

CANCEROLOGY

2010

This booklet « Cancerology » has been implemented by the Research Administrations of the Académie universitaire Louvain (FUCAM, FUNDP and UCL) with the precious help of a reading committee composed of Professors O. Feron (UCL - Angiogenesis and Cancer Research Laboratory, IREC - Institute of Experimental and Clinical Research), B. Flamion (FUNDP - College of Medicine), B. Gallez (UCL - Laboratory of Biomedical Magnetic Resonance, LDRI - Louvain Drug Research Institute), M. Hamoir (UCL - St Luc Cancer Center) and C. Michiels (FUNDP - Cellular Biology Unit).

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Cover: human chromosomes, National Cancer Institute-The Cancer Genome Atlas. <http://cancergenome.nih.gov>

Foreword

The main objective of this document is to highlight the excellent level of research in cancerology within the Académie universitaire Louvain in order to promote synergies, to enrich existing partnerships and generate new ones. It also aims at supporting industrial innovation by raising industrial awareness of university competencies in cancerology and, *in fine*, improving the quality of health care.

In addition to being an important public health issue, cancer is a complex pathology the study of which requires the collaboration of all scientific disciplines. The approach to cancer diseases involves multidisciplinary teams to deal with complex sequences of research and care: diagnostic, surgery, drug therapy, radiotherapy, rehabilitation, psychological support...

The level of international cooperation already in place in the research teams within the Académie universitaire Louvain will be obvious from this booklet, which presents their research topics, recent achievements and current developments. These topics are classified in ten categories, according to the main scientific or technological approach.

The last part gathers different research centers and non-profit organizations established within the Académie universitaire Louvain and devoted to cancer research.

- ▶ Prevention and epidemiology
- ▶ Mechanisms of cancer
- ▶ Diagnostic – Imaging
- ▶ Immunology – Genetics
- ▶ Biomarker
- ▶ Clinical study
- ▶ Anti-cancer treatment
- ▶ Surgery
- ▶ Radiotherapy
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K.3 - The Brussels Branch of the Ludwig Institute for Cancer Research

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Fertility preservation for cancer patients: Cryobanking and transplantation of reproductive tissues

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- ▶ Jean-Luc SQUIFFLET
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- ▶ Dominique DEMYLLE
- ▶ Christiani AMORIM
- ▶ Anne VAN LANGENDONCKT

Research Field and Subjects

CRYOPRESERVATION AND TRANSPLANTATION OF OVARIAN TISSUE

For women who are to undergo chemotherapy or radiotherapy, the loss of ovarian function will result in premature menopause and loss of fertility. The storage of ovarian tissue provides a means of restoring long-term fertility in such patients. We performed the first successful transplantation of cryopreserved ovarian tissue in a woman who had previously received chemotherapy for Hodgkin's disease.

During the last ten years, we have set up a bank including ovarian tissue from 340 patients undergoing treatment that may irreversibly damage the oocyte population.

After thawing, primordial follicles enclosed in ovarian tissue need to reach the antral stage in order to obtain mature oocytes that can be fertilized. Two approaches are implemented in our laboratory to achieve this maturation step: in vitro culture of ovarian tissue and transplantation of human ovarian cortical slices or isolated follicles.

Three main projects are currently under way:

1. The aim of our first project is to optimize grafting conditions for human ovarian tissue. For this purpose, an experimental model was set up in immunodeficient mice allowing us to test the site of transplantation, the size of the graft, the factors promoting the revascularization of the graft and the treatment required to sustain follicle growth after transplantation.
2. Our second project is designed to optimize cryopreservation protocols for ovarian fragments and entire ovaries.
3. Another main project consists in the development of a scaffold for the grafting of isolated human follicles and the support of their growth.

MALE FERTILITY PRESERVATION AFTER GONADOTOXIC TREATMENT

Aggressive chemotherapy and radiotherapy can severely affect male germ cells and lead to permanent loss of fertility. Cryopreservation of immature testicular tissue either in the form of a cell suspension or whole pieces of tissue is the only way of preserving fertility in prepubertal boys. Our experimental project focuses on the development of an appropriate cryopreservation protocol for immature testicular tissue, allowing survival and functioning of

spermatogonia and somatic cells. In order to evaluate tissue and cell functionality after freezing and thawing, we developed an orthotopic xenografting model in immunodeficient mice and an in vitro culture system for testicular explants. The xenografting model will be implemented to optimize transplantation conditions for human immature testicular tissue with a view to clinical implementation of autografting of stored tissue.

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Patent

European Patent Application n° 07117661.4-1219 : « Scaffolds for follicle transplantation », C. ANDRADE AMORIM, M.M. DOLMANS, A. VAN LANGENDONCKT, J. DONNEZ

Partnership

- ▶ Inter-university: Ulg, ULB & UCL.
- ▶ CERM Ulg
- ▶ VUB : PROF SMITZ , Follicle Development Unit

Funding

- ▶ Mécénats
- ▶ FNRS
- ▶ Fondation contre le Cancer, Fondation Saint Luc

Main Equipment

- ▶ Programmable freezers
- ▶ Liquid nitrogen tanks
- ▶ Facilities for cell, follicle and embryo culture
- ▶ Tissue chopper

Products and Services

- ▶ Ovarian and testicular tissue cryobanking
- ▶ Experimental transplantation in nude mice and rats
- ▶ Evaluation of neoangiogenesis

KEY WORDS FOR R&D

Cryopreservation
Transplantation
Fertility preservation
Post-chemotherapy
Follicle isolation
Artificial ovary
Scaffold
Ovarian tissue
Testicular tissue
Follicle isolation

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Methodological support in epidemiology and biostatistics applied to research in cancer

SENIOR SCIENTIST :

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Research Field and Subjects

Epidemiology and biostatistics can be applied to cancer research especially in the study of cancer incidence by products or in the estimation of anticancer drugs efficiency.

► **Cancer incidence and mortality among cohorts of pesticides producing workers, etc.**

Epidemiological studies are conducted in order to assess if there is an excess of cancer cases in current and ex-workers from a plant and to identify workplace exposures which may explain such a demonstrated excess.

Vital- and cancer status according to the ICD10 codes (international classification of diseases) are established for all workers, and life table analyses are conducted, using the Belgian mortality and the regional (Flanders, French community) registry of cancers.

Age- and sex standardised mortality (SMR) and incidence (SIR) ratios are stratified by duration of employment, job title, time since first employment, and time between the end of the job at the plant for workers who left the plant. These occupational data are used as latency- and intensity surrogates for testing the hypothesis of a relationship between occupational exposure and cancer development.

► **Progression-free survival in solid tumors: qualities of estimators of clinical efficiency and inefficiency for designing Phase II trials.**

Phase II trials play a key role in the development of new potential anticancer drugs because they are crucial in deciding whether or not proceeding to a phase III trial.

Phase II trials are conducted in order to assess the clinical efficiency (P1) or the clinical inefficiency (P0) of new treatments. The number of patients enrolled in a phase II trial closely depends on P0 and P1 values. An underestimation of P1 can lead to rejection of an active treatment and an overestimation of P0 can lead to keep a useless treatment. The classical definition of P0 and P1 is based on death rates because mortality is an objective measure of response to therapy. Recent developments in anticancer

agents are however oriented to antitumoral drugs, and consequently call for a new definition of early response to therapy, taking into account a decrease in the size of cancer lesions or a stabilization of disease.

“Progression-free survival” and “Time to progression” are valuable alternative definitions of response to treatment, since a recent harmonization of guidelines has been proposed to assess the progression of cancer in solid tumors (RECIST *Therasse P. and al. J. Nat. Cancer Inst. 2000, 92:205*). Progression-free survival can be estimated using retrospective analyses of phase III trials, in order to derive P0 and P1 values. Such analysis has been done for soft tissue sarcomas (*Van Glabbeke and al. Eur. J. Cancer 2002, 38:543-549*). We plan to extend those analyses to other solid tumors such as lung cancers, bladder cancers, or breast cancers.

Efficiency and inefficiency estimations derived from such analyses may be sensitive to loss-to-follow data, to left rather than right censored data, or to variations in the cancer progression assessment. Sensitivity analyses will be conducted, together with the consequences on size computations in designing phase II trials.

► **Ultrasound-based cancer detection technique: modeling of raw data and determining its place in clinical management of ovarian cancers**

In Belgium the incidence rate of ovarian cancer in 2002 was of 20.5 per 100000 (for Western Europe 18.9 per 100000³). With a mortality rate of ovarian cancer in 2002 of 15.3 per 100000³ (Western Europe 13 per 100000³), it can be seen that ovarian cancer has high mortality rates. This is merely due to the anatomical position of the ovaries which often leads to late detection of the cancer when it has already progressed to an advanced stage. In addition, the poor survival is leading to an approach of prudence which results in surgical removal of the ovaries because of an abnormal image at ultrasound, while in fact there is no cancer.

Because of its non-invasive and radiation free nature, its relatively low-priced and easy operation, ultrasound imaging may prove to be a valuable tool for cancer detection.

A new software technology (from a Belgian company) can be used as an add-on to ultrasound imaging and can improve the use of ultrasound imaging for diagnosis and detection of soft-tissue cancers. The new software technology targets women with symptoms. In this group of women, the software aims at detecting ovarian cancer. As a consequence, better disease management is expected.

Ultrasonic acquisition is typically based on the transmission, and backscattering of ultrasonic pressure waves that propagate through the human body. The use of the statistics of the back-scattered signal for the identification, characterization and classification of different tissues is justified by the random nature of the ultrasound echoes.

We therefore investigate the ultrasonic backscattered waves. The statistical nature of the scatterers are considered in terms of distributions in order to derive a model that might characterize the data.

Our team also investigates the clinical and economical advantages of using the new software technology as a part of the existing diagnostic protocols (clinical surveillance method, estimation of the health effects and resource costs, Model of Natural history of ovarian cancer, predictions, decision tree and decision analytical models, and comparison with the analysis of the clinical trials outcomes and date).

Products and Services

- ▶ Support for protocol design
- ▶ Data analysis and publications of results on a contractual basis.

Main Equipment

Statistical and Epidemiological softwares: BMDP, The SAS System, SPSS, Splus, EPLinfo, EPICURE.

Funding

- ▶ Industry
- ▶ Occupational health services
- ▶ Competitive research funds

Partnership

European Organization for Research and Treatment of Cancer (EORTC).

KEY WORDS FOR R&D

Applied statistics
Clinical trials
Drug evaluation
Epidemiology
Health- and medical statistics
Occupational medicine
Preventive medicine
Pharmacotherapy

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Study of the endoplasmic stress response mechanisms in multiple myeloma

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Research Field and Subjects

Using a sensitive proteomic approach, the aim of this project is to get a molecular signature from multiple myeloma cells isolated from urine/blood in order to characterize soluble and membranous proteins and their putative processing such as « shedding ».

The expected results will help to set up new diagnostic assays to characterize these cancer cell types according evolution as well as to determine molecular markers to follow patient treatments. The study will also evaluate the effects of proteasome inhibitors (Velcade®) or ER stressing molecules on apoptotic and autophagic multiple myeloma cell responses to better delineate cell resistance to drug adjustment/adaptation.

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Funding

Télévie – FNRS

Partnership

Prof. G. BERCHEM, Dr V. PALISSOT. RP-Santé Luxembourg

Main Equipment

Proteomics facilities, Imaging technology (Confocal Microscopy)

Products and Services

Proteomic analyses, identification of molecular signature

KEY WORDS FOR R&D

Cancerology
Myeloma
Cell death
Signal transduction
Proteomics
Apoptosis
Autophagy

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Oxidative stress and cancer cell death

SENIOR SCIENTISTS :

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- ▶ Julien VERRAX

Research Field and Subjects

Due to oncogenic stimulation and high metabolic rates, cancer cells exhibit high levels of reactive oxygen species (ROS) that stimulate cell proliferation and promote genetic instability. Such a biochemical difference between transformed and non-transformed cells represents a redox vulnerability of malignant cells that can be targeted by chemotherapeutic intervention using redox modulators. Since cancer cells usually lack antioxidant enzymes, we hypothesize that their selective exposure to an oxidative stress, induced by the combination between pharmacologic doses of ascorbate and a redox-active quinone (menadione), will kill tumour cells. Ascorbate plays a key role because it is preferentially taken up by cancer cells, which favours the in situ formation of ROS. In addition, such an oxidative stress affects the chaperoning function of heat shock protein 90 (Hsp90). Since the stability of several proteins (like Bcr-Abl, Akt, RIP,...) that are essential for malignant transformation, is made possible by Hsp90, its inhibition represents an interesting target for cancer therapies. We have recently reported that an oxidative stress affects hsp90 activity, inducing both degradation of its client proteins and cancer cell death. Given the major role of hsp90 in cancer cell survival, we anticipate that such an approach may have potential clinical applications. In addition to the study about the role of hsp90 cleavage on Bcr-Abl degradation and the subsequent leukemia cell death, two additional subjects are currently under study. They include:

- a) The mechanism involved in the activation of Nrf2 and the acquisition of cancer cell resistance to chemo-therapy;
- b) Calcium homeostasis and ER stress in cell death by autophagy during an oxidant injury.

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Funding

- ▶ FNRS-FRSM-TÉLÉVIE-FRIA
- ▶ Région Wallonne
- ▶ FSR

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- ▶ JACQUES PIETTE (U. Liège, Belgium)
- ▶ ROZANGELA CURI (U. Santa Catarina, Brazil)
- ▶ JULIO BENITES (U. Arturo Prat, Iquique, Chile)

Main Equipment

- ▶ Fluorescence and light microscopes
- ▶ Western blot
- ▶ Cell culture
- ▶ Ultracentrifuge
- ▶ HPLC
- ▶ Luminometer/fluorimeter

Products and Services

Expertise in cell death analysis

KEY WORDS FOR R&D

Apoptosis
Autophagy
Bcr-Abl
Cancer
Cell death
ER stress
Hsp90
Leukemia
Menadione
Oxidative stress
Vitamin C

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Pathologic activation of tyrosine kinases in leukemia and myeloproliferative neoplasms

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- ▶ Stefan N. CONSTANTINESCU
- ▶ Jean-Christophe RENAULD
- ▶ Jean-Baptiste DEMOULIN

Research Field and Subjects

Hematopoietic growth factors bind to receptors which signal through JAK kinases and STAT transcription factors, leading to cell survival, proliferation and differentiation. Researchers at the De Duve Institute have identified a number of alterations of this pathway that lead to hematopoietic cell transformation. They initially showed that an autocrine loop involving interleukin-9 can favor the development of lymphoma. They contributed to the discovery of the JAK2 V617F mutation in human myeloproliferative neoplasms and of mutations in TYK2 or in JAK1, the latter being involved in adult T cell leukemias. These mutations activate STATs and other pathways in the absence of receptor ligand interaction. It was also shown that mutations in cytokine receptors or overexpression of JAK kinases can lead to cell transformation. Chromosomal translocations involving receptor tyrosine kinases, such as PDGF receptors in myeloproliferative neoplasms, are also studied. In each case, the detailed mechanisms leading to cell transformation have been analyzed *in vitro* and *in vivo*, pointing to the key role of the STAT factors. The identification of novel alterations is pursued using classical molecular biology, sequencing and microarrays. These findings are opening new avenues for the therapy of these diseases.

Representative References

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Awards

- ▶ J.-C. RENAULD: Interbrew-Baillet-Latour
- ▶ Health Prize, 2000
- ▶ Prix Pfizer, 2008

Funding

- ▶ FNRS, Actions de Recherches Concertées, Région Wallonne
- ▶ Fondation contre le Cancer, Fondation Salus Sanguinis
- ▶ Ludwig Institute for Cancer Research
- ▶ European commission
- ▶ NIH

Partnership

- ▶ Ludwig Institute for Cancer Research
- ▶ Hematology unit, Cliniques universitaires Saint-Luc

Main Equipment

Microarray technology

Products and Services

- ▶ Microarray hybridization
- ▶ Bioinformatics for microarray data analysis
- ▶ Identification of novel genetic alterations from patient samples
- ▶ Signal transduction assays

KEY WORDS FOR R&D

JAK
STAT
Cytokine
Growth factor
Receptors
Signal transduction
Polycythemia vera
Interleukin

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Are type I MAGE genes involved in tumorigenesis ?

SENIOR SCIENTIST :

▶ Olivier DE BACKER

Research Field and Subjects

The MAGE genes of type I have been identified in 1991 by the team of Thierry Boon at the Brussels's branch of the Ludwig Institute for Cancer Research. These genes are well known because they specify tumor-specific antigens targeted in cancer immunotherapy. The type I MAGE genes are completely silent in most somatic tissues, but are ectopically expressed in a significant fraction of tumors of different histotypes (melanomas, gastro-intestinal, lung, prostate, breast, bladder, neuroblastomas ...). However, the function of the MAGE proteins and the role they could play in tumor development remain largely to be elucidated. One of our ongoing projects is to unravel the role of the type I MAGE proteins in tumorigenesis, by forcing their ectopic expression in transfected cells and in transgenic mice.

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- ▶ A. LORIOT, C. STERPIN, O. DE BACKER, AND C. DE SMET. *Mouse embryonic stem cells induce targeted DNA demethylation within human MAGE-A1 transgenes* Epigenetics. 3 38-42, **2008**.

Patents

- ▶ VAN DEN EYNDE, DE BACKER, BOON-FALLEUR. Isolated peptides derived from tumor rejection antigens, and their use. US 5,648,226, 1997.
- ▶ VAN DER BRUGGEN, VAN DEN EYNDE, DE BACKER, BOON-FALLEUR. Isolated peptides derived from the GAGE tumor rejection antigen precursor and uses thereof. US 5,858,689, 1999.
- ▶ DE BACKER, VAN DEN EYNDE, BOON-FALLEUR. Isolated, nucleic acid molecules which code for GAGE tumor rejection antigen, the tumor rejection antigen, and uses thereof. US 6,013,481, 2000.

Partnership

- ▶ B. VAN DEN EYNDE (Ludwig Institute for Cancer Research)
- ▶ T. BOON-FALLEUR (UCL)
- ▶ P. VAN DER BRUGGEN (UCL)

Funding

- ▶ FRFC
- ▶ FRSM
- ▶ FSR

Main Equipment

ABI 3130 Genetic Analyzer

Products and Services

Manipulation of mouse ES cells

KEY WORDS FOR R&D

MAGE gene
ES cells
Transgenic mice

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Genetic and Epigenetic Alterations of the Genome

SENIOR SCIENTISTS :

- ▶ Anabelle DECOTTIGNIES
- ▶ Charles DE SMET

Research Field and Subjects

Preservation and regulation of genetic information is essential for proper cell function. Consequently, cells have evolved mechanisms of telomere maintenance, DNA repair and epigenetic regulation which defines heritable gene expression patterns. These processes are functionally linked and converge on chromatin, the complex structure formed by DNA and proteins, in the nucleus of eukaryotic cells.

Deregulation of these processes contributes to the appearance and progression of cancer cells, which are characterized by genomic rearrangements and dysregulated gene expression patterns.

1. DNA damage repair in fission yeast *S. pombe*

DNA repair processes have been well conserved throughout evolution, and yeast has proven to be a good model for their study. We use *S. pombe* to dissect the mechanisms of DNA double-strand break repair, a type of genetic lesion arising after exposure to genotoxic agents or during DNA replication. We focus on improper DSB repair resulting from either deletion or insertion of nucleotides at the repair junction.

2. Mechanisms of telomere maintenance

Telomeres are specialized protein-DNA structures, which prevent chromosome ends from being recognized as DNA double-strand breaks. Synthesis of telomeric DNA sequences in replicating cells requires telomerase. Cancer cells often show an increased level of telomerase, and this contributes to their unlimited proliferation potential. Certain tumor cells however lack telomerase, and rely on an alternative mechanism (ALT) to maintain their telomeres. We are comparing telomerase-positive and -negative human cell lines to get more insight into the ALT mechanism and to dissect the "non-canonical" functions of telomerase that are not directly related to telomere repeat addition but modulate cellular gene expression. We are also interested in studying the role of subtelomeric DNA methylation in the maintenance of telomeres.

3. DNA hypomethylation and aberrant gene activation in cancer
DNA methylation is an essential mechanism of epigenetic regulation. It is associated with gene repression. Virtually all tumor

cells show genome-wide loss of DNA methylation. We have found that this alteration results in the activation of a set of genes, which are normally restricted to the germ line. We are currently investigating the mechanisms targeting DNA demethylation towards these "cancer-germline" genes in tumor cells.

4. Setting of DNA methylation patterns in embryonic stem cells
Embryonic stem cells are characterized by a remarkable epigenetic plasticity. The processes underlying the setting of DNA methylation patterns in these cells are studied, with a particular emphasis on cancer-germline gene promoters.

