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Institut National de La Recherche Et de La Santé Médicale (inserm)

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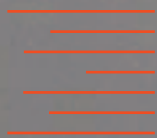
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Scientists at the National Institute of Health and Medical Research work toward improving human health

ACTIVITY REPORT

2005



Inserm

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Inserm is the only French public organization entirely dedicated to biological, medical and public health research. Inserm researchers are committed to studying all human diseases, whether common or rare.



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Since 2001, Inserm has been introducing a series of reforms in order to acquire new developmental tools. The year 2005 is the year of maturity, these tools having now come to fruition for implementing Inserm's missions in basic research and public health.



For Inserm, people are the number one priority. By 2012, 20 to 30% of researchers, engineers and technicians will be retiring. Renewal of this workforce is therefore a permanent concern demanding a strategy centered on the individual. In 2005, Inserm worked on increasing career attractiveness, diversity and mobility, as evidenced by the development of the Avenir program to promote the emergence of young researchers, and the organization of internal seminars allowing individual follow-up of professional progress. A public company logic is thus emerging, which involves analyzing the difficulties individuals may encounter at the various stages of their career and looking for appropriate solutions.

Innovation in 2005 also involved the introduction of interface contracts internal to the Institute as opposed to external contracts directed toward hospitals, universities and industry. Such internal contracts involve leadership of research units or federative research institutes, management of major national and European programs, or knowledge transfer to society. These contracts allow Inserm to recognize the excellence of men and women engaged in the life of the Institute.

Inserm is both committed to research and public health. It is therefore crucial that the Institute ensure the continuum from basic research upstream to clinical, therapeutic and public health research downstream. In the course of 2005, we were able to adapt our

research support so as to complement, rather than compete with, strategies deployed by hospitals in this domain. Thanks to the action of Inserm Transfert, Inserm was able to finance a number of innovative clinical and therapeutic trials, thus widening the scope of the Institute's activities. Following a similar complementarity rationale, the number of interface contracts for hospital physicians went over the symbolic threshold of 100. Finally, the Inserm School, which selects 20 of the most promising medical students every year, delivered its first research masters degrees in 2005 to students from the 2003 promotion.

This ambitious policy is associated with improved intellectual asset management and knowledge transfer to industry. Inserm's mission is to create value for the Country, which it can reinvest in the form of research support by managing the patents portfolio, industrial partnerships and company creation. The merger of Inserm Transfert with the Department of Technology Transfer (DVT), completed in 2005 and due to take effect in early 2006, is guided by this strategy of deployment and conquest.

2005 was a year for reinforcing the European and international influence of the Institute. Considerable work was accomplished to ensure the follow-up of the 6th Framework Program for Research and Technological Development (FPRTD) and the preparation of the 7th FPRTD (2007-2013). Symbolically, Inserm also inaugurated this year its very

first research unit in North America, in Montreal, in the wake of those created in Glasgow, Heidelberg and Shanghai.

Finally, the year 2005 saw the conclusion of a detailed study that required over a year's work by the Department of Scientific Evaluation in order to assess the Institute's scientific production. In the context of current discussions on the value of research in France and the reforms that should be considered, this study has crucially revealed major errors resulting from over superficial studies and linked to the administrative complexity of research organization in France. The study we conducted shows that Inserm's scientific worth is equivalent to that of the Medical Research Council in the United Kingdom, an internationally recognized standard in biomedical and health research.

Christian Bréchet, Director General

INSERM'S GOALS, PRIORITIES AND CHALLENGES

05 ENSURING THE RESEARCH CONTINUUM

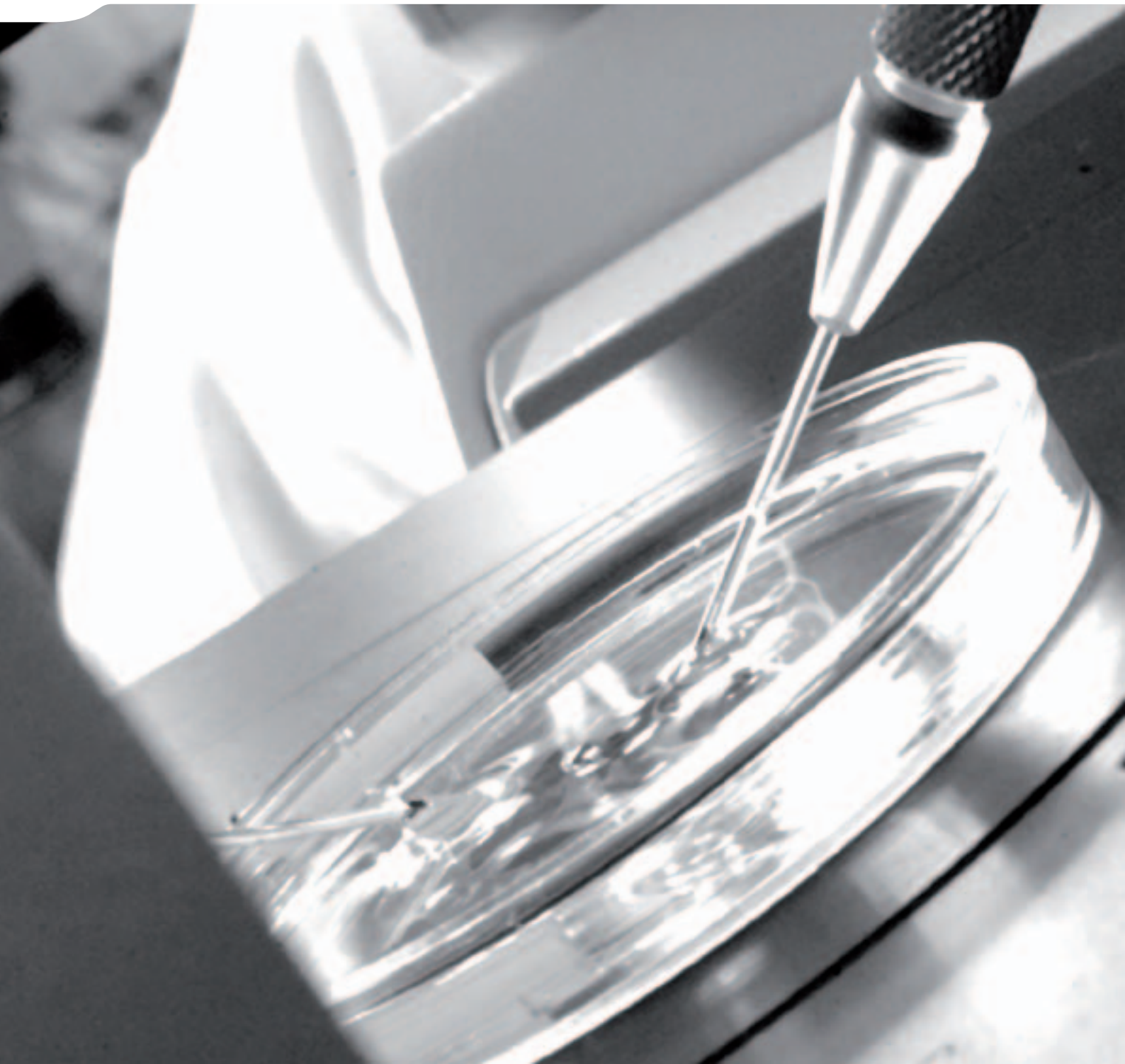
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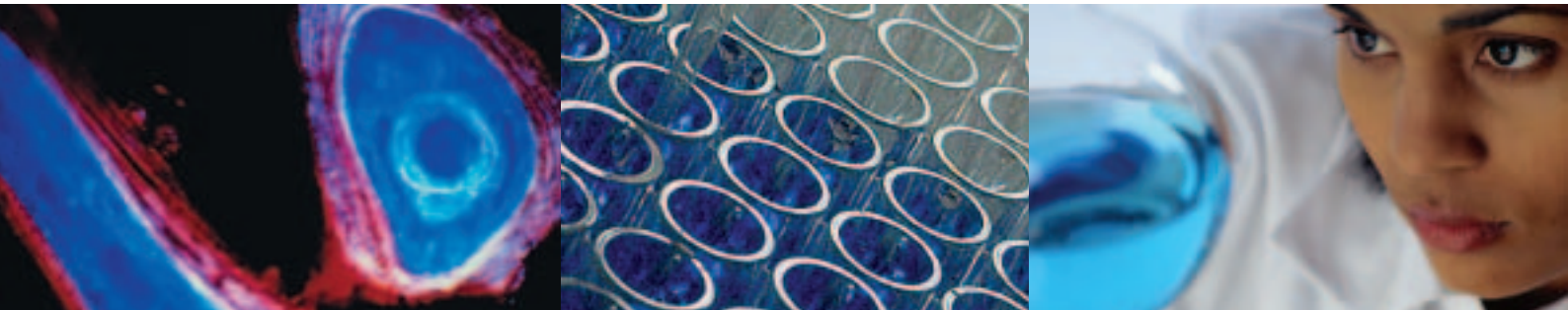
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Inserm is the only French public institution dedicated to research and public health and has, as such, a highly specific mission. Its primary goals are to ensure the attractiveness and mobility of biomedical careers by assisting individuals in their professional choices, organizing the research continuum from basic to clinical, therapeutic, and ultimately public health research, to promote the knowledge produced in the process by maintaining a permanent link with industry, and finally to develop a conquering European and international policy.



Ensuring the Research Continuum

There cannot be a discontinuity in health and life sciences between basic research and clinical, diagnostic and therapeutic applications, all of which are crucial for the progress of public health and the well-being of the population. Understanding the intimate mechanisms of living beings and their pathologies naturally grows through improvement of prevention and therapy. Inserm stands at the interface between the major research and public health players: universities, hospitals and industry. The Institute must not only ensure that the various institutions are complementary, but also organize synergistic partnering and promote added value for its initiatives.

Powerful tools now exist to carry out these tasks. Interface contracts (with hospital and industry) ensure optimal knowledge transfer toward clinical activities and maximum support for innovative actions. Major national research programs concentrate the teams and means available on primary public health challenges (obesity, cancer, cardiovascular diseases, etc.). Clinical research centers and concerted thematic actions coordinate common approaches in a flexible and decentralized manner. Finally, the creation of the

SALIENT FEATURES IN 2005

- The Department of Clinical and Therapeutic Research (DCTR) was created in order to maximize the performance of clinical research platforms and boost therapeutic innovation;
- Cossec was endowed with a preselection cell to accelerate clinical trial procedures;
- 8 calls for candidates were launched for interface contracts;
- 16 interface contracts were signed with industry, 101 with hospitals, cancer centers and health agencies;
- 31 projects and 115 teams were funded as part of National Research Programs;
- 3 cohorts (EDEN, Suvimax, SIRS) were supported by the Virtual Institute for Public Health Research (IVRSP);
- There are now more than 40 CRCs and over 300 beneficiaries in clinical research.

Clinical and Therapeutic Research Department (DCTR) and the work of the Strategic Planning and Clinical Trial Monitoring Committee (Cossec) illustrate Inserm's determination to play a key role in the research continuum.

Strengthening Knowledge Management

The cost of clinical and therapeutic research has steadily increased in the last decades. The sustained growth of necessary financial investment needs counterbalancing with continuous intellectual asset management through permanent transfer to the commercial domain. Industrial property is today at the heart of Inserm's preoccupations in the form of

management of the patents portfolio. The creation of new companies and the signature of R&D and technology transfer contracts with existing companies ensure the creation of value, which in return sustains the Institute's research and public health programs.

This inspired the merger in 2005 between the private subsidiary Inserm Transfert and the Department of Technology Transfer (DVTT), which became effective at the beginning of 2006. Training workshops and a new edition of the Inventor's Guide (*Guide de l'inventeur*) allowed researchers to come to grips with new knowledge management issues, in particular through the use and good practice of patenting.

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SALIENT FEATURES IN 2005

- 81 invention claims processed;
- 70 new priority patent requests;
- 5 company creations supported;
- 1,100 ongoing contracts involving 550 researchers and 426 companies;
- 153 new R&D and 52 new technology transfer contracts signed;
- Transfer activities have grown by 12% since last year;
- 17 European projects supported by Inserm Transfert submitted as part of the 6th FPRTD;
- 163 researchers benefited from profit-sharing revenues through intellectual asset management.

Developing International Overture

While globalization is a relatively new phenomenon in the economic and financial world, it has always been present in the world of science and health. The acceleration of European and international exchanges is a source of mutual enrichment and new challenges. Inserm's mission is to work with its national partners within the frame of European integration, and particularly on the ambitious framework programs of the European Union. The development of international cooperation, whether it be in Asia, North America or Africa, has become essential to guarantee the attractiveness of research at the Institute and the notoriety of its researchers. The year 2005 saw the creation of the Department of Regional and European Policy (DREP) with a view to reinforce reciprocal cooperation, pool

skills, ensure a critical size for associated European laboratories, pursue follow-up work on the 6th FPRTD and above all prepare the next FPRTD (2007-2012). On an international level, inaugurating the first research unit in North America, making contact and launching projects with some of the most prestigious institutions (MIT, NIH in the United States, Riken in Japan,

Major Research and Public Health Issues

For some years now, the Institute has placed particular emphasis on a number of thematic areas, which have all been evaluated in terms of performance. The pie chart below indicates the relative allocation of funds in different research areas.

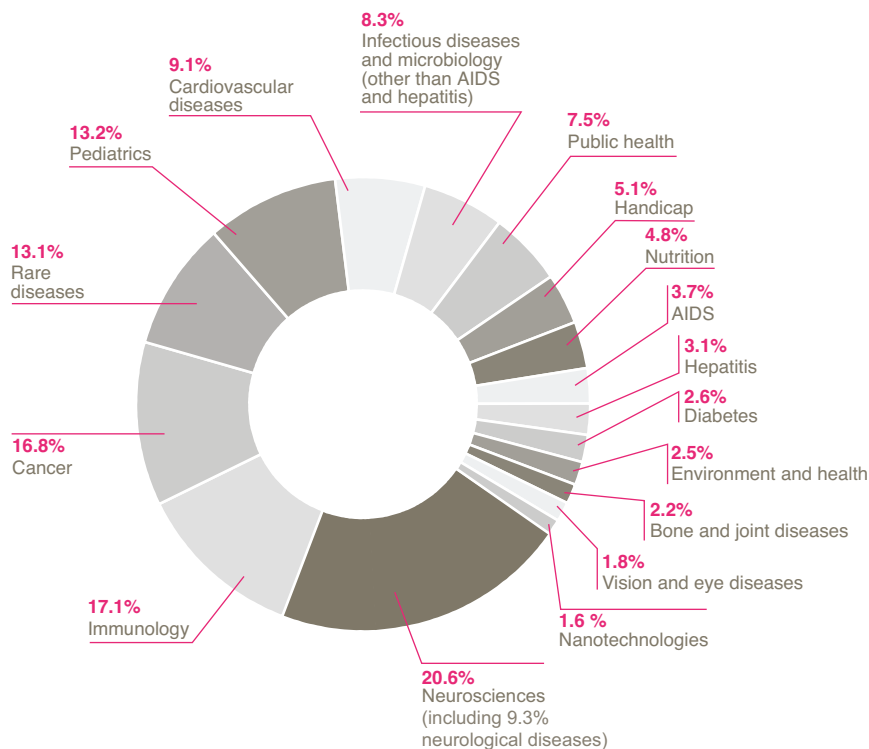
SALIENT FEATURES IN 2005

- 22 European projects coordinated by Inserm (5 networks of excellence, 3 integrated projects, 10 Specific Targeted Research Projects and 4 specific support actions);
- 3 new prizewinners as part of the EURYI program;
- 130 short-term researcher exchanges took place and 3 new associated European laboratories are being planned;
- 21 cooperation agreements signed in 14 different countries outside the European Union;
- 66 international research projects supported, involving 138 international and 109 French researchers;
- Meetings with NIH and MIT, and seminars on American university campuses have increased Inserm's visibility;
- A laboratory associated with Riken was created in Japan;
- Inserm Unit 743 in Montreal (first Inserm research unit in North America) became operational.

the University of Nanjing in China, Glasgow and Heidelberg) have definitely increased the visibility of the Institute.

Inserm Commitment by Thematic Area (outside incentive actions) in 2002-2005

Inserm supports all sectors of basic and applied research in its areas of competence. A number of thematic areas correspond to major public health issues and are the basis for major national research programs. Inserm plays a central catalytic role in such efforts and ensures proper synergy between the players involved (other public research institutions, health agencies, hospitals, insurance funds, associations, etc.).

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N.B.: A single laboratory is often involved in several research areas. Inserm's total financial commitment is therefore greater than 100%.

In addition to being engaged in major programs, Inserm is developing a multi-disciplinary approach to research in all priority sectors of modern biology. This is illustrated, for instance, by its transversal action in biotherapy or pharmacoepidemiology. Inserm's efforts have also stimulated leading-edge research areas with considerable potential in the long term, such as nanotechnologies or the biology of complex systems.

Such actions clearly depend on the quality of scientific evaluation of research units and projects. For a number of years, the Institute has been committed to a policy of sustained reinforcement of quality indicators. This evolution has been characterized by a better use of bibliometric data and the integration of all relevant components (such as commercial development and clinical research). The Scientific Council welcomes a growing number of international experts, which

also reinforces Inserm's international overture on this matter.

Finally, thanks to the Ermes committee and collective expert reports, Inserm works with due respect for ethics and acknowledging the crucial importance of its participation in the great societal debates arising from research progress.

Assisting People

Biomedical research and public health involve the commitment of thousands of men and women. Population ageing is also a tangible issue for the scientific and medical sector: over a quarter of the Institute's researchers, engineers and technicians will have retired by 2012. This phenomenon happens to coincide with a general crisis in terms of scientific vocations in France and Europe, meaning that Inserm must meet both a demographic and professional challenge.

SALIENT FEATURES IN 2005

- The Avenir program has so far supported 109 tenured or non-tenured scientist laureates;
- Students from the first promotion (2003) at the Inserm School have obtained their research Master's degree and 17 laureates are currently continuing their studies;
- 70 12 to 24-month contracts for young researchers and 29 3 to 5-year contracts have been set up;
- 159 international researchers have been hosted by Inserm;
- 2 seminars have allowed 89 young researchers and 92 senior researchers to benefit from individual career follow-up;
- 211 individual mobility analyses were performed at the request of Inserm staff;
- 2,488 staff members expressed a need for further training through the automated GAIA system.

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Inserm is reacting to this along three broad axes: career attractiveness, diversity and mobility. The recognition and management of top medical students (Inserm School) or the professional recruitment of Ph.D. students or post-doctoral researchers (12 to 24-month and 3 to 5-year contracts) contributes to this process by assisting

individuals in obtaining attractive positions. Individual follow-up is also a priority, both for young and senior researchers. Tools introduced a few years ago for the personalization of professional careers have now reached maturity and are fully operational in 2005. This is clearly demonstrated by the success of the GAIA system,

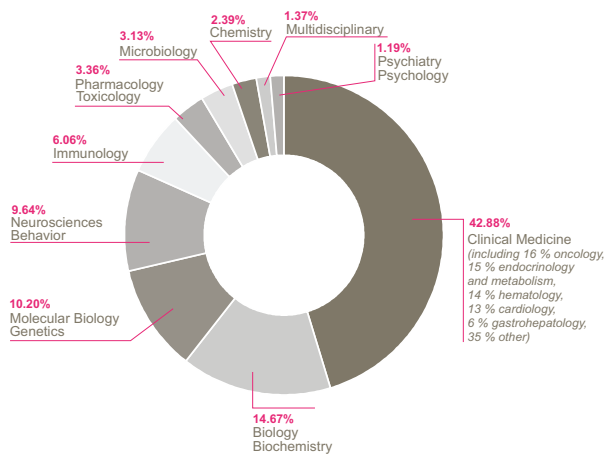
the good attendance at counseling and orientation seminars, and the rise in the demand for mobility analyses. Inserm is also committed to recognizing and promoting excellence in work performed at the Institute, which is reflected in the emergence of internal interface contracts.

SALIENT FEATURES IN 2005

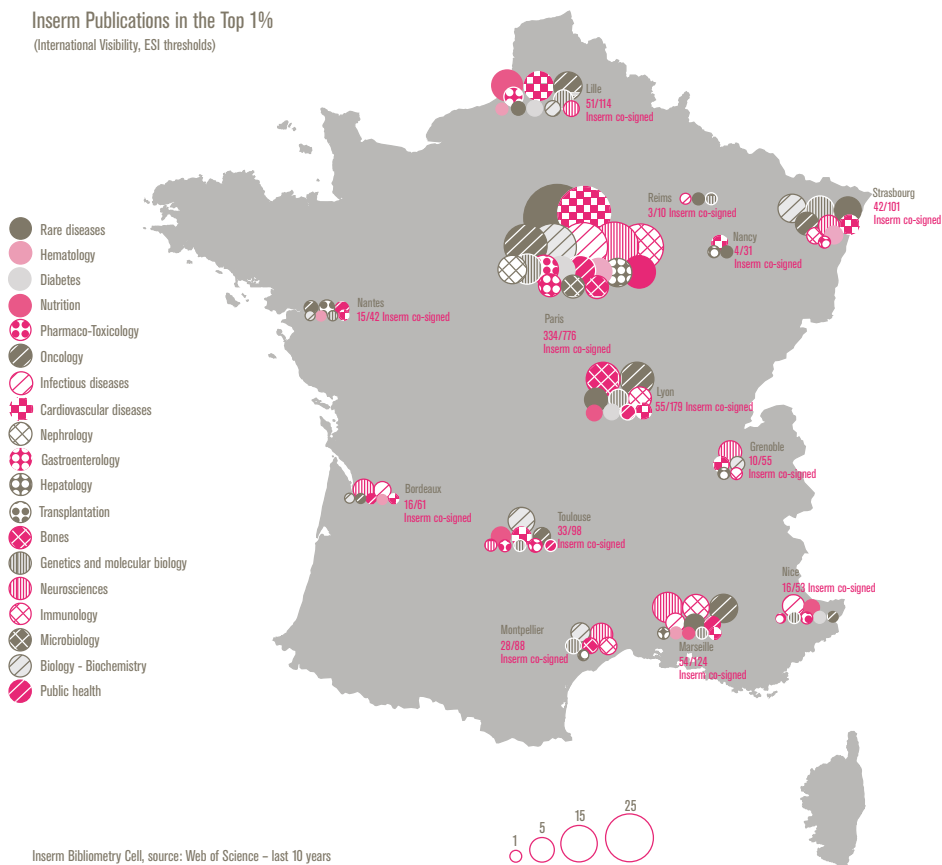
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| 11 | PUBLIC HEALTH | 21 | CARDIOLOGY | 28 | ENDOCRINOLOGY,
REPRODUCTION |
| 13 | ONCOGENESIS | 23 | DERMATOLOGY | 31 | IMMUNOLOGY,
INFECTIOUS DISEASES,
AUTOIMMUNE DISEASES |
| 15 | GENETICS | 24 | GASTROENTEROLOGY,
HEPATOLOGY | 33 | DIABETES, METABOLISM |
| 16 | MICROBIOLOGY | 26 | NEPHROLOGY | 34 | BIOTHERAPIES |
| 17 | NEUROSCIENCES | 27 | MEDICAL TECHNOLOGIES | | |
| 20 | PSYCHIATRY | | | | |



Research, which is at the heart of Inserm's activities, faces great health and scientific challenges. To illustrate this, salient features of current research have been identified in several of Inserm's areas of competence: public health, genetics, neurosciences, psychiatry, medical technologies, microbiology, gastroenterology, hepatology, nephrology, dermatology, oncogenesis, diabetes and metabolism, and biotherapies.



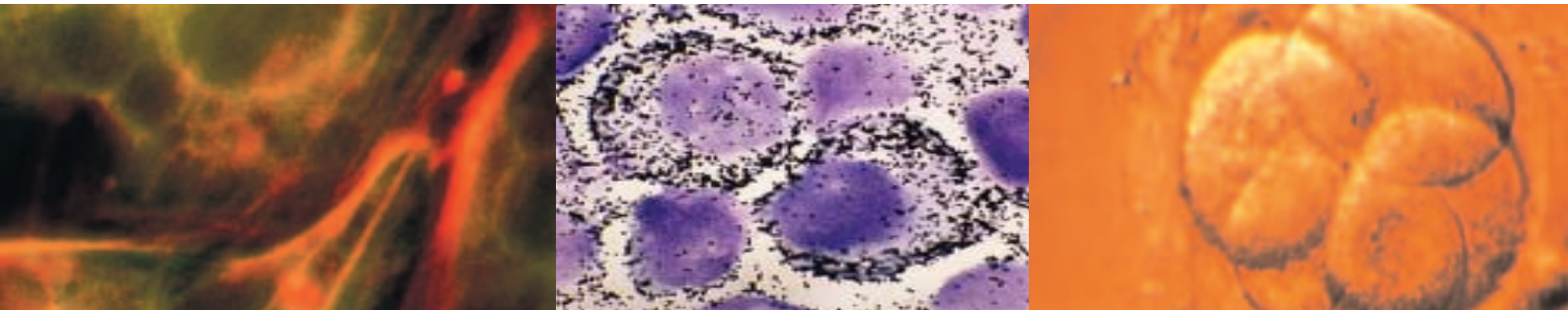
Inserm Publications in the Top 1%
(International Visibility, ESI thresholds)



- Rare diseases
- Hematology
- Diabetes
- Nutrition
- Pharmaco-Toxicology
- Oncology
- Infectious diseases
- Cardiovascular diseases
- Nephrology
- Gastroenterology
- Hepatology
- Transplantation
- Bones
- Genetics and molecular biology
- Neurosciences
- Immunology
- Microbiology
- Biology - Biochemistry
- Public health



PUBLIC HEALTH



Sudden Death in Adults

Sudden (cardiac) death in adults is a major problem in France where it is responsible for 40,000 deaths each year. It is therefore important to identify predisposed subjects early. Inserm Unit 258 (Cardiovascular and Metabolic Epidemiology) recently found that the heart rate profile upon exertion is an important risk factor. The Parisian prospective survey recruited 6,100 middle-aged men having undergone an exertion test in the 70's and monitored for over 20 years to determine mortality.

The characteristics of the exertion test for the subjects deceased by sudden death during follow-up were retrospectively examined. The results showed that these subjects had a higher heart rate at rest than other subjects, a lower maximum heart rate upon exertion, and presented a lower and slower decrease in heart rate during recuperation. These results are important as they help understand sudden death, which is most often due to a sudden acceleration of the heart (ventricular fibrillation) caused by an occlusion of the coronary arteries that irrigate the cardiac muscle. There appears to be an underlying susceptibility to ventricular rhythm disorders even before atheroma (responsible for coronary artery occlusion) develops. This work suggests that primary prevention

measures such as moderate and regular exercising are worth considering for subjects at risk.

Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetière P, New Eng. J. Med., 2005; 352 (19):1951-58.

Improving Evaluation of Clinical Trial Efficiency

The tools used to evaluate management efficiency in many clinical trials are scores based on items. Clinical trial results are presented as score variations between the beginning and the end of the trial, in the form of mean differences and standard deviations. What do these variations mean exactly? One of the difficulties for the investigator is to determine the clinical relevance of trial results and communicate this to clinicians, who will then decide whether or not to take the results into account in their daily practice. Two emerging concepts can help interpret such results. The MCII (Minimally Clinical Important Improvement) is defined as being the smallest score difference or variation that patients might perceive as a genuine improvement, i.e. the smallest variation that is relevant for patients. The PASS (Patient Acceptable Symptom State)

reflects a symptomatic state (rather than a variation) below which the patient considers he/she is well. This is an intermediate state between active disease and remission. One may therefore speak of partial remission. The two concepts introduce a dichotomy in a situation where the variable is continuous, thereby allowing examination of clinical trial results in terms of percentage of patients showing improvement, or patients having attained a symptomatically acceptable state at the end of the trial.

Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, Bombardier C, Felson D, Hochberg M, van der Heijde D, Dougados M, Ann. Rheum. Dis., 2005 ; 64 (1) : 29-33.

Genetic Signatures of Cancer

In order to study the reliability of molecular signatures, Inserm Unit 605 (Cancer Epidemiology: Radiocarcinogenesis and Iatrogenic Effects of Treatments) conducted seven of the most important studies in oncology. The expression of tens of thousands of genes was measured using DNA biochips. In each study, researchers worked on a sub-population known as the "test sample" in order to identify genes expressed differently in relapse compared

to normal patients. By drawing lots repeatedly in order to select test samples, researchers showed that the list of genes with highest relapse prediction value was very unstable and that prediction in the remaining population was rather poor. The study of thousands of genes on a few dozen patients therefore leads to a weakly reproducible and rather inefficient prognostic tool that cannot be used at present to modify patient management.

Michiels S, Koscielny S, Hill C, Lancet, 2005 ; 365 (9458) : 488-92.

Importance of Occupational Risks in Severe Asthma

Asthma is the most common occupational respiratory disease. It is caused by exposition to asthmogenic substances such as isocyanates and flour. Inserm Unit 472 (Research in Epidemiology and Biostatistics) has shown that asthmogens increase the severity of asthma, an aspect that had not been studied so far. Comparison of 148 cases of adult asthma, the severity of which was well characterized, and 228 non-asthma sufferers in an epidemiological study on genetic and environmental factors for

asthma (EGEA) showed that exposure to asthmogens is highly damaging in cases of severe asthma, especially when onset occurs in adult life. The results underscore the necessity for clinicians to take into account occupational exposure in severe asthma, which represents a serious public health problem.

Le Moual N, Siroux V, Pin I, Kauffmann F, Kennedy SM, Am. J. Resp. Crit. Care Med., 2005 ; 172 (4) : 440-45.

ONCOGENESIS

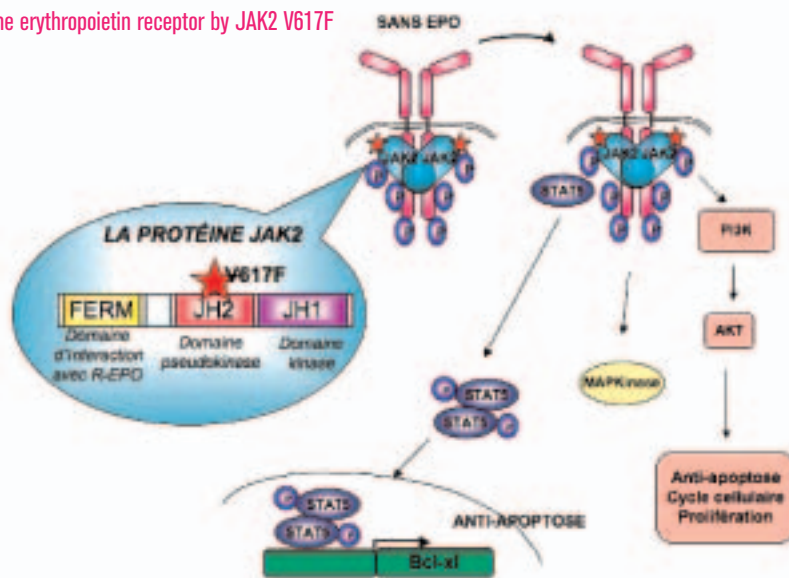


Single JAK2 Mutation and Vaquez Disease

Myeloproliferative syndromes (MPSs) are clonal hemopathies characterized by an overproduction of blood cells. Previous studies on chronic myeloid leukemia (CML) had shown that the disease was linked to the constitutive tyrosine kinase activity of BCR-ABL. However, the molecular defect in classical myeloproliferative syndromes such as Vaquez polyglobulia (VP), essential thrombocythemia (ET) and idiopathic myelofibrosis (IMF) had not been identified. A team from Inserm Unit 362 (Hematopoiesis and Stem Cells) in Villejuif has shown that the molecular anomaly in VP mimics Epo/Epo receptor signaling and is linked to a gain-of-function mutation of JAK2 tyrosine kinase. This point mutation (G1849T) is acquired and results in the substitution of a valine residue by a phenylalanine (JAK2^{V617F}). After introducing JAK2^{V617F} by means of hematopoietic cells in a murine transplantation model, the mice developed Vaquez disease. The JAK2^{V617F} mutation was identified in over 85% of patients suffering from VP and in about 50% of those with ET and IMF, thus defining a new type of MPS. Discovering this mutation has already facilitated MPS diagnosis and should allow the development of targeted therapies.

James C, Ugo V, Le Couedic JP, Staerk J,

Constitutive activation of the erythropoietin receptor by JAK2 V617F



Delhommeau F, Lacout C, Garçon L, Raslova H, Berger R, Bennaceur-Griscelli A, Villeval JL, Constantinescu SN, Casadevall N, Vainchenker W, *Nature*, 2005 ; 434 (7037) : 1144-48.

Cell Death: Apoptosis and Autophagia

While apoptosis is a programmed destruction of the entire cell, autophagia involves sequestration followed by disintegration of part of the cell cytoplasm. Certain events in cell death are accompanied by an accumulation of autophagic vacuoles and there has been a tendency to believe that death could be due to autophagia. The team lead by Guido Kroemer has shown that autophagia

is a strategy used in response to cellular stress and that inhibition of autophagia can accelerate triggering of cell death by apoptosis. The team put forward the hypothesis that rather than causing death, autophagia delays its occurrence. Furthermore, the group shows that the point of no return in the so-called “autophagic death” process is determined by the apoptotic permeabilization of mitochondrial membranes.

Boya P, Gonzalez-Polo RA, Casares N, Perfettini JL, Dessen P, Larochette N, Metivier D, Meley D, Souquere S, Yoshimori T, Pierron G, Codogno P, Kroemer G, *Mol. Cell. Biol.*, 2005 ; 25 (3) : 1025-40.

Epigenetic Approach of Acute Myeloid Leukemia

Chromatin is a dynamic molecular structure undergoing constant epigenetic modifications. Its role is to regulate gene expression specifically. Deregulation of chromatin structure can lead to abnormal expression of growth regulators and can ultimately be responsible for the development of cancer. The fact that numerous human diseases have an etiology based on gene expression has stimulated the development of epigenetic therapies. For example, inhibitors of histone deacetylases (HDACs) arrest the proliferation and maturation of cancer cells both in vitro and in vivo, resulting in their apoptosis, without affecting normal cells. Furthermore, HDACs are currently being studied in several clinical trials.

The team from Inserm unit 596 (Molecular Biology and Genetic Engineering) has therefore studied the molecular mechanisms underlying the tumoral selectivity of HDACs. The team has shown that HDACs induce the expression of p21 and TRAIL (Apo2L, TNFSF10) by directly activating the TNFSF10 promoter, thus triggering cell death in a cell model for acute myeloid leukemia (AML) and in blasts derived from AML patients. RNA interference experiments indicated that the induction of p21, the induction of TRAIL and differentiation are independent activities of HDACs. Indeed, HDACs induce proliferation arrest, TRAIL-mediated apoptosis, and suppression of clonogenicity in blasts from AML patients, independently of status, karyotype or grade (FAB classification). In addition, no apoptosis induc-

tion was observed in normal CD34+ progenitor cells. These results identify TRAIL as an important mediator in the anticancer activity of HDACs.

Nebbioso A, Clarke N, Voltz E, Germain E, Ambrosino C, Bontempo P, Alvarez R, Schiavone EM, Ferrara F, Bresciani F, Weisz A, de Lera AR, Gronemeyer H, Altucci L, Nature Med., 2005 ; 11 (1) : 77-84.

GENETICS



Lamina Pathology: Progeria and Restrictive Dermopathy

Mutations in the LMNA gene are responsible for numerous allelic pathologies, known as laminopathies, the severity of which is highly variable. The LMNA gene codes for A/C lamin proteins, which are components of the lamina and ensure the preservation of nuclear structure. Inserm Unit 491 (Medical Genetics and Development) has identified a new laminopathy, called restrictive dermopathy (RD), as being the most severe of the

whole clinical spectrum after Hutchinson-Gilford progeria (HGPS). This syndrome is always linked to a defect in the maturation of lamin A. RD, which rarely results from dominant autosomal transmission linked to de novo LMNA mutations, is far more often acquired by recessive autosomal transmission linked to ZMPSTE24 mutations. The latter encodes a metalloprotease that is directly involved in lamin A maturation. This work has also shed light on a new physiopathological mechanism, common to RD and progeria,

involving toxic accumulation of farnesylated precursors in the cell nuclei of patients. These discoveries open new therapeutic prospects for progeria and related diseases, thanks to the contribution of relevant animal models.

Navarro CL, Cadinanos J, Sandre-Giovannoli AD, Bernard R, Courier S, Boccaccio I, Boyer A, Kleijer WJ, Wagner A, Giuliano F, Beemer FA, Freije JM, Cau P, Hennekam RCM, Lopez-Otin C, Badens C, Levy N, Hum. Mol. Gen., 2005 ; 14 (11) : 1503-13.

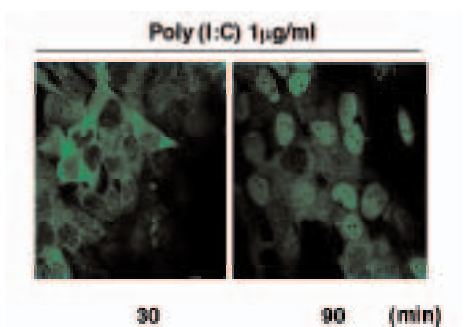
MICROBIOLOGY



TLR3 and the Effect of Influenza on the Lungs

Influenza A viral infection is responsible for human flu, an acute lung pathology. Flu viruses can also facilitate secondary bacterial infections or exacerbate chronic pathologies such as asthma and mucoviscidosis. The mechanisms responsible for causing these effects on people are poorly understood. TLR3 was recently identified as being the receptor of the double-stranded RNA viral replication intermediate. Insertm team E0336 (Innate Defenses and Lung Inflammation) has demonstrated the constitutive and regulatable expression of TLR3 in lung epithelial cells, the main target for the flu virus. In addition, it has established TLR3 plays an essential role in the deleterious inflammatory response induced by the virus. In time, this data can help develop specific TLR3 antagonists in order to counter the deleterious effects of flu virus dsRNA.

Guillot L, Le Goffic R, Bloch S, Escriou N, Akira S, Chignard M, Si-Tahar M, J. Biol. Chem., 2005 ; 280 (7) : 5571-80.



Translocation of the transcriptional factor NF- κ B in the nucleus of human bronchial epithelial cells after activation by synthetic poly(I:C) dsRNA.

Cultivating the Hepatitis C Virus

Studying the way the hepatitis C virus (HCV) enters the cell and developing antiviral molecules capable of blocking this step of the viral cycle have been hampered by the inability to grow the virus in culture cells. Insertm Unit 412 (Human Virology) at ENS in Lyon has circumvented this difficulty by generating infectious HCV pseudoparticles (HCVpp) that faithfully mimic the known properties of the wild-type virus and allow the study of the humoral response in patients.

The team's results show that HCVpp can be obtained from the main genotypes and

subtypes of HCV and that the early steps of HCV infection are conserved. The use of HCVpp for studying early phases of infection is easily achieved in an L2 laboratory. Moreover, the system is sufficiently robust to allow high throughput screening of patient sera, monoclonal antibodies or synthetic molecules in order to identify inhibitors of HCV entry and determine their mechanism of action. This tool should facilitate the production of vaccines or specific anti-HCV agents.

Lavillette D, Tarr AW, Voisset C, Donot P, Bartosch B, Bain C, Patel AH, Dubuisson J, Ball JK, Cosset FL, Hepatology, 2005 ; 41 (2) : 265-74.

NEUROSCIENCES



Pathophysiology of Usher Syndrome

Usher syndrome (USH) is the most common cause of hereditary deaf-blindness. It involves both sensorineural deafness and retinitis pigmentosa. Five genes have been found to be involved in type-1 Usher syndrome (USH1), 3 of which have been identified by Inserm Unit 587 (Genetics of Sensory Deficits). Two genes involved in the type-2 syndrome have also been isolated. These recent results have led to the conclusion that a single pathogenic process is responsible for the deafness component of the syndrome. Among the 5 USH1 proteins, two (cadherin 23 and protocadherin 15) form fibers that link the various components of the ciliary bundle, the structure of auditory sensory cells

where the acoustic energy received is converted into electrical signals. The tip links that interconnect stereocilia and unite them with the kinocilium are anchored to the cytoskeleton by another USH1 protein, harmonin, a PDZ-domain containing protein, while the two other USH1 proteins, myosin VIIa and Sans (an ankyrin-domain protein) ensure harmonin transport. Cohesion of the growing ciliary bundle was found to involve adhesion forces between stereocilia, on the one hand, and stereocilia and the kinocilium, on the other. Furthermore, recent studies have allowed these conclusions to be extended to the pathology of type-2 Usher Syndrome. The two known genes also code for transmembrane proteins (usherin and VLGR1), which are components of other

interstereociliary links. VLGR1 is probably also linked to a G protein so that interstereociliary links may have more than a simple mechanical role.

Adato A, Kikkawa Y, Reiners J, Alagramam KN, Weil D, Yonekawa H, Wolfrum U, El-Amraoui A, Petit C, Hum. Mol. Genet., 2005 ; 14 : 347-56. Adato A, Lefèvre G, Delprat B, Michel V, Michalski N, Chardenoux S, Weil D, El-Amraoui A, Petit C, Hum. Mol. Genet., 2005 ; 14 : 3921-32. Michel V, Goodyear RJ, Weil D, Marcotti W, Perfettini I, Wolfrum U, Kros C, Richardson GP, Petit C, Dev. Biol., 2005 ; 280 : 281-94.

Stress, Memory and the MAP Kinase Pathway

Aversive experiences establish a far more stable and durable mnemonic trace than other life events. This process is extremely important for psychiatric pathologies since it is involved in anxiety, depression and post-traumatic stress.

The biological mechanisms underlying such memory amplification for aversive events remain for the most part unknown. Inserm Unit 588 (Pathophysiology of Behavior) has described one of the first molecular cascades by which stress increases the memory of events to which it is linked. In particular, it has shown there is a direct interaction between glucocorti-

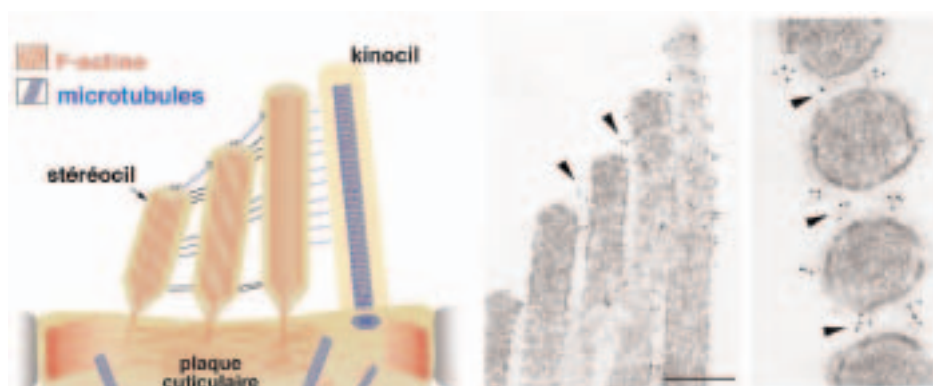


Diagram of the stereocilia and kinocilium of the ciliary bundle with a set of tip links. Ciliary bundle under electron microscopy: vertical section (center), horizontal section (right). Arrowheads indicate the staining of tip links by antibodies directed against cadherin 23

coid hormones, one of the main hormonal responses to stress, and the MAP kinase pathway, an intracellular signaling cascade, the activity of which modifies gene transcription. This knowledge will contribute to develop therapeutic tools to reverse negative effects induced by traumatic events.

Revest JM, Di Blasi F, Kitchener P, Rouge-Pont F, Desmedt A, Turiault M, Tronche F, Piazza PV, Nature Neurosc., 2005 ; 8 (5) : 664-72.

Unilateral Optical Ataxia: a Motor or Visual Lesion?

Unilateral optical ataxia following a lesion of the posterior parietal cortex results in a lack of precision to reach objects that are presented in the peripheral visual field on the opposite side of the lesion. There were two persisting interpretations of this neurological pathology: one, essentially motor in origin, proposed a visual-manual deficit in the transformation of peripheral visual information under motor command; the other, more visual, suggested a general visual-spatial deficit in the processing of object localization in peripheral vision. Inserm Unit 534 (Space and Movement) has set up a protocol allowing the initial presentation of a target in the defective peripheral visual field of such patients, before making them move their eyes to bring the position of the target (in a blind spot) into the healthy visual field and recording the precision of the pointing movement and vice versa. Errors turned out to be linked to the final position of the eyes at the time of execution of the pointing movement. The team was thus able to determine that the lack of precision in pointing is not conditioned by the visual field in which the object position is initial-

ly coded, but by the visual field in which its position is actually pointed. Besides validating the visual-motor interpretation of optical ataxia, this protocol allows diagnosis of optical ataxia to be established even in a case of primary visual deficit following a brain lesion (hemianopsia).

Khan AZ, Pisella L, Vighetto A, Cotton F, Luaute J, Boisson D, Salemm R, Crawford JD, Rossetti Y, Nature Neurosc., 2005 ; 8 (4) : 418-20.

