METABOLIC VULNERABILITIES OF CANCER

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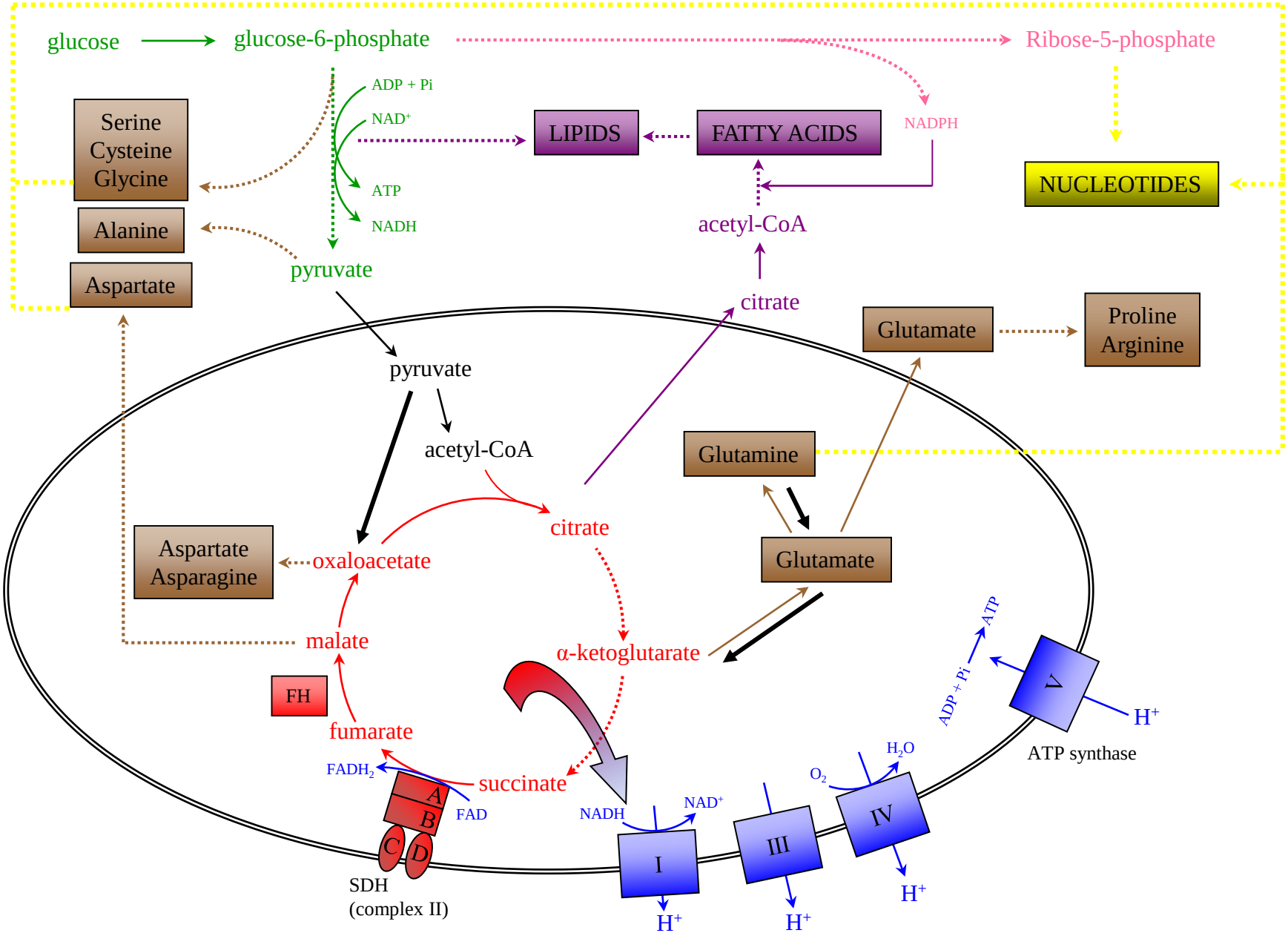
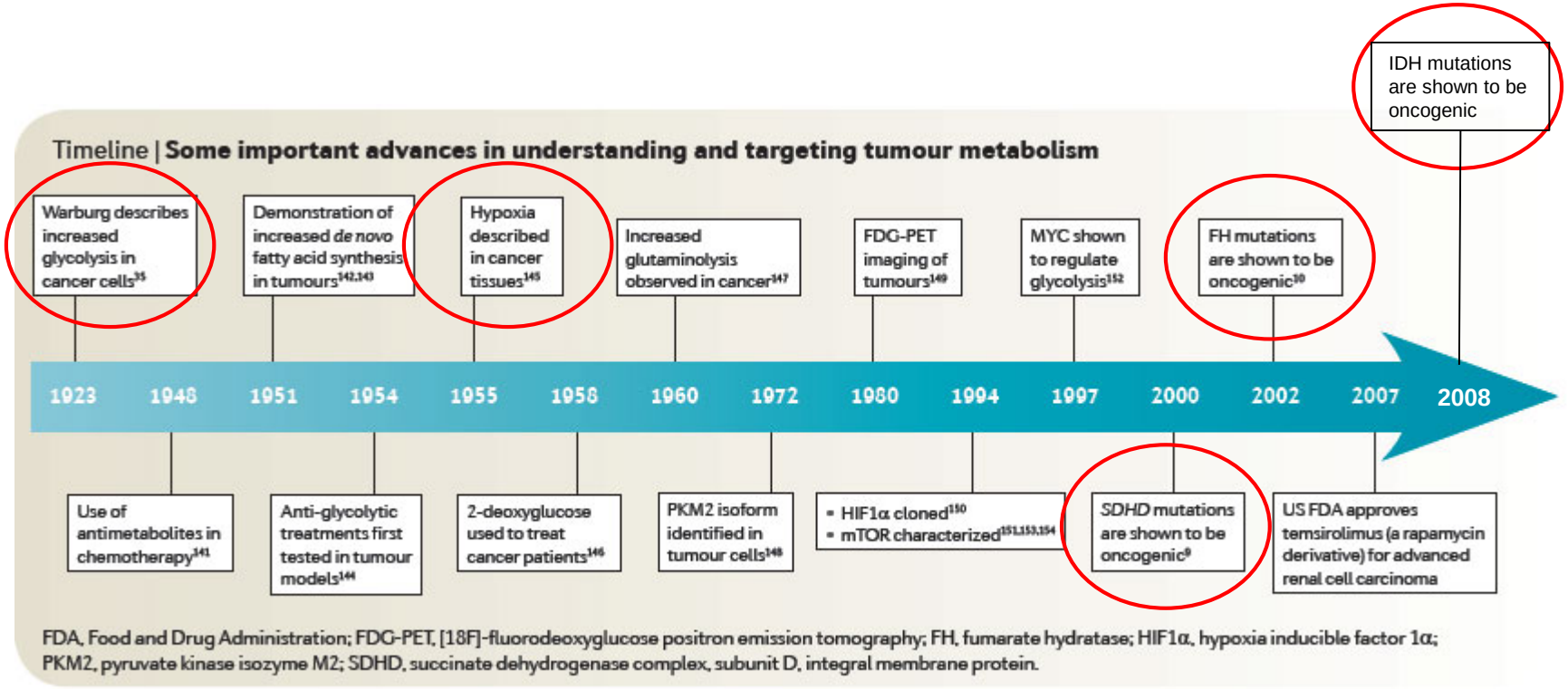
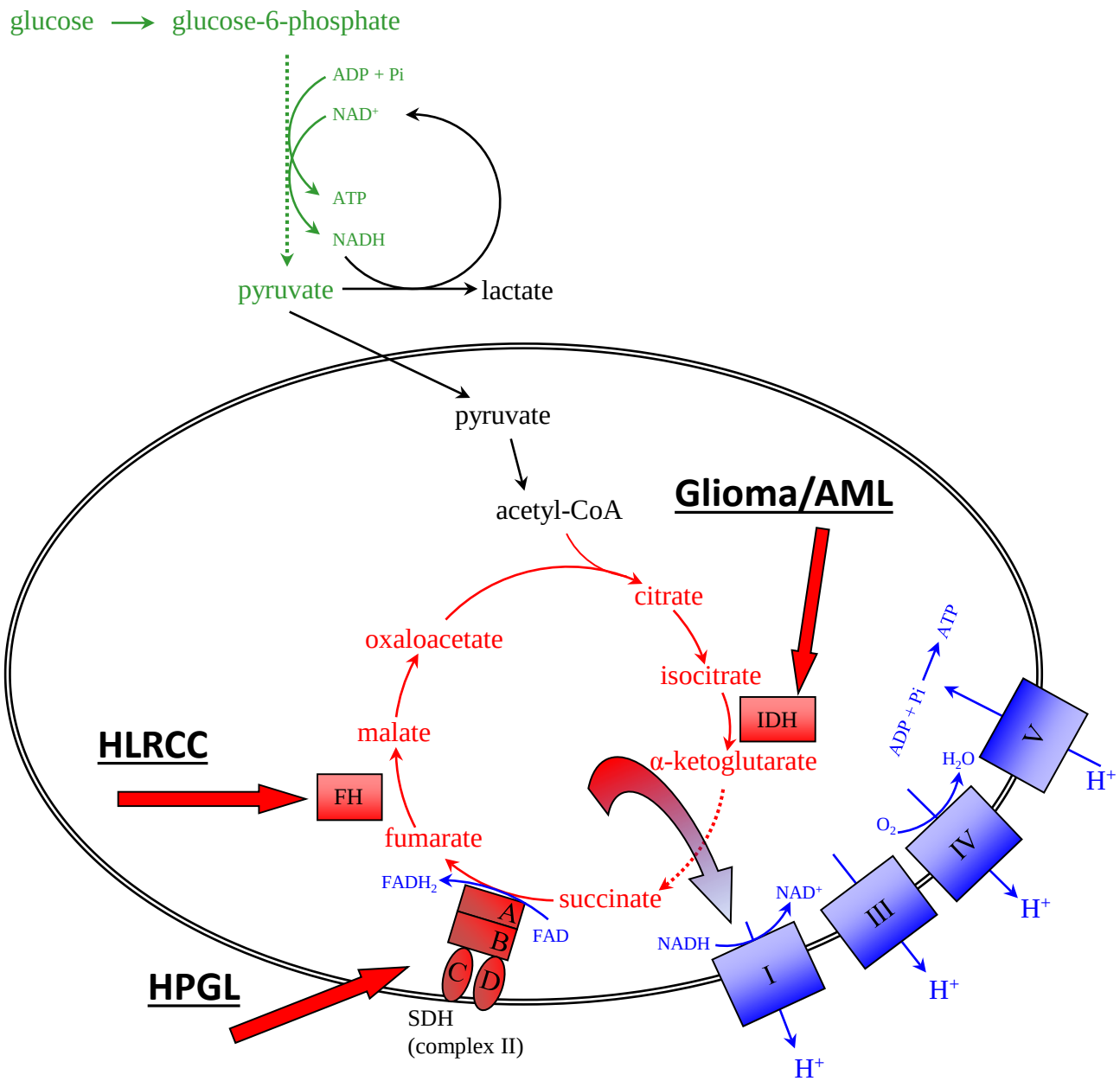
Cancer and metabolism: the anabolic angle

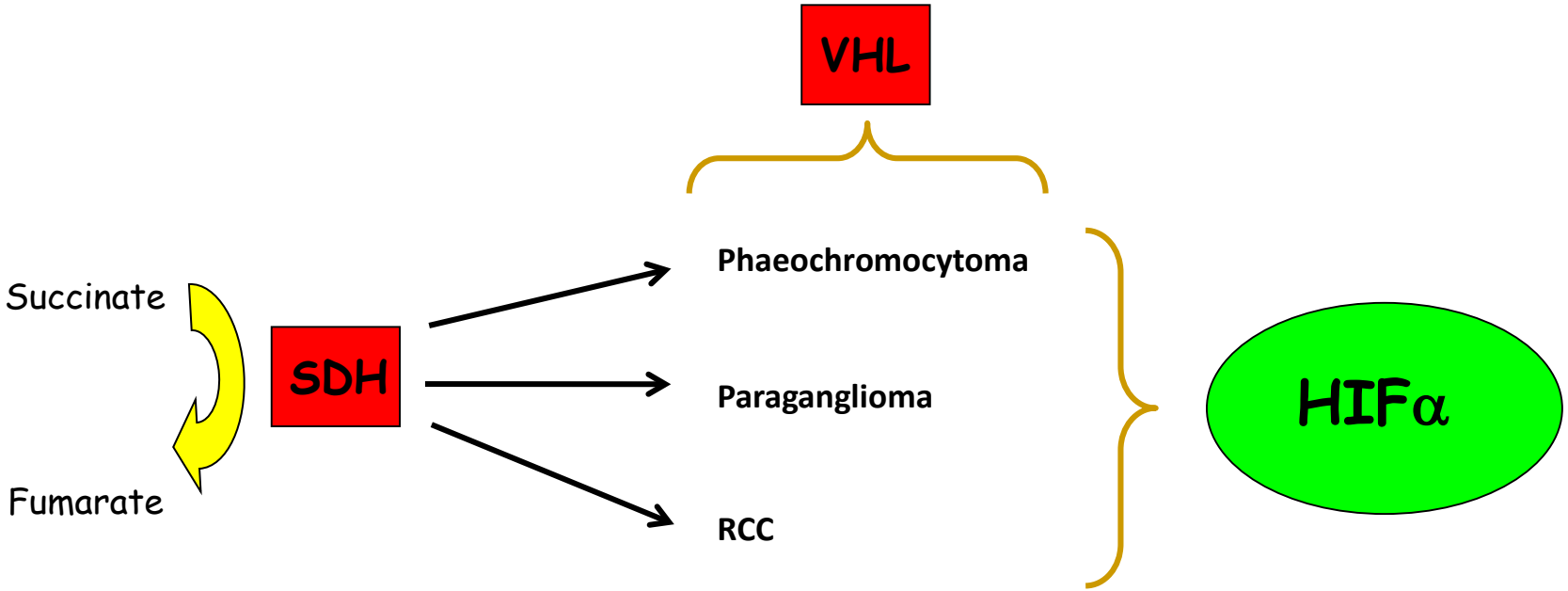


Cancer and metabolism: historic perspective

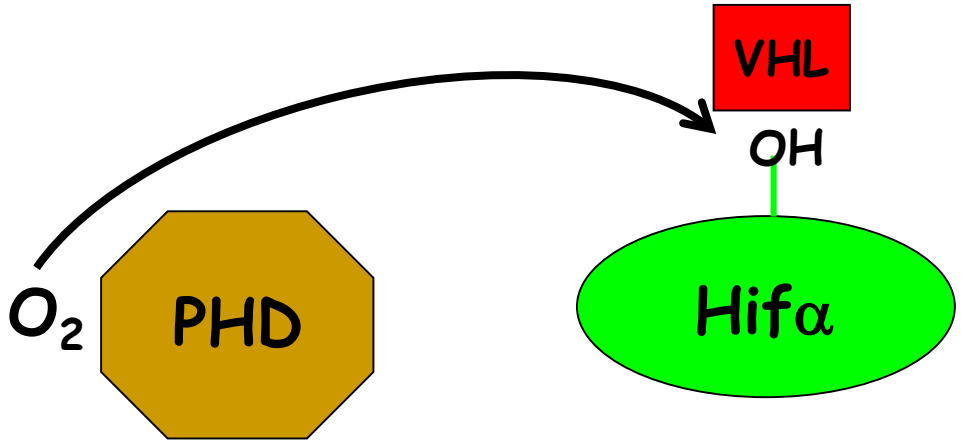


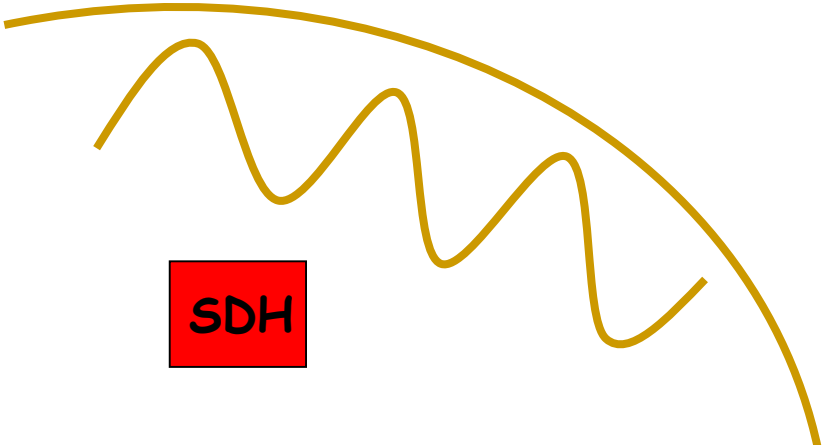
Cancer and metabolism: the bioenergetic angle



