



**CENTRE DE RECHERCHE
DES CORDELIERS**



Judith Favier

Inhibition de la succinate déshydrogénase et cancer :
de la prédisposition génétique aux risques potentiels
d'utilisation des fongicides SDHI



Inserm





Genetics and Metabolism of Rare Cancers lab

Judith Favier, DR1 Inserm

Anne-Paule Gimenez-Roqueplo, PU-PH

Nelly Burnichon, PU-PH

Charlotte Lussey-Lepoutre, PU-PH

Alexandre Buffet, MCU-PH

Eric Clauser, PUPH

Laurence Amar, PU-PH

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Rebecca Westbrook, post-doc

Tom Drossart, PhD student

Amandine Jacquet, PhD student

Sara Cajamarca Ocampo, PhD student

Roseline Vibert, PhD student



Past members: Aurélie Morin, Luis Castro-Vega, Judith Goncalves, Sophie Moog



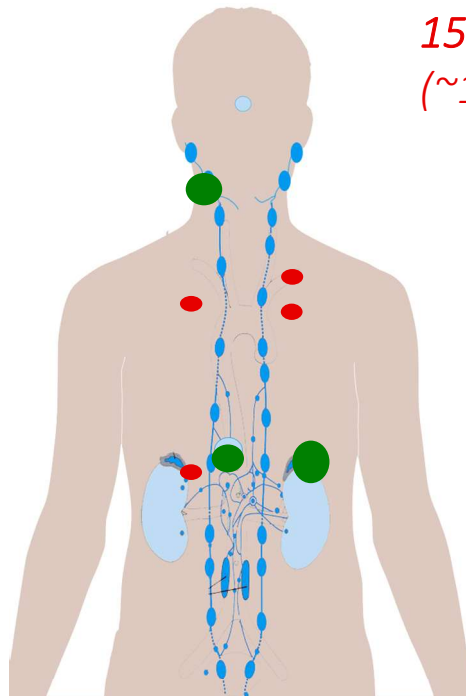
Pheochromocytomas and paragangliomas (PPGL)



Head and Neck PGL



Thoraco-Abdomino-Pelvic PGL



*15% of PPGL become metastatic (MPP)
(~10% of Pheo, 40% of PGL)*

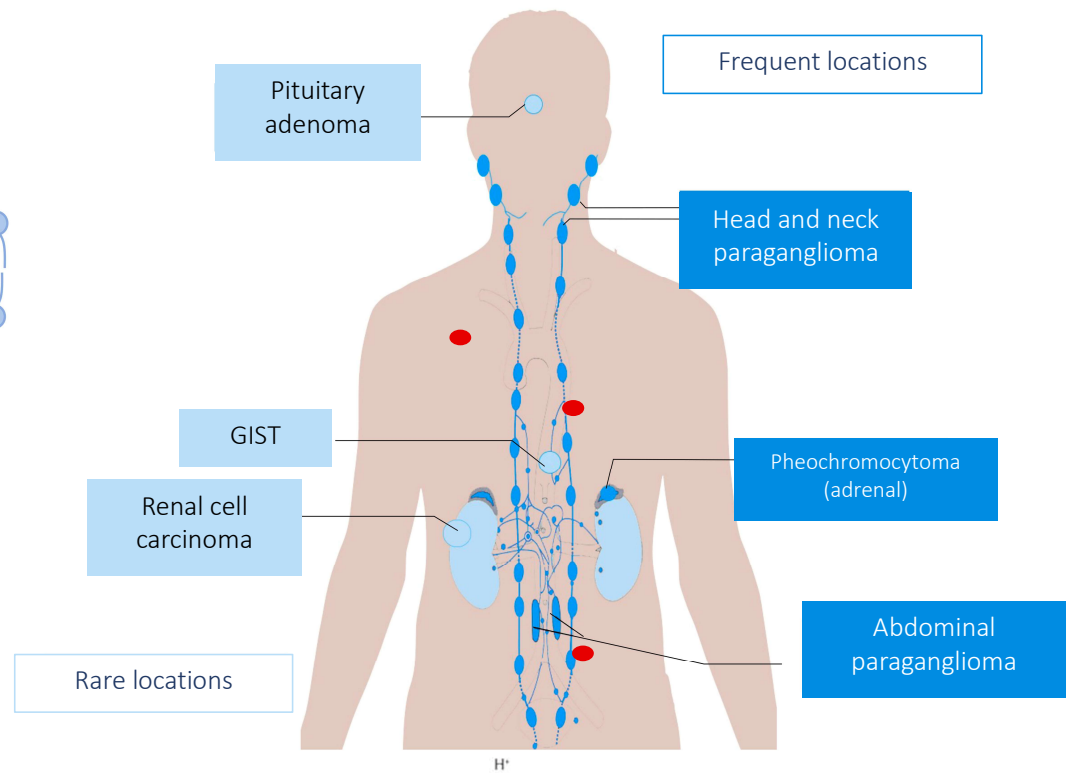
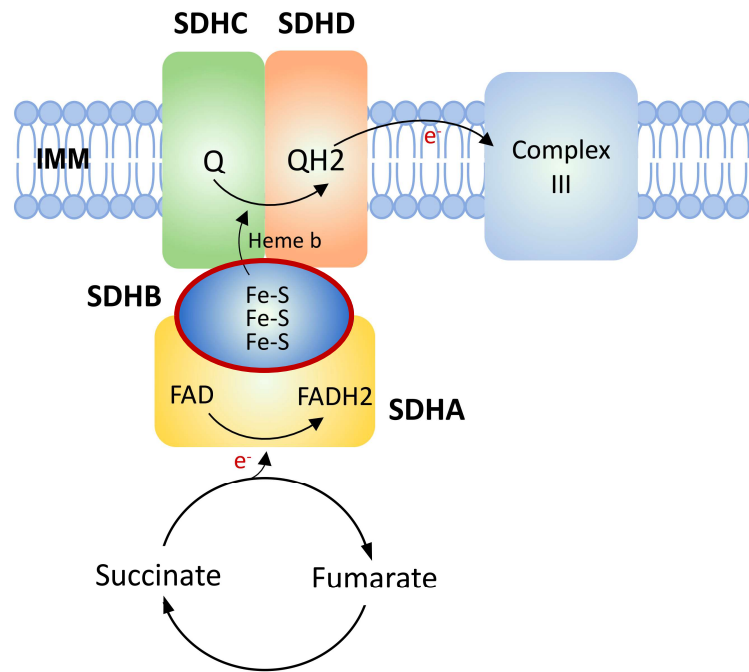


Adrenal PGL (Pheo)

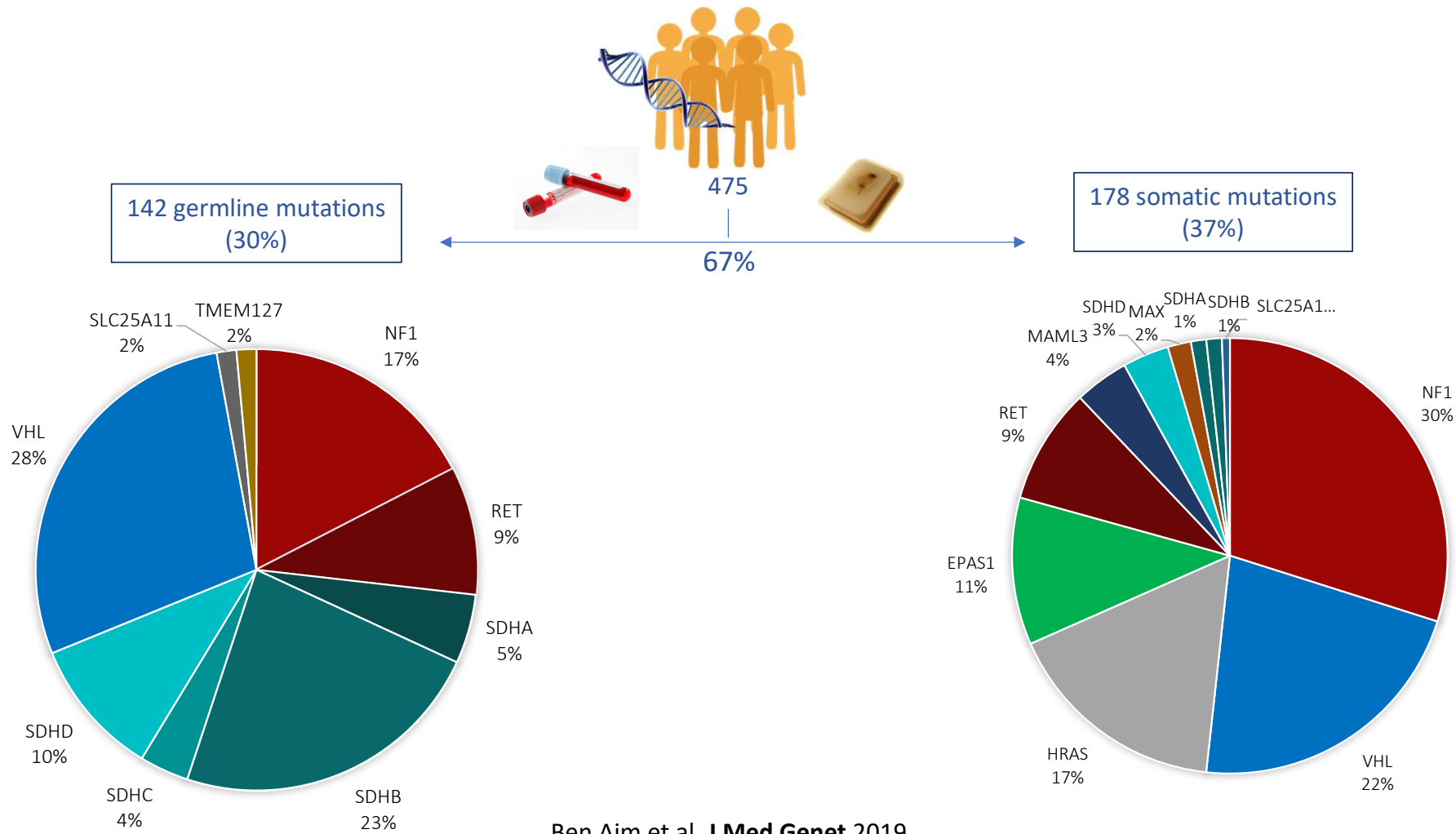
Mutations in *SDHD*, a Mitochondrial Complex II Gene, in Hereditary Paraganglioma

