CLARA

CANCÉROPÔLE LYON AUVERGNE RHÔNE-ALPES

SPEEDING UP PROGRESS

Activity report 2008

Under the aegis of the Bullukian Foundation

To be aware of one's ignorance is the best path towards knowledge.

Chinese proverb

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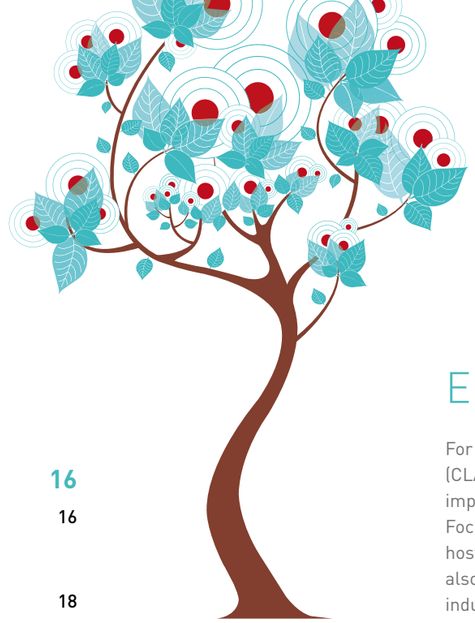

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Edito

For the Cancéropôle Lyon Auvergne Rhône-Alpes (CLARA), 2008 was the year of operational implementation of the ProCan program with its six Focus Areas, the launch of structural programs and the hosting of a number of forums and symposiums. CLARA also introduced a variety of new actions to strengthen industrial-academic partnerships.

CLARA has made a considerable effort to extend the Proof of Concept program to the entire region. Two top-priority themes - Nanomedicine & Cancer and Infections & Cancer (in collaboration with LyonBiopôle) - were promoted in 2008 calls for projects and five promising new initiatives have now been added to our portfolio thanks to the financial support of local authorities in the Rhône-Alpes Auvergne region.

The vitality of local research teams in the field of cancer was also observed in the number of proposals relayed by CLARA in the framework of the INCa calls for projects in February and November 2008.

In this thriving environment, CLARA intensified its collaboration with other organizations involved in research, such as LyonBiopôle and the Synergie Lyon Cancer and Finovi Foundations, in particular as part of ProCan Focus Area II on "Infections and Cancer." CLARA will continue this approach and its promotion of scientific activities through a policy of outreach to other cancer clusters and through international development.

CLARA's structure is now well in place, allowing the cluster to fully assume its role as a federating force. This is achieved by a scientific strategy aimed at optimizing resources and targeting skills. It takes strength from the effectiveness of industrial-academic partnerships, another key asset which will once again be a major focus in 2009.

Today, CLARA's genuine contribution to cancer research has become increasingly visible, which enables the cluster to play a crucial role in coordinating the efforts of the Rhône-Alpes Auvergne region.

Peter Pauwels,
Executive Director CLARA

CLARA: landmarks

Role

To coordinate the region's skills and infrastructures to benefit cancer research in order to meet the aims of the French Cancer Plan.

A dual aim

To bring researchers, clinicians and industrial partners together in a single network and channel their joint efforts into operational research programs that promote:
- rapid transfer of academic knowledge towards patient care
- marketable applications for the research findings

A broad network

- 130 academic research teams
- 80 clinical services
- 60 industrial partners

A privileged region: Lyon Rhône-Alpes Auvergne

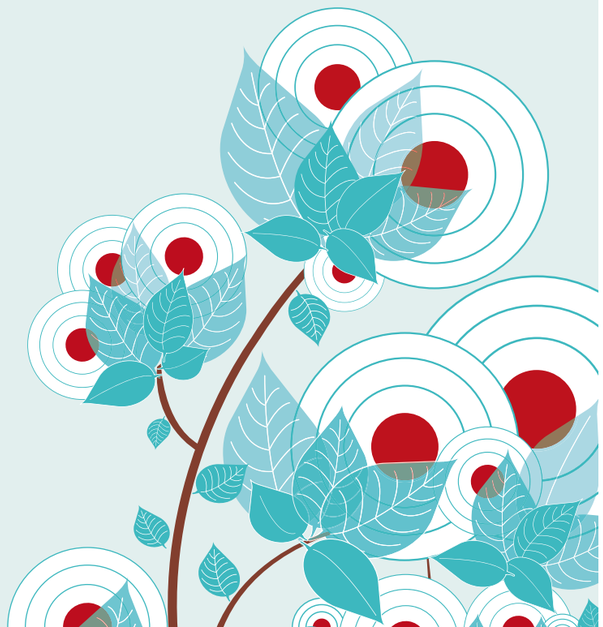
The Rhône-Alpes region has been a leading force in the fight against cancer for many years. Combined with the Auvergne region, it features:
- Five universities, four university hospitals, the International Agency for Research on Cancer (IARC), two Cancer Centers (Léon Bérard in Lyon and Jean Perrin in Clermont-Ferrand), the Loire Cancer Institute (ICL in Saint-Etienne) and the Albert Bonniot Institute in Grenoble, as well as teams from the French National Institute for Health and Medical Research (INSERM), the French National Center for Scientific Research (CNRS), the Ecole Normale Supérieure Graduate School (ENS) and the French Nuclear Energy Commission (CEA).
- High-level technological platforms
- Network organizations, including the Lyonbiopôle competitiveness cluster and the Grenoble nanotechnology cluster, the "Synergie Lyon Cancer" RTRS Research Foundation and the Hadrontherapy project of the Centre Etoile.

A unique industrial-oriented research program

In order to develop partnerships between the academic and industrial spheres in Rhône-Alpes Auvergne, CLARA has set up a program to support high-potential innovative projects, leading to a Proof of Concept and to industrial transfer. Named "Proof of Concept," this program has received €13 million funding from industrial partners to benefit 14 projects selected by CLARA.

A total budget of €110 million and diverse sources of funding

Since CLARA was founded, it has been granted subsidies from local authorities (€50 million), the French State and National Cancer Institute (€45 million), and industrial partners (€13 million). In addition, CLARA partners coordinate European projects accounting for an overall budget of €15 million.



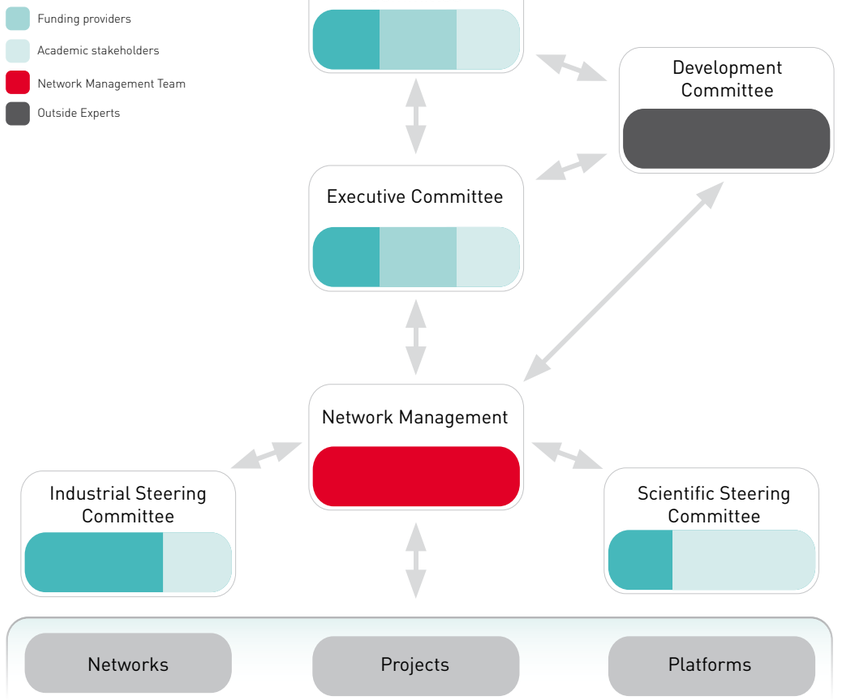
I - Mobilizing region's players

In 2008, CLARA's new governance became operational, thus confirming that the organizational choices made in 2007 were sound.

1. Collegial governance

Cancéropôle relies on collegial governance that actively involves all of the network's stakeholders. Funding providers, academic organizations and industrial partners all play a key role in the cluster's governance through five committees:
- The Strategic Orientation Committee determines CLARA's major orientations.
- The Executive Committee is in charge of implementing the decisions made by the Strategic Orientation Committee. It approves and allocates the funding.
- The Development Committee, created in 2008, guides CLARA's scientific orientations.
- The Scientific Steering Committee manages CLARA's scientific activities.
- The Industrial Steering Committee represents the interests of industrial partners.

CANCÉROPÔLE CLARA GOVERNANCE



2. An operational scientific steering committee

The Scientific Steering Committee specifically focuses on orienting and meeting the objectives of CLARA's six focus areas. This multidisciplinary body is composed of 14 members.

Its missions:

- Facilitating progress in translational research.
- Optimizing the process for answering to calls for projects.
- Organizing CLARA's Scientific Forum.
- Setting out effective strategies for collaborating with other research clusters.

SPOTLIGHT

In 2008, CLARA's Scientific Forum in Lyon featured:

- 460 participants
- 210 abstracts submitted
- 20 platforms represented

This collegial scientific management model has received support from its members. After one year of existence, its operations have resulted in concrete achievements, namely:

- The startup of several core programs
- The setup of a program to enhance the mobility of young researchers
- The organization of high-profile symposiums on specific topics
- The setup of a regulatory unit combined with a training program, in order to facilitate the transition between research and product development.

These actions unite a number of the Rhône-Alpes Auvergne regional partners in the field of cancer research. We hope that this dynamic will continue to build and will benefit from the attractiveness of the network, which can bring in new members and further strengthen the working groups with their expertise.

CORE PROGRAMS TO...

- Implement an integrated approach to research (fundamental, translational and clinical) and industrial development by uniting CLARA members and various regional institutions.
- Mobilize competitive teams and resources able to take CLARA research to a European level in 2010
- Gradually pool high-level projects and teams working towards a common aim, including those from other cancer research clusters or other countries.

