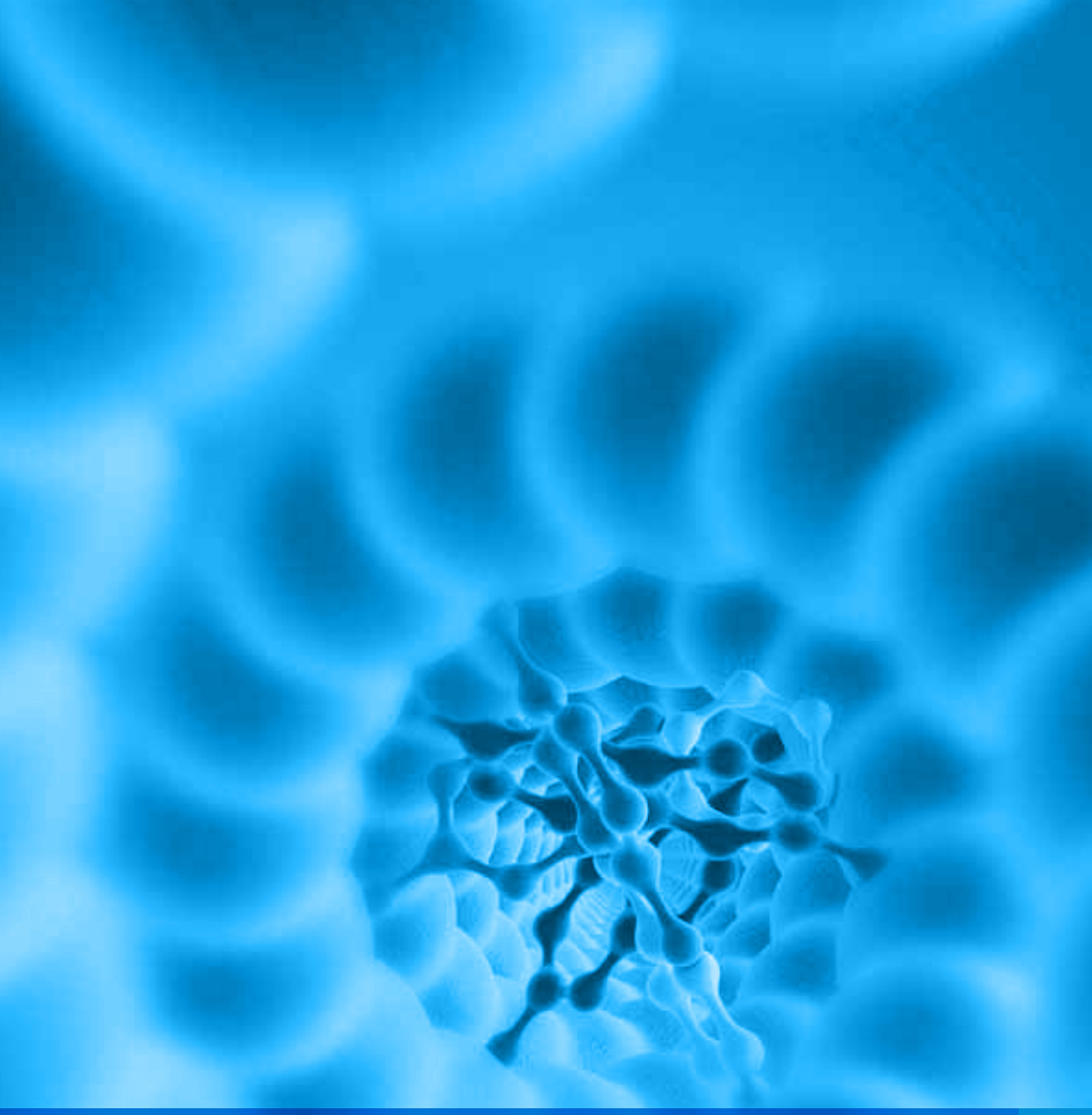

LABORATORIES

BIO-INFORMATICS MATHEMATICS

BIOPHYSICS BIOCHEMISTRY

BIOTHERAPIES VACCINOLOGY

GENOMICS POSTGENOMICS

MEDICINE TELEMEDICINE

ENGINEERING SCIENCES

LABORATORIES

The public research organisms and universities (supervisory bodies) of the academic laboratories

INSERM

- The Genethon Research Division
- Institute for Stem Cell Therapy and Exploration of Monogenic Diseases - I-Stem
- Molecular Immunology and Innovative Biotherapies
- Stem Cells and Cardiogenesis
- Structure and Activity of Normal and Pathological Biomolecules
- Unit for Integrated Biology in Adaptations to Exercise (UBIAE)

CNRS

- The Genethon Research Division
- Institute for Systems and Synthetic Biology (iSSB)
- Laboratory for Analysis and Modeling in Biology and the Environment (LAMBE)
- Metabolic genomics
- Statistics and the Genome

INRA

- Plant Genomics Research Unit (URGV)
- Statistics and the Genome

CEA

- Genoscope
- Laboratory for Analysis and Modeling in Biology and the Environment (LAMBE)
- Laboratory for the Genomics and Radiobiology of Keratinopoiesis
- Metabolic genomics
- The National Genotyping Center (CNG)
- Tumor Functional Genomics and Epigenetics

UNIVERSITY OF ÉVRY

- The Genethon Research Division
- GenHotel
- Institute for Stem Cell Therapy and Exploration of Monogenic Diseases - I-Stem
- Institute for Systems and Synthetic Biology (iSSB)
- IT for Integrated Biology and Complex Systems (IBISC)
- Laboratory for Analysis and Modeling in Biology and the Environment (LAMBE)
- Metabolic genomics
- Molecular Immunology and Innovative Biotherapies
- Plant Genomics Research Unit (URGV)
- Statistics and the Genome
- Structure and Activity of Normal and Pathological Biomolecules
- Unit for Integrated Biology in Adaptations to Exercise (UBIAE)

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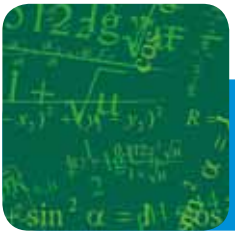

| Bio-informatics | Mathematics
| Systems Biology |

BioIntelligence Program

MAIN TOPIC

An integrated software environment for the life sciences industry

FIELD OF ACTIVITY

- Drug discovery.
- Systems biology.
- Product lifecycle management.
- Applications in oncology & toxicology.

KEYWORDS

Drug discovery - Oncology - Toxicology - Systems biology - Product lifecycle management.

Supervisory body Genopole®
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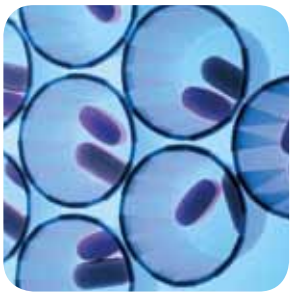
RESEARCH THEMES

The institute of Systems and Synthetic Biology is developing the Bio Intelligence Program *(cf page 33)*.

