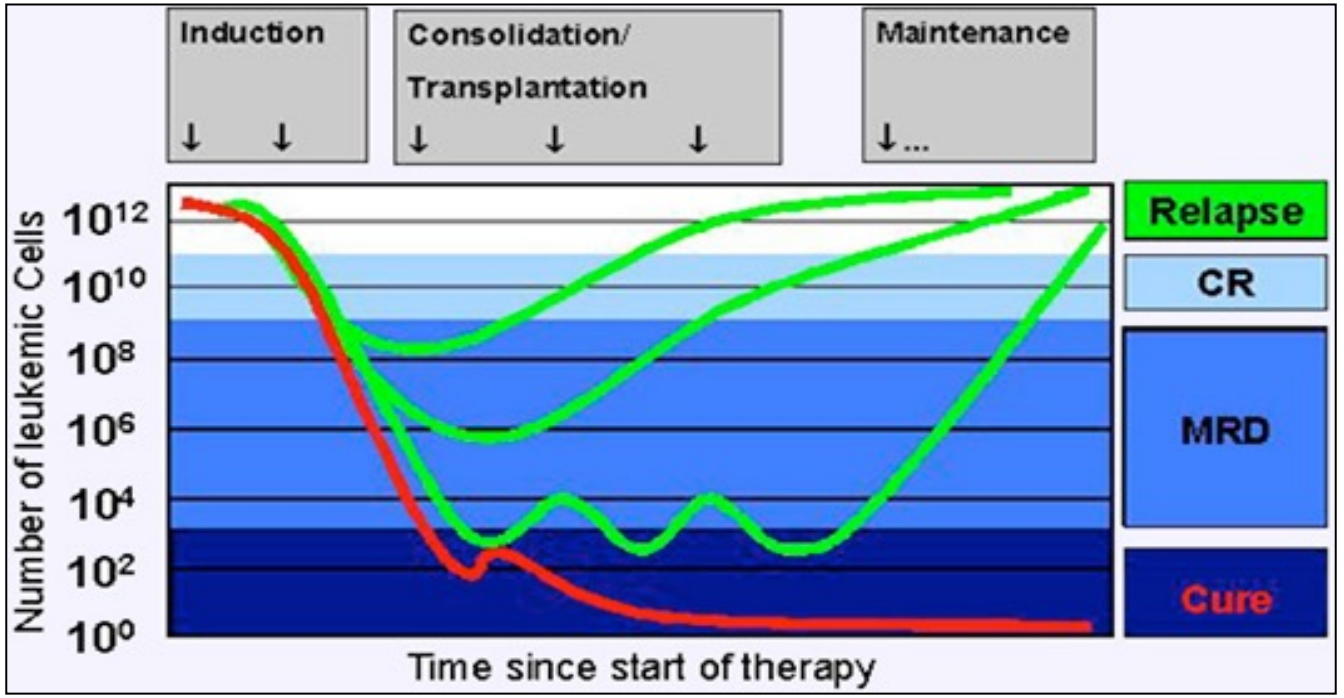
Tumor and host metabolism driving drug resistance in acute myeloid leukemia

Jean-Emmanuel Sarry

Team METAML – METabolism and drug resistance in Acute Myeloid Leukemia

Cancer Research Center of Toulouse

Relapses and drug resistance in cancer

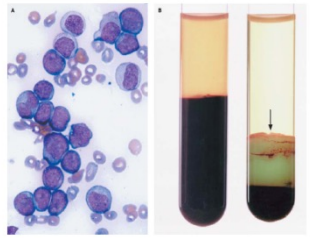


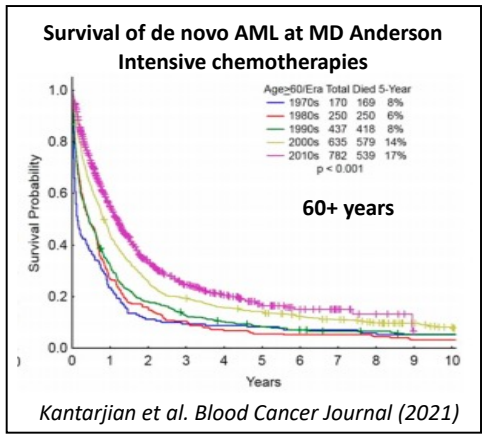
Relapse: regrowth of **tumor-regenerating drug-resistant cells** following initial clinical benefit

Drug resistance: genetic and non-genetic mechanisms induced through the selective pressures imposed by therapy

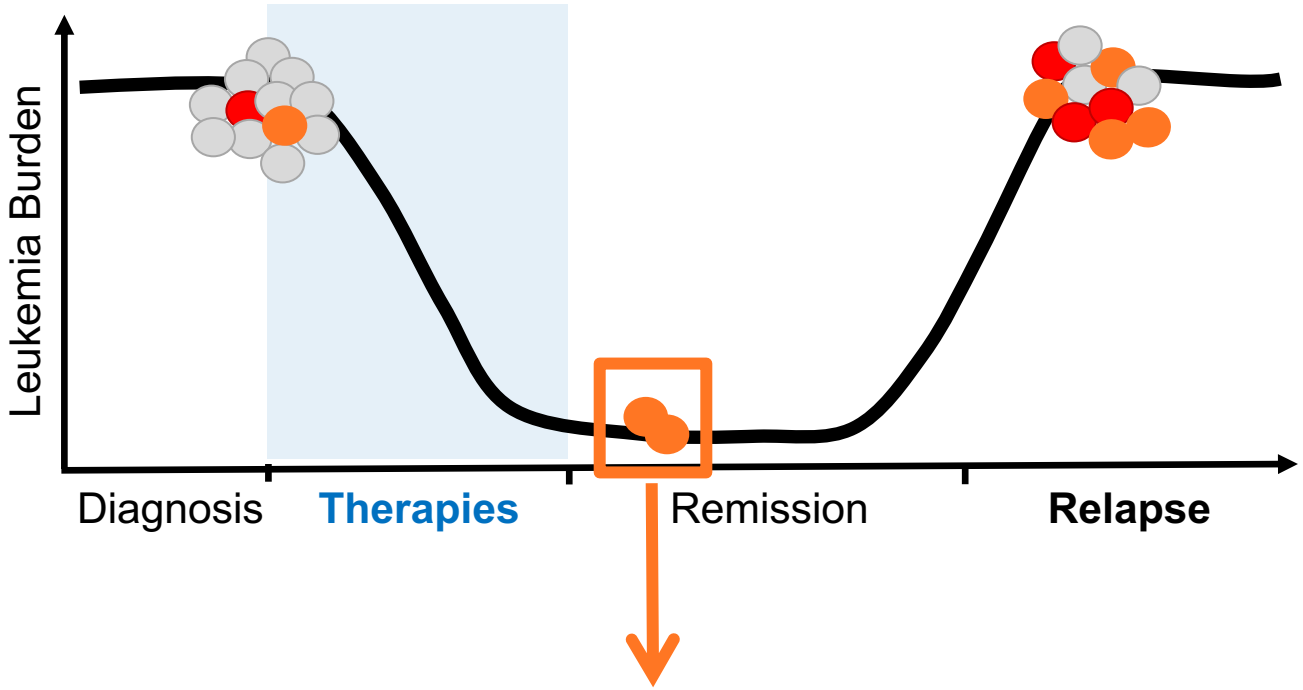
Drug persistence: **minimal residual disease** that remains after an effective anti-cancer therapy

Drug persistence within residual disease in acute myeloid leukemia





Kantarjian et al. Blood Cancer Journal (2021)

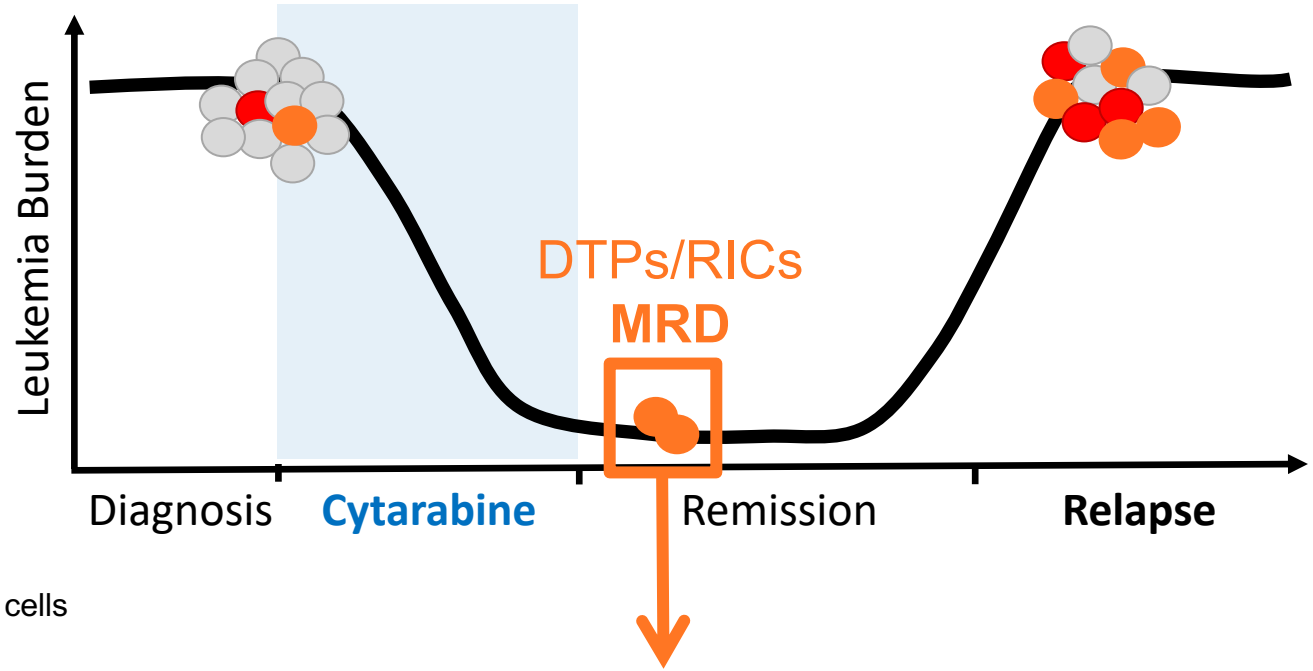


What is the biology of **Relapse-Initiating Cells** (RICs)
or Drug-Tolerant Persisters (DTPs)
enriched within Minimal Residual Disease (MRD) *in vivo* ?

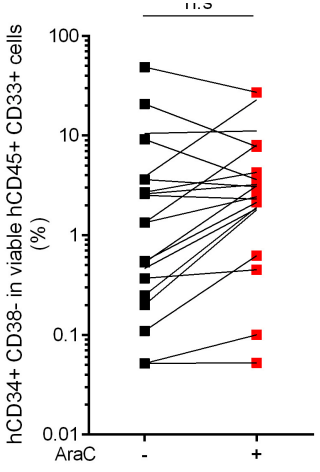
RICs are not necessarily enriched in AML stem cells when assayed in NSG mice

AML stem cells are also heterogeneous in their response to AraC

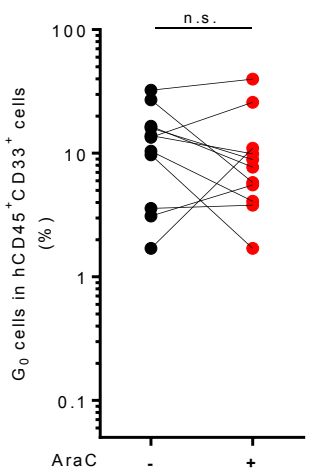
AML PDX Models
NSG Mice
+CYTARABINE
(AraC)



CD34$^+$ CD38$^-$ cells



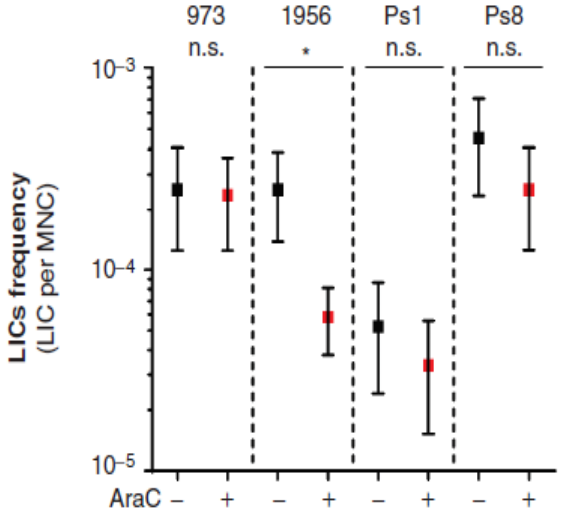
Quiescent (G_0) cells



Canonical Leukemic Stem Cell features

(CD34 CD38 phenotype, G_0 cells, cell cycle markers, stem cell genes, LIC frequency) **were similar** in control and resistant cells

LICs Frequency

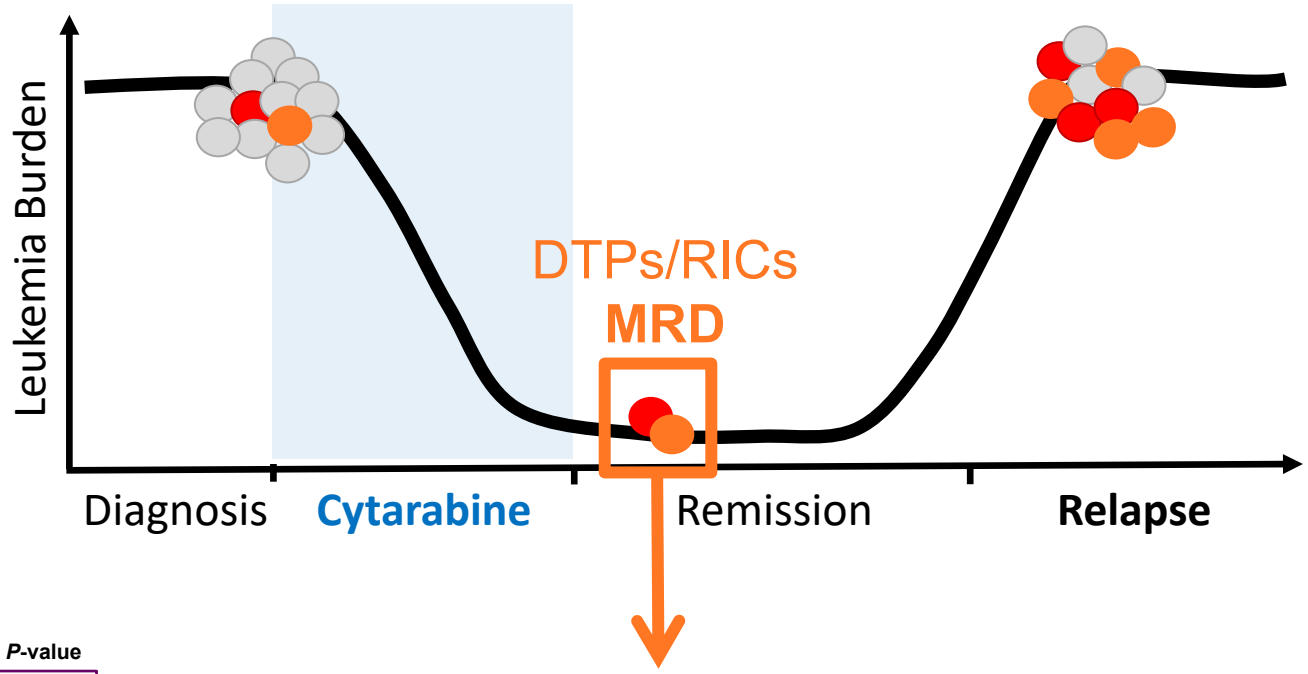


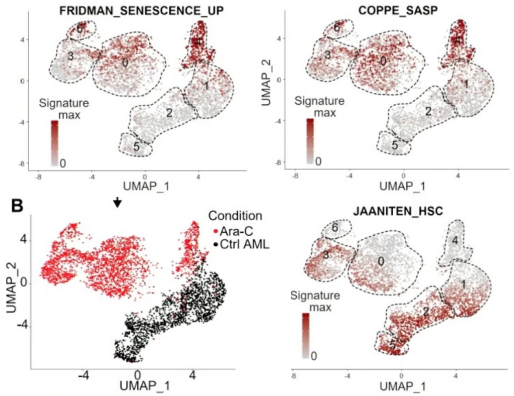
Collab. M. Carroll, G. Danet-Desnoyer (UPenn)

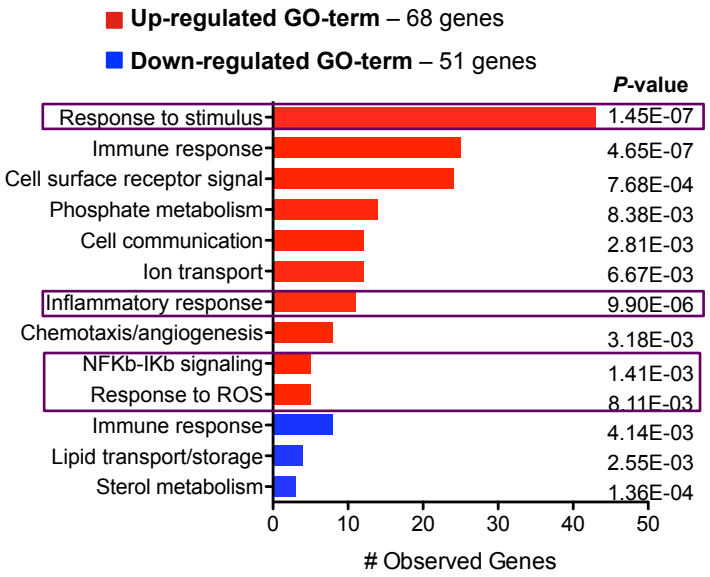
Duy et al. Cancer Discov. 2021; Boyd et al. Cancer Cell 2018; Farge *et al.* Cancer Discov. 2017

RICs are enriched in resilient cells with an inflammatory/senescent phenotype

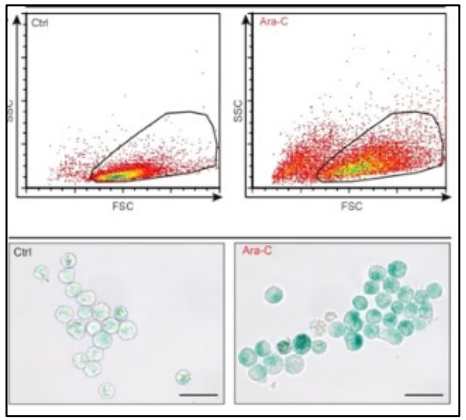
AML PDX Models
NSG Mice
+CYTARABINE
(AraC)

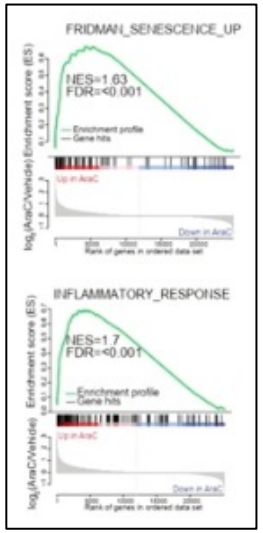






↗ **Senescence-like resilient cells**
with latent state and
↗ stress/inflammatory response
↗ EMT phenotype

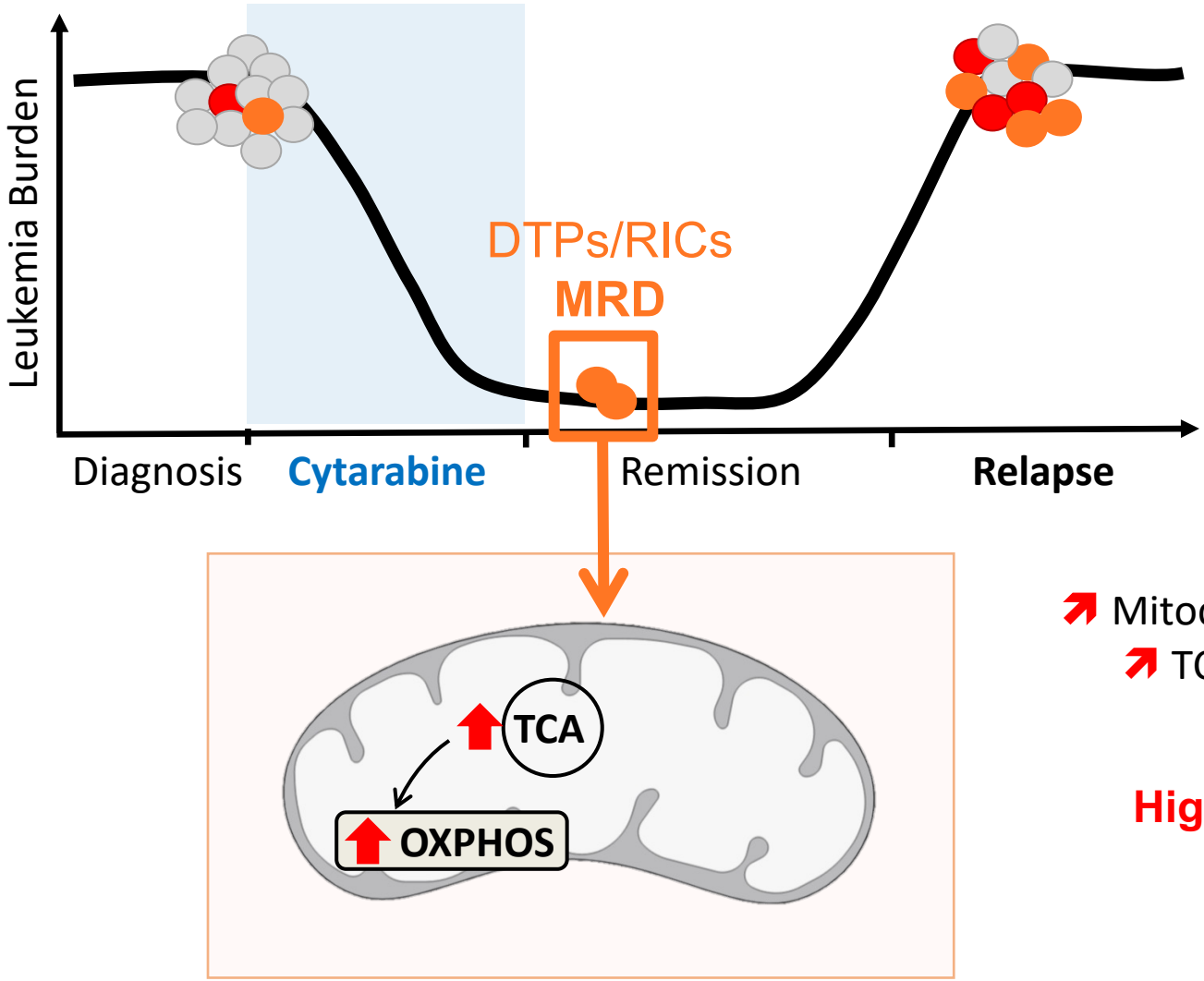




Guiraud *et al* in prep; Duy et al. Cancer Discov. 2021
Aroua*, Boet*, Ghisi* *et al*. Cancer Discov. 2020; Farge* *et al.* Cancer Discov. 2017

Minimal Residual Disease is enriched in Relapse-Initiating Cells with Drug-Tolerant Persisters and an increased mitochondrial oxidative (High OxPHOS) metabolism

AML PDX Models
NSG Mice
+CYTARABINE
(AraC)



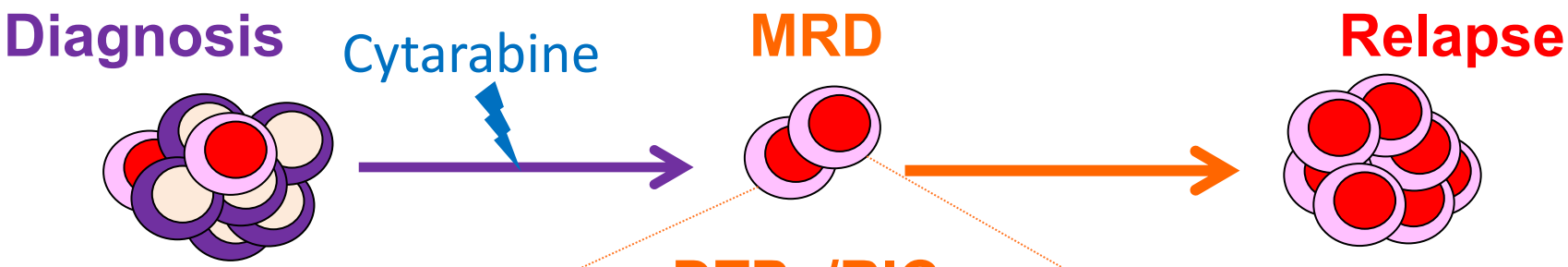
↗ Mitochondrial respiration+ATP
↗ TCA cycle intermediates
↗ ROS content

High OxPHOS activity and phenotype

Collab. Y. Collette (CRCM, Marseille)
Collab. M. Carroll, G. Danet-Desnoyer (UPenn, USA)
Collab. M. Selak (UPenn, USA), M. Brand (Buck Institute, USA)

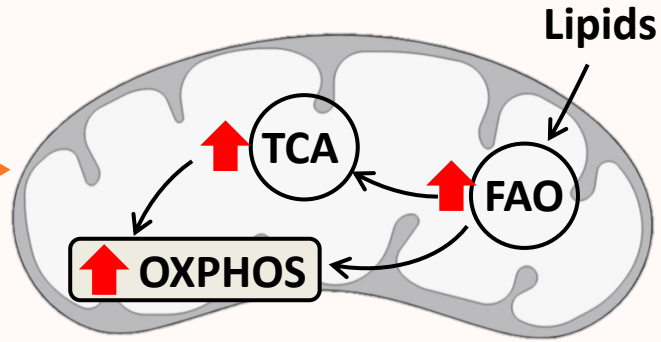
Hosseini *et al.* Cancer Res. 2019
Farge* *et al.* Cancer Discov. 2017

High OxPHOS phenotype of RICs is the consequence of enhanced mitochondrial metabolic activities with lipid oxidation

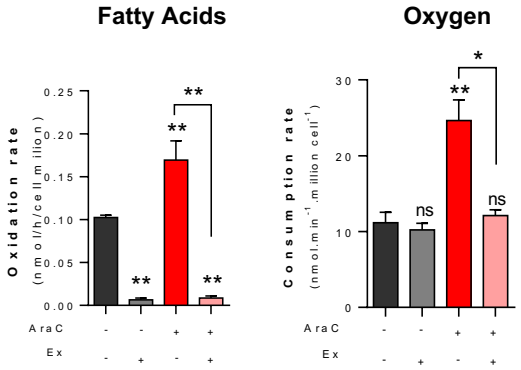


DTPs/RICs

↗ Mitochondrial metabolic activities
↗ fatty acid oxidation



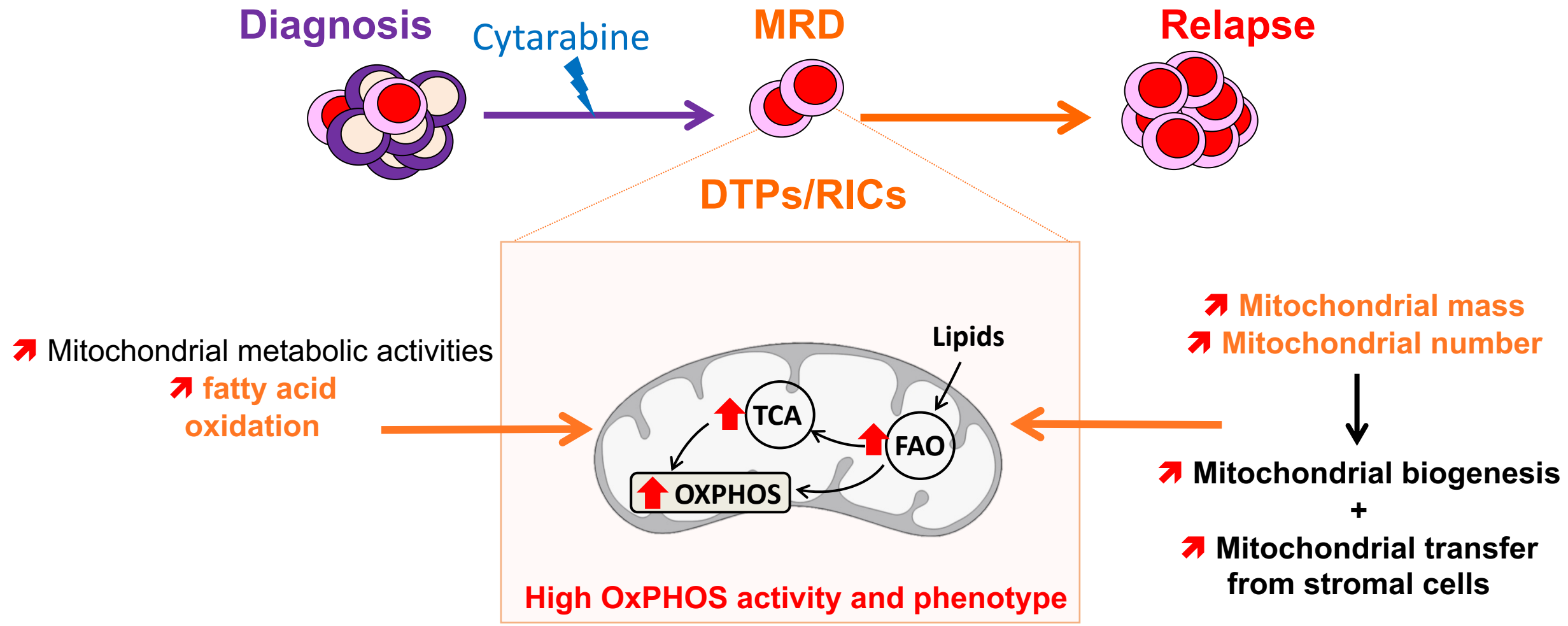
High OxPHOS activity and phenotype



Collab. M. Selak (UPenn, USA), M. Brand (Buck Institute, USA)

Farge* *et al.* Cancer Discov. 2017

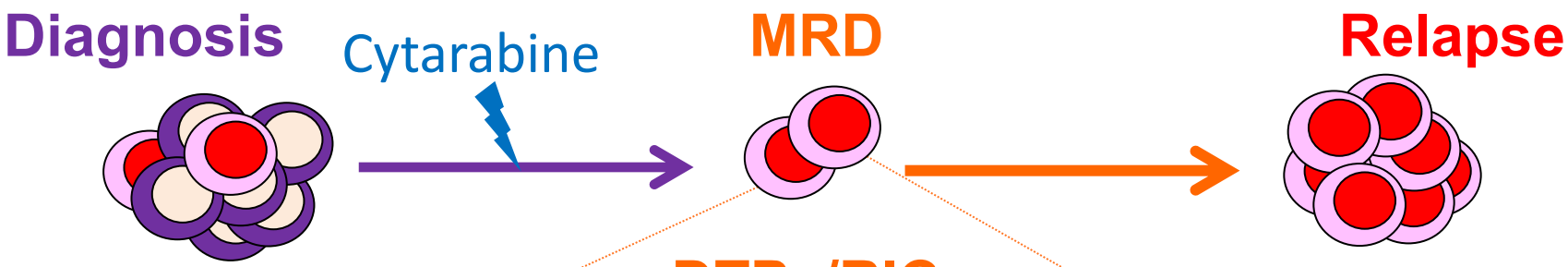
High OxPHOS phenotype of RICs is the consequence of enhanced mitochondrial machinery



