Headline

From molecular biology to integrated systems

Research in molecular biology is forging ahead. After having successfully described the building blocks of life, it is now addressing how life itself works. With numerous applications on the horizon...

>>> François AMALRIC, professor at UPS, Director of the IPBS; Marc HAENLIN, CNRS senior scientist, Director of the CBD

Biology has made great progress over the last fifty years, going from observation to analysis and from description to explanation. Following the discovery of the fundamental principles of living organisms, unearthed from structure-function studies of fundamental macromolecules like DNA, RNA, proteins, lipids and glycoconjuguates, research in biology has undergone huge change in recent times thanks to new approaches to research and important technological advances. Large-scale studies have been made, with the most important being the sequencing of numerous genomes, including the human genome.

It is now possible to study individual molecules and how they are assembled as well as cells and tissues and individuals and groups of individuals in an integrated manner. As a result, it has become obvious that the complexity seen in animals is not a result of the number of genes they contain (which is only slightly larger than those in drosophila) but comes instead from a combination of factors whose description requires diverse methodology, in vitro, in vivo, in situ and new technological protocols, going from experimentation to theoretical modelling. This is also why single disciplines have given way to more multidisciplinary research teams and collaborations in recent times.

Macromolecules

At Paul Sabatier University, six joint laboratories CNRS-UPS (1) have been set up, making this collaboration -- which integrates research, teaching and knowledge transfer -- one of the most successful outside Paris. The team focuses on three major areas: individual molecules and multimolecular complexes; cells and complex bodies; and the individual and groups of individuals (populations). Based on competitive fundamental research, the domains of biotechnology and health have been developed, together with as general science and information techniques.

The study of life-supporting molecules -- macromolecules -- has been made possible by exceptional developments in molecular biology that combine genetics and biochemistry. At Paul Sabatier, several internationally recognised research groups are involved in structure-function studies of such molecules. For example, an important collaboration (LBME, IPBS and LMGM) is working on RNAs. The researchers routinely use highly sophisticated NMR, crystallography and proteomic platforms, which they also develop and maintain to the highest standards. Proteomics, a field that has developed quickly over the last five years, is crucial for research in biology and allows researchers to access the composition of multimolecular complexes. In addition, a strong imaging platform (CBD, LBME, IPBS) allows further studies on the dynamics of these molecules. These platforms are open to the entire university community and also support numerous collaborations in industry. They have strong connections with physics and chemistry, notably in the field of membrane biophysics, membrane proteins and nucleic-acid/protein complexes. Such a regrouping of skills allows new concepts and novel biological research tools to be developed.

Cells

Most of the research teams at Paul Sabatier are focusing on cells, using bacteria and nucleated cell models. This community is interested in how bacteria function and studies genome stability and replication, biochemistry of membranes and walls and the pathogenicity

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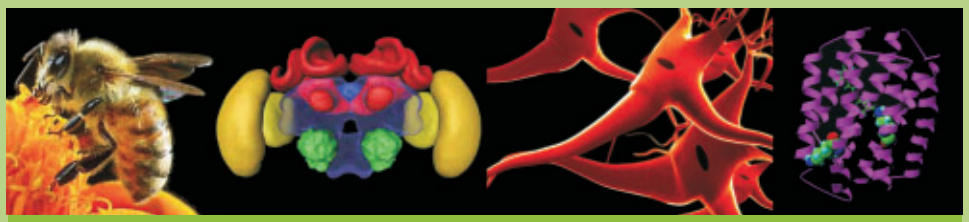
Technological Platforms

In a sustained collective effort, the IFR 109 laboratories and IPBS have established and share powerful technological platforms, some of which have received the national IbiSA label. They are open to research and development partners in both the private and public domains. They include proteomic, bio-crystallography, biological NMR, imaging, animal experimentation and transgenesis, allowing the study of individual molecules up to the whole animal. A description of these platforms can be seen on the following websites
http://www.ipbs.fr/ and http://www.iefg.biotoul.fr

Headline



>>> FROM MOLECULES TO INDIVIDUALS AND VICE VERSA from left to right: rhodopsine molecule, neurons, insect brain, honey bee.

of mycobacteria that cause diseases like tuberculosis (LMGM and IPBS). These biochemists and microbiologists also belong to a wider community that includes research groups at INSA and INRA who study eukaryotic cells as models for complex systems. Molecular and cellular biology methodologies coupled with concepts and tools from biophysics, such as high-resolution imaging (LBME, IPBS, CBD), are employed in this field too. The researchers analyse fundamental process functioning in cells, differentiation processes and the malfunctioning of pathological cells -- more particularly that of cancerous cells (LBME, IPBS, CBD).

