Drug persisters arise from mitochondrially and metabolically adaptable cell populations in acute myeloid leukemia

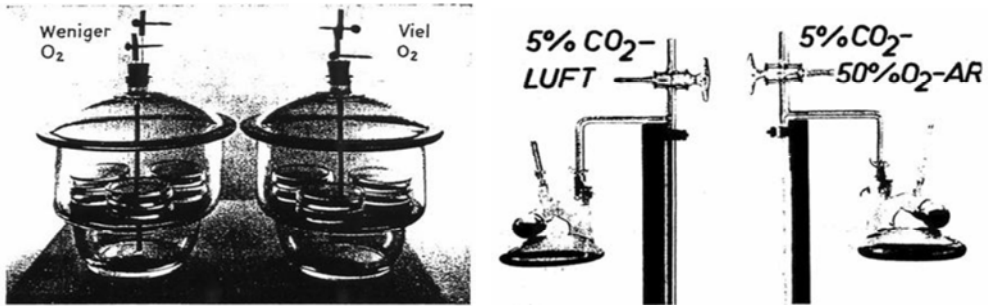
Jean-Emmanuel Sarry

Journée François Jacob ”Stress Response”

Team METAML “Metabolism and Drug Resistance in Myeloid Leukemia”

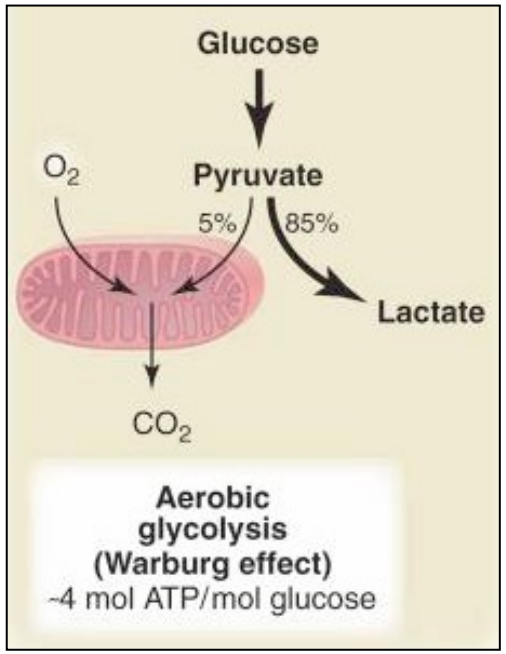
Cancer Research Center of Toulouse

Warburg and beyond!

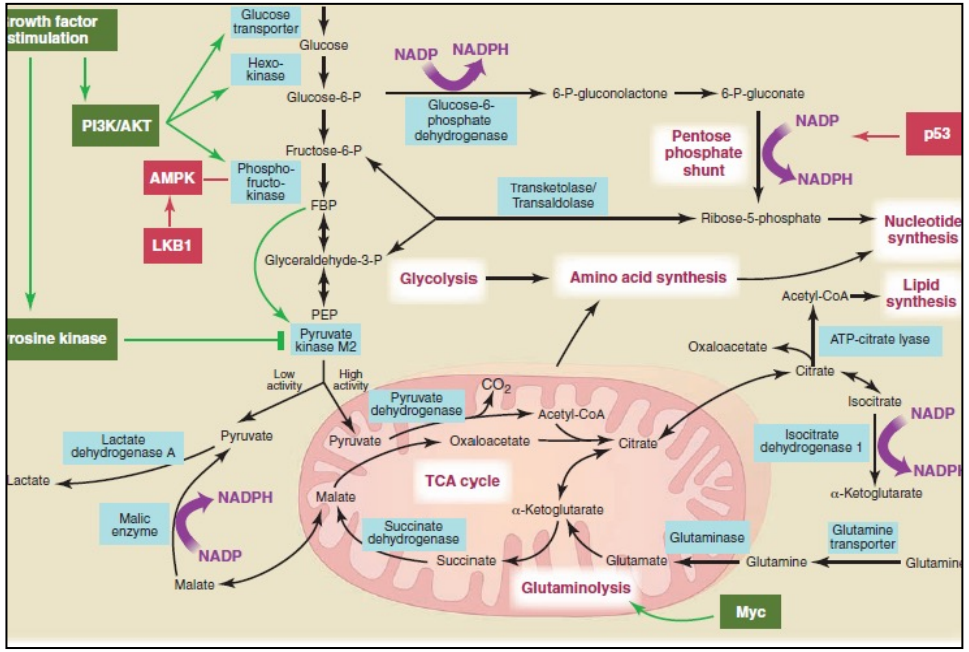


1931, Nobel Prize in Physiology and Medicine
1931, Science, The Metabolism of Tumours

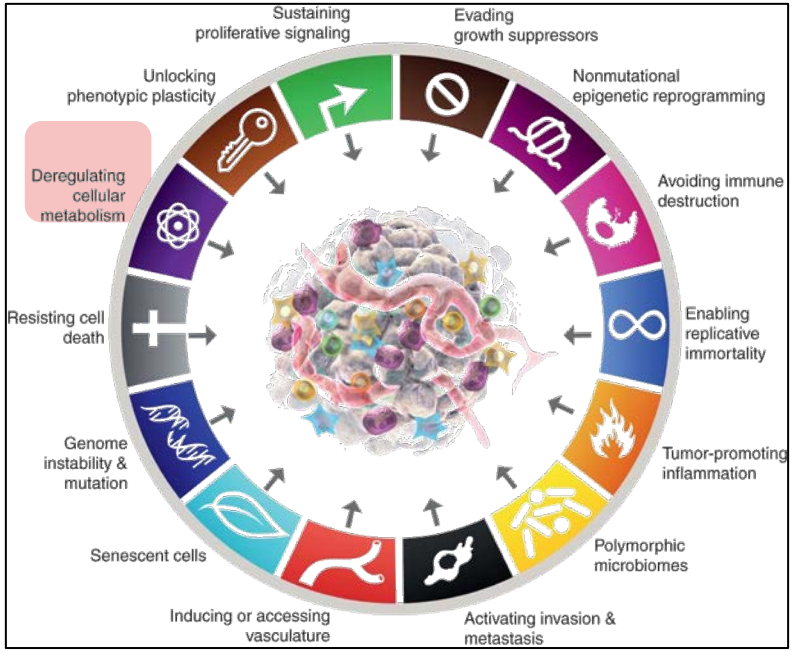
"Warburg effect"



Vander Heiden *et al.* Science. 2009.

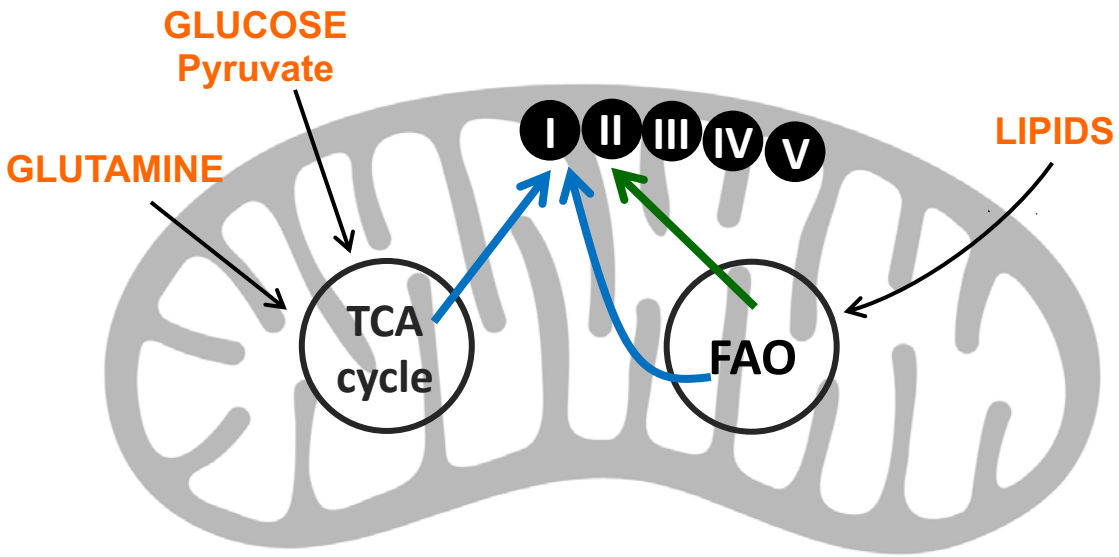


Vander Heiden *et al.* Science. 2009.



Hanahan Cancer Discov.2022
Hanahan and Weinberg. Cell. 2011
Hanahan and Weinberg. Cell. 2000

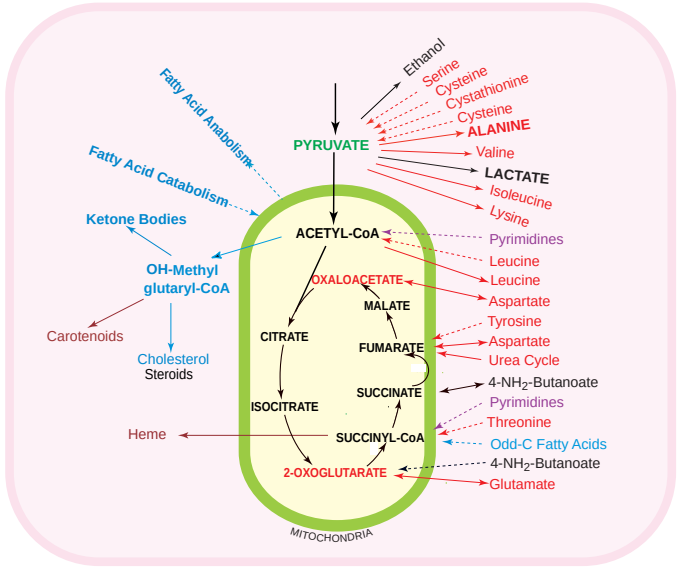
Essential Functions of Mitochondria

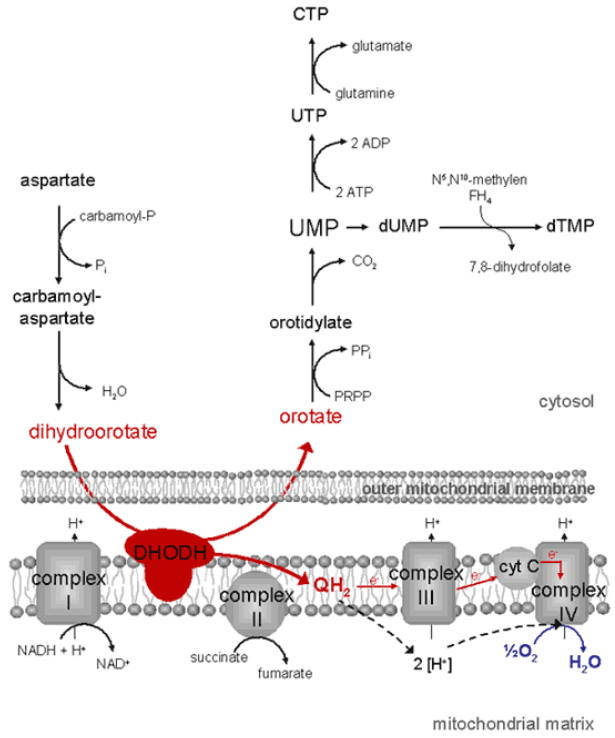


CELLULAR
BIOENERGETIC BALANCE
Oxidative Phosphorylation

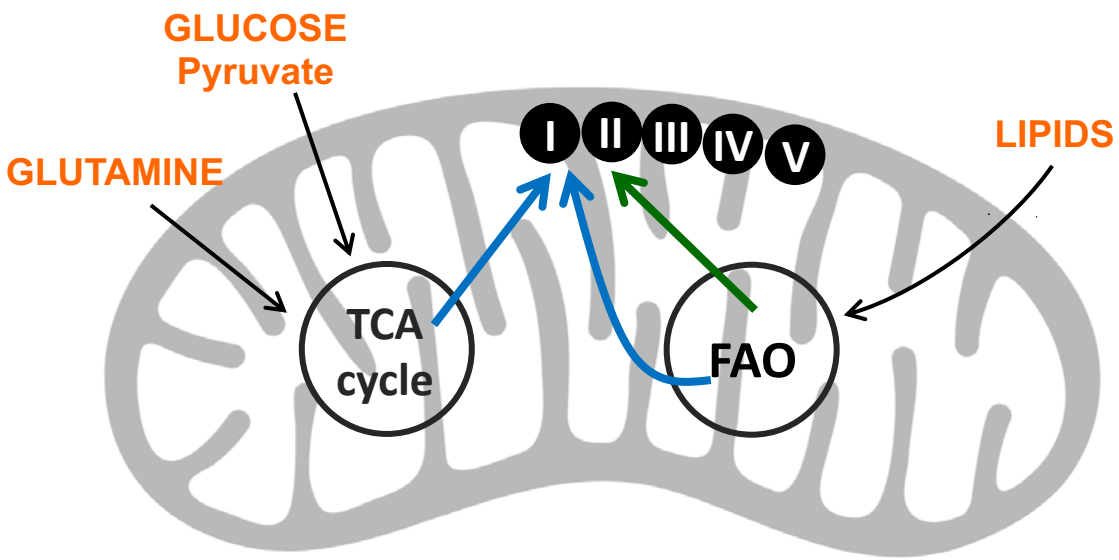
The Hub of Metabolism

Biosynthetic and anapleurotic reactions
Substrate cycling and exchange





Essential Functions of Mitochondria



CELLULAR BIOENERGETIC BALANCE

Oxidative Phosphorylation

The Hub of Metabolism

Biosynthetic and anapleurotic reactions
Substrate cycling and exchange

Redox balance

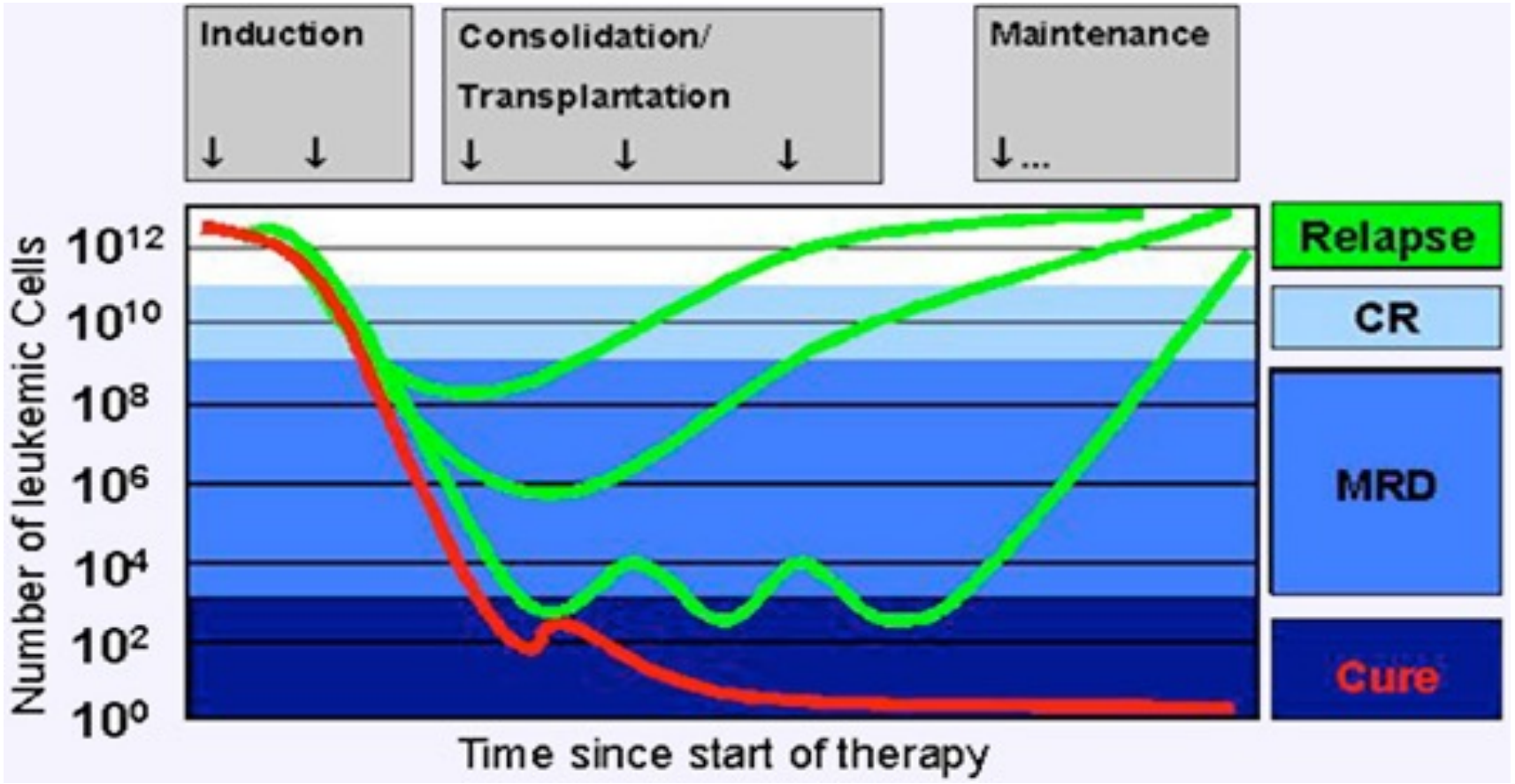
Heme/nonheme biosynthesis
Iron metabolism
ROS production

