



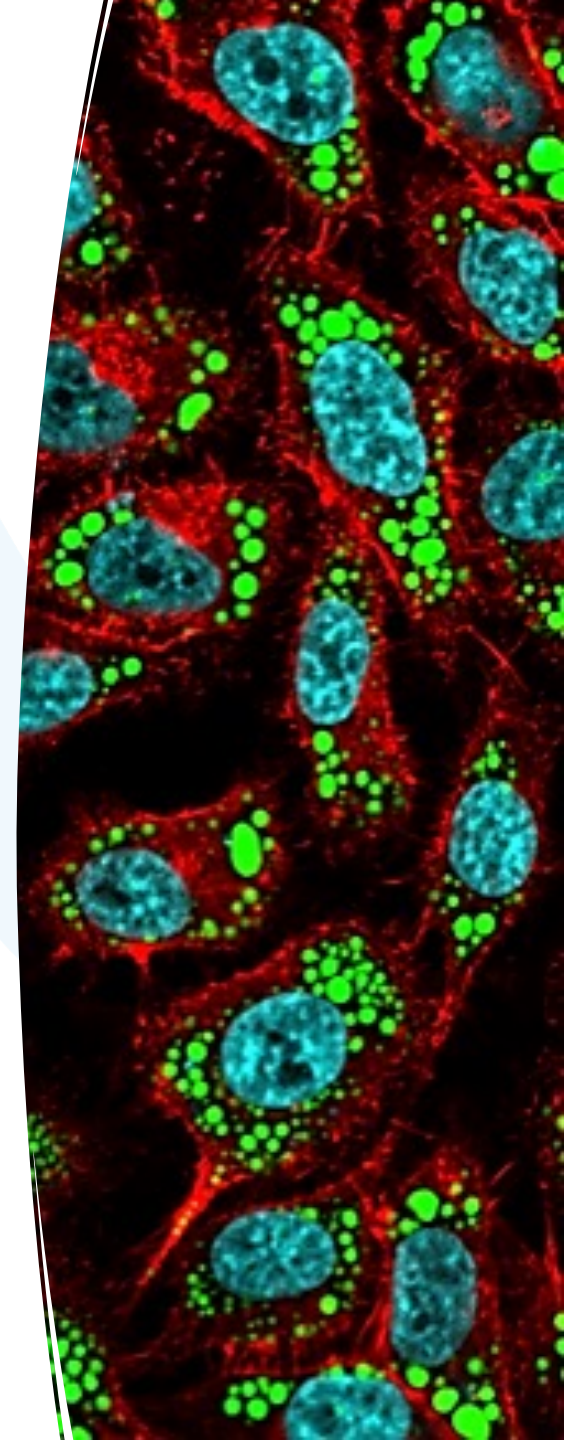
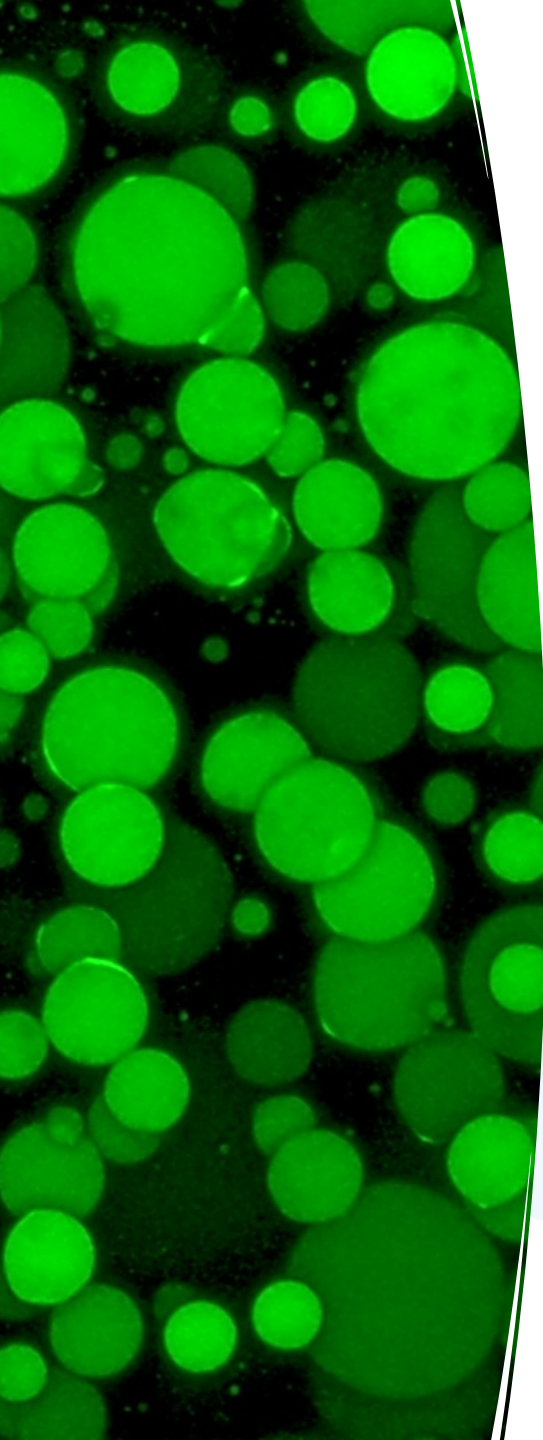
A metabolic crosstalk occurs between human bone marrow adipocytes and prostate cancer cells

Marine HERNANDEZ

3rd year PhD Student

Team: Microenvironment, Cancer and Adipocytes (Pr. Catherine MULLER)
Institute of Pharmacology and Structural Biology, Toulouse, FRANCE

Supervisor: Dr Camille ATTANÉ



Prostate cancer

1st Men cancer

3rd Cause of mortality by cancer in men



Diagnosis : 64 years old



Early stage cancer: 90% of survival,
curative treatments

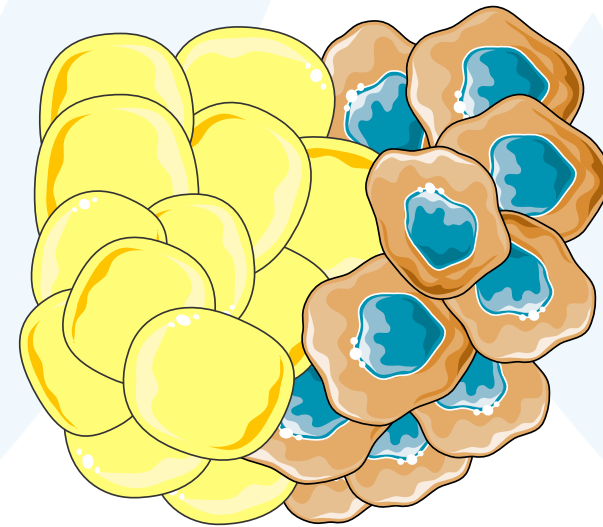
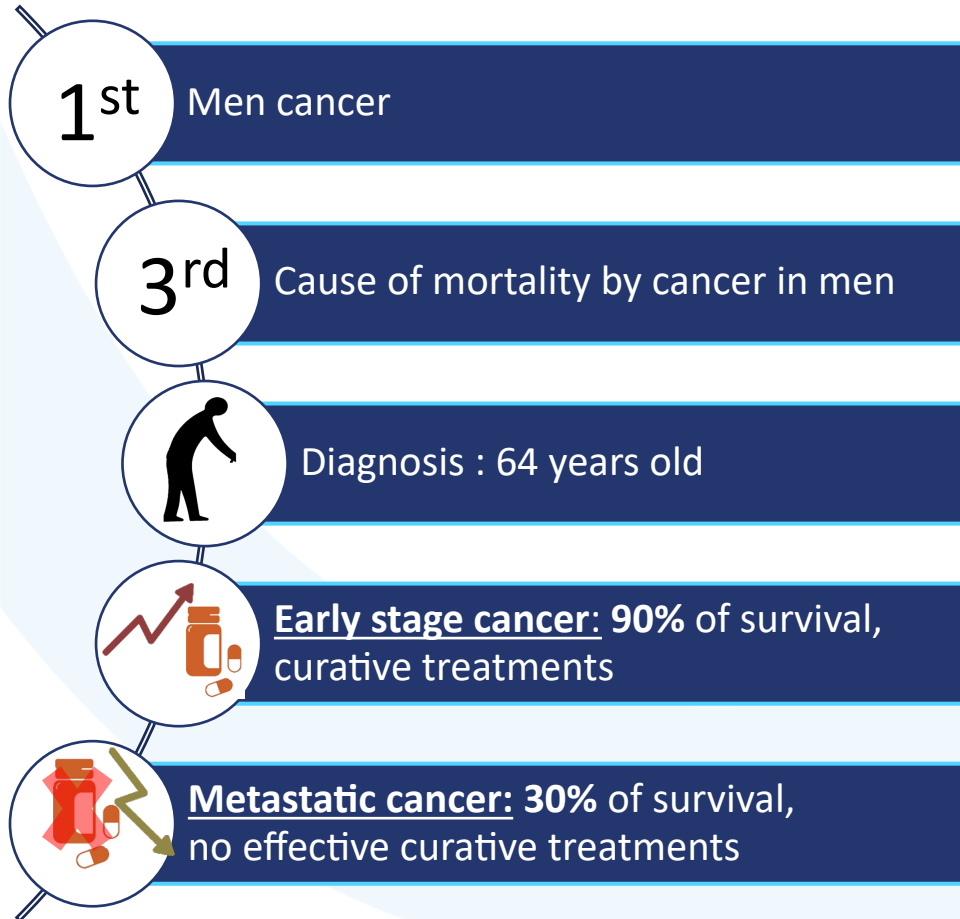


Metastatic cancer: 30% of survival,
no effective curative treatments

INCa, 2023

Siegel et al, *A Cancer Journal for Clinicians*, 2022

Prostate cancer and adipocytes



Adipocytes Cancer cells

**TUMOR
PROGRESSION**

INCa, 2023

Siegel et al, *A Cancer Journal for Clinicians*, 2022

Nieman et al, *Nature Medicine*, 2011

Wang et al, *JCI Insight*, 2017

Laurent et al, *Molecular Cancer Research*, 2019

Clement et al, *The EMBO Journal*, 2020

Prostate cancer and adipocytes

1st Men cancer

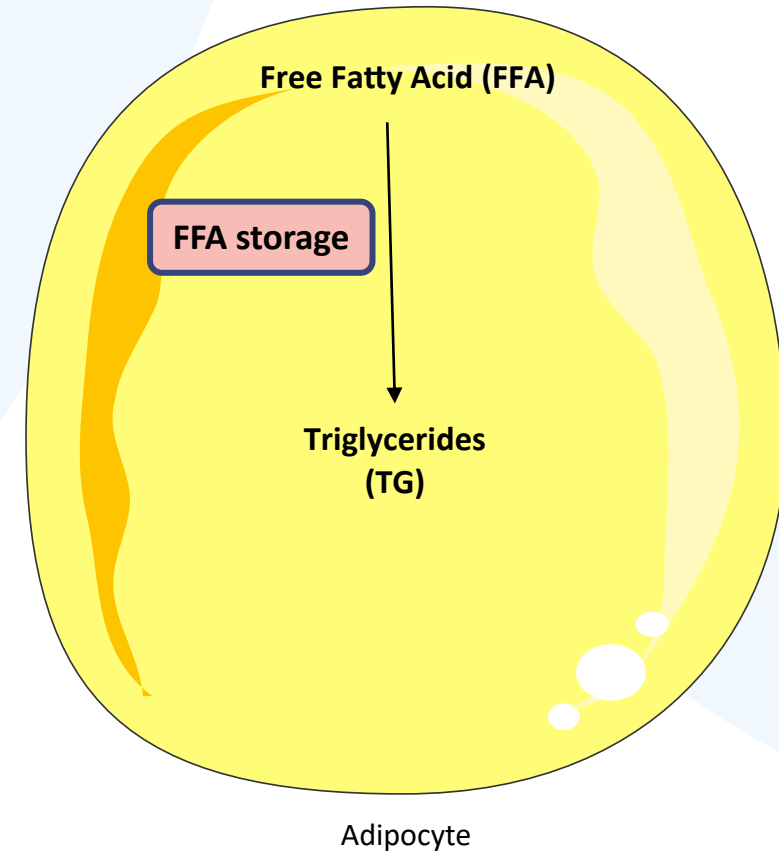
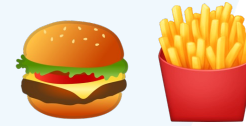
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Metabolic function



