INSTITUT NATIONAL DU CANCER

CANCÉROPÔLE

LYON AUVERGNE RHÔNE-ALPES

sous l'égide de la Fondation L&N Bullukian

Progress Report 2005

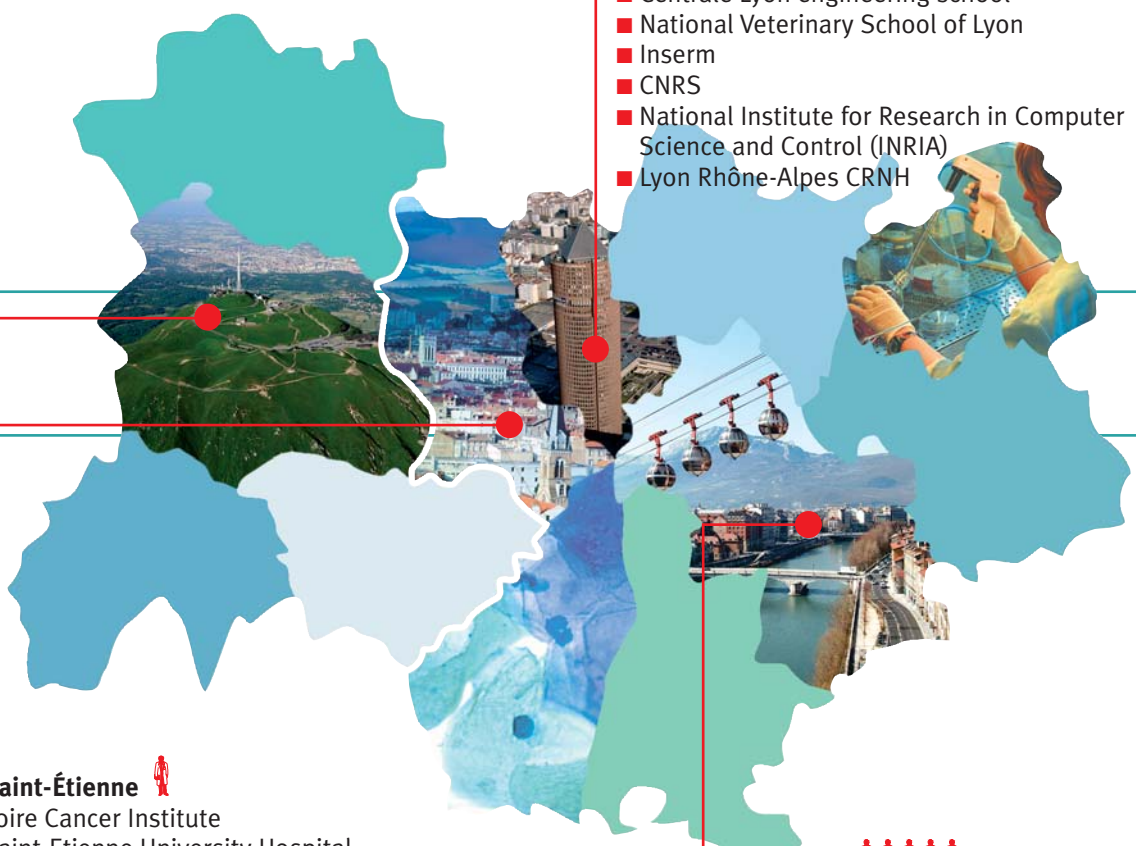
Key players in cancer research in the Rhône-Alpes and Auvergne regions

Clermont-Ferrand

- Jean Perrin Cancer Center
- Clermont-Ferrand University Hospital
- Clinical Investigation Center (CIC)
- Auvergne University
- Blaise Pascal University
- National Institute for Health and Medical Research (Inserm)
- National Scientific Research Center (CNRS)
- INRA Agronomics Research Institute
- Auvergne Human Nutrition Research Center (CRNH)

Lyon

- International Agency for Research on Cancer (IARC)
- Léon Bérard Cancer Center
- Lyon Civil Hospitals (HCL)
- Clinical Investigation Center
- French Blood Institute (EFS Rhône-Alpes)
- Positon Emission Medical Research Center (CERMEP)
- Rhône-Alpes Thyroid Cancer Registry
- Platform for Assistance in Clinical Research on Cancer - Auvergne Rhône-Alpes
- Claude Bernard Lyon 1 University
- Ecole Normale Supérieure de Lyon graduate school
- INSA Lyon engineering school
- Centrale Lyon engineering school
- National Veterinary School of Lyon
- Inserm
- CNRS
- National Institute for Research in Computer Science and Control (INRIA)
- Lyon Rhône-Alpes CRNH



Saint-Étienne

- Loire Cancer Institute
- Saint-Etienne University Hospital
- Clinical Investigation Center (CIC)
- Jean Monnet University
- Ecole Nationale Supérieure des Mines de Saint-Etienne engineering school
- Inserm
- CNRS

Grenoble

- Grenoble University Hospital
- Clinical Investigation Center (CIC)
- EFS Rhône-Alpes
- Joseph Fourier University
- Inserm
- CNRS
- French Atomic Energy Commission (CEA)
- INRIA
- Isère Cancer Registry
- Albert Bonniot Institute
- Structural Biology Institute
- Biological Investigation Center

Relative importance of the biopharmaceutical industry

This is the first complete Cancéropôle Lyon Auvergne Rhône-Alpes progress report. It shows that CLARA became fully operational in 2005, under the impetus of both the French National Cancer Institute, in charge of steering the Cancer Plan, and the local authorities of the Auvergne and Rhône-Alpes regions.

A new momentum is building.

A momentum driven by the network, gathering strength from the energy and commitment of each of the public and private organizations that make up CLARA. These stakeholders express not only their specific interests, which is to be expected, but also a shared desire to produce collective results which go far beyond individual initiatives.
This momentum also involves transformation: the potential power of this network lies in its capacity to establish a set of common practices and create abundant opportunities for cooperation and innovation.

Thanks to this momentum, CLARA aspires to rank among Europe's leading research clusters. In order to achieve this, however, it must also be carefully monitored, in a transparent, collegial and diligent manner.

These are but the first of CLARA's achievements. The roadmap for 2006/2007 is aggressive, yet realistic. We still have a very long way to go, but researchers, whether they have already joined the CLARA initiative or are preparing to take part, all share a common aim: to make a significant contribution to fighting the scourge of cancer, for the benefit of patients.

Mireille Guigaz, Executive Director
Jean-Yves Blay, Yves-Jean Bignon, Scientific Directors
Jean-Luc Balzer, Director Industrial Development and Programs

editorial

1

Voici la première livraison d'un rapport d'activités complet du Cancéropôle Lyon Auvergne Rhône-Alpes.
Il témoigne que 2005 a vu s'accomplir la phase d'émergence du CLARA, sous la double impulsion de l'Institut National du Cancer, chargé de piloter le Plan Cancer, et des collectivités territoriales de l'inter-région Auvergne/Rhône-Alpes.

Une dynamique nouvelle est née.

C'est une dynamique de réseau. Elle puise ses forces dans la bonne volonté, l'énergie et l'engagement de chacune des mailles constitutives du CLARA, publiques et privées, chacune exprimant, comme c'est normal, ses intérêts et ses objectifs, mais également la volonté de produire une résultante allant bien au-delà des initiatives individuelles.

C'est une dynamique de transformation : ce maillage est potentiellement puissant par sa capacité de mise en cohérence et de création de très nombreuses opportunités de coopération et d'innovation.

Grâce à cette dynamique, le CLARA peut espérer se positionner parmi les clusters de recherche à taille européenne. Cependant, pour ce faire, il faut également qu'il soit réellement monitoré, dans la transparence, la collégialité et la rigueur.

Le CLARA n'en est qu'au début de ses réalisations. Sa feuille de route pour 2006/2007 est volontariste, mais néanmoins réaliste. Certes, le chemin à parcourir est encore long, mais les acteurs de la recherche, qu'ils soient déjà engagés dans la démarche CLARA ou prêts à se mobiliser, ont tous en commun une finalité majeure : contribuer sensiblement à la réduction de ce fléau qu'est le cancer, au bénéfice du patient.

Mireille Guigaz, Déléguée Générale
Jean-Yves Blay, Yves-Jean Bignon, Directeurs Scientifiques
Jean-Luc Balzer, Directeur du Développement Industriel et des Programmes

Contents

Sommaire

Setting goals

Under the dual impetus of state and local authorities

⊙ **2001:** Political leaders from the Rhône-Alpes region decide to invest their energy in tackling a major public health issue and opt for cancer research.

⊙ **July 14th, 2002:** French President Jacques Chirac makes the fight against cancer one of the three main priorities for his second term.

⊙ **March 24th, 2003:** The French Cancer Plan (2003-2007) is launched, led by the Ministries of Health and Research. This nationwide mobilization plan features 70 measures, 5 of which focus on research.

Aims of the Cancer Plan in the area of Research:

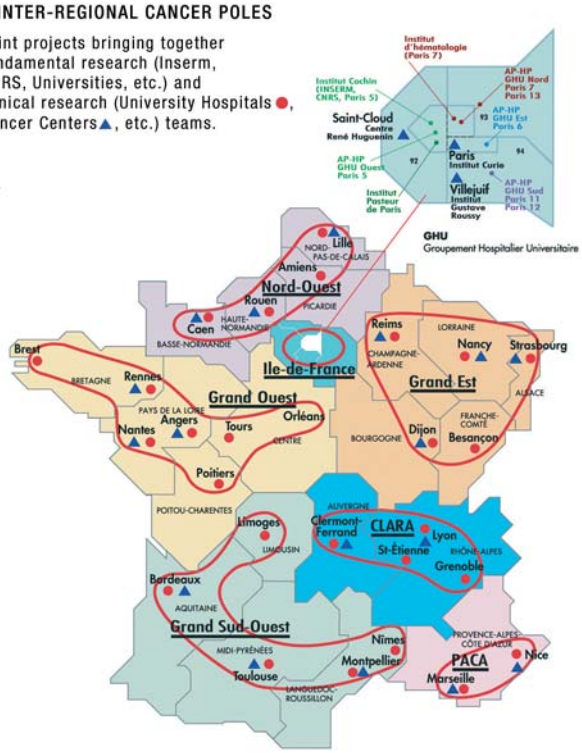
Providing oncology research with new impetus and improved coordination. Ensuring it meets the highest international standards, in particular in new fields stemming from the genomic revolution as well as in social sciences and economics. Specific aims include:

- **Identifying "Cancer Poles" at the regional or inter-regional level, to ensure a care-to-research continuum from patient back to patient, linking reference hospitals to certified research units.**
- **Developing, in particular through the National Cancer Institute, a program-based research policy encouraging partnerships between public and private sector research.**
- **Fostering the emergence of world-class sites and developing international cooperation, in particular within Europe.**

4 Building

7 INTER-REGIONAL CANCER POLES

Joint projects bringing together fundamental research (Inserm, CNRS, Universities, etc.) and clinical research (University Hospitals ●, Cancer Centers ▲, etc.) teams.



Cancéropôle Grand Est : Alsace, Bourgogne, Champagne-Ardenne, Franche-Comté, Lorraine • **Cancéropôle Grand Ouest** : Bretagne, Centre, Pays-de-la-Loire, Poitou-Charentes • **Cancéropôle Grand Sud-Ouest** : Aquitaine, Languedoc-Roussillon, Limousin, Midi-Pyrénées • **Cancéropôle IDF** : Ile-de-France • **Cancéropôle Nord-Ouest** : Basse-Normandie, Haute-Normandie, Nord-Pas-de-Calais, Picardie • **Cancéropôle PACA** : Provence-Alpes-Côte d'Azur • **Cancéropôle CLARA** : Lyon, Auvergne, Rhône-Alpes.

The Cancer Plan resulted in the creation of 7 regional or inter-regional Cancer Poles ("cancéropôles"), including CLARA.

⊙ **August 9th, 2004: Public health law to create the French National Cancer Institute (INCa).**

In the Rhône-Alpes / Auvergne area, CLARA drives the policy set out by the National Cancer Institute. At the same time, the Cancéropôle has developed its own unique ambitious strategy for economic development based on scientific research. In this way, CLARA's efforts serve a twofold purpose: to provide cancer patients faster access to resources to help fight their disease and to boost the region's economic development via the creation of a highly attractive research cluster.

Defining a roadmap for 2005/2007

CLARA's overall strategy was set out by the Steering Committee at its November 29th, 2004 meeting. In the first months of 2005, the new management team began to implement this strategy. The management's main aims are to prioritize, organize and coordinate the setting up of CLARA's platforms and programs, and to position the Cancéropôle so that it is competitive at the regional, national and European levels.

The roadmap for 2005/2007 was built step-by-step and with great care concerning the main focuses.

