Towards new therapeutic opportunities in prostate cancer : revisiting lipid metabolism

Journées Scientifiques
Cancéropole Est

Ludovic Enkler, Chair of Excellence - Junior PI
UR3072 - CRBS
28th Nov. 2025

Prostate cancer (PCa): Epidemiology

PCa in numbers

- **2nd cancer** in male worldwide
- **3rd** cause of **cancer-related death** in France
- Median age **69 years old** at diagnosis
- **20%** of treated patients become **metastatic**
- +3.6%/year **mortality**

Adapted from Uo et al., Front. Oncol. 2020 and Pujana-Vaquerizo et al., Brit. J. Cancer 2024; World Health Organization

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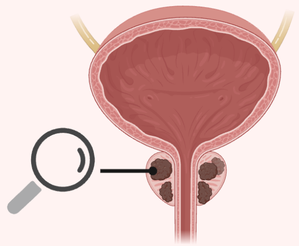
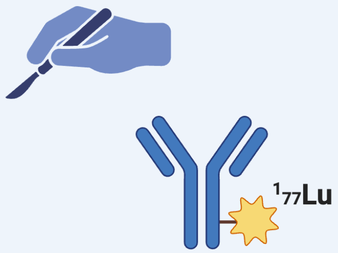
Risk category	Grade group	Gleason Score	Key features
LOW	1	<6	PSA <10 ng/mL, cT1-T2a
INTERMEDIATE - FAVORABLE	2	3+4	PSA 10-20 ng/mL, <50% positive cores
INTERMEDIATE - UNFAVORABLE	3	4+3	PSA 10-20 ng/mL, >50% positive cores
HIGH	4-5	8-10	PSA >20 ng/mL, cT3-T4

Treatment strategies

Active surveillance



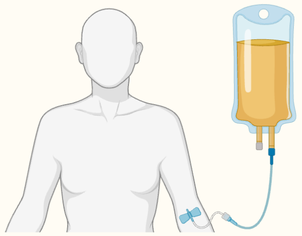
Surgery / Radiation



Androgenotherapy

Abiraterone acetate, enzalutamide...

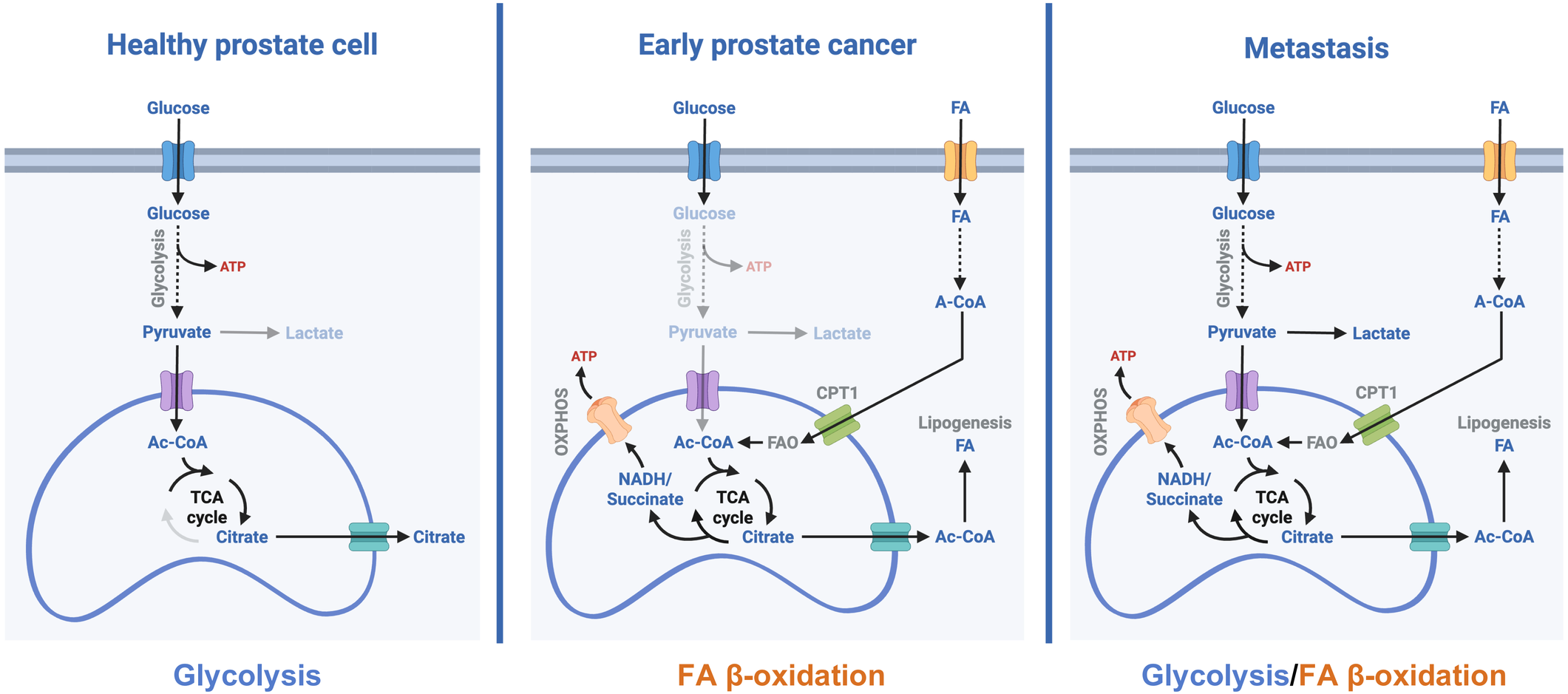
Chemotherapy



Docetaxel

Adapted from Uo et al., Front. Oncol. 2020 and Pujana-Vaquerizo et al., Brit. J. Cancer 2024; World Health Organization

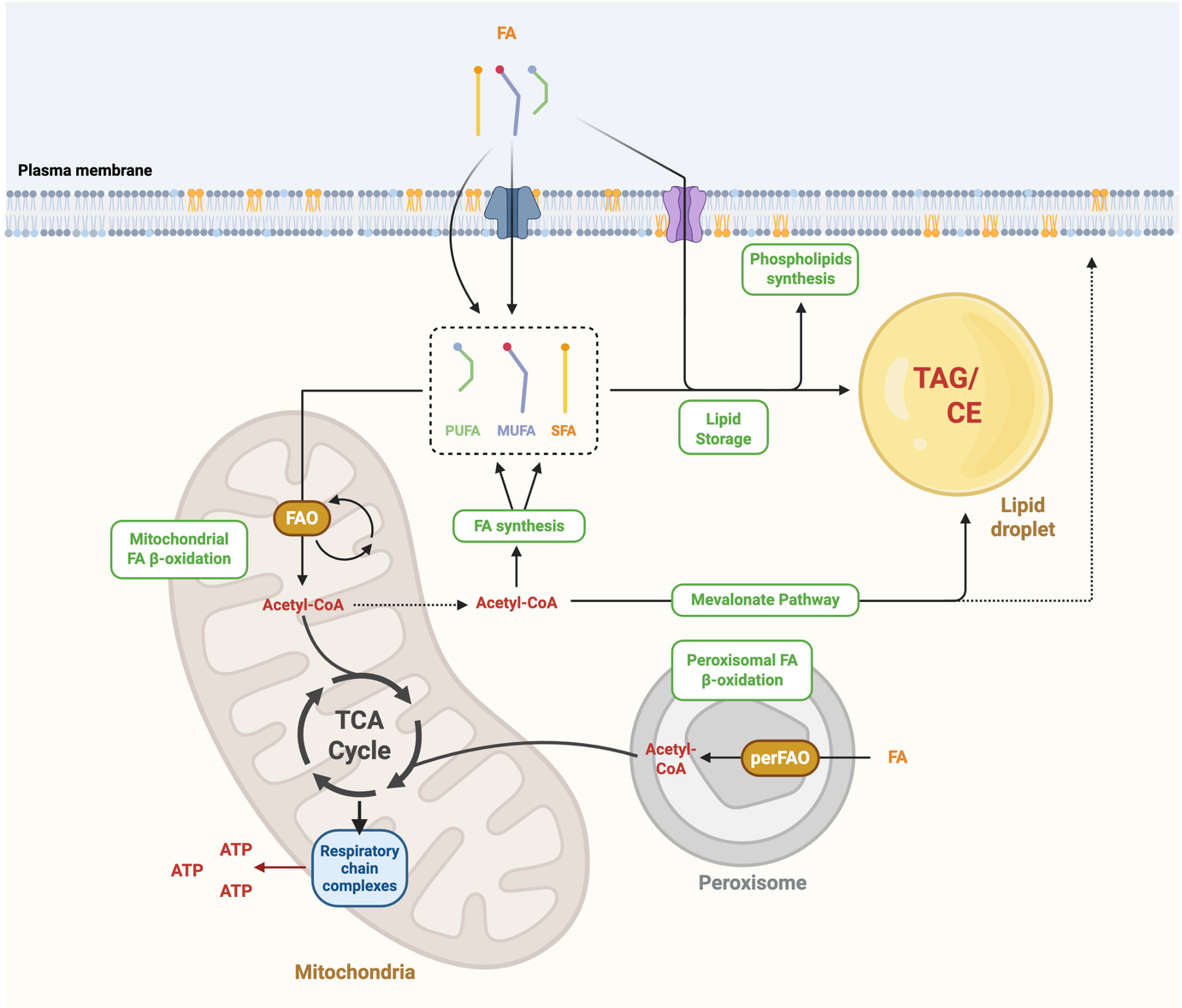
Prostate cancer (PCa): an increased taste for fat



Glycolysis | FA β-oxidation | Glycolysis/FA β-oxidation

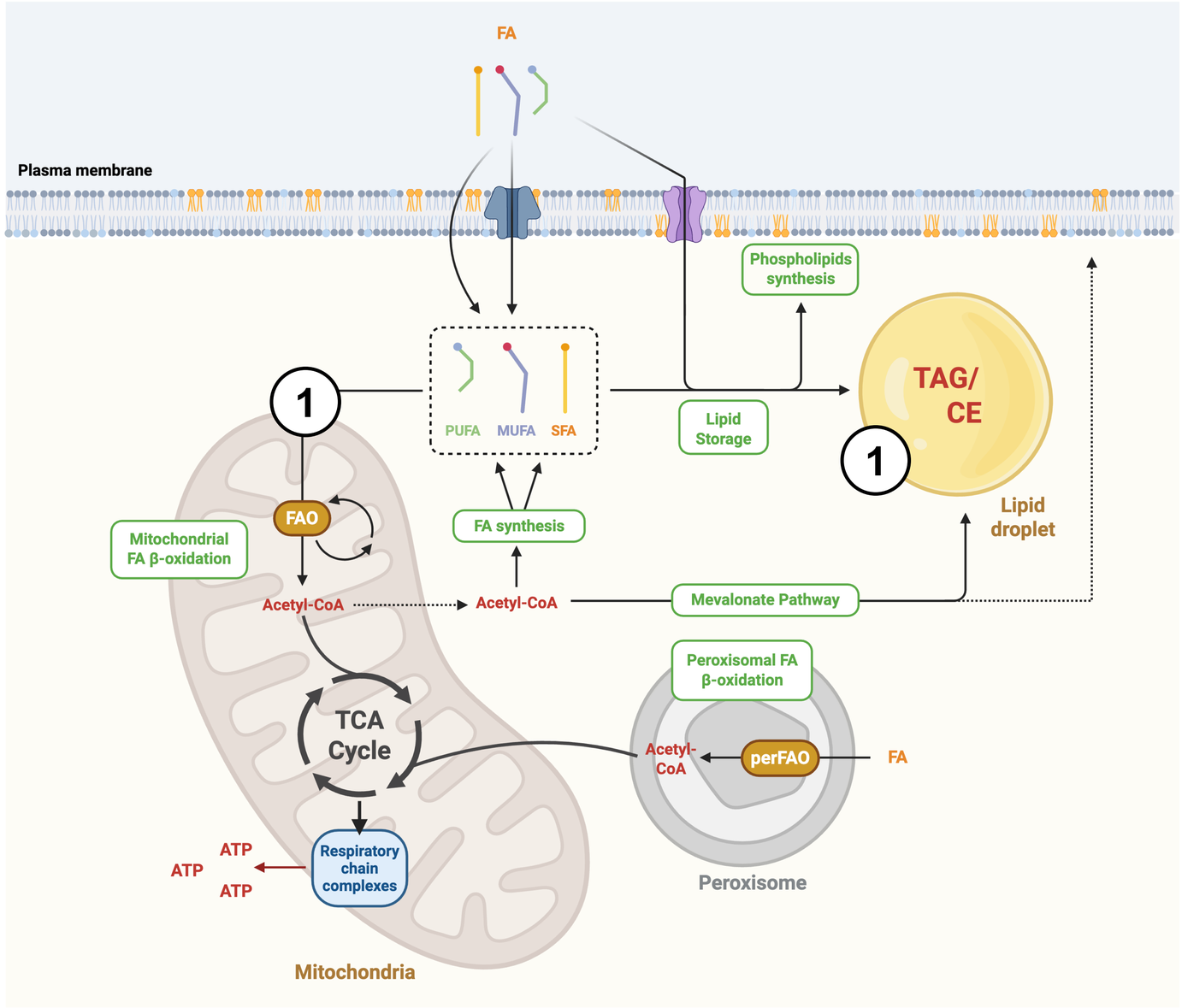
Adapted from Uo et al., Front. Oncol. 2020 and Pujana-Vaquerizo et al., Brit. J. Cancer 2024; World Health Organization

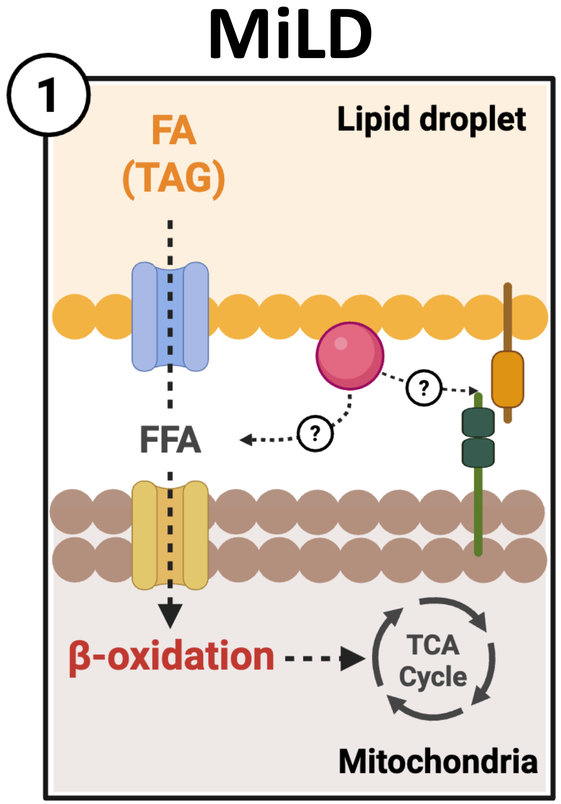
Overview of fatty acid metabolism in PCa



- **Acquired** and ***de novo*** **FA biogenesis**
- **Stored** in lipid droplets (**LD**) & **processed** by peroxisome or mitochondria **(MT)**
- **Metabolized** by MT to produce **ATP**

Contact sites are essential for metabolites transport



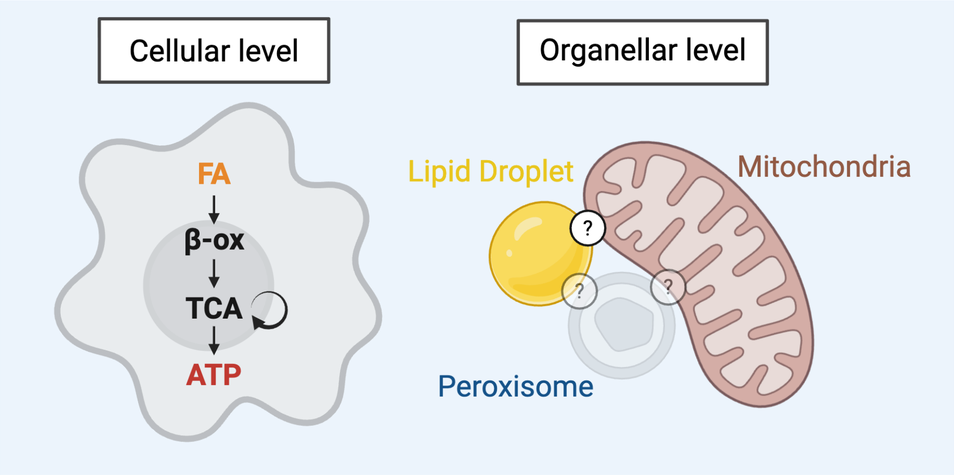


Very little is known about organellar biologies & contact sites in PCA…

‘Metabolic compartmentalization’ lab

Our axes of research

Plasticity of **prostate cancer cells**



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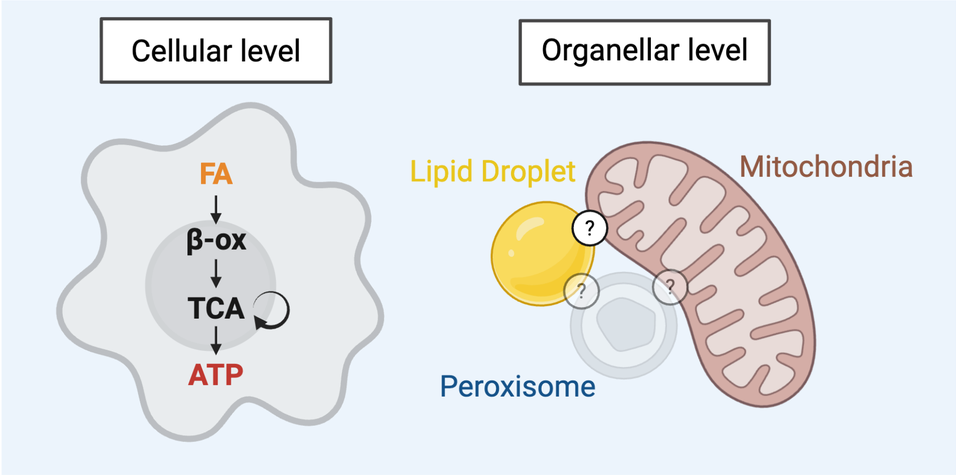
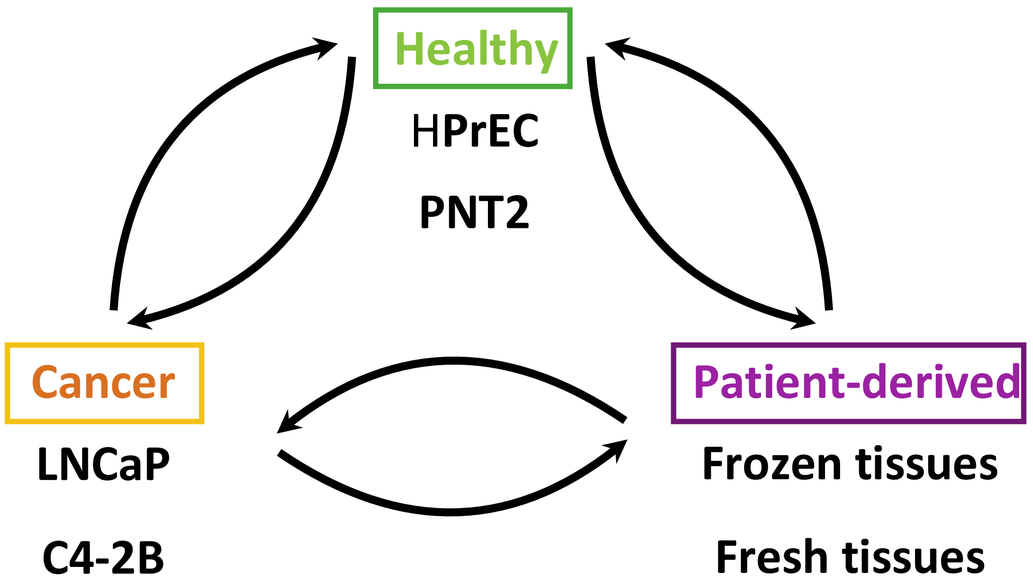


