Coding gene expression of the Ets1 transcription factor in a kidney carcinoma.
The struggle against cancer represents a national commitment for France, and CNRS is a key player in this area. CNRS’ vast range of scientific competences constitutes a great asset in overcoming this multi-faceted enemy. CNRS, alongside its public and private partners, is actively involved in this battle, within the framework of the national action plan against cancer, the *Plan Cancer*.

One of our priorities in the field of Human Life, both for now as well as for the future of medicine, is to identify and mobilize our strengths in this area. This issue of the CNRS focus series was put together to present the multidisciplinary contributions made by CNRS to cancer research, and to show what future potential is being developed in this area.

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CNRS has already contributed to cancer care through a number of major advances in both its diagnosis and treatment. CNRS remains focused on the future and one of its primary roles is to develop basic knowledge and understanding of the principles that will help to develop the medicine of tomorrow.

Cancer is one of life’s intimate diseases, a major challenge to our knowledge and a test of our intelligence, whilst also being a therapeutic emergency. We are humbled by this menace and its incidence is increasing in line with the increase in life expectancy despite considerable progress in its management and treatments with combined therapies.

We must stop cancer and this will only be possible once we have sufficient biological knowledge to correctly select the appropriate therapy. Whether it is a single therapy or a combination of treatment types, close collaboration between physicians and biologists is essential to increase the risk/benefit ratio. This partnership will allow the probability of the all too common event of resistance to treatment to be predicted or indicate when treatment should be modified to avoid or overcome resistance mechanisms. For example, monoclonal antibodies that selectively modify the function of an active target protein in the tumor have already started to prove their efficacy in additive therapy.

**Biodiversity, a major challenge for cancer**

For prevention, we also need a better understanding of cancer risk factors. We are not all equally susceptible to cancer and inherited traits are a complex part of biodiversity. For example, some heavy smokers never have to suffer the destructive effects of lung cancer whilst the rest of us take a risk with each cigarette that we smoke. What is true for susceptibility is also true for therapy but this is rarely adapted specifically to an individual. Decoding the human genome and more general progress in genetics will allow us to take up the real challenge for new anti-cancer treatments; the possibility of a personalized response that takes natural variation into account. This means that in the future we will need to be able to analyze a patient’s genetic background. We have to continue to study the human genome and to advance towards a complete and clear understanding of genetic diversity that goes far beyond the initial sequencing that has been completed recently.

**Systems biology, a weapon against cancer’s complex nature**

Developing new treatments requires a more complete investigation of tumor biology, extending from how the normal cell cycle is modified to what determines how aggressive a tumor is. All the diverse data that large-scale analytical technologies can provide has to be integrated at the highest level. Research to find reliable markers for tumors is impeded because, as in biology in general, cancer scientists cannot reduce the complexity of life to a few isolated indicators and expect that such data describing an entire population can be applied to or be useful in individual situations.
We must, therefore, continue to improve and rationalize the identification and bio-clinical use of markers. This requires considerable scientific effort as we try to find answers today to the major questions of tomorrow’s “systems biology”. As we progressively discover keys to the complexity of living beings, we are also providing ourselves with the means to evaluate these biomarkers and their appropriateness for an individual and a tumor. To achieve this, we have to represent, as faithfully as possible, the dynamic function of the networks, involving thousands of interactions among proteins, which organize the ballet of life within each cell.

Molecular medicine is the routine clinical use of basic science and applications derived from molecular genetics and biology. It is playing an ever increasing role in our response to the challenge of biodiversity by adding to our understanding of these complex systems. It will make a major contribution to our progress as it helps us rationalize therapeutic targeting and treatment combinations.

Interdisciplinarity in the service of the overall combat

The issues for the therapeutic management of cancer are not only related to biology. Progress is also needed in physics, in instrumentation, in informatics, in mathematics, in surgery, in chemistry and in analytical sciences. We already have or will have in the future new irradiation methods that are more effective and better focused even at a microscopic level to considerably improve therapeutic or diagnostic targeting; high precision robots and video-assisted surgery on even smaller tumors, new chemical substances that are better adapted for tumor destruction or control, analytical methods that are more powerful and ultra-specific for monitoring treatments … Computers and information analysis will make an essential contribution and already allow mathematical analyses and modeling to provide three-dimensional representations, analyses of gene clusters, representations of tumor dynamics … At all levels, from particle physics to pharmacology, frank and full exchanges between the academic world and commercial partners, in small or large hi-tech companies, are essential to effectively convert our understanding and discoveries into medical innovations and developments.

All of science and all the sciences and technologies must be invested in the fight against cancer. When one remembers that the patient is the focus of our mission, the need to make progress is even more imperative. A patient can never be considered simply in terms of a genetic and physiological mixture. The campaign against cancer also has important human and social components: cultures and partners, socialization of the sick, biotechnological and medical ethics, education and health economics. We must increase our scientific activity in these areas too, in collaboration with government and charitable sectors.
Cancer cannot be considered simply in terms of a list of molecular and cellular perturbations because it is a disease of the individual, a systemic disorder. Nevertheless, so far as we can judge, a cancer starts with a modification of hereditary material in a single initial cell that causes it to start uncontrolled multiplication. Apart from explaining genetic predispositions for a number of cancers, observing changes in cancer cells has shown us where the key stages of oncogenesis occur. Our ability to fully understand the complexity of life is relatively poor and this has led to some concepts that are over simplistic such as ‘oncogenes’ or ‘onco-suppressors’. Oncogenesis is a dynamic and complex process of change from normal to cancerous and involves much more than what we previously called oncogenesis. Every new bit of knowledge or information related to the functioning of normal cells, normal organs or normal individuals contributes to our understanding of cancer and provides a means to stop it.

In 1948, Darlington said that cancer stands at what might be the meeting place, but is in fact the no man’s land between infection, heredity and development. Although the search for characteristic genetic changes in cancer cells has become a central theme in cancer research, it has slowly become clear that cancer does indeed involve the coming together of many factors and that the environment has a role of growing importance. However, even now, this focal point remains mysterious and CNRS is contributing to its illumination.

Our genetic background is continuously threatened by alterations in cellular mechanisms due to stress from numerous chemical products; for example those present in tobacco or in the environment; ultraviolet solar radiation the intensity of which is increased because of the destruction of the stratospheric ozone layer. In most cases, the damage is dealt with by repair and surveillance systems. Surveillance occurs at cell cycle control points, the same ones that cause the cell to divide, stop growing or die.
Cell Cycle Disturbances

The study of cell cycle control became a new research area as a result of pioneering work conducted twenty years ago by geneticists studying yeast and by biochemists working on amphibian eggs or marine invertebrates. Understanding how cells work and identifying the molecular bases of pathological perturbations are major issues for the basic science research conducted in CNRS laboratories. Cell cycle dysfunctions are found in many cancers and targeting changes in cell division could provide researchers with new therapeutic approaches for pharmacological cancer treatments.

A Crucial Stage in the Mechanism of Oncogenesis: Mitosis

Several CNRS teams are contributing to our detailed knowledge of the properties and control mechanisms of the proteins that manage the successive stages that are involved when a cell divides to produce two daughter cells during a process called mitosis. The methods used for identifying the molecular mechanisms that control this cell division are the product of multidisciplinary research and they use advances in fields such as the genome, cell imaging and physics that were developed using a variety of model systems including starfish, yeasts and fruit flies. These mechanisms involve enzymes. Cycline dependent kinases (CDK) are enzymes that phosphorylate structural or control proteins and the control mechanisms use them to activate different target proteins. The CDK are also regulated by phosphorylation and dephosphorylation reactions or by association with inhibiting factors. These control mechanisms are a critical part of a cell’s response to any extra- or intra-cellular signals and ensure that cell division is performed perfectly and at the best moment for the harmonious functioning of a living being.

Part of the CNRS work involves studying the phosphatases of the CDC25 family that activate CDK and start mitosis. Understanding the function of these phosphatases, their regulation and their dysfunction in tumors should lead to the development of new anti-cancer treatments.