INCa, 2023

Siegel et al, *A Cancer Journal for Clinicians*, 2022

Church et al, *Adipocyte*, 2012

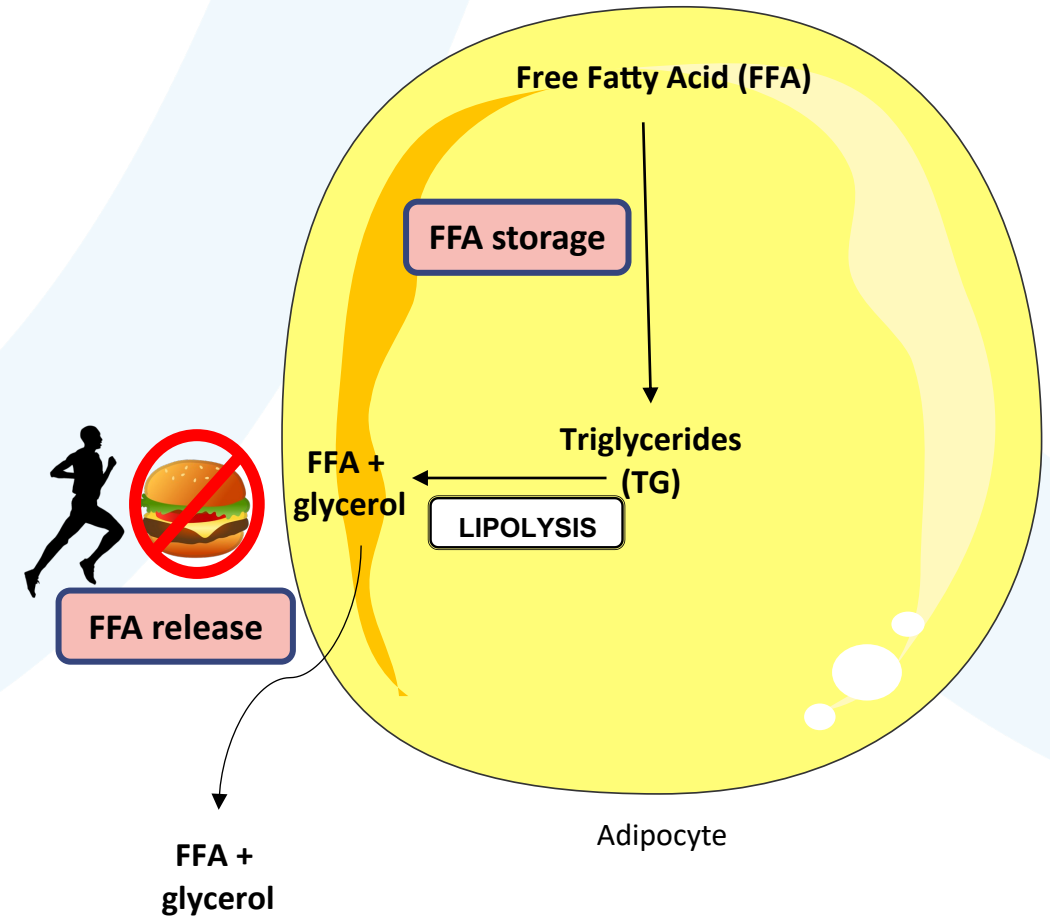
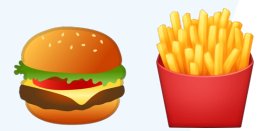
Laurent et al, *Medecine Sciences*, 2014

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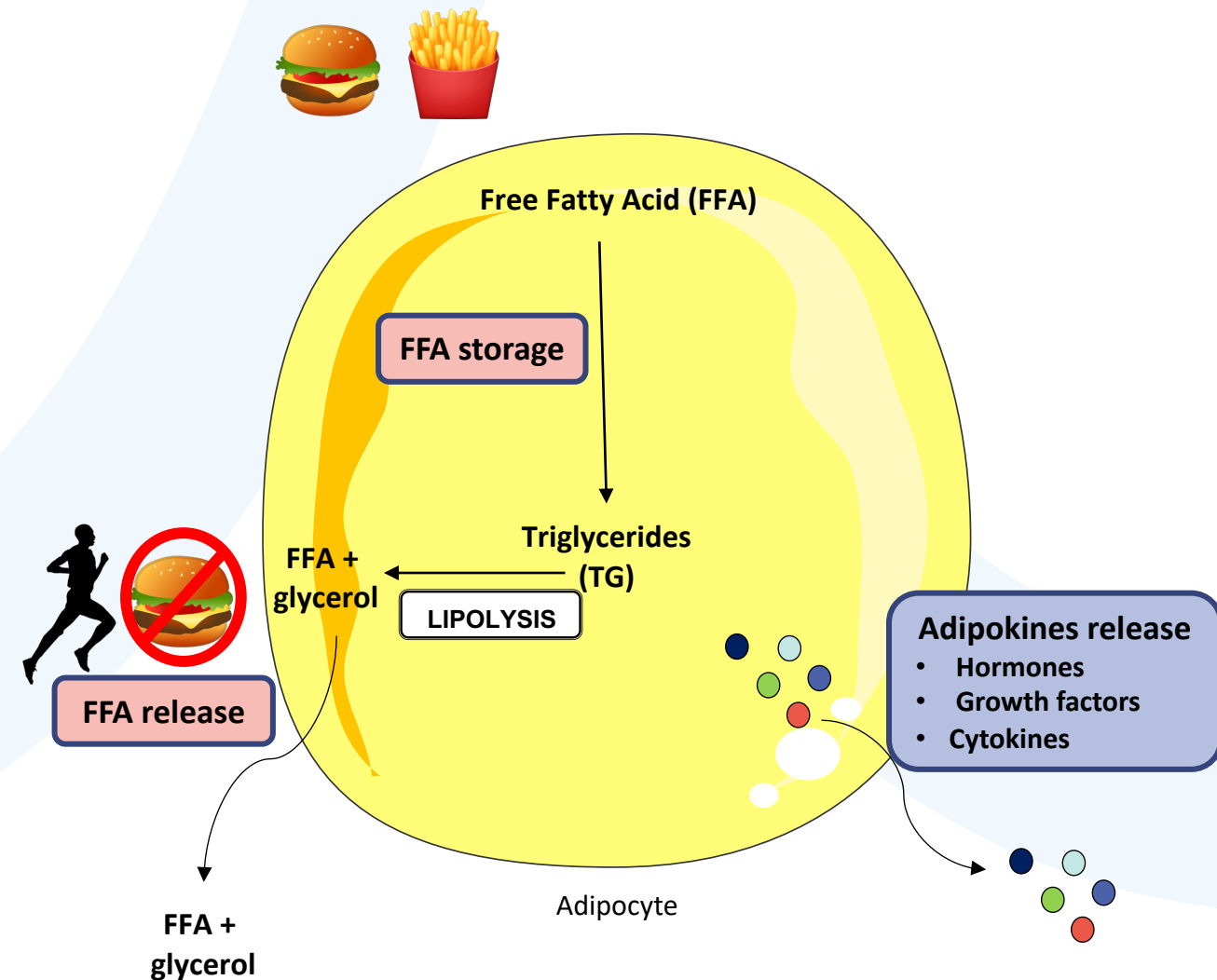


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Prostate cancer and adipocytes

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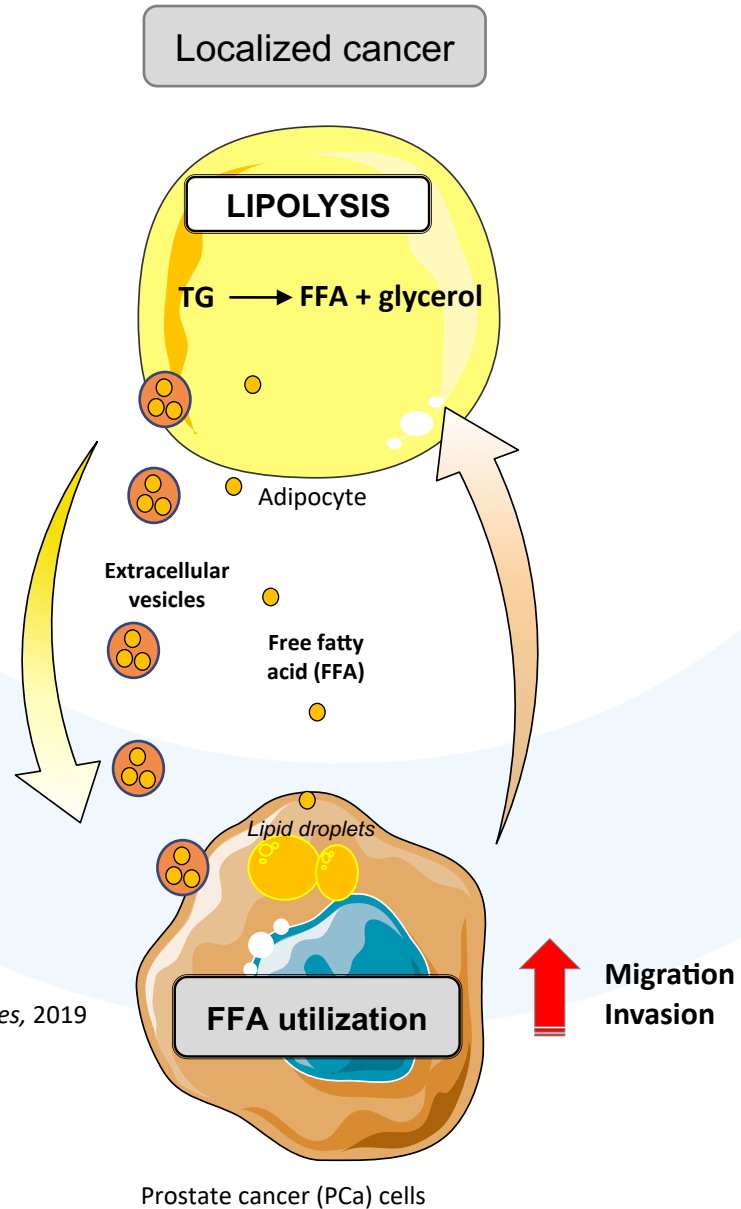
Metabolic function Endocrine function



INCa, 2023
 Siegel et al, *A Cancer Journal for Clinicians*, 2022

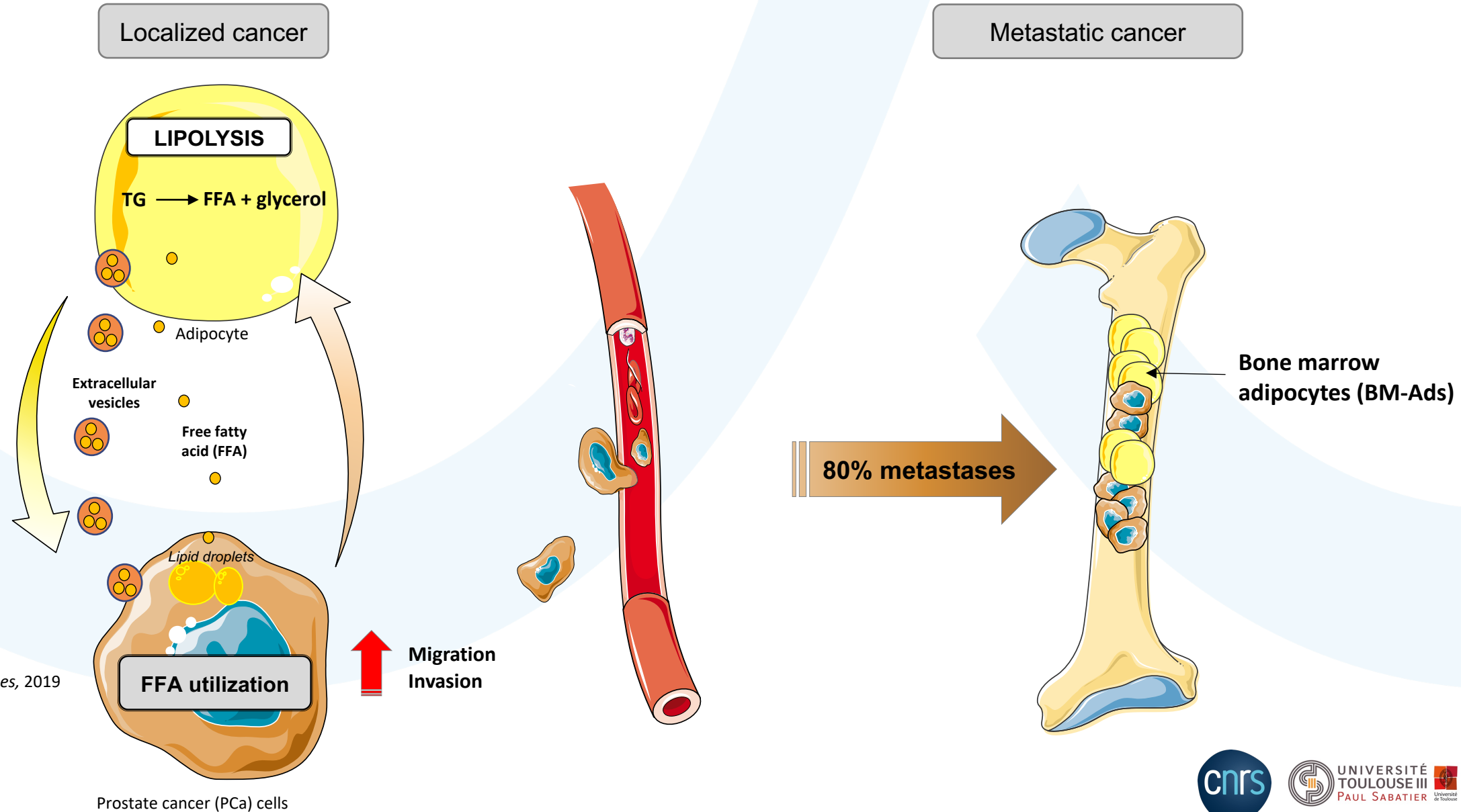
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Metabolic crosstalk between PCa cells and adipocytes at primary tumor site



Laurent et al, *Mol Cancer Res*, 2019

Metabolic crosstalk between PCa cells and adipocytes at primary tumor site

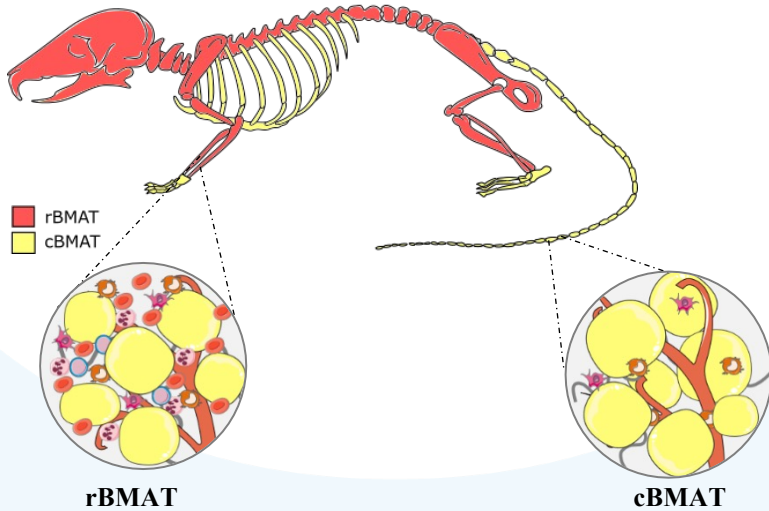


Laurent et al, *Mol Cancer Res*, 2019

Prostate cancer (PCa) cells

Bone: an adipocyte rich organ

- 2 types of BMAT characterized in rodents: **regulatory bone marrow adipose tissue (rBMAT) in red BM** and **constitutive BMAT (cBMAT) in yellow BM** with specific properties.

