PRIX DE RECHERCHE 2018
DU GROUPE D'ETUDES DES TUMEURS NEURO-ENDOCRINES (GTE)
Règlement

## PRESENTATION

Le Prix de Recherche du GTE a été créé par le GTE en 2009.

## OBJECTIF

Le but est d'aider le financement de projets de recherche translationnelle ou clinique dans le domaine des tumeurs neuroendocrines et au sein des réseaux.

## PROVENANCE DES FONDS

Les fonds proviennent de financements de l'industrie pharmaceutique (pour 2018 : IPSEN (30 000 €uros), AAA (20 000 €uros), Novartis (15 000 euros), Keocyt (10 000 euros), Pfizer (10 000 euros)) ou biomédicale, de dons privés (associations de patients) ou d'institutions publiques ou de revenus du GTE de toutes natures.

## MONTANT ET UTILISATION DES FONDS

La totalité des fonds recueillis chaque année est destinée à cette aide, néanmoins les fonds peuvent être débloqués sur 2 années en cas de versement particulièrement important une année. En cas de projet de montant inférieur à la somme totale d'une bourse, le budget restant sera conservé pour la bourse de l'année suivante. Le montant global de l'aide apportée chaque année est préalablement défini par le Conseil d'Administration et le Conseil Scientifique. Le montant maximal attribué à un projet est également défini par le Conseil d'Administration. Des thématiques ciblées sont envisageables.

Le montant de l'aide est versé à un organisme et non à un individu. L'organisme destinataire a la responsabilité du règlement d'éventuelles charges (sociales, assurances, …), la somme versée comprenant celles-ci.

Pour l'année 2018, le montant du fonds de recherche est de 85 000 Euros. Quatre projets de recherches translationnelle, cliniques, ou nucléaires seront financés à hauteur d'un montant de 15 000 euros, 2 bourses de 20 000 euros et 30 000 euros (respectivement GTE-NOVARTIS, GTE-AAA, GTE-KEOCYT-PFIZER, , GTE-IPSEN).

## JURY

Le jury est constitué de l'ensemble des membres du Conseil d'Administration et du Conseil Scientifique du GTE. Les principales spécialités sont représentées. Le Président du Jury, désigné par le Conseil d'Administration, a voix prépondérante. Les membres du jury concernés par un des dossiers ne votent pas pour ce dossier. Les dossiers sont classés selon leur pertinence par chaque membre du jury. La synthèse des classements est réalisée lors de la réunion du jury. Cette réunion est physique, par téléphone ou électronique.

## CONSTITUTION DU DOSSIER

- *Candidat*
  - Sans limite d'âge,
  - Le candidat doit être membre du GTE ou, à défaut, avoir demandé son adhésion avant la soumission,
  - Il s'engage à faire mention de la provenance de l'aide du GTE dans toute publication orale ou écrite et à présenter ses résultats lors du Congrès National des Tumeurs Neuroendocrines du GTE à la demande du Conseil d'Administration.

- *Thématique*
  - Tumeurs neuroendocrines de toute localisation,
  - Les projets ne concernent pas les cancers thyroïdiens hors CMT, les tumeurs hypophysaires, les corticosurrénalomes,
  - Recherche fondamentale, clinique ou préclinique.

- *Soumission*
  - La soumission se fait exclusivement par voie électronique.
  - Le dossier doit tenir en un seul document numérique comprenant tous les éléments demandés, et doit être envoyé par e-mail, en document attaché, au secrétariat du GTE.
  - Le dossier (joint) doit être rédigé selon les recommandations.

## CALENDRIER 2018

- Date de mise en ligne : le mercredi 20 juin 2018, sur le site internet du GTE : http://www.reseau-gte.org
- Date limite de dépôt des demandes : le mercredi 31 octobre à minuit,
- Adresser le dossier au secrétariat du GTE, à l'adresse suivante : secretariatgte@gmail.com
- Remise officielle de la bourse lors du Congrès National des Tumeurs Neuro-endocrines du GTE les 6 et 7 décembre 2018 à Paris.

