Headlines

Laser in research

Cardiovascular diseases

with the participation of

Délégation Midi-Pyrénées du CNRS
Happy birthday!

June 2004...June 2010: The magazine has successfully completed its sixth year, and is now sailing at “cruising speed” over the ocean of knowledge. We hope it has also reached its intended objective, which was to bring the quality and diversity of research at Paul Sabatier University to the attention of a non-specialist public audience. The layout of our magazine, which is based around thematic headlines that update the reader in key areas of science, technology and social science, seems to be going down extremely well.

The members of our editorial committee are proud of the success of this voluntary work devoted to diffusing scientific knowledge.

2010 is the 50th anniversary of the discovery of laser. So, it is particularly timely to present the first article of this issue as an overview of the very diverse and flourishing applications of laser technologies in research, based on the work of our outstanding famous young scientists. The second headline concerns the current research on cardiovascular diseases, which remain one of the most frequent causes of death in developed countries. There is still much to be learned about the origin of cardiovascular diseases and how to prevent them. Our world-renowned Toulouse University teams are actively involved in this research area.

I wish you a very pleasant moment with our magazine

Gilles FOURTANIER
President of Paul Sabatier University

Currently used abbreviations

UPS: Paul Sabatier University (Toulouse, France)
CNRS: French National Center for Scientific Research
INSERM: French National Institute for Health and Medical Research
INSA: National Institute of Applied Science
INRA: National Institute for Agricultural Research
INPT: National Polytechnic Institute of Toulouse
ANR: National Research Agency
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On-line Scientific Magazine UPS:

http://www.ups-tlse.fr/27503789/1/fiche___pagellbre/&RH=rubrech03
The laser is at the heart of CD-readers and printers but also, since 1974, in the barcode scanner you see being used at the supermarket. Laser shows produce visual displays by using beam effects and the laser's ability to be focused to a pinpoint makes it ideal as a precision scalpel in medicine, for example to reshape the cornea or to kill tumors without any risk of damaging nearby healthy tissue. It also serves as an ultra-precise optical tweezer to transport nano-objects and biological molecules.

In 50 years, the laser has become part of our daily lives. Its power has fascinated us since the beginning, like in the movie Goldfinger, where the laser is used as a frightening arm against 007. Its power allows to cut, drill, mark and clean stones, steels, papers and plastics. Today these applications represent 35% of the laser market. Inside fiber optics, analogous to a complicated version of Morse code, the light can carry with it vast amounts of data over long distances. Laser beams are also used to align roads and tunnels and implement 3D reconstruction. The LIDAR technique allows to analyze pollutants in the atmosphere.

The laser's exceptional properties are also useful in fundamental research. At Paul Sabatier, the laser is used to cool atoms to temperatures just barely above absolute zero (a technique known as Bose-Einstein condensation), to factorize numbers, follow the dynamics of chemical reactions in real time, study and manipulate nano-objects, image biological samples in 3D, study their composition, create an artificial star in order to optimize telescope resolution, study turbulence, detect pollutants, and analyze the composition of paintings. This issue of our magazine will present some of these applications.

Since 1960, nine Nobel prices have been awarded to laser scientists (for holography, non-linear optics, spectroscopy, metrology, the observation of chemical reactions and cold atoms).

Future projects, like the simulation of thermonuclear reactions as well as interstellar chemical reactions, biology imaging, probing matter with attosecond pulses and particle beam generation for medical applications, are further opening up a fruitful route for this 50-year old discovery.

Contact: beatrice.chatel@irsamc.ups-tlse.fr

LASERS

The lasers, 50 years on and still full of promise

The laser, which is short for Light Amplification by Stimulated Emission of Radiation was first demonstrated by Theodor Mainman on May 16th 1960. This pure lab product was initially solely devoted to research. But thanks to its unique properties (such as directivity, coherence, power and monochromaticity), it rapidly became useful for a host of other applications.

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LCAR: Laboratoire Collisions Agrégats et Réactivité/ Collisions, Aggregates and Reactivity Laboratory

IMFT: Institut de Mécanique des Fluides de Toulouse/ Toulouse Institute of Fluid Mechanics

LMTG: Laboratoire Mécanismes de Transfert en Géologie/ Laboratory for Mechanisms and Transfer in Geology

LAAS: Laboratoire d’Analyse et d’Architecture des Systèmes/ Laboratory for Analysis and Architecture of Systems
The laser revolution in fluid mechanics

The laser has allowed fluid mechanics researchers to measure movement without interfering with flow. A revolution that continues today.

Lasers have had a considerable impact on the field of fluid mechanics. Indeed, the laser is now the elementary building block of most modern techniques for measuring gas or liquid flow in which we need to determine, if possible, local and instantaneous characteristic parameters such as velocity, concentration of a species, and the size of droplets or particles.

Laser Anemometry

Several techniques are widely used for measuring the velocity of fluid flow at a single point, such as the Pitot tube or hot wire probes. The main drawbacks of these techniques are their invasiveness and the need for frequent calibrations of the thermal anemometers. In 1964, Yeh & Cummins proposed a Laser Doppler Anemometer (LDA). Here, two coherent collimated laser beams intersect to create a measurement volume whose dimensions are around several tens of microns in diameter and a millimeter in length. The light scattered by the two beams is collected by a photodetector and its frequency is proportional to the velocity of tracers through the measurement volume. This technique, at a single point, is non-intrusive and requires no calibration. The use of a continuous laser source (He-Ne) and the different spectral lines of argon were used to measure multiple velocity components. In the 1980s, this technique was extended to measure the size of particles (Doppler phase) using multiple photodetectors. The diameter of solid or liquid particles, in this case, is proportional to the phase of Doppler signals collected by different photomultipliers.