Collab. M. Selak (UPenn, USA), M. Brand (Buck Institute, USA)
Collab E. Griessinger, JF Peyron (C3M, Nice)

Ducau et al. unpublished data
Farge *et al.* Cancer Discov. 2017
Moschoi …. Griessinger. Blood. 2016

High OxPHOS phenotype of RICs is the consequence of enhanced mitochondrial machinery with heme/ISC biosynthesis



DTPs/RICs

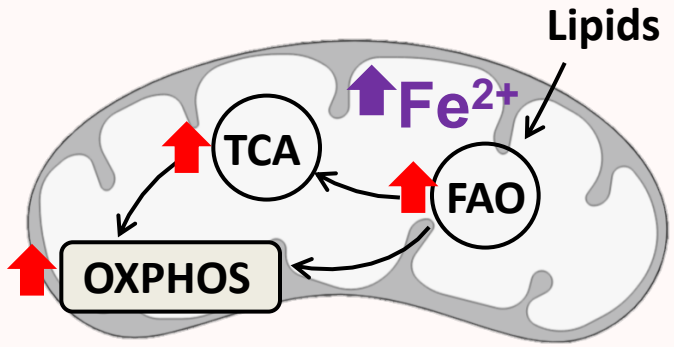
↗ Mitochondrial biogenesis

↓

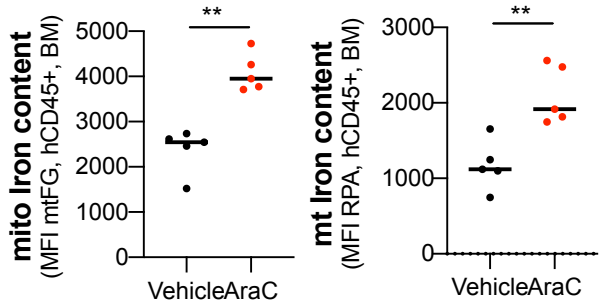
↗ Mitochondrial iron and ferritin content

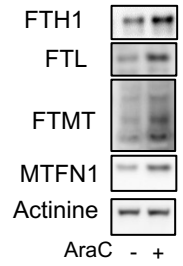
+

↗ Heme/porphyrin and ISC biosynthesis



High OxPHOS activity and phenotype



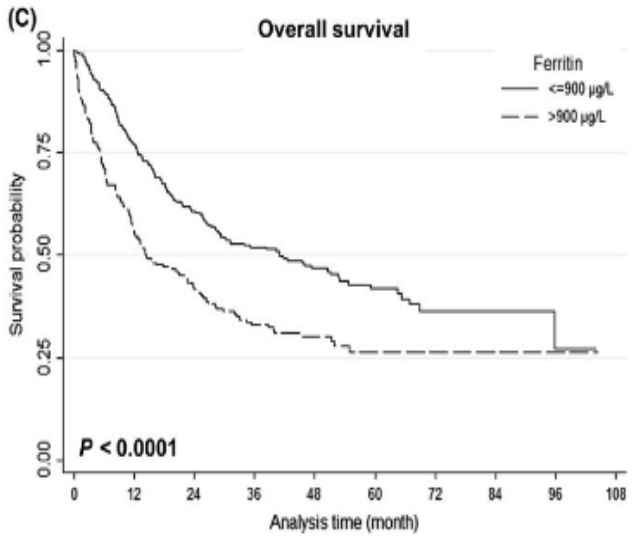


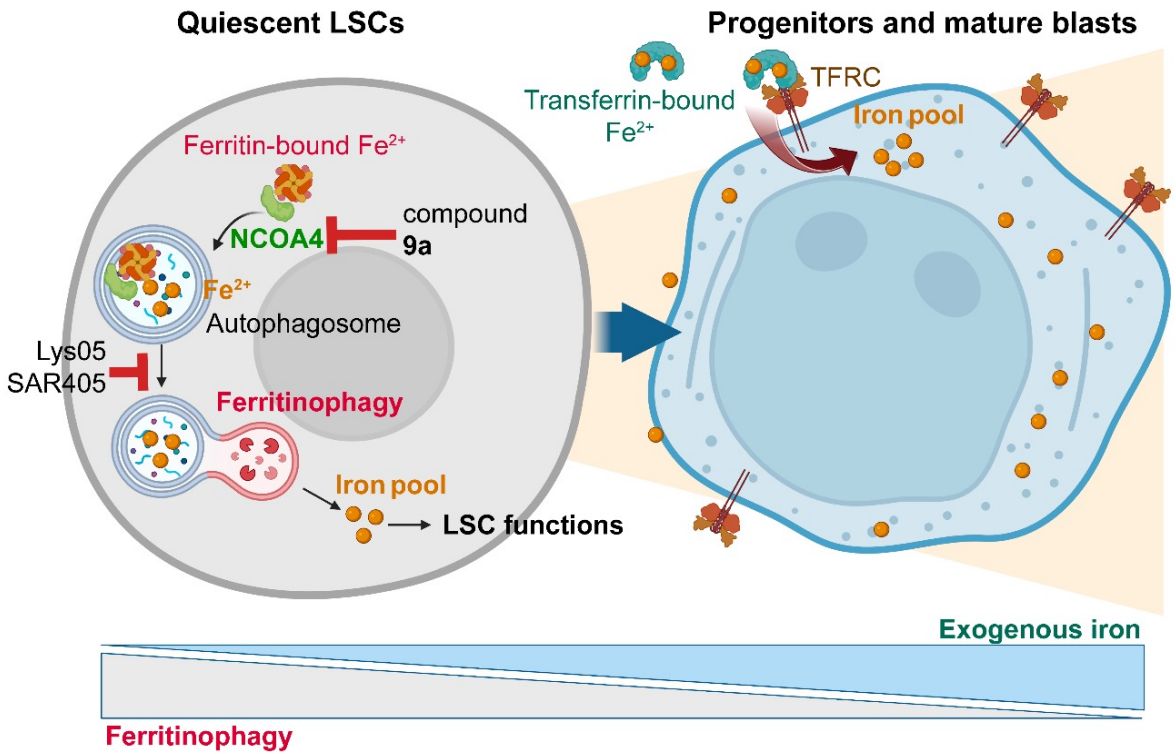
Saland et al. in prep

Iron homeostasis (ferritin) is associated with bad prognosis in AML patients

Ferritin

(Bertoli and al. EJH, 2019)





Chemoresistant cell compartment

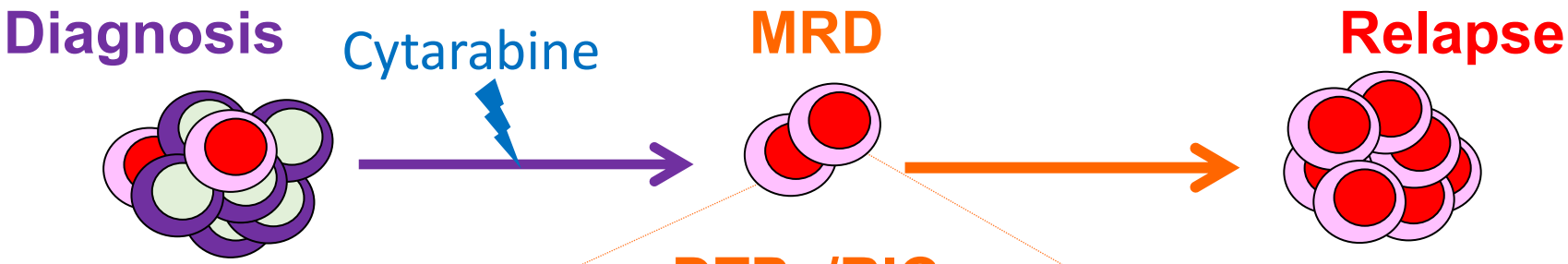
Chemosensitive cell compartment

Clément Larrue

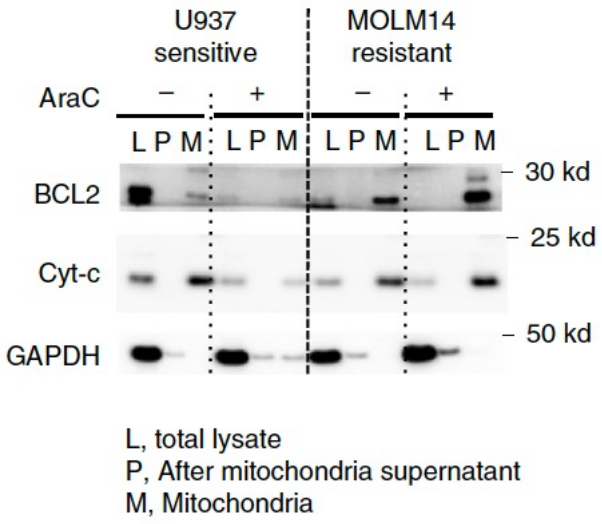
Larrue *et al.* STM. In revision

J. Tamburini's Team, Gevena University

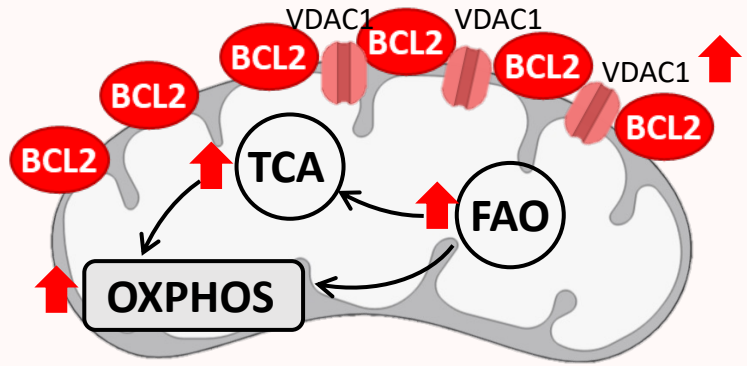
Increased VDAC1 and mitochondrial relocation of BCL2 in drug persisters



DTPs/RICs



L, total lysate
P, After mitochondria supernatant
M, Mitochondria



High OxPHOS activity and phenotype

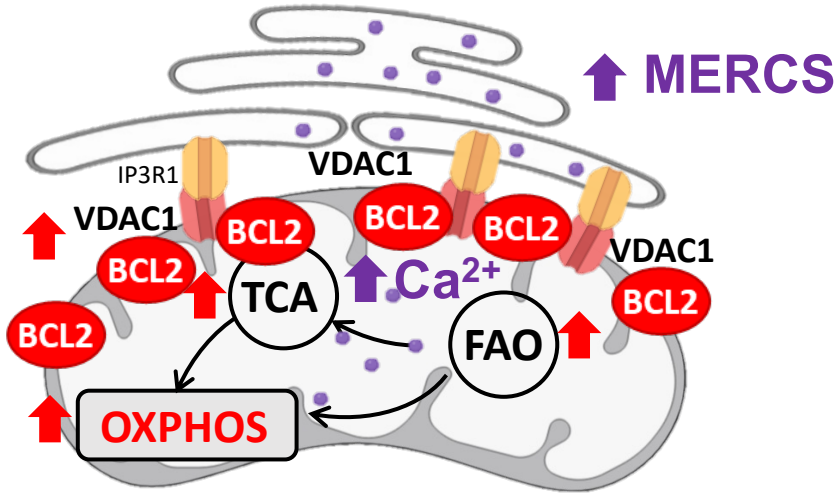
↗ VDAC1 expression and mitochondrial BCL2 translocation

↗ Mitochondrial Calcein Retention = inhibition of MPTP opening

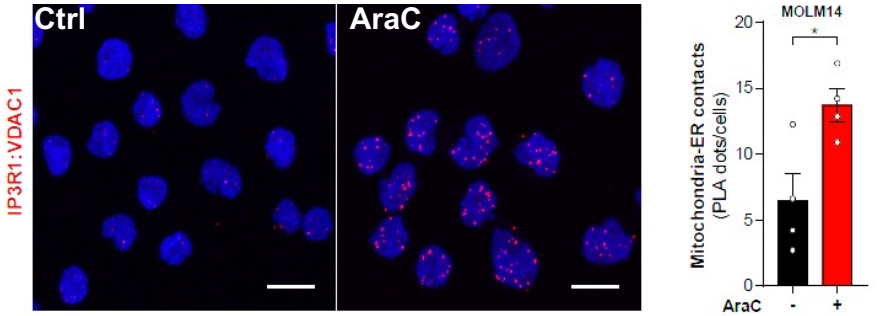
↗ BCL2 dependence

Bosc *et al*. Nature Cancer. 2021

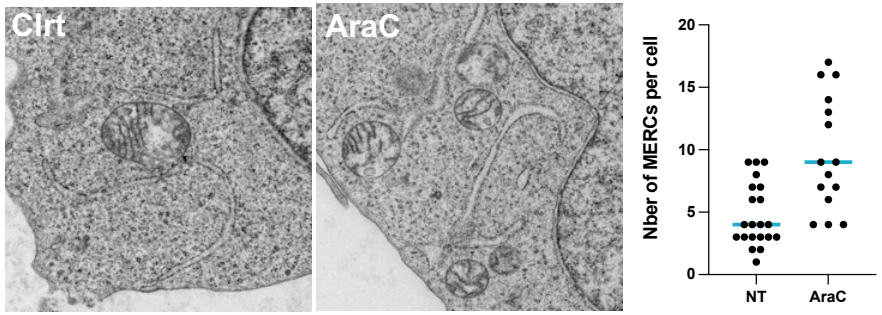
Increased mitochondria-ER contact sites (MERCS) in Drug Persisters



High OxPHOS phenotype



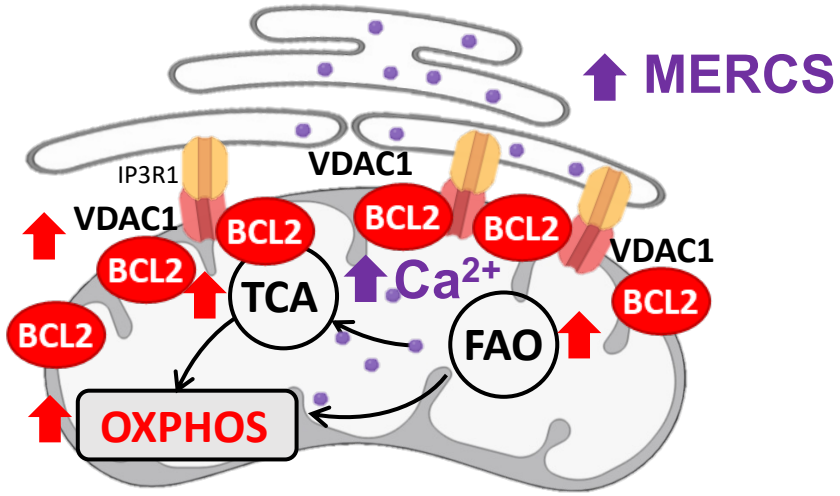
Proximity Ligation Assay IP3R1 / VDAC1



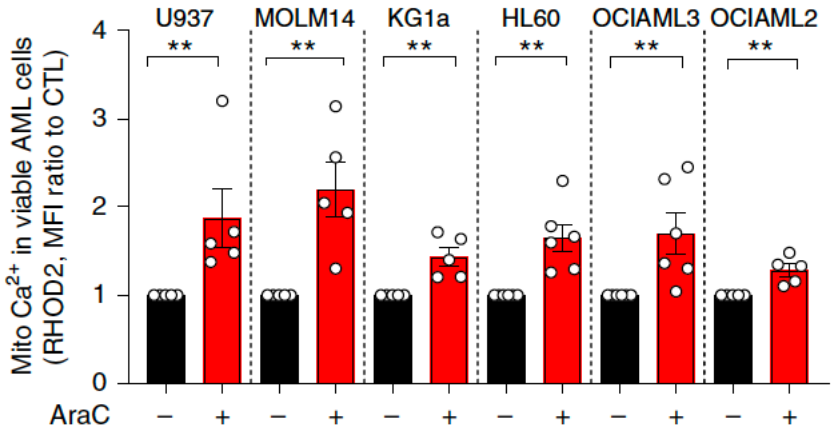
Electronic microscopy

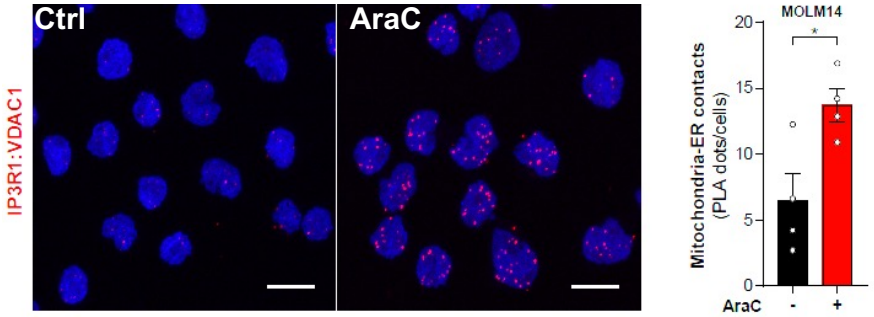
Ducau et al. unpublished data.
Bosc *et al* Nature Cancer 2021

Increased mitochondria-ER contact sites (MERCS) in Drug Persisters

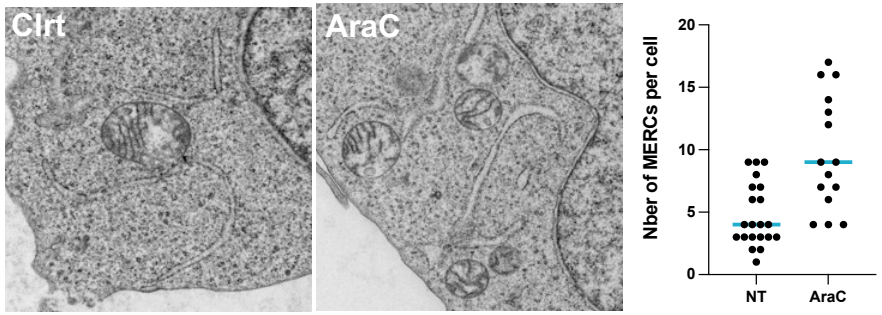


- Transfer of Ca^{2+} from ER to mitochondria





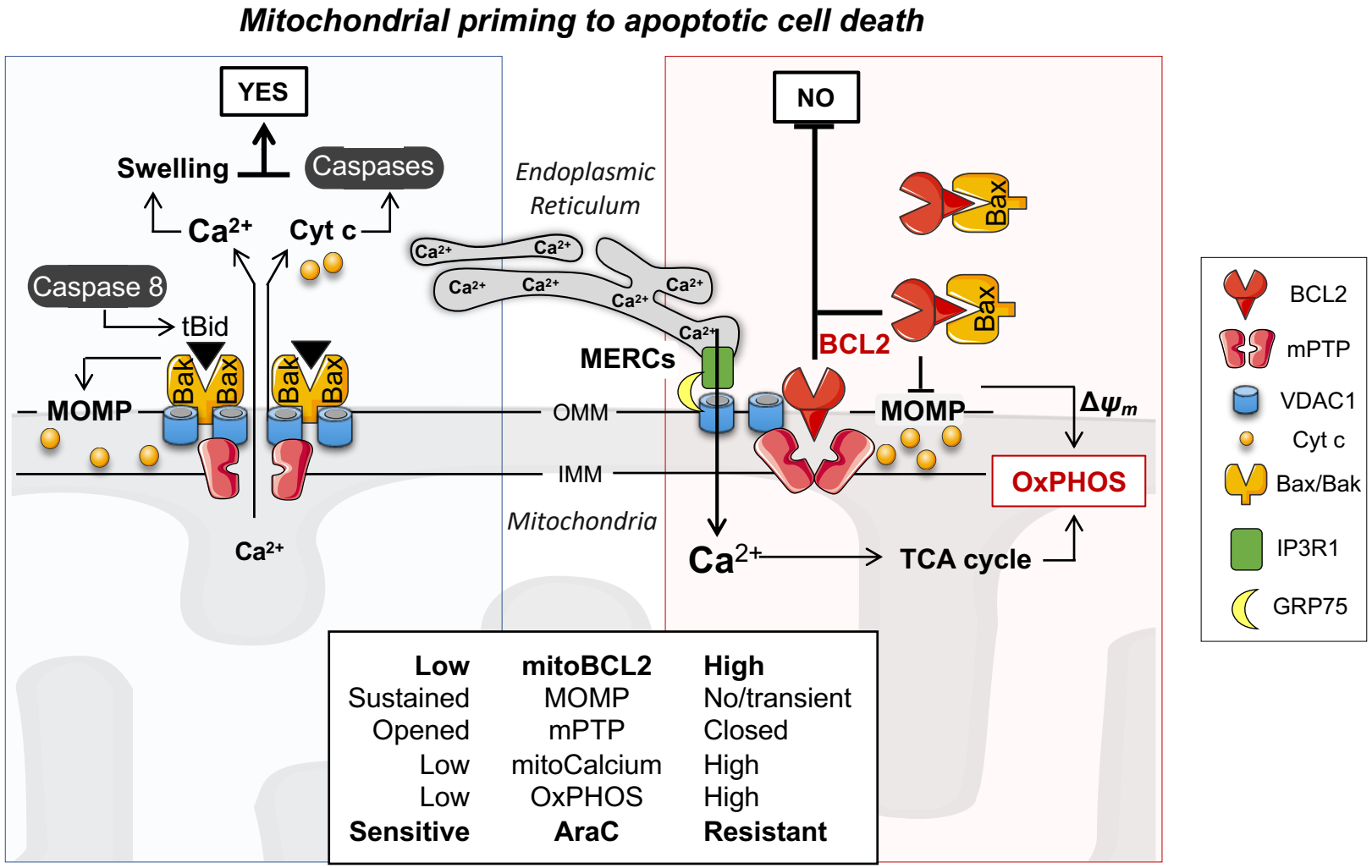
Proximity Ligation Assay IP3R1 / VDAC1



Electronic microscopy

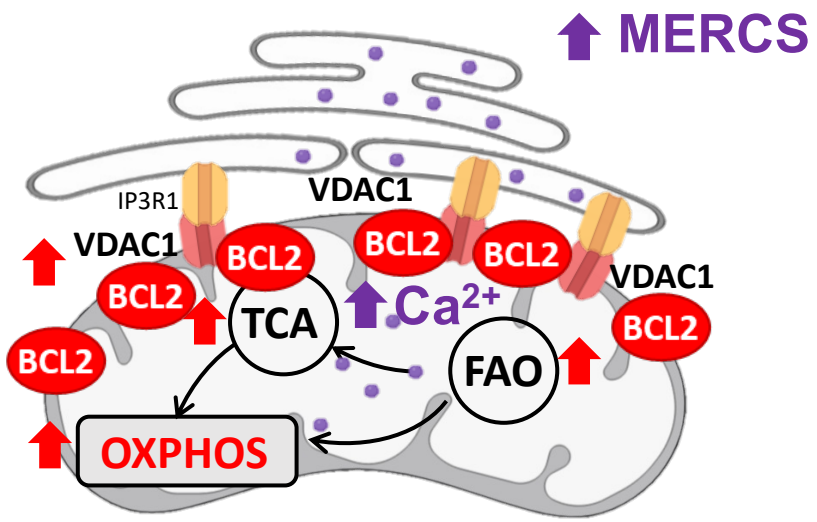
Ducau et al. unpublished data.
Bosc *et al* Nature Cancer 2021

Co-evolutionary interplay between OxPHOS state, mitochondrial BCL2 dependence and MERCS, redox balance, inflammation, drug persistence/resistance to apoptosis in AML



Bosc *et al*. Nature Cancer. 2021

Increased mitochondria-ER contact sites (MERCS) in Drug Persisters

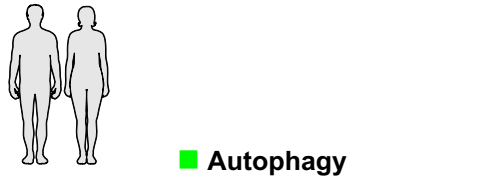


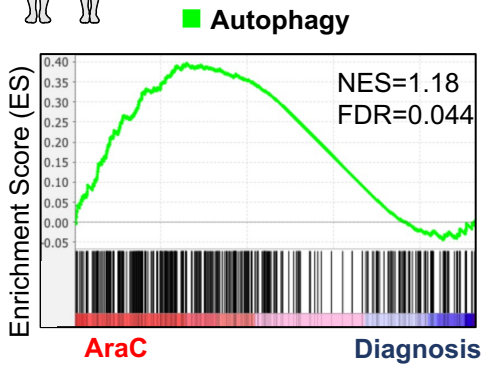
- Transfer of Ca^{2+} from ER to mitochondria

- Site of autophagosomes formation

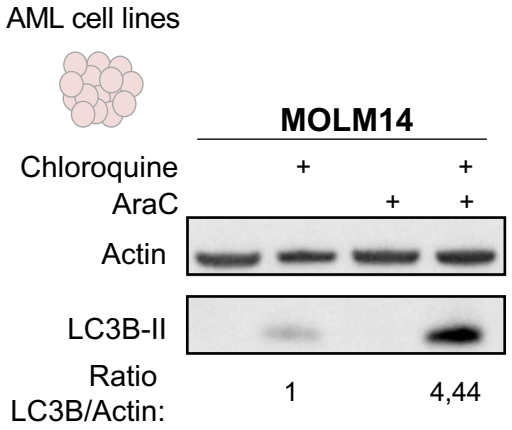
Hailey et al, ***Cell****, 2010*
Hamasaki et al, ***Nature,*** *2013*
Garofalo et al, ***Autophagy****, 2016*

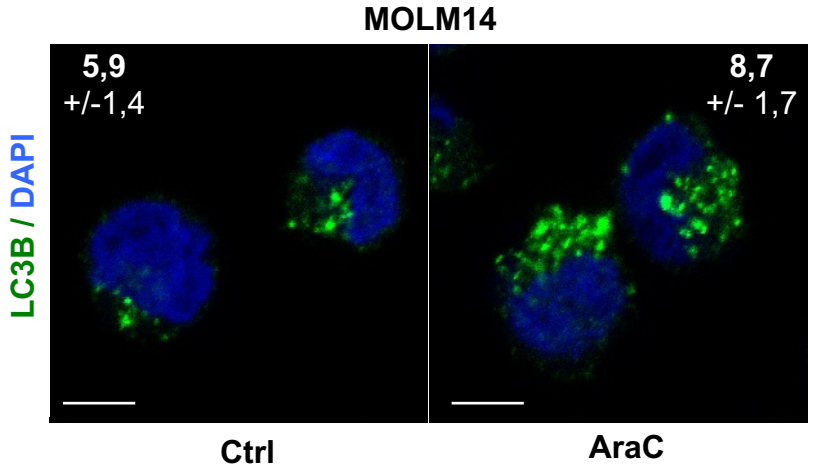
Autophagy is activated in drug persisters

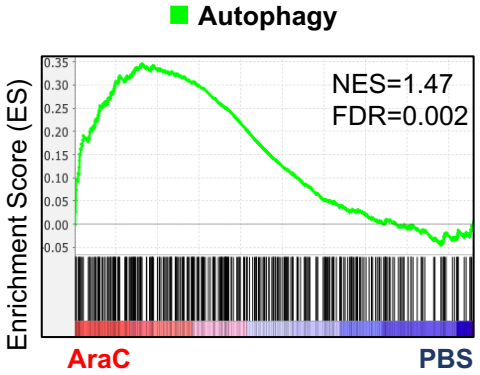




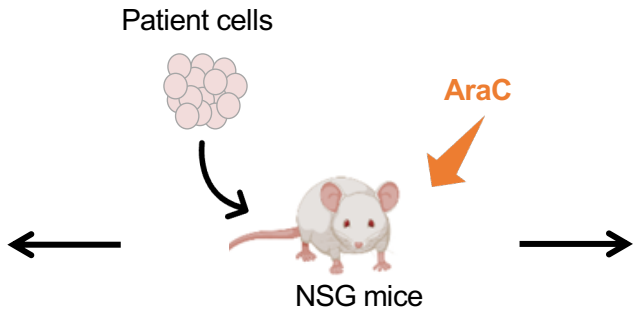
Duy et al, Cancer Discov, 2021

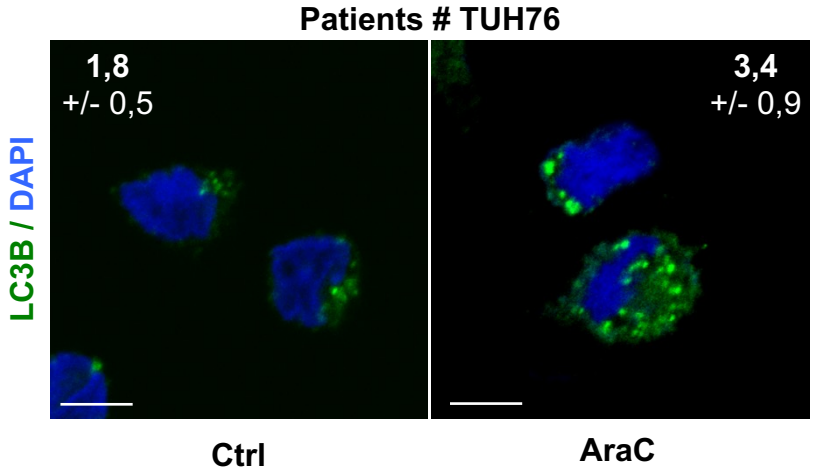






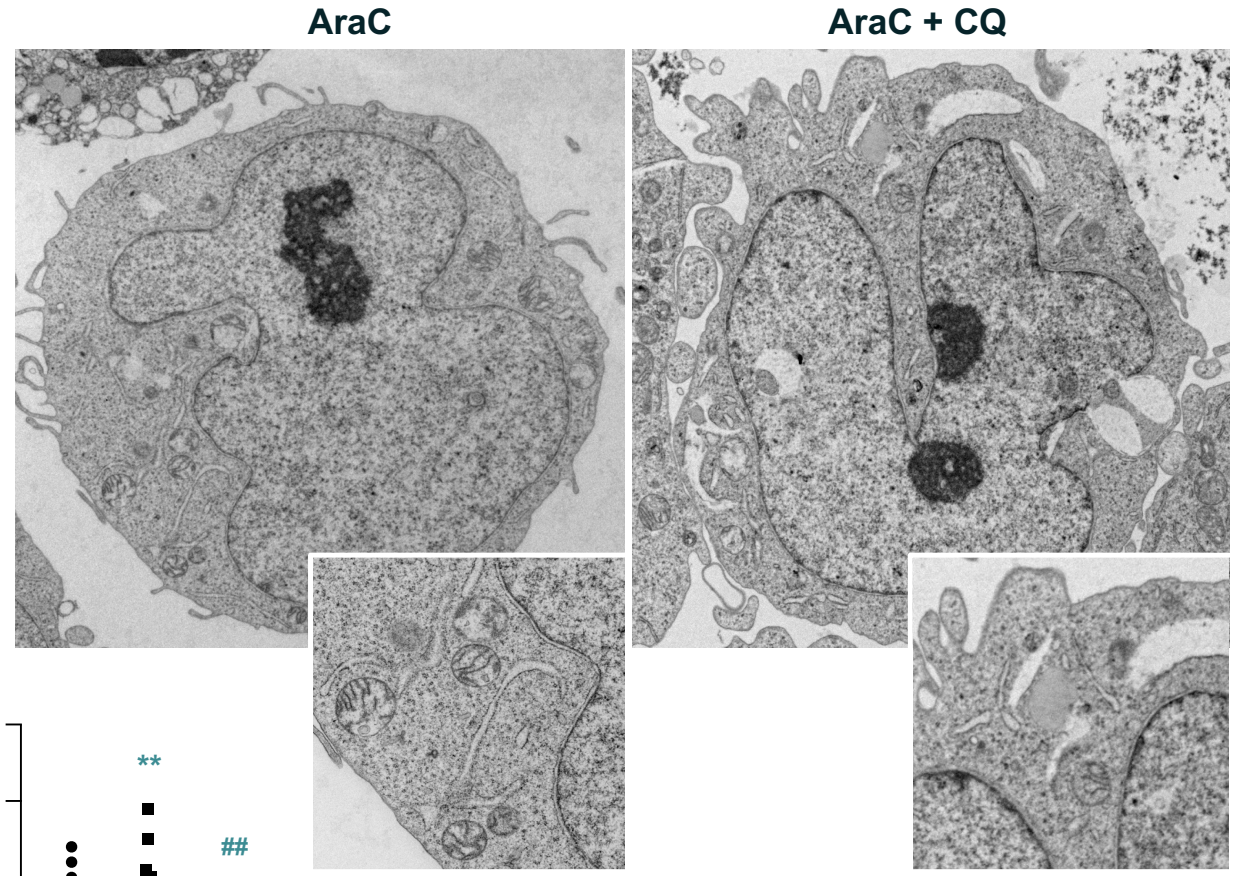
Farge et al, Cancer Discov, 2017

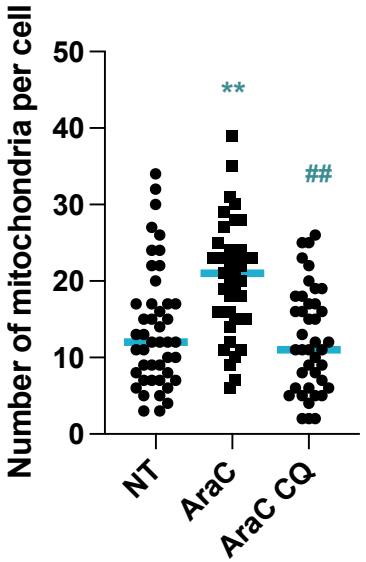


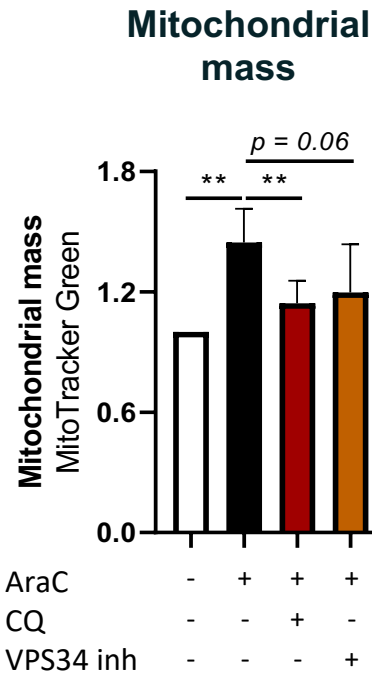


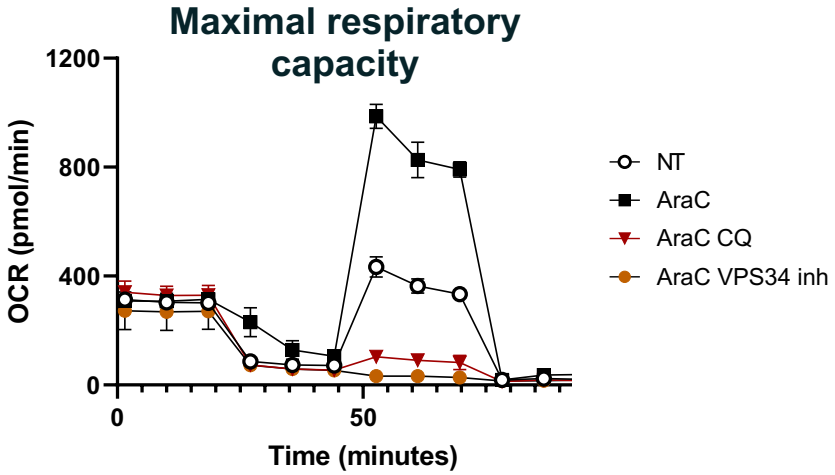
Ducau et al. unpublished data..

