APPEL A PROJETS LABEX/ CALL FOR PROPOSALS

2010

OncoChannel

DOCUMENT SCIENTIFIQUE B / SCIENTIFIC SUBMISSION FORM B

Acronyme du projet/ Acronym of the project	**Oncochannel**
Titre du projet en français	Oncocanalopathies : approche interdisciplinaire « high-tech » pour la médecine innovante
Project title in English	Oncochannelopathies : high-technology interdisciplinary approach for innovative medicine
Coordinateur du projet/Coordinator of the project	Nom/Name : PRES ULNF Etablissement/institution : PRES ULNF/University of Lille Laboratoire/Laboratory : Cell Physiology Numero d'unité/Unit number: Inserm U1003
Aide demandée/ Requested funding	**12,400,000 euros HT**
Champs disciplinaires (SNRI) / Disciplinary field	☒ Santé, bien-être, alimentation et biotechnologies / Health, well-being, nutrition and biotechnologies ☐ Urgence environnementale et écotechnologies / Environnemental urgency, ecotechnologies ☐ Information, communication et nanotechnologies / Information, communication and nantechnologies ☐ Sciences humaines et sociales / Social sciences ☐ Autre champ disciplinaire / Other disciplinary scope
Domaines scientifiques/ scientific areas	Cellular physiology, membrane biology, biochemistry, biophysics, nanotechnologies
Participation à un ou plusieurs projet(s) « Initiatives d'excellence » (IDEX) / Participation in an « Initiatives d'excellence » project	☐ oui ☒ non

Affiliation(s) du partenaire coordinateur de projet/ Organisation of the coordinating partner

Laboratoire(s)/Etablissement(s) Laboratory/Institution(s)	Numéro(s) d'unité/ Unit number	Tutelle(s) /Research Organisation reference
Laboratory of Cell Physiology/ PRES ULNF/University of Lille	U1003	PRES/ University of Lille1/Inserm

Affiliations des partenaires au projet/Organization of the partner(s)

Laboratoire(s)/Etablissement(s) Laboratory/Institution(s)	Numéro(s) d'unité/ Unit number	Tutelle(s)/Research Organisation reference
Laboratory of Cell Physiology (LCP)	U1003	Inserm - Lille 1University
Glycobiology of Cell Signalling and Glycopathologies (GCSG)	UMR 8576	CNRS - Lille 1 University
Genetics and Evolution of Plant Populations (GEPV)	FRE 3268	CNRS - Lille 1 University
MALDI Imaging Team (MIT)	FRE 3249	CNRS - Lille 1 University
Laboratory of Biochemistry and Integrated Structural Biology (LBISB)	UMR3078	CNRS - Lille 1 University
NanoBioInterfaces (NBI)	UMR 3078	CNRS - Lille 1 University
Biostructures and drug discovery (BDD)	U761	Inserm – UDSL, Institut Pasteur de Lille
Interventional Therapies Assisted by Image and Simulation (ITAIS)	U703	Inserm – Lille2 University

1. RESUME / SUMMARY

Title of the project: *Oncochannelopathies: high-technology interdisciplinary approach for innovative medicine.*

***The OncoChannel* Laboratory of Excellence is a research structure unique in France, centralizing intellectual and up-to-date technological expertise in the field of "Ion channels and Cancer". Given the present achievements and future synergistic strength of the teams involved in the Laboratory of Excellence, the *OncoChannel* project is highly competitive not only in France, but also in Europe and all over the world. Thereby our coordinated efforts and expertise will allow making the most of the promises of a new "scientific niche"". *OncoChannel* is sure to provide France a place among the world leadership in this promising field. The implementation of this Laboratory of Excellence will catalyze the development in France and Europe of innovative biophysical technologies applied to cancer research, by assembling research teams working on oncochannelopathies into national and European networks. *OncoChannel's* efforts in the context of industrial partnerships could allow the project to become financially autonomous in future and also contribute to the common challenge of European economic growth.**

I. Scientific context and main objectives of the project.

Recent progress in modern medicine has shown that numerous pathologies (cystic fibrosis, myotonias, hypertension etc.) are actually channelopathies (i.e. alterations in an ion channel's structure and function). Accumulating evidence tends to demonstrate that the development of some cancers could also involve such ion channel aberrations and, therefore, could be classified as channelopathies. Indeed, a new concept in oncological research (based upon the fact that ion channels control almost all the "hallmarks of cancer") has been developed and promoted over the last decade **paving the way to a new chapter of oncology coined '*Oncochannelopathies*'**.

These first achievements have led to the firm expectation that ion channels constitute a diagnostic and therapeutic target for a number of malignancies. ***However, based on this proof of concept, an integrated high-technology, interdisciplinary approach is needed to develop new therapeutic drugs and new methods for tumour treatment, early diagnoses and personalized prognoses.***

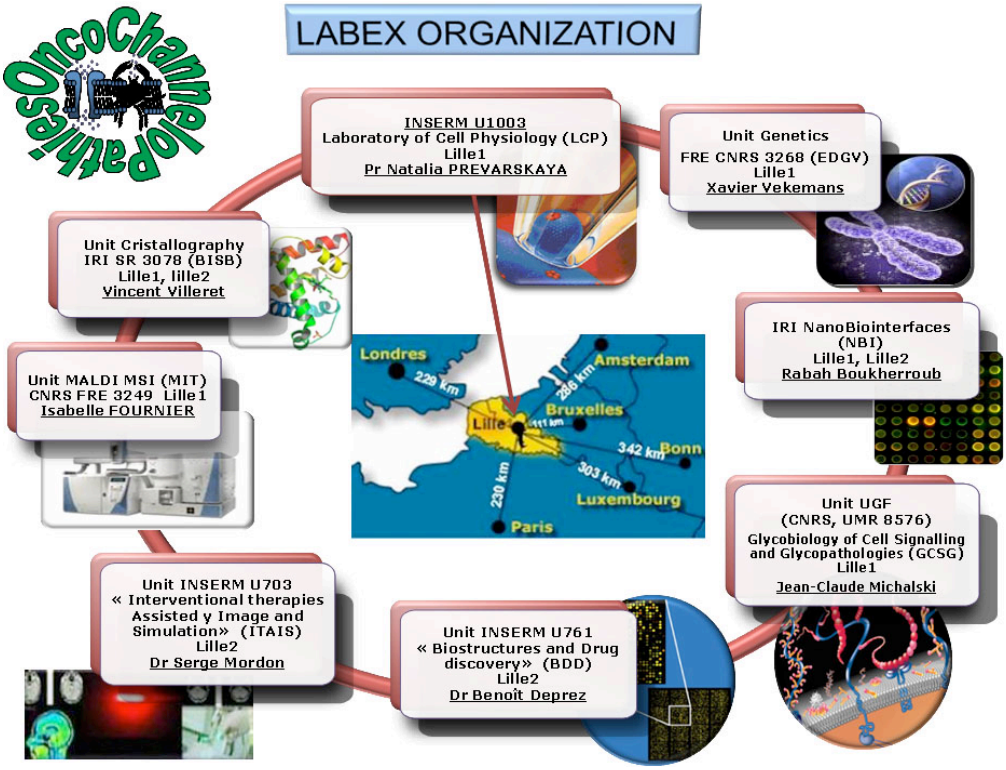
To rise to this highly challenging objective, we intend to create an ***Oncochannel* Laboratory of Excellence,** which will focus on prostate cancer. Indeed, prostate cancer (PCa) is the most common non-cutaneous human malignancy and the second most lethal tumour among men, with the highest incidence in industrialized countries. The incidence of prostate carcinoma, over half a million new cases every year in the world, increases proportionally to the increase in life expectancy. The intimate association of fundamental scientific studies with clinical applications would therefore provide beneficial effects for patients. Understanding the mechanisms involved in the processes leading to prostate cancers, could help in developing new therapeutic targets and, therefore, is necessary to improve both the survival rate and the every day life of patients.

The purpose of the Laboratory of Excellence is to generate a synergistic effort from the best regional scientific teams in this promising research field which was pioneered by the coordinator of *the Oncochannel*, Pr. Natalia Prevarskaya. Therefore, we have brought together, into a highly coordinated project, 8 internationally recognized and complementary research teams, having at their disposal 6 high-technology infrastructures and significant collaborative links with industrial partners. All teams involved in the project of the Laboratory of Excellence **were ranked** in 2009 by international committees **among the top (A+ and A grades)** in France, many of them being also considered amongst the world-top ranking teams in

their discipline.

Indeed, this Laboratory of Excellence provides us with **a unique chance to concentrate** at the same site **a critical mass of methodological and scientific expertise combining a wide range of approaches "from gene to therapy" :** molecular electrophysiology (scientific coordinator's team, partner 2); glycobiology (Jean-Claude Michalski's team, partner 3); genetics (Xavier Vekemans's, team, partner 4); imaging and mass-spectroscopy (Isabelle Fournier's, partner 5); structural biology (Vincent Villeret's team, partner 6); nano-technologies (Rabah Boukherroub's team, partner 7); biochemistry and drug design (Benoit Deprez's team, partner 8); imaging-assisted therapy of tumours (Serge Mordon's team, partner 9). "Lille Nord de France University - Research and Higher Education Cluster" (called PRES) is considered as partner 1.

Such a multimodal interdisciplinary approach (bordering 3 disciplines: biology, physics and chemistry) should provide important new results, otherwise inaccessible.

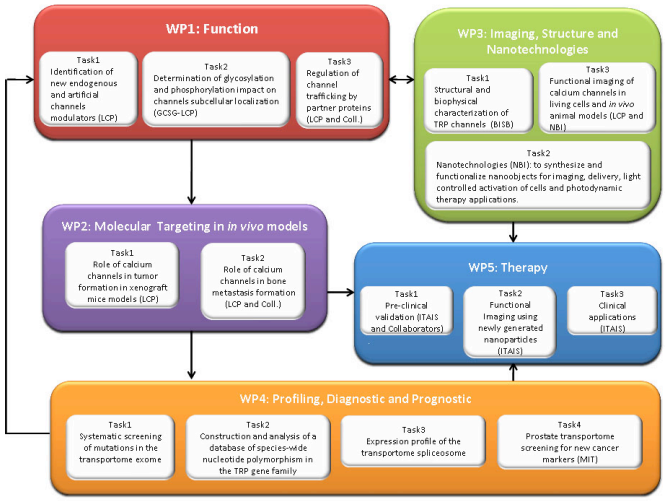


II. Work programme.

Thus, the project of the Laboratory of Excellence is divided into five scientific work packages (WPs) allowing for a synergistic effort on fundamental research as well as on use/training/dissemination between internationally recognized laboratories as being leaders in their respective domains.

The **continuum of our previous work** will be described in **WP1 (Function)** and **WP2 (Molecular targeting in *in vivo* models)**. Using our already established *in vitro* models, WP1 will decipher the functional channelopathies in PCa, i.e. provide a functional background to the role of the previously selected channels in PCa progression. A crucial aspect of WP2 is the establishment and refinement of **innovative *in vivo* models reverse-translating** the clinical pathological features of PCa. Structural aspects and potential applications of nanotechnologies to

the research on oncochannelopathies will be investigated in **WP3 (Structure and nanotechnologies).** Through the incorporation of two teams from IRI (Institute for the Interdisciplinary Research) into our new structure, we aim to develop two new **"high-gain/high-risk" approaches** applied to the oncochannelopathies question: crystallography applied to oncogenic channels and nanotechnologies. While highly challenging even a partial structure of these channels would represent a great asset for any future drug-design targeting oncogenic channels. We also wish to apply nano-technologies to our research subject through the development of a new technology for dynamic imaging. If successful, this approach would provide us with new tools of unprecedented sensitivity, and could also be applied to medical imaging needs. **In WP4 (Profiling: Diagnosis and Prognosis),** there will be a continual exchange with WP2. The scientific framework necessary for interpreting the diagnostic potential of the transportome expression data obtained from tissue (mouse models, patients) in WP4 will rest on the functional data obtained in WP1. Following a clearly defined decision-making selection, relevant members of the transportome will be evaluated for their diagnostic (WP4) and **therapeutic potential (WP5). WP5 (Therapy)** will functionally assess the key properties a transportome protein must possess in order to be categorized as a diagnostic and/or therapeutic target. These properties include an altered expression (derived from WP4), a functional impact on PCa progression (determined in WP1) and availability to modulating/targeting agents. When applicable, novel targeting agents will be produced and evaluated in patient samples. Novel (targeted) therapeutic strategies will be designed and tested in the *in vivo* pre-clinical models developed in WP2. Hence, the continual integration of the data emerging from the first four WPs will be critical for the successful design of novel therapies in WP5, whose proof-of-concept will be demonstrated in pre-clinical mouse models representing a first stage before any eventual clinical protocols.



In this way, the "*Oncochannel"* Laboratory of Excellence will achieve a **dual breakthrough** constituting major progress **beyond the state-of-the-art,** since it will be:

1. first to exploit the therapeutic and diagnostic concepts of oncochannelopathies and deliver original and as yet unexplored tools by introducing a new dimension to the presently available state-of the-art approaches;
2. first to take advantage of structural and nano-technological approaches for studying oncochannelopathies and other diseases where these channels are involved. For this "**high-gain/high-risk**" project, the creation of a Chair of Excellence (3 years) is expected.

The results of the *OncoChannel* project, i. e. novel biomarkers and pre-clinically validated concepts will be of high relevance for clinical oncology, patient organizations and SMEs / industry, thereby **driving the socio-economic impact of the project.**

III. The *OncoChannel* Laboratory of Excellence's higher education project .

We expect this project to also have a broader impact as an excellent new training experience for students as its educational programme consists in :

1) the setting up of an **"In-business PhD" label**, which will form a training track along which the student will acquire knowledge in management / business strategy / project management ... and will have the opportunity to learn first-hand (contacts, field experience), the notions of corporate organization. This label is a real training programme, in conjunction with the professional project of the students.

2) Development of a new Master of Science.

The laboratory, together with its partners, proposes new postgraduate courses and technological workshops that will be available for MSc and PhD students and for higher education. Partner laboratories propose the **development of a new Master of Sciences entitled "Molecular Biophysics of Biological Membranes,"** which would supplement the existing Master Degrees, by proposing new and innovative teaching in the field of biophysics. In this framework, many lectures or technological workshops will be provided in English by internationally renowned researchers. This Master's Degree, at the crossroads of Biochemistry and Biophysics, would focus on new developments in membrane biophysics, both structurally and functionally.

3) Supervision of Masters' and Doctoral students in close partnership with European laboratories.

4) Development of Technological Workshops for the practical training of PhD students.

IV. *OncoChannel* Laboratory of Excellence project for the use of its scientific results.

Expected results will be valorized by **scientific communications** including publications and conferences. If possible, results **will be patented**. Indeed, a significant commercial value can be created with these new patents. We expect the OncoChannel Laboratory of Excellence will allow us to **strengthen our present industrial partnerships** (J&J; Pierre Fabre; XenTech) and to **develop new partnerships with private companies** (locally, nationally, and internationally). **All together, Oncochannel will help promoting the forefront position and growth of the European biomedical industry**.

The *OncoChannel's* Laboratory of Excellence will offer many applications in clinical, veterinary and fundamental research fields, using a combination of imaging, structural characterization, quantification and complex analyses of ion channels, related antibodies, drugs and quantum dots. Important applications will especially be found for clinical studies thanks to the possibility of imaging and identifying potential markers for diagnosis and resistance to the treatment of pathologies**.** This explains why such a project falls within the **context of the Nutrition-Heath-Longevity Programme of the Nord region and the "Nord-Pas-de Calais" Regional Council research initiative, as well as the National Institute for Cancer Research and European PCRD's 7th Health programme.** Our strategy includes a **specific new start-up, "OncoChannel"** (based on the combination of high throughput molecular electrophysiology and imaging platforms) to be launched in 4-5 years. The corresponding department of the University of Lille1 (which accommodates and helps project managers of innovative enterprises) will participate in this project.

V. Project governance.

The overall management of the project will be performed via close interaction between participating team leaders (**Direction Committee**), scientific task leaders (**Scientific Committee**), **management infrastructure** (supported by the "Nord de France University") and International Scientific Advisory Board. Every 3 months, the project coordinator will arrange a **Coordination meeting** for the heads of the participating teams and for the researchers from the Coordinator's team in charge of the corresponding partnerships**.** General **Scientific meetings** for all Labex members will be organized yearly. The **website** dedicated to this Labex will be created

as soon as the project is funded. An independent **International Scientific Advisory Board** will be elected by the scientific committee of the Labex. Every two years, this advisory committee will evaluate the results obtained by the Labex teams, analyse the scientific strategy for coming years and give their objective recommendations.

VI. Integration of the project in the general strategy of the supervising institution (University of Lille1).

Through the LABEX "Fundamental and interdisciplinary approach for innovative medicine" project, the PRES "Université Lille Nord de France" aims to become an international leader in the field of 'Oncochannelopathies" and to actively contribute to both the challenging researches concerning health and to the territorial and socio-economic development through innovation. This LABEX is highly supported by the partners, the PRES, Inserm, CNRS, Lille 1 and Lille 2 Universities, because of the excellent scientific potential and activity of the research groups. It emanates from a major multidisciplinary scientific field in the region with more than 400 scientists, PhD students and administrative and technology staff.

We believe that the excellent potential of this LABEX together with the high quality management and the strong support of partners through additional human resources and scientific facilities will present an attractive environment for talent scientists and students and for the development of promoting innovative risky research.

In conclusion, the implementation of the"Oncochannel" Laboratory of Excellence will ultimately improve the quality of life and care of patients with prostate cancer, which is the cancer "most common to men"; potentiate European economics growth of and strengthen Higher Education programmes for young Europeans.

2. CANDIDATURE AUX ACTIONS DU PROGRAMME INVESTISSEMENTS D'AVENIR/ APPLICATION TO THE ACTIONS OF THE PROGRAMME « INVESTISSEMENTS D'AVENIR »

Nom de l'action	*Acronyme du projet (préciser si le projet est déposé ou envisagé)*	*Nom du coordinateur*	*Consortium /partenariat impliqué*
EQUIPEX	Imaginex biomed	F. LAFONT	UMR8204-U1019-U1011-UFR142-UM8576-U771-U1003-UMR3078
EQUIPEX	PharmaR^3	B.DEPREZ	U761, U1008, UMR 8207, FRE 3249, Imabiotech, Inserm NTI

3. ORGANISATION DU PARTENARIAT/ MANAGEMENT OF THE PARTNERSHIP

3.1. COMPOSITION DU PARTENARIAT/ COMPOSITION OF THE PARTNERSHIP

Nom du partenaire	*Affiliation*	*Effectifs / Catégorie de personnel (chercheurs, ingénieurs, doctorant …)*
Natalia Prevarskaya	Inserm	3 PR – 4 CR – 1 PU/PH – 1 PU – 3 MCU – 2 AI – 2 TS – 1 AJT – 2 DOCT
Jean-Claude Michalski	CNRS	1 DR – 3CR – 3 PR – 5 MCU – 1 POST-DOCT – 1 IE – 2 AI – 1 TCE – 9 DOCT
Xavier Vekemans	CNRS	1 PR – 3 CR –1 IR 1 POST DOCT

Isabelle Fournier	CNRS	2 PR – 2MCU -1 TR – 1 AJT
Vincent Villeret	CNRS	2 DR – 4 CR – 1 MCU – 2 IR – 1 IE – 1 AI – 2 DOCT
Rabah Boukherroub	CNRS	1 DR – 1 PR – 2 CR – 1 IE – 4 POST DOCT
Benoit Deprez	Inserm	5 PR – 1 CR - 5 MCU – 2 IE – 3 TR – 6 POST DOCT – 2 DOCT
Serge Mordon	Inserm	1 DR – 1 CR – 2PU/PH - 2 MCU/PU – 1 IR – 1 AI

Short CVs of the partners:

Natalia Prevarskaya, project coordinator, Doctor of Science (Biophysics) since 1985. She is full professor of Physiology since 1996 at the University Lille1. She heads the Inserm Unit 1003 on Cellular Physiology with 30 people. She won the prize of "Young researchers for Health" in1996, the prize from FRM (Foundation for Medical Research) in 2004 and the prize from the French Society of Science in 2006. She published 97 articles in peer-reviewed journals, 9 invited reviews and 7 chapters. During last 5 years she has been invited to give 28 lectures at international meetings (FASEB, GORDON conferences, Experimental Cell Biology, IUPS …). She was the coordinator of 2 European collaborative projects INTAS, of national collaborative project on Cancer (INCA [2006-2008] and ANR [2007-2009]). She is member of Inserm scientific commission and University National Committee. She is also Member of the scientific council of ARTP (Association for the Research against Prostate Tumours). She is a reviewer for many international journals (Nature Reviews Cancer, J.Clin. Invest. …) and grant applications (Welcome Trust, MRC, FP7 …). She is an associate editor for the Journal "Frontiers in Pharmacology of Ion Channel and Channelopathies". Her work is focused on the role played by ionic channels and intracellular calcium in prostate cancer.

Jean-Claude Michalski is Director of Research at INSERM (DR1). He is head of the Lille Glycobiology Institute (UGSF) from January 2000 and Head of the Biochemistry Department at University Lille 1. He obtained his PhD degree in Biochemistry at University of Lille 1 in 1978, and his Habilitation (Doctorat d'Etat) in 1984. At the Institut de Recherche sur Le Cancer de Lille, he was the first to describe a new group of genetic diseases associated with a neuraminidase deficiency, the "Sialidosis". In 1980 he obtained an EMBO long term fellowship grant (1980-1982) and joined the group of Professor Roland Schauer, Kiel, Germany, where he developed a new field of research on the characterization and isolation of human liver sialidases. Iin 1981, he started working on the catabolic pathway of glycoproteins glycans and became one of the pioneers in the field of glycomics. He is internationally recognized in the glycobiology community for his work on lysosomal storage disorders and glycoproteins catabolism combining development of structural methods for glycomics and glycoproteomic (mostly mass-spectrometry and NMR based), with an interest for the biological functions of glycans and their dysregulations in human pathologies. He is the French representative at the International Glycobiology organisation (IGO), he was president of the French Glycobiology Society (GFG) (2000 -2002), and he is member of the steering committee of the European Science Fundation (ESF) network in glycosciences (Euroglycoforum) in charge of the Education. He has organized several international meetings including training schools in glycobiology (FEBS and EMBO). He is member of many national scientific committees (Ligue Nationale Contre le Cancer, Vaincre la Mucoviscidose, FRM Nord-Pas de Calais, Member of the CNRS national Committee (CoCNRS) section 21). He is co-Director of the Doctoral School "Biologie Santé de Lille–ED BSDL). He received the Maurice Nicloux award from the "Société Française de Biochimie et Biologie Moléculaire" and the "Prix des Glucides" from the French Glycobiology and Glycochemistry Society. He is organizer of several national and international meetings (16th Meeting of the International Association for Protein Structure Analysis and Proteomics. Methods in Post-Translational modifications analysis, 2006; EMBO WORSHOP "Glycoscience and Development, 2009...). He is one of the creator and organiser of the bisannual "Training Course in Glycobiology" (practical school).

Xavier Vekemans obtained his PhD in Biology at the University of Brussels in 1992. After two years of postdoctoral research at Berkeley University, he became Assistant Professor at the

University of Brussels. In 2002 he moved to Lille 1 University as Professor, and joined the GEPV laboratory, where he founded an ATIP CNRS team on the population genomics of self-incompatibility systems in plants. Since 2007, he is heading a CNRS research group (GDR CNRS 1928) on Population Genomics and Evolutionary Genomics comprising 33 research teams from CNRS, INRA and INSERM, as well as several universities. His research focuses on population genetics, evolutionary genomics, and molecular evolution of genetic systems involved in plant reproduction. He has published 66 papers in peer-reviewed international journals, and has an h-index of publication of 26. He has obtained recently funding from ANR (two projects), CNRS (ATIP), Région Nord-Pas de Calais (ARCIR), and FRB. He is referee for many international scientific agencies (NSF, SNSF, SATW, FWF, FWO,…), and scientific journals (Science; Genetics; Evolution; Molecular Biology and Evolution; Molecular Ecology;…).

Isabelle Fournier is 36 yrs. old and is a specialist of mass spectrometry in the field of biomolecules analysis. Since 2002 Pr. Fournier is developing MALDI Mass Spectrometry Imaging and has established her own group. In 2009, she became full Professor at the University of Lille and was then distinguished by a nomination at the Institut Universitaire de France. Pr. Fournier has mentored 10 PhD students since 2004. She has published 41 publications, 5 book chapters and 7 patents, had participated to national and international projects and is co-founder of the start-up Imabiotech. Her work is currently focused on developments of MSI and its applications to biological problematic including pathologies in the field of cancer such as ovarian and prostate cancer.

Vincent Villeret is heading the Interdisciplinary Research Institute USR3078 at Villeneuve d'Ascq. Since 2001 he is research director at the CNRS and leads his own research group in the field of structural biology. Vincent Villeret is an expert in protein crystallography and biophysics and has been working for many years in the field of membrane transport and signalisation. He solved recently the first structure of a transmembrane protein from the BamA/TpsB superfamily (Clantin et al., 2007). He has also been involved in structured-based drug design programs. His research team has expertise in protein expression, purification, crystallization and structural analyses of soluble as well as membrane proteins. The team is part of beam allocation groups at ESRF and SOLEIL synchrotrons that allow easy and frequent access to beamlines, including micro-focused beamlines. VV is also scientific adviser of the research group GDR334 "Assemblages supramoléculaires et membranes biologiques" created in 2010 by the CNRS.

Rabah Boukherroub received a PhD in chemistry from the University Paul Sabatier in Toulouse in 1993. His PhD thesis work involved the synthesis of small heterocyclic compounds containing silicon or germanium. After a postdoctoral research position at McMaster University (Hamilton, Canada) on organosilicon photochemistry, he joined the Steacie Institute for Molecular Sciences (SIMS) at the National Research Council Canada (CNRC) in Ottawa as an Assistant Research Officer to work on surface functionalization of semiconductor surfaces for applications in bioelectronics. In 2001, he moved to the Laboratory of Condensed Matter Physics at Ecole Polytechnique (France) as a visiting scientist. Since 2003, he is a group leader at the Interdisciplinary Research Institute (IRI) at University of Lille1. Since 2008, R. Boukherroub is an adjunct Professor at Shandong University, China.

Dr. Boukherroub is on the editorial advisory board of Open Condensed Matter Physics Journal. He is the author of over 190 research publications and 4 book chapters, in subjects related to nanotechnology, materials chemistry, biosensors, and lab-on-chip devices. He has 7 patents or patents pending. He has supervised several undergraduate, graduate, and post-doctoral research students.

Dr. Boukherroub research interests are in the area of functional materials, surface chemistry and photophysics of semiconductor nanostructures with emphasis on lab-on-chip applications, nanomedicine and development of new tools for studying molecular dynamics in vivo.

Benoit Déprez a degree of pharmaceutical sciences from the school of pharmacy of Lille and a PhD in medicinal chemistry in the Lab of André Tartar at the Institut Pasteur de Lille (1997). With André Tartar, he created the High Throughput Chemistry laboratory of the Institut Pasteur that became in 1997 the chemistry department of Cerep. In 1999, after 3 years spent at Cerep as Head of Chemistry and Site Manager, he was hired by Devgen, a Belgian start-up in Gent

(Flanders), where he set up High Throughput Screening using C.elegans and Medicinal Chemistry activities. From 1995 on, he managed several collaborations between biotech or academic labs and pharmaceutical companies (Glaxo, Merck KGa, Sanofi, Genentech, Sumitomo, Fournier Pharma). Benoît Deprez is currently Professor of Chemistry at the Faculty of Pharmacy (U. Lille2) and heads Inserm Lab U761 based at the Institut Pasteur de Lille and the Faculty of pharmacy. His research interests primarily focus on drug discovery and medicinal chemistry. Areas that he explored with his team include novel targets in infectious diseases, cancer and Alzheimer (metalloproteases, allosteric receptor modulation and protein-protein interactions). He is a member of the strategic committee of Inserm-transfert, correspondent member of the Académie Nationale de Pharmacie and editor of several journals including Chemical Biology and Drug Discovery. He is also expert for several companies SME involved in drug discovery (Cytomics, Poxel, Diverchim, Inserm Transfer) and Venture Capital investors (Edmond de Rotschild Investment Partners).

Serge Mordon, PhD is working in Lille, France for the French National Institute of Health and Medical Research (INSERM). He is the director of INSERM U 703 (Interventional Therapies Assisted by Image and Simulation) and the director of the Photomedicine Center (Lille University Hospital). Since 1981, he has been involved in the medical applications of lasers, particularly in dermatology and plastic surgery. More recently, he has focused his research on laser-assisted cartilage reshaping and Photodynamic Therapy. He is an internationally recognized expert in laser-tissues interaction and laser applications in medicine. He has authored over 240 articles and book chapters. Pr. Mordon is the author of ten issued patents. He is an associate editor of the editorial board for the journal, *Lasers in Surgery and Medicine.*

3.2. QUALIFICATION DU COORDINATEUR DE PROJET /RELEVANT EXPERIENCE OF THE PROJECT COORDINATOR

The coordinator of this project, Natalia Prevarskaya, is a professor of Physiology at the University of Lille1 and a head of Inserm Unit 1003. She arrived at the University of Lille 1 in 1996 and started to develop a new research project focusing on the role of ion channels in human prostate cancer progression. She initiated this project on the basis of electrophysiology. At this time the team consisted of two lecturers and one PhD student. On 1998 she presented her research project for Inserm evaluation and obtained the **label of Inserm** team and the first financial support for 4 years. This funding was renewed several times after each quadrennial period following an evaluation procedure of Inserm and international peer review. **During the past years the laboratory staff has been considerably strengthened (more than 30 members) and has become a united, dynamic and motivated multidisciplinary team.** Further, in 2004, the laboratory, directed by Natalia Prevarskaya received a **'label' from 'The National League against Cancer** (Ligue Nationale contre le Cancer)' for a period of three years. This label was renewed for the periods of 2007-2009 and 2010-2013. She got and directed grants from the 'Association for Research on Prostate Tumours ARTP' (3 grants), the 'Regional League against Cancer' (3 grants), the 'Association for Cancer Research ARC (1 grant) and the 'Foundation for Medical Research FRM' (2 grants). The laboratory has enabled the creation of a true molecular electrophysiological training centre in the North Region for postgraduate students and research scientists (both French and foreign).

15 PhD theses have been directed by Natalia Prevarskaya since 1996.

Natalia Prevarskaya won the "Young researchers for Health" prize in 1996, the FRM prize in 2004 and from the Sciences Academy in 2006.

The group directed by Natalia Prevarskaya became one of the top ranked research teams working in the field of ion channels and cancer. Indeed, the team was evaluated in 2009 and was ranked A+ by international and independent committee, AERES (Agence d'évaluation de la recherche et de l'enseignement supérieur).

Coordination of national and international projects.

She developed a number of regional, national and international collaborations and successfully coordinated: two national French projects funded by

- INCA (National Institute of Cancer Research) grant, 2006-2009 « The roles of trpm8 and trpv6 ion channels in prostate cancer: functional studies and molecular targeting for the elaboration of new therapeutic strategies" with 4 French laboratories CNRS UPR 9079 ; INSERM U407 ; INSERM U664 ; EA 2086;

- and ANR (Agency for National Research) grant, 2007-2010, « Role of TRPM8 cationic channel in physiopathology of prostate and testis: involvement in reproduction" with INSERM U407

two European projects funded by INTAS:

- N° 1248, 2003-2006, "Volume - regulated anion channels (VRAC) in prostate cancer cells with two other partners: Prof.B.Nilius, Belgium; Prof. Y.Shuba,Ukraine.

N° 05-10008-8223, 2006-2009 « Normal and pathological roles of TRPM8 cold receptor » with three other partners:Dr. C. Romanin, Autriche; Prof. Y.Shuba, Ukraine.

Exploitation of results.

Natalia Prevarskaya signed a number of research contracts with pharmaceutical companies. The interest of these companies (Pierre Fabre, Johnson & Johnson, Sanofi-Aventis, and Bayer) in the research shows that the project developed by Natalia Prevarskaya's laboratory is a promising one.

Furthermore, invitations to give lectures (more than 20 during past 5 years) and to organize scientific sessions at such prestigious meetings as FASEB, GORDON conferences, Experimental Biology, IUPS… shows that the research of Natalia Prevarskaya's team is recognized internationally.

4. DESCRIPTION DE L'EXISTANT/ DESCRIPTION OF THE EXISTING

4.1. PRESENTATION DES PARTENAIRES

4.1.1 PARTENAIRE 1/ PARTNER 1: PRES

"Lille Nord de France University - Research and Higher Education Cluster" (later named *PRES ULNF*) was founded in January 2009 in order to increase regional academic potential, promote its visibility and enhance its international standing. With 17 higher education institutions (Universities and Grandes Ecoles), 130 000 students, 4 600 researchers and research fellows, 3 000 doctoral students in 6 doctoral schools, Lille Nord de France University focuses largely on public research in the Nord-Pas de Calais region. It also supports the academic community to work in close collaboration with national research organisations and business and techno clusters. All of its activities lead to development in regional research and higher education.

4.1.2 PARTENAIRE 2/ PARTNER 2: NATALIA PREVARSKAYA

4.1.2.1 RECHERCHE ET INNOVATION / RESEARCH AND INNOVATION

The laboratory of Cell Physiology, Inserm U1003, is one of the world leaders in the field of "Ion channels in cancer". The team was evaluated in 2009 and was ranked A+ by international and independent committee, AERES, according to all criteria of this agency such as: the originality and the relevance of the research activity, the notoriety of the research, the quality and the impact of scientific publications, the importance and relevance of scientific cooperations, the implication in national and international networks the quality and relevance of the partnership with the industry, the contribution to the PhD, graduate and undergraduate programs…

Initially, the team was formed by Natalia Prevarskaya who remains the **group leader** (see part 3.2 of the document) with the established authority in the field confirmed during last years by

the publications score as a senior author (see part 7.1.) in such prestigious journals as Cancer Cell (ISI Impact Factor: 25.288**)**, Cancer Research (ISI Impact Factor: 8.194), J. Clin. Investigation (ISI Impact Factor: 16.592), J. Cell Biology (ISI Impact Factor: 10.121), invited review in Trends in Molecular Medicine, 2010 (ISI Impact Factor: 12.51)) and by numerous invitations for the national and international meetings (28 during last 5 years). She published 97 articles, 9 invited reviews and 7 chapters. Natalia Prevarskaya won the "Young researchers for Health" prize in 1996, the FRM prize in 2004 and from the Sciences Academy in 2006.

In 2010, the Inserm U1003 is constituted by 10 permanent researchers (4 Inserm researchers, 3 professors, 3 lecturers-researchers) and 2 clinicians. Four researchers have their **Prime of Excellence**.

The presence and support of promising young research scientists.

The recruitment and support of young research scientists is one of the laboratory's priorities. Thus, four young scientists have been recruited of the last 5 years: (1) Fabien Vanden Abeele, recruited in 2005 by Inserm as a researcher, CR2 (Chargé de Recherche); (2) Vyacheslav Lehenkyi, recruited in 2008 by University of Lille1 as a lecturer-researcher; (3) Loic Lemonnier, recruited in 2008 by Inserm as a CR2; (4) Dimitra Gkika recruited in 2009 by University of Lille1 as a lecturer-researcher. Before being recruited Fabien Vanden Abeele and Dimitra Gkika were funded by EMBO European fellowships, Loic Lemonnier by NIH grant in Jim Putney (USA) laboratory, Vyacheslav Lehenkyi by INCA grant. High competitive levels of these fellowships attest the scientific excellence of young researchers.

These researchers have their own research axes within the common Unit theme and already benefit from budgets allocated to their research projects (Ligue contre le Cancer; INCA (Institute for Cancer Research); BQR (Bonus for Quality Research) from the University).

Other young scientists (Gabriel Bidaux, presently doing his post-doctoral work at the laboratory; Benjamin Beck, doing his post-doctoral work in Brussels) intend to take the Inserm and University competitive exams in coming years.

Important event and distinctions of the Unit.

- Attribution by the laboratory of a 'label' from 'The National League against Cancer (Ligue Nationale contre le Cancer)' in 2004 for a period of three years. This label was renewed for the periods of 2007-2009 and 2010-2012.
- Attribution by the laboratory of a 'label': "Emblematic laboratory of INSERM" and shooting a movie on laboratory's activity in 2008.

The importance and pertinence of scientific partnerships, position in national and international networks.

The laboratory's strategy consists in establishing regional, national and international collaboration in order to enrich its research with complementary skills and/or to acquire indispensable new tools to prove its working hypotheses.

Moreover, for those projects requiring the constant involvement of laboratories with complementary skills, the laboratory has initiated several **research contracts with specific budgets:**

-The laboratory director coordinated the national INCA project (2006- 2008)

« The roles of TRPM8 and TRPV6 ionic channels in prostate cancer: functional studies and molecular targeting for the elaboration of new therapeutic strategies » with 4 other **French laboratories:** (Dr. F.Cabon CNRS UPR 9079; Dr. M. Benahmed INSERM U407; Dr. P. Clezardin INSERM U664; Pr. H.Ouadid EA 2086). Each of these teams possesses internationally recognised specific scientific expertise and methodological skills (F. Cabon - si RNA in vivo in xenografted prostatic tumor models; P. Clezardin – bone metastasis; M.Mohamed – apoptosis mechanisms; H. Ouadid – ionic channels and breast cancer).

- The laboratory director coordinated the 'ANR blanc' project (2007 – 2009), « The role of the TRPM8 channel in prostatic and testicular physiopathology ». IN this project, the skills of the co-participating laboratory (Inserm U 670, Nice) in the field of reproduction, contributed significantly to this work.

- Professor Roudbaraki is the scientific director of the national project, entitled « The environment: ionic channels, environmental factors and prostate cancer » in which, as in the above project, the skills of the co-participating laboratory in the field (Inserm U 670, Nice) make a significant contribution.

On the international level:

The laboratory director coordinates the **European INTAS project** N° 05-10008-8223 (2006-2009) « Normal and pathological roles of TRPM8 cold receptor » with 3 other partners**:** Prof. C. Romanin, Institute for Biophysics, Austria; le Prof. Y.Shuba, Physiology Institute, Kiev, Ukraine ; le Prof. E. Pirogov, Urology Institute, Kiev, Ukraine.

This 'Cancer-channel' theme has attracted several teams of European and American scientists over the last few years. These teams are united in a network to generate a dynamic 'exchange of ideas'. International congresses 'Ion channels and cancer' have been organised regularly since 2007. In **addition, the major international conferences** (FASEB 2009; Gordon 2009; Experimental Biology 2010, Biophysical Society 2010) have organised sessions devoted to this theme, which is considered by the international scientific community as being promising from both the pure and applied point of view. The Inserm U1003 Cellular Physiology Laboratory is at the hub of this international network and takes part in all the discussions and round tables on new subjects for discussion at the congress and/or on shared strategies to advance the theme. The head of laboratory sits on the pilot board of the European Project called 'IonTrac' (with 10 other European laboratories 2 Industries) within the framework of the call to tender for a 'Cancer' project organised by the FP7.

Collaborations:

REGIONAL

- Dr. R. Polakowska, Inserm U 837 is working on keratinocytes models and the role of TRP channels on theses cells, ;
- Dr. Y. de Launoit CNRS l'UMR 8117 is studying the non-genomic effects of androgens on TRPM8 channel.

NATIONAL

- Dr. F. Cabon CNRS UPR 9079, Villejuif, brings her expertise in transgenic mice and is studying the role of TRP channels in tumour formation in xenograft mice models. The generation of the murine strains capable of spontaneously inducing cancer, as well as the knock-out of the TRPs genes which may be used to test the specificity of pharmacological compounds.
- Dr. M. BENAHMED, Inserm U670, Nice. As "environmentally relevant dose" or EDC, of endocrine disrupting compounds may increase the susceptibility of the prostate gland to carcinogenesis in adults, this team specialized in endocrinology and reproduction is studying the influence of environmental risk factors on ion channels expression and human prostate cancerogenesis and the role of TRPM8 channel in reproduction; while
- Professor A. Echalier et Dr. Jérôme Busserolles , Inserm U766, Clermont-Ferrand is working on « *in vivo* » studies of non-genomic effects of androgens on TRPM8.
- Dr. P. Clezardin, Inserm U403, Lyon, studies the mechanism and treatment of bone metastasis. As prostate cancer is prone to metastases during the final stages, this team is studying the roles of TRP and especially CaV3.2 channels in bone metastasis formation, we have shown to be involved in calcium homeostasis, secretion, proliferation and apoptosis resistance of the prostate.
- Moreover, N. Prevarskaya has coordinated a national grant from INCA (National Institute of Cancer Research) grant , 2006-2008 on « The roles of trpm8 and trpv6 ion channels in prostate cancer: functional studies and molecular targeting for the elaboration of new therapeutic strategies" with 4 other french laboratories (CNRS UPR 9079 ; INSERM U407 ; INSERM U664 ; EA 2086).

INTERNATIONAL

Related to our research themes, the following teams collaborate in:

- Prof. B. Nilius, Katholieke Universiteit, Leuven, Belgium: characterization of the volume-regulated anion channels in prostate cells;
- Prof. Y.Shuba, Bogomoletz Institute of Physiology, Kiev, Ukraine: characterization of the TRPM8 channels in prostate cells;
- Dr. J. Parys and Dr. F. Wuytack, Katholieke Universiteit, Leuven, Belgium : characterization of IP3 receptors and calcium pumps in the prostate cells;
- Dr. R. Buttyan, Department of Urology, Columbia University, College of Physicians and Surgeons, New York, USA : the effects of oncoprotein Bcl-2 on calcium homeostasis in the prostate cancer cells;
- Prof. V. Flockerzi, Universität des Saarlandes, Homburg, Germany : regulation of TRPM8 and TRPV6 channels;
- Prof. V. Bolotina, Boston University School of Medicine, USA : regulationof ORAI1 and TRPM8 by iPLA2;
- Dr. C. Romanin, Institute for Biophysics, University of Linz, Austria : role of TRPM8 and ORAI1 in prostate cancer
- Professors Rene Bindels et Joost G.J. Hoenderop, Department of Physiology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands : proteins-partners of TRPV6 channel in prostate cancer cells.

The originality of the research.

The originality of the project resides in its innovative character: the Cellular Physiology Laboratory, U1003 has been a pioneer in the research field of the potential role of ionic channels in cancers (in general) and in prostate cancer in particular. This laboratory has also introduced a molecular electrophysiological methodological approach to the study of the mechanisms involved in the development of cancer.

Interest of the research

The work undertaken by the laboratory over recent years has allowed us to identify those ionic channels which play a major role in apoptosis, proliferation and differentiation of cancerous prostate cells. Thus, the accomplishment of this research project over coming years, (devoted to the understanding of mechanisms that deregulate these channels during tumoral development) may lead to a non-negligible contribution to the bio-medical field and more particularly to the discovery of new molecular targets (by specifically affecting ionic channels) and to the proposal of new therapeutic strategies (by intervening in the regulation of prostatic neuroendocrines) for benign hyperplasia and prostate cancer. The interest shown by pharmaceutical laboratories in this work shows how promising this route is.

Major scientific results obtained during last years.

Over these last few years, we have focused our attention on the identification and characterisation of ion channels playing important roles in prostate cancer hallmarks such as 1) self-sufficiency in growth signals and aberrant cell proliferation, 2) insensitivity to antigrowth signals, 3) evasion of programmed cell death (apoptosis), and 4) tissue invasion and metastasis. Furthermore, we made efforts for establishing "calcium and ion channels signatures" for prostate cancer staging in order to develop reliable prognostic markers and define new therapeutic treatment strategies.

1) Self-sufficiency in growth signals and aberrant prostate cancer cell proliferation: role of ion channels

Normal cells require mitogenic growth signals in order to transit from the quiescent into the active proliferative state. Three factors underlie the switch to autonomic tumour cell growth : first, the acquisition by the heterogeneous neoplastic cell population of the ability to produce and release their own, intrinsic mitogens, which act in an autocrine or paracrine manner, second, alteration of the expression and/or properties of cell surface receptors and ion channels that accept growth-stimulatory signals and transmit them to downstream targets and, third, dysregulation of intracellular pathways that ultimately target gene expression.

a) Neuroendocrine differentiation

One important source of intrinsic growth factors within the tumours comes from neuroendocrine differentiated cells. To various extents, neuroendocrine differentiation can be encountered in many human neoplasms derived from different organs and systems including the most common carcinomas: colorectal (Grabowski*, et al.*, 2001), lung (Howe*, et al.*, 2005), breast (Makretsov*, et al.*, 2003) and prostate (Bonkhoff, 2001). **We have been particularly involved during the last four years in the study of voltage-dependent CaV3.2 T-type calcium channels and their role in the development and progression of prostate cancers,** since we previously showed that treatments inducing neuroendocrine differentiation of prostate cancer epithelial LNCaP cells induce an overexpression of such calcium channels (Mariot*, et al.*, 2002). We have demonstrated that prostate cancer tissues express more CaV3.2 than hyperplastic tissues. Moreover, cells expressing CaV3.2 channels in prostate tissues are epithelial neuroendocrine cells expressing chromogranin A and serotonin. Though this allowed us to validate our cell model (LNCaP), it is not feasible to carry out all our studies on human samples. We have shown (Gackiere*, et al.*, 2006) that CaV3.2 T-type calcium channels participate in basal calcium entry at resting membrane potential and thus maintain the cytosolic calcium concentration. We have studied the role of CaV3.2 T-type calcium channels in the secretion of prostate cancer cells. It is likely that these secretions may physiologically regulate prostate growth and development. In addition, it is supposed that the neuropeptides, synthesized and released by the prostate, may participate in the uncontrolled tumour development through their mitogenic actions on epithelial cells in the surrounding tissue. We have demonstrated that prostate cancer LNCaP cells display calcium-dependent regulated pathways of secretion and that CaV3.2 calcium channels participate in this secretory pathway, noticeably by regulating basal secretion of PAP (Gackiere*, et al.*, 2008)**.** Through the stimulation of secretion, they are able to enhance the release of mitogenic factors (as serotonin) by prostate neuroendocrine cells and thereby facilitate the proliferation of surrounding epithelial cells, therefore participating in the paracrine loops long suspected of amplifying prostate cancer growth.

b) <u>Aberrant prostate cancer cell proliferation</u>

Aside from being surrounded by the excess mitogens, cancer cells develop an intrinsic potential for uncontrolled proliferation owing to altered expression and/or function of not only cell cycle regulators that directly control the correct entry and progression through the cell-cycle, but also of membrane receptors and ion channels that accept external signals.

We have been mostly interested in the role of members of Ca^{2+}-permeable channels from the **TRP (Transient Receptor Potential) -channel family in cell proliferation** since the expression of some of these channels have been shown to be altered in cancer in general, and in prostate cancer in particular. Among these, the main evidence concerns the epithelial Ca^{2+} transporter, namely the transient receptor potential vanilloid type 6, TRPV6, (Prevarskaya*, et al.*, 2007)**.** TRPV6 is proposed as a prognostic marker of prostate cancer progression, since its expression strongly increases in high-grade tumours with a Gleason score of ≥7, whilst in normal and benign prostate tissues it is virtually undetectable (Fixemer*, et al.*, 2003). Using the model system of androgen-dependent human prostate cancer LNCaP cell line, we have shown that TRPV6 is directly involved in the control of proliferation, as siRNA-mediated TRPV6 silencing slowed down the proliferation rate, decreased the accumulation of LNCaP cells in the S-phase of the cell-cycle and lowered the expression of the proliferating cell nuclear antigen (PCNA) (Lehen'kyi*, et al.*, 2007)**.** The evidence indicates that pro-proliferative role of TRPV6 consists in supporting the basal Ca^{2+} entry required for the activation of Ca^{2+}/calmodulin/calcineurin-dependent transcription factor NFAT (nuclear factor of activated T-cell) (Lehen'kyi*, et al.*, 2007)**,** whose transcriptional activity alters the expression of cell-cycle regulators. Noteworthily, we have demonstrated that the activation of the same Ca^{2+}/calmodulin/calcineurin/NFAT pathway leads to proliferation in the primary human prostate cancer epithelial cells by Ca^{2+} entry via another TRP family member – TRPC6 (Thebault*, et al.*, 2006)**.** However, in this case, agonist-mediated stimulation of α1-adrenoceptor (α1-AR) is required to generate the lipid messenger diacylglycerol (DAG), by recruiting a phospholipase C (PLC)-catalyzed phospholipid breakdown pathway, which in turn directly gates TRPC6 channels (Thebault*, et al.*, 2006). More, the α1-AR must be expressed as a full-length isoform in order to initiate the calcium signal as we have shown that the lack of the long receptor isoforms hinders calcium entry. Indeed, in DU145 cells, treatment with phenylephrin provoke a recruitment of TRPC6-containing vesicles towards the plasma membrane as well as a

rearrangement of the sub-membranous cytoskeleton, a rearrangement of the receptor containing microdomains along with a modification of microdomain lipidic composition, as seen by an increase in ceramides, cholesterol, sphingomyelin and phosphatidylserin leading to a shift towards lighter densities of the rafts and a modification of the membrane fluidity (Katsogiannou*, et al.*, 2009). **Hence, it would seem that the TRPV6 channel is involved in the control of basal proliferation rate of prostate cancer cells, whilst TRPC6 supports the direct mitogenic effect of catecholamines via their release by sympathetic nerves**.

K+ channels are central to the maintenance of resting membrane potential, which makes them a vital part of all cells. **We have studied the role of IK_{Ca1} potassium channels in the proliferation** of prostate cancer cells. IK_{Ca1} potassium channels were expressed in human androgen-sensitive and -insensitive PCa cell lines, as well as primary cultured human PCa tissues. Interestingly, our results have shown that the IK_{Ca1} channel protein appeared to be overexpressed in PCa compared to BHP tissues (Lallet-Daher*, et al.*, 2009). We also showed that inhibiting the IK_{Ca1} channel induced up-regulation of the $p21^{Cip1}$ and $p27^{kip1}$ cell cycle regulator mRNAs, resulting in PCa cell growth arrest. Activation of IK_{Ca1} channels hyperpolarized membrane potential and induced passive calcium entry by increasing the electrochemical driving force for Ca^{2+} ions. We identified TRPV6 as the channel responsible for this hyperpolarization-evoked calcium entry. Moreover, immunoprecipitation experiments strongly suggested that IK_{Ca1} was associated with TRPV6. **In conclusion, our results suggest that the IK_{Ca1} potassium channel controls PCa cell proliferation by close regulation of passive calcium entry via TRPV6 (Lallet-Daher*, et al.*, 2009).**

2) Insensitivity to antigrowth signals

Balanced tissue homeostasis is supported by the combined action of multiple mitogens along with extracellular growth inhibitory signals, which help to reduce proliferative activity by inducing proliferation arrest, apoptosis or differentiation, resulting in cells no longer being able to continue the cell-cycle. Our results have clearly shown that both a decrease in the basal filling of endoplasmic reticulum (ER) Ca^{2+} store and a sustained increase in $[Ca^{2+}]_i$ play anti-growth roles [our reviews (Capiod*, et al.*, 2007; Prevarskaya*, et al.*, 2007; Prevarskaya*, et al.*, 2004; Prevarskaya*, et al.*, 2007).