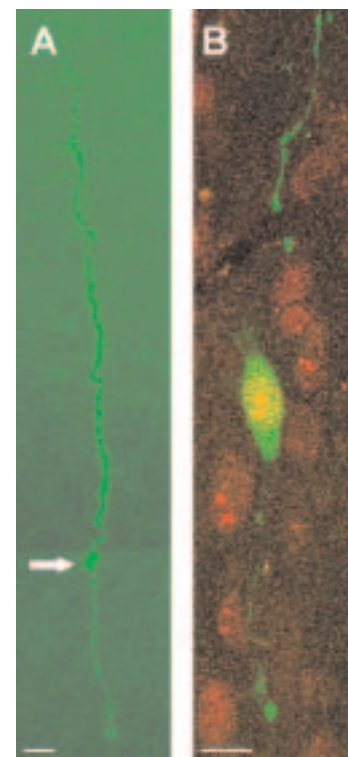
Access to Awareness of Visual Information

What is the brain activity scenario that leads us to be conscious of what we see? Inserm Unit 562 (Cognitive Neuroimaging), led by C. Sergent, has recorded EEG brain activity signals of awake volunteers seeing - consciously or unconsciously - a word presented in the middle of their visual field. No difference was observed between the two types of processing during the first steps of visual word analysis. However, following a rapid transition (200 to 300 milliseconds after presentation of the word), conscious words elicited a cascade of belated activities, which was not the case for words perceived unconsciously, demonstrating sustained activity in a set of frontoparietocingular regions. This work suggests that becoming aware of visual information depends on the triggering of a second phase of brain processing, which allows amplification and retention of sensory and conceptual representations derived from visual stimuli, thereby making them available to a wider cerebral network.

Sergent C, Baillet S, Dehaene S, Nature Neurosc., 2005 ; 8 (10) : 1391-1400.

G1/S, Primate Cortex and Encephalization

The cerebral cortex is the seat of higher cognitive functions and is divided into distinct cortical areas. The mechanisms that control the individualization of cortical areas during development remain poorly understood. The work on primates by C. Dehay's team at Inserm Unit 371 (Brain and Vision), led by H. Kennedy, has shown that regulation of the G1 phase of the precursor cell cycle is a fundamental element that specifies the identity of cortical areas. This work has also unveiled unique characteristics in primate corticogenesis, which are not found in rodents. These results suggest that the G1/S restriction point in the cell cycle could constitute a genetic target responsible for the increase in cerebral



Confocal microscopy photograph of a primate cerebral cortex precursor on an organotypic slice. In primates, neurons of the supragranular layers in the cerebral cortex are produced by a specialized germinal zone that has no equivalent in rodents.

cortex thickness in the course of evolution, a thickness that reaches a pinnacle in the human primate. These results show that the control of a biological process as fundamental as the G1 phase of the cell cycle determines the cytoarchitecture of cortical areas and hence the computational capacity of our cerebral cortex.

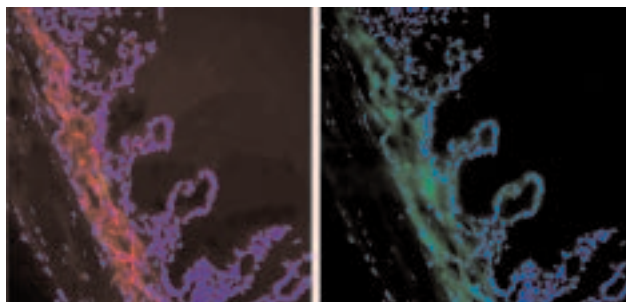
Lukaszewicz A, Savatier P, Cortay V, Giroud P, Huisoud C, Berland M, Kennedy H, Dehay C, Neuron, 2005 ; 47 (3) : 353-64.

mation, which are becoming more common as the population ages. This discovery also involved Inserm Unit 598 (Pathophysiology of Eye Diseases: Therapeutic Innovations) and Inserm Unit 640 (Chemical and genetic Pharmacology), both of which are associated with the Rothschild Hospital, the CNRS, Universities Paris V and VI and ENSCP.

Bloquel C, Bejjani RA, Bigey P, Bedioui F, Doat M, BenEzra D, Scherman D, Behar-Cohen F, FASEB 2005 ; Epub dec 13 (2006 ; 20 (2) : 389-91).

Improved Ciliary Muscle Transfection

A promising technique for treating a variety of eye pathologies has been developed. Using very weak electrical fields, the method allows efficient plasmid-mediated transfection into eye ciliary muscle. This rapid treatment (a few seconds) is well tolerated and allows local and durable production of proteins in the eye. Therapeutic efficiency was obtained in a model of acute eye inflammation (experimental uveitis) by using a plasmid encoding a soluble TNF-alpha receptor. This work opens genuine therapeutic prospects for eye diseases such as glaucoma, retinal dystrophies, or intraocular inflam-



The muscle revealed by immunolabeling of smooth muscle actin is transfected with a plasmid carrying the green fluorescent protein (GFP) gene (nuclei are labeled with a blue dye). Other proteins such as therapeutic proteins have been produced in a similar way.

PSYCHIATRY



Vulnerability to Suicide and Decision Making

Understanding the pathophysiology of suicidal vulnerability is necessary to propose targeted prevention measures eventually. In this study, Inserm team E0361 (Pathologies of the Nervous System: Epidemiological and Clinical Research) has studied decision-making, a particular cognitive function, which, like suicidal vulnerability, involves ventromedial prefrontal cortex function and modulation by the serotonergic system. Four groups of subjects were evaluated by the Iowa Gambling Task, which requires making choices in a situation of uncertainty and learning to sacrifice immediate reward for long-term benefits. The results suggest that anomalies in decision-making are an element in suicidal vulnerability, independently of the effect of being in a state of depression. In addition, the results open new prospects for psychophysiological neuroimaging research.

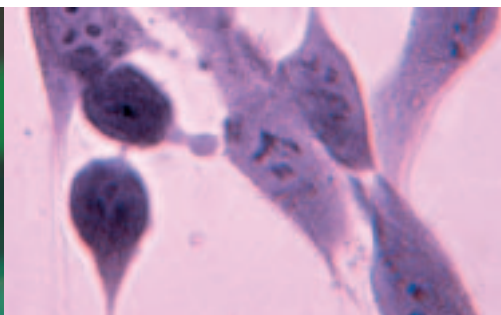
Jollant F, Bellivier F, Leboyer M, Astruc B, Torres S, Verdier R, Castelnau D, Malafosse A, Courtet P, Am. J. Psychiatry, 2005 ; 162 (2) : 304-10.

Role of the PRODH Gene in Schizoaffective Disorder

In France, over 600,000 people suffer from schizophrenia. The genetic analysis of this pathology is difficult due to its complex hereditary pattern and its clinical heterogeneity. The high frequency of psychosis in DiGeorge's syndrome, which results from a deletion at position 22q11, suggests that genetic risk factors are present in this chromosome region. Earlier work indicated that the PRODH (proline dehydrogenase gene), located at 22q11, might be a possible candidate. The work by Inserm Unit 314 (Medical and Functional Genetics of Cancer and Neuropsychiatric Diseases) shows that there is a link between hyperprolinemia - resulting from the PRODH gene anomaly - and schizoaffective disorder.

Jacquet H, Demily C, Houy E, Hecketsweiler B, Bou J, Raux G, Lerond J, Allio G, Haouzir S, Tillaux A, Bellegou C, Fouldrin G, Delamillieure P, Menard JF, Dollfus S, D'Amato T, Petit M, Thibaut F, Frebourg T, Campion D, Mol. Psychiatry, 2005 ; 10 (5) : 479-85.

CARDIOLOGY



Reducing the Final Infarct Size

A number of recent experimental studies have shown that producing short episodes of ischemia in the first minute of reperfusion following prolonged myocardial ischemia can reduce the final size of infarct by about 40 to 50%. This phenomenon has been called “postconditioning”. This observation demonstrates the long-debated existence of reperfusion necrosis. While there is no controversy about the fact that stopping ischemia is necessary, it is worth considering that reperfusion may also kill some of the cardiomyocytes. Recent work has shown that postconditioning can be performed in patients with acute myocardial infarction. Four one-minute episodes of inflation-deflation of the angioplasty balloon, immediately after reopening the occluded artery, have allowed Inserm team E0226 (Cardioprotection) to reduce the size of infarct by an average of 36%. This study opens a new therapeutic avenue for patients with acute myocardial infarction.

Argaud L, Gateau-Roesch O, Raisky O, Loufouat J, Robert D, Ovize M, Circulation, 2005 ; 111 (2) : 194-97.

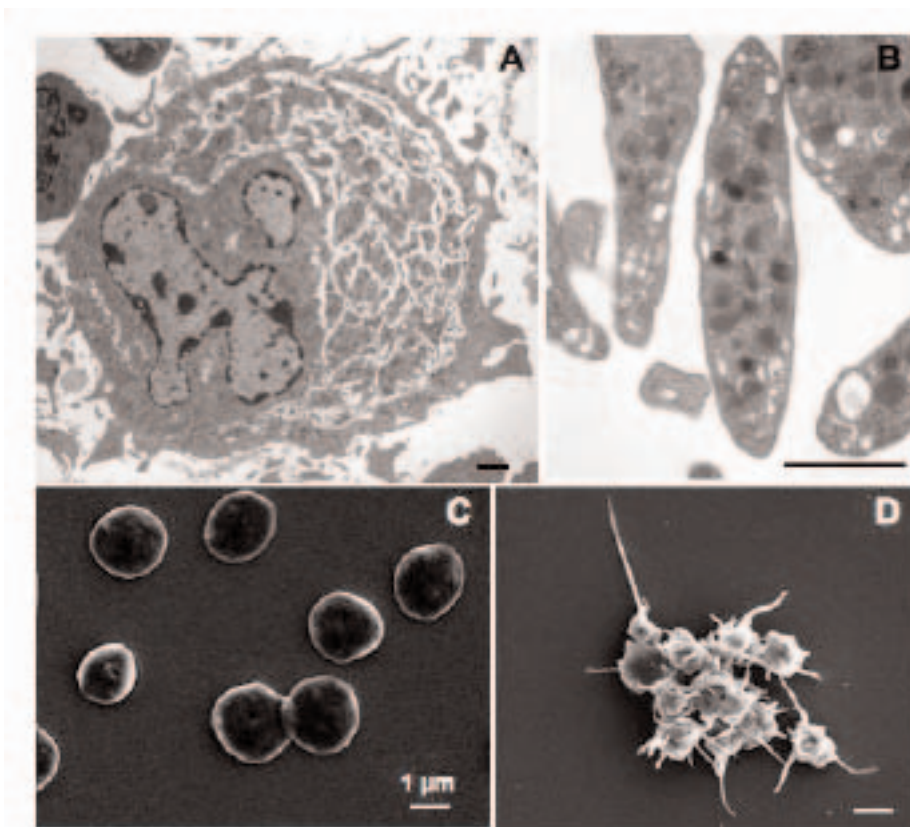
Variability of the Response to Clopidogrel

Clopidogrel is an antiplatelet medication with proven efficiency in secondary pre-

vention of ischemic accidents. However, 5 to 20% of patients treated with clopidogrel are subject to thrombotic recurrence. Among the methods generally available to evaluate the antiplatelet efficacy of this medication, flow cytometry determination of the platelet reactivity index by quantitative analysis of VASP (Vasodilator Stimulated Phosphoprotein) phosphorylation is the most selective. Indeed, the

degree of phosphorylation of this protein depends on the intracellular concentration of cyclic AMP, the production of which is inhibited when the P2Y₁₂ receptor (the target of the clopidogrel active metabolite) is activated.

In a joint study by research teams from Inserm Unit 311 (Biology and Pharmacology of Hemostasis and Thrombosis), the French Blood Transfusion Service (EFS) in Alsace



A, B: Platelets (B) are derived from the fragmentation of megakaryocytes (A). At rest, their shape is discoid (C). When activated, they become aggregated (D).

and the Service of Interventional Cardiology from the Orangerie Clinic in Strasbourg, this test revealed high interindividual variability in the biological response of patients treated with the usual chronic dose of the drug. Moreover, the study shows that 30% of patients treated with clopidogrel have reactivity indexes similar to those of untreated subjects, suggesting that they are insufficiently protected. The mechanisms of such variability are still unknown but there are good reasons to believe that hepatic metabolism of the drug is involved. The cause-and-effect link with recurrence of thrombotic accidents remains to be demonstrated.

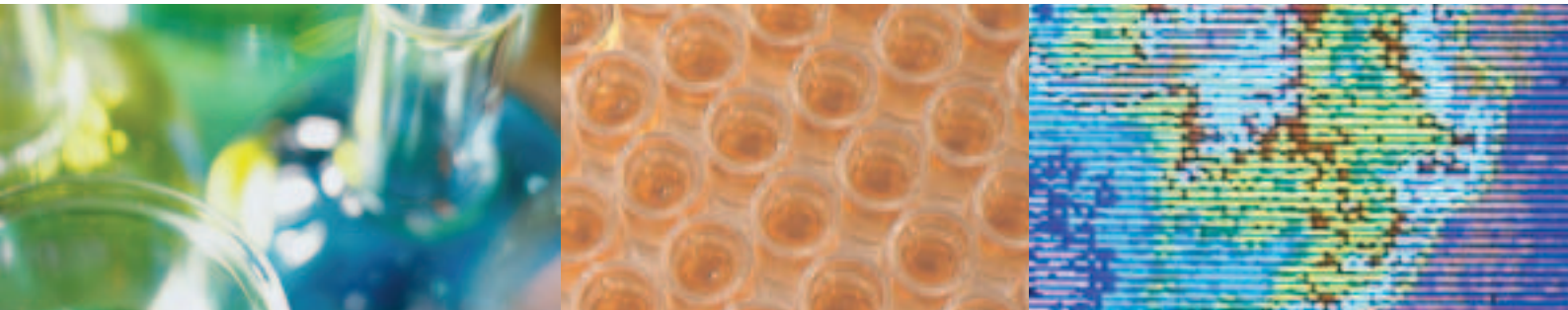
Aleil B, Ravanat C, Cazenave JP, Rochoux G, Heitz A, Gachet C, J. Thromb. Haemost., 2005 ; 3 (1) : 85-92.

Lactadherin and Ischemia

Research by Inserm Unit 689 (Lariboisière Cardiovascular Research Center) demonstrated that lactadherin was an endogenous factor modulating the VEGF/VEGFR2-dependent signaling pathway through interaction with integrin $\alpha v \beta 3$. The activation of integrins can affect angiogenesis even in the absence of growth factors. This has been demonstrated in the case of the lactadherin analog, Del-1. Similarly, this work shows that lactadherin interacts with integrins $\alpha v \beta 3$ and $\alpha v \beta 5$, and can activate the development of new blood vessels after ischemia by an Akt-dependent mechanism and in the absence of exogenous VEGF. A therapeutic strategy based on overexpression of lactadherin could therefore be proposed for the treatment of ischemic pathologies.

Silvestre JS, Thery C, Hamard G, Boddaert J, Aguilar B, Delcayre A, Houbron C, Tamarat R, Blanc-Brude O, Heeneman S, Clergue M, Duriez M, Merval R, Levy B, Tedgui A, Amigorena S, Mallat Z, Nature Med., 2005 ; 11 (5) : 499-506.

DERMATOLOGY



Mitochondria, Apoptosis and Keratinocytes

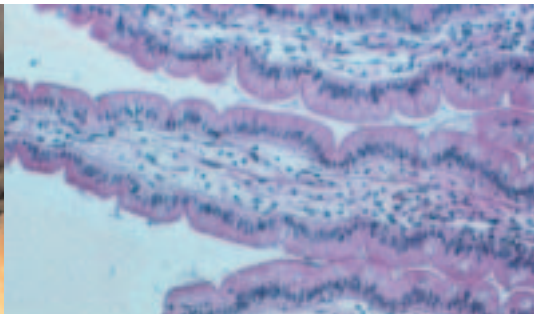
The work of Inserm Unit 459 (Signals, Receptors and Cell Differentiation) demonstrates the involvement of apoptosis pathway relays during differentiation of human skin keratinocytes. The differentiation of keratinocytes is coordinated in time and space with a gradual expression of markers of the mitochondrial apoptosis pathway. A model has been proposed according to which the induction of epidermal terminal differentiation is associated with a parallel derepression of the

mitochondria-dependent apoptotic death pathway. Recent experimental evidence shows there is a mechanistic link between the differentiation program and the apoptotic machinery of keratinocytes. Using apoptogenic stimuli targeting mitochondria and various modulators of their activity, researchers were able to show that expression of early molecular and morphological markers of differentiation depends on apoptotic mitochondrial modifications and especially on the induction of ROS production. This data also suggests that the stimuli affecting mitochondria can

either induce differentiation or apoptosis, according to the competence of keratinocytes to engage in differentiation. Such competence appears to depend on Bcl-2.

Tamiji S, Beauvillain JC, Mortier L, Jouy N, Tual M, Delaporte E, Formstecher P, Marchetti P, Polakowska R, J. Invest. Dermat., 2005 ; 12 (4) : 647-58.

GASTROENTEROLOGY, HEPATOLOGY



Evaluating Hepatic Fibrosis without Biopsies

The FibroScan is a medical device based on ultrasound elastography and used for diagnosis and noninvasive quantitation of hepatic fibrosis. The device generates a vibrator-mediated mechanical wave. By measuring the speed of wave propagation through the hepatic parenchyme, elasticity and hence the extent of fibrosis can be evaluated. The E0362 Inserm team (Hepatic Fibrosis and Liver Cancer) compared the efficiency of FibroScan elastography and analysis of serum markers (by the FibroTest or AST-to-platelet ratio index [APRI] scoring) with that of liver biopsy for 183 patients suffering from chronic hepatitis C. The best results were obtained by joint use of the FibroScan and FibroTest, particularly for cirrhosis diagnosis. These results suggest that the combined use of the FibroScan and FibroTest as a first-line approach could help avoid making liver biopsies in the majority of patients suffering from hepatitis C.

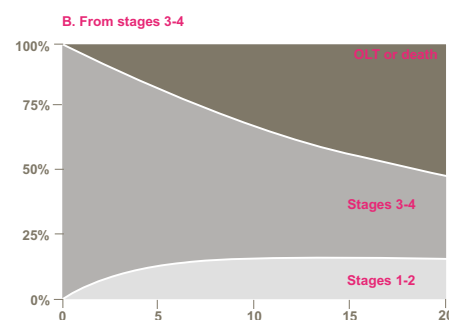
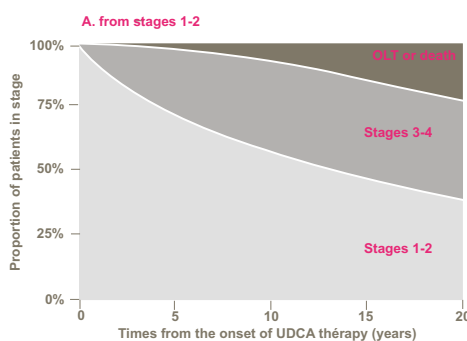
Castera L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, Darriet M, Couzigou P, De Ledinghen V, Gastroenterology, 2005 ; 128 (3) : 343-50.

Treating Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC) is a chronic liver disease of unknown origin anatomopathologically characterized by inflammation and destruction of small intrahepatic bile ducts. This disease, which mainly affects middle-aged women, is responsible for a chronic cholestase that can evolve toward fibrosis and eventually lead to liver insufficiency. Ursodeoxycholic

Unit 370 (Hepatic Carcinogenesis and Molecular Virology) has shown that when treatment is initiated early on in the disease (stages 1 or 2), patient survival is normalized. This result justifies the introduction of early screening for this disease.

Corpechot C, Carrat F, Bahr A, Chrétien Y, Poupon RE, Poupon R, Gastroenterology, 2005 ; 128 (2) : 297-303.

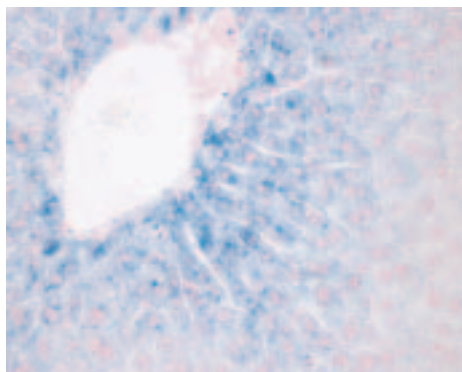


Predicted percentages of patients at different stages of the disease (early stages 1-2, late stages 3-4, deceased or transplant patients) depending on the length of treatment (predictions over a 20-year period).

acid (UDCA) is currently the only medication with proven efficacy in terms of patient survival. The long-term prognosis of patients treated with UDCA is nonetheless poorly defined because the disease is rare and slow in its progression. Using modelization of disease progress, Inserm

Hepcidin and Liver Macrophages

Hepcidin is a small circulating hormonal peptide produced by hepatocytes and playing a central role in iron homeostasis. In both mice and humans, expression of its gene is induced by iron and inflammation.



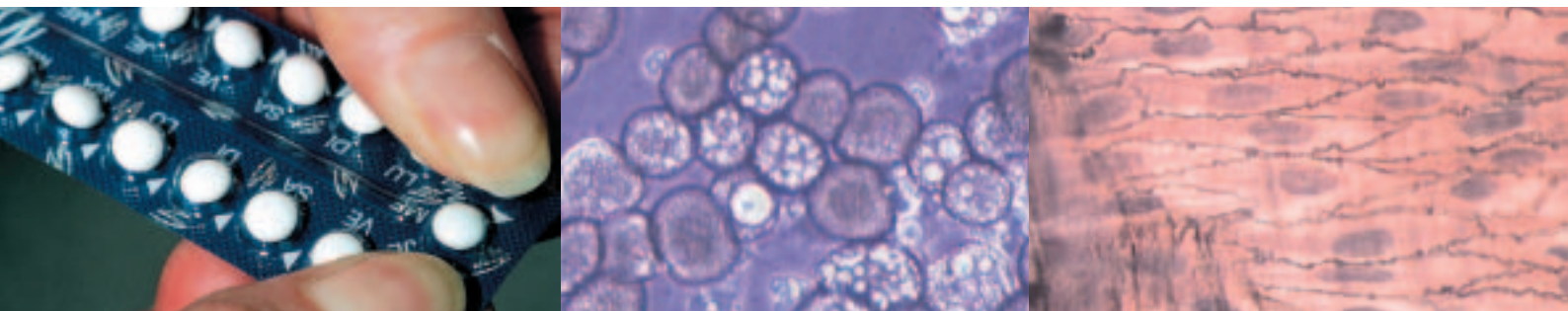
Iron (blue staining) accumulates in hepatocytes and induces hepcidin. The latter regulates the level of serum iron by limiting intestinal iron absorption from food and releasing iron from macrophages.

Curiously, these effectors are unable to increase the hepcidin level in isolated hepatocytes in culture, indicating that a cellular intermediate is required. Liver macrophages (Kupffer cells) seemed to be the ideal cells to fulfill this function. These cells are indeed sensitive to circulating iron and produce a certain number of cytokines, including interleukine 6, which is known to induce hepcidin. In order to test this hypothesis, the drug clodronate, which specifically destroys Kupffer cells, was injected intravenously. Surprisingly, macrophage destruction did not inhibit hepcidin induction in mice on a high-iron diet or injected with the liver inflammatory agent, LPS. Similarly, the hepcidin gene was perfectly well induced by iron or

inflammation in interleukin 6-deficient mice. These results suggest that other cellular factors and/or cytokines could be involved in the control of liver hepcidin. The different stages in the regulation of the pathophysiological expression of hepcidin remain to be elucidated and characterized in order to define potential therapeutic targets.

Lou DQ, Lesbordes JC, Nicolas G, Viatte L, Bennoun M, Van Rooijen N, Kahn A, Renia L, Vaulont S, Hepatology, 2005 ; 41 (5) : 1056-64.

NEPHROLOGY



CRI, Lanthanum Carbonate and Hepatic Risk

Chronic renal insufficiency (CRI) is often associated with hyperphosphoremia, which needs to be controlled. This can be done with phosphate binders such as lanthanum carbonate, a recently developed compound. Lanthanum being an oligoelement, it is important to ensure that oral intake of massive doses does not induce potentially toxic product accumulation, as was previously described in the case of aluminum. Inserm Unit 507 (Mechanisms of Inflammation and Cellular Adherence in Renal Diseases) from Necker Public Children's Hospital observed that in a CRI rat model, administration of lanthanum

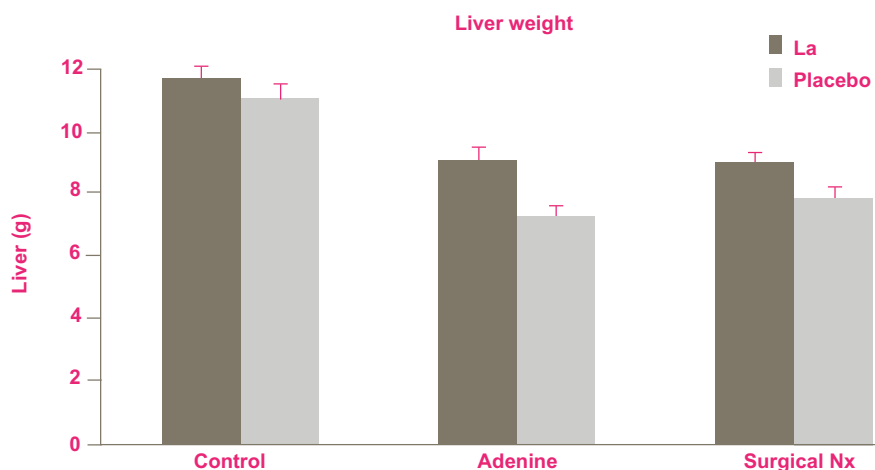
carbonate quantities comparable to those prescribed clinically, leads to major accumulation of lanthanum in most of the tissues examined, resulting in alarming liver weight loss.

Lacour B, Lucas A, Auchere D, Ruellan N, Patey NMD, Druke AB, Kidney Int., 2005 ; 67 (3) : 1062-69.

MDRD Formula for Chronic Renal Disease

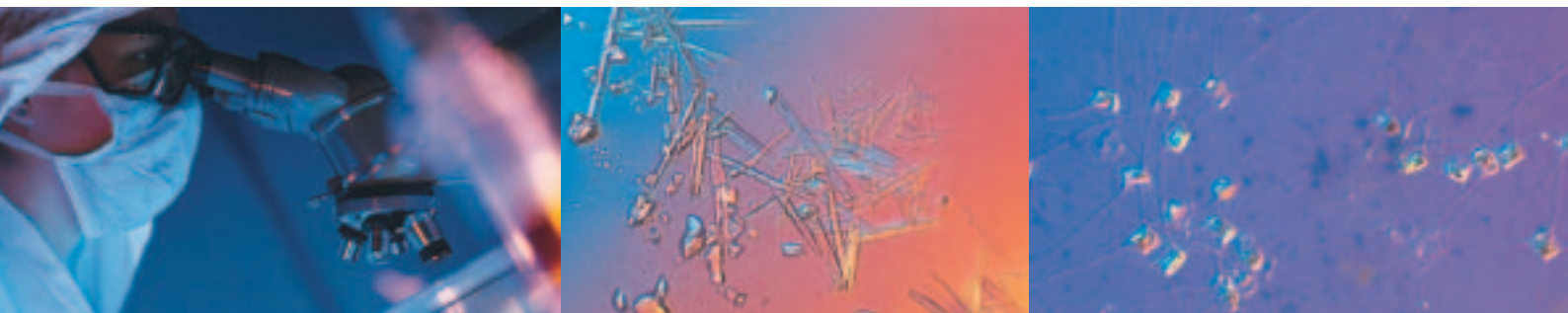
Chronic renal disease has been recognized as an important issue in the last few years. Recent international recommendations insist on the necessity to screen for renal insufficiency using formulae that allow estimation of the glomerular filtration rate from plasma creatinin concentration. Among the formulae available for adults, the formula developed by Cockcroft and Gault in 1976 and the abbreviated MDRD formula, developed in 2000, are the most commonly used. Their performance was assessed with reference to standard renal function measurements in a population of 2,095 adult patients. The main result is that the MDRD formula, which does not show significant bias in old or obese subjects, is more efficient than the Cockcroft and Gault formula. These results, obtained by Inserm Unit 652 (Vascular and Renal Physiology and Pharmacology), have led to the recommendation of the MDRD formula in the new international classification for chronic renal disease.

Froissart M, Rossert J, Jacquot C, Paillard M, Houillier P, J. Am. Soc. Nephrology, 2005 ; 16 (3) : 763-73.



Effects of lanthanum carbonate (versus placebo) in a control experiment with rats

MEDICAL TECHNOLOGIES



Improving MRI

Intensity inhomogeneity, which is an inherent defect of magnetic resonance imagery (MRI), hampers visual analysis of images by radiologists and interferes with their use for quantitative analysis by algorithms. Researchers from the Center for Research on Image and Signal Processing and its Applications (Creatis), which is composed of Inserm Unit 630 and CNRS Unit UMR 5515, have developed an entirely new approach to correct this artifact. This is based on a mathematical model allowing representation of a signal or its spectrum by linear combination of single functions. This approach involves removing the low spatial frequencies of an image, which are corrupted by intensity inhomogeneity, then rebuilding them from the

non-polluted high spatial frequencies. This eliminates artifacts caused by intensity inhomogeneity without damaging the useful information contained in the image. Furthermore, the proposed method does not require making the assumption that the spectra of signals corresponding to

anatomical structures and those due to field inhomogeneity are independent.

Luo JH, Zhu YM, Clarysse P, Magnin J, IEEE Trans. Med. Imag., 2005 ; 24 (8) : 1067-85.

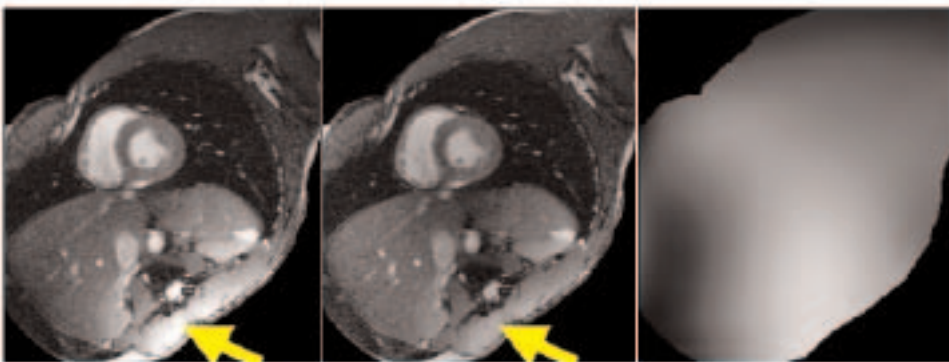
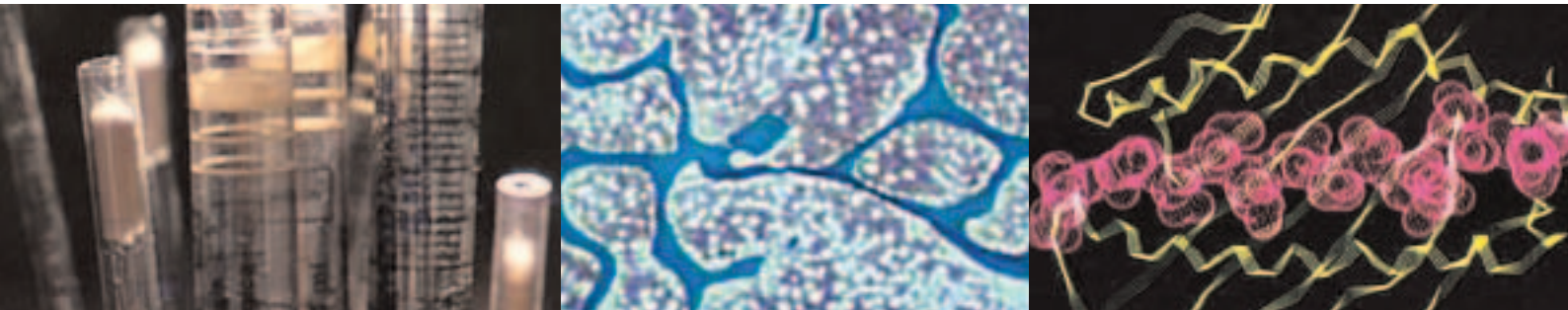


Image before correction

Image after correction

Intensity inhomogeneity

ENDOCRINOLOGY, REPRODUCTION



Prevention of Fractures by Strontium Ranelate

Strontium ranelate was developed as a result of collaboration between the Servier laboratories and Pierre Marie, a researcher from Inserm Unit 606 (Bones and Joints) at the Lariboisière Hospital in Paris. Its mode of action on bone cells is still partially unknown. Strontium ranelate treatment has been commercialized for a few months in Europe on the basis of clinical studies



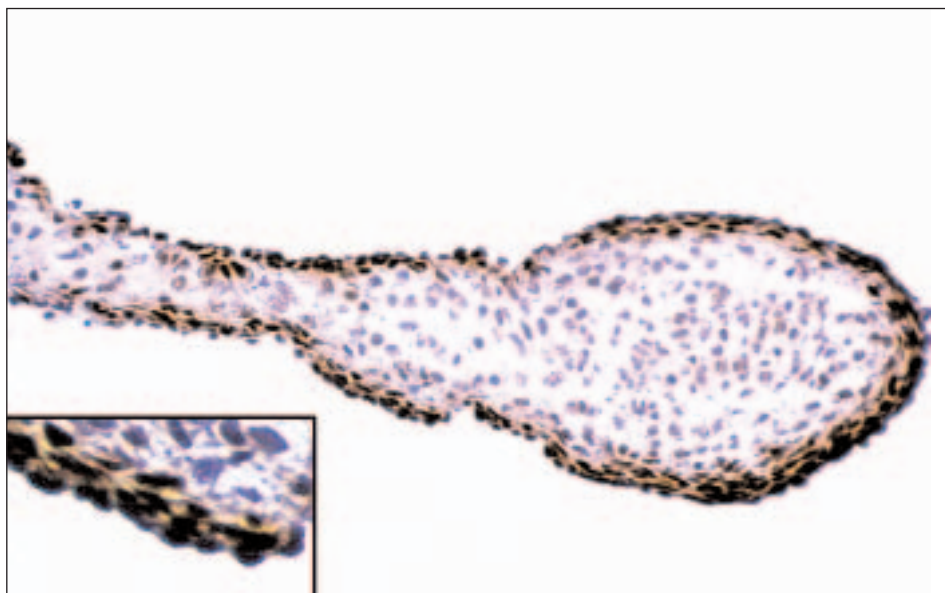
Top: wrist fracture. Bottom: femoral neck fracture

showing that it reduces the incidence of vertebral and peripheral fractures. A clinical study conducted in several centers, including the Lariboisière Hospital Center, has shown that strontium ranelate reduces the number of peripheral fractures (of the wrist, arm and femoral neck particularly) in a population of elderly women (aged 74 on average).

Reginster JY, Seeman E, De Vernejoul MC, Adami S, Compston J, Phenekos C, Devogelaer JP, Curiel MD, Sawicki A, Goemaere S, Sorensen OH, Felsenberg D, Meunier PJ, J. Clin. Endocrin. Metab., 2005 ; 90 (5) : 2816-22.

Cryptorchidia and Estrogen Alpha Receptors (ESR1)

Cryptorchidia is a condition in which the testicles fail to migrate down and out of the body. It affects 1 to 2 % of children and results in hypofertility or even sterility (depending on whether this failure is partial or complete) as well as an increase in the risk of testicle cancer. Two hormones - androgens and insulin-like factor 3 (INSL3) - are known to be involved in the phase of transabdominal downward testicle migration. Androgens alone, on the other hand, allow the ultimate traction of gonads from the lower part of the abdomen into the scrotum, after playing a role in the involution of a structure known



Immunolocalization of ESR1 (dark staining) in fetal gubernaculum

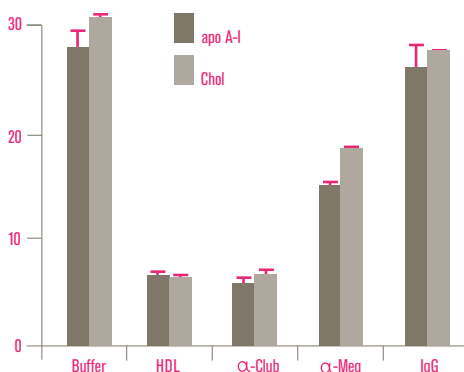
as the gubernaculum testis. A study led by Inserm Unit 271 (Hepatitis Viruses and Associated Pathologies) demonstrated the presence of the estrogen alpha receptor (ESR1) in the fetal gubernaculum, in the form of two proteins of 66 and 46 kDa, produced by alternative splicing. The study also revealed that ESR1 is colocalized with the androgen receptor in the gubernaculum and that the profile of the expression level ratio for the two receptor isoforms follows the various key stages of gubernaculum evolution. These observations, and the fact that the 46 kDa ESR1 isoform is considered to be a competitive inhibitor of the 66 kDa active form of the receptor, have led the authors to hypothesize that estradiol modulates the action of androgens in testicular descent.

Staub C, Rauch M, Ferrière F, Trepos M, Dorval-Coiffec I, Saunders PT, Cobellis G, Flouriot G, Saligaut C, Jegou B, Bio. Reprod., 2005 ; 73 (4) : 703-12

Development of the Embryo, Cubilin and Megalin

During early embryonic development, two structures play an essential role in embryonic nutrition: the trophectoderm (TE) at the blastocyst stage, then the visceral yolk sac endoderm until the formation of the allantoid placenta. Inserm Unit 538 (Membrane Traffic and Signaling in Epithelial Cells) has shown that these two epithelial structures express two multiligand endocytic receptors, cubilin and megalin, which appear to be very important for protein, and above all lipid internalization during peri-implantation development. The two receptors form a complex that appears to allow rapid and simultaneous internalization of high and

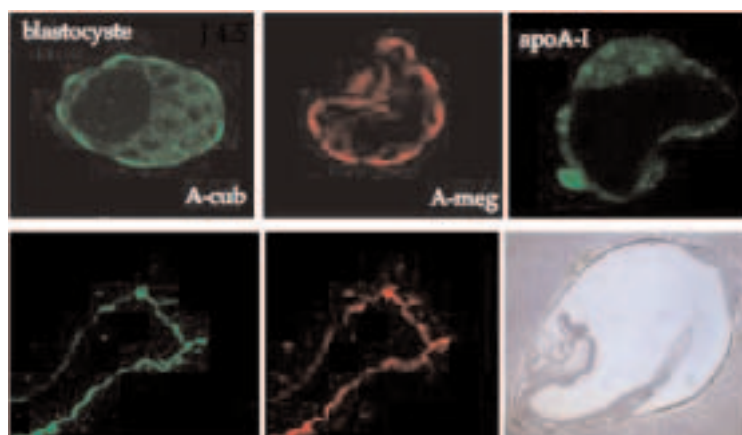
low-density lipoproteins, a source of cholesterol for the embryo, as well as vitamins and iron. This process is particularly important for normal embryonic and post-natal growth. Indeed, any interference with yolk sac function and cubilin in particular, affects embryonic development. The expression of cubilin and megalin by the human placenta and their capacity to bind substances other than nutrients, such as morphogenes, suggests they play an important role during early human embryonic growth.



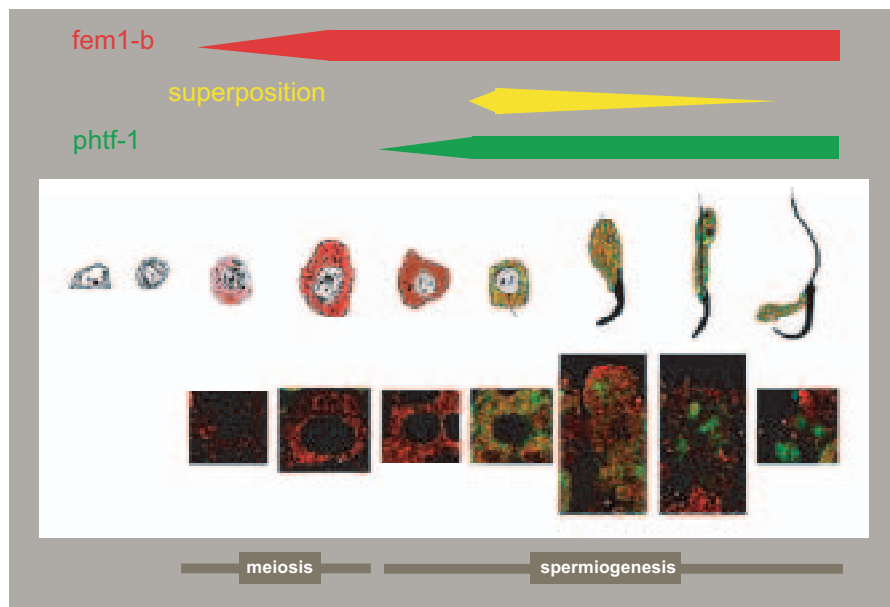
Assemat E, Vinot S, Gofflot F, Linsel-Nitschke P, Illien F, Chatelet F, Verroust P, Louvet-Vallee S, Rinninger F, Kozyraki R, Bio. Reprod., 2005 ; 72 (5) : 1079-86.

FEM1B, the Genetic Partner of PHTF1

The PHTF1 gene codes for a membrane protein expressed in large quantities in male germinal cells. Using the double-hybrid technique, a team from Inserm Unit 567 (Cochin Institute) identified FEM1B, an ortholog of the feminization factor 1 (FEM-1) gene in *C. elegans*, as being the genetic partner of PHTF1. This interaction takes place via the ankyrin domain of FEM1B and the N-terminal end of PHTF1. Expression of the two proteins coincides in the same cells during meiosis and later on, during spermatogenesis. FEM1B binds to various intracellular organelles while PHTF1 recruits FEM1B on the endoplasmic reticulum membrane. Different *in vitro* experiments had suggested that FEM1B was involved in apoptosis. The present study, using germ cells,



Top: internalization of apolipoprotein A-I by cubilin and megalin expressed by the TE at the blastocyst stage. Bottom: internalization of apolipoprotein A-I and cholesterol (radiolabeled HDL) by yolk sac cubilin and megalin (A-cub, A-meg: anti-cubilin and anti-megalin antibodies, IgG: non-immune serum, HDL: cold HDL).

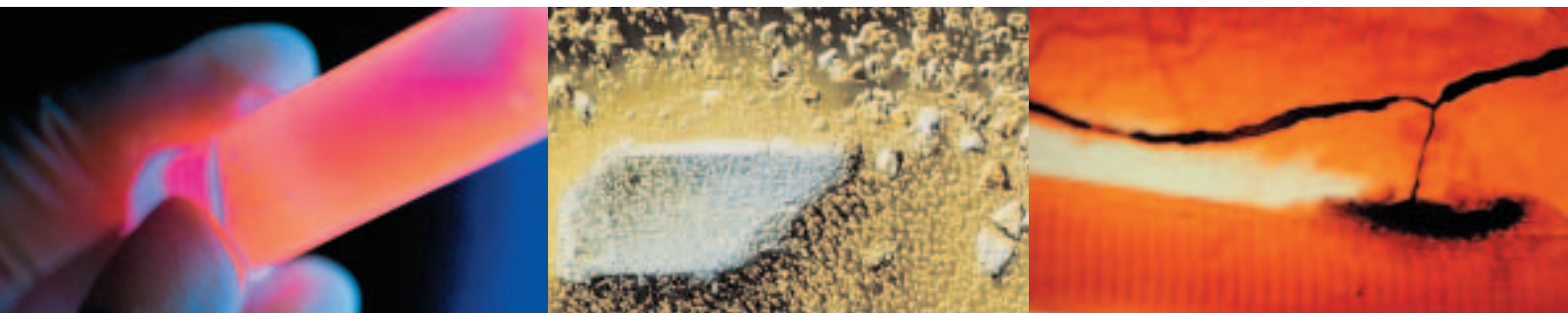


Colocalization of PHTF1 and FEM1B.

has shown that neither of the two genes is directly involved in apoptotic events of the seminiferous tubules. Using FEM1B ^{-/-} mice, it was recently shown that FEM1B is involved in glucose homeostasis. PHTF1 could also belong to this genetic pathway.

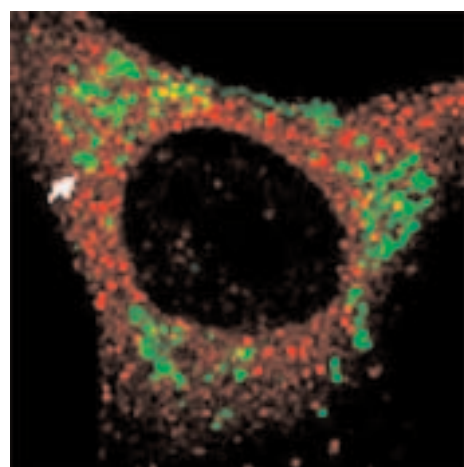
Oyhenart J, Benichou S, Raich N, Bio. Reprod., 2005 ; 72 (4) : 780-87.

IMMUNOLOGY, INFECTIOUS DISEASES, AUTOIMMUNE DISEASES



Brucella and Cyclic Glucane

Brucella mutants unable to synthesize their own cyclic glucane (C β G) have been shown to be attenuated in a murine infection model. The work of Inserm Unit 631 (Center of Immunology Inserm-CNRS-Université de la Méditerranée de Marseille-Luminy) has shown that these mutants cannot avoid fusion of their vacuole with lysosomes and fail to replicate. However, when such mutants are treated with purified C β G, they become equipped to control the maturation steps of their vacuole and survive inside infected cells. This study introduces a new concept, analogous to the Trojan horse principle.



C β G-deficient *Brucella abortus* mutants are treated with purified C β G before infection. Mutants (white arrow) can now colonize the infected cell, in this case a macrophage derived from mouse bone marrow.

Brucella produces cyclic glucanes that modify the bacterial environment in order to position it near the endoplasmic reticulum and allow it to replicate. C β Gs are the first *Brucella* effectors, the function of which has been explained in molecular terms.

Arellano-Reynoso B, Lapaque N, Salcedo S, Briones G, Ciocchini AE, Ugalde R, Moreno E, Moriyon I, Gorvel JP, Nat. Immunology, 2005 ; (6) : 618-25.

