

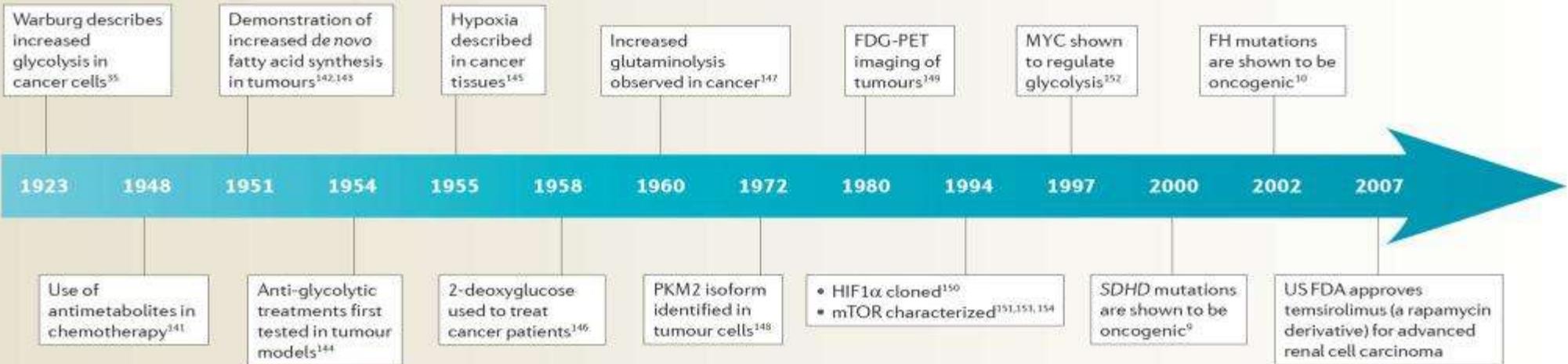


Imagerie moléculaire par IRM – Application à l'imagerie des altérations génétiques

Charlotte Lussey-Lepoutre
PARCC Inserm U970, Paris, France
Module technologies avancées
Bichat, le 9 Décembre 2015

Cancer et métabolisme : une vieille histoire...

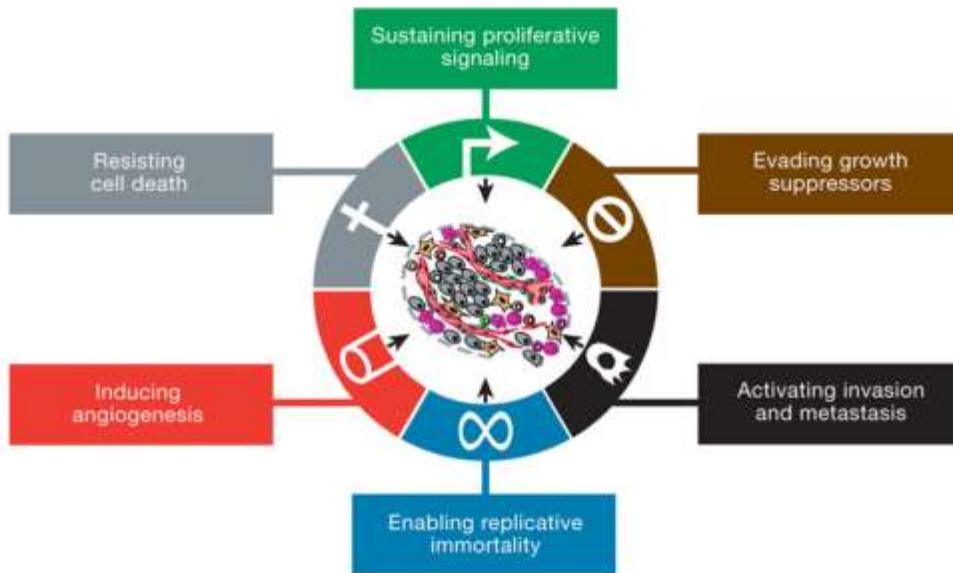
Timeline | Some important advances in understanding and targeting tumour metabolism



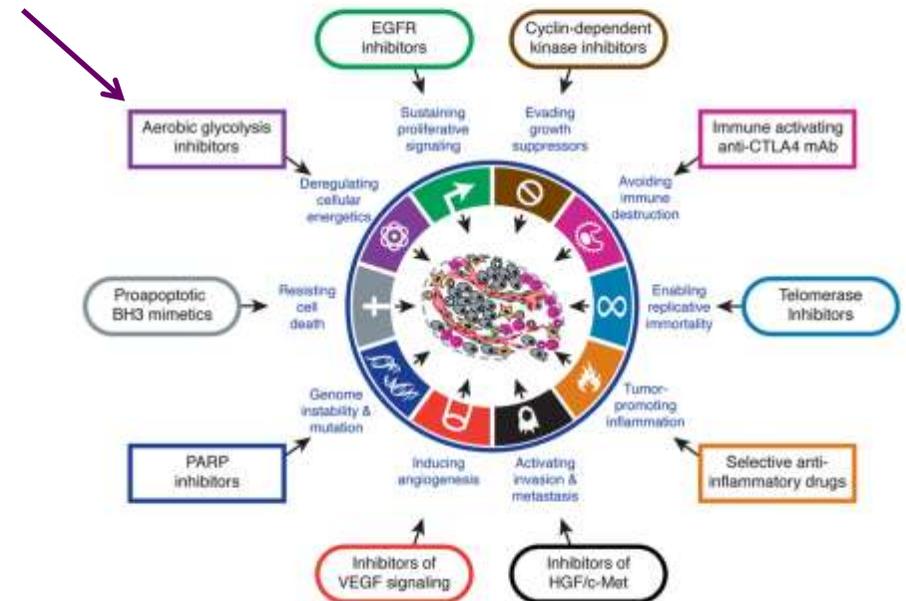
FDA, Food and Drug Administration; FDG-PET, [18F]-fluorodeoxyglucose positron emission tomography; FH, fumarate hydratase; HIF1 α , hypoxia inducible factor 1 α ; PKM2, pyruvate kinase isozyme M2; SDHD, succinate dehydrogenase complex, subunit D, integral membrane protein.

« Hallmarks » du Cancer d'après Hanahan et Weinberg

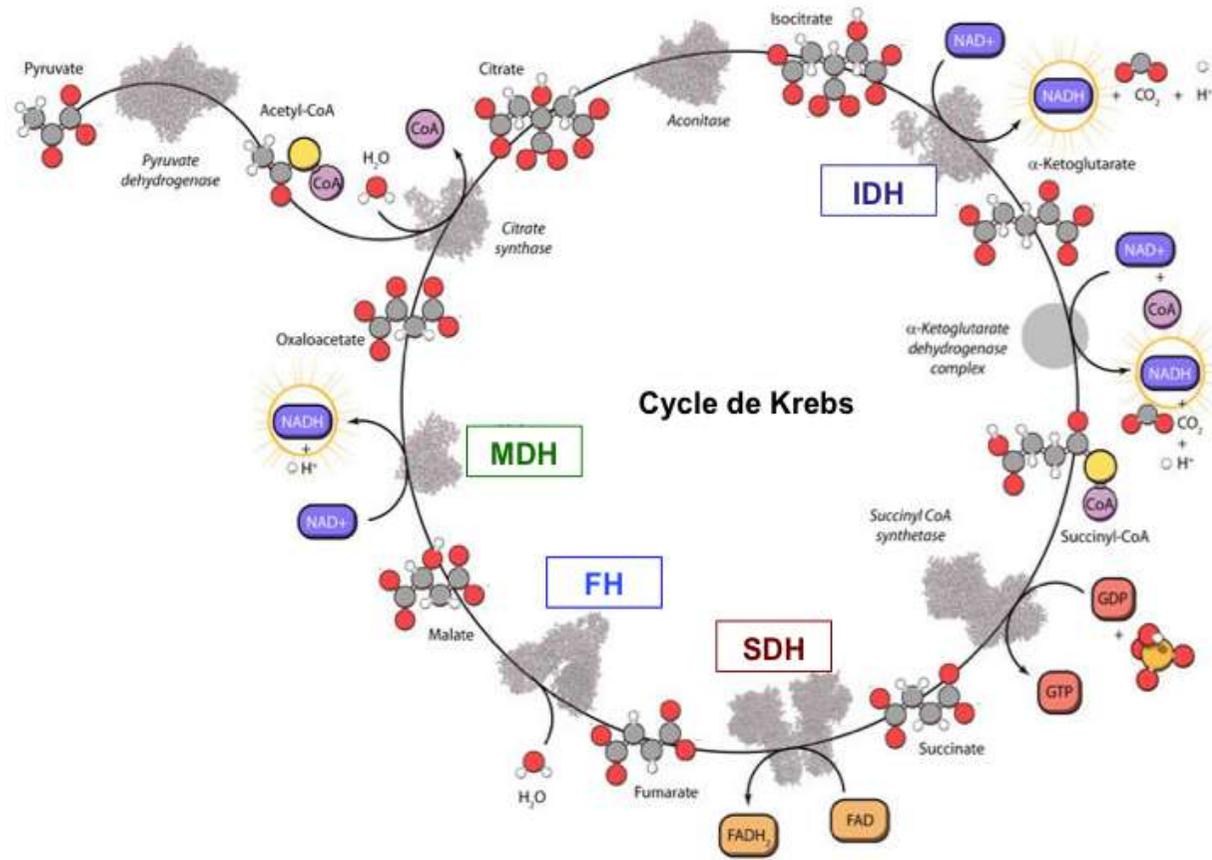
Hallmarks of Cancer in 2000



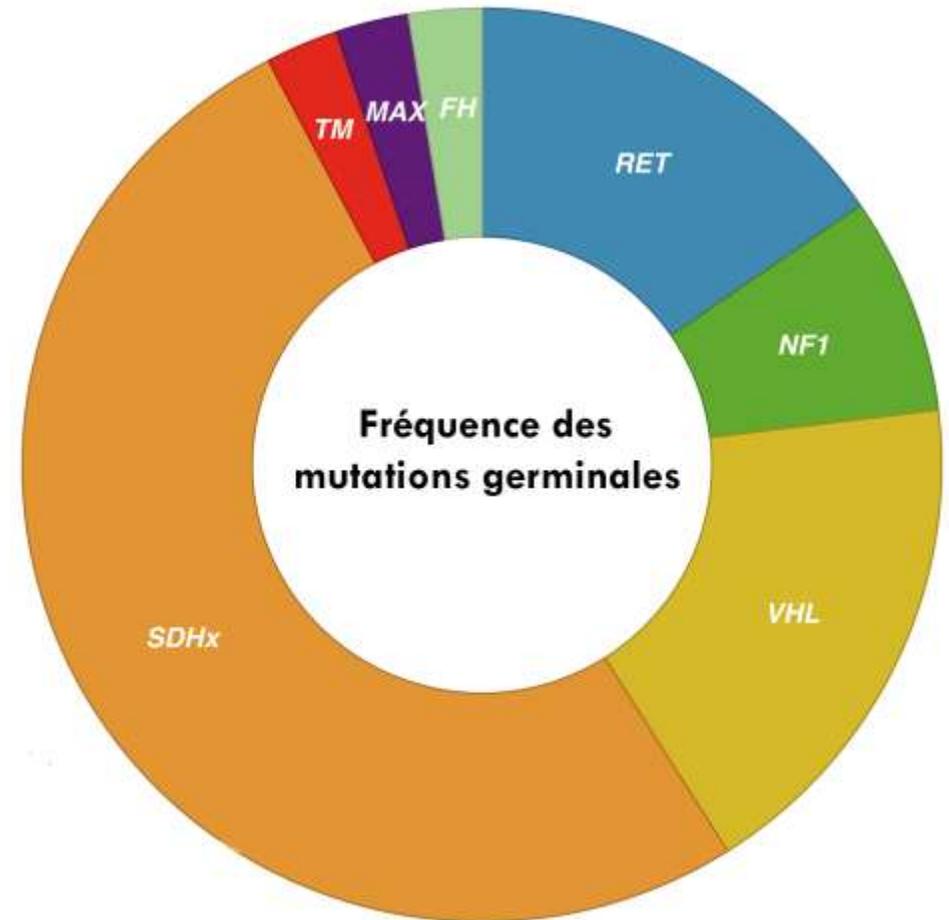
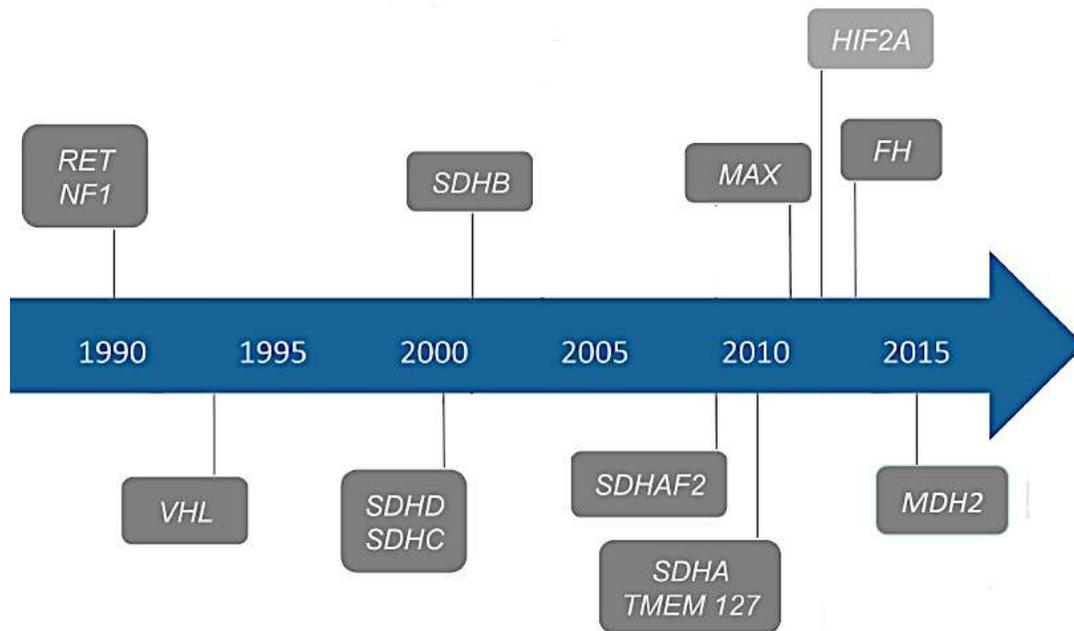
Hallmarks of Cancer and therapeutic targets in 2011