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Funding

- ▶ Fonds National de la Recherche Scientifique
- ▶ Fondation Contre le Cancer
- ▶ Région bruxelloise (Life Science Impulse)

Partnership

“Brubreast: Development of diagnostic and therapeutic tools for the optimal management of the individual breast cancer patient” (Région de Bruxelles-Capitale); C. SOTIRIOU (IJB-ULB), F. FUKS (Erasme-ULB), J. DE GRÈVE (UZ-VUB)

Products and Services

- ▶ DNA methylation analyses (sodium bisulfite sequencing and MS-PCR)
- ▶ FISH and CO-FISH (detection of telomeric sister chromatid exchanges) on telomeres
- ▶ Detection of telomerase activity in cell extracts by the TRAP assay
- ▶ Extrachromosomal DSB repair assay in yeast

KEY WORDS FOR R&D

Telomeres
Telomerase and alternative lengthening of telomeres
Genomic stability
Gene expression
DNA repair
DNA methylation
Stem cells
Cancer-germline genes

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Identification of genes involved in hypoxia-induced metastasis, using statistical and bioinformatics analysis of DNA array data, and confirmation of their differential expression in in vitro et in vivo models

SENIOR SCIENTISTS :

- ▶ Eric DEPIEREUX
- ▶ Carine MICHIELS

Research Field and Subjects

One of the major causes of death by cancer is metastasis. Determining mechanisms of production and development of metastases should thus improve diagnostic and therapy. However, the cellular mechanisms to invade surrounding tissues, detach from primary tumor, migrate and colonize distant organs are very complex and regulated by different signalling pathways. Hypoxia is a key feature of the tumor microenvironment that greatly influence cancer cell metabolism and aggressiveness. Moreover, changes in gene expression induced in hypoxia and leading to a migratory and invasive phenotype of tumor cells have been highlighted.

In order to define new regulatory pathways that influence cell migratory and invasive phenotype and to find new genes induced by hypoxia enabling cancer cells to metastasize, we are re-analysing several DNA microarray datasets from the public field, that are related to metastasis and/or hypoxia. Our methodology combines published well-known steps from classical analysis with new approaches developed in our laboratory to analyze several datasets at once. The existence of numerous methods and of an evolving methodology, combined with the observation of unstable results, offers an attractive challenge made possible by the emergence of public databases such as Gene Expression Omnibus (GEO) and ArrayExpress which collects millions of expression data. Datasets can be reanalysed from scratch with new parameters (e.a. alternative CDFs) and by combining several datasets relative to a same biological question in a same analysis. Data mining and gene ontology analysis will lead to the identification of candidate genes that may be involved in regulating cancer cell metastasis under hypoxic conditions. In vitro validation will be performed, first to confirm differential expression and then to characterize their role in this process.

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protection against etoposide-induced apoptosis: molecular profiling of changes in gene expression and transcription factor activity. Mol Cancer 7, 27, **2008**.

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Funding

TÉLÉVIE

Partnership

- ▶ BioXpr
- ▶ GSK

Main Equipment

- ▶ Cell culture facilities, hypoxic chambers
- ▶ General equipment for biochemical and molecular biology assays
- ▶ Absorbance, fluorescence, luminescence microplate readers
- ▶ real-time PCR, equipped for microfluidic cards
- ▶ Full proteomic platform with Maldi and MS-MS mass spectrometers
- ▶ Confocal microscope
- ▶ Computing cluster

Products and Services

- ▶ DNA microarray data analysis
- ▶ Cellular models for the evaluation of the capacity of drugs to induce apoptosis and/or autophagy, to influence cell migration
- ▶ Proteomic platform

KEY WORDS FOR R&D

Hypoxia
Chemotherapy
Apoptosis
Microarray
Autophagy
Resistance
Signal transduction
Gene expression

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Mechanisms of p53-dependent apoptosis

SENIOR SCIENTIST :

▶ Patrick DUMONT

Research Field and Subjects

The tumor suppressor p53 carries the distinction of being the most frequently mutated gene in human cancer, with an overall mutation rate over 50%. As a transcription factor, p53 has the ability to induce or repress the expression of a variety of genes which products have respectively a pro-apoptotic (NOXA, PUMA, KILLER, ...) or a pro-survival (MDR1, SURVIVIN, ...) function. In addition to this well-known role of p53, we and others have described that, upon apoptosis induction, a fraction of p53 translocates to the mitochondria where it exerts a pro-apoptotic function by acting analogously to "activating" BH3-only proteins. Mitochondrial p53 is able to interact with BAK, to induce its oligomerization at the outer mitochondrial membrane and therefore can trigger the release of the mitochondrial effectors of apoptosis, such as cytochrome c, from the intermembrane space into the cytoplasm.

Our main aim is to decipher this pathway of p53-mediated apoptosis. We are interested at determining what post-translational modifications of p53 are required for or influential to its mitochondrial trafficking and pro-apoptotic activity at the mitochondria. We are also characterizing new interactions between p53 and mitochondrial proteins and analyzing their role in this pathway.

Representative References

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N-([2-[2-(dimethylamino)ethyl]-1,3-dioxo-2,3-dihydro-1H-benzo[de]isoquinolin-5-yl]carbonyl)acetamide (UNBS3157), a novel nonhematotoxic naphthalimide derivative with potent antitumor activity. J. Med. Chem. 50, 4122-4134, **2007**.

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Awards

- ▶ The 2000-2001 René de Cooman Award (Belgium)
- ▶ The 2002 Edward David Lustbader Award (USA)
- ▶ The 2003 FCCC Board of Associates Fellowship (USA)
- ▶ The 2004 Edward David Lustbader Award (USA)

Partnership

Collaboration with Professor M.E. MURPHY, Fox Chase Cancer Center, Philadelphia, USA

Main Equipment

Regular cellular and molecular biology

Products and Services

- ▶ Establishment of stable (inducible or not) cell lines (over-expression and knock-down)
- ▶ Generation of resistant cell lines
- ▶ In vitro and cell based models for characterizing the pro-apoptotic activity of molecules.

KEY WORDS FOR R&D

Tumor suppressor genes
p53
Molecular and cellular biology
Mitochondria
Bcl-2 family members
Apoptosis
Post-translational modifications

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Hyaluronan metabolism in cancer stem cells

SENIOR SCIENTIST :

► Bruno FLAMION

Research Field and Subjects

Hyaluronan or hyaluronic acid (HA) is a ubiquitous high MW unbranched polymer that is prominent in vertebrate extracellular matrix during embryogenesis, inflammation, and wound healing, whenever there is rapid tissue turnover and repair, but particularly in neoplasia. HA is intimately involved in the cross-talk between cancers and the host peritumor stromal response. The major receptor for HA, CD44, is expressed on the surface of virtually all stem cells, including cancer stem cells (CSC).

CSC can be identified in all tumors and in most cancer cell lines through specific surface markers such as CD44, $\alpha 2\beta 1$ integrins, and β -catenin, or functional assays such as dye and drug efflux via the membrane transporter ABCG2 (this assay defines a "side population"). Targeting CSC has become one of the major goals of anticancer chemotherapy.

We have recently shown that MCF7 and Du145 stem/progenitor cells isolated through a cloning technique display a thick pericellular coat of HA which may help them evade immune recognition, and prominent membrane protrusions or microvilli which are involved in their motility.

Our lab has been involved in the study of HA metabolism in various tissues since 1997. We have cloned the first Hyal2 isoform of the hyaluronidase family and have generated the first Hyal2 knockout mice. These mice display skeletal and haematological anomalies. We have recently shown that hyaluronidases, in particular Hyal2, play a crucial role in controlling the pericellular HA coat and CD44 function in various cell types.

The aim of this oncology project is to examine the expression and function of various actors of HA metabolism including HA synthases, hyaluronidases, CD44, and the pericellular HA-rich coat in CSC isolated from cancer cell cultures and human tumors and to correlate these expressions to the ability of CSC to generate tumors in nude mice and to respond to various chemotherapies. The relationship between HA metabolism and key membrane transporters such as ABCG2 will be examined.

Our ultimate goal is to understanding how cancer cells, especially CSC, commandeer their own HA metabolism and that of stromal cells in order to grow, evade immune rejection, induce angiogenesis and metastasize.

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Partnership

- PROF. ARMIN BUSCHAUER, Institute of Pharmacy, University of Regensburg, Germany.
- DR GREG FROST, Halozyme Inc., San Diego, CA, USA.

Main Equipment

- Molecular and cellular biology equipment; single-cell real-time RT-PCR; video-microscopy (cooled CCD camera)

Products and services

Hyaluronidase-1 and -2 knockout mice

Funding

Institutional funds (FUNDP)

KEY WORDS FOR R&D

Hyaluronan
Hyaluronic acid
Hyaluronidase
CD44
Cell coat
Glycocalyx
Cancer stem cell
ABCG2

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Role of intracellular calcium homeostasis in apoptosis of cancer cells

SENIOR SCIENTISTS :

- ▶ Philippe GAILLY
- ▶ Nicolas TAJEDDINE

Research Field and Subjects

Resistance to cytotoxic drugs is an important cause of treatment failure in advanced cancer and is frequently due to an impairment of the mitochondrial pathway of apoptosis. Several evidences point out the role of calcium in the regulation of apoptosis. Indeed, it seems that calcium content in the endoplasmic reticulum is a major determinant of sensitivity to apoptosis. The aim of our studies is to understand the alterations in calcium homeostasis leading to chemoresistance. More particularly, we are interested in the role of a specific class of calcium/cationic channels, so-called TRP, in the control of apoptotic cell death. We hope that our results will permit to find novel targets and compounds able to increase chemosensitivity in advanced cancers.

Representative References

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- ▶ D. PIGOZZI, T. DUCRET, N. TAJEDDINE, J.L. GALA, B. TOMBAL AND P. GAILLY. *Calcium store contents control the expression of TRPC1, TRPC3 and TRPV6 proteins in LNCaP prostate cancer cell line.* Cell Calcium 39(5), 401-415, **2006**.

Award

Prix Clément Perdieus et Cécile Petit, 2009

Funding

FNRS – TÉLÉVIE – Action concertée de recherche

Partnership

Service d'Urologie, Cliniques universitaires Saint-Luc, Bruxelles, Belgium

Main Equipment

- ▶ Microspectrofluorimetry for dynamic live cells measurements
- ▶ Patch-clamp
- ▶ Cell culture
- ▶ Real-time RT PCR

Key Words for R&D

Apoptosis
Calcium
TRP
Endoplasmic reticulum
Mitochondria
Chemoresistance

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pending

Hox transcription factors and cancer

SENIOR SCIENTIST :

► René REZSOHAZY

Research Field and Subjects

Hox proteins are transcription factors playing crucial roles during mammalian embryonic development. They contribute to pattern the central nervous system, the axial skeleton and the limbs, they control several organogenetic processes and they modulate differentiation pathways. Beside their normal developmental roles, accumulating data provide evidence that misregulation or mutation of *Hox* genes is associated with cancerogenesis.

Our research objectives aim at understanding the mode of action of Hox proteins: what are their functional domains, how do they govern gene expression programs, what are their target genes and what are the partner proteins they interact with.

Most of our investigations to date were connected to the developmental functions of Hox proteins. However, we accumulated data on mutant Hox proteins, target genes and partner proteins, we currently transpose to unravel their involvement in cancer biology.

For a first pilot study on the mode of action of a Hox protein, we focused on Hoxa1. Hoxa1 has been shown to play a pivotal role in certain breast tumors under the influence of autocrine growth hormone.

We generated series of Hoxa1 mutants that have been screened for loss or gain of activity. We consequently mapped functional domains of the protein that are required for transcription activation, DNA binding specificity and interaction with cofactors. We screened extensive libraries to look for proteins interacting with Hoxa1 and identified tens of new Hox partners. We identified and characterized target enhancers of Hoxa1 useful to assay the activity of the protein, its cofactors and its mutant derivatives. We developed *in vitro* cell models to address the oncogenic potential of Hoxa1, of its mutant derivatives and of their combined activity with cofactors. Finally, we generated genetically engineered mice which code for mutant Hoxa1 proteins to study the impact of specific Hox mutations onto mammary carcinogenesis. Other recombinant mouse lines are under development with collaborating research teams to develop new *in vivo* models to dissect the oncogenic properties of Hox proteins.

In the framework of collaborations with the clinic (Prof. C. Sotiriou, Institut Jules Bordet, Bruxelles), we currently aim to anchor our data into a better classification of *Hox*-gene associated cancers as well as into a deeper understanding of their etiology. The other way around, previous collaborations (Prof. G. Cornu and Prof. Ch. Verellen-Dumoulin, UCL) allowed us identifying *Hox* mutations in patients with lymphoid malignancy and to demonstrate they corresponded to mild loss-of-function mutations.

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Funding

- ▶ FNRS, FRSM
- ▶ TÉLÉVIE
- ▶ Walloon region, WALEO II programme

Partnership

- ▶ Member of the Institut des Sciences de la Vie, UCL, Belgium
- ▶ Belgian representative for a European COST action on “Hox and TALE transcription factors in development and disease”
- ▶ PROF. F.M. RÜLLI, Friedrich Miesscher Institute, Basel, Switzerland
- ▶ PROF. M. VIDAL, Harvard University, USA
- ▶ PROF. A. NOËL, University of Liège, Belgium
- ▶ PROF. C. SOTIRIOU, Institut Jules Bordet, Free University of Brussels, Belgium

Main Equipment

- ▶ Cell culture facilities
- ▶ General equipment for biochemical and molecular biology assays
- ▶ Animal house

Products and Services

- ▶ Expression vectors for constitutive or inducible expression of Hox proteins and cofactors, and mutant versions thereof, for animal cell models, yeast and bacteria
- ▶ Tagged variants of Hox proteins for detection or immunoprecipitation
- ▶ Cell lines and *in vitro* models for carcinogenesis
- ▶ Animal models for *Hox* gene mutations or *Hox* gene misregulation

KEY WORDS FOR R&D

Hox
Pbx
Transcription factors
Interactors
Gene regulation
Recombinant mice
Breast cancer

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Semi-automatic delineation, non-rigid registration and dose accumulation for adaptive treatment in radiotherapy and proton therapy

SENIOR SCIENTISTS :

- ▶ Anne BOL
- ▶ Xavier GEETS
- ▶ Vincent GREGOIRE
- ▶ John LEE
- ▶ Benoit MACQ
- ▶ Vincent NICOLAS

Research Field and Subjects

The efficacy of radiotherapy and protontherapy treatments relies on accurate localization and delineation of the tumor and invaded nodes. As the treatment are typically fractionated over several weeks, with daily dose deliveries, it is of prime importance to maintain this accuracy during the entire course of the treatment, in order to adapt the dose according to the tumor shrinkage and other morphological changes (such as weight loss). In this context, our work has been focused on the development and clinical validation of image processing tools for improving treatment planning.

The collaboration between the Center for Molecular Imaging and Experimental Radiotherapy (V.Gregoire) and the Communications and Remote Sensing Laboratory (B. Macq) intertwines both technical and medical environments, and has allowed fast transfers from image processing theory to clinical practice.

The collaboration currently targets three challenges: the automatic segmentation of tumors in PET images, the segmentation of organs at risk in the head and neck region based on the nonrigid registration of atlas images, and the development of adaptive radiotherapy and dose accumulation along treatment using inter-fraction non-rigid registration.

As to PET segmentation, the most prominent difficulty resides in the low resolution of the images, which causes a large variability in the results. In order to improve the delineation accuracy, specific image processings have been developed, such as denoising and deblurring tools.

The purpose of atlases is twofold. They primarily speed up treatment planning, by automatically contouring some of the volume of interest, such as the organs at risk. Simultaneously, such an auto-contouring helps reducing the inter-observer variability. Atlases in the head and neck region are challenging for the registration tools they rely on, and raises many issues as to the regularization of the deformation fields.

Adaptive radiotherapy attempts to answer two questions. How can we estimate the cumulative dose deposit after each daily treatment fraction and how can we adapt the treatment during

its course in order to maintain its optimal balance between high probability of tumor control and minimized adverse effects. Non-rigid registration plays an important part in this application as well.

All tools developed in the abovementioned projects are integrated in an open source platform called MedicalStudio. It aims at providing the user with interactivity and advanced 2D/3D visualization interfaces for medical image processing tasks. MedicalStudio has been designed by B. Macq's team and relies on widely approved software libraries such as the Visualization Toolkit (VTK) and the Insight Toolkit (ITK).

Representative References

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- ▶ A. PARRAGA, A. SUSIN, J. PETTERSON, B. MACQ, M. DE CRAENE. *3D Atlas Building in the Context of Head and Neck Radiotherapy Based on Dense Deformation Fields*. *Computer Graphics and Image Processing*, **2007**.
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- ▶ J.A. LEE, X. GEETS, V. GREGOIRE, A. BOL. *Edge-preserving filtering of images with low photon counts*. *IEEE Transactions on Pattern Analysis and Machine Intelligence*, 30(6): 1014-1027.

Patent

J. MARCHAND, V. GREGOIRE, O. JOSSE, D. LABAR, (1999) European patent n° 99870172.6 "Methods for preparing perfluorinated [18F]-radiolabelled itroimidazole derivatives for cellular hypoxia detection

- ▶ Rigid and non-rigid registration tools
- ▶ Dose accumulation and treatment planning tools
- ▶ MedicalStudio, a 3D visualization platform with integrated image processing tools
- ▶ PET tracers synthesis

Funding

- ▶ Walloon Region : project PAINTER
- ▶ Fond pour la formation à la recherche dans l'industrie et l'agriculture (FRIA)
- ▶ Fonds national de la recherche scientifique (FNRS)
- ▶ Fonds de la recherche scientifique médicale (FRSM)
- ▶ European Community
- ▶ Fonds Joseph Maisin
- ▶ Interuniversity Attraction Poles Programme of the Belgian Federal Science Policy Office

Partnership

- ▶ Ion Beam Applications S.A., Louvain-la-Neuve, Belgium
- ▶ SIMILAR (European Network of Excellence)
- ▶ Maastricht Clinic, Maastricht, The Netherlands
- ▶ Multitel asbl, Mons, Belgium
- ▶ Tomotherapy Inc. (Madison, WI, USA)

Main Equipment

- ▶ Software : MedicalStudio
- ▶ Imaging devices: PET/CT scanner, animal PET, MRI systems, 4D-CT scanner
- ▶ Treatment systems: helical tomotherapylinear accelerators with IMRT capabilities

Products and Services

- ▶ PET-based automatic tumor segmentation
- ▶ Anatomical atlas-based segmentation

KEY WORDS FOR R&D

Adaptive radiotherapy
Image segmentation
Image registration
Atlases
Dose accumulation.

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Functional magnetic resonance (NMR, EPR) spectroscopy and imaging in tumors

SENIOR SCIENTISTS :

- ▶ Bernard GALLEZ
- ▶ Bénédicte JORDAN

Research Field and Subjects

The major theme of the research is to understand how the tumor microenvironment influences the response to treatments. Three main areas of research are involved:

1. Development of sensors for monitoring the oxygen in tissues by EPR

Selection of paramagnetic materials possessing favourable features for oximetry. Microencapsulation of oxygen sensors in biocompatible films to improve their performance in vivo and their biocompatibility.

2. Applications of MR (EPR and NMR) to characterize the microenvironment in tumors and modulate the response to anti-cancer treatments

Use of combination therapies against cancer (vasoactive agents + radiotherapy / antiangiogenesis + radiotherapy / ...) to improve the response of tumors to treatments: characterisation of pO₂, flow, oxygen consumption, permeability of vessels, nitric oxide,... and correlation with the tumor growth.

3. Development of predictive biomarkers of tumor response to a treatment

NMR spectroscopy in vivo, diffusion imaging, contrast agents targeted to cell death,...

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Patents

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- ▶ B. GALLEZ, R. ANSIAUX, Methods and compositions for the treatment of cancer, WO/2006/094539, PCT/EP2005/011145

Awards

- ▶ B. GALLEZ :
Prix 1995 de la Société Belge des Sciences Pharmaceutiques
Prix 1998 des Alumni de la Fondation Universitaire (Section : Sciences médicales, pharmaceutiques et vétérinaires)
Prix Paul Van de Velde 2000 (Nouveaux outils diagnostiques ou thérapeutiques)
Young Investigator Award of the International EPR Society 2000
Prix Léopold et Marthe Delsaux-Champy 2004 (Prévention, traitement ou physiopathologie de maladies cardiovasculaires ou cancéreuses)

Prix du Concours ordinaire de la 5^e section de l'Académie Royale de Médecine de Belgique
Période 2005-2006

‣ B. JORDAN :

Prix Ishango francophone 2003

Funding

- NCI (National Cancer Institute, USA)
- FNRS (FRSM, Télévie, IISN)
- PAI
- ARC
- Fondation contre le Cancer
- Fonds *Joseph Maisin*
- FSR

Partnership

- Pharmacotherapy Unit (UCL)
- Molecular Imaging and Experimental Radiotherapy Unit (UCL)
- Gynecology Unit (UCL)
- Experimental Surgery Unit (UCL)
- Organic and Medicinal Chemistry Unit (UCL)
- Dentistry and Stomatology Unit (UCL)
- Pharmaceutical Technology Unit (UCL)
- Vesalius Research Center, VIB-Vlaams
- Instituut voor Biotechnologie (KUL)
- NMR and Molecular Imaging (University of Mons)
- EPR Research Center (Dartmouth Medical School, USA)

Main Equipment

- NMR spectrometer and imaging 11.7 T for small animals
- 2 EPR spectrometers (9 GHz, X-Band) for in vitro experiments
- EPR spectrometer (1 GHz, L-Band) for in vivo experiments
- EPR imaging (1GHz and 9GHz)
- OxyLite (pO₂ measurements by fluorescence quenching)
- OxyFlo (laser-doppler)

Products and Services

- EPR: in vitro (free radicals, spin trapping)
- EPR in vivo in small animals
- NMR imaging in small animals
- Oxygen measurements
- Flow measurements

KEY WORDS FOR R&D

Angiogenesis
Biocompatibility
Biomarkers
Biomaterials
Cancer
Chemotherapy
EPR
Free radicals
Functional imaging
Imaging
MRI
NMR
Oxygen
Pharmacology
Radiotherapy
Spectroscopy
Spin trapping
Tumor

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Intuitive And Standardized Annotation For Cancer Prevention And Diagnosis

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- ▶ Vincent NICOLAS
- ▶ Pierre-Yves SCHOBENS

Research Field and Subjects

Cancer detection and diagnosis are very complex tasks requiring inter-domain data management. Image-based detection, as an example, must deal with a lot of parameters such as morphology, texture or time evolution and can be enhanced by information retrieved from the patient record.

