

## Oncopole: a driver for cancer research in Toulouse

In November 2005, our scientific magazine described cancer research being carried out in Toulouse, including the main results published by a network of cognitive and clinical labs that work in the field.



>>> Christophe CAZAUX, professor at UPS, vice-president of the Oncopole de Toulouse association and researcher at the Institut de Pharmacologie et Biologie Structurale (IPBS, UPS/CNRS)

Six years later and taking the recent evolution of cancerology in Toulouse into account, we now review this scientific field again. Indeed many of the Toulouse teams specialized in cancerology now look set to benefit from the Oncopole (the next City -polis- of Cancer), whose clinical and scientific programme is now well defined.

### Clinical trials

With respect to clinical and translational research, the Oncopole will be strongly involved in both haematological and gynaecological neoplasia. In particular, it will develop early clinical trials devoted to promote “first-in-human” tests of new molecules.

Regarding basic science, tumour microenvironment, tumour immunology and genome maintenance will be especially studied at the Oncopole.

Beside the teams that will work directly at the Langlade Oncopole, other research teams will also belong to the Toulouse Cancer cluster. All these teams will belong to the RTRS foundation and will bring complementary knowledge, such as gene expression, development and integrative biology, immunology and structural biology to the fore. Here we present the main strategies and last data to come out from the four Oncopole divisions - namely clinical and basic research, technological transfer and pharmaceutical R&D.

### University hospital and research

Paul Sabatier University is the common denominator behind all the academic programs of the Oncopole : it is the “U” of the University Cancer Institute, which includes the next Cancer Hospital and its adjoining Cancer Research Centre (INSERM/UPS/CNRS) as well as the ITAV lab at the Pierre

Potier Centre (University of Toulouse/CNRS). UPS is also moving forwards with the support of the Innabiosanté foundation, a national organisation. It also supports TOUCAN (Toulouse Cancer) Labex and SIRIC (Site de Recherche Intégré sur le Cancer) as well as the “museum of cancer medicine” at the Oncopole. Besides this key role as leading organizer, UPS will encourage the biotech companies to set up in the area by encouraging interdisciplinary programs at the Oncopole.

*IPBS: Institut de Pharmacologie et Biologie Structurale/ Institute of Pharmacology and Structural Biology*

*ITAV: Institut des Technologies Avancées en sciences du Vivant/ Advanced Technology Institute in Life Sciences*

*CRCT: Centre de recherche en cancérologie de Toulouse/ Cancer research centre at Toulouse*

*CHU: Centre Hospitalo-universitaire/University Hospital*

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>>> The Oncopole of Toulouse.

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## Finding new therapeutic approaches: the great challenge of CRCT



>>> Jean-Jacques FOURNIE, Senior CNRS scientist, Head of the Cancer Research Center of Toulouse (CRCT, Inserm/UPS/ERL/CNRS)

Early diagnosis, gene therapy, treatments designed and tailored to cancer aggressiveness and to patient response. Anticancer approaches being studied in the Cancer Research Centre at Toulouse are more accurate, targeted and efficient.

The accumulation of genetic disorders explains why a healthy cell becomes a cancer cell. Identifying distorted cells in each cancer and finding new ways to fix these disorders are a major subject of research. As part of phase I/II clinical testing led by Toulouse Hospital, Louis Buscaill's team is testing gene therapy in pancreatic cancer and hepatocellular carcinoma.

### Aggressiveness matters

Cancer aggressiveness depends on the microenvironment, meaning that tumour development is linked to its surrounding healthy tissue. One of the major lines of research in CRCT is the study of this tumour microenvironment. Recently, new markers that determine the aggressiveness of pancreatic and lung cancers have been discovered.

The CRCT teams are also interested in the resistance of cancer cells to chemotherapy and induced relapse. The aim of this work is to increase the duration of remission and improve the quality of life for patients. The research particularly targets blood cancer (leukemia, lymphoma and myeloma) and focuses on acute myeloid leukemia and lymphoma as real hope exists in improving treatments for such pathologies.