FONDS DE RECHERCHE
DU GROUPE D'ETUDES DES TUMEURS NEURO-ENDOCRINES (GTE)
Fiche de candidature 2018

Les dossiers doivent être adressés par voie électronique directement au secrétariat du GTE (secretariatgte@gmail.com). Le secrétariat du GTE se charge de transmettre tous les dossiers aux membres du jury.

Le dossier doit être composé de la fiche de candidature et du projet de recherche rédigé selon les recommandations suivantes

Les dossiers doivent être reçus au plus tard le 31 octobre 2018 à minuit pour être pris en compte.

| **ETAT CIVIL DU CANDIDAT** | |
|---|---|
| Titre : **Dr** | Nom : **BROUTIN** |
| Prénom : **Sophie** | |
| Date de naissance : **12/09/1978** | |
| Fonction actuellement occupée : Praticien spécialiste des CLCC | Jusqu'à : CDI |
| Adresse professionnelle : **Institut de cancérologie Gustave Roussy** | |
| Département de Biologie et Pathologie Médicales - 114 rue Edouard Vaillant | |
| Code Postal : 94805 | Ville : Villejuif |
| Téléphone : 0142114057 | Mobile : 0622435093 |
| E mail : **sophie.broutin@gustaveroussy.fr** | |
| Membre du GTE depuis l'année : 2018 (demande faite en parallèle) | |

***Si non membre, je m'engage, sur l'honneur, à déposer une demande d'adhésion auprès du secrétariat du GTE, avant la soumission de ce dossier de candidature.***
***Le document est en ligne sur le site du GTE : http://www.reseau-gte.org***

| TITRE DU PROJET (en minuscules) |
|---|

**Evaluation préclinique et clinique du succinate comme biomarqueur diagnostique et de réponse dans les phéochromocytomes *SDHB* muté.**

| DEPENSES ET CREDITS DEMANDES (budget détaillé) |
|---|

| | Détails | Montants |
|---|---|---|
| Achat de matériels | Licence Calcusyn® (licence pour déterminer les index de combinaison) | 500 |
| Dépenses de fonctionnement | Consommables culture cellulaire, drogues & réactifs, pré-colonne et colonne HPLC, consommables LC-MS/MS | 11300 |
| Vacations | Etudiant Master 2 (6 mois) | 3100 |
| **Somme totale demandée** | **15000** | |

* : Justifier brièvement l'achat de matériel dans le cadre du projet soumis** : Le coût indiqué comprend les charges sociales ; les autres coûts doivent être en TTC.

| AUTRES SOURCES EVENTUELLES DE FINANCEMENT DU PROJET (obtenues ou demandées) |
|---|

| |
|---|
| Organisme : / |
| Date : / |
| Somme : / |
| Lieu et date : / |
| E mail : / |

Je m'engage sur l'honneur à remplir exactement la fiche de candidature et, à adhérer sans réserve au règlement du Fonds de Recherche du GTE.

Fait à : Villejuif Le : 31/10/2018

SIGNATURE DU CANDIDAT (obligatoire, elle doit être scannée et insérée ci-dessous)

**Recommandations de rédaction de l'exposé scientifique**

1.) **Responsable** : Dr Sophie BROUTIN

2.) **Curriculum vitae du responsable** (1/2 page)