There are a lot of people working on the acquisition and storage of these sparse information. We are working on intelligent and intuitive presentation and interaction of these in medical workstations for diagnostic.

One of our tests case is breast cancer detection and diagnosis, a complex user activity including several specific tasks such as image screening, lesion detection and description and reporting. Our research efforts undertake to design, implement and evaluate a breast cancer oriented interactive system which integrates the functionalities of mammogram visualization, annotation, characterization, diagnosis and reporting. Owing to its high naturalness and mainly to its convenience to satisfy the annotation requirement, pen-based interaction with a graphic tablet was chosen as the modality to interact with the system. The usefulness requirement is ensured by the compliance of the system with the BI-RADS, which is a quality assurance tool for breast imaging and reporting, providing an approved and standardized terminology for describing findings. The usability requirement is ensured by the development method, combining user-centered design process together with usability development methods.

Such an approach combining usefulness and naturalness allows us to design and develop systems that help specialists doing their tasks while avoiding them to lose time on gathering information. We are applying the same method on other domains such as pulmonary nodule detection, radiotherapy planning, etc.

The tools are implemented in a common software platform called MedicalStudio. Its architecture allows creating generic components which will be parameterized to create applications for specific domains. Components currently implemented allow

image visualization, 3D rendering, volumetric rendering, image segmentation, DICOM conformance, etc.

A lot of information is used by our tools and they also produce more information. Such an information management is achieved by using ontologies. Each ontology describes a specific domain (for instance an ontology based on the BI-RADS terminology describes the breast cancer domain) and allows us to face the complexity of biomedical information and its heterogeneity. They are implemented with OWL (Web Ontology Language) which is recommended by the W3C consortium. OWL guarantees compatibility between different system and offers more expressiveness than other languages. It can also be accompanied with some rule language and query language.

Rule language permits the creation of rules used for reasoning about information and then inferring new facts. With these new facts we can consider the possibility to guide and help the practitioner during the diagnosis step.

Thanks to query language we can express queries to retrieve information from the databank built by our tools or to update it. Combining queries with reasoning provides more effective results and performances for media (images, videos, texts, etc.) storage and retrieval than the well known text based querying.

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Funding

- Brussels Region : project DIAMANT
- Walloon Region : project VIGILE

Partnership

- Cancer prevention department of Bordet Institute, Brussels, Belgium
- Radiology department of St-Luc Hospital, Brussels, Belgium
- Radiology department of Mont-Godinne Hospital, Yvoir, Belgium

Products and Services

- MedicalStudio : a visualization platform with integrated image processing tools.
- Mammography image segmentation.
- Ontology based information knowledge

KEY WORDS FOR R&D

Prevention
Diagnostic
Mammography
Usability
Interaction
Segmentation
Ontology
Visualization
User-centered design
Semantics.

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Impact of intra-operative MRI at 3 Tesla on the degree of tumor resection and long-term survival rate in patients with intracranial glioma, and development of neuronavigation on intra-operative images

SENIOR SCIENTISTS :

- ▶ Christian RAFTOPOULOS
- ▶ Jose Geraldo VAZ
- ▶ Edward FOMEKONG

Research Field and Subjects

Having used the intra-operative MRI suite at 3 Tesla for 3 years, the aim of our research protocol is to determine its impact on the rate of complete tumor removal, neurological outcome, progression free survival and survival in glioma (all WHO grades) operated patients. We will analyse these items with respect to data published using other iMRI devices.

Furthermore, we intend to improve the iMRI suite at 3 Tesla by adding the possibility to use the neuronavigation on the intra-operative MR images. Currently, if a tumor residue is observed on the iMRI, the neurosurgeon cannot benefit from the computer guided neuronavigation to accurately and specifically remove the residue. The upgrading of the existing system would allow precise and safe removal of the remnant through the direct injection of iMRI images into the neuronavigation system and through the fusion of both pre-operative and intra-operative images.

Main Equipment

- ▶ MRI scanner (Achieve 3T; Philips Medical Systems, Best, The Netherlands)
- ▶ VectorVision neuronavigation system (BrainLAB, Munich, Germany)
- ▶ Doro Radiolucent Headrest system with MRI-compatible disposable cranial pins (Pro Med Instruments GmbH, Freiburg, Germany)

Funding

Fond National de la Recherche Scientifique.

Representative references

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- ▶ T.P. DUPREZ, A. JANKOVSKI, C. GRANDIN, L. HERMOYE, G. COSNARD, C. RAFTOPOULOS. *Intraoperative 3T MR imaging for spinal cord tumor resection: feasibility, timing, and image quality using a "twin" MR-operating room suite*. AJNR Am J Neuroradiol. 29(10):1991-4, **2008**.

KEY WORDS FOR R&D

Cerebral tumor
Glioblastoma
Glioma
Intra-operative MRI
MRI 3.0 Tesla
Neuropathology
Neuroradiology
Neurosurgery
Surgery
Surgical medicine

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Genetic analysis of T lymphocytes infiltrating human tumors

SENIOR SCIENTISTS :

- ▶ Pierre COULIE
- ▶ Pierre VAN DER BRUGGEN
- ▶ Sophie LUCAS

Research Field and Subjects

Vaccination of cancer patients with defined tumor antigens recognized by T lymphocytes, notably cytolytic T lymphocytes, is followed by tumor regressions in 5-10% of the patients. Our objective is to increase this proportion. Our immunological analysis of vaccinated patients indicated that the main limiting factor to clinical efficacy is not the immunogenicity of the vaccine, but rather a functional impairment of the tumor-specific lymphocytes when they are localized within the tumors.

There are numerous mechanisms of immunosuppression that have been reported to play a role in the tumor microenvironment, most of them studied in animal models. We wish to characterize T lymphocytes present within human tumors, to explain their apparently pacific coexistence with tumor cells. Our approach consists in a genetic analysis, carried out with expression microarrays, of small numbers of T lymphocytes microdissected from human tumors. We usually start from about 100 cells laser-microdissected from frozen tumor sections. After extraction of RNA and conversion to cDNA, we use a global cDNA amplification method to obtain enough material for gene profiling with the Affymetrix technology.

We have compared the gene expression profiles of CD8 T lymphocytes infiltrating cutaneous melanoma metastases, where they appear to be paralysed, to that of lymphocytes present in rare primary melanomas showing histological signs of immune attack. The results provide an unbiased view of some functional differences between these T lymphocytes present in the same tissue, the skin, and at least for some of them recognizing the same tumor antigens.

Representative References

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Patent

A portfolio of patents covering human tumor antigens recognized by T lymphocytes

Awards

- ▶ P. COULIE : 1993 Annual Prize of the « Fondation Maggy & Robert de Hovre »
- ▶ P. COULIE : 1998 Prize of the « Fondation Alexandre et Gaston Tytgat »
- ▶ P. COULIE : 2007 « Mme Veuve Matthys-Bove » Prize
- ▶ P. VAN DER BRUGGEN : 1995 Annual Prize of the Fondation « Maggy et Robert de Hovre »
- ▶ P. VAN DER BRUGGEN : 1998 Prize of the « Fondation Alexandre et Gaston Tytgat »
- ▶ P. VAN DER BRUGGEN : 2009 Allard-Janssen Prize

Funding

- ▶ Commission Européenne (FP6),
- ▶ Belgian Programme on Interuniversity Poles of Attraction (PAI)
- ▶ Région Wallonne (Pôle de compétitivité “Sciences du Vivant”)
- ▶ Fonds National de la Recherche Scientifique
- ▶ Fondation contre le Cancer, Brussels

Partnership

Brussels branch of the Ludwig Institute for Cancer Research Ltd.

KEY WORDS FOR R&D

Melanoma
Vaccination
Immunotherapy
Expression profiling

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Therapeutic vaccination of cancer patients with tumor specific antigens

SENIOR SCIENTISTS :

- ▶ Nicolas VAN BAREN
- ▶ Jean-François BAURAIN
- ▶ Thierry BOON

Research Field and Subjects

Tumor cells carry antigens such as MAGE antigens that are absent from normal tissues, and that can be targeted by cytolytic T lymphocytes (CTL). While it is possible to make such CTL recognize and kill autologous tumor cells in vitro, the precise way to induce an effective CTL response against a MAGE antigen in cancer patients is not known yet. In clinical vaccination trials, patients with a MAGE expressing cancer, often melanoma, are treated repeatedly with a MAGE vaccine. These trials have two main objectives. First, the effectiveness of various vaccination modalities can be assessed by following the clinical evolution of the tumor, by analyzing whether a specific CTL response to the vaccine antigen occurred, and by determining whether immunological and clinical responses are correlated. Secondly, T lymphocytes and tumor samples collected at different timepoints during vaccination can be analyzed in detail, which improves our understanding on what happens in the minority of patients who experience regression of metastatic lesions upon vaccination, and which may explain why this does not happen in the majority of patients, who have overall disease progression. It seems that most tumors have acquired the capacity to resist destruction by the immune system. This resistance is selected during tumor progression in face of spontaneous T lymphocyte responses directed at tumor antigens. Our current work is focused on the identification of tumor resistance mechanisms, and on the development of counter-measures against this resistance which, associated with cancer vaccines in new clinical trials, will likely improve the anti-tumoral effects of the vaccines.

Representative References

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P. VAN DER BRUGGEN, T. BOON, A.M. EGGERMONT, M. MARCHAND. *Phase 1/2 study of subcutaneous and intradermal immunization with a recombinant MAGE-3 protein in patients with detectable metastatic melanoma.* International Journal of Cancer, 117 : 596-604, **2005**.

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Patents

Many patents covering clinical applications of tumor-specific antigens in cancer immunotherapy

Awards

Prize of the "Fondation Clément Perdieus et Cécile Petit, 2002"

Funding

- ▶ Ludwig Institute for Cancer Research
- ▶ FNRS and TELEVIE
- ▶ EU-FP6 program
- ▶ Federation belge contre le cancer

Partnership

Academic collaborations

- ▶ UCL, Centre du Cancer, Brussels (J.P. MACHIELS)
- ▶ ULB, Brussels (D. LIENARD)
- ▶ VUB, Brussels (B. NEYNS)
- ▶ KUL, Leuven (M. STAS)
- ▶ CHU de Nantes (B. DRENO)
- ▶ University Erlangen (G. SCHULER)

Industrial collaborations

- ▶ GLAXOSMITHKLINE BIOLOGICALS, Rixensart, Belgium
- ▶ PROSPECT THERAPEUTICS, USA

International networks

- ▶ EORTC: Melanoma Cooperative Group
- ▶ Cancerimmunotherapy (EU-FP6 PROJECT)
- ▶ THERAVAC (EU-FP6 PROJECT)

Main Equipment

Zeiss Mirax Midi digital microscopy platform

KEY WORDS FOR R&D

Cancer treatment
Cancer vaccines
Cancerology
Cytolytic T lymphocytes
Immunology
Immunotherapy
Tumor antigens
Tumor resistance
Melanoma

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Mechanisms of tumor resistance to the immune system and development of a mouse model of inducible melanoma

SENIOR SCIENTISTS :

- ▶ Benoît VAN DEN EYNDE
- ▶ Catherine UYTENHOVE
- ▶ Didier COLAU
- ▶ Vincent STROOBANT

Research Field and Subjects

Crucial to the success of cancer immunotherapy is a precise understanding of the interplay between growing tumors and the anti-tumor immune response. For example, tumors may develop a variety of mechanisms to escape immune attack. In that context, we have observed that a majority of tumor cells express an enzyme called indoleamine 2,3-dioxygenase (IDO), which rapidly degrades tryptophan, an essential amino acid whose supply is mandatory for the activity of T lymphocytes. Thus, by locally degrading tryptophan, tumor cells completely inactivate T lymphocytes and thereby blunt the anti-tumor immune response. We have also shown that this resistance mechanism can be blocked by treating animals with 1-methyl-tryptophan, an inhibitor of IDO. These results suggest that the efficacy of cancer immunotherapy could be improved by combining immunization strategies with a treatment aimed at inhibiting IDO. We are trying to develop novel inhibitors of IDO for that purpose. We are also studying other mechanisms of tumoral immune resistance.

In order to obtain meaningful information from mouse studies with melanoma, we have also developed a new model of mice that develop melanomas upon local application of tamoxifen. The induction of melanomas is based on Cre-lox recombination and involves conditional activation of oncogene Ras and inactivation tumor-suppressor gene INK4A. Tumors developing slowly within a normal tissue are likely to represent the status of human cancers much more closely than the transplanted tumors currently used. Such a model will be particularly useful to optimize strategies of cancer immunotherapy, but will undoubtedly be also of great interest in other contexts, such as the molecular definition of the successive steps involved in carcinogenesis, local invasiveness and metastasis.

Representative References

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Patents

A large portfolio of about 80 issued patents and patent applications on tumor antigens and their use for cancer therapy.

Awards

- ▶ 1998 : Prize of the « Fondation Clément Perdieus et Cécile Petit »
- ▶ 1998 : Annual Prize of the « Fondation Maggy et Robert de Hovre »
- ▶ 1998 : Prize of the « Fondation Alexandre et Gaston Tytgat »
- ▶ 2001 : Prize of the 165th anniversary of the « Académie Royale de Médecine de Belgique »
- ▶ 2005 : Francqui Chair at the Université Libre de Bruxelles
- ▶ 2007 : GlaxoSmithKline Prize

Funding

- ▶ Ludwig Institute for Cancer Research Ltd
- ▶ Commission Européenne (FP6)
- ▶ Région Wallonne (Programme d'Excellence "Marshall", "Pôle de compétitivité "Sciences du Vivant")
- ▶ Fonds National de la Recherche Scientifique
- ▶ Fondation contre le Cancer, Brussels
- ▶ UCL, Mandats FSR

Partnership

- ▶ Macromol Biologique, Centre d'Ingénierie des Protéines, Université de Liège
- ▶ Laboratoire de Chimie Biologique Structurale, Faculté Universitaires Notre-Dame de la Paix, Namur
- ▶ Laboratoire de Physiologie Animale, Institut de Biologie et de Médecine Moléculaires (IBMM), ULB
- ▶ Centre d'Immunologie INSERM-CNRS de Marseille-Luminy, Marseille France
- ▶ DKFZ - Deutsches Krebsforschungszentrum (German Cancer Research Center), Heidelberg, Germany
- ▶ Ludwig Institute for Cancer Research Ltd, Lausanne branch, Switzerland

Main Equipment

Laser-assisted microdissection and laser pressure catapulting (P.A.L.M.®, Microlaser Technologies AG, Benried, Germany)

Products and Services

- ▶ Screening assay for the development of new IDO inhibitors
- ▶ New mouse model of inducible melanomas

KEY WORDS FOR R&D

Biochemistry
Cancer vaccines
Cancerology
IDO inhibitors
Immune escape
Immunology
Immunotherapy
Inducible melanoma model
Tumor antigens

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Intracellular processing of tumor antigens recognized by cytolytic T lymphocytes : role of the proteasome and other cytosolic proteases

SENIOR SCIENTISTS :

- ▶ Benoît VAN DEN EYNDE
- ▶ Vincent STROOBANT

Research Field and Subjects

Tumor antigens recognized by Cytolytic T Lymphocytes (CTL) consist of peptides that are presented by MHC molecules at the cell surface and derive from intracellular proteins that are degraded by the proteasome. The intracellular pathway leading from the protein to the peptide/MHC complex is known as "antigen processing". Our group focuses on the proteasome and recently described a new mode of production of antigenic peptides by the proteasome, based on cutting and pasting peptide fragments to form a new spliced peptide. The first example was a peptide derived from human melanocyte protein gp100. This antigenic peptide is nine-amino acid long and is produced by the splicing of two fragments that were initially non-contiguous in the parental protein. The splicing is made by the proteasome, is tightly coupled to the proteolytic reaction, and appears to occur by transpeptidation involving an acyl-enzyme intermediate. We further described a second example of spliced peptide, where the two fragments are rearranged before splicing.

We also study the processing differences between the standard proteasome, which is present in most cells, and the immunoproteasome which is found in dendritic cells and in cells exposed to interferon-gamma. Several tumor antigens were found to be processed differently by the two proteasome types, usually because of a preferential cleavage made by one or the other proteasome within the antigenic peptide itself. We are currently working on the characterization of proteasome types that are intermediate between the standard proteasome and the immunoproteasome.

Representative References

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Patents

A large portfolio of about 80 issued patents and patent applications on tumor antigens.

Awards

- ▶ 1998 : Prize of the « Fondation Clément Perdieus et Cécile Petit »
- ▶ 1998 : Annual Prize of the « Fondation Maggy et Robert de Hovre »
- ▶ 1998 : Prize of the « Fondation Alexandre et Gaston Tytgat »
- ▶ 2001 : Prize of the 165th anniversary of the « Académie Royale de Médecine de Belgique »
- ▶ 2005 : Francqui Chair at the Université Libre de Bruxelles
- ▶ 2007 : GlaxoSmithKline Prize

Funding

- ▶ Ludwig Institute for Cancer Research Ltd
- ▶ Commission Européenne (FP6)
- ▶ Région Wallonne (Programme d'Excellence "Marshall", "Pôle de compétitivité Sciences du Vivant")
- ▶ Fonds National de la Recherche Scientifique,
- ▶ Fondation contre le Cancer, Brussels
- ▶ UCL, Mandats FSR

Partnership

- ▶ Fred Hutchinson Cancer Institute, Seattle, WA, USA
- ▶ Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA
- ▶ Department of Immunobiology, Yale University, School of Medicine, New Haven, CT, USA

Main Equipment

Mass spectrometry

Products and Services

- ▶ Mass spectrometry
- ▶ Proteasome purification

KEY WORDS FOR R&D

Antigen processing
Biochemistry
Cancer vaccines
Immunology
Immunotherapy
Proteasome
Tumor antigens

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Regulation of T lymphocyte function in tumors

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- ▶ Didier COLAU
- ▶ Nathalie DEMOTTE
- ▶ Danièle GODELAINE

Research Field and Subjects

We have recently discovered a new type of anergy of human CD8 T cells, which is observed on tumor-infiltrating lymphocytes. We are analyzing the mechanism of this type of anergy and we study agents that reverse this anergy. The analysis of the T cell responses of melanoma patients vaccinated against tumor antigens has led us to consider the possibility that the limiting factor for therapeutic success is not the intensity of the anti-vaccine response but the degree of anergy presented by intratumoral lymphocytes. We therefore intend to pursue clinical trials involving the use of these agents in combination with anti-tumoral vaccination.

A scenario to explain the low level of clinical responses in vaccinated patients

The identification of specific tumor antigens recognized by T lymphocytes on human cancer cells has elicited numerous clinical trials involving vaccination of tumor-bearing cancer patients with defined tumor antigens. These treatments have shown a low clinical efficacy. Among metastatic melanoma patients, about 5% show a complete or partial clinical response following vaccination, whereas an additional 10% show some evidence of tumor regression without clear clinical benefit.

▶ Recent analyses of the T cell responses of melanoma patients has led us to consider the following scenario. Most melanoma patients produce a spontaneous T cell response against melanoma tumor antigens at a relatively early stage of the disease (primary tumor or early metastatic tumor). These T cells can eliminate some tumors at an early stage, but often they do not succeed in eliminating the tumor and they become anergic. Thus, the tumors of the patients about to receive the vaccine, already contain anergic T cells directed against tumor antigens. Presumably this anergy is maintained by immunosuppressive factors present in the tumor. A few patients show tumor regression following vaccination because some T cells generated by the vaccine penetrate inside the tumor, attack some tumor cells and succeed in reversing the local immunosuppression, possibly by releasing cytokines or chemokines. Accordingly, our working hypothesis is that the crucial difference between the responding and the

non-responding patients is not the intensity of their direct T cell response to the vaccine but the intensity of the immunosuppression inside the tumor. It is therefore important to know which immunosuppressive mechanisms operate in human tumors.

