PJ1

LETTRE D'ENGAGEMENT DE L'ORGANISME GESTIONNAIRE RELATIVE A LA SUBVENTION « PROGRAMME LABELLISE FONDATION ARC 2013 »

*A retourner dûment remplie **au plus tard le 2 SEPTEMBRE 2013** par courrier postal à :*
FONDATION ARC - DAS (Direction de l'Action Scientifique)
BP 90003 - 94803 VILLEJUIF CEDEX

En cas de montant accordé inférieur au montant demandé, la nouvelle ventilation financière doit être saisie sur internet (date limite 2 septembre 2013) dans le respect de la ventilation initiale :
www.recherche-cancer.net/gap

La Fondation ARC pour la recherche sur le cancer, située au 9 rue Guy Môquet, 94803 Villejuif Cedex, a décidé de soutenir financièrement le projet ci-après :

Dossier Fondation ARC n° : SL 220130607088
Subvention accordée par décision **du Conseil d'Administration de la Fondation ARC pour la recherche sur le cancer en date du** 25-06-2013

Titre du projet de recherche *en français* (ci-après « **le Projet** ») : L'implication du VEGF-C **dans les propriétés métastatiques et invasivesacquises des tumeurs en réponse aux traitements anti-angiogéniques**
Nom du Responsable Scientifique (Bénéficiaire): GILLES PAGES
Nom de la formation de recherche (laboratoire) : Centre Cancer et Veillissement (UMR7284)
Adresse du laboratoire : 28 avenue Valombrose - 06107 Nice Cedex 02

E-mail : gilles.pages@unice.fr
Téléphone : 04 93 37 76 99
Télécopie : 04 93 37 76 76

LE FINANCEMENT DE LA FONDATION ARC EST SUBORDONNE A LA SIGNATURE DE LA PRESENTE LETTRE D'ENGAGEMENT PAR L'ORGANISME GESTIONNAIRE DU FINANCEMENT.

1. Organisme gestionnaire

Nom de l'Organisme gestionnaire : « Intitulé » (ex : INSERM, CNRS, ...)
(ci-après « l'Organisme gestionnaire»)
Centre National de la Recherche Scientifique - Délégation Côte d'Azur (CNRS - DR20)
Forme sociale : Etablissement Public à caractère scientifique et technologique
Adresse : 250 rue Albert Einstein - 06560 Valbonne

Nom du représentant légal : Madame Béatrice SAINT-CIRCQ
Personne habilitée à émettre l'appel de fonds et à signer la présente lettre d'engagement
Qualité du représentant légal : Déléguée Régionale

BENEFICIAIRE (nom, prénom) : Gilles PAGES DossierFondationARC n°: SL220130607088

2. **Financement accordé par la Fondation ARC (CA du 25 juin 2013)**
Montant du financement alloué par la Fondation ARC à l'Organisme gestionnaire : 350 000.00 €
Date limite d'utilisation 1ere tranche: 30/06/2016

La Fondation ARC s'engage à verser la présente subvention à l'Organisme Gestionnaire selon la procédure définie à l'article 5 des Conditions générales de la Fondation ARC.

La Fondation ARC effectue les versements à l'Organisme Gestionnaire par virement aux coordonnées bancaires suivantes :

Banque : Trésorerie Générale des Alpes Maritimes
Compte ouvert au nom de : L'Agent Comptable Secondaire du CNRS
Code banque : 10071
Code guichet : 06000
N° de compte : 00001005422
Clé RIB ou RIP : 23

Coordonnées de l'Agent Comptable de l'Organisme Gestionnaire :

NOM, Prénom : BUSBY Murielle
Adresse postale :CNRS – 250 rue Albert Einstein – 06560 Valbonne
Téléphone : 04 93 95 43 34
Adresse e-mail : murielle.busby@cnrs.fr

3. **Droits et obligations de la Fondation ARC, de l'Organisme gestionnaire et du Bénéficiaire**
La signature de la présente lettre d'engagement par l'Organisme Gestionnaire et par le Bénéficiaire vaut acceptation des termes des « Conditions générales relatives à l'utilisation des fonds de recherche » de la Fondation ARC (*Réf. : DFC notification CA 25-06-2013).*
Document à télécharger : www.recherche-cancer.net/financements/notif

Signatures :

REPRESENTANT LEGAL	**RESPONSABLE SCIENTIFIQUE**
de l'Organisme gestionnaire	**(bénéficiaire)**
Béatrice SAINT-CRICQ	**Gilles PAGES**
Date :	**Date :**

Cachet de l'Organisme gestionnaire :

RESEARCH SERVICE CONTRACT
N° EPPA 185765-G

BETWEEN:

Roche, a simplified joint-stock company (SAS) with a capital of € 38 168 895,55 whose registered office is located at 30, cours de l'Ile Seguin, 92650 Boulogne-Billancourt Cedex, France, SIREN N° 552 012 031 in the Trade Register of Nanterre

Represented by,

Dr. Ariel Savina, Scientific Partnerships Leader

Hereinafter referred to as the "**Company**"

OF THE ONE PART

AND

The **CENTRE NATIONAL de la RECHERCHE SCIENTIFIQUE**, public establishment for scientific and technological research, with registered offices located at 3 rue Michel Ange 75794 Paris Cedex 16, France, SIREN no. 180 089 013, APE/NAF 9311, represented by its President, Alain Fuchs, having given signatory power for this agreement to Pierre Dauchez, Regional Delegate of the Delegation Côte d'Azur,

referred to hereinafter as "the **CNRS**"

AND

The **UNIVERSITE NICE SOPHIA ANTIPOLIS,** scientific cultural and professional public establishment with registered offices located at 28, Avenue Valrose- Grand Château, BP 2135, 06103 Nice Cedex 2, France, SIRET 19060931300019, represented by its president, the Professor Frédérique Vidal,

referred to hereinafter as "**UNS**"

The CNRS and the UNS collectively referred to hereinafter as "the **Service Provider**", acting for and on behalf of IRCAN, UMR 7284, INSERM, directed by M. Eric Gilson, referred to hereinafter as "the Laboratory"

OF THE OTHER PART

With the **Company** and **Service Provider** being hereinafter referred to, whether collectively or otherwise, as the "Party (ies)".

PREAMBLE

The **Service Provider** has expertise in exploring the mechanisms of tumorigenesis and antitumor agent.

The **Company** develops molecules as potential therapies and wishes to study mechanisms of action more deeply.

NOW, THEREFORE, THE PARTIES HAVE AGREED AND DECIDED AS FOLLOWS:

ARTICLE 1 – DEFINITIONS

In this contract, and unless the context clearly indicates otherwise, the terms starting with a capital letter are defined as follows, it being understood that words in the plural may be understood in singular and vice versa.

"Service Provider's Own Knowledge": means the information, know-how, inventions, technologies, industrial property rights, biological or chemical molecules, as well as any biological material, whether covered by an intellectual property right or otherwise, acquired or developed by the **Service Provider** during its own research or in collaboration with third parties, prior to signing the Contract or independently of the Contract and which are necessary to realize the Study. The development of cell lines models is a Service Provider's Own Knowledge.

"Confidential Information" means all information and/or all data in any form and of any kind whatsoever, including, in particular, all written or printed documents, all samples, models and/or knowledge patentable or otherwise, disclosed by one Party to one or more other Parties under the Contract.

"Contract": means this document and its appendices.

"Effective Date" means the date of the last signing of the Contract.

"Study": means the study entitled *"In vitro study for the predictive role of Tristetraprolin polymorphism for testing sensitivity or absence of efficacy of Trastuzumab and/or Pertuzumab in patients with breast cancer over-expressing her2"*, conducted by the **Service Provider** in accordance with the Study Program.

"Science Contact": means Dr. Ariel Savina, personnel of the **Company**, correspondent of the Laboratory within the **Company**.

"Material": means Trastuzumab, 200mg and Pertuzumab, 200mg for the whole Study, as stated in Appendix 2, as well as all documentation or information relating to it (use, conditions of storage, safety, etc.) required by the **Service Provider** to conduct the Study.

"Study Program": means the Study Program, as defined in Appendix 1.

"Middle and Final Reports": means the reports drawn up by the Science Manager at the end of the second semester and at the end of the Study respectively, as defined in article 4.2.

"Results": means all the results obtained at the time of conducting the Study, namely, the scientific and technical knowledge, whether patentable or not or otherwise, arising directly from the work carried out during the course of the Study and obtained as part of this Contract. Improvements obtained, whilst conducting the Study Program, on the Service Provider's Own Knowledge, are not Results.

"Science Manager": means Dr. Gilles Pages, personnel of the **Service Provider**, in charge of the scientific aspects of the Study.

ARTICLE 2 – PURPOSE

Under the Contract, the **Company** appoints the **Service Provider** to conduct the Study as provided for in the Study Program.

ARTICLE 3 – TERM OF THE CONTRACT

3.1 The Contract is entered into for a term of eighteen (18) months as from its Effective Date.

3.2 The Study shall start as from the reception of the Material by the **Service Provider**.

3.3 The Contract may be renewed by mutual written agreement between the Parties by means of a supplementary agreement stating the purpose and terms, especially financial, of this renewal.

ARTICLE 4 – CONDUCTING THE STUDY

4.1 The **Service Provider** shall conduct the Study, under the scientific responsibility of the Science Manager, in accordance with the Study Program.

If the Science Manager or Science Contact is prevented, for any reason whatsoever, from fulfilling his obligations under the Contract, the Parties shall seek, by mutual agreement, a replacement solution. If no agreement can be reached within two (2) months following the occurrence of the prevention, the Contract may be terminated on the initiative of the earliest petitioner, under the conditions of article 10 below.

4.2 The Science Manager shall keep the Science Contact informed of the state of progress of the Study, especially by sending him a detailed Middle and Final Reports, no later than one (1) month after the end of the second semester and at the end of Study respectively. Further, to the end of ensuring an appropriate progress of the project, the **Service Provider** and the **Company** will organize follow up meetings or call conferences every 6 (six) months during the Research Study Period. The **Service Provider** shall send to the Science Contact a pre-reading presentation of the results (PP or PDF format) at least one (1) week before the date of the meeting.

4.3 Within forty-five (45) days after signing of the Contract, the **Company** undertakes to supply the Material free of charge to the **Service Provider**. The Material shall be delivered to the following address:

Dr. Gilles Pages

Institut Cancer et Vieillissement de Nice (IRCAN)

UMR 7284/U1081; Université de Nice Sophia-Antipolis, Centre A. Lacassagne

33 Avenue de Valombrose

06189 Nice, France

Tél : 04 92 03 12 31

Fax : 04 92 03 12 35

gpages@unice.fr

It is understood that the Study may not start until the Material has been received by the **Service Provider**.

Under no circumstances may the **Service Provider** be held responsible and/or liable for a delay or non-realization of the Study in case of:

- default or delay by the **Company** in supplying the Material;
- non conformity of the Material, especially if the Material does not comply with the technical characteristics described in Appendices 1 and 2. In this case, the **Service Provider** may terminate the Contract under the conditions set out in article 10.

4.4. The **Service Provider** shall conduct the Study in accordance with the applicable laws and guidelines regarding animal testing in the country where the Study is conducted. **Service Provider** herewith confirms that it will strictly apply to the corresponding applicable legal provisions and that it will use its best efforts so that the welfare of the animals involved with the testing is adequately and fairly protected.

4.5 The **Service Provider** will perform the Study with fully qualified and trained personnel with the required level of knowledge and experience.

4.6 **Company** will have the right, but not the obligation, to audit the conduct of animal testing performed under this Contract. **Service Provider** will allow the **Company** designated staff access to all animal testing under this Contract for inspection. Visits by the **Company** designated staff, will be arranged by mutual convenience and shall be submitted to the obligation of confidentiality mentioned at Article 7.

4.7 Should any local and/or national government authority conduct, or give notice of intent to conduct, an inspection or take any other regulators action with respect to the services provided by **Service Provider** under this Contract, **Service Provider** will promptly give **Company** notice thereof, supply all information pertinent thereto and **Company** shall have the right, but not the obligation, to be present at any such inspection or regulatory action.

4.8 If, during an audit, the **Company** designated staff discovers non-compliance with the applicable laws and regulations in the treatment of the animals, **Company** can request immediate correction or terminate the Contract with immediate effect.

ARTICLE 5 – FINANCIAL CONDITIONS

5.1 Amount of the Study

5.1.1 In consideration of the complete performance of the **Service Provider**'s obligations hereunder, the **Company** shall pay to CNRS the sum of thirty thousand (30 000) euros, taxes excluded, as follows:

a) 15 000 euros, excluding taxes, upon execution by both Parties of this Contract;

b) 10 000 euros, excluding taxes, at the receipt of the Middle Report at the most 13 months after the Effective Date.

c) 5 000 euros, excluding taxes, at the receipt of the Final Report at the most 19 months after the Effective Date.

This is an all-inclusive payment that includes, but is not limited to, salary of the staff and any related costs, costs of the Study, overhead, consumables, equipment, support functions, and additional costs such as insurance (excluding VAT, see section 5.1.2).

5.1.2 The amounts indicated above will be increased by VAT (19,6 %), at the rate in force on the day of the chargeable event.

5.1.3 **Service Provider** shall not be entitled to any further financial reimbursement under this Contract without written approval of **Company**. Any extension to the Study Program may bring about a revision of the contractual amounts indicated above, by mutual agreement between the Parties. This revision shall be recorded in a supplementary agreement to this Contract.

5.1.4 A part of this amount may be allocated to remuneration of personnel by the **Service Provider** appointed to conduct the Study.

5.1.5 Furthermore, with the prior agreement of the **Company**, the latter shall cover the travel expenses incurred in conducting the Study by the Science Manager and the personnel of the **Service Provider** involved in conducting the Study.

5.2 Payments

5.2.1 The **Company** shall make settlements on presentation of invoices issued by the CNRS in the name of the **Company** by transfer into the account:

CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE
DELEGATION CÔTE D'AZUR

Relevé d'Identité Bancaire

TRESOR PUBLIC
Trésorerie Générale des Alpes-Maritimes 15 bis rue Delille 06073 NICE CEDEX 1

Code Banque	Code guichet	N° de compte	Clé RIB
10071	06000	00001005425	23

Domiciliation
TRESOR TRESOR GENERALE

Identifiant International de Compte Bancaire - IBAN

IBAN (International Bank Account Number)						
FR76	1007	1060	0000	0010	0542	27?

BIC (Bank Identifier Code)		
TRPUFRP1		

Titulaire du Compte
Agent Comptable Secondaire du CNRS Délégation Côte d'Azur
Lucioles 1
250 rue Albert Einstein
F - 06560 VALBONNE

5.2.2 Payment shall be made within forty-five (45) days of receipt of the invoices. In case of late payment, the **Company** shall pay late interests to CNRS. These shall be calculated at a rate of three (3) times the legal interest rate per day late, and payable as from the day following the payment due date appearing on the invoice.

Late payment penalties will be invoiced specifically.

All invoices shall be addressed to:

Roche

Comptabilité Fournisseurs 86167951

30, cours de l'Ile Seguin

92650 Boulogne-Billancourt Cedex

5.2.3 Each invoice must contain:

- the Laboratory's name and address;
- the time period to which the invoice relates;
- a description of activities for which payment is sought, in reasonable detail;
- the amount invoiced;
- VAT number, if VAT is charged;
- bank account information to which payment shall be made;
- the name of ROCHE's contract manager, i.e. Ariel Savina; and
- the purchase order number EPPA185765-G.

ARTICLE 6 – INTELLECTUAL PROPERTY RIGHTS

6.1 The Material that the **Company** provides to the **Service Provider** to conduct the Study remains the property of the **Company**.

6.2 All the Results shall be the entire and exclusive property of the **Company**, which may use them and protect them freely.

6.3 However, the **Service Provider**'s Own Knowledge which it uses to conduct the Study, as well as improvements that might be made remains the property of the **Service Provider**.

ARTICLE 7 – CONFIDENTIALITY - PUBLICATION

7.1 Publication

7.1.1 All publications or public presentations that the **Service Provider** or **Company** might envisage and which might refer to the Study must, during the term of the Contract and five (5) years following its expiry or termination, be submitted beforehand to the other Party so that the latter can check that the envisaged publication or presentation does not contain any Confidential Information and/or Results that could be protected by industrial property right.

These draft publications or communications shall be examined within one (1) month by the requested Parties, which may request amendments to be made and/or request the removal of information that might be likely to affect exploitation of the Results or to disclose Confidential Information belonging to them. The reasons for any removal or amendment request by a Party concerning a draft publication or communication must be given in writing by the latter. Such removals or amendments must not alter the scientific content or conclusions of the envisaged publication or communication

After this one (1) month period and if no answer is received from the requested Party, the **Service Provider** or **Company** may go ahead with the envisaged publication or public presentation. The above deadline may be extended up to a maximum period of ninety (90) days starting from the date of the initial submission, if information contained in the draft publication and/or draft public presentation has to be protected through an industrial property title.

All publications and communications must clearly state the contribution by each Party to the realization of the Study. In addition, the Science Contact shall be mentioned in all communication and publication as co-author.

7.1.2 However, the provisions of this Article 7.1 may not hinder:

- the obligation on each person participating in the Study to submit an annual report to his/her affiliated and/or membership body, in so far as this communication does not constitute a disclosure within the meaning of this Contract and of the laws governing industrial property;

- supporting theses of individuals whose scientific activity is related to the purpose of the Contract.

7.1.3 The name of the authors appearing on any publication or communication shall be mutually agreed between the Science Manager and the Science Contact, in accordance with the international standards in force.

7.2 Confidentiality

7.2.1 The Parties undertake to keep confidential all Confidential Information received from the other Party. They undertake to have their employees comply with this commitment.

7.2.2 The confidentiality commitments mutually binding the Parties in accordance with this article 7.2 do not apply to Confidential Information for which the Party receiving it is able to prove:

a) that the Confidential Information was in the public domain at the time it was communicated by the other Party or that the Confidential Information was placed in the public domain after this communication, without fault on its part;

b) that the Confidential Information was received from a third party authorized to disclose it;

c) that the disclosure of the Confidential Information was required by the implementation of a legal or regulatory requirement or by the implementation of a definitive court ruling or an arbitration award, provided that the receiving Party gives the disclosing Party sufficient notice to permit disclosing Party to seek a protective order or other similar order with respect to such Confidential Information;

d) that the Confidential Information was developed by the Party that received this Confidential Information, independently of the Confidential Information provided by the other Parties.

e) that the Confidential Information can be shown by the receiving Party to have been in its possession or control on an non confidential basis prior to the date of disclosure hereunder;

The aforementioned exceptions are not cumulative.

7.2.3 This confidentiality obligation shall remain in force for the entire duration of the Contract and for five (5) years after its expiry or termination.

7.2.4 Any disclosure of Confidential Information to **Service Provider** by (i) the **Company** or any of its Affiliates or (ii) any unaffiliated third party at the request of the **Company** or any of its Affiliates, shall be deemed to be a disclosure made by the **Company** under this Contract. For the purposes of this Contract, the term "Affiliates" shall mean:

a) an organization, which directly or indirectly controls a Party to this Contract;

b) an organization, which is directly or indirectly controlled by a Party to this Contract;

c) an organization, which is controlled, directly or indirectly, by the ultimate parent company of a Party;

"Control" as per a) to c) is defined as owning more than fifty percent of the voting stock of a company or having otherwise the power to govern the financial and the operating policies or to appoint the management of an organization.

With respect to the **Company** the term "Affiliate" shall not include Chugai Pharmaceutical Co. Ltd., 1-1, Nihonbashi-Muromachi 2-chome, Chuo-ku Tokyo, 103-8324, Japan ("Chugai"), unless the **Company** opts for such inclusion of Chugai by giving prior written notice to the **Service Provider**.

ARTICLE 8 – USE OF NAME OF THE PARTIES

Each Party undertakes not to use, in writing or verbally, the name of the other Party or of one of its employees without the prior written agreement of the person concerned.

The provisions of this article shall remain in force notwithstanding the expiry or termination of the Contract.

ARTICLE 9 – WARRANTIES

9.1 The **Company** acknowledges that the Results obtained from the Study are of an experimental nature. No **ex**press or tacit warranty of any kind whatsoever is given by the **Service Provider** or any inventors concerning the Results, especially regarding the commercial merchantability of the Results or their fitness for any particular purpose or against any offence. In particular, the **Service Provider** does not warrant that the use of the Results obtained from the Study do not infringe the intellectual property rights of third parties.

9.2 The **Company** warrants that any use of the Results and the Reports that are handed over to it pursuant to the Contract is exclusively its own responsibility and the **Service Provider,** its agents, managers and employees shall not be associated or incur any liability of any kind whatsoever regarding the use, distribution and operation of these Results and the Reports.

9.3 The **Company** warrants that it holds the rights required to supply the Material to the **Service Provider** for the realization of the Study in accordance with the Contract.

9.4 The provisions of this article 9 shall remain in force notwithstanding the expiry or the termination of the Contract.

ARTICLE 10 – TERMINATION

10.1 The Contract may be automatically terminated by either Party if the other Party does not fulfill one or more of its obligations. This termination shall only become effective one (1) month following written notification stating the reasons for the complaint by the complaining Party, unless, by this deadline, the defaulting Party has fulfilled its obligations or has provided proof of prevention resulting from a case of force majeure pursuant to article 11.6. Exercising this termination option does not exempt the defaulting Party from fulfilling the contractual obligations up to the effective date of the termination, without prejudice to payment of damages due by the defaulting Party in compensation for the loss possibly suffered by the complainant on account of the early termination of the Contract.

10.2 The Contract may be automatically terminated if the **Company** is subject to a judicial insolvency or liquidation procedure, without prejudice to implementation of articles L. 622-13 and L. 641-10 of the Commercial Code.

10.3 In case of early termination of the Contract, articles 6, 7, 8, 9 and 12 shall remain effective and shall apply to the Results obtained up to the date of termination of the Contract.

10.4 In case of early termination for any reasons whatsoever, amounts owed by the **Company** under this Contract shall be calculated pro rata to work already carried out and to amounts that the **Service Provider** has incurred as of the date of termination of the Contract. Notwithstanding the above, the **Company** undertakes to meet the definitive financial commitments made by the **Service Provider** for the realization of the Study being already understood that, except in case of fault of **Service Provider**, the salary for the staff participating to the Study incurred by **Service Provider** will be entirely paid by the **Company**.

ARTICLE 11 – MISCELLANEOUS

11.1 Entire agreement

The Parties hereto acknowledge that this Contract contains the entire agreement between them with respect of its subject matter, and that it supersedes any and all prior oral or written agreement, promise or representation between them as to the subject matter.

11.2 Inalienability

The present Contract is concluded intuitu personae. It is therefore personal, non-transferable and non-assignable to third parties. For the purpose of this Contract, Affiliates of **Company** shall not be considered as third parties, provided that said Affiliates are bound by the same obligations and duties under the Contract, the **Company** remaining liable for the good performance of the Contract.

11.3 Waiver

Neither the waiver by either Party hereto of any breach or default under any of the provisions of this Contract, nor the delay or failure of either Party to enforce any of the provisions of this Contract or to exercise any right hereunder shall be construed as a waiver of any subsequent breach or default or as a waiver of any such rights or provisions hereunder, nor shall any single or partial exercise of any right or remedy hereunder preclude any other or further exercise thereof or the exercise of any other right or remedy granted by law or in equity.

11.4 Independent contractors

The Contract may not, under any circumstances, be interpreted as creating a relationship of association or a company, even de facto, between the Parties. Each Party is to be regarded as an independent contractor.

11.5 Severability

In the event that any one or more of the provisions contained in this Contract and in their Amendment contracts shall, for any reason, be held to be invalid, illegal or unenforceable in any respect (pursuant to a law, regulation and, especially, the French law, or further to a definitive decision of a competent court), such invalidity, illegality or unenforceability shall not affect any other provisions of this Contract, and all other provisions shall remain in full force and effect.

In such case, the Parties shall immediately make the necessary changes, whilst respecting, as much as possible, the meeting of minds existing at the time of signing this Contract.

11.6 Force majeure

Each Party shall be excused for not fulfilling its obligations and cannot be held responsible or liable for damages towards the other Party if the non-fulfillment is due to a case of force majeure within the meaning of decisions based on article 1148 of the Civil Code, or even because of the disruption of its services resulting, in particular, from strike, resignation or any other event beyond its control. The Party finding that it is impossible to fulfill its contractual obligations because of a case of force majeure must inform the other Party of this immediately. If this impossibility or delay in fulfillment due to a case of force majeure continues for longer than three (3) months, the latter Party may automatically terminate the Contract at any time by written notification sent to the other Party.

11.7 Communication - Notifications

Any communication or notification for the attention of the Parties must be made by confirmed fax or by letter sent by recorded delivery to the addresses indicated below, when and as long as they have not been notified in writing of a change of address:

- For the **Service Provider**:

CNRS - Délégation Côte d'Azur,

250, rue Albert Einstein

06560 Valbonne - Sophia Antipolis

- For the **Company**:

Roche

30, cours de l'Île Seguin

92650 Boulogne-Billancourt Cedex

ARTICLE 12 – LAW GOVERNING THE CONTRACT

12.1 The Contract is governed by French law.

12.2 In case of dispute, if the Parties fail to reach an agreement to settle their dispute amicably within two (2) months following notification from the complaining Party, The competent courts in Paris (France) shall have sole jurisdiction for any litigation relating to the existence, validity, interpretation or execution of the present Contract.

12.3 This article shall remain in force notwithstanding all the cases of expiry or termination of the Contract.

Drawn up in three (3) original copies.

For CNRS

Signed in Valbonne

On the ..... 19 AOUT 2013

CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE
250 rue A. Einstein
06560 SOPHIA ANTIPOLIS
VALBONNE
DÉLÉGATION CÔTE D'AZUR

Mr. Pierre Dauchez

Regional Delegate of the Delegation Côte d'Azur

For Roche

Signed in Boulogne-Billancourt

On the ..... July 24, 2013.

Dr. Ariel Savina

Scientific Partnerships Leader

For the University of Nice Sophia Antipolis

Signed in

On the .....

Pr. Frédérique Vidal

President Le Président de l'Université de Nice Sophia Antipolis

UNIVERSITE DE NICE - SOPHIA ANTIPOLIS 1.1.1965

Seen, the Service Prévidel Frédérique VIDAL

On the .....

28 AOUT 2013

Dr. Gilles Pages

Science Manager

APPENDIX 1

STUDY PROGRAM

In vitro study for the predictive role of Tristetraprolin polymorphism for testing sensitivity or absence of efficacy of Trastuzumab and/or Pertuzumab in patients with breast cancer over-expressing her2

1) STATE OF THE ART

Modulation of mRNA stability plays a central role in physiological cellular homeostasis (*1*). The post-transcriptional fate of a given mRNA is governed by the interaction of specific mRNA sequences, such as adenylate and uridylate (AU)-rich elements (AREs), with specific trans-acting factors such as mRNA-binding proteins or microRNA. mRNA decay is regulated by the relative amount of RNA-stabilizing and RNA-destabilizing factors. Tristetraprolin (TTP), also named ZFP36 (zinc finger protein 36; MIM 190700), is one of the most important and best studied proteins. TTP is a member of a family of three human genes (ZFP36, ZFP36L1 and ZFP36L2) which are characterized by two tandemly repeated zinc finger motifs through which they bind to ARE elements in mRNA and mediate ARE-mediated mRNA decay (*2*). TTP is an early response gene that accumulates very quickly after the stimulation of numerous cell types with several kinds of stimuli, including insulin and other growth factors, and stimulators of innate immunity such as endotoxin lipopolysaccharide (LPS) (*3*). The activated protein is highly phosphorylated at serine residues mainly due to the activity of p38-MAPK and, to a lesser extent, to the Ras/ERK kinase cascade (*4-5*). The phosphorylation level of the protein plays a crucial role in TTP activity, localization and stability, representing an important mechanism of post-translational control (*5-6*). In vivo and in vitro studies indicate that TTP is involved in the resolution phase of the inflammatory response by destabilizing the mRNA of many cytokines (*2*). Mice deficient in TTP

develop a severe inflammatory syndrome, including polyarticular arthritis, myeloid hyperplasia and autoimmunity (*7*). Several studies showed that TTP mRNA and protein levels were significantly reduced in glioma and in thyroid, lung, breast and colon cancers (*8-10*). Accordingly, all these studies suggest that loss of TTP expression can represent a selective advantage for cancer cells affecting key tumorigenic cell phenotypes such as cell proliferation and expression of angiogenic factors (VEGF and IL8) (*5, 11*). Breast cancer is the most common type of malignant cancer and is the leading cause of cancer-related deaths among women. Breast cancer cells are highly invasive and have a high metastatic potential. Despite significant advances in diagnosis and treatment, the incidence of breast cancer is increasing worldwide (*12*).We have recently demonstrated that TTP down-regulation correlates with breast cancer cell aggressiveness. We have also shown that TTP protein level do not exactly follow mRNA level. Hence we have highlighted a TTP gene polymorphism in the coding region. This polymorphism is conservative in a sense that the corresponding amino acid is not modified. However, its presence strongly decreases translational efficiency of the mRNA containing the mutation. Hence, protein level is decreased consequently. We have shown a trend toward an increased of the presence of this polymorphism in patients with a HER2-positive breast cancer compared to of healthy donors. Moreover, a statistically significant increase in the frequency of this polymorphism was shown in patients presenting a resistance to Trastuzumab (*13*). An international patent has been accepted on this topic (PCT/EP2012/060807). Hence, detection of **this germinal polymorphism** may represent a rapid and efficient method to predict Trastuzumab efficiency or inefficiency to others antibodies targeting HER2 or more widely to receptors of the HER family (EGFR/HER1, HER3, HER4). Since HER targeting are systematically associated with a conventional chemotherapeutic agents generally a taxane derivative our preclinical experiments will associate such compounds to HER2 targeting agents.

2) OBJECTIVE

Determine in *in vitro* and *in vivo* assays in mice that the presence of the TTP polymorphism is associated with progression of tumors treated with the combination Trastuzumab/Pertuzumab/Taxane

3) EXPERIMENTAL PROCEDURES AND MATERIALS

A) Development of pertinent model cell lines

They will be developed to test the relevance of TTP polymorphism on the efficiency of the Tratuzumab/Pertuzumab/Taxane combination on breast cancer cells. We have to face to two challenges:

a) The availability of breast tumor cells expressing HER2

b) These cells must not express TTP to reintroduce the wild-type and the mutated form of TTP. Equivalent copy number must be expressed for comparison of the two cell lines.

We have compared TTP expression in MCF7 cells (a model of HER2 minus and hormonal receptor positive cell line) to three independent HER2+ model cell lines, ZR75, BT549 and SKBR3 (*13-14*). Only the SKBR3 is TTP deficient. We developed bicistronic vectors for the wild type and the mutated form of TTP. The second cistron code for luciferase which serves to normalize TTP mRNA amounts (*13*). Expression of luciferase allow for the determination of tumor growth and metastasis by luminescence (*15*).

B) *In vitro* sensitivity to Trastuzumab/Taxanes and Pertuzumab/Taxane of the different model cell lines

MTT tests will be performed in the presence or absence of serum (*16, 17*). The implication of TTP expression on apoptosis, autophagy and angiogenesis will also be (caspase activity, presence of cleaved form or caspase 9 or PARP, expression of BNIP3/BNIP3L, expression of different angiogenic factors (VEGF, interleukin 8 (13-17)).

Cells will be exposed to increasing concentrations of Trastuzumab and/or Pertuzumab (from 0.1 to 100 ⊠g/ml (*16*)) in the presence of docetaxel (1 nM) (*18*). The triple combination will also be tested. Proliferation, apoptosis, autophagy will be evaluated as described above. The activity of major signaling pathways implicated in cell proliferation (ie: RAS/RAF/MEK/ERK and PI3KAKT/mTOR) will be by analyzed by testing the phosphorylated/active partners of these pathways by Western blotting.

C) *In vivo* sensitivity to Trastuzumab/Taxanes, Pertuzumab/Taxane and Trastuzumab/Pertuzumab/Taxanes on the different model cell lines

The different cells will be subcutaneously injected in the flank or in the mammary gland of nude mice. 10 animals will be treated for at least 8 weeks as the following when tumors will reach a 100mm3:

a) Control IgG
b) Trastuzumab (30 mg/kg loading dose then 15 mg/kg weekly (*19*)) + docetaxel (30 mg/kg weekly, (*20*))
c) Pertuzumab (30 mg/kg loading dose then 15 mg/kg weekly (*19*)) + docetaxel (30 mg/kg weekly, (*20*))
d) Trastuzumab + Pertuzumab + Docetaxel

Tumor growth will be evaluated with a caliper and by luminescence for the presence of metastasis twice a week. Tumors will be analyzed by immunohistochemistry for proliferation (Ki67), apoptosis (cleaved caspase 3), angiogenesis (CD31), for major signaling pathways, apoptosis and autophagy by western blot (ERK and AKT activity, caspase, BNIP3, LC3I/II) and major pro- and anti angiogenic factors by ELISA (VEGF, interleukin 8, CXCL4, VEGFxxxb).

4) TRASTUZUMAB AND PERTUZUMAB NEEDED AMOUNTS

They will be devoted for *in vitro* and *in vivo* studies.

Trastuzumab: for one mouse (0.6 mg loading dose + 0.3 mg for 8 weeks = 3 mg)

Thus 30 mg/10 mice, three model cell lines (SKBR3 cont, TTP WT, TTP mut;) and for a given cell line two conditions using Trastuzumab (SKBR3 cont Trastuzumab and Trastuzumab + Pertuzumab; SKBR3 TTP WT Trastuzumab and Trastuzumab + Pertuzumab; SKBR3 TTP mut Trastuzumab and Trastuzumab + Pertuzumab) = 180 mg

Pertuzumab: for one mouse (0.6 mg loading dose + 0.3 mg for 8 weeks = 3 mg)

Thus 30 mg/10 mice. Hence, the needs of Pertuzumab are the same than Trastuzumab 180 mg.

We need additional products for in vitro experiments hence a total of 200 mg of Trastuzumab and Pertuzumab.

5) REFERENCES

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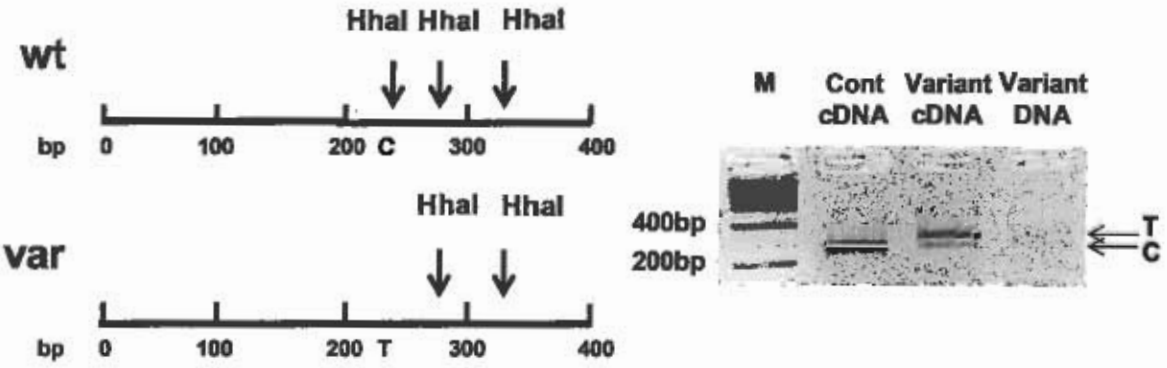

Figure 1: Detection of c.309C/T polymorphism in control or variant patient.

Scheme and digestion analysis on cutting PCR fragments with the enzyme Hha1.

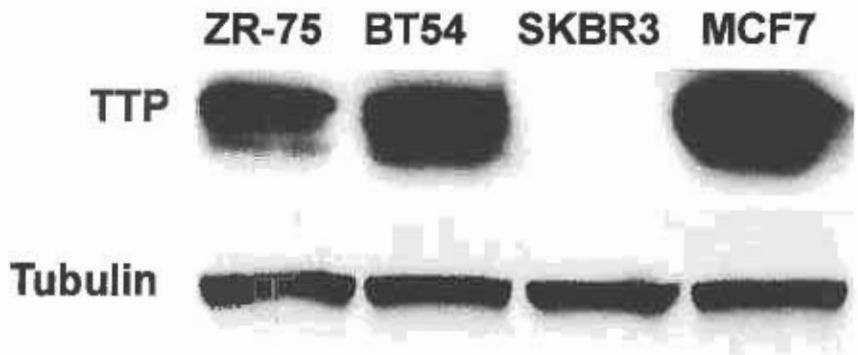

Figure 2: Analysis of TTP expression by western blot on control (MCF7) and HER2 positive breast tumor cells

GLOBAL COSTS

a) Consumables

Cell culture including plastics, serum, culture medium for a total of 2500 Euros

Antibodies (ERK, pERK, AKT, pAKT, Caspase, BNIP3) for a total of 2500 Euros

Molecular Biology (oligo nucleotides, qPCR experiments, cloning devices, plasmid vector and preparation) for a total of 2500 euros

b) Animals and animal house cost

120 animals for control SKBR3 or SKBR3 expressing the wild-type or mutated form of TTP

ID for fibroblasts

Hence 120 mice animals at 30 euros per mouse

Total cost 3600 euros X 2 (SKBR and fibroblasts) + 5000 euros of global costs for the accessibility to the animal house facility: Total 8600 euros.

c) Human resource

We ask for an assistant engineer for 6 month including social charges 13900 euros

The global cost will be **7,500 + 8,600 + 13,900= 30,000 Euros**

APPENDIX 2 - MATERIAL

Two hundred (200) mg of Trastuzumab and two hundred (200) mg of pertuzumab will be provided free of charge by Genentech under a MTA signature between Genentech and the Parties. A copy of the signed MTA will be annexed to this contract.

INSTITUT NATIONAL DU CANCER
PRÉSIDENTE DU CONSEIL D'ADMINISTRATION

CNRS - DR Côte d'Azur UDCA
21 OCT 2013

Monsieur Pierre DAUCHEZ
Délégué Régional
CNRS Délégation Côte d'Azur
250 rue Albert Einstein
Bâtiment 3
06560 Valbonne-Sophia-Antipolis

Boulogne-Billancourt, le 18 OCT. 2013

Dossier suivi par :
Hélèna SOUSA
Gestionnaire Conventions
Tél. : 01 41 10 14 12
hsousa@institutcancer.fr

Nos références : 13-10/411/AB-LC-HS

Lettre recommandée avec accusé réception

Objet : Notification de la décision attributive de subvention N° 2013-087
Coordonnateur du projet : PAGES Gilles

Monsieur le Délégué Régional,

Par le présent courrier, nous vous notifions un acte attributif de subvention qui revêt la forme d'une décision attributive référencée ci-dessus, dont vous trouverez ci-joint, un exemplaire original dûment paraphé et signé.

Conformément au règlement des subventions allouées par l'INCa que vous vous êtes engagés à respecter, vous devez nous fournir :

- un rapport d'activité selon la périodicité suivante : six mois après la présente notification, puis dix-huit mois et trente mois après la présente notification, et enfin, au plus tard quatre mois après la fin de la durée du projet telle que fixée dans l'acte attributif ci-joint, pour le rapport d'activité final,
- un rapport financier au plus tard quatre mois après la fin de la durée du projet telle que fixée dans l'acte attributif ci-joint.

Nous vous rappelons qu'en application de l'article 4.4.3 dudit règlement, l'absence d'un de ces rapports au cours du déroulement du projet pourra amener la suspension du versement de la subvention, voire la réclamation de tout ou partie des fonds déjà versés.

Nous vous prions d'agréer, Monsieur le Délégué Régional, l'expression de nos sincères salutations.

Agnès BUZYN
Présidente

Par délégation
La directrice générale
Anne BURSTIN

Copie à : PAGES Gilles – Coordonnateur de projet

Institut National du Cancer
52, avenue André Morizet · 92513 Boulogne-Billancourt Cedex · France
Tel. +33 (0) 1 41 10 50 00 · Fax +33 (0) 1 41 10 50 20 · www.e-cancer.fr
N° SIRET : 187 512 777 000 25 - Code APE : 8412 Z

INSTITUT NATIONAL DU CANCER

DECISION ATTRIBUTIVE DE SUBVENTION
N° 2013 - 087

Vu *les articles L1415-2 et D1415-1-8 du code de la santé publique relatifs aux missions de l'Institut National du Cancer (ci-après dénommé « **l'INCa** »),*
Vu *l'action 5.3 du plan cancer 2009-2013,*
Vu *le texte de l'appel à projets intitulé « **Projets libres de recherche Biologie et Sciences du Cancer** » diffusé par l'INCa en septembre 2012,*
Vu *le dossier de candidature transmis à l'INCa et signé notamment par le Centre National de la Recherche Scientifique, dont le siège social se trouve au 3 rue Michel Ange – 75794 Paris Cedex 16, représenté par délégation par Monsieur Pierre DAUCHEZ, Délégué Régional, CNRS Délégation Côte d'Azur – 250 rue Albert Einstein – Bâtiment 3 - 06560 Valbonne-Sophia-Antipolis, dûment habilité, immatriculé sous le numéro SIREN 180 089 013, ci-après dénommé « **le Bénéficiaire** »,*
Vu *le règlement relatif aux subventions allouées par l'INCa N°2011-01 (ci-après dénommé « **le Règlement** »),*
Vu *les propositions du comité d'évaluation,*

IL EST RAPPELE CE QUI SUIT :

La présente décision est régie par le Règlement sus-visé que le Bénéficiaire s'est engagé expressément à respecter. En conséquence, en cas de non-respect du Règlement par le Bénéficiaire, l'INCa pourra suspendre le versement de la subvention visée dans la présente décision et/ou réclamer sa restitution en tout ou partie (cf article 4.4.3 du Règlement).
Les dispositions dudit Règlement, non contraires à la présente décision s'appliquent à celle-ci.

Article 1 : PROJET SELECTIONNE ET MONTANT DE LA SUBVENTION

La Présidente de l'INCa décide d'attribuer au Bénéficiaire une subvention d'un montant de **350 000 € (trois cent cinquante mille Euros)** en vue de la réalisation du projet décrit dans le dossier de candidature sus-visé et intitulé **« L'implication du VEGF-C dans les propriétés métastatiques acquises des tumeurs en réponse aux traitements anti-angiogéniques »**, ci-après dénommé « **le Projet** ».
Le résumé du Projet est joint en annexe 1 à la présente décision attributive.

Article 2 : DUREE DE REALISATION DU PROJET

Le Projet doit être réalisé par le Bénéficiaire ou, le cas échéant par les équipes associées à la réalisation du Projet, désignées dans le dossier de candidature sur une période de **48 (quarante-huit) mois** courant au plus tard 1 (un) mois après la notification de la présente décision.

Conformément à l'article 3.2 du Règlement, cette période correspond à la période pendant laquelle les dépenses doivent être payées.

Article 3 : MODALITES DE VERSEMENT

L'INCa versera, au Bénéficiaire, une subvention d'un montant de **350 000 € (trois cent cinquante mille Euros)**, selon le budget prévisionnel joint en annexe 2 et selon les modalités prévues à l'article 4.4.2 du Règlement, à savoir:

- 30 % à la suite de la notification de la présente décision,
- 20 % 12 (douze) mois après l'envoi de la notification de la présente décision,
- 20 % 24 (vingt-quatre) mois après l'envoi de la notification de la présente décision,
- 20 % 36 (trente-six) mois après l'envoi de la notification de la présente décision,
- 10 % après la validation, par l'INCa, du rapport financier et du dernier rapport d'activité.

  Le solde sera versé dans la limite du montant total des dépenses certifiées dans le rapport financier et dans la limite du montant total de la subvention allouée. Si le montant desdites dépenses est inférieur au montant total de l'acompte versé, l'INCa émettra un titre de recettes, afin de récupérer les sommes non utilisées.

Le cas échéant, le Bénéficiaire procédera au versement des fonds auprès des organismes dont relèvent les équipes associées à la réalisation du Projet et ce, dans les plus brefs délais, sauf empêchement dûment justifié à l'INCa.

Article 4 : UTILISATION DE LA SUBVENTION

Conformément au texte de l'appel à projets, la subvention versée par l'INCa ne pourra pas financer :

- de l'équipement supérieur à 150 000 € TTC (cent cinquante mille Euros toutes taxes comprises),
- les salaires des doctorants.

Article 5 : RAPPORTS

Conformément au Règlement, il est rappelé que le Bénéficiaire doit adresser à l'INCa les rapports ci-après, par courrier, en deux exemplaires, à l'adresse suivante :

INCa - Service Conventions
52 avenue André Morizet
92513 Boulogne-Billancourt cedex.

5.1 Rapports d'activité (régis par l'article 6 du Règlement)
Les rapports d'activité doivent être établis selon le modèle figurant sur le site internet de l'INCa et selon la périodicité suivante :

- Un premier rapport d'activité devra être transmis à l'INCa, au plus tard, **6 (six) mois** après la notification de la présente décision,
- Un deuxième rapport d'activité devra être transmis à l'INCa au plus tard, **18 (dix-huit) mois** après la notification de la présente décision,
- Un troisième rapport d'activité devra être transmis à l'INCa au plus tard, **30 (trente) mois** après la notification de la présente décision,
- Un quatrième rapport d'activité devra être transmis au plus tard, **4 (quatre) mois après le terme du Projet** [soit au plus tard 53 (cinquante-trois) mois après la notification de la présente décision].

5.2 Rapport financier (régi par l'article 5 du Règlement)
Un rapport financier doit être établi par le Bénéficiaire selon le modèle figurant sur le site internet de l'INCa et être signé par le comptable public du Bénéficiaire.

Il doit être envoyé au plus tard **4 (quatre) mois après le terme du Projet** [soit au plus tard 53 (cinquante-trois) mois après la notification de la présente décision].

Si le Projet est réalisé en collaboration avec des équipes relevant d'un organisme différent de celui du Bénéficiaire et ayant perçu, via ce dernier, tout ou partie de la subvention, le Bénéficiaire centralise également les rapports financiers des différents organismes (signés par le comptable public desdits organismes, à défaut par leur représentant légal,) avant de les transmettre à l'INCa, accompagnés d'un rapport consolidé et de son rapport financier.

Article 6 : PUBLICATION – COMMUNICATION (régies par l'article 10 du Règlement)

Toute publication, sous quelque forme que ce soit, réalisée dans le cadre du Projet devra ol soutien apporté par l'INCa à la réalisation du Projet. Le texte sera communiqué pour information Les communications relatives à la réalisation du Projet et, particulièrement les communications mentionneront le soutien apporté par l'INCa.

Fait à Boulogne-Billancourt,
En 3 (trois) exemplaires originaux
Le 18 OCT. 2013

La Présidente,

Par délégation
La directrice générale
Anne BORSTIN

Agnès BUZYN

annexe 1

Résumé du projet	
Numéro du projet	PLBIO13-042
Coordonnateur **Etablissement de rattachement du coordonnateur**	PAGES Gilles INSERM U1081, NICE (coordonnateur scientifique)
Organisme gestionnaire	Délégation Régionale Côte d'Azur (CNRS DR20), VALBONNE
Durée du projet	48 mois
Montant du financement	350000 euros

Acronyme du projet

Titre en français

L'implication du VEGF-C dans les propriétés métastatiques acquises des tumeurs en réponse aux traitements anti-angiogéniques

Résumé en français

Le développement d'un réseau vasculaire anormal représente un phénomène clé de la croissance. Cette découverte a incité le développement de thérapies ciblant des facteurs de croissance impliqués dans la formation pathologique de vaisseaux sanguins (VEGF et ses récepteurs VEGFR1 et VEGFR2). Cependant, après quelques années d'utilisation de ces thérapies, les résultats ont été très décevants. Même si certains patients bénéficient grandement des traitements avec des rémissions pendant de nombreuses années, la majorité des patients évoluent plus ou moins rapidement de manière inéluctable. Les traitements induisent une diminution transitoire de la taille de la tumeur ou des métastases mais la sélection de cellules tumorales plus agressives a été systématiquement observée. Ainsi, au lieu d'avoir un effet curatif, ces composés conduisent rapidement à l'évolution de la maladie avec une aggravation de la situation. Le problème majeur associé à des patients cancéreux traités par des agents anti-angiogenèse est la récurrence des métastases et même le développement de nouvelles niches métastatiques. Nous pensons que la surexpression d'un autre membre de la famille des facteurs de croissance VEGF, le VEGF-C, un facteur de croissance pour les cellules endothéliales vasculaires et lymphatiques, serait à l'origine de la dissémination des cellules tumorales en réponse à des médicaments anti-angiogéniques en maintenant le réseau vasculaire existant et en favorisant la création d'un réseau lymphatique.

Ce projet se divise en deux parties, fondamentale et translationnelle. Les objectifs sont les suivants:

1- Analyser la présence de VEGF-C dans le plasma de patients atteints de carcinome rénal métastatique traités par le sunitinib ou de patients avec glioblastome traités par le pazopanib. La présence de VEGF-C sera corrélée avec le risque de récidive après traitement.

2- Déterminer les mécanismes moléculaires conduisant à l'expression de VEGF-C sous thérapies anti-angiogéniques. Nous mettrons l'accent sur la régulation de la transcription de VEGF-C, la stabilité de son ARNm et la maturation du pro-peptide VEGF-C. Nous déterminerons si ces enzymes de maturation sont de nouvelles cibles thérapeutiques dans les cas de résistance au traitement. Cet objectif se fera par l'utilisation de modèles cellulaires et animaux pertinents

3- Nous analyserons la présence de mutations acquises des récepteurs de facteurs angiogéniques ciblées par les thérapies anti-angiogéniques ou des mutations dans les voies de signalisation en aval (RAS / RAF / MEK) et PI3 kinase AKT mTOR

Pour des raisons non évidentes, les thérapies anti-angiogéniques ont induit l'adaptation génétique des cellules tumorales sans doute parce qu'elles expriment les récepteurs ciblés par les médicaments anti-angiogéniques. Par conséquent, l'objectif final est d'identifier des partenaires importants qui jouent un rôle clé dans la fuite à des thérapies qui auraient dû être curatives. Nous croyons que le VEGF-C est l'un des principaux acteurs de ce processus.

Titre en anglais

Implication of VEGF-C in the acquired metastatic properties of tumors in response to anti-angiogenesis treatments

Résumé en anglais

The development of an abnormal vascular network is a key phenomenon for tumor development. This discovery has prompted the development of therapies targeting growth factors involved in the formation of pathological blood vessels (VEGF and its receptors VEGFR1 and VEGFR2). However, after a few years of use of these therapies, the results were very disappointing. Although some patients benefit greatly from treatments with remissions for many years, tumors of the majority of patients progress ineluctably. The treatments induce a transient decrease of the size of the tumor or of the size of metastases but induce the selection of more aggressive tumors cells has been systematically observed. Instead of having a curative effect, these compounds rapidly lead to the evolution of the disease with a worsening of the situation. A major problem associated with cancer patients treated with anti-angiogenesis is the recurrence of metastases and even the development of new metastatic niches. Thus, we believe that the over-expression of another member of the VEGF family of growth factors, VEGF-C, a growth factor for vascular and lymphatic endothelial cells, is the cause of the release of tumor cells in response to anti-angiogenesis.

This project is divided into two parts, basic and translational research. The objectives are:

1- Analyze the presence of VEGF-C in the plasma of patients with metastatic renal cell carcinoma treated with sunitinib or glioblastoma patients treated with pazopanib. The presence of VEGF-C will be correlated with the risk of recurrence after treatment.

2- Determine the molecular mechanisms leading to the expression of VEGF-C after treatment with anti-angiogenesis therapies. We will focus on the transcriptional regulation of VEGF-C, the stability of its mRNA and maturation of the VEGF-C pro-peptide. We will determine whether maturation enzymes are therapeutic targets in cases of resistance to treatment. This objective will be through the use of relevant cellular and animal models

3- We will analyze the presence of acquired mutations on receptors for angiogenesis factors targeted by anti-angiogenesis therapies or mutations in downstream signaling pathways (RAS / RAF / MEK) and PI3 kinase AKT mTOR.

For not obvious reasons, the anti-angiogenesis therapies have led to the genetic adaptation of tumor cells probably because they express the receptors targeted by anti-angiogenesis drugs. Therefore, the ultimate goal is to identify important partners that play a key role in the escape to therapies that should have been curative. We believe that VEGF-C is one of the main actors implicated in this process.

Équipes associées

- Equipe 1 : PAGES Gilles - INSERM U1081, NICE.
- Equipe 2 : KHATIB Abdel-Majid - INSERM U1029, TALENCE.
- Equipe 3 : MAIRE Pascal - CNRS UMR8104 - INSERM U1016 - Institut Cochin, PARIS.

annexe 2

INSTITUT NATIONAL DU CANCER

Appel à projets 2013 Projets libres de Recherche « Biologie et Sciences du Cancer » Annexe financière Renseignements administratifs *Attention ce tableau est complété automatiquement à partir de l'onglet récapitulatif par équipes*	
Titre du projet	Implication of VEGF-C in the acquired metastatic proprerties of tumors in reponse to anti*angiogenesis treatments
Nom / Prénom du coordonnateur principal	PAGES GILLES
Organisme bénéficiaire de la subvention INCa	Centre National de la Recherche Scientifique - Délégation Côte d'Azur
Nom / Prénom du représentant légal	DAUCHEZ Pierre
Nombre d'équipes	3

Budget récapitulatif du projet		
	DEPENSES DU PROJET (en €)	
	Dépenses directes liées à l'exécution du projet	Dépenses demandées et éligibles INCa
Dépenses de personnel relatives aux fonctionnaires d'état, hospitaliers ou territoriaux	1 755 894	non éligible
Dépenses de personnel non statutaire	446 243	111 308
Dépenses de fonctionnement (1)	231 770	231 770
Dépenses d'équipement (2)	0	0
Frais de gestion (3)	6 922	6 922
TOTAL	**2 440 829**	**350 000**

	RECETTES LIEES AU PROJET (en €)
Subvention demandée à l'INCa	350 000
Autre(s) subvention(s) financant le projet (financeurs à préciser)	334 935
Autres ressources (à préciser) dont fonds propres du bénéficiaire (4)	1 755 894
TOTAL	**2 440 829**

Le budget doit être présenté en équilibre :
le montant pévisionnel des dépenses doit être égal au montant prévisionnel des recettes

(1) achats de fournitures, prestations de services, locations, prestations intellectuelles, études, subventions versées, ... (liste non exhaustive)

(2) logiciels, équipements informatiques, mobiliers, gros matériels, ... (liste non exhaustive)

(3) montant éligible s'élevant à un maximum de 4% de la subvention demandée à l'INCa

(4) toute autre ressource (dons, cessions, apport des équipes bénéficaires inclus...) servant à financer le projet

A Monsieur le Président du Centre Scientifique de Monaco

Le Professeur Patrick Rampal

Monaco, le 23 Septembre 2014

Monsieur Le Président,

Dans le cadre du don de 15.000 Euros que j'ai désiré faire afin de soutenir le projet du Docteur G.Pages , au sein du CSM, je me permets de vous adresser la deuxième et dernière partie de la somme prévue , soit 5.000 Euros : le premier versement de 10.000 euros a donné lieu à un excellent rapport d'activités significatif et précis sur le projet.

Je suis donc très motivée en vous adressant le solde de ce don de 15.000 Euros , sachant que cela contribue à faire avancer la recherche au sein du CSM.
Croyez à mes sentiments les meilleurs et à mon admiration pour les équipes de chercheurs au sein du CSM que vous avez bâti ensemble

Fabienne Mourou

Chèque de 5.000 Euros, ce 23 septembre 2014

Le Cancer du Sein, Parlons-en !

Paris, le 3 Mai 2016

GRAND PRIX RUBAN ROSE DE LA RECHERCHE

Madame, Monsieur,

Nous avons l'honneur de vous informer que le Grand Prix Ruban Rose de la Recherche 2015 d'un montant de 100 000 euros a été décerné à Mr Gilles Pages de l'Institut de recherche sur le cancer et le vieillissement de Nice pour son travail sur :

"La protéine Tristetrapoline et ses cibles, les cytokines ELR et CXCL en tant que marqueurs pronostiques et prédictifs de thérapies ciblées et nouvelles cibles thérapeutiques".

Mr Gilles Pages devra présenter un rapport d'utilisation des fonds dans un délai de trois ans et devra faire état dans les résultats de leurs travaux, dans la communication de ceux-ci, tels que publication scientifique etc… du prix reçu de l'Association leur ayant permis de mener à bien ces travaux.

Anne Vincent Salomon

Présidente d'honneur du Comité scientifique

PELEGRY Cristophe

Objet: TR: TR: PRIX RUBAN ROSE

DE : Duconge, Nathalie [mailto:nduconge@fr.estee.com] ENVOYÉ : mardi 25 août 2015 15:50 À : gpages@unice.fr
OBJET : PRIX RUBAN ROSE

Cher Docteur,

Le comité scientifique de l'Association Le Cancer du Sein, Parlons-en !
vous a décerné le Grand Prix Ruban Rose de la Recherche 2015 dont la dotation cette année est de 100 000 euros.

Nous serons honorés de vous remettre ce prix lors de notre grande soirée de gala qui se tiendra à Paris le 28 septembre 2015 au Palais de Chaillot en présence de nombreuses personnalités du monde médical, scientifique, des médias et en présence d'Anne Hidalgo .

A ce titre nous prenons en charge si besoin votre déplacement et votre hébergement. Faites le moi savoir.

Je vous serais reconnaissante de me communiquer par retour votre adresse postale pour l'envoi du carton d'invitation.

Je suis à votre entière disposition pour toutes questions .

Bien à vous

Nathalie Ducongé

Responsable des Partenariats

Association Le Cancer du sein, Parlons-en !

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