Autophagy implicates in AraC-induced mitochondrial adaptation



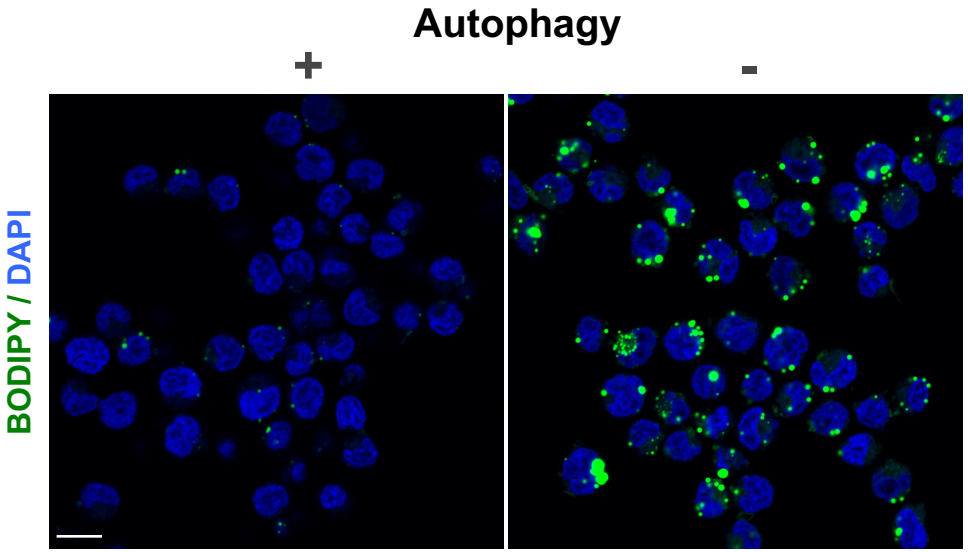


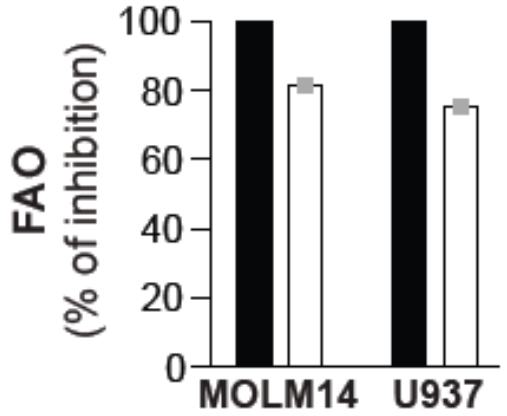


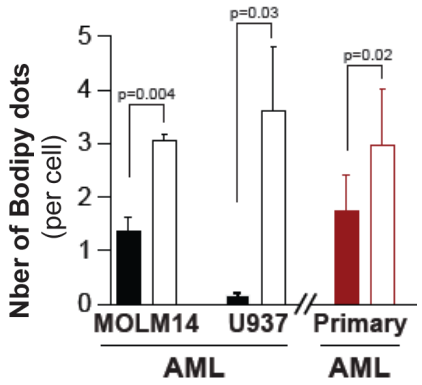


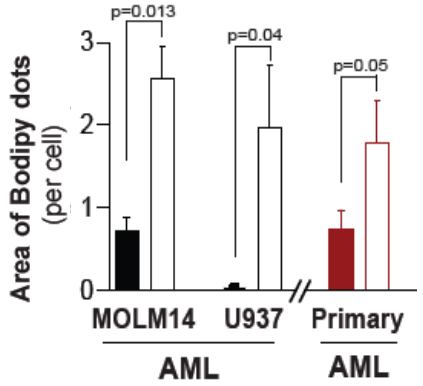
Ducau et al. unpublished data.

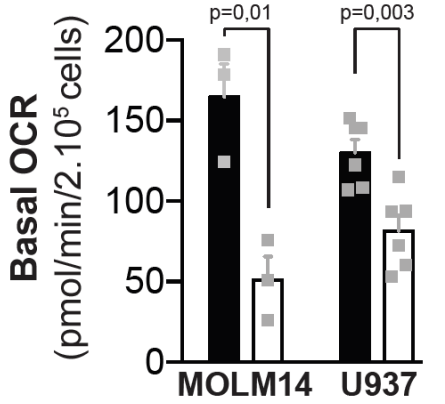
Autophagy regulates lipid catabolism to support OxPHOS





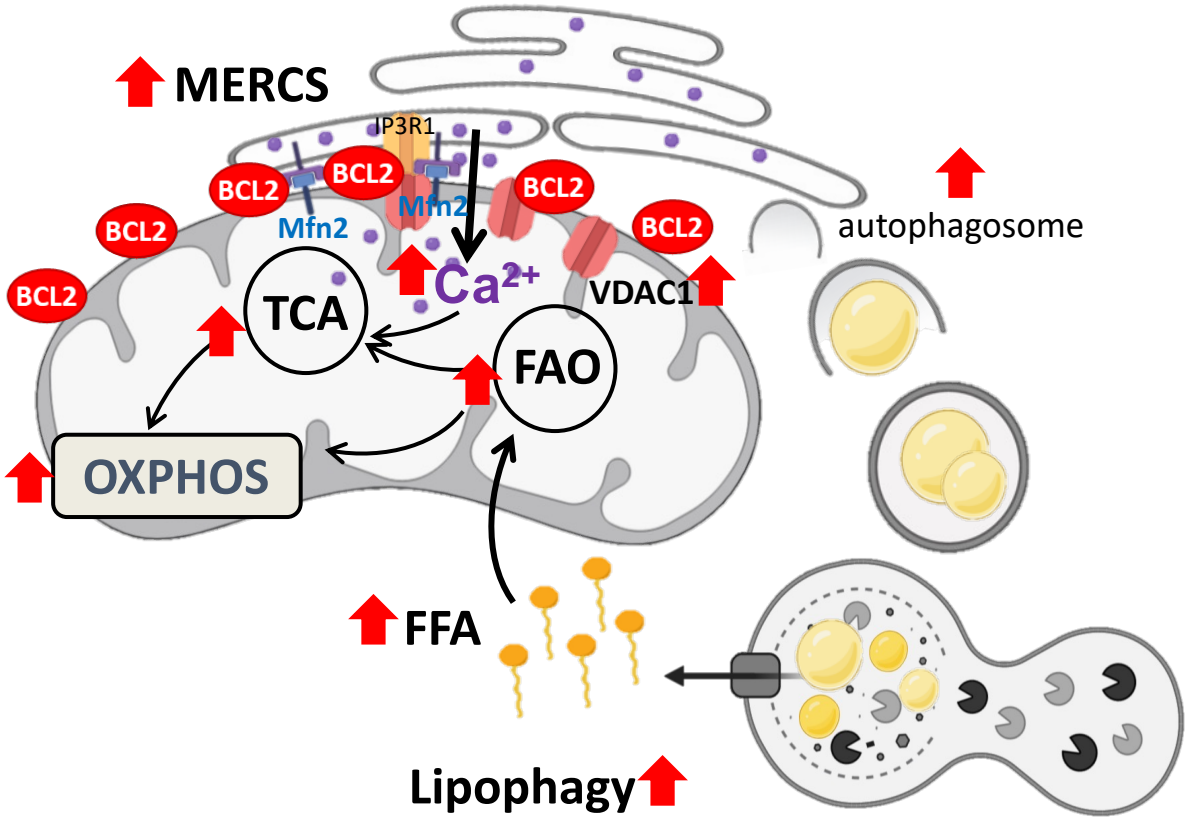






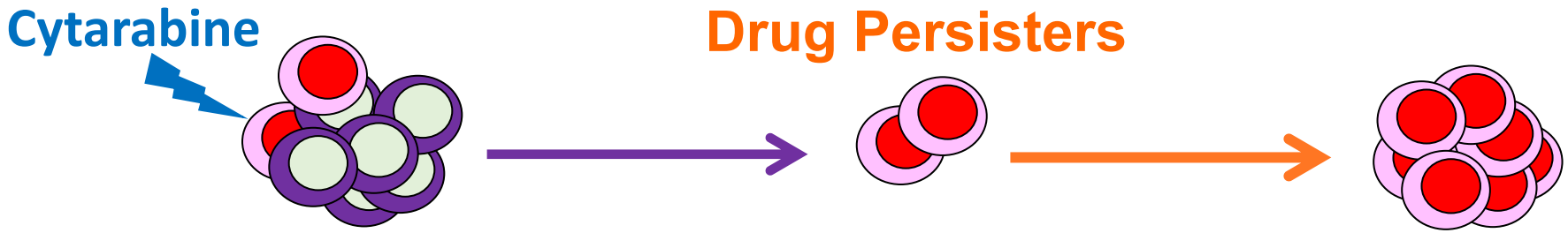
Bosc* *et al* Nature Comms 2020.

MERCS-dependent lipophagy is activated to support FAO and OxPHOS in drug persisters



Bosc *et al* Nature Cancer 2021; Bosc* *et al* Nature Comms 2020.

OxPHOS phenotype reflects a mitochondrial adaptation induced by a specific transcriptional program in response to an early AraC-triggered mitochondrial stress



↘ ΔΨm → ↗ ROS ↗ mtDNA release ↘ ATP → ↗ cAMP-PKA ↗ ATF4 → *PGC1α* *TFAM* *NRF1/2* → ↗ FAO and OxPHOS ↗ Mito biogenesis ↗ Antioxidants

Mitochondrial Transient Dysfunction → **Mitochondrial Stress Response** → **Mitochondrial Recovery/Adaptation** → **Drug tolerance Drug resistance**

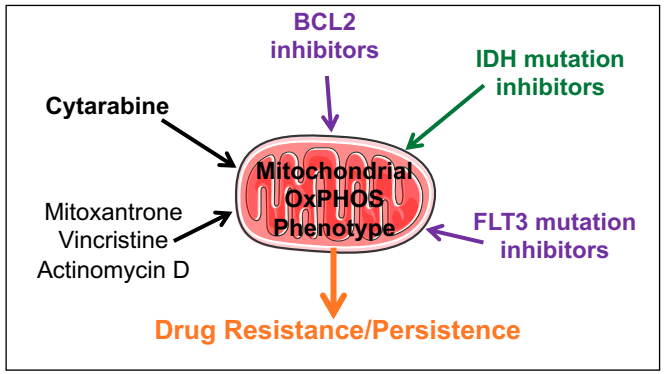
Boet et al. in prep
Aroua*, Boet*, Ghisi* *et al*. Cancer Discov. 2020

Summary I

> Changes in mitochondrial energetics, metabolism, and structure are **hallmarks of drug resistance:** central role of adaptations in mitochondrial dynamics and OxPHOS flexibility during therapy, driving residual disease and drug tolerance/persistence in AML

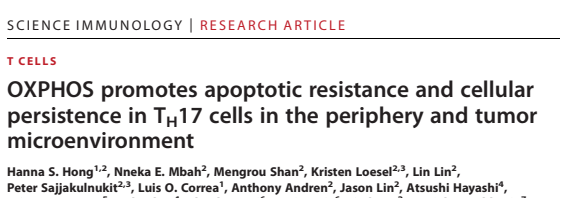
> Inhibiting ANY aspect of mitochondrial OxPHOS metabolism circumvents adaptive resistance to drugs and enhances the sensitivity of AML cells to chemotherapy or currently approved targeted therapies

> Mitochondrial metabolism associated with drug resistance/persistence in other blood cancers and several therapy-resistant solid cancers including melanoma, PDAC, TNBC, sarcoma, metastatic grade…




LETTER

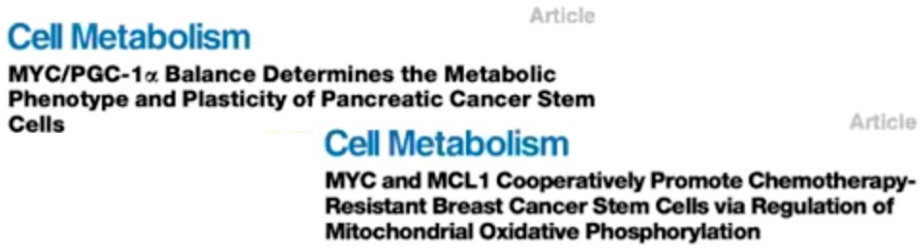
Oncogene ablation-resistant pancreatic cancer cells depend on mitochondrial function


SCIENCE IMMUNOLOGY | RESEARCH ARTICLE

T CELLS

OXPHOS promotes apoptotic resistance and cellular persistence in T_H17 cells in the periphery and tumor microenvironment

Hanna S. Hong[1,2], Nneka E. Mbah[2], Mengrou Shan[2], Kristen Loesel[2,3], Lin Lin[2], Peter Sajjakulnukit[2,3], Luis O. Correa[1], Anthony Andren[2], Jason Lin[2], Atsushi Hayashi[4],


Article

Cell Metabolism

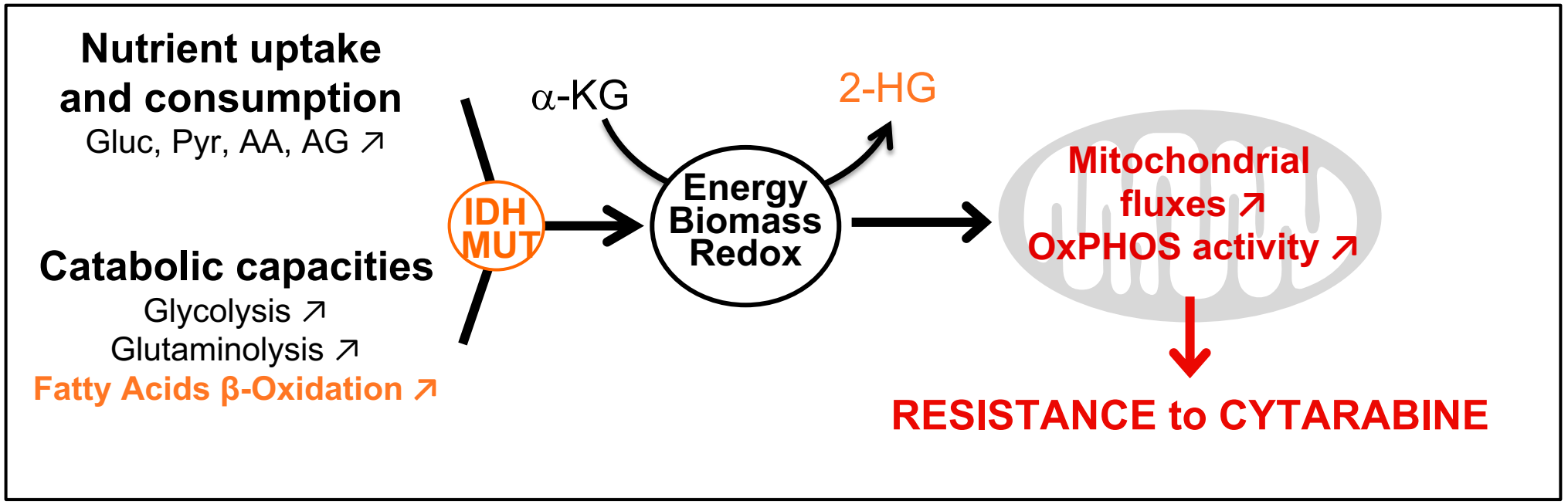
MYC/PGC-1α Balance Determines the Metabolic Phenotype and Plasticity of Pancreatic Cancer Stem Cells

Article

Cell Metabolism

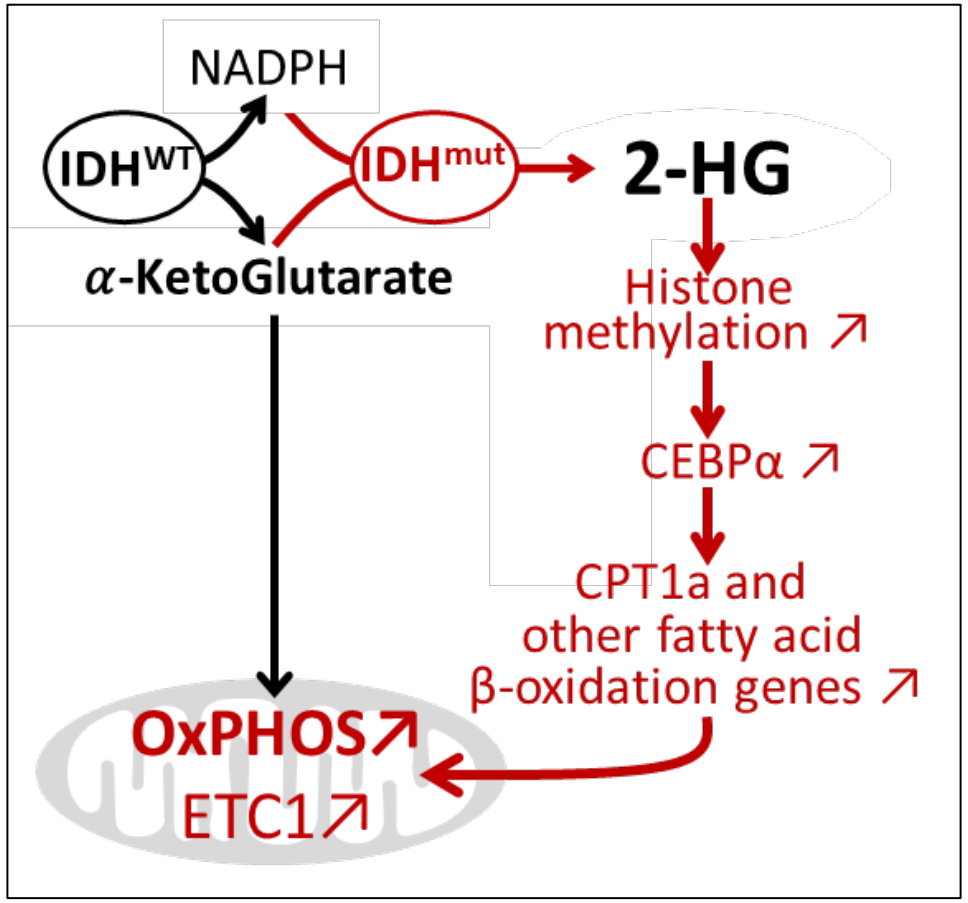
MYC and MCL1 Cooperatively Promote Chemotherapy-Resistant Breast Cancer Stem Cells via Regulation of Mitochondrial Oxidative Phosphorylation

High OxPHOS activities are the metabolic consequence of an enhanced catabolic capacities and flexibility in IDH1/2 mutant AML



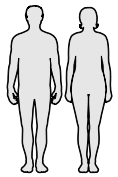
Stuani *et al*. in prep; Hucteau *et al*. in prep
Stuani *et al*. IJMS. 2019; Stuani *et al*. JEXPMED. 2021

Mitochondrial OxPHOS supports IDH mutant cell proliferation and chemoresistance in a C/EBPα-dependent manner



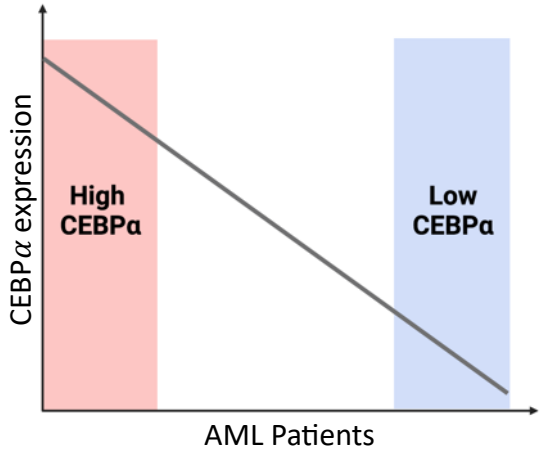
Stuani *et al*. JEXPMED. 2021

Might C/EBPα be implicated into other metabolic pathways or subgroups of AML patients ?

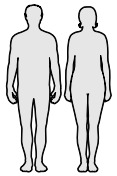


Transcriptomes AML patients

3 independent cohorts
TCGA-LAML, BEATAML
Verhaak



Patients over-expressing C/EBPα are associated with FLT3 mutations



Transcriptomes AML patients

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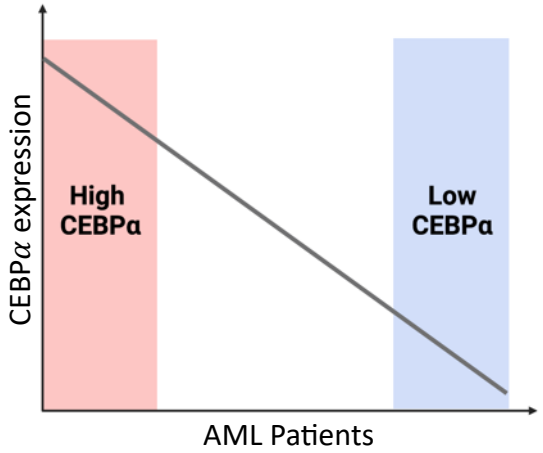
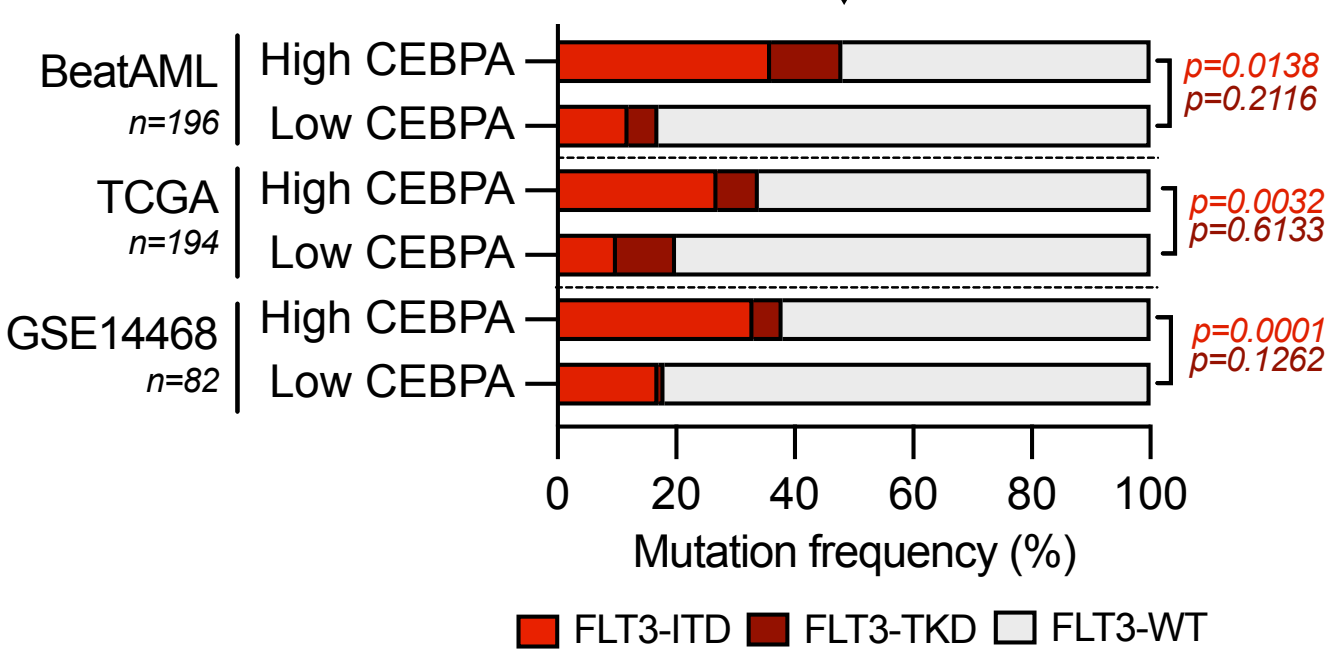
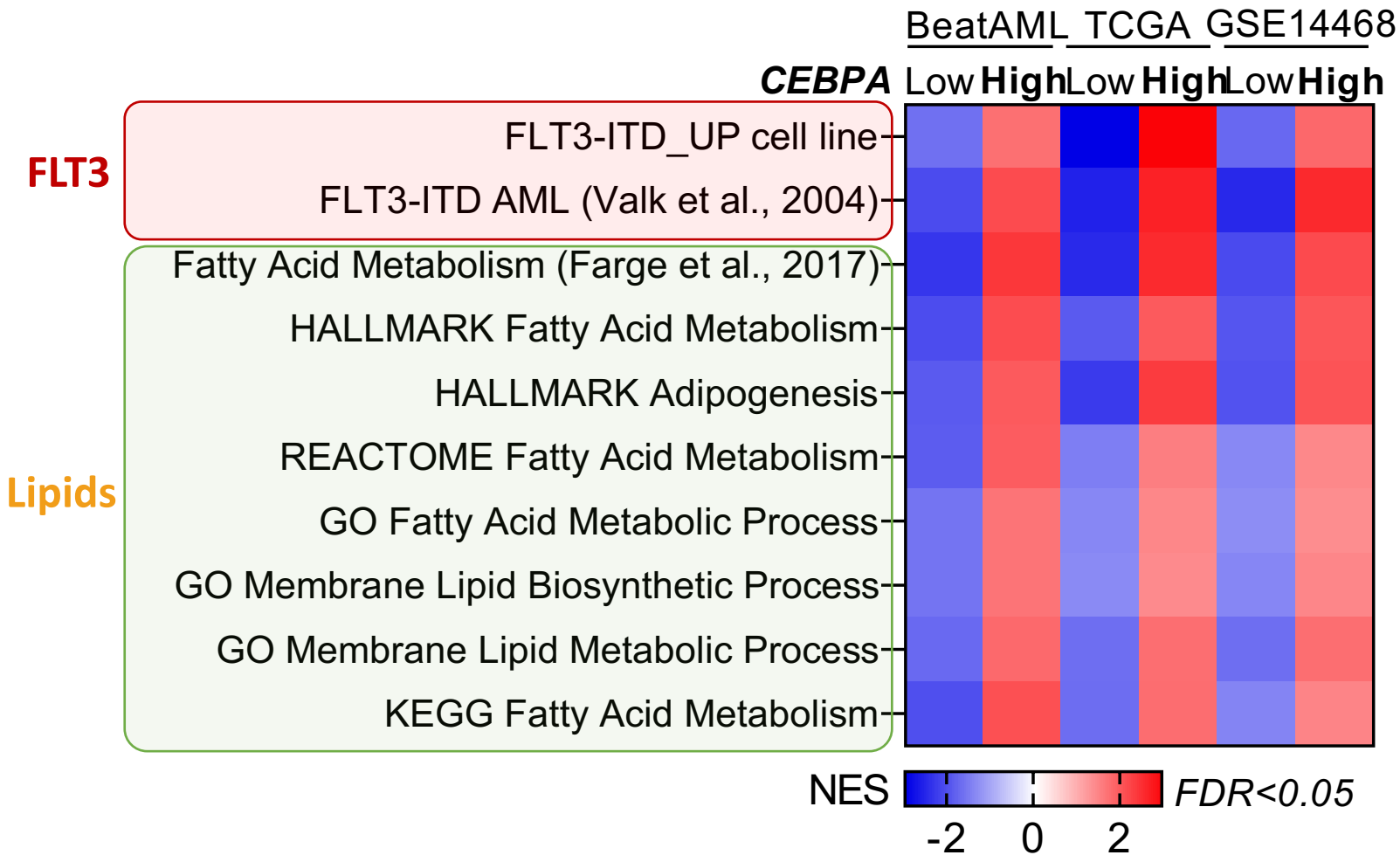
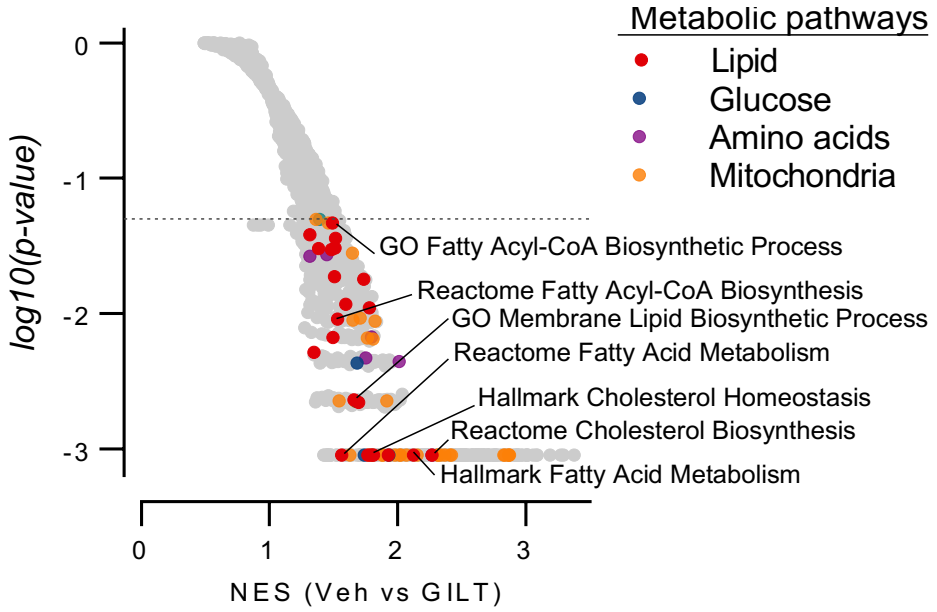




