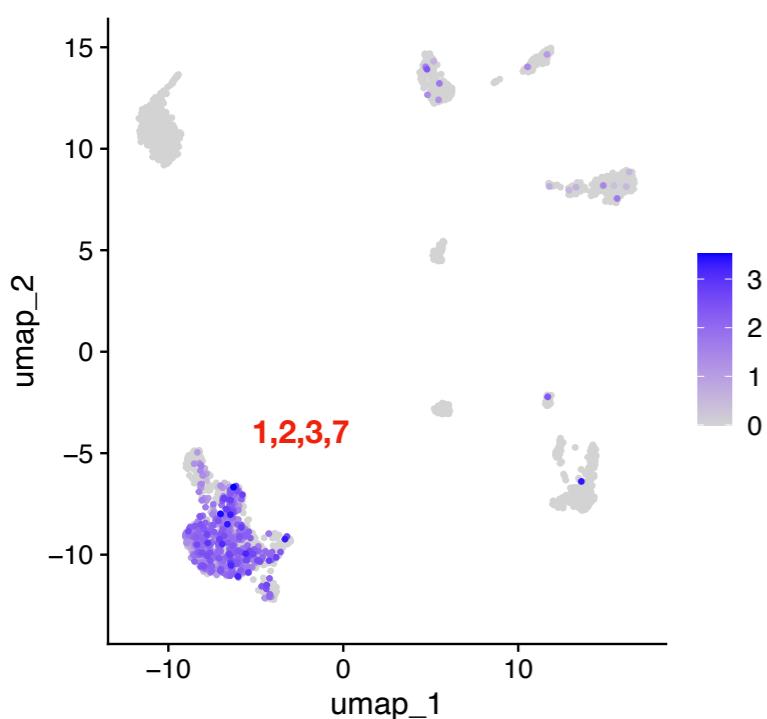
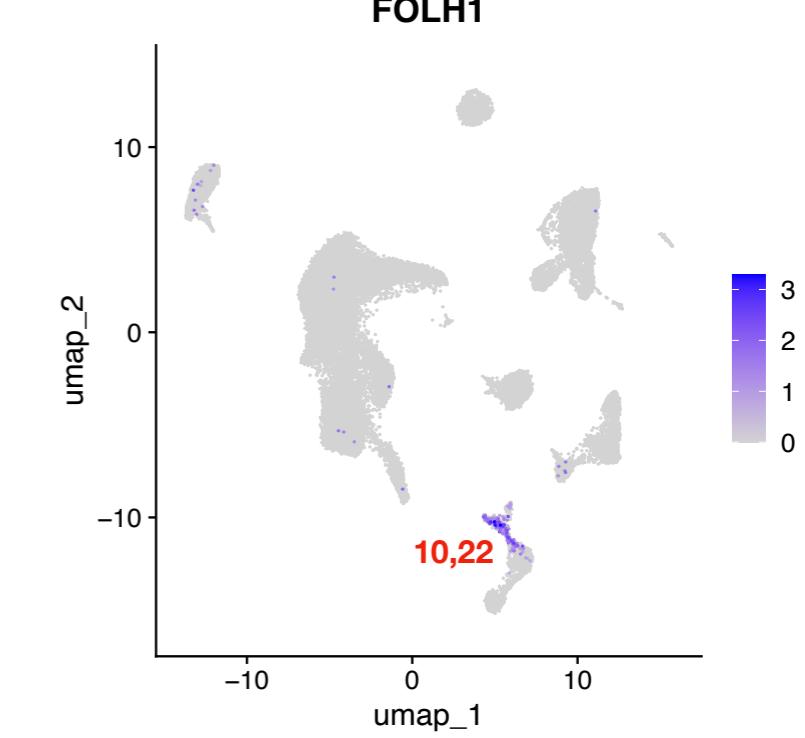
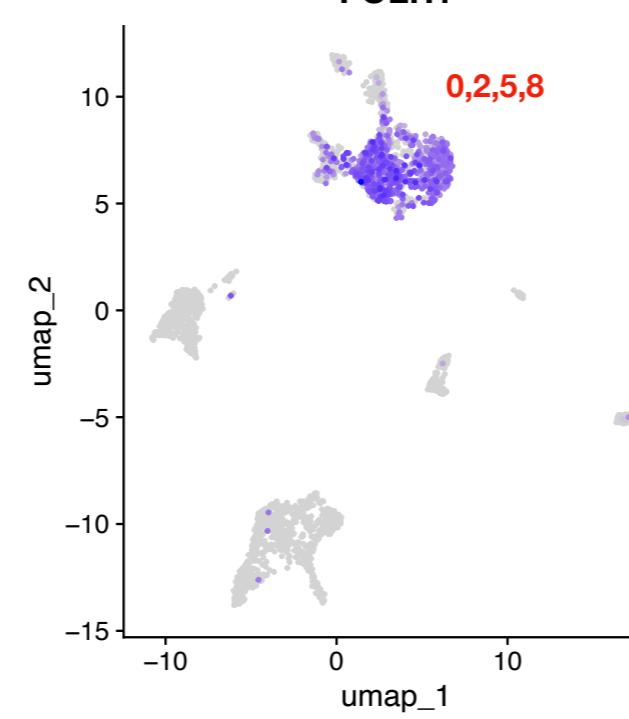