The Cell Death that is Essential for Life: Apoptosis

Programmed cell death (apoptosis) plays a key role in cellular homeostasis by eliminating cells with a damaged genome. The alteration of key apoptosis genes (for example P53, Bcl-2/Bax) provides tumor cells with an intrinsic survival advantage and makes them resistant to anti-cancer treatments. The physical changes seen during apoptosis are partly due to the activation of specific proteases, the caspases, which are responsible for two main apoptotic processes. One of these processes is being studied by a CNRS – Institut Gustave Roussy team. This process involves an increase in the permeability of mitochondrial membranes that seems to seal the cell’s fate. It leads to the release of caspase activators and of non-caspase related lethal factors and induces a major metabolic failure. Different stages of oncogenesis (or the consequences of chemotherapy) are associated with failures of apoptosis control mechanisms. Understanding this phenomenon will provide new indicators for determining the prognosis and new therapeutic approaches, such as inducing apoptosis by a chemotherapy that interferes with mitochondrial membrane proteins.
Understanding the Mechanisms of Oncogenesis

Structure and Function of Genetic Material

Cancer is considered to be primarily a disease of genetic material and its expression. Each of our cells contains all the information required for our bodies to work properly. This information is ‘written’ on our DNA as a genetic code involving about 3 billion cryptograms. The DNA is compacted and stored in chromatin which has to be very reactive and flexible as the code must be available for consultation and use at all times. The smallest error in this sophisticated system can lead to disruption of the genome, modified expression of the genes and, ultimately, cell dysfunctions.

Relationship between DNA Structure and its Metabolism

During the life of a cell, the DNA must be accurately copied and correctly transferred to daughter cells. If a structural lesion occurs, it must be quickly repaired so as not to compromise the expression and transmission of our genetic material. Evolution has selected very effective mechanisms to perform and control the replication of DNA. A CNRS – Institut Curie team is studying the replication of genetic material, the factors which regulate it and the coordination of this replication with other cellular activity. The scientists are particularly interested in three-dimensional areas in the cell nucleus that appear to be ‘factories’ within which the DNA is copied and, when needed, repaired. These factories can be observed by using a DNA replication protein that is made fluorescent. The team uses this technique to make films that let them monitor the dynamics of DNA replication and identify the genes that control it. The results obtained in *Schizosaccharomyces pombe* yeast cell models indicate that these factories are only present during the DNA replication phase, that their number is limited, that they develop in an orderly fashion and that they are mobile within the nucleus. These nuclear structures are another potential opportunity for developing new diagnostic tools and could be targets for anti-cancer therapies.

Chromatin Dynamics

In a cell, DNA is folded around proteins, histones, to create a three-dimensional object called a nucleosome. Nucleosomes are the structural blocks of chromatin, which is found in the nucleus. In addition to the genetic data encoded by the DNA, this packaging of our genome provides epigenetic information that defines a characteristic epigenome for each cell type. Another CNRS – Institut Curie research team is trying to understand how this epigenetic information is created, inherited, controlled or modified. They have identified significant factors in the post-translational modification of histones (acetylation, methylation...) as well as factors for creating and maintaining chromatin structure (factors CAF-1, HIRA and ASF-1). Some of these structural factors appear to be very good markers for cell proliferation. Their regulation during the cell cycle and in response to genotoxic stresses has demonstrated their importance, within functional domains such as the heterochromatin, in the organization of the nucleus. Applications for medical diagnosis in cancerology and for evaluating genotoxic risk are already being developed. Studying the three dimensional anatomy of the nucleus and chromatin dynamics will help us understand the dysfunctions that are signs of genetic instabilities that predispose to cancer.
New Molecular and Cellular Investigation Methods

Cancer is a disease of the individual involving a number of complex molecular and cellular dysfunctions. Continued technological progress, providing increased specificity and sensitivity, is required to identify and understand these dysfunctions. This progress depends on our ability to apply mathematical, physical and chemical tools to living beings. A CNRS strength is interdisciplinary teamwork and this provides the opportunity to fully investigate single isolated molecules using these new methods for observing the living.

An Enzyme that Unravels DNA: Topoisomerase

Topoisomerase inhibitors block cell division and are thus used in anticancer chemotherapy. In order to better understand how topoisomerases work, scientists in a CNRS – ENS – Universités Paris 6 & 7 laboratory have perfected a new technique for micro-manipulating DNA molecules so that they can observe the action of these enzymes on isolated DNA molecules. Their technique consists in anchoring one or two DNA molecules to a magnetic micro bead and then using little magnets to turn it, which twists and shortens the DNA. As the topoisomerases unwind the DNA, the bead rises under magnetic tension. This apparently simple technique has been able to demonstrate that topoisomerases of higher species are biochemically different from their bacterial counterparts.

Understanding Cellular Motility to Control Metastasis

Metastatic cells are very motile and move with abnormal speed. One of the most important proteins involved in this movement is actin. A bio-mimetic system for this movement has been developed in which microscopic objects move at speeds of several microns per minute in cellular extracts. This model system has helped us understand the physics of this movement and has also resulted in two patents for methods of identifying anti-metastatic drugs. The objective is to test the effect of these drugs in this bio-mimetic system. As they will affect cellular mobility using the same biochemical mechanism, they could prevent metastasis.

Detection by Spectral Confocal Microscopy

The teams in the CNRS – Institut Curie research laboratories work in close cooperation with the medical section of the Institut with the following four goals to identify genes that have had their expression modified in tumors (DNA chips); to develop animal models to study the progression of tumors; to improve new intracellular targeting methods for anticancer molecules; to perfect new therapeutic tools such as recombinant antibodies. A subject of special interest is imaging. The laboratory has made a considerable investment in this area to improve our understanding of the dynamics of sub-cellular structures in normal and cancerous cells. The combined use of a spectral confocal microscope with new algorithms for image analysis has resulted in significant progress in the detection of cancer cells within tissues.
Understanding the Mechanisms of Oncogenesis

A Major Site for Alterations in Cancer Cells: DNA

Growing knowledge about chromatin and the structure of DNA and its expression has allowed us to develop our understanding of how a normal cell functions and the potential sites for changes that cause it to become a cancer cell. What is involved when such a change occurs?

Evaluating the Risk from Exposure to Low Doses of Radiation

A major issue in radiobiology is the response mechanisms of a cell when it is exposed to a weak ionizing ray (radioactive gas such as radon). These weak doses are very difficult to reproduce on cell lines in the laboratory using normal irradiation methods. What we really need to be able to do is study what happens when a single cell is hit by a single ion. A CNRS – Université Bordeaux 1 team has used a micro-beam that lets them make targeted irradiations, cell-by-cell and ion-by-ion, of critical parts of the cell such as the nucleus. This technique overcomes problems of dose fluctuations due to multiple impacts, the incertitude as to which intracellular targets are actually hit (nucleus or cytoplasm), or indirect effects from impacts on neighboring cells. The team has made a real contribution to the evaluation of the risks from chronic exposure to natural and workplace irradiations. They have also added to our knowledge of the intracellular and sub-cellular signaling mechanisms that are involved in oncogenesis and, finally, provided us with a new avenue of research for anticancer therapy using charged particles (protontherapy, hadrontherapy ... ).

Replication Mechanisms of a Damaged Genome

So as to prevent changes becoming permanent genetic mutations, repair mechanisms normally deal with any DNA damage. However, replication can occur before all the damage has been repaired and this can lead to the creation of cancer cells. CNRS scientists have been able to directly observe the replication of damaged DNA. They have demonstrated the role of specialized DNA polymerases on altered DNA sections where they help the normal replication enzymes. The DNA lesion blocks replication and these ‘translesional’ DNA polymerases are able to restart it and launch the repair of the DNA. These enzymes represent new potential targets for pharmacological research.

Diseases of DNA Repair and Skin Cancers

Researchers use diseases of DNA repair as models to study oncogenesis of skin cancers induced by ultraviolet solar radiation. Patients with xeroderma pigmentosum are hypersensitive to ultraviolet rays because they have a defect in their DNA repair system and they develop multiple cutaneous tumors at a young age. To understand and, hopefully, treat these cutaneous cancers one day, skin has been reconstructed in vitro using cells (keratinocytes and fibroblasts) isolated from these patients. In vitro analysis of growth and differentiation anomalies in this skin and their treatment with normal repair genes will help us understand the genesis of these tumors, both in these individuals and in others who do not have xeroderma pigmentosum.
A Major Site for Alterations in Cancer Cells: Proteins

The recent decoding of the human genome has provided a rich map of over 30,000 genes and gives us new opportunities for identifying the abnormalities that are responsible for serious genetic diseases, such as cancer, and for developing new therapies. However, we still have little or no knowledge about the role of some genes. Genes contain the code for synthesizing proteins, including enzymes, whose catalytic activities manage the multiple tasks involved in cellular metabolism. These proteins are therefore the main factors responsible for the proper functioning of the cell.