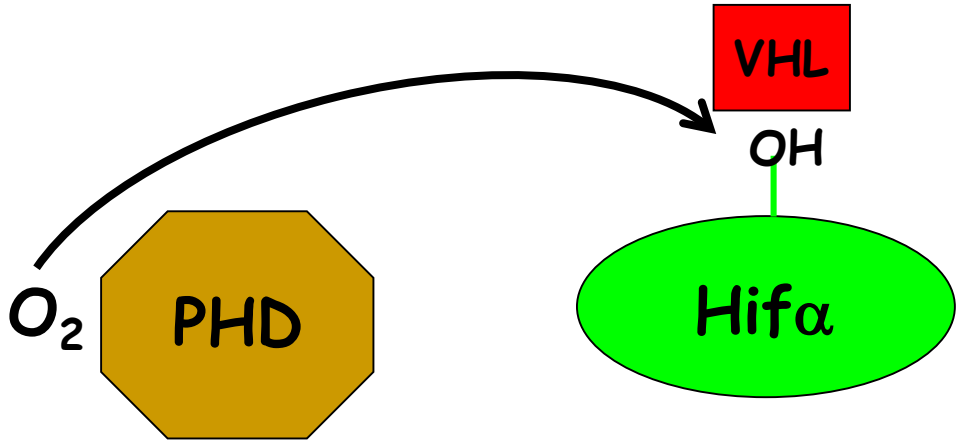

VHL
Succinate
SDH
Fumarate
Phaeochromocytoma
Paraganglioma
RCC
HIFα

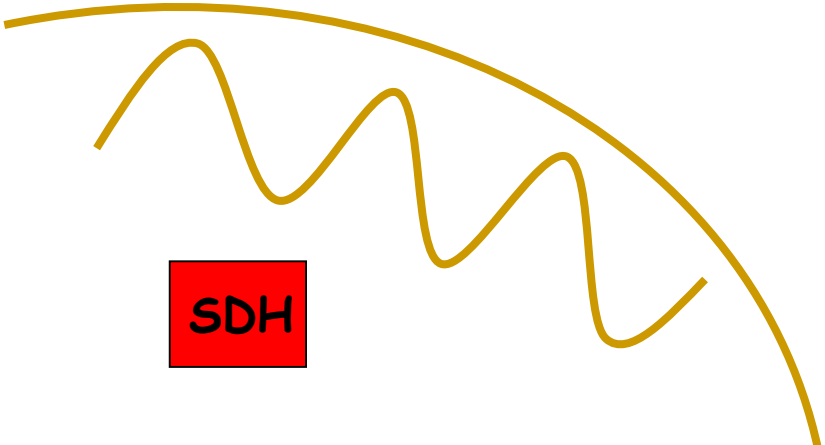
1) HIF regulation by oxygen



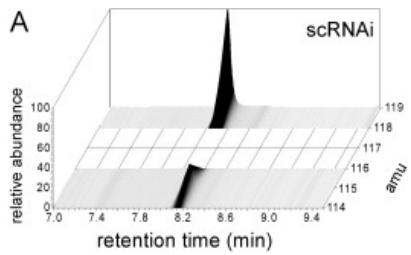


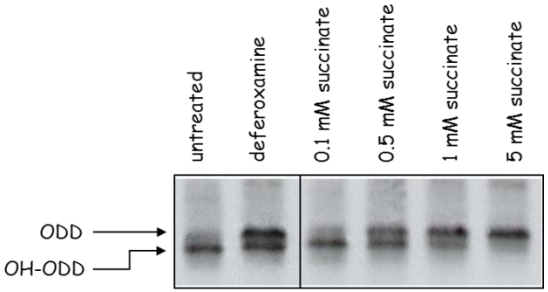
2) HIF regulation by VHL

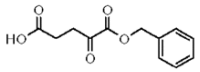
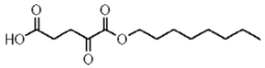
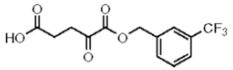




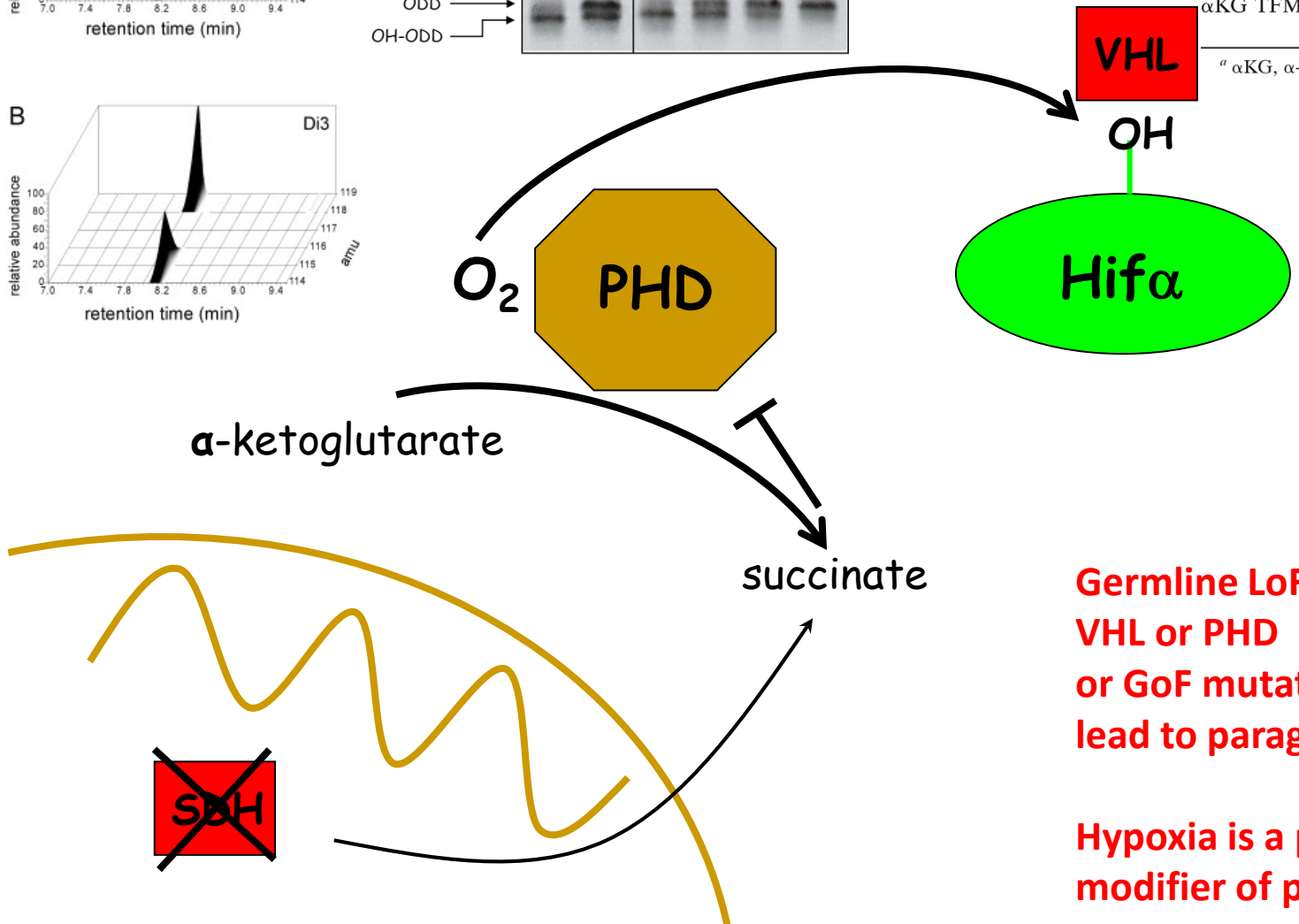
3) HIF regulation by succinate





Compound name	Compound structure
αKG[a] benzyl ester	
αKG octyl ester	
αKG TFMB ester	

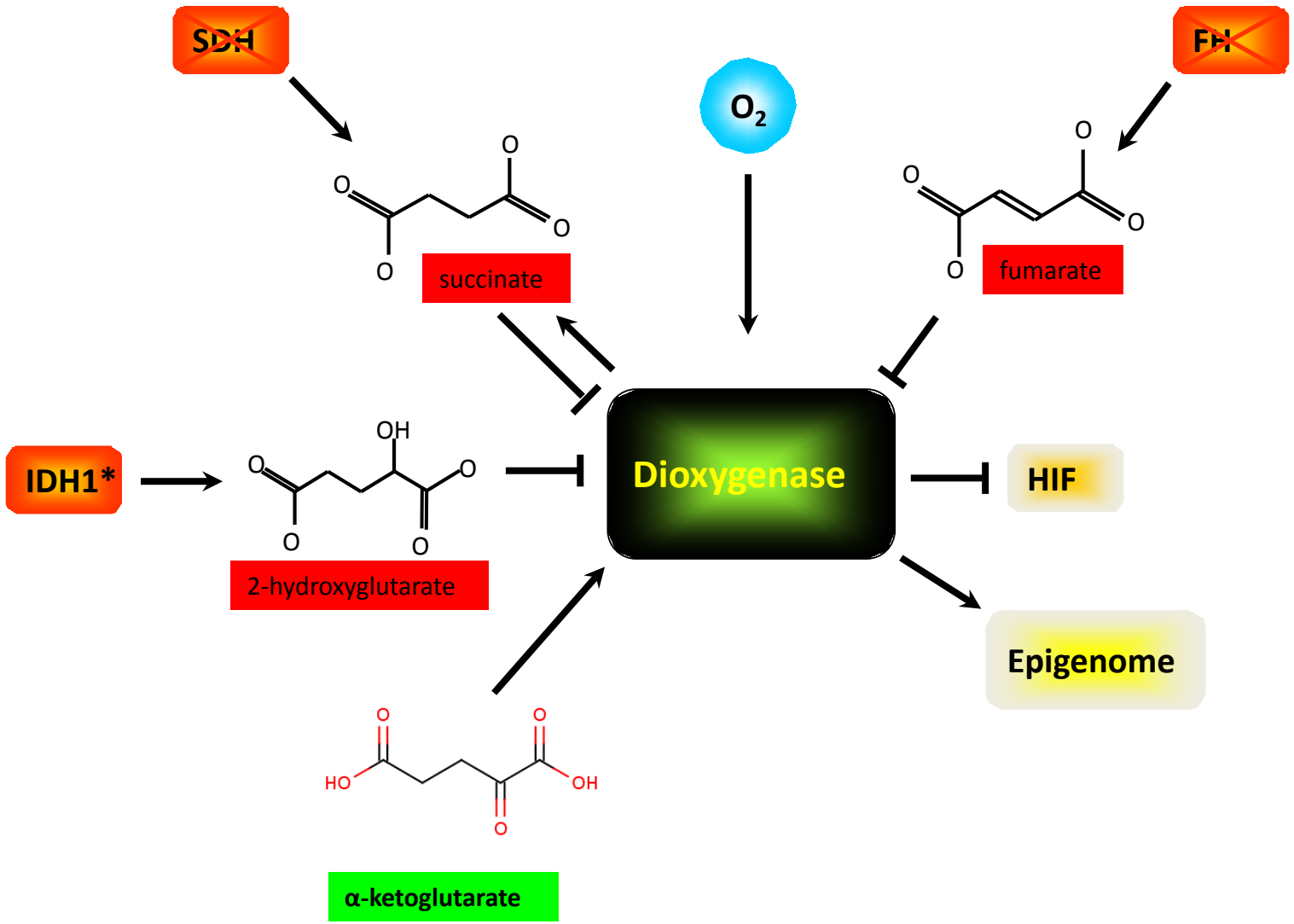
[a] αKG, α-ketoglutarate.



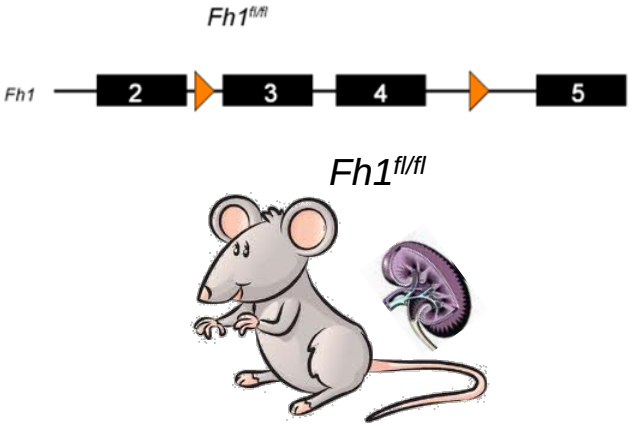
Germline LoF mutations in SDH, VHL or PHD or GoF mutations in HIF2α can lead to paraganglioma!

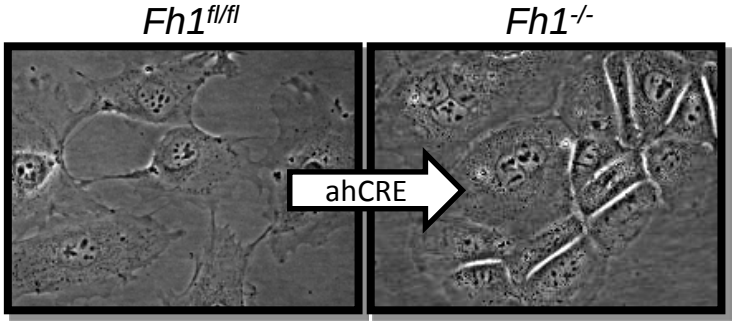
Hypoxia is a positive phenotypic modifier of paraganglioma

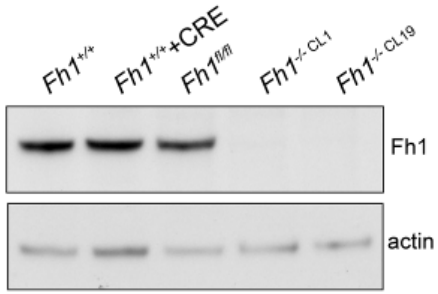
The birth of a new concept: Oncometabolites

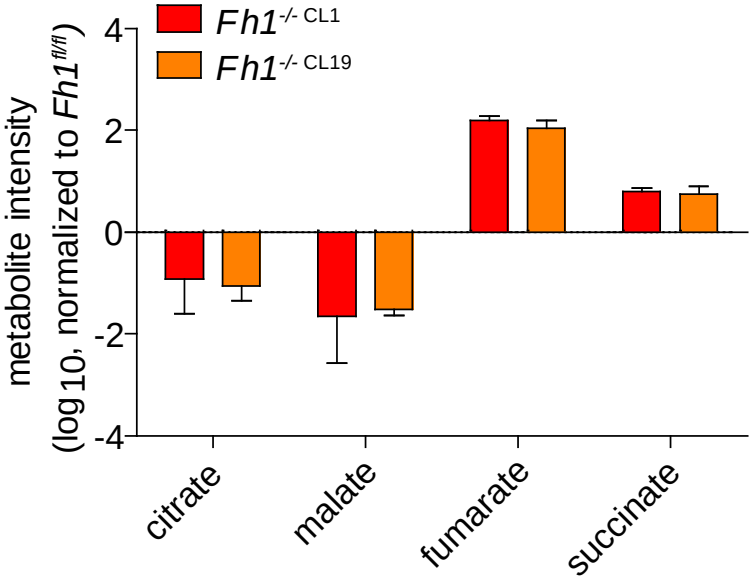


Fumarate hydratase deficient (*Fh1*$^{-/-}$) cells

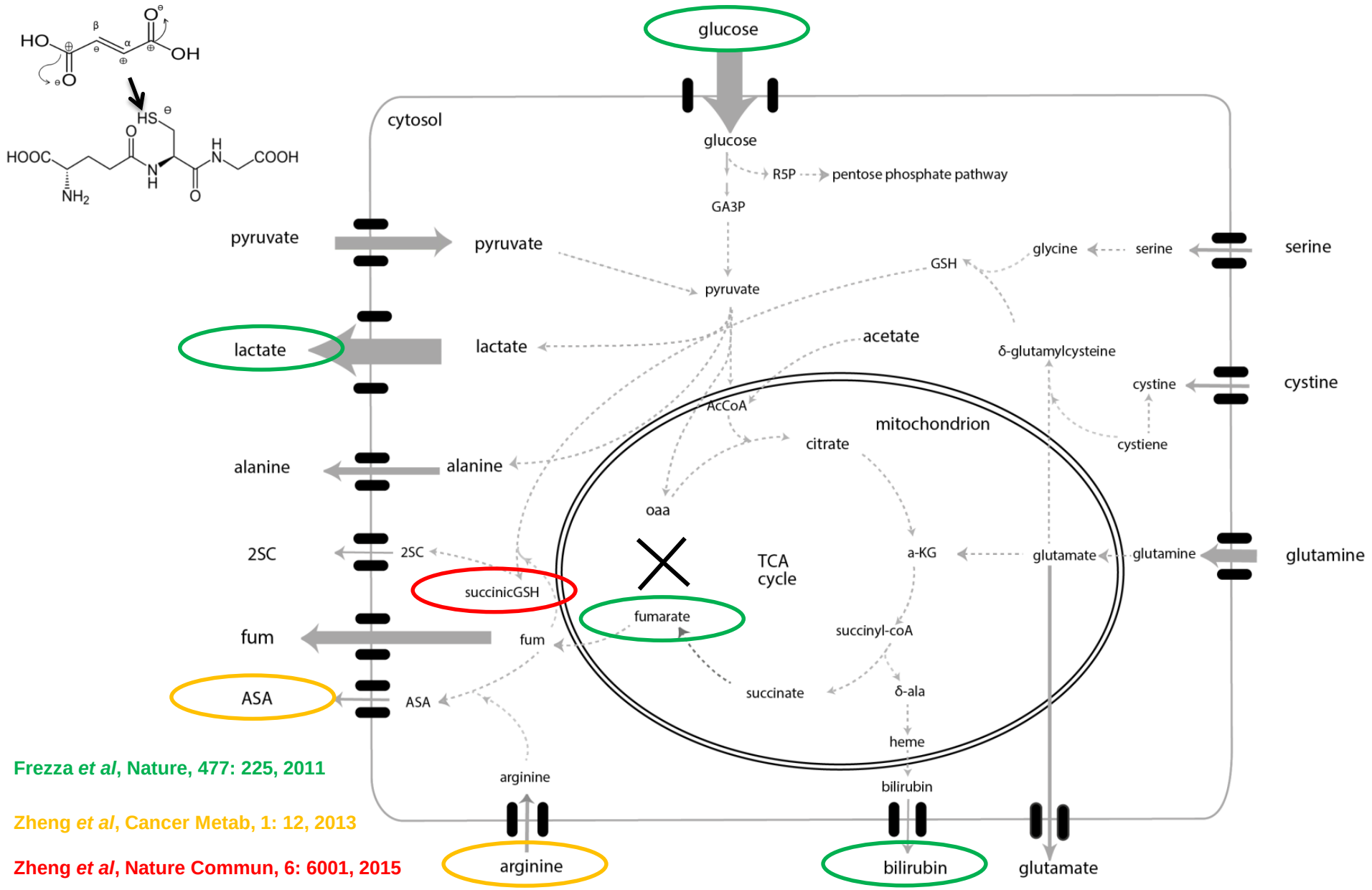








Metabolic adaptation and vulnerabilities of FH-deficient cancers

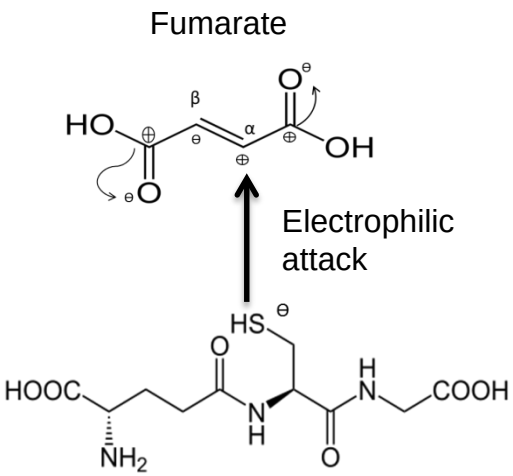


Frezza *et al*, Nature, 477: 225, 2011

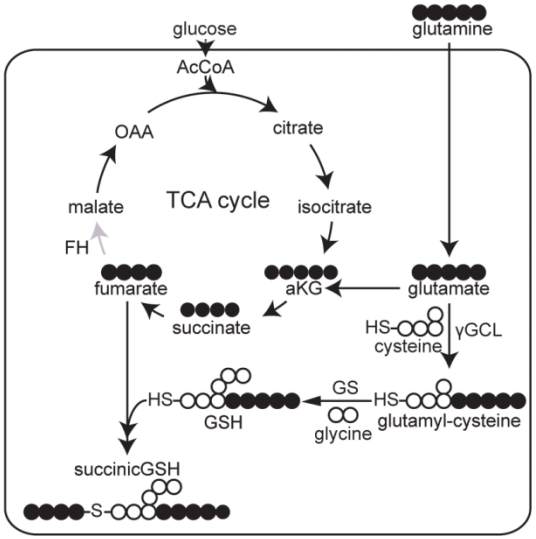
Zheng *et al*, Cancer Metab, 1: 12, 2013