The process had three main steps:

I. A precise analysis of the Scientific Advisory Board's recommendations, and an in-depth interview with its President, Christian Bréchot, Managing Director of Inserm;

II. A survey conducted by Ernst & Young, in close collaboration with the Network Management team, given to twenty members of the Guidance Board;

III. A discussion phase, with the participation of the Network Management team and CLARA's two scientific directors, led by a consultant from the EM Lyon School of Management.

This roadmap was approved by the Guidance Board on July 6th, 2005. It features 5 strategic actions:

1. Building platforms and management on a program-by-program basis

This top priority action for 2005 aims to highlight CLARA's research potential to the greatest possible extent, to encourage many high quality partnerships between the academic and industrial spheres, to report on how the funding is being used and to ensure its continuity.

The Network Management commissioned a consulting firm specialized in the management of complex programs, Algoé Consultants, to lead this organization phase. Thanks to the involvement of the platform managers and industry representatives, an efficient monitoring system will be operational in February 2006.

(See page 18 - Close monitoring of platforms and projects)

2. Developing an integrated cross-platform project, focusing on CLARA's top scientific know-how and aiming to be a leader in Europe.

This key program will include other European research teams, will be built around strategic partnerships with firms and will rely on CLARA's Biological Resource Center *(see page 34)*.

In 2005, a map of CLARA's scientific know-how, with a European benchmark, was built with the help of TecKnowMetrix, a Grenoble start-up firm, and the active contribution of CLARA's scientific experts.

(See pages 36 to 37 - Identification of CLARA's joint fields of excellence)

3. Economic development through innovation in oncology.

This aim will be met through optimal implementation of the platforms and programs, through the large-scale integrated cross-platform project and, more specifically starting in 2005, through the Proof of Concept program *(see pages 32 to 33)* and scientific leadership bringing together the industrial and academic spheres *(see pages 20 to 22)*.

4. European ambitions.

CLARA's European ambitions will take strength from the large-scale project and the search for European partner teams and European financing.

The CONTICANET project, a European network of excellence on sarcoma coordinated by CLARA, is the first concrete example of this *(see page 35)*.

5. Strengthening of relations with the National Cancer Institute.

CLARA researchers will be encouraged to actively participate in INCa working groups in order to build its strategy, and the Cancéropôle will make a clear commitment to the priorities chosen by the Institute.

(see page 22 - Integration of CLARA members into the work carried out by INCa)

Organization

Obtaining subsidies from various funding sources

CLARA benefits from a significant level of primarily public funding, which comes from the French state and from local authorities in both regions.

Local funding sources

In the framework of the State-Region development plan, €45 million in funding will be allocated to CLARA in order to equip its platforms for the period 2004 - 2007. Of this total, the Rhône-Alpes region, the Rhône *département* (county) council and the Greater Lyon Urban Community will each provide €15 million. The local authorities of the Auvergne region, using a simple calculation based on the number of researchers, decided to grant approximately €10 million to CLARA for the same period.

This funding will be used both for operating costs, in order to support programs and projects, and for investments in the Clermont-Ferrand platform.

This situation is exceptional compared to France's other Cancer Poles, thanks to the high level of subsidies granted, in particular those earmarked for investment.

The motivations of the local funding providers are clear. The aim is to promote research to benefit cancer patients by speeding up the transfer of knowledge and discoveries from the scientific world to the business sphere so that new treatments can be used more quickly.

In this way, it also aims to promote economic development, to encourage the founding of new firms and to boost employment. This is perfectly consistent with the mission of these local authorities.

CLARA wants the local authorities, so deeply committed to the project, to be proud of the results obtained and to be encouraged to continue their support for the fight against cancer via the Cancéropôle.

The French state

The French state, both at the central level of the National Cancer Institute and at the decentralized level, through various funds (FNADT), is another of CLARA's major funding providers.

The National Cancer Institute (INCa), through its operating subsidies, supports CLARA's Network Management in running and coordinating the network. Six of France's Cancer Poles were granted €250,000 each.

The seventh, the Cancéropôle Ile-de-France, the biggest of the Cancer Poles, was given a larger amount. CLARA devoted a large part of its 2005 subsidy to its Biological Resource Center project *(see page 34)*.

Nevertheless, INCa's primary function, as regards the research aspect of the Cancer Plan, is to encourage the emergence and funding of new projects in specified areas of research. Like all large research organizations, it does this via calls for projects, using a competitive procedure to select projects from throughout the country that have been assessed and approved from a scientific standpoint.

In this framework, the funding acquired by each Cancéropôle is based on the capacity of its research teams to mobilize and participate in the calls for projects within the allotted time frames, as well as on the quality of the projects presented. In 2005, CLARA ranked third among France's Cancéropôles, behind Ile-de-France, and practically on par with the Cancéropôle PACA *(see pages 27 to 31 - Projects started in 2005 as part of INCa's call for projects)*. The aim is to improve, but not simply by moving up in the ranking. CLARA strives to encourage innovation and truly multidisciplinary and cross-platform projects enabling the Auvergne and Rhône-Alpes teams to gain increased renown at the European level.

⊙ Private funding

One of CLARA's stated aims is to bring in private funding alongside the high level of public financing it has already acquired. These additional resources will be entirely devoted to developing projects of all sizes, enabling the human and technological resources from the public and private spheres to work together more closely and more consistently than they do today.

In 2005, the efforts made to bring in this funding were insufficient in view of the priorities that had been specified.

Nevertheless, CLARA has made substantial efforts in the search for funding, by mobilizing the members of its Business Club *(see page 20)* - in particular the Board of this Club - and through excellent projects that have already been set up (*see page 31)*.

CLARA

7

⊙ Funding for operating costs and human resources by institutional partners

Funding in the form of subsidies earmarked for investments in equipment and projects do not account for all of the financial resources circulating within the CLARA network.

It will be essential to determine the value of resources contributed by partners, in particular the human resources allocated to CLARA projects and programs. CLARA did not focus on this aspect in 2005, but plans to do so in 2006.

See the "Funding and allocation" section on pages 38 to 43.

Inter-regional collaboration

THE INTEGRATION OF AUVERGNE WAS PLANNED WHEN THE 7 CANCÉROPÔLES WERE BUILT AS PART OF THE CANCER PLAN. THIS INTEGRATION, AN EXPRESS REQUEST OF AUVERGNE'S LEADERS IN CANCER RESEARCH, HAS BEEN A COMPLETE SUCCESS.

● GRENOBLE

Auvergne has from the very start been fully incorporated into the Cancéropôle, which is now known as "Cancéropôle Lyon Auvergne Rhône-Alpes" or "CLARA". There is one Network Management team, one Scientific Advisory Board, one Guidance Board, shared operating guidelines and joint projects that include teams from both the Auvergne and Rhône-Alpes regions. Indeed, this full integration seemed to be the best means to encourage the development of a joint scientific policy based on excellence and the close collaboration of research teams on cross-platform projects in a variety of subject areas.

However, day-to-day, in the field management of the Auvergne partners is carried out by a special team named "PAC" (Pôle Auvergne du Cancéropôle), based in Clermont-Ferrand and headed by Professor Yves-Jean Bignon.

8 Building

The four Auvergne *départements* (counties) - Allier, Cantal, Haute-Loire and Puy-de-Dôme - the Auvergne Regional Council and Clermont Metropolitan Community provided their first financial support to CLARA in 2005 *(see page 39)*.

Uniting the cancer research leaders in the Auvergne and Rhône-Alpes regions is part of a larger movement. Thus, Auvergne's State Regional Strategic Action Project (PASER) calls for "the identification of fields of research, higher education and cutting edge technology in which Auvergne can form partnerships with Rhône-Alpes in order to join a national and European network of centers of excellence." Political leaders from both regions often cite CLARA as the perfect example of a successful partnership, with advantages for both parties, which should inspire new cooperative ventures in other fields.

● CLERMONT-FERRAND

Quotes...

Brice Hortefeux, Deputy Minister from the Ministry of the Interior and Regional Development in charge of Local Authorities, and Regional Councilman from Auvergne:

"CLARA is the fruit of a partnership between Lyon, Auvergne and Rhône-Alpes. Auvergne will play an important role in this network by contributing its expertise on human nutrition and the risk of cancer."

Jean-Pierre Lacroix, Prefect of the Rhône-Alpes Region and coordinator of the Inter-regional and European Cooperation Study and Development Mission (M.E.D.D.C.I.E.) for Rhône-Alpes, Provence Alpes Côte d'Azur, Languedoc-Roussillon, Auvergne and Corsica:

"The contribution of Clermont-Ferrand and the Auvergne Region has helped to create a cluster that complements Lyon's. Clermont-Ferrand's "nutrition and cancer" cluster is supported by agribusiness firms whereas the Lyon and Saint-Etienne clusters focus on genomics and pharmacological biology. Clermont-Ferrand has thus brought in complementary scientific expertise and funding."

Michel Mercier, Senator of the Rhône County, President of the Rhône County General Council:

"The Cancéropôle is indeed proof that the Auvergne and Rhône-Alpes regions are capable of sharing their resources and assets in terms of hospitals, scientists and research. This will inspire us to consider other types of cooperation."

In Prospective Rhône-Alpes-Méditerranée - Special Issue - December 2005

CLARA

● Lyon

● Saint-Étienne

Building a relationship with the Bullukian Foundation

Fondation reconnue d'utilité publique

⊙ The Foundation as a parent organization

At its November 29th, 1994 meeting, after examining the results of a call for proposals it had sent out several months beforehand, the Cancéropôle's Steering Committee decided to place CLARA under the aegis of a parent organization, the Léa and Napoléon Bullukian Foundation.
The Bullukian Foundation, a "public interest" organization since October 23rd, 2003, has three specific missions:

- Providing assistance to the Armenian community,
- Providing support for the arts,
- The fight against cancer.

The Foundation serves as CLARA's parent organization as part of this final mission.

The details of the Foundation's role as CLARA's parent organization were specified by the Foundation's Board of Directors at its January 5th, 2005 meeting:

CLARA is a "specific account (public funds) managed by the Bullukian Foundation, without its own legal status." The Board of Directors appointed Ms. Mireille Guigaz as Executive Director of the Cancéropôle within the Foundation. Her mission is to head the "Network Management" team, coordinate the Cancéropôle's activities and, by delegation of the Foundation's President, manage CLARA's separate bank account.

For purposes of reciprocity, the President of the Foundation, Jean-Pierre Claveranne, is a member of CLARA's Guidance Board.

⊙ Financial relations

From a financial standpoint, under the terms of the Bullukian Foundation's role as parent organization, two bank accounts have been opened in CLARA's name at the Crédit Lyonnais bank. These accounts appear in the Foundation's accounting. The first account is a current account, managed directly by CLARA's Executive Director. The second is a treasury account entrusted to the Foundation and managed according to the legal stipulations of prudence and transparency required of any "public interest" foundation.

During the first six months of 2005, while waiting for the subsidies granted by public organizations and local authorities to be transferred to CLARA's account, the Foundation advanced funds, thus enabling the Cancéropôle to begin its operations. As soon as the first subsidies were received, the Foundation was paid back in full.

● Léa and Napoléon Bullukian

La Malmaison, headquarters of the Bullukian Foundation

The Cancéropôle's budget and accounting operations are examined annually by the Léa and Napoléon Bullukian Foundation's Auditor for certification, and then presented to the Foundation's Board of Directors for approval. CLARA's Executive Director is closely supported by the Foundation's accounting firm. This firm is required to produce all of the required accounting documents, from account books to the balance sheet, to the trading account of assets and liabilities. These documents, once certified by the Auditor, are then submitted to the members of CLARA's Finance Committee. The Cancéropôle is thus managed similarly to a private sector firm.

CLARA

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Human resource management

The Cancéropôle's Network Management does not have any specific expertise in the legal management of human resources. The employees of the Network Management are private sector employees, with the exception of the Executive Director, who is a civil servant in a secondment position.

The legal aspect of employee contracts is handled by the Lamy law firm, which also manages the contracts of the Foundation's own employees. The work contracts are verified by the firm, ensuring that they strictly comply with the French Labor Code. These contracts are signed by the President of the Bullukian Foundation, acting as the employer.

In all, management costs for the arrangement in which the Bullukian Foundation serves as CLARA's parent organization accounted for €62,427 in 2005, i.e. 1.4% of the Network Management's total expenses.

This procedure, thanks to its flexibility and responsiveness, as well as to the trusting relationship built between the Network Management and the Foundation, enabled CLARA to emerge smoothly from both a financial and operational standpoint.

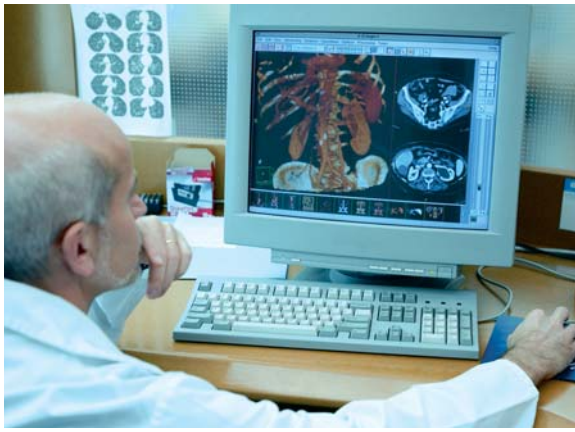
The question remains as to the advantage and/or need to give CLARA its own legal status. This is not specific to CLARA. All of the Cancéropôles are required to have a legal status. INCa has requested that they set up as Public Interest Groups (GIPs). This subject is to be addressed in 2006. CLARA has commissioned a legal study for this purpose.