Individuals and populations

Understanding how the molecular and cellular mechanisms that dominate development, reproduction and, more broadly, physiological and higher cognitive functions in animals, requires experimental systems on the scale of the individual and populations. Many research units use a variety of animal models, which allow genetic (drosophila, zebrafish and mouse), embryological (xenopus and chicken) and behavioural and cognitive methodologies (drosophila, honey bee and mouse). Sequencing the genome of the majority of these models has already been realised or is underway.
One of the most striking findings to come from modern biology concerns not only the extraordinary evolutionary conservation of proteins coded by genomes but also the conservation of the biological processes in which they participate. Indeed, a variety of model systems, in both invertebrates and vertebrates, have considerably increased our understanding of how living organisms function. Mechanisms studied concern reproduction, embryonic development, organogenesis (neurogenesis, myogenesis, haematopoiesis and angiogenesis), oncogenesis and metabolism (CBD, IPBS, MPM). Research on cognition focuses on cue-based, spatial and contextual learning and memory, as well as on collective behaviour in animal societies supporting distributed cognition phenomena. The establishment of a technological platform for imagining provides an ideal environment for studying molecular and cellular mechanisms at the single-molecule level right up to the scale of the entire organism.

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(1): Microbiology and Molecular Genetics Laboratory (LMGM), Eucaryote Molecular Biology Laboratory (LBME), Institute of Pharmacology and Structural Biology (IPBS), Centre for Developmental Biology (CBD), Animal Cognition Research Centre (CRCA), Metabolism, Plasticity and Mitochondria (MPM). Four laboratories, LMGM, LBME, CBD and MPM are part of the Federative Institute of Functional Investigation of Genomes (IFR 109).

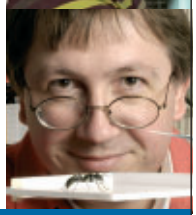
A New Research Federation

These six laboratories belong to the ***Research Federation*** located on the Paul Sabatier University campus. This Federation will eventually include approximately 150 CNRS and Inserm researchers, 90 university researchers, 150 technicians, 60 post-docs and 140 graduate students. Currently, the Federation publishes more than 200 papers a year in international journals, including in high-impact non-specialized journals (Nature, PNAS and Science). It will also help to improve knowledge transfer in the domains of biotechnologies and health (cancer, neurosciences and infectious diseases).

Headline

The systems biology approach to understanding the dynamics of interaction networks in genome and insect societies

How do ants organise their work in a colony? How do particular genes influence genome dynamics as a whole? Systems biology has now started to answer these and other questions.



>>> Olivier GADAL, CNRS scientist, Institute for Exploratory Functional Genomics (joint laboratory UPS/CNRS)
Guy THERAULAZ, CNRS senior scientist, Research Centre on Animal Cognition, (joint laboratory UPS/CNRS).

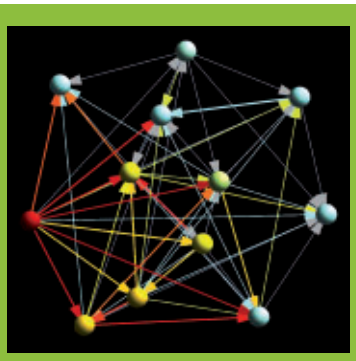
Systems biology is a whole new way of studying and understanding how living systems work. The main goal of this burgeoning field is to understand how properties observed at a given level of biological organisation (genome, cell, brain and societies) emerge from the complex networks of interactions that exist among its components (genes, proteins, neurons, individuals). Interactions among these elements are highly non-linear and give rise to self-organised properties at the collective level.

Gene movements

To understand these phenomena, systems biology combines experimental and theoretical approaches in which mathematical modelling and computer simulations play a key role. Understanding the expression of genetic information in the eukaryotic genome requires a precise description of the laws that govern the movement and the spatial organisation of genes in the nucleus. In fact, eukaryotic genomes are not randomly distributed in the nuclear volume, and the way genetic units are positioned relative to specific nuclear sub-domains affect how accessible they are. The spatial organisation of chromatin structures must also be described by statistical quantities, such as the probability distribution of positions within a population, or average chromatin compaction levels, because of the stochastic nature of gene motion. Similarly, gene motion must be described by parameters such as diffusion coefficients and confinement radii. Such descriptions are crucial for accessing the laws underlying chromatin motion - an approach that allows us to understand how gene movement allows complex genetic programs.

