

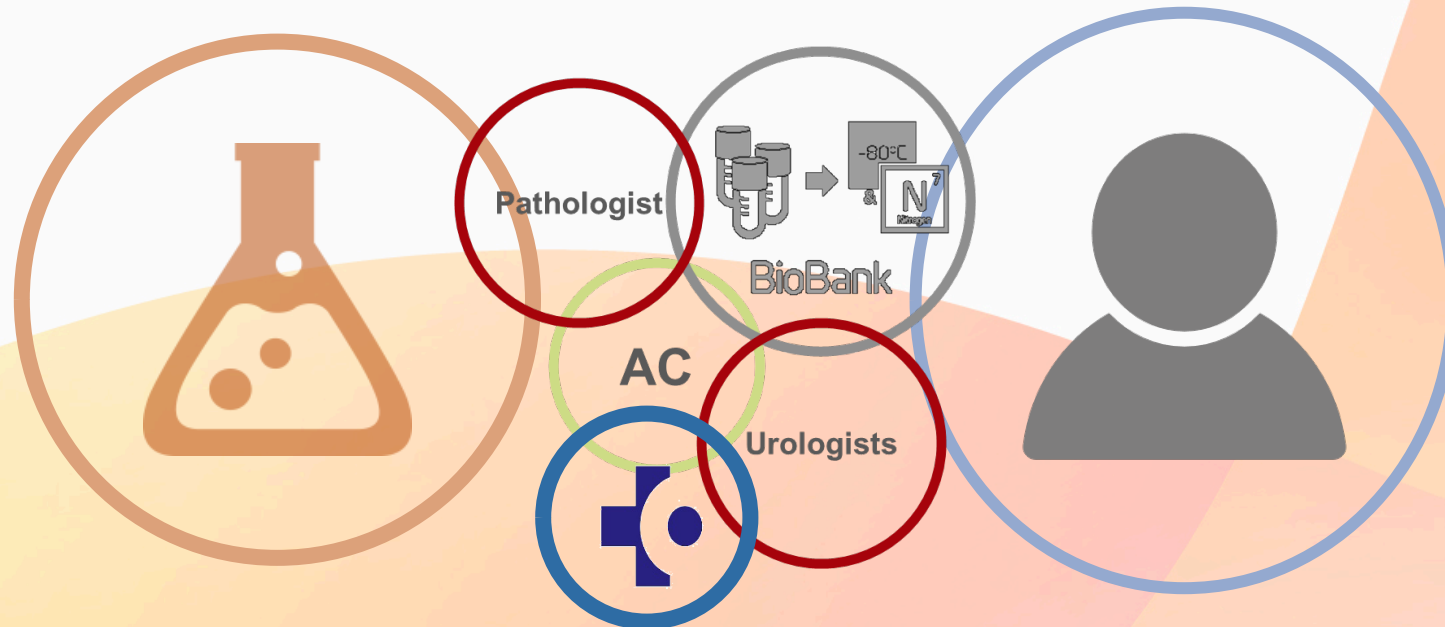
Molecular processes underlying aggressive prostate cancer

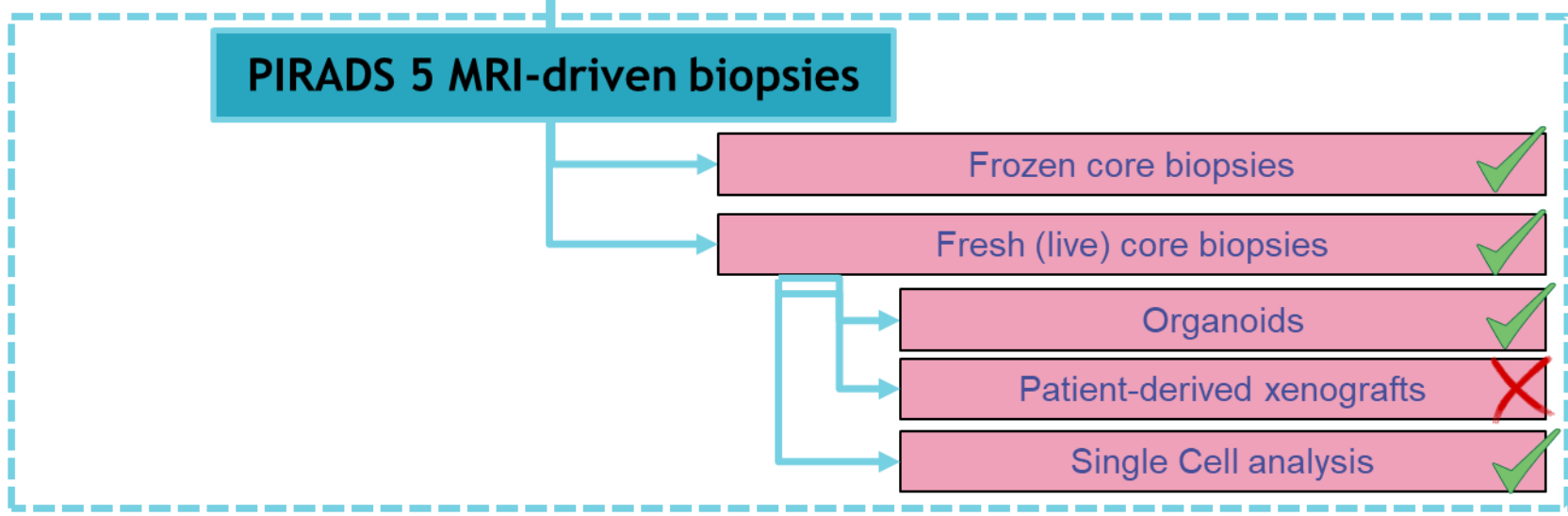
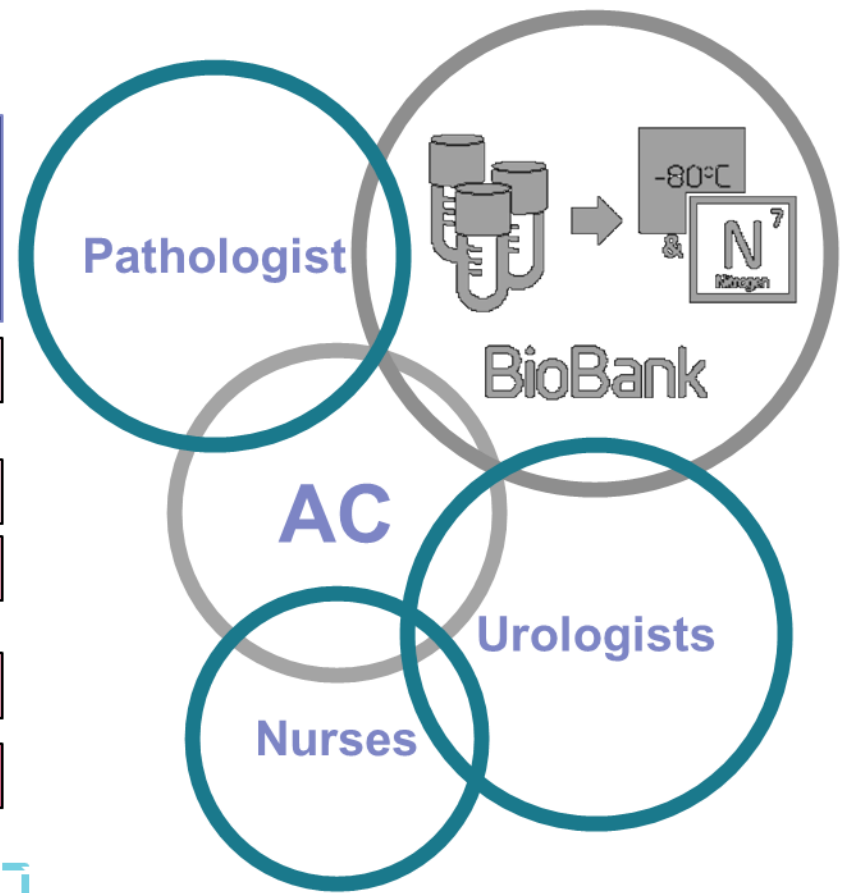
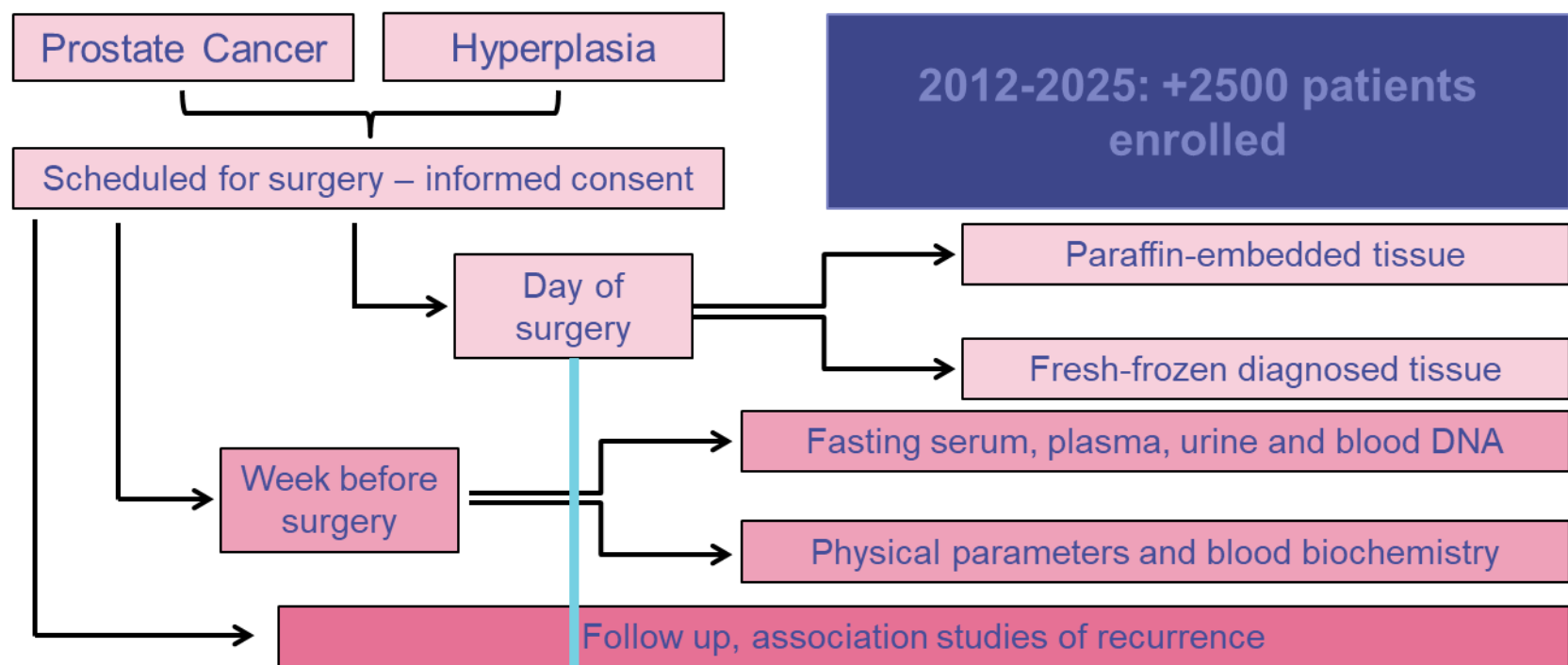
Arkaitz Carracedo



Our strategy:

To consolidate a well-structured multidisciplinary team

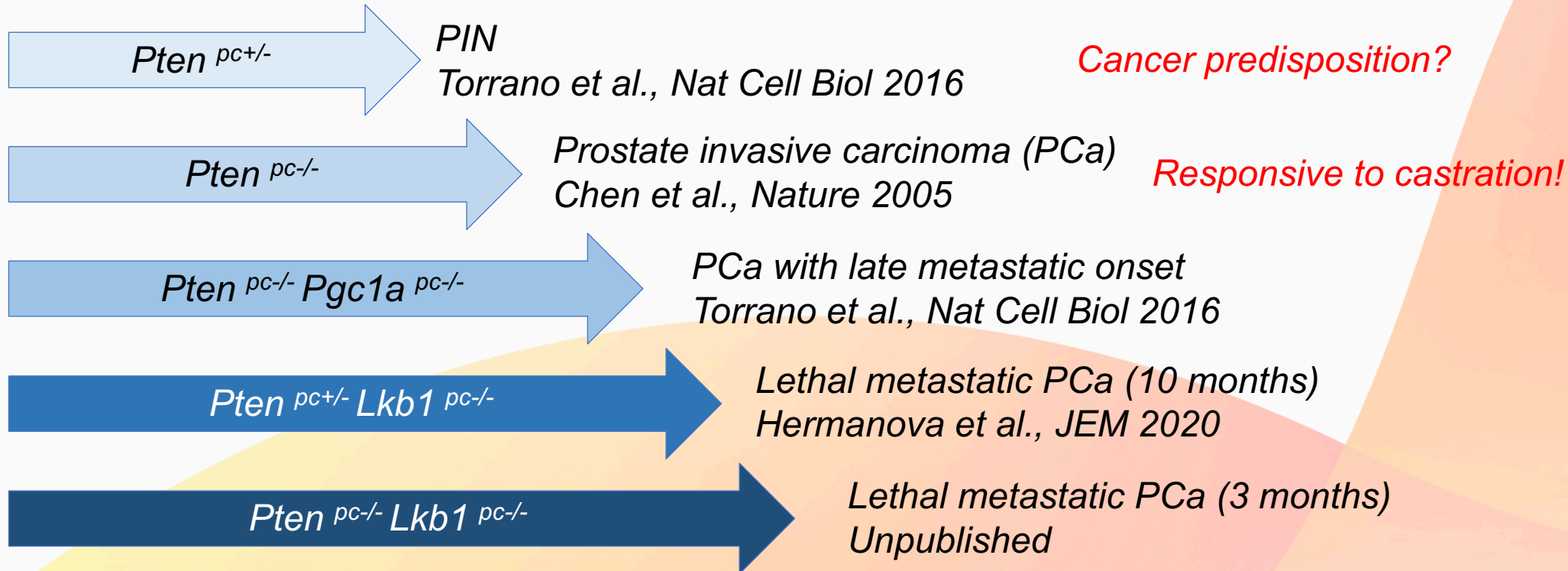




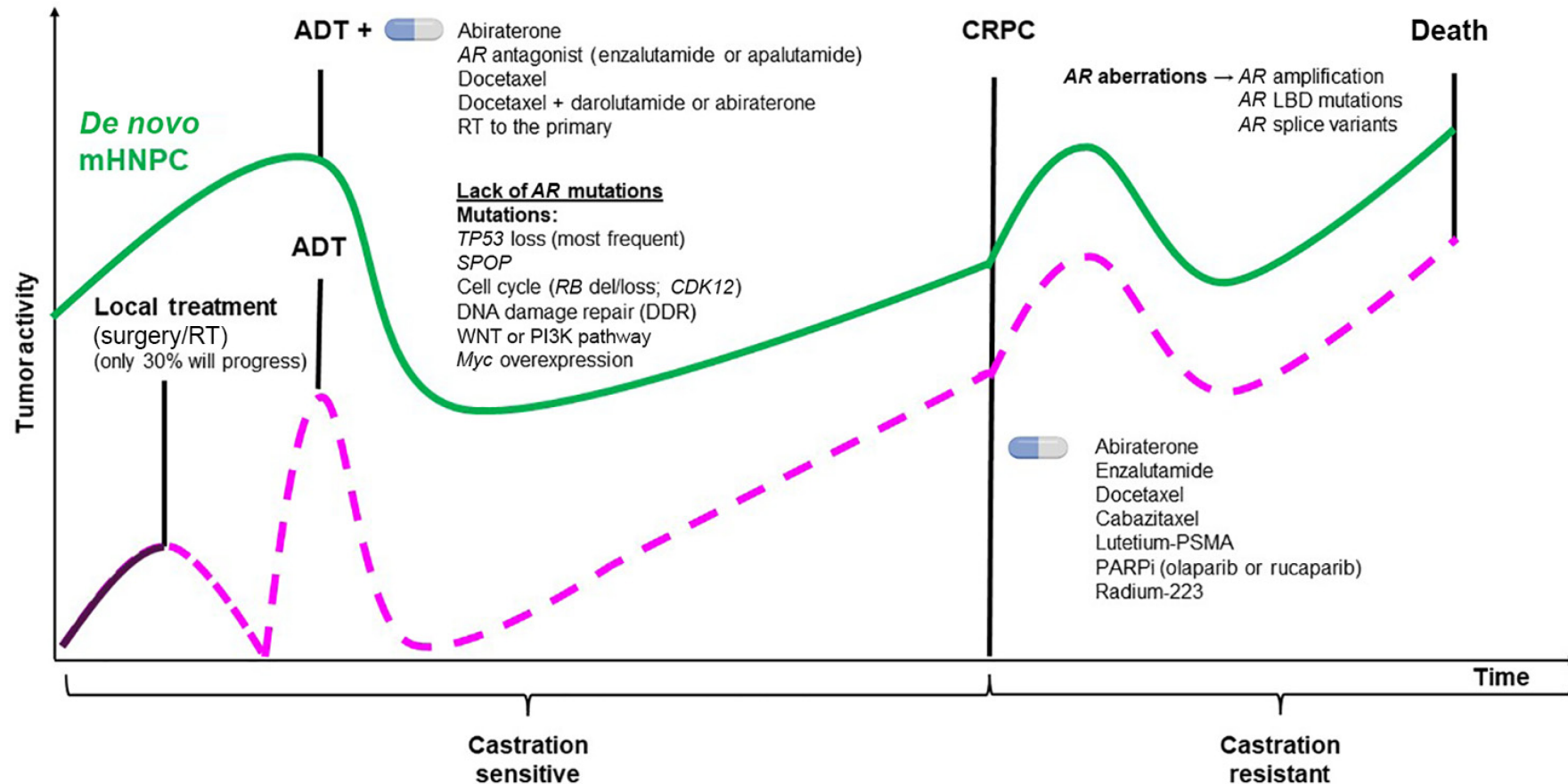
Modeling prostate cancer in the mouse



Probasin Cre-driven conditional gene perturbation

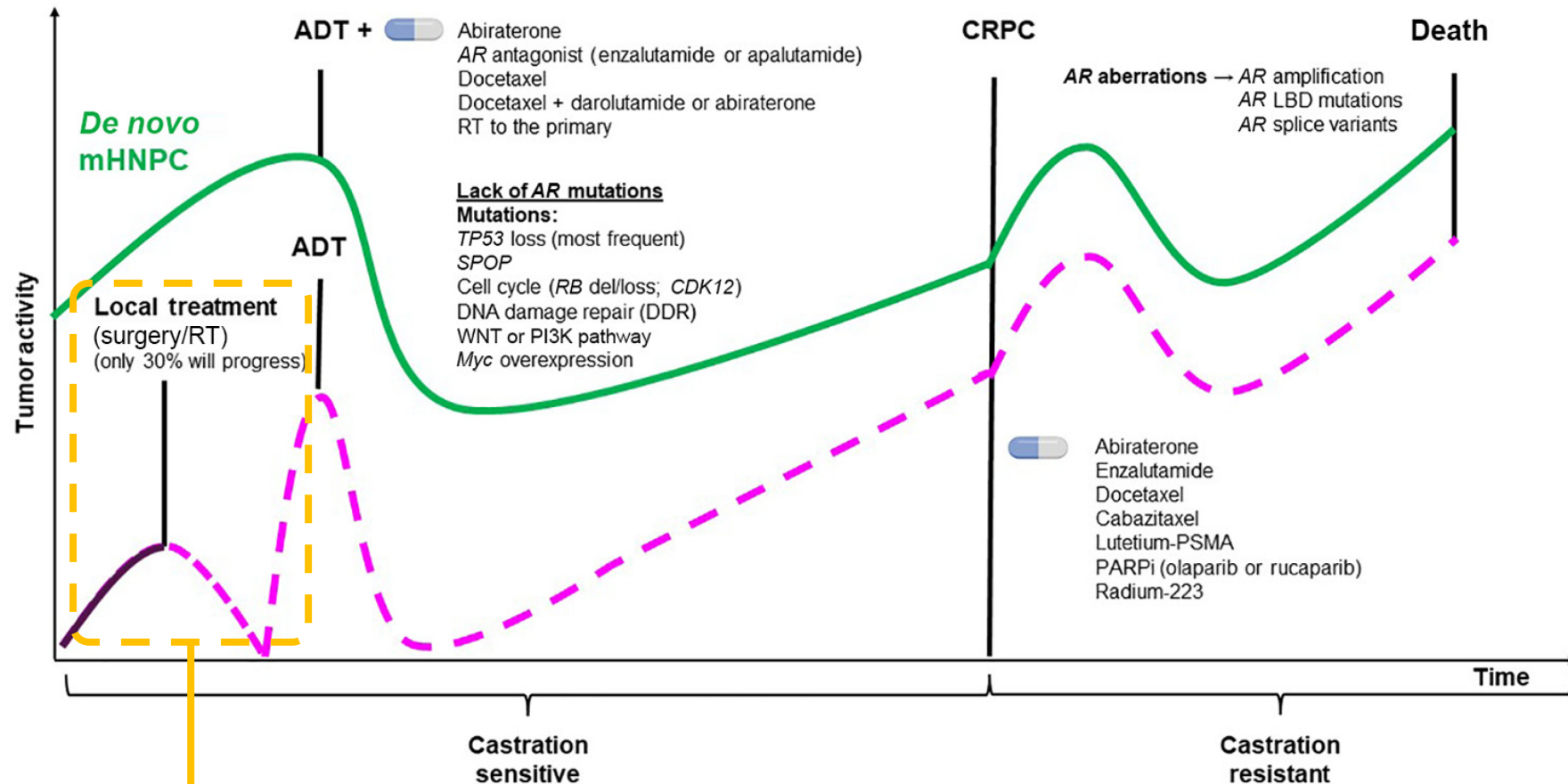


The natural history of prostate cancer



Trends in Cancer

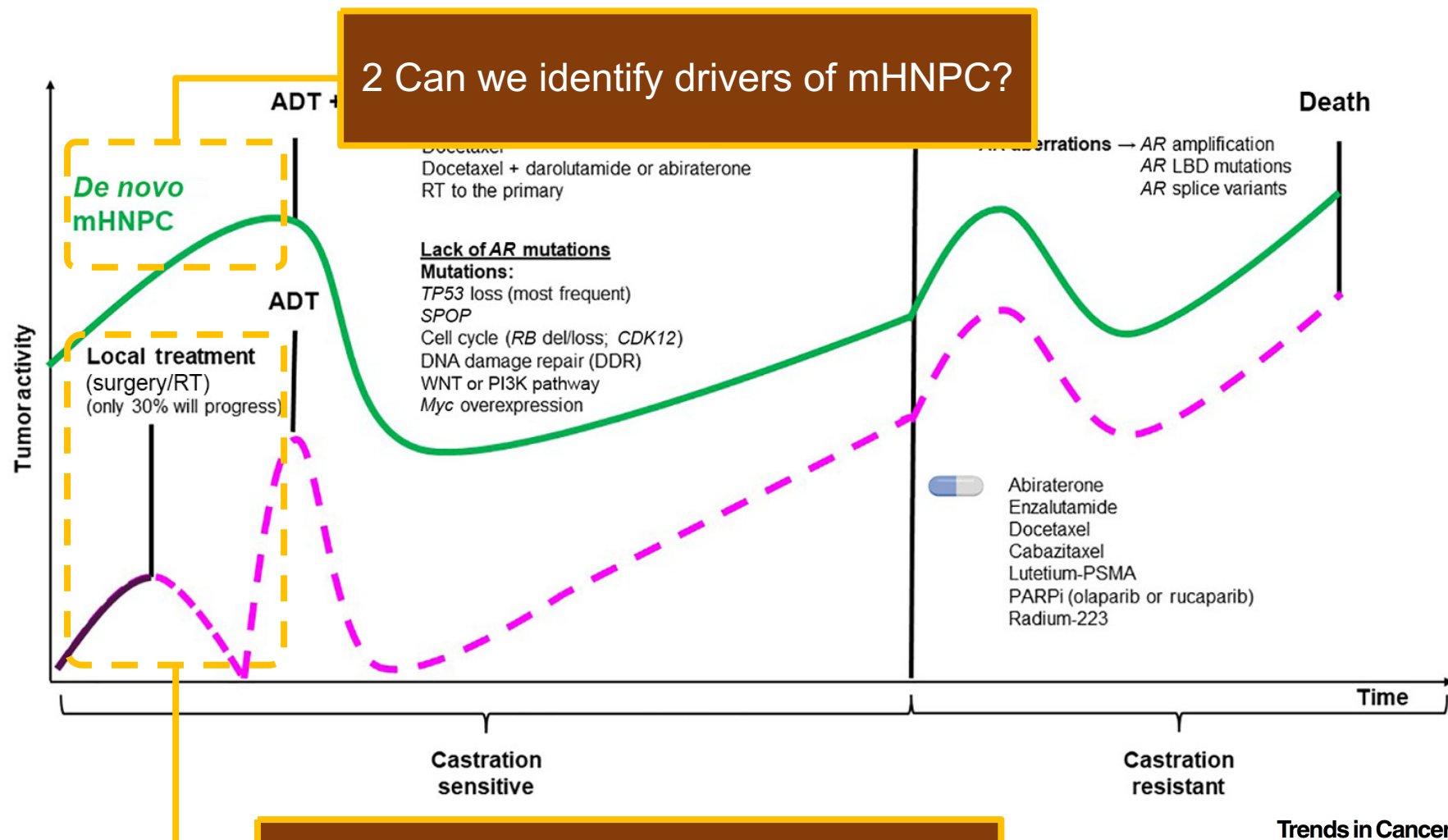
The natural history of prostate cancer



Trends in Cancer

1 Can we identify distinctive molecular features of PCa with bad prognosis?

The natural history of prostate cancer



1 Can we identify distinctive molecular features of PCa with bad prognosis?

The natural history of prostate cancer



Tumor-induced education of the tumor microenvironment as a convergent lesson learned



Candidate identification

Independent prostate cancer datasets with prognostic data (Disease-free survival)

Taylor
(N=131)

TCGA
(N=497)

Glinsky
(N=79)

Fraser
(N=73)

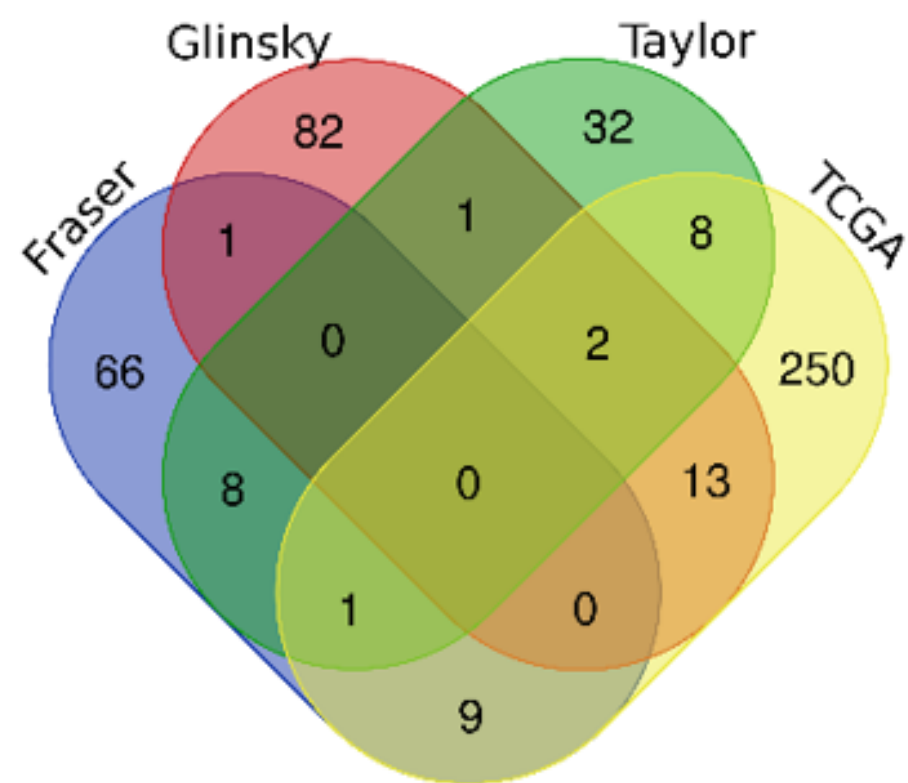
Search for metabolic genes (KEGG) with:

- **Significant**
- **Coherent**

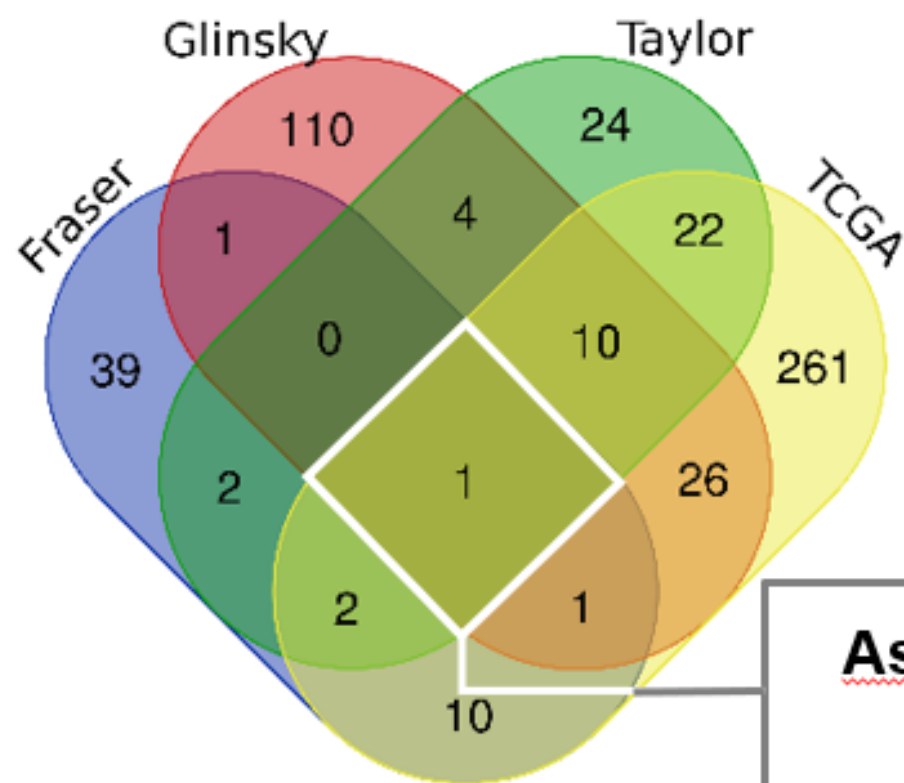
Prognostic potential

In at least 75% of the datasets

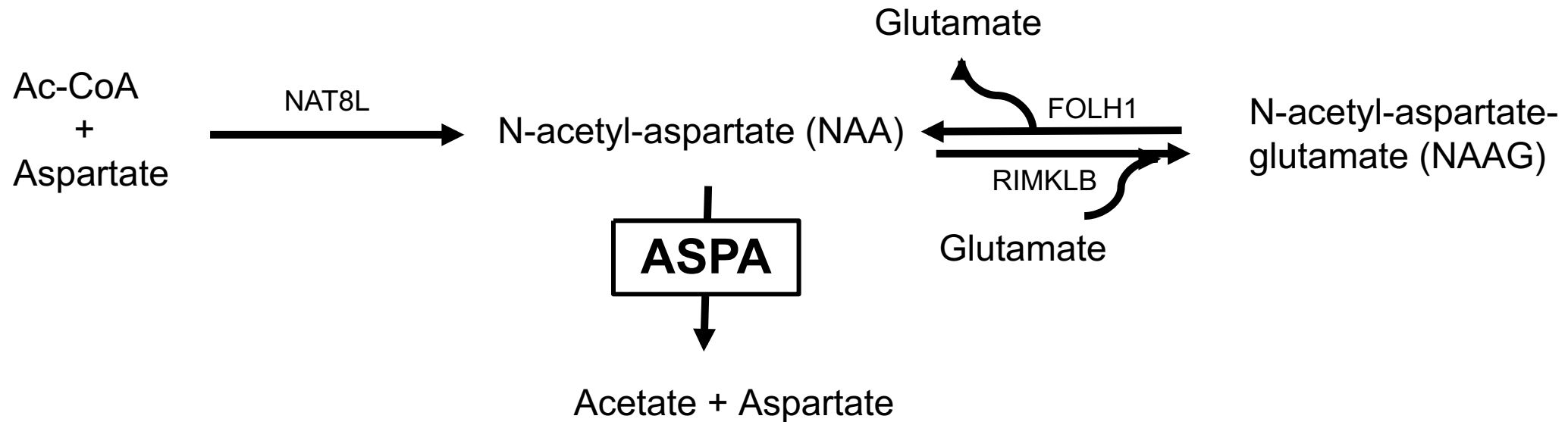
UPREGULATED GENES



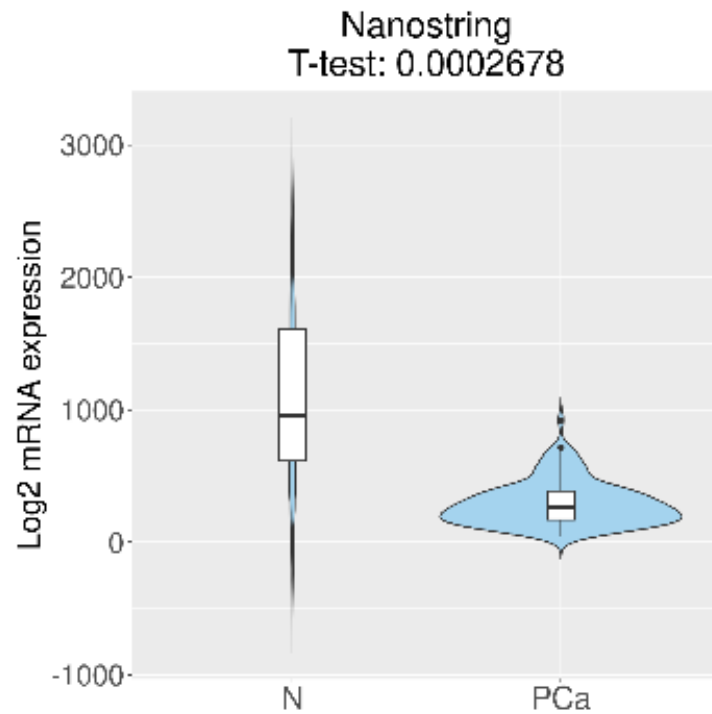
DOWNGREGULATED GENES



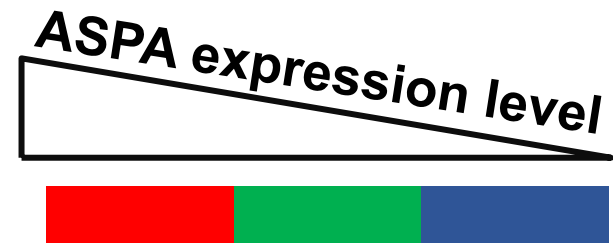
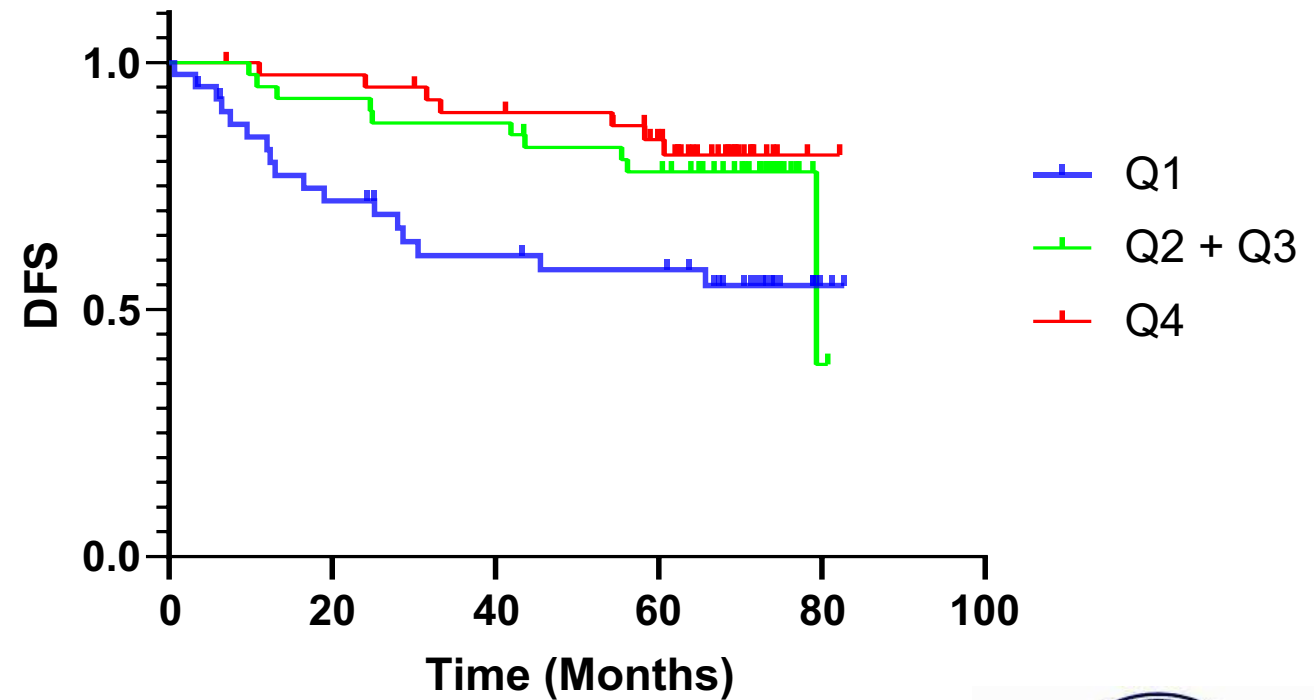
ASPA metabolizes NAA to acetate and aspartate



Validation of the prognostic potential of ASPA in PCa



N=150, Nanostring



Regulation of ASPA protein levels in PCa

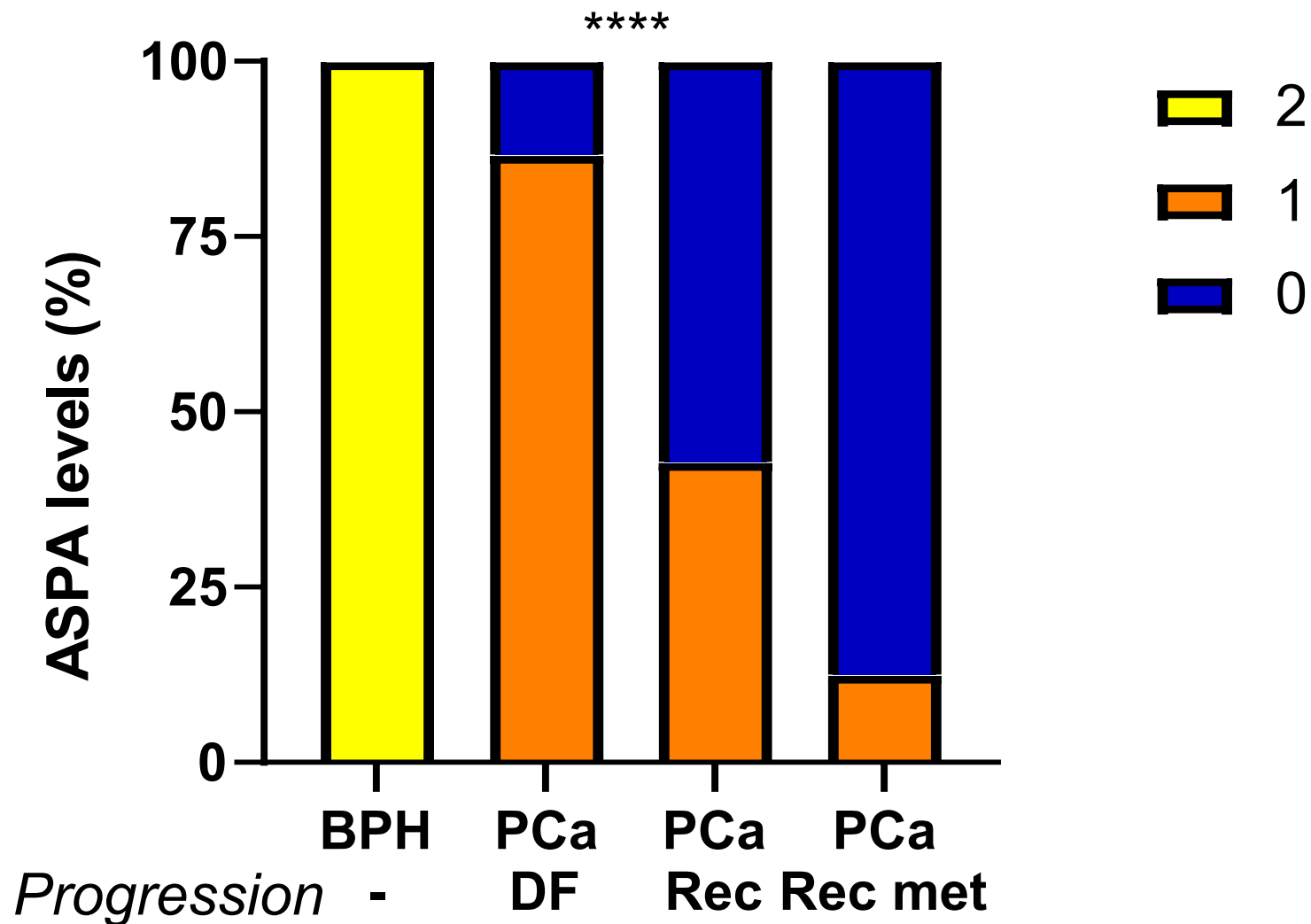
ASPA analysis with increased field of view