Prostate tumour/gland: **70% of the prostate**

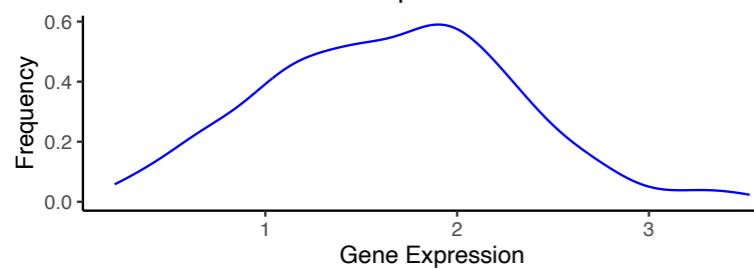
Remaining **30%**: **fibromuscular tissue and stroma**

We can use FOLH1 to evaluate PSMA expression

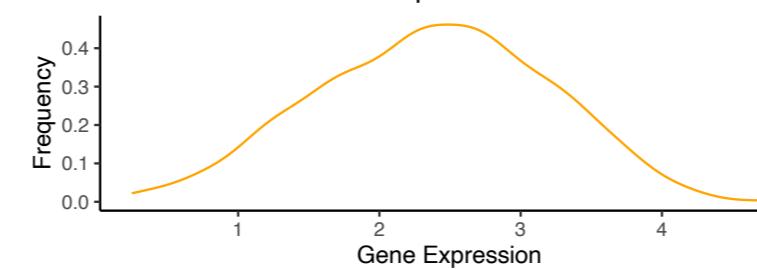


GSE176031_1 (Inter-High grade)**GSE176031_2 (Inter-High grade)****GSE181294 (High grade)****FOLH1****FOLH1**