Six programs were initiated in 2008

3. A dynamic industrial steering committee

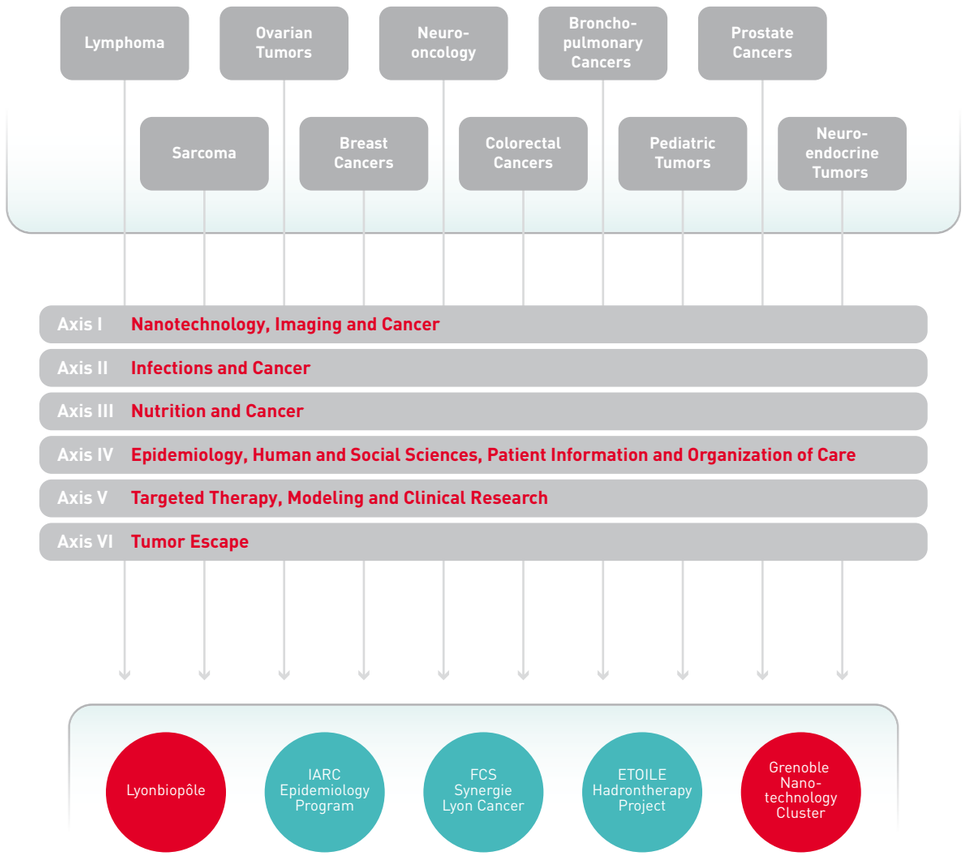
From its set up, CLARA initiated immediately an **Industrial Steering Committee** that represents its industrial partners in order to guide the cluster's activities. Giving industrial partners an active role within CLARA illustrates the network's strong willingness to transfer research findings towards clinical applications more quickly, to maximize the economic potential of these breakthroughs and to make the region more attractive.

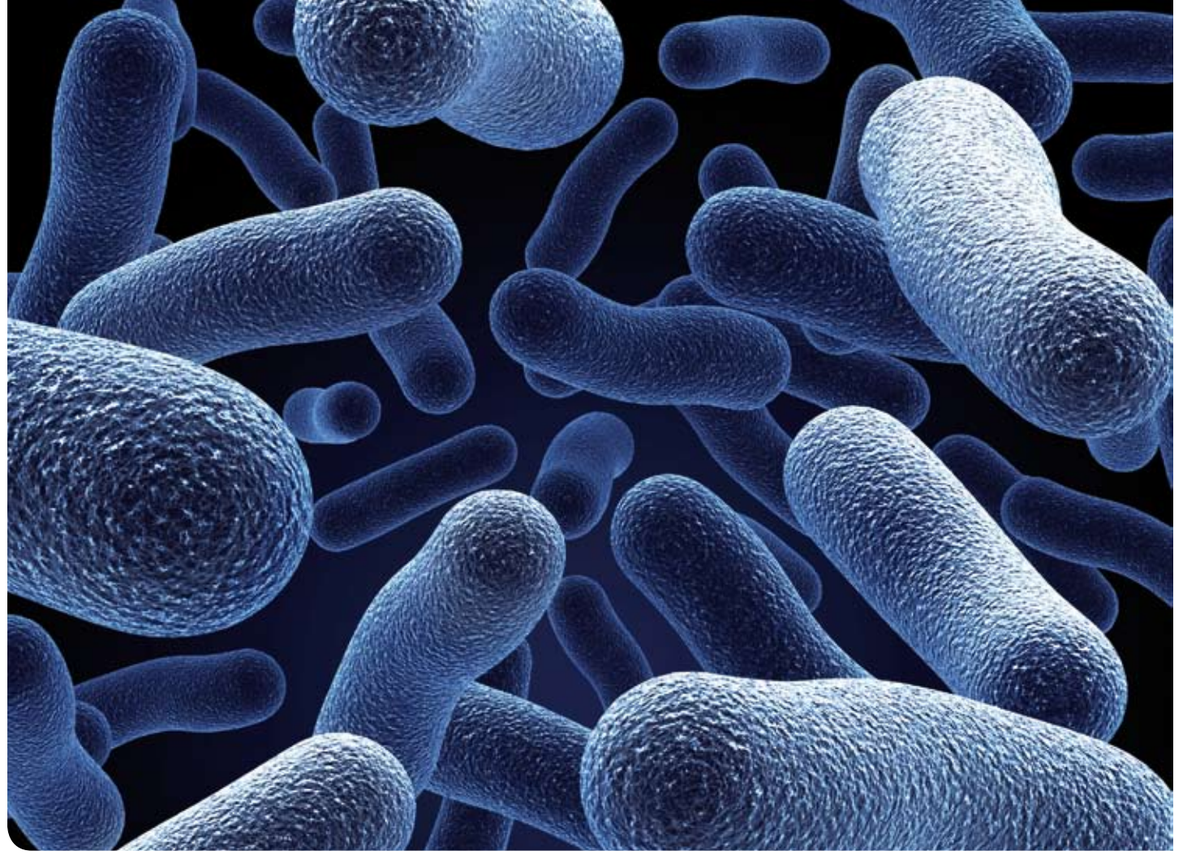
In October 2008, this Committee organized an «Industrial - Academic Forum.» Based on a business convention concept, this event aims to encourage collaboration between academic, clinical and industrial partners and to prompt the development of concrete partnerships. The success of this «Industrial - Academic Forum» has revealed the industrial's growing interest in CLARA.

II - Organizing research around six key focus areas

The French National Cancer Institute (INCa) has renewed its trust in CLARA as part of the "ProCan 2007-2010" program. This trust has played a decisive role in its actions.
In 2008, it led CLARA to organize the research efforts of the Auvergne Rhône-Alpes region's 210 research teams around six focus areas. These strengths provide a true value for France's national cancer research program.

STRENGTHS OF CANCER RESEARCH IN THE AUVERGNE RHÔNE-ALPES REGION





III - Cancer research in Rhône-Alpes Auvergne

1. New nanotechnology-based diagnostics and treatment tools

Focus area I: Nanotechnology, Imaging and Cancer

Focus Area I aims to design new tools to detect and treat cancer, as well as to better understand the mechanisms of malignant tumors via imaging and nanotechnology. Combined with the analytical power of nanotechnology, the miniaturization of imaging tools enables earlier detection of cancers and less invasive treatment thanks to the development of more specific targeted therapies.

The scientific missions of Focus Area I

- Improving access to micro and nanotechnology: miniaturization, surface modification, microfluidics and nanoparticles.
- Developing imaging and contrast enhancement methodology.
- Integrating innovative biological analysis tools, from in vitro diagnostics (proteomics and genomics of circulating biomarkers) to molecular imaging.
- Contributing to the development of new molecular therapeutic strategies.
- Developing nanotoxicology research programs.
- Studying the social, economic and ethical impact of these new approaches.

SPOTLIGHT

CLARA is France's only cancer research cluster with a top priority focus area on nanotechnology research.

FOCUS AREA I ADVANCES IN 2008

High-impact scientific activities and events

Scientific activities and events are a cornerstone of Focus Area I. As nanotechnology originates from a non-medical technological field, its use requires complementary expertise. Thus, new participants are contributing to cancer research. CLARA sent out a call for letters of intent to identify research teams able to develop clinical applications for nanotechnology in the field of cancer. This process helped to highlight areas of expertise, as well as to build a targeted scientific activities and events program. Thus, topics such as nanoparticles, radiotracers, nanotracers, biomarkers, imaging and regulatory aspects of nanoparticles have mobilized the region's researchers. Coordinated by a steering committee that represents research, clinical and industrial partners from Clermont-Ferrand, Grenoble, Lyon and Saint-Etienne, these scientific activities and events are playing their intended role. In addition to organizing meetings between the various parties, they have led to new collaborative ventures, including two new programs.

Vital to the consistency of scientific activities in the region, theme-related events are the prelude to new collaborative projects. It helps:
- to promote the scientific aims
- to identify teams and bring them together in specific topic areas
- to encourage a cross-disciplinary approach.

Two new programs

"Nanotracers"
This program aims to assist projects involving nanotechnology during the phase in which research findings are transferred to application for patients.
Launched in partnership with Lyon Civil Hospitals (HCL), this initiative results from the observation that there is a lack of guidelines on study regulations and on the development of biological products derived from nanotechnology research. This program has enabled the setup of a regulatory unit. It is composed of a quality specialist with expertise in regulatory aspects, a specialist in pharmacotoxicology and an expert in charge of clinical evaluation. A training program on the regulatory aspects of nanotracer development completes this program (see box).

"Biomarkers"
This program involves implementing an integrated approach to nanomedicine for personalized prescription of antiangiogenics. This cross-disciplinary program brings together oncologists, biologists and technology specialists in order to validate a process to predict response to targeted therapies.

Outside collaborative projects: the PACA Cancer Research Cluster

The CLARA and PACA cancer research clusters have pooled their energies in the field of imaging. This collaborative venture is currently being set up.

TRAINING PROGRAM: "DEVELOPMENT OF A BIOLOGICAL AGENT FROM LAB BENCH TO HUMAN: REGULATORY ASPECTS"

This training program aims to specify the regulatory and practical framework for developing a biological product and transferring its use in humans. The principles of evaluation, processes and related issues are presented. The "Quality," "Toxicology" and "Clinical evaluation" aspects are explored from a theoretical perspective as well as through actual case studies by specialists in the field.

PORTFOLIO

The main theme addressed in Focus Area I is the optimization of nanotechnology development in order to improve imaging, diagnostics and therapy.
This innovative and promising focus area has convinced a range of funding providers:
- **INCa is supporting 10 projects related to breast, lung and brain cancers and to technological innovation studies.**
- **Six projects have been selected as part of the "Proof of Concept" program.**
- **Seven projects have received funding from the French National Research Agency (ANR) and European bodies.**

In 2008, two patents were filed as a result of research conducted by CLARA teams. These results attest to the effectiveness of the cluster's research transfer efforts.

