



Judith Favier

Mutations des gènes SDH et paragangliomes : rôle des oncométabolites dans le cancer

Instituts
thématiques



Inserm

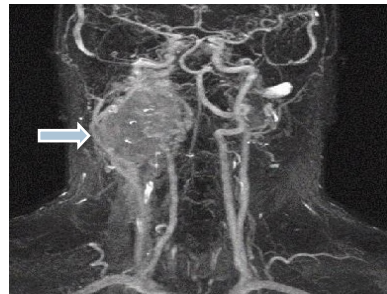
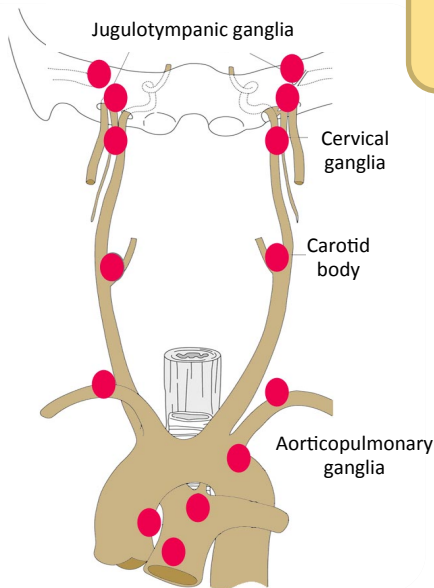
Institut national
de la santé et de la recherche médicale



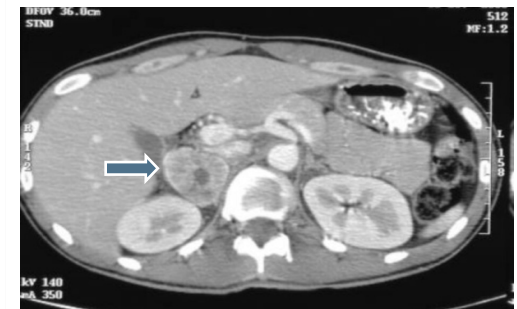
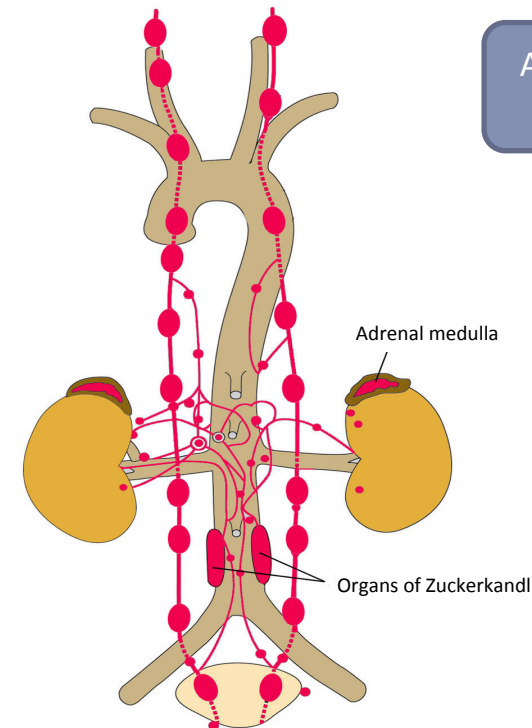
Pheochromocytomas and paragangliomas

- Pheochromocytomas (PCC) and paragangliomas (PGL) are rare tumors arising from neural crest-derived tissues.

PGL arise from
parasympathetic or
sympathetic ganglia

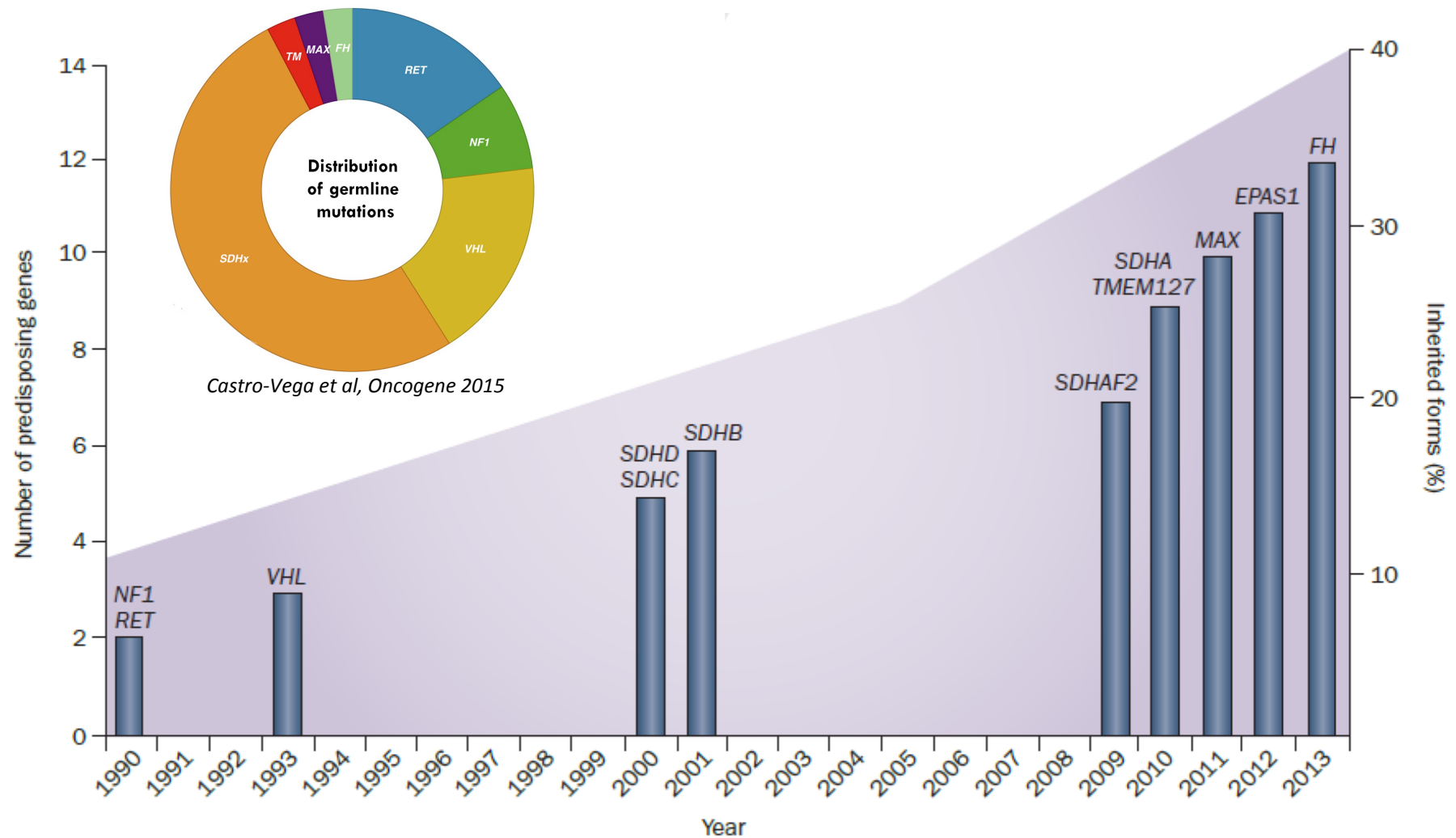


A PCC is a PGL that develops in the
adrenal medulla



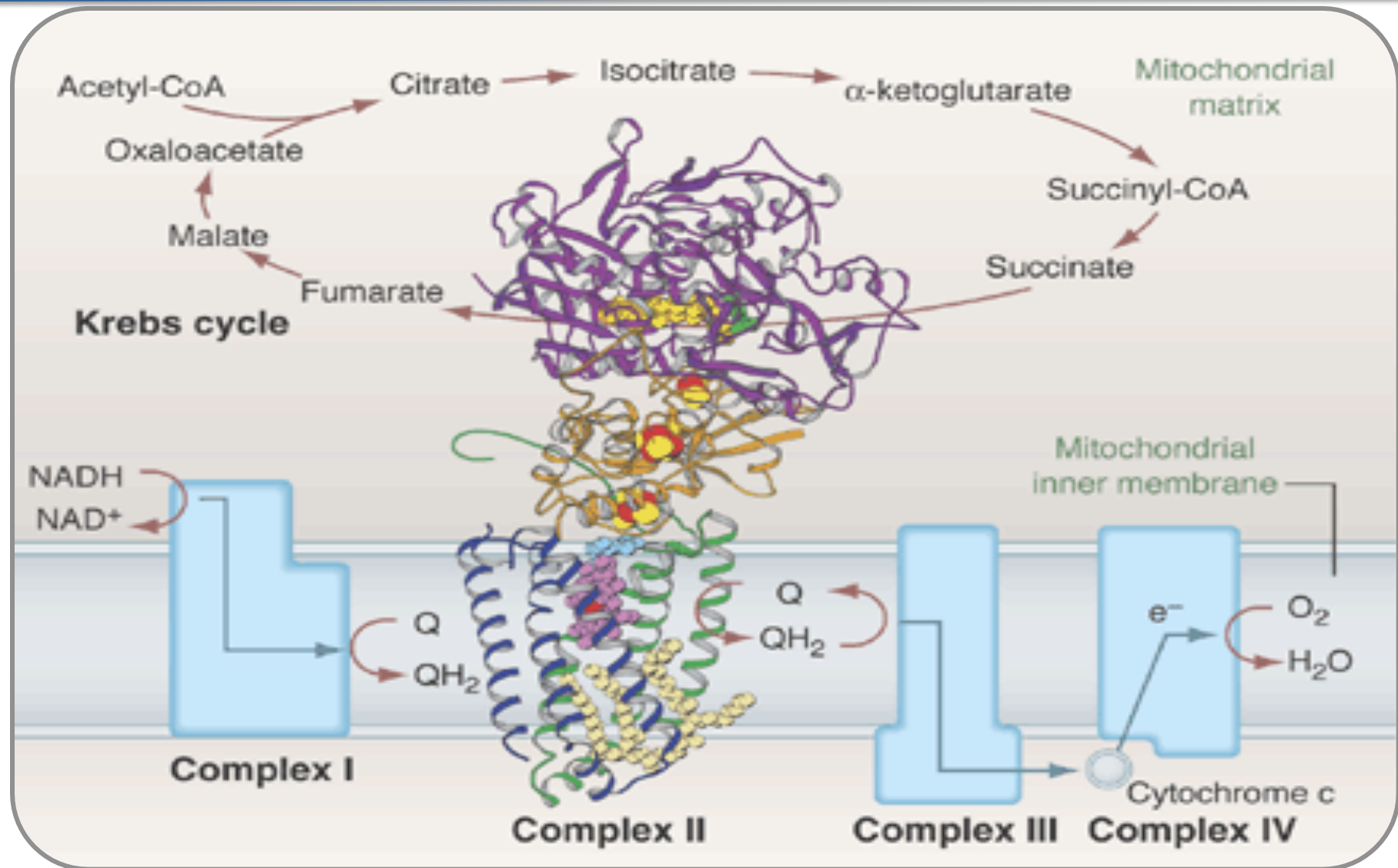
- PGL/PCC are neuroendocrine tumors often secreting catecholamines, resulting in hypertension, headache, sweating, palpitations...
- Non-functioning tumors do not produce catecholamines and are difficult to diagnose.