Our models of study



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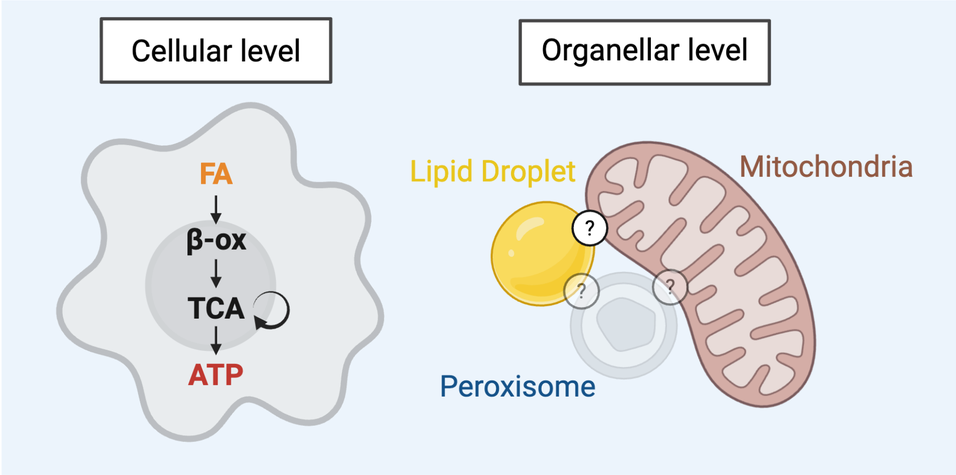

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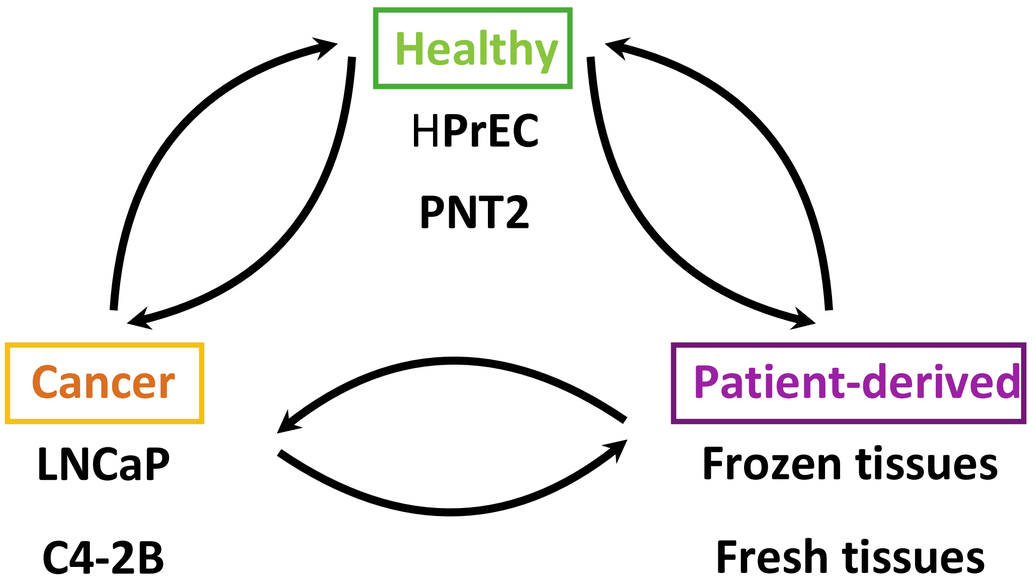

The question that drives us

How prostate cancer cells adapt to starvation & fatty acid metabolism ?

‘Metabolic compartmentalization’ lab

Our axes of research

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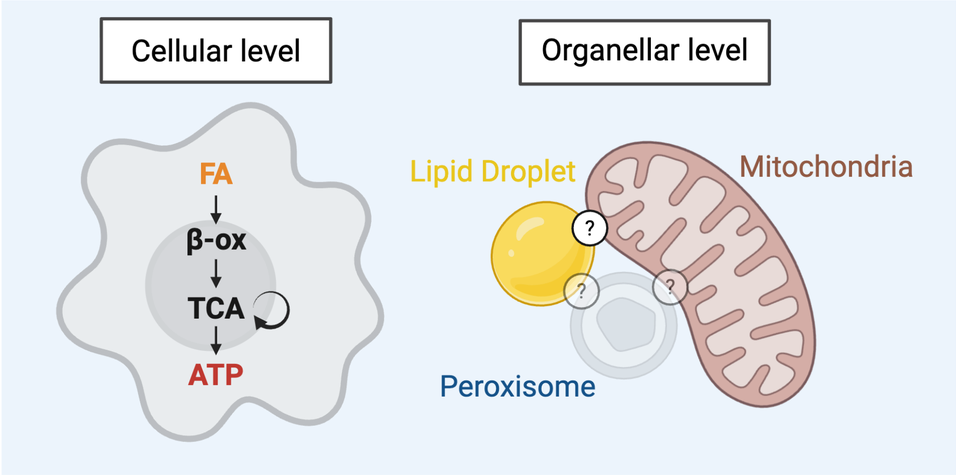

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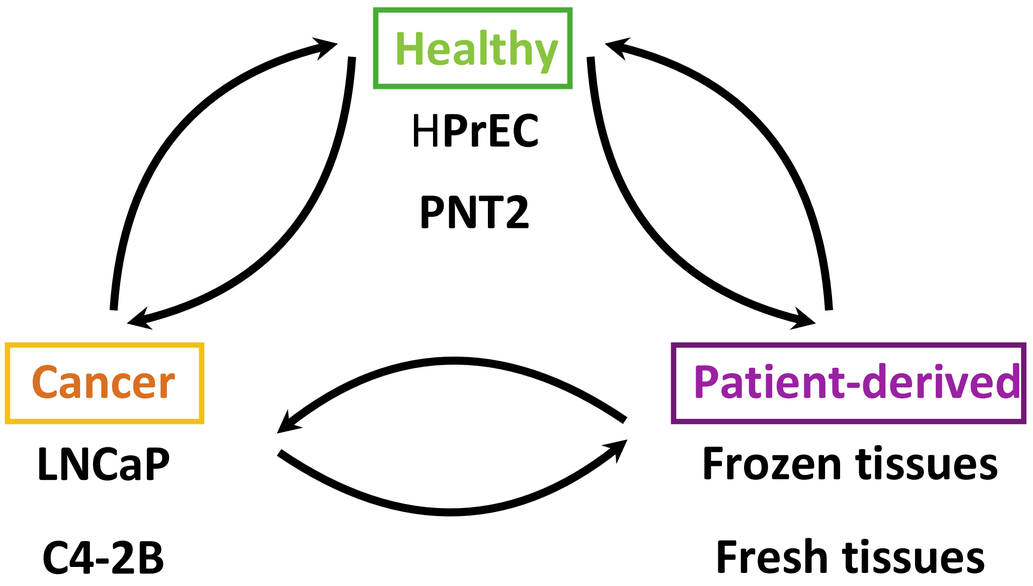

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How prostate cancer cells adapt to starvation & fatty acid metabolism ?

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Understand prostate cancer metabolism at the fundamental level & identify new molecular targets

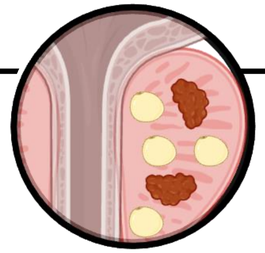
1

ESTABLISHMENT OF NEW MODELS TO STUDY PCa PLASTICITY

Mimicking cellular adaptation to metabolic niches

RPMI

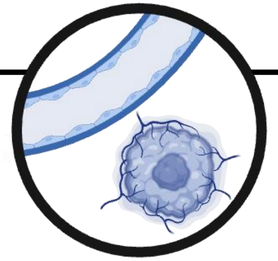
- **High carbohydrates** diet
- **Locally advanced PCa**
- **Lymphatic system, brain tissue**



HBSS

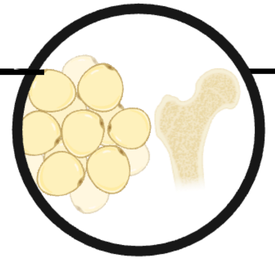
- **Low carbohydrate low nutrients**
- diet

Tumor core (necrotic/hypoxic regions)

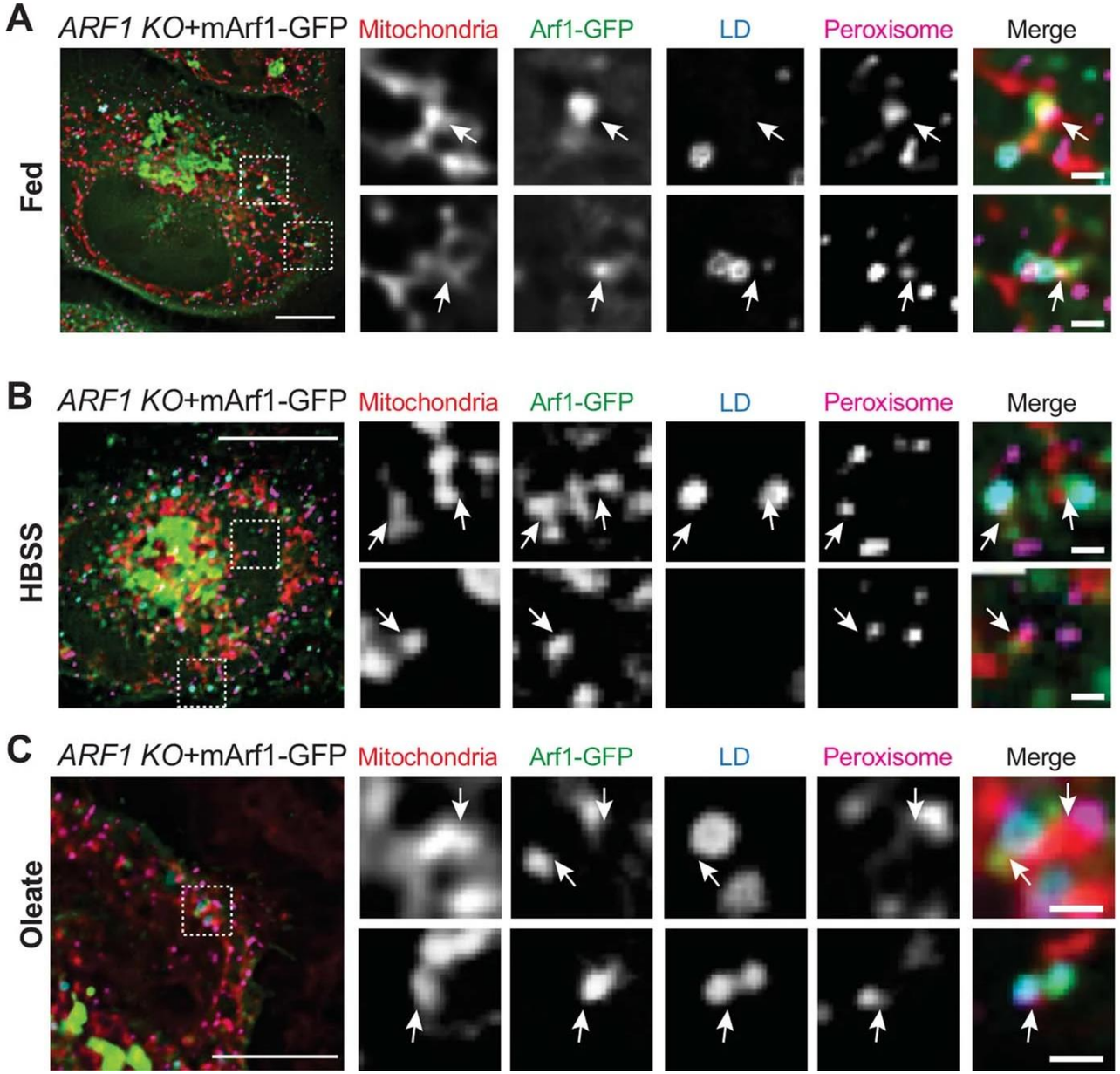


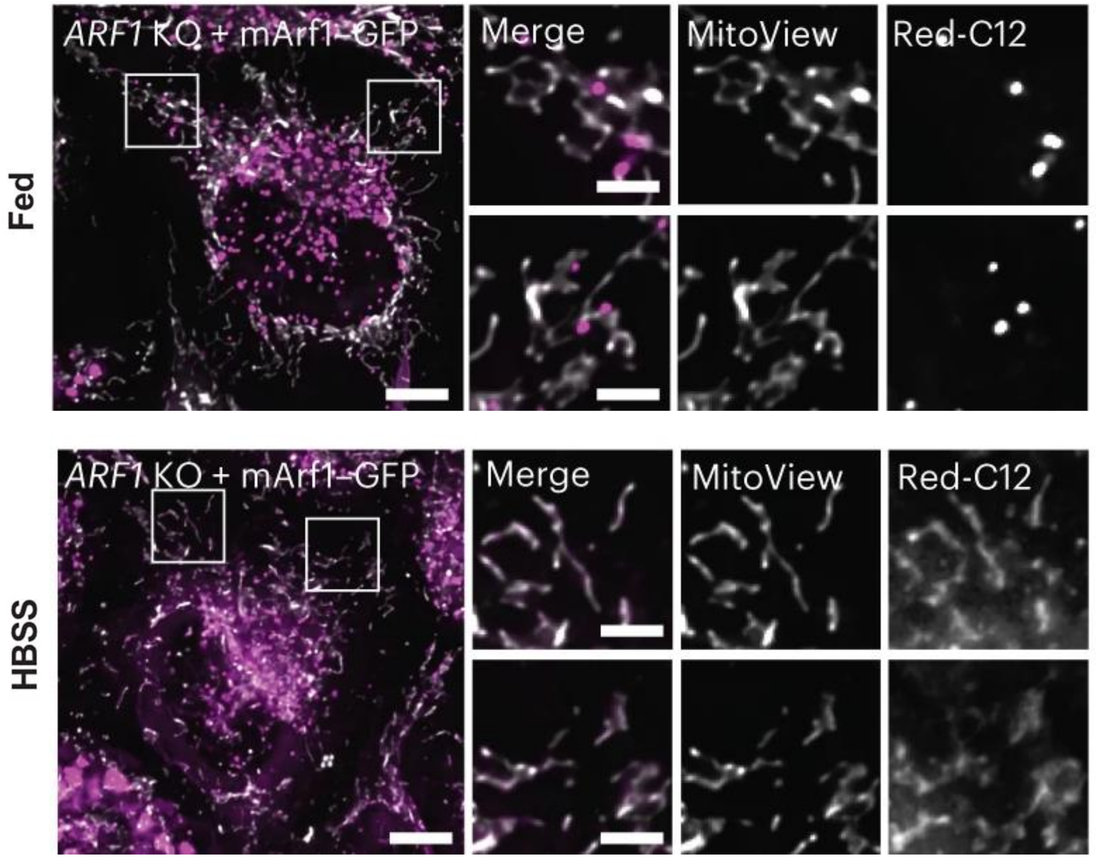
Oleate

- **High fat** diet
- **Bone marrow niche**
- **Adipose tissues** in prostate TME