Setting up governance bodies

Operational governance...

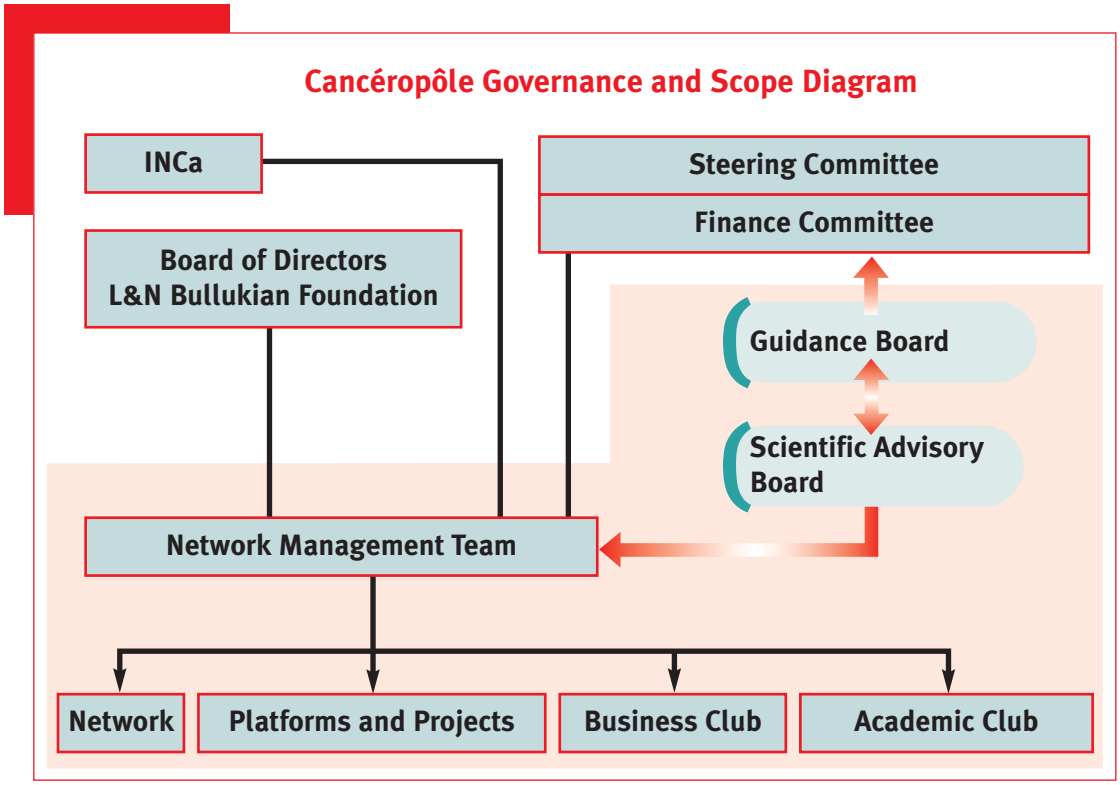
Under the authority of its parent organization, the Léa and Napoléon Bullukian Foundation, CLARA's organization and operation have been determined by internal regulations that specify the nature, missions and responsibilities of the network's various governance bodies.

These internal regulations were approved by CLARA's Guidance Board at its first meeting on July 6th, 2005, and by the Steering Committee on September 16th.



The governance chart was designed to meet specific aims:

Scientific excellence	THE SCIENTIFIC ADVISORY BOARD
Effective participation of parties involved	THE GUIDANCE BOARD
Integration of academic and business interests	THE BUSINESS CLUB THE ACADEMIC CLUB
Consistency and monitoring	THE NETWORK MANAGEMENT



CLARA

... WHICH CAN BE ADAPTED TO THE REALITIES AND ACTIONS IN THE FIELD...

The Cancéropôle's emergence phase is thus completed, but this does not mean that the network's organization is set in stone.

In our daily activities, we can already see several changes that can or should be made, such as:

- A visibly closer relationship between the Business Club and the Academic Club,
- Enlarging the Scientific Advisory Board to include a representative from the business sphere.

... BUT WHICH IS ALREADY AN EFFECTIVE ORGANIZATION

All of CLARA's governance bodies met during 2005 and deliberated and/ or made decisions and recommendations on subjects within their scope of competence:

- The Finance Committee: **March 21st and September 13th**
- The Scientific Advisory Board: **March 25th**
- The Guidance Board: **July 6th**
- The political Steering Committee (inter-regional government monitoring body): **September 16th**

Focus on recommendations...

● from the Scientific Advisory Board:

- To use a standard format for presenting projects, including the CVs of the main investigators;
- To set up and lead cross-platform projects based on the technological platforms financed by local authorities and present them at upcoming sessions of the Scientific Advisory Board;
- To continue developing the method for setting up the network research activity;
- To give a detailed presentation on allocation of resources to platforms and projects;
- To define the chosen strategy to provide the platforms with the human resources required for their projects;
- To standardize the procedures for the Biological Resource Center and better define its aims;

For the Proof of Concept program:

- To schedule competitive calls for projects, assessed externally, 2 to 3 times per year, in order to have a total of approximately ten projects supported simultaneously, with a budget of €300,000 each;
- To standardize the procedure for selecting assessors.

● from the Guidance Board:

- To encourage transparency, dialog, collaboration and cooperation between all of the Cancéropôle's stakeholders, in order to make it more efficient;
- To promote synergy with other large-scale life sciences projects underway in the Rhône-Alpes and Auvergne regions.

Building

● The Scientific Advisory Board

Building the Network Management Team

CLARA's small management structure was set up step-by-step between January and November 2005.

The Network Management missions are as follows:

- To provide impetus to the scientific strategy and build projects and programs based upon it,
- To lead and coordinate the stakeholders,
- To ensure everyone's access to financial resources,
- To report to funding providers on how financial resources are being used and assess the programs,
- To handle the Cancéropôle's internal and external communication,
- To promote CLARA internationally.

This team of seven permanent members is supported by two Scientific Directors, Jean-Yves Blay and, since September 2005, Yves-Jean Bignon. These Scientific Directors are not CLARA employees, but have kindly been made available by their respective institutes (Lyon Civil Hospitals and Jean Perrin Cancer Center) on a part-time basis.

Finally, as the team is not destined to grow significantly, CLARA also calls upon outside service providers, who bring complementary expertise when required and thus enable the Network Management to work more effectively. In particular, Bruno Cristau, an on-site consultant, works closely with the Cancéropôle's Network Management on setting up the Biological Resource Center.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1. Mireille Guigaz, Executive Director
2. Jean-Luc Balzer, Deputy Executive Director, Industrial Development and Programs
3. Laurent Lévy, Director of Calls for Projects and Partnerships
4. Simon Baconnier, Project Coordinator for CLARA's European Development
5. Joëlle Parry, Communications Manager
6. Nathalie Najberg, Executive Assistant
7. Muriel Vatan, Management Assistant

Platform development

Six core platforms

CLARA IS A NETWORK OF RESEARCH TEAMS, INSTITUTIONS AND FIRMS INVOLVED IN FUNDAMENTAL, CLINICAL AND TRANSLATIONAL RESEARCH IN THE FIELD OF CANCER. BUILT AROUND MEMBERS AND INSTITUTIONS, WITH A SMALL NETWORK MANAGEMENT TEAM, CLARA AIMS TO ENCOURAGE THE EMERGENCE OF INNOVATIVE COLLABORATIVE RESEARCH PROJECTS IN ORDER TO DEVELOP CLINICAL APPLICATIONS FOR THE RESULTS OBTAINED THROUGH FUNDAMENTAL RESEARCH IN BIOLOGY, CHEMISTRY AND PHYSICS, AS WELL AS IN HUMAN AND SOCIAL SCIENCES.

At its first meeting, on August 4th, 2004, the Scientific Advisory Board approved CLARA's organization based on platforms in the areas where key players in cancer research are located. Thus, CLARA is currently divided into six platforms: Grenoble, East Lyon, South Lyon, The International Agency for Research on Cancer, Saint-Etienne and Clermont-Ferrand.

Each of these platforms is built of a network of research institutions and organizations, including firms involved in oncology projects, and features multidisciplinary expertise. However, each of the various platforms has a specific focus area that is illustrated in the research projects it is involved in.

Platform	Specific field(s) of expertise	Coordinator(s)
International Agency for Research on Cancer (IARC)	Cancer epidemiology	Peter Boyle
Clermont-Ferrand	Nutrition and cancer	Yves-Jean Bignon
Grenoble	Clinical proteomics Lung cancers	Marie-Christine Favrot and Christian Brambilla
East Lyon	Functional genomics Pharmacogenomics Breast cancers, sarcoma, cerebral tumors, children's tumors	Charles Dumontet and Alain Puisieux
South Lyon	Epigenomics Malignant lymphoma, hormone-sensitive tumors, digestive carcinoma	Eric Gilson and Gilles Salles
Saint-Etienne	Patient education	Franck Chauvin

This table in no way intends to give a restrictive view of the research activities carried out at the above-mentioned platforms. Furthermore, all of the projects currently underway are conducted at several sites and bring together researchers from several platforms.

Promising economic development potential

In July and August 2005, CLARA, in cooperation with Lyon Civil Hospitals (HCL), commissioned Alcimed to conduct a study aiming to assess the economic development potential of the South and East Lyon platforms, which are financed by Greater Lyon. At the same time, Alcimed explored possible synergies between certain CLARA projects and those underway at the Lyon BioPole competitive cluster.

This study resulted in several findings:

1. These platforms are an excellent breeding ground for innovation as, beyond the field of cancer and even before the creation of CLARA, research teams at the facilities had helped to start up 3 firms and 3 organizations specialized in managing clinical trials.
2. These platforms have had a positive track record since 2002, thanks to a true skills continuum between fundamental research, translational research and clinical research:
   - They are internationally renowned for conducting clinical trials with leaders in the pharmaceutical industry, particularly for sarcoma and lymphoma;
   - Nanobiotix opened a Lyon office in July 2005 in order to coordinate its research activities, as part of the Proof of Concept project in partnership with Inserm research unit 433 *(see page 33)*;
   - 13 collaborative ventures with firms were set up, with international leaders (bioMérieux, sanofi-aventis and Lilly) as well as with domestic biotechnology firms (Aptanomics, GenOway, Genome Express, Genopoietic, Helios, Idealp'Pharma and Transat);
   - European networks of excellence, such as CONTICANET *(see page 35)* or EPIGENOME, help strengthen the Region's influence in the health field.

3. East Lyon and South Lyon both hold promise for the future, thanks to the development of 3 mature focus areas for the development of innovative cancer treatments - functional genomics, pharmacogenomics and immunointervention - and 2 newer focus areas - epigenetics and protein transduction. Thus, 18 new projects with economic development potential are currently being considered by these HCL platforms.
4. These 5 focus areas work in synergy with the programs currently underway at the Lyon BioPole world competitive cluster, in particular with the "Autochip" and "Vaccines and Biomedicines" programs.

A few definitions:

⊙Functional genomics: the study of how genes function in order to identify new diagnostic markers and/or new therapeutic targets.

⊙Pharmacogenomics: studies the genetic specificities of tumors and patients in order to better adapt treatments, make them more effective and minimize their side effects.

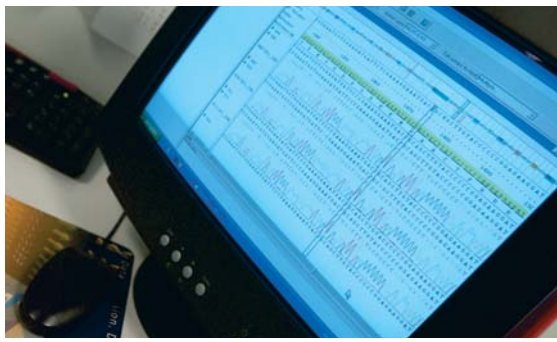
⊙Immunointervention: enables us to use the immune system's extreme specificity and remarkable ability to recognize cancer cells to eliminate them.

⊙Epigenetics: involves studying chemical changes within the genome (other than those affecting the genome sequence, such as modification of histones and cytosines, etc.) that impact gene regulation.

⊙Biotherapy through protein transduction: biotherapy through protein transduction uses the properties of some peptide fragments to make it easier for molecules to enter a cell. Combining these peptide fragments with an active ingredient will enable the development of medicines for cancer and infectious diseases that are more effective at lower doses.