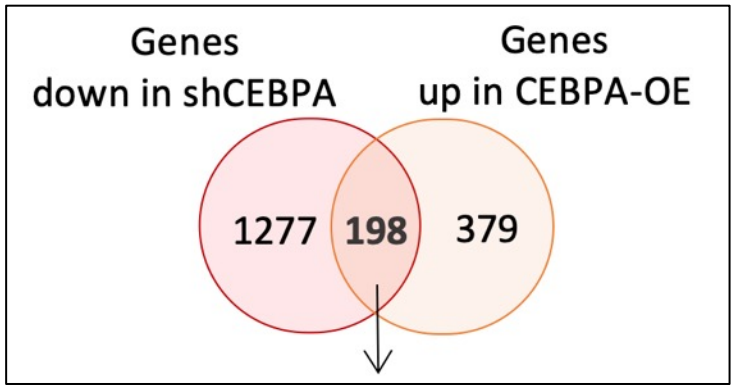
Patients overexpressing C/EBPα are associated with FLT3 mutations and are enriched in gene signatures related to lipid metabolism



Gene set enrichment In 6 FLT3-ITD PDX models



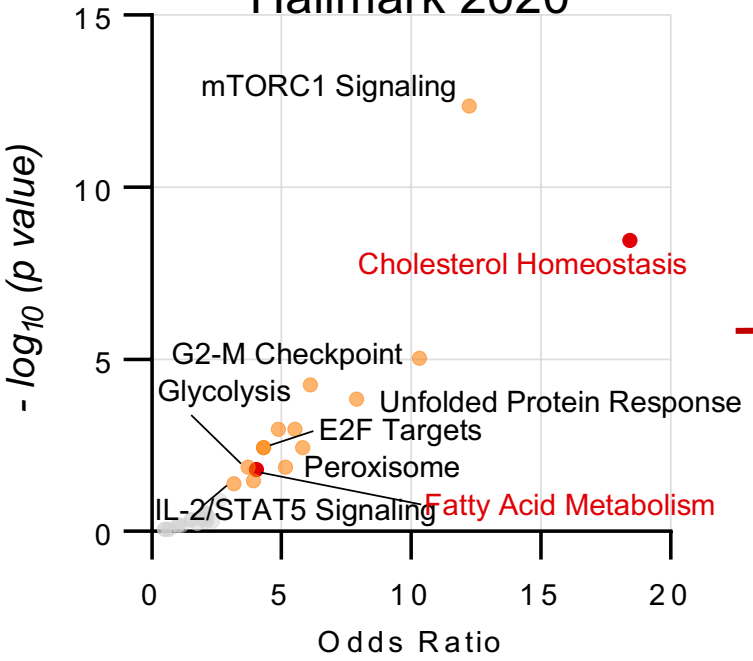
C/EBPα activation is linked to FLT3-ITD mutations and lipid biosynthesis

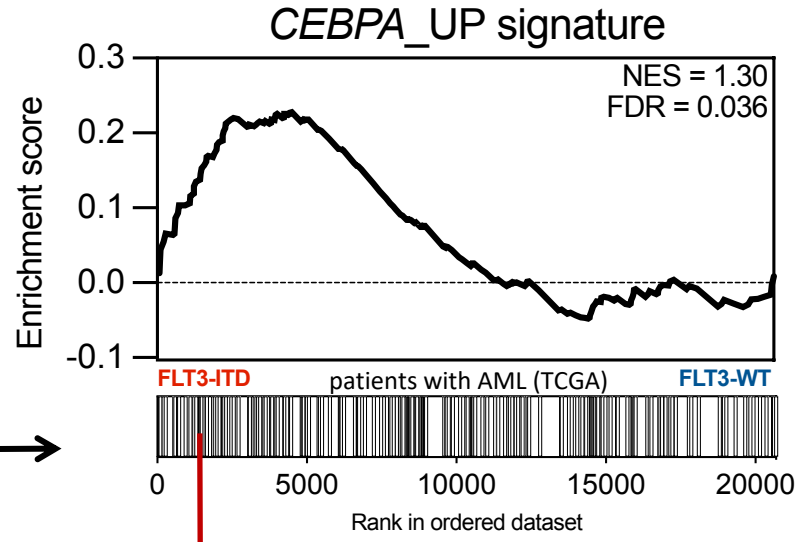


*CEBPA*_UP signature

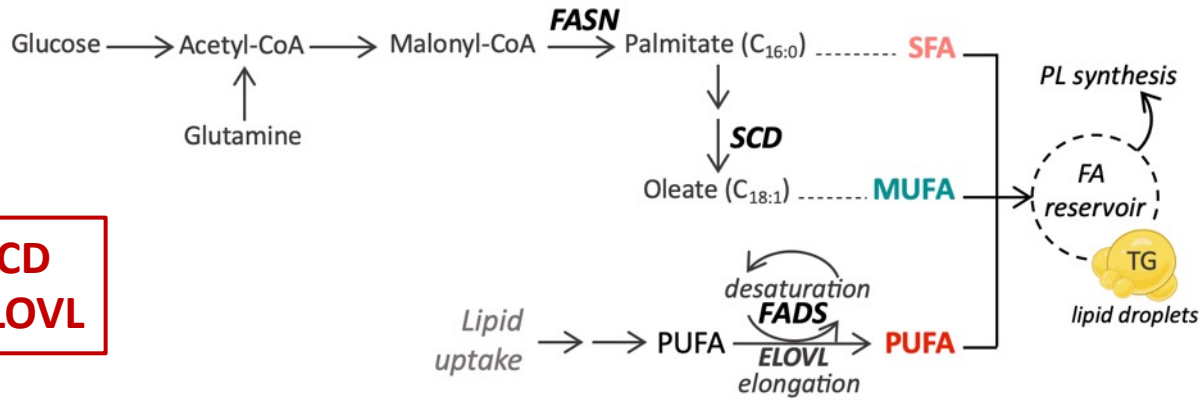
↓

Hallmark 2020





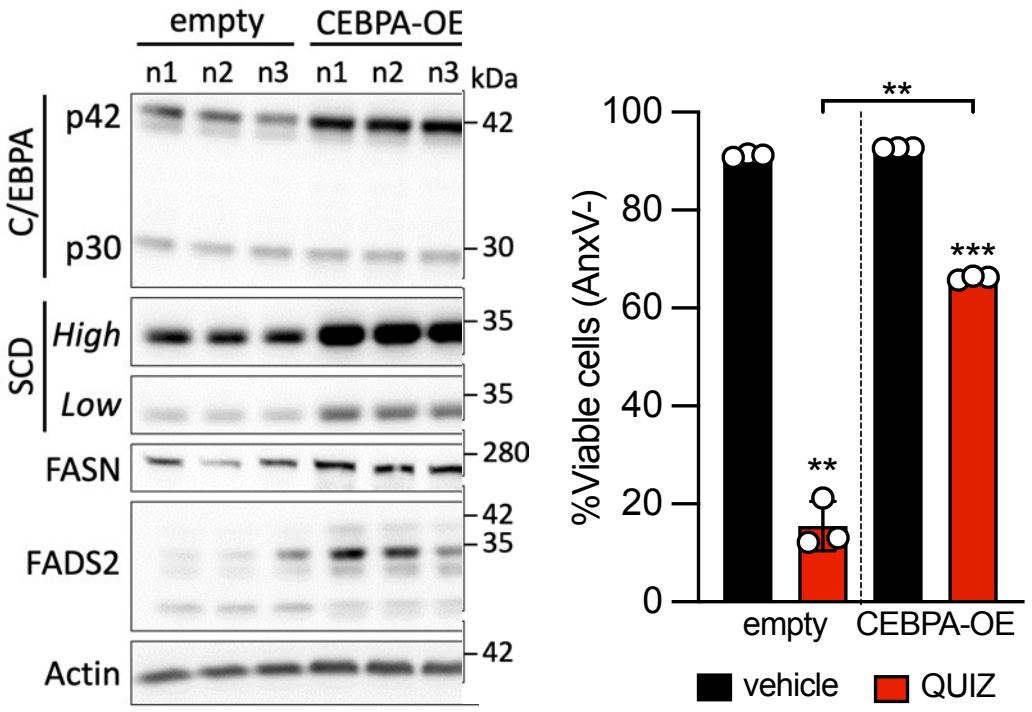
FASN, SCD
FADS2, ELOVL



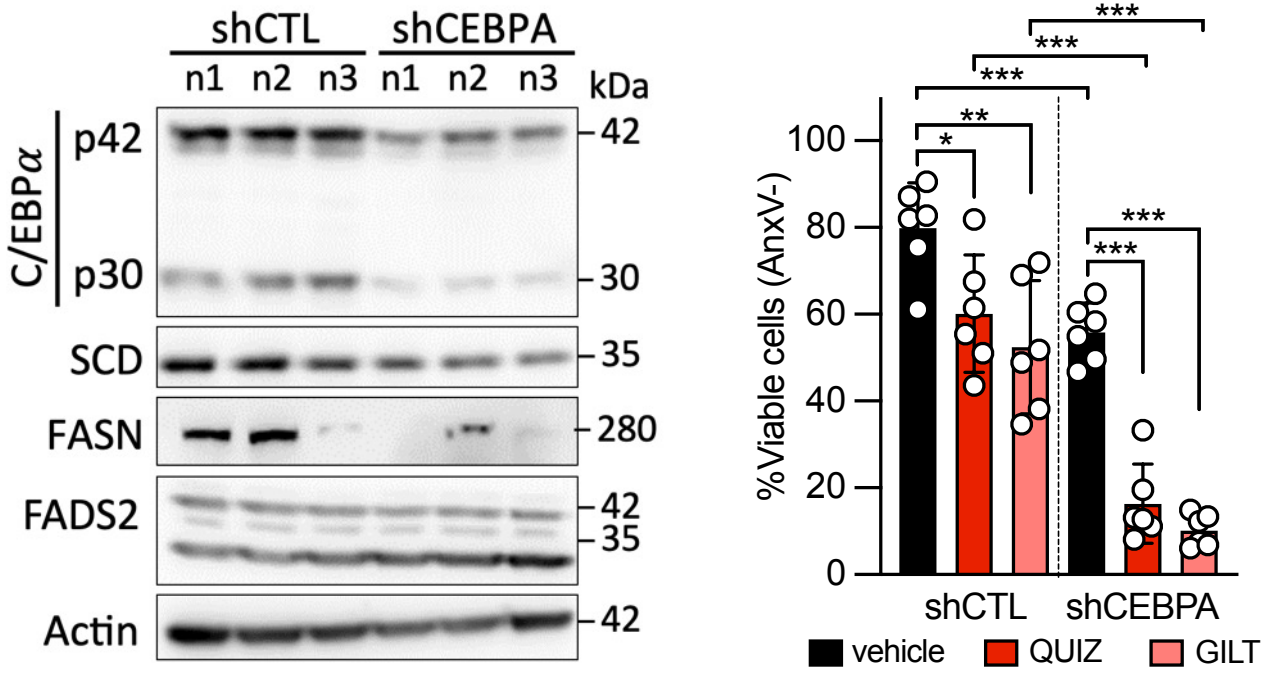
FA: fatty acids; **SFA**: saturated fatty acids
MUFA: mono-unsaturated fatty acids;
PUFA: poly-unsaturated fatty acids

FLT3i-induced cell death is dependent on CEBPα

CEBPα overexpression



CEBPα invalidation



QUIZ and GILT: FLT3-ITD inhibitors

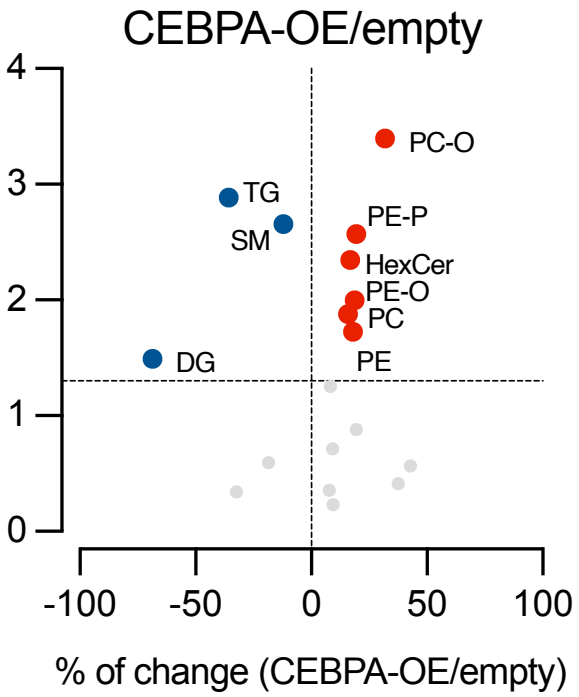
CEBPα regulates the lipidome of FLT3-ITD AML cells

CEBPα overexpression

PHOSPHOLIPIDS ↗

SPHINGOLIPIDS ↘

TRIGLYCERIDES ↘

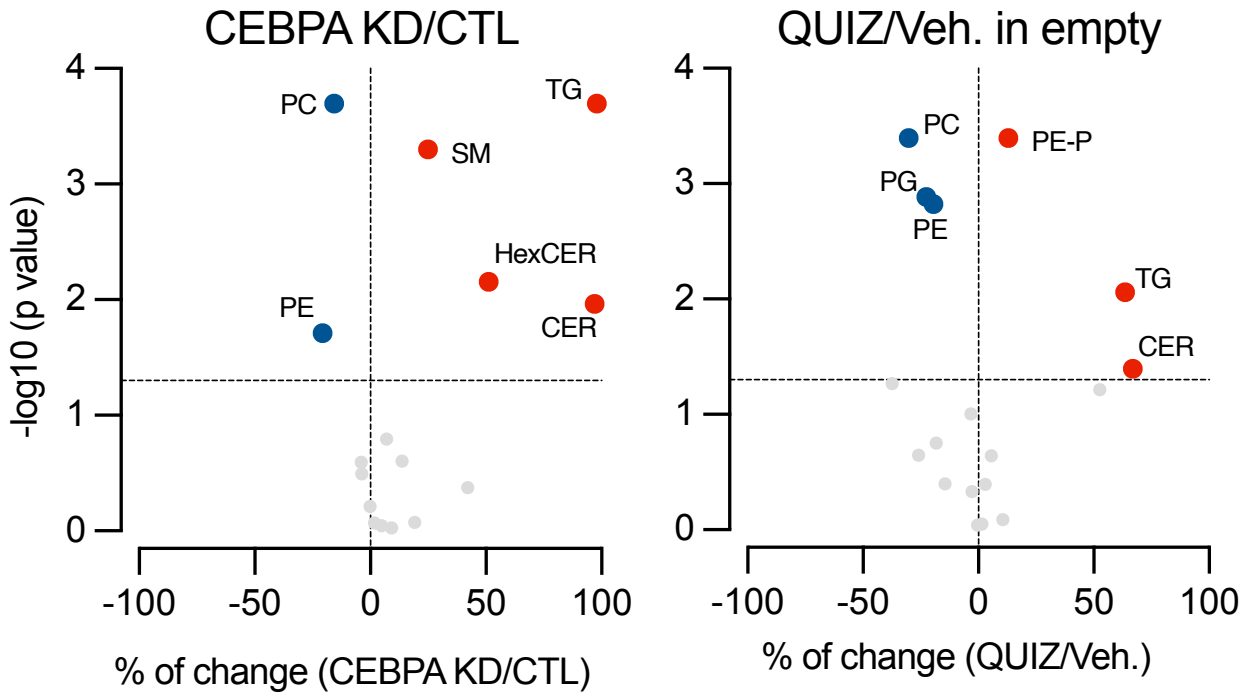


CEBPα or FLT3 inhibiton

PHOSPHOLIPIDS ↘

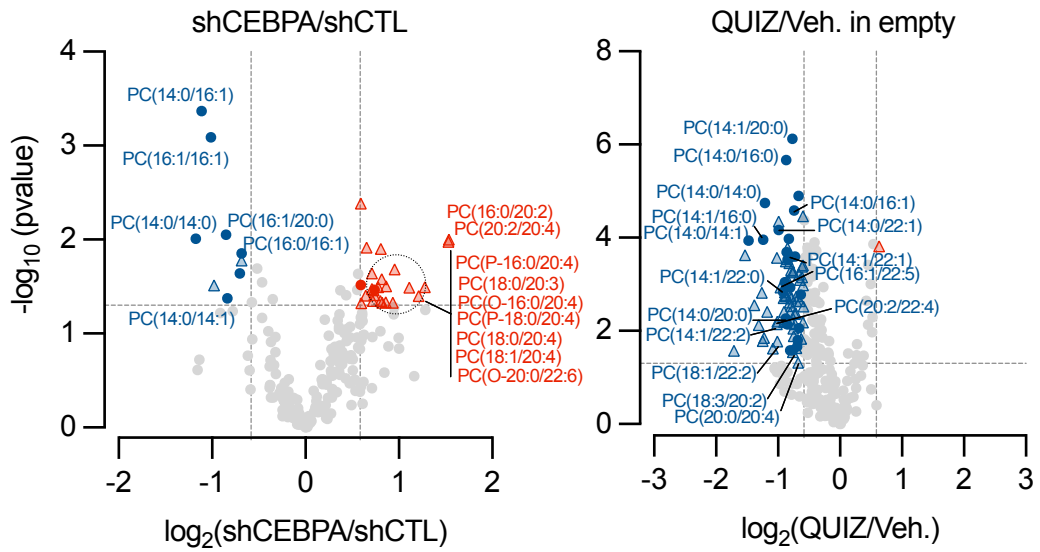
SPHINGOLIPIDS ↗

TRIGLYCERIDES ↗



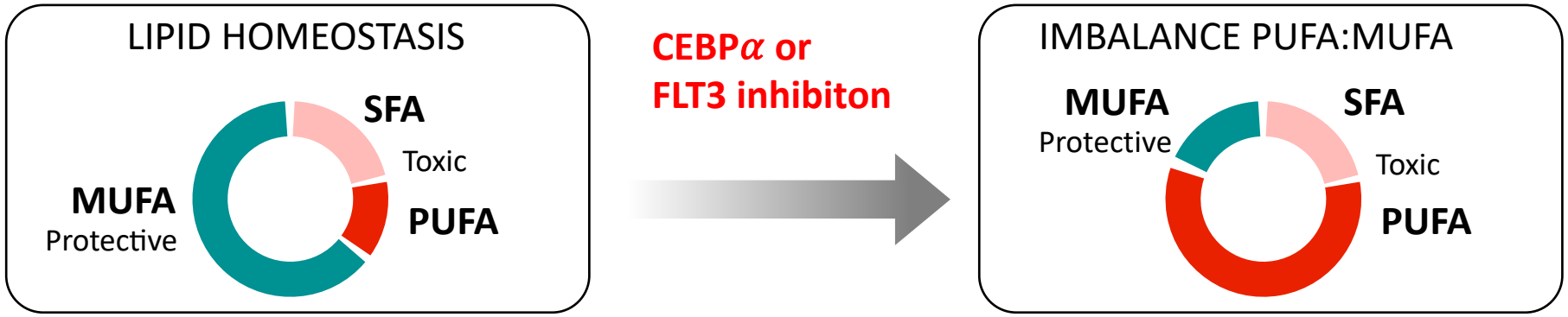
FA saturation distribution in FLT3^{MUT} AML cells in a C/EBPα-dependent manner

CEBPα invalidation or FLT3 inhibiton

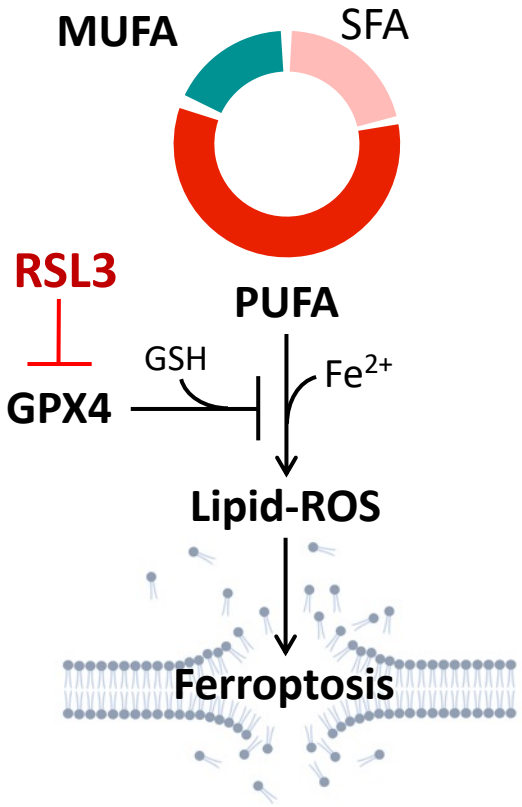


SFA-MUFA ↘

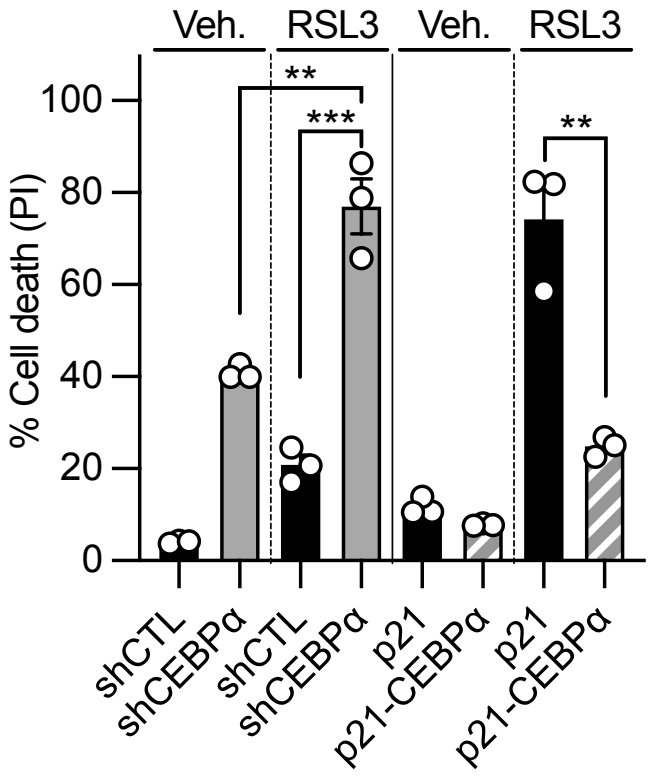
PUFA ↗



C/EBPα mediates sensitivity to lipid oxidative stress induced by ferroptotic inducer

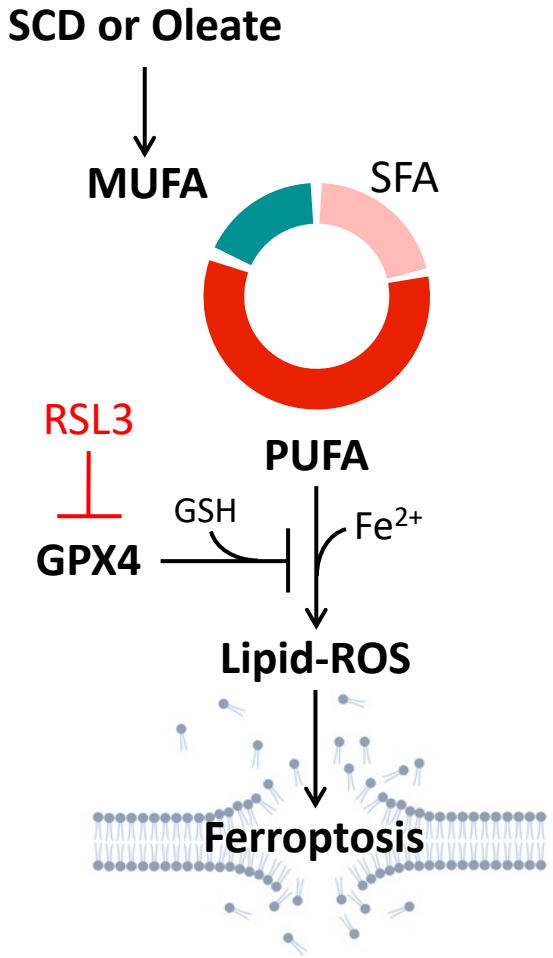


Invalidation vs. Overexpression of CEBPα

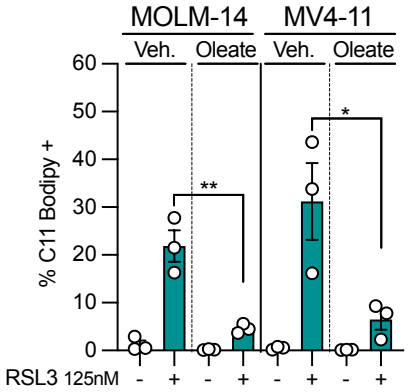


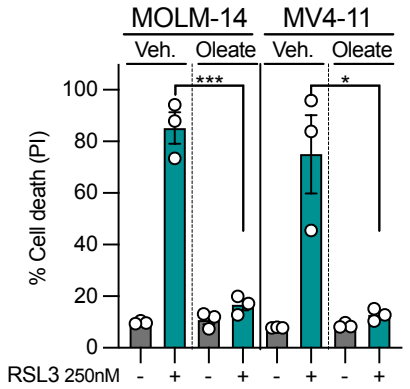
RSL3: GPX4 inhibitor

SCD mediates sensitivity to lipid oxidative stress induced by ferroptotic inducer