Moreover, the same mechanism related to ER calcium store depletion was implicated in the anti-proliferative action of another growth inhibitory signal, extracellular ATP, in the prostate cancer DU-145 cell line and in primary prostate cancer cells (Thebault*, et al.*, 2006; Vanoverberghe*, et al.*, 2003). **Thus, in order to become insensitive to growth inhibitory signals, cancer cells must develop protective mechanisms against reductions in the ER Ca^{2+} store content and the activation of Ca^{2+} influx.**

3) Evasion of programmed cell death (apoptosis)

Our results of these last years have shown that to effectively evade apoptosis, cancer cells must first of all elaborate mechanisms that prevent or substantially reduce Ca^{2+} influx by down-regulating the expression of plasma membrane Ca^{2+}-permeable channels and/or signalling pathways that lead to their activation . Indeed, as we have shown in LNCaP, the prostate cancer cell line is transformed into two androgen-independent apoptosis resistant phenotypes, one over-expressing Bcl-2, an anti-apoptotic protein and another one subjected to NE-differentiation, which are both characterized by reduced store-operated calcium entry (SOCE) (Prevarskaya*, et al.*, 2004; Vanden Abeele*, et al.*, 2002; Vanoverberghe*, et al.*, 2004)**.** Such a reduction effectively prevents cytosolic Ca^{2+} overload in response to pro-apoptotic assaults, thereby decreasing the efficiency of mitochondrial and cytoplasmic apoptotic pathways. SOCE is a mechanism which occurs after any procedure inducing ER depletion. This process is triggered in order to refill internal Ca^{2+} stores and constitutes the main way of inducing cytoplasmic Ca^{2+} increase in non-excitable cells. For the last 15 years, the best candidates for SOC channels have belonged essentially to the TRP channel family. Moreover, we have proved that members of this ion channel family are involved in the SOCE of epithelial prostate cancer cells (Vanoverberghe*, et al.*, 2004) Nevertheless, for the last years, studies have shown that two other proteins play a major role in SOCE. The first is STIM1, a Ca^{2+} sensitive protein expressed in ER membrane, which detects Ca^{2+} concentration decrease within the ER and activates SOC following Ca^{2+} store depletion (Zhang*, et al.*, 2005). The second is Orai1, a Ca^{2+} channel required for SOCE in T-cells (Soboloff*, et al.*, 2006). Hence, these data raise

the question of the role of STIM1 and Orai1 in the SOCE of prostate cancer cells. Therefore, we wanted to determine whether these proteins are involved in the appearance of apoptosis resistance in the androgen deprived prostate cancer cells. Our results demonstrated that Orai1 is the sole actor of SOCE whose expression decreases after androgen deprivation while the expression of STIM1 and TRPC1 does not change. This decrease leads to a diminution of SOCE, in agreement with our previous results, and therefore to a decrease in apoptosis. We show that reciprocally, Orai1 knockdown protects LNCaP cells against apoptosis. Thus, Orai1 plays a pivotal role in the progression of prostate cancer and this constitutes the first example of a role of Orai1 in physiopathology outside the immune system (Flourakis*, et al.*, 2010).

4) Tissue invasion and metastasis

Due to their high potential for migration, motility and invasion, tumour cells can penetrate blood or lymphatic vessels, circulate through the intravascular stream, and then proliferate at another site: a process called metastasis. The cyclical, morphological and adherence changes observed during cell migration are accompanied by repetitive changes in $[Ca^{2+}]_i$, which usually take the form of Ca^{2+} spikes or oscillations (Clapham, 2007).The $[Ca^{2+}]_i$ signal in turn depends on Ca^{2+} influx via channels in the plasma membrane whose molecular nature is still largely unknown for migrating cells in general and even more for metastatic cancer cells.

We have detected TRPV2 expression in metastatic androgen-resistant prostate cancer cell lines PC-3, DU-145, and LNCaP C4-2. TRPV2 silencing drastically reduced the migration of prostate cancer cells, whereas the overexpression of TRPV2 increased their migration. TRPV2 also increased the basal intracellular calcium level ($[Ca^{2+}]i$) in prostate cancer cells, suggesting a constitutive activity of this channel and a role for $[Ca^{2+}]i$ in TRPV2-mediated cell migration. We have also shown that common endogenous lysophospholipids, lysophosphatidylcholine (LPC) and lysophosphatidylinositol (LPI) stimulate calcium influx and increase the migration potential in prostate cancer PC3 cells. TRPV2 silencing with shRNA abolishes the stimulatory effect of lysophospholipids on both calcium entry and migration, pointing to a role played by TRPV2 channels in cancer cell migration (Monet*, et al.*, 2009; Monet*, et al.*, 2010). **Thus, we have identified lysophospholipids as new physiological stimuli for TRPV2 channels. A particular insight has been made into the role of this channel in a previously unrecognized mechanism by which lysophospholipids stimulate cancer cell migration.**

5) Ion channels as potential prognostic markers for prostate cancer

In this respect, the TRPM8 (TRP, Melastatine member 8) channel attracted our attention as the most promising candidate.

More than 100 biomarkers (for diagnosis and/or prognosis) have been proposed for prostate cancer, most of which, unfortunately have not been translated into practical clinical applications. **Consequently, there is an acute need for a subcategorization of prostate cancers using different molecular markers in order to identify these groups of men.**

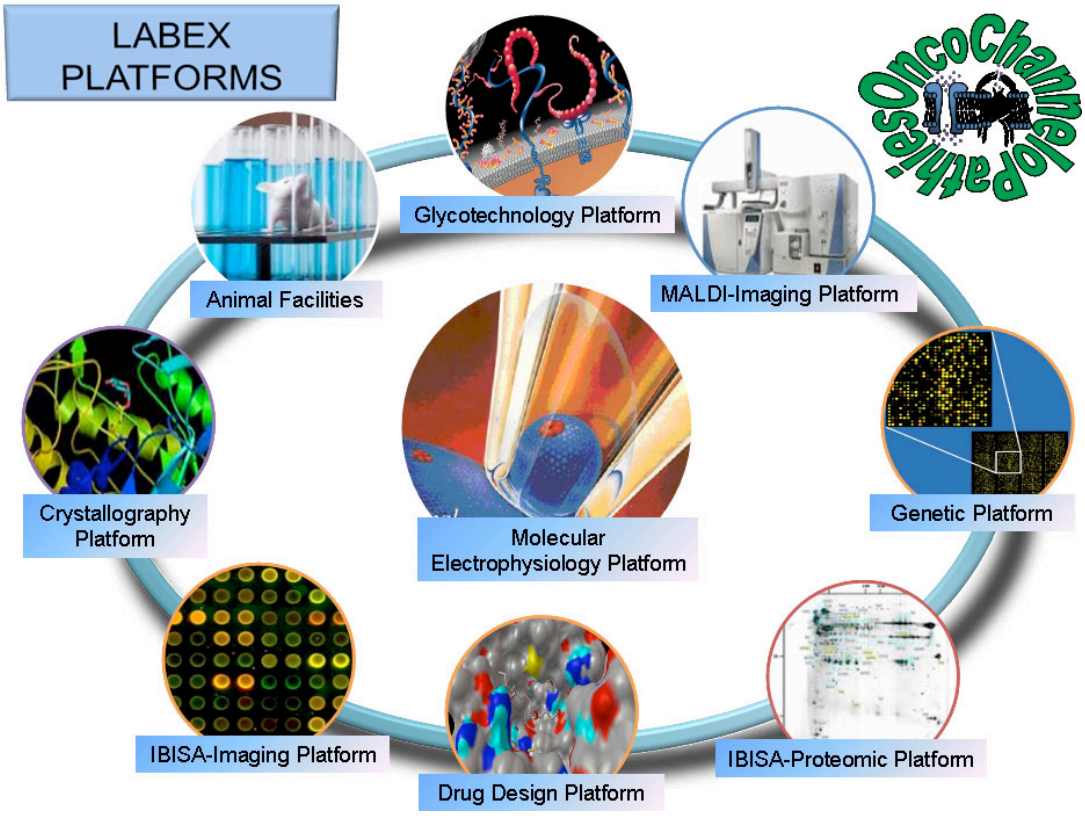
We have firstly designed a study to determine the mechanisms by which androgens regulate TRPM8 mRNA expression in human prostate cells, and also to identify the phenotype of TRPM8 channel-expressing cells. **We demonstrated that the androgen receptor activation is a key-element for the up-regulation of trpm8 gene expression by DHT (Bidaux*, et al.*, 2005).** We have functionally characterized TRPM8 channel in the human prostate cancer LNCaP cell line (Thebault*, et al.*, 2006). In these cells, TRPM8 is highly expressed, but is almost exclusively localized in the endoplasmic reticulum (ER) membrane, where it acts as an ER Ca^{2+} release channel involved in supporting the androgen-dependent component of store-operated Ca^{2+} entry (Thebault*, et al.*, 2006)**.** We also investigated how TRPM8 localization and activity are regulated depending on the differentiation and oncogenic status of Prostate Primary Epithelial cells (PrPE). Our results have shown for the first time that only highly differentiated PrPE luminal cells express functional plasma membrane TRPM8 ($_{PM}$TRPM8) channels. Importantly, prostate primary epithelial cancer cells (PrPCa) obtained from in situ PCa biopsies were characterized by significantly larger $_{PM}$TRPM8-mediated current density than normal or BPH cells. This $_{PM}$TRPM8 activity was abolished in dedifferentiated PrPE that had lost their luminal secretory phenotype. In contrast, endoplasmic reticulum TRPM8 ($_{ER}$TRPM8) remained functional irrespective of the differentiation status of prostate cells. We explain this differential regulation of TRPM8 activity by the complex regulation of

$_{ER}$TRPM8 and $_{PM}$TRPM8 isoforms by androgen receptors. **Taken together, these data suggest that TRPM8 may contribute to the initiation, promotion and progression of carcinogenesis in prostate epithelial cells and represent a new reliable prognostic marker for prostate cancer. These results have been published in the Journal of Clinical Investigation (Bidaux*, et al.*, 2007).**

Conclusion

The results obtained in our laboratory during the last years have clearly shown the importance of ion channels and calcium channels in particular in such fundamental processes as cell growth, proliferation, apoptosis, migration, and differentiation of cancer cells. These data will consequently provide for the numerous research perspectives for the study of physiological and pathological roles of ion channels and calcium in the above tissues.

Scientific infrastructures, equipments, services.



1. **An IbiSa 'Cellular Imagery' platform** named Bio Imaging Center Lille Campus Lille 1", part of the "Bio Imaging Center Lille North of France, BICEL, directed by Dr. Frank LAFONT) was created at the site of Lille (new label in 2010) with the active participation of laboratory members. Together with several other laboratories we applied for the **EquipEx** (equipment of excellence), entitled "High-throughput & ultra-high-content screening microscopy facility". The proposal consisted in setting up a **new Facility** dedicated to the screening and analysis based on **functional high content screening microscopy**. Although some HCS system are already in place in France, our project is unique in the integration of the techniques, in the confinement zones where the systems will be located, and the cross-comparison of the results between different fields in order to find different applications for selected hits increasing their value. This will establish a highly competitive Facility at the international level.

2. Christian Slomianny, Inserm researcher in U1003, directs an **IbiSa Image Analysis Centre** at the University of Lille 1. The Centre Commun de Mesures Imagerie Cellulaire (CCMIC) is intended to support research in Biology especially in the field of cellular imaging, through the activities of photonic microscopy (fluorescence & confocal microcopy), transmission & scanning electron microscopy, image processing, digital imaging... Two engineers provide consulting and technical implementation services. Elodie RICHARD and Loïc BRUNET (respectively biologist and physicist) are specialized in scientific instrumentation and experimental techniques. The CCMIC and its partner "the Biophotonics Cellular Functional" staff (from the Interdisciplinary Research Institute, IRI) are constituting the "Bio Imaging Center Lille Campus Lille 1", part of the BICEL, The CCMIC is accessible to all laboratories in the Faculty of Biology of Lille 1 but also opened to any public or private structures (after agreement).

3. R. Skryma, professor in U1003, has developed a **« Molecular electrophysiology platform** with an automated Patch », for industrial collaboration. The new confocal microscope (funded by Inserm and Region Nord-Pas de Calais) has been combined with the patch-clamp set-up. Several collaborative experiments have been carried out thanks to the unique skills of the laboratory on the Lille site.

4. **IbiSa 'Proteomics" platform** (directed by Dr Christian Rolando) is composed with a principal medium throughput proteomics stage equipped with state-of-the art instruments and automation tools for sample preparation, mass spectrometry-based analysis and data treatments (USR CNRS 3290, MSAP, Dr Caroline Tokarski, Dr Christian Rolando), and 3 specialized stages: glycoproteomics (UGSF UMR 8576, Pr Jean-Claude Michalski), MALDI Imaging (LNA FRE 2993, Pr Isabelle Fournier, see details below point 6) and clinical proteomics (Institut Pasteur, INSERM U744-IPL, Pr Florence Pinet). The commercial value of the instruments installed in the proteomics facility reaches roughly 2.5 million euros plus the FT-MS instrument (1.0 million euros). Specific tools and techniques developed for the separation and identification of membrane proteins will be applied to the study of ion channels and receptors. For example, hydrophobic gel electrophoresis, which allows separation of proteins including up to 11 transmembrane domains, will be used.

In charge of: ANR FT-ICR 2D project 2011-2014 (supervisor Dr Christian Rolando), ANR ProteoArt project 2009-2011 (supervisor Dr Caroline Tokarski), 08140-8 FAPESP/CNRS project 2010-2011 (supervisor Dr Caroline Tokarski). Participation to: ANR ONCOPOP project 2007-2010 (supervisor Pr Robert Barouki, INSERM UMR-S 747).

5. **Platform MALDI-Imaging**, (I. Fournier) is based on the MALDI Imaging Team (MIT) which was created by granting to I. Fournier of a National Starting Grant (ACI Jeunes Chercheurs, 2004). Since 2009 the MIT platform is included in the IbiSa Proteomics platform hold by Dr. C. Rolando. The platform includes several mass spectrometer instruments like MALDI-TOF-TOF or MALDI-LTQ-Orbitrap and other instrumentation such as capillary electrophoresis coupled to Ion-Trap, or LESA-TRIVERSA coupled to ionTrap, sample preparation devices all related to MALDI imaging and its application to biology and clinics. The services activities of the MIT are covered by the Start-up Imabiotech that was emerged from the research group and is incubated in the laboratory. MIT is part of 2 AAP Equipex Programs. The first EQUIPEX named PharmaR^3 is coordinated by B. Desprez (Uni. Lille 2, Lille, France) and supported by the PRES Lille-Nord de France. This EQUIPEX aims in setting up a platform including several activities for pharmaceutics studies among which MALDI MSI is implicated in DMPK and ADME studies. In the EQUIPEX Imabiotech will be call for service for drugs imaging in animal models on Whole Body Animals (WBA). The MIT will ensure the development of equipments and strategies for studying the variations of proteome under drugs challenge. The second EQUIPEX is a national EQUIPEX coordinate by DR. J. Chamot-Rooke (Polytechnic School, Palaiseau, France) for High Field FT-ICR aiming in equipping different groups with strong background in the field with superior resolution FT-ICR mass spectrometers. In this EQUIPEX, MIT will develop MALDI MSI using high resolution 15T FT-ICR.

6. **An IbiSa 'Genomic' platform**.

The core genomic laboratory (directed by Martin Figeac) gives access to micro-array (U133+2.0, SNP.6, CGH-array, miRNA-array, ChIP/chip, Medip-chip) and to NGS studies (target-

resequencing, RNA-seq, sRNa-seq, ChIP-seq and Medip-seq). The laboratory also offers services or data analysis in high throughput projects (computational biology, biostatistics and computer science). The core genomic lab is associated to the LIGAN (Lille Genomic Network) and develops the genomic research on cancer. We are also associated to the Lille branch of the franch National Institute for Research in Computer Science and Control (INRIA) which brings us an oustanding expertise in cutting edge NGS bioinformatics.

We already have one SOLiD 4 system and access to one Roche 454 and one Illumina GA2x. We plan to get 2 more SOLiD 4 which will be upgraded to SOLiD 4hq (5500 xl) and 2 Illumina HiSeq 2000. We also plan to developp Single Molecule Sequencing and we have an agreement to have one of the first machines under test by the end 2011.

4.1.2.2 VALORISATION / EXPLOITATION OF RESULTS

1. The advancement of knowledge.

Our results taken as a whole show that ionic channels and calcium play a major role in the mechanisms that regulate cancerous cells (prostate and liver) and open numerous research perspectives into the physiological and pathological functions of these organs.

The expertise.

- Members of the laboratory are experts in the assessment of international grants (NIH(USA), « Human Frontier », European (6 PCRD and 7 PCRD, INTAS), « Cancer Research UK » and the « Welcome Trust » in Great Britain, the Ligue Bernoise in Switzerland) as well as national grants (ANR, INCA, ARC, Ligue Nationale Contre le Cancer, FRM, AFM, ARTP)

-Members of the laboratory are referees for several scientific journals: Nature Cancer reviews ; PNAS, Cancer Research, Oncogene, JBC, Cell Calcium, FASEB, J. Physiol., BBA…

- The director of the laboratory has been a member of the Inserm 'Endocrinology' CSS 6 (2003 – 2007) and is at present member of the CNU 'Physiology' Section 66 (2008 – 2011); member of the ARTP scientific council. (The ARTP is the Association for Research into Prostate Tumours) since 2007.

- Members of the laboratory regularly sit on doctoral and HDR thesis juries.

- Invitations to Laboratory members to organise scientific training courses:

Training Workshop on Calcium Imagery Seix, 2003-2008, T.Capiod;
Training Workshop on microscopy and imagery, Lille 2007, C.Slomianny, P.Mariot.

Technological impact and the quality of scientific tool development (software, methodology, platforms…).

Members of the laboratory participate actively in the development of tools to improve our methodological strategy. Its tools are made available to the regional scientific community:

- an IbiSa 'Cellular Imagery' platform was created at the site of Lille with the active participation of laboratory members;

- C. Slomianny directs an Image Analysis Centre at the University of Lille 1 (electronic microscopy, development of 3 new software programmes for image-processing);

- C. Slomianny takes part in an ANR project for the development of new methodologies: "Micro fluids and Nano-electrodes for the electromagnetic spectroscopy of single cells";

-R.Skryma has developed a « Molecular electrophysiology platform with an automated Patch », for industrial collaboration;

-The confocal microscope has been combined with the patch-clamp rig. Several collaborative experiments have been carried out thanks to the unique skills of the laboratory on the Lille site.

2. The importance, and pertinence of relationships with socio-economic partners.

The policy of Cell Physiology encompasses the valorisation of the Laboratory's research through very close collaboration with pharmaceutical companies. As a result, a number of contracts have been signed with pharmaceutical companies over recent years:

- four contracts with Pierre Fabre Médicament (France) 2000-2007;

- two contracts with «Johnson & Johnson» (USA) 2007-2011;

- the common project (between the Cellular physiology laboratory and Pierre Fabre Medicines, "Bio-engineering" on the subject of 'The study of the involvement of ionic channels in the development of prostate cancer' was developed within the framework of a call for project tender by the Ministry of Research;
- one researcher was financed by Pierre Fabre during three years for post-doctoral training ;
- a doctoral student is preparing his thesis (2008-2010) which is co-financed by Johnson & Johnson USA) and the Nord Pas de Calais regional authority.

In 2004 the laboratory received **a 'label' from 'The National League against Cancer (Ligue Nationale contre le Cancer)'** for a period of three years. This label was renewed for the periods of 2007-2009 and 2010-2012 taking into account the criteria of valorisation of laboratory results. Several specific laboratory projects have also been supported by
- the 'Association for Research on Prostate Tumours ARTP' (4 grants);
- the 'Regional League against Cancer' (3 grants);
- the 'Association for Cancer Research ARC (1 grant);
- the 'Foundation for Medical Research FRM' (1 grant).

3. The quality of operation knowledge produced, its transfer and socio-economic valorisation.

- scientific publications that are usable by industrial scientists
- presence at fairs
- participation in conferences for publics from the world of industry.

4. Contribution to the spread of knowledge and scientific culture, to corporate intelligence.

- Organised by the Inserm workshop: "How to transfer scientific knowledge through teaching" Paris, 2006, T. Capiod.
- Several courses (differing in level and length) are organised at the laboratory for students on scientific and professional courses (IUT, Lille) as well as tutoring of Msc students studying for the "Mission – enterprise" diploma, has been set up.
- Organisation of courses for sixth-form teachers in Lille, to show and explain molecular electrophysiology combined to calcium imagery.
- Presentations to the general public by unit members through meetings organised by La Ligue Contre le Cancer (National and Regional)(League against Cancer) and the Fondation de la Recherche Médicale (National and Regional)(Medical research foundation).
- The organisation of scientific courses by unit members:
- 'Calcium imagery training workshop' Seix, 2003 – 2009, T.Capiod;
- 'Microscopy and imagery training workshop', Lille 2007, C. Slomianny, P. Mariot.

4.1.2.3 ENSEIGNEMENT SUPERIEUR / HIGHER EDUCATION

Each year about 18,000 students are enrolled in degree courses at the University of Lille 1, a member of *PRES ULNF*, and about 2000 in life sciences and health, main vocational field in which our laboratories are involved. University lecturers and professors working in the candidate LABEX Research Laboratories participate in a wide range of Degree courses from the Bachelor Degree (BSc of Natural Sciences, Biochemistry, Cell Biology and Physiology), to the Master and PhD programs and in in-service training for business. In this context, faculty members are also responsible for a large number of teaching units, courses and technological workshops.

1) Undergraduate Degree

Laboratory members are responsible for various course modules in first year Biology ("Cell Physiology and Biophysics": responsible P. Mariot, Associate Professor) and second year Biology ("General Physiology": P. Mariot, "Cell communication": Prof. M. Roudbaraki).

Each year, our laboratories provide the opportunity for many undergraduates (BSc, IUT or BTS) to carry out their internship, allowing them to take contact with the scientific research community.

2) Postgraduate Studies

I- Master Degree

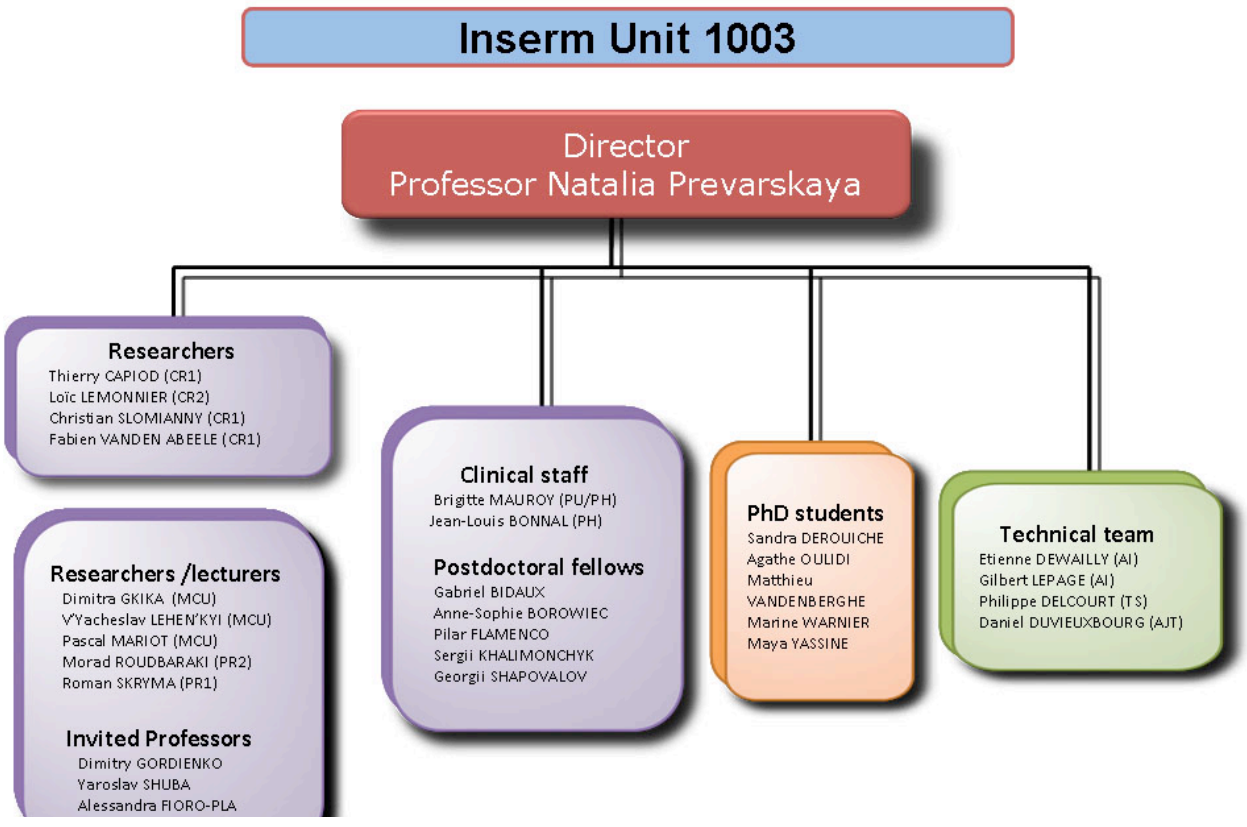
In the Master's courses, in addition to the organization of theoretical lectures (courses in physiology and cell biology, membrane biophysics ...), our laboratory organizes seminars and technological workshops in our area of expertise. Laboratory members are responsible for two course modules in first year Master ("Integration of physiological signals: from molecule to organism" and "Cell calcium homeostasis and pathophysiology" : responsible : Prof N. Prevarskaya). Furthermore, our laboratory organizes three seminars each year in M2. In addition, workshops in molecular electrophysiology and fluorescence imaging are held each year in order to initiate students to advanced techniques in the field of life sciences and health.

II-PhD formation

Doctoral formation in which lecturers and professors participate in the lab belongs to the postgraduate school of "Biology and Health" jointly accredited by the Universities of Lille 1 and Lille 2. Each year the postgraduate school trains about 60 new doctoral students. These students are enrolled after a drastic selection occurring at the end of the M2 of Biology and Health. Within our team, 15 students submitted a thesis for the last 10 years. Of these 15 students, 7 obtained a permanent position in France or abroad (2 INSERM researchers: Loic Lemonnier and Fabien Vanden Abeele, a university professor: Fabien Vancopenolle, a research associate working abroad in Mexico: Stephanie Thebault, a teacher in nursing school: Marie Debarbieux, a clinical researcher working in the Bordeaux Hospital: Karine Vanoverberghe, a project manager at Stratelys, a private company: Guillaume Legrand) and 8 still hold a post-doctoral position.

So far, 6 members of the lab (Professors: N. Prevarskaya, M. Roudabaraki, R. Skryma, Assist. Professor: P. Mariot, Inserm researchers: C. Slomianny and T. Capiod) have the HDR (Habilitation to supervise research) which authorizes to supervise PhD students.

4.1.2.4 ORGANISATION / ORGANISATION



Currently, the unit has a single theme and operates as a team, directed by Professor N. Prevarskya. She is responsible for the choice of global strategies of the project and the research axes followed by the post-doctoral and other students for whom she is responsible. The research scientists and teacher-researchers (including the director) have their own specific research axes and the researchers with the HDR are responsible for their respective students. The researchers have specific methodological skills and place these skills at the disposal of all the laboratory members to assist with the progress of their research projects. The clinicians participate in reflection on the potential clinical applications of our research; they also participate in the analysis of results for our channel markers of interest, depending on the development stage of tumours. The technicians are involved in all the laboratory's projects, using their specific technical skills. However, each technician reports to a named researcher.

The recurrent funding of Inserm and USTL is shared equally between the laboratory's researchers; funding obtained for specific projects (ANR, INCA…) are used for those projects and is controlled by the person in charge of each respective project.

Fundings obtained by the members of the laboratory

Funding origin/ Name of coordinator	Project title	Duration	Amount (k€)/year
ANR / N. Prevarskaya	***Rôle du canal ionique TRPM8 dans la physiopathologie de la prostate et des testicules : implication dans la reproduction***	2006 - 2010	37.5
ANR / C. Slomianny	***FENOTIP – Microfluidique et nanoélectrodes pour la spectroscopie électromagnétique de cellules uniques.***	2005 - 2008	4.5
INCa / N. Prevarskaya	***The roles of TRPM8 and TRPV6 ion channels in prostate cancer: functional studies and molecular targeting for the elaboration of new therapeutic strategies.***	2006 - 2009	130
INCa / N. Prevarskaya	***Caractérisation fonctionnelle et moléculaire du canal cationique membranaire, le canal TRPM8 : implication dans la cancérisation de la prostate.***	2007 - 2010	25
INTAS / N. Prevarskaya	***Normal and pathological roles of TRPM8 cold receptor***	2006-2009	4.5
National League / N. Prevarskaya	***La signature calcique cellulaire : un marqueur tumoral potentiel. Ciblage moléculaire des canaux ioniques pour le diagnostic, le pronostic évolutif et le traitement du cancer de la prostate.***	2010 - 2012	85
National League / N. Prevarskaya	***Développement d'un modèle de souris Knock-down du canal TRPM8 : vers une meilleure compréhension de la physiopathologie de la prostate.***	2007 - 2009	19
National League / L. Lemonnier	***Rôle du canal TRPM8 dans la cancérisation de la prostate.***	2007 - 2009	5
Pierre Fabre / N. Prevarskaya	***Rôle des canaux TRP dans la différenciation des kératinocytes humains***	2004-2008	35
Région Nord-PDC / M. Roubaraki	***Exposition néonatale aux oestrogéno-mimétiques et cancer de la prostate***	2007 - 2010	30

Distribution of resources.

In general, we have two kinds of funding:

- recurrent funding from INSERM (160 k€ per year) and from the Research Ministry (38k€ per year) during 4 years (for last quadrennial contract) for the common project of our laboratory;
- funding for specific projects from different European (INTAS), French (The National League against Cancer, ANR, INCa…) and regional organisms 'Regional League against Cancer', Region of Nord-Pas de Calais … or from pharmaceutical companies (Pierre Fabre). See the table below.

Our strategy is to equally distribute the "recurrent" credits between the members of our staff to cover the common expenses such as cell cultures, basic products for molecular and cell biology sectors, fluorescent dyes, common pharmacological tools for electophysiological studies… The funding for the specific projects is controlled by the project leaders and is used according to the respective programs. Approximately 20% of each grant is generally used for common laboratory expenses. Most of the big equipments were acquired by means of this kind of funding: confocal microscope, real time PCR.

All the permanent teacher-researcher staff together with representative students and technicians meets in council twice a year.

The research results obtained by members of the laboratory are discussed weekly at laboratory meetings. The laboratory director also organises personal discussions with the researchers (three times a year on average) and with the technician's Staff (twice a year, on average).

As mentioned above, the laboratory organizes weekly meetings to discuss the results obtained and the scientific strategy to be followed. 'Journal club' meetings were initiated in 2008; the laboratory's policy consists in regularly inviting French and foreign scientists to give seminars and to discuss the laboratories results. Thus several renowned researchers have already come to Lille: Jim Putney (USA) ; V. Bolotina (USA) ; I. Ambudkar (USA) ; J. Parys (Belgique) ; A. Tepikin (Great Britain); M. Zhu (USA).

Researchers and students attend national and international congresses.

4.1.3 PARTENAIRE 3/ PARTNER 3 : JEAN-CLAUDE MICHALSKI

4.1.3.1 RECHERCHE ET INNOVATION / RESEARCH AND INNOVATION

The team:" ***Glycobiology of Cell Signalling and Glycopathologies "(GCSG)*** *–Group leader: Jean-Claude Michalski-* is one of the 10 teams constituting UGSF. It was ranked **A** by AERES (2A + $2A^+$).

The team gather **30 people** including **12 permanent researchers** { 1 Research Director (DR1) INSERM, 3 "Chargés de Recherche" (CR1, CNRS), 3 Professors, 5 Assistant Professors (Maitre de Conférences), 1 invited Professor, 1 Post-Doc, 9 PhD students ,3 undergraduates (Master2) students and 4 technical staff members : 1 ingenior (IE ,CNRS), 2 Assistant Ingenior (AI, CNRS) , 1 technician (TCE,INSERM)}

The general research of GSCG is focused on glycomic, glycoproteomic and covers different aspects of functional glycobiology with a special emphasis for glycopathologies.

1) ***Glycomics and glycoproteomics*** :

Willy Morelle, Catherine Robbe-Masselot,Jean-Claude Michalski

Application and development of glycomics and glycoproteomic strategies to establish the structure/function relationships of glycans of cellular glycoproteins of biological interest (membrane-bound and secreted glycoproteins) and the evaluation for consequences of glycosylation changes for the understanding of physio-pathology of human diseases (Congenital disorder of glycosylation , colon cancer , Alzheimer disease) . A special interest is devoted to the study of human gastro-intestinal mucins glycosylation in colon cancer as well as the involvement of mucins glycans in microbial interactions

2) ***Biological functions of cytosolic and nuclear glycosylation O-GlcNAc***

Tony Lefebvre, Anne-Sophie Vercoutter-Edouart, Ikram El Yazidi. , Annick Pierce, Christophe Mariller

The research lines concern the role of O-GlcNAcylation in proteasomal degradation and control of cell cycle and the regulation by the O-N-acetylglucosaminylation/ phosphorylation interplay of delta-lactoferrin (ΔLf) and include new research directions concerning the function of O-GlcNAcylation in the insulin-resistance and glucotoxicity phenomenon as well as the transcriptional regulation of O-GlcNAc transferase (OGT)

3) Regulation of the Glycosylation metabolism in the physiology of the normal and pathologic cells.

François Foulquier, Dominique Legrand, Sandrine Duvet

Our interest is for the quality control machinery for glycoproteins biosynthesis inside the ER and Golgi apparatus, with a special emphasis for free oligosaccharides (FOS) metabolism and transport inside the cytosol. The second aspect is devoted to the regulation of the glycosylation metabolism in the physiology of the normal and pathologic cells with a special interest for the Congenital Disorders of Glycosylation (CDGs) and lysosomal storage disorders.

All together this project combined researchers with differing scientific backgrounds ranging from structural glycobiology , biochemistry, cellular biology to molecular biology .The experimental models are themselves extremely diverse going from human samples (Biopsies, urine , serum), mammalian cell cultures including glycosylation mutants (Lec mutants CHO cells, human fibroblasts from CDGs patients), animal models such as *Drosophilia* or *Zebra Fish* models . Strong interactions are established between the different team members combining their scientific and methodological knowledges. Glycomics, glycoproteomic, cell imaging represent central tools for all the projects.

The three axes leaders, in spite of their youngness for some of them, are internationally recognized as expert in their research field.

Jean-Claude Michalski is Director of Research at INSERM (DR1). He is head of the Lille Glycobiology Institute (UGSF) from January 2000 and Head of the Biochemistry Department at University Lille 1. He is one of the pioneers in the field of glycomics. He is internationally recognized in the glycobiology community for his work on lysosomal storage disorders and glycoproteins catabolism. His research combined development of structural methods for glycomics and glycoproteomic (mostly mass-spectrometry and NMR based), as well as interest for the biological functions of glycans and their dysregulations in human pathologies. Jean-Claude Michalski is the French representative at the International Glycobiology organisation (IGO), he was president of the French Glycobiology Society (GFG) (2000 -2002), and he is member of the steering committee of the European Science Fundation (ESF) network in glycosciences (Euroglycoforum) in charge of the Education. He has organized several international meetings including training schools in glycobiology (FEBS and EMBO). He is member of many national scientific committees (Ligue Nationale Contre le Cancer, Vaincre la Mucoviscidose, FRM Nord-Pas de Calais, Member of the CNRS national Committee (CoCNRS) section 21) He is co-Director of the Doctoral School "Biologie Santé de Lille –ED BSDL) .

Tony Lefebvre is Professor of Biochemistry at University Lille 1, after a fellowship at the Institute of Biology de Lille (IBL) Team of Dominique Stehelin (2002-2003), devoted to the study of the tumour suppressor HIC1, he joined Jean –Claude Michalski team , developing a research on a new glycosylation (O-GlcNAcylation) in balance with phosphorylation controlling the activity of many cytoplasmic and nuclear proteins (transcription factors, cytoskeletal proteins …) His current research concern the metabolic relevance of this glycosylation in relation with diabetes type 2 and colon cancer . He is recipient of a grant from La Ligue de Recherche sur le Cancer.

François Foulquier is Chargé de Recherche at CNRS (CR1). He was a post-doctoral fellow at KU Leuven, Belgium (Long term Marie-Curie IEF, 2003-2007) under the supervision of Professor Gert Matthys, working on Congenital Disorders of Glycosylation (CDGs). He was recipient of a Marie Curie Return Grant (ERG). His research concern the study of quality control of glycoproteins biosynthesis and the study of new unclassified forms of CDGs involved in vesicular trafficking .He is recently recipient of an "ANR Jeunes Chercheurs" (2010)

Scientific score:

The GCSG team has published 106 articles (see 7.1) in international reviews from 2005. The major contributions are in the characterization of new glycomarkers associated with a wide range of genetic or acquired pathologies, using new glycomics and glycoproteomic strategies, the demonstration of the biological and cellular functions of the O-GlcNAcylation /phosphorylation balance, the biochemical characterization of new Congenital Disorders of glycosylation, the changes of intestinal mucins glycosylation in relation with colon cancer.

Instruments facilities:

As previously mentioned GCSG researches cover different methodological approaches ranging from structural biology (glycomic, proteomic), biochemistry, cellular biology, molecular biology, cellular imaging, animal models …). Most of the technical facilities are available at UGSF (Molecular biology platform, cell cultures, proteins expressions and purification, molecular interactions (Biacore) ... Moreover a specific technical platform so-called "glycotechnology " (see platforms) has been develop in-house for the glycomic approach (Proteomic lab, GC and GC-MS instruments, Phosphor –Imager, Biacore, Anionic exchange chromatography –DIONEX…) The GSCG has also a privileged access to the IBISA Proteomic platform of University Lille 1 (Christian Rolando) combining different mass-spectrometry instruments (MALDI, MALDI TOF-TOF, ESI MS-MS, and Ion-Trap MS-MS). Many of our co-workers are formed in mass-spectrometry analyses .Additively UGSF is responsible for huge NMR instruments (400, 600, 800 and 900 MHz instruments).

4.1.3.2 VALORISATION / EXPLOITATION OF RESULTS

GSCG is one of the reference lab for glycomics. Much collaboration is engaged with Biotechs labs for the characterisation of glycosylation profiles of recombinant therapeutics (rGPs). Collaborations are also engaged with academical research labs for establishing the glycosylation pattern of cellular glycoproteins of biological relevance or for searching for diseases associated glycomarkers (Diagnosis). GSCG has also a strong interaction with clinical labs for the characterisation and diagnosis of Congenital Disorders of Glycosylation. A special interest is also devoted for the study of intestinal mucins in colorectal cancers in relation with clinician's .More generally CGSG is associated through research grants with pharmaceutical companies searching for new "Glyco" drugs.

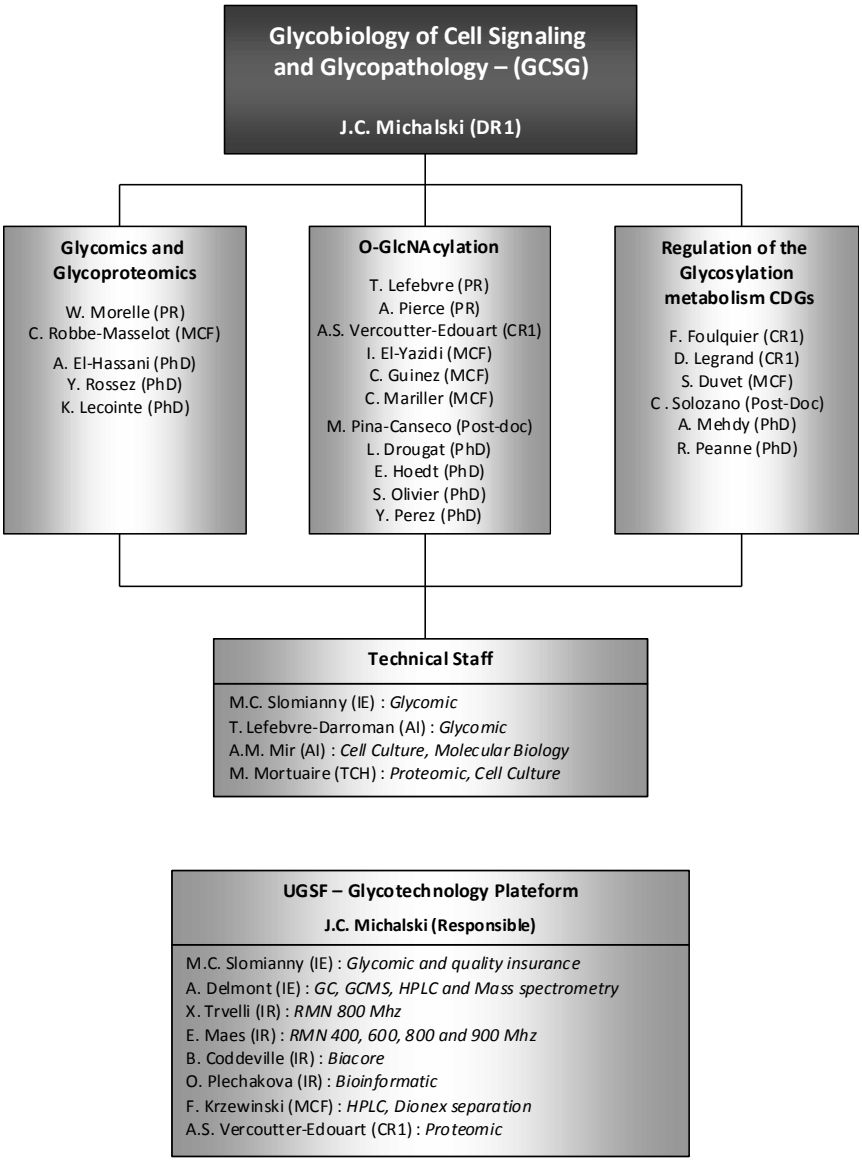
4.1.3.3 ENSEIGNEMENT SUPERIEUR / HIGHER EDUCATION

Many of GCSG members have teaching duties in Biochemistry. Jean-Claude Michalski is co-Director of the Doctoral School "Biology and Health" from Lille. Annick Pierce is responsible of the biochemistry teaching at the Master 1 level. GSCG organises practical formations in the field glycotechnologies gathering researchers from private companies and academic researchers. Four practical formations organised from 2009-2010.

Jean-Claude Michalski is in charge of glycobiology "teaching" at the European level (ESF Glycoforum) and is organiser of international glycobiology courses (Glycomarkers for disease, Wierzba,Poland ,September 2010 ; EMBO workshop "Glycoscience and development , Lille 2008; 16th Meeting of the International Association for Protein Structure Analysis and Proteomics. Methods in Post-Translational modifications analysis, Lille, 2006)

4.1.3.4 ORGANISATION / ORGANISATION

The team is currently structured around the three research directions respectively : 1)Glycomics and Glycoproteomics , 2) O-GlcNAcylation , 3) Regulation of the glycosylation metabolism and Congenital Disorders of Glycosylation (CDGs)



"The glycotechnologies" platform

As previously mentioned most of the researches of the team are driven by glycomic/glycoproteomic approaches, for that reason we have developed in our lab, an independent technical platform (see organisation chart), which mission is to develop and applied new technologies related to the glycosylation analysis of glycoproteins of biological interest, or the glycomic analysis of biological fluids such as human serum searching for the characterization of new "**glyco"-biomarkers.**

Glycomics

Advances in glycomics are anticipated to be driven by improvements in glycan sequencing methods and bioinformatics as well. One of the key bottlenecks in the development of glycobiology has been analysis of glycan structures, which are often only available in small quantities from natural sources. In the past, analytical tools have lagged far behind those used on DNA and proteins, but this landscape has changed considerably over the last decade. In particular, as in proteomics and metabolomics, **mass spectrometry methods** have come to the fore as a powerful tool for sensitive and definitive glycan analysis (Morelle and Michalski, 2007). MALDI-TOF can be exploited in screening strategies, thereby permitting very complex cell, tissue, and biological fluids glycomes to be profiled and important minor structures to be identified on a timescale of a few weeks. In this respect we have developed high throughput strategies for the analysis of serum N-and O-glycomes which appears very useful for the characterization of **Glyco-biomarkers** in different pathological states (e.g. Cancer, alcoholism, human genetic disorders …). These methods also provide a window on the dynamics of glycome expression.

In contrast, ESI-MS/MS and MALDI-TOF/TOF methods can be used for detailed analysis of selected structures, or for the study of individual isolated glycoproteins of biological or industrial interest .Many collaborations are engaged with **Biotechs companies** for the characterization of the glycosylation pattern of **recombinant therapeutics** (Aventis, Sanofi, Meristem Therapeutics, LFB Biotech, Crucell…). Glycomics approaches could underpin opportunities for technology development for monitoring and control of glycosylation of recombinant protein therapeutics.

Glycoproteomics of cells and cell-membranes

Glycoproteomics approaches can be used to define the variant glycans located at specific attachment sites within glycoproteins analyzing these different **'glycoforms'** is an important issue for proteomics because they can significantly alter protein function. In this respect we specially focus on the development of strategies for the proteomic characterization of membrane glycoproteins. Most membrane-bound are post-translationally modified by glycosylation. This process is species-, tissue- as well as cell-specific and is subject to changes due to (patho) physiological processes. This aspect of research is very challenging due to the difficulty 1) to solubilise these proteins 2) to the impossibility to use conventional 2-D electrophoresis methods for their separation due to their high hydrophobicity.

For that reason we put our effort in the development of new "differential proteomics approaches" based on *in-gel* detection of glycoproteins using **lectins-based** staining methods , and the separation of selected glycoproteins by serial lectins affinity chromatography and/or anion-exchange chromatography. Such methods have been applied for the characterization of endothelial cell-membrane glycoproteins (Slomianny*, et al.*, 2006), breast cancer cells glycoproteins, colon cancer cells (Andre*, et al.*, 2007; Vercoutter-Edouart*, et al.*, 2008)

4.1.4 PARTENAIRE 4/ PARTNER 4 : XAVIER VEKEMANS

4.1.4.1 RECHERCHE ET INNOVATION / RESEARCH AND INNOVATION

Ranked A+ by AERES in 2009, the **GEPV** lab (**Genetics and Evolution of Plant Populations**), associated to CNRS (I.N.E.E.) is specialized in the **evolutionary genetics and genomics** of plant biodiversity. Genetic and genomic data from natural plant population samples and from experimental fields are used to investigate evolutionary processes responsible for the dynamics of biodiversity. Research projects focus on two main axes. The first axis concerns the evolution of genetic systems controlling plant reproduction, and the genomic effects of the selective processes acting on chromosomal regions involved in these reproductive systems. The

second axis concerns the evolutionary genetics and genomics of environmental adaptation, focusing on deciphering the genetic architecture involved in major adaptations in plants. The laboratory' specificity in the national and international research community lies in its double expertise in the **dynamics of neutral or selected genomic diversity** in plant populations and on the **inference and modeling of evolutionary processes** responsible for these patterns of diversity. At the national level, the laboratory is strongly implicated in the development of the field of **population genomics** (GDR CNRS 1928, headed by X. Vekemans and comprising 33 research teams from CNRS, INSERM, INRA and different universities), and this research theme has been boosted in the laboratory by the recruitment of Vincent Castric at CNRS as CR1 in 2010 (formerly assistant professor in Lille 1 University). Since the recruitment of Fabrice ROUX as CR2 CNRS in 2007, the laboratory has reached an international leadership in application of GWA-mapping (Genome-Wide Association mapping) to decipher the genetic architecture of major plant adaptations.

Since 2005, the laboratory has published **87 papers in international peer-reviewed journals** (26 in 2010; 15 in 2009), with among others, publications in **Nature, Science, Nature Reviews Genetics, Trends in Ecology and Evolution, Current Opinion in Plant Science, Molecular Biology and Evolution**,…

Research at GEPV is funded by International and European grants, national grants, and regional grants.

- **Selected international grants**:
  - 2006 2008 E.U., Marie Curie programme « Metolevol » (N° 024683) Validation of genes potentially responsible for the tolerance and haevy metal hyperaccumulation in higher plants using QTL mapping and the tools of molecular evolution ». (204 k€)
  - 2005-2007: E.U. INTERREG II programme "Biodiversité transmanche". Participation au projet (35 k€)
  - 2005: Fulbright Grant (P. Touzet). (13 k€).
  - 2003-2006 E.U. Framework 5, Research Training Network "Molecular Mechanisms of Metal Homeostasis in Higher Plants, METALHOME".. Contrat N°HPRN-CT-2002-00243 (151.6k€).
- **Selected national grants:**
  - 2010-2013: ANR Programme Blanc. QUANTIREX. "Identification of key genes underlying quantitative resistance to Xanthomonas campestris in Arabidopsis thaliana by Genome Wide Association mapping and QTL analysis". (150 k€).
  - 2007-2010: ANR Programme Blanc, discipline Biologie Santé. Heading of project SELMULTILOC "The effect of selection at multiple loci on molecular polymorphism within a chromosomal region ". (300 k€).
  - 2007-2010: ANR Programme Biodiversité, TRANSBIODIV: "Biodiversité trans-spécifique neutre et fonctionnelle: Développements théoriques et quantification chez des organismes modèles". (170 k€).
  - 2003-2008: CNRS ATIP and ATIP-Plus programme, Départements Sciences du Vivant et EDD "Comparaison de la structure fine et des séquences génomiques de la région du locus d'auto-incompatibilité entre lignées haplotypiques au sein du genre Arabidopsis" (165 k€).
  - 2006-2009 : ANR Jeune chercheur, Pascal Touzet, "Dynamique évolutive de la gynodiœcie chez Beta vulgaris ssp maritima et Silene nutans. Des génomes aux population" (120 k€).

The scientific activities of the laboratory rely on several essential **technical platforms**:

- Greenhouses facilities: this platform is dedicated to cultivation of plants, maintenance of collections, and phenotyping of life history traits (conventional greenhouses and GMO greenhouse S2). It involves 4 permanent technical staff members.
- A phenotyping platform: 2 Phytotrons, a particles meter for pollen counting (CASY_ model TT, Innovatis), an analyzer of seed size (Elmor C3, Elmor) and a mineralisator microwave (Ethos More, Milestone).

• The molecular ecology laboratory of the unit: this platform is equipped with 10 PCR benches, a bench of quantitative PCR analysis LightCycler 480 (Roche), 2 automatic DNA sequencers LiCor, and an automatic 16 capillaries DNA sequencer (ABI 3130, Applied Biosystem). It involves two permanent technical staff members.

• The bioinformatic platform: this platform (with CTAI CNRS certification) has been created in 2010 with the recruitment of Sophie Gallina (IR CNRS). It contains several Linux servers for in-house mathematical data mining, high capacity disk storage, and has an interface with local and remote computing grids.

4.1.4.2 VALORISATION / EXPLOITATION OF RESULTS

Most scientific production of the GEPV laboratory corresponds to fundamental research that is communicated through high profile scientific journals, and congress communications. Applied research projects in plant biodiversity are promoted through the implication of the laboratory in the Nord-Pas de Calais regional GIS Biodiversity initiative, headed by Yves Piquot, member of the GEPV lab.

4.1.4.3 ENSEIGNEMENT SUPERIEUR / HIGHER EDUCATION

Members of the GEPV lab are key players in the training in Ecology and Evolution at the Graduate level (Biology degree, specialty in **Population and Organism Biology**, headed by Patrick De Laguérie, GEPV), the Master level (**Master in Ecology**, headed by Xavier VEKEMANS, GEPV), as well as the PhD level (**Ecole Doctorale SMRE**, headed by Joel CUGUEN, director of GEPV) at Lille 1 University.