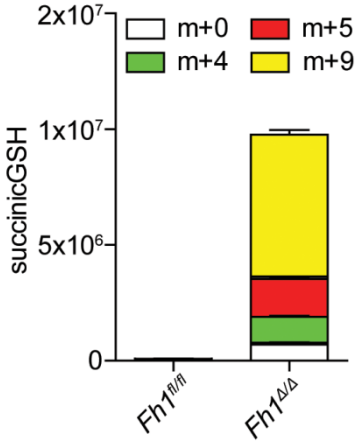
Zheng *et al*, Nature Commun, 6: 6001, 2015

The biosynthetic pathway of succinic-GSH

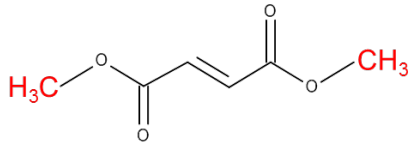


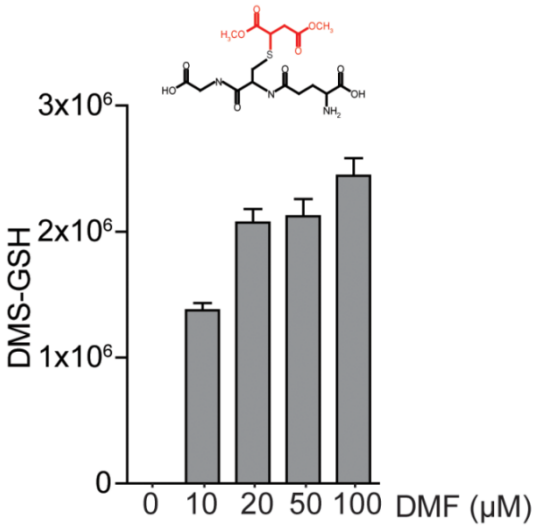
Glutathione (γGlu-Cys-Gly)

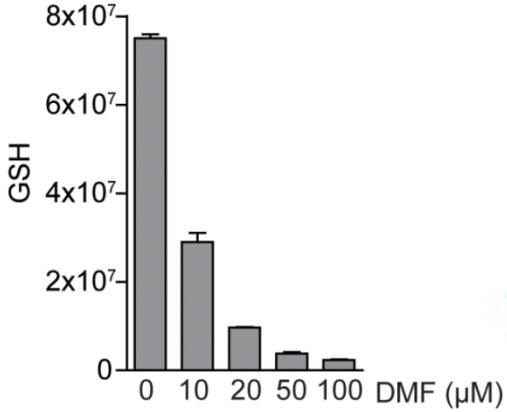




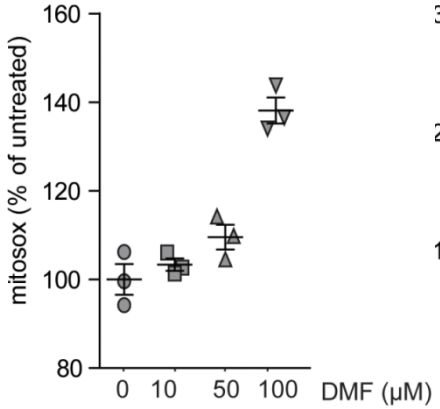
Fumarate attack on GSH induces oxidative stress

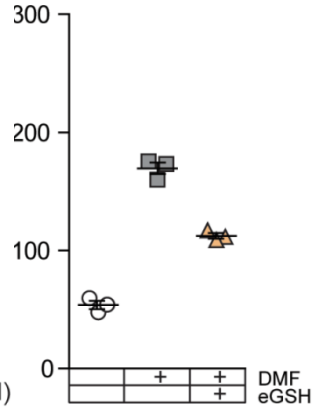




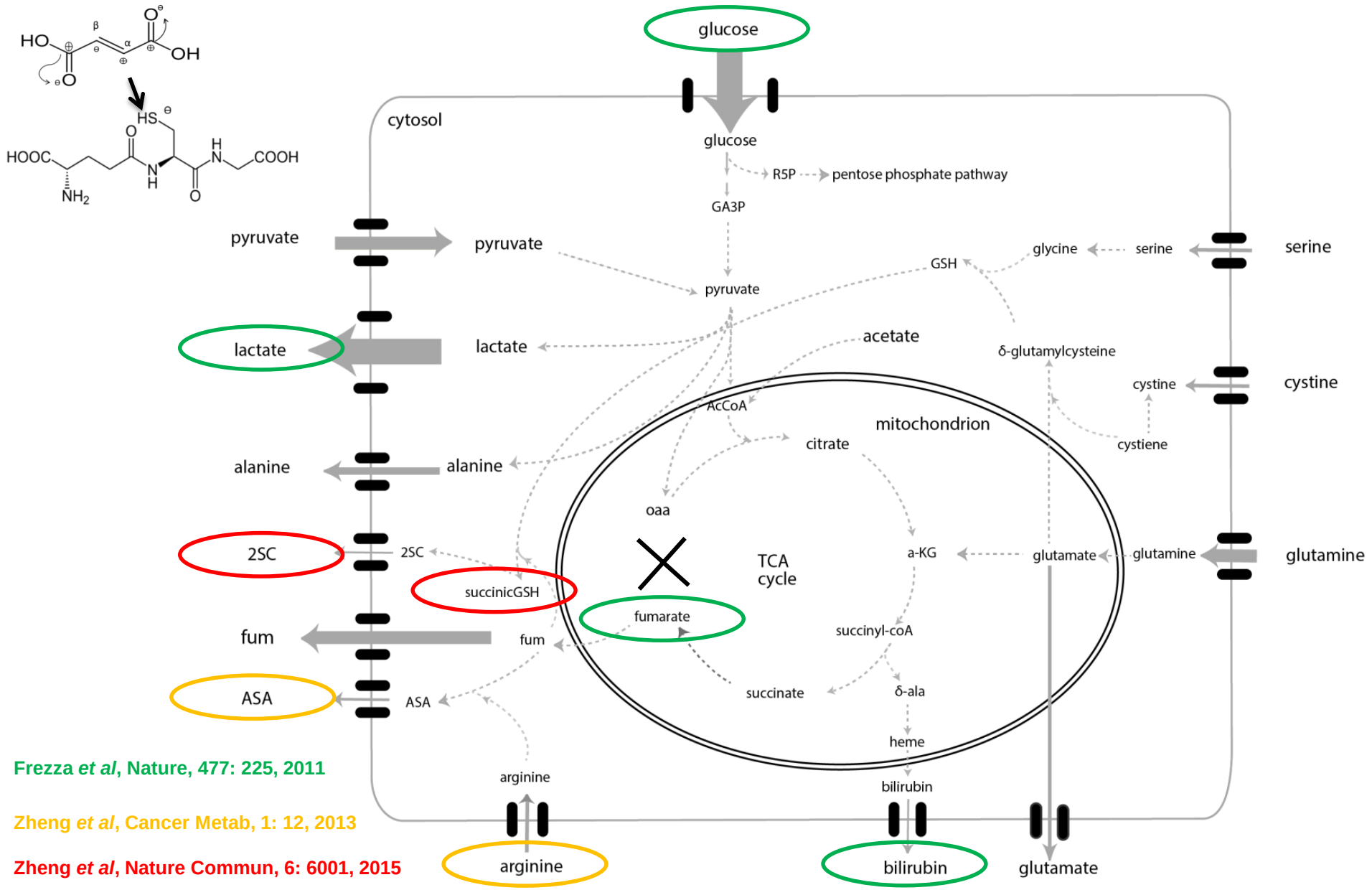


New and now FDA approved!
Tecfidera™
(dimethyl fumarate), also known as BG-12.





Metabolic adaptation and vulnerabilities of FH-deficient cancers



Frezza *et al*, Nature, 477: 225, 2011

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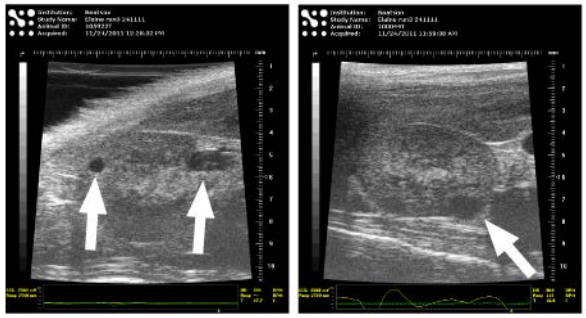
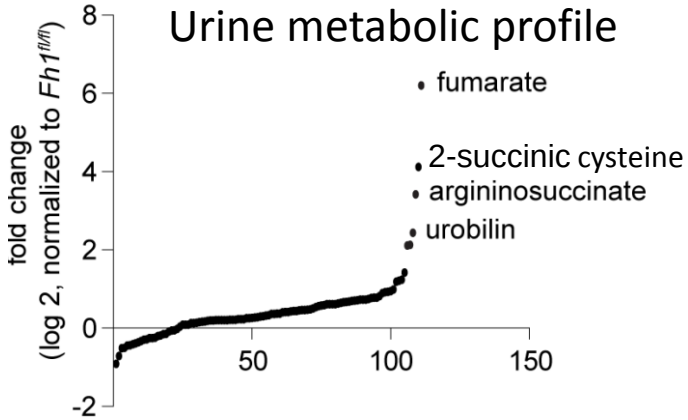
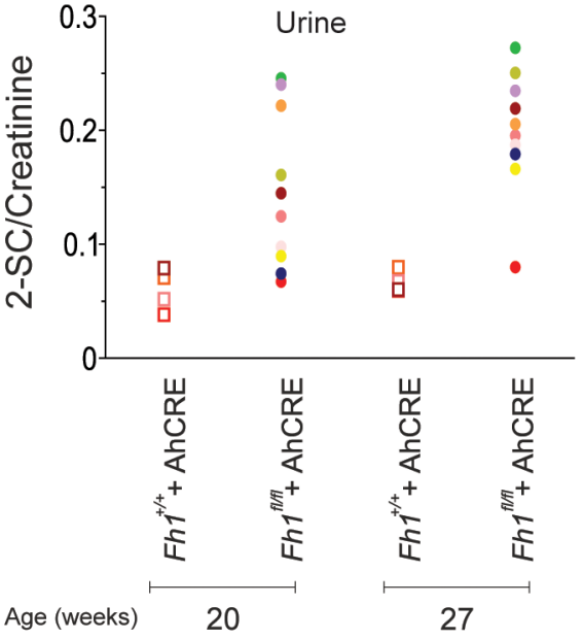
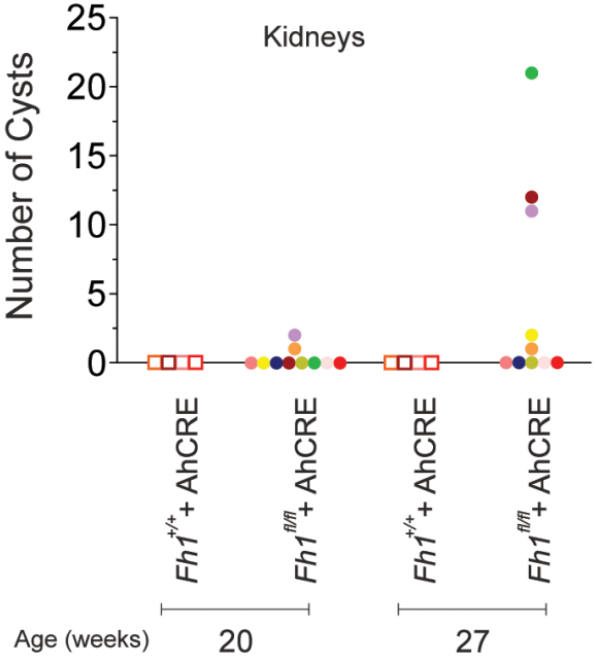
Cysts-bearing, FH-deficient mice excrete metabolites (biomarkers) in the urine

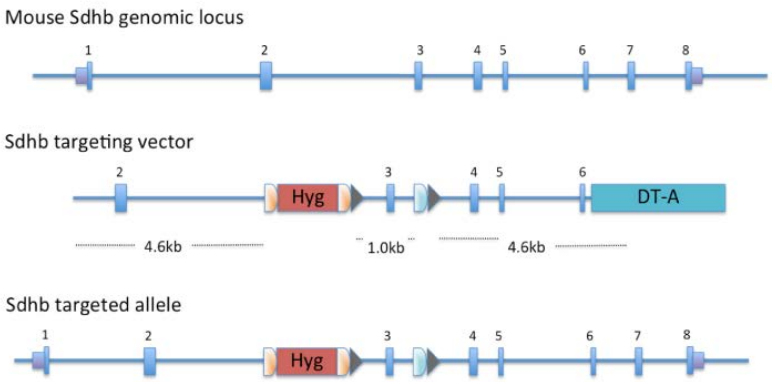


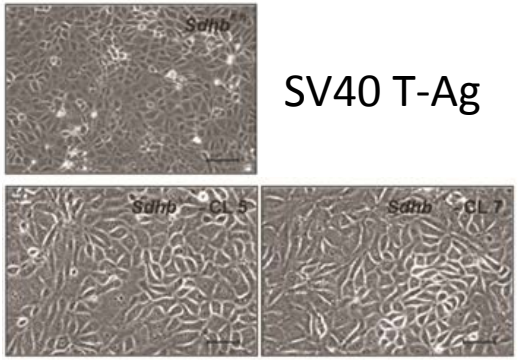




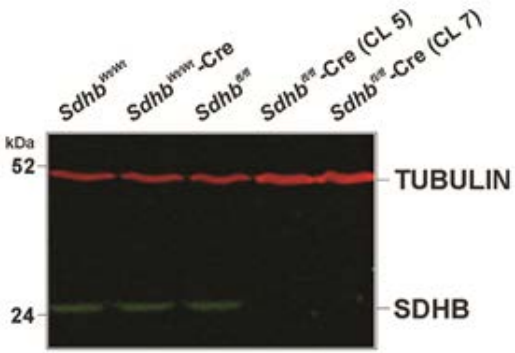


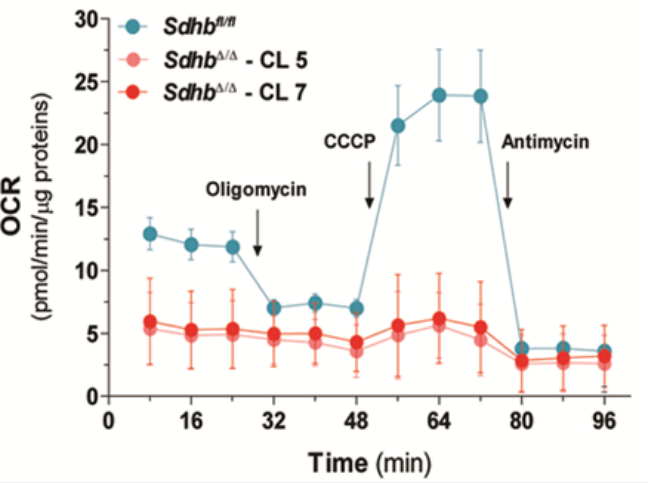
A new in vitro model for SDH-deficient cancers