The goal of the BioIntelligence Project is to elaborate an integrated software environment for product and compound R&D in the life science industry, with emphasis on the pharmaceutical and crop protection industries.

This innovative digital environment will:

- deliver a unified platform for collaborative biological synthesis and analysis;
- generate mathematical models for use in *in silico* digital simulation and comparison with experimental data;
- optimize life science R&D processes.



Center for Mechanical Engineering and Automation Studies and Research [CERMA]

MAIN TOPIC

Engineering sciences.

FIELD OF ACTIVITY

- Development of new production methods, feasibility studies and specifications for products and machines requiring a multi-disciplinary approach.
- Applications in manufacturing, research and biology.

KEYWORDS

Mechanical engineering - Robotics - Automation - Instrumentation - Process: development and feasibility - Prototyping.

Supervisory body EDE-innov

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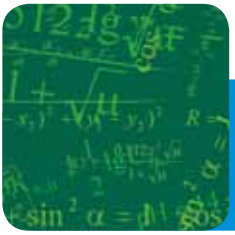
RESEARCH THEMES

The CERMA stands out by its ability to provide total management of complex projects (from initial specification to commissioning) in fields including mechanical engineering, electronics, special sensors and industrial IT. As a Technology Transfer Center of the University of Évry, it designs, builds and implements innovative machines, products and automated processes for a range of industrial sectors (notably in the field of biology). The CERMA has particularly focused its work on the high-throughput automation of electrophoretic analysis and related techniques: sample preparation, dilution, PCR, UV luminescence imaging, etc.

The CERMA collaborates with other public-and private-sector establishments: CNS *(cf page 31)*, Genethon *(cf page 96)*, University of Évry (the IBISC lab *cf page 34*), University of Paris 7, University of Paris 11, the Gustave Roussy Institute, INRETS (LIVIC), Danone Research, etc. Since its creation, the CERMA has handled more than 250 projects in a variety of sectors: automated workstations in genetics, crash test beds in the automotive industry, industrial inkjet printers, medical electronics, etc.

INDUSTRIAL COLLOBARATIONS

- Several private-sector users: Oligo Express (oligonucleotide synthesis) in Montreuil, France; Metabolic Explorer (a green chemistry company developing and patenting industrial processes based on fermentation) in Saint-Beauzire, France.
- Equipment manufacturers and reagent producers: Genome Express (oligonucleotide synthesis) ; DNAagency.
- Other industrial collaborations: Danone Research, EDF, Traiteurs de Paris, Ces, Biobank, Alam Medical, CEA, Primadiag, Qualicyt, Herdegen, IRSN, Corning, Risoud Precision, Ehbio, Aegilops, Cornilleau, Fanuc, Genewave, Adres, Comelli, Thema Concept.



| Bio-informatics | Mathematics
| Systems Biology |

Epigenomics Program

MAIN TOPIC

A multidisciplinary modeling approach for systems biology and synthetic biology.

FIELD OF ACTIVITY

- Modeling and simulation of biological processes in a (post)genomics context.
- Epi-organization of genomes.

KEYWORDS

Modeling - Simulation - Engineering - Macromolecular networks - Epigenesis.

Supervisory body Genopole®

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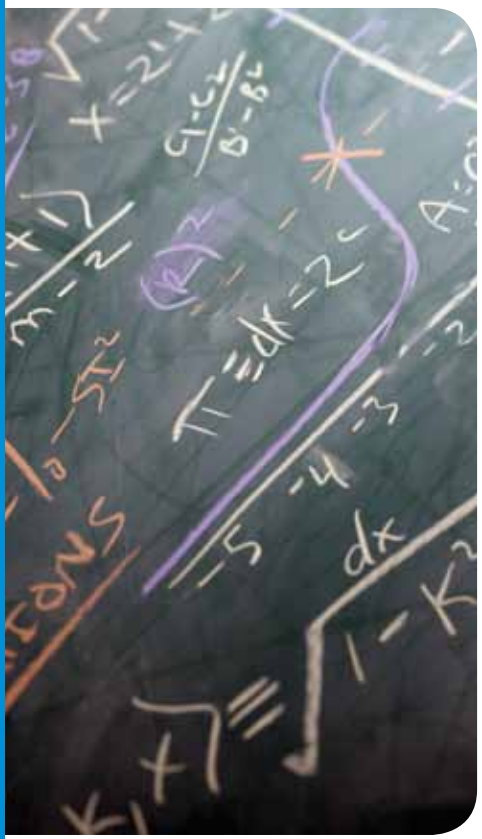

RESEARCH THEMES

The Institute of Systems and Synthetic Biology is developing the Epigenomics Program *(cf page 33)*.

The Genopole Epigenomics Project (founded in 2002 and whose slogan is "modeling for understanding") aims first and foremost to be a forum for dialogue in order to catalyze research on complex biological problems *via* contributions from a range of disciplines: biology, computing, mathematics, theoretical physics, artificial chemistry and so on.

The Program simultaneously serves as :

- a vector for training researchers in disciplines other than their own,
- a visiting researcher program,
- a hotbed of pioneering science (stimulating the invention of new research subjects and supporting them through targeted, thematic activities),
- a collaborative program that federates Évry-based research efforts on modeling in biology.

All the activities funded by the Epigenomics Program are highly thematically targeted and are based around a small number of leading researchers.

| Genomics | Postgenomics
| Biotherapies |

Euroas Genomic Bank

MAIN TOPIC

Genomics and postgenomics of spondylarthropathies.

FIELD OF ACTIVITY

- Constitution of DNA banks and clinical/ immunological databases.
- Physiopathology of spondylarthropathies.
- Characterization of genetic factors other than HLA B27.
- Function of HLA B27.
- Clinical epidemiology.

KEYWORDS

Genetics - Immunology - Ankylosing spondylitis - Spondylarthropathies.

Supervisory bodies
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RESEARCH THEMES

Ankylosing spondylitis (AS) is the archetypal (and most frequent) spondylarthropathy. The Euroas association (which consists of 10 rheumatology research labs and clinical centers from 9 European countries) has achieved one of its main objectives: building an European genomic bank (EGB) for cataloguing the genetic and clinical characteristics of patients suffering from SA or other spondylarthropathies and those of their families. The bank's current collection of 7 000 samples (collected by the consortium members from 1 230 families) includes a large cohort of B27-negative subjects and some B27-positive subjects.

The EGB has enabled selection of a large research cohort and the launch of a high-resolution MHC and genome study. The goal is to screen for potential susceptibility and/or severity genes involved in the genesis of spondylarthropathies in general and SA in particular, thus elucidate the fundamental molecular mechanisms of these diseases and open up new opportunities for developing novel diagnostic techniques and treatments (including cell and gene therapies).

| Genomics | Postgenomics
| Biotherapies |

The Genethon Research Division

MAIN TOPIC

Gene therapy for rare genetic diseases.