4.1.4.4 ORGANISATION / ORGANISATION

The GEPV laboratory, headed by Joel Cuguen, is administrated as a single research team, organized into four different research axes: (1) Evolutionary dynamics of gynodioecy, from genomes to populations (headed by Pascal Touzet); (2) Evolutionary genomics of self-incompatibility systems (headed by Xavier Vekemans); (3) Genetics and Evolution of heavy metal tolerance (headed by Pierre Saumitou-Laprade); (4) Evolutionary genomics of adaptation (headed by Fabrice Roux). The laboratory comprises **16 permanent members of the scientific staff** (3 belonging to CNRS and 13 to Lille 1 University), and **12 permanent members of the administration and technical staff**. The laboratory is member of the IREPSE Institute from Lille 1 University (Institute for Environmental Research), and is associated to **CNRS** (**INEE** Institute).

4.1.5 PARTENAIRE 5/ PARTNER 5 : ISABELLE FOURNIER

4.1.5.1 RECHERCHE ET INNOVATION / RESEARCH AND INNOVATION.

The MALDI Imaging Team (MIT), Laboratoire de Neuroimmunologie et Neurochimie Evolutives, (CNRS FRE 3249) is one of the world leader in the field of a new emerging cutting-edge technology which is MALDI Mass Spectrometry Imaging. He was the first in Europe to have introduced and developed this novel technology in 2002. The Team was evaluated in 2009 by national AERES comity and was **ranked A** with as commentaries that it was a young and very promising research group.

MIT was initiated in 2004 with a national Starting grant (ACI Jeunes Chercheurs) obtained by Dr. Isabelle Fournier. This first grant had allowed the establishment of the team. Since 2004 the MIT had shown is expertise in the field of MALDI Mass Spectrometry Imaging and is now recognized as a major player in the international community.

In 2010, the MIT is constituted still leaded by Pr. I. Fournier and constituted by 13 researchers. Pr. I. Fournier has published **41 manuscripts** including 4 reviews, 7 book chapters in the highest ranked Journals of her discipline like Analytical Chemistry, Molecular and cellular Proteomics, Journal of Proteomic Research (H index 16). She has been invited to present her work in 59 conferences among which 41 are on invitation from which 20 are at the international (ASMS 2007, 2008; HUPO 2007, KHUPO 2008, KHUPO 2010, HUPOBBB 2010, EUPA 2009). She has trained 8 PhD students, got EU or International grants as PI or co-PI from ANR (2), INCA, EU COST, KORANET FP7, and De Internationale Stichting Alzheimer Onderzoek (ISAO), NSF (Total 1.3 million €) and performed 9 patents (PCT). Pr. I. Fournier was distinguished in 2009 by a nomination at the prestigious "**Institut Universitaire de France**".

Three of the four permanents have their **Prime of Excellence** (Pr. I. Fournier, Pr. M. Salzet, Dr. A. Tasiemski). The Two team leaders Pr. I. Fournier and Pr. M. Salzet are recognized by the Institut Universitaire de France (Pr. I Fournier in 2009 and Pr. M. Salzet 1998).

Pr. M. Salzet is distinguish Professor, received in 2003 the grand prix of the Science Academy. He published (H index: 34) more than 208 publications (148 original articles, 40 reviews, 20 book chapters in some high ranked journals like Nature Immunology, Circulation, Blood, Trends Immunology, Molecular and Cellular Proteomics). He is scientific delegate at the CNRS, board member of the European Science Foundation (LESC), FWO, FNRS and member of the scientific council of the National Museum of Natural History from Paris. Pr. M. Salzet is currently in charge of the Omics Program for the ESF. He has been invited in 89 conferences to present his work among which 41 are internationally on 31 invitations. He trained 15 PhD students, got NIH, NSF, FRSQ, IRSC, MDEIE, CQDM, FWO international grants (total : 15 million €), and performed 15 patents. According to "les Echos", Pr.M. Salzet is ranked since 2000 among the 250 authors of excellence ranked A^+. Pr. M. Salzet is currently the president of the French Society for Mass Spectrometry.

Dr. J. Franck was recently awarded by the price from the French Society of Mass Spectrometry (SFSM) and received a price from the Lille Science Academy in September 2010 (Wickart-Heigelstein Medal).

Both Pr. I. Fournier and Pr. M. Salzet are co-founders of the start-up "IMABIOTECH" (http://www.imabiotech.com). IMABIOTECH is laureate of the OSEO competition (Emerging 2009, Creation 2010, INPI, 2009). At present, MIT is a European Leader in MALDI Mass Spectrometry imaging technology. In 2010, Pr. M. Salzet is cofounding with Dr. A. Tasiemski, HIRUDICA which is incubating at EURSASANTE. HIRUDICA will develop drugs for treating arthritis (inflammation, pain, nosocomial diseases) from leech saliva.

From the last 5 years, the MIT has published 43 original manuscripts, 15 book chapters, 29 invited conferences and seminars, 20 conferences, 23 proceedings, 43 posters and 12 patents. 14 grants (EU, International and National) for a total of 2.25 million €.

The current equipment available at MIT is presented Table 1. This includes the equipments that is already present or should arrive before the end of the year on the MIT platform but for which granting has already been obtained. The MIT is part of two AAPEquipex. First MIT is involved in the EQUIPEX $PharmaR^3$ coordinate by B. Deprez (Uni. Lille 2) and supported by PRES University Lille-Nord de France for the development of a platform for pharmaceutics. In this project the MIT will develop new tools and strategy for studying proteome modifications due to drugs up taking. MIT is also part of the National EQUIPEX coordinate by J. Chamot-Rooke (Plytechnic School, Palaiseau) on High Field FT-ICR to develop MALDI Mass Spectrometry Imaging using high resolution instrument. MIT is also involved in the submitted proposal for the "Sites de Recherche Intégrée sur le Cancer: SIRIC" of Lille Nord-de-France as one of group implicated in VAD cancer biomarker tracking.

Table 1: MIT Platform equipments

Equipment	MIT	Obtenti on date

MALDI-LTQ-Orbitrap mass spectrometer	Thermo Fisher Scientific	Dec. 2010
MALDI- TOF mass spectrometer	Bruker Autoflex III (1000Hz)	Dec 2010
Capillary electrophoresis coupled to MS	PA 800, Beckman-Coulter	Oct 2010
HPLC-2D	PF2D, Beckman-Coulter	Oct 2010
ESI-IT Mass spectrometer	Esquire 3000 +, Bruker Daltonics	Dec 2010
Microextraction & Hightroughput nanoESI using microfluidics	LESA-TriVersa Nanomate, Advion	Nov 2010
ESI or nanoESI-IT Mass spectrometer	Esquire 3000 +, Bruker Daltonics	Oct 2009
Speed-Vac (Savant)	Thermo Fisher Scientific	Oct 2009
Nano-LC	Dionex	Feb 2009
Tissue Sample Preparation for MALDI MSI by micro-spraying	ImagePrep, Bruker Daltonics	Oct 2009
Tissue Sample Preparation for MALDI MSI by piezoelectric micro-spotting	CHIP 1000, Shimadzu, Chip1000	Oct 2008
MALDI-TOF-TOF	Bruker Ultraflex II (200 Hz)	July 2006
Capillary Electrophoresis	PA 5000 & PA 5500, Beckman	Oct 2005
Cryomicrotome	LEICA	Oct 2005
MALDI-TOF mass spectrometer	Voyager STR, Applied Biosystem	Oct 2003
HPLC	Perkin Elmer	Oct. 2000
MicroLC with Blotter	Applied Biosyst	Oct. 2001

Major scientific results:

- MIT was the first team to work in the field of MALDI MSI in France and one of the first team to be involved in this emerging technology development at the international level. Since 2004 MIT activities have been dedicated to both development and applications of MSI.

Fundamental and methodological development of MALDI MSI:

MALDI MSI was introduced at the end of the nineties consecutively to the work of Pr. Caprioli (Caprioli*, et al.*, 1997).First publications were dedicated to the direct analysis of tissue sections using MALDI and method automation in order to produce ion density maps from MALDI data (molecular images). First molecular images of tissue sections were then published in 2002. At the period MALDI MSI was already a promising and cutting-edge methodology with great expectations for biological applications and in particular clinics. However, at the time MALDI MSI was clearly lacking of spatial resolution (150 µm), speed (2 days to produce an image of such resolution of a 2 cm^2 tissue), sensitivity, biomolecules studied, delocalization of molecules of interest due to tissue preparation and applications. In this context the MIT was involved in developments for improving performances of the technology especially in the field of pepdidomics and proteomics.

Tissue preparation. Many efforts were given to improve analytical performances for peptides and proteins analysis. In particular, new MALDI matrices for increase analytical performances were studied. Ionic matrices (IMs) were found to be a new class of MALDI matrix with high potential for MALDI MSI (Lemaire*, et al.*, 2006). Many solid ionic matrices (SIMs) were synthesized and tested and some of them were shown to improve peptides and proteins detection from tissue sections compared to conventional MALDI matrices by increase in the intensity and number of molecules detected, increase in S/N, better stability under vacuum conditions during acquisition step and lower material ablation rate. With respect to physico-chemical properties of proteins, different strategies were settled-up to reach highly hydrophobic or membrane proteins. This was achieved by improving the extraction from the tissue and incorporation within matrix crystals during the co-crystallization phase (Franck*, et al.*, 2009). Therefore, by playing with

physic-chemical properties of molecules it was possible to analysis proteins of different molecular weight and hydrophobicity in sequential MALDI analysis. MIT was also involved in the development of matrix deposition methods in order to avoid delocalization of molecules of interest during matrix addition. Consequent work was performed to set-up robust deposition methods using either micro-spotting (Franck*, et al.*, 2009) or micro-spraying devices. (Fournier*, et al.*, 2008).

Proteins identification. One major advantage of MALDI MSI is to allow for both imaging and identification of biomolecules at the tissue level. MIT was greatly involved in the development of identification strategies at the tissue level and in particular Bottom-Up Imaging strategies. On tissue Bottom-Up require the possible digestion of proteins at the tissue level preserving molecular distribution of subsequently generated digestion peptides by using automated micro deposition methods (Franck*, et al.*, 2009; Franck*, et al.*, 2009). All the developments at MIT had given access to a highly robust method for proteins identification.

FFPE samples from hospital libraries. A major point of clinical researches is the use of Formalin Fixed and Paraffin Embedded (FFPE) tissues retrieved from hospital libraries. Use of FFPE tissues is an unavoidable step for clinical researches by accessing large cohorts of samples in retrospective studies. However, paraformaldehyde fixation induces a cross-linking of proteins within the tissues rendering these tissues inaccessible for proteomics analysis. MIT was then the first group to introduce a strategy for MALDI MSI and proteins identification from such samples (Lemaire*, et al.*, 2007; Wisztorski*, et al.*, 2008). We established that Bottom-Up approach was possible from FFPE samples and could be automated using micro-spraying and micro-spotting devices. We also showed that Bottom-Up strategy could be performed directly after histological coloration on the slide used by pathologist in order to combine histological and molecular diagnosis (Stauber*, et al.*, 2010; Stauber*, et al.*, 2008).

Specific MALDI-MSI (Tag-Mass) and ISA-MS. a new concept was also developed in the team. This concept was first proposed to access MALDI MSI of oligonucleotides (mRNA) because large oligonucleotides are still difficult to be detected by MS. The concept was further enlarged to specifically image antigens and saccharides or glycoproteins. Tag-Mass combine the use of classical hybridization methods namely ISH for mRNA or IHC for antigens with a detection step using MALDI MSI. For this the conventional probe is modified by the addition of a specific group including a photocleavable moiety and a peptide reporter (Lemaire*, et al.*, 2007). The probe is designed so that the reporter can be liberated under the MALDI laser irradiation, thereof allowing imaging a probe based on the m/z signature of its specific reporter. Specific MALDI MSI has the great advantage to be not limited in the number of reporters to be used and allow unique multiplexing at the tissue level. This concept can be used for oligonucleotides probes to image mRNA after ISH or for antibodies ones to image antigens. Extension of this concept to ELISA by ImmunoSorbent Assay using Mass Spectrometry (ISA-MS) allow to quantify antigens using MS detection giving access to a 1000 fold increase in sensitivity in comparison to peroxydase tagged antibodies with UV quantification (Stauber*, et al.*, 2010; Stauber*, et al.*, 2008).

Applications to clinics

Oncology. Since several years, MIT is also involved in programs for application of MALDI-MSI to clinics. Since 2004, MIT has developed a strong collaboration with MD at Gynecology clinic of the Hospital Jeanne de Flandres in Lille (Pr. D. Vinatier, Pr. P. Collinet, Dr. J-P. Lucot) to study ovarian cancer in the contexte of the researches for biomarqueurs for this cancer using MALDI-MSI (El Ayed*, et al.*, 2010; Franck*, et al.*, 2009; Lemaire*, et al.*, 2007; Lemaire*, et al.*, 2006)We identified various highly differentially regulated markers for ovarian cancer stage III and IV. Some of them were identified according to different strategies such MS/MS after on tissue enzymatic digestion or MS/MS after on tissue extraction. In peculiar markers such as a C-term fragment of the Reg-Alpha protein (immunoproteasome 11s) was found to be highly specific for ovarian cancer. Several other identified proteins such as Orosomucoid, Mucin-9, Lumican also suggest an immune tolerance. The presence in the identified proteins of several truncated ones suggests modifications of splicing through viral DNA transposons integration. We thereof hypothesized a possible viral etiology of ovarian cancer. Different MALDI-MSI and MS experiments have then shown the presence of oncoviral proteins. This was confirmed by qPCR experiments from patients biopsies.

Patients with ovarian cancer were found a high level of transcript of HHV6 and EBV viruses. These results allow to think of a therapeutic strategy by developing humanized therapeutic antibodies directed against Reg-Aplha fragment and Mucin-9. In a further work, the efficiency of the therapy will be access by tracking in the serum the oncoviral proteins (El Ayed*, et al.*, 2010; Franck*, et al.*, 2009; Lemaire*, et al.*, 2007; Lemaire*, et al.*, 2006).

Neurodegenerative diseases. In 2007, MIT has worked on model animals of Parkinson disease (6OHDA injected animals). In this study, brain FFPE tissues from both normal (not injected) and 6OHDA models were compared using both on tissue extraction after enzymatic digestion and subsequent analysis in nanoLC-nanoESI-IT MS and MS/MS and MALDI-MSI (Stauber*, et al.*, 2008). In this study, we were able to identify more than 100 proteins from the FFPE tissues including 10 differentially regulated proteins in control and injected samples. Among these proteins 5 were already previously described in literature and found by other strategies (genomics, transcriptomics and proteomics) and 5 others were for the first time described for these animal models. Among them, 2 proteins of the Collapsin Response Mediator Proteins (CRMP1 and CRMP2) were of high interest because of their role in axonal guidance and their possible implication in Alzheimer disease. The distribution of these proteins was obtained by MALDI MSI after on tissue digestion and molecular images generated based on the proteins digestion fragments. This allowed to show that the CRMP's proteins were specifically distributed in brain regions were neurodegenerative processes occur. Currently, several programs are undergoing at MIT to study Alzheimer in collaboration with Pr. Y-M. Park (KBSI, Seoul, Corea) and Pr. H. Steinbusch (Uni. Maastricht, Netherlands).

4.1.5.2 VALORISATION / EXPLOITATION OF RESULTS

The MIT group is highly involved in research valorization. The valorization politics in the group is based on active collaboration with companies in the field of mass spectrometry and pharmaceutics as well as valorization of scientific researches by patenting and Start-up creation. In terms of collaboration, the MIT has established strong collaboration for MALDI-MSI with Bruker Daltonics (Bremen, Germany, Dr. D. Zuckau), Shimadzu Corporation (Kyoto, Japan, Dr. M. Mreyen), COVAL'X (Zurich, Switzerland, Dr. A. Nalzabal) and a future collaboration with Thermo Fischer (Bremen, Germany, Dr. K. Strupat). The MIT has also collaborations with pharmaceutical companies such as IPSEN Pharma and Galderma. Concerning scientific researches the group has deposited several patents (12) among which 3 are in worldwide extension and approval phase for delivery. Pr. I. Fournier and Pr. M. Salzet from the MIT have also promoted for the creation of a start-up based on the development of MALDI Mass Spectrometry Imaging. The Start-Up Imabiotech (www.imabiotech.com), incubated in the laboratory has its activities in the field of service for companies in MALDI-MSI. Imabiotech was 2 times Laureate of OSEO competition, first for emergence in 2008 and second for creation in 2010. The Start-up is currently providing services for different pharmaceutical companies in order to study the distribution of drugs within model animal organs or within the whole body (WBA) tissue sections. Currently, a second company should be launched next year by Pr. M. Salzet and Dr. A. Tasiemski. This company (HIRUDICA) will provide new drugs for arthrosclerosis based on natural substances. The project is in incubation and supported by EURASANTE.

4.1.5.3 ENSEIGNEMENT SUPERIEUR / HIGHER EDUCATION

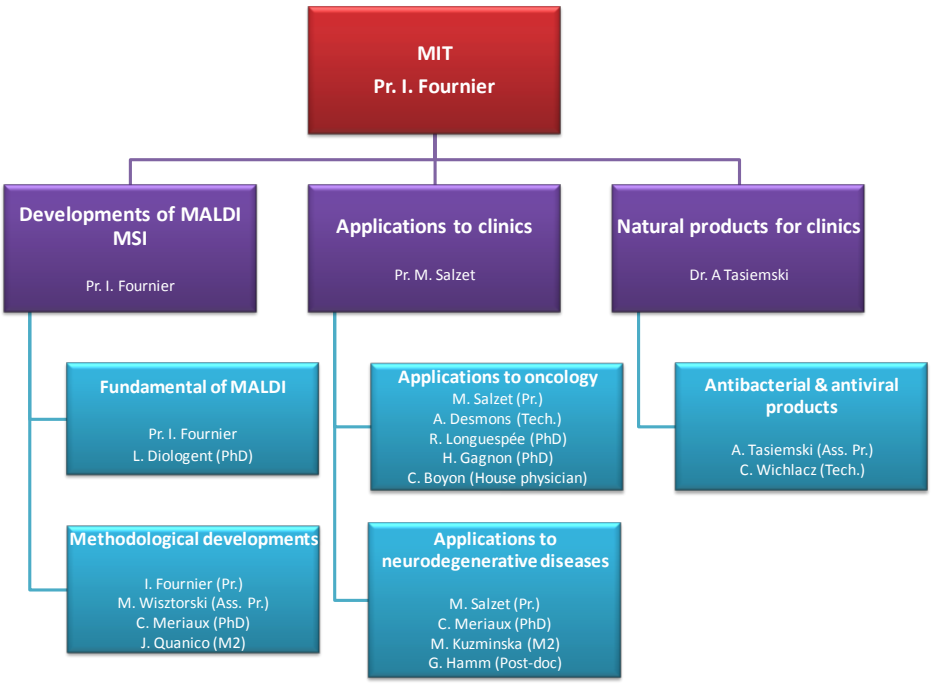
Members of the MIT are highly involved in educating programs both locally and internationally. Locally at the University of Lille 1, Pr. M. Salzet had created in 2001 a new education formation which is a Master 2 in Proteomics (http://www.univ-lille1.fr/master-proteomique/). This formation was the first one in Proteomics in France and one of the internationally referenced. This formation allows french and international students (Europe, USA, Canada) to acquire a strong competence in proteomics. Different members of the MIT are actively

participating to teach in the Proteomics Master and in peculiar for the teaching of mass spectrometry, chromatography and electrophoresis capillary (Pr. M. Salzet, Pr. I. Fournier, Dr. M. Wisztorski, Dr. J. Franck). Pr. I. Fournier is responsible of one teaching unit in the Master of Proteomics. Dr. M. Wisztorski is in charge of a one week proteomics practical unit. It allows student to directly access highly performing instrumentation and learn to run them. This includes mass spectrometers (MALDI-TOF/TOF and ESI-IT) as well as chromatography (HPLC and nano-LC), which is a unique opportunity for students to acquire a strong practical background using instruments that they should work with for their future job. Pr. M. Salzet is also responsible for teaching units of Immunology at University Lille 1. Since its nomination as professor in 1997 he has settled-up the immunology teaching. Pr. I Fournier and Pr. M. Salzet are also both involved in the M1 Genomics and Proteomics at the university. Pr. I. Fournier is responsible for this teaching unit. Pr. I. Fournier is also involved in education for Masters by teaching of Mass Spectrometry applied to biology for M1 students of the International master Advanced Spectroscopy in Chemistry on ERASMUS Mundus programs and for M2 students in Physic-Biology which is a master aiming to interface physic and biology. Dr. M. Wisztorski is involved in lectures for the PHD students in Grenoble on MALDI-MSI as well as Pr. I. Fournier for the same formation in University of Paris Descartes. Pr. M. Salzet and Pr. I Fournier are involved in a European teaching granted by FP7 on MALDI MSI for PhD and researchers. These lectures occur every 6 months in different place on 3 days including lectures and lab practices (Amsterdam, Netherlands, March 2009; Turku, Finland, December 2009, Basel, Switzerland, August 2010). Higher education is also performed by supervision of students in the lab. Many M2 students have been supervised in the MIT since its creation (1 to 3 students supervised each year).

4.1.5.4 ORGANISATION / ORGANISATION

The MIT is organized according to different research axis; mainly 3 research axes are covered which are developments in the field of MALDI MSI including fundamental and applied developments, applications of MALDI MSI to clinics with applications in the field of oncology (ovarian and prostate cancer) and neurodegenerative diseases (Alzheimer) and study of natural substances with relevant biological activities for clinics. Scheme 1 describes the global organization of MIT.

Scheme 1. Research axis and organization at MIT



4.1.6 PARTENAIRE 6/ PARTNER 6 : VINCENT VILLERET

4.1.6.1 RECHERCHE ET INNOVATION / RESEARCH AND INNOVATION

The Laboratory of Biochemistry and Integrated Structural Biology (BISB) is an expert in the field of structural biology. It was evaluated in 2008 and was ranked overall as A ($1A^+$ + 3A) by AERES. The team received an A+ score for its scientific production.

The team has made pioneering research in the field of membrane proteins and determined recently the crystal structure of the bacterial translocator FhaC, a member of the TpsB/BamA superfamily. This superfamily includes proteins from prokaryotic and eukaryotic organisms and so

far FhaC represents the only structure reported for the superfamily. The team contributed also recently to the structural characterization of the membrane sensor kinase BvgS. In addition, the team has also contributed many other integrated structural studies by various techniques including X-rays, SAXS, SANS, NMR, and is recognized as a major player in the field at the national and international level.

The Villeret's team was initially created in 2002 at the IBL (Institut de Biologie de Lille) with the support of an ATIP program of the CNRS. This grant, combined with support from the Nord Pas-de-Calais region, allowed the team to set up the complete infrastructure for macromolecular crystallography, including all the equipment required for protein expression in bacteria, purification, crystallization and X-ray diffraction analysis.

Vincent Villeret published so far **53 articles**, many in prestigious journals such as Science, Mol Cell, Embo J, PNAS,.. and was invited frequently to national and international meeting (23 during the last 5 years). Since its creation, the team has been granted four ANR contracts, two FRM and one ARC contracts. The team also collaborated with pharmaceutical companies in the structural characterization of drug targets, notably nuclear receptors.

In 2010 the team moved to the Interdisciplinary Research Institute (IRI) in Villeneuve d'Ascq to create the Laboratory of Biochemistry and Integrated Structural Biology. Vincent Villeret also took the lead of the Institute. This move represents an opportunity to reinforce structural biology at the University and also to develop within IRI one of the "Hôtel à Projets" of the CNRS, in close partnership with the University. These two points are at the centre of this LABEX initiative. At IRI the current equipment available for macromolecular crystallography includes an X-ray rotating anode generator equipped with an Imaging Plate detector and a cryo system, systems for easy crystal visualization, a crystallization robot, three Akta for protein purification, and all the lab equipment for molecular biology, biochemistry, and protein expression in bacteria. The laboratory has also recently acquired equipment for nanovolume crystallization, isothermal titration calorimetry and is part of "Beamtime Allocation Groups" or "BAGs" at synchrotrons ESRF and Soleil, which guarantee easy and frequent access to the best beamlines at these synchrotrons, an important factor in the study of membrane proteins. The team has also access to NMR facilities via the TGIR initiative from the CNRS, one of these facilities being implemented nearby IRI. The team is now constituted of seven permanent CNRS researchers and four engineers. One engineer (Bernard Clantin) has been awarded a "CRISTAL" from the CNRS in 2008, for his contribution to the structure determination of membrane proteins. Vincent Villeret has been awarded the Prime of Excellence from the CNRS in 2010.

The presence and support of promising research scientists

The team, in its present composition, is the result of an evolution in three major steps since its creation in 2002 at IBL. The structural biology team was initially composed of two researchers and two engineers and devoted its studies to prokaryotic membrane systems. Then at IBL, the main focus of the unit was in the field of cancer, and the team opened its research to this field by fusing with part of the team of Yvan de Launoit, the director of IBL. At this stage two CNRS researchers joined the "historical" team and brought their expertise in cellular biology, mainly in the field of transcriptional regulation, and in biophysics, with the goal of boosting the overall expertise of the two previous teams. A young researcher was also recruited (Alexis Verger, who spent five years at the University of Sidney). In 2010 the team moved to IRI to reinforce the structural biology pole at the University. Since then a young researcher has been recruited at the CNRS as a CR1 (Emanuele Biondi), with expertise in prokaryotic membrane systems and we were also joined by two senior DR2 CNRS (Marc Aumercier and Ralf Blossey) and a professor from the University of Lille 1 (Pierre-Olivier Angrand). These senior scientists bring additional expertise which will be involved at later stages of the project. In particular, Ralf Blossey is developing a novel approach to treat solvatation effects in proteins based on a continuum electrostatics approach. The application of this approach to ion channels appears promising to support deciphering of their function but requires the input of structural data and is therefore foreseen at a later stage of the project. Also, Pierre-Olivier Angrand has an expertise in Zebrafish models. The complete scientific production of the team for the last ten years is given in 7.1.

The importance of scientific partnerships

The laboratory's strategy consists in establishing networks that boost our research by bringing complementary expertise at the functional level or in the exploitation at the pharmacological level of potential drug targets. Many of these collaborations have been granted by research contracts. The studies on prokaryotic membranes have been developed with the laboratory of Dr. Françoise Jacob-Dubuisson (UMR8204), who has an internationally recognized expertise in the field of bacterial translocation systems, and with the laboratory of Dr. Alain Baulard (U629), for the study of drug targets in Mycobacteria. We have initiated a strong collaboration with the ICSN Institute in Paris to include NMR expertise to our projects. We have also developed a strong collaboration with the U761 (director Benoit Déprez) for drug discovery programs involving structural biology. These collaborations resulted over the last years in high level publications (Science, PNAS, Mol Cell, Nature Medecine…) and patents.

Major scientific results obtained over the last years.

Here are presented only the work devoted to membrane systems and drug design.

Since its creation in 2002 as an ATIP of the CNRS, one of our main focus has been to gain insights into the structural and functional aspects of the virulence of bacterial pathogens that are closely related to membrane systems. Since then we used as a main technique X-ray diffraction, to study stable and structured proteins or domains. Many proteins that are emerging in connection with pathological processes appear to possess structural heterogeneities resulting from a multi-domain topology and/or the presence of intrinsically unstructured regions. Thus their structural characterization can't be achieved solely by diffraction techniques but requires the use of other methods. We have over the years acquired new skills, allowing "multifacet" approaches of biological problems, including molecular biology, biochemistry, bioinformatics and use of biophysical tools such as light scattering, small angle diffusion techniques or NMR.

Type V secretion: the Two-Partner Secretion (TPS) pathway

TpsB transporters are components of TPS systems, the most widely distributed secretion mechanism known, which is devoted to the secretion of large, mostly β–helical proteins serving generally as virulence factors in Gram-negative bacteria and collectively called "TpsA" proteins

In spite of their implication in critical physiological processes such as membrane biogenesis and secretion of virulence proteins, the molecular mechanisms of protein translocation or integration by those transporters remain poorly understood and in particular, no X-ray structure was available for any of the partners of such secretion systems when we initiated our studies.

We have determined i) the crystal structure of the TPS domain of FHA and ii) the crystal structure of the transmembrane transporter FhaC that mediates specifically the translocation to the bacterial surface of FHA. FHA transits through the periplasm in an extended conformation before its transport across the outer membrane by FhaC and as such, must be protected from degradation. Recently, the periplasmic chaperone Par27, the prototype of a new group of parvulins, was shown to bind to FHA fragments. Par27 also displays affinity for other proteins rich in amphipathic β structure such as outer membrane porins, and therefore, it has been proposed to serve as a general periplasmic chaperone in *B. pertussis*. We have also determined the structure of Par27, using a combination of X-ray crystallography, SAXS and modelling analyses.

All these data have been complemented by site-directed mutagenesis studies, biochemical assays and topological studies. Some of these results have been already published (Clantin*, et al.*, 2007; Clantin*, et al.*, 2004; Clantin*, et al.*, ; Delattre*, et al.*, ; Hodak*, et al.*, 2006; Jacob-Dubuisson*, et al.*, 2009; Meli*, et al.*, 2006; Wohlkonig*, et al.*, 2008). Our long term objective is to unravel at the structural and functional level the secretion process mediated by TPS systems, and further extend our research to the TpsB/BamA superfamily. In particular we have already crystallized a second member of the TpsB family, *HxuB* from heamophilus influenza. We are also developing tools to express mitochondrial members of the superfamily in bacterial systems.

Regulation and effectors of virulence

A) Two Component Systems

Import of nutriments and solutes is required for bacterial survival and adaptation to environmental conditions. They may also represent various modulators of virulence, via for example the two-component signal transduction pathway, a common mechanism used by bacteria to sense changes in their environment and controlling the synthesis of virulence effectors. In Gram-negative bacteria, these molecules must transit via the periplasm and, in ABC, Trap or TTT transporters, their import involves various periplasmic binding proteins (PBPs) which bind specific ligands and deliver them to their respective inner membrane partners. Many such proteins have been identified in *Bordetella pertussis*, and some of them are among the most abundant periplasmic proteins, suggesting important but yet poorly characterized function. Hence these last year's our team has structurally and functionally characterized, in collaboration with microbiologists, so-called "Bug" proteins from *B. pertussis*, which form a large family of periplasmic solute-binding receptors. These structures reveal high conservation of the Bug architecture, despite limited sequence identity. They display a specific ligand-binding motif highly conserved and designed to accommodate carboxylated solutes. The vast expansion of the Bug family in several bacterial genera is likely to be explained by the possible diversity of ligands. We also characterized PBPs potentially involved in regulation of virulence in *B. pertussis*: Bug27, Dctp6 and Dctp7. These studies allowed to propose mechanisms of ligand - protein interactions, and also paved the way to the study of the Two-Component System BvgA-BvgS, the master regulator of virulence controlling virtually all known virulence traits of *B. pertussis*, which also involves PBP-like domains. These studies on PBPs have been published (Herrou*, et al.*, 2007; Huvent*, et al.*, 2006; Huvent*, et al.*, 2006; Rucktooa*, et al.*, 2007; Rucktooa*, et al.*, 2006).

The BvgA-BvgS TCS is a signal transduction device responding to changing growth conditions. We have initiated the study of the periplasmic part of the inner membrane regulator BvgS, which is constituted by two covalently linked "PBP-like" domains. We have determined the high resolution structure of one of this PBP domain (Herrou*, et al.*). We have also crystallized the full-length periplasmic part, but obtained twinned crystals unsuitable for structure determination. We have now obtained the global structure of the full-length periplasmic part by a combination of X-rays, SAXS and modelling techniques (In preparation).

B) heparin-binding haemagglutinin (HBHA), the major adhesin in Mycobacterium tuberculosis virulence.

M. tuberculosis, the worldwide leading causative agent of death owing to a single etiologic agent, adheres to epithelial cells via the HBHA, a 199-residue protein that recognizes heparan sulphate proteoglycans (HSPG). HBHA has been shown to be involved (i) in the mycobacterial interaction with epithelial cells, but not with professional phagocytes and (ii) in the extrapulmonary dissemination of the bacilli by a mechanism that still remains to be explained. The HBHA-mediated adherence seems to rely at least in the interaction of its C-terminal lysine-rich domain with HSPG receptors present on the surface of its target cells. But in spite of its crucial implication in *M. tuberculosis* virulence, this adhesin has been only poorly characterized. We have tried to determine its X-ray structure, having succeeded in producing large amounts of highly pure and stable protein. All our crystallization trials proved unsuccessful. By using various approaches such as circular dichroïsm, cross-linking experiments, light scattering and SAXS, we were able to show that the protein contains large unstructured regions (probably preventing crystallization). Using these techniques, we have determined a low resolution molecular envelope of HBHA. Our studies have also shown the importance of the disordered regions in the recognition process of the adhesin with its various ligands. We have also shown that HBHA shrinks during its interaction with a sulfated disaccharide, which mimics sulfated chondroitines present at the surface of epithelial cells. This shrinking could be involved in the phagocytic process of the bacilli. These results allow to progress in understanding the interactions of HBHA with its ligands, despite the unstructured nature of the protein. These results have still to be published. Preliminary data have been reported (Dupres*, et al.*, 2005; Verbelen*, et al.*, 2008).

Creation of Regional X-ray crystallography platform in 2004

In the context of the structural biology and drug design,our research team also collaborated on different research programs.

- Side effects associated with tuberculosis therapy brings with it dangers of non-compliance and subsequent drug resistance. Increasing the therapeutic index of antituberculosis drugs should

thus improve treatment effectiveness. Several antituberculosis compounds require *in situ* metabolic activation to become inhibitory. Various thiocarbamide-containing drugs, including ethionamide (ETH), a well known second-line drug, are activated by EthA, the production of which is controlled by the repressor EthR.

In 2002, we initiated a fundamental study of this repressor, in order to understand how it could bind cooperatively to its target DNA and form an unusual octamer. In 2004, we reported the crystal structure of EthR without bound DNA. The structure was found to be fortuitously liganded, resulting in a conformational state of EthR incompatible with repressor function. Such a conformation would lead *in vivo* in ethA derepression and consequently to an increased sensitivity to ethionamide and other thioamides. This let us to propose a strategy, based on the crystal structure, to increase the sensitivity of *M. tuberculosis* to ETH. This strategy would broaden its therapeutic window and render it effective at lower dosages, minimizing side effects and allowing its use as a first line drug (Frenois*, et al.*, 2006; Frenois*, et al.*, 2004). In collaboration with pharmacochemists (B. Déprez, Lille2) and microbiologists (A. Baulard, IPL), we took part in a drug design program aiming at the discovery of synthetic EthR inhibitors boosting antituberculosis activity of ethionamide. Our goal was to identify drug-like inhibitors of EthR to boost the bio-activation of ethionamide. Compounds designed and screened for their capacity to inhibit EthR-DNA interaction were co-crystallized with EthR. 3D-structures were exploited for the synthesis of improved analogs that boosted more than 10 fold the ethionamide potency in culture. In *Mycobacterium*-infected mice, a substantially reduced dose of ethionamide associated with compound BDM31343 lessened the mycobacterial load as efficiently as the conventional treatment. This provides proof-of-concept that inhibiting EthR improves the therapeutic indexes of thiocarbamide-derivatives, permitting to reconsider their use as first line drugs. This work has been published in *Nature Medecine* in 2009. Patents covering these findings have been issued.

- In collaboration with Dr. Wintjens at the ULB, we have determined and analyzed the structures of a glutaminyl cyclase and a chitinase isolated from papaya latex (Azarkan*, et al.*, 2005; Huet*, et al.*, 2008; Huet*, et al.*, 2008; Wintjens*, et al.*, 2006)

- In collaboration with J.P. Bohin at the USTL, we have determined the structure of a glycosyltransferase involved in osmoregulated periplasmic glucans in the cell wall of gram-negative bacteria (Hanoulle*, et al.*, 2004).

- We finalized a functional study on inositol phosphatases that had been conducted in collaboration with C. Erneux at the ULB. Two papers were published on this (Vandeput*, et al.*, 2006; Wohlkonig*, et al.*, 2008).

- Recently, we contributed structural analyses, in collaboration with J.C. Sirard, from IPL, on a bacterial flagellin (Nempont*, et al.*, 2008) and with V. Fafeur, from our UMR, on the MET tyrosine kinase (Deheuninck*, et al.*, 2009).

4.1.6.2 VALORISATION / EXPLOITATION OF RESULTS

The goal of the research carried out by the CNRS USR3078/IRI is to understand how the different levels of organization of macromolecular machines determine their function. Most proteins form a network of interactions with other proteins and many are components of large complexes *in vivo*. Our understanding of how proteins assemble to form such complexes and how these complexes function remains limited. Using interdisciplinary approaches, IRI aims to establish fundamental principles underlying the assembly of multi-protein complexes, define their structures, gain insight into their activities and regulation, identify roles for proteins of unknown function and use all this knowledge for the design of synthetic biological nanomachines. We focus on complexes which play fundamental roles within the cell (regulation of gene expression, signal transduction, transport processes), some with clear potential for applications in medical, pharmaceutical, and technological areas.

Our expertise integrate cell biology, biochemistry, molecular, structural and systems biology, genetics, at the frontiers between biology, physics and chemistry to probe structural, functional, dynamical and robustness properties of macromolecular machines. To promote interdisciplinary research, IRI is, in addition to a Research Unit, a "Hotel à Projets" from the CNRS, which is devoted to welcoming visiting teams for a limited period of time. In the context of this Labex

proposal, we anticipate that over the years new research initiatives will emerge from the results obtained by the founding groups of this Labex, that will boost research in the field of TRP channels.

Presently the Unit is made up of 15 permanent researchers (12 CNRS, 2 Professors) and 13 engineers, technicians and administrators. In order to welcome visiting teams, IRI is opened to share resources not only between permanent teams but also when possible with visitors. This implies a strong level of organization for facilities. The Unit is thus divided into 4 laboratories, which organize and share resources and equipments in their area of expertise, and which cover the fields of biochemistry and integrated structural biology, nanobiosciences and chemistry for life processes, physics for life processes and computational biology. The four laboratories highly promote scientific contacts between them to foster emerging interdisciplinary concepts.
IRI has also state of the art facilities, such as a biophotonic platform, and L2 and L3 labs which are key elements for the attractiveness of the Institute towards visiting teams.

4.1.6.3 ENSEIGNEMENT SUPERIEUR / HIGHER EDUCATION

So far the teaching programs in structural biophysics/biology at the University of Lille 1 have not been developed. With the arrival of our team at IRI in 2010, we decided to be involved in new teaching modules in structural biology. We have no professor or University lecturer in our team, thus CNRS researchers have to be involved in these new courses. Starting this academic year, laboratory members are responsible for various course modules in different masters. We are involved in the M1 of Biology and Biotechnology, and in the M2 of Chemistry and Biology, and in the M2 of Biological and medical physics.

Also, each year, the laboratory provides the opportunity for undergraduate student to carry out their internship, allowing them to have a first contact with the scientific research community. We also assume formations at the PhD level. Doctoral formation in which CNRS researchers are involved belongs to the postgraduate school of "Biology and Health" jointly accredited by the Universities of Lille1 and Lille2. Within our laboratory, 4 students submitted a thesis for the last five years. We also welcomed students and researchers from the free University of Brussels. So far three members of the lab (V. Villeret, M. Aumercier, JL Baert) have the HDR which authorizes to supervise PhD students. Three young CNRS CR1 researchers in the lab will get their HDR in 2011, boosting our capacity to welcome more students.

4.1.6.4 ORGANISATION / ORGANISATION

The Laboratory of Biochemistry and Integrated biology is led by V. Villeret and organized according to different research axes. A first axis concerns membrane proteins and involve three researchers (V. Villeret, Coralie Bompard, Emanuelle Biondi) and all the technical staff (four engineers: Bernard Clantin IR2, Frédérique Dewitte AI, Elizabeth Ferreira and Zoé Lens, IE). A research engineer is highly qualified in membrane protein biochemistry and crystallography, while the other are more specialized in molecular biology and protein expression. A second axis concerns the study of macromolecular complexes involved in eukaryotic transcriptional regulation. In this axis 4 other researchers are involved: Alexis Verger, Jean-Luc Baert, Didier Monté, all CR1 CNRS and Marc Aumercier DR2 CNRS and they benefit from technical support provided by the engineer staff. These researchers bring to the project their expertise in eukaryotic protein expression, and also in other biophysical methods such as isothermal titration calorimetry, surface plasmon resonance, small angle X-ray and neutron scattering, and NMR.

4.1.7 PARTENAIRE 7/ PARTNER 7 : RABAH BOUKHERROUB

4.1.7.1 RECHERCHE ET INNOVATION / RESEARCH AND INNOVATION

Nanotechnologies and Biophotonics Imaging (NBI) partner, coordinated by Dr. Rabah Boukherroub, consists of members of two teams from the Interdisciplinary Research Institute (IRI). On the one hand, the team "Nanobiointerfaces" led by Dr. Rabah Boukherroub and on the other hand, the team "Functional and Cellular Biophotonics" directed by Dr. Laurent Héliot. These two teams work together for several years to develop branding strategies and perform measurements of molecular activity in living cells and tissues. Each of the two teams was evaluated separately in 2009 by the national AERES committee and ranked "A" (3A + 1A$^+$).

1."Nanobiointerfaces" group

The NanoBioInterfaces group is affiliated to the Interdisciplinary Research Institute (CNRS-USR 3078 & University of Lille1). The aim of the Nano-Bio-Interfaces group is to exploit the physico-chemical properties of metallic and semiconductor nanostructures, to take advantage of controlled surface chemistry, patterning (micro- and nanometer scale), and surface analysis to study biomolecular interactions at a solid substrate/biological system and in complex biological media. Our main projects are focused on: (i) Synthesis of metal, semiconductor nanostructures (nanoparticles, nanowires,….) and lipidic nanocapsules, ii) Surface chemistry, (iii) Development of electrochemical and optical biosensors, (iv) Lab-on-Chip devices, (v) nanomedicine

The NanoBioInterfaces group was created in October 2003 by R. Boukherroub. It was initially established at the Institute of Electronics, Microelectronics and Nanotechnology (IEMN), 2003-2008 where it developed several collaborations (BioMEMS, Physics, Optics,…). After the move in the new building in the close vicinity with biologists, while one permanent staff and 5 PhD students stayed at IEMN, we have initiated several collaborations on different aspects related to nanobiotechnology (collaborations with the groups of P.O. Angrand, J.F. Bodart & L. Héliot).

Since the creation of the NanoBioInterfaces group (10/2003), R. Boukherroub has published over than 120 original papers (total > 180) including 3 review articles, 4 book chapters, and filed 4 patents. Since 2008, he is also an adjunct professor at Shandong University, China. He trained 8 PhD students and got several grants: ANR, European, DGA, (Table 1). R. Boukherroub is in the editorial advisory board to Open Condensed Matter Physics Journal; Co-editor of ECS transactions, volume 43, 218th ECS Meeting, Las Vegas, NV, October 10-October 15, 2010; Secretary/treasurer of the European section of electrochemistry; Expert for the Observatory for Micro and Nano Technologies (OMNT); Member of the National Research Committee on Semiconductor Nanowires (GdR nanofils semi-conducteurs); Member of the scientific committee of the platform "peptide and protein biochips". He is involved in organizing summer schools and symposia: Summer school on semiconductor nanowires, 3SN'2008, 15-20 June 2008, Roscoff, France; Summer school "Nano-objects in living cells: from physics to physiology", 1-4 September 2008, Villeneuve d'Ascq, France; Lead organizer, symposium: "Pores and Pits IV", 218th Electrochemical Society Meeting, October 10-15, Las Vegas, NV, USA.

In 2007, Pr. S. Szunerits joined the NanoBioInterfaces group (CNRS delegation: 09/2007-09/2009) and got a Professor position at the University of Lille1 in 2009 (exchange of position with INP Grenoble). She was promoted to Pr1 position in 2010. Since 2009, she is an adjunct professor at Shandong University, China. Pr. Szunerits has published over 114 original papers including 3 review articles, 5 book chapters and filed 7 patents. She is an Associate Editor for Electrochemistry section of the "Global Journal of Physical Chemistry; Editorial Board Member of "The Open Corrosion Journal"; Editorial Board Member of "Recent Patents on Corrosion Science". She has trained 5 PhD students and got several grants such as « ANR Jeunes Chercheurs et Jeunes Chercheuses » and exchange programs (EGIDE).

Major scientific results

The major contributions of the NanoBioInterfaces group are in the areas related to semiconductor (bulk, nanowires and nanoparticles) surface chemistry, wetting properties of nanostructured surfaces, and designing original metal nanostructured substrates for highly sensitive detection of biomolecular interactions using Localized Surface Plasmon Resonance

(LSPR). In the last years, the group has also acquired a high experience in the preparation of lipidic nanocapsules for encapsulating active agents for potential applications in nanomedicine.

Functionalization of diamond nanoparticles

In the search for new and versatile strategies to functionalize diamond nanoparticles (NDs), we have recently applied "click chemistry" for covalent linking of various compounds bearing a terminal acetylene group (1-decyne, electroactive ethynyl-ferrocene and fluorescent *N*-propargyl-1-pyrenecarboxamide) to azide-terminated NDs particles (primary diameter of 4 nm).

Because of its gentle nature and specificity, the chemistry developed in this work can be used as a general platform for the preparation of functional nanoparticles for various applications. More recently, we have used this chemistry to introduce carbohydrates (mannose) onto NDs nanoparticles for effective inhibition of adhesion of whole bacteria to yeast cells.

Preparation of lipidic nanocapsules

Lipidic nanocapsules (LNC) belong to the generation of stealth colloidal carriers. These nanocapsules are obtained without organic solvent using pharmaceutically acceptable components. Such nanocapsules present a stable monodisperse size distribution and their mean diameter can be well-controlled in the range of 20–95 nm. They consist of an oily liquid triglyceride core surrounded by a hydrophilic surfactant, solutol® HS15, which exposes a medium PEG chain containing an average of 15 ethyleneglycol units conferring long-circulating properties and inhibiting the P-glycoprotein efflux pump (P-gp). LNC were formulated at nominal sizes of 25, 50, 100 nm using a phase inversion method of an oil/water system.

Encapsulation of hypericin in lipidic nanocapsules

We have recently succeeded in encapsulating hypericin (Hy), a naturally occurring photosensitizer extracted from *Hypericum perforatum* plants, commonly known as St. John's wort, in lipid nanocapsules (LNC). The rationale behind this approach is to improve the aqueous solubility, the delivery and increase phototoxicity efficacy by nanoencapsulation of Hy using the phase inversion process, described above. Hy-loaded LNC with average diameters of 25, 50 and 100 nm were prepared.

Cytotoxicity and toxicity studies of diamond nanoparticles

Recently, nanodiamond particles (NDs) have emerged as a promising tool in the field of nanobiotechnology. However, studies about the impact of ND on living organisms are still limited to raw materials and primarily confined to *in vitro* studies.

We investigated the cytotoxicity and *in vivo* toxicity of ND correlated with their chemical surface functionality (-OH, $-NH_2$ or $-CO_2H$). Two model systems have been used, human embryonic kidney 293 (HEK293) cells and *Xenopus laevis* embryos. Cell viability assays revealed that nanodiamond particles were not cytotoxic to HEK293 cells for concentrations below 50 µg/mL. Our data suggest that the cytotoxicity may be due to the affinity of cationic particles to the negatively charged cell membrane. In parallel, visual monitoring of microinjected early-stage embryos showed a potential embryotoxicity and teratogenicity for carboxylated ND-CO_2H. NDs seem to have a negative impact on the gastrulation and neurulation stages inducing phenotypical abnormalities and high mortality.

2 "Functional and Cellular Biophotonics"group

The scientific interests and area of expertise of **Biophotonic group** cover quantification of molecular dynamics and interactions in living cell and tissues, through the development of novel micro-spectroscopy approaches and tools. It is organized according to 3 research axes:

- Multimodal Microscopy for measurement of molecular dynamics and interactions in living cell
- Non linear optic advance in news molecular imaging in cells and tissues in association with Nanobiointerfaces group of IRI.
- Development of software for molecular dynamics and interactions image analysis and quantification

Biophotonic group has implemented several Fluorescence Resonance Energy Transfer techniques (FRET) in living cell (Waharte*, et al.*, 2006) and new original microscopy technologies

based on fluorescence lifetime and spectrum measurement (SLIM) (Spriet*, et al.*, 2008; Spriet*, et al.*, 2007) These techniques has been used with very high success in the studies of dynamics and interactions of several nuclear and cytoplamic proteins (Karpova*, et al.*, 2008; Mietton*, et al.*, 2009; Miserey-Lenkei*, et al.*, 2007; Yockell-Lelievre*, et al.*, 2009). In particularly, we has previously characterised by fluorescence resonance energy transfer (FRET) the activation of PKA by EPA regulation of Na^+ channels in living cells (Mies*, et al.*, 2007). Since 2007, this group has obtained with success two ANR grants. Additionally, Biophotonic group has developed several softwares for amelioration of FRET analysis in living cell (Leray*, et al.*, 2009; Leray*, et al.*, 2009; Spriet*, et al.*, 2008). In order to define whether interacting factors are part of large transcription factories or signalling platforms, we are currently coupling FLIM with Fluorescence Correlation (Cross) Spectroscopy (FCS/FCCS) in collaboration with Jörg Langowski (DKFZ, Heidelberg) and Xavier Darzacq (ENS, Paris).

Biophotonic is a young and dynamic team constituted with 2 researchers and 3 engineers. It should be stressed that Aymeric Leray just been hired as a researcher in the CNRS team in 2010 and Corentin Spriet was recruited in 2009 as a research engineer. These two young scientists are widely recognized in the community of microscopy for their great skills.

Since 4 years, the Biophotonic group has published 20 publications in the microscopy field and this team is considered as a leader in FRET and multimodal microscopy development with 2 software licenses and one patent for hardware development. Additionally, a partnership has been established with Leica Microsystems for the development of FRET technology.

Laurent Heliot has received a scientist prize in 2006 for his scientific achievements. Since 2003, he is actively engaged into the creation of interdisciplinary French biophotonic networks (GDR2588/RTmfm). Currently, this consortium gathers more than 100 laboratories and core facilities. From 2004 to 2009 he is the national coordinator of the Technological Network in microscopy (RTmfm). In January 2009, Laurent Héliot has taken the head of the Scientific Network in Biophotonic (GDR2588-CNRS).