Swarm intelligence

Understanding collective behaviour in social insects -- such as how the division of labour is regulated, how nest-building activities are coordinated, or explaining the processes responsible for collective decisions -- requires mathematical models that can describe interactions among individuals and how these interactions give rise to the properties observed at the collective level. Such models are built on statistical laws describing individual behaviour. Numerical simulations are then used to precisely evaluate the quantitative and qualitative impact of each model's parameters on the resulting spatial and temporal collective dynamics. Simulations are also used to make testable predictions. Following step-by-step methodology provided by the theory of complex systems, we can now understand a large number of collective behaviours at different levels of organisation. In this integrated approach, all the processes implemented in the models represent real biological phenomena and the models themselves become more realistic.



>>> The network of hierarchical wasp interactions in a Polistes dominulus colony with 13 individuals. In these colonies, self-organisation processes reinforce successful individuals in such a way that the link weight distribution of the interaction network follows a power law.

Book: CAMAZINE, S., DENEUBOURG, J.L., FRANKS, N., SNEYD, J., THERAULAZ, G. & BONABEAU, E. 2001. *Self-Organization in Biological Systems*. Princeton University Press.

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Cancer: therapeutic targets for tomorrow

Transcription regulation and protein synthesis are modified in tumour cells. A better understanding of the mechanisms involved in deregulation and abnormal protein production compared to normal cells is crucial for developing new therapies.

>>> Jean-Philippe GIRARD, Senior scientist Inserm ,(IPBS, joint laboratory UPS/CNRS) and Kerstin BYSTRICKY, assistant professor at UPS, (LBME. Joint laboratory UPS/CNRS).

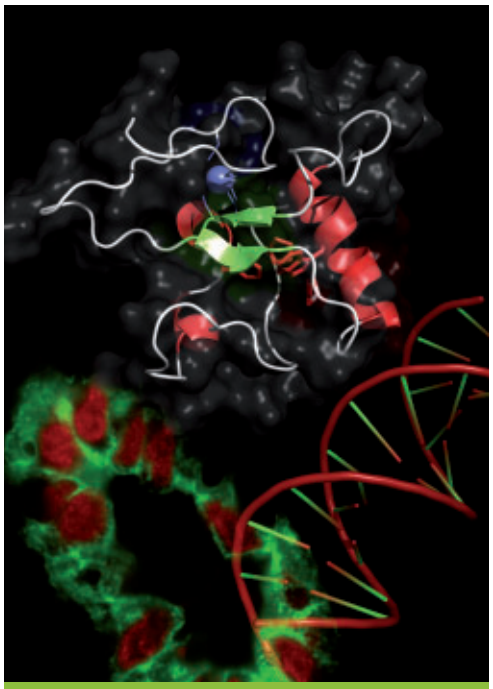
The main objective of the Biology Federation research teams at Paul Sabatier University is to better understand the fundamental mechanisms of life with a view to applying the knowledge gained to develop new anti-cancer therapies. The research combines both new technologies and models that go from the scale of molecules (DNA, RNA, proteins) to cells (yeast and vertebrate) and all the way to entire organisms (mice, flies, fish). Such a multidimensional approach is in line with the strategic objectives of the biggest cancer research centres in Europe and the US.

Functional genomics and proteomics

With the entire sequence of the human genome, and many other organisms' genomes, now complete, the challenge is to understand how genomes are decoded, how gene expression is regulated and how their products – proteins -- are integrated into cellular networks and signalling. An important area of research at Paul Sabatier University is to study genetic and epigenetic control of gene expression in normal and tumour cells, particularly in breast cancers and leukaemia. Current research activities aim at determining the role of cellular architecture, nuclear dynamics and chromatin organisation (DNA and structural proteins) in the regulation of gene expression as well as the analysis of DNA replication, recombination and repair mechanisms. Several teams specialise in analysing ribonucleic particles and RNA-mediated post-transcriptional regulation. The study of large multiprotein complexes involved in these processes requires approaches that involve "proteomics", which allows the state of all the proteins in a tissue or cell under specific conditions to be determined. This allows normal and tumour cells to be compared and changes in the precise composition of functional multi-protein complexes and their posttranslational modifications can be determined.

