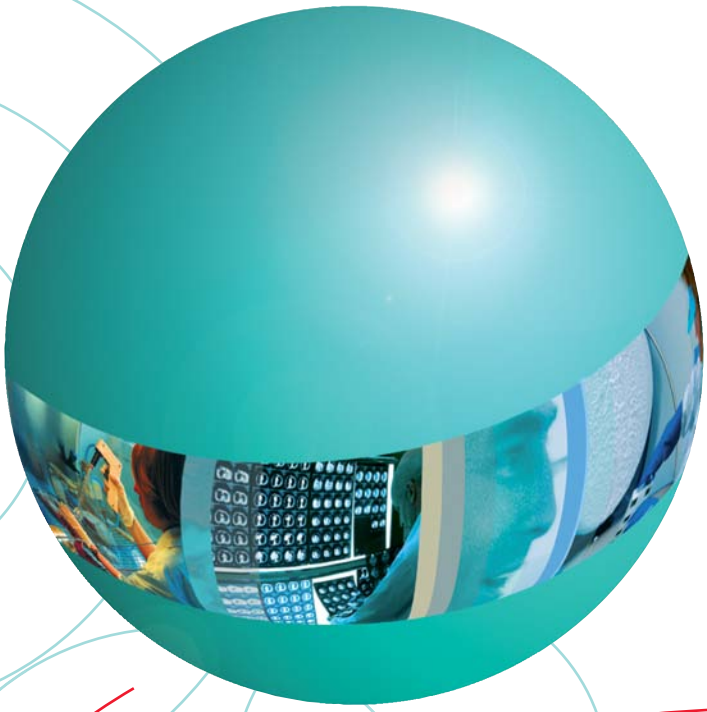
mixing cultures, speeding up breakthroughs



HIGHLIGHTS IN CANCER RESEARCH IN RHONE-ALPES AUVERGNE-JUNE 2007

CLARA

CANCÉROPÔLE LYON AUVERGNE RHÔNE-ALPES

SPEEDING UP PROGRESS

Under the aegis of the Bullukian Foundation

THANKS

This document could not have been produced without the active and efficient participation of researchers and representatives of research institutes and hospitals in the Rhône-Alpes Auvergne area.

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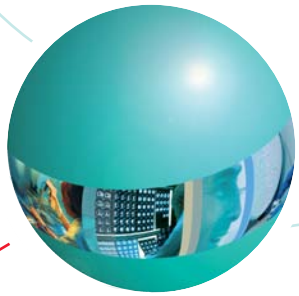
The conception, composition and coordination of this document are the work of Betty Dodet, Director of Dodet Bioscience, on the request of the "Cancéropôle Lyon Auvergne Rhône-Alpes" (CLARA).



CONTENTS

INTRODUCTION

CANCER, A WORLDWIDE BURDEN

A reliable epidemiological basis is absolutely essential where prevention, organisation of care and research are concerned, and necessary also for conceiving and applying the key elements of the fight against cancer. Incidence and mortality data are crucial not only for identifying and quantifying the problems to be solved, but also for developing hypotheses as to the causes of cancer and evaluating the results of various policies and programmes.

With 25 million people throughout the world affected by cancer, the disease constitutes one of the greatest human, socio-economic, medical, and scientific challenges at the beginning of the 21st century.

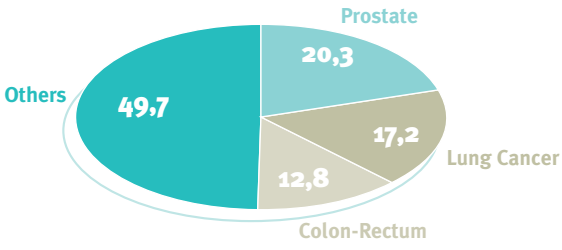
Every year in the world, 7 million people die of cancer, and nearly 11 million new cases are diagnosed. There is no region in the world that is not affected. Whereas cancer had been qualified as a disease of rich countries, it now weighs heavily on countries of poor or intermediary income. Both men and women are concerned, and children are not spared either. The types of tumours the most frequently diagnosed depend on a large number of factors, such as sex, geographical location or socio-cultural status.

In Europe, despite better prevention and better treatments, the number of new cases of cancer diagnosed each year has increased by 300 000 between 2004 and 2006. The International Agency for Research on Cancer (IARC) estimates that in 2006, there were 3.2 million new cases of cancer (excluding non-melanoma skin cancer) and 1.7 million deaths from cancer throughout Europe. The 25 EU countries accounted for nearly 2.3 million of the new cases and over one million cancer deaths.

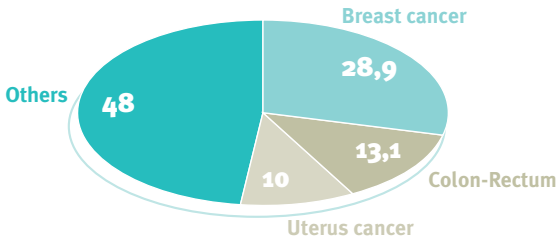
This increase can be attributed in part to the ageing of the population and, in certain cases, such as for breast and prostate cancer, to improved screening, notably at an earlier stage.

Breast cancer is now the most frequent cancer with 429 900 new cases, that is 13.5% of all cancers, followed by colorectal cancer (412 900 cases, 12.9%) and lung cancer (386 300 cases, 12.1%).

Distribution of cancer by type
(Ferlay at al, 2007)



Major Cancers diagnosed in Men (in %)



Major Cancers diagnosed in Women (in %)

Lung cancer remains the most deadly of cancers, with an estimated 334 800 deaths in 2006, that is 19.7% of the total number of deaths from cancer, followed by colorectal cancer (207 400 deaths), breast cancer (131 900 deaths) and stomach cancer (118 200 deaths). The overwhelming majority of lung cancers is due to smoking. Anti-smoking efforts are thus clearly a priority for France.
The study of the incidence of cancer in different populations and its evolution in time, associated with experimental studies, has led to a certain number of causes of cancer being identified. Thus, tobacco, asbestos and aflatoxins have been identified as major carcinogens. A further 20% of cancers are associated with chronic infections, mainly viruses such as hepatitis B (HBV) and hepatitis C (HCV), and bacteria such as *Helicobacter pylori*. Lifestyle factors such as nutrition, physical activity and alcohol consumption also play a role in the development of cancer, in interaction with genetic factors.

Note:

The European Union in 2006 included Austria, Belgium, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, the Netherlands and the United Kingdom.
Europe included the 25 EU countries plus Albania, Belarus, Bosnia Herzegovina, Bulgaria, Croatia, Iceland, Macedonia, Moldova, Norway, Romania, the Russian Federation, Serbia and Montenegro, Switzerland and Ukraine.

References:

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THE FRENCH CANCER PLAN

In 2003, France launched a plan for a general mobilisation in the fight against cancer. It includes 70 measures in order to "prevent, screen, provide care, give support, train, understand and discover". The Cancer Plan led to the creation of the National Cancer Institute (INCa) in 2004, and 7 regional or inter-regional cancer research networks ("cancéropôles"). These cancer research networks bring together, at the inter-regional level, all the projects, stakeholders, and means necessary for cancer research and ensure a close articulation between basic and clinical research.
The «Cancéropôle Lyon Auvergne Rhône-Alpes» (CLARA) is part of this scheme. It is the result of the coupling of the Rhônes-Alpes cancer research network created in 2001 and the lifeblood of the Auvergne region in the same field. CLARA's strength comes from the synergy between Lyon, Grenoble, Saint-Etienne and Clermont-Ferrand, and also from a solid network of academic and industrial stakeholders. All of this endows the Rhône-Alpes Auvergne area with great advantages for developing research projects of European scope.

This document presents the salient points and strengths of cancer research in Rhône-Alpes Auvergne. By way of examples, it illustrates the strengths and dynamism of this research. It does not constitute however a complete list: certain projects may not be mentioned despite their pertinence and the quality of the research teams directing them.

1 - RHÔNE-ALPES AUVERGNE: INNOVATION AND ENTREPRISE

The area of Rhône-Alpes Auvergne covers 69 700 km² and has a population of 7.3 million, equivalent to that of Switzerland. The region profits from a powerful economy with a yearly GDP of over 150 billion euros. Many famous entrepreneurs and industrial leaders come from the region and currently the number of large and medium size companies is growing in Rhône-Alpes Auvergne thus offering favourable conditions for decision making centres. The proximity of important markets, the qualifications of human resources, the quality of life, the conditions of implementation of economic activities are so many strong advantages in terms of attractiveness. Furthermore, Rhône-Alpes is well situated at the heart of European highways and high speed trains, and the Lyon-Saint-Exupéry airport has the potential to become the second most important airport in France as well as a major entryway into Europe. The performance of the regional economy is also linked to its powerful international position.

The industrial make-up of the inter-region continues to change with the growth of the electronic area and new materials industries, as well as industries related to health or using biotechnologies. Activities in mechanics, plasturgy, and textile are also constantly adapting in order to ensure their competitiveness on key markets, such as automobiles and aeronautics.
Innovation is at the heart of the industrial dynamics of Rhône-Alpes which is part of the large European backbone of the most active regions in R&D. Rhône-Alpes ranks 5th in Europe when it comes to technological and scientific potential; it includes important public research centres and companies who file numerous patents. It is the 9th region in the European Union in terms of requests for patents. Rhône-Alpes comes just after the Ile-de-France for 70% of scientific specialities, often largely outstripping other regions. Its contribution to national innovations is highly significant in nuclear techniques, electronics (components, visualisation, memory), supraconductor materials, macromolecular chemistry, medical engineering, and textile.

The combined potentials of Rhône-Alpes and Auvergne make the inter-region one of the leading European areas in terms of research. Among the six “global competitive clusters” launched in France in 2005, three are located in Rhône-Alpes: Lyonbiopôle (infectiology), MINALOGIC (nanotechnologies), and AXELERA (chemistry-environment). These “competitive clusters” seek to support innovation, bringing together research centres, universities and companies at the regional level.

The cities

Rhône-Alpes Auvergne has four major cities: Clermont-Ferrand, Grenoble, Lyon and Saint-Etienne.

Clermont-Ferrand developed around the Michelin company, the world leader in pneumatics. Auvergne profits also from companies in the top world rankings of mechanical robotics and in seeds; Limagrain is the leading seed producer in Europe and the fourth in the world. The National Institute for Agricultural Research (Inra) is an important partner in regional development and enjoys international scientific recognition; it possesses some thirty research units located in Auvergne (Theix, Clermont-Ferrand, Aurillac, Marcenat, Orcival-Laqueuille/Les Monts Dore), in Limoges and in Lyon, that represent 40% of the public research potential of Auvergne. The city of Clermont-Ferrand with 35 000 students and 6 000 researchers is notably renowned for its engineering schools.

Grenoble, endowed with 200 laboratories, has focused on the fields of mathematics, physics, nuclear research, engineering sciences, electronics/computer sciences and materials. This concentration of public research centres is accompanied by many R&D units within companies, notably in the fields of electronics, computer sciences, chemistry and paper. Over a fourth of the 18 200 jobs are in private research. The city was also chosen to incorporate one of the antennas of the European Molecular Biology Laboratory (EMBL), which is associated with two prestigious European structural biology research centres: the Laue-Langevin Institute (ILL) with a nuclear reactor furnishing bundles of large flux neutrons, and the European Synchroton Radiation Facility (ESRF) which possesses one of the three largest generators of bundles of X-rays in the world.

The metropolis of Lyon hosts 510 research laboratories, both public and private. The research is characterised by its diversity and transversal dimension. The main fields of public research are health and life sciences, basic physics, fine and molecular chemistry, engineering and material sciences, applied mathematics and computer sciences. Besides cancer, research in Lyon enjoys international renown in molecular genetics, virology, the neurosciences, medical imaging, catalysis, aggregate physics, and astrophysical instrumentation.

The region of Lyon can boast of being a major world centre in the prevention of human and animal communicable diseases, given the presence of two large companies in the vaccine industry, sanofi pasteur and Merial, one of the leaders in the in vitro diagnostics industry, bioMérieux, as well as one of the largest European laboratories of medical biology (Marcel Mérieux Laboratory). The World Health Organization (WHO) set up in Lyon its Office for National Epidemic Preparedness and Response.

Historically, the city of **Saint-Etienne** developed thanks to the trimmings, armaments and cycle industries and coal mines. Following the industrial crisis of the 1970s, the town converted and diversified its activities of high technology, in particular with regard to its centre of medical technology which counts for a third of the Rhône-Alpes' potential in medical technologies and 60% of the French production of medical textiles. There thus exists a competent network of industry researchers, scientists, medical and surgical teams, and instructors which develops exchanges, favours technological transfers and adapts training to the needs of companies, while looking for new markets and new industrial or scientific partners. The city's optics and vision centre includes leaders such as Thales-Angénieux, a world recognized specialist of zooms, as well as high performance optics, notably in the field of infrared and medical optics (endoscopy and cold light projectors).

Important scientists

Historically renowned scientists were either born or worked in Rhône-Alpes Auvergne: **Rabelais** practised medicine at the Hôtel-Dieu Hospital in Lyon from 1546 to 1548. The mathematician, physicist and theologian **Blaise Pascal** was born in Clermont-Ferrand in 1623. **Claude Bourgelat** created in Lyon the first veterinary school in the world in 1762. **Ampère,** who is famous for his contributions to physics and mathematics, was born in Lyon in 1775. As for **Claude Bernard** (1813-1878) who is considered one of the founders of experimental medicine, he remained faithful throughout his life to the Beaujolais village where he was born. The 1912 Nobel Prize in physiology and medicine was awarded to **Alexis Carrel,** born in the Lyon area, for the work he carried out in the United States on the suture of vessels and transplantation.

The University of Grenoble was founded in 1810 by **Joseph Fourier,** creator of mathematical physics and friend of the Grenoble resident **Champollion. Louis Néel,** born in Lyon in 1904 and awarded the Nobel Prize in physics in 1970, played an important role in the scientific development of Grenoble. It was he who was at the origin of the creation of the Laue-Langevin Institute, the European Synchroton Radiation Facility (ESRF), the Grenoble CNRS and CEA physics laboratories, and the development of applied mathematics and biology.

Yves Chauvin studied at the Lyon School of Chemistry, Physics and Electronics (CPE) and won the Nobel Prize in Chemistry in 2005 for the development of the metathesis method in organic synthesis. He is currently emeritus director of research in the surface organometallic chemistry laboratory of CNRS/CPE Lyon, having made his career in research at the French Petrol Institute.

Innovation and entreprise

The Lyon dweller **Joseph-Marie Jacquard** (1752-1834) is renowned for having invented the semi-automatic weaving machine. In Saint-Etienne, **Thimonnier** invented the sewing machine for which he filed a patent in 1830. In 1889, the brothers **André** and **Edouard Michelin** founded Michelin & Co. in Clermont-Ferrand: it was to become the world leader in pneumatics.

It was in Lyon that the brothers **Auguste** and **Louis Lumière** invented the cinematograph, which was patented on 13 February 1895. The same year, **Marius Berliet** constructed his first automobile. In 1898, **Geoffroy Guichard** founded a dry goods shop in Saint-Etienne, thereby laying the basis for the Casino group and food supply chains.

Having set up homeopathic pharmacies in the early 1930s, the Lyon dwellers **Jean** and **Henri Boiron** developed the principle of homeopathy on an industrial scale. The Boiron laboratories, whose headquarters and production factories are located in the Lyon suburbs, are the world leader in homeopathy since the 1970s.

Marcel Mérieux and his descendants created and then developed the vaccine and diagnostics industry in Rhône-Alpes. The son of a silk producer and a collaborator of Louis Pasteur, Marcel Mérieux (1870-1937) founded in Lyon a laboratory of medical analysis and produced tuberculin, serums and vaccines. His younger son, Dr **Charles Mérieux** (1907-2001), took over in 1937 and with his son Alain Mérieux ensured the wonderful expansion in the production of human and veterinary vaccines. Descended from the Institut Mérieux, sanofi pasteur is the world leader in human vaccines and Merial is one of the leaders in veterinary vaccines. In 1963, **Alain Mérieux** created bioMérieux, specialised in in vitro diagnostics and world leader in microbiology.

2 - RHÔNE-ALPES AUVERGNE IN THE FIGHT AGAINST CANCER

A LONG TRADITION OF FIGHTING CANCER

Research, prevention and treatment of cancer have been among the priorities of Rhône-Alpes Auvergne for several decades.

The first comprehensive cancer centre in Lyon was founded in 1923 by the surgeon Léon Bérard (1870-1955) with the financial help of Auguste Lumière, co-inventor of the cinematograph and inventor of the famous sofra-tulle for wounds. Today, the Léon Bérard Cancer Centre (CLB) is one of the 20 French Regional Cancer Centres (CRLCC).

In 1965, Lyon was chosen to host the International Agency for Research on Cancer (IARC). This United Nations Agency, attached to the World Health Organization (WHO) coordinates and conducts epidemiological and biological research. Its contribution to the epidemiology of cancer, to the identification of the causes of cancer and the evaluation of carcinogenic risks is recognized throughout the world.

Rhône-Alpes Auvergne was a pioneering force in genetic counselling applied to cancer and opened as early as 1988 the first official consultations in oncogenetics in France, in Clermont-Ferrand and later in Lyon.

Furthermore, Rhône-Alpes was one of the first pilot regions to install in 1989 organised breast cancer screening, which later spread throughout France. Reflection regarding psychological and sociological aspects of communicating on the subject of cancer was present from the start and continues.

The last thirty years have been marked by the development of research units devoted to cancer, in parallel with the establishment of technological centres. Finally, the development of clinical research in Rhône-Alpes Auvergne also became operational in the middle of the 1980s, in the fields of lymphoma, paediatric tumours and breast cancers.

A NEW MISSION: RALLYING AND ENSURING THE DYNAMICS OF CANCER RESEARCH

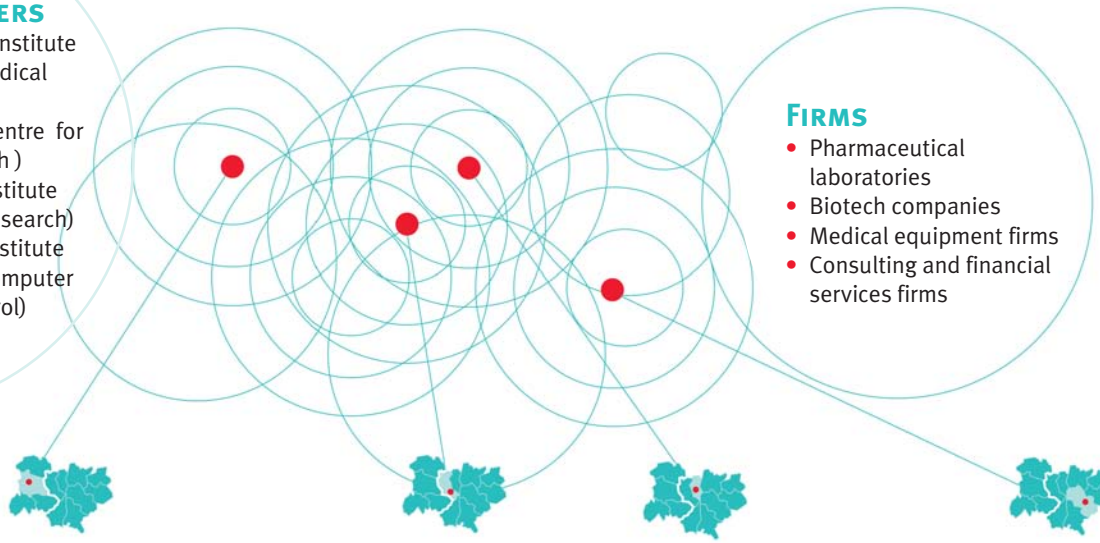
The "Cancéropôle Lyon Auvergne Rhône-Alpes" (CLARA) was founded at the crossroads of the national policy of mobilisation against cancer as defined by the Cancer Plan (2003/2007) and of an earlier regional will to invest in cancer research.