Table 1: Grants obtained by the NBI partner [2004-2010]

Years	Program	Coordinator	Title	Granting
2005-2008 3 years	**ANR Blanc**	R. Boukherroub	Nanostructuration des surfaces de diamant hydrogéné et dopé au bore : applications en biosciences	**217 k€ H.T.**
2006-2010 3 years	**ANR Jeunes Chercheurs et Jeunes Chercheuses**	S. Szunerits	Génération des plasmons de surface localisés (LSPR) : détection sensible d'interactions biomoléculaires	**150 k€ H.T.**
2006-2010 3 years	**ANR PNANO**	D. Stiévenard (IEMN)	Conception et réalisation d'un nanocapteur à base de nanofils silicium pour la détection électrique d'interactions entre polypeptides	**70 k€ H.T.**
2007-2010	**ANR PFTV**	L.Heliot	Microscopy for molecular dynamics and interactions in cell and tissues	**400 k€ H.T.**
2010-2013	**ANR Blanc**	A.Harduin-Lepers	Molecular and cellular regulation of beta1,4-GalNAcT-II in physiological and pathological states	**300 k€ H.T**
2009-2012 3 years	**FP7-KBBE-2008-2B**	Päivi Heimala (VTT, Finland)	Nano- and microtechnology -based analytical devices for real-time measurements of Bioprocesses (NANOBE)	**350 k€ H.T.** (CNRS, IEMN + IRI)
2009-2013 4 years	**Programme transfrontalier Interreg IV** « Coopération territoriale européenne » France - Wallonie – Vlaanderen	Jean-Pierre Vilcot (IEMN)	Microtechnologies appliquées à l'instrumentation pour la biologie : biocapteurs à performances étendues sur base de résonance plasmonique de surface	**196 k€ H.T.**
2006-2010 4 years	**FUPL** Université Catholique de Lille	D. Stiévenard (IEMN)	Micro et NanoBiosciences	**6 k€ H.T./ year**
2007-2008 2 years	Defence Science and Technology Laboratory, Malvern, UK	V. Thomy (IEMN)	Testing & Design for an Integrated Electro Wetting System	**30 k€ H.T.**
2007	C'nano Nord Ouest	R. Boukherroub	Etude des propriétés optiques de nanofils de silicium : effet de la terminaison chimique	**10 k€ H.T.**
2008	C'nano Nord Ouest	D. Stiévenard (IEMN)	Nouveau capteur photovoltaïque à base	**14 k€ H.T.**

			de nanostructures 0D et 1D	
2008	Programme interdisciplinaire CNRS : Interface Physique Chimie Biologie – Soutien à la prise de risque	R. Boukherroub	Etude de la Méthylation des Histones par l'Exaltation Raman de Surface (SERS)	**30 k€ H.T.**
2009-2011 30 months	Programme : Recherche Exploratoire et Innovation (REI), Direction Générale de l'Armement	D. Stiévenard (IEMN)	Nouveau capteur à haut rendement et à bas coût à base de nanofils et de nanoparticules	**42 k€ H.T.**
2009	Programme interdisciplinaire CNRS : Interface Physique Chimie Biologie – Soutien à la prise de risque	P.-O. Angrand (IRI)	Application des Quantum Dots à l'étude du développement et de la cancérogénèse chez le poisson-zèbre	**50 k€ H.T.**
2010	Programme interdisciplinaire CNRS : Interface Physique Chimie Biologie – Soutien à la prise de risque	L. Héliot (IRI)	Mise en place du premier microscope par diffusion Raman stimulée (SRS) par Exaltation de Surface (SERS) pour l'étude de la méthylation des histones	**50 k€ H.T.**
2010-2011 2 years	Accueil Jeune Chercheur – Région Nord Pas de Calais	R. Boukherroub	Application des Quantum Dots à l'étude du développement et de la cancérogénèse chez le poisson-zèbre	**88 196 €**
2006-2007 2 years	**CNRS–JSPS** exchange program with Tokyo University of Agriculture and Technology, Japan 2 years	R. Boukherroub	Porous Silicon-directed Silicon Nanowires Growth. Optical and Electrical Properties of the Nanohybrid Material	**8300 € H.T/year**
2006-2007 2 years	**PAI PROCORE** exchange program with University of Erlangen, Germany 2 years	R. Boukherroub	E-beam Nanopatterning of Chemically Modified Semiconductor Surfaces for Applications in Biosciences	**2000 € H.T/year**
2006-2009 4 years	**CMEP Tassili** exchange program with UDTS, Algeria 4 years	J.-N. Chazalviel (Ecole Polytechnique)	Greffage d'espèces organiques sur silicium et croissance de couches minces de *a*-Si et *a*-$Si_{1-x}C_x$	**3600 € H.T/year**
2009-2010 2 years	**CNRS/PAN** exchange program with Polish Academy of Sciences 2 years	R. Boukherroub	Electrochemical generation of submicrometer metal structures at three phase junction and their applications for biosensing	**2000 € H.T/year**
2010-2011 2 years	**CNRS/NSFC** exchange program with Shandong University, China 2 years	R. Boukherroub	Short and Long Range Sensing on Metal Nanostructures Coated with Thin Carbon-Based Materials Using Localized Surface Plasmon Resonance (LSPR)	**4000 € H.T/year**
2010-2013 4 years	**PHC Volubilis** exchange program with University of Kenitra, Morocco 4 years	J.-N. Chazalviel (Ecole Polytechnique)	Surfaces de silicium fonctionnalisées pour la realization de connexions contrôlées et de biocapteurs	**8500 € H.T/year**

Table 2: Available equipments

The NanoBioInterfaces group of the IRI has three different laboratories (about 100 m^2) fully equipped for organic, QDs and nanocapsules synthesis, surface chemistry and characterizations. The Biophotonic group has six experimental rooms (about 110 m^2) with biological bench with equipment for cell biology; culture cell room; 4 photonic rooms with for each an optical bench and adapted photonic tools. Furthermore, these groups have also access to other facilities available at the IRI such as the microscopy core facility and L2 & L3 laboratories.

Additionally, the NanoBioInterfaces group is associated to the Institute of Electronics, Microelectronics and Nanotechnology (IEMN). The institute is very well equipped for design, fabrication and characterization of devices and nanostructures.

Equipment	Partner NBI	Purchase date
FTIR	To be purchased	2011
Ball milling	To be purchased	2011
Zeta sizer	Malvern	Jan. 2010
HPLC	Shimadzu	Jan. 2010
Ultrasonicator	Branson	Sept. 2010
Rotavap	Büchi	Sept. 2009

UV/Vis	Perkin Elmer	Dec. 2008
DigiDrop	GBX	Dec. 2008
HPLC Äkta Purifier	Amersham Biosciences	Oct. 2008
SP5 Confocal microscope	Leica	2008
Lifetime Spinning microscope	Nikon-Roper-Errol	2010
STP-PALM	home made	2011
A1 Spectral Confocal	Nikon	2009
Pulsed laser Cameleon	Coherent	2009
FRAP station	Nikon-Roper	2007
Video-microscopy station	Leica	2008
Cellvision-station	Nikon	2011
Lifetime-TCSPC station	Picoquant	2009
Fluorescence microscopy	Nikon	2006
Lifetime-TCSPC station	Becker-hickl	2006
Image analysis station	Imaris/Roper	2009
Atomic Force Microscope (AFM)	Veeco	Oct. 2006
Fluorescence microscopy	Nikon	Nov. 2006
SPR	Autolab	Nov. 2005
Potentiostat (x2)	Autolab	Oct. 2004
Microwave oven	Milestone	May 2004
Photochemical reactor	Homemade	Oct. 2004

4.1.7.2 VALORISATION / EXPLOITATION OF RESULTS

The two groups of the NBI partner are involved in research valorization through:

- filing patents and licenses (7)
- participation in the education of interdisciplinary students which we consider an important aspect for future research and knowledge transfer to industry;
- publications in leading journals in the field
- organization of scientific meetings and workshops in our field of research

- Transfer /partnership

Patent License Option for Kerdry (Lannion, France) to produce SPR substrates coated with ITO thin films. "Dépôts stables de couches minces d'ITO sur films d'or. Applications pour la détection par résonance plasmon de surface électrochimique (E-SPR)" French Patent application FR 01485-01, filed on june 27, 2007 ; PCT N°EP2008/067356, filed on december 11/2008 ; Publication N° WO 2009/074660 A1, issued on June 18/2009.

Biophotonic Group has a partnership with Leica Microsystems for the development and teaching of fluorescence lifetime imaging (2010-2013).

4.1.7.3 ENSEIGNEMENT SUPERIEUR / HIGHER EDUCATION

Local

Prof. Szunerits is responsible of the course « Nanostructures et biomolécules (40 h Cours + 8 h TP) of the Master 2 PBM (Physique, Biologique et Médicale). The objective of this course is to acquire a basic knowledge concerning surface chemistry and functionalization of nanoparticles for biological and medical applications. In addition, a special focus is put onto the understanding of surface properties such as wettability and charge. In this course, the students are confronted with different methods used in modern biotechnology for the construction and characterization of DNA and peptide chips. For the student to be well prepared to follow all these different aspects, Prof. Szunerits gives an introductory class entitled "Introduction to Organic Chemistry" (30 CTD) in the master M1 of the same Master program.

Prof. Szunerits is also involved in the "Master of Applied Spectroscopy (ASC)", an Erasmus Mundus Program. She teaches "Plasmonic based spectroscopies for biological applications" (10 h Cours + 8 h TP). The objective of this course is to acquire a basic understanding of the physical principles underlying plasmonic spectroscopies together with the concept and interest of label-free detection schemes. In addition, the recent developments for miniaturized plasmonic transducers (e.g. optical wave guides, pulsed optical fibers, resonant cavities, etc.) are discussed together with their challenges for biological sensing.

Dr. R. Boukherroub currently provides Master 2 MNT (Micro et Nanotechnologies, U Lille1) students teaching of surface chemistry and different surface analysis techniques (8 h). The course consists on surface functionalization of metal and semiconductor surfaces with organic monolayers. A special emphasize is given on the different techniques (FTIR-ATR, XPS, CA measurements,…) used for surface analysis and finally, applications of the resulting hybrid materials for biosensing and molecular electronics are detailed.

Dr. Y. Coffinier is providing master students, Master "Pro Génie Cellulaire et Moléculaire" (U Lille1, 8 h), with various aspects related to nanobiotechnology.

The members of the team are involved in the physics master 1 and 2 course "introduction to cell and molecular biology" and "systemic biology and biophotonics" (~50H, U.Lille1) ; master 1 "biochemistry and cell biology" (10H, U.Lille1) ; License of "biology and development" (2H, U.Lille1)

We are organizing thematic days in master 2 in biology about "imaging of transcription regulatory network" as well as a course of "biophotonics" (~16H, U.Lille1)

We are also in charge of several teaching in "introduction to microscopy for cell biology" open to researcher and students. (10days/year)

We organized two microscopy training of 4 days by year with CNRS and Inserm "formation Permanente".

National

R. Boukherroub is also involved in the Master of Biomedical Engineering, ParisTech & University Paris 5 (3 h). The aim of this class is to provide (in a seminar form) the students with a multidisciplinary approach to undertake a research project at different interfaces.

Y. Coffinier is also teaching in an engineering school, SupBiotech (Villejuif, 100 h) the following courses: miniaturization, microfluidics, and nanobiotechnology. The objective of these courses is to acquire a basic knowledge in different areas related to micro- and nanofabrication of devices and their applications in modern biology and medicine.

Biophotonic team members have participated or organized national teaching and training in Gif/Yvette, Bordeaux,… (CS, DT, BV, LH, AL 50H /year).

Laurent Héliot is the organizer of national events in microscopy such as MiFoBio, a thematic interdisciplinary summer school about latest developments in biophotonics gathering more than 250 participants every two years (7 days).

We are also organizing regularly specialized courses and training with the CNRS and Inserm such as "dynamics and interaction studies in living cells" dedicated to an interdisciplinary community of researchers (5 days).

International

Since 2008, both R. Boukherroub and S. Szunerits are Adjunct Professors at Shandong University, China. Their duties are to supervise PhD students from Shandong University (M. Wang, PhD defense 2009; Q. Wang started her PhD on 15/10/2010) and give, every year in a form of seminars, classes to graduate (master and PhD) students in different areas related to analytical and physical chemistry, materials science and biotechnology.

4.1.7.4 ORGANISATION / ORGANISATION

The group consists of:

- 5 Permanent staff

- Mr. Rabah Boukherroub (DR2 CNRS)
- Mrs Sabine Szunerits (Pr1 ULille1)

- Mr. Yannick Coffinier (CR2 CNRS)
- Mr. Lionel Marcon (CR2 CNRS)
- Mr. Alexandre Barras (IR2 CNRS)

- 3 Postdoctoral fellows

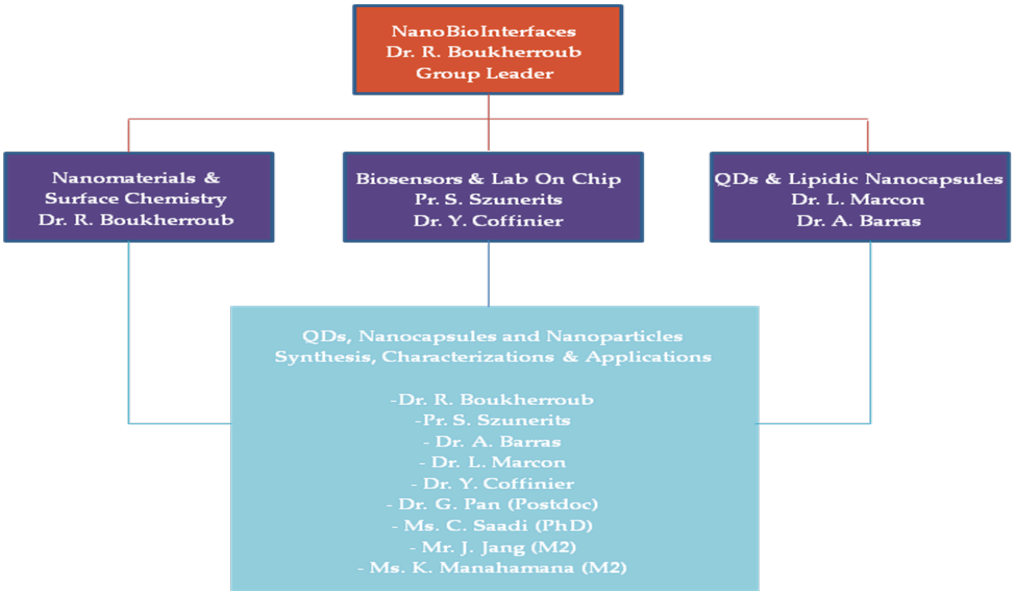
- Mr. Slimane Ghodbane (RhoBest, Austria)
- Mr. GuoHui Pan (Region Nord Pas de Calais)
- Mr. Subramanian Palaniappan (European grant, starting in december 2010)

- 10 Visitors/year

The NanoBioInterfaces group is organized according to 3 different research axes:

- Synthesis and funtionalization of nanomaterials
- Design of functional and highly sensitive biosensors and Lab-On-Chip devices
- Synthesis, functionalization and applications of QDs and lipidic nanocapsules

The different activities are tightly connected.
Scheme 1 describes the global organization of the NanoBioInterfaces group.



Partner	Surname First name	Position	Domain	% Involvement	Contribution in the project
Partner NBI Coordinator R. Boukherroub	BOUKHERROUB Rabah	DR2	Surface Chemistry	20%	**Coordination**
	SZUNERITS Sabine	PR1	Physical Chemistry	20%	**Characterizations of QDs**
	COFFINIER Yannick	CR2	Materials Science	10%	**Surface Functionalization**
	MARCON Lionel	CR2	Biochemistry	20%	**Toxicity studies**
	LERAY Aymeric	CR2 CNRS	Photonic for biology	10%	**Photonic and image anlysis**
	HELIOT Laurent	IR1 CNRS	biophotonic	20%	**STP PALM developement**
	SPRIET Corentin	IR2 CNRS	biophotonic	30%	**Multimodal microscopy**
	BARRAS Alexandre	IR2	Organic Chemistry	60%	**Lipidic nanocapsules: synthesis, characterizations & applications**
	TRINEL Dave	CR2 CNRS	Image analysis	30%	**Image analysis**

Collaborations :

A first contact with partner 1 was established early this year for an eventual collaboration on the use of QDs for ion channels imaging and light controlled activation of cells. Independently, a scientific discussion with Dr. S. Mordon (WP5) was initiated on 09/017/2010 regarding the use of encapsulated photosensitizers in lipid nanoparticles for photodynamic therapy applications. Furthermore, the NanoBioInterfaces group has developed a strong collaboration with another partner of the LabEx (L. Héliot, IRI) during the last three years (3 projects funded by the "Programme interdisciplinaire CNRS: Interface Physique-Chimie-Biologie – Soutien à la prise de risque). It is thus obvious that the present project will reinforce the existing collaborations, but also will allow working more synergistically with the different partners involved in the LabEx.

The NanoBioInterfaces group has effective collaborations within the region, but also at the national and international levels. The group is currently involved in two different European projects on various aspects related to materials science, surface chemistry and Lab-On-Chip applications.

The group is also implicated in two new funding applications (FP7 program):

- Inorganic Nanostructured Delivery Platform for Oral Delivery of Peptides "IN-POD"
- High-selective nanoporous alumina membranes with tunable pore size and functional (antifouling) coatings

Since its creation, the group has actively participated in various CNRS or EGIDE (Germany, Poland, Japan, China, Algeria, and Morroco) programs for exchange of researchers. Within these programs, our PhD students had the opportunity to stay abroad for a limited period (one month) in the partners' laboratories. In the meantime, several PhD students, Postdoc fellows and permanent researchers joined our group for 1-6 months.

Since 2008, we initiated a strong collaboration with Pr. M. Opallo's group (Polish Academy of Science). In 2009, Mrs J. Niedziolka-Jonsson, a permanent staff from Opallo's group, spent 6 months as a visiting fellow (University of Lille1) in our group. In 2011, Ms. Izabela Kaminska, a PhD student from Opallo's group, will join the NanoBioInterfaces group for one year to work on the preparation of metal nanostructures, their functionalization and applications as SERS active substrates.

The NanoBioInterfaces group has also a strong link with the group of Pr. M. Li at Shandong University (China). Since 2007, R. Boukherroub has visited Shandong University 5 times and supervised or co-supervised two Chinese PhD students (M. Wang, 2007-2009; Q. Wang, since 09/2010).

Below is a list of collaborators within Lille, but also at the national and international levels:

Local

- Oleg Melnyk, groupe Chimie de Biomolécules, IBL
- Didier Stiévenard, groupe de Physique, IEMN
- Vincent Thomy, Vincent Senez et Philippe Coquet, groupe BioMEMS, IEMN

- Jean-Pierre Vilcot, groupe Optoélectronique, IEMN
- Abdellatif Akjouj & Yan Pennec, groupe Ephoni, IEMN
- Bernard Pinchemel and Mohamed Bouazzaoui, PhLAM
- Patrice Woisel, UMET, Université Lille 1
- Brigitte Sieber, UMET, Université Lille 1
- Christine Faille, INRA Lille
- Christian Slomianny, Inserm, Lille 1
- Dominique Legrand, Université Lille 1

National

- François Ozanam & Jean-Noël Chazalviel, LPMC, Ecole Polytechnique, Palaiseau
- Aloysius Siriwardena, Université Picardie, Amiens
- Christine Enjalbal, Université Montpellier 2
- Sébastien Bonhommeau & David Talaga, Université Bordeaux 1
- Pierre-Michel Adam, Université Technologique de Troyes
- Xavier Castel, IUT Saint Brieux
-

International

- Nobuyoshi Koshida, University of Agriculture and Technology, Tokyo, Japan
- Musen Li, Shandong University, China
- Patrik Schmuki, University of Erlangen, Germany
- Jarno Salonen, Turku University, Finland
- Doris Steinmüller, RhoBest, Austria
- Gunther Wittstock, University of Oldenburg, Germany
- Marcin Opallo, Academy of Sciences, Warsaw, Poland
- Amene Schneider, Austrian Competence Center of Tribology, Austria
- Vladimir Zaitsev, University of Kiev, Ukraine
- Caroline Schauer, Drexel University, USA

4.1.8 PARTENAIRE 8/ PARTNER 8 : BENOIT DEPREZ

4.1.8.1 RECHERCHE ET INNOVATION / RESEARCH AND INNOVATION

Ranked A (1 A^+ + 3A in 2009) by AERES and Inserm, Deprez' team is specialized in the identification and optimization of small organic molecules that modulate biological processes. It is composed of experts is in the fields of medicinal chemistry (from chemistry to pharmacokinetics), high throughput screening and chemoinformatics who collaborate with biologists working on novel target discovery and validation. Their mission is to design and prepare ligands modulating the effects of these proteins targets *in vitro* first and in animal model ultimately. These compounds serve first as pharmacological probe to validate therapeutic approaches and then as drug prototypes. Their know-how is a combination of academic and industrial experience. They collaborate with academic labs (Pasteur Lille, Paris Descartes; U.Gent, Belgium; U Chicago, USA; Imperial College, UK, Pasteur Institute, Korea) and industrial researchers (Galderma, Diverchim, Targeon). Deprez *et al* are in charge of the regional screening platform and all the required databases and interfaces for its use (this platform, part of C-dithem is accredited by **GIS IBISA**). This lab is also the coordinator the **Equipex** proposal **PharmaR^3**. Pr. Benoit Deprez is a recognized expert in medicinal chemistry who has been previously in charge of the development of screening and lead optimization programs in two world-known biotech companies (Cerep SA and Devgen NV). He is also expert for several companies SME involved in drug discovery (Cytomics, Poxel, Diverchim, Inserm Transfer) and Venture Capital investors (Edmond de Rotschild Investment

Partners). This team is constantly exposed to academic and industrial drug discovery projects and their needs.

U761 is the leading group of PRIM, the regional consortium in drug discovery (www.drugdiscoverylille.org).

The team members have published 127 papers since 2000 and 8 patents (one in national phase). The main achievements of this team are:

Technically:

1/ a 75.000 compound library for screening,

2/ a screening platform,

3/ a DMPK platform (mouse/rat + *in vitro* metabolism) high throughput LC-MSMS.

4/ a medicinal chemistry laboratory including high throughput synthesis and purification (MS-autopurification system).

Scientifically, we have designed lead or drug candidates in several applications:

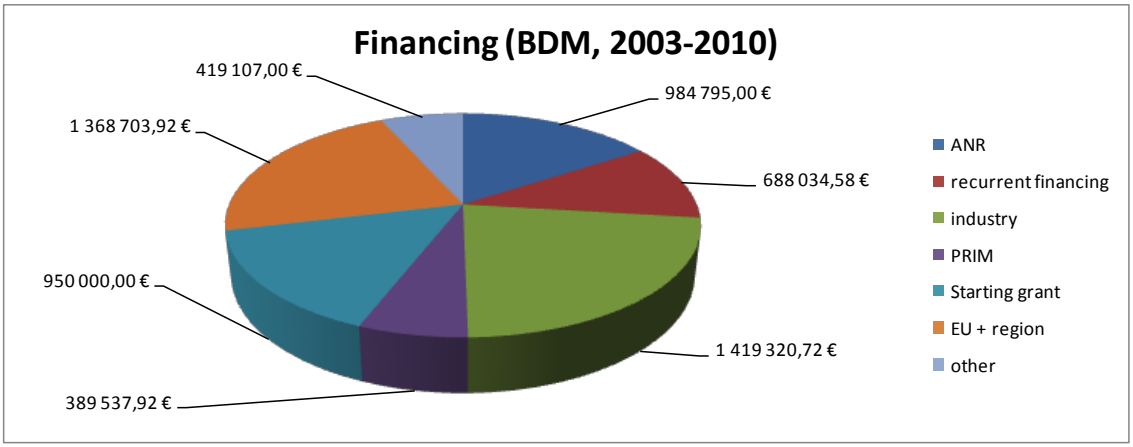
1/ MDR tuberculosis : a series of ethionamide boosters that have reached the development status, negotiations on going with Novartis Institute for Tropical Diseases, Regulatory Preclinical to be started in Q1 2011. Project leader: Nicolas Willand.

2/ Duchenne's Myopathy & Cystic Fibrosis : a compound inhibiting Non Sense Mediated mRNA decay that protects mRNAs containing a premature stop codon from degradation and promoting the expression of full length protein. Clinical trials to be initiated Q4 2011. Project leader: Terence Beghyn.

3/ Diabetes and Alzheimer: the first example of a pathway-dependant protease modulator that helps clearing amyloid beta and prevents insulin degradation by IDE in cells. Project leader : Rebecca Deprez-Poulain.

4/ A chemical platform specialized in nature-inspired synthesis that has a special interest in protein-protein interactions and channel modulation.

In terms of financing, U761 has raised from inception (2003) more than 6 million euros. A large part comes from industrial contracts and competitive grants.



4.1.8.2 VALORISATION / EXPLOITATION OF RESULTS

Since 2006, the laboratory has filed a family of patent on Ethionamide Boosters for the treatment of tuberculosis. The project leader (Nicolas Willand) was recipient of the OSEO emergence prize for industrial innovation in 2009. A candidate for regulatory preclinical development and several follow up compounds are considered by Novartis for in licensing and partnership.

A patent on a family of compounds that are intended for development in Cystic fibrosis and Hemophilia A/B has been filed. Orphan drug designation for one of these conditions will be seeked in 2011.

A patent on insulysin modulation by small organic compounds has been filed.

Access to the drug discovery platform is made available to academic partners and industry. A 3 year collaboration with a pharmaceutical company is being negociated. Terms include research financing and milestone payments.

Patents :

1. Carniato, D.; Jaillardo, K.; Busnel, O.; Gutmann, M.; Briand, J.; Deprez, B.; Thomas, D.; Bougeret, C. Composés utiles pour le traitement des cancers. FR 08 53944, 2008.
2. Deprez, B.; Beghyn, T.; Laconde, G.; Charton, J. Chiral Tetra-hydro beta-carboline derivatives, applications thereof as antiparasitic compounds. WO2008044144, 23rd Apr., 2008.
3. Déprez, B.; Willand, N.; Dirié, B.; Toto, P.; Villeret, V.; Locht, C.; Baulard, A. R. Compounds having a potentiating effet on the activity of ethionamide and uses thereof. WO2008003861, 10th Jan., 2008.
4. Deprez-Poulain, R.; Charton, J.; Deprez, B.; Leroux, F.; Gauriot, M.; Tang, W.-J.; Totobenazara, J. Ligands of Insulin Degrading Enzyme and Their Uses. EP_20100330093425, 4th mar, 2010.
5. Guillet, J. G.; Bourgaud-Villada, I.; Dupuis, M.; Gras-Masse, H.; Bourel, L.; Melnyk, O.; Joly, P.; Bonnet, D.; Malingue, F.; Grandjean, C.; Georges, B. Use of Lipopeptides for preparing vaccines. 14 Mars, 2002.
6. Melnyk, O.; Bonnet, D.; Bourel, L.; Gras-Masse, H. Method for coupling in solution of a peptide with a lipophilic vector and use thereof…. 14 Mars, 2002.
7. Melnyk, O.; Fruchart, J.-S.; Bourel, L.; Gras-Masse, H. Solid Support for the synthesis of compounds having an alpha-oxo-aldehyde group and peptides made by solid phase synthesis using such supports. 2 Novembre, 2000.
8. Verwaerde, P.; Anthonissen, C.; Deprez, B. Lipid uptake Assay. 24 July, 2002.

4.1.8.3 ENSEIGNEMENT SUPERIEUR / HIGHER EDUCATION

The laboratory is involved in two Master courses of Université Lille Nord de France. (M1/ M2 Biologie Santé, M2 Chimie Biologie)

The courses are intended to provide up-to-date information on chemical, biological and pharmaceutical sciences applied to drug discovery and development. Lectures are based exclusively on case studies (drug discovery, drug development, chemical development) from recent literature and the own experience of teachers.

Students work in small groups on topics selected by the teachers and each year organize a scientific symposium where they give their presentation in front of a panel of experts from academia and industry.

The laboratory is also a training lab for the practical aspects of the formation (Master and PhD).

4.1.8.4 ORGANISATION / ORGANISATION

The laboratory is organised in a matrix combining technology platforms and project.

All equipments are operated in a client/provider relationship, even for internal use.

Project leaders recruit resources in the platform for their project.
The platforms (library, screening, ADME, analysis, parallel synthesis and automated purification) are operated under strict quality guidelines and are accredited by GIS IBISA (C-dithem) since 2008.

Collaborations :

	Collaborator	Location		Subject
U761	Wei Jen Tang	Chicago USA	Ben May Institute	IDE modulators
U761	Vincent Villeret	Lille (labex)	CNRS	Ethionamide boosters
U761	Bruno Villoutreix	Paris, France	Inserm	Molecular modeling and design
U761	Louis Maes	Antwerp, Belgium	U Antwerp	Compound screening
U761	Joost Schymkowitz	Leuven, Belgium	KU Leuven	Protein protein interaction . screening
U761	Vincent Jarlier	Paris, France	AP-HP	Tuberculosis
U761	Nagase	London, UK	Imperial College	Protease inhibitors

4.1.9 PARTENAIRE 9/ PARTNER 9 : SERGE MORDON

4.1.9.1 RECHERCHE ET INNOVATION / RESEARCH AND INNOVATION

INSERM U703 "interventional therapies Assisted by Image and Simulation" has been evaluated in December 2008 and was ranked **A** by international and independent committee, AERES. The theme of the scientific unit INSERM U703 "interventional therapies Assisted by Image and Simulation" is oriented towards minimally invasive therapies, including laser therapy and radiotherapy, guided by the image, pre-operative (simulation, planning), per-operative (interventional imaging) or post-operative (monitoring, evaluation therapeutic). Closely inserted into the Lille University Hospital campus, U703 enjoys particularly favorable conditions to maintain close collaboration with many clinical partners. Based on its biophysics, mathematics and computing expertise, INSERM U703 also collaborates with CNRS and INRIA laboratories (coordination or participation to methodological and clinical projects) and several foreign universities.

The scientific project for the period 2010-2013 is based on two major themes: 1) **New therapies for pelvic cancers and pelvis mobility 2**) **New therapies and Assistance to gestures in Neurosurgery**. Each of these themes is divided into sub-themes brought jointly by academic researchers and clinical researchers (see table).

Axis 1 "New therapeutic pelvic cancers and pelvic mobility"

Regarding Axis 1 "New therapeutic pelvic cancers and pelvic mobility, an important part of our research activity is devoted to prostate cancer, especially to the diagnosis and development of focal therapies by Interstitial laser therapies. The extraction of relevant information from the MRI images is an essential step to diagnosis assistance. To do so, the purpose is to extract the prostate peripheral zone that contains 80% of tumors. We have developed a method of image fusion using a multi-parameter approach based on the theory of evidence in order to segment the prostate in these two areas: peripheral zone and transition zone. Another possibility is to use T2 weighting images. We have developed a method of analysis of the peripheral zone. We used texture analysis tools based on fractal geometry to adapt the images of the prostate.

The unit has responded as a partner to PAIR Prostate 2009 (Cartographix Project "Evaluation of the position, volume and aggressiveness of prostate cancer foci of multi-parametric imaging"). This project was selected by the ANR (Duration 36 months). This project will start early 2011. The unit has launched this year 2 projects: ProstateAtlas & ProstateWeb. The goal is to develop an atlas of prostate and associate it to a synthesized MRI prostate images simulator. The idea is to propose to the urologic community a simulator similar to BrainWEB (www.bic.mni.mcgill.ca / brainweb) which is now considered an useful tool for the neuroscience community.

Concerning the **treatment by interstitial photodynamic therapy of prostate cancer**, we are involved in an ongoing clinical evaluation at the University Hospital of Lille using Tookad developed by the company Steba Biotech. So we have access to MR and ultrasound images and all parameters of laser treatment. Collaboration has been initiated with this company for developing a treatment planning software for focal treatment of prostate cancer. Experimental evaluations on **LITT (Laser Interstitial ThermoTherapy)** have been pursued, in particular the experiments on animal models (rats Copenhagen). Thanks to a 7Testla MRI, **a correlation between laser parameters and the necrotic volume has been established**. Finally, a phantom compatible to multimodality imaging and laser therapy was developed. (Patent pending). To carry out this work, a student has obtained a grant from the AFU (15,000 euros) and INCA (35 000 euros).

Finally, this work was presented to the symposium "Interventional therapies assisted by medical imaging and surgical robotics," organized by the Technologies for Health ITMO

Pr. Damien Huglo in charge of the project "Contribution of Metabolic imaging in prostate cancer" was promoted PU-PH in September 2010. He is now the head of the Nuclear Medicine department. Regarding the use of metabolic imaging for the visualization of prostate tumors, the microPET-CT, installed at the DHURE (Département Hospital Universitaire de Médecine Expérimentale) has been operational since February: first *in vivo* microTDM examinations, delivery of fluorinated tracers (including fluorocholine)..

Research on fractional photodynamic therapy treatment of peritoneal carcinomatosis of ovarian origin after injection of hexaminolevulinate have been successfully pursued. In order to be able to treat the entire peritoneal cavity, we have modeled the peritoneal cavity of rats through the implementation of a phantom cavity in order to determine by mathematical modeling an optimal optical fiber positioning. The inclusion of patients in Phase 2 clinical protocol "Cervira - Photocure ASA, Norway" which aims to assess the effectiveness hexaminolevulinate of PDT for the treatment of cancers of the cervix was completed in June 2010. The results should be available early 2011. This clinical evaluation was conducted by the department of Gynaecology of University Hospital of Lille (Pr Collinet) in partnership our research unit.

Research on pelvic mobility have been the subject of several publications (Urogynecol J Pelvic Floor Dysfunt Int J Urol) and communications in 2010. The team (especially Chrystèle Rubod) was the coordinator of a project entitled "An Integrated Multiscale Virtual Woman Pelvic Mobility Model Application to Physiological aging and genital prolapsed" submitted to FP7. This project brought together 12 teams among them 2 from Belgium, 2 from Germany and one from Switzerland. This project benefited from the support of Inserm-Transfert in its preparation. Unfortunately, this project was not selected.

Patrick Dubois is a member of the leadership team of the GDR STIC-Santé (Theme F: Learning gestures and assistance to medical technology, in charge of organizing multidisciplinary theme days (in 2010: "simulators in use, Assessments and Perspectives ")

Axis 2 "New therapies and Assistance to gestures in Neurosurgery"

Prof. Jean Paul Lejeune and Drs Nicolas Reyns and Laurent Thines, all 3 members of the Centre for Neurosurgery CHRU Lille, have decided to join our unit. Indeed, the unit 703 (especially Maximilien Vermandel) works for several years with them on new imaging techniques allowing the inclusion of data during vascular neurosurgery, essential to ensure the efficiency of the treatment and more important to avoid possible collision of surgical tools with arterial or venous system. This new team will particularly focus their research on the role of photodynamic therapy (PDT) in the treatment of high grade gliomas. Unit 703 has acquired over the years, a proven expertise in the field of PDT and is supported by several manufacturers. Several clinical evaluations are underway at the University Hospital of Lille. It is possible to include the protocol on the PDT treatment of prostate cancer with the Department of Urology (Prof. A. Villers is a member of the unit) or the PDT treatment of cancer of the cervix with the Department of Gynecology (Dr. P. Collinet is a member of the unit).

A new method for segmentation of the cerebral vasculature, quasi-automatic and independent operator has been developed. This method involves the fuzzy set theory and the possibility theory to take into account the uncertainty and inaccuracy inherent to images. Good

results were obtained on images obtained from phantoms or simulations. This work (published in IEEE Trans. Medical Imaging) has been recognized by the international community. Therefore unit 703 will be responsible for a WP project eurostars "VWG optimal segmentation in PET imaging-through automatic contouring techniques and consensus evaluation method " recently submitted with Aquilab (Spin off of the unit 703) which aims to develop the automatic segmentation of PET applied to radiotherapy treatment. Furthermore, a European patent application: MEASURING AND CORRECTION OF DISTORTION IN MRI was filed on September 10 as No. PCT/EP/2010/063329

In 2010, U703 members have published more than 80 articles in peer-reviewed journals (list is enclosed).

Partnerships

Research teams

CERLA - CNRS 2416	Univ. Lille 1	Villeneuve d'Ascq	Physique Laser
ENSAIT - Ecole d'Ingénieur	Univ. Lille 1	Roubaix	Textile
LMP - EA 2443	UVHC	Maubeuge	Biomatériaux
LAGIS - CNRS 8146	Univ. Lille 1	Villeneuve d'Ascq	Automatique
Alcove - INRIA	Univ. Lille 1	Villeneuve d'Ascq	Informatique
LML - CNRS 8107	Ec Centrale Lille	Villeneuve d'Ascq	Mécanique
Biophysique	Faculté de Médecine	Monastir (Tunisie)	Physique médicale
Multitel	Faculté Polytechnique	Mons (Belgique)	Laser
Institute of Theoretical and Applied Informatics.	Polish Academy of Sciences	Gliwice (Pologne)	Automatique
Institut de Physique Générale,	Russian Academy of Sciences,	Moscou (Russie)	Physique
Institute of Laser and Information Technologies,	Russian Academy of Sciences,	Troitsk (Russie)	Laser

Medical teams

Service de Médecine Nucléaire,	Hopital Huriez, CHRU Lille
Service Central de Médecine Nucléaire,	Hopital Salengro, CHRU Lille
Service de Dermatologie,	Hôpital Huriez, CHRU Lille
Service de Gastroentérologie,	Hôpital Huriez, CHRU Lille
Service d'Urologie,	Hôpital Huriez, CHRU Lille
Service de radiologie néphro-urologique	Hôpital Huriez, CHRU Lille
Service de Gynécologie,	Hôpital Jeanne de Flandres, CHRU Lille
Service de Neuroradiologie,	Hôpital Salengro, CHRU Lille
Service de Neurochirurgie,	Hôpital Salengro, CHRU Lille
Service de Pédiatrie néonatale,	Hôpital Jeanne de Flandres, CHRU Lille
Service de Radiologie Cardiovasculaire,	Hôpital Cardiologique, CHRU Lille
Service de Radiologie Digestive,	Hôpital Huriez, CHRU Lille
Service de Réanimation,	Hôpital Huriez, CHRU Lille
Service de Radiothérapie	CRLCC O. Lambret, Lille
Service de Radiologie,	CHRU Montpellier
Service de Neuroradiologie,	Hôpital Lariboisière, APHP Paris
Service de Pédiatrie,	Hôpital Nord, CHRU Amiens
Service de Médecine Nucléaire,	Hôpital Sud, CHRU Amiens
Service de Médecine Nucléaire,	CHU - CHB Rouen, France
Radiation Oncology Dept & Radiotherapy,	Brussels, Belgique
Hospital Regional Cancer Centre,	Ottawa, Canada

Industrial Partners

Aquilab SAS	Lille France	Quality control – Multimodality	Vascular - Cerebral
Hitachi Medical Systems	Paris France	IMRI	Medical Imaging

LLTec	Lille France	OCT imaging systems	Medical Imaging
SynthInnove	Paris, France	Fluorescent dyes	Medical Imaging
Steba Biotech	Den Haag Nederland	Photosensitizers	Photodynamic Therapy
Photocure ASA	Oslo Norvège	Photosensitizers	Photodynamic Therapy
Fujinon	Japon	Endoscopes	Medical Imaging
Osyris SA	Villeneuve d'Ascq France	Medical lasers	Medical lasers
Quantel Derma	Erlangen Allemagne	Medical lasers	Medical lasers
Medligh	Lausanne, Suisse	Optical fibers	Laser fibres
Boston Scientific	Boston USA	Interventional radiology equipment	Vascular - Cerebral
Ethicon	Norderstedt Allemagne	Surgical implants	Pelvis mobility
Transvalor	Sophia Antipolis	Numerical simulation	Pelvis mobility
Esaote	Florence, Italie	Ultrasound imaging	Mecical Imaging

Relationships with industrial partners are managed for the most part through collaboration contracts. The industrial partners involved in the TLAI project wish to pursue their relationship with U 703 through a GIS.

4.1.9.2 VALORISATION / EXPLOITATION OF RESULTS

Patents:

- Mordon S, Rochon P. "Embout diffusant pour fibre optique". Demande de brevet déposée en Europe le 7 Mai 2008 sous le n° 08008613.5 au nom de l'Inserm

- Mordon S, Rochon P. "Procédé et dispositif de cartographie du pH intra-rétinien, dispositif de photocoagulation des zones de la rétine périphériques" http://v3.espacenet.com/textdoc?DB=EPODOC&IDX=US2006241362&F=0

- Rousseau, J., Vermandel, M., Huglo, D., "Fantôme Pour Le Contrôle De Qualité En Imagerie Tomographique Et Notamment En Imagerie TEP", FR0609994, Université du Droit et de la Santé de Lille 2 Centre Hospitalier Régional Universitaire de Lille, 2007
http://v3.espacenet.com/publicationDetails/biblio?DB=EPODOC&adjacent=true&locale=en_V3&FT=D&date=20080521&CC=EP&NR=1923000A2&KC=A2

M. Vermandel, J. Rousseau, N. Betrouni *et al.*, *DISPOSITIF DE MESURE ET CORRECTIONS DES DISTORSIONS EN IRM* EUROPE PCT/EP/2010/063329, 2010.

Agence de protection des programmes (APP)

1. "DicomViewer", IDDN.FR.310005.000.S.A.2007.000.31230, INSERM, France, 2007
2. "CQ TEP", IDDN.FR.001.310002.000.S.A.2007.000.31230, INSERM, France, 2007
3. "SISCOM", IDDN.FR.001.310004.000.S.A.2007.000.31230, INSERM, France, 20072007
4. "ArtiMED", IDDN.FR.001.310003.000.S.P.2007.000.31230, INSERM, France, 2007

4.1.9.3 ENSEIGNEMENT SUPERIEUR / HIGHER EDUCATION

Medical school: several members of U703 teach biophysics to graduate medicine students and multimodality Medical imaging analysis to Master students

Each year, students in Master 2 (mostly residents) perform their research program in the laboratory. U703 collaborate with 2 universities in Paris.

- Master 2 de Sciences Chirurgicales - Parcours Cancérologie - Université PARIS XI, Faculté de Médecine PARIS SUD
- Master 2 Physique Médicale - spécialité Imagerie Médicale, Université Paris Sud 11*
- Master Sciences Pour L'ingénieur, spécialité Signaux et Images en Médecine, UPEC, Université Paris-Est Créteil, Val de Marne

4.1.9.4 ORGANISATION / ORGANISATION

In 2010, the Inserm U703 is constituted by 4 permanent researchers (2 Inserm researchers: Serge Mordon,PhD Director and Nacim Bertouni,PhD. 2 lecturers-researchers, Maximilien Vermandel , PhD and Patrick Dubois, PhD). Among the clinicians, members of INSERM U703, Arnaud Villers, MD, PhD is the head of the Urologic Department, and Philppe Puech, MD, PHD, radiologist, specialist in MRI imaging of the prostate.

INSERM U703 Members

Serge Mordon	Director, DR INSERM	
Nacim Betrouni	CR Inserm	
Zohra Boucherim	Secretary	
Pascal Briche	Technician	
Bruno Buys	IR	
Pierre Collinet	MCU-PH	
Michel Cosson	PU-PH	
Anne-Sophie Dewalle	AHU	
Guy Dhelin	TR	
Patrick Dubois	MCU-PH	
Olivier Ernst	MCU-PH	
Damien Huglo	MCU-PH	
Jean-Paul Lejeune	PU-PH	
Bertrand Leroux	AJT	
Jean-Claude Lesage	AI	
Renaud Lopes	Post-Doc	
Philippe Puech	MCU-PH	
Nicolas Reyns	PH	
Chrystèle Rubod	MCU-PH	
Laurent Thines	MCU-PH	
Maximilien Vermandel	MCU-PH	
Arnauld Villers	PU-PH	

4.2. COLLABORATIONS EXISTANTES / EXISTING COLLABORATIONS

Collaborations between the different partners involved in the project are effective for many years as evidenced by the research articles below (Annex 7.2). Our collaborations consist in:

- Prof JC Michalski, UMR 8576 : The research works conducted by all teams aim at understanding the structure-function relationships of complex free or conjugated carbohydrate molecules. With Dr F. Foulquier we are studying the glycosylation of the TRPM8 channel using confocal imaging.

- Dr R Boukherroub, IRI, FRE 2693 : The aim of their research program is to take advantage of controlled surface chemistry, patterning (micrometer and nanometer scale), and surface analysis to study biomolecular interactions at a solid substrate. We are currently studying the interactions and the effects of nanowires on cell morphology at the ultrastructural level.

- Prof I Fournier, Since 1 year partner MIT and partner 1 has developed a collaboration in order to use MALDI MSI to study prostate cancer and implication of ion channels in the pathology. Partner MIT has several other collaborations regionally, nationally and internationally. MIT is collaborating with Pr. D. Vinatier and his team at the Clinique Gynécologique if the Hospital Jeanne de Flandres in Lille since 2004 in order to search for diagnosis and prognosis markers of ovarian cancer. This strong collaboration is recognized by several publications and communications in international conferences as well as taking part of the INCA SIRIC program of CHRU Lille. MIT has also a strong collaboration with the Proteomics platform of Dijon (Dr. P. Ducoroy) for which an INCA grant was obtained. Dr. P. Ducoroy is specialized in studying plasma and sera which is has analyzed in the ovarian cancer project. MIT s has also since its creation a strong collaboration with Pr R. Day (Uni Sherbrooke, Canada). Pr R. Day is a specialist of Prohormoe convertase enzymes (PC). Since two years Pr. Day has demonstrated the strong implication of PCS in prostate cancer showing the possible regression of tumors on PCs KO animals. MIT has also a collaboration network in Europe with the groups involved in MSI. This has led to an active teaching through FP7 granting as well as submission of a FP7 call and a COST action. MIT has collaboration with Pr. E. Macagno (USCD, USA), Pr. Terry Gasterland (Scripps Institute, San diego, USA) and Pr. V. Bafna (USCD, USA) in order to develop new bioinformatics tools for MALDI MSI including new statistical analysis of data and identification processes. Finally, MIT has also collaboration for research in the field of Neurosciences for studying neurodegenerative diseases. Principal collaborators are Pr. Y-M. Park (KBSI, Seoul, Corea), Pr. H. Steinbusch (Uni Maastricht, Netherlands) and Pr. K. Markus (Bochum, Germany). For this MIT is involved in the recently launch project of HUPO (http://www.hupo.org/) dedicated to proteome of the huma brain, namely the Human Brain Proteome Project (http://www.hbpp.org/).

The own partnership of the other partners is indicated in their respective chapters.

5. DESCRIPTION SCIENTIFIQUE ET TECHNIQUE DU PROJET / TECHNICAL AND SCIENTIFIC DESCRIPTION OF THE PROJECT

5.1. ETAT DE L'ART / STATE OF THE ART

Channelopathies.

Ion channels are integral plasma membrane (PM) proteins that allow the passive transfer of certain ions, along their electrochemical gradient, into and out of the cell. Ion channels are structures that can open or close (gate) in response to specific stimuli, to selectively allow passage of only specific ion(s), to sense various regulatory signals and to react to physical and chemical characteristics of the surrounding medium. The first important role ascribed to PM ion channels over 60 years ago was their function in cellular electrogenesis and electrical excitability. Numerous subsequent studies have established the contribution of ion channels to virtually all basic cellular processes as well as many pathological states. Some of these pathological states (e.g., myasthenia gravis, congenital and acquired long QT syndrome, episodic ataxia type 2, cystic fibrosis, myotonia congenita, etc.), **dubbed channelopathies**, **directly result from the malfunction of certain ion channels** as a result of inherited mutations in their genes or acquired impairment of their function (for instance due to adverse effects of medications), whilst development of many others is accompanied by altered expression and/or function of ion channels, which thereby contribute to their pathogenesis. As such, ion channels potentially represent viable targets for therapeutic interventions. **Among the disease states for which there is strong evidence that ion channels may play essential roles are such common ones as cardiovascular diseases, diabetes-related complications and cancer.**

Oncochannelopathies.

Cancer is responsible for approximately 13% of all deaths worldwide (http://www.who.int/mediacentre/factsheets/fs297/en/). There are over a 100 distinct types of cancer, which are defined by specific genotypes, and much research effort is directed towards identifying new genes with altered expression in specific cancers.

Accumulating evidence tends to demonstrate that the development of some cancers could involve ion channel aberrations and, therefore, could be classified as channelopathies. Indeed, a new concept in oncological research has been developed and promoted during last decade. This novel research paradigm is based upon the fact that ion channels control some of the "hallmarks of cancer" such as evasion of apoptosis or self-sufficiency in growth signals. Exploding progress over the last years in the molecular identification of ion-channel types and availability of new research tools for the detection and manipulation of their expression fully confirmed this concept and allowed to further it to other cancer-related processes such as malignant angiogenesis, migration and metastasis **paving the way to a new chapter of oncology**. Moreover, it has been show that some of the channels have an oncogenic potential by themselves, and others are altered during oncogenic transformations. Cancer-related alterations in ion channel structure, function and expression could be **termed "Oncochannelopathies"** so far. This new developpement in the field is the reason why researchers and clinicians are now concerned with ion channel studies for the elaboration of clinical approaches aiming at treating these cancers by targeting ion channels with pharmacological and molecular tools. Indeed, ion channels represent good potential pharmacological targets due to their localization on the plasma membrane. In addition, the tissue-specific localization of these channels and their variable structure could render the treatment of channelopathies possible, without causing considerable side effects to the other organs (liver, kidney, central nervous system, medulla etc).

The groundwork for this novel concept was laid in primarily by members of the European IonTraC network (the coordinator of this proposal is on the pilot board of this network). They were the first to recognize that K^+ channels (Schwab*, et al.*, 1999), Cl^- channels (Ullrich and Sontheimer, 1996) and voltage-gated Na^+ channels (Grimes*, et al.*, 1995) are required for tumour cell proliferation, migration and invasion. Another major breakthrough was the discovery that the overexpression of a voltage-gated K^+ channel, $K_V10.1$ (also designated as EAG1), confers tumourigenicity on non-cancer cells (Pardo*, et al.*, 1999). Subsequently, members of the transient receptor potential (TRP) channel family, most of whom are Ca^{2+} -permeable channels, entered the field as important players in cancer cell pathophysiology (for review see (Prevarskaya*, et al.*, 2010)). The importance of such developments was highlighted by the organization in 2008 and 2010 of two international meetings of the scientists, oncologists and representatives of the pharmaceutical industry interested in understanding the role of ion channels in the development and progression of cancer and the possibility of their exploitation for cancers diagnosis and treatment (Fraser and Pardo, 2008).

In the context of European cooperation, the team of the project coordinator (Natalia Prevarskaya, LCP) mainly studies the role of calcium-transporting channels in oncogenic transformations. The achievements during last years have made this team a world-recognized leader in the "Calcium-Cancer" field.

The most important results were obtained on the role of calcium and calcium-transporting channels in prostate cancer.

Prostate cancer.

Prostate cancer (PCa) is the most common non-cutaneous human malignancy and the second most lethal tumour among men, with the highest incidence in industrialized countries. The incidence of prostate carcinoma, over half a million new cases every year, increases proportionally to the increase in the **life expectancy**. This context justifies the development of clinical and scientific research strategies aiming to understand the pathological processes involved in carcinogenesis of prostate tissue. The intimate association of scientific studies with clinical applications would therefore provide beneficial effects for patients.

Focal therapy for localized PCa and early stage prostate cancer treatment. Whole-gland radical therapies of PCa have provided evidence from both the Scandinavian trial and the European Randomized Study of Screening for PCa (ERSPC) of benefit in reducing disease-specfic

mortality in screened populations. Currently, the accepted options for treating patients with low-risk PCa lie between radical whole-gland treatment (surgery, external-beam radiation, or brachytherapy) and AS (Active surveillance). Although mortality from AS is low, follow-up is relatively short. As such, it has not yet been proven completely "safe", the risk being that the window of opportunity to treat with a single modality is potentially lost in some patients. **Focal therapy (FT), at least initially**, is gaining attention as a potential modality that might naturally extend the AS concept. The similarities being that like AS, FT has a low risk for lifestyle-altering complications generally associated with whole-gland treatment, and it also aims to achieve cancer control. More recently, there has been a shift toward less-invasive ablation that aims to destroy the cancer and just the small zone of normal tissue around it rather than previously treated larger areas. This has been possible with the investigation of modalities such as focal laser ablation which have ushered in this new era of FT. **Such FT techniques rely upon accurate imaging and biopsy information to guide the FT.** The challenge remains in the detection of small tumours.