Genetic susceptibility to pheochromocytomas and paragangliomas



Judith Favier, Laurence Amar and Anne-Paule Gimenez-Roqueplo

Genetic susceptibility to pheochromocytomas and paragangliomas

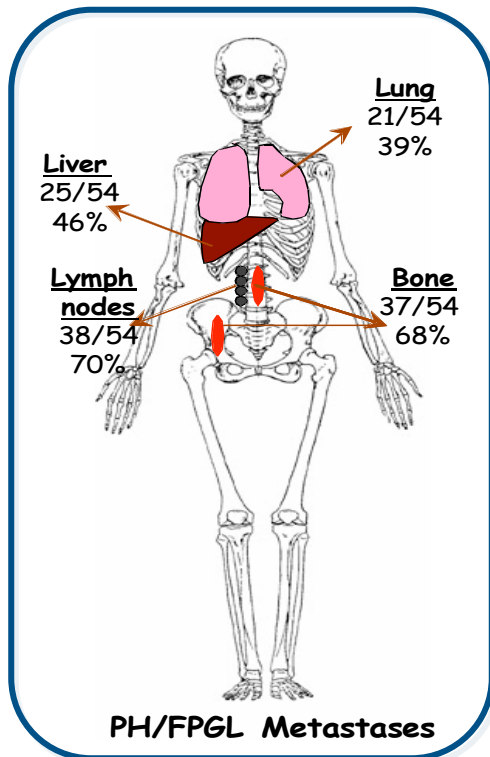


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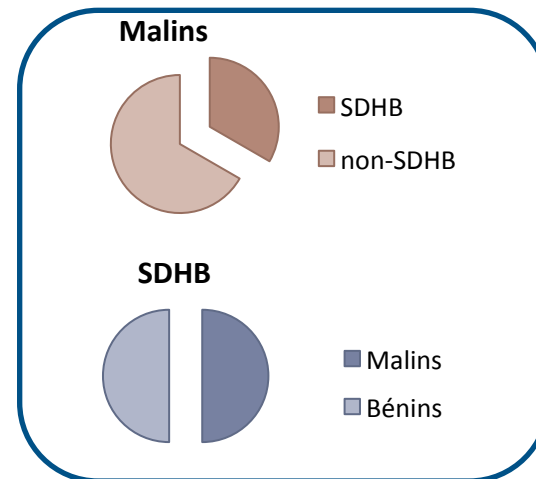
SDHB mutations and the metastatic phenotype

- PGL/PCC are generally benign but 10-15% of all cases develop metastases.
- SDHB mutations confer a 19-fold higher risk of metastasis and a shorter survival than patients with malignant tumors but no SDHB mutation.

Malignancy: 10-15% of cases

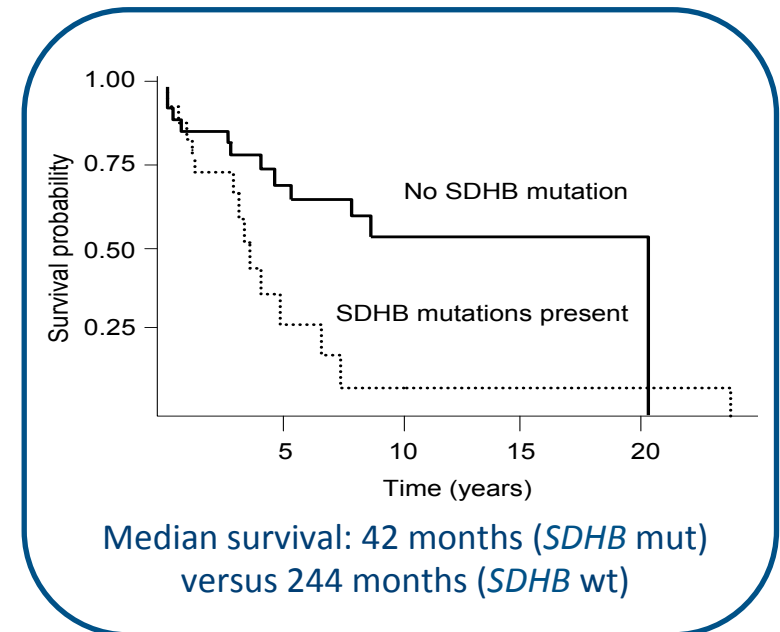


Metastatic progression



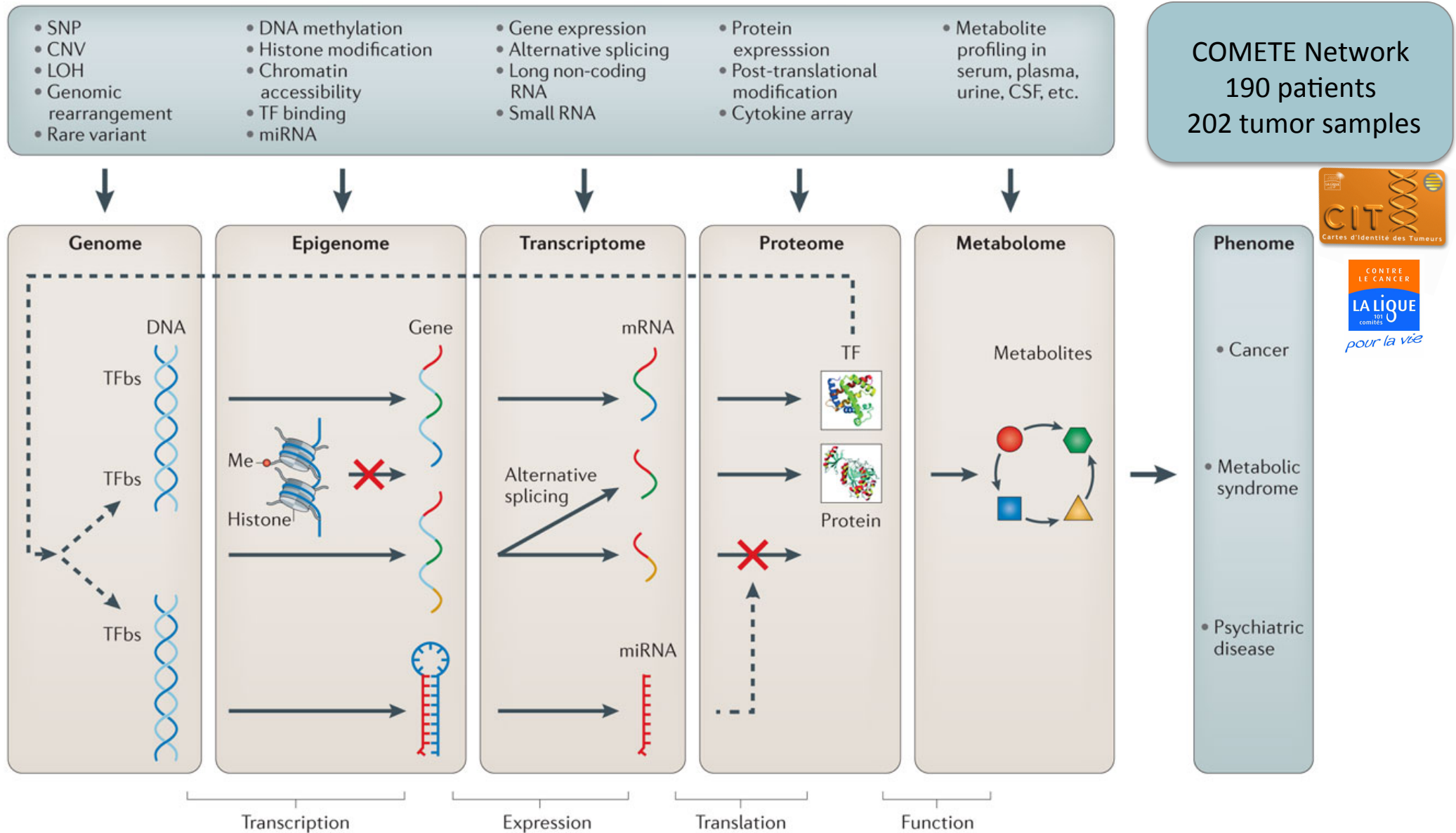
Gimenez-Roqueplo et al., Cancer Res 2003
Amar et al., J Clin Oncol 2005

Survival in malignant PGL/PCC



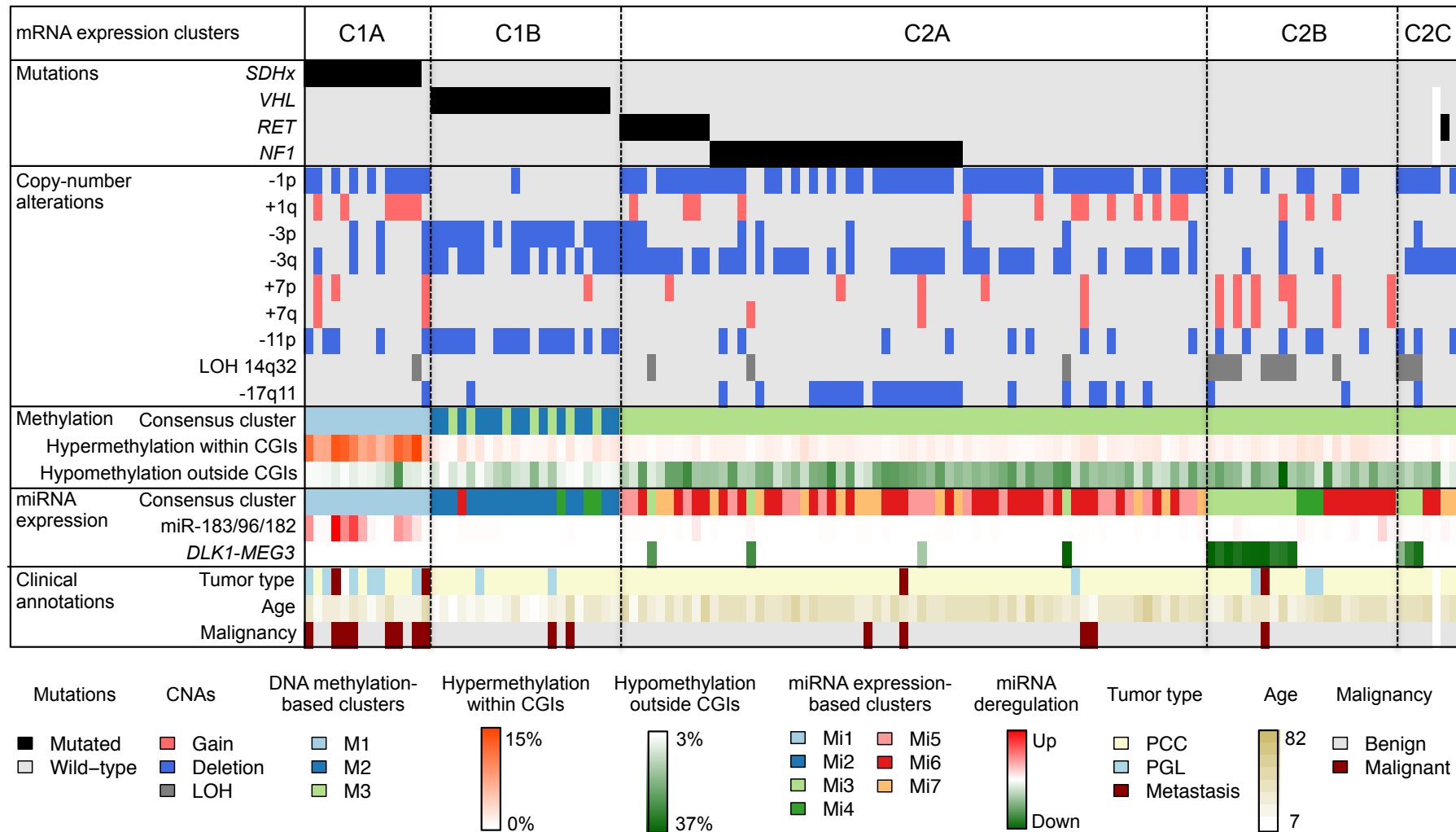
Gimenez-Roqueplo et al., Cancer Res 2003
Amar et al., J Clin Oncol 2005
Amar et al., J Clin Endocrinol Metab 2007