Genetics and imaging techniques

Anti-cancer strategies are based on the functional characterisation of genes and proteins in a wide variety of original animal models being developed by the Biology Federation. Potential new pharmacological targets can be tested and confirmed



>>> 3D structure of the THAP domain.

in vivo using site-directed mutagenesis (drosophila, yeast) or gene invalidation techniques (mice). Innovative approaches also include characterising the interactions between cells and their micro-environment.
Visualising many different biological phenomena is possible thanks to the RIO Imaging Platform at Toulouse. Highly sophisticated microscopes (confocal and multi-photon as well as electron microscopes) allow in situ and in vivo studies ranging from single molecules to cells and animals.
The goal is to transfer discoveries made in basic research to the patient, so collaborating with clinicians and industrial partners is a priority. The Biology Federation has plans to establish links with the Canceropole at Langlade (Toulouse Cancer Campus) and with members of the Canceropole Grand-Sud-Ouest.

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Head line

Molecular machines control cellular growth

Many human diseases are caused by defects in the molecular machines responsible for expressing the genome and for maintaining its integrity.

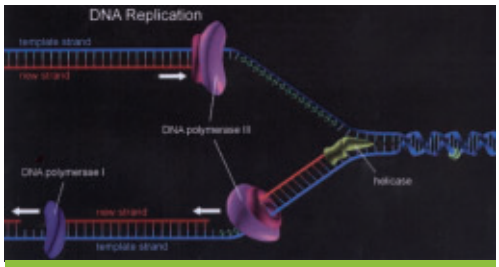
>>> Yves HENRY, CNRS senior scientist, head of the Ribosomes and Telomeres team at the Eukaryote Molecular Biology Laboratory (LBME, joint laboratory UPS/CNRS) and Patrice POLARD, CNRS senior scientist, at the Microbiology and Molecular Genetics Laboratory (LMGM, joint laboratory UPS/CNRS).

In order to grow and divide in a controlled fashion, the cell – be it of bacterial or human origin -- must express and duplicate its genome in an appropriate way. This depends on detecting any damage the cell sustains and repairing it. Correct expression, duplication and repair of the genome relies on numerous chemical reactions that rely on specific biological catalysts. Several of these catalysts are made from an assembly of macromolecules, mainly proteins and RNA. When these molecular machines become less reliable or when their production becomes defective or uncontrolled, diseases, including cancer, can develop.

Genome expression

The Research Federation teams at Paul Sabatier University study the composition, structure, mode of assembly and function of these molecular machines under normal and pathological conditions. These studies employ several model systems (bacterial cells, yeast, *drosophila,* mice and human cells in culture) and experimental methods combining genetics, biochemistry and structure determination. Work is carried out at the proteomic, NMR and cell imaging labs at Paul Sabatier.

The expression of the genome, which is made of DNA, refers to the production of copies of certain portions of this genome in the form of RNA and the further processing and fate of these RNA copies. These RNA replicas are produced in a process known as “transcription” and require several molecular machines that interact with genomic DNA and which can be grouped into three main classes. Machines in the first class (the “activators”) trigger the transcription process, while machines in the second class (the “RNA polymerases) are responsible for actually synthesising the RNA replica. Finally, machines in the third class (“mediator complexes”) connect the activators with the RNA polymerases. The research teams work on all three types of machines. The RNA replicas can be used as made, or can be “scanned” by huge molecular machines called ribosomes to produce proteins. The researchers study the assembly of these ribosomes and also work on Diamond-Blackfan anaemia, which is caused by defects in ribosome assembly and function.



>>> molecular machines in the process of duplicating the DNA of a cell.

Faithful duplication

Correct genome expression depends on strictly controlling genome integrity and repairing any damage the genome suffers when necessary. It also depends upon faithful duplication of the genome prior to cell division. Molecular machines (such as the “DNA recombination complexes”, “DNA polymerases” and “telomerase complexes”) repair DNA damage or participate in genome duplication. Defects in genome duplication and repair can have highly deleterious consequences, in particular chromosomal instability that can induce cell death (“apoptosis”), numerous cancers and certain syndromes such as “dyskeratosis congenita”. These defects can also, in some cases, be advantageous in that they provide genetic changes that confer a selective advantage. For example, some processes utilising specific molecular machines seem to produce genetic variability, such as DNA transposition and natural transformation. We are working on the modes of synthesis and function of all these machines and on the molecular defects responsible for certain cancers or for dyskeratosis congenita. The production and destruction of these molecular machines are themselves catalysed by other machines, termed molecular chaperones and proteasomes, whose structure and function are being studied by some of our research groups. The ensemble of our research aims to understand how molecular machines function in a coordinated fashion relative to each another.