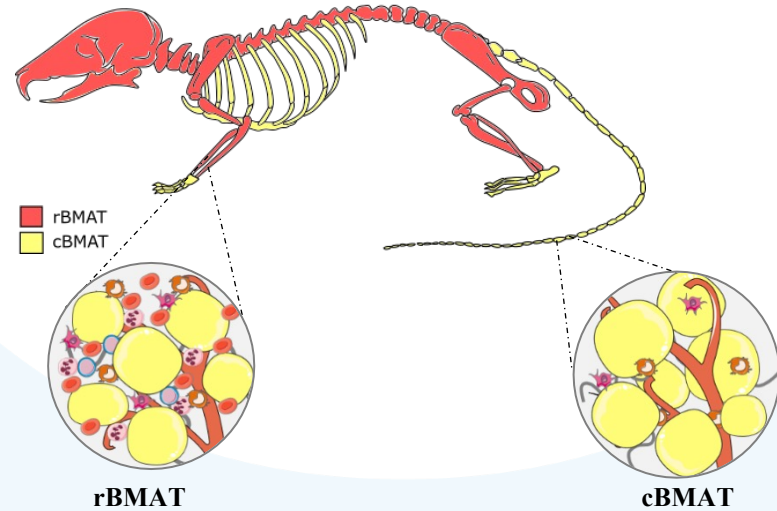


- Develop later
- Contain more saturated lipids
- Decreased size of BMAd with acute fasting, exercise and cold exposure

- Develop first
- Contain more unsaturated lipids
- No effect of fasting, exercise and cold exposure on BMAd size

Bone: an adipocyte rich organ

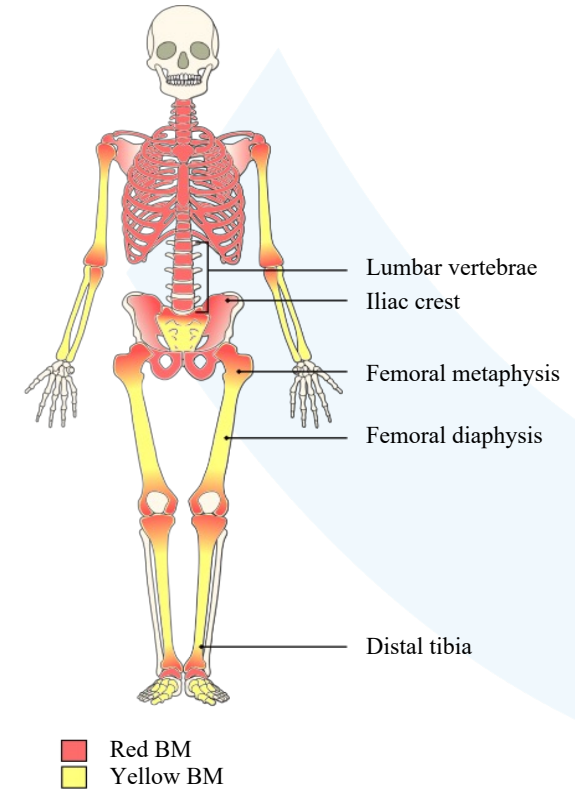
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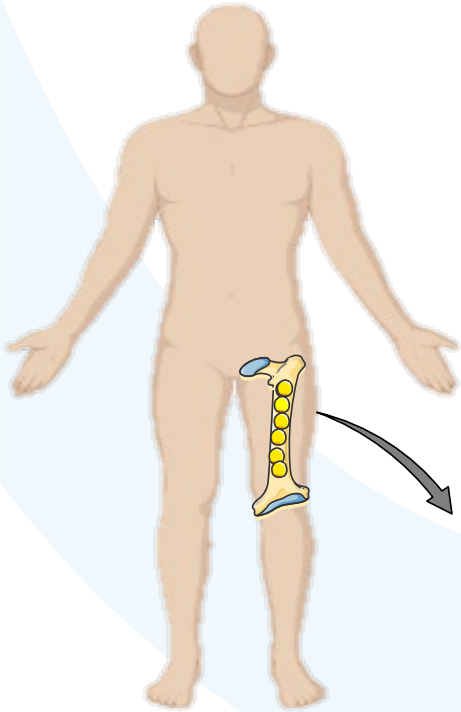
- Develop first
- Contain more unsaturated lipids
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- **Red BM** and **yellow BM** seems to be present in humans but no identification of these 2 types of BM-Ads.



Bone: an adipocyte rich organ with specific metabolism

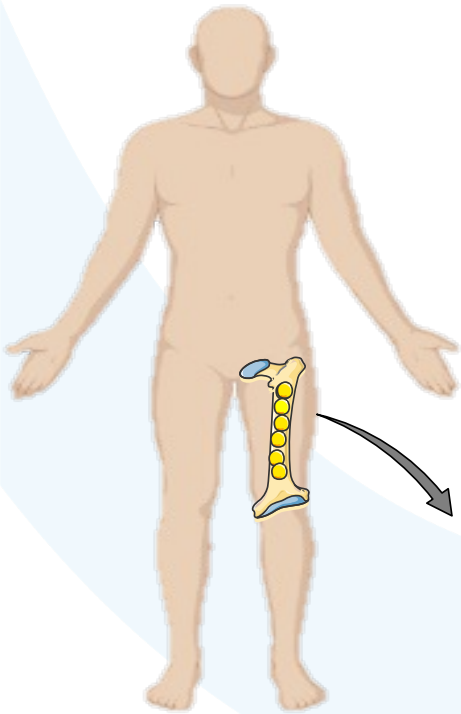
■  ■
Hospitaux de Toulouse
■ ■
Pr. Nicolas Reina



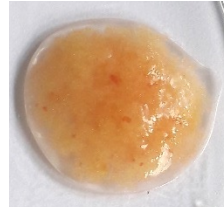
Bone marrow

Bone: an adipocyte rich organ with specific metabolism

Hôpitaux de Toulouse
Pr. Nicolas Reina

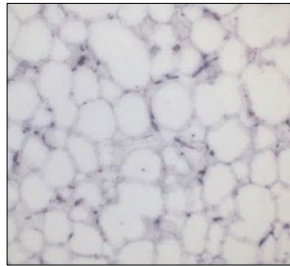


Bone marrow



Yellow-BMAT

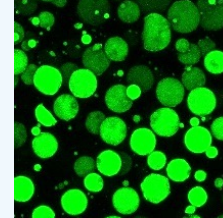
Attané et al, *Star Protocols*, 2021



Digestion



Yellow BM-Ads

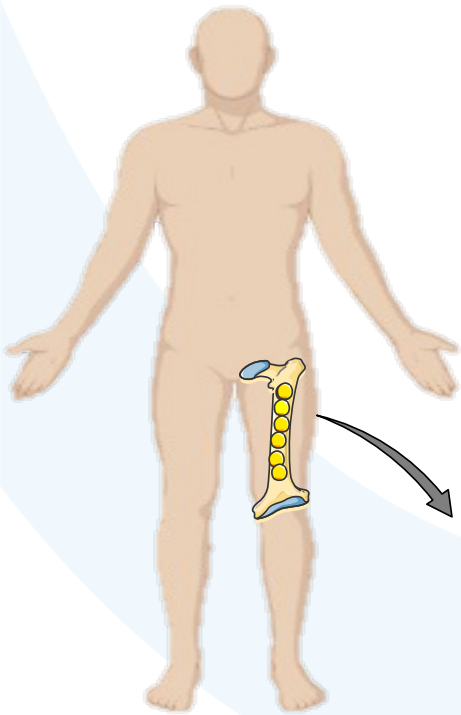


- Cohesive cells
- No lipolysis activity
- Cholesterol oriented metabolism

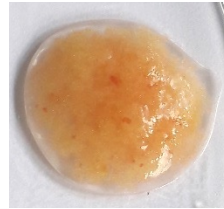
Attané et al, *Cell Reports*, 2020

Bone: an adipocyte rich organ with specific metabolism

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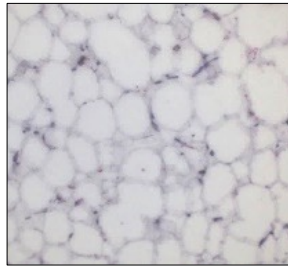


Bone marrow



Yellow-BMAT

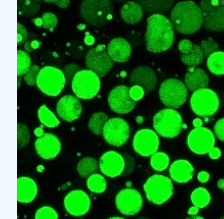
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Digestion

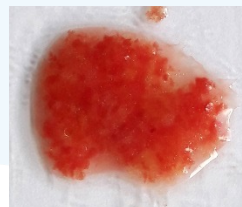


Yellow BM-Ads

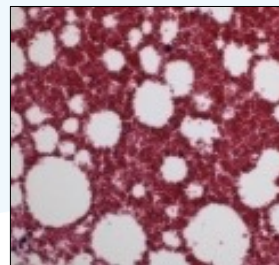


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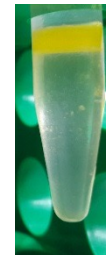
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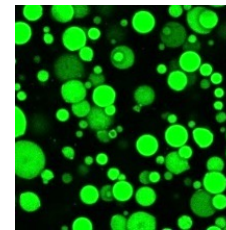
Red-BMAT



Digestion



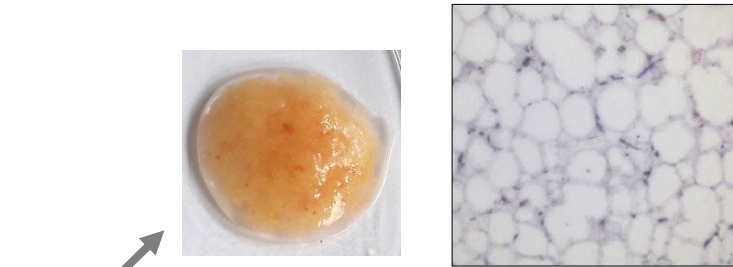
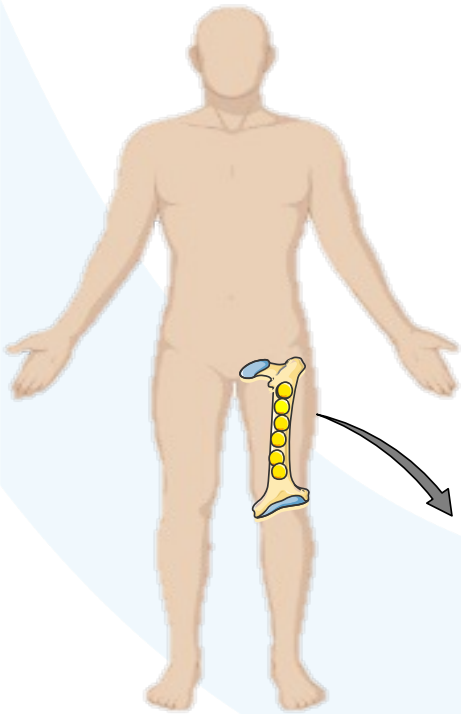
Red BM-Ads



- Less cohesive cells
- Surrounded by hematopoietic cells
- Similar morphology of yBM-Ads but smaller

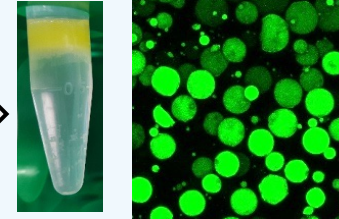
Bone: an adipocyte rich organ with specific metabolism

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Pr. Nicolas Reina



Yellow-BMAT
Attané et al, *Star Protocols*, 2021

Digestion



Yellow BM-Ads

- Cohesive cells
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Bone marrow