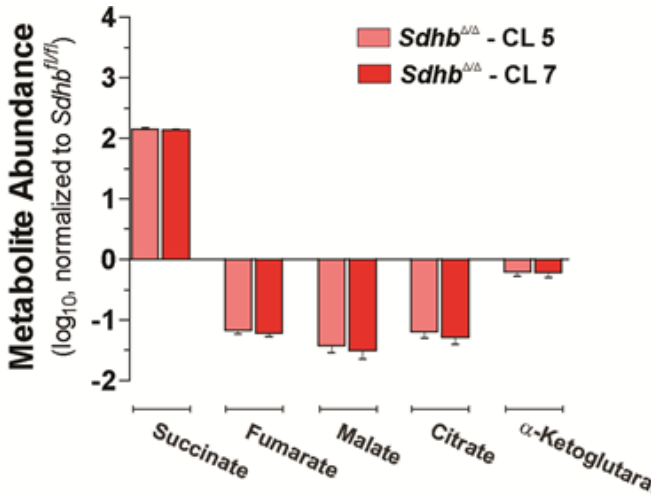


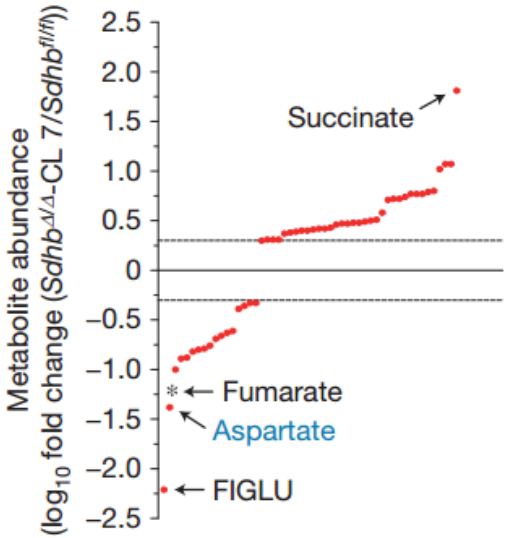


SV40 T-Ag

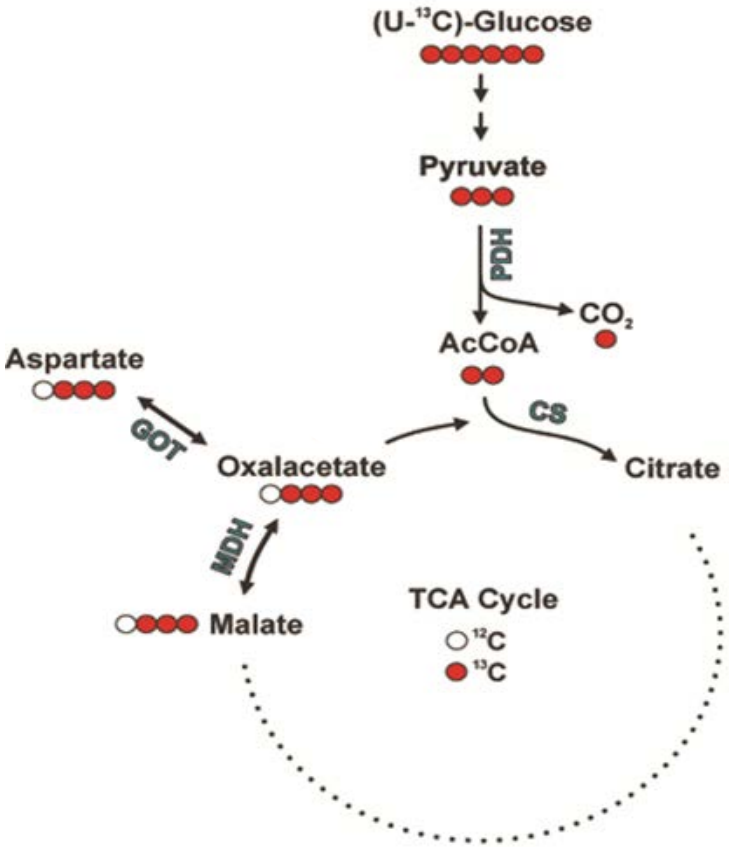


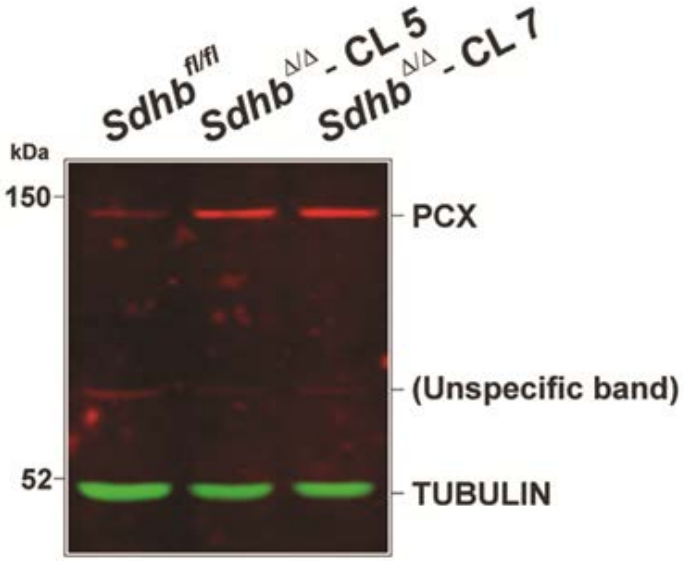


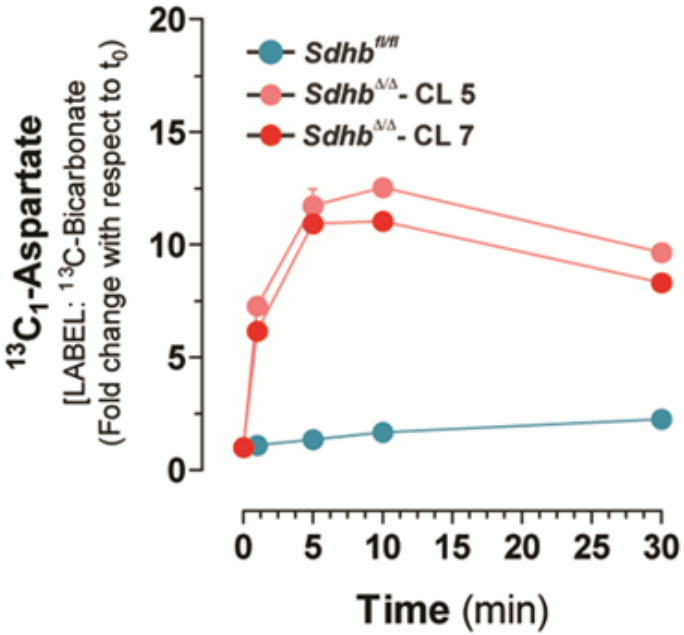




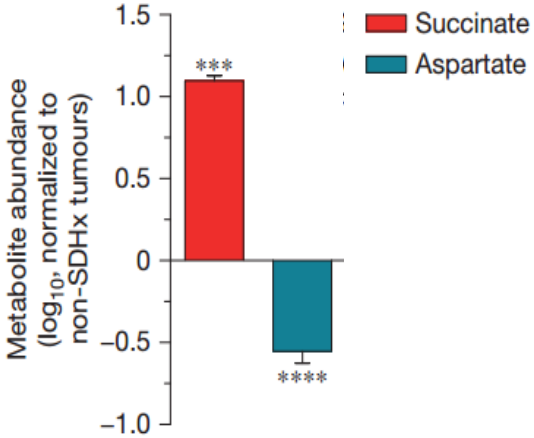
SDH deficient cells depend on Pyruvate Carboxylase for sustaining aspartate levels

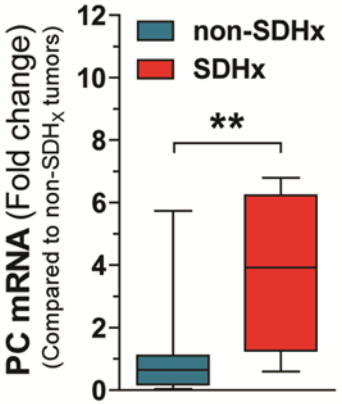


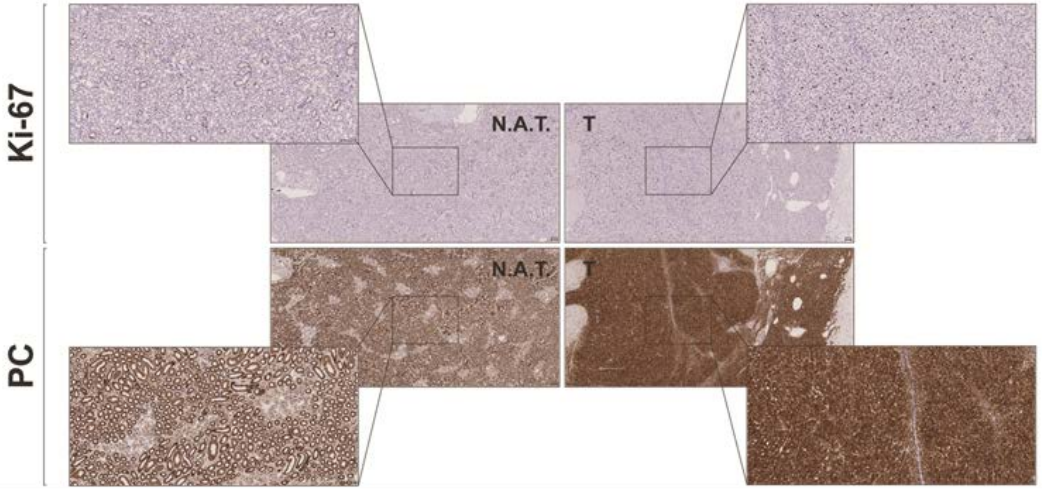




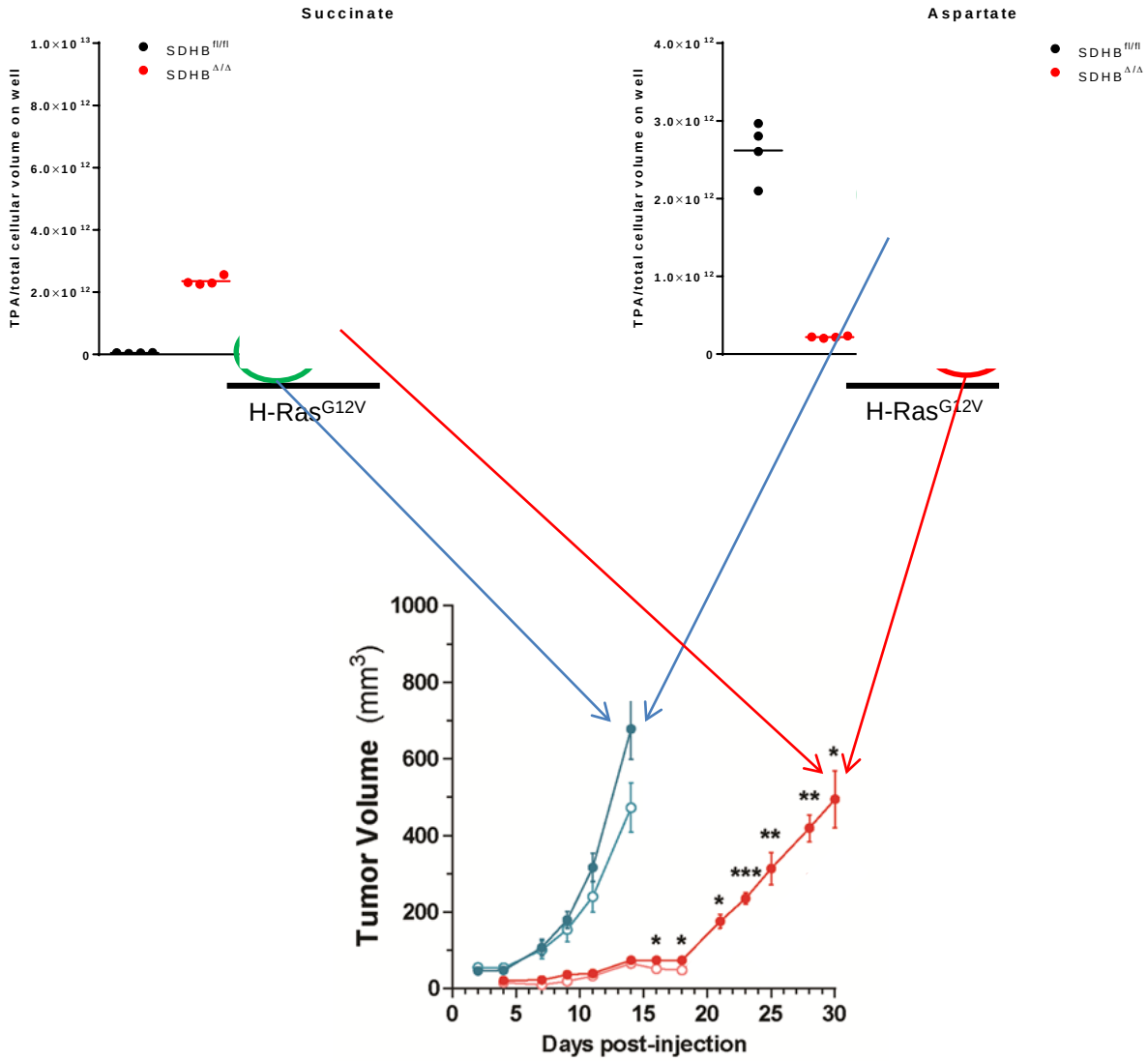
Aspartate limitation and PC expression in SDH-deficient tumors



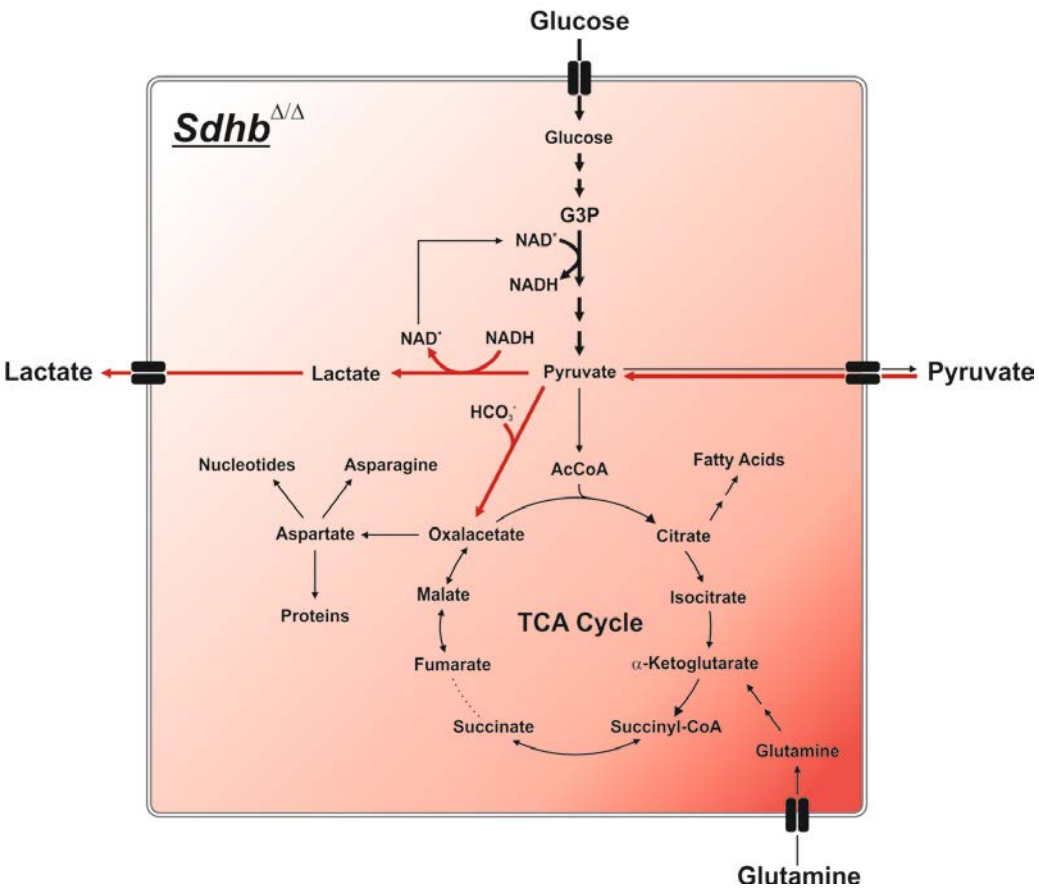


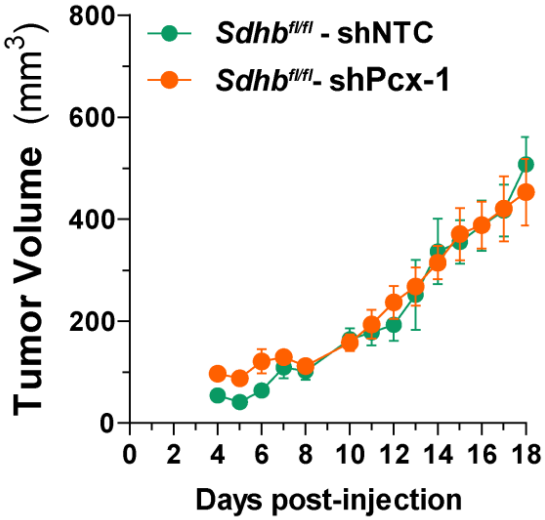


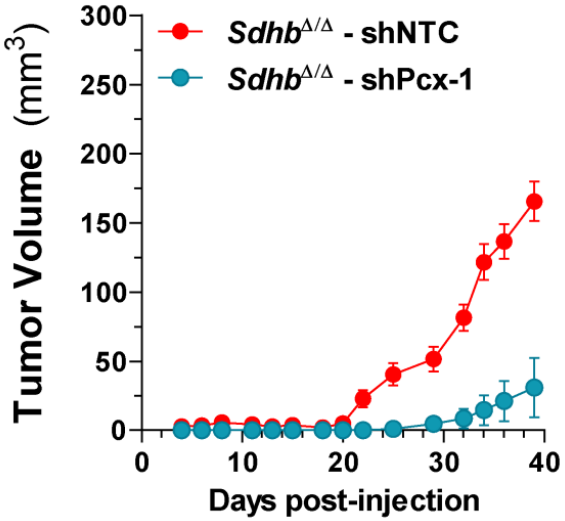
H-Ras^{G12V} transform SDH-deficient cells



Metabolic vulnerabilities of SDH-deficient tumours







Conclusions

- Metabolomics is a robust and efficient tool for mechanistic studies of metabolic adaptabilities and vulnerabilities, but also as an important sensor of biomarkers for early prognosis and detection of recurrence disease

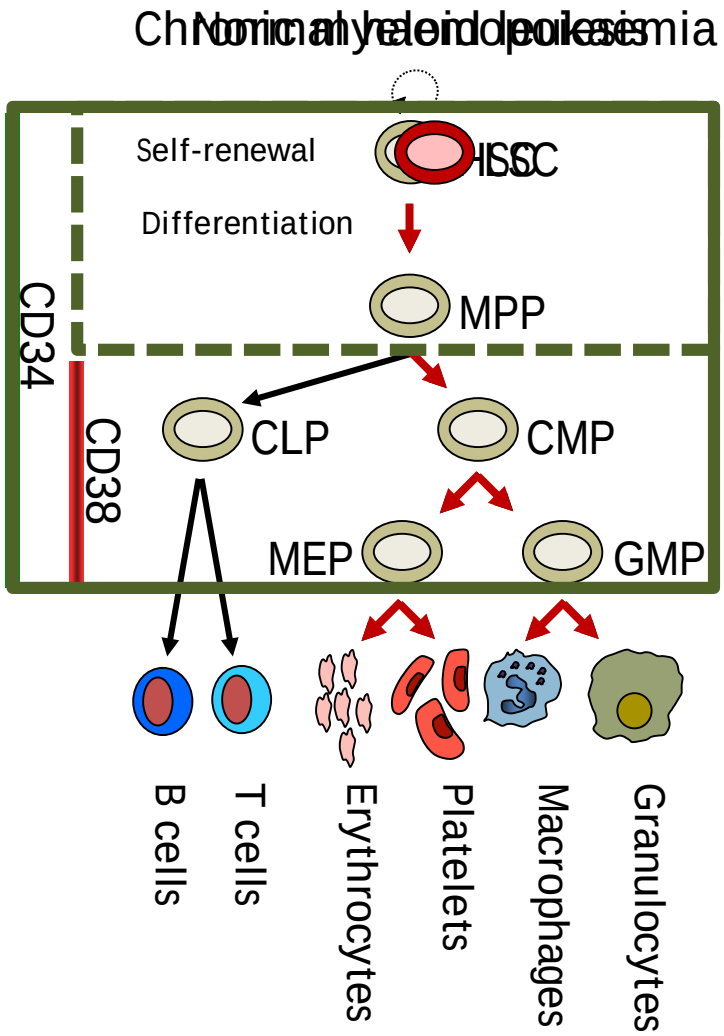
- FH or SDH loss of function leads to the accumulation of fumarate or succinate, respectively, and to the inhibition of dioxygenases, including DNA demethylases