Bora E. Baysal,^{1*} Robert E. Ferrell,² Joan E. Willett-Brozick,¹
Elizabeth C. Lawrence,² David Myssiorek,⁵ Anne Bosch,⁶
Andel van der Mey,⁷ Peter E. M. Taschner,⁶
Wendy S. Rubinstein,³ Eugene N. Myers,⁴ Charles W. Richard III,⁹
Cees J. Cornelisse,⁸ Peter Devilee,⁶ B. Devlin¹

Succinate dehydrogenase and cancer



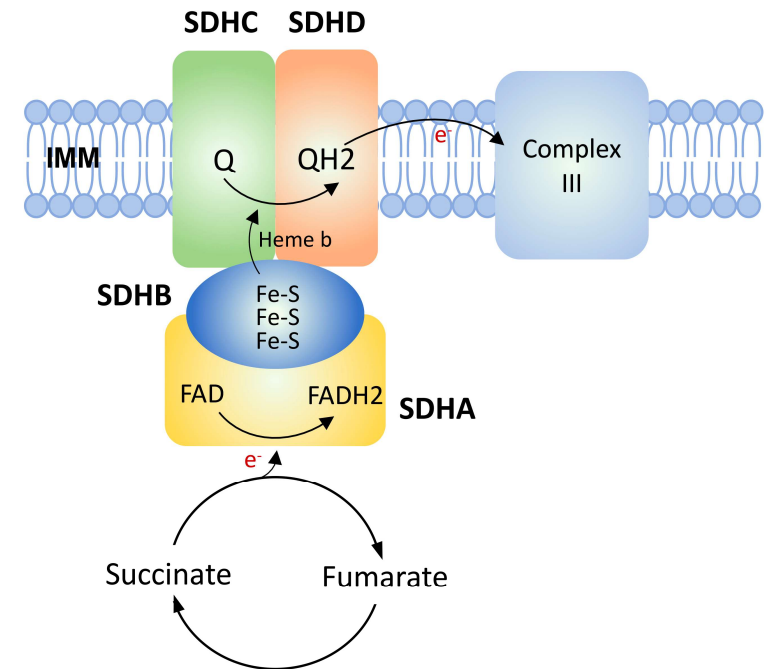
Determination of genetic status on germline and/or tumor DNA with NGS assay



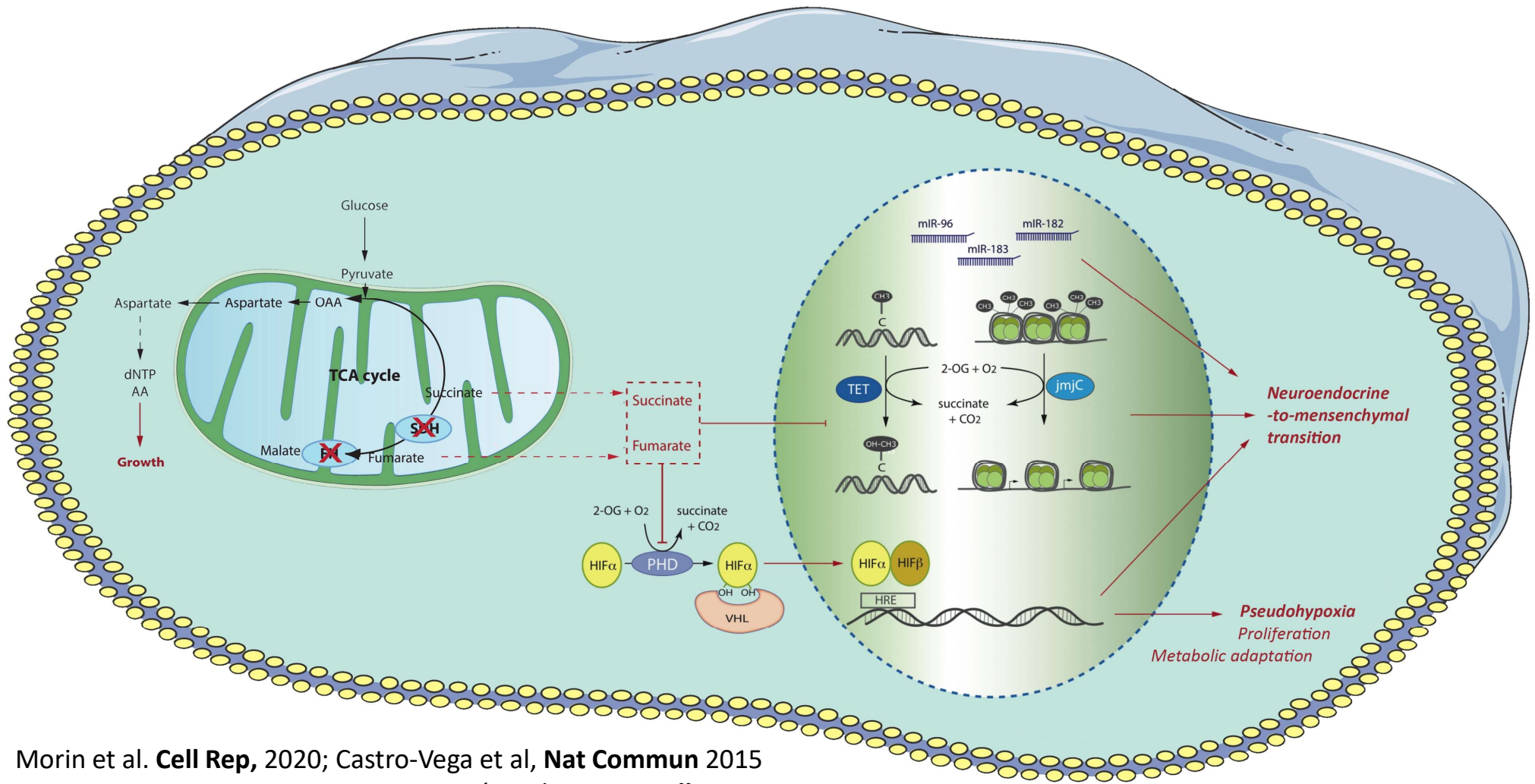
Ben Aim et al, *J Med Genet* 2019
Drossart*, Buffet* et al, *JCEM* 2024

Main questions

- How do cells survive to SDH deficiency?
- How does SDH loss cause tumorigenesis?
- Why are *SDHB* mutations specifically associated to metastatic progression?