Tracer particles

Measuring the concentration of species in a flowing fluid can be achieved by taking samples over periods longer than a millisecond. This measurement can also be made instantaneously by Laser-Induced Fluorescence (LIF). Molecules injected into the flow are excited at the wavelength of a laser source. The light re-emitted by fluorescence is then captured by a photocathode or a sensor matrix. The amplitude of this signal is, in a certain range, proportional to the concentration of the molecular marker.

In the 1990s, another velocimetry technique appeared and was a great success: Particle Image Velocimetry (PIV). Particle “tracers” are illuminated by a laser sheet. Two short pulses then “freeze” the position of the tracers in the flow, which is recorded by a camera. We measure the local displacement of groups of markers that move as the fluid moves. This provides an instant map of the velocity field in any slice of the flow. In the standard configuration, two components of velocity are simultaneously mapped (2D-2C). In two geometry-viewing cameras, three velocity component vector fields (2D-3C) can be simultaneously measured. If you work with at least four cameras, an entire volume is illuminated and you enter the field of Tomographic PIV, which gives access to three velocity components in a volume of small size (currently, the size of a cellular phone for gas flows and the size of a small book for liquid flows). Importantly, recent improvements in pulsed lasers delivering several tens of millijoules at kHz frequencies has increased data rate acquisition for these three techniques and has allowed scientists to explore many transient phenomena.

The use of lasers in fluid mechanics has made non-invasive measurements possible. At the beginning, it was used only for small volume samples but the technique is now is becoming three-dimensional and time-resolved.

Contact: cid@imft.fr
A laser for ultra-precise measurements

A group in Toulouse specialized in precision optical measurements has built a novel laser-based device capable of measuring light velocity with such accuracy that it can detect the deformations generated by magnetic and electric fields in matter.

Laser levels, laser rangefinders. The laser is found everywhere, even on construction sites. The laser level takes advantage of the good spatial definition of a laser beam, which allows for precise pointing several tens of meters away. The rangefinder principle is more interesting, since it consists of measuring the dephasing of the laser wave diffracted on the target after a round trip. Standard devices have an accuracy of around one millimeter at distances of 100 m, hence a relative precision of $10^{-5}$.

Atomic clocks

Present-day metrology experiments do not use this principle anymore because measuring frequencies yields much higher accuracies. Frequency is indeed the world’s best measured quantity, in particular in the optical range thanks to the extremely well-defined wavelength of lasers. Converting any quantity into a frequency and measuring it accurately can be achieved with a high finesse optical resonator, in which light can be confined provided it has the proper frequency. Recent progress in optics and electronics allows to control and measure optical frequencies with relative accuracies below $10^{-18}$. These ultra-precise measurements are performed, for example, in atomic clocks, in optomechanical measurements aimed at studying the coupling between radiation and a macroscopic mechanical element, and in gravitational wave interferometers.

Directional anisotropy

Our group specializes in this type of measurement. We have thus developed an experiment aimed at measuring very weak optical anisotropies induced in gases by magnetic and electric fields using frequency metrology. For example, electrodynamics predicts that if crossed transverse electric and magnetic fields are applied, light does not propagate at the same speed in both directions. Although this directional anisotropy was predicted more than 30 years ago, it has never been observed for lack of sensitive enough apparatus. A few weeks ago, our group achieved this for the first time in nitrogen. We detected a refractive index difference between the two propagation directions, hence a light velocity difference, which is on the order of a few picometers per second, compared with the 300 000 m/s velocity of light in vacuum! Other magneto-electro-optical effects are within experimental reach too and measuring these will enrich our knowledge of how light interacts with simple atoms and molecules. Beyond the physico-chemical interest of these studies, our apparatus, once optimized, will be the tool of choice for testing fundamental laws and symmetries, which are the foundation stones of contemporary physics.

Contact: cecile.robilliard@irsamc.ups-tlse.fr
Chemistry at the femtosecond scale

By using state-of-the-art femtosecond lasers combined with the latest developments in the imaging of charged particles, it is now possible to follow a chemical reaction in real time at the molecular level.

A chemical bond is electrons shared by several atoms and defines a molecule. The energy shared is called the bonding energy. In a chemical reaction, this shared energy becomes redefined between potential and kinetic energies as the reagents approach each other. The bonding energy depends therefore on the relative position of the atoms. Determining this dependency and understanding what is at the heart of the chemical reaction is thus the main goal of physical chemistry that combines experiments and numerical simulations with quantum mechanics.

Understanding a chemical reaction means, among other things, identifying the set of forces that trigger the relative motion of atoms. The molecules are produced in the gas phase where they are free of interactions. Experiments therefore directly probe the relaxation that takes place within the molecule and these can be directly compared to ab initio calculations. In general, information is delivered by frequency-resolved experiments in which laser interactions occur over nanosecond scales. By comparing the absorption and fluorescence spectra, photoionization and photoelectron spectra as well as by measuring the appearance energy of dissociation, for instance, and branching ratios, the chemical reaction can be reconstructed with all the main parameters. But it is like being in a detective story with only clues and not actually a witnessing what is really going on.

Large speed

How can one become a witness then? The atoms inside the molecule can travel as fast as 2 km/s over a distance of a few Angströms and the typical time involved in this atomic movement is in the range of femtoseconds (a millionth of a billionth of a second). Up to now, no electronics alone could resolve such fast dynamics. Femtochemistry is a spectroscopy based on femtosecond laser pulses that allow researchers to follow a reaction triggered by laser excitation in real time.

A first laser pulse initiates the molecular dynamics by exciting its electrons. This laser pulse is called the pump pulse and its main aim is to set t=0 for the reaction. Due to this initial extra energy brought by the pump pulse, the molecule will relax via the movements of the electrons and the nuclei - known as electronic and vibrational relaxation. The molecules might dissociate too. A second laser pulse then interacts with the excited molecules at a variable delay relative to the pump pulse. This delay is the main variable of any femtochemistry experiment. The second pulse is called the probe pulse and its function is to photoionize the excited molecules. Next, the photoelectrons and the photoions are recorded as a function of the delay between the pump and the probe. It is not only the amounts and the masses of these two entities that carry information about molecular dynamics, but their energy distribution and angular distributions as well. These energy and moment balances are recorded by velocity map imaging.

