

dates for your diary

innovations

From 25 to 28 March 2008

The French Cell Biology Society is organizing a symposium on the "Cell Cycle and Cancer" in Toulouse (France). Biologists from the world over will come to take stock of the latest discoveries regarding the cell cycle and how it is perturbed in tumor cells, and of the therapeutic targets that may be derived from such discoveries.

15 April 2008

"The Extraordinary Story of Radiation" in the **Tuesdays at the Institut Curie lecture series** will describe the craze for radioactivity that followed its discovery.

6 pm in the Constant-Burg Lecture Theater, 12 rue Lhomond, Paris 5th arrondissement.

The complete lecture series program is available at: www.curie.fr/conferences

27 May 2008

"How the Immune System Protects the Body" in the **Tuesdays at the Institut Curie lecture series** will review immunotherapy.

6 pm in the Constant-Burg Lecture Theater, 12 rue Lhomond, Paris 5th arrondissement.

The complete lecture series program is available at: www.curie.fr/conferences

From 30 May to June 2008

The **44th Congress of the American Society of Clinical Oncology (ASCO)** will be held in Chicago (Illinois, United States). Considered as one of the most important in oncology, this meeting will be attended by specialists from around the world and will review the latest developments in the field.

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

Pharmacology

THE CHEMICAL LIBRARY, OR HOW TO DISCOVER NEW DRUGS

The chemical library of the CNRS/Institut Curie "Design, Synthesis and Targeting of Biomolecules" unit is the fruit of 30 years of research, and now has over 10 000 chemical compounds in a single databank. It can be used for high-throughput testing of drug candidates.

A new class of antiviral drugs was recently discovered after screening of a collection of molecules of this chemical library by researchers of the Montpellier Molecular Genetics Institute (CNRS, Université de Montpellier 1 et 2). One such, IDC16, blocks infection by the AIDS virus HIV-1 by preventing its splicing, ie, by stopping maturation of the viral RNA and hence replication of the virus.

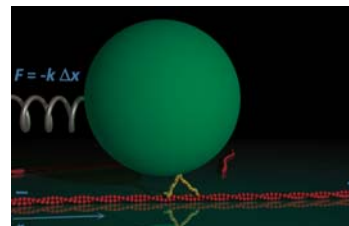
This completely new approach avoids problems of resistance by attacking the cellular mechanisms used by the virus to multiply. The chemical library of the Institut Curie is therefore at the forefront of various medical fields, notably oncology.

"Small-Molecule Inhibition of HIV pre-mRNA Splicing as a Novel Antiretroviral Therapy to Overcome Drug Resistance." N. Bakkour, YL. Lin, S. Maire, L. Ayadi, F. Mahuteau-Betzer, CH. Nguyen, C. Mettling, P. Portales, D. Grierson, B. Chabot, P. Jeanteur, C. Branlant, P. Corbeau, J. Tazi
PLoS Pathog. 26 October 2007, vol. 3, p. 1530-1539.

Biophysics

TRACKING A MOLECULAR MOTOR

Two teams of the "Curie Physical Chemistry" CNRS/Institut Curie unit have tracked the movements of myosin V. This molecular motor, by moving along actin filaments, can transport a molecule from one end of the cell to the other. But how does this protein transform the chemical energy, produced by hydrolysis of the "fuel" ATP, into mechanical work? Using the detection technique of interferometry, coupled with optical tweezers, the researchers manipulated myosin V and followed its movements with nanometer and microsecond precision. The stepping mechanism of myosin V has three stages: first, when myosin V binds to ATP, it slips 5 nm; then, faster, it jumps 23 nm away from the actin fiber; lastly, it diffuses to its new anchoring site, 36 nanometers further on, and resumes its original conformation. In this way, myosin V converts chemical energy into mechanical energy.



"Myosin V Stepping Mechanism."