Close monitoring of platforms and projects

AMONG THE 5 PRIORITY FOCUSES FOR 2005/2007 SET OUT BY THE GUIDANCE BOARD ON JULY 6TH, 2005 WAS THE NEED TO PRIORITIZE, ORGANIZE AND COORDINATE THE SETTING UP OF CLARA'S PLATFORMS AND PROGRAMS (SEE PAGE 5).



This need is justified by the context:

- All of the funding for investments and operating costs amount to a total projected budget of nearly €75 million for the four-year period 2004 to 2007.
- The CLARA program is based on four broad categories of stakeholders - Hospitals, Firms, Universities and Institutes - that have their own approaches, issues, aims and expectations (with medical, economic and scientific aspects) and must cooperate with one another.

Thus, the monitoring of scientific platforms and projects aims to ensure the implementation of existing projects by integrating the scientific, organizational and financial aspects. This efficient, operational system must provide feedback on project details and enable the Network Management team to make decisions on technical or scientific projects that it does not necessarily have a clear view of.

This type of organization must ensure the overall consistency of the CLARA network and clarify its aims, in order to:

- Leverage research potential, emphasizing the integration of resources and expertise in cross-platform projects,
- Provide impetus to all participants in the CLARA project, and more specifically to partnerships between firms and academic research institutions,
- Properly manage funding and raise additional funds.

METHODOLOGY AND HOW THE PROCESS WORKS

CLARA's monitoring system is based on a program management approach (project engineering) that emphasizes:

- A focus on managing the interface,
- The principle of subsidiarity, in order to adapt the level of action (project manager, platform/focus area manager, Network Management, etc.) to the nature and level of risk or opportunity.

This process includes 5 phases, running from September 2005 to February 2006:

Phase 1: Discussing the issues and identifying the program's opportunities and risks.

Phase 2: Organizing the program and assessing the 6 platforms.

Phase 3: Planning deliverables and building the program Master Plan.

Phase 4: Specifying the monitoring process and creating management charts.

Phase 5: Starting monitoring and conducting an initial review.

Difficulties to overcome

The main difficulties in setting up the CLARA program's monitoring system concern:

- The complexity related to the contacts and communication between scientists, businesses and institutions,
- The high level of uncertainty regarding scientific projects and the difficulty in fully mastering their content,
- The fact that very few of the partnerships are based on proper contracts,
- The large number of funding sources, making it more complex to consolidate and manage financial resources,
- The need for additional human resources for the platforms.

Prospects for the CLARA program

This process brought to light:

Internally

- A need for balance between monitoring and services in the Network Management,
- A request to develop a set of shared standards, knowing that CLARA stakeholders all work at different speeds,
- The need to better distribute funding between the investment and operating budgets,
- The need to organize and encourage communication and sharing, in order to make interdisciplinary, inter-regional scientific/industrial projects a reality.

Externally

- The major interest of developing synergy with the Lyon BioPole and Minalogic competitive clusters,
- The need to develop good relationships with INCa and national research institutes (CNRS, Inserm, CEA, ENS, etc.).

Mobilizing key players in the business and academic worlds

The Business Club

CLARA is located in a region with a strong biopharmaceutical sector, which accounts for more than 30% of French activity in the field. It brings together world leaders (Merck Santé, bioMérieux, Sanofi Pasteur and others), medium-sized firms (OPi, Genome Express and others) and a number of start-ups (Transat, Meristem Therapeutics and others). The Auvergne and Rhône-Alpes Regions also boast a wide range of custom research, consulting and financial services (Amorçage Rhône-Alpes and others).

In this dynamic environment, the Business Club brings together some fifty firms working in the field of oncology research and development. It aims to strengthen partnerships between firms and between the business and academic worlds and to support the creation of new innovative firms.

In 2005, the Business Club held 2 meetings, in order to share ideas and information during a year in which businesses played an increasingly important role.

The Business Club is headed by a Board of 6 members, which was renewed on a voluntary basis in 2005, making it even more dynamic. Its missions include communicating with and providing information to Club members, evaluating projects in terms of their economic development potential and participating in the management and strategy of the Cancéropôle.

The Board is headed by Gilles Alberici (OPi) and includes François Pons (Genome Express), Dominic Cellier (Merck Santé), Sophie Chappuis (Transat), Catherine Boisgard (Meristem Therapeutics) and Karine Lignel (Amorçage Rhône-Alpes).

2005 saw the full integration of the Auvergne Region and a very high level of activity, with 4 work meetings.

The Board worked on developing the Proof of Concept program *(see pages 32 to 33)*. Gilles Alberici heads the Evaluation Committee for this program.

In addition, this team was involved in preparing and running the "CLARA Forums" *(see opposite)*, as well as in:

- Setting up the platform and project management systems *(see page 18)*, that involve businesses;
- Building a map of CLARA's scientific expertise with a European benchmark *(see page 36)*, with a view to setting up a large-scale, integrated, cross-platform project based on strategic partnerships between firms and academic institutions.

Finally, the Board met representatives of the Rhône and Auvergne Delegations of the Association of French Businesses for the Fight Against Cancer (GEFLUC).

CLARA Forums

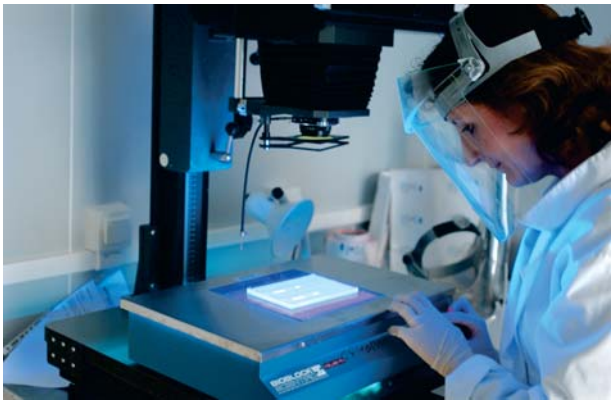
On April 1st and October 21st 2005, key players in the academic and business spheres came together to share ideas at the "CLARA Forums".

Created in order to promote the transfer of scientific knowledge towards routine patient care, while contributing to the region's economic growth, the Forums helped the CLARA network get up and running and strengthened communication between the worlds of academic research and industrial development. The Forums have thus resulted in several concrete projects.

These Forums were run by members of the Business Club's Board and managers of the various platforms.

in action

21



The April 1st Forum drew 74 attendees, with equal-sized delegations from the business and academic spheres. Sixteen research projects were presented.

A survey conducted in September showed that most of these projects had advanced from the design stage and preliminary discussions to the writing of the partnership contract, or even the start-up of the project. The same survey also revealed that other projects had been initiated thanks to first contacts between individuals who had never met prior to the Forum.

During the October 21st Forum, with 77 attendees, 11 new research projects were presented.

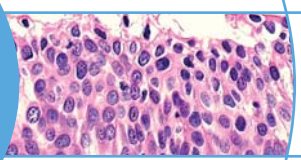
The Academic Club

THE ACADEMIC CLUB, CLARA'S "PILLAR", FORMED AND MET FOR A GENERAL ASSEMBLY IN LYON ON NOVEMBER 14TH, 2005.

Since this meeting, a 22-member Board has been set up. It is headed by Professor Charles Dumontet of Lyon, who is assisted by 3 vice presidents: Professor Yacine Merrouche of Saint-Etienne, Doctor Sophie Rousseaux of Grenoble and Professor Yves-Jean Bignon of Clermont-Ferrand.

The Board's missions are as follows:

- To participate in elaborating CLARA's scientific orientations and in running the scientific network;
- To initiate projects and generate ideas, in particular to participate in calls for projects from INCa, The National Research Agency (ANR) and Europe, in collaboration with CLARA's Business Club, Lyon BioPole, NanoBio and Europe;
- To organize and build teams in the framework of these projects;
- To communicate: The Academic Club's Board is a vital link between the scientific community and CLARA's Network Management and vice-versa, and is in close contact with research teams;
- To contribute to assessing CLARA's programs and projects, prior to evaluation by the Scientific Advisory Board and INCa;
- To establish a relationship with the Business Club.



Integration of CLARA members into the work carried out by the National Cancer Institute (INCa)

CLARA researchers actively participate in INCa working groups:

- Theme-based working groups: on biological resource centers, proteomics and functional genomics tools, or programs to make innovative treatments available before they are approved for sale (PTT Herceptine).
- Clinical Studies Groups (GEC), designed to make an inventory of all of the clinical research programs on various tumors or subjects (clinical pharmacology, etc.), to accredit the programs identified, to assess the clinical research programs submitted to INCa and to propose innovative research programs in targeted subject areas.

  INCa's efforts aim to increase and encourage patient participation in clinical research programs currently underway in our country. As part of this effort, two researcher-clinicians from CLARA member institutions lead one of the 22 GECs that have been selected, on the topics of radiotherapy and sarcoma. Several others are participating in GECs in the fields of breast tumors, clinical pharmacology and lung cancers.
- Regular meetings of Cancéropôle coordinators.

In addition, CLARA members help assess projects participating in INCa's call for projects and set up core networks, designed to organize multi-platform, interdisciplinary research programs between institutions (*see pages 27 to 31*).

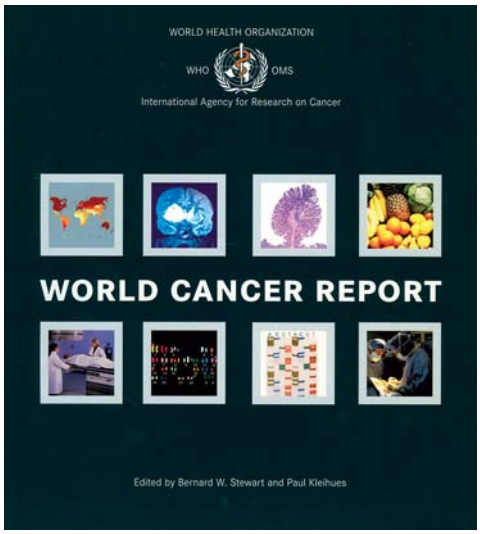
Dynamic platforms

The International Agency for Research on Cancer (IARC)

During 2005, the International Agency for Research on Cancer held several meetings with CLARA's key players in epidemiology:

- **February 7th:** presentation of IARC's activities and of the European Cancer Network (ECN);
- **February 28th:** presentation of 3 epidemiological groups on the themes of thyroid cancer in the Rhône-Alpes area, the registry of gestational trophoblastic diseases and the children's cancer registry's data on incidence and survival;
- **March 18th:** presentation of the regional cancer epidemiology observatory and the Loire-area melanoma network.

CLARA members were also regularly invited to IARC internal seminars, held two Tuesdays per month.



Finally, the IARC has collaborated in a number of projects with teams from ENS, Léon Bérard Cancer Center, Edouard Herriot Hospital, The Neurocardiological Hospital, South Lyon Hospital, Inserm, Claude Bernard University, CIFAL, Rockefeller Medical School, Laënnec Medical School, Lyon Civil Hospitals, CNRS, Aptanomics S.A. (in Lyon), the Albert Bonniot Institute, Albert Michallon University Hospital, the Isère Cancer Registry (in Grenoble), the Rhône-Alpes Region's Child Cancer Registry, Saint-Etienne University, the Loire Cancer Institute (in Saint-Etienne), and the Clermont- Ferrand Medical School.

The Grenoble platform

CLARA's Grenoble platform focuses primarily on the development of proteomics, nanotechnologies and functional imagery for treating cancer patients.

2005 was essentially dedicated to setting up the platform's functional organization in order to meet the expectations and aims of the various members. This process included setting up the biology innovation center, which enabled the local participants to come together around functional, shared technical platforms, homogeneous management of the various equipment and scientific coordination. Over time, thanks to the efforts of the oversight bodies, an engineer has been or will be assigned to each technical platform (*see below*).

CLARA's Grenoble platform brings together Joseph Fourier University (UJF) and the University Hospital and is part of the soon-to-open Inserm/UJF "oncogenesis and ontogenesis" research center. More than a dozen scientific projects are underway at these technical platforms, thanks to the biological resource center, which has now been set up (with the help of the CLARA partners, the Tumorotek software is being adapted to Grenoble's requirements). 2006 will be devoted to opening the platform for regional academic or industrial collaborative projects, which should be made easier with the opening of the Biopolis business incubator on the facility.

● University Joseph Fourier

Setting up the platform

The "medical proteomics" platform (technical and scientific managers: M. Seve and K. Sadoul (UJF engineer) with 1 UJF engineer on contract) aims to highlight and identify protein markers using normal and diseased biological samples. One part of the equipment (a MALDI TOF-TOF Applied 4800 mass spectrometer) was purchased and construction work to install this equipment was completed in 2005. The workshop is operational and the equipment purchased completes the SELDI TOF previously acquired by F. Berger at the University Hospital facility and the equipment available at the Albert Bonniot Institute.
In 2006, a SELDI/MALDI adaptor, a digester/spotter and a 2D Nano Chromatography device will be purchased thanks to funding from the NanoBio program.