As early as 2001, the local authorities (Rhône-Alpes Region, Rhône County, Greater Lyon) and the State decided to invest in the creation of a network of local research on cancer, assembling representatives from industry and academic research. The goal was twofold: to make it possible for a greater number of patients to have access to innovating treatments and to reinforce a centre of multiple and complementary knowledge with regard to economic development

Thus CLARA was different from other French cancer research networks from the very start, given the amplitude of multi-annual funding ensured by the local authorities.

NATIONAL PLAYERS

- Inserm (National Institute for Health and Medical Research)
- CNRS (National Centre for Scientific Research)
- INRA (National Institute for Agricultural Research)
- INRIA (National Institute for Research in Computer Science and Control)



FIRMS

- Pharmaceutical laboratories
- Biotech companies
- Medical equipment firms
- Consulting and financial services firms

CLERMONT-FERRAND

- Auvergne University
- Blaise Pascal University
- Clermont-Ferrand University Hospital
- Jean Perrin Cancer Centre

SAINT-ÉTIENNE

- Jean Monnet University
- Ecole des Mines graduate school for science and technology
- Saint-Etienne University Hospital
- Loire Cancer Institute

LYON

- Claude Bernard Lyon 1 University
- ENS Lyon graduate school
- INSA Lyon engineering university
- National Veterinary School of Lyon
- Lyon Civil Hospitals
- Léon Bérard Cancer Centre
- International Agency for Research on Cancer (IARC)

GRENOBLE

- Joseph Fourier University
- Grenoble University Hospital
- French Atomic Energy Commission
- EFS Rhône-Alpes (French Blood Establishment)

Solid roots

Cancer research in Rhône-Alpes Auvergne benefits from numerous assets.

The region possesses **a dense network of health care establishments with both a hospital and university vocation:** 4 University Hospitals (CHU), 2 Regional Cancer Centres (CRLCCs), and the Loire Cancer Institute (ICL) in Saint-Etienne.

The national centre for light-ion hadrontherapy (bundles of carbon ions) is currently being established in Lyon and should receive its first patients in 2012. The construction of the ETOILE National Centre was foreseen by the Cancer Plan in the chapter concerning projects to be led as part of European cooperation.

Teaching in the field of medicine and life sciences is ensured by numerous academic institutions. Besides the universities and university hospitals, the Ecole Normale Supérieure (ENS) which benefits from research laboratories of the highest international level in all major scientific fields (biology, chemistry, computer sciences, geosciences and sciences of the universe, mathematics, physics) should be mentioned. The Claude Bernard Lyon I University (UCBL) and the ENS propose a joint Masters in cellular and molecular biology, cancer. Training for medical physicists was established in the Rhône-Alpes region in the autumn of 2004. Furthermore, the IARC offers courses and summer universities that take place for the most part in Lyon.

The network of research units devoted to cancer is particularly dense. Rhône-Alpes Auvergne disposes of 1 700 researchers in the academic sector, dispersed in 123 research units often situated at the heart of treatment centres, and linked to the local universities, the National Institute for Health and Medical Research (Inserm), the National Centre for Scientific Research (CNRS), the French Atomic Energy Commission (CEA), the IARC, the Saint-Etienne Graduate school for science and technology (Ecole Nationale Supérieure des Mines), the French Blood Establishment (EFS), the ENS, the National Veterinary School of Lyon (ENVL), the National Institute for Agricultural Research (INRA), the National Institute for Research in Computer Science and Control (INRIA). Several of these research units have been grouped together into federative institutes, as for example the Albert Bonniot Institute (Grenoble), labelled as a Research Centre by the Inserm and the Joseph Fourier University, which brings together 11 research teams and 5 biotechnological platforms focused on ontogenesis and molecular oncogenesis and its clinical applications.

A bibliometric study conducted in 2006 by CLARA showed that Rhone-Alpes Auvergne contributes 18% of French publications in the field of cancer and comes second after the Ile-de-France. A high proportion constitute outstanding publications: 3.4% of interregional publications are within the top world 1%.

The research teams of Rhône-Alpes Auvergne coordinate or participate in **large European projects**. The Childhope (immunotherapy of leukaemia / paediatric lymphoma) and Hermione (dependence receptors) projects are coordinated by the Léon Bérard Cancer Centre (Lyon). The network of excellence Conticanet (treatment of cancers of connective tissues) which brings together 20 partners from 9 European countries is coordinated by Lyon Civil Hospitals and the Lyon 1 University. The Virgil network (resistance of viruses to treatment), that includes over 70 laboratories in more than 16 countries of the European Union is coordinated by a Lyon Inserm laboratory. Several teams from Rhône-Alpes Auvergne are associated with European projects and networks, notably the Epigenome network (ENS, Lyon), the MetaBre (breast cancer, Inserm), Promet (prostate cancer, Inserm) and Inca (chronic infection and cancer, IARC) projects. In the field of nanotechnologies, Nano2Life is piloted by the CEA in Grenoble. The Claude Bernard Lyon I University participated in the European network Enlight, which coordinated European research in the field of hadrontherapy from 2000 to 2005 , and is participating currently in the elaboration of an Englight++ project within the 7th framework programme for research and technological development.

Thanks to the **top rate large equipment and technological platforms** existing in Rhône-Alpes Auvergne, functional and molecular exploration can be carried out on man and laboratory animals.

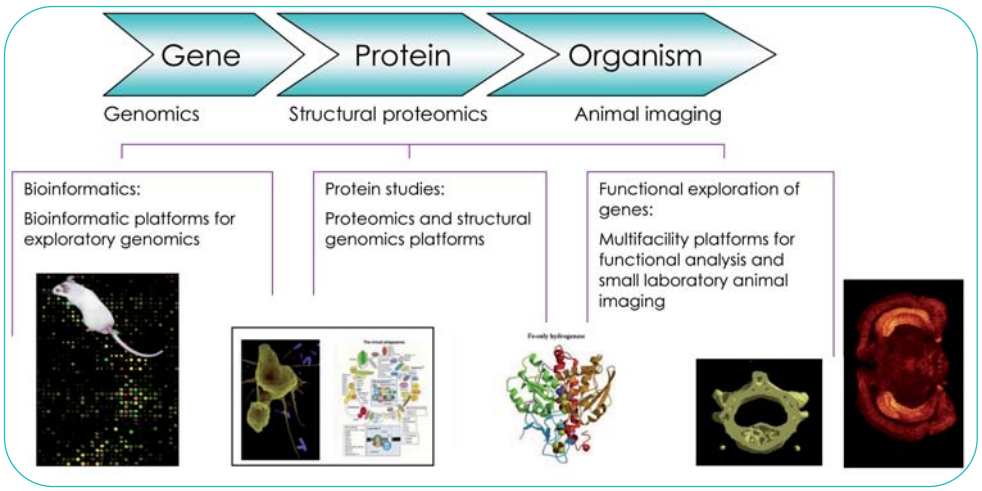
The establishments have put together **collections of biological resources and tumour banks** composed of perfectly characterised tissues, serums and biological fluids, which contain structured clinical information.

Rhône-Alpes Auvergne benefits from the presence of **dynamic companies**: some fifty such companies (from start-ups to large companies) have established partnerships with inter-regional teams in the field of cancer. The exchanges between academic and industrial stakeholders are catalysed by CLARA's "Business Club" which federates those companies with activities linked to research and development in the field of cancer in connection with regional research.

A CONCENTRATION OF RESOURCES AND TECHNICAL PLATFORMS

By profiting from the complementary qualities of public and private sector partners, Rhônes-Alpes Auvergne has developed an integrated network of technological platforms in the field of life sciences, so as to treat genomic and postgenomic data and propose a series of technologies going from the identification of gene products to the study of their function in their integrated biological environment.

source : Fondation Rhône-Alpes Futur



A series of technologies ranging from the identification of gene products to the study of their function in their integrated biological environment

Functional and structural genomics – The teams of Rhône-Alpe Auvergne have at their disposal the necessary instruments for gene sequencing, the identification of gene mutations as well as new approaches to functional genomics involving the expression of genes and their role in their original physiological environment, the living organism. As such, scientists working on the technical platform RoBioMol in Grenoble benefit from an automate for cloning genes and studying protein expression developed by the Structural Biology Institute (IBS) and the Protein'eXpert company. Most of the research in epigenetics in the region is organised within a structuring network supported by the French National Cancer Institute (INCa), which brings together 19 teams working on the EpiPro project (Epigenetic Profiling).

Proteomics – Research in proteomics benefits from the latest technologies in terms of protein microanalysis. Both proteomics platforms in the region are situated in Grenoble (the Inserm/J. Fourier University platform hosted by the University Hospital, and the Inserm/CEA platform hosted by the CEA within "Rhône-Alpes Génopole"). These platforms offer services to academic scientists as well as to industry within the framework of national and international programmes. More specifically, these two platforms allow researchers to analyse complex mixtures of proteins, notably biological fluids and cell and tissue extracts, using two complementary approaches: a classical approach based on 2D electrophoresis coupled with robotics, and a second very innovating approach using 2D nanochromatography and quantitative proteomics.

The Institute of Structural Biology (IBS) which is part of the French Atomic Energy Commission (CEA, Grenoble) is developing a large scale approach using cristallography and NMR spectrometry in order to discover high-resolution structure of proteins chosen according to various criteria, such as their structural originality or their contribution to a certain pathology. The IBS also benefits from an analytical ultra-centrifugation platform, which is unique in France.

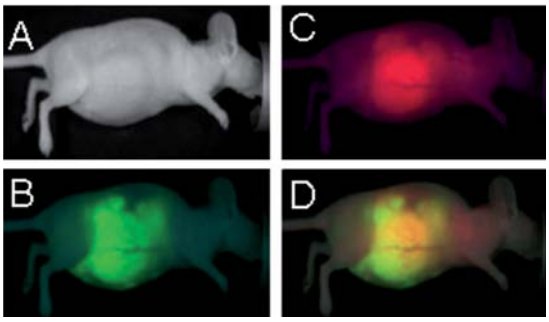
Animal models – The partners have developed animal models for testing and validating the pertinence of new concepts, testing or identifying diagnostic markers or new therapeutic agents. The animal models include transgenic mice (colon, liver, lung cancers), models of viral pulmonary carcinogenesis, heterotopic or orthotopic xenotransplants imitating a large variety of primitive or metastatic tumours, as well as viral-induced models. The analysis of these small animals (mice, rats) benefits from a highly structured network of technical platforms: ANIGENE (transgenesis), ANIMET (analysis of the energetic metabolism), ANIPATH (anatomopathological analysis and tissue engineering), ANIMAGE (imagery for the phenotyping and in vivo analysis of gene expression) and ANIPHY (physiological exploration). The regional scientists work also with the Institute of Experimental Surgery (Léon Bérard Cancer Centre), which offers the possibility of studying larger animals (pigs).

Imaging and functional exploration – Thanks to the available equipment, functional exploration can be performed in parallel on man and on the laboratory animal. The Centre for Exploration and Medical Research by Positron Emission (CERMEP), which brings together the academic partners of Lyon, Grenoble, and Saint-Etienne (Inserm, CNRS, University Hospital), is employing a technique of functional imaging that makes it possible to study *in vivo* the functioning of the human body and, in the field of cancer, the evaluation of the degree of tumour extension and of therapeutic efficacy. The applications of MRI for cancer in human clinical practise are studied in Grenoble (MRI 3T regional platform). The platform of small animal functional exploration ANIMAGE offers a remarkable variety of services: ultrasounds, X rays, magnetic resonance, isotopic imaging including scintigraphy and tomography by emissions of positrons. Methods of bioluminescence mean that tumours and metastases can be followed in a non invasive way: in order to do so, the small animal optic imaging platform of the Inserm at the Albert Bonniot Institute in Grenoble proposes couples of apparatus / molecules which have turned out to be a very powerful tool for the preclinical validation of new drugs.

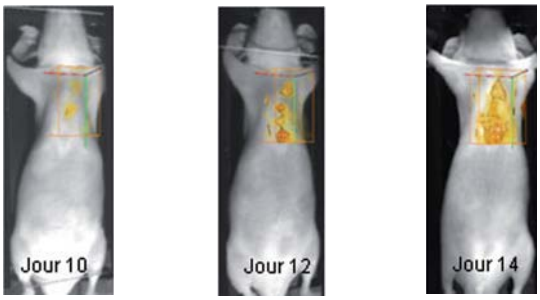
Tissue and cell engineering and imaging – Custom made cellular models are proposed by the company Transat, which uses RNA interference to inhibit the expression of specific proteins in cells. The region benefits from platforms specialised in cellular exploration imaging, with stations of confocal microscopy, electronic microscopy, and a station of Quantum dots of videomicroscopy.

Screening bioactive molecules – Rhône-Alpes Auvergne has two molecule screening platforms. The Centre for Screening Bio-Active Molecules (CMBA) is part of the CEA of Grenoble since early 2002 and is the first French academic platform dedicated to high throughput screening devoted to the study of cellular systems. Its purpose is to discover – on the basis of collections of chemical molecules and original pharmacological targets – new biologically active molecules constituting new research tools and/or candidates for new drugs. Lyon Drug Discovery (LYDD), in Lyon, concentrates on proteomics at the junction between public research and the pharmaceutical industry, thus bringing together the technological platform of the Claude Bernard University and the Idealp-Pharma company specialised in synthetic chemistry and bioactive molecule screening. It is the industrial partner that ensures the development of products of diagnostic or therapeutic interest.

Biofluorescence / bioluminescence applied to cancer research



2D (2D-FRI) fluorescence imaging of a peritoneal carcinoma in a live mouse
Tumours marked by luciferase are not visible in natural light (A) but appear in bioluminescence (B). The targeted drug marked by cyanine 5 is then injected intravenously (C). The fusion of the B and C images shows in yellow the co-localisation of the drug and the tumour mass.



3D TomoFluo imaging
This apparatus was tailor made by Inserm researchers in Grenoble and the CEA/Léti. Its pre-industrial validation is on-going (start-up Fluoptics in creation). This apparatus gives access to information from deep-seated organs and shows the progression of metastases, a phenomenon which is not visible in 2D.

Fields of excellence

Cancer research in Rhône-Alpes Auvergne is developing multiple collaborations in fields of excellence related to the life sciences.

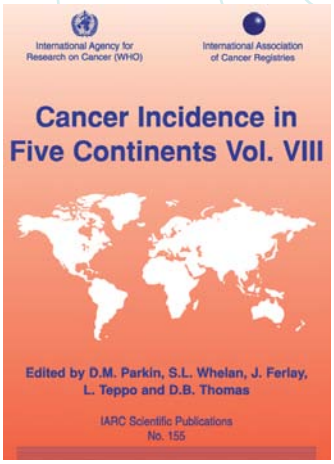
Epidemiology – The International Agency for Research on Cancer (IARC) brings together top quality scientists from all over the world. Inter-regional teams are associated with their work.

Micro- and nano- technologies – Cancer research in Rhône-Alpes Auvergne is also supported by the NanoBio centre for multidisciplinary innovation in nanobiotechnologies. It was founded by the CEA/Léti and the Joseph Fourier University in order to develop new tools for imaging, proteomics analysis or the development of targeted diagnostic or therapeutic tests.
In Grenoble, 4000 scientists work in the field of micro- and nano- technologies, among whom 300 are specialised in health-related applications (NanoBio). The project is relayed at the European level by the network of excellence Nano2Life coordinated by the CEA and which includes 23 partners and over 200 researchers. The "Nanotechnologies and Cancer" research program is centred on the application of nanotechnologies to diagnostic and therapeutic practise.

Infectiology, immunology, vaccinology – Lyonbiopôle, labelled as a « global competitive cluster » in vaccines and diagnostics, includes 2 500 scientists in infectiology. Collaborations in the area of cancer focus on viral-induced cancers (EBV, HPV, HBV, HCV, HTLV, HHV8), the biology of the immune response and the mechanisms allowing tumours to escape surveillance of the immune system.

Neurosciences – The study of brain tumours is sustained by the international level of the Federative Neurosciences Institute of Lyon, which specialises in brain imaging. In the field of neuro cancer, this Institute associates basic, preclinical, and clinical research. The Research and Care Theme Network (RTRS) "Neurocap", labelled by the French government in 2007, brings together treatment and research establishments in Rhône-Alpes Auvergne in favour of research on neurological handicaps.

Tissue metabolism – Rhône-Alpes Auvergne benefits from a specific expertise in the morphological and functional exploration of bone tissue. Teams from Inserm and Lyon Civil Hospitals (HCL) are particularly renowned for their work in epidemiology and therapeutic research concerning osteoporosis and bone alterations during cancer. They collaborate with cancer scientists in the study of soft tissue sarcomas and bone metatstasis.



Nutrition – Two of the four French Human Nutrition Research Centers (CRNH) are located in Rhône-Alpes Auvergne: one in Lyon and the other in Clermont-Ferrand. The Clermont-Ferrand team notably studies the role of nutrients in the prevention of cancer as well as their role during treatment (increasing the effectiveness of chemotherapy by the absorption of food deficient in methionine).

Synthetic chemistry – The Laboratory of Dynamic and Structural Studies of Selectivity (LEDSS – combined CNRS research unit in Grenoble) is highly engaged in synthetic chemistry for nanobiotechnologies. In collaboration with the Institute of Chemistry of Natural Substances in Gif-sur-Yvette, it has developed synthetic procedures for the drugs Taxol® and Taxotère® produced by Sanofi-Aventis for cancer treatment.

An asset for Rhône-Alpes Auvergne: the IARC, world observatory of cancers

It is in Lyon, at the International Agency for Research on Cancer, that world data from cancer registries in different countries (represented by the International Association of Cancer Registries, IACR) are assembled and analysed. Maps describing the frequency of various cancers in different parts of the world are drawn up and published in the series *Cancer Incidence in Five Continents*.
Thanks to these data which reach back some thirty years, one can study the evolution of the incidence of cancers in time and as a function of geographical zones as well as develop hypotheses as to their origin.

On the basis of the epidemiological studies carried out at the IARC, accompanied by laboratory studies, the role of the human papillomavirus in cancer of the cervix was identified and this in turn led to the development of a vaccine distributed in Europe by sanofi pasteur MSD, whose headquarters are in Lyon.

A European Cancer Observatory has been established at the IARC thanks to CLARA funding. It gathers the most recent data on cancer incidence and mortality in Europe and creates computer and biostatistical tools which make possible a "real-time" analysis of all data registered at the IARC. This observatory will favour the collection of data on the stage of cancer at the time of diagnosis, which will improve the evaluation of the impact of screening and treatments.