FIELD OF ACTIVITY

Design, development and production of innovative therapies for rare genetic diseases with a specific focus on neuromuscular diseases.

KEYWORDS

Rare diseases - Immunodeficiencies - Muscular dystrophy - Neuromuscular diseases - Gene therapy, cell therapy - Therapeutics based on genetic knowledge - Vector targeting technology - Biomanufacturing - Gene transfer, stem cells - Pharmaceutical development - GMP facility for the production of gene transfer vectors.

Supervisory bodies Genethon - INSERM - Université d'Évry-Val-d'Essonne - CNRS

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RESEARCH THEMES

The Genethon Research Pole is active in four main research areas:

- Identification of new therapeutic approaches for monogenic neuromuscular diseases, including Duchenne Muscular Dystrophy, progressive limb-girdle muscular dystrophies, X-linked myotubular myopathy and Charcot-Marie-Tooth neuropathies. The research includes the investigation of physiopathological mechanisms, the search for new biomarkers, and the identification of new therapeutic strategies in particular based on locoregional or systemic administration of adeno-associated viral vectors.

This research is carried out by the groups of Isabelle Richard, Ph.D. (DR1 CNRS, part of the joint unit UMR 8587), Anna Buj-Bello, Ph.D. (CR2 INSERM, ATIGE research group) and Fedor Svinartchouk, Ph.D.

- Gene therapy of inherited immunodeficiencies, including Wiskott-Aldrich syndrome, chronic granulomatous disease and Arthemis-deficient severe combined immunodeficiency. The research includes the development of new lentiviral vectors for the genetic modification of hematopoietic stem cells, the analysis of stem cell differentiation, and the study of the genetic and epigenetic consequences of gene transfer in the human genome.

This work is performed in the INSERM Unit U951 led by Anne Galy PhD (DR1 INSERM) *(cf page 38)*.

- Development of innovative approaches for gene and vector targeting, and vector biosynthesis and manufacturing. The research addresses the study of new approaches for targeted transgenesis and the development of innovative technologies for the production and large-scale manufacturing of lentiviral and adeno-associated viral vectors.

This work is performed by the groups of Otto Merten, Ph.D. and Fulvio Mavilio, Ph.D.

- Characterization and control of immune response to gene transfer. The research is addressing the humoral and cell-mediated immune responses to in vivo administration of viral vectors in pre-clinical small and large animal models, and new methods to monitor and control immune responses in the context of gene therapy clinical trials.

This work is carried out by the groups of Carole Masurier, Ph.D., and by researchers from the INSERM U951 led by Anne Galy PhDH *(cf page 38)*.

| Genomics | Postgenomics
| Biotherapies |

GenHotel
European Research Laboratory for Rheumatoid Arthritis - EA 3886

MAIN TOPIC

Genomics - Postgenomics.

FIELD OF ACTIVITY

Research on the genetic susceptibility to rheumatoid arthritis and on the pharmacogenetics of the disease.

KEYWORDS

Rheumatoid Arthritis - Family studies - Autoimmune and multifactorial diseases - Pharmacogenetics

Supervisory body
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RESEARCH THEMES

Rheumatoid Arthritis, the most common autoimmune disease, is a painful chronic disease which leads to progressive joint destruction. This multifactorial disease probably involves a large number of genetic factors. New biotherapies have recently improved the treatment outcomes for RA.

GenHotel's goal is to determine the multifactorial determinism of rheumatoid arthritis (RA) by studying genetic and environmental factors in sufferers and their families. This work should lead to new drug targets, with a view to preventing and curing this disease. The research methodology will be extended to other diseases with a major impact on public health. Familial studies performed at GenHotel contribute significantly to the confirmation of new genetic factors.

GenHotel has confirmed the importance of five suspected factors and is now studying 25 newly proposed factors. Additional analyses of genomic variations are being performed. In parallel, familial studies are being extended by a GenHotel group based in the Auvergne region of central France. The objective is to specify the risks due to the association of genetic and environmental factors in RA families.

COLLABORATIONS

- GenHotel is involved in several collaborations on the Genopole® campus, notably with the Statistics and Genome Laboratory (Professors C. Ambroise and B. Prum; *cf page 41*), Genoscope (Professor J. Weissenbach; *cf page 31*) and the French National Genotyping Centre (R. Olaso, Gene-Expression Platform; *cf page 39*).
- GenHotel has set up programs at the South Ile-de-France Medical Center in Évry-Corbeil (Professor Hilliquin) and at Lariboisière University Medical Center in Paris (Professor Bardin), in order to develop transcriptome analysis and study the pharmacogenetics of RA biotherapies.
- One of GenHotel's particular characteristics is its commitment to sharing, thanks to funding from the French Rheumatoid Arthritis Society (Association française des polyarthritiques): sharing funds by hosting guest researchers in its labs, sharing results on the www.genhotel.com website and sharing skills in additional projects.

Genopole® Plant Process Innovation

MAIN TOPIC

Development of vaccines and therapeutic proteins via plant molecular farming.

FIELD OF ACTIVITY

Research and development of vaccine and recombinant protein production systems using plant-based transient expression.

KEYWORDS

Virus-like particles (VLP) - Recombinant antibodies - Therapeutic proteins - Vaccines - Diagnostics - Transient expression - Plant molecular farming.

Supervisory body Genopole®
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Project manager **Andéol Falcon de Longevialle**
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RESEARCH THEMES

The Genopole® laboratory Plant Process Innovation (PPI) develops new and innovative processes for the production of recombinant proteins using genetically engineered plants.

PPI is equipped with VLPExpress™, a high-throughput virus-like particle (VLP) testing platform developed by the Canadian biotechnology company Medicago. The platform speeds the identification of candidate VLPs and in turn the development of therapeutic or diagnostic vaccinal and recombinant antibody applications. The laboratory thus benefits from:

- an alternative expression method in plants;
- a miniaturized and automated production process;
- the ability to test a wide spectrum of strategies simultaneously;
- the rapid elimination of uninteresting candidates.

This allows the laboratory to attain two objectives:

- assure R&D in the transient expression of VLPs or recombinant antibodies;
- provide a high-level infiltration system for studies in recombinant protein transient expression.

COLLABORATIONS

- Medicago
- URGV (Plant Genomics Research Unit, *cf page 40*).

Genoscope - CNS
CEA/Genomics Institute

MAIN TOPIC

Genomics and post-genomics of various species, including microorganisms sourced from the environment.

FIELD OF ACTIVITY

- High-throughput production of DNA sequences.
- Genome analysis.
- Functional genomics.
- Applications (research on biological solutions for the replacement of chemical synthesis).

KEYWORDS

Sequencing - Genomics - Biochemistry - Metabolism - Bioconversion - Comparative genomics - Metabolic engineering.