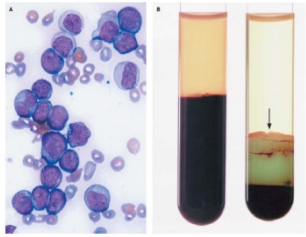
Calcium homeostasis and signaling

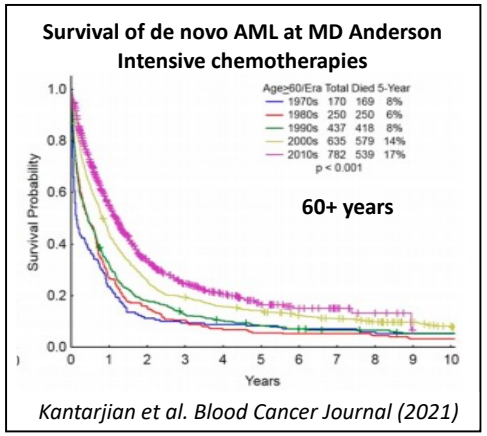
Programmed cell death

Intrinsic apoptosis
Feroptosis

Relapses and drug resistance in cancer

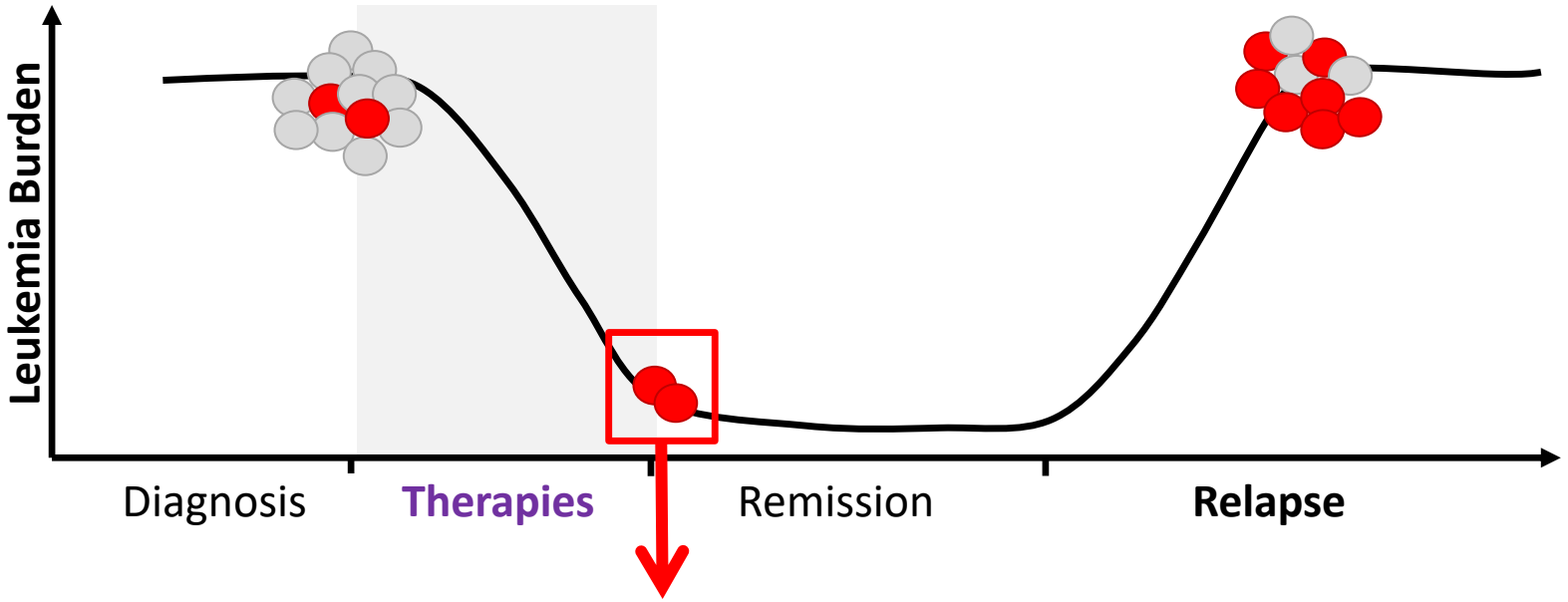






Acute Myeloid Leukemia
AML

Therapy resistance and relapses in cancer

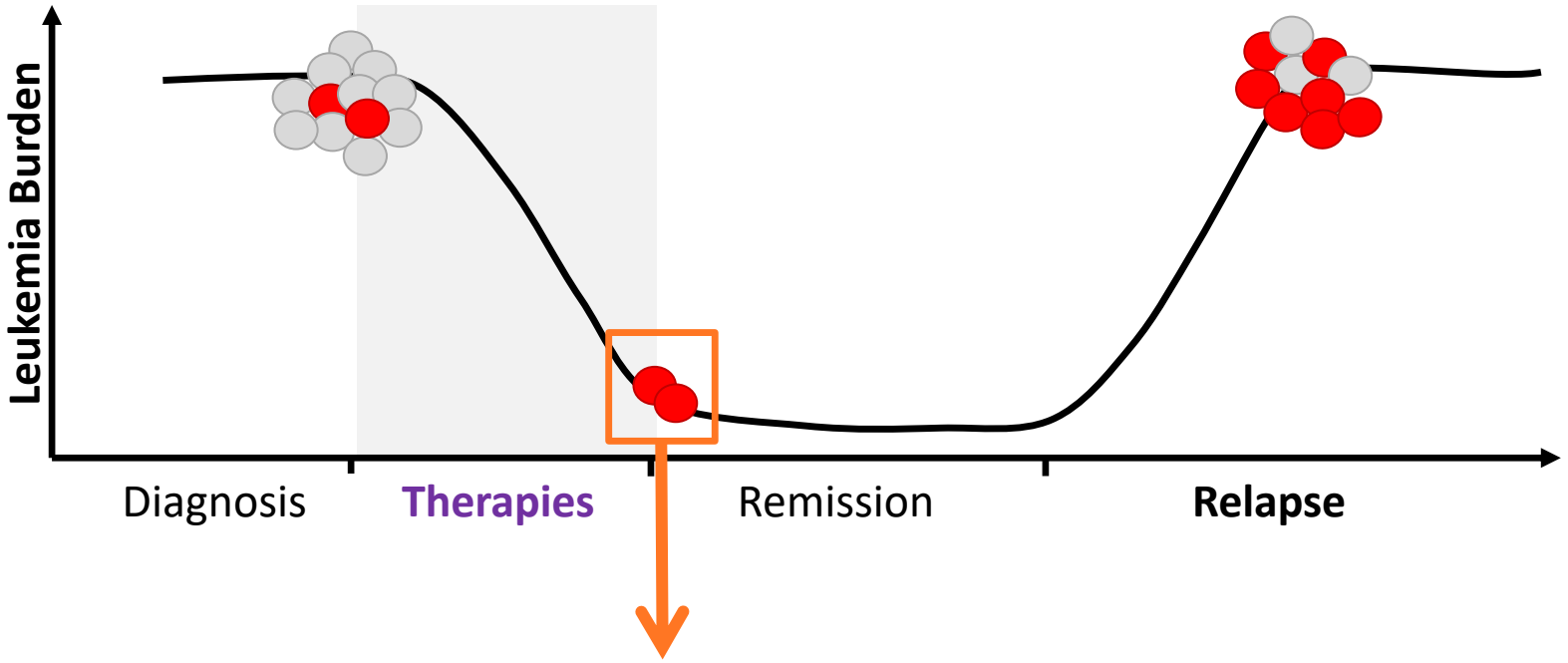


Minimal Residual Disease = MRD

Relapse-Initiating Drug-Tolerant Persisting **Cells**

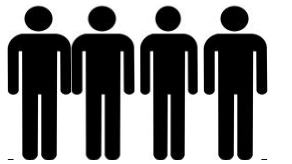
RICs or Persisters

Residual disease and relapse-initiating cells in AML

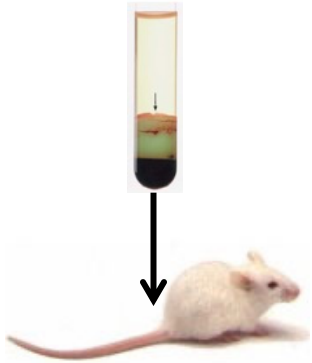


Role of Mitochondria in Drug Persisters within Residual Disease responsible for Relapse in Acute Myeloid Leukemia ?

Persisters have an increased mitochondrial oxidative metabolism

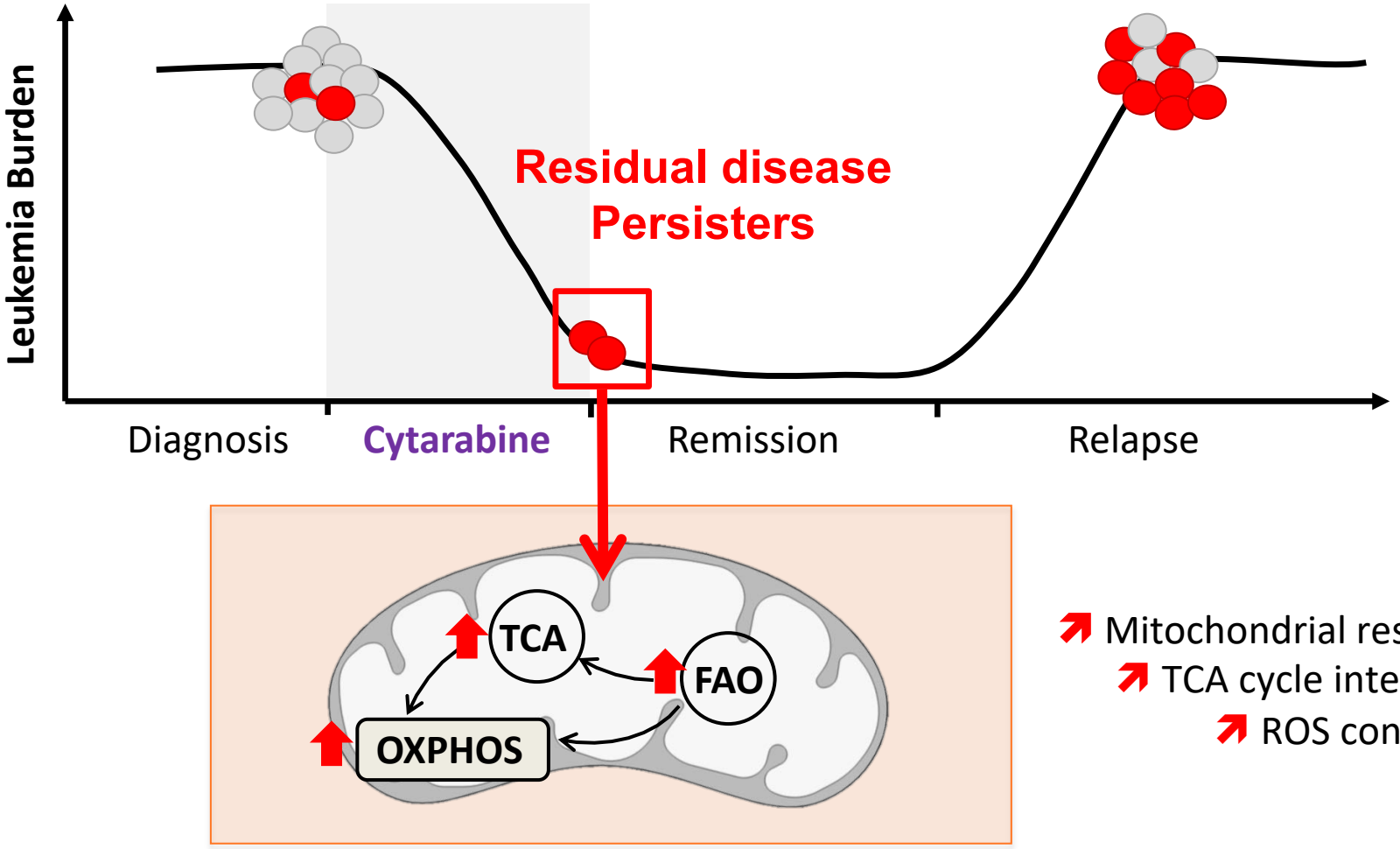


AML patient specimens



PDX Models
NSG Mice

+CYTARABINE



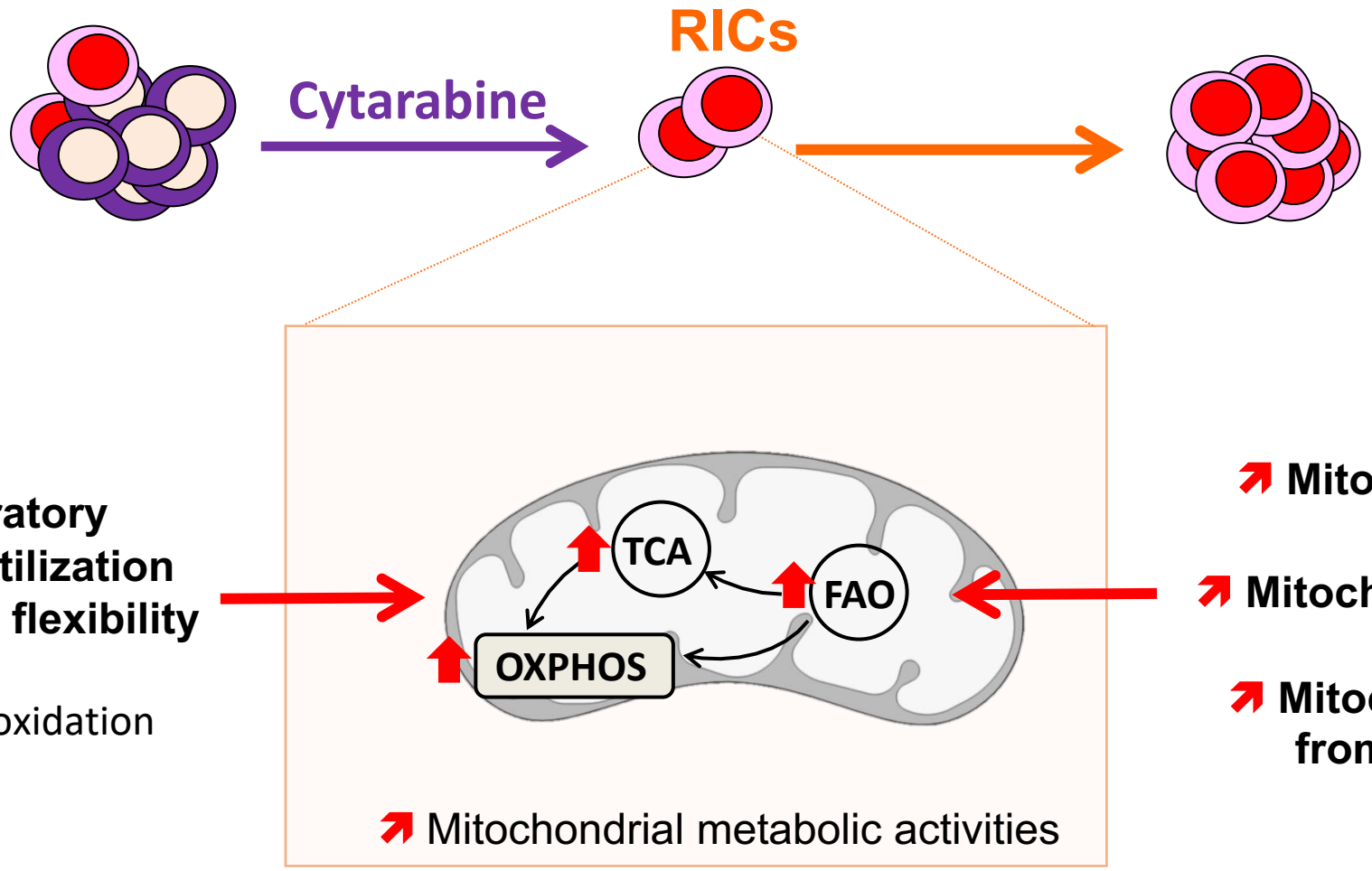
↗ Mitochondrial respiration+ATP
↗ TCA cycle intermediates
↗ ROS content

