

dates for your diary

innovations

From 17 September to 10 December 2007

The Institut Curie invites the public to come and discover **the world of research through the beauty of instruments:** everyday objects, out of the ordinary or surprising. This exhibition of photographs will be displayed on the railings of the Curie Campus (rue d'Ulm and rue Pierre-et-Marie Curie, Paris, 5th arrondissement).

25 September 2007

The first talk in the 2007-2008 **Tuesdays at the Institut Curie** lecture series will be on "Living with Cancer" and will be given at 6 pm in the Constant-Burg Lecture Theater, 12 rue Lhomond, Paris 5th arrondissement. Free entry. The complete lecture series program is available at: www.curie.fr/conferences

From 17 to 20 October 2007

The **Second Euro-Mediterranean Congress** will be held in Hammamet, in Tunisia. Its theme will be: **Cancer and targeted therapies:** biological and clinical applications.

29 October 2007

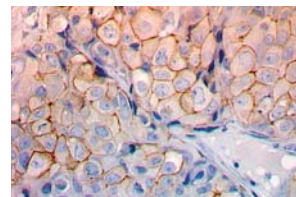
The Institut Lumière de Lyon is playing host to a congress **reviewing kinases and cancer**, organized by the French Biochemistry and Molecular Biology Society, and the Lyon Auvergne Rhône-Alpes Cancer Research Network.

All the meetings on the web site: www.curie.fr/congres

Breast cancer

A NEW PRECLINICAL RESEARCH TOOL

At the Institut Curie, Inserm researchers and physicians have established the largest ever panel of human breast cancer xenografts in animal models. Because of their similarity to patient tumors, these models are an exceptional tool for testing the efficacy of new drugs, adapting treatments to tumor characteristics, unraveling resistance to certain treatments, and as a result limiting the need for clinical trials in patients. Institut Curie and Inserm medical oncologists, surgeons, pathologists and biologists collaborated on these 25 breast tumor models which can now be extended to other types of cancers.



« A new model of patient tumor-derived breast cancer xenografts for preclinical Assays »
 E. Marangoni, A. Vincent-Salomon, N. Auger, A. Degeorges, F. Assayag, P. de Cremoux, L. de Plater, C. Guyader, G. De Pinieux, J-G. Judde, M. Rebucci, C. Tran-Perennou, X. Sastre-Garau, B. Sigal-Zaffrani, O. Delattre, V. Diéras, M-F. Poupon
Clinical Cancer Research, 1 July 2007, vol. 13, p. 3989-3998.

→ press release at: www.curie.fr

Bioinformatics

ACTuDB, A NEW DATABASE



The development of new techniques for genome analysis generates a huge volume of data and thereby a need for relevant references to analyze these findings. The Bioinformatics department of the Institut Curie has just developed a new tool to optimize the analysis of results collected using array-based comparative genomic hybridization: the array-CGH tumor database (ACTuDB). This database holds the genomic profiles of tumors, with particular emphasis on the regions of loss or gain of genetic material, the grand finale of the analysis of this type of DNA chip. The number of copies of certain regions of the tumor DNA depends on the nature and even the aggressiveness of the tumor.

At present, 1500 published profiles of tumors of the breast, bladder, mouth, and pancreas are freely accessible and utilizable at <http://bioinfo.curie.fr/actudb/>. Researchers and clinicians can therefore compare their results with those of the database.

« ACTuDB, a new Database for the Integrated Analysis of Array-CGH and Clinical Data for Tumors. »
 P. Hupé, P. La Rosa, S. Liva, S. Lair, N. Servant, E. Barillot
Oncogene, 14 May 2007, online publication.

Notepad

At the Institut de France Awards Ceremony on June 13 last, **Professor Jean-François Joanny**, director of research unit UMR 168 Physical Chemistry Curie (CNRS/Institut Curie), and **Professor Jacques Prost**, who runs a group within this unit and is General Director of the École supérieure de physique et chimie industrielles in Paris, received the **Scientific Prize of the Simone and Cino del Duca Foundation**. This 300 000-euro award is in recognition of their work on the concepts and physical techniques used in life science research.



The **Eurocancer Grand Prize** was awarded last 26 June to **Dr Olivier Delattre**, director of Inserm/Institut Curie Unit 830 Genetics and Biology of Cancer, for his work on Ewing's sarcoma. The tomotherapy team received **First Prize for Presentations** at the Eurocancer Radiological Technologist meeting on June 28 last, for the talk given by **Carine Claudon** of the **radiotherapy unit**: Tomotherapy: a new technique in radiotherapy.



All the bioinformatic and biostatistical analyses of the Institut Curie, which were previously done by several different groups, are now performed by the **Biological and Clinical Analyses In Silico (ABCIS) working group** coordinated by Emmanuel Barillot. The aim of this regrouping is twofold: to optimize members' work and to facilitate access to such analyses by Institut Curie healthcare staff and researchers.



editorial

Professor Paul Nurse, biologist and winner of the 2001 Nobel Prize in Physiology or Medicine, President of Rockefeller University in New York (United States), has done us the great honor of accepting the presidency of the Scientific Board of the Institut Curie. Having been a member from 1999 to 2007, Paul Nurse has now taken over from Howard Green, Professor of Cellular Biology at Harvard Medical School (United States), who had been president of the board since 1999.

The Scientific Board, whose members are eminent research scientists and directors of prestigious institutions, advises on the major strategic, scientific and medical policies of the Institut Curie. With this nomination, the Institut Curie will assure its role as a European leader in oncology.

*Professor Claude Huriel,
 President of the Institut Curie*

news

Lymphoid Malignancies

DISCOVERY OF A NEW THERAPEUTIC STRATEGY

CNRS « Oncogenes and Hematopoietic Cell Differentiation » team at the Institut Curie has shown that calcineurin, a protein phosphatase, is activated in lymphoma and certain cases of acute lymphoblastic leukemia. Preclinical studies in an *in vivo* model show that calcineurin activation is crucial to the survival of these tumors of the hematopoietic system, which renews blood cells throughout life. On the basis of these findings,

the researchers have devised a new therapeutic strategy by targeting calcineurin. Because of its role in the rejection of grafts, calcineurin is already the therapeutic target of two immunosuppressants used clinically, cyclosporin A and FK506 (tacrolimus), which inhibit calcineurin activity and kill tumor cells. A clinical trial is scheduled to start very shortly at the Institut Curie to assess the potential of this new strategy, parti-

cularly FK506, in the treatment of lymphomas.

« Targeting Calcineurin Activation as a Therapeutic Strategy for Lymphoid Malignancies »
 H. Medyouf, H. Alcalde, C. Berthier, MC. Guillemain, NR. dos Santos, A. Janin, D. Decaudin, H. de Thé, J. Ghysdael
Nature Medicine, June 2007, vol. 13, p. 736-741.

→ Press release at: www.curie.fr

Biophysics



In mammals, DNA is never naked, but rather is complexed with proteins, the histones, which form a structure called chromatin. The CNRS « Macromole-

DNA TWISTING TO REGULATE GENE EXPRESSION?

cules and Microsystems in Biology and Medicine » team at the Institut Curie and groups of the Université Pierre et Marie Curie, and of the Institut Jacques Monod are studying the effect of twisting an individual chromatin fiber—a filament one hundred thousandth of one millimeter in diameter—whose ends they manipulate using magnetic tweezers. They have just shown that by applying torsions comparable to those exerted within the cell by polymerases, proteins that copy the genetic code, it is possible to change the conformation of this chromatin, and so to alter the

accessibility of the genes. The torsion of DNA is therefore probably one of the physical mechanisms by which the cellular machinery regulates gene expression *in vivo*.

« Nucleosome Chiral Transition under Positive Torsional Stress in Single Chromatin Fibers. »
 A. Bancaud, G. Wagner, N. Conde e Silva, C. Lavelle, H. Wong, J. Mozziconacci, M. Barbi, A. Sivolob, E. Le Cam, L. Mouawad, J-L. Viovy, J-M. Victor, A. Prunell
Molecular Cell, 6 July 2007, vol. 27, p. 135-147.

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Research

SURVEY REVEALS MIXED RESULTS FOR FRENCH BIOMEDICAL RESEARCH, BUT GOOD NEWS FROM THE INSTITUT CURIE

Biomedical research in France is conducted by 12 500 statutory researchers working in 1 000 research units, 90 institutions, 25 large groups, all funded by 2.3 billion euros of public and private money. Some 10 000 articles are published every year, ie, 5% of all publications and scientific citations, which places France fifth in the world in absolute terms, behind the United States, the United Kingdom, Germany, and Japan.

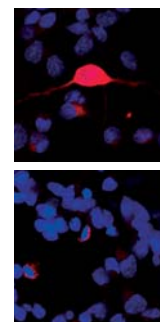
A bibliometric survey launched at the end of 2005, at the request of the Institut Necker and the University of Paris 5, has compiled up the first review of biomedical research. Despite a rather negative appraisal, seven institutions stand out because of their excellence: the Institut Necker, the Strasbourg Institute of Genetics and Molecular and Cellular Biology (IGBCM), the Institut Pasteur, the Institut Curie, the CNRS at Gif, the Marseille Luminy Immunology Center, and the Strasbourg Molecular and Cellular Biology Institute (IBMC).

By implementing a bold scientific policies, four institutions, including the Institut Curie, have in recent years confirmed their positions as national leaders and their international standing. The Institut Curie is in fifth position in absolute terms among 90 national institutions and third among 30 institutions in the Paris Ile-de-France region. The Institut Curie can boast 5 of the 101 authors of publications of excellence, 5 of the 60 young researchers acknowledged for the quality of their work, and 4 of the 63 best publications in France in 2006.

This first wide-ranging scientific survey of French biomedical research reveals the shortcomings and weakness of the research organizations. By reaffirming that Paris leads the way, the survey also points up the need for a critical mass of researchers if the capital is to be emulated. The life sciences in France are at the heart of progress and of what is at stake in the future and should, so the authors of the survey report argue, be reorganized so as to accord more freedom to researchers and to institutions that have proved their worth, and to provide help for organizations and people in difficulty.

→ The full study can be consulted at www.lesechos.fr

Huntington's Disease



HUNTINGTIN, A DOUBLY TOXIC PROTEIN

Damage to the genetic material is observed in cancer, neurodegenerative diseases, and aging. At the Institut Curie, « Signal Transduction and Neuronal Death » (CNRS, Inserm) team has characterized the role of phosphorylation—a chemical change—of the protein huntingtin by kinase Cdk5 in response to these alterations in DNA. The mutation of huntingtin causes Huntington's disease, which is characterized by the abnormal death of neurons in the striatum.

As an early response to the presence of damaged DNA, normal huntingtin is phosphorylated by the kinase Cdk5 thus regulating cell death. If this phosphorylation does not happen, the huntingtin is then toxic and cell death induced by DNA lesions is accelerated.

Conversely, the mutant huntingtin phosphorylated by the kinase Cdk5 is no longer toxic. The accumulation of damage to the genetic material results in the inactivation of the kinase Cdk5. So, in the later stages of the disease when more lesions have accumulated, the mutant huntingtin is not phosphorylated and, consequently, is even more toxic for the neurons.

« Phosphorylation of Huntingtin by cyclin-dependent kinase 5 is Induced by DNA Damage and Regulates Wild-Type and Mutant Huntingtin Toxicity in Neurons. »

S. Anne, F. Saudou, S. Humbert
J Neurosci, 4 July 2007, vol. 27, p. 7318-7328.

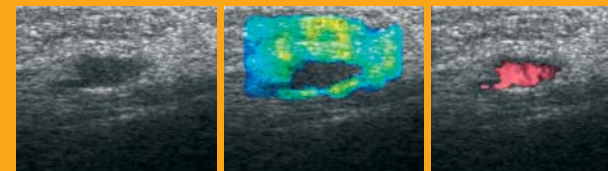
ELASTOGRAPHY: WHEN IMAGING INCLUDES THE ELASTIC PROPERTIES OF TISSUES



To improve the characterization of breast lesions, the CNRS team of the physicist Mathias Fink, with the assistance of Dr Anne Tardivon and Dr Alexandra Athanasiou of the Medical Imaging Department of the Institut Curie, is studying the performances of elastography in ultrasonography. This novel technique provides not only an anatomical image, but also information on tissue elasticity.

When breast lesions that are uncharacterized or suspected of being cancerous are detected by ultrasound scanning following screening or mammography, fine-needle biopsy may prove necessary to determine whether or not the lesion is benign.

Elastography is the latest innovation from the Waves and Acoustics Laboratory, which is headed by Mathias Fink at the École supérieure de physique et de chimie industrielles de Paris. It evaluates *in vivo* the elastic properties of tissues: a benign lesion is usually firmer than normal breast tissue, but softer than a cancer. The probe



used in ultrasonography directs additional painless acoustic waves towards the area to be analyzed. In a sense these extra waves are used to “palpate” the lesion. Once emitted, they will move at speeds that reflect the elasticity of the target tissues. The waves return to the probe and their analysis gives the radiologist a quantitative image of the elasticity of the tissue, and this image can be used to compare the hardness of the lesion with that of the surrounding normal tissue.

So far, 54 patients with breast lesions uncharacterized on ultrasound have undergone this new technique at the Institut Curie. This work has shown that the elasticity values of cancerous tissues differed significantly from those of benign lesions. Elastography also characterizes fluid-filled lesions and benign cysts, which are sometimes difficult to diagnose by anatomical ultrasound because the signals of thick fluids can mimic that of a tissue nodule. It has proven very useful in characterizing and delimiting lesions under one centimeter in size.

In time, physicians hope to be able to use this new ultrasound technique to select which breast lesions should be biopsied.

This promising technique can be used to study other organs (thyroid, kidney, liver, muscles), and many areas of application remain to be explored.

Epigenetics

BRCA1 NOT GUILTY IN THE INACTIVATION OF CHROMOSOME X

Two breast cancer predisposition genes have been discovered so far: BRCA1 and BRCA2. However, their exact functions in the cell remain unknown and have given rise to much speculation, including that BRCA1 could be involved in the inactivation of the X chromosome in women. Yet « Mammalian development and Epigenetic »'s team, in collaboration with physicians and researchers of the Institut Curie, has just shown that the loss of BRCA1 does not affect the inactivity of the X chromosome in breast tumors.

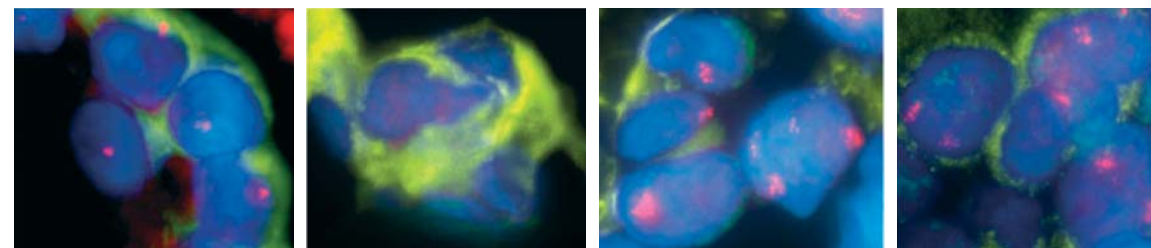
In women, one of the two X chromosomes—that inherited from the father or mother—is inactivated randomly during embryogenesis. This is essential to avoiding imbalance between men, who have only one X chromosome, and women, who have two. To this end, each X chromosome has an inactivation

center (Xic) which is able to inactivate it, through the production of a non-coding RNA, Xist.

Suspected of recruiting RNA Xist, BRCA1 has now been cleared after the analysis of 11 breast tumors with a mutation of this gene. BRCA1 does not participate in the association of this RNA with the X chromosome and does not seem to lead to the reactivation of this chromosome in breast tumors.

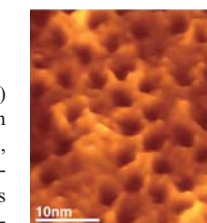
« X Inactive-Specific Transcript RNA Coating and Genetic Instability of the X Chromosome in BRCA1 Breast Tumors. »

A. Vincent-Salomon, C. Ganem-Elbaz, E. Manie, V. Raynal, X. Sastre-Garau, D. Stoppa-Lyonnet, M.H. Stern, E. Heard
Cancer Res, 1 June 2007, vol. 67, p. 5134-5140.



Atomic Force Microscopy

VDAC, REGULATOR OF APOPTOSIS



At the Institut Curie (CNRS/Inserm Avenir) « Structure and Assembly of Membrane Proteins in Native Membranes by Atomic Force Microscopy », team has just used atomic force microscopy to investigate the distribution of the most abundant proteins in the outer membrane of mitochondria—the voltage-dependent anion channel (VDAC). These proteins form channels essential to the activity of mitochondria, and so during programmed cell death, or apoptosis, the cytochrome needed for respiration, a crucial activity of the mitochondria, is eliminated by VDAC.

The higher the density of VDAC (80%), the more porous is the membrane. So the density regulates the exchanges between the mitochondria and the outside medium. Having determined the structure of the VDAC and analyzed the areas where it is present, the researchers proposed a model of its distribution. As apoptosis is one of the mechanisms perturbed in tumor cells, knowledge of the structure and function of VDAC could one day enable us to manipulate its properties and so act on this mechanism.

« Supramolecular Assembly of VDAC in Native Mitochondrial Outer Membranes. »

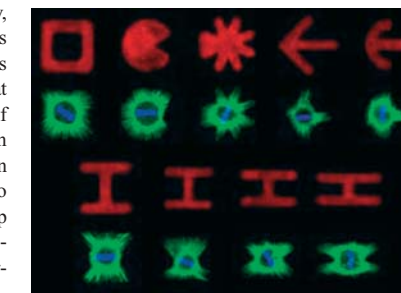
RP. Gonçalves, N. Buzhynskyy, V. Prima, JN. Sturgis, S. Scheuring
J. Mol. Biol. 1 June 2007, vol. 369, p. 413-418.

innovations

Cell Division

HOW A CELL INTERACTS WITH ITS MICROENVIRONMENT

Division is a key step in the life of every cell and involves a host of molecules involved in a complex interplay. The CNRS team of Michel Bornens at the Institut Curie, in collaboration with theoretical physicists at the Max Planck Institute in Germany, has now devised a theoretical model of cell division of great predictive value. Microtechnology can be used to study individual cell divisions as a function of variations in their environment. From their observations on a very large number of cells, the researchers have described a predictive model of the orientation of cell division. This model, based on the calculation of the forces acting on the mitotic spindle inside the cell, describes how cell division unfolds normally, and also what happens when this process goes awry. The model shows that certain configurations of the microenvironment can induce asymmetric division of cells. When applied to tissues, the model will help refine diagnosis by describing how division is perturbed in diseased cells.



« Experimental and Theoretical Study of Mitotic Spindle Orientation. »
M. Théry, A. Jiménez-Dalmaroni, V. Racine, M. Bornens, F. Jülicher
Nature, 24 May 2007, vol. 447, p. 493-49.

→ Press release at www.curie.fr