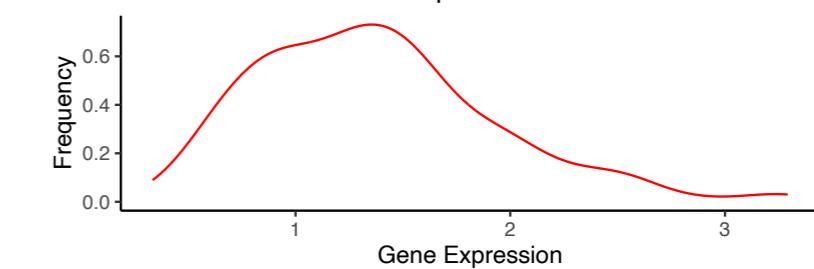
Distribution of FOLH1 Expression



Distribution of FOLH1 Expression



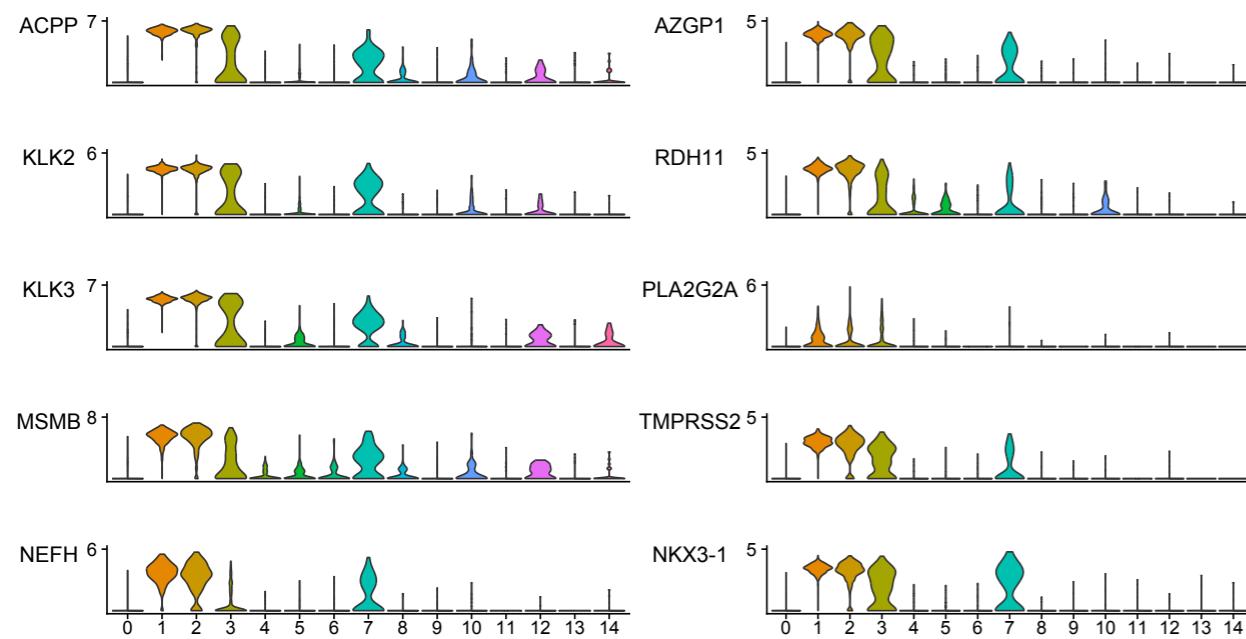
Distribution of FOLH1 Expression



FOLH1 is mainly expressed in prostatic epithelium