OMICS strategy

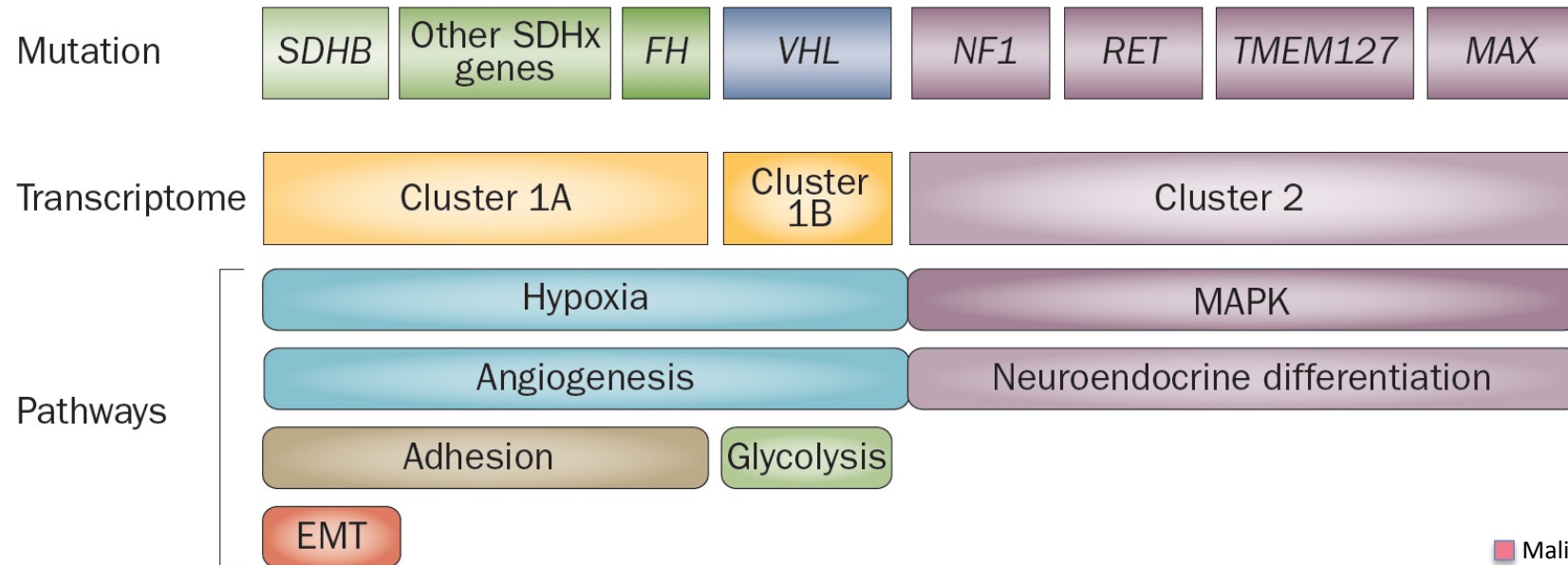


multi-OMICS analysis of the COMETE cohort: a major influence of genetics

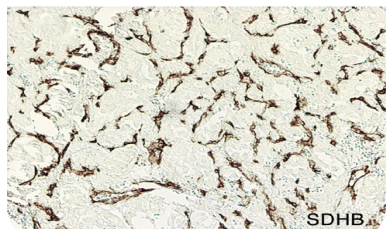
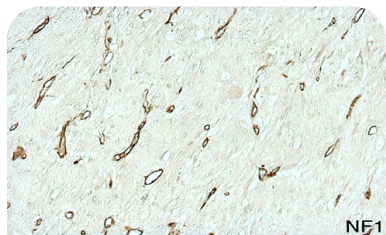
Transcriptome (Affymetrix UG U133 2+), **CGH-BAC array**, **SNP array**, **Méthylome** (puces 27K et 450K, RRBS), **miRnome** (Hiseq)



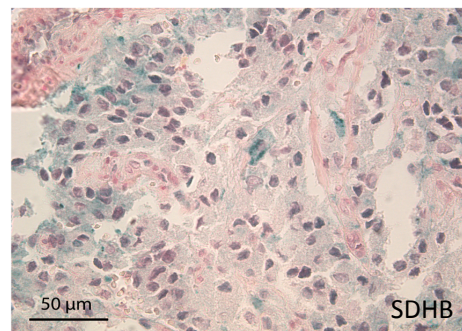
Gene expression studies



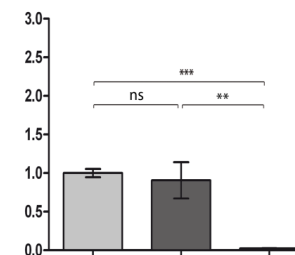
■ Malignant-SDHB
■ Malignant-non SDHB
■ Benign



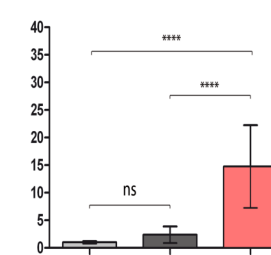
Snail Nuclear translocation



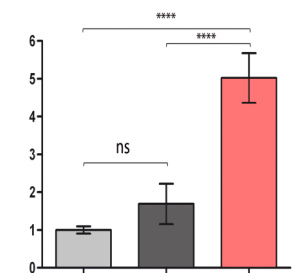
KRT19



TWIST1



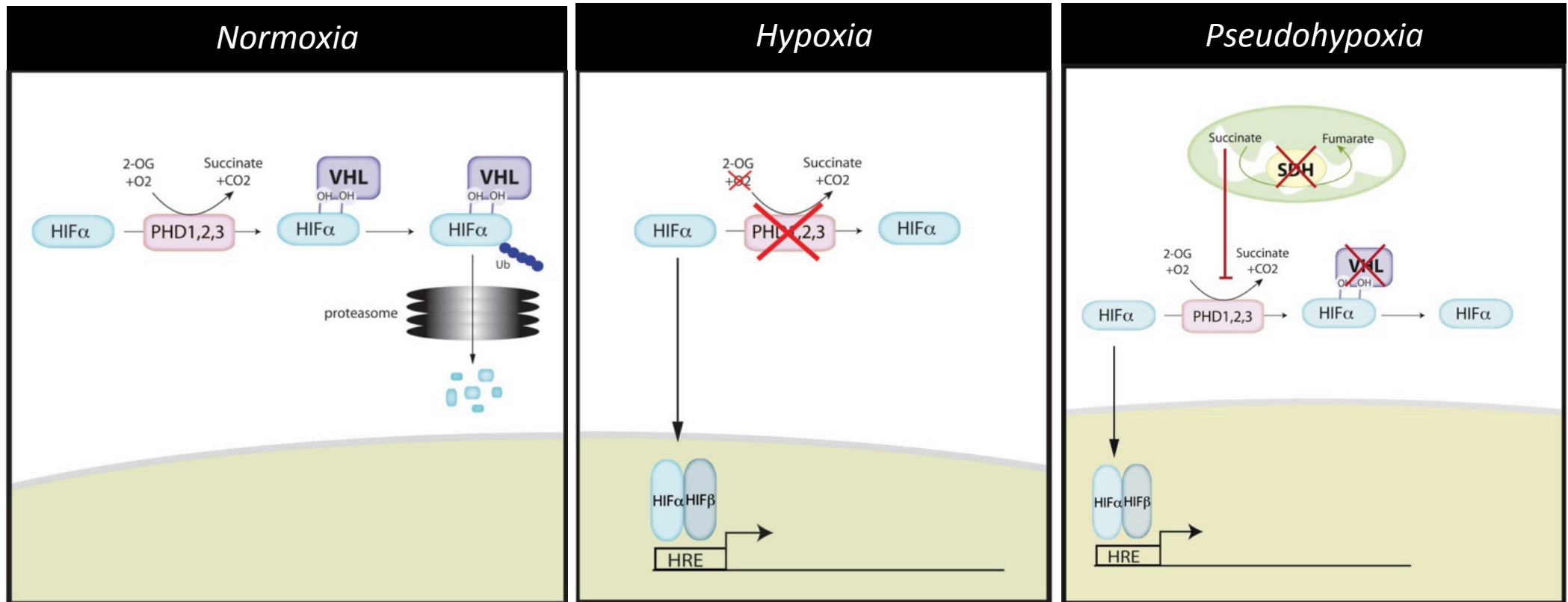
LOXL2



Favier et al PloS One, 2009

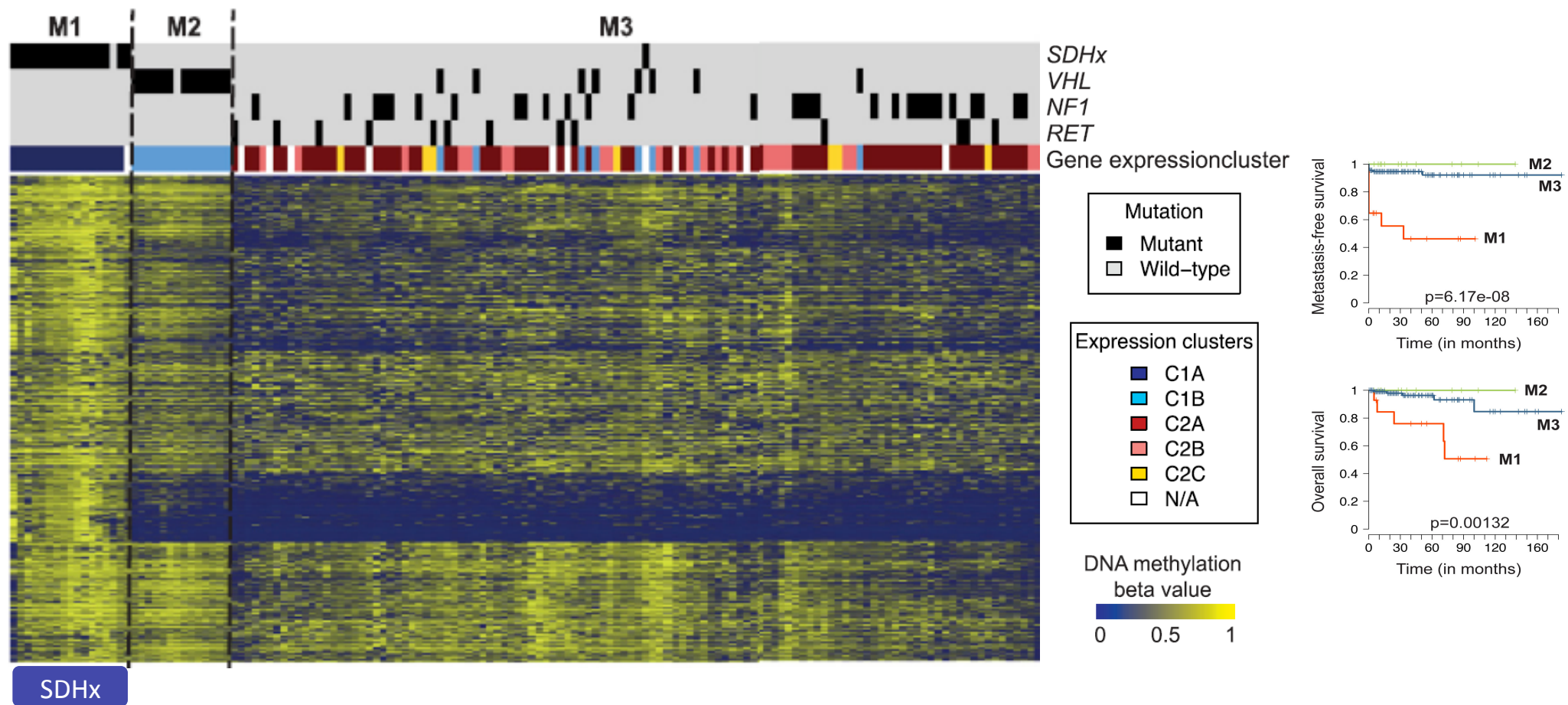
Loriot et al. J Clin Endocrinol Metab, 2012