N=52, surgical piece

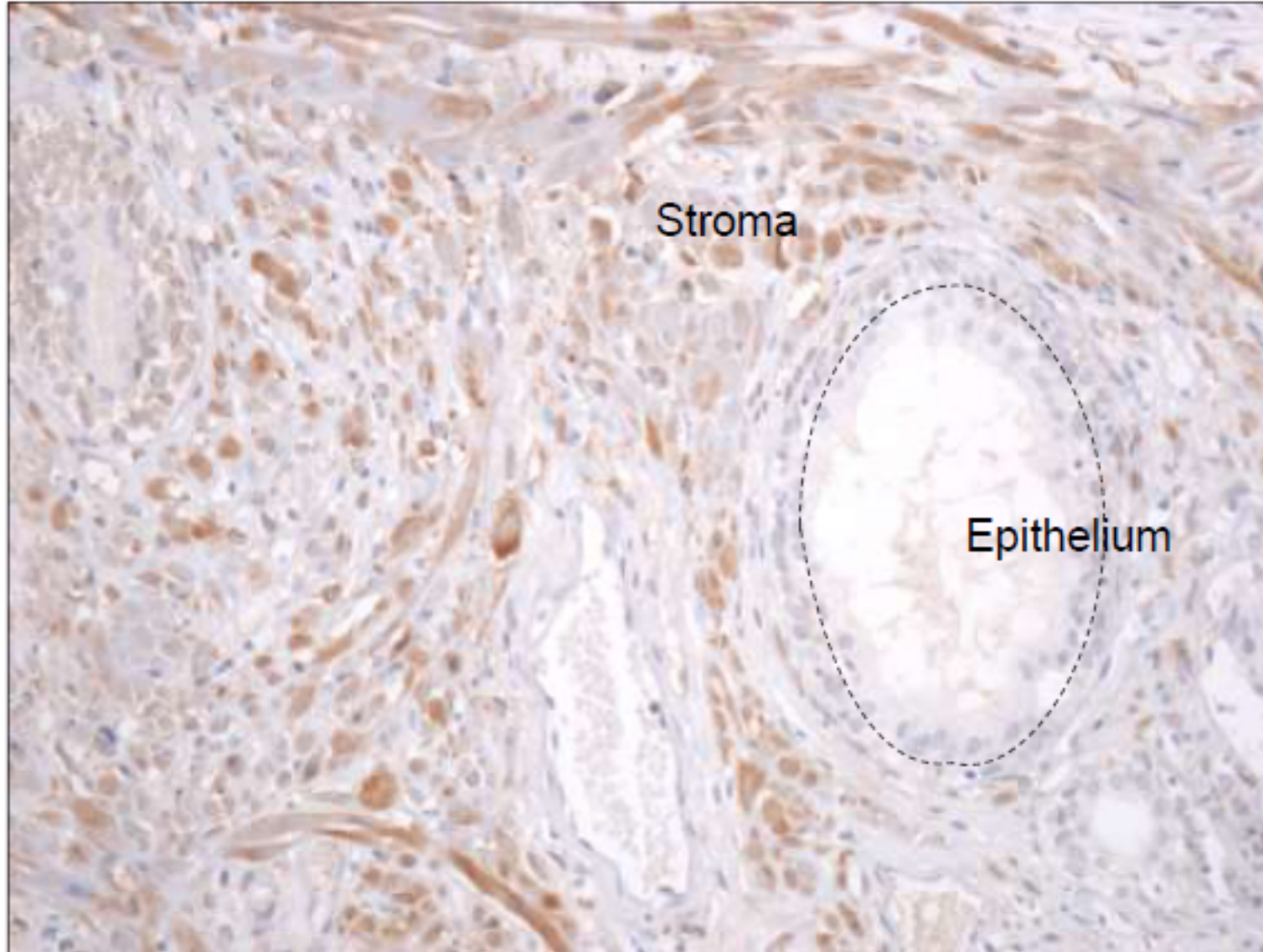
DF: Disease-free

Rec: Recurrent

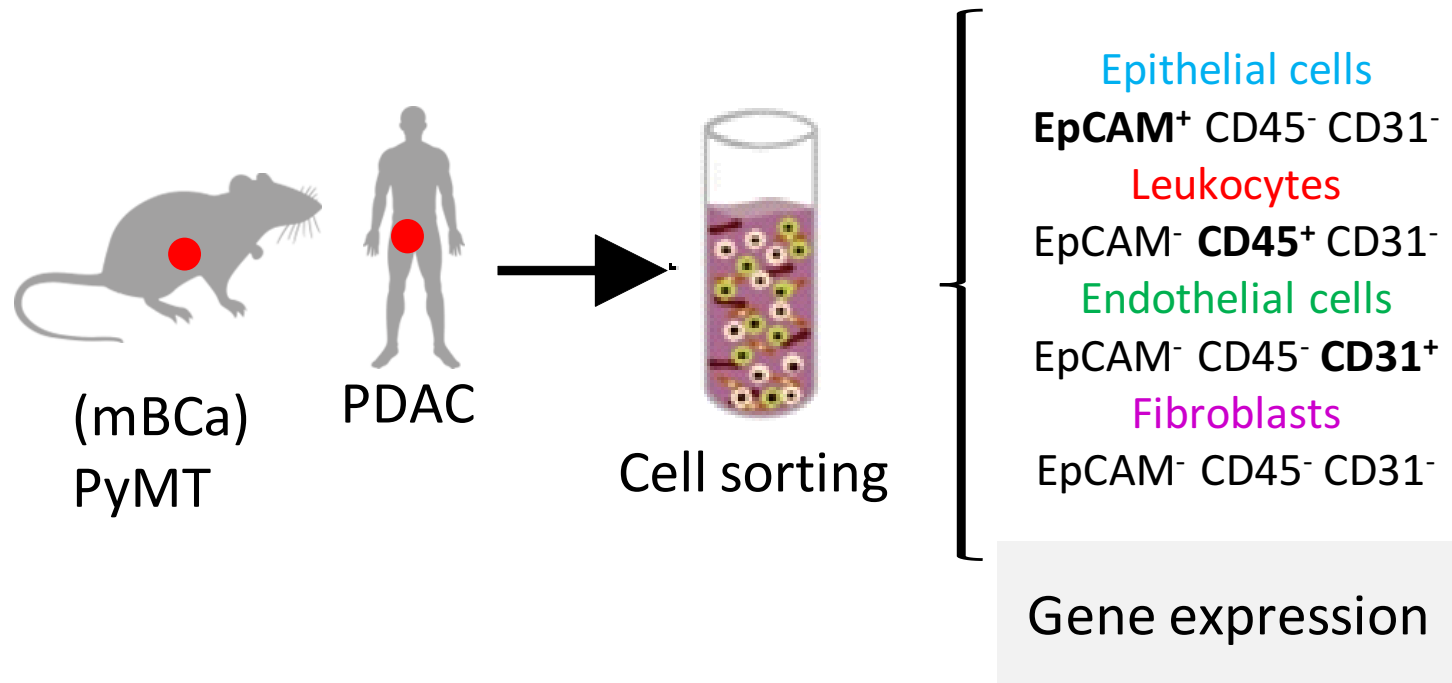
*Rec Met: Recurrent
and metastatic*



What was the protein expression pattern of ASPA in tissues?



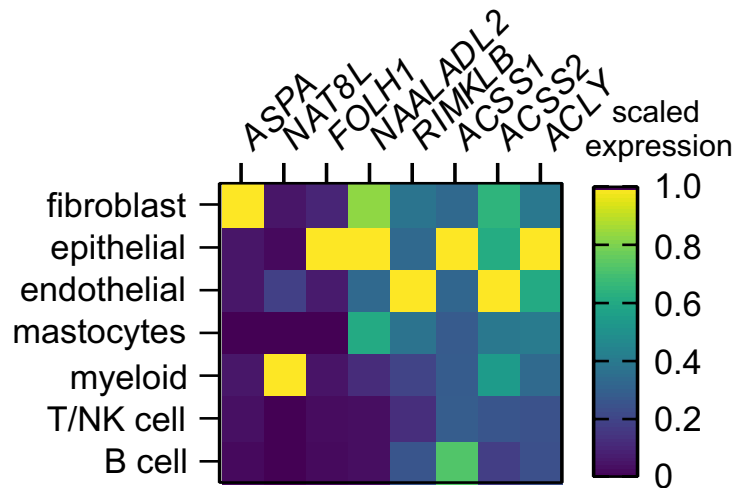
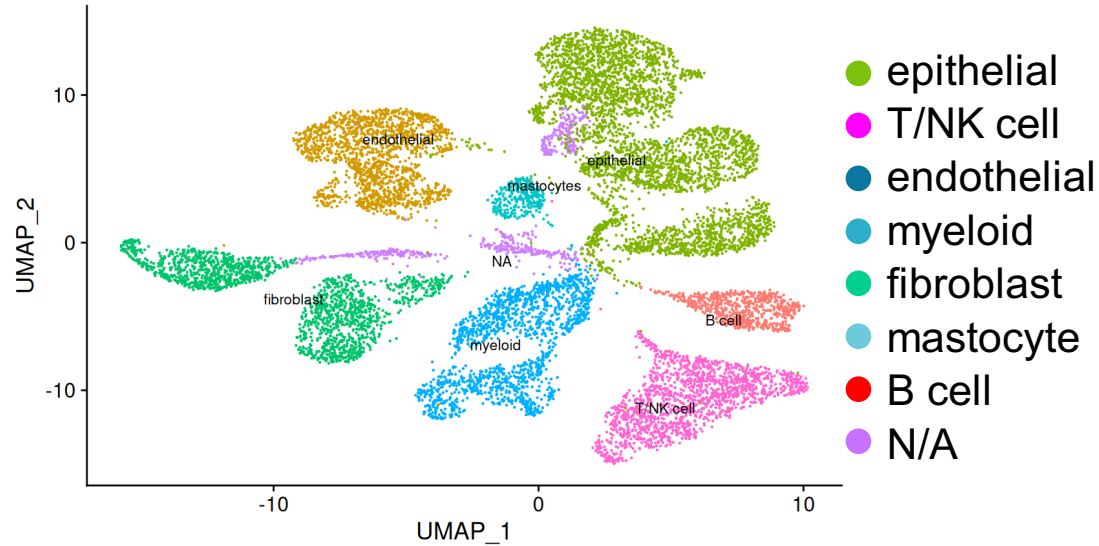
Loss of ASPA expression in cancer-associated fibroblasts in PDAC and BCa



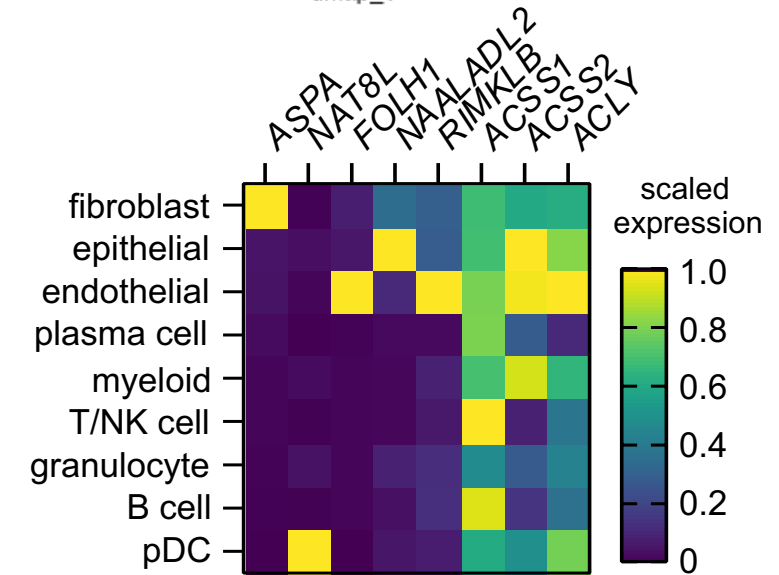
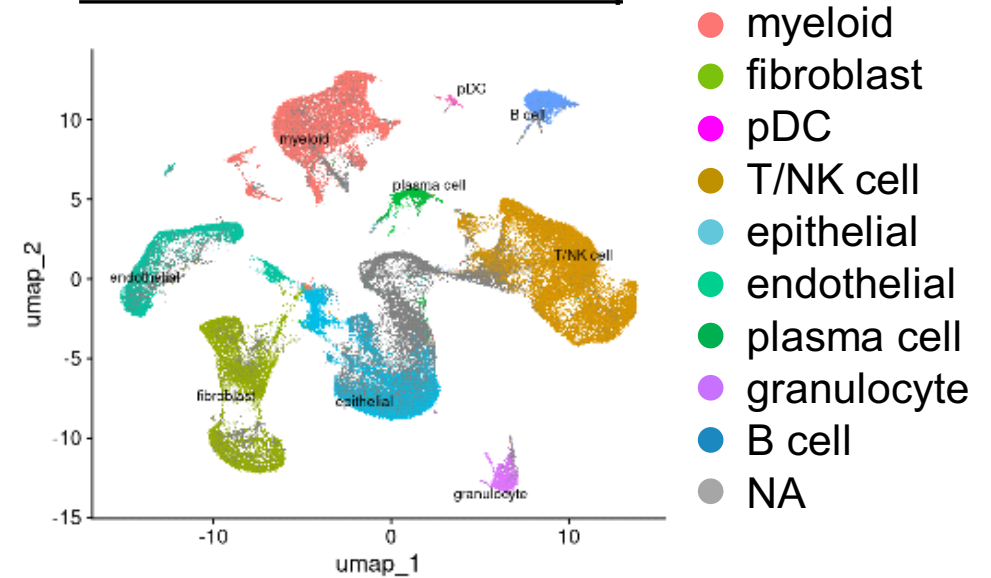
Collaboration with
Elisa Espinet & Andreas Trumpp
Fernando Calvo