ERAP1 and ERAP2 in the Major Histocompatibility Complex

The generation of peptides presented by class-I molecules of the major histocompatibility complex (HLA-I) and recognized by CD8+ cytotoxic T lymphocytes involves several proteolytic steps. Until recently, only the first of these steps, which takes place in the cytoplasm and involves the proteasome, was well characterized. Peter van Endert's team at Inserm Unit 580 (Type-1 Diabetes: Mechanisms and Immunological Treatment), has just characterized the final proteolytic step, which takes place in the endoplasmic reticulum (ER). In man, this step involves two peptidases, ERAP1 and ERAP2, which have complementary specificities and act in

concert on the N-terminal end of peptides that reach the ER lumen. This concerted action is facilitated by a quasi-perfect colocalization of these enzymes in the ER and their capacity to form complexes.

Saveanu L, Carroll O, Lindo V, Del Val M, Lopez D, Lepelletier Y, Greer F, Schomburg L, Fruci D, Niedermann G, van Endert PM, Nature Immunol., 2005 ; 6 (7) : 689-97.

DNA Polymerase and Immunoglobulins

The process of immunoglobulin gene hypermutation is responsible for the maturation of antibody affinity during the immune response. This process is initiated by a specific enzyme, AID (activation-induced cytidine deaminase) and involves DNA polymerases that specialize in bypassing DNA lesions during replication (translesion DNA synthesis). As expected, patients with XP-V (a variant of *Xeroderma Pigmentosum*), who have an activity defect in one of these enzymes, DNA polymerase eta (pol eta), have an altered mutational profile. The team from Inserm Unit 373 (Development of the Immune System) has developed an animal model for this disease, in which expression of the gene coding for pol eta is totally absent, thus eliminating the variability

observed in XP-V patients. This model has not only allowed confirmation that pol eta is involved in the hypermutation process but has also helped establish that the enzyme plays a more important role than anticipated. It remains to be determined whether this polymerase is recruited for its lesion bypassing activity or whether the hypermutation process distracts this enzyme from its usual function to work on mutagenic repair.

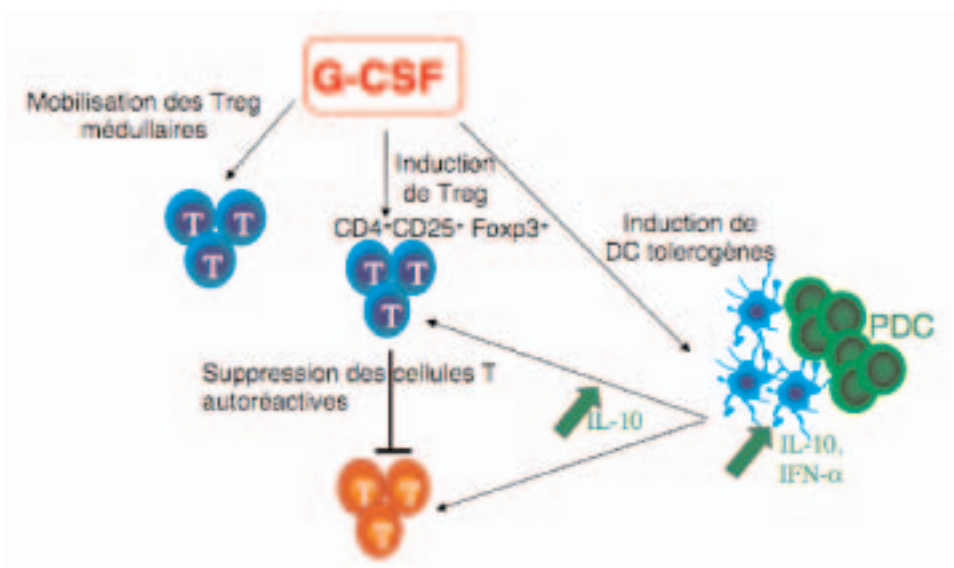
Delbos F, De Smet A, Faili A, Aoufouchi S, Weill JC, Reynaud CA, J. Exp. Med., 2005 ; 201 (8) : 1191-96.

G-CSF and Autoimmune Diseases

Patients treated with the hemopoietic factor G-CSF (Granulocyte Colony Stimulating factor) exhibit a reduced T immune response. This observation led Flora Zavala and Lucienne Chatenoud from Inserm Unit 580 (Type-1 Diabetes: Mechanisms and Immunological Treatments) to evaluate the capacity of G-CSF to protect from autoimmune diseases. Researchers have shown that treatment with G-CSF prevents the emergence

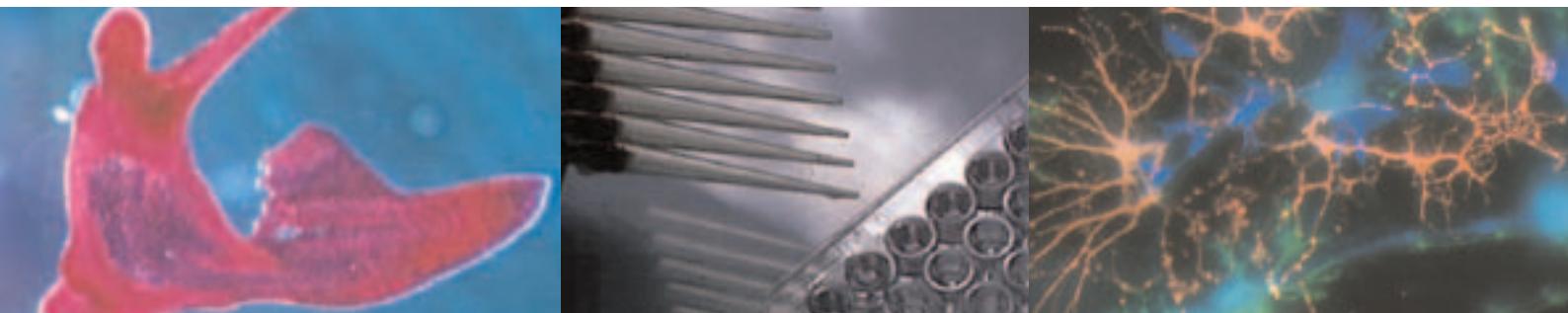
of type-1 diabetes in non-obese diabetic mice. G-CSF promotes differentiation of tolerogenic dendritic cells, which in turn recruit T regulator cells in peripancreatic ganglia, responsible for controlling diabetogenic cells. G-CSF is well tolerated clinically and could be associated with T activation inhibitors for the treatment of human type-1 diabetes or multiple sclerosis. Furthermore, G-CSF being an endogenous factor in the response to infection, it could partly explain the protective effect of infection in autoimmune diseases.

Kared H, Masson A, Adle-Biassette H, Bach JF, Chatenoud L, Zavala F, Diabetes, 2005 ; 54 (1) : 78-84.



Principle mechanisms of self tolerance recovery induced by G-CSF.

DIABETES, METABOLISM



A Target for Type-2 Diabetes

Inserm Unit 568 (Molecular Signaling and Obesity) at the Faculty of Medicine in Nice is interested in obesity and associated pathologies (resistance to insulin, type-2 diabetes). Recruitment of new fat cells, i.e. adipocyte differentiation, plays a major role in the development of obesity. Research has shown that protein kinase erk1 (an isoform of the erk protein kinase) is involved in the development of obesity. Indeed, erk1 knockout mice (erk1 $-/-$), generated by the CNRS UMR6543 laboratory led by J. Pouyssegur, are resistant to obesity induced by a high-fat diet. This phenotype is characterized by lower fat

lead to the development of new treatments for obesity and type-2 diabetes.

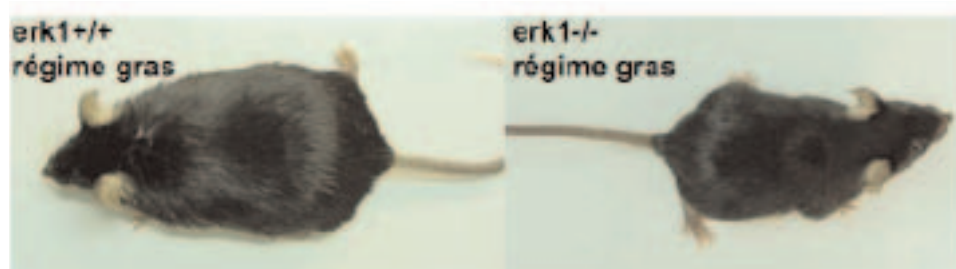
Bost F, Aouadi M, Caron L, Even P, Belmonte N, Prot M, Dani C, Hofman P, Pages G, Pouyssegur J, Le Marchand-Brustel Y, Binetruy B, Diabetes, 2005 ; 54 (2) : 402-11.

CD3 Against Type-I Diabetes

This work by Inserm Unit 580 (Type-1 Diabetes: Mechanisms and Immunological Treatments) concerns the clinical application of a new strategy of immunointervention to restrain durably the progression of

patients having recently developed diabetes (no more than 4 weeks of treatment with insulin), the antibody allowed a significant decrease in the need for exogenous insulin up to 18 months after treatment completion. These highly encouraging results represent a first in terms of efficient treatment of the cause of the disease, i.e. the autoimmune reaction responsible for the destruction of beta cells in the islets of Langerhans.

Keymeulen B, Vandemeulebroucke E, Bach JF, Pipeleers D, Chatenoud L, New Eng. J. Med., 2005 ; 352 (25) : 2598-608.

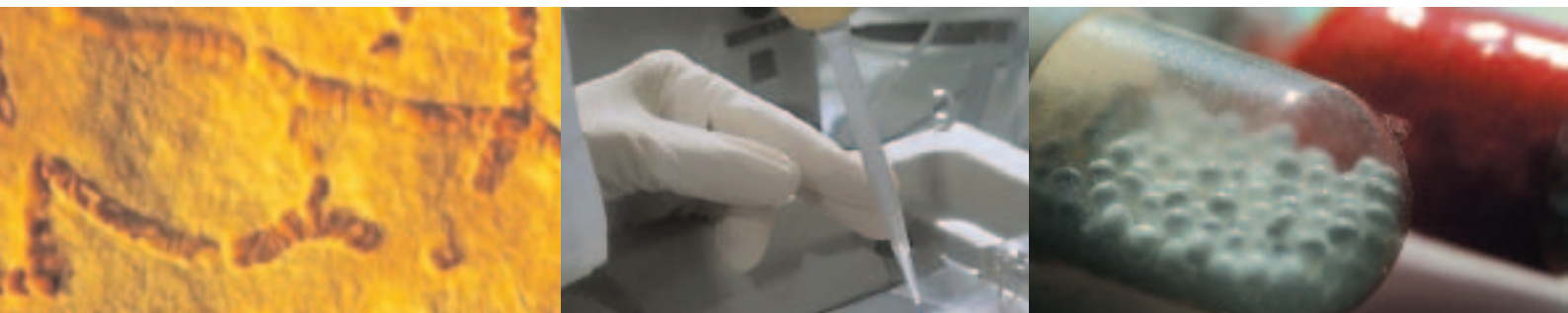


Erk1 knockout (erk1 $-/-$) and wild type (erk1 $+/+$) mice after 7 weeks on a high-fat diet.

deposition in the animals due to a defect in adipocyte differentiation and an increase in energy metabolism in the post-prandial period. In addition, these mice exhibit an increased sensitivity to insulin. Medication targeting erk1 specifically could therefore

an established autoimmune disease such as insulin-dependent (type-1) diabetes after a treatment lasting only 6 days. The medication used is an antibody that specifically recognizes the molecule CD3, a receptor on the surface of T lymphocytes. In

BIOETHERAPIES



Syntenin and Metastatic Development

Preventing the propagation of tumor cells in the blood and the occurrence of metastases remains a major challenge today for cancer treatment. Using a rapid subtraction hybridization technique and a relevant model for the study of spontaneous metastasis in melanoma, Habib Boukerche from Inserm Unit 590 (Oncogenesis and Tumor Progression), in collaboration with Columbia University in New York and the Hôtel-Dieu Department of Dermatology in Lyon, has identified a new essential factor in metastases development: the syntenin gene. Through their remarkable localization at adhesion focal points and their PDZ domains, syntenins play a role in the regulation of cytoskeleton dynamics and organization for cell motility, which involves the c-Jun N-terminal MAP kinases (JNK) and p38. By transplanting melanoma tumor cells expressing the syntenin antisense gene into newborn rats using a recombinant adenovirus, the research team was able to induce regression of pulmonary metastases. This study demonstrates the prometastatic role of syntenin, which could become a new target for therapeutic strategies in the treatment of cancer.

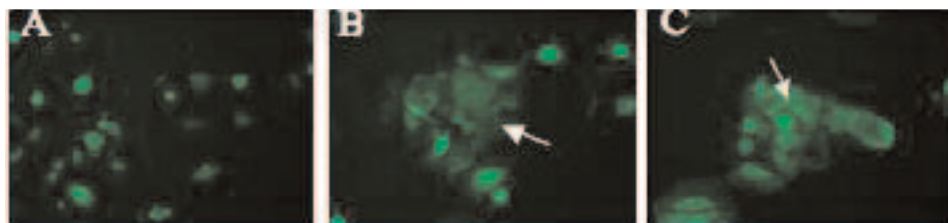
Boukerche H, Su ZZ, Emdad L, Baril P, Balme B, Thomas L, Randolph A, Valerie K, Sarkar D, Fisher P, Cancer Research, 2005 ; 65 (23).

Treating Hereditary Bullous Epidermolyses

Hereditary bullous epidermolyses (HBE) are rare and incurable genetic diseases characterized by an extreme fragility of epithelial tissue, which separates from underlying tissue at the slightest trauma. This disease affects approximately 500,000 people worldwide. Certain clinical forms that are seriously invalidating or even lethal are often associated with the development of aggressive skin cancers. HBEs are caused by genetic mutations affecting constituents of hemidesmosomes and anchorage fibrils, the adherence structures that fix the basal cells of stratified epithelium to the underlying mesenchyme.

HBEs associated with a defect in the expression of laminin 5, the main adherence ligand of epithelial cells (junctional BE), constitute a particularly useful model to demonstrate the feasibility of a genetic therapeutic approach for skin diseases. Inserm Unit 634 (Skin Biology and Physiopathology: genetic expression, Signaling and Therapy) conducted in vitro preclinical studies involving transfer of

recombinant retroviral vectors into keratinocytes from HBE patients in order to restore laminin 5 expression. These experiments demonstrated that the genetic defect can be totally and durably corrected in transduced cells. Furthermore, genetically modified keratinocytes produce artificial epithelia that can be grafted by commonly used methods in the case of severe burns. However, the success of human clinical trials relies on being able to evaluate the persistence of genetically modified cells, the stable expression of the curative gene and the possible risk of rejection by the patient. In order to address these issues, researchers focused on the identification of dog families (the German shorthaired pointer) presenting cases of spontaneous recessive junctional BE. Genetic studies on a vast number of dogs have shown that the mutation responsible for the disease is carried by the lama3 gene encoding the alpha-3 chain of laminin 5. The isolation of the cDNA encoding alpha-3 and its transfer in cultures of dog JBE keratinocytes have enabled researchers to demonstrate the phenotypic reversion of these cells. In addition, they were able to proceed with the construction of transplantable autologous epidermal sheets, in which the recombinant alpha-3 polypeptide was stably expressed at therapeutic level. JBE dogs therefore constitute a rele-



JBE dog keratinocytes (A) express a mutated lamin 5 that is not detectable in vitro. After transduction with a retroviral vector expressing the wild type alpha-3 polypeptide (B), the keratinocytes secrete a recombinant lamin 5 at levels comparable to those observed in normal dog keratinocytes in culture (C).

vant model for ongoing trial studies designed to validate genic therapy in an immunocompetent host. These results have also allowed systematic screening of healthy canine carriers and eradication of this disease in the German shorthaired pointer.

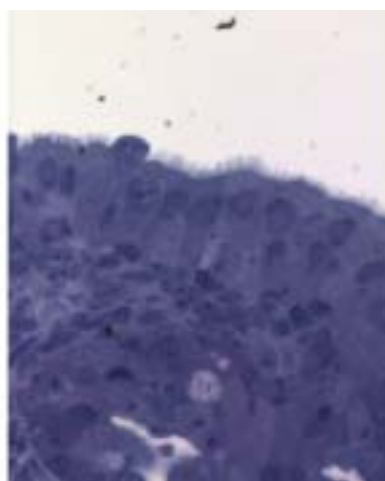
Capt A, Spirito F, Guaguere E, Spadafora A, Ortonne JP, Meneguzzi G, J. Invest. Dermatol. 2005, 124 (3) : 530-35.

Stem Cells and Epithelium Regeneration

Embryonic stem cells (ESC) are derived from the internal mass of the embryonic blastocyst. Their characteristics include being perpetually self-renewable and being pluripotent. The work of Inserm Unit 514 (Cellular and Molecular Dynamics of the Respiratory Mucosa) has demonstrated that induction by a matrix protein under given culture conditions could induce murine ES cells to differentiate into respiratory epithelial cells and reconstitute a

differentiated and functional respiratory epithelium in vitro. ES cells represent an unlimited source of material for tissue engineering of upper respiratory epithelium, an essential tissue that for the development of new therapeutic strategies, the screening of new pharmacological molecules and the evaluation of genic or cellular therapy efficiency.

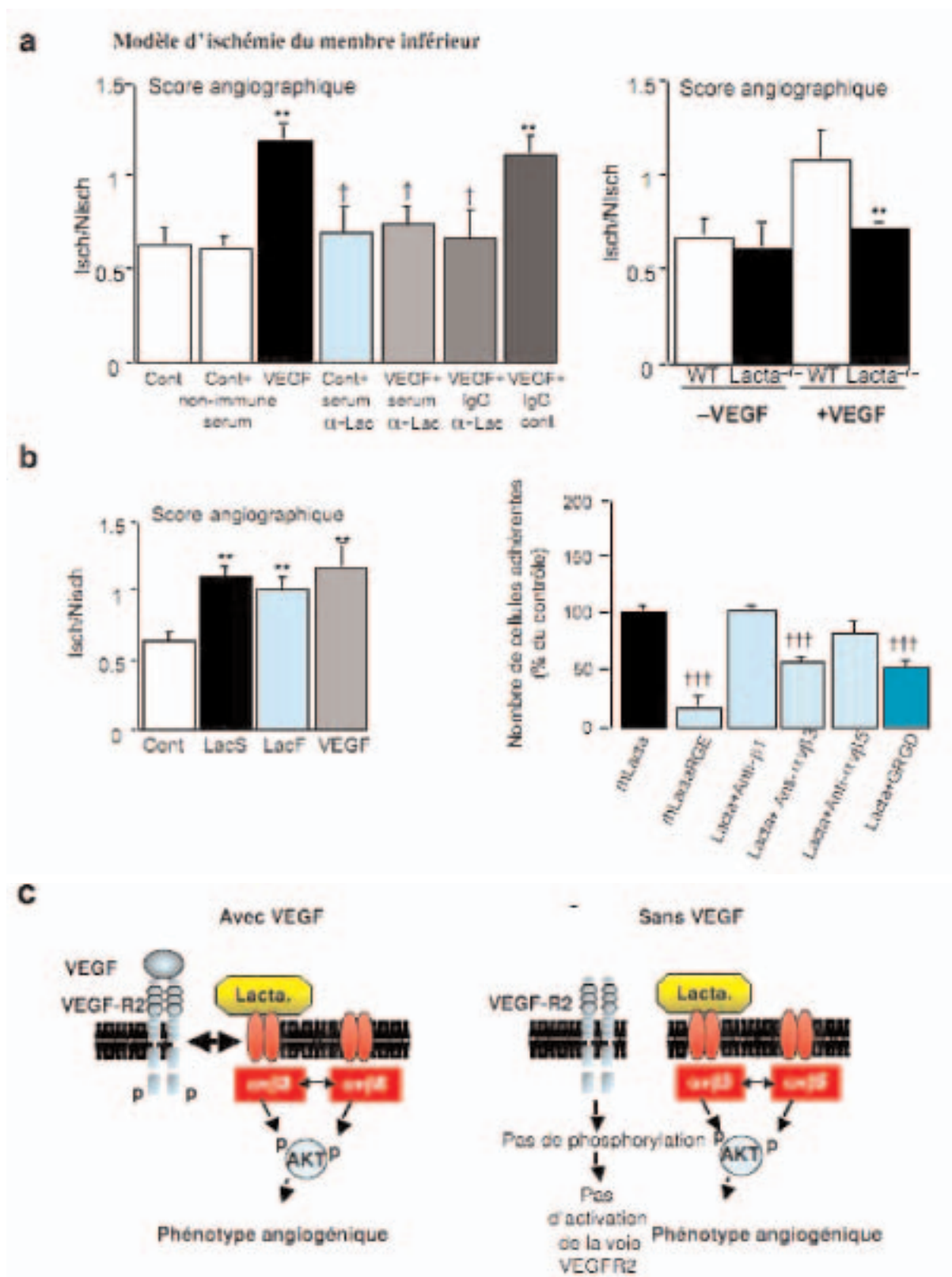
Coraux C, Nawrocki-Raby A, Hinnrasky J, Kileztky C, Gaillard D, Dani C, Puchelle E, Am. J. Resp. Cell Mol. Biol., 2005 ; 32 (2) : 87-92.



Respiratory epithelium from mouse trachea

Respiratory epithelium derived from murine ES cells

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a) Left: evaluation of vascular density, 21 days after ischemia, in the lower limb of mice treated with or without VEGF and a serum directed against lactadherin (α -lac serum), purified IgG directed against lactadherin (α -lac IgG) or control IgG (IgG cont, directed against the endothelial cell marker, thrombospondine-1). Right: evaluation of vascular density, 21 days after ischemia, in the lower limb of control (WT) or lactadherin-deficient mice (lacta^{-/-}) treated with or without VEGF.

b) evaluation of vascular density, 21 days after ischemia, in the lower limb of control mice treated with or without an empty plasmid (Cont) or a plasmid coding for the short form of lactadherin (Las S), the long form of lactadherin (Lac F) or VEGF (VEGF). ** p<0.01 versus control. Quantification of the number of human epithelial

cells (HUVEC) adhering to lactadherin (rhLacta) or a mutated form of lactadherin (rhLactaRGE) in the presence or absence of a neutralizing antibody directed against integrin β 1 (Lacta+Anti- β 1), integrin α v β 3 (Lacta+Anti- α v β 3), or integrin α v β 5 (Lacta+Anti- α v β 5), or in the presence of the GRGD peptide (Lacta+GRGD). P<0.001 versus rhLacta.

c) Diagram illustrating the mechanism of action of lactadherin. In the presence of VEGF, phosphorylation of its receptor, VEGF-R2, allows the formation of a VEGF-R2/lactadherin/integrin α v β 3 tri-molecular complex that initiates the angiogenic process. In the absence of VEGF, lactadherin is capable of initiating the development of new blood vessels by interacting directly with integrin α v β 3.

MISSIONS AND CHALLENGES

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AT THE HEART OF HEALTH AND SOCIETAL ISSUES

From the moment it was created, Inserm has been committed to working on the great scientific, health and social issues in biomedical and public health research. This mission requires constant adaptation to change in terms of scientific challenges, public health problems and society's expectations.



A Worldwide Demographical and Epidemiological Revolution

Over the past 50 years, life expectancy worldwide has increased by almost 20 years¹. In developing countries, this increase is due to the rapid fall in mortality linked to infectious diseases in children and young adults. In industrialized countries, this rise in life expectancy (2 to 3 months in France between 1990 and 2000) results from a decrease in mortality among the elderly. Hence the new concept of “healthy life expectancy”, recently introduced by the World Health Organization (WHO).

These important changes are accompanied by stagnation or a fall in the birth rate (particularly in developed countries), which has major consequences on world population ageing with a significant increase in the over-60 population. Projections of the French National Institute for Statistics and Economic Studies (Insee) predict that by 2040, one in three French people will be over 60. The repercussions in terms of morbidity are considerable due to the expected increase in the prevalence of chronic diseases linked

to age (cancers, cardiovascular and neurodegenerative diseases), incapacity and autonomy loss¹.

At the same time, infectious and parasitic diseases continue to be rampant around the world, with the emergence of new infectious agents, as health disparities increase between rich and poor countries.

Obesity, diabetes, or more generally “metabolic syndromes”, have become one of the most alarming public health issues. In the face of their galloping increase over the last few years, crucial questions arise about the link between our way of life and health, and particularly the impact of sedentarity and inappropriate diet.

Finally, the importance of diseases known as “rare” has now become obvious as one of today's public health issues. With 5,000 to 8,000 rare diseases and 4 to 6% of the population affected throughout the world, the pursuit of research and the development of biotherapies and new medications has become a necessity.

INSERM WAS CREATED TO ENSURE RESEARCH CONTINUITY

Inserm was born in 1964 from a need to reconcile research with clinical practice. This need was first recognized in the 1950s by a new generation of Paris public hospital physicians, such as Jean Bernard and Jean Hamburger: “We were convinced developing wide-ranging contacts between research and clinical practice was a necessity” (Jean Hamburger). The Debré hospital reforms of 1958 promoted such interaction by ensuring that the functions of care, teaching and research be carried out in one and the same place, i.e. the hospital. Inserm was thus created in order to develop close links between basic and clinical research, thereby hastening progress in both areas.

Since its creation, Inserm has been fulfilling its mission as a French organization fully dedicated to biological, medical and public health research, and studying all human diseases, whether common or rare. For nearly 40 years, Inserm has been at the heart of major scientific and medical advances. It has addressed existing public health issues and opened new and extraordinary perspectives in pathology by pursuing research in biochemistry, immunohematology, cellular and molecular biology, genetics, and new therapeutics.

¹ The mean life expectancy from birth has gone from 49.5 years in 1950-1955, to 65.2 years in 2002 worldwide (Source: World Health Report, WHO, 2003)

Environmental Impact on Health

The environment and its impact on health have become inescapable issues for public health, hence the necessity for prevention and health security programs concerning the environment.

Society's Changing Expectations

Society's expectations and concerns have changed dramatically and new ideas have

emerged, posing fundamental health challenges. Medical practice has had to adapt to such changes and is no longer a matter of merely treating disease. It must also contribute to the "quality of life" and "well-being" of patients. The redefinition of health by WHO reflects this: "Health is a state of complete mental, physical and social well-being, and not merely the absence of disease or infirmity". Psychiatry, psychopathology and mental health are particularly involved in meeting these expectations.

French people as a whole consider there is

insufficient management of substance abuse and risky behavior, obesity, pain, suicide, people in vulnerable situations or terminally ill patients².

Helping people to stay in good health and ensuring good quality of life, especially in old age, are today the major challenges for public health policy.

² Source: Credoc survey on "French people's life conditions and aspirations" at the beginning of 2003. The survey comprised a series of questions on the perception the French have of major health policy issues. These questions were added at the request of the Office General for Health.

INSERM ENSURES RESEARCH CONTINUITY

Inserm generates knowledge and promotes its transfer for the development of new means of prevention, diagnosis and treatment.



Promoting Innovation in Human Health

Inserm has developed a policy encouraging researchers and clinicians to transfer knowledge, thus promoting innovation in human health. Inserm has established a process based on quality assurance in its laboratories. This process covers everything from scientific monitoring and health expertise, to cognitive, clinical, diagnostic, therapeutic and public health research programs. It further extends to the development and promotion of institutional clinical research and the reinforcement of its knowledge management policy.

Developing Partnerships in France and Abroad

This policy is implemented on a national, European and international level. All Inserm partners are involved: responsible Ministries and institutional partners, hospitals, health and regulatory agencies, other

research organizations and universities, social protection agencies, foundations and associations, local authorities and the European Community, European and international laboratories, the pharmaceutical industry and the biotechnology sector.

THE EXPERTISE MISSION

Inserm plays a role as a key independent expert to inform public authorities and private decision makers (ministries, parliamentary offices, health insurance funds, associations, complementary health insurance funds, industry, etc.). Collective expert reports constitute a summary of scientific and medical knowledge for the benefit of researchers, health professional, students and a wider public.

Propositions emanating from such expert reports may guide decision-makers and help them define research, prevention and care undertakings.

Inserm is particularly keen on reinforcing its mission as an independent public health expert and has once more led a number of initiatives in this direction in 2005.

Collective Expert Reports

Collective expert reports were initiated in 1993 with the aim of assessing the status of international scientific and medical knowledge on a precise subject.

For each collective expert report, Inserm gathers a pluridisciplinary group of experts, made up of scientists (who may or may not be from Inserm) and physicians with international notoriety. The experts conduct a critical analysis of the international scientific literature on given pathologies and make propositions concerning research program development, prevention and management.

In 2005, Inserm published four collective expert reports:

- Suicide: psychological autopsy, a research tool for prevention (DGS)
- Cancer: a methodological approach to the link with the environment (AFSSET)
- Conduct disorders in children and adolescents (CANAM)
- Obesity: current status and evaluation of prevention and management programs (OPEPS)

INSERM ENSURES
RESEARCH CONTINUITY↑ [back to contents: click here](#)

Reinforcing Research, Knowledge Management and Expertise

This year, Inserm has again broadened its scope of action and developed further partnerships with hospitals, reinforcing the promotion of its clinical, therapeutic and health research. The Institute also pursued its efforts to improve knowledge

management and consolidate its role as an independent expert to assist in public health decision-making.

Inserm has succeeded in creating a genuine synergy between researchers, clinicians, institutions and partners of all kinds in order to meet society's expectations regarding new means of preventing, diagnosing and treating disease.

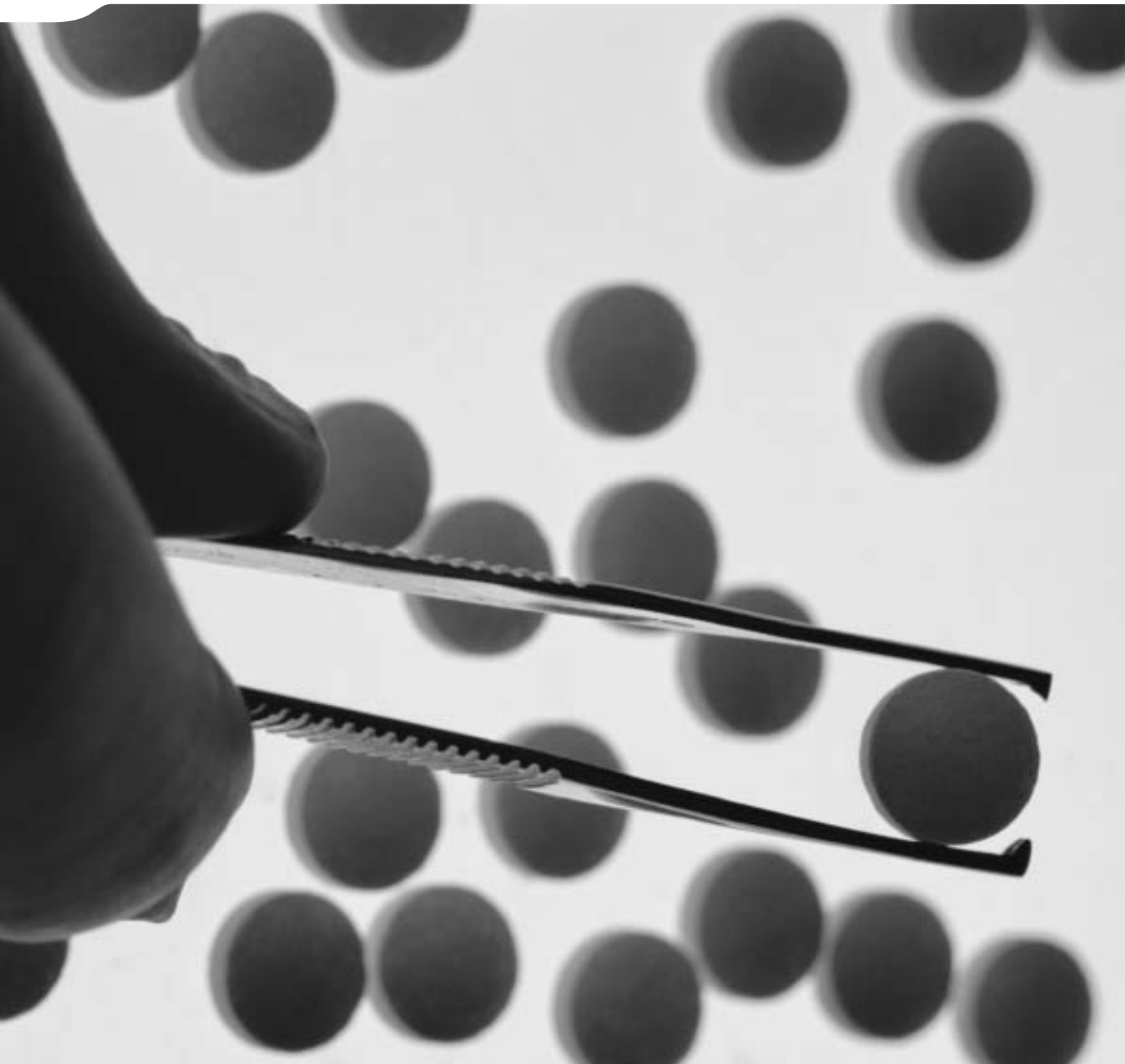
RESEARCH DEVELOPMENT STRATEGY

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ENSURING THE CONTINUUM FROM BASIC TO PUBLIC HEALTH RESEARCH

Inserm's mission is to mobilize all the players to ensure continuous and coherent transfer along the chain linking basic research innovations with public health applications.



Inserm is continuously engaged in transferring basic research results to medicine and public health. To achieve this, the Institute has developed a coherent strategy involving actions and programs that are coordinated along the transfer chain in collaboration with its partners. Upstream, Inserm develops activities of watch and expertise in science and public health. These activities allow Inserm and its research and health partners to draw conclusions and define the major basic and clinical research programs that need to be supported, developed and coordinated, such as the National Research Programs (NRP) and the Virtual Institute for Public Health Research (IVRSP).

Downstream, Inserm develops the promotion of solid clinical and public health institutional research. In parallel to this, the Institute sets up and supports life sciences and clinical research programs, and encourages the organization of research networks in order to ensure program continuity.

All along the transfer chain, Inserm relies on a knowledge management policy that has been reinforced by the growing know-how of its Technology Transfer Department and private subsidiary Inserm Transfert. Finally, Inserm has set up a quality control policy that is essential for running its projects in accordance with good laboratory

and clinical practice. This concerted strategy is itself anchored in a regional, national and European movement. At each stage, the Institute analyzes the situation and coordinates its actions with the help of all its regional, national and European partners in biomedical and health research: responsible ministries and other institutions, health and regulatory agencies, other research organizations, local and regional authorities, hospitals, universities, foundations and charities, cancer centers, patients associations, medical specialty societies, social protection agencies, the biotechnology and pharmacology sector, the European Commission and European laboratories.

THEMATIC RESEARCH: MAJOR PUBLIC HEALTH PROGRAMS

Through Concerted Thematic Actions (CTA), National Research Programs (NRP), the Virtual Institute for Public Health Research (IVRSP) or the preparation of the 7th FPRTD, Inserm impels a lasting research momentum to face and meet great public health challenges.



DEFINING RESEARCH OBJECTIVES

In order to establish priorities, Inserm relies on:

- Inserm's own collective expert reports;
- Inserm's scientific Council;
- Inserm's scientific commissions, each gathering 15 to 25 experts on specific research areas, who may or may not be affiliated with Inserm. Scientific commissions regularly uncover priority research areas to be developed in their particular fields of expertise;
- The public health law of 9 August 2004, which identifies 100 broad objectives and 5 strategic axes for public health policy in France.

- **Biotherapies:** to develop research potential in biotherapy and particularly stem cells, immunomonitoring, vaccinology, and cellular/genic therapies.
- **Alcohol:** to attract research teams with little involvement in this area to the field of alcohol and alcoholism.
- **Medication and vectorization:** to develop the drug research potential by ensuring a continuum between proof of concept and clinical use, especially for therapeutic screening, vectorization, drug delivery, pharmacogenetics and pharmacoepidemiology.

National Research Programs

National Research Programs (NRP) and the Virtual Institute for Public Health Research (IVRSP) were created on Inserm's initiative after Thematic Concerted Actions, which they prolong and broaden. They are long-term endeavors aiming to unite all the players involved in a particular research area. These programs gather all public and private research partners, research organizations, scientific and technological public institutions, industrial and commercial public institutions, universities, hospitals, health agencies, charities, foundations, medical specialty societies, social protection agencies, patients associations and industry.

Concerted Thematic Actions

Launched by Inserm in 2001, Concerted Thematic Actions (CTA) aim at bringing together scientists and clinical researchers working in priority public health areas in order to form networks of multi-disciplinary national and international teams.

Thanks to a flexible funding system and by launching calls for proposals, CTAs have allowed support for research projects in targeted areas over a period of three years. Three CTAs were continued in 2005:

SALIENT FEATURE

Response to Anticoagulants According to Patient Genotype

Response to medication varies widely from one individual to another both in terms of efficiency and side effects. This is the case for oral anti-vitamin K anticoagulants, commonly prescribed for the treatment of venous and arterial thromboembolism but responsible for a large number of accidents. The work of Inserm Unit 490, led by Philippe Beaune, has just shown that two genetic polymorphisms can explain alone 50 % of the variability in patient response to treatment. The genes are cytochrome P450 2C9 (CYP2C9), involved in liver metabolism of oral anticoagulants, and VKOCR1, the main target for anti-vitamin K agents. This discovery should lead to the development of a simple genetic test (genotyping) to predict the patient's response and thus limit the risk of overdose.

Bodin L. et al., Blood, 2005 ; 106 :135-40.

These programs, which are organized as networks, bring together basic, clinical, therapeutic and public health research in order to facilitate the transfer of innovation derived from basic research towards medical applications. NRP missions are to:

- define a scientific research policy that is coherent with European and international programs;
- facilitate interaction between specialist teams in the area of interest and researchers or clinicians from other specialties;
- define a training policy for young researchers.

Launch of Calls for Projects

The launch of call for projects concerns the entire scientific community, irrespective of institutional affiliation. Selective evaluation, conducted by a scientific council solely composed of international experts, offers all players in the area of interest (research institutions, industry, foundations, associations, etc.) the possibility of complementing funding for an existing project or supporting new projects that have not yet received funding.

National Research Program Operation (NRP)

National Research Program operation relies on a steering committee, a strategic planning committee, and a scientific council:

- **the strategic orientation committee** is a body open to all public or private partners (medical specialty societies, patients associations and industry) who wish to join the program. As a result, the number of members in the committee is variable.

In collaboration with the steering committee, this body defines the broad lines, and the research and training policy of the program. It organizes developmental actions, ensures the follow-up of funded projects and compiles the results of program activities.

- **The steering committee** is the body responsible for drawing up the program. It is composed of top-level researchers internationally recognized for their expertise in the field as scientists or clinicians. The steering committee members collectively determine the thematic research axes to be developed, submit the thematic axes and calls for projects to the strategic orientation committee, and select the college of international experts that constitutes the scientific council.
- **The scientific advisory** ensures independent and anonymous evaluation and selection of scientific projects submitted in response to the call for projects. It is mainly composed of international experts having recently published in high-impact journals.

The strategic orientation committee is in charge of making contacts to conclude agreements with industrial partners, local authorities, specialized medical societies and patients associations for the partial or total funding of priority projects according to the college of experts. Thus the policy-making, incentive and evaluation structures Inserm has set up allow better research coordination and funding in a given field.

National Research Programs have acquired an international dimension through the development of a partnership policy with

major research organizations abroad and in particular the National Institutes of Health in the United States.

In 2005, the Five National Research Programs (NRP) involved:

- support actions for young researchers;
- partnership missions with specialized medical societies and patients associations;
- international events such as the December 2004 meeting with the National Institute of Arthritis and Musculoskeletal and Skin diseases (NIAMS) and the National Institutes of Heart Lung and Blood (NHLB). Seminars were also organized in November 2005 with the National Research Program on Bone and Joint Diseases (NRPBJD) and NIAMS.

Each NRP focuses on a specific area of public health:

- Cardiovascular Diseases (NRPCD);
- Diabetes (NRPD), in partnership with the CNRS;
- Bone and Joint Diseases (NRPBJD);
- Human Nutrition (NRPHN), in partnership with INRA; this program relays the TCA on nutrition;
- The Virtual Institute for Public Health Research (IVRSP).

2005 saw the launch of the NRP on Sensory Organs and three new NRPs are being organized for 2006: Dermatology, Endocrinology and Reproduction, and Hepatogastroenterology.

NRP Partnerships

In 2005, the NRPD benefited from a partnership with the Association for Research on Diabetes (ARD), which allowed sup-

port of 7 young-researcher projects for a total budget of 140 k€. As part of the NRPCD, a project selected from a list outside the 2004 call for projects received financial support from AstraZeneca.

The Virtual Institute for Public Health Research (IVRSP)

Setting up a public health policy requires a research policy in the field of interest. Methodology development and specific research therefore need to accompany the implementation and follow-up of such a policy. The creation of the Virtual Institute for Public Health Research (IVRSP) sprang from a desire on the part of institutions to develop and promote public health research by building a flexible partnership respecting the autonomy of all partners. Eighteen partners gathered around a convention, with a view to constitute a scientific community of international size capable of meeting the developmental needs of public health research and contributing to the implementation of the aims stated by law.

In order to attain this objective, IVRSP wishes to promote an efficient cooperation between research teams gathered within a flexible national structure organized into regional research poles, and the various national and local players involved in public health or public health training.

Action and Organization of IVRSP:

Calls for Cohort Projects in 2005

Their objective is to define a strategy allowing a better coordination of means.

The call for projects launched by Inserm in November 2003 in collaboration with a large number of partners aimed at evaluating the number of existing or planned cohorts. This program was the first action IVRSP partners undertook.

In 2005, three cohorts were supported with a total of 200 k€:

- EDEN (Health Determinants and Development in Children);
- Suvimax (nutritional supplements);
- SIRS (public health, sociology).

Funds were allocated to help set up the new cohort, ELFE.

A steering committee laid the foundations of the Institute, drew up the convention, and designated the members of the strategic orientation committee (SOC), which relayed the steering committee.

The SOC, comprising representatives of national and regional partners, defines the budget, strategies, general policy and annual programs.

The scientific advisory board, comprising a president and 10 members, half of whom are from abroad, evaluates and expresses opinions on the broad lines of action of the Institute. It met for the first time in May 2005.

In June 2005, IVRSP launched its first call for projects on the subject of health social inequalities. Among IVRSP's 18 partners, the DREES¹, Inserm, the DGS² and InVS³ contributed to the funding of the program. The National Cancer Institute also contributed, thus anticipating its future participation in IVRSP. Among the 33 projects received, 12 were selected for funding with a total of 787 k€.

Creation of the NRA⁴ Public Interest Group

The creation of the NRA PIG in February 2005 and the launch of thematic and non-thematic programs have brought very substantial financial support for laboratories, particularly in biology. Owing to the launch of the Cardiovascular Diseases, Obesity, Diabetes NRA program in 2005, NRPs involved in these research fields (NRPCD and NRPD) did not launch calls for projects in 2005.

The Inserm-NRA Cell

Inserm is responsible for managing the calls for projects of four NRA programs. The Inserm-NRA cell was set up in 2005 to ensure the scientific, administrative and financial management of the following four NRA programs:

- Cardiovascular Diseases, Obesity and Diabetes,
- Neurosciences, Neurology and Psychiatry,
- Microbiology and Immunology,
- Rare Diseases.

After launching calls for projects, the scientific and administrative management of programs consists in collecting project proposals, organizing and following their scientific evaluation (by NRA evaluation committee members, on the one hand, and international experts on the other hand). This management in 2005 was the responsibility of the Department of Strategies and Scientific Partnering. Financial management was entrusted to the Department of Finance and Logistics.

¹ General Office for Research, Studies, Evaluation and Statistics

² General Office for Health

³ Health Monitoring Institute

⁴ National Research Agency

EPM: Electronic Management of Calls for Projects

In order to manage NRA's Biology and Health programs, Inserm has developed an online database for the management of calls for projects. This tool covers the various phases of the calls for proposals, from receipt of submissions to response to applicants after evaluation. The tool comprises secured extranet functions and access, specific to the various players involved (candidates, experts, scientific council).

In 2005, EPM served to manage three calls for projects (600 proposals, 900 expert evaluations):

- Cardiovascular Diseases, Obesity and Diabetes,
- Neurosciences, Neurology and Psychiatry,
- Microbiology and Immunology.

RESEARCH FACILITIES

The French Ministry of Research is supporting a joint endeavor by French research organizations (Inserm, CNRS, INRA and CEA) and universities designed to evaluate the current state of research facilities in France. The aim of this program is to maximize the use of resources by improving their visibility and providing targeted support so as to meet the needs of the scientific community. These facilities have been classified on the basis of six broad themes.



The National Network

A charter drawn up in 2002 defines common platform operation criteria (overture to the scientific community, management of service cost, quality control, knowledge management, technological monitoring, training). In 2003, the census report based on the criteria announced in the charter helped identify 85 platforms and 3 national banks of biological material. Based on this census, platforms were classified into three levels:

- national platforms, which are high-technology centers of national and international recognition, equipped and staffed to manage high throughput work or possessing highly specialized equipment;
- platforms of a more modest size with a regionally based influence;
- site technical platforms open to the local scientific community (FRI¹).

Efforts on the part of research organizations are closely coordinated with the national network of genopoles, the national sequencing center and the national center for genotyping as part of the national genomic research Consortium, presided by Inserm's Director General until January 2006. Over the last few years, networks of

platforms with similar or complementary interests have been set up in order to become more competitive on a European and international level. National networks were created, in particular for transcriptome research, bioinformatics, cellular imagery, small animal imagery, and, in 2005, transgenesis centers. The organization of transgenesis centers into networks aims at facilitating exchanges of mutant mice between the various centers. This requires setting up health statutes defined by guidelines, choosing software for animal house management allowing the rapid exchange of information, localization of animals and recording of transfer conditions. Such networks allow coordination of the potential available. They facilitate interacademic collaboration and, above all, partnerships with industry.