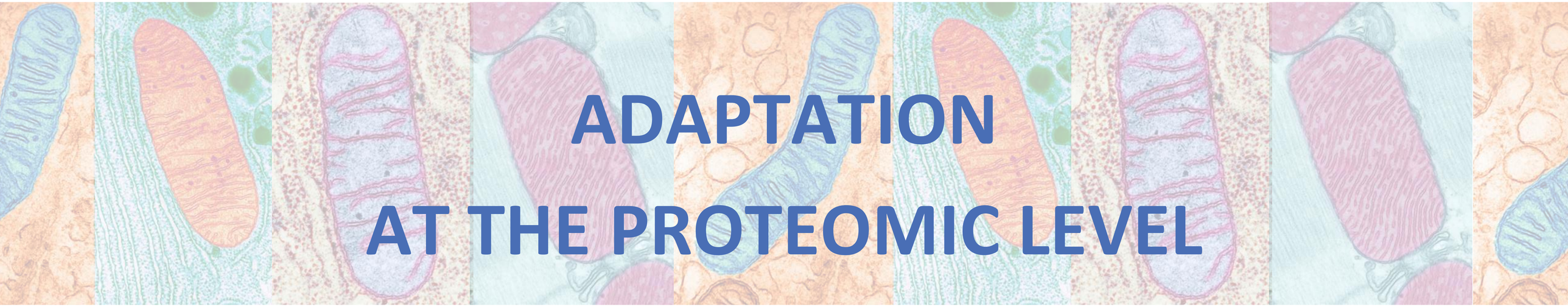


Starvation and high FA increase contact sites & FA transfer



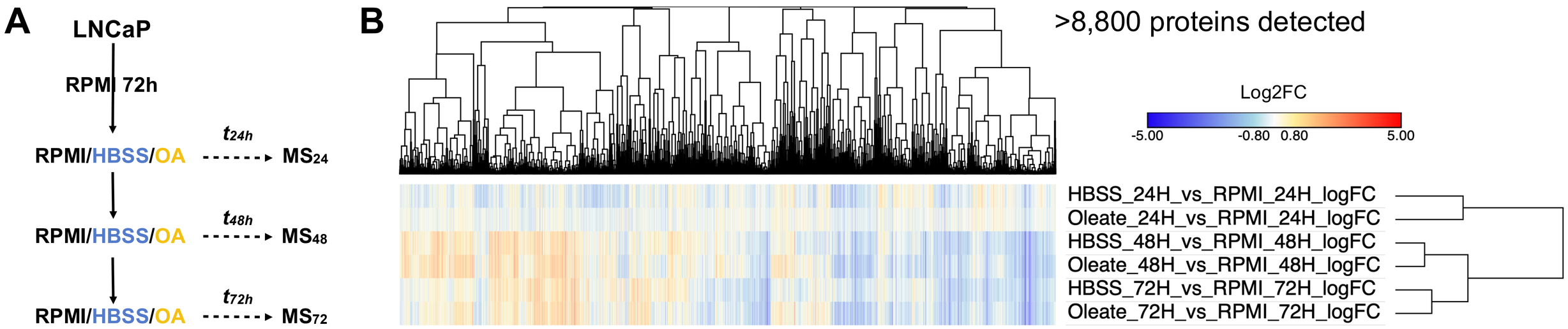


Enkler et al., Nat Cell Biol 2023

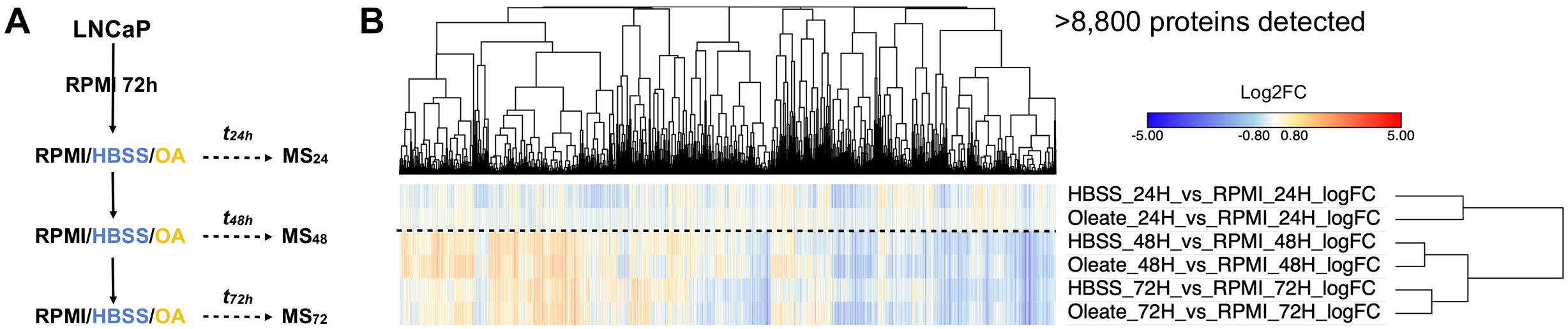


ADAPTATION AT THE PROTEOMIC LEVEL

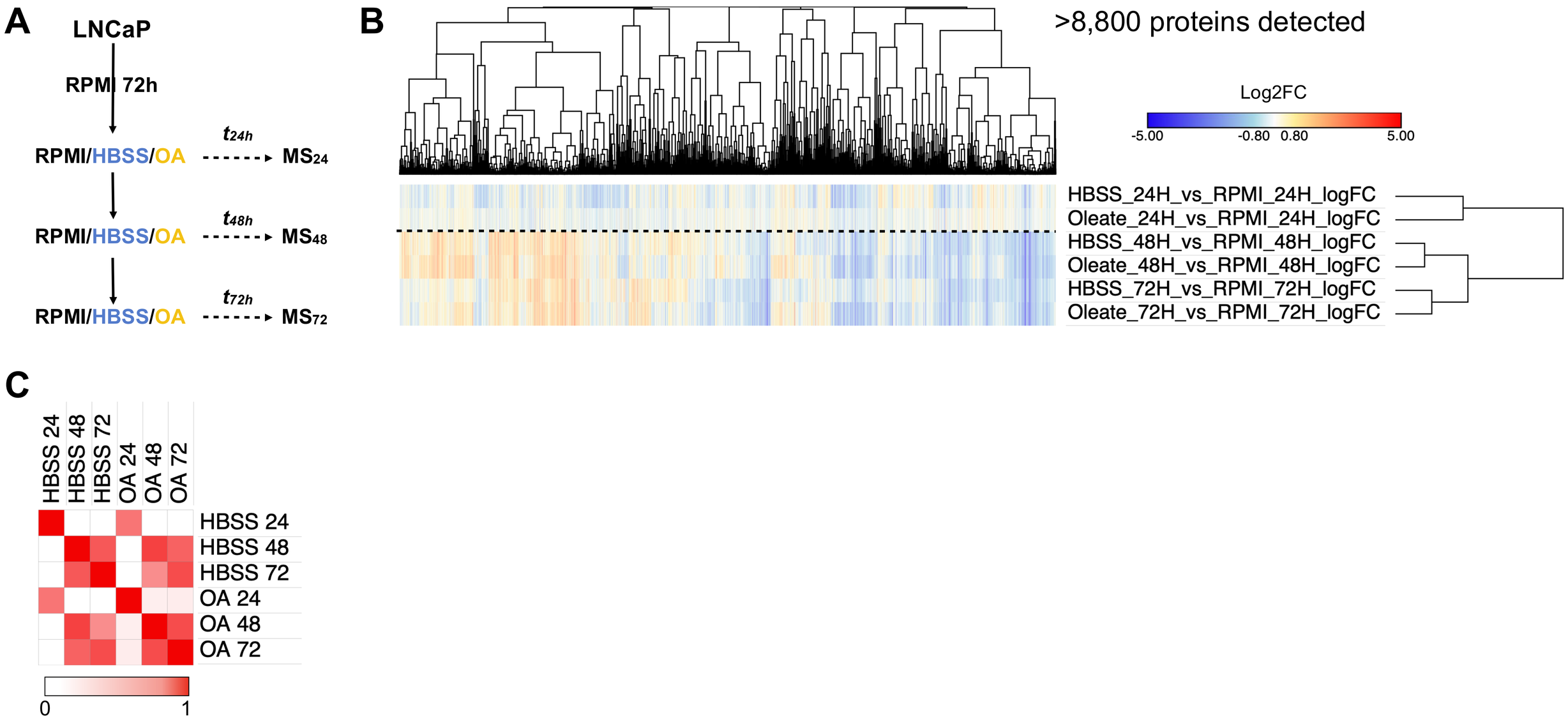
Temporal plasticity of LNCaP cells



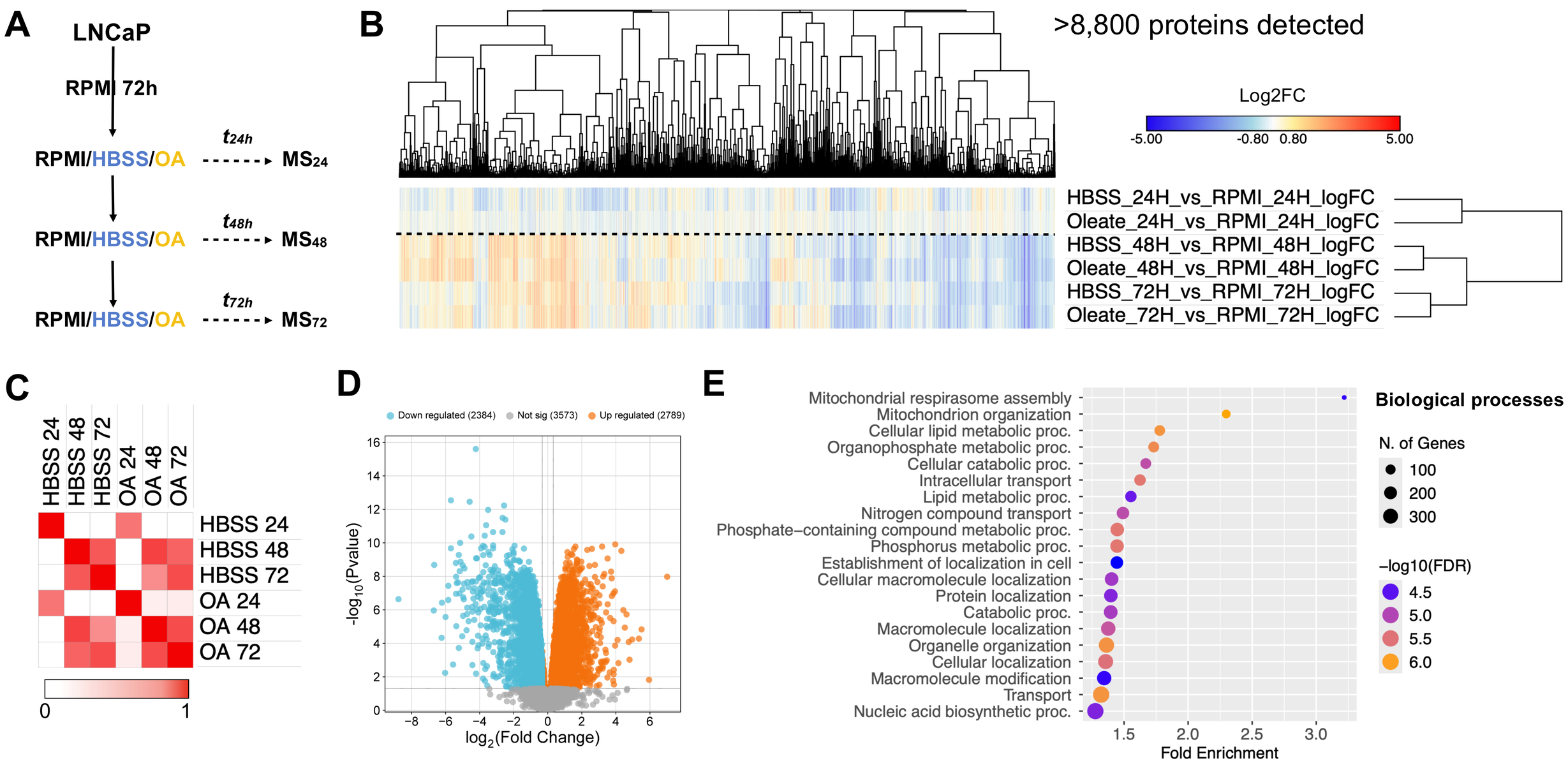
Temporal plasticity of LNCaP cells: the 48h switch



Proteomes at 48-72h share similarities



Temporal plasticity of LNCaP cells: Oleate t48h



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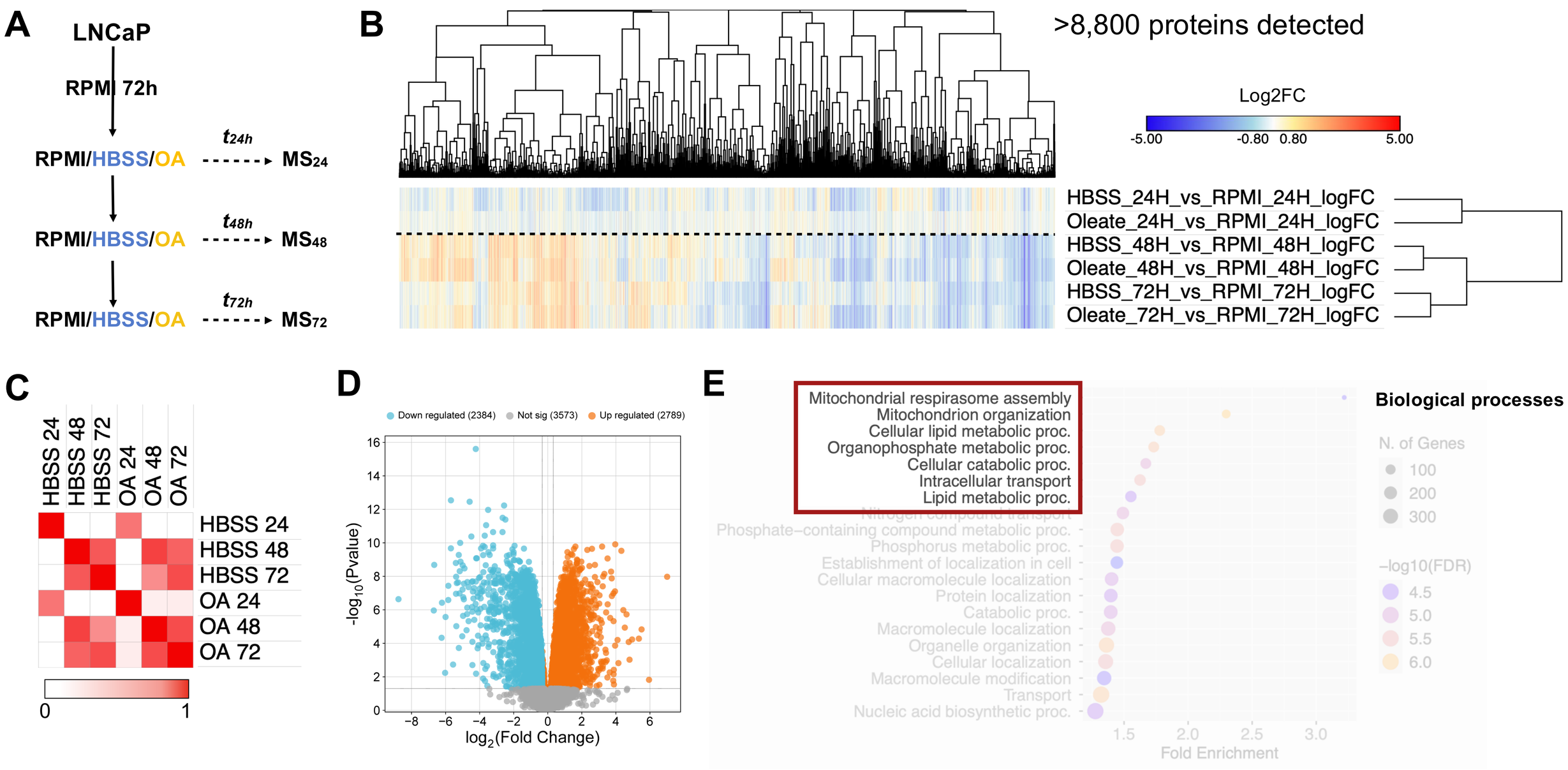