Stroboscopy

Femtochemistry allows us to directly visualize a chemical reaction. It is a stroboscopy technique involving femtosecond laser pulses. What is the timescale involved in the different steps of the reaction, what are the conditions that enhance or inhibit some reactions? These are some fundamental questions that femtochemistry experiments can now answer.

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>> Valérie BLANCHET, CNRS scientist at the Laboratoire de Collisions, Agrégats, Réactivité (LCAR, UPS/CNRS).

Energy distribution of the photoelectron produced after a pump-probe delay in which the pump triggered the predissociation of CH₃I. Drastic changes appear when predissociation takes place, leading to CH₃+I* fragments.
Lasers decipher minerals

Analysis of materials by laser ablation is undergoing a major revolution. It is helping us to better understand the composition of tiny pieces of complex materials.

The technique was developed in the mid 80s and can determine the composition of minerals at the scale of a few tenths of millimeters. This analytical technique (called Laser Ablation Inductively Coupled Plasma Mass Spectrometry or LA-ICP-MS) involves using a laser to “shoot” the solid being analyzed. The aerosol produced is then introduced into a plasma source mass spectrometer to detect chemical elements. The value of in situ analyses by laser ablation is that it allows us to study complex heterogeneous materials, such as those encountered in nature.

Magmatic rocks and shells

At the Observatoire Midi-Pyrénées (part of Paul Sabatier University), LA-ICP-MS is used to analyze elements at concentrations of around parts per million. These measurements are made on minerals from the Earth’s mantle and magmatic rocks, on their melt or fluid inclusions, or on experimental charges produced at temperatures and pressures exceeding 1000°C and several gigapascals. They allow to determine the nature and origin of aqueous or siliceous fluids that affect the depths of the Earth but which do not exist on the surface of our planet. Experimental work on marine shells using LA-ICP-MS have also demonstrated the importance of animal diurnal cycles on environmental records that can be obtained through analysis of the animals’ shell.

The first LA-ICP-MS techniques were not without flaws however. They used ruby lasers emitting long duration pulses, exceeding the microsecond in the infrared. This meant that transparent materials, such as quartz or calcite, were impossible to analyze. Ablations generated by this kind of laser produced thermal effects that substantially degraded the accuracy and precision of analyses.

Transparent materials

Major advances were made in the 90s with the use of “Q-switched Nd: YAG” or “excimer” lasers and the use of shorter wavelengths, in the near ultraviolet. Transparent materials could be analyzed and thermal effects were significantly reduced. The lower wavelengths and the evolution of optical systems have also improved the spatial resolution of mineral analyses to the scale of tens of microns, thereby extending the scope of possible studies.

The 2000s have seen us crossing a new threshold with the implementation of femtosecond laser pulses 100,000 times faster than the nanosecond lasers used previously. This new field continues to evolve and allows a significant improvement in chemical analysis, not least by dramatically reducing the thermal phenomena. Matrix effects, by which the behavior of a material during its ablation greatly varies depending on its nature, are also virtually eliminated.

The Observatoire Midi-Pyrénées, in collaboration with the Laboratoire Collision Aggrégats Réactivité (LCAR, CNRS-UPS) and with the support of the company Amplitude Technologies, a French manufacturer of ultrafast lasers, is at the international forefront in developing this technique. This group experimentally studies the mechanisms of femtosecond laser-matter interactions and their analytical implications. Crater ablation and generated particles are being studied for the first time by transmission electron microscopy. This work should lead to improved quality and reliability of in situ analyses of solids. They will also help to develop new fields of applications for this technique, such as in situ measurements of stable metal isotopes.

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Contact: franck.poitrasson@lmtg.obs-mip.fr
Smaller and smarter – a new generation of laser diodes

Researchers at the LAAS Photonics Group are overcoming two challenges: inventing laser diodes that can be integrated onto a chip; and functionalizing them for new applications.

Semiconductor lasers, or laser diodes, are everywhere we look. At the heart of optical telecommunications networks, they continue to become more and more sophisticated as the Internet becomes increasingly complex. Semiconductor lasers are also central to computers and multimedia equipment, such as optical mice, in information storage and retrieval via hard disks, for transmitting data, and for communication between networks. These lasers are also widely used in many industrial processes, as surgical tools, to analyze biological samples and to monitor the environment.

Semiconductor lasers are becoming more elaborate thanks to advances in materials and nano-science, and the fundamental domains of optics and photonics is directly benefiting a diverse variety of other disciplines, such as biology and cosmology.

The Photonics Group at LAAS was a pioneer when it came to understanding different generations of laser diodes, in fields such as visible light emission, increasing laser power and obtaining surface emission. Current challenges include integrated laser diodes and optical functions to make optical “lab-on-a-chips”, as has already been done in microelectronics.

Micro-cavities

The Photonics Group exploits quantum phenomena and forbidden band-gap engineering to make lasers diodes that are radically different from existing ones. The LAAS-CNRS technological facility, which is part of the Basic Technological Research Labs (rtb.cnrs.fr), has fabricated gallium arsenide-based laser sources that emit at around 1 micron. The planar photonic crystals used in these devices allow for high quality factor coefficient micro-cavities. The team has also recently integrated single-mode planar laser diodes entirely defined by photonic crystals with a precise control of the wavelength emission to better than 0.3 nm. This new cavity architecture, compatible with planar integration, is a turning point for realizing integrated photonic circuits in on-chip laser systems.