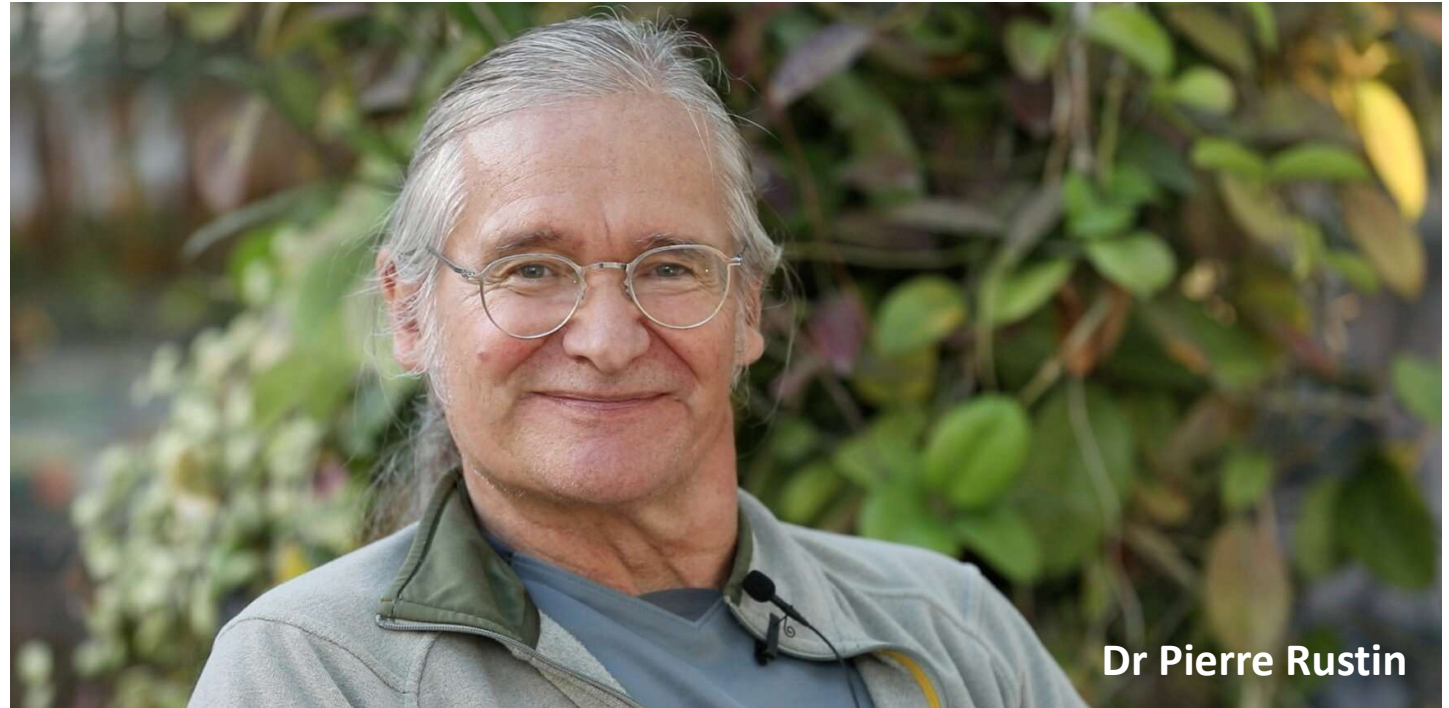
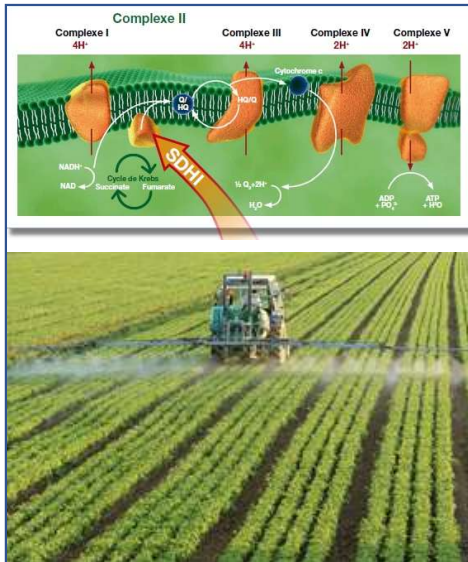
Consequences of SDH loss of function



Morin et al. **Cell Rep**, 2020; Castro-Vega et al, **Nat Commun** 2015

Lussey-Lepoutre C, **Nat Commun**, 2015, Letouzé et al. **Cancer Cell**. 2013

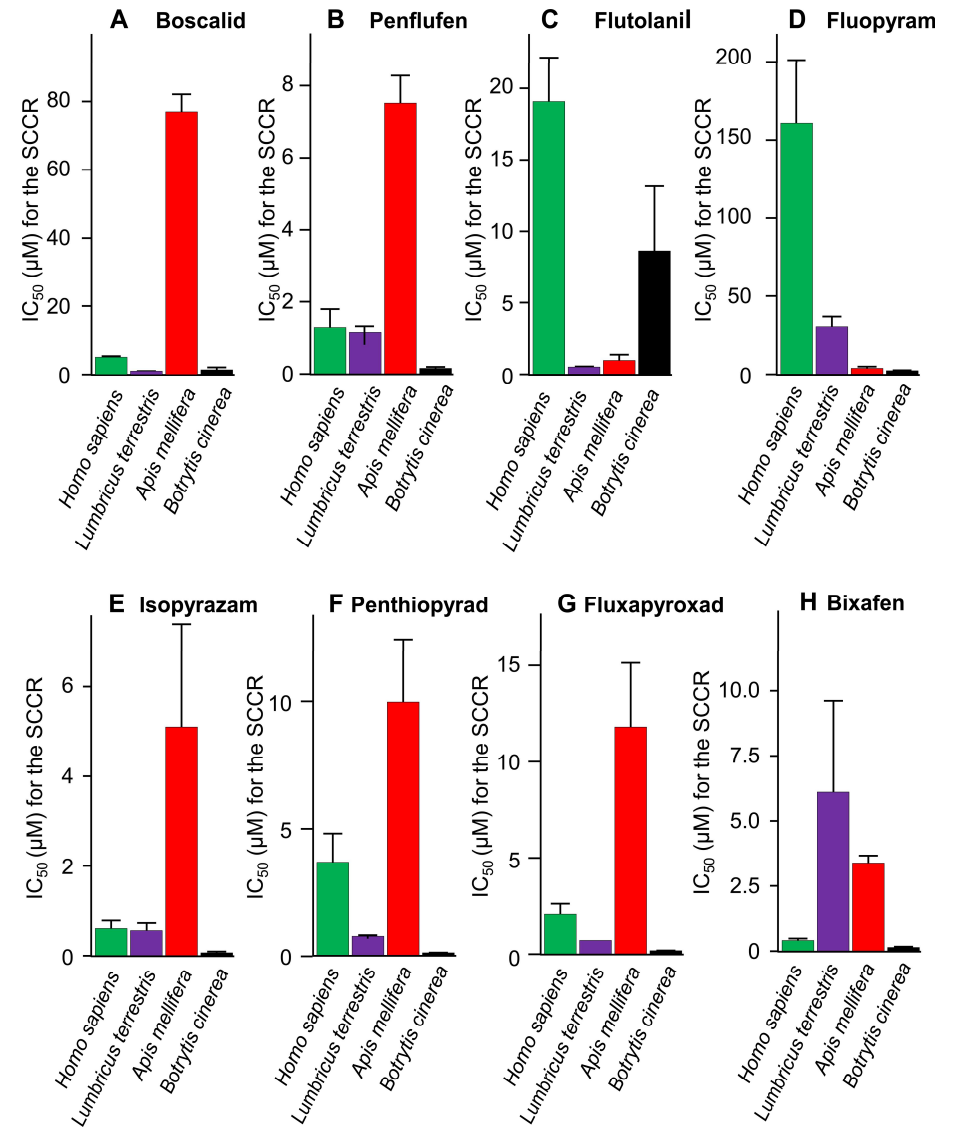
SDHi are fungicides used to control moulds



IC50 values of SDHIs on the succinate cytochrome c reductase in different species



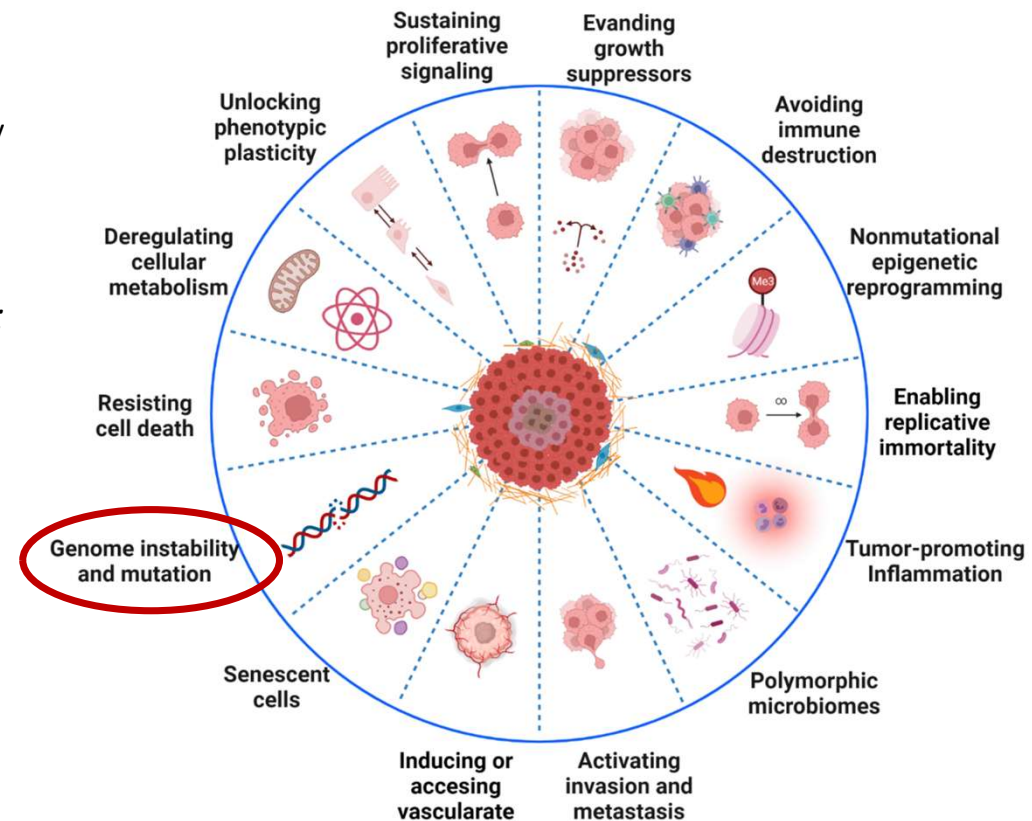
Dr Paule Benit



SDHi pesticides and cancer: what are the issues?