A Protein Responsible for the Development of Metastases: Akt Protein

As long as cancer cells stay together, the tumor can be considered as circumscribed and can thus be overcome by local treatments. Treatment becomes more difficult when these cells acquire the ability to move and invade other tissues, leading to the development of metastases. Scientists have identified a protein that has an important role in the movement of epithelial cancer cells within the body. This Akt protein, which is involved in many vital cellular processes, is continually active in many cancers including those of the ovary, pancreas, breast and thyroid.

A team has shown that this constant activation of Akt (abnormal mode) rather than an alternating activation / inactivation cycle (normal mode) leads to a modification in the expression of anchoring proteins and their repositioning in the cell. These proteins are normally found on the exterior of the cell membrane and ensure the cohesion of tissues. If they receive an order to move to the interior of the cell, the anchors are broken. Scientists have observed that this results in both a loss of cohesion between cells and an increase in the speed of cell movements. They have concluded that the abnormal constant activation of Akt gives cells the mobility they need to invade other tissues. This discovery provides new therapeutic potential as affecting Akt protein could prevent the occurrence of metastases.

Retinoic Acid Receptors Against Cancer

The retinoid group of anti-cancer drugs consists of retinoic acid and its synthetic derivatives. It is an extremely promising group with applications not only for curing but also for preventing cancers. At the cellular level, retinoids bind to nuclear receptors (RAR and RXR) and change their activity. They either induce or inhibit cell differentiation, growth and programmed death (apoptosis). It is therefore essential that we understand how retinoids act on these receptors to improve the specificity of these anti-cancer drugs. Researchers from a CNRS – Université Strasbourg 1 – Inserm laboratory have just made a huge step forward by explaining the hierarchy that exists between the different retinoid receptors and showing that the RXR receptor is subordinate to the RAR receptor. The objective of this work is to develop retinoids, which have had their anti-cancer activity established by clinical trials and in experimental models, with greater specificity and fewer of the secondary effects that are often associated with chemotherapy.
The diagnosis of a disease is based on a combination of results, from examining a patient to analyzing samples, through various methods of physical investigation. It must be carried quickly and with the greatest accuracy. This requires new approaches that are products of laboratory-based research, such as that conducted by CNRS - fundamental work tailored to serving patients’ needs.

Diagnosis starts at a cellular or even molecular level because the degeneration of a cell due to apoptosis (programmed cell death) can be monitored by physico-chemical methods. Other approaches are provided by optical sciences with natural applications for diagnosing cancer. The interaction between light and certain molecules that appear in tissues during the early stages of tumor development causes fluorescence. Spectroscopic imaging, known as spectrometry, provides information on intra- and extra-cellular events during cell alterations and is an untapped source of products that could be transferred straight from laboratory to bedside in the future.

A recently awarded Nobel Prize for Medicine gave prominence to magnetic resonance imaging (MRI) technology. But are we really aware of the wealth of information that this method could provide when its spectroscopic capability is applied to many of the atomic nuclei that make up our bodies? We are now capable of examining humans and providing information on the progress of tumors with great accuracy as the examples on the following pages show. Diagnostic choices which can be used for cancer exist amongst known analytic methods and proven techniques such as specific antibodies, markers of cell status, revolutionary contrast media for tissues and organs. The fields of application of existing investigative methods can be increased by spectacular adaptations.
Molecular Diagnosis

For multi-faceted diseases, such as cancer, detailed knowledge of the enemy is a decisive advantage for improving the diagnosis. To provide more accurate diagnosis and prognosis, we need to increase the range of molecular markers and tests that are available.

A Mapping Tool for Tumors: The ‘Proteome’

The proteome provides an exhaustive analysis of all the proteins in a cell (proteome) and can therefore identify cells that have modified protein expression caused by oncogenesis. Physico-chemical methods, such as mass spectrometry, are used to identify the proteins. Scientists in a CNRS - Université Nancy 1 laboratory are using a differential proteomic analysis to compare the proteomes of chondrocytes and cells from a chondrosarcoma, in other words, a normal articular cartilage cell, with its cancerous version. The proteins from the two samples (healthy and cancerous) are marked by fluorescent molecules with different colors. Proteins with modified concentrations following transformation of a normal cell to a cancerous cell are detected by analyzing high resolution images. The widespread use of this technique for tumor mapping will help us discover new markers for oncogenesis and tumor growth.

Tumor Markers Identified by DNA Chips

In tumor cells, there are numerous rearrangements of chromosomes with segments being lost and gained. In cells, the lost segments cause a deactivation of the genes concerned and the extra segments cause an increased expression. We can now identify these DNA losses and gains and then establish correlations with the type of tumor, its stage, or the evolution of the disease, by using new high resolution mapping techniques based on DNA chips (CGH array). Using this method, a team from a CNRS - Université Strasbourg 1-Inserm laboratory is trying to identify the regions and the genes involved in chromosome 3 that are regularly amplified in cancers of the head, neck and lungs. They will use their results to try to develop dedicated DNA chips so that evaluating the prognosis and making therapeutic choices become easier.

An Aid to Evaluating the Prognosis: A Metalloprotease

In the early nineties, another team in this same laboratory, in collaboration with CIS Biointernational, perfected a test for detecting a peptide, the ElsappS2 kit, which allows us to predict the probable response of a tumor to hormone therapy. This team is now studying a matrix metalloprotease, the ST3, which is over-expressed in 90% of invasive mammary carcinomas and has levels in primitive tumors that correlate with their aggressiveness. In these carcinomas, ST3 is present in fibroblasts in the tumor’s stroma [the tissue that surrounds the tumor] and not in the cancer cells themselves. ST3 has a paracrine (local) effect during tumor development. This molecule will be used as a biological marker to improve both the diagnosis and the evaluation of the prognosis. Synthetic ST3 inhibitors could also be used to control the development of the tumor and current research is concentrated on this therapeutic potential.
Improving Diagnosis

Cellular and Tissue Diagnosis

A current priority is the search for new methods for diagnosing cancer and making an early prognosis. The clinician requires markers that can predict the response to chemotherapy. Today, scientists have developed innovative methods for investigating cells and tissues and have created new diagnostic and prognostic tools as a result of new emerging techniques in bio-photonics and biotechnology.

Diagnostic Use of Auto-fluorescence

Auto-fluorescence of biological tissues uses light’s analytical finesse and non-invasiveness. Only the superficial layers of tissues are observed using proximal UV light but physicists in a CNRS – Université Paris 13 laboratory have adapted this approach and applied it to the endoscopic detection of bladder tumors. The laboratory has made a multifiber probe that uses a light beam to excite the bladder wall. A sensor detects the auto-fluorescence of a component of cellular respiration and a metabolite, tryptophane and nicotinamide adenine dinucleotide respectively. An initial clinical study on very small zones has confirmed the value of this method: it provides an excellent early diagnosis of squamous cell carcinomas of the bladder that are not visible using classical endoscopy. In the near future, a second clinical trial is planned to evaluate the automated detection of tumor regions using auto-fluorescent imagery.

Optical Micro-spectroscopy, Cancers and Predictive Markers

Bio-photonics has benefited from a number of technological advances that have led to the development of functional cell and tissue micro-spectro-imagery. A CNRS – Université de Reims Champagne-Ardenne laboratory has developed new approaches to the early diagnosis and prognosis of tumors based on optical spectrosopes (Raman and/or infrared) that are non-invasive and provide much information at a molecular level. The results obtained are very promising and short-term applications include defining predictive markers for use with personalized treatment protocols and guiding surgery during tumor resection (interventional micro-imagery).

‘Intelligent’ Antibodies for Diagnosis

Antibodies are proteins produced by the immune system that have the ability to recognize specific antigenic proteins. This ability is often used to identify abnormal cells in the body by detecting an excess or an absence of certain proteins in these cells. However many proteins regulate their activity by changing their shape and some dysfunctions are caused by proteins that are present in normal quantities but are folded in a particular way. Scientists in a CNRS – Institut Curie laboratory have produced synthetic antibodies with special properties: they are selected in vitro after a few days and are sensitive to the shape of the protein that they recognize. They can be used to detect proteins that are folded in specific ways associated with disease, such as in some cancers, and could provide the basis for innovative diagnostic methods.
Improving MRI Techniques

Magnetic resonance imaging (MRI) uses the magnetic resonance of the protons of water molecules present in the body to represent different zones of the body with great precision. Magnetic resonance spectrometry (MRS) uses protons and other nuclei, such as the phosphorus that is present in metabolites arising from energy production. These two approaches are therefore very close to each other and more and more often combined in new installations.