Micro-tips

Apart from the challenge of making an integrated laser, researchers also need to broaden the field in which laser diodes are used today. These include all-optical circuits, “smart” systems that associate optics with software, opto-fluids (which combine optics with biology or chemistry), micro- or nano-systems with optical functionalities, electronics, and micro- and nano-mechanical systems (NEMS and MEMS). An important research area is the study of vertical-cavity surface-emitting lasers (VCSELs) that integrate optical filtering and photodetection, as well as micro-optics based on polymers for smart sources with weak divergence. Very recently, the team succeed in integrating self-aligned micro-tips on a VCSEL. This result opens the way to new applications in near-field spectroscopy or optical manipulation for biological analyses.

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New energy storage micro-systems

New work by a team at Cirimat, in collaboration with Drexel University in the US, could lead to the fabrication of high-density storage micro-systems – something that was difficult to achieve until now. Patrice Simon and Pierre Louis Taberna describe their research.

What is your subject of research?
We have been working on developing electrochemical systems for energy storage. There are three types of energy-storage device: batteries, capacitors and supercapacitors. Each has its own special characteristics and applications. A battery stores a lot of energy but gives it up only slowly, over several hours. In contrast, a capacitor gives up a small amount of energy very quickly (over a matter of milliseconds). Our team is interested in supercapacitors, which lie in between batteries and capacitors. Supercapacitors provide energy over time periods of seconds and have the added advantage of being able to stabilize the voltage in an electric circuit.

What are the other advantages of supercapacitors?
One of their major advantages is that they can function at high currents (several hundreds of amps) during both charge and discharge, and at temperatures as low as -30°C. In contrast, lithium-ion batteries are less efficient during recharge and discharge, and only work in a certain temperature range.

Moreover, a battery ages because it works using chemical reactions whereas a supercapacitor is more stable over time thanks to the fact that it is based on physical interactions (electrostatics).

What applications could supercapacitors be used in?
With the development of portable equipment and its associated electronics, we need to miniaturize the energy storage devices that power them. One particularly interesting application of supercapacitors is for energy recovery and for acceleration in hybrid vehicles. Supercapacitors can also recover the energy normally lost during braking. This energy can then be used to either recharge batteries or to accelerate the vehicle.

Could you describe your recent discoveries?
In 2006, our team developed carbon-based materials to make micro-supercapacitors. At the time, the materials were synthesized as powders but today we can make them in the form of thin films that are just several microns thick. They were made using bulk titanium carbide that was transformed into thin films of carbon using processes that are compatible with microfabrication techniques. The thin carbon film forms in situ and is porous with a large surface area. For example, one gram of powder has a surface area of over 1000 m². By varying the thickness, we observed that the storage density of films 1 micron thick was multiplied by a factor of three compared to classic supercapacitor electrodes made from carbon powders.

What are next stages in your research?
We have patented the materials we made and are now working with Magali Brunet and David Pech of LAAS to develop materials for use in microelectromechanical systems (MEMS). Collaboration with our colleagues at Drexel University in Philadelphia is being undertaken as part of a French-American Partner University Fund program, with our participation in the Erasmus Mundus Master “Materials for storage and converting energy”. This will also allow us to reinforce exchange between students and researchers.

Interview by par Christelle Labruyère et Isabelle Dixon
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A team at Paul Sabatier’s Brain and Cognition Research Center has shown that the activity of neurons in the brain’s visual cortex increases when we look sideways, to make objects in front of us more visible. Yves Trotter, head of the team, explains the research.

→ What is your area of research?
We are working on neuronal mechanisms of 3D vision and of spatial localization of objects. We are studying how the electrical activity of neurons in the visual cortex is modified by the position of visual stimuli in terms of retinal and gaze coordinates. Indeed, modulations of neuronal activity evoked by visually identical stimuli localized in different parts of space allow a better understanding on how spatial information is coded by the brain.

→ What are your most recent discoveries?
Our studies have focused on neuronal coding of the central region of the visual field. We wanted to extend these studies to the peripheral visual field to find out whether similar neuronal mechanisms of spatial localization take place. Surprisingly, we found that the neuronal activity responsible for coding objects in the periphery changed as a function of their positions according to the body’s axis. In fact, when we look sideways, objects that are located in front of the body are better detected because neurons responsible for the periphery have a higher sensitivity when their receptive fields (small perceptual windows of the neurons) are brought in front of the body by a corresponding angular deviation of the gaze.

→ What does this imply?
The region of space situated directly in front of the body is processed by the brain in a privileged way, which probably reflects the ecological importance of this spatial axis. For example, when we look straight ahead as we walk in the street, the part of the brain that analyzes the central region of the visual field naturally functions efficiently and reacts to any changes in the environment to prevent us bumping into obstacles. If, then, we hear something to our left or right, we may immediately look sideways so that our visual axis is no longer straight ahead but to the side. Objects located straight ahead are now processed by peripheral vision. Without even realizing, we automatically become more sensitive to whatever is found on the side... as this direction is now in front of the body!

→ What are you working on at the moment?
These results were obtained by electrophysiological recordings performed on the brains of non-human primates. We have now begun behavioral tests in humans and the first results appear to correlate. In fact, humans react more efficiently and rapidly to eccentric visual stimuli brought directly straight ahead by deviating the gaze compared to their eccentric positions according to the body’s axis.

→ What are the implications of these results?
These findings reveal a link, hitherto unknown, between visual sensitivity and the localization of objects in our surrounding environment. This discovery could help patients who rely solely on peripheral vision – as is the case in macular degeneration, a common disease in the elderly.

Further information: Privileged processing of the straight-ahead direction in primates are V1, Neuron, 2010

Interview by Christelle Labruyère

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Cardiovascular diseases: the battle gets more intense

Researchers at Toulouse study the risk factors that lead to cardiovascular diseases. These studies focus on molecular mechanisms, preclinical research on animal models, as well as clinical research and epidemiology.