Setting up quality control procedure is essential to define the operational mode for the various platforms and to harmonize the offer of services and partnerships between academic institutions and other institutions or industry.

In 2004 and 2005, research organizations and the national genopole network supported the setting up of the quality control policy. Thanks to funding by the National Consortium for Genomic Research, a person was recruited to coordinate the quality

control process at the national level. Inserm and CNRS organize training sessions every year and tailored assistance has been provided for around ten platforms.

Research organizations are also pursuing their efforts to recruit engineers and technicians every year and ensure the good operation of these platforms. From 2003 to 2005, 155 positions were created across 63 platforms.

The visibility and coordinated operation of such shared facilities represent an advantage for the implementation of national research programs launched by the NRA.

The High-Security Jean-Mérieux Laboratory

Since 2004, Inserm has taken over the use of the P4 Jean Mérieux high-security laboratory based in Lyon. Its mission includes the conservation and study of high-risk emerging and bioterrorism agents. In 2005, the laboratory was subject to a periodic major maintenance service to ensure full availability in case of requisitioning by public authorities.

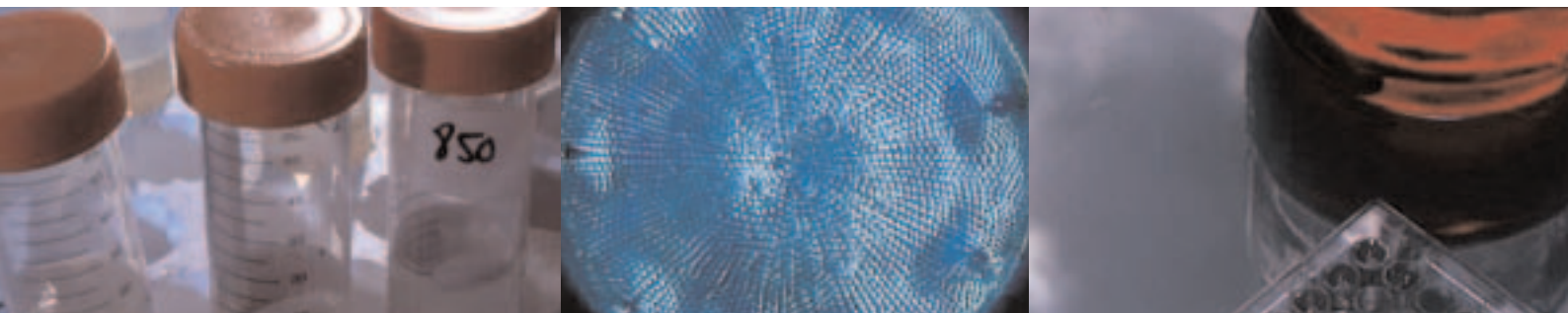
The Institute's take over of the P4 facility was part of a scheme to reinforce research on infectious and, particularly, emerging diseases at Inserm and on a national level.

¹ Federative Research Institutes

Inserm has redefined the management of the P4 laboratory by setting up a scientific council to evaluate all projects systematically. These developments are part of an overall determination to reinforce the activities of the P4 facility on a national, European and international level. In this context, Inserm has conducted several missions, particularly in Asia, to transfer its know-how to countries wishing to build similar facilities.

BROAD AIMS OF THE 7TH FPRTD

A new aid policy for research facilities is being set up through the 7th FPRTD. European support for very large facilities in the physical sciences and engineering has existed for a long time whereas aid for life sciences facilities has been lagging very far behind. One of the objectives of the next FPRTD is to remedy this situation by setting up a support strategy for leading-edge biological and medical technology facilities open to the European scientific community.



The action lead in France since 2001, as part of the RIO (inter-organization support program) was very important in allowing the mapping of technical and research platforms. Identification of research platforms by the census analyses conducted in 2001 and 2003, and the setting of charter criteria have allowed competitive national facilities and platform networks to become visible at the European level.

Several actions were initiated in 2005, many of them by Inserm, in order to convince the European Commission to support facilities, particularly in the field of life sciences. These initiatives include:

- the organization of a coordination and discussion meeting on existing and emerging facilities, held in Paris in January on the initiative of Inserm and EMBL¹. The third European conference on research facilities was held in Nottingham;
- a survey led by the European Commission in January was designed to identify facilities meeting the criteria to be open to the national and European scientific community; this survey allowed the selection of 24 existing life sciences European facilities in France, 20

of which have been identified as national or regional interorganization coordination RIO platforms;

- the preparation of the 7th FPRTD and its specific program on “Capacities”.

The idea of setting up a common support policy for large facilities emerged at the Strasbourg Conference in September 2000. From this sprang the work group, ESFRI (European Strategy Forum on Research Infrastructures), which gathers two representatives of each Member State and one representative of associate members. Its mission is to define axes of general interest for the development of existing facilities and structures to be created in the next 10 to 15 years.

In order to make strategy propositions for the 7th FPRTD, ESFRI subgroups were set up in three areas:

- physical sciences and engineering (led by Carlo Rizzuto),
- biological and medical sciences (led by Ruth Barrington),
- human and social sciences (led by Bjorn Henrichsen).

This year saw the development of a support strategy for the various types of facilities. The four RIO organizations (Inserm, CNRS, INRA and CEA) drew up a list of thematic propositions in collaboration

with the Ministry of research and submitted it to ESFRI. Seven life sciences axes were selected for the 7th FPRTD:

- advanced facility for cerebral and whole body imagery,
- bioinformatics facility for Europe,
- European network of leading-edge clinical research centers,
- network of biobanks and genomic resource centers,
- high-security laboratory for new diseases and public health threats,
- facility for the functional analysis of complete mammalian genomes,
- model experiment facilities for biomedical research.

Groups of European scientific experts in various areas (genomics, clinical research, biodiversity and the environment) were set up to define needs more precisely within each research area and develop thinking so as to develop a medium and long-term strategy.

¹ European Molecular Biology Laboratory

CLINICAL RESEARCH

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CREATION OF THE CLINICAL AND THERAPEUTIC RESEARCH DEPARTMENT

Created by decision of the Director General in May 2005 and directed by Eric Postaire, the Department of Clinical and Therapeutic Research (DCTR) is dedicated to the following missions: clinical research, clinical and therapeutic research platforms, therapeutic innovation and promotion of clinical research.



Clinical Research

The Clinical and Therapeutic Research Department (DCTR) drives the Committee for Strategic Planning and Clinical Trial Monitoring (Cossec), whose experts are responsible for evaluating and monitoring translational research projects and clinical research programs. The committee ensures a continuum between research results, experimental validation of target molecules (proof of concept) and setting up of clinical trials (mainly phase I, phase II, and medicoepidemiological follow-up) for the projects selected.

Clinical and Therapeutic Research Platforms

The DCTR is in charge of operational follow-up for the following clinical research facilities/activities:

- clinical research centers (CRC), i.e. 23 CRC-P (plurithematic CRCs), 7 CRC-EC (epidemiological and clinical CRCs) and 11 CRC-BT (biotherapy CRCs),
- biological collections,
- clinical research networks,
- clinical and epidemiological investigations (cohorts),
- clinical trial registers,
- the Concerted Thematic Action on medication: setting up a platform and networks in pharmacogenetics.

Therapeutic Innovation

Focus on biotherapies

The Biotherapy CTA is currently focusing on supporting research programs working as a network on the subject of stem cells.

Cellular Therapy and Stem Cells

Remarkable progress has been made over the last few years for isolating and characterizing stem cells from many animal species, including primates, and demonstrating their therapeutic potential.

Ambitions in this area are manifold: identifying new markers for the precise evalua-

tion of in vitro cell line potential, improving techniques for the isolation of human embryonic stem cells (ES cells) from surplus embryos, improving stem cell amplification techniques in vitro, developing controlled systems of precursor cell differentiation into specific tissues, reducing stem cell immunogenicity, controlling in vivo migration of injected stem cells, and using human and animal ES cells with a genome defect causing a congenital deficiency to look for therapeutic molecules by large-scale screening of chemical and target banks.

I-Stem

Since January 2005, the French Association against Myopathies (AFM) has been supporting a Stem Cell Institute research program, led by Marc Peschanski, for the treatment and study of monogenic diseases. The program aims to carry out research on embryonic stem cells. The I-Stem project will initially focus on Huntington's disease, Duchenne muscular dystrophy and Steinert myotonic dystrophy.

Marc Peschanski has been entrusted with validating the following two concepts within a period of two years: the use of human embryonic stem cells in cellular therapy and the study of pathological ES cell lines by high throughput screening. This will allow modelization of monogenic disease pathology in order to identify signals linked to mutations in the cells of patients.

To achieve this, Marc Peschanski and his team aim to:

- import and create biological resources, including stem cell lines carrying mutations,
- set up technological resources,
- ensure recruitment and training of scientific personnel,
- establish necessary scientific and technical partnerships,
- define agreements required for integrating public and private contributions to I-Stem.

The Minister of Health and the Delegate Research Minister signed three rulings on 15 February 2005, authorizing 3 teams of biologists from Inserm, CNRS and the University Hospital (CHU¹) in Montpellier to

The ad-hoc committee for ES cell research

Since September 2004, 40 authorizations have been delivered by the ministers in charge of research and health thanks to a temporary procedure introduced by the law on bioethics. This procedure only concerns research bearing on ES cells created abroad. Such authorizations, delivered after consultation with an ad-hoc committee, have allowed a dozen teams to begin research on stem cell lines created abroad. Recommendation is based on an evaluation of the scientific relevance of the research protocol and its potential for public health. It also takes into account the facilities, equipment, materials, procedures and teams involved in the project proposal. In 2006, the Biomedicine Agency will take over from the ad-hoc committee and ensure follow-up of the protocols authorized by the committee.

The International Stem Cell Forum (ISCF)

This forum, created 4 years ago, aims at promoting good stem cell research practices. The 19 member organizations originating from 17 countries work jointly to promote the following principles:

- clarifying ethical issues and, if possible, harmonizing international ethical norms,
- sharing available stem cell lines,
- accepting universal norms for the characterization and registration of stem cells.

import human ES cells for research purposes. According to the rulings, the authorizations, pertaining to research protocols only and permitting stem cell conservation for a maximum of 5 years only, specifically concern:

- Marc Peschanski – Inserm Unit 421 - I-Stem
- Bernard Klein – Inserm Unit 475 - IRB Montpellier
- Jacques Hatzfeld, Anne-Lise Bennaceur-Griscelli, William Vainchenker – Inserm Unit 362 CNRS – Institut André Lwoff
- Daniel Aberdam – Inserm Unit 634
- Pierre Savatier – Inserm Unit 371
- Edith Puchelle – Inserm Unit 514
- Anne Weber – Inserm EMI 00-20
- Patrick Maurel – Inserm Unit 632 - IFR 122.

International Stem Cell Forum

Inserm has welcome the “board” and ethical work group of this informal body. In addition, the DCTR organized a scientific seminar entitled Stem Cell Research in France: Progress and Objectives from Basic to Translational Research. This seminar presented the main basic research advances that have been transferred to clinical applications in France. The seminar was directed towards the scientific community, Stem Cell Forum international representatives and responsible ministries.

Genic Therapy

It is worth remembering that in 2000, an Inserm team was responsible for the first successful use worldwide of human genic therapy to treat severe combined immunodeficiency. Following the observation of leukemia side effects in two of the children treated, the trial was suspended in 2002.

After elucidating the reason for this complication, due to a problem of retroviral vector insertion, the trial was resumed in May 2004 using a modified protocol. However, a third case showing complications lead to a further suspension of the trial in 2005. However, the results of the trial, which included 16 patients, demonstrated the efficiency of the method. Indeed, immune system correction was obtained in 15 patients and was still present after 6 years. At present, the challenge is to reduce the toxicity linked to the vector, and in particular the risks of developing tumors due to uncontrolled vector insertion in the human genome.

Various avenues are being investigated, including the modification of viral vectors and the development of non-viral vectors (plasmid or synthetic vectors).

In addition, several Inserm teams have obtained very encouraging genic therapy results in different models of neuromuscular (spinal amyotrophy), demyelinating neurological (adrenoleucodystrophy), and autoimmune pathologies or in degenerative eye disorders.

Clinical Research

The clinical research mission ensures proper operation and monitoring of administrative steps necessary for the promotion, implementation and follow-up of clinical trials. The mission for data processing and liberties is responsible for the administrative management of authorization proposals and modification notifications to the National Data Processing and Liberties Commission (CNIL²).

¹ Centre hospitalier universitaire

² Commission nationale informatique et libertés

SALIENT FEATURE

Habib Boukerche and Biotherapy

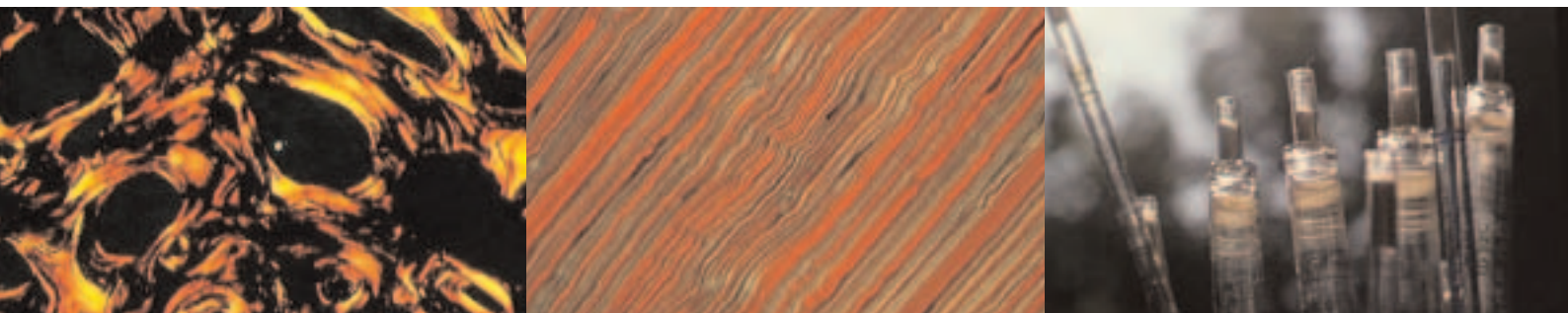
Preventing the propagation of tumor cells in the blood and the occurrence of metastases remains a major challenge in the treatment of cancer. Using a rapid subtractive hybridization technique and a pertinent model for the study of spontaneous melanoma metastasis, Habib Boukerche from Inserm Unit 590, in collaboration with Columbia University in New York and the Hôtel-Dieu Dermatology Department in Lyon, has found that the syntenin gene plays an essential role in the development of metastases. Through their remarkable localization at adhesion focal points and their PDZ domains, syntenins play a role in the regulation of cytoskeleton dynamics and organization in cell motility, which involves the c-Jun N-terminal MAP kinases (JNK) and p38. By transplanting melanoma tumor cells expressing the syntenin antisense gene into newborn rats using a recombinant adenovirus, the research team was able to induce regression of pulmonary metastases. This study demonstrates the prometastatic role of syntenin, which could become a new target for therapeutic strategies in the treatment of cancer.

At the end of 2005, there were 126 ongoing clinical trial projects. Items processed in the course of 2005 included:

- 43 in-principle agreements promoted by Inserm,
- 28 initial declarations of intent,
- 69 ancillary declarations of intent.

SUPPORT FOR CLINICAL RESEARCH FACILITIES

Since 1992, the mission of Clinical Research Centers (CRCs) has been to develop exchanges between Inserm laboratories and hospital departments. Located inside hospital facilities and created jointly by Inserm and the DHOS¹ at the Ministry of Health, they are Inserm structures designed to work in collaboration with university hospitals and in some cases, universities.



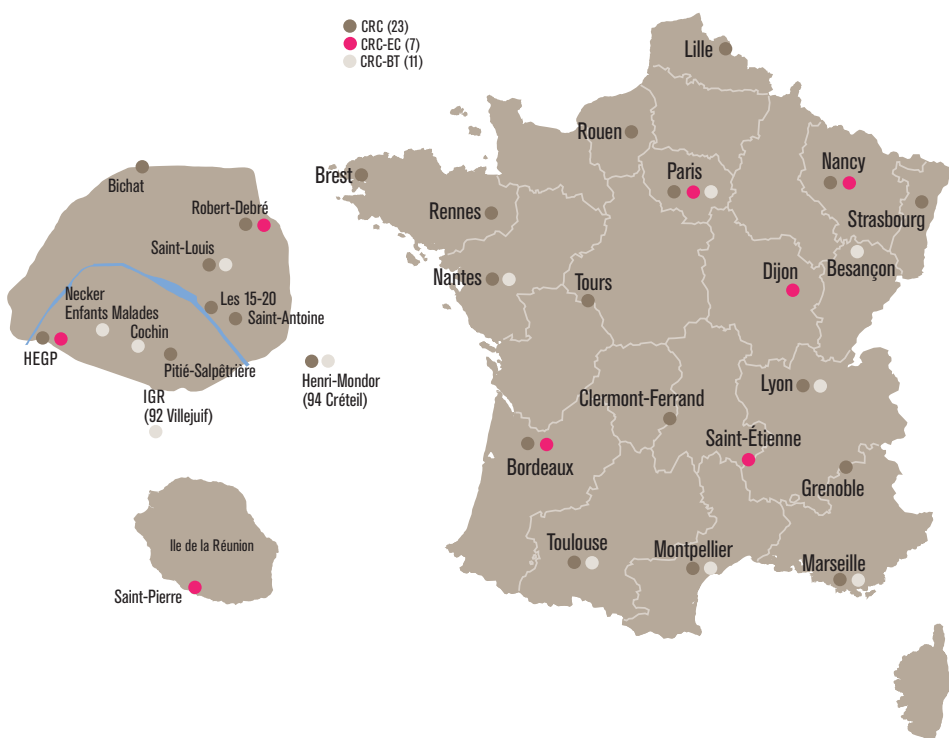
CRCs are entirely dedicated to the implementation of clinical, pathophysiological, epidemiological, diagnostic or therapeutic studies. The studies go from proof of concept (to validate in man new potential therapeutic targets or therapies emanating from upstream preclinical research in animals) through to early therapeutic phase or even post-marketing studies. Their dual mission is to promote transfer of basic research towards diagnostic and therapeutic applications and participate in medication policy in France. They are situated in university hospitals, where they may have several beds available for research (for outpatient investigations or day/night hospitalizations). CRCs welcome investigators wishing to conduct institutional or industrial research projects.

In partnership with the Ministry of Health (DHOS), Inserm has pursued its policy of clinical research support by launching a new call for projects for the creation of integrated biotherapy CRCs (CRC-BT) at the end of 2003. Inserm received 15 CRC-BT project proposals, which led, after scientific evaluation, to the creation of 11 CRC-BTs.

CRCs in 2005

There are now 41 CRCs (see their national distribution in the adjoining map), 23 of which are plurithematic (CRC-P), 7 are for clinical epidemiology/clinical trials (CRC-EC), i.e. units helping with clinical epidemiology and clinical trial methodology, and 11 are dedicated to biotherapy (CRC-BT). CRCs provide a pool of 120 hospital beds and over 300 professionals dedicated to clinical research (physicians, pharmacists, biostatisticians, nurses, nursing assistants, clinical research assistants and technicians).

On Inserm's initiative and in collaboration with university hospitals, CRCs have been organized into 6 broad research networks: cardiovascular diseases-diabetes, metabolism and gastroenterology, hepatology-neurosciences, mental diseases, thrombosis, and pediatrics. The aim is to reinforce inter-CRC collaboration around research projects in strategic areas for Inserm, maximize the efficiency of geographically distant facilities and improve their visibility on a national and international level.



Specialty area of studies conducted in 2005 (%)

Heart and blood circulation	21
Brain and nervous system	19
Cancer	12
Digestive tract and liver	8
Diabetes and metabolic diseases	6
Lung and respiration	5
Infectious and parasitic diseases	4
Mental health / Psychiatry	4
Hematology	4
Kidney and urinary tract	3
Nutrition / Obesity	3
Bones and joints	2
Endocrinology	2
Muscles	2
Sensory organs	2
Other (skin, handicap, odontology)	3

The support CRCs have received and their individual organization have led to an

Distribution of studies led in 2005 (%)

Pediatrics	13
Ageing and geriatrics	4
Women's health	3
Rare and/or genetic diseases	17

ECRIN (European Clinical Research Infrastructures Network)

ECRIN is a network of Inserm-coordinated facilities currently covering 6 European countries (Sweden, Denmark, Germany, Italy, Spain and France), with contracts reaching beyond the European Union. With a view to spread further a field, ECRIN is currently promoting the creation of national networks in Europe. ECRIN aims to interconnect national networks of clinical research centers in Europe in order to:

- harmonize procedures, tools and practices as well as develop the quality of clinical research,
- play a supporting role for academic or institutional promoters for conducting multinational studies in Europe,
- stimulate the articulation of specialized networks across borders in order to create a genuine European clinical research arena.

ECRIN was launched in 2004 thanks to funding from the European Union (6th FPRTD) and a Reciprocal Knowledge Program (RKP). ECRIN is now going through its second phase, with the setting up of transnational work groups to establish the foundations of a harmonized high-quality network. Its first efforts bear on ethics, regulations and the management of side effects, data management, monitoring and quality control.

From 2007-2008 onwards, ECRIN will be in a position to rely on the production of its work groups in order to propose services that facilitate multinational academic studies in Europe. ECRIN is also organizing a joint debate on clinical research in Europe - and beyond with the collaboration of WHO - with patients, patients associations, public promoters, industry, and investigators (International clinical trial day on 20 May).

Demotes-Mainard J., Ohmann C., European clinical research infrastructures network : Promoting harmonisation and quality in European clinical research, Lancet, 2005, 365, 107-108.

increase in the number of research protocols promoted by hospitals and Inserm. In 2005, ongoing CRC projects total almost 770 research protocols, more than one third of which involve physiology-pathophysiology and genetic studies. The subject matter of the studies conducted in 2005 is presented in the adjoining table.

This network naturally plays a role in the ambitious project of creating a European research area. Inserm is providing active support to allow the CRC network to participate, along with its European partners and in close collaboration with the French

network of clinical trial units, in the ECRIN project coordinated by Jacques Demotes.

Last year's experience was reconducted with the organization of another annual seminar in April 2005 in Bordeaux. The presentations bore on CRC thematic networks, their implication in translational research, and their relationship with National Research Programs and interface committees. The ECRIN project and clinical research facilities were also discussed as were the role of research in the hospital reform, the presentation of inter-CRC pro-

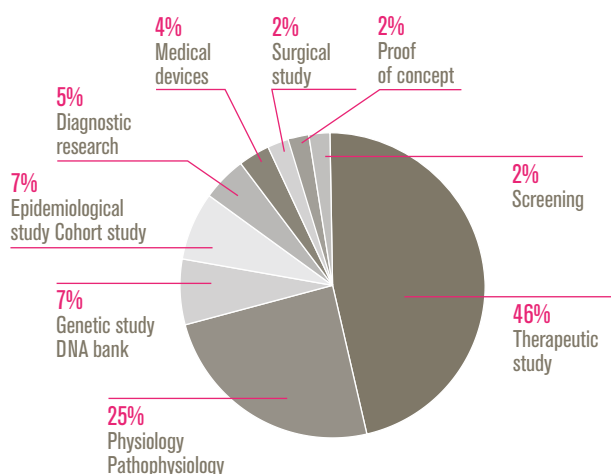
11 CRC-BTs received accreditation in 2005

CRC-BT	Coordinating physicians	Affiliation
Saint-Louis	Marc Benbunan	IUH-IFR105
Necker-Enfants malades	Marina Cavazzana-Calvo	Inserm Unit 429 and 768
Nantes	Brigitte Dreno	Inserm Unit 601
Mondor-Créteil	Marc Peschanski	Inserm Unit 421
Cochin	Odile Launay	Inserm Unit 567
Besançon	Jean-Marc Chalopin	Inserm Unit 645
IGR / Curie	Olivier Lantz	Inserm Unit 653
Lyon	Gilles Salles	Lyon Hospital Center (JE 2267)
Montpellier	Bernard Klein	Inserm Unit 475
Marseille	Christian Chabannon	Inserm Unit 59
Toulouse	Louis Buscail	Inserm Unit 531

ocols and the various results of discussion groups.

Integrated biotherapy clinical research centers (CRC-BTs)

On the joint initiative of Inserm and the DHOS, in collaboration with the French Blood Institute (EFS), the Biomedicine Agency and the French Association against Myopathies (AFM), a call for proposals to create integrated biotherapy CRCs was launched in 2003. The 17 proposals submitted were studied and scientifically evaluated with the help of 4 international experts, leading to the accreditation of 11 sites in 2005 (5 in the Paris region and 6 in other French regions), some of which were grafted onto existing CRC structures.



BIOLOGICAL COLLECTIONS AND CENTERS OF BIOLOGICAL RESOURCES

High throughput technologies can produce large quantities of data the quality and relevance of which depend on the biological material analyzed and related information.



Recorded human biological samples and derived products (nucleic acids, proteins, antibodies) are essential for quality research. They allow identification and validation of therapeutic targets, proposal of candidate medications and identification of biomarkers that are crucial from upstream research through to validation of targets in the preclinical and clinical phase. Ensuring quality during the process of collecting, transforming, preserving and accessing biological samples is a major challenge from the scientific, economic and ethical point of view. This has motivated the creation of a network of human biological resource centers.

Since 2001, Inserm has been engaged in an active policy of identification, support and promotion of human biological sample collections. In coordination with the ministerial Office General for Technology (Bioengineering Department), Inserm launched three calls for proposals in 2001, 2002, and 2003 with an equally shared funding of 5.6 M€. Forty-seven projects were accepted on the criteria of scientific excellence and quality control. In 2005, Inserm acted as supporting institution for the NRA (National Research Agency) call for projects for the certification of collections and Biological Resource Centers (BRCs). The aim is to facilitate upgrading

of collections associated with validated research projects, and to integrate them within future BRCs meeting the international quality guidelines proposed by the OECD work group.

BRCs are also strongly implicated in the university-hospital environment, in synergy with the 41 clinical research centers focusing on clinical epidemiology and multicentered clinical trials, with cohorts, and with registers.

Inserm is endowed with a steering committee for human biological resources whose mission is to:

- evaluate projects
 - organize events linked to the French network of human biological collections (seminars, training, work groups);
 - develop a European network;
 - contribute to drawing up specifications for future European BRCs: harmonizing procedures and practices, setting quality control guidelines, writing supporting documents;
 - assist with future collection certifications.
- Inserm's action in this domain works in synergy with the recognition of tumor banks in cancer poles.

Inserm has recently participated in setting

up procedures that have considerably clarified the path to follow in order to use human biological samples for research purposes. The Institute also took part in drawing up the application decrees related to the law on public health policy.

- **Ethical framework:** the international declaration of 8 October 2003 on human genetic data complements the Declaration on the human genome adopted by the United Nations in 1998. It defines the conditions of access to biological collections according to universal principles relative to the protection of the individual and the sharing of benefits.

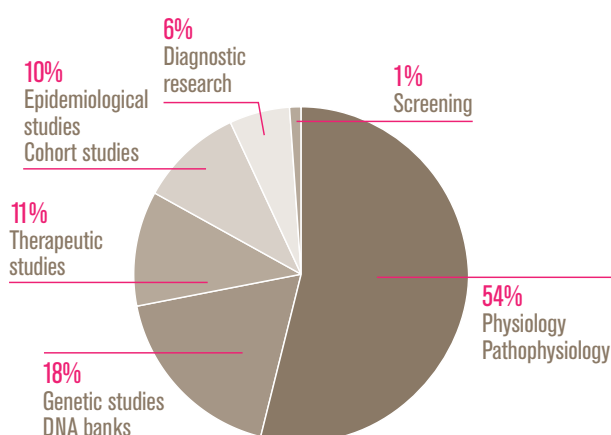
- **Technical framework:** the OECD work group, presided by an Inserm department director, has defined the criteria for the constitution of BRCs that possess, validate and distribute biological collections. A set of guidelines on quality control, traceability, security, and access to resources is available for writing up the standard requirements for BRC recognition at State level and thus build an international system of exchange of biological samples.

- **Regulatory framework:** the French Public Health Code (modified by Law n°2002-303 of 4 March 2002 on the rights of patients, Law n°2004-800 of 6 August 2004 relative to bioethics and Law n°2004-806 of 9 August 2004 on public health policy) fixes the rules that regulate collection activities,

and preservation and distribution of human biological samples. The Law n°78-17 relative to data processing and liberties (modified by Law n°2004-801 of 6 August 2004) defines the modalities for processing personal data in order to ensure the protection of the individuals concerned.

INSERM AS AN INSTITUTIONAL PROMOTER

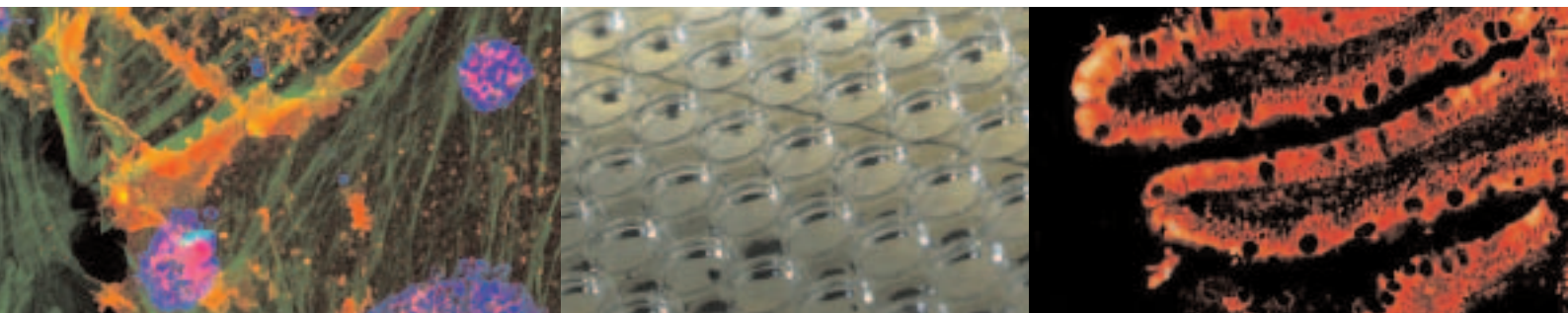
In 2005, Inserm's activity to promote clinical research was complementary to the clinical research efforts of hospitals and the therapeutic trials conducted by industry. The specific objectives of the Institute in this area remain to run early-phase clinical trials in order to validate new therapeutic targets.



Inserm has pursued its institutional promoter activity in favor of Inserm researchers, particularly in the context of CRCs. In 2005, Inserm focused more specifically on the promotion of physiology and pathophysiology studies (54%) and genetic studies (18%).

THE STRATEGIC PLANNING AND CLINICAL TRIAL MONITORING COMMITTEE (COSSEC)

Inserm plays an essential role in clinical research in France, along with hospitals and industry. The Institute provides momentum to institutional clinical research by funding research conducted within hospitals as well as organizing the research apparatus.



With a view to increase the efficiency and speed of project management, Inserm set up in 2005 a preselection work group comprising 5 members who meet on a weekly basis. Their role consists in examining biomedical research projects as soon as they are submitted to Inserm and by-pass the Cossec committee when projects have already reached a high level of maturation. This fast-track procedure presents a dual advantage: it relieves the workload of thematic Cossec committees and accelerates trial procedure, thereby reducing the time required to set them up.

The Cossec offers project applicants an integrated management of the entire procedure necessary for the development of a discovery through to preclinical validation, initial clinical trials and post-marketing studies.

The Cossec's mission is to:

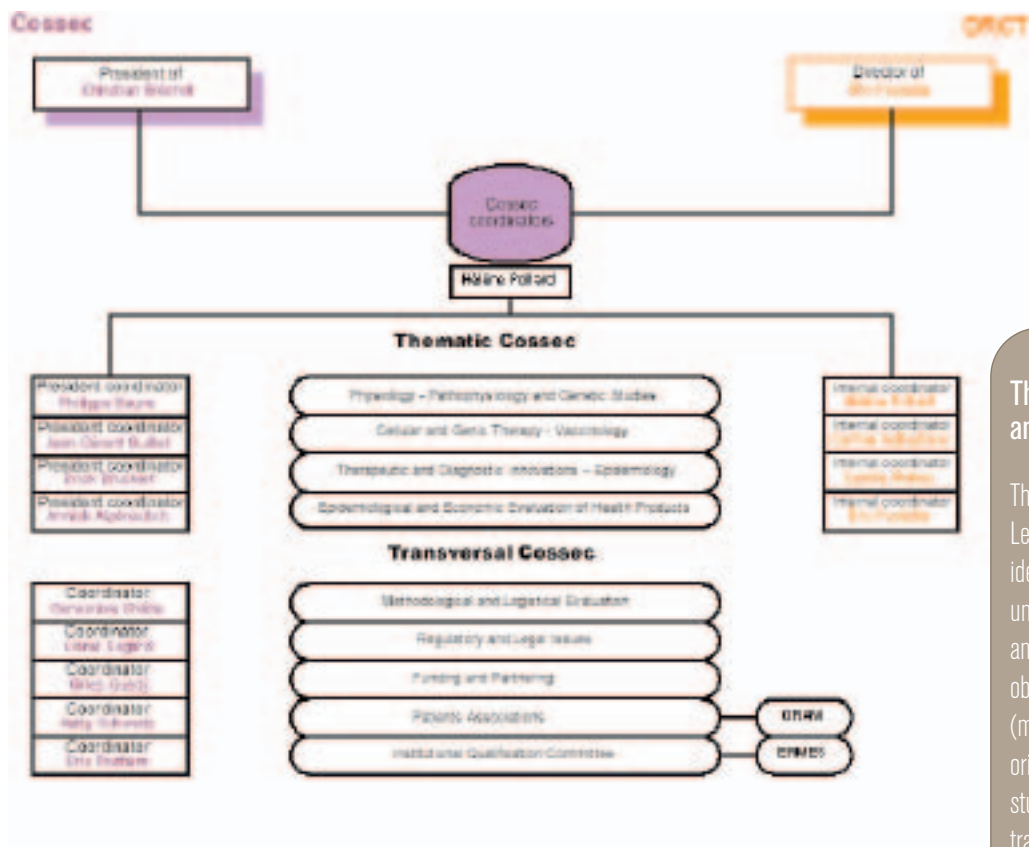
- allow validation of new therapeutic molecules, new therapeutic or vaccination concepts and new tools emanating from technological transfer;
- establish innovative development strategies in collaboration with all partners (funding bodies, associations and regulatory agencies);
- facilitate proof of concept and transfer at all stages of preclinical and clinical development;
- identify appropriate industrial and institutional collaborators to establish strategic partnerships;
- evaluate and define:
 - the priority of basic research projects emanating from Inserm laboratories in all therapeutic domains,
 - the strategy for their development,
 - the level of scientific and administrative coordination of innovative therapeutic projects that Inserm proposes to promote while Cossec ensures their integrated management;
- give an opinion on ethics, particularly with regard to research that:
 - does not fall within the jurisdiction of the Huriet-Sérusclat law,
 - is financed by academic or foreign private partners,
 - is conducted in countries that are not equipped with ethical bodies;
- propose training opportunities for professionals involved in transfer and developmental research;
- contribute to feeding the knowledge database open to the scientific community;
- propose scientific promotional events in order to improve its missions.

The Cossec committee, presided by Inserm's director general, comprises scientists, clinicians, and representatives of the pharmaceutical/biotechnological industry and patients associations. It is assisted in its task by four presidents of thematic sub-committees, acting as coordinators:

- Physiology - Pathophysiology and Genetic Studies: Philippe Beaune;
- Cellular and Genic Therapy - Vaccinology: Jean-Gérard Guillet;
- Therapeutic and Diagnostic Innovations - Epidemiology: Éric Bruckert;
- Epidemiological and Economic Evaluation of Health Products: Annick Alépovitch;

and five coordinators from transversal support groups:

- Methodological and Logistical Evaluation: Geneviève Chêne;
- Regulatory and Legal Issues: Gilles Guedj;
- Funding and Partnering: Lionel Ségard;
- Patients Associations: Ketty Schwartz;
- Institutional Qualification Committee: François Hirsch and Eric Postaire.



The Physiology, Pathophysiology and Genetics Cossec

The Cossec has decided to support Marion Leboyer's research project. Her team works on identifying factors of genetic susceptibility underlying various psychiatric pathologies with an onset in childhood (child autism and obsessive compulsive disorder) or in adulthood (manic depression and schizophrenia). The originality of this approach is that rather than studying such pathologies by relying only on traditional psychiatric nosography, one is trying to achieve a phenotypic partitioning in order to identify homogeneous sub-groups that are pertinent for studying underlying factors. The research strategy initially consists in phenotypic classification and validation at the clinical and family level, then working at the genetic level by looking for susceptibility factors involved in the disease. Marion Leboyer's team uses classical methods such as genetic linkage studies using genomic screening, candidate gene studies, and mutations identification studies. This research is being carried out within Inserm Unit 513 (Neurology and Psychiatry) at the University Hospital in Créteil. The team has succeeded in gathering clinical and cognitive data, a DNA bank and cell lines from a population of 3,500 subjects. The team has published over 120 international articles, 40 articles in French and two books. The team has also registered one patent.

Cossec operation comprises the following steps:

- peer evaluation of the project submitted by the investigator in order to assess its scientific and therapeutic value; selection criteria include translational research,

relevance to National Research Programs, running of trials in appropriate CRCs given the research topic;

- the decision to support a project deemed to have priority by the committee as a whole, excepting those members who feel there is a conflict of interest;
- the setting up and follow-up of the project in coordination with the Department of Clinical and Therapeutic Research (DRCT).

SALIENT FEATURE

The clinical research project led by Claire Lévy-Marchand on the treatment of child lipodystrophic diabetes using recombinant leptin is being continued by a phase-II clinical trial after obtaining very encouraging results in an initial phase-I trial.

The integrated management of projects allows for continuity between research results, experimental validation (by bringing proof of concept), and the setting up of clinical trials (mostly phases I and II).

QUALITY CONTROL

Inserm has developed a quality control policy over a number of years. This is crucial for the appropriate running of its projects, and guarantees good practice usage in the Institute's laboratories, both in preclinical and clinical research.



Preclinical Research

The missions of the Research Quality Control Division are:

- the setting up of quality control procedures, respecting good laboratory practices with or without ISO certification; several Inserm entities (units, networks, platforms) have been or are on the way to being certified;
- assistance for personnel training;
- implementation of internal quality audits;
- participation in the national research quality commission that draws up all the information brochures (AFNOR) in order to implement research quality control procedures;
- participation in interorganization quality control actions initiated in 2003, as part of the development of life sciences research platforms (RIO program).

Clinical Research

The clinical research quality control mission is responsible for the quality of clinical trials promoted by Inserm. It assists Inserm project leaders as well as project managers at the time of project implementation. It is responsible for carrying out internal and external trial audits and organizes training programs for leading investigators and their teams, in close collaboration with the national office for continuing education (Human Resources Department) and the Department of Legal Affairs.

ETHICS

65 ETHICS COMMITTEE FOR MEDICAL AND HEALTH RESEARCH (ERMES)

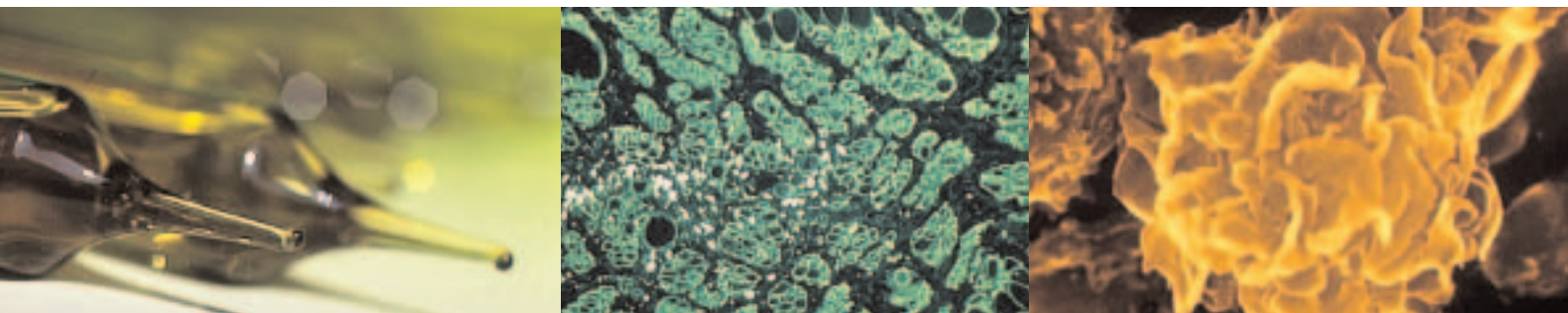
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ETHICS COMMITTEE FOR MEDICAL AND HEALTH RESEARCH (ERMES¹)

Inserm is committed to developing policy-making in ethics. The activities of the Ermes committee, which is open to the general public, correspond to this necessary commitment at a time when public opinion is seeking to understand the implications of scientific and medical progress. Ermes' reflection in 2005 focused among other things on the role of collective expert reports and patients associations, as well as the implications of genetic testing.



The goals of Ermes are several-fold:

- reflecting upon ethical problems arising in the biomedical field;
- facilitating the integration of ethical thinking in biomedical research;
- sensitizing and educating people on ethical questioning;
- playing a full role in the dialogue between Inserm's scientific and medical community, and society.

Thinking Sessions

The committee met on 7 occasions in the course of 2005. The principle themes addressed are summarized below.

Collective Expert Reports

Following the reactions generated by Inserm's collective expert report on the evaluation of psychotherapies, the Ermes committee decided to engage in a thorough exploration of scientific expertise. The committee is convinced that expertise involves a deeply ethical and democratic dimension, as long as it is conceived not as a prescription but as a dialogue with society, allowing the latter to willingly gain knowledge and understand its implications. During a meeting with Jeanne Etienne²

on this issue, in March 2005, the Ermes committee recommended that one anticipate and prepare the post-expertise stage. The idea is to facilitate and accompany the development of a public debate on the scientific, medical and ethical implications of collective expert reports. The committee proposed that Inserm collective expert reports with important ethical implications be made as part of a public debate organized by the committee members involved.

Joint Exploration with Patients Associations

The Inserm-Associations mission and the Ermes committee organized a first meeting in May 2005. The goal was to get a better understanding of the ethical problems raised by patients associations, to share the committee's own questions on this issue and facilitate the emergence of a joint exploration process.

Genetic Testing

The Ermes committee was contacted concerning the public announcement by a biotechnology company about the development of a genetic test for the diagnosis of autism. The committee organized hearings, in collaboration with the Inserm-Associations mission and initiated a general reflection on the ethical implica-

tions of developing genetic testing. Beyond testing, the committee examined the ethical implications of research aiming at elucidating the cause of invasive developmental disorders, diagnosing these pathologies and managing the education and therapy of children and adults suffering from such handicap.

Sensitizing and Educating on Ethical Questioning

A partnership has been established between Inserm's further training workshops and their scientific committee. The aim is to include sensitization sessions on ethical questioning relevant to specific topics being addressed in workshops. Setting up of a similar partnership is currently being discussed with the Continuing Education Department. Members of the Ermes committee regularly participate in teaching the biomedical research course for the Ethics, Science, Health and Society Masters degree (Paris XI University Hospital). Ties have also been woven with institutions that facilitate reflection on research and organize debates with the general public (*Cité des sciences et de l'industrie, Ecole normale supérieure*).

Meetings with Other Ethical Committees

The Ermes committee regularly participates in joint meetings with ethical com-

¹ *Comité d'éthique en recherche médicale et en santé de l'Inserm*

² Jeanne Etienne is in charge of Inserm collective expert reports

mittees from other scientific and technological public institutions (CNRS, INRA, IRD) and other ethical institutions such as the ethical forum of Paris public hospitals (AP-HP). Within this informal network, the committees consult each other on their respective approaches and initiate actions to examine and work on common areas of interest.

Review Articles

From April 2005 onwards, the Ermes committee published a weekly newsletter summarizing the week's news on ethics. The articles, which are very thorough, are compiled from the national and international press, broad-spectrum scientific journals such as Nature and Science, news gathered from specialized Web sites and ethical committees. At the end of 2005, Ermes prepared a database of the bibliography used to produce these articles on Basis.

MEETINGS AND CONFERENCES

In 2005, Inserm's health *cafés* began to address ethical issues and a meeting organized at ENS¹ (Paris) worked towards assessing the ethical implications of new biological research areas.



- An event entitled “New Frontiers in Biology, New Frontiers in Ethics” was organized at ENS in Paris. This 3-hour evening event of encounter and debate was organized by the Ermes committee on 13 April 2005. The audio recording of the event is available on the ENS Website.

- The first Inserm Health *Café* on Ethics took place in December 2005, gathering 70 people at Inserm headquarters to debate on the theme: “Collective Expert Reports: What are the Ethical Implications?” Ermes Deputy Director, Bénédicte de Boischevalier, led the debate. The presence of representatives from the CNRS ethical committee and

from the collective expertise body of the Development Research Institute (IRD²) opened an immediate discussion on ethical problems raised by expertise in the various scientific and technological public organizations. This Inserm Ethics Health *Café* initiative will no doubt be reconducted.