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 machinery and mitochondrial utilizations



↗ **Respiratory substrates utilization And catabolic flexibility**

↗ Fatty acid oxidation

↗ **Mitochondrial number**

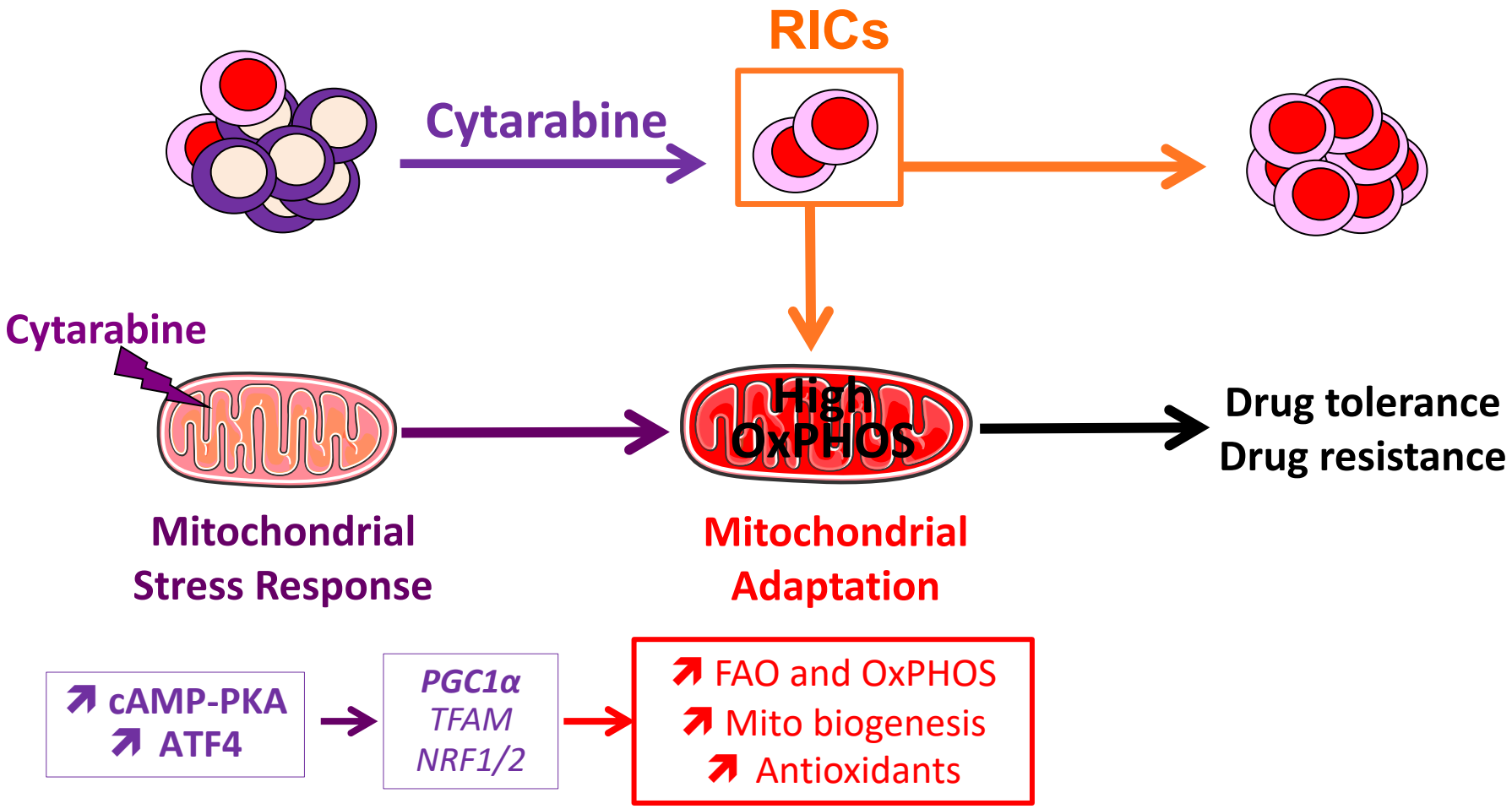
↗ **Mitochondrial biogenesis + Mitochondrial transfer from stromal cells**

↗ Mitochondrial metabolic activities

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

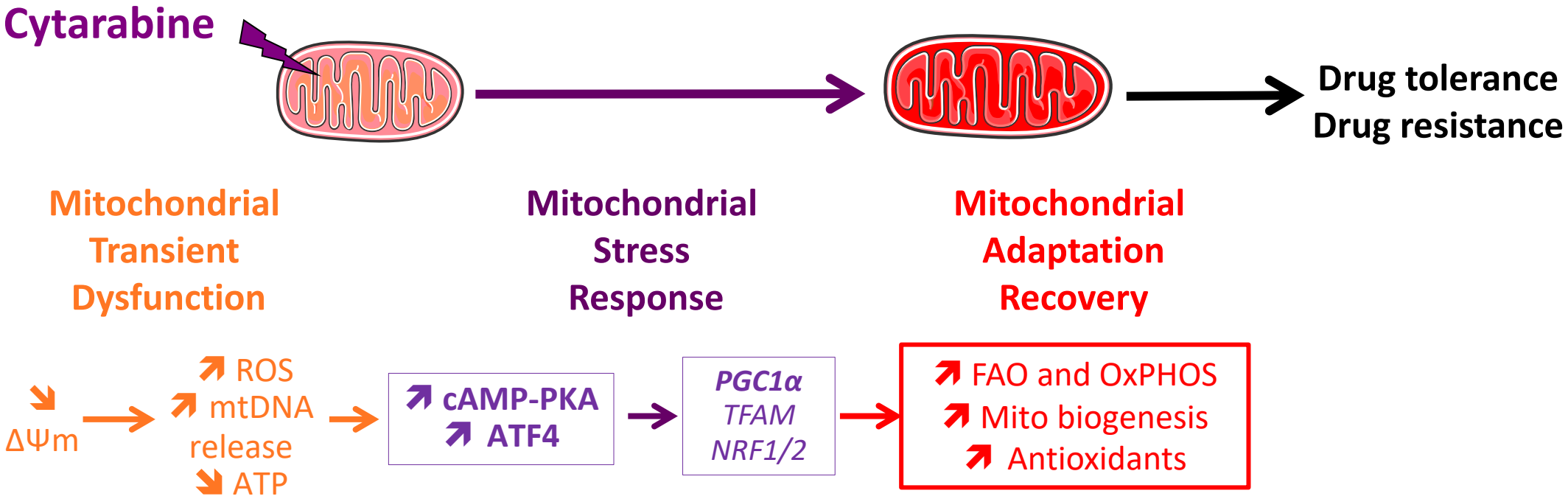
Ducau *et al*. unpublished data
Farge *et al.* Cancer Discov. 2017
Moschoi …. Griessinger. Blood. 2016

OxPHOS phenotype reflects a mitochondrial adaptation induced by a specific transcriptional program



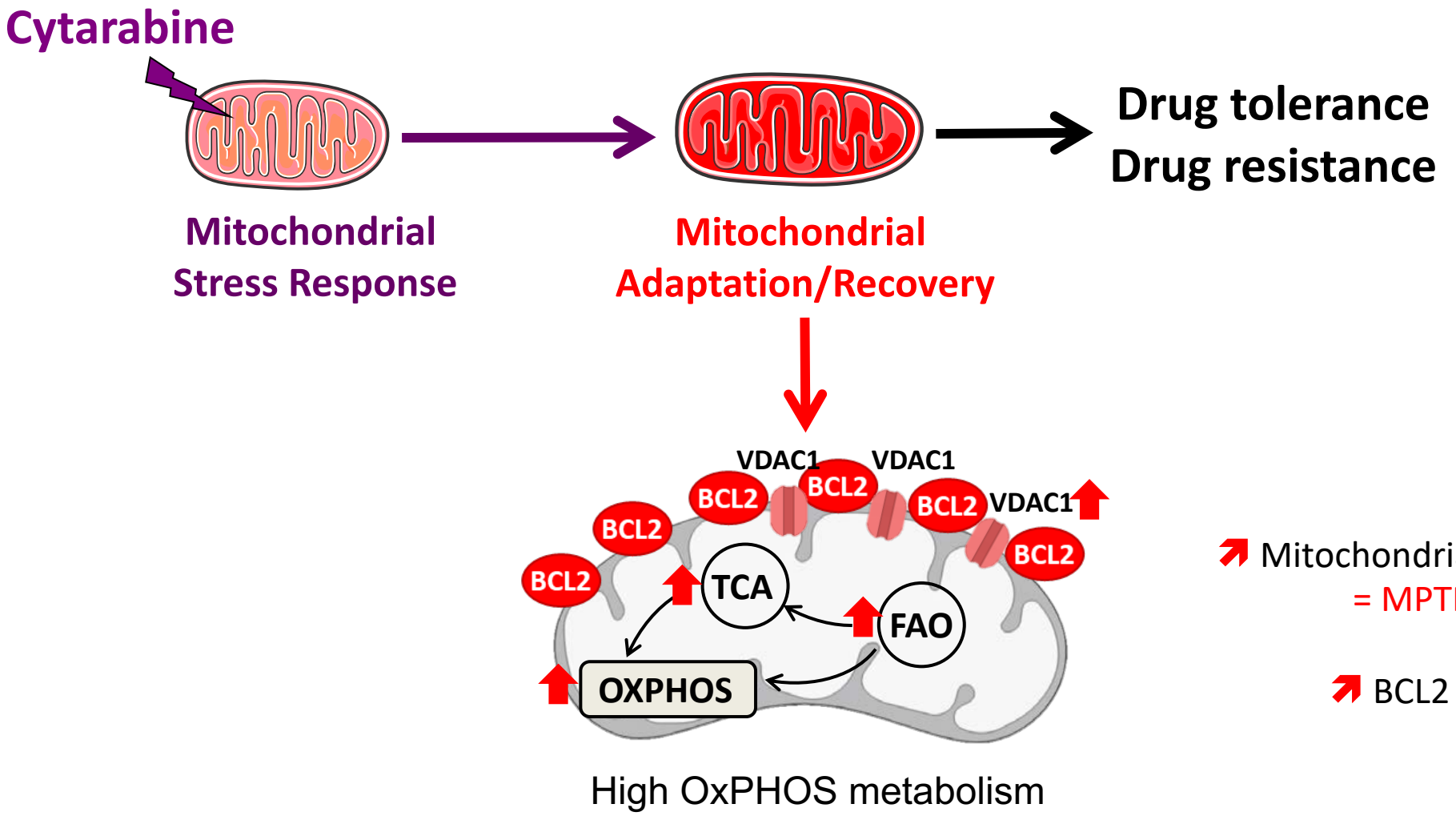
Aroua, Boet, Ghisi *et al*. Cancer Discov. 2020

Induction of response to early AraC-triggered mitochondrial stress



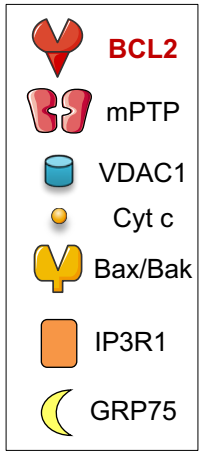
Boet, Saland. Unpublished
Aroua, Boet, Ghisi et al. Cancer Discov. 2020

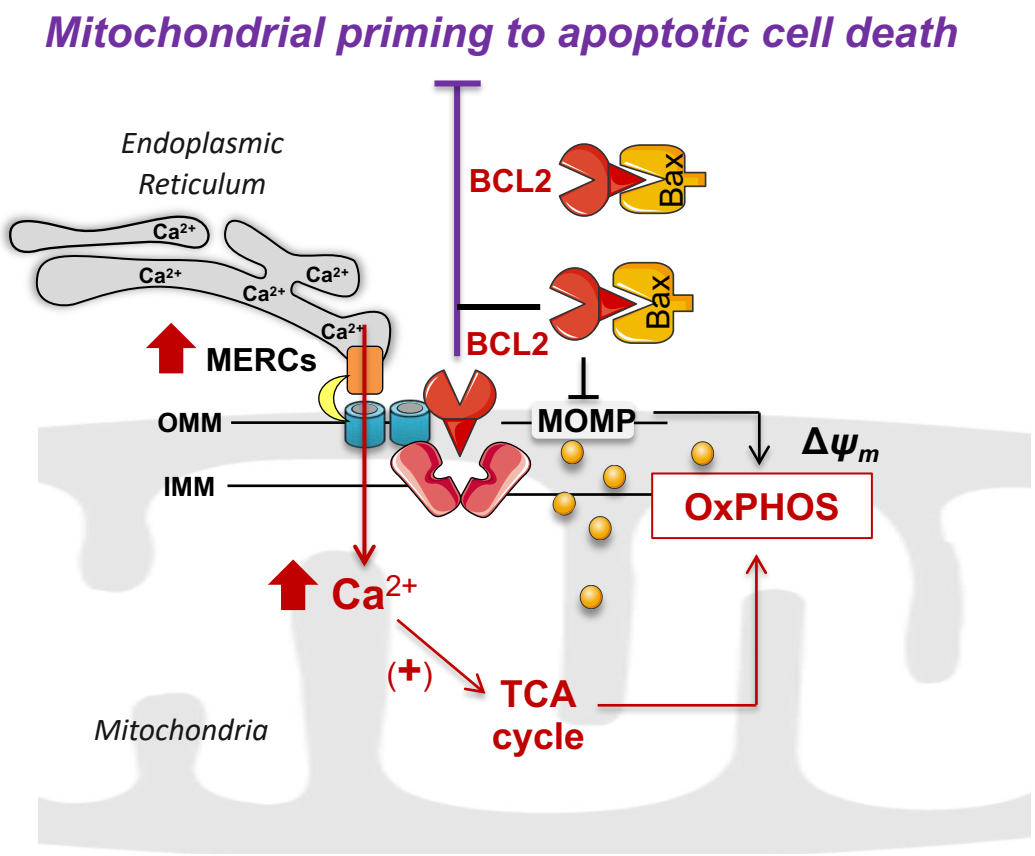
Mitochondrial relocation of BCL2 and increased VDAC1 in drug persisters



Bosc *et al*. Nature Cancer. 2021

Increased mitochondria-ER contact sites (MERCs) and mitochondrial calcium content in RICs