## Expériences professionnelles

| | |
|---|---|
| 2009- | **Praticien hospitalier spécialiste des CLCC** – Gustave Roussy & Université Paris-Sud 11, *France*<br>Attaché (2009-2010), AHU (2010-2012), Praticien (2012-2014), Praticien Spécialiste (2014-)<br>❖ **Activités cliniques et de recherche** – **Service de Pharmacologie** (Pr A Paci)<br>Suivi thérapeutique pharmacologique ; Développement analytique ; Etudes PK/PD<br>❖ **Activités de recherche** – **Unité CNRS 8203** (Dr L Mir / Pr A Paci) – depuis 2015<br>Etudes pharmacologiques et recherche de biomarqueurs des cancers *SDH-x*<br>❖ **Activités de recherche** – **Unité CNRS 8200** (Dr P Kannouche / Pr JM Bidart) – 2009-2013<br>Pharmacologie moléculaire de thérapies moléculaires ciblées seules, ou en association<br>❖ **Enseignements** – **Faculté de Pharmacie** (Pr JM Bidart) – 2010-2012 - Biotechnologies |
| 2013-2014 | **Post-doctorante** – Institute Of Cancer Research & Royal Marsden Hospital, *Sutton/London, UK* (Dr U Banerji)<br>**Détermination préclinique de bases rationnelles pour l'évaluation clinique de l'association d'inhibiteurs des voies de signalisation MAPK et PI3K/AKT/mTOR en cancérologie** |
| 2006-2011 | **Master 2 & Doctorante** - Gustave Roussy, *Villejuif, France* UMR8200 (Dr P Kannouche ; Pr JM Bidart)<br>**Pharmacologie moléculaire du sunitinib et du vandetanib, deux inhibiteurs d'activité kinase, dans le cancer médullaire de la thyroïde.** |
| 2002-2007 | **Internat en Pharmacie Hospitalière et de Collectivités** – *Ile-de-France* |

## Compétences

| | |
|---|---|
| Pharmaceutique | **Validation analytique et biologique des analyses pharmacologiques ;** |
| Techniques | **Biologie cellulaire** (lignées humaines, tests de prolifération, transfection) ; **Etudes *in vivo*** (xénogreffe, suivi échographique, dissection) ; **Biochimie** (western-immunoblotting, ELISA, MSD® arrays) ; **Biologie moléculaire** (extraction, purification et quantification d'ADN et d'ARN, Q RT PCR, microarrays) ; **Protéomique** (LC-MS/MS, HPLC-UV, RPPA, IHC) |
| Management | **Gestion de projets multidisciplinaires ; Encadrement**: techniciens et étudiants |
| Enseignement | **Master 2, Faculté de pharmacie** (UE56)**, personnel de Gustave Roussy** (étudiants, techniciens, biologistes) |
| Communication | **Préparation de rapports pour communications orales et écrites** |
| Langue | **Français**, courant. **Anglais,** scientifique courant (écrit et parlé) |
| Informatique | **Microsoft office®**; **GraphPad Prism®; Rosetta resolver®, Ingenuity®; Bio1D®** |

## Diplômes et formation universitaire

| | |
|---|---|
| 2011 | **Doctorat d'Université Cancérologie-Biologie-Médecine-Santé** – Université Paris-Sud 11 |
| 2008 | **DUERCC** DU Européen de Recherche Clinique en Cancérologie – Université Paris-Sud 11 |
| 2006 | **Master 2 Biologie et pharmacologie cellulaire** – Université Paris Descartes |
| 2007 | **DES de Pharmacie Hospitalière et des collectivités** – Université Paris Descartes |
| 2007 | **Doctorat de Pharmacie** – Université Paris Descartes, *France* |

3.) **Résumé du projet** (environ 250 mots)

Malignant paraganglioma/pheochromocytoma (MPP) are a very rare subgroup of neuroendocrine tumors. Identification of molecular alterations involved in MPP oncogenesis such as *SDHB* germline mutations has suggested new therapeutic strategies in the context of personalized medicine. Inactivating *SDHB* mutations induce an intracellular accumulation of succinate. It has been demonstrated that detection of succinate by (1)H-MRS allowed *SDHB* mutations detection, suggesting a role of succinate as biomarker.

Identification of surrogate biomarkers that can identify mutated patients and/or early determine patients who achieve clinical benefits is of major interest.

The aim of this translational project is to evaluate succinate as a potential pharmacodynamic biomarker in *SDHB* mutated cancers using preclinical and clinical models. Succinate will be quantified using a simple and fully validated LC-MS/MS method, suitable for clinical applications.

4.) **Exposé du projet** (10 pages maximum en double interligne, présentant les points suivants) :

- ✓ Position du problème

Malignant pheochromocytoma and paragangliomas (MPP) are a rare subgroup of neuroendocrine tumors (NETs) with an incidence less than 1 per million people per year. Regarding this very low incidence, setting up clinical trials for MPP is very challenging and up to now, only a few prospective studies have investigated potential therapies for the disease (Baudin et al., 2014; Ezzat Abdel-Aziz et al., 2015). Antitumor therapeutic options for MPP depend on disease progression and rely on imaging-guided therapy, surgery, MIBG-therapy and chemotherapy. Currently, MIBG-therapy and dacarbazine-based chemotherapy are recommended for MPP patients with aggressive tumors but display low tumor response rates ranging from 22 to 48% and no complete response (Baudin et al.,

2014; Hadoux et al, 2014; Ayala et al. 2012). Development of new drugs is thus of major need and research in this area mainly relies on identification of molecular targets, one of the leading therapeutic strategy in oncology.

MPP are characterized by the presence of various mutations and in particular at *SDHx* genes which encode for the succinate dehydrogenase, a mitochondrial enzyme composed of four subunits (A to D). Physiologically SDH participates in both the electron transport chain and the citric acid cycle (TCA cycle or Krebs cycle) catalyzing the oxidation of succinate to fumarate (Bardella et al., 2011 ; Raimundo et al., 2011).

*SDHB* germline mutations are found in 40% of metastatic MPP patients (Letouzé et al., 2014; Favier et al., 2015; Hescot et al., 2013) but also in 7.5% of GIST and <0.2% of Renal Cell Carcinoma (Kuroda N, et al., 2016; Miettinen M, Lasota J., 2014). As a consequence, when mutated, *SDHB* losses his function, leading to accumulation of its substrate, the succinate, which acts as an oncometabolite by inhibiting 2-oxoglutarate dependent dioxygenases. In particular, abnormal high concentrations of succinate lead to inhibition of prolyl hydroxylase domain (PHD), an enzyme that converts HIF2α in HIF2α dihydroxylated. This inhibition results in an accumulation of HIF2α, a proangiogenic factor, and thus triggers the pseudo-hypoxic response. Antiangiogenic drugs have been thus considered as potential treatments for *SDHB* mutated MPP. Antitumor activity of sunitinib, a well-known antiangiogenic drug, has been reported in a retrospective study in MPP patients (Ayala-Ramirez et al., 2012) and currently sunitinib is under clinical investigation for MPP patients in a prospective international randomized phase 3 trial, FIRSMAPP (First Randomized STudy in Malignant Progressive Pheochromocytomas ; P.I. : Dr E. Baudin, Gustave Roussy).

Succinate accumulation also leads to histones and DNA demethylases inhibition and induces a hypermethylator phenotype. Indeed, inhibition of the TET (Ten Eleven Translocation) family enzymes, hampers the transformation of 5-methylcytosine in 5-hydroxy-methylcytosine, which

results in DNA hypermethylation. This DNA modification has been implicated in tumor degeneration through the inactivation of tumor suppressor genes (Letouzé E, et al., 2014). Additionally, it has been demonstrated that 5-methylcytosine could generate mutations by spontaneous deamination resulting in a transition mutation in the genetic code from cytosine to thymine, by increased absorption of UV rays, and by increased binding of carcinogens. The use of demethylating agents, such as azacytidine, has been suggested as a new therapeutic strategy to treat MPP patients (Powers et al., 2014).

Finally, succinate accumulation has been shown to induce hypermethylation of the promoter of the gene encoding for MGMT enzyme (O-(6)-methylguanine-DNA methyltransferase), leading to a decreased expression of MGMT protein, a demethylation enzyme involved in DNA damage repair induced by alkylating agents. In line with this finding, anti-tumor activity of temozolomide (TMZ), an alkylating agent, has been recently reported with a 35% response rate and 19.7 months median PFS but only in *SDHB* mutated patients (Hadoux et al., 2014). A French phase 2 clinical trial of personalized medicine in progressive MPP patients, the JuMMPPinT01 trial, will start in 2019 (PHRC-K15-184 / 102, P.I.: Dr E. BAUDIN, Gustave Roussy). This trial will be guided by germline and somatic molecular portrait of patients and will evaluate, in particular TMZ, in a prospective cohort of *SDHB* mutated patients.

Identification of surrogate biomarkers that can easily identify mutated patients and/or early determine patients who achieve clinical benefits, is of major interest for clinical management of MPP patients. Interestingly, *SDHB* mutation causes a loss of function of the enzyme, which results in an accumulation of succinate, a TCA marker. Recently, it has been shown that detection of succinate by (1)H-MRS allowed *SDHx* mutations detection (Lussey-Lepoutre et al., 2016), suggesting that succinate could be a metabolic biomarker of SDH-x diseases like 2- hydroxyglutarate (2- HG) in IDH mutated acute myeloid leukaemia (AML) (Lendvai et al., 2014). Indeed, 2-HG, is a neo-

oncometabolite, produced when IDH, another TCA enzyme, is mutated, avoiding Isocitrate transformation in α-ketoglutarate but leading to 2-HG neo-production. Interestingly, high serum concentrations of 2-HG (over 2µM) have been correlated with the presence of an IDH mutation and is used as a biomarker of the AML IDH mutated disease (Janin et al., 2014). The Pharmacology and Drug analysis department at Gustave Roussy has acquired expertise in TCA biomarker quantification since 5 years, especially in 2-HG quantification (Poinsignon et al., 2016).

Finally, it has to be pointed out that up to now there are no good predictors of response that would help to identify MPP responders and non-responders in order to propose alternative therapeutics.

- ✓ Nature de la recherche (diagnostique, thérapeutique, étiologique, autre…)

This project is a translational research study evaluating a potential diagnostic and/or treatment response biomarker of *SDHB* mutated MPP. Preclinical and clinical evaluations will be performed.

- ✓ Durée prévue du projet

This proposed project is part of a PhD program and will be performed over 1 year.

- ✓ Objectif de la recherche

The aim of this study is to evaluate succinate as a potential diagnostic serum biomarker of SDHB cancers and a potential early biomarker of treatment response.

- ✓ Méthodes

<u>1- Preclinical models</u>

In vitro, *SDHB* gene has been stably invalidated in hPHEO1 cells using the innovative CRISPR-Cas9 system (Ran et al., 2013). hPHEO1 is a human cell line derived from a human MPP (Ghayee et al.,

2013). Two *SDHB* invalidated clones have been obtained and will be used and compared to the parental *SDHB* wild-type (wt) cell line.

2- Clinical models

In collaboration with the Endocrine Oncology Department headed by Dr Eric Baudin, serum samples and clinical data of MPP patients will be collected. A prospective collection has already been initiated (currently, n=88 patients).

3- Drugs

Regarding molecular alterations induced by *SDHB* mutations, promising molecular treatments, currently under clinical evaluation, have been identified:

- Temozolomide, an alkylating agent. We have obtained preliminary data using cell line models and we showed promising results such as a decrease of cell viability in SDHB SiRNA cell line models, in line with clinical data.

- Anti-angiogenic drugs: Sunitinib, a well-known tyrosine kinase inhibitor which targets platelet-derived growth factors (PDGFR), VEGFR, KIT and FLT3 ; BAY 87-2243, a potent and selective hypoxia-inducible factor (HIF) inhibitor.

- Azacytidine, a demethylating agent targeting hypermethylation of DNA identified in *SDHB* mutated MPP.

These drugs are already available in our lab.

4- Determination of $IC_{50}$

For each cellular model (hPHEO1 wt and the 2 clones), antiproliferative effects of each drug will be evaluated and $IC_{50}$ will be determined using the WST1® reagent (Roche). Drugs combination index (CI) will be defined for all drugs' combinations using WST1® and the CalcuSyn® software.

5- SDH activity

Characterization of enzymatic SDH activity will be assessed for each cellular model, untreated and treated with the previously defined $IC_{50}$ of each drug, using the Mitochondria Isolation Kit® and the SDH activity assay® (Sigma).

6- Succinate quantification & evaluation as a biomarker

Succinate levels will be quantified using a fully validated liquid tandem mass spectrometry (LC-MS/MS) by the pharmacology lab (Pr. A. Paci).

Its putative role as a potential biomarker of SDHB mutation will be investigated in vitro and in vivo: succinate will be quantified in preclinical (cell pellets, culture supernatants of the 3 cellular models) and clinical (human serum) samples at baseline.

Its putative role as a potential early biomarker of follow-up of treatments response will be investigated in vitro: succinate will be quantified in cell pellets and culture supernatants of each cellular model (parental hPHEO1 and the 2 SDHB invalidated clones), untreated and treated with the previously defined $IC_{50}$ of each drug and the best drugs combinations concentrations.

7- Statistics

Statistics will be performed using the GraphPadPrism® software, available in our lab.

This project will be headed by Dr Sophie Broutin, PharmD-PhD, working both in the UMR8203 and in the Pharmacology and Drug analysis department at Gustave Roussy. Dr Broutin is a pharmacologist whose research activities are in line with drug 'combinations and biomarkers' of response. During her post-doctoral fellowship (Clinical Pharmacology & Trials unit headed by Dr Banerji -The Institute of Cancer Research, London, UK) she investigated insights into significance of combined inhibition of MEK and m-TOR signalling output in KRAS mutant non-small-cell lung cancer (Broutin et al., 2016). At Gustave Roussy institute, Dr Broutin is involved in Krebs cycle biomarkers such as 2-

hydroxyglutarate in IDH mutated cancers (Poinsignon et al., 2016) and succinate in SDH-x mutated pathologies (supervision of a Msc candidates since 2015).

In order to set up this project, Dr Broutin will supervise Constance Lamy(PhD student, 2nd year) who obtained a PhD funding by the French ministry of higher education and research and a Master 2 student. Experiments will take place in the UMR8203 research team and in collaboration with the pharmacology laboratory, headed by Pr Paci. Dr Baudin and Dr Hadoux will be involved in the clinical part of this project.

- ✓ Population de patients étudiés

At the preclinical level, hPHEO1 cells, a human cancer cell line of pheochromocytoma, will be used (Ghayee et al., 2013). At the clinical level, serum from MPP patients treated at Gustave Roussy cancer center will be studied (Dr Baudin and Dr Hadoux).

- ✓ S'il y a eu une étude antérieure de faisabilité, la rappeler brièvement et indiquer ses résultats.

A fully validated liquid tandem mass spectrometry (LC-MS/MS) has been developed by the pharmacology laboratory (Pr. A. Paci) and allows succinate quantification in serum, cell pellets and cell supernatants.

At the preclinical level, SDHB invalidated clones have been obtained by Constance LAMY during her first year of PhD and will be used for this project.

At the clinical level, succinate has already been quantified in 169 serum samples from 58 patients. Results have been recently presented at the 2017 European Congress of Endocrinology meeting (Lisbon), showing a significant increase of succinate level in patients with SDH-B mutated MPP (n=70) compared to MPP wild-type patients (n= 65) and MPP SDH-D mutated patients (n=13).

✓ Résultats attendus

This research project aims to evaluate succinate as a biomarker of SDHB MPPs. Identification of surrogate biomarkers that can easily identify mutated patients and/or early determine patients who achieve clinical benefits is of major interest. Thus this program is expected to improve therapeutic management of *SDHB* patients using a simple and cheap test, suitable for clinical applications.

✓ Suite envisagée au terme de l'étude

We aim to deal with the evaluation of succinate as a biomarker of treatment response in depth, using in vivo models of MMP (xenografted mice and PDX models) and serum patient's samples through their treatments. It has to be pointed out that Dr Baudin is involved in promising clinical MPP projects heading FIRSTMAPP and JuMMPPinT01 clinical trials with a collection of patient's serum samples during treatments. FIRSTMAPP evaluates sunitinib and JuMMPPinT01 involves different treatments of which temozolomide.

**Références**


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✓ Justification du financement demandé

Le financement demandé a pour but de couvrir les dépenses suivantes :

| | € |
|---|---|
| **Achat de matériels** | |
| Licence Calcusyn® | 500 |
| **Dépenses de fonctionnement** | |
| Consommables culture cellulaire (milieux dont ACL4, plastiques, comptage) | 2800 |
| Drogues (témozolomide, azacitidne, sunitinib, PT2385) | 1100 |
| Réactifs (WST-1®, test d'activité enzymatique SDH®) | 3500 |
| Pré-colonne et colonne HPLC (CSH Phenyl-Hexyl® 1,7 µm - 2,1 x 50 mm - Acquity Waters) | 1600 |
| Consommables LC-MS/MS (poudre mère, étalon interne, solvants,…) pour le dosage du succinate | 2300 |
| **Vacations** | |
| Etudiant Master 2 Recherche (6 mois de stage) | 3100 |
| **Somme totale** | **14900** |

✓ Avis du Comité d'Ethique (un avis favorable est nécessaire pour l'attribution de crédits à toute étude impliquant une expérimentation humaine) : NON applicable.

**5.)** **<u>Equipes impliquées dans le projet</u>** (pour chaque participant : titre, prénom, nom, adresse, appartenance)

- **Dr Eric BAUDIN**, MD-PhD, Institut Gustave Roussy (Villejuif), Département de Médecine nucléaire et d'endocrinologie
- **Dr Sophie BROUTIN**, PharmD-PhD, Institut Gustave Roussy (Villejuif), UMR8203 & Service de pharmacologie
- **Dr Julien HADOUX**, MD-PhD, Institut Gustave Roussy (Villejuif), Département de Médecine nucléaire et d'endocrinologie
- **Constance LAMY**, doctorante, Institut Gustave Roussy (Villejuif), UMR8203
- **Lionel MERCIER**, technicien de laboratoire, Institut Gustave Roussy (Villejuif), Service de pharmacologie
- **Pr Angelo PACI**, PharmD-PhD, Institut Gustave Roussy (Villejuif), UMR8203 & Service de pharmacologie
- **Etudiant en Master 2 Recherche**, Institut Gustave Roussy (Villejuif), UMR8203

**6.)** **Publications antérieures du demandeur** (donner la liste des principales publications du responsable du projet ; 10 maximum) ;

**2018**

1. **Mutational profiling of isolated myeloid sarcomas and utility of serum 2HG as biomarker of IDH1/2 mutations.** Willekens C, Renneville A, Broutin S, Saada V, Micol JB, Delahousse J, Poinsignon V, Bories C, Berthon C, Itzykson R, Boissel N, Quivoron C, Terroir-Cassou-Mounat M, Bosq J, Preudhomme C, Paci A, Penard-Lacronique V, De Botton S. *Leukemia. 2018 Feb 26.*

2. **Circulating oncometabolite D-2-hydroxyglutarate enantiomer is a surrogate marker of isocitrate dehydrogenase-mutated intrahepatic cholangiocarcinomas.** Delahousse J, Verlingue L, Broutin S, Legoupil C, Touat M, Doucet L, Ammari S, Lacroix L, Ducreux M, Scoazec JY, Malka D, Paci A, Hollebecque A. *Eur J Cancer. 2018 Feb;90:83-91.*

**2017**

3. **AG-221, a First-in-Class Therapy Targeting Acute Myeloid Leukemia Harboring Oncogenic IDH2 Mutations.** Yen K, Travins J, Wang F, David MD, Artin E, Straley K, Padyana A, Gross S, DeLaBarre B, Tobin E, Chen Y, Nagaraja R, Choe S, Jin L, Konteatis Z, Cianchetta G, Saunders JO, Salituro FG, Quivoron C, Opolon P, Bawa O, Saada V, Paci A, Broutin S, Bernard OA, de Botton S, Marteyn BS, Pilichowska M, Xu Y, Fang C, Jiang F, Wei W, Jin S, Silverman L, Liu W, Yang H, Dang L, Dorsch M, Penard-Lacronique V, Biller SA, Su SM**.** *Cancer Discov. 2017 Feb 13***.**

**2016**

4. **The IDH2 R172K mutation associated with angioimmunoblastic T-cell lymphoma produces 2HG in T cells and impacts lymphoid development.** Lemonnier F, Cairns RA, Inoue S, Li WY, Dupuy A, Broutin S, Martin N, Fataccioli V, Pelletier R, Wakeham A, Snow BE, de Leval L, Pujals A, Haioun C, Paci A, Tobin ER, Narayanaswamy R, Yen K, Jin S, Gaulard P, Mak TW. *Proc Natl Acad Sci U S A. 2016 Dec 27;113(52):15084-15089.*

5. **Insights into significance of combined inhibition of MEK and m-TOR signalling output in KRAS mutant non-small-cell lung cancer.** Broutin S, Stewart A, Thavasu P, Paci A, Bidart JM, Banerji U. *Br J Cancer. 2016 Aug 23;115(5):549-52*.

6. **Dyslipidemia causes overestimation of plasma mitotane measurements.** Paci A, Hescot S, Seck A, Jublanc C, Mercier L, Vezzosi D, Drui D, Quinkler M, Fassnacht M, Bruckert E, Lombès M, Leboulleux S, Broutin S, Baudin E. *Endocrinol Diabetes Metab Case Rep. 2016;2016:150135*.

7. **Quantitation of isocitrate dehydrogenase (IDH)-induced D and L enantiomers of 2-hydroxyglutaric acid in biological fluids by a fully validated liquid tandem mass spectrometry method, suitable for clinical applications.** Poinsignon V, Mercier L, Nakabayashi K, David MD, Lalli A, Penard-Lacronique V, Quivoron C, Saada V, De Botton S, Broutin S, Paci A. *J Chromatogr B Analyt Technol Biomed Life Sci. 2016 Jun 1;1022:290-7.*

**2015**

8. **Lipoprotein-Free Mitotane Exerts High Cytotoxic Activity in Adrenocortical Carcinoma.** Hescot S, Seck A, Guerin M, Cockenpot F, Huby T, Broutin S, Young J, Paci A, Baudin E, Lombès M. *J Clin Endocrinol Metab. 2015 Aug;100(8):2890-8.*

**2014**

9. **Changes in signaling pathways induced by vandetanib in a human medullary thyroid carcinoma model, as analyzed by reverse phase protein array.** Broutin S, Commo F, De Koning L, Marty-Prouvost B, Lacroix L, Talbot M, Caillou B, Dubois T, Ryan AJ, Dupuy C, Schlumberger M, Bidart JM. *Thyroid. 2014 Jan;24(1):43-51.*

**2011**

10. **Identification of soluble candidate biomarkers of therapeutic response to sunitinib in Medullary Thyroid Carcinoma in preclinical models.** Broutin et *al., Clin Cancer Res. 2011 Apr 1;17(7):2044-54.*

**7.)** **<u>Coordonnées du compte gestionnaire des crédits</u>** :

Institut de cancérologie Gustave Roussy (cf RIB en pièce jointe)

Banque : BNP Paribas

IBAN : FR76 3000 4008 3400 0100 6312 686

Compte n° 00010063126

BNP PARIBAS

Bank Identification Number / IBAN

**INSTITUT GUSTAVE ROUSSY**
**IGR**
**DIRECTION AFFAIRES FINANCIERES**
**39 RUE CAMILLE DESMOULINS**

**94805 VILLEJUIF CEDEX**

Bank: **BNP Paribas**
Account currency: **EUR (EURO)**
Account type: **Compte chèque**

IBAN*(1)*: **FR76 3000 4008 3400 0100 6312 686**

BIC*(2)*: **BNPAFRPPXXX**

RIB*(3)*:

| Bank code | Dom. code | Account number | RIB key | Domiciliation |
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| **30004** | **00834** | **00010063126** | **86** | **CENTRE D'AFFAIRES IDF INSTITUTIONS** |

*(1) International Bank Account Number* *(2) Business Identifier Code* *(3) Relevé d'identité Bancaire*

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