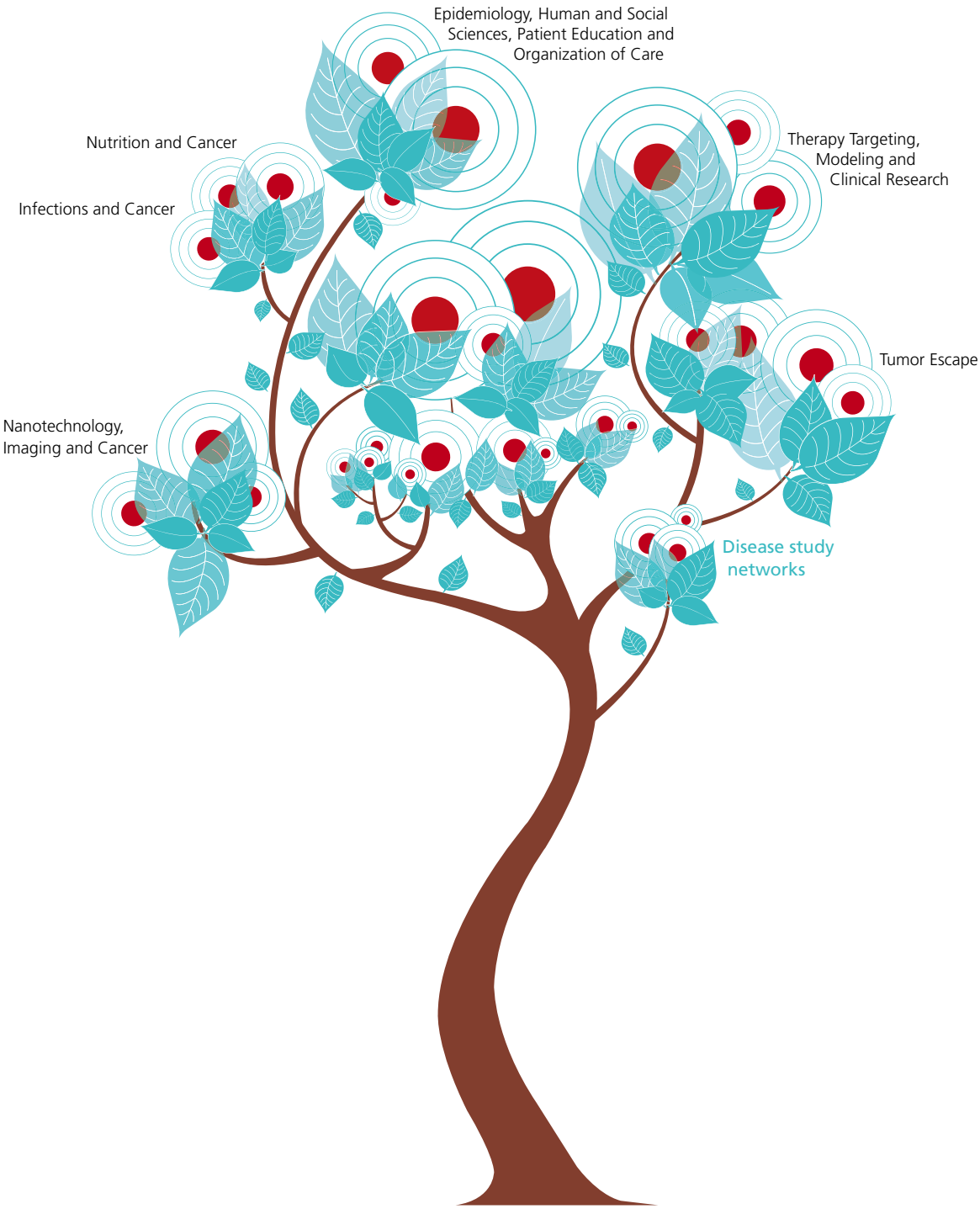


PROGRESS REPORT 2007

CLARA
CANCÉROPÔLE LYON AUVERGNE RHÔNE-ALPES

SPEEDING UP PROGRESS

Under the aegis of the Bullukian Foundation

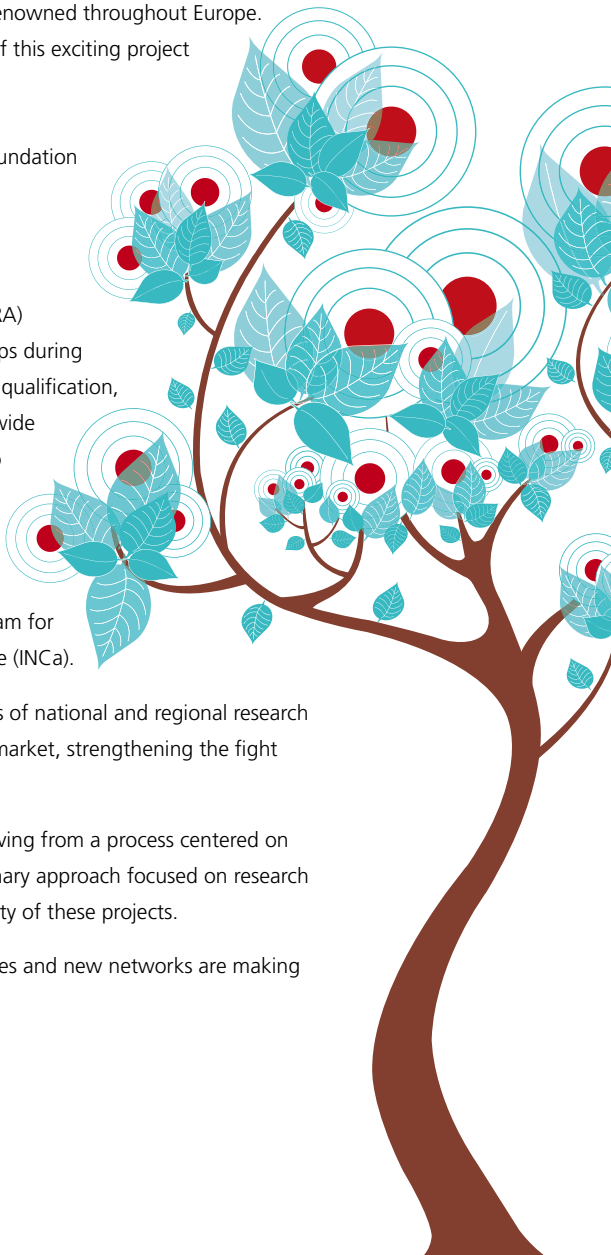
CONTENTS

EDITORIAL

For three years, the Léa and Napoléon Bullukian foundation has been working alongside the scientific community of the Rhône-Alpes/Auvergne region in its cancer research activities through CLARA. At the end of this three-year period, we can see positive results from these efforts, the success of which is based on high quality research groups and the Network Management which assists them in their efforts by listening attentively to their needs.

In a particularly "dense" research environment, CLARA's management team is striving to build links between the various stakeholders while taking care not to weigh down an already complex organization. Bringing Core Projects to light, coordinating cancer research activities and clarifying their aims are the priorities that CLARA's management has chosen to build synergy between the people and organizations involved in research. This process is supported by the French National Cancer Institute (INCa) which, by renewing its support for the coming three years, has enabled CLARA to become a center of excellence in cancer research renowned throughout Europe. Now more than ever, the Léa and Napoléon Bullukian Foundation is part of this exciting project with a commitment to facilitate the work of all concerned.

Jean-Pierre Claveranne, President of the Léa and Napoléon Bullukian Foundation



Between 2003 and 2007, Cancéropôle Lyon Auvergne Rhône-Alpes (CLARA) steadily built up its activities. Since the start of theme-based working groups during the "emergence" phase between 2003 and 2004, it has moved on to the qualification, constitution and funding (€45 million) of seven platforms dedicated to a wide range of specific topic areas (from functional genomics to epidemiology to human and social sciences), and to supporting the creation of promising interdisciplinary cancer research projects.

The year 2007 was a turning point for our cancer research cluster.
One highlight was the development and launch of the Cancéropôle Program for 2007-2010 (ProCan), at the request of the French National Cancer Institute (INCa).

This involves developing a roadmap to ensure coherence with the priorities of national and regional research activities with a constant focus on developing research and bringing it to market, strengthening the fight against cancer and, above all, helping patients.

In the past year, CLARA has undergone major organizational changes, moving from a process centered on the enhancement and organization of its platforms to a more interdisciplinary approach focused on research projects. The number one aim now is to boost both the quality and quantity of these projects.

Like a tree, CLARA is continuing to grow, thriving in fertile soil. New focuses and new networks are making the organization stronger, and new projects are already budding.

Peter Pauwels, Executive Director, CLARA

Organization

A YEAR OF INTERNAL TRANSITIONS

A new Executive Director

Mireille Guigaz, who was Executive Director of CLARA since January 2005, was named French Ambassador and Permanent Representative to the United Nations Food and Agriculture Organization (FAO) in Rome.
She left the network management team at the end of August.
We would like to thank her for her personal investment in CLARA for more than two years, in particular for her contributions to building the Cancéropôle organization.

Peter Pauwels, CLARA's Deputy Executive Director since September 2006, was named Interim Executive Director as of September 1st, before being confirmed in his new position by the Board of Directors of the Bullukian Foundation on October 23rd.

Exploring potential orientations for CLARA

The transition period in CLARA's management team led to an exploration of potential orientations, headed by the President of the Finance Committee, in cooperation with the President of the Bullukian Foundation and network members.

The first brainstorming session, which brought a dozen of the region's leaders in cancer research to Lyon in July, led to a larger meeting in Saint-Etienne on September 21st and 22nd.

During the first day, discussions with researchers focused mainly on CLARA's new scientific strategy, as part of the ProCan program (see page 7), changes in governance, the prospects of a new three-year contract with local authorities, development of the Proof of Concept program, support for the setup and running of the platforms, and the agenda for the 3rd Scientific Forum.

The second morning was devoted to presenting the new governance, new core research focuses and key issues for the period 2008 - 2011 to the management of CLARA's partner organizations.

Saint-Etienne, September 22nd, 2007

Setup of a collegial scientific management system

One of the major changes stemming from this brainstorming period is the setup of a collegial scientific management system, embodied in the new "Scientific Steering Committee".

CLARA's Scientific Steering Committee (CPS) brings together the heads of the focus areas and the disease study networks, as well as representatives of industry, academic institutes and competitive clusters. It replaces the former Academic Club.

Within this body, an Executive Board manages CLARA's scientific activities. It carries out the following missions:

- Defining CLARA's scientific policy;
- Implementing the ProCan 2007-2010 program;
- Liaising with the Scientific Advisory Board;
- Arbitrating between funding and scientific aims;
- Organizing the Scientific Forums.

The full Committee is to meet two or three times every year, whereas the Executive Board is to meet seven or eight times per year.

Members of the Executive Board of the CPS

- **François Berger – Grenoble, University Hospital**
- **Yves-Jean Bignon – Clermont-Ferrand, Jean Perrin Cancer Centre**
- **Jean-Yves Blay – Lyon, Léon Bérard Cancer Centre**
- **Christian Brambilla – Grenoble, Albert Bonniot Institute**
- **Dominic Cellier – Lyon, Merck Santé**
- **Jean Chabbal – Grenoble, CEA**
- **François Chauvin – Saint-Etienne, Loire Cancer Institute**
- **Patrice Marche – Grenoble, Albert Bonniot Institute**
- **Patrick Mehlen – Lyon, Léon Bérard Cancer Centre**
- **François Pons – Grenoble, Cogenics**
- **Alain Puisieux – Lyon, Léon Bérard Cancer Centre**
- **Gilles Salles – Lyon, South Lyon Hospital**
- **Véronique Trillet-Lenoir – Lyon, South Lyon Hospital**
- **Marie-Paule Vasson – Clermont-Ferrand, Auvergne University**
- **Peter Pauwels – CLARA**
- **Laurent Lévy – CLARA**

Reorganization of network governance

In addition to determining a collective, shared scientific strategy, many CLARA members and partners wished to simplify its governance. A new structure was thus created to meet several aims: to take into consideration the interests of all network stakeholders, to accelerate the process for making key decisions on CLARA operations, and to obtain support from all parties.

The Strategic Orientation Committee - replaces the former Steering Committee and the former Guidance Board

This body determines CLARA's major orientations and approves what is to be submitted to the deliberative assemblies.

It brings together heads of the local authorities and academic institutions which are CLARA partners, as well as representatives from private firms and patient associations.

The Executive Committee - replaces the former Finance Committee

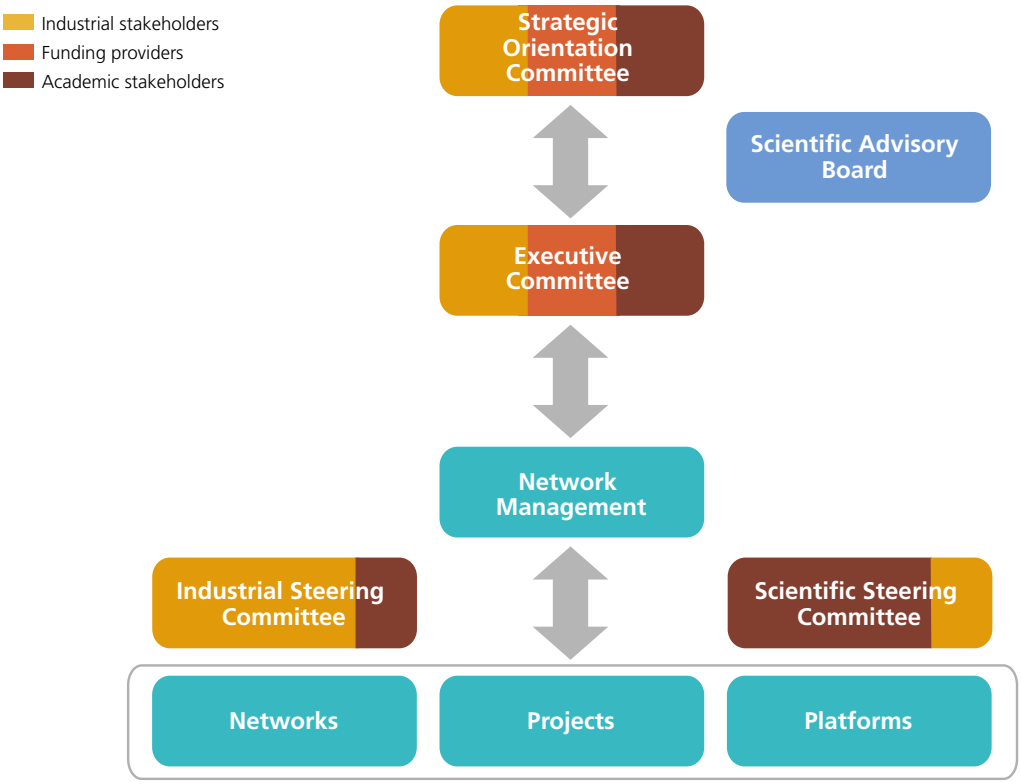
This body implements decisions made by the Strategic Orientation Committee, approves and allocates funding and clarifies the differences in funding payments.