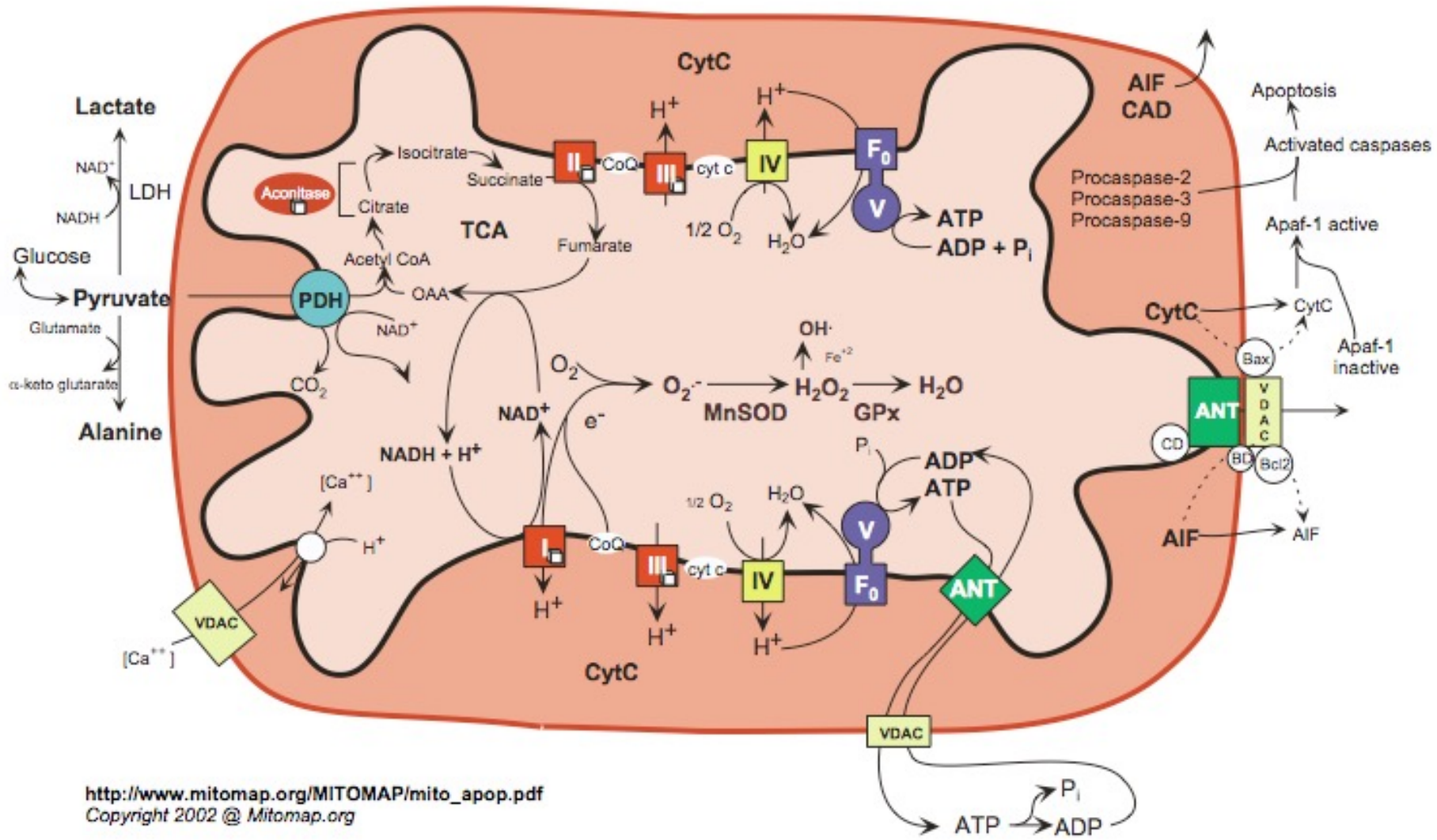




mitoBCL2	**High**
MOMP	No/transient
mPTP	Closed
mitoCalcium	High
OxPHOS	**High**
AraC	**Resistant**

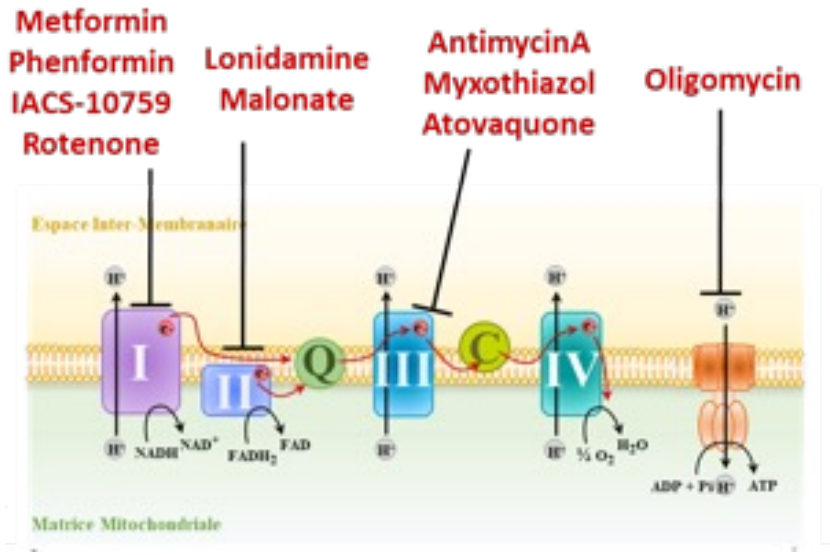
Bosc *et al*. Nature Cancer. 2021
Bosc *et al*. Nature Comm. 2020

Link between mitochondrial metabolism and resistance to apoptosis in MRD

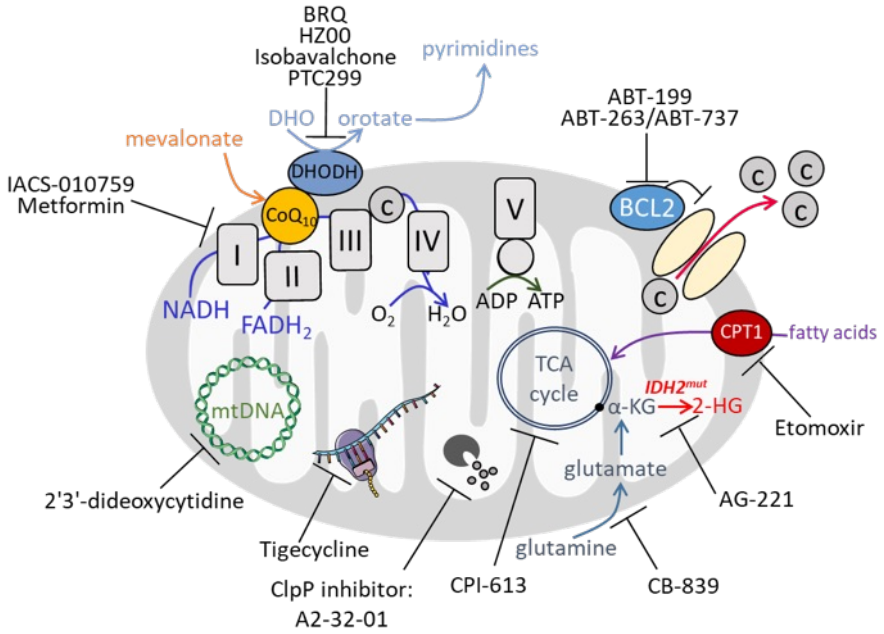


RICs are more sensitive to mitochondrial inhibitors

Selective ETC/OxPHOS inhibitors

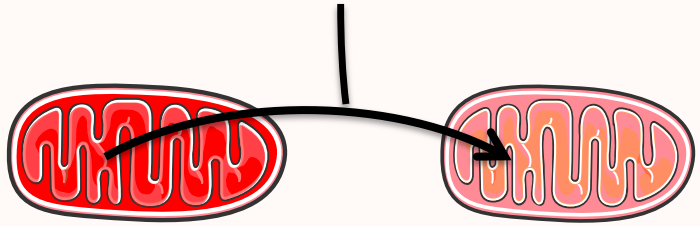


Indirect ETC/OxPHOS inhibitors



Targeting any aspect of High OxPHOS metabolism

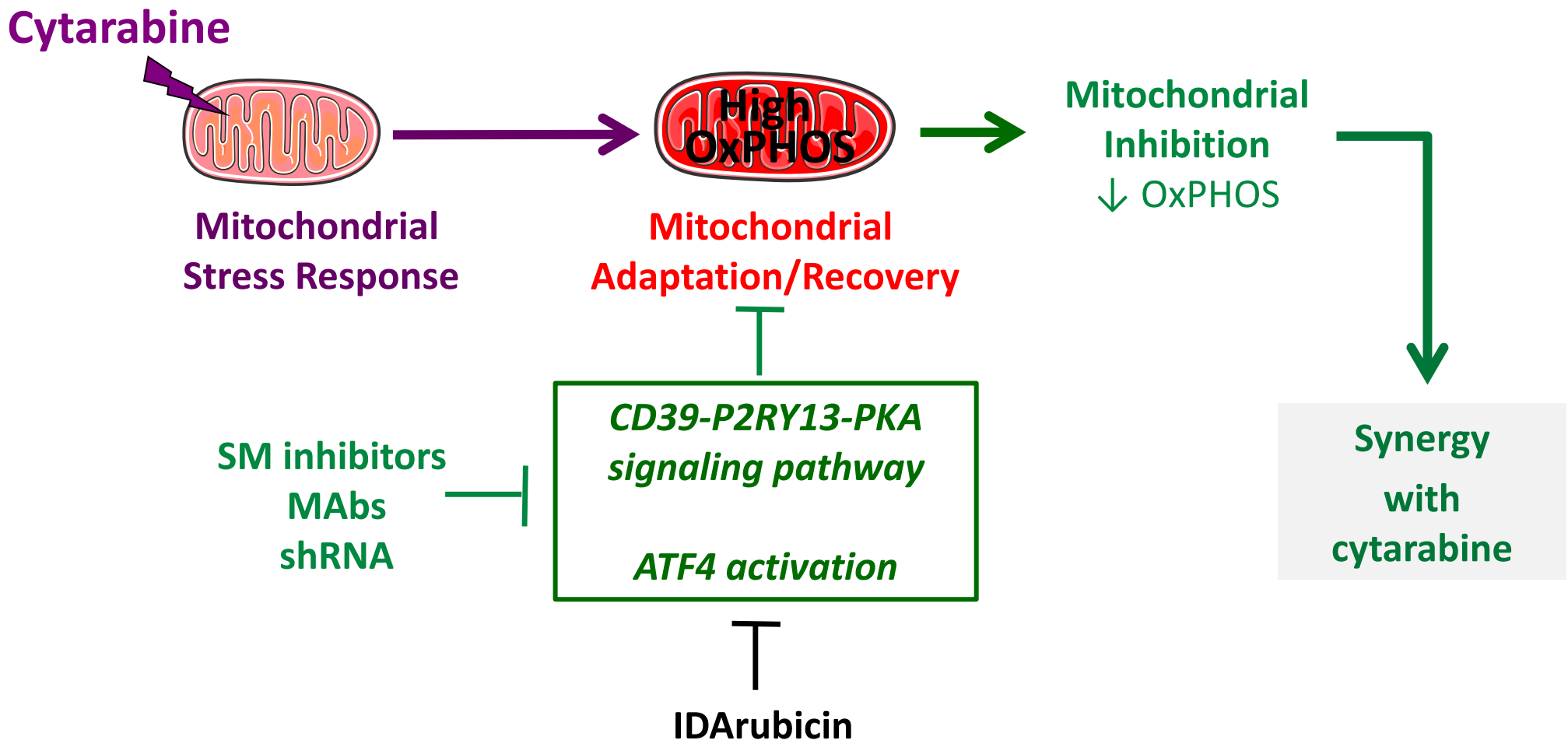
Resistant to AraC



Sensitive to AraC

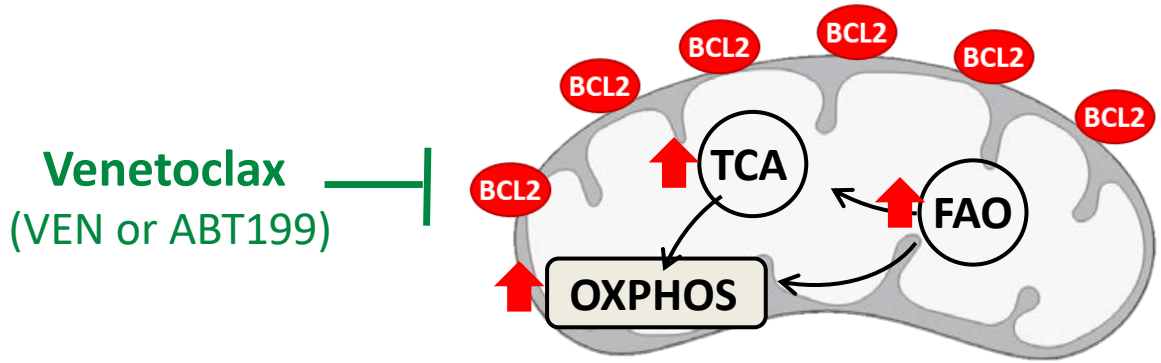
Stuani *et al*. BMC Biol. 2019; Bosc *et al*. Cell Metab. 2017
Farge et *al.* Cancer Discov. 2017; Samudio et al. JCI. 2010

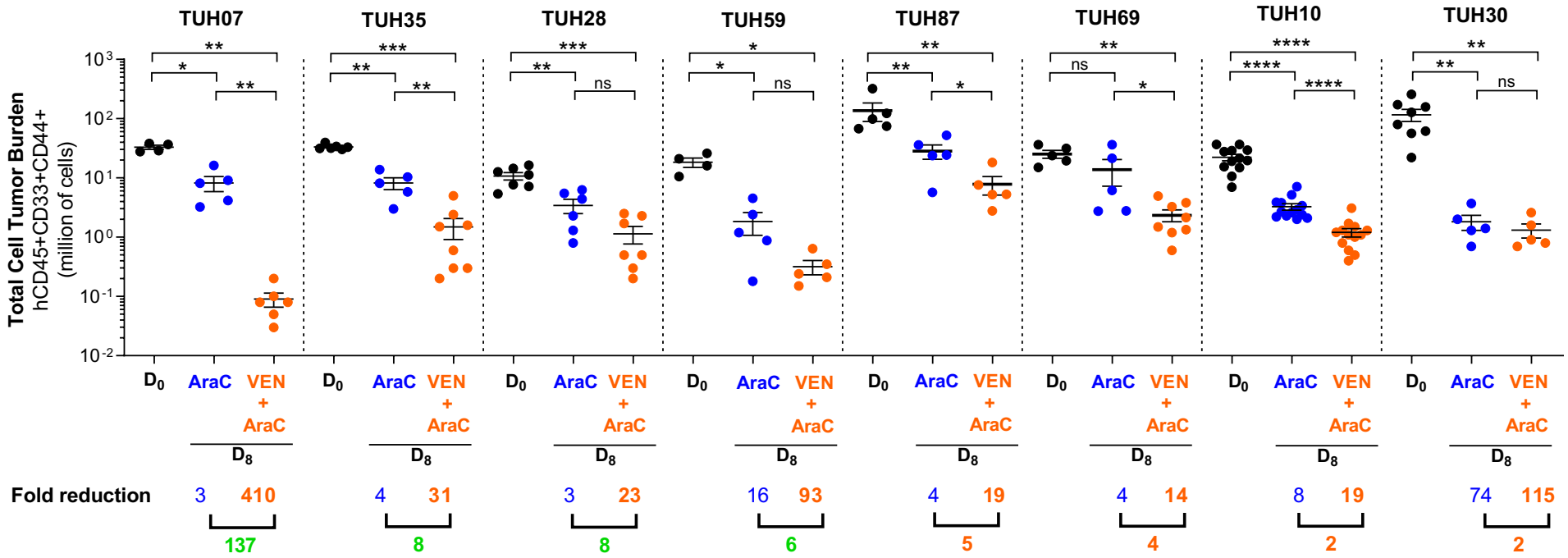
Blocking mitochondrial adaptation by targeting adenosine-PKA-ATF4 axis in AML