In order to detect early stage prostate cancer, the team directed Serge Mordon, partner ITAIS, and has mainly focused its research on Multiparametric Magnetic Resonance imaging. However, it is important to improve pre-operative detection and local staging of prostate cancer. These multiparametric MR images are usually combined, as in doing so, complementary information is obtained. In this aspect, the using oncogenic ion channels as specific complementary markers for the early stages of prostate cancer would be of great importance.

Progression of prostate cancer to advanced stages and hormonal therapy. Initially, tumours develop from epithelial cells and remain androgen-dependent. Therefore, once the disease has progressed, become highly invasive or metastatic, the reduction of the circulating levels of androgens by castration or administration of androgen antagonists is the standard treatment. However, its efficiency is time-limited and tumours inescapably become refractory to hormonal treatments, leading to more than 200,000 deaths per year. **Understanding the processes leading to prostate cancers and developing new therapeutic targets are necessary to improve both the survival and the every day life of patients. It is, therefore, an urgent need to understand the mechanisms of tumour progression, metastasis dissemination and to develop pharmacological tools to treat advanced prostate carcinomas.**

Bone metastasis is a serious complication occurring in up to 70% of patients with advanced prostate cancer. It depends on a reciprocal interaction between prostate cancer cells and the bone micro-environment leading to the formation of mainly bone-forming (osteoblastic) as well as destructive (osteolytic) lesions. The consequences of these bone lesions for the patients are often devastating (pathological fractures, bone pain, spinal cord compression). However, the reasons why prostate cancer cells metastasize to bone, proliferate and set up this cycle of bone destruction or formation are still largely unknown. Distinct mechanisms are expected to be involved during the interplay between prostate cancer cells and osteoblasts or osteoclasts for the formation of osteoblastic or osteolytic lesions, respectively. ***In this respect, the mechanisms leading to prostate cancer bone metastasis are currently poorly understood.***

One of the major challenges in prostate cancer research is to provide new discriminative prognostic markers for low-risk, indolent PCa *versus* invasive highly metastatic tumours.

In this context, **MALDI Mass Spectrometry Imaging (MALDI MSI)** is of great since classical methods such as Immunohistochemistry (IHC) have shown to be relatively difficult.

MALDI MSI is an emerging technology of molecular imaging within surfaces such as tissue sections. Images are acquired by focusing the laser at a specific location of the surface to be analyzed and scanning the entire surface (or part) according to a raster of points regularly distributed and spaced by at minimum the diameter of the laser beam. At the end of acquisition, a collection of mass spectra for each raster coordinates is generated. **MALDI-MSI has thus the great advantage to be a non targeted approach not requiring the development and use of labeled probes** but also to allow after one acquisition the reconstruction of many images, one for each detected signal. **MALDI MSI is thereof a very powerful and promising technology**.

MALDI-MSI combines both biomarker identification and validation in a single step (El Ayed*, et al.*, 2010; Lemaire*, et al.*, 2007). In MALDI-MSI the identification of compounds, no extraction or separation is required, while anatomical and spatial resolution are maintained (Stauber*, et al.*, 2009). In a single experiment, molecular information on hundreds of chemical or biological molecules can be retrieved. By automation of this method and data processing, molecular maps of compounds can be generated from tissue sections (Stauber*, et al.*, 2010; Wisztorski*, et al.*, 2010). MALDI-MSI is a non-targeted analysis, but due to its high data acquisition, permits the establishment of a classification of cell phenotypic changes at the molecular level, which can be used in complement to histology techniques. Combined with powerful multivariate analyses like the hierarchical classification and principal component analyses (PCA) (D'Anjou*, et al.*, 2004), it is possible to identify biomarkers present in carcinoma region from one in a stromal area, from those in an interstitial region. Therefore, in a single analysis we can access all potential biomarkers present in a region of interest, characterize them *in situ*, without any tissue extraction.

The MALDI Imaging Team (MIT), directed by Isabelle Fournier, is one of the world leaders in the field of this emerging cutting-edge technology. The common project on new biomarkers (based on ion channels) could improve the quality of low-risk and high-risk PCa detection, and, thereby, could help an urologist to take a right decision of how to treat a disease.

Calcium and cancer: particular role of TRP and Orai channels.

Indeed, Ca^{2+} -permeable channels are of utmost importance since Ca^{2+} is the key messenger regulating signalling pathways important in such cellular processes as proliferation, apoptosis, gene transcription, and angiogenesis (for reviews see(Monteith*, et al.*, 2007; Roderick and Cook, 2008)). Their importance is perhaps most strikingly exemplified by their role in life-and-death decisions (Roderick and Cook, 2008). Each cellular phenotype, whether normal or pathological, is characterized by a particular "Calcium Signature" (reflecting its kinetics, amplitude and sub-cellular localization of the calcium signals). Recent years have seen a growing appreciation of the extent to which components of Ca^{2+} signalling pathways are remodelled or deregulated in cancer (for reviews see (Monteith*, et al.*, 2007; Prevarskaya*, et al.*, 2007; Prevarskaya*, et al.*, 2010; Roderick and Cook, 2008)These changes were suggested to be drivers that are required to sustain the transformed phenotype. However, the mechanisms of "how the Ca^{2+}-transporting proteins are remodelled in tumour cells" and the significance this has for the maintenance of the cancer phenotype remained poorly understood.

The results obtained by the coordinator's team during the last years have clearly shown the importance of calcium-permeable channels in such fundamental processes as cell growth, proliferation, apoptosis, migration, and differentiation of prostate cancer cells (see part 4.1.2, "Description of the existing").

Among these channels, those forming TRP (Transient Receptor Potential) family of cationic channels seem to play a major role. Indeed, according to a growing number of articles, altered expression of **TRP channels contribute to malignancy**. About thirty members of the TRP superfamily identified in mammals are classified in six different families: TRPC for «Canonical», TRPV for «Vanilloid», TRPM for «Melastatin», TRPML for «Mucolipins», TRPP for «Polycystins» and TRPA for «Ankyrin transmembrane protein». The members of this channel family display an extraordinary diversity regarding their activation mechanisms (Montell, 2003). The first evidence that TRP channels expression is correlated with different types of cancers came from the analysis of TRPM1 expression. The expression of TRPM1 gene is inversely correlated with the aggressiveness of melanoma malignant cells, which suggests the ability of TRPM1 to behave as a tumour suppressor gene (Duncan*, et al.*, 1998; Fang and Setaluri, 2000). A second member of the TRPM subfamily, TRPM5, was shown to be responsible for the Beckwith-Wiedemann syndrome, a disease characterized by a childhood predisposition to tumours.

The post-translational modifications such as phosphorlation or glycosylation could also alter the expression and the localization of the channels, altering their intracellular trafic and thus the calcium homeostasy (Dietrich*, et al.*, 2003; Xu*, et al.*, 2006). The expression of modified or abherrant glycans at the cell surface could also modify the cell recognition leading to cancerization or metastasis (Hakomori, 1996). ***Studying the glycosylation rate, type and site occupancy is***

the research field of JC Michalski's team, BCSG, a worldwide recognized laboratory in glycobiology and partner in this project.

TRP channels could play a key role in cancer progression and could characterize the cancer cell phenotype. Indeed, this seems to be the case for some of TRP channels in prostate cancer:

TRPM8 as a marker of androgen-dependent prostate tumours. TRPM8 is expressed in normal prostate; however, its expression increases in ADCaP (Tsavaler*, et al.*, 2001) while it is again decreased with tumour progression to an androgen-insensitive late and invasive stage (Henshall*, et al.*, 2003). TRPM8 is a target gene of the androgen receptor (AR) and that the TRPM8 response to androgens requires a functional AR (Bidaux*, et al.*, 2005) and is expressed also in the endoplasmic reticulum membrane (Thebault*, et al.*, 2006; Zhang*, et al.*, 2005). However, the mechanisms which determine the preferred localization of TRPM8 in cells of different phenotypes are so far unknown. We hypothesized that in prostate epithelial cells, localization may depend on cell phenotype and on androgen status (Bidaux*, et al.*, 2007). Prostatic Specific Antigen (PSA) is an activator of TRPM8 channel and reduces the prostate cancer cells motility, suggesting a protective role of the plasma membrane TRPM8 in prostate cancer progression (Gkika*, et al.*, 2010). ***Taken together, these data suggest that TRPM8 may be involved in the regulation of cell survival and migration, contributing to the initiation, promotion and progression of carcinogenesis in prostate epithelial cells.***

TRPV6 as an advanced prostate tumour marker. TRPV6 transcripts are not detectable either in the normal prostate, in benign or in high grade prostate intraepithelia neoplasia. These transcripts are detected in 20% of tumours graded pT2a and pT2b, 79% of pT3a and more than 90% of pT3b tumours which present extra prostatic extensions (Fixemer*, et al.*, 2003). In addition, TRPV6 transcripts are abundantly expressed in lymph node metastasis of prostate origin (Wissenbach*, et al.*, 2001). We have recently shown that TRPV6 is directly involved in the control of proliferation of prostate cancer cells (Lehen'kyi*, et al.*, 2007). The pro-proliferative role of TRPV6 consists in supporting the basal Ca^{2+} entry required for the activation of Ca^{2+}/calmodulin/calcineurin-dependent transcription factor NFAT (nuclear factor of activated T-cell)**,** whose transcriptional activity alters the expression of cell-cycle regulators.

The capacity of TRPV6 to regulate calcium homeostasis may explain the observed upregulation of this channel along with the tumour progression in prostate cancers. However, it is unclear at present whether TRPV6 expression is a cause or a consequence of tumourigenesis.

TRPV2 channel as a marker of neuroendocrine differentiated prostate cancer cells. TRPV2 is expressed in the more aggressive androgen-resistant prostate cancer cells and its expression is increased by treatments inducing neuroendocrine differentiation (Monet*, et al.*, 2010). Indeed, neuroendocrine differentiation has been shown to be associated with the androgen-independent stage of prostate cancer (Weinstein*, et al.*, 1996). This neuroendocrine phenotype of prostate cancer cells is dependent on the presence of TRPV2, since its inhibition by siRNA down-regulates neuron-specific enolase, a neuroendocrine marker (Monet*, et al.*, 2010). Physiological regulation of the TRPV2 channel has so far been poorly described. It was shown that this channel can be activated when plasma membrane targeting is stimulated by growth factors (IGF1), phosphatidylinositol-3 kinase pathway and osmotic stimuli (Kanzaki*, et al.*, 1999). ***The activation mechanisms, regulation and modulation of TRPV2 channels in prostate cancer cells and its role in advanced prostate cancer with neuroendocrine differentiated phenotype remain unclear.***

Two other than TRP calcium-permeable channels have attracted our attention as important players in prostate carcinigenesis.Indeed, TRPV2 is not the only calcium channel over-expressed during neuroendocrine differentiation.

CaV3.2 channel as marker of neuroendocrine differentiated prostate cancer cells regulating the secretion of mitogens. Neuroendocrine features include the appearance of neuroendocrine cell foci surrounded by proliferating epithelial cells (Bonkhoff*, et al.*, 1991). Since neuroendocrine prostate cells secrete many neuropeptides with mitogenic activities, it has been proposed that paracrine secretion of neurosecretory products released by neuroendocrine cells

could be responsible for the progression of cancer towards an androgen-independent stage (see (Bonkhoff, 2001) for review).

We have demonstrated that CaV3.2 calcium channels are expressed in neuroendocrine-differentiated cells obtained from biopsies and control the secretion of mitogenic factors (Gackiere*, et al.*, 2008). **The potential use of Cav3.2 channels as prognostic markers for the most aggressive neuroendocrine differentiated stages of prostate cancer needs to be further studied.**

ORAI1 as marker of apoptosis-resistant phenotype of prostate cancer. Store-operated Ca^{2+}-permeable channels (SOC) seem to play a major role in the development of the apoptosis-resistant phenotype in prostate cancer cells, since the density of these channels is dramatically reduced in apoptosis resistant cells (Vanden Abeele*, et al.*, 2002; Vanoverberghe*, et al.*, 2004). For years, TRP channels have been considered as only molecular candidates for SOCs. However, recently, a new major SOC-player has been found (Feske*, et al.*, 2006; Vig*, et al.*, 2006; Vig*, et al.*, 2006). Orai1 is a widely expressed, 33 kDa plasma-membrane protein with a lack of significant sequence homology to other ion channels. Nevertheless, very little is known about the physiological role and pathological implications of Orai1 outside the immune system. Recently, we have demonstrated that the downregulation of both Orai1 expression and the SOC activity is used by the prostate cancer cells to develop the apoptosis resistance crucial for cancer development and its progression to the hormone-refractory stage (Flourakis*, et al.*, 2010).

Quite unexpectedly, ORAI1 has been recently implicated in breast tumor cell migration *in vitro* and in xenograft tumor metastasis in mouse model (Yang*, et al.*, 2009). It is, therefore, not exluded, that ORAI1 could play multiple roles in cancer. Further studies are needed to understand the mechanisms.

Profiling of TRP channels and the transportome in prostate carcinogenesis.

As the importance of the TRP channel family has emerged since only two decades ago, their genetic properties (sequence polymorphism, alternative splicing) are still largely unknown. In the majority of cases channelopathies are characterized by alterations of genes encoding channels via either their primary sequence or their pattern of splicing; hence, TRPpathies could represent a significant risk factor in human health (Nilius and Owsianik, 2010). An important step towards a better understanding of the TRP genes is to analyze variation in their primary sequence and expression, and their possible relation, via specific mutations, with prostate cancer development. Clearly, increasing the biomarkers number would improve both the sensitivity and the specificity for diagnosis. Our major challenge will be to find a set of markers allowing not only detecting clinically evident prostate cancer, but also early disease before the occurrence of symptoms.

To detect mutations we will use targeted sequencing approaches since they have the general advantage of an increased sequence coverage of the regions of interest — such as coding exons and promoter regions of TRP genes — at a lower cost and higher throughput compared with random shotgun sequencing. Cutting edge Pair-End Sequencing using Next Generation Technologies, associated to highly accurate read count combined with new bioinformatics tools constitute very powerful approaches for mutation screening. To investigate alternative splicing we will use the emerging technology of RNA-seq since it allows quantifying the number of transcripts in cells with an unprecedented accuracy by sequencing total RNA after rRNA depletion. At last but not least, we will associate the detected mutations in miRNA sequences to quantitative data on miRNAs obtained by micro-array. These three sides of the genetic part of the project (DNA mutations, mRNA splicing, miRNA mutation and expression) are together an exciting emerging area of research.

Indeed, even though it is estimated that 74% of human genes encode transcripts undergoing splicing, and that 15% of human genetic diseases are associated with mutations in either splice junctions or in the spliceosomal apparatus (Lee, 2008 #3), very little has been done on TRP channels nucleotide polymorphisms and on sequence changes associated to tumoral cells. The second step after primary sequence analysis is the characterization of alternative mRNAs and their associated protein isoforms. Our previous data on TRPM8 (Bidaux*, et al.*, 2007) as well as studies on other TRP channels (Gkika and Prevarskaya, 2009), have demonstrated the presence of several alternative mRNAs for these genes. Some of the subsequent protein isoforms differed from the classical ones. Whereas the prototypic TRPM8 isoform is explicitly addressed to the plasma membrane, we have identified in prostate tumor cells a new isoform, containing the pore, but

retained at the endoplasmic reticulum membrane. Interestingly, these two isoforms appear to be differentially expressed at different prostate cancer stage (Bidaux*, et al.*, 2007).

Finally, we will screen for the transportome miRNA expression profiles. Few data are available on the regulation of ion channels by miRNAs in pathology (mainly on cardiovascular disease), however miRNA have been linked to the aetiology, the progression and the prognosis of cancer (Kumar*, et al.*, 2007). Because of their functional association with cancer, their small gene size and their ability to simultaneously affect a multitude of genes, miRNA are unique candidate loci to confer cancer susceptibility. Moreover, small genetic changes in miRNA sequence can theoretically lead to widespread phenotypic effects (Garzon*, et al.*, 2009; Ryan*, et al.*, 2010).

Altogether, our previous results on *TRP* genes (mentioned above) have opened new insights in term of molecular targeting and specific design of diagnosis and prognosis markers. A new framework for the identification and validation of the transportome markers should include new high-throughput technologies such as second-generation sequencing methods and advanced computational analysis. The major challenge will be to make biological sense of the large genomic dataset generated. This will require computational, biological and clinical analyses. The computational analyses will assess reproducibility and statistical significance; the biological analyses will address the functional relevance of detected mutations; and the clinical analyses will assess relationships of genome alterations.

Xavier Vekemans, the leader of GEPV team, is internationally recognized expert in evolutionary genetics and genomics. His participation in the OncoChannel project will certainly help Laboratory of Excellence to identify the prostate cancer transportome and to address the complex issue of TRP channels genetics.

One of the important and challenging issues for understanding oncochannelopathies and for the drug discovery of oncogenic channels is the knowledge of their crystal structure. Since TRP channels seem to be the most promising targets against PCa, in the framework of Laboratory' of Excellence project we will try to advance in such complex but critical for further studies field as TRP channels crystal structure.

Structural biology of TRP channels

Ion channels are embedded in the membrane and membrane proteins represent roughly one-third of the proteins encoded in the genome. Particular excitement has been observed with successes in determining the structure of membrane proteins from higher eukaryotes including humans. One significant example is the progresses made on GPCRs, thanks to painstaking work in a variety of fields that have come together to provide a new tools for any membrane protein biochemist to delve into and apply to new targets (for a review, see (Cherezov*, et al.*, 2010)).

The structural biology of TRP channels is an important research field, since these channels are important physiological "sensors" and their mutations and functional abnormalities have been shown to be involved in a wide range of pathologies, including cancer (for reviews see). These pathologies were named TRPpathies (Kiselyov*, et al.*, 2007), since many human diseases are caused by mutations in TRP channels.

Determining their 3D structure and functional properties is critical to deciphering their role in cellular function. Despite their fundamental importance, structural information on TRP channels remains limited. Two major bottlenecks make structural studies on TRP channels particularly challenging. First, structural studies require the production of large amounts of pure, stable and functional protein solubilized in amphiphiles. Second, TRP channels are very large tetramers composed of 70 to 250 kDa subunits that are each formed of multiple domains (Venkatachalam and Montell, 2007). This places TRP channels out of reach for high-resolution solution NMR techniques and requires X-ray diffraction and electron microscopy techniques to probe their structures. Major differences between TRP channels lie in the large N and C terminal cytosolic domains which contain putative protein interaction and regulatory motifs and have distinct features of each TRP channel subfamily (Venkatachalam and Montell, 2007). Determining the 3D structure and functional properties of these domains is thus critical to deciphering their role in TRP channel function and regulation. To date, the structural data on TRP channel domains are limited to ankyrin repeat domains of TRPV channels (Phelps*, et al.*, 2008), to the coiled-coil domain and to the structure of the alpha kinase domain of TRPM7 (Fujiwara and Minor, 2008; Yamaguchi*, et al.*, 2001). The crystal structures of the ARD domains of TRPV channels, the coiled coil domain present in the C terminus of TRPM7 and kinase domain of TRPM7 have provided important hints about

channel assembly and the mechanisms that lead to the modulation of TRPV1 responses to noxious stimuli (for review see (Latorre*, et al.*, 2009)). Electron cryomicroscopy studies of the TRPV1 channel have been reported, showing a 19 angstrröm resolution structure exhibiting four fold symmetry. These studies point out that the different TRP channel subfamilies may not share the same structural design. Thus, the structural information remains very limited at the molecular level for the TRP channels family.

One of the partners of the Laboratory of Excellence, Vincent Villeret, the leader of "Structural biology" team, BISB, is internationally recognized expert in the field of structural biology. Therefore, this proposal is a unique opportunity to bring together structural biology and channel knowledge as well as permit technological and methodological and technological projections in these challenging structural biology targets. Furthermore, the participation in this project of Benoit Desprez, Drug Discovery team leader, BDD, will be of great importance for future drug design based on oncogenic channels structure.

Another important issue of innovative medicine is the development of Nanotechnologies for drug delivery and non-invasive diagnostic procedures.

Quantum dots (QDs) QDs are colloidal nanocrystalline semiconductors with unique optical and electrical properties. These tiny light-emitting particles, on the nanometer scale, are emerging as a new class of fluorescent probe for *in vivo* biomolecular and cellular imaging. Despite their relatively large size (2–8 nm diameter), recent research has shown that bioconjugated QD probes behave like fluorescent proteins (4–6 nm) and do not suffer from serious binding kinetic or steric hindrance problems.

Fluorescence recovery after photobleaching (FRAP) and quantum dot tracking have been used to examine the mechanisms underlying Kv2.1 potassium channels containing surface domains in both HEK cells and cultured hippocampal neurons. The results clearly indicate that the channel within the surface cluster is mobile (O'Connell*, et al.*, 2006). Using dual color labeling with quantum dots, it was possible to detect single hIK1 channel molecules within the plasma membrane (Nechyporuk-Zloy*, et al.*, 2008; Nechyporuk-Zloy*, et al.*, 2006).

From the above report and others, we anticipate that the technology of QDs can be easily applied for TRP channels. Subsequently, separate binding of an extracellular domain of subunit A and an intracellular domain of subunit B after permeabilization with different colored QDs should facilitate the stoichiometry analysis of the channel subunit composition.

Nanoparticulate drug delivery systems.

The ability to use nanotechnology to alter the characteristics of a drug to increase solubility, decrease degradation during circulation, and concentrate the drug at the desired site of action promises to increase efficacy while decreasing unwanted side effects. The enormity of this opportunity has spurred much funding and research aimed toward the development of various nanoparticulate drug delivery systems (Adair*, et al.*, 2010; Bechet*, et al.*, 2008).

In our laboratory, we have used lipid nanocapsules, initially developed by the team of J.-P. Benoit, (Heurtault*, et al.*, 2002) for encapsulating hypericin and other active agents (Richard*, et al.*, 2008). The advantage of such a system is the ease of its formulation and the possibility to tune the surface properties to address a specific target.

In this project, we will initially focus on the use of lipid nanocapsules for the encapsulation of small organic molecules such as drugs (calcium channel blockers), pre-designed siRNA or photosensitizes for photodynamic therapy.

One of the partners of the Laboratory of Excellence, Rabah Boukherroub, the leader of NanoBioInterfaces (NBI) team, is internationally recognized expert in nanoscience. Therefore, the implementation of OncoChannel will allow to apply the expertise of Rabah Boukherroub to oncogenic channels and, thereby, to develop new "nanomedical" tools for studying molecular dynamics in vivo.

In conclusion,

Previous work from other groups and our own work give firm expectation that ion channels play a crucial role in the progression of PCa and will thereby constitute a diagnostic and/or therapeutic target. However, based on this proof of concept, an integrated interdisciplinary approach is needed to develop new therapeutic drugs and imaging-assisted methods for the

treatment and diagnostic/prognostic purposes.

In this way, the Laboratory of Excellence "*Oncochannel*" will achieve a twofold breakthrough constituting a major progress beyond the state-of-the-art. We will be:

- first to exploit therapeutic and diagnostic concepts of oncochannelopathies and deliver original as yet unexplored therapeutic and diagnostics tools by introducing a new dimension compared to the presently available state-of the-art approaches to combat PCa.

- first to employ basic structural and nanotechnological approaches for oncochannelopathies and other diseases where these channels are involved.

5.2. OBJECTIFS DU PROJET PAR RAPPORT À L'ÉTAT DE L'ART ET LIENS AVEC LA SNRI/ OBJECTIVES OF THE PROJECT COMPARED TO THE STATE OF THE ART AND IN RELATION TO THE SNRI

5.2.1 PRESENTATION SCIENTIFIQUE DU PROJET DE RECHERCHE/ SCIENTIFIC PROGRAMME

The main objectives of *the Laboratory of Excellence "Oncochannel"* are

- **to determine the expression, structure and function of ion channels required for the progression of Prostate Cancer, and**
- **to provide validated therapeutic and diagnostic concepts as well as tools that are based on ion channels serving as novel drug targets and/or biomarkers.**

Overall strategy of the work plan.

Our goal is to demonstrate that ion channels not only promote prostate cancer progression but also represent novel, and as yet unexplored targets for the diagnosis and treatment of what remains the most lethal malignancy among men.

To achieve this highly challenging scientific issue, we intend to create a new Laboratory of Excellence that will focus its activity on Oncochannelopathies. **The purpose** of such a new structure is to **synergize** the efforts of the **best scientific regional teams** (all graded A or A+ by **AERES**) in a new and promising research field. We have therefore brought together into a **highly coordinated project 8 internationally recognized and complementary research teams, all of them having long-standing expertise in their respective field.**

Inside this new Laboratory of Excellence, we will **concentrate in a single site a critical mass** of methodological and **scientific expertise** covering a wide range of approaches **"from gene to therapy"** (molecular electrophysiology; glycobiology; proteomics; genomics; structural biology; nanotechnologies; physico–chemistry; mass spectrometry; high-tech cellular imaging; imaging-assisted therapy of cancer). Both basic and reverse-translational aspects will be investigated by this new Laboratory.

OncoChannel Laboratory of Excellence **aims to create new international networks** with the idea of sharing fundamental knowledge (channels crystal structure) as well as technical tools (nanoparticles, high-resolution confocal imaging devices, clinical procedures). In this regard, *Oncochannel* Laboratory of Excellence meets with the criteria of several regional, national and international in (EUROPE 2020) **itiatives.** Region Nord Pas de Calais is already supporting our structure through its recent funding of a new state-of-the-art electrophysiology platform located in LCP premises. This platform includes a high-throughput patch-clamp robot devoted to drug screening which will become a cornerstone during the projected creation of a start-up linked to our Labex. This strong support of the region to our project has been recently confirmed through the

signature of a **CPER (Contrat de Projet Etat-Région)** giving us the resources to buy a new confocal microscope. At the national level, the creation of an oncochannelopathies Labex perfectly answers the objectives developed in the new **SNRI (Stratégie Nationale de Recherche et d'Innovation)** by:

-developing research programs focusing on the exploration and modelization in life sciences;
-inscribing its research in a dynamic of innovation;
-placing life sciences at the center of society, and French research in a prominent position inside the European zone.

Today, we are already supported on a national level by a "Ligue Nationale Contre le Cancer" label, and 2 INSERM Theme Institutes (Metabolism and Cancer). After Laboratory of Excellence creation, we intend to apply for several calls including national (INCa) and European ones (7^{th} framework programme). These applications will help us to increase ***OncoChannel*** **visibility** in Europe, and should provide us with many opportunities to expand our actual networks to other major teams.

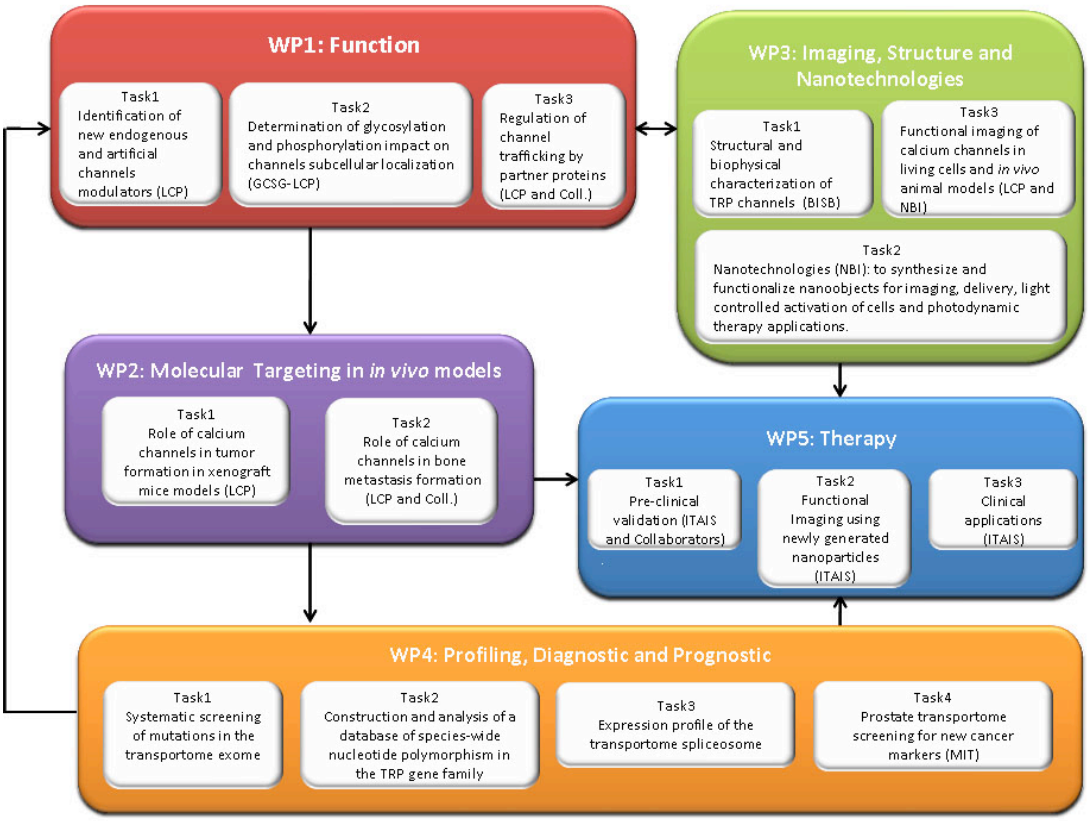
Our previous studies (set out in the "Description of the existing" report of Partner 2) led us to identify several ion channels playing an important role in prostate pathophysiology through their capacity to modulate key cell behaviours (apoptosis, proliferation, migration and cell differentiation). According to these results, ion channels imprinting the calcium signature would appear to be the best potential candidates as tumour markers and pharmacological targets for prostate cancer.

In the context of the cooperative project of the Laboratory of Excellence, we will adopt the **following strategies:**

- First, we will **exploit our previous results** and concentrate a research axis on the regulation/modulation mechanisms of the most promising channels. Indeed, the apparition of aberrations in these mechanisms could lead to the development of specific cell phenotypes associated with prostate cancer. We will therefore study the remodelling of these channels in tumour cells and its significance in maintaining the cancer phenotype.
- We will also focus our efforts on the **molecular targeting** of channels for the elaboration of reliable markers and effective therapies, which will then be **validated in animal models** developed by our new structure.
- Through the incorporation of two teams from IRI (Interdisciplinary Research Institute) into our structure, we aim to develop two new "**high-gain/high-risk**" approaches to the oncochannelopathies issue: crystallography applied to TRP channels and the nanotechnologies. Indeed, despite several previous attempts, TRP channels crystal structure has still to be resolved. While highly challenging even a partial structure of these channels would represent **a great asset for any future drug-design targeting oncogenic channels**. We also wish to apply **nano-technologies** to our research subject through the development of a new technology for dynamic imaging. If successful, this approach would provide us with new tools of unprecedented sensitivity, and could also be applied to medical imaging needs.
- **Global high–throughput approaches** for "Channel profiling" in prostate tumours will be used. Indeed, despite their success, previous investigations of ion transport proteins in cancer fall short of a comprehensive, integrative approach covering the entire transportome of a given tumour entity.
- Finally, with our **"Therapy" team** we will try to develop a "global detection framework" allowing optimal characterization of tumours for the focal treatments of prostate cancer.

The information obtained will fuel the understanding of the role of ion channels in cancer progression. It will be the basis for new diagnostic and therapeutic concepts and tools that will contribute to overcoming the current treatment failure for patients.

WP1 Function. WP leader: Pr. Natalia Prevarskaya (LCP).



The main objective of WP1 is to identify major ion channels functional alterations in PCa. Based on our previous results, we have identified 5 channels (TRPM8, TRPV6, TRPV2, Ca V3.2, ORAI1) as being instrumental in PCa genesis and/or progression. In addition to new **mechanistic insights,** WP1 will deliver **molecular tools** (antibodies, siRNA, shRNA in viral vectors, small molecules) capable of specifically modulating and/or targeting those channels, as well as biophotonic tools that will enable to image in living cells the dynamic interactions between ion channels and their partners, and the ensuing changes in the activity of these channels.

Task 1.1 Identification of new channels modulators (LCP - BDD).

It is well established that Lysophospholipids (LPL), which can be released by cancer cells and function in autocrine and paracrine manner, are significant actors in tumour development, since they stimulate angiogenesis, growth, survival and migration of malignant cells. Moreover, LPL levels are increased in patients with prostate cancer. However, despite those observations, LPLs signalling and their potential role in cancer are still poorly understood. It has been previously shown that TRPM8, TRPV2 and CaV3.2 are activated by LPLs in over-expression models. However, their respective mechanisms of activation remain unclear. We will thus investigate, using patch-clamp and calcium imaging approaches, the mechanisms by which LPLs activate these channels in prostate cell models. The effects of LPLs on cell migration, growth and apoptosis will also be assessed in these models. The recent discovery that the orphan receptor GPR55 is a specific and functional LPL receptor has fuelled novel interest on the role of this LPL in cancer. We will therefore carry out confocal analysis of subcellular localization (FRET), co-immuno-precipitation assays and single channel analysis of these channels to study their possible colocalization with GPR55 and the existence of a possible signalplex.

Target modulation of ion channels by organic molecules (preferably, low molecular-weight and non-peptidic molecules) is complementary to genomic or transcriptomic interventions. We have recently developed a partnership with Drs. A. Jain and E. Wei (Berkeley University, USA) which led to the identification of potent TRPM8 activators. We intend to maintain this collaboration and, using our high throughput electrophysiological screening platform, to develop it by testing new compounds for their pharmacological potency as agonists and antagonists for TRPM8 in transfected HEK-293 and prostate cancer cells. In parallel, we will also test these compounds in proliferation, migration and apoptosis assays using prostate cancer cells. We will also test these compounds in proliferation, migration and apoptosis assays using prostate cancer cells. In parallel, using the regional compound library (75.000 compounds) enriched in nature-inspired structures (DOS strategy), and the screening platform available in Deprez' group, we will identify new modulator chemotypes. These chemotypes will provide other modulation profiles and reach other binding sites (within the structure of the channels or partner proteins). These compounds will help crystallisation efforts and be critical tools to answer the important question whether the role of the target protein in cancer phenotypes is dependant on the channel ion channel function or protein-protein interactions. The equipment provided by Equipex "Imaginex", if granted will greatly accelerate the screening phase. Compound displaying the best *in vitro* profiles will be further optimised to provide compounds suitable for in vivo testing (WP5).

Task 1.2 Determination of glycosylation impact on channels subcellular localization (BCSG-LCP).

Cellular processing functions include protein folding, stabilization, trafficking, subcellular localization and activities, and incorrectly processed proteins are most of the time subjected to proteasome-mediated degradation. Carcinogenesis is due to a disturbance of these mechanisms. Given that N-glycosylation is necessary for a number of these cellular processing functions, it is interesting to study the glycosylation state of calcium channels during cancer progression and to show the impact of the glycosylation site occupancy.

- We will first investigate the glycosylation state of our target calcium channels and correlate, if possible, glycosylation site occupancy and carcinogenesis.
- Then, we will study the trafficking of these channels in order to gain further insights into the impact of N-linked glycosylation site occupancy on the synthesis, degradation, subcellular localization and activities of the surface membrane expression of calcium channels in relation with cancer grade. Expression , trafficking and degradation will be monitored by Western blot analyses, pulse chase metabolic labelling experiments, cell-surface biotinylation, confocal microscopy, and subcellular fractionation experiments. The impact of glycan structure on calcium channels functionality will then be studied. To address the impact of the glycan structure on the synthesis, degradation, subcellular localization and activities of the calcium channels surface membrane expression, we will use the available collection in our lab of Chinese hamster ovary (CHO) cells and their glycosylation-defective Lec mutants.
- Finally, in the long term, if it is shown that the glycosylation state of some channels is correlated with a cancer state and with specific glycan motives, we will target anomalous glycosylation motives by a strategy using lectins or lectin-like drugs.

Task 1.3 Regulation of channel trafficking by partner proteins in prostate (LCP - NBI).

TRP channels, like all ion channels, are regulated by intracellular factors acting on their trafficking to the plasma membrane or directly on their stabilization and activity within plasma membrane. For example, TRPM8 presents a dual localisation in plasma membrane (PM) and endoplasmic reticulum (ER), which determines the channel's functionality. We have shown it to be related to the progression of prostate malignancy from the androgen-dependent to the more aggressive stage of androgen-independent tumour. The partner proteins regulating TRPM8 targeting to the PM still remain unknown. In order to identify new regulatory proteins for TRPM8, we have used a GST pull-down assay using TRPM8 cytosolic N- and C-terminal tails as bait on lysates of healthy mouse prostates. Among the interacting proteins, five candidates were chosen

based on their properties available in the literature and their interaction with TRPM8 was confirmed *in vitro* to rule out false-positives. We will now proceed with the functional analysis of the partner proteins on TRPM8 channel activity with spectroscopic, biochemical, molecular, and electrophysiological techniques. Partner proteins subcellular distribution and co-localization with TRPM8 will be further investigated using our collaboration with Dr. Héliot team (see WP3, task 3.1). The effect of those partner proteins on cell behaviour will also be assessed through cell proliferation, migration and apoptosis assays. The acquired results will then be validated in primary cells and animal models and will substantiate the auxiliary proteins role not only under physiological conditions, but also during the progress of cancer development.

The same approach will be applied to the search for prostate-specific partner proteins of TRPV6, TRPV2 and Cav3.2, and for the role of these partners in oncochannelopathies and prostate cancer progression.

Understanding the role of calcium channels and their regulation during PCa development require to follow the dynamics of these channels and their functional interactions with their partners in the context of living cells and tissues (e.g. in animal model). Imaging the activation of these channels and the downstream signalling pathways in living cells is a major challenge with several technological bottlenecks. To perform this challenge, the Biophotonic team proposes in WP3 task 3.4, to adapt and develop new techniques of microscopy (FRET, FLIM, FCS/FCCS, SPT, PALM and their integration in multimodal microscopy module) dedicated to the studies of interplay between Ca^{2+} channels and signalling proteins.

Expected results and deliverables:

- New molecular tools/agonists/antagonists for calcium channels study, refined tools and techniques for live cell imaging;

- small molecule candidates for structure /property optimization (supply of WP5).

- Increased fundamental knowledge of calcium channels regulation in prostate cells, identification of the main alterations affecting their regulation (phosphorylation, glycosylation) during prostate carcinogenesis;

- New targets (partner proteins, glycan motives) for future diagnostic, prognostic and therapeutic applications.

WP2 Molecular targeting in *in vivo* models. WP leader: Pr. Natalia Prevarskaya (LCP).

The main objective of WP2 is to establish innovative and appropriate experimental *in vivo* models, reverse-translating the clinical pathological features of PCa such as localized PCa tumours, neuroendocrine differentiated tumours, bone metastasis and chemo-resistance.

Identifying a set of channels that importantly contribute to PCa progression and creating the respective modulating/targeting tools is the **prerequisite for evaluating their clinical potential** in WP5. Previously selected channels will be validated for their oncogenic activity in *in vivo* models. siRNA-based treatments against these channels will be employed to study their role in tumour growth and metastasis development. The development of new in-vivo imaging techniques for these animals is described in WP3 task 3.4. The Role of calcium channels in tumour formation will be investigated in xenograft mice models (LCP). To evaluate the importance of these channels in the onset of androgen-dependent, as well as hormone refractory tumours, cells stably transfected with shRNA-TRPM8, shRNA-TRPV6, shRNA-TRPV2, shRNA-CaV3.2 or shRNA-control will be grafted in nude mice. Alternatively, cells over-expressing these channels will be grafted in nude mice to assess the role of these channels in tumour formation and development. To do so, we will measure the number of mice developing tumours and the date of tumour onset. We will analyse the expression level of the channels in tumours and quantify cell proliferation by KI67 labelling. Apoptosis will be measured by tunnel and the cytodeath reagent.

The role of calcium channels in bone metastasis formation will then be studied (LCP and collaborators). This study will be primarily realised through our **collaboration with Dr. P. Clezardin whose team is internationally recognized for its work on prostate and breast cancers bone metastasis**. TRPM8, TRPV6 or CaV3.2-over-expressing prostate cancer cells, and transfectants silenced for these same channels will first be co-transfected to stably express

luciferase. Luciferase-expressing transfectants will then be directly inoculated into the bone marrow cavity of tibiae from immuno-deficient mice. Tumour-bearing mice analyzed by radiography will also be examined by non-invasive, whole-body bioluminescence imaging. The osteolytic area (or osteoblastic) lesions and the extent of tumour burden (as judged by bioluminescence photon emission) will be measured using computerized image analysis systems. After sacrifice, all hind limbs with metastases will be collected for further histological analysis. Transfectants selected for their ability to induce osteolytic or osteoblastic lesions will be further studied using an orthotopic model in which cancer cells are directly inoculated into the prostate gland of immuno-deficient animals. The development of prostate tumours as well as the spontaneous dissemination of cancer cells into other organs will be examined by non-invasive bioluminescent imaging of live animals and by non linear optic imaging. Biosensors for monitoring the physiological status of cancer cells such as hypoxia will be developed and implemented in these animal models. Histological and histo-morphometrical analyses will be performed on tibial metaphysis, using computerized image analysis systems. In addition, osteoclasts are detected *in situ* after TRAP (tartrate-resistant acid phosphatase)-staining of metastatic bone tissue sections. For immuno-histochemistry, tissue sections of demineralized metastatic hind limbs are immuno-stained using antibodies that specifically recognize TRPM8, TRPV6 or CaV3.2.

Expected results and deliverables:

- Innovative *in vivo* models.

- Validation of the pro- or anti-oncogenic roles of ion channels which may be used for the selection of therapeutical strategies in humans.

WP3 Structure, Nanotechnologies and New developments in quantified imaging.

WP leader: Dr. Vincent Villeret (BISB).

Task 3.1 Structural and biophysical characterization of TRP channels (BISB).

Structural approaches will allow us to improve our understanding of how the modular architecture of TRP channels correlates with protein function and how the different modules assemble to form a functional unit. TRP channel interaction with different ligands (identified from WP1.1) and/or protein partners (identified from WP1.3) will be further investigated using structural and biophysical techniques and will yield information on how the function of these proteins can be modulated. Such data will be invaluable in terms of drug design prospects targeting TRP channels.

Grasping a better understanding of TRP channel function will require the integration of structural and physiological approaches to advance from static 3D structures to the description of dynamic processes such as conformational changes and ligand interactions.

3.1.1 Protein expression (BISB).

Our first task will be to establish expression systems which will allow us to generate protein for structural analysis. TRP channels are transmembrane proteins and as such are challenging targets to apprehend. We nevertheless will develop two different parallel approaches to overcome the risks inherent to such a project.

Our first approach will be to express the different cytosolic modules of the targeted TRP channels as separate soluble proteins. Domain mapping of these modules will be initially done using bioinformatic tools and will be followed by medium throughput cloning using ligation independent **c**loning towards initial overexpression trials in *E. coli*. For "difficult-to-express" protein targets that resist the classical approach of bioinformatics and PCR cloning, we shall use strategies employing the principles of directed evolution whereby a diverse random library of DNA constructs is generated and screened to identify rare clones of interest which represent soluble expressers.

Our second approach will be to express the more challenging full length TRP channels. In order to maximize our chances of success, different channels will be processed in parallel. Previous Cryo-EM studies performed on TRPV1 expressed in yeast have shown that eukaryotic expression systems are well suited for TRP channel overexpression. Hence, we shall focus on establishing different eukaryotic expression systems including yeast, insect and human cells towards an

improved full length protein expression. State of the art screening techniques such as fluorescence-detection size-exclusion chromatography, coupled to small scale expression trials, will be implemented to investigate the best detergent and buffer conditions for protein extraction and solubilisation.

In this task, we shall also aim at expressing partners relevant to the modulation of TRP channel function (WP2.3 and the TRIP database (Shin*, et al.*, 2010) either as full length proteins or as individual domains. These proteins will then be further used in the biophysical characterization of protein-protein interactions (Task 3, 1.2) and for co-crystallization with the TRP modules and/or channels (Task 3, 1.3).

3.1.2 Investigation of interactions of TRP channels with partners and ligands (BISB).

To better understand how TRP channels are integrated in functional networks in their cellular environment, we shall through this task, characterize the interaction of TRP channels or TRP channel modules with proteins which modulate their function. These partners are being identified by the team of project coordinator, (Inserm U1003) and will be reported in WP2.3. The TRIP database will also provide us with potentially interesting targets to pursue. Our aim will be to use surface plasmon resonance (SPR) and/or isothermal titration calorimetry (ITC) to assay the interactions between TRPs or TRP modules with either full length partners or relevant domains from these partners. Investigating these interactions and characterizing their tightness will not only provide us with key information concerning how TRP function is modulated but will also give us hints about the stabilizing effect that some of the partner domains might have on TRP modules. Information derived here can be potentially crucial towards higher success rates in task 1.3 and will pave the way to the structural characterization of TRP channel complexes. SPR and ITC will also be used to characterize the kinetic and thermodynamic parameters of the interaction of TRP modules with different ligands which will be identified from WP1.

3.1.3 Protein crystallization (BISB).

The first crystallization targets we shall address will consist of the individual modules making up different TRP channels. For this, our laboratory is currently well geared for high throughput crystallization assays through the use of a CyBio crystallization robot. Following these initial crystallization trials, we shall exploit results obtained in WP1 and tasks 1.1 and 1.2 pertaining to identification, expression and biophysical characterization of TRP partners, to proceed with co-crystallization trials of TRP modules with relevant partners or partner domains. Along the same lines, we shall proceed with the co-crystallization of TRP modules with different synthesized in WP1.2(??) and characterized in task 1.2. Structural data derived from these experiments, supported by the biophysical characterization (task 1.2.) will foster a rational and innovative structure-based drug design strategy.

A major challenge within this work package is the structural determination of a complete TRP channel. Whereas our current equipment level is suited for processing soluble proteins and, to some extent prokaryotic membrane proteins, it is clear that nano-volume crystallization will be required for processing eukaryotic membrane proteins, given the low expression yields for such targets. We shall therefore setup nano-volume crystallization to reduce amounts of material required for exhaustive screening of crystallization space. We shall, in addition to the "classical' crystallization in detergents, explore alternate crystallization techniques by exploiting lipidic mesophases. The success of using lipidic phases for GPCR studies is attributed to the creation of a more native, membrane-like stabilizing environment for membrane proteins just prior to nucleation and to the formation of highly ordered and strongly diffracting crystals. Interesting partners and ligands identified in WP2.3 and WP1.2 (??) will be integrated in co-crystallization trials with the full length TRP channels. Structural data derived on the full length TRP channels will obviously further enhance our understanding of the mechanisms governing their mode of action, and will provide us with a competitive edge in the pursuit of drug design strategies targeting these proteins.

Task 3.2 Nanotechnologies (NBI).

Our objective is to synthesize and functionalize nanoobjects of different nature (semiconducting, oxide, metallic and lipidic) for imaging, delivery (small organic

molecules such as drugs, siRNA, DNA,…), light controlled activation of cells and photodynamic therapy applications. A close interaction with different work packages is expected from the beginning of the project to its end.

3.2.1 Synthesis of quantum dots.

The preparation of quantum dots (QDs) with high quantum yields and good photostability, which does not blink will be achieved through the reported methods. We will also use a new approach, consisting of encapsulating organic dyes in lipidic nanocapsules. The QDs will be used to study the mobility of ion channels at high temporal and spatial resolution. We will combine the QDs technology with confocal or super resolution microscopy systems such as SIM (Structured Illumination Microscopy) to monitor single channel mobility. Furthermore, coupling of QDs with FCS (Fluorescence Correlation Spectroscopy) will permit to quantify the mobility and formation of heteromers in the cell membrane.

3.2.2 Encapsulation of small organic molecules and siRNA.

Lipidic nanocapsules, known as drug carriers, will be used for the encapsulation of small organic molecules such as drugs (calcium channel blockers), pre-designed siRNA or photosensitizes for photodynamic therapy. The technique is well established in our laboratory. The nanocapsules size and composition will be optimized to reach high loading efficiency and controlled release of the bioactive agent. Covalent (metabolically labile) coupling between the active component and the carrier may be needed. To characterize the in vivo availability of compounds, the ADME platform (to be reinforced by Equipex PharmaR3) will be used.

3.2.3 Functionalization.

Inorganic quantum dots lack solubility in aqueous solutions. Increasing their dispersion in aqueous solutions is often achieved through surface functionalization or polymer coating. For QDs of small diameters (< 10 nm), we propose to encapsulate them in lipidic nanocapsules. This way, they become easily dispersible in buffered aqueous solutions. Furthermore, it is also possible to encapsulate QDs of different nature and physical properties (photoluminescent and magnetic QDs) or QDs + siRNA or drugs in one nanocapsule. These systems will offer a possibility for simultaneous release and imaging. Moreover, surface functionalization of the nanoobjets will allow inhibiting non specific adsorption of biomolecules on the nanoobject's surface, but also to address and direct specifically the nanoobjects to the target ion channel. The QDs will be conjugated with F(ab')2 antibody to direct against a specific endogenic or exogenic epitope (for example: HA tag).

3.2.4 Toxicity.

The toxicity of nanoobjects is a critical issue to be addressed in the present project. Cytotoxicity studies regarding the impact of the nanoobjects on living organisms will be first investigated in vitro (cell culture) and then in vivo using small animal models (zebra fish and xenopus embryos both available at IRI) and finally in mice. The impact of nanoobjects concentration and surface chemical composition will be studied in details.

3.2.5 Large scale synthesis of functional nanoparticles.

One challenging issue in the use of nanobojects is their production at a large scale (gram scale). During this project, we will develop a novel and relatively inexpensive technique for the preparation of nanoparticles of controlled diameter through planetary ball milling. In this technique, the nanoparticles are composed of only biocompatible molecules and the loading is achieved by simply mixing all the components. The system will allow for controlled, protected and targeted release and delivery of any type of active agents including antigen and therapeutic proteins.

3.2.6 Characterizations.

The microstructural, physical properties and chemical composition of the nanoobjects will be characterized using transmission electron microscopy (TEM), optical techniques (microscopy, fluorescence and photoluminescence), dynamic light scattering (DLS), zeta potential, X-ray photoelectron spectroscopy (XPS) and infrared (FTIR) spectroscopy.

Expected results and deliverables

- New high resolution confocal methods applied to channels-partner proteins localization/interactions.

- Domain mapping of TRP modules expressing as soluble proteins.

- Structure of TRP modules and complete TRP channel alone or in complex with ligands or partner proteins

- Generation of QDs targeting our channels of interest and their partner proteins.

- Assessment of QDs efficiency in prostate cancer treatment (animal models and human in WP5)

Ta*sk 3.3* New developments in quantified imaging of living cells and tissues (NBI and LCP).

As indicated above, the translocation of the ion channels between the PM and the ER and the regulation of their activity are highly dynamic processes mediated by numerous interactions with several partners during prostate cancer development. Biochemical studies have only provided snapshots of different steps in these processes. The accuracy of the protein dynamics and interaction measurements in living cells has been a major limitation for a long time. To tackle this limitation, tremendous progress has been made recently in hardware, automated acquisition, and analysis algorithms. However, **imaging the activation and the translocation of ion channels** in living cells and tissues, **stay a major challenge**. In fact, the functional studies of Ca^{2+} -permeable channels activity at the molecular scale is currently limited by three technological bottlenecks that should be overcome: i) the need of correlated measurements of molecular dynamics and interactions in living cells with new multimodal approaches, ii) the need of improved spatial and temporal resolution in microscopy, iii) the need of molecular interactions and dynamics measurements in living animal models with sensitive and non invasive techniques. **The biophotonic team lead by L. Héliot (NBI and BioImaging platform IbiSa, described in 4.1.2.1) is internationally recognized for the development of imaging technologies in microscopy for studies of molecular dynamics and interaction,** which will find here a direct application within project. The first step in this task will be to produce fluorescent fusion proteins between appropriate GFP variants and TRPM8, TRPV6, TRPV2, Cav3.2, ORAI1,... or their mutants. Additionally, photoactivable and photoinducible proteins will be built to monitor molecular dynamics and to study the functional effects of sub cellular modifications by local activation or depletion of proteins. Then, several imaging techniques will be adapted and developed.