- Known mechanism of action: inhibition of SDH encoded by genes considered to be tumor suppressors
 - Clinical evidence of loss of SDH activity in humans
 - Lack of specificity of SDHi towards fungi (*Bénil et al., 2019; Sierotzki and Scalliet, 2013*)
 - Available data on carcinogenic effects of SDHi
 - Regulatory/firm evaluation tests
 - Rodent tumors
 - BUT no genotoxicity
- > Most SDHi (10/13) are classified as NON-CARCINOGENIC.

➤ Potential impact on other cancer hallmarks?



Santé

Alerte scientifique sur les fongicides

Après les effets nocifs des insecticides et herbicides utilisés dans l'agriculture, des chercheurs dénoncent dans «Libération» des produits, les «SDHI», qui empêchent le développement des champignons en bloquant leur respiration. Passant dans la chaîne alimentaire, ils pourraient affecter gravement la santé des humains.



SDHi projects

SOHO-EpiMetCan

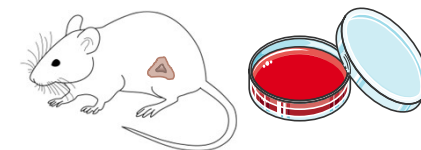
Impact of the use of SDHi :
Epidemiological, epigenetic and metabolic
evaluation in relation to cancer

SOHO-SDHi ecOHealth

Agro-socio-economic, epidemiological
and toxicological evaluation

PGL-EXPO

Impact of environmental exposures on
tumor risk in subjects at risk of SDH-
determined hereditary paraganglioma



Epigenetic changes, EMT



HOLIMITOX



anses
agence nationale de sécurité sanitaire
alimentation, environnement, travail

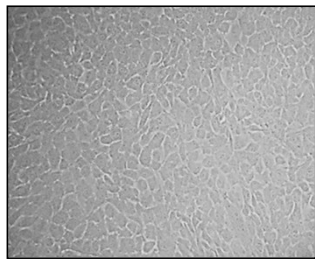


Collaborators: HolliMitox consortium (L. Huc (INRAE) S. Bortoli (Inserm), B. Fervers (Léon Bérard center, Inserm))



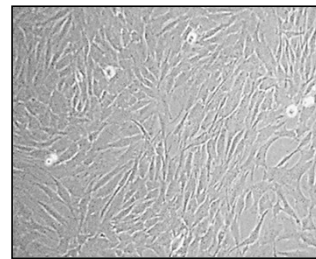
Impact of SDHi exposure in human colon cells?

- Route of exposure of the general population to SDHi: **diet**
- Target organ: **colon**
- Cellular models



HCEC-1CT

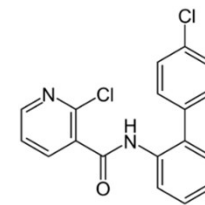
Immortalized human colon epithelial cell line derived from a biopsy of healthy colon



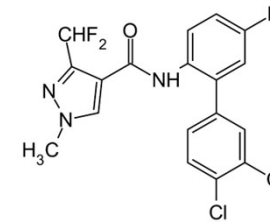
HCEC-1CTRPA

HCEC-1CT cells with driver mutations of CRC

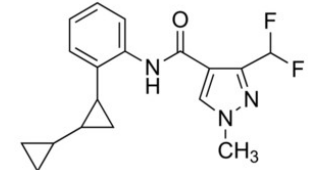
APC -/-
KRAS +++
TP53 -/-



Boscalid



Bixafen



Sedaxane

SDHi

Doses

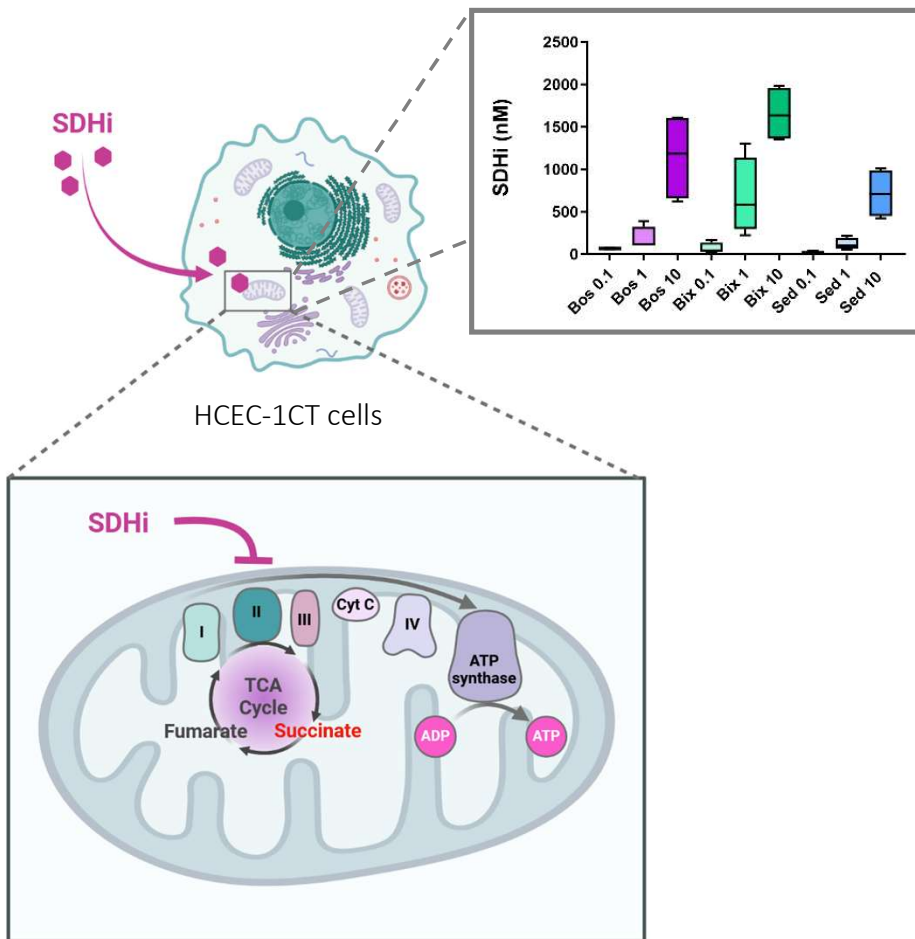
0.1, 1 and 10 μ M
(extrapolated from Acceptable Daily Intake)

Exposition

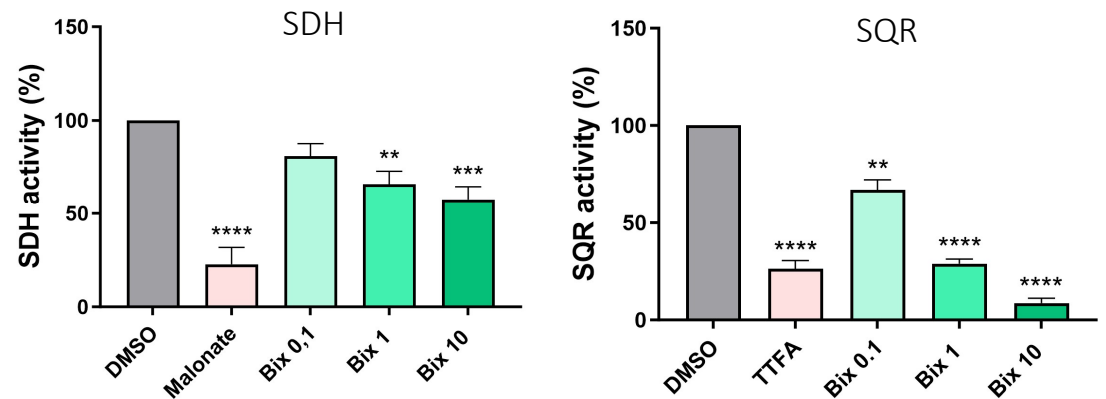
Short \rightarrow 48h
Sub-chronic \rightarrow 3 weeks

Duarte Hospital et al, Environment Int 2025

Bixafen inhibits the 2 functions of the SDH complex and leads to an accumulation of succinate.

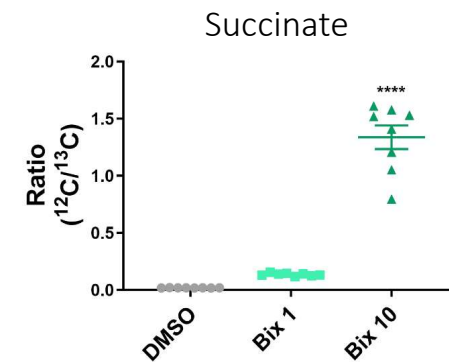


Activity of complex II of the mitochondrial respiratory chain



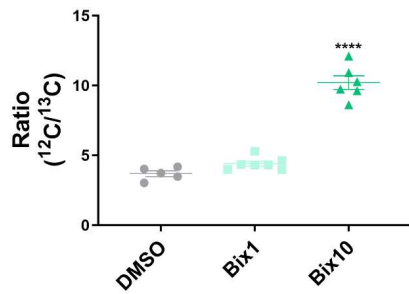
SDH activity catalyzes the oxidation of succinate into fumarate; SQR activity transfers electrons from FADH₂ to the ubiquinone

HCEC-1CT cells exposed for 3 weeks to bixafen

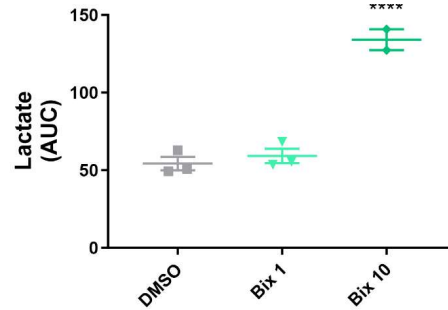


Bixafen induces metabolic reprogramming...