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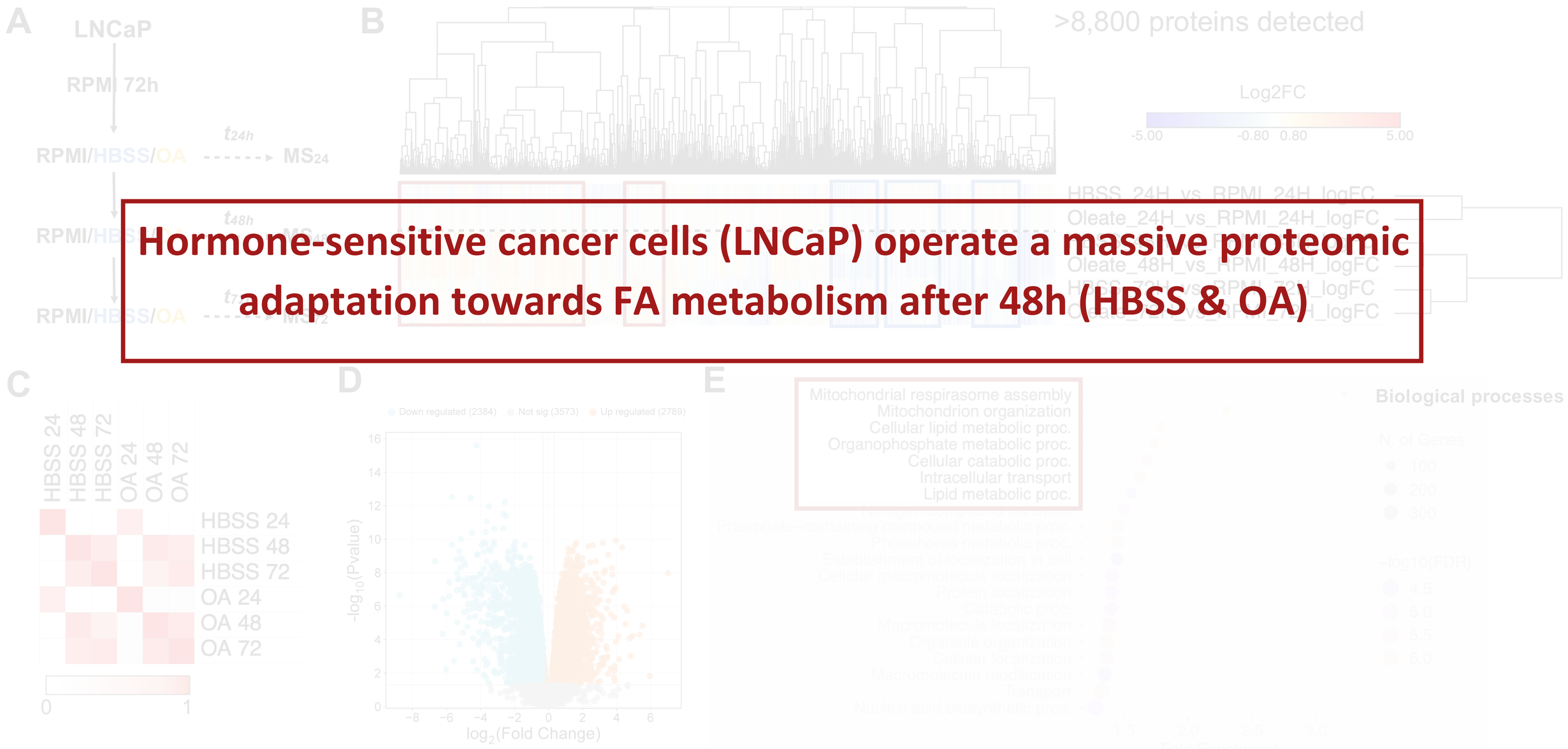
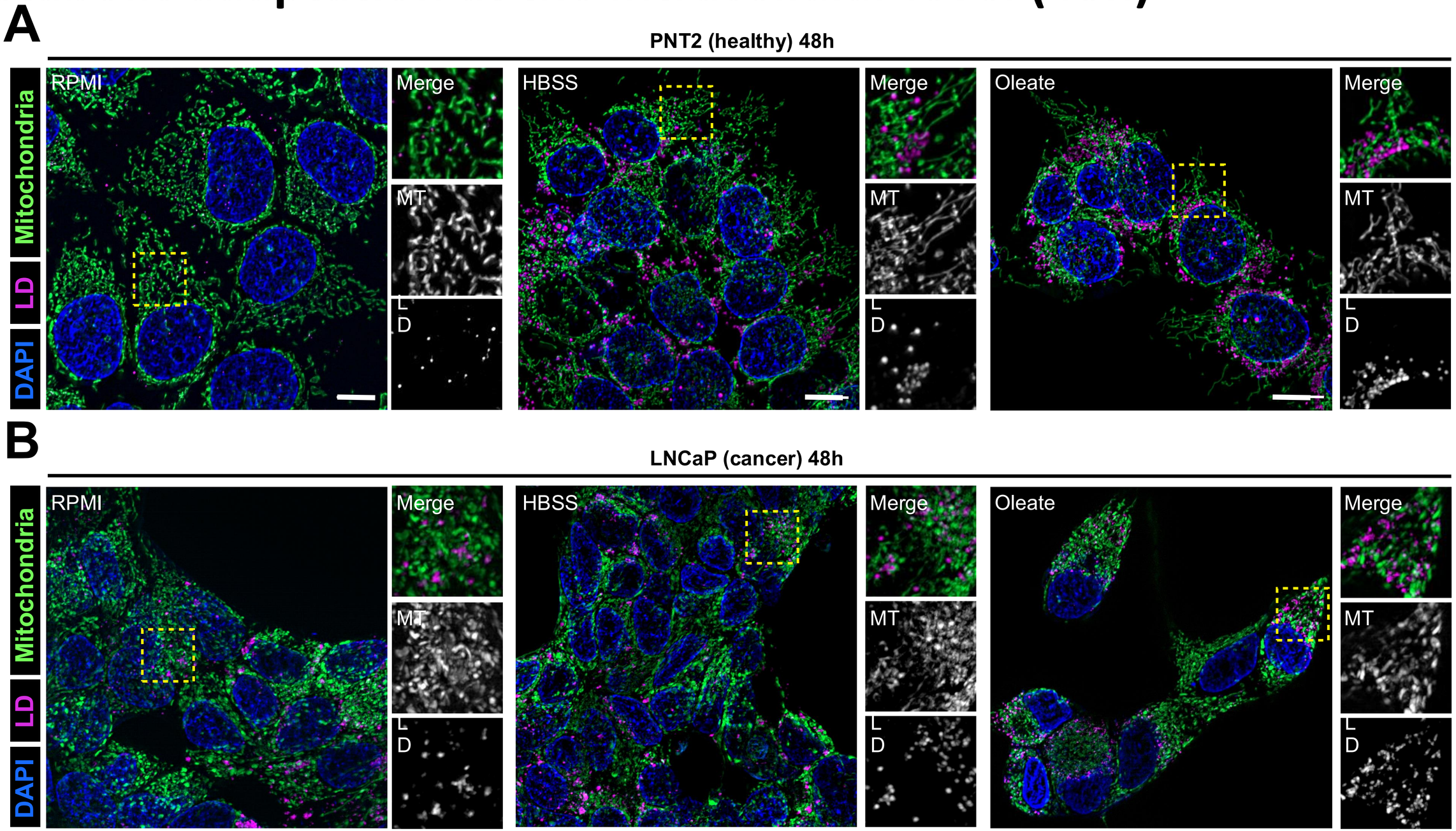


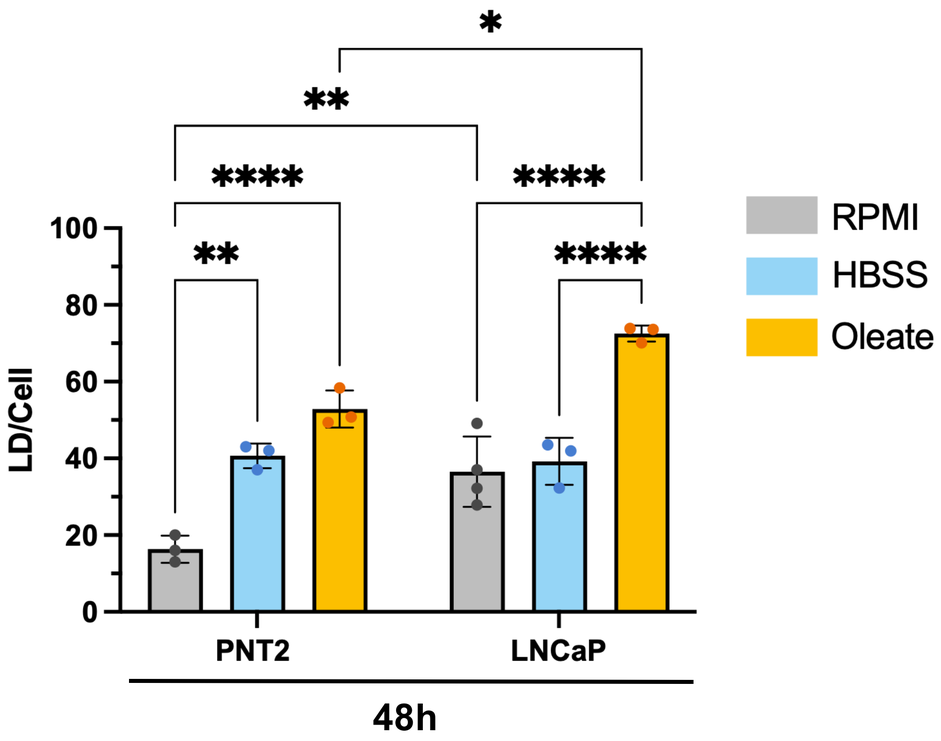
Hormone-sensitive cancer cells (LNCaP) operate a massive proteomic adaptation towards FA metabolism after 48h (HBSS & OA)

ORGANELLAR MORPHOLOGIES IN HEALTHY vs CANCER CELLS

Metabolic adaptation at the intracellular level (48h)



LD number and organization are dysregulated in cancer cells



- → More LD in cancer cells vs healthy at 24 & 48h
- → Homeostatic level of LD at 24 and 48h
- → Cancer cells accumulate more LD in OA

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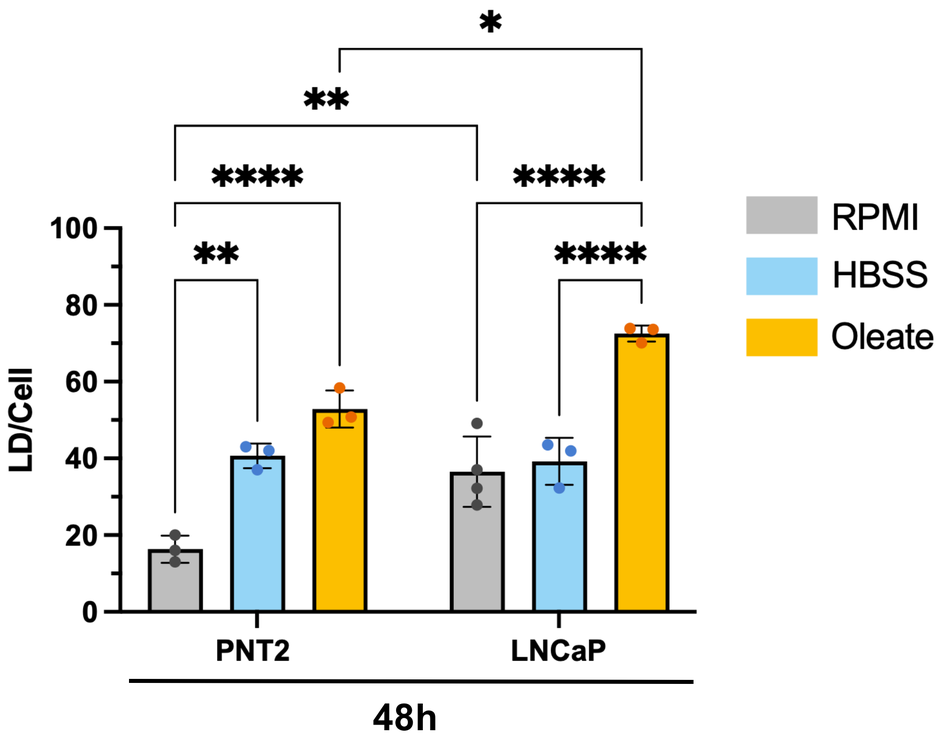

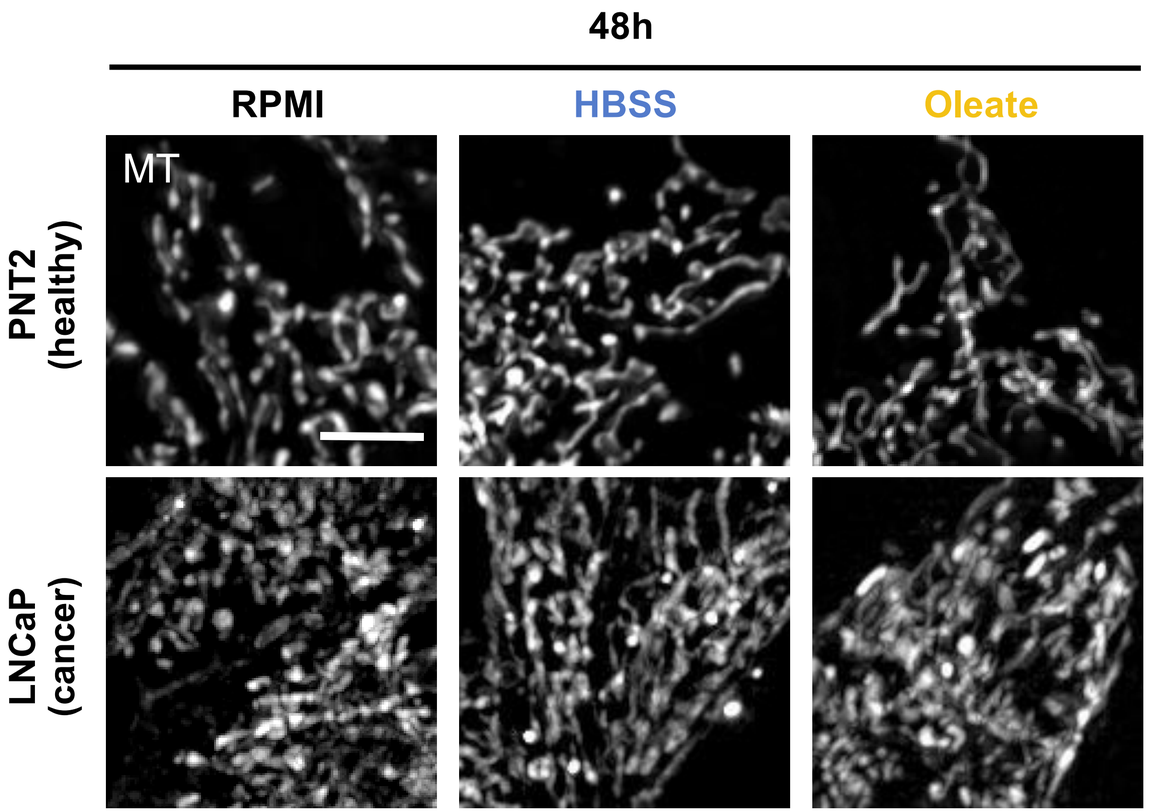

- → More LD in cancer cells vs healthy at 24 & 48h
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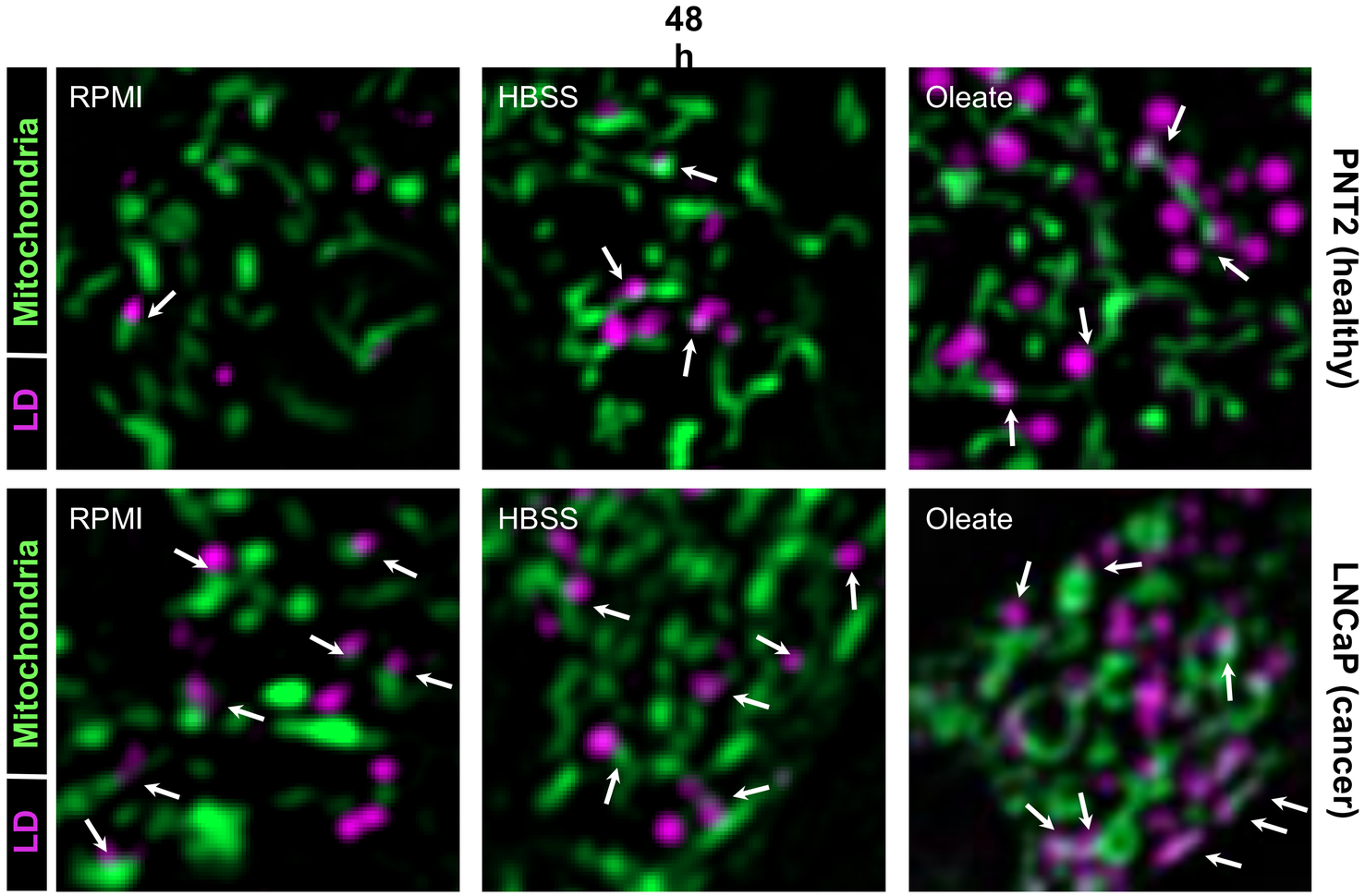
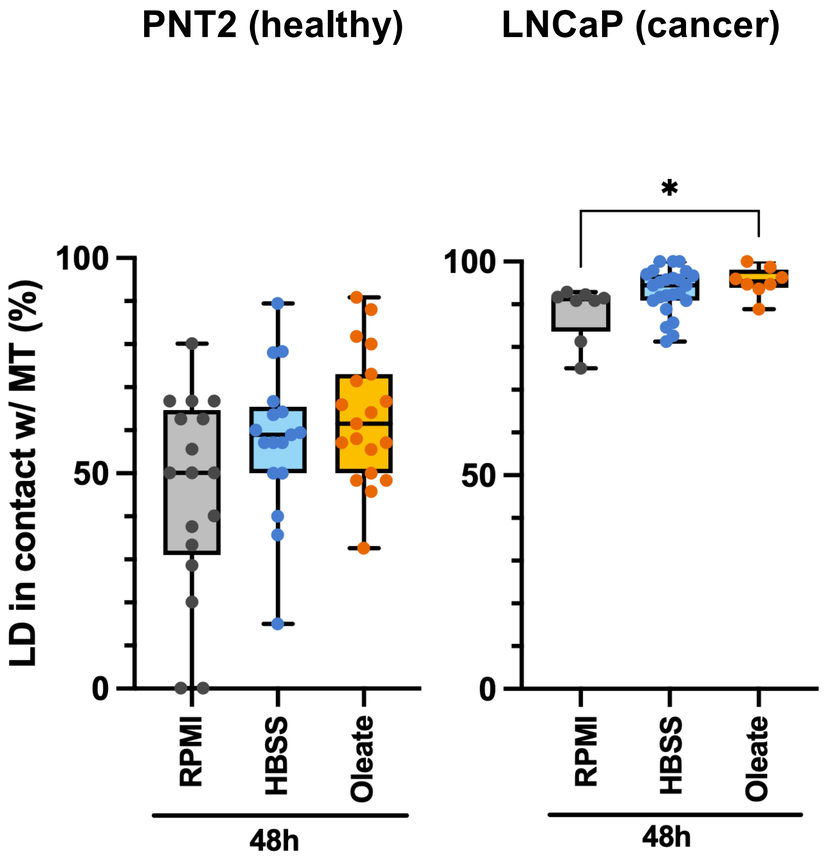
- → Mitochondria are tubular in PNT2 *vs* fragmented in LNCaP
- → Mitochondria become tubular in LNCaP in HBSS & OA