A unique structure
Most of the teams at Paul Sabatier working in the domains of metabolic and cardiovascular diseases are today grouped at the Institut de Médecine Moléculaire de Rangueil (I2MR). This institute was created in January 2007 by Inserm and UPS, and will soon change its name to “Institut des Maladies Métaboliques et Cardiovasculaires” (I2MC).

The I2MC will boast three new teams. The first two (“Lipoproteins, Lipidic Transport and Dyslipidemies” and “Signaling and Phosphoinositides in Hematopoietic cells”) come from the Purpan site and the third comes from Paris. The arrival of these three teams at I2MC will allow researchers to put forward a unique project focusing on risk factors, in particular obesity, diabetes, dyslipidemies, and how they lead to cardiovascular complications such as thrombosis, and renal and cardiac failure.

Partnerships
The different teams have established numerous national and international collaborations through ANR and European projects in the fields of atherosclerosis, cardiac and renal failure, and cellular therapy of cardiovascular diseases. Collaboration with industrial laboratories (such as Sanofi-Aventis, Servier and Glaxo-SmithKline) and with local companies (like Urosphere; Physiogenex and Ambiotis) are also important.

The second cause of death
In this magazine, we present the main fields of research in Toulouse focusing on cardiovascular diseases. A variety of topics is looked at, from atherothrombosis (where blood vessels become progressively blocked) to studies on the heart and the influence of hormones, which play a key role in blood circulation. Our research still needs to explore many other aspects of cardiovascular disease with a view to reducing the morbidity and mortality related to these pathologies.

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I2MR: Institut de Médecine Moléculaire de Rangueil/ Rangueil Institute of Molecular Medicine

I2MC: Institut des Maladies Métaboliques et Cardiovasculaires/ Institute of Metabolic and Cardiovascular Diseases
A better understanding of heart failure

By recording the activity of sympathetic nerves using a new technique, specialists from the Toulouse Rangueil Hospital now have a better understanding of heart disease and how to treat it.

Heart failure is the final stage in most cardiovascular diseases. Despite huge advances over the last 20 years, the prognosis for heart failure remains bad with a median life expectancy of just four years, up to 150,000 hospital stays and 32,000 deaths per year in France.

Heart failure is characterized by the activation of humoral and neuronal systems like renin-angiotensin-aldosterone and sympathetic systems respectively. The sympathetic nervous system, through noradrenaline release and a large variety of adrenergic receptors, regulates vascular tone and intrinsic heart functions (such as heart rate, contractility and excitability). One of the research axes of our team focuses on the mechanisms underlying sympathetic hyperactivity during heart failure and how important it is to measure this activity for understanding the effects of drugs or to evaluate prognosis. In fact, sympathetic activation is, in the short term, a mechanism that compensates for the fall in cardiac output. However, over the more long term, sympathetic hyperactivity leads to the progressive worsening of heart failure and increased risk from sudden cardiac death at the severe stages of the disease.

Gold standard

Thank to the expertise of Atul Pathak, we have developed a technique in the Department of Cardiology of the Toulouse University Hospital that is available in only a few laboratories worldwide and considered as the gold standard for testing sympathetic nervous system activity. This technique, called muscle sympathetic nerve activity (MSNA), consists of recording the activity of sympathetic fibers using an electrode inserted within the fibular nerve. Quantifying sympathetic activity involves calculating the number of bursts per minute, for instance.

This research has yielded important results so far. It first allowed us to conclude that a rise in sympathetic activity during heart failure leads to an increase in renal failure and anemia. These two anomalies are frequently observed in heart failure patients and have been identified as bad prognosis factors. The mechanisms by which anemia and renal failure further increase sympathetic activity during heart failure are not totally understood but involve activation of chemoreflexes. These reflexes induce changes in lung ventilation in response to variations in oxygen and/or carbon dioxide concentrations in blood. They also modulate sympathetic activity and thus contribute to cardiovascular homeostasis.

Another finding concerns inotropic drugs used in acute decompensated heart failure. These drugs improve heart contractility but those that increase sympathetic activity have all been shown to be associated with an increased risk of rhythm disturbances and of sudden cardiac death. We have recently demonstrated that only one drug from this therapeutic class, levosimendan, significantly decreases sympathetic nerve activity measured using MSNA.

Sudden cardiac death

Sudden cardiac death, after rhythm disturbances, is frequent during heart failure and avoids the use of implantable defibrillators. In the frame of a large clinical study we will try to correlate the risk of sudden death (using discharge from defibrillator as a surrogate) and the level of sympathetic activity measured using MSNA. The aim of this study is to determine the clinical characteristics of patients who absolutely need such a devices, which are expensive.

Contact: senard@cict.fr

A better understanding of heart failure

By recording the activity of sympathetic nerves using a new technique, specialists from the Toulouse Rangueil Hospital now have a better understanding of heart disease and how to treat it.

Heart failure is the final stage in most cardiovascular diseases. Despite huge advances over the last 20 years, the prognosis for heart failure remains bad with a median life expectancy of just four years, up to 150,000 hospital stays and 32,000 deaths per year in France.

Heart failure is characterized by the activation of humoral and neuronal systems like renin-angiotensin-aldosterone and sympathetic systems respectively. The sympathetic nervous system, through noradrenaline release and a large variety of adrenergic receptors, regulates vascular tone and intrinsic heart functions (such as heart rate, contractility and excitability). One of the research axes of our team focuses on the mechanisms underlying sympathetic hyperactivity during heart failure and how important it is to measure this activity for understanding the effects of drugs or to evaluate prognosis. In fact, sympathetic activation is, in the short term, a mechanism that compensates for the fall in cardiac output. However, over the more long term, sympathetic hyperactivity leads to the progressive worsening of heart failure and increased risk from sudden cardiac death at the severe stages of the disease.