Métabolisme et mutations dans le cancer

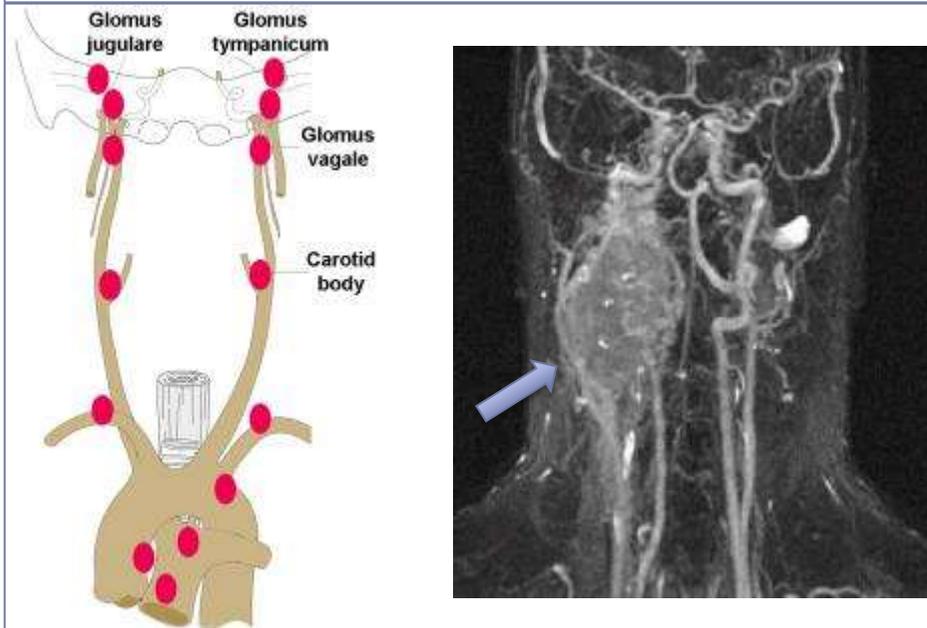


- 40% prédisposition génétique
- 13 gènes de susceptibilité

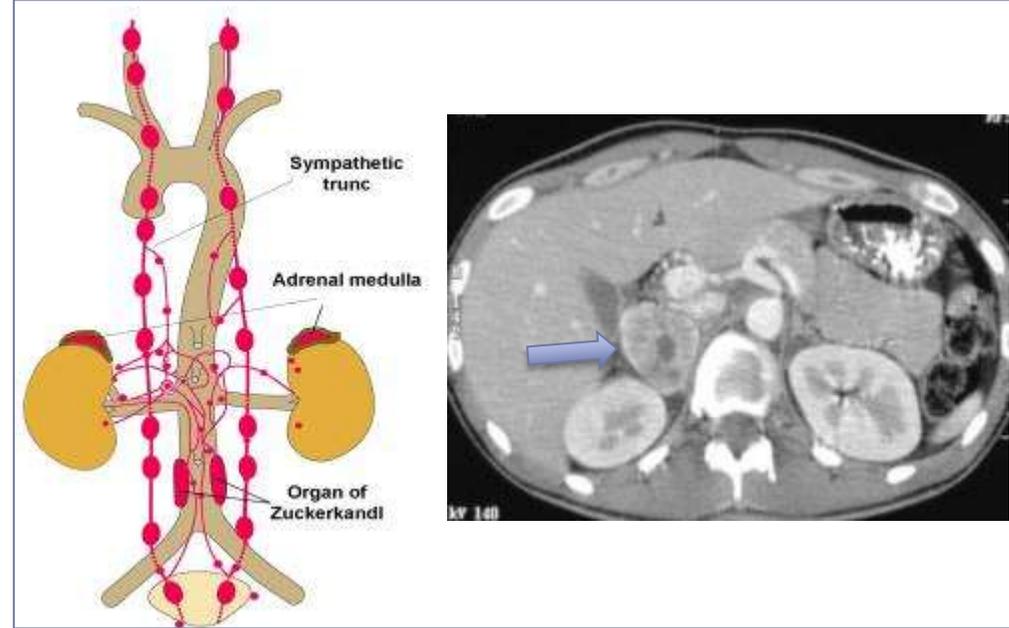


Phéochromocytome/Paragangliome : définition

PGL parasymphathiques



PGL sympathiques

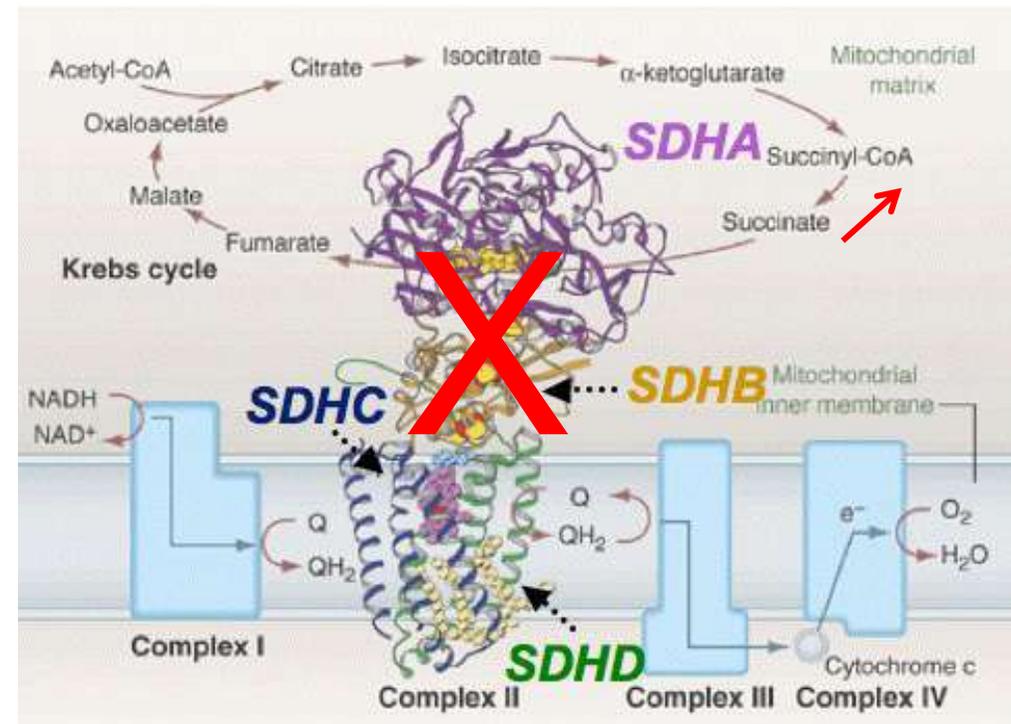
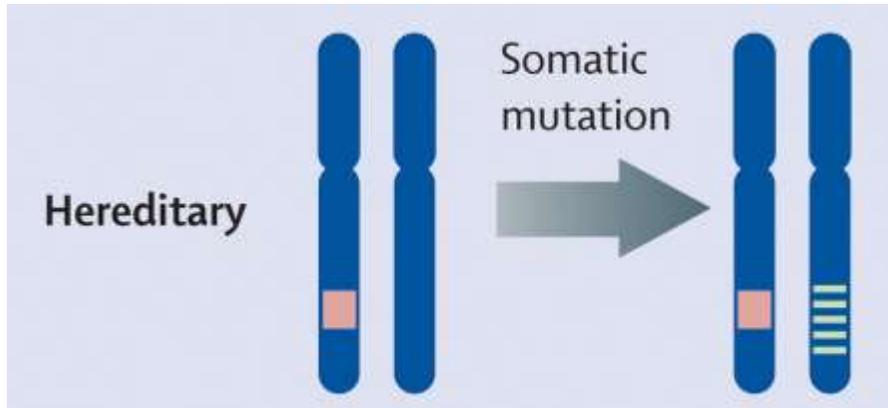


- ✓ Tumeurs neuroendocrines rares (1/30000)
- ✓ Hypervascularisées
- ✓ Fonctionnelles (sympathiques) ou non (parasympathiques)
- ✓ Phéochromocytome (PCC) = paragangliome (PGL) de la glande médullosurrénale