Red-BMAT

Red BM-Ads

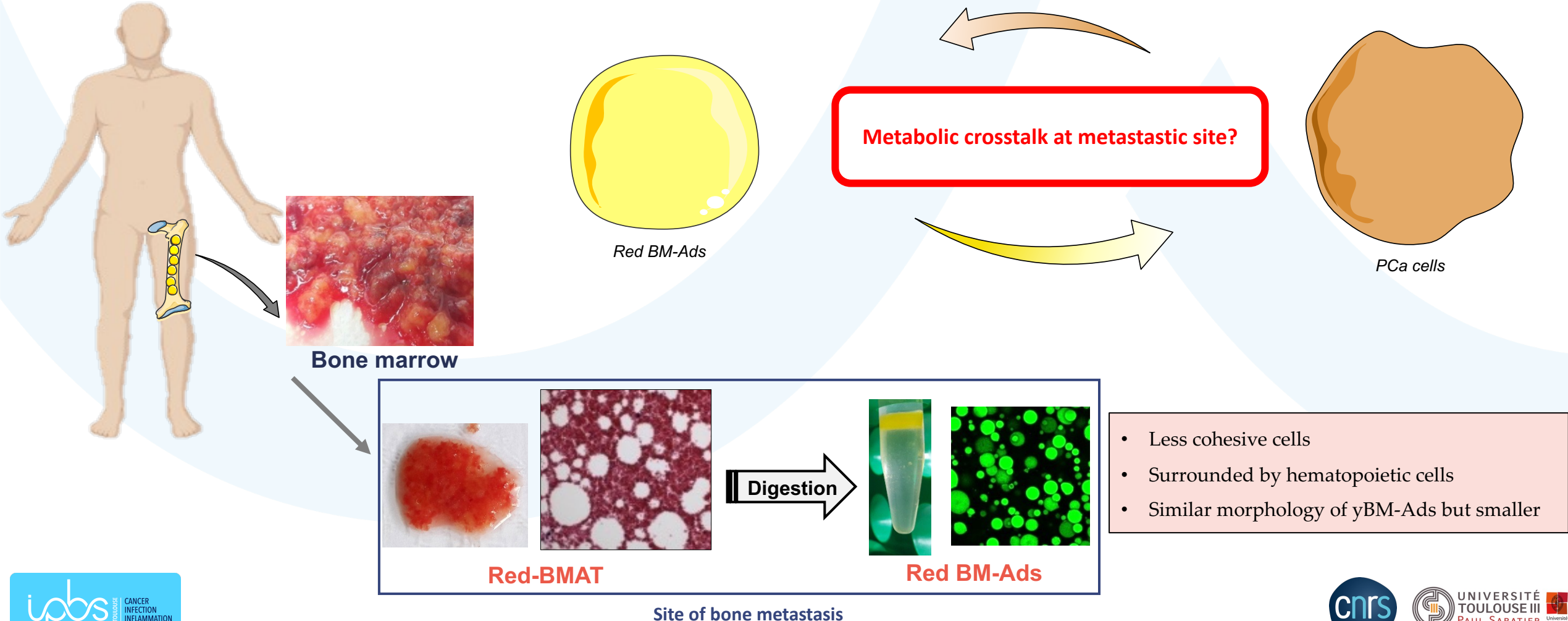
Digestion

- Less cohesive cells
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Site of bone metastasis

Bone: an adipocyte rich organ with specific metabolism

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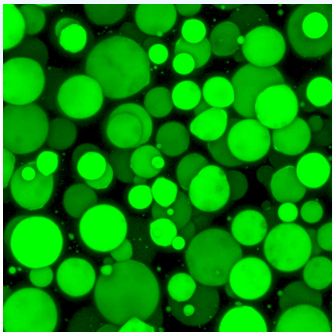
Development of 3D model to maintain human red BM-Ads over time



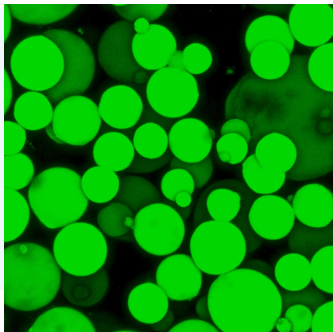
Isolation of **red BM-Ads** suspension

Inclusion of **red BM-Ads** in fibrin gel

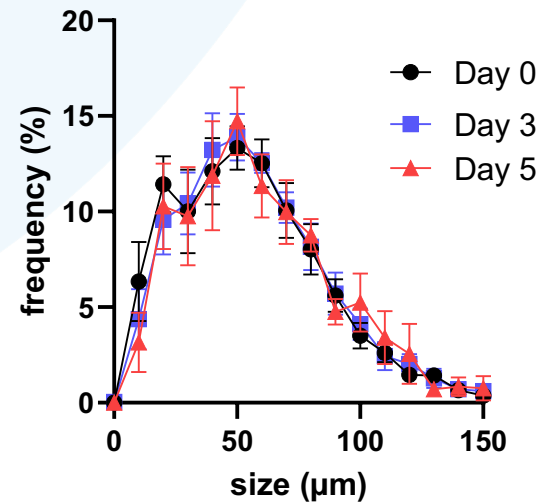
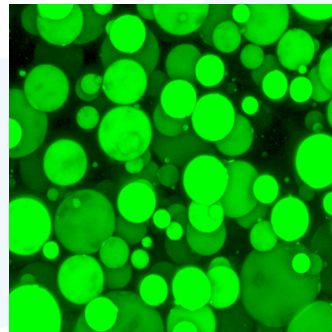
Day 0



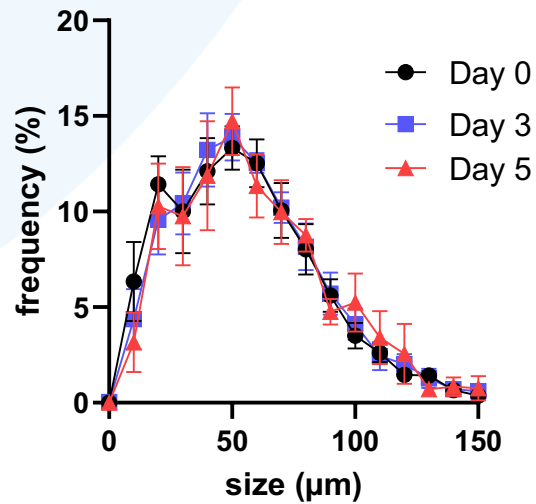
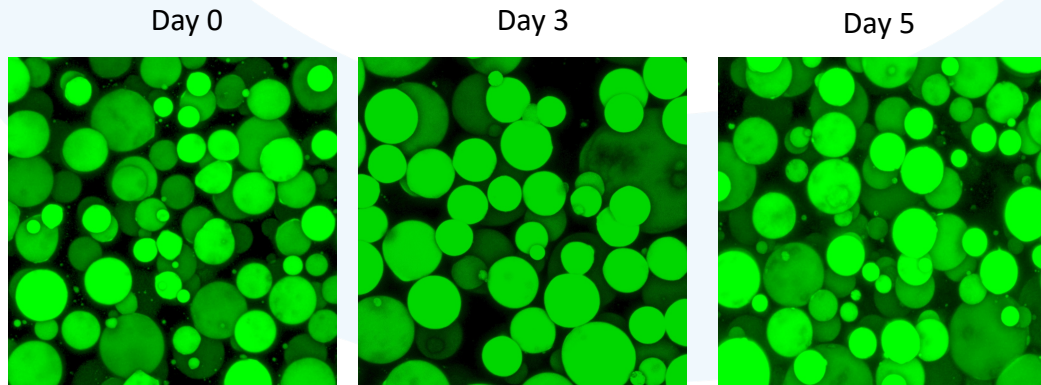
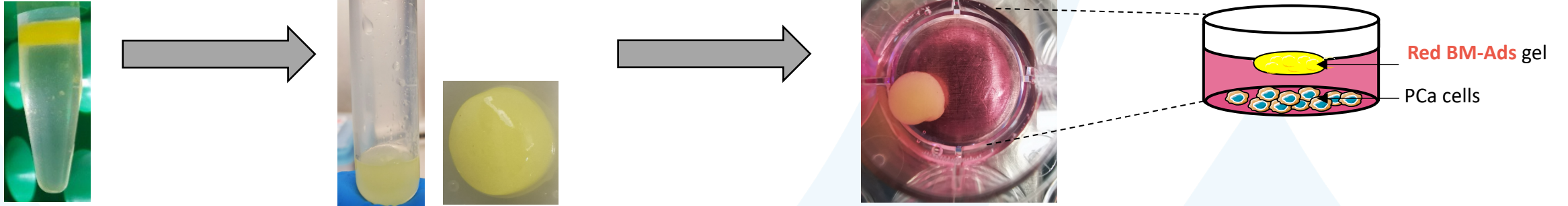
Day 3



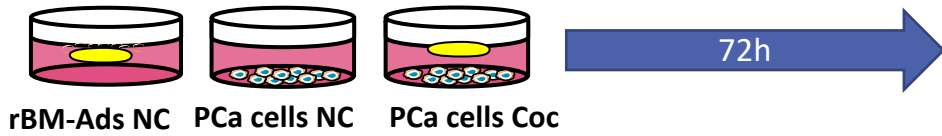
Day 5



Development of 3D model to maintain human red BM-Ads over time



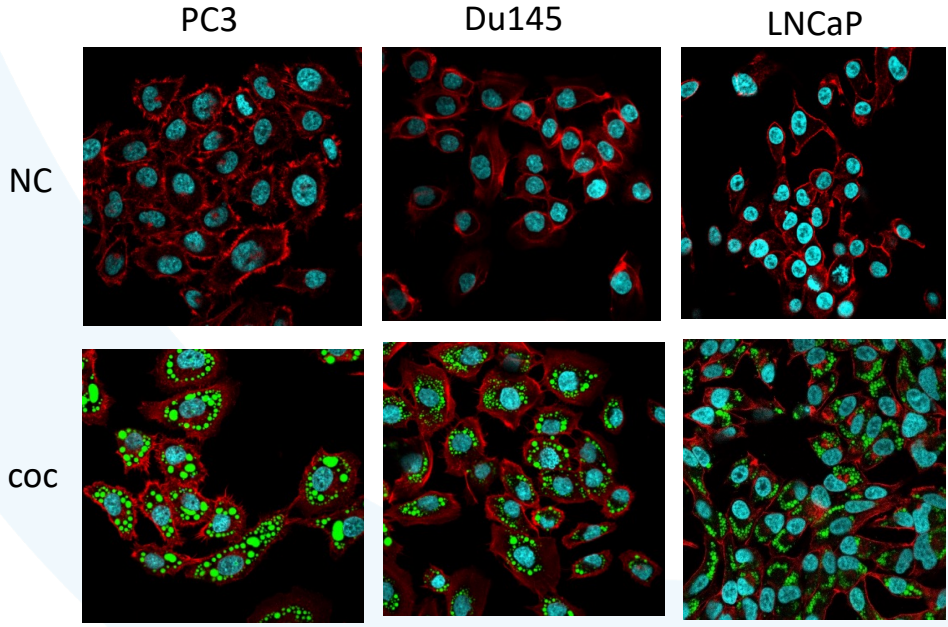
Cocultivated PCa cells accumulate neutral lipids



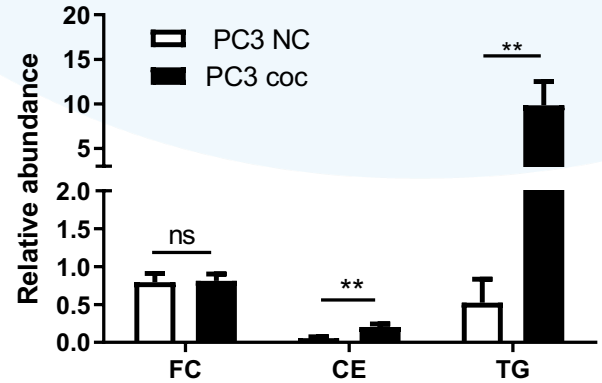
Microscopy and Lipidomic analyses



PC3: bone metastatic PCa cell line
Du145: brain metastatic Pca cell line
LNCaP: lymph node metastatic PCa cell line

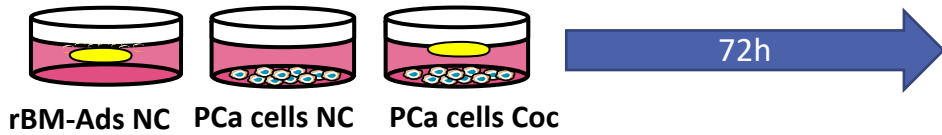


Dapi
 Rhodamin-phalloidin
 Bodipy: neutral lipids



FC: Free cholesterol
 TG: Triglycerides
 CE: Cholesterol ester

Cocultivated PCa cells accumulate neutral lipids



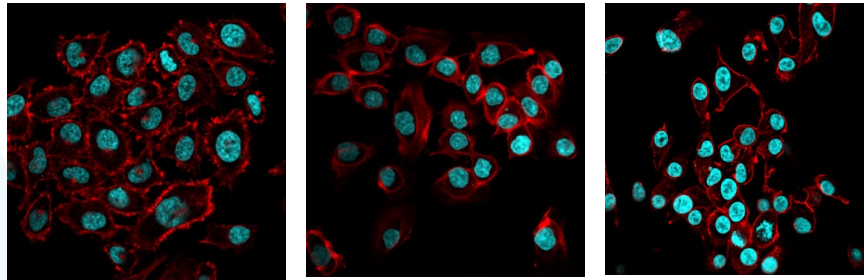
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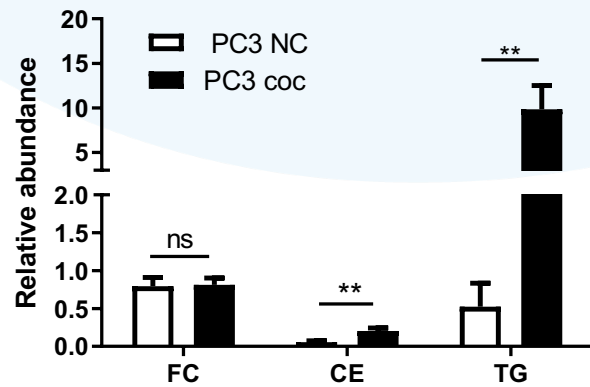
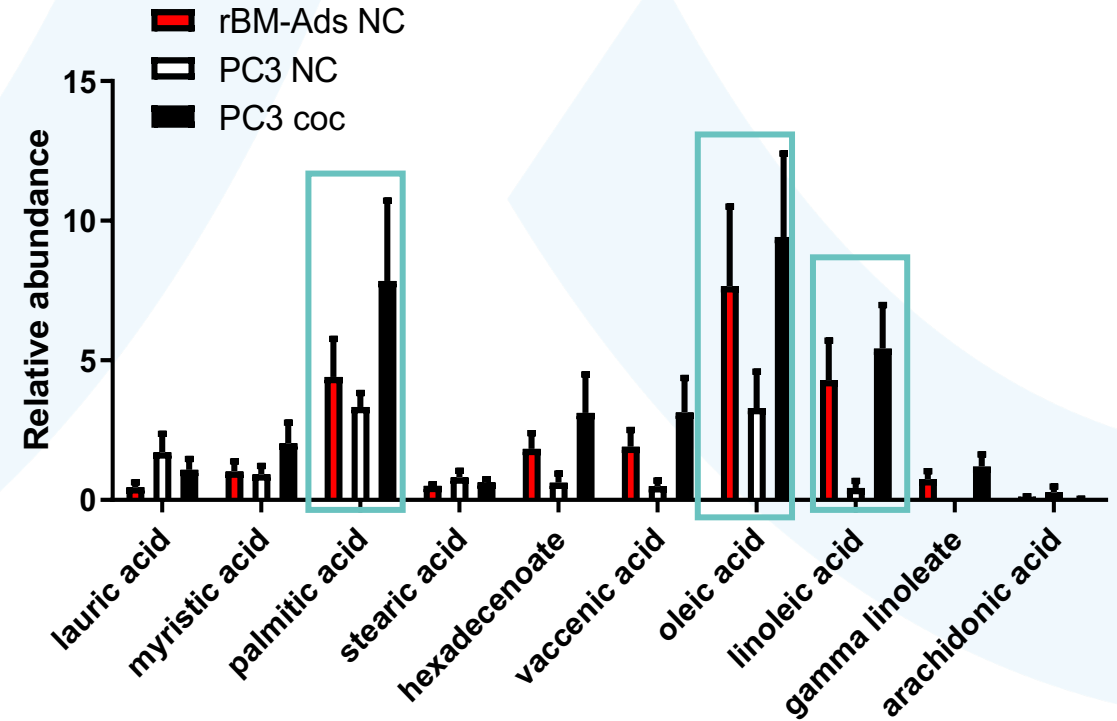
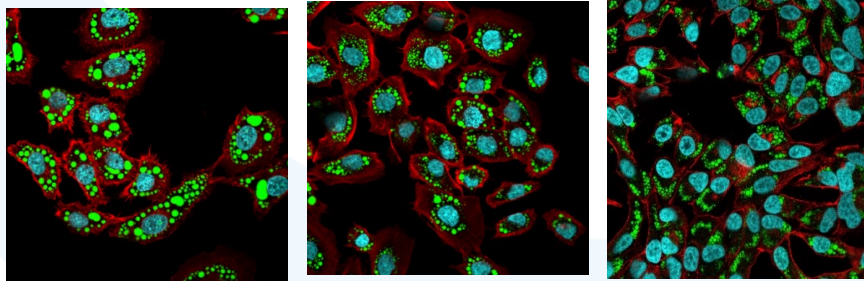
PC3 Du145 LNCaP