The IARC monographs identify environmental factors likely to increase the risk of cancer for man (chemical products, complex mixtures, professional exposures, biological and physical agents, behavioural factors). Public health agencies can then use this information as scientific evidence in their actions seeking to prevent exposure to such potential carcinogens. Interdisciplinary working groups made up of international scientific experts meet in Lyon to examine the published studies and evaluate the degree of risk of carcinogenicity with regard to a specific agent. Since 1971, over 900 agents have been evaluated among which 400 have been classified as being carcinogenic or potentially carcinogenic for man. As early as 1976, the IARC warned against the effects of asbestos. Several times, the Agency informed against the negative effects of tobacco, not only for active smokers but also for those passively exposed. It proved the role of viruses (Epstein-Barr virus, human papilloma virus) in the induction of cancers, identified chromosome abnormalities and genes implicated in various tumours.

The IARC is coordinating a vast prospective European study on the relation of nutrition to cancer (European Prospective Investigation into Cancer and Nutrition - EPIC). Over 500 000 people have been included since 1992. This study has already demonstrated the protective role of fibre in colorectal cancer, the role of metabolic (obesity) and hormonal (endogenous steroids) factors in breast cancer as well as the role of obesity in endometrial cancer.

In partnership with the European Commission, the Rhône Committee of the French National Cancer League and the Urban Community of Lyon, CLARA has launched an international project called ACCIS (Automated Childhood Cancer Information System). This programme is coordinated by the IARC and uses the cancer registries of 35 European countries in order to collect, present, interpret and spread information on childhood cancers collected over the last 30 years. Up to now, the ACCIS has accumulated data on 140 000 tumours in patients aged under 15 years. On the basis of this information, the IARC is coordinating a new international etiological study regarding risk factors for certain embryonic tumours in children.
Epidemiological data concerning France comes from French cancer registries assembled by the FRANCIM network which analyses the data in collaboration with the Biostatistics Service of Lyon Civil Hospitals and the IARC. As a member of the FRANCIM network, the Isère Cancer Registry coordinates various studies of geographical epidemiology (thyroid cancer and radioactive fallout from Chernobyl, risks related to the proximity to an incinerator of household waste) and descriptive epidemiology (incidence, prevalence). It also evaluates the campaigns of breast, cervical and colon cancer screening in the County (département) of Isère. Together with the Rhône-Alpes Pathology Statistics and Data Centre (CRISAP), the Isère Registry is setting up a regional evaluation of breast cancer screening.
In France, the number of new cases of cancer in 2000 was evaluated to be approximately 280 000 and the number of deaths – 150 000. The most deadly are lung, colorectal and certain oral cancers (lips, mouth, and pharynx).

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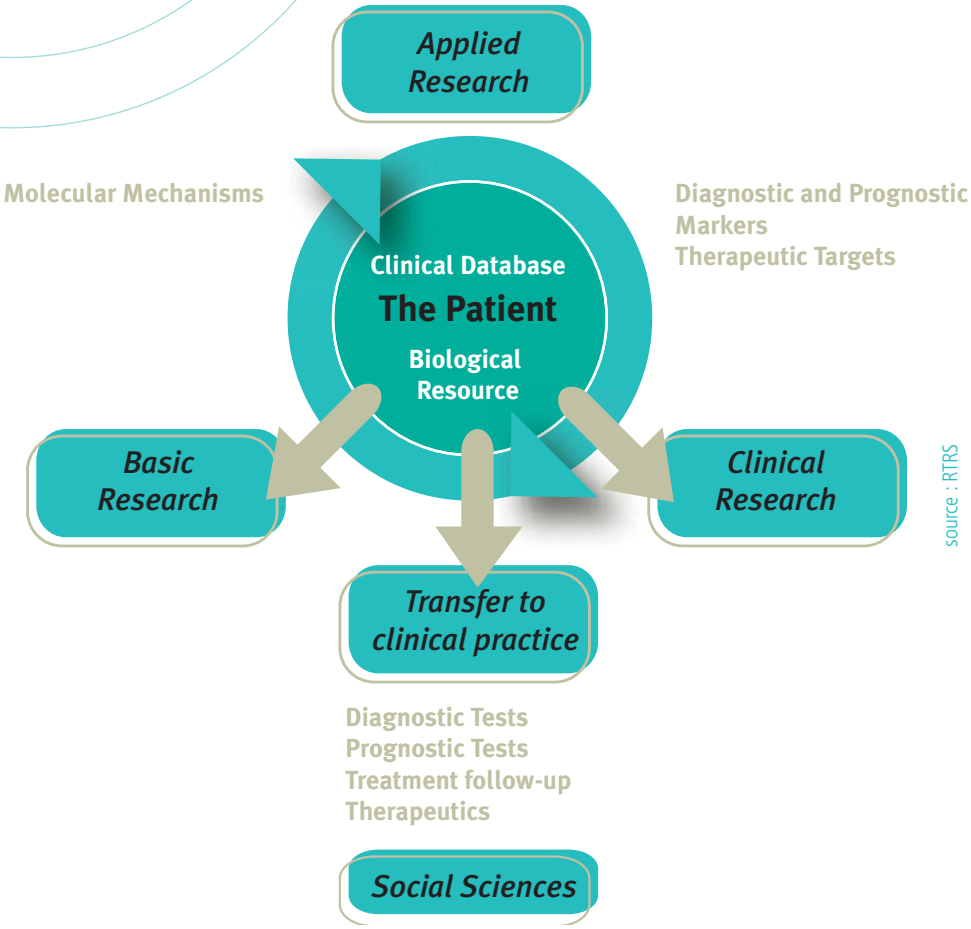
3 - THE PATIENT AT THE KEY STAGES OF RESEARCH

THE PATIENT AT THE HEART OF THE FIGHT AGAINST CANCER

The patient is at the heart of the fight against cancer: the intricacy of health care and research has become one of the major characteristics of scientific medicine.



source : RTRS

Within CLARA, teams of Rhône-Alpe Auvergne scientists work in close collaboration with clinical teams and industrial partners.

CLARA is keen to accelerate the transfer of scientific knowledge and the development of its clinical application by accompanying innovating projects until proof of concept and by stimulating partnerships with industry. It thus participates in the economic development through research applications.

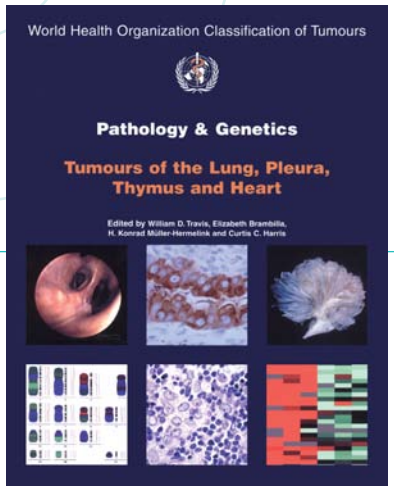
A RENOWNED MEDICAL EXPERTISE

The treatment of cancer in Rhône-Alpes Auvergne represents an average of 250 000 yearly hospitalisations (of which over 4 500 in paediatrics). These hospitalisations correspond to nearly 300 000 sessions of radiotherapy, over 35 000 surgical stays and more than 140 000 cycles of chemotherapy.

Rhône-Alpes Auvergne is working on establishing one of the largest European centres in paediatric cancer, the Institute of Haematology and Paediatric Oncology (IHOP), which will bring together the competences of Lyon Civil Hospitals (HCL) and the Léon Bérard Cancer Centre, already recognized as a centre of excellence.

The expertise of Rhône-Alpes Auvergne's cancer teams in various cancers is recognized internationally: lung cancer, breast cancer, oncohaematology, paediatric tumours (neuroblastomas and sarcomas) and rare adult tumours (sarcomas, neuroendocrine tumours, peritoneal tumours). Thanks to the existence of an important sector in medical and surgical neurology, the region has become a reference centre for brain tumours.

Several University Hospital teams have been selected at the national level to establish pilot coordinating units to deal with rare adult tumours. Four of the ten national projects selected by the National Cancer Institute in 2006 are coordinated by Lyon Civil Hospitals. They focus on: diagnosis and classification of adult neuroendocrine tumours, treatment of rare primitive malignant tumours of the peritoneum (National Network of Primitive Malignant Tumours of the Peritoneum – RENAPE), early screening and treatment of throphoblastic tumours and the treatment of rare malignant pulmonary tumours, both mediastinal and cardiac. The coordination for the treatment of ovarian tumours is jointly carried out by physicians from the Léon Bérard Cancer Centre in Lyon, Paris Hospitals and the Gustave Roussy Institute in Villejuif.



Classification of tumours

Several regional teams participate in the WHO classification of tumours and in the elaboration of clinical standards at the national and European levels.

Lung cancer – The University Hospital of Grenoble is reputed for its expertise in lung cancer. One of its members plays a leading role in various international boards as chair of the pathology panel of the International Association for the Study of Lung Cancer (IASCL); co-author and co-editor of the latest WHO classification of lung and thoracic tumours. The international group for the new TNM (tumour, lymph node, metastasis) lung cancer classification of the International Union against Cancer (UICC) also benefits from their expertise and from the contribution of the Isère Cancer Registry.

Reference:

• Travis WD, Brambilla E, Muller-Mermelink HK, Harris CC, eds, WHO Classification of Tumours - Pathology and Genetics – Tumours of the Lung, Pleura, Thymus and Heart, IARC Press, Geneva, Switzerland, 2004.

Lymphoma – The teams of Lyon researchers at the International Agency for Research on Cancer, Lyon Civil Hospitals and the Léon Bérard Cancer Centre have contributed to the identification and WHO classification of lymphoma and haematological tumours. They have participated in the description and listing of new entities of lymphoma, in the identification of translocations and other chromosomal rearrangements that characterise these diseases. Collaborating with teams from Grenoble, they have also worked on the development of techniques of *in situ* hybridization on chromosomes. These tools are used daily for an improved diagnosis and prognosis and for predicting the response to new targeted therapies.

Sarcoma – The recognized expertise of the Lyon practitioners in the treatment of sarcoma, including gastrointestinal stromal tumours (GIST) is rewarded by a privileged position in national and international working groups such as the French Sarcoma Group, the Soft Tissue and Bone Sarcoma Group of the EORTC, the head committee of the Connective Tissue Oncology Society. The Lyon team which directs the CONTICANET (Connective Tissue Cancers Network) has participated in the new classification of GIST following the demonstration of the KIT protein as a diagnostic marker and therapeutic target. The molecular diagnosis of sarcoma is carried out in a small number of centres in Europe and France and joint work in standardisation is currently being conducted by national and European research programmes.

Lyon teams have also contributed to the identification and classification of diverse **rare tumours**: recognition of a new entity of pineal tumour in 2006 and its WHO classification; constitution of an international registry of colorectal carcinomatoses, and classification of peritoneal carcinomatoses.

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Networks of care

Rhône-Alpes Auvergne applied ahead of time the recommendation of the 1997 National Health Conference **"to offer patients suffering from cancer a concerted multidisciplinary treatment so that all have access to nearby quality care"**.
Around 30 years ago networks of care in cancerology began to be established in Rhône-Alpes Auvergne. In Grenoble, the Unit of Cooperation in Cancerology, created in 1976 within the University Hospital, conducted pioneering work concerning multidisciplinary opinions regarding the treatment of patients within the hospital but also with hospitals in the Alpine region by bringing together surgeons, cancerologists, radiotherapists, organ specialists, and anatomopathologists.
The stakeholders - clinicians specialised in various disciplines, general practitioners, researchers, pharmacists, nurses, psychologists and social workers – organised themselves within five networks (Arc Alpin, Concorde, OncAuvergne, Oncoloire and Oncora) all of which converge for optimal patient treatment and nearby access to care. Oncora has developed practise frames of reference within the network and then at the national level (Standards, Options and Recommendations or SOR) and has participated in the establishment of practise evaluation systems.
These networks have allowed for standardised and therefore optimal treatment of patients and have also encouraged closer relations between scientists and clinicians. They have made it easier to share biological resources and are now contributing to the development of clinical research in partnership with reference centres in cancerology.

Family cancers and genetic counselling

Around 5 to 10% of cancers are associated with an inherited constitutional mutation. IARC and CNRS teams in Lyon have contributed to the study and the identification of genetic alterations in particular genes that predispose to frequent cancers (BRCA1 and BRCA2 genes for breast cancer, MMR gene for colon cancer). The MEN-1 gene responsible for multiple endocrine neoplasia was isolated thanks to the work of the European consortium led by scientists from the IARC, the CNRS and the University of Lyon.
These discoveries have greatly modified the evaluation of individual cancer risk and have led to the establishment of consultations in oncogenetics. The purpose of these consultations is to identify those families who have a major hereditary predisposition to cancer, to answer their questions on the risk of developing cancer, to inform them of appropriate prevention measures and screening as well as treatment strategies. Currently there are about a hundred such consultations in France. The regional teams who set up the first hospital structures devoted to genetic diagnosis of monogenic forms of cancer (polyposis, familial adenomatosis, multiple endocrine neoplasia, neurofibromatosis type 1, von Hippel Lindau disease) participated in the creation of national expert groups who contribute to the development of diagnostic and treatment protocols for patients predisposed to such syndromes.

Consultations in oncogenetics are associated with laboratories devoted to basic research and the analysis of mutations implicated in cancers. The Lyon, Grenoble and Clermont-Ferrand teams are pursuing their research on genes involved in breast and ovarian cancer as well as cancer of the colon, endocrine and neuroendocrine tumours, pituitary tumours, surrenal and thoracic tumours. The department of oncogenetics of the Jean Perrin Cancer Centre in Clermont-Ferrand leads an international consortium including scientists from 5 countries on the genetic analysis of mammary cancers. Together with Cogenics Europe (a company providing services in the field of DNA sequencing), the teams of the Léon Bérard and Jean Perrin Cancer Centres are in the process of high throughput sequencing of genes which could be involved in human cancers and notably cancers of the breast, colon, lung, osteosarcoma and neuroblastoma, with the objective of identifying new targets of diagnostic and therapeutic interest, while contributing to the comprehension of the mechanisms involved in cancer development.

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The evaluation of medical practise and health economics

The optimisation of clinical practise requires constant evaluation. Within the Analysis of Healthcare Systems Laboratory (LASS), the Research Group in Health Economics and Networks in Oncology (GRESAC) is devoted to the evaluation of medical practise so as to optimise it. The research conducted by GRESAC also includes economic aspects and is concerned with the medical-economic evaluation of new technologies and types of treatment.

Their first work project showed the influence of networks of care on the modifications of practise. A new study is evaluating the quality of treatment of patients suffering from sarcoma of the soft tissues with regard to its compliance with the Standards, Options and Recommendations (SOR). The analysis will look at the entire course of care (initial treatment, possible relapse, follow-up) over a foreseen period of observation of 4 years. This project is piloted by the Léon Bérard Cancer Centre and supported by funding from Merck Santé.

The University Hospitals of Lyon and Grenoble, the CRLCCs of Lyon (Léon Bérard Cancer Centre) and Clermont-Ferrand (Jean Perrin Cancer Centre) as well as the hospital centres of various towns in Rhône-Alpes Auvergne are currently participating in the medical-economic evaluation of Herceptin® in metastatic breast cancer, within the framework of a national programme of Support for Innovating and Costly Techniques (STIC).

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Patient information and the doctor-patient relationship

Research in human sciences is one of the thematic axes in the fight against cancer in Rhône-Alpes Auvergne. The Loire Cancer Institute (ICL) in Saint-Etienne is the regional leader of "research-action" in cancer prevention and education. Its' vocation is to coordinate research and create dynamics in the field by inciting various human and social sciences teams to become involved in the field of cancer. A regional resource Centre for information, education, and prevention of cancer (Hygée Centre) will be built on the Saint-Etienne site.
The ICL proposes and evaluates programmes of patient education in cancerology in various centres of Rhône-Alpes Auvergne. It is coordinating a national study on information given to women convened for breast screening. Another study which is soon to begin will focus on the factors of acceptance or refusal of HPV vaccination in the primary prevention of cervical cancer.
These "research-actions" concentrate on the psychological and social aspects of prevention, screening and compliance with treatment, while stressing the doctor-patient relationship in such diverse situations.

Therapeutic options : help in shared decision making

Patient information is both a legal and ethical obligation. Shared decision making goes even further in that it completes the information by a choice among several options of treatment differing with regard to quality of life, while seeking to respect the patients' values.
The Research Group in Health Economics and Networks in Oncology (GRESAC) participated in the elaboration and validation of tools meant to help in the decision making process and which allow the doctor to deliver quality information to his/her patient and the latter to reveal his/her true preference. The Group used a methodology similar to that of "SOR Patient Knowledge" by associating a medical team, a team of multidisciplinary professionals, and patient representatives.

Reference:

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4 - OUTSTANDING CLINICAL RESEARCH

Clinical research in Rhône-Alpes Auvergne benefits from an important recruitment of patients with diverse oncological diseases. Clinical and applied research is also enhanced by biological banks and series constituted by health care institutions, the excellence of which is recognised by the Ministry of Health. Patients can thereby benefit from the most recent therapeutic innovations in cancerology.
Rhône-Alpes Auvergne possesses several approved centres for conducting clinical trials from phase I to III and relies on four investigation centres qualified by Inserm (Clermont-Ferrand, Grenoble, Lyon, Saint-Etienne).
From 1996 to 2006, 60 clinical trials in cancerology were piloted in Lyon by hospital units in the context of Hospital Clinical Research Programmes (PHRC). In 2005, the clinical trials coordinated by Lyon teams included 123 adult patients suffering from sarcoma, 160 patients affected by lymphoma, and 15 children presenting with neuroblastoma.

Platforms for clinical research

Assistance to clinical research in cancerology
Besides the Clinical Investigation Centres of the University Hospitals and the Regional Cancer Centres, Rhône-Alpes Auvergne possesses an Assistance Platform for Clinical Research on Cancer (PARCC-ARA). This platform provides methodological support (help in formulating the problem, in elaborating protocols and methodologies for the analysis of biomolecular and clinical data, and in organising complex studies), as well as assistance in carrying out the projects (constitution of a network of investigators, logistics and co-ordination of multicentric studies, quality control, data collection and management of data bases, follow-up of security and efficiency, statistical analysis). At the end of 2006, 17 clinical trials had been examined and supported, besides the specific studies conducted within PARCC-ARA such as the study of the impact of radiotherapy in cancerology, related to the ETOILE project (hadrontherapy).

Pharmacological targeting and modelling of the effect of anti-cancer treatments
This academic platform situated in South Lyon includes clinical, pharmacological and biomathematical competences with the object of optimising therapeutics in clinical cancer care. It develops projects seeking in particular to model the future of drugs and their interactions with different biological processes, to follow the relations between pharmacokinetics and pharmacodynamics in order to adjust the therapeutic effects, and to develop new molecules and test them in phase I studies. It also conducts clinical trials with new dosage adjustment and throughput of anti-cancerous drugs with the assistance of a mathematical model allowing for the control in “real-time” of the hemato-toxicity and the anti-tumour efficacy. A trial of proof of

concept is on-going for breast cancer. Basic work is carried out in collaboration with the ENS-Lyon and the Science Faculty of Marseille in order to develop mechanistic and phenomenological models for describing biological realities: cell proliferation, signal transduction, angiogenesis, cytotoxic effects and resistance to drugs, haematopoisis regulation. Certain models are tested on the request of the pharmaceutical industry for the optimisation of the preclinical development of new anti-cancer drugs (partnership with Grunenthal Germany and Astra Zeneca).

Five of the 28 national Clinical Study Groups (GEC) created by the French National Cancer Institute are piloted by CLARA stakeholders. Their studies focus on lymphoma, sarcoma, ovarian tumours, oncogeriatrics, and radiotherapy.