It brings together representatives of local authorities, hospitals and academic institutions.

The Industrial Steering Committee

Alongside the Scientific Steering Committee, an Industrial Steering Committee now represents the interests of CLARA's Business Club.

The potential merging of CLARA's Scientific Advisory Board with that of the "Synergie Lyon Cancer" Scientific Cooperation Foundation is currently being considered.



CLARA's governance

PROCAN 2007 / 2010

In 2007, INCa renewed its support for CLARA, granting it €3.6 million for the coming three years. Here is a look back on the highlights of this past year…

A new call for projects

In 2003, the Ministries of Research and Health launched a call for projects entitled **Emergence of Cancer Research Clusters,** with a budget of € 16.5 million for the period 2003 - 2007, which led to the creation of seven such clusters in France. The aim of this first phase was to set up the technological and scientific infrastructures.

In Spring 2007, INCa launched a call for projects to "overhaul" the cancer research clusters, called **Programme Cancéropôles 2007 - 2010 (ProCan),** with a total of €26.5 million in funding. Designed to continue and bolster the momentum started in 2003, this call for projects revolved around updating the scientific strategy of the cancer research clusters, strengthening their technological resources, and establishing new organizational activities and scientific events.

The commission set up by INCa to assess CLARA includes renowned scientists from outside of the Institute (A. Bernard, L Buscail, M. Marty, N. Milpied, J. Pouysségur) as well as representatives of INCa (F. Calvo, F. Amalric and S. Le Ricousse).

The ProCan file has two main parts: the review of scientific activity between 2003 and 2007 and the scientific project for the period 2007 - 2010. The main criteria for assessment are the network's scientific production, the quality and feasibility of the 2007 - 2010 strategic project, the market potential of the research and resulting applications.

Conclusions of the INCa Assessment Committee Report - June 11th -12th, 2007

All of the Committee members mentioned the excellence of CLARA's governance as well as the integration of academic research and care organizations alongside industrial firms and local authorities. Here was a Cancer Research Cluster that showed its cutting-edge research teams (for example the Synergie Lyon Cancer RTRS research network), in contrast with the setup project in 2003.

Strengths

- Excellent governance backed by a top-flight international Scientific Advisory Board;
- Creation of the RTRS research network, a driving force behind high quality translational research (merging the Scientific Advisory Boards of the RTRS network and CLARA would give more visibility);
- International-caliber fundamental research teams;
- Possibility of creating a Cancer Biology Center; (governance with CNRS, Inserm, Centre Léon Bérard and universities) to give CLARA greater visibility internationally (at the heart of the RTRS research network);
- Excellent potential for innovation (particularly in the fields of nanotechnology, imaging, physics/chemistry and proteomics);
- An excellent "Proof of Concept" program, to be maintained;
- An excellent effort to bring the academic and industrial spheres together.

Weaknesses

- With the exception of the RTRS projects, there is a lack of visibility for innovative research projects;
- Start from high-quality teams to drive innovation and not from platforms;
- Given the number of teams and researchers within the CLARA region, we would hope to see more success in the INCa Calls for Projects;
- CLARA is involved at the European scale, but not at the expected level with regard to its research potential.

The new subsidies granted to CLARA, for a total of €3.6 million over three years, are intended to support the organization of research programs. They will enable CLARA to more firmly establish itself through areas of excellence, to strengthen scientific coordination and to encourage the emergence of core projects.

This budget will be divided primarily among six top-priority focus areas (between €300,000 and €600,000 per focus area); funding has also been earmarked for the development of disease study networks (around €40,000 per network).

A new scientific strategy for 2007- 2010

CLARA's new matrix strategy, organized around research teams, is based on a strong foundation consisting of the Lyonbiopôle competitive cluster, the Grenoble cluster dedicated to nanotechnology in life science applications, the Synergie Lyon Cancer RTRS research group, the International Agency for Research on Cancer, and the ÉTOILE hadrontherapy project.
This foundation will support and strengthen the six central cancer research focus areas that are the cornerstone of CLARA:

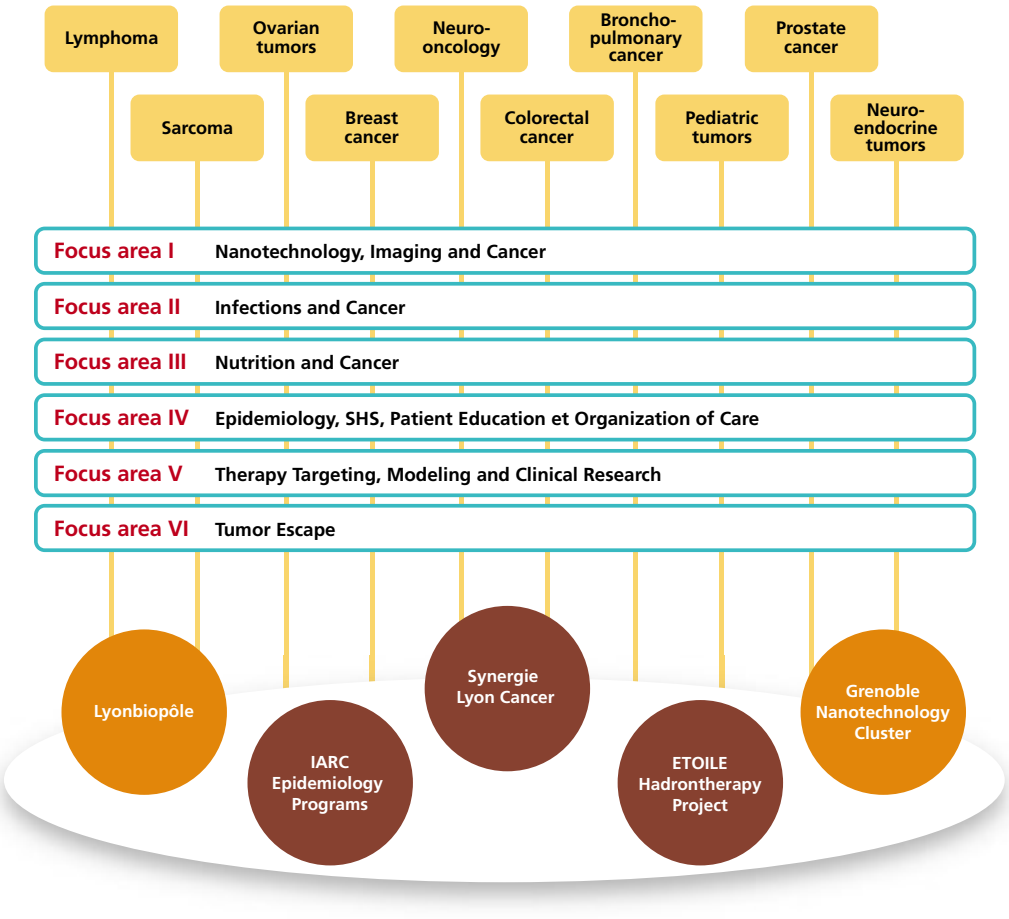
- **Focus I: Nanotechnology, Imaging and Cancer**
- **Focus II: Infections and Cancer**
- **Focus III: Nutrition and Cancer**
- **Focus IV: Epidemiology, Human and Social Sciences, Patient Education and Organization of Care**
- **Focus V: Therapy Targeting, Modeling and Clinical Research**
- **Focus VI: Tumor Escape**

At the same time as the six primary focuses were implemented, in order to strengthen the network's research potential, CLARA launched a program to organize and run research activities grouped by disease. By bringing together all of the high-level players working on one specific tumor or for whom this tumor is a pertinent model for study, these networks aim to encourage interaction between the various players involved and to bring new projects to light.

The first aim is to give the players involved in fundamental and clinical research the opportunity to present their research topics and proposed strategies in their field. In concrete terms, this involves giving a broad, comprehensive vision of the tools available in order to foster cooperation between various organizations within the two regions and to make optimal use of the platforms. The long-term aim is to increase the critical mass of the research teams working on a given disease, enabling them to better coordinate their work on larger-scale projects and to shorten the time required to test new methods of treatment and diagnosis for patients.

At the end of 2007, four networks had begun their organization process:
- **Multidisciplinary neuro-oncology,** led by Jérôme Honnorat;
- **Neuroendocrine Tumors,** led by Jean-Yves Scoazec;
- **Pediatric Oncology,** led by Raphaël Rousseau;
- **Ovarian Tumors,** led by Isabelle Ray-Coquard.

As part of the ProCan program, this initiative will increase in scope and focus on six other diseases, i.e. **Lymphoma** (Gilles Salles), **Sarcoma** (Jean-Yves Blay), **Breast Cancer** (Thomas Bachelot), **Colorectal Cancer** (Jean-Christophe Saurin), **Bronchopulmonary Cancer** (Elisabeth Brambilla), **Prostate Cancer** (Laurent Guy).



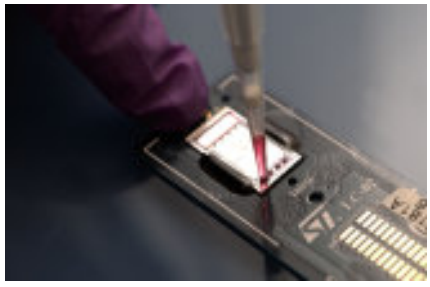
Six priority focus areas

Focus area I: Nanotechnology, Imaging and Cancer

Coordinators: François Berger, Marc Janier

This focus area aims to:

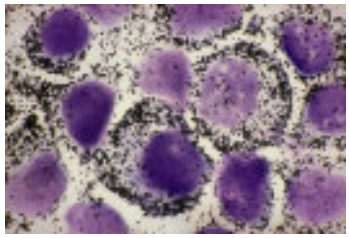
- Improve access to micro and nanotechnology: miniaturization, surface modification, microfluidics and nanoparticles;
- Develop imaging and contrast accentuation methods;
- Set up innovative biological analysis tools, ranging from *in vitro* diagnostics to molecular imaging;
- Contribute to the development of new molecular therapeutic strategies;
- Develop research programs in the field of nanotoxicology;
- Study the social, economic and ethical impact of these new approaches.



The use of nanotechnology aims to provide tools enabling us to detect, identify and treat tumors earlier and less invasively, at the molecular stage. This involves both better understanding oncogenesis mechanisms and developing new, increasingly targeted therapies.

Focus area II: Infections and Cancer

Coordinators: Fabien Zoulim, Patrice Marche



Cancers caused by or linked with infections account for 15 to 20% of cancers worldwide, thus making them a major public health concern.
This involves in particular liver cancer, with the hepatitis B (HBV) and C (HCV) viruses; cervical cancer, with human papillomavirus (HPV); lymphoma, with Epstein-Barr virus (EBV); leukemia, with human T-cell lymphotrophic virus (HTLV-1); Kaposi's Sarcoma, with human herpesvirus 8 (HHV8); and gastric cancer, caused by the *Helicobacter pylori* bacterial strain.

Two themes have been specified for this focus area:

- Immune response in cancers and infections;
- Molecular mechanisms involved in cancer transformation.

There will also be cross-disciplinary programs aiming to develop diagnostic and therapeutic applications for cancer prevention and treatment.

Focus area III: Nutrition and Cancer

Coordinators: Marie-Paule Vasson, Martine Laville

The Nutrition and Cancer focus aims to develop interdisciplinary research bringing together teams of fundamental and clinical researchers, thus facilitating the transfer of new research discoveries to clinical care of patients. This project, which combines nutrition, oncology, integrative physiology and genetics, aims to provide a sounder scientific basis for the nutritional recommendations promoted as part of national and international cancer prevention campaigns.

The scientific project has two main facets:

- Identifying nutrients likely to curb the occurrence of hormone-dependent cancers (breast and prostate cancers) and describing their mechanisms for action, focusing on the molecular level;
- Understanding the links between obesity and development of breast cancer, and devising new nutrition-based prevention strategies.

Focus area IV: Epidemiology, Human and Social Sciences, Patient Education and Organization of Care

Coordinators: Franck Chauvin, Nadine Bossard

This focus aims to:

- Encourage interaction between various fields (epidemiological studies, human and social sciences, care practices and patient education) in order to enable patients to benefit from all of the knowledge produced by these disciplines, which are typically separated from one another;
- Increase research in specialty areas that generally focus little on oncology;
- Pinpoint research topics that match the various disciplines, taking into consideration evolutions in the disease (chronicization, patient aging, rationalization of resources, development of prevention and more).

The scientific project features four themes:

- Cancer Epidemiology;
- Human and Social Sciences and Oncology;
- Patient Information and Education;
- Hospital Engineering and Oncology.

Focus area V: **Therapy Targeting, Modeling and Clinical Research**

Coordinators: Véronique Trillet-Lenoir, Alain Leizorovicz, Yacine Merrouche

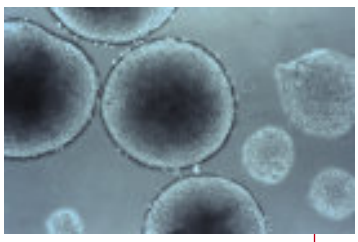
This focus area centers on the reciprocal transfer of innovations between fundamental research and clinical practice, in the framework of clinical trials and the development of predictive models.

Three topics will be addressed:

- Biological study of target molecules during treatment and therapeutic innovation;
- Digital modeling of therapies and application of effect-model theory;
- Clinical research.

This focus will mainly explore the implementation of a single regional service in oncology for phase I-IIa trials targeted to diseases and early development of medicines. This will help to make the region more visible and more efficient in this field, particularly in the eyes of industrial firms, and to generate synergy between clinical, pharmacogenomic and clinical pharmacology teams. In order to meet this aim, the first step involves taking a census of the activities and skills, in addition to the review of phase I-II-III research teams which is already being carried out by PARCC-ARA*, with production of promotional materials targeting industrial firms.

* PARCC-ARA = Auvergne Rhône-Alpes Platform to Assist Oncology Clinical Research.



Focus area VI: **Tumor Escape**

Coordinator: Patrick Mehlen

This focus aims to expand the research topic being explored at the Lyon-based Synergie Lyon Cancer Scientific Cooperation Foundation (FCS) to other cities in the CLARA region, i.e. Grenoble, Saint-Etienne and Clermont-Ferrand.

It aims to explore the means to restore physiological cell protection and immune response mechanisms, in order to prevent metastasis and resistance to treatments. It is centered on two main topics:

- Verification of cell survival, apoptosis and senescence;
- Immunosurveillance and tumor escape.