NC



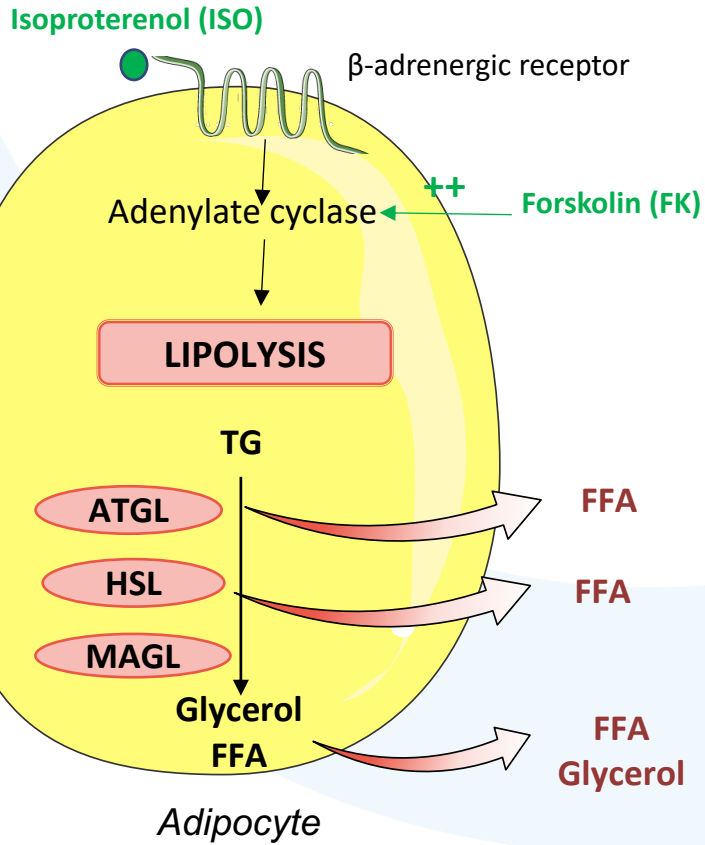
Dapi
 Rhodamin-phalloidin
 Bodipy: neutral lipids

COC

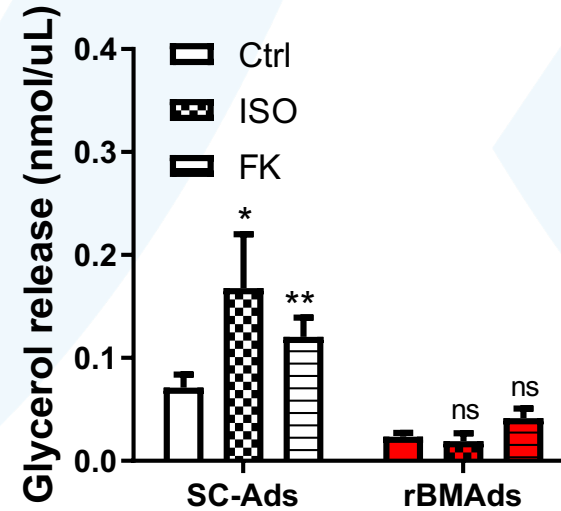
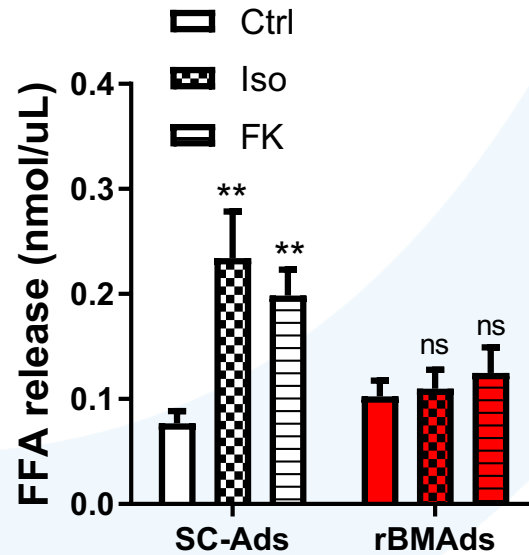
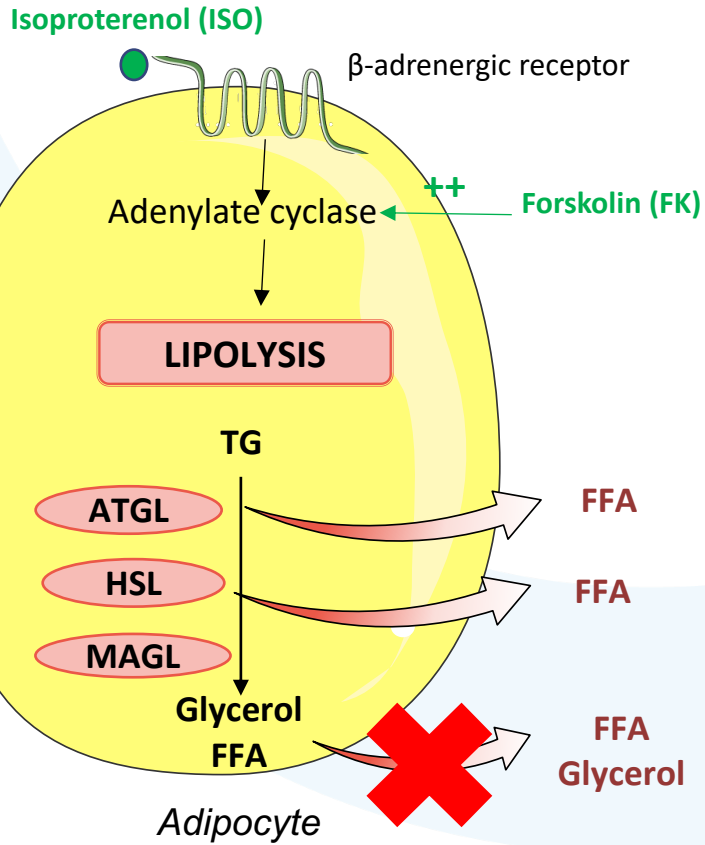


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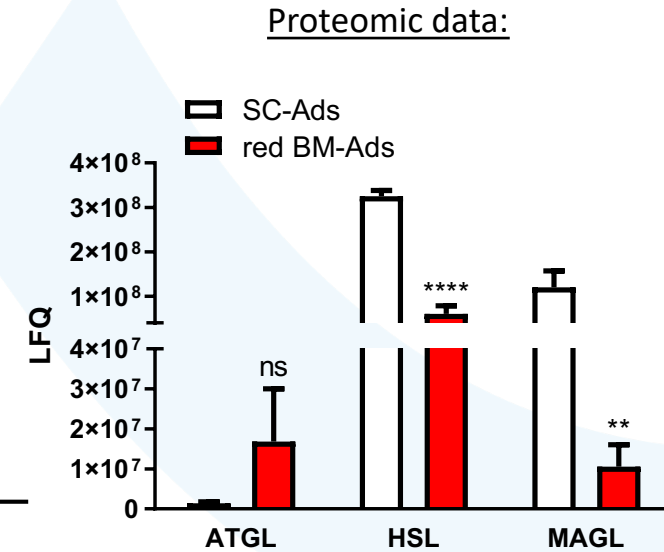
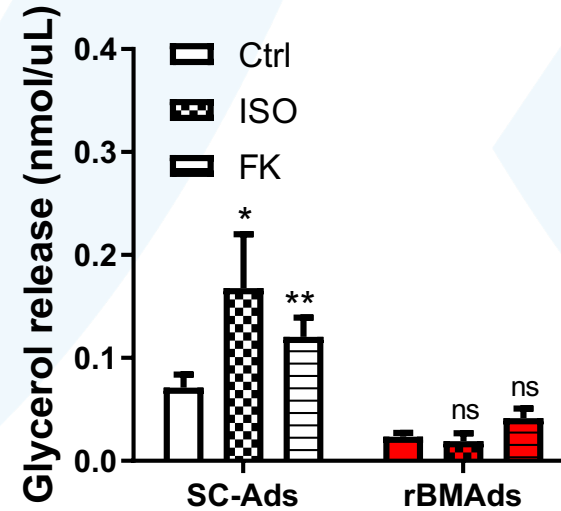
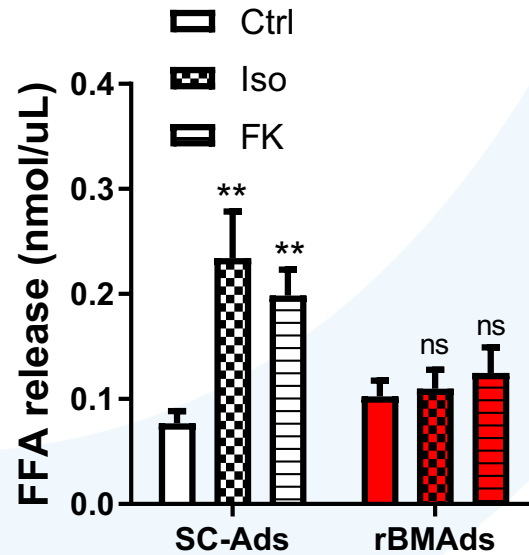
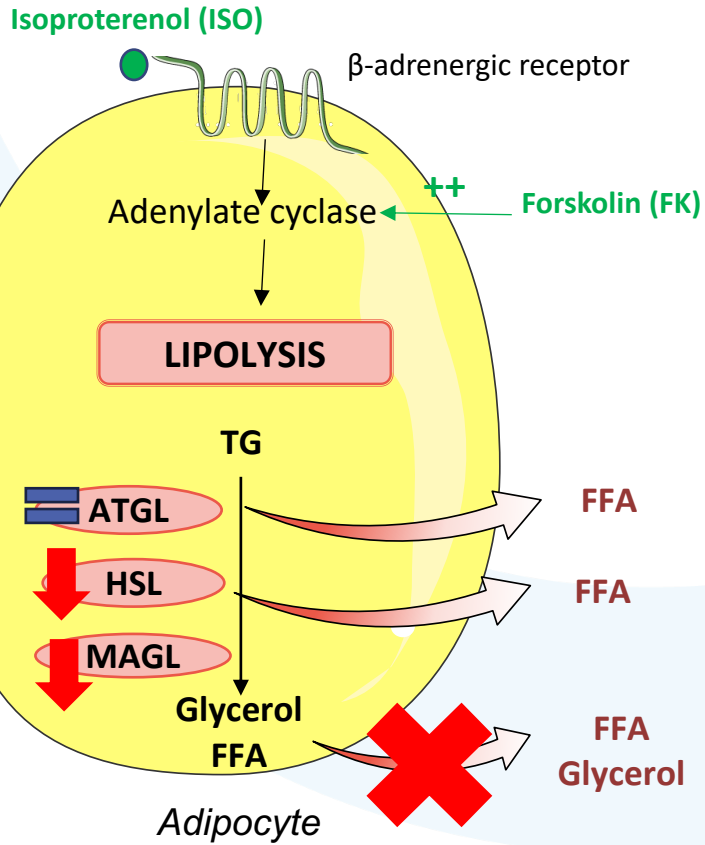
Red BM-Ads are devoid of lipolytic activity, the main function of adipocytes