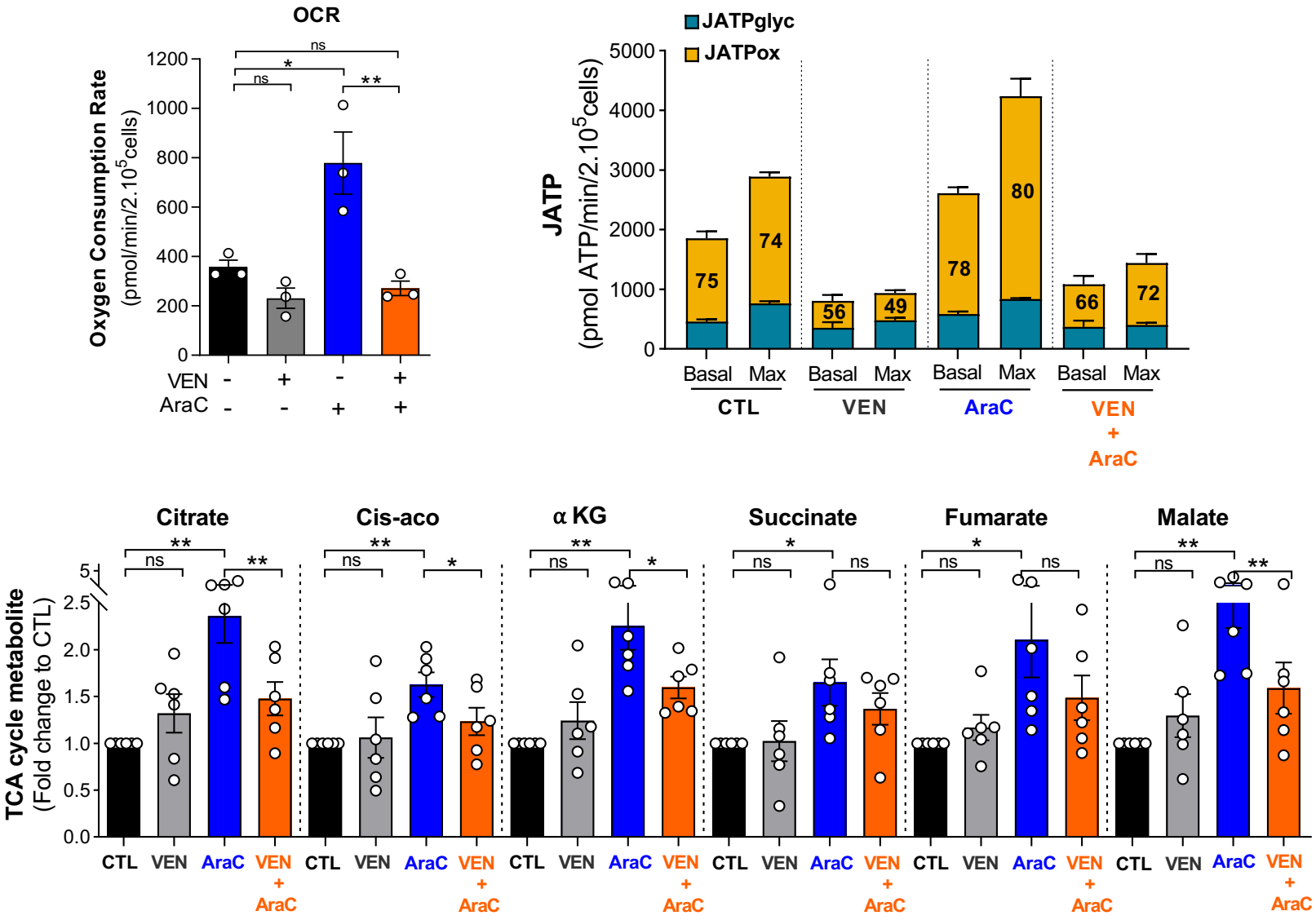
Mouchel *et al*. in prep
Aroua, Boet, Ghisi *et al*. Cancer Discov. 2020

VEN+AraC doublet therapy better than AraC alone in PDX



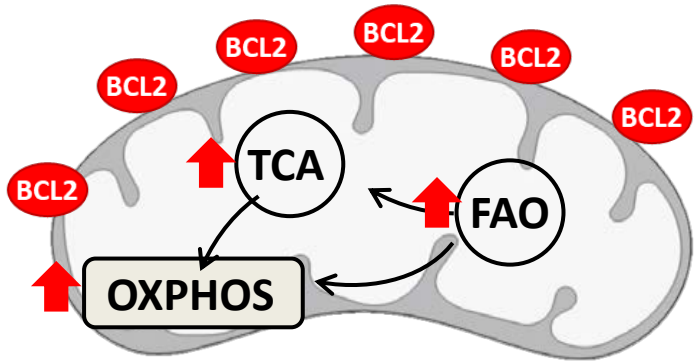


AraC-induced high OxPHOS state is blocked by VEN+AraC doublet therapy



Efficacy of VEN+AraC doublet therapy in unfit patients

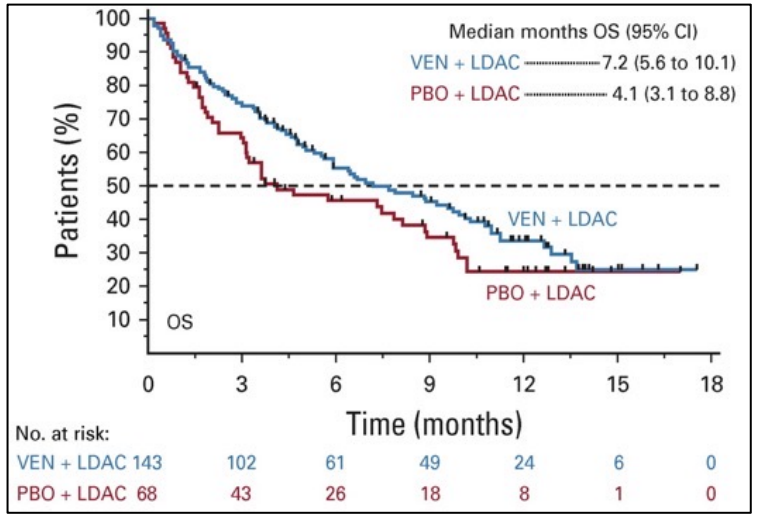
Venetoclax
(VEN or ABT199)



Synergy with cytarabine
(LDAC or AraC)

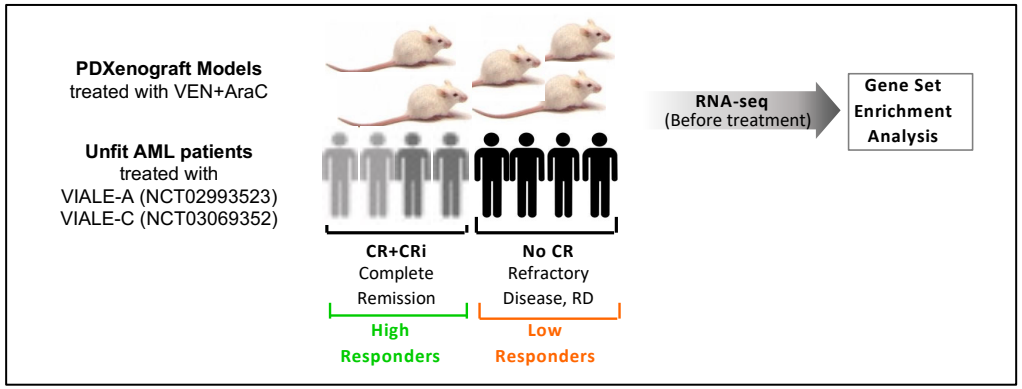
Response	VIALE-C	
	VEN (n = 143)	PBO (n = 68)
CR/CRi, %	48	13
CR, %	28	7
Duration of CR, months	17	8

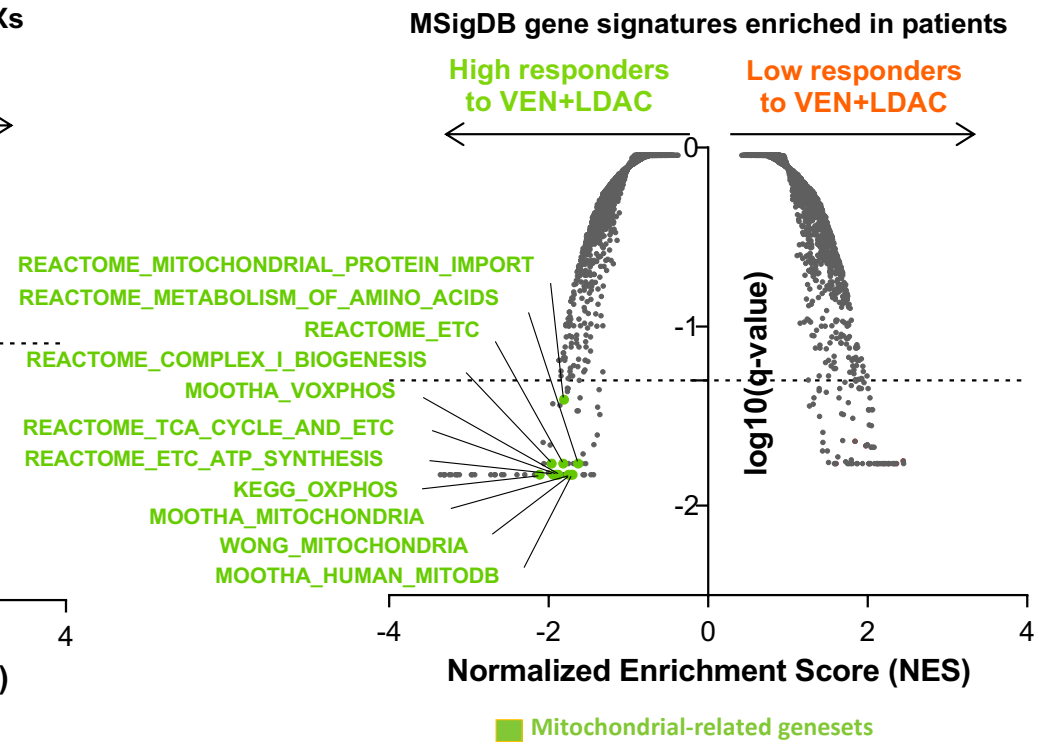
VIALE-C : Phase III VEN+**LDAC**
de novo AML patient unfit for intensive chemotherapy
NCT03069352

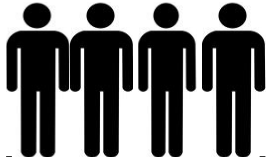


Wei et *al.* Blood 2020
Wei et al. JCO 2021

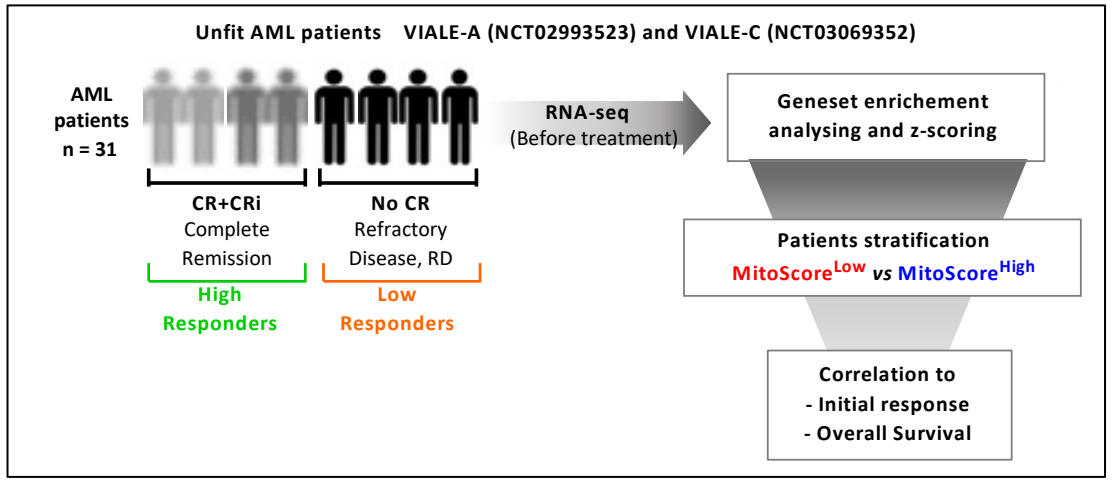
Mitochondrial gene signatures are enriched in transcriptomes of patients who are high responder to Ven+AraC in PDXs and patients

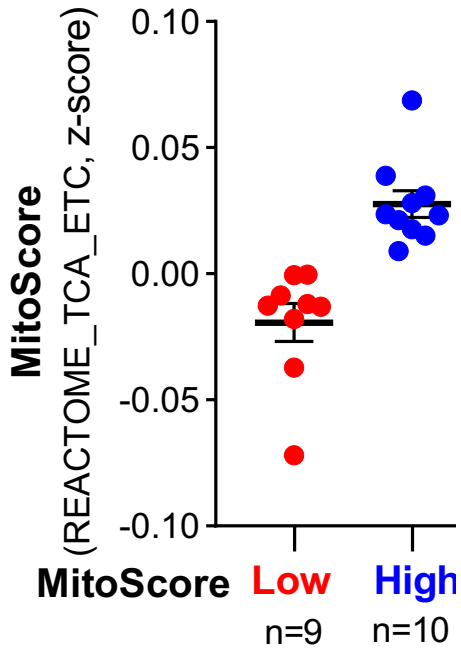






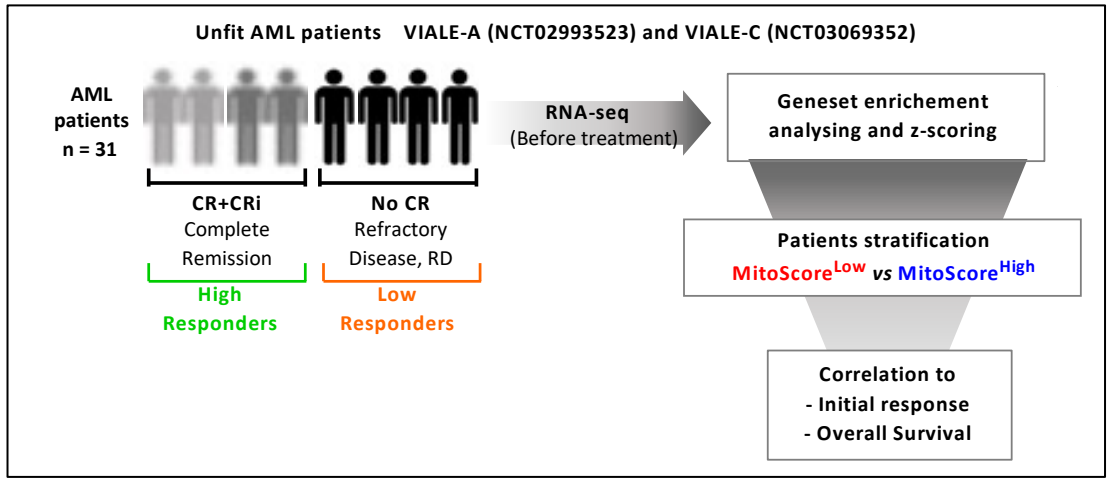
High MitoScore predicts a better response to VEN+LDAC in unfit AML patients