These will be explored using upstream models as well as physiopathological models that are as similar to human tumors as possible.

The objective is to intensify development of these preclinical models in order to enable screening of target tumors and therapeutic molecules.

It should be noted that the strong desire for integration between Synergie Lyon Cancer and CLARA is also illustrated by the membership of the FCS leaders, Alain Puisieux and Gilles Salles, on CLARA's Scientific Steering Committee, alongside the leaders of the ProCan focus areas. This commitment is further illustrated by the fact that the Cancéropôle facility is currently providing an office to host the Foundation's new Executive Director, Michael Courtney. In addition, CLARA holds a seat as a partner on the Board of Directors of the FCS.

Census of the teams

At the end of 2007, as part of the overhaul of its scientific strategy, CLARA carried out a census of the fundamental and clinical research teams in the region which are involved in the field of Cancer and have a direct link with its six priority focuses and its disease study networks.

At the end of 2007, there were 133 academic teams and 82 clinical units among CLARA members.

A list of CLARA's academic and clinical research teams is available online at the www.canceropole-clara.com website

Geographical breakdown

City	Number of academic teams	Number of clinical units
Lyon	72	45
Grenoble	38	14
Saint-Etienne	8	13
Clermont-Ferrand	15	10

Breakdown by ProCan focus area

Focus area	Number of academic teams	Number of clinical units
Nanotechnology, Imaging and Cancer	38	27
Infections and Cancer	28	9
Nutrition and Cancer	11	9
Epidemiology, Human and Social Sciences, Patient Education and Organization Care	19	8
Therapy Targeting, Modeling and Clinical Research	16	30
Tumor Escape	44	16

Note: Some teams and clinical units may be involved in several focus areas.

Teams that meet at least one of the following criteria were listed in the above-mentioned census:

- The team was involved in building the ProCan 2007 - 2010 strategy assessed by INCa in June 2007;
- The team submitted a project as part of the INCa calls for projects in 2007;
- The team was identified as part of the "Highlights in Cancer Research in Rhône-Alpes Auvergne" document published by CLARA in 2007 (see page 40);
- A researcher from the team participated in a meeting on a ProCan focus area or disease study network.

NEW ORIENTATIONS AND PRIORITIES

A threefold approach

The new scientific strategy laid out by CLARA is part of a threefold approach:

1. At the national level
Implementing the ProCan program to run scientific programs and organize research, in association with the French National Cancer Institute (INCa).

2. In the Rhône-Alpes / Auvergne region
Consolidating links with the region's centers of excellence and highlighting the potential of the region's research. With a view to bringing the results of cancer research to market, the negotiation of a new three-year contract with local authorities aims to, among other issues, increase the scope of the Proof of Concept program in partnership with Lyonbiopôle, set up a new Cancer Nano Transfer program with the Grenoble nanotechnology cluster, in order to support the development of nanomedicine applications in the field of cancer, and launch a core epidemiology program for the region.

3. Within CLARA
Improving the number and quality of submissions to INCa calls for bids in order to increase the success rate at the national level.

With this in mind, the CLARA roadmap for 2007 - 2010 features four main focuses:
- Scientific coordination of the network and organization of research within the region;
- Incentive and support for research projects, particularly through the building of core programs;
- Support in transforming the results of cancer research into marketable applications;
- Promoting the region's research potential and expertise in oncology.

Consolidating links with the ETOILE project

In February 2007, the French Ministry of Health confirmed the setup of the first national hadrontherapy center in Lyon and promised to support the project with €1.25 million per year for the period 2007 - 2010.

In connection with the upcoming treatment center, the ETOILE (European Light Ion Oncology Treatment Center) project is also presenting a multidisciplinary research program focusing on hadrontherapy. This program links with the CLARA program in several ProCan focus areas:

- As part of focus area V, scientists will work to model the hadrontherapy approach with support from PARCC-ARA*, in order to facilitate therapeutic decision making (conventional radiotherapy, proton therapy, hadrontherapy using carbon ions or mixed therapy with a "boost" of carbon ions).
- As part of focus area VI, joint research will enable the identification of tumors that can be treated by hadrontherapy, namely those that are radio-resistant.
- Focus area IV will investigate patient selection and the management of patient treatment at the ETOILE Center.

The ETOILE Center and Research Program is represented on CLARA's Scientific Steering Committee by its Director, Professor Jacques Balosso.

* PARCC-ARA = Auvergne Rhône-Alpes Platform to Assist Oncology Clinical Research.

Strengthening the role of business within CLARA

From the very beginning, CLARA has been actively committed to a process that aims to encourage marketable clinical and industrial applications for therapeutic innovations to benefit patients. This means closely involving business in CLARA projects and supporting collaborative work between researchers, clinicians and private firms.

To strengthen the role of business, company representatives will be involved at the outset, during the definition of CLARA's strategic orientations, as well as during the setup of large scale projects. This will enable better consideration of business needs and will facilitate links with fundamental, translational and clinical research.

Finally, the strengthening of collaborative projects which bring together public and private groups will be accomplished by continuing and broadening the "Proof of Concept" program (see pages 36 to 38).

STRENGTHENING LINKS WITH PARTNERS

Relations with the Bullukian Foundation

Continuing their productive collaboration, CLARA and the Bullukian Foundation have built stronger links in several areas.

First of all, the Foundation provided CLARA with the services of Elisabeth Ogier-Buratti, an accountant and management controller at the Bullukian Foundation, in order to handle the Network Management's funding agreements with local authorities and INCa, as well as to manage CLARA's cash accounts.

At the same time, regular meetings with the Foundation's President, Professor Jean-Pierre Claveranne, have enabled valuable sharing of experience that will help CLARA implement the ProCan 2007-2010 program.

Relations with funding providers

Local authorities (Rhône-Alpes Region, Rhône County, Greater Lyon, Loire County, Saint-Étienne Métropole, Auvergne Region, Clermont Urban Community and Puy-de-Dôme, Allier, Cantal and Haute-Loire counties) and the French State (including INCa) have actively supported CLARA's setup and growth, granting a total of €80.5 million for the period 2003 - 2007. Local authorities granted €44.4 million, including €36.4 million devoted to CLARA platforms. The French State contributed €29.2 million* to CLARA, including €18.8 million for research projects as part of competitive calls for projects.

Throughout the year, a number of meetings with funding providers from Auvergne, in particular Clermont Urban Community, the Region, the Prefecture and Auvergne University (the contracting authority for funding from Auvergne local authorities for the CLARA network) aimed to review and improve the funding process for the Clermont-Ferrand platform.

*These figures do not include funding granted as part of the PHRC and STIC calls for projects, i.e. €1.8 million in 2007.

During its November 15th session, the CLARA Finance Committee confirmed its intention to continue supporting the network beyond 2007. Noting that local authorities had made major investments in the setup of CLARA platforms since 2003, it proposed that local authorities now focus their support on the Network Management team and its various activities: scientific coordination, support for the emergence of research and transfer projects, administrative and financial management and funding of target programs which complement those of the French State and INCa, such as the Proof of Concept program.

The local authorities which are already partners of the Network Management (Greater Lyon, Rhône County and Rhône-Alpes Region) are being asked to continue providing at least the same level of support. Local authorities from Isère, Loire and Auvergne have been invited to join them in 2008.

The Network Management team began negotiations on this subject with the three local authorities of Isère (City of Grenoble, greater Grenoble and Isère County) at the end of last year.

See appendix on Funding acquired and allocation – pages 45 to 50

PLATFORMS

Most of the platforms continued their setup process during 2007 and entered the operational phase. They will be completed at the end of 2008, with the exception of the Saint-Etienne platform, where construction of the Centre Hygée is scheduled to begin in 2009.

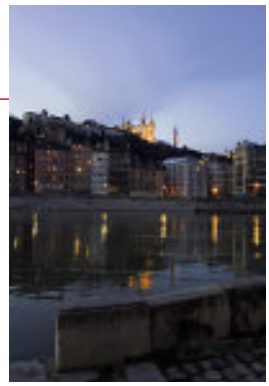
Monitoring

In agreement with CLARA's Finance Committee and Guidance Board, the Network Management has been working on implementing a platform monitoring program since the end of 2006. It was developed and implemented in close collaboration with a working group which includes the representatives of the organizations that manage these platforms as well as their partner local authorities. This program is composed of a set of indicators and a joint charter for the CLARA platforms.

The indicators for the platforms are designed to give CLARA's governing bodies a comprehensive view of the main areas of progress or difficulties stemming from their implementation and operation, and to help highlight their impact. They were tested in early 2007 at three pilot sites - East Lyon / Léon Bérard Cancer Centre, South Lyon and Grenoble - before being extended to the other platforms (with the exception of Clermont-Ferrand) during the year.

The "joint charter" of the CLARA platform was written at the beginning of 2007 and is based largely on the national charter of "RIO" platforms. It was designed to summarize the joint principles for management of the platforms, such as setting up Steering Committees in which CLARA's Network Management participates, developing internal regulations which specify the terms and conditions for access to the shared platforms and carrying out economic impact studies. In order to be "officially" adopted, the various charters must be appended to the funding agreements signed between the local authorities and the organizations which manage the platforms.

The Lyon platforms



Two of the year's highlights for the Lyon platforms brought together CLARA's researchers and funding providers on March 8th:

- The groundbreaking ceremony at the new "Cheney D" research building at Léon Bérard Cancer Centre, whose construction is being funded by an €8 million subsidy from the Rhône County Council.

- The grand opening of the premises and welcoming of researchers at the South Lyon Hospital (Lyon Civil Hospitals - HCL) and the South Lyon Medical School (Claude Bernard Lyon1 University) – with a €5.5 million subsidy from Greater Lyon.

The Cheney D groundbreaking ceremony

The East Lyon / CLB functional and structural genomics platform

The "Structural and functional genomics" section of the East Lyon platform, located at the Léon Bérard Cancer Centre (CLB) and coordinated by Alain Puisieux, aims to:

- Identify prognostic markers and predictive markers for response to treatment;
- Highlight new therapeutic targets and develop innovative therapeutic approaches;
- Identify circulating markers (both early diagnostic markers and therapeutic surveillance markers).

Support for this program from local authorities is aimed at:

- The construction of a 7-storey, 3,452 sq. m. / 37,200 sq. ft. "Cheney D" research building;
- The construction of a Biosafety Level 3 lab at CLB;
- The installation of equipment, including: Facs Vantage Cytometer Cell Sorter, an automatic sequencer, a laser microdissector, a fluorescent microinjection and microscope system and a confocal microscope.

This first equipment is now up and running. Construction is scheduled to finish and the research teams are slated to move into Cheney D during summer 2008.

> Scientific accomplishments

In 2007, the functional and structural genomics teams carried on their work in three core programs. The **MutaCancer** program aims to identify genes that are modified in a recurrent manner in human cancers. Four types of cancer (breast cancer, colon cancer, lung cancer and neuroblastoma) are being studied. The consequences of these alterations are then studied with cellular models generated as part of **InaCancer.** The **CirBioCancer** program aims to identify circulating diagnostic and prognostic markers. These teams published some twenty international scientific articles in 2007.

- The "MutaCancer" program: **the search for recurrent genetic mutations in human cancers.**

To date, the coding region of 101 genes has been sequenced in 24 cell lines (breast cancer, colon cancer and neuroblastoma). This analysis has led to the detection of alterations (not including known polymorphisms) in 30 genes. Among these potential alterations, 44% are missense mutations, 3% non-sense mutations, 7% insertions/deletions, 5% splice site or intronic mutations, as well as 41% silent mutations (these mutations do not alter the structure of the protein, but may have

an impact on splicing). These mutations have been identified in different tumoral cell lines: 11 in breast cancer cell lines, 24 in colon cancer cell lines -including 7 in the same HCT116 cell line (a cell line with microsatellite instability) - and 12 in neuroblastoma cell lines.

All of these modifications are currently being evaluated in order to:
1. Confirm them with sequencing of the concerned amplicon on an independent PCR product;
2. Determine if missense mutations are rare or non-described polymorphisms, or potentially deleterious mutations.
Due to the absence of normal tissue for the tested cell lines, this analysis is performed by using a panel of DNA coming from the general population (blood samples provided by the French Blood Agency). The first studies on primary tumors (at CLB's Biological Resource Center) have been started on genes in which deleterious mutations were identified in cell lines.

● The InaCancer program
Breast cancer is the first type of tumor being studied. The models come from mammary epithelial cells immortalized first with h-Tert (telomerase catalytic subunit), and then with the overexpression of oncogenes or the inactivation of tumor suppressor genes (through RNA interference or dominant-negative mutants) known to be involved in mammary carcinogenesis (p53, E-cadherin, c-myc, CCNE, CCND1, erbB2). The characteristics of the generated cellular systems are studied in 3D culture and *in vivo* in "nude" mice (at CLB's small animal laboratory).
More than 30 different cell lines have been generated following various combinations of oncogene activation and tumor suppressor gene inactivation.

● The CirBioCancer program: **identification of circulating markers in breast cancer patients and neuroblastoma patients.**
A low but detectable level of serum DNA ("circulating DNA") is found in all individuals. An increase in this level, attributed to cellular necrosis or apoptosis, has been shown in cancer patients. The analysis of mutations, loss of heterozygoty or methylation profiles in this circulating DNA has been performed in different types of cancers in order to evaluate its potential diagnostic and prognostic value. However, in a large number of tumors, the analysis of serum DNA is limited due to a lack of available markers (namely recurrent mutations).

The Léon Bérard Cancer Centre's Molecular Oncology Unit has shown a very high increase in nucleotidic sequences of N-myc using quantitative RT-PCR in serum from neuroblastoma patients presenting an amplification of this oncogene within the tumor. Beyond its involvement in these pediatric tumors, this observation opens the door to detecting the signature of an intra-tumoral gene amplification in serum. Based on these results, two kinds of targeted analysis of serum DNA from breast cancer patients have been developed in the laboratory. This analysis is underway in 70 serum samples from breast cancer patients taken at diagnosis and 70 serum samples from healthy people (with no known pathology).

Moreover, the CLB Molecular Oncology Unit and the ProfileXpert group (J. Lachuer, Lyon) have begun developing a method for comprehensive analysis of structural modifications in circulating DNA, in order to compare circulating DNA and tumor DNA. The exhaustive characterization of circulating DNA is performed using a pangenomic approach (the Affymetrix SNPs chip).

Based on preliminary results, this approach may enable discrimination of plasma from "healthy" people (with no known pathology) from plasma of neuroblastoma or breast cancer patients. These results must of course be confirmed with a larger number of samples. The analysis of tumor/plasma pairs in lung cancer or liver cancer patients will be performed next.