Single-Cell RNA Seq analysis in BCa and PCa

Human PCa scRNA-Seq



Human BCa scRNA-Seq



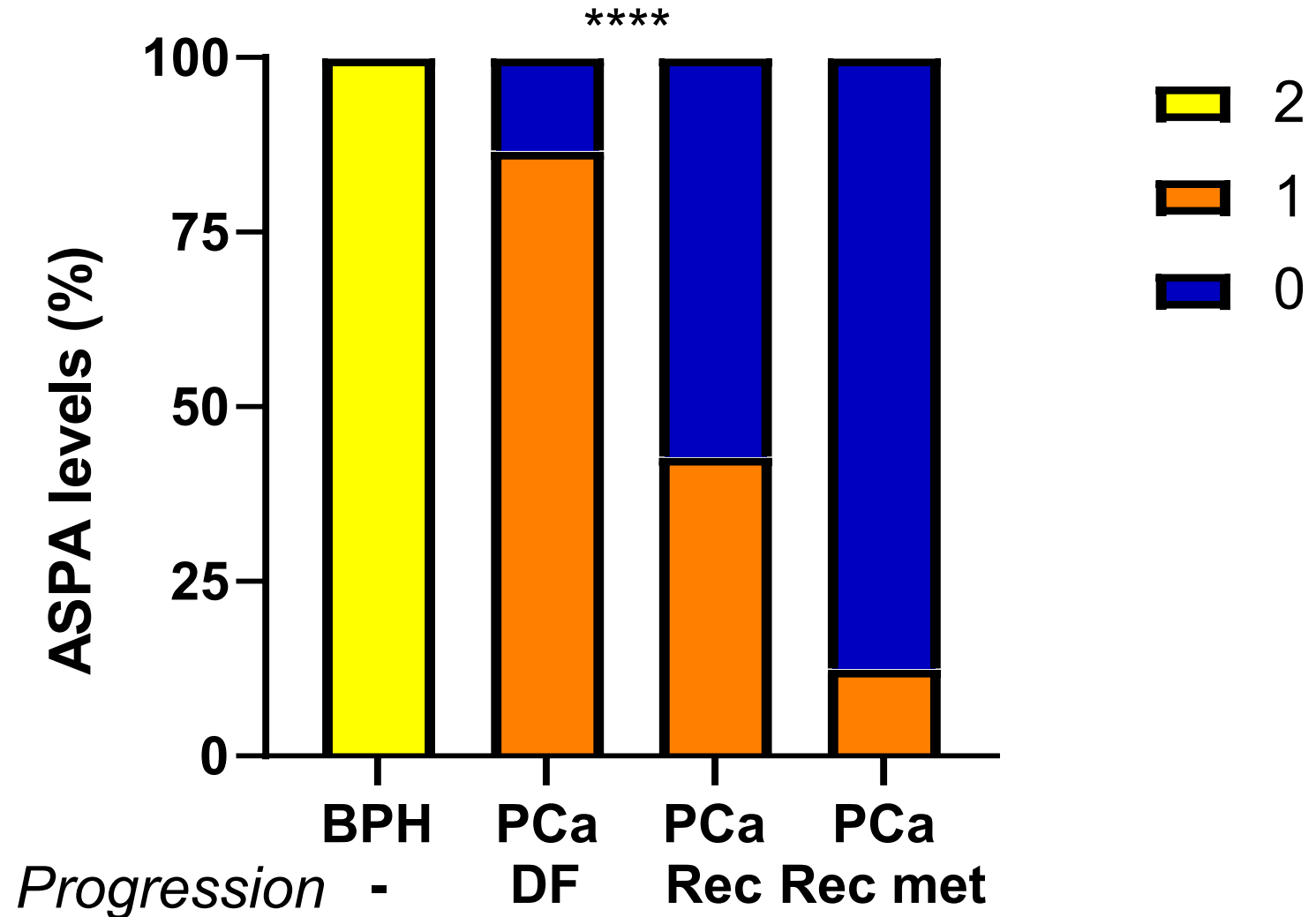
Back to this piece of data

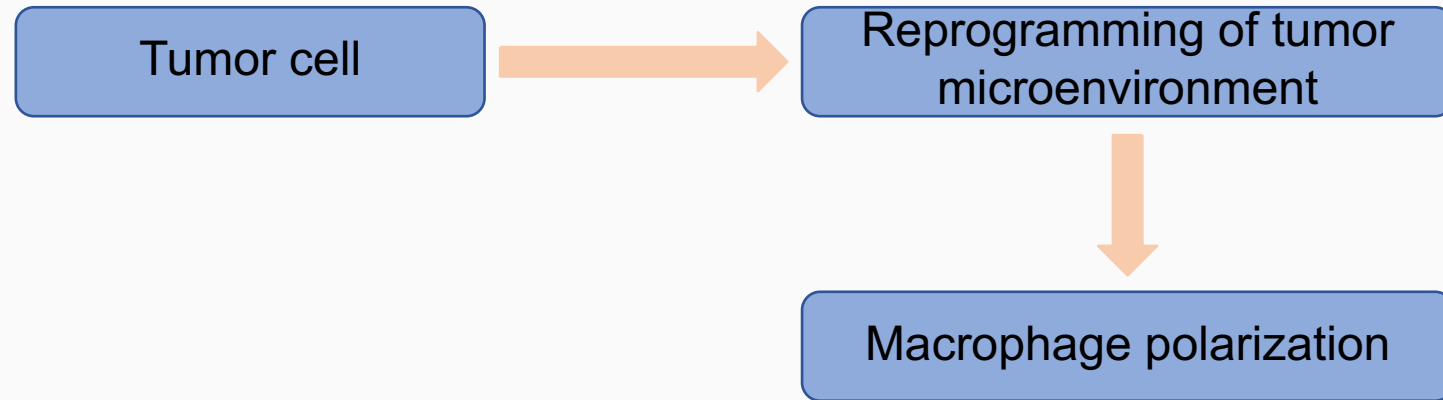
N=52, surgical piece

DF: Disease-free

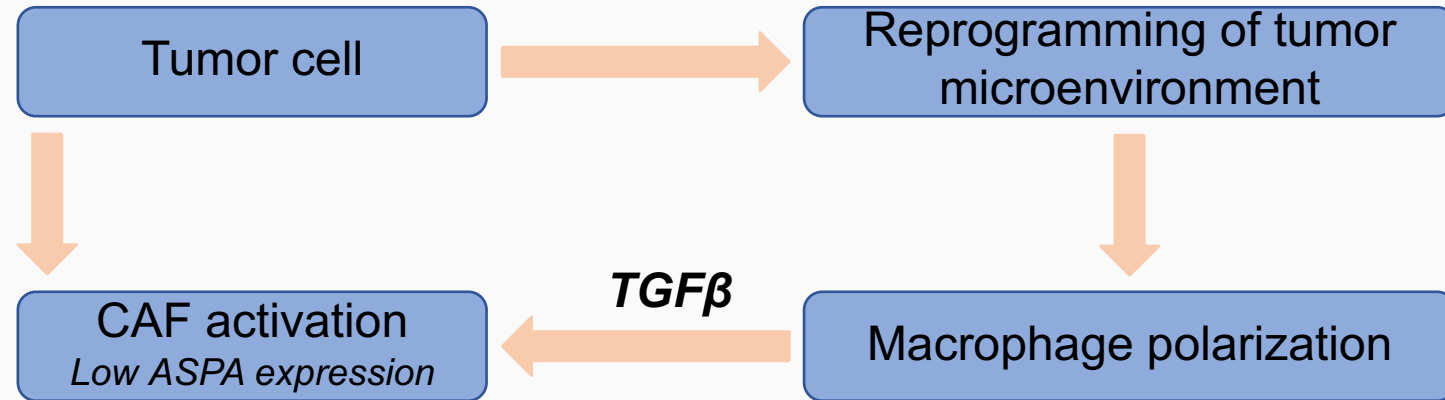
Rec: Recurrent

*Rec Met: Recurrent
and metastatic*

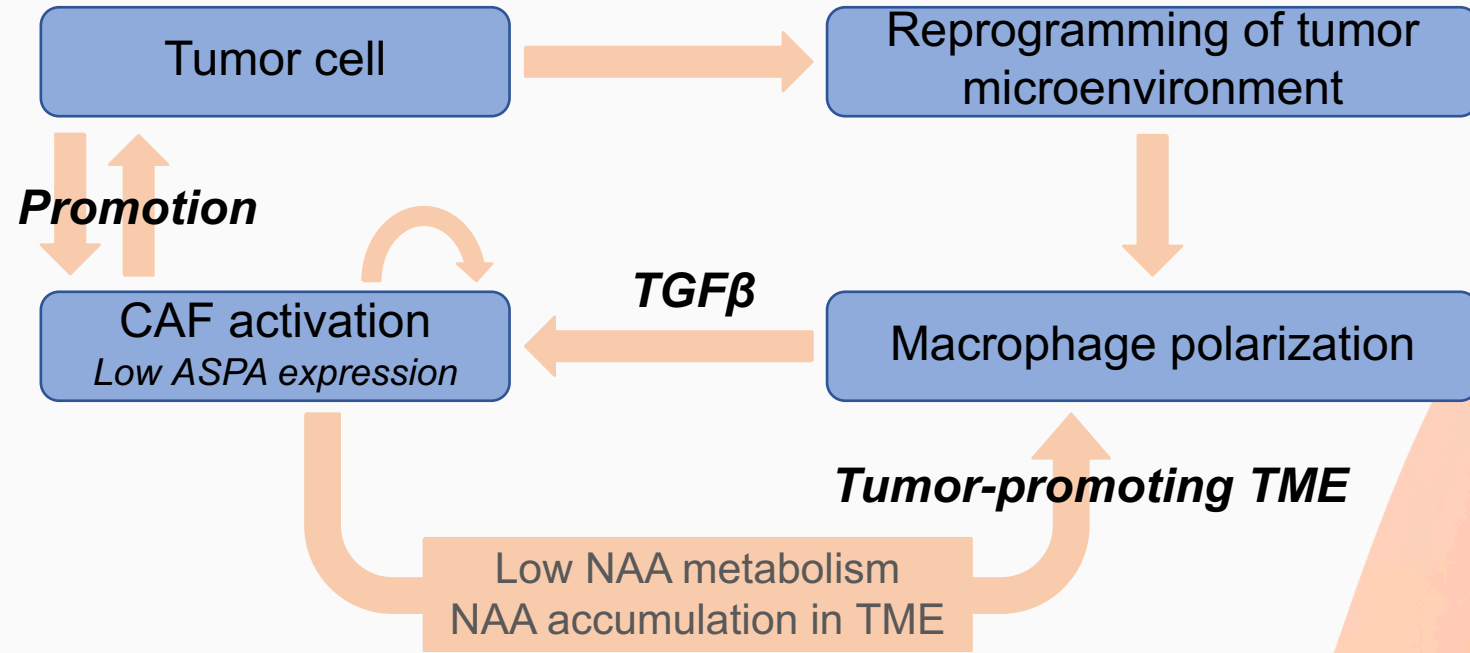




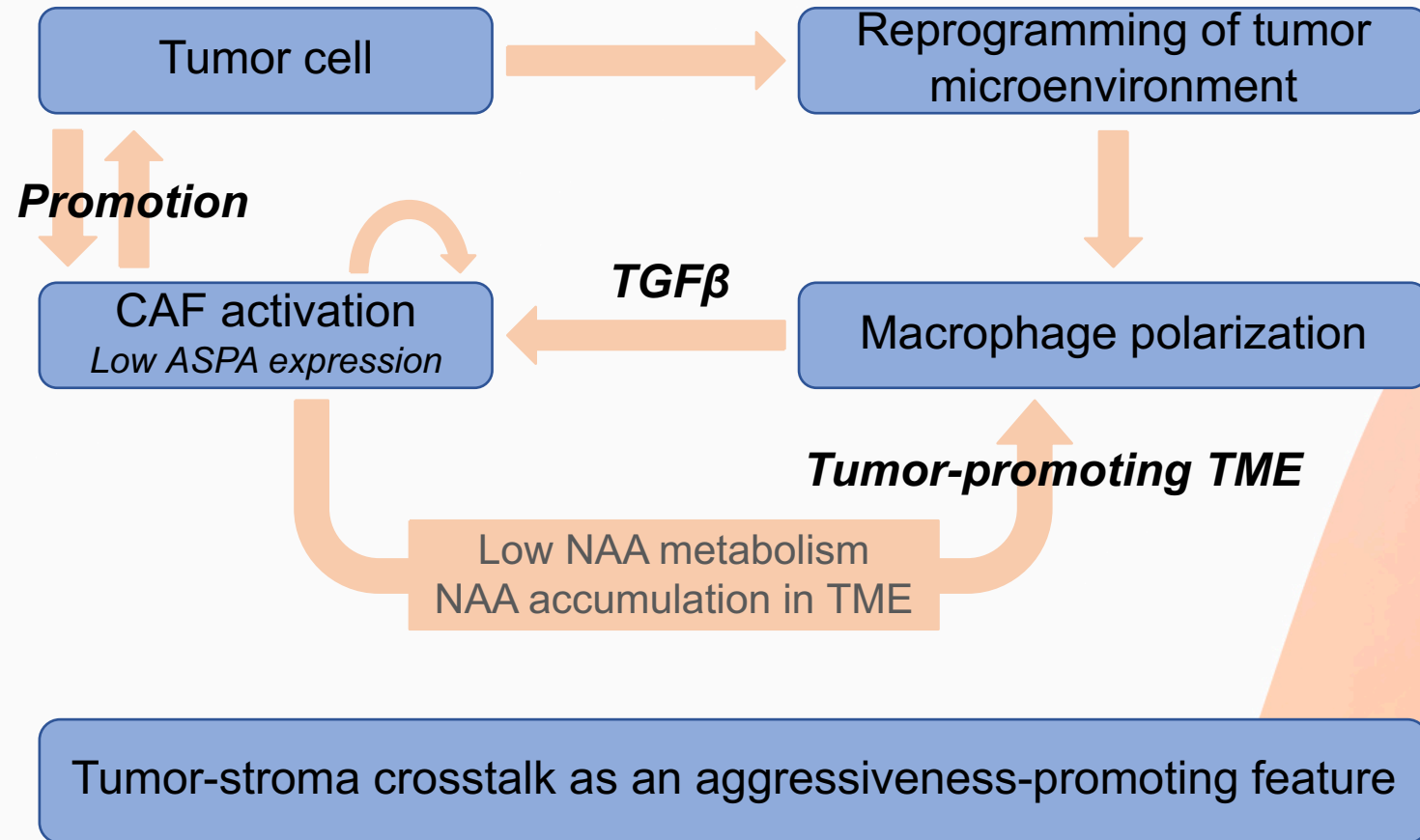
Astobiza, Capo, Viera et al., Nat Comm 2026