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Neurogenesis and pathologies of the nervous system

Understanding how neurons are born and differentiate will help in developing strategies to cure neurodegenerative disorders, such as Alzheimer's.

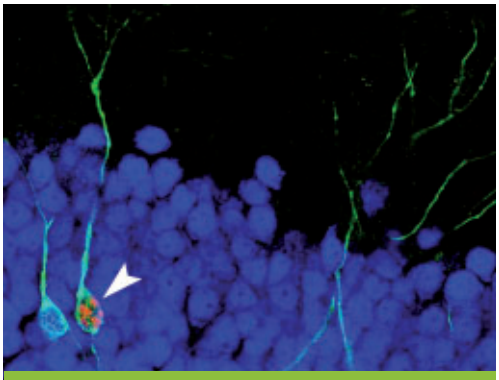
>>> (from left to right) : Claire RAMPON, CNRS scientist at CRCA, (joint laboratory UPS/CNRS), Marie-Lise MADDELEIN, CNRS scientist at IPBS (joint laboratory UPS/CNRS), Philippe COCHARD, CNRS Senior scientist at CBD (joint laboratory UPS/CNRS) and Pascale BELENGUER, Professor UPS at MPM (joint laboratory UPS/CNRS).

The brain -- the most complex organ in the human body -- is made up of 100 billion neurons, as many as the number of stars in our galaxy! And it contains ten times more glia, cells that are crucial for proper neuronal function. How do these countless forms of neurons and glial cells develop? Using model systems adapted to each type of species (fly, fish, frog, chick, rodent), researchers in our laboratories are now beginning to answer this basic question -- an essential prerequisite for defining therapeutic strategies for neurodegenerative diseases.

A problem of choice !

Development is the main topic of research at the CBD. One area concerns the crucial role that calcium plays in the initial phases of brain construction -- crucial because blocking calcium movements very early on in the embryo produces an animal virtually devoid of a nervous system. Once neural stem cells are generated, they must actively proliferate: in humans, more than 250,000 neurons are generated every minute.
The mechanisms that control such an active proliferation are under study and we have shown that, contrary to the established dogma, a cell that is forced to divide can nevertheless become a neuron.

Another research domain deals with the dialogue between neighbouring stem cells, to understand how specific signals dictate the choice a neural stem cell makes -- either to keep proliferating and maintain itself or to stop dividing and undergo terminal neuronal differentiation. Through a series of decisions, neural stem cells will then give rise, at the right time and place, to specific types of neuron and glial cell.
Genetic analysis shows us how the specific information encoded in each group of neural precursors is interpreted, leading the cell towards a fate unique among the large variety of neuronal phenotypes possible. Another major choice for a stem cell is to either become a neuron or a glial cell.
We made the surprising discovery that a diffusible signal responsible for the genesis of particular sets of neurons is also required for glial cell formation.
We have provided evidence for a gene that could explain how this signal controls the formation of these two totally different cell types.



>>> Birth of new neurons in the adult brain of a mouse model in Alzheimer's disease. Specific fluorescent markers and confocal microscopy allow us to visualise a newborn neuron (arrowhead, orange-stained cell nucleus) together with immature neurons, labelled in green.

New neurons in the adult brain

The belief that neurons are never generated in the adult brain was shattered a few years ago: new neurons are continuously generated in some brain regions and can take part in mnesic function. This major finding means that the dramatic neuronal losses associated with neurodegenerative diseases could be compensated for. Teams at CRCA, IPBS and MPM are working in this new field and have shown that new neurons are indeed produced in the brain of a mouse model in Alzheimer's disease, but that these neurons are unable to survive in the long term.
It is therefore critical to understand what prevents them from further developing into mature neurons.
Alzheimer's is caused in part by aggregation of a peptide, A, amyloid, into senile plaques.
We characterise this aggregation at the molecular level by studying plaque formation *in vivo* with fluorescence microscopy in model organisms (yeast) and in neurons.
We have also discovered that a gene responsible for neurodegenerative retinopathy controls the dynamics of mitochondria -- a process involved in mitochondrion morphology and which regulates its function.
This has led us to explore the impact of mitochondrial dynamics on neurogenesis, and neuronal differentiation and function.