MRS for Improving Diagnosis of Cerebral Tumors

Magnetic resonance spectrometry (MRS) is a non-invasive technique that shows the chemical and functional content of living tissue. It can be performed as part of a conventional MRI examination and provides a metabolic profile of the tissue being examined, e.g. the brain. For cerebral tumors, the spectra are often indicative of the type and stage of advancement of the tumor. The most common cerebral tumors are the gliomas and their prognosis is heterogeneous; patient survival ranges from 1 to 15 years. Cerebral gliomatosis has a very poor prognosis but cannot be diagnosed in a living patient because neither the conventional MRI nor biopsy is capable of differentiating it from other types of glioma. The use of MRS has made it possible for scientists at a CNRS – Université Lyon 1 laboratory to make objective diagnoses of gliomatosis and, as a result, adapt the therapeutic strategy.

Helium for Lung MRI

Diagnosing lung tumors involves using medical imaging based on ionizing radiation or radioactive molecules: pulmonary radiography, X-ray scanning and position emission tomography (PET). Magnetic resonance imaging (MRI) provides information on the distribution of water molecules in the body and has recently been adapted by scientists at a CNRS – Université Lyon 1 laboratory for use with two non-radioactive gases: helium-3 and xenon-129. MRI using these gases provides images of the airways and pulmonary blood vessels. These new imaging methods are already being used clinically to diagnose pulmonary emphysema. In the longer term, MRI using helium-3 and xenon-129 gases, which are not dangerous to health, could be used to detect pulmonary tumors.

Future Contrast Media for MRI

By creating a random local magnetic field, magnetic nanoparticles modify the relaxation time for nearby protons and thus create a contrast where they are concentrated. These particles are capable of crossing biological barriers in the body to enter the tissues and interact in a predetermined manner with cells. Scientists at a CNRS – Université Paris 6 laboratory intend to use them as ‘intelligent’ markers. Their strategy consists of guiding lipid spheres (liposomes) containing magnetic nanoparticles to target cells by coupling a specific ligand to them that is recognized by receptors in the cell membrane. This innovative technique will make it possible to use MRI clinically to detect the abnormal genetic expression caused by cancer.
The arsenal of therapeutic methods used for treating cancers can be summarized as surgery, chemotherapy and radiotherapy. Chemists and physicists are naturally present at the source of these methods.

More than half the active ingredients used for anti-cancer chemotherapy originate from natural substances. They can be unchanged natural substances, derivatives produced by modification of the initial molecular structure or synthetic molecules based on their natural models. About a third are substances conceived and synthesized independently of any natural model. CNRS has had some great successes in this area during the last decade. Docetaxel (Taxotere®) and vinorelbine (Navelbine®) are testimony to this. Other successes are hoped for. These achievements confirm both the need to continue to conduct innovative synthetic chemistry research at the highest level and the importance of interdisciplinary program where biologists and chemists are sharing ideas.

There are two new trends in the research for molecules with anti-cancer properties. The first is to increase both the number of molecules tested and the range of applications of therapeutic properties for which they are evaluated. This medium or high-throughput screening is only possible because of recent technological advances and now forms part of the CNRS strategy, which is often conducted in partnership with private laboratories. These partnerships provide better return on public investment and include the setting up of a national chemical library that could be extended into a target library. The second development is the extension of research for anti-cancer molecules to include macromolecules (particularly proteins) from the living world and CNRS is also involved in this promising development.

Finally, ever since Marie Curie and the discovery of the importance of ionizing radiation as a treatment for cancers, France has recognized that a permanent liaison between nuclear physics and chemistry and the development of radiotherapy is paramount.
Research Applied to Surgery

Computer assisted surgery has developed very quickly over the last twenty years. The key success factor is being able to use all the available pre-surgical information (anatomic and functional imagery using large pieces of equipment such as scanners, MRI ... ) in combination with peri-surgical imagery (ultra-sound, radiography ... ) that shows the actual position of the patient and the instruments. This makes guidance easier resulting in more precise and quicker movements by the surgeon and a less invasive operation.

A Miniature Gamma Camera for Peri-surgical Imagery

Successful surgical treatment of cancer requires that it is precisely located and that the tumorous tissues are completely ablated. In response to this need, the introduction of miniaturized scintigraphy [a nuclear detection method using radioactive tumor markers] to the operating theater is a major advance in guidance for the surgeon and helps ensure that the cancer tissue is completely excised. To increase the efficacy of this assistance by radio-guidance, a CNRS – Université Paris 11 laboratory has developed a miniature high-resolution gamma camera, baptized the per-operative compact imager (POCI). It can be in contact with the surgical site and provide real time identification of cancerous and normal tissues.

Monitoring Revascularization of a Facial Implant

Unfortunately, removing a tumor by surgery can result in permanent mutilation. Tissue grafts using strips of tissue can limit this effect particularly for cancers of the upper airways or digestive system. Whether or not the graft takes is always a preoccupation and its survival is linked to the quality of its revascularization; the existence of an arterial afferent flow and venous efferent flow. Previously, care staff only had empirical methods such as the color of graft for evaluating these flows. A team from a CNRS – Université Paris 7 laboratory had the idea of adapting a Doppler laser velocimeter, a simple non-traumatic method, for monitoring the revascularization of facial implants. The technique provides real time data on the graft’s perfusion during and after transplant and can show any vascular occlusion, should it occur, before it has clinical effects.

Stereotaxy for Treating Prostate Cancer

Stereotaxic methods use an ultra-sound image of a cancerous prostate to make three-dimensional segments. These are then used either to position a patient more accurately for a radiotherapy session [to ensure that the dose is as prescribed] or to make it easier to position iodine 125 implants in the prostate for an in situ irradiation. A new method for combining peri-radiotherapy echography data with pre-radiotherapy MRI or scanner data has been developed by CNRS and Joseph Fourier University, Grenoble, and confirmed in collaboration with the Grenoble teaching hospital. The objective is to apply a more precise irradiation with reduced secondary effects. Computer assisted radiotherapy is currently being evaluated whilst patient positioning is being developed commercially by Praxim in collaboration with Zmed/Varian.
Optimizing Natural Substances with Chemical Engineering

An important part of the work of CNRS involves having detailed knowledge of the chemical structure of natural products, whether extracted from flora or fauna, and perfecting innovative chemical methods for their synthesis. The ability of CNRS to test chemicals for anti-cancer properties at the same time as chemical engineering expertise is used to optimize their structure has led to notable therapeutic and commercial successes, via industrial partnerships.

**Taxotere®, a Leading Anti-cancer Treatment**

Scientists at a CNRS laboratory at Gif-sur-Yvette are looking for natural substances that attach to tubuline, which is a protein that is crucial to cell division. This led them to synthesize Taxotere® (docetaxel) from a natural component isolated from the European yew tree *Taxus baccata*. Docetaxel is an analogue of Taxol® (paclitaxel) which was isolated from the bark of Pacific yews, *Taxus brevifolia*. The first hemi-synthesis of Taxol was then achieved by a CNRS – Université Joseph Fourier laboratory in collaboration with the researchers at Gif. Taxotere® was developed by Aventis Pharma directly from the work in the CNRS chemistry laboratory and is amongst the world’s leading pharmaceutical products in terms of sales revenues.

**Vinflunine, a Successor to Navelbine®**

The Madagascan periwinkle, *Catharanthus roseus* L.G. Don, contains alkaloids used for treating cancers. Four members of this family are currently used including Navelbine®, produced by hemi-synthesis. In collaboration with Laboratoires Pierre Fabre, a CNRS laboratory linked to Poitiers University has developed a successor to Navelbine® called Vinflunine (Javlor®). The research team was successful in synthesizing this di-fluoro analogue of Navelbine® in super-acid conditions because of its knowledge of chemistry under extreme conditions. Using very acidic media allowed new reactions to occur in molecular positions that are inert under more normal conditions. Vinflunine is currently in phase III clinical trials and its even greater anti-cancer efficacy means it could replace Navelbine®.