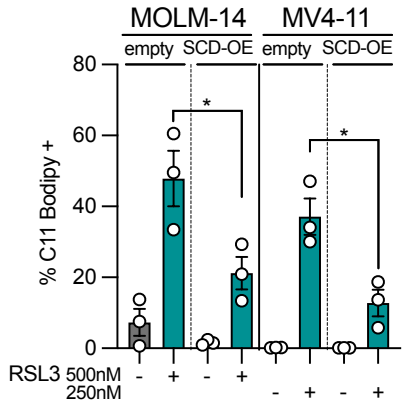


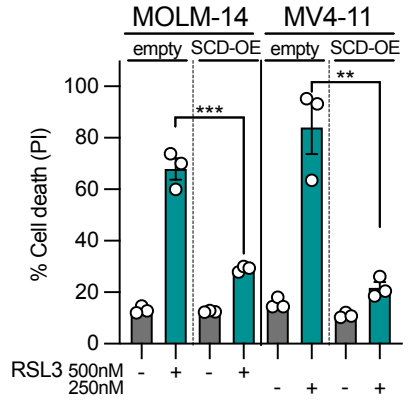
Supplemented MUFA oleate



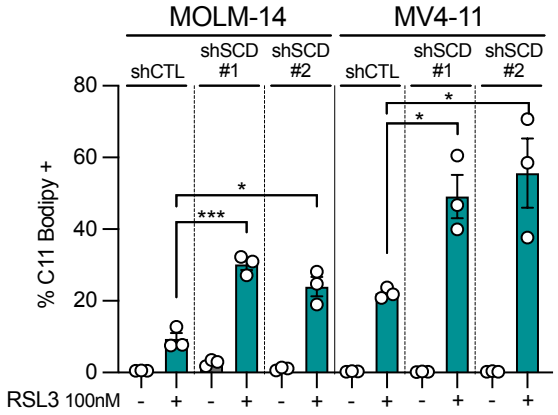


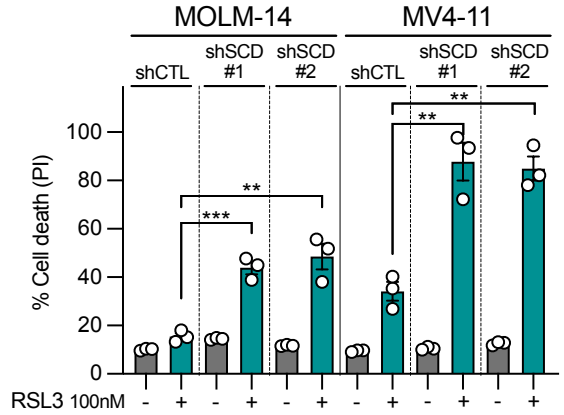
Overexpressed SCD



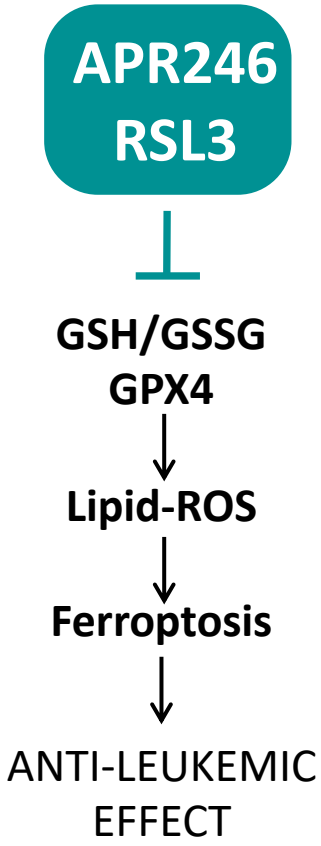


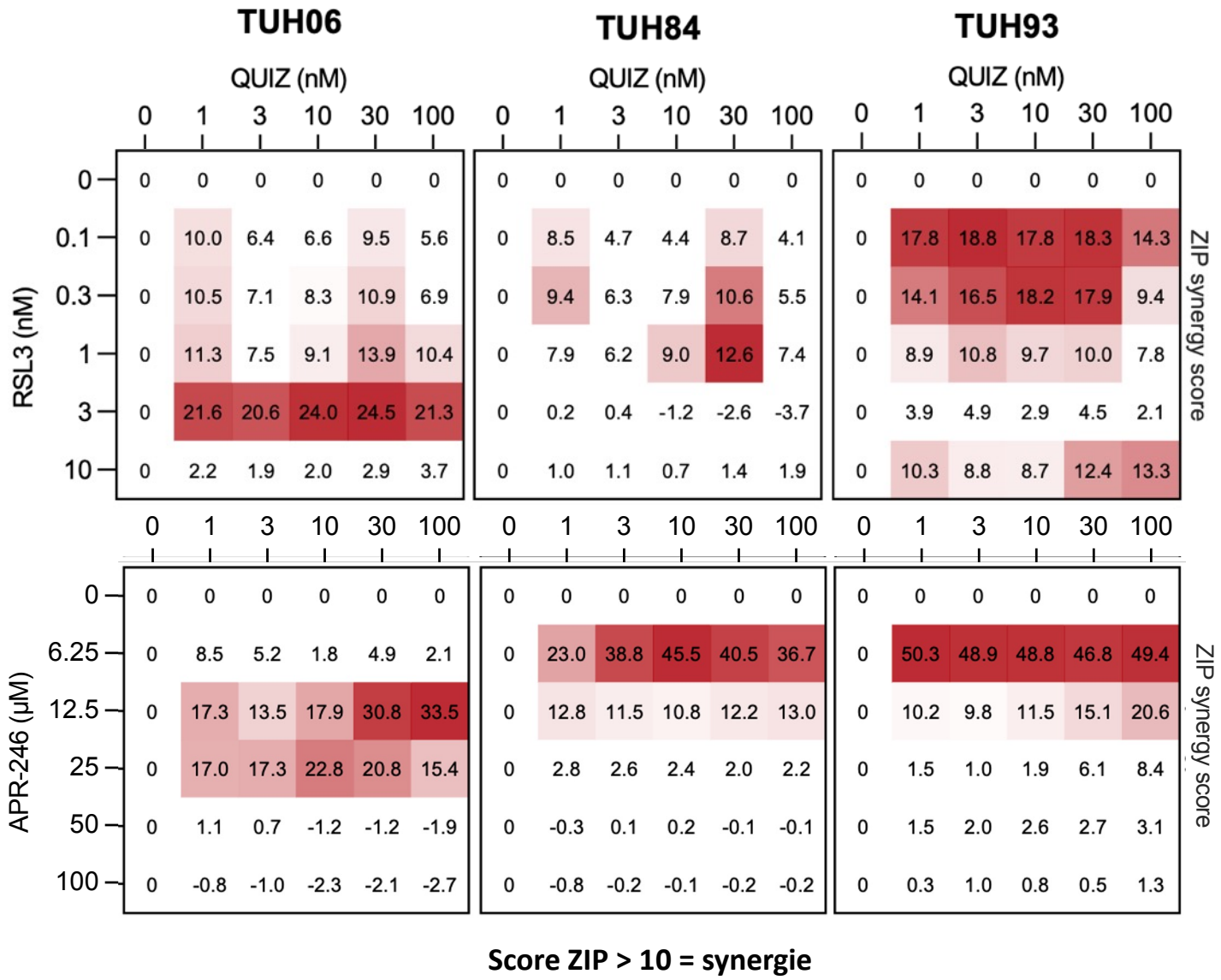
Silenced SCD





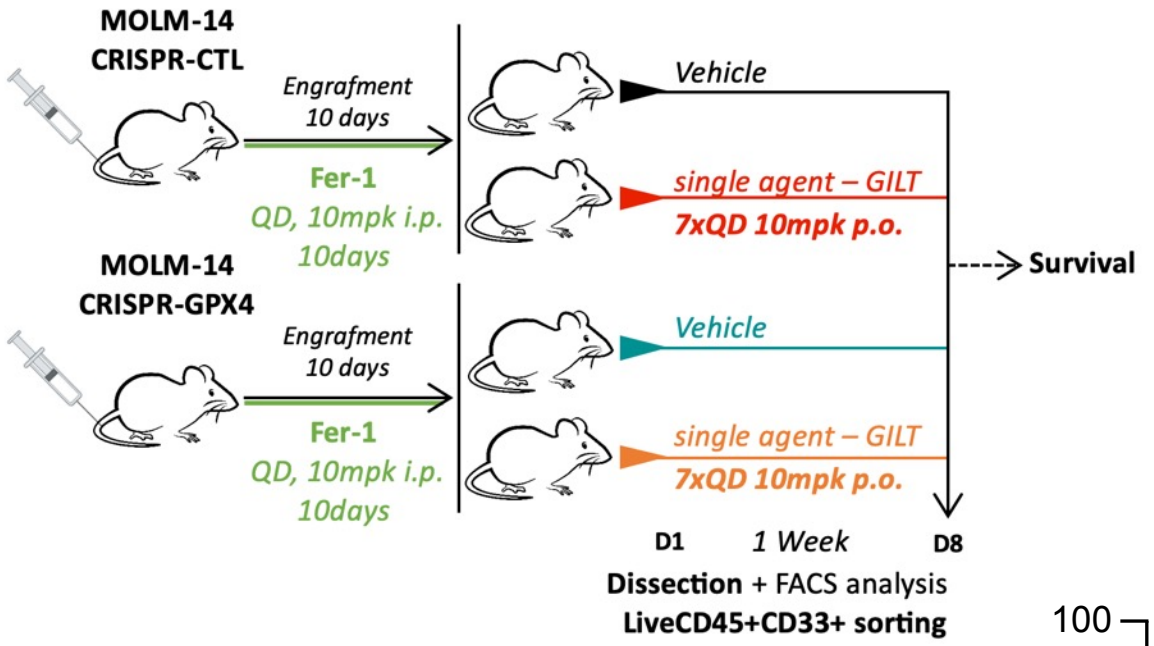
Combination of GPX4i (ferroptosis inducers) with FLT3i enhances cell death in FLT3-ITD primary cells *ex vivo*

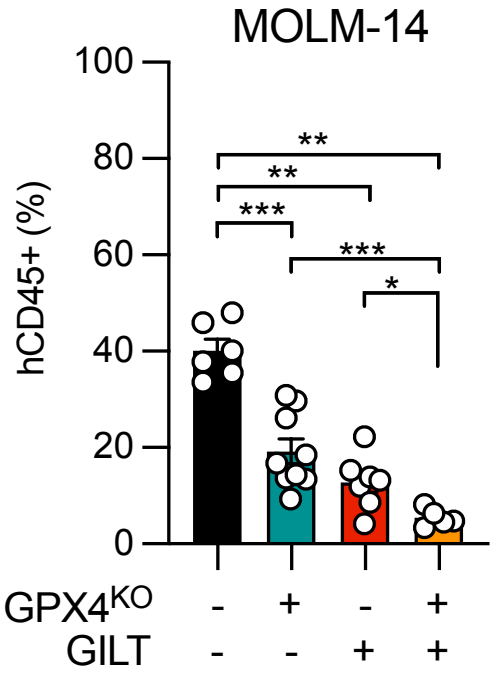


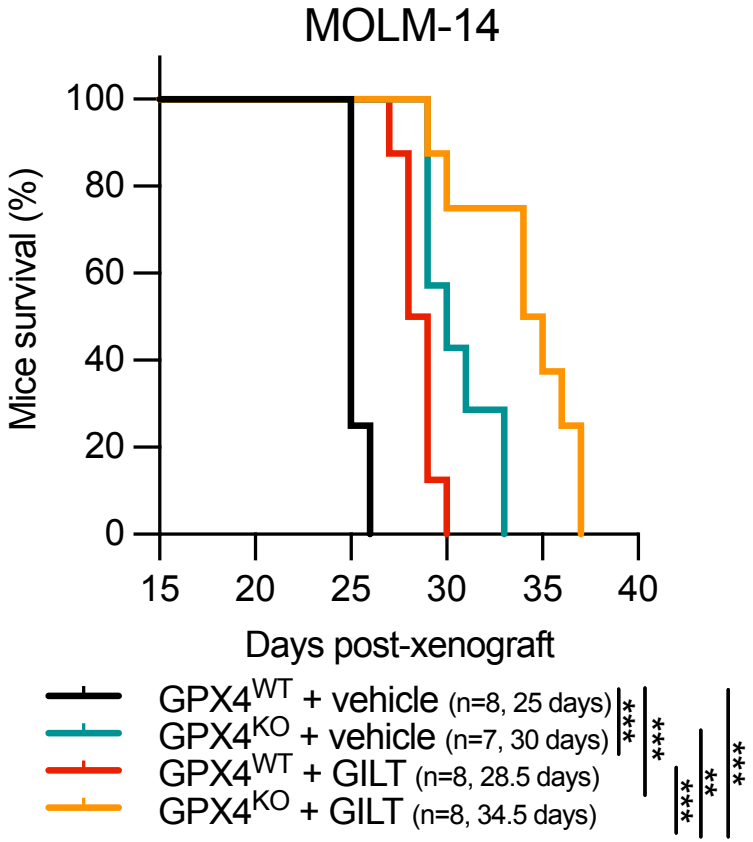


Score ZIP > 10 = synergie

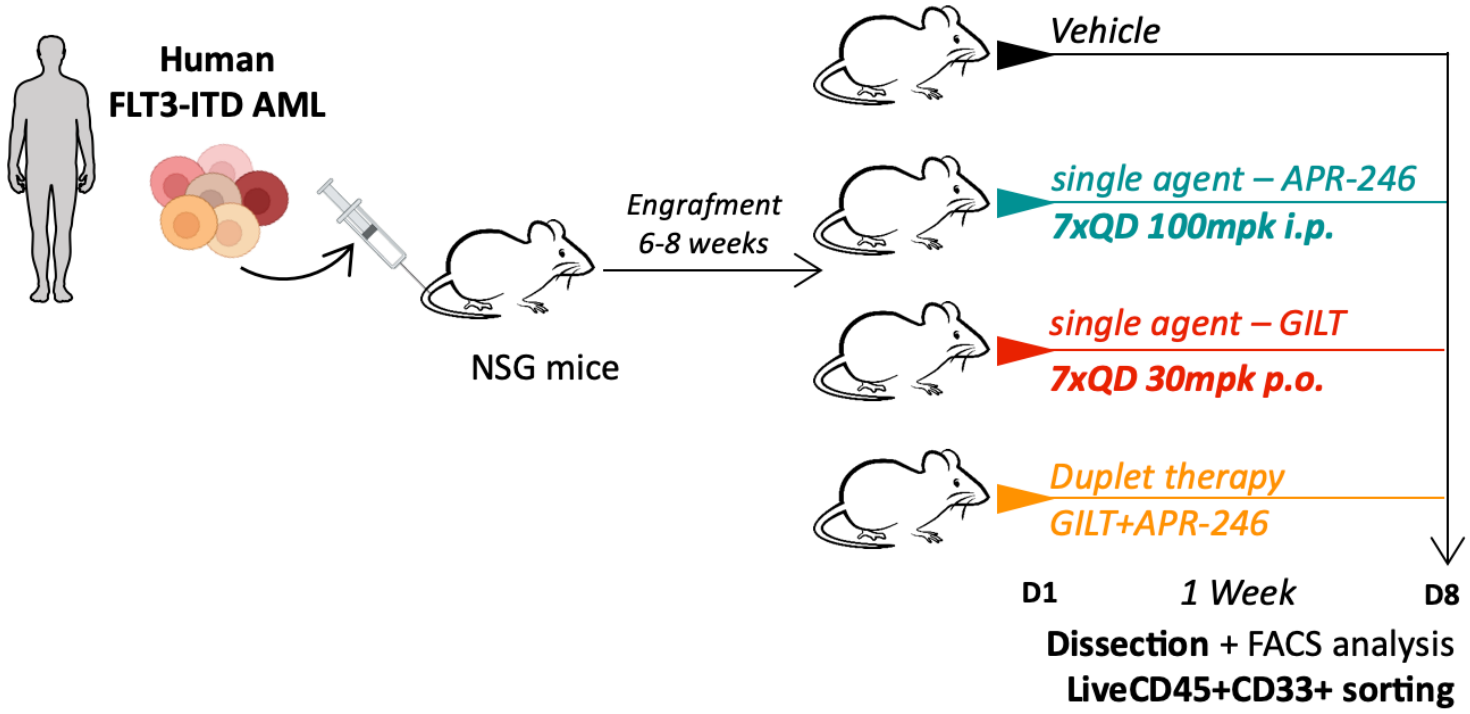
Genetic invalidation of GPX4 increases anti-leukemic effect of GILT *in vivo*

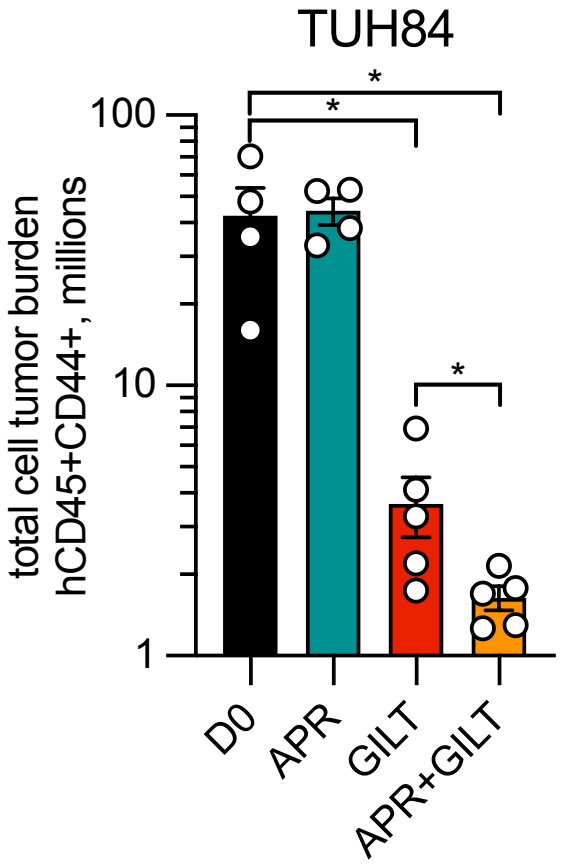




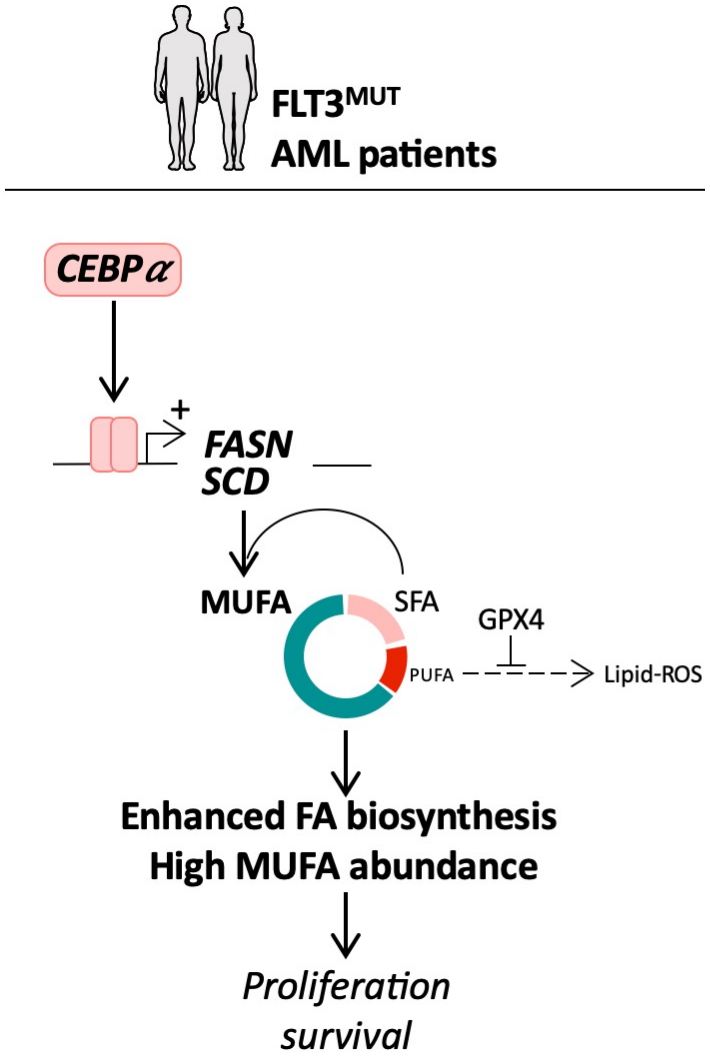


GPX4 inhibitor APR-246 increases anti-leukemic effect of GILT *in vivo*





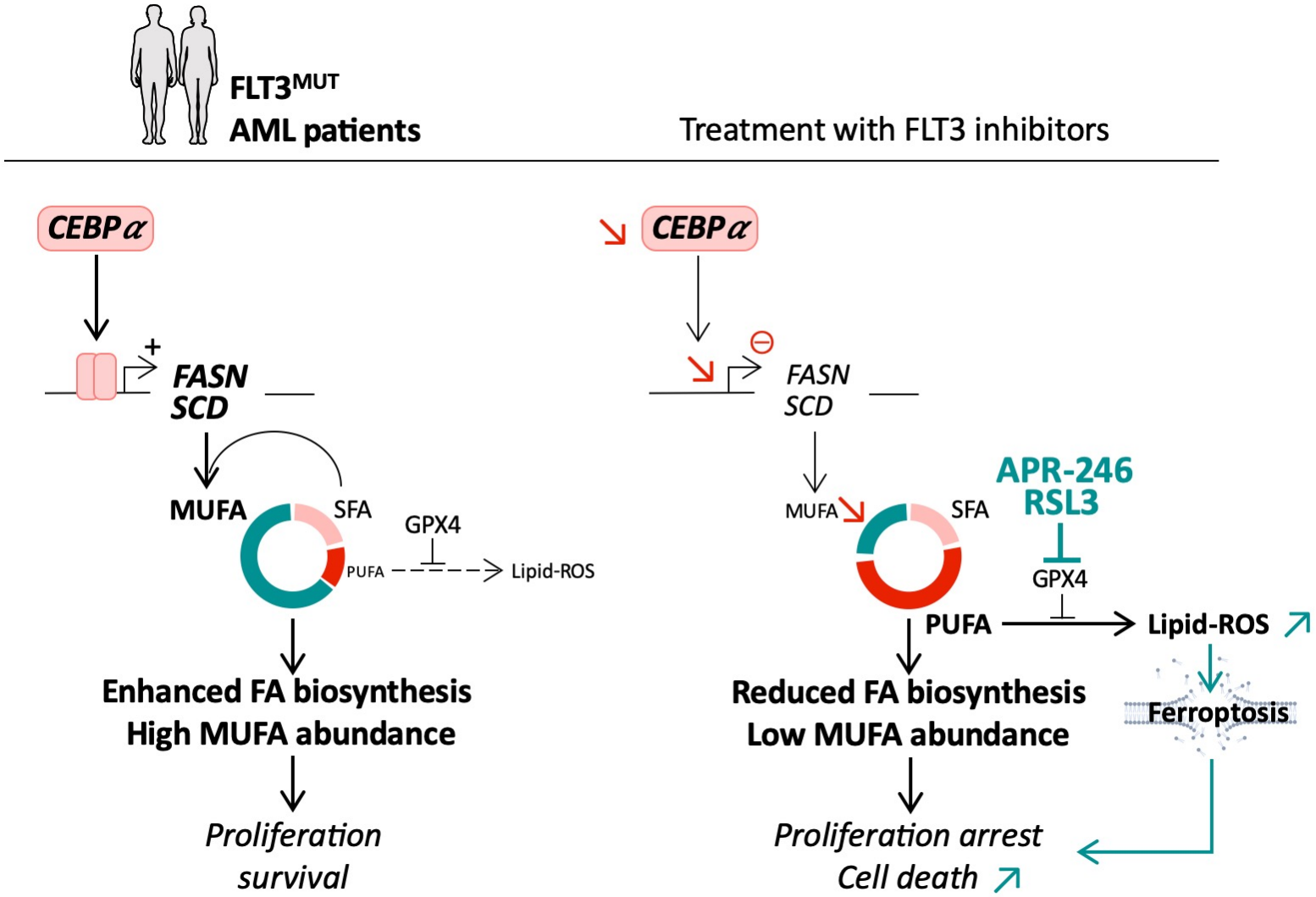
C/EBPα confers dependence to fatty acid anabolic pathways in FLT3-mutant leukemia



Collaboration : Jérôme Tamburini (University of Geneva)

Birsen*, Sabatier*, **Lauture***, Mouche*, ……., **Tamburini*** and Sarry*. Cancer Discovery. July 2023.

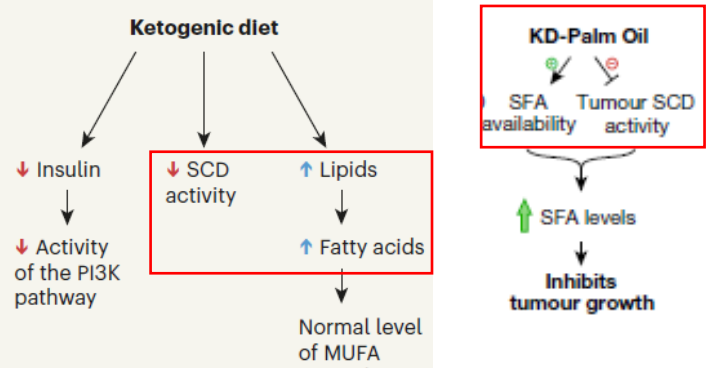
C/EBPα confers dependence to fatty acid anabolic pathways in FLT3-mutant leukemia



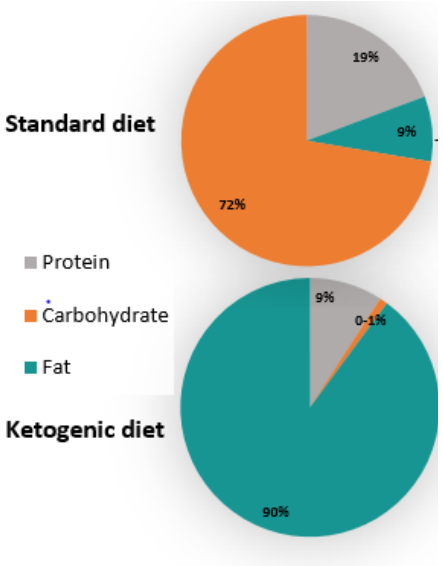
Collaboration : Jérôme Tamburini (University of Geneva)

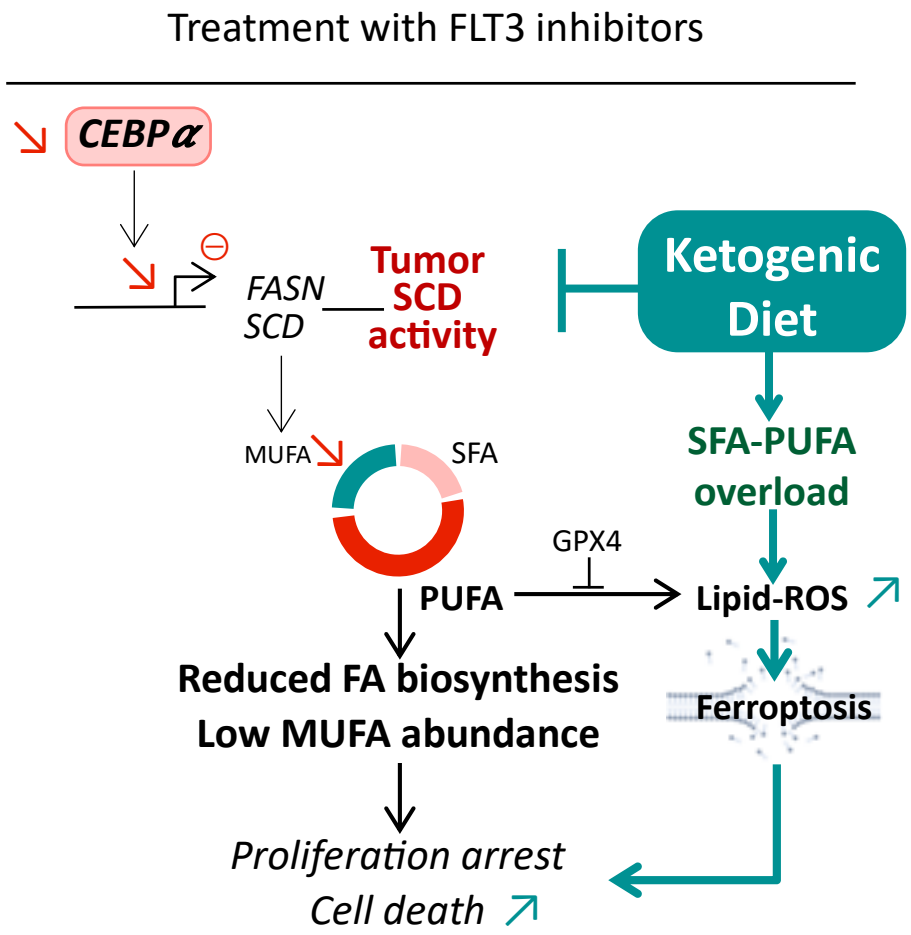
Birsen*, Sabatier*, **Lauture*,** Mouche*, ……., **Tamburini*** and Sarry*. Cancer Discovery. July 2023.

Could ketogenic diet enhance anti-leukemic effect of GILT *in vivo ?*



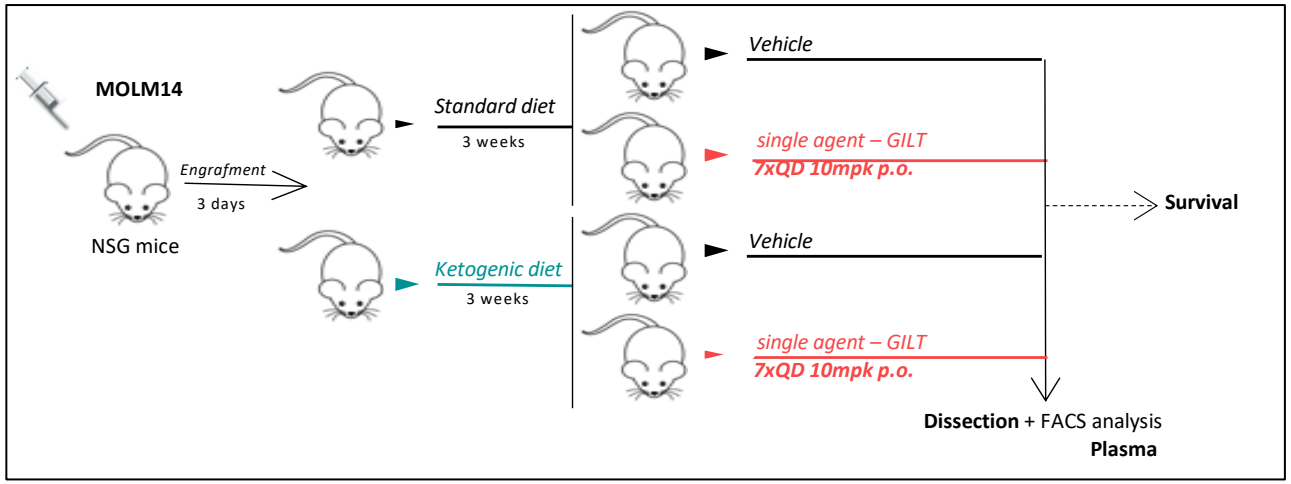
Salvadori and Longo, Nature, 2021; Lien and al, Nature, 2021

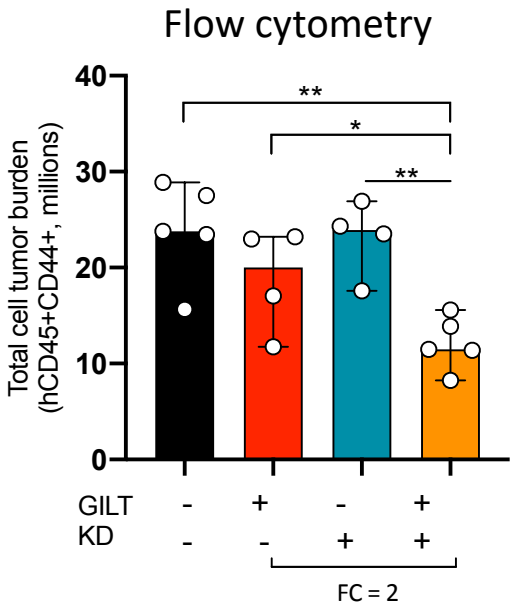


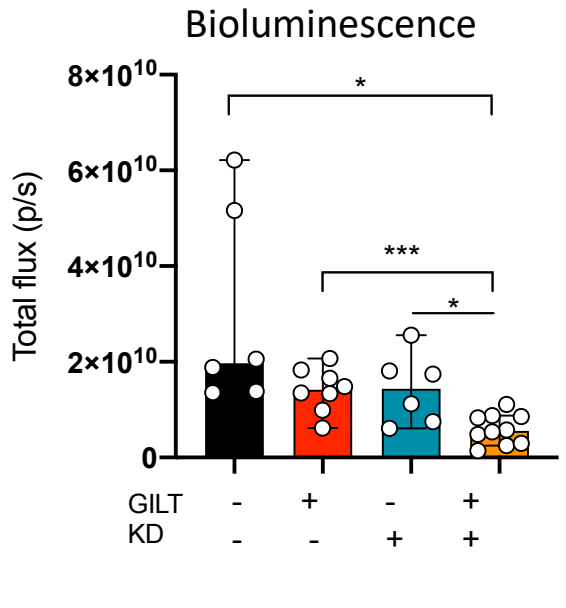


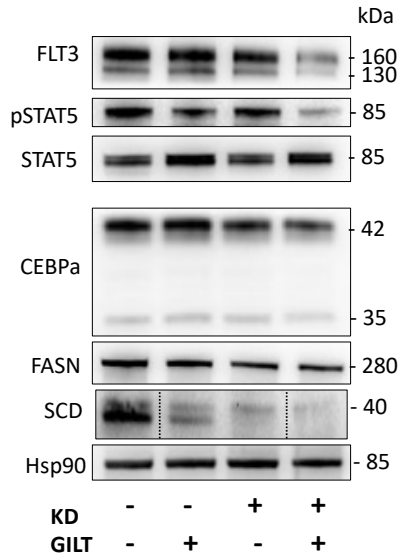
Goupille et al. unpublished; Collaboration with ENVT (N Bourges, F Granat)

Ketogenic diet enhances anti-leukemic effect of GILT *in vivo*



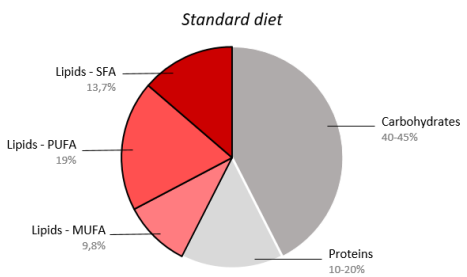


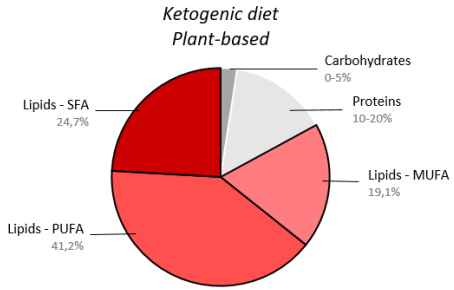


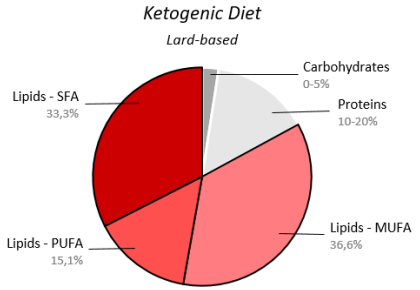


Goupille et al. Unpublished.