Normoxia, Hypoxia, Pseudohypoxia



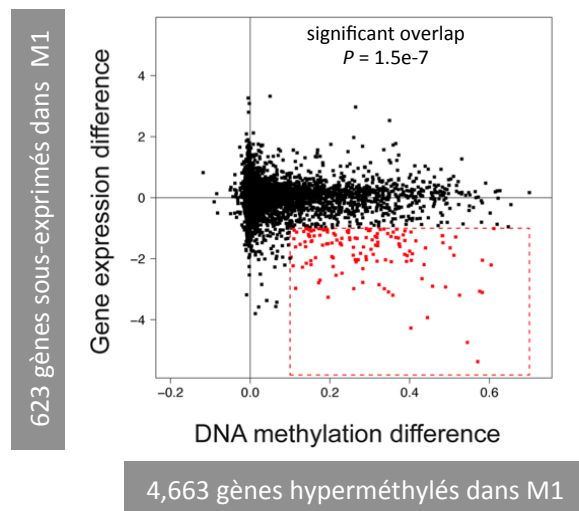
DNA methylation-based classification of PGL/PCC

- Consensus clustering reveals 3 homogeneous tumor clusters
- DNA methylation subgroups are highly associated with molecular subtypes and survival:

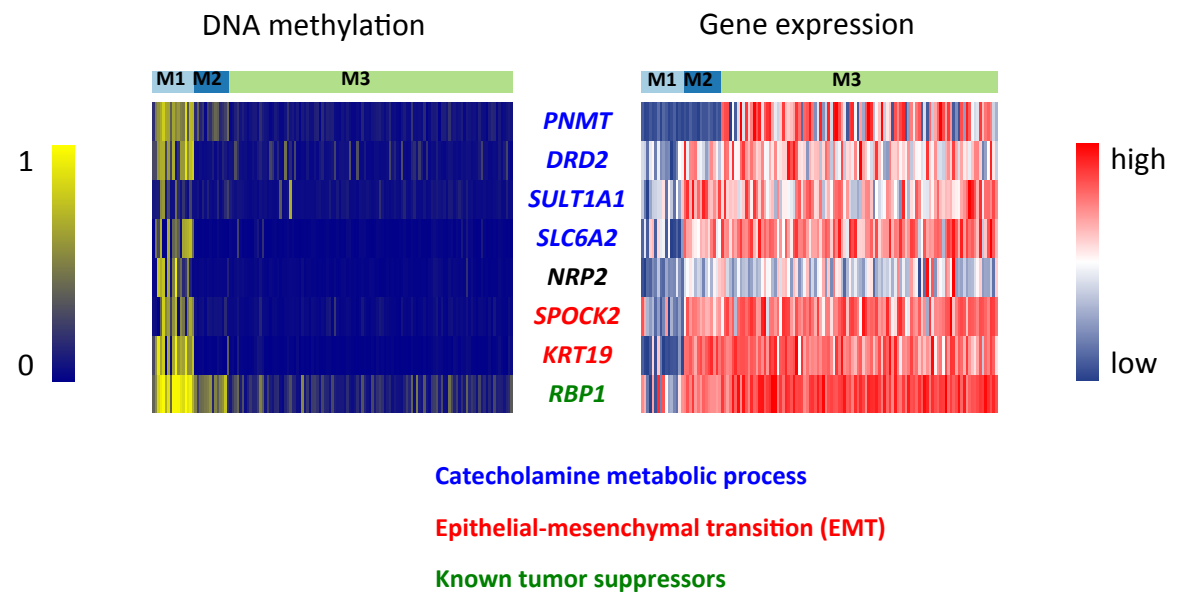


Genes epigenetically silenced in SDHx tumors

11.5% of hypermethylated genes (beta-value difference > 0.1) are down-regulated in M1 tumors.



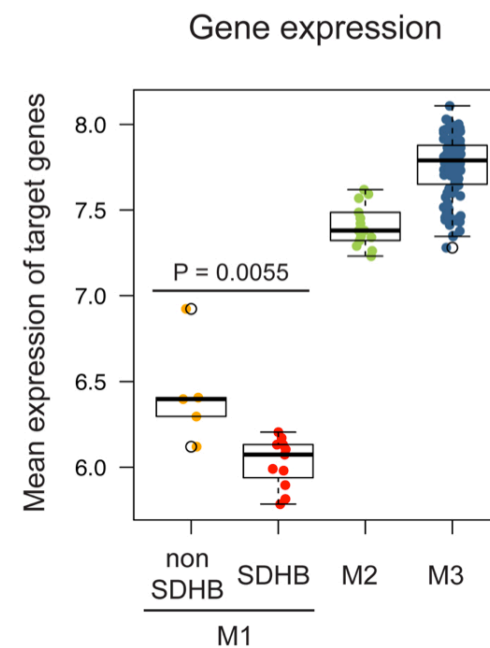
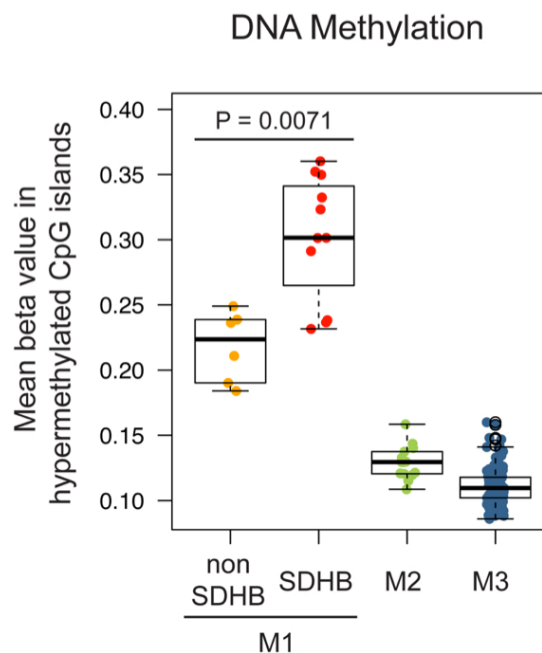
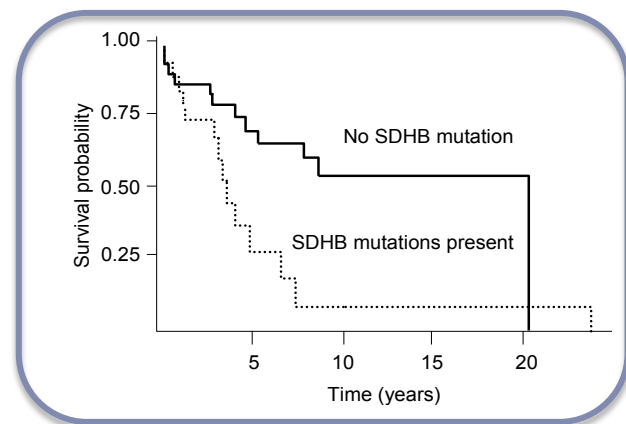
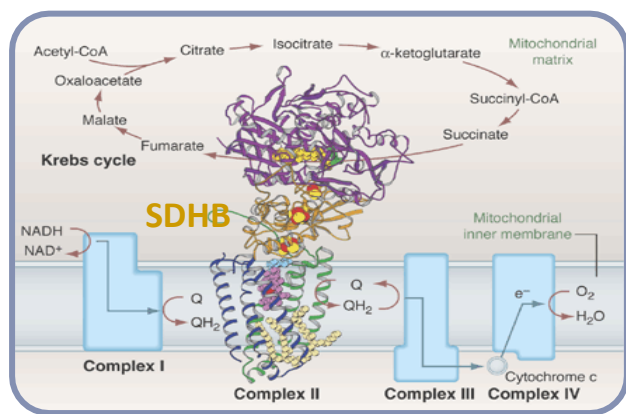
191 genes are significantly hypermethylated and down-regulated in SDHx tumors



-> Epigenetic silencing of genes implicated in chromaffin cell differentiation and EMT explains the phenotypic characteristics of these tumors.

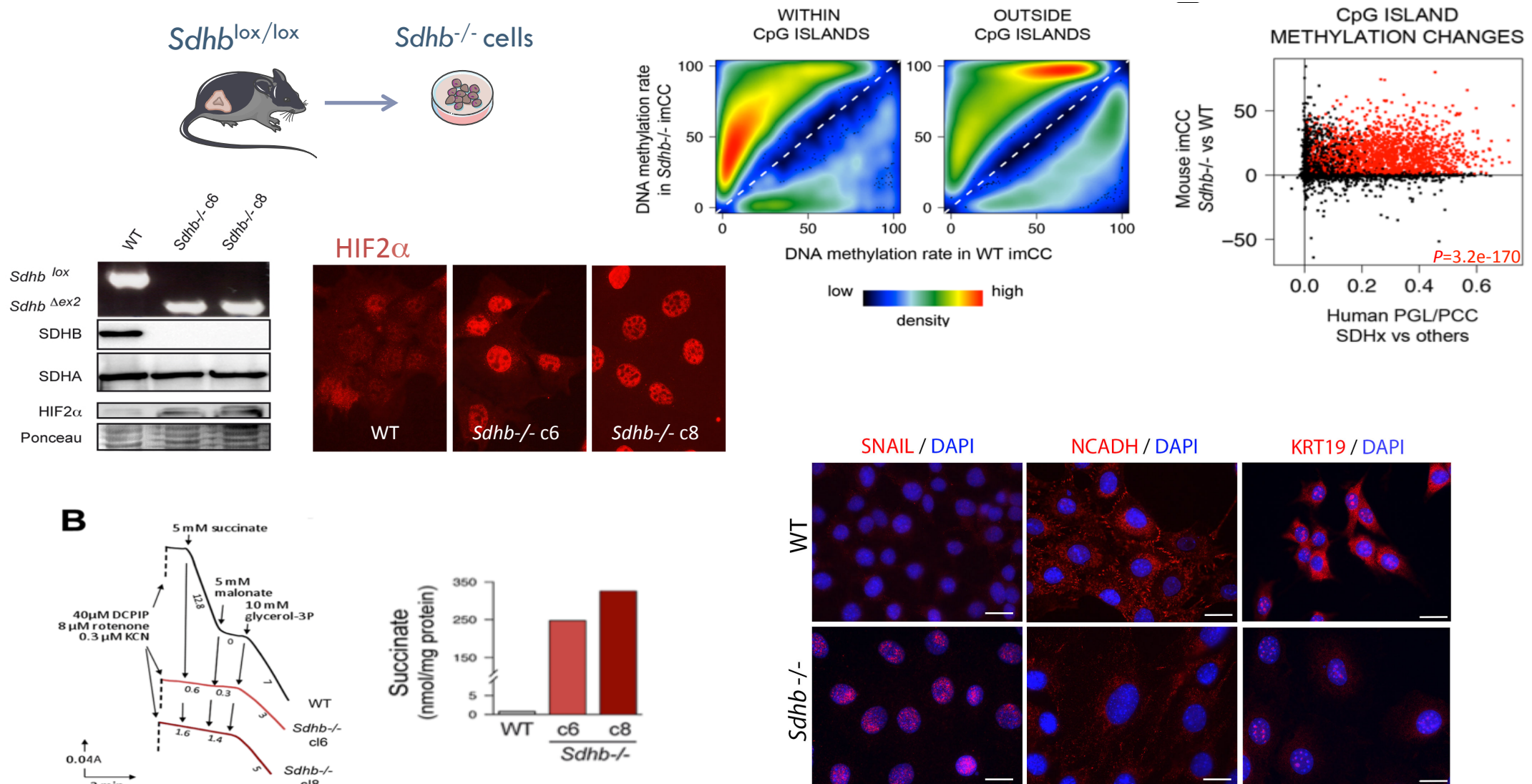
The DNA hypermethylator phenotype is stronger in *SDHB*-mutated tumors