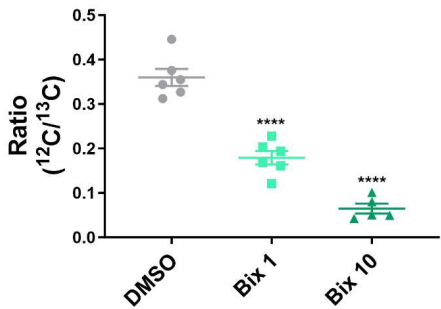
Fructose 1,6 BP



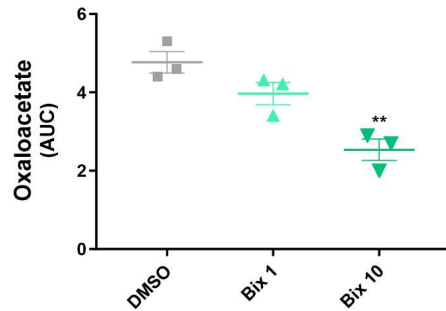
Lactate



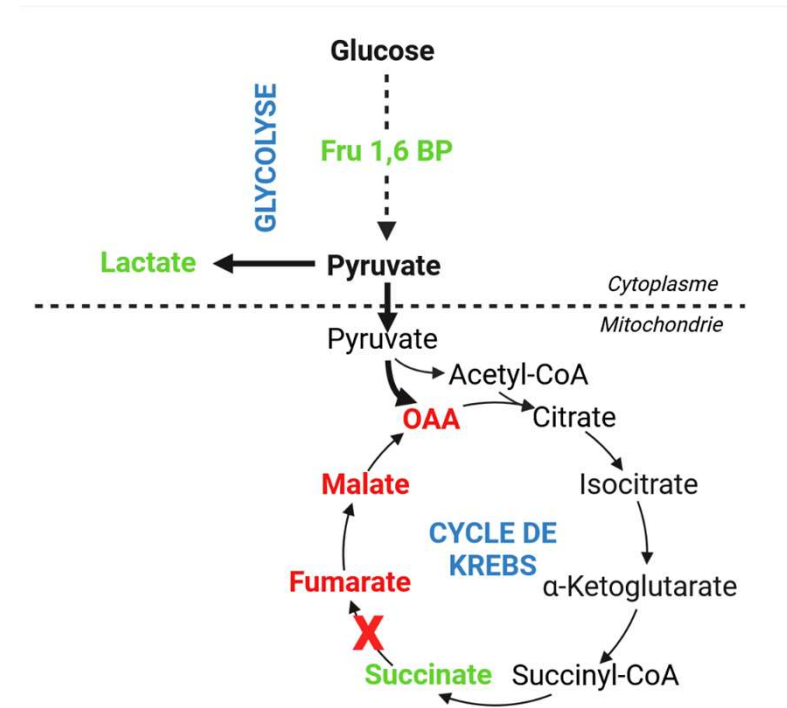
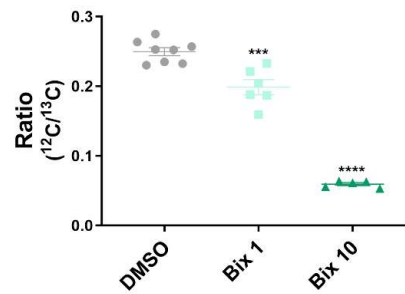
Fumarate



Oxaloacetate

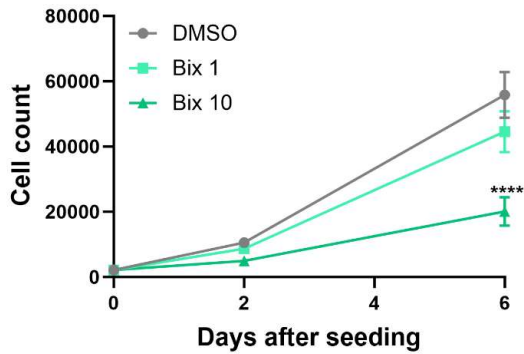


Malate

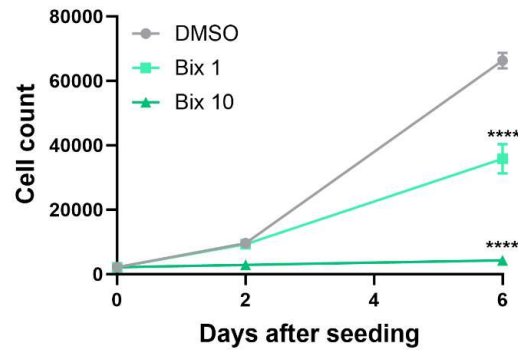


...associated with slower cell proliferation

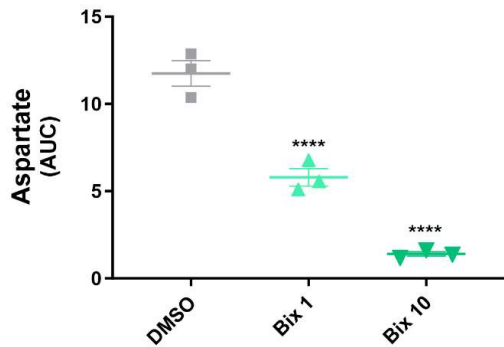
Cell growth in complete medium (CM)