Highlights of Ermes' Actions in 2005

- Therapeutic cloning, British Council, British Embassy.
- First general conference on handicap: a time for commitment, Unesco, Paris.
- Behavior determinism, CCNE³ annual event on ethics, Paris V René-Descartes University
- Brain Sciences and Society/Meeting of Minds, first debate between European citizens on the implications of neurosciences development, *Cité des sciences et de l'industrie*.
- Public audition on stem cells, National Assembly, Parliamentary Office for the Evaluation of Scientific and Technological Choices.
- Public audition on scientific expertise, National Assembly, Parliamentary Office for the Evaluation of Scientific and Technological Choices.
- Participation in the conception of a two-hour radio program (on France Culture) on the ethical implications of research in developing countries.

¹ *Ecole nationale supérieure* (a national higher education institution)

² *Institut de recherche pour le développement* - Development Research Institute

³ *Comité consultatif national d'éthique* - National Consultation Committee on Ethics

ETHICS: INSERM'S INTERNATIONAL PARTNERS

The international ethics mission has reinforced Inserm's European and global commitment in 2005. This is illustrated by the progress of the Eureth.net, Ethicsweb and Eulabor projects, and the mission's active participation in the Global Forum on Bioethics in Research (GFBR).



In the course of 2005, the international ethics mission essentially focused on the setting up and implementation of international projects funded by the European Commission, such as Eulabor, Inserm's leading bioethics project. It also participated in numerous European encounters, including a one-day Network Meeting on International Research Ethics to reflect on ethics education in developing countries. As a permanent member of the organization committee, the international ethics mission has finally contributed to the organization of the 6th GFBR, which took place in Malawi.

Documentation, Information and Communication on Ethics

Inserm has successfully led two European projects in this area. Eureth.net, which was completed in June, is a network of ethics documentation centers with a common database by the name of EUROETHICS. The other large scale European project currently being set up (Ethicsweb) is derived from the previous feasibility study entitled Faster.

Ethics and Developing Countries

Eulabor (European and Latin American Ethical Regulation Systems of Biomedical

Research: Comparative Analysis of its Pertinence and Application for Human Subject Protection) is a project coordinated by the international ethics mission and financed by the European Commission as part of the Science and Society program (6th FPRTD).

The goal of Eulabor is to carry out a comparative and critical evaluation of ethical regulation forums on biomedical research, including research ethics committees, research organizations, the scientific community, health agencies and the general public. This evaluation bears on man and human tissues in Europe and Latin America. Based on this analysis, Eulabor's partners will make new propositions for ethical, theoretical and practical evaluations. Ethics training programs that meet today's necessities will then be drawn up.

This project started in September 2005 and the international meeting marking its launch was held on 10 and 11 October. Inserm's international ethics mission is currently finalizing the first phase of the project, which includes evaluating the current state of the ethical regulation system in each of the countries involved:

- Germany: IWE (*Institut für Wissenschaft und Ethik*) in Bonn;
- Argentina: Bio & Sur Foundation;

- Brazil: Oswaldo Cruz Foundation;
- Chile: Santiago University, with the participation of the Chilean Ministry of Health and the University of Chile;
- Spain: *Epson Ibérica* Foundation (Technoethics) in Barcelona;
- France: Inserm (coordinator), with the participation of researchers from the Lille Medical Ethics Center;
- Mexico: CNB (*Comision nacional de bioética*);
- Uruguay: *Universidad de la Republica*.

Global Forum on Bioethics in Research

For some years now, the international ethics mission has been a permanent member of the GFBR leading committee.

The GFBR offers representatives of developing and developed countries an arena to debate on ethical questions concerning collaborative international research efforts. The GFBR is funded by industrialized countries and is being implemented in developing countries. GFBR partners include the National Institutes of Health (United States), the Medical research Council (United Kingdom), the Wellcome Trust (United Kingdom), WHO (Geneva), the Council for Health Research and Development (NGO), Inserm (France),

Aga Khan University (Pakistan), the University of Buenos Aires (Argentina) and the European Commission.

The first global forum took place in 1999. The various forums were devoted to key areas of international collaborative research, such as:

- difficulties encountered to draw up ethical guidelines and evaluate clinical trials in developing countries;

- traditional medicine, genomics and worldwide health;
- the sharing of benefits, intellectual property and enlightened consent;
- the duties of researchers and promoters with respect to clinical trial volunteers and their community.

The 6th forum, which took place in March 2005 in Malawi, was entitled: “What Happens after Research has been Completed?”

It dealt with researcher and research promoter obligations upon completion of clinical trials. A project for the funding of a permanent GFBR secretarial office, entitled Health Ethics Research and submitted by the steering committee, was accepted by the European Commission towards the end of 2005, for a period of three years.

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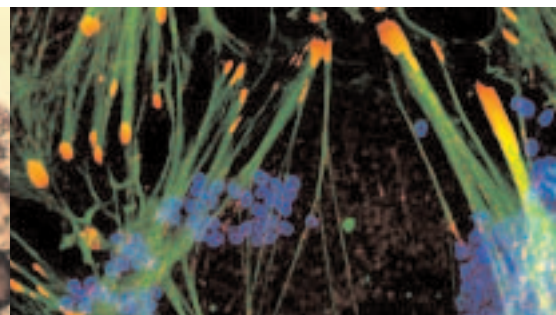
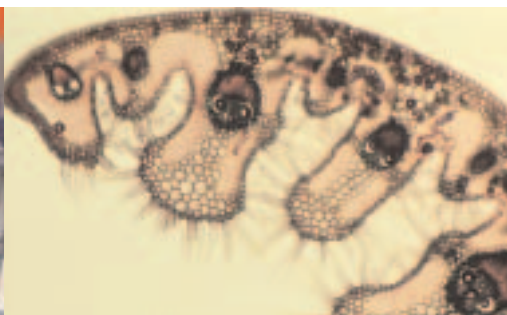
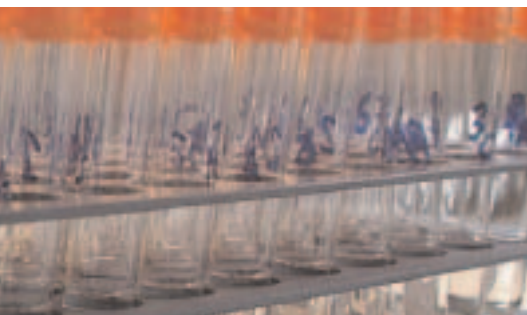
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RESPONSIBLE MINISTRIES



An integrated policy

From the very moment a project is conceived, Inserm develops multipartnering strategies involving institutions (ministries, hospitals), scientific partners (research organizations, universities and schools, health agencies, specialized medical societies), social protection agencies (national and complementary health insurance funds), foundations, charities, and private companies (pharmaceutical groups, biotechnology firms, knowledge management and knowledge transfer companies).

In order to establish future lines of collaboration and ensure the follow-up of ongoing actions, Inserm organizes annual coordination committee meetings with its partners. Inserm's action in this area involves signing agreements such as biomedical research project agreements, partnering and funding conventions, collective expert report contracts, and framework conventions.

Ministry of Health and Social Protection

The Office General for Health (DGS¹) and Inserm signed a framework convention in 2005.

As a partner of the Virtual Institute for Public Health Research, the DGS participated in the call for projects on health inequalities.

The DGS contributes to the operational cost of host research positions for general practitioners. The DGS has entrusted Inserm with the task of generating collective expert reports such as "Suicide: a Psychological Autopsy, a Research Tool for Prevention" and "Cancer: Long-Term Prognosis".

The DGS also funded 6 Avenir Program laureates from 2002 to 2005 and contributed, along with health agencies, to the launch of the Interface Contracts Program. The DGS has supported around twenty public health projects within Inserm research units and continues to support the rare diseases database Orphanet®.

Finally, the DGS supports the protected transmission of death certificates.

The Office for Hospitalization and Care Organization (DHOS²)

The DHOS has supported the development of new Clinical Research Centers (3 plurithematic CRCs) and is participating in the general and biotherapy-vaccinology CRC call for offers. It funded 8 Avenir Programs from 2001 to 2004.

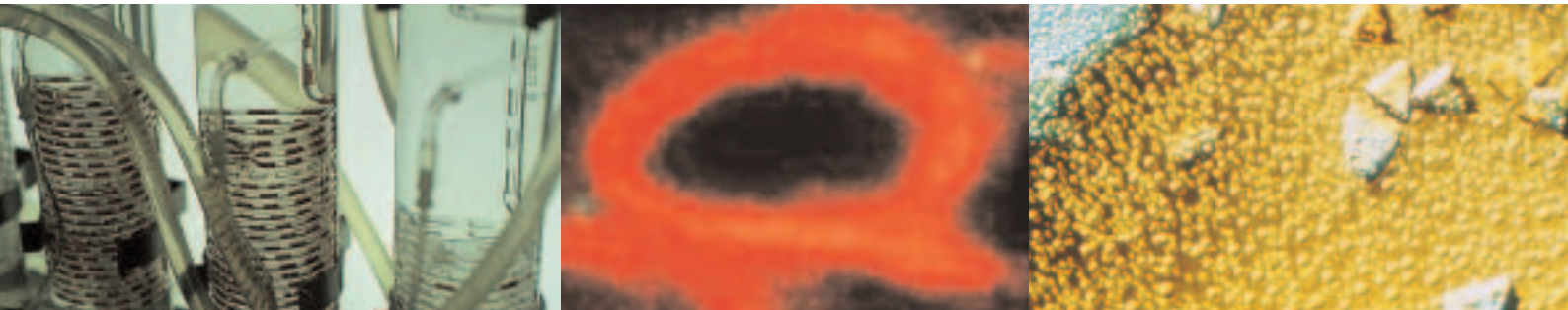
Ministry for Youth, Education and Research

The Ministry supports cancer poles. It is also participating in the funding of projects selected after an Inserm call for projects on adult stem cells.

¹ Direction générale de la santé

² Direction de l'hospitalisation et de l'organisation des soins

INSTITUTIONAL PARTNERS



The Interministerial Mission for the Fight against Drugs and Drug Addiction (MILDT¹) regularly commissions Inserm to produce collective expert evaluations. MILDT-Inserm calls for projects are launched on an annual basis and the projects emanating from the 2000 call for projects were presented at a meeting in February 2005. The next call for projects will be launched in partnership with the National Cancer Institute (INCa²).

The Parliamentary Office for the Evaluation of Health Policies (OPEPS³) signed a convention in 2004 entrusting Inserm with a collective expert evaluation (in 2005) entitled Obesity, Status Quo and Evaluation of Prevention and Management Programs.

The Parliamentary Office for the Evaluation of Scientific and Technological Choices (OPECST⁴) works in close collab-

oration with Inserm. OPECST often invites Inserm researchers to sit on steering committees and give their opinion on studies that fall within the realm of Inserm expertise. The modification of the law on bioethics has led to the reinforcement of the partnership between Inserm and OPECST.

The French Weather Forecast Service

Inserm and the French weather forecast service signed a collaborative convention to introduce a health-risk monitoring and alarm system based on epidemiological data in the event of a heat wave.

Health agencies

French Work and Environment Health Safety Agency (Afsset⁵) signed a framework agreement with Inserm so as to support evaluation and research efforts on health and the environment. Afsset is a partner of the Virtual Institute for Public Health Research and has commissioned Inserm to update the 1999 collective expert evaluation on glycol ethers and several other collective expert evaluations on cancer and the environment.

The Health Monitoring Institute (InVS⁶) is a partner of the Virtual Institute for Public Health Research. InVS and Inserm

signed an agreement in 2005 to study the impact of the 2003 heat wave on mortality and identify the major risk factors involved. With similar aims in mind, InVS supports the Sentinelles[©], FivNat and France Coag networks. The Institute is also involved in register policy, which has both a monitoring and research function. In 2005, Inserm cofunded 30 registers with a total of 540 K€. Finally, InVS is a partner in the call for proposals on thyroid cancer.

The National Institute for Health Prevention and Education (INPES⁷) is a partner of the Virtual Institute on Public Health Research.

The Biomedical Agency⁸ (formerly EFG) signed a convention with Inserm at the end of 2004 concerning a network for the follow-up of dialysis patients (REIN project⁹). The agency is a partner of the Virtual Institute for Public Health Research.

French Sanitary Safety Agency for Health Products (Afssaps¹⁰) is a partner of the Virtual Institute for Public Health Research. It actively participates, with Inserm and other institutional promoters, in the transposition of the 2001/20/CE directive on clinical drug trials and in the formulation of decrees for its application.

¹ Mission interministérielle de lutte contre la drogue et la toxicomanie

² Institut national du cancer

³ Office parlementaire d'évaluation des politiques de santé

⁴ Office parlementaire d'évaluation des choix scientifiques et technologiques

⁵ Agence française de sécurité sanitaire de l'environnement et du travail

⁶ Institut de veille sanitaire

⁷ Institut national pour la prévention et l'éducation en santé

⁸ Agence de la biomédecine

⁹ Kidney epidemiology and information network (Réseau épidémiologique et information en néphrologie)

¹⁰ Agence française de sécurité sanitaire des produits de santé

The Biomedical Agency

This public body, under the aegis of the Ministry of Health, was created during the process of modification of the laws of 6 August 2004 on bioethics. Starting in early 2006, Inserm will be developing close ties with this new agency in order to support research programs in regenerative medicine.

The National Agency for Health Accreditation and Evaluation (Anaes¹), now replaced by the Higher Health Authority (HAS²), continues to be a partner of the Virtual Institute for Public Health.

The French Blood Transfusion Service (EFS³) is participating in the joint Inserm/DHOS program to set up integrated biotherapy CRCs.

The National Agency for AIDS Research and Hepatitis (ANRS⁴) will ensure the continuation of the hepatitis C CTA initiated by Inserm through support for basic research in this field.

¹ Agence nationale d'accréditation et d'évaluation en santé

² Haute autorité en santé

³ Etablissement français du sang

⁴ L'Agence nationale de recherche sur le sida et les hépatites

SOCIAL PROTECTION AGENCIES

The French Health Insurance Fund for Independent Professions (Canam¹) has funded three Avenir Programs from 2002 to 2005, and three public health doctoral studentships as part of the Biomedical Sciences, Health and Society program directed by CNRS-SHS (human and social sciences), the DREES² and Inserm. Over the period, 2002-2005, Canam entrusted Inserm with four collective expert evaluations on behavioral disorders, specific learning deficits, auditory, growth and puberty disorders, in addition to an operational evaluation on screening in children

and teenagers. Canam is also a partner in the Virtual Institute for Public Health Research.

The Health Insurance Fund for Salaried Employees (Cnam-TS³) and Inserm have cofinanced four research positions for general practitioners since 2003 as part of the research program on general medicine. The call for projects for this program was renewed in 2005. CNAM-TS, Inserm and the DGS signed a convention to set up a SIG for the epidemiological evaluation of health products. This aims at organizing medico-epidemiological studies in order to follow certain health products after marketing, a need expressed by the commission for transparent public health follow-up. The CNAM-TS is continuing to

support the Gazel cohort, in partnership with the French public gas and electricity company EDF-GDF. CNAM-TS is a partner of the Virtual Institute for Public Health Research and renewed its framework agreement with Inserm at the end of 2004. In 2005, CNAM-TS entrusted Inserm with the ongoing collective expert evaluation on genetic testing.

The Complementary Health Insurance for Public Education Personnel (MGEN⁴) has been supporting health research along side Inserm for about twenty years. In 2005, MGEN continued to fund a collective expert evaluation on voice disorders among teachers. It participates in large ongoing epidemiological surveys such as the E3N cohort on cancer risk factors in

¹ Caisse nationale d'assurance maladie pour les professionnels indépendants

² General Office for Research, Studies, Evaluation and Statistics

³ Caisse nationale d'assurance maladie des travailleurs salariés

⁴ Mutuelle générale de l'éducation nationale

women, which it is funding. In 2005, MGEN funded four new research projects on screening of speech disorders in children, the evaluation of risk associated with taking medication during pregnancy, the

relationship between hormonal replacement therapy and the risk of osteoporosis, and prescription practices among general practitioners. MGEN's support has also allowed the production of an expert report

on prenatal diagnosis. MGEN remains a faithful partner of Inserm's Young People Network.

Projects funded by MGEN

Title	Trial coordinator	Unit affiliation
Developmental dyslexia: Functional MRI evaluation of the prognostic and therapeutic value of various reeducation programs	Jean-François Demonet	Inserm Unit 455
SNAC (<i>study of nomegestrol acetate on coagulation</i>): study on the impact of nomegestrol acetate on blood coagulation in menopausal women	Pierre-Yves Scarabin	Inserm Unit 258
Neuropsychology and functional neuroanatomy of post-traumatic stress syndrome: memory deficits and their neurobiological basis	Bérangère Guillery-Girard	E218
Study on clinical, environmental and genetic vulnerability factors in suicidal behavior	Bruno Giros	Inserm Unit 513
Child epilepsy: analysis of specific diagnoses, therapeutic management and resulting integration in school, for the cohort followed at the Robert-Debré Hospital (clinical epidemiology project)	Alexis Arzimanoglou	CRC Robert-Debré

ASSOCIATIONS



Inserm is actively developing a policy of greater overtture, dialog and partnership with associations for patients or disabled people and their families. This approach relies on the Patients Associations Liaison Group (Gram¹) and the mission Inserm-Associations.

The four priority goals, defined in 2004 and pursued in 2005, are being pursued through a number of actions:

- participation of associations in Inserm committees and work groups, resulting in the integration of seven associations in three national research programs: Cardiovascular Diseases, Bone and Joint Diseases, and Diabetes. Four Inserm collective expert reports also required work sessions with associations upstream and at the time of report circulation; the reports concerned psychological autopsy of suicide, cancer prognosis, learning disorders and genetic testing;
- Gram has become a support group for Cossec², who will be integrating the various associations in its transversal work groups;
- amplification of the training program by pursuing the “Understanding Clinical Research Protocols” cycle and launching

the “Biomedical Information on the Web” cycle, in collaboration with the Leem³, Eurordis⁴ and the European Federation for Rare Diseases. The 17 training sessions were attended by a total of 260 individuals;

- the development of Inserm-Associations’ database, gathering data on 420 associations including 80 European federations as part of the CIPAST⁵ European contract.

The third annual meeting gathered 120 association representatives and gave Alain Vanvossel, Director of the Major Diseases Division of the European Research Commission, the opportunity to present the 7th FPRTD policy of overtture towards patients associations.

¹ Groupe de réflexion avec les associations de malades

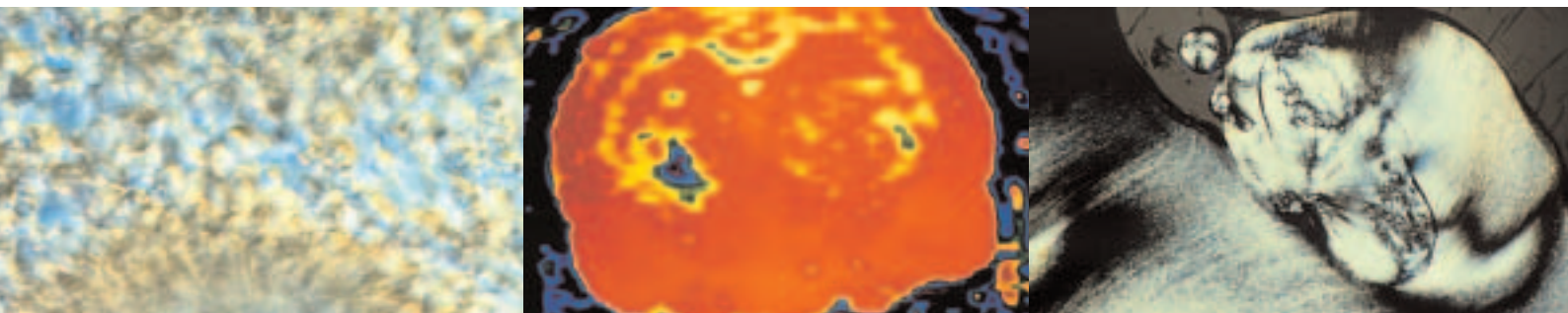
² Strategic Planning and Clinical Trial Monitoring Committee

³ National Union for the Pharmaceutical Industry

⁴ European Organization for Rare Diseases

⁵ Citizen Participation in Science and Technology

RESEARCH ORGANIZATIONS



Inserm and the National Institute for Demographic Studies (INED) are engaged in a collaboration effort on the recording of medical causes for the voluntary termination of pregnancy with the General Office for Research, Studies, Evaluation and Statistics (DREES¹) and the use of differential mortality data according to social or professional categories with the National Institute for Statistics and Economic Studies (INSEE). INED is a partner of the Virtual Institute for Public Health Research. In 2005, it collaborated with Inserm, InVS², INSEE, DEP³, DREES and DGS⁴ in order to set up a cohort of children as part of the plan on Health and the Environment. Inserm and the Gustave-Roussy Institute (IGR) signed a framework agreement on 29 March 2005, concerning the modalities of cooperation in cancer research, including joint support to mixed research units.

In 2005, Inserm also signed a new framework contract allowing the creation of

mixed units with EPHE⁵ in the case of units receiving strong support from the latter.

CNRS

Inserm and CNRS⁶ are working jointly on a large number of programs, such as the work group on disability and the National Research Program on diabetes (NRPD). In 2005, CNRS, Inria and Inserm launched a joint call for projects entitled Health Information and Technologies. The eight projects selected received total funding of 605 k and involved three fixed-term post-doctoral contracts.

CEA

CEA⁷ is a partner in the environmental nuclear toxicology program, along with INRA and CNRS.

Inra

Inra⁸ is a partner in the National Research Program on Human Nutrition (NRPHN).

Inria

In 2005, Inria⁹, CNRS and Inserm launched the call for projects entitled Health, Information and Technologies (see above).

¹ General Office for Research, Studies, Evaluation and Statistics

² Health Monitoring Institute

³ Office for Evaluation and Prospective Studies

⁴ Office General for Health

⁵ EPHE is a higher education institution, *Ecole pratique des hautes études*

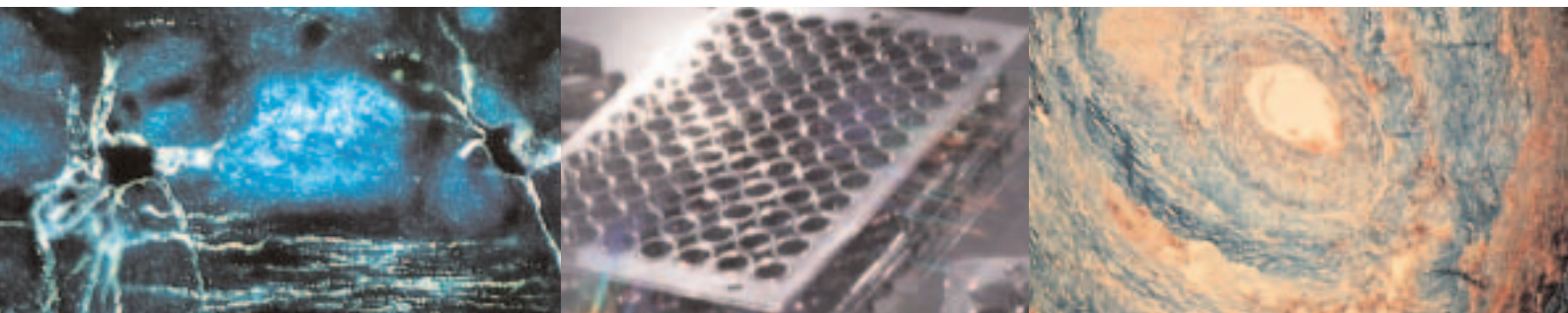
⁶ National Institute for Scientific Research

⁷ Atomic Energy Commission

⁸ National Institute for Agronomical Research

⁹ National Institute for Research on Information Technology and Automation

INDUSTRY



Pharmaceutical Groups and Industry

In 2004, Inserm and Inserm Transfert set up a large number of coordination committees with large pharmaceutical groups and companies in order to identify broad lines of partnership and develop strategic alliances. Inserm and Inserm Transfert met with Bayer Pharma, Servier, LEO Pharma, Serono, the Leem¹, Amgen, and AstraZeneca. The coordination committee meetings are organized once a year. In 2005, Inserm and Inserm Transfert expressed the wish to continue having annual meetings with their industrial partners.

Development of Private-Public Partnerships

The National Union

for the Pharmaceutical Industry (Leem)

A framework convention and associated group-specific agreements on rare diseases have been signed with the common services that develop the Orphanet® database and the Rare Diseases Institute SIG. The Leem has also participated in the organization of a seminar on unstable atherosclerotic plaque biomarkers. Workshops were organized to analyze the formation of a

prospective cohort to identify predictive or diagnostic markers of acute coronary syndrome. A proposal was made to set up a bioresources center for the conservation of a large number of biological samples and associated clinical and paraclinical data.

Affymetrix and Inserm are working on a partnership agreement in order to set up a pharmacogenetics platform. Affymetrix is planning on developing a 5000-SNP² chip, a general-purpose tool (property of Inserm) that will be made available to different pharmacogenetics networks including anticancer, organ/autoimmunity, and bone marrow transplantation networks.

Amgen

Amgen is pursuing a clinical research program at the Robert-Debré Public Hospital CRC in partnership with Inserm (Unit 690) and Inserm Transfert. This program aims at developing a treatment for the child orphan disease known as lipodystrophic diabetes. In another partnership with Amgen and Inserm Transfert, Inserm is promoting a trial on the treatment of patients suffering from lipodystrophy with associated leptin deficiency. This trial is being conducted in collaboration with the Saint-Louis Public Hospital CRC. Amgen has also contributed to the funding of a meeting organized by the Cellular Therapy and Vaccinology Club. Finally, Amgen par-

ticipates in the strategic orientation committee of the National Research Program on Bone and Joint Diseases (NRPBJD).

AstraZeneca supports Stéphane Laurent's Cossec-approved research project (Inserm Unit 652 and CRC 9201) on the mechanical and structural characteristics of the carotid plaque.

Baxter

A research contract is being drawn up for an exploratory study, due to be promoted by Inserm and conducted at the Bordeaux CRC, concerning the evaluation of performance, clinical efficiency and safety of the bone substitute TRICOS™ in functional bone regeneration.

Bristol-Myers Squibb participates in the strategic orientation committee of the National Research Program on Cardiovascular Diseases (NRPCD).

Ely Lilly supports Dominique Simon's CENTRED study (Inserm Unit 258) approved by Cossec. The aim of the study is to get a precise estimation of the prevalence of diabetic complications in France and analyze the factors involved. Ely Lilly also participates in the strategic orientation committee of the National Research Program on Diabetes (NRPD).

¹ National Union for the Pharmaceutical Industry

² Single nucleotide polymorphism

GlaxoSmithKline is contributing to the setting up of a project to study the effect of niacin on lipid metabolism. The company also participates in the strategic orientation committees of the National Research Programs on Diabetes (NRPD) and Cardiovascular Diseases (NRPCD).

The **Pierre-Fabre Research Institute** participates in the strategic orientation committees of the National Research Programs on diabetes (NRPD) and Cardiovascular Diseases (NRPCD).

Ipsen

Ipsen and Inserm are jointly initiating a new research program in oncology. This new ambitious program comes in addition to agreements signed in previous years. This agreement, based on an Inserm basic research discovery under patent protection, will allow the development of a prolactin antagonist, a new recombinant molecule for the treatment of prostate and breast cancer.

Novartis

A research partnership with Novartis aims at providing funding and drugs for an open and multicentered, phase-II therapeutic trial with no direct individual benefit, for the Glivec® neoadjuvant treatment of Darier-Ferrand dermatofibrosarcoma. The trial, promoted by Inserm, is being conducted at the Saint-Louis public hospital CRC. A second partnership is being set up for a phase II trial to evaluate sando- statin in the treatment of lung fibrosis. Novartis participates in the strategic orientation committees of the National Research Programs on Diabetes (NRPD) and Cardiovascular Diseases (NRPCD).

Novonordisk has signed a contract with Inserm agreeing to provide clinical drugs. The project, led by Pierre Bougnères, concerns the possible use of growth hormone for treating familial hypophosphatemic rickets in children.

Procter & Gamble

A convention is being established to provide clinical drugs for Inserm-promoted research on a rare disease.

Sanofi-Aventis participates in the strategic orientation committee of the National Research Program on Diabetes (NRPD).

Servier

An Inserm/IRIS/ADIR research convention has been drawn up to evaluate a drug, currently being developed by Servier, on patients with Mild Cognitive Impairment, in collaboration with the Francis Eustache Unit (E 218). Servier participates in the strategic orientation committees of the National Research Programs on Bone and Joint Diseases (NRPBJD), Cardiovascular Diseases (NRPCD) and Diabetes (NRPD).

Takeda

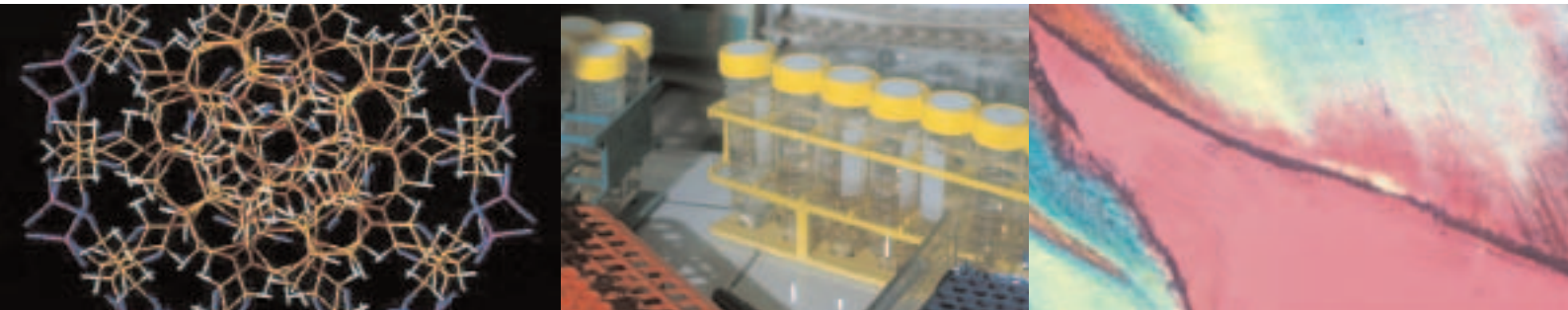
A convention was signed to provide clinical drugs to run a comparative trial on two pharmacological treatments for pedophilia. Takeda participates in the strategic orientation committee of the National Research Program on Diabetes (NRPD).

Électricité de France (EDF), Gaz de France (GDF)

Inserm is pursuing its collaboration with EDF-GDF and CNAM-TS¹, in order to study environmental and biological risk factors on over 20,000 EDF-GDF volunteers (Gazel Cohort) followed since 1989.

¹ Health insurance fund for salaried employees

INTERFACE COMMITTEES AND SPECIALIZED MEDICAL SOCIETIES



Inserm is reinforcing the role of interface committees designed to bring together researchers and clinicians representing the diverse specialized medical societies. This allows regular exchange and ensures continuity between basic research and clinical practice. From 2004 onwards, Inserm

strongly encouraged the committees to think actively about setting up National Research Programs on cardiovascular diseases, diabetes and metabolic diseases, bone and joint diseases, and nutrition. In 2005, three new National Research Programs are being put in place with the

contribution of committees on endocrinology and reproduction, dermatology, and gastroenteropathology. In addition, these committees were involved in the formation of clinical research networks.

RESEARCH SITE POLICY

81 RESEARCH CENTERS

81 DEVELOPMENT POLICY
AND ATTRACTIVITY

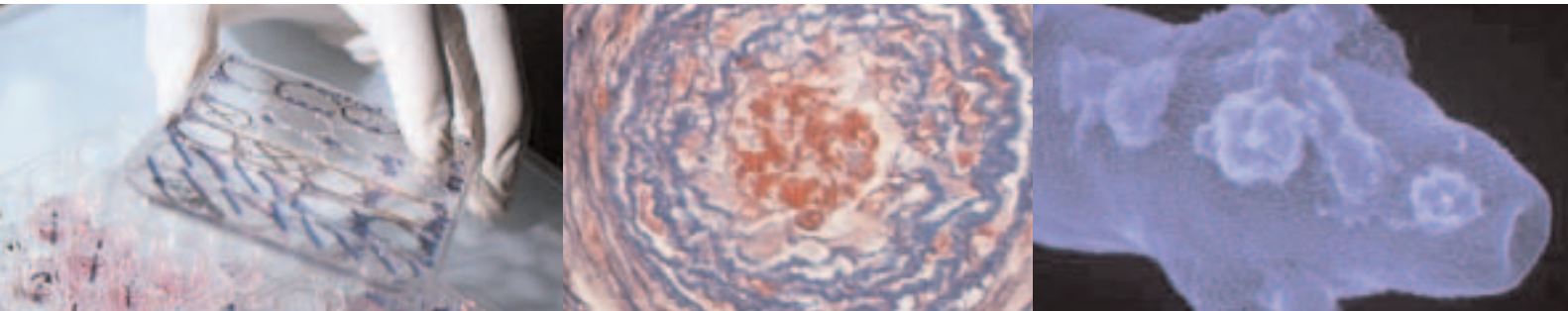
84 COMPETITIVE POLES

85 CANCER POLES



RESEARCH CENTERS

Inserm is pursuing its site structuring policy by helping organize mixed research centers jointly with universities or other public scientific and technological organizations, anchored in hospital structures (university hospitals or cancer centers). Such research unit groupings, reaching a critical mass of over 100 people (generally 150 to 350 people), are impelled by a genuine scientific policy that makes them both visible and attractive.



A new research center, the Bichat-Beaujon Biomedical Research Center, was created after the 2005 evaluation session, raising the number of centers to ten. This new Inserm Unit (U 773) is implanted in the

Bichat University Hospital in Paris. Thirteen other applications for center creations were submitted in October 2005. Inserm is pursuing its incentive policy in this area and recruited 23 engineers, tech-

nicians or administrative officers for research center positions at the end of 2005.

DEVELOPMENT POLICY AND ATTRACTIVITY

Inserm's development policy is taking shape thanks to a number of tools: Avenir programs, ESPRI contracts, as well as regionally funded doctoral and post-doctoral grants. This strategy is backed by the reinforcement of attractivity, in partnership with university hospitals, universities and local authorities, so as to attract high-quality young researchers and teams.

Development policy

In order to keep the momentum and renew the human potential in public health and biomedical research, a development policy is being pursued through implementation of Avenir programs and setting up of teams supported by Inserm and regional funding.

Since 2002, 18 ESPRI contracts have been set up across 11 regions, two of which have become Inserm-university research units. Over the same period, four other applica-

tions were submitted to obtain Inserm Unit status. The year 2005 alone witnessed the signature of five ESPRI contracts.

Regions participate in the implementation of Inserm's development policy via two major strategies:

- providing support for young researchers by joint funding of doctoral grants (97 ongoing grants in 2005, across 17 French regions). Twenty-nine new grants were awarded in 2005;
- 7 regions participated in the Avenir pro-

gram through funding or cofunding of doctoral and postdoctoral grants, technical personnel or equipment.

Attractivity

Reorganization efforts can only be conceived and implemented as part of a close and long-term consultation with Inserm's natural partners such as local authorities and, above all, university hospitals.

In this respect, Inserm coordinates actions

to generate attractivity by launching international calls for candidates and implanting young and talented researchers and teams in centers of excellence or emerging research sites. Inserm also contributes to the implementation of National Research Agency or region-funded chairs of excellence for junior or senior researchers. In 2005, Inserm assisted with two international calls for candidates (at the Paris-Lariboisière center and the Molecular Biology Mediterranean Research Center in Nice, C3M). The Institute consolidated established research units in Paris (Inserm

Myology Unit 787, at the Pitié-Salpêtrière, led by David Sassoon, with the University Pierre-et-Marie-Curie and the French Myopathy Association, and the support of Paris Public Hospitals) and in Strasbourg (Inserm Unit 748, “Pathogeny of Hepatitis C Viral Infection”, led by Thomas Baumert, with the University Louis-Pasteur and the support of the Strasbourg University Hospitals). This approach offers the best candidates a package jointly provided by all partners, involving a research position (external selection of a research director or university hospital position), a laboratory

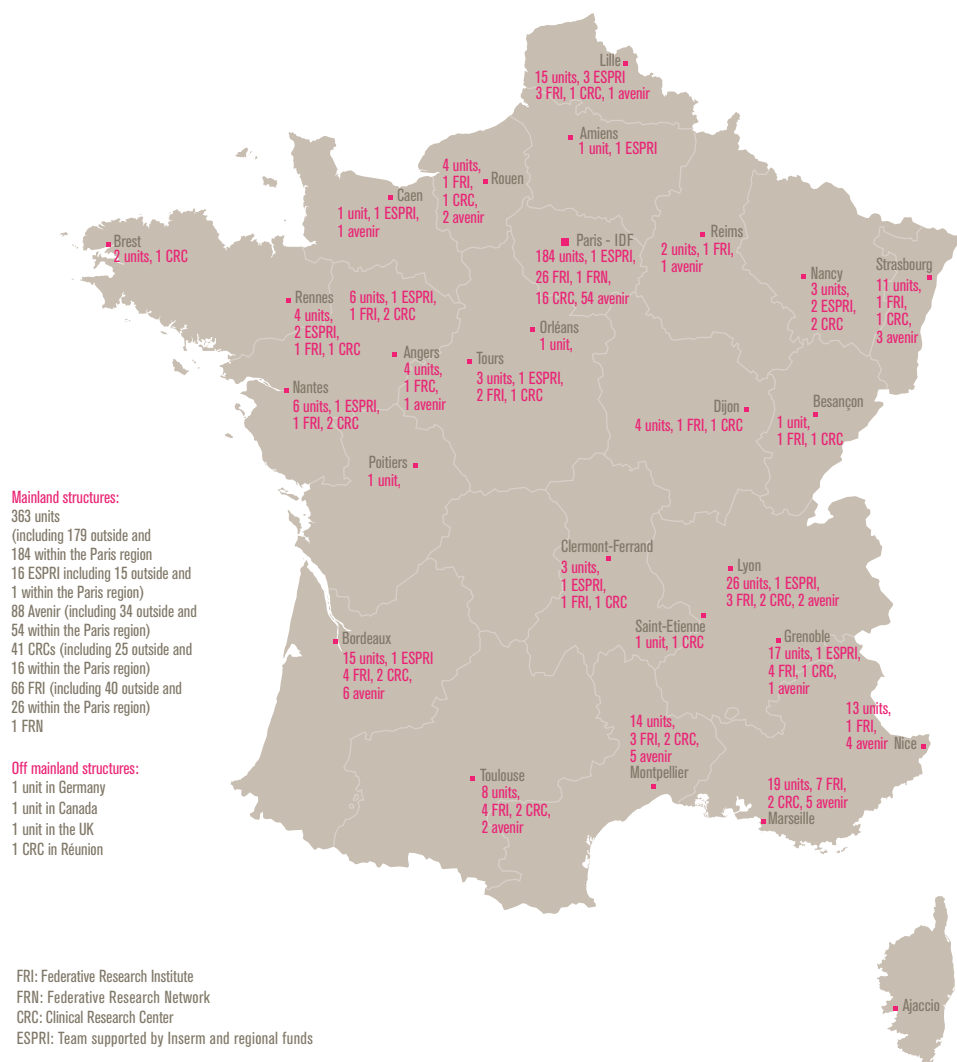
FACTS AND FIGURES

Out of 366 units (in 2005), 3 depend on European and international partnership, 362 (i.e. 99% of all units) are mixed with a higher education institution or another research organization (such as CNRS, Inra, Pasteur Institute, CEA, IGR, Curie Institute), 341 are mixed with a higher education institution (93%) and 41 (11%) are created on a multipartnership basis.

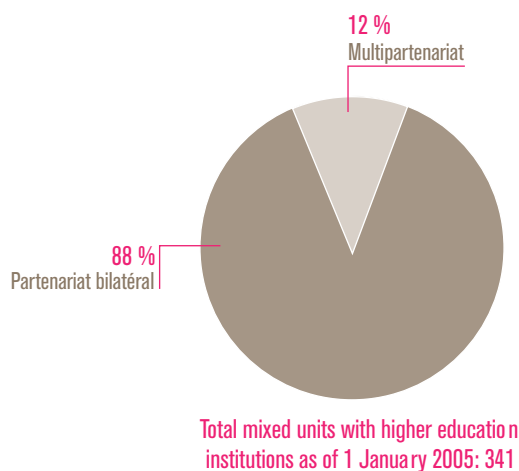
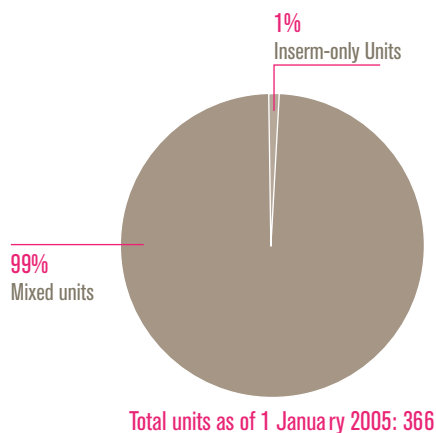
set up (facilities and equipment) and access to Avenir programs, fixed-term contracts (for young researchers) and chairs of excellence.

In 2005, Inserm assisted three laureates in obtaining junior or senior National Research Agency chairs of excellence:

- Thomas Baumert,
- Jeremy Luban,
- Moïse Devarieux.



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Facts and Figures: Partnership with University Hospitals

- Inserm plays a key third-party role as a representative of public scientific and technological institutions involved in biomedical research in the application of the new administration ordinance on university hospitals and the redefinition of the relationship between universities and hospitals. Inserm's position within Regional Consultation Committees, now renamed Biomedical and Public Health Research Committees, is soon to be made official by decree.
- Inserm is accelerating the setting up of consultative partnership with universities involved in mixed units by a very early exchange of information on each partner's contribution in terms of human means, equipment, contract management and publication rules. The aim is to set up a consultative research site policy also involving university hospitals, which are Inserm's natural partners. In May 2005, Inserm signed two new master agreements with the University of Aix-en-Provence and the University of Orléans.

COMPETITIVE POLES

Competitive poles, launched by the government in 2004, bring together companies, academic institutions and research laboratories. Inserm has been directly involved in the creation of 8 health and biology competitive poles in 8 different regions. Over 50% of Inserm teams work in various capacities within such poles.



The interministerial zoning commission CIADT¹ of 12 July 2005 made the accreditation of 67 competitive poles official, eight of which are health and biology centers: Meditech Santé (Ile-de-France) and

the Lyon Biopole (Rhône-Alpes) qualify as international centers; Therapeutic Innovation (Alsace) is destined to acquire global visibility. The other health-oriented competitive poles are: Biotherapy (Pays-de-la-Loire),

(Languedoc-Roussillon), Nutrition, Health and Longevity (Nord-Pas-de-Calais) and Prod'Innov (Aquitaine).

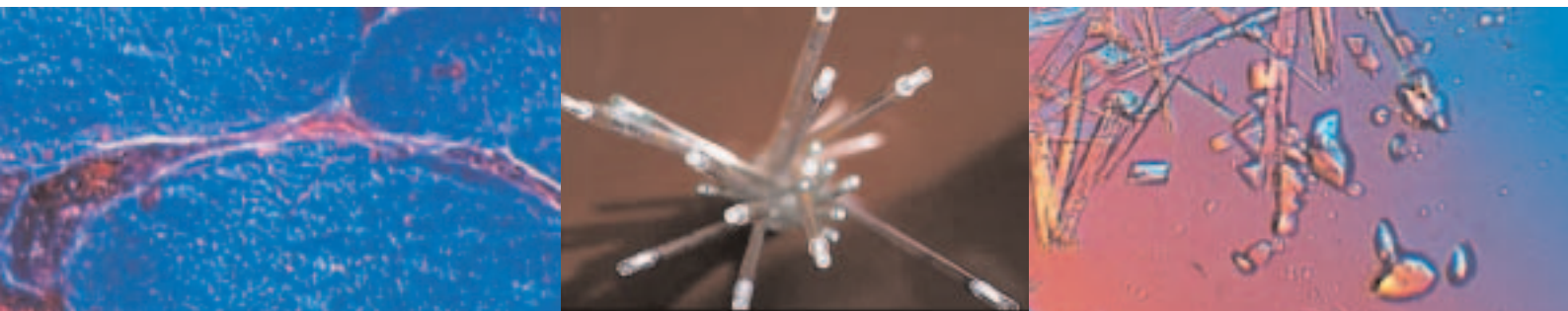
Inserm, though not involved in the actual creation of all eight competitive poles, is a founding or associate member of all of them and actively participates in the thematic and strategic committees of their governing bodies.

Inserm research teams were involved in six of the eight projects selected for funding in 2005 by the Ministry for Industry, after accreditation by the Lyon Biopole and Meditech Santé competitive poles.



¹ Comité interministériel d'aménagement du territoire

CANCER POLES



The seven cancer poles, created in 2003 on the initiative of the ministries in charge of health and research, have a mission to stimulate interfacing between research, clinical research activities, health care, and industry.

Inserm plays a crucial role through involvement of its teams in cancer pole projects (half of Inserm's research force works in oncology in some capacity) and being in charge of cancer pole facilities. Over half of the project leaders direct an Inserm unit or are affiliated with Inserm.

In 2005, Inserm teams obtained 50% of the projects approved for funding by the National Cancer Institute (INCa) in the following two categories of calls for proposals: free topic projects and networks including human sciences networks. Inserm has also launched a joint action with INCa in order to recruit high-level French and international researchers.

A proactive policy in French Overseas Departments and Territories (Dom-Tom)

Réunion

Following its creation in 2004, the CRC-EC implemented an ambitious public health program, particularly concerning nutrition and therapies for type-II diabetes. This action was led with the support of the Saint-Pierre and Saint-Denis hospitals, the general union of non-hospital-based practitioners (URML¹) and Inserm.