2. Improving diagnostics, treatment and prevention of viral-induced cancers

Focus Area II: Infections and Cancer

Cancers either induced or associated to infections are a veritable public health scourge. This results from the action of specific infectious agents, mainly viruses:
- Liver cancer, with the hepatitis B and C viruses
- Cervical cancer, with human papillomavirus (HPV)
- Lymphoma, with Epstein-Barr virus
- Leukemia, with adult leukemia virus (HTLV)
- Kaposi's sarcoma with the human herpes virus (HHVB)
- Gastric cancer caused by the *Helicobacter pylori* bacterial strain.

The primary aim of the "Infections and Cancer" focus area is improving the prevention, diagnosis and treatment of viral-induced cancers. Prevention strategies, in particular, are a critical focus, as they provide an effective means of curbing incidence of these types of cancers.

SPOTLIGHT

15 to 20% of cancer cases worldwide (liver cancer, cervical cancer, leukemia, and others) are caused by or related to infections.

The scientific missions of Focus Area II

- Identifying mechanisms of immune responses and their regulation/deregulation in cancers, infections and more particularly viral-induced cancers.
- Describing the molecular mechanisms of malignant transformation, particularly in viral-induced cancer models.
- Developing new diagnostic and therapeutic strategies for improved treatment of cancers, particularly those related to infections.

IN THE RHÔNE-ALPES AUVERGNE REGION, A NUMBER OF ORGANIZATIONS ARE INVOLVED IN THE INFECTIONS AND CANCER FOCUS AREA:
- Lyonbiopôle
- Synergie Lyon Cancer Foundation (RTRS network)
- The Finovi Foundation (RTRA network)
- The International Agency for Research on Cancer (IARC)
- The Léon Bérard Cancer Research Center
- Albert Bonniot Institute
- Ecole Normale Supérieure Graduate School (ENS)
- Lyon Civil Hospitals (HCL)
- French Blood Agency (EFS)
- INSERM, CNRS, Universities
- and CLARA, whose federating role is essential to structuring the research efforts.

FOCUS AREA II ADVANCES IN 2008

Structured scientific activities and events

In 2008, the program of scientific activities and events for Focus Area II revolved around two key areas:
- Immune response in cancers and infections.
- Molecular mechanisms in malignant transformation.

Three core programs

"Dissection and targeting of telosome dysfunctions in telomerase during viral-induced carcinogenesis"
This program aims to verify the gene regulation of telosome and of the hTERT promoter for diagnostic, prognostic and therapeutic purposes (development of potentially antineoplastic peptides).

Project Leader: Eric Wattel (CNRS UMR 5537 - Claude Bernard University, Léon Bérard Cancer Center, Oncovirology and Biotherapies)

"Federative program on Toll-Like Receptors (TLR) and innate immunity"
This program aims to bring together the tools available in the Rhône-Alpes Auvergne region on Toll-Like Receptors (TLR) and innate immunity. It also meets the need to implement new tools and techniques.

Coordination: Massimo Tommasino (International Agency for Research on Cancer – IARC, Infections and Cancer Biology Group)

"A platform to isolate primary human hepatocytes and progenerative hepatic cells"
This program is devoted to setting up a platform to prepare and store human hepatocytes from resections and to analyze the early steps in carcinogenesis.

Co-leaders: Philippe Merle (INSERM U871 - Claude Bernard University, Hepatology and Gastroenterology Unit, Hôtel-Dieu Hospital, Molecular Physiopathology and new treatments for viral hepatitis, Pathogenesis of Viral Hepatitis B and C, and Viral-Induced Hepatic Oncogenesis) and Bakary Sylla (International Agency for Research on Cancer – IARC, Infections and Cancer Biology Group).

Outside collaborative projects: Grand-Est Cancer Research Cluster - DFKZ (Germany) - International Agency for Research on Cancer (IARC) - Lyonbiopôle - Synergie Lyon Cancer Foundation (RTRS) – Finovi Foundation (RTRA)

The dynamism of the CLARA cancer research cluster's partnership policy has led it to build relations with regional players active in the various topics within the "Infections and Cancer" focus area. In 2008, several initiatives and accomplishments materialized:
- A brainstorm session (April 14, 2008) with the Lyonbiopôle competitiveness cluster, the Synergie Lyon Cancer Foundation (RTRS) and the Finovi Foundation (RTRA) in order to determine CLARA's positioning in relation to these other organizations. This process led to stronger relations with Lyonbiopôle, namely the publication of a special "CLARA" issue of Lyonbiopôle's newsletter, FOCUS.
- Preparation of a joint symposium featuring the CLARA and Grand-Est cancer research clusters, DFKZ (Germany) and the International Agency for Research on Cancer (IARC).
- A workshop project on the theme of "virology and cancer", in partnership with the Mérieux, FINOVI and Synergie Lyon Cancer Foundations and Lyonbiopôle.

PORTFOLIO

In anticipation of the INCa call for projects in the "Hepatocellular Carcinoma" category (November 2008), the network emphasized the consistency of its submissions by carrying out letters of intent to request funding. This was followed by a coordination meeting between potential project initiators.

- INCa is supporting seven projects related to breast and ovarian cancers, to hepatocellular carcinoma, to plasmacytoid dendritic cells and to leukemia.
- Four projects from the "Proof of Concept" program involve industrial members of the Lyonbiopôle competitiveness cluster.
- 17 national (ANR - ANRs) and international projects are underway. They involve immunology, apoptosis, epigenetics and various types of viral-induced cancers.

The advances generated by research in the "Infections and Cancer" focus area led to two patent filings in 2008. The transfer of these findings to the industrial phase will thus enable them to be used in humans more quickly.

3. Nutrition-based cancer prevention strategies

Focus Area III: Nutrition and Cancer

Combining nutrition, oncology, integrated physiology and genetics in order to prevent cancer is the aim of Focus Area III. Its ambition is to give a more solid scientific basis to nutritional recommendations made as part of national and international cancer prevention policies.
The research in this focus area falls under two main areas:
- Identifying food components able to curb the occurrence of hormone-dependent cancers (breast and prostate) and to describe their mechanisms of action using molecular approaches.
- Understanding the links between obesity and breast oncogenesis and developing nutrition-based prevention strategies.

The scientific missions of Focus Area III

- Developing cross-disciplinary research in order to foster complementary skills.
- Specifying the nature and effects of active food substances and their metabolites in cancer prevention.
- Encouraging preventive and curative translational research.

FOCUS AREA III ADVANCES IN 2008

Structured scientific activities and events

The activities in the *"Nutrition and Cancer"* focus area target breast and prostate cancers and, more particularly, the identification of food components able to curb the occurrence of hormone-dependent cancers and understanding the links between obesity and breast oncogenesis.
In 2008, the scientific activities and events were geared towards:
• Finding research projects that are complementary from a scientific and clinical perspective.
• Broadening the expertise of the researchers in Focus Area III.
At an operational level, this was illustrated through networking at forums and meetings, actions to encourage mobility for young researchers and creation of three new core programs.

Three new core programs

"Ambivalent effects of soy phytoestrogens in breast cancer"
This program is dedicated to research on phytoestrogens' epigenetic modifications of the BRCA1 and BRCA2 genes.

Leader: Dominique BERNARD-GALLON – Oncogenetics Department, Jean Perrin Center, Clermont-Ferrand.

"A study of the function of the LKB1 tumor suppressor and its interaction with HDAC6 during nutritional stress"
This study focuses on researching the effect of nutritional stress on the expression of the LKB1 and HDCA6 genes, suspected of playing a role in tumor development.

Leader: Jean-Louis Couderc – "Epithelial Differentiation and Morphogenesis" team, GReD, UMR CNRS 6247, INSERM Unit 391, Clermont University Medical School."

"Understanding and identifying lipid components in food capable of delaying or accelerating tumor development in the prostate or colon"
This program focuses on the role of lipids in tumor progression and on dialog between the LXR and AR receptors.

Leader: Jean-Marc A. Lobaccaro – "LXR, Oxysterols and Steroidogenic Tissues" team - GReD, UMR CNRS 6247 INSERM Unit 931 Clermont University.

Strengthened expertise

In 2008, CLARA stepped up its drive to bring new multidisciplinary expertise into the "Nutrition and Cancer" focus area.

The launch of a "Young Researcher Mobility" call for projects enabled five researchers to gain the knowledge required to move forward in "Nutrition et Cancer" research projects. These scientists gained this valuable expertise at laboratories such as:

• Bayer CropScience in Sophia-Antipolis, France.
• The Marseille-Luminy Immunology Center.
• Institut für Toxikologie und Genetik, in Eggenstein-Leopoldshafen, Germany.

In addition to learning new techniques, these collaborative projects strengthened relationships between research teams and encouraged the design of new core programs.

Seven new teams were identified and contacted to participate in Focus Area III research projects. The events staged by CLARA, namely the Focus Area III Scientific Forum, held on June 3, 2008, brought to light prospects for joint projects. Clinical teams (urologists) showed their interest to take part, particularly in the field of prostate cancer.

New collaborative projects

In 2008, CLARA strengthened its relationships with regional institutions involved in research in the "Nutrition and Cancer" focus area, namely with:
• The Human Nutrition Research Centers (CRNH) in Auvergne and Rhône-Alpes.
• The European Ultra-High Field NMR Center (Lyon), which will bring its expertise in metabolomics.

The CLARA cluster has also been building links beyond the region. It initiated a national **"Obesity, adipokines and cancer"** network, which involves academic and clinical researchers beyond the Lyon – Rhône-Alpes Auvergne cluster framework.

4. New disciplines in cancer research

Focus Area IV: Epidemiology, Human and Social Sciences, Patient Information and Organization of Care

The multidisciplinary "Epidemiology, Human and Social Sciences, Patient Information and Organization of Care" focus area aims to enhance research projects with the perspectives of various disciplines that traditionally are not so much involved in the study of cancer. Thus, this focus area combines Rhône-Alpes Auvergne research teams active in the fields of human and social sciences, epidemiology, patient support and care management. These research groups seek to assess the factors promoting cancer, to meet patient needs and to help medical staff and treatment teams to better understand the issues related to the disease.

SPOTLIGHT

Epidemiological studies include assessing the impact of mobile phone use, the risks of various types of pollution, the influence of ionizing radiation on the risk of cancer...