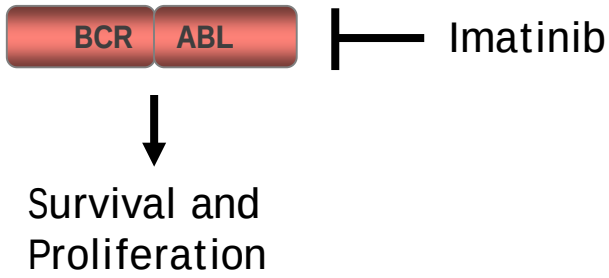
- SDH loss of function renders cells more dependent on PC to sustain aspartate and nucleotide biosynthesis

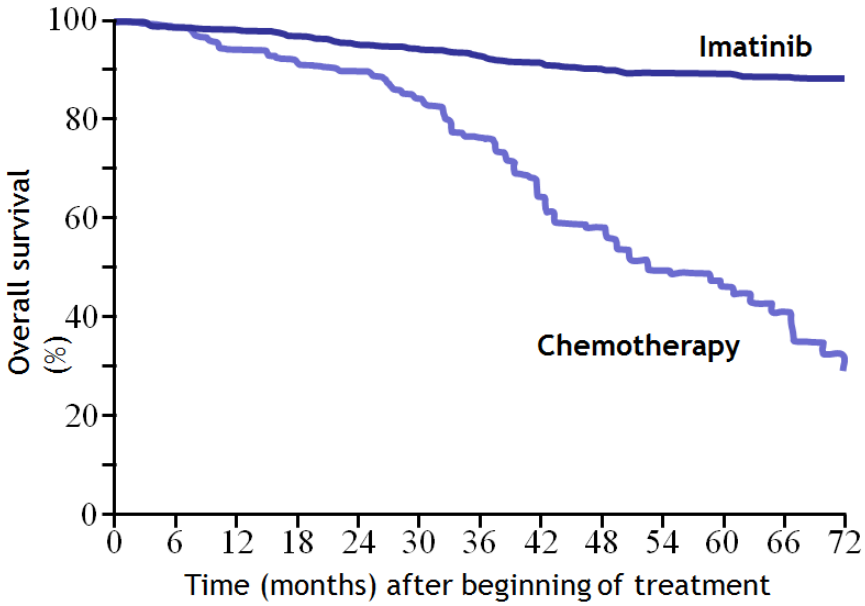
- SDH loss in the kidney leads to hyperproliferative benign cyst formation in-vivo (in GEMMs)

- HRas activation in the kidney does not demonstrate any phenotype, but it dramatically accelerate cyst formation and size in SDHB ablated genotype

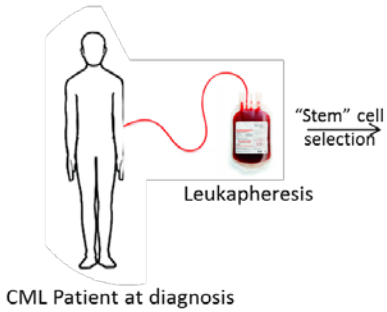
CML is a stem cells disease

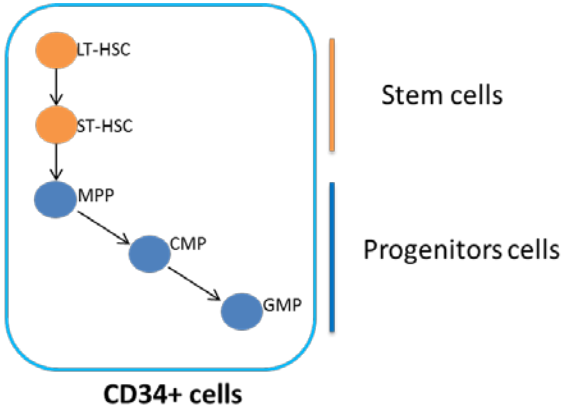


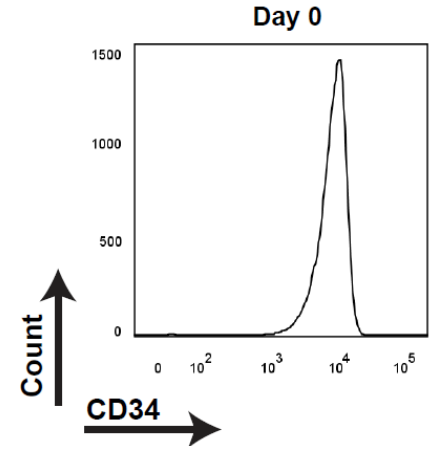


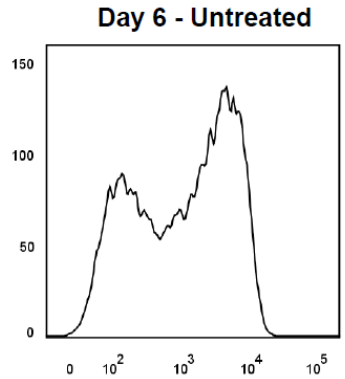


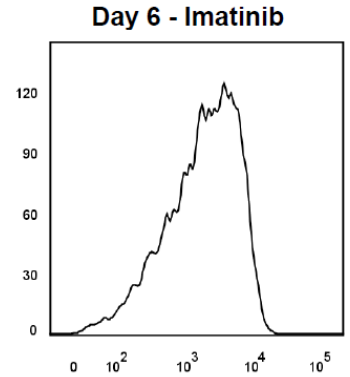
TKIs do not target CML stem cells

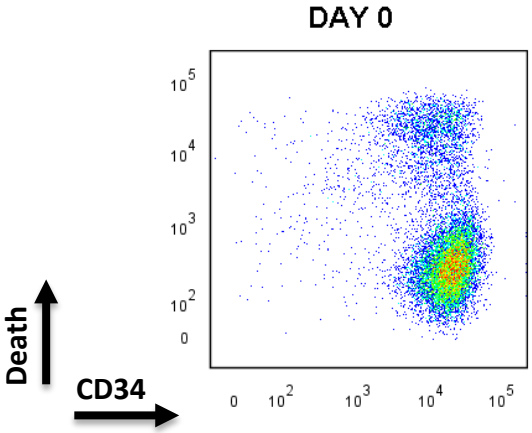


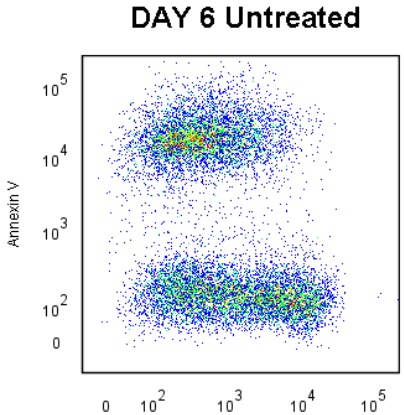


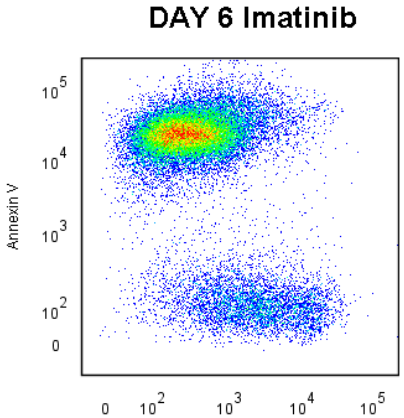






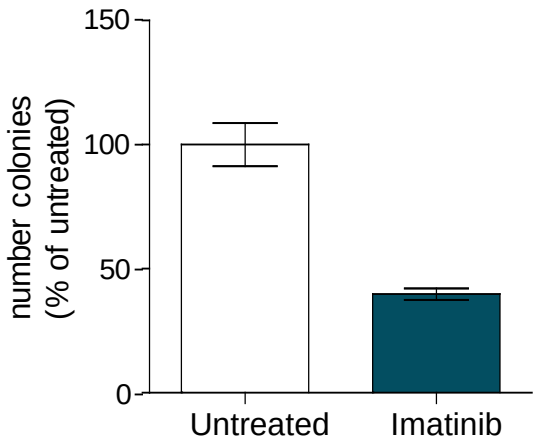


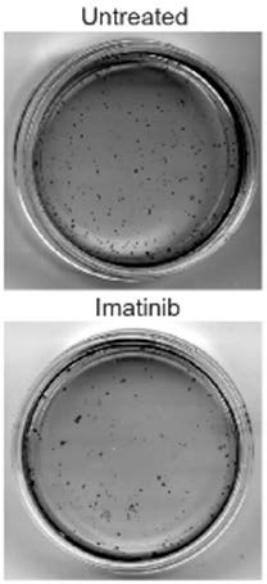




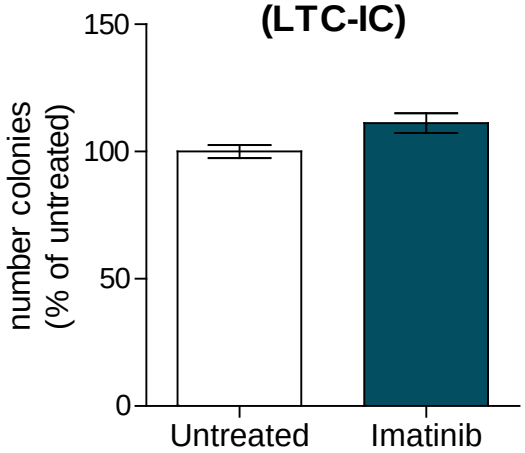
TKIs do not target CML stem cells

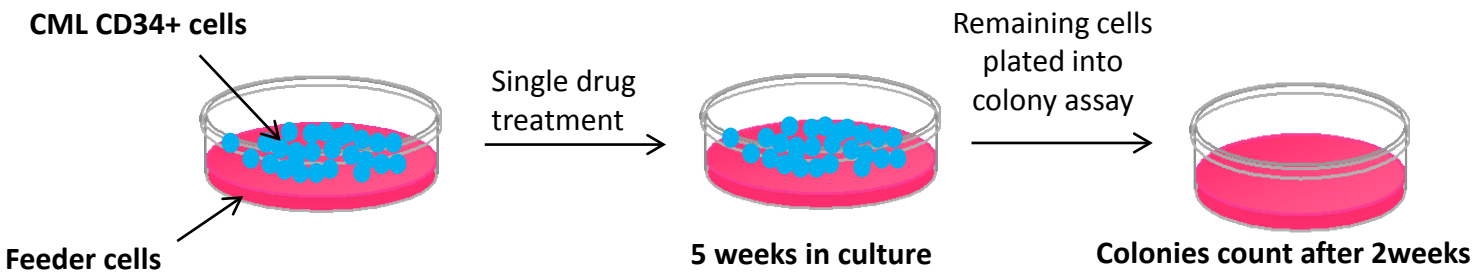
Progenitors cells
Short-term colony formation assay





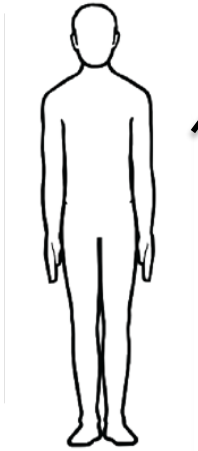
CML Stem cells
Long- term colony formation assay
(LTC-IC)