Research which has impacted on practise

The Rhône-Alpes Auvergne teams have acquired international renown in the conduct of trials which have succeeded in elaborating and/or validating new methods of prevention, diagnosis or new therapeutic approaches. They are pursuing their research with the objective of optimising diagnosis and treatments.

Cancer screening
After having participated in setting up breast cancer screening in France, the region played a major role in the European study which showed that the establishment of systematic neuro blastoma screening programmes for infants was not justified.

Oncohaematology
At the heart of the oncohaematology activity developed in Lyon and in Rhône-Alpes Auvergne, the field of malignant lymphoma has occupied a special place for two decades. Doctors from Lyon Civil Hospitals working on the disease have developed clinical and translational research of international reputation. Physicians and scientists involved in the study of lymphoma have become associated with the Study Group of Adult Lymphomas (GELA) and now cooperate by leading many therapeutic trials (over 5000 patients). GELA has, among other things, demonstrated the therapeutic advantage of certain molecules (interferon, growth factors) or certain therapeutic strategies (intensification of autologous transplants for severe cases, cessation of radiotherapy in most localised forms of aggressive lymphoma). This group organised in Lyon the first international study which showed the benefit of monoclonal antibodies (rituximab) for the treatment of diffuse large cell lymphoma – which has marked an important stage and has been recognised the world over.

Autologous transplants of haematopoietic stem cells constitutes a far reaching activity in Rhône-Alpes Auvergne. The Lyon teams were the first to show the contribution of autologous transplants in the treatment of malignant lymphoma. They went on to develop new techniques in this field and pursued the evaluation of treatments.
Allogenic transplantation and new immunotherapy techniques are developed in the field of leukaemia and myeloma (Lyon, Grenoble), with the coordination of several French or European teams, within the framework of the European Group for Bone Marrow Transplantation (EBMT) or the International Bone Marrow Transplant Registry (IBMTR).
The goal of the European project CHILDHOPE, coordinated by the Léon Bérard Cancer Centre, is to develop immunotherapy for advanced and resistant paediatric haematopoietic tumours (acute lymphoblastic B-cell leukaemia, non-Hodgkin B-cell lymphoma, acute myeloid leukaemia). This translational research project ranges from the preclinical validation to the clinical use of activated T lymphocytes for children suffering from haematopoietic diseases. This project is structured around a network of European partners and the international confederation of parents of children affected by cancer.

Treatments for sarcoma and digestive stromal tumours
The group of researchers and clinicians of the Claude Bernard University, the Léon Bérard Cancer Centre and Lyon Civil Hospitals specialised in the treatment of sarcoma is participating in the elaboration and evaluation of new molecules and therapeutic options for treating sarcoma and in particular gastro-intestinal stromal tumours (GIST). Thus a phase III study conducted with the French Sarcoma Group recently showed that one should not interrupt treatment with imatinib (Glivec®) for patients affected by GIST for whom the drug had been able to control the disease, because of the risk of rapid progression.

Treatment of peritoneal tumours
A group of physicians and surgeons from Lyon Civil Hospitals introduced in Europe in 1989 the concept of peritonectomy combined with intra-peritoneal chemo-hyperthermia in the treatment of peritoneal metastases of colorectal cancers. Since then, the team has acquired international experience. It associated its' activity of clinical research with an activity in technological research, based on animal models. This led to the development, in collaboration with the EFS Electronic company, of the Cavitherm machine with which several French and European University Hospitals are equipped today. A contract was signed with the Saint-Etienne Graduate School for Science and Technology (Ecole Nationale Supérieure des Mines) for the development of Bodytherm (interface software which allows "real-time" surveillance and monitoring of intra-peritoneal chemohyperthermia).
Furthermore, a phase II clinical trial is currently being conducted for a protocol of anti-tumour vaccination in peritoneal carcinosis, in collaboration with scientists from Lyon Civil Hospitals and the Génopoïetic company.

Treatment of prostate cancer and adjuvant therapies
Randomised trials coordinated by the University Hospital of Grenoble within the framework of multicentric studies of the EORTC have been able to specify the role of radiotherapy, hormonotherapy and prostatectomy in the treatment of prostate cancer. Administration of an adjuvant hormonal treatment at the same time as radiotherapy improves survival of patients with a locally advanced prostate cancer.
Likewise, the association of adjuvant radiotherapy with a prostatectomy diminishes the risk of recurrence.

Immunotherapy
The lymphoid cell pathology team at Lyon Civil Hospitals studies genetic determinants of the immune response for cancer. The team was the first to show the influence of certain nucleotide variations in cytokine genes (TNF and IL-10) on the prognosis of lymphoma, and it has extended these observations to other molecules involved in the therapeutic activity of monoclonal antibodies. These programmes continue with cohort studies of several hundred patients treated in clinical trials. For renal cancer, the group from the Léon Bérard Cancer Centre has shown that circulating levels of IL-6 constitute a factor of good prognosis.
However, the studies conducted by these scientists with the French group of immunotherapy showed that cytokines (IL-2, IFN-α) are active only in a very limited number of patients and that the combination of cytokines induces non negligible toxicity. Owing to its' expertise in the treatment of kidney cancer, this group is participating in the elaboration of treatment protocols at the national level and plays a major role in collaborative studies at the international level.

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Lung cancer: an example of integrated biological research in the "Cancéropôle"

Research in lung cancer was initiated by a Grenoble team including thoracic surgeons, lung specialists and anatomopathologists who set up a group of biological research and have constituted a bank of over 2000 frozen tumours with a follow-up of clinical data reaching back 20 years for the oldest ones. This group has set up 2 prospective protocols:

Biomarkscan is a protocol of early cancer screening of the respiratory tract (lungs, head and neck cancer) calling for a tomodensitometry (scanner) and innovating techniques of fluorescent endoscopy in order to discover very small lesions in high risk patients (smokers, patients with chronic obstructive broncho-pneumopathy, patients having recovered from a previous cancer of the respiratory tract) with the objective of validating molecular biomarkers for early diagnosis on non invasive samples (blood, expectoration). The inhibition of expression of tumour suppressor genes by hypermethylation of their promoter is a common and early epigenetic phenomenon associated with tumour development. The Grenoble team launched in 2001 a programme for the early detection of lung cancer, by enrolling a thousand patients for 5 years. Thanks to sensitive methods of detection, methylation profiles were defined and the preliminary results show that hypermethylation of the promoter of the FHIT gene is a potential early marker of the development of non small cell lung cancer (NSCLC). Very encouraging results have also been obtained for head and neck cancer which share the same risk factors (alcohol and tobacco).

The second protocol, **Pharmacogenoscan**, has set out to validate molecular biomarkers in order to achieve better treatment for patients, improve its efficacy, and limit its toxicity. CLARA played a key role by allowing efforts to be grouped together and having centres of thoracic oncology recruit patients and samples and by providing research laboratories with high quality material.

All of this is put to use by common research projects within the framework of clinical (PHRC) or biological projects with the National Cancer Institute. Thus, regional teams direct two of the five sub-projects of the Lung Cancer National Project of Excellence, coordinated by the IARC, and they participate actively in the other projects. Beyond the region, this collaboration concerns foreign partners, among which the National Tumour Institute in Milan.

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Preclinical Research

Vectorisation

The use of activatable nanoparticles in the treatment of glioblastoma

This proof of concept project supported by CLARA and coordinated by the Nanobiotix company and a Lyon Inserm team seeks to realize the proof of efficacy of the NanoMag technology in the field of glioblastoma. This technology is based on nanoparticles composed of an activatable core covered with biological agents, which should allow the specific targeting of tumour cells and their selective destruction, thus leaving intact the healthy tissues. This project is currently in its' pre-clinical stage.

The use of red blood cells as drug vectors

Erythrocytes have physiological properties which make them an excellent vector for therapeutic molecules. For example, they enjoy a long half-life *in vivo* and are capable of encapsulating molecules according to a procedure patented by the ERYtech Pharma company for industrial use, and this can be done with the patient's own cells so as to avoid immunological incompatibility. Several projects use this powerful means of administration of molecules in the framework of collaborations involving ERYtech Pharma, the French Blood Establishment (EFS) and teams from Inserm, the Claude Bernard University, Lyon Civil Hospitals and the Léon Bérard Cancer Centre:

- intra-erythrocyte encapsulation of asparaginasis to improve tolerance and optimise the use of the drug in acute lymphoid leukaemia (the product is in phase II development).
- intra-erythrocyte encapsulation of 5FU for screening the liver in the treatment of hepatic metastases of colorectal cancer (pre-clinical stage of proof of concept).

Development of innovating technologies applied to therapy

Treatment of cancer by focused ultrasounds

The treatment of prostate cancer by high intensity focused ultrasounds offers today an alternative to prostatectomy: it is more targeted and less invasive. Emitted by an endorectal catheter and focused on the prostate, the rays passing through different tissues can produce at a focal point intense heat which, associated with other physical and well mastered parameters (cavitation and diffusion) provokes the instantaneous and definitive destruction of the targeted tissue.
Focused ultrasounds have been studied and used for many years by Lyon Inserm scientists, who today are among the world leaders in the field. With several patents, they conceived an apparatus for treating prostate cancer (Ablatherm, commercialised by Edap Technomed) and are seeking now to apply the benefits of focused ultrasounds to other cancers targeting soft tissues. New apparatuses are being developed for the treatment of thyroid nodules (with Theraclion) and for liver metastases (clinical study of proof of concept by Edap and the Léon Bérard Cancer Centre).

Hadrontherapy

Hadrontherapy by carbon ions is a new advanced treatment by radiotherapy, experimented since 1994 in Japan and Germany. It is capable of treating effectively hard to cure tumours, either because they cannot be operated on or are radio-resistant, for example certain tumours of the lung, the head and neck, the pancreas and liver, malignant melanoma and sarcoma. Medical and technical studies seeking to establish a national centre of hadrontherapy in the Lyon area have been carried out under the direction of the Lyon I University thanks to funding provided by the Rhône-Alpes Region, the Ministry of Research and the Urban Community of Lyon. The research involved various regional health care centres and the universities of Lyon and Grenoble. Cooperation with Germany, Italy, Austria, and Japan was very productive and the studies also benefited from the European project Enlight.

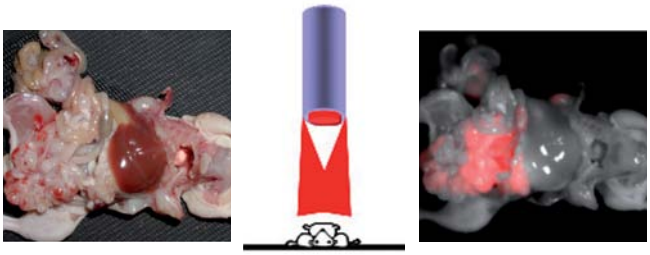
Imaging

Medical imaging in surgery and the follow-up of treatments

The work carried out jointly in Grenoble by Inserm, CNRS and CEA/Léti laboratories has led to the development and patenting of a new vector molecule (RAFT-cRGD4) which can treat and image tumours of the small animal. This work is currently being pursued in view of a phase I clinical application in partnership with the Léon Bérard Cancer Centre. The objective is to demonstrate that this vector molecule, associated with a system of optic imaging in fluorescence elaborated by these teams, can improve the surgery of osteosarcomas, which are frequent tumours in adolescents. The same molecule can vectorize cytotoxic agents and should be developed through a partnership between the Albert Bonniot Institute and industry.

Assistant robot for minimally-invasive cancer surgery

This research was born of a project initiated in 2001 at the Joseph Fourier University (Grenoble) and seeks to develop and commercialise an assistant robot for laparoscopic surgery (endoscope holding robot). It has been selected to be introduced in early 2007 and is managed by the EndoControl company, the CNRS-Joseph Fourier University laboratory and the University Hospital of Grenoble.



Imaging guided surgery in a murine model

Peri-operation apparatus

This is a portable system which allows one to visualise a marker molecule accumulated in tumours. The illumination of the operation area in near infrared light should allow the surgeon to visualise better the micro-nodules and to carry out the excision. It should also improve the vision of the tumour edges and refine the surgical intervention. (On-going phase I clinical application, collaboration with CLB Lyon).

Hybrid nanoprobes for a multimodal imaging of cell follow-up in cancerology

A Lyon CNRS / University laboratory is specialised in the development of contrasting agents for imaging, notably in hybrid nanoparticles (particles made from rare earth or gold oxides with a diameter of some 10 to 20 nanometres). These scientists were pioneers in the field of polyfunctional contrast agents with a lanthanide core, that allows for a positive and quantifiable detection in RMI, and a "master" patent was filed in 2004 (used by the company Nano-H). Nano-H has developed a method for producing and enveloping the surface of nanoparticles with a fine shell of silica which makes particles compatible with a large variety of fluids, resins, and polymers and allows their dispersion in organic fluids. Several biological applications are concerned by these nanoparticles, such as diagnosis and research in cell therapy. For example, luminescent hybrid particles have been produced by enveloping a paramagnetic core of gadolinium oxide in an organic shell carrying fluophores. These particles circulate freely in the blood vessels without undesirable accumulation in the organs and can be used as a contrast agent for an RMI bimodal imaging / fluorescence *in vivo*.

5 - HIGH LEVEL BASIC AND TRANSLATIONAL RESEARCH

The increasing interaction between research and patient care means that fundamental results lead much more quickly to new diagnostic and prognostic tests, as well as to new therapeutic strategies. CLARA supports research on the mechanisms of cancer development and the identification of the molecular characteristics of cancer cells. Such markers can be used in order to better detect tumours, to detect them earlier, to evaluate the prognosis more precisely and to choose the most appropriate treatment. They can constitute targets for new, more specific drugs, while both improving overall survival and limiting undesirable side effects.

In order to accelerate the application of progress in fundamental research, CLARA supports research associating both public and private stakeholders until the companies themselves can ensure the following stages of development.

Tumour development

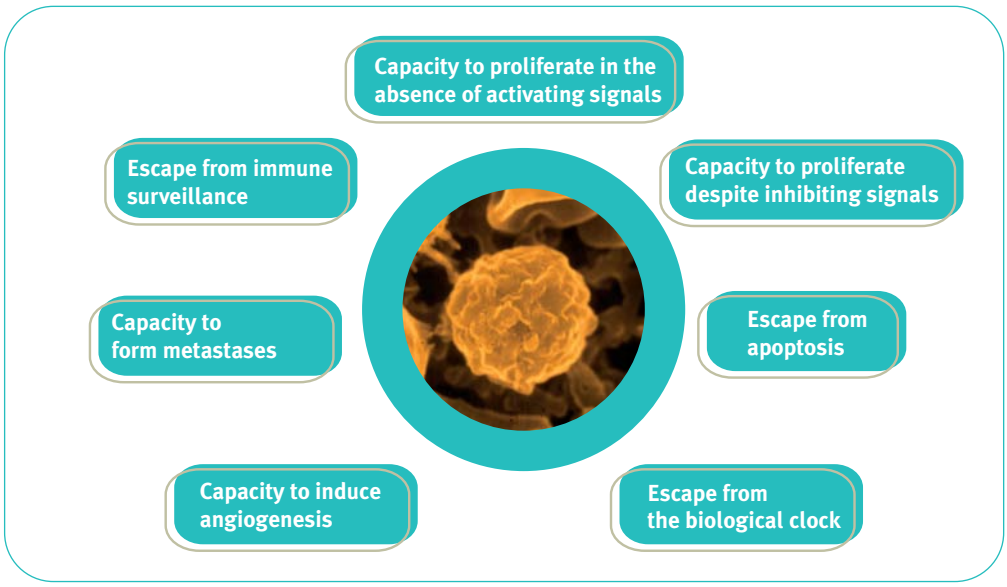
Cancer arises from the anarchic proliferation of abnormal cells. Such cells, which are unaffected by normal control mechanisms, can be situated in any of the organs. They can migrate to other organs and give rise to metastases.

The human body contains about one million billion cells, each one of which plays a specific role. They are organised and grouped together so as to form tissues and organs. Some of them are constantly renewed. The death and proliferation of cells are controlled by a highly complex regulation system, ensuring homeostasis.

In order to become cancerous, cells must escape from the various mechanisms that regulate proliferation. They must acquire the capacity to proliferate in the absence of proliferation signals, ignore the signals which block such proliferation, escape programmed cell death (apoptosis), overcome the limits of their potential for replication, induce the formation of new blood vessels (angiogenesis) and, finally, invade neighbouring tissues and produce metastases at a distance, in a hostile environment, all the while escaping the surveillance of the immune system. Each one of these newly acquired capacities during tumour development corresponds to a new breach in signalling and control systems of cells and tissues.

Malignant transformation is thus a multi-stage process linked to the progressive accumulation of alterations concerning the genes involved in cellular signalling (oncogenes and tumour suppressor genes), each stage leading to the progressive conversion of normal cells into cancerous cells. There are different types of alterations: genetic mutations (point mutations, amplifications, deletions, and translocations) which directly affect the structure of genes, and epigenetic modifications (hypermethylation and modification of heterochromatin), which modify their expression.

The diversity of the causes of cancer reflects the multitude of molecular partners involved in cellular signalling; these molecules also represent potential markers and therapeutic targets.



Acquired characteristics of cancer cells

Capacity to proliferate in the absence of activating signals

In order to proliferate, normal cells require signals. Different types of molecules, such as diffusible growth factors, components of the extracellular matrix, and intercellular adhesion molecules, act as signals which are captured by cell membrane receptors. The signal is then further transmitted to the cellular command centre inside the cell via a chain of second messengers involving enzymes such as protein kinases.

Tumour cells are capable of proliferating in the absence of such signals. Following alterations in particular genes (called oncogenes), the cells begin to produce their own growth factors, thus reducing their dependence on signals from the surrounding tissue. Either their receptors remain activated in the absence of their ligand, or else the signal transduction pathway is activated in the absence of stimulation.

Thus, for example, the c-Myc protein (coded for by the *myc* gene) is part of the signal pathway inducing cell division. In neuroblastoma, the N-Myc protein is over-expressed following the amplification or translocation of the N-*myc* gene. In Burkitt's lymphoma, the *myc* gene is over-expressed because of its translocation near the gene of the immunoglobulin heavy chain. The protein kinase CK2 is overexpressed in chronic myeloid leukaemia and in various solid tumours such as prostate adenoma. This overexpression contributes to the resistance of tumour cells to chemotherapy or radiotherapy induced apoptosis.

Protein kinase CK2: a diagnostic and prognostic marker for prostate cancer

Prostate cancer, the most frequent cancer in men, represents a complex and heterogeneous disease. Currently available prognostic factors do not precisely predict the evolution of this cancer.

Teams of scientists from the University Hospital (CHU) and the CEA in Grenoble have shown in a panel of prostate cancers that nuclear overexpression of the protein kinase CK2 is correlated to other markers indicating a poor prognosis. Detecting overexpression of protein kinase CK2 could become an additional tool in prostate cancer management. In collaboration with the Centre for Bio-Active Molecules Screening, these research teams are developing pharmacological inhibitors of protein kinase CK2 for preclinical validation as anticancer agents.

Reference:

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Targeting the Wnt pathway

Wnt family proteins regulate the cellular growth and migration during embryogenesis. They are captured by receptors of the "frizzled" (FZD) family situated on the surface of cells, and the signal is transmitted to the nucleus via a pathway involving β-catenins. An Inserm team in Lyon is studying the role of the Wnt/FZD signal pathway in hepatic oncogenesis of viral and non-viral origin. The scientists have shown that the overexpression of the FZD7 receptor is very frequent in hepatocellular cancers, and that it intervenes early in the process of cancer development.