- Comparison of DNA methylation and gene expression changes in M1 tumors with different *SDHx* mutations:



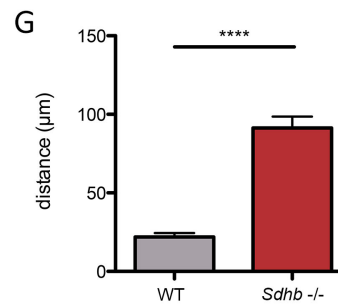
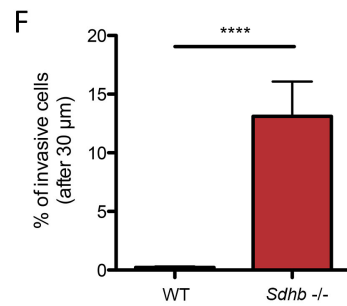
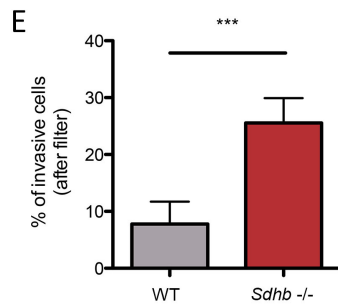
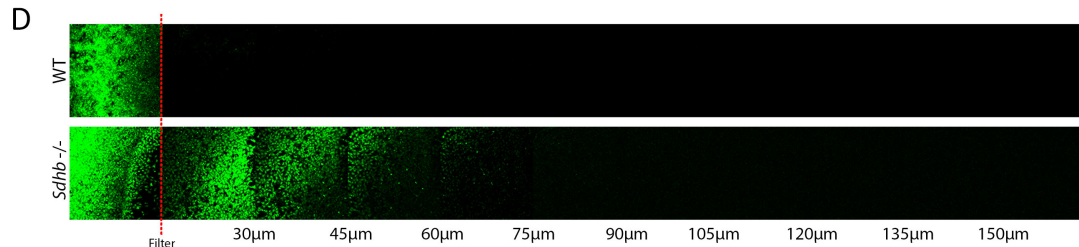
-> A stronger hypermethylator phenotype and associated gene silencing may explain the particular aggressiveness of *SDHB*-mutated tumors.

Generation and validation of *Sdhb*^{-/-} mouse chromaffin cells

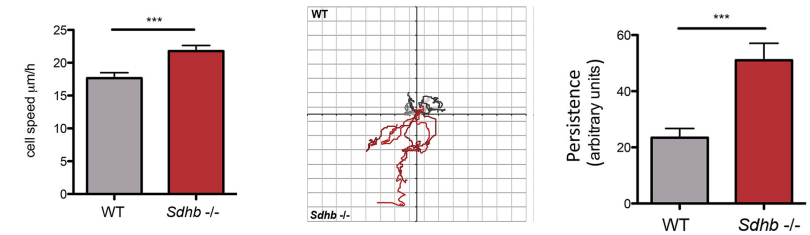
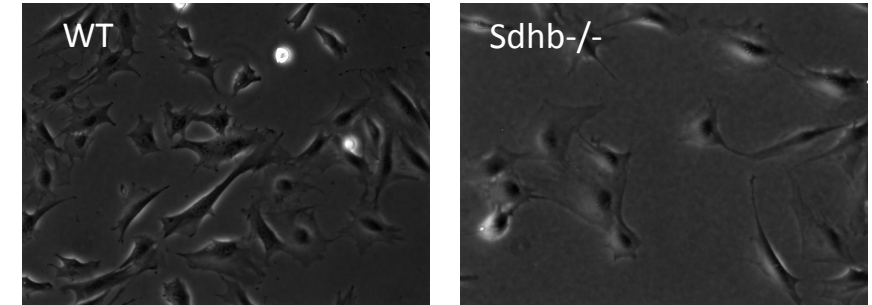


Metastatic hallmarks of *Sdhb*^{-/-} cells

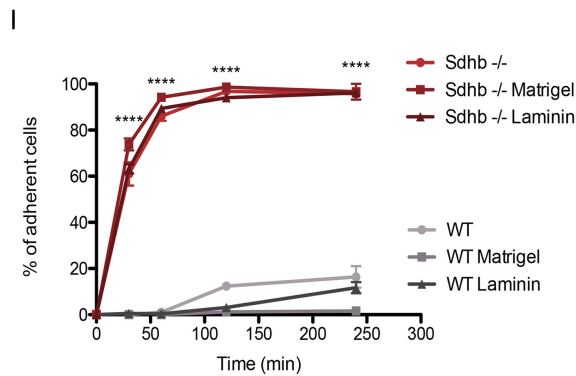
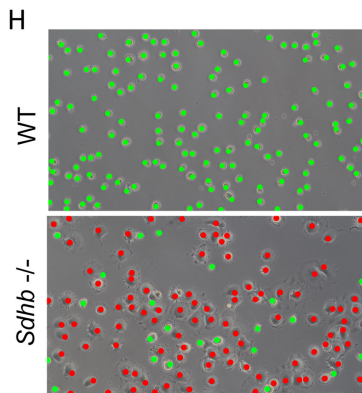
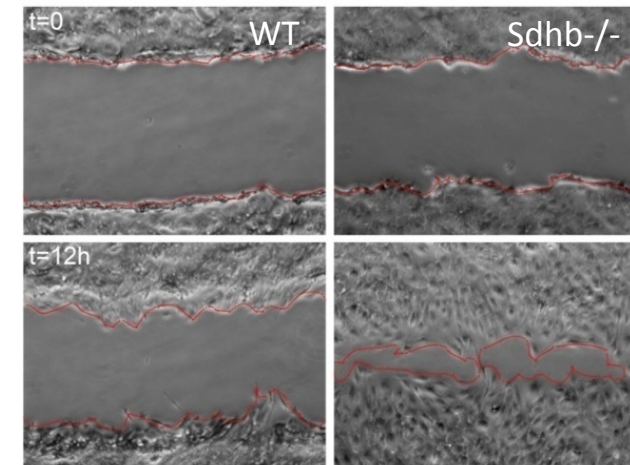
Invasion



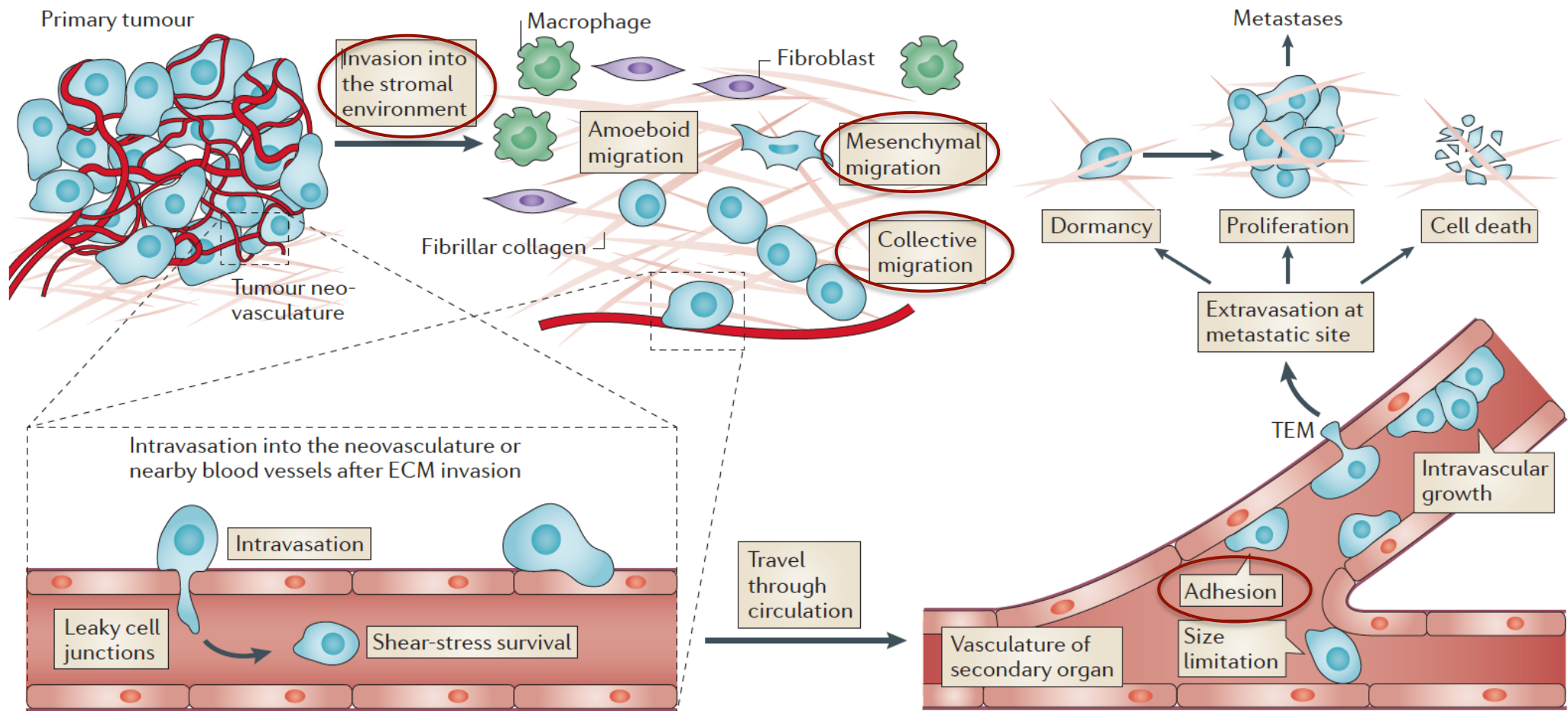
Individual migration (Single cell tracking)



Collective migration (wound scratch)