The results that have been obtained so far show the relevance and the power of the genomic approach using microarray for the identification of prognostic factors in circulating DNA from cancer patients. Eventually, the current analysis should help to identify a limited list of genes or loci showing a prognostic or even diagnostic value that could help clinicians in their therapeutic choices.

The East Lyon / HCL pharmacogenomics platform

The pharmacogenomics platform managed by Lyon Civil Hospitals (HCL), directly linked with CLB, aims to be the reference organization in oncological pharmacogenomics for academic and industrial researchers from the Rhône Alpes / Auvergne area, to be integrated into a single interregional system for developing anti-cancer agents in the future.

The analysis of clinical sample sets annotated during clinical protocols sponsored by hospital physicians or the pharmaceutical industry will enable the identification and validation of biological parameters. These parameters could be further promoted as predictive or prognostic markers. This leading-edge activity will contribute to the influence of the Lyon area in the cancer field and to its national and international attractiveness.

The Molecular Tumor Description Laboratory (LCMT) platform relies on:

- Renovating and equipping premises at the Rockefeller Medical School in order to accommodate an Affymetrix platform;
- Setting up a chemotherapy day treatment unit at Edouard Herriot Hospital (HEH), housing a unit for new medicine development, originally named SERNOMA, which will later be joined with the traditional day unit opened in December 2006, known as the Multidisciplinary Medical Oncology Day Unit (UJOMM);
- Installing tools for biomarker analysis (flow cytometry and *in vitro* cytotoxicity assessment).

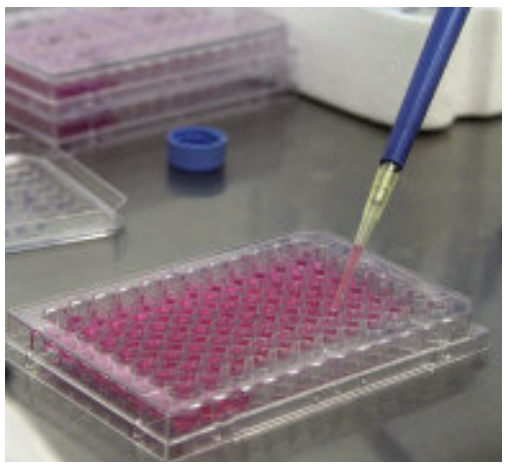
After a 6-month work period, the platform opened at the end of August 2007, in a 200 sq. m. / 2150 sq. ft. space at the Rockefeller Medical School. This area, fully renovated and likely to be certified to European standards, includes an area for storing clinical biological samples (linked to the HCL Biological Resource Center), a protected area for extraction and analysis of nucleic acids (Affymetrix platform, Agilent platform and PCR machines), a cell culture area, a multipurpose area, and a bioinformatics area.

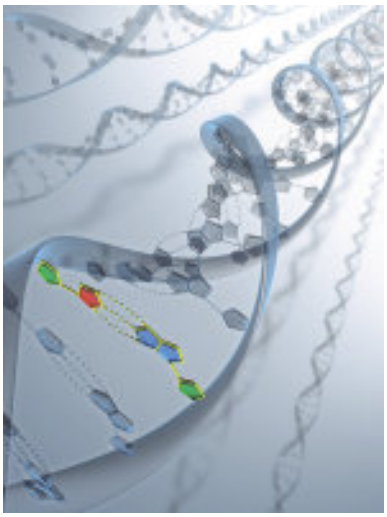
> Scientific accomplishments

Several on-going projects have already enabled hundreds of clinical samples to be collected, as part of Hospital Projects in Clinical Research or in collaboration with international multi-center groups. Additional funding (from INCa, various national multicenter groups and industrial contracts) for the purchase of biological reagents has been obtained. This transfer activity benefits from the pharmacological expertise of the Inserm team (headed by Charles Dumontet), which has many industrial contracts in the field of anti-cancer agents (sanofi-aventis, Pierre Fabre, Merck Serono, Lilly, Bristol-Myers Squibb and Roche) and is part of a comprehensive package of services including pharmacokinetics, modeling and running of clinical studies from phase I to phase III.

- Pharmacogenoscan

The aim of this interregional project (Lyon, Grenoble, Saint-Etienne and Clermont-Ferrand under lead investigator Christian Brambilla) started in May 2006 is to determine genetic factors of sensitivity to chemotherapy in lung cancer patients. More than 350 samples out of a planned total of 600 samples have already been collected. This biological resource will allow scientists to carry out a number of projects, including the search for lung cancer susceptibility genes (in association with the Evry Génopole), the search for candidate genes (APEX protocol) and the correlation with tumor-specific prognostic factors.





● Intergroupe Francophone du Myélome (IFM) protocols

This international project (with more than 120 patient recruitment centers in France, Belgium and Switzerland) is carried out as part of IFM, the world's largest multicenter hematological group. This study, the only one of its kind in the world and with already more than 1000 samples, will enable predictive factors of sensitivity to the various innovative and/or intensive treatments in this disease - still incurable today - to be identified. The first polymorphism analyses were performed in 2007 and should continue in collaboration with other French teams in 2008.

● Breast cancer project

This project, in collaboration with the Léon Bérard Cancer Centre and bioMérieux aims to explore potential uses of nucleic markers for the treatment of cancer. It will work to develop predictive tests in cancer patients at an early stage for more effective treatment.

● Thyroid cancer project

This project will examine the expression pattern of thyroid cancer patients in order to identify the predictive factors for the risk of metastasis development. As part of this project, headed by Bernard Rousset, a set of about 60 clinically annotated samples will be analyzed in 2008.

● Industrial contracts

An initial project on the effect of a Merck Serono molecule on fresh acute leukemia cells was performed in 2007. Several other contracts, in the fields of targeted therapeutics, monoclonal antibodies and novel agents, are currently being negotiated with pharmaceutical industry partners.

> Development prospects

The projects targeted by the platform will be led by researchers from the region and will make use of existing banks within the region (such as the thyroid tumor bank).

The LCMT environment is particularly favorable, as it is part of the East Lyon platform. Moreover, it should benefit from the recent accreditation of Lyon's oncology expertise in the Theme Research and Care Network (RTRS). In addition, a number of academic research laboratories are located nearby. These include Inserm and CNRS units, which should soon be brought together in a Cancer Research Center, as well as some transfer laboratories – the Pathology Laboratory at HEH and CLB, the Cellular Hematology Laboratory at HEH (C. Dumontet), the Molecular Biology Laboratory at HEH (A. Calender) and the laboratories of the International Agency for Research on Cancer (IARC) and Bioparc Laënnec.

A large portion of the new projects hosted at the platform are to be carried out as contracts with the pharmaceutical industry. In addition to greater knowledge and improved use of medicines investigated during these studies, which helps to increase the likelihood and / or speed of marketing of the drug, LCMT will also receive funding enabling it to finance the recruitment of technicians. The participation of bioMérieux as a partner in this platform gives it an important competitive advantage.

At the national and international levels, LCMT aims to position itself as a reference in the field of transfer genotyping for cancer research. In this capacity, it will seek to participate in and / or run national or European-scale programs for genotyping samples for cancer research.

The South Lyon platform

The Gerland South Lyon Cancer platform is located at two facilities: South Lyon Hospital (CHLS – Lyon Civil Hospitals) and the Gerland campus (IFR 128).

Setup of this platform includes:

- Renovating and equipping research facilities at the South Lyon Medical School (CERVO – Oncology Study, Research and Development Center): 1400 sq. m. / 15,000 sq. ft. to house some 12 teams;
- Purchasing equipment, namely: a clinical epigenetics platform, a cell sorter, a confocal microscope, a flow cytometer, a 3D FISH microscope station, a quantitative PCR system, clinical pharmacology, a microarray reader and a protein analysis platform.

This platform is characterized by its link with various fields in fundamental biology (cell biology, immunology, infectiology, modeling and more) and with clinical research. The industrial partnerships are particularly productive, at all levels of the research programs undertaken. Concretely, in 2007 the various research teams were up and running at the South Lyon Medical School facility, a process started in 2006.

> Scientific accomplishments

The programs started three years ago are continuing in the following topic areas: epigenetics (description of telomere signatures), biotherapies (telomerase and Wnt pathway targeting), hormonal receptors (particularly in prostate cancer) and immuno-intervention (analysis of effector populations in tumors and antitumor immunization). They are based on collaboration between Gerland and South Lyon teams, within CLARA, as well as in France and abroad.

These programs also link with clinical research, namely in the following fields:

- Interaction of carbon ions with cells and the role of stress proteins in the tissular damage induced by radiotherapy, in association with the ETOILE program;
- Pharmacological analysis and modeling of anti-cancer treatments in the pharmacological screening platform, one of the cornerstones of ProCan focus area V;
- Programs related to Lyonbiopôle for vaccination and development of new monoclonal antibodies, as well as the new projects on the relationships between hepatitis and lymphoma within ProCan focus area II;
- Several clinical programs funded by the Hospital Programs in Clinical Research (PHRC) or international calls for projects in the field of urological tumors, lymphoma, leukemia and ovarian cancer.

The setup on the platform of Inserm unit U870 on "Metabolic regulation, nutrition and diabetes" enabled the emergence of new projects in ProCan focus area III.

All of these programs are based on a number of industrial partnerships. During 2007, several potential research projects were investigated with bioMérieux and these may be conducted in a new organization, a mixed cancer bioMérieux-HCL research unit (based on the model already being used in East Lyon for inflammation) which should be set up at the facility by the end of 2008.

This year of strong development saw the emergence of a highly dynamic research environment at the platform, with great potential for new collaborative ventures between the academic and industrial spheres.

IARC platform

In the European Cancer Observatory project, supported by CLARA, a bilingual website (French/English) to show epidemiological data in Europe is under development.

This site will contain two levels of information:

- ***Profile*** pages will show incidence and mortality per cancer from the most recent national statistics for each European country. These pages target a broad readership including researchers, journalists, health professionals, institutions, pharmaceutical laboratories and more.
- ***Analysis*** pages will show more detailed data (coming from cancer registries) enabling analysis of trends or forecasting. These data will be updated yearly. They target a more limited readership, i.e. epidemiologists and researchers.

Epidemiological data will be organized into two groups: population (country) or cancer type.

The 27 European countries whose assessment was calculated in 2006 (Ferlay et al., Annals of Oncology 2007 18(3):581-592; doi:10.1093/annonc/mdl498) are concerned. The cancers (approximately 12) are those included in the same study.

Work done at the end of 2007

A first page was developed (with an example link towards a cancer and country profile page), the database was set up and test data were sent to the provider.

European Center for Ultra-High Field NMR in Lyon

The European Center for Ultra-High Field Nuclear Magnetic Resonance (CERMN) is a unique platform for metabolic profiling and cancer metabolomics. It has received €20.35 million in funding from the French State, the Rhône-Alpes region and the Lyon Urban Community.

Construction ended in December 2007, and the teams moved in during January 2008. The facilities include several 500 MHz and 700 MHz NMR spectrometers and the first 900 MHz spectrometer in France. During the second half of 2008, the first 1000 MHz spectrometer in the world (the "GigaHertz" project) will be delivered.

The scientific rationale behind the CERMN is mainly interdisciplinary and multidisciplinary, blending chemistry, physics, bioinformatics, biology and medicine. The CERMN's expertise enables a full range of structural and dynamic analyses in systems such as small organic molecules or proteins, in both structural biology and metabolomics.

Concerning biomedical research, CERMN is developing a topic area on metabolomics (a study of metabolism by NMR without *a priori* knowledge) focused on understanding biological mechanisms of insulin resistance, ageing and cancer. A partnership has been initiated with Laurent Ségalat (CGMC, UBCL1) on the functional genomics of ageing in the *Caenorhabditis elegans* model organism.

The CERMN is now involved in cancer research, through a newly formed partnership with Thomas Bachelot and Olivier Tredan (Léon Bérard Cancer Center) on breast cancer, in order to assess the metastatic potential of the tumor.

The Grenoble platform

CLARA's Grenoble platform, located on the Health campus, is open to laboratories of the city's "Scientific Polygon" and to CLARA members. This Health campus includes the University Hospital (CHU) – enabling recruitment of large numbers of patients with malignant diseases – the Medical School, the Inserm/Joseph Fourier University (UJF) research centers in cancer and neurology (including brain tumors), as well as CNRS/UJF microbiology and healthcare engineering laboratories. These labs are united in two Federative Research Institutes (IFR) and one Federative Technological Research Institute (IFRT).

Some 350 researchers, physicians, technical staff, industrial firms and start-ups are working together on this platform, which gives Grenoble and its Health Campus great exposure in the fields of proteomics and nanotechnology applied to healthcare concerns, more particularly cancer. Validation of prototypes developed by CEA/Léti at CLARA's Grenoble platform will encourage industrial transfer and the creation of new businesses. The platform has an overall provisional budget of €4.5 million. It has been mostly operational since March 2007 and will be fully up and running at the end of 2008.

> Functional imaging

● Pre-clinical and clinical MRI (Jean-François Lebas and Chantal Rémy)
The Grenoble Magnetic Resonance Imaging (MRI) platform is one of the first imaging platforms to have received RIO certification. There are two main areas: the first with three "full body" Nuclear Magnetic Resonance (NMR) imaging facilities and the other with four "small animal" NMR imaging facilities.
The projects, research studies and funding planned for the "Grenoble CLARA Platform" have gone according to schedule.

Clinical component (J.F. Le Bas) - Developments in perfusion imaging and the clinical evaluation of these methods in brain tumor pathology today enable us to have a quantitative approach to tumoral neovascularization in the novel antiangiogenic therapies currently used at the University Hospital (Campto-Avastin).

Methodological and pre-clinical component (C. Rémy)
For the last 4 years, the team has worked on developing original NMR blood volume imaging methods to study vascularization and tumoral angiogenesis.
Intravital two-photon excitation microscopy has been used to study the short-term effects of microbeam radiation on healthy brain microvascularization in mice.

● Small animal optical imaging (Jean-Luc Coll)
The first focus of this platform is real-time non-invasive optical imaging of luminescent reporter genes and fluorescent products in mice or small animals for the detection of tumors and the study of their growth kinetics under targeted treatment. The platform's second area of interest is the validation of prototypes created by CEA/Léti, as well as molecules and nanoparticles for tumor diagnosis and therapy. It aims at organizing the transfer of findings towards patient care and market development of the techniques. The building of a clinical optical imaging laboratory is under discussion and a trial in optical imaging-assisted surgery on osteosarcoma is currently underway in collaboration with Raphaël Rousseau's laboratory at Léon Bérard Cancer Research Center.