Astobiza, Capo, Viera et al., Nat Comm 2026

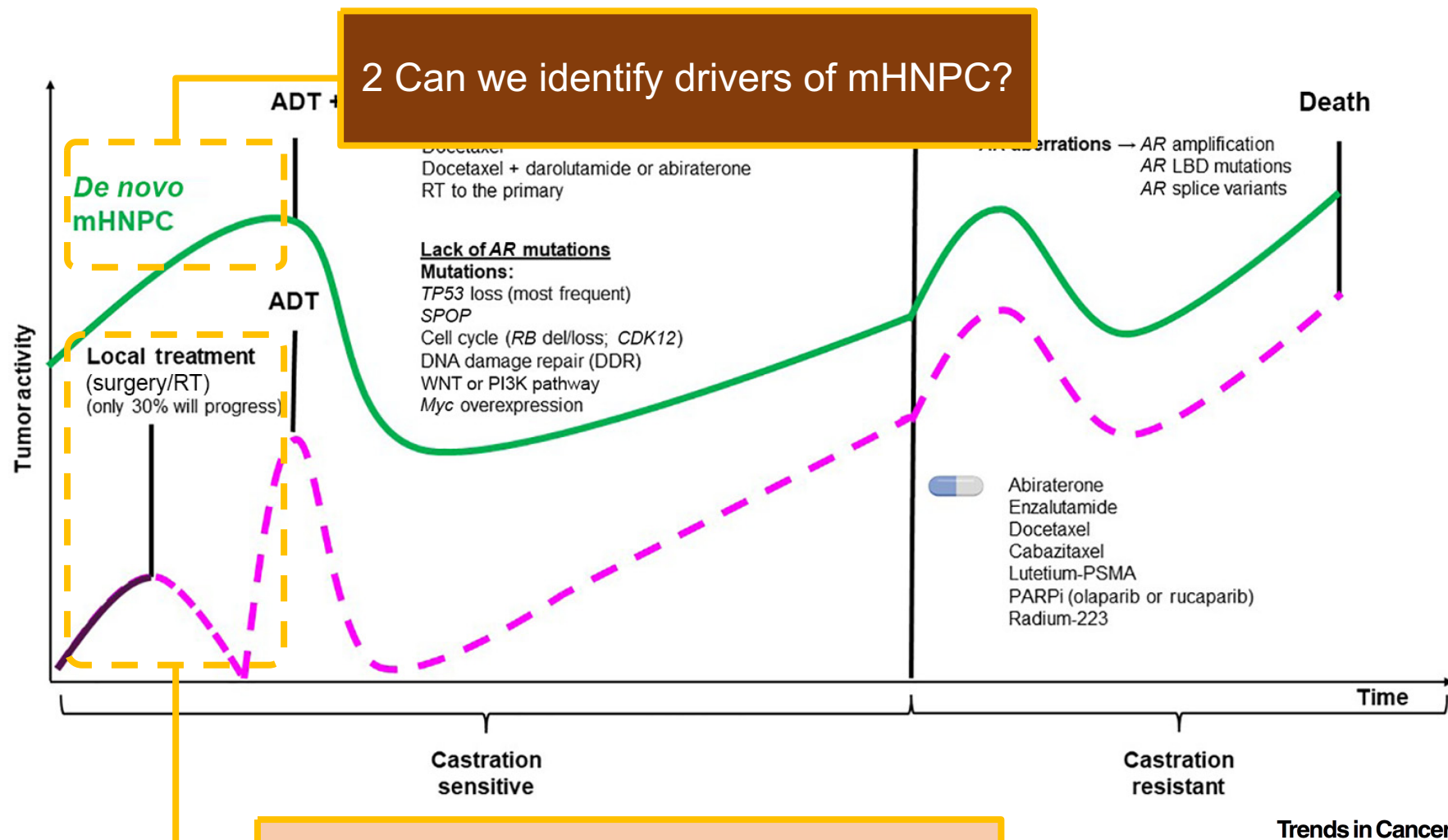


Astobiza, Capo, Viera et al., Nat Comm 2026

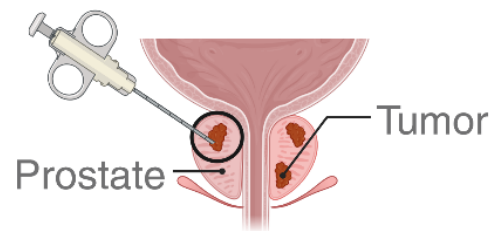


Astobiza, Capo, Viera et al., Nat Comm 2026

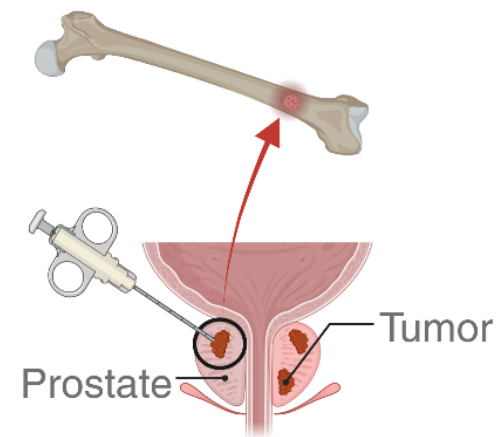
The natural history of prostate cancer



#guardsymposium2026
X @GuardConsortium



LPC



mHNPC

Bulk RNA-seq

Cohort size (n)

Discovery

47 - 31

Validation

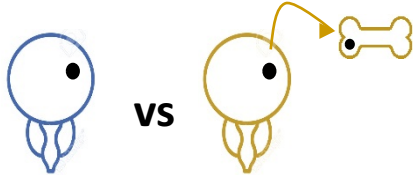
17 - 15



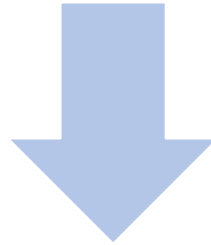
morales meseguer
Hospital General Universitario

Localizado

hHNPC



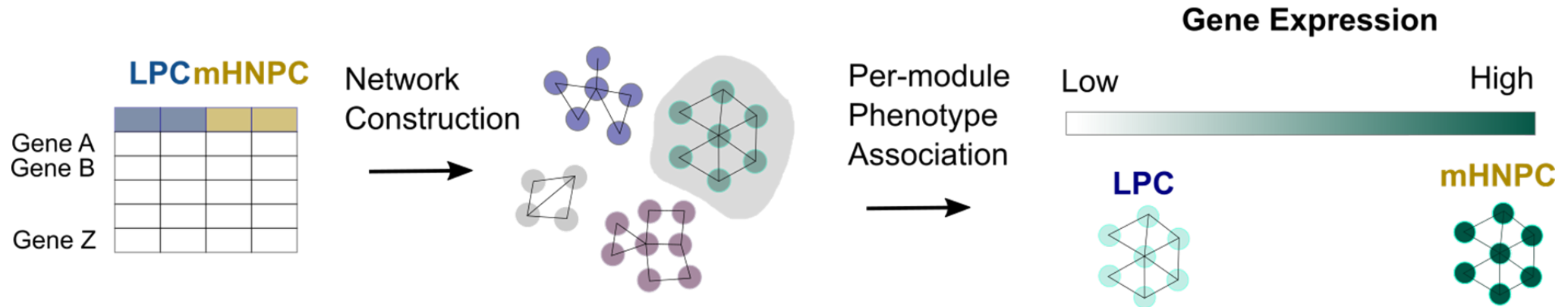
**We found profound changes in the
transcriptional landscape of mHNPC**



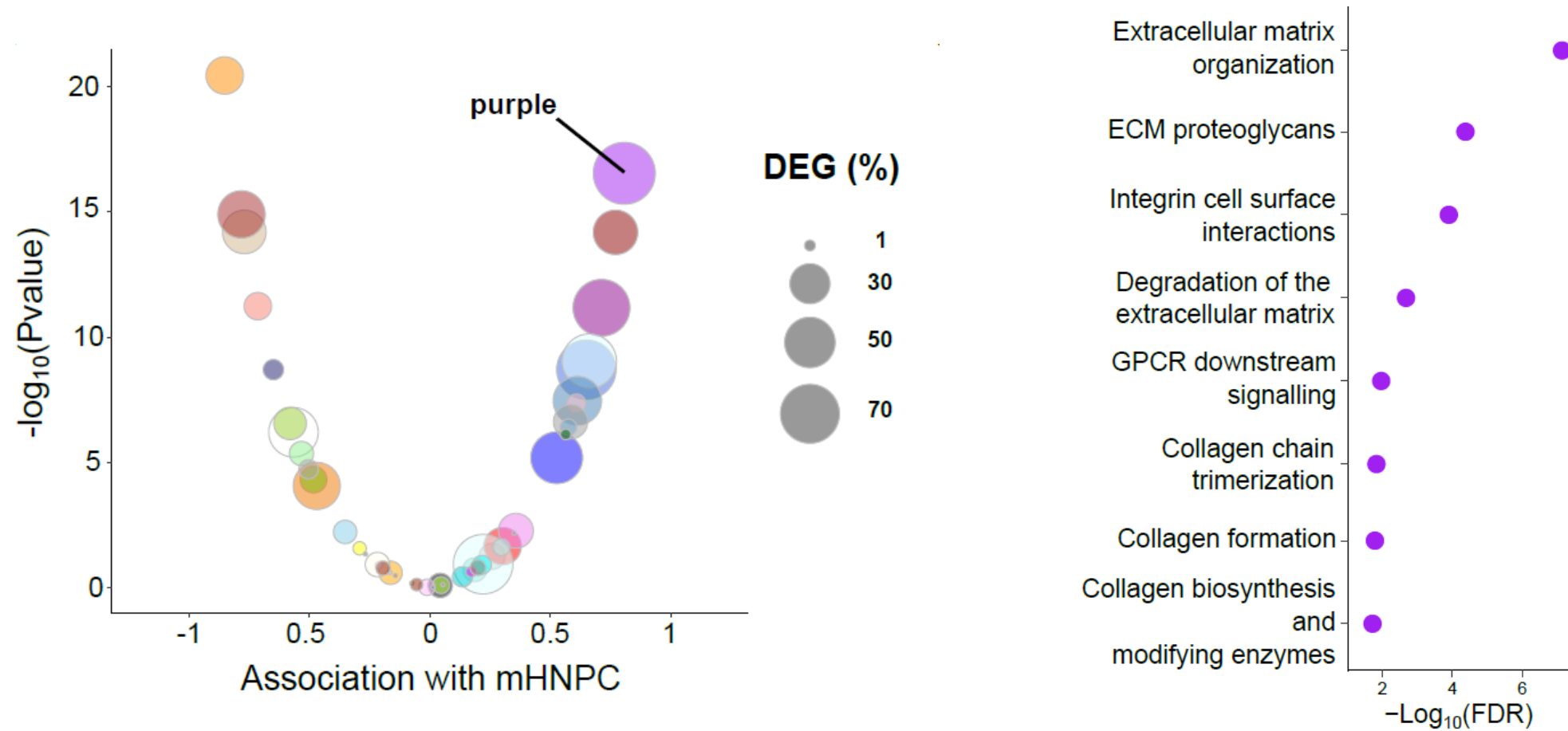
**Computational biology to identify critical
processes in mHNPC**