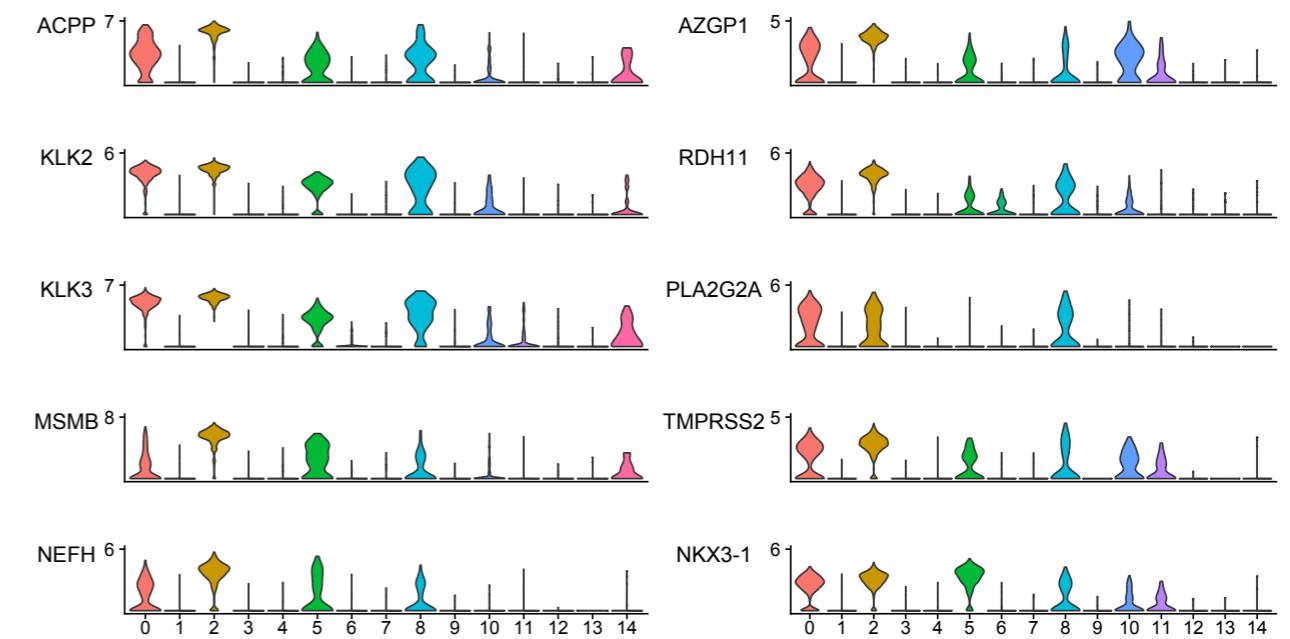
GSE176031_1

Epithelium: 1,2,3,7



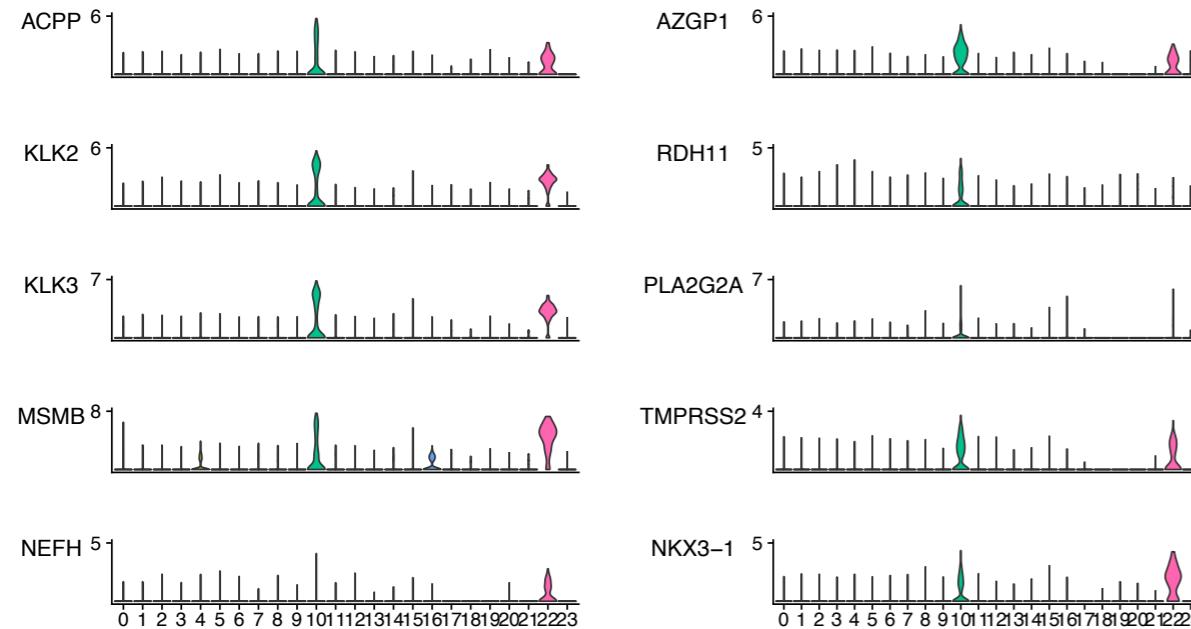
GSE176031_2

Epithelium: 0,2,5,8



GSE181294

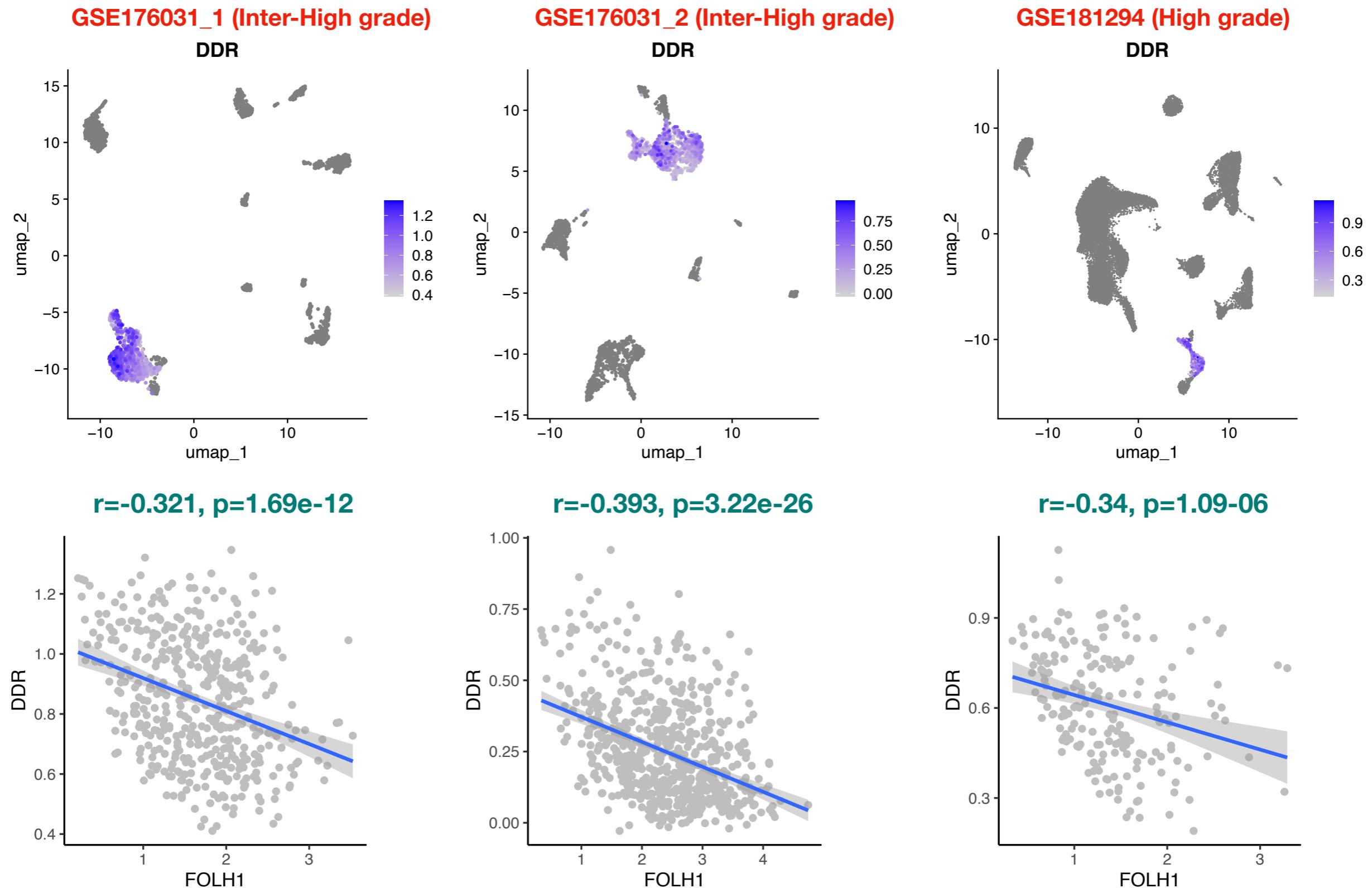
Epithelium: 10,22