G. Cappello, P. Pierobon, C. Symonds, L. Busoni, J.C. Gebhardt, M. Rief, J. Prost
PNAS. 25 September 2007, vol. 104, p. 15328-15333.

Notepad

● **Nicolas Stransky**, of CNRS/Institut Curie "Subcellular Structure and Cellular Dynamics" UMR 144 has been awarded the 5000 euro Prize for the **Best Interdisciplinary Thesis by the EADS Corporate Research Foundation**. This prize is in recognition of his work on bioinformatic identification of genes and genomic regions involved in cancer.

● **Dr Dominique Stoppa-Lyonnet**, Head of the Genetics Department of the Institut Curie, has received the title of Laureate of the National Academy of Medicine by winning the **Henry and Mary-Jane**



for work in the fight against cancer.

● **Roselyne Bachelot-Narquin**, the Minister of Health, has just appointed **Dr Alain Livartowski**, Head of the Medical Information Department, to the working group in charge of the **Personal Health Record (PHR)**. This appointment is recognition of the

expertise of the Institut Curie and all its specialists in electronic medical records.

● **Jacques Prost**, who runs the "Physical Approaches to Biological Problems" team (UMR 168 CNRS/Institut Curie) with Jean-François

Joanny, and who is General Director of the École supérieure de physique et chimie industrielles of the City of Paris, was elected a member of the **Academy of Sciences** on 11 December 2007. His work relates to the description of cell movement and is based on the concepts of soft matter physics.



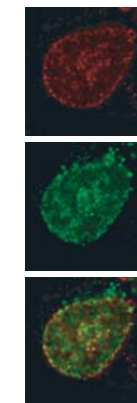
editorial news

The Institut Curie is a reference center for treatment of breast cancer and actively participates in the development of new therapeutic strategies, and in the use of a global approach to patient care. For 60 years Institut Curie physicians have favored the development of conservative treatments that minimize the impact on patients' functional and anatomic integrity.

The Institut Curie is perpetuating a long tradition of patient care and is fully committed to the elaboration of a modern conception of public health. The "intimacy and sexuality after breast cancer" survey is a perfect example of an approach that combines psychological and social support, dietary advice, and functional rehabilitation.

Prof Pierre Bey,
Director of the Institut Curie Hospital

Epigenetics



ASF1, THE PROTEIN THAT OVERSEES DNA REPLICATION AND PACKAGING IN THE CELL

At the Institut Curie, the "Chromatin dynamics" team (UMR 218 CNRS/Institut Curie) has just discovered how the protein Asf1 ensures the correct (re)organization of duplicated DNA. During DNA replication, all the in-

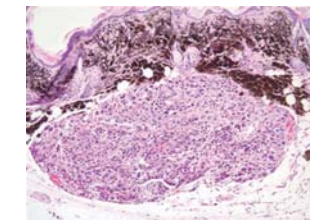
formation in the mother cell must be transmitted to the daughter cells. The DNA must be faithfully copied, of course, but also properly organized within the cell. DNA is wrapped around proteins called histones, to form chromatin. This complex structure contains so-called epigenetic information, which governs gene expression and gives each cell its specific identity. The histone chaperone, Asf1, coordinates the removal of histones from the chromatin to allow the replication machinery to move along the DNA, with the supply of new histones to

reform the chromatin once the replication machinery has passed. This discovery sheds new light on the transmission of epigenetic information in cells.

"Regulation of Replication Fork Progression through Histone Supply and Demand." A. Groth, A. Corpet, A. Cook, D. Roche, J. Bartek, J. Lukas, G. Almouzni
Science, 21 December 2007, vol. 318, p. 1928-1931.