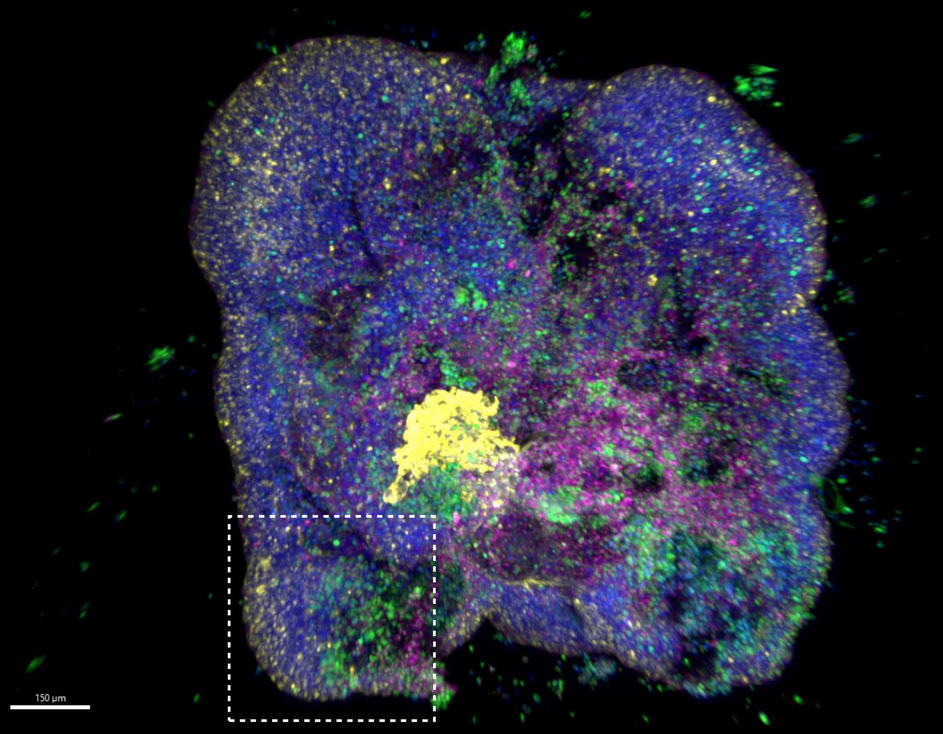
Mitochondria-LD (MiLD) contacts increase in HBSS & Oleate





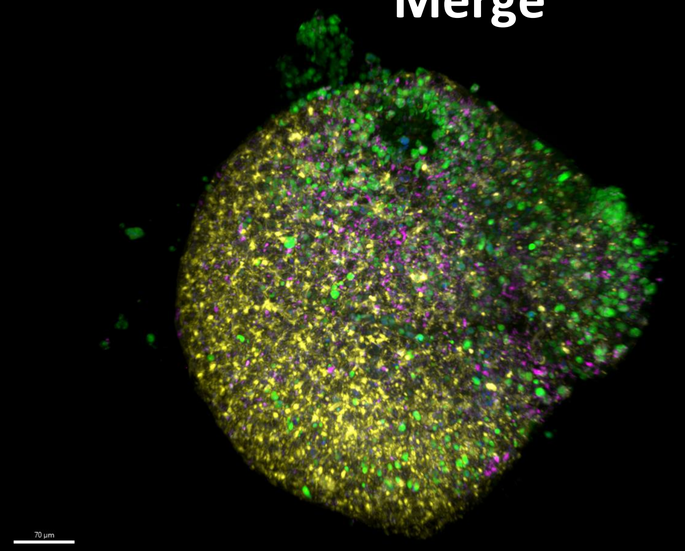
Towards organellar characterizations in organoids

LNCaP (cancer cell line)
Olympus SR- 10x/30x

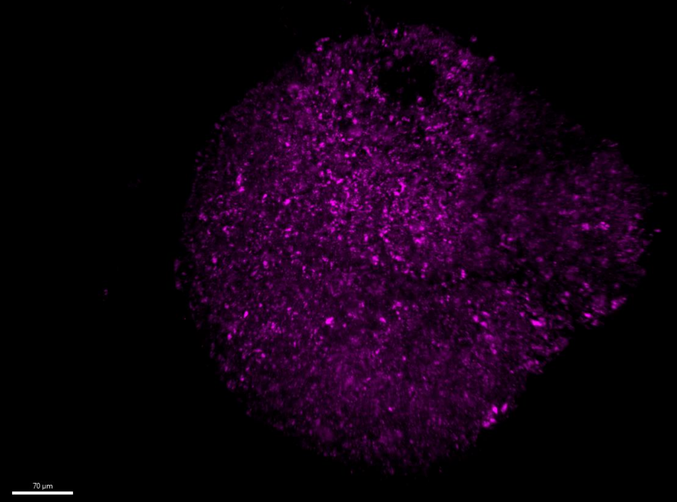


Nucleus LD Mitochondria Actin

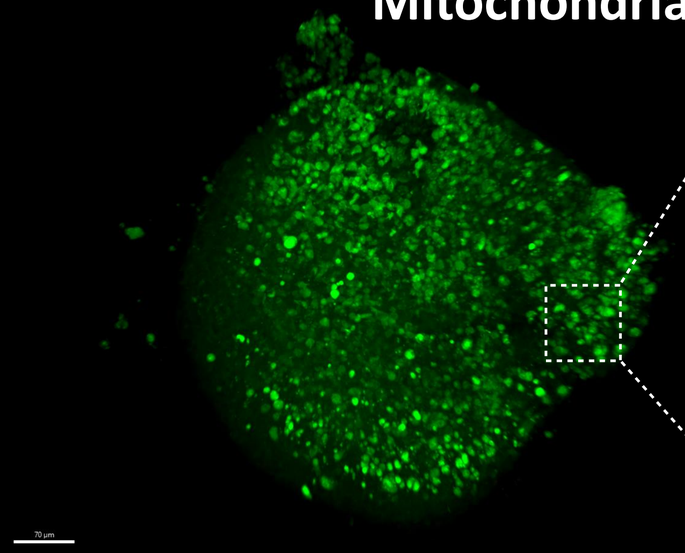
Merge



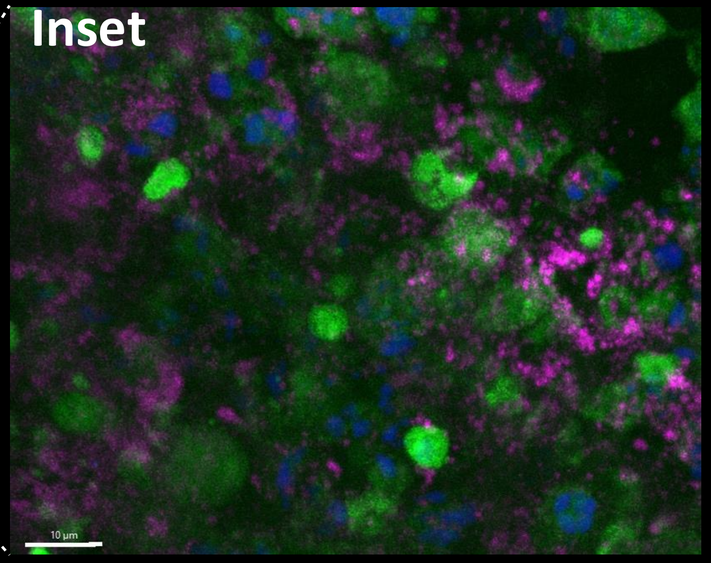
LD



Mitochondria

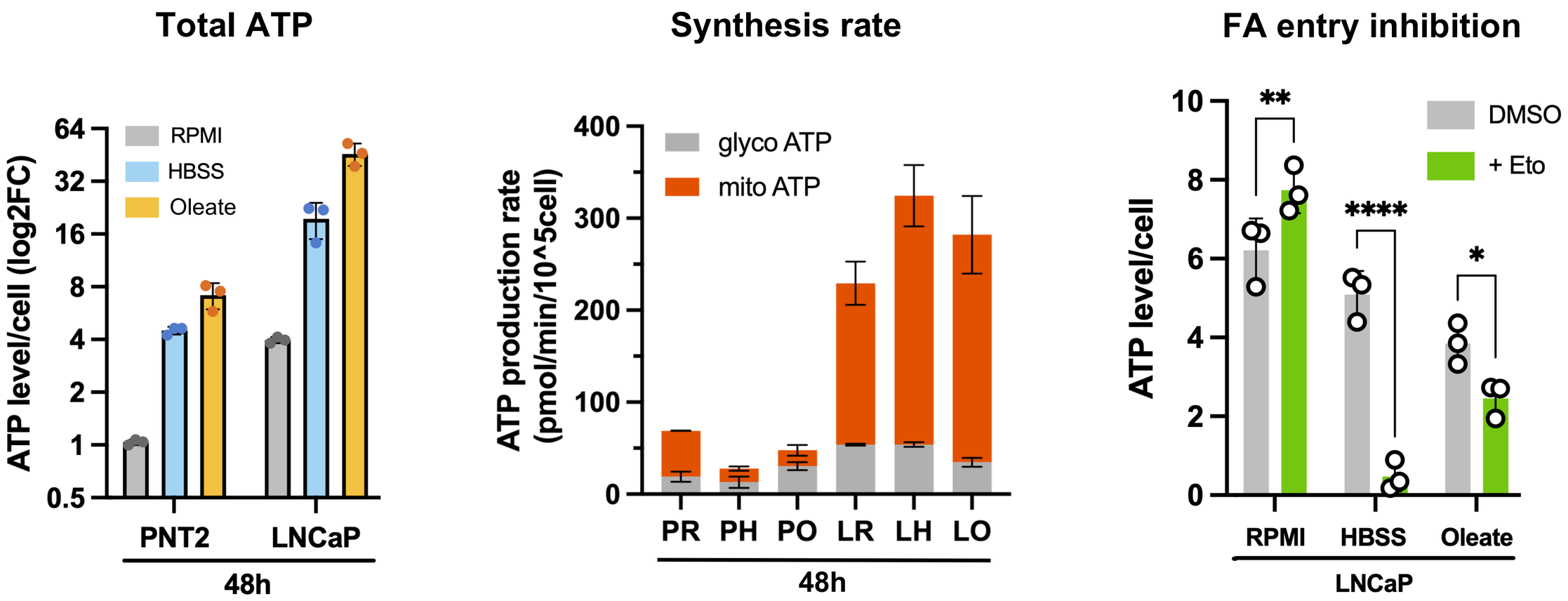


Inset



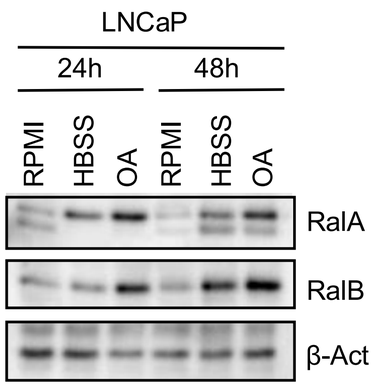
DO MORPHOLOGICAL FEATURES AFFECT METABOLISM IN LNCaP ?

LNCaP produce and accumulate excessive levels of mt-ATP (48h)

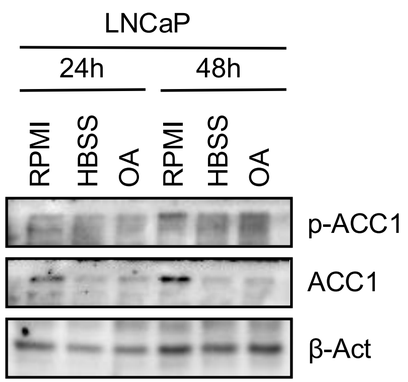


Towards a better characterization

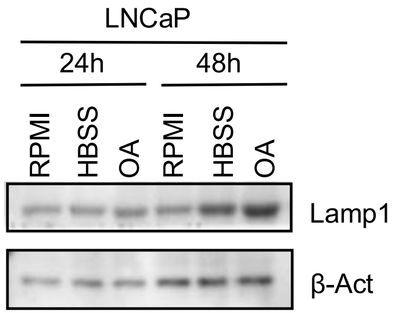
mTORC1 regulation (LD biogenesis/autophagy)

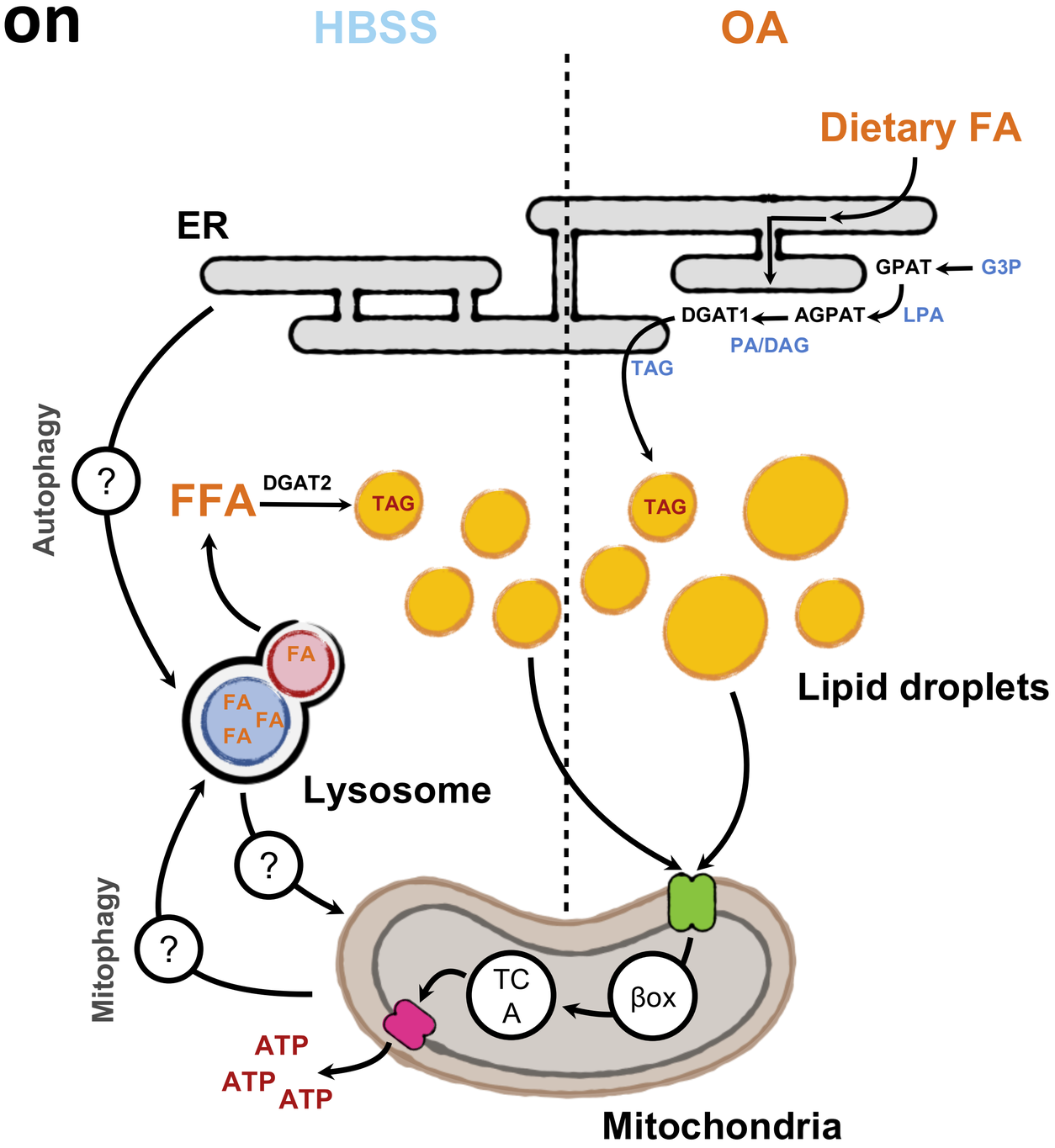


FA *de novo* synthesis



Late endosomes /lysosomes





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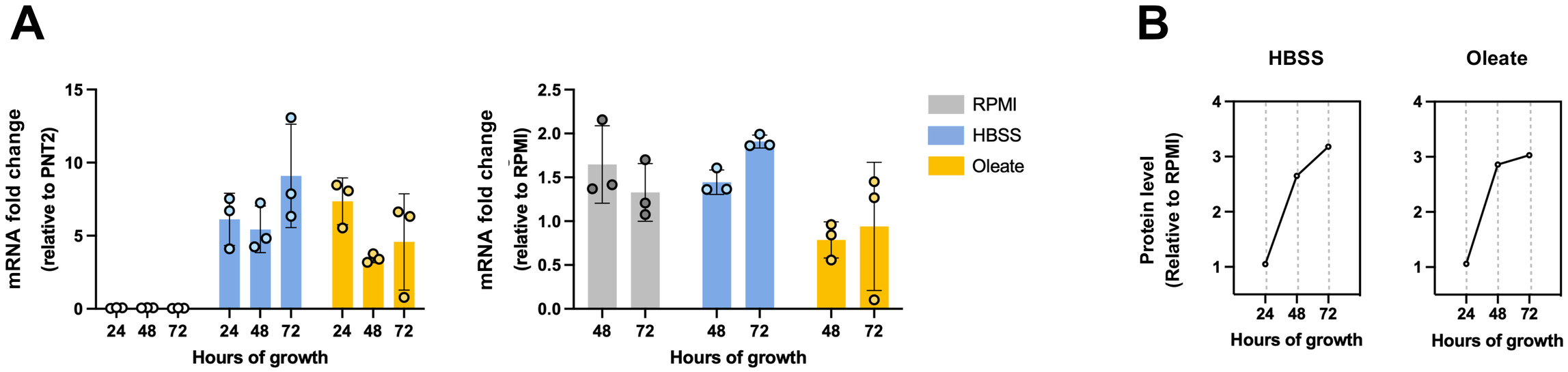
tmc_PRAD2 - A POTENTIAL CANDIDATE