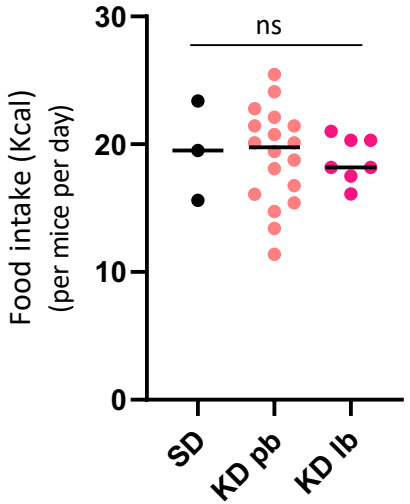
Both vegetal-/animal-based ketogenic diets enhance anti-leukemic effect of GILT *in vivo*

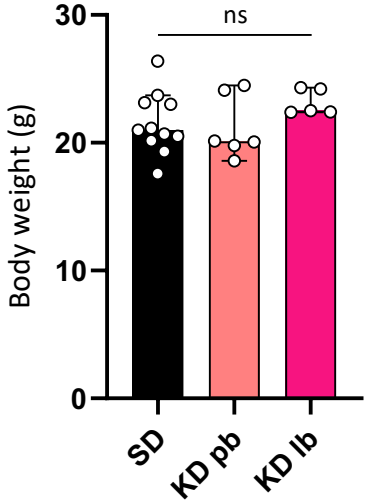




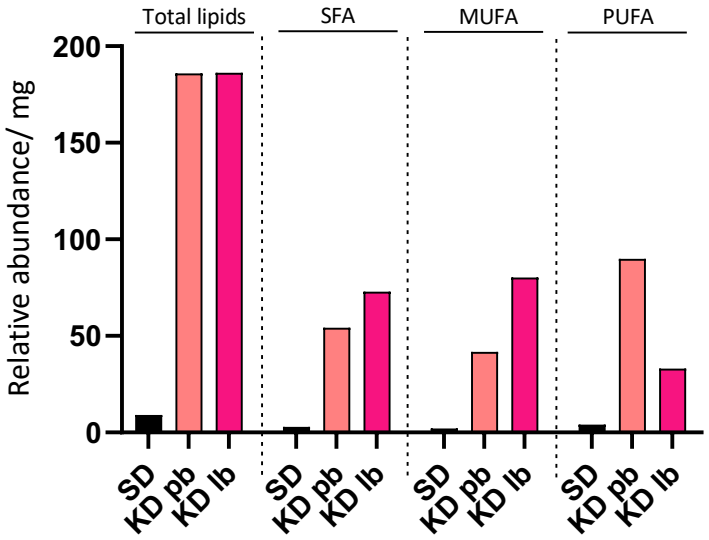


At dissection



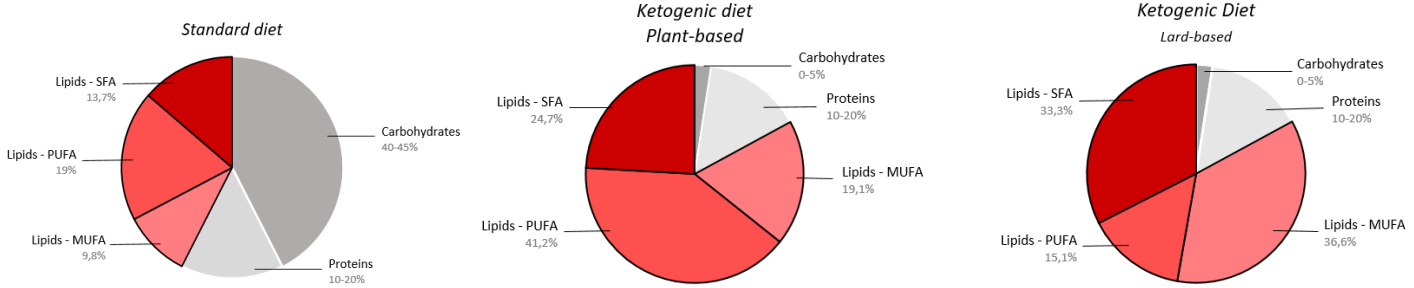


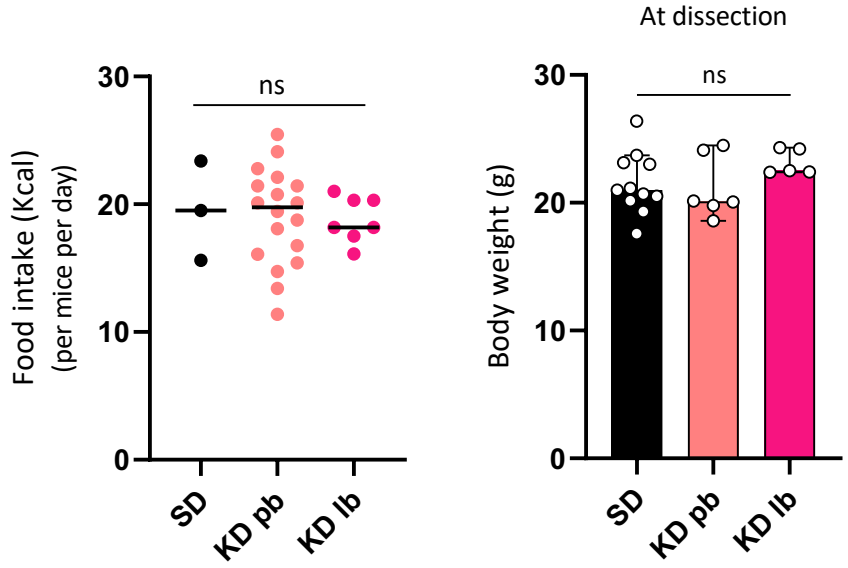
Lipid abundance in diets



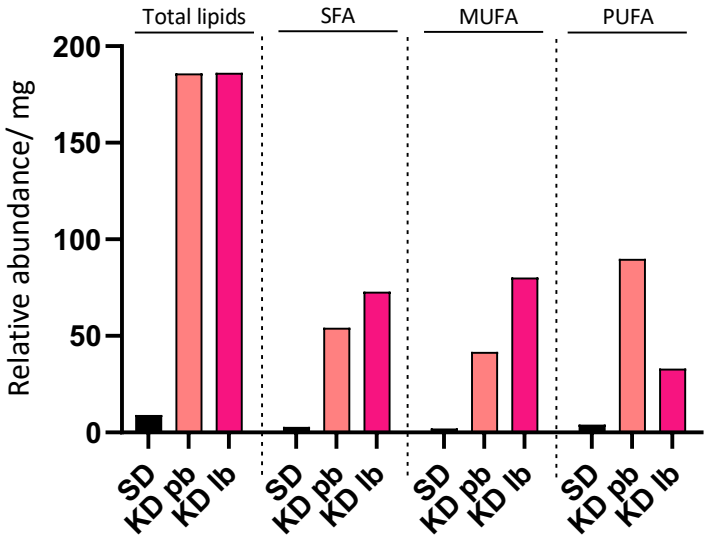
Goupille et al. Unpublished.

Both vegetal-/animal-based ketogenic diets enhance anti-leukemic effect of GILT *in vivo*

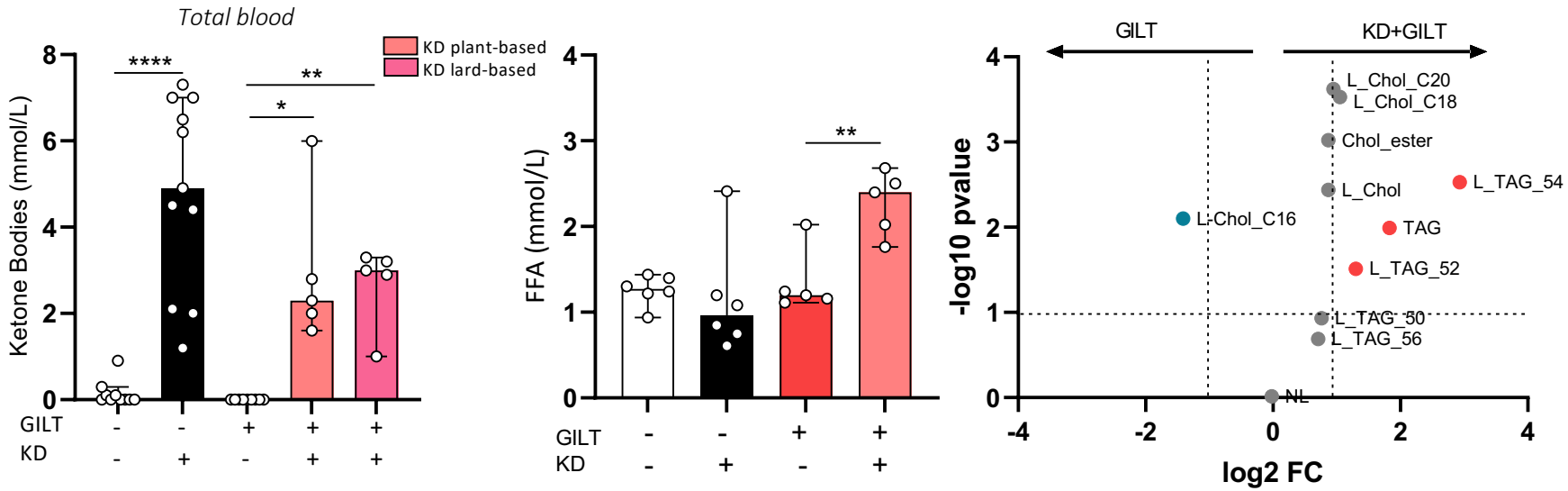




Lipid abundance in diets



Host lipid abundance (mice blood)



Goupille et al. Unpublished.

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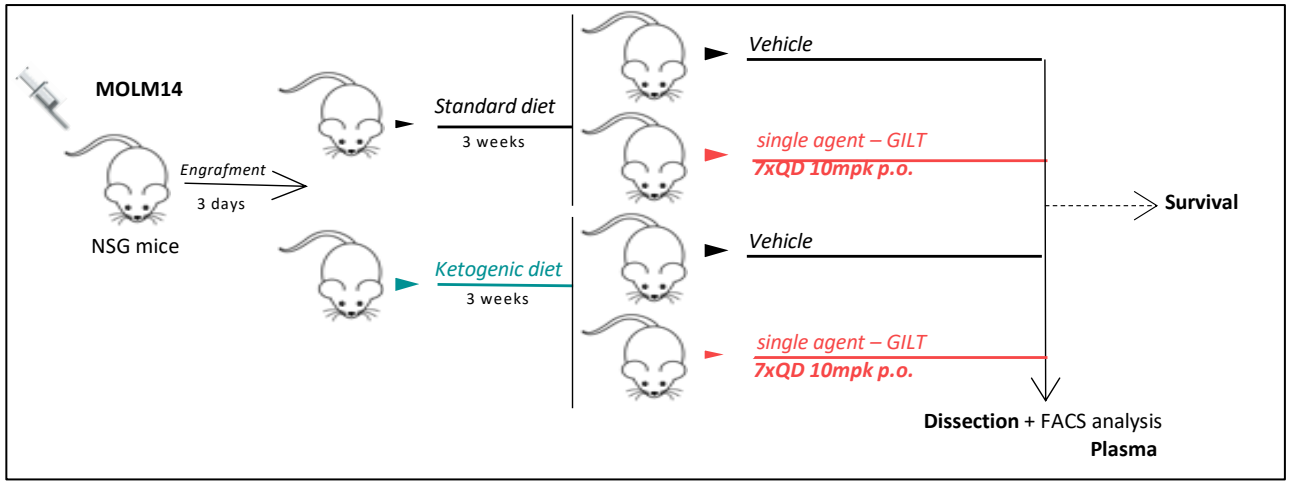
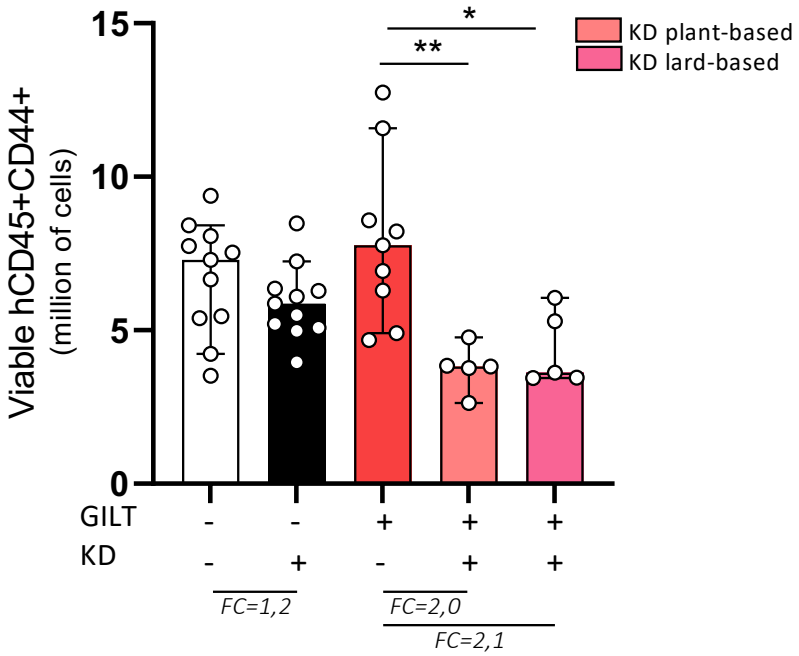


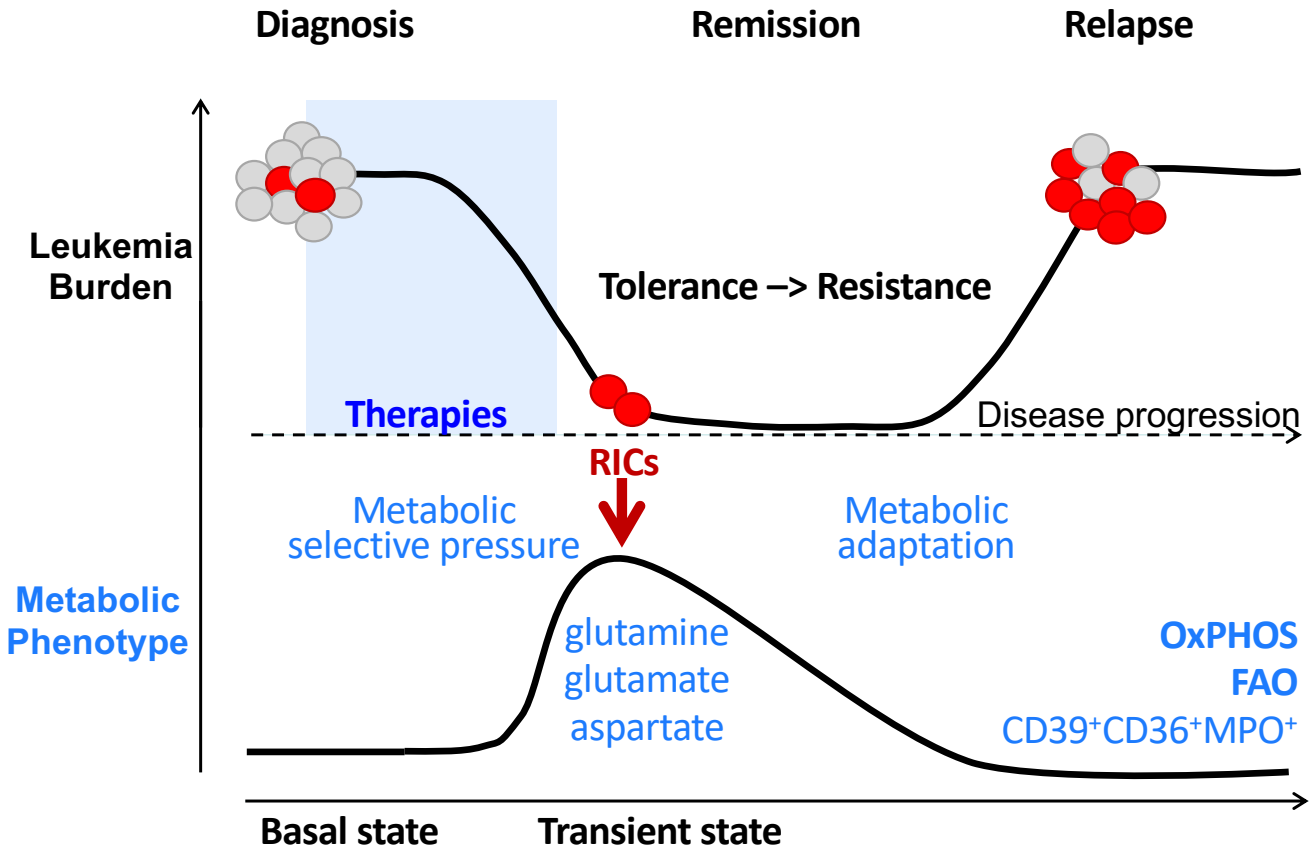


Goupille et al. Unpublished.

Summary II

> Tumor FAS/FAO balance and host lipid metabolism might modulate drug response in AML: **precision diets based on the drug resistance mechanism** (GILT *versus* AraC) **!**

> Metabolic model of drug resistance in AML **but relevant to multiple therapy-resistant solid cancers including melanoma, PDAC, TNBC, sarcoma, metastatic grade…**



Solid tumors: Passaniti et al Mol. Carci. 2022; Xue et al. J Med Chem. 2022; Evans et al. Cancer Res. 2020; Marine et al, Nature Review Cancer. 2020
Heme tumors: Stuani and Sarry. Cell Metab. 2020; Van Gastel et al. Cell Metab. 2020;

Acknowledgements

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Margherita Ghisi
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PhD/Research Assistant/Postdoc positions in 2024/2025

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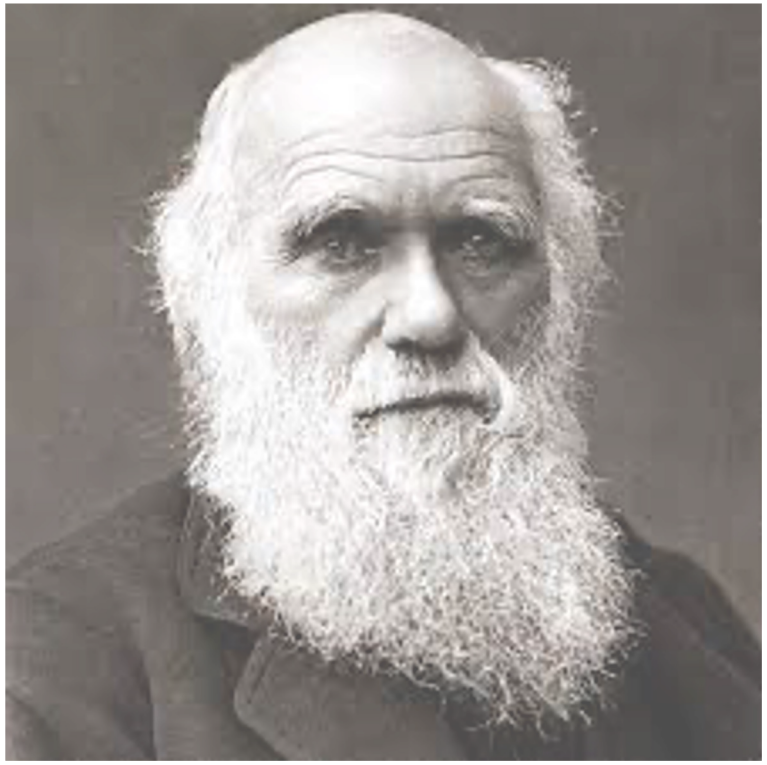
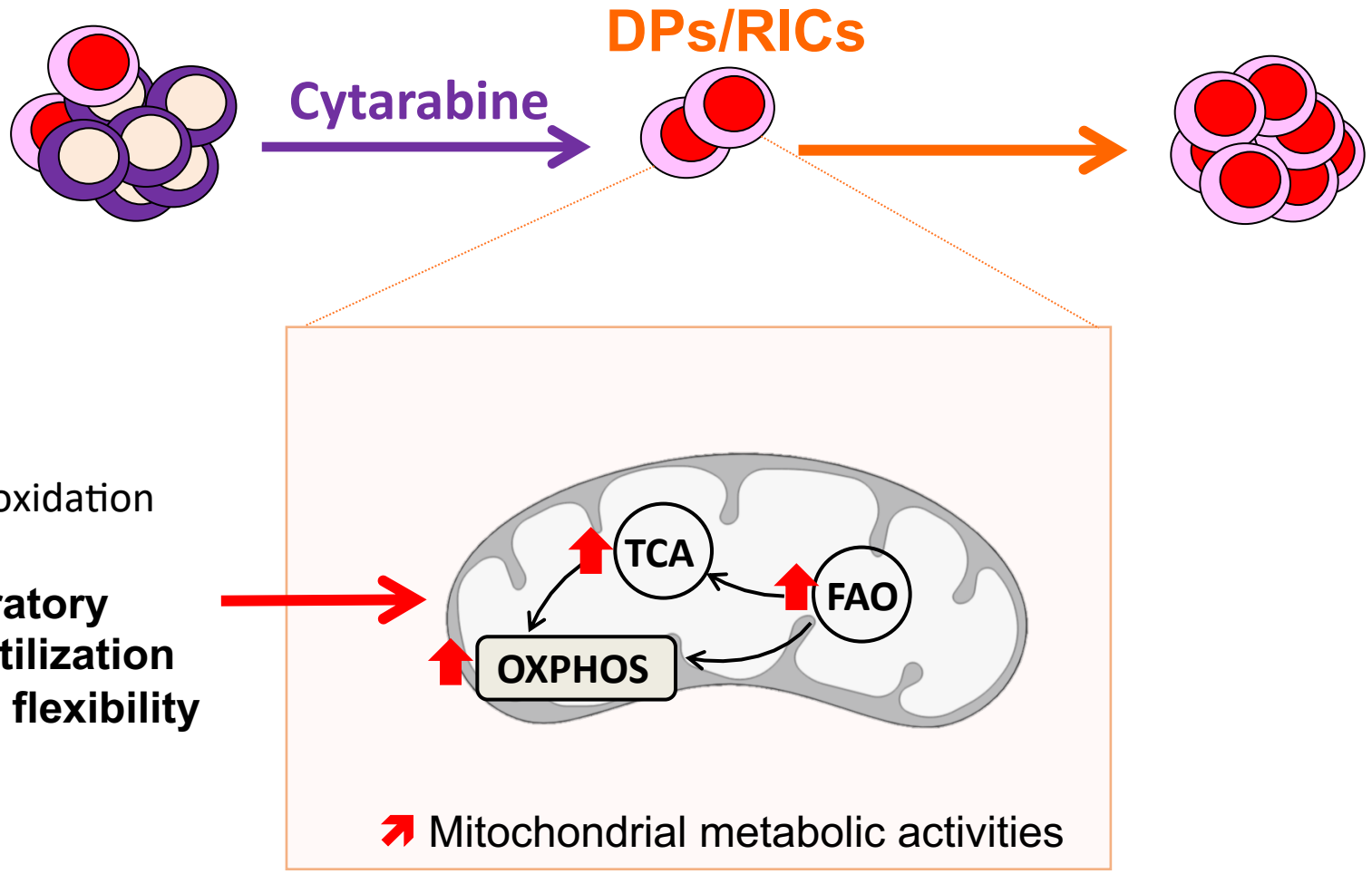
A. Wei (Melbourne)



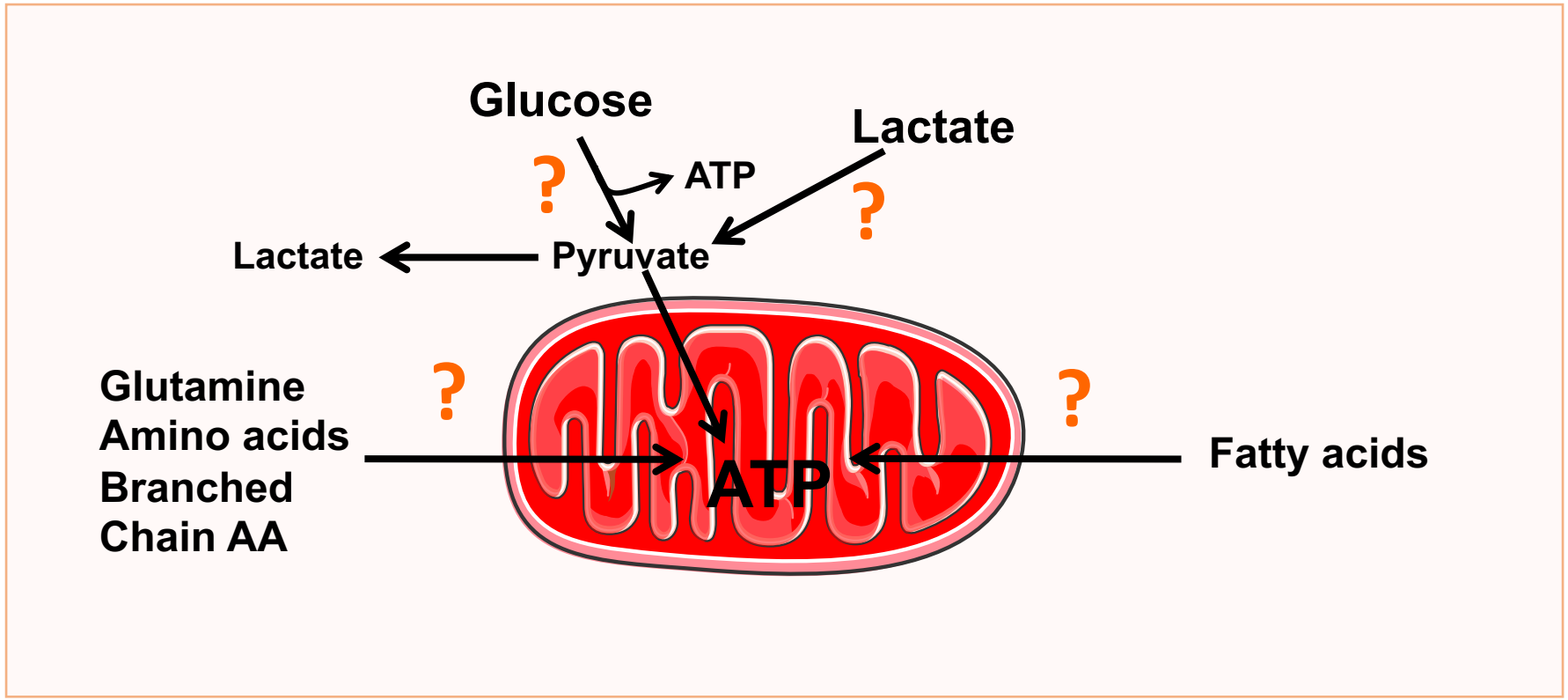
*"It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is the most (**mitochondrially**) adaptable to change."*

High OxPHOS phenotype of Drug Persisters is the consequence of enhanced mitochondrial substrate utilizations

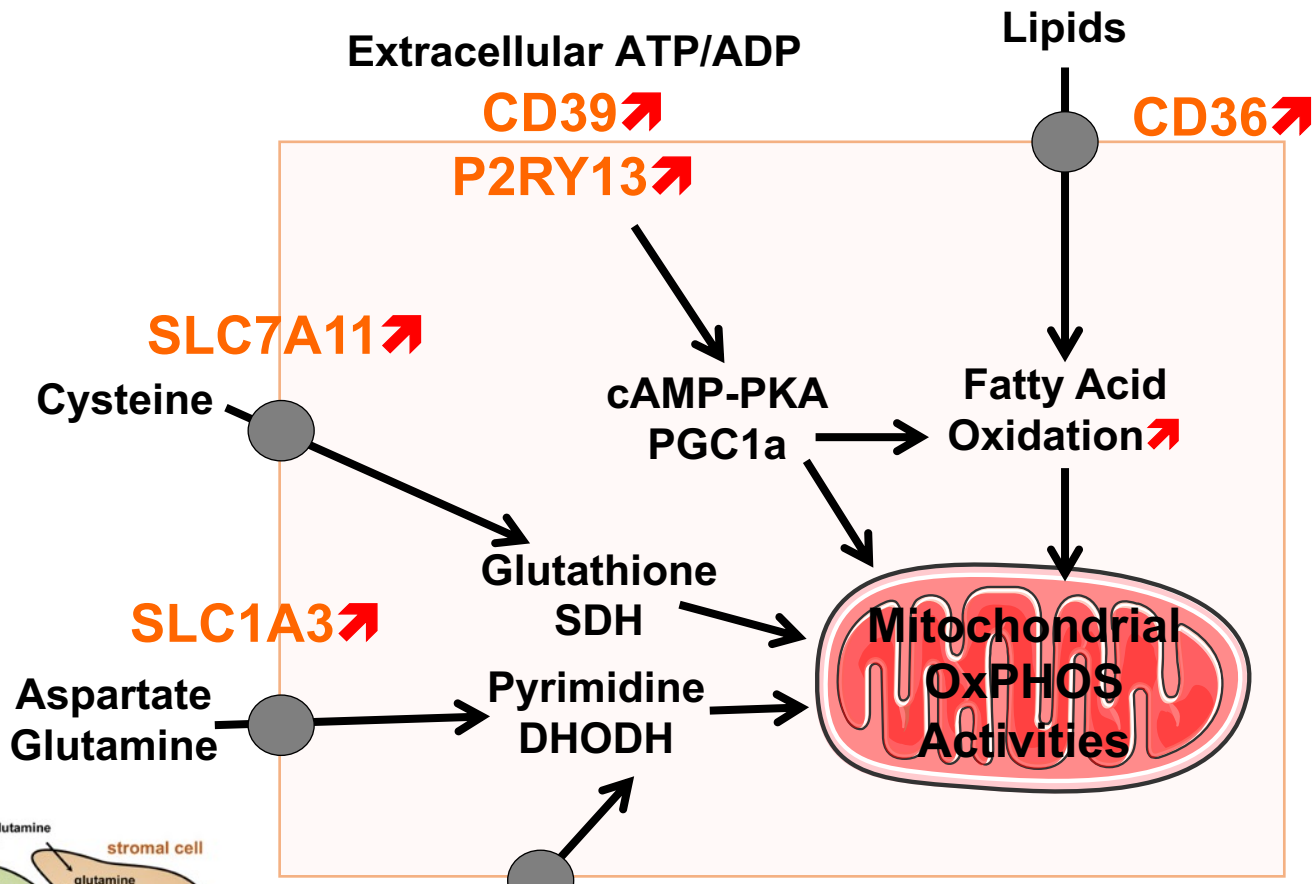


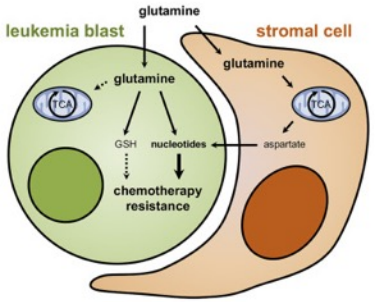
Cognet *et al*. unpublished data
Stuani *et al.* in prep.
Van Gastel *et al* Cell Metabolism. 2020.
Farge *et al.* Cancer Discov. 2017

What metabolic pathways support this High OxPHOS activity and mitochondrial phenotype of RICs *in vivo* ?