Succinate déshydrogénase

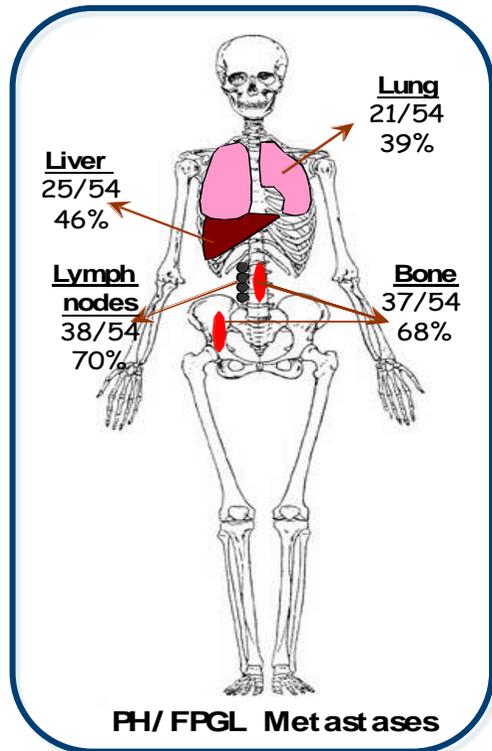
Gènes suppresseurs de tumeurs

➤ Le modèle de Knudson

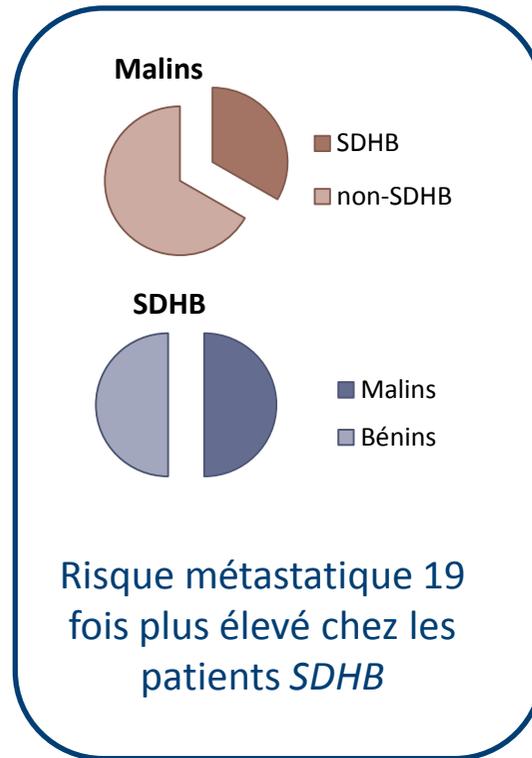


SDHB : malignité et mauvais pronostic

Malignancy: 10-15% of cases

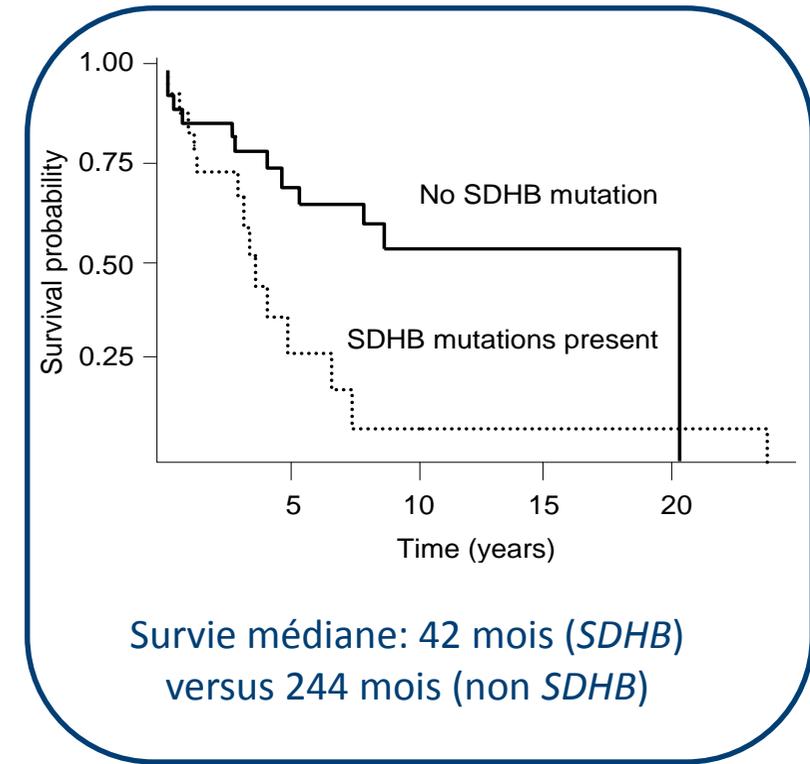


Progression Métastatique



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

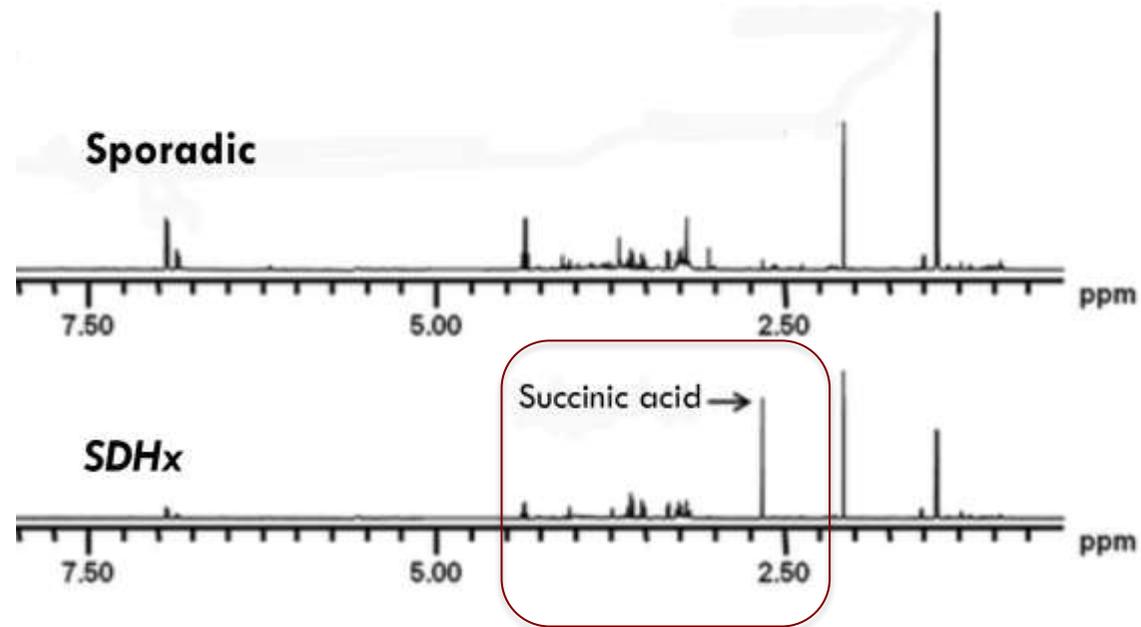
Survie des PGL/PCC malins



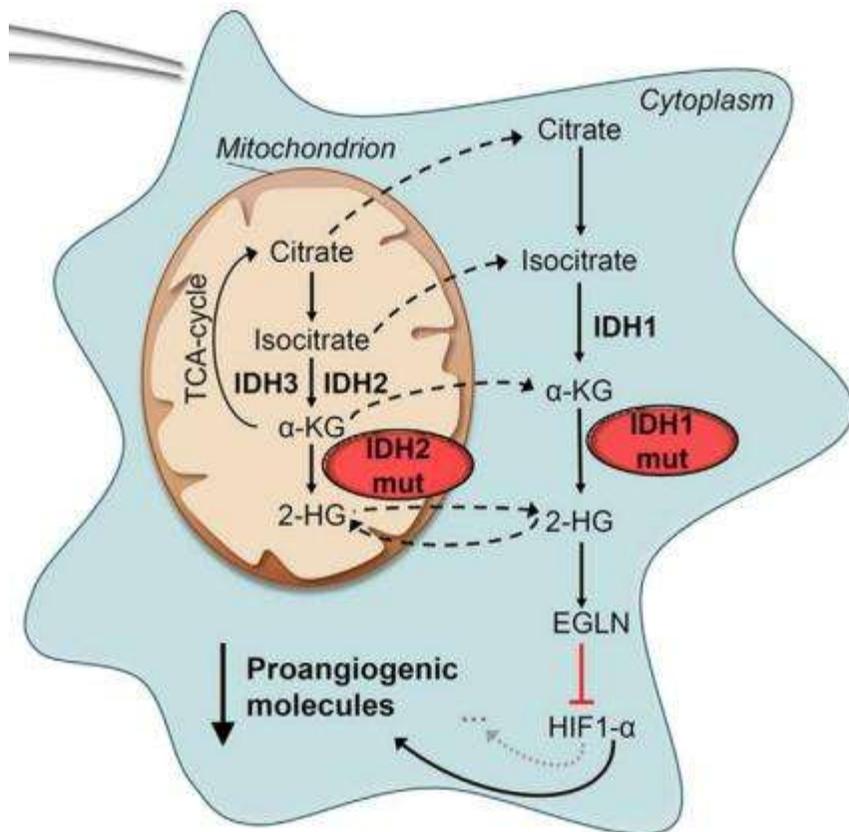
Gimenez-Roqueplo et al., Cancer Res 2003
Amar et al., J Clin Oncol 2005
Amar et al., J Clin Endocrinol Metab 2007

SDH inactivation in PPGL

L'accumulation de succinate détectée in vitro dans la tumeur est un marqueur spécifique de mutation SDHx

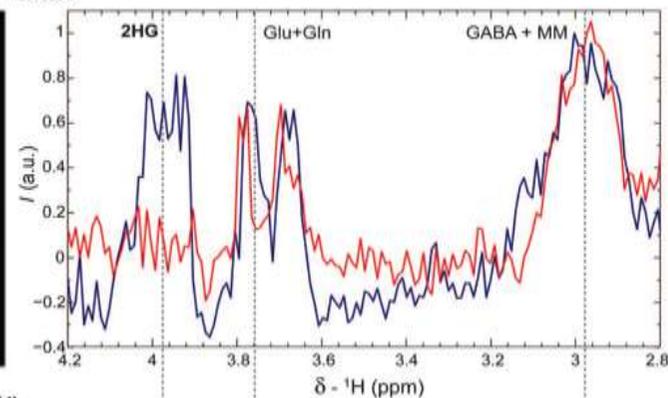
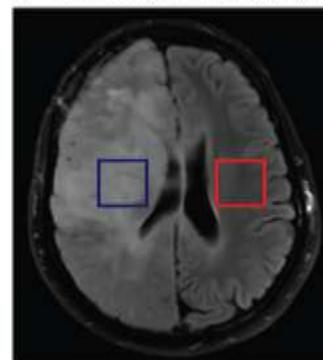


Adapted from Rao et al, J Clin Endocrinol Metab 2015

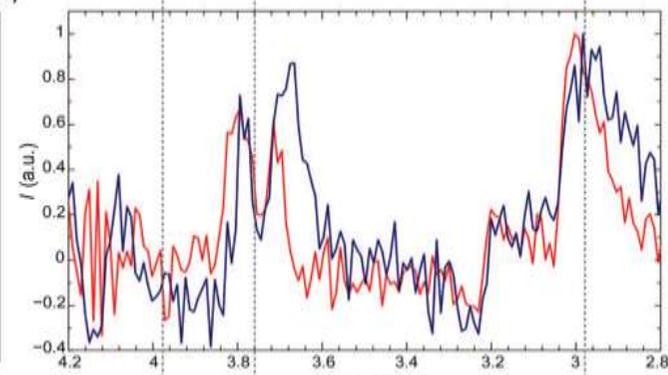
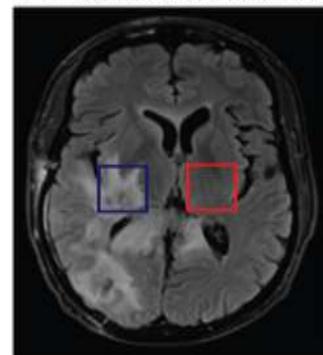


Kickingereder et al, *Sci Rep* 2015

A Secondary glioblastoma (*IDH1*_{R132H})

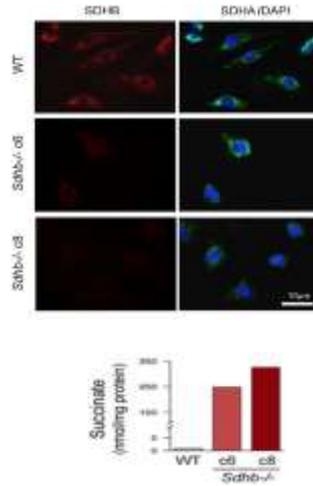
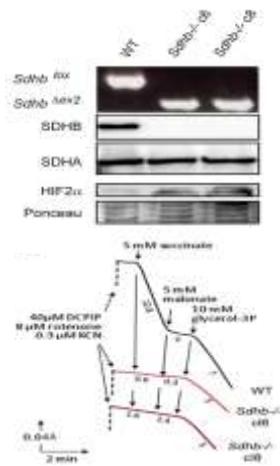
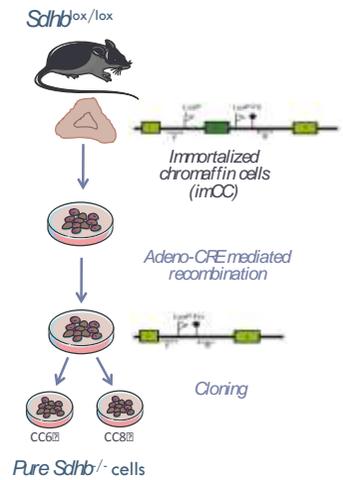


B Primary glioblastoma (wt-*IDH1*)