Supervisory body CEA
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RESEARCH THEMES

Since 1998, Genoscope has been responding to the high-throughput sequencing needs of the French scientific community (380 Mbases per day).

Genoscope has also participated in international collaborative sequencing efforts such as the Human Genome Project (chromosome 14), plant genome projects (algae, the banana plant, *Arabidopsis*, grapevine, rice, cocoa tree, medicago truncatule, etc.) and animal genome projects (*Tetraodon*, *Anopheles*, etc.), fungi (truffles, a fungal pathogen, *Leptosphaeria maculans* and *botrytis cinerea*) and has sequenced more than fifty prokaryotic genomes.

The Genoscope lab keeps up with the state of the art in sequencing and sequence analysis; 97.3 % of our DNA sequence output is generated using the latest Flex and Illumina technologies. The sequencing facility is constituted by 3 Roche 454 GS FLEX Titanium, 2 Illumina GAIIX and 1 SoliD machines and 17 ABI 3730 capillary sequencers, which will be progressively replaced by new-generation sequencers. The current average daily throughout is around 10 billion bases.

Genoscope is currently focusing its research activity on the genomics of environmental micro-organisms in particular marine protists (the "TARA Oceans" project), the bacterial flora of the human digestive tract and those involved in effluent treatment.

The exploitation of sequence data (now extended to the identification of biological functions, notably in the biocatalysis field) is opening up new perspectives for developments in industrial biotechnology. In the field of sustainable development, Genoscope is searching for biological solutions in synthetic chemistry, in order to reduce pollution and energy & fossil fuel consumption.

To this end, the centre has developed an enzyme activity screening platform and a metabolic engineering laboratory. This research is performed in close collaboration with the UMR 8030 Metabolic Genomics research unit *(cf page 37)*.

INDUSTRIAL COLLABORATIONS:

- Global Bioenergies *(cf page 101)*
- Isthmus
- Suez Environnement.

| Genomics | Postgenomics | Biotherapies |

Institute for Stem Cell Therapy and Exploration of Monogenic Diseases I-Stem

MAIN TOPIC

Postgenomics and cell therapy of monogenic diseases.

FIELD OF ACTIVITY

Evaluation of the full therapeutic potential of all types of human pluripotent stem cells (stem cells from all sources) in the treatment of monogenic diseases. Set against this background, the group is particularly exploring substitutive cell therapies for degenerative diseases on one hand and the use of stem cell lines carrying pathological mutations as drug screening targets on the other.

KEYWORDS

Cell therapy - Disease modelling - Stem cells - Monogenic diseases.

Supervisory bodies INSERM
Université d'Évry-Val-d'Essonne
AFM-Téléthon - CECS
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RESEARCH THEMES

I-STEM is composed by two research entities : INSERM/ UEVE and CECS. I-STEM is developing 12 research themes:

- Neurodegenerative diseases (cell therapy, modeling of Huntington's disease).
- Neuromuscular diseases (disease modeling of myotonic dystrophy).
- Motor neuron diseases (molecular and cell mechanisms involved in the development of motor neuron diseases such as myotonic dystrophy).
- Muscle diseases (disease modeling, repair).
- Neuroplasticity and therapeutics (study of molecular mechanisms involved in neural development).
- Neurovascular damage (disease modeling and cell therapy).
- Retinopathies and neural development diseases (cell therapy, disease modeling).
- Genodermatoses (disease, cell therapy).
- Biotechnology of human stem cells (mass production of cells, genetic engineering).
- High-throughput screening.
- Use of induced pluripotent stem cells as disease models in drug screening.
- Functional genomics (development of dedicated technological tools for the study of monogenic diseases).

Participation in French National Research Agency programs, a Medicen Paris Region cluster program and several European Union projects.

ASSOCIATED RESEARCH GROUPS

"Differentiation of human melanocytic lineage and pathological modelling of waarenburg Syndrome using mutant human Embryonic Stem Cells". Leader: Christine Baldeschi.

INDUSTRIAL COLLABORATIONS

- GenoSafe *(cf page 99)*
- LTKFarma *(cf page 110)*
- Roche
- Cellectis.

| Genomics | Postgenomics | Biotherapies
| Systems and synthetic biology |

Institute for Systems and Synthetic Biology (iSSB)

EA 4527 - CNRS UPS 3509

MAIN TOPIC

Systems and synthetic biology.

FIELD OF ACTIVITY

- Modeling, simulation and engineering of biological processes.
- Metabolic engineering.
- Molecular Biology.
- Bioinformatics.
- Microfluidics.

KEYWORDS

Synthesis - Engineering - Modeling - Simulation - Macromolecular networks.

Supervisory bodies
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RESEARCH THEMES

The Institute of Systems & Synthetic Biology (iSSB) is structured into 5 research teams. Systems Biology integrates experimental, theoretical, and computational studies to model living systems. In this research area, the MEGA and Metamorphosys teams study the structure, architecture, expression, and evolution of genomes. Synthetic biology uses systems biology models to design, build, and test new biological circuits and devices (Xenome, Synth-Bio and Bio-RetroSynth teams). The overreaching goal of the iSSB projects is to design, construct and characterize biosafe spatio-temporal gene circuits in order to understand and control genetic expression.

The **Mega** research group analyses the topology of transcriptional networks in time and space. Its recent work has dealt with the functional organization of the nucleus, genome evolution & organization and links between carbon metabolism and DNA replication. The group's theoretical work is prompting bench experiments that examine the cell's regulatory networks on the genome-wide scale.

The **Metamorphosys** group studies three aspects of the genome of the African clawed frog *Xenopus tropicalis*: genome structure (DNA transposons and their use in genome engineering experiments), expression of the genome during ontogenesis, and genome evolution.

The **Synth-Bio** research group is developing computational methods for designing biological and metabolic circuits within bacteria. These biological circuits are then characterized *in vivo*. Lastly, the bench data feed into established models and thus close the loop.

The **Bio-RetroSynth** group's research interests cover the use of retrosynthetic methods for designing and building new metabolic networks. Retrosynthesis consists in choosing a set of exogenous enzymes which, when introduced in a host organism, produce the desired target compound. The method is being applied to the production of drug compounds in bacteria.

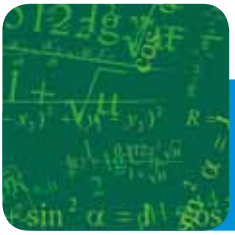
The ultimate aim of the **Xenome** team is to design and engineer novel cellular components ("xeno"-nucleic acids, XNA) to elaborate safe GMOs whose *in vivo* generation and functionality can be strictly controlled, and which therefore allow the development of new and advanced applications in biotechnology.

ASSOCIATED "ATIGE" RESEARCH GROUPS

"Xenome".
Leader : Piet Herdewijn.

INDUSTRIAL COLLABORATIONS

- WatchFrog *(cf page 142)*.
- Isthmus.



| Bio-informatics | Mathematics | Systems Biology |

IT for Integrated Biology and Complex Systems - Ibisc

MAIN TOPIC

Computer science, bioinformatics, ICT and engineering science applied to biological systems.