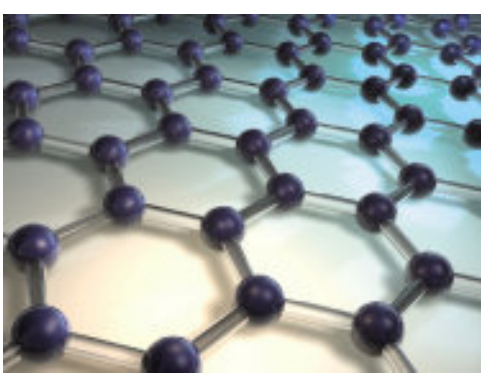
● Functional, cellular and molecular nuclear imaging (Daniel Fagret)
This program required the purchase of a second camera head in 2007 for the tomographic system. In addition, CEA/Léti developed a high-performance functional imaging tool in collaboration with UJF. After simulation studies, the various components of the prototype were built by Léti teams.

> Molecular Analysis

● *In situ* analysis

***In situ* molecular detection** (Elisabeth Brambilla) - This platform, housed in the premises of the Department of Pathological Anatomy and Cytology, aims to help cancer diagnosis and to host research work requiring *in situ* analysis by immunohistochemistry and *in situ* hybridization. In 2007, this platform handled 24,000 slides, one-third of which have been used for research. This work was carried out as part of two European projects (Lung EU ELCD NSCLC and Lung IALT) and 8 national projects (funding from PHRC, INCa and the French League Against Cancer). This work led to the publication of 13 articles in international journals in the "lung cancer" focus area in 2007.

Semi-automated cancer molecular cytogenetics platform (Dominique Leroux) - This high-throughput platform (Metasystems) has been fully operational since the end of 2006. It was equipped with Rare Cell Detection RDD software in November 2007 (with funding from CLARA), particularly for FISH experiments in myeloma. Located in the cellular and molecular hematology laboratory (at the Biology Center), it is above all dedicated to traditional and molecular cytogenetics for diagnosis of malignant hemopathies. In the past year it has hosted work on *in situ* molecular genetics in solid tumors (EGFR/lung cancer, HER2/breast cancer and glioma 1p/19q). These uses will be developed following INCa's 2007 accreditation of the university hospital platform for molecular genetics in the field of cancer.



● Proteomics

Medical proteomics platform (Michel Sève) - This platform handles analysis of biological samples from small projects, with only few proteins to identify, and from more complex projects, with a large number of samples requiring pre-fractionation and fractionation, as well as quantitative and qualitative proteomics analysis. The platform also aims to demonstrate the clinical interest of proteomics for the diagnosis of pathologies such as cancer. It collaborates with research groups for the development of the bioinformatic and statistical tools required for the combined analysis of proteomics data and clinical data, as well as with bio-clinical groups with large retrospective banks and able to coordinate large multicenter prospective trials. This program is innovative in its link between clinicians and biologists, as well as between experts in proteomics and biotechnology developers.

Dynamic Proteome Study Laboratory (Jérôme Garin) - This Rhône-Alpes Genopole platform is the functional IBiSA platform that serves as the basis for the scientific activity of the Inserm/CEA/UJF U880 mixed research unit. On the strength of its expertise in biochemistry, mass spectrometry and informatics, the platform offers its proteomics services to the scientific community and is developing new analysis methods. In January 2007, the platform was organized in four complementary technological groups. The know-how of these groups is put to use in partnerships with academic and industrial laboratories. The scientific collaborations are mainly conducted on a contractual basis, following acceptance in a national or international call for projects. Thus, some 12 large-scale collaborative projects are currently underway. Three of these projects are funded by the EC, four by ANR, two by INCa and one by CEA. Four of the projects deal directly with cancer.

● Nanotechnology / Clinical platform (François Berger)
The applications primarily involved the setup and validation of innovative technologies in the search for biomarkers in collaboration with CEA/Léti.

• **Molecular biopsy project:** development of a microstructured, chemically-altered microsystem to perform molecular biopsies alongside microbiopsies carried out for cancer diagnosis. The fields of application are glioma, bronchial tumors and sarcoma.

• **Validation of the serum equalization technique,** which enables access to the minority proteome with demonstration of its quantitative feature. Application fields are CSF (cerebrospinal fluid) in carcinomatous meningitis, and serum for the search of peripheral markers in glioblastoma.

● Epigenetics / EPIMED platform (Sophie Rousseaux)
The EPIMED platform aims to share and/or develop the often complicated concepts and tools required to identify and validate the epigenetic factors and alterations involved in malignant transformation.
Tools include the analysis of expression of repetitive regions in the human genome (Repchip macroarray), analysis of epigenetic factors expressed in cancers in an aberrant manner or "testis cancer" factors (CTchip), the search for new "testis cancer antigens" which could be used as markers in the serum of cancer patients and as targets in a therapy, as well as the systematic search for chromatin alterations in tumors (antibody development).
A European patent is currently being filed (by Université Joseph Fourier and Inserm).

● Immunomonitoring platform (Patrice Marche)
The Inserm/UJF team led by P. Marche and the EFS Immunology Laboratory have set up innovative methods for the analysis of immune system parameters. In addition, patented technological innovations are being developed and validated in biomedical applications. This namely involves evaluating the diversity and dynamics of the immune response by analyzing all antigen receptors expressed by T lymphocytes, as well as searching for serum circulating markers using miniaturized systems, such as peptide-protein chips.

Saint-Etienne platform

The CLARA regional public health platform is designed to organize public health research and activities in the field of cancer, as well as to build research programs in various areas of prevention. In addition to coordinating the region's public health activities, the public health team develops work on its own research topics.

The platform was initiated by the Loire Cancer Institute (ICL) and is led by a team including Franck Chauvin, Yacine Merrouche and Philippe Ruch (Hygée Center for cancer information, prevention and education).

The platform will be strengthened with the building of a regional Cancer Information, Prevention and Education Resource Center at the Saint-Etienne university campus. Its name – the "Hygée Center", inspired by the name of the Greek goddess of health and prevention - was registered with the French National Patent Office (INPI) in April 2007.

The overall construction budget is €8.8 million, €1 million of which is to be provided by the Loire County Council. Project consulting firm Athegram has been chosen as planner for the project. The technical and functional program was delivered to Saint-Etienne Métropole, the contracting authority, at the end of last year. Delivery of the Hygée Center is scheduled for 2010 and the search for additional funding is underway, particularly for the Center's equipment.

> Scientific accomplishments

The evaluation phase of the Dealing with Pain and Dealing with Fatigue Patient Education Programs started with two randomized multicenter intervention studies (Loire Cancer Institute, Léon Bérard Cancer Center, Jean Perrin Cancer Center and South Lyon Hospital).
It will continue throughout 2008. The *Fatigue* program was funded by INCa (Human and Social Sciences, 2005) and the 2006 Cancer PHRC. The *Pain* program received funding from INCa (Clinical Research, 2005).

Two other therapeutic education programs started in 2007:
- The Observance program, designed to assess how the method for developing a therapeutic education program can be adapted for use in cancer treatment, funded by Roche laboratories;
- The Tobacco Patient Education Program (education program targeting female smokers who are moderately or highly dependent on tobacco and treated for breast cancer at a cancer treatment center), funded by DHOS/INCa (2006).

ICL, on behalf of CLARA's Public Health Platform, is the sponsor of the REMPAR (Research and Assessment of Means of Protection Against HPV in Rhône-Alpes) program carried out in collaboration with Léon Bérard Cancer Center and P. Vanhems' team (Lyon Civil Hospitals).

This program, funded by Sanofi Pasteur MSD (2007) and Ligue Contre le Cancer (2007) aims to:
- Study the perception and use of the anti-HPV vaccine by family practitioners and gynecologists, as well as the trends over time;
- Study how the vaccine is perceived by women;
- Identify sociological, ethnic, socio-demographic and cultural considerations that may be limiting factors for the vaccine in France;
- Describe the target populations actually vaccinated;
- Identify the reasons for refusal of the vaccine;
- Assess whether the vaccine is an alternative or a complement to screening by pap smear in vaccinated women.

A "Malnutrition and Cancer" survey, funded by Massif Central FNADT and ERDF was conducted in collaboration with Jean Perrin Cancer Center in Clermont-Ferrand and will be the basis for the development of patient education programs designed to improve prevention of the consequences of cancer on nutrition.

The Public Health platform assessed the PREAMBUL study conducted by Association for the Development of Prevention and Nutritional Education (ADPEN) of Plaine du Forez under the supervision of Laurence Jacquin, nutritionist and specialist in diabetes at Feurs Hospital. This study aims to assess the feasibility and effectiveness of an educational program for overweight or diabetic patients.

A University Diploma in Prevention has been created at the Saint-Etienne Medical School.

Finally, the Hygée Center is a partner in the regional campaign to encourage early cancer diagnosis in people older than 75 years of age. This program, directed by Professor Chauvin, has been conducted by the Association of Complementary Health Insurance Providers (Union des Mutuelles) of Rhône-Alpes since 2005.

The Cancéropôle's Auvergne Cluster (PAC)

The year 2007 gave new momentum to the Cancéropôle's Auvergne Cluster (PAC). Thanks to the commitments of the Auvergne Regional Council, Clermont Urban Community, FEDER, Ligue Contre le Cancer, Auvergne GEFLUC and local institutions, funding was invested in the imaging and structural and functional genomics platforms. Once set up in 2008, these tools will serve the local scientific community and its research projects.

Another highlight of 2007 was the inclusion of the "Onco-theranostics", "Nutrition and Cancer", "Imaging" and "Targeted Therapy Transfer (TTC)" programs in the Auvergne State-Region Contract Project (CPER).
Another important event was the three-year scheduling of the research projects through the INCa-funded ProCan program. In this program, the Auvergne teams participate in five of the six top-priority research focus areas, in particular, leading focus area III on "Nutrition and Cancer".

> Onco-Theranostics

This program brings together three main research themes on breast cancer through the following databases:

- Neoadjuvant database: includes 710 operable breast cancer patients, and has enabled the study of predictive and prognostic factors, comparison of anatomopathological classifications and establishment of a new classification quantifying tumor residue. It has also revealed the importance of evaluating the hormonal receptors on the residual tumor. Future plans include the creation of a predictive oncology group, continuation of the study on response to neoadjuvant chemotherapy, continuation of the study on residual disease after neoadjuvant chemotherapy and launching of a new multicenter trial (adaptation of neoadjuvant chemotherapy depending on response, with study of biological parameters).

- Adjuvant database: under development. The aim is to create a database comprising 500 patients treated by adjuvant hormone therapy in order to check if survival rates improve in the event of a switch.

- Metastatic database: contains 857 patients in whom the impact of taxanes and anti-aromatases on survival has been studied. The study will also investigate survival based on the number of chemotherapy lines, as well as the role of continued treatment after a response is obtained via chemotherapy (switch and biological treatments).

Several national and international clinical trials are underway (PACS01, PACS04, MABEL, PETTAC8), as are research projects on targeted therapeutics. Two of these, TENEO and VECTIBIX (sponsored by Jean Perrin Cancer Center), are multicenter studies targeting EGFR in triple negative breast cancers. These trials will feature a search for predictive markers, including EGFR and C-myc. Collaborative projects are underway with the TAXHER-GETNA1 trial and the PACS04 trial (investigating response to Herceptine); as part of a national PHRC and the PETTAC8 study (investigating response to Erbitux); and with Dr Milano (based in Nice) as part of a pre-clinical study of angiogenic therapeutics.

> Nutrition and Cancer

The Nutrition and Cancer focus area is conducting multidisciplinary research linking teams in both fundamental and clinical research, and thus promoting the transfer of research findings to the patient care. It is supported by existing research and care structures (such as CRNH, CLCC, ICL and CHRU).

There are four main areas of activity:

- Bio-mechanical examination of the effects of some nutrients (phytoestrogens, lycopen and oxysterols) on the development of hormone-dependent cancers (breast and prostate cancer), using experimental models (animals and cells) as well as in clinical research.
- Investigation of the involvement of adipokines in mammary carcinogenesis, and any relation with obesity, using both experimental (on cell lines) and clinical (on a patient cohort) approaches.
- Preventive nutritional intervention for women with a hereditary risk of breast cancer (carriers of BRCA1/ BRCA2 mutations) in order to reduce the risk of cancer via an appropriate diet and lifestyle.
- Evaluation of the benefits of an appropriate diet (via methionine depletion or immunonutrition) in cancer patients treated by chemotherapy, in terms of treatment potentialization or prevention of side effects. The cancers being studied are colon carcinoma, melanoma and head and neck cancers.

The ProCan program's support of the Nutrition and Cancer focus area will, through the development of its scientific activity, promote the integration of new teams and the emergence of core projects.

> Imaging

Cartilage tracers allowing the diagnosis of degeneration of this tissue can be used in experimentally validated applications for early diagnosis of arthrosis and chondrosarcoma. An INCa-accredited free project between CLARA and Cancéropôle Grand Ouest has been set up to study applications in chondorsarcoma. It is now entering a transfer phase, with support from OSEO, in partnership with Cyclopharma.

Melanoma radiotracers are being supported by ANR, with a patent filed in 2006 that is currently being extended to the field of internal radiotherapy. A second patent is being filed for a dual PET/internal radiotherapy diagnostic approach using the same molecule. In 2008 this project will apply for a "Proof of Concept" program in association with Cyclopharma.

> Structural and functional genomics and "post-genomics"

This topic explores the molecular disorders that lead to malignant cellular transformation.

Several topic areas have emerged: a study of breast and prostate hormone-dependent cancer transcriptome, high-throughput sequencing of genes involved in mammary and ovary tumors ("Mutacancer" program – see page 16), a study on the first steps in the development of prostate and adrenal tumors using transgenic animal models, a study on genetic instabilities, a "Beyond BRCA" program that studies non-BRCA susceptibility genes for breast cancers in oncogenetics.

The European "Lifegrid" program has enabled the development of bio-informatics tools required to interpret the results of structural genomics, functional genomics and patient clinical data in an integrative manner. This will benefit both fundamental and clinical – or, more precisely, bio-clinical - research.

Scientific coordination

THE FIRST TOP PRIORITY FOCUSES

Nanotechnology and Cancer

Nanotechnology is a great opportunity for medicine as it enables molecular-level interaction with the matter that makes up living beings. Thus, starting in 2006, CLARA, alongside CEA/Léti, began developing the "Nanotechnology and Cancer" multidisciplinary cancer research focus area in order to generate R&D projects bringing together nanotechnologists, biologists and clinicians (see CLARA Progress Report 2006, pages 9 to 11).