Inserm is also assisting a hospital team and a university team, and facilitates exchanges and collaborations with mainland units working on adipocyte metabolism and the genetics of rare diseases.

Guadeloupe

Inserm is present with Unit 458 (Paris VII University, University Antilles-Guyane), working almost exclusively on drepanocytosis. This facility, located in Pointe-à-Pitre will continue to develop a research effort consistent with the work being carried out in collaboration with the Guy-Mérault Drepanocytosis Center (prevention and screening), which is also located in the university hospital.

In addition, Inserm has set up interface contract funding for a young hospital practitioner, whose research activity focuses on neurodegenerative diseases (Parkinson's). This work is being carried out in close collaboration with teams from the Pitié-Salpêtrière hospital in Paris.

Martinique

A university team, working at the Fort-de-France University Hospital, is developing a dual research activity in retrovirology (HTLV1) and neurological diseases (multiple sclerosis). Two doctoral students from Lyon, trained in Inserm unit 433, and a young researcher from Inserm Unit 532 have recently joined the French West Indian team.

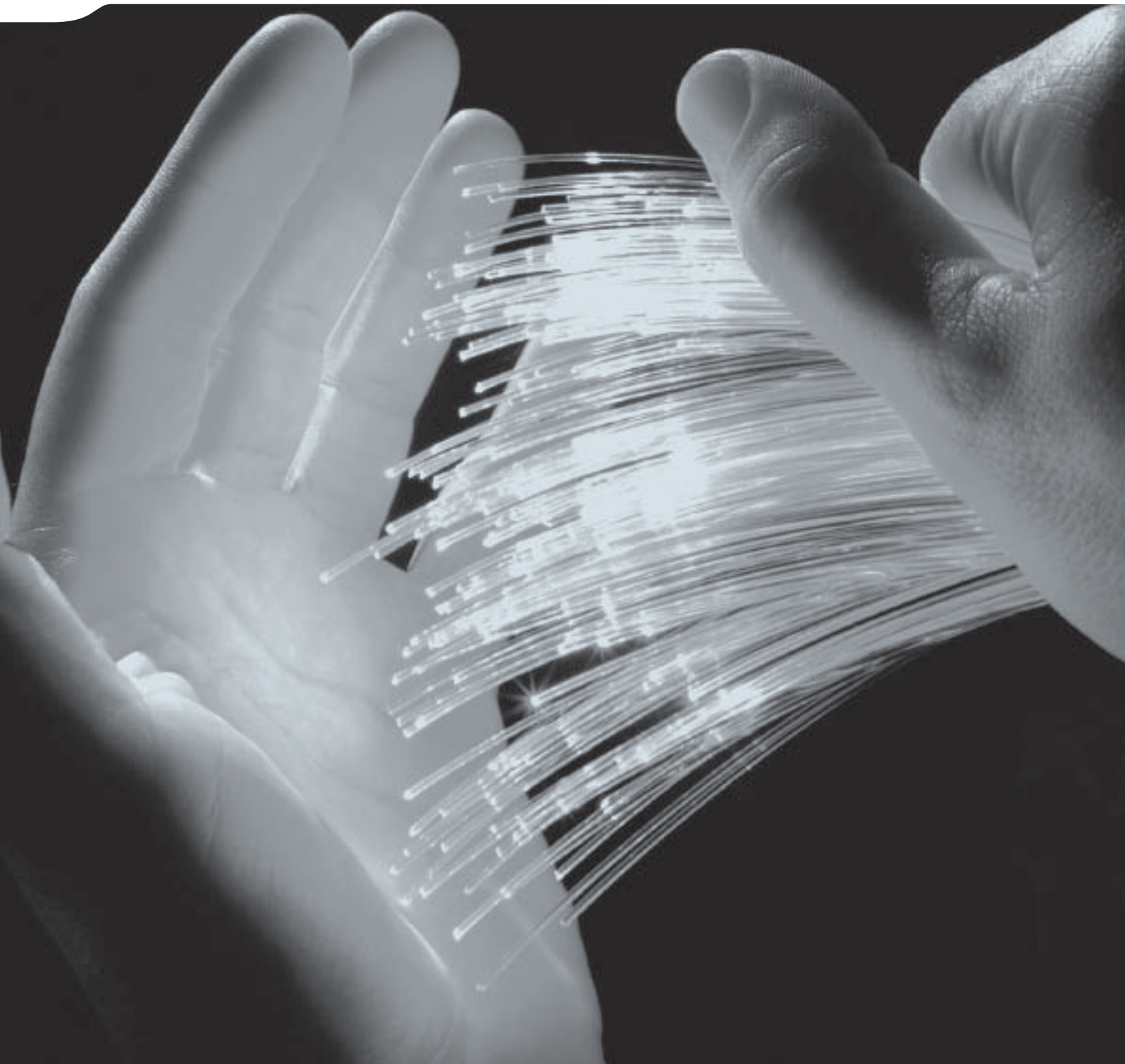
In the case of Réunion and Guadeloupe, Inserm's initiative to set up health and medical research coordination committees has allowed significant bridging between the university and the hospital environment.

¹ Union régionale de médecins libéraux

INTERNATIONAL DEVELOPMENT

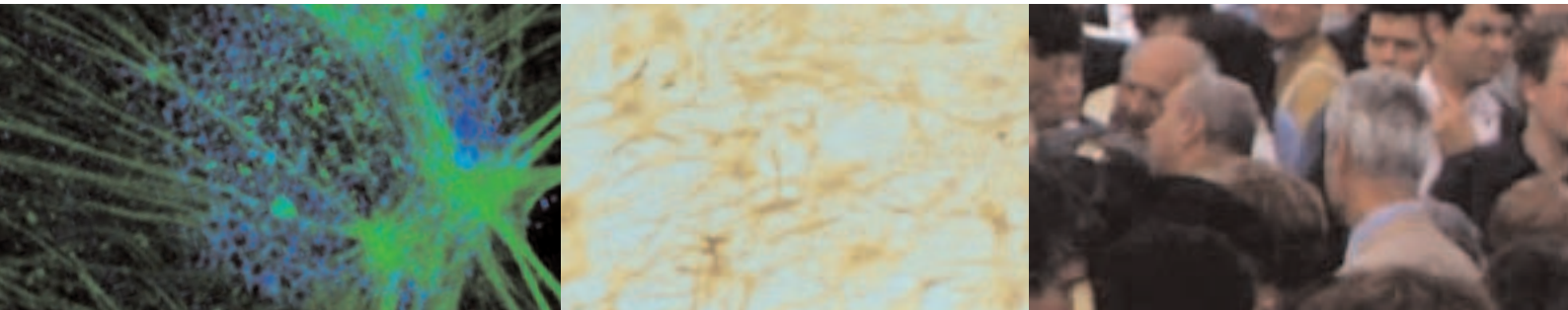
87 EUROPEAN OVERTURE

92 INTERNATIONAL OVERTURE



EUROPEAN OVERTURE

European policy integration led in 2004 to the emergence of a division dedicated to European policy within Inserm's department of international affairs. Then, as regional and European policies became more closely intertwined, the two existing services merged into a single Department of Regional and European Policy (DPRE) in May 2005.



The directorate general has defined the following major objectives for the DPRE:

- maximizing integration of European overture policies and adoption of European project approach by research sites;
- reinforcing bilateral cooperation efforts and researcher mobility within Europe, through the constitution of Associated European Laboratories (AEL) or even mixed units abroad;
- accentuating the synergy with Inserm's biomedical research partners by pooling skills and building networks in order to develop an organized, more efficient European policy all over France, together with universities, hospitals and other Scientific and technological Public Institutions, and the support of local authorities;
- pursuing the transversal efforts of the Europe office and pooling the complementary skills of Inserm headquarter departments, the Institute's regional administration services and Inserm Transfert for the constitution, management and monitoring of European projects.

In 2005, assistance to researchers for European project coordination and participation continued, in close collaboration

with Inserm Transfert. Within the realm of its particular skills, Inserm was also involved in defining research priorities and rules of participation in order to prepare for the 7th FPRTD (2007-2013). Furthermore, the impetus given to research site policy development abroad was sustained. European associated laboratory projects have given exchanges between researchers a genuine momentum and encouraged the definition of joint and complementary long-term objectives.

Multilateral Cooperation

Eleven new projects were selected in 2005 as part of 6th FPRTD initiatives, 8 of which were coordinated by Inserm. The close collaboration between Inserm and Inserm Transfert in assisting with the preparation and management of European projects has allowed the Institute to participate in 99 European projects. As of 31 December 2005, Inserm is coordinating 25 projects: 5 networks of excellence, 4 integrated projects, 12 specific targeted research projects and 4 specific support actions.

Inserm Transfert is working with Inserm's Department of Technology Transfer (DVTT)¹ in order to set up and negotiate consortium agreements for projects between European academic and industri-

al partners. In 2005, the DVTT participated in the negotiation of 50 consortium agreements, involving approximately 400 universities, university hospitals or European research institutions and close to 100 companies.

¹ *Département valorisation et transferts technologiques (DVTT)*

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European projects under Inserm scientific coordination and Inserm Transfert management

Project	Type	EC contribution (M€)	Duration (years)	Scientific coordinator
Virgil	NoE	9	4	T. Zoulim, Inserm Unit 271
EVGN	NoE	9	5	A. Tedgui, Inserm Unit 689
EMBIC	NoE	7.4	4	G. Chaouat, Inserm Unit 131
Myores	NoE	12.5	5	K. Jagla, Inserm Unit 384
Genostem	IP	8.8	4	C. Jorgensen, Inserm Unit 475
EuroHear	IP	12	4	C. Petit, Inserm Unit 587
EVI-Genoret	IP	10	4	J. Sahel, Inserm Unit 592
ATD	STREP	2.3	3	D. Gautheret, Inserm Unit 206
Cobra	STREP	2.99	3	L. Gutmann, Inserm Unit 655
Neuprocf	STREP	2.35	3	A. Edelman, Inserm Unit 467
Skintherapy	STREP	2.08	3	G. Meneguzzi, Inserm Unit 634
Moleda	STREP	2.45	3	D. Scherman, Inserm Unit 266
Therapeuskin	STREP	1.54	3	A. Hovnanian, Inserm Unit 563
PILDU	STREP	2.35	3	N. Bajos, Inserm Unit 569
Signalling & Traffic	STREP	1.5	3	T. Gali, Inserm Unit 536
Rescue	STREP	2.7	3	A. Privat, Inserm Unit 583
Nano4drug	STREP	2.45	3	P. Cumi, Inserm Unit 706

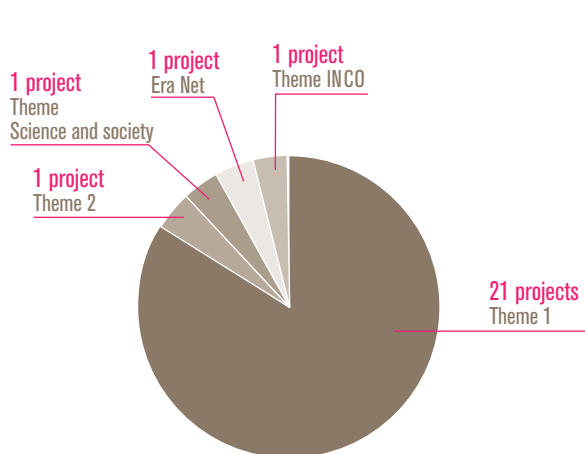
NoE: Network of Excellence; IP Integrated Project; STREP: Specific Targeted Research Project

Thanks to the know-how it has gained from working with Inserm, Inserm Transfert is coordinating 4 other European projects that are not being coordinated by Inserm. The close relationship between Inserm Transfert and Inserm's Regional and European Policy Department (DPRE) promotes optimal assistance for researchers in the preparation and management of European projects.

European projects under non-Inserm scientific coordination and Inserm Transfert management

Project	Type	EC contribution (M€)	Duration (years)	Scientific coordinator
Neurone	NoE	8.3	4	Cambridge University, UK
GALEN	NoE	12	5	Gant University, Belgium
SARS-DTV	STREP	2.4	3	Leiden University Hospital, the Netherlands
Trylediag	STREP	2.39	4	Tropical Medicine Institute, Belgium

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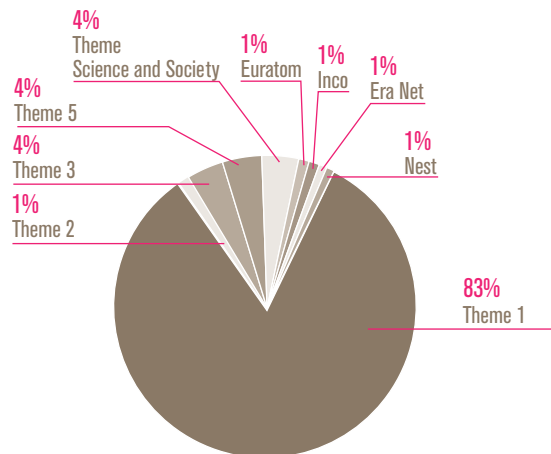
Theme 1
Life sciences
Genomics and
health-oriented
biotechnology: 21 projects

Theme 2
Information
technology: 1 project

Theme
Science and society:
1 project

Theme INCO:
1 project coordinated
by Inserm

Era Net:
1 project coordinated
by Inserm



Theme 1
Life sciences
Genomics and
health-oriented
biotechnology: 82 projects

Theme 2
Information
technology: 1 project

Theme 3
Nanotechnologies: 4 projects

Theme 5
Food safety: 4 projects

Theme
Science and society:
4 projects

Theme Euratom:
1 project

Theme INCO:
1 project

Era Net:
1 project

Nest:
1 project

Distribution of 6th FPRTD projects coordinated by Inserm in 2005 (a total of 25 projects)

Summary of Inserm's participation in the 6th FPRTD in 2005 (99 projects in total)

EU-financed projects: 241
Projects coordinated by France: 40
Projects coordinated by Inserm: 17

Seventh FPRTD (2007-2013)

In parallel to setting up the management of new projects under Inserm coordination, the Institute actively participated in 2005 in preparing to implement the 7th FPRTD. In particular, Inserm made itself the voice of the scientific community and promoted its own strategic plans in terms of facilities dedicated to biomedical and clinical research, measures encouraging mobility and definition of specific program content. Particular attention was given to the following points, which are at the heart of the Institute's mission:

- making health a priority among the the-

matic priorities of the specific Cooperation program;

- integrating biomedical and clinical research in programs designed to support research facilities as part of the specific Capacities program, mainly through ESFRI funding;
- supporting the European technological platform "Innovative Medicines for Citizens in Europe". Inserm, as France's delegate among other European member state representatives, led the reflection with its French academic partners and federated the initiatives and positions they adopted. Inserm was careful to inte-

grate this action with those of industrial partners involved in the public-private partnership underlying European technological platforms;

- actively considering the possibility of permanently establishing the networks of excellence supported as part of the 6th FPRTD. Such tools can be reused when implementing the 7th FPRTD;
- making its position known concerning the European Research Council (ERC) as part of the specific program entitled "Ideas";
- promoting approaches initiated by Inserm (Avenir programs, international

interface contracts) so as to increase researcher mobility and attractiveness as part of the Marie-Curie actions in the “People” specific program of the next FPRTD;

- increasing the involvement of Inserm and its partners (through the Virtual Institute for Public Health Research) in activities developed by the European public health framework program (2003-2008) coordinated by the Sanco Directorate General of the European Commission.

EURYI

Inserm participates in the European Young Investigators Awards program (EURYI), a prestigious award given by European Heads of Research Councils (EUROHORCs), coordinated by the European Science Foundation (ESF). The aim is to support projects of young postdoctoral researchers displaying scientific excellence by giving them the opportunity to set up an internationally visible research team. In 2005, three new laureates received awards under this program, bringing the number of award winners to four since 2004.

Bilateral Partnerships

Bilateral exchanges between Inserm and its European partners are very fruitful and may lead to more formal means of cooperation such as the creation of Associated European Laboratories. Such exchanges also serve as the basis for access to multi-lateral programs of the European Commission and the FPRTD in particular. Exchange or joint-project programs are funded either by cooperation agreements between the Institute and its European homologues or through Integrated Action

Programs jointly funded by the Ministry of the Environment (MEA) and the Ministry for Higher Education and Research (MESR).

In the course of 2005, the eight ongoing bilateral agreements have led to nearly 130 short-term research exchanges between Inserm and partner organizations in Spain, Portugal, Germany, Italy, Belgium, the Netherlands and the Czech Republic.

By promoting bilateral partnerships and mobility, Inserm is pursuing its elitist policy of Associated European Laboratory creation. This policy relies on an ambitious

high-quality long-term scientific program defined in terms of resulting added value and based on the combination of researcher exchanges and bilocalized complementary skills and tools.

Three new AELs are currently in the preparation phase with Italian (Rome and Milan) and Scottish (Dundee) partners. In addition, and as a counterpart to the setting up of mixed Inserm units abroad, such as the ones at DKFZ in Heidelberg and the University of Glasgow, the possibility of creating a mixed unit with DKFZ in France is currently being examined.

Laureate of the first EURYI call (2004)

SURNAME	KOECHLIN
Name	Étienne Paul
Nationality	French
Country of origin	France
Host laboratory	Inserm Unit 742 - University Pierre et Marie-Curie - Dir Marc MAIER
Field	Neurosciences
Project title	Executive control and the functional organisation of the human prefrontal cortex

Laureates of the second EURYI call (2005)

SURNAME	ALBERT	SINGH-MANOUX	TADDEI
Name	Mathew	Archana	François
Nationality	American	French	French
Country of origin	USA	France/UK	France
Host laboratory	Pasteur Institute, Paris	Inserm Unit 687 Paris - St-Maurice Dir France Lert	Inserm Unit 571 CHU Necker – Paris Dir Miroslav Radman
Field	Immunology	Human and Social Sciences Public Health	Molecular Genetics
Project title	Apoptotic cell death and Immunity	Determinants of health inequalities in ageing populations: evidence from the French Gazel and British Whitehall II cohort studies	Causes and consequences of natural patterns of phenotypic variability, aging and death in cellular lineages

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AEIs and mixed Units in 2005

● **Mixed units in Europe:**

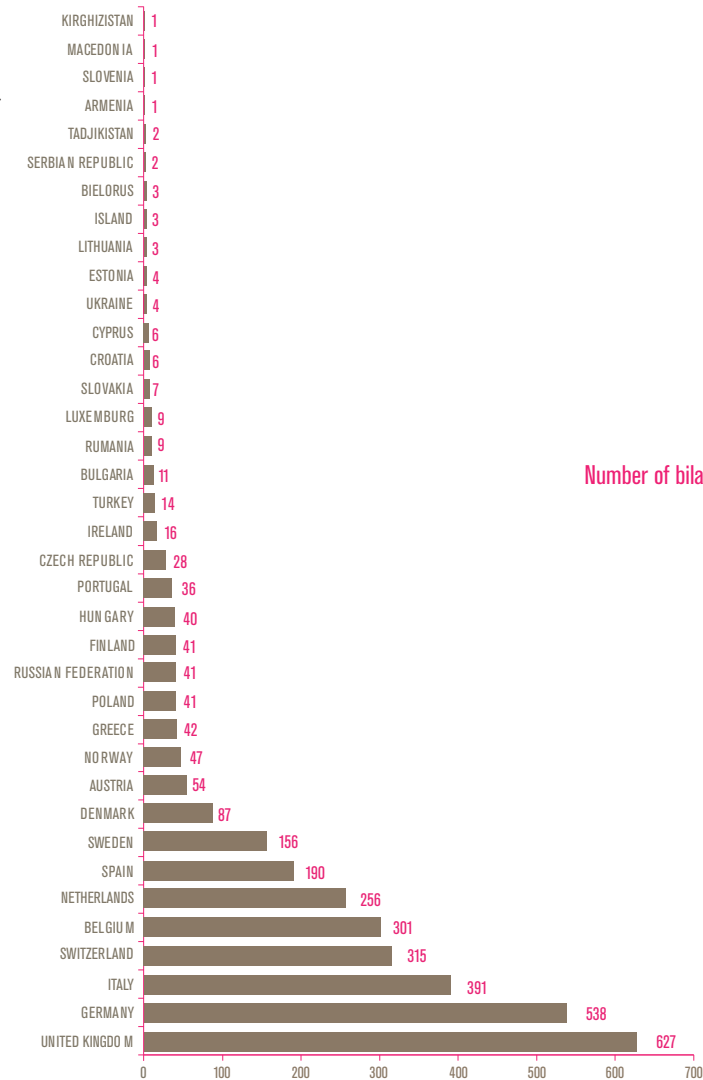
Glasgow University: C. Doerig, Inserm Unit 609
 DKFZ / J. Rommelaere Inserm Unit 701

★ **Associated European Laboratories (LEA)**

Toulouse: D. Langin Inserm Unit 586 / Prague: V. Stich (Charles University)
 Lille: M. Capron Inserm Unit 547 / Brussels: M. Goldman (IMI)



Another of Inserm’s priorities in terms of bilateral European cooperation is to reinforce the Institute’s interactions and visibility with respect to research institutions and laboratories in Central and Eastern Europe. To do this, prospective actions have been initiated in 2005 in the Czech Republic as well as Hungary, Poland and Rumania (visits, joint seminars, exchange programs).



Number of bilateral cooperation efforts in Europe

INTERNATIONAL OVERTURE

Inserm's goals at the international level are to reinforce scientific partnerships, ensure the visibility of the Institute, its researchers and their research as well as promote the setting up of units and associated laboratories abroad. The Director General's foreign missions in the United States, Canada and China, either in a bilateral situation or to meet his homologues, have greatly contributed to the set up of such facilities.



Reinforcement of Bilateral Scientific Partnerships

Inserm manages 21 cooperation agreements with 14 countries outside Europe. The agreements were negotiated with homologous organizations abroad in order to meet researcher demand. In 2005, Inserm collected 150 applications for joint projects and 40 applications for mobility. Evaluations, entrusted to recognized Inserm unit members, focus on project scientific quality, originality, the intention to involve young researchers and/or doctoral students and intrinsic team quality. Following a rigorous evaluation process, Inserm promotes projects demonstrating scientific excellence and funds high-quality joint projects that ensure visibility of the Institute with respect to its partners.

Setting up Associated Laboratories and Inserm Units Abroad

Through joint development with its partners abroad (research institutions, universities), Inserm is setting up innovative facilities in the form of associated international laboratories, Inserm units abroad and foreign partner facilities in France. These novel forms of partnerships allow the Institute to develop new research programs based on complementarity and team interdisciplinarity, to reinforce long-term exchanges of tenured or non-tenured

researchers, to share access to technological facilities, to set up common clinical trials, to make joint grant applications to national and international funding bodies, and to increase the visibility and notoriety of the Institute.

International Visibility

With a view to stimulate the evolution of cooperation agreements, Inserm organizes bilateral workshops on topics defined in collaboration with its partners. These workshops, organized with the participation of French embassies abroad, offer Inserm researchers an opportunity to meet their future partners. They ensure visibility for the Institute and increase its attractiveness. In addition to this strategy, exploratory missions allow the Institute to define its policy in different countries. Strategic and prospective monitoring actions are organized as part of missions of scientific and technological monitoring on the part of French embassies abroad.

Industrialized Countries

The United States

A North American office has been created to reinforce transversality between the various Inserm departments and promote the development of all facets of cooperation with the United States: scientific partner-

ships, human resources policy, scientific and technological monitoring, assistance in project set up.

A mission was created to assist in the development of projects to be submitted to American funding agencies (NIH, Bill & Melinda Gates Foundation, Howard Hughes, DoD, DoE). This reflects Inserm's desire to make the Institute's research more attractive.

Links with the University of Pittsburgh have been strengthened with a view to implant an Inserm Unit within the University and work on stem cells and cellular therapy.

The launch of the Inserm-NIH Postdoctoral Contract Program which is designed to provide a framework for the return of researchers doing their postdoctoral work at NIH. These five-year two-phase contracts comprise a phase 1 with 3 years of postdoctoral work at one of the NIH institutes and a phase 2 allowing, after evaluation, two transition years in an Inserm unit or a university, in partnership with the Institute. An NIH follow-up committee is set up to evaluate the running of the program. In the third year of phase 1, laureates submit a research project and reintegration plan to Inserm. The first pro-

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gram session took place at the end of 2005. Ten applications were submitted and two candidates were selected. By 2006, the call for projects will be permanent and applications will be evaluated every three months.

Inserm is reinforcing its ties with the NIH through research programs such as the National Research Programs and Thematic Concerted Actions with the dual objective of keeping an open dialogue with the NIH and defining common research axes. In 2005, Inserm-NIAAA¹ and Inserm-NIAMS² meetings took place in the United States.

Closer Ties with MIT, which are being facilitated by the Director General's mission, are part of Inserm's strategy to reinforce its presence in parts of the United States and maintain the continuum between basic research, translational research, clinical research and knowledge management. The goal is to facilitate researcher exchanges as part of the MIT-France program set up by the Ministry for Foreign Affairs and prepare the implantation of Inserm Transfert in the Boston area. This will ensure greater visibility of Inserm's patent portfolio and work towards developing a relationship between the Inserm School and the Harvard-MIT MD-PhD programs.

Inserm's representative in the United States is organizing seminars in the most prestigious American universities. These give the Institute a better visibility and an opportunity to identify the best researchers for future recruitment.



Japan

Creation of a laboratory associated with the Riken Institute to work on lipidomics.

Inserm and INSA³ have created an associated laboratory with the Riken Institute (one the most prestigious research institutes in Japan) in order to study lipid nanostructure. This common research project was born from an association between Inserm Unit 585 and two labora-

tories from the Riken Institute, in the suburbs of Tokyo. It is based on the combination of specific and complementary know-how in synthetic chemistry and cellular engineering, which should help understand more precisely the physico-chemical interaction and the molecular structure of lipids, a crucial step in the development of targeted therapies.

The tripartite meeting (France-Japan-United States) on the biology of stem cells in Kobe (Japan), aimed to ensure the long-term survival of the operation launched in 2004 in order to constitute a research group involving the three poles working on the biology of stem cells. This should facilitate researcher exchanges and access to complementary technological platforms. The adopted strategy is based on the identification of potential markers to characterize stem cells and on functional gene analysis so as to develop a common research project.

A clinical research collaboration was set up with Kyoto University. As part of an active policy for the industrial development of biotechnologies, Japan and the University of Kyoto have created an important translational research entity in

KEY FIGURES IN 2005

▪ Cooperation efforts

Total number of cooperation efforts: 5,973

With Europe: 3,334 (EU: 2,874)

With the US and Canada: 1,770

▪ Agreements

21 cooperation agreements including 13 that allow funding of joint research projects

66 research projects supported in 2005 with 138 foreign researchers hosted by Inserm and 109 French researchers on detachment.

▪ 900 researchers from abroad hosted by Inserm laboratories. The most frequently represented nationalities were Chinese, Italian, German, Lebanese, Spanish, Algerian and Moroccan.

¹ National Institute on Alcohol Abuse and Alcoholism

² National Institute of Arthritis and Musculoskeletal and Skin Diseases

³ University of Science and Technology in Lyon

order to have closer contacts (know-how and joint projects) with the Saint-Louis Hospital CRC.

Canada

Inserm Unit 743 was inaugurated at the University of Montreal. Created in partnership between the University of Montreal and the Montreal University Hospital, Inserm Unit 743 is the first of its kind in North America. This new unit, working on human immunity, bridges basic research (molecular and cellular mechanism of the immune response) and clinical research (therapeutic and vaccination strategies).

Israel

The Higher Council has launched calls for proposals for Franco-Israeli scientific and technological research and cooperation. Launched in order to fund network research programs in human genetics and medical imagery, the programs selected a total of 12 projects including 8 emanating from Inserm laboratories.

Preparation of a convention for the creation of an international laboratory associated with the Rappaport Institute at the Technion University in Haifa. This laboratory will focus on human embryonic stem cells as a source material for epidermis and cornea reconstitution.

Emerging countries

China

Continuing support is being provided for the pole in Shanghai in partnership with CNRS and the Pasteur Institute. With the selection of three new research teams, the Shanghai research pole is beginning to

bear fruit. The teams currently in place have obtained significant results and the French presence is being reinforced with the appointment of a full-time researcher. Research projects are being developed in collaboration with the Pasteur Institute in Shanghai.

An agreement has been prepared for the creation of an associated laboratory between Inserm, the University of Rennes and South East Nanjing University. The program of the future Sino-French biomedical information research center revolves around the reconstruction and analysis of image sequences, involving an experimental and clinical facet on the one hand (common protocols and clinical evaluation conditions) and a technological facet (materials, software, computer assisted medicine) on the other hand.

Closer links are being woven between Inserm and the Shanghai incubator network. The dynamic development of the Shanghai area has manifested itself through the development of the Pudong zone. Inserm is a partner of the Sino-French innovation network designed to facilitate closer collaboration between French and Chinese biotechnology companies.

India

The fifth joint working group meeting between the Indian Council for Medical Research (ICMR) and Inserm took place in New Delhi. It allowed an assessment to be made on the current state of Inserm-ICMR collaboration: organization of workshops, report on subsidized ongoing projects, selection of new projects (particularly on tuberculosis, prenatal genetics

and malaria), and selection of future fields of collaboration (biomarkers in cardiovascular diseases and diabetes).

The Franco-Indian conference on clinical research, which took place in Calcutta, revolved around a general presentation of clinical research know-how and its illustration in three particular fields: infectious diseases, cardiovascular diseases and cholera/enterobacterial diseases.

South Korea

The exploratory mission by the president of Inserm's administration board and some researchers, set up in order to study the possibilities of cooperation between Inserm and South Korea, has highlighted Korea's research and development effort as well as the importance for Inserm to develop collaborations and facilitate interfacing between biomedical research, bioengineering and nanotechnologies.

Brazil

The scientific conference to commemorate the 15th year of the Inserm-Fiocruz agreement gathered all the French and Brazilian directors of projects supported since 2000 as part of the Inserm-Fiocruz agreement in order to analyze achievements and discuss the lines of cooperation to develop in the years to come.

The cooperation agreement with the Oswaldo Cruz Foundation was reinforced. Ten projects were selected for 2006-2007, with special focus on virology, Parasitology and immunology as well as pharmacology and cardiovascular diseases. This underscores the tendency towards diversification of collaborations, from endemic parasitic diseases to more fundamental approaches or research on civilized-world pathologies.

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Northern Africa

Morocco

CNRST (National Center for Scientific and technological Research) is seeking cooperation with Inserm for the Institute to bring its experience in setting up life sciences and health platforms. A first bilateral cooperation meeting took place in January 2005, in Rabat, in order to have a collective discussion and identify the necessary equipment required to set up a platform in Morocco. In April 2005, workshops were organized in Rabat in order to allow the scientific community to participate in a common discussion on existing possibilities and needs in the field of life sciences, and more particularly to define the types of investment necessary in the fields of genomics, proteomics, imagery and bioinformatics. The workshops were followed by a transcriptomics training session in July 2005 and subsequent visits on French sites in November 2005.

A project for the creation of a study and research center for infectious diseases and

AIDS (CERMIS) aims to acquire more knowledge on infectious diseases and particularly emerging diseases of a viral nature such as AIDS (HIV virus). It should serve as a reference for Sub-Sahara African countries, Northern Africa and African Mediterranean regions.

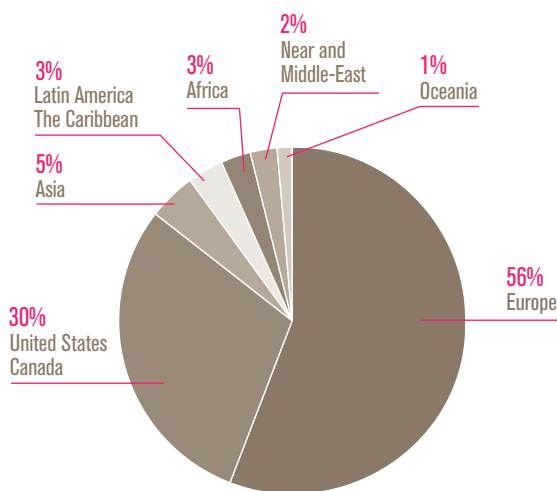
Algeria

Collaboration is continuing in the field of genetics. Inserm is carrying out an expert evaluation as part of the reflection on the development of the scientific research evaluation system in Algeria.

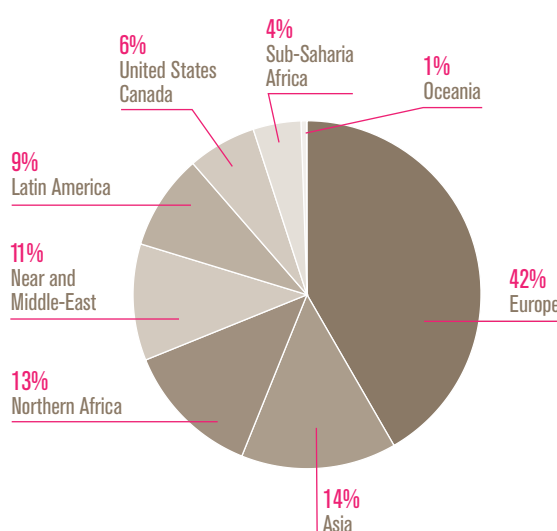
Tunisia

An exploratory mission and discussions have taken place in view of the signature of the cooperation agreement with the Tunisian research directorate. The goal is to set up a mixed consultative committee made up of ten experts representing the most promising fields for this cooperation (oncology, genetics, infectious diseases, clinical research) by using the possible areas of cooperation: development of associated laboratories, interface leave con-

tracts for tenured Inserm researchers funded by the Tunisian side, long-term hosting of Tunisian post-doctoral researchers in France.



International cooperation



Origin of foreign researchers hosted by Inserm Units

KNOWLEDGE TRANSFER

97 KNOWLEDGE MANAGEMENT
AND TECHNOLOGY TRANSFER

103 INSERM TRANSFERT
DEVELOPMENT AND
PREPARATION OF THE MERGER
WITH THE DEPARTMENT OF
TECHNOLOGY TRANSFER (DVTT)



KNOWLEDGE MANAGEMENT AND TECHNOLOGY TRANSFER

Knowledge Management of biomedical research being a primary concern for Inserm, the Institute is increasingly involved in sharing and transferring knowledge and technology. In 2005, the Department of Technology Transfer (DVTT) concentrated on assisting and advising research teams, on helping projects emerge or identifying those likely to be of interest to potential partners, and on proposing procedures and tools allowing the organization of such projects. It also multiplied contacts with pharmaceutical and biopharmaceutical companies, as well as the biotechnology and biomedical technology industry.



Industrial property

Industrial property is a major research knowledge management tool for Inserm. It contributes to the structuring of exchanges and collaborations between research teams and companies. It is also a key element for technological transfer and company creation. In 2005, Inserm focused on achieving optimal protection of its teams' inventions by defining appropriate strategies in each case.

A new version of the Inventor's Guide has been widely distributed among the scientific community and to biotechnology companies, and is also available online on Inserm's Website.

Knowledge management workshops organized on research sites have given a great deal of attention to industrial protection and case studies. They allow researchers to get a better understanding of the role of patenting in intellectual asset management and become aware of the need to use "good practices", required by patent laws.

The portfolio in 2005

- 81 declarations of inventions were processed by Inserm (-14 % 2005/2004).
- 70 new priority patent applications were submitted on the initiative of Inserm or

its partners, as part of mixed laboratory projects or collaborative projects with industry. It is to be noted that even if this figure is likely to rise somewhat (due to applications made at the end of 2005 by Inserm partners and not available to date), a marked decrease in applications is being recorded for the first time this year (-26% 2004/2005). Several factors could be responsible for this:

- the fall in the number of declarations of invention submitted to Inserm;
- Inserm's selection in order to protect inventions meeting patenting criteria, which are constantly evolving in the field of biotechnology, and having sufficient commercial potential (about half

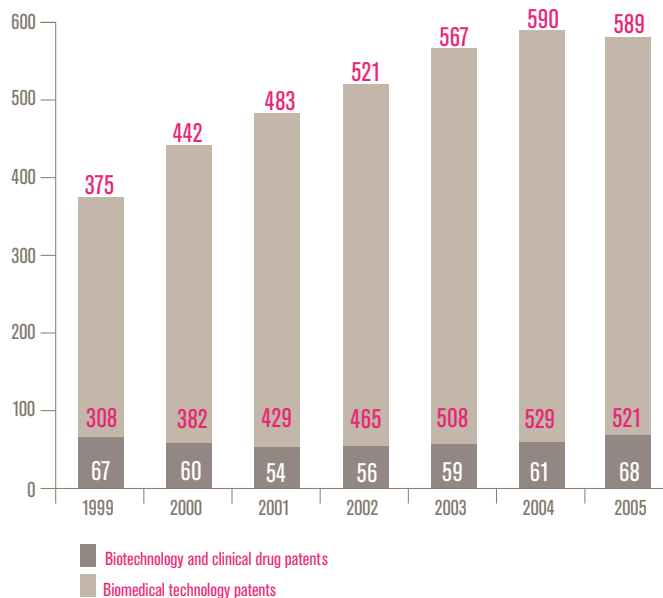
of the declarations of inventions are eventually selected for patenting);

- the reduction in the number of new company creation projects, based on industrial protection by patenting, to 5 in 2005 as against 7 in 2004, 2003 and 2004.

The number of patent families in the portfolio has stabilized at 589.

Fields of Application

All fields of medical application and over half of patent families are represented (immunology, neurology, infectious pathologies and oncology).



Progression of Inserm's patents portfolio (1999-2005)

Co-ownership

The existence of Inserm-University mixed laboratories and the involvement of Inserm teams in research collaborations and networks results in a high level of co-ownership of patent filing with French and international academic institutions or industry (72% of the portfolio, including 27% co-owned with industry).

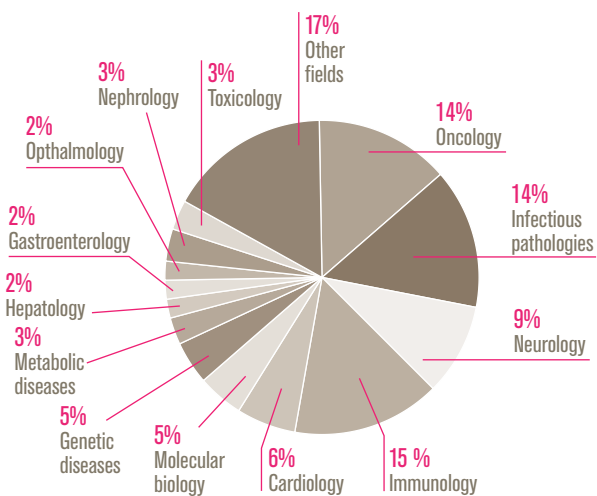
Patent Filing Country

In the field of health, patent protection needs to be considered at international level. In this regard, Inserm is submitting

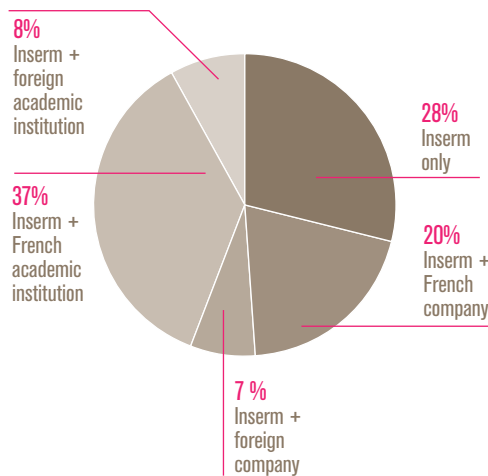
an increasing number of projects through European channels (twice as many in 3 years). European patenting has several advantages: writing patent applications is easier because patenting offices work from scientific publications written in English. In addition, seeking industrial partners on an international level is easier and translation fees at the national stage are limited. Finally, the European Patents Office gives a first opinion on the patenting potential of inventions at the time of research report (i.e. 8-9 months after submission), which helps guide the industrial protection strategy.

Contracting

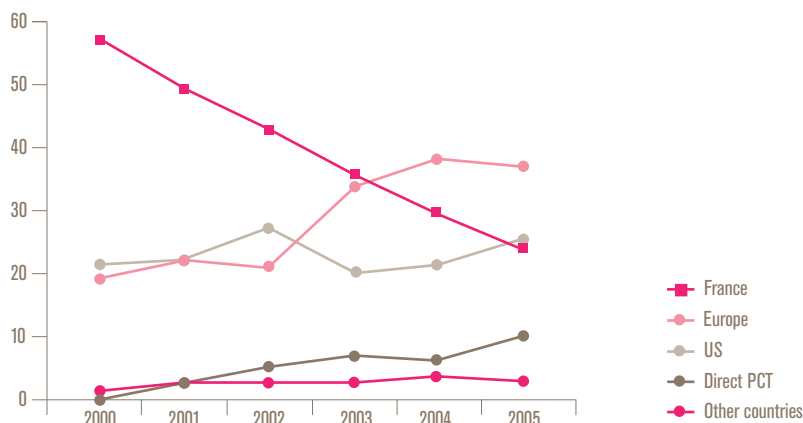
Contracting of the patents portfolio requires 2 to 3 years in order to finalize transfer towards one or more companies. One year is generally necessary to consolidate the invention and 2 to 3 years to find potential industrial partners and negotiate transfer. Excluding the patent families filed in 2004 and 2005, contracting of the total portfolio has increased from 55 to 68%.



Distribution of Inserm's patents portfolio by field as of 31 December 2005



Ownership of the patents portfolio as of 31 December 2005



Geographic distribution of priority patent filing

Cost of Industrial Property

In the field of health, maintaining a patents portfolio is costly. Broad international protection is essential to encourage long and risky investments for the development of diagnostic and therapeutic products. Patent filing costs somewhere between 10,000 and 15,000€ per country. A further cost of 15 to 20,000€ per country is incurred before a patent is issued and another 250,000€ are needed to maintain the patent in 8 to 10 countries. Inventions can sometimes be patented in the early stages of development. This is for instance the case for inventions leading to new approaches in immunotherapy or cellular therapy, in which case it is difficult to predict the exact commercial application(s) and estimate the return on investment. Inserm must nonetheless take the financial risk of protecting such inventions, which are prototypes for future innovative therapeutic drugs meeting medical needs.

In 2005, maintenance of the 589-family portfolio cost Inserm 1,461 K€, an amount that only represents part of the total portfolio cost. Indeed, portfolio co-owners (78% of the portfolio families) are responsible for part of the protection cost. Furthermore, such costs are born by companies if they obtain exclusive licensing rights for a patent. However, in the case of young companies emanating from Inserm research or having exclusive rights on an Inserm patent, the Institute continues to bear the cost of industrial protection for 1-2 years after transfer so as to avoid using all the cash flow of these young partner companies.

Since the Law on innovation began to be implemented, 72 patent families have been

transferred to young innovative companies (i.e. over 18% of the total portfolio) and 20 other families are due to be transferred.

Industrial Partners and Intellectual Asset Management Projects

The portfolio

There are over 1,100 ongoing contracts involving 550 scientists and 426 French and foreign companies. Half of these contracts concern the following fields: oncology, immunology, neurobiology/ neurology, molecular biology and cellular biology (including genetic engineering).

Projects

- 462 R&D contracts (153 new contracts)
- 544 TT contracts (52 new contracts)

Patents

- 589 effective patents (70 new patents)

Industrial Partnerships and Intellectual Asset Management Projects

In 2005, Inserm managed 462 R&D contracts (-7% 2004/2005), including 153 new contracts (+4% 2004/2005) involving 230 companies

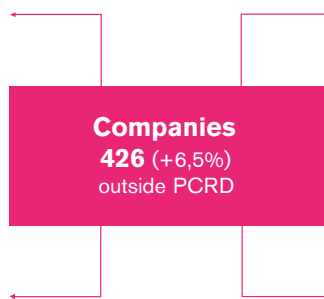
This year, Inserm continued to reinforce its technology transfer activity: 544 ongoing

Revenues

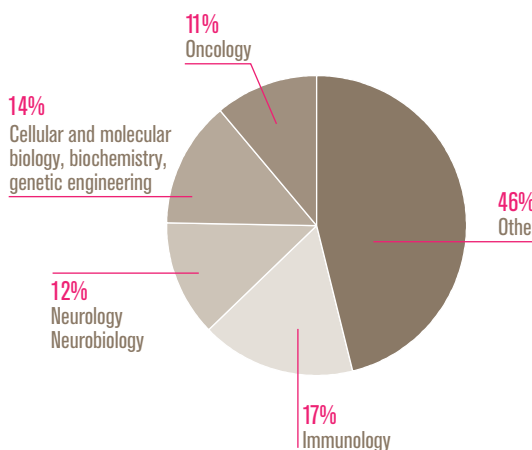
- TT contracts: 13.3 M€ gross (+ 12% 2004/2005)
- R&D contracts: 11.8 M€ (stable)

Men and women

- 550 scientists
- ≈ 110 researchers and creators of 66 young innovative companies

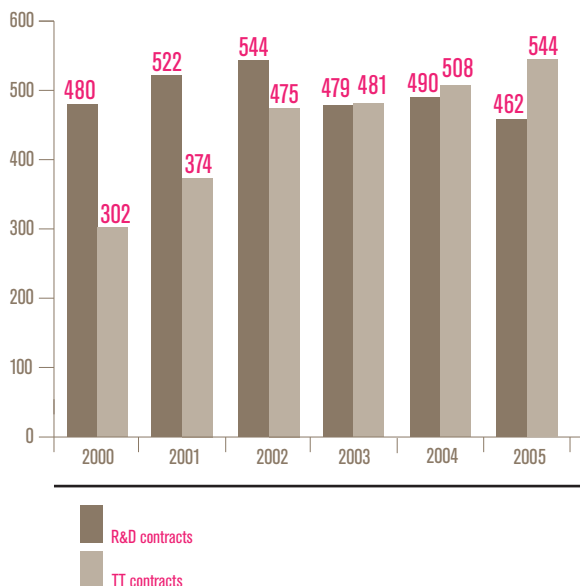


Knowledge management and technology transfer (TT) as of 31 December 2005



Distribution of ongoing contracts by field

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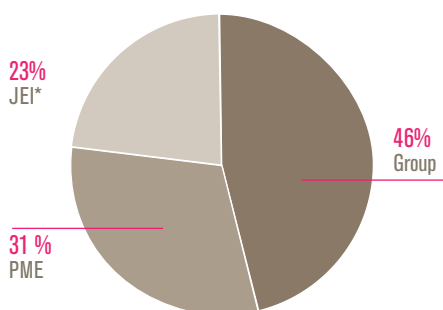


Progression of ongoing contracts (2000-2005)

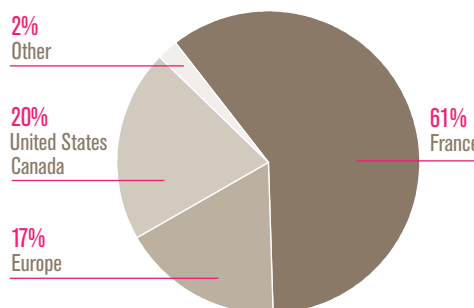
contracts (+7% 2004/2005) including 52 new contracts, involving 249 companies. The technological transfer activity with young innovative companies is particularly intense since 72 patent applications have been transferred in the context of company creations since the Law on innovation was voted.