A new mechanism causing anergy of human tumor-infiltrating lymphocytes

We observed that, a few days after antigen stimulation, CTL clones lose the capacity to secrete cytokines and in some case the cytolytic activity. These functions are recovered gradually and are usually completely restored after two weeks. TCRs and CD8 co-receptors were co-localized at the cell surface of functional CTL but, on the contrary, distant at the cell surface of non-functional CTL.

▶ Human CD8 tumor-infiltrating T lymphocytes were isolated from tumor ascites or solid tumors and compared with T lymphocytes from blood donors. TCR were observed to be distant from CD8 on the cell surface of tumor-infiltrating lymphocytes, whereas TCR and CD8 co-localized on blood T lymphocytes. The tumor-infiltrating lymphocytes were anergic, being unable to secrete INF- γ or other cytokines after non-specific stimulation with anti-CD3 and anti-CD28 antibodies.

Glycoprotein-galectin lattices restrain mobility of TCR

On the basis of the work of other groups, we hypothesized that the absence of TCR-CD8 co-localization at the cell surface of anergic T cells is due to the loss of mobility of the TCR, which is trapped in a lattice of galectin-3. The presence of galectin-3 in ascites and solid tumors has been shown in many studies. To test this hypothesis, tumor-infiltrating lymphocytes were incubated with N-acetyllactosamine, a disaccharide ligand of galectin-3. This treatment restored the TCR-CD8 co-localization and the capacity to secrete IFN- γ and other cytokines after stimulation.

Towards a clinical trial combining vaccination and galectin-binding polysaccharides

These observations indicate that *ex vivo* human tumor-infiltrating lymphocytes can recover their effector functions with galectin lig-

ands and suggest that treatment of cancer patients with galectin ligands could correct the anergy of tumor-infiltrating lymphocytes. It is possible that peptide vaccination combined with local injection of a galectin ligand will be more effective at producing tumor regression than vaccination alone. We have recently identified a polysaccharide already approved for clinical use that was more efficient than N-acetyllactosamine to correct the anergy of CTL clones and human tumor-infiltrating lymphocytes. We therefore intend to launch a clinical trial combining peptide vaccination and injections of galectin-binding polysaccharides in melanoma tumor-bearing metastatic patients.

Representative References

- ▶ T. BOON, P.G. COULIE, B. VAN DEN EYNDE AND P. VAN DER BRUGGEN. *Human T cell responses against melanoma*. Annu. Rev. Immunol. 24, 175-208, **2006**.
- ▶ N. DEMOTTE, V. STROOBANT, P.J. COURTOY, P. VAN DER SMISSEN, D. COLAU, I.F. LUESCHER, C. HIVROZ, J. NICAISE, J.-L. SQUIFFLET, M. MOURAD, D. GODELAINE, T. BOON AND P. VAN DER BRUGGEN. *Restoring the association of the T cell receptor with CD8 reverses anergy in human tumor-infiltrating lymphocytes*. Immunity 28, 414-424, **2008**.

Patents

About 70 patents.

Awards

- ▶ Prix Maggy et Robert de Hovre, October 1995
- ▶ Prix Alexandre et Gaston Tytgat, 1998
- ▶ Prix Allard-Janssen, 2009

Funding

- ▶ Ludwig Institute for Cancer Research
- ▶ Fondation contre le cancer
- ▶ F.R.S.-FNRS
- ▶ European Grants (COCHISE, CANCERIMMUNOTHERAPY)

Partnership

- ▶ UCL, Brussels, Belgium (P.J. COURTOY)
- ▶ VUB, Brussels, Belgium (K. THIELEMANS)
- ▶ Cliniques Universitaires Saint-Luc, Brussels, Belgium (B. WEYNAND, E. MARBAIX, J.-L. SQUIFFLET, J. DONNEZ, J.-F. BAURAIN, J.-P. MACHIELS)
- ▶ Hôpital Cochin, Paris, France (A. TRAUTMAN)
- ▶ Prospect Therapeutics, Woburn, MA, USA (F. TAO)

Products and Services

Construction of fluorescent MHC-peptide tetramers

KEY WORDS FOR R&D

Tumor
Immunology
Vaccine
Anergy
Glycobiology
Galectin-3
CTL
Lymphocyte
Melanoma
Ovarian carcinoma

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Gene profiling, prognosis and diagnosis

SENIOR SCIENTIST :

► Pierre DUPONT

Research Field and Subjects

1. Gene Profiling for Prognosis or Prediction in Clinical Studies

In the context of clinical studies, *gene profiling* aims at identifying gene signatures on which patients can be classified. Based on such genetic biomarkers, *prognosis models* aim at predicting the future status of a patient while *predictive models* aim at predicting the outcome of a treatment.

Gene profiling is, from a computational viewpoint, a feature selection problem. We develop novel machine learning techniques to tackle this problem. Our methods include multivariate statistical analysis to monitor the joined influence of several genes rather than looking at them individually. A multivariate selection is more complex to implement but also more relevant from a biological viewpoint.

Applying prognosis models from gene profiles is part of an effort towards a personalized medicine, to better assess the best treatment for each patient. It can also reduce the associated costs and time of large clinical studies. Counseling our partners in the biological and pharmaceutical fields about sound statistical evaluation protocols and predictive quality metrics is also part of our expertise. The type of data on which such profiling can be performed include microarray data, Single Nucleotide Polymorphism data, Copy Number Variation data, etc. Our work also covers the rigorous assessment of several signatures, proposed by external partners, both in terms of predictive power and robustness with respect to the set of patients used as reference.

2. Robust Gene Signature Identification for Cancer Modeling

Understanding mechanisms regulating cancer generally implies the analysis of genomic processes such as gene-gene, gene-protein or protein-protein interactions. High throughput technologies such as microarray data, Single Nucleotide Polymorphism data or Copy Number Variation data allow the measurement of tens of thousand genes in a single experiment. Such wide spectrum technologies are efficient but they also raise the difficulty of identifying only a few genes which are really implied in the process under study. The cost of those experiments also limits their reproducibility.

A *genetic signature* for a given pathology, or a biological condition, is a set of genes on which a model can be built. A genetic signature can be associated with a diagnosis model, when the objective is to assess whether such a genetic profile is typical of a certain cancer type or stage. Alternatively, a gene signature can be predictive of the positive reaction of a patient to a treatment.

The large difference between the number of genes measured and the number of available samples with high throughput technologies makes analysis prone to a lack of robustness. Our research focus on advanced statistical analysis and mathematical optimization techniques to address those issues.

With our partners, we pay special attention to the biological interpretation of the extracted signature. If a signature is robust and has a high predictive power, it can be considered as probably highly informative about the evaluated conditions and the underlying processes. Such robust signatures then form strong clues to guide further research on cancer mechanisms.

We also develop dedicated machine learning techniques to make use of prior biological knowledge in the form of candidate genetic biomarkers. Those candidate markers guide the final gene signature identification. Such techniques offer an independent validation methodology to confront predicted markers with actual expression data.

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- J. LOUAHED, S. GAULIS, T. HELLEPUTTE, P. DUPONT, O. GRUSELLE, A. SPATZ, W. KRUIT, B. DRENO, F. LEHMANN, V. BRICHARD, *Clinical response to the MAGE-3 immunotherapeutic in metastatic melanoma patients is associated with a specific gene profile present prior to treatment*. In: 33th European Society for Medical Oncology (ESMO) Congress, Stockholm, Sweden, **September 12-16, 2008**.
- T. HELLEPUTTE, P. DUPONT. *Feature Selection by Transfer Learning with Linear Regularized Models*. European Conference on

Machine Learning (ECML), Bled, Slovenia, **September 7-11, 2009**.

▶ T. HELLEPUTTE, P. DUPONT. *Partially Supervised Feature Selection with Regularized Linear Models*. 26th International Conference on Machine Learning (ICML), Montreal, Canada, **June 14-18, 2009**.

Products and Services

- ▶ Genomic Data Analysis
- ▶ Gene Profiling/Biomarker Identification
- ▶ Experimental Protocol Assessment
- ▶ Pro/Diagnosis Models Estimation & Evaluation

Patents

UK and US Patents Pending

Funding

- ▶ Walloon Region (Biowin)
- ▶ Fonds pour la formation à la Recherche dans l'Industrie et dans l'Agriculture (FRIA)
- ▶ GSK Biologicals

Partnership

- ▶ Christian de Duve Institute for Cellular Pathology (ICP)
- ▶ UCL/MD/MED/GYPE - Département de gynécologie, d'obstétrique et de pédiatrie
- ▶ UCL Laboratory for Applied Molecular Technologies (LTMA)
- ▶ UCL MD/MED/MINT/RUMA - Unité de rhumatologie et de métabolisme phosphocalcique
- ▶ Bioinformatics group of the Department of Plant Systems Biology, Ghent University
- ▶ GlaxoSmithKline Biologicals

Main Equipment

Center for Intensive Computing and Mass Storage (CISM) Computing Grids

KEY WORDS FOR R&D

Gene Profiling
Biomarkers
Prognosis
Diagnosis
Microarray Data
Feature Selection
High Throughput Technologies
Clinical Studies

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Study of the seric and serological proteomes of cancer patients to identify and validate predictive / prognostic / monitoring biomarkers

SENIOR SCIENTISTS :

- ▶ Olivier FERON
- ▶ Florence DEFRESNE

Research Field and Subjects

The goal of the cancer biomarker field is to develop simple, non-invasive tests that indicate cancer risk, allow early cancer detection, classify tumors so that the patient can receive the most appropriate therapy and monitor diseases progression, regression and recurrence. In addition, biomarkers can be used to assess response to therapy.

The ease with which the blood can be sampled makes it a logical choice for biomarker applications. Among the blood components that provide an indication of cancer status or response to anticancer treatments, we focus our attention on serum auto-antibodies (directed against tumor-associated antigens), peptides associated with plasma macro-proteins and circulating tumor/progenitor cells. We use a variety of techniques including 2D-DIGE and SERPA (serological proteome analysis) to identify and validate biomarkers from plasma and serum of cancer patients or mice bearing human tumor xenografts. Correlations with circulating or micro-dialysed end-products of tumor metabolism (including nitrites and lactate) are also evaluated. Current studies are dedicated to colon, liver, breast and bladder carcinoma.

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- ▶ C. BOUZIN, O. FERON. *Targeting tumor stroma and exploiting mature tumor vasculature to improve anti-cancer drug delivery*. *Drug Resist Updat*.10(3):109-20, **2007**.
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kills hypoxic tumor cells in mice. *J Clin Invest*.118(12):3930-42, **2008**.

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Awards

- ▶ Prize Belgian Soc Pharm Sci (1997)
- ▶ Prize Galien (1999)
- ▶ Prize Eugène De Somer (2008)

Funding

- ▶ FNRS, FRSM, TELEVIE
- ▶ Fondations Maisin & St luc
- ▶ Fondation belge contre le cancer
- ▶ Communauté française : ARC
- ▶ Private companies

Partnership

- ▶ Cliniques Saint-Luc (Drs C. CHANTRAIN, J-P. MACHIELS, V. GRÉGOIRE, Y. HORSMANS)
- ▶ AZ VUB (Drs M De RIDDER, S SERMEUS)
- ▶ Prof. MARTINE RAES, URBC, FUNDP, Namur

Main Equipment

- ▶ Ettan IpgPhor III (GE) [1st dim-electroph]
- ▶ Ettan DALT6 (GE) [2nd dim-electroph]
- ▶ TE77 transfer units GE
- ▶ Ettan DIGE Imager (GE)
- ▶ Decyder analysis software (GE)
- ▶ SE600 large gels electrophoresis unit (GE)
- ▶ SG100 gradient maker (GE)
- ▶ Ettan Spot Picker (GE)

- ▶ Home-made ELISA kit development
- ▶ Microplate reader & injectors (Victor 5, PE)
- ▶ Microscale liquid chromatography
- ▶ Access to Mass Spectrometry for protein identification
- ▶ The above proteomic platform is completed with various pre-clinical imaging technologies (in vivo bioluminescence detection, laser Doppler, intravital microscopy set-up) and high-standard molecular biology/biochemistry and cell biology equipments.

Products and Services

- ▶ Biomarker detection and validation from plasma and serum of cancer patients and mice bearing human tumor xenografts
- ▶ Original auto-antibodies as prognostic, predictive or monitoring cancer biomarkers
- ▶ 2D-DIGE experiments to identify differential expression of proteins, post-translational modifications (PTM) or protein-protein interactions

KEY WORDS FOR R&D

Proteomic
 2D-DIGE
 Auto-antibody
 Tumor-associated antigens
 Biomarker
 Prognostic
 Predictive
 Treatment monitoring

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New treatments of cancer : Immunotherapy and targeted therapies

SENIOR SCIENTISTS :

- ▶ Jean-François BAURAIN
- ▶ Jean-Pascal MACHIELS

Research Field and Subjects

Cancer is characterized by an inappropriate activation of molecular pathways leading to uncontrolled tumor proliferation. In addition, the immune system is not able to recognize the tumor cells and to eliminate them. Therefore, our main interests are cancer vaccines and molecular targeted therapies.

Our group is conducting academic clinical trials. We are taking care of designing, writing and coordinating these protocols. These clinical studies are performed in various tumor types such as melanoma, brain, head and neck, prostate or rectal cancer. We are currently running these trials in Belgium but also in France investigating these new approaches. Our aim is also to perform translational research to better understand the mechanisms of resistance and response to these innovative treatments. Biological samples (T cells, plasma, tumor biopsies, ...) are taken from our patients during treatment to be analyzed in the lab. We are also trying to develop pre-clinical mouse models investigating for example the radio-sensitizing properties of molecular agents.

Representative References

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therapy in patients with rectal cancer. *Ann Oncol*. 18, 738-44, **2007**.

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- ▶ J.F. BAURAIN, M. STAS, F. HAMMOUCH, A. GILLAIN, A. FEYENS, N. VAN BAREN, I. TROMME, R. VAN WIJCK, M. GARMYN, P.G. COULIE. *Association of primary melanoma ulceration and clinical benefit of adjuvant vaccination with tumor-specific antigenic peptides*. *Proceedings of the American Association of Clinical Oncology*. abstr. 3022, **2009**.

Awards

- ▶ J.P. MACHIELS. Translational Research Award, first prize at John Hopkins Oncology cancer center, 2000
- ▶ J.P. MACHIELS. AMGEN award, belgian Society of Medical Oncology, 2002
- ▶ J.F. BAURAIN. Straetmans prize, Académie Royale Belge de Médecine, 2002
- ▶ J.F. BAURAIN. Pfizer educational awards, 2003
- ▶ J.F. BAURAIN. AMGEN award, belgian Society of Medical Oncology, 2005

Funding

- ▶ FRSM & FNRS
- ▶ Fondation belge contre le cancer
- ▶ Industrie pharmaceutique
- ▶ Fondation Maisin

Partnership

- ▶ Ludwig Institute for Cancer Research, Brussels Branch
- ▶ Katholieke Universiteit Leuven
- ▶ Several academic and non academic clinics in Belgium and France

Main Equipment

- ▶ Data managing unit
- ▶ Cell culture facilities
- ▶ Molecular analysis equipment

Products and Services

- ▶ Opportunities for non-commercial clinical trials
- ▶ Facilities for data collection (patients, blood, tumor samples,...)

KEY WORDS FOR R&D

Cancer vaccines
Immunotherapy
Tumor antigens
Molecular targeted therapies
Translational research
Academic clinical trials

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Clinical studies in hematology

SENIOR SCIENTISTS :

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- ▶ Laurent KNOOPS
- ▶ Lucienne MICHAUX
- ▶ Eric VAN DEN NESTE
- ▶ Marie-Christiane VEKEMANS

Research Field and Subjects

AML HOVON Protocols

HOVON 92 : Randomized induction and post induction therapy in adult patients (≤ 60 yrs of age) with acute myelocytic leukemia (AML) or refractory anemia with excess of blasts (RAEB, RAEB-t) with IPSS score ≥ 1.5 .

The aim is to evaluate Laromustine during induction I and II, for achieving complete and partial remission, and its effect on survival.
HOVON 81 : Randomized induction and post induction therapy in older patients (≥ 61 yrs of age).

The aim is to evaluate the effect of bevacizumab during induction and consolidation on survival without event.

LNH Protocols

LNH2007-3B : Comparison between 2 chemotherapy regimens, both with Rituximab, with a PET-scan after 2 courses, in patients with a large B cell lymphoma.

GEN 415: Ofatumumab in relapsing LNH.

PTLD: Rituximab alone vs Rituximab + chemotherapy in post-transplant lymphoproliferative diseases.

Mantle cell lymphoma $< 65y$: 6 x R-CHOP + autoPBSCT vs R-CHOP/R-DHAP + HD-AraC + auto-PBSCT.

ACT-1: peripheral T-cell lymphoma, $<65y$; Campath-CHOP14 vs CHOP14, both with autologous PBSCT consolidation.

ACT-2: peripheral T-cell lymphoma, $>65y$; Campath-CHOP14 vs CHOP14

CC-5013-TCL-001: Revlimid (lenalidomide) for relapsing or refractory T-cell lymphoma.

ALL Protocol

EWALL : acute lymphoblastic leukemia, age > 55 y; includes dasatinib during induction and consolidation chemotherapy.

CLL (chronic lymphocytic leukemia) Protocols

HOVON 68: Fludarabine-cyclophosphamide vs fludarabine-cyclophosphamide-campath in poor prognosis CLL.

LUCID: fludarabine-cyclophosphamide-Rituximab vs fludarabine-cyclophosphamide-Rituximab-Lumiliximab in relapsing CLL.

CAM203: subcutaneous Campath for CLL relapsing after fludarabine based therapy, and in patients previously treated with alkylating agents.

Hx-CD20-406: Humax CD20 monoclonal humanized antibody for CLL refractory to fludarabine and Campath.

EFC6663: Flavopiridol for relapsing CLL, previously treated with alkylating agents, and refractory to fludarabine.

Acadesine: phase I/II, Relapsing or refractory CLL, after alkylating agents or after fludarabine.

Multiple myeloma

IFM 01-01 : Melphalan-prednisone, with or without thalidomide in patients ≥ 75 years. Objectives: study of the survival without progression, complete remission rate after 6 months, toxic death rate.

CC-5013-MM-020 (IFM 2007-01) : Patients who are not candidates for transplantation; 3-arms study: a/ lenalidomide until progression b/ every 4 weeks, up to a total of 18 courses c/ melphalan/prednisone/thalidomide every 6 weeks, up to a total of 12 courses.

Objective: to compare the response rate and the survival probability between the 3 therapies.

MMVAR : Velcade-thalidomide-dexamethasone vs thalidomide-dexamethasone in patients with progressive disease or relapsing after autologous transplantation.

MMY-3021 : subcutaneous vs intravenous bortezomib.

Hodgkin's lymphoma

H10 : stage I/II ; treatment adapted according to the results of a PET-scan after 2 courses of chemotherapy.

Objective: to evaluate the prognostic impact of PET-scanning.

H 3-4 : Randomized prospective treatment trial in stage III-IV Hodgkin's lymphoma: comparative evaluation of the effectiveness and the toxicity of two treatments: ABVD and BEACOPP.

Representative References

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J.J. GARNIER, T. LAMY, D. JACCARD, A. FERRANT, F. OFFNER, O. HERMINE, A. MOREAU, S. FAFI-KREMER, P. MORAND, L. CHATENOU, N. BERRIOT-VAROQUEAUX, L. BERGOUGNOUX, N. MILPIED. *Efficacy and safety of rituxiab in B-cell post-transplantation lymphoproliferative disorders: results of a prospective multicenter phase 2 study.* Blood.,107:3053-3057, **2006**.

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► E. VAN DEN NEST, V. ROBIN, J. FRANCAERT, A. HAGEMEIJER, M. STUL, P. VANDENBERGHE, A. DELANNOY, A. SONET, V. DENEYS, S. COSTANTINI, A. FERRANT, A. ROBERT, L. MICHAUX. *Chromosomal translocations independently predict treatment failure, treatment-free survival and overall survival in B-cell chronic lymphocytic leukaemia patients treated with cladribine.* Leukemia 21 : 1715-22, **2007**.

KEY WORDS FOR R&D

AML
Clinical medicine
CLL
Lymphoma
Hematology
Hodgkin
Multiple myeloma
Phase I/II
Randomization
Stem cell transplantation

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Funding

In part by Fondation Salus Sanguinis

Partnership

Multicentric, international studies

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Lung cancer - mesothelioma - clinical research in diagnosis - active treatment - supportive care

SENIOR SCIENTISTS :

- ▶ Daniel RODENSTEIN
- ▶ Philippe COLLARD
- ▶ Giuseppe LIISTRO
- ▶ Thierry PIETERS

Research Field and Subjects

The pneumology unit participates since many years to randomized phase I, II, III or IV clinical trials in the treatment of lung cancer or mesothelioma and in the diagnosis of lung cancer. Most of studies are financially supported and/or conducted by pharmaceutical companies.