The purchase of a MALDI FT-MS, which will enable technological development downstream from clinical applications, was co-funded at the proteomics research center headed by J. Garin.

The "*in situ* molecular detection" platform (scientific manager: E. Brambilla; technical manager: P. Lorimier, University Hospital engineer) brings together all of the techniques, equipment and personnel dedicated to in situ detection of proteins via immunohistochemistry and detection of nucleic acids via in situ hybridization (D. Leroux). The platform is operational. The additional equipment, purchased thanks to the Cancéropôle, will arrive in 2006, along with a new conservation system, purchased thanks to INCa/DHOS funding.

The EPIMED platform (scientific manager: S. Rousseaux; 1 engineering position was created by UJF) aims to share technical knowledge and skills in the field of epigenetics and develop new analysis tools such as the repchip, which is currently being tested.

The small animal imaging platform (scientific manager J. L. Coll and technical manager V. Josserand: engineer funded by Rhône-Alpes Genopole).

The platform brings together a set of devices enabling *in vivo* tracking of the expression of fluorescent molecules by normal or malignant cells in mice, and the study of the biodistribution of molecules marked with a fluorochrome. The equipment, purchased with the assistance of the Cancéropôle, was designed in collaboration with CEA/LETI and was transferred to industrial use after being validated on the platform.

The immunomonitoring platform is currently being set up.

East Lyon

The East Lyon platform is composed of a functional genomics platform located at the Léon Bérard Cancer Center (CLB) and a pharmacogenomics platform supported by Lyon Civil Hospitals (HCL).

At the CLB facility, the program is based on high-priority research areas (the study of the inhibition of cell monitoring processes during tumor progression and identification of invasion and chemoresistance mechanisms), developed by Inserm Unit 590, UMR CNRS 5201 and FRE CNRS 2870. These research areas are supported by the setting up of two programs designed to result in concrete medical applications, led by the CLB's Molecular Oncology Unit:

- The "MutaCancer" program, in partnership with Genome Express, which aims to identify recurrent genetic alterations in breast, colon and lung cancers and in neuroblastoma;
- The "InaCancer" program, in collaboration with Transat, which aims to generate original tumor progression cell models.

Léon Bérard Cancer Center

Development of these programs, which are directly related to fundamental research projects conducted in the accredited research units, enable scientists to identify the events responsible for malignant transformation and to test their biological consequences. The cell models developed in the InaCancer project will also enable the testing of molecules (siRNA banks and combinatorial libraries) to determine their anti-cancer activity.

The pharmacogenomics platform supported by Lyon Civil Hospitals should open in September 2006. Its vocation, directly related to the work carried out at CLB, will be to perform genomic and genotype analyses on samples coming from prospective clinical series. These samples come from several projects, some of which started in May 2005. These include the Pharmacogenoscan project (on lung cancer), the multiple myeloma genotyping project, the radio-induced pulmonary fibrosis project, the anthracycline toxicity project, and the breast cancer chemotherapy sensitivity project. Three university employees and one HCL staff member will participate in setting up the projects for this platform, which will soon require additional human resources. In addition, this platform will help to coordinate the genomics platforms of the various Cancéropôles nationwide.

The Auvergne Cluster

The Cancéropôle's Auvergne Cluster (PAC) brings together approximately 300 scientists, 26 accredited research teams and 10 firms. It is active in several areas of research (functional genomics, imaging, pharmacogenomics and public health) and brings an original new focus, the subject of "nutrition and cancer".

The PAC's organization

The Board, composed of fourteen members representing all of the institutions involved in cancer research, oversees the PAC's administrative organization and scientific orientations. As the PAC's driving force and executive body, it meets on average once a month and is the main contact for CLARA's Network Management.

Five Technical Committees coordinate regional projects in five subject areas: nutrition and cancer, imaging, functional genomics, development and proof of concept and the biological resource center.

Jean Perrin Cancer Center

The Strategic Committee is the link between PAC researchers and institutional, financial and political partners. It is composed of 48 members.

Scientific orientations and 2005 in review

The PAC's activities focus on areas of excellence in research that bring together different institutions from both regions. In 2005, Auvergne researchers were involved in 13 inter-regional research programs financed by INCa or by large regional programs (€3 million in funding in 2005).

Within CLARA, PAC is best known for its work in the field of nutrition and cancer. It aims to clarify the impact of nutrients on the various stages of cancer, from cancerogenesis to the nutrition of cancer patients, to the adjuvant role that foods play in cancer therapy. This field is composed of four main areas of action:

- The study of the protective effects of some foods (retinoids and phytoestrogens) on the occurrence of hormone-dependent cancers (breast and prostate cancer);
- Evaluation of the nutritional consequences of cancer on patients, with the aim of developing a nutritional intervention strategy for cancer patients (ENT, colon and skin melanoma cancers) is being developed;
- Sensitization to chemotherapy through a diet that is low in methionine. Colon and melanoma cancers are being studied.

In functional genomics, there are five main areas of research: the study of transcriptome in hormone-dependent cancers; high-speed sequencing of genes involved in breast and lung tumors (Mutacancer program); the study of the first stages in the development of prostate tumors and adrenal tumors, using transgenic animal models; the study of genetic instabilities; the relationships between the expression of certain cytokines and chemosensitivity of cerebral glioma and malignant lymphoproliferation.

The imaging focus is based on the expertise of the Clermont-Ferrand Inserm facility and clinical teams in the development of radiotracers, from pharmacology up to clinical trials in humans. This research benefits from a business environment that features pharmaceutical firms specialized in the production and marking of tracers (benzamides and fluor18-deoxyglucose). One of the aims is to develop specific melanoma tracers for diagnostic purposes (scintigraphy). Future prospects include the development of molecules enabling specific internal radiotherapy or radiochemotherapy.

A growing portfolio of scientific projects

In 2003, CLARA identified the primary focus areas in which several research teams were involved:

- Functional genomics,
- Pharmacogenomics,
- Epigenomics,
- Biotherapy,
- Epidemiology,
- Public health,
- Clinical research,
- Imaging.

Since then, these focus areas have been expanded with the integration of Auvergne's researchers and institutions into the CLARA network. The Nutrition and Cancer focus area thus became a key field of expertise for the Cancéropôle in 2005.

in action

Projects started in 2005 as part of INCa's call for projects

In all, researchers from CLARA member institutions have submitted 46 projects to INCa. Seventeen of these projects have been partially or fully funded.

1. Core networks

Two of the 4 projects presented were chosen:

Epigenetic profiling of cancers (EpiPro)

Heads: S. Khochbin, E. Gilson
Focus: Functional genomics
Platform: South Lyon
Funding provided over 2 years: €400,000

This project includes two work packages (WP). The first aims to define new epigenetic parameters that can be used in clinical oncology, based on prior research and focusing on several epigenetic topics that have been studied in-depth by CLARA research teams. These include telomeres, heterochromatin or chromatin complexes that involve nuclear hormone receptors. The second WP includes transfer towards medical research in order to develop epigenetic profiles for some or all areas of the genome or for specific genes. These studies should result in the definition of new epigenetic markers enabling detection, diagnosis, prognosis or even new therapeutic approaches. Special emphasis will be placed on lymphoid cancers and lung carcinoma.

Nutriprotection and hormone-dependent cancer

Heads: M. Ferrara, Y.-J. Bignon
Focus: Nutrition and Cancer
Platform: Clermont-Ferrand
Funding provided over 2 years: €100,000

This project aims to identify the effects of isoflavones and other components of tomatoes on gene expression and cell survival in hormone-dependent tumors, breast and prostate cancers.

The "Creation of a core network in human and social sciences: information, shared decision making and patient education" project submitted by Franck Chauvin for the Saint-Etienne platform was not selected. Nevertheless, it is still being considered by INCa's Human Science Research - Cancer Economics team, with the prospect of support for an amended project.

2. Open projects

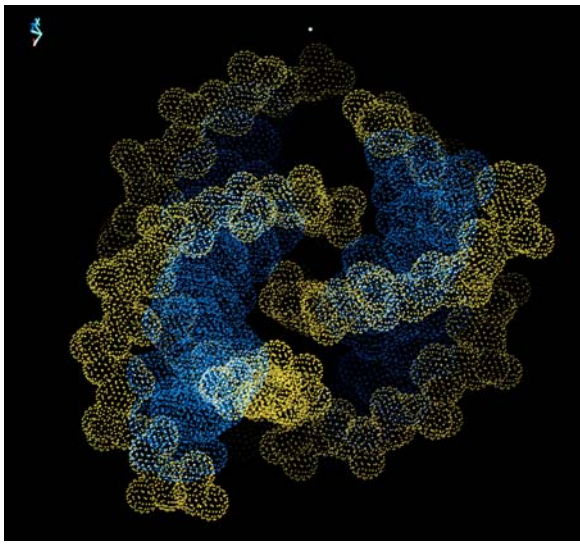
Five of the 19 projects submitted received funding:

⊙ **Apoptosis and immunity in cancer: development of therapeutic strategies by combining tumor cells apoptosis and immune activation**

Head: C. Caux
Focus: Biotherapies
Platforms: East Lyon, South Lyon, Grenoble
Funding provided over 2 years: €460,000

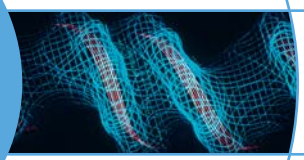
This project aims to analyze the immunological consequences of various apoptosis induction pathways involving p53, dependence receptors, hormone therapy, and targeted therapeutics, using molecular anomalies involved in tumorigenesis. Its impact on the immune activation effects of cells with the antigen will be studied.

This project may potentially lead to combining oncogene-targeting therapies and activation of the immune system.



⊙ **Role of dependence receptor pathways in malignancy**

Head: C. Dumontet
Focuses: Biotherapies, Functional genomics
Platforms: East Lyon, South Lyon
Funding over 2 years: €600,000



Dependence receptors, the most classic example of which is DCC (Deleted in Colorectal Cancer) induce apoptosis in the absence of ligands. They can thus act as suppressor genes by inducing apoptosis of tumor cells that tend to multiply in inappropriate circumstances. Netrin receptors, DCC and UNC5H, are known to be deleted or mutated in a large number of cancers. Little is known about the role of these pathways in tumorigenesis and tumor aggressiveness. This project aims to analyze the role of netrin signaling pathways in digestive and pulmonary adenocarcinoma and in acute myeloid leukemia by quantitative RT-PCR and immunohistochemistry. It also aims to develop and describe animal models showing modification of the netrin pathways in digestive, lung and hematopoietic tissue. Finally, the project sets out to determine the effects of inhibition of netrin signaling both in animal models and on fresh leukemia cells.

⊙ **Mechanisms of invasion and metastasis in breast cancer**

Head: M. Billaud
Focuses: Biotherapies, Functional genomics
Platforms: East Lyon, South Lyon, IARC, Grenoble
Funding provided over 2 years: €500,000

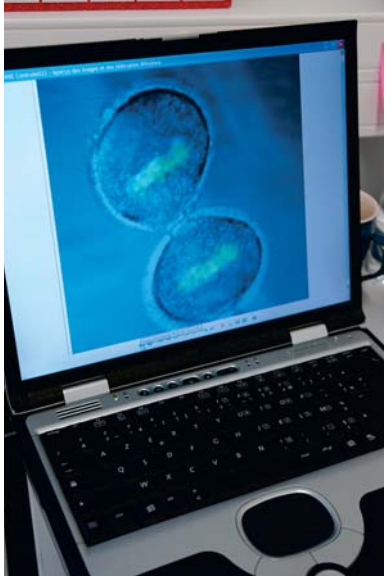
This program aims to identify new molecular mechanisms involved in the migration and dissemination of breast cancer cells. Several key processes will be studied in order to better define the molecular basis for the formation of metastases in particular those responsible for dissemination to the bones. This project will study the processes related to the loss of cell polarity and the aberrant reactivation of epithelial and mesenchymatous transitions. The mechanisms enabling tumor cells to survive in the blood and bone microenvironment will also be analyzed. The role of the effectors of the analyzed signal pathways (kinase proteins that are partners of the oncosuppressor PTEN protein, the transcription factor Twist, dependence receptors DCC/UNC5H and their ligand, netrin-1) in the acquisition of a metastatic phenotype will be systematically tested in animal models.

⊙ Glial tumors: towards new therapeutic and physiopathological approaches

Head: J. Baudier
Focuses: Biotherapies, Functional genomics
Platforms: Grenoble, East Lyon, South Lyon
Funding provided over 2 years: €440,000

This project brings together six teams from the Rhône-Alpes Region and aims to analyze the biology of cerebral tumors. The research features three main focus areas:

1) Description of a chemically-induced murine glioma model, developing new therapeutic strategies that can result in clinical applications;
2) Identification of tumor transformation mechanisms, in particular the involvement of cerebral stem cells;
3) A work package destined to describe the angiogenetic mechanisms in these tumors using vascular imaging techniques.