### The efficacy of treatments may vary

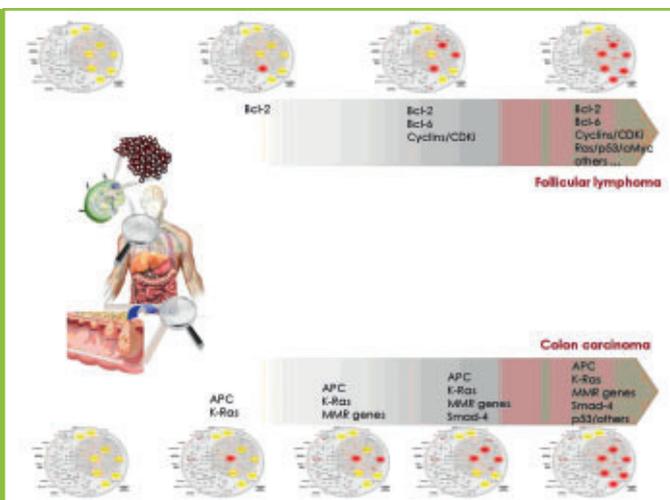
The efficacy of treatments is different from one patient to another. In order to improve the efficacy of current treatments and, obviously, to propose better ones, several CRCT teams are focusing on the reasons for such differences. These new therapeutic options are still at an experimental stage and will be developed at the Institut Universitaire du Cancer (IUC) in collaboration with the CRCT teams.

We share a "bench to bedside" approach, meaning that our aim is to adapt our fundamental research to specific clinical problems in patients. From the genome of a small sample of malignant cells, we should be able, in the short term, to identify abnormalities involved in patient cancer. Then, clinicians from the IUC will be able to treat such personalized information in order to offer the patient the best therapeutic options.

### "A la carte" treatment

Due to the personalization of medicine, the emergence of new technologies in early diagnosis and the development of low-cost sequencing of the human genome, the panorama of oncology is growing larger each day. Whereas the upcoming challenges in cancer research will be scientific, medical and technological, some challenges also need to be faced in the sociological, ethical and economics fields. To rise to these challenges, mathematicians, physicians, specialists in IT, in social sciences and in the economy will join the CRCT teams to develop various research projects. Consequently, the research topics and fields developed at the CRCT in the coming years will be multidisciplinary - a major vocation of our research center.

>>> LCancer develops by mutation of genes in the nuclei of our cells. Each type of cancer results from the gradual accumulation of multiple mutations occurring sequentially.



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>>> Martine KNIBIEHLER, CNRS research engineer, executive director of ITAV (CNRS/UPS/INSA)

## Spheroids and 3D imaging to better understand tumour proliferation

ITAV (Institute of Advanced Technologies in Life Sciences) is a “hotel à projets” dedicated to interdisciplinary research and innovative technologies in the field of health and life-science studies. The project teams benefit from a remarkable technological environment composed of three platforms in the areas of multi-scale photonic imaging, automated chemical synthesis and bionanotechnology (<http://www.itav-recherche.fr/>).

The ITAV teams (led by B. DUCOMMUN and C. VIEU) focus on the development of new models of 3D cell culture, engineering of microdevices and the implementation of new imaging tools to study tumour proliferation and assess response to treatment. A major achievement in the laboratory has been the development of a new cell imaging system, called SPIM, to visualize three-dimensional biological structures and large organizations under the conditions that allowed their development.

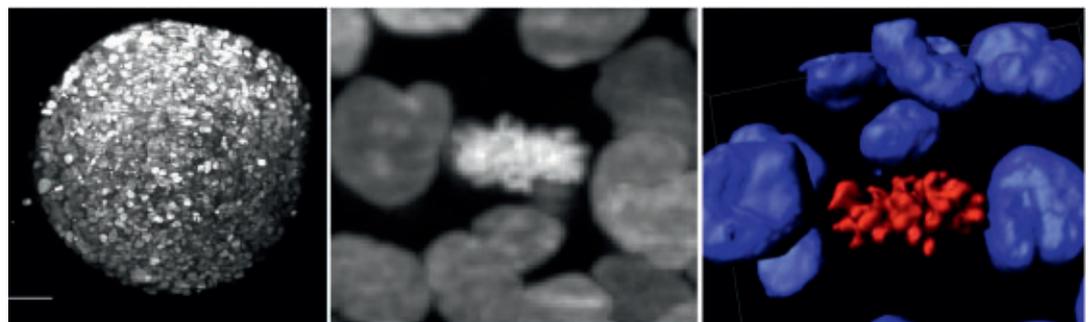
A “SPIM routine” is now open to the scientific community and available on the ITAV imaging core facility at the Genotoul and certified IBISA\*. This achievement and the pursuit of original developments in imaging are based on collaborations with teams from IRIT and IMT.

To study tumour proliferation, the teams are also focusing on original models of spheroids, a 3D model closer to tumours than monolayer cell cultures,

mimicking their organization in vitro. Development of devices to control growth can be used to study the effect of mechanical stress on tumour development. SPIM microscopy also allows in-depth imaging of the spatio-temporal aspects of the dynamics of cell proliferation in 3D spheroids as shown in the figure. These cell models, engineering original devices, and the development of imaging tools open the way to the study of how 3D structures respond to chemotherapeutic agents and ionizing radiation.

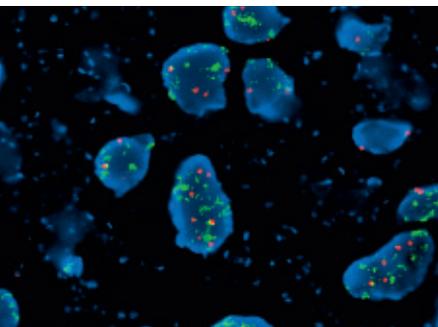
\* *The development of this new instrument would not have been possible without the financial support of the following institutions and charities: CNRS, Université Paul Sabatier Toulouse 3, Région Midi-Pyrénées, MRCT, fondation InNaBioSanté, Cancéropôle Grand-sud Ouest, GIS IBISA, Ligue contre le Cancer, Association pour la Recherche sur le Cancer.*

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>>> Spheroids imaging by SPIM. (Left): Spheroid of HCT116 cells expressing the fluorescent nuclear protein Histone H2B-HcRed (bar: 50  $\mu$ m). (Centre): An in-depth image of the reconstruction shown on the left on which a mitotic cell with condensed chromosomes is visible. (Right): 3D reconstruction of the image shown in the centre. Isosurfaces correspond to nuclei in interphase (blue) and in mitosis (red).

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>>> Detecting tumour  
chromosomal anomalies.

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## Therapeutic strategies in myeloma

In 1990, a patient with myeloma could be expected to live for just two years. Thanks to several phase II and III clinical research programmes, begun and coordinated by the Toulouse centre for haematology, the average life expectancy has increased to more than 10 years, with a hope for a complete cure for an increasing number of patients. A new phase III trial, promoted by the CHU of Toulouse and which brings together more than 100 French and American, centres, is currently under way. Its goal: to include all progress that has been achieved in the last 10 years in therapeutic strategies, but also to analyse the complete genome of 1000 patients with myeloma.

## The Institut Universitaire du Cancer, a unique care establishment in France

A collaboration between the University Hospital Centre (CHU) of Toulouse and the Claudius Régaud Institute, this new research hospital with more than 300 beds will open in 2013 on the Oncopole site.

The Institut Universitaire du Cancer (IUC) will focus on fundamental and clinical research, and its aim is to provide “bench-to bedside” solutions to patients. Its main goal is to offer patients the latest in cancer treatment. Wards will be dedicated to research and associated with 13 platforms on the same site that take advantage of the latest technology in cancerology, together with the Toulouse Centre of Research in Cancerology (a joint Inserm/UPS/CNRS research unit). Finally, a biology resource centre in oncology – one of a kind in the mid-Pyrénées region – will be put in place on the IUC site too.

### Improving patient care

To speed up initial patient care, a specialised multi-task consultation platform will be created. To ensure that all cancer patients in the region have equal access to care, the IUC will organise a therapeutic decision-making and patient-guide centre. This centre will bring together public health care organisations. A special exchange and teaching centre for health professionals will also be set up.

The IUC is a great opportunity to restructure and rationalise public health care in oncology for the Toulouse region. Three establishments in the area (the IUC, Rangueil-Larrey and Purpan) will thus be specialised in oncology. The IUC itself specialises in haematology, female oncology, ear, nose and throat (ORL) cancers, melanomas, sarcomas (rare but very aggressive and resistant tumours)

and urology. Other cancers will continue to be treated at the Purpan and Larrey-Rangueil hospitals. Moreover, the IUC will be home to a certain number of highly specialised infrastructures that will be shared with these hospitals and partner establishments in the region, such as intensive care, specialised radiotherapy and research centres.

### Screening

At present, screening is in place for a certain number of cancers. However, once performed, the patient is often left to his own devices for the follow-up medical. The IUC hopes to remedy this by co-coordinating the organization of patient care and creating a special centre dedicated to screening follow-up if anomalies are found during the initial procedure. This organization will allow the epidemiological study of early-stage cancers and their detection.

**Michel Attal, professor at the university hospital, head of the haematology department at the CHU of Purpan, president of the Groupement de coopération sanitaire de préfiguration at the IUC.**

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>>> Paola ARIMONDO, senior CNRS scientist, head of the USR, CNRS-IRPF, ETaC, and François SAUTEL of Pierre Fabre, head of the "Chimie des Substances Naturelles Bioactives" team at ETaC

## A new public-private partnership to discover novel anticancer agents.

For more than 20 years now, the CNRS and the Pierre Fabre Laboratories have been developing common research programs aimed at discovering new anti-tumour agents. This partnership has been very successful and two alkaloids of the *Vinca rosea* are now being commercialized as anti-tumour drugs: Navelbine® (vinorelbine), used for the treatment of lung and breast cancer, and Javlor® (vinflunine), recently registered in Europe for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract.

In January 2011, the Institut de Recherche Pierre Fabre (IRPF) and the CNRS founded a new joint laboratory, the Unité de Service et de Recherche (USR n°3388) entitled "Epigenetic Targeting of Cancer" (ETaC), which brings together basic and applied research.

The USR ETaC is based on three functional and complementary departments: two technological platforms dedicated to the chemistry of bioactive natural products (plant and microbial biodiversity, extractive and analytical chemistry, semi-synthesis and organic synthesis) and to pharmacological screening. The latter is a national screening platform. It received the IBISA label in 2009 and plays a key role in the "Plateforme Intégrée de Criblage de Toulouse" (PICT) - miniaturization and robotization and chemical screening.

The USR ETaC is composed of a third team of chemists and biologists dedicated to the epigenetic regulation of cancer. Chemists and biologists work together to study the role and control of the epigenetics markers in cancer, in particular in metastatic melanoma, in close collaboration with the teams from Pierre Fabre Oncology Research.

The Laboratory works on basic topics (new targets and new molecular mechanisms) while keeping an eye on applications (candidate drugs).

Molecular and cellular level studies will bring a better understanding of epigenetic regulation, in particular DNA methylation, which is essential in tumorigenesis and in certain chemioresistance. The design of pharmacological and chemical tools (such as new DNA methylation inhibitors) will also allow us to understand the biological processes that are found in cancer, to propose new therapeutic targets and to discover new anti-tumour agents.

### Towards clinics

The USR ETaC is based at the Oncopole of Toulouse in the new Pierre Fabre Research and Development Centre (CRDPF). As a joint unit, it collaborates extensively with other partner laboratories. The Oncopole (CRDPF, Centre Pierre Potier ITAV and soon the Institut Universitaire du Cancer and the Centre de Recherche en Cancérologie de Toulouse) will develop new innovative and collaborative projects that will go from basic research to the patient ("from bench to bedside") through technology and pharmaceutical development.

The USR ETaC is very active in local scientific life too (it is member of the Institut de Chimie de Toulouse) and at the national and international level through many collaborations.



>>> *Poikilospermum suaveolens* (Blume) Merr. (Cecropiaceae) from Koh Kong.  
Credit: Christophe Long/ETaC-IRPF

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