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Pathogenic Bacteria: The best way to fight them is a better understanding

The fight against pathogenic bacteria is far from over because these organisms are becoming more resistant to antibiotics. New vaccines and antibiotics are thus needed today more than ever.

>>> Mamadou DAFFE, CNRS Senior scientist, director of the Molecular Mechanisms Mycobacterial Infections Department at IPBS and Claude GUTIERREZ, professor at Paul Sabatier University and Director of LMGM.

Eighty years after the discovery of penicillin, infectious diseases remain a major global health problem. For instance, tuberculosis causes two millions deaths a year worldwide and we are also facing a real re-emergence of multi-resistant strains. New antibiotics and vaccines are thus urgently needed. The best way to achieve this goal is to decipher the mechanisms by which pathogenic bacteria cause disease and resist treatment. Some of these are being studied at the IPBS and LMGM.

Tuberculosis and leprosy

The teams in the Molecular Mechanisms of Mycobacterial Infections department at IPBS are studying *Mycobacterium tuberculosis* and *M. leprae,* the bacteria that cause tuberculosis and leprosy. The genomes of these bacteria have recently been sequenced, with the aim of defining virulent factors and how they work and identifying novel enzymes involved in the biosynthesis of components essential for the survival of the bacilli to use them as targets for the development of new drugs and finding new vaccines -- either by modifying the currently used BCG vaccine, or by using non-peptidic antigens. This strategy combines a genetic approach together with the unique composition and immunological properties of the mycobacterial envelope.

The seven teams that make up the department possess complementary skills that include chemistry and biochemistry, structural biophysics, molecular and cellular biology and immunology. Over the last three years, the department has discovered four novel therapeutic targets and new mycobacterial non-peptidic antigens that interact with receptors of T-lymphocytes. The results include five patents, collaboration with pharmaceutical firms and numerous scientific publications.

Resistance to antibiotics

At the LMGM, 12 research teams study the fundamental processes that govern the organisation, dynamics and expression of microbial genomes, including those of several pathogenic bacteria.

Many bacteria can acquire new genetic determinants of both pathogenicity and antibiotic resistance by "horizontal exchange" of DNA via transformation, transduction or conjugation. The mechanisms involved in the mobility and capture of such elements are studied in *Escherichia coli or Vibrio cholerae.* The mechanism of bacterial transformation in *Streptococcus pneumoniae* is also under study. Transformation contributes to the genomic plasticity of *S. pneumoniae* and thereby allows this bacterium to circumvent host defence mechanisms using high antigenic variability or by rapidly evolving genes conferring antibiotic resistance. A particularly important finding from these studies is that the presence of sub-lethal doses of antibiotics induces transformations and helps bacteria evolve drug resistance. Among the current research topics at LMGM is the epidemiologic analysis of emergent pathogenic *E. coli* strains and discovering how they adapt to environmental stress. This study includes looking at the stress encountered by the phytopathogen *Xanthomonas campestris* upon infecting its host cells. A very promising and patented work involves T4-type bacteriophages and their use in antibacterial therapy or as an alternative to antibiotherapy.

To summarise, the IPBS and LMGM teams perform excellent and internationally recognised research in molecular and cell microbiology and strongly contribute to the efforts of Paul Sabatier University, and more largely the Toulouse research conglomeration, a place of reference for research in microbiology.

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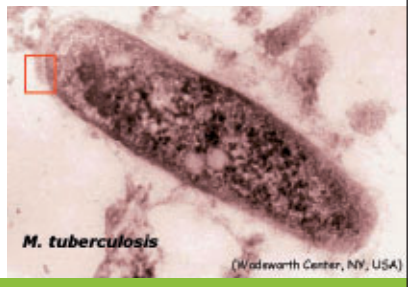


>>> The mycobacterial envelope is very complex and unique. Its biogenesis is specially targeted by anti-tuberculosis drugs.