⊙ Mutacancer

Head: A. Puisieux
Focus: Functional genomics
Platforms: Grenoble, East Lyon, South Lyon, Clermont-Ferrand

This project, which is supported by €200,000 in special funding, aims to describe recurrent genetic alterations on tumor lines and fresh tumors as part of a partnership between the academic and business spheres.

3. Human and social sciences

4 projects were presented, one of which was selected:

⊙ Development and implementation of a patient education program applied to the treatment of fatigue in cancer

Head: F. Chauvin
Focus: Public health
Platform: Saint-Etienne
Funding provided over 2 years: €100,000

This project aims to develop, implement and assess a regional pilot patient education program (PEP) in the care of patients treated with chemotherapy. It aims to enhance patient quality of life through improved checking of symptoms and better anticipation of potential difficulties. It also sets out to enable patients, by getting them involved in treatment plans, to discuss their priorities and preferences in order to become fully-fledged participants in the decision making process. The expected short-term result is a significant decrease in fatigue in patients treated by chemotherapy who have benefited from a personalized patient education program. The longer-term aim is to assess the impact of this program on patient quality of life and on the ways of using the patient care system in comparison with traditional patient care programs.

4. Clinical research

Five of the 15 projects submitted were selected by INCa:

⊙ Multicenter phase I/II study evaluating the efficacy and toxicity of imatinib in adult patients with aggressive fibromatosis that cannot be treated by surgery or curative radiotherapy

Lead investigator: J.-Y. Blay, for the French Sarcoma Group (GSF)
Platforms: East Lyon, Clermont-Ferrand, Saint-Etienne
Funding provided over 2 years: €100,000

This project aims to determine the antitumoral effects of imatinib in treating resistant fibromatoses, in the framework of a multicenter trial conducted by the French Sarcoma Group (GSF). Molecular analysis of predictive factors of response on tumor samples prior to treatment is planned. 40 patients are enrolled and an interim analysis of this project, which began in 2005, will be presented at ASCO in 2006.

⊙ Implementation and evaluation of a cancer pain education program

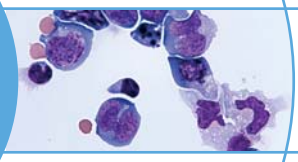
Lead investigator: D. Perol
Platforms: East Lyon, Saint-Etienne
Funding provided over 2 years: €100,000

This project concerns adult patients with histologically confirmed malignant tumors that suffer from pain assessed at 30 mm or more on a visual analog scale. The patients are to be treated by a care provider (physician or nurse) trained in pedagogy. At first, the care provider is to identify the behaviors and skills that the patients must acquire in order to optimize the treatment of their pain ("educational diagnosis"). Patients will be offered an educational program, based on a contract specifying the objectives, following this diagnosis phase. The expected results from this project, assessed as part of a randomized study, are a significant reduction in the average level of pain experienced by cancer patients having benefited from a personalized education program compared to those receiving conventional treatment.

⊙ French-language "Observatory for rare malignant tumors of the ovaries" website: management of malignant adult ovarian tumors (germ cell and sex cord-stromal tumors)

Lead investigator: I. Ray-Coquard,
for the National GINECO Group
Platforms: East Lyon, South Lyon, IARC, Grenoble, Saint-Etienne, Clermont-Ferrand
Funding provided over 2 years: €100,000

This project will create an Internet-based inventory of the clinical observations of rare ovarian tumors, offer recommendations on clinical practices and provide a prospective analysis of the results. So far, 86 patients have been enrolled.



⊙ Kinesins and Cancer: Development of specific inhibitors for human mitotic Rabkinesin 6 in view of chemotherapeutic applications

Head: F. Kozielski
Platforms: Grenoble, East Lyon and South Lyon
Funding provided over 2 years: €150,000

The majority of the small molecules used in chemotherapy (i.e. Paclitaxel and Docetaxel) target tubulin, the fundamental element for polymerisation of mitotic microtubules (MT). The success of these inhibitors against tubulin suggests that other key elements for the setup of the mitotic spindle, such as the molecular motors that move along the microtubules, are targets of equal or better quality. At least 12 kinesins are involved in various aspects of the setup and operation of the mitotic spindle, and the expression of many of these motors is restricted to proliferating tissues. It is therefore not surprising that many of these motors are potential targets for the development of anti-cancer drugs (the most advanced kinesin inhibitor, monastrol, is currently in clinical phase II). Rabkinesin 6 (RabK6, also called MKLPII) is an essential kinesin for metaphase/anaphase transition and cytokinesis. Inhibition of RabK6 by small molecules should selectively inhibit cell proliferation by inhibiting meta-phase/anaphase transition or cytokinesis. The aim of this request for funding is to develop interdisciplinary approaches to identify mitotic kinesin RabK6 inhibitors.

⊙ Lung pharmacogenoscan

Lead investigator: P. Roy
Platforms: East Lyon, South Lyon, IARC, Grenoble, Saint-Etienne, Clermont-Ferrand
Funding provided over 2 years: €100,000

This project finances the clinical research part of the Pharmacogenoscan project financed in 2003 and 2004.

5. Post-doctoral program

Three post-doctoral students received support (total funding of €126,000) to work in a CLARA network research team on the following projects:

- **Non-viral transfer of apoptogenic molecules into neo-angiogenic cells for the treatment of lung cancer; therapeutic efficacy and molecular imaging**

Head of team: J.-L. Coll
Head of laboratory: M.-C. Favrot
Platform: Grenoble
Focus: Biotherapy

- **Diagnostic and prognostic validation of new tumoral protein targets**

Head of team: F. Berger
Head of laboratory: A.-L. Benabid
Platform: Grenoble
Focus: Biotherapy

- **Plasmacytoid dendritic cells in immunity against cancer**

Head of team: J. Marvel
Head of laboratory: V. Lotteau
Platform: South Lyon
Focus: Biotherapy

Projects supported by private funding

One project that had received funding from the Breast Cancer Research Foundation in 2004 was once again supported by the same Foundation in 2005:

- **Immune cell infiltration in breast cancer II project**

Heads: J. Y. Blay, C. Caux
Focus: Biotherapy
Platform: East Lyon
Funding provided for 2005: $250,000
(approximately €200,000)

This project continues to describe the nature and function of immunocompetent cells that infiltrate localized breast adenocarcinoma, as well as the precision of their prognostic value through long-term follow-up. The funding will provide for the purchase of a tissue micro array enabling simultaneous analysis of a large number of samples.

This project benefits from a high level of interaction with the PDC and cancer project, as the presence of plasmacytoid DCs is associated with a particularly poor prognosis.

Finally, one project is supported by funding from a firm that is highly active in the Business Club, Merck Santé, through a special partnership set up when CLARA was created:

- **EMS project: A study of variations in medical practices in treating sarcoma**

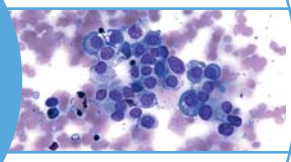
Head: I. Ray-Coquard
Focuses: Epidemiology, clinical research, functional genomics
Platform: East Lyon
Funding provided over 4 years: €700,000

This project aims to create an exhaustive collection of the clinical and anatomopathological records of patients with sarcoma in the Rhône-Alpes Region over a 3-year period, in order to establish a link between patient survival and practices in these rare diseases. It will be paired with a molecular biology project on these tumors carried out in cooperation with researchers involved in the molecular description of sarcoma at the East Lyon platform (Léon Bérard Center and Édouard Herriot Hospital). It constitutes CLARA's contribution to a network of excellence supported by the European Commission's Sixth Framework Programme (3rd call). This network, called CONTICANET, brings together 20 teams from 9 countries and is led by the Lyon team *(see page 35)*.

Research application to industry: The Proof of Concept program

During the November 29th, 2004 Steering Committee meeting, CLARA decided to set up a fund to support "Proof of Concept" projects in cancer research. This program aims to foster the development of partnerships that bring together public (academic institutions and hospitals) and private (firms) stakeholders in the field of cancer research, innovation and technology transfer.

The Proof of Concept program was designed by CLARA's Network Management team, in cooperation with many experts and partners including Anvar, Amorçage Rhône-Alpes, CNRS, Créalys, Ezus, INPI, Inserm, Inserm-Transfert, the Rhône-Alpes Region and the Board of CLARA's Business Club (OPi, Genome Express, Merck KGaA and Sanofi Pasteur).



Targeted projects

The fund targets research projects with high medical and industrial potential that a firm is ready to begin developing, once assured that it can count on technological and scientific support from the academic sphere in order to test the validity in animals or in patients (pre-clinical or clinical proof of concept).

The steps in the proof of concept phase are crucial in the long, costly development chain for a new active ingredient or medical technology. These steps take place after the core work of the academic institutions, which are more devoted to research, and prior to the work of the big pharmaceutical firms, which are increasingly focused on the advanced stages of clinical development, production and distribution. New innovative firms in the life sciences field often perform the work during these phases, but they run into major financial difficulties when the proof of concept is not established at the clinical phase.

CLARA's role

CLARA works alongside academic institutions to bring them additional financial resources enabling the institutions to fully play their role as partners with the industrial world. In principle, there is no absolute maximum limit to the amount of funding CLARA can provide. Nevertheless, the amount is limited to the budget that the firm itself is ready to devote to the project.

A pilot project

One pilot project was assessed and set up in 2005. It brings together start-up firm Nanobiotix and Inserm's "Experimental Neurobiology and Physiopathology" Unit 433 and aims to establish the first proof of concept in animals on a new technology, "NanoMag", developed by Nanobiotix. This technology will be applied to the treatment of glioblastoma, the most common cerebral tumors in adults, for which there is currently no truly effective treatment. Nanoparticles covered with biological agents and composed of a core that can be remotely activated will enable tumor cells to be specifically targeted and selectively destroyed, thus leaving healthy tissue intact.

● The actors of the Nanobiotix/Inserm Glioblastoma Project

Paris-based Nanobiotix, which has a facility at the Bioparc to coordinate its research activities, has chosen Lyon as the base to carry out the proof of concept thanks to the city's particularly favorable environment:

- The presence of Inserm Unit 433 in the heart of a highly talented neurosciences cluster that combines scientific expertise, a unique bank of human glioblastoma samples (via the Neurobiotec organization) and patients from the neurology hospital. This environment will carry the project all the way up to the clinical trial phase.
- The ability to obtain support from CLARA in setting up, funding and running the partnership with Inserm, as well as in establishing relationships with other potential partners in the Auvergne and Rhône-Alpes regions.

Cancéropôle has promised to provide Inserm with up to €372,000 in funding over 2 years. Nanobiotix plans to invest €1.8 million in the project.

A first call for projects

CLARA launched its first competitive call for Proof of Concept projects in June 2005. It received 12 candidate projects, which were assessed in detail by outside experts - including Inserm-Transfert, INPI and the Lavoix and Beau de Loménie consulting firms, specialized in intellectual property. The projects were also examined by an evaluation committee, headed by a representative of the Board of CLARA's Business Club, which included ARTEB, OSEO-Anvar and Amorçage Rhône-Alpes. The final step in the selection process was ratification by CLARA's Scientific Advisory Board.

This procedure led to the selection of 3 new projects that are currently being set up:

- Treatment of hepatic metastases of colorectal cancer via liver targeting - intraerythrocyte encapsulation of 5 fluorouracil; project initiated by Erytech Pharma and Léon Bérard Cancer Center;
- Validation of new protein biomarkers with diagnostic and prognostic potential in oncology; project initiated by Genome Express and Inserm "Preclinical Neurosciences" Unit 318;
- *In vivo* evaluation of tIL-6 as a natural inhibitor of IL-6; project initiated by OPi, Léon Bérard Cancer Center, Lyon Civil Hospitals, Inserm Unit 590 and Claude Bernard University.

Program funding

The local authorities that finance CLARA have promised to provide the "Proof of Concept" program with €3 million in funding over 3 years. Greater Lyon provided €350,000 in funding in 2005, which enabled the launching of the pilot project, and will continue to provide financial resources. The provisional budget required for 2006 is €1 million, which will provide support for the 3 additional projects selected during the first call for projects in 2005 and enable the launching of 2 new calls for projects during the year.

The challenge of the Inter-regional Biological Resource Center

In order to meet the goals of INCa's Cancer Plan, the Cancéropôle aims to federate institutional Biological Resource Centers (CRB) in order to provide tumor samples required by academic and industrial researchers for their ambitious projects. The Biological Resource Centers are the ideal organizations for providing access to characteristic, high-quality samples.

Assessing existing resources

These institutional CRBs, used for research purposes, benefited from changes in tumor sample collections between 2001 and 2004. These changes were initiated by the Hospitalization and Organization of Care Division (DHOS) in order to address the issue of diagnosis in clinical practice.

CLARA has capitalized on all of the breakthroughs previously made.

The first efforts to set up CLARA's own CRB began in June 2005 with the identification of already existing resources, through discussion with the heads of tumor sample collections in the Rhône-Alpes and Auvergne Regions (Lyon Civil Hospitals, Léon Bérard Center, Jean Perrin Center, Saint-Etienne University Hospital and Grenoble University Hospital) and visits to currently operating CRBs.