Significant correlation between DDR pathway activity and FOLH1 expression in prostatic epithelium for inter-high grade cancer

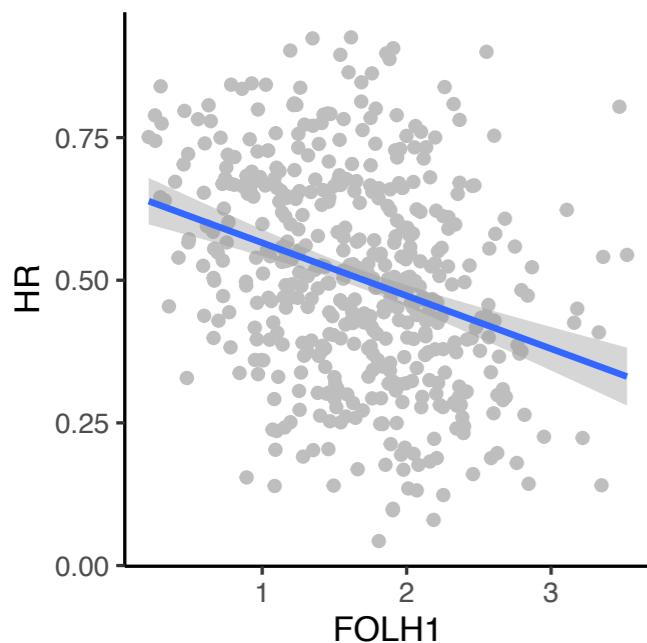
HALLMARK_DNA_REPAIR.v2023.2.Hs

Activity estimated by single sample gene set enrichment analysis (ssGSEA)