Red BM-Ads are devoid of lipolytic activity, the main function of adipocytes

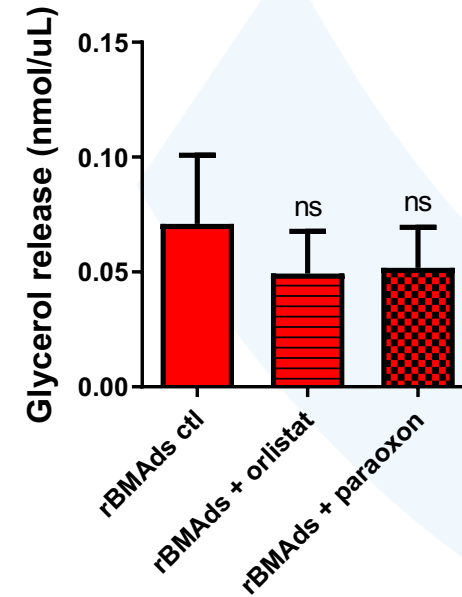
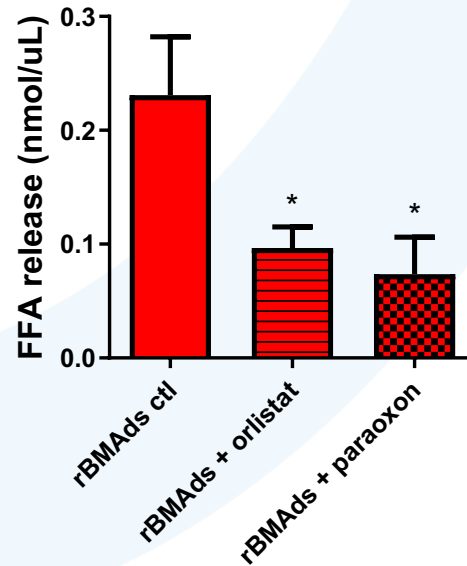
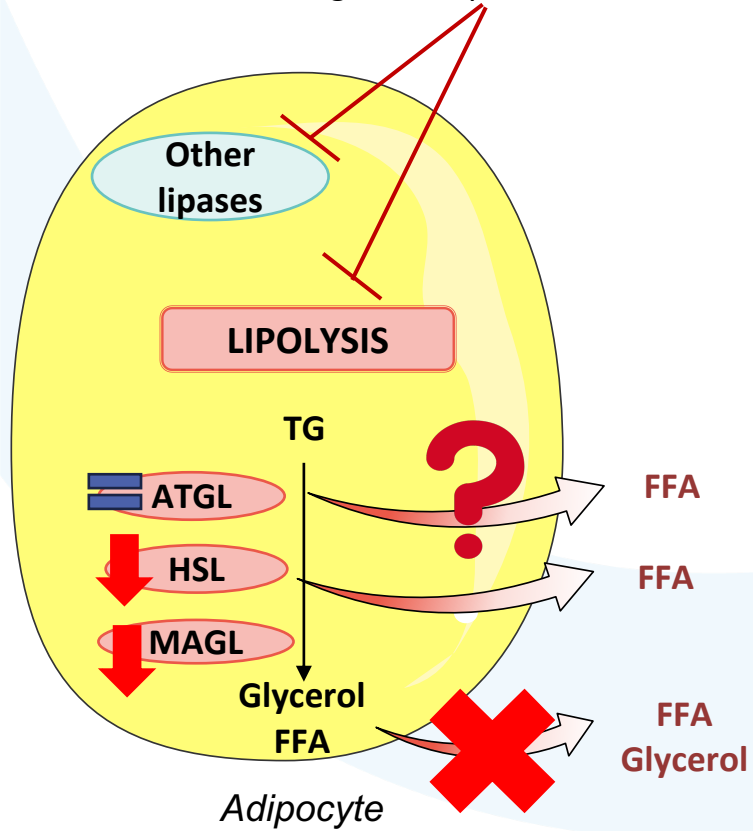


Red BM-Ads are devoid of lipolytic activity, the main function of adipocytes

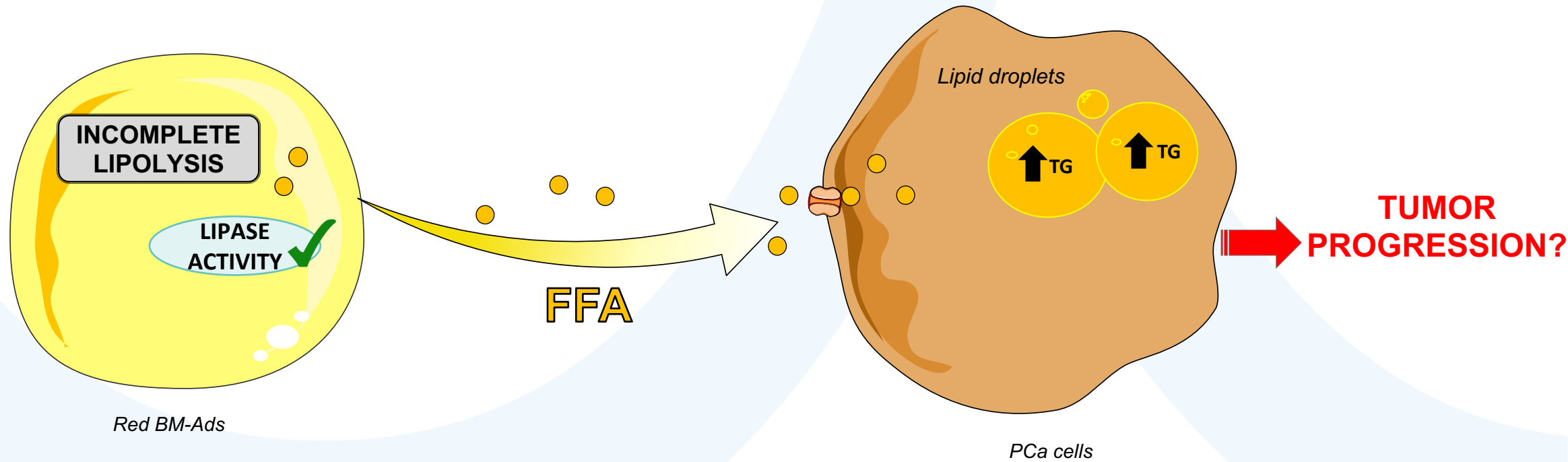


FFA release is due to lipase activity in red BM-Ads

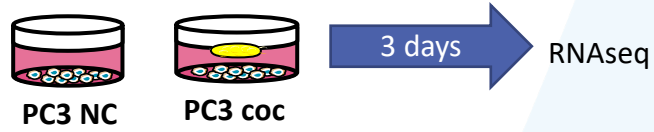
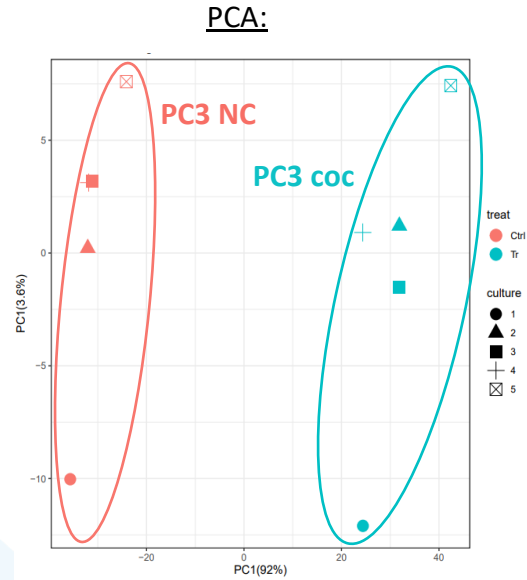
Paraoxon ethyl or orlistat:
general lipase inhibitor



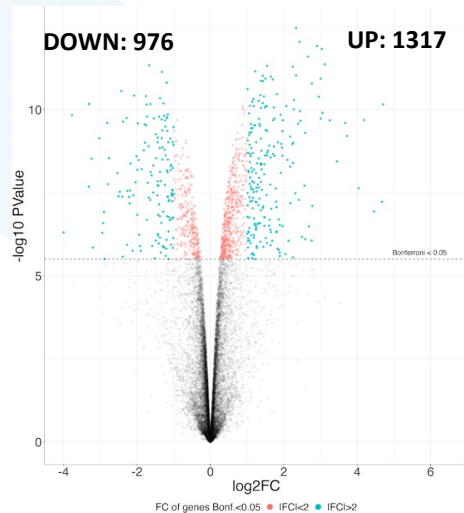
Metabolic crosstalk occurs between red BM-Ads and PCa cells



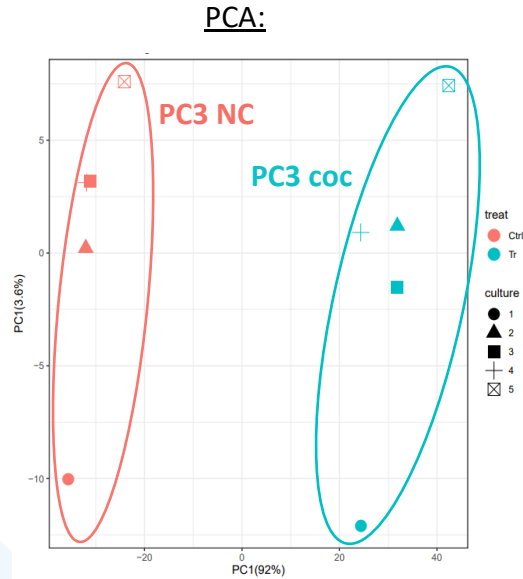
Red BM-Ads increase expression of migration-related genes



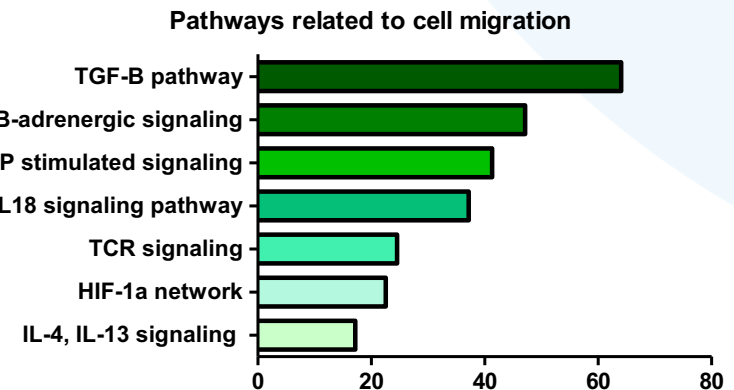
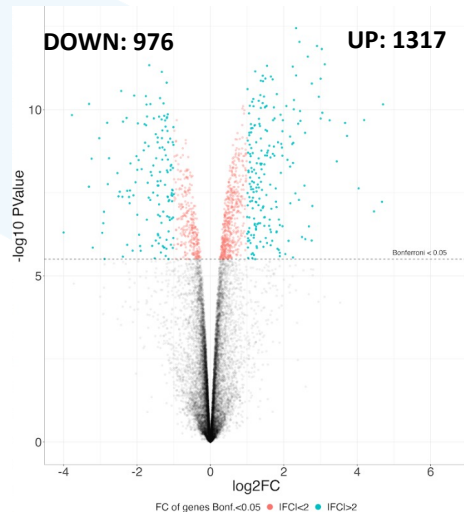
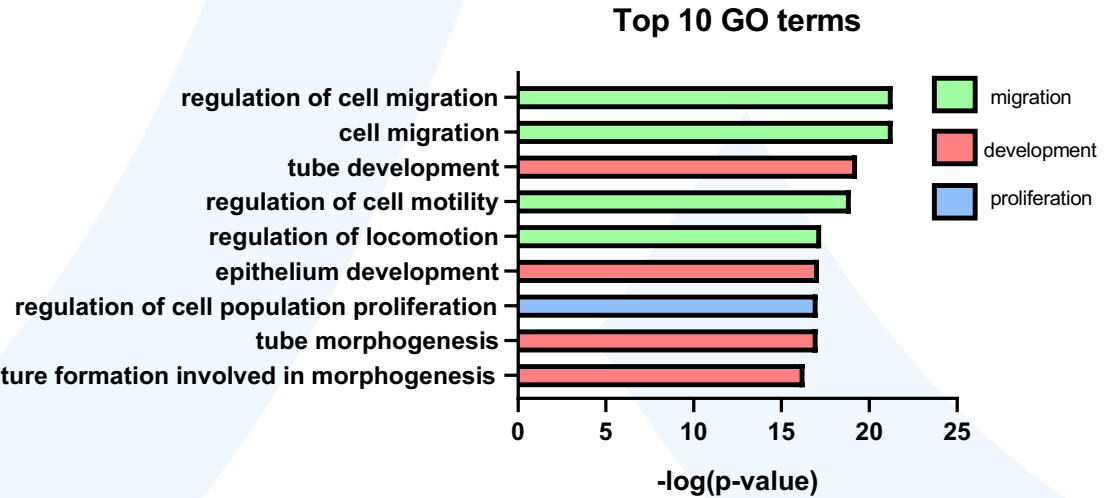
Analysis in progress