3.3.1 Molecular dynamics and interaction approaches for Ca^{2+} -permeable channels studies in PCa

In first step, Ca^{2+} channel dynamics in living cells can be studied by photoactivation or Fluorescence Correlation Spectroscopy (FCS) and more recent techniques such as Fluorescence Lifetime Correlation Spectroscopy (FLCS) or Single Protein Tracking (SPT). The measurement of molecular interaction dynamics in live cells could be performed by Fluorescence Resonance Energy Transfer (FRET) experiments. However, the interpretation of these results remains often ambiguous in live cells due to the complexity and dynamics of molecular species and their variation during the acquisition time. Consequently, none of these single measurement techniques is able to conclude on the study of Ca^{2+} channels dynamics in prostatic cancer. In order to overcome this technological bottleneck, we need to measure and correlate different aspects or characteristics of fluorescence such as: intensity, diffusion, lifetime and spectrum.

3.3.2 Development of multimodal microscopy for Ca2+ channel analysis in living cell and animal models

We propose to develop, in association with partners of WP1, a dedicated multimodal microscope associating the FRET, SLIM, FCCS and FLCS approaches to study the relationships between the locations, dynamics, interactions and functions of Ca^{2+} channels in living cells. The simultaneous correlated measurements of several fluorescence modalities through dedicated software will make diffusion measurements more accurate, but it will also enable to get multi-information from a single experiment: the kinetics of monomers and dimers, the local concentrations of proteins and their different states, their relative stoichiometry...

The ubiquitous function of the calcium as an intracellular second messenger requires that its actions are spatially and temporally restricted to regulate specific signaling cascades. A significant gain in resolution by super-resolution photonic and dedicated analysis tools are required for understanding the relationship between the subcellular localization, the mobility of Ca^{2+} channels, the interaction with their partners and their appropriate functions. The optical diffraction limits the resolution of conventional light microscopes to approximately 250 nm. We will then use super-resolution techniques such as single particle tracking/photoactivated localization microscopy (SPT-PALM) to monitor the localization and the dynamic of individual active Ca^{2+} channels in living cells.

3.3.3 Measurements in physiological conditions in living animal models
Last but not least, our ambition is to make these measurements in physiological conditions in living mouse models (see WP2). This is the third technological bottleneck and a very high challenge for the next ten years. To lead this challenging step, we will lie on our internationally recognized experience in Non Linear Optic (TPE) that we have applied to perform dynamics and interaction measurements in tissues. Due to the heterogeneous nature of the cancerous tissue, it is necessary to rethink our imaging methods into tissue in order to obtain a good imaging depth (500 µm to 800µm) with low laser power to limit phototoxic effects. For this purpose, we will couple our multiphoton multimodal microscope with adaptive optics. This adaptation of multiphoton multimodal microscopy for monitoring the Ca2+ channels in-vivo (in mice and rats) with the control of phototoxicity will be a very interesting challenge, which necessitates new developments in both hardware and software. This development is directly necessary for the work with nanoparticules proposed in WP3 task 2 and WP5 with teams of R. Boukherroub and S. Mordon.

Expected results and deliverables

1. Dynamic of Ca^{2+}channels modifications induced by PCa in single living cell.
2. Monitoring and quantification of Ca^{2+} channels activity regulation mediated by interactions with their partners during early PCa.
3. New multimodal microscopy tools for studies of cellular pathways in tumour cell.
4. Monitoring and quantification of Ca^{2+} channels activity, at the cell level, during the PCa development and metastasis, in living animal models.

WP4 Profiling, diagnosis and prognosis. WP leader: Pr. Xavier Vekemans/Pr. I. Fournier (DEGV/MIT).

In order to understand molecular alterations occurring during carcinogenesis and also provide new discriminative prognostic markers for the early stages of prostate cancer, it is of great importance to use high-throughput cutting edge profiling techniques. We will focus on mining all possible sources, since a disadvantage of one approach could be the advantage of another. Transcriptome and proteome-wide approaches combined with a computational approach using publicly available datasets will lead not only to the identification of critical mutations of TRP channels during carcinogenesis but also to the characterization of new tumour marker candidates. This, **WP4** will generate a **comprehensive unbiased dataset on the "transportome"** in cells and tissue from **patient samples**, human normal prostate cells, **cell lines** and **animal models delivered by WP2**. We will correlate altered mRNA and protein expression/localization, and/or altered posttranslational modifications of selected transportome members and transportome-associated changes in miRNA profile in defined samples from PCa patients with their clinical characteristics. Patient samples and clinical data are available from the Tumour biobank in Lille.

Task 4.1 Systematic screening of mutations in the transportome exome (DEGV).

Systematic screening of transport genes mutations in 140 associated tumoral and healthy samples will be performed in the Functional and Structural Genomics Centre of Lille (Director: Martin Figeac) using targeted resequencing (SureSelect from Agilent combined with SOLiD NGS). We will focus on deep sequencing from TRP, ORAI and Cav gene families: exons, promotor regions,

intronic conserved regions and noncoding RNA. Systematic screening on DNA with SureSelect (1ug of starting DNA) will facilitate the use of patient samples.

Task 4.2 Construction and analysis of a database of species-wide nucleotide polymorphisms in the transportome (DEGV).

This task is intended to improve our knowledge about selective constraints occurring across the regulatory and coding regions of gene members of the "transportome" in humans, in order to identify, among the mutations detected in Task1, strong candidates for use as biomarkers. To achieve this goal, molecular evolution analyses will be applied on a database built by screening public databases on human nucleotide polymorphisms and on related primate sequences.

Task 4.3 Expression profile of the transportome spliceosome (DEGV).

It is estimated that 74% of human genes encode transcripts that undergo splicing, and that 15% of human genetic diseases are associated with a mutation in either splice junctions or the spliceosomal apparatus. We will therefore perform RNA-seq studies on 36 samples (10 µg of RNA). The outcome will reveal a potential role for alternative mRNA splicing of the transportome in tumour progression.

Task 4.4 Prostate transportome screening for new cancer markers (MIT).

Pathologies that cause changes in signal transduction pathways generally result from changes in specific cell phenotypes. MALDI-MSI will allow the establishment of a classification of cell phenotypes changes at the molecular level, and could lead to the identification of new diagnosis biomarkers and new therapeutic targets.

4.4.1 Samples preparation.

Frozen or Formalin-fixed paraffin embedded (FFPE) tissues will be collected by our clinician team (Hospital Saint-Vincent, Lille). Tissue microarrays (TMA) will be then performed for MALDI-MSI analysis in parallel to cytochemical staining. This tissue collection will be completed *via* our collaboration with Trans-Hit Biomarker company. THB has indeed a unique access to a worldwide proprietary database of 1000 biobanks with retrospective biospecimen collections (www.trans-hit.com) including prostate tissues collections (prostate cancers, normal adjacent tissues).

All molecular images thus obtained will be subjected to multivariable statistical analyzes (PCA and hierarchical clustering) in order to confirm tissue classification (stage, grade, cancer type). All validated slides will be then used for molecular biomarker identification.

4.4.2 Biomarkers identification.

After PCA, all the putative biomarkers found in carcinoma or interstitial regions will be subjected to a molecular validation, starting with calcium channels. For this, three complementary strategies will be used ***(i)*** bottom-up proteomics using tissue trypsin digestion followed by N-terminal derivatization and MS/MS analyses using MALDI-Orbitrap, ***(ii)*** tissue sections will be washed with solvents to remove peptides/proteins contained in matrices, and then subjected to shotgun analyses with trypsin digestion followed by nanoLC-ion trap analyses or ***(iii)*** micro-tissue extraction using LESA-TRIVERSA (Advion System) coupled to nanoLC-orbitrap with electron transfer dissociation (ETD) for top-down analysis. For FFPE tissues, a shot-gun strategy will be performed using specific magnetic beads C18, C8, C4 deposited on top of the tissue section after trypsin deposition using a microspotter. Peptides on beads will be removed and analyzed using nanoLC-orbitrap for identification. FFPE studies will be complementary to fresh tissue data obtained above.

In parallel, we will carry out the identification of biomarkers in the serum of the same patients from which we obtained tissue biopsies. The combined data collected from both tissue and serum studies should reveal which biomarkers are potential candidates for further development as diagnostic tools.

Diagnostic and prognostic values of those biomarkers will then be evaluated in plasma by high-throughput quantitative mass spectrometry assays on larger populations of patients

diagnosed with prostate cancer at different stages and other prostatic diseases using "Proteome-Hit": (Multiple Reaction Monitoring assays).

Finally, using a highly sensitive technique developed by our group, we will establish a ISA-MS Tag-mass technology based on the identified and validated serum biomarker in order to develop a diagnostic kit.

Expected results and deliverables

- Identification and characterisation of critical mutations in the TRP, ORAI and CaV gene channel families in prostate cancer
- Delivery of a transportome members list with potential diagnostic/prognostic value.

WP5 Imaging and Therapy. WP leader: Dr. Serge Mordon (ITAIS)

WP5 represents part of the translational potential of the *IonTraC* project. The final targets will be selected on the basis of the knowledge gained in WP1, WP2, WP3 and WP4, i.e. on the basis of their impact on disease progression, and/or of the availability of modulating agents, and/or of their significant enrichment in PCa tissue. We will provide **preclinical proof-of-concept** for previously-unexplored diagnostic, prognostic and therapeutic strategies against PCa.

Task 5.1 Pre-clinical validation of nanoparticles (ITAIS and collaborators).

The development of tissue-specific biomarkers at different disease stages is important as PCa can have multiple stages, with each stage exhibiting a distinct signature. The multiple-variable information gained from the biomarkers can help improve the accuracy of diagnosis and treatment.

Magnetic nanosized particles have already been known for over 50 years, but research into their potential use in medicine and pharmaceutics is now the hot topic in this domain. The unique combination of high magnetization and paramagnetic behaviour opens these materials to a very wide range of applications. Particularly, the possibilities of nanoparticle modification by biologically active compounds to use them in controlled drug delivery systems and as agents in magnetic resonance imaging is very interesting.

Efforts in recent years have been focused on design of MRI contrast agents (MRI-CAs), which either target biomarkers, or take advantage of the different physiology of cancer cells. **MRI-CAs** based on gadolinium complexes, ferrumoxides, or other metallic nanoparticles have been investigated.

Thanks to nanotechnologies mastered by two teams from the IRI (Interdisciplinary Research Institute), nanoparticles targeting members of the transportome will be used for MRI-CAs.

Several methods for iron nanoparticle preparation will be investigated. First, Fe2O3 nanoparticles, where a magnetic core covered by an amorphous silica shell will be fabricated. In a second step, liposomal-based gadolinium (Gd) nanoparticles will be developed. The highest atoms per nanoparticle will be determined, and the best suited will be used as MRI contrast agents. The effects of different variants of these agents on MRI signal will be assessed on traditionnal 1.5T or 3T clinical devices, such as on 7T research MRI devices. The biocompatibility of these different nanoparticles will be evaluated on an animal model developed by INSERM U703. This model is the Dunning R3327 rat prostate adenocarcinoma which arises spontaneously in male Copenhagen rat. Since initial isolation, several sublines have been developed and are well characterized. Syngenic Dunning prostate R3327-AT2 carcinomas is a poorly differentiated subline with a potential volume doubling time of 3 days. Investigations were conducted in accordance with accepted ethical and human practices, and approved by the local animal care committee at our institution.

The different nanoparticles targeting members of the transportome will be evaluated by a systemic injection in the vein in order to mimic a clinical situation aiming at determining the maximum dosage inducing toxicity. These preclinical tolerance studies in terms of animal survival, behavior and pathological assessment indicated capture by the reticulo-endothelial system and negligible toxicity are necessary even for dose-maximization situations. In a second step, the selective retention and alteration of functional pathway will be determined using confocal microscopy techniques and compartments staining or immunolocalisation of calcium channels in association with histological analysis and monitoring of nanoparticles in tumors. This work will be performed by biophotonic team of IRI.

Task 5.2 Functional imaging using newly generated nanoparticles (ITAIS).

In order to **detect early stage prostate cancer**, INSERM U703 has mainly focused its research on **multiparametric Magnetic Resonance imaging (mpMRI**), in collaboration with the imaging department of the Lille university hospital (Philippe PUECH, MD, PhD ; Laurent LEMAITRE, MD). New MRI techniques such as dynamic contrast-enhanced MRI (DCE-MRI), T2-weighted (T2-w), diffusion weighted imaging (DWI) and spectroscopic MRI (MRSI) improve pre-operative detection and local staging of prostate cancer. This team works on fractal analysis of PCa on T2-w imaging, on semi-quantitative and quantitative analysis of dynamic contrast enhanced MRI using gadolinium chelate contrast agents, and, since more recently, on diffusion-weighted imaging. New targeted MRI-CAs will be assessed for the purpose of increasing the accuracy of PCa detection at time of diagnosis. Also, the potential benefits of these agents for contours, shape and volume assessement, such as extraprostatic extension assessment will be evaluated.

The MRI examinations will be performed on animals by INSERM U703 using a *7 Tesla* Biospec research MRI system (*BRUKER* BioSpin MRI, Germany). Again, they will consist of a systemic injection in the veinous system in order to mimic a clinical situation with bio-compatible doses determined in step 1. Different MRI sequences (T2-w with different echoes, diffusion weighted imaging, fast spin-echo T1-w and dynamic gradient-echo T1-w) will be carried out in order to evaluate selectivity, sensitivity of the MRI-CA and potential variants. Resulting images will compared with histological slides of the same prostate tumor sampled on the sacrified animal, then analyzed by immunochemistry. Investigations will be conducted in accordance with accepted ethical and human practices, and approved by the local animal care committee at our institution.

Task 5.3 Clinical applications (ITAIS).

We believe the ultimate goal in focal therapy is to target specifically the cancerous site while ablating it and the smallest zone of normal prostate tissue around it to obtain cancer control.

To achieve this goal, one is dependent on high-quality imaging:

i) to locate the cancerous lesion and have it assist in guiding the ablative modality toward the lesion;

ii) to monitor the ablation in real time;

iii) to accurately assess the extent and totality of the ablation post-treatment, and finally to use it to follow-up and monitor the prostate in search of a recurrence of cancer in the treated area or the development in new zones.

INSERM U703 is already involved in 2 protocols, the first one on PDT treatment using Tookad Soluble (Steba Biotech, France), the second one on Focal Laser Ablation in Partnership with the US Company, Visualase.

The clinical evaluation of these techniques based on this new **Multiparametric Magnetic Resonance imaging using** nanoparticles targeting members of the transportome will be performed.

Risks and associated contingency plans

Each Work Package Leader (WPL) is responsible for tasks and deliverables on WP level. The WPLs monitor progress guaranteeing high quality work, in particular the follow-up of deliverables. The WPLs report any deviation from workplan, risks, and opportunities to the Scientific Committee. The Scientific Committee decides by 2/3 majority on ad hoc actions, if necessary. Below a number of risk factors and contingency plans, as identified for quick decision. The Scientific Committee will handle emerging risks beyond this list, as well. All reports on risks, deviations and opportunities and the resulting decisions of the Scientific Committee are documented to be scrutinized during the next Full Assembly. The coordinator will discuss all planned actions with the International Scientific Advisory Board.

Risk	Probability	Contingency plan
R1.1: Non-specific effects and partial effects	medium	Testing different drugs/antibodies to reduce side-effects. Combinations of drugs/antibodies will be used to target multiple channels in case of partial effects

		or the expression of compensatory pathways. Improvement of target organ exposure and contrast with respect to whole body exposure by chemical modifications (small molecules) that modify tissue distribution and clearance from blood stream.
R1.2-1.3: Inability to identify any new target	Low	Use of any potential target identified in WP4
R2.1: No role of calcium channels in xenograft models	Moderate	Test the role of partner proteins, of other targets provided by WP4
R2.2: No role of calcium channels in bone metastasis formation	Moderate	Test the role of partner proteins, of other targets provided by WP4
R3.1: Failure to obtain interaction data of TRP channels or TRP modules with ligands and protein partners	Low	Once the partners and ligands have been identified or designed, the lab expertise in biophysical techniques provides confidence to obtain interaction data.
R3.1: Failure to solve structures of TRP modules and complete TRP channels	High	State of the art crystallization techniques are well handled in the lab, including nanovolume crystallization. Collaboration with experts in crystallization using lipidic phases are planned. The risk is minimized in the case of TRP modules which will be treated as soluble proteins.
R3.2: Toxicity of the QDs	Moderate	Encapsulate organic dyes or GFP in lipidic nanocapsules or milled nanoparticles. The fluorescence intensity is quite high to enable *in vivo* imaging.
R3.2: Toxicity of the lipidic nanocapsules	Low	Preliminary experiments using xenopus embryos showed very limited or no toxicity of the lipidic nanocapsules
R4.1-3: Poor quality and/or quantity of RNA	Moderate	The screening for mutations will be performed on DNA, available with high quantity and quality (Task1). Work only on 36 sampes for the RNAseq assay (Task3)
R4.1-3: Contamination of healthy tissue" - healthy tissue is not always made entirely of 100% of non cancerous cells	Medium	Our two alternatives: a) We obtain normal DNA not originating from the peripheral tissue: this avoids contamination but this material is more difficult to obtain (research purposes only). b)We use samples from the peripheral tissue: simple and already available, and we apply a correction allowing up to 20% of contamination by tumoral cells
R5.1: Unacceptable toxicity	Medium	In case toxicity events are detected, targeted delivery with vector molecules directed against specific targets will be attempted
R5.2: Poor sensitivity and sensibility	Medium	Higher dosages will be screened. Alternate MRI sequences will be evaluated
R5.3: Lack of efficacy	Low	Combined therapies, immunotoxic, immunoradioactive….

Time table of deliverables

Work Packages	deliverables	Year 2	Year 4	Year 10
WP1	Increased fundamental knowledge of calcium channels regulation in prostate cells			
WP1	New targets for future diagnostic, prognostic and therapeutic applications			
WP1	New molecular tools for calcium channels study			
WP2	Innovative *in vivo* models			
WP2	List of potential therapeutical targets			
WP3	Domain mapping of TRP modules			
WP3	Structure of a complete TRP channel			
WP3	nanoparticles targeting channels of interest			
WP3	Assessment of nanoparticles efficiency in prostate cancer treatment			
WP3	New high resolution confocal methods			
WP4	List of transportome members with potential diagnostic/prognostic value			
WP4	Identification of critical mutations in our channels of interest			
WP5	Validation of nanoparticles as non-toxic contrast agent in animal models			
WP5	Transfer of nanoparticle technologies to human treatment			

5.2.2 VALORISATION, TRANSFERT ET EXPERTISE/ EXPLOITATION OF RESULTS, TRANSFER AND EXPERTISE

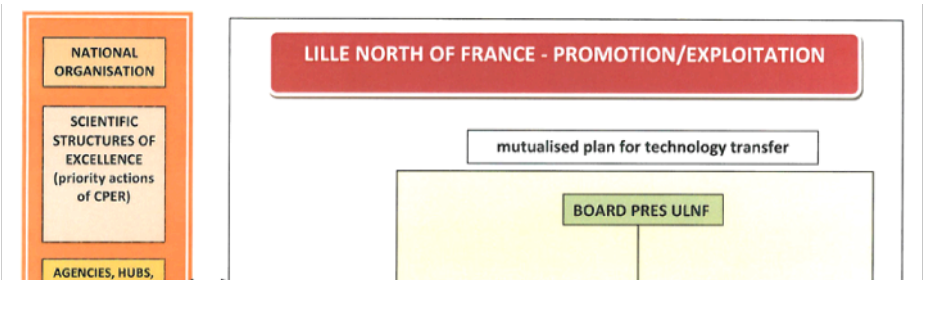
Operational activities carried out by Lille Nord de France Valo Centre:

- Awareness -raising, training and information for researchers
- Detection of research results with applied economic potential, and transferable to economic actors (all kinds of companies, either already in existence or/ being created). This identification work undertakes the necessary actions to assess scientific, legal, technical and economic factors, well beyond just active monitoring of research.
- Help in project development: scientific evaluation, identification of stepping stones to cross/obstacles to clear, with means available to attain the goals;
- Protection, exploitation of viable results to include, effective industrial protection ;
- Research of opportunities, markets and industrial operators likely to follow up research results, and to develop, exploit and commercialize them through key innovation strategies;
- Negotiation of research partnerships, of transfer and concession of rights on inventions and innovative know-how transferred to industry, plus the actual drafting of appropriated contracts and agreements;
- Incubation, creation, financial support mechanisms and monitoring of start-ups and spin-offs, promotion of research work within the PRES ULNF.

These development activities and procedures have been organized at regional level which is the right scale for high level skills to be mobilized and optimized. The organization of the Lille Nord de France Valo Centre provides every researcher in the Nord-Pas de Calais with quality service in terms of project engineering, help in drafting projects, the handling on intellectual property, mediation with addressing economic conditions, undertaking market research, and also with contracts or negotiating.

The PRES ULNF has decided to group together the existing development structures in a **"SATT" (Acceleration of Technology Transfer Company)** named "Nord de France Valo". This new structure is being set up in association with the University of Picardie Jules Vernes (UPJV, Amiens) and the University Rheims Champagne Ardennes (URCA, Rheims).
Considering the research areas of the future SATT, the PRES ULNF and its partners have devised their project with the nine competitiveness clusters of our inter-regional area, including: *ITRANS* (Transport), *NSL – Nutrition Santé Longévité* (Biology / Health), *PICOM* (ICT and Retailing of the future), *MAUD* and *UP-TEX* (Chemistry and Materials), *IAR* (Agro-resources), *TEAM ²* (Energies) and *AQUIMER* (Halieutics).
The SATT, as a unique service centre for researchers and companies, will become a privileged interlocutor for the competitiveness clusters in terms of the identification of innovative projects and collaborative partnerships.
It will integrate the incubation activities, project engineers (promotion, R&D, business) from specific regional actions, and a part of the activity of an ADER (regional economic development agency)…
The organization of the SATT will be based on the strengths of its activities and competences. A **first strand** will gather the legal, economic, fiscal, and strategic competences in relation to the intellectual property issues (management and exploitation of the patent portfolio) in a specific cross-disciplinary department. **A second strand**, the financial department (heart of the SAS – Simplified Stock Company) will be in charge of the financial and funding strategy as well as the recruitment policy. **A third strand** will cover the management and the follow up of projects such as industrial contracts (collaborative contracts and service agreements), European and international contracts, and national contracts (including the contracts with the ANR, the French national research agency). **A fourth strand** will be organized around both top-down and bottom-up activities of economic promotion including marketing research, economic benchmarking, and industrial prospecting for technology transfer.
Finally, a **disciplinary interface unit** will be organized around 7 thematic departments on Biology and Health, ICT, Materials science, Transport, Human and Social Sciences, Environment and Agro-resources. Follow-up committees will be set up for each thematic department to ensure their smooth functioning and to coordinate promotion activities with full respect to the rules of confidentiality and the code of ethics.

This central disciplinary structure will be built on the model of the existing *Biovalo* technology transfer office. *Biovalo* is an office of technology transfer that groups together the **CHRU** in Lille, **Lille2 University**, **INSERM** and **Eurasanté**. It is also a unique service provider which aims at simplifying the procedure to pursue, protect, package, and license to business the intellectual property generated from the research in Biology and Health. The French *AERES* (the national Evaluation Agency for Research and Higher education) has recognized the excellence of the *Biovalo* model. This is why *biovalo* intends to become the Department of economic development for biology & health and its legal and administrative structure will be the foundation for the creation of the SATT.
The SATT activities will address in particular raising awareness, detection, maturation, protection and management of the intellectual property, contracts and project management, transfer and incubation, and finally business engineering.



The Project of the data (obtained by the Laboratory of Excellence) exploitation and its potential transfer to the industry:

I. Publication record & communications.

The Laboratory of Excellence will successfully continue its scientific activity to obtain more data representing high scientific and industrial values.

1. During the past decade we have succeeded to publish our data in the well-known peer-reviewed journals that are highly acknowledged by the scientific community all over the world. The most important of them: **Cancer Cell** 2002; **J Clin Invest** 2003, 2007; **Cancer Res** 2004, 2006, 2010; **J Cell Biol** 2006; **Hepatology** 2008. The Laboratory of Excellence has as its primary goal to increase the quality and the scientific value of publications by submitting and publishing articles in the peer reviewed scientific journals with the impact factor exceeding 10.
2. The Laboratory of Excellence is also known to attend the scientific meetings organised by the famous scientific societies which are also attended by representatives from the pharmaceutical and biotechnological industries. The data from Laboratory have been presented at the most important congresses as: **FASEB, Gordon's conferences, Experimental Biology, IUPS (Japan), Biophysical Society** etc. During the last 5 years only 28 congresses and conferences have been attended by the director of the laboratory Prof. Natalia Prevarskaya. The Laboratory of Excellence will enlarge the number of the congresses and conferences to attend to increase the dissemination of information about Laboratory to the industry and its impact on the scientific community.

II. Valorisation of the scientific data to be obtained.

The data obtained during the last decade allow to open new perspectives for the Laboratory of Excellence as to perform and/or order pre-clinical studies, to propose certain services to pharmaceutical and biotechnological companies, to provide consulting and/or prognosis of the perspectives of the market development, to fill in the intellectual property applications, and finally to create and to run our own startup based on our knowledge and expertise.

1. A number of scientific articles already emerged and to be published in the nearest future allow us to develop and/or to collaborate with the leading pharmaceutical companies to perform our preclinical studies based on the data obtained. We have found some channels which represent particular interest as prospective biomarkers of tumour development and progression as well as potential pharmaceutical targets to be used *in vivo*. Currently collaborating with two leading pharmaceutical companies (**Johnson&Johnson** and **Pierre Fabre Médicaments**) we will seek to obtain more research contracts and engage more pharmaceutical companies to shift our studies to

more applied than fundamental science. We are currently negotiating the research contract with **Hybrigenics** pharmaceutical Company and **Bayer** chemical and pharmaceutical company. The Laboratory of Excellence intends to enlarge its network of collaboration with the industry to boost the valorisation of data.

2. The Laboratory of Excellence possesses High Output Electrophysiological Platform allowing the bioscreening of prospective pharmaceutical compounds. Using our cell models expressing channel of interest we can provide the respective service to any pharmaceutical company. We are currently developing mice *in vivo* xenograft model (in collaboration with **XenTech**) allowing us using both drugs and siRNA delivery strategies to target human cancer cell lines (in collaboration with **Dr. Bruno Pitard, INSERM UMR915**). This service will be also proposed to the pharmaceutical companies (as we have already proposed to **Hybrigenics**) in the future.
3. Being recognised experts in the field of cancer research we plan to **provide the consulting and/or prognosis service** to the companies as of the perspectives of the market development. This information is very valuable for the companies since the advanced scientific expertise is needed to objectively assess and to foresee the risk and the perspectives of e.g. drug development.
4. Our data allow to demonstrate in a clear way that some channels may be potentially used either as biomarkers or even as prospective pharmacological targets. One of the main goals of the **Laboratory of Excellence is to claim its intellectual property rights** on the discoveries and data obtained inside the Laboratory. For that exist such services as SAIC (industrial and commercial activities unit) at University of Lille1 taking care of exploitation of patents and intellectual property rights. As an example Lille 1 owns about 70 families of patents among which 12 are exploited by companies and 20 softwares with half of them exploited.
5. We plan in the nearest future to create and **to run our own startup** based on our knowledge and expertise. Again, as in the case of intellectual property the corresponding service of University of Lille1 will be used which hosts and helps projects managers of innovative enterprises and takes care of the link with laboratories. About 30 companies have been created since 2002 when a specialized department (Cré-Innov) has been created to help starts-up to raise.

III. The timetable of the valorisation process.

The following timetable is designed and based according to the experience obtained by the Laboratory of Excellence during the last decade.

1. The scientific activity of the Laboratory, the quality and the impact of publication on both scientific and industrial world will be developed continuously from today throughout its existence.
2. The Laboratory of Excellence will continue developing new approaches and techniques such as a new three laser confocal microscopy, high-output electrophysiological platform, approaches in using *in vivo* animal models and *in vivo* treatment tools.
3. In approximately **two years** the Laboratory of Excellence intends to fill in the patent applications regarding the use of some channels as the direct targets in prostate cancer treatment *in vivo*. This first step will be followed by further applications issue from the scientific activity of the Laboratory of Excellence.
4. In **two or three years** the Laboratory of Excellence will plan to create its own startup based on, e.g. the use of the high output electrophysiological platform. This startup has also intentions to help the Laboratory of Excellence to develop its own projects in applied science. At the beginning, it may be associated with the research contracts or service contracts with the pharmaceutical or biotechnological companies, followed by the independent both scientific and commercial activities. Again, a specialized department (Cré-Innov) created at University of Lille1 will be used to help our startup to raise.
5. The implementation of new technologies, strategies, and approaches resulting in both scientific and industrial activity of the Laboratory of Excellence to be developed in the coming **two-five years** will definitely influence the economy of France and the European Union as well.

IV. The impact on the diverse socio-economical activities.

1. The development of the Laboratory of Excellence will allow employing directly new people such as PhD-students, postdocs, engineers, technicians, secretaries etc.
2. The elaboration of new strategies and approaches will have its effect on the Pharmaceutical and Biotechnological Industry that in its turn, will help to create new job opportunities for the people from different social levels.
3. The development of Laboratory of Excellence will be accompanied by increase in the general level of expertise of the specialists working within the Laboratory. These specialists are tended to be qualified for various both scientific and industrial processes such as consulting, public communications, knowledge exchange, participation in different congresses and conferences etc.

5.2.3 ENSEIGNEMENT SUPÉRIEUR, INSERTION / HIGHER EDUCATION, INTEGRATION INTO THE WORKPLACE

With a turnover of € 23 054 304, the Universities of the region Nord-Pas de Calais represent 11 % of the continuing education activity of the entire French universities.
The Labex initiative is an opportunity for the PRES ULNF to go even further in its **lifelong learning offer towards:**

- **Master students and PhD candidates**; this new offer will rely on the excellence of our research laboratories:
  ° Introduction of Lifelong learning units in the students' initial curriculum "Becoming a lifelong learner";
  ° Assistance in the promotion of the students' qualifications and in their projects management;
  ° Tools to keep in touch with the University:
  - A biannual Newsletter that presents the latest research developments in the laboratories of excellence;
  - Pluri-annual Seminars directed by the world's leading specialists in the domain;
  - Creation of a Partnership Resource Center based on contributions by the researchers of excellence which will enable specific exchanges following the recent developments of the state of the art research.
- **Firms**; a tailor-built relations will be established via the biannual Newsletter but also by direct contacts with laboratories and alumni:
  ° Personalized welcome of the company staff in the laboratories of excellence;
  ° Access to high-level technological platforms and equipment;
  ° International scale seminars, animated by renowned specialists. They will be in common with those proposed to the students.
  ° Short-term placement scheme open to staff all along the year;
  ° Access to the Partnership Resource Center.

The PRES ULNF developed a range of specialized training courses combining specific units and research laboratories. This scheme, dedicated to the socio-economic world, is based on a network of help desks specialized in the management of careers.
To be found in these centers:
- Engineers able to consider requests from individuals and companies;
- Tools to serve professional development throughout life (support for career management, validation of prior learning, skills assessment, assistance in project identification, specific short courses, ...) offered by a team of occupational psychologists and counselors in training.

Finally, the PRES ULNF is engaged in numerous partnerships. For instance; it is active in *programs* funded by the Ministry of Industry bringing together the MEDEF (the largest union of employers in France) and OPCALIA (official training fund raiser for firms), *framework agreements* with specific companies on the engineering and training, it provides *tailor-made services* towards companies to introduce the validation of learning through experience into their "human resources" management,

or, in the scientific sector, by implementing *lab training sessions* of 4 to 5 days and seminars with researchers on specific themes.

The creation of regional **Doctoral Schools** in 2006 launched a new pooling process of professional training (*'Doctoriales'*, seminars open to the socio-economic world ...). This scheme aims at preparing PhDs for their functions as highly strategic decision-makers within private and public companies and their role as a medium for innovation within these structures.

This dynamics were reinforced at the time of the creation of PRES ULNF in 2009, the desire to develop a unit dedicated to promote PhD students outside academia was materialized through the identification of a "Careers and Employment Department" (Département Carrière et Emploi-DCE) within the Doctoral College.

I - The actual achievements

Actions towards doctoral students:

The shared regional system of support for professional integration of PhDs, coordinated by the DCE, has recorded about 500 entries in 09/10 (+89% compared to 08/09), divided between 16 thematic seminars with the following objectives:

- Develop knowledge of the business world: organization / strategy / role of innovation....
- Situate the research work in the economic and institutional environment
- Identify and promote skills, including "soft skills" acquired during doctoral training

Actions towards the regional socioeconomic world

- Regular contacts with MEDEF NPC and partnership at national level between MEDEF and the Bernard Gregory Association (ABG) have led to the organization in late 2008 in Lille of an event that brought together personalities from the academic and business world to discuss: "Why deprive oneself of PhDs?"
- Thematic seminars offered to students are mostly run by speakers from the regional socio-economic circles.

Actions in the border area

The PRES ULNF is a leading operator of the PRODOC project "(INTERREG IV for the period 2009 to 2012)

Project goal: work on the employability of PhDs in trans-borders areas so as to spur on extra business development.

Among the activities: Franco-Belgian "Doctoriales" (one seminar per year, with visits of French and Belgian firms); perception survey of doctoral degrees by firms in the trans-border region...

II- General development prospects for doctoral formation

The acquired experience and the parallel constitution of partner networks form solid foundations, essential to the development of a later stage: **a true philosophy of contracting with the socio-economic world at the regional level first and then within the framework of the Euro region.**

Some propositions of future prospects are:

° The need of communication tools to develop professional communication in English for all PhDs.

° Setting up of a "PhD into the Enterprise" label, which materializes a training track in which the student:

- Would have acquired knowledge in management / business strategy / project management ...
- Would have had the opportunity to learn first-hand (contacts, field experience) the notions of corporate organization

This label is a true training program, in conjunction with the professional project of the PhD student

°Extension of such a label to the trans-border area and more generally, the euro region area (Strategic position of the NPC Region)

Given the experience gained during four years of the project steering PRODOC, the contacts initiated with partners of the Flemish universities and the Franco-Dutch Virtual University to better cooperate on career offerings in the Euro region, the label "Doctor and Enterprise" could develop into a Euro regional label …

°Establishment of regional clubs "Universities – Business"

Contacts are underway with the MEDEF NPC and the CRCI to support a regional mission statement, following the framework agreement signed the 22 of June 2010 between the MEDEF, the Ministry of Education and the Ministry of Education Higher Education and Research.
This will create a link that brings together regional stakeholders to build a strategy and make it work. The Socio-economic commission of the PRES ULNF will be associated in this project
The goal (to be finalized) would be to lead, at least once per year, one or more initiatives to be exploited and promoted.

III - Involvement of the laboratory of excellence "*Oncochannel*" in postgraduate courses

1) PhD and masters

The laboratory, together with its partners, proposes new postgraduate courses and technological workshops that will be available for MSc and PhD students and for continuing education.
Partner laboratories propose to develop a new Master of Sciences entitled "Molecular Biophysics of Biological Membranes," which would supplement the existing Masters by proposing new and innovative teaching in the field of biophysics. In this framework, multiple interventions (lectures or technological workshops) will be provided in English by internationally renowned researchers. Various foreign researchers already give lectures regularly for the students of the first year Master of Biology and Biotechnology (Dimitri Gordienko: University of London, Alex Zholos: University of Belfast). We propose that these interventions be formalized through partnerships not only between laboratories but also between universities. This Master will ultimately, using partnerships with European Universities (Brussels, Belfast, London for example), obtain a European Master Label. The purpose of this Master would be to level the Master's training with research topics and technological approaches developed by on-site laboratories (including Inserm unit U1003 Cell Physiology laboratory, and Interdisciplinary Research Institute, Inserm Unit U761 at the Institut Pasteur de Lille)), i.e. essentially biophysical techniques.

This Master, at the crossroads of Chemistry, Biochemistry and Biophysics, would focus on new developments in membrane biophysics, both structurally and functionally. In particular will be discussed in the different Master's Modules:

- Biophysics of lipid-protein interactions in the membrane (membrane cohesion, lipid heterogeneity) by paying attention to their role in the formation of membrane domains (rafts).
- Physical methods for the study of membrane macromolecules. Basics of fluorescence. FRET. FRAP. Solid state NMR applied to the study of lipids and membrane proteins Macromolecular crystallography and scattering by concentrated solutions of macromolecules. Cryo-electron microscopy and three-dimensional reconstruction of biological macromolecules.
- Membrane coupling (receptor signal transduction)
- Biomechanics of the cell mechanical characterization, rheology, and mechanotransduction cellular response to environmental.
- Biophysics of membrane interaction with the environment. Cell adhesion on the extracellular matrix.
- Biophysics of membrane ion channels.
- Application to drug discovery and chemical biology :
    - Screening methods
        - Design of read out for high throughput screening,
        - Basics of screening technologies and implementation,
    - Medicinal chemistry of ion channels
        - Case studies,

- Specific issues and opportunities of ion channels as drug targets

This program will be intended for students with a biological /biochemistry / Pharmacy / Medicine background. Student will be selected on the basis of their CV. Not only will the results at the exams be taken into account but also their professional experience and their mobility. Priority will be given to students coming from other regions of France and to Erasmus students coming from other European countries.
This Masters will offer to the possibility of pursuing studies in a second year Master Degree in the already existing Master 2 of Biology and Health (Biophysics specialty) or the Master 2 of Biomedical Physics. This then will lead to a PhD of Biophysics in a laboratory of the University of Lille 1. Priority will be given to students engaged in a PhD co-directed by international partners. In addition, this Master 1 will offer the opportunity to train students to be attractive on the labour market in the field of business, instrumentation and biotechnology.
To develop these new topics, recruitment of three researchers/lecturers (one professor and two associate professor) in biophysics of membranes would be essential.

2) Supervision of students at Masters and Doctorate
It is necessary that the evolution of both the labour market and science be taken into account from the M2 degree and during the PhD. Indeed, it is generally accepted that the PhD is only a period during which students learn how to carry out research (especially technical skills) and how to produce knowledge (publications), though many other skills characterize the daily tasks of a scientist today. These functions include editorial tasks (writing papers, projects, reports), evaluation (of articles, projects), promotion of their work (Patents), seeking partners ... It is therefore necessary that students enrolling in Master 2 and PhD are sensitized as soon as possible to those functions that will be needed on the labour market. To do so, a proposed training will promote students awareness of "scientific writing and development of scientific work." The purpose of this course will be to educate, train future researchers and doctoral students, in particular on technological watch survey, quality and laboratory practices in research, business creation, drafting contracts, evaluating the cost of projects...
Finally, the LABEX should be an opportunity for rising additional funding to train doctoral students. Thus, the LABEX is expected to fund PhD students by offering them the opportunity to apply for LABEX research grants. We propose that the LABEX fund each year 2 new PhD students (PhD funding for 3 years) for a PhD that would be carried out under co-supervision by another partner, if possible a European partner laboratory.
The scientist function also implies mobility in the forms of long postdoctoral positions (one year or more) or of short working visits (2 or 3 months). The mobility of students during the PhD should also be strengthened by travel grants and scholarships awarded annually to the best projects submitted by PhD students. These scholarships will be awarded to enable PhD students to develop new experimental approaches in laboratories abroad and will enable them to shelter and meet their daily needs, but also to carry out their research during these three months. We plan to fund two short study visits per year.

3) Practical training for students during their PhD
PhD Students are generally trained and become competent for techniques directly available in their laboratory during their thesis, or through continuing education courses given by Inserm and CNRS institutions. Developing Technological Workshops, as they already exist during the first year Master of Biology and Biotechnology, would allow students to discover the theoretical underpinnings and practices of other approaches they wish to develop.
We propose to develop high technology workshops accessible to students in PhD or Master 2. The workshops will include, among others, training on Membrane Biophysics: patch-clamp, crystallography ... as a prolongation of the proposed Master of Membrane Biophysics.

4) Involvement of the laboratory in Lifelong Learning
With a turnover of € 23 054 304, the Universities of the region Nord-Pas de Calais represent 11 % of the continuing education activity of the entire French universities. The Labex initiative is an opportunity for the PRES ULNF to go even further in its **lifelong learning offer towards:**

- **Master students and PhD candidates**; this new offer will rely on the excellence of our research laboratories:
  ° Introduction of Lifelong learning units in the students' initial curriculum "Becoming a lifelong learner";
  ° Assistance in the promotion of the students' qualifications and in their projects management;
  ° Tools to keep in touch with the University:
  - A biannual Newsletter that presents the latest research developments in the laboratories of excellence;
  - Pluri-annual Seminars directed by the world's leading specialists in the domain;
  - Creation of a Partnership Resource Center based on contributions by the researchers of excellence which will enable specific exchanges following the recent developments of the state of the art research.

- **Firms**; a tailor-built relations will be established via the biannual Newsletter but also by direct contacts with laboratories and alumni:
  ° Personalized welcome of the company staff in the laboratories of excellence;
  ° Access to high-level technological platforms and equipment;
  ° International scale seminars, animated by renowned specialists. They will be in common with those proposed to the students.
  ° Short-term placement scheme open to staff all along the year;
  ° Access to the Partnership Resource Center.

The PRES ULNF developed a range of specialized training courses combining specific units and research laboratories. This scheme, dedicated to the socio-economic world, is based on a network of help desks specialized in the management of careers.

To be found in these centers:
- Engineers able to consider requests from individuals and companies;
- Tools to serve professional development throughout life (support for career management, validation of prior learning, skills assessment, assistance in project identification, specific short courses, ...) offered by a team of occupational psychologists and counselors in training.

Finally, the PRES ULNF is engaged in numerous partnerships. For instance; it is active in *programs* funded by the Ministry of Industry bringing together the MEDEF (the largest union of employers in France) and OPCALIA (official training fund raiser for firms), *framework agreements* with specific companies on the engineering and training, it provides *tailor-made services* towards companies to introduce the validation of learning through experience into their "human resources" management, or, in the scientific sector, by implementing *lab training sessions* of 4 to 5 days and seminars with researchers on specific themes (For example in biotechnology, in the form of Workshop Technology : Patch-Clamp, crystallography, fluorescence imaging)..

5.2.4 GOUVERNANCE DU LABEX/ GOVERNANCE

The overall management of the project will be performed via close interaction between participating team leaders (Direction Committee), scientific task leaders (Scientific Committee), management infrastructure (supported by the "Nord de France University" and International Advisory Board.

Professor Natalia Prevarskaya, INSERM U1003**,** is defined as **project coordinator** (the role of the coordinator is summarized in the Table below).

Table : Role of the coordinator.

	Follow-up	**Communication**

Scientific	Initiating and leading regular meetings	Group communication and collaboration between teams and tasks
	Planning, monitoring and reporting of progress, validation of deliverables and milestones	Organization of the communication and knowledge dissemination towards the scientific/industrial community
	Proposal and enforcement of solutions/strategies in case of critical problems (delays, technical difficulties, disagreements, etc.)	Facilitation of the potential and future exploitation/valorisation of results, so far as possible
Financial, administrative & contractual	Proposition of a "consortium agreement" to the partners to settle issues of intellectual property, confidentiality, publication, etc.	Intermediary between LABEX and the PRES (transfer of information, reporting at the end of each scientific period)

General points of management and financial aspects of projects will be discussed by the **Direction Committee** (Coordinator and the heads of the participating teams). The Coordinator administers the funding allocation between the partners according to the agreements, keeps records of the financial management, and informs the corresponding French national agency about the financial transfers.

If necessary, decisions will be taken at the **majority of votes** (one vote per task leader, or one vote per partner according to the cases). Nevertheless, in case of arbitration difficulty, the coordinator will make the **final decision**.

Each of the tasks is assigned to a particular team and each team is responsible for the quality, reliability, and timeliness of the part of the work assigned.

The task leaders will be responsible for the scientific and technical administration of their task. Their role will consist in:

- ✓ organizing the work on a day-to-day basis
- ✓ monitoring the progress of partners' work for their task and reporting to the coordinator
- ✓ collecting the partners' contribution and preparing the deliverable reports relative to their task at the corresponding time schedules
- ✓ detecting any problem and reporting it to the coordinator; if possible, finding or proposing a solution
- ✓ implementing the decisions taken during meetings.

The project participants will regularly keep in touch by means of the telephone and/or e-mail with the project coordinator, to communicate the data obtained, which will permit exchanges with not only "views and news", but also with experimental material in the form of graphs, recorded raw data and results of the analysis and also to maintain general awareness of the course of the works performed. Therefore, the **management** of the labex will be **transversal** between the different partners and their locations. The **minimal official report** timetaken will be 6 months, the time sufficient to monitor the efficacy of the teams' contribution, to adjust the research schedule of the interrelated teams, and to efficiently supervise the work conducted to fulfill the specific objectives of the research proposal. It remains at the project coordinator's discretion as to whether the data obtained is valuable enough and usable in proceeding to the next related issue, and should any data arise that was not envisaged within the framework of this research proposal, to make a decision as to the further course of the studies.

Every 3 months project coordinator will arrange a **Coordination meeting** for the heads of the participating teams and for the researchers from the Coordinator's team in charge of the corresponding partnerships **(Scientific Committee)** to allow the visual demonstration and discussion of the data obtained. The strategic decisions will be made at these coordination meetings regarding the priority of specific tasks with respect to potential reward, their change or modification depending on world progress in the field, discontinuing some tasks or adoption new ones based on the potential outlook for preliminary data obtained.

General **Scientific meetings** for all Labex members will be organized yearly to allow the visual demonstration and the common discussions of the data obtained. The authors' participation in the collaborative scientific works to be published as articles in leading peer-reviewed specialized scientific journals will be decided according to the each individual's and team's contribution to the data to be published. The decisions on any changes in the direction of the studies will be taken at coordination meetings as described above.

Each 2 years, at the **"Milestones analysis"** coordination meeting to take place at the project coordinator's laboratory, all the participating teams will present their final data to compose a general report on the fulfillment and probable industrial and /or clinical implementation of the data obtained.

Apart from scientific Direction Committee, two specific committees will be created:

- **"Labex-transfer" committee**, that will be in charge of the strategy of the exploitation and the valorisation of the results obtained by the members of the Labex;
- **"Labex-training and education" committee**, which will be in charge of the Labex-related educational programmes and their actualisation, the organisation of the "student work-shops"…

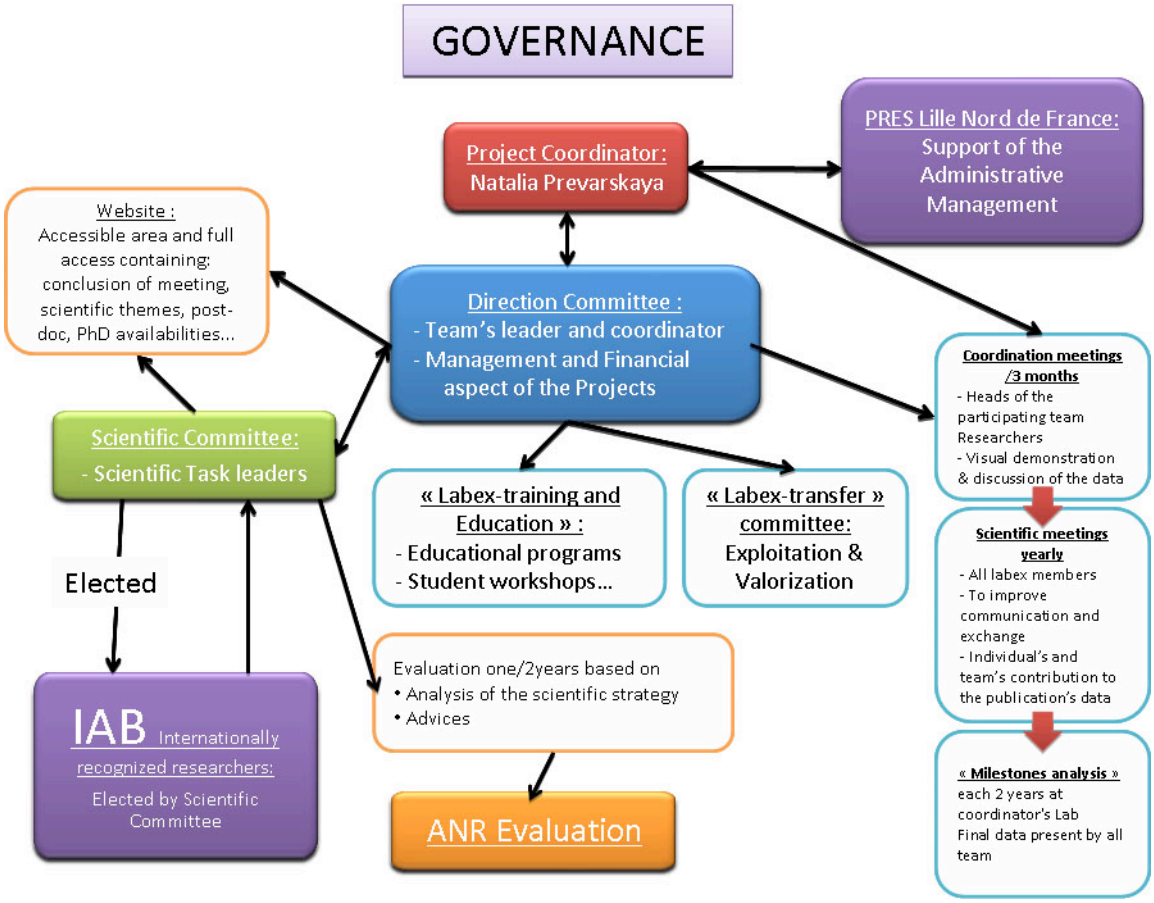
The **website** dedicated to this Labex will be created as soon as the project is funded where the scientific themes, major scientific achievements per year, post-doc and PhD availabilities, future scientific meetings and work-shops, publications, patents and the education programmes will be presented. The Labex website will consist of a public and an internal area. All agreements, guides and procedures will be put on the internal website for quick reference. Finally the internal website will contain an upload feature, to store reports, conclusions of meetings, and background information.

An independent **International Scientific Advisory Board** will be elected by the scientific committee of the Labex. Since the Labex project has interdisciplinary character, all corresponding disciplines will be represented by the internationally recognized researchers. Each two years this advisory committee will evaluate the results obtained by the Labex teams, analyse the scientific strategy for next years, give their objective recommendations and prepare the evaluation report. For this purpose specific "Advisory" meetings will be organized in Lille. The evaluation reports will be sent to ANR.

The **PRES Lille Nord de France will be the support for the administrative management** of the Labex project.

This support has following objectives:

1. Financial management
2. Setup of the 'management infrastructure' (Boards, website, templates)
3. Support of Day-to-day management (helpdesk and back-office)
4. Support to the coordination of periodic reporting and reviews
5. Support the organisation of all meetings (incl. telephone conferences, video coferences, webmeetings)
6. Support the updating of the Workplan and the Plan for Use and Dissemination
7. Support the timely maintenance of all agreements of legal nature



5.2.5 ATTRACTIVITE/ATTRACTION

Every one of the members of higher education within the PRES-ULNF organises an integrated welcome and arrival facilities for their international students and researchers (from PhD to senior professors) but the procedures have not as yet been standardised.