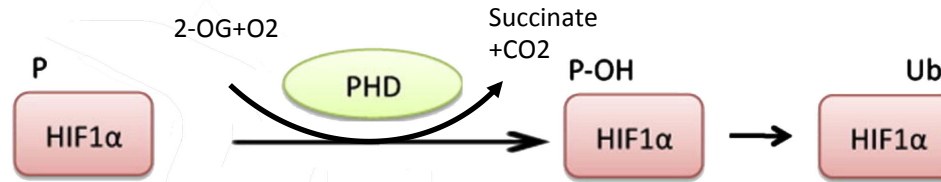


The different steps of metastatic dissemination

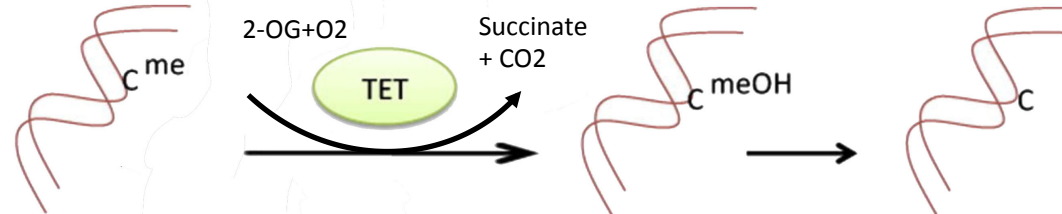


Linking *SDH* to *méthylation* : 2-OG dependent dioxygenases

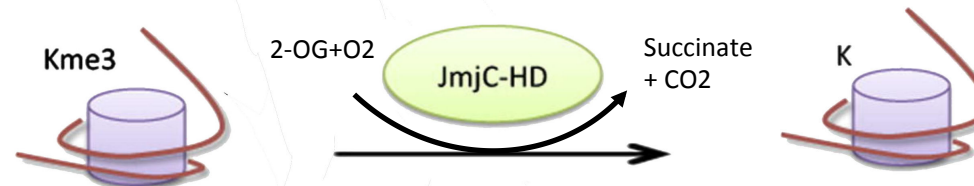
HIF-prolylhydroxylases



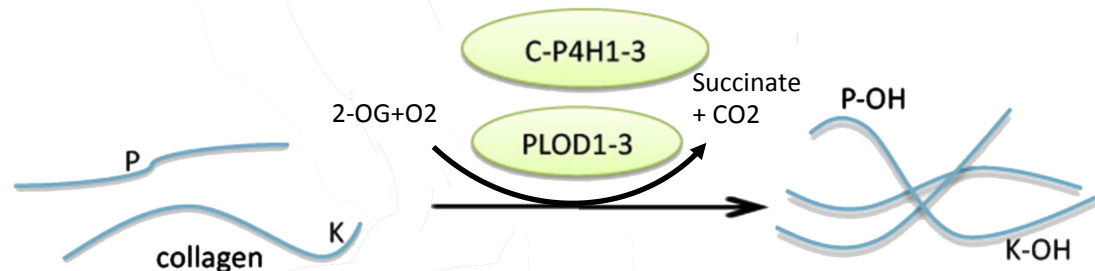
DNA demethylases (TET)



Histones demethylases (JmjC)

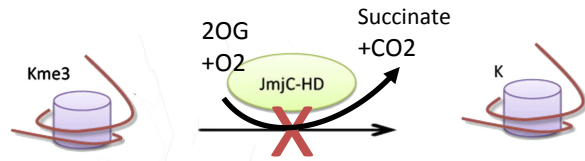


Collagene prolylhydroxylases

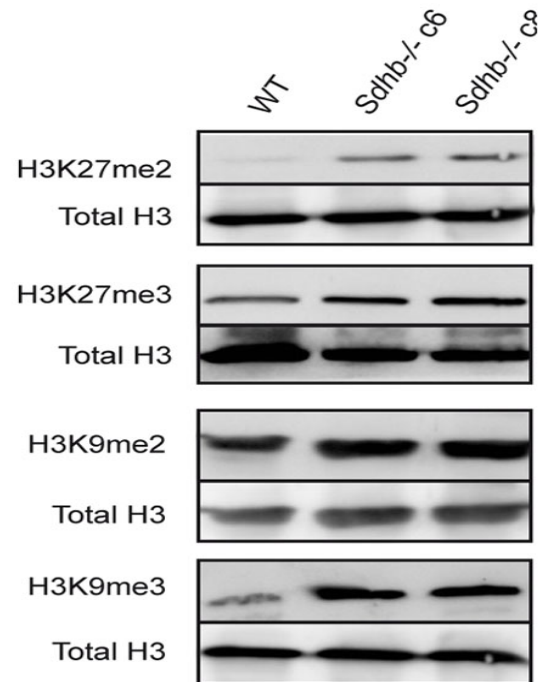
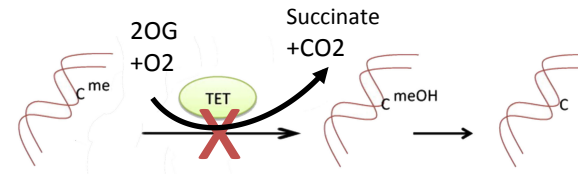


DNA and histone methylation in *Sdhb*^{-/-} mouse chromaffin cells

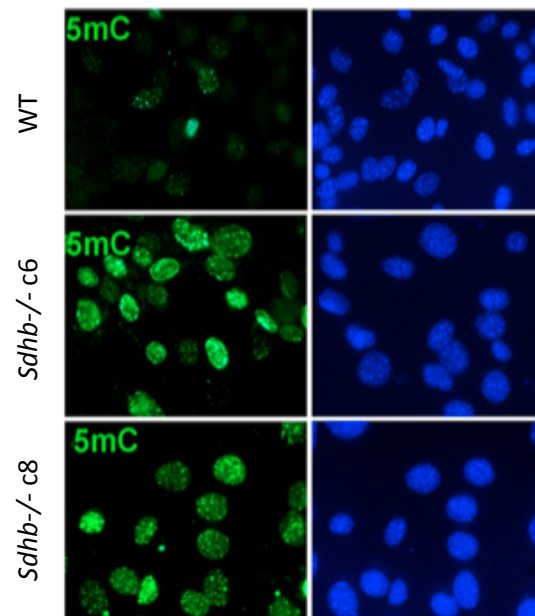
Histone methylation in *Sdhb*^{-/-} imCC