→ Press release at: www.curie.fr

Skin cancer



How does a simple mole – or naevus – turn into a melanoma? This type of cancer, the incidence of which is doubling every ten years in western countries, has a high metastatic potential which makes it particularly difficult to treat. The

FROM A NAEVUS TO A MELANOMA: HOW MELANOCYTES BECOME IMMORTAL

"Developmental genetics of melanocytes" team (UMR 146 CNRS/Institut Curie) has recently identified one of the mechanisms responsible for the immortalization of melanocytes, cells in the epidermis that synthesize melanin, giving the skin its color and providing protection against UV rays. This immortalization is a crucial stage in transformation into a melanoma and this work constitutes a major advance in our understanding of this disease.

"B-Catenin Induces Immortalisation of Melanocytes by Suppressing p16INK4a Expression and Co-Operates with N-Ras in Melanoma Development." V. Delmas, F. Beermann, S. Martinuzzi, S. Carreira, J. Ackermann, M. Kumasaka, L. Denat, J. Goodall, F. Luciani, A. Viros, N. Demirkan, B.C. Bastian, C.R. Goding and L. Larue.
Genes Dev. 15 November 2007, vol. 21, p. 2923-2935.

→ Press release at: www.curie.fr

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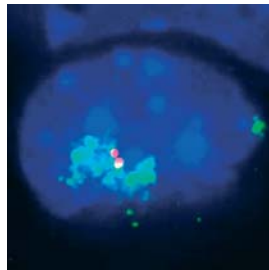
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news

Developmental Biology

HOW DO X CHROMOSOMES COUNT UP TO TWO?

Sex chromosomes of different sizes could have been the source of a genetic injustice among mammals. The Y chromosome, which characterizes males, is small and contains far fewer genes than the X chromosome. To avoid genetic inequality, female mammals inactivate one of their two sex chromosomes during embryogenesis. This inactivation must only happen in females and requires the cell to choose between the X chromosome inherited from the father and that inherited from the mother. How does this happen? The "Mammalian development and Epigenetics" team (UMR 218 CNRS/Institut Curie) has just discovered that in the first instance a particular chromosomal region, Xpr, brings together the X chromosomes and counts them: if there are two X chromosomes, one must be inactivated. Xpr is therefore the key player in this verification and is essential to avoid untimely inactivations and their harmful consequences.



"Sensing X Chromosome Pairs Before X Inactivation via a Novel X-Pairing Region of the Xic."
S. Augui, G. Fillon, S. Huart, E. Nora, M. Guggiari, M. Maresca, A. F. Stewart, E. Heard
Science, 7 December 2007, vol. 318, p. 1632-1636.

→ Press release at: www.curie.fr

Cell biology

PROTEIN GSK3, PRO- OR ANTITUMOR?

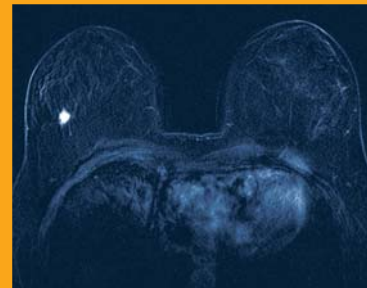
Maf proteins play an important role in tumor progression, particularly in human multiple myelomas: they are overexpressed in about 50% of cases of these blood cancers. The "Raf and Maf Signaling in Oncogenesis and Development" team (UMR 146 CNRS/Institut Curie) has just shown that the activity of the transcription factor MafA is regulated by a cellular "double agent", the protein GSK3. Thanks to a chemical modification, phosphorylation, GSK3 increases the transcription activity of MafA, leading notably to the expression of several genes involved in cell migration and metastatic processes. There is, however, automatic feedback control of this function: phosphorylation destabilizes and then degrades MafA. And there is another paradox: GSK3 was already known to regulate the activity of other transcription factors, but by inhibiting their tumorigenic potential. GSK3 may therefore play a pro- or antitumor role and become a "double-edged" therapeutic target.