FIELD OF ACTIVITY

- Bioinformatics, analysis, modeling.
- Identification and simulation of biological processes.
- Software engineering.
- Operational research.
- Communication & transport networks.
- Agent-based & communicative systems.
- Biomedicine & healthcare (signals, machine-assisted medical procedures, Assistance robotics for people with loss of autonomy and their support providers).
- Assistance robotics for people with loss of autonomy and their support providers.
- Biometrics.
- Multimodal man-machine inter-facing.
- Road safety.
- Biology of the cellular micro-environment/ Modeling in physiology.

KEYWORDS

Bioinformatics - Postgenomics - Data integration and advanced databases - Formal methods - Algorithmics - Optimization - Learning - Complexity sciences - Data - Signal and image processing - Virtual reality - Augmented reality - Haptics interaction - Human-robot interactions - Intelligent vehicles - Cell migration - Cell environment - Experimental biology.

Supervisory body Université d'Évry-Val-d'Essonne

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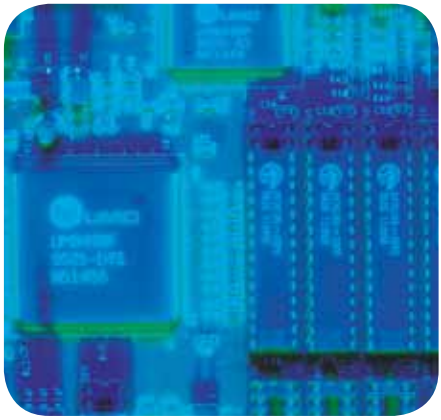

RESEARCH THEMES

The group's scientific activity is organized into three themes: biological systems, assistance robotics and airborne vehicles.

Within Genopole®, IBISC's specificity involves studying potential applications of computing science and automation to genomics and systems biology. Research in this area covers three main themes:

- The representation, analysis and comparison of DNA, RNA and protein sequences; the determination of functional motifs, annotation, etc.
- The organization and analysis of transcriptomic, proteomic and metabolomic data, together with statistical learning based on these data with a view to the development of systems biology tools.
- The representation, modeling, simulation and identification of biological processes, with a focus on the simulation of cellular and tissue processes; regulatory networks and cell / micro-environment interactions during metastatic spreading.

INDUSTRIAL COLLABORATIONS

In addition to its participation in around ten European Union projects and twenty or so French National Research Agency projects, IBISC collaborates directly with a number of industrial partners, including: Arevent - Cliris - Continental - Oktal.

| Biophysics | Biochemistry
| Nanotechnologies | Biomaterials |

Laboratory for Analysis and Modeling in Biology and the Environment (Lambe) - CNRS UMR 8587

MAIN TOPIC

Chemistry, biology and physics applied to the analysis and modeling of biomolecules and materials.

FIELD OF ACTIVITY

- Mass spectrometry structural analysis of macromolecular synthetic systems of biological interest.
- Classical and *ab initio* modeling of the structure, dynamics and reactivity of biomolecules.
- Electrochemistry and activity of materials at interfaces in confined media (toxic radioactive elements), development of electrochemical sensors for trace analyses.
- Biophysics and macromolecular synthesis for therapeutics and the environment.

KEYWORDS

Mass spectrometry (MS) – Biomolecule modeling and simulation – Proteomic analyses – Development of new analytical strategies (MS / separation techniques coupling) - Electrochemistry - Corrosion – Electrochemical sensor development – Macromolecular chemistry – Supramolecular assemblies – Macro and supramolecular synthesis of biosourced materials – Membrane transport – Natural and synthetic nanopores – Gene therapy – Extracellular matrix and the cellular microenvironment.

Supervisory bodies
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RESEARCH THEMES

- Proteomic studies (analysis of post-translational modifications, immunopurified protein complexes, etc.) by using MALDI/TOF, electrospray/Q/TOF, capillary electrophoresis/ion trap and LTQ orbitrap mass spectrometers.
- Development of new capillary electrophoresis/ surface plasmon resonance (SPR)/ mass spectrometry coupling.
- Study of the role of metal cations in the catalysis and activation of model biological compounds (amino acids, nucleotides, saccharides, etc.) in the gaseous phase.
- Multiscale modeling of the structure and function of biological assemblies.
- Development of course-grained force fields *via* protein-protein binding.
- Prediction and modeling of the long-term behavior of final electronuclear waste.
- Study of the transport (translocation) of single macromolecules through nanometer-scale protein-based pores and artificial biomimetic pores (nanolithography).
- Development of electrochemical sensors and biosensors for pollutant analyses.
- Synthesis of polymer gene therapy vectors and analysis of their *in vitro* and *in vivo* structure and function.
- Synthesis of biosourced polymers.

ASSOCIATED "ATIGE" RESEARCH GROUPS

«Protein translocation and folding at the nanopore outlet: a comparison between natural and biomimetic systems; applications». Leader: Juan Pelta.

INDUSTRIAL COLLABORATIONS

- EDF
- AREVA
- ANDRA (French National Agency for the Management of Radioactive Waste)
- ARCELOR
- Synchrotron Soleil
- CEVA (Centre for the Study and Exploitation of Algae)
- Global Bioenergies *(cf page 101)*
- Horiba Jobin Yvon
- Onidol
- SNPE.

| Genomics | Postgenomics | Biotherapies |

Laboratory for the Genomics and Radiobiology of Keratinopoiesis

MAIN TOPIC

Stem cells of the human epidermis.

FIELD OF ACTIVITY

- Stem cell biology.
- Radiobiology.
- Cancer.

KEYWORDS

Somatic stem cells - Human skin - Genomics - Transcription factors - Skin organogenesis - Regenerative medicine - Cancer - Hypersensitive patients - Ionizing and UV radiation - DNA damage and repair

Supervisory body CEA (iRCM)

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RESEARCH THEMES

Homeostasis, regenerative potential and radiosensitivity of human epidermal stem cells.

Human interfollicular epidermis is the multilayered epithelium that covers the human skin. This tissue is in perpetual renewal, a process named keratinopoiesis which is maintained through stem cells and their ability to self-renew.

Although potentialities of human epidermal stem cells have been exploited for clinical purposes for more than 20 years, they are still poorly known. Keratinocyte stem cells are located in the basal layer of epidermis.

They are defined as undifferentiated and quiescent cells, capable of a large proliferative potential when stimulated. Their direct progeny, called keratinocyte progenitors, are responsible for the short-term maintenance of epidermis. Our laboratory aims at better characterizing these two basal cell populations, both in normal skin homeostasis and after genotoxic stress.

Our group dissects the determinants of stemness and self-renewal in keratinocyte stem cells, notably those related to the TGF-ß1 network. We also aim at understanding the mechanisms that maintain genomic stability in the basal keratinocytes, which are the major target of skin carcinogenesis after ionizing or UV radiation. DNA damage and repair are characterized in normal and hypersensitive skin, derived from patients with rare genetic dermatologic diseases.