Knowledge Management

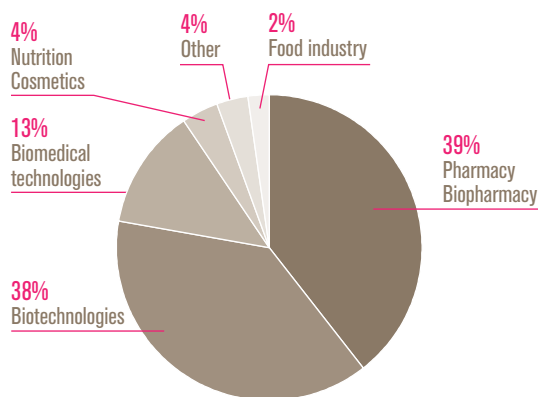
Gross contract revenues are distributed as follows: 11.8 M€ for R&D contracts (stable over 2004/2005) and 13.3 M€ (+12% 2004/2005) for transfer contracts.



Distribution of company size for ongoing contracts
*YIC: young innovative companies



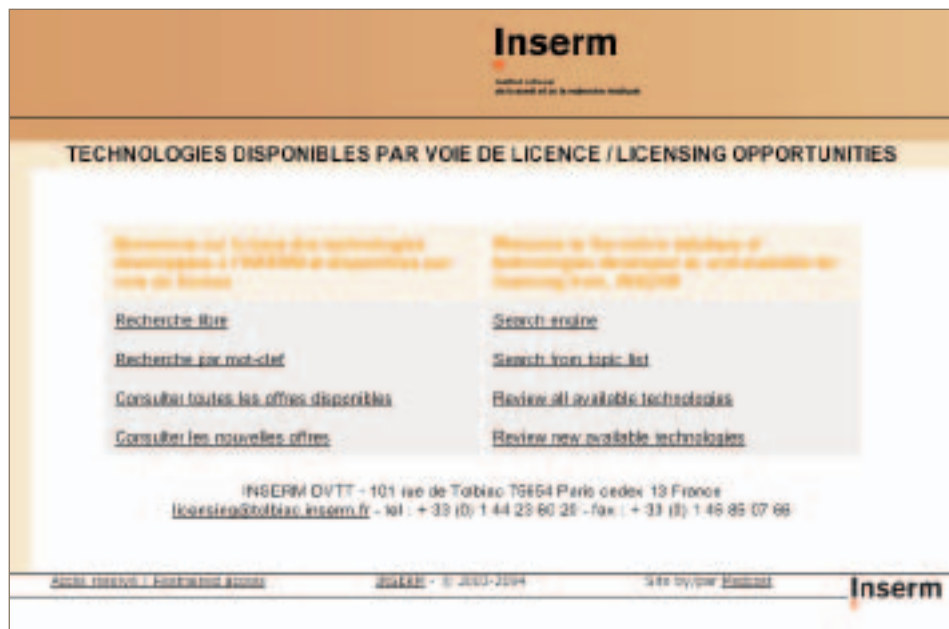
Geographic distribution of companies with ongoing contracts



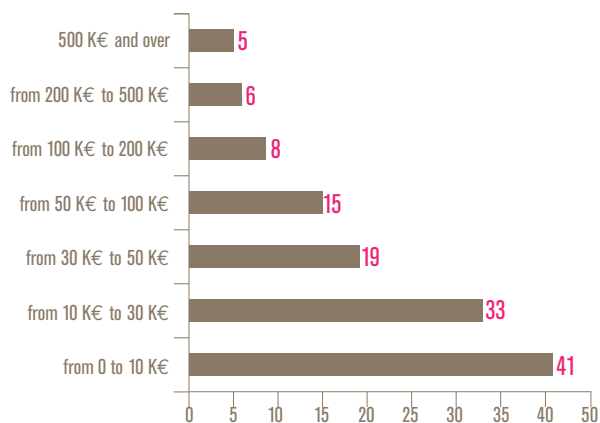
Distribution of industrial activity sectors for ongoing contracts

The bilingual (English-French) database recording technologies available for license gives access to more than 270 patented and non-patented offers, classified by biomedical and biotechnological specialty. In 2005, a census recorded 10,000 visits on the site, approximately half of which originated from France.

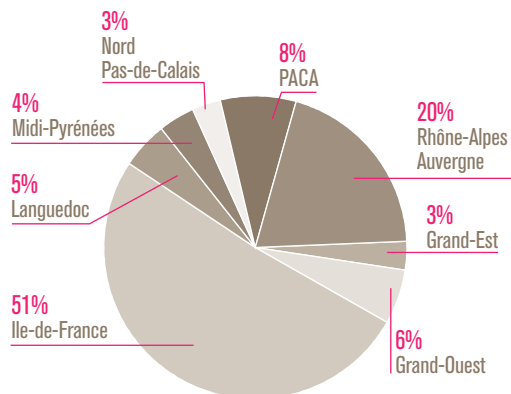
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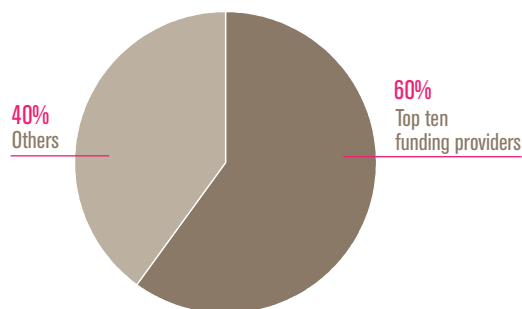
Home page of the website <http://licensing.inserm.fr>



Number of partners per funding bracket for 2005



Regional distribution of R&D contract funding in 2005



Relative weight of R&D contract funding providers in 2005

R&D Contract Revenues

Revenues received in 2005 for ongoing R&D contracts are stable, at 11.8 M€, but do not reflect the contract activity generated by Inserm in collaboration with industry. Indeed, they only concern funding of projects managed by Inserm without taking into account funding managed by other partner institutions involved in mixed Inserm laboratories (universities, hospitals, other research institutions).

Revenues from Technological Transfer Contracts

Transfer activities have generated a gross revenue totaling 13.3 M€, which represents a growth of 12% with respect to 2004. This progression results essentially from the transfer of research tools optimally and internationally marketed thanks to an online service platform displaying available technologies. This platform allows for better research tool visibility and facilitates access by industry while reducing transaction time. Transfer contracts involve patent or know-how transfer, particularly concerning biological materials.

Transfer contracts are a source of revenues in the form of fixed installments linked to the success of development by the licensee as well as revenues from product commercialization. In 2005, 167 licenses generated revenues, approximately 80% of which were derived from only 10 licenses.

- transgenic animal models (approximately 20 pharmaceutical groups and biotechnology companies);
- monoclonal antibodies (Coulter, Immunotech, Santa Cruz, Pharmigen);
- a diagnostic molecular probe (Athena, Cerba).

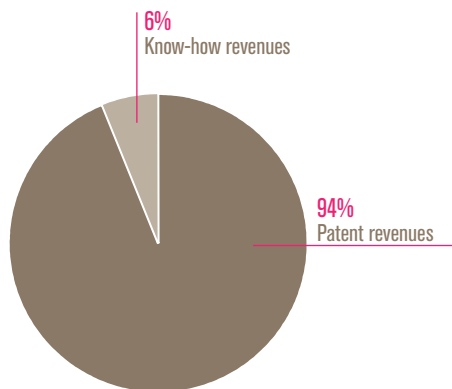
Products and Research Tools

They include:

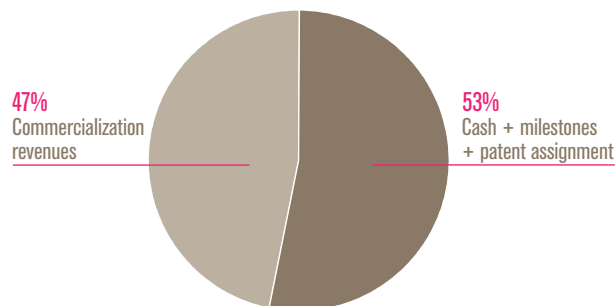
- an HPV test (Digene and Roche);
- a hepatitis recombinant vaccine (GSK and Sanofi-Pasteur);
- Sonolith, Ablatherm (EDAP/Technomed);
- diagnostic kits (Biomérieux, Immunotech, Coulter);
- cell lines, the Cerep receptor;

Profit Sharing

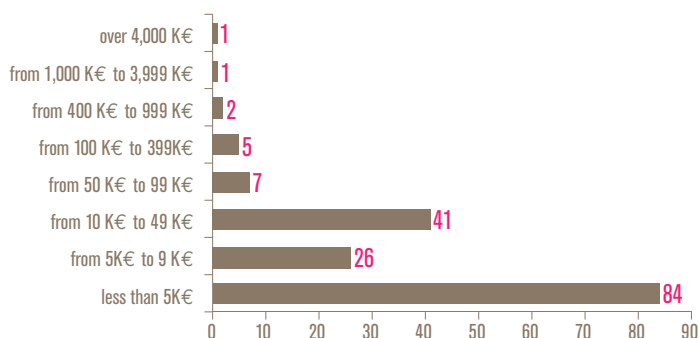
Gross revenues from transfer contracts are distributed among the co-owners of know-how and transferred patents. The 41% Inserm has earned have served to honor profit sharing obligations to inventors. Profit sharing among the 163 researchers concerned varies between 1,000 and 5,000 euros per year in 40% of cases.



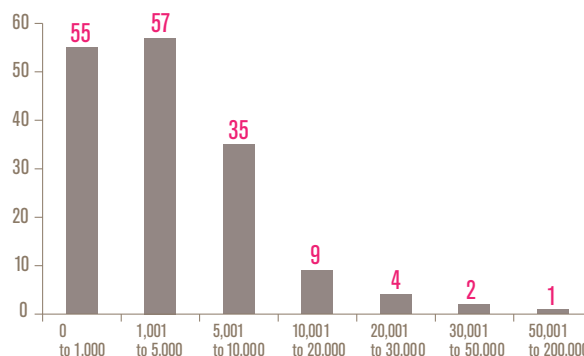
Distribution of gross revenues from know-how and patents



Distribution of gross revenues from licensing in 2005



Number of licenses per revenue bracket for 2005



Number of inventors per profit sharing bracket

NUMBER OF INVENTORS PER PROFIT SHARING BRACKET INSERM-TRANSFERT DEVELOPMENT AND PREPARATION OF THE MERGER WITH DVTT

In 2005, Inserm Transfert strengthened its action in the four fields it encompasses: European project management, clinical research support, company creation and industrial partnership. It also worked towards tightening the links with the Department of Technology Transfer (DVTT) in view of their merger in 2006.



Merger of Inserm Transfert and the DVTT was approved by Inserm's Administration Board in October 2005 and is due to become effective in January 2006. Apart from administrative reasons, bringing the two entities closer together revolved around three activities: company creation, industrial partnerships and maturation projects.

European Project Management

In collaboration with the Department of Regional and European Policy (DPRE), Inserm Transfert assists researchers with the conception, negotiation and management of European projects. In this capacity, Inserm Transfert manages numerous networks of excellence, integrated projects and specific targeted research projects (STREP) funded by the European Commission and scientifically coordinated by Inserm.

In 2005, following the second and third calls for projects of the 6th FPRTD in life sciences, genomics and biotechnologies for health, 10 new projects managed by Inserm Transfert were funded and launched, 8 of which were and 2 were not coordinated by Inserm. Inserm Transfert manages a total of 25 European projects with a budget of almost 272 M€ (124 M€

of which are contributed by the European community). To do this, the Inserm Transfert team responsible for the management of international projects was strengthened by the appointment of 4 senior and 5 junior European project managers.

Furthermore, 17 new projects coordinated by Inserm and managed by Inserm Transfert were submitted at the end of 2005, in response to the fourth 6th FPRTD call for projects. Results will be known during the first semester of 2006.

Support for High-Potential Projects

Proof of Concept and Maturation Projects

The first level of action of Inserm Transfert consists in facilitating the characterization of candidate clinical drugs during preclinical development. Such support aims at helping project applicants to obtain proof of concept, showing that a product or strategy is indeed efficient. Transfer of research results towards patients can then be achieved either by industrial partners or by the creation of innovative companies.

Proof of concept consists in bringing experimental proof that a candidate drug can correct or attenuate a given pathology. It confirms the therapeutic or diagnostic potential of a new approach or medical device. This step requires both means and a clear idea of the significant elements neces-

sary, either to propose a license under optimal conditions or consider the creation of a company with the maximum chances of success. With this in mind, Inserm Transfert brings support to secure funding through the various institutional calls for proposals or for developing contacts with investors.

The proof of concept rationale was recently used in the call for projects entitled Emergence and Maturation of High-Potential Biotechnology Projects, launched and funded with a total of 5 M€ by the National Research Agency (NRA). In 2005, NRA entrusted Inserm and Inserm Transfert with the scientific, administrative and financial management of these projects, selected on the basis of the following criteria: scientific excellence, intellectual property and meeting a hitherto unmet medical need. In this framework, Inserm's DVTT brought its expertise to collaborate with Inserm Transfert on intellectual property at the time of application selection.

This NRA call for projects provided funding enabling 11 projects to achieve further development and run complementary studies required to reinforce their protection and commercialization. This approach facilitates their subsequent promotion and transformation into innovations along two possible axes:

- by transfer towards industrial partners with a special interest in this approach;
- through the creation of a company having reached a sufficient stage of maturation to attract investors.

Other projects depended on other sources of funding than NRA. They were judged sufficiently mature to be proposed directly to industry or to warrant the creation of a company.

Support for Clinical Development

After proof of concept, transfer of a medication to the patient goes through a phase of preclinical development. This involves product safety studies, setting up of a manufacturing process of clinical quality and preparation of optimal clinical protocols in order to identify the target population and the benefits the drug can bring.

To do this, Inserm Transfert recruited a preclinical development manager to consolidate and develop preclinical and clinical research projects emanating from basic research carried out by Inserm and its partners. Such projects are identified and supported by Inserm's Strategic Planning and Clinical Trial Monitoring Committee (Cossec).

Inserm Transfert has brought its experience of project operational management to the collaborative effort with the Department of Clinical and Therapeutic Research (DRCT). Inserm project applicants were assisted in managing the development of preclinical projects, interacting with the players involved (drug safety CRO, manufacturers), and seeking opportunities for financial support. In particular, this approach concerns an ongoing project targeting rare diseases, funded by the French Association against Myopathies

(AFM) as part of a greater collaboration between the Pasteur Institute, Inserm, AFM and the National Veterinary School in Nantes.

Industrial Partners and Clinical Studies

Clinical projects may serve therapeutic or interventional purposes (testing a new drug in patients or evaluating the possible benefit of a therapeutic extension) or observational purposes (learning about the pathophysiology and mechanism of certain diseases, or studying the use of certain prescriptions and their impact on public health). In both cases, some of the steps can be conducted within Inserm while others require interfacing with industrial partners. This partnership development represents an important part of Inserm Transfert's activity.

Support for Clinical Research

In 2005, Inserm Transfert intervened in the management of clinical trials managed by Inserm, particularly in Clinical Research Units. This involves seeking and identifying pharmaceutical partners willing to provide financial support for such programs. Inserm Transfert helps define partnerships and support for the management of clinical trials as well as investigator-promoter and Inserm-industry interfacing. In this respect, Inserm Transfert negotiated the financial participation of several industrial partners in clinical research studies such as an epidemiological study on type-2 diabetes, emanating from the National Research Program on Diabetes (PNRD), and a study to validate new methods for monitoring atheromatous plaque, as part of the National Research Program on Cardiovascular Diseases (PNRCD).

Promotion of Inserm's Expertise

Inserm Transfert not only promotes the development of Inserm programs but also supports promotion of Inserm structures through managing projects commissioned by industry or health agencies. In 2005, this activity consisted in negotiating and setting up observation studies on the use of medication in real situations, for a number of industrial groups. Two projects of this type, involving two pharmaceutical groups, were launched in 2005 in addition to other industrial partnership projects.

Transversal Management and Project Call Follow-up

Expertise on interfacing between public and private research through its network of experts from both horizons, has allowed Inserm Transfert to propose services for the management and follow-up of calls for specific projects. For instance, Inserm Transfert ensures the coordination and monitoring of the Biotox call for projects on biosecurity, which is being financed by the Aventis Pharma and Bayer Pharma groups with a total of 4.6 M€. Furthermore, Inserm Transfert has been entrusted with the mission of managing the NRA call for projects entitled Emergence and Maturation of Biotechnology Projects with High Promotional Potential.

Aid to Entrepreneurial Researchers

Assistance in company creation projects is provided through close collaboration between Inserm Transfert and the Department of Technology Transfer (DVTT). DVTT is responsible for defining the patenting strategy and managing industrial property as well as negotiating license contracts. Inserm Transfert complements this action by helping researchers with the creation and development of their company through early financial investment to facilitate the delicate phase of launching the young company.

Ever since the Law on innovation was implemented, Inserm has initiated the creation of more than 60 young innovative companies (YIC). Over 100 scientists from Inserm are involved in YICs or participate in some 15 industrial projects. Inserm has transferred a total of 72 patent families to such young innovative companies.

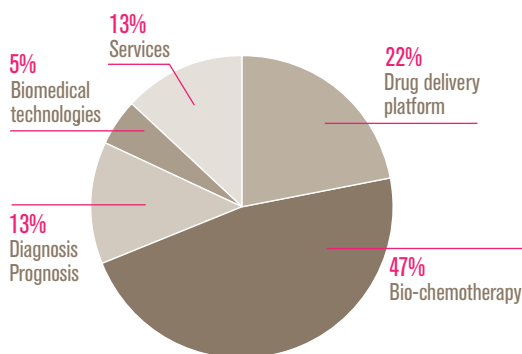
In order to assist with the company creation process, Inserm Transfert also intervenes by sensitizing researchers to the Law on innovation, detecting innovative projects within laboratories, creating partnerships with regional bioincubators, and funding the early stages of company creation (pre-seeding).

In 2005, Inserm Transfert invested in a young innovative biotechnology company in the Nantes area. The company, TcLAND, specializes in immunotherapy. Inserm Transfert participated in the setting up of three other companies due to be launched in the first semester of 2006. In 2005, Inserm Transfert's shareholding portfolio

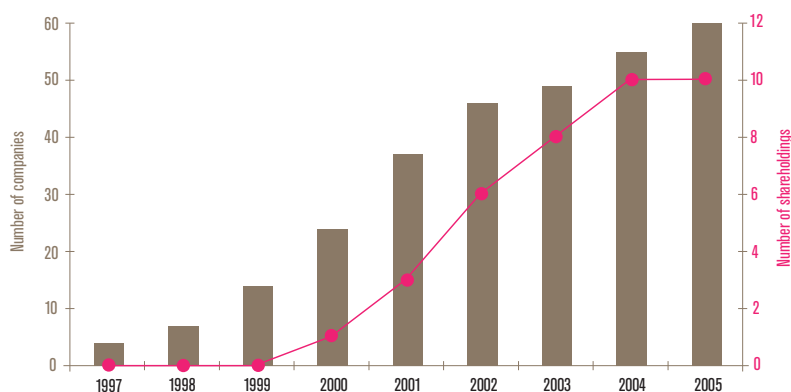
totaled 800,000€ distributed among 11 young innovative biotechnology companies, which have raised a total of 85 M€ in investments. Inserm Transfert funds the first stages of development of young innovative companies emanating from Inserm. Inserm Transfert has shares in the capital of 11 young innovative companies derived from Inserm, namely ImmuPharma Ltd SA, GenoScreen, CliniGenetics, TxCell, Innate Pharma, Metagenex, Ciltechnologies, Mutabilis, Vaxon Biotech, Carex and TcLand.

2005, a Year for Consolidation

As a limited liability company with a capital of 4,573,471€, Inserm Transfert achieved



66 companies emanating from Inserm research created since 1997



Number of companies emanating from Inserm research and Inserm Transfert participation

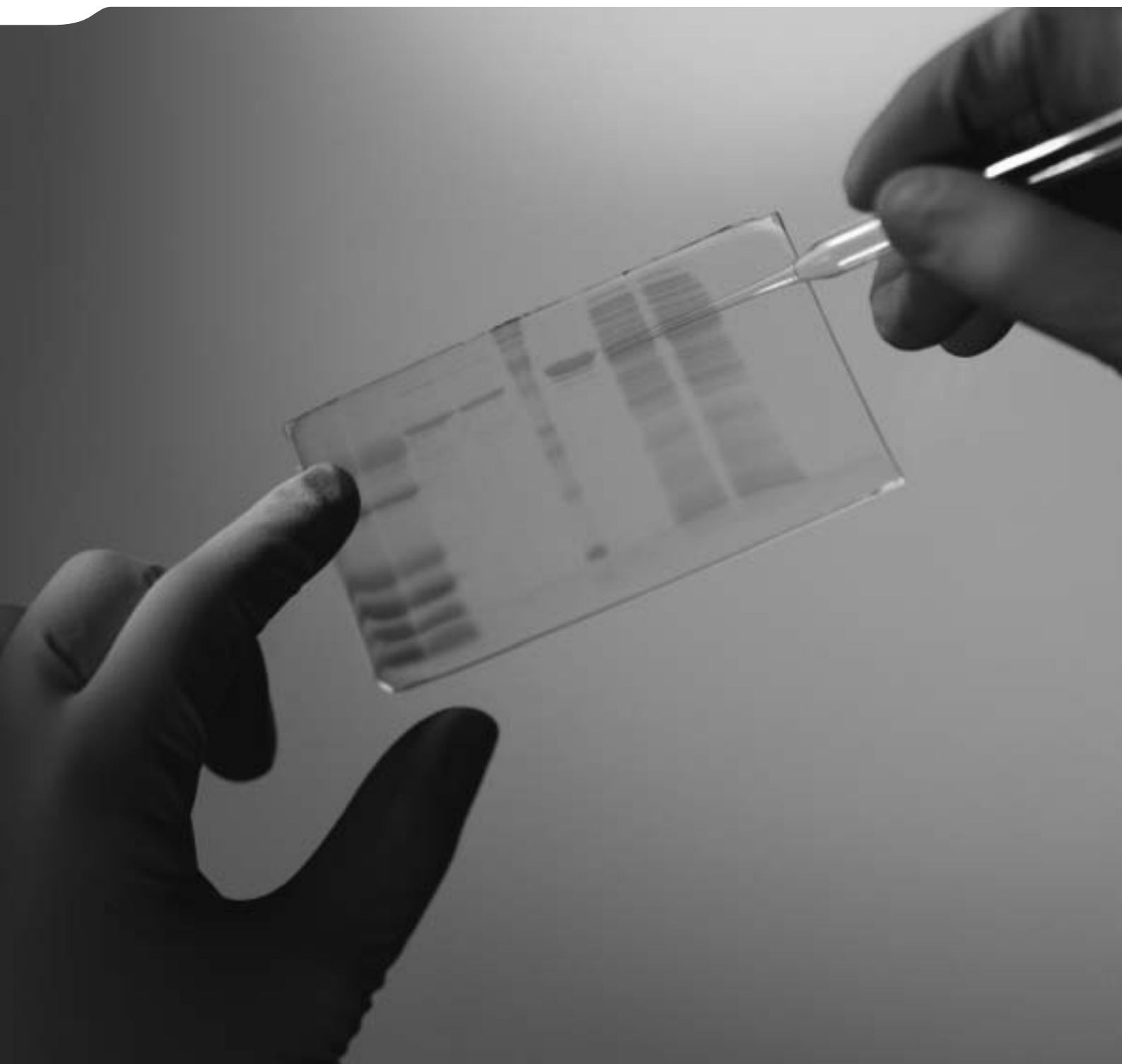
One-Day Showcase Event in 2005

The fourth edition of Inserm's one-day showcase event, organized by Inserm Transfert, took place as a preamble to the 9th European Biotechnology Crossroads, on 28, 29 and 30 November 2005, in Lille. This day event gathered 150 people and allowed the presentation of the National Research Programs on Diabetes, Bone and Joint Diseases, and Cardiovascular Diseases, as well as 20 or so platforms and technological offers emanating from Inserm to numerous players from the biotechnology sector, the pharmaceutical industry and the capital investment sector.

operating revenues of 2.6 M€ in 2005, as against 1.2 M€ in 2004. The year 2005 was a year of consolidation for the company, with a financial result of over 12 M€ in 2005. These results demonstrate the effort the subsidiary has made to reinforce its activity of industrial partnership management while ensuring all of its recurrent missions such as the management of international projects or the creation of innovative companies.

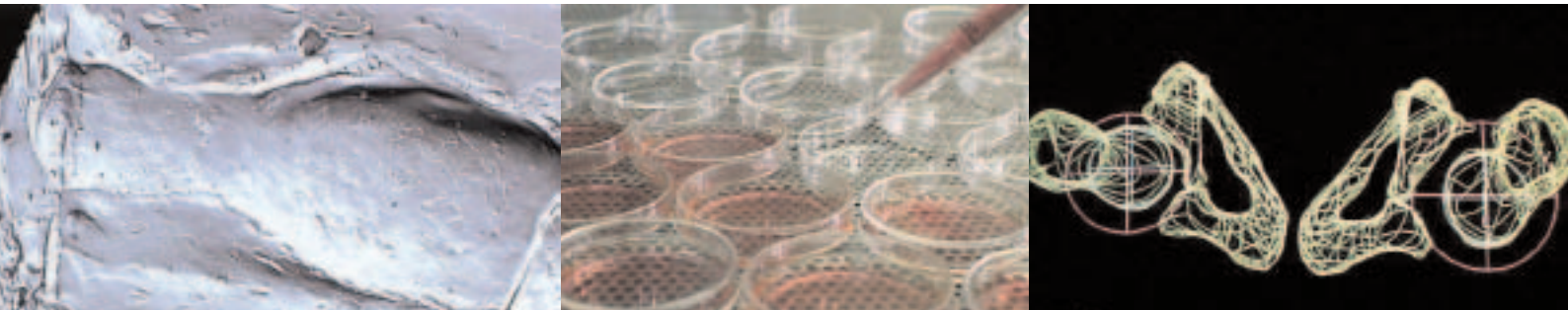
HUMAN RESOURCES

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HUMAN RESOURCES MANAGEMENT, A STRATEGIC ISSUE FOR RESEARCH

One researcher in 5 will have retired by 2010 and at present, less than 5% of all research directors have received medical training. This demographic and institutional development represents a major challenge for the organization of human resources.



One of the key issues for scientific employment in France today, and more particularly in the life sciences, is the renewal of staff in the public sector. The goal is to counter the massive wave of researcher retirement in the five years to come. Between 2005 and 2010, nearly 25% of researchers will be leaving, including 20% for retirement! In order to attract top-level scientists (whether junior or senior) to Inserm laboratories, it is essential to offer more attractive career possibilities, both in terms of salaries and financial means to constitute an autonomous research team. More flexibility in career management, such as mobility possibilities between the research setting and the hospital, universi-

ty or industrial environment, also needs to be developed. Given today's national demography and the difficulty in organizing health care in hospitals, Inserm faces the added challenge of recruiting medically trained researchers. Indeed, from 1998 to 1999, less than 5% of the research directors recruited had received medical training, as against 30% in 1980. Well aware of this problem, Inserm has set up several innovative actions since 2001 as part of its human resources policy. In 2005, the Institute reinforced its action through interface contracts, the Avenir program, the 3 to 5-year young researcher program, postdoctoral programs, the Inserm School, the hosting mission, and continuing education.

The year 2005 was also dedicated to implementing the assistance program for researchers and their careers by modernizing the system through the introduction of three actions:

- extending individual researcher follow-up to all researchers;
- integrating the forms requesting further training into the automated system for the career management of engineers, technical and administrative personnel (GAIA);
- diversifying exchange and communication tools.

INDIVIDUAL FOLLOW-UP OF RESEARCHERS: ASSISTANCE IS REINFORCED

The Department of Human Resources carries out individual and institutional follow-up of researchers using a number of different tools: counseling seminars, career orientation one-day events, meetings with doctoral schools, interaction with scientific commissions.

Human resources indicators allow evaluation of the actions undertaken at any given time, in terms of professional mobility for example.



Researcher Mission

The researcher mission stems from the original young researcher mission and now addresses the scientific community as a whole.

Other than promoting training through individual and institutional follow-up of young researchers, management of human resources was extended to tenured researchers in 2005. The goal is to help them choose on a professional course and propose career progression prospects. To do this, Inserm organizes seminars, which

are followed by individual interviews during which researchers can meet an advisor on a confidential basis, independently of any scientific evaluation.

In 2005, two seminars were organized:

- the first seminar was aimed at recently recruited young researchers; 92 researchers were invited; among the 56 participants, 33 were Senior Research Associates¹ and 23 Junior Research Associates²;
- the second seminar was essentially aimed at senior researchers; 88 researchers were invited; among the 67 participants, 38 were Senior Research Associates, 3 were

Senior Research Directors³ and 26 Junior Research Directors⁴.

The year 2005 was also witness to the setting up of:

- a one-day event dedicated to young researchers on fixed-term contracts in order to help them in their career choices;
- meetings between doctoral schools and Inserm, in order to inform doctoral school directors about the different recruiting measures created for young researchers and raise awareness about the MD/PhD program offered at the Inserm School.

The researcher mission

Young researcher contracts (1 or 3/5-year fixed contracts)

- Individual researcher follow-up
- Career course evaluations

Avenir program

- Coordination
- Individual follow-up of laureates and their teams
- Career course evaluations

Partners

- Scientific & Technological Public Institutions
- Universities
- Doctoral Schools
- Schools of Engineering
- Foundations and associations

Hosting researchers

Follow-up and evaluation for engineers, interns and veterinarians

ASSISTANCE WITH CAREER DEVELOPMENT TARGETED ORIENTATION

Human Resources follow-up of tenured Inserm researchers

- Incentive seminars
- Individual interviews
- Career prospect propositions

The Marie Curie Program

- Help in project conception
- Hotline
- Follow-up and evaluation

Inserm-regional doctoral grants

- Analysis of doctoral populations
- Follow-up of doctoral students

Tools

- Evaluations and indicators
- Exchange platforms
- Web portals
- « Accueil à l'Inserm / Hosting at Inserm »
- Databases

¹ *Chargé de recherche* (1st class): CR1

² *Chargé de recherche* (2nd class): CR2

³ *Directeur de recherche* (1st class): DR1

⁴ *Directeur de recherche* (2nd class): DR2

Reinforcing Interactions with Scientific Commissions

Following the two-yearly evaluation of researcher activity by scientific commissions (SC), the Department of Human Resources organized forty individual interviews with researchers, SC presidents, and note takers. The goal of such interviews is to understand the difficulties a researcher may encounter in the course of his/her career and bring scientific support and HR advice. The DHR ensures follow-up of the interviews, for instance by organizing mobility and offering evaluation of professional skills.

HR Policy Indicators

A number of professional evaluations were conducted for young and tenured researchers in 2005. Various indicator figures are recorded below:

Inserm-Regional Grants and Doctoral Students

Inserm-regional grants: 29 new co-funded grants were awarded across France excluding the Ile-de-France region.

- 3,000 doctoral students (15 % from abroad) were working on their thesis in 2005, 15 % of them were medical practitioners.
- 600 doctoral students defended their science thesis in 2005 and 50 % of them went on to do one or more post-doctoral fellowships.

Becoming a Post-Doctoral Fellow

- In 2005, 725 French or foreign post-doctoral researchers were working in Inserm laboratories.
- 72 % of young researchers having defended their thesis in 1997 have found a stable position.

Individual Researcher Mobility

Following the decentralization of administrative management in 2004, the setting up of a Mobility Division within the Researchers Bureau has helped generate statistical indicators on overall research mobility in order to conduct a first analysis. This initial evaluation pointed to the necessity for HR assistance measures.

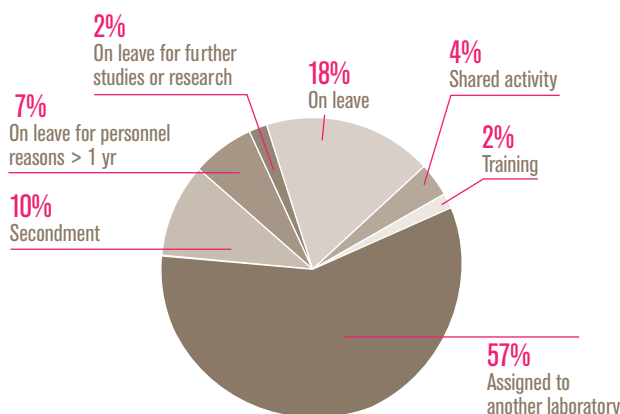
Mobility requests made by researchers in 2005 confirmed a researcher mobility rate of about 10 %, which corresponds to 211 mobility decisions in 2005.

The HR director and the Researchers Bureau followed each request individually. Certain situations demanded individual interviews, which were organized by the DHR.

Several observations can be made about mobility in 2005:

- as in 2004, requesting mobility is mainly motivated by the desire to change laboratory. Mobility occurs in 75% of cases towards Inserm units. The flow from Paris to the Provinces is rather weak (6% of all requests) as opposed to 21% towards Ile-de-France;

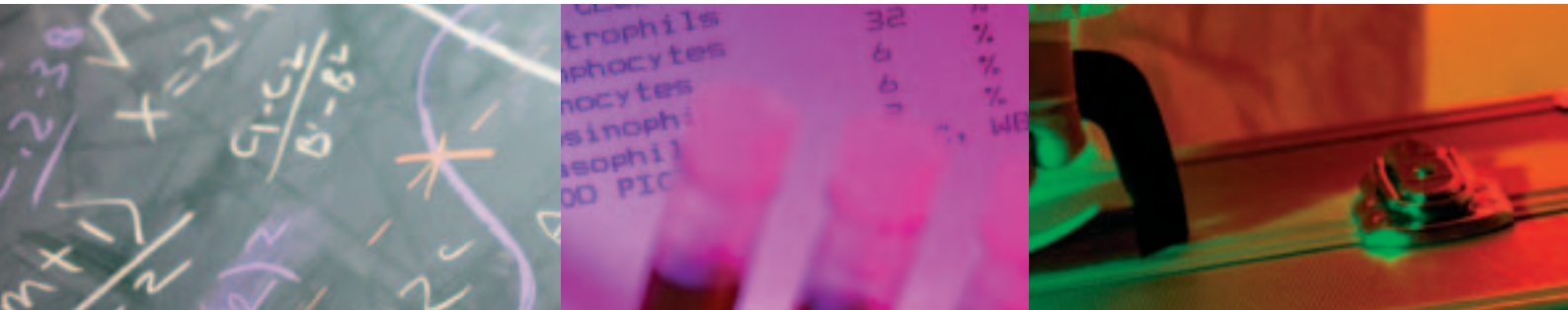
- 122 mobility requests emanated from CR1 researchers (almost 58%), and DR2 researchers (29%);
- The 40-49 age group corresponded to 40% of mobility requests in 2005, followed by the 50-59 age group (33%);
- 30 mobility arrangements were made in 2005 towards foreign organizations, either as leave or secondment, North America being the most frequent destination. The number of researchers benefiting from mobility arrangements was 45 as of 31 December 2005. The mean length of stay for mobility arrangements in a foreign organization is 3 years.



Distribution of different types of mobility

CONSOLIDATION OF INNOVATIVE ACTIONS IN HUMAN RESOURCES MANAGEMENT

In parallel to promoting individual management of human resources and careers, Inserm pursued and institutionalized innovative actions such as interface contracts, the Avenir Program, hosting contracts for young researchers, and the Inserm School.



Interface Contracts: Reinforcement of the Mechanism

Since 2002, calls for tenders for interface contracts have diversified, allowing the development of new partnerships.

Other than career attractiveness for researchers and research engineers, the goals are still to improve knowledge transfer towards clinical activities, support innovative teaching efforts and develop industrial promotion activities.

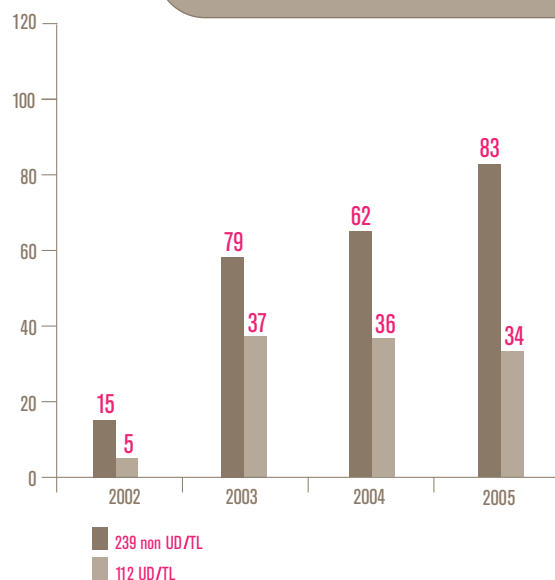
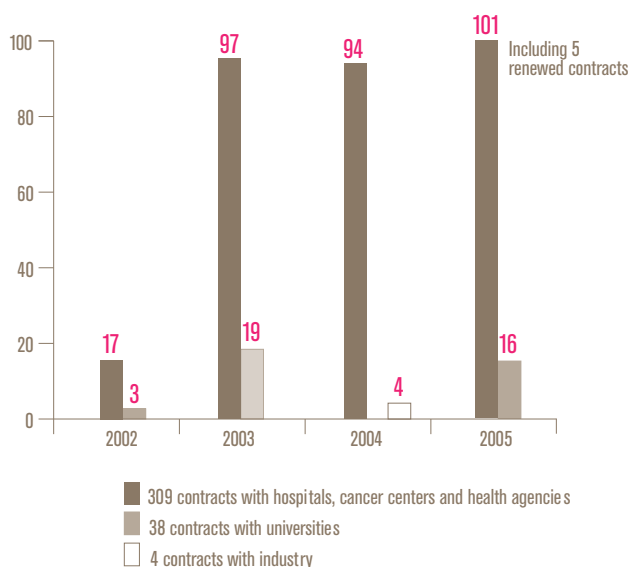
Eight calls for candidates were launched in 2005:

- researcher interface contracts with hospitals, in partnership with the Ministry of Health, cancer centers and the French Blood Transfusion Institute;

- researcher interface contracts with the Office General for Health and health agencies;
- researcher interface contracts with universities in partnership with the Ministry for Higher Education;
- researcher interface contracts with veterinary schools;
- consultancy and scientific support contracts with industry;
- interface contracts for hospital-based personnel;
- interface contracts for university-based personnel;
- interface contracts for veterinary researchers-lecturers.

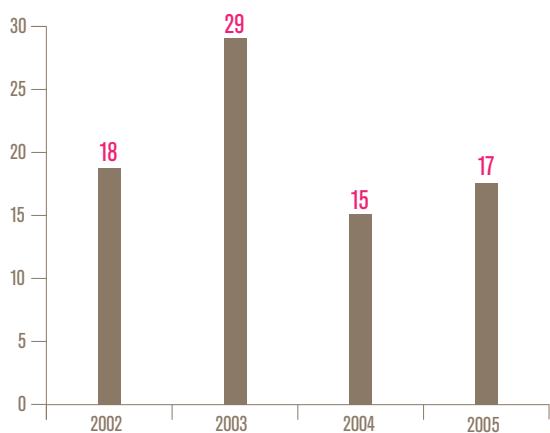
KEY FIGURES FOR THE PERIOD 2002-2005

- 665 applications for researcher interface contracts
- 351 completed or ongoing researcher interface contracts
- 107 unit directors selected for an interface contract
- 140 applications for hospital personnel interface contracts
- 79 completed hospital personnel interface contracts
- 56 framework conventions signed or about to be signed with hospital and university partners

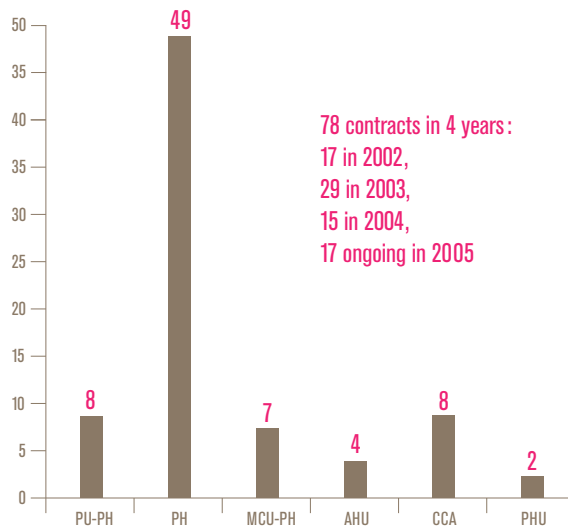


Research interface contract partnerships since 2002 (for a total of 351 contracts)

Status of researcher interface contract laureates



Number of hospital contracts since 2002



Status of hospital interface contract laureates

78 contracts in 4 years:
17 in 2002,
29 in 2003,
15 in 2004,
17 ongoing in 2005

In addition to such calls for candidates, the Join Inserm program involves applying for an interface contract while being a candidate for researcher selection.

The Directorate General also wishes to allocate part of the contracts to directors of facilities who can justify such an interface. Long-term establishment of this mechanism involved discussions with partners as early as 2005 concerning the renewal of such contracts.

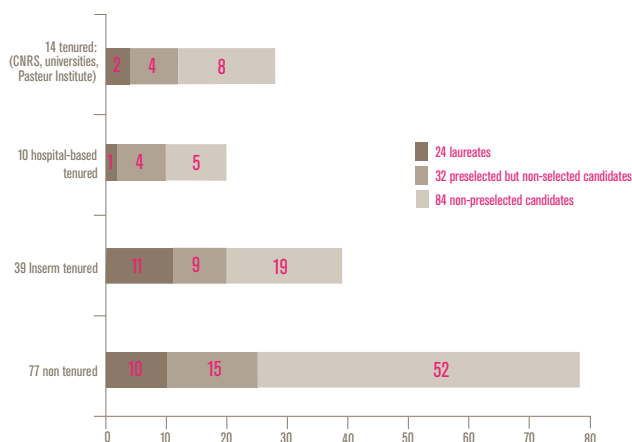
The Avenir Program

The Avenir Program has been intensified and is being institutionalized. Originally launched in 2000, this program has awarded contracts to a total of 109 laureates. It provides support for tenured and non-tenured researchers to conduct projects whether they are medically or scientifically trained. Under this program, non-tenured young researchers may be offered 3 to 5-year contracts. Originally supported by the Ministry of Health, private foundations

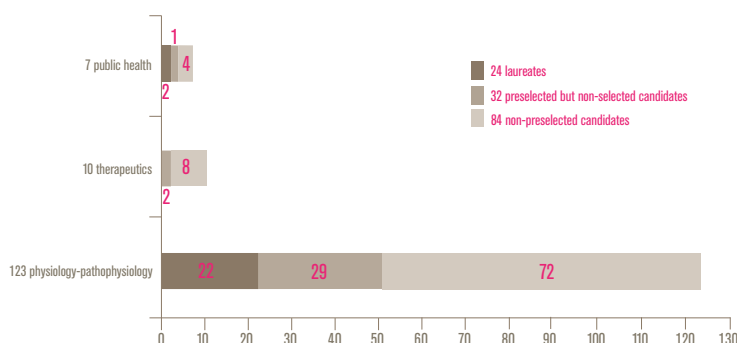
and associations (AFM, ARC, LNCC, FRM, Fondation de France) and the CANAM, the program is now also supported by regional funds, the Bettencourt-Schueller Foundation and industry, as with the Pierre-Fabre company.

Among the 109 laureates, 29 are medical doctors (18 of whom are tenured).

The 2005 Avenir program totaled 24 laureates, 3 being medical doctors (one of whom is tenured).



Avenir 2005 - Professional background of candidates (140 people), preselected candidates and laureates



Avenir 2005 - Study area of candidates (140 people), preselected candidates and laureates

3 to 5-year Young Researcher Program

Originally launched by the Ministry for Research in 2003, this program was consolidated in 2005 by setting up 3 to 5-year contracts.

A national call for candidates was launched for these contracts according to the selection criteria listed below:

- scientific quality of the project presented by the applicant and consistency with the hosting laboratory;
- scientific background, publications and intellectual asset promotion activities;
- quality of the hosting laboratory;
- relevance of the project with respect to Inserm missions;
- professional project considered at the end of the hosting contract.