**New Anticancer Agents: Acronycin Derivatives**

Acronycin is an alkaloid that was isolated in 1948 from a little tree in Australia, *Acronychia baueri*. It has anti-cancer properties and is effective against many types of cancer but also has inconveniences: it is not very effective or very soluble in water or biocompatible solvents. Scientists at a CNRS – Université Paris 5 laboratory have therefore synthesized derivatives of acronycin that are both more active and effective. One of them is very active in vivo with remarkable activity in experimental models of lung, colon and ovarian cancer and is now in the late stages of pre-clinical development with Laboratoires Servier. These results show, once again, the important role of chemical engineering for improving the anti-cancer properties of natural substances.
New Anticancer Chemotherapies

The discovery of anti-cancer drugs owes much to the study of natural substances. Nowadays, advances in chemical concepts and the creativity of scientists are pushing back the limits for the development of new therapeutically active molecules. The close collaboration between chemists and biologists allows us to understand the effects of these new molecules in model systems.

Extraordinary Protein Inhibitors: Cytotoxic Components

A CNRS–Université Clermont 2 laboratory is working on topoisomerase 1 inhibitors. Topoisomerase 1 is an enzyme involved in uncoiling DNA, which is an essential step in DNA replication and its transcription into RNA. The team is studying analogues of rebeccamycin, a bacterial metabolic topoisomerase 1 inhibitor. By making structural modifications, they have obtained molecules that are very selective for cancer cell lines (which is not the case for rebeccamycin) and have a very strong anti-proliferation effect in vitro. Another laboratory (CNRS – Université d’Orléans) is using models from bacterial cultures (indolocarbazoles) or marine sources (hymenialdisine from the sponge Pseudaxinyssa cantharella). After synthesis, many chemical modifications are made to obtain analogues with enhanced biological properties that are usually strongly cytotoxic and good enzyme inhibitors (CDK, PKC). These laboratories have already developed new and patented products in collaboration with Laboratoires Servier.

Anti-angiogenic Molecules to Prevent Tumor Growth

Perturbing its relations with its environment can destroy a tumor cell. In order to grow, the tumor cell needs the oxygen and nutrients that are found in the newly formed blood vessels that perfuse it. These new vessels develop (neo-angiogenesis) in response to growth factors liberated by the tumor, and anti-angiogenic molecules prevent this development and thereby limit the growth of the tumor mass and the spread of tumor cells (metastasis). More than fifty anti-angiogenic molecules are currently known. Steroids, macrolactonic and cyclopeptic structures have been synthesized by a CNRS – Université Paris 11 unit. These molecules have shown marked in vitro inhibitory activity against the vascular endothelial growth factor (VEGF) that is responsible for neo-angiogenesis. Fluorinated inhibitors of matrix metalloproteases that are involved in the same activity are also being studied.

An Effective Synergy Against Leukemia: Retinoic Acid and Arsenic

Acute promyelocytic leukemia involves the formation of an abnormal protein following chromosome breakage. This abnormal protein blocks normal cell death and differentiation. Both a hormone derived from vitamin A, retinoic acid, and arsenic can restore cell differentiation and induce remissions. A CNRS laboratory has shown that these two molecules target the abnormal protein directly and cause its degradation. Scientists have also identified the biochemical routes and molecular determinants involved in this degradation process. In an animal leukemia model they have demonstrated the synergetic effect of these two components as their association eradicates the leukemia whilst monotherapy by retinoic acid or arsenic alone prolongs survival but never produces a complete cure.
Imagining the Therapies of the Future

Chemical and Biological Diversity Applied to Pharmacology

Anti-cancer therapy hardly exists in traditional European pharmacopoeias but now requires new specific and effective molecules. The primary reservoir for these molecules is without doubt the natural world, especially the flora. It is the role of research to identify and purify these substances, to determine their structure and explain their means of action. It is our collective responsibility to catalogue and conserve them in chemical libraries that are a resource for scientists who can revisit them each time new information provides a new potential biological target.

From Plants to Candidate Drugs

The natural world is a great source for bio-active molecules. Plants are harvested, particularly in tropical countries where the biodiversity is greater and less well known. Whilst some are chosen because of their use in a traditional pharmacopoeia or because they belong to a family of plants rich in alkaloids, most are systematically harvested rather than being preselected. Every part is sampled: leaves, barks, fruits ... At the same time, dried specimens are prepared for examination by botanists so as to classify them, an important step prior to any chemical study.

Crude extracts for the different parts of the plant are complex mixtures and rich in polar substances. In order to be used in biological screening, they need to be fractionated either by using solvents with increasing polarity or by automated high performance liquid chromatography (HPLC) before they can be used in biological screening. The purified fractions are then placed in multi-well trays to be screened for activity on target enzymes or membrane receptors as part of a public - private cooperation. Each biological screen, particularly the many aimed at detecting anti-cancer substances, allows identification of active fractions that are then purified until the single active molecule is isolated. All the fractions and molecules that do not give a positive response in tests are conserved and supplied the chemical library.

Demonstrating that a natural molecule has a desired activity leads to chemical studies [structure determination, study of relationships between structure and activity, synthesis / hemi-synthesis] and pharmacological research to explain its biological mechanism and toxicology. This is followed by clinical evaluations and, if it reaches commercial development, results in the creation of a new pharmaceutical product.

National Chemical Library Available to Researchers

So as to make the most of the significant number of molecules synthesized or extracted from nature by research laboratories over the years, CNRS created a chemical library in 2003. It manages this collection and database where more than 20,000 molecules are currently stored and classified. This chemical library regularly receives new molecules and data from scientists. Eventually, it will also receive material from prospecting and collection campaigns on all five continents. The chemical library is a national response to the need to organize and rationalize both our efforts and our chemical assets. It connects CNRS with twenty French universities and other research organizations. This molecule collection is available to the scientific community and is a wonderful resource for high-volume screening, a method that has already yielded a number of cytotoxic substances that could become anticancer agents of the future.
Screening: From the Virtual To the Real

The development of medium or high volume screening methods means we can analyze large numbers of natural or chemically modified molecules for any use for which a biological screening method can be developed. Whilst this approach is always a bit of a gamble, CNRS is betting on the collaboration between biologists, physico-chemists, modelers, chemists and pharmacologists who share the common motivation of wanting to participate in the creation of a new drug.

Identification of Targets and Design of Biological Tests

Cell division is an extremely complex process that is regulated by many intracellular factors. Each one is involved for only a short time and they follow a precise sequence. Several cell cycle regulators of different importance are involved in cancer formation and it is difficult to know which are the most important in oncogenesis. Several CNRS laboratories are looking at over-expressed or mutated proteins that are present in different cancers to confirm if they are targets. In other words, to determine if they have an essential role in the transformation of a normal cell into a tumor which means their inhibition could be the basis for a therapy. A team from a CNRS – Université Paris 5 laboratory has selected and confirmed the cell signaling protein Grb2 as a target. Other CNRS teams are working on another family of target proteins, the kinases.

Medium and High Throughput Screening

Once a target is confirmed, the research teams have to develop a screening test: an automatic experimental protocol that is reliable, reproducible and easy to apply. A very large number of natural and synthetic molecules are tested by automated screening systems (a research tool that can perform as many as 10,000 tests per day) so as to detect if they have any biological activity. It’s here that a chemical library reveals its potential. When a positive result is obtained, the molecule is re-tested at low throughput so as to make a detailed analysis of its spectrum of biological activity. They then conduct animal tests, by preference with a commercial partner. Several of the inhibitors identified and classified recently by CNRS have reached the stage of pre-clinical and clinical trials. One of these is roscovitine, a kinase inhibitor that is currently in phase II clinical trials against for and breast cancer.

Computer Screening

Knowing the three dimensional structure of target macromolecules with potential anticancer roles (proteins, nucleic acids) opens the field for ‘virtual screening’. This involves predicting which molecules will have the most affinity for the target’s active site and therefore be capable of activating or inhibiting it. Computer based screening methods can be used to test all molecules for which we know the structure (from real or virtual chemical libraries). The throughputs already obtained are of 50,000 molecules tested per day and several hundreds of thousands of molecules can rapidly be classified. The most promising candidates are retained for experimental study as this is the only way of confirming the anti-cancer activity of the substance. A team at the CNRS - Université Strasbourg 1 is dedicated solely to this virtual screening technique.
Imagining the Therapies of the Future

Innovative Vector Strategies ...