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Contact: senard@cict.fr
Blood platelets play a key role in the pathogenesis of thrombosis. In physiology, these small anucleated cells originating from megakaryocyte fragmentation, rapidly interact and aggregate at the site of an injured vessel wall to form a thrombus and lead to the formation of a fibrin clot that allows bleeding to stop. Thus, functional platelets are crucial for promptly stopping bleeding. Inherited or acquired platelet defects are therefore associated with mild to severe bleeding disorders. Under pathological conditions, such as rupture of an unstable atherosclerotic plaque, platelets become activated and can form an occlusive thrombus that prevents oxygen from reaching the brain or heart, which results in myocardial infarction or stroke.

The pharmacological control of platelet function is critical in preventing such thrombotic complications. Antiplatelet medication is also used to prevent thrombosis during angioplasty, particularly during coronary artery stenting. Currently, thienopyridines, in combination with aspirin, are the treatment of reference for controlling platelets.

Hemorrhagic risk
So far antiplatelet drugs have been used to target the mechanisms of platelet activation. These treatments do reduce the mortality and morbidity in different groups of patients but their efficiency still has to be improved. Indeed, many problems need to be solved, including drug resistance, efficacy and safety (hemorrhagic risk), dosage, administration requirements and combination therapy. Importantly, none of the current therapies adequately meets the most sought after requirement, which is namely the ability to inhibit platelet contribution to thrombosis without increasing bleeding. Therefore, novel, improved antiplatelet therapies are needed to efficiently prevent thrombosis without increasing the risk of hemorrhage. The development of such agents presupposes an accurate understanding of the complex mechanisms involved in platelet activation, aggregation and thrombus formation. Indeed, specific membrane receptors and/or downstream intracellular signaling enzymes represent potential antithrombotic drug targets.

Protected mice model
Our group is investigating the mechanisms of signal transduction involved in the different steps of platelet production and activation, particularly by using genetically modified mouse models. We have shown that invalidation of specific enzymes in lipid metabolism (kinases and phosphatases) selectively in megakaryocytes and platelets can protect mice from occlusive thrombus formation upon carotid injury without increasing the hemorrhagic risk. Our aim is to find new targets for antithrombotic drug targets and to propose new risk markers for thrombosis as well as molecular markers that will allow us to monitor the efficiency of antiplatelet drugs in the clinic. The collaboration between our research group with the cardiovascular and the neurovascular departments at Rangueil Hospital as well as the Department of Vascular Medicine and the Laboratory of Hemostasis allowed us to set up a translational research center and transfer advances in basic research into the medical field. This strategy has also allowed us to set up new methods to identify and characterize genetic and acquired platelet dysfunctions leading to hemorrhagic syndromes. Finally, a better understanding of the molecular processes of megakaryocyte maturation and platelet production, still poorly known, should allow potential interventions that correct or hijack processes such as biogenesis of platelet granules, which contain a number of substances involved in hemostasis, thrombosis but also inflammation and healing.

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Understanding the protective effect of estrogens on metabolic and vascular diseases

Estrogens are produced by the ovaries before the menopause. Beyond their crucial role in reproduction, these steroid hormones have numerous effects, in particular on the cardiovascular system and in energy metabolism.

Before the menopause, women are less prone than men to developing metabolic diseases, such as diabetes type 2, but also cardiovascular diseases, suggesting that endogenous estrogens have a protective effect. Furthermore, administering estrogens to animal models prevents the onset of diabetes and atherosclerosis, the main cause of cardiovascular disease.

Demonized hormones
A random trial intervention conducted in 2002 in the United States (Women Health Initiative) showed that, although reducing the incidence of diabetes type 2, these hormones did not confer cardiovascular protection, thereby questioning a belief held for several decades. However, this study was not representative practice because it involved older women (treatment was begun late, on average 11 years after the age of menopause) and thus wrongly "demonized" estrogens!

The aim of our team is thus to understand the mechanisms responsible for the protective effect of estrogens in metabolic and vascular diseases and why these hormones do not confer cardiovascular protection when they are administered far after the menopause.

Delaying ageing
It is known that estrogens can prevent risks of fracture, brought about by bone demineralization. They also prevent the onset of metabolic diseases, like obesity and diabetes, and atheroma lesions, the main cause of cardiovascular disease. Thereby, estrogens could even delay some aspects of ageing, and this probably represents the major challenge when modulating estrogen receptors.

Estrogens do not only concern women, because androgens (the male sex hormones) are partially converted, in many tissues of the body, into estrogens too. Thanks to a new model of transgenic mice that consists of inactivating one of the two trans-activating functions of the estrogen receptor, we recently showed that it is possible to activate this receptor and retain the vasculo-protective effects of estrogens - in particular, in the prevention of atheroma, without producing the classic sexual effects. If, as a famous writer once said, "woman is the future of man", feminine sex hormones could protect the futures of both men and women.

Risk of cancer
The long-term administration of estrogens increases, in a moderate but significant manner, the risk of cancer of the uterus and breast. Molecules that selectively modulate estrogen receptors already exist and are used to treat breast cancer and also prevent bone demineralization, demonstrating the feasibility of the approach. However, they do not confer cardiovascular or metabolic protection.

Based on the results from partial deletion of the estrogen receptor, our strategy derives from the postulate that molecules partially activating the receptor might lead to a new generation of estrogens. This approach requires a better understanding of how the estrogen receptor functions, that is, the in vivo "dissection" of the cellular and molecular targets thanks to the use of integrated models of genetically modified mice. Our ultimate goal is to contribute to the design and/or screening of molecules modulating the estrogen receptor with an optimized benefit-to-risk.

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Heart failure is defined by the inability of the heart to supply sufficient blood flow to meet the body’s needs. It is now, in the 21st century, a major public health concern in the west. Despite recent advances in the diagnosis and care of heart failure, the prevalence and incidence of this disease is still growing. It essentially affects the elderly and around 15% of individuals over 80 suffer from the pathology.