The missions of Focus Area IV

At the operational level, the work of Focus Area IV aims to provide new perspectives on:
• Cancer prevention (e.g. the risk of tobacco-related cancer, etc.).
• The development of therapeutic support for patients resulting from advances in patient care and longer patient lifespan.

FOCUS AREA IV ADVANCES IN 2008

Multidisciplinary scientific activities and events

This CLARA cancer research cluster aims to encourage dynamic interactions between fields as diverse as epidemiology, the social and human sciences, patient information and care management and organization. This will provide patients, healthcare professionals and decision makers with a broad range of interrelated knowledge.
With this in mind, CLARA implemented a program of multidisciplinary special events in 2008 that helped to:
• **Specify top-priority research topics,** namely cancer screening and at-home hospitalization.
• **Perform a census of the Rhône-Alpes Auvergne region's research teams related to the four aspects of Focus Area IV:** of the more than 30 teams identified in the region, two-thirds do not necessarily work in the field of cancer (in particular in the Human and Social Sciences). One of the aims for the coming year will be to convince them to take part in multidisciplinary research programs in the field of cancer.
• **Initiate multidisciplinary projects:** in October 2008, CLARA sent out a call for letters of intent in order to support core research programs. The ultimate aim is to build a portfolio of high-potential, high-quality projects with a view to answering INCa calls for projects. Seven projects have been selected, and they will be approved following an audit by a non-CLARA, third-party body. The results will be made public in February 2009.

Finally, the Focus Area IV team wrapped up 2008 with a major event, a symposium entitled **"Epidemiological data on cancer: How can we interpret them? – What information do they provide for research and for public health action?"**. Held in Lyon on December 17 and 18, 2008, this event drew more than 160 participants, primarily epidemiologists, clinicians and specialists in human and social sciences.
This symposium presented the major epidemiological results in terms of cancer incidence and survival. It aimed to highlight the vital links between the clinical and epidemiological spheres and to encourage new research teams to take part in focus area projects.

PORTFOLIO

• 19 projects related to patient information, social and human sciences, epidemiology, quality of care and public health are funded by INCa.
• CLARA funded a project on validation of a breast cancer registry system and assessment of organized screening. The goal is to set up an exhaustive, high-quality histopathological registry of breast tumors in the Rhône-Alpes region. This registry can be used by public health laboratories, by the International Agency for Research on Cancer, and by the biological bank management center as a fundamental resource for overall assessment of screening.

5. Towards an information portal for early-phase drug trials

Focus Area V: Targeted Therapy, Modeling and Clinical Research

The "Targeted Therapy, Modeling and Clinical Research" focus area is setting up an information portal in the Rhône-Alpes Auvergne region for performance of early-phase drug trials. The aim is to avoid the dispersion of research efforts for the initial phases of development of candidate drugs. This portal will provide a true benefit to translational research and will provide industrial firms with a good view on the teams in the Rhône-Alpes Auvergne region with the expertise required to carry out clinical trials. It will also help to foster synergy between clinical, pharmacogenomic and clinical pharmacology teams.

The resulting increase in the volume of early-phase trials will lead to a greater number of therapeutic options for cancer patients. Thanks to their heightened visibility, research teams in Rhône-Alpes Auvergne will help to make the region more competitive.

SPOTLIGHT

Early-phase clinical trials help to assess the efficacy of new molecules in humans. The quality of the studies contributes to advances in translational research.

The missions of Focus Area V

- Incorporating the various approaches to targeted therapy (identification of cellular and molecular targets, pharmacogenetics , pharmacogenomics, pharmacokinetics and pharmacodynamics) via mathematical modeling, in order to predict the effects of therapeutics and personalized treatments.

The Hospital Clinical Research Program takes the form of competitive calls for projects sent out by DHOS.
The best clinical research projects (clinical and therapeutic trials, epidemiological and medical practice surveys, and predictive or prognostic factor research programs) receive financial support.

FOCUS AREA V ADVANCES IN 2008

A research team census phase

In order to prepare the setup of a shared information portal, CLARA performed in 2008 a census of teams that are conducting early-phase trials in the field of cancer. To accomplish this, the cluster put together an inventory of teams involved in early-phase development of cancer medications. It used information from a survey performed by the Clinical Research in Cancer in Auvergne, *Rhône-Alpes Assistance Platform (PARCC-ARA)*. So far, about 30 early-phase clinical trials have been collected.

In order to better meet the needs of CLARA's industrial partners, a working group dedicated to the early-phase trial information portal has been initiated within the Industrial Steering Committee.

PORTFOLIO

- **Eight projects on lymphoma, breast cancer, ovarian tumors, aggressive fibromatosis and bronchopulmonary cancers are being funded by INCa.**
- **Four new projects were funded by the Hospitalization and Care Organization Division (DHOS) in 2008 as part of the Hospital Clinical Research Program (PHRC). These projects focus on lymphoma, colorectal cancer, adult glial tumors and pediatric oncology.**
- **One project (on early stage cervical cancer) was selected as part of the Costly Innovative Techniques Support Program (STIC) in 2008.**

6. PREVENTING METASTATIC DISSEMINATION AND RESISTANCE TO TREATMENTS

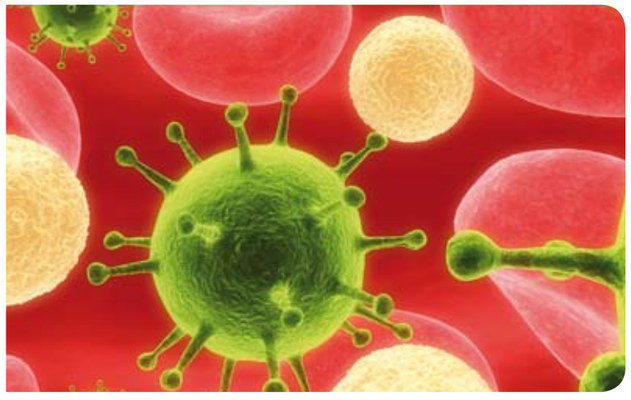
Focus Area VI: Tumor Escape

The "Tumor Escape" focus area explores the means of re-establishing the physiological mechanisms for cell protection and immune response in order to prevent metastatic dissemination and drug resistance. This focus area builds upon the expertise of the Synergie Lyon Cancer Scientific Cooperation Foundation. Today, the goal is to get laboratories of other cities of the CLARA region (Grenoble, Saint-Etienne and Clermont-Ferrand) connected to this topic.
Focus Area VI concentrates primarily on studying cell survival, apoptosis and senescence, immunosurveillance and tumor escape. The research is performed using physiopathological models similar to human tumors. This involves speeding up development of these preclinical models in order to enable screening of tumor targets and therapeutic molecules.

FOCUS AREA VI ADVANCES IN 2008

Close collaboration with the synergie Lyon Cancer Foundation

In 2008, Michael Courtney came on board as Director of the Synergie Lyon Cancer Foundation. His mission is to provide support for research on tumor escape and therapeutic targeting, to facilitate the development of diagnostic and therapeutic applications, to promote the collaboration between clinical and fundamental research groups and to promote the Synergie Lyon Cancer network internationally.



Setup of a tumor model laboratory

The CLARA cancer research network contributed to the setup of a tumor modes laboratory in cooperation with Synergie Lyon Cancer and Claude Bernard University Lyon.
Four options for models are being considered:

- Xenograft studies with samples of human tumors.
- Predisposition models for specific tumors.
- Metastasis development and drug resistance models.
- Humanized mice to study immune surveillance and escape mechanisms.

This laboratory enables scientists to use tumor models, highly similar to human tumors and that are controlled by using anatomopathological analysis. The lab adds genuine value to the setup of large-scale research projects.

PORTFOLIO

- **27 projects are being supported by INCa, including four new projects in 2008.**

In 2009, Focus Area VI will channel its efforts into setting up projects on the following research topics:

- **Epigenetic profiling of cancers.**
- **Signaling pathways in cancer.**
- **Cancer and Nuclear Magnetic Resonance.**
- **Tumor radioresistance and genetic epidemiology of cancer.**

IV - Visible results: a concrete project portfolio

1. The INCa project portfolio in 2008

In 2008, CLARA teams stepped up their efforts in response to calls for projects, in particular those from the INCa. As part of the INCa call for projects, sent out in spring 2008, 10 new projects were selected. They account for a budget of €3.6 million. Targeted tumors are lymphoma, sarcoma, glioma, endocrine and ovarian tumors, as well as breast and lung cancers. Thus, seven of CLARA's 10 disease study networks are moving forward. The winning projects benefit from unique access to collections of tumors removed from patients, thus strengthening CLARA's positioning in translational research.

SPOTLIGHT

In spring 2008 : 10 new projects supported by INCa, with a total budget of €3.6 million

SUMMARY OF INCa CALLS FOR PROJECTS - SPRING 2008

NAME	Institution	Project Title	Budget*
J.J. DIAZ	UCB Lyon	Role of ribosomal alterations and translational specificity in tumorigenesis	600
N. FORAY	INSERM, Grenoble	Assessment of the response of normal and tumour human brain cells to anti-glioma treatments	400
E. GILSON	ENS Lyon	Telomere functions as targets for new therapeutic approaches against cancer	700
J.Y BLAY	INSERM-CLB, Lyon	Molecular epidemiology of sarcomas in the Rhône-Alpes region: 2005-2006	350
P. BOFFETTA	CIRC, Lyon	Gene-smoking and gene-occupation interactions in lung carcinogenesis	300
P. HAINAUT	CIRC, Lyon	Genomics and Functions of genes associated with predisposition to Lung Cancer : biological, pathological and clinical significance	519
G. SALLES	HCL, Lyon	Genetic and outcome in aggressive lymphoma: analysis of DNA polymorphisms in a cohort of diffuse large B-cell lymphoma patients in the GELA LNH2003 study	480
M. KOSSAI (F. Penault-Llorca)	CJP, Clermont-Ferrand	Tumeurs Mammaires de moins de 1cm : identification des tumeurs potentiellement agressives candidates à un traitement adjuvant	48
S. LABIDI (A. Puisieux)	CLB, Lyon	Functional and phenotypic evaluation of intratumoral plasmacytoid dendritic cells (pDC) and regulatory T lymphocytes (Treg) in ovarian cancer	110
B. BLAISE (P. Toulhoat)	RMN, Lyon	Métabonomique des tumeurs endocrines par RMN à Très Hauts Champs	68

*in thousands of €

This momentum is building, illustrating the commitment of local research teams to playing an active role: 44 projects were submitted in response to INCa's autumn 2008 call for projects.
Finally, moving beyond French borders, the CLARA project entitled "Candidate peptides of the molecular chaperones Bag-1L and NPM for molecular prostate cancer therapy"* was selected as part of the "Joint Translational Research Program on Cancer" with the German Academic Exchange Service.

