agence d'évaluation de la recherche
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Section des Unités de recherche

AERES report on the canceropole

Canceropole CLARA

From the

Institut du Cancer

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February 2011

Canceropole

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Report

1 • Introduction

- **History and geographical localization of the canceropole, and brief presentation of its field and scientific activities**

The canceropole Lyon Auvergne Rhône-Alpes (CLARA) has made major progress since 2007 making a number of significant contributions mainly in three areas: 1) Tumor escape, cell plasticity and therapeutic targeting, 2) Infections and cancer and 3) Nanotechnology, imaging and cancer. CLARA is a unique academic-clinical-industrial integrated research network focused on oncology at the inter-regional scale in Rhône-Alpes-Auvergne.

The management team is overall excellent and the leadership of its Executive Director has greatly contributed in valuing the scientific activities of this Group. In addition, the clarity of his presentation during the review process has been highly appreciated by the reviewer panel.

A number of internal/external committees have been implemented to make the activities of CLARA more efficient and outcomes oriented. The following committees are part of the CLARA network: *Industrial Steering Committee*, *Development Committee*, *Strategic Orientation Committee* and the *Executive Committee*. The *Development Committee* is composed of independent internationally renowned experts and this is an additional strength ensuring transparency in setting up priority lines. The Executive Committee is actually in charge of approving and allocating funding and it consists of representatives of local authorities, academic institutions, industrial partners and patient associations. In particular, the inclusion of Patient Association is of great ethical value. Indeed, cooperation with patient associations is encouraged as a means for boosting patient involvement in research (IOM report, *A national Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program, http://www.iom.edu/*).

2 • Overall appreciation on the Canceropole

- **Summary**

The input/output ratio is excellent. The visibility of CLARA in terms of scientific publications is overall excellent as concern particularly Axis 1 and 2.

- **Strengths and opportunities**

- The very high quality of the management resulting in very effective integration, (i.e. sharing platforms), project implementation, communication policy, scientific animation (meeting organization);

- The certification of several platforms and biological resources centers, the growing success of calls for proposals, the increasing development of marketable applications of research findings and the international outreach;

- The management implemented in the CLARA canceropoles represents a possible exportable template for the other canceropoles. Indeed the level of transparency in terms of activities implemented and funded projects are in line with many of the top-level academia institutions in the USA. Having an independent committee ("Development Committee") that evaluates on regular basis the CLARA's work is indeed an added value;

- Significant contribution of CLARA researchers to high-impact journals in the field of cancer (23 % of national total with impact factor > 20, period 2005-2009);

- The very strong support by the region Rhone-Alpes;

- The success in attracting biotech and pharmaceutical companies to the area;

- The long-term presence of IARC in Lyon provides substantial opportunities to develop international research cooperation that will be exploited;

- The willingness to implement the translational research axis.

- **Weaknesses and threats**

- The lack of an external SAB;

- Axis 4 (see general comment about this axis); the scientific output of Axis A (formerly Axis IV) is the weakest part of the CLARA group and there is lack of international connections that would be necessary to allow this line of research taking off from the ground.

- **Recommendations to the head of the Canceropole**

- Take action to become a driving force and establish synergies with other Canceropoles including GSO;

- Current activities and future initiatives of AXIS IV should be upgraded to a national level in order to better define top priorities in this line of research and get an international visibility in this area;

- Keep going in this direction.

3 • Specific comments:

- **Contribution of the Canceropole to the structuration of the research at the local level**

Appreciation on the quality of the partnership between the Canceropole and scientific and industrial clusters: Excellent. This is also facilitated by the important link established by the CLARA and key scientific Agencies in the region, i.e. ARC.

Appreciation on the quality of the partnership between the Canceropole and the local funded agencies (conseil général, conseil régional, universities): Excellent.

Appreciation on the strategy, management and life of the Canceropole: Excellent.

Relevance of the Canceropole's organization, quality of the management: Excellent.

Relevance of the Canceropole's communication policy: Excellent. Canceropole CLARA activities are regularly presented and commented on local radio and television, and comments are equally regularly made in press articles.

Relevance of the initiatives aiming at the scientific animation: Excellent.

- **Appreciation on the project**

Relevance of the project according to the INCa priority 1 (structuration of the research at the local level): Good.

Relevance of the project according to the INCa priority 3 (valorisation): CLARA has a major added value to regional cancer research.

Relevance of the project according to the INCa priority 4 (Europe): CLARA has established a number of international networks increasing European visibility: cooperation with the clinical PARCC-ARA platform (Lyon); Creation of an European Lymphoma Institute (ELI) as initiated in 2009; Creation of a World Sarcoma Network (WSN) as started in 2009; Collaboration between OncoTherapyScience, Léon Bérard Centre and CLARA on a clinical Proof of concept project Synfrizz in 2010; Initiation of a European Lung Institute and support of a dedicated endowed chair in lung cancer for translational research (Grenoble).

- **Appreciation on the quality of SWOT analysis**

SWOT analysis is effective and presents strengths and weaknesses; no additional comments are to be made by the Panel.

4 • Appreciation theme by theme

- **Title of the theme: Axis 1: Nanotechnology, imaging and cancer**
- **Name of the theme leaders: Mr François BERGER and Mr Marc JANIER**

Number of teams involved in this theme in 2007: 14 research teams and 1 Company.

Number of teams involved in this theme in 2010: 39 research teams and 9 companies.

- **Appreciation on the results**

This Axis is definitely a key asset for this Group and the scientific production is excellent. Overall 13 projects have been funded by INCa, leading to the publication of 86 scientific publications in peer-reviewed journals and 12 publications currently under review.

Three original projects have been launched in the following areas:

- LIPID NANO PARTICLES AS AN ORGANIC NANO-CARRIER FOR IMAGING AND DRUG DELIVERY APPLICATIONS

- IRON BASED BIOACTIVABLE CONTRASTING AGENTS WITH VARIABLE SPIN STATUS FOR IN VIVO MRI

- DEVELOPMENT AND VALIDATION OF INNOVATIVE STRATEGIES FOR BLOOD AND TISSUE BIOMARKERS USING MICRO-NANO-BIO-HARVESTING

- **Relevance and impact of the initiatives aiming at the scientific animation and at the emergence of cutting edge projects**

Scientific animation activity is good as demonstrated for example, by the setting up of the International Symposium « OncoNano » that took place in Paris in October 2009 and the inter-cancéropoles and international meeting dedicated to —Clinical applications of nanotechnologies in the field of cancer that was organized in Montpellier in January 28-29, 2010. European visibility is also good. However, the co-participation to other canceropoles activities or the setting up of joint projects in this area would be of particular value in sharing the outstanding knowledge of this Group in this Axis with other relevant research teams of other canceropoles.

- **Conclusion**

The industrial relationships and the ability to get funding from the INCa framework are among the key assets of this Group. Several innovative technologies have emerged from this line of research and the Group is encouraged to keep going in this direction. It would be good to expand this knowledge to other canceropoles by setting up for example, joint educational seminars in this area.

- **Title of the theme: Axis 2: Infection and cancer**
- **Name of the theme leaders: Mr Fabien ZOULIM and by Mr Patrice MARCHE**

Number of teams involved in this theme in 2007: 21.

Number of teams involved in this theme in 2010: 23.

- **Appreciation on the results**

Three original projects have been launched in the following areas:

- PRIMARY HUMAN HEPATOCYTES AND PROGENITOR HEPATIC CELLS PLATFORM

- ABILITY OF DOUBLE STRANDED DNA ONCOGENIC VIRUSES TO ALTER TLR9 PATHWAY

- VALIDATION IN PATIENT THAT THERAPEUTIC EFFICACY OF NEO-ADJUVANT CHEMOTHERAPY IN LOCALISED BREAST CANCER RELIES ON ANTI-TUMOUR IMMUNE RESPONSE

The number of patents and publications is excellent and major links with key international society have been created. Overall, 11 projects have been funded by the INCa.

- **Relevance and impact of the initiatives aiming at the scientific animation and at the emergence of cutting edge projects**

In terms of scientific animation there have been major efforts and, overall, axis II achieved maturity in terms of the participation in and the integration of a number of excellent teams of Rhône-Alpes Auvergne that are involved in the field of Infections and cancer. The development of an international translational program on HCC is a major contribution.

- **Conclusion**

Major strengths are: the recognition at the national level as a main player in the field of hepato-cellular carcinoma research a significant contribution to transfer of research findings in the field of infections and cancer and Inter-canceropole, International development: association with IARC, canceropole GE and DKFZ Heidelberg and European projects. Time is now mature for this Group to move beyond this cancer disease site and expand research interest in other disease sites as well.

- **Title of the theme: Axis 3: Nutrition, metabolism and cancer**
- **Name of the theme leaders: Ms. Marie-Paule VASSON and Ms. Martine LAVILLE**

Number of teams involved in this theme in 2007: 11 teams.

Number of teams involved in this theme in 2010: 34 teams.

- **Appreciation on the results**

The axis objectives have been to develop a cross-disciplinary research based on complementary skills in order to specify the nature and effects of active nutrients and their metabolites in cancer prevention; to understand the links between alterations in nutritional status and the occurrence of the malignancy; and to encourage translational research trial.

Three original projects have been launched in the following areas:

- INVOLVEMENT OF ADIPOKINES IN BREAST CARCINOGENESIS

- ROLE OF OXYSTEROLS AND LIVER X RECEPTORS (LXRS) IN PROSTATE CARCINOGENESIS

- MODELLING THE EVOLUTION OF TRANSCRIPTIONAL REGULATORY NETWORKS DURING CARCINOGENESIS - EFFECT OF NUTRITIONAL SUPPLY

The number of publications is not at the same high quality level of Axis 1 and 2, and can be improved.

Overall, the INCA funding in terms of projects in this area has not been as successful as it was in the previous AXIS (I and II).

- **Relevance and impact of the initiatives aiming at the scientific animation and at the emergence of cutting edge projects**

The projects initiated are of interest and the scientific production is overall reasonable. Further connections and integration with international working teams in this area can be of value.

- **Conclusion**

Major strengths are the quantitative progression of this axis, as a result of an active axis “animation”. Identification of new themes can further help the production of this Group in terms of scientific publications.

- **Title of the theme: Axis 4: Epidemiology, SHS, patient education and organization of care**

- **Name of the theme leaders: Ms. Nora MOUMJID-FERDJAOUI and Ms. Christine DURIF-BRUCKERT**

Number of teams involved in this theme in 2007: 19 teams.

Number of teams involved in this theme in 2010: 39 teams.

- **Appreciation on the results**

This axis has not shown a major impact on the international scientific community in terms of production, although 32 projects have been funded by the INCA. While the efforts made by the researchers in this area have been appreciated by the reviewer panel, there is a clear need to take major actions to take off from the ground this line of research from a purely regional level to an international platform. The number and quality of publications should be improved.

Three original projects have been launched in the following areas:

- VALIDATING A RECORDING SYSTEM OF BREAST CANCERS TO EVALUATE ORGANISED SCREENING IN RHONE-ALPES REGION OF FRANCE AND STRUCTURING ACTIONS TO STUDY BREAST DISEASES

- ANALYSIS OF THE DETERMINANTS OF COLLECTIVE DECISION IN THE FORMULATION OF RECOMMENDATIONS FOR CLINICAL PRACTICE

- PROJECTS RELATED TO PATIENT'S INVOLVEMENT IN HEALTHCARE DECISION-MAKING (INFORMATION AND SHARED DECISION-MAKING BETWEEN HEALTHCARE PROFESSIONALS AND HEALTHCARE USERS)

- **Relevance and impact of the initiatives aiming at the scientific animation and at the emergence of cutting edge projects**

The scientific production is underperforming compared to the number of projects that have started and have been funded by the INCA; there is large room for improvement.

- **Conclusion**

The scientific production is mainly at the loco-regional level and no major impact-making publications have been seen in this AXIS. There is a need to set up more structured links at an international level with relevant stakeholders in this area. Providing more funding to this AXIS might not be the best option to improve production and visibility as this line of research (Axis 4) has been broadly shown to be underperforming in all canceropoles. As has been highlighted in the general report to INCA a possible approach is to bring all research activities of Axis 4 in all canceropoles to a national level. By doing that, French research in this area might be in a more prominent position to get international visibility (see general comments for Axis 4).

- **Title of the theme: Axis 5: Therapy targeting, modeling and clinical research**

- **Name of the theme leaders: Ms TRILLET-LENOIR, Ms LEIZOROVITCH and M. MERROUCHE**

Number of teams involved in this theme in 2007: 16 teams.

Number of teams involved in this theme in 2010: 20 teams.

- **Appreciation on the results**

20 projects (5 clinical research projects and 15 PHRC) have been funded by the INCA (success rate: 27%). Major Contributions are: the creation of a European Lymphoma Institute (ELI) as initiated in 2009 (Pr Coiffier, Lyon); the creation of a World Sarcoma Network (WSN) as started in 2009 (Pr Blay, Lyon) and Initiation of an European Lung Institute and support of a dedicated endowed chair in lung cancer for translational research.

Three original projects have been launched in the following areas:

- ACTIVE SURVEILLANCE OF PROSTATE CANCER PRESENTING LATENCY CRITERIA: IMPACT ON SPECIFIC SURVIVAL AT 10 YEARS

- THE CONTRIBUTION OF FDG PET/CT AND DIFFUSION-WEIGHTED MRI IN THE TUMOUR RESPONSE ASSESSMENT AFTER RADIOCHEMOTHERAPY AND BRACHYTHERAPY TREATMENT OF OPERABLE CERVICAL CANCER STAGE IB2, IIA AND IIB

- EVALUATION IN PATIENTS NEEDING A RESECTION SURGERY OF LIVER METASTASIS FOR COLORECTAL CANCER WITH THE USE OF PER-OPERATORY HIGH INTENSITY FOCALISED ULTRA-SOUNDS (HIFU): FEASIBILITY, INNOCUITY, AND TARGETING CAPACITY

- **Relevance and impact of the initiatives aiming at the scientific animation and at the emergence of cutting edge projects**

The scientific production is underperforming in this area compared to the number of projects that have started and have been funded by the INCA and there is room for improvement in some areas. As an example the area of hematological malignancies should be expanded since a number of targeted therapy have been developed and this might be the basis to enlarge the research portfolio in this Axis as concern clinical research.

- **Conclusion**

The setting up of some key network and institutions (e.g. ELI) with international visibility are the main strengths of this Axis. Further collaboration with other canceropoles in this area and in the development of other projects in other cancer disease sites (e.g. hematology) is recommended.

- **Title of the theme: Axis 6: Tumor escape**
- **Name of the theme leaders: Mr. Laurent MOREL, Ms. Corinne ALBIGES-RIZO, Ms. Sylvie GAZZERI and Mr. Serge MANIÉ**

Number of teams involved in this theme in 2010: 23 teams.

- **Appreciation on the results**

More than 300 researchers and clinicians, organized in 23 research units, are involved in this topic, constituting the major thematic axis of CLARA. The scientific production is very good and strong international connections have been established.

Three original projects have been launched in the following areas:

- PHARMACOGENOMICS IN RELATION TO TUMOUR ESCAPE AND THERAPEUTIC TARGETING

-TUMOUR BANKING AND ENDOCRINE TUMOUR RESEARCH

-TUMOUR GENOMICS AND BIOINFORMATICS AS PART OF INTERNATIONAL CANCER GENOMICS CONSORTIUM ICGC

- **Relevance and impact of the initiatives aiming at the scientific animation and at the emergence of cutting edge projects**

The scientific production is good with publication in high impact factor Journals. The scientific animation is also good with some events organized in collaboration with other canceropoles such as GSO.

- **Conclusion**

The research activities of the Axis VI are mainly developed in the fields of basic cancer biology and translational research and the establishment of a Tumour Model laboratory is one of the key assets of this Axis.

CLARA's feedback to AERES Report on the Cancéropôle CLARA from the Institut National du Cancer

On behalf of the CLARA scientific steering committee, we express our great appreciation to the members of the Review Committee and the Observers for their time and very positive evaluation of the CLARA activities. We appreciate, in particular, *CLARA represents a possible exportable template for the other Cancéropôles. Indeed the level of transparency in terms of activities implemented and funded projects are in line with many of the top-level academia institutions in the USA*.

Comments to the overall appreciation of the Cancéropôle

We like to correct within *Weaknesses and threats: the lack of an external SAB*. We apologize but we have an external Development Committee, which corresponds to a SAB, and which is chaired by Dr. I Tannock (Princess Margaret Hospital, Toronto, Canada). This Committee meets once a year in Lyon and provides recommendations to CLARA scientific and development (research transfer activities) strategy. In addition, this committee evaluates and guides systematically important CLARA strategic decisions.

Take actions to become a driving force and establish synergies with other Cancéropôles. We fully agree with this comment. Besides several research projects supported by INCa, which witness of collaborations with other Cancéropôles (in particular with Cancéropôle Ile-de France), we also co-organized with another Cancéropôle (Ile-de-France, Grand-Est, Grand-Sud-Ouest or PACA) during 2009 and 2010 eight scientific events on specific CLARA topics to facilitate collaboration. We are aware that these actions represent a first step and that much more has to be done to stimulate inter-Cancéropôle cooperations. Our CLARA project 2011-2014 emphasizes clearly both inter-Cancéropôle and international actions.

Current activities and future initiatives of CLARA axis IV should be upgraded to a national level in order to better define top priorities in this line of research and get an international visibility in this area. We agree with this comment as critical mass is a key-issue. We look forward to INCa to construct together projects within this field with other Cancéropôles with a national and competitive dimension.

Comments related to the different CLARA thematic axes

Axis I: Nanotechnology, imaging and cancer

The co-participation to other Cancéropôles activities or the setting up of joint projects in this area would be of particular value in sharing the outstanding knowledge of this Group in this axis with other relevant research teams of other Cancéropôles. Axis I members are yet involved in research projects which involve partners from other Cancéropôles. For instance, a FUI funded project THERANEAN (Therapy through Neutron Activation using Nanoparticles) with Cancéropôle Grand-Ouest; an ISI funded project MIOTherIS (Micro Innovative Onco Therapeutic Injection System) with Cancéropôle Grand-Est ; an ANR Emergence APTAPROBE aiming at developing nanoparticles functionalized by aptamers with Canceropole Grand Sud-Ouest ; and two projects granted by INCa in 2010 involve partners from Cancéropôle Grand-Sud-Ouest: PORO-COMBO (Toxic peptides targeting tumour *in vivo*) and LIGHTUP (Development of fluorescent biosensors for non-invasive optical imaging of cyclin-dependent kinases in animal tumour models). Moreover, the organisation of the "Clinical applications of nanotechnologies in the field of cancer" symposium as organized by CLARA, Cancéropôle Grand-Sud-Ouest and the Spanish Institute for Bioengineering of Catalonia was planned to stimulate inter-Cancéropôle and international networking.

It would be good to expand this knowledge to other Cancéropôles by setting up for example, joint educational seminars in this area. The "Nanoparticles targeting workshop" in Grenoble in 2010 that gathered participants from different Cancéropôles for fostering collaborations was a first step in this direction. In a near future action will be undertaken to share with other Cancéropôles (e.g., Cancéropôle Grand-Sud-Ouest) the expertise acquired within the CLARA Regulatory Unit which addresses transfer of nanomedicine projects to the development phase.

Axis II: Infections and cancer

Time is now mature for this Group to move beyond this cancer disease site (hepato-cellular carcinoma, HCC) and expand research interest in other disease sites as well. We remind we proposed in CLARA project 2011-2014 to focus exclusively on viral-induced cancers within this axis, especially on HCC and Human Papilloma viruses (HPV)-associated cancers. In addition, an ambitious and novel project by a bottom-up approach addressing either an emerging oncogenic pathogen related to cancer development or a new and highly competitive project in the field of virus-induced cancer will also be addressed.

Axis III: Nutrition, metabolism and cancer

Identification of new themes can further help the production of this Group in terms of scientific publications. In response to the priorities of the Cancer Plan II (Measures 3.1, 3.2), the CLARA project 2011-2014 will focus on two main research thematics:

- environmental factors, including the occupational environment, with two identified priority topics: pesticides and cancer, and engineered nanomaterials and cancer;
- nutrition and cancer focusing on two topics: nutrient effects on carcinogenesis and biomarker identification in the continuity of the 2007-2010 ProCan period, and nutrition intervention (diet and physical activity) in secondary prevention.

The active participation of IARC and the CENS project (Centre for European Nutrition Safety and Health) in Lyon on this thematic will foster development of further connections and integration with international working teams in this area.

Axis IV: Epidemiology, human and social sciences (HSS), patient information and organization of care

There is a clear need to take major actions to take off from the ground this line of research from a purely regional level to an international platform. The number and quality of publications should be improved. Although 32 projects have been funded by INCa, 11 are coordinated by patients' advocations groups and are not *per se* intended to publish. Regarding the remaining 21 projects, 14 are not yet finalized. Out of the 7 completed projects, 5 led to 14 publications. Four epidemiological projects and one HSS project have papers published in international peer-reviewed journals. For instance:

- Knaapen L., Cazeneuve H., Cambrosio A., Castel P., Fervers B., Pragmatic evidence and textual arrangements : a case study of french clinical cancer guidelines. Soc Sci Med. 2010 Aug;71(4):685-92. (AERES, A+)

- Moussata D, Nancey S, Lapalus MG, Prost B, Chavaillon A, Bernard G, Ponchon T, Saurin JC. Endoscopy. Frequency and severity of ileal adenomas in familial adenomatous polyposis after colectomy. Endoscopy. 2008 Feb;40(2):120-5. (IF = 6.1)

- Sassolas G, Hafdi-Nejjari Z, Remontet L, Bossard N, Belot A, Berger-Dutrieux N, Decaussin-Petrucci M, Bournaud C, Peix JL, Orgiazzi J, Borson-Chazot F. Thyroid cancer: is the incidence rise abating? Eur J Endocrinol. 2009 Jan;160(1):71-9. (IF = 3.8)

- Lurkin A, Ducimetière F, Ranchère Vince D, Decouvelaere AV, Cellier D, Gilly FN, Salameire D, Biron P, de Laroche G, Blay JY, Ray-Coquard I. Epidemiological evaluation of concordance between initial diagnosis and central pathology review in a comprehensive and prospective series of sarcoma patients in the Rhone-Alpes region. BMC Cancer. 2010 Apr 19;10:150. (IF = 3.1)

Axis IV as an emerging axis was not established to address immediately international collaborations. The objective was first to identify and federate regional research teams working on different research disciplines and in a second step to identify federative research topics. As this first stage is now accomplished, national and European/international collaborations should be set up to build international visibility.

It should be noted that at the national level, several actions have already been initiated: besides national/international collaborations set up in the context of ongoing research projects, the CLARA Hygée platform (Centre for Information and Education about Cancer as a platform for public health research) is part of the French National Network for Information, Health Education and Prevention of Cancers (RIEPCA) which aims federating the French national structures acting in the field of health education and cancer prevention. Furthermore, the PACTE team in Grenoble is part of two European networks (ESPANET - European Social Policy Analysis Network, and EHPG - European Health Policy Group); and a collaboration between Shanghai Jiao Tong University (China) and ENSMSE / LASPI laboratories in Saint-Etienne is already effective on operations management of cancer treatment. But as mentioned above, we agree that critical mass is a key-issue and look forward to INCa to construct together projects within this field with other Cancéropôles with a national and competitive dimension.

Axis V: Therapeutic targeting, modeling and clinical research

Further collaboration with other Cancéropôles in this area and in the development of other projects in other cancer disease sites (e.g. hematology) is recommended. Scientific activity and production in this field is likely to have been underestimated as a certain number of national and international projects coordinated in either Lyon or Grenoble had been initiated before the creation of the Cancéropoles and the implementation of the national Cancer Plan and have not consistently involved INCa or the Cancéropôle CLARA due to pre-existing networks. These projects involve key opinion leaders such as Pr Coiffier in the field of lymphoma, Pr Blay in the field of sarcomas and Pr Brambilla in the field of lung cancer, all domains which are currently giving rise to international Institutes or Networks. Hematological malignancies represent a highlight in the Rhone-Alpes region with an internationally renowned centre in the field of lymphoma and one of the largest centres for the treatment of acute leukaemia in Europe. This centre is also strongly involved in translational research in myeloma, including collaboration with IARC for the identification of familial cases of this disease. Several preclinical and clinical groups are involved in the development of tyrosine kinase inhibitors and therapeutic monoclonal antibodies both in solid tumours and in haematological malignancies. One of the challenges during the 2011-2012 period will be to develop closer ties between clinical researchers and the Cancéropôle CLARA. These will be encouraged by several incentives, including support to translational platforms, enhanced interaction with biotech and pharmaceutical companies as well as support for methodological approaches and scientific meetings.

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Axis VI: Tumor escape

No comment.

Peter Pauwels, PhD

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Lyon, March 31, 2011