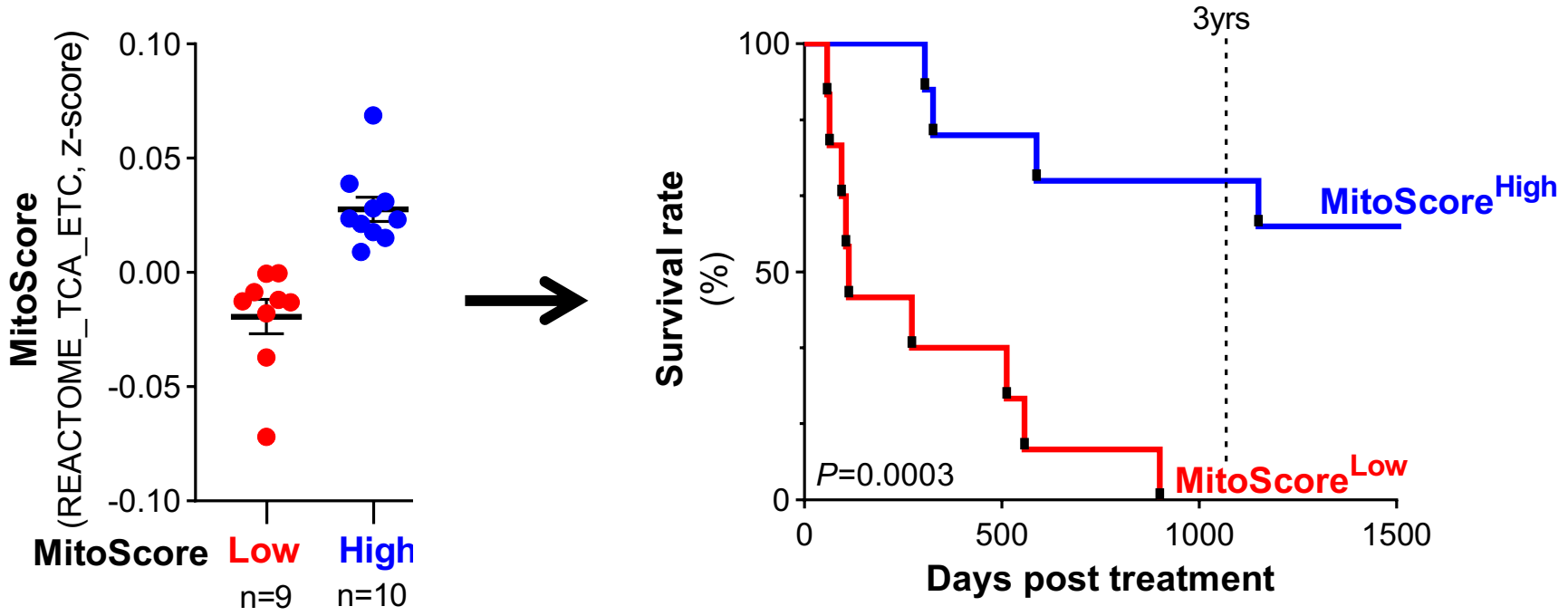




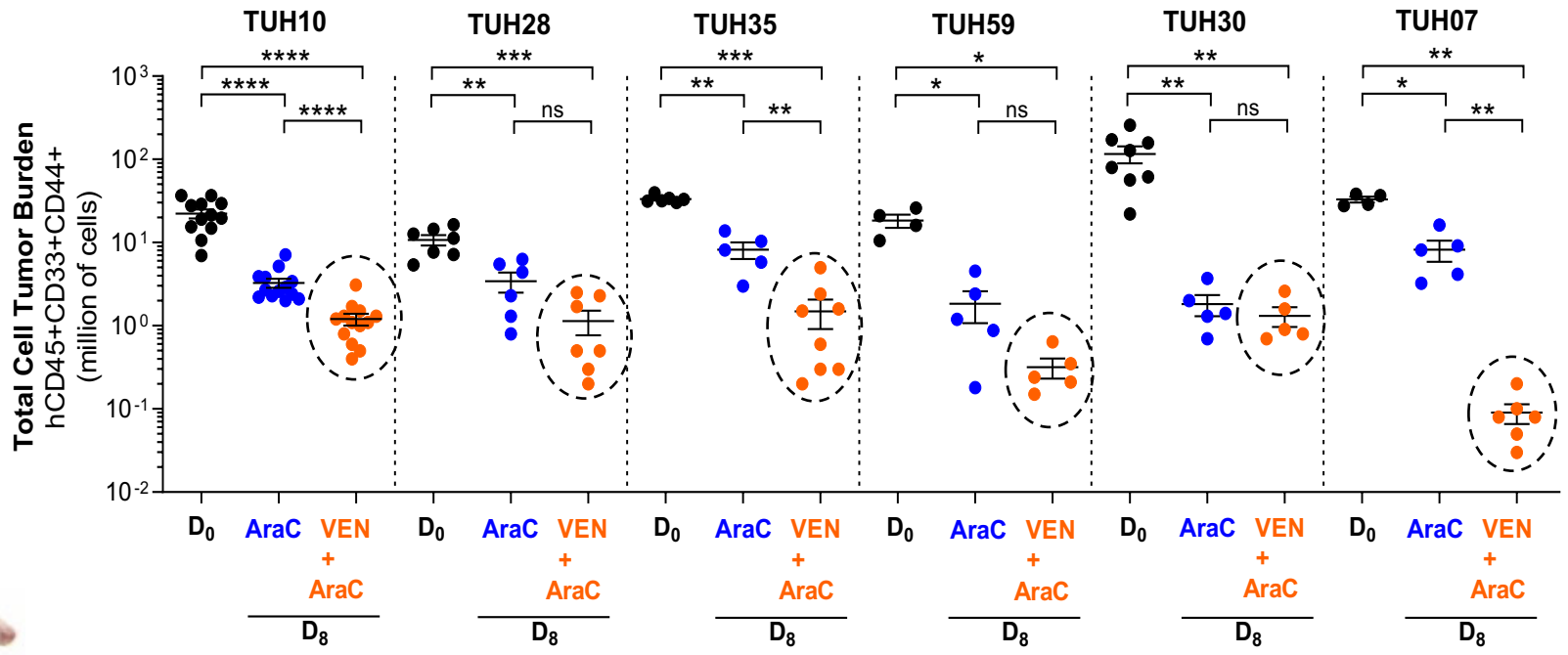
Collaborations : T. Kaoma (LIH, Luxembourg)
IS. Tiong, A Wei (Melbourne)

High MitoScore predicts a better response to VEN+LDAC in unfit AML patients





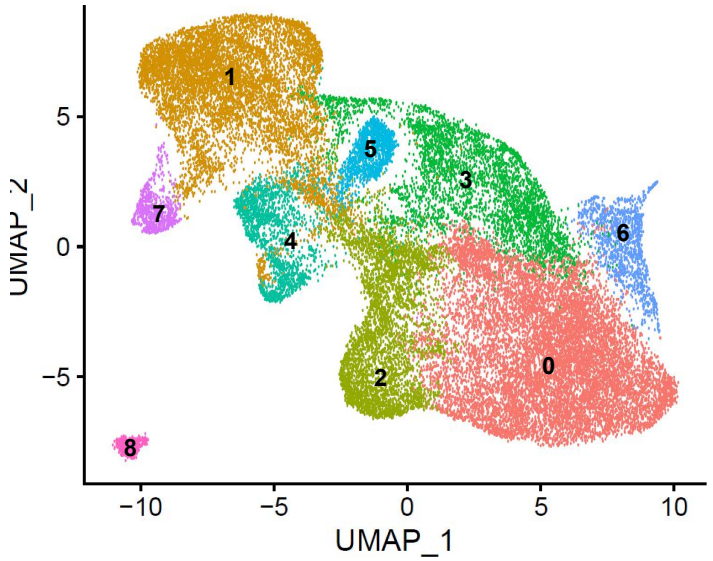
Residual cells persist after doublet therapy VEN+AraC *in vivo*



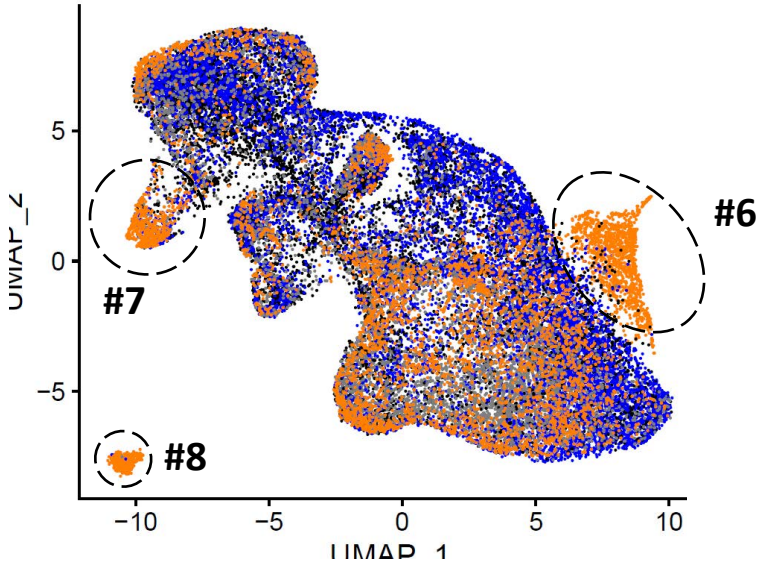
PDXenograft Models
NSG Mice

Single cell RNA-seq reveals three transcriptionally distinct cell subpopulations post-VEN+AraC *in vivo*

Seurat gene expression clustering



Gene expression clustering *per* condition



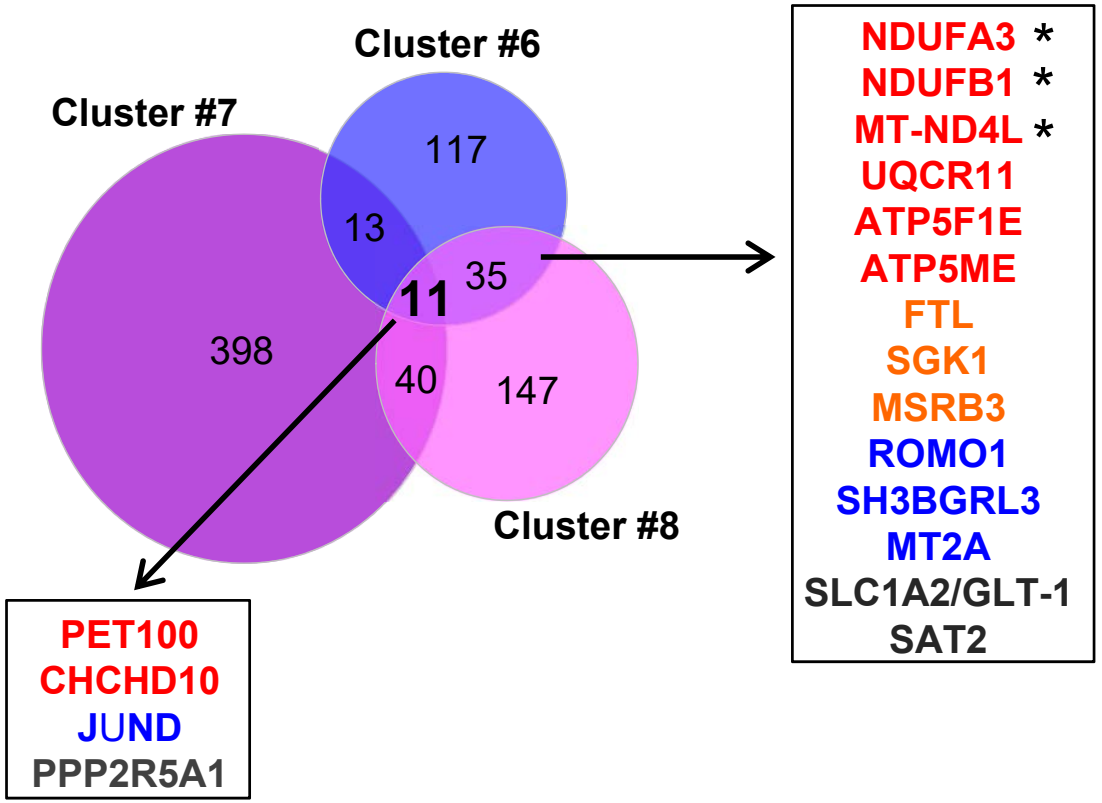
From 2 different PDX models

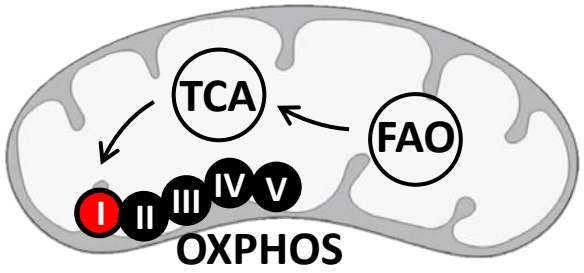
D0
VEN
AraC
VEN + AraC
D8

Collaborations : C. Mazzotti, H Avet-Loiseau, M. Tosolini (IUCT/CRCT)
JC Marine, F Rambow, A Bousard (VIB, Brussels)
Aibar et *al.* Nat Methods 2017

Residual disease after VEN+AraC maintains ETC/OxPHOS homeostasis

Clusters involved in VEN+AraC resistance

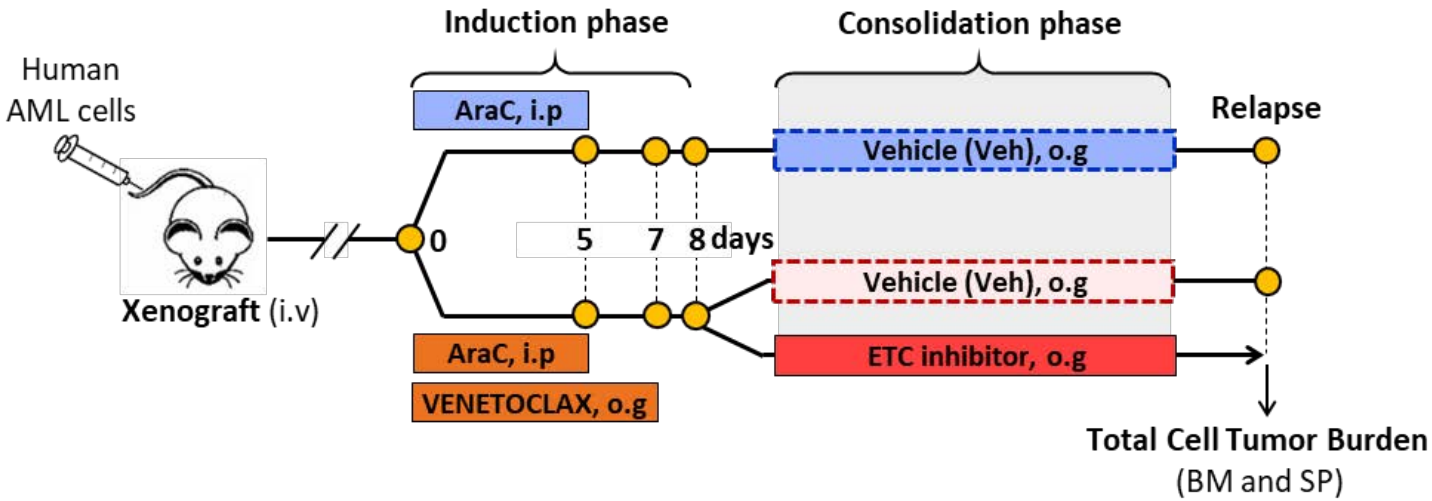




ETCI: electron transport chain complex I

- **OxPHOS related hits** *ETCI subunits
- **Other Mitochondria related hits**
- **ROS related hits**
- **Metabolism related hits**

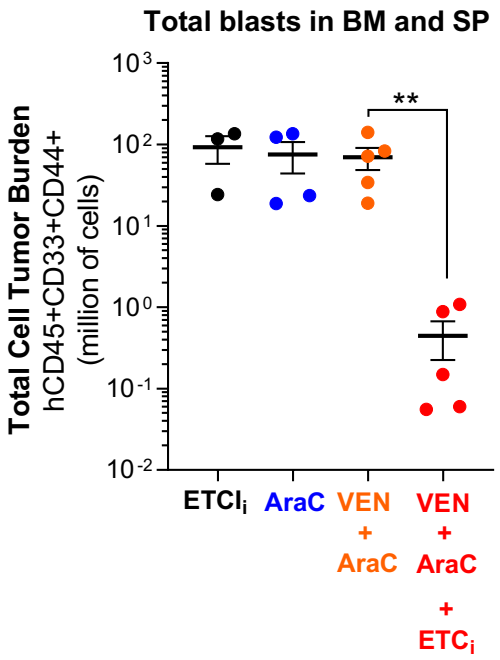
Does targeting ETCI of residual cells prolong mice survival *in vivo* ?