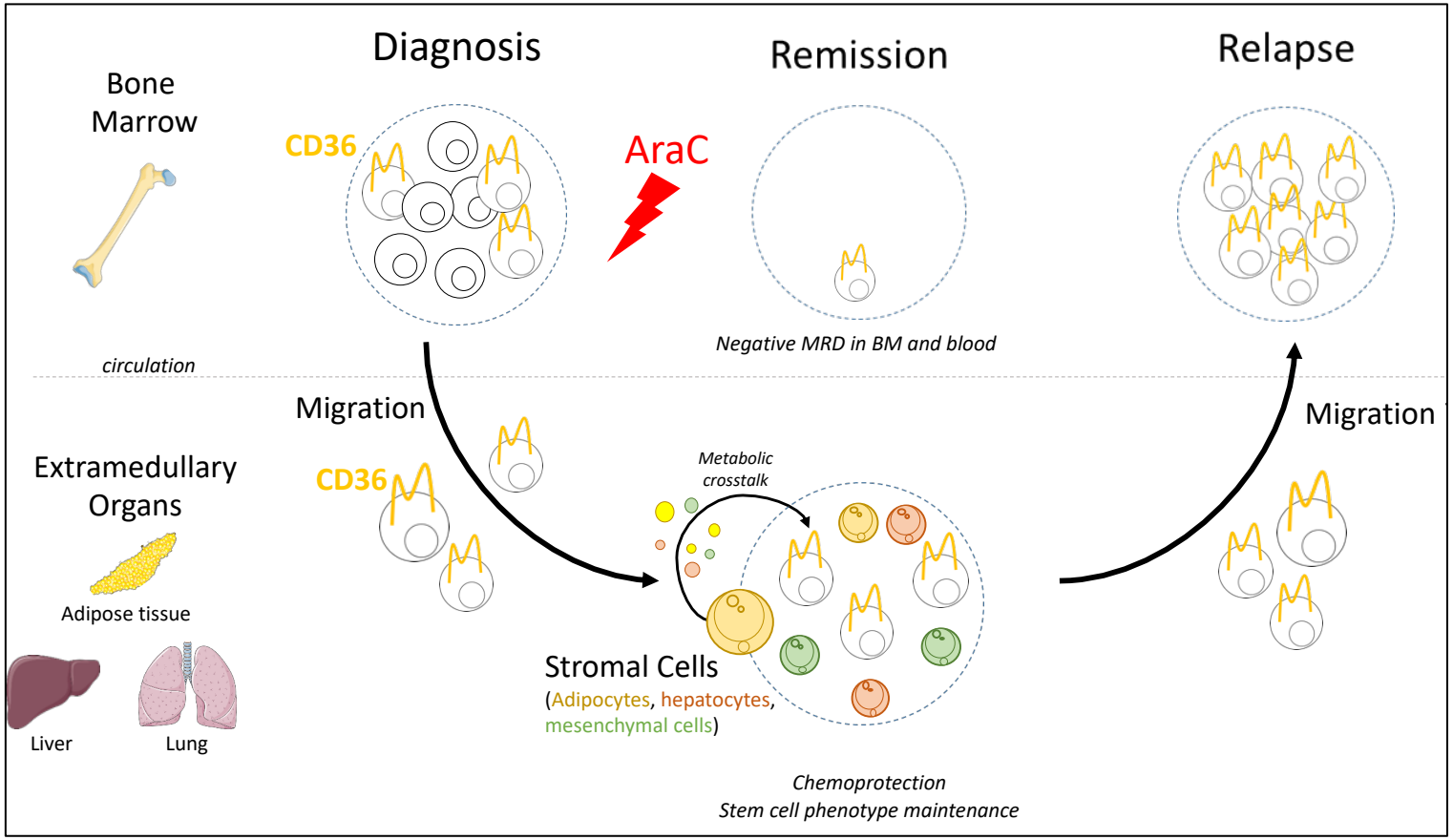
Highly expressed metabolite transporters and increased nutrient utilization in High OxPHOS RICs





Guiraud et al unpublished
Stuani and Sarry. Cell Metab. 2020.
Aroua, Boet, Ghisi *et al*. Cancer Discov. 2020.
Van Gastel et al. Cell Metab. 2020; Jones et al Blood 2019;
Farge *et al.* Cancer Discov. 2017.

CD36^{pos} extramedullary RICs induced lipid crosstalk within tissues to favor blast dissemination that leads to relapse in PDX and patients

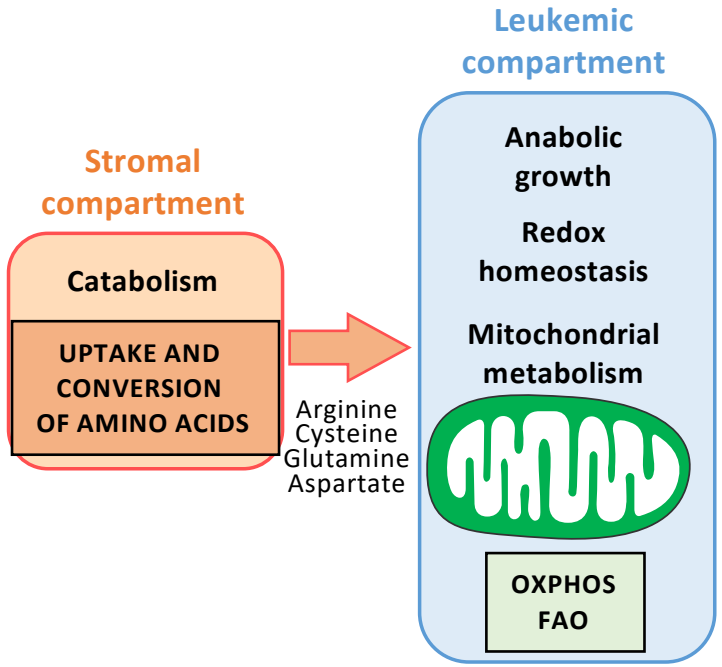


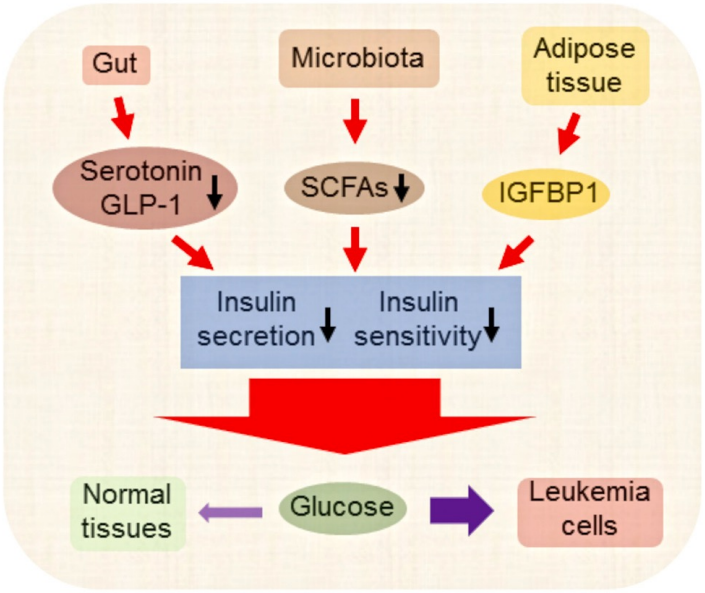
AML: a model metastatic disease with a metabolic driver

Farge et al in prep

Current unanswered questions

- How do **intra-/inter-tissue metabolic dialogues and host metabolism** support the OxPHOS metabolism of **persisters**?

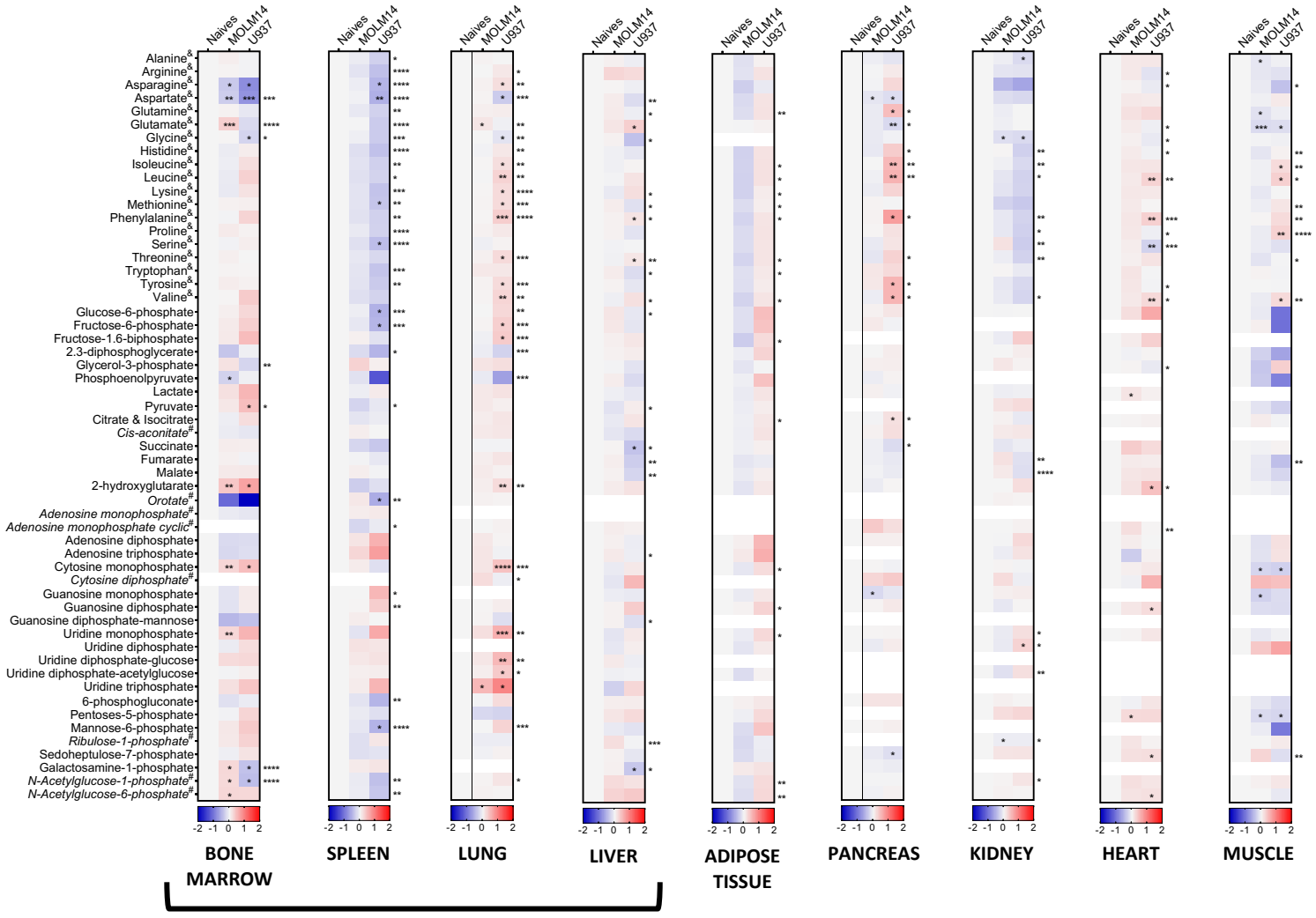




BM and **extramedullary persisters** redirect carbon and nitrogen metabolism within tissues and from host (mice and patients)

Farge et al. in prep; Stuani and Sarry. Cell Metab. 2020; Ye *et al* Cancer Discov. 2020.; Ye *et al.* Cancer Cell. 2018

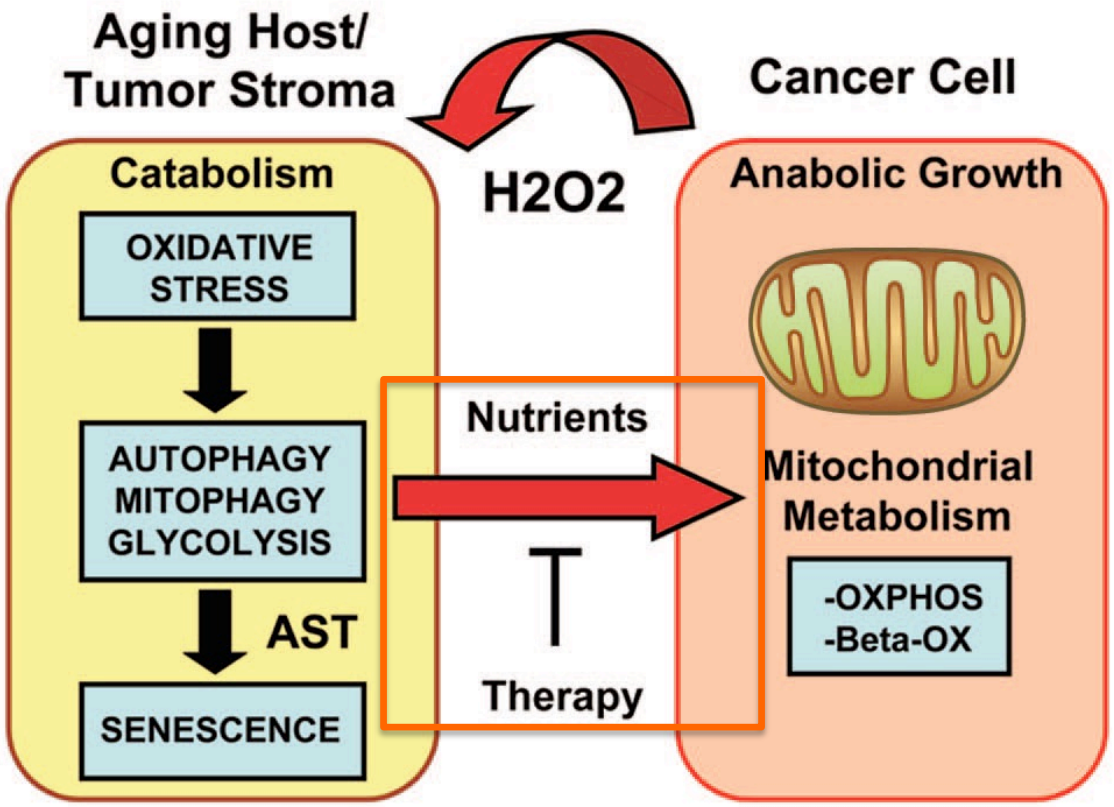
BM and extramedullary RICs redirects carbon and nitrogen metabolism within tissues in PDXs



Tissue reservoirs of blasts

Cognet et al in prep

Perspectives – Novel paradigms

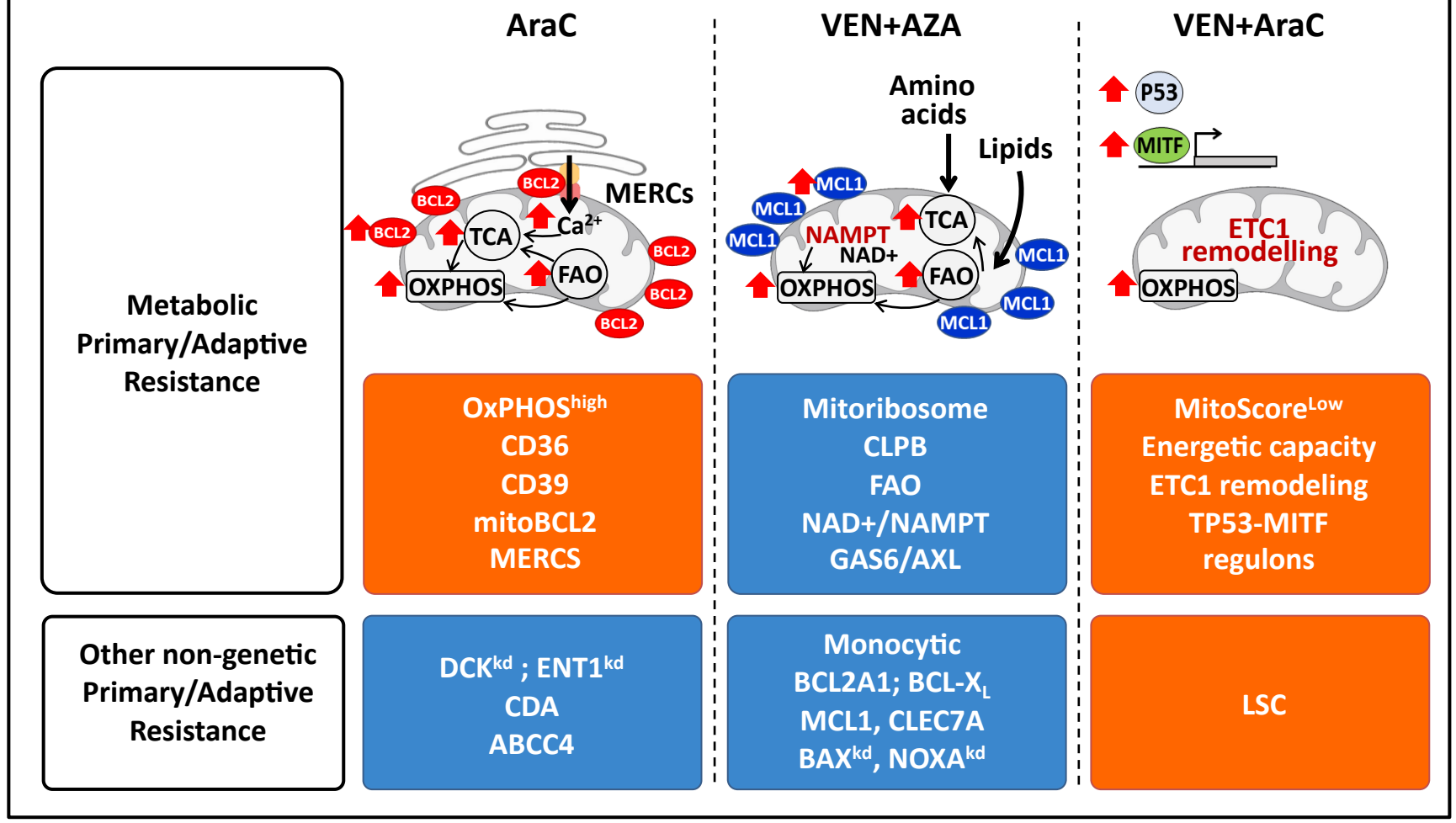


Two-compartment
Tumor metabolism

How microenvironment, host metabolism and diets support the OxPHOS metabolism ?

Adapted from Lisanti et al. 2011

Intrinsic and adaptive mechanisms of resistance in AML

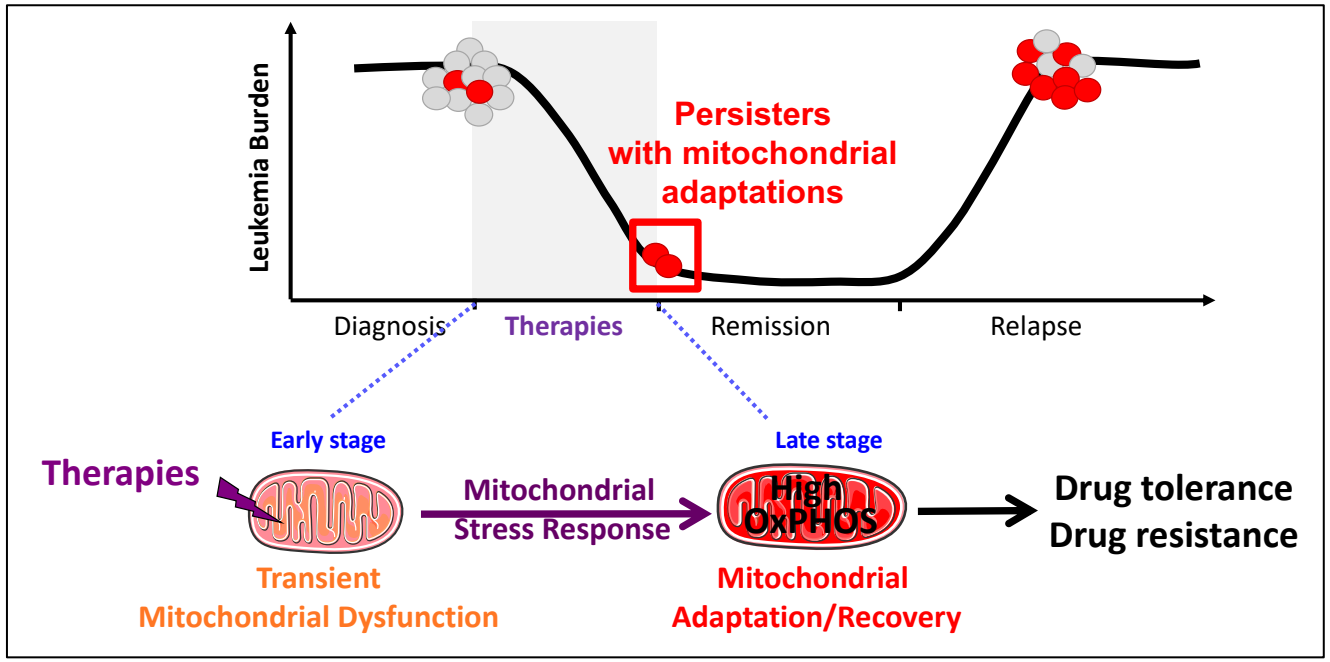


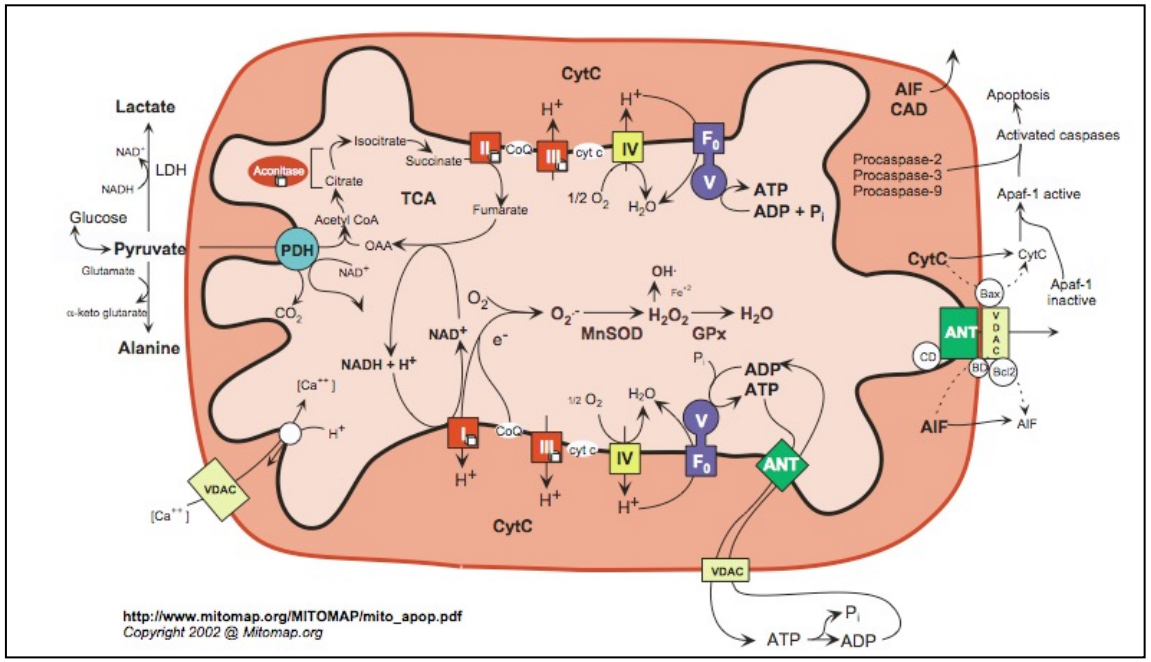
In orange: our published and unpublished works; in blue from our labs

Summary I

> MRD is enriched in persisting cells with **High OxPHOS metabolism, as the consequence of a mitohormetic Darwinian process of adaptive response to stress**

> Evolutionary interplay between mitochondrial metabolism/state and resistance to apoptosis occurs in drug persisters within MRD

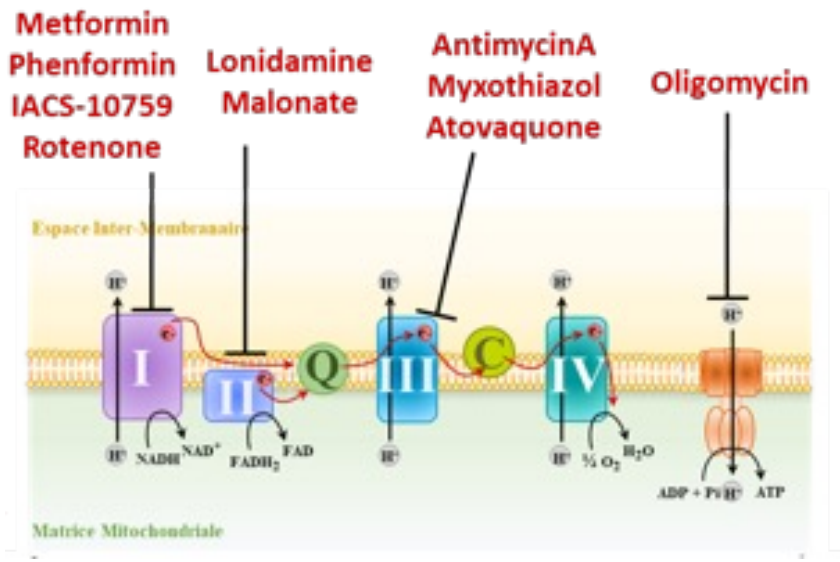




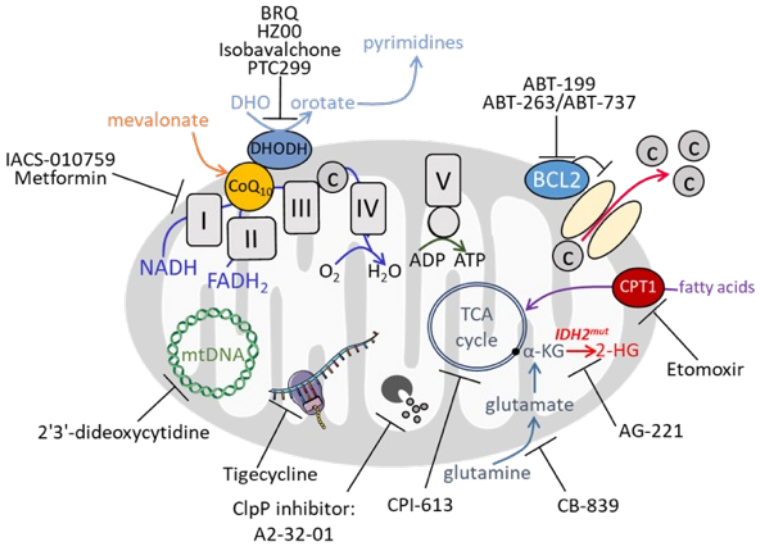
Saland *et al*. in prep; Bosc *et al*. Nature Cancer. 2021
Stuani and Sarry. Cell Metab. 2020; Aroua, Boet, Ghisi *et al*. Cancer Discov. 2020; Hosseini *et al*. Cancer Res. 2019; Farge *et al*. Cancer Discov. 2017

Drug persisters are more sensitive to mitochondrial inhibitors

Selective ETC/OxPHOS inhibitors

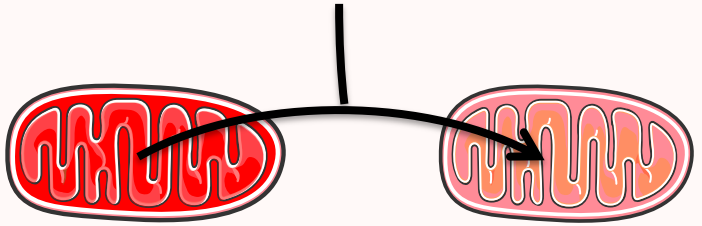


Indirect ETC/OxPHOS inhibitors



Targeting any aspect of High OxPHOS metabolism

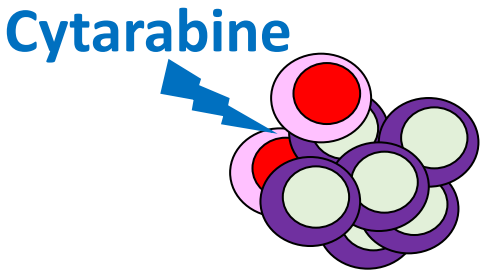
Resistant to AraC

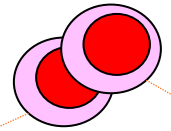


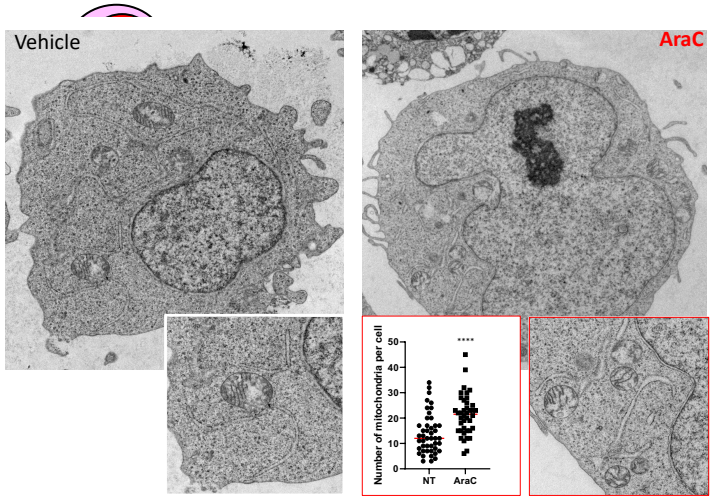
Sensitive to AraC

Stuani *et al*. BMC Biol. 2019; Bosc *et al*. Cell Metab. 2017
Farge et *al*. Cancer Discov. 2017; Samudio et al. JCI. 2010

High OxPHOS phenotype of RICs is the consequence of enhanced mitochondrial machinery and mitochondrial utilizations