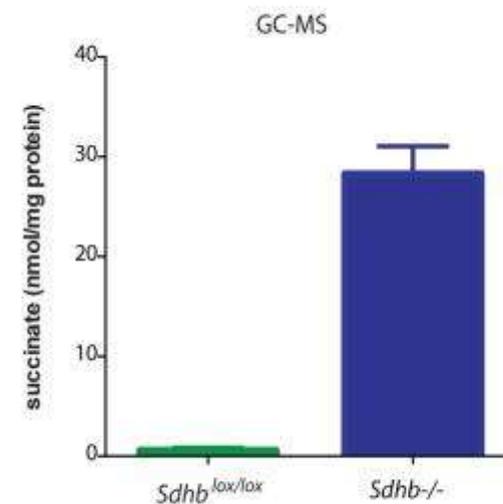
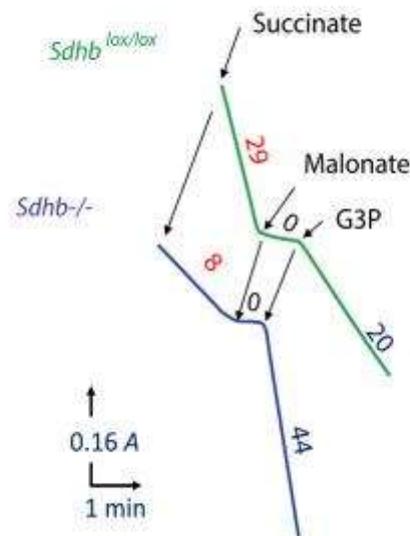
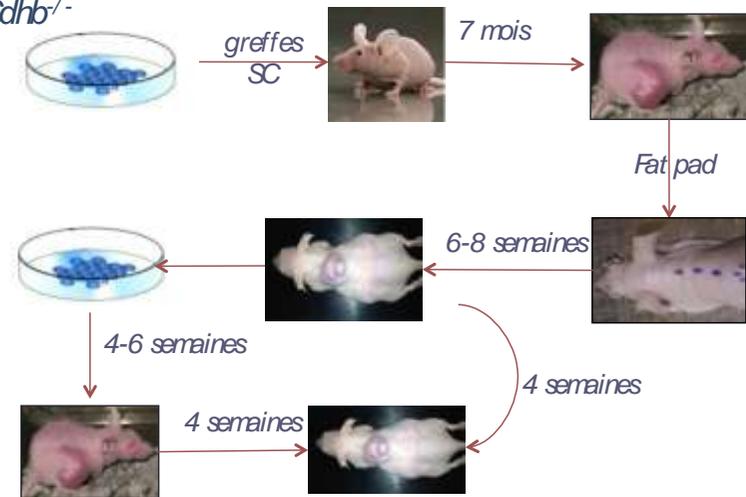


Andronesi et al, *Sci Transl Med* 2012
Choi et al, *Nat Med* 2012

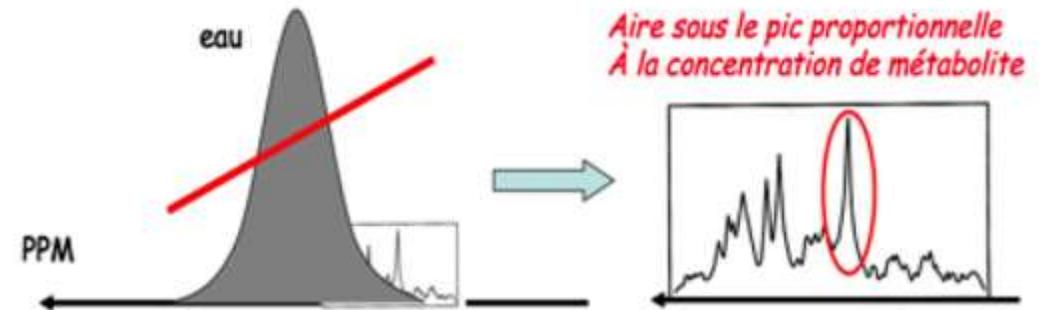
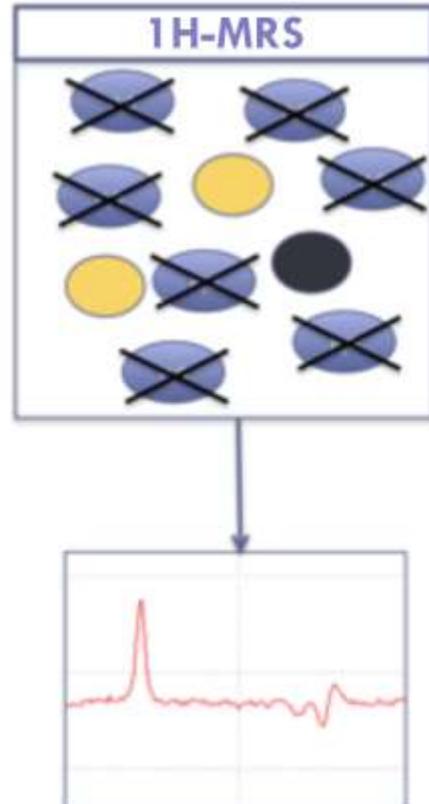
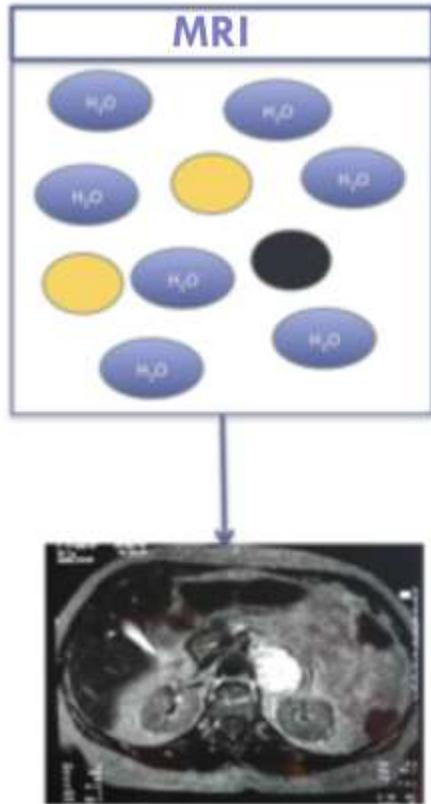
Modèle murin d'allogreffe de cellules chromaffines *Sdhb*^{-/-} (imCC)



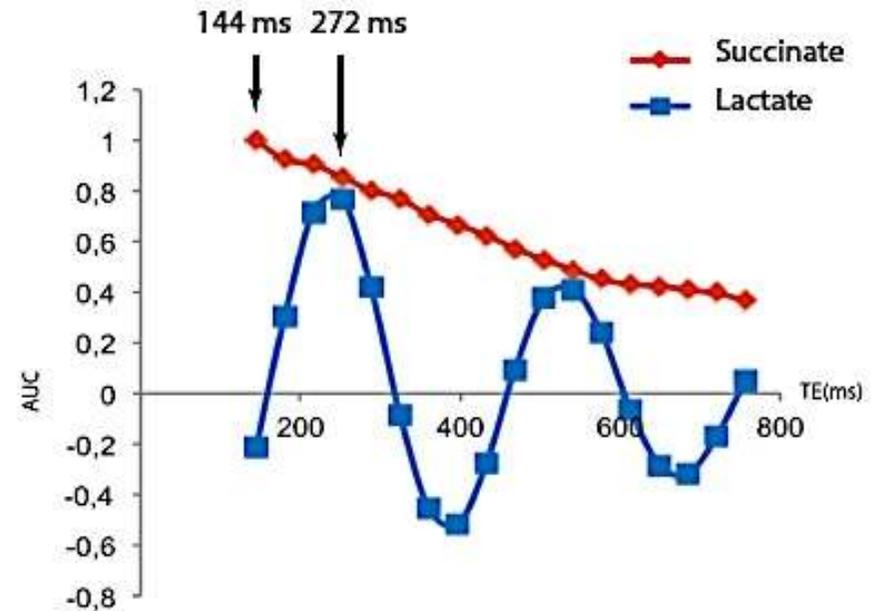
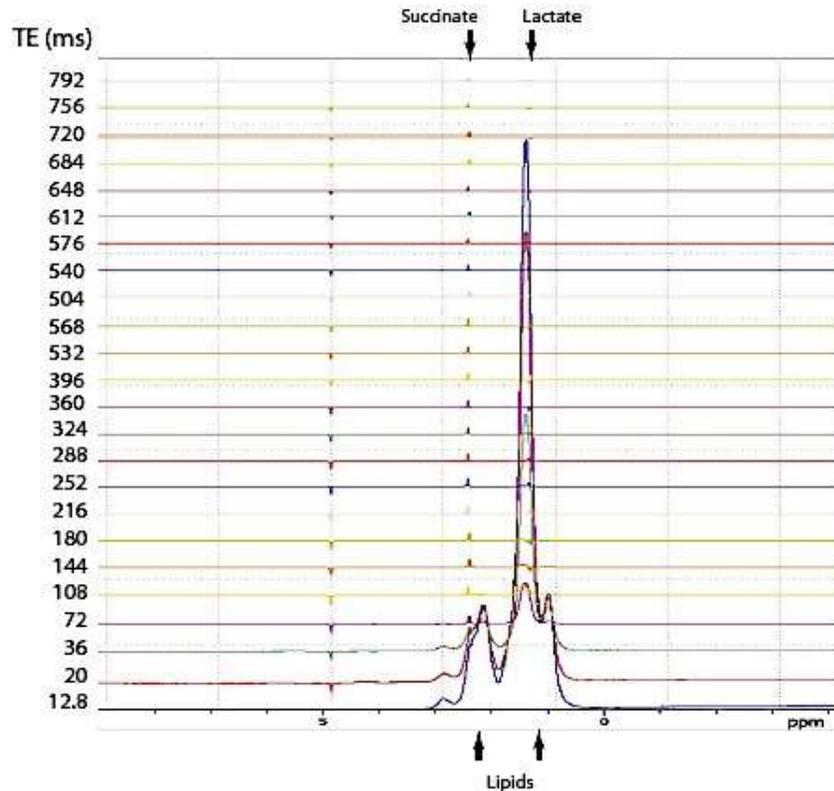
imCC Sdhb^{lox/lox}
imCC Sdhb^{-/-}



Spectroscopie par résonance magnétique (^1H -SRM)