"GSK-3-Mediated Phosphorylation Enhances Maf-Transforming Activity."
N. Rocques, N. Abou Zeid, K. Si-Felice, L. Lecoq, M.P. Felder-Schmittbuhl, A. Eychène, C. Pouponnot
Mol Cell, 30 November 2007, vol. 28, p. 584-597.

focus

SURVEY: INTIMACY AND SEXUALITY AFTER BREAST CANCER MORE THAN 40% OF WOMEN REPORT DIFFICULTIES IN THEIR SEX LIVES AFTER BREAST CANCER



The company Simone Pérèle has supported the Institut Curie in a study that has identified the difficulties of an intimate and sexual nature encountered by women treated for a breast cancer.

Breast cancer generates in many women a feeling of loss of worth and of femininity, even sometimes of identity. Surgery alters the patient's body image and cancer treatments often impair sex life and hamper intimacy. Relationship problems may arise, but are rarely dealt with in medical follow-up. Sponsored by the company Simone Pérèle, Institut Curie psychologists have evaluated the problems and symptoms affecting quality of life and the impact of disease on body image and sexuality, in women treated for breast cancer at the Institut Curie.

Sexuality after breast cancer

Half of the 850 women questioned in the survey reported psychological suffering. Some 26% felt less sexually attractive or unhappy with their body image. In terms of

their sex lives, 41% of the women felt affected by the cancer or its treatments and over half reported that their sexual desire had decreased or disappeared.

Notable differences are seen as a function of treatment. Body image and perception of sexuality are less perturbed after conservative surgery than after mastectomy. Women undergoing chemotherapy or hormone therapy are more affected in their sexuality than others. With hindsight, many of these women feel that there was lack of information about the impact of breast cancer and its treatments on sexuality. "To meet this demand, our physicians (surgeons, nurses...) will shortly be receiving specific training on how to help with the sexuality and fertility problems encountered by women with breast cancer", declares Dr Sylvie Dolbeault of the Institut Curie who jointly undertook this survey with Drs Laure Copel and Pascale This, and the psychologists Anne Bredart and Cécile Flahault.

The next step could be to train nurses, who are an important contact for patients, to help women deal with sexual difficulties. Improvement of information on the impact of breast cancer on sex life is an important step in the optimization of overall management of women with this disease.

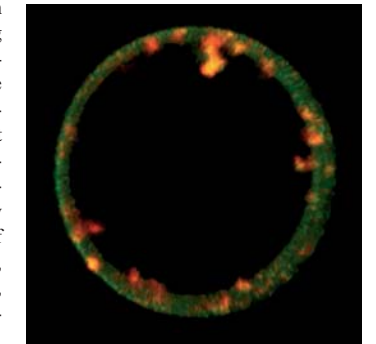
→ Press release online at www.curie.fr



Intracellular transport

NEW PORTALS OF ENTRY INTO CELLS FOR PATHOGENIC AGENTS AND FOR MEDICINAL PRODUCTS

How does the cell membrane capture pathogenic agents bound to its surface? Surprisingly, the membrane invaginates through a spontaneous and autonomous movement and swallows pathogens. This mechanism has been demonstrated in cells, and also in a minimal artificial membrane system. An international collaboration between physicists, chemists, and cell biologists at the Institut Curie, has observed this process at work with a particular pathogen, Shiga toxin. The work has been done by the "Traffic, Signaling and Delivery" team (UMR 144 CNRS/Institut Curie), using the Institut Curie's imaging equipment. The results shed new light on unexpected aspects of a fundamental process in biology—endocytosis. They also point to new leads in the search for the portal of entry of certain pathogenic agents, or to expedite the entry of drugs, therapeutic vaccines, or diagnostic agents in cancer cells.



"Shiga Toxin Induces Tubular Membrane Invaginations for its Uptake into Cells."
W. Römer, L. Berland, V. Chambon, K. Gaus, B. Windschiegel, D. Tenza, M.R.E. Aty, V. Fraisier, J.-C. Florent, D. Perrais, C. Lamaze, G. Raposo, C. Steinem, P. Sens, P. Bassereau, L. Johannes
Nature, 29 November 2007, vol. 450, p. 670-675.