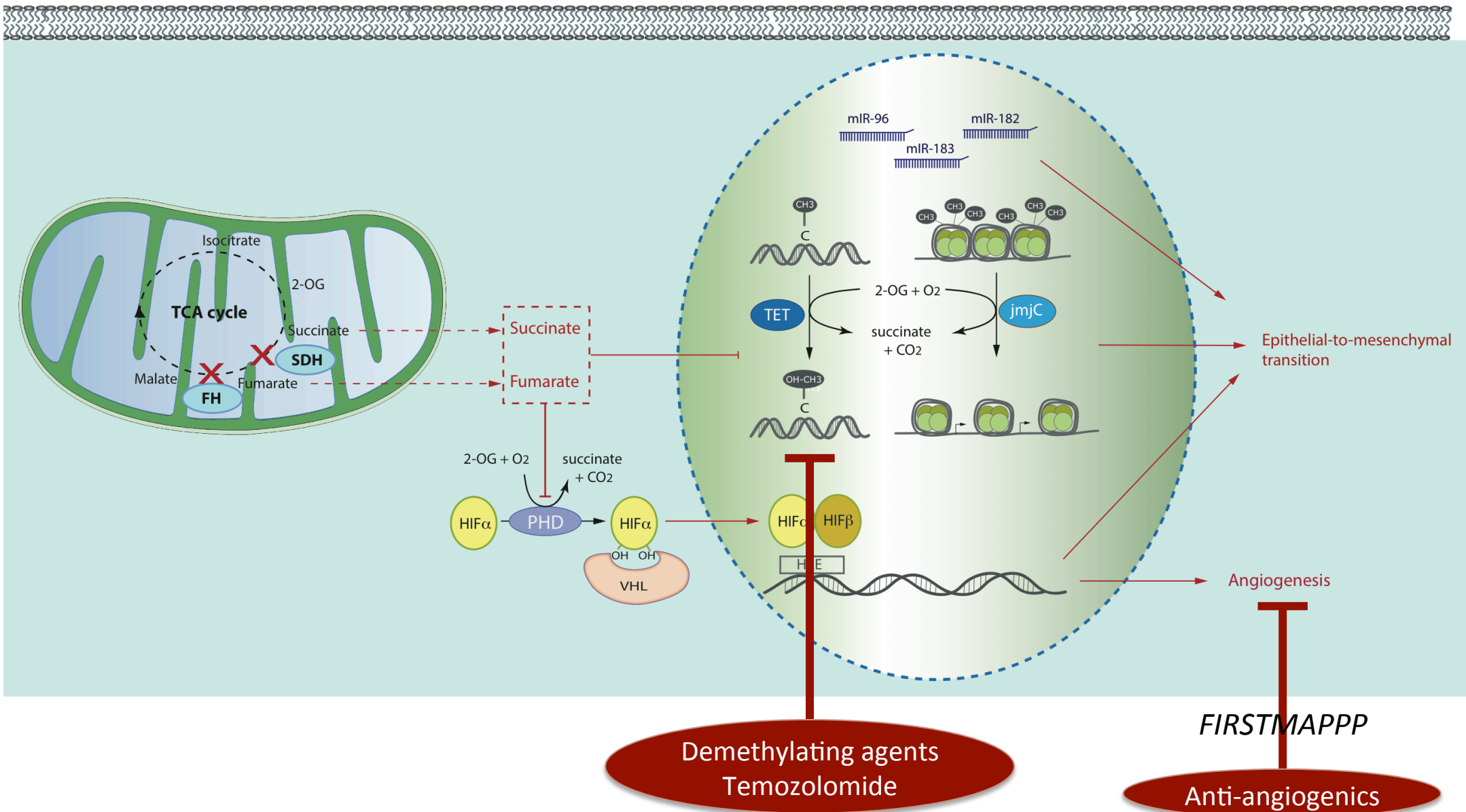
5-methylcytosine in *Sdhb*^{-/-} imCC



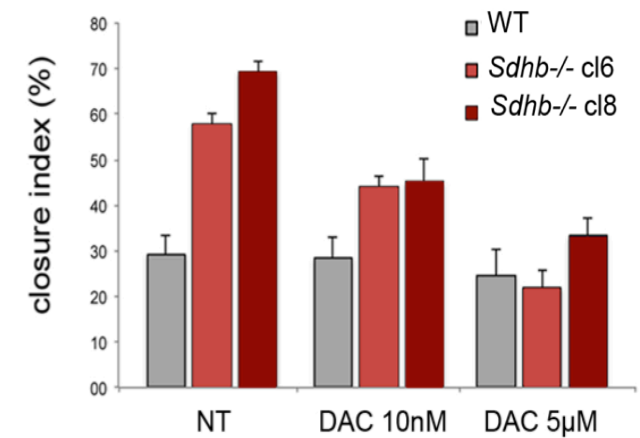
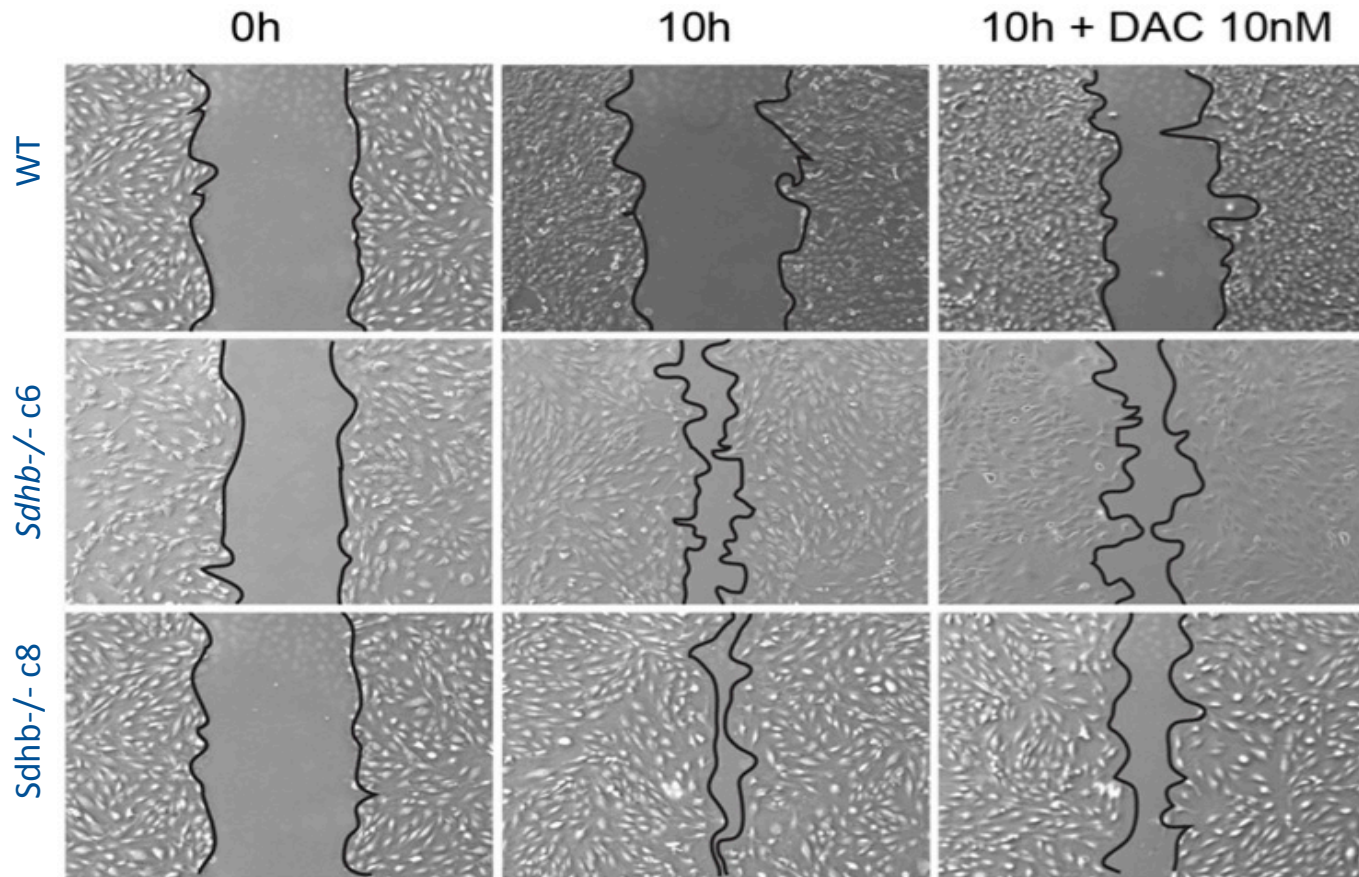
Standard medium



Therapeutic targets

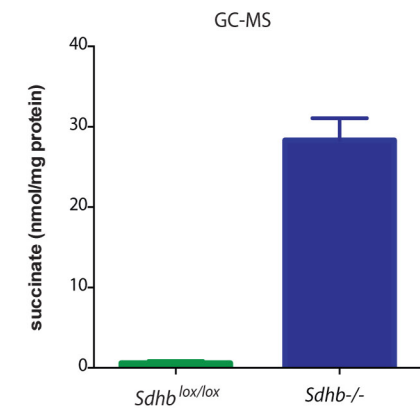
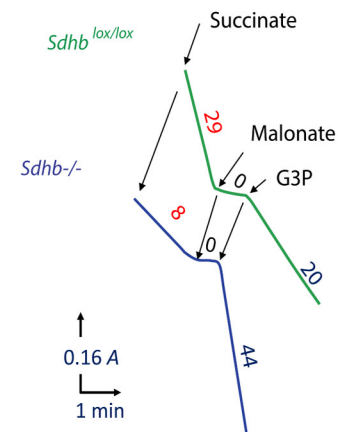
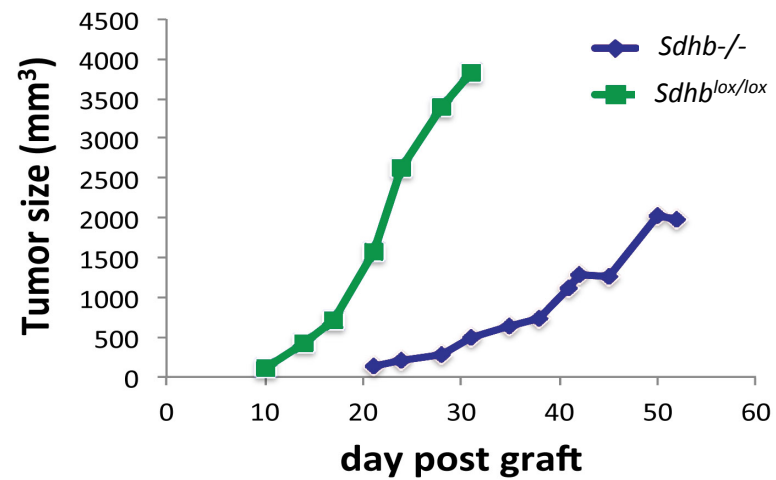
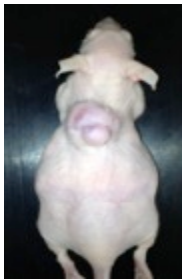


Reversion of the migratory phenotype by DNA demethylation



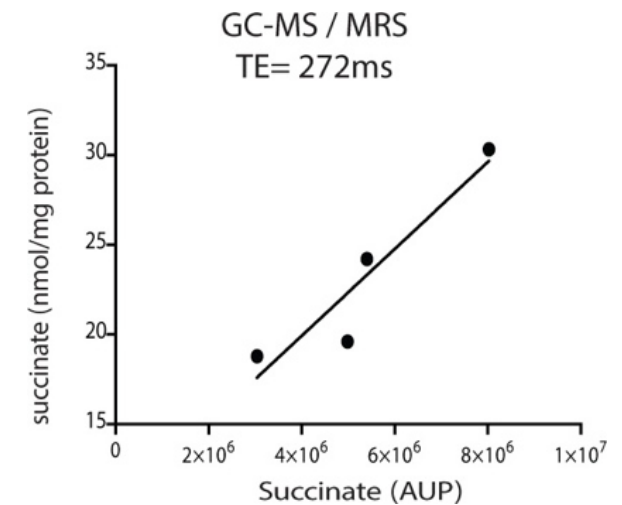
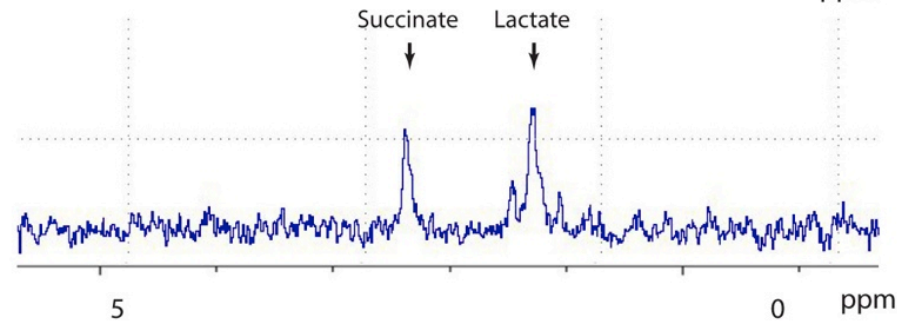
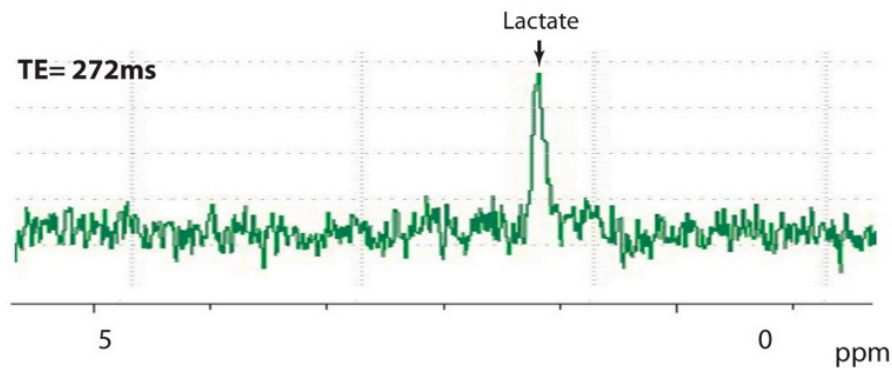
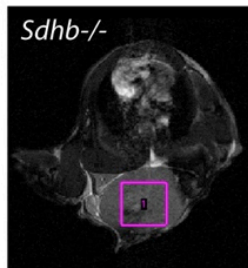
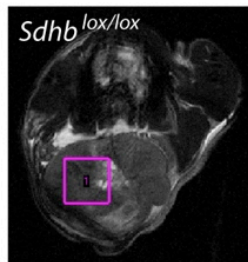
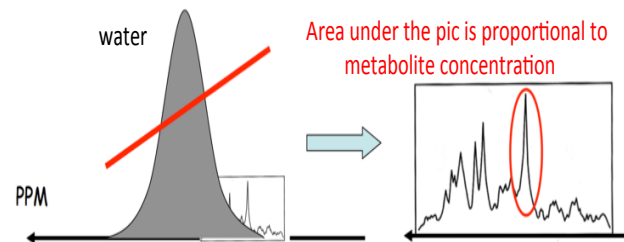
- > *Sdhb*^{-/-} cells do not proliferate fast but display a migratory phenotype.
- > Reversal of this phenotype by DAC suggests the use of demethylating agents to treat these aggressive tumors.

Allograft model of *Sdhb*^{-/-} imCC



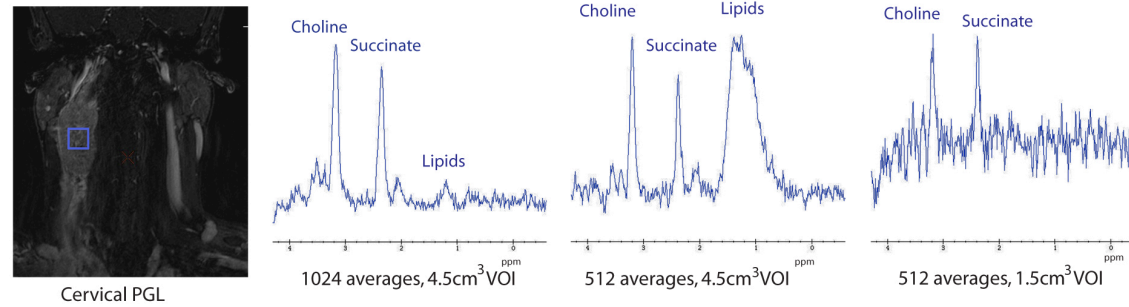
Magnetic resonance spectroscopy (^1H -MRS)