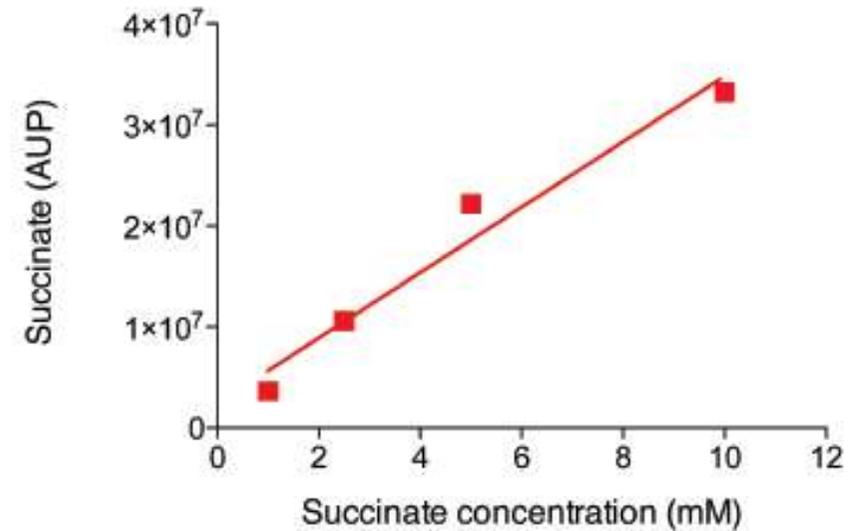
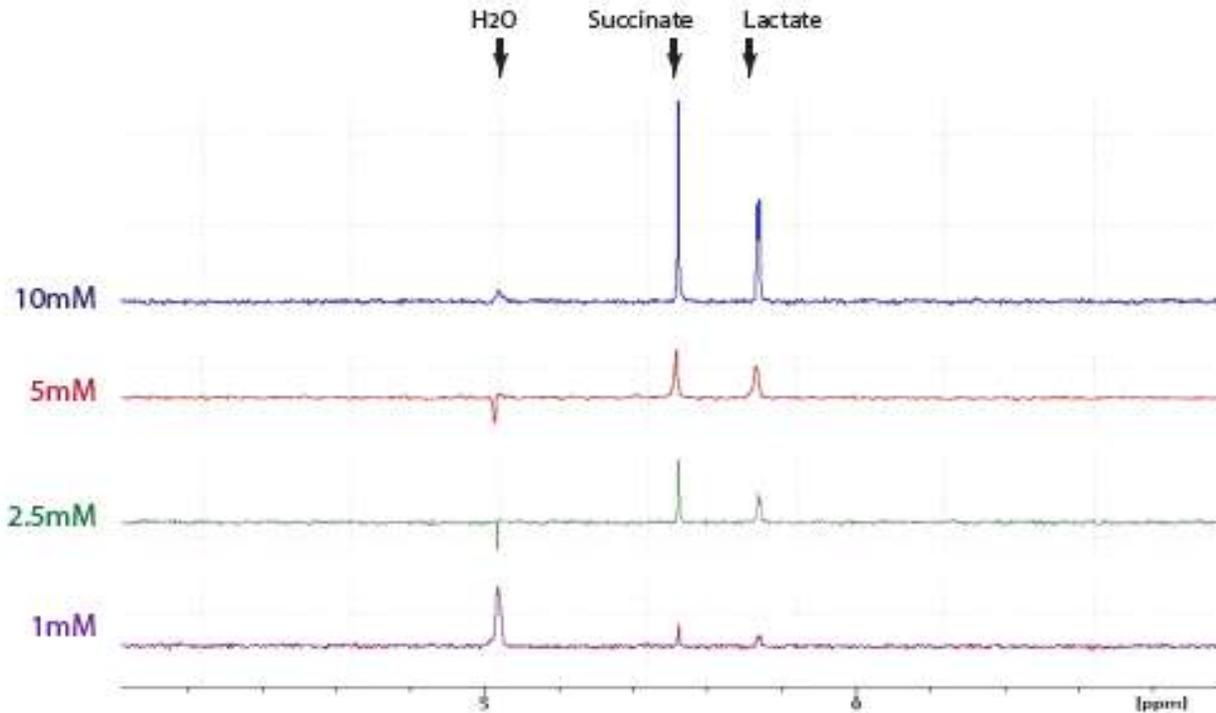


^1H -SRM : mise au point sur l'IRM 4,7 T



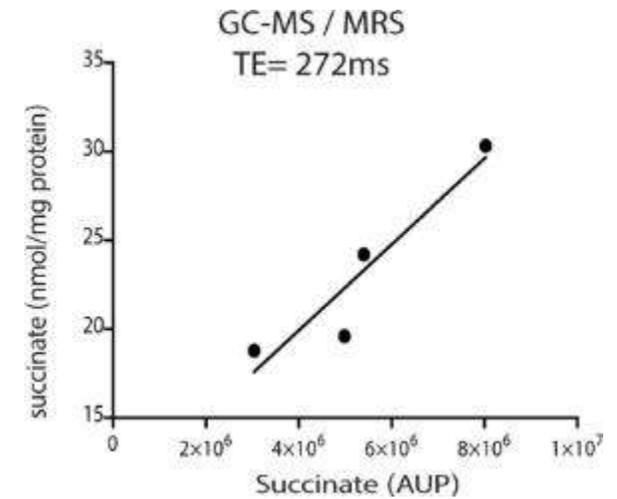
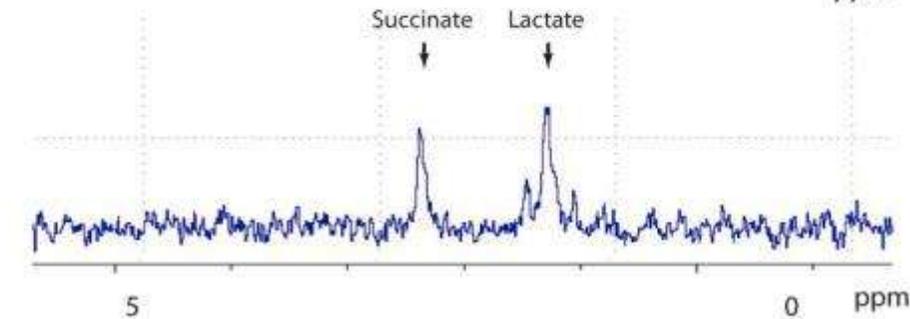
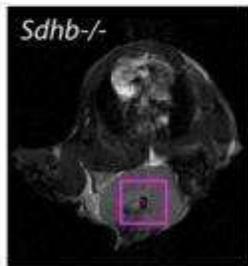
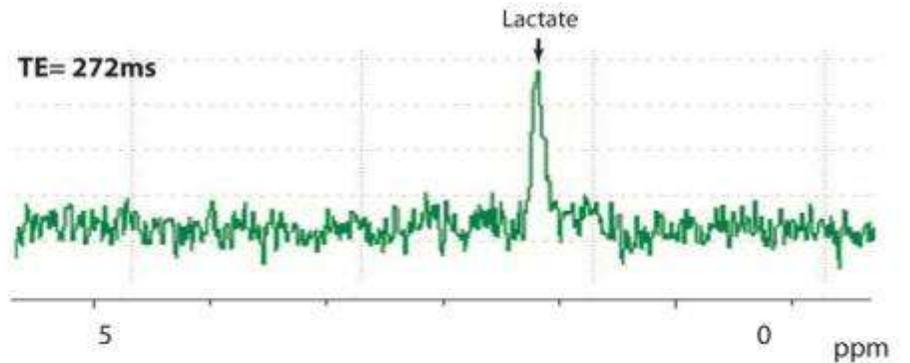
- Séquence PRESS asymétrique
- TE 144 et 272 ms

^1H -SRM : mise au point sur l'IRM 4,7 T



➤ Corrélation AUP/ concentration de succinate *in vitro*

4.7 Tesla MRI

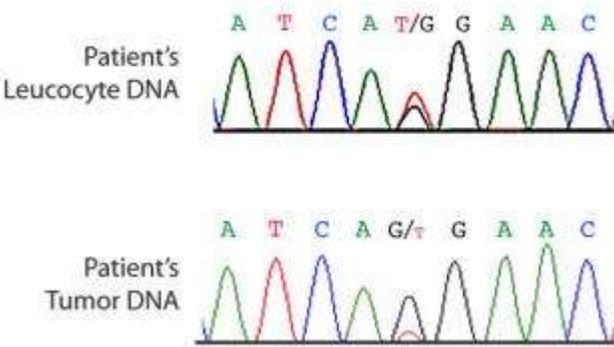


SUCCES (*SUCC*inate Estimation by Spectroscopy)



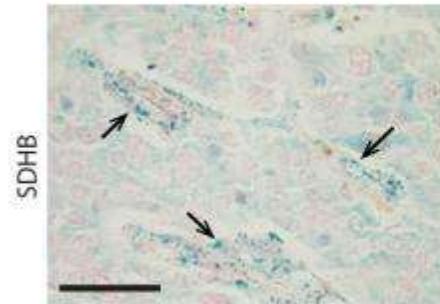
$^1\text{H-SRM SUCCES}$: validation d'une mutation SDHB

Analyses génétiques

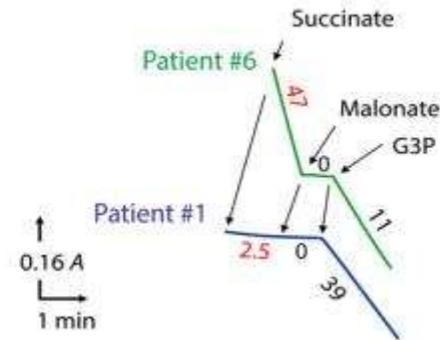


c.740T>G, p.Met247Arg (VUS)

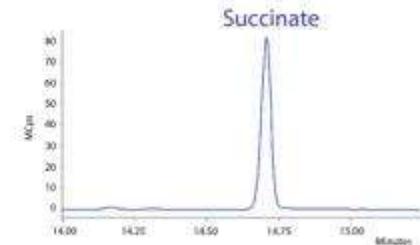
IHC SDHB



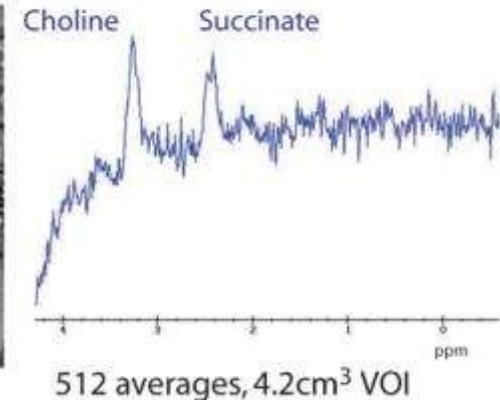
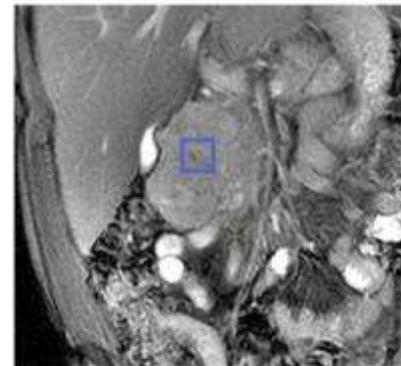
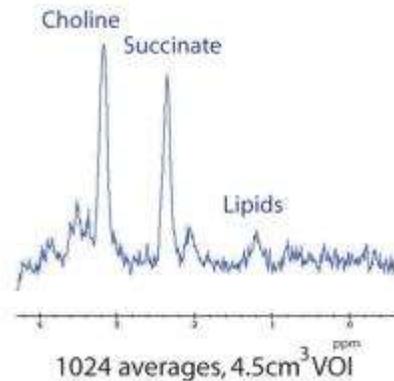
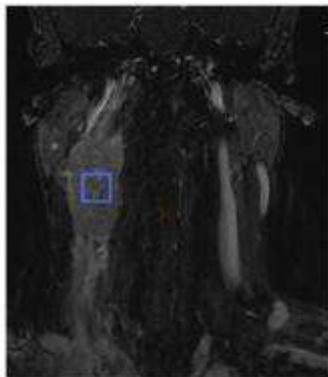
Activité SDH