Metabolic Genomics
CEA/Genomics Institute - UMR 8030

MAIN TOPIC

Diversity study of living systems.

FIELD OF ACTIVITY

- Genomics of eukaryotes, prokaryotes and metagenomes.
- Metabolic biochemistry, biocatalysis, anaerobiosis.
- Bioremediation.
- Organic chemistry, analytical chemistry.

KEYWORDS

Sequencing - Biochemistry - Metabolism - Metabolomics - Comparative genomics - Functional genomics - Enzyme - Biocatalysis - Transcriptomics - Mass Spectrometry.

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RESEARCH THEMES

The unit's themes are as follows:

- Sequence analysis of eukaryotic and prokaryotic genomes.
- Metabolic and microbial biodiversity of wastewater treatment plants.
- Reconstruction of metabolic pathways and systematic, functional gene analysis in *Acinetobacter baylyi*.
- New enzymatic functions.
- Research of new biocatalysts.

The Metabolic Genomics Group (UMR 8030) is the basic research structure of the Genoscope-National Sequencing Center *(cf page 39)*. Historically, the main theme of the Metabolic Genomics Group (UMR) was tightly linked to Genoscope's primary mission of furnishing large-scale sequencing to the French scientific community. This mission was maintained when Genoscope was integrated within the CEA in 2007. Currently most of the sequencing capacity is still meant to serve the scientific community. Not stopping there, Genoscope and UMR also provide this community with bioinformatics analysis, an expertise usually lacking in the academic teams behind the projects.

In our various national and international collaborative projects we explore organism biodiversity via genome analyses, thus participating significantly in the exploration of life on earth.

Over the last three years, new sequencing techniques have profoundly changed genomics research by making access to sequencing data commonplace and by extending sequencing knowledge to cover all biodiversity with, in particular, the ability to study metagenomes.

Two large projects fall within this focus:

- The exploration of the biodiversity of ocean life (Tara Oceans), a project involving the sequencing bioinformatics analysis team (P. Wincker);
- The analysis of the human intestinal microbiome over several European projects, in partnership with the Metagenomics of Prokaryotes Laboratory (D. LePaslier).

This flood of *de novo* sequencing data walks hand in hand with a growth in the number of identified genes whose purpose is currently a mystery. Genoscope and UMR have thus decided to extend our biodiversity focus to the study of the chemical reactions of organisms according to two major axes:

- The discovery of novel biochemical reactions to increase the knowledge of prokaryotic metabolism (Laboratory of Genomics and Metabolic Biochemistry, M. Salanoubat, Laboratory of Bioinformatics Analysis in Genomics and Metabolism, C. Médigue);
- The discovery of new biocatalysts to provide alternatives to synthetic chemistry (Biocatalytic Activity Screening Laboratory, V. De Berardinis*, Laboratory of Organic Chemistry and Biocatalysis, A. Zaparucha).

This new focus is part of our actions for a sustainable chemistry that moves away from fossil-based sources, reduces pollution and uses less energy.

The development of this enzyme-based industrial biotechnology will contribute significantly to new methods of production that are of interest in the quest to meet the goals of the Kyoto Protocol.

* Genoscope Laboratory excluding UMR

| Genomics | Postgenomics
| Biotherapies |

Molecular Immunology and Innovative Biotherapies

INSERM Unit 951

MAIN TOPIC

Immunology and biotherapies for rare genetic diseases.

FIELD OF ACTIVITY

Effects of gene therapy on the immune system. Treatment of genetic diseases of the blood and immune system.

KEYWORDS

Gene therapy – Rare diseases - Clinical trials – Immune deficiencies -Wiskott Aldrich syndrome – Chronic Granulomatous Disease – Hematopoietic gene therapy – Stem cells - Lentiviral vectors - Adeno-associated vectors - Muscular dystrophies – Eye.

Supervisory bodies Genethon - INSERM
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RESEARCH THEMES

This Research Group is constituted of researchers from the public sector (INSERM, University of Évry-Val-d'Essonne, École Pratique des Hautes Etudes) and from Genethon. The group is established within Genethon's facilities in Évry thereby facilitating the development of research projects into pluri-disciplinary therapeutic programs.

The research projects cover:

- The development of novel approaches in gene and cell therapies to treat inherited immunodeficiencies, including Wiskott-Aldrich syndrome, chronic granulomatous disease and Artemis-deficient severe combined immunodeficiency. These projects are integrated within preclinical and clinical programs at Genethon.
- The use of stem cells in cell and gene therapies, including transduction with integrative vectors, the study of epigenetic modifications induced and analyses of the stability of gene expression.
- Analysis and control of immune reactions to vectors or transgenes following systemic administration of viral vectors (lentiviral or adeno-associated vectors). These projects concern in particular the treatment of muscular dystrophies and the study of gene transfer into immune sanctuaries such as the eye.

The National Genotyping Center [CNG]

CEA/Genomics Institute

CNG CENTRE NATIONAL DE GENOTYPAGE

cea

MAIN TOPIC

Genomics and postgenomics of human diseases.

FIELD OF ACTIVITY

The CNG is primarily devoted to the discovery and characterization of genes involved in human disease.

KEYWORDS

Genotyping sequencing bioinformatics and related genomics technologies.

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RESEARCH THEMES

Being part of the Genomics Institute of the CEA since 2007, the CNG is one of the founding partners of the "France Génomique" national infrastructure, which was created in 2011 thanks to a € 60 million grant from the "Investissements d'Avenir". As such, one of the key missions of the CNG is to make its cutting-edge genomics expertise as well as its high-throughput data production and analysis platforms available for collaborations on projects that will be submitted by the French scientific community and selected on the basis of their scientific excellence.

Since its creation, the CNG has maintained its international competitiveness by incorporating the many technological developments produced worldwide in the field of genotyping. It has set up a whole range of integrated platforms for studying the genes responsible for diseases or other traits (cardiovascular, auto-immune, neurological, psychiatric, dermatological and infectious diseases, diabetes, etc.):

- A biological resource laboratory.
- High-throughput genomics platforms for performing whole-genome association studies and linkage analyses:
  - SNP genotyping: ultra high-density Illumina or Affymetrix chips
  - Whole exome or whole genome resequencing on Illumina HiSeq2000 instruments
- An SNP discovery and mutation detection platform.
- High-resolution genotyping and gene mapping (MALDI-TOF, KASPar, Taqman, Sequenom, GS Junior).
- High-throughput RNAseq and gene expression analysis platform.
- Epigenetics laboratory & epigenomics platforms.
- A bioinformatics and computational biology laboratory.