Today however, within the PRES, the **Euraxess** Service and Mobility centre offers its expertise, that has been developed since its creation in 2004, greatly facilitating mobility schemes for professors and researchers, together with their families when needed. A range of services are on offer to cater for specific needs such as: housing, administrative papers, on-hand assistance with integrating the family (locating appropriate maternity needs, day-nurseries and schools), organising day-to-day life, practical information, etc. The welcome procedure corresponds to the international standards of researchers, and clearly aims to remove each and every obstacle that can impair international mobility, removing the hassle of inevitable issues, thus contributing to the attractivity and appeal of an international academic and research experience within the Nord-pas-de-Calais region.

It is an absolute necessity to restructure further the regional organisation of the welcome procedure of first-class researchers as an actual strategy to enhance the appeal of our higher education institutes. This will be achieved by developing a specific welcome platform for international research staff and students that will focus on the existing mobility centre.

This fully-comprehensive centre will be an essential lever in the following:

- the regional centre for resources and networking (pooling experience and skills, on-line regional guide,…)

- choice of accommodation offers
- range of tailor-made services
- information on available French as a foreign language programmes (prior to arrival and on the spot)
- individual support
- discovering the cultural and economic assets of the region
- highlighting social activities for the international community
- intercultural training for local admin staff on each campus
- working closely with local government (the Prefecture for official papers, CAF family allowance Office, CPAM Social Security centre, etc…)

The know-how devised from this new platform will bring extra added-value to the stay of all the international researchers, facilitate their stay, and enhance the image of research in the North of France.

Euraxess, The European Services Network: the European network for mobility and service centres that gives information and offers personalised services for researchers within Europe and from third countries. http://ec.europa.eu/euraxess

As part of its international relation policy, Lille 1 University annually hosts over 4000 international students representing over 20% of the total student population. These students are welcomed as part of exchange programs, agreements between universities or as independent candidate. The International Relations Office strives to facilitate the arrival and integration of these students and provides all necessary information throughout their time at university. In 2007, Lille 1 University received the European quality label awarded by the European Commission for its approach to mobility.

In the context of exchange programs, the Lille 1 University:

- welcomes international students from within programs such as Erasmus, Erasmus Mundus CREPUQ, MAUI, NEA, or through inter-university agreements
- helps and guides students through the administrative, housing and integration in the components of Lille 1
- Gives French courses at the House of Languages (Lille 1 University)
- Provides academic recognition back in the home institution with the European Credit Transfer System (ECTS)

A first clue to attract students is to provide a high quality education in connection with a high level of scientific research. To do so, a policy of regular invitation of foreign scientists together with an initiation to up-to-date science technologies is necessary, associated with travel missions funding. In addition, a policy of regular recruitment of permanent staff with high qualification is also a condition for attracting young scientists.

I - Recruitment of PhD students and young or senior postdoctoral fellows:

The laboratory is already an attractive institution for foreign scientists. In the context of international programs, the laboratory regularly invites foreign professors and post-doctoral research scientists. For instance, an associate professor position has been granted by the French Department of Education and Science to Professors Y. Shuba (Institute of Physiology, Kiev, Ukraine), D. Gordienko (Medical College of London) or A. Zholos (Belfast University) these last years. The invited professors not only participate to research in the lab but also provide high level lectures in English to post-graduate students. Furthermore, In the last years, several postdoctoral position have been offered to young (Maya Yassine (These Bourse Erasmus): Libanon, Dimitra Gogka (EMBO): Greece, Georges Shapovalov (Post Doct - FRM (3 Ans)), Vacheslav Lehenk'yi (Post Doct (Ater) University), Sergii Khalimonchyk (Post Doct (Ater) University) : Ukraine, Pilar Flamenco : Argentina) or senior foreign scientists (A.Zholos, UK, Yaroslav Shuba: Ukraine, Alessandra Fioro Pla (Dai Visiting Professors 2010 - Pres): Italy).

It is important that our laboratory still be an attractive research centre for foreign scientists. To that purpose, developing PhD funding and travel grants through LABEX will be an opportunity to attract European and non European foreign students to carry out a

PhD in our laboratory. In addition, during the next ten years, we will increase the proportion of lectures given by foreign scientists in first and second year Master.

II - Recruitment of permanent staff:

The recruitment policy of our laboratory consists in attracting brilliant young researchers (with the methodological skills required by the laboratory) and presenting them for the competitive exams held by the University's research bodies. The laboratory staff has thus been considerably strengthened and has become a united, dynamic and motivated multidisciplinary team which is capable of carrying out projects in the medium term. **In the few years, we are expecting to attract more permanent research and teaching staff and to recruit young research scientists by means of INSERM and University of Lille1. This recruitment of permanent staff is necessary for the creation of a new Master formation. Indeed,** to develop these new topics, recruitment of three researchers/lecturers (one professor and two associate professor) in biophysics of membranes would be essential.

III - Equipment investment for educational purpose:

Owing to funding that have been granted to the laboratory, we have been able to modernise the existing Cellular Physiology Laboratory equipment and complete them with modern molecular electrophysiology and calcium imaging techniques (described in the research project), which are essential to our project (a patch clamp for recording the activity of 'unitary channels', a system for measuring exocytosis in single cells, two calcium imaging installations and an electrophysiology set-up combined with a confocal microscope have been installed in the laboratory in recent years). Moreover, thanks to the "Nord- Pas de Calais Regional funding" we have equipped our laboratory with a "High throughput electrophysiological screening" platform: Set-up "Fly-ion" and 5 conventional patch-clamp set-ups. This platform will be used for the research of specific physiological agonists and antagonists of ion channels and also for testing pharmacological channel modulators. In the last years, the laboratory has enabled the creation of a true molecular electrophysiological training centre in the North Region. This platform is used in teaching workshops for postgraduate students and for research scientists (both French and foreign) working in public or private companies.

In addition, Lille 1 University funding has allowed buying a fluorescence equipment for undergraduate and postgraduate students. This setup is used for calcium imaging experiment demonstrations. We need in the next years to equip our teaching laboratories with more microscopic fluorescence setups. So far, with one setup, we can only perform demonstration for students. In order to be able for the students to carry out experiments, we would need at least 2 more imaging setup comprising each an inverted microscope, a CCD camera, a fluorescence light source with relevant filters and an imaging software to record and analyse the data. In addition, in order to develop a real technological platform for educational purpose, which would not only rely on research platforms, we propose to equip our teaching rooms with 1 complete setup of electrophysiology.

5.3. STRATEGIE DES ETABLISSEMENTS TUTELLES/ STRATEGY OF THE SUPERVISING INSTITUTION

Scientific Strategy for the LABEX

A) The scientific strategy of the PRES - University Lille de France

The Establishments of Research and Higher Education supporting the LABEX project have a common research strategy within the PRES University Lille Nord de France (PRES – ULNF)». Through this strategy, the PRES-ULNF aims to be an international leader in research/training in certain scientific fields of high socio-economic impact with a domino effect to other fields with high research potential. It also aims to drive the territorial and socio-economic development through innovation. The roadmap for this strategy includes the following priorities:

- Organization of research around excellent scientific clusters
- Increasing the international attractiveness of research and training programs.
- Enhancing the education and lifelong training programs.
- Reinforcement of the research impact on the territorial and socio-economic development through innovation

Organization of the research around excellent scientific clusters

The scientific strategy of the University Lille Nord de France consists in the structuring of the research around excellent clusters having already a strong international recognition with a domino effect for sectors with high research potential. The scientific programs of these clusters correspond to the priorities of the 7th Framework Program for Research and Technological Development (FP7) in particular, Health, Information and Communication Technologies; Nanosciences, Nanotechnologies; Materials and new Production Technologies, Environment (including climate change), Transport and Socio-economic Sciences and Humanities. They also correspond to the three priorities of the National Strategy of Research and Innovation (SNRI):

- Health, food and Biotechnologies;
- Environment urgency and Ecotechnology;
- Information, communication and nanotechnologies.

For each cluster, the partners' strategy is based on the creation of six LABEX around the research groups A+ enhanced by some research groups A presenting a high scientific potential. Within the framework of the PIA, the research perimeter of excellence is based on the following projects:

- A Labex in the field of Science and Technology of Communication and Information "Information COmmunications and Nanotechnologies"
- Two LABEX in the field of Biology/Health:
  - EGID – European Genomics Institute for Diabetes
  - Oncochannel - high-technology interdisciplinary approach for innovative medicine
  - RespInfEX – Infections respiratoires : pathogenèse, prévention et traîtement
- A LABEX in the field of the Environment "Physico-Chemistry of the Atmosphere"
- A LABEX in the field of Materials Science "Materials under complex Environment"
- A LABEX in the field of the Human Social Sciences "Argumentation"

Each LABEX is created on the basis of a scientific project with a flexible structure in charge of supporting management by project, multidisciplinary research and emergence of new projects on challenging issues. A particular attention is paid to the emergence of scientific leaders recognized by international, European and national evaluation. A logistic support will be devoted for the preparation and management of both ANR and European projects. Clusters have to intensify the international partnership through various forms of research association (LEA, LIA GDRI,…). In addition to the European space, they should reinforce their partnership with countries with high scientific capacity, such as North America, China, India, South Korea, Brazil and Russia.

Cluster are expected to develop multidisciplinary research within each cluster (hard /soft in ICT; physics and chemistry in Materials Science and Environment; biology, chemistry and imaging in Biology and Health, ...) and between clusters such as SHS with ICT; physics with all sectors; biology with chemistry, ICT, computer science and mathematics.

The scientific equipment constitutes also a priority. It concerns the reinforcement of the capacity of scientific facilities through an ambitious investment policy and the allocation of human resources. The objective is the positioning of the scientific facilities at the international standards. Particular interest is given to the access of these facilities to the scientific community by encouraging various forms of hosting and the establishment of "Project Hotel". PRES – ULNF provided a support for EQUIPEX projects related to excellent clusters. The management of these projects will be conducted in synergy with LABEX through an integrated management.

Enhancing the internal attractiveness

The attractiveness is a fundamental part of the scientific policy of the University Lille Nord de France. The development of clusters of excellence is subjected to the ability of these clusters to attract both highly talented researchers and students to the master and PhD degrees. A proactive policy of attractiveness will be implemented with the support of Local Authorities. This policy will be based on the allocation of specific resources to attract and keep talented researchers. These means include both the scientific environment (scientific equipment, logistic support, scientific position, research grants post-doc, high-level training for masters and doctoral programs,..), and the establishment of attractive careers. Attractiveness will be developed through tracking actions and the implementation of various procedures such the PRES international Chair and an extensive use of the local, national and European opportunities such as the chairs of excellence of the Region, the ANR program (Chair of Excellence program and post-return, ..) and the PEOPLE / Marie Curie FP7 program.

Enhancing the education and life-long training programs

Clusters already rely on a large base of training programs (masters, engineering schools and doctoral schools). The objective of the PRES -ULNF is to emerge international training programs to attract talent candidates and to train students in an open international environment. This action aims to establishing a recruitment pool of doctoral students and to train executive graduates to creative and scientific approach. Specific resources will be devoted to these training programs to reinforce their national and international attractiveness.

The life-long raining constitutes also a priority for the clusters policy. This training beneficiates of the great achievement and expertise in this field of the PRES-ULNF members. The doctoral program will be re-organized by the creation of a doctoral school for each cluster. Doctoral Schools will focus on providing doctoral students with an additional high-level scientific training, interdisciplinary openness and an awareness of intellectual property and societal and international issues. They should also widely implement the international mobility and the doctoral attractiveness program.

Enhancing the research impact on the territorial and socio-economic development through innovation

Innovation is a key element for both the promotion of research and for the economic and social development. Both the innovation and technology transfer activity constitute a high priority of the PRES-ULNF. Substantial support will be given to the establishment of an innovation ecosystem in partnership with the support of the Local Authorities, the State and economic partners. Priority is given to establishing strategic relation with leading companies, to support small and medium companies and to reinforce the partnership with the competitiveness clusters. A particular attention is paid to the territorial development through the involvement in the competitiveness clusters in the Region (I-Trans, NSL, PICOM, MAUD, UPTEX, AQUIMER, TEAM2), the Economic Excellence Clusters created within the framework "Regional Scheme for Economic Development (SRDE) and the park of technology: EURASANTE (Health/Biology), Haute Borne (Sciences/Technology), Euratechnologies (IT) and Plain Image (image creation).

The development of the innovation/transfer activity will be enhanced by the establishment of a SATT (Society for the acceleration of the transfer and technology) comprising members of the PRES-ULNF and the Universities of Amiens and Reims. The SATT will be in charge of the maturation of innovative projects, management of intellectual property and technology transfer. It will also provide a high level of expertise in legal, financial and management of partnership projects with the industry.

B) Strategy for the LABEX "Oncochannelopathies: high-technology interdisciplinary approach for innovative medicine"

Many biological research centers, belonging to the top national as well as the european level (all teams involved in the project were evaluated in 2009 by international committees and were ranked among the A+ and A quotes in France) have emerged on the site of Villeneuve d'Ascq. They are combining topics as diverse as nanotechnology, structural biology, proteomics, glycobiology, genomic, physiology and cell biology. Each field of research has required specific

equipments for which the PRES-UNLF has strongly participated by helping the implantation of efficient high technology plate-forms, all of them approved by a national qualification: TGRE/RA of RMN, IBISA platforms of proteomics/glycobiology and cell imaging.

A new research topic: oncochannelopathies has recently emerged from the research on intracellular calcium and ionic channels in the physiopathology of the prostate supervised by the group leader N. Prevarskaya. The PRES-UNLF has thus decided to particularly reinforce this thematic by recruiting in the same geographical place a critical mass of methodological and scientific expertises combining a wide range of approaches: molecular electrophysiology (scientific coordinator's team, partner 2); glycobiology (the team of Jean-Claude Michalski, partner 3); imaging and mass-spectroscopy (the team of Isabelle Fournier, partner 4); genomic (the team of Xavier Vekemans, team 5); structural biology (the team of Vincent Villeret, partner 6); nanotechnologies (the team of Rabah Boukherroub, partner 7) as well as external partners from clinical and pharmacological researches (biochemistry and drug design (the team of Benoit Deprez, partner 8) and imaging-assisted therapy of tumors (the team of Serge Mordon, partner 9). This future network will generate a fantastic environment leading to a synergy allowing the birth of a worldwide institute devoted to the understanding of the prostate organ. This organization " Oncochannelopathies: high-technology interdisciplinary approach for innovative medicine" could result from the national call Labex.

We believe that the excellent potential of this LABEX, together with the high quality management and the strong support of partners through additional human resources and scientific facilities, will present an attractive environment for talented scientists and students. This environment will also be conducive for student training, innovation and the development of researches for the challenging issue concerning health and socio-economic development.

The university Lille1 largely supports this project. In addition to the actual human resources, scientific equipment and building infrastructure, the university is committed to providing subnational additional support for this LABEX, in particular:

- Human resources support (4 faculty members, doctorate and post doc grants, positions for inviting talent international researchers for long period,..)
- Building a new animal house and space for welcoming the needed plat-forms with the help of the "Plan Campus"
- Financial support for the equipment of animal experimentation, structural biology and electrophysiology.

Oncochannel laboratory of excellence is **also supported by Inserm** (co-supervising institution of the scientific coordinator). See their following support letters.

Support letters from the industrial partners will be forwarded with the final ratified document on 22 December.

Université Lille1
Sciences et Technologies

DIRVED
Direction de la Recherche,
de la Valorisation et
des Etudes Doctorales

Commitment of the Université Lille1 – Sciences et Technolgies for the Labex "Oncochannelopathies, high-technology interdisciplinary approach

for innovative medicine"

The scienific strategy of the Unversity Lille1 concrerning the LABEX is presented in section 5.3 of the proposal.

The Labex "Oncochannelopathies, high-technology interdisciplinary approach for innovative medicine" concerns a strategic field of the university Lille1. Our objective is to be an international leader in this field and to be a major actor in the health sector for driving the socio-economic development through innovation.

Research groups involved in this project were ranked A+ and by the 2009 AERES evaluation. They combine topics as diverse as nanotechnology, structural biology, proteomics, glycobiology, genomic, physiology and cell biology. This labex is supported by an excellent scientific equipment and efficient technology plate-forms, with a national qualification: TGRE/RA of RMN, IBISA platforms of proteomics/glycobiology and cell imaging. They are also supported by a wide training program in biology, biotechnology as well as in nanotechnology.

We believe that the excellent potential of this LABEX, together with the high quality management and the strong support of partners through additional human resources and scientific facilities, will present an attractive environment for talented scientists and students. This environment will also be conducive for student training, innovation and the development of researches for the challenging issue concerning health and socio-economic development.

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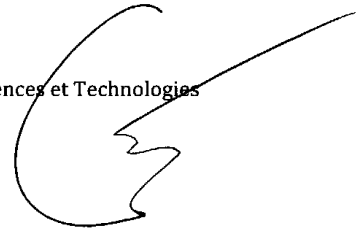
Friday, November 19, 2010

Professor Philippe Rollet

President of the Université Lille 1 – Sciences et Technologies



Cité Scientifique - Bâtiment A3 - 59655 Villeneuve d'Ascq Cedex
Tél. +33 (0)3 20 43 44 37 | www.univ-lille1.fr

Instituts thématiques

Inserm

Institut national
de la santé et de la recherche médicale

Le Président-directeur général
101, rue de Tolbiac
75654 Paris Cedex 13
Tél. +33 (0)1 44 23 60 62
Fax : +33 (0)1 44 23 60 65
E-mail : janine.gaudinot-gomez@inserm.fr

Dossier suivi par :
Mme Elli Chatzopoulou
Responsable du Pôle
Partenariats et Politique de site
Département des Partenariats
et des Relations extérieures
Tél. +33 (0)1 44 23 63 24
Fax : +33 (0)1 44 23 60 15
E-mail : elli.chatzopoulou@inserm.fr

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Madame Natalia Prévarskaya
Directrice
Inserm U.1003
Laboratoire de Physiologie cellulaire
Université Lille-1 – UFR de Biologie
Bâtiment SN3, 2ème étage, porte 232
59655 Villeneuve d'Ascq Cedex

Paris, le 19 NOV. 2010

Objet : Appel à projets « Laboratoires d'excellence » des Investissements d'Avenir

Madame,

Vous allez soumettre le projet « Oncocanalopathies : approche interdisciplinaire 'high-tech' pour la médecine innovante » dans le cadre de l'appel à projets « Laboratoires d'Excellence » des Investissements d'Avenir, pour lequel vous avez sollicité l'Inserm.

Ce projet, qui implique plusieurs équipes de recherche de l'Inserm, vise à catalyser localement une synergie d'action des meilleures équipes de recherche régionales dans le domaine des cancers impliquant des aberrations de canaux ioniques, appelées « oncocanalopathies ». Les retombées économiques et diagnostiques sont attendues en tirant notamment parti des d'approches structurales et nanotechnologiques appliquées aux oncocanalopathies.

En tant qu'institution, l'Inserm est sur le principe favorable au dépôt de ce projet, soutenu et porté par le PRES Université Lille Nord de France, qui répond à des enjeux majeurs pour les recherches en sciences de la vie et de la santé.

Vous comprendrez aisément que notre engagement formel ne pourra être décidé qu'à l'issue de l'évaluation effectuée par les jurys internationaux, et en fonction de l'ensemble des décisions qui seront prises sur les différents appels à projets des Investissements d'Avenir.

Par ailleurs, vous savez que nous avons proposé que, si les jurys le demandaient, Aviesan puisse être amenée à émettre un avis, non pas sur la qualité scientifique des projets que les jurys seront parfaitement à même d'apprécier, mais sur leur adéquation avec les grandes orientations proposées par les instituts thématiques multi-organismes. Pour répondre à cette éventualité, je vous serais reconnaissant de bien vouloir me faire parvenir le projet finalisé lorsqu'il sera remis en réponse à l'appel à projets.

Vous félicitant pour le travail que vous avez effectué, je vous prie d'agréer, Madame, mes salutations cordiales.

Pr. André Syrota
Président-directeur général

Copie : M. Sergheraert, Président du PRES Université Lille Nord de France
Mme Mazingue, Déléguée régionale de l'Inserm

5.4. RELATION AVEC LE MONDE SOCIO-ECONOMIQUE/ CONNECTIONS TO THE SOCIO-ECONOMIC WORLD

Impact of *Oncochannel* on the quality of life.

Based on the national population projections EUROPOP 2008, within the next 20 years the number of people aged 65 years or over in the total population will rise by approximately 50 % and that of people aged over 80 years will almost double. This not only represents **a great socio-economic challenge**, but will also lead to an **increase of the incidence of diseases of the elderly including prostate cancer (PCa)**. Indeed, PCa is the most common noncutaneous human malignancy and the second most lethal tumor among men, with the highest incidence in industrialized countries. All men are at risk for developing PCa. About one man in six will be diagnosed with PCa during his lifetime. Various parameters (age, race, and family history), among which age is undoubtedly the greatest risk factor, may contribute to the risk of developing PCa. About two-thirds of all PCas are diagnosed in men aged 65 years and older.

The complex management of the different stages of PCa, the improvement of detection techniques, and the increasing variety of treatment options led to a growing interest in a multidisciplinary approach for the diagnosis and treatment of PCa over the last few years. An example of a multidisciplinary approach in PCa can be found in the treatment of newly diagnosed high-risk PCa for which the objectives of treatment are two-fold. There is a need for local tumour control, as well as a need for treatment of microscopic metastases likely to be present but undetectable until disease progresses. Therefore, the optimal treatment approach in these patients should be multimodal.

***OncoChannel* will undertake an integrative and systematic approach in order to exploit proteins involved in ion transport, i.e. selected members of the transportome, as novel drug targets and/or biomarkers appropriate for therapeutic, diagnostic and prognostic interventions for prostate cancer.**

By combining the expertise of 7 academic teams, 6 high-tech infrastructures and 2 industry / SME collaborative partners *OncoChannel* is the first coordinated project to investigate in an integrative way all aspects of channelopathies in PCa. *OncoChannel* thereby introduces an entirely new paradigm to oncology aiming to **overcome treatment failure of PCa**. We will target as yet unexploited but highly promising pathways, centred on ion channels and their impact on the major intrinsic properties of PCa: neuroendocrine differentiation, chemo-resistance and invasion / metastasis. We will determine the expression of transportome members and their contribution to PCa progression. This knowledge in itself already constitutes a major breakthrough. The positive impact of this knowledge will be reinforced by the development of concepts and tools for diagnostics and therapy of PCa. The approach is fully derived by **reverse-translation** from clinical oncology and **proof-of-concept** will be achieved using innovative models closely mimicking PCa. The results of the *OncoChannel* project, i. e. novel biomarkers and preclinically validated concepts for treating PCa, will therefore be of **high relevance** for **clinical oncology, patient organizations and SMEs / industry**.

The impact of the knowledge produced by our project is not only restricted to PCa. The integrated knowledge of the transportome of PCa, the diagnostic and therapeutic concepts and tools derived thereof will be of great value for **other malignancies**, too. Again, it should be emphasized that basic and cellular physiology has been mostly neglected up till now in molecular oncology. Thus, it is our firm belief that *OncoChannel* work on PCa will for example cross-fertilise research in pancreatic, liver, colon and breast cancers, melanoma, leukaemia, brain tumours or other frequent and difficult-to-treat tumour entities.

In addition, **other disciplines** will also profit from *OncoChannel's* results, since some of our concepts, targets and tools can be applied to other cell types, too. Such examples include **immune, neurological, urological and dermatological diseases** and those affecting the **vascular system**. *OncoChannel's* work on the PCa channelopathies can serve as a blueprint for

triggering **the respective research communities** to apply our paradigm to these non-oncological diseases as well. Hence, our dissemination activities will explicitly address these beneficiaries. Conversely, *OncoChannel* will profit from new developments in these areas.

The results to be obtained are likely to be patentable. We expect that significant commercial value can be created with new patents and related to tumour-specific transport proteins and miRNAs. This view is supported by **our industrial partners**. Their participation will also ensure compliance with regulatory and quality control requirements during preclinical development processes. In addition, our industrial partners have available all resources to promote validated oncological targets toward pharmaceutical development. All together, therefore, this will promote the forefront position and growth of the French and European biomedical industry thus building a competitive advantage over US and Asian companies.

In conclusion, the implementation of this new Laboratory of Excellence "Oncochannel" and successful delivery of the project's milestones will ultimately improve survival and quality of life of patients with PCa, a "most common to men" cancer. Moreover, we are convinced that Oncochannel's concepts will be applicable to other diseases as well. This will have a prominent impact on the economy of France and European Union as well since billions of euros are spent every year on the health and social security systems.

Impact of *Oncochannel* on the Cost of Health Care.

Prostate cancer (PCa) is one of the most important medical problems facing an aging male population. Therefore, the cost of health care relative to this disease has been rising constantly for the last decades due to the increase in life expectancy. This disease is accompanied by a cohort of health disorders such as urinary tract infections, incontinence, sexual impotency after surgery, and psychological disorders such as mental depression. This of course reduces the quality of life of the patients and increases the cost for the Health Care Services.

The prostate cancer itself but also its surgical treatment (radical prostatectomy) is responsible for some of these troubles and one may need alternate therapies, such as Focal Therapy, to reduce the cost of the treatment and its negative effects on the quality of life of the patients. As an example, Focal Therapy requires only one day hospitalization without surgery complication instead of 7 days after radical prostatectomy with serious complications. Therefore, reducing the number of prostatectomy, when possible, will reduce hospitalization costs. In addition, by a reduction of the medications used for incontinence or sexual impotency, a treatment like FT will lead to a decreased cost for Health Services. Furthermore, radical prostatectomy leads to prolonged sick leaves which could be shortened by Focal Therapy.

Impact of *Oncochannel* on the creation of new activities.

The development of the Laboratory of Excellence and the creation of a startup will allow employing directly new people such as PhD-students, postdocs, engineers, technicians, and secretaries etc. that will create new job opportunities and diminish unemployment.

The elaboration of new strategies and approaches will have some effect on the Pharmaceutical and Biotechnological Industry that in turn will help to create new job opportunities for people from different social levels.

The development of Laboratory of Excellence will be accompanied by an increase in the general level of expertise of the researchers working within the Laboratory. These specialists will tend to be qualified for various new scientific and industrial processes such as consulting, public communications, knowledge exchange, participation in different congresses and conferences etc.

Lille 1 university has got an incubator (Cré-innov) which helps to the emergence of new companies in collaboration with laboratories and Lille 1 is thus indirectly creating jobs.

Lille 1 university directly creates jobs (PhD, post doc, technicians, engineers, secretaries,...) when national or European projects are accepted and then indirectly when results of these projects are further exploited by companies. The "Exploitation Department", SAIC, sells patents licensing,

negotiates technological transfer and provisions of services to companies which help them to acquire and develop new technologies and which thus involves indirectly the creation of new and usually highly qualified jobs.

5.5. EFFET D'ENTRAINEMENT POTENTIEL/ PULL EFFECT

This project of *Oncochannel* Laboratory of Excellence will combine strong electrophysiological and biochemical expertise of the coordinator's team with biophysical, structural, computational and clinical approaches, allowing a more in-depth investigation of ion channels involved in prostate cancer development. This should lead to the **acquisition of important results inaccessible by regular means**, and significantly advance the state of the art of cancer research while providing useful insights into its treatment.

Multiple high profile scientific papers resulting from this project will have **the additional effect of further improving France renown in the international scientific community**, attracting even more quality research personnel to the country.

The collaborative nature of this project should provide **an additional effect by establishing closer scientific ties with involved groups.**

Identification of ion channels associated with cancer onset will provide drug targets that can be used by pharmacological industry, thus stimulating its development and eventually resulting in the creation of effective drugs. This will certainly advance theoretical knowledge and will allow formulating successful strategies by combining molecular dynamic simulations and other theoretical approaches with experimental ones, thus providing a better insight into the function of involved ion channels and providing, for the first time, an important avenue of **interaction between scientists specializing in experimental and theoretical approaches**.

Indeed, these interactions between scientists, both within the Laboratory of Excellence and outside of it through collaborations with industrial partners, will allow creation in Lille of a new **"Multidisciplinary centre for screening and treatment of prostate cancer"** which will materialize a training track of "New methods for PCa detection and treatment". Within this centre, the development of a "Spin off" of the Laboratory of Excellence partners is expected for the commercialisation of screening tests, treatment systems (lasers, fibres, etc ..ex: Ekkyo : spin off U703 www.ekkyo.com ; software for the planning and the control of treatment (ex: d'Aquilab : spin off de l'U703 : http://www.aquilab.com).

***OncoChannel* will catalyze the development in France and Europe of innovative biophysical research applied to cancer by assembling research teams working on oncochannelopathies into national and European networks.**

The impact of the knowledge produced by our project is not restricted to PCa. The integrated knowledge of the transportome of PCa, the diagnostic and therapeutic concepts and tools derived thereof will also be of great value for **other malignancies**. Again, it should be emphasized that basic and cellular physiology have been mostly neglected up till now in molecular oncology. Thus, it is our firm belief that OncoChannel's work on PCa will for example cross-fertilise research in breast, pancreatic, liver cancer, melanoma, leukaemia, brain tumours or other frequent and difficult-to-treat tumour entities. **It should therefore allow the members of *OncoChannel* to enter European and international networks on cancer and to introduce the *OncoChannel's* knowledge in these communities.** OncoChannel will certainly profit from conceptual, experimental or technological developments within "neighbouring" networks and could potentially profit from the concepts and models developed by these consortiums.

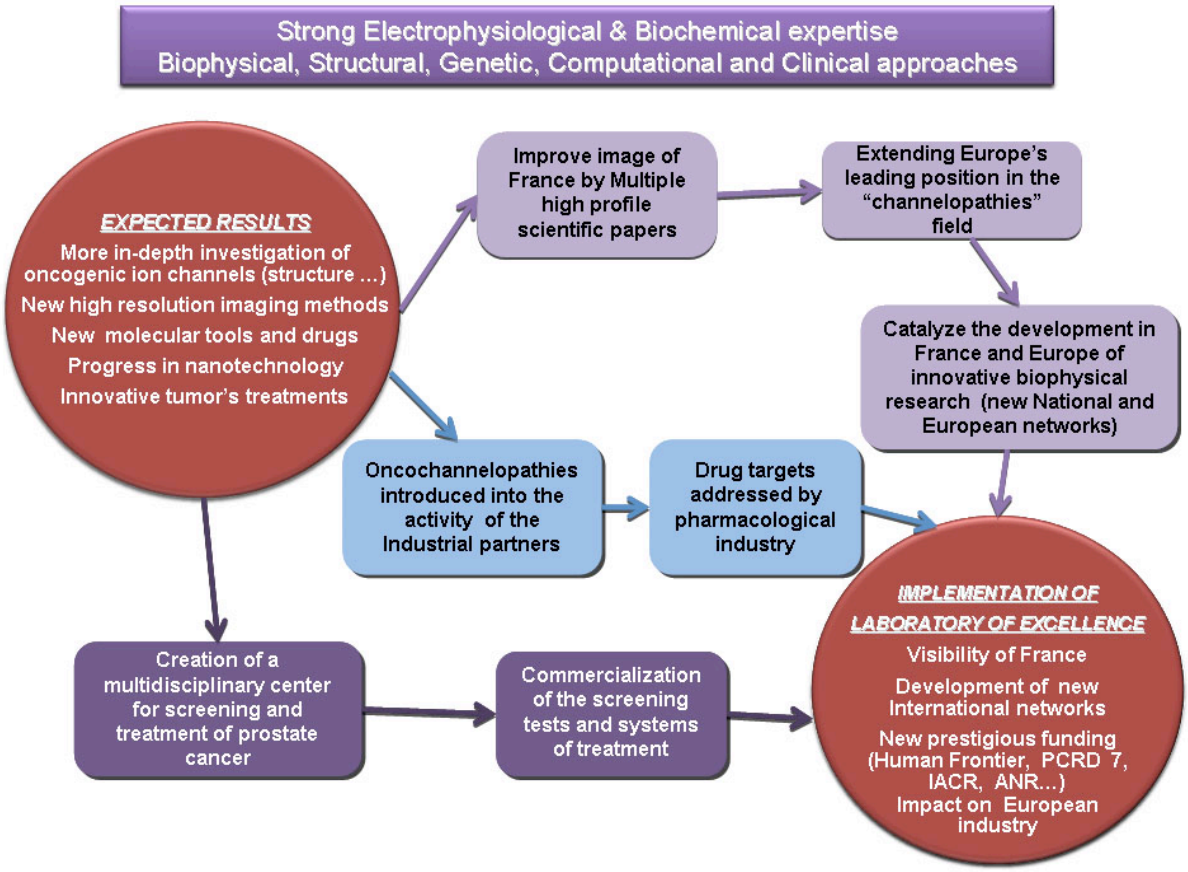
Indeed, when the OncoChannel's integrated interdisciplinary approach will be applied to different types of cancer, a new European network could be created which would bundle and focus expertise in this important and rapidly growing research area. This European Network on Ion channels and Cancer will become an even stronger European consortium by integrating the world

leaders in basic oncological research with clinically oriented oncologists as well as pharmaceutical industry. This will be of overall strategic value by opening a completely new approach to combat cancer and thereby **extending Europe's leading position in this important emerging field**.

New tools and methodological concepts of Oncochannel will be also applied to other pathologies (**immune, neurological, urological and dermatological diseases)** thereby allowing the Laboratory of Excellence to be involved in new "non-oncological" European networks.

In addition, **the results obtained by** *OncoChannel* would be of great importance for the frontier disciplines such as nanoscience for exemple. Close interaction of scientists at the border of their respective disciplines will definitely enlarge the spectrum of the project applications and thereby will have a strong "pull effect" on the Laboratory's of Excellence future position in scientific word.

OncoChannel's efforts put into industrial partnership (at least 3 industrial collaborations per team supported by contracts) could allow a huge "pull effect" on the Laboratory of Excellence since oncochannelopathie's application will be introduced into the activity of the industrial collaborators of the OncoChannel partners.



In conclusion, we are **expecting that the implementation of the Laboratory of Excellence will improve the visibility of France in the 'channelopathies' field** and allow us to develop new networks (at the regional, national and international levels) which in turn will help to obtain new prestigious funding: French ANR (http://www.agence-nationale-recherche.fr/); French InCa (http://www.e-cancer.fr/); European PCRD 7 (http://cordis.europa.eu/fp7); European Marie Curie (http://ec.europa.eu/research/research-eu); Association for International Cancer Research (http://www.aicr.org.uk/ApplyingforResearchGrants.stm); Human Frontier (International Program https://extranet.hfsp.org/AllApplication/Default.aspx).

These potential funding, contracts with industrial partners, establishment of our own start-up on oncochannelopathies could allow OncoChannel to become financially autonomous in the future and, even more, to contribute to the common challenge of the European economics growth.

6. JUSTIFICATION SCIENTIFIQUE ET FINANCIERE DES MOYENS DEMANDES / FINANCIAL AND SCIENTIFIC JUSTIFICATION FOR THE MOBILISATION OF THE RESOURCES

6.1. JUSTIFICATION DES MOYENS DEMANDES (SUR 10 ANS) / JUSTIFICATION FOR THE MOBILISATION OF THE RESOURCES

6.1.1 PROJET DE RECHERCHE/ RESEARCH PROJECT

- *Équipement / Equipement (coût unitaire supérieur à 4000 euros HT)*

We have participated in the application for "Equipment of Excellence":

- 3 partners (LCP, BCSG and NBI) are participating in High-throughput & ultra-high content screening microscopy Facility "ImaginEx BioMed". The proposal consists in setting up a new Facility dedicated to the screening and analysis based on functional high content screening microscopy. This equipment will help for the realization of WP1, 5.
- 2 partners (BDD and MIT) are involved in PharmaR3. This proposal is intended to accelerate compound optimization and targeting by providing cutting edge *in vitro*, *in vivo* and *in silico* tools for ADME profiling. This equipment will be helpful for WP2, 5.

However, the Labex will be viable even if the Equipex will not be funded.

Cell Imaging:

The successful outcome of the research project requires a technology that allows high-speed detailed imaging of the phenomena on many living samples. The future of cell or tissue imaging is the super-resolution, ie a technique able to visualize objects smaller than the theoretical limit of 250 nm resolution. This new methodology, called SIM PALM or STED (Structured Illumination Microscopy, Photo-Activated Localization Microscopy, Stimulated Emission Depletion Microscopy), is now commercially available and allows a resolution better than 50 nm. This opens the prospect of visualizing live cell events occuring in very small organelles, typically intracellular trafficking. The devices required in this project will therefore improve the existing park of microscopes and open the doors to the super-resolution. The required device (SIM) will complete the existing confocal and greatly enhance its capabilities.

Cost: 478,500 euros

Electrophysiology:

The Patchliner® is a fully automated patch clamp platform offering medium throughput and vast experimental freedom. Because of its high data quality, robust recordings and superior level of automation, the Patchliner® is an exceptional tool routinely used by the pharmaceutical industry, CROs and academic institutions.

Applications range from routine ion channel screening to sophisticated experiments on primary cells. A consistent and high success rate is seen across a range of different cell lines.

Up to 48 cells can be analyzed without user intervention making the Patchliner® an ideal tool for compound screening.

Alternatively, protocol changes can be made on-the fly meaning not only that assay development is more efficient, but that research type experiments are also possible with increased throughput.

On the Patchliner®, eight cells are recorded in parallel and thanks to the rapid cycle times and high success rates for completed recordings, the Patchliner® achieves a data throughput of 500 data points per day.

Such flexibility combined with the throughput and high success rates places the Patchliner® in a league of its own.

Cost: 240,000 euros

Nanotechnologies:

The preparation of the nanomaterials is complicated and uses hazardous compounds. The need of a closed hood is necessary to fully protect the worker against the aerosols.

Cost: 111,700 euros

MRI:

3D printer: Dimension uPrint Plus

U703 has developed disposable phantom for MRI. In order to evaluate different sizes, a specific software was created. This software allows to print 3D prostate molds. These molds are used to generate MRI compatible phantoms. Nanoparticles could be inserted into these phantoms in order to evaluate the detection limits of MRI. A 3D printer will be necessary to generate the 3D molds.

Cost: 25,000 euros

Histologic slides reader: NanoZoomer 2.0 (R.S.) of Hamamatsu Photonics

To be able to finely localize the nanoparticles in the organe, the histologists will need to make a great quantity of sections in it and mount them on glass slides for examination. They need to observe a huge number of serial sections and an automation of this process will help the study. This system converts glass slides into digital slides by scanning them at high resolution and high speed. Digital slides can be stored as high-definition, high quality image data. These slides are used as ground truth in the retrospective studies for the validation of the cancer detection algorithms.

Cost: 200,000 euros

Genomics :

Bioinformatic workstation for evolutionary analysis. This device is indispensable for the data analysis of the high throughput profiling WP4.

Cost: 5,990 euros

- *Personnel / Personnel cost*

1 - One of the priorities of the laboratory of excellence is to invite top level researchers **to develop the most challenging axes** of the project. In this context we have already identified a candidate for the nanotechnology work package. We propose Alex Savtchenko, (Ph.D 2004-till now Principal Scientist, Invitrogen), for **a chair of excellence** for 3 years renewable. He has a strong background in nanoscience/biophysics and a broad scientific knowledge of cell biology including advanced technical expertise in microscopy, high content screening, and image analysis, extensive hands-on knowledge of all electrophysiology techniques and a great experience in drug discovery applications. We plan to maintain the chair during the entire project according to the achievments of each work packages.

2 - To attract internationally recognized **senior scientists** already having a tenure position in their respective university, we are planning to create 2/4 positions of invited professors per year for 3/6 months.

3 - The structural project will require a **senior post-doctoral fellow** for an initial period of 5 years. The strategy is to hire a young talented researcher already involved in the structural study

of membrane proteins, and thus who has expertise in state of the art techniques in the field of protein expression in eukaryotic systems and biophysical characterization of these proteins. After the project is launched, a period of 3 to 5 years should allow the labex to obtain the first breakthroughs in the TRP field and thus allow this young researcher to apply successfully for a permanent position (CNRS, INSERM, university). Once the project is started (at year 2) a PhD student will also join the team. In case we don't obtain a permanent position, the post-doctoral position must be extended for up to ten years. A post-doctoral candidate has already been identified, Dr. Prakash Rucktooa. Dr. Rucktooa is currently working in the laboratory of Prof. Titia Sixma, at the Netherlands Cancer Institute in Amsterdam,a leading laboratory for structural biology. Dr. Rucktooa is studying nicotinic receptors and homologs, characterizing these proteins with various biophysical methods in order to provide detailed information into the ligand binding process and regulation in this pharmaceutically important family of ion channels. He is also managing the lab participation to European consortia in the field of structure-function relationships on membrane proteins.

4 - To make this project viable, a **highly qualified staff** is required. Whereas the researchers and technicians in place are recognized for their skills in microscopy and electrophysiology, the new devices required for this project will need more people to make them efficiently work. Wherever possible, most of teams will have **a postdoc or an engineer position** per year. However, according to the progress of the work or if a hard point is encountered, the team concerned may be temporarily assigned to another staff support. The following needs have already been identified:

- A post-doctorate will be in charge of the experiments directly related to the project concerning MALDI Imaging for markers studies.
- Building database of transportome polymorphisms: 6 months [1-6]
- Molecular evolution analysis of polymorphisms in the transportome: 8 months [7-14].
- Filter analysis of mutations detected in the exome sequencing project
- an engineer for confocal microscopy / SIM
- A software engineer will manage the imaging platform and will integrate the algorithms and methods developed for the automatic cancer detection and staging from the multiparametric MR images

In summary, the total personal cost will be:

- Scientific international chair of excellence: 1,000,000 euros
- Senior scientist: 2/4 invited scientists per 3/6 months for 10 years: 850,000 euros
- Scientific staff: 6 engineers or postdocs per year for 10 years: 2,500,000 euros

- *Prestation de service externe / Subcontracting*

1- The work package 4 "Profiling" needs the subcontracting from the core genomic common service:

- Systematic screening of mutations in the transportome exome
- Construction and analysis of a database of species-wide nucleotide polymorphisms in the transportome
- Expression profile of the transportome spliceosome

For the whole project (3 years), we will need 263,000 euros (see the 4 invoices from Service commun de Génomique".

2 - The NanoBioInterface group of IRI has some equipment in common with the Institute of Electronic, Microelectronic and nanotechnology (IEMN, UMR CNRS 8520). For the technology and the surface analysis: 15,000 euros/per year for 10 years (150,000 euros)

3 - MRI studies will be performed with a 7 T MRI apparatus (Biospec System 70/20, Bruker) located at the DHURE (Departement Hospitalo Universitaire de Recherche Expérimentale). Numerous histological slides will be performed on the preclinical model. 25 euros X 1500/year per slide, ie 50,000 euros for 10 years

4 – For preclinical animal models, we will need subcontracting by Oncodesign company establishing prostate cancer animal models: 120,000 euros for the whole project

5 - The IbiSa Bioimaging Center is a core facility dedicated to cellular imaging. The use of the different microscope will cost 8000 euros per year (80,000 for 10 year)

The total cost for subcontracting will be: 626,000 euros

- *Missions/ Travel*

- International conferences per year: 15 x 1800 = 27,000 euros
- National meetings or workshop per year: 8 x 800 = 6400 euros
- International workshops for PhD students: 4 x 800 = 3200 euros
- Invitations for conferences and participation of PhD students training of internationally recognized researchers: 5 x 1600 = 8000 euros
- Costs of International Advisery Board = each 2 years for 6 people : 30,000 euros

The total amount for travel is: 746,000 euros

- *Autres dépenses de fonctionnement/ Other working costs*

Cellular Biology expenses:
Antibodies (lysosomal, endosomal, ER and Golgi markers); pH and Ca2+ fluorescent probes ; Transfection products (Lipofectamine, Fugene Amaxa system); siRNA Oligos; Consumables for confocal microscopy

Cell culture expenses:
Cell culture medium; Plastic consumables and Antibiotic selection agents.
Biochemistry expenses:
Consumables for western blot experiments; Radioactive tritiated mannose; Consumables for ultracentrifugation

Molecular Biology expenses:
Plasmids expressing different tags (GFP, RFP, 3X-FLAG); PCR reactifs; Plasmid and PCR purification Kits; RNA extraction kits; Consumables for PCR and Q-RT-PCR reactions.

MALDI imaging :
chemical reagents, high purity solvents, ITO glass slides, consumables for micro-spraying and micro-spotting devices, enzymes, peptides, proteins, LC columns, small cinsumables for mass spectrometry, fluids for mass spectrometers (N2, Ar, He) as well as publication fees for high impact journals.

Nanotechnologies :
- Chemical reagents
- Biological reagents
- Substrates
- Glassware

In average and taking into account the peculiarity of our disciplines, we estimate the total working costs of consumables as 400,000 euros per year, ie 4,000,000 for the 10 years.

6.1.2 PROJET PEDAGOGIQUE/ EDUCATIONAL PROJECT

- *Équipement / Equipement (coût unitaire supérieur à 4000 euros HT)*

In order to develop a new formation of Membrane Biophysics, we need in the next years to equip our teaching laboratories with more microscopic fluorescence setups and electrophysiological setups. In order to be able for the students to carry out experiments, we would need at least 2 more imaging setup comprising each an inverted microscope, a CCD camera, a fluorescence light source with relevant filters and an imaging software to record and analyse the data. In addition, in order to develop a real technological platform for educational purpose, which would not only rely on research platforms, we propose to equip our teaching labs with 1 complete setup of electrophysiology.

Cost of a complete electrophysiological setup: 77,500 euros
Cost of a complete imaging setup: 30,000 euros
Total cost: (2 imaging setups and one patch-clamp setup): 137,500 euros

- *Personnel / Personnel cost*

One PhD grant a year. This gives 10 students to be funded in the 10 years project.
Cost of a PhD student: 90,000 euros/3 years.
Cost of 10 students: 900,000 euros/10 years.

- *Missions/ Travel*

For PhD students: two travel missions per year for 10 years. Each 3 months mission should comprise: lodgement (800 euros/month), living expenses (600/month), travel (one return ticket 600 euros) and experiments (6000 euros). This makes 12,000 euros per student, therefore 216,000 euros for a 10 years project (18 students).

6.1.3 VALORISATION/ EXPLOITATION OF RESULTS

- *Personnel / Personnel cost*

For our molecular electrophysiology platform and a future setup based on this platform, we need a engineer qualified in electrophysiology: 43,000 per year (430,000 for 10 years)

- *Missions/ Travel*

Participation in workshops and collaborations with industrial partners. Travel per year: 800 euros (8,000 for 10 years).

- *Autres dépenses de fonctionnement/ Other working costs*

Consumables related to the platform: 11,000 euros per year (110,000 for 10 years)

6.1.4 GOUVERNANCE/ GOVERNANCE

- *Personnel / Personnel cost*

  We will ask the University of Lille 1 to support a part time secretary/administration position.