Following the first two meetings held in 2006 to raise awareness and make initial contact, CLARA helped to organize a seminar entitled "Emerging nanotechnology-based oncology" with Inserm and European networks of excellence Conticanet and Nano2life. This seminar, held on January 11th - 12th, 2007 in Archamps, brought together some fifty representatives of the medical and scientific communities, experts in oncology and/or in micro and nanotechnology, from 14 European countries. Their aim was twofold:

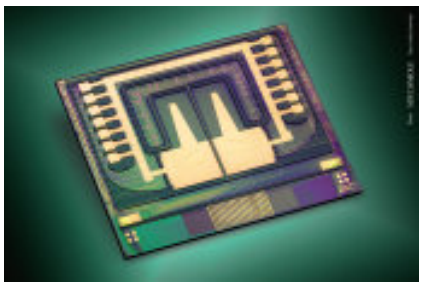
- To carry out an inventory of the needs of the medical world in terms of diagnostics and care, in light of technological innovations made possible by micro and nanotechnology;
- To set priorities and determine actions at the European level in order to optimize the application of nanotechnology in the fight against cancer.

Partnership agreement between CLARA and CEA/Léti

On March 27th, CLARA and CEA/Léti signed a partnership agreement to support joint projects in the field of micro and nanotechnology applied to cancer research. These projects will focus in particular on *in vivo* imaging, solid samples (biopsy) and blood samples.

As it brings new hope for cancer patients, this research topic area remains a top priority for CLARA. It has been included in the cluster's new scientific strategy as part of focus area I of the ProCan program, entitled "Nanotechnology, Imaging and Cancer" (see page 9).

Moreover, a new program called "Cancer Nano Transfer" has been set up to specifically fund cancer-related nanomedicine projects, with the startup of a pilot project entitled Ganglio Tool (see pages 38 & 39).

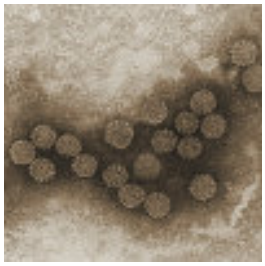


CLARA / Lyonbiopôle collaboration

Starting in 2006, CLARA initiated close collaboration with the Lyonbiopôle competitive cluster (see the CLARA Progress Report 2006, pages 8 & 9). These two organizations are clearly complementary: the cluster's industrial network, CLARA's academic and clinical network and a number of players linking the fields of virology and cancer.

Thus, it was natural for "Infections & Cancer" to be included among the six top-priority focus areas for CLARA's new scientific strategy, developed for the ProCan 2007 - 2010 call for projects (see page 10).

This focus area draws upon the internationally renowned expertise and excellence of Rhône-Alpes / Auvergne research teams in the fields of molecular virology, virus-induced oncogenesis mechanisms, immune response and clinical and therapeutic research. It brings together existing organizations (CLARA, Lyonbiopôle, the Synergie Lyon Cancer RTRS research network and the Innovations in Infectiology RTRA research network), which will help to improve the integration of research topics. At the same time, it will also encourage international development, via the International Agency for Research on Cancer (IARC), with programs targeting developing countries where the incidence of some virus-induced cancers is a major public health concern.



The work that has been carried out by the six CLARA / Lyonbiopôle working groups is now continuing within ProCan focus area II.

Collaboration between CLARA and Lyonbiopôle has also been illustrated in their joint work on the Proof of Concept program. A call for projects is scheduled for 2008 in order to support projects bringing together Lyonbiopôle partners. This effort will help to fund projects upstream while a "pre-accreditation" process will help to ensure that the projects are of interest to industrial players willing to carry them forward.

LAUNCHING OF THE PROCAN FOCUS AREAS AND DISEASE STUDY NETWORKS

The aim of the scientific coordination falling within the six ProCan focus areas is to help the emergence of projects and programs likely to obtain funding in the calls for projects, with the INCa calls being the top priority. Another goal is to improve the quality of CLARA research in its fields of excellence and to give the network and its findings greater exposure.

Meeting of the interdisciplinary neuro-oncology network on April 27th, 2007

With this in mind, the Network Management held a series of meetings starting in April in order to prepare the application for the INCa call for projects and to specify the research topics and players involved in each focus area.

Between early October and late November 2007, five of the six ProCan focus areas were launched, with varying levels of development.

Focus areas I and II, based on topics explored within the network starting in 2006, were immediately opened to the entire CLARA community. These focus areas began with a call for letters of intention in order to:

- Pinpoint promising research teams and projects in the region;
- Highlight areas of synergy and complementarity for capitalization;
- Gather recommendations and opinions based on international assessments;
- Help identify potential funding, with INCa being the top priority.

These letters of intention were assessed by experts from outside the CLARA region.

For focus area I: of the 17 letters of intention assessed, ten were identified as complementary for building a core program in the field of imaging. In addition, four high-potential nanotechnology projects are moving forward to be presented to INCa.

For focus area II: 12 letters of intention were examined, nine of which were accepted.
These nine projects were presented and debated. Eight of them were selected for presentation to InCa, including four on lymphoma, two on hepatocarcinoma and two on virus-induced cancerogenesis. The ninth project was transferred to focus area I.

Focus area II continued this work through a "Core Programs" call for proposals, aiming to pinpoint two or three core programs during 2008.

These programs, to remain a top-priority for the coming three years, will enable the focus area to:

- Mobilize teams and resources that are immediately competitive at the European level;
- Implement an integrated multidisciplinary, innovative approach (fundamental, transfer and clinical research followed by industrial development), bringing together several CLARA institutes and sites;
- Gradually add high-level teams and projects, including those from other cancer clusters and countries, and as part of European programs;
- Aim for significant results, in 2010 and beyond, in order to place CLARA research at the European echelon.

Focus areas IV and V were launched in smaller committees, the primary aim being to specify target research topics and lay out a clearly defined roadmap before widening the circle to include other academic and industrial players.

For **focus areas III and V,** a call for letters of intent will be sent out in spring 2008.

Only **focus area VI** has not yet started. It will be launched at the beginning of 2008 as part of the Synergie Lyon Cancer Scientific Cooperation Foundation that is currently being set up.

The Executive Board of CLARA's Scientific Steering Committee and the Steering Committees of the various focus areas have of course been sharing information and recommendations throughout this process.

Alongside the launch of the top-priority focus areas, the Network Management has also worked to assist the startup and building of the disease study networks, in particular the interdisciplinary neuro-oncology network started at the end of April, and the endocrine tumor network, which began in early June.

THE CLUBS

The Business Club

At its January 18th, 2007 meeting, CLARA's Business Club revamped its Executive Board, choosing a new President, Dominic Cellier, Head of Scientific Affairs at Merck Santé (Merck Serono Group).

The composition of the new Executive Board reflects the diversity of the Rhône-Alpes and Auvergne firms active in the field of cancer, which include pharmaceutical laboratories, small biotech companies, medical device and equipment firms, service providers and more.
In addition to Dominic Cellier, the Executive Board also includes Michel Jolivet (bioMérieux), François Pons (Genome express), Sophie Chappuis (Transat), Christine Guillen (OPi), Catherine Boisgard (Meristem Therapeutics) and Pascal Mayer (Haploys).
This new Executive Board is committed to pursuing the activities of CLARA's Business Club, in particular by developing collaborative ventures with public research, participating in the assessment of research projects in terms of their market potential and representing CLARA.

A PR kit was created in French and English versions. It helped Executive Board members to be effective spokespersons for CLARA, throughout the year, in relations with LEEM (the French Pharmaceutical Companies Association), with other cancer clusters, with competitive clusters and in foreign countries (namely Switzerland and Italy).

A presentation of CLARA's Business Club by **D. Cellier** at Cancéropôle Grand Sud-Ouest, in Bordeaux, on October 4th, 2007

These efforts have been productive as *"big pharma"* firms from outside the region have shown an interest in working with CLARA and participating in the Executive Board's activities. The decision to expand the Business Club to include firms from outside the region was approved in 2007 and will take effect in 2008.

In terms of project assessment, Michel Jolivet took part in the examination of the ACI 2004 (Concerted Incentive Action) proposals.

Finally, 2007 was a year in which CLARA's academic and industrial communities worked together more closely than ever, with three joint meetings of the Executive Boards of both clubs together. This closer working relationship was illustrated by the business community's significant involvement in the organization of the 3rd Scientific Forum (held March 18th- 19th, 2008).

As part of the reorganization of CLARA's governance undertaken in late 2007, (see page 6), the Business Club is now led by an "Industrial Steering Committee," the counterpart of the "Scientific Steering Committee."

It aims to take into consideration the needs of the region's businesses and coordinate them, to assist in the deployment of CLARA's promotional activities and to make sure that industrial players are represented in the cluster's various decision-making bodies.

With representatives on the Executive Board of the Scientific Steering Committee, industrial firms are fully involved in the specification, implementation and follow-up of CLARA's scientific program. Likewise, the Industrial Steering Committee will be opened to two representatives from the academic community in 2008.

The Academic Club

The Academic Club's aim for 2007 was to be place for scientific debate and to disseminate information, representing the entire scientific community.

Its main activities involved organization of the Scientific Forum, participation in the updating and development of the Web site, financial support to cancer-related scientific events throughout the region, and building links with the business community.

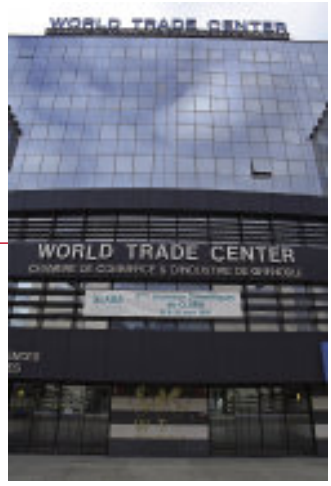
It should also be noted that the joint meeting of the Executive Boards of the two Clubs on April 4th, 2007, kicked off the process to build CLARA's ProCan program, in response to the INCa call for projects (see page 7).

As part of the reorganization of CLARA's governance, in particular the setup of a Scientific Steering Committee (CPS - see page 5), the question on whether or not to maintain the Academic Club was raised. As the missions of the CPS overlapped with those of the Club, the latter was disbanded. Its work will of course be carried on in the Scientific Steering Committee, which is now the scientific counterpart of the Business Club.

We would like to thank all of the members of the Academic Club's Executive Board who invested their time and energy throughout the year to help CLARA move forward.

CLARA'S 2ND SCIENTIFIC FORUM

CLARA's 2nd Scientific Forum was held March 19th - 20th, 2007 at Grenoble-Europole. More than 350 people turned out for the event, which received submissions of over 140 scientific abstracts.



Plenary and parallel sessions helped provide a look into the research being carried out at CLARA's various platforms in the following topic areas:

- **Angiogenesis: therapy and imaging**
- **Micro and nanotechnology for oncology and technological innovations in the search for biomarkers**
- **Nutrition and cancer**
- **Cancer epigenomics**
- **Innovations in locoregional treatments**
- **Virus-induced cancers: a model for immunotherapy**
- **Social science and cancer.**

In addition, a round table on **"Clusters and Innovation: the challenge for CLARA"** kicked off the debate on the potential of the cluster approach for concentrating and enhancing skills and efforts, in order to work together more effectively in the interest of all stakeholders involved.

The first new aspect of this edition of the Forum was CLARA's clear support for young researchers. This was illustrated through the organization of "junior workshops," one of which helped young scientists to prepare an article for publication, and the awarding of the **"CLARA Prize"** to three young researchers whose work was judged particularly promising.

Another innovation was the opportunity for private firms to present their activities in a special area of the Forum.

For all who took part, this Scientific Forum was a big success in terms of the quality of the presentations and the number and diversity of participants.

Nonetheless, it was acknowledged that industrial partners must be more concretely and actively involved in preparing for upcoming Forums, namely in finding means to encourage young researchers to work more closely with the industrial sector.

These points were taken into consideration when organizing the 3rd Scientific Forum, held March 18th - 19th 2008 in Lyon.

Project portfolio 2007

In 2007, CLARA teams continued their efforts in submitting proposals to calls for projects, in particular INCa calls.

The French National Cancer Institute (INCa)

CLARA's Network Management sent cluster members information on 25 calls for projects (not including PHRC and STIC) involving INCa, sometimes in association with other funding providers such as ARC, ANR, DHOS or Ligue Nationale Contre le Cancer.

To our knowledge, this resulted in the submission of 99 application files coordinated by CLARA teams (compared to 77 in 2006), including 91 via the Network Management.

At the end of January 2008, most of the results of the INCa calls for projects were known. Of 98 projects submitted, 30 were selected, giving a success rate near the national average (30%). The success rate reached 37% for research projects in the strict sense, i.e. not including doctoral and post-doctoral scholarships (24 projects selected out of 65 applications filed).

The budget granted to the 30 projects selected in 2007 is €5.52 million. In 2006, it was €4.94 million for a total of 36 projects.

In 2008, INCa and the cancer research clusters will continue to standardize their procedures for replying to calls for projects and make them more consistent. The clusters are also being asked to strengthen their role as relays for INCa in the field.

The Cancéropôle Web site www.canceropole-clara.com lists the CLARA projects selected by INCa, ARC and the Ligue in 2007.

Renewal of Concerted Incentive Actions 2004 for the years 2007 – 2009

INCa has decided to fund the best projects in the Concerted Incentive Actions 2004 program for two additional years. Of the five projects submitted by CLARA members, three were selected:

- Clinical translation of innovative technologies to catch circulating and tissue proteomic biomarkers, led by François Berger (Grenoble University Hospital, UJF and Inserm);
- Plasmacytoid dendritic cells in immunity against cancer, led by Joël Plumas (EFS Rhône-Alpes, Inserm and UCBL);
- Targeting of tumor angiogenesis: preclinical and clinical evaluation of novel anti-angiogenic biomolecules with bioassays and *in vivo* imaging technologies, led by Marie Favrot (Grenoble University Hospital).

Mobile Clinical Research Teams

In November 2006, INCa sent out a call for projects entitled "Mobile Clinical Research Teams" (EMRC) (see CLARA Progress Report 2006 - page 39). This call aimed to enable the recruitment of clinical research assistants to work at hospitals and private clinics, in order to provide local assistance to investigators and encourage patient enrolment in clinical trials.

INCa granted the region's research teams funding enabling the recruitment of ten clinical research assistants, to be split between the Oncauvergne, Concorde, Oncora and Oncoloire networks, Chambéry/Annecy Hospital, the Grenoble Private Cancer Research Institute and the Healthcare Facilities of Northern Haute Savoie.

The EMRC Steering Committee asked CLARA to host its meetings, making this activity part of ProCan focus area V on "Therapy Targeting, Modeling and Clinical Research".

Data Processing Centers

At the end of March, INCa sent out a call for proposals entitled "Accreditation of Data Processing Centers" in order to strengthen and financially support existing operational organizations in cancer clinical research.

Of the 11 applications selected nationwide, two involve CLARA:

- PARCC-ARA (Rhône-Alpes Platform to Assist Cancer Clinical Research), Lyon (coordinator: Alain Leizorovicz);
- Adult Lymphoma Study Group (Gela), Lyon (coordinator: Professor Bertrand Coiffier, Lyon Civil Hospitals).

The dual methodological and clinical expertise of these two organizations was thus acknowledged.