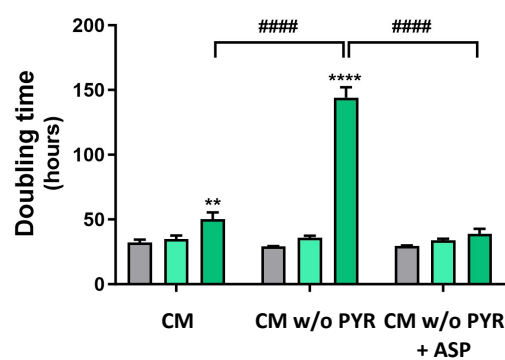
Cell growth in CM without pyruvate



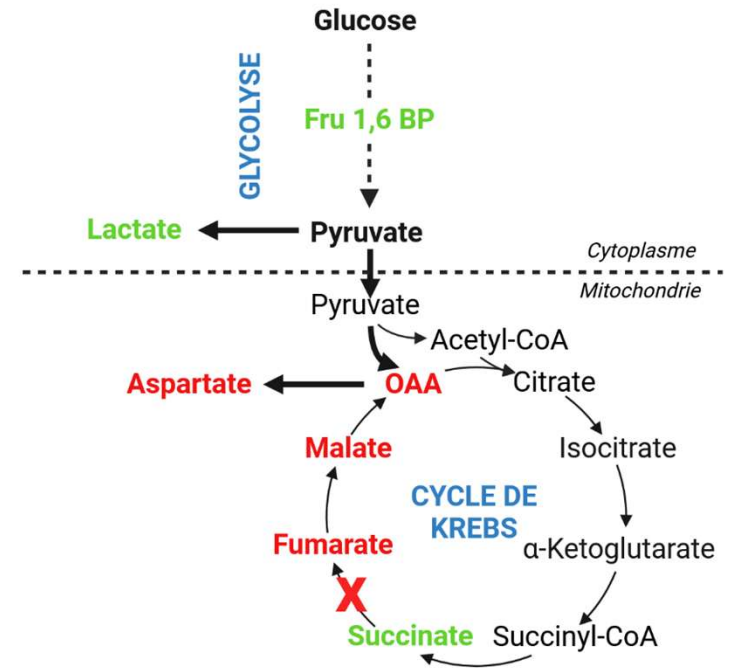
Aspartate



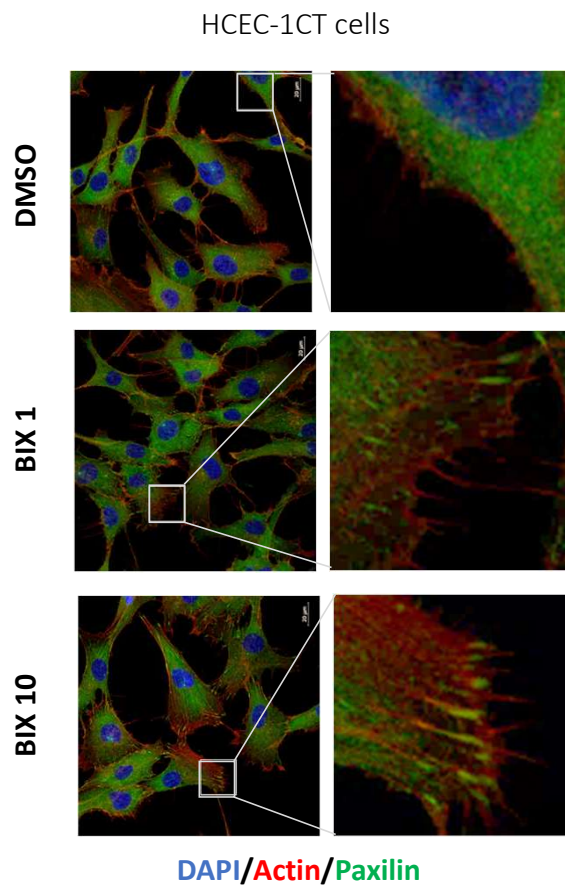
Doubling time



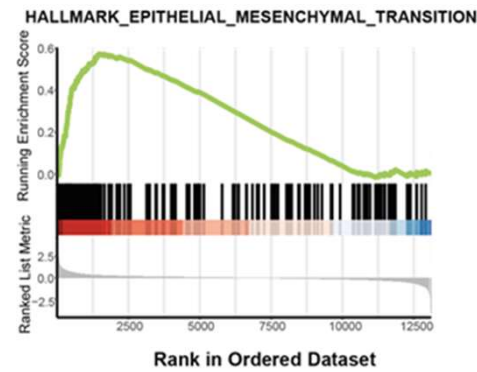
+ ASP



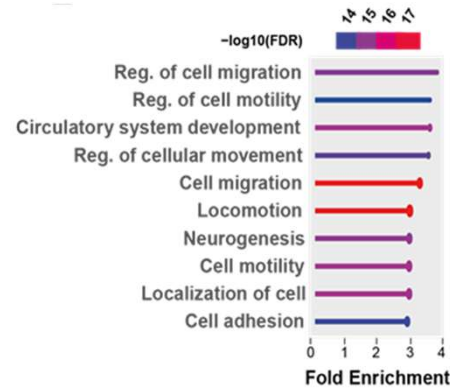
Bixafen induces morphological changes typical of EMT



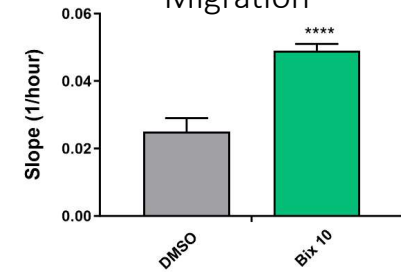
GSEA analysis



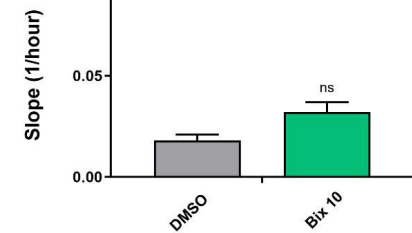
Pathway enrichment



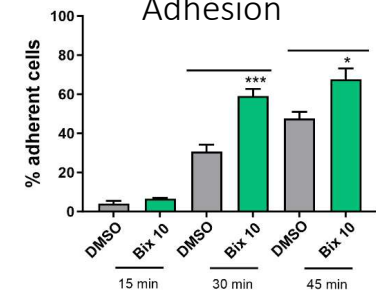
Migration



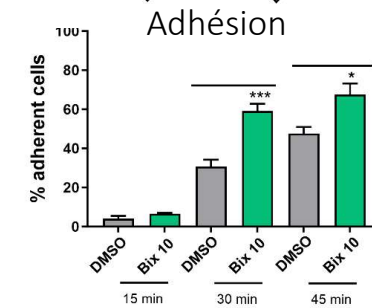
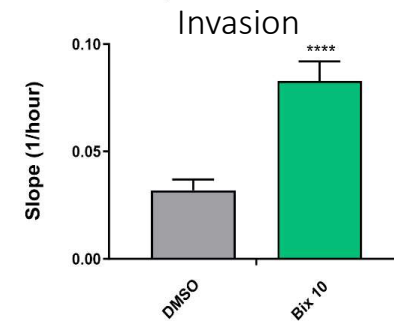
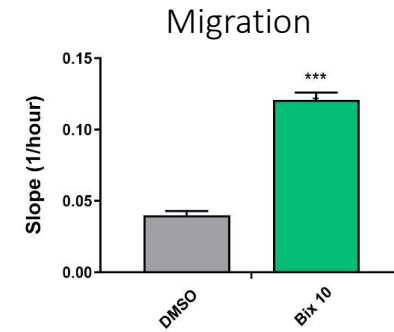
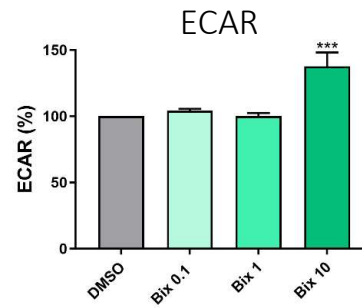
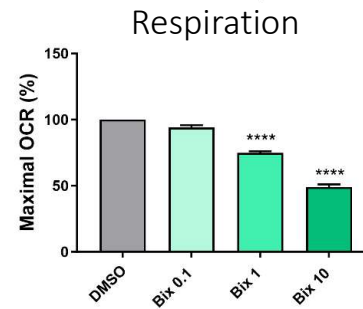
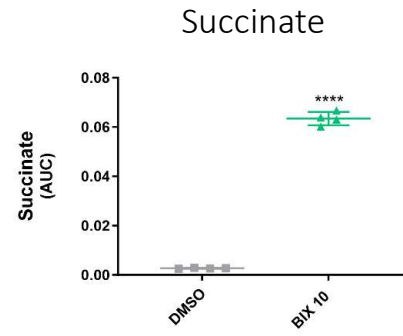
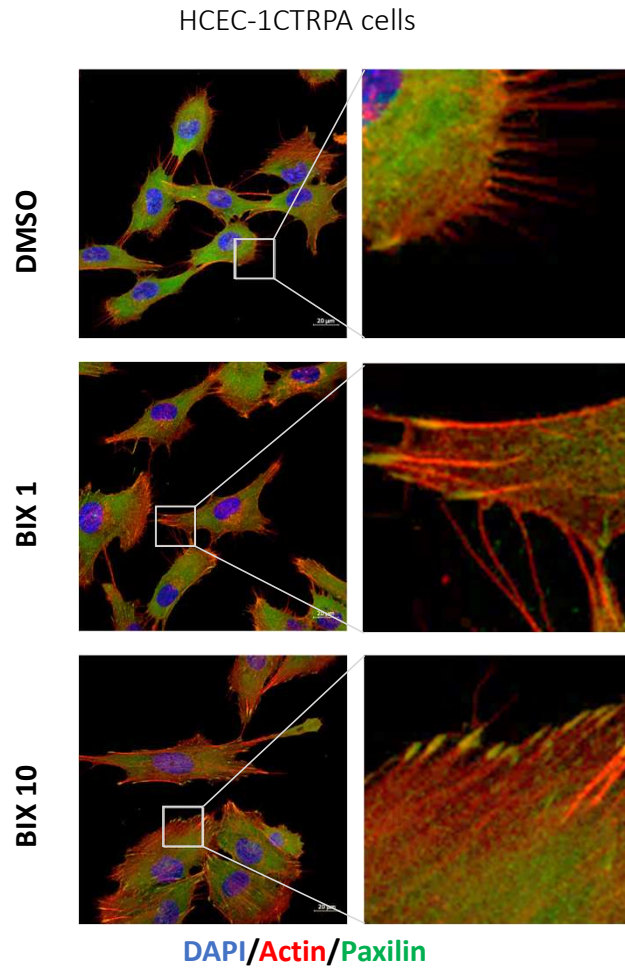
Invasion



Adhésion



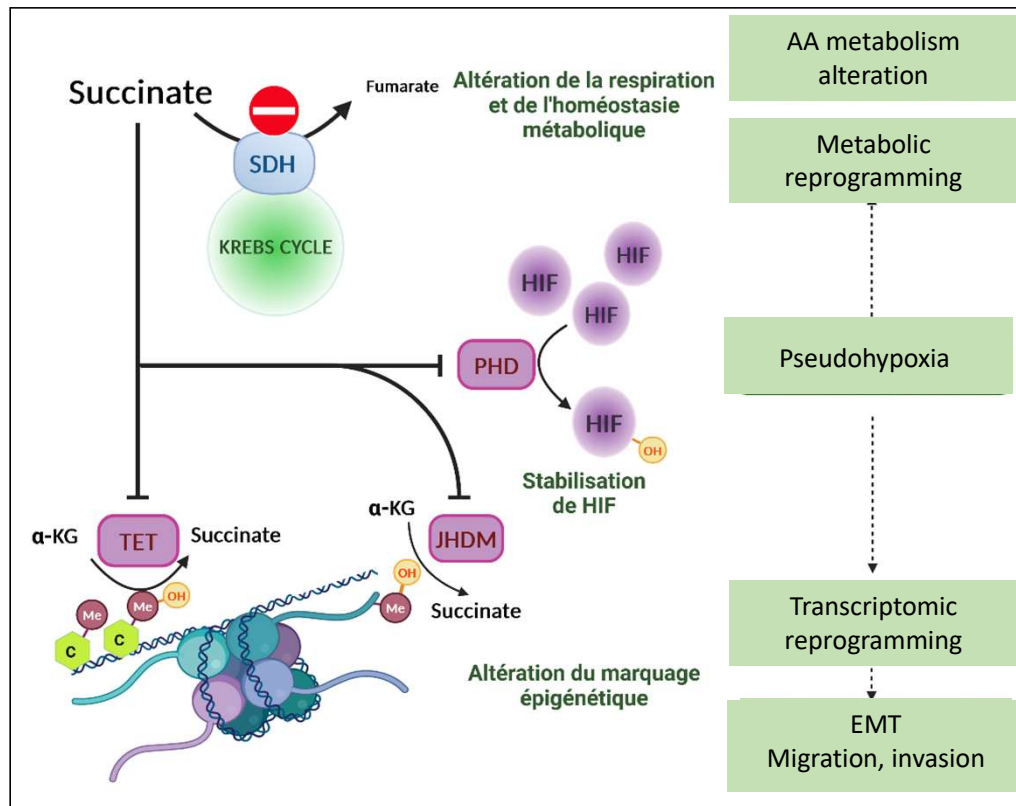
The effects of bixafen are enhanced in transformed colon cells