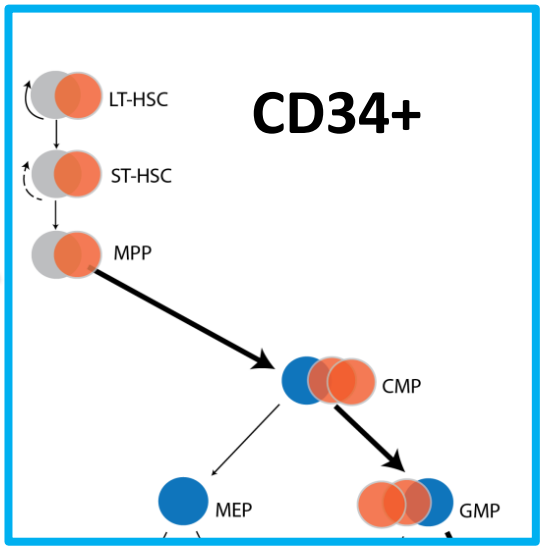
Measures drug effect on stem cells

Metabolomics in CML CD34+ cells versus CML CD34- cells

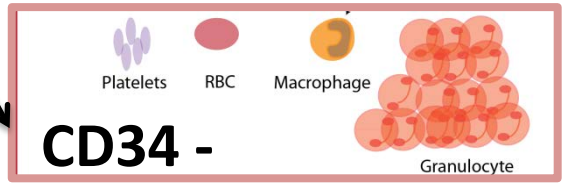


CML Patient
at diagnosis

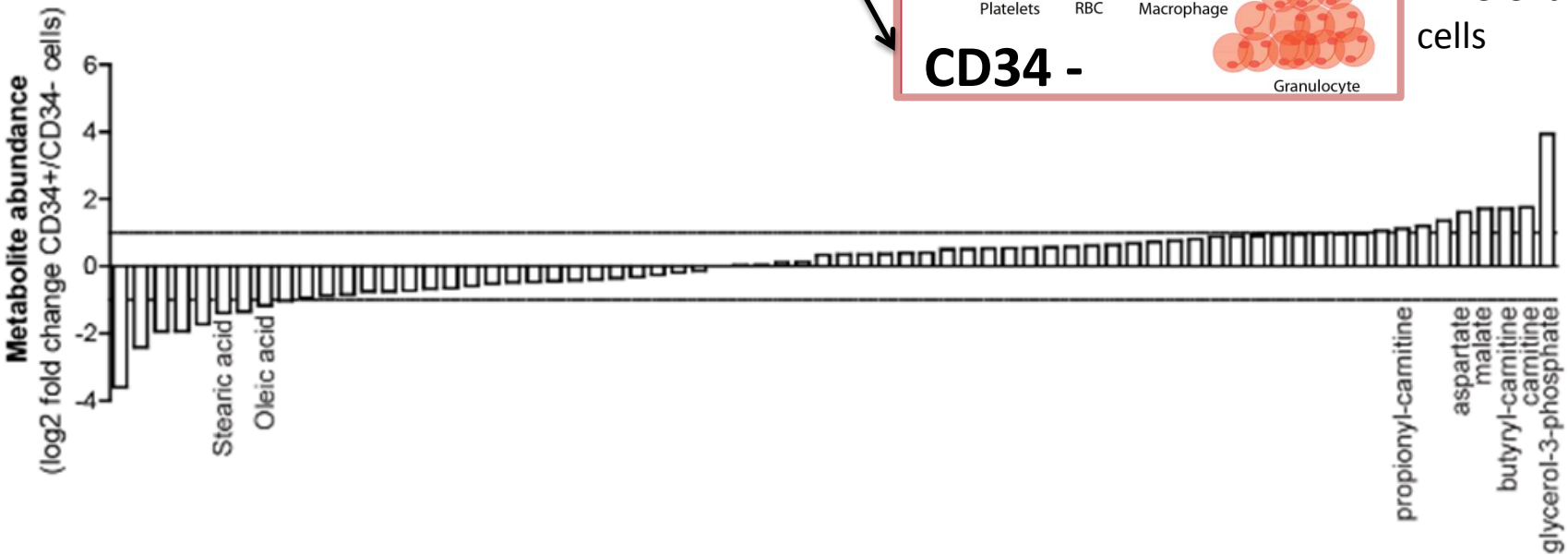
MNC



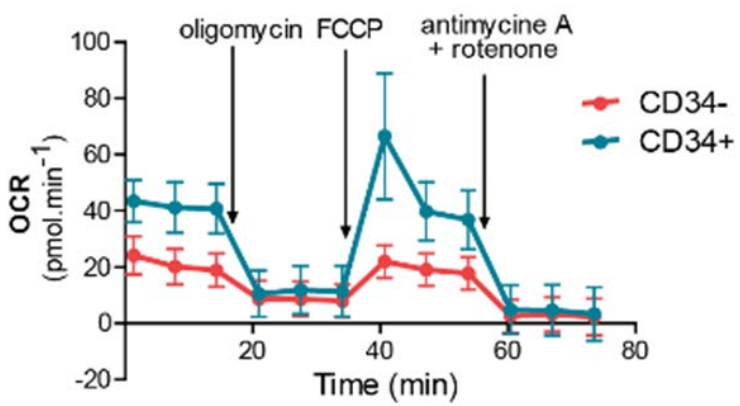
Stem+
Progenitors
cells

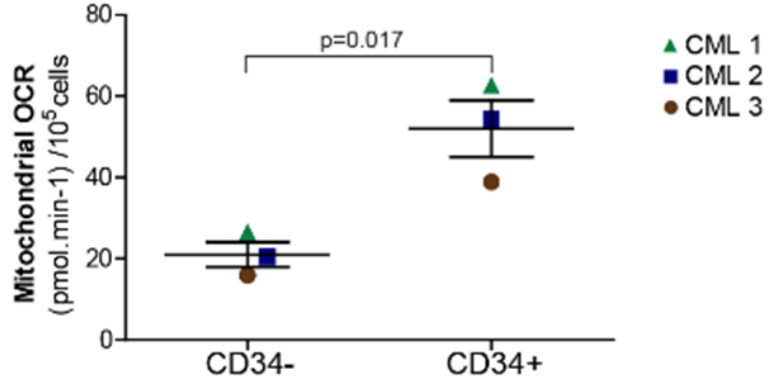


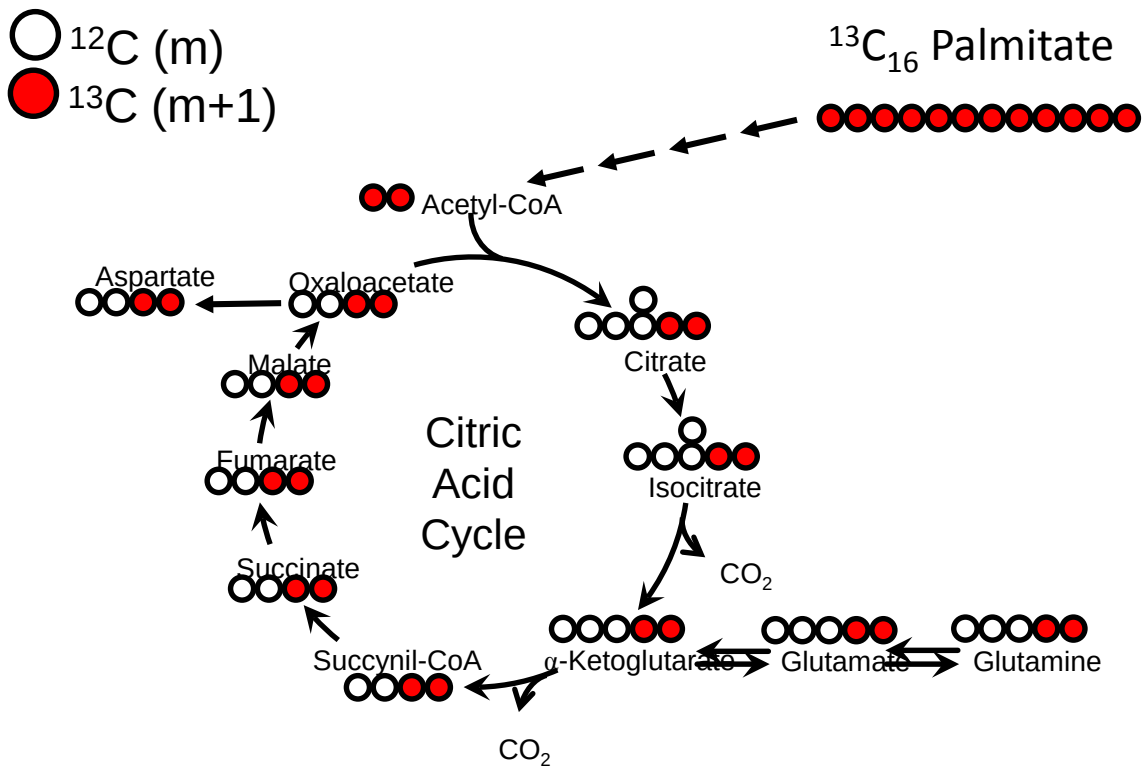
Differentiated
cells



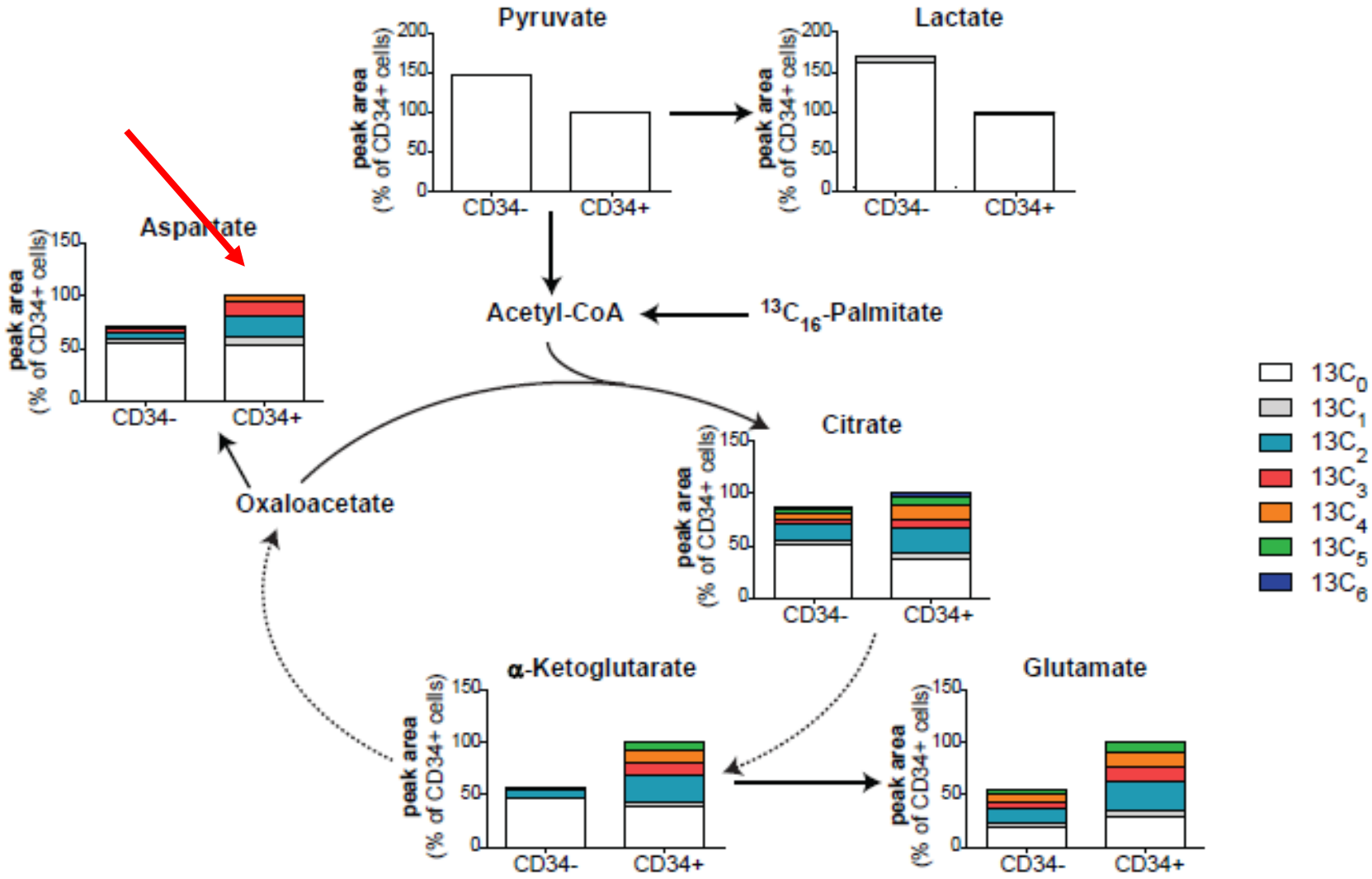
Fatty acid oxidation is increased in CML CD34+ cells



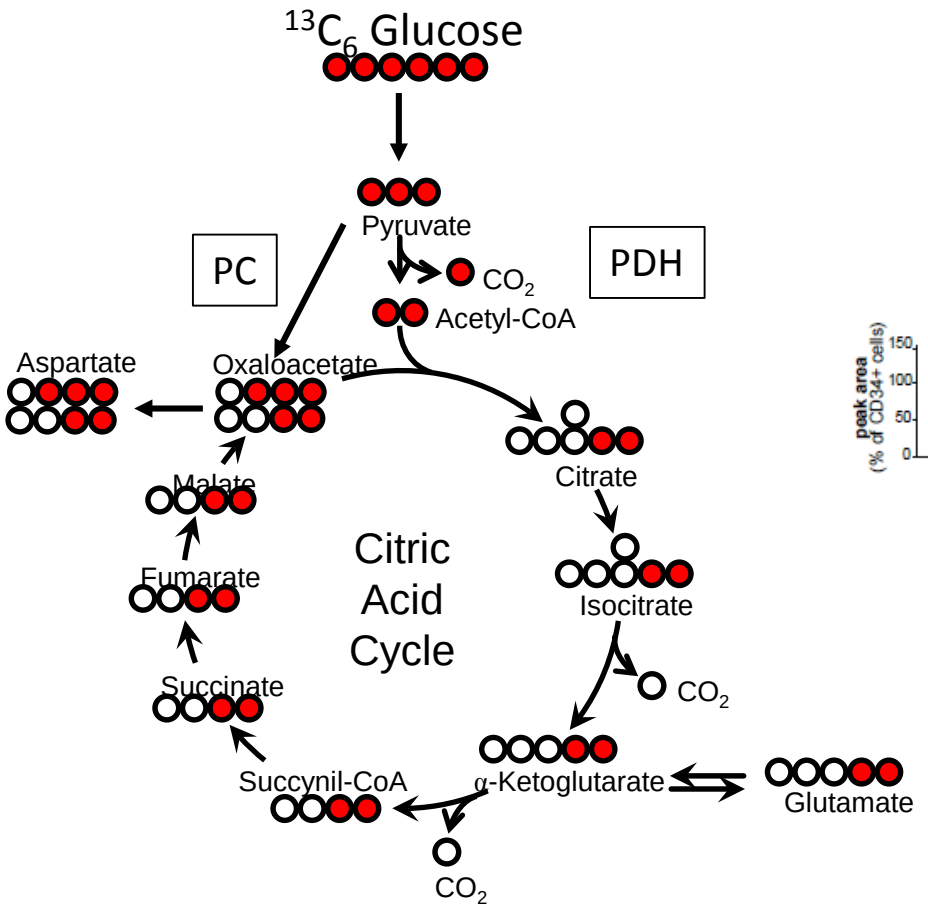


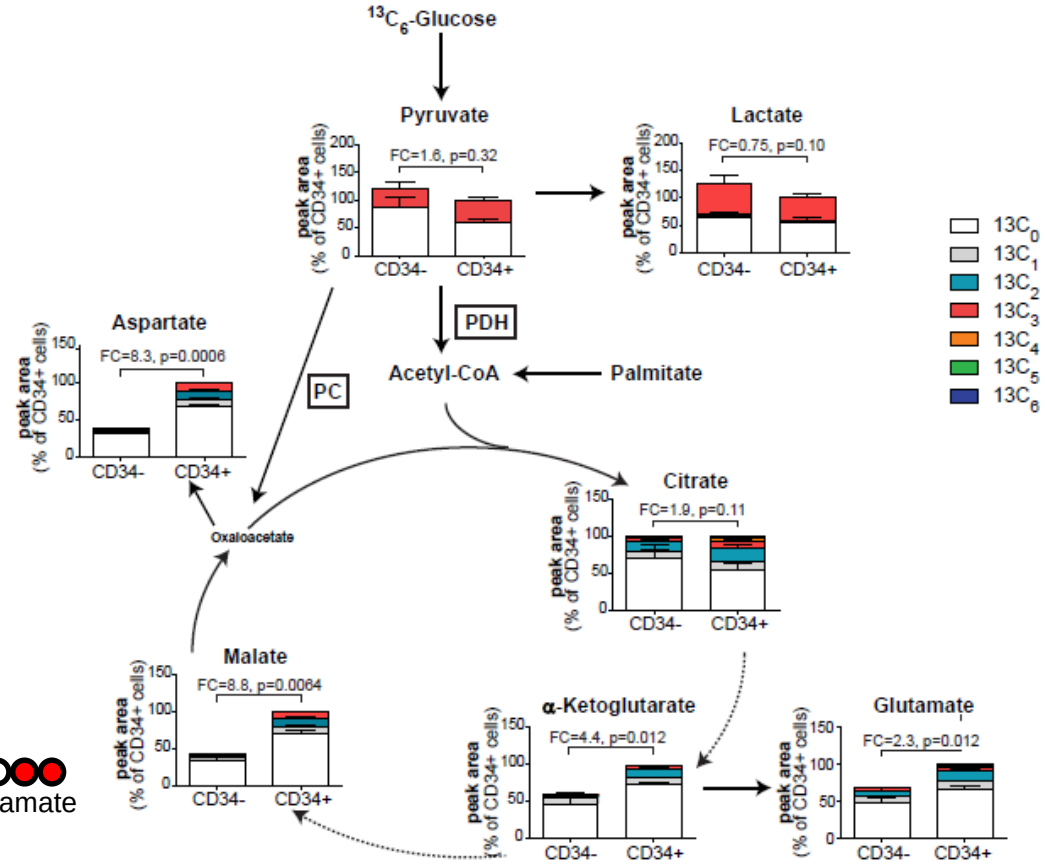


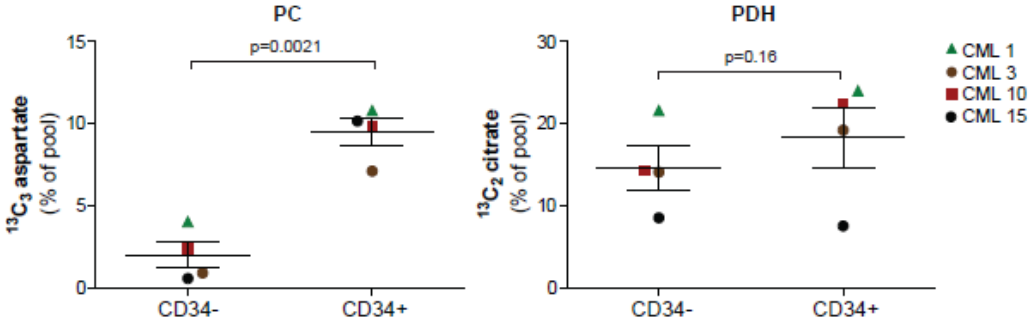
Fatty acid oxidation is increased in CML CD34+ cells



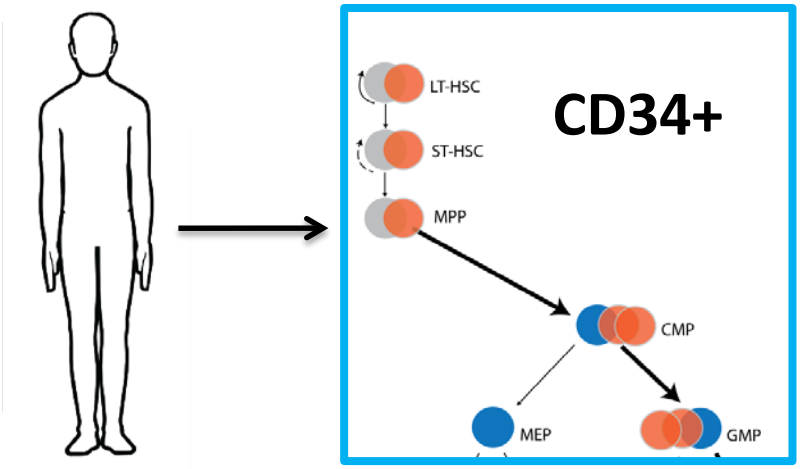
CML CD34+ cells have an increase in oxidative metabolism