Towards new molecular targets: case study of tmc_PRAD2



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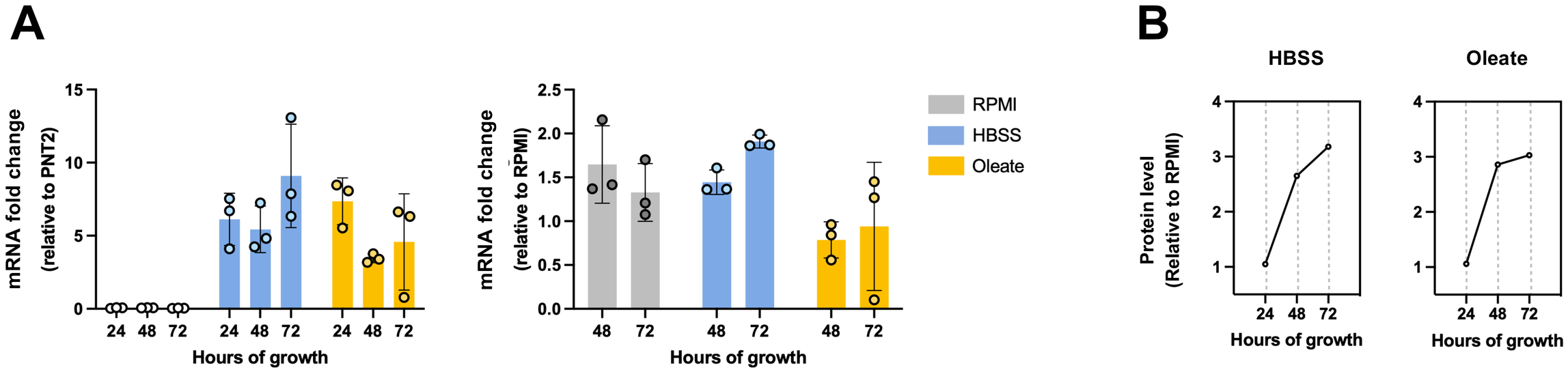
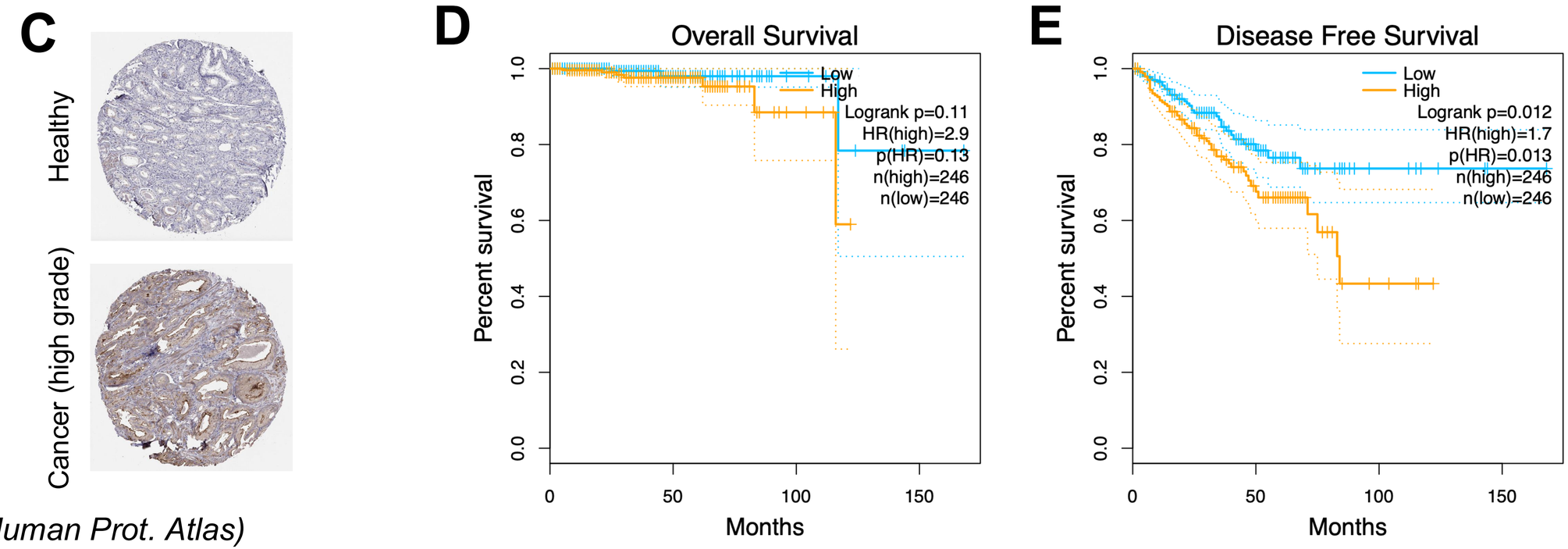
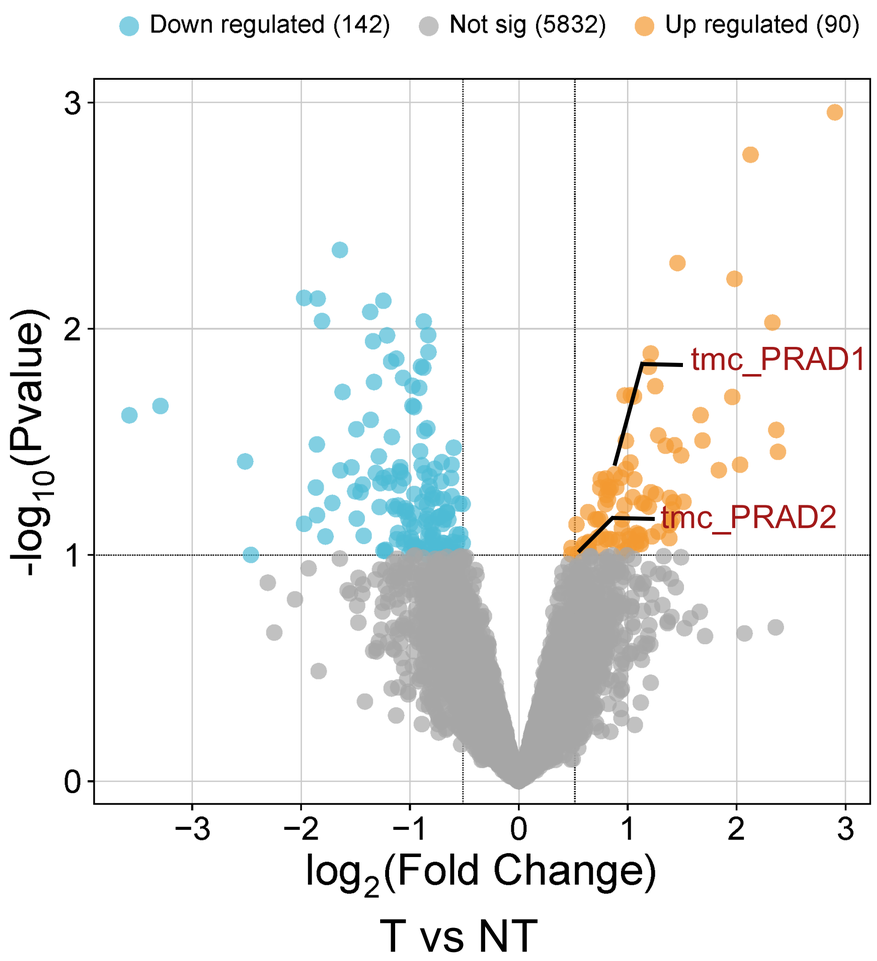




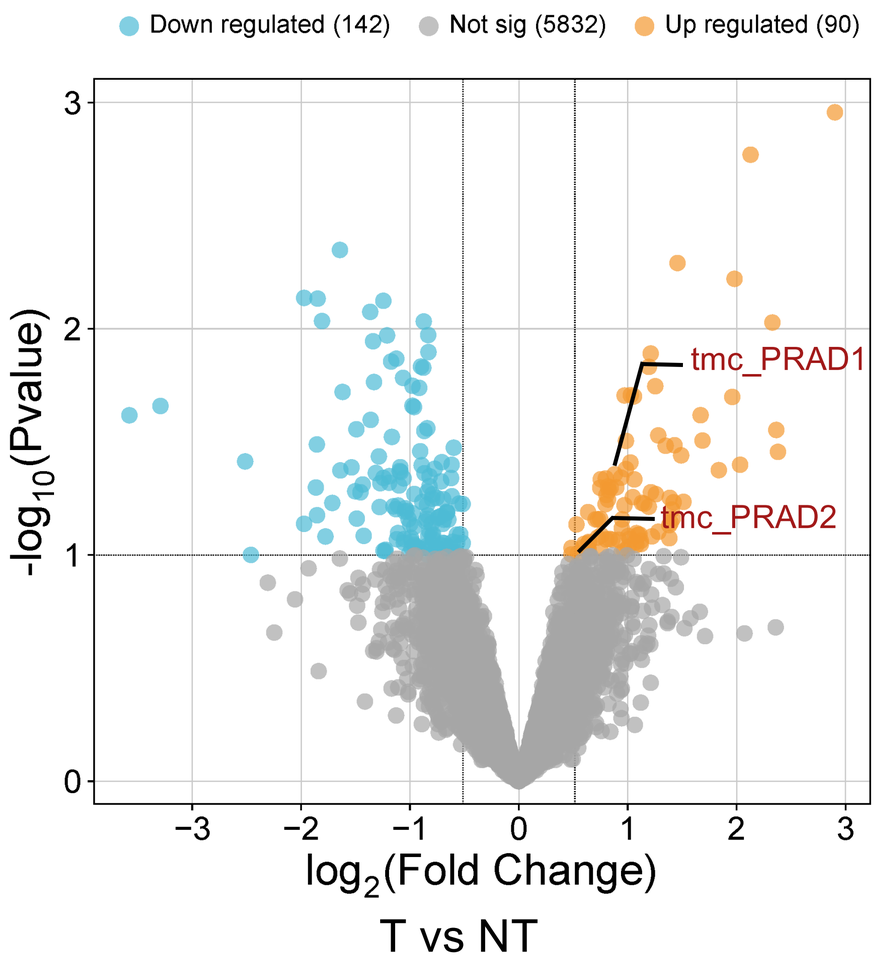
IHC (source Human Prot. Atlas)

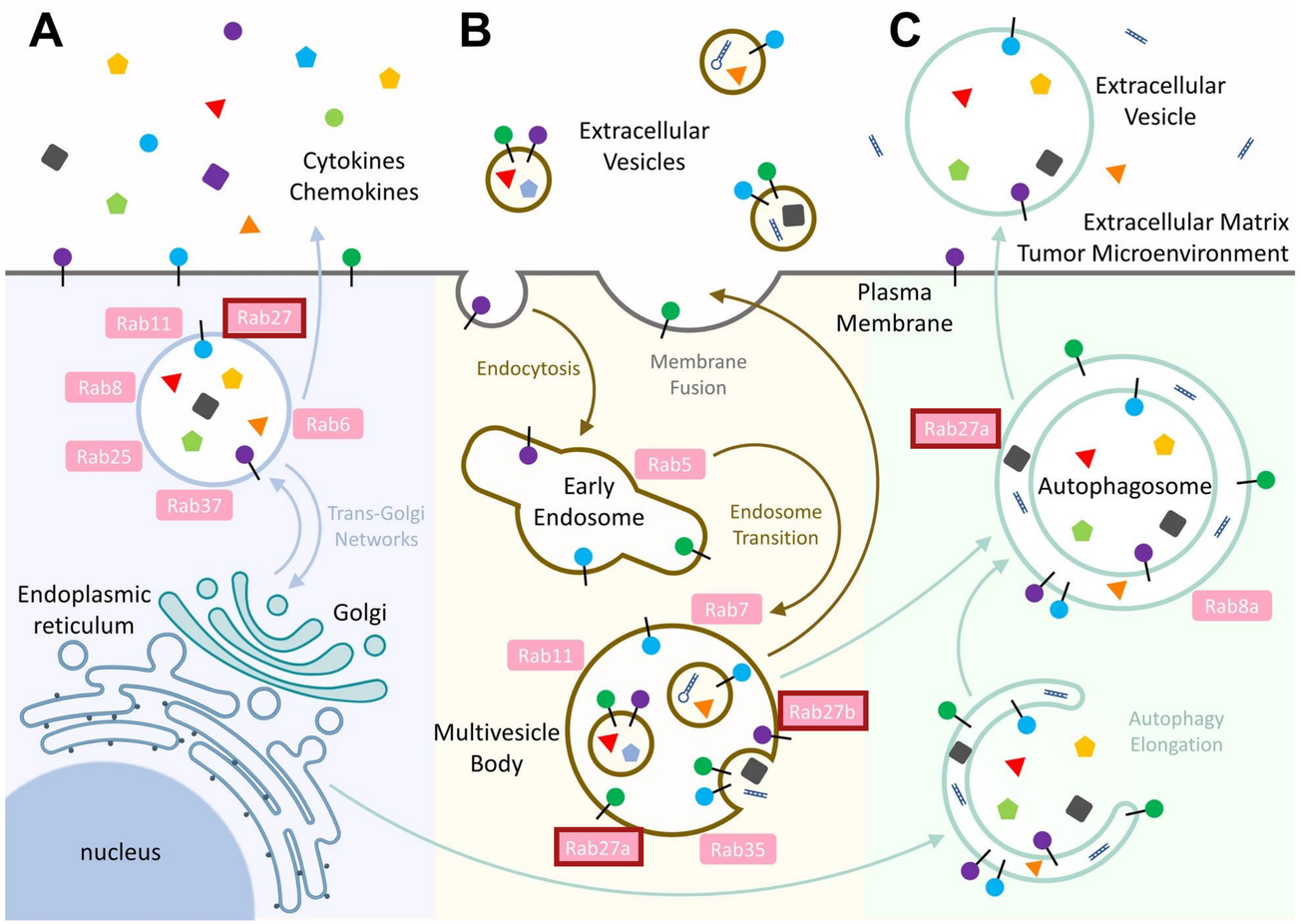
tmc_PRAD and its paralog are enriched in patient tissues



5 patients (GS 6-8)