Diagnostics

- Comparison of FDG-PET and transthoracic needle biopsy for the diagnosis of lung cancer. - The value of FDG-PET and endoscopic ultrasound-guided fine-needle aspiration to detect mediastinal lymph node involvement in lung cancer.

Treatment

- Several clinical studies of chemotherapy combinations. - Studies with different Tyrosine Kinase Inhibitors (of EGFR and VEGFR). - combination of an inhibitor of the CDK2/cyclin E complex with chemotherapy .

In the future, the unit will develop studies in the early diagnosis (autofluorescence endoscopy) and local tumor therapy (radiofrequency coagulation).

Product and services

- ▶ Opportunities for clinical research on about one hundred new patients each year.
- ▶ Facilities for data collection (oncology care coordinator full-time available).

Main Equipment

- ▶ Modern endoscopic equipment for diagnostic and therapeutic approach of bronchial carcinoma and pleural diseases.
- ▶ Modern computed radiological tomographic systems and nuclear imaging technics (SPEC-PET).
- ▶ 22 inpatient beds unit where oncologic patients can be admitted. Day hospital oncologic facility for ambulatory chemotherapy.

Funding

- ▶ External funds from pharmaceutical companies
- ▶ FNRS (Fonds National de la Recherche Scientifique)

Partnership

- ▶ UCL multidisciplinary thoracic oncology group.
- ▶ Numerous studies in collaboration with the pharmaceutical industry.
- ▶ Collaboration with the Belgian Society of Pneumology (oncology and interventional endoscopy).
- ▶ International interuniversity program in pneumology, including onco-pneumology

KEY WORDS FOR R&D

Chemotherapy
Cytology
Diagnosis
Histology
Immunotherapy
Internal medicine
Lung cancer
Molecular biology
Prognostic factor of molecular markers
Pulmonology
Surgical medicine
Treatment

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Mechanisms of ovarian toxicity of chemotherapeutic agents used in breast cancer

SENIOR SCIENTISTS :

- ▶ Martine BERLIERE
- ▶ Etienne MARBAIX,
- ▶ Christine GALANT
- ▶ Jean-Pascal MACHIELS

Research Field and Subjects

Gonadotoxic effects of chemotherapeutic agents used in breast cancer patients are frequently described and well documented in clinical studies but the prevailing mechanisms of this toxicity are not well understood. Some studies have suggested that chemotherapeutic agents induced apoptotic changes in pregranulosa cells that subsequently develop into follicles but it has not been confirmed, other studies found abnormalities of ovarian vascularisation.

We have initiated a mice model with young adult mice (wild type FVB). They are given intraperitoneal injections of Cyclophosphamide (200mg/kg.) Apoptosis (western blotting-immunohistochemistry) and vascularisation of ovaries are studied. Intraperitoneal injections of taxanes and adriamycin are planned and thereafter combined intra peritoneal injections of the three different agents. This study is associated with a prospective multicentric clinical study of the incidence of reversible amenorrhea in premenopausal breast cancer patients receiving chemotherapy. We study the ovarian recovery of ovarian function, the interest of biological data (hormonal values) and the impact of amenorrhea on the prognosis.

Representative References

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Awards

- ▶ Grant Fonds Joseph Maisin 2007
- ▶ Grant GGOLFB (groupement des gynécologues de langue française), 2007

Funding

Joseph Maisin Foundation

Partnership

- ▶ Christian De Duve, Institut Cancer Center
- ▶ Cancer Center Claudius Regaud (Toulouse)

Main Equipment

Multiphoton Microscope

KEY WORDS FOR R&D

Chemotherapy
Mouse
Ovarian toxicity
Fertility
Apoptosis
Neovascularisation.

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Nucleoside analogues in leukaemia

SENIOR SCIENTISTS :

- ▶ Françoise BONTEMPS
- ▶ Eric VAN DEN NESTE

Research Field and Subjects

The major interests of the group are the pharmacologic and therapeutic effects of nucleoside analogues in cancer, and particularly in leukaemia.

The current investigations aim at understanding the mechanisms of progressive chemoresistance of lymphoid malignancies to 2-chlorodeoxyadenosine (CdA) and fludarabine and at finding strategies to improve their therapeutic efficacy in B-cell chronic lymphocytic leukemia (B-CLL).

Research topics:

1. Study of deoxycytidine kinase, a key enzyme in the conversion of CdA and fludarabine into their active triphosphate form.
2. Mechanisms of action of nucleoside analogues, and in particular study of their interaction with the cell cycle in B-CLL cell lines.
3. Search for markers of defective damage response in B-CLL lymphocytes.

Representative References

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- ▶ C. SMAL, E. VAN DEN NESTE, M. MAERVOET, X. POIRE, I. THEATE AND F. BONTEMPS. *Positive regulation of deoxycytidine kinase activity by phosphorylation of Ser-74 in B-cell chronic lymphocytic leukaemia lymphocytes*. Cancer Lett., 253, 68-73, **2007**.
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- ▶ E. DE VIRON, L. KNOOPS, T. CONNEROTTE, C. SMAL, L. MICHAUX, P. SAUSSOY, P. VANNUFFEL, E. BEERT, M-C. VEKEMANS, C. HERMANS, F. BONTEMPS AND E. VAN DEN NESTE. *Impaired up-regulation of polo-like kinase 2 in B-cell chronic lymphocytic leukaemia lymphocytes resistant to fludarabine and 2-chlorodeoxyadenosine: a potential marker of defective damage response*. Br. J. Haematol., **2009** (in press).

Main Equipment

- ▶ Cell culture facilities
- ▶ General equipment for biochemical and molecular biology assays
- ▶ HPLC technology
- ▶ Microplate reader
- ▶ Liquid scintillation analyzers

Products and Services

- ▶ Cell lines
- ▶ Expression vectors
- ▶ Enzymatic assays

Awards

Pierre and Colette Bauchau Award (2002) :
F. BONTEMPS and E. VAN DEN NESTE

Funding

- ▶ FNRS
- ▶ TELEVIE
- ▶ Fondation Salus Sanguinis
- ▶ Fonds Maisin

Partnership

Dr L. KNOOPS, Hematology and Ludwig Institute for Cancer Research, Cliniques universitaires St Luc, 1200-Brussels

Staff

Total: 7

KEY WORDS FOR R&D

Cancer
Lymphoid malignancies
B-cell chronic lymphocytic leukemia
Nucleoside analogues
2-chlorodeoxyadenosine (cda)
Fludarabine
Deoxycytidine kinase (dck)
Polo-like kinase 2 (plk2)
Apoptosis
Dna damage response
Protein phosphorylation

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Screening of synthetic and natural compounds for anti-tumor and anti-angiogenic activity

SENIOR SCIENTISTS :

- ▶ Olivier FERON
- ▶ Romain BOIDOT

Research Field and Subjects

New experimental modes of screening and selection of drugs with a higher selectivity for the tumor vasculature or tumor cells are avidly needed. Hypoxia is recognized as a hallmark of most tumor types. Hypoxia triggers angiogenesis and is a source of resistance to anticancer treatments. We have therefore implemented a technological platform wherein hypoxia is integrated as a parameter to screen synthetic and natural compounds for their anti-angiogenic and anti-tumor activity.

In vitro cytotoxicity assays and specific tests to evaluate anti-angiogenic activity, both under strictly controlled hypoxia (0.1-1% O₂, cyclic or continuous hypoxia) allow to identify and validate the therapeutic potential of drugs through the establishment of dose-response curves. The lab is also equipped to perform high-standard preclinical evaluation of selected compounds in a variety of validated mouse tumor and metastases models.

The sources of compounds are issued from chemical libraries (or de novo synthesis) and from natural extracts of plants.

Representative References

- ▶ O. FERON. *Targeting the tumor vascular compartment to improve conventional cancer therapy*. Trends Pharmacol Sci., 25(10):536-42, **2005**.
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- ▶ E. SBAA, J. DEWEVER, P. MARTINIVE, C. BOUZIN, F. FRÉRART, J.L. BALLIGAND, C. DESSY, O. FERON. *Caveolin plays a central role in endothelial progenitor cell mobilization and homing in SDF-1-driven postischemic vasculogenesis*. Circ Res., 98(9):1219-27, **2006**.
- ▶ J. DEWEVER, F. FRÉRART, C. BOUZIN, C. BAUDELET, R. ANSIAUX, P. SONVEAUX, B. GALLETZ, C. DESSY, O. FERON. *Caveolin-1 is critical for the maturation of tumor blood vessels through the regulation of both endothelial tube formation and mural cell recruitment*. Am J Pathol., 171(5):1619-28, **2007**.
- ▶ C. BOUZIN, O. FERON. *Targeting tumor stroma and exploiting mature tumor vasculature to improve anti-cancer drug delivery*. Drug Resist Updat., 10(3):109-20, **2007**.

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▶ F. FRÉRART, P. SONVEAUX, G. RATH, A. SMOOS, A. MEQOR, N. CHARLIER, B.F. JORDAN, J. SALIEZ, A. NOËL, C. DESSY, B. GALLETZ, O. FERON. *The acidic tumor microenvironment promotes the reconversion of nitrite into nitric oxide: towards a new and safe radiosensitizing strategy*. Clin Cancer Res., 14(9):2768-74, **2008**.

▶ P. SONVEAUX, F. VÉGRAN, T. SCHROEDER, M.C. WERGIN, J. VERRAX, Z.N. RABBANI, C.J. DE SAEDELEER, K.M. KENNEDY, C. DIEPART, B.F. JORDAN, M.J. KELLEY, B. GALLETZ, M.L. WAHL, M.W. DEWHIRST*, O. FERON* (*co-last author). *Targeting lactate-fueled respiration selectively kills hypoxic tumor cells in mice*. J Clin Invest., 118(12):3930-42, **2008**.

Patent

- ▶ PCT/EP00/07731: O. FERON & J.L. BALLIGAND. Use of compound or pharmaceutical composition for the prevention and/or the treatment of ischemic heart and cerebral diseases, tumor development and for wound healing.

Awards

- ▶ Prize Belgian Soc Pharm Sci (1997)
- ▶ Prize Galien (1999)
- ▶ Prize Orbita (2001)
- ▶ Prize MSD-BLC (2001)
- ▶ Prize Eugène De Somer (2008)

Funding

- ▶ FNRS, FRSM, TELEVIE
- ▶ Fondations Maisin & St luc
- ▶ Région bruxelloise
- ▶ Private companies

Partnership

- ▶ PROF. J. QUETIN-LECLERCQ (Pharmacognosy), LDRI, UCL
- ▶ PROF. O. RIAANT AND J MARCHAND (Chemistry), CHOM, UCL
- ▶ PROF. R. KISS (Pharmacognosy), Toxicology, ULB
- ▶ DR CHALTIN, CD3 (Centre for Drug Design and Discovery), KUL, Leuven

Main Equipment

- ▶ Hypoxia workstation (Ruskin, In Vivo500) for cell handling and cultures
- ▶ Microscope Axio-observer (Z1, Zeiss) incl. O₂ and CO₂ modules and videomicroscopy set-up to track angiogenesis, cell migration and cell death
- ▶ Microplate reader & injectors (Victor 5, PE)
- ▶ Automatic liquid handler for sample dilution
- ▶ The lab has also high-standard molecular biology, biochemistry and cell biology equipments; imaging technologies are available to evaluate the impact of selected drugs in a variety of mouse models of human tumor xenografts and metastases:
 - ▶ In vivo bioluminescence detection (IVIS, Xenogen)
 - ▶ Intravital microscopy: fluorescence microscopes (Axioskop, Zeiss) + camera EBCD (Hamamatsu)
 - ▶ Laser Doppler imager (LDI, Moor)
 - ▶ Axio-Imager and Apotome pseudo-confocal microscopy (Zeiss) + AxioCam
 - ▶ Telemetry (DSI) for hemodynamic measurements
 - ▶ Local animal facilities for mouse maintenance and breeding

Products and Services

- ▶ Screening of synthetic or natural compounds for anti-tumor and/or anti-angiogenic activity under hypoxic and/or normoxic conditions
- ▶ Original lead compounds with (hypoxia-selective) anti-tumor and/or anti-angiogenic activity

KEY WORDS FOR R&D

Drug discovery
Drug library
Medicinal plant
Natural products
High-throughput screening
Anti-tumor activity
Angiogenesis
Hypoxia

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Influence of the tumor microenvironment including tumor hypoxia and metabolism on cancer progression and metastases

SENIOR SCIENTISTS :

- ▶ Olivier FERON
- ▶ Pierre SONVEAUX

Research Field and Subjects

It is known for many years that cellular metabolism within a solid tumour is markedly different from that of the corresponding normal tissue. One of the most recognized reasons for altered tumor metabolism is hypoxia and the consecutive induction of the transcription factor HIF1 or hypoxia-inducible factor 1. The net result of HIF1 activation is to shift energy production by increasing glycolysis and decreasing mitochondrial function. Interestingly, the exacerbated tumor cell capacity to uptake glucose -even under aerobic conditions (the so-called Warburg effect)- is associated with a higher invasive potential.

Lactate, the end-product of glycolysis, and more generally monocarboxylate transporters within tumor cells, are key actors in the interplay between tumor cell metabolism and local invasion/metastatic progression. Through the use of a variety of in vitro and in vivo models, we aim to characterize pathways (ie, therapeutic targets) that regulate lactate homeostasis and to identify new drugs to interfere with them.

Representative References

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- ▶ E. SBAA, J. DEWEVER, P. MARTINIVE, C. BOUZIN, F. FRÉRART, J.L. BALLIGAND, C. DESSY, O. FERON. *Caveolin plays a central role in endothelial progenitor cell mobilization and homing in SDF-1-driven postischemic vasculogenesis*. Circ Res., 98(9):1219-27, **2006**.
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- ▶ C. BOUZIN, O. FERON. *Targeting tumor stroma and exploiting mature tumor vasculature to improve anti-cancer drug delivery*. Drug Resist Updat., 10(3):109-20, **2007**.

▶ C. BOUZIN, A. BROUET, J. DE VRIESE, J. DEWEVER, O. FERON. *Effects of vascular endothelial growth factor on the lymphocyte-endothelium interactions: identification of caveolin-1 and nitric oxide as control points of endothelial cell anergy*. J Immunol., 178(3):1505-11, **2007**.

▶ F. FRÉRART, P. SONVEAUX, G. RATH, A. SMOOS, A. MEQOR, N. CHARLIER, B.F. JORDAN, J. SALIEZ, A. NOËL, C. DESSY, B. GALLEZ, O. FERON. *The acidic tumor microenvironment promotes the reconversion of nitrite into nitric oxide: towards a new and safe radiosensitizing strategy*. Clin Cancer Res., 14(9):2768-74, **2008**.

▶ P. SONVEAUX, F. VÉGRAN, T. SCHROEDER, M.C. WERGIN, J. VERRAX, Z.N. RABBANI, C.J. DE SAEDELEER, K.M. KENNEDY, C. DIEPART, B.F. JORDAN, M.J. KELLEY, B. GALLEZ, M.L. WAHL, M.W. DEWHIRST*, O. FERON* (*co-last author). *Targeting lactate-fueled respiration selectively kills hypoxic tumor cells in mice*. J Clin Invest., 118(12):3930-42, **2008**.

Patents

- ▶ PCT/EP00/07731: O. FERON & J.L. BALLIGAND. Use of compound or pharmaceutical composition for the prevention and/or the treatment of ischemic heart and cerebral diseases, tumor development and for wound healing.
- ▶ WO 2006113540 and US 7,338,670 B2. M.W. DEWHIRST, J.S. STAMLER, T.J. McMAHON & P. SONVEAUX. Use of an agent that restores tissue perfusion and oxygenation.

Awards

- ▶ Prize Belgian Soc Pharm Sci (1997 & 2005)
- ▶ Prize Galien (1999)
- ▶ FECS-EJC Award 2007
- ▶ VARIAN-Juliana Denekamp Award 2008
- ▶ Prize Henri Fauconnier 2008
- ▶ Prize Eugène De Somer (2008)

Funding

- ▶ FNRS, FRSM, TELEVIE
- ▶ Fondations Maisin & St luc

- ▶ Fondation belge contre le cancer
- ▶ Communauté française : ARC
- ▶ Région wallonne
- ▶ Private companies
- ▶ European Research Council

- ▶ Axio-observer (Z1, Zeiss) microscopy incl. O₂ and CO₂ modules
- ▶ Axio-Imager and Apotome pseudo-confocal microscopy (Zeiss) + AxioCam Mrc5

The lab has its own peripheral animal facilities for mouse maintenance and breeding

Partnership

- ▶ Prof MW. DEWHIRST (Duke University, USA)
- ▶ Program COST TD0901 Hypoxia sensing, signaling and adaptation

Products and Services

- ▶ Screening of synthetic or natural compounds interfering with the tumor cell metabolism
- ▶ Original lead compounds with inhibitory activity on lactate transporters (MCT)

Main Equipment

The lab has high-standard molecular biology, biochemistry and cell biology equipments, including:

- ▶ Real-time PCR device (iQ5, Biorad)
- ▶ Nanodrop and 96-well PCR devices
- ▶ virus and plasmid handling platforms
- ▶ 6 electrophoresis and transfer units
- ▶ Proteomic platform including DIGE imager, spot picker and microscale LC
- ▶ Micro- and ultracentrifuges
- ▶ Chemi- and fluo imager (Geliance, PE)
- ▶ 4 laminar fluxes and 6 CO₂ incubators
- ▶ Cell counter
- ▶ MACS and local access to flow cytometer
- ▶ Cryostat (MicroM HM560, Prosan)
- ▶ Hypoxia workstation (Ruskin, In Vivo500)
- ▶ Microplate reader & injectors (Victor 5, PE)
- ▶ Microdialysis analyzer (ISCUS)

The lab is also equipped with imaging technologies to characterize tumor and metastatic progression in a variety of mouse models of human tumor xenografts and metastases:

- ▶ In vivo bioluminescence detection (IVIS, Xenogen)
- ▶ Axioskop Intravital microscopy (Zeiss) + camera EBCD (Hamamatsu)
- ▶ Axiovert Fluorescence microscopy (Zeiss) + MRC5 camera (Zeiss)
- ▶ Laser Doppler imager (LDI, Moor)

KEY WORDS FOR R&D

Tumor microenvironment
 Tumor hypoxia
 HIF
 Tumor metabolism
 Lactate
 Monocarboxylate transporter
 Metastases

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Prevention and treatment of hepatocellular carcinoma

SENIOR SCIENTISTS :

- ▶ Yves HORSMANS
- ▶ Peter STÄRKEL
- ▶ Ivan BORBATH

Research Field and Subjects

The aim of the project is to assess the potential role of drugs in the chemoprevention of primary liver cancer, namely hepatocellular carcinoma (HCC).

The drugs that are studied are lanreotide, a somatostatine analogue, studied *in vitro* and *in vivo*, as in human population and the synthetic Ras inhibitor FTS.

The effects of the two drugs have been assessed in rats having induced cirrhosis, to look at the preventive effect on neoplastic nodules in an already pre-neoplastic organ, and preliminary results have already been published.

We have shown that lanreotide was efficient in the reduction of the size of pre-neoplastic and neoplastic nodules. The mechanisms of its action are not fully understood at the present time, but preliminary data show differential alteration of proliferation and apoptosis, inhibition of fibrogenesis and angiogenesis. Further analyses will be performed to determine the effect of lanreotide on fibrogenesis, of which the main actors are hepatic stellate cells (HSC). We will isolate HSC from HCC-bearing rats to analyse changes in their morphotype as well as their sensitivity to Lanreotide.

The ras oncoprotein plays an important role in the regulation of normal cellular proliferation and differentiation but may also be implicated in carcinogenesis. Activation of the ras proto-oncogene seems to be a frequent event in hepatocellular carcinoma. Our second pole of HCC research focuses on the *in vitro* and *in vivo* evaluation of the inhibitory effect of the synthetic Ras inhibitor FTS on proliferation and apoptosis of human HCC cell lines as well as on the development and/or regression of chemically induced hepatic carcinomas in rats. The molecular pathways that might be implicated in this potential anti-tumour effect are also studied. Preliminary results confirm an anti-tumor effect of the compound *in vivo* by inducing apoptosis in transformed hepatocytes. Further confirmation that ras and ras-dependent pathways might be important in liver tumour development and the possibility of inhibiting them by FTS, could represent a novel source for developing new therapeutic strategies.