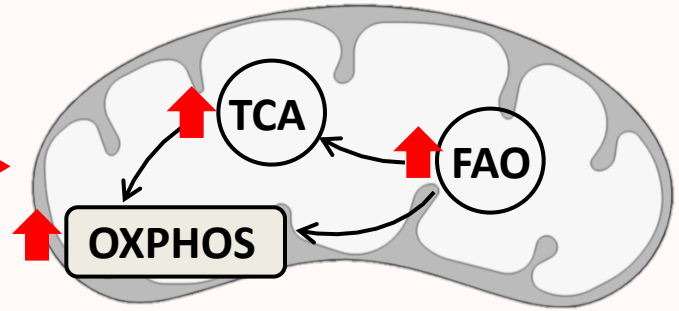


↗ **Respiratory substrates utilization**

FA oxidation

glucose/pyruvate/lactate oxidation

AA oxidation



↗ Mitochondrial metabolic activities

↗ **Mitochondrial number**

↓

↗ **Mitochondrial biogenesis**

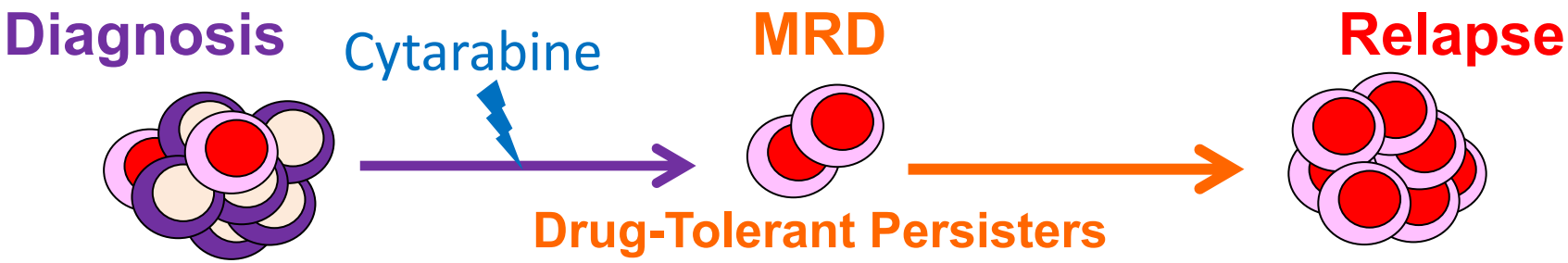
+

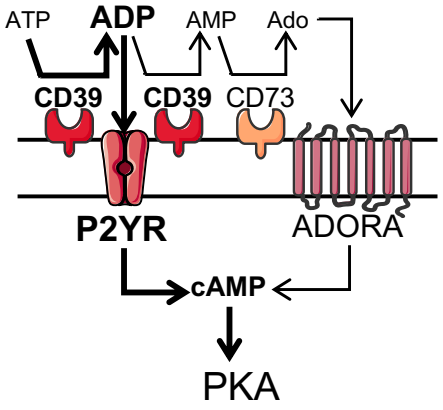
↗ **Mitochondrial transfer from stromal cells**

Collab. M. Selak (UPenn, USA), M. Brand (Buck Institute, USA)
Collab E. Griessinger, JF Peyron (C3M, Nice)

Ducau et al. unpublished data
Farge *et al.* Cancer Discov. 2017
Moschoi …. Griessinger. Blood. 2016

OxPHOS phenotype reflects a mitochondrial recovery as a mitochondrial stress response induced by an ATF4-driven transcriptional program and adenosine-CD39-PKA pathway upon AraC





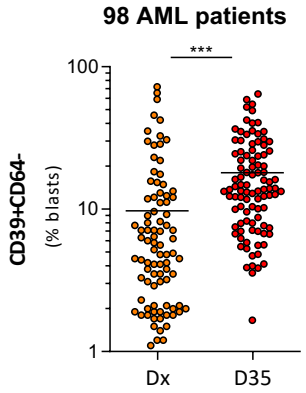
↗ Adenosine-CD39

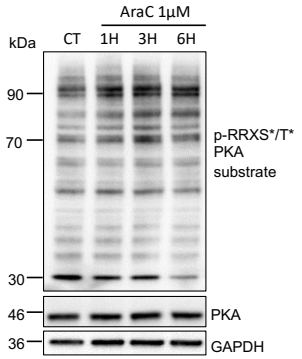
↗ cAMP-PKA → *PGC1α* *TFAM* *NRF1/2* → ↗ Mitochondrial biogenesis

↗ ATF4

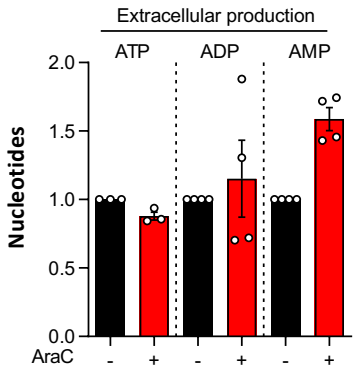
↗ FAO and OxPHOS

↗ Antioxidants



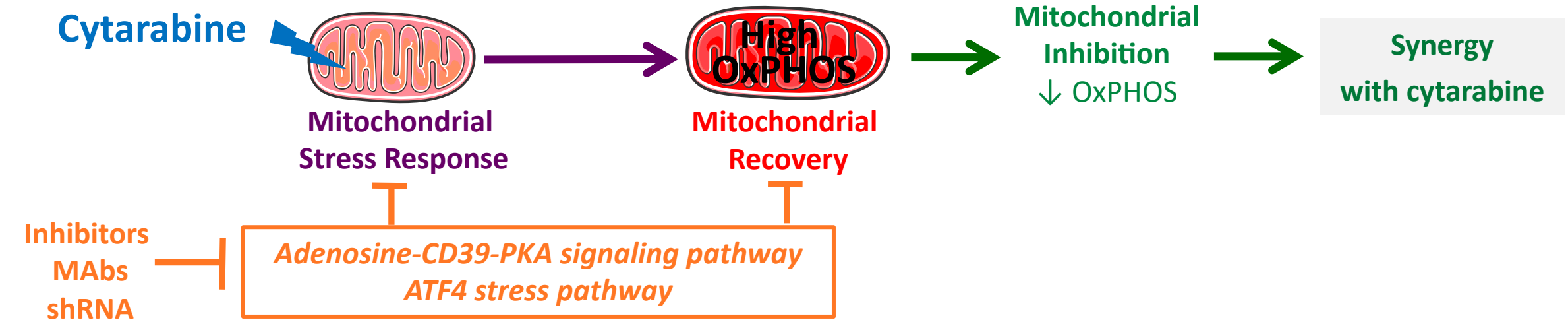


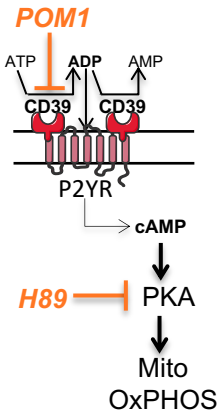
Mitochondrial Integrative Stress Response → **Mitochondrial Recovery**

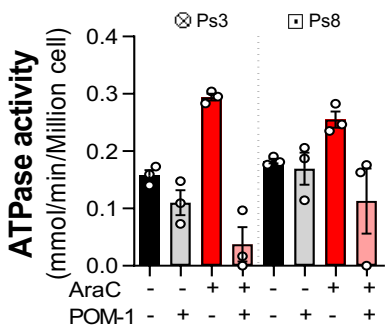


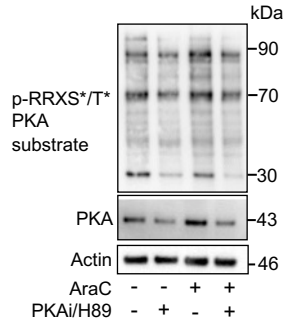
Aroua*, Boet*, Ghisi* *et al*. Cancer Discov. 2020

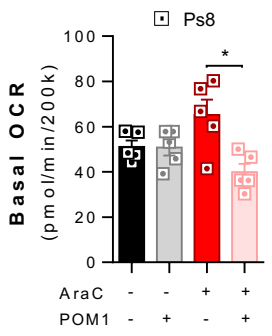
Blocking mitochondrial recovery by targeting adenosine-CD39-PKA-ATF4 axis *in vivo*

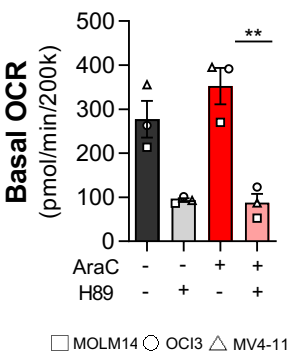


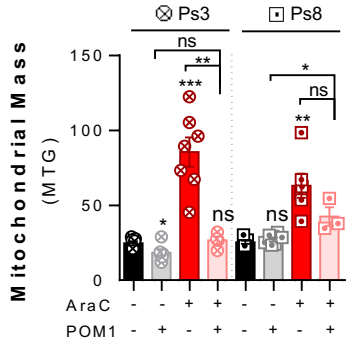


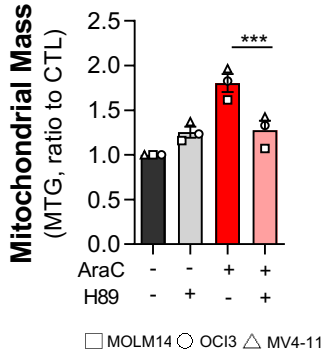


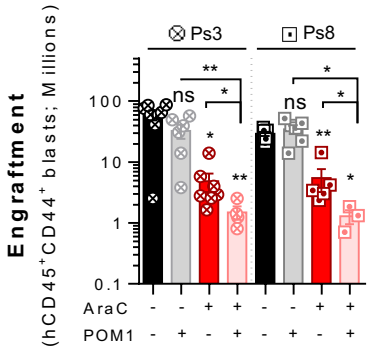


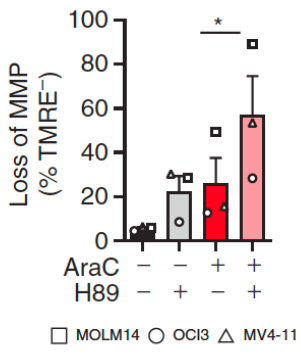


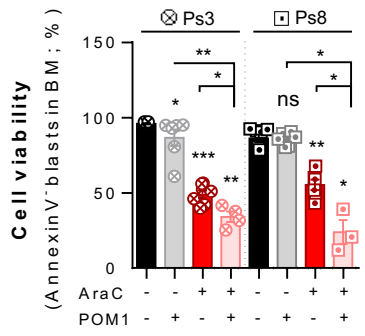


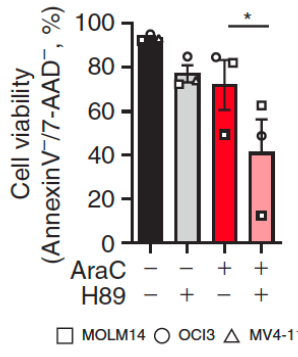






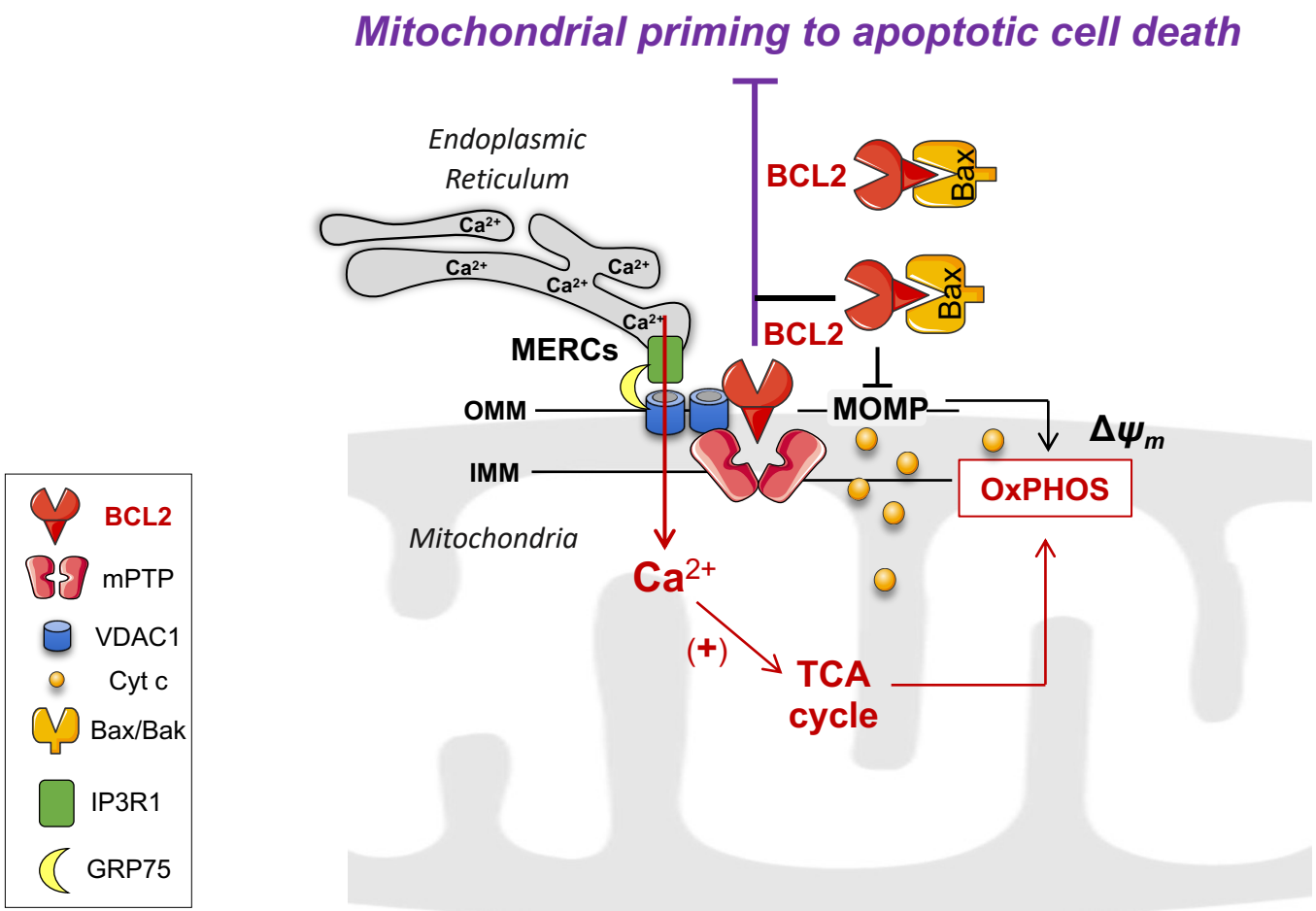






Aroua*, Boet*, Ghisi* *et al*. Cancer Discov. 2020

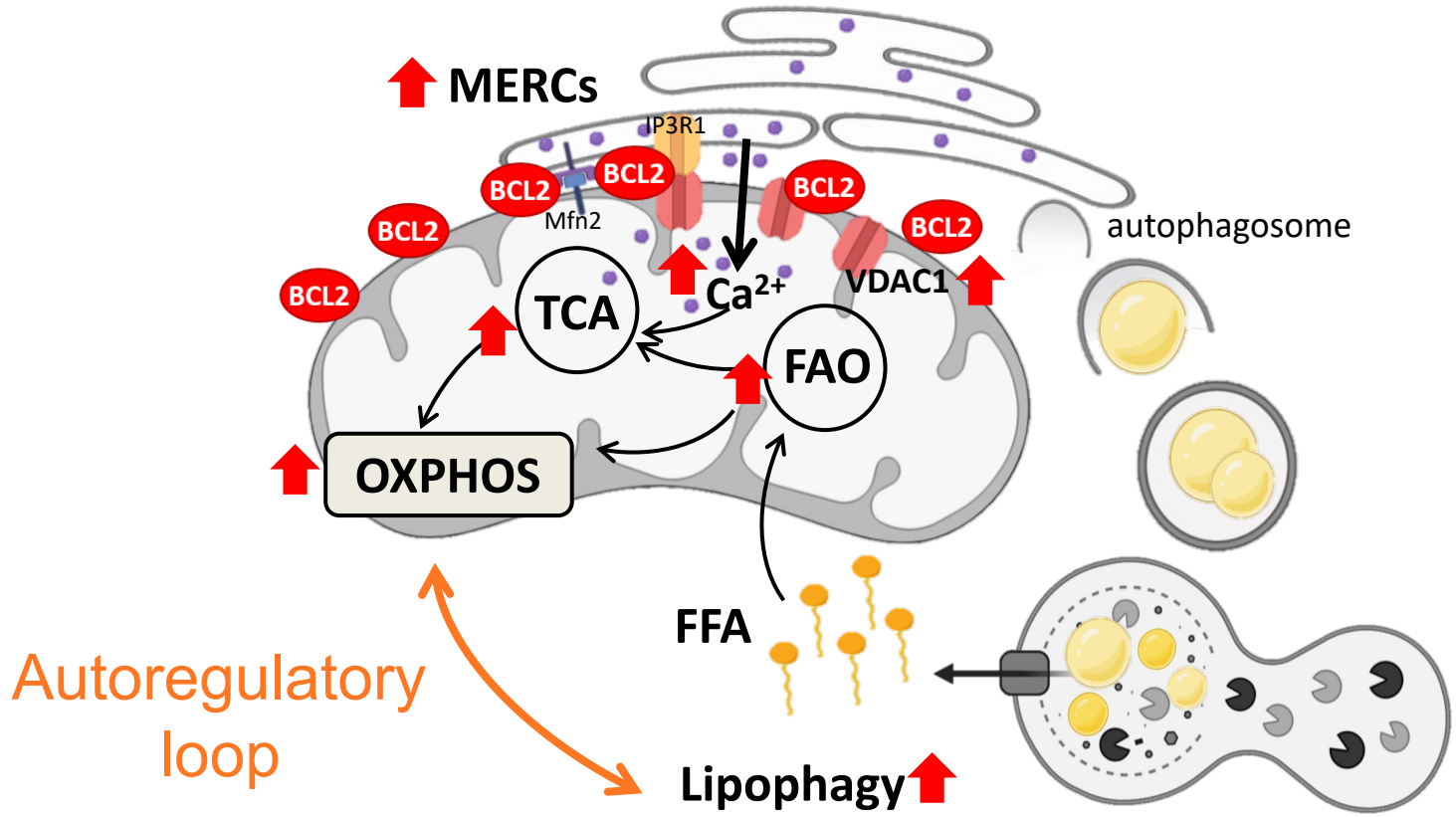
Link between high OxPHOS, mitochondrial BCL2 dependence and resistance to apoptosis in drug persisters: increased mitochondrial calcium content



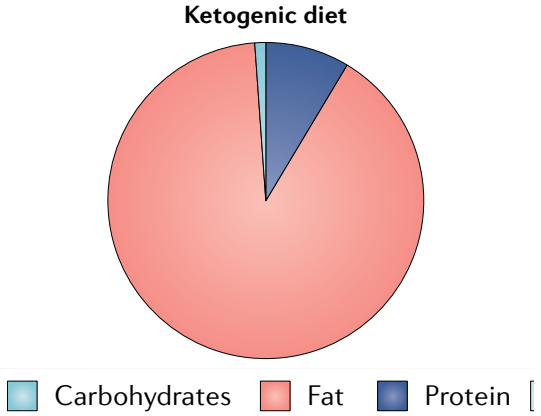
mitoBCL2	**High**
MOMP	No/transient
mPTP	Closed
mitoCalcium	High
OxPHOS	**High**
AraC	**Resistant**

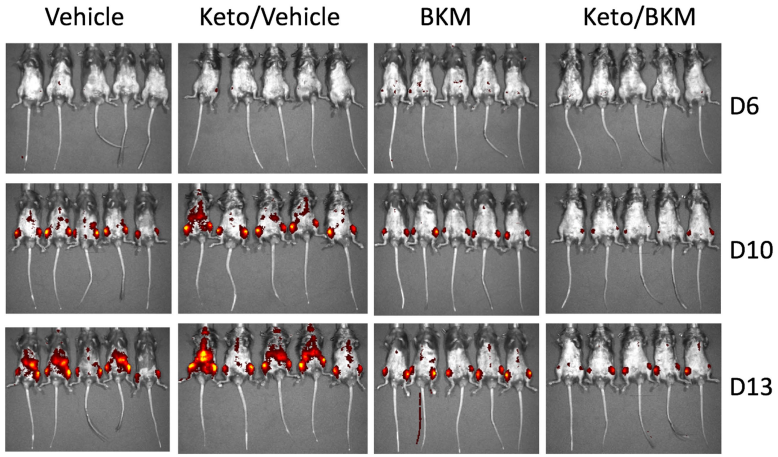
Bosc *et al*. Nature Cancer. 2021
Bosc *et al*. Nature Comm. 2020

Mitochondria autoregulate their own substrate availability to support OxPHOS of RICs

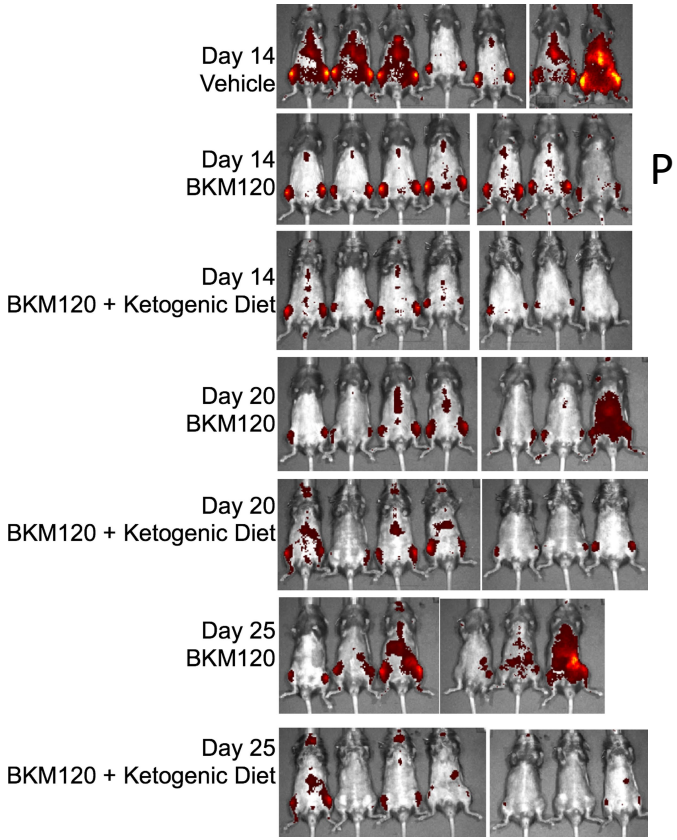


Ketogenic diet enhanced PI3Ki efficacy in cancer and AML

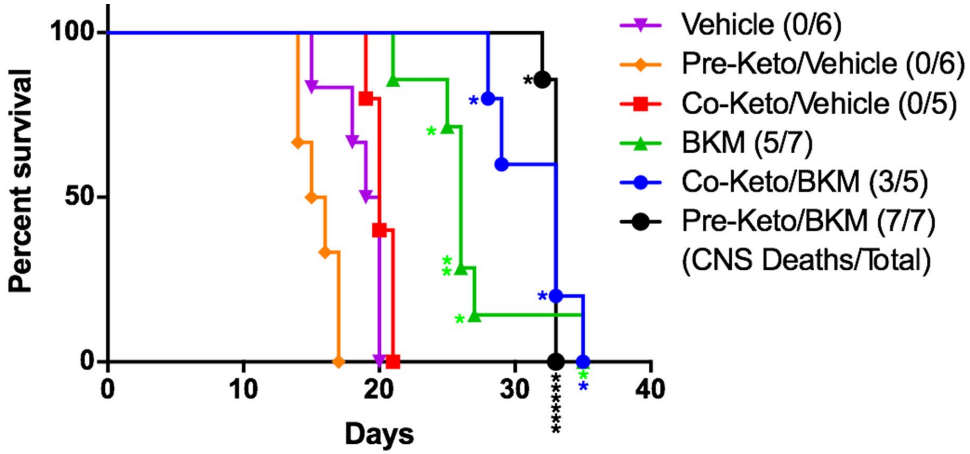




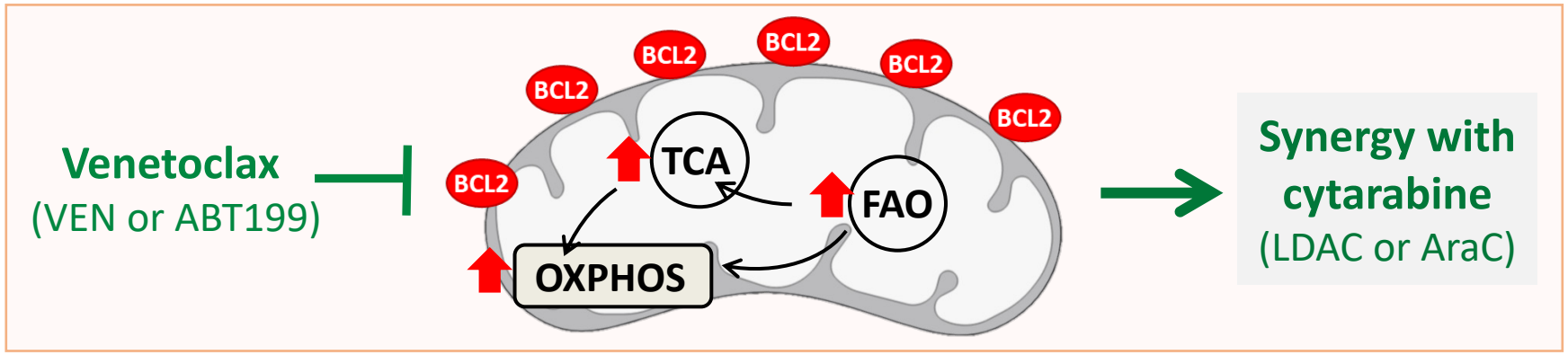
Co-treatment



Pre-treatment

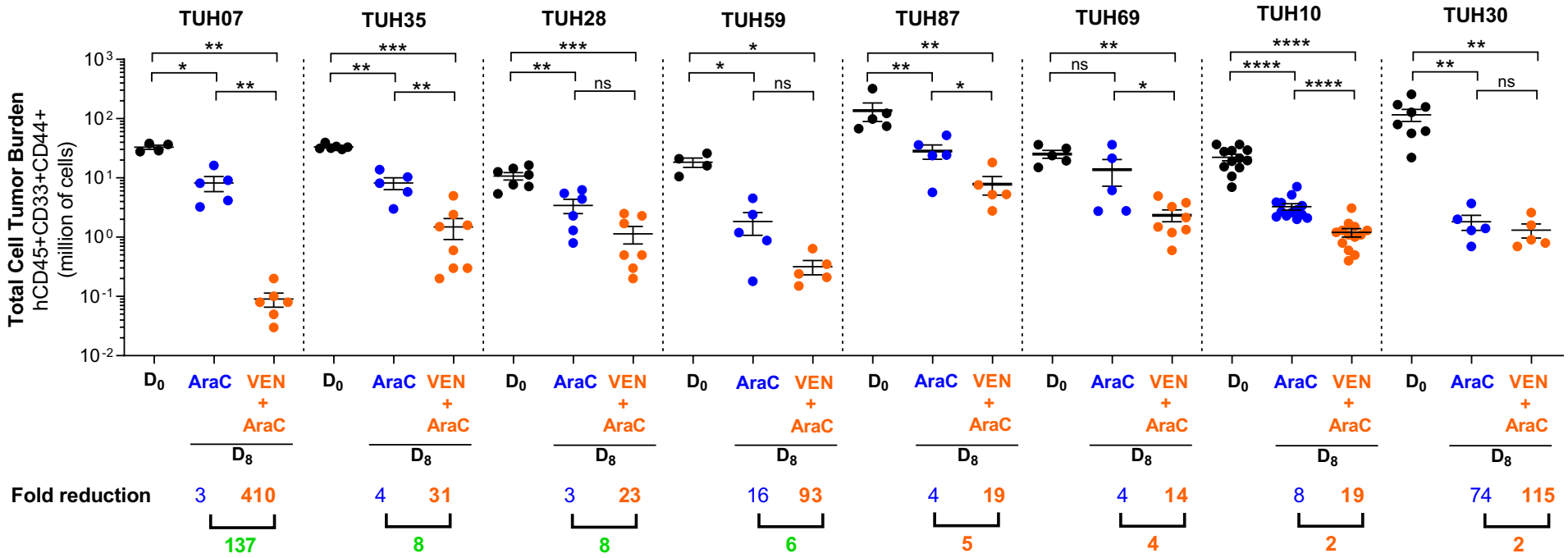


VEN+AraC doublet therapy better than AraC alone in PDX



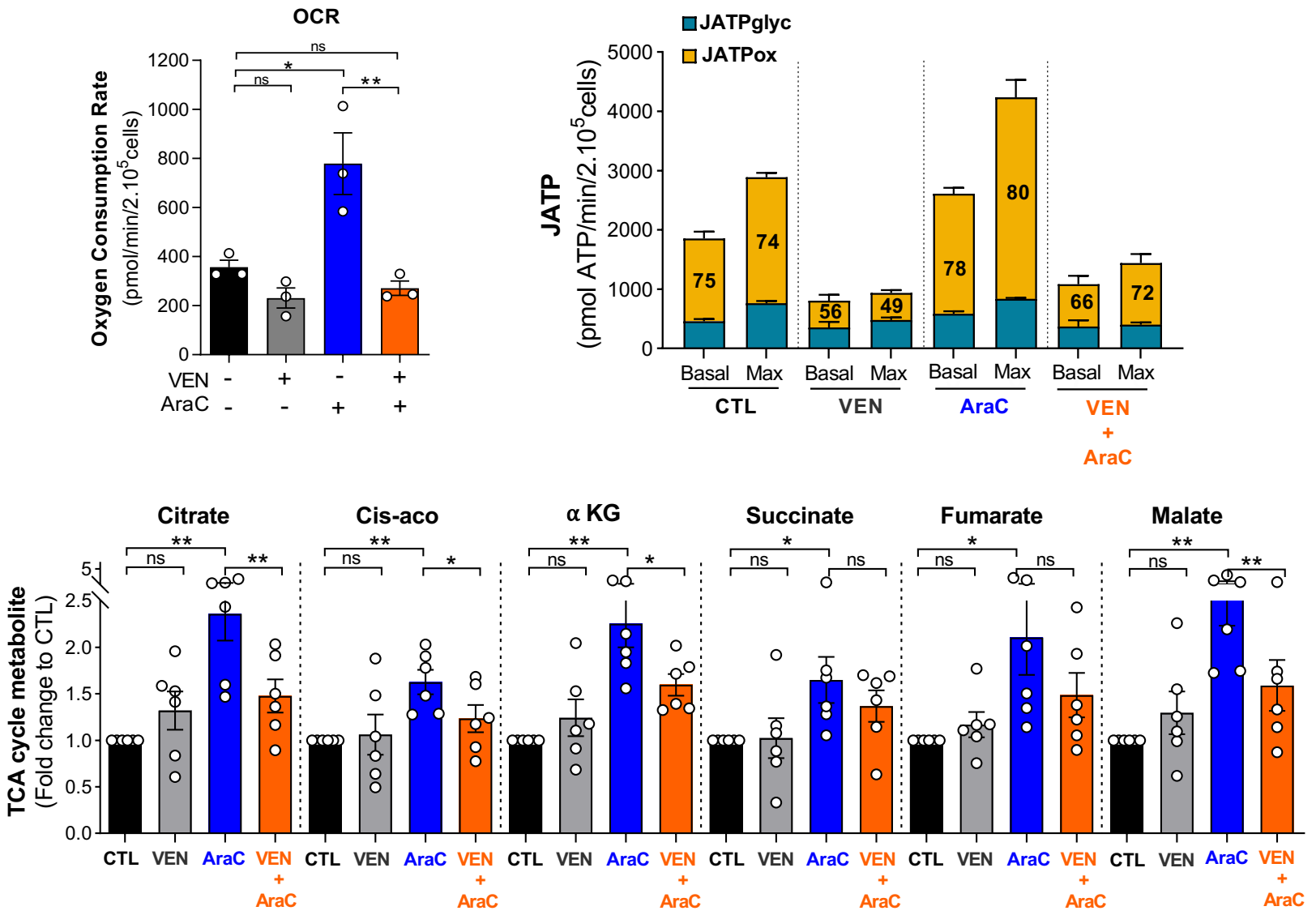
AML PDX Models
NSG Mice

CYTARABINE (AraC)
vs
VENETOCLAX
(VEN)+**AraC**



Bosc *et al* Nature Cancer 2021

AraC-induced high OxPHOS state is blocked by VEN+AraC doublet therapy



Bosc *et al* Nature Cancer 2021