Computational biology to the rescue

Joint Module Construction



WGCNA: From thousands of genes to tens of modules

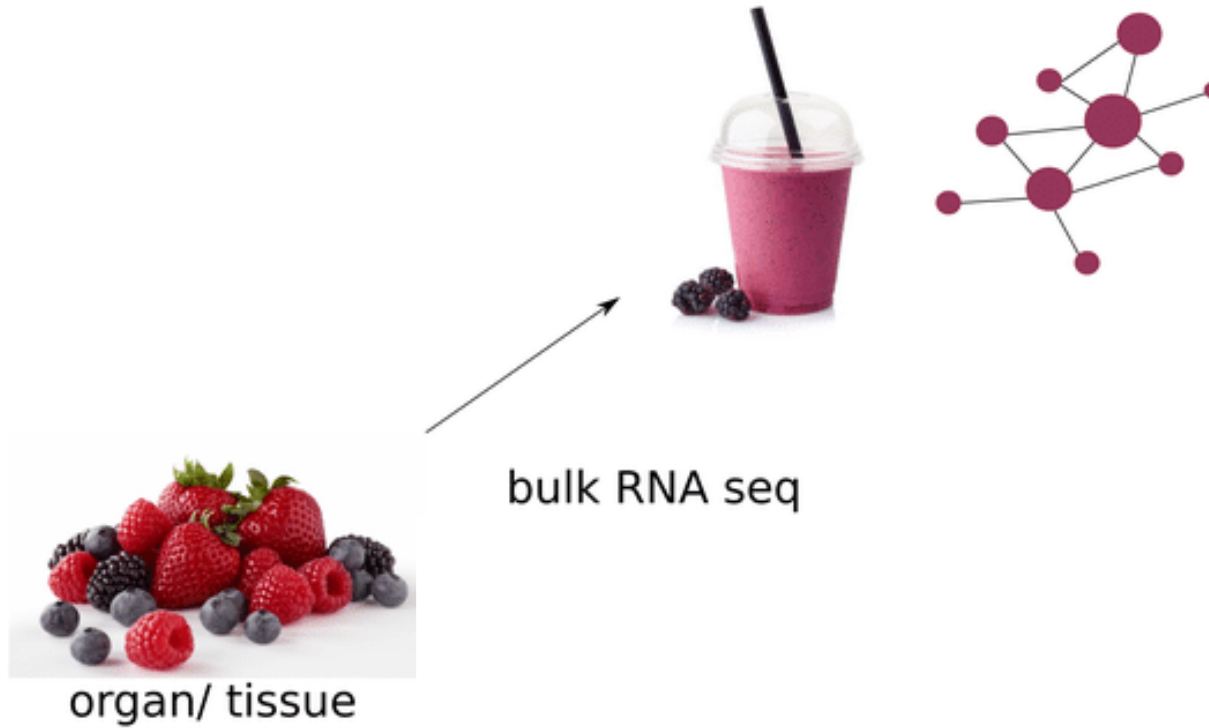


Conclusion:
mHNPC is a distinct molecular
entity

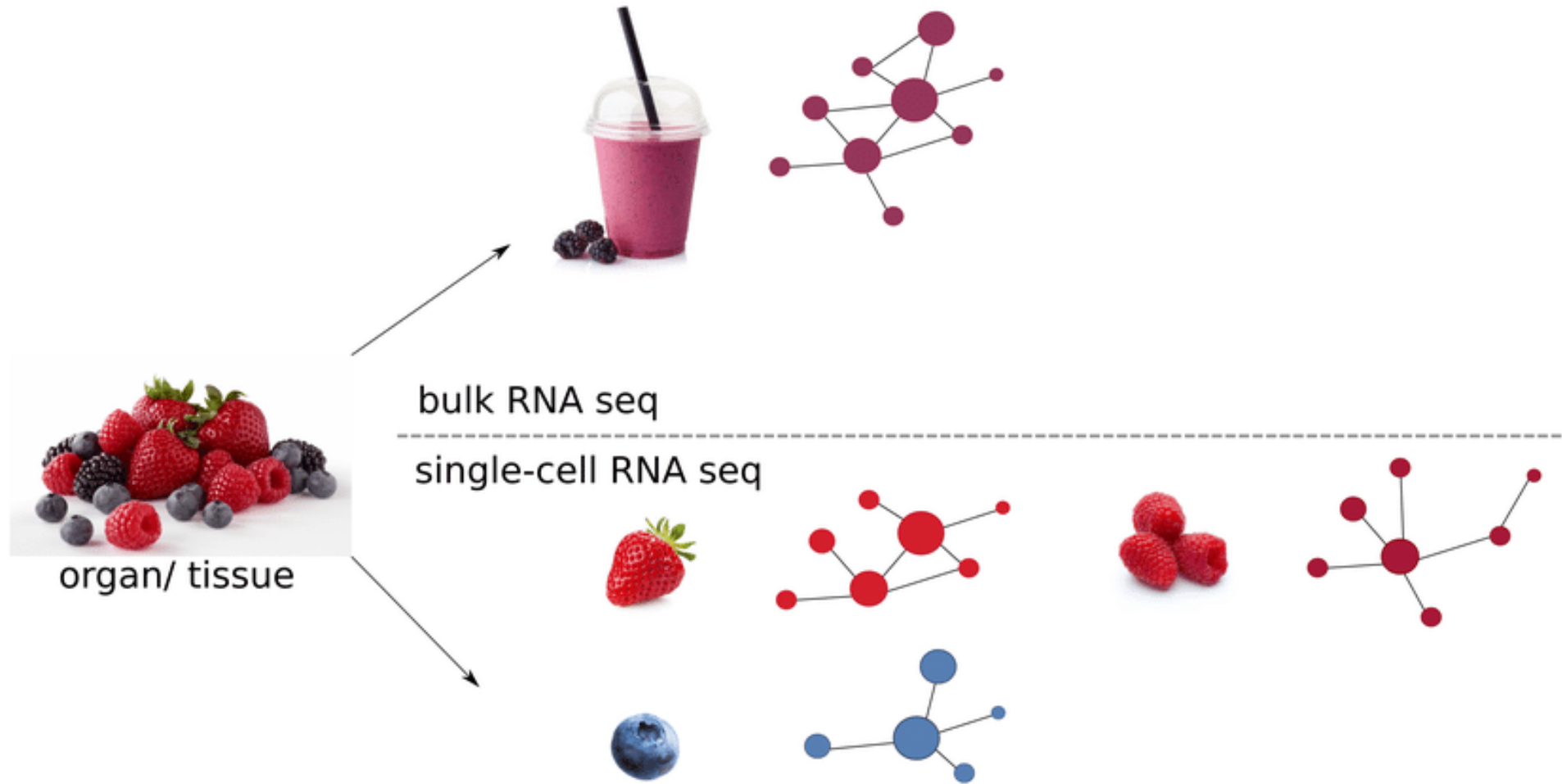


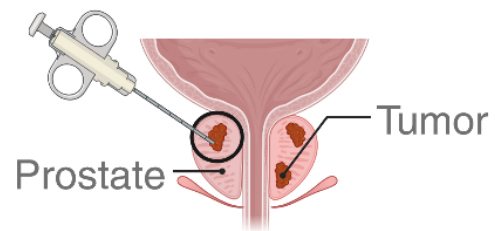
Is it cell reprogramming or composition?

Stromal alterations: Quantity or quality?

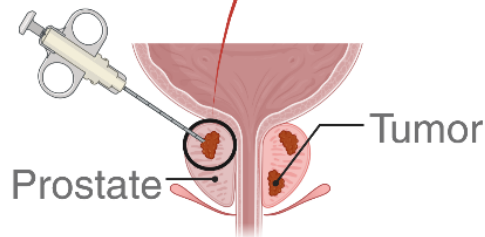
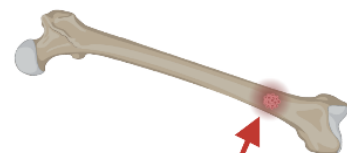


Stromal alterations: Quantity or quality?



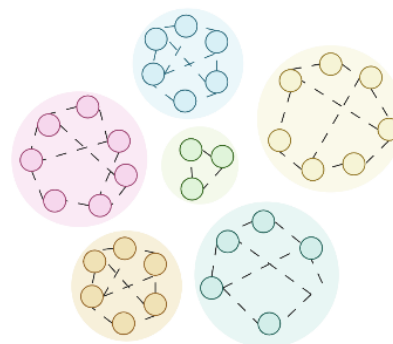


LPC

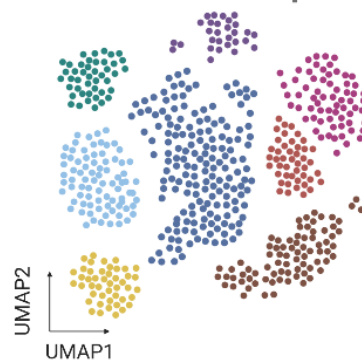


mHNPC

Bulk RNA-seq
Gene-network analysis



Single-cell
RNA-seq



Cohort size (n)

Discovery

47 - 31

Validation

17 - 15

Discovery
PMID: 33420488

8 - 3

Validation

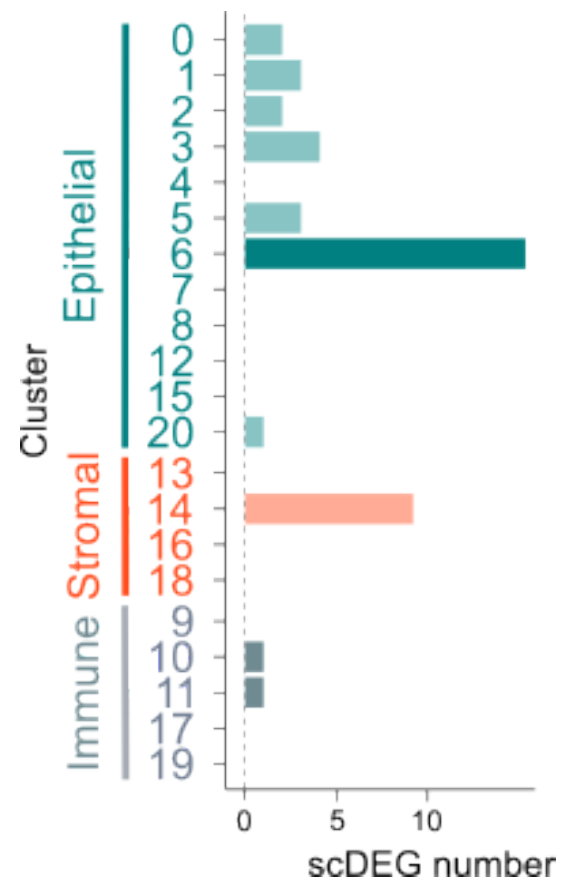
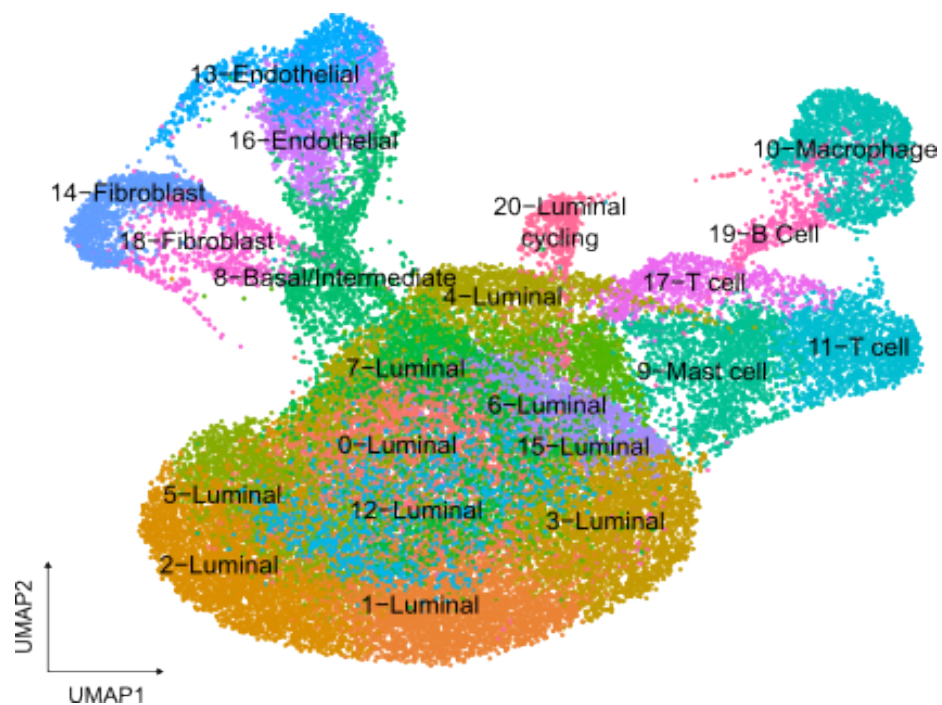
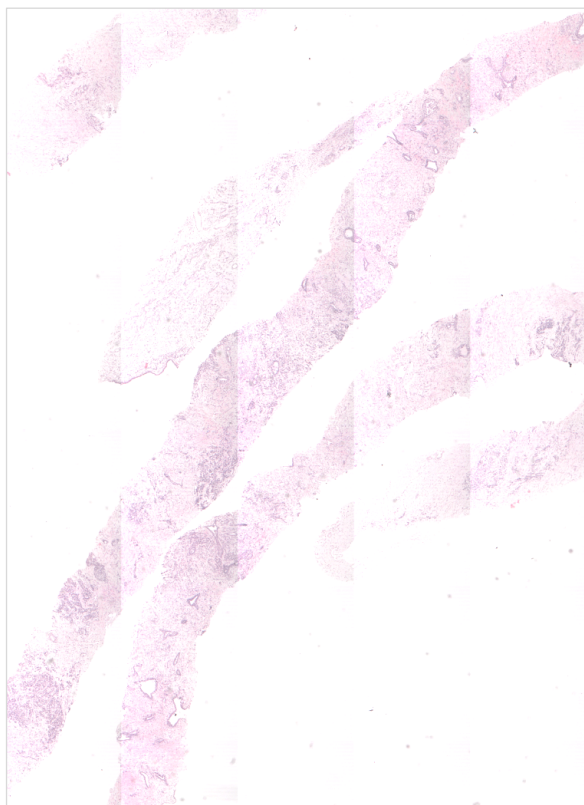
2 - 2



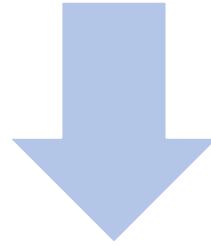
morales meseguer
Hospital General Universitario

Publicly available

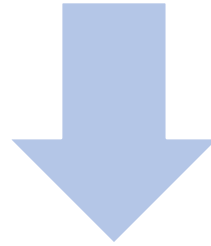




Identification as the most different tumor cell cluster in mHNPC



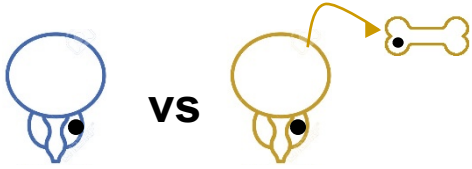
Analysis of tumor cell communication with the stroma