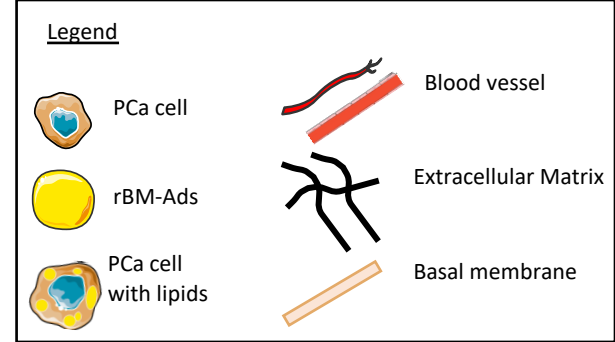
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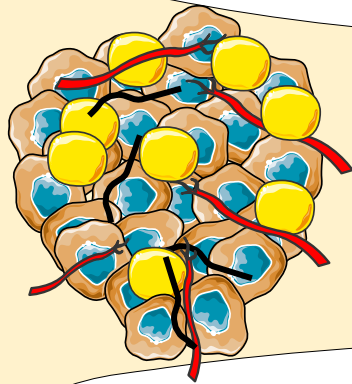
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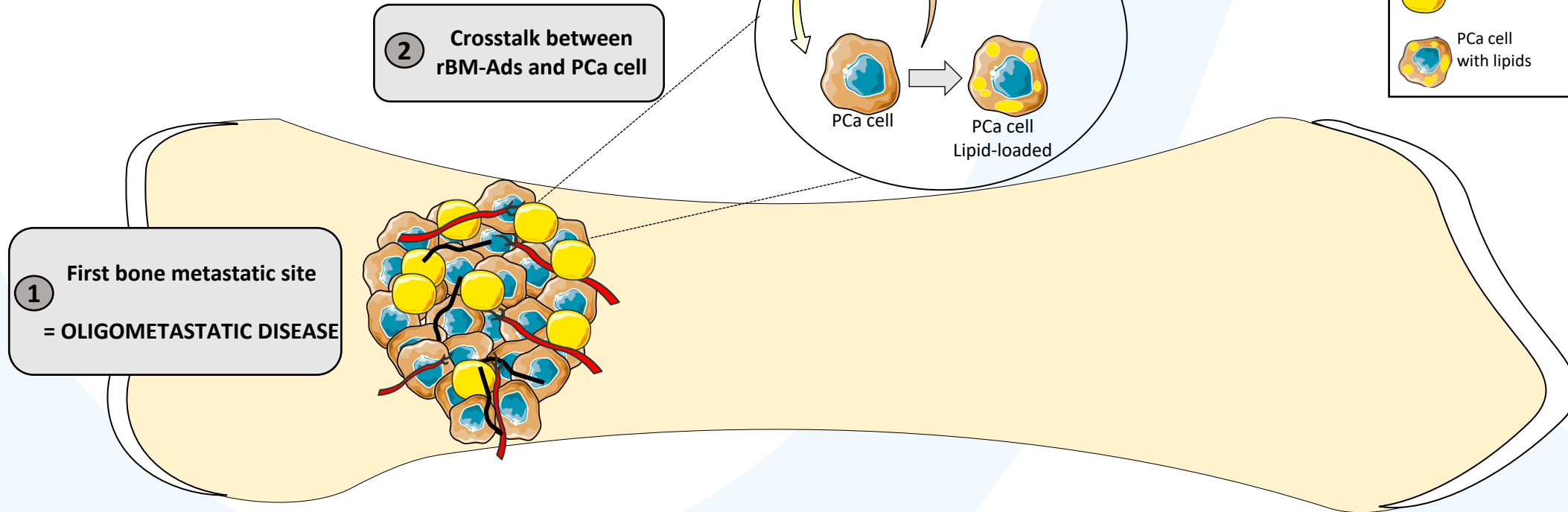
Importance of migration in multiple metastatic sites in PCa



1 First bone metastatic site
= OLIGOMETASTATIC DISEASE

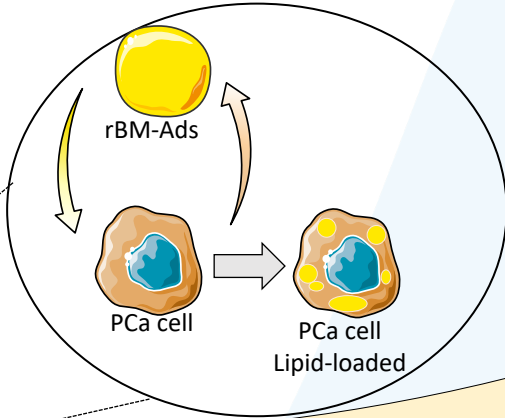


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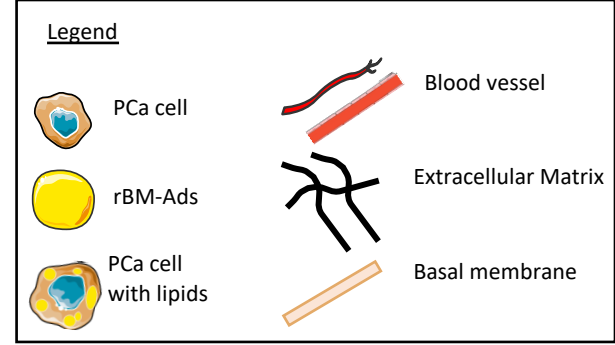
2 Crosstalk between
rBM-Ads and PCa cell



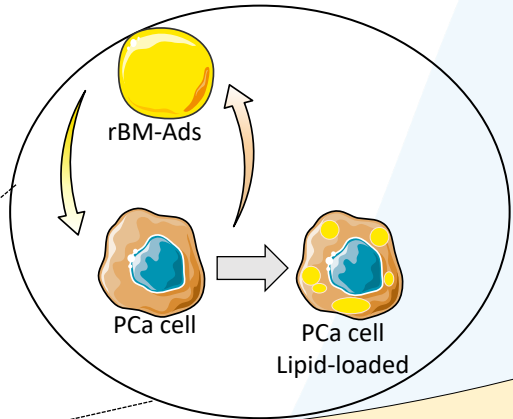
Legend

- PCa cell
- rBM-Ads
- PCa cell with lipids
- Blood vessel
- Extracellular Matrix
- Basal membrane

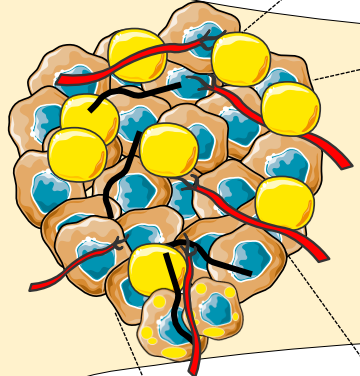
Importance of migration in multiple metastatic sites in PCa



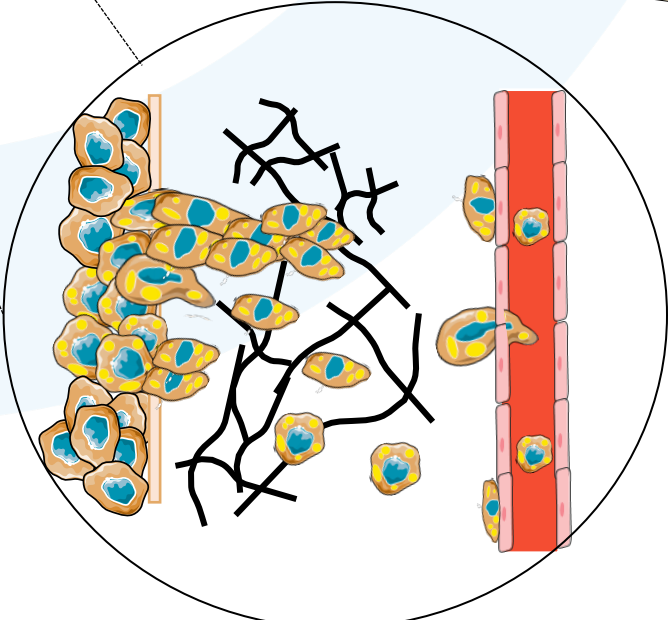
2 Crosstalk between rBM-Ads and PCa cell



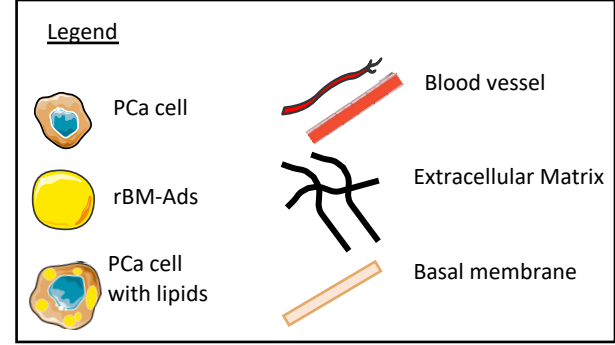
1 First bone metastatic site = OLIGOMETASTATIC DISEASE



3 PCa cell escape from metastatic site via invasion and migration mechanisms

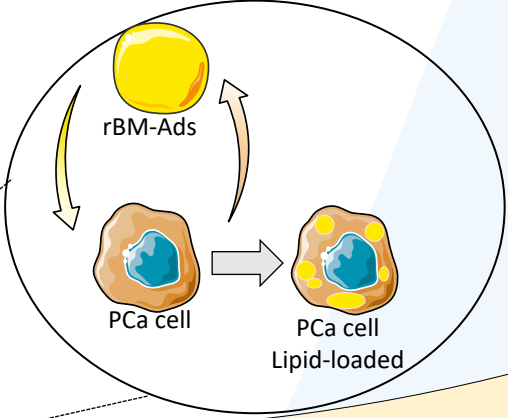


Importance of migration in multiple metastatic sites in PCa



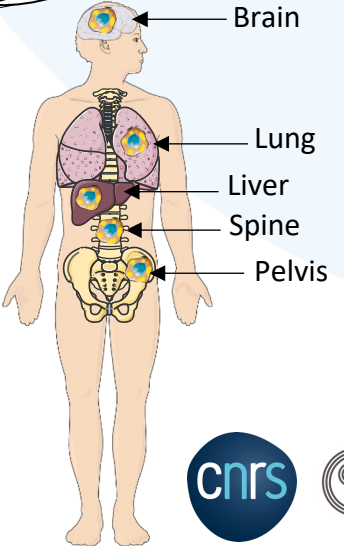
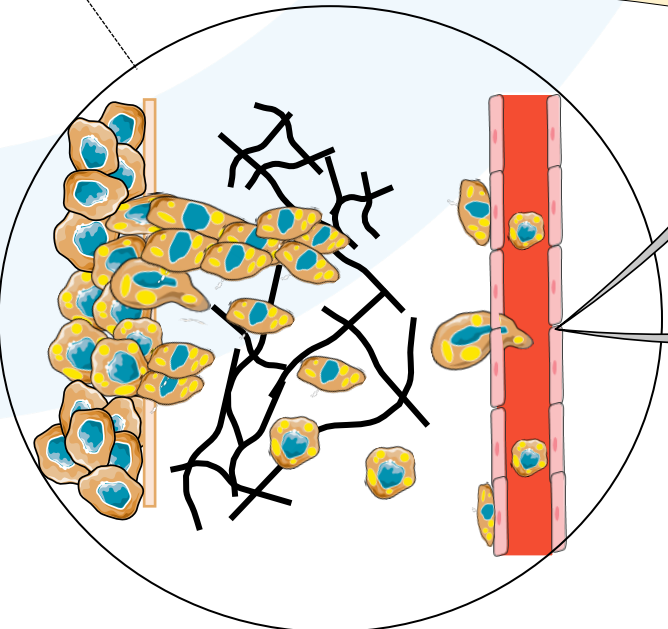
1 First bone metastatic site
= OLIGOMETASTATIC DISEASE