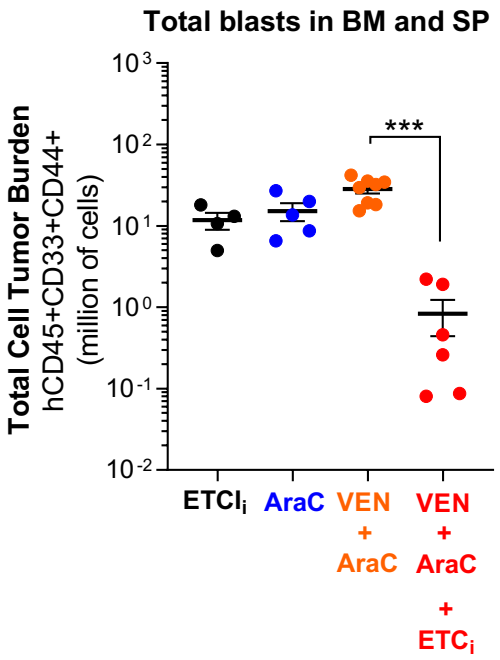


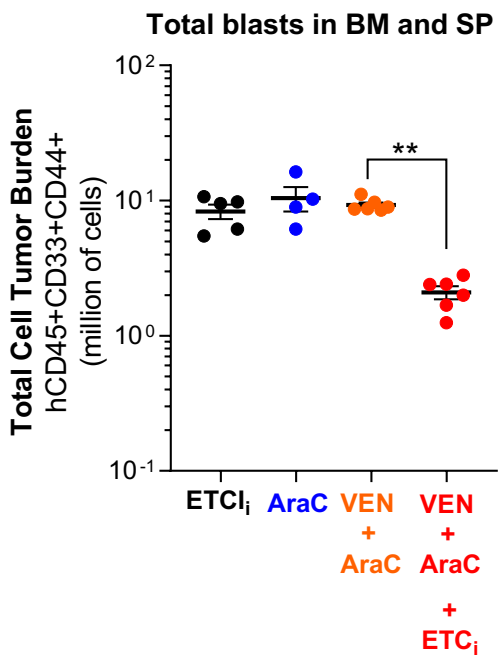
Direct selective ETCI inhibitor : IACS-10759

Indirect ETCI/OxPHOS inhibitor : ONC-212 (mitochondrial ClpP protease agonist)

Targeting ETCI of residual cells following doublet therapy VEN+AraC reduces tumor burden *in vivo*

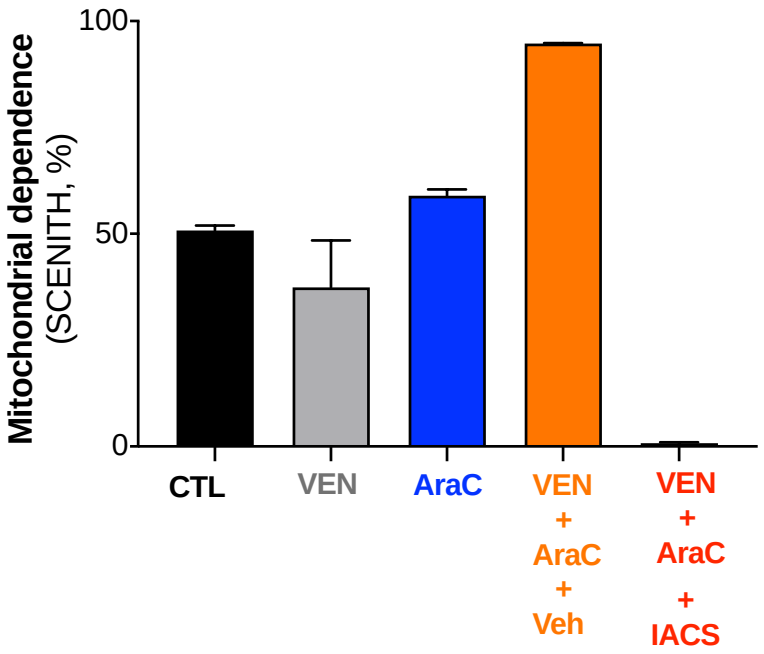


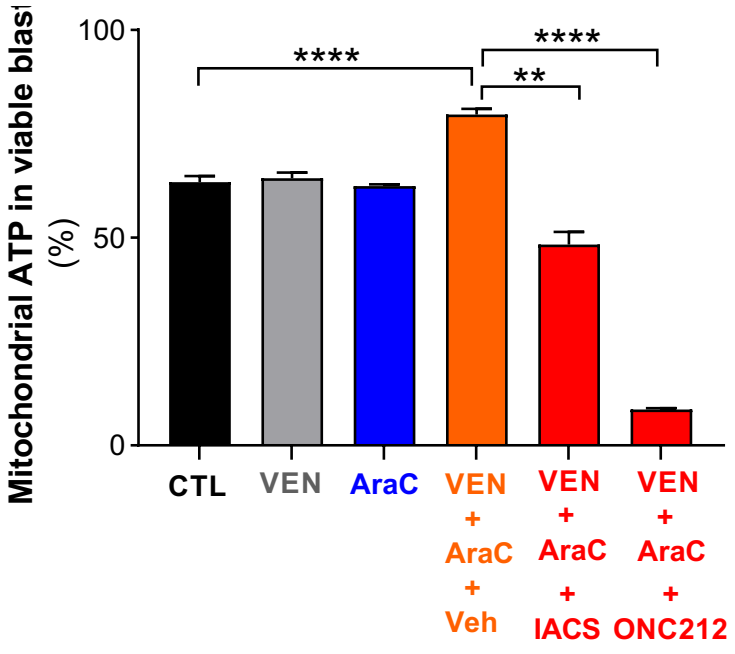


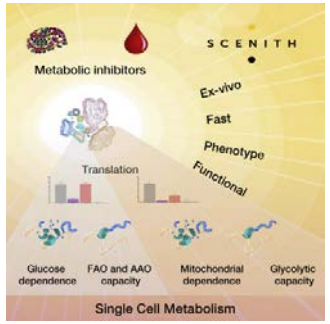


ETCi : IACS-010759 or ONC212

Targeting ETCI of residual cells following VEN+AraC doublet therapy blocks mitochondrial energetic recovery *in vivo*



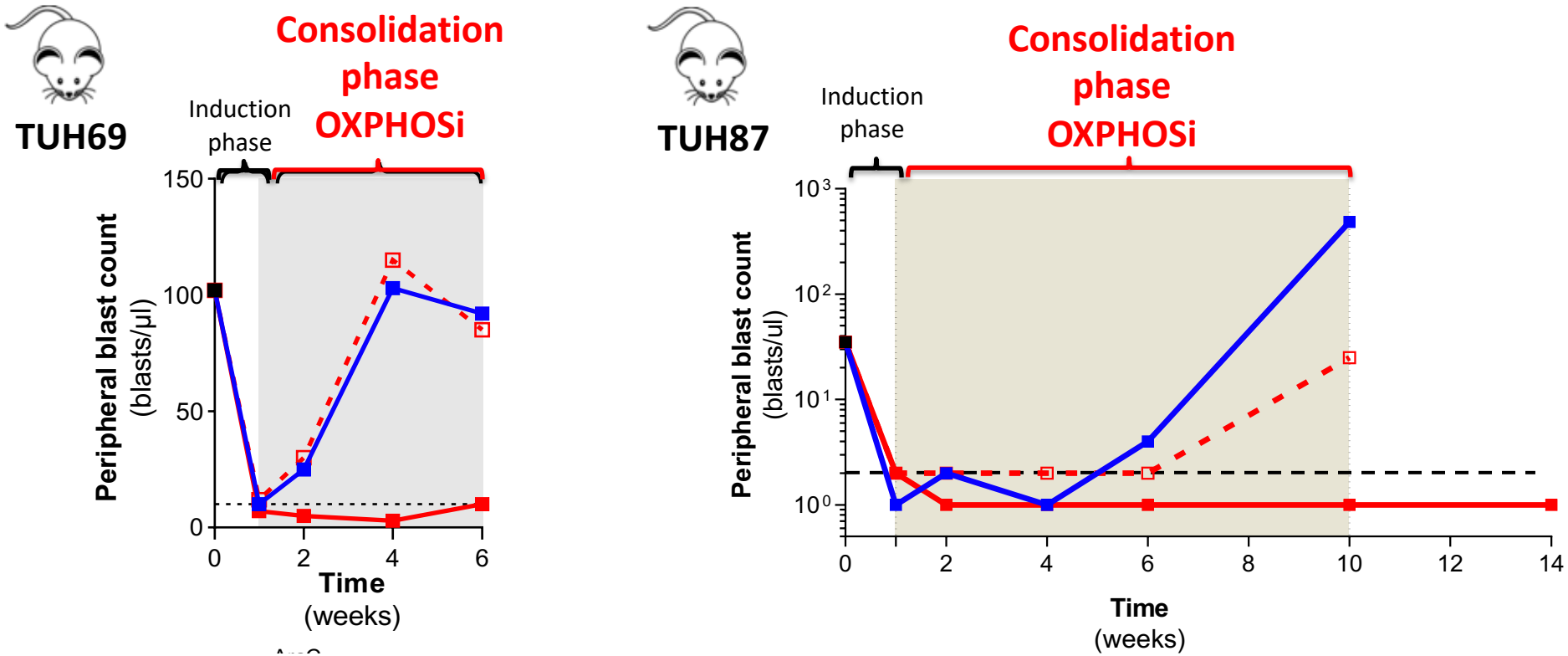




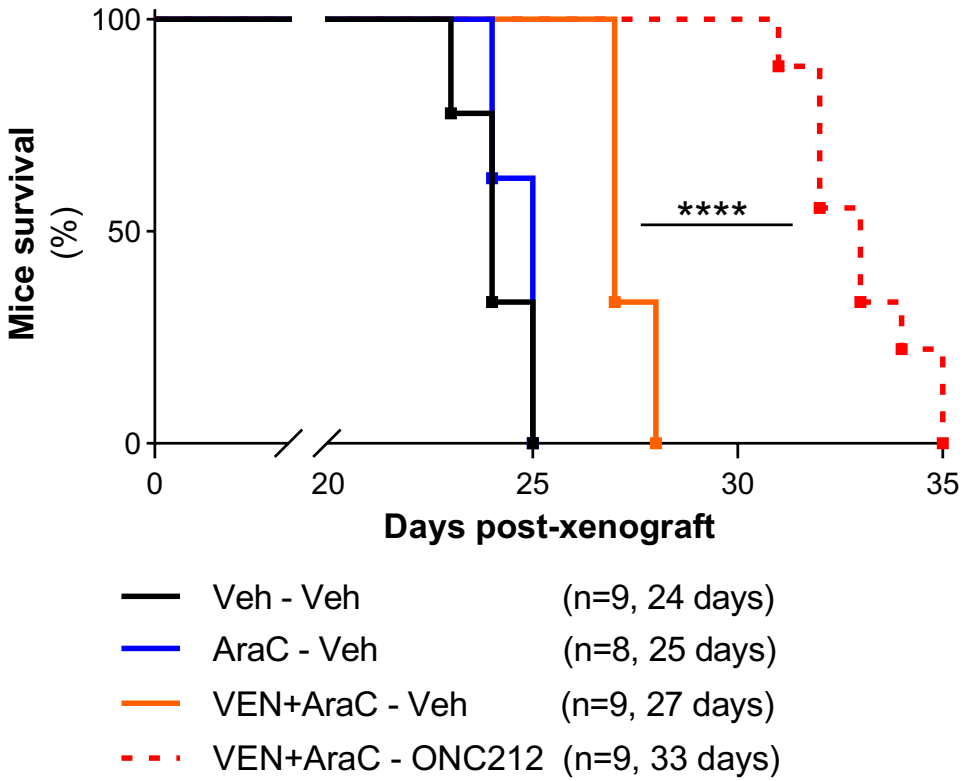
Collaboration : Rafael Arguello (CIML, Marseille)

Arguello et *al.* Cell Metab. 2020. SCENITH: A Flow Cytometry-Based Method to Functionally Profile Energy Metabolism with Single-Cell Resolution

Targeting ETCI of residual cells following VEN+AraC doublet therapy reduces tumor burden and prevent relapse



Targeting ETCI of residual cells following VEN+AraC doublet therapy does prolong mice survival *in vivo*

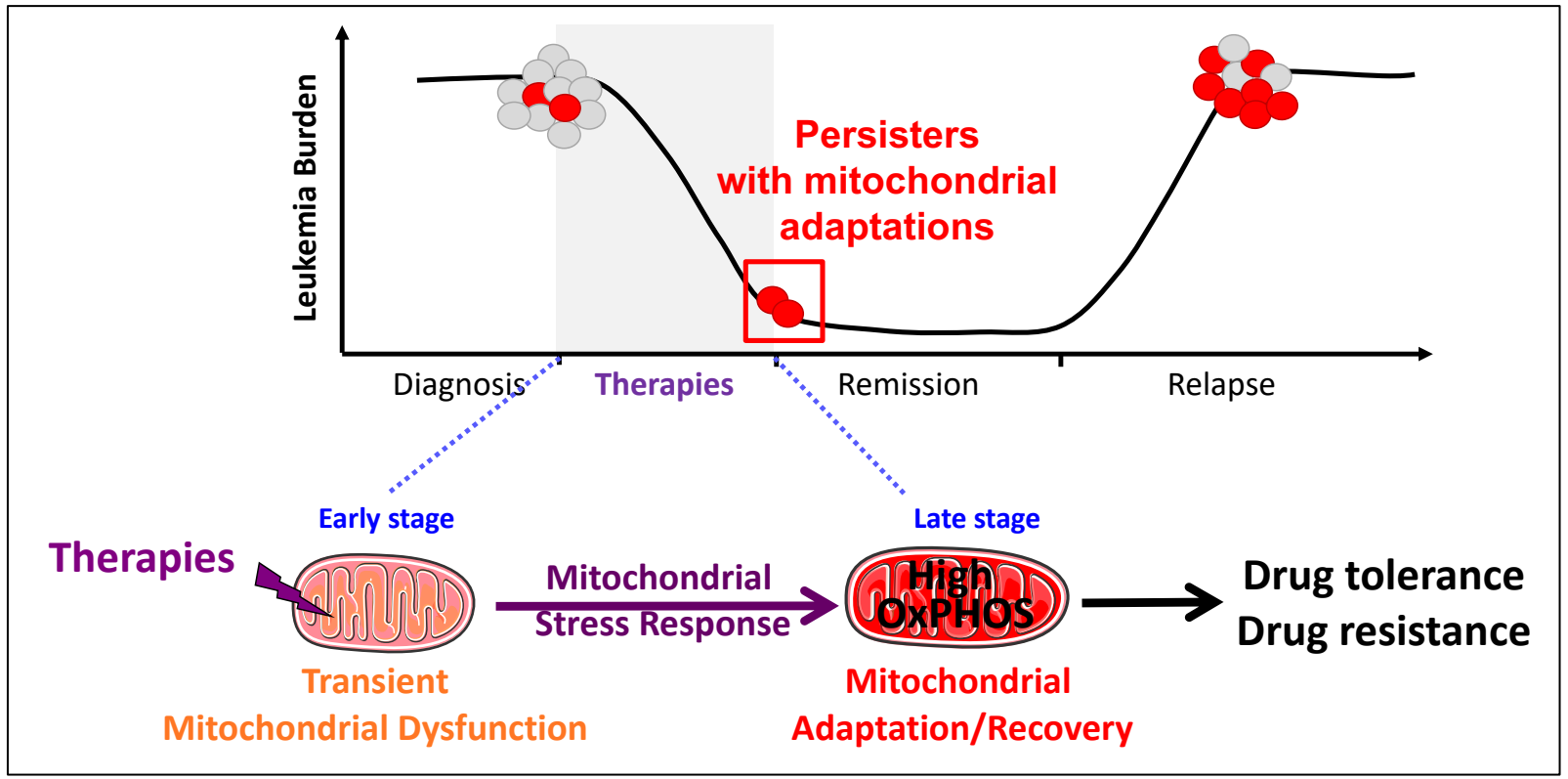


Bosc *et al*. Nature Cancer. 2021

Summary – Basic principles

> MRD is enriched in persisting cells with **High OxPHOS metabolism**

> High OxPHOS phenotype of AML persisters is the consequence of
a mitohormetic and Darwinian process of adaptive response to stress