Setting up the project

On the recommendation of the Scientific Advisory Board in March 2005, the stakeholders involved in the CRB-CLARA project met on August 30th, 2005 under the supervision of Mr. Bréchot, Managing Director of Inserm and President of CLARA's Scientific Advisory Board, in order to clarify the aims of the project.

The following actions were decided upon:

- To collect and assess the quality procedures of the various institutions;
- To count the various tumors stored at the institutional CRBs;
- To choose two projects, one on a common tumor and the other on a rare tumor, using retrospective samples for one and prospective samples for the other.

A steering committee was set up. It validated the constitution of five working groups that bring together all of the institutions mentioned above:

- A group dedicated to identifying the needs of academic and industrial researchers (samples, derivative or related biological products, annotations, etc.) and to designing the information system to be set up;
- Two groups in charge of testing the operating procedures through the two pilot projects;
- A support group to ensure the quality of the samples;
- A support group to make an inventory of the available tumors.

These working groups have now begun carrying out their activities. They report to the project's steering committee.

Selection of the pilot projects

The aim was to select two scientific projects that were ready to begin, based on their capacity to bring together tumors. A call for projects was held.

The MutaCancer project, initiated by Mr. Puisieux of Léon Bérard Center, and the Thyroid Cancers project, initiated by Ms. Sassolas of the Rhône-Alpes Register of Thyroid Cancers, were selected.

CLARA and the world

CLARA and Europe

2005 was a turning point for CLARA on the European research scene. In particular, the network's European dimension took shape around the CONTICANET project.

In this context, and with a view to supporting CLARA members on the European stage, a project coordinator, Simon Baconnier, was hired in the middle of the year. He works in two main areas: operational support for the CONTICANET project and assistance in developing other projects initiated by the network members from the academic and industrial spheres, as part of the European Commission's Sixth Framework Program (2002-2006).

⊙ The CONTICANET project

One of the cornerstones of the Sixth Framework Program is a "network of excellence". Through this network, funding is provided to help organize research in a given focus area and to make research more consistent throughout Europe. Through such networks, Europe provides funding for the integration of key players and community resources into joint programs.

In November 2004, the CONTICANET (Connective Tissue Cancer Network) network of excellence project, coordinated by Professor Jean-Yves Blay (Claude Bernard Lyon 1 University), was presented to the European Commission in reply to the 3rd call for proposals on the theme of "Life Sciences, Genomics and Biotechnology for Health."

This project focuses on connective tissue cancers, in particular sarcoma.

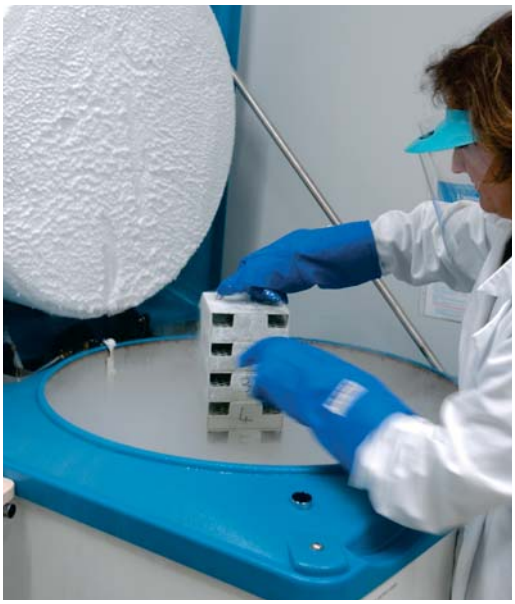
In March 2005, the Commission decided to grant €9.5 million in funding to the project, which will begin on February 1st, 2006 for a period of 5 years.

The CONTICANET project brings together 20 partners from 9 European countries. All of the key players - academic research, clinical research and industry - are represented.

⊙ Other projects

Projects were also proposed in the latest call for proposals on the subject of Life Sciences and Health. Raphaël Rousseau (Léon Bérard Center), who had received a Marie Curie European Reintegration Grant, submitted a Specific Targeted Research Project on the topic of "Innovative diagnostic approaches and novel therapies of childhood cancers." The submitted project focuses on the development of safe and effective new adoptive immunotherapy treatments for children with recurrent malignant tumors.

Dr. Rousseau's involvement provides solid support for CLARA members in preparing for the Seventh Framework Program on Research and Development (2007-2013).



Identification of CLARA's joint fields of excellence

THE CANCÉROPÔLE'S STRATEGY AIMS TO STRENGTHEN ITS POSITION IN EUROPE, STARTING IN 2006, BY LEVERAGING ITS FIELDS OF EXCELLENCE IN ONE OR TWO LARGE-SCALE PROJECTS. IN ORDER TO DECIDE UPON THESE PROJECTS, CLARA MUST DEVELOP A SHARED, OBJECTIVE VISION OF ITS "JOINT" FIELDS OF EXCELLENCE IN CANCER R&D.

In order to achieve this, CLARA launched a bibliometric study in 2005 aiming to analyze the production of scientific articles by researchers from the Rhône-Alpes and Auvergne Regions compared to the national and world averages. This comparison was performed for the field of cancer as a whole, and for certain specific cancer fields that are well represented at the worldwide or inter-regional levels. These fields range from epidemiology (cancer incidence, risk factors, detection, prevention, etc.) to fundamental research (tumor cell anomalies, gene mutations, etc.) to experimental research (in vitro tests, animal experiments, etc.) to clinical research (trials and development of potential new medicines or therapeutic protocols in humans, etc.).

⊙ The process and study partners

The CLARA team carried out this study from September to December 2005 in conjunction with TecKnowMetrix, a Grenoble start-up firm specialized in Business Intelligence.

It was supported by a Steering Committee that included CLARA's Scientific Directors, two representatives of the Business Club's Board - its President G. Alberici (OPi) and D. Cellier (Merck KGAa) - and academic representatives of the network's platforms, including M. Ferrara and F. Penault-Llorca from Clermont-Ferrand, M.C. Favrot and C. Brambilla from Grenoble, C. Dumontet and A. Puisieux from East Lyon, G. Brun from South Lyon, F. Chauvin from Saint-Etienne and J.Y. Scoazec from the Biological Resource Center Program. Methodology experts from outside the region, including Ms. Filiatreau from the Observatory of Science and Technology (OST), Ms. Haeffner-Cavaillon and Ms. Aubertin from Inserm central services and Mr. Bansard from Inserm Unit 642, were also consulted.

⊙ Results of the study and interpretations

During the recent period studied (January 2003 to October 2005), Rhône-Alpes and Auvergne published an average of 228 scientific articles per year in international peer-reviewed journals. The experts believe that, of these, 121 articles per year were published in high-level journals (with an impact factor higher than 3) and 15 per year were published in very high-level journals (with an impact factor higher than 10), which is very similar to the French and worldwide averages. Quantitatively, the Rhône-Alpes and Auvergne Regions produce approximately 15% of France's publications in the field of cancer and 0.6% of the publications worldwide. A more detailed analysis of Rhône-Alpes' and Auvergne's positioning by topic highlighted six broad areas of excellence. The field that stands out most is epidemiology. It is both a field of excellence and a field of specialization compared to the French and worldwide averages, and is directly related to the activities of the WHO's International Agency for Research on Cancer (IARC), located in Lyon. This field includes cancer incidence and risk factors, including nutrition, occupational risks and hormone-related risks.

The next two fields of excellence stand out at the national and international levels. The first concerns local and regional cancer treatments, especially radiotherapy, as well as imaging and surgery. The second involves the clinical development of new medicines, especially those for rare tumors such as sarcoma.

A fourth field of excellence stands out internationally rather than nationally, as France has a remarkably high level compared to the rest of the world. This field is hematology ("blood cancer"), which focuses in particular on leukemia, myeloma, lymphoma and blood transplants ("bone marrow transplants").

The two remaining fields of excellence stand out at the national level. The first field is the biological analysis of tumors (phenotypic and molecular description), along with proteomics and microarrays, clinical prognostic factors and immunohistology. The final field of excellence combines assessment of clinical practices and patient and physician education.

⊙ Interest and limitations of the study, and future prospects

This study clearly highlighted six joint fields of excellence within CLARA. Nevertheless, this approach was not designed to be exhaustive. There are likely to be other fields of excellence that remain to be identified, in particular those that are emerging, multidisciplinary or linked with other fields, such as viro-immunology or nanotechnology. In addition, these fields of expertise have to be compared with the most promising fields in terms of international development potential.

The Cancéropôle and its governing bodies will thus use the study with discernment, in particular when considering the development of a large-scale cross-platform project in 2006.

Action plan for 2006

WHILE 2005 WAS THE YEAR THAT CLARA EMERGED ON THE SCENE, 2006 WILL BE THE YEAR THAT IT GAINS MOMENTUM. IT WILL ACHIEVE THIS BY CONTINUING AND STRENGTHENING THE PROGRAMS STARTED IN 2005 AND STARTING UP NEW CORE PROJECTS IN ORDER TO MEET NEW NEEDS AND CAPITALIZE ON NEW OPPORTUNITIES.

Two issues that were not within CLARA's scope until September 2005 will now be integrated into the roadmap:

- The link between the Cancéropôle and the Lyon BioPole competitive cluster in the field of infectious diseases. This competitive cluster was officially chartered in July 2005. The two clusters have been in contact with a view to developing a special focus on Infectious Diseases and Cancer.
- The emergence of a Human and Social Sciences Research focus in order to fight cancer. INCa has created a Human Sciences Research department and the first call for projects has been launched.

The Cancéropôle's rise will also require collaboration with another large-scale project in the Rhône-Alpes Region, NanoBio, with the application of nanotechnology to new diagnostic and therapeutic practices.

In addition, there is a set of initiatives designed to encourage harmonizing of efforts within the network:

- The first CLARA Scientific Forum on March 16th & 17th in Clermont-Ferrand;
- A communication plan, including a web site that is designed to be a true means of sharing information within the CLARA community and a showcase to France and the entire world;
- Closer collaboration between the Business Club and the Academic Club.

Finally, CLARA will seek to raise private funding, particularly through the Association of French Businesses for the Fight Against Cancer (GEFLUC).

Funding and allocation

This information completes the "Obtaining subsidies from various funding sources" section on pages 6 and 7 of this report..

I. Funding acquired

The amounts indicated for public funding providers are those allocated for the financial year 2005.

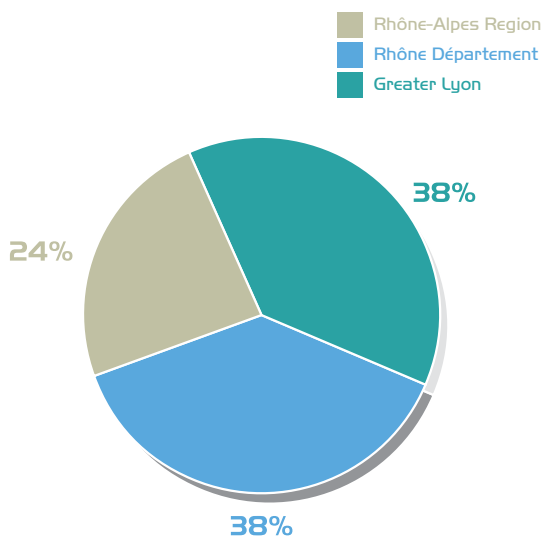
State

Origin of funding	Amount
INCa	€3,826,000*
Rhône-Alpes DRRT	€37,000
Rhône-Alpes FNADT	€108,000
Massif Central FNADT	€355,000
Total State Funding	***€4,326,000***

* The amount shown for INCa includes the amounts granted to scientific projects selected in the 2005 calls for projects. These sums will be paid over several years (overall total: €3,476,000).

Rhône-Alpes local authorities

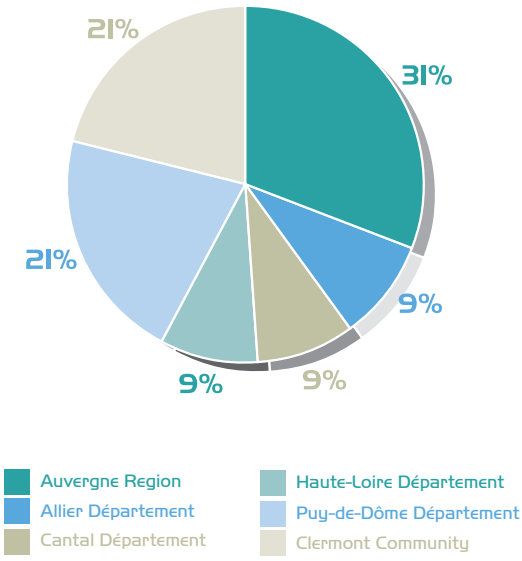
Origin of funding	Amount
Rhône-Alpes Region	€1,948,000
Rhône *Département*	€3,000,000
Greater Lyon	€3,000,000
Total	***€7,948,000***



Auvergne local authorities

2005 should be considered as an "initial provision of funding". The subsidies were dedicated to the new emerging focus area within CLARA, Nutrition and Cancer.