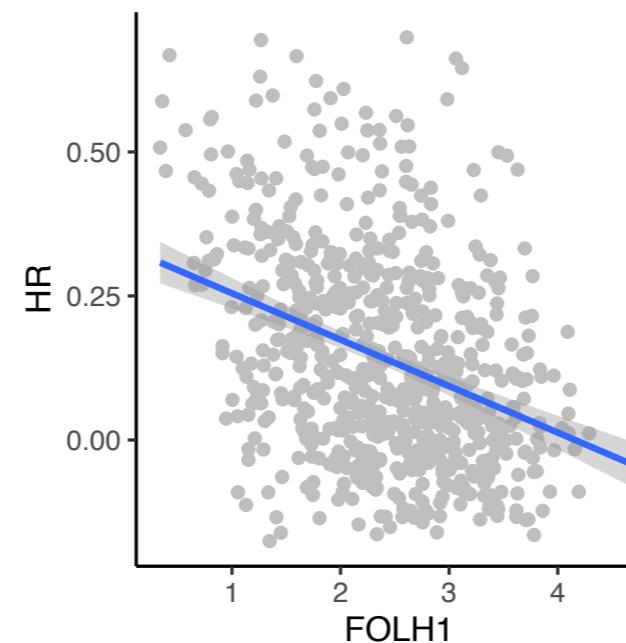


GOBP_REGULATION_OF_DOUBLE_STRAND_BREAK_REPAIR_VIA_HOMOLOGOUS_RECOMBINATION

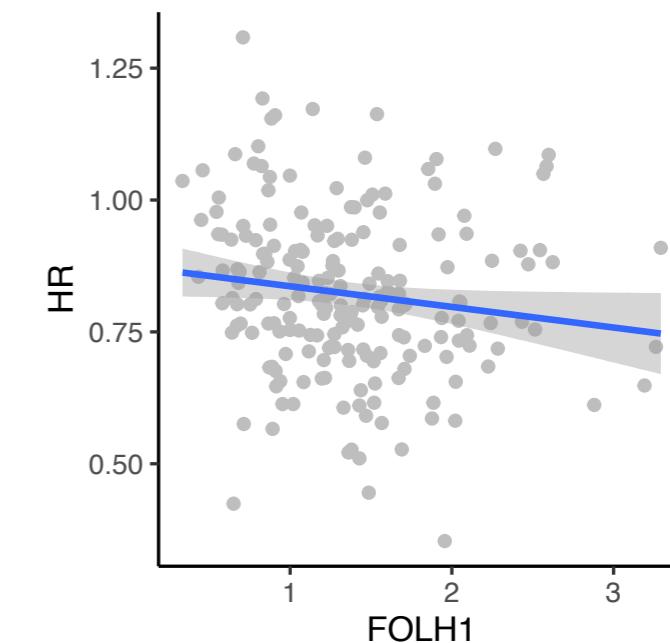
$r=-0.321, p=9.97e-13$



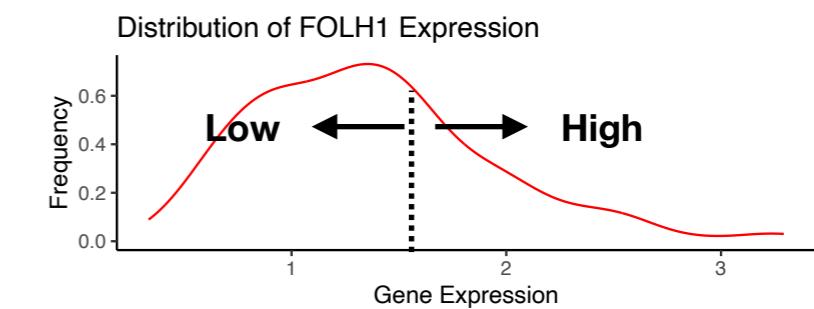
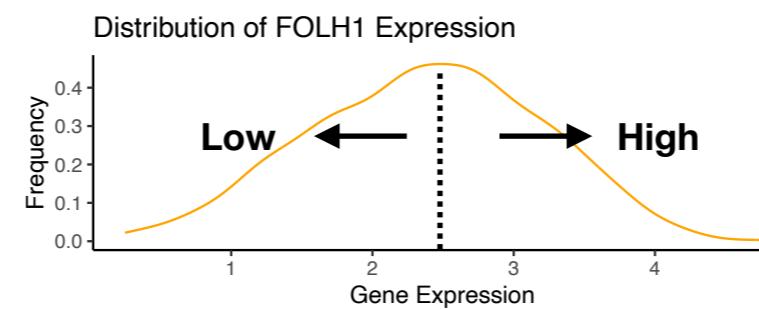
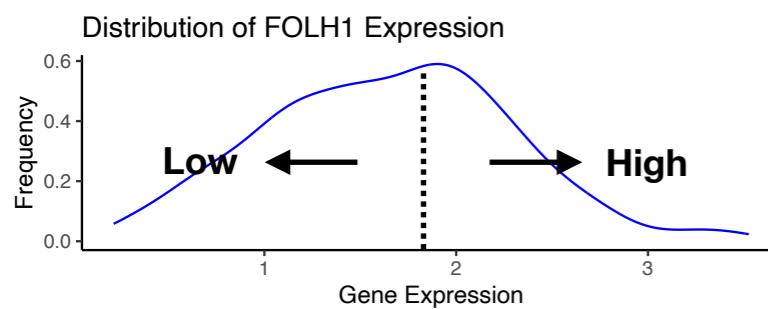
$r=-0.332, p=9.53e-19$



$r=-0.187, p=0.0086$