Cardiac remodeling
Heart failure in the elderly results from an increase in cardiovascular risk factors (including diabetes, high blood pressure and dyslipidemia) but also from age-related intrinsic factors. Heart failure is the terminal stage in the long term remodeling of the heart, characterized by hypertrophy, fibrosis and ventricular dilation. At present, the molecular mechanisms involved in cardiac remodeling associated with ageing are not clearly defined.

During the last few years, our team has focused a large part of its activity on the role of the mitochondrial monoamine oxydase A enzyme (MAO A) and of its main substrate, serotonin, in cardiac remodeling and failure during ageing. Our results have allowed to demonstrate that MAO-A generates large amounts of reactive oxygen species during the degradation of serotonin in the heart, and that this production increases in a very significant way in old animals.

Cell death
In order to determine if the increase in the expression of cardiac MAO could have pathological consequences on the heart, we studied transgenic mice that overexpressed this enzyme specifically in cardiac cells. In agreement with the hypothesis of the deleterious role of MAO and reactive oxygen species in the heart, we observed that an increase in cardiac MAO-A leads to massive death of cardiomyocytes, and to spontaneous heart failure. These results allowed us to identify MAO-A as a new key factor involved in cardiac cell death, and in the appearance of heart failure. On the other hand, we also demonstrated that an increase in cardiac serotonin content, due to a modification of the synthesis and/or the degradation by MAO, plays a key role in cardiac remodeling by two mechanisms: the induction of cardiomyocyte hypertrophy and the reorganization of the extracellular matrix by the activation of fibroblasts. In both types of cardiac cells, the effects of the serotonin involve the activation of the serotonin receptor subtype 5-HT2A.

All these results allow us to identify for the first time the duo MAO-A/serotonin as one of the main factors involved in cardiac remodeling and failure. These observations make MAO and serotonin receptors 5-HT2A promising and original targets for the pharmacological prevention and treatment of cardiac failure during ageing.

A duo of molecules comprising monoamine oxydase A and serotonin participates in cardiac ageing and failure.
Stem cells at the bedside of cardiovascular diseases

Stem-cell based therapies represent innovative biotherapies for myocardial infarction, cardiac failure and vascular diseases. Toulouse’s teams in basic, translational and medical research have joined forces to take up this challenge.

Stem cells are able to self-renew and give rise to different specialized phenotypes. Embryonic and fetus stem cells are considered as totipotent or pluripotent because they display a higher differentiation potential than adult stem cells that are multipotent or unipotent only.

Despite this lower differentiation potential, adult stem cells present unquestionable advantages with respect to embryonic stem cells. Firstly, as they can be used in autologous settings, the risk of rejection is totally avoided. Secondly, their lower differentiation potential limits the risk of tumorogenesis and they are very easy to cultivate in a secure and safe manner. In general, they also pose few ethical problems.

Regenerative potential

Over the last few years, a complementary research consortium has been focusing on understanding the biology of mesenchymal stem cells present in conjunctive tissues and their clinical uses to treat different cardiovascular diseases. Adult mesenchymal stem cells that display mesenchymal potentials and a strong paracrine activity represent promising candidates for cell therapy and regenerative medicine for central or peripheral ischemic diseases. All these pathologies are characterized by a large decrease in arterial blood supply.

This consortium brings together different teams: Remodelage Cardiaque: Aspects Physiopathologiques et Nouvelles Therapeutiques from the I2MR (led by Angelo Farini), Stromalab (Louis Castella), the Etablissement Français du Sang Pyrénées Méditerranée (Philippe Bourin), the functional unit Biothérapie du CIC 9302 (Louis Buscaill), and the Service de Cardiologie (Jérôme Roncalli) et Médecine Vasculaire (Alessandra Bura-Rivière) of CHU Rangueil.

Bone marrow and adipose tissue

The teams of A. Farini and L. Castella are working on mesenchymal stem cells from bone marrow and adipose tissue respectively. These teams have characterized cell and molecular mechanisms involved in the therapeutic effects associated with these cells and set-up different processes to increase their survival rate and efficiency after transplantation. Thanks to the consortium, new insights from basic science have been efficiently transferred to clinical trials. Thus BONAMI, a multicenter clinical trial on the use of bone marrow derived cells in myocardial infarction is already finished and its results are being published. Moreover, MESAMI, a pilot study, is investigating the benefits associated with the autologous transplantation of bone marrow mesenchymal stem cells in chronic myocardial infarction. Finally, AcellDream is investigating the use of autologous adipose derived stem cells to treat chronic leg ischemia.

According to its expertise in basic science as well as in translational research, our consortium and Toulouse itself are well recognized in the research field of adult stem-cell based therapy. The close link between scientists and clinicians is a major asset for setting up innovative biotherapies.

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Atherosclerosis is a consequence of the progressive ageing of medium and large arteries (such as the aorta, coronaries and carotides). It is characterized by the presence of lipid-rich plaques in the vascular wall. Atherosclerosis is the main cause of cardio- and neurovascular accidents (for example, infarctus and stroke), and a leading cause of morbidity and mortality in industrialized countries. A huge number of risk factors are involved in the development of atherosclerosis, in particular ageing, gender (male), familial and genetic factors, pathologies such as diabetes, hypertension and obesity, as well as dietary habits, sedentarity or smoking.

**Cholesterol**

Lipids are transported in the blood by specific proteins, such as low density lipoproteins (LDL), which transport cholesterol from the liver to tissues. Cholesterol-rich diets increase the plasmatic LDL and LDL-cholesterol levels, and cause atherosclerotic lesion formation.