Theory

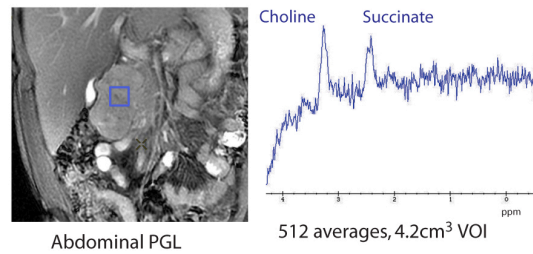


SUCCES in humans at 3T: an SDHB mutation

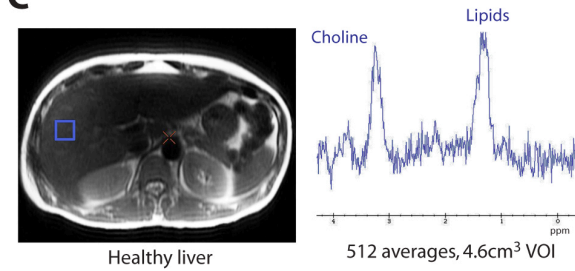
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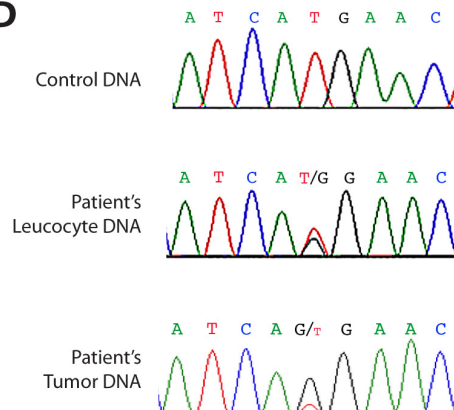
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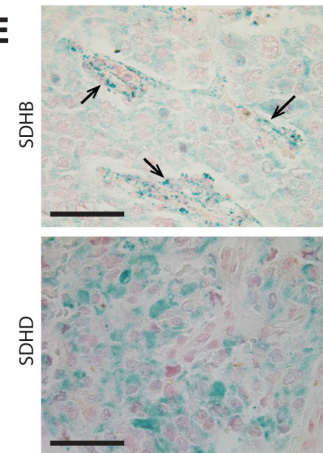
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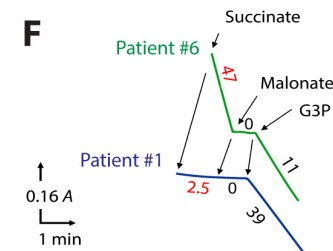
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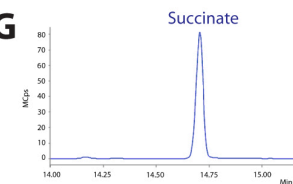
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F

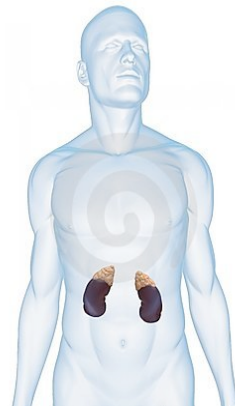
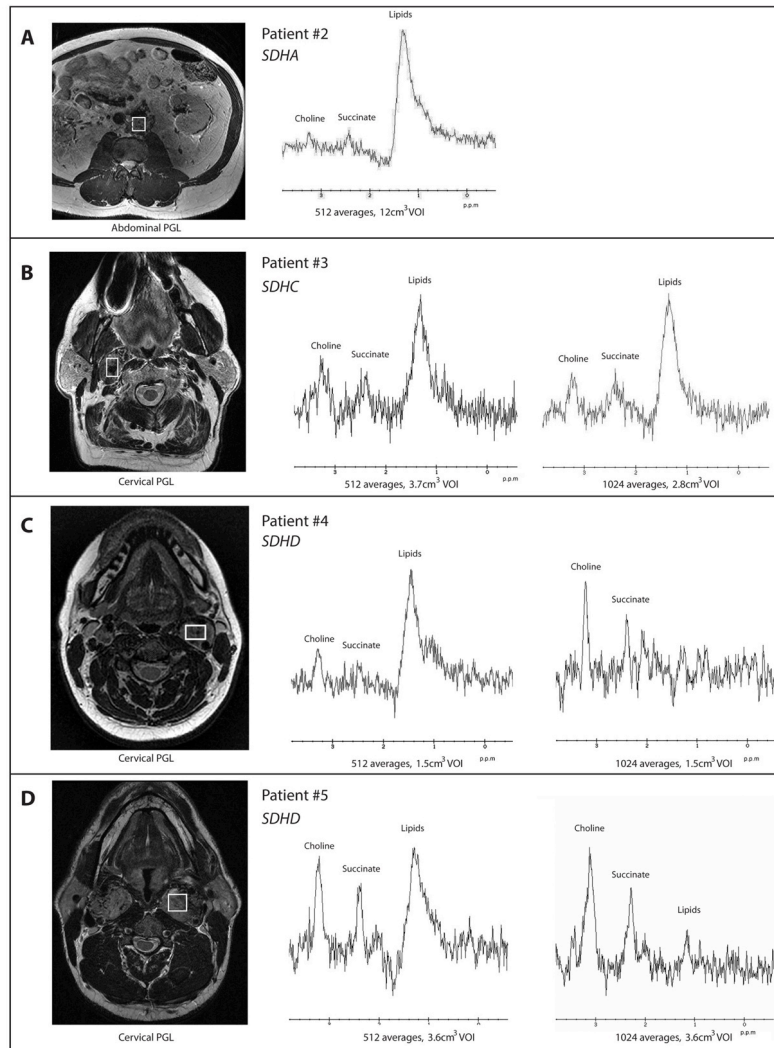


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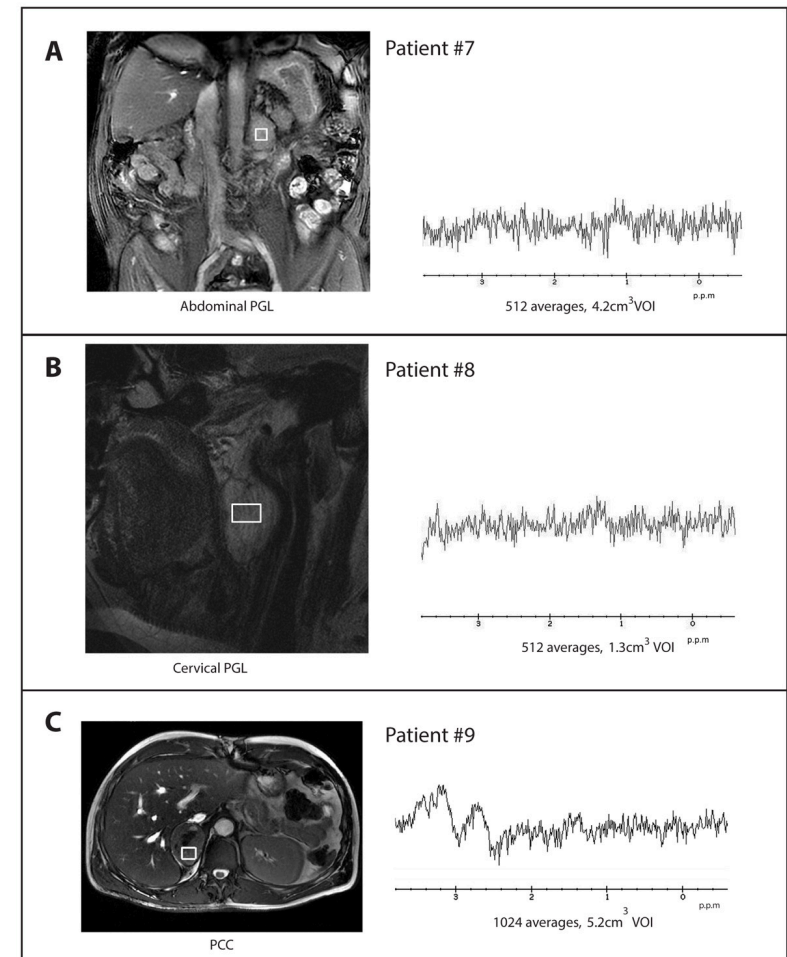


^1H -MRS in humans at 3T

SDHx mutations



no SDHx mutation



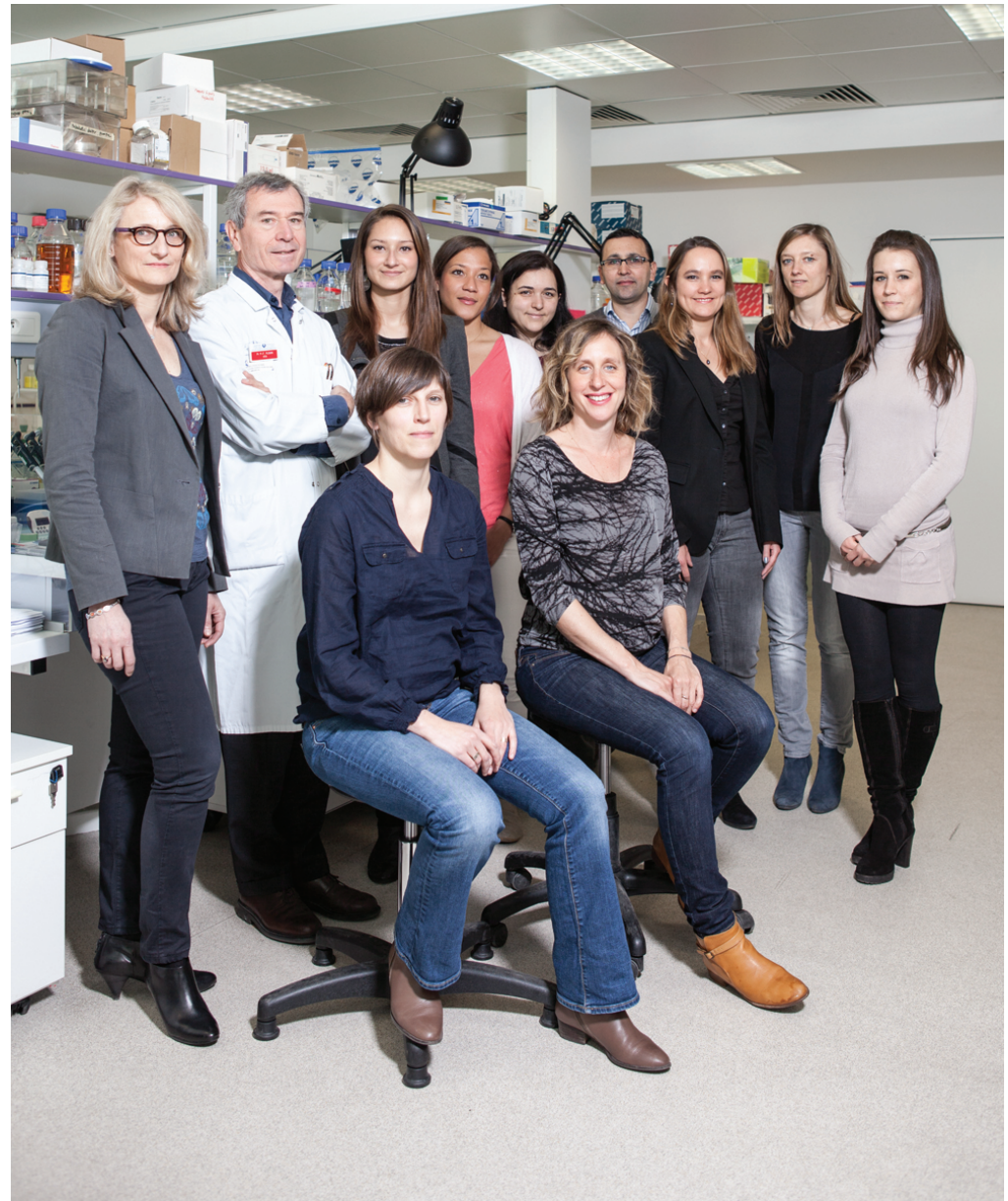
Acknowledgements

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Anne-Paule Gimenez-Roqueplo, PU-PH
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Céline Lorient, PhD
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