Identification of the genes orchestrating the communication in mHNPC

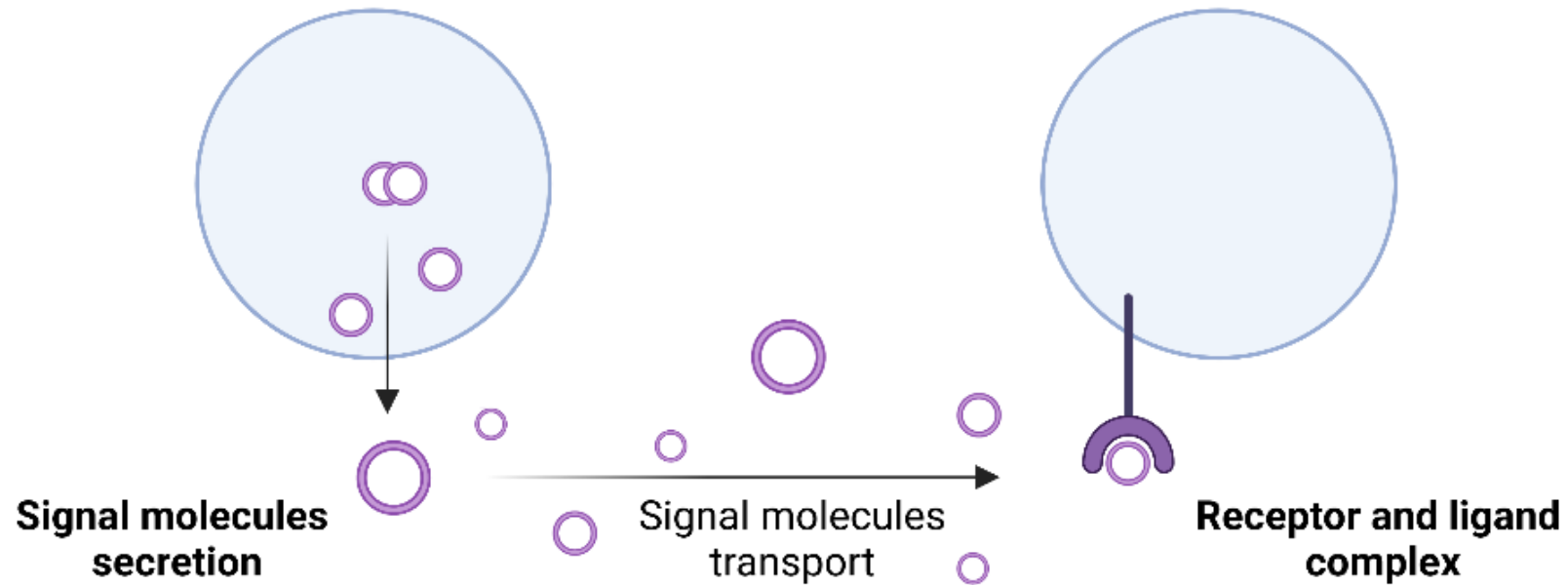
Inferring the modes of intercellular communication in the tumor

Localizado mHNPC



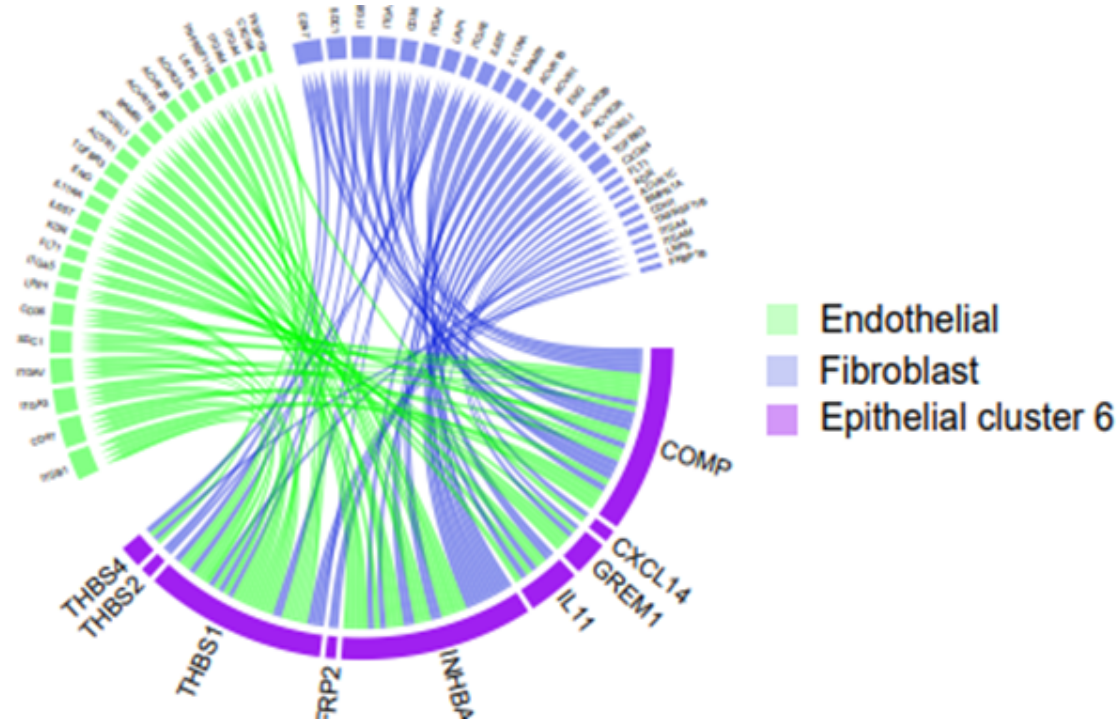
Cluster 6: Epithelial

Stromal and immune cells



Inferring the modes of intercellular communication in the tumor

Ligand-receptor pairs



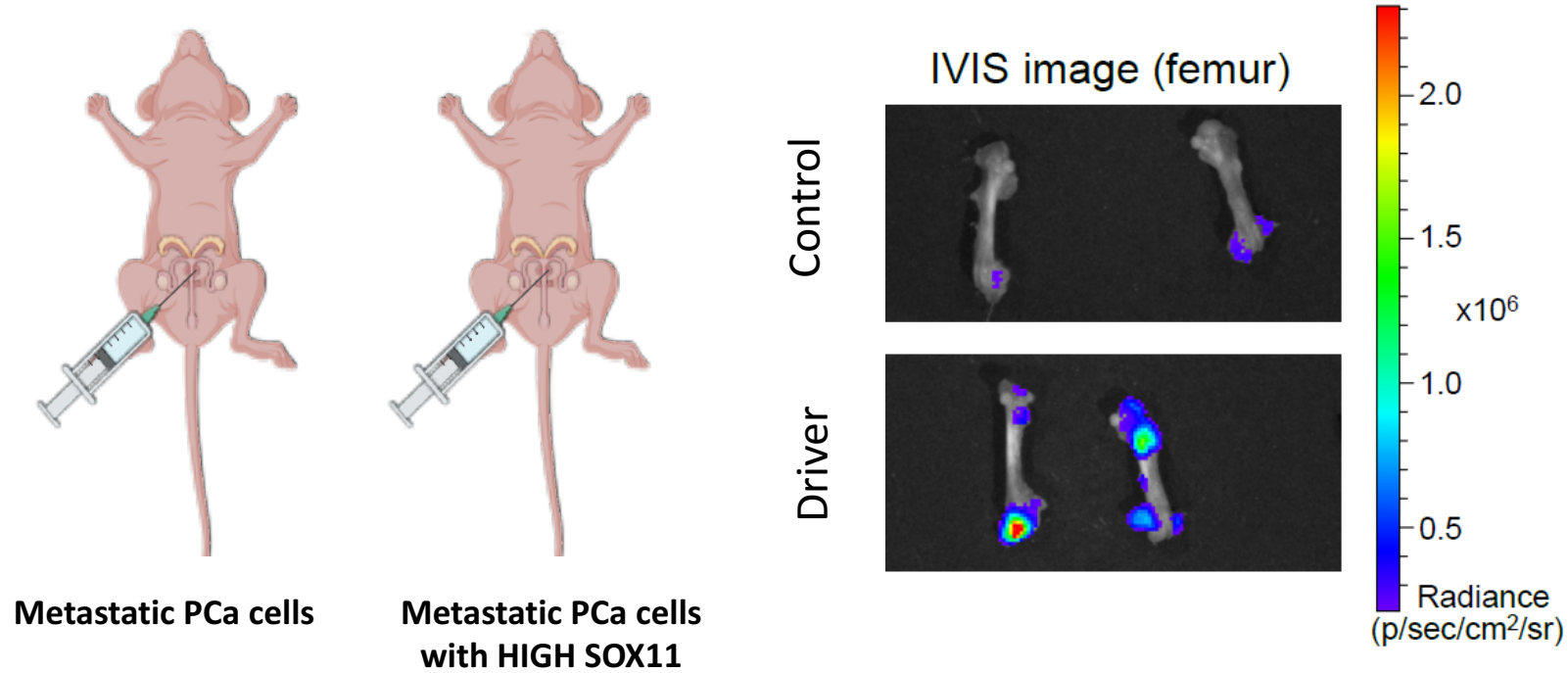
Identification of ligands

Inference of upstream transcriptional regulators

SOX11

In vivo validation

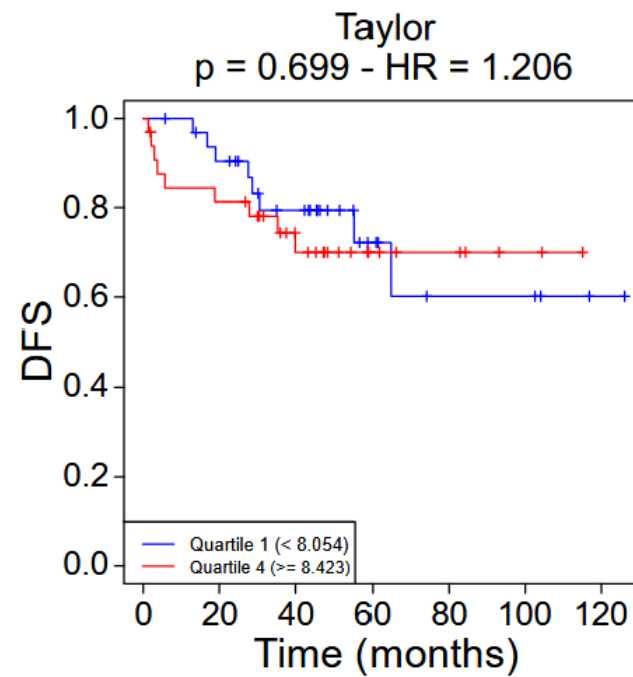
Using murine models to assess metastasis



**Could this information be valuable
to stratify patients with localized disease?**

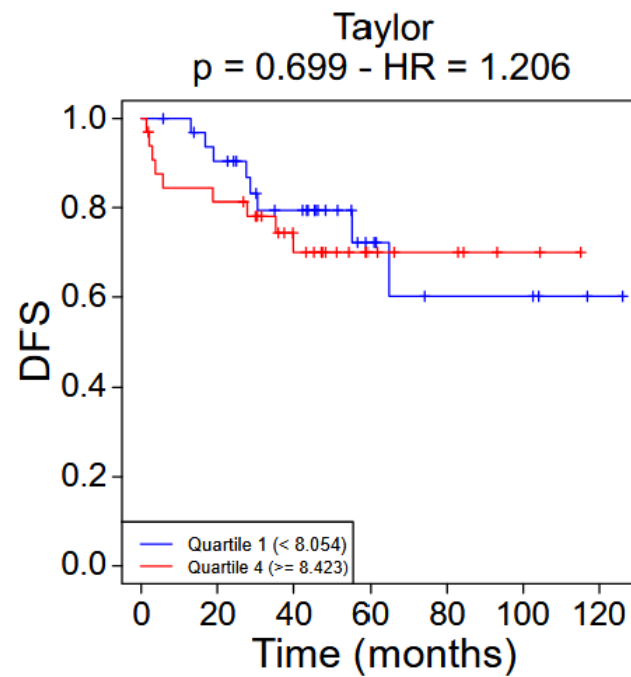
Could this information be valuable to stratify patients with localized disease?

SOX11 prognostic potential

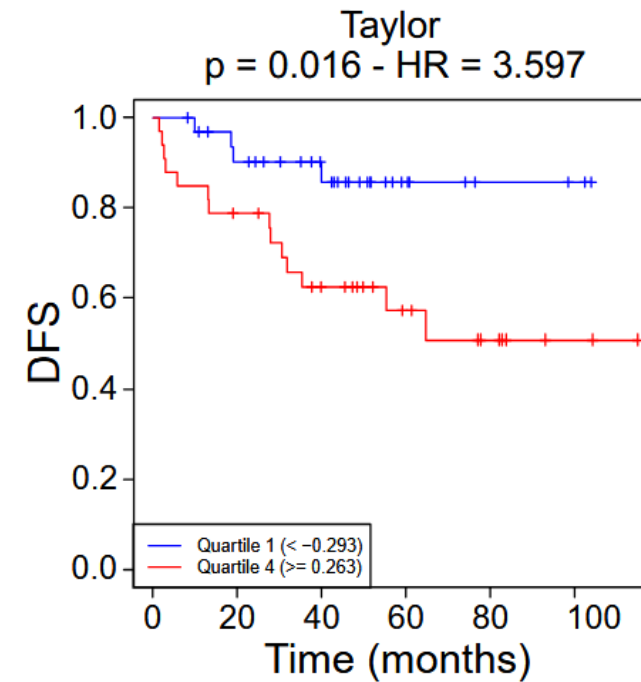


Could this information be valuable to stratify patients with localized disease?

SOX11 prognostic potential



SOX11 paracrine program prognostic potential



CONCLUSION

1. We can learn about new cancer drivers by looking at rare variants within a common disease
2. *A bidirectional translational research strategy is instrumental in cancer*

Martín-Martín et al., Genome Biol. 2025

¡Gracias!