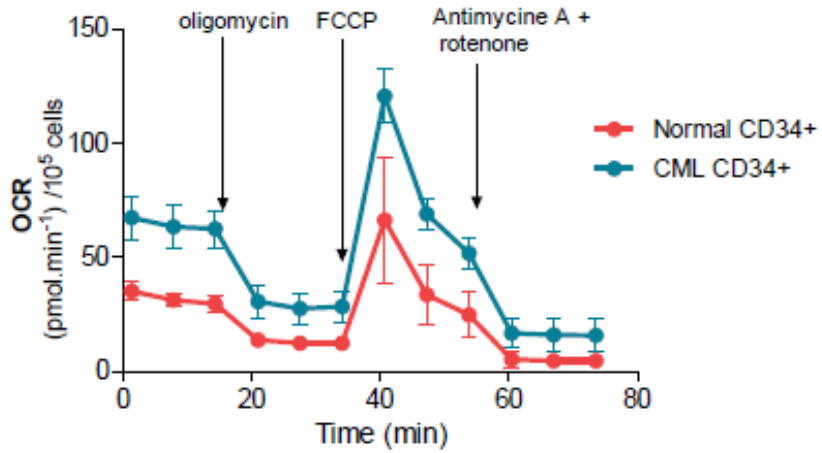


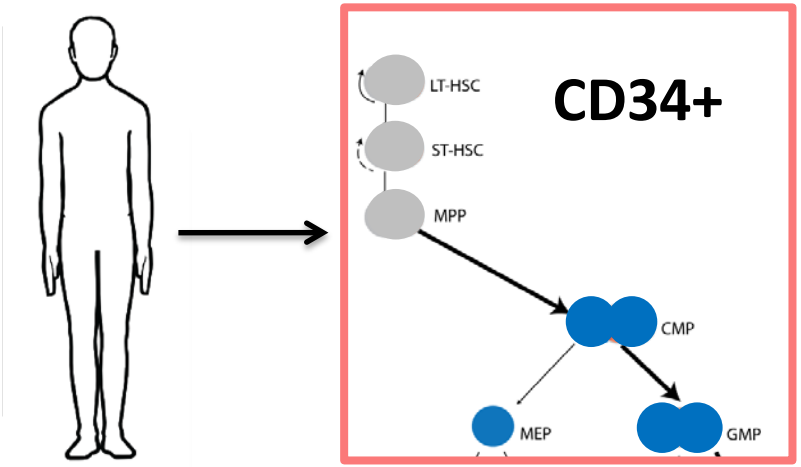


increased oxidative metabolism in CML CD34+ Vs. normal CD34+ cells

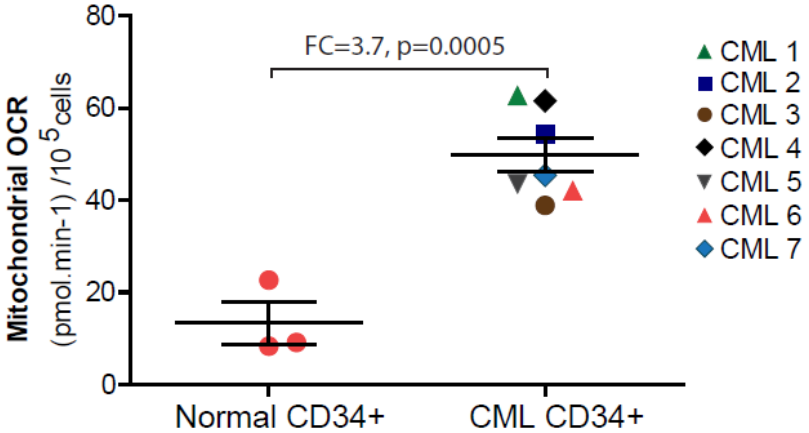


CML Patient at diagnosis

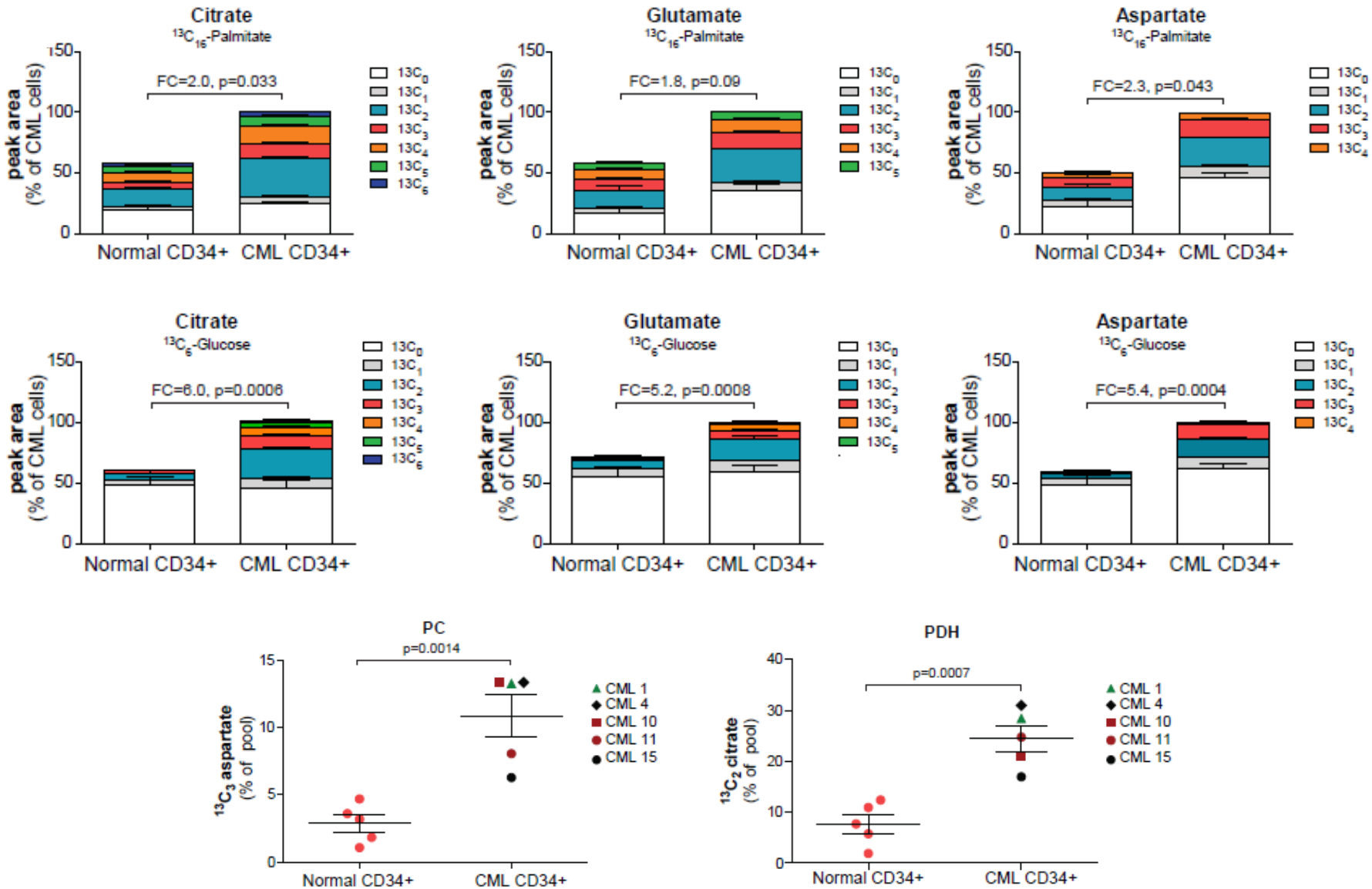




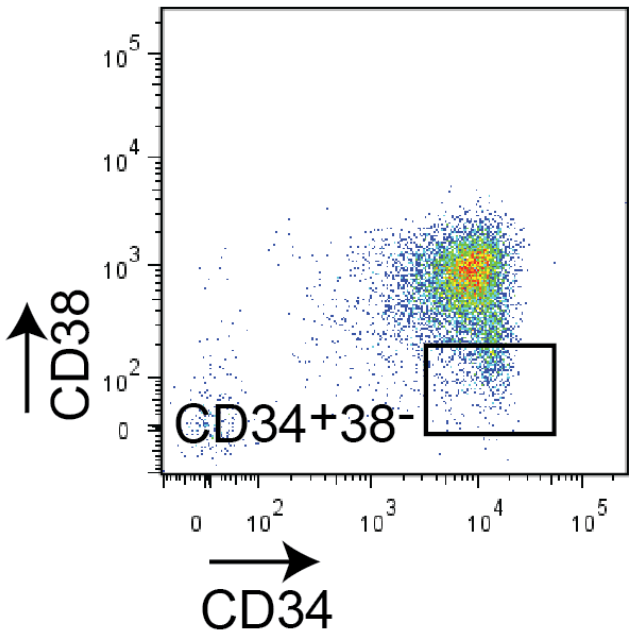
Healthy donor

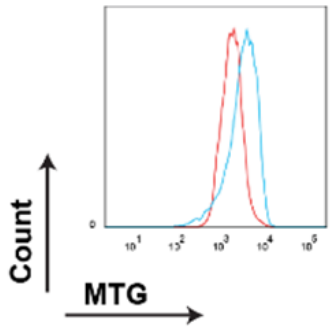


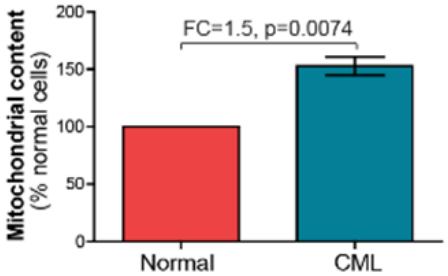
increased oxidative metabolism in CML CD34+ Vs. normal CD34+ cells

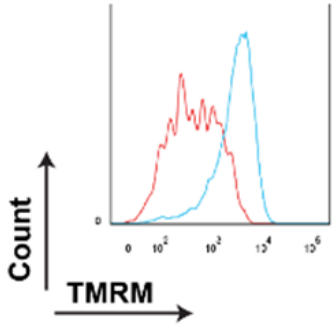


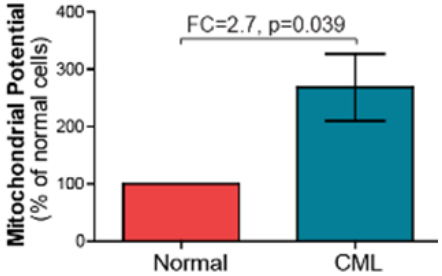
increased oxidative metabolism in CML stem cells

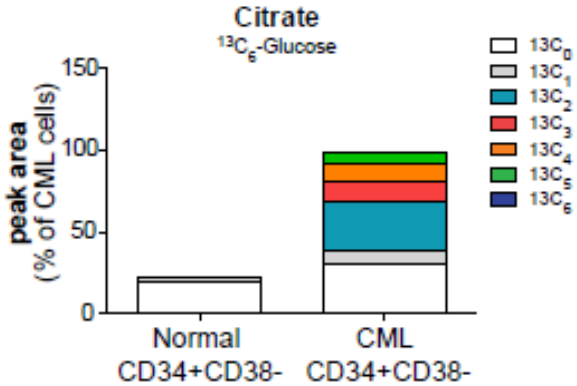


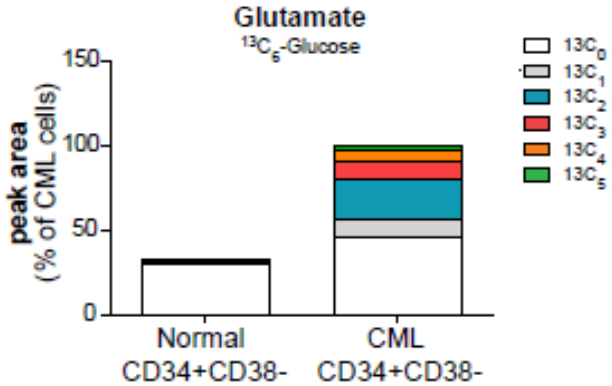


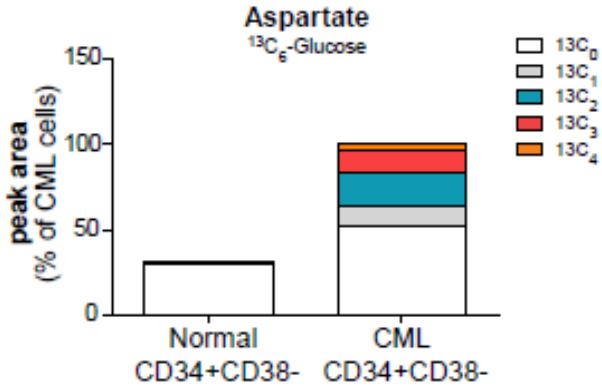






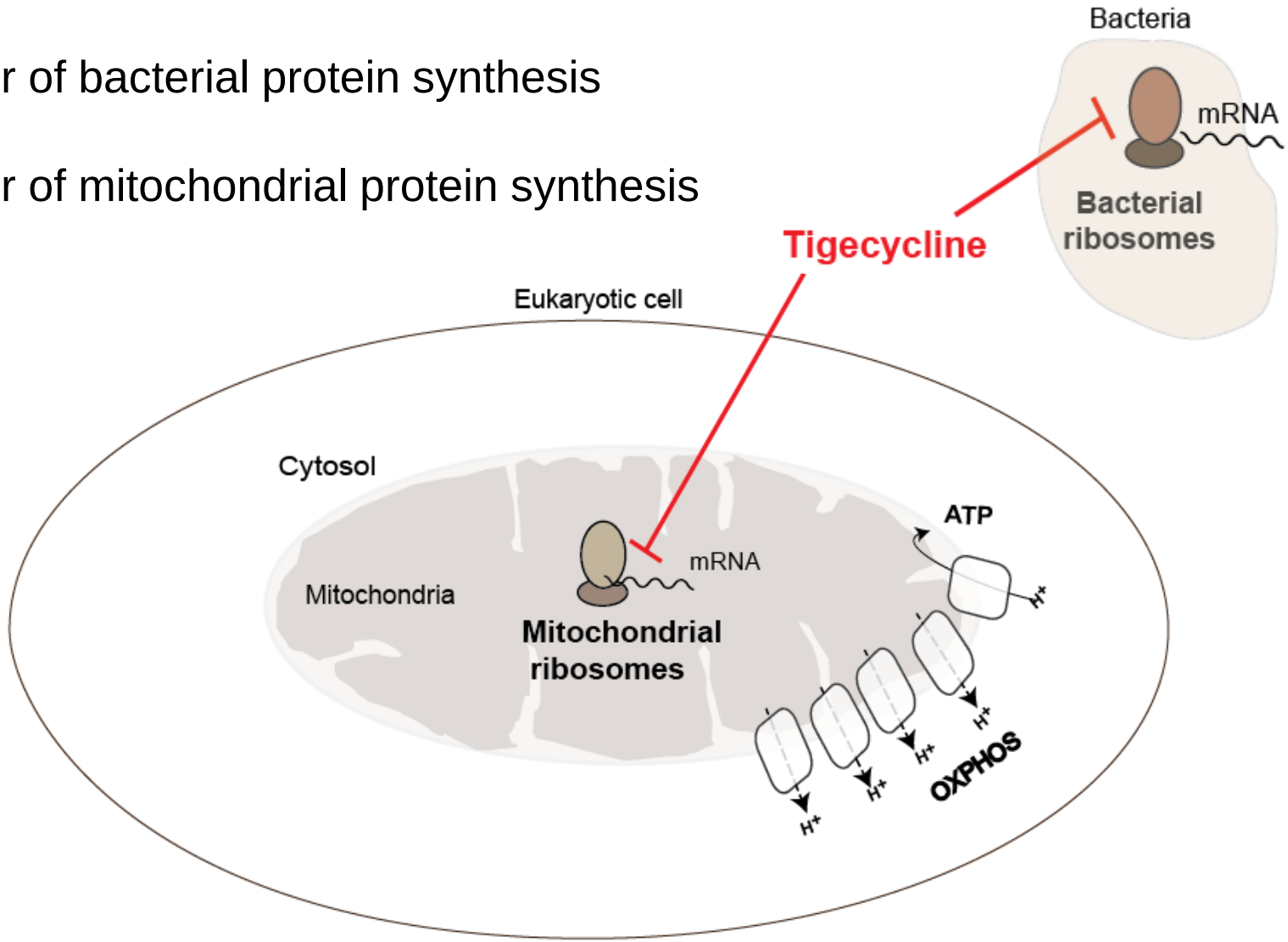




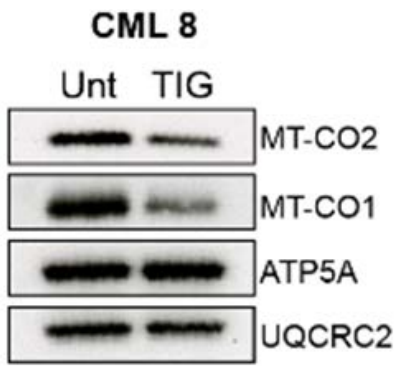


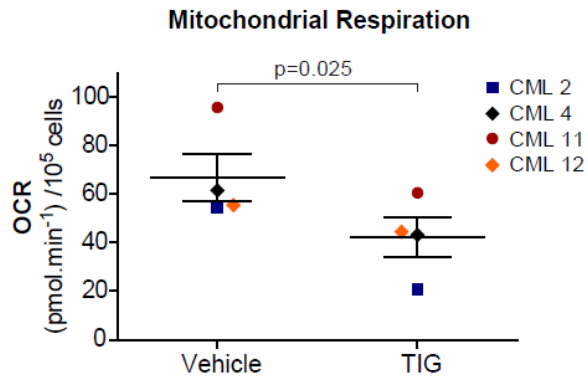
PHARMACOLOGICAL INHIBITION OF MITOCHONDRIAL METABOLISM WITH TIGECYCLINE

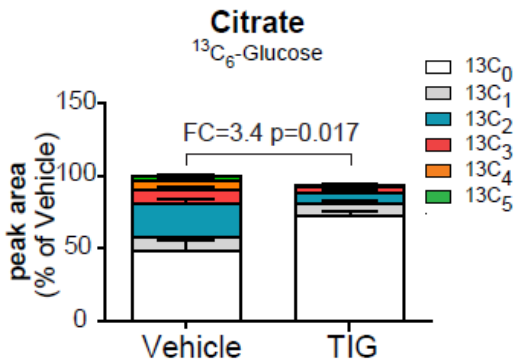
- FDA approved antibiotic
- Inhibitor of bacterial protein synthesis
- Inhibitor of mitochondrial protein synthesis

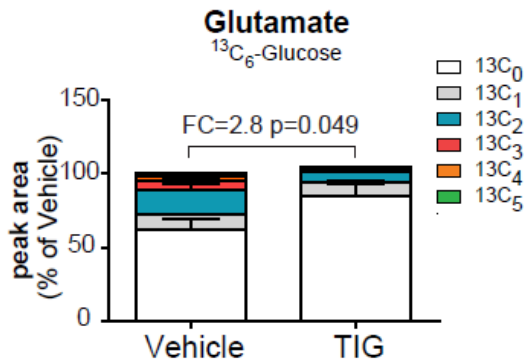


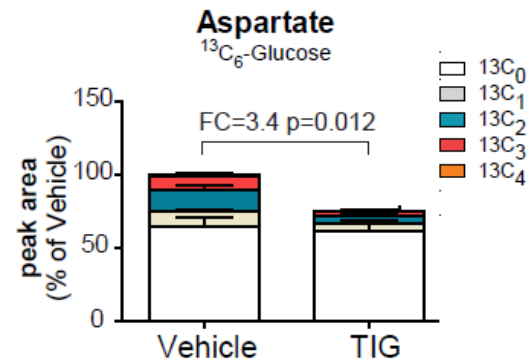
Inhibitor of mitochondrial oxidative metabolism decreases proliferation of CD34+ CML cells