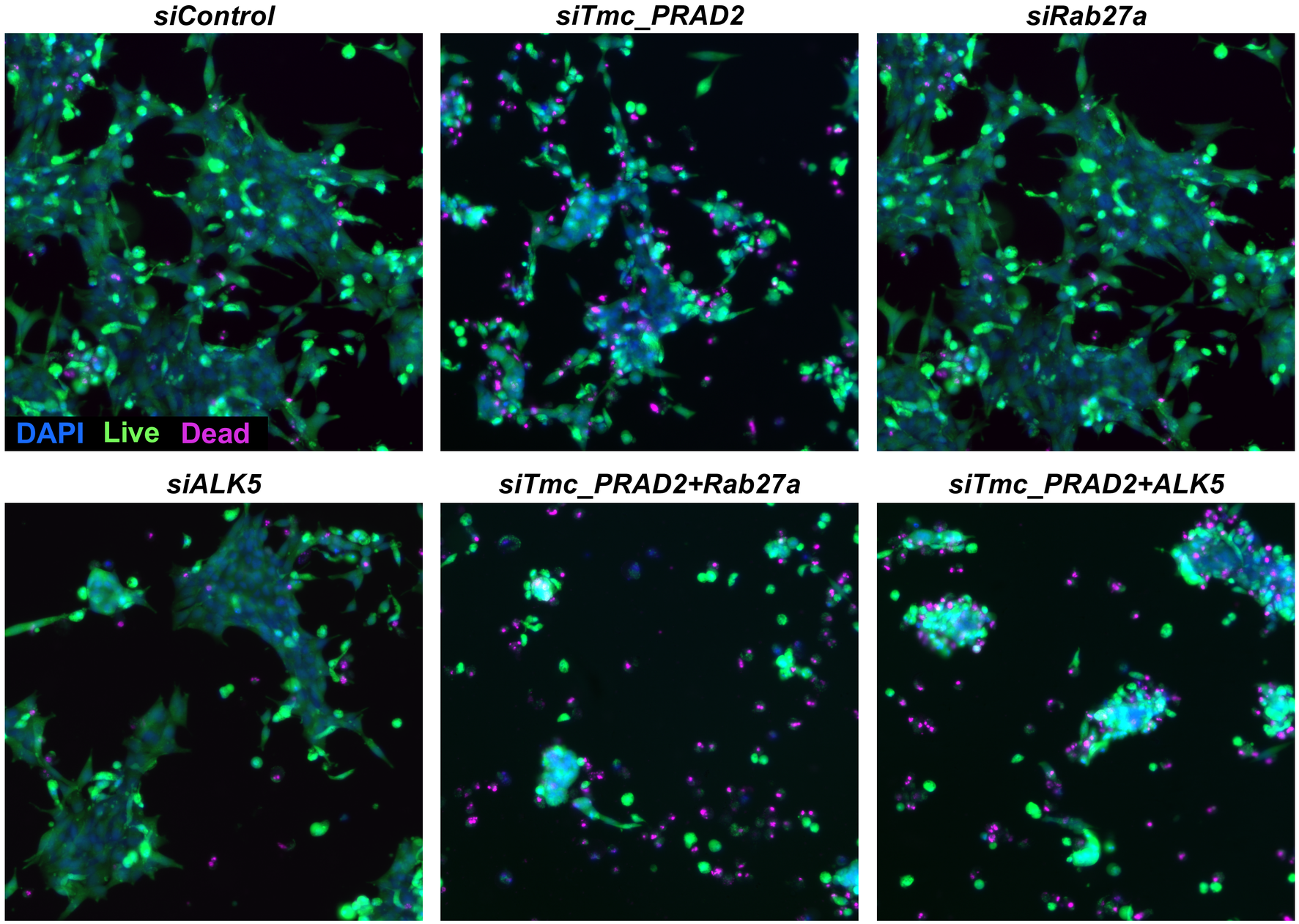
tmc_PRAD and its paralog are enriched in patient tissues

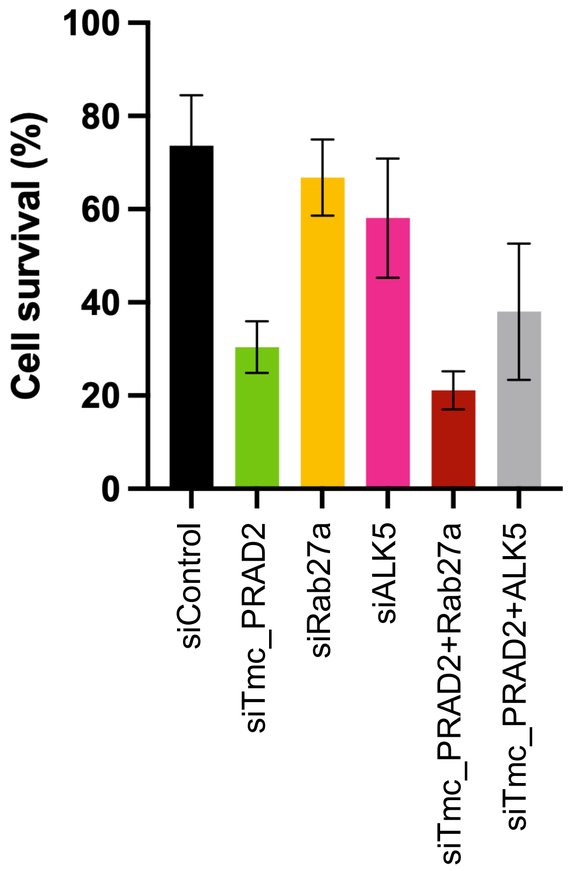




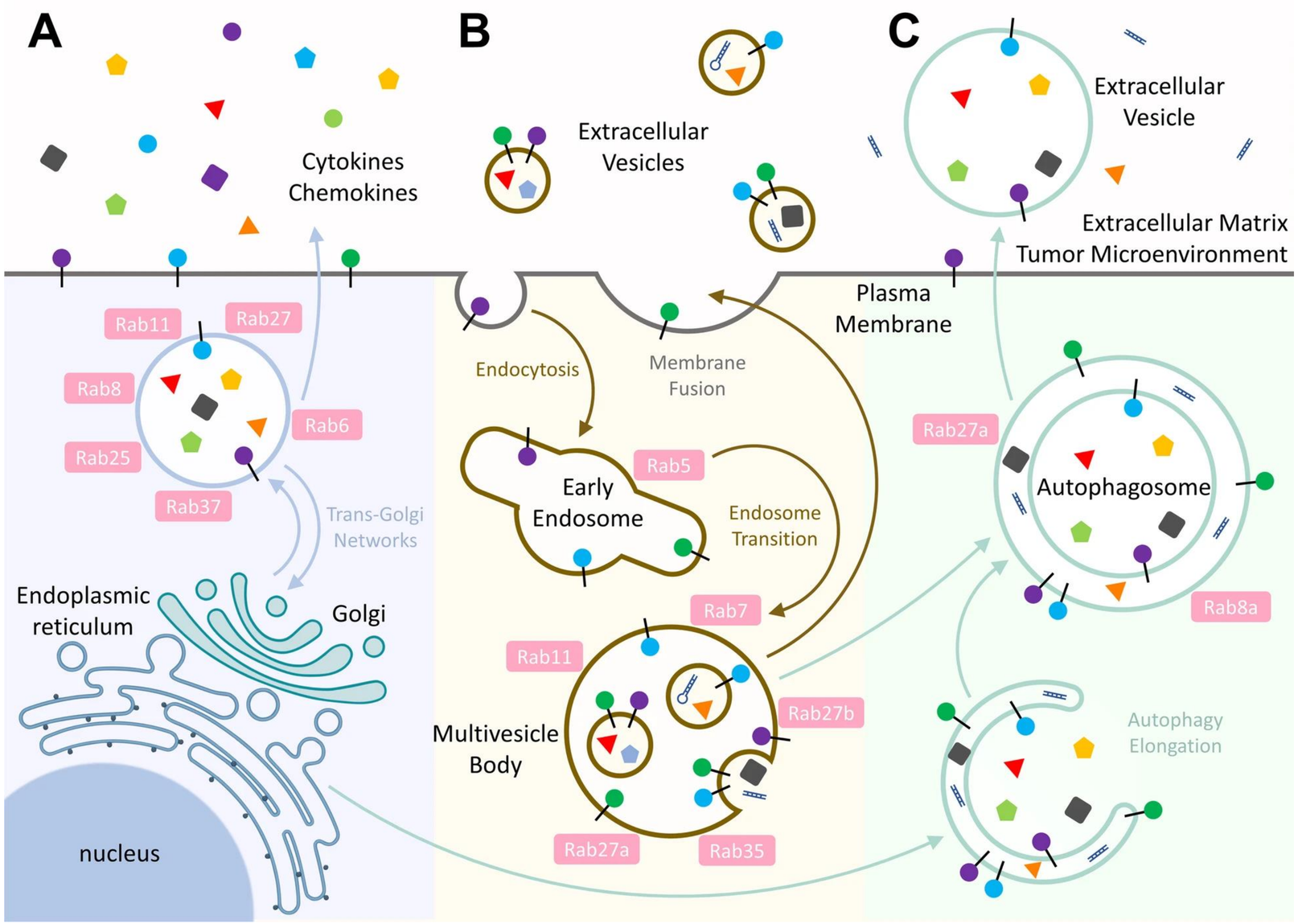
Kuo et al., JBS 2022

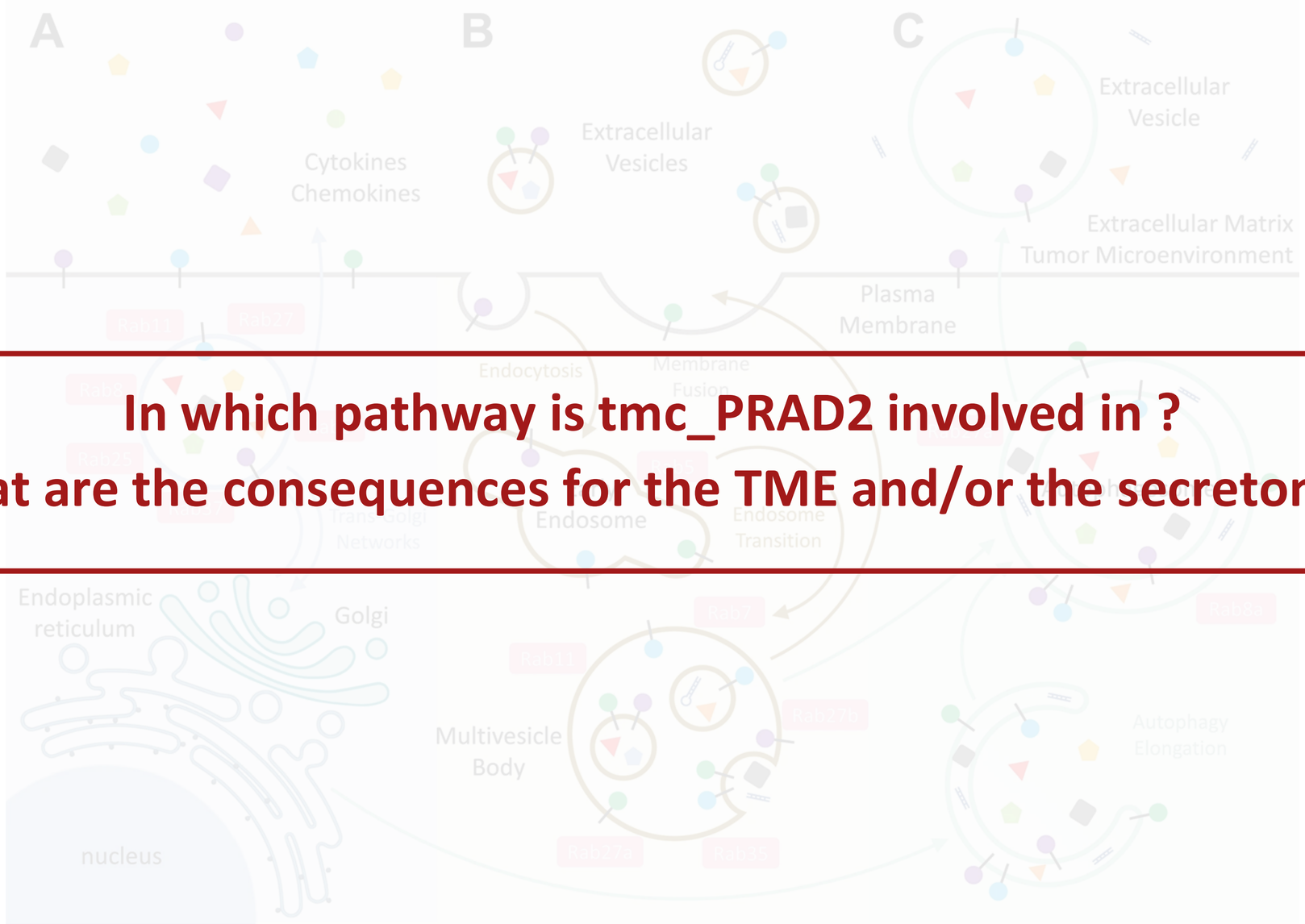
Inhibition of tmcPRAD2 leads to cancer cell death (RPMI 72h)





Overview of the secretory pathways





In which pathway is tmc_PRAD2 involved in ?

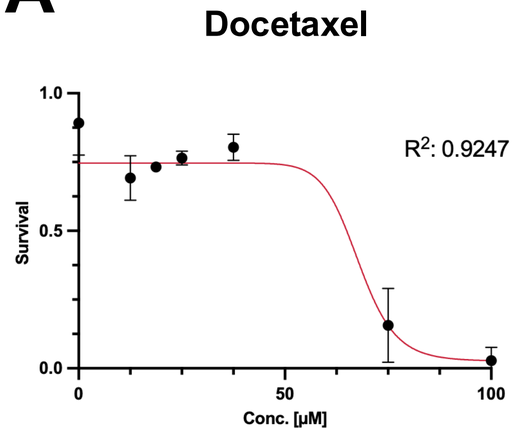
What are the consequences for the TME and/or the secretome ?

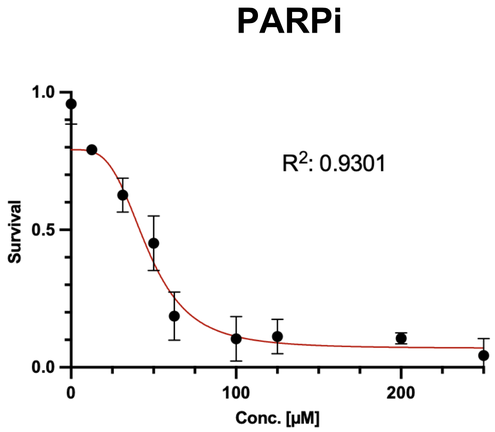
3

DRUG COMBINATIONS

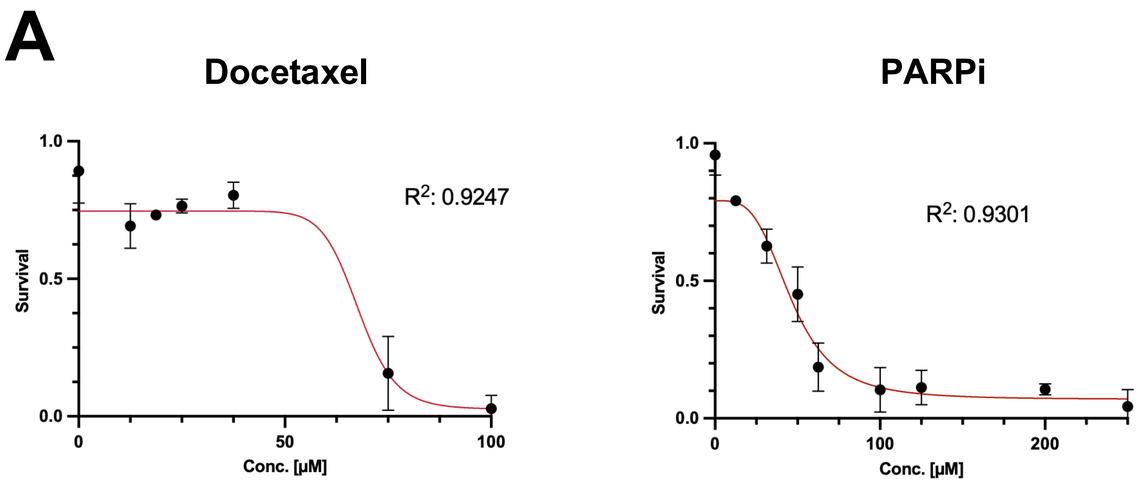
Chemotherapy shows synergistic effect with PARP inhibitor