2 Crosstalk between rBM-Ads and PCa cell

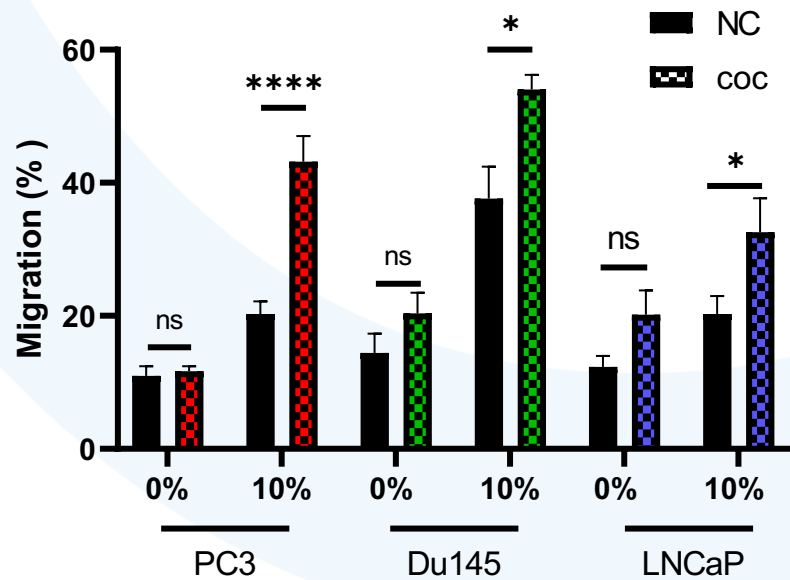


4 Formation of other metastatic sites in the same organ or in different organs
= POLYMETASTATIC DISEASE

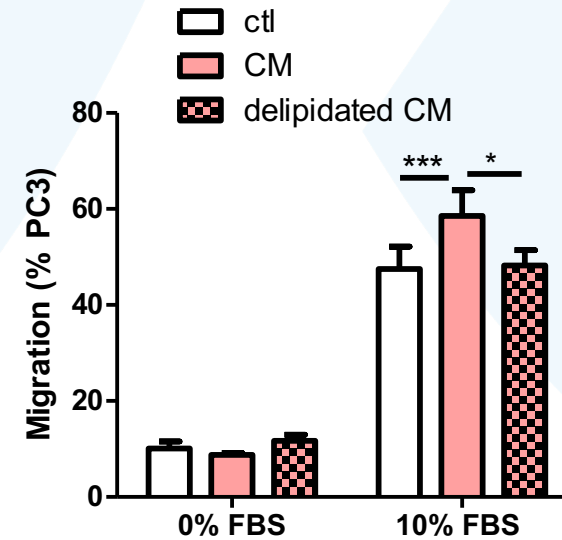
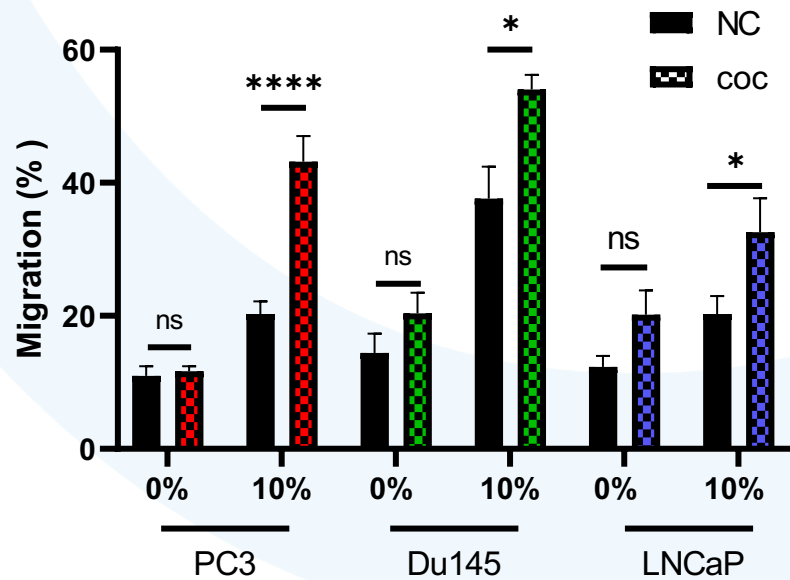
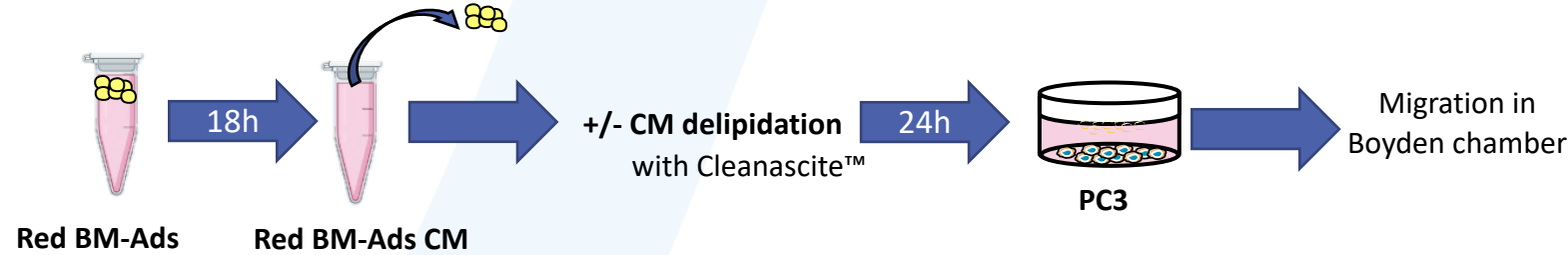
3 PCa cell escape from metastatic site via invasion and migration mechanisms



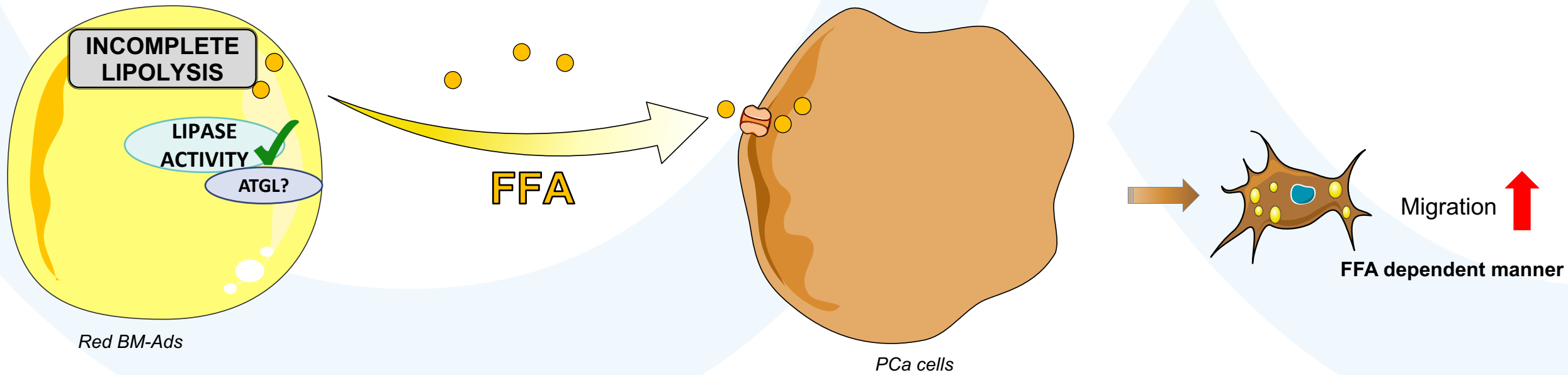
Red BM-Ads increase migration of PCa cells



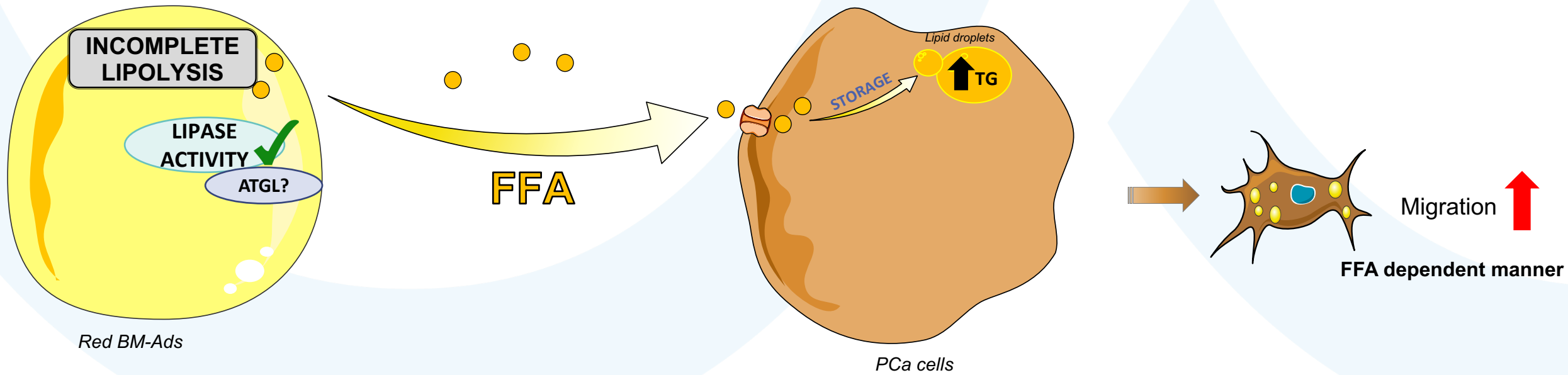
Red BM-Ads increase migration of PCa cells in FFA dependent manner



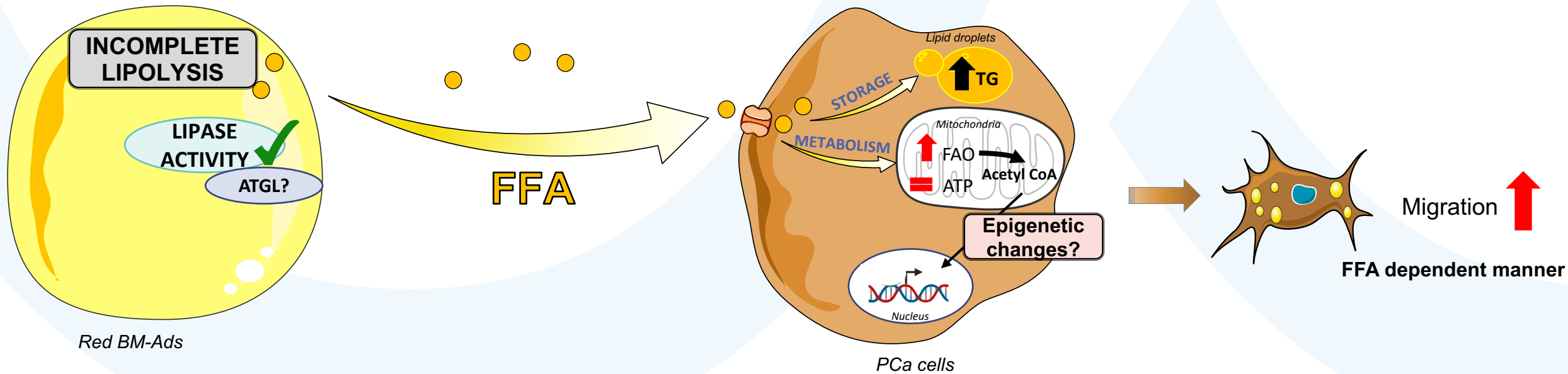
Conclusion and perspectives



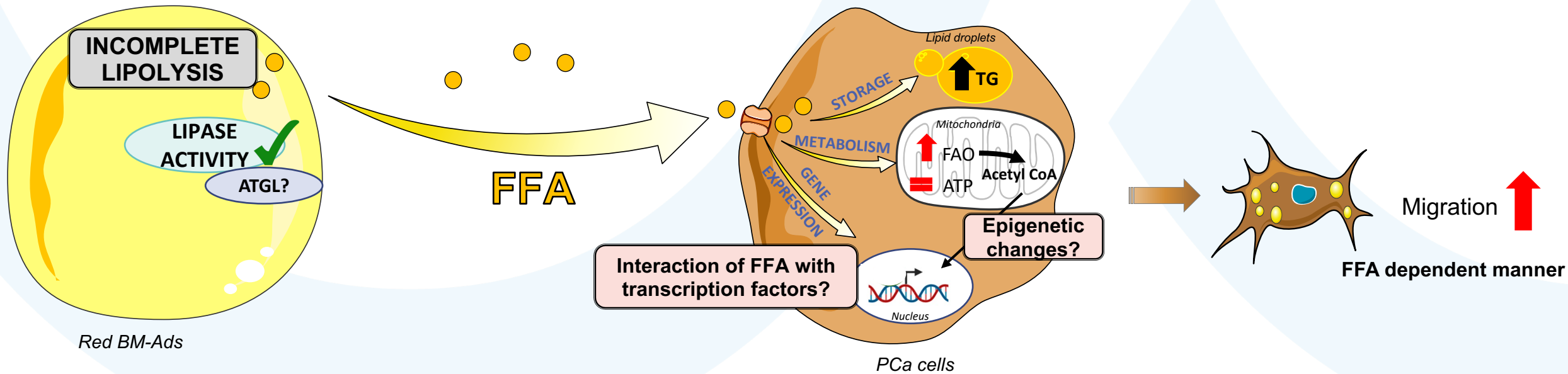
Conclusion and perspectives



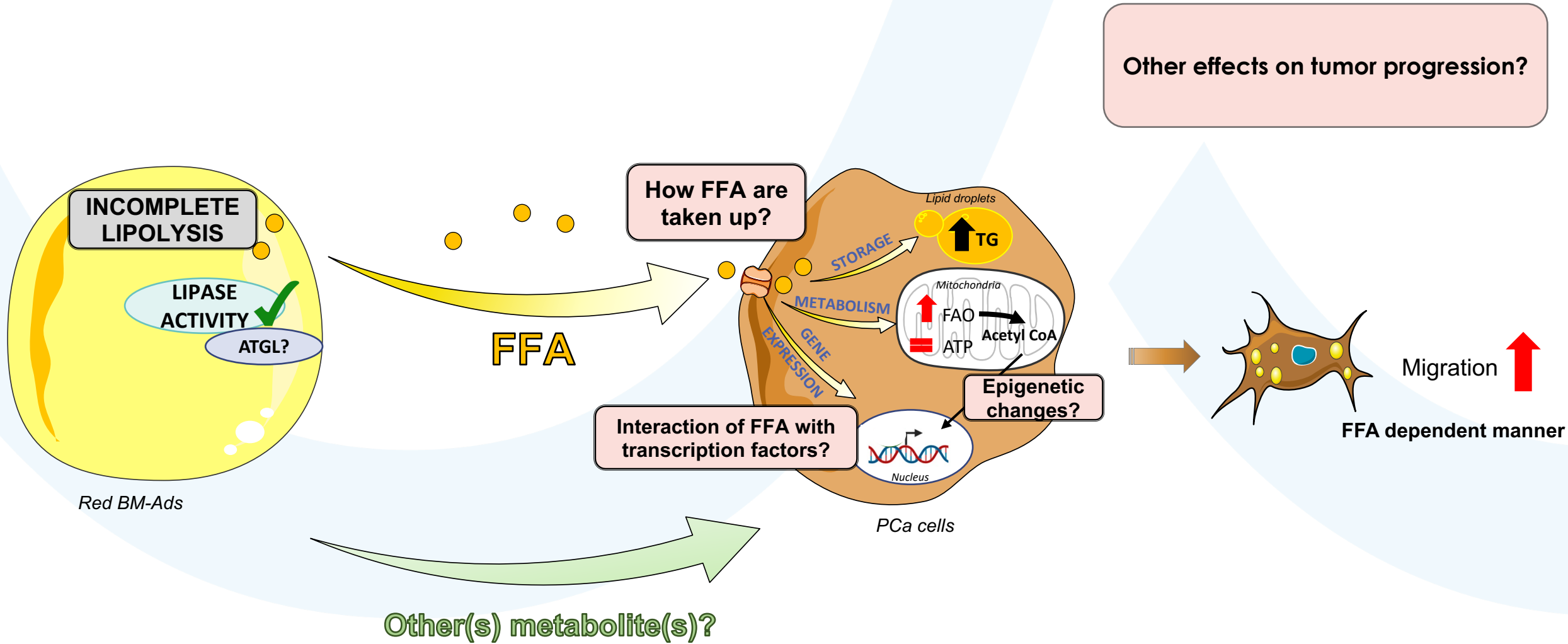
Conclusion and perspectives



Conclusion and perspectives



Conclusion and perspectives



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