- *Missions/ Travel*

  Costs of International Advisery Board = each 2 years for 6 people: 30,000 euros

6.2. AUTRES RESSOURCES / OTHERS RESOURCES

In general, we have 3 sources of funding:
- recurrent funding from INSERM, CNRS and from the Research Ministry during 4 years (for last quadrennial contract) for the common project of our laboratory;
- funding for specific projects from different International, European, French (The National League against Cancer, ANR, INCa…) and regional organisms 'Regional League against Cancer', Region of Nord-Pas de Calais …
- industrial partners

We are presenting here three examples of fundings obtained by the Labex partners:

Fundings obtained by the LPC (except salaries and postdoc fellowships)

Inserm dotation: 160,000 euros per year
Ministry of Education: 60,000 euros per year
Regional funding for equipment: molecular electrophysiology (500,000 euros), confocal microscope (480,000 euros).
Renovation of laboratory premises: 1,100,000 euros

Funding origin/ Name of coordinator	Project title	Duration	Amount (k€)/year
ANR / N. Prevarskaya	***Rôle du canal ionique TRPM8 dans la physiopathologie de la prostate et des testicules : implication dans la reproduction***	2006 - 2010	37.5
ANR / C. Slomianny	***FENOTIP – Microfluidique et nanoélectrodes pour la spectroscopie électromagnétique de cellules uniques.***	2005 - 2008	4.5
INCa / N. Prevarskaya	***The roles of TRPM8 and TRPV6 ion channels in prostate cancer: functional studies and molecular targeting for the elaboration of new therapeutic strategies.***	2006 - 2009	130
INCa / N. Prevarskaya	***Caractérisation fonctionnelle et moléculaire du canal cationique membranaire, le canal TRPM8 : implication dans la cancérisation de la prostate.***	2007 - 2010	25
INTAS / N. Prevarskaya	***Normal and pathological roles of TRPM8 cold receptor***	2006-2009	4.5
National League / N. Prevarskaya	***La signature calcique cellulaire : un marqueur tumoral potentiel. Ciblage moléculaire des canaux ioniques pour le diagnostic, le pronostic évolutif et le traitement du cancer de la prostate.***	2010 - 2012	85
National League / N. Prevarskaya	***Développement d'un modèle de souris Knock-down du canal TRPM8 : vers une meilleure compréhension de la physiopathologie de la prostate.***	2007 - 2009	19
National League / L. Lemonnier	***Rôle du canal TRPM8 dans la cancérisation de la prostate.***	2007 - 2009	5
Pierre Fabre /J&J N. Prevarskaya	***Rôle des canaux TRP dans la différenciation des kératinocytes humains***	2004-2008 2008-2010	35 80
Région Nord-PDC / M. Roubaraki	***Exposition néonatale aux oestrogéno-mimétiques et cancer de la prostate***	2007 - 2010	30

Granting obtained by MIT since its creation [2004-2010]

Years	Program	Coordinator	Title	Granting
2004-2007	ACI « Jeunes Chercheurs et jeunes Chercheuses » (ACI JC4074)	I. Fournier	*Developments of peptides/proteins and transcripts MALDI-TOF MS Imaging of tissue sections and biopsies: MALDI Image*	**85 k€ H.T.**
2005	Transfer help CNRS	I. Fournier	Technological transfer to Bruker Daltonics	**70 k€ H.T.**
2006-2009	Institut de Recherche en Santé du Canada (IRSC)	M. Salzet	*Rôle des Prohormones convertases dans la réponse immunitaire innée*	**450 CAD**
2006-2008	Institut National du Cancer (INCA)	P. Ducoroy / I. Fournier	*Biomolecules Imaging Mass Spectrometry in Cancer Research*	**120 k€ H.T.**
2007	CNRS-DPI	I. Fournier / M. Salzet	*MALDI-TOF/TOF instrument for the MALDI MSI project*	**80 k€ H.T.**
2007	CNRS-SDV	I. Fournier / M. Salzet	*MALDI-TOF/TOF instrument for the MALDI MSI project*	**70 k€ H.T.**
2007	IFR 147	M. Salzet	*MALDI-TOF/TOF instrument for the MALDI MSI project*	**30 k€ H.T.**
2007-2010	National Agency for Research (ANR), PCV Program, (PCV07 188992)	I. Fournier	BioSpIM : Biomolecules Specific Imaging	**260 k€ H.T**
2008	University Lille 1-BQR	I. Fournier	*MALDI-TOF/TOF instrument for the MALDI MSI project*	**50 k€ T.T.C**
	Contract with IPSEN-Pharma	M. Salzet	MALDI MSI of pharmaceutics	**65 k€ T.T.C**
2008-2012	National Agency for Research (ANR) Blanc Program, (BLAN08-2_368559)	G. Bolbach / I. Fournier	FUN-MALDI : FUNdamental MALDI for MALDI imaging	**356 k€ H.T.**

2008-2009	OSEO-Eurasanté	M. Salzet	Technological transfer to Imabiotech Start-up	**60 k€ H.T.**
2010-2013	National Agency for Research (ANR) PIRIBIO Program, (PIRIBIO09_449204)	PI: J-P. Both Lille PI: M. Wisztorski	*MASDA-EYE :* Mass Spectrometry imaging Data Analysis in EYE	**116,297 k€ H.T.**
2010-2011	The Internationale Stichting Alzheimer Onderzoek (ISAO)	PI : H. Steinbusch France PI : I. Fournier	Hippocampus analyses by MALDI imaging from human brain suffering of Alzheimer diseases	**50 k€ H.T.**
2010-2012	KORANET (7PCRD)	PI : Y-M. Park France PI: I. Fournier	EPIMOD : Epigenetics in ageing & neurodegeneration	**14,5 k€ H.T.**
2010-2013	ARCIR/FEDER (Nord Pas de Calais Region)	I. Fournier	MALDI-LTQ-Orbitrap instrument for identification of proteins in MALDI MSI	**300 k€ H.T.**
2010-2014	FRSQ-CREC (Canada)	PI: R. Day PI: M. Salzet	MALDI imaging & Developments of PACE4 inhibitors for prostate cancer curing	**400 CAD H.T.**

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Grants obtained by the NBI partner [2004-2010]

Years	Program	Coordinator	Title	Granting
2005-2008 3 years	**ANR Blanc**	R. Boukherroub	Nanostructuration des surfaces de diamant hydrogéné et dopé au bore : applications en biosciences	**217 k€ H.T.**
2006-2010 3 years	**ANR Jeunes Chercheurs et Jeunes Chercheuses**	S. Szunerits	Génération des plasmons de surface localisés (LSPR) : détection sensible d'interactions biomoléculaires	**150 k€ H.T.**
2006-2010 3 years	**ANR PNANO**	D. Stiévenard (IEMN)	Conception et réalisation d'un nanocapteur à base de nanofils silicium pour la détection électrique d'interactions entre polypeptides	**70 k€ H.T.**
2007-2010	**ANR PFTV**	L.Heliot	Microscopy for molecular dynamics and interactions in cell and tissues	**400 k€ H.T.**
2010-2013	**ANR Blanc**	A.Harduin-Lepers	Molecular and cellular regulation of beta1,4-GalNAcT-II in physiological and pathological states	**300 k€ H.T**
2009-2012 3 years	**FP7-KBBE-2008-2B**	Päivi Heimala (VTT, Finland)	Nano- and microtechnology -based analytical devices for real-time measurements of Bioprocesses (NANOBE)	**350 k€ H.T.** (CNRS, IEMN + IRI)
2009-2013 4 years	**Programme transfrontalier Interreg IV** « Coopération territoriale européenne » France - Wallonie – Vlaanderen	Jean-Pierre Vilcot (IEMN)	Microtechnologies appliquées à l'instrumentation pour la biologie : biocapteurs à performances étendues sur base de résonance plasmonique de surface	**196 k€ H.T.**
2006-2010 4 years	**FUPL** Université Catholique de Lille	D. Stiévenard (IEMN)	Micro et NanoBiosciences	**6 k€ H.T./ year**
2007-2008 2 years	Defence Science and Technology Laboratory, Malvern, UK	V. Thomy (IEMN)	Testing & Design for an Integrated Electro Wetting System	**30 k€ H.T.**
2007	C'nano Nord Ouest	R. Boukherroub	Etude des propriétés optiques de nanofils de silicium : effet de la terminaison chimique	**10 k€ H.T.**
2008	C'nano Nord Ouest	D. Stiévenard (IEMN)	Nouveau capteur photovoltaïque à base de nanostructures 0D et 1D	**14 k€ H.T.**
2008	Programme interdisciplinaire CNRS : Interface Physique Chimie Biologie – Soutien à la prise de risque	R. Boukherroub	Etude de la Méthylation des Histones par l'Exaltation Raman de Surface (SERS)	**30 k€ H.T.**
2009-2011 30	Programme : Recherche Exploratoire et Innovation (REI), Direction Générale de	D. Stiévenard (IEMN)	Nouveau capteur à haut rendement et à bas coût à base de nanofils et de nanoparticules	**42 k€ H.T.**

months	l'Armement			
2009	Programme interdisciplinaire CNRS : Interface Physique Chimie Biologie – Soutien à la prise de risque	P.-O. Angrand (IRI)	Application des Quantum Dots à l'étude du développement et de la cancérogénèse chez le poisson-zèbre	**50 k€ H.T.**
2010	Programme interdisciplinaire CNRS : Interface Physique Chimie Biologie – Soutien à la prise de risque	L. Héliot (IRI)	Mise en place du premier microscope par diffusion Raman stimulée (SRS) par Exaltation de Surface (SERS) pour l'étude de la méthylation des histones	**50 k€ H.T.**
2010-2011 2 years	Accueil Jeune Chercheur – Région Nord Pas de Calais	R. Boukherroub	Application des Quantum Dots à l'étude du développement et de la cancérogénèse chez le poisson-zèbre	**88 196 €**
2006-2007 2 years	**CNRS–JSPS** exchange program with Tokyo University of Agriculture and Technology, Japan 2 years	R. Boukherroub	Porous Silicon-directed Silicon Nanowires Growth. Optical and Electrical Properties of the Nanohybrid Material	**8300 € H.T/year**
2006-2007 2 years	**PAI PROCORE** exchange program with University of Erlangen, Germany 2 years	R. Boukherroub	E-beam Nanopatterning of Chemically Modified Semiconductor Surfaces for Applications in Biosciences	**2000 € H.T/year**
2006-2009 4 years	**CMEP Tassili** exchange program with UDTS, Algeria 4 years	J.-N. Chazalviel (Ecole Polytechnique)	Greffage d'espèces organiques sur silicium et croissance de couches minces de *a*-Si et *a*-$Si_{1-x}C_x$	**3600 € H.T/year**
2009-2010 2 years	**CNRS/PAN** exchange program with Polish Academy of Sciences 2 years	R. Boukherroub	Electrochemical generation of submicrometer metal structures at three phase junction and their applications for biosensing	**2000 € H.T/year**
2010-2011 2 years	**CNRS/NSFC** exchange program with Shandong University, China 2 years	R. Boukherroub	Short and Long Range Sensing on Metal Nanostructures Coated with Thin Carbon-Based Materials Using Localized Surface Plasmon Resonance (LSPR)	**4000 € H.T/year**
2010-2013 4 years	**PHC Volubilis** exchange program with University of Kenitra, Morocco 4 years	J.-N. Chazalviel (Ecole Polytechnique)	Surfaces de silicium fonctionnalisées pour la realization de connexions contrôlées et de biocapteurs	**8500 € H.T/year**

We are expecting at least to **maintain our dynamics** in the obtention of academic and industrial fundings. We are estimating the current annual budget of the 8 different Labex partners to be as high as 3,600,000 euros. Therefore, apart from a potential Labex support, we are convinced to be able to raise **36,000,000 euros within the next 10 years**.

As mentioned in the "Pull effect" section, we are expecting to develop new networks (at the regional, national and international levels) which in turn will help to obtain new prestigious funding: French ANR (http://www.agence-nationale-recherche.fr/); French InCa (http://www.e-cancer.fr/); European PCRD 7 (http://cordis.europa.eu/fp7); European Marie Curie (http://ec.europa.eu/research/research-eu); Association for International Cancer Research (http://www.aicr.org.uk/ApplyingforResearchGrants.stm); Human Frontier (International Program https://extranet.hfsp.org/AllApplication/Default.aspx).

Altogether, these potential funding, our contracts with industrial partners, and the income from our own start-up on oncochannelopathies should allow *OncoChannel* to become financially autonomous in the future and, even more, to contribute to the common challenge of the European economics growth.

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7. ANNEXES / APPENDICES

7.1. REFERENCES BIBLIOGRAPHIQUES DE L'ETAT DE L'ART/STATE OF THE ART REFERENCES

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PARTENAIRE 3 – Jean-Claude MICHALSKI

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7.3. DEVIS/ESTIMATE

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16371865 / 12.10.2010

Page
2

Pos.	Grp.	Article Désignation	Quantité	Unité prix	Devise EUR Valeur
0130		MBN11200 FILTRE GIF, 45MM, VERT-INTERFÉRENTIEL	1 PC		
0140		MBN11710 FILTRE NCB11/45MM	1 PC		
0150		MBN21802 FILTRE GRIS ND2A, 45MM	1 PC		
0160		MBN21816 FILTRE GRIS ND16A, 45MM	1 PC		
0170		MEB52320 TI-TD Tube binoculaire type D.	1 PC		
0180		MEB55800 TI-T-B Base de tube binoculaire simple	1 PC		
0190		MAK10100 CFI OCULAIRE 10X/22	2 PC		
0200		MEP59390 TI-ND6-PFS Tourelle Perfect Focus	1 PC		
0210		MEF55020 TI-RCP Boitier télécommande de contrôle	1 PC		
0220		MEL51000 TI-C tourelle Condenseur modulaire 4 positions vides pour intégrer les modules phase, DIC ou NAMC	1 PC		
0230		MXA20660 Cache poussiere condenseur	1 PC		
0240		MEL56200 TI-C-LWD optique de cond ON:0,52 /DT30mm	1 PC		
0250		MEE54100 TI-FL Bras épi fluorescence(diaphragmes)	1 PC		
0260		MEV51110 TI-FLC-E Tourelle EpiFluo Motorisée	1 PC		
0270		MBE41300 CUBE FILTRE EPI-FL POUR DAPI	1 PC		
0280		MBE44720 CUBE FILTRE EPI-FL POUR FITC	1 PC		
0290		MBE45600 CUBE FILTRE EPI-FL POUR TRITC	1 PC		
0300		MBF72665 HG Intensilight motorisé	1 PC		
0310		MBF75600 C-HGFIEC Boîtier de contrôle Générateur	1 PC		
0320		MBF72311 C-HGFIB HG 100W ADP pour series I & TI	1 PC		
0330		MBF71630 C-HGFIF15 fibre optique 3000 mm	1 PC		

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16371865 / 12.10.2010

Page
3

Pos.	Grp.	Article Désignation	Quantité	Unité prix	Devise EUR Valeur
0340		2D3C1001			
		CORDON SECTEUR BE BIPOLAIRE	1 PC		
0350		MED53200			
		TI-BSUK70 Kit complet de rehausse 70mm	1 PC		
0360		MEC56100			
		TI-S-ER Platine motorisée avec encodeurs	1 PC		
0370		MEF55710			
		TI-S-CON boitier contrôle platine motor.	1 PC		
0380		MEF55700			
		TI-S-EJOY Joystick XYZ (platine motor)	1 PC		
0390		MXU91990			
		Contrôl. USB &insert Piezo Nano Z100 TI	1 PC		
0400		MXA22090			
		TI PZT Câble de contrôle piezo	1 PC		
0410		MXU91991			
		Porte lame 1x3 " pour insert piezo TI	1 PC		
0420		MXU91993			
		Porte boite pétri 35mm po insert piezo	1 PC		
0430		MEE59117			
		TI TIRF LSC Sécurité Laser TIRF/Piezo	1 PC		
0440		MXA22024			
		HUILE IMMERSION NF 50CC POUR FLUO UV	1 PC		
0450		MQD42120			
		PROJECTIF 2,5X-C	1 PC		
0460		MQD42000			
		ADAPTATEUR C-MOUNT DIRECT/ISO	1 PC		
0470		MRD01991			
		CFI Apochromat 100x TIRF huileH ON 1.49	1 PC		
0480		MRD07650			
		CFI Plan Apo IR 60XWI ON 1,27 DT 0,17	1 PC		
0490		MRD70200			
		CFI Plan Apochromat VC 20X ON:0,75 DT:1m	1 PC		
0500		MZA00897			
		IXON ULTIMATE SENSITIVITY DU897	1 PC		
0510		MEE59800			
		TI-N-SIM Eclairage	1 PC		
0520		MEV51130			
		TI-FT N-SIM Tourelle Filtre Motorisée	1 PC		
0530		MEF56500			
		LU5 N-SIM Lsaer Unit	1 PC		
0540		MEV52000			
		TI-SB N-SIM Shield Box	1 PC		
0550		MEE59030			
		LU-MF N-SIM Multi Mode Fibre	1 PC		

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Page
4

Pos.	Grp.	Article Désignation	Quantité	Unité prix	Devise EUR Valeur
0560		MHX00157 200MW SAPPHIRE 488nm Laser Systeme	1 PC		
0570		MHX00160 COBOLT Laser 561nm JIVE 100mW	1 PC		
0580		MXK37884 Rack for LU5 N-SIM 5 Laser Module	1 PC		
0590		MXK37885 Rack for Piezo stage controller and PC	1 PC		
0600		MXK37886 CCD Camera for TIRF-SIM Alignment	1 PC		
0610		MXK37889 C mount lens for TIRF-SIM Alignment	1 PC		
0620		MXK37887 USB cable AUMFC50	1 PC		
0630		MXK37888 USB cable U2C-B50K	1 PC		
0640		2EMPS3000RT3 Onduleur 2700 Watt	1 PC		
0650		2EMPS2200RT3 Onduleur 1980 Watt	1 PC		
0660		2D3C6SC3060 Lot de 6 cables pour onduleur	2 PC		
0670		2T1442789 Table anti vibratoire pour SIM Table anti vibratoir Clean Top 2 1000X1500X100 mm avec roulettes rétractables + Livraison au RDC extérieur (sans manutention)	1 PC		
0680		MHS50000 NIS-Elements C	1 PC		
0690		MPX00662 HP WORKSTATION Z800 pour A1	1 PC		
0700		2HPMONL30 ECRAN PLAT 30 POUCES HP	1 PC		
0710		2SAV1003 Contrat Maintenance -Tranquillité Une visite de maintenance préventive par an Deux visites de maintenance curative comprenant : la main d'oeuvre et les frais de déplacements la fourniture des pièces détachées	1 PC		

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Page
5

Pos.	Grp.	Article Désignation	Quantité	Unité prix	Devise EUR Valeur
Total postes					478.494,61
Net Value				478.494,61	
TVA			19,60 %	478.494,61	93.784,94
Escompte*			0,70- %	572.279,55	4.005,96-
Total					572.279,55

dipsi
INDUSTRIE

N/Réf : fd/dm
V/Réf : **Mme Natacha PREVARSKAYA**

Inserm U 1003 / USTL
Laboratoire de Physiologie Cellulaire
Bât. SN3
59655 VILLENEUVE D'ASCQ CEDEX

Devis n°: DMLS101104

Châtillon, le 4 novembre 2010

Materiels Nanion

Qté	Réf	Désignation	P.U.H.T.	P.T.H.T.
1	*	**NPC-16 Patchliner Octo** (8 channels) Each Platform includes : 1 NPC-16 Patchliner recording station 2 EPC-10 Heka Quadro (only with Patchliner 8-channels) 1 Patchmaster Software 1 PatchControl HT Software 1 Tool Kit 1 Electrode Starter Kit 1 Solution Starter kit 1 PC with 20" TFT monitor	240 000,00	240 000,00
1	*	1 Temperature Control option	10 000,00	10 000,00
200	*	NPC-16 chip (at bulk discount rate, list price 80 Euros / chip (min 20 chips))	65,00	13 000,00
1	*	1 year service contract for NPC-16 (first year is free of charge)	15 000,00	15 000,00

Suite page 2

1	*	Vesicle Prep Pro for making lipid vesicles	4 400,00	4 400,00
1	*	Packaging and transport	1 250,00	1 250,00

Training : 3 days on-site training offered at the time of the delivery
We also offer the option for one or more user staff to visit Nanion during each year of the service contract to obtain further training. Expenses for such visits, such as travels and accommodation shall be covered by the user

TOTAL HT Euros	**283 650,00**
TVA 19,60 %	55 595,40
TOTAL TTC Euros	339 245,40

Emballage, port et assurances compris
Garantie : 1 an pièces & main d'œuvre, retour atelier à la charge du client
Conditions de règlement : par virement à 45 jours
Validité de l'offre : 3 mois
Délai de livraison : 12 semaines à réception de votre commande

Fabrice DUBOIS

DIPSI Immeuble Vecteur-Sud 70-86 avenue de la République F-92325 CHATILLON CEDEX
Téléphone: 01 49 65 67 20 - Télécopie: 01 49 65 67 29 - dipsi@dipsi.com - www.dipsi.com
S.A.R.L. au capital de 50000€ - R.C. Nanterre B331 734 806 - APE 7490B - SIREN 331 734 806

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Université de Lille 2
Institut de Médecine **P**rédictive et de **R**echerche **T**hérapeutique (IFR 114)
-o-
Plateau *SOLiD*
Institut pour la **R**echerche sur le **C**ancer de **L**ille
Place de Verdun 59045 Lille Cedex - Tél.: 03.20.16.92.20 - Fax. : 03.20.16.92.29 - mail: martin.figeac@inserm.fr

Réf Facture : SOLiD-NP-LABEX_70Tumors-19. ***Organisme***
Objet : Target-seq 70 échantillons
1 run SOLiD 4 (target : 1Mb) **Adresse**
Etude Prostate 70 tumors LABEX
Compte **Siret**
Responsable

Devis

Demandeur **Natalia Prevarskaya** ***Tel / Mail*** ***Laboratoire***

Désignation	**Prix Unitaire HT**
Enrichissement cible SureSelect MP3 0.5Mb-1.5Mb (100)	31 778,00 €
SureSelect AB Adaptator Set 7x10 (70)	1 309,50 €
SOLiD Library Construction kit (72)	8 995,00 €
SOLiD bead deposition kit (70)	320,00 €
SOLiD Instrument buffer kit (70)	221,00 €
Bio analyzer DNA 1000	200,00 €
Bio analyzer HS DNA Kit	200,00 €
Ladder 50bp	11,00 €
Dynal Magnetic Beads	300,00 €
Min Elute PCR Purif Kit Qiagen	100,00 €
DH10 + 22x assay QPCR	2 500,00 €
8 ePCR (Full Scale)	4 400,00 €
Barette + Slide pour WFA	200,00 €
Consommables ePCR	1 500,00 €
Barcoding Kit 1-80	4 170,00 €
Consommables (gants, tubes, …)	3 500,00 €
Run (chimie) 50x35x10	2 565,00 €
Sous Total HT	62 269,50 €
Participation aux frais et maintenance	12 453,90 €
Total HT	**74 723,40 €**
TVA 19,6%	**14 645,79 €**
Total TTC (TVA : 19.6 %)	**89 369,19 €**

Valeur en votre aimable règlement chèque ou virement bancaire
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T.P. LILLE 10071 59000 00001003894 60
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Réf Facture : SOLiD-NP-LABEX_70Controls-19 ***Organisme***
Objet : Target-seq 70 échantillons
1 run SOLiD 4 (target : 1Mb) **Adresse**
Etude Prostate 70 controls LABEX
Compte **Siret**
Responsable

Devis

Demandeur **Natalia Prevarskaya** ***Tel / Mail*** ***Laboratoire***

Désignation	Prix Unitaire HT
Enrichissement cible SureSelect MP3 0.5Mb-1.5Mb (100)	31 778,00 €
SureSelect AB Adaptator Set 7x10 (70)	1 309,50 €
SOLiD Library Construction kit (72)	8 995,00 €
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SOLiD Instrument buffer kit (70)	221,00 €
Bio analyzer DNA 1000	200,00 €
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Ladder 50bp	11,00 €
Dynal Magnetic Beads	300,00 €
Min Elute PCR Purif Kit Qiagen	100,00 €
DH10 + 22x assay QPCR	2 500,00 €
8 ePCR (Full Scale)	4 400,00 €
Barette + Slide pour WFA	200,00 €
Consommables ePCR	1 500,00 €
Barcoding Kit 1-80	4 170,00 €
Consommables (gants, tubes, …)	3 500,00 €
Run (chimie) 50x35x10	2 565,00 €

Sous Total HT	62 269,50 €
Participation aux frais et maintenance	12 453,90 €
Total HT	**74 723,40 €**
TVA 19,6%	**14 645,79 €**
Total TTC (TVA : 19.6 %)	**89 369,19 €**

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Réf Facture : SOLiD-NP-LABEX_36RNA-seq-1 ***Organisme***
Objet : RNA-seq 36 échantillons
9 runs SOLiD 4 **Adresse**
Etude Prostate 36 RNA-seq LABEX
Compte **Siret**
Responsable

Devis

Demandeur **Natalia Prevarskaya** ***Tel / Mail*** ***Laboratoire***

Désignation	Prix Unitaire HT
RiboMinus Kit	3820
Ribominus concentration kit	216
BioAnalyzer Nano, Pico DNA 1000 chips	500,00 €
Min Elute PCR Purif Kit	101,00 €
SOLiD Whole Transcriptome Analysis kit	6 315,00 €
Gel Novex TBE/Urée	537,20 €
Gel TP	200,00 €
Gel Ladder	220,00 €
Sybr Gold	128,00 €
Pure Link PCR Micro Kit	60,00 €
DH10	1 800,00 €
TaqMan 20x assay	984,00 €
TaqMan 2x assay	2 028,00 €
SOLiD ePCR Kit	9 400,00 €
SOLiD Bead enrichment Kit	8 920,00 €
SOLiD Bead deposition Kit	5 270,00 €
SOLiD ePCR Tubes and Caps	640,00 €
SOLiD Buffer Kit	895,00 €
SOLiD Emulsion Collection Tray Kit	145,00 €
SOLiD Slide Pack Kit	1 734,00 €
SOLiD Fragment Library Sequencing 50x35x5	22 500,00 €
SOLiD Instrument Buffer Kit	598,00 €
SOLiD Fragment Library Seq. Barcoding	1 614,00 €
SOLiD WFA	2 000,00 €
Consommables	2 160,00 €
Sous Total HT	72 785,20 €
Participation aux frais et maintenance	14 557,04 €
Total HT	**87 342,24 €**
TVA 19,6%	**17 119,08 €**
Total TTC (TVA : 19.6 %)	**104 461,32 €**

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Réf Facture : SOLiD-NP-LABEX_20sRNA-seq-1 ***Organisme***
Objet : sRNA-seq 20 échantillons
1 run SOLiD 4 **Adresse**
Etude Prostate 20 sRNA-seq LABEX
Compte **Siret**
Responsable

Devis

Demandeur **Natalia Prevarskaya** ***Tel / Mail*** ***Laboratoire***

Désignation	Prix Unitaire HT
Enrichment small RNA	1 900,00 €
BioAnalyzer Nano, Pico, DNA 1000 chips, small	1 000,00 €
Min Elute PCR Purif Kit	101,00 €
SOLiD Total RNA Analysis kit	2 105,00 €
Gel Novex TBE/Urée	268,60 €
Gel TP	100,00 €
Gel Ladder	110,00 €
Sybr Gold	128,00 €
SizeSelect gel 10%	360,00 €
Pure Link PCR Micro Kit	60,00 €
DH10	1 000,00 €
TaqMan 20x assay	656,00 €
TaqMan 2x assay	1 352,00 €
SOLiD ePCR Kit	1 880,00 €
SOLiD Bead enrichment Kit	1 784,00 €
SOLiD Bead deposition Kit	1 054,00 €
SOLiD ePCR Tubes and Caps	128,00 €
SOLiD Buffer Kit	179,00 €
SOLiD Emulsion Collection Tray Kit	29,00 €
SOLiD Slide Pack Kit	578,00 €
SOLiD Fragment Library Sequencing 35x10	1 147,00 €
SOLiD Instrument Buffer Kit	598,00 €
SOLiD Fragment Library Seq. Barcoding	3 228,00 €
SOLiD WFA	400,00 €
Consommables	1 200,00 €
Sous Total HT	21 345,60 €
Participation aux frais et maintenance	4 269,12 €
Total HT	**25 614,72 €**
TVA 19,6%	**5 020,49 €**
Total TTC (TVA : 19.6 %)	**30 635,21 €**

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Boîte Postale n° 70478
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Villebon, le 27 octobre 2009

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Thermo Electron S.A.S.
16 avenue du Québec
SILIC 765
91963 COURTABOEUF CEDEX
Tél. 01 60 92 48 00
Fax 01 60 92 49 00

Sophie BENOIST
Ingénieur des Ventes
Tél : 01.34.16.58.07
Mobile : 06.82.86.80.34
Mail : sophie.benoist@thermofisher.com

Devis établi par Virginie CROIZER – Assistante Commerciale - Tél. : 01 60 92 48 42

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Référence	Désignation	Prix Unitaire € H.T.	Qté	Prix Total € H.T.
SRVYR-64000	**Package SURVEYOR PLUS avec SRVYR-UV5P** **SRVYR-LPMPP Pompe SURVEYOR PLUS** Pompe HPLC à gradient quaternaire. Dégazage intégré sous vide à 4 canaux. 4 électrovannes de gradient. Pompe à 2 pistons. Pression maximum: 400 bars (6000 psi). Plateau de solvants (SRVYR-TRAY) **SRVYR-ASP Passeur automatique SURVEYOR PLUS** Passeur d'échantillons pouvant utiliser divers flacons: Jusqu'à 200 flacons de 1.8ml, ou micro flacons, ou micro tubes de centrifugation sur 5 plateaux standards. Quatre réservoirs de 20 ml pouvant contenir des échantillons, des réactifs de dérivation, des solvants de dilution, etc… Flacon de 125 ml pour solvant de rinçage intérieur et extérieur de l'aiguille d'injection. Adaptateur pour micro plaques de 96 ou 384 puits. Peut recevoir jusqu'à 3 plateaux de l'un ou l'autre type. Seringue standard de 250 µl permettant d'injecter de 1 à 160 µl avec une précision meilleure que 0.5% à 5 µl. Des seringues optionnelles de 100 et 2500 µl permettent d'injecter depuis 0.1 µl jusqu'à 1600 µl. Température des plateaux stable à +/- 0.5°C entre 0 et 60°C. Four pouvant contenir 2 colonnes de 25 cm, stable à +/-0.5°C entre 5 et 95°C. 13 commandes peuvent être combinées pour personnaliser la préparation d'échantillons: dilution, dérivation précolonne, extraction liquide-liquide, etc… Temps de cycle minimum: 30 secondes Câble de communication éthernet avec PC / Xcalibur version 1.4 **SRVYR-UV5P Détecteur UV-Visible Double longueur d'onde** Détecteur SURVEYOR Plus UV-Visible programmable à double longueur d'onde en simultané (190-365 nm : lampe deutérium ; 366-800 nm : lampe tungstène). Livré avec une cellule Light Pipe de 10µl et 50 mm de trajet optique.	36554.00	1	36554.00

Devis établi par Virginie CROIZER – Assistante Commerciale - Tél. : 01 60 92 48 42

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91963 Courtabœuf CEDEX
Siret 326 556 578 00069
16, avenue du Québec
France
APE 4652Z
+33 (0)1 60 92 48 00
+33 (0)1 60 92 49 00 fax

Établissement Secondaire
Immeuble le Minnesota - BP 50249
95615 Cergy Pontoise CEDEX
Siret 326 556 578 00085
5, allée Rosa Luxembourg
France
APE 2651B
+33 (0)1 34 32 51 00
+33 (0)1 34 32 51 01 fax

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	SRVYR-SYSKT Kit d'accessoires SURVEYOR Comprend tous les accessoires permettant de rendre le système opérationnel : - Un plateau conçu pour recevoir 4 bouteilles à solvant et contenir tout solvant éventuellement renversé. (Se pose sur le dessus du système HPLC). - 4 bouteilles à solvant d'un litre. - Les frittés d'aspiration et tous tubes pour haute et basse pression. - Câbles et hub éthernet, câble de synchronisation. - 2 packs de flacons de 1.8ml avec bouchons et septa. **00109-01-00007 Colonne Hypersil Gold C18 4.6 x 100mm**			
CHROM-64510	**Logiciel CHROMQUEST V. 5.0** Système multitâche permettant le pilotage, l'acquisition et le retraitement des signaux chromatographiques. Comprend : * le logiciel * une clé de protection (disquette) * les câbles nécessaires. Fonctionne sous Windows 2000 professionnel (SP4) ou XP professionnel (SP3) (fourni avec le PC). Nécessite un PC équipé d'un processeur Pentium IV à plus de 1,8 GHz, au moins 512 Mo de RAM, un disque dur de plus de 80 Mo et un lecteur de CDROM. Pilotage d'un Surveyor Plus ou d'un Spectra System avec CHROM-64001.	**4375.00**	**1**	**4375.00**
PFT-S-US	**Participation aux frais de transport Système Surveyor Plus / Accela**	**136.00**	**1**	**136.00**
Recycl-Surveyor	Recyclage et valorisation du système proposé (dans le cadre du décret 2005-829 relatif aux traitements des Déchets Electriques et Electroniques – DEEE)	**100.00**	**1**	**100.00**

	Total en €
Prix Total Net en € H.T	**41165.00**
PRIX TOTAL REMISE EN € H.T.	**22136.00**
T.V.A. 19,60%	4338.65
TOTAL EN € T.T.C.	26474.65

Nous tenons à vous informer que nous sommes à votre disposition pour vous apporter des solutions de financement pour votre acquisition. Pour de plus amples informations, n'hésitez pas à contacter votre interlocuteur commercial habituel qui vous fournira tous les détails.
Les propositions financières sont soumises à approbation de crédit.

Devis établi par Virginie CROIZER – Assistante Commerciale - Tél. : 01 60 92 48 42

3

Thermo Electron SAS
Immeuble Mimosa-SILIC 765
91963 Courtabœuf CEDEX
Siret 326 556 578 00069
16, avenue du Québec
France
APE 4652Z
+33 (0)1 60 92 48 00
+33 (0)1 60 92 49 00 fax
www.thermofisher.com

Établissement Secondaire
Immeuble le Minnesota - BP 50249
95615 Cergy Pontoise CEDEX
Siret 326 556 578 00085
5, allée Rosa Luxembourg
France
APE 2651B
+33 (0)1 34 32 51 00
+33 (0)1 34 32 51 01 fax

IBAN FR 76 1873 9000 0100 2007 1988 290 - SAS capital de 30 716 154,57 €uro - RCS Evry 326 556 578 - TVA FR 10 326 556 578

JACOMEX

DEVIS *10 000477*

Le *28/06/10*

TÜV CERT EN ISO 9001 Certificat N°71 100 D 289

Chargé d'affaire : *OLIVIER ROUSSEL*
Id TVA : *FR57965502610*
Client : *CNRS5910* / *CNRS5910*
Votre Ref. :
A l'attention : **M. COFFINIER**
Commentaire :

UNIVERSITE DE LILLE 1
PARC SCIENTIFIQUE DE LA HAUTE
BORNE
50 AVENUE DE HALLEY VILLE
59658 LILLE CEDEX

Tél : *0320197987*
Fax :

Page : 1

Code article	Désignation article	Quantité	Px unitaire	Montant HT
BIGP0001	GP(CONCEPT)-T2 BOITE A GANTS MODULABLE inox 304L : - Dimensions utiles L/H/P : 1200 x 900 x 725 mm - Sas à vide cycles automatiques, inox électropoli Ø 400, longueur 600 mm (à droite ou à gauche) - Châssis inox sur roulettes et vérins - Pompe à vide 2 étages, 21m3/h avec séparateur de brouillard - 1 traversée électrique 220V - 2 passages obturés ISO KF40 - Alarme voyant rouge (paramétrable sur écran tactile) suivant les concentrations O2/H2O - Filtre Hepa - 3 étagères inox UNITE AUTONOME DE PURIFICATION simple ligne avec: - Système de régénération (gestion automatisée) - Régulation de pression automatique - Circulateur à débit variable - Capacités d'adsorption: O2=30L; H2O=1440g - <1ppm O2/H2O - Interface par écran tactile - Module inox, sur roulettes - Configuré pour recevoir un module de piégeage solvants P(SYS)-CA - Niveau sonore de la boîte à gants: 47dB(A) en purification/régulation Autres caractéristiques: suivant brochure jointe	1,00	23000,00	23000,00

DELAI :

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Visas

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Ces montants sont en EUROS

Montant HT en €	
Escompte	
Montant TVA	
Montant TTC	
Acompte	
Net à payer €	

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Code article	Désignation article	Quantité	Px unitaire	Montant HT
PAPL0009	PANNEAU AVANT PC T2 - Ø186 Polycarbonate. Epaisseur 10 mm	1,00	300,00	300,00
MEAC0010	ANALYSEUR O2 Caractéristiques sur brochure jointe	1,00	2000,00	2000,00
MEAC0011	ANALYSEUR H2O Caractéristiques sur brochure jointe	1,00	2000,00	2000,00
SEBI0045	MINI SAS Ø150 LG 400MM Caractéristiques sur brochure jointe	1,00	1500,00	1500,00
UPPU0004	PIEGE A SOLVANTS (CA-VC) Module extérieur "GROSSE CAPACITE" Charge CHARBON ACTIF : 6 KG Piquages arrières KF40 pour remplacement facile. Echange de charge sans polution du circuit de purification / conditionnement par mise sous vide. Réacteur, tuyauteries et vannes by-pass et 3 voies en inox 304L Grande autonomie et efficacité.	1,00	3000,00	3000,00
SETR0303	1 TRAVERSEE ET VANNE POINTEAU/NW40 POUR BULLAGE	1,00	250,00	250,00
SETR0302	1 TRAVERSEE AVEC 2 VANNES 1/4 TOUR POUR CIRCUIT REFROIDISSEMENT	1,00	400,00	400,00
SETR0402	1 TRAVERSEE SOUFFLETTE N2 AVEC	1,00	250,00	250,00

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Montant TVA	
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Page : 3

Code article	Désignation article	Quantité	Px unitaire	Montant HT
	PRISES, FLEXIBLE ET SOUFFLETTE			
FX0032	FORFAIT UNE JOURNEE COMPRENANT: TRANSPORT, INSTALLATION MISE EN ROUTE, FORMATION (Moyens de levage, de grutage et manutention lourde non compris) GARANTIE 2 ANS PIECES & MO Pour tout problème, dépannage préalable, assistance technique par téléphone ou intervention après accord téléphonique. Cette garantie s'entend pour tout vice de matière, de construction ou de matériels (hors consommables tels que gants), dans le cadre d'une utilisation normale, à compter de la date de livraison. CONGES D'ETE : semaines 32,33,34	1,00	1500,00	1500,00
	Condition de paiement /irement à 30 jours FDM			

DELAI : PLANS : 2 SEMAINES HORS CONGES AP COMMANDE
FABRICATION : 10 SEMAINES HORS CONGES
APRES ACCORD SUR PLANS

VALIDITE DE L'OFFRE : 2 MOIS

Service commercial | Direction technique

Visas

Base TVA	Taux	Montant TVA
34200,00	*19,60*	*6703,20*

Ces montants sont en EUROS

Montant HT en €	**34200,00**
Escompte	
Montant TVA	**6703,20**
Montant TTC	**40903,20**
Acompte	
Net à payer €	**40903,20**

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INDUSTRIE

Inserm U 1003 / USTL
Laboratoire de Physiologie Cellulaire
Bât. SN3
59655 VILLENEUVE D'ASCQ CEDEX

N/Réf : fd/dm
V/Réf : **Mme Natacha PREVARSKAYA**

Devis n°: DMLS101103 (estimatif) Châtillon, le 4 novembre 2010

Station intégrée d'électrophysiologie

Equipements principaux

Qté	Réf	Désignation	P.U.H.T.	P.T.H.T.
		Matériels Heka Instruments		
		Amplificateur & système d'acquisition traitements		
1	*	EPC 10 USB Patch Clamp amplifier Patch Clamp Amplifier and data acquisition USB version with LIH 8+8 interface	13400,00	13400,00
1	*	Patchmaster software Multi-channel stimulation / acquisition software, includes a Pulse license in the same dongle	2970,00	2970,00
		Matériels Olympus		
		Microscope Inversé IX71		
1	N2661900	Statif IX71S1F-3-5 100% gauche Statif de Micro Inv IX71S1F-3-5 Sortie 100% côté gauche	7441,19	7441,19
1	N1510400	Tête Binoculaire U - BI90-1-2	1007,63	1007,63
2	N1508000	Oculaire WHN10X/22	230,79	461,58
1	037917	Illuminateur IX - ILL100	2270,19	2270,19
1	N2212100	Boitier Lampe U-LH100L-3-5 U-LH100L-3-5 boitier lampe halogen avec câble long	362,02	362,02
1	N2659600	Transformateur TH4-200	406,85	406,85
3	035359	Lampe Halogène 12V 100W HAL-L	52,32	156,96
2	N1133300	Housse pour IX81/71/51	14,60	29,20
1	035754	Platine IX2-SFR (260x201mm)	1580,43	1580,43
1	035771	Condenseur RC IX2-MLWCD 45 mm	3422,78	3422,78
1	035772	Polariseur IX2-MLWPO	1251,19	1251,19
2	E01X3800000	Câble branchement secteur	10,84	21,68
1	035763	Illuminateur Fluo IX2-RFA	1520,14	1520,14
1	035765	Tourelle 6 cubes IX2-RFAC	837,05	837,05
1	N2691400	Adaptateur Video C CMAD3.2 à monture C	121,26	121,26
1	N2691800	U-TV1X-2-2 Adaptateur Video	58,46	58,46
1	N2249200	Objectif UPLFLN10X2 - Objectif UPLFLN10X2 U Pian semi apo	731,79	731,79
1	N1492700	Obj. LUCPLFLN20X/0,45 Distance de travail variable de 6.4mm à 7.6mm	2054,65	2054,65
1	N1492800	Obj. LUCPLFLN40X/0,60 Distance de travail variable de 2,7mm à 4mm	2841,59	2841,59
1	N1507100	Obj. LUCPLFLN60X/0,70 Distance de travail variable de 1.5mm à 2.2mm	4528,11	4528,11

Suite page 2

1	035751	Analyseur DIC/FL IX2-AN	709,57	709,57
1	N1504700	Module U-DIC60 à utiliser avec U-TLD	745,31	745,31
1	N1504500	Module U-DIC40 à utiliser avec U-TLD	604,57	604,57
1	037881	Prisme contraste DIC U-DICT	2811,90	2811,90
1	N1506400	Module IX2-DIC60 - compatible avec le condenseur IX2-LWUCD	1150,59	1150,59
		Matériels Cairn / Monacor		
		Caméra avec moniteur N&B		
1	*	High sensitivity CCD camera for infrared viewing	680,00	680,00
1	*	Moniteur N&B	150,00	150,00
		Matériels Sutter		
		Micromanipulateur		
1	MP-225	Micromanipulateur motorisé MP-225 : - Course : 25 mm x,y,z - Résolution : 0,0625 - 2 µm / pas - Vitesse maximale : 2 mm / sec *Préciser la configuration à la commande : Droit ou gauche*	6032,00	6032,00
		Matériels TMC		
		Table antivibratoire & Cage		
1	*	Table anti-vibrations - Dimensions 900 x 750 (plateau) - Plateau taraudage M6/25mm (4 in stainless steel)	3900,00	3900,00
1	*	Périmètre complet pour cage de faraday	310,00	310,00
1	*	Cage de Faraday Type II 750 x 900 mm	1565,00	1565,00
2	*	Accoudoir	55,00	110,00
		Matériels Automate Scientific		
		Système de perfusion		
1	13-01-23	ValveBank®4 Teflon Perfusion System ValveBank4 = 4 solutions, 4 Teflon Valves mounted and cabled, 1/16" tubing, Ringstand set with bracket, 4-into-1 manifold with flow control, 4 x 60ml syringes, stopcocks with drippers	2636,00	2636,00
		Matériel Siskiyou		
		Micromanipulateur mécanique		
1	MX130	dovetail manipulator, 4-axis	690,00	690,00
		Matériels Cairn		
		Système d'illumination		
1	*	Stabilised OptoLED power supply for the controlled illumination and modulation of twin LEDs. Unit includes feedback photodiodes for enhanced temperature stability and digital TTL control interface.	2696,00	2696,00
1	*	Olympus IX / BX microscope coupling - Epicondenser	1999,00	1999,00
1	*	White LED light souce head with optical feedback	444,00	444,00

Suite page 3

		Matériels informatique et installation tests		
1	*	Prestation de service incluant (estimatif) - Définition de la configuration du PC avec 1 écran plat 20" - Fourniture du PC de pilotage de la station d'électrophysiologie - Deux disques 160 Go 1 graveur lecteur de DVD - 4 Go de RAM - Installation des cartes et logiciels - Tests fonctionnels (24h)	1900,00	1900,00

SOUS-TOTAL Euros (estimatif)	76 608,69
Participation aux frais de port	900,00
TOTAL HT Euros (estimatif)	**77 508,69**
TVA 19,60 %	15 191,70
TOTAL TTC Euros (estimatif)	92 700,39

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Leica Microsystèmes SAS
8, avenue de l'île Saint Martin
F-92737 NANTERRE CEDEX
Téléphone: 0811 000 664
Télécopie: 01 56 05 23 23

Leica MICROSYSTEMS

M. Pascal Mariot
UNIVERSITE de Lille I
59655 VILLENEUVE D'ASCQ CEDEX
Tél: 03 20 33 71 93
Courriel: pascal.mariot@univ-lille1.fr

DEVIS CW0338C
N° SAP 0001085952

Date 2 / Nov / 2010
Ingénieur de vente Clément Laigle (06 22 85 07 85)
Assistante commerciale Michèle Hatier (01 56 05 23 38)

Article	Désignation	QTE	Montants EUR	Remise	Total EUR
	Leica DM IL LED Fluo.				
100	Leica DM IL LED microscope inversé,dédié aux applications Bio, avec éclairage LED en transmission. Eclairage LED: - avec température de couleur constante qui offre une belle luminosité - la durée de vie de la LED est de 50000 heures environ - la lampe s'éteint automatiquement après 2 heures sans utilisation - la luminosité de la LED est ajustée automatiquement lors du changement de méthode de contraste. Statif comprenant: - platine fixe - double bouton de commande coaxiale fine et grossière du focus - révolver 4 positions - optique à l'infini avec lentille de tube 1x - support de condenseur réglable avec collecteur et support de filtre - interrupteur marche/arret - Interface IMC - alimentation avec câble secteur - glissière pour fluorescence prévue pour 3 blocs de filtres. **No : 11521258**	1	3,194.00	20.0 %	2,555.20
200	Plaque de protection fluo pour DM IL LED **No : 11521263**	1	72.00	20.0 %	57.60
300	Guide-objet pour supports de DM IL **No : 11521248**	1	769.00	20.0 %	615.20
400	Support universel.Frame M pour guide-objet de platine fixe de DMIL ou DMI3000/4000/6000. Pour boites de Pétri (dia. 24mm à 68 mm) ou 1 lame (25x75mm) **No : 11520688**	1	702.00	20.0 %	561.60
500	Tube trinoculaire HC ILT inclinaison à 45° **No : 11521249**	1	978.00	20.0 %	782.40
600	Condenseur S40 / 0,45 distance de travail 40mm,ouverture numérique 0,45. Equipé pour les applications fond clair, contraste de phase et modulation de contraste intégré. **No : 11521251**	1	215.00	20.0 %	172.00
700	Glissière avec anneaux précentrés PH0, PH1 et PH2	1	170.00	20.0 %	136.00

Frais de gestion de 35€ HT pour toute commande inférieure à 200€ HT

Page 1 de 5

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8, avenue de l'île Saint Martin
F-92737 NANTERRE CEDEX
Téléphone: 0811 000 664
Télécopie: 01 56 05 23 23

M. Pascal Mariot
UNIVERSITE de Lille I
59655 VILLENEUVE D'ASCQ CEDEX
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Article	Désignation	QTE	Montants EUR	Remise	Total EUR
	pour condenseur S40 **No : 11521253**				
800	Housse pour DMIL/DMILM **No : 11512596**	1	51.00	20.0 %	40.80
	Equipement optique				
900	Oculaire HC PLAN 10x/20 pour porteurs de lunettes **No : 11507801**	1	165.00	20.0 %	132.00
1000	Oculaire HC PLAN 10x/20 M pour porteurs de lunettes **No : 11507802**	1	263.00	20.0 %	210.40
1100	Objectif N PLAN 20/0,40 PH1 Distance de travail 0,39mm Couvre-objet de 0,17mm d'épaisseur **No : 11506098**	1	866.00	20.0 %	692.80
1200	Objectif N PLAN 40/0,65 PH2 Distance de travail 0,36mm Couvre-objet de 0,17mm d'épaisseur **No : 11506099**	1	970.00	20.0 %	776.00
	Equipement pour fluorescence				
1300	Source de lumière EL 6000 type métal halide comprenant : - un variateur d'intensité lumineuse (5 paliers). - un shutter ultra rapide (6 ms). - un témoin lumineux de la position de shutter. - un filtre-calorique. - une sortie RS 232. - un compteur horaire. L'ensemble est livré avec une ampoule HXP R120/45C. **No : 11504115**	1	4,993.00	20.0 %	3,994.40
1400	Fibre optique pour EL6000 **No : 11504116**	1	418.00	20.0 %	334.40
1500	Adaptateur de fibre 1" EL6000 pour microscopes inversés type DMI 4/6000 (première génération) et pour tous les microscopes droits (nouvelle génération). **No : 11504117**	1	349.00	20.0 %	279.20
1600	Manchon d'adaptation pour connection de la fibre EL6000 sur statifs de DMIL et DM1000 **No : 11504127**	1	93.00	20.0 %	74.40
1700	Câble pour shutter EL6000 **No : 11500331**	1	140.00	20.0 %	112.00

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DEVIS	CW0338C	**Date**	2 / Nov / 2010
N° SAP	0001085952	**Ingénieur de vente**	Clément Laigle (06 22 85 07 85)
		Assistante commerciale	Michèle Hatier (01 56 05 23 38)

Article	Désignation	QTE	Montants EUR	Remise	Total EUR
1800	Combinaison de filtres A4 ET pour excitation dans l'UV (360/40 nm) Dichroïque 400 DCLP Filtre d'arrêt 470/40 mm **No : 11504172**	1	1,459.00	20.0 %	1,167.20
1900	Combinaison de filtres L5 ET,s. Excitation BP480/40, dichroique 505nm LP, émission BP527/30 **No : 11504176**	1	1,459.00	20.0 %	1,167.20
2000	Combinaison de filtres TX2 ET,s. Excitation BP560/40, dichroique 595nm LP, émission BP645/75 **No : 11504180**	1	1,459.00	20.0 %	1,167.20
	Caméra Leica DFC360 FX				
2100	Caméra digitale monochrome Leica DFC360FX Caméra ultra-rapide et ultra-sensible (visible et IR), avec refroidissement, pour les applications en fluorescence. Pilotage par logiciels Leica LAS (fourni avec la caméra)et Leica AF. Capteur : CCD 1,4 Mpixels Taille du capteur : 9,0 mm x 6.7 mm (Type 2/3") Images : Format standard 1392 x 1040 (20 images/s) Modes binning : 2 x 2, 3 x 3, 4 x 4, 8 x 8 Balayage progressif Taille du pixel : 6,45 x 6,45 µm Convertisseur A/D : 12/8 bit Exposition : 4µs à 10mn Refroidie par effet Peltier Interface : Firewire IEEE1394b 9 pin(câble non fourni) Compatible Windows 2000, Windows XP et Mac OS Monture C recommandée : 0.7x La caméra Leica est livrée avec le logiciel Leica LAS Core. Ce logiciel permet d'acquérir facilement des images, de les ajouter ensuite à la galerie de vignettes et les archiver dans un dossier défini. Toutes les commandes de la caméra peuvent être réglées pour répondre aux exigences individuelles, qu'il s'agisse de l'exposition, du gain et du gamma ou des niveaux noir et blanc de l'histogramme. L'acquisition des images peut se faire avec une grande variété de tailles, de profondeurs de couleur et formats de fichiers pour fournir une flexibilité encore plus grande. LAS Core permet également de définir une région de mise au point sur une image en direct, de façon à identifier facilement les zones significatives et à faire plus rapidement la mise au point. Il est possible d'enregistrer tous les paramètres et toutes les configurations et de les rappeler ultérieurement. L'outil d'annotation permet d'inclure un nom de fichier. Il est possible d'ajouter et de personnaliser de façon individualisée des réglettes graduées et des lignes. Les annotations peuvent être enregistrées avec l'image ou	1	9,644.00	12.0 %	8,486.72

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M. Pascal Mariot
UNIVERSITE de Lille I
59655 VILLENEUVE D'ASCQ CEDEX
Tél: 03 20 33 71 93
Courriel: pascal.mariot@univ-lille1.fr

DEVIS CW0338C
N° SAP 0001085952

Date 2 / Nov / 2010
Ingénieur de vente Clément Laigle (06 22 85 07 85)
Assistante commerciale Michèle Hatier (01 56 05 23 38)

Article	Désignation	QTE	Montants EUR	Remise	Total EUR
	fusionnées avec elle de façon à ce que les données soient toujours visibles en cas d'exportation. **No : 11547000**				
2200	Bague HC monture C 0,70x **No : 11541543**	1	610.00	12.0 %	536.80
2300	Station PC Standard écran 19"TFT analogique et DVI avec moniteur graphique plat Wide 19"(16/10) GETEK : Leicastd Boîtier petite tour noir 200*355*430mm Processeur Intel Core 2 Duo à double noyau - dual core 2.6 Ghz RAM 2 Go DDR3 (1333 Mhz) Disques durs 2 x Serial ATA2 160 Go Carte graphique chipset Nvidia GF 9500GT 512Mo Lecteur/Graveur Combo graveur de CD R/W, lecteur DVD Carte 2 ports série 1 port Firewire IEEE 1394a Ensemble clavier/souris Windows XP Pro multilingue Moniteur 19 TFT NEC AS191WM Garantie 1 an sur France métropolitaine J+1 ouvrés **No : 8080817**	1	1,457.00	12.0 %	1,282.16
2400	Carte PCI Express Firewire-b **No : 12730210**	1	284.00	12.0 %	249.92
2500	Cable FireWire800 b-b, 3.0 m **No : 12730186**	1	150.00	12.0 %	132.00
2600	Carte port parallèle PCI Express **No : 8022615**	1	108.00	12.0 %	95.04
2700	Leica MM Fluor : pour l'acquisition et l'analyse d'expériences ratiométriques et calciques; **No : 11640905**	1	5,310.00	12.0 %	4,672.80
	Sous-Total:				30,483.44
	Total H.T. :				**30,483.44**
	Frais d'expédition				35.14
	Montant total hors taxes				**30,518.58**
	TVA 19,6%				5,981.64
	Total TTC :				**36,500.22**

Conditions de facturations : France Public Administration - 45 days

Conditions de livraison : CPT - VILLENEUVE D'ASCQ

Validité : 02/11/10 **au** 31/12/10

Délai de livraison : 4 à 6 semaines à réception de commande.
Installation et mise en service assurées par nos soins.
Formation des utilisateurs comprise dans notre offre de prix.
Durée de garantie : 1 an, pièces et main d'oeuvre sur le site.
www.leica-microsystems.com/eu/fr.

Frais de gestion de 35€ HT pour toute commande inférieure à 200€ HT

Page 4 de 5

Leica Microsystèmes SAS
8, avenue de l'île Saint Martin
F-92737 NANTERRE CEDEX
Téléphone: 0811 000 664
Télécopie: 01 56 05 23 23

Leica MICROSYSTEMS

M. Pascal Mariot
UNIVERSITE de Lille I
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Page 5 de 5

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DEVIS N° : TAD/UNI/3682/10/11_41

Date de création : 22/