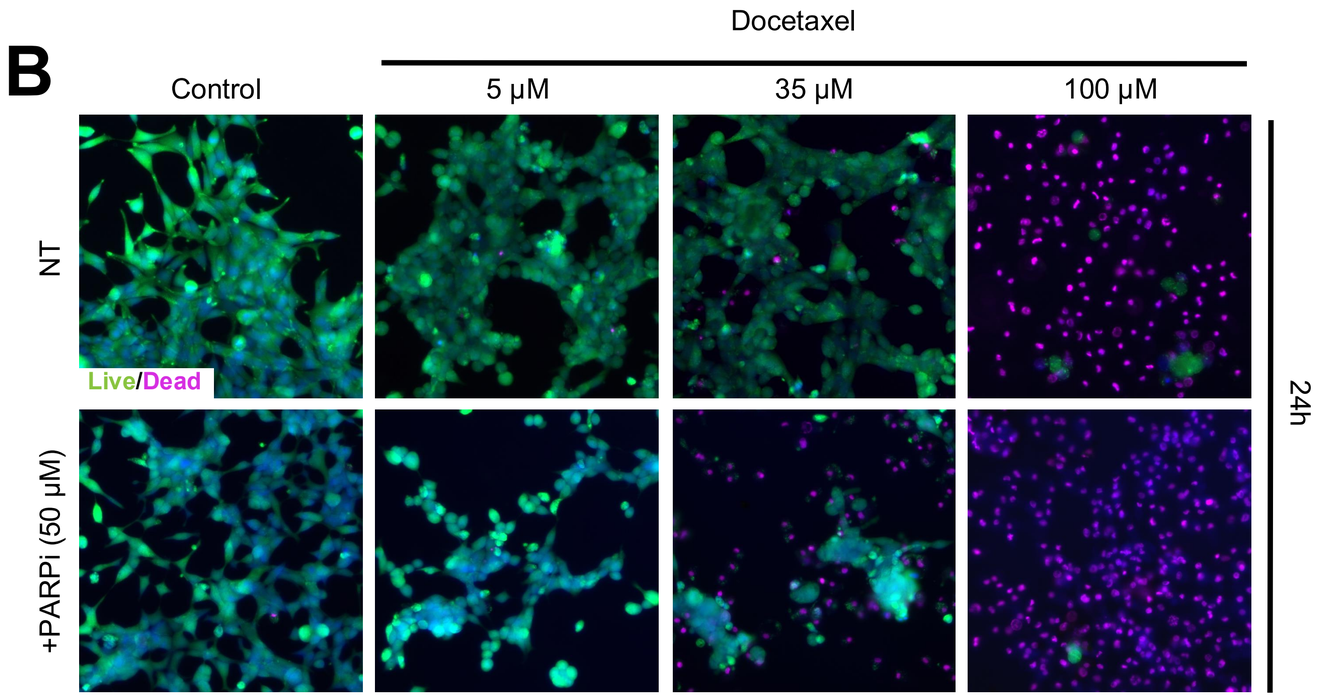
A

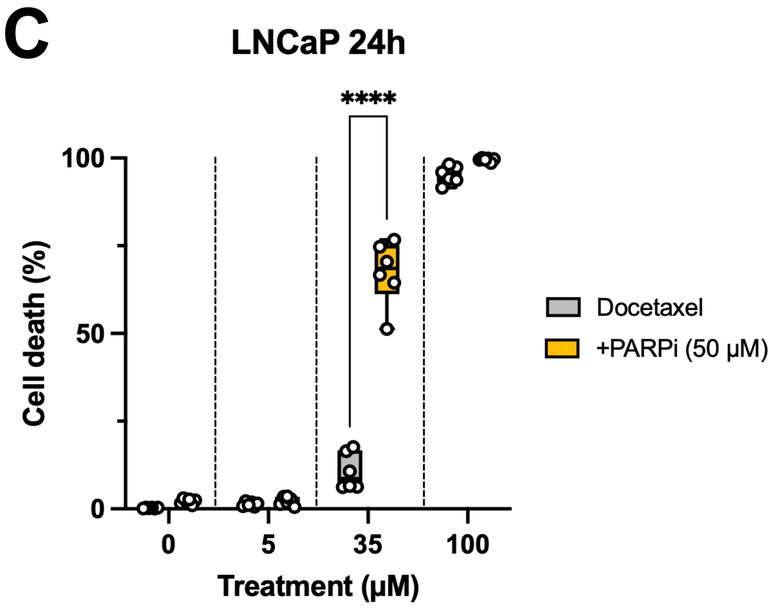




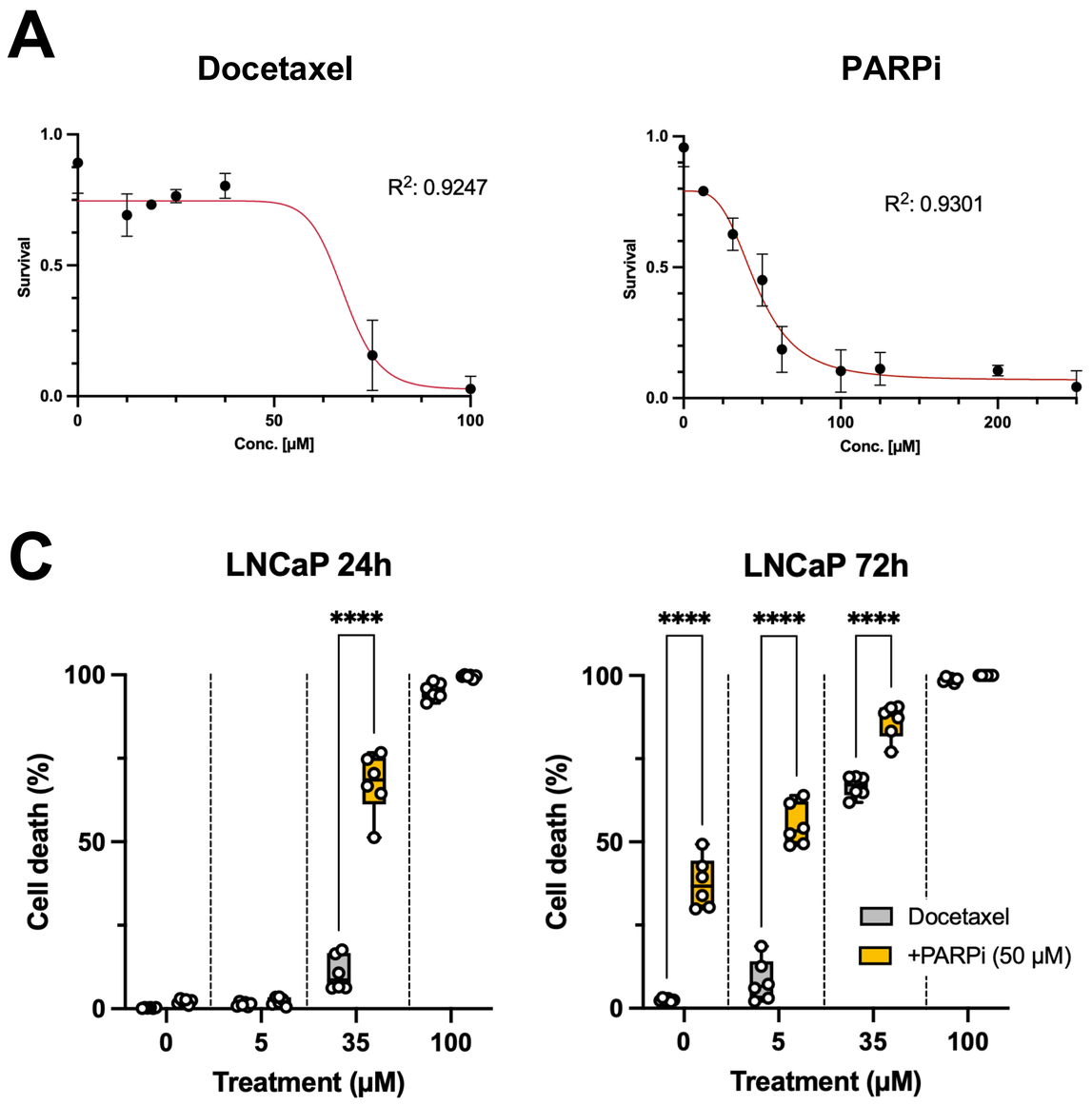
Chemotherapy shows synergistic effect with PARP inhibitor

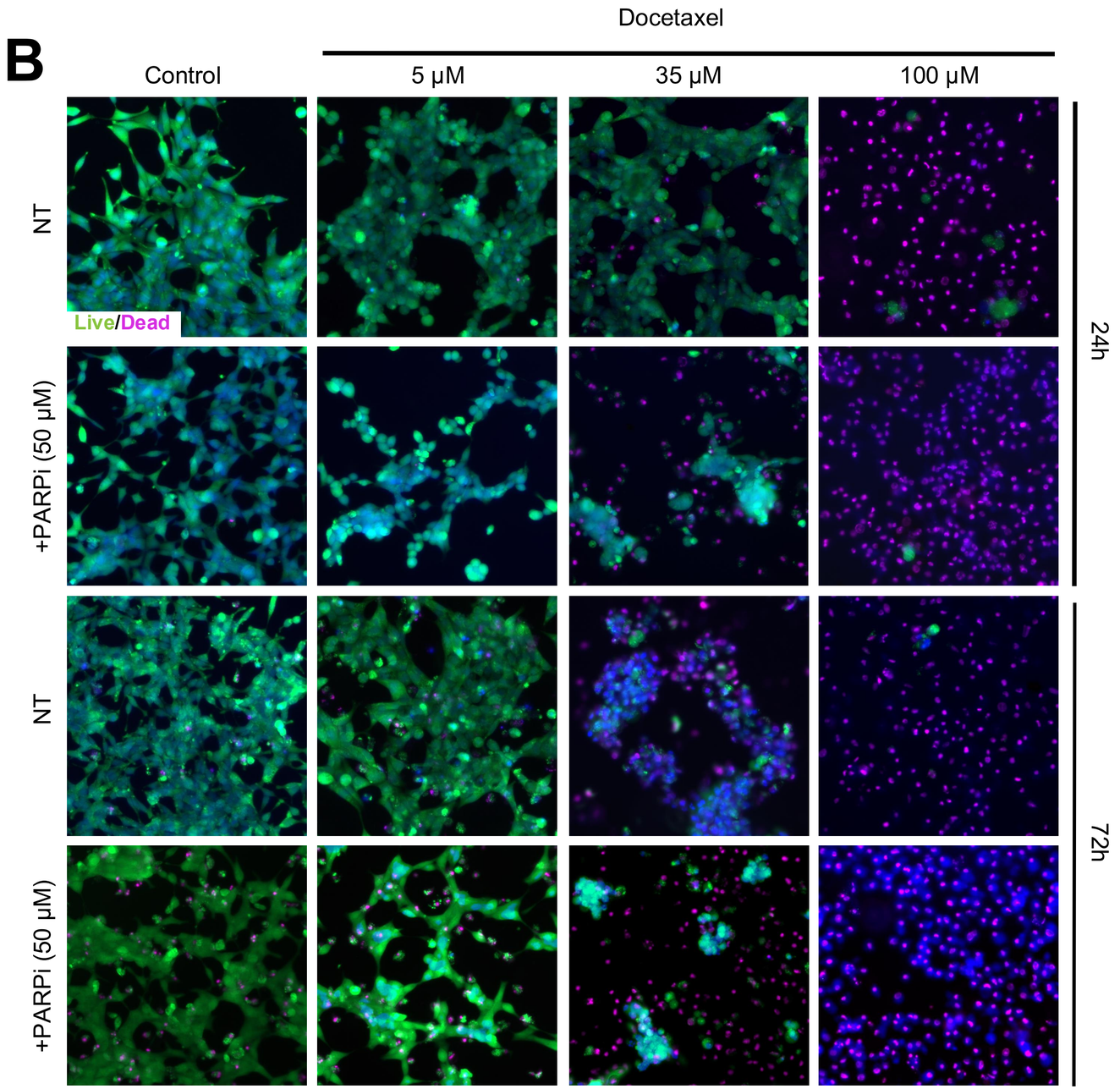




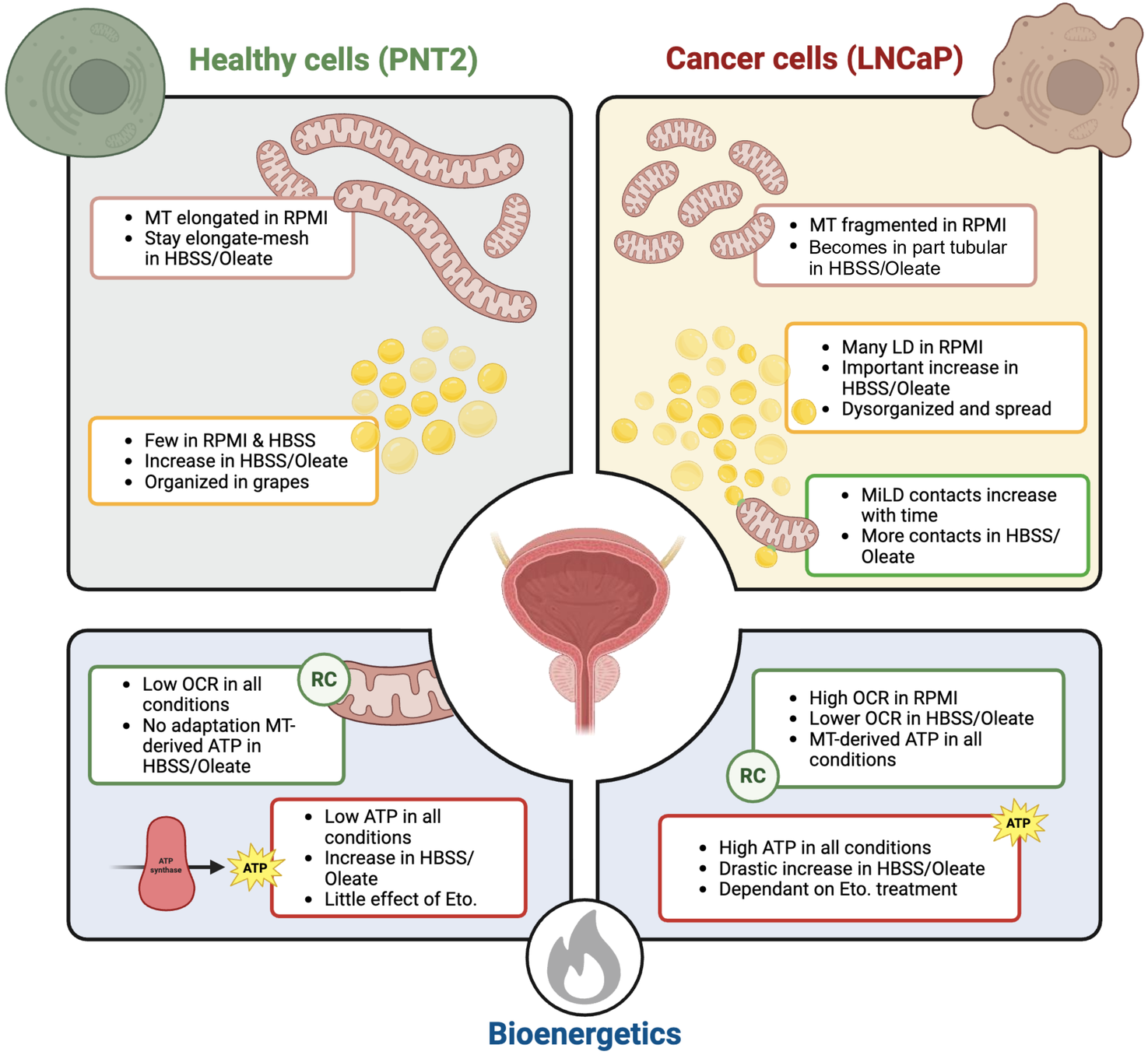


Chemotherapy shows synergistic effect with PARP inhibitor





Conclusions…



Acknowledgements

Team MCMO (UR3072)
Aaron Cohen (Post-doc)
Séléna FRAASS (M2 student)
Aikaterini Fefe (M1 student)
Katharina Lobsien (L3 French-german track)
Shania Lamahewage (L3 Erasmus - Warwick)
Laura Di-Renzo (L3 Erasmus - Montreal)

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Alizée Heith
… And all members from the UR3072

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CRBS

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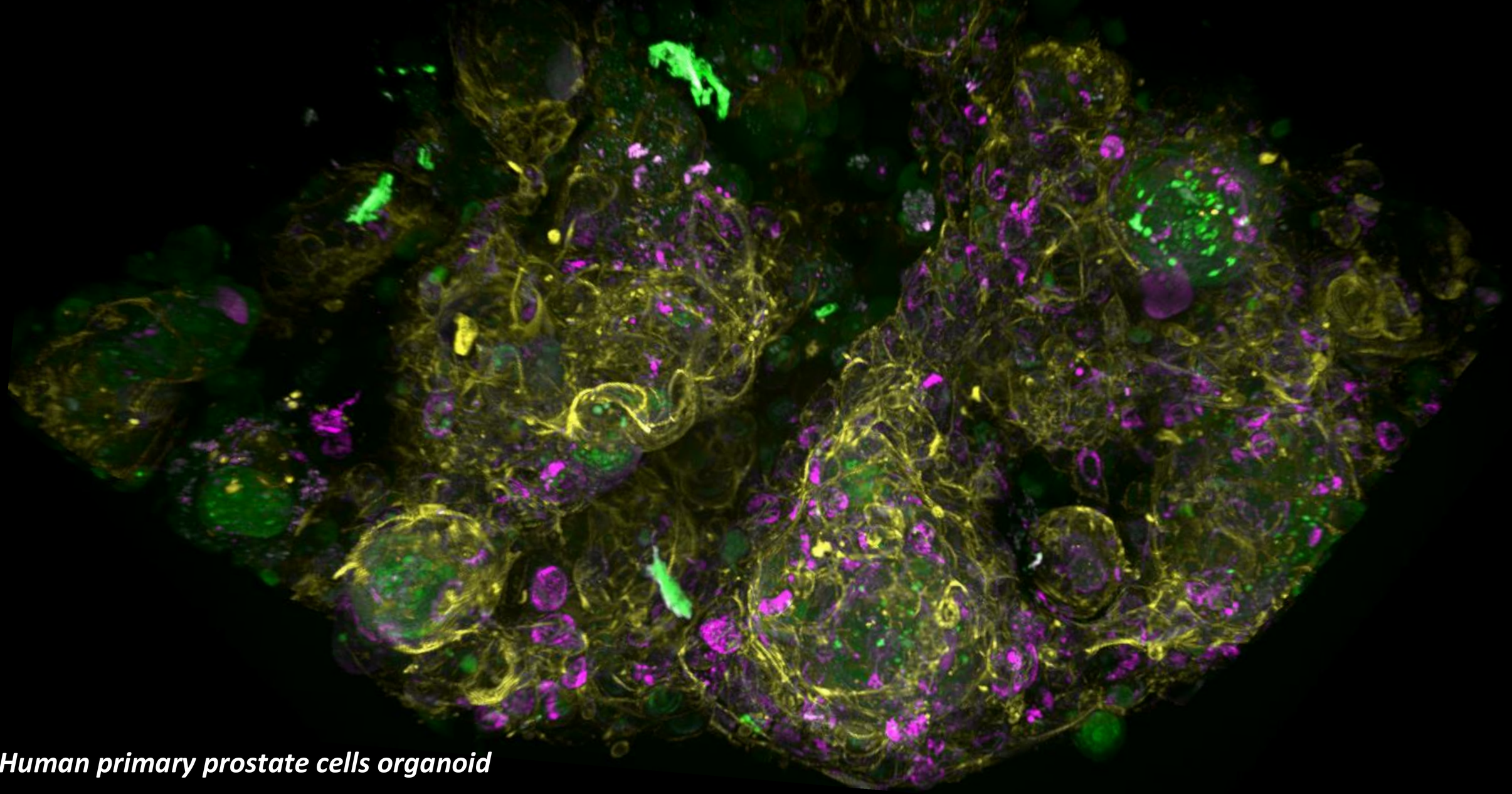
THANK YOU !



Human primary prostate cells organoid