Strategies using chemical engineering, physical chemistry or genetics could provide means of guiding drugs to their targets. The therapeutic effect of a biologically active molecule depends on its ability to cross the biological barriers between its site of administration and its site of action. Supra-molecular chemistry provides the basis for creating novel macromolecular complexes that contain the active substance (particle systems or assemblies resembling Lego® blocks). These will provide effective guidance to the site of action and release their active component at the appropriate moment.

Morphology of nanocapsules (a, b) and nanospheres (c) of polyalkylcyanoacrylate using electron microscopy. Images b and c are after cryofracture.

Nanotechnologies and Pharmacological Vectors

Scientists are trying to develop sub-micron particle systems (nanoparticles, liposomes) to transport drugs to their targets. After intra-vascular administration, these vectors are opsonized, that is, covered in proteins, and recognized by hepatic and splenic macrophages. Amongst other things, this particular distribution should allow hepatic metastases to be targeted. The specificity of the targeting provides a means of minimizing the toxic effects of some anticancer molecules. For example, doxorubicine can be transported by biodegradable polyalkylcyanocrylate-based nanoparticles and the cardiac toxicity of this anticancer drug is greatly reduced due to its increased concentration in the liver. Scientists are also developing ‘furtive’ nanoparticle systems, which, contrary to those mentioned above, are able to stay undetected by the liver or spleen and stay in circulation much longer.

Molecular Lego® for Future Drugs

Scientists at a CNRS – Université Joseph Fourier, laboratory in Grenoble are developing new guided designer molecules against cancer based on the principle of Lego®. Chemists are grafting bio molecules that have recognition roles (targeting) and efficacy functions (diagnosis and / or therapy) to cyclo-peptide molecular chasses under physiological conditions that do not change their chemical properties. The great modularity of this system provides a made-to-measure solution as either the guide molecule or the effective molecule can be changed. Using this technique it is possible to target neovascular endothelium (using integens \(\alpha_\text{v}\beta_3\)) so as to both detect neovascularised tumors and then destroy them. These systems are not only capable of selecting cells expressing a specific receptor but can use active endocytosis to cross biological barriers. They will be the first synthetic system that behaves in a similar way to proteins.

Targeting Angiostatin to Asphyxiate Tumors

A new therapeutic approach to cancers, anti-angiogenesis, means that we do not have to destroy the tumors themselves but simply block their growth by stopping the development of the blood vessels that nourish them. Scientists in a CNRS – Institut Gustave Roussy-Université Paris 11 laboratory have shown that transferring the gene that codes for angiostatin, a fragment of plasminogen, has considerable anti-cancer activity and inhibits the development of intra-tumorous blood vessels. A study has been performed in mice using an adenovirus vector to produce this factor in the tumor, resulting in local continuous production of the protein drug. Furthermore, the anti-cancer activity of this factor increases the efficacy of more conventional treatments such as radiotherapy or chemotherapy.
... for Targeting Tumors

Research for new anticancer therapeutic strategies must be interdisciplinary to be effective. In addition to chemical and biological methods, scientists are also investigating procedures that are more related to physics. One of these is the use of electric impulses that cause temporary pores to form in cell membranes that can help drugs to enter the cells. The same can be said for magnetic nanoparticles that are guided to the tumor and then spun by a magnetic field thereby increasing the temperature in the zone to be destroyed.

Electro-chemotherapy

When cells are subjected to very short electrical impulses of sufficient strength, their membrane undergoes reversible structural changes that cause an increase in its permeability. This electro-permeabilization allows molecules, such as drugs or nucleic acids, that do not normally cross the cell membrane, to enter the cell. This is the basis for electro-chemotherapy (ECT). A CNRS - Institut Gustave Roussy – Université Paris 11 laboratory, coordinator of the European ESOPE project is going to treat patients who suffer from cutaneous or sub-cutaneous nodules following breast, skin or ENT cancer. The treatment consists of administering intravenous or intratumoral chemotherapy (depending on the type of nodules being treated) followed by applying electrical impulses to the nodules using appropriate electrodes. The efficacy and tolerance of this technique has already been demonstrated in animals and man for the treatment of cutaneous and sub-cutaneous metastases. Improving this type of local treatment is more than ever a pressing issue because the better the degree of control of tumors in their early stages, the fewer later complications arise.

A Promising Route: Magnetic Hyperthermia

A magnetic liquid, or ferro-fluid, is a colloidal suspension of nanometric magnets in a transporting liquid. Under certain conditions, an alternating magnetic field can convert magnetic energy into heat. Each magnetic nanoparticle is a nanosource of potential heat. A CNRS and Université Paris 6 laboratory uses these properties to target tumors and for the controlled local release of drugs. The teams encapsulate an active molecule and magnetic nanoparticles in lipid spheres (liposomes). These magneto-liposomes are attracted to the tumor by externally applied magnets. The scientists are studying the possibility that when heated by the effect of the magnetic field, these magneto-liposomes will release their active molecule. The scientists are also engaged in another very promising direction that was provided by recent experiments on mice in Japan. These experiments have shown that after injecting magnetic nanoparticles into a tumor and exposing it to a radio-frequency magnetic field, the size of the tumor regressed whilst an identical tumor implanted on a control animal increased 8-fold in a few fortnights. Other experiments suggest that exposure to magnetic fields can cause an activation of the immune defenses against tumor cells which can lead to the destruction of metastases.
Research Applied to Radiotherapy

Treating cancers with radiotherapy uses tools and methods that are familiar to scientists and engineers in nuclear and particle physics. For example, the need for the accurate control of electron or ion beams is as important in physics experiments as when treating a patient. This is also true for measuring the beams to ensure greater precision in the dose administered. The use of new projectiles (for example, carbon ions) that are well known to accelerator constructors could significantly improve the treatment of some tumours.

Intensity Modulation for Better Precision in Irradiation ...

Cancer radiotherapy needs to be improved by developing increased precision in the irradiation to better destroy cancer cells whilst reducing the secondary effects of the treatment. Radiotherapy using intensity modulation aims to refine the contours of the zone getting the high dose of radiation so as to reduce the dose delivered to organs near the tumor. This involves the patient being exposed to several beams with directions and intensities that are finely adjusted. The virtual simulation and preparation for such a treatment currently requires half a day, which limits the number of patients that can benefit from it. A team in a CNRS laboratory is studying ways of improving the modelling system for dose delivery and to accelerate the calculation of treatments by using a new tool in information technology, the computer grid. Eventually, this will provide hospitals with unlimited calculation ability for all their computerized applications.

... and a Precise Measurement of the Dose Delivered

The complex techniques of radiotherapy by intensity modulation require a rigorous control of irradiation ballistics at the moment that the firing routes are defined (quality control) and a measurement of the dose received by the patient during the treatment’s application (in vivo measurements). A passive dosimeter using scintillating fiber optics has recently been developed in a CNRS – ENSI Caen laboratory for in vivo measurements of the doses delivered and will be commercially available in early 2004. Its reliability, precision and its high spatial resolution makes it a tool of choice as a dosimeter for modulated beams. A second piece of equipment, the Dosimap can characterize a radiotherapy beam in three-dimensions with a resolution in millimeters in only a few minutes. A commercial version should be available in early 2005.

An Innovative Project Using Hadron Therapy: Etoile

Etoile is the name of a proposed construction project for a medical center dedicated to the treatment of tumors by carbon ion beams produced by a synchrotron. More precise and more biologically effective than X-rays, carbon ions are characterized by a depot of energy that is higher at the end of their journey which means that healthy tissues upstream and downstream are less effected. Clinical results from Japan, since 1994, and Germany, since 1997, have shown their efficacy for treating inoperable cancers that resist conventional rays. If the construction is endorsed, Etoile could treat 1,000 patients per year. CNRS, along with the CEA and Claude Bernard University at Lyon, has contributed its scientific expertise and know-how in the construction of particle accelerators for the preparation of the technical feasibility study for Etoile. The consolidation of this project is ongoing and involves hospitals and the regions of Rhone-Alpes and Basse-Normandie.
Neutron Therapy

CNRS and the Regional Hospital Center teams at Orleans are a perfect illustration of the collaboration between fundamental research and anti-cancer therapy. In this example, the fundamental research supports clinical research as it studies the effects of boron atoms that capture thermal neutrons. This could lead to a sort of mini-bomb for cancer cells working on the scale of an atom.