Representative References

- ▶ P. STÄRKEL, C. DESAEGER, C. SEMPOUX, E. LEGRAND, I. LECLERCQ, Y. HORSMANS. *Blunted DNA synthesis and delayed S-phase entry following inhibition of CDK2 activity in the regenerating rat liver*. *Lab Invest*; 85:562-71 (IF 2005: 3,859), **2005**.
- ▶ I. BORBATH, I.A. LECLERCQ, J. ABARCA-QUINONES, ET AL. *Inhibition of early preneoplastic events in the rat liver by the somatostatin analog lanreotide*. *Cancer Sci*; 98(12):1831-1839, **2007**.
- ▶ I. BORBATH, I. LECLERCQ, P. MOULIN, ET AL. *The PPARGgamma agonist pioglitazone inhibits early neoplastic occurrence in the rat liver*. *Eur J Cancer*; 43(11):1755-1763, **2007**.
- ▶ A. DA SILVA MORAIS, A. SALIEZ, I. LECLERCQ, Y. HORSMANS, P. STÄRKEL. *Inhibition of the RAS oncoprotein reduces proliferation of hepatocytes in vitro and in vivo in rats*. *Clin Sci (Lond)*; 114s:73-83 (IF 2007: 3,900), **2008**.
- ▶ T. SCHNEIDER-MERCK, I. BORBATH, N. CHARETTE, C. DE SAEGER, J. ABARCA, I. LECLERCQ, Y. HORSMANS, P. STARKEL. *The Ras inhibitor farnesylthiosalicylic acid (FTS) prevents nodule formation and development of preneoplastic foci of altered hepatocytes in rats*. *Eur J Cancer*; in press (IF 2007: 4,454), **2009**.

Main Equipment

- ▶ Western Blot
- ▶ Real-time PCR
- ▶ Immunohistochemistry
- ▶ Flow Cytometry
- ▶ Laboratory animal handling and surgery

KEY WORDS FOR R&D

Chemoprevention
Gastroenterology
Liver
Liver tumors

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Anti-cancer drug discovery and synthesis

SENIOR SCIENTISTS :

- ▶ Bernard MASEREEL
- ▶ Johan WOUTERS

Research Field and Subjects

This research axis of the laboratory is a drug discovery program aimed at finding new chemical entities presenting anti-cancer properties by inhibiting the immunosuppression mediated by indoleamine 2,3-dioxygenase (IDO) and/or tryptophane 2,3-dioxygenase (TDO) expression in tumors. Indeed, IDO is an immunomodulatory enzyme produced by some alternatively activated macrophages and other immunoregulatory cells (also used as an immune subversion strategy by many tumors). This enzyme catalyzes the degradation of the essential amino acid L-tryptophan to N-formylkynurenine. IDO is the first and rate limiting enzyme of Tryptophan catabolism through Kynurenine pathway, thus causing depletion of tryptophan which can cause halted growth of microbes as well as T cells.

Part of the research also encompasses a phase I/II clinical trial with a first-generation IDO inhibitor, and a diagnostic application leading to the development of new diagnostic test for detecting IDO-positive cancers.

A similar approach is used to develop inhibitors of carbonic anhydrase type IX which is overexpressed in cancer cells.

Representative References

- ▶ A. THIRY, S. ROLIN, D. VULLO, A. FRANKART, A. SCOZZAFAVA, J.-M. DOGNÉ, J. WOUTERS, C.T. SUPURAN, B. MASEREEL. *Indanesulfonamides as carbonic anhydrase inhibitors and anticonvulsant agents: structure-activity relationship and pharmacological evaluation*. Eur. J. Med. Chem., 43, 2853-2860, **2008**.
- ▶ A. THIRY, A. DELAYEN, L. GOOSSENS, R. HOUSSIN, M. LEDECQ, A. FRANKART, J.-M. DOGNÉ, J. WOUTERS, C. SUPURAN, J.-P. HENICHART, B. MASEREEL. *Synthesis and biological evaluation of a new family of anti-benzylanilinosulfonamides as CA IX inhibitors*. Eur. J. of Med. Chem., 44, 511-518, **2009**.
- ▶ A. THIRY, M. LEDECQ, A. CECCHI, R. FRÉDÉRICK, J.-M. DOGNÉ, J. WOUTERS, B. MASEREEL, C. SUPURAN. *Ligand-based and structure-based virtual screening to identify carbonic anhydrase IX inhibitors*. Bioorg. Med. Chem., 17: 553-557, **2009**.

Partnership

- ▶ University of Louvain
- ▶ University of Liège
- ▶ Euroscreen
- ▶ GSK
- ▶ Maastru Lab (The Netherlands)
- ▶ University of Florence (Italy)
- ▶ ICPAL, University of Lille (France)

Main Equipment

- ▶ Differential calorimetric analysis apparatus
- ▶ Monocrystal/powder diffractometer
- ▶ Dipolemeter
- ▶ Spectrometric analyses (FPLC, GC, IR, UV...)
- ▶ Viscosimeter

Funding

- ▶ FNRS-FSR
- ▶ RW (Biowin)

Products and Services

Crystallography, organic synthesis, molecular modeling, characterization, drug design, medicinal chemistry

KEY WORDS FOR R&D

IDO
TDO
Immunotherapy
Carbonic anhydrase
Inhibitor
Cancer treatment

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Mechanisms involved in cancer cell resistance to apoptosis and/or autophagy induced by chemotherapeutic drugs under hypoxia

SENIOR SCIENTISTS :

- ▶ Carine MICHIELS
- ▶ Thierry ARNOULD

Research Field and Subjects

Chemotherapy is an integral component of standard care for solid tumors. However, recurrence may occur, with a poor clinical outcome. During tumor growth, the central area becomes hypoxic due to poor access to blood vessels capable of delivering oxygen. Hypoxic regions have been evidenced in a wide range of cancers. Low tumor oxygenation has been identified as an independent negative prognostic factor and is associated with a higher risk of metastatic spread. In addition, hypoxia contributes to resistance to radiation therapy and to chemotherapy. Hypoxia may lead to treatment resistance by modulating gene expression resulting in resistance to cell death.

The aim of our work is to better understand the mechanisms by which hypoxia modulates the sensitivity of cancer cells to chemotherapeutic drugs, both regarding the induction of apoptosis but also of autophagy.

In previous work, we showed that hypoxia protected HepG2 cells against etoposide-induced apoptosis but other cell lines and other agents are under investigation. In order to define the mechanisms initiated by hypoxia which are responsible for its protective effects, molecular profiles of changes in gene expression and transcription factor activity induced in these conditions are established. mRNA levels of genes encoding proteins involved in the regulation of apoptosis process are assayed using DNA microarrays or microfluidic cards. Unbiased cluster analyses are performed to evidence correlations between expression profiles, profiles of transcription factor activity and apoptotic profile. Validation of candidates is then performed using siRNA silencing.

Representative References

- ▶ J.P. PIRET, D. MOTTET, M. RAES AND C. MICHIELS. *Is HIF-1 α a pro- or an anti-apoptotic protein?* Biochem Pharmacol 64, 889-892, **2002**.
- ▶ J.P. PIRET, E. MINET, J.P. COSSE, N. NINANE, C. DEBACQ, M. RAES AND C. MICHIELS. *Hypoxia-inducible factor-1-dependent overexpression of myeloid cell factor-1 protects hypoxic cells against tert-butyl hydroperoxide-induced apoptosis.* J Biol Chem 280, 9336-9344, **2005**.
- ▶ J.P. PIRET, J.P. COSSE, N. NINANE, M. RAES AND C. MICHIELS. *Hypoxia protects HepG2 cells against etoposide-induced apoptosis via a HIF-1-independent pathway.* Exp Cell Res 312, 2908-2920, **2006**.
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- ▶ A. SERMEUS, J.P. COSSE, M. CRESPIAN, V. MAINFROID, F. DE LONGUEVILLE, N. NINANE, M. RAES, J. REMACLE AND C. MICHIELS. *Hypoxia induces protection against etoposide-induced apoptosis: molecular profiling of changes in gene expression and transcription factor activity.* Mol Cancer 7, 27, **2008**.
- ▶ J.P. COSSE AND C. MICHIELS. *Tumour hypoxia affects the responsiveness of cancer cells to chemotherapy and promotes cancer progression* Anticancer Agents. Med Chem 8, 790-797, **2008**.

Funding

- ▶ T EL EVIE
- ▶ FNRS/FRIA

Partnership

Biowin : Keymarker project

Main Equipment

- ▶ Cell culture facilities, hypoxic chambers
- ▶ General equipment for biochemical and molecular biology assays
- ▶ Absorbance, fluorescence, luminescence microplate readers
- ▶ real-time PCR, equipped for microfluidic cards
- ▶ Full proteomic platform with Maldi and MS-MS mass spectrometers
- ▶ Confocal microscope

Products and Services

- ▶ Cellular models for the evaluation of the capacity of drugs to induce apoptosis and/or autophagy
- ▶ Proteomic platform

KEY WORDS FOR R&D

Hypoxia
Chemotherapy
Apoptosis
Autophagy
Resistance
Signal transduction
Gene expression regulation

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Active and passive targeting of anticancer nanomedicine

SENIOR SCIENTISTS :

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- ▶ Olivier FERON
- ▶ Jacqueline MARCHAND

Research Field and Subjects

Nanomedicines, in particular polymeric micelles and nanoparticles, loaded with anticancer drugs, siRNA or diagnostic substances have been developed i) to enhance the solubility of poorly soluble drugs (e.g., paclitaxel) ii) to protect drugs from degradation (e.g. si RNA) iii) to passively target anticancer drugs to the tumor by the Enhanced Permeation Retention (EPR) effect through the leaky tumor endothelium iv) to actively target the anticancer drugs to the tumor endothelium or to tumor cells by grafting of specific ligands (e.g., RGD) or by external triggering.

The research focuses at developing new nanosized drug delivery systems of poorly soluble anticancer drugs or siRNA, comparing the efficacy of active and passive targeting of those drugs and developing new ligands of tumor endothelium to be grafted on the nanoparticles.

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of PCL-PEG for the Covalent Immobilisation of Biomolecules. Biomacromolecules, doi: 10.1021/bm900027r. **2009**.

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Award

- ▶ Prize Galien (OF)

Partnership

Different small biotechs and big pharmas

Funding

- ▶ TÉLEVIE
- ▶ FRSM
- ▶ Biowin « Targetum »
- ▶ Waleo « Targan »

Main Equipment

- ▶ Nanosizer ZS (Malvern)
- ▶ Cell culture facilities
- ▶ HPLC
- ▶ In vivo bioluminescence detection (IVIS, Xenogen)
- ▶ Intravital microscopy: fluorescence microscopes (Axioskop, Zeiss) + camera EBCD (Hamamatsu)

- ▶ Microscope Axio-observer (Z1, Zeiss) incl. O₂ and CO₂ modules and videomicroscopy set-up to track angiogenesis, cell migration and cell death
- ▶ Laser Doppler imager (LDI, Moor)
- ▶ Telemetry (DSI) for hemodynamic measurements
- ▶ Local animal facilities for mouse maintenance and breeding
- ▶ Organic synthesis facilities and structural analysis (MS, NMR 500 MHz, ...)
- ▶ Access to surface analysis (XPS, SiMS, AFM, ...)

Products and Services

- ▶ Formulation and physicochemical characterisation of drug-loaded nanoparticles
- ▶ In vitro and in vivo screening of therapeutic nanomedicine for anti-tumor and/or anti-angiogenic activity
- ▶ Synthesis of biologically active molecules and linkers for grafting on materials.

KEY WORDS FOR R&D

Nanoparticles
 Polymeric micelles
 Tumor targeting
 Angiogenesis
 Hypoxia
 Peptidomimetics
 Integrin ligands

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Isolation and structure determination of cytotoxic, anticancer or anti-angiogenic compounds from plants

SENIOR SCIENTISTS :

- ▶ Joëlle QUETIN-LECLERCQ
- ▶ Gabrielle CHATAIGNE

Research Field and Subjects

Plants are a large reservoir of original molecules which may act on new targets or possess new modes of action and can be used as prototypes by chemists. The aim of our studies is to isolate, by different preparative or semi-preparative techniques (Centrifugal Partition Chromatography (CPC), MPLC, overpressure laminar chromatography (OPLC),...), cytotoxic and anti-angiogenic molecules from plants selected on an ethnopharmacological basis. Structures are determined by comparison with known compounds and spectroscopic methods (UV, IR, HPLC-MS, 1 or 2D, NMR).

Several new bioactive terpenic structures have been identified as well as alkaloids.

The mode of action and cellular targets of the most interesting compounds are analysed in collaboration with specialized teams and derivatives are synthesised in collaboration with chemists to study structure-activity relationships. Methods for quantification of these bioactive molecules in extracts are also developed.

Representative references

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Funding

Brussels region

Partnership

- ▶ Université libre de Bruxelles (ULB)
- ▶ Brussels Region (Nathypox)

Main Equipment

- ▶ Preparative MPLC
- ▶ HPLC/UV, HPLC-DAD, HPLC-MS, high resolution HPLC-MSⁿ (Orbitrap)
- ▶ GC-FID, GC-FTIR, GC-MS.
- ▶ Overpressure Laminar chromatography (OPLC)
- ▶ Microwave extraction
- ▶ Centrifugal Partition Chromatography (CPC)

Products and Services

- ▶ Analysis and quantification in complex extracts of natural bioactive compounds.
- ▶ Preparative purification techniques.
- ▶ Structure analysis

KEY WORDS FOR R&D

Medicinal plants
Pharmaceutical sciences
Pharmacognosy
Separation techniques
Structural chemistry

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Treatment of skin carcinoma using phototherapy

SENIOR SCIENTIST :

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Research Field and Subjects

The project aims to develop an original phototherapy to induce the cell death of cancer cells in the context of skin carcinoma. This approach is based on metallic complexes able to react with biological macromolecules such as nucleic acids after illumination. Using this approach we hope to develop a new gene silencing based therapy using complexed antisense oligonucleotides (ASO), targetting specific RNA messengers. The method will be first developed and evaluated on immortalized keratinocytes cultured in monolayers or in organotypic culture in vitro. In a second step, we will use a xenograft model of HPV positive cells in NOD/SCID mice. The project also aims to screen the transfection efficiency of cationic polymers, with controlled architecture to vectorize the complexed ASO as well as to optimize the galenic formulation of the complexed AOS, compatible with their transcutaneous delivery.

The interdisciplinary project is based on a consortium of 6 laboratories from 4 universities (see Partnership).

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Funding

Walloon Region, DGO

Partnership

Carcinom Network DGO-Waleo-2 (Walloon Region): PHILIPPE DUBOIS (UMH), ANDRÉE KIRSCH-DE MESMAEKER & CÉCILE MOUCHERON (ULB), JACQUES PIETTE, PHILIPPE DELVENNE & GÉRALDINE PIEL (ULg)

Main Equipment

Imaging technology (confocal Microscopy), Gene expression tools, Cell culture facility

Products and Services

Imaging technology (confocal Microscopy), Gene expression tools

KEY WORDS FOR R&D

Cancerology
Keratinocytes
Skin-carcinoma
Phototherapy
Antisense-oligonucleotides
Metallic-complexes
Gene-silencing
Cationic-polymers
Controlled-synthesis
Transfection

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Design, synthesis, and biological evaluation of mixed DNA methyl transferase and Histone Deacetylase inhibitors as epigenetic regulators

SENIOR SCIENTISTS :

- ▶ Johan WOUTERS
- ▶ Didier LAMBERT

Research Field and Subjects

Deregulation of gene expression is a hallmark of cancer. It has become increasingly recognized that aberrant epigenetic modifications play major roles in the tumorigenic process in addition to genetic lesions. These modifications are imposed on chromatin, do not change the nucleotide sequence of DNA, and are manifested by specific patterns of gene expression that are heritable through many cell divisions. The present research is a drug discovery program aimed at finding, preparing and evaluating mixed inhibitors of DNA methyltransferases and Histone deacetylase as potential anticancer drugs. It also encompasses biological evaluation of enzymes, cells, and animals and a Phase I trial. It gets support from the Télévie (FNRS).

Partnership

- ▶ University of Louvain
- ▶ University of Liège & Gembloux: LUCAS WILLEMS, PHILIPPE DELVENNE
- ▶ University of Brussels : CARINE VAN LINT, JEAN-PAUL SCULIER, FRANÇOIS FUKS
- ▶ Hôpital Bordet

Main Equipment

- ▶ Differential calorimetric analysis apparatus
- ▶ Monocrystal / powder diffractometer
- ▶ Dipolemeter
- ▶ Spectrometric analyses (FPLC, GC, IR, UV...)
- ▶ Viscosimeter

Funding

- ▶ FNRS-FSR (TELEVIE), FRIA

Products and Services

Molecular modelling, organic synthesis, crystallography, characterization, drug design, medicinal chemistry

KEY WORDS FOR R&D

Epigenetic modifications
Cancer treatment
HDAC
DN
Methyl transferase
Histone deacetylase
Drug design

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Limb salvage in tumor surgery with massive bone allografts (Bone Bank)

SENIOR SCIENTISTS :

- ▶ Christian DELLOYE
- ▶ Olivier CORNU
- ▶ Xavier BANSE
- ▶ Pierre-Louis DOCQUIER

Research Field and Subjects

- Study of massive allografts complications (fracture, infection, non-union) ;
- Bone allografts incorporation ;
- Treatment of non union or delayed union by autologous cell therapy ;
- Computerized selection of bone allografts ;
- Computer-guided navigation of tumor resection and bone allograft cutting.

Bone allografts have a long history as a substitute for limb reconstruction after tumor resection. They are commonly used because they provide immediate structural support that can be associated with a prosthesis or with osteosynthesis. Among several advantages, their use allows anatomical reconstruction of the skeletal defect, biological union to host bone through callus formation, soft tissue adherence around the grafted bone and the possibility of tendon reinsertion on its counterpart left on the bone graft. Among possible disadvantages, there are the risk, albeit remote, of disease transmission through the implant, and a high rate of non union and fracture. These complications are related to the non vitality of the bone graft.

Research projects are conducted to remote disadvantages of bone allografts. Methods of bacterial screening and graft decontamination are assessed by *in vitro* testing. Using the graft as an antibiotic delivering system is also considered.

As a bone allograft serves primarily as an osseous spacer that allows osteoconduction of host cells into its mass, biological answer results in a progressive incorporation of the graft into the host bone. Incorporation includes a series of events leading to gradual replacement of the grafted bone by host bone through a mechanism of osteoclastic resorption followed by new bone deposition. This intricate process however is very limited in time and space, leaving eventually a mass of dead bone that has been poorly substituted by new bone. Efforts are made to overcome this limited substitution through improvement of the revascularisation and revitalisation of the bone. The research is organised to explore the different avenues available to achieving a better incorporation and avoiding a mechanical failure.

Another research area is the introduction of computerised navigation for bone tumor resection and cutting of a bone allograft in order to obtain millimetric adjustment between the host bone and the allograft. It is hypothesized that such adjustment will give better chance to allograft healing.

Representative References

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Products and Services

The Tissue Bank is able to deliver massive bone allografts to surgeons for skeletal reconstruction (bos-orto@uclouvain.be). Research projects may cover all fields of interests from microbiological studies (*in vitro* testing of bacterial screening and decontamination) to *in vivo* model of allografts incorporation (Tibial critical defect in sheep). Mechanical and morphological assess-

ment of allograft reconstruction may be performed. Among the different avenues to improve allograft incorporation and bone healing, autogenous cell augmentation represents an indirect approach.

Main Equipment

- ▶ Bone morphological analysis
- ▶ Cell culture and Cleanroom facilities
- ▶ Digitalisation table
- ▶ Exact saw
- ▶ Fluoroskan Ascent
- ▶ Hip walking simulator
- ▶ Leitz saw 1600
- ▶ Microradiography (Bemtograph)
- ▶ Microscopy
- ▶ Microtome Leica.
- ▶ Multiscan RC200-240C
- ▶ p-QCT, model XCT Research SA+® Stratec (RUMA)
- ▶ Radiographic digitizer (Widar)
- ▶ Tissue Bank
- ▶ UTS model 100-1 (ERM)
- ▶ Zwick model Z50/TH3A (ERM)

Awards

- ▶ Dr D. DUFRANE BELACT - 2000
- ▶ Dr A. BAVADEKAR EFORT – Rhodos - 2001
- ▶ Dr D. DUFRANE ESACT – Tylösand - 2001
- ▶ Dr P.L. DOCQUIER – SORBCOT– 2004

Funding

- ▶ TELEVIE-FNRS
- ▶ Salus Sanguinis foundation.

Partnership

- ▶ Royal Military School - Engineering (PROF VAN THOMME), Bruxelles, Belgium
- ▶ University of Toronto – Phospho-calcic metabolism Lab (PROF GRYPAS), Toronto, Canada
- ▶ Institut Rizzoli (PROF DONATI), Bologne, Italy.
- ▶ Azienda Ospedaliera Careggi (PROF CAPANNA), Florence, Italy

KEY WORDS FOR R&D

Allografts
Anatomopathology
Autologous cell therapy
Bacteriology
Biomechanic
Bone induction
Bone remodeling
Delayed-union
Fracture
Infection
Limb salvage
Orthopaedic
Surgery
Transplantation

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Molecular imaging of cancer and experimental radiotherapy

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- ▶ Hubert MEURISSE
- ▶ Stéphane VYNCKIER
- ▶ Stéphane WALRAND
- ▶ Thomas DOUMONT
- ▶ Jacques GILLART
- ▶ Daniel LABAR

Research Field and Subjects

- Biological targeting in conformal (3D-CRT) and intensity modulated (IMTR) radiation therapy
- Use of functional imaging with PET and MRI for treatment planning in conformal radiotherapy of head and neck and brain tumors.
- Dosimetry studies with Palladium-103
- Dosimetry intercomparisons for hadron beams
- Detection of tumor hypoxia with chemical probes
- Radiosensitization by nucleoside analogues
- Biological effects and radiobiological calibration of non conventional radiation beam.