→ Press release at: www.curie.fr

Leukemia

WHEN CDKN1B IS IN SHORT SUPPLY

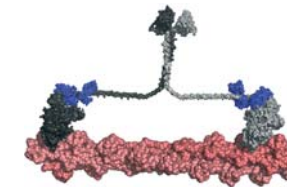
A team of the Inserm "Cancer Genetics and Biology" unit at the Institut Curie has found that the inactivation of one of the two copies of the CDKN1B gene actively promotes development of T-cell prolymphocytic leukemia, a rare disease in which regulation of T-cell proliferation is perturbed. The unaltered copy of the CDKN1B gene functions normally and is expressed, and so the protein CDKN1B is produced, but in smaller amounts. The researchers have shown that this quantitative reduction of CDKN1B is part of the tumorigenic transformation of cells. This same research team had already implicated a tumor suppressor, the ATM gene, in this leukemia, but the alterations in this gene are reflected in the leukemic cells by a total absence of corresponding functional proteins. The new form of mutation involved in T-cell prolymphocytic leukemia reduces expression of the CDKN1B gene, a cell cycle inhibitor. This so-called haploinsufficiency mechanism, ie, the insufficiency of one of the two copies of a gene, is one of the links in the development of this leukemia.

"Haplo-Insufficiency of CDKN1B Contributes to Leukemogenesis in T-Cell Prolymphocytic Leukemia."
E. Le Toriellec, G. Despouy, G. Pierron, N. Gaye, M. Joiner, D. Bellanger, A. Vincent-Salomon, M.H. Stern
Blood, 15 February 2008, vol. 111, p. 2321-2328.

Cell biology

MYOSIN VI IN THE STARTING BLOCKS

The "Structural Motility" team (UMR 144 CNRS/Institut Curie) is using crystallography to study the atomic structure of a family of molecular motors essential to cellular dynamics—myosins. Myosin VI is one of the most enigmatic of these as it moves along actin filaments in the opposite direction to other myosins. Having studied myosin VI at the end of its movement and understood how it moves "backwards", the researchers have studied it just before it begins moving. In the starting blocks, the lever arm that ensures its movement assumes a conformation never seen before with other myosins, which enables it to produce large swings or powerstrokes along the actin filament. To achieve this, the lever arm-positioning region of myosin VI is conformationally rearranged. The structure of myosin VI is therefore different from that of other myosins that move in the "right direction". It remains to be seen what other configurations this motor can assume.



"The Structural Basis for the Large Powerstroke of Myosin VI."
J. Ménétrey, P. Llinas, M. Mukherjea, H.L. Sweeney, A. Houdusse
Cell, 19 October 2007, vol. 131, p. 300-308.

innovations

Breast cancer

CANCER RECURRENCE: DISTINGUISHING A NEW TUMOR

When cancer site appears in a breast cancer patient who has already been treated, it may be a new tumor or a recurrence caused by tumor cells not destroyed by the first treatment. Through a multidisciplinary collaboration, physicians and researchers of the Institut Curie have developed a new technique to distinguish a "true" recurrence from a second, independent cancer. Hitherto, physicians either compared the histological characteristics of tumor cells or determined the changes in the number of copies of DNA. These changes reflect the presence of anomalies in the chromosomes, at preferred sites. The idea is to use these chromosomal "Achilles tendons" as markers: a recurrence will have the same weaknesses as the tumor from which it derives. This new technique has proven more effective than previous methods.

"High-Resolution Mapping of DNA Breakpoints to Define True Recurrences Among Ipsilateral Breast Cancers."
M. Bollet, N. Servant, P. Neuvial, C. Decraene, I. Lebigot, J.P. Meyniel, Y. De Ryck, A. Savignoni, G. Rigall, P. Hupé, A. Fourquet, B. Sigal-Zafrani, E. Barillot, J.P. Thiery
J. Natl. Cancer Inst. January 2008, vol. 100, p. 48 - 58