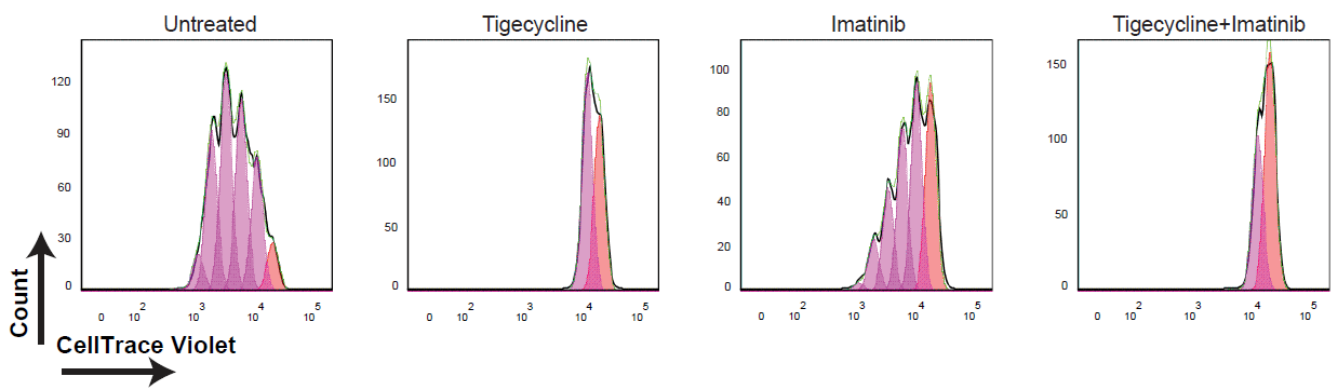




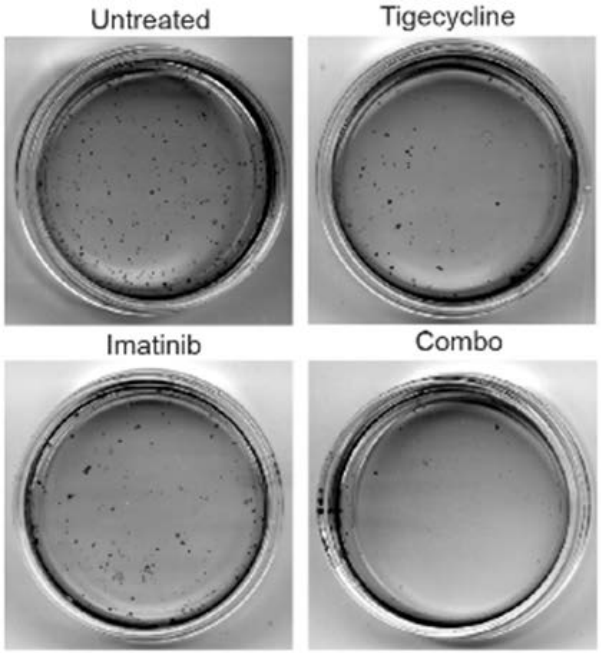


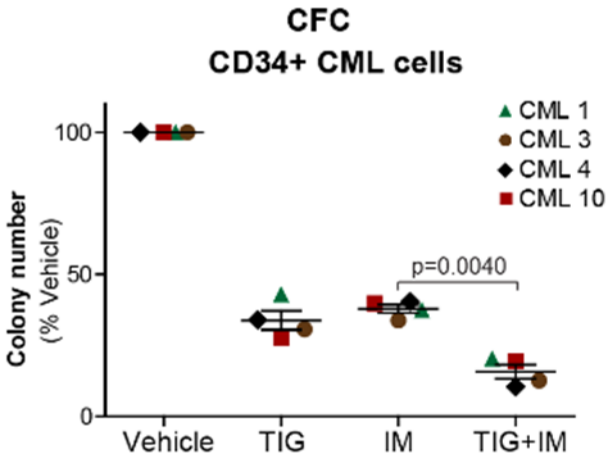


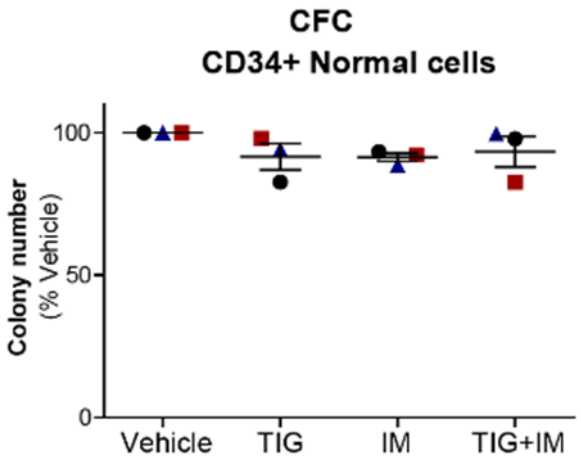


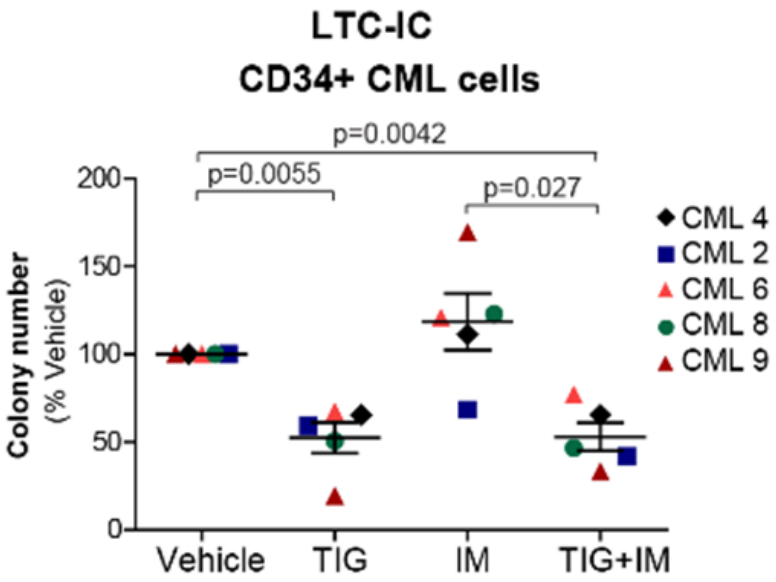


Inhibition of mitochondrial oxidative metabolism targets CML stem cells









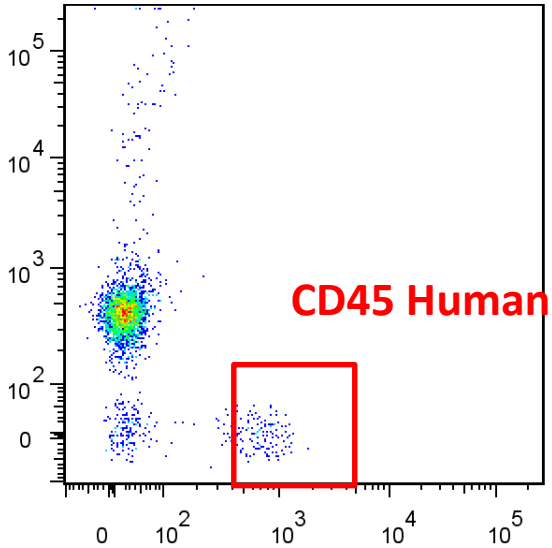
In vivo model to study drug effect on CML Stem Cells

NSG MICE
NOD scid gamma
N=24

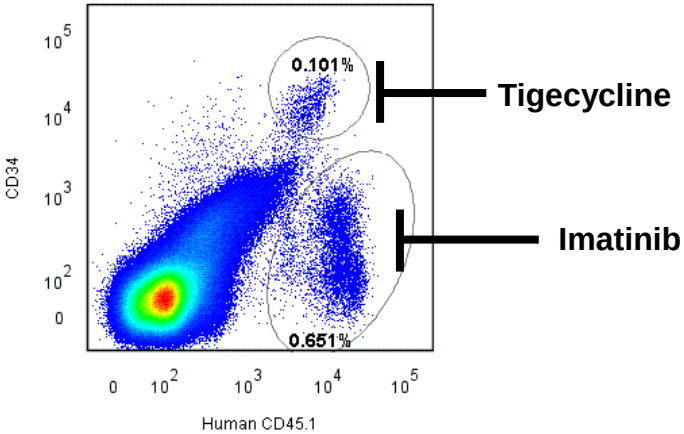
Sub-lethal irradiation →

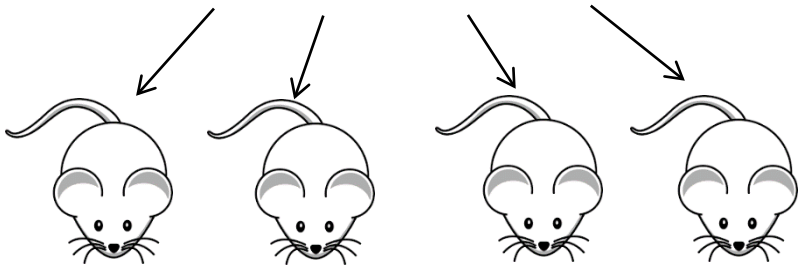
Tail vein injection
CML CD34+ cells

6 weeks engraftment →



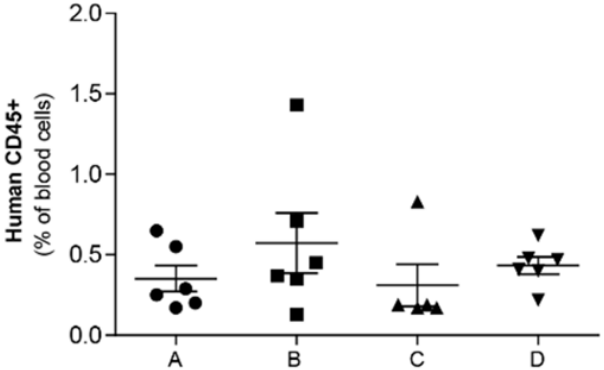
Confirmation of engraftment

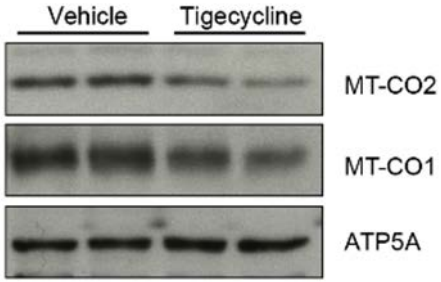




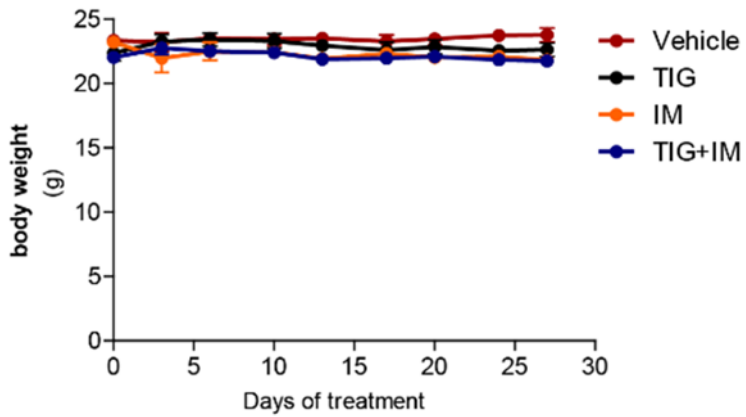
Vehicle (n=6)	TIG (n=6)	IM (n=5)	IM+TIG (n=6)

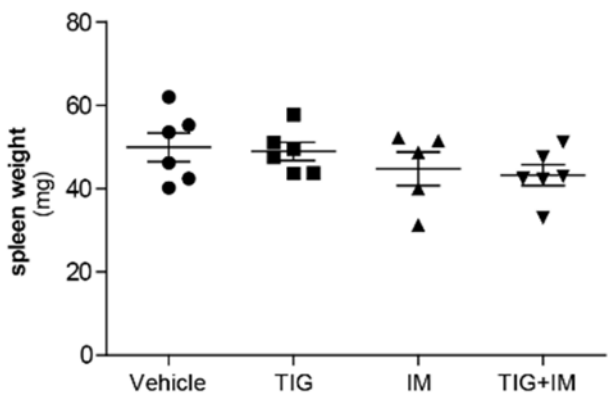
In vivo drug treatment for 4 weeks

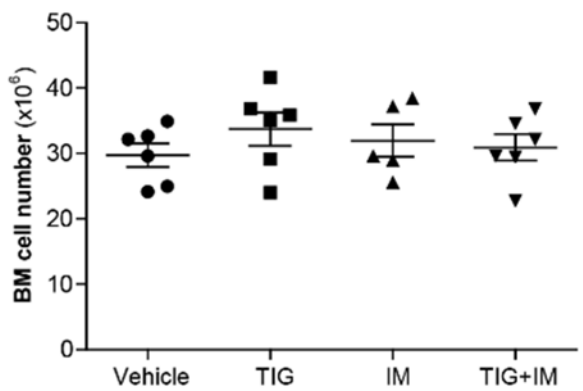




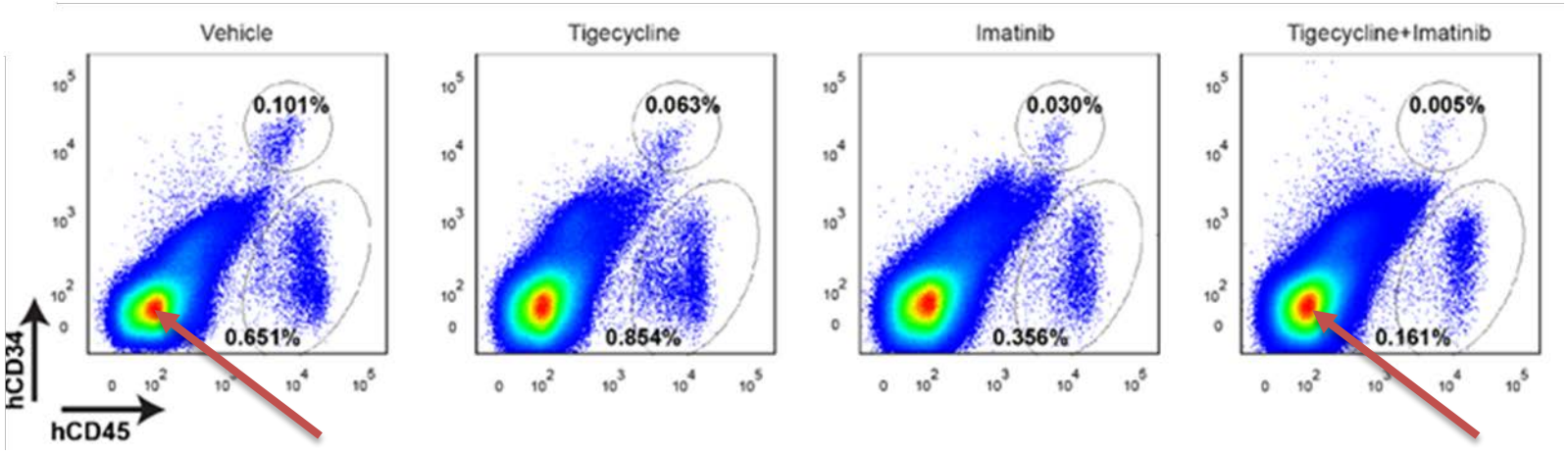
Inhibition of mitochondrial oxidative metabolism in-vivo is tolerated in treated mice

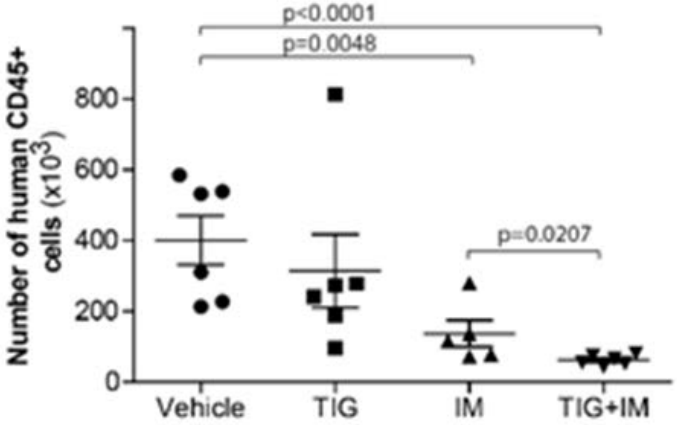


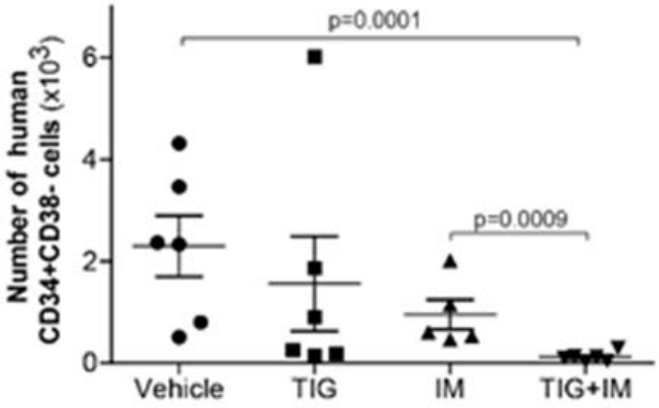




Inhibition of mitochondrial oxidative metabolism eradicates CML stem cells in-vivo

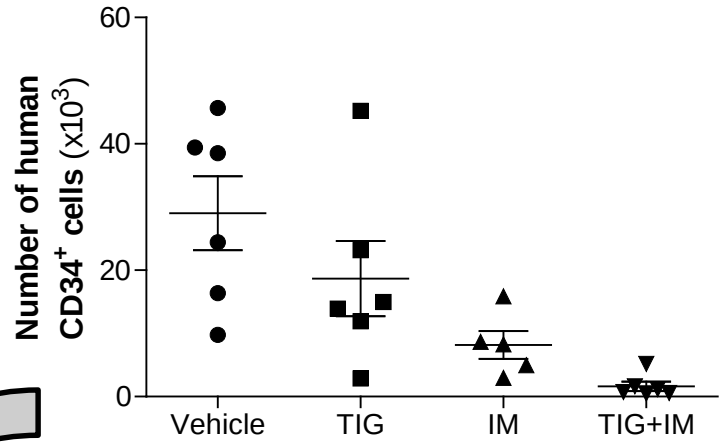






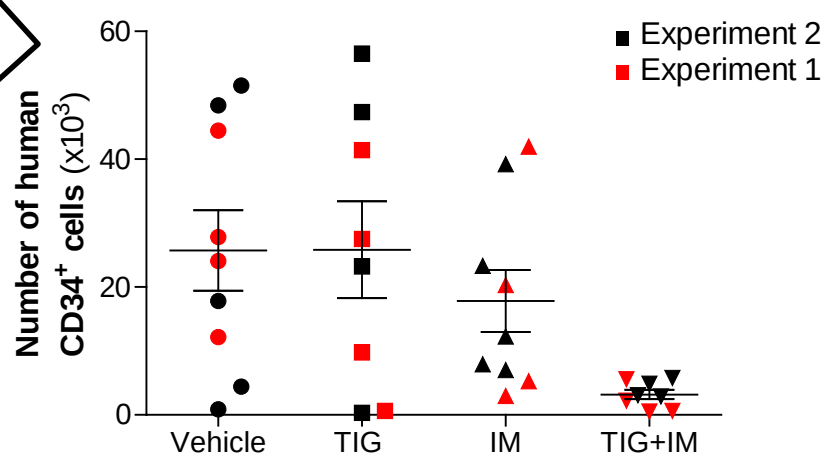
Inhibition of mitochondrial oxidative metabolism delays disease relapse after Imatinib withdrawal

After 3 weeks of treatment



2 or 3 weeks of treatment discontinuation

After 2-3 weeks of treatment discontinuation



Acknowledgements

Gottlieb Lab

Current members

Elaine MacKenzie
Simone Cardaci
Henry Däbritz
Jiska van der Reest
Elodie Kuntz
Johan Vande Voorde

Past members

Mary Selak
Christian Frezza
Leon Zheng

Metabolomics

Gillian McKay
Niels van den Broek

CANCER RESEARCH UK | BEATSON INSTITUTE

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