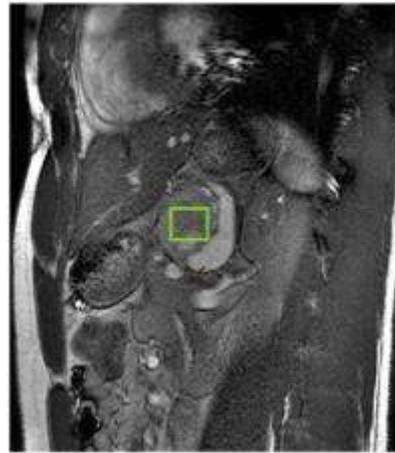
Spectrometrie de masse



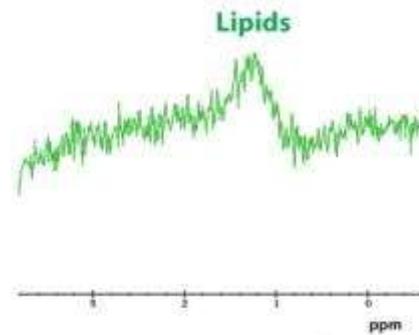
$^1\text{H-SRM - SUCCES}$



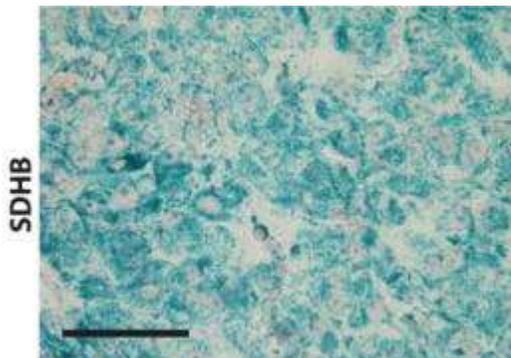
^1H -SRM SUCCES : pas de mutation SDHx



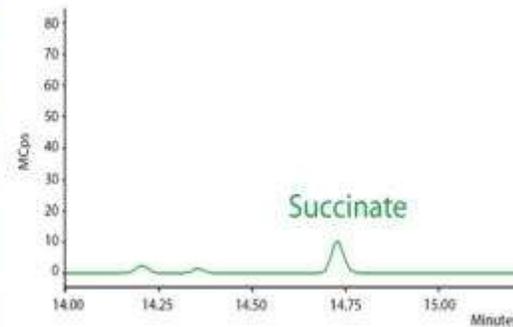
PCC



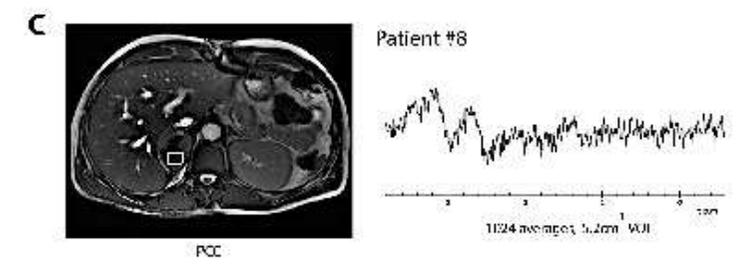
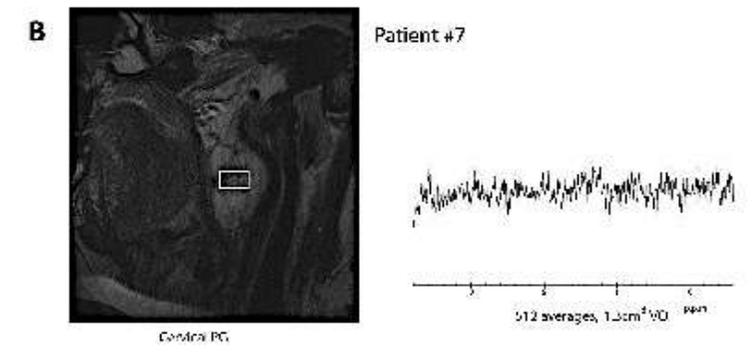
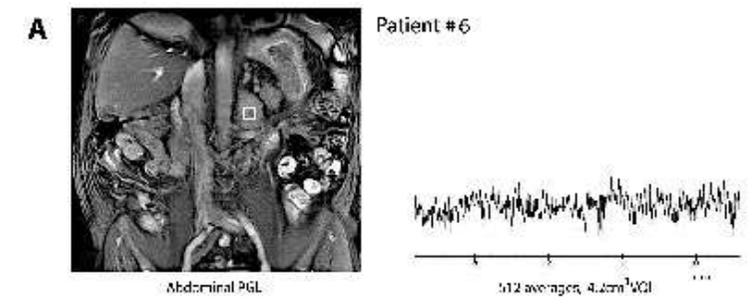
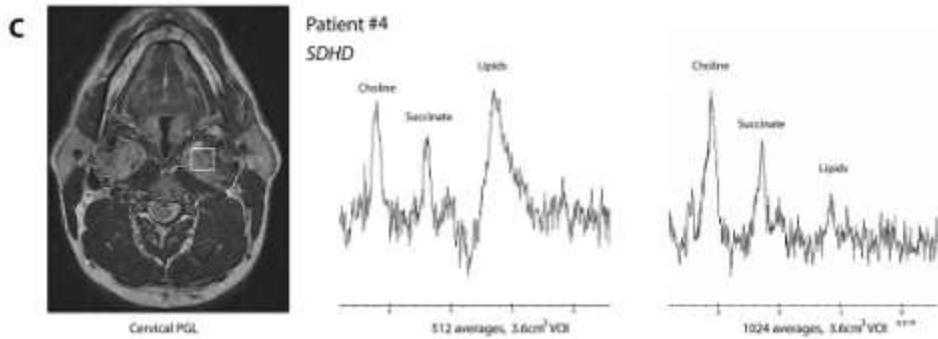
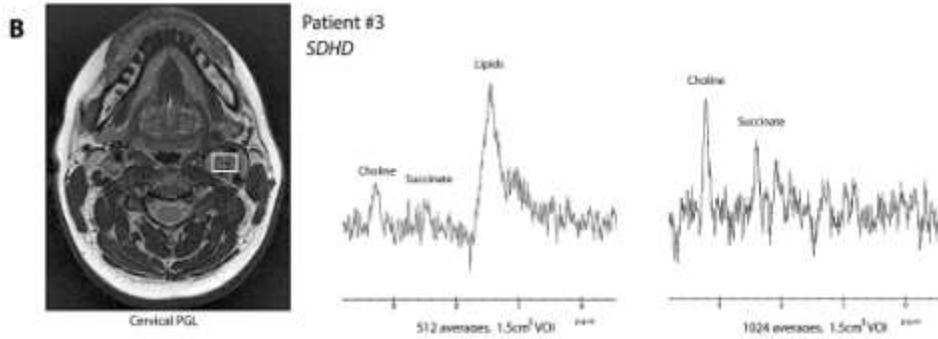
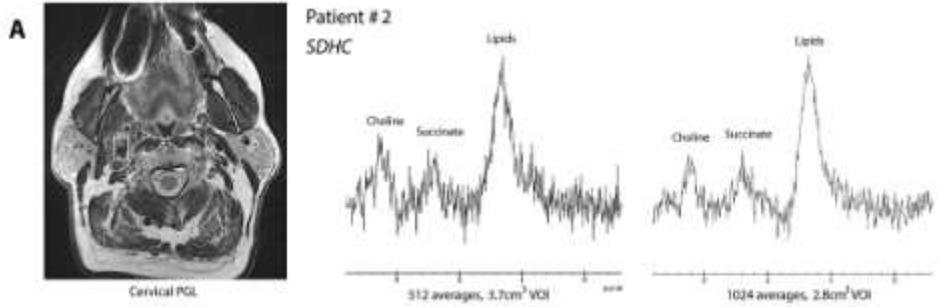
1024 averages, 6.2cm³ VOI



SDHB

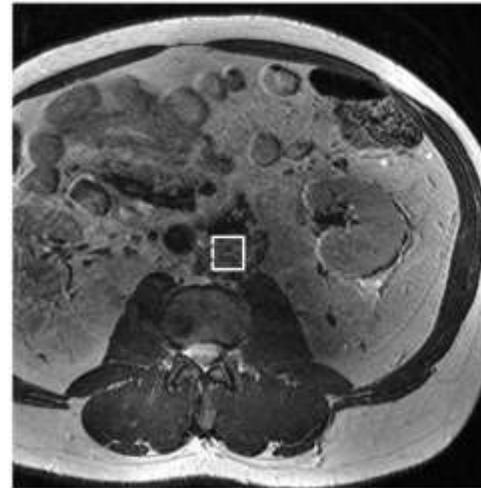


^1H -SRM SUCCEs : transfert en clinique à 3T

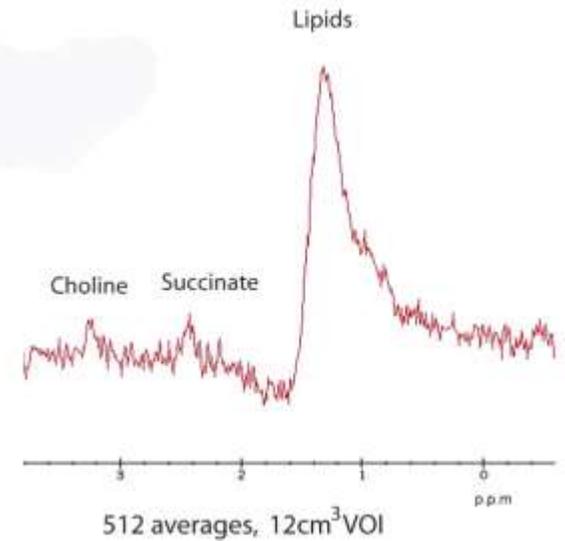


SUCCES : découverte d'une mutation SDHA

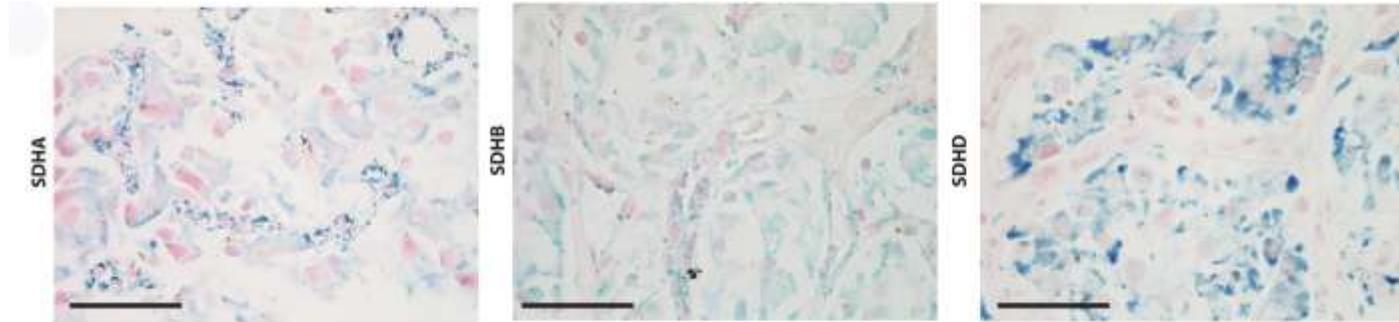
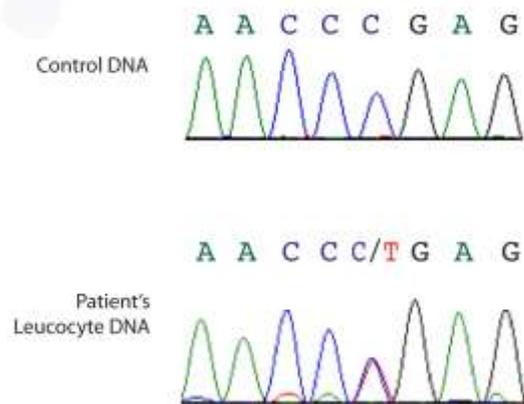
Patient 48 ans
PGL abdominal 50 mm
Absence d'histoire familiale
Absence de mutation *SDHB*, *SDHD*



Abdominal PGL



SDHA
c.91C>Tp.Arg31Ter

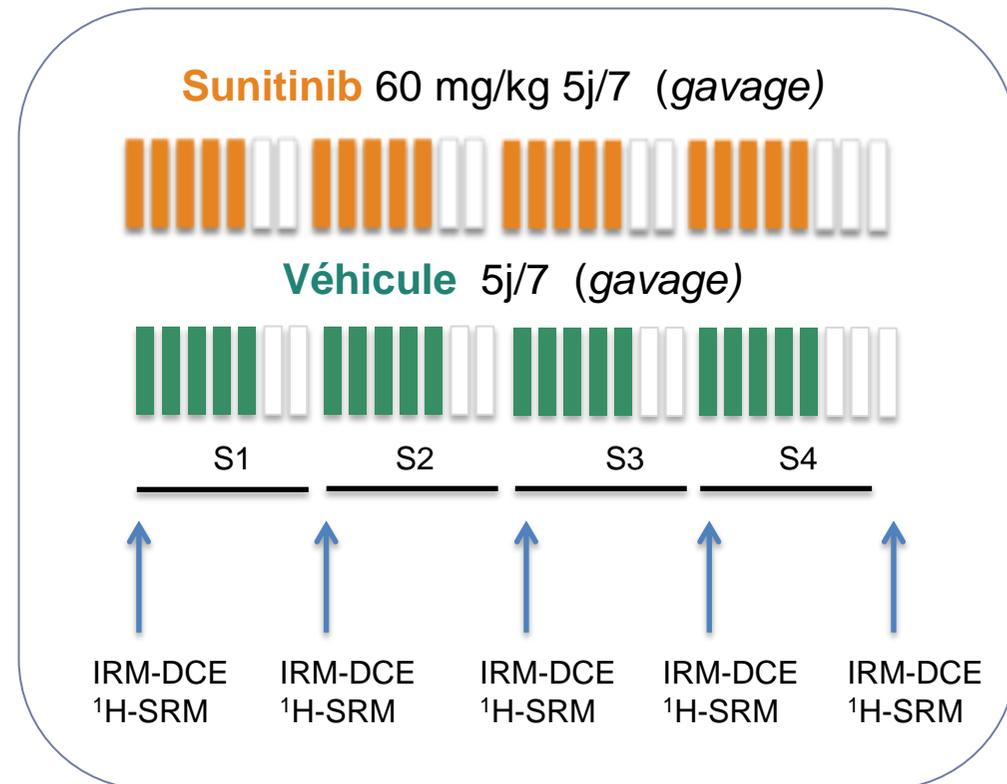


Perspective: évaluation de la réponse au sunitinib ?