Representative References

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Patent

J. MARCHAND, V. GRÉGOIRE, O. JOSSE, D. LABAR (1999) European patent n° 99870172.6 "Methods for preparing parfluorinated [18F] radiolabelled nitroimidazole derivatives for cellular hypoxia detection.

Partnership

- ▶ American Association for Cancer Research (AACR)
- ▶ American Radiation Research Society (RRS)
- ▶ American Society for Therapeutic Radiology and Oncology (ASTRO)
- ▶ Belgian Association for Cancer Research (BACR)
- ▶ European Laryngological Society (ELS)
- ▶ Head and Neck group of the European Organization for Research and Treatment of Cancer (EORTC)
- ▶ Radiotherapy group of the European Organization for Research and Treatment of Cancer (EORTC)
- ▶ European Society for Therapeutic Radiology and Oncology (ESTRO)
- ▶ Société Belge de Radiothérapie Oncologie (ABRO)

Funding

National Collaborations

FNRS – Télévie
Belgian Federation against Cancer
Walloon Region

International Collaborations

European Commission
INCa – C. Oscar Lambret

Main Equipment

- ▶ 6 radio-HPLC 1 ψ -spectrophotometer HPGe Canberra
- ▶ 3 GC 1 ψ -counter
- ▶ 1 radio-TLC (Raytec)1 β -counter A
- ▶ Phosphoimager Fuji
- ▶ PET Siemens HR961 (ded. to research : human, monkey, pig, dog,...)
- ▶ PET Philips Mosaic
- ▶ PET Siemens HR+
- ▶ SPECT Linoview
- ▶ PET-CT Philips
- ▶ Cyclotron cyclone 30 (IBA)
- ▶ Cyclotron cyclone 18 (IBA)
- ▶ Remote systems for radiolabeled molecules production

Products and Services

- ▶ Biological calibration of beams of particles by missions on site of the team of radiobiology UCL (3-6 weeks)
- ▶ Center radiobiological experiments near Cyclotron (CERCYL): neutron irradiation facilities, making it possible to irradiate and treat biological samples in the same place.

KEY WORDS FOR R&D

Biological targeting
Radiation therapy
Functional imaging
Head and neck and brain tumors
Dosimetry
Tumor hypoxia
Nucléoside analogues

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Study of the effects of direct irradiation or using targeted nanoparticles containing several radioactive atoms on the interactions between tumor cells and endothelial cells

SENIOR SCIENTISTS :

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- ▶ Carine MICHIELS
- ▶ Bernard MASEREEL

Research Field and Subjects

We started a close collaboration with several groups in order to investigate the molecular mechanisms of the cell responses to radiation with the aim to improve or to design new therapeutic strategies for cancer patients. Two main projects are developed.

The TARGAN project is aimed to develop a nanocluster containing several radioactive atoms, coupled to a monoclonal antibody targeting a specific marker of the tumoral endothelial cells. Nanoparticles containing ^{99m}Tc or ^{90}Y are functionalized using plasma deposited polymerized allylamine film. Alternatively, gold or other nanoparticles are coated with polyelectrolytes. The amine functions of this coating are then used to couple monoclonal antibodies that will target the nanocluster to the tumor. In vitro and in vivo studies in mice are performed to characterize the specificity of the targeting. Simultaneously, modelisation for dosimetry using these radioactive nanoparticles is performed for vascularized and necrosed solid tumors. These clusters can be used for diagnostic or therapy.

The Télévie project is aimed to study the cell responses to various radiations. A facility for broad beam in vitro cell irradiation has been developed in the center of Physics of matter and Radiation (PMR) of the Physics Department, using a particle accelerator (named ALTAIS). The irradiation conditions (dose rate, energy, pulsed or unpulsed beam) are controlled in real time and the experimental setup allows to irradiate the cells with different particles (proton, alpha, lithium or carbon). Radiation-responsive bioassay measurements including survival curves for tumor cells but also for endothelial cells are then performed. In addition, changes in gene expression and cytokine secretion are investigated. The effects of cell irradiation on co-cultures of tumor and endothelial cells will then be studied

Representative References

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Patent

RADIOACTIVE DEVICE, 2006, EP1838354, WO2006063418.

Partnership

- ▶ UCL (Mont Godinne Hospital) : PROF. T. VANDER BORGH
- ▶ UCL (Brussels) : PROF. O. FERON, FATH, PROF. B. GALLEZ, CMFA
- ▶ IBA-Molecular (Fleurus)
- ▶ Institut des Radioéléments (IRE) (Fleurus)

Funding

- ▶ Waleo project TARGAN
- ▶ TÉLÉVIE

Main Equipment

- ▶ Tandetron accelerator and associated irradiation station
- ▶ Radioactive nanoparticle synthesis reactor (physical methods)
- ▶ All type radiation detection systems
- ▶ Nanoparticle measurement techniques (TEM, SEM, BET,...)
- ▶ Cell culture facilities
- ▶ General equipment for biochemical and molecular biology assays
- ▶ Absorbance, fluorescence, luminescence microplate readers
- ▶ Real-time PCR, equipped for microfluidic cards
- ▶ Full proteomic platform with Maldi and MS-MS mass spectrometers
- ▶ Confocal microscope

Products and Services

- ▶ Complete hadrontherapy platform for in-vitro cell irradiation
- ▶ Cellular models for the evaluation of radiation effects
- ▶ Proteomic platform

KEY WORDS FOR R&D

Radiobiology
Nanoparticles
Gold
Antibody
Apoptosis
Signal transduction
Gene expression regulation

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http://www.fundp.ac.be/recherche/projets/page_view/05272202/
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Psycho-oncology

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- ▶ Maud COLMANT

Research Field and Subjects

Appraisal of a systematic psychological consultation for cancer patients.

Studies about depression, anxiety and coping strategy in oncology.

Psychotherapy in oncology.

Consultation-liaison psychiatry.

KEY WORDS FOR R&D

Psycho-oncology
Psychological support
Coping strategy
Systematic consultations
Psychotherapy
Consultation-liaison psychiatry

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Representative References

- ▶ *Appraisal of a systematic psychological follow-up for patients who suffer from cancer.* International psycho-oncology society congress **2009** (poster).
- ▶ *Appraisal of a systematic psycho-oncologist consultation with patients who suffer from breast cancer.* ECCO15, **2009** (poster).

WEB SITE

www.centreducancer.be

Partnership

Faculty of Psychology (Pr E. ZECH) - Université Catholique de Louvain

Main Equipment

Psychological tests, questionnaires

Research institutes of international reputation are present within the Académie Louvain: the St Luc Cancer Center, with its Head and Neck Oncology Program and the Ludwig Institute for Cancer Research (LICR). Additionally the Académie Louvain laboratories closely collaborate with a European platform, present at Woluwe and which gathers research teams specialized in oncology clinical trials, radiotherapy, surgical oncology, and patient advocacy (EORTC, NCI-LO, ESTRO, ESSO, ECCO).

Cancer Center at UCL and Saint Luc academic hospital

Mission

A reference centre for Europe, the Cliniques Universitaires Saint-Luc Cancer Centre is a leader in cancer care in French-speaking Belgium. The successor to the Cancer Institute, inaugurated in Louvain in 1927, the Cancer Centre carries on a tradition of excellence in terms of care, research and teaching.

Its location within a general teaching hospital guarantees all patients comprehensive care of excellent quality, with particular emphasis on the human aspect.

Our main mission is to FIGHT CANCER

By guaranteeing patients comprehensive care of optimum quality.

By developing cutting-edge research in oncology and facilitating exchanges between clinicians and scientists.

By providing training for tomorrow's doctors and researchers.

As part of a general hospital, we care for patients, not just tumours. Patients thus have a guarantee that everything to do with their health will be taken into account and they will benefit from the expertise of every Cliniques Universitaires Saint-Luc specialists. Each patient's medical file is computerised and directly and fully accessible to every doctor. This sharing of information, combined with proximity, ensures perfect communication between staff members.

In the fight against cancer, patients are at the centre of our team-based care. Teams make their expertise and knowledge of the various academic domains fully available, always paying particular attention to the human aspect of patient care.

In this perspective, we have also created a job unique in Belgium, the Oncology Care Co-ordinator or CSO. This co-ordinator ensures that thorough care is provided, accompanies patients throughout their treatment, plays a key role in keeping patients and their relatives informed and supported and provides perfect co-ordination between everyone involved.

Activities

Over the years, the Cliniques Universitaires Saint-Luc Cancer Centre has organised itself so as to provide optimum care for patients. Here are some things that set the centre apart:

Expertise : With its tradition of excellence and innovation, the Universitaires Saint-Luc Cancer Centre is the leader in cancer treatment in French-speaking Belgium in terms of numbers of patients cared for each year. It is the only Belgian centre that treats all types of cancer in both adults and children. This gives its specialists a huge wealth of experience in cancer patient care.

A global hospital : The Cancer Centre is fully integrated within Cliniques Universitaires Saint-Luc. This means that every patient treated in the Cancer Centre has the guarantee of global care, which takes account of everything to do with his or her state of health.

For example, cancer patients with diabetes will be given global care, benefiting from the expertise of different doctors treating the cancer and the diabetes in the same location. Patients are also guaranteed perfect communication between all carers, thus guaranteeing each carer full knowledge of what is on the patient's medical file.

Treating patients as human beings

To guarantee optimum quality of care for all patients, the Cancer Centre has created a job unique in Belgium, the oncology care co-ordinator or CSO. The co-ordinator accompanies patients throughout their treatment, playing a key role in keeping both patients and relatives informed and supported. The co-ordinator also ensures perfect co-ordination between the various people involved.

When cancer strikes, both patients and families can be plunged into fear and distress. The support of a psychologist will be offered, and the psychologist may be involved in all stages in the disease.

To provide the best care, all specialists involved in diagnosing and treating the patient must meet together beforehand to discuss the methods of the treatment.

Multidisciplinary approach

The Cliniques Universitaires Saint Luc Cancer Centre contains several multidisciplinary groups, which cover all types of cancer and, as their name suggests, consist of specialists from different disciplines: oncologists, haematologists, radiotherapists, house doctors, surgeons, radiologists, anatomopathologists and genetic specialists. Each group specialises in one type of cancer. Each patient's case is discussed individually and specifically during these multidisciplinary meetings, thus guaranteeing optimum care and personalised treatment, based on the expertise of the multidisciplinary group, international literature and the latest scientific progress in diagnostic and therapeutic tools.

Multidisciplinary groups :

Adult haematology

Breast tumours - The Breast Clinic

Cancers of the head, neck and upper respiratory system

Chest and lung tumours: Oncology and chest surgery group

Colo-rectal Tumours

Endocrine and thyroid tumours

Eye tumours

Hepato-Bilio-Pancreatic Tumours

Locomotive system or Sarcoma

Oesogastric tumours

Paediatric haematology and oncology

Pelvic Tumours

Tumeurs de la peau - Clinique du mélanome

Tumours in the central nervous system

Urinary system tumors

The teaching aspect

The Cancer Centre is an integral part of Cliniques Universitaires Saint-Luc, which has a basic threefold teaching mission: to provide top-quality care, develop up-to-date research and offer excellent teaching facilities.

All these activities are combined on the same site, guaranteeing optimal interaction between actors. This close collaboration between researchers and clinicians allows us to perfect new treatments aimed at improving the prevention, treatment and cure of cancer. Our patients are the first to benefit from proximity and exchanges.

Intensive research activities

The Cancer Centre is actively involved in cancer research, through laboratories and clinical studies managed by the doctors.

A specific feature of teaching centres with a direct link to a medical faculty, basic research is carried out in the laboratory. At the Woluwé site of the Catholic University of Louvain (UCL), a number of laboratories are dedicated exclusively to research into new cures for cancer.

This is the location of ICP (Christian de Duve Institute of Cellular Pathology), an international biomedical research institute. Among other organisations, it houses the Brussels branch of the

Ludwig Institute, whose laboratories are world-famous for their cancer research.

Clinical research offers patients opportunities to test new molecules or combinations of molecules before they are marketed. These are clinical trials offered by pharmaceutical firms and studies initiated by the Cancer Centre clinicians.

The aim of these trials is twofold: on one hand, to offer patients the most up-to-date treatment, and on the other hand, to advance research in the fight against cancer. We therefore offer patients the opportunity to benefit from the latest updated treatments.

The forefront of innovation

People

Over the years, we have created a network linking numerous world-famous hospitals and cancer centres.

Many doctors are regularly sent abroad to improve their medical knowledge, learn new surgical techniques, and familiarise themselves with new technology. All this keeps the Saint-Luc Cancer Centre at the forefront with the latest innovations.

New technology

We invest continually in new equipment, to offer patients the best care and also to help research progress.

Among our latest acquisitions is tomotherapy hi-art, a real revolution in radiotherapy, one of the first machines of its kind installed in Europe and the first to be operational in French-speaking Belgium. It helps us treat even the most inaccessible tumours effectively.

We also have a latest generation PET-CT, which helps us provide more efficient examinations when diagnosing certain types of cancer.

CHIP (intra-peritoneal chemohyperthermia) is a recent technique used on colorectal cancer patients. It involves administering chemotherapy at the end of an operation during which cancer-affected organs are removed. This technique, involving some twenty different specialities, has improved the prognosis for patients with advanced colorectal cancer.

Finally, in the laboratories, each tumour is individually mapped in order to determine the hereditary risk of certain cancers and the interest of specific targeted treatments.

Methodology

Oncology boards are meant to bring together the various cancer experts in the hospital, around individual patient cases, in order to discuss the diagnosis, treatment and follow-up strategy that seems the most appropriate. The ultimate goal is to bring homogeneity in the quality of care in oncology at the level of the hospital.

At regular intervals, depending on the type of cancer, the radiation oncologist, medical and surgical oncologist, pathologist, specialist in imaging, research nurse, psychologist meet to discuss the new cancer cases, diagnosed since the previous board meeting. For frequent tumours, like lung cancer, weekly meetings are required.

Every individual case is discussed prior to any therapeutic intervention. The board makes proposals and a registry is maintained for recording the board decisions. Doctors are seating as peers and the decisions are collegial.

It is the mission of each board to produce documented protocols for diagnosis, treatment and follow-up, the so-called guidelines or SOR (standards, options, and recommendations), and to enforce them in the routine practice.

The principles of operation are based on the collegial structure in the decisions, the correct stadification of all the patients and the recording of all the data in a computerized way. The treatments are applied according to the "guidelines", strictly and regularly confronted to the data of the literature; the doctors of the clinic take part in many clinical studies on the level of various national and international authorities of cancer research (EORTC, GORTEC, ...).

Structure of operation :

- ▶ investigations necessary to allow a therapeutic decision
- ▶ standardized staging (TNM).
- ▶ protocols of treatment used in routine with their limits (age, index of performance, etc). They must be based on the evidence (french SOR, NCI, START. ..).
- ▶ research protocols with their eligibility criteria.
- ▶ recommendations in terms of monitoring (frequency, standard examinations, patient contact or MT, etc.), including the decentralized monitoring.
- ▶ a multidisciplinary decision-making for each patient, either before or after surgical operation according to the anatomical site.
- ▶ therapeutic discussion of the attitude at the time of new events in the oncological history of a patient.
- ▶ regular update of the protocols (staging and treatment).
- ▶ discussion of research protocols and assessment.

Partnership

- ▶ EORTC, GORTEC, GELA, SIOP
- ▶ Fondation Belge contre le Cancer
- ▶ Vivre comme avant
- ▶ Cancer et psychologie

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- ▶ Jean-Christophe DEGOLS
- ▶ Jean-Marc GERARD
- ▶ Michèle MAGREMANNE
- ▶ Pierre MAHY
- ▶ Sandra SCHMITZ

Research Field and Subjects

Evidence-based guidelines for the management of patients with Head & Neck tumors.

First edition, September 2001

Second edition, September 2003

Third edition, May 2006

Fourth edition, June 2009

Clinical trials : see website

<http://www.md.ucl.ac.be/ccmf/>

<http://centreducancer.be>

Detection of tumor hypoxia with chemical probes

Radiosensitization by nucleoside analogues

Translational research in immunotherapy with analysis of the immune response from vaccinated patients

Use of functional imaging with PET and MRI for treatment planning in conformal radiotherapy of head & neck and brain tumors

Identification of molecular markers predictive of lymph nodes metastasis

EGFR blockade in head and neck squamous cell carcinoma

p53 status and radiosensitivity

Representative References

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- ▶ N. CHRISTIAN, J.A. LEE, A. BOL, M. DE BAST, B. GALLEZ, V. GRÉGOIRE. *Immobilization device for in vivo and in vitro multimodality image registration of rodent tumors.* Radiother Oncol., 87: 147-51, **2008**.
- ▶ O. COMMOWICK, V. GRÉGOIRE, G. MALANDAIN. *Atlas-based delineation of lymph node levels in head and neck computed tomography images.* Radiother Oncol., 87: 281-9, **2008**.

tion of lymph node levels in head and neck computed tomography images. Radiother Oncol., 87: 281-9, **2008**.

- ▶ F. JANOT, D. DE RAUCOURT, E. BENHAMOU, C. FERRON, G. DOLIVET, R.J. BENSADOUN, M. HAMOIR, B. GÉRY, M. JULIERON, M. CASTAING, E. BARDET, V. GRÉGOIRE, J. BOURHIS. *Randomized trial of postoperative reirradiation combined with chemotherapy after salvage surgery compared with salvage surgery alone in head and neck carcinoma.* J Clin Oncol., Dec 1;26(34):5518-23, **2008**.

- ▶ M. MAGREMANN, C. VERVAET. *Melanoma of the oral mucosa.* Rev Stomatol Chir Maxillofac. Jun;109(3):175-7, **2008**.

- ▶ P. MAHY, M. DE BAST, T. DE GROOT, A. CHEGUILLAUME, J. GILLART, K. HAUSTERMANS, D. LABAR, V. GRÉGOIRE. *Comparative pharmacokinetics, biodistribution, metabolism and hypoxia-dependent uptake of [(18)F]-EF3 and [(18)F]-MISO in rodent tumor models.* Radiother Oncol., 89(3):353-60, **2008**.

- ▶ A. PERSU, M. HAMOIR, V. GRÉGOIRE, P. GARIN, E. DUVIMIER, H. REYCHLER, G. CHANTRAIN, G. MORTIER, M. MOURAD, D. MAITER, M. VIKKULA. *High prevalence of SDHB mutations in head and neck paraganglioma in Belgium.* J Hypertens. Jul; 26(7):1395-401, **2008**.

- ▶ S. SCHMITZ, J.P. MACHIELS, B. WEYNAND, V. GREGOIRE, M. HAMOIR. *Results of selective neck dissection in the primary management of head and neck squamous cell carcinoma.* Eur Arch Otorhinolaryngol. 266(3): 437-43, **2008**.

- ▶ S. VAN DER VORST, A.F. DEKAIRESLE, L. IRENGE, M. HAMOIR, A. ROBERT, J.L. GALA. *Automated cell disruption is a reliable method of isolating RNA from fresh snap-frozen normal and malignant oral mucosa samples.* Clin Chem Lab Med. Feb 5, **2009** (Epub ahead of print).

Partnership

- ▶ American Head and Neck Society: M. HAMOIR
- ▶ American Society of Clinical Oncology (ASCO): J.P. MACHIELS (Member)
- ▶ Belgian Society of Medical Oncology: J.P. MACHIELS (Vice secretary)
- ▶ European Society for Therapeutic Radiology and Oncology (ESTRO): V. GRÉGOIRE (Président)
- ▶ Governing council of the International Federation of Head and Neck Oncologic Societies (IFHNOS): M. HAMOIR
- ▶ Groupe de contact de Pathologie cervico-faciale from FNRS: V. GRÉGOIRE, M. HAMOIR, P. MAHY, H. REYCHLER

- ▶ Groupe interuniversitaire de chirurgie cervico-faciale: M. HAMOIR
- ▶ Groupe d'Oncologie Radiothérapie Tête et Cou (GORTEC): V. GRÉGOIRE, M. HAMOIR, J.P. MACHIELS
- ▶ Groupe radiothérapie from EORTC: V. GRÉGOIRE (treasurer and Vice-Chairman)
- ▶ Groupe Tête et Cou from EORTC V. GRÉGOIRE, M. HAMOIR, J.P. MACHIELS, B. WEYNAND

Main Equipment

As a multidisciplinary comprehensive center, we can profit from the equipment of all the partners units and from the cliniques universitaires Saint Luc.

Products and Services

- ▶ Multidisciplinary concertation
- ▶ Treatment of patient with head and neck tumors
- ▶ R&D
- ▶ Establishment of guidelines and update.

KEY WORDS FOR R&D

Tumor hypoxia
 Radiosensitization
 Immunotherapy
 Functional imaging
 Molecular markers

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The Brussels Branch of the Ludwig Institute for Cancer Research

Mission

The purpose of the Ludwig Institute for Cancer Research is to conduct long-range research programmes directed to the ultimate goal of eradicating cancer.