Median split



Differential expression analysis

Differentially expressed genes

ChEA3-Transcription factor prediction

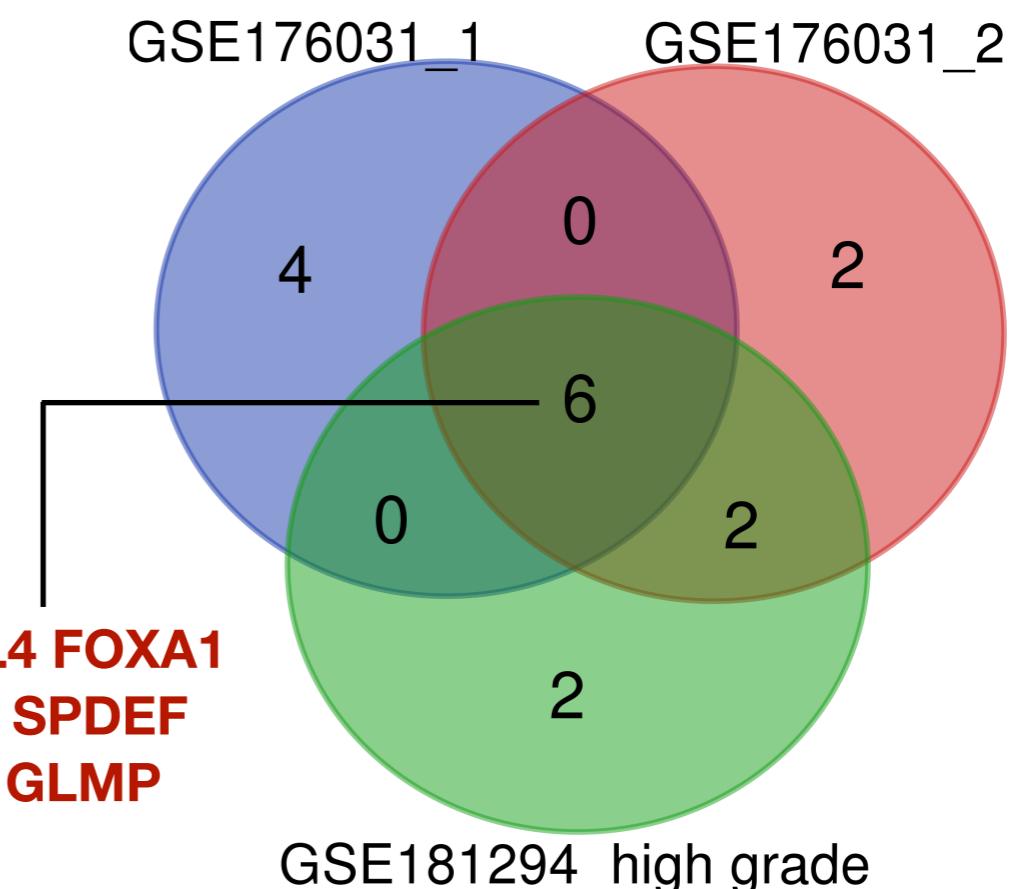
Top 10 TFs for each dataset

Library	Unique TFs
ARCHS4 Coexpression	1628
ENCODE ChIP-seq	118
Enrichr Queries	1404
GTEx Coexpression	1607
Literature ChIP-seq	164
ReMap ChIP-seq	297