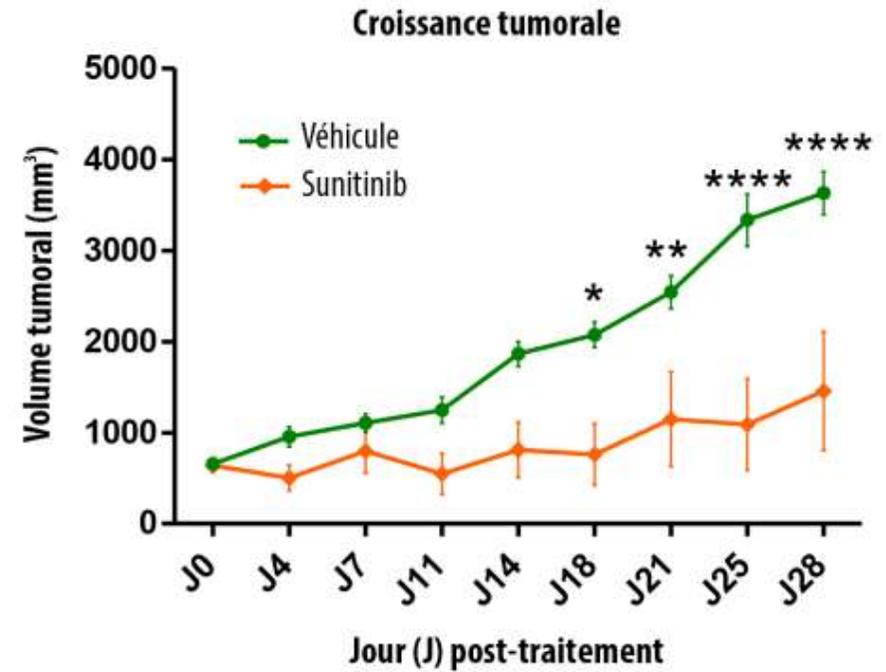
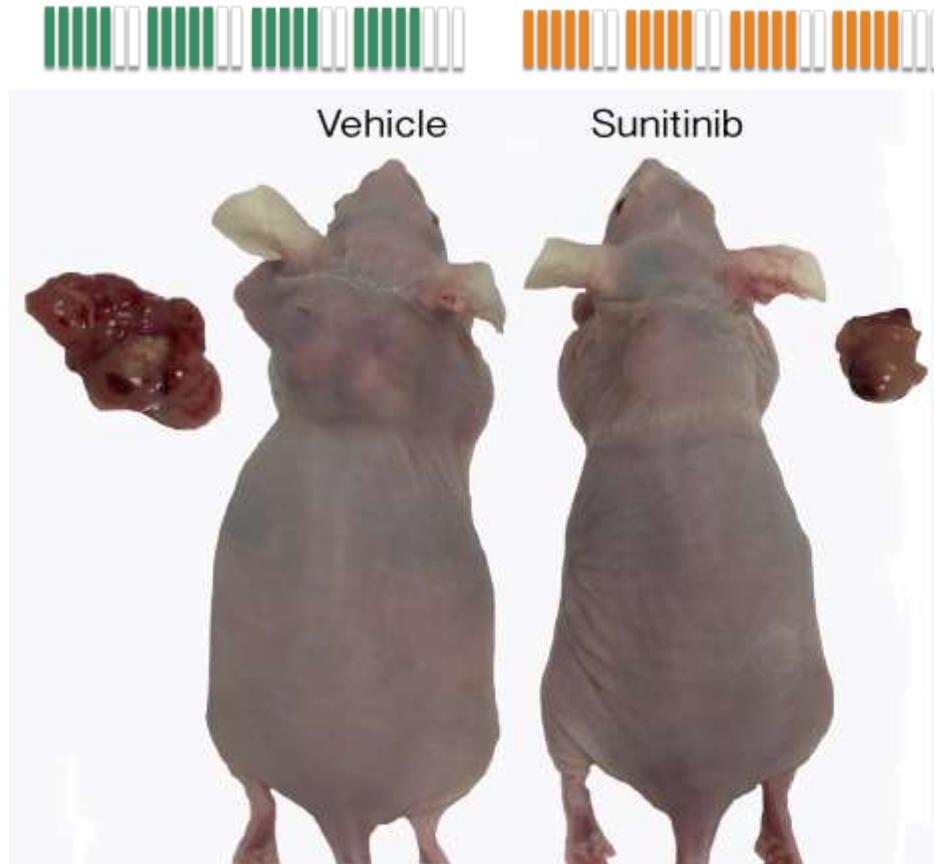
- *Succinate: biomarqueur de la réponse au traitement?*
- *Diminution des taux de succinate sous traitement détectable in vivo ?*

Résultats préliminaires : réponse au sunitinib

- 13 souris *Sdhb*^{-/-}
- 4 semaines de traitement
 - ✓ Sunitinib
 - ✓ ou véhicule



Effet du traitement sur la croissance tumorale



Histologie : nécrose ischémique

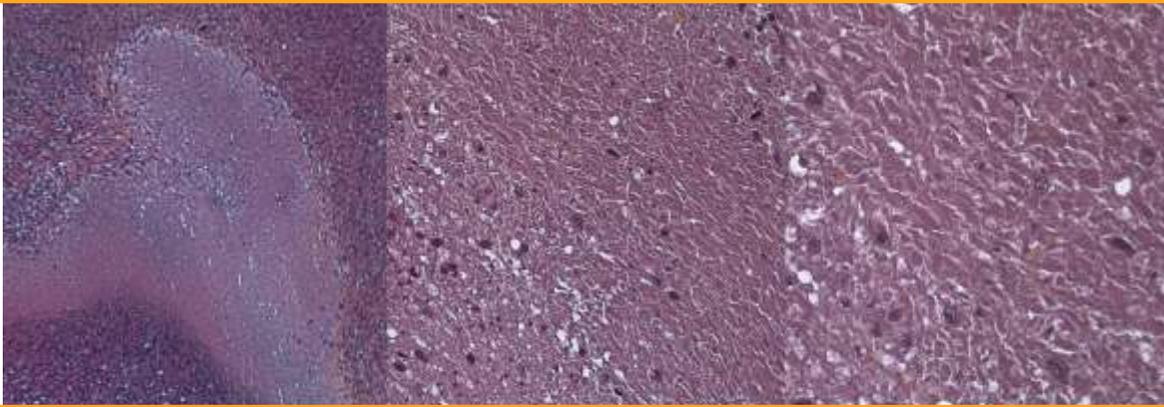
Collaboration : Pr Cécile Badoual

X 2,5

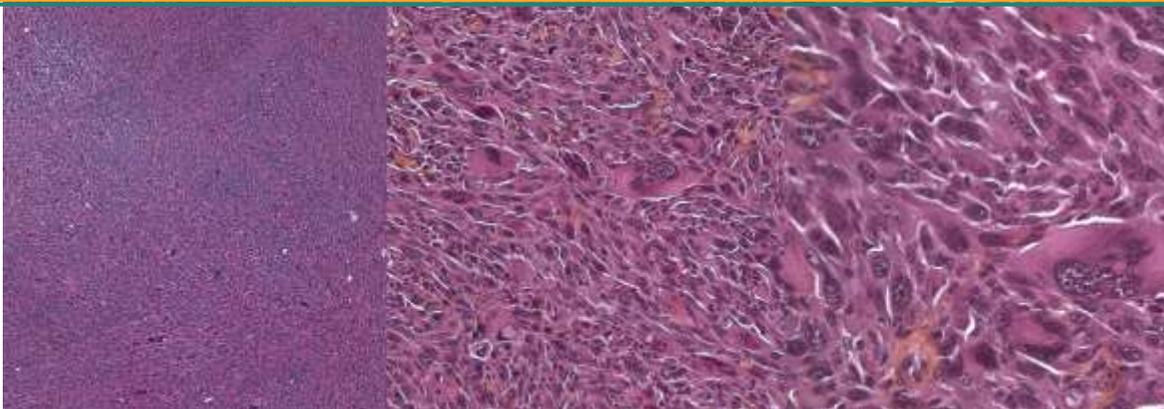
X 20

X 40

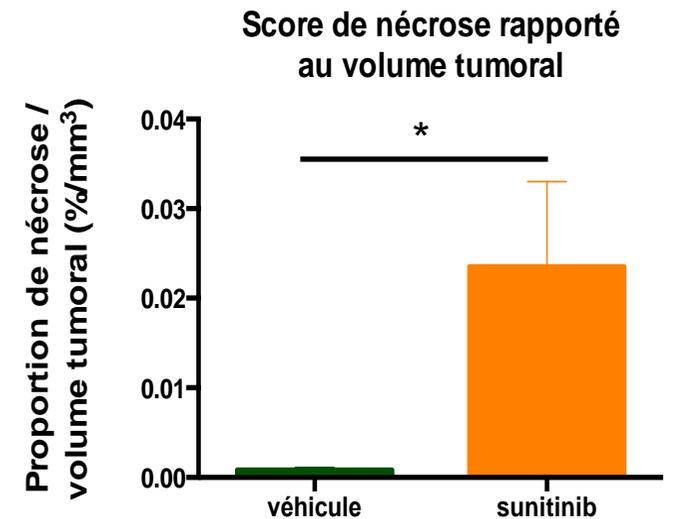
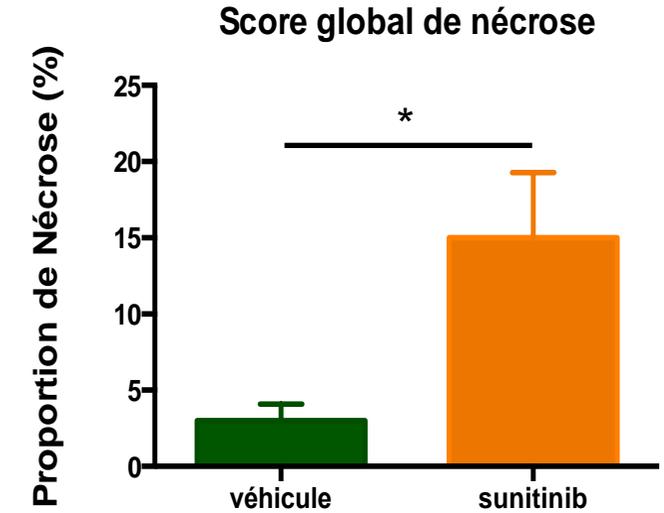
Sunitinib