Exposure to SDHi reproduces some of the effects observed in SDH-/- tumors

Genetic inactivation of SDH

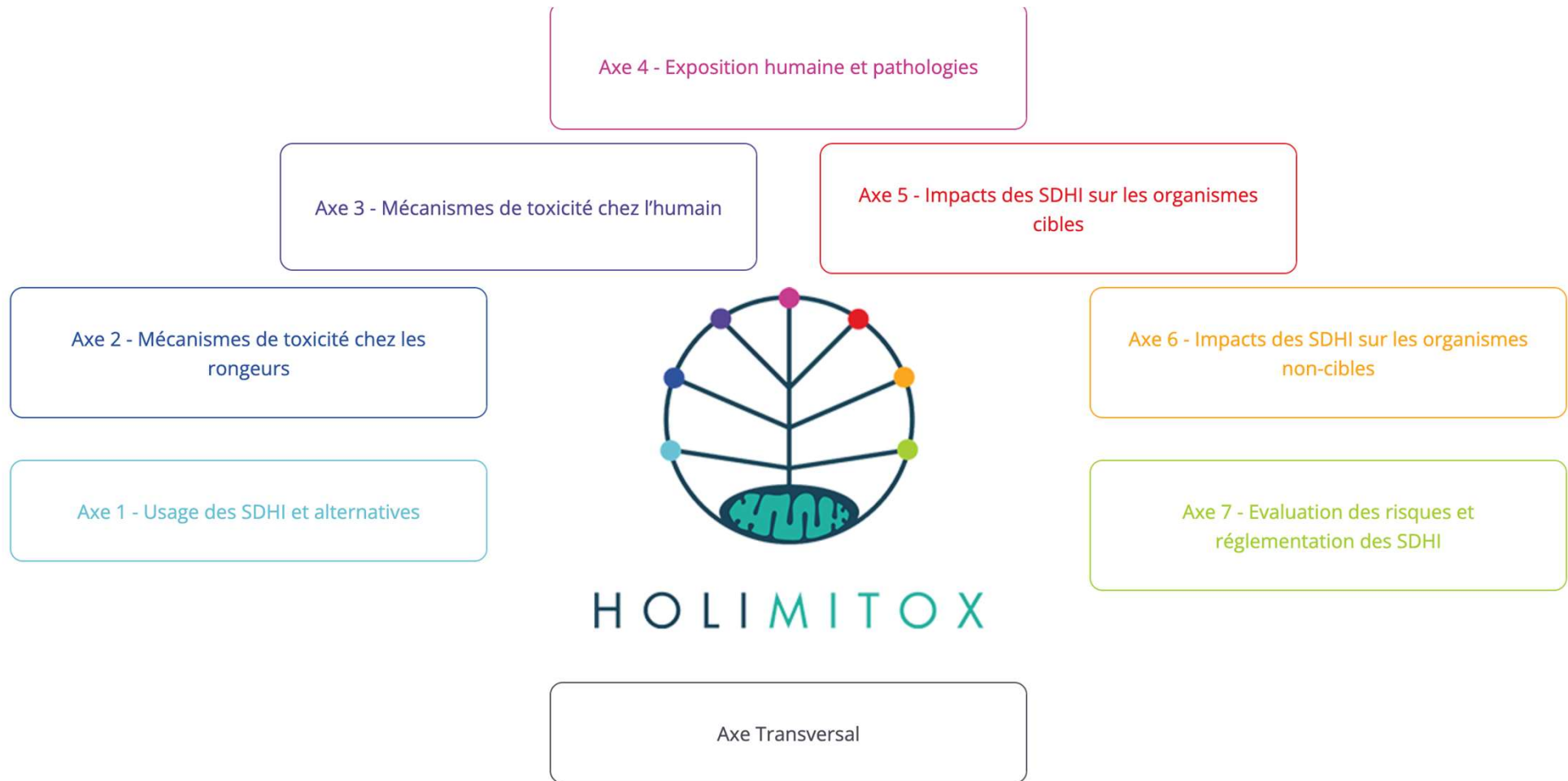
Chemical inactivation of SDH by SDHi



- ✓ AA metabolism alteration
 - ✓ Metabolic reprogramming
 - ✓ Pseudohypoxia
 - ✓ Transcriptomic reprogramming
 - ✓ EMT Migration, invasion
- ✓ Succinate accumulation
 - ✓ Pyruvate and aspartate dependence
 - ✓ Metabolic Switch OXPHOS → glycolyse
 - ✓ Transcriptomic reprogrammation
 - ✓ Migration, invasion, adhesion

HOLIMITOX

scientific network for the integrated assessment of pesticides toxic to mitochondria

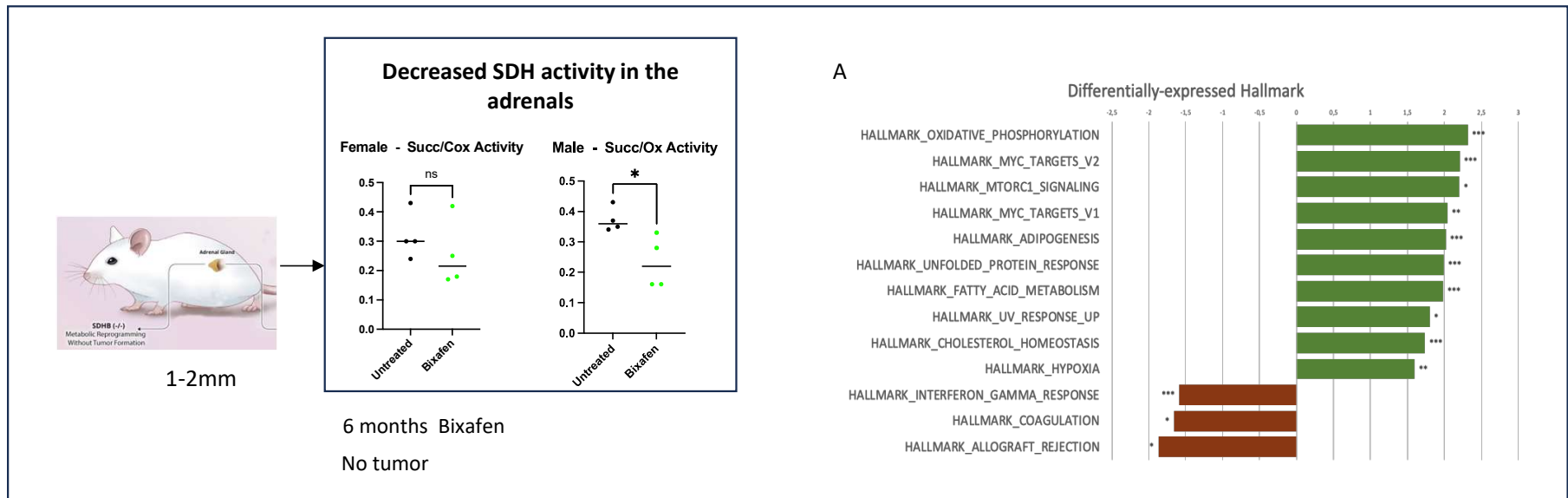
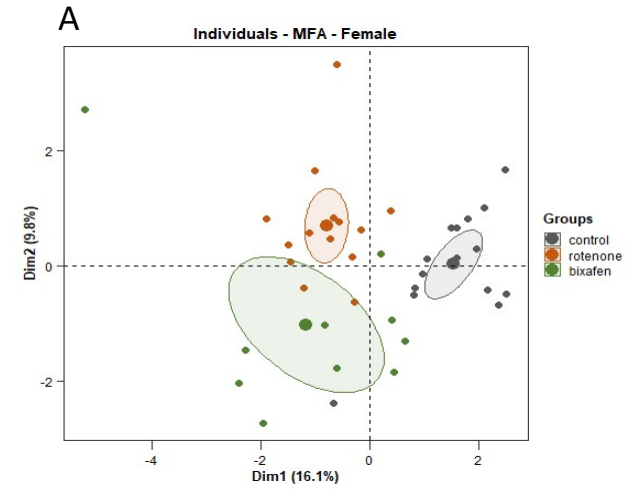


Toxicity in rodents



Laurence Huc and co

Multivariate analysis





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thématiques

Inserm

Institut national
de la santé et de la recherche médicale



INSTITUT
DE VEILLE SANITAIRE


PGL.EXPO :
Impact of environmental exposures on tumor
risk in subjects at risk for SDH-determined
hereditary paraganglioma.