In collaboration with scientists from the CNRS/ Ecole Normale Supérieure, the Lyon Inserm team is developing therapeutic peptides of the PTD (protein transduction domain) type, capable of inactivating the FZD7 receptor. These anti-FZD7 peptides inhibit the β-catenin and PKC pathways; *in vitro* they induce the apoptosis of human and murine FZD7+ cancer hepatocytes. These discoveries have now led to collaboration with the Parisian company BioAlliance Pharma.

References:

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Hormone receptors control cellular proliferation

Certain hormones, such as thyroid hormone and androgens, act via receptors which are located in the cell nucleus and directly control the expression of their target genes. A team from the University of Lyon at ENS and at the South Lyon Hospital has shown that, in the murine intestine, the thyroid hormone receptor activates the proliferation of epithelial precursor cells by activating the Wnt/β-catenin pathway. In addition, in human prostate cells, the same group has identified target genes of the androgen receptor which may constitute markers of tumour progression.

Reference:

- Plateroti M, Kress E, Mori JI, Samarut J. Thyroid hormone receptor alpha1 directly controls transcription of the beta-catenin gene in intestinal epithelial cells. Mol Cell Biol 2006;26:3204-14.

Circulating DNA and cancers

The presence of abnormally high levels of DNA circulating in the plasma or serum of patients affected by cancer was discovered some thirty years ago. More recently, research has concentrated on the application of this property to the diagnosis, prognosis, and observation of the evolution of cancer. Diverse alterations of circulating DNA have been characterised for a large variety of tumour types: point mutations, the loss of heterozygoty or epigenetic modifications such as the hypermethylation of regulating sequences or microsatellite instability. In several cases, these alterations are found in the patient's primary tumour, supporting the hypothesis of a tumoral origin of this DNA. Using circulating DNA has many advantages, and its availability without the patient undergoing a painful, invasive procedure makes it a highly useful biological marker.

The CirBioCancer programme brings together scientists from various institutions (IARC, Léon Bérard Cancer Centre, Inserm, Claude Bernard University, and the ProfileXpert platform of the Federative Institute of Neurosciences) within the framework of CLARA. Its goal is to develop an integrated network for evaluating the range of detectable genetic alterations in circulating DNA that may be identified as clinical biological markers. Four types of solid tumours have been selected: breast carcinoma, liver carcinoma, pulmonary carcinoma and neuroblastoma.

The amplification of the N-*myc* oncogene in neuroblastoma cells is a factor of poor prognosis which is used to determine therapeutic choices. Scientists in Lyon and Grenoble have shown that in neuroblastoma patients, high levels of N-*myc* sequences are present in the peripheral blood, even in the early stages of the disease. International validation on a large number of patients, however, is required before these tests can be used for diagnostic purposes.

The Lyon company bioMérieux, in partnership with ExonHit Therapeutics (Paris), has produced a blood screening test for breast cancer, based on DNA microarrays; this test is currently undergoing clinical validation. Ongoing research concerns screening of colon, prostate and lung cancer.

References:

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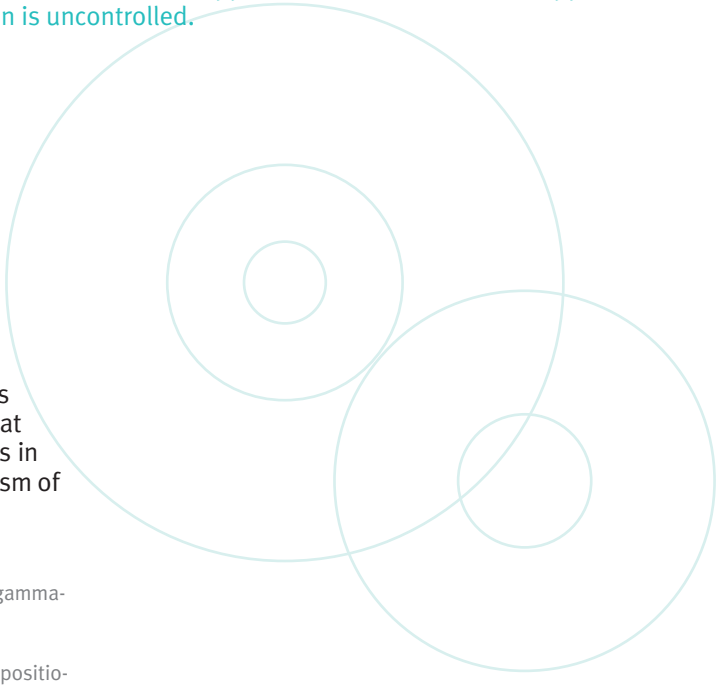
Capacity to proliferate despite inhibiting signals

In normal tissues, numerous signals are capable of inhibiting cellular proliferation. These can be soluble inhibitors or inhibitors immobilised in the extracellular matrix or on the surface of neighbouring cells. These inhibiting signals, just as the activating signals, are captured by transmembrane receptors at the surface of the cells, coupled with intra-cellular signal transduction mechanisms.

Inhibiting signals can momentarily stop the cell cycle or induce differentiation. Genetic or epigenetic alterations can inactivate the genes involved in the inhibition of proliferation (tumour suppressor genes); when this happens the cell does not respond to inhibiting signals and proliferation is uncontrolled.



Epigenetics and malignant lymphoma

Pursuing their work on mapping chromosomal abnormalities in malignant B-cell lymphoma, scientists in Grenoble have identified frequent qualitative and quantitative abnormalities in a region of constitutive heterochromatin (chromosome 1q12) in a large series of lymphoma and myeloma. Having demonstrated that 1q12 abnormalities induce major epigenetic alterations in malignant B cells, they are now elaborating a mechanism of recurrent oncogenesis in lymphoma.

References:

- Callanan MB, Le Baccon P, Mossuz P et al. The IgG Fc receptor, Fcgamma-RIIB, is a target for deregulation by chromosomal translocation in malignant lymphoma. Proc Natl Sci USA 2000;97:309-14.
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Alteration in translation and oncogenesis

The complex dynamic architecture of eukaryotic cells is an important element in the control of genetic expression. Indeed the size, morphology and number of nucleoli constitute validated criteria and are used routinely as prognostic markers of the development of numerous cancers. However, their role in the regulation of genetic expression and in tumour development is as yet unspecified.
A CNRS team at the Claude Bernard University is developing several research programmes in order to determine the role of nucleoli in the development of breast and colon cancers and endocrine tumours. Proteomic analysis has shown deep modifications in the nucleoli of tumour cells that affect translation. These modifications contribute directly to the pathology by altering the exactness of translation. Potential therapeutic targets such as the Nolex protein are being validated. The team works in close collaboration with clinicians (Lyon Civil Hospitals) and the Idealp-Pharma company to use these targets in the elaboration of molecules for prognostics and/or therapeutics.

References:

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- Coute Y, Burgess JA, Diaz JJ et al. Deciphering the human nucleolar proteome. Mass Spectrum Rev 2006;25:215-34.

Diagnosis of paraneoplastic neurological syndromes

Paraneoplastic neurological syndromes (PNS) are defined as remote effects of cancer that are not caused by the tumour and its metastasis, nor by infection, ischemia or metabolic disruptions. PNS are caused by autoimmune processes triggered by the cancer and directed against “onconeuronal” antigens common both to cancer cells and the nervous system. A group of Inserm scientists in Lyon identified one of these onconeural antigens, the CRMP5 protein. It turned out that the CRMP5 protein is a specific marker for neurological syndromes associated with small cell lung cancer, paving the way for a new diagnostic test for early detection of this type of cancer (patent filed).

Reference:

- Honnorat J, Antoine JC. Paraneoplastic neurological syndromes. Orphanet J Rare Dis 2007; May 4;2:22.

Escape from apoptosis – TP53 at the crossroads of cell-signalling

The increase in population of tumour cells depends not only on the rate of proliferation but also on the proportion of cells that survive. Tumour growth is due to the imbalance between the proliferation and the death of cancer cells.

Apoptosis, or programmed cell death, is important for the maintenance of tissue homeostasis. Cells that are "useless" or dangerous for the organism are eliminated through this process. Apoptosis counterbalances the oncogenetic potential of many oncogenes, such as *myc*.

Apoptosis is triggered either by internal factors through the "intrinsic pathway", or by external signals through the "extrinsic pathway". In the intrinsic pathway, intracellular sensors detect DNA lesions, imbalances provoked by the activation of oncogenes or hypoxia. This leads to the intervention of mitochrondria and proteins of the Bcl-2 family, an ambivalent family with pro-apoptotic (Bax, Bak, Bad, Bin, Bim) or anti-apoptopic (Bcl-2, Bcl-XL, Bcl-W) properties.

The extrinsic pathway is activated by external signals captured by specific receptors situated on the surface of the cell. The binding of ligands to their receptors (CD95, FAS or members of the TNF receptor family) activates the death-inducing signalling complex (DISC) which triggers apoptosis via the activation of caspase-8.

The TP53 protein plays an essential role in the regulation of cell proliferation. It is at the crossroads of signalling networks leading to DNA repair or cell death. It intervenes in cases of cellular DNA lesions (from irradiation or free radicals), hypoxia, heat shock, oncogene activation.... If the damage can be repaired, TP53 puts the cell cycle on hold and activates DNA repair. If the damage proves to be irreparable, it triggers programmed cell death by apoptosis.

The TP53 gene coding for this protein, considered as the "guardian of the genome's integrity" is one of the most important cancer suppressor genes. It is inactivated in over 50% of cancers.

Database of TP53 mutations

Since 1989, the IARC has maintained a database compiling all mutations of TP53 described in the literature. Regularly updated, this tool will be completed by a new database integrating epigenetic alterations affecting genes that are key to tumour development.

Dependence receptors: from concept to therapeutics

The survival of a cell depends on messages activated by the binding of ligands on surface receptors. Data obtained by scientists at a CNRS unit at the Léon Bérard Cancer Centre argue for a complementary and novel form of signal transduction leading to apoptosis which is activated by stimulus withdrawal. This negative signal transduction is mediated by specific "dependence receptors", which induce apoptosis only when unbound to their ligand. The expression of these receptors therefore creates states of cellular dependence on their respective ligands, such a netrin-1.

This protective mechanism limits tumour invasion and metastasis by inducing the apoptosis of cells which proliferate or migrate into tissues where their ligand is unavailable.

Tumour cells can escape this phenomenon either by losing these receptors (DCC and UNC5H1-4 receptors) or by gaining an autocrine expression of the ligand.

The European project HERMIONE, coordinated by the Léon Bérard Cancer Centre, is dedicated to the study of the relation between dependence receptors (DRs), downstream effector molecules and apoptosis, with the goal of identifying potential new therapeutic targets. This project should lead to better understanding of the signalling pathways of DR implicated in the apoptosis of tumour cells.

Collaborations with pharmaceutical firms and biotechnology companies have been established to develop therapeutic applications of this concept.

References:

- Mazelin L, Bernet A, Bonod-Bidaud C, et al. Netrin-1 controls colorectal tumorigenesis by regulating apoptosis. Nature 2004;431:80-84.
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- Mehlen P. The dependence receptor notion: another way to see death. Cell Death Differ 2005;12:1003.

Dysregulation of the mitochondrial pathway

In Lyon, teams from the Institute of Biology and Chemistry of Proteins (IBCP), Inserm, and the Claude Bernard University have been studying certain proteins (A1/Bfl-1, NR13, HSP27) crucial to the control of apoptosis and previously identified as potential targets in different types of cancer. This research has led to the identification of small peptides called aptamers which block the activity of anti-apoptotic proteins, or induce programmed cell death. Research suggests that aptamers targeting anti-apoptotic proteins of the Bcl-2 family could eventually be used as antitumour therapies.

Thus, Inserm scientists are screening a bank of aptamers and developing interfering RNAs targeting the anti-apoptopic protein Bfl-1. They have shown that inhibiting the expression of Bfl-1 in cells where it is overexpressed (cell lines obtained from patients with diffuse large B cell lymphoma) makes these cells sensitive to apoptosis induced by chemotherapeutic agents or anti-CD20 antibodies. The identification of Bfl-1 as a marker of this type of lymphoma reinforces the relevance of Bfl-1 as a potential therapeutic target. Screening of anti-Bfl-1 aptamers has led to filing a patent application.

References:

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Non-small cell lung cancer: a new apoptosis inhibition pathway

The Inserm non-small cell lung cancer research group at the Albert Bonniot Institute (Grenoble) has identified a new apoptosis inhibition pathway used by bronchial tumour cells, involving amphiregulin (AR) and insulin-like growth factor-1 (IGF-1): amphiregulin (a survival signal) activates the IGF-1 receptor, which then induces secretion of AR and IGF-1. AR and IGF1 cooperate to prevent apoptosis by activating a specific PKC-p90(rsk)-dependent pathway, which leads to Bad and Bax inactivation.
This team has also demonstrated the function of the P14ARF gene, a tumour suppressor gene that induces a TP53-independent G2 cell cycle arrest in response to DNA lesions.
They have identified the signalling pathways contributing to this G2 checkpoint and highlighted the interrelated roles of p14ARF and the Tip60 protein in the initiation of this DNA damage signalling cascade. The function of the P14ARF gene is lost in 40% of lung cancers.

The same team has dissected the functions of an essential cell cycle protein, E2F1, and demonstrated its apoptotic functions. This protein plays a role in the regulation of the splicing machinery. The alternative splicing of RNA is responsible for the production, from a single message, of proteins with different and sometimes opposite functions. E2F1 is involved in the splicing of the FLIP gene, a caspase 8 inhibitor, to yield its Flip-short pro-apoptotic form. E2F1 is lost in non-small cell lung cancers.

References:

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Inhibiting Twist for cancer cell death

Scientists at the IARC and the Léon Bérard Cancer Centre have long been working on the control mechanisms for senescence and apoptosis. They have observed the overexpression of transcription factor Twist-1 in several human cancers in which the TP53 gene is not mutated, strongly suggesting that an alternative cooperating event circumvents this safeguard against oncogene-driven neoplasia. The oncogenic cooperation of N-Myc and Twist-1 in the development of neuroblastoma, the most common and deadly solid tumour of childhood, perfectly illustrates such a process. N-Myc promotes cell proliferation, whereas Twist-1 counteracts its pro-apoptotic properties by knocking-down the ARF/p53 pathway.

Scientists have shown that experimental inactivation of Twist-1 by RNA interference in tumour cells either results in senescence or apoptosis. A proof of concept project of the use of Twist-1 as a tumour marker is underway, in a collaboration between the Léon Bérard Cancer Centre and the company CovalAb, while chemical Twist-1 inhibitors are being developed in collaboration with the company Idealp-Pharma.

References:

- Puisieux A, Valsesia-Wittmann S, Ansieau S. A twist for survival and cancer progression. Br J Cancer 2006;94:13-7.
- Valsesia-Wittmann S, Magdeleine M, Dupasquier S, et al. Oncogenic cooperation between H-Twist and N-Myc overrides failsafe programs in cancer cells. Cancer Cell 2004;6:625-30.

Escaping control of the biological clock

The capacity for growth in the absence of activating signals, resistance to inhibitor signals and resistance to apoptosis are not sufficient for tumour growth. Somatic cells have a biological clock which limits their potential for replication. They cease to proliferate after a certain number of divisions, despite the presence of activating factors.
This "biological clock," the telomeres, located on the ends of chromosomes, is made of segments of condensed DNA. Upon each round of cellular division, the cell looses a piece of its telomeres; below a critical threshold, the cell cycle permanently stops. In more than 85% of cancers, this barrier is broken by the expression of an enzyme, the telomerase.

Targeting the TRF2 protein to re-establish control of the telomeres

TRF2, a protein which is overexpressed in a large number of human cancers, is part of a complex that binds to telomeric DNA and prevents its alteration. In collaboration with Italian scientists, a CNRS/ENS team has shown that the inactivation of TRF2 limits the capacity of human cancer cell lines to form xenografts in immunodeficient mice. The screening of peptide antagonists and chemical libraries is currently underway to develop new therapeutic strategies targeting TRF2 and the telomeres in chronic B-lymphoid leukaemia and prostate adenocarcinoma.

Reference:

• Biroccio A, Rizzo A, Elli R, et al. TRF2 inhibition triggers apoptosis and reduces tumourigenicity of human melanoma cells. Eur J Cancer 2006; 4:1881-88.

Telomere shortening in early stages of non-small cell lung cancer

Teams from the University Hospital, Inserm and CEA in Grenoble studying non-small cell lung cancer have shown that telomere shortening represents an early genetic abnormality in bronchial carcinogenesis, preceding telomerase expression and p53/Rb inactivation. Targeting telomerase activity may be a promising pathway for the development of preventive chemotherapy agents in high-risk patients such as heavy smokers with pre-invasive bronchial lesions with short telomeres.

Reference:

• Lantuejoul S, Soria JC, Morat L,et al. Telomere shortening and telomerase reverse transcriptase expression in preinvasive bronchial lesions. Clin Cancer Res 2005;11:2074-82.

Telomeres and viral-induced cancers

Transient inactivation of telomerase activity in HTLV-1- infected cells could play a role in the early phase of viral leukemogenesis.
The human T-cell leukaemia type 1 virus (HTLV-1) is associated with adult T cell leukaemia/lymphoma. Its oncogenicity is linked to the expression of viral oncoproteins possessing a pleiotropic effect on the cellular metabolism. The HTLV-1-encoded Tax oncoprotein is only expressed during the premalignant phase of adult T cell leukaemia/lymphoma, but it plays a central role in the clonal expansion of infected cells and the early steps of carcinogenesis, by interfering with genome repair, cell cycle, and apoptosis. A group of CNRS/Claude Bernard University/Lyon Civil Hospitals scientists has shown that HTLV-1 propels untransformed CD4+ lymphocytes into the cell cycle while protecting CD8+ cells from death. They also showed that in addition, Tax inhibits the human telomerase reverse transcriptase (hTERT) and thus blocks telomerase activity. By inhibiting both TP53 and hTERT in persistently proliferating cells, Tax fosters persistent telomere dysfunction, thereby allowing accumulation of increased unbalanced chromosomal rearrangements which, if coupled with accumulating somatic mutations, help move the cell towards the malignant genotype. Persistent TP53 inactivation associated with decreased Tax expression could then allow telomerase reactivation, thus endowing infected cells with immortal growth potential, stabilizing the genome and finally leading to leukaemia/lymphoma. In contrast to Tax, oncoproteins from other viruses such as the human papillomavirus (HPV) have been found to transactivate hTERT expression, highlighting the distinct oncogenic strategies used by viruses.

References:

• Gabet AS, Mortreux F, Charneau P, et al. Inactivation of hTERT transcription by Tax. Oncogene 2003;22:3734-41.
• Sibon D, Gabet AS, Zandecki M, et al. HTLV-1 propels untransformed CD4+ lymphocytes into the cell cycle while protecting CD8+ cells from death. J Clin Invest 2006;116:974-83.