The Brussels branch is active in the field of cancer immunology and cancer genetics. Main orientations of the branch are the study of tumor rejection antigens and that of cytokines.

Activities

Cancer is a major concern in human health. The prospects for bringing cancer under control require linked innovative basic and clinical research. In this view, Daniel K. Ludwig created in 1974 the Ludwig Institute for Cancer Research, an international organization bringing together scientists and clinicians from around the world. Ludwig investigators are active in many areas of science, involving genetics, bioinformatics, immunology, virology, cell biology and signal transduction.

Faithful to the organizing principles laid down by Mr Ludwig, the Institute conducts its research through ten Branches, located in seven countries. The Branch structure allows the Institute to interact with a number of different research and clinical environments. Each Branch is focused on a research program defined by the Branch Director in relation with the overall objectives of the Institute. The Branches are established in association with University Hospitals, to stimulate close collaborations between research laboratories and the clinic. By organizing and controlling its own clinical trials programs, the Institute has indeed created a continuum that integrates laboratory and clinical research.

Branch staffs vary in size from 30 to over 70, and internationally the Institute employs some 600 scientists, clinicians and support personnel. The quality of the research is monitored on an ongoing basis by the Institute's Scientific Committee and by an external peer review process.

The biological properties of any given cancer cell constantly change, allowing tumors to spread and become more aggres-

sive. To overcome these obstacles, the Ludwig Institute has developed a broad-based discovery program that seeks to understand the full complexity of cancer. Research is organized according to the four major programmatic themes that define the Institute : genetics, cell biology, cell signalling and immunology.

Research fields

- ▶ Tumor immunology and antigen processing group : <http://www.licr.ucl.ac.be/brussels/research/tiap/tiap.html>
- ▶ Genes expressed in cancer and germline cells group : <http://www.licr.ucl.ac.be/brussels/research/gecgc/gecgc.html>
- ▶ Regulation of T Lymphocyte Function in Tumors group : <http://www.licr.ucl.ac.be/brussels/research/rtlf/rtlf.html>
- ▶ Immunotherapy Analysis group : <http://www.licr.ucl.ac.be/brussels/research/iman/iman.html>
- ▶ Therapeutic vaccination and expression profiling group : <http://www.licr.ucl.ac.be/brussels/research/tvep/tvep.html>
- ▶ Cytokines in immunity and inflammation group : <http://www.licr.ucl.ac.be/brussels/research/cii/cii.html>
- ▶ Signal transduction group : <http://www.licr.ucl.ac.be/brussels/research/stg/stg.html>

Partnership with UCL

In 1978 the Ludwig Institute for Cancer Research decided to base its Belgian branch within the walls of UCL, at the de Duve Institute. A happy collaboration between the two Institutions has been pursued since that time. Even though the two Institutes are completely independent, the collaborations between the scientists of ICP and the Ludwig Institute is extremely close and the sharing of resources is considerable.

The Brussels Branch, under the leadership of Thierry Boon, specializes in cancer immunology and cancer genetics. The notion that the immune system might be enlisted to rid the body of cancer draws on past work at the Branch which revealed that most human tumors bear antigens that can be recognized by cytotoxic T lymphocytes (CTLs). Some of these antigens are

highly tumor-specific, others are expressed on certain normal cells. A number of antigens have been found on many different types of tumors, suggesting that a therapeutic strategy targeting such antigens could be used to treat a wide range of cancers. The Branch continues the search for tumor antigens, and evaluates their therapeutic potential in vaccine trials of cancer patients.

The Brussels Branch is also involved in research on the immunological functions of several cytokines, particularly IL-9 and IL-22, which have been discovered at the branch. Signal transduction by certain cytokine receptors is also under intense study.

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<http://www.licr.ucl.ac.be/brussels/research/tvep/tvep.html>
<http://www.licr.ucl.ac.be/brussels/research/cii/cii.html>
<http://www.licr.ucl.ac.be/brussels/research/stg/stg.html>

The European CanCer Organisation – ECCO

Introduction

ECCO – the European CanCer Organisation (formerly FECS – the Federation of European Cancer Societies) is a Non-Profit Organisation that serves as an interconnective platform to respond to all stakeholders in oncology Europe-wide, promote multidisciplinary and advance education through the organisation of leading conferences and timely initiatives.

Through its 24 member organisations – each representing the interests of their respective professions/groups spanning the entire spectrum from basic, applied and translational research to practice, treatment, care, prevention and advocacy – ECCO not only serves over 50,000 professionals but also benefits the oncology community at large.

Mission

ECCO exists to uphold the right of all European cancer patients to the best possible treatment and care, and promote interaction between all organisations involved in cancer research, education, treatment and care at the European level.

Activities

Following the philosophy that every cancer patient deserves the best, ECCO's core activities focus on creating awareness of patients' needs and wishes, encouraging progressive thinking in cancer policy, training and education, and advancing European cancer research and its application through the organisation of international multidisciplinary meetings.

The continued support, willing and collaboration of ECCO's member societies and a unified approach aimed at strengthening policy on cancer are central to these efforts. To ensure that cancer stays at the top of the EU health and research policy agenda, ECCO, through the expertise of its Policy Committee, aims to provide the collective voice of European oncology professionals and engage with policymakers to promote the interests of cancer patients, those who care for them, and those

without whose research there would be no advances in treatment and care.

ECCO also plays an important role in advancing education through the implementation and development of initiatives and programmes such as its eLearning educational opportunities online for oncologists and researchers, its patient information section aimed at patient advocates and organisations, as well as a special Young Professionals zone which is being set up to cater to the needs of young physicians, practitioners and scientists. With the goal of ultimately establishing a harmonised CME system in Europe, ECCO also endorses and actively promotes the Accreditation Council of Oncology in Europe (ACOE) - the unique European multidisciplinary accreditation body in oncology through which to endorse the quality, value and recognition of Continuing Medical Education (CME) across Europe (visit: www.acoe.be).

Partnership

The partnership of ECCO with UCL is mainly through the membership of its member societies, some of which are also established on the Woluwe UCL campus including the European Society for Therapeutic Radiology and Oncology (ESTRO), the European Society of Surgical Oncology (ESSO), the European Oncology Nursing Society (EONS), the European Organisation for Research and Treatment of Cancer (EORTC) and the European Society for Paediatric Oncology (SIOPE).

ECCO's especially appointed Committees welcome physicians, researchers and oncology professionals from the UCL to actively contribute to the implementation of ECCO's mission and objectives.

In addition, their participation in ECCO's educational programmes as well as conferences organised by ECCO – in particular the joint biennial ECCO – ESMO Multidisciplinary Congresses either as faculty members, speakers or participants contribute to further developing interaction with UCL.

STAFF

ECCO incorporates a staff of 21 highly dedicated and driven individuals, who, in embracing ECCO's mission, have collectively defined their own vision and values of ECCO. To find out more about who we are and what we do visit the ECCO website at: www.ecco-org.eu (select 'Contact').

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ECCO communicates and connect with the European cancer community through its website where visitors can browse the latest news, issues and comment, select from a wide variety of educational resource and tools, and discover the many reasons for attending some of the leading congresses and conferences in oncology across Europe: www.ecco-org.eu

European Organisation for Research and Treatment of Cancer-EORTC

Mission

Establishing new standards of cancer care with high-quality research

Activities

The European Organisation for Research and Treatment of Cancer (EORTC) is an international association under Belgian law, created in 1962 by prominent European cancer specialists.

The aims of the EORTC are to promote, coordinate, analyze and publish cancer research performed by multi-disciplinary groups of clinicians and scientists in Europe. These research groups include surgeons, radiotherapists, chemotherapists, pathologists, immunologists, basic researchers and numerous other specialists as well as health care professionals. The ultimate goal of the EORTC is to establish state-of-the-art cancer treatment to improve survival rate, quality of life and quality of care for all patients with cancer.

The EORTC is primarily devoted to :

- Translational research and clinical studies, to evaluate new anti-cancer agents including cytotoxic drugs but also innovative agents as well as modalities such as vaccines, biological response modifiers and other novel treatments resulting from breakthrough discoveries in genomics etc...
- High-quality clinical research, to establish optimal therapeutic strategies via large multi-center clinical studies in a multidisciplinary approach leading to state-of-the-art treatment and quality of cancer care.

The EORTC headquarters

The Headquarters play a coordinating role in all activities and deal with the scientific, legal and administrative issues related to the EORTC. The Headquarters also include the Education Office and the Cancer Communication Office.

Progress in the treatment of cancer requires high quality research

The EORTC is collaborating with the pharmaceutical industry to decrease the time needed to develop new anti-cancer agents and to minimize the delay between laboratory discoveries and

therapeutic benefit for patients.

After testing promising agents in the laboratory and on animals, the next step is testing on humans; these clinical studies will determine whether or not a new anti-cancer agent will be registered, i.e. approved by health authorities and then marketed.

The EORTC also promotes and funds translational research on new compounds/ concepts discovered in universities and private research institutions. In this way, it facilitates the passage of experimental discoveries into state-of-the-art treatment.

Evaluation of the best therapeutic approaches and development of new standards of cancer care

EORTC clinical groups, are dealing with a specific type of cancer (breast cancer, lung cancer, gastrointestinal cancer, genitourinary tract cancer, leukemia, soft tissue and bone sarcoma and others) or therapeutic modality (radiation therapy).

These groups conduct large clinical trials to quickly assess a sufficient number of patients for the results to be statistically meaningful, convincing and widely applicable and thereby to have maximum impact on the quality of cancer care. These results are analyzed in a scientific, objective and independent manner at the EORTC Headquarters.

All studies are conducted according to national legal and ethical requirements as well as to the international Guidelines of Good Clinical Practice.

All EORTC research projects and clinical studies are peer reviewed and have to be approved by the relevant committee including the protocol review committee.

The EORTC Headquarters, a unique center of excellence in Europe

Overall, there are more than 6.500 new patients treated each year according to EORTC protocols.

All research observations made by EORTC members are forwarded to the EORTC Headquarters which comprises more than 160 staff members (14 nationalities) including medical doctors, statisticians, quality of life specialists, health economists, lawyers, other scientific and administrative staff, computer specialists, as well as research fellows and health care professionals.

The Headquarters' methodology (working procedures and Standard Operating Procedures) to evaluate new anti-cancer agents and to conduct clinical studies was filed at the Food and Drug Administration in 1998. This greatly facilitates the submission of EORTC clinical data for drug registration in the USA.

The Headquarters computerized clinical trials management system (VISTA) interfaces with the EORTC website. The central registration and randomisation server (ORTA) allows clinicians to enroll their patients into EORTC clinical studies 24 hours a day. E-forms is a remote data entry system developed by the EORTC.

A permanent Independent Data Monitoring Committee reviews the status of clinical trials and makes recommendations on safety and efficacy leading to trial's continuation, modification and/or discontinuation.

Quality control procedures are conducted by the Quality Assurance Unit in collaboration with the Quality Assurance Committee. The overall functioning of the groups is reviewed by the Scientific Audit Committee, an advisory committee to the EORTC Board.

The activities of the EORTC Headquarters are evaluated regularly by a committee of experts from the National Cancer Institute (NCI) of the USA. These assessments have always been very positive and the financial support allocated to the EORTC Headquarters by the NCI has been continuous since 1974.

Other sources of funding for Headquarters are the EORTC Charitable Trust, the Fonds Cancer, corporate sponsorship, private donations and The National Lottery of Belgium. In addition, support is provided by the pharmaceutical industry (for clinical studies on new anti-cancer agents performed in cooperation with the EORTC) and occasionally by the European Commission (for specific research projects).

The EORTC has initiated a European tumour bank project to improve and harmonise the histological review and the prospective tissue collection to facilitate translational research in the context of EORTC trials, by providing rapid access to tumour tissues and to clinical databases.

"Strength through unity"

The EORTC is a unique research network which coordinates the research of about 2000 European clinicians and scientists and

works in more than 300 university hospitals or affiliated institutions located in 32 countries.

There is a true need to promote participation of all partners in clinical trials in Europe and worldwide. Therefore the EORTC is also actively involved in intergroups studies. The Intergroup office deals with all logistic, legal and methodological issues to enable inter-group collaboration.

Publication of the results of EORTC research

Every year, the EORTC has hundreds of scientific articles published in prestigious international peer reviewed journals and over 250 scientific communications are presented at international scientific meetings.

This wide dissemination of EORTC studies plays a crucial role in assuring optimal treatment of all patients including for those treated outside research oriented institutions.

Partnership with UCL

In 1972, the National Cancer Institute established his liaison office adjacent to the EORTC headquarters on the UCL campus, in Brussels.

Scientific collaborations with St Luc Hospital and Ludwig Institute.

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European Society Of Surgical Oncology – ESSO

Mission

The European Society of Surgical Oncology (ESSO) was founded in 1981 to advance the art, science and practice of surgery for the treatment of cancer.

ESSO aims to promote the highest standards of surgical care in the management of patients with solid tumours. By facilitating the dissemination of knowledge and expertise, ESSO strives to ensure that the highest possible standard of surgical treatment is available to cancer patients throughout Europe. Further, the society aims to optimise the clinical management of cancer patients through multidisciplinary collaboration.

Activities

Leading Education, Exchange and Debate

ESSO is highly committed to promoting education in cancer surgery. By providing the European Surgical Oncology community with a wide range of educational opportunities and initiatives, ESSO contributes to the advancement of knowledge and expertise in oncology surgery and the clinical management of cancer patients:

- ▶ ESSO's Biennial Congresses provide oncology surgeons with the most expansive and interconnective educational platform in Europe;
- ▶ ESSO's Training Fellowship Programme offers young surgeons the opportunity to visit a specialist centre, expand experience, and acquire new insight;
- ▶ ESSO organises multidisciplinary projects and courses in partnership with other leading organisations such as: quality assurance project on outcomes of cancer treatment, advanced course on interdisciplinary treatment of lung cancer, advanced course in Colorectal Metastases Management, masterclass on colorectal cancer, etc.
- ▶ ESSO offers Travel Fellowships to attend ESSO Congresses and the ECCO/AACR/ASCO Workshop on Methods in Clinical Cancer Research
- ▶ ESSO furthers education through the European Board of Surgery examination and Core Curriculum in Surgical Oncology

- ▶ ESSO provides surgical expertise and support for ECCO – the European CanCer Organisation's Congresses, of which ESSO is co-organiser

Partnership

ESSO is a member society of ECCO-the European Cancer Organisation, and has interconnections with the other cancer societies and organisations also established onsite.

Physicians from the UCL regularly contribute as speakers or participants to the scientific programme of ESSO biennial congresses or as teachers in courses organised by the society or in joint co-operation with ECCO, EONS, EORTC, ESTRO or SIOPE, the other onsite cancer organisations.

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European Society for Therapeutic Radiology and Oncology-ESTRO

Mission

The European Society for Therapeutic Radiology and Oncology, ESTRO, was founded in Milano in September 1980 as a Society of individual members working in the field of radiotherapy and oncology.

Its principal objectives are to :

- ▶ Foster radiation oncology in all its aspects
- ▶ Develop benchmarks, tools and methodologies for assuring the quality of radiation oncology in Europe and stimulate their implementation in clinical practice
- ▶ Improve the standards of cancer treatment by enscribing radiation oncology as a clinical specialty in the multidisciplinary approach to cancer treatment
- ▶ Promote international exchange of scientific information on radiotherapy & oncology and related fields of science such as radiophysics and radiobiology and stimulate research
- ▶ Develop guidelines for education and best practice in radiation oncology and associated professions
- ▶ Establish relationships and co-operation with international, regional and national societies and bodies in the field of radiation oncology.

Activities

ESTRO, coveted and imbedded in its early years in the UZ KULeuven hospital environment, moved in 1997 to the UCL site to join other cancer societies such as EORTC and FECS already established there.

ESTRO's core activities are articulated in its mission statement. Besides activities for the exchange of scientific information and for the education and training of radiotherapy professionals, as evidenced below, ESTRO has generated with support from various EU programmes, a broad range of initiatives for the development of guidelines and infrastructures for the surveillance of the quality in RT, for drafting best practice guidelines and encouraging research for the optimisation of radiation oncology.

- ESTRO scientific meetings

Each year, ESTRO organises several scientific meetings, reviewing advances in radiotherapy and oncology and encouraging a multidisciplinary approach to the treatment of cancer.

- ESTRO education program

The society's continuously evolving and expanding offer of course modules is designed to assist national radiation oncology, medical physics and radiation technologists' societies in the provision of adequate teaching for the topics described as mandatory in the European curricula developed by it. Gradually also the offer in the field of continued professional development is being built up and broadened.

The ESTRO teaching courses play an important role in the growing cohesiveness of the European radiation oncology community. By adding a European dimension to the education of young professionals, mobility within Europe is both encouraged and supported. The ESTRO Board also recognised the importance of exchange and transfer of expertise by committing resources to the extremely successful Technology Transfer Grant Programme for short visits to other departments which, in previous years, was funded by the European Commission

Partnership with UCL

Besides its geographical proximity to the UCL Faculty of Medicine campus as a tenant in an UCL-owned building, ESTRO became closely associated with its "landlord" through the active involvement of department heads and other professionals of the UCL radiation oncology department in ESTRO structures and activities.

UCL experts have served or still function as members of ESTRO scientific, website and education committees, are active as members of the society's international teaching faculty, coordinators or co-partners in ESTRO projects, co-editor of its journal and other publications. Finally they served in the ESTRO Board as secretary and executive administrator.

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The U.S. National Cancer Institute Liaison Office - NCI L.O.

Mission

The **US National Cancer Institute** is the US Federal Government's principal agency for cancer research and training. It coordinates the National Cancer Program, which conducts and supports research, training, health information dissemination and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer.

The **NCI Liaison Office** in Brussels was created in 1972 and was initially part of NCI's Division of Cancer Treatment & Diagnosis. It is now an integral part of the Office of International Affairs. It facilitates the interchange of information, ideas, experimental drugs, scientific expertise and scientists, and works in collaboration with the EORTC, with Cancer Research United Kingdom (CRUK), as well as with other European cancer research institutes and pharmaceutical/chemical industries, in areas of mutual interest in preclinical and clinical cancer research. The collaboration has been extended to closer interactions with the International Network for Cancer Research & Treatment, INCTR, a unique organization dedicated to helping patients in developing countries, which is also located in Brussels and partially supported by the NCI's Office of International Affairs.

The Office is the European hub for NCI's **TELESYNERGY® Medical Consultation WorkStation***). This sophisticated video-conference system allows numerous research collaborators at greatly separated geographic sites to interact as if they were in the same room, viewing the same medical images. By integrating powerful telecommunications technology into health care research and delivery, telemedicine enables clinical researchers to simultaneously communicate and view and manipulate data necessary for collaborations, including patient diagnosis and care, such as x-ray films and pathology samples.

Activities

The Office provides a European contact point for NCI and the European cancer research community, and assists NCI staff in matters related to European collaborations and cancer research programs.

It acts as a link between NCI headquarters in Bethesda and EORTC, CRUK, and other European cancer research organizations and Institutes (i.e. the Mario Negri Institute in Italy, the Max-Delbrück Zentrum in Germany) as well as the European pharmaceutical/chemical industries.

For more than 25 years the Office has assisted with the international exchange of experimental drugs for preclinical and clinical evaluation. A web-based submission process for new potential anti-cancer compounds to be tested in NCI's in-vitro screen has been made available via the NCI Developmental Therapeutics Program (DTP) website (<http://dtp.nci.nih.gov>), and the NCI L.O. assists European suppliers with inquiries of all kinds related to the submission and selection of their compounds.

The Office collects, submits and updates European cancer research protocols for the Office of Communications and Education, International Cancer Research Databank Branch (ICRDB), NCI, for inclusion in NCI's clinical database PDQ <http://www.cancer.gov>. **The office actively seeks new European groups with an interest to submit their research protocols to the NCI's clinical protocols database.** It also coordinates the additional review of EORTC PhIII protocol outlines by selected NCI specialists.

Through the NCI Liaison Office, the NCI is represented on various European committees involved in new drug development, as well as on the EORTC Board and Council and the CRUK Ph/II clinical trials committee. The office assists with the organization of joint NCI-European meetings and symposia, and coordinates the use of the TELESYNERGY® MEDICAL WORKSTATION.

**) TELESYNERGY® MEDICAL WORKSTATION*

Researchers of the National Cancer Institute and the Center for Information Technology of the U.S. National Institutes of Health developed TELESYNERGY®, a telemedicine system with broadcast-quality multi-site conferencing capabilities that is also capable of transmitting most types of diagnostic-quality medical images. By making the knowledge and experience of oncology experts accessible regardless of where in the world those

experts are, TELESYNERGY® has the potential to dramatically accelerate cancer research and improve cancer care by facilitating unique collaborations and connections.

Note : The TELESYNERGY® Workstation is available to outside collaborators for a very low cost. For further information please feel free to contact the NCI Liaison Office.

Partnerships with UCL

Through the collaboration with EORTC (European Organization for Research and Treatment of Cancer)

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