Overall, €330,000 in funding was granted. Below is a breakdown of the sources:



Origin of funding	Amount
Auvergne Region	€100,000
Allier *Département*	€30,000
Cantal *Département*	€30,000
Haute-Loire *Département*	€30,000
Puy-de-Dôme *Département*	€70,000
Clermont Community	€70,000
Total	***€330,000***

Europe

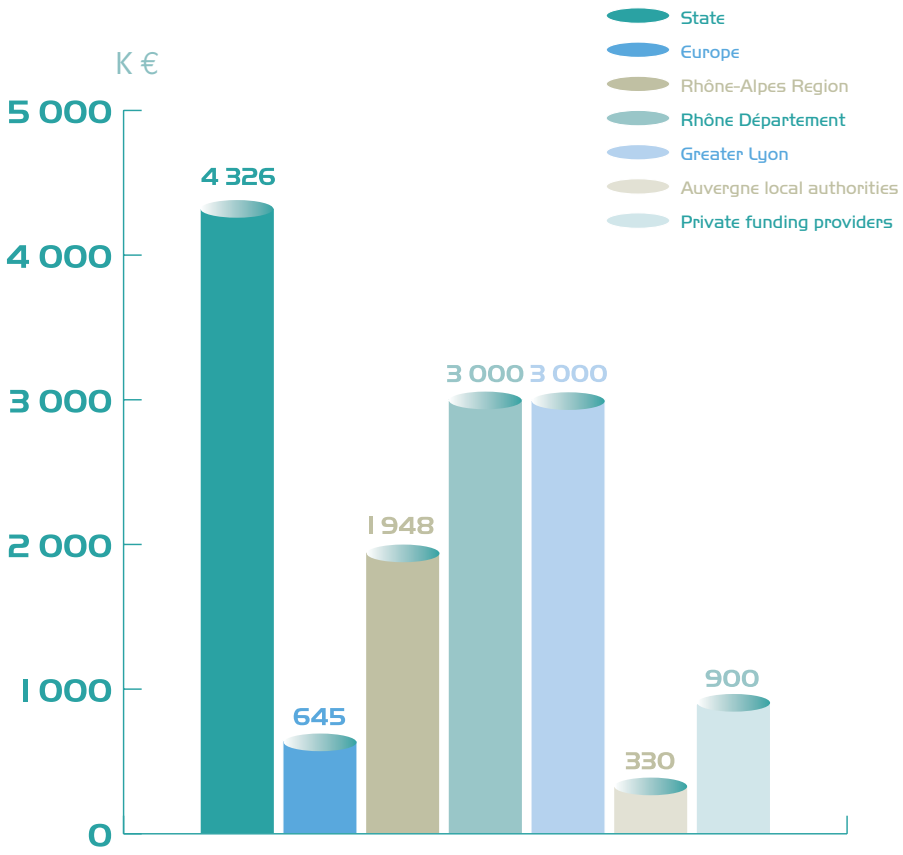
The Clermont platform received €645,000 in funding from the Auvergne and Loire European Regional Development Fund (ERDF).

Private funding

Origin of funding	Amount
Merck Santé	€700,000*
Breast Cancer Research Foundation	€200,000
Total	***€900,000***

* The figure shown for Merck's funding of the EMS project (see page 31) represents the total amount granted, to be paid over several years.

A number of funding sources



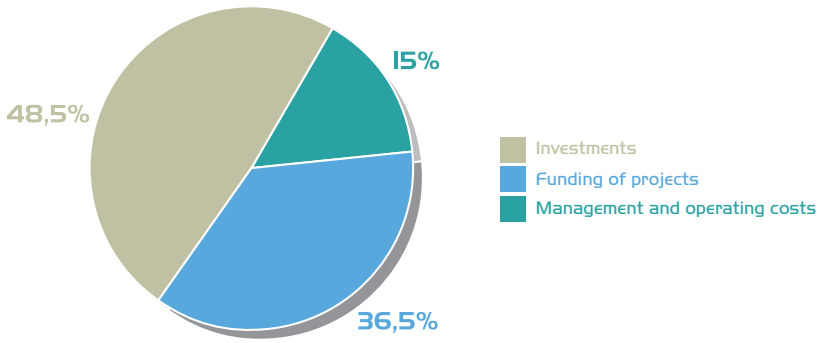
II. Allocation of funding

Overall allocation of funding by type of operation

We can distinguish 3 types of operations:

- Funding of scientific projects
- Investments in platforms, in particular purchases of equipment
- Management and operating expenses (Network Management and platforms)

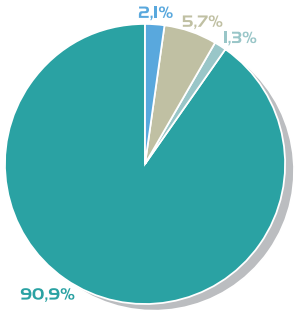
Type of operation	Breakdown	Amount
Funding of projects	Biological Resource Center	€328,000
	Proof of Concept	€437,000
	Projects selected by INCa	€3,476,000*
	Other projects	€900,000
	Total	***€5,141,000***
Investments	Léon Bérard Cancer Center	€2,500,000
	Lyon Civil Hospitals	€2,000,000
	Grenoble platform	€1,688,000*
	Clermont-Ferrand platform	€671,000
	Total	***€6,859,000***
Management and operating costs	Network Management	€1,140,000
	International Agency for Research on Cancer	€350,000
	Clermont-Ferrand platform	€659,000
	Total	***€2,149,000***
Total		*€14,149,000*



* The amount shown for INCa includes the amounts granted to scientific projects selected in the 2005 calls for projects. These sums will be paid over several years - For the details on the amounts allocated to each project, see pages 27 to 31: *Projects started in 2005 as part of INCa's call for projects.*

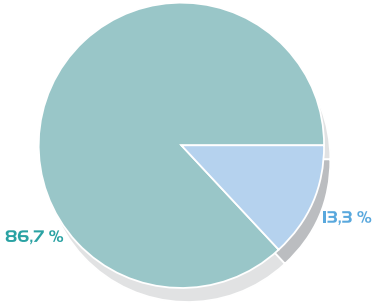
Allocation of sums provided by main funding sources

Origin of funding	Allocation	Amount
INCa	Network Management	€80,000
	Biological Resource Center	€220,000
	Proof of Concept	€50,000
	Scientific projects	€3,476,000 *
	Total	***€3, 826,000***



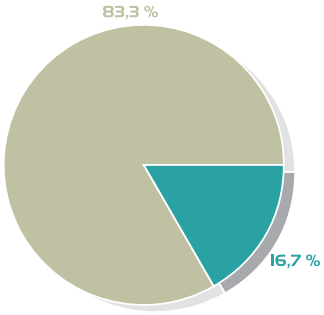
Scientific projects
Biological Resource Center
Proof of Concept
Network Management

Origin of funding	Allocation	Amount
Rhône-Alpes Region	Network Management	€260,000
	Grenoble platform	€1,688,000
	Total	***€1,948,000***



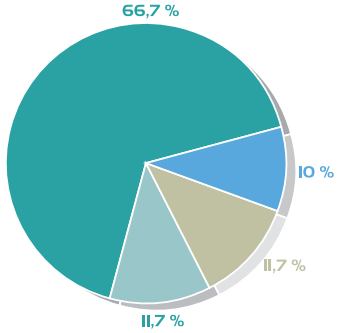
Grenoble platform
Network Management

Origin of funding	Allocation	Amount
Rhône *Département*	Network Management	€500,000
	Léon Bérard Cancer Center	€2,500,000
	Total	***€3,000,000***



Léon Bérard Cancer Center
Network Management

Origin of funding	Allocation	Amount
Greater Lyon	Network Management	€300,000
	Proof of Concept	€350,000
	International Agency for Research on Cancer	€350,000
	Lyon Civil Hospitals	€2,000,000
	Total	***€3,000,000***



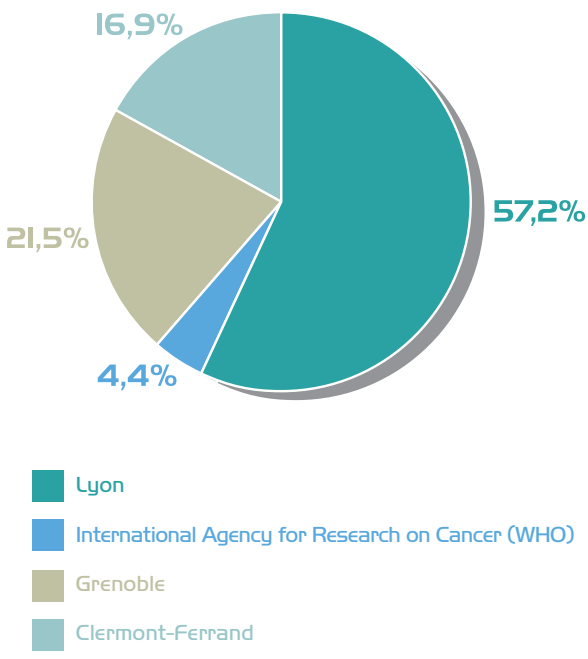
Lyon Civil Hospitals
Proof of Concept
International Agency for Research on Cancer
Network Management

* The amount shown for INCa includes the amounts granted to scientific projects selected in the 2005 calls for projects. These sums will be paid over several years - For the details on the amounts allocated to each project, see pages 27 to 31: *Projects started in 2005 as part of INCa's call for projects.*

III. Geographical breakdown of funding

The geographical breakdown of funding earmarked for investment or operating costs for the platforms is as follows:

Site	Amount
Lyon	€4,500,000
International Agency for Research on Cancer (WHO)	€350,000
Grenoble	€1,688,000
Clermont-Ferrand	€1,330,000
Total	***€7,868,000***



We are unable to show the breakdown of funding dedicated to scientific projects by site.

Photo credits:
J. Leone/Greater Lyon, Cancéropôle Lyon Auvergne Rhône-Alpes, Pathological Anatomy and Cytology - Léon Bérard Cancer Center, C. Da Costa/CG63, Léa and Napoléon Bullukian Foundation, Promega (www.promega.com), International Agency for Research on Cancer, Saint-Etienne Urban Community Photo Library, Grenoble Communication - 2006, Greater Lyon, Joseph Fourier University/François Enry, Joseph Fourier University/Communications Dept., Rhône-Alpes Region/F. Boisjoly, Léon Bérard Cancer Center, Jean Perrin Cancer Center, CNRS Photo collection - Plailly Philippe, CNRS Photo collection.

ADDENDUM
Dynamic Platforms

South Lyon

From a scientific standpoint, the programs underway at the platform were carried out as planned. In particular, two programs made significant headway in terms of organization in 2005:

- The epigenetics program initiated by the South Lyon and Grenoble platforms, coordinated by E. Gilson, was strengthened through INCa funding from the EPIPRO project. This project includes two "Work Packages" (WP). The first of these WPs aims to better define new epigenetic parameters (namely telomeres, heterochromatin or chromatin complexes involving nuclear hormone receptors) that can be used in the study of cancer. The second focuses on building epigenetic profiles of tumors (in particular lymphoid cancers and lung cancers) that can be used as markers for detection, diagnosis and prognosis or even for new therapeutic approaches.
- The therapeutic targeting programs led to the proposal of a second regional core program to INCa (not funded in 2005) on the screening of new anti-cancer agents. This program is coordinated by G. Gillet. Seed funding was provided through subsidies from the regional government.

The programs on hormone-dependent cancers and lymphoid cancers continued their work, as did those on immunological profiling and immunointervention in tumors. In the latter field, we must mention the start of a phase II clinical trial on antitumor vaccination in peritoneal carcinosis, coordinated by F. Bérard, which is the direct result of research carried out by the platform's teams in collaboration with a local firm, Génopoietic. Research on the use of physics in the treatment of tumors was reinforced by the emergence of a team led by C. Rodriguez as part of the region's "Etoile" project on hadrontherapy.

In addition to the collaborative projects already underway with many regional, national or international firms, two important projects were carried out in conjunction with OPi, a firm based in nearby Dardilly. The first, coordinated by G. Freyer, studied the pharmacokinetics and dynamics of a new immunomodulator. The second program, accredited and funded as part of the Lyon BioPole competitive cluster, aims to develop new monoclonal antibodies for therapeutic use in virally induced lymphoma.

All of these projects strengthened the relationships between the platform's various partners (HCL, UCB, ENS, CNRS and Inserm) as well as those with other teams from CLARA and with local firms.

Regarding work to build and equip the platform at the South Lyon facility, the part of the work funded by UCBL was completed. However, the work to set up and equip the laboratories was started only at the beginning of 2006. As soon as HCL received the first part of the funding from local authorities (Greater Lyon), it sent out calls for bids and placed orders for new equipment.

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