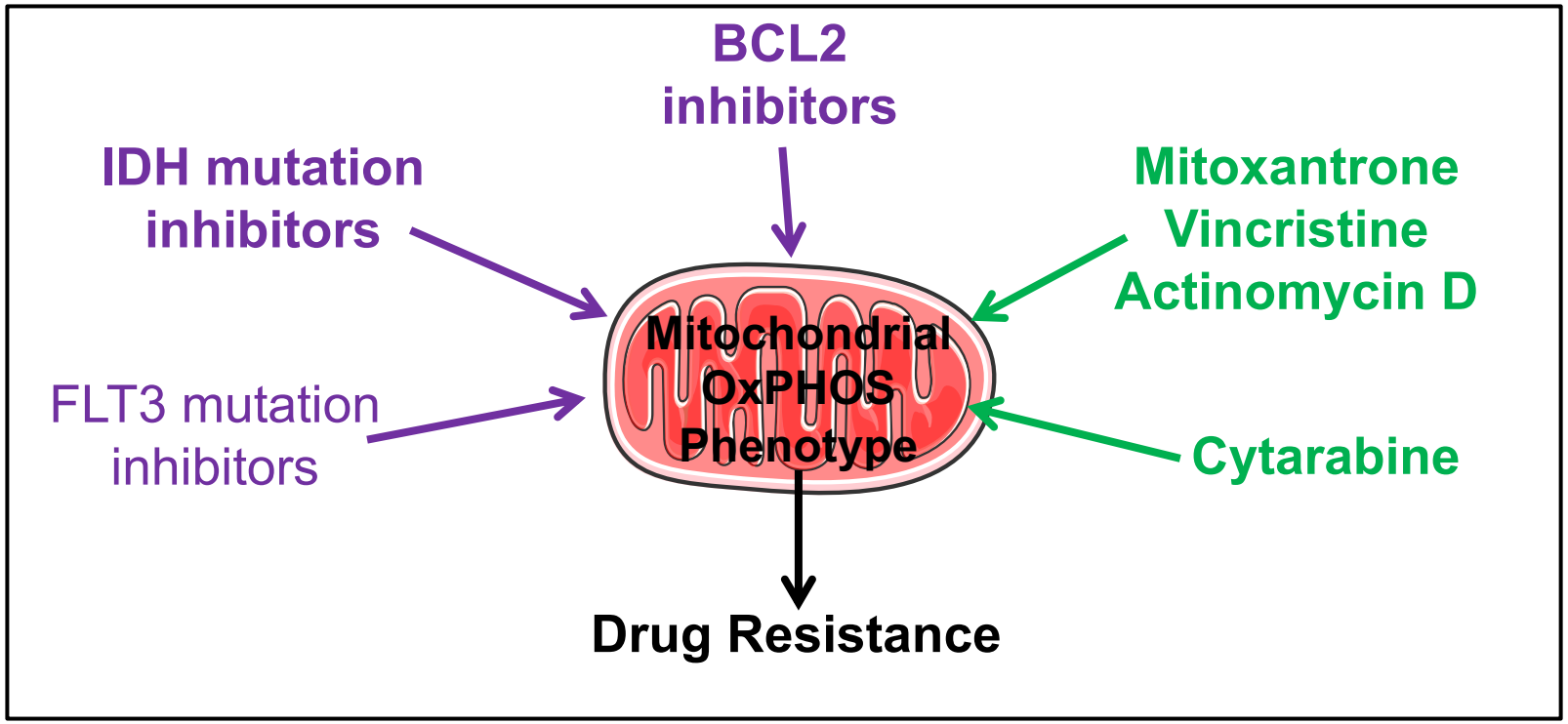


Saland *et al*. in prep; Bosc *et al*. Nature Cancer. 2021
Stuani and Sarry. Cell Metab. 2020; Aroua, Boet, Ghisi *et a*l. Cancer Discov. 2020; Hosseini *et al*. Cancer Res. 2019; Farge *et al.* Cancer Discov. 2017

Summary – Basic principles

> Changes in mitochondrial energetics, metabolism, and structure are hallmarks of drug resistance

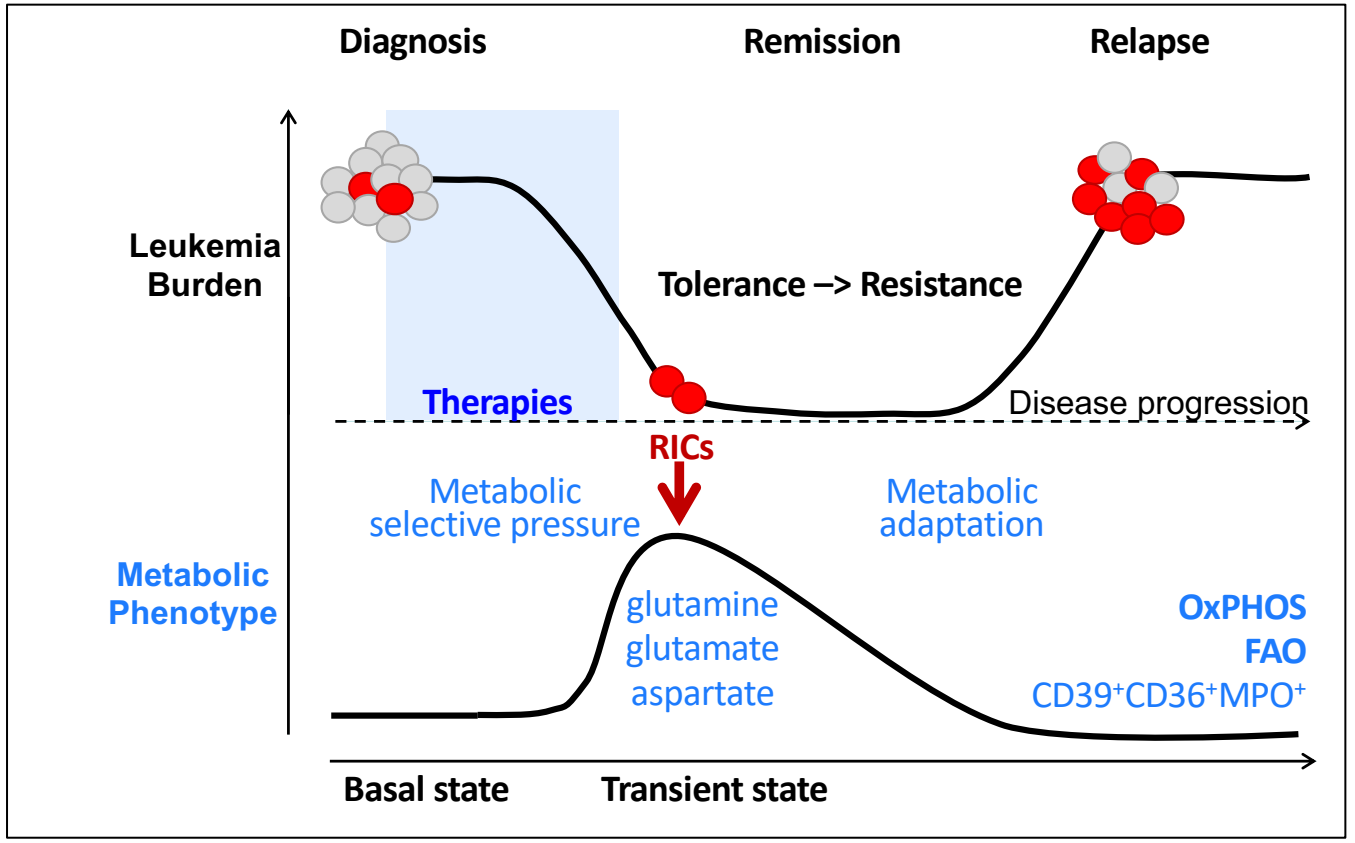
> **Central role of OxPHOS flexibility and adaptations in mitochondrial dynamics and metabolism** during therapy, driving residual disease and drug tolerance/persistence in AML



Sabatier, Birsen *et al*. BioRxiv. 2022. in revision; Fisher-Wellman et al. FASEB J. 2022; Wu *et al*. Cancer Discov. 2021; Bosc *et al*. Nature Cancer. 2021; Garciaz *et al* Cancer Discov. 2021; Fisher-Wellmann *et al* Cancer/Metabo 2021; Stuani *et al*. JEXPMED. 2021; Salunkhe et al. BBA. 2020; Jones *et al*. Blood. 2019; Jones *et al*. Cancer Cell. 2019 ; Ghen, Gytshou et al. Cancer Discov. 2019 ; Sharon *et al*. STM. 2019; Lin *et al*. Cell Metab. 2019; Farge *et al*. Cancer Discov. 2017

Summary – Basic principles

> Metabolic Model of Drug Resistance in AML **but relevant to several therapy-resistant solid cancers including melanoma, PDAC, sarcoma, metastatic grade…**

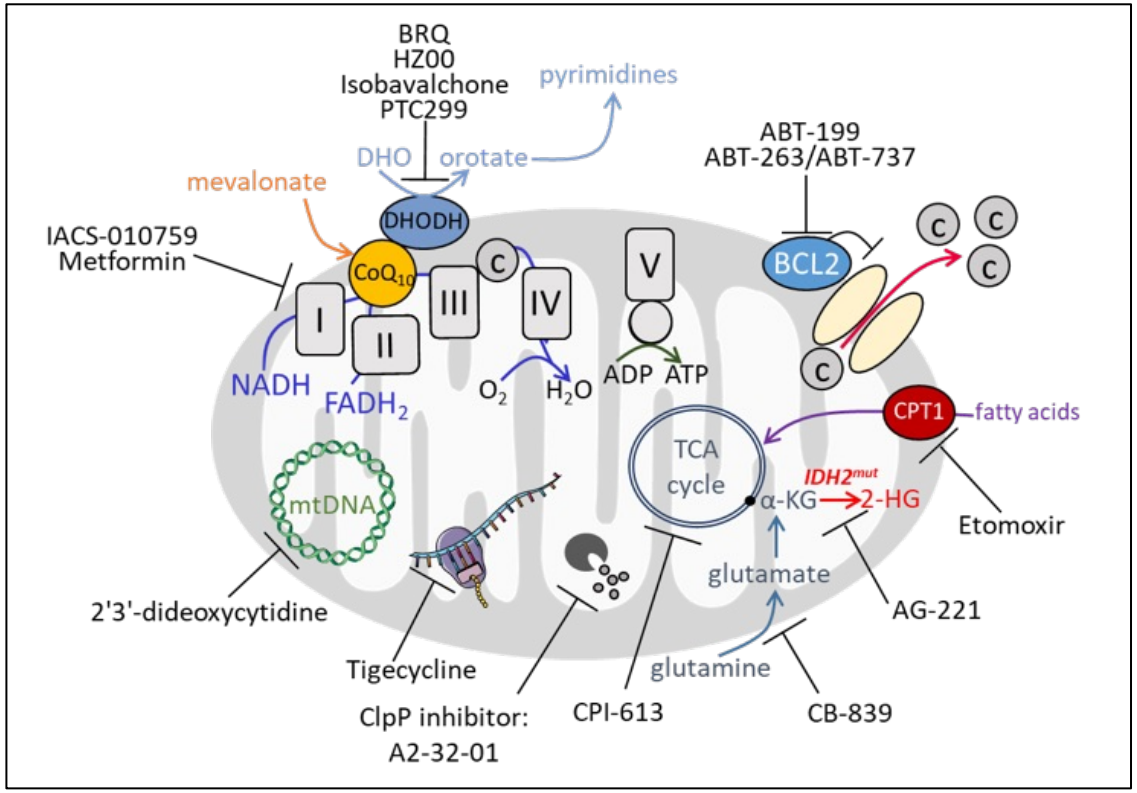


Solid tumors: Passaniti et al Mol. Carci. 2022; Xue et al. J Med Chem. 2022; Evans et al. Cancer Res. 2020; Marine et al, Nature Review Cancer. 2020
Hematological tumors: Stuani and Sarry. Cell Metab. 2020; Van Gastel et al. Cell Metab. 2020;

Summary – Translational applications

> Always good to remember that chemotherapy is a metabolic therapy !

> 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/combinations > especially in AML patients with high MitoScore



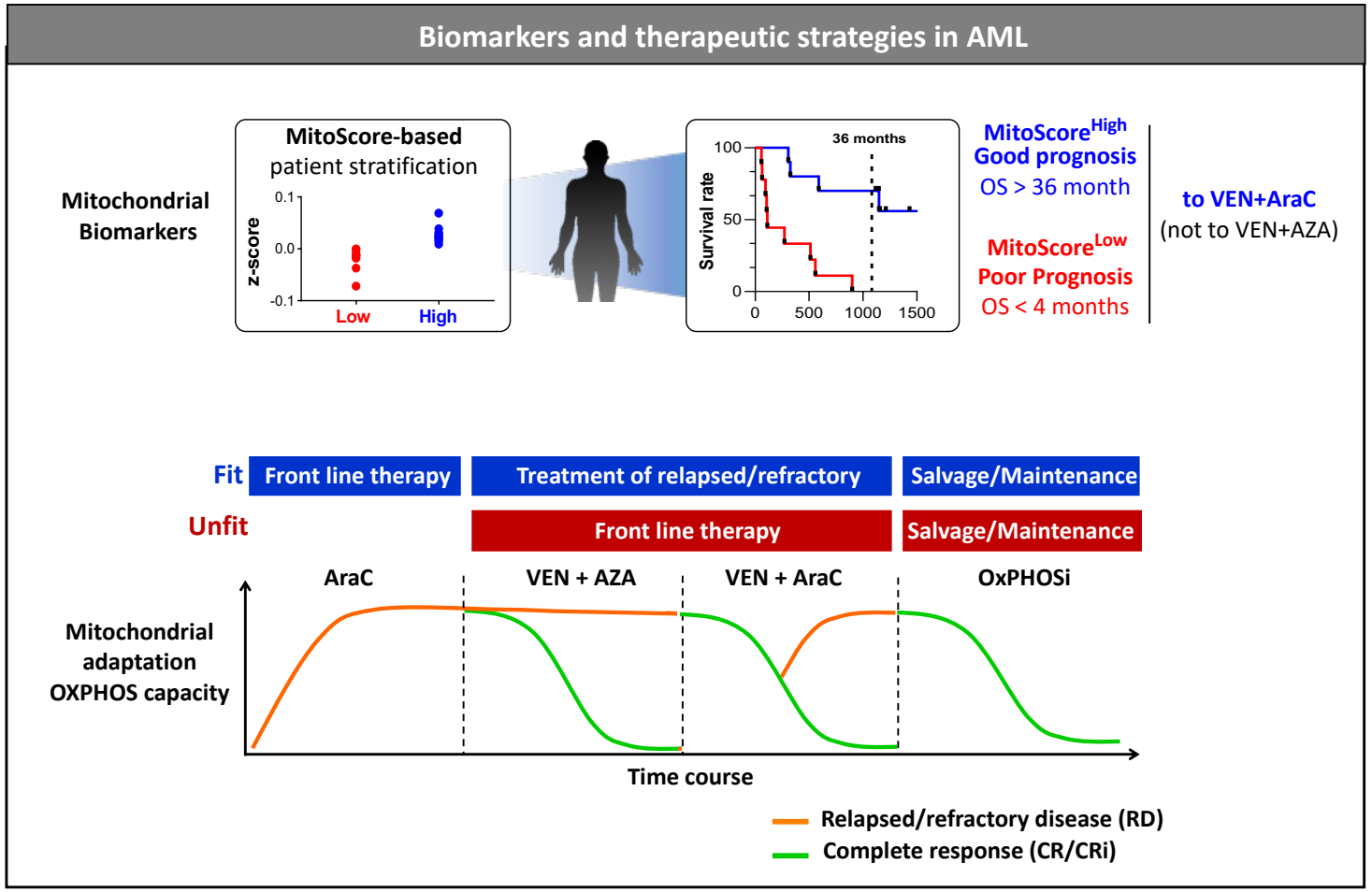
Stuani *et al*. BMC Biol. 2019; Bosc *et al*. Cell Metab. 2017

Clinical perspectives in cancer metabolism

> Development of combinatory metabolic precision medicine:

targeting or preventing mitochondrial adaptations and metabolic evolution with anti-AML cocktails

alternating chemoTx or BCL2i combo + OxPHOSi +/- precision diets



Acknowledgements

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Gabriel Lemercier
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Fabienne de Toni
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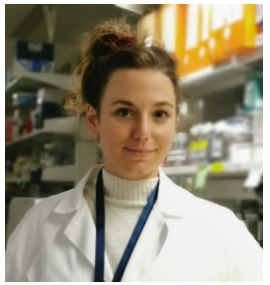

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