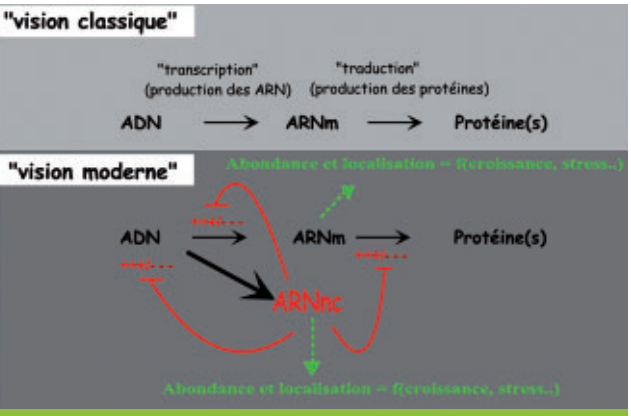
The hidden life of RNA

>>> Jérôme CAVAILLÉ, CNRS senior scientist at the Molecular Eukaryote laboratory (LBME, joint laboratory UPS/CNRS).

Until recently, RNA was thought to be a simple intermediary in the production of proteins from DNA. It is now known to be a crucial regulator in DNA expression itself.

DNA contains genetic information that is passed on from generation to generation (it is a major component of chromosomes and thus of genes). Proteins, encoded by genes, are involved in a large number of essential cellular functions including catalysis of chemical reactions (enzymes), cell shape (cytoskeleton), interactions and communications between cells (antibodies and hormones) and transport of other molecules (such as haemoglobin). For a long time, RNA molecules, which are copies of certain segments of DNA, were seen simply as intermediaries, carrying genetic information from DNA to proteins. Hence, the majority of them are called messenger RNAs or mRNAs. This protein-centric point of view, routinely described in student textbooks, is now being overturned.

Remarkably, only a small fraction of our DNA content (< 2%) is dedicated to protein synthesis. For many years the remaining, extra DNA (also referred to as "junk DNA") was thought to be unimportant. This situation is dramatically changing and the scientific community now accepts that junk DNA might have unexplored functions. Indeed, a huge number of studies have demonstrated that a large fraction of this noncoding DNA generates RNA molecules that play key roles in cell metabolism by regulating DNA replication, protein synthesis or maturation of other RNAs. The repertoire of these noncoding RNAs (ncRNAs) might thus be as complex as that of mRNAs themselves and studies of these molecules are now revolutionising our vision of genome evolution, genome regulation and gene functions. This can be illustrated by the recent identification of a novel class of small non-coding RNAs involved in gene silencing (the so-called microRNA, siRNAs and piRNAs).
The discovery of the RNA-mediated gene silencing phenomena was recently acknowledged by the Nobel Prize in Medicine 2006, awarded to Andrew Fire and Craig Mello.



>>> Although RNAs have long been seen as just intermediaries in gene expression (top), they are now believed to act as key players in the control of gene expression (bottom).

It is not enough to simply synthesise RNA in the cell, its abundance, availability and subcellular location must be controlled as well. To this end, numerous molecular mechanisms are able to fine-tune the production and decay rate of RNA according to cell growth and it is now accepted that mRNA/ncRNA degradation plays an important role in the regulation of cell proliferation and differentiation, and apoptosis (programmed cell death).

Through a vast number of experiments and models in eukaryotes and prokaryotes (bacteria and Archaea), research teams at LBME, LMGM, CBD and IPBS are discovering the molecular and cellular mechanisms that underlie RNA function. For example, the LBME groups are studying how regulatory small RNAs are synthesised and how these molecules work. RNAs are never "naked" in the cell but are associated with specific proteins and form stable RiboNucleoProtein (RNP) complexes. Assembly and intracellular trafficking of these RNPs are also under intense study. At LMGM, researchers are developing molecular and genetic methodologies to understand how RNA is degraded in bacteria and ongoing research is underway in Archaea, in which RNA degradation mechanisms need to be explored. By combining transgenic mice and molecular experiments, a team in the CBD is focusing its attention on proteins called AUBPs that specifically bind mRNAs in their untranslated regions and so control the stability of these molecules. Regulatory small RNAs (for example, siRNAs) can be used by researchers as a tool too to inhibit gene expression. For instance, a team at the IPBS is studying electrically-mediated siRNA delivery in mice tissues and tumours.

Although this is clearly basic science, these ongoing research programmes will shed more light on the pathology of several human disorders in which RNA biosynthesis and/or function is deregulated. This occurs in many cancers and several rare diseases, including Prader-Willi syndrome, Diamond-Blackfan syndrome or congenital dyskeratosis.

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