Anne-Paule GIMENEZ-ROQUEPLO

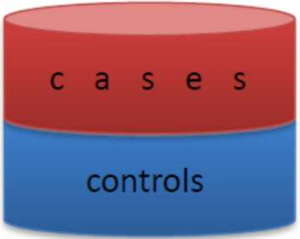
Béatrice FERVERS



Impact of environmental exposures on tumor risk in subjects at risk for SDH-determined hereditary paraganglioma.



PGL.R (2013-):
Registre Français du paragangliome héréditaire
Pr A-P Gimenez-Roqueplo



REDCAP database housed by HEGP research clinic unit



Pr B. Fervers

Environmental Health

METHODOLOGY Open Access

Accuracy of two geocoding methods for geographic information system-based exposure assessment in epidemiological studies

July 2019, Case-MN (arXiv:1907.00001v1 [cs.LG])



PGL.EXPO-1
PGL.EXPO-2
PGL.EXPO-3
PGL.EXPO-4

Pilot feasibility study (2020-2)
National case-control study (2024-7)
Prospective multicenter cohort
Genetic and epigenetic studies



Projet Phyto Pharmaco Vigilance

Impact de l'exposition aux fongicides SDHi sur le risque de paragangliome chez les sujets à risque de paragangliome héréditaire déterminé par SDH : étude de faisabilité



Astrid Coste ⁽¹⁾, **Alexandre Buffet** ⁽²⁾, **Margaux Duboeuf** ⁽¹⁾, **Sabrina Boudif** ⁽²⁾, **Lény Grassot** ⁽¹⁾, **Bouthaina Ouelaa** ⁽²⁾, **Annabelle Sueur** ⁽¹⁾, **Timgad Lounis** ⁽²⁾, **Olivia Pérol** ⁽¹⁾, **Béatrice Fervers** ⁽¹⁾, **Anne-Paule Gimenez Roqueplo** ⁽²⁾

1, Centre Léon Bérard, Département Prévention Cancer Environnement ; INSERM UMR 1296 Radiations : Défense, Santé, Environnement ; 28 Rue Laënnec 69008 Lyon
 2, Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Service de Génétique, F-75015 Paris, France; Université Paris Cité, F-75006 Paris, France



ETUDE PGL-EXPO
Impact des expositions environnementales sur le risque de paragangliome
DOCUMENT D'AIDE A LA PREPARATION DE L'ENTRETIEN TELEPHONIQUE

Vous avez accepté de participer à l'étude PGL-EXPO et nous vous en remercions. Un enquêteur professionnel de la société IPSOS vous contactera dans les prochains jours pour programmer un rendez-vous, à un moment qui vous conviendra, afin que vous puissiez répondre au questionnaire lors d'un entretien téléphonique d'environ 45 minutes à 1 heure. Vous ne serez pas sollicité davantage suite à cet échange téléphonique. Nous vous remercions par avance du temps que vous consacrez à cette étude.

Le présent document a pour but de vous aider à préparer cet entretien téléphonique. En effet, les questions auxquelles vous allez devoir répondre peuvent faire appel à votre mémoire et/ou à celle de vos proches. Il vous sera demandé, l'adresse exacte de tous les domiciles que vous avez habités depuis votre naissance, et votre parcours professionnel. C'est pourquoi nous vous conseillons de remplir ce document avant l'entretien téléphonique et de le conserver proche de vous au moment de l'appel de l'enquêteur. Vous munir de votre carnet de santé pourra aussi être utile pour répondre à certaines questions.

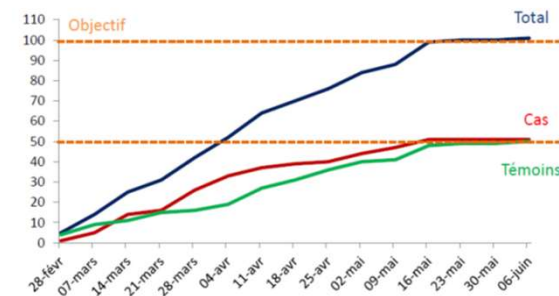
Dans tous les cas, l'enquêteur sera là pour vous aider. En cas de doute sur la question posée, n'hésitez pas à lui demander des explications complémentaires. Vous pouvez également demander à un proche d'être présent avec vous au moment du rendez-vous téléphonique.



Etes-vous prêt.e ?



Nombre d'inclusions cumulées



**101 subjects included (1 centre: HEGP), 82 interrogated
 Participation rate: 81.2%**

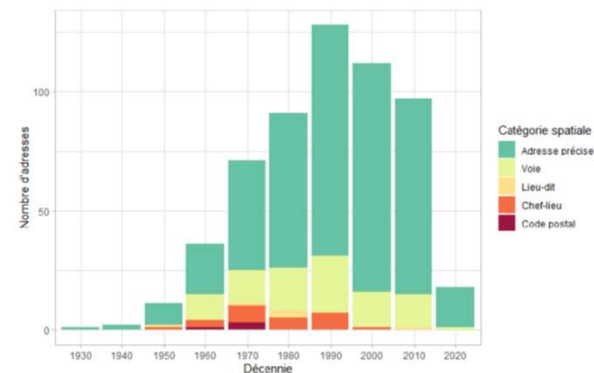


Figure 10. Détail de la répartition des adresses PGL-EXPO-1 par catégorie spatiale en fonction de la décennie.

Bonne qualité du géocodage



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PGL.EXPO 2 :
Impact of environmental exposures on tumor risk in subjects at risk
for SDH-determined hereditary paraganglioma.

Clinical Trial NCT06408402

650 cases/650 controls in 26 centers in France
inclusions ongoing



Exposure to SDHi reproduces effects observed in SDH^{-/-} tumors

TAKE HOME MESSAGE

- ✓ Chemical inactivation of SDH by bixafen mimics several key events observed during genetic inactivation in SDHx-deficient cancers
- ✓ These effects might be involved in tumor development in rodents in response to chronic SDHi exposure but are not specifically explored by regulatory evaluation tests
- ✓ SDHi exposure might induce progression to a more aggressive phenotype in patients with cancers linked to SDHx mutations → PGL.EXPO Project
- ✓ Other susceptible populations?



Genetics and Metabolism of Rare Cancers lab

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HOLIMITOX
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Acknowledgements

Metabogroup

Arnaud Tête

Carolina Duarte

Hospital

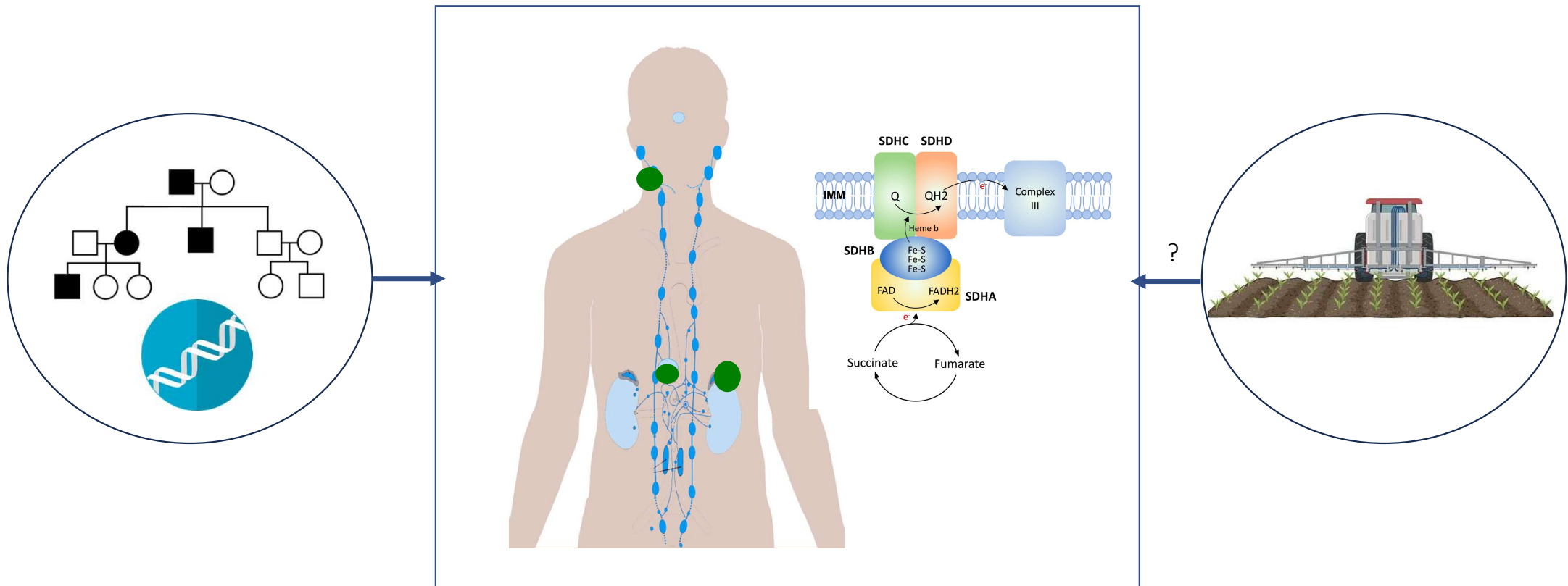
Kloé Debizet

Jules Imler

Xavier Coumoul



Thank you for your attention





Acknowledgements