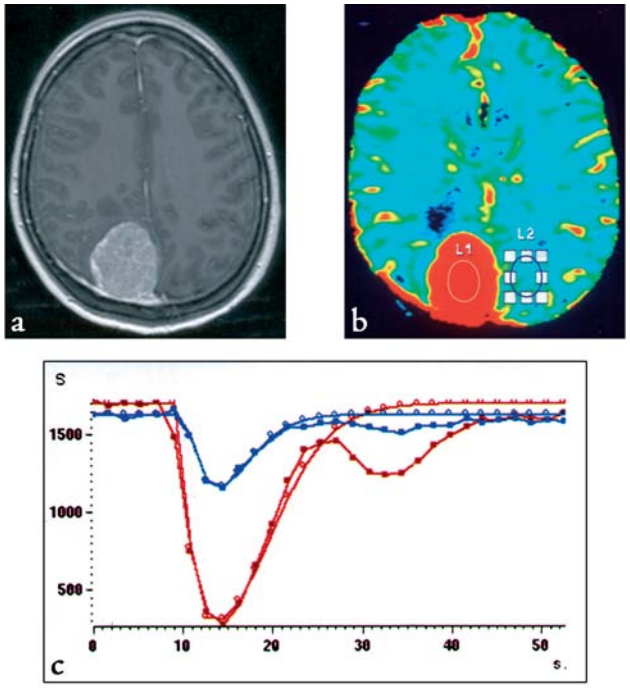
Capacity to induce angiogenesis

Cancer cells can develop into tumours only if they receive a sufficient supply of oxygen and nutritive resources from blood. Consequently, they need a vascularized environment.

The growth of new blood vessels, or angiogenesis, is a physiological process that is essentially activated during organogenesis and is carefully regulated by the balance between induction and inhibition factors. In tumours, angiogenesis is activated following the modification of the balance between the inductors and the inhibitors, most often due to alterations in gene transcription. Several tumours produce growth factors such as the vascular endothelial growth factor (VEGF) or the fibroblast growth factor (FGF).
The loss of function of the TP53 gene, which is observed in more than 50% of cancers, also favours angiogenesis, since it also controls expression of one of these inhibitor factors, thrombospondin-1.

Imaging of brain tumour angiogenesis:
a key element in the initial diagnosis and follow-up of tumour evolution.

Researchers at the University Hospital in Grenoble have developed Magnetic Resonance Imaging (MRI) techniques to explore brain tumour angiogenesis, which constitutes an important element in the initial diagnosis and follow-up of the evolution of brain tumours. These scientists were among the first in France to study the application of these methods in humans in a clinical context, while applying them to the experimental study of implanted tumours in the rat.



References:

- Le Bas JF, Grand S, Lefournier V, Tropres I, Remy C. Perfusion MR imaging in brain tumors. J Radiol 2006;87:807-21.
- Troprès I, Grimault S, Vaeth A, et al. Vessel size imaging. Magn Reson Med 2001;45:397-408.
- Troprès I, Lamalle L, Peoc'h M, et al. In vivo assessment of tumoral angiogenesis. Magn Reson Med 2004;51:533-41.

Angiogenesis network

The Inserm/CEA/Joseph Fourier University unit in Grenoble working on angiogenesis was at the origin of the French Angiogenesis Network, created in 1996, and participated in the FP5 European project T-ANGIOVASC, on angiogenic signalling in cancer and cardiovascular diseases. Working on basic mechanisms of tumour angiogenesis, these scientists have shown that TGF-β1 binds to the ALK5 receptor, and induces vascularisation in a VEGF-independent manner, at early stages of tumour development. Later on, differentiated endothelial cells express both ALK1 and ALK5 receptors, that are both implicated in inhibition of sprouting angiogenesis.
This group is currently developing screening programmes to identify new anti-angiogenesis agents.

Reference:

- Mallet C, Vittet D, Feige JJ, Bailly S. TGFbeta1 induces vasculogenesis and inhibits angiogenic sprouting in an embryonic stem cell differentiation model:respective contribution of ALK1 and ALK5. Stem Cells. 2006 Nov; 24:2420-27.

Anti-angiogenic activity of collagen fragments

Results obtained by scientists at the Institute for the Biology and Chemistry of Proteins (IBCP), the Claude Bernard University and Lyonbiopôle suggest that collagens may be strong regulators of the angiogenic process, especially fibrillar collagens I and V and non-fibrillar collagens XV and XVIII. Two bioactive fragments, HepV and endostatin, are currently being studied in order to determine specifically the mechanisms for their activity, especially via heparin sulphate and integrin fixation sites. A partnership has been formed with the company Novotec for the production of antibodies against certain collagen domains.

Reference:

- Ricard-Blum S, Beraud M, Raynal N, Farndale RW, Ruggiero F. Structural requirements for heparin/heparan sulfate binding to type V collagen. J Biol Chem 2006; 281:25195-204.

Capacity to invade neighbouring tissues and form metastases at a distance

The capacity to invade and colonise distant sites is a major characteristic of malignant tumours. The events leading to cancer metastases include modification of adhesion with neighbouring cells and with the extracellular matrix; alterations of the shape, deformability and motility of the cell; the invasion of normal neighbouring tissues; access to the lymphatic or vascular system; dissemination via the blood or lymph; survival and proliferation in a new environment; and escape from the host defence mechanisms.

Several classes of proteins involved in the attachment of cells to their environment are altered in metastatic cells. This is the case with molecules from the cell adhesion molecule (CAM) family, such as cadherins, which govern cell-cell interactions, or the integrins, which are responsible for the junction between cells and the extracellular matrix. The function of cadherin-E is lost in most metastatic cells, further to mutation, repression of transcription of the gene or proteolysis of its extracellular domain. In certain cancers (Wilm's tumour, neuroblastoma and small-cell lung cancer), the N-CAM expressed is different from normal N-CAM. Normal N-CAM is very adhesive, while the modified form is much less so, or it may even be repellent. The invasive cells also express extracellular proteases which can degrade the extracellular matrix.

Several Rhône-Alpes Auvergne teams are developing studies aimed at characterising the mechanisms of invasion and metastatic diffusion, and are working to identify and validate new therapeutic targets. High-throughput screening programmes and animal models have been developed in order to study, with the help of non-invasive methods, the effects of the modification of gene expression and/or pharmacological agents on the development and progression of metastases.

Study of the extracellular matrix

Far from being an inert cement structuring extracellular space, the extracellular matrix plays an essential role in tissue homeostasis as well as in the control of adhesion and cell proliferation. Teams at the Claude Bernard University and the Institute for the Biology and Chemistry of Proteins (Lyon) are studying interactions between epithelial cells and the extracellular matrix, particularly the ability of matrix proteins to affect adhesion and the migratory capacity of epithelial tumour cells.

Characterisation of cellular adhesion systems

At the interface with physics, a team at the Albert Bonniot Institute (Grenoble) is developing *in vitro* and *in vivo* biological approaches of the dynamics of cell adhesion in both physiological and pathological situations. Scientists are studying the role of integrins and cadherins in adhesion and signalling pathways. Using osteoblasts and enterocytes as model systems, they are studying the role of assembly and disassembly of adhesive structures, and the impact of differentiation in the functioning of normal and cancer cells.

References:

- Fournier HN, Dupe-Manet S, Bouvard D, et al. Nuclear translocation of integrin cytoplasmic domain-associated protein 1 stimulates cellular proliferation. Mol Biol Cell 2005;16:1859-71.
- Bouvard D et al. Development 2007;in press.

Imaging of interactions between the cells and the extracellular matrix

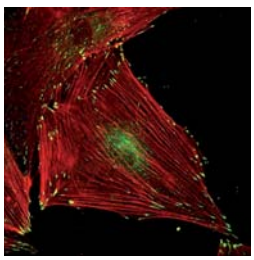


Photo a

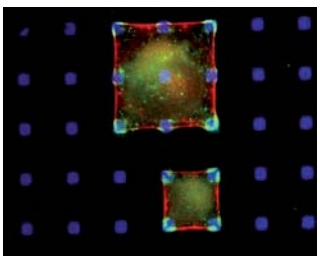


Photo b

Photo a: The focal adhesions (green) anchor fibroblasts to the extracellular matrix and assure connection to the actin cytoskeleton (red).
Photo b: Fibroblasts adopt geometrical shapes on the network of fibronectin 7-10 fragments (blue). The anchoring points are assured by focal adhesions at angles (viniculin marking, green) and are connected to the actin cytoskeleton (phalloidin marking, red).

Disorganisation of cellular architecture and invasion of cancer cells

The disorganisation of cellular architecture (loss of polarity and epithelial-mesenchymatous transition) directly participates in tumour development and the invasive phase resulting in the spread of cancer cells. A CNRS/ University team in Lyon has established that an oncosuppressive protein kinase called LKB1 controls cell polarity. This same group developed an original cellular model which allows for high throughput screening to identify molecules that inhibit epithelial-mesenchymatous transition. The development of a chemical library screening program aimed at identifying antagonists that inhibit epithelial-mesenchymatous transition is underway, in collaboration with the CEA/Inserm platform for bioactive molecules screening (CMBA), in Grenoble.

Reference:

• Forcet C, Etienne-Manneville S, Gaude H, et al. Functional analysis of Peutz-Jeghers mutations reveals that the LKB1 C-terminal region exerts a crucial role in regulating both the AMPK pathway and the cell polarity. Hum Mol Genet, 2005, 14, 1283-92.

Metastases and expression of lysyl oxidases

Lysyl oxidases allow for the maintenance of cutaneous homeostasis by determining the resistance of collagen fibres and elasticity of elastic fibres, but they also play a role in tumour development and metastatic propagation. CNRS scientists in Lyon are studying the specificity of the interaction of lysyl oxidases with their extra- and intracellular substrates, as well as their role in ageing and the regulation of cellular proliferation and differentiation. The work underway also focuses on the identification of vegetal extracts that induce the expression of lysyl oxidases in the epidermis.

References:

• Bouez C, Reynaud C, Noblesse E, et al. The lysyl oxidase LOX is absent in basal and squamous cell carcinomas and its knockdown induces an invading phenotype in a skin equivalent model. Clin Cancer Res 2006 Mar 1; 12:1463-9.

• Cenizo V, Andre V, Reymermier C, Sommer P, Damour O, Perrier E. LOXL as a target to increase the elastin content in adult skin: a dill extract induces the LOXL gene expression. Exp Dermatol 2006;15:574-81.

The role of metalloproteinases

Another group (Inserm/University, Lyon) is studying the role of matrix metalloproteinases (MMPs), especially MMP7. This enzyme is generally not expressed by normal differentiated epithelial colon cells, but has been shown to be up-regulated in human colon adenomas and adenocarcinomas. They showed that MMP7 is likely to play a crucial role in the regulation of carcinoma cell migration by targeting specific proteolytic processing of the LN5β3 chain.

Reference:

• Remy L, Trespeuch C, Bachy S, Scoazec JY, Rousselle P. Matrilysin 1 influences colon carcinoma cell migration by cleavage of the laminin-5 beta3 chain. Cancer Res 2006;66:11228-37.

γ-secretases: new targets for cancer therapy?

The CD44 protein is an extracellular adhesion molecule. CD44 and its variants are abnormally expressed in several types of cancer and this receptor participates in the acquisition of metastatic capacity via a mechanism that requires its proteolytic cleavage by metalloproteases. A CNRS team in Lyon (Domaine Rockefeller) has shown that secondary cleavage of CD44 by γ-secretases is a major event in tumourogenesis. The γ-secretase inhibitors are undergoing clinical trials for the treatment of neurodegenerative diseases. A study programme aiming at evaluating the antitumour effects of these inhibitors is currently led by the team in preclinical models.

Reference:

• Pelletier L, Guillaumot P, Freche B, et al. Gamma-secretase-dependent proteolysis of CD44 promotes neoplastic transformation of rat fibroblastic cells. Cancer Res 2006, 66, 3681-87.

Vascular permeability and metastatic escape

The permeability of tumour blood vessels is highly increased with regard to that of normal blood vessels, which favours the escape of metastatic tumour cells. Vascular permeability is controlled by adhesion molecules at endothelial intercellular junctions. In Grenoble, an Inserm/CEA/ Joseph Fourier University team is studying the mechanisms of regulation of intercellular adhesion activity of tumour blood vessels.

References:

- Lambeng N, Wallez Y, Rampon C, et al. Vascular endothelial-cadherin tyrosine phosphorylation in angiogenic and quiescent adult tissues. Circ Res 2005;96:384-91.
- Wallez Y, Cand F, Cruzalegui F, Wernstedt C, Souchelnytskyi S, Vilgrain I, Huber P. Src kinase phosphorylates vascular endothelial-cadherin in response to vascular endothelial growth factor: identification of tyrosine 685 as the unique target site. Oncogene 2007;26:1067-77.

The role of dependence factors

According to the concept developed by the CNRS/ Inserm team at the Léon Bérard Cancer Centre, tumour cells must break free from the control of the ligand-receptor dependence system in order to migrate and establish metastases.

Restoring the dependence of tumour cells on "dependence" factors constitutes a novel research axis for metastatic invasion. Research focuses on metastatic breast or colon tumours that seem to have been selected to loose their dependence on these receptors.

References:

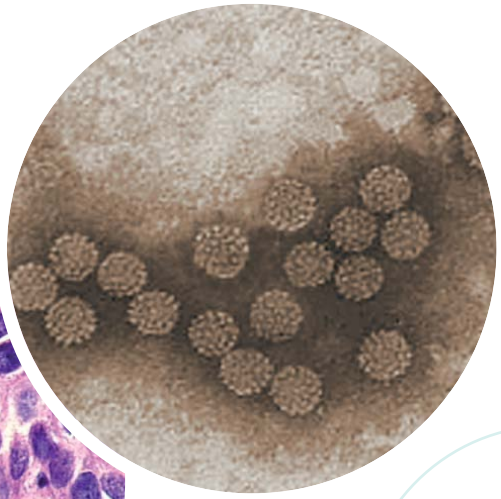
- Bredesen DE, Mehlen P, Rabizadeh S. Receptors that mediate cellular dependence. Cell Death Differ 2005; 12 : 1031-43.
- Mazelin L, Bernet A, Bonod-Bidaud C, et al. Netrin-1 controls colorectal tumorigenesis by regulating apoptosis. Nature 2004; 431: 80-84.
- Mehlen P, Puisieux P. Metastasis : a question of life or death. Nature Rev Cancer 2006 ;6 :449-58.

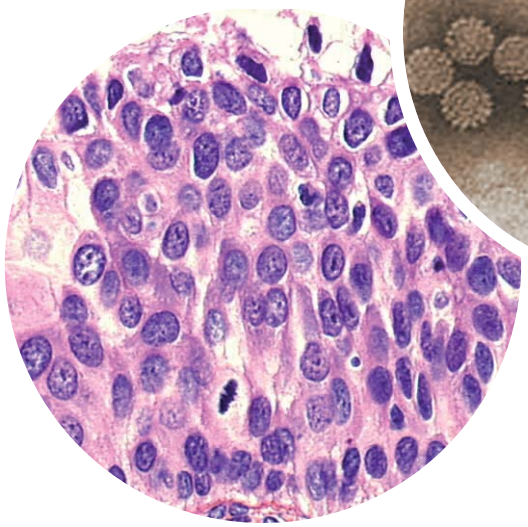
Factors associated with the bone tropism of metastatic cells in breast and prostate cancer

Bone tissue is the favourite metastatic site for several cancers, notably for breast and prostate cancers. Within the framework of the European PROMET (prostate) and MetaBre (breast) programmes, a Lyon team associating scientists in cancerology and bone tissue specialists is interested in the molecular mechanisms explaining bone tropism. Notably, their work led to the identification of a type 1 lysophosphatidic acid receptor and of angiostatin as potential therapeutic targets in patients with bone metastases.

References:

- Boucharaba A, Serre CM, Guglielmi J, Bordet JC, Clezardin P, Peyruchaud O. The type 1 lysophosphatidic acid receptor is a target for therapy in bone metastases. Proc Natl Acad Sci USA 2006;103: 9643-48.
- Daubine F, Le Gall C, Gasser J, Green J, Clezardin P. Antitumor effects of clinical dosing regimens of bisphosphonates in experimental breast cancer bone metastasis. J Natl Cancer Inst 2007; 99:322-30.
- Peyruchaud O, Serre CM, NicAmhlaoibh R, Fournier P, Clezardin P. Angiostatin inhibits bone metastasis formation in nude mice through a direct anti-osteoclastic activity. J Biol Chem 2003; 278: 45826-32.





Stem cells and tumour development

While tumours are formed of heterogeneous groups of cells, only a small subpopulation of cells are capable of initiating and maintaining cancerous growth, according to the "hierarchic oncogenesis model." This fraction of stem cells (not more than 5% of the tumour mass) is necessary and sufficient for the regeneration of the tumour. If it is confirmed, this concept opens new perspectives for the understanding and treatment of cancers.

The involvement of precursor stem cells in the generation of tumours of the central nervous system may explain the heterogenicity of glioblastoma tumours. To verify this hypothesis, teams at Inserm and the CEA in Grenoble and Lyon first validated a model of chemically induced glioma in the rat. The scientists then identified the IQGAP1 protein as a new stem cell marker that may help to discriminate human glioblastoma from oligodendrogliomas. Neoplastic IQGAP1+ cells from glioblastoma can be expanded in culture and possess all the characteristics of cancer stem-like progenitors. Research continues with the aim of identifying the functions of IQGAP1 in cancer stem cells, and demonstrating the role of interactions between endothelial cells and cancer stem cells in tumour growth.

In human glioblastoma exclusively, IQGAP1 specifies a subpopulation of amplifying nestin+ cancer cells. Neoplastic IQGAP1+ cells from glioblastoma can be expanded in culture and possess all the characteristics of cancer stem-like progenitors. The similarities between amplifying neural progenitors and glioblastoma amplifying cancer cells may have significant implications for understanding the biology of glioblastoma.

Reference:

• Balenci L, Clarke ID, Dirks PB, et al. IQGAP1 protein specifies amplifying cancer cells in glioblastoma multiforme. Cancer Res 2006;66:9074-82.

Escape from immune surveillance

The immune system contributes to protecting the body against the development of tumours with a process called tumour immunosurveillance. However, it has also been established that the immune system can facilitate tumour progression via different mechanisms such as the production of cytokines or the induction of immune tolerance.

The strength of Rhône-Alpes Auvergne in cancer immunology research is based on the close collaboration of clinical teams involved in immunotherapy protocols, antitumour vaccination and cellular therapy, and research teams working on basic immunological mechanisms common to infection and cancer.

Research aims at identifying the mechanisms of immune evasion and developing strategies to restore a therapeutic antitumour immune response.

Development of experimental models

Researchers from the French Blood Establishment in Grenoble have generated and patented a human plasmacytoid dendritic cell line that induces *in vitro* tumour antigen specific T cell responses. In collaboration with teams in Lyon and in partnership with a team from the animal high-technology platform in Grenoble, they have set up an original tumour xenograft model in immunodeficient mice reconstituted with human T lymphocytes, dendritic cells and tumours.

Reference:

• Chaperot L, Blum A, Manches O, Lui G, Angel J, Molens JP, Plumas J. Virus or TLR agonists induce TRAIL-mediated cytotoxic activity of plasmacytoid dendritic cells. J Immunol 2006;176:248-55.

The role of immune infiltrate in tumour progression

Several teams in Lyon and Grenoble are accumulating data showing that tumour environment corrupts the immune system and favours tumour progression in different types of cancers: breast, ovarian, lung, head and neck cancers, sarcoma, melanoma, lymphoma, and peritoneal carcinosis. The tumour alters the dendritic cells necessary for the initiation of immune responses. Tumoural infiltration by plasmacytoid dendritic cells is a factor of poor prognosis for breast cancer.