The CNG participates in major European programs on both technological development and disease research. It is involved in major French national programs such as the "Alzheimer" project, funded by the Alzheimer foundation and coordinated by the INSERM, or the "Genomics and Cancer" national program in collaboration with other programs funded by the French National Cancer Institute. The CNG production infrastructure has been widely used by the French and European scientific communities. Following scientific review, CNG groups have performed over 200 research projects submitted by scientists from about 300 French labs and 60 labs from outside France. Since its creation, the CNG teams have coauthored more than 500 publications.

The Center also hosts training fellowships (over 110 researchers since 1999) and student projects (over 100 interns and 70 students since 1999). It provides mid-term hosting of external research groups involved in collaborative projects (INRA) and has run international exchange programs with countries such as Japan, Russia, and Thailand.

| Genomics | Postgenomics
| Systems biology |

Plant Genomics Research Unit (URGV)
INRA UMR 1165

MAIN TOPIC
Genomics, transcriptomics and proteomics of model plants and crop plants.

FIELD OF ACTIVITY
Genomics and computing resources in plant biology.

KEYWORDS
Plant genomics - Plant models - Crop plants.

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RESEARCH THEMES

The URGV's goals are to develop plant genome analysis tools and use them to identify genes which impact on agriculture (crop growth and seed production), the environment (disease resistance genes) and/or the agrifood industry (genes influencing the quality of crop-derived products).

The unit's research themes fall into three main categories:

Functional analysis of the *Arabidopsis* model genome

- Development of transcriptome analysis tools and of RNAseq.
- Development of pan-genome microarray chips.
- Post-transcriptional studies/protein modifications.
- Analysis of the PPR (pentatricopeptide repeat) family involved in organelle function.
- Analysis of MAP kinases and their role in adaptation to biotic and abiotic stress.

Analysis of crop genomes

- Comparative analysis of plant genome structure (wheat, canola, grapevine and forest trees).
- Positional cloning of agriculturally important genes.
- Development of reverse genetic tools (gene tilling).
- Studies of polyploidy, gender determinism and viral resistance.
- Grapevine genome transcript analysis.

Bioinformatics

- Development of a database (FLAGdb) on the *Arabidopsis* model genome and bioinformatics tools for managing and analyzing the data outputs.
- Creation of new analysis tools for facilitating genome synteny conservation studies and work on plant improvement. Development of analytical tools for gene regulation sequences.
- Collaboration with the Genoscope and URGI on the annotation of the grapevine and canola genome.

INDUSTRIAL COLLABORATIONS:

- Biogemma
- Genewave *(cf page 98)*
- Serial Genetics
- Partnerchip *(cf page 125)*
- BASF
- Bayer
- Semillas Fyto
- Medicago.

| Bio-informatics | Mathematics |

Statistics and the Genome
CNRS UMR 8071 - INRA 1152

MAIN TOPIC

Mathematics and bioinformatics applied to the analysis of genomic and post-genomic data.

FIELD OF ACTIVITY

- Development of mathematical models and tools for the analysis of biological sequences and networks (Gene expression, Data analysis).

KEYWORDS

Statistical analyses - Bayesian Modeling - Sequence evolution - Large-scale comparisons - Genetics.

Supervisory bodies CNRS - Université d'Évry-Val-d'Essonne - INRA

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RESEARCH THEMES

Design of statistical methods for the analysis of DNA/protein sequence & expression data.

Making these methods available to the community of biologists via the internet.

Our research axes notably include:

- Sequence analysis using Markov chains or hidden Markov chains.
- Statistical inference of biological networks (interaction, regulation, metabolic pathways) from statistical or dynamical data.
- Analysis of genomic data for the identification of genes involved in the etiology of diseases (SNP analysis); time-domain analysis of gene expression mechanisms (Markovian modeling or otherwise).
- Study of inter-gene relationships, support for automatic annotation *via* large-scale sequence comparisons. Transposable elements.
- Study of protein sequence evolution.
- Analysis of transcriptome/proteome data.

Stem cells and cardiogenesis

INSERM UMR 633–FRM* Label team

Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

MAIN TOPIC

The genetic and epigenetic mechanisms underlying the cardiac specification of embryonic stem cells (ESCs): early cardiogenesis.

FIELD OF ACTIVITY

- Genetic and epigenetic regulation of cardiogenesis, using embryonic cells and early mouse embryos.
- Modeling of genetic heart diseases using reprogrammed somatic cells from patients (laminopathies and cardiomyopathies, filamin A mutations and valve diseases).
- Preclinical studies of cell therapies for ischemic and congenital heart diseases.

KEYWORDS

Early cardiac development - Cell therapy - Disease modeling - Stem cells - Reprogrammed cells.

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RESEARCH THEMES

The group is working on 4 topics:

- Understanding the dual role of the transcription factor Oct-4 in the pluripotency and mesendodermal & cardiac specification of human ESCs and mouse embryos. This projects also aims at discovering new transcriptional cardiogenic pathways.
- Establishing heart valve progenitors for use in research on the embryonic development of heart valves; Modeling genetic diseases (filamin A mutations) that affect the valves; cell therapy for valve degeneration.
- Modeling of laminopathies by using a mutated ESC model and reprogrammed somatic cells from patients: the study of structural and transcriptional hypotheses (including chromatin modifications) in this disease context.
- The use of cardiomyocyte progenitors for regenerative medicine in patients suffering from ischemic or congenital cardiomyopathies: preclinical and clinical studies.

COLLABORATIONS

- Professor Philippe Ménasché: HEGP, INSERM U633 (Paris, France): cell therapy of ischemic cardiomyopathies (a clinical project).
- Dr Mark Mercola, Burnham Institute, La Jolla, CA, USA: high-throughput screening of molecules and miRNA, inducing early and late cardiac specification in ESCs and cardiac progenitor cells.
- Dr Stéphane Zaffran, INSERM UMR 910 (Marseilles, France): valve progenitors in the embryo. Novel cardiogenic pathway.
- Dr Viginie Lambert and the group led by J.-F. Renaud (Marie Lannelongue Hospital and the CNRS unit at Le Plessis Robinson); cell therapy of congenital cardiomyopathies in a porcine model.
- Dr S Evans, UCSD, La Jolla, CA, USA: lineage tracing of cardiac progenitors in vivo.
- Dr R Markwald, Charleston University, USA (valve project).
- Dr Jose luis de la Pompa CNIC Madrid , Spain, (valve project. Coordinator transatlantiic network of excellence SHAPEHEART Leducq Fondation 2012-17.

* Fondation pour la recherche médicale (Foundation for the medical research)

| Biophysics | Biochemistry
| Nanotechnologies |

Structure and Activity of Normal and Pathological Biomolecules

INSERM - UEVE U829

Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

MAIN TOPIC

Tubulin dynamics.

FIELD OF ACTIVITY

- Cell biology.
- Cancer.
- Neuroscience.
- Medicine.
- Drug design.

KEYWORDS

Structure - Proteins - NMR - AFM - Tubulin - Cancers - Nervous system - Mutations - AIDS.