Other funding providers

Cancer DHOS - PHRC

Eight of the 10 projects submitted were selected, strengthening clinical research in the region:

- Evaluation of the association between conformation radiotherapy and hepatic arterial chemoembolization as a neoadjuvant treatment of surgical resection of large hepatocellular carcinoma – P. Merle, Lyon Civil Hospitals
- Evaluation of the axillary sentinel lymph node technique in breast cancer of more than 2 cm – H. Mignotte, Léon Bérard Cancer Center
- Therapeutic combination optimization program – Sylvie Négrier, Léon Bérard Cancer Center
- Medulloblastoma and cognitive scars: an anatomo-functional study of working memory by MRI – A. Pagnier, Grenoble University Hospital
- CONVERT (Concurrent ONce-daily VERsus Twice-daily Radiotherapy in LD SCLC) study – P. Fournel, Saint-Etienne University Hospital
- Active surveillance of prostate cancer showing latency criteria: impact on 10-year specific survival. A national multicenter prospective study – N. Mottet, Saint-Etienne University Hospital
- The role of a silicon prosthesis in the prevention of tracheobronchial stenosis during the evolution of non-small cell obstructive lung cancers – J.M. Vergnon, Saint-Etienne University Hospital
- Prognostic impact of minimal residual disease (MRD) quantified by RT-PCR for Tyrosine Hydroxylase transcript (TH mRNA) in children treated for a neublastoma (NEUROMAR 3) – J. Kanold – Clermont-Ferrand University Hospital

Non-profits

These organizations provide significant funding for cancer research by Rhône-Alpes / Auvergne teams, in particular:

- **ARC**

In 2007, the Board of Directors of ARC voted to allocate CLARA researchers a total of €3.14 million, to be split between grants for young researchers, fixed subsidies and funding for research equipment.

- **Ligue Contre le Cancer - LCC (French League Against Cancer)**

In 2007, the Ligue awarded €2.11 million to CLARA teams at the national level. Additional funding was awarded by local county committees of LCC.

Research application to industry

CLARA stands out from other cancer clusters in the amount of pluriannual funding it has been granted by local authorities from the beginning. This unique advantage has led to the cluster's strong emphasis on market development, which goes hand in hand with the aims of scientific excellence and public health improvements presented in the National Cancer Plan. For the past three years, CLARA's strategy has therefore focused part of its effort on developing marketable applications for the results of scientific research.

The **"Proof of Concept"** program launched by CLARA in 2005 aims to support high-potential innovative projects which bring together academics, clinics and industrial firms. Targeted projects aim to demonstrate the efficacy of new drugs, diagnostic products or technologies in animals or humans (pre-clinical or clinical phases). If successful, the project can then be continued by the industrial partner.

CLARA funding covers the related costs incurred by the academic partner, and at most may match the amount of funding provided by the industrial partner. Thus, the "Proof of Concept" program complements other sources of funding for innovative projects primarily geared to businesses (Oséo - Anvar, Research Tax Credit (CIR) and others).

Proof of Concept program in 2007

No new calls for projects for the Proof of Concept program were published in 2007, as all of the available funding (€2.5 million) had been allocated in 2005 and 2006.

Two projects selected in the September 2006 call for projects received their first funding and started in 2007:

- **A robot to assist in minimally invasive cancer surgery,** led by EndoControl and the TIMC-IMAG laboratory (UMR 5525 UJF & CNRS) in close collaboration with Grenoble University Hospital;
- **Treatment of hepatic metastases by focused ultrasound,** led by Edap TMS, Inserm Unit 556 and the Experimental Surgery Unit at Léon Bérard Cancer Center.

The 3rd project selected in 2006 should start in January 2008:

- **Hybrid nanosensors for multimodal imaging of cell tracking in cancer,** led by Nano-H and Animage in collaboration with CREATIS (UMR 5515, U630), GEMPPM (UMR 5510), LPCML (UMR 5620), Inserm Unit 449 and Inserm Unit 548.

These three projects account for a total of €939,000 in funding from CLARA and €1.11 million from industrial partners for the period 2007 – 2009.

"Proof of Concept: excellent program, to be maintained"

"Excellent effort at integrating the academic partners with the industrial partners"

INCa - June 2007

David Melodelima (Inserm U556)
and **Raphaël Varona** (Edap TMS)

Thus, the Proof of Concept portfolio featured seven active projects in 2007. These projects were closely tracked throughout the year. Ten Steering Committees brought together the academic and industrial sponsors of the projects, while representatives of the organizations responsible for marketing the results were occasionally involved. These meetings, held at key phases in the project ("Go / No Go"), helped to update the aims in a concerted manner based on difficulties experienced or opportunities presented. If necessary, the projects are reoriented towards alternatives enabling a positive return on the initial investment. The scheduling and duration of CLARA funding were also adjusted when required.

In all, CLARA contributed to these seven projects for a total of €780,000 during the year.

Prospects for marketable applications

It is too early to assess the impact of the Proof of Concept program, as the first projects will not be completed until late 2008 and late 2009. Nonetheless, after the first two years of operation, we can see that the program is highly rated by its partners. In addition, this program received a very positive assessment by INCa during the ProCan audit (see page 7).

CLARA support of the program has a definite impact on industrial R&D investments: partner firms promised to give €11 million on top of CLARA's €2.5 million in funding.

Moreover, it is interesting to note that six partner firms of the first Proof of Concept projects have reached significant growth milestones:

- **Nanobiotix:** Seed funding (March 2005), risk capital funding (€7 million, November 2006);
- **Genome Express*:** Acquired by Clinical Data (March 2006);
- **Innate Pharma:** Initial Public Offering (October 2006);
- **Erytech:** Risk capital funding (€12 million, December 2006);
- **OPi:** Acquired by EUSA ($175 million, March 2007);
- **EndoControl:** Fundraising (€1 million, January 2008).

We cannot claim that CLARA's support is the sole reason for these developments, but we are proud that the cluster assisted them during this period.

* The project in which Genome Express was a partner has been withdrawn due to a strategic re-orientation of the company after it was acquired by Clinical Data; thus, the project no longer appears in the current portfolio.

Extension of the program starting in 2008

With such a promising start, CLARA will continue and extend the Proof of Concept program in several areas starting in 2008, with a first call for projects planned for the 3rd Scientific Forum in March.

The extended Proof of Concept program will enable continued support, when necessary, for the most promising projects underway. This may involve finalizing a project which needs additional funding, or supporting its early move into the clinical phase.

In addition, the program must be able to initiate new projects with high potential for innovation and market success. Discussions with local authorities are underway in order to geographically extend support for projects to the entire Auvergne / Rhône-Alpes region. Less strict financial rules have also been proposed, in order to encourage the inclusion of start-ups, in particular those that operate a technological platform.

Projects which fit in with CLARA's top priority strategic focuses are particularly in demand, especially in the **"Infections and Cancer"** and **"Nanotechnology and Cancer"** focus areas, as part of close collaboration with the Lyonbiopôle competitive cluster and the Grenoble nanotechnology for life sciences cluster, respectively.

Cancer Nano Transfer

A variant of the Proof of Concept program named **"Cancer Nano Transfer"** has been developed in partnership with CEA/Léti in order to encourage the emergence of projects in the specific area of "Nanomedicine and Cancer". This program supports projects including teams of biologists / clinicians and teams of nanotechnology specialists, but not necessarily an industrial partner. All of these teams benefit from the same terms and conditions for funding.

The first pilot project to test the program has been identified. This project, named **GanglioTool,** aims to develop a tool for minimally invasive lymph node samples and to test it in the pre-clinical and clinical phase in the field of lymphoma and other mediastinal metastatic adenopathies.

Based on CEA/Léti and Inserm patents, the project includes the following partners:

Nanotechnology

- CEA-Léti/MINATEC, Department of MicroTechnology for Biology and Health, SBSC – *In Vivo* Components Laboratory, M.L. Cosnier

Toxicology

- Ecole des Mines de Saint-Etienne – Engineering and Health Center - LPMG, UMR CNRS 5148 – IFRESIS, IFR Inserm143, Prof. Bernache-Assollant and Prof. Cottier

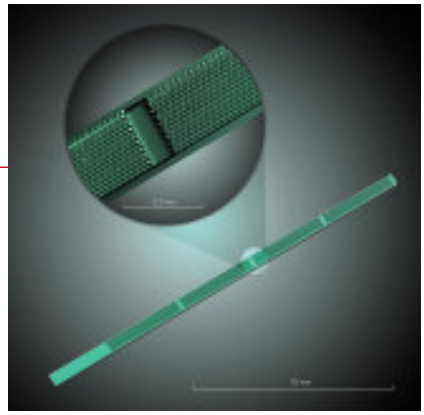
Pre-clinical

- Grenoble University Hospital, Unit 836 CRI Inserm GIN, team 7, Prof. F. Berger
- Lyon Civil Hospitals – South Lyon, Hematology Department, Prof. G. Salles

Clinical

- Lyon Civil Hospitals – South Lyon, Hematology Department, Prof. G. Salles
- Saint-Etienne University Hospital, Prof. Vergnon and Prof. Tiffet

After an in-depth assessment of the project by four independent auditors, and thanks to support from the Rhône-Alpes Regional Council, CLARA confirmed it would provide €250,000 to this project over a one-and-a-half-year period.



The GanglioTool concept

At hospitals and clinics, direct analysis of tissues and tumors is essential. Molecular analysis provides crucial information for diagnoses. Micro-invasive sampling would be an undeniable benefit to patient comfort. Moreover, it would enable analysis of tumors that are ever smaller when detected (infracentimetric) thanks to the sensitivity of today's imaging methods and screening policies.

Surgical node biopsy remains the gold standard for supracentimetric sampling in malignant lymphoma. However, several complex clinical situations (such as aged patients, biopsies performed outside the university hospital, patients in relapse, and deep masses in the thorax or abdomen) make this procedure difficult, and microbiopsy via scanner is then performed. Although the technical performance provides physicians with material generally suitable for morphological analysis, it does not provide the type of material required for cytogenetic (cell culture or FISH) or molecular (DNA and RNA) studies. However, these complementary studies appear to play an increasingly crucial role in making more precise diagnoses for lymphoma patients. Thus, the development of a technological tool to improve sampling quality is a great step forward.

Similar difficulties may be encountered for metastatic adenopathies, particularly at the mediastinal level, at the stage of diagnosis where mediastinoscopy is required, and during surgery on bronchopulmonary tumors (detection of the sentinel lymph node).

The portfolio of current Proof of Concept programs, as well as detailed information on the program and calls for projects can be found on the CLARA Website:
www.canceropole-clara.com

Prospects

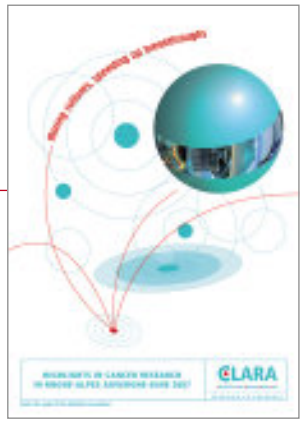
INTERNATIONAL PROSPECTS

A panorama of what makes Rhône-Alpes Auvergne cancer research so strong

At the end of June 2007, CLARA published **"Highlights in Cancer Research in Rhône-Alpes Auvergne",** the first panorama of the driving forces behind cancer research in Rhône-Alpes Auvergne.

This document is the result of an information-gathering and study project carried out in close collaboration with research institutes and healthcare facilities in Clermont-Ferrand, Grenoble, Lyon and Saint-Etienne. Although it is not exhaustive, the document clearly showcases the region's strengths in fundamental, clinical and translational research, along with its human and social science focus, in the field of cancer.
This new pillar of CLARA's communication campaign – a true map of the region's fields of excellence in cancer research – aims above all to promote the expertise and potential of Rhône-Alpes and Auvergne research teams and facilities to potential stakeholders around the globe. It is designed to highlight the region's specific know-how and attractiveness in order to expand its research horizons internationally.
Distributed in a large number of countries and to the directors of national institutes of cancer from around the world who met at IARC from July 11th-13th, Highlights in Cancer Research in Rhône-Alpes Auvergne clearly asserts CLARA's identity and raises awareness in the international scientific community.

This document can be downloaded at the CLARA website: www.canceropole-clara.com



Continued cooperation with Milan and Lausanne

In 2006, INCa offered to support CLARA collaborative projects with other cancer research clusters in Europe. Two projects were selected, and the programs were set up at the end of the year.

The first collaboration was initiated by Christian Brambilla, director of the Inserm/UJF U823 Research Center, with the team of Gabriella Sozzi of the Milan Tumor Institute, as part of the project entitled **"Validation of apoptosis and cell cycle parameters as biomarkers for lung cancer early detection".** The extension of this program to other CLARA teams will be discussed in the coming months, as the first period of INCa funding ends in November 2008.

The second collaboration was initiated by Patrick Mehlen, director of the CNRS Mixed Research Unit on "Apoptosis, Cancer and Development" at Léon Bérard Cancer Center / Lyon 1 University, with the team of Prof. Jurg Tschop at the University of Lausanne, as part of a project on **"The dependence receptor signaling pathway and colorectal tumor progression".**
This project is to be extended at the start of 2008, with the addition of other CLARA and Lausanne teams, thus enabling a new request for funding from INCa.

Preparing for FP7

CLARA is well aware that the European Union, through its calls for projects for the 7th Framework Program for Research and Technological Development, can be an important source of funding for Cancer research, as a complement to the funding available at the national and regional levels. Nonetheless, setting up European programs is a complex process. Furthermore, there are already European units in many institutions and in no way do we wish to compete with them.

Thus, in 2007 CLARA revamped its way of working in order to assist the region's teams in setting up European projects. There is no longer a specific person on the Network Management team dedicated to providing this support. However, we are in constant contact with an expert advisor to the European Commission, Paul Janiaud, in order to inform the network of any opportunities which may arise relating to the ProCan program. Financial aid to set up projects is also still possible, provided that these projects fall directly into one of the core focus areas that are now CLARA's top priority.

Closer relations between Rhône-Alpes and the Weizmann Institute of Science

Closer working relations with the Weizmann Institute in the field of Cancer were initiated in 2006, under the auspices of the Rhône-Alpes France-Israel Chamber of Commerce, the Rhône-Alpes Region, the Mérieux Foundation and Léon Bérard Cancer Center, with assistance from CLARA (see the CLARA Progress Report 2006, page 41).

In March 2007, a committee from the above-mentioned institutions identified five Rhône-Alpes teams interested in starting or developing relations with the Weizmann Institute. All of these teams are internationally renowned and come from a wide range of organizations (Léon Bérard Cancer Center, Lyon Civil Hospitals (HCL), Inserm, CNRS and Grenoble University Hospital), geographical locations (East Lyon, South Lyon and Grenoble), research topics (P53, dependence receptors, nanomedicine, epigenetics, and mathematical modeling) and research phases (from fundamental to translational clinical research).