Mean Rank (higher accuracy)



**CREB3L4 FOXA1
ZBTB42 SPDEF
NKX3-1 GLMP**

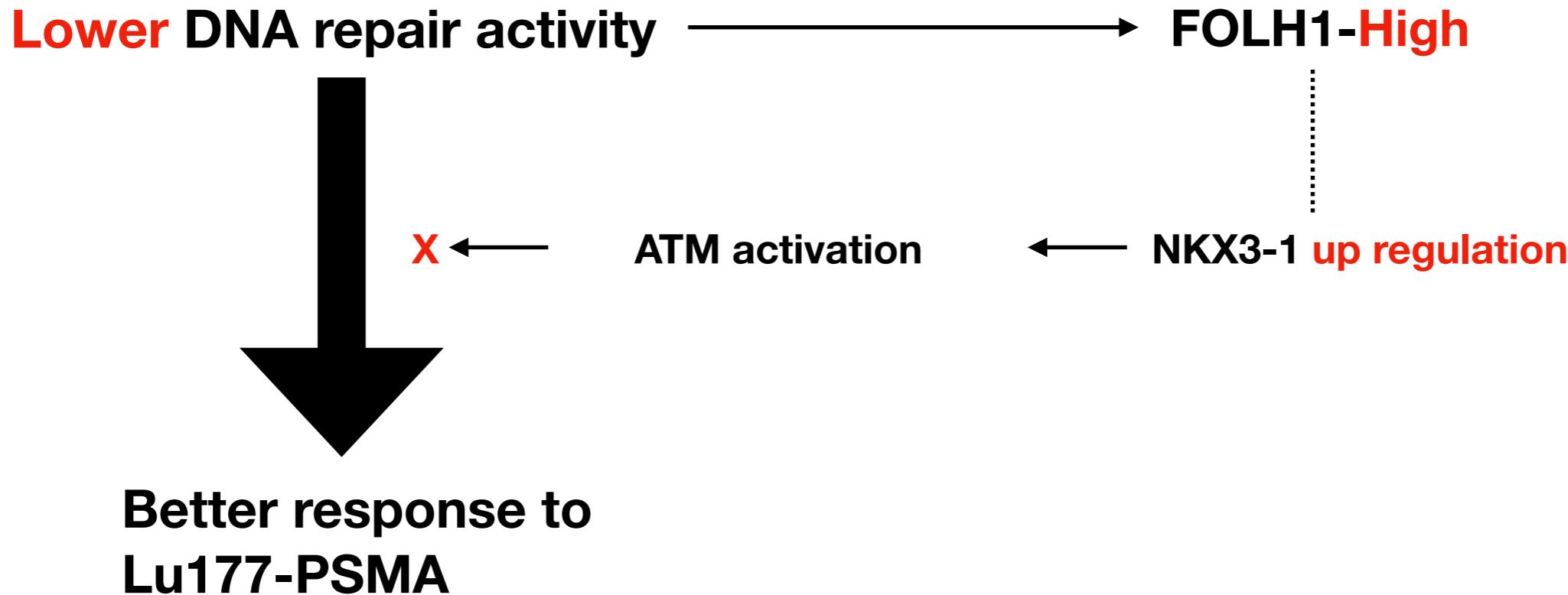


Differentially expressed transcription factors

CREB3L4 FOXA1 SPDEF NKX3-1 XBP1

Cumulative mean rank

- Top1: NKX3-1
- Top2: SPDEF
- Top3: CEREB3L4
- Top4: FOXA1
- Top5: XBP1



Future work

- Patient-derived xenograft of prostate cancer model
- Single cell RNA analysis (**special focus on DNA repair activity and NKX3-1**)
- In vitro validation of bioinformatics results