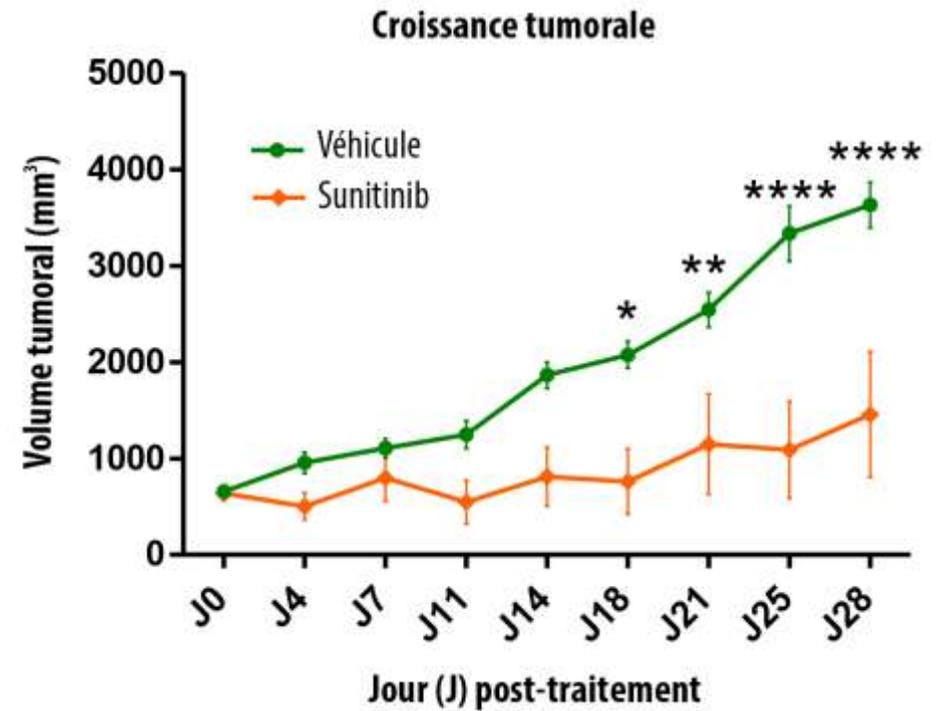
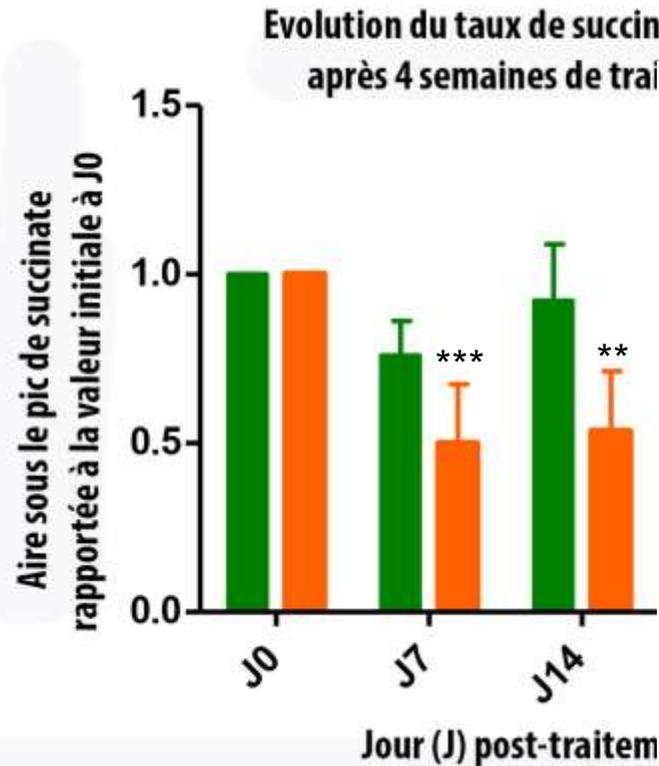


Véhicule

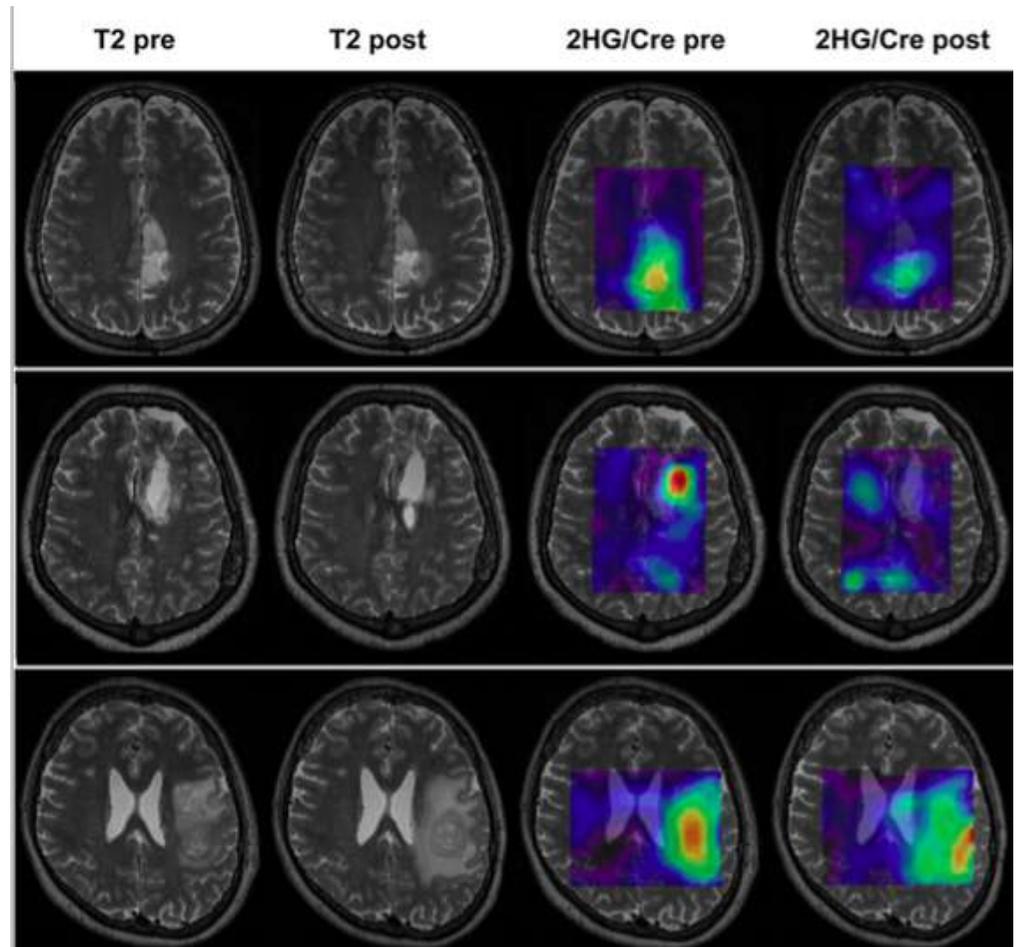


Coloration HES

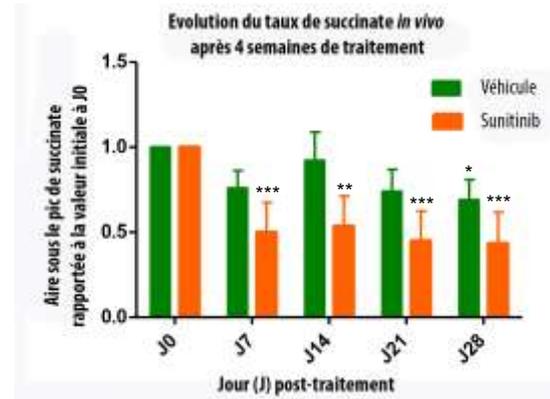
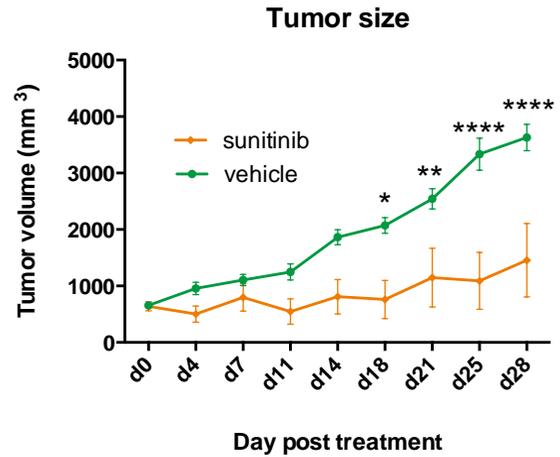
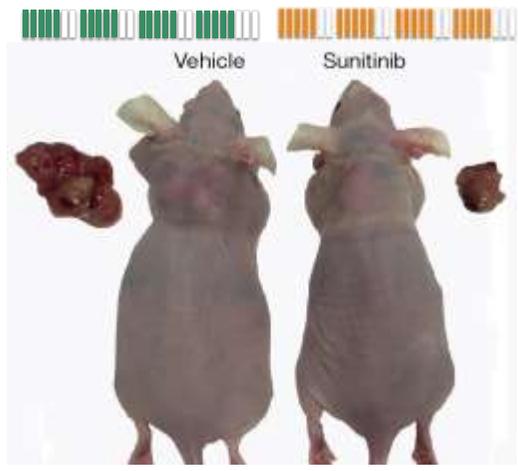
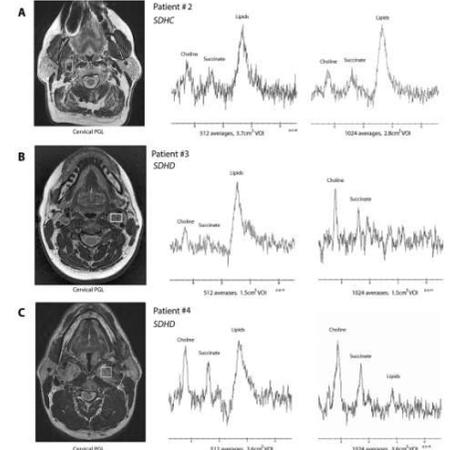
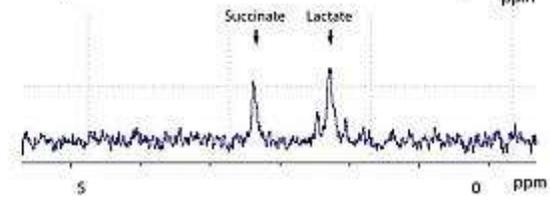
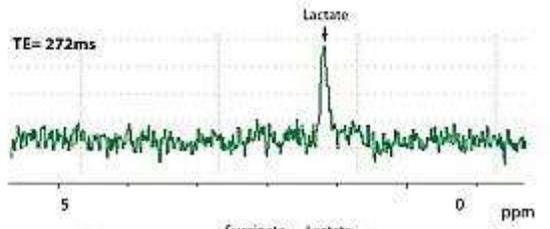
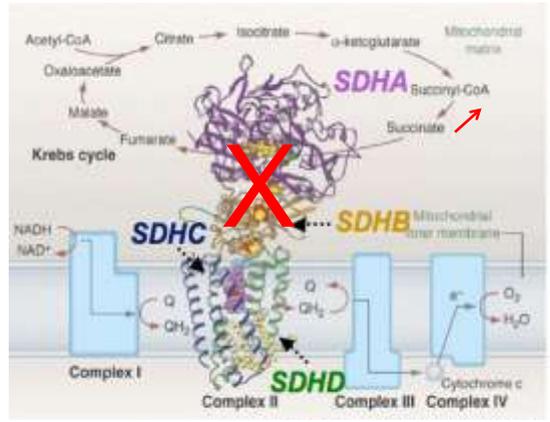




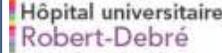
- 9 IDH-mutant glioma patients
- Adjuvant Radiation + temozolomide



Conclusion



Acknowledgements



INSERM, U1124, Paris, France
Hôpital Robert Debré
Dr Pierre Rustin
Dr Paule Benit



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Anne-Paule Gimenez-Roqueplo, PU-PH
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Patient	Gender	Age	Gene	Mutation type	Multiple locations	Type of tumor analyzed	Largest tumor diameter (mm)	VOI size (cm ³)	Succinate level on GC-MS (nmol/mg protein)
1	M	33	SDHB	c.740T>G p.Met247Arg	Yes	VPGL	80	4.6 ± 1.5	ND
						APGL	94	19.2	89.3
2	M	70	SDHC	c.397C>T p.Arg133Ter	No	VPGL	42	3.7	ND
3	F	32	SDHD	c.210G>T p.Arg70Ser	Yes	CBPGL	24	1.5	ND
4	M	41	SDHD	c.325C>T p.Gln109Ter	Yes	CBPGL	39	3.6	ND
5	M	25	none	NA	No	PCC	55	6.2	0.84
6	M	60	none	NA	No	APGL	35	4.2	0.54
7	F	74	none	NA	Yes	CBPGL	30	1.3	ND
8	M	47	none	NA	No	PCC	30	5.8	ND
9	M	48	SDHA	c.91C>T p.Arg31Ter	No	APGL	50	12	72.17

^1H -MRS in humans at 3T

SUCCEs

PRESS PROBE monovoxel

TR: 2500ms

TE: 144ms

Averages:

- ✓ 512 (22min acquisition)
- ✓ 1024 (44 min acquisition)