Atherosclerotic lesions develop in the vascular wall, turbulent blood flow areas where endothelial cells lining the inner vessel wall become more permeable to leukocytes and macromolecules such as LDL. Once in the vascular wall, LDLs are oxidized by reactive oxygen species (ROS), which are continuously produced by vascular cells. Oxidized LDLs are taken up by macrophages which accumulate lipid droplets in the cytosol and are progressively transformed into “foam cells”. The accumulation of foam cells constitute the fatty streaks already visible during childhood in areas predisposed to the formation of atherosclerotic lesions. The progressive remodeling of early lesions results in the formation of more complicated plaques, characterized by a necrotic lipid-rich core, formed of intra and extracellular cholesterol deposits, macrophages and cellular debris, and centered by a fibrous cap, which determines the fate (stability or fragility) of the plaque. In some cases, lesion progression may theoretically reduce the diameter of vessels and blood flow, thereby inducing chest pain or cramp. Finally, the rupture or erosion of “fragile” plaques trigger clot formation and thrombotic events, resulting in neuro- and/or cardio-vascular accidents.

**Toxic events**

Oxidized LDLs play a central role in the formation of atherosclerotic lesions and their evolving to more advanced states. This is due to the fact that oxidized LDL transports and introduces bioreactive molecules (oxidized lipids) inside the cells.

Our group has been working for several years on the biological properties of oxidized lipids. We have shown that most oxidized lipids and oxidized LDLs trigger various cellular responses which differ as a function of their local concentration. At low concentrations, these agents trigger mitogenic and inflammatory responses, while at higher concentrations they induce toxic pro-apoptotic responses. For instance, some oxidized lipids bind tissular proteins and modify their structure and function. The accumulation of modified proteins inhibits cellular migration and proliferation and generates inflammatory events. Oxysterols may substitute for cholesterol in cellular membranes, thus modifying membrane structure and inducing cell death. We notably reported that the local presence of oxidized molecules maintains a pro-oxidant environment prone to fragilizing vascular cells. The effects of oxidized lipids can be observed in vivo in atherosclerotic lesions.

An important challenge for our team consists in developing natural or synthetic pharmacological agents able to block the deleterious effects of oxidized lipid mediators, which should limit the development of lesions and stabilize plaques, thus preventing or reducing the occurrence of atherothrombotic events.

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**From lipids to vascular accidents**

How can lipid accumulation in arteries lead to atherosclerosis? A crucial question for a leading cause of death worldwide.
The prevalence of obesity is increasing across the world with over 300 million people suffering from the ailment. Obesity is linked to an elevated cardiovascular morbi-mortality. Only a few studies have focused on the cardiomyopathy of the obese, thought to be secondary to arterial hypertension and metabolic disorders. However, obesity is an important risk factor for sudden death and heart hypertrophy that is far greater than the expected rate due to arterial blood pressure. Moreover, it has recently been shown that obesity is an independent risk factor for heart failure: a body mass index over 30 kg/m² doubles heart failure risk. Underlying mechanisms are poorly known but probably involve adipose tissue secretions (such as fatty acids and adipokines).

Heart genes
To study how the heart adapts to obesity, our team has studied the heart transcriptome to look for regulations of gene expression induced by obesity in a nutritional model of obesity generated by 9 weeks on a high fat diet. We have shown heart gene regulations that indicate the onset of early mechanisms leading to heart remodeling in the obese. This work was further conducted in humans using microarray chips.

Preventing lipid accumulation in the heart
Analysis of the results clearly shows that the molecular picture of the heart in the obese is very specific and strongly differs from what is observed in hypertensive or obese-hypertensive patients. Computer analysis of differentially expressed genes reveals a set of genes encoding for proteins not yet characterized. Amongst these, we identified new proteins with putative important functions: a new transcription factor and a new apolipoprotein that we named Apolipoprotein O (ApoO). We have observed that ApoO expression is induced in the hearts of diabetic patients and that ApoO expression is strongly correlated with apoptosis-related gene expression. We are currently investigating the pathophysiological role of ApoO in the heart using cellular models, transgenic mice and human heart samples. ApoO could represent a pharmacological target to prevent heart pathological remodeling.

Blood biomarkers for pre-heart failure
In addition, we are investigating for new and early heart failure (HF) biomarkers. Over 60 million patients around the world have HF. HF is a progressive disease that evolves from an asymptomatic phase (asymptomatic left ventricular dysfunction: ALVD) to severe stages that are difficult to treat. Identifying ALVD patients could prevent symptomatic HF development by early care and treatment of these patients. However, identifying ALVD is impossible today in general care practice. Patient history and physical examination is generally not sufficient for ALVD diagnosis, which requires specialized techniques such as echocardiography. We looked for blood ALVD biomarkers using transcriptome, metabolome and proteome analyses in patients with cardiovascular risk factors. Our results have already revealed a set of ALVD biomarkers (patenting in progress). Understanding the origin and the physiopathological role of these biomarkers could also set up a base for more fundamental investigations. However, the immediate spin-off of these studies should be a routine large-scale identification of ALVD patients, especially in ageing populations. Routine large-scale screens should allow for early care of ALVD patients and prevent HF development, which despite recent advances in treatments, remains difficult to control at its advanced stages and leads to a large number of deaths.

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Research at Paul Sabatier University

Research at Paul Sabatier University is developed in 62 laboratories organised in research units, supported both by the University and by at least one of the following research institutions: CNRS, INSERM, IRD, INRA, CNES...

The research staff includes about 2550 scientists whereas the administrative and technical staff consists of 1200 people.

The main research themes developed on our campus site are:

- Mathematics, Computer sciences and information systems, Engineering: 9 laboratories.
- Physics, Chemistry and Materials Sciences: 12 laboratories.
- Sciences of Earth, Space and Universe, Environment: 7 laboratories, 1 observatory.
- Life and Health Sciences: 20 laboratories.
- The Humanities and Social Sciences, 3 laboratories.

The number of graduate students is around 1600 in 11 doctoral schools.