Rapid Neutron Rays Against Cancer

Radiotherapy, either on its own or associated with surgery and/or chemotherapy provides high levels of control of solid tumors. There are 180 radiotherapy centers in France. Only Orleans has a rapid neutron beam system and 2,000 patients have already been treated with it. These special rays are useful for tumors that are resistant to photons, X-rays and gamma rays. So far, the best results involve tumors of the face (particularly salivary glands), osteosarcomas, soft tissue low grade sarcomas and localized prostate tumors. However, the vulnerability of nervous tissue means that this process cannot be used for glioblastomas, cerebral tumors with a particularly poor prognosis, unless it is possible to produce a differentiated effect at the cell level, that is to say, selectively deliver a significantly higher dose to tumor cells. Capturing neutrons with borium is an attempt to achieve this objective.

Perspective: an Intracellular Nuclear Reaction to Give an Extra Dose to Tumor Cells

The principal of potentiation consists of irradiating the area containing the tumor cells with rapid neutrons at a dose that is below the toxic level for the healthy cells surrounding the tumor and to provide a supplement in the tumor cells so as to provoke a nuclear reaction in them. A fraction of the rapid neutrons are slowed as they pass through tissue by multiple diffusions caused by protons in water. These inoffensive thermal neutrons are captured by $^{10}\text{B}$, a boron isotope. There then follows an ‘explosion’ of the new nucleus to produce an alpha ($\alpha$) particle and a lithium nucleus. These two particles are very destructive but have a journey of only a few micrometers: the size of a nucleus or a cell. If tumor cells can be made to absorb a drug containing $^{10}\text{B}$ and then irradiated with rapid neutrons, the thermal neutrons created will be captured by the boron. We can therefore deliver the additional dose required to kill them into the heart of tumor cells. Optimizing the parameters so that the greatest supplement possible can be obtained is the work of a CNRS team at Orleans, working in collaboration with the Regional Hospital Center. This very multidisciplinary work involves physicists, physical-chemists and physicians using different particle sources (cyclotrons at Orleans, Nice and Essen, heavy ion accelerator [grand accélérateur national d’ions lourds – GANIL], Laboratoire Léon Brillouin). The first basic studies are very encouraging.
The battle against cancer has symbolic importance for the public that goes beyond pure economic considerations, despite the considerable means that are deployed. CNRS is committed to do everything possible to ensure that innovation and technology transfer in this area are both efficient and ethical.

The campaign against cancer is a strategic axis for CNRS research and for a number of years it has been a focus for both human and budgetary resources. Nearly 150 patents have been submitted by CNRS during the last 10 years for inventions in the field of cancer. These patents, through about 20 licenses, have led to the development of new products or new therapeutic strategies. More than 130 million euros have been raised for research since 1994 by CNRS technology transfers.

As part of its mission to add value to research and to exchange technology, CNRS is involved in a voluntary program of transfer by and for commercial companies. At a simple level, this added value derives from partnerships with existing large and small companies that are responsible for exploiting the information discovered in CNRS laboratories. Two new anticancer therapies using molecules that were first synthesized by CNRS laboratories; Navelbine, a leading product for Laboratoires Pierre Fabre, and Taxotere®, a second tier product for Aventis Pharma, are drugs in current use. Other pharmaceutical products will soon be available.

Additionally, since a change in French law in July 1999, more than 140 companies have been created either directly or in collaboration with CNRS researchers. A number of them are directly involved in the campaign against cancer or are working on technologies that will almost certainly lead to opportunities in this field. The following examples show that both these companies and CNRS believe that increasing the value added by research is an important factor in the anticancer campaign.
CNRS Aiding in Direction of Innovative Companies

Through research partnerships or licensing agreements, CNRS enables the development of young companies where discoveries made in its laboratories find a privileged place for application and technology transfer.

Towards a Revolution in Medical Diagnosis

Mauna Kea Technologies (MKT) creates and produces in vivo cell imagery instruments for medical research or early diagnosis of major diseases such as cancer. This technology field, which is in full development, is called bio-photonics and will completely change medical diagnosis in the next few years. The MKT scientists plan future instruments that will use technologies and know-how currently used for astronomy. Observing stars or cells involves the same physical problems (weakness of signal, background noise, optic distortion by the media to be crossed ...) and similar technical solutions can be used. Collaboration with astro-physicists at the Observatoire de Paris-Meudon and CNRS has played an important role in the ongoing development of this technology.

Heavy Ions Against Deep Tumors

Nuclear physicists in the CNRS - Université Joseph Fourier Grenoble laboratory are developing multi-charged heavy ion sources so as to increase the energy available in particle accelerators. This process, called Electron Cytotron Resonance (ECR), has a medical use to solve the problems caused by the ionizing effects and lack of precision of protons which have been used for over thirty years for tumor therapy with very good results. Scientists have experimented on deep tumors using multi-charged heavy ions that have more energy and do not ionize tissue until the end of their journey, exactly where the tumor is. Excellent results have been obtained in this experimental phase – using a standard physics synchrotron as a source – and have convinced the company Pantechnik to develop and perfect the Supernanogan source.

An Approach to Genetic Cancer Treatments

GenOdyssee, a European company created in 1999 with the support of Génopole at Évry, CNRS and Inserm (all three shareholders via Génopole jour and FIST), develops products aimed at the immunotherapy of cancers using an approach involving genetic variability. Since the sequencing of the human genome, GenOdyssee scientists have worked to find variants of human therapeutic proteins that increase natural resistance to diseases. GenOdyssee has discovered and characterized natural variants of human alpha-interferon that show greater efficacy at inhibiting tumor growth and have less toxicity than the alpha 2a and 2b interferons that are currently available. First indications are that these candidate interferons provide an improvement to the current treatments for melanomas and renal cancers. Clinical trials are planned for 2004 and if successful will be extended to other immunogenic cancers, such as breast cancer.
CNRS Spin-off Companies Helping to Develop ...

Several CNRS scientists are, through their work, at the origin, creation and support of companies that are developing new therapeutic strategies. This involvement stems from their particular interest in seeing the fundamental discoveries made in their laboratories being rapidly available for patients.

Genomic Progress in the Fight Against Cancer

Cellectis was founded in December 1999 with patents shared by CNRS and Institut Pasteur. It is a biotechnology company that specializes in re-writing genomes - at will. They are developing innovative and unique technologies for using a particular enzyme group, the meganucleases. These enzymes are able to cut DNA in a very specific way, even inside a living cell. Cellectis is developing a recombinant system using meganucleases [meganuclease recombinant system - MRS] which makes it possible to re-program the genome of any living organism, from bacteria to man. The future for this technology is promising and has many applications such as pharmaceutical research, industrial biotechnology or agriculture. With genetic progress and the complete decoding of many genomes, including the human genome, the limiting factor for the use of this knowledge is the identification of the function of genes. The technique developed by Cellectis will allow us to remove a specific gene and thereby determine its function. For cancer, one can envisage identifying susceptibility genes or anticancer genes for certain cancers in normal tissue. In the longer term, we may be able to eliminate or change the genes involved in cancer and thereby increase the cells’ capacity to resist the development of cancer.

Stimulating an Immune Response to Cancer

Innate Pharma is a biopharmaceutical company founded in 1999 by four European scientists (two from CNRS) and two biotechnology managers. Innate Pharma is developing immuno-therapeutic anti-cancer products. This therapeutic strategy involves stimulating the immune system so as to start or increase the anti-cancer response. Innate Pharma is applying a new immunotherapy strategy that targets populations of non-conventional lymphocytes (NK cells, T gamma delta lymphocytes and NKT lymphocytes) that function at the borders between acquired and innate immunity. During the 1990’s, the Innate scientists contributed greatly to a number of scientific advances that resulted in our knowledge changing from a cellular description to a molecular understanding of these lymphocyte populations and which opened the way for targeted pharmacological interventions. Innate Pharma currently has three products in development: a small injectable molecule that specifically activates T gamma9-delta2 lymphocytes [Phosphostim™], a cell therapy procedure used ex vivo with the same component [Innacell™] and an antibody intended to treat a minor indication in cancer [Kiromab™]. Two of these products are in phase I clinical trials for cancer treatment [Innacell™ and Phosphostim™]. Additionally, Innate Pharma possesses intellectual property for second-generation immuno-modulators targeting NK cells. One of these products is part of a commercial collaboration with Novo Nordisk, a Danish pharmaceutical company that is world leader in diabetes and therapeutic proteins.
... New Therapeutic Approaches

These companies use the intellectual property developed by public research and become significant partners of the laboratories through new research collaborations that provide mutual enrichment.