In order to more thoroughly explore the potential for collaboration between teams from Rhône-Alpes and the Weizmann Institute, a scientific seminar was held at the Les Pensières conference center, in Veyrier-du-Lac, in July 2007.

At this conference, the Rhône-Alpes Region, the Weizmann Institute and CLARA signed a draft partnership agreement that outlines three areas for cooperation:

- Development of joint research projects, co-led by a researcher from CLARA and a researcher from the Weizmann Institute, with funding from CLARA and the Region;
- Joint scientific conferences, held alternately in France and in Israel;
- Exchanges involving researchers, physicians and students.

From left to right: **Robert Parienti,** Delegate General, Weizmann Institute of Science – **Thierry Philip,** Vice President, Rhône-Alpes Region – **Alain Mérieux,** President, Weizmann Europe Rhône-Alpes Delegation – **Haim Garty,** Vice President, Weizmann Institute – **Peter Pauwels,** Deputy Executive Director, CLARA
July 5th, 2007

CLARA hosts a Senegalese delegation

On April 26th, 2007 CLARA hosted a Senegalese delegation led by Mr Moussa Mbaye, Secretary General of the Ministry of Health and Medical Prevention.
This delegation spent one week in France to study the organization of the healthcare system and explore potential partnerships in the field of cancer.

Professor Jean-Marie Dangou, who coordinates Senegal's newly founded program to fight cancer, clearly expressed his desire to make use of CLARA's expertise to "speed up breakthroughs", as the cluster's slogan says, in his country. This cooperation could take the shape of assistance in implementing screening strategies and in developing primary prevention, one of the main focuses of Senegal's Cancer Plan.

As part of their visit to CLARA, members of the delegation visited the International Agency for Research on Cancer (IARC), where they saw a presentation on epidemiological studies and experiments with early detection carried out in emerging countries. The delegation also visited the radiotherapy department at Léon Bérard Cancer Center.

CLARA'S POSITIONING

At the end of 2006, CLARA launched a communication campaign based on a slogan - **"Mixing cultures, speeding up breakthroughs"** - and an object which symbolizes this action: the cocktail shaker (see the CLARA Progress Report 2006, page 43).

This campaign continued in 2007, with the shakers first appearing in posters, then materializing in the hands of CLARA members, partners and visitors.

Thus, when CLARA decided to start a newsletter, the publication was fittingly named **"SHAKER"**. The aim of this new promotional tool is to share the region's scientific advances with the players and partners of the network, to help them to better know one another, to detect new opportunities, and thus strengthen the network to help the fight against cancer.

People, projects, institutions, an environment (local, regional and international), actions, interactions, relations… these are the ingredients put into two issues of Shaker, in June and September 2007.

CHANGING THE IMAGE OF CANCER

In 2007, CLARA headed down a new path with a communication campaign for the general public in order to show cancer in a less dramatic light and break down taboos on the topic.

Indeed, seven Lyon cancer research organizations – CLARA, the International Agency for Research on Cancer, Léon Bérard Cancer Center, CNRS, Lyon Civil Hospitals, Inserm and Claude Bernard Lyon 1 University – came together to provide the general public an educational exhibit that brings new hope.

The Journey of a Troubled Cell aims to show the leads explored by researchers, particularly in Lyon, in fighting the disease. Through a journey in which a normal cell becomes a cancerous cell, it provides answers to questions such as "How does a cell function?", "How does a cell become cancerous?" and "What are we doing to prevent this?"

The main character, Lady Cell, helps the general public to understand the world of cells, the various harmful events leading to cancer and how defective cells can be spotted and repaired. At each step, she explains the methods used by researchers and physicians to identify the risk factors, to prevent any dysfunctions as soon as possible or to eliminate any cells that have become abnormal. At the same time, she shows what research is doing to support patients in their fight against the disease.

This exhibit was presented from April 17th to 28th at the Bachut Marguerite Duras Media Center, and from May 3rd to 31st at the Bullukian Cultural Forum. Designed as a traveling exhibit, it can be displayed at organizations that wish to host it. For more information, contact CLARA.

Action plan for 2008

The CLARA roadmap has both national and regional implications. At the national level, it is part of the new dynamism sparked by the ProCan process. At the regional level, it lays the foundations for the cluster's strategic vision for the future.

These joint processes must be conducted in a way which helps to set coherent, complementary goals, ensure the efficiency and impact of the funding, and incorporate in-the-field realities and acquired experience, all with the aim of bringing new teams into the CLARA network and serving the advancement of INCa policy.

In 2008, the strategy to build and energize the CLARA network will involve:

- Intensifying cooperation with the Léa & Napoléon Bullukian Foundation in order to make CLARA's governance and Network Management as efficient as possible.
- Implementing the collective strategy, concentrating on priority focus areas while moving forward in the ProCan program and strengthening relations with centers of excellence in the region.
- Promoting research by improving the number and quality of submissions to national and European calls for projects.
- Strengthening the role of private firms within CLARA for greater cooperation with academic players.
- Maximizing the marketability of the cluster's research results by launching two new calls for projects for the "Proof of Concept" and "Cancer Nano Transfert" programs.
- Boosting the international exposure of the Rhône Alpes / Auvergne cancer research cluster.

This strategy will be implemented in 2008 via four operational mechanisms:

1. The network's scientific coordination and organization of the region's research.
2. Incentive and support for research projects, in particular through the building of core programs.
3. Support in bringing the cluster's research results to market.
4. Promoting the region's research potential and expertise in the field of cancer.

Appendix
Funding obtained and allocation

SUMMARY OF THE MULTI-YEAR SCHEDULING OF THE CLARA PROGRAM, 2003-2007

Note: The financial information presented in this report was not audited by the statutory auditor prior to publication.

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

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

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RÉPUBLIQUE FRANÇAISE

Amount in thousands of €	2007					Total	
Recipient (funding)	Investment		Operation		Total paid	Overall total approved 2003-2007	Overall total paid 2003-2007
	Approved	Paid	Approved	Paid			
High-field NMR - CNRS (MENRT)	-	-	-	-	-	9,000	9,000
Emerging cancéropôles (MENRT) (1)	-	-	-	-	-	4,769	4,769
INCa calls for projects (INCa) (2)	-	-	5,520	2,061	2,061	14,070	8,568
Proof of Concept (DRRT RA)	-	-	-	-	-	37	37
Biological Resource Center (CRB) (FNADT RA)	-	-	-	-	-	108	108
Lyon Civil Hospitals for Biological Resource Center (Ministry of Health)	-	-	-	-	-	1,027	1,027
Network Management (FNADT RA)	-	-	-	-	-	216	216
Network Management (INCa)	-	-	1,400	613	613	2,100	1,313
ProCan focus areas (INCa)	-	-	2,550	765	765	2,550	765
Total	-	-	9,470	3,439	3,439	33,877	25,803

(1) Estimated amount
(2) The figures given are for the amounts allocated to scientific projects selected as part of calls for projects in 2007 (not including PHRC and STIC). These sums will be paid over several years.
At the time this report was published, the results of the Young Researchers call for projects were not yet known.

RhôneAlpes Région

Amount in thousands of €	2007					Total	
Recipient (funding)	Investment		Operation		Total paid	Overall total approved 2003-2007	Overall total paid 2003-2007
	Approved	Paid	Approved	Paid			
Grenoble University Hospital	360	-	-	-	-	1,708	1,004
Joseph Fourier University Grenoble	360	-	-	-	-	2,323	957
Inserm Grenoble	-	-	-	-	-	453	404
Subtotal Grenoble	**720**	**-**	**-**	**-**	**-**	**4,484**	**2,365**
Saint-Etienne University Hospital	-	-	-	-	-	410	67
High-field NMR - CNRS	1,500	450	-	-	450	8,500	7,450
Proof of Concept	-	-	-	-	-	260	260
Cancer Nano Transfer	-	-	250	-	-	250	-
Network Management	-	-	520	260	260	2,404	1,724
Total	**2,220**	**450**	**770**	**260**	**710**	**16,308**	**11,867**

RHÔNE
LE DÉPARTEMENT

Amount in thousands of €	2007					Total	
Recipient (funding)	Investment		Operation		Total paid	Overall total approved 2003-2007	Overall total paid 2003-2007
	Approved	Paid	Approved	Paid			
Léon Bérard Cancer Center - East Lyon	-	-	-	-	-	7,500	2,500
IARC	-	-	600	400	400	600	400
Network Management	-	-	-	-	-	1,651	1,651
Total	**-**	**-**	**600**	**400**	**400**	**9,751**	**4,551**

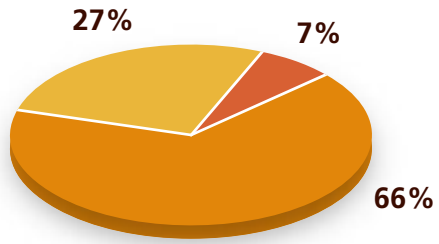
GRANDLYON communauté urbaine

Amount in thousands of €	2007					Total	
Recipient (funding)	Investment		Operation		Total paid	Overall total approved 2003-2007	Overall total paid 2003-2007
	Approved	Paid	Approved	Paid			
Lyon Civil Hospitals	-	-	-	-	-	8,500	5,600
IARC	-	-	-	-	-	500	500
High-field NMR	-	-	-	-	-	2,350	2,350
Proof of Concept	-	-	1,140	912	912	2,040	1,812
Network Management	-	-	500	400	400	1,464	1,320
Total	**-**	**-**	**1,640**	**1,312**	**1,312**	**14,854**	**11,582**

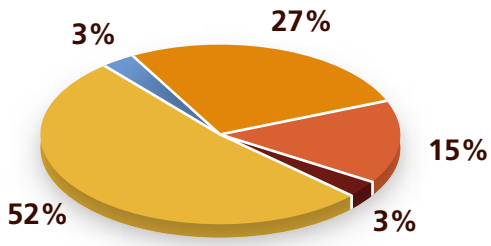
SAINT-ETIENNE métropole

Amount in thousands of €	2007					Total	
Recipient (funding)	Investment		Operation		Total paid	Overall total approved 2003-2007	Overall total paid 2003-2007
	Approved	Paid	Approved	Paid			
Saint-Etienne Platform	1,697	-	-	-	-	1,697	-
Total	**1,697**	**-**	**-**	**-**	**-**	**1,697**	**-**

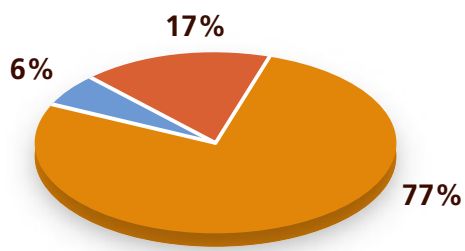
Allocation of the funds approved by the main funding providers during the period 2003/2007



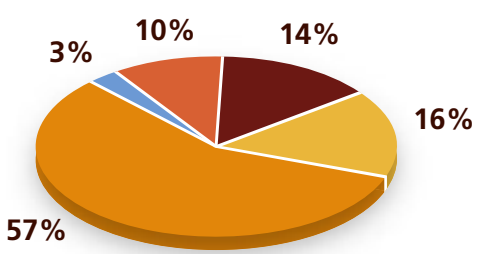
State



Rhône-Alpes Region



Rhône County



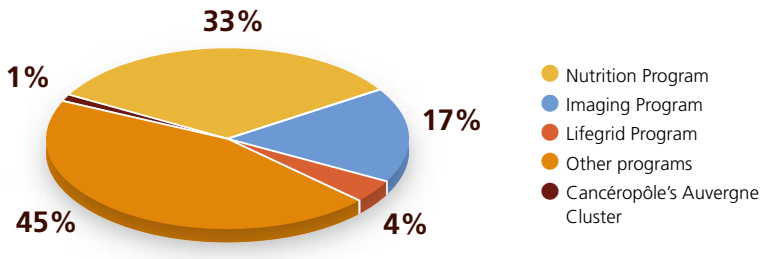
Greater Lyon

Status of the main sources of funding in the Auvergne area

Amount in thousands of €	2007					Total	
Funding	Investment		Operation		Total paid	Overall total approved 2005-2007	Overall total paid 2005-2007
	Approved	Paid	Approved	Paid			
Massif Central ERDF (1)	-	-	-	-	-	945	171
Region ERDF	-	-	-	-	-	720	-
Massif Central FNADT	-	-	-	-	-	505	180
Auvergne Region	-	-	550	-	-	1,355	639
Clermont Community	-	-	110	-	-	245	-
Puy-de-Dôme County	-	-	-	-	-	100	23
Allier County	-	-	-	-	-	50	-
Cantal County	-	-	-	-	-	40	40
Haute-Loire County	-	-	-	-	-	40	40
Total	-	-	660	-	-	4,000	1,093

(1) Massif Central ERDF covers Auvergne and Loire County (42).
Source: Auvergne University – 28/01/08

Allocation of the funds granted during the period 2003/2007

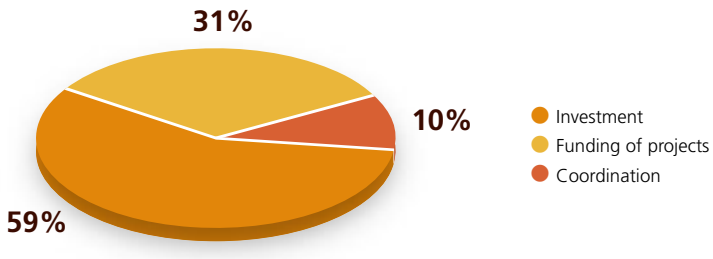


OVERALL ORIENTATION OF FUNDING BY TYPE OF OPERATION

In thousands of €			
Type of operation	**Breakdown**	**2007**	**Overall 2003-2007**
Investment	Lyon Civil Hospitals	-	8,500
	Léon Bérard Cancer Center	-	7,500
	Grenoble Platform	720	4,484
	Saint-Etienne Platform	1,697	2,107
	IARC Platform	600	1,100
	Auvergne Platform	660	4,000
	High-field NMR – CNRS	1,500	19,850
	Total	5,177	47,540
Funding of projects	Emerging cancéropôles + INCa*	5,520	18,839
	ProCan focus areas (INCa)	2,550	2,550
	Proof of Concept projects	1,140	2,337
	Cancer Nano Transfer projects	250	250
	Biological Resource Center	-	1,135
	Total	9,460	25,111
Coordination	Network Management	2,420	7,835
	Total	2,420	7,835

* Estimated amount

Orientation of funding during the period 2003-2007



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CLARA
CANCÉROPÔLE LYON AUVERGNE RHÔNE-ALPES
SPEEDING UP PROGRESS

Under the aegis of the Bullukian Foundation