Reference:

• Treilleux I, Blay JY, Bendriss-Vermare N, et al. Dendritic cell infiltration and prognosis of early stage breast cancer. Clin Cancer Res 2004;10:7466-74.

Antitumour immune response following induction of tumour cell death

Recent work by Inserm/University/Lyon Civil Hospitals immunologists in Lyon has shown that the induction, by certain anticancer drugs, of apoptosis of tumour cells transplanted in mice leads to the development of an antitumour immune response *in vivo*. In partnership with teams working on apoptosis, they are developing strategies combining targeted anticancer therapy inducing cell death and the stimulation of the immune system against specific tumour antigens.

Reference:

• Verschelde C, Michonneau D, Trescol-Biemont MC, Berberich I, Schimpl A, Bonnefoy-Berard N. Overexpression of the antiapoptotic protein A1 promotes the survival of double positive thymocytes awaiting positive selection. Cell Death Differ 2006;13:1213-21.

Restoring the immune response against tumour cells

Another approach aimed at restoring the immune response consists of 'activating' dendritic cells *ex vivo* (loading with peptides or tumour lysate), cytotoxic T lymphocytes (treatment of melanoma), or macrophages (treatment of lymphoma). These studies are directed by scientists in Grenoble (CHU and EFS).

The project "Recombinant proteins for immunology and anti-cancer use" (Pravic) associates teams from Lyonbiopôle, Lyon Civil Hospitals and the Léon Bérard Cancer Centre, and the biotechnology companies OPi (project leader), and Protein'Expert. The objective is to identify targets for recombinant enzymes or humanised monoclonal antibodies in rare viral-induced cancers, especially certain types of acute lymphoma and leukaemia.

A proof of concept project on the *in vivo* validation of the use of truncated interleukin-6 (IL-6) as an inhibitor of natural IL-6 is being coordinated in Lyon by scientists (Inserm, Claude Bernard University, Léon Bérard Cancer Centre and Lyon Civil Hospitals) and the company OPi, with a support from CLARA.

Preventing liver cancer through vaccination against hepatitis C virus

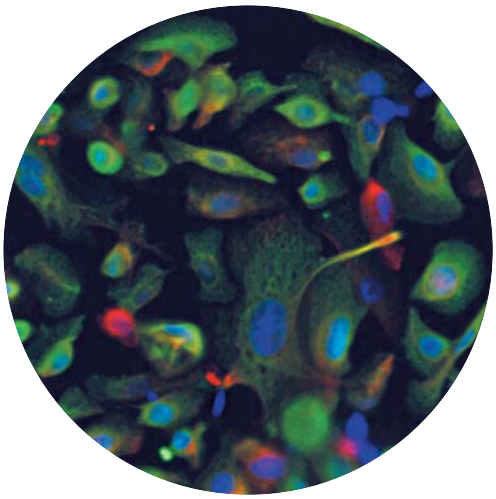
The Biotherapic project, supported by Lyonbiopôle, brings together scientists from Inserm and CNRS, Lyon Civil Hospitals, the University Hospital in Grenoble and the companies Transgène and Epixis. It aims at developing a therapeutic vaccine against hepatitis C. Also supported by Lyonbiopôle, the Alpha Vac project aims at developing a therapeutic vaccine with a prolonged effect due to vectorisation with nanoparticles. This project associates Inserm scientists, Flamel Technologies (project leader), Transgène, Lyon Civil Hospitals and University Hospitals in Grenoble, Geneva and Lausanne.

Toll-like receptors

Toll-like receptors (TLRs) are molecular sensors of infectious agents, which trigger protective responses, ranging from the secretion of cytokines that increase resistance to infection to chemokines that recruit immune cells. They also induce programmed cell death that limits microbe spreading.
Several groups in Lyon study TLR-mediated induction of the specific immune response and apoptosis. A team is working on the proapoptotic properties and mechanisms of human TLR3 expressed by cancerous cells. They have shown that TLR3 agonists may have a direct proapoptotic effect on tumour cells. This could lead to the development of multifunctional adjuvants that are able to both kill the tumour and enhance the host's immune response. This new targeted therapeutic approach is currently under study as a collaborative proof of concept project carried out by researchers at Lyon Civil Hospitals and the Claude Bernard University in collaboration with the company Innate Pharma, and with the support of CLARA.

References:

- Cottalorda A, Verschelde C, Marcais A, et al. TLR2 engagement on CD8 T cells lowers the threshold for optimal antigen-induced T cell activation. Eur J Immunol 2006;36:1684-93.
- Salaun B, Coste I, Rissoan MC, Lebecque SJ, Renno T. TLR3 can directly trigger apoptosis in human cancer cells. J Immunol 2006;176:4894-901.



A team at IARC has recently shown for the first time that the oncogenic human papilloma virus type 16 (HPV16), responsible for human cervical cancer, interferes with innate immunity by affecting the expression of TLR: infection of primary human keratinocytes by recombinant retroviruses expressing HPV16 proteins E6 and E7 inhibits transcription of TLR9, and consequently inhibits the pathways of immune activation initiated by TLR9. This work suggests that inhibition of the innate immune response is a crucial step in cancer induction by HPV. Understanding the mechanisms used by the virus to lower host immune defences is a crucial step in the development of preventive and curative approaches.

Reference:

- Hasan UA, Bates E, Takeshita F, et al. TLR9 expression and function is abolished by the cervical cancer-associated human papillomavirus type 16. J Immunol 2007;178:3186-97.

Use of Toll-like receptors as diagnostic tools

The **Deminap** project consists of using TLRs in the detection of microorganisms for diagnostic and therapeutic purposes. Cell lines expressing Toll-like receptors may allow for the rapid detection of infectious agents; while agents targeting these same Toll-like receptors may have pro-apoptotic and immunomodulatory activity. This project, supported by Lyonbiopôle, brings together teams from the IARC and the Claude Bernard University, the Léon Bérard Cancer Centre and the companies bioMérieux and Innate Pharma.

APPENDIXES

APPENDIXES

APPENDIX 1: MAJOR PROJECTS

Appendix 1.1:

Lyonbiopôle : a global competitive cluster focused on the fight against infectious diseases

Lyonbiopôle, a centre of excellence in vaccines and diagnostics, was officially recognized as a "global competitive cluster" by the French Government on July 12, 2005. It has adopted a global approach to animal and human infectious diseases, from diagnostics and prevention to treatment, integrating original delivery systems.
This integrated approach aims at elaborating a "health shield" to assure the protection of populations.
The "pole" relies on the synergy and complementary competencies of two cities: Lyon and Grenoble. Large-scale industrial production and functional biology are the strong points of Lyon, whereas structural biology and micro-nanotechnology are the realm of expertise in Grenoble.

The pole's assets
- International industrial leadership (bioMérieux, sanofi pasteur, Merial and Becton Dickinson);
- An entrepreneurial atmosphere (small and medium sized enterprises and start-ups);
- Scientific and technological excellence, based on the complementarities of the two sites;
- International visibility,
  Sites with major international scientific equipment (P4 laboratory, EMBL, ESRF...),
  European networks of excellence (VirGil and Nano2Life),
  Events: Biovision;
- Support from local authorities.

Results
For the past two years, Lyonbiopôle has helped in the development and recognition of collaborative projects; 25 projects representing an investment of 104 M€ have obtained 34 M€ in public funding.

Main areas of development in cancerology
Scientific themes:
- Immune system escape and physiopathology
- Viral-induced cancer – molecular mechanisms of transformation
- Immunostimulating and viral therapies

Target tumour models (model confrontation):
- Liver cancer
- Non-melanoma skin cancer
- Cervical cancer
- Breast cancer
- Leukaemia
- Lymphoma

Target viruses: HPV, HPV16, HPV38, HTLV 1, HCV, EBV, HBV, HHV8, HIV.
Other pathogenic agents: *H. pylori*...

Main programmes related to cancerology

ADNA
Objective: The ADNA programme (Diagnostic Advances for New therapeutic Approaches), coordinated by the Mérieux Alliance, aims to contribute to the development of personalised medicine in the field of infectious diseases, cancer and genetic diseases, providing innovative tools for the field of bio-diagnostics and new therapies for healthcare stakeholders.
Partners: bioMérieux, GenoSafe, Généthon, Transgene.
Budget: 231 M€ over 10 years.
www.aii.fr

ALPHA VAC
Objective: A new therapeutic approach to the treatment of infections due to hepatitis C virus using the combination of a therapeutic vaccine (Transgene) and a long-acting formula vectorised by nanoparticles (Flamel Technologies).
Partners: Flamel Technologies (project leader), Transgene, Inserm U548, Hôtel Dieu (HCL), University-hospital in Grenoble, Cantonal hospital in Geneva, University-hospital in Lausanne.

BIOTHERAPIC
Objective: Therapeutic vaccine against hepatitis C virus.
Partners: Transgene (project leader), Epixis, HCL, Grenoble University Hospital, Inserm, CNRS
www.transgene.fr

DEMINAP
Objective: Use of toll-like receptors (TLR) in the detection of microorganisms and their ligands in diagnostics and therapeutics.
Partners: Innate Pharma (project leader), bioMérieux, International Agency for Research on Cancer (IARC), Claude Bernard University

PRAVIC
Objective: Antibodies and enzymes for the treatment of certain lymphomas.
The project "Recombinant proteins for immunology and anticancer use" (Pravic) consists of developing drugs for treating rare and viral-induced cancers, such as certain kinds of acute lymphoma and leukaemia. Several innovative therapies are being explored, such as artificially produced enzymes and monoclonal antibodies – highly pure antibodies that could be directed against tumour cell antigens in order to destroy them specifically.
Partners: OPi (project leader), Protein'eXpert, Lyon Civil Hospitals (HCL), Léon Bérard Cancer Centre.

For further information: www.lyonbiopole.com

Appendix 1.2: Nanotechnologies and Cancer

Minatec and micro-nanotechnologies

Léti/DTBS is the largest European research unit in health-related micro- and nanotechnologies based at the "Minatec pole", a large, world-class site bringing together the CEA, the CNRS and the Grenoble Institute of Technology (INPG).

Main axes of development in cancerology

Oncology research in Rhône-Alpes Auvergne can rely on "NanoBio", a programme for multidisciplinary innovation in nanobiotechnology initiated by the CEA/Léti and the Joseph Fourier University for the development of new tools for imaging, diagnostic tests, and targeted therapeutics. Grenoble has at its disposal 4,000 micro- and nano- technology scientists, 300 of whom are specialised in health-related applications (NanoBio).
This project is integrated at the European level by the network of excellence "Nano2Life" coordinated by the CEA, which includes 23 partners and over 200 scientists.
Scientists are developing a "Nanotechnologies and Cancer" axis in association with NanoBio in Grenoble and the European network of excellence Nano2Life, which is centred on the application of nanotechnologies to new diagnostic and therapeutic practices.

Objective

The objective is to adapt the concepts of micro- and nano- technologies (integration of functions, miniaturisation, sensitivity, specificity) to medical problems in clinical oncology, especially in diagnostics: X- and gamma-ray detectors, instruments for molecular imaging (optics and probes), microchip laboratories, and *in vivo* microsystems.

Fields of application

- Diagnostics and biomarker research;
- Detectors (technology validated and transferred to industry);
- Fluorescence imaging (validated for small animals, under study for proof of concept for humans);
- Lab on chips (validation ongoing for cancer, validated and transferred for infectious agents);
- *In vivo* microsystems (validated for stimulation, validation ongoing for molecular diagnosis).

Nanotechnology – CLARA Alliance

The objective is to develop innovating tools in cancerology currently unavailable on the market, which will generate intellectual property and economic development. Concretely, this will mean specific projects using human resources at the interface between clinical research and technological development.
In addition, synergies with regional (CLARA, NanoBio) and European (Conticanet, Nano2Life) networks will be encouraged in order to identify new projects, and ensure their development and funding.

Main on-going projects in the CLARA inter-region in 2006

Name	Project	Objectives	Partners
Protool	Silica chip for molecular or cellular fingerprinting, chemically functional	Nanobiopsy and nanobanking concepts *In vivo* sampling near brain tumours	Inserm U318, CEA/Léti
IMOPT3D	Fluorescence optical 3D tomography 2D system in FRI operational	Preclinical functional imaging, biodistribution and intra-tumoural activity in live mice Activatable fluorescent probes have been developed	Inserm U578 UJF/LEDSS Animage CEA/Léti
SIMALOC	High sensitivity, high resolution µ SPECT detector (CdZnTe)	Micro Gamma Imager for small animal functional imaging	Inserm U340, CEA/Léti
Proof of concept	Nanobiotix	Activatable nanoparticles (nanobiodrugs™), preclinical studies for glioblastoma	Nanobiotix, Inserm U433

Appendix 1.3: The ETOILE project and Hadrontherapy

The Healthcare Centre
The project was initiated in 1997 by the Claude Bernard Lyon 1 University, and received support in the framework of the State-Region Development Plan Contract from 2000 to 2006. It was included in the Cancer Plan in 2003, and received definitive authorisation from the Minister of Health in February, 2007. It will be conducted in Lyon by the Health Cooperation Group ETOILE in the framework of a public-private partnership including "competitive dialogue." The construction of the centre by the designated industrial partner will begin in 2009. The first patients will be received in 2012.

The centre will be able to treat 1 000 patients per year, with carbon ions or protons, using the ballistic and biological properties of ion beams, which are remarkable in comparison to those of X-rays and conventional radiotherapy. Ion beam performance has been demonstrated in Japan and Germany in over 3,000 patients, in phase 1 and 2 clinical trials. The main indications concern inoperable and radiotherapy resistant tumours which are currently difficult to cure. In particular, it concerns certain brain and neck tumours, certain sarcoma, malignant mucosal melanoma and certain lung, liver and pelvic tumours. Patients will be recruited by the Medical Organisation of Recruitment for Carbon Ion Radiotherapy supported by the National Cancer Institute (INCa) within a European carbon ion treatment network.

The associated research programme
The objective of this programme is the improvement and safety of carbon ion and proton therapy. However, in many cases the research will be a source of innovation for radiotherapy in general. The main axes of this programme are described below.

a) Modelling of organs which move during irradiation. The simulation of respiratory movement, for example, is particularly important in the treatment of thoracic tumours.
b) Modelling of the biological efficacy of ions, as compared to that of photons, which requires taking into account many physical and biological phenomena. This very complex overall picture is a fundamental parameter in patient treatment because it concerns not only the tumour but also the healthy tissues crossed by the beam.
c) The properties of nuclear fragmentation, which may occur when the ions penetrate tissues, are poorly understood for hadrontherapy. Simulations, validated by experiments with the beams, are thus needed to improve the precision required for the physiological doses deposited within the tumour and healthy tissues.
d) The phenomena of fragmentation produces new β+ emitters which will be used in the development of positron emission tomography (PET) imaging of the dose deposited with regard to the target (the tumour). The development of this "imager" requires several technological innovations (rapidity, efficacy ...) in comparison with existing PET imaging apparatus.
e) Radiobiology with hadrons poses several specific problems compared to classical radiobiology with photons, notably for the cellular interpretation of the phenomena of radioresistance and pharmacomodulation of the response to exposure.

f) Microeconomic models are needed to evaluate the cost of carbon ion treatments in comparison with the cost of conventional proton therapy and radiotherapy.
g) Finally, R&D is needed to develop new scanning methods to determine tumour volume using the ion beam and to perform a study on a cryogenic device rotating the beam around the patient, called an "isocentric gantry," which allows the doctor to choose the best direction from which to reach the tumour. Cryogenics may help to lighten the weight of the magnets (several hundred tons!) which are used for the rotation.

Finally, it should be noted that this research programme is accompanied by a training programme, at the 'Masters' level, in order to train future medical doctors assigned to the ETOILE centre.

National and European positioning of the regional programme
At the national level, research concerning proton therapy and carbon ion treatment will be coordinated by the National Hadrontherapy Research Programme. This programme will be under the direction of the National Cancer Institute for the identification of calls for proposals needed for the improvement of clinical treatments. All French teams that might contribute to this programme may apply.

At the European level, from 2000 to 2005, hadrontherapy research was coordinated by the European Network for Light Ion Therapy (ENLIGHT). The French groups, notably those from the Rhône-Alpes region, largely contributed. Since the end of this FP5 programme, work has been preparing the formation of a new network (ENLIGHT++). This work is supported by the COST network, in the framework of the BSMS (biomedicine) field. Within the framework of FP7, a call for proposals on hadrontherapy is planned for 2008. The informal ENLIGHT++ network is preparing a response to this call for proposals.

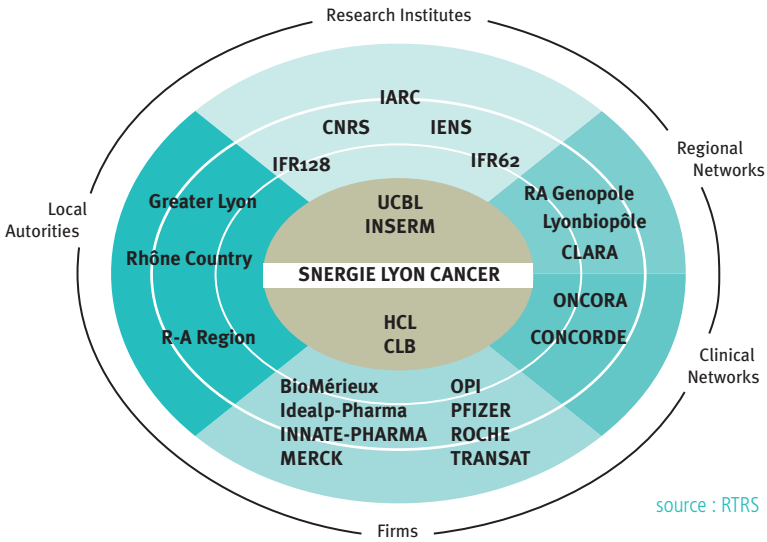
Appendix 1.4 : The "Synergy Lyon Cancer" project on therapeutic targeting and tumour escape

The Research Programme Law of April 18th, 2006 created three distinct new entities that aim to encourage research teams to combine their activities in order to boost their potential and become more visible on the international scene. These entities are the Higher Research and Education Clusters (PRES), the Advanced Research Theme Networks (RTRA) and the Research and Care Theme Centres or Networks (RTRS-CTRS).

To make cancer research a part of this new drive, CLARA provided support in preparing the application file initiated by the Claude Bernard University and Lyon-based cancer research teams in reply to the RTRS-CTRS call for proposals that closed on December 22nd, 2006. One aspect of this support involved funding a consulting firm to help design and prepare the project.

The project application entitled "Synergy Lyon Cancer – Therapeutic targeting and tumour escape" mobilised the members of 21 Lyon research units, teams of clinicians at Lyon Civil Hospitals (HCL) and the Léon Bérard Cancer Centre (CLB) and senior management at the founding organisations and partners, in order to submit a high quality project to the Ministry of Higher Education and Research.

On February 6th, 2007, the national body responsible for examining candidate projects ranked the Lyon initiative among the projects to receive funding in 2007. As a result, a Scientific Cooperation Foundation (FCS) will soon be created and will have an ambitious budget, estimated at €9.6 million for the period 2007/2011.



source : RTRS

APPENDIX 2:
THE "RIO" TECHNOLOGICAL PLATFORMS OF RHONE-ALPES AUVERGNE

The platforms of the Inter-Organisational Network (RIO) correspond to the gathering on the same site of equipment and human resources of four research organisms in the Life Sciences: Inserm, CNRS, INRA and CEA. The objective is for scientists to be able to share top quality technologies. In 2007, Rhône-Alpes Auvergne has 12 thematic RIO platforms.