A Micro-laboratory to Control Protein Degradation

The processes of protein degradation play a fundamental role in cell life. Their dysfunction can lead to the undesirable accumulation of proteins in tissues and this event is the origin of genetic diseases and numerous pathological conditions: cancers, neuro-degenerative disorders or chronic inflammatory syndromes. The company Cytomics Systems was born as a result of this observation and several founding members are scientists at CNRS. Its principal mission is to discover and develop molecules that, by controlling protein degradation, could become treatments in the future. This research for potential treatments is based on an innovative concept developed by Cytomics Systems, the Yeast Micro-Lab. This technology combines the use of genetically modified yeast cells, real micro laboratories where the degradation mechanisms for human proteins are reconstituted, with highly sensitive fluorescence measuring techniques. The Yeast Micro-Lab can be used as a high volume screening system when integrated in an automated chain. Cytomic Systems first research and development programs opened up the route to the discovery of new highly specific molecules targeting fungal infections, inflammatory diseases and some types of cancers. After a promising beginning in a start-up incubator (IFSI), the company completed a first round of fund-raising in the first quarter of 2003 that has enabled it to recruit staff and move to a new laboratory on the CNRS campus at Gif-sur-Yvette.

Protein Interactions as Therapeutic Targets

Scientists at CNRS, Institut Pasteur and Institut Curie have worked together to perfect a new technological approach that they are exploiting with the creation of Hybrigenics. This biotechnology company, specialized in functional proteomics, uses the double hybrid technique on a large scale to identify protein-protein interactions and to define functional protein networks in different cell types and under different physiological conditions. Knowledge of the protein networks means that therapeutic targets can be characterized and the ability of chemical products to inhibit or activate certain interactions between specific proteins can be tested.

Hybrigenics has developed automatic screening platforms combining biological experiments and the virtual data originating from bioinformatics. This automation has helped identify and map a large number of interactions between proteins. These maps are useful not only for clarifying the process of oncogenesis but also to help identify, select and confirm therapeutic targets and their corresponding ligands.

The Hybrigenics strategy is to use these platforms on an industrial scale to advance bio-marker identification programs and the development of chemical molecules with therapeutic potential that are isolated by the screening. Within this framework, Hybrigenics works in close collaboration with CNRS, INSERM, French and foreign universities and with the pharmaceutical and biotechnology industries.
The relationships between biomedical, health and social sciences are undergoing significant changes. Clear examples of this are our longer life expectancy, greater technical ability and increased efficiency in medicine with its rising costs. Our society is confronted with new questions concerning disease prevention, the care of the sick and their consequences. Cancer is symbolic of our hopes and fears in the face of scientific progress because of its prevalence, the extraordinary amount of research effort dedicated to trying to control it and its status as a disease of our times. Furthermore, it makes us confront disease, pain and death in our personal and social daily lives. This makes it an ideal subject for research in human and social sciences calling for a specific theoretical approach from all disciplines (sociology, anthropology, history, law and economy) and requiring the development of inter-disciplinary analysis abilities. The overall complexity of cancer with its biological, human and social aspects reinforces the need for life sciences to collaborate closely with human and social sciences.

The advances in our knowledge aimed at improving diagnosis and imagining for the therapies of the future have been discussed earlier. Underpinning these advances is a change in how scientists work (more cooperation and multidisciplinary teams, mixing basic research and industry), a change in the practice of medicine (medical practitioners mastering and perfecting new concepts and tools that are far removed from the traditional clinical practice) along with changes in how we are ill (potential patient due to predictive medicine, chronic patient alternating between relapses and phases where the cancer is controlled). Human and social sciences need to help us understand these situations by trying to make our world – where we live and which we help to build – more intelligible. They are there not simply to shed light on the human and cultural aspects of the disease but also to produce knowledge about how we should confront cancer.
Human and Social Sciences and Cancer

Cancer is a multidisciplinary subject for human and social sciences. The relevant distinctions are mainly in terms of analytical scales and methods. Four axes orient current research, some of which are being developed within a joint biomedical, health and social sciences program – [Sciences bio-médicales, santé et société – CNRS – Inserm – MiRe].

Cancer and Health Systems

Research conducted by CNRS at the macro-social level concerns the constitution, the transformation and the organization of local and national policies on cancer and their different developments from screening to making innovations available. Problems of allocation and distribution of resources, unequal access to care, economic and political choices, new regulations, economic, professional, legal and ethical standards, and the tools and institutions linked to their management are dealt with.

Cancer Management and Treatment Practices

Developments in cancer (screening, acute treatments, phases between interventional and palliative care) cause deep transformations in the care teams, the patient and their entourage. The research questions that CNRS is helping to answer are those of how management of the patient is restructured (nearness of the network, continuity of care), of the appearance of new participants in hospitals and at the heart of the teams (general practitioners, independent nurses and volunteers), of the evaluation of therapeutic practices, of making difficult decisions including sharing both the responsibility and the ethical issues that accompany them, and, more recently, of the transformation of the notion of cancer risk (preventive strategies and innovative therapeutics).

Cancer, Research and Innovations

As part of the practice of experimentation and medical know-how there is the study of clinical trials and their transformations as well as the problems posed by the need for disease - including genetic modeling. Questions related to industry, production and gathering of knowledge are dealt with by CNRS by examining research systems (public-private relationships, open science), the question of patents and adding value to knowledge. Finally, there is a renewal of the questions about innovation and new drug usage.

Cancer and the Sick

The questions in this area range from the individual to the policies. Centered on an analysis of different ways of experiencing disease, CNRS examines problems relating to maintenance and changes of personal and group identity, the ‘live with it’ attitude, the self-support concept and the provision of information. More generally, the question of patients as participants in the health system is studied as a result of the appearance and organization of associations of patients, of their roles and the consequences of their actions, as much at the level of society (patient’s rights, health democracy ...) as at the level of the individual patient’s experience of the disease.
Faced with a disease that kills more than 150,000 people in France each year, the French government has launched a national action plan against cancer. Whilst research is only one of its many components, it is clearly mentioned as the 'hope for cancer patients'.

This hope depends on having a detailed and fundamental knowledge of all the molecular and cellular mechanisms that are involved in oncogenesis, which is the only way of developing an objective basis for conceiving targeted and personalized therapies. It also depends on our ability to continue to revolutionize investigation and treatment techniques through an indispensable interdisciplinary collaboration. One of the main issues in the campaign against cancer is prevention and this also requires great synergy between scientific competences, techniques, teaching and the institutions to achieve an effective reduction in the cancer risks caused by our behavior and the environment.

At the heart of a targeted action plan (reduce mortality due to cancer by 20% in France within 5 years), the objective expected from research is to convert knowledge into therapeutic applications that directly benefit patients as rapidly as possible. Clinical and therapeutic researches are not intrinsically part of the CNRS’ work. However, the ‘patient’, the driving force behind all biomedical research, is never far from the preoccupations of CNRS. In fact, at the source of the real clinical work at the bedside, CNRS trademark is preventive and therapeutic research with multiple projects and a multidisciplinary approach. With its eight scientific divisions, it is only institution in France that can claim to have the required diversity of competences to make the future advances in clinical cancer research. It is thus a privileged partner of those intervening directly in public health. That said CNRS has proven that, in addition to its involvement in medicine for the future, it is very much involved in the challenges facing medicine today and the battle against the medical and social scourge of cancer is top of this list.

Due to the size of the challenges and what is required in terms of knowledge, innovation and social organization, reducing the incidence and mortality due to cancer can be considered a sort of essential evolution in our relationship with the world and each other.
A Few Indicators:

- More than half the research teams recognized by the National League against cancer are teams associated with CNRS.
- More than 10% of published papers on cancer in France come from CNRS.
- 14 authors affiliated with CNRS are present amongst the 10% of authors the most cited in articles on cancer (source ESI: Essential Science Indicators).
- 15 files or inventions have led to 19 commercial licenses that have generated more than 170 million euros of royalties since 1994.
- 96 teams within 69 units of the Life Sciences department of CNRS claim to be involved in the area of cancer research; their consolidated budget is 50 million euros.
- 25 laboratories in the CNRS Chemical Sciences department conduct studies in this area.
- Nearly 90% of the royalties received by CNRS come from the major anti-cancer medicaments Navelbine® and Taxotere®.