Supervisory bodies Université d'Évry-Val-d'Essonne - INSERM

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RESEARCH THEMES

- Physiopathology of the microtubule cytoskeleton and impact on the cell cycle and neuronal function.
- Structure, folding, stability & dynamics of proteins in solution.
- Protein/protein, ligand/protein and protein/nucleic acid interactions.
- Development of a multifunctional biomolecule fluorescent marker based on nanodiamonds.

ASSOCIATED "CHAIR OF EXCELLENCE"

¨Cellular neurobiology and the cytoskeleton¨.

INDUSTRIAL COLLABORATIONS

- Bioquanta (a biotech R&D service company), Genopole®, Évry.
- Saudi Aramco (Oil company produces, manufactures, markets, ships crude oil, natural gas and petroleum products), Dahran (Saudi Arabia).

| Medicine | Telemedicine
| Clinical research |

Study and Research Center for the Intensification of Diabetes Treatment [CERITD]

MAIN TOPIC

Study and research for the intensification of diabetes treatment.

FIELD OF ACTIVITY

- Healthcare center for diabetic patients treated with external insulin pumps.
- Translational clinical research center.

KEYWORDS

Type 1 diabetes, Type 2 diabetes - Genetics - Insulin pump - Clinical research - Telemedicine.

Supervisory body Ceritd Association loi 1901
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RESEARCH THEMES

Genetics:

- Establishment of a computerized database (clinical, medical history, social-economic and biological data) and a DNA bank (6000 patients) under the management of Prof. Froguel's team in Lille, France.
- Sponsor of a clinical trial focused on validating a method for detecting glycemic abnormalities at different ages in the children of people with type 2 diabetes (the Descendants program).

Innovative technologies:

- Sponsor of clinical studies on continuous blood sugar monitoring, patient psychological profiles, patch pumps.
- Founding member of a French consortium for the development of a semi-closed loop glycemia control system in diabetic patients.
- Modeling of postprandial glycemia in type 2 diabetes patients.
- Modeling of glycemia during different levels of physical activity.

Epidemiological cohort monitoring:

- Prospective monitoring of patients treated by insulin pumps in the southern Greater Paris area.
- European collaborative study to assess the quality of type 2 diabetes management and its coherence with existing recommendations in 8 European countries.

Telemedicine:

- Development of algorithms to automatically calculate insulin doses; decision-making support and patient coaching via electronic blood glucose journals for type 1 and type 2 diabetes patients.
- Development of a shared information system for health professionals (ePEP software) permitting telemedical monitoring of patients using electronic blood glucose journals

COLLABORATIONS

Numerous collaborations over many projects in the fields of type 2 diabetes genetics and maturity onset diabetes of the young (MODY).

| Genomics | Postgenomics
| Biotherapies |

Tumor Functional Genomics and Epigenetics - An Atige Research Group

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MAIN TOPIC

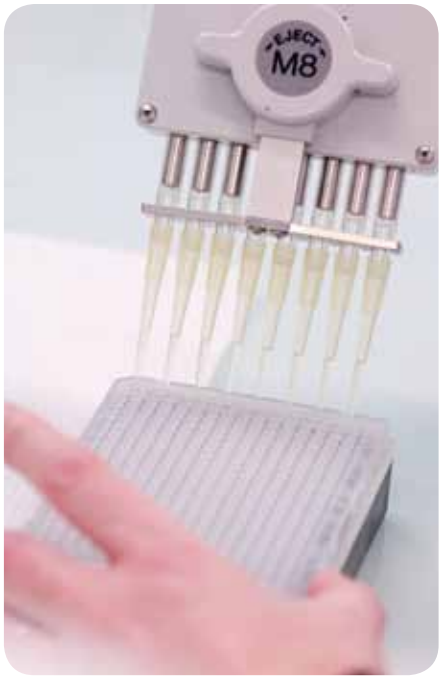
Tumor genomics, postgenomics and biotherapies.

FIELD OF ACTIVITY

- Functional genomics for translational research.
- Regulatory networks.
- Epigenetics.

KEYWORDS

RNA interference - Synthetic lethality - Gene regulation - Epistasis - Cancer in humans - Cell models - Drug targets - prognostic markers.



RESEARCH THEMES

Genome-wide identification of synthetic lethal genetic interactions with recurrent oncogenic mutations (TP53, KRAS, NRAS, BRCA1...).

By using isogenic human cell pairs to model critical steps of cancer progression and by exploiting genome–wide short hairpin RNA libraries, we assess the vulnerabilities induced by defined oncogenic alterations. We are especially seeking to identify interfering RNAs that are synthetic lethal with oncogenic mutations in our model system and then evaluate their significance in relevant clinical situations. This uncovers the genetic and epigenetic reprogramming of human cells by oncogenic events and provides new therapeutic leads for translational research.

Identification of genes involved in therapeutic resistance.

We are currently investigating genes involved in Olaparib resistance in BRCA 1 deficient cancers.

| Genomics | Postgenomics |
| Telemedicine |

Unit for Integrated Biology in Adaptations to Exercice (UBIAE)
INSERM U902

MAIN TOPIC

Physiology, genomics and post-genomics for the implementation of physical exercise protocols.

FIELD OF ACTIVITY

- Genomics and bioenergetics of muscle activity in healthy subjects and patients
- Analysis of the physiological responses to acute and chronic exercise (training) in the mammal (the human, the mouse and the horse in particular).
- E-learning for health by exercise by electronic and GPRS data transmission.
- Analysis of physiological and perceptive response to exercise.

KEYWORDS

Cardiovascular and muscular capacity - Exercise - Heart - Mitochondrion - Muscle - Oxygen uptake and deficit - V02max.

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RESEARCH THEMES

The laboratory's work is set against a public health context, with the objective of optimizing motor performance. Our group analyzes the bioenergetic responses to muscle exercise (from physiology to molecular biology) in humans and animals (with murine and equine models). Our expertise in the field of effort training and re-training enables improvements in motor performance in both patients and experienced athletes. In fact, we develop physical training methods, which are specifically adapted to an individual's physiological profile, in order to reconcile performance and health.

Unit 902 performs research in physiology and integrative biology. One particular novel feature relates to the Unit's integrative approach on four different levels:

- In terms of experimental models, we study the mouse and the horse, as well as humans.
- In terms of methodological approaches, we study the biological reactions to physical exercise on the physiological, cellular and molecular (genetic) levels.
- Our approach is based on human exercise performed in the laboratory but also in the field, so as not to interfere with spontaneous regulation of the speed of movement (notably during competitive sport).
- Our goal is to contribute to health by prevention thanks to the education for health by exercise with the e-learning and telemedicine and physiological measurement.

In summary, our laboratory is at the cutting edge of efforts to develop new methods for analyzing bioenergetic responses to exercise (from physiology through to molecular biology) in healthy or diseased humans and animals. This involves a wide range of techniques, from the validation of DNA chips to the use of telemedicine.