* Laurent Morel (Blaise Pascal University, Clermont-Ferrand) in collaboration with A. Cato (Institute of Toxicology and Genetics - Karlsruhe – Germany)

2. Projects selected as part of the hospital clinical research program (PHRC)

This year, four Hospital Clinical Research Program (PHRC) applications were selected, for a total of €1,000,000.

The four selected PHRC projects:

• A randomized phase II study of two associations of rituximab and chemotherapy, with a PET-driven strategy, in patients from 18 to 60 with DLBCL CD20 + lymphoma and 2 or 3 adverse prognostic factors of the age-adjusted IPI – €600,000.

Leader: Prof .Bertrand Coiffier - Lyon Sud Hospital Center

• An evaluation of the efficacy of bioresorbable membranes on preventing the formation of post-operative abdominal and perihepatic adherences in colorectal cancer patients requiring surgical resection of hepatic metastases in two separate operations – €100,000.

Leader: Michel Rivoire - Léon Bérard Cancer Research Center, Lyon

• Urinary Metabolomics, Pharmacogenetics and Enzyme Activity of Aldehyde Dehydrogenase as Predictive Markers of induced Ifosfamide Nephrotoxicity in Pediatric Oncology (pilot study) – €115,000.

Leader: Matthias Schell - Centre Léon Bérard Cancer Research Center, Lyon

• Determining the impact of radiotherapy on good prognosis of glial tumors in adults on neurocognitive functions: a prospective multicenter study – €184,000.

Leader: Marie-Pierre Sunyach - Centre Léon Bérard Lyon Cancer Research Center

3. Projects selected as part of the Support for Innovative Costly Techniques program (STIC)

In 2008, CLARA obtained one of five projects selected in France as part of the Support for Innovative Costly Techniques (STIC) program in the field of cancer research.

• «Senticol-2: Comparison between pelvic lymphadenectomy versus isolated removal of the sentinel ganglion in early-stage cervical cancer: a randomized multicenter study with evaluation of economic impact» - €600,000.

Leaders: Professors Patrice Mathevet and Fabrice Lecuru – Lyon Civil Hospitals (HCL)

Since 2000, the ministry program on Support for Innovative Costly Techniques (STIC) has enabled annual based funding of national-scale research projects. In 2008, 5 out of 30 projects submitted in France, five were selected, including one presented by CLARA.

4. Projects supported by non-profit associations

Non-profit associations also collect funding for research conducted by teams in the Rhône-Alpes Auvergne region, in particular:

• The French Association for Research on Cancer (ARC)
In 2008, the ARC's Board of Directors voted to grant K€3,936 in funding to researchers and their teams in the CLARA region. This funding was allocated in the form of young researcher awards, fixed subsidies and infrastructure funding for research teams.

• The French League Against Cancer
In 2008, the League granted K€1.833 to CLARA research teams at the national level. Additional funding was provided by Local Committees.

V - Promoting the transfer of research findings to industry

Building partnerships between industrial partners, clinical and academic teams as part of oncology research and innovation projects is one of CLARA's top priorities, as seen in several key objectives:

• Developing high-level innovative translational research.
• Speeding up the transfer of research findings to clinical applications.
• Promoting economic development and making the region more attractive.

The speed at which patients have access to therapeutic innovations is based on interactions between the industrial and academic spheres. The effectiveness of these innovations requires clarity and a solid understanding of each stakeholder's aims. CLARA plays a pivotal role in the development of this partnership strategy. With its operational vision, the Lyon Auvergne Rhône-Alpes cluster is a vital link between the academic and industrial spheres.

1. Transfer opportunities for INCa 2005-2006 projects

The CLARA network management team conducted a review of INCa 2005 and 2006 projects in order to identify available results for collaborative ventures with academic and, more importantly, industrial partners. The participation of project initiators in this process was truly remarkable and several opportunities were pinpointed:

• The identification of H4K20me3 as a biomarker of interest for detection and prognosis of lung cancers.
• The identification of new factors that are proteins combined with chromatin, based on the detection of antibodies directed against these factors in the sera of patients with non-small-cell lung cancer.
• Netrin-1 as a prognostic marker of the development of metastases of breast cancer and the possibility of eliminating metastases or preventing their occurrence by causing the death of tumor cells by netrin-1 titration. Netrin could also be a valuable target for treatment of colon cancer.
• Autotaxin regulates the metastatic dissemination of breast cancer cells, suggesting that autotaxin targeting would enable a new anti-lysophospholipid therapeutic approach in the prevention of metastases.
• The detection of a high level of CA9 messenger RNA in the serum of more than 90% of patients with clear-cell renal adenocarcinoma in contrast to control subjects.
• The identification of a new cancer stem cell marker specific to glioblastoma, the protein IQGAP1.
• The discovery of Apollo as a new telomeric protein that can be a target for the design of new anticancer molecules.

This non-exhaustive list illustrates the capacity of the CLARA network researchers to make advances in new areas of diagnostic and therapeutic research.

In 2009, the results of projects started in 2007 will be examined with the same aims.

2. CLARA's Proof of Concept Program

Launched in 2005 with a pilot project, CLARA's «Proof of Concept» program took on a new importance in 2008, as one of the keys to develop applications for life sciences research in Rhône-Alpes Auvergne. 14 diverse innovative projects are currently underway. They account for an overall budget of nearly €18 million, including €13 million brought in by 11 industrial partners. Each project brings academic and clinical innovators in oncology together with industrial partners ready to take their breakthroughs to development.

LANDMARK

CLARA is France's first cancer research cluster to have set up a Proof of Concept program.

A very good vintage in 2008: five new projects, including one «cancer nano transfer» project

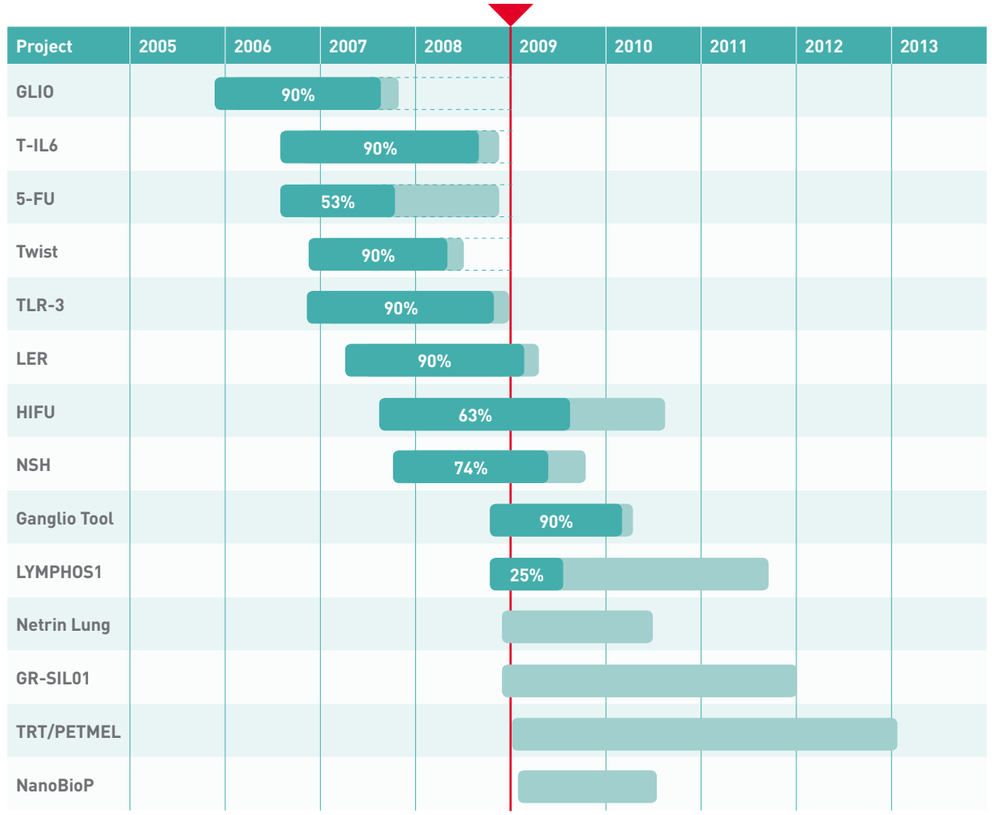
In 2008, CLARA continued and extended its "Proof of Concept" program and a new «Cancer Nano Transfer» line specifically supports «Nanotechnologies & Cancer» liaison projects.
The *"Proof of Concept"* call for projects, sent out in March 2008, featured an abundance of high-quality submissions and enabled the initiation of five new projects.

SUMMARY OF PROOF OF CONCEPT PROJECTS

Projects	Acronym	Approach	Objective	Indication	ProCan Axis	Academic Coordinator	CLARA*	Research Application Partner	Budget*
Traitement des glioblastomes après vectorisation ciblée de nanoparticules magnétiques dans les cellules tumorales	GLIO	Nanotech	Therapy	Glioblastoma	I	J. Honnorat	372	Nanobiotix	1800
IL-6 tronquée en inhibiteur naturel de l'IL-6 : sa démonstration in vivo	t-IL6	Bio-molecule	Therapy	Multiple	II	L. Alberti	305	IDD Biotech	305
Traitement des métastases hépatiques du cancer colorectal par ciblage du foie ; encapsulation intra-erythrocytaire du 5-FU	5-FU	Drug delivery	Therapy	Hepatic Metastases	V	M. Rivoire	312	ERY tech Pharma	312
TwistCancer. Twist-1, new diagnostic, prognostic and predictive marker of aggressive and chemoresistant cancers	Twist	Antibody	Diagnostic	Breast Neuro-bloastoma	VI	S. Wittman	120	CovalAb	150
TLR3 agonists for treating human breast cancer	TLR-3	Bio-molecule	Therapy	Breast	II	S. Lebecque	400	Innate Pharma	7200
A robot to assist in minimally invasive cancer surgery	LER	Tech Med	Therapy	Prostate		J. Troccaz	212	EndoControl Medical	213
Treatment of hepatic metastases by focused ultrasound	HIFU	Tech Med	Therapy	Hepatic Metastases	I	J.Y. Chapelon	420	EDAP TMS	590
Hybrid nanosensors for multimodal imaging of cell tracking in cancer	NSH	Nanotech	Imagery	Melanoma	I	C. Bilotey	307	Nano-H	307
Ganglio Tool	Ganglio Tool	Nanotech	Diagnostic	Lymphoma Medrastinal Metastic Adenopathies	I	M.L. Cosnier	249	CEA	128
Tracking TCR repertoire distortions to predict lymphopenia and prevent deaths due to infections associated with chemotherapy in patients with breast cancer	LYMPHOS 1	Instrument	Diagnostic	Breast	II	C. Caux	425	ImmunID Technologies	428
Proof of concept of the efficiency of a candidate drug in the treatment of lung cancer	NETRIN LUNG	Bio-molecule	Therapy	Lung	VI	J.G Delcros	400	Netris Pharma	410
Use of red blood cells to deliver siRNA for treating an inflammatory condition	GR-SIL01	Bio-molecule	Therapy	Liver	II-VI	T. Renno	515	ERY tech Pharma	693
Development of new heteroaromatic halogenated radiotracers for PET imaging and targeted radionuclide therapy of melanoma	TRT/PETMEL	Molecule	Imagery	Melanoma	I	N. Moins	416	Cyclopharma	416
An innovative strategy for molecular nanoBiopsy using magnetic nanoparticles	NanoBioP	Nanotech	Diagnostic	Brain Liver	I	F. Berger	350	CEA	51