Topic	City	Scientific manager Technical manager	Institution	Website address
Laboratory animal housing Functional exploration	Lyon	Jacqueline Marvel marvel@cervi-lyon.inserm.fr Marc Janier	ENS, UCBL, RA Genopole	www.ifr128.prd.fr/PBES.htm
Laboratory animal housing Functional exploration	Lyon	Alain-Jean Georges Hervé Raoul raoul@cervi-lyon.inserm.fr	Inserm	www.cervi-lyon.inserm.fr
Bioinformatics	Lyon Grenoble	Christian Gautier cgautier@biomserv.univ-lyon1.fr	RA Genopole	www.prabi.fr
Structural Biology	Grenoble	Eva Pebay-Peroula eva.pebay-peyroula@ibs.fr	RA Genopole, CEA, CNRS	www.ibs.fr
Cellular imaging	Lyon	Yves Tourneur Yves.tourneur@univ-lyon1.fr	UCBL	http://quantimetrie.univ-lyon1.fr
In vivo imaging	Grenoble	Jean-François Le Bas jflebas@chu-grenoble.fr Laurent Mamalle and Hervé Mathieu	IFR	www-ifr1.ujf-grenoble.fr/3T/
In vivo imaging	Lyon (Cermep)	Gérard Gimenez secretariat@cermep.fr	CERMEP	www.cermep.fr
In vivo imaging	Lyon (Animage)	Marc Janier marc.janier@univ-lyon1.fr	UCBL	www.rhone-alpes-genopole.com/index.php?pageID=18
Lipidomics	Lyon	Michel Lagarde Michel.Lagarde@insa-lyon.fr Michel Guichardant Michel.Guichardant@insa-lyon.fr	Inserm, CNRS, INRA, INSA, UCBL	www.insa-lyon.fr/imbl
Electronic microscopy	Lyon	Gérard Morel Gerard.morel@univ-lyon1.fr Béatrice Burdin beatrice.burdin@univ-lyon1.fr	UCBL	www.lyon1-microscopie.net
Proteomics	Grenoble	Jérôme Garin jgarin@cea.fr Myriam Ferro mferro@cea.fr	IFR 27, RA Genopole, CEA	www.rhone-alpes-genopole.com
Sequencing	Clermont-Ferrand	Pierre Sourdille Gilles Boutet gboutet@clermont.inra.fr	INRA	www.clermont.inra.fr/clermont/l_inra_en_auvergne/grands_outils_de_biologie

APPENDIX 3 :
CLARA's INSTITUTIONAL, ACADEMIC AND INDUSTRIAL PARTNERS

Funding Providers

French Ministry of Research	www.enseignementsup-recherche.gouv.fr
French Ministry of Health	www.sante.gouv.fr
National Cancer Institute (INCa)	www.e-cancer.fr
Rhône-Alpes Regional Council	www.rhonealpes.fr
Greater Lyon Urban Community	www.grandlyon.com
Rhône County (« Département »)	www.rhone.fr
Loire County	www.loire.fr
Saint-Etienne Métropole	www.agglo-st-etienne.fr
Auvergne Regional Council	www.cr-auvergne.fr
Clermont Communauté	www.clermontcommunaute.net
Puy-de-Dôme County	www.puydedome.com
Allier County	www.allier.fr
Cantal County	www.cg15.fr
Haute-Loire County	www.cg43.fr

Health Care and Research Centres

Comprehensive cancer centres	
Léon Bérard Cancer Centre (CLB)	http://oncora1.lyon.fnclcc.fr
Jean Perrin Cancer Centre (CJP)	www.cjp.fr
Loire Cancer Institute (ICL)	www.icloire.com
University Hospitals (CHU)	
Clermont-Ferrand University Hospital	www.chu-clermontferrand.fr
Grenoble University Hospital	www.chu-grenoble.fr
Lyon Civil Hospitals (HCL)	www.chu-lyon.fr
Saint-Etienne University Hospital	www.chu-st-etienne.fr
Universities	
Claude Bernard Lyon I University (UCBL)	www.univ-lyon1.fr
Joseph Fourier University (UJF), Grenoble	www.ujf-grenoble.fr
Jean Monnet University, Saint Etienne	http://portail.univ-st-etienne.fr
Auvergne University, Clermont-Ferrand	www.u-clermont1.fr
Blaise Pascal University, Clermont-Ferrand	www.univ-bpclermont.fr
Graduate schools	
ENS Lyon	www.ens-lyon.fr
Ecole Nationale Supérieure des Mines de Saint-Etienne, graduate school for science and technology	www.emse.fr
National Veterinary School of Lyon (ENVL)	www.vet-lyon.fr
INSA Lyon engineering university	www.insa-lyon.fr

Research institutes

International Agency for Research on Cancer (IARC)	www.iarc.fr
National Centre for Scientific Research (Centre National de la Recherche Scientifique - CNRS)	www.cnrs.fr
French Atomic Energy Commission (Commissariat à l'Energie Atomique - CEA)	www.cea.fr
French Blood Establishment (Etablissement Français du Sang - EFS)	www.efs.sante.fr
National Institute for Agricultural Research (Institut National de la Recherche Agronomique - INRA)	www.inra.fr/
National Institute for Research in Computer Science and Control (Institut National de Recherche en Informatique et en Automatique - INRIA)	www.inria.f
National Institute for Health and Medical Research (Institut national de la santé et de la recherche médicale - Inserm)	www.inserm.fr
Centre for Exploration and Medical Research by Positron Emission (Centre d'Exploration et de Recherche Médicale par Emission de Positons - CERMEP)	www.cermep.fr
Auvergne Human Nutrition Research Center (Centre de Recherche en Nutrition Humaine - CRNH)	www2.clermont.inra.fr/crnh
Lyon Rhône-Alpes Human Nutrition Research Center (CRNH)	www.lyon.inserm.fr/CRNHL
Albert Bonniot Institute (Institut Albert Bonniot - IAB)	www-iab.ujf-grenoble.fr
Institute for the Biology and Chemistry of Proteins (Institut de Biologie et Chimie des Protéines -IBCP)	www.ibcp.fr
Jean-Pierre Ebel Institute of Structural Biology (Institut de Biologie Structurale - IBS)	www.ibs.fr

Regional networks of care

Arc Alpin	www.arcalpin-onco.org
Concorde	www.reseau-concorde.org
Oncauvergne	www.oncauvergne.com
Oncoloire	www.icloire.com
Oncora	oncoranet.lyon.fnclcc.fr

Industry

Companies located in Rhône-Alpes Auvergne

Advanced Accelerator Applications SA	www.adacap.com
Aguettant	www.aguettant.com
Alphelys	www.alphelys.com
Aptys Pharmaceuticals	www.aptys-pharmaceuticals.com
Axcell biotechnologies	www.axcell-bio.com
BASF Engelhard (formerly Coletica)	www.engelhard.com
Becton Dickinson France (BD)	www.bd.com
Biofidal	www.biofidal.com
Biocorp	www.biocorp-online.com
bioMérieux	www.biomerieux.com
Bioviron	www.bioviron.com
CERMA	www.cerma-med.com
Charles River Laboratories	www.criver.com
Clininfo	www.clininfo.fr
Cogenics Europe (formerly GENOME Express)	www.cogenics.com
Covalab	www.covalab.fr
Cyclopharma Laboratories	www.gimra.info/fr/cyclopharma.html
Denditrics	www.dendritics.net
Diagnogene	www.diagnogene.fr
Districlass Médical SA	www.districlass.com
Edap TMS	www.edap-tms.com
EFS Electronic	www.efs.fr
EndoControl	www.endocontrol-medical.com
Epixis SA	
ERYtech Pharma	www.erytech.com
EUSA – Opi	www.orphan-opi.com
Fenics	www.fenics-sas.com
Ferco Développement	www.ferco-dev.com
Ferlux SA	www.ferlux.com
Flamel Technologies	www.flamel.com
Genopoïetic – Avax	www.genopoietic.fr
GenOway	www.genoway.com
Gensilence	http://82.238.77.78/gensilence
Haploys	www.haploys.com
Helioscopie	www.helioscopie.fr
Hikma Biotech	www.hikma.com
HLA-G Technologies SA	
Idealp-Pharma	www.idealp-pharma.com
Imaxio (formerly Avidis + Diagnogene)	www.avidis.fr
ImmunID Technologies	www.immunid.com
Indicia Biotechnology	www.indicia.fr
Innate Pharma	www.innate-pharma.com
Intuiskin	www.memscap.com
Mapi CRO	www.mapi-research.fr
Mapi Naxis	www.mapi-naxis.fr
MDS Pharma Services	www.mdsps.com
Merck Santé	www.mercksante.fr
Merial	http://fr.merial.com
Meristem Therapeutics	www.meristem-therapeutics.com
Nano-H	www.nano-h.com
Neuromic	www.neuromic.com
Neuronax	www.neuronax.com

NovoCIB	www.novocib.com
Novotec	www.novotec-labs.com
Pierre Fabre	www.pierre-fabre.com
Praxim Medivision	www.praxim.fr
Protein'eXpert	www.proteinexpert.com
Proteodynamics	www.proteodynamics.com
PX' Pharma	www.pxpharma.com
Roche Diagnostics	www.roche.com
sanofi aventis	www.sanofi-aventis.com
sanofi pasteur	www.sanofipasteur.com
Sanofi Pasteur MSD	www.spmsd.com
Siliflow	www.siliflow.com
Stem Cell Technologies	www.stemcell.com
Themis	www.themis-rd.fr
Theralys	www.theralys.com
Thiebaud biomédical instrument	www.thiebaud.fr
Transat	www.biotransat.com
Transgène	www.transgene.fr
Trixell	www.trixell.com

Companies outside Rhône-Alpes Auvergne

Amgen	www.amgen.com
Astra Zeneca	www.astrazeneca.fr
BioAlliance Pharma	www.bioalliancepharma.com
Bristol-Myers Squibb	www.bms.com
Ciphergen	www.ciphergen.com
Cyclacel Pharmaceuticals	www.cyclacel.com
Elekta	www.elekta.com
Eli Lilly	www.lilly.com
ExonHit Therapeutics	www.exonhit.com
GlaxoSmithKline	www.gsk.com
Greenpharma	www.greenpharma.com
Grunenthal	www.grunenthal.com
Ipsogen	www.ipsogen.com
Johnson & Johnson	www.jnj.com
Nanobiotix	www.nanobiotix.com
Novartis	www.novartis.com
OncoDesign	www.oncodesign.com
Pharmamar	www.pharmamar.com
Pfizer	www.pfizer.com
Roche	www.roche.com
Schering Plough	www.schering-plough.com
Servier	www.servier.com
Siemens	www.siemens.fr
Theraclion	www.theraclion.fr

APPENDIX 4 : ABBREVIATIONS AND ACRONYMS

ACCIS	Automated Childhood Cancer Information System
CEA	Atomic Energy Commission (Commissariat à l'Energie Atomique)
CERMEP	Centre for Exploration and Medical Research by Positron Emission (Centre d'Exploration et de Recherche Médicale par Emission de Positons)
CHU	University Hospital (Centre Hospitalo-Universitaire)
CLARA	Cancéropôle Lyon Auvergne Rhône-Alpes
CLB	Léon Bérard Cancer Centre
CMBA	Centre for Bio-Active Molecules Screening
CNRH	Human Nutrition Research Center (Centre de Recherche en Nutrition Humaine)
CONTICANET	Connective Tissue Cancer Network
CNRS	National Centre for Scientific Research (Centre National de la Recherche Scientifique)
CRISAP	Pathology Statistics and Data Centre (Centre de Regroupement Informatique et Statistique en Anatomie et Cytologie Pathologiques)
CRLCC	Regional Cancer Centre (Centre Régional de Lutte contre le Cancer)
DCC	Deleted in Colorectal Cancer
DISC	Death-Inducing Signalling Complex
EBMT	European Group for Bone Marrow Transplantation
EBV	Epstein-Barr Virus
EMBL	European Molecular Biology Laboratory
EORTC	European Organisation for Research and Treatment of Cancer
EPIC	European Prospective Investigation into Cancer and Nutrition
ESRF	European Synchrotron Radiation Facility
GDP	Gross Domestic Product
GEC	Clinical Study Group (Groupe d'Etudes Cliniques)
GELA	Study Group of Adult Lymphomas (Groupe d'Etude des Lymphomes de l'Adulte)
GIST	Gastro-Intestinal Tumour
GRESAC	Research Group in Health Economics and Networks in Oncology (Groupe de Recherche en Economie de la Santé et réseaux de soins en Cancérologie)
HBV	Hepatitis B Virus
HCL	Lyon Civil Hospitals (Hospices Civils de Lyon)
HCV	Hepatitis C Virus
HHV8	Human Herpesvirus 8
HPV	Human Papillomavirus
HTLV	Human T-Lymphotropic Virus
IARC	International Agency for Research on Cancer
IBCP	Institute for the Biology and Chemistry of Proteins (Institut de Biologie et Chimie des Protéines)
IBMTR	International Bone Marrow Transplantation Registry
IBS	Structural Biology Institute (Institut de Biologie Structurale)
ICL	Loire Cancer Institute (Institut de Cancérologie de la Loire)
ILL	Laue-Langevin Institute (Institut Laue-Langevin)
INCa	French National Cancer Institute

INPG	Grenoble Institute of Technology (Institut National Polytechnique de Grenoble)
Inra	French National Institute for Agricultural Research (Institut national de la recherche agronomique)
INRIA	National Institute for Research in Computer Science and Control (Institut National de Recherche en Informatique et en Automatique)
Inserm	National Institute for Health and Medical Research (Institut national de la santé et de la recherche médicale)
LEDSS	Laboratory of Dynamic and Structural Studies of Selectivity (Laboratoire d'Etudes Dynamiques et Structurales de la Sélectivité)
Léti	CEA Laboratory of electronics and information technology (Laboratoire d'électronique et de technologies de l'information)
Léti/DTBS	Léti Department of micro Technolgies for Biology and Health (Département des micro Technologies pour la Biologie et la Santé)
LYDD	Lyon Drug Discovery
MEN	Multiple Endocrine Neoplasia
MRI	Magnetic Resonance Imaging
NMR	Nuclear Magnetic Resonance
NSCLC	Non small cell lung cancer
PARCC-ARA	Platform of Assistance to Clinical Research in Cancerology (Plateforme d'Aide à la Recherche Clinique en Cancérologie – Auvergne Rhône-Alpes)
PHRC	Hospital programmes of clinical research (Programmes Hospitaliers de Recherche Clinique), financed by the French National Cancer Institute
PNS	Paraneoplastic neurological syndromes
RTRS	Research and Care Theme Network
STIC	Support for Innovating and Costly Techniques (Programme financed by the French National Cancer Institute)
SOR	Standards, Options, Recommendations
UCBL	Claude Bernard University, Lyon
UJF	Joseph Fourier University, Grenoble
UICC	International Union Against Cancer – Union Internationale Contre le Cancer

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Small animal optic imaging platform, Inserm, Grenoble (13),
International Agency for Research on Cancer (14, 15, 17),
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D. Dantchev/Inserm (27), J.F. Lebas/Grenoble University Hospital (33),
C. Albigès-Rizo, Inserm/UJF (34), Pathological Anatomy and
Cytology/Léon Bérard Cancer Centre (36L),
M. Tommasino/IARC (36R, 38)

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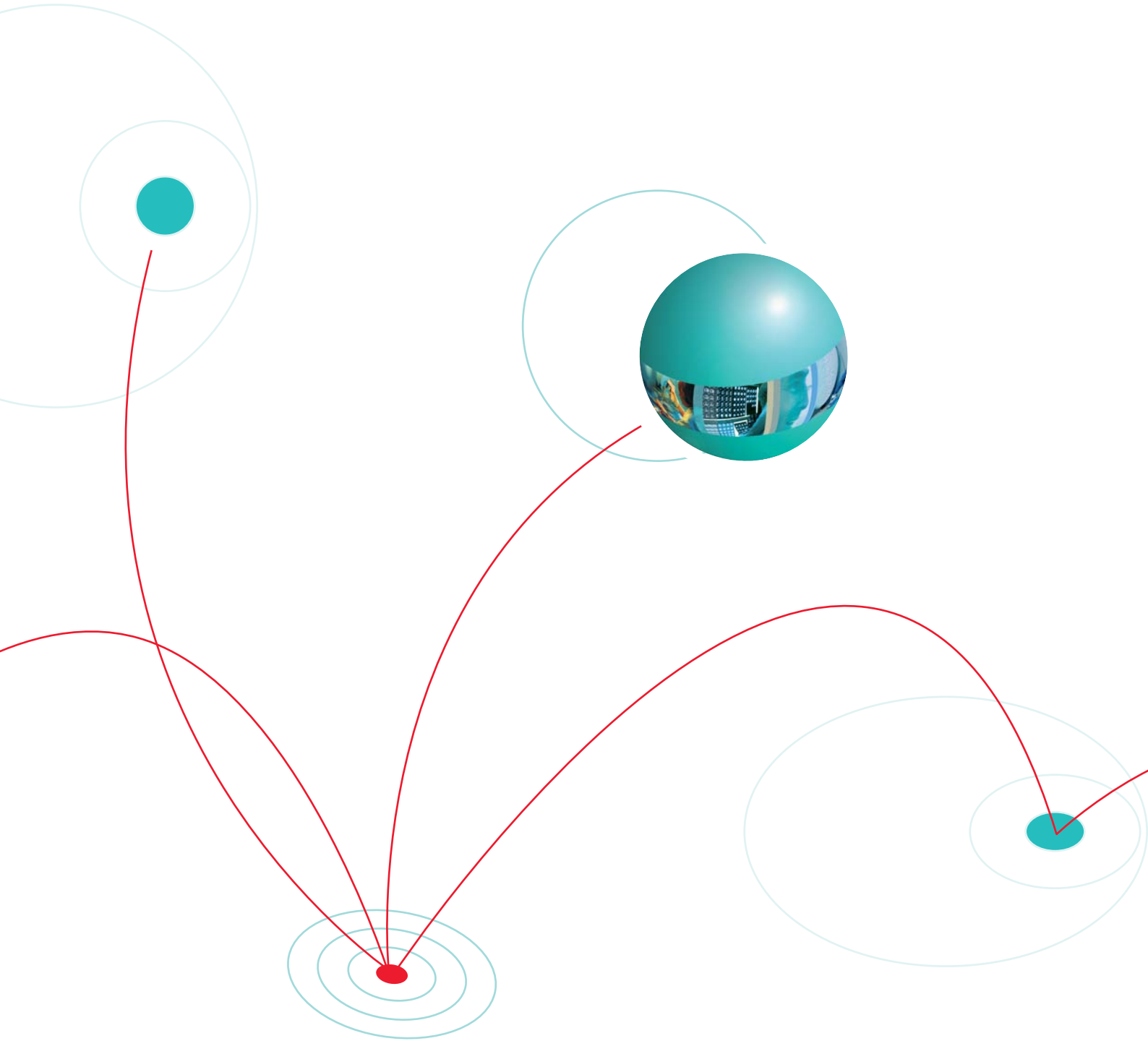

CLARA

CANCÉROPÔLE LYON AUVERGNE RHÔNE-ALPES

SPEEDING UP PROGRESS

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