126 applications were submitted:

- 39% of candidates were also candidates for researcher selection;
- mean candidate age was around 34;
- 29 contracts were set up;
- 41% of candidates had their doctorate for less than 4 years.

Since 2003, 174 contracts have been set up:

	2003	2004	2005
Length of contract	18 months	12 months	3 ans
			12 mois
			3 ans
Number of contracts set up	36	25	14
			70
			29

Post-Doctoral Programs

70 12-month contracts designed for young post-doctoral researchers were allocated in 2005. In addition to this entry measure, the following programs have been maintained for post-doctoral applicants:

- the Avenir Program: 3-year fixed-term funding by Inserm partners for post-doctoral laureates;
- Hosting positions: 2-year fixed-term contracts (possibly renewable for one year) designed for medical doctors completing their internship, pharmacists, odontologists and veterinarians as well as hospital residents or university hospital assistants. In total, 17 new contracts were drawn up in 2005.
- Grants that are cofinanced by regional funds, essentially designed for doctoral students: 29 new grants in 2005.

Inserm School: from Experience to Institutionalization

The first session of research training for medical students was set up in 2003. Students from this session obtained their research Master's degree in 2005, in agreement with their respective universities, before resuming - for the most part - their medical studies at the end of 2005. A fraction of the students pursued their studies

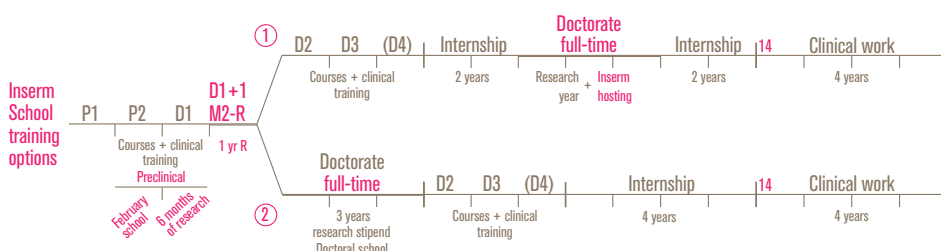
to obtain a science doctorate and will resume their clinical studies in 3 years' time. In 2005, the students of the 2004 session are following their preclinical courses while training for six months in an Inserm research unit.

Hosting Mission

The creation of the Hosting Mission within the Social Policy Bureau reflects the will on the part of Inserm to set up a genuine policy in this area. This mission is designed to improve hosting conditions for foreign researchers within Inserm research structures.

This mission can assist foreign researchers by providing necessary information on administrative procedures to follow before arriving in France. It can also provide practical information and advice in order to facilitate their stay in France. This includes requests for short and long-term housing, opening a bank account, registering with social security to obtain health protection, getting personal and workplace liability insurance, organizing the hosting of their family, and obtaining a property mortgage.

As part of this mission, Inserm has set up various measures to facilitate access of its foreign researchers to housing. It succeeded



The various MD/PhD options at the Inserm School at the Inserm School Medical course

in obtaining the reservation of six City of Paris furnished lodgings at the Récollets International Housing Center in Paris.

Furthermore, in order to promote the development of the hosting policy, a census of all the hosting mechanisms was undertaken by Regional Delegate Administrations from 2004 onwards.

In 2005, 159 foreign researchers sought assistance from the hosting mission.

Innovative Training

The three-year 2003-2005 clinical research training plan was updated and proposed once more to project-bearing researchers and clinicians. New training opportunities

were also introduced, based on skills available on research platforms. Two new actions illustrate the closer ties woven between basic research and clinical research, and the training support afforded by research platforms.

At Regional Level: Biotherapies

In April 2005, Inserm's continuing education department in Lyon offered a training course on stem cells. The use of stem cells being tightly regulated, this training session proposed a general overview of the subject and related therapeutic applications. Professor Frédéric Bérard (Inserm Unit 503 - Lyon-Sud University Hospital) was in charge of scientific coordination. This is a good example of Inserm partner-

ship with other entities to offer continuing education opportunities. The entities concerned were the French Blood Transfusion Service (ESF), the Léon-Bérard Center, the Lyon hospitals and the cellular therapy platform.

In 2005, a biotherapy CRC was also created.

At National Level: Clinical Proteomics

The national continuing education bureau decided on running a training course on biochips and proteins in 2005. Scientific coordination was ensured by Professor François Berger (Inserm Unit 318-Grenoble) and training was provided in collaboration with the proteome/transcriptome platform in Grenoble.

EXCHANGE AND COMMUNICATION TOOLS

Several initiatives have improved the circulation of information. They include the Avenir brochure and forum, the Young researchers/host laboratories exchange platform, the commitment charter, the profile database, and information guides targeted at particular groups.



The Avenir Brochure

The Avenir brochure, produced by the Department of Scientific Information and Communication, lists all the Avenir laureates since the program was created, and provides full relevant scientific information.

The Avenir Forum

The Avenir forum, available online on Inserm's website since 2005, provides information and allows communication on Avenir laureates.

Communication Platform

A brochure was widely distributed in order to raise awareness about the existence of the Young Researchers/Host laboratories communication platform, which aims at facilitating closer ties and contacts between young researchers and laboratories.

Commitment Charter

A commitment charter with respect to researchers recruited on fixed-term contracts has been drawn up. It describes the variety of funding and assistance opportunities available for this population in terms of social policy, training and reception logistics.

Profile Database for Researcher Individual Mobility

A database of profiles has been set up in order to offer mobility opportunities to tenured researchers from Inserm or other science and technology public institutions. In 2005, 50 research profiles were proposed by unit directors and displayed on Inserm's human resources website. The profiles concern research functions as well as interfacing and research assistance. Nine researchers were able to benefit from mobility opportunities using this system.

And...

Other guides have been created or reedited: the reception brochure (circulated among newly recruited researchers, engineers and technicians), the professions guide, the guide entitled Being a Civil Servant Intern, and the guide to using the information tool Pégase. The 2006 program of public health training seminars has also been circulated.

PROGRESS IN THE AUTOMATED MANAGEMENT OF ENGINEERING, TECHNICAL AND ADMINISTRATIVE STAFF EVALUATION

Launched in 2004, the GAIA (automated system for the management of engineering, technical and administrative staff evaluation) site was improved in 2005 through changes allowing the recording of training needs and the registration for internal selection exams.



The GAIA site (www.gaia.inserm.fr), is entirely dedicated to the annual campaign of evaluation and advancement of engineering, technical and administrative (ITA) personnel at Inserm. It was improved in 2005 by adding an online information-gathering feature to collect requests for further training. This feature allows agents to express their training needs for the following years and their directors to express an opinion on each request. This information gathering is instrumental in drawing up plans for regional and national training programs.

In 2005, the evaluation campaign generated the following figures:

- 2,488 applications were validated;
- 88.4% of agents were interviewed by their director prior to evaluation;
- 55.3% of agents expressed at least one need for further training;
- 33.5% of needs involved scientific techniques;
- 66.5% of needs concerned research assistance techniques.

Other projects to extend the scope of GAIA were pursued in 2005, namely:

- access for the National Bureau for Continuing Education and for training personnel to a large number of detailed statistics on the needs expressed, with a view to implementing relevant training for the 2006 evaluation campaign;
- electronic registration for internal selection exams, eligibility management and examination of applications by the jury, with a view to implement such features for the 2006 campaign of selection for internal promotion.

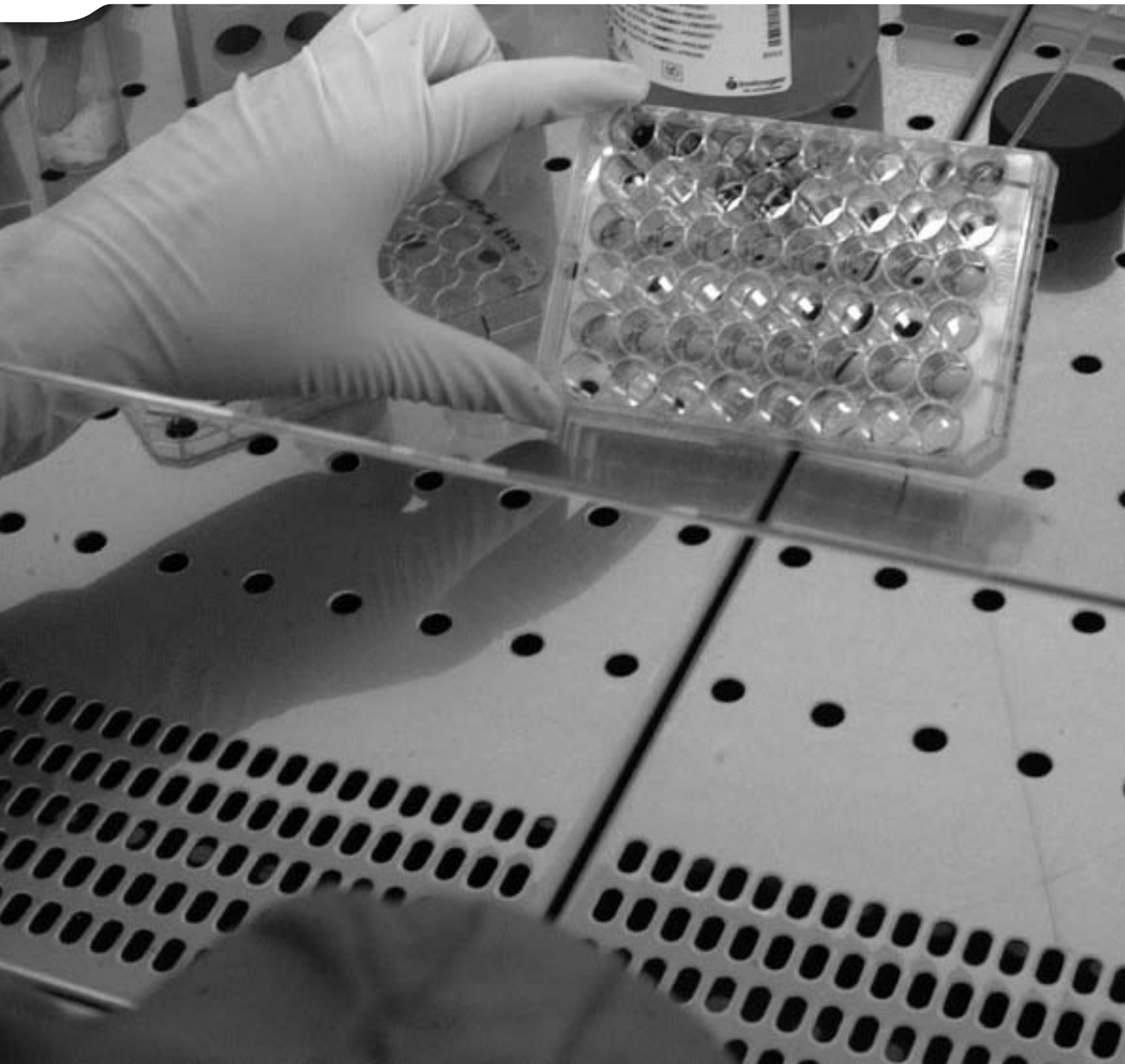
RESEARCH ASSISTANCE

118 EVALUATION

122 FINANCIAL MANAGEMENT
AND LOGISTICS

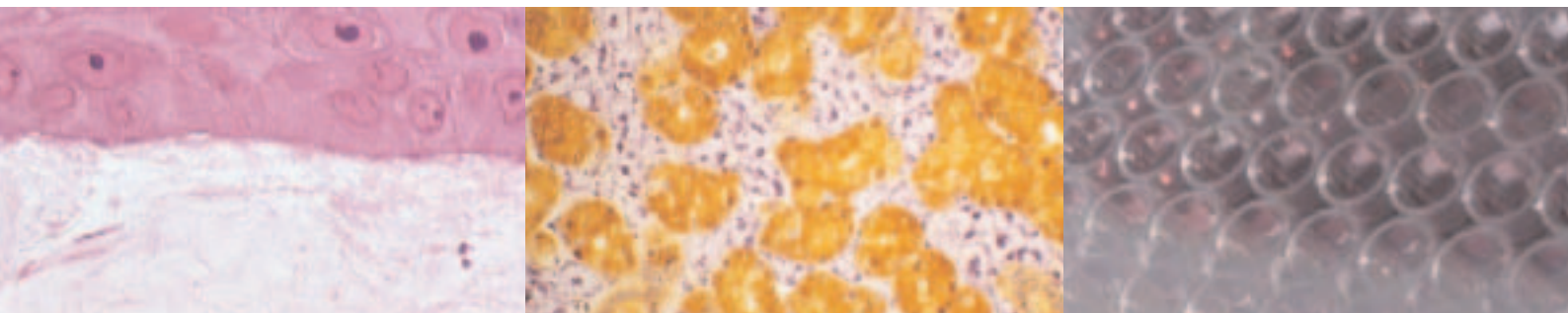
124 INFORMATION SYSTEMS

125 SCIENTIFIC INFORMATION
AND COMMUNICATION



EVALUATION

Scientific evaluation of a research institution classically depends on three aspects: evaluation of men and women, laboratories or projects, and facilities. Implementation and follow-up of the first two items are entrusted to the Department of Scientific Evaluation (DES), which is also instrumental in providing scientific production indicators that bring objective elements to evaluate the Institute.



The DES works in accordance with good scientific evaluation practices, which include:

- evaluation by European and international peers recognized for their expertise;
- comparative evaluation;
- transparent evaluation based on predefined criteria (communicated to the people concerned);
- before-and-after evaluation;
- independent evaluation of decision-making bodies.

Evaluation is implemented by the Scientific Council, specialized commissions, ad hoc committees and external experts. In order to reinforce evaluation objectivity, the DES also consults or uses:

- anonymous experts who evaluate projects on the basis of reports. This procedure relies on a group of experts selected by the DES based on propositions made by the scientific community and databases of international publications. These expert evaluations are kept in the file throughout the evaluation process and are available for consultation by the committees and Scientific Council, who discuss and defend them;
- bibliometric studies allowing after-the-fact evaluation of scientific production, as well as researcher and team notoriety. Such studies, which are communicated to

the scientific organization, researcher or laboratory under evaluation, include the following items:

- number of articles, reflecting the level of production;
- identification of articles in the top 10%, 20%, 50%, which reflects the international visibility of the work (corrected for each field and for the year of publication);
- success rating (% excellence): number of articles in the top 10% over the total number of articles;
- citations for each publication, total number of citations and mean citation index;
- citation index corrected for position: the number of citations of a given article corrected for author position provides a more accurate estimate of author visibility. This indicator reduces the value of collaborations and favors principle-author publications;

- journal impact factor (IF) for each article (mean IF and IF corrected for position): as before, journal IF is counterweighted by author position. This indicator reflects the difficulty an author had to overcome in order to publish;
- mean position of the researcher on the articles he/she signs or co-signs.

The procedure is not static and evolves according to the items being evaluated. For example, an innovative procedure was set up in 2005 in order to evaluate research centers.

In such a procedure, the Scientific Council auditions the project leader as well as the team of project directors. It also relies on evaluations made by relevant commissions. Finally, it takes into account the scientific policy of the research center and the procedures set up for internal and external

Classification	Number of teams	Percentage
A+	36	16.75
A	88	40.93
B	91	42.32
Total	215	100

Classification of the teams in 2005

[↑ back to contents: click here](#)

evaluation of participating teams or teams likely to joint the center. Specific sessions allow evaluation of processes to facilitate the pooling of activities, interfacing, technological transfer and training of young people.

The participation of a number of international experts, proposed by the Medical Research Council and the *Deutsche*

Forschungsgemeinschaft (DFG) reinforces objectivity and links with European partners.

Bibliometry Division

The Department of Scientific Evaluation (DES) created a division exclusively dedicated to bibliometry, which encompasses

four major aspects: assistance for scientific evaluation, definition of discipline-specific evaluation indicators, thematic studies and identification of salient features in France.

Assistance for Scientific Evaluation

The bibliometry division produces studies on the publication activity of researchers and research units. These studies are pri-

Type of assessment	No. cases examined
Four-yearly evaluation	30
Research Center creation	5
Multi-team unit creation	29
Single-team unit creation	39
Team mobility	9
Research Director selection	197
Research associate selection	462
Research activity	1,014
Researcher promotion	196
Researcher tenuring	67
Researcher interface contracts	91
Hospital staff interface contracts	33
Hosting positions for interns and veterinarians	65
Total	2,237

Evaluations in 2005

[↑ back to contents: click here](#)

Closure/Creation	Creation from an existing unit	Creation by reopening after 1 year or more	<i>De novo</i> creation	ESPRI
Aiach Martine - U 428	Emmerich Joseph	Baumert	Aubourg Patrick	Boissier Marie-C
Amouyel Philippe - U 508	Amouyel Philippe	Croisy Alain	Barillot Christian	Hofman Paul
Beaune Philippe-Henri - U 490	Barouki Robert	Levi Francis	Binart Nadine	Launoy Guy
Bertoglio-Matte Jacques - U 461	Bertoglio-Matte Jacques	Luban Jérémy	Buee Luc	Roingeard Philippe
Bungener Martine - U 502	Bungener Martine		Chneiweiss Hervé	
Charnay Patrick - U 368	Rosa Frédéric		Clement Karine	
Chauvel Patrick - E 9926	Chauvel Patrick		Daéron Marc	
Chouaib Salem - U 487	Chouaib Salem		Deprez Benoit	
Codogno Patrice - U 504	Codogno Patrice		Duval Alex	
Daculsi Guy - E 9903	Weiss Pierre		Eschalié Alain	
Darlix Jean-Luc - U 412	Cosset François-Loïc		Goffin Vincent	
Edelman Aleksander - U 467	Edelman Aleksander		Henrion Daniel	
Elion Jacques - U 458	Elion Jacques		Jeunemaitre Xavier	
Evain Brion Danièle - U 427	Evain Brion Danièle		Kremsdorf Dina	
Fischer Alain - U 429	Fischer Alain		Laburthe Marc	
Fischmeister Rodolphe - U 446	Fischmeister Rodolphe		Laurent-Puig Pierre	
Formstecher Pierre - U 459	Formstecher Pierre		Paterlini-Bréchet Patrizia	
Friedlander Gérard - U 426	Friedlander Gérard		Pende Mario	
Galanaud Pierre - U 131	Emilie Dominique		Prévost Vincent	
Hémon Denis - U 170	Clavel Jacqueline		Samuel Didier	
Kerckaert Jean-Pierre - U 524	Quesnel Bruno		Sassoon David	
Lombardo Dominique - U 559	Lombardo Dominique		Terzi Fabiola	
Marden Michael - U 473	Marden Michael			
Mauger Jean-Pierre - U 442	Combettes Laurent			
Meyer Dominique - U 143	Freyssinet Jean-Marie			
Moreau Thierry - U 472	Moreau Thierry			
Munnich Arnold - U 393	Munnich Arnold			
Picard Jean-Yves - U 493	Picard Jean-Yves			
Reynaud Claude-Agnès - U 373	Reynaud Claude-Agnès			
Sansonetti Philippe - U 389	Sansonetti Philippe			
Schumacher Michael - U 488	Schumacher Michael			
Tonnel André-Bernard - U 416	Lassalle Philippe			
Triller Antoine - U 497	Triller Antoine			
Vainchenker William - U 362	Vainchenker William			
34	34	4	22	4

Overview of Inserm unit closures and creations

- 34 creations from existing units
- 4 creations by reopening after 1 year or more
- 22 *de novo* creations
- 4 ESPRI programs
- 20 closures
- 16 unfulfilled requests

marily designed for use by members of Inserm scientific committees but are made available to the researchers and teams concerned.

Indicators Designed for Discipline-Specific Evaluation

The bibliometry division defines appropriate indicators to evaluate biomedical research in France by discipline or medical specialty:

- determination of the mean number of French citations per year and citation thresholds corresponding to the mean, top 10 % and top 1 % for France with respect to each medical specialty;
- measurement of productivity, mean index, etc.;
- analysis of indicators that need to be included in the evaluation, with respect to patents, contracts, expert reports, etc.

Thematic Studies: Bibliometric Prospective Studies for Virtual Institutes and National Research Programs

The bibliometry division also conducts studies on broad research themes such as nutrition, diabetes, neurosciences and cancer. Such studies make it possible to assess the current research situation in the various areas both at national and international level. Such studies are published online as soon as they are completed.

Salient Features in France

Every year, the bibliometry division assesses the current situation in terms of discoveries and leading-edge research for France generally and Inserm in particular (see Salient Features on page 9). The bibliometry division conducted a study showing that scientific production visibility for research organizations in France and

Inserm in particular suffers from poor address nomenclature. Whereas Inserm has been implicated in 500 publications in the top 1% worldwide over the last ten years, international studies have only assigned 20% of these articles to Inserm (*Nature* 438, 7068:559-559 Dec. 1 2005). In order to counter this problem, the bibliometry division has set up a procedure enabling verification of address nomenclature, in agreement with a large number of partners. Nomenclature directives are available on the web pages dedicated to bibliometry on www.eva.inserm.fr. In three months, over 2,000 visitors consulted these pages and over 300 researchers requested validation of the address on their articles.

FINANCIAL MANAGEMENT AND LOGISTICS

The two major lines of action in 2005 were to continue modernizing management to improve its efficiency, and to implement the new financial framework, involving management of new means of public research funding.



Pursuing the operational stabilization of SAFIr¹ in 2005 allowed new work assignments to be taken on, including:

- making new editions available for the community of users, enabling full monitoring of the use of different resources such as research contracts;
- setting up a monthly management and accounting follow-up system for delegate administrations allowing the monthly closure of accounting periods. This enables regular processing of anomalies and ensures more reliable financial and accounting entries throughout the year. As a result, account closure for the 2005 financial year was very rapid;
- setting up the operation of the FA (fixed assets) module, which allows each delegate administration to take fixed assets into account and monitor all incoming, outgoing and transferred fixed assets;
- taking into account major developments, such as the implementation (in January 2006) of the new budget and accounts framework, and the automated management of the change in tax regime (see below).

The development of specific applications for purchases allowed meeting regulation-

al demands in terms of procedure dematerialization, and guaranteeing and facilitating traceability of competitive selection of potential service providers. Training was also offered to over 200 unit administrators, who were introduced to public market regulations and use of the above applications.

Implementation (on 1 January 2006) of the new budget and accounts framework² and the organic finance law was prepared in the course of 2005 and required major contributions from:

- experts from the Department of Finance and Logistics, and more particularly from the budget office;
- experts from the Department of Human Resources because of the impact on the management of funds allocated to personnel;
- operational and technical experts from SAFIr and SIRENE (integrated system for human resources management) in order to analyze and take into account the constraints resulting from the new measures on computer management tools.

A specific seminar was organized in October 2005 for Inserm administrative executives, enabling them to relay the information to the Institute's staff as a whole, using appropriate communication strate-

gies in view of the impact this major reform might have on their particular activity.

The change in Inserm's tax regime, effective since 1 January 2005, required the updating of instructions and the organization of numerous training and information sessions for managing staff. In this respect, the Department of Finances and Logistics achieved considerable work in collaboration with the main and secondary accounting offices.

Involvement with the Inserm-NRA bureau concerned financial and administrative management of programs financed by The National Research Agency (NRA). Major participation of contract office personnel and outsourcers allowed setting up support for the 5 programs entrusted to Inserm (microbiology, rare diseases, neurosciences, cardiology-obesity-diabetes and emergence of innovative projects) on schedule. A total of 191 projects were selected and 414 participating structures obtained funding for a total of 59 M€, 19.5 M€ of which were allocated in 2005.

Regarding non decentralized programs, including incentive actions and the Avenir program, the contract bureau set up research contracts for a total of 23 M€.

¹ *Systèmes algébriques formels pour l'industrie et la recherche*
Formal Algebraic Systems for Industry and Research

² *Nouveau cadre budgétaire et comptable (NCBC)*

Management of 6th FPRTD contracts was ensured through support of the contract bureau for regional delegate administrations in keeping with the financial commitment for projects supported by the European Community.

Development of manager networks with a more business-oriented approach involves purchasing managers, income managers, as well as fixed and movable asset managers. Such development requires specifically designed information meetings and training sessions. A special effort was made in 2005 to help external resources man-

agers take into account the Institute's new tax regime and to assist movable and fixed assets managers with monitoring of immobilized assets and managing of real estate assets. For the latter, the Department of Finance and Logistics and the main accounting office drew up an Inventory Guide that is an essential reference tool for efficient management.

Development of partnership among public scientific and technical institutions was reinforced in terms of legal monitoring of purchases and pooling of procedures and tools.

INFORMATION SYSTEMS

Progress in major national software has demonstrated the efficiency of the information system modernization undertaken over the last few years. The profound reorganization of the Information System Department was completed in order to ensure mastery of the processes involved.



The SAFIr system, specifically designed for budget and accounting management, has attained a satisfactory level of stability. It has above all been able to absorb the major changes imposed by the new budget and accounting framework, and the application of the organic finance law. The system was implemented successfully in January 2006, as planned.

The recent investment into and experience acquired with the EVA system allowed optimal management of NRA¹ calls for offers entrusted to Inserm. The project, named GEP, was developed in a matter of weeks using the Livelink Open Text mod-

ules previously used with EVA. Numerous extensions are currently being worked on, for monitoring the management of selected projects, for example.

The Department of Human Resources benefited from a major extension of the GAIA system features. By enabling follow-up of evaluation files, the GAIA system can now take into account training needs and selection for internal promotion. The success of the rh.inserm.fr web site has also encouraged a number of restructuring initiatives, broadening of content and ergonomic improvement.

Other software products have undergone major changes in order to adapt to new operational needs or demands. In this respect, MISVAL (patent management), the research information bank (BIR), and Chimed (assistance for workplace medicine) have brought considerable technical progress.

Finally, the continued development of more advanced visual communication solutions now allows the use of visioconference technology on a daily basis. All French regions are due to be equipped by 2006.

¹ National Research Agency

SCIENTIFIC INFORMATION AND COMMUNICATION

The information continuum was consolidated in 2005 by a strategy hinging on three essential missions: offering medical and scientific researchers the information they need, displaying Inserm's collective achievements and communicating Inserm research results to the general public.



Information for Researchers and Engineers

In 2005, a grouped ordering system emanating from the Couperin Consortium, CNRS, INRA and Inserm was set up under the aegis of the Ministry for Research and Higher Education in order to negotiate access to the catalogue of the publisher Elsevier-Science Direct.

A three-year contract was signed to allow electronic-only access to the full text of the entire Freedom Collection (comprising 1,800 titles) and the 10 titles of the Cell Press collection. The contract allows access to the full text of all the articles published since 1 January 1995 via the BiblioInserm portal, using individual identification coding.

BiblioInserm, a web portal designed in collaboration with INIST¹ and CNRS to enable access to scientific information, allows researchers to navigate from the PubMed bibliographic reference to the full-text article. Thanks to this system, all

Inserm units now have equal access to information, regardless of their geographical location. As soon as it was launched, BiblioInserm was an immediate success and was largely responsible for the progress in access to information by the French scientific community.

Inserm Supports Open Access: HAL Inserm

Inserm is committed to the movement for open access to knowledge and has proven this by signing the Berlin declaration for the promotion of free access to scientific information. This represents a major issue for research and society in general. Inserm has joined with other research institutions to draw up a common policy of open access, including the creation of institutional (or open) archives.

In September 2005, CNRS, CPU², INRA³, INRIA⁴ and Inserm drew up an agreement protocol in order to coordinate the constitution of open archives of scientific production at national level. This protocol aims at providing the framework for joint management of a shared national platform named HAL (hyper articles on line), developed by the center for direct scientific communication (CCSD/CNRS).

Setting up a single national archive system, with a depositing/consultation interface that is specific for each institution, ensures

better long-term visibility of their work and publications.

Communication With the Media

The Inserm Press office draws the media's attention on Inserm research by producing information documents for the benefit of written press or audiovisual media journalists. The documents, in the form of press releases, communications and press reviews, are written with researchers and aim to inform the general public about the latest scientific advances. In 2005, approximately one third of all press documents circulated to journalists were co-signed with two or three partners, including CNRS, the Pasteur Institute, the Curie Institute, and AFM.

In 2005, 96 press documents were circulated to journalists. Over 20 press meetings, breakfasts, conferences, seminars, fairs, and symposia were organized depending on the nature of the information to convey. Inserm's press office reinforced "Meet a Researcher" events in the form of monthly breakfast encounters. Overall, in 2005, Inserm was cited in the press on average 318 times per month and 79% of the articles involved editorial content on Inserm.

¹ *Institut national d'information scientifique et technique* - National Scientific and Technical Information Institute

² *Conférence des présidents d'université* - Conference of University Deans

³ *Institut national de la recherche agronomique* - National Institute for Agronomical Research

⁴ *Institut national de la recherche en informatique et automatique* - National Institute for Research in Information Technology and Automation

With the General Public

As in previous years, Inserm was present at the MEDEC medical fair. Doctors attending were able to participate once again in Inserm “Health Café” sessions on the subjects of diabetes, mental health, cardiovascular diseases and eye pathologies. Over 10,000 Collective Expert Report brochures, on display at the Inserm stand, were distributed in 2005.

In March 2005, Inserm Publications were present, as in previous years, on the Ministry of Research stand at the annual national book fair. Science “bar” sessions were organized, each around particular publications of Inserm researchers.

Inserm participated, in collaboration with the Ministry of Research, in the first general public event dedicated to innovation at the European Fair on Research and Innovation organized in Paris (June 2005). Over 23,000 people attended the conferences and round tables at the fair.

As part of the science fair, Inserm offered the general public a series of events throughout France. The theme chosen was “Man and Movement”, which was presented with supporting research results at the Inserm stand in the Luxemburg Gardens in Paris, in collaboration with INRETS¹.

Launch of the New www.inserm.fr Web Site and Follow-Up of the Inserm Letter

Inserm’s new institutional web site, launched in March 2005, is the fruit of a

collective effort over several years and is now considered a reference site for biomedical research in France. The graphical concepts adopted totally adhere to Inserm’s new visual identity since 2004. Since it was launched, over 65,000 unique visitors regularly visit the site every month.

In addition, it appeared essential for Inserm to implement the coherent development of regional web sites attached to regional delegate administrations (ADR). The Department of Scientific Information and Communication (DISC) therefore set up a joint pilot project with the PACA² Region ADR.

The website can be found at:
<http://www.inserm.fr>

Finally, in order to ensure consistent circulation of information, national editorial reinforcement of the weekly Inserm Letter was introduced in June 2005. The letter is written by regional communication managers and by the DISC.

Research and Young People

For almost twenty years, Inserm’s Young People Network has offered its members places and opportunities for dialogue with the scientific community. The topics approached are always biomedical and health research subjects relevant to current societal issues.

Inserm’s Young People Network is aimed at high school and college students. In 2005, it offered opportunities for members to learn more about research careers and the scientific process, and to reflect, personally and collectively, on progress in biomedical sciences and its applications to health. This

involves the organization of thematic Inserm Café sessions by young people in the Network.

There are currently 18 active branches of Inserm’s Young People Network in mainland France, and 9 in Europe, Quebec and Africa. Inserm is well aware of MGEN³’s unwavering support for the network since 1991 and has been committed to maximizing this support since 2004.

For the last two years, Inserm Young People Health Cafés have been very successful both with local branches and branch leaders. Indeed, since the beginning of the year, many have put in requests to organize sessions. These attract a varied audience and require active joint organization and preparation on the part of local branch members. Such sessions enable branches to become better known in the neighborhood or town.

For the first time this year, Inserm suggested, for the sake of consistency, that all branches organize Inserm Young People Health Cafés on the same topics, namely addiction and nutrition.

Inserm News: the New Formula

In August 2005, after more than a year’s absence, Inserm’s information magazine received a new lease of life in a totally novel form. Originally a paper magazine, it has now gone to online format only, thus allowing a monthly publication rhythm. The main objective of the magazine remains the presentation of research work being conducted at Inserm. This online magazine is built around a central reporting item dealing with a major scientific topic, around which sections such as

¹ *Institut national de recherche sur les transports et leur sécurité* - National Institute for Research on Transport and Transport Safety

² *Provence - Alpes - Côte d’Azur*

³ *Mutuelle générale de l’éducation nationale* - Complementary Health Insurance for Education Personnel

“Science News”, “In the Words of Researchers”, and “Encouragement” are organized. The magazine has a circulation of 14,000.

Inserm Publications in 2005

Inserm’s strategy of publishing jointly with private publishers, initiated in 2004, was truly implemented in 2005 with the joint Inserm-Vuibert publication of a book in the Health Issues series. Work is currently underway with La Découverte in order to popularize some of Inserm’s Collective Expert Reports.

Collective Expert Report Series

- **Suicide: Psychological Autopsy, a Research Tool for Prevention**, 2005, 180 p.
- **Cancer: A Methodological Approach of the Link with the Environment**, 2005, 108 p.
- **Behavioral Disorders in Children and Teenagers**, 2005, 448 p. (joint publication)
- **Health and Care Experience: From Individuals to the Social Environment**, dir. P. Chauvin and I. Parizot (with the collaboration of S. Revet), Inserm/Vuibert, 2005 (exclusively distributed by Vuibert).

Orchestration of the Network of Regional Communication Directors

Regional communication directors operationally depend on the Department of Scientific Information and Communication (DISC). Their most significant contribution in 2005 was to participate in the regional organization of actions and events such as the Science Fair.

They also initiated a number of press communication actions with regional media and relayed national communication efforts.

Finally, regional communication directors participated in the conception of brochures designed to raise awareness in Inserm research laboratories, following a graphic charter defined by the DISC.

Scientific Images at the Heart of Two Exhibitions

“When Science Becomes Art” (*Quand la science rejoint l’art*)

This Inserm exhibition was presented in 2005 in 47 different cities. This raises the number of host countries to 50 and the total number of visitors who have been able to discover the world of biomedical research through this collection of photographs to 7 million. Abroad, the collection was shown in Barcelona, Montreal, Kuala Lumpur, Lasi, Athens and Monaco. In France, the exhibition has been circulating in over twenty different cities and has provided opportunities for numerous conferences and guided visits.

“Six Senses for Life”

This health educational project initiated by Inserm has become a playful and interactive exhibition. After being inaugurated at the end of 2004 in Romans by the Prefect of the Drôme Department, this 150-m² exhibition is achieving a fair success. After Valence, Saint-Vallier, Die, Crest, Montélimar, Nyons, Nice, and Chambéry, the exhibition is already filling its reservation book.

BUDGET AND FINANCIAL ACCOUNT

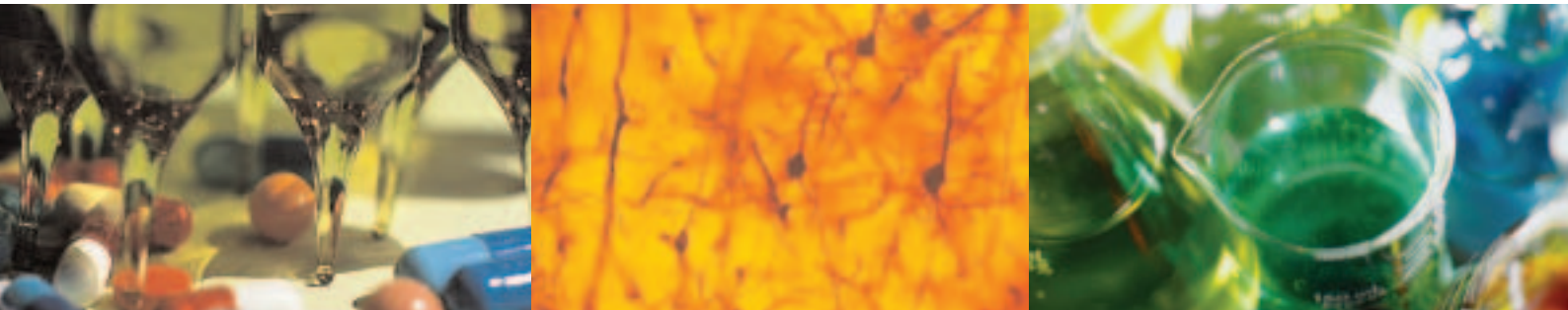
129 THE 2005 BUDGET

130 FINANCIAL ACCOUNT



THE 2005 BUDGET

In 2005, Inserm's budget (funds allocated in the original budget and after subsequent modifications) was 588 M€ (excluding stock exchange operations), representing an increase of 7.2% relative to the previous year.

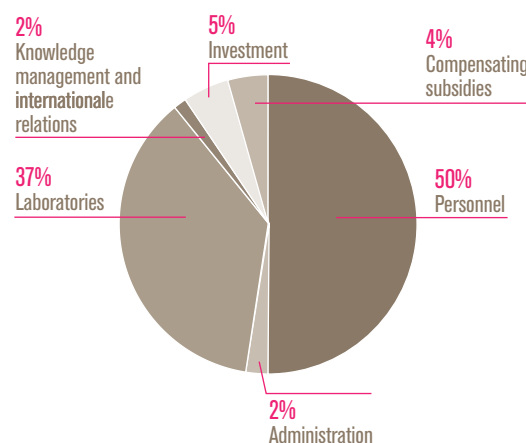


The amount of authorized expenditure in 2005 was 517 M€, corresponding to a gross utilization of 88% of the provisional budget. If non-commissioned expenses are taken into account (42 M€), the net utilization factor is 95 %, which is slightly higher than the figure for 2004 (94,5%).

Revenues for the 2005 financial year totaled 536 M€, which represents a marked increase compared to 2004 (up by 47 M€). Further details concerning the budget are given in the diagrams below.

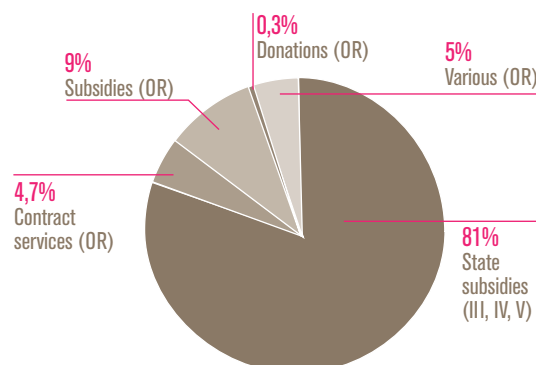
Total Budget for 2005

In 2005, Inserm's budget totaled 588 M€ (excluding stock exchange operations), distributed as follows:



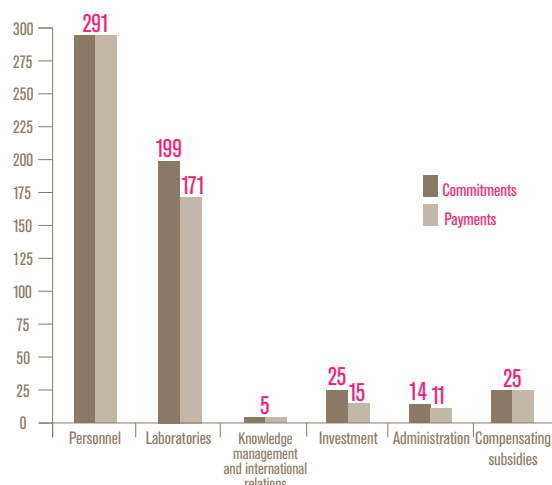
2005 Budget: revenues

Origin of revenues (in M€) and forecasted revenues according to nature of revenue:



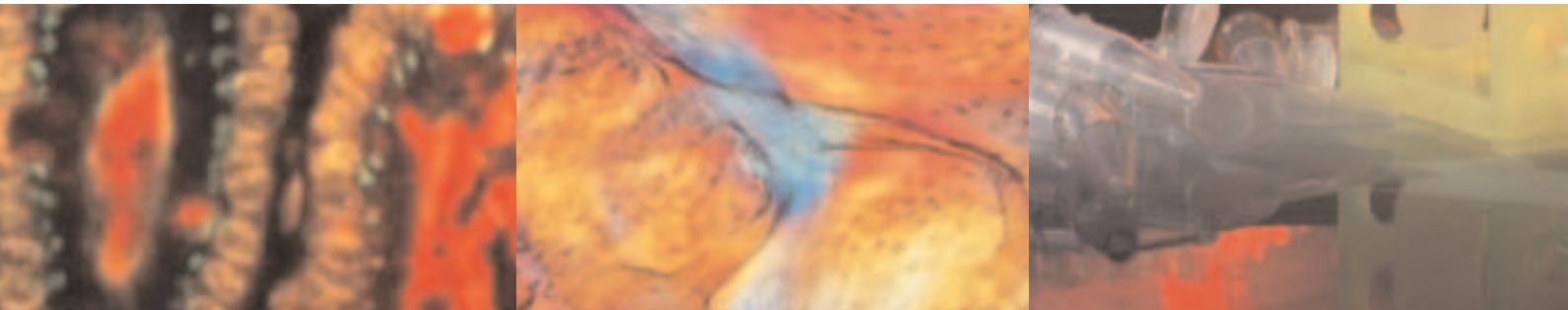
2005 Budget: expenditures

Commissioned expenditures in 2005 totaled 517 M€ (excluding stock exchange operations), which corresponds to a utilization factor of 88%. This percentage goes up to 95% if non-commissioned expenses (42M€) are included.



FINANCIAL ACCOUNT

In 2005, new computerized account revision procedures were set up to improve internal control and external certification. The balance sheet as of 31 December amounts to 316 M€, representing an increase of 9% compared to the figure for 2004.



Thanks to the efficient computer system now being used at Inserm, the year 2005 was devoted to setting up new tools and procedures for account monitoring, prior to the full implementation of the new internal control procedure and future external account certification.

Efforts this year included:

- the revision of modalities for including subsidies on the balance sheet;
- the production of a new Inserm inventory guide;
- the definition of quality standards for third-party accounts;
- a self-diagnosis guide for ancillary accounting departments.

This work was formalized into a finance and accounting modernization protocol due to be signed in 2006 by Inserm's Director General, the chief officer for national accounting (represented by the deputy director in charge of the organization and modernization of public spending) and the main accounting officer.

2005 Balance Sheet

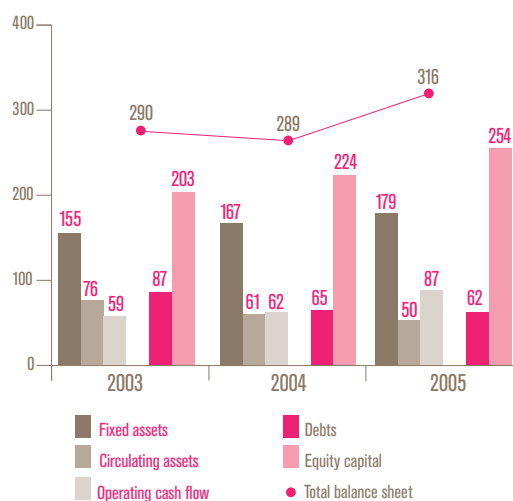
The balance sheet gives a snapshot of the Institute's assets as of 31 December. It records, on the active side, all goods (fixed assets, stocks, accounts receivable, liquid assets) and, on the passive side, the financial sources of assets. The difference between third-party assets and liabilities corresponds to the organization's own capital, which may increase or decrease depending on operating account results.

The balance sheet total has increased by 9% between 2004 and 2005 (316 as against 259 M€).

On the active side, the increase was more marked for circulating assets (+15 M€) than for fixed assets (+12 M€), with the result that the percentage of fixed assets fell from 58 to 56%. On the passive side, equity capital went up by almost 30 M€ while debts decreased by more than 3 M€.

The percentage of equity capital has therefore progressed to reach the figure of 80% of the total balance sheet (as against 77% in 2004) as against 20% for debts (compared to 23% in 2004).

Such changes resulted in a significant increase (about 18 M€) in operating cash flow.



Progression of the Balance sheet (in M€)

Operating Account

The operating account shows the current, financial and exceptional transactions for a given fiscal year. The difference between income and expenditure determines the result of the fiscal year.

The operating account total went up by 5% and represents close to 524,5 M€.

The Institute's overheads are essentially operating expenses, which have gone up from 92% (2004) to 96% (2005) of the

total operating account. On the other hand, the figures for financial and exceptional expenses (1.1 M€ and 6.5 M€ respectively) have remained similar since last year.

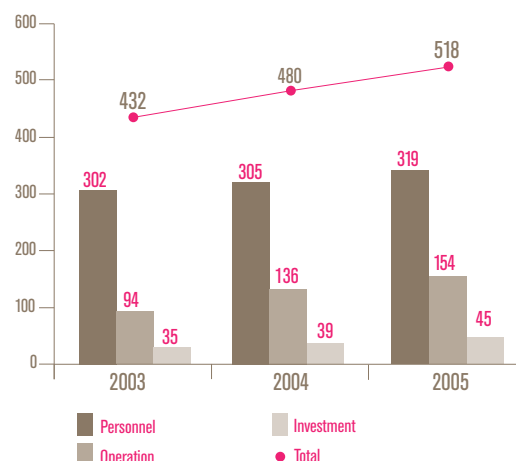
Similarly, operating revenues constitute the best part of the Institute's revenues. Their relative contribution to the operating account has gone up from 94% to 97%. Financial revenues have increased by 59% in 2005 but remain relatively non significant (1.2 M€). Conversely, the relative

contribution of exceptional revenues has gone down from 6 to 3%, which represents a 50% decrease between 2004 and 2005.

The 2005 accounting results remain above 18 M€, i.e. 3.5% of the operating account, which is lower than the figure for 2004, when the volume of exceptional revenues largely explained the figure of 30 M€ for accounting results.



Progression of expenses and revenues from 2003 to 2005 (in M€)



Progression of expenses, excluding stock exchange operations (in M€)

Inserm is the only French public organization
entirely dedicated to biological, medical
and public health research.

Inserm researchers are committed
to studying all human diseases,
whether common or rare.

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Inserm



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