*in thousands of €

STATUS OF PROOF OF CONCEPT PROJECTS
% OF PAIDOUT CLARA FUNDING



PROJECTS SELECTED IN 2008 AS PART OF THE "PROOF OF CONCEPT" PROGRAM

• Development of a new radiotracer that can be used for both Positron Emission Tomography (PET) imaging and vectorized internal radiotherapy of disseminated melanoma

With sharply rising incidence, melanoma is becoming a public health concern in industrialized countries. This project involves the various phases of preclinical development of a new compound for clinical applications as a radiopharmaceutical that can be used in vectorized internal radiotherapy of melanoma. The work will include design, chemical synthesis, radioactive labeling and preclinical evaluation (with two aspects, imaging and therapy) in order to lead to the selection of a candidate compound for transfer to clinical applications.

Coordination: Nicole Moins - EA 4231, University of Auvergne, in association with Cyclopharma Laboratories (Auvergne).

• Tracking distortions of the TCR (T-cell receptor) repertoire to predict lymphopenia and prevent death following chemotherapy-related infections in breast cancer patients

One woman in 10 will develop breast cancer in her lifetime. In 25% of cases, death occurring at the beginning of the relapse phase is due to infections. The team of Professors J.Y. Blay and C. Caux's team (Léon Bérard Center – INSERM Unit 590) has demonstrated that this mortality is essentially related to an immune system dysfunction that leads to lymphopenia, which is at the origin of opportunistic infections. The Lymphos1 project aims to validate the use of an immunoprognostic tool, ImmunTraCkeR®, developed by ImmunID. By analyzing the immune repertoire, this tool enables identification of patients with a high risk of mortality following chemotherapy treatment. This tool will directly enable clinicians to adjust the dose and type of chemotherapy for immunodeficient patients, and to prescribe personalized alternative treatments.

Coordination: Christophe Caux of the «Cytokines and Cancers» team of INSERM Unit 590 (Léon Bérard Cancer Center, Lyon), in association with start-up firm ImmunID Technologies (Grenoble).

• Proof of Concept: Anetrine in lung cancer
This project aims to develop a first anticancer molecule based on the concept of dependence receptors discovered by CNRS laboratory UMR 5238 (Léon Bérard Center, Lyon). The creation of a start-up company from this project (NETRIS Pharma) aims to develop various molecules produced by this innovative research. As part of the project, a proof of concept study in animals to assess the efficacy of a molecule on lung cancer has been proposed. For this purpose, an optimized batch of this molecule will be produced, and its pharmacokinetic and pharmacodynamic (PK/PD) parameters will be determined, thus enabling in vivo studies on murine models.

Coordination: Jean-Guy Delcros of the UMR 5238 "Cancer, Apoptosis and Development" Research Unit (Léon Bérard Cancer Center, Lyon), in cooperation with start-up firm NETRIS Pharma (Lyon).

• Development of a new therapeutic approach for the treatment of hepatocarcinoma
Hepatocellular carcinoma (HCC) is one of the world's leading causes of death by cancer. There are few therapeutic options in cases of advanced HCC: systemic chemotherapy is very often ineffective and radiotherapy rarely used due to hepatic tissue's poor tolerance of irradiation. The project aims to conduct the pre-clinical proof of concept of an innovative approach to treatment of hepatocellular carcinoma.

Coordination: Toufic RENNO of UMR CNRS UNR 5201, Lyon 1 University (Léon Bérard Cancer Center, Lyon), in association with Professor Jean-Yves Scoazec (ANIPATH, Lyon 1 University) and ERYtech Pharma (Lyon).

• An innovative Micro-Nano invasive biocapture strategy (Cancer Nano Transfer)
Accessing low-concentration biological compounds, tumor complexity/heterogeneity and inaccessible peritumoral compartments are major aims in oncology. The key is reaching the most dynamic disease regions that express the most pertinent therapeutic mechanisms and targets. The highlighting of biomarkers of interest in the disease, ideally combined with tumor physiopathology and therapy is a scientific aim that has been a relative failure, due to a high concentration of major proteins in serum and the difficulties of access to the tissue.
To meet these challenges, this project focuses on the pre-clinical validation of a new nano-invasive method of collecting molecular information in oncology for both tissues and biological fluids. The chosen strategy uses chemically-altered nanoballs to capture the low-concentration proteome, which can be activated in the diseased tissues.

Coordination: Professor François Berger of INSERM Unit 836, Joseph Fourier University (GIN, Grenoble), in association with Grenoble teams: UMR SPrAM 5819 CNRS/CEA, Louis Neel Institute, INSERM-UJF Unit 823 (IAB), LIPC2S Pierre Mendès France University and CEA LETI/DTBS.

Eight projects to be concluded soon

The eight projects started between 2005 and 2007 have been monitored by CLARA's steering committees. In general, 75% of the budgets planned for these projects have been paid out and most will finish by the end of 2009. Based on this, CLARA will conduct a posteriori assessment of the selected projects. In addition to evaluating whether or not proof of concept will be obtained, the program will also examine the various types of direct and indirect impact (in terms of jobs, patents, prospects for collaborative ventures, regional attractiveness, etc.), along with possible areas for improvement.
These eight projects were published in the Bulletin du Cancer for the 3rd CLARA's Scientific Forum held in Lyon in March 2008.

Prospects for 2009-2011

As part of the Framework Agreement with Local Authorities, for the period 2009-2011, CLARA plans a yearly *"Proof of Concept"* call for projects.
The following orientations initiated in 2008 will be continued:
• Additional support for the most promising projects, particularly when they move into clinical phase
• Extending the program's geographical coverage thanks to financial support from Isère and Auvergne local authorities from 2009 onwards
• Promoting the involvement of start-ups by supporting academic partners who wish to use their services
• Emphasize CLARA's key scientific areas, in particular Focus Area I on "Nanotechnology, Imaging & Cancer" and Focus Area II on "Infections & Cancer" as part of a close partnership with the Grenoble Nanotechnology cluster and the Lyonbiopôle competitiveness cluster, respectively.
In addition, another initiative being studied is support for "Proof of Concept" projects that have market potential but do not yet have a well-established industrial partner. This support could be channeled via economic development organizations and academic incubators, based on the methods as used by Cancer Nano Transfer.

VI - Platforms: high-performance tools

1. The East Lyon functional and structural genomics and pharmacogenomics platform

Functional and structural genomics / Léon Bérard Cancer Research Center

In 2008, construction of the Cheney D Building was completed at the Léon Bérard Cancer Research Center site, where Unit 590, the Lyon Civil Hospitals / Léon Bérard mixed unit, the Léon Bérard transfer laboratory and CNRS UMR 5201 are now located. Various investments have been made, including creation of a Biosafety Level 3 laboratory, a Cytometrics platform, Experimental Surgery Platform and the extension of a building for "small animal" studies. An Affymetrix platform was acquired for the Rockefeller University site as part of the pharmacogenomics platform run by Lyon Civil Hospitals.
The InaCancer, MutaCancer and CirBioCancer programs are ongoing at these facilities.

A collaborative industrial venture is underway with bioMérieux on the development of circulating nucleic markers for the treatment of breast and colorectal cancer patients. Several CLARA «Proof of Concept» programs - «t IL-6» with IDD Biotech, «5-FU» with ERYtech Pharma, «HIFU» with EDAP TMS, «TWIST» with CovalAb and, since late 2008, «Lymphos1» with ImmunID and «Netrin Lung» with Netris Pharma - are also involved.

Pharmacogenomics / Lyon Civil Hospitals

The Molecular Characterization of Tumors Laboratory (LCMT) at the Rockefeller University (Lyon Civil Hospitals) facility aims to develop tests to predict individual patients' sensitivity to existing or new cancer drugs (pharmacogenetics / pharmacogenomics) in order to personalize cancer therapies.

The research programs on lung cancer (Pharmacogenoscan), Myeloma (IFM), breast and colorectal cancers (with bioMérieux), thyroid cancer and several collaborative projects with pharmaceutical firms such as Roche and Pierre Fabre are continuing.

LCMT will integrate a high-speed nucleic acid analysis platform that brings together local research leaders such as the University, INSERM and Lyon Civil Hospitals. A second facet of the platform's development involves setting up a small-animal pharmacogenomics study that will enable data on the anticancer activity of new molecules from xenografts to be correlated with the expression profiles of various tumors.

2. The South Lyon epigenomics and targeted therapy platform

Installation of the South Lyon platform continued, with the setup of new equipment at the South Lyon Hospital Center facility (CHLS – HCL) and at the Gerland campus (IFR 128). The main focus of the platform is targeted therapy. This involves developing tools to treat cancer based on a better knowledge of tumors and of how anticancer agents act on the disease.

In the fundamental research sphere, current projects include epigenetics in chronic lymphocyte leukemia, biotherapy in acute leukemia, the development of new vaccine strategies that take into account the role of lipids in immune response to hepatitis C, as well as a partnership with bioMérieux on screening markers in prostate cancer. Links with clinical research are being built, with the growth of pharmacological targeting and modeling platform of the effect of anticancer treatment, the collaboration program with the Etoile Hadrontherapy Center and studies on viral-induced cancers in association with Lyonbiopôle.

Economic development potential is also enhanced thanks to industrial partnerships with firms such as EFS Electronics (development of a second device for chemotherapy-hyperthermia), Génopoïetic (a clinical trial on a cancer vaccine), bioMérieux (validation of an early diagnostic marker in breast cancer), Innate Pharma (immunotherapy), Roche/Genentech (biological factors that can predict the activity of Rituximab) and ImmunID (analysis of immune cell repertoires in leukemia and lymphoma). In connection, Saint-Etienne University Hospital has set up a hemopathy and solid tumor genomics and proteomics platform. It is used for diagnosis and follow-up of hematology patients in national and international study protocols, as well as in applied and clinical research by the immunology team in order to identify new molecular tumor markers.

3. Saint-Etienne public health platform

The regional Public Health platform run by the Loire Oncology Institute (ICL) is designed to organize public health research in the oncology field and to develop research programs in various areas of primary prevention (HPV and obesity-related risks), secondary prevention (screening of breast and colon cancers, and of cancers in the elderly; shared decision making in breast cancer) and tertiary prevention (patient information on pain, fatigue, compliance with oral chemotherapy prescriptions, motivation in quitting smoking, and prevention of breast cancer relapse through nutritional intervention).

A legal study was carried out on creation of the Hygée Center, for which Saint-Etienne Métropole will serve as contracting authority. An impact study, carried out beforehand in cooperation with key Rhône-Alpes Auvergne stakeholders in prevention and public health, will help fine-tune the project.

4. European Cancer Observatory / IARC

The European Cancer Observatory project led by IARC featured the construction of a bilingual (French/English) internet site. This site provides a homogeneous presentation of data and epidemiological trends for 20 tumor types and 27 European countries.
The site is scheduled to go online for public access in April 2009.

5. The European Ultra-High-Field NMR Center in Lyon-Villeurbanne

The European Ultra-High-Field NMR Center (CRMN) is operational since April 2008. It provides the environment for methodological and technological developments in NMR for cutting-edge liquid and solid phase spectroscopy applications in the fields of biology, medicine and materials. Key target applications include early diagnosis of cancer and chemical/biological analysis.

Three scientific projects involving CLARA researchers are currently underway in the field of breast cancer, neuroendocrine tumors and oncocytoma.

6. The Grenoble proteomics and imaging platform

The Grenoble platform aims to transfer advances in proteomics, nanotechnology and functional imaging to cancer patients.
The technological research emphasizes three main areas:
- Development of innovative protein analysis methods for clinical use.
- Development and validation of micro/nano-tools for the analysis of tumor mini-samples.
- Development of innovative functional imaging, optical, SPECT and NMR techniques in collaboration with industrial partners (in particular for the anti-angiogenics study).

In clinical research, the developments target:
- Identification of the proteins involved in cancer, followed by identification of biomarkers, thanks to the Biological Resource Centers associated with lung cancer, lymphoma and brain tumors.
- Description of the proteins involved in antitumor immune response and in its variations under immunotherapy.
- Application of functional imaging, MRI, SPECT or optics for in vivo characterization of therapeutic targets, analysis of biodistribution and drug efficacy.

7. The Auvergne Platform

The *"Nutrition and Cancer"* focus area, which includes both fundamental and clinical research, is coordinated by the Auvergne Platform. It relies on an INCa-accredited regional core network and on the Clermont-Ferrand Human Nutrition Research Center. This platform aims to study the impact of food components on the various steps in cancer, from carcinogenesis to nutrition for cancer patients, to the adjuvant action of food components in anticancer therapy.

The Auvergne research teams are also studying on functional imaging and therapeutics vectored by radiopharmaceuticals, functional genomics, tumor escape and clinical research.

VII - Action plan for 2009

CLARA's roadmap involves pursuing the national ProCan program in order to strengthen the cluster's focus areas, with top priority given to translational research. As well, the new Three-Year Plan for 2009-2011, finalized with local authorities in the Rhône-Alpes Auvergne region, aims to boost Cancéropôle's capacity to identify and support academic-industrial partnerships.

The success of these two related approaches depends largely on the quality of scientific events and activities in the CLARA network and on its capacity to build several categories of research and development projects:
- Research Projects, which bring together several CLARA academic/clinical partners and are submitted to national competitive calls for projects.
- Core Programs, which bring together several CLARA partners. They do not aim to fund the work of individual teams, but rather to support a resource-pooling or coordination process for CLARA.
- Proof of Concept Projects, which involve at least one academic/clinical partner and, if possible, one of CLARA's industrial partners. These projects aim to establish the pre-clinical or clinical Proof of Concept of a healthcare product in the field of cancer, with a view to industrial transfer and clinical use.

CLARA has the following objectives:
- To enhance its access to other Networks of Excellence in the region and build relationships with them.
- To strengthen its collaborative projects at the international level, namely with the International Agency for Research on Cancer and French-speaking Switzerland.
- To build relations with Patient Associations.

These aims will be adapted according to the Cancer Plan II.

VIII - Financial support

THE 2009-2011 FRAMEWORK AGREEMENT BETWEEN CLARA AND LOCAL AUTHORITIES

As early as 2001, even before the French National Cancer Plan was launched in 2003 and the birth of the Cancéropôle concept, several local authorities and personalities from the scientific, medical, and industrial spheres met in order to design an ambitious cancer research program uniting the region's academic, clinical and business leaders. One of the main aims was to attract industrial partners and create, via innovative public-private partnerships, the conditions for greater economic development and creation of high-level jobs.

Since 2003, the Cancéropôle CLARA concept has become a reality, thanks to support from the French National Cancer Plan led by the National Cancer Institute (INCa), as well as from local authorities, in particular the Rhône-Alpes Regional Council, the Rhône County Council and Greater Lyon. Local authorities have granted CLARA nearly €50 million, primarily for the setup of seven cutting-edge platforms (€38 million).
In 2008, CLARA was on a twofold transition process, towards a partnership with the French State and a new partnership with local authorities. The State, through INCa, supports French cancer research clusters via the «ProCan 2008 – 2010» scientific activities program as well as through its national calls for research projects. Local authorities, after a period of large-scale investments, prefer to focus on the activities of CLARA's Network Management in the areas of economic development and regional network activities. The 11 local authorities will thus allocate an annual budget of €2.5 million for the 2009 – 2011 period, with the majority of funding earmarked for the "Proof of Concept" program.

With this in mind, a Framework Agreement between CLARA and local authorities has been drafted for 2009-2011. It was presented to CLARA's Executive Committee on October 27, 2008. The Agreement is subject to ratification by the following local authorities in early 2009: the Rhône-Alpes Regional Council, the Rhône County Council, the Lyon Urban Community, the Loire County Council, Saint-Etienne Métropole, the Isère County Council, Grenoble Alpes Métropole, the City of Grenoble, the Auvergne Regional Council, the Puy-de-Dôme Regional Council and the Clermont Urban Community.

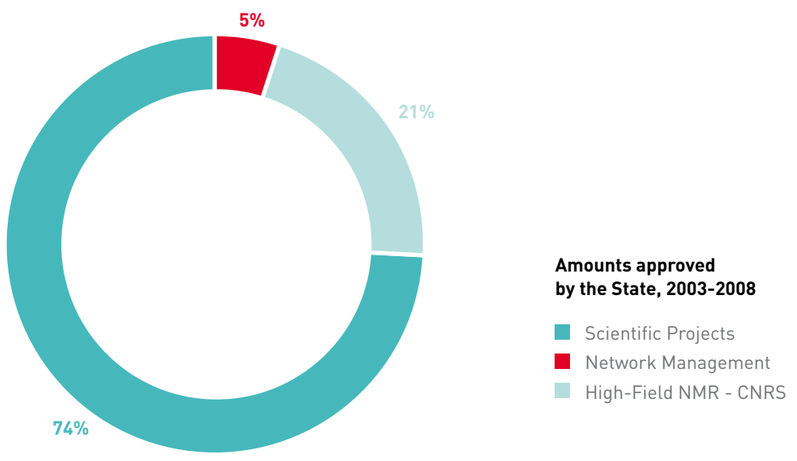
Summary of the multi-year scheduling of the CLARA program, 2003-2008

Status of the main sources of funding on a national level

Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE

In thousands of €	2008				TOTAL	
Recipient (funding)	Investment		Operation		Overall total approved 2003-2008	Overall total paid 2003-2008
	Approved	Paid	Approved	Paid		
High Field NMR - CNRS (MENRT)	-	-	-	-	9 000	9 000
INCa* Calls for Projects			5 302	1 950	28 885	23 452
Biological Resource Center (CRB)	-	-	-	-	1 027	1 027
Network Management	-	-	38	34	2 138	1 346
PROCAN Scientific Axes (INCa)	-	-	-	-	2 550	765
Total	**-**	**-**	**5 340**	**1 984**	**43 600**	**35 590**

*Estimated amounts for Cancer Plan and INCa, STIC and PHRC included



Updated December 31, 2008
As per standard practice and in order to simplify the presentation, payments are indicated in the year they were approved.

Summary of the multi-year scheduling of the CLARA program, 2003-2008

Status of the main sources of funding in the Rhône-Alpes area

Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE

In thousands of €	2008				TOTAL	
Recipient (funding)	Investment		Operation		Overall total approved 2003-2008	Overall total paid 2003-2008
	Approved	Paid	Approved	Paid		
Biological Resource Center (CRB)	-	-	-	-	108	108
Proof of Concept (DRRT RA)			-	-	37	37
Network Management	-	-	-	-	216	216
Total	**-**	**-**	**-**	**-**	**361**	**361**

RhôneAlpes Région

In thousands of €	2008				TOTAL	
Recipient (funding)	Investment		Operation		Overall total approved 2003-2008	Overall total paid 2003-2008
	Approved	Paid	Approved	Paid		
CHU Grenoble	-	-	-	-	1 708	1 369
UJF Grenoble			-	-	2 323	1 649
INSERM Grenoble	-	-	-	-	453	453
Grenoble Subtotal	-	-	-	-	4 484	3 471
CHU Saint-Étienne	-	-	-	-	410	225
Saint-Étienne Hygée Center	1 000	-	-	-	1 000	-
High Field NMR - CNRS	-	-	-	-	8 500	7 450
Proof of Concept	-	-	-	-	510	385
Network Management	-	-	520	260	3 032	2 352
Total	**1 000**	**-**	**520**	**260**	**17 936**	**13 883**

RHÔNE
LE DÉPARTEMENT

In thousands of €	2008				TOTAL	
Recipient (funding)	Investment		Operation		Overall total approved 2003-2008	Overall total paid 2003-2008
	Approved	Paid	Approved	Paid		
CLB - East Lyon	-	-	-	-	7 500	6 500
IARC			-	-	600	400
Proof of Concept	-	-	1 300	660	1 300	660
Network Management	-	-	500	500	2 151	2 151
Total	**-**	**-**	**1 800**	**1 160**	**11 551**	**9 711**

GRANDLYON
communauté urbaine

In thousands of €	2008				TOTAL	
Recipient (funding)	Investment		Operation		Overall total approved 2003-2008	Overall total paid 2003-2008
	Approved	Paid	Approved	Paid		
HCL	-	-	-	-	8 500	6 000
IARC			-	-	500	500
High Field NMR - CNRS	-	-	-	-	2 350	2 350
Proof of Concept	-	-	600	480	2 640	2 520
Network Management	-	-	146	117	1 610	1 537
Total	**-**	**-**	**746**	**597**	**15 600**	**12 907**

SAINT-ETIENNE
métropole

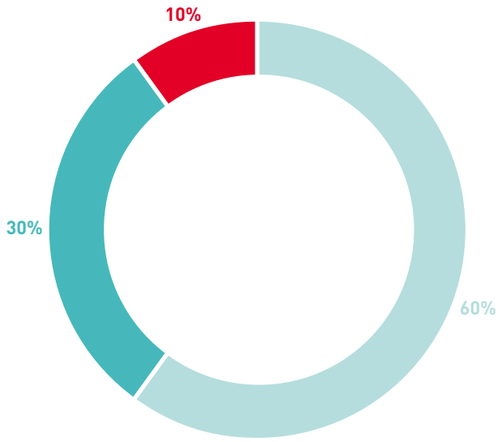
In thousands of €	2008				TOTAL	
Recipient (funding)	Investment		Operation		Overall total approved 2003-2008	Overall total paid 2003-2008
	Approved	Paid	Approved	Paid		
Saint-Étienne	-	-	-	-	1 697	-
Network Management	-	-	125	-	125	-
Total	**-**	**-**	**125**	**-**	**1 822**	**-**

Conseil général
LOIRE
EN RHÔNE-ALPES

In thousands of €	2008				TOTAL	
Recipient (funding)	Investment		Operation		Overall total approved 2003-2008	Overall total paid 2003-2008
	Approved	Paid	Approved	Paid		
Saint-Étienne Hygée Center	1 000	-	-	-	1 000	-
Total	**1 000**	**-**	**-**	**-**	**1 000**	**-**

Total Rhône-Alpes Region	**2 000**	**-**	**3 191**	**2 017**	**48 270**	**36 862**

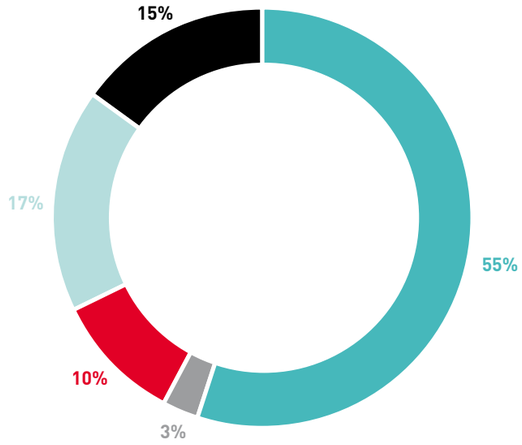
Updated December 31, 2008
As per standard practice and in order to simplify the presentation, payments are indicated in the year they were approved.



Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE

Amounts approved by the State in the Rhône-Alpes area, 2003-2008

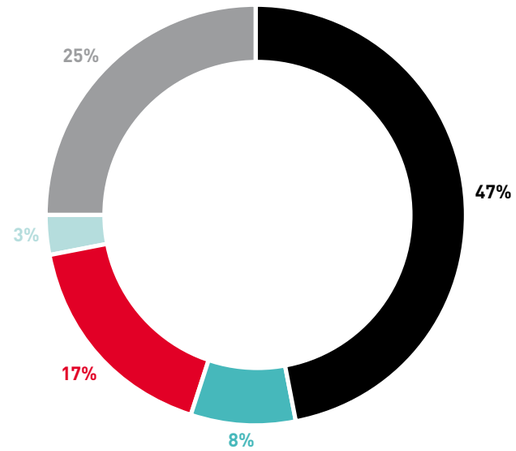
- Biological Resource Center
- Network Management
- Proof of Concept



GRANDLYON communauté urbaine

Amounts approved by the Greater Lyon, 2003-2008

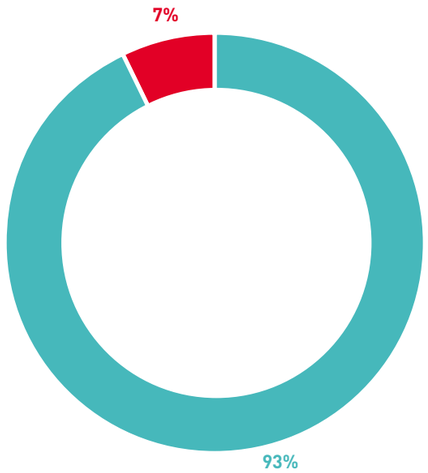
- East Lyon and South Lyon - Lyon Civil Hospitals
- Network Management
- Proof of Concept
- International Agency for Research on Cancer
- High-Field NMR



RhôneAlpes Région

Amounts approved by the Rhône-Alpes Region, 2003-2008

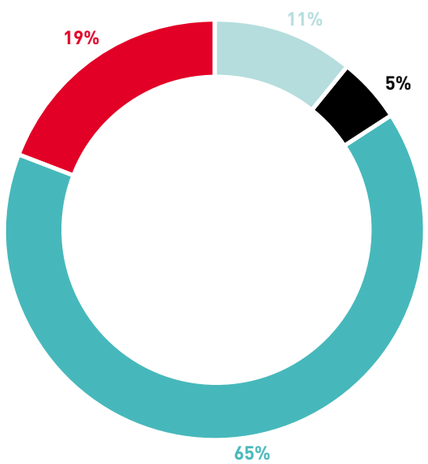
- Saint-Étienne Platform
- Network Management
- Proof of Concept
- Grenoble Platform
- High-Field NMR



SAINT-ETIENNE métropole

Amounts approved by Saint-Étienne Métropole, 2003-2008

- Saint-Étienne Platform
- Network Management



RHÔNE
LE DÉPARTEMENT

Amounts approved by the Rhône County, 2003-2008

- East Lyon - Léon Bérard Cancer Center
- Network Management
- Proof of Concept
- International Agency for Research on Cancer

Conseil général LOIRE EN RHÔNE-ALPES

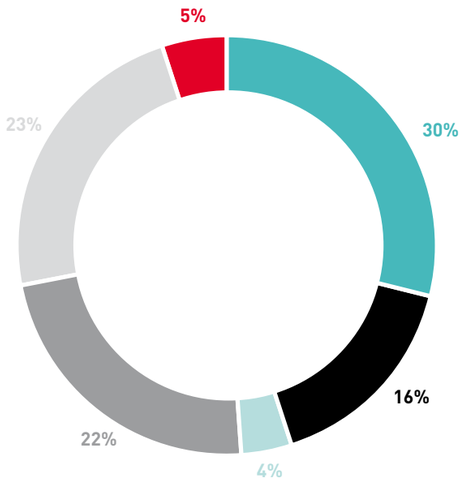
Amounts approved by the Loire County, 2003-2008

- Saint-Étienne Platform

Status of the main sources of funding in the Auvergne area

In thousands of €	2008				TOTAL	
Recipient (funding)	Investment		Operation		Overall total approved 2003-2008	Overall total paid 2003-2008
	Approved	Paid	Approved	Paid		
Massif Central ERDF*	-	-	-	-	945	945
Region ERDF			-	-	720	720
Massif Central FNADT	-	-	-	-	505	505
Auvergne Region	-	-	125	125	1 480	1 270
Clermont Community	-	-	60	60	335	290
Puy-de-Dôme County	-	-	25		125	100
Allier County	-	-	-		50	50
Cantal County	-	-	-		40	40
Haute-Loire County	-	-	-		40	40
Total	**-**	**-**	**210**	**185**	**4 240**	**3 960**

*Massif Central ERDF covers Auvergne and Loire County.



Amounts approved in the Auvergne area, 2003-2008

- Nutrition Program
- Imaging Program
- Lifegrid Program
- Cancéropôle's Auvergne cluster
- Other programs
- Network Management

Updated December 31, 2008

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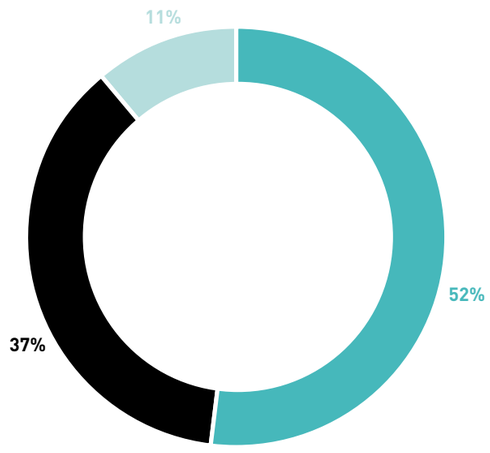
Overall orientation of approved funding during the period 2003-2008

CLARA CANCÉROPÔLE LYON AUVERGNE RHÔNE-ALPES

Approved amounts in thousands of €

Program		TOTAL	
		2008	Overall total 2003-2008
Platforms	Lyon Civils Hospitals	0	8 500
	Léon Bérard Cancer Center	0	7 500
	Grenoble Platform	0	4 484
	Saint-Étienne Platform	2 000	4 107
	IARC Platform	0	1 100
	Auvergne Platform	10	4 040
	High-Field NMR - CNRS	0	19 850
	Total platforms	**2 010**	**49 581**
Funding of Projects	INCa 2003 - 2008 Calls for Projects	5 302	28 885
	ProCan Scientific Axes (INCa)	0	2 550
	Proof of Concept Projects	1 900	4 487
	Biological Resources Center	0	1 135
	Total	**7 202**	**37 057**
Coordination	Network Management	1 529	9 364
	Total	**1 529**	**9 364**



Overall Orientation of approved funding during the period 2003-2008

- Investment
- Funding of projects
- Coordination

Updated December 31, 2008

As per standard practice and in order to simplify the presentation, payments are indicated in the year they were approved.

Under the aegis of the Bullukian Foundation

CLARA

CANCÉROPÔLE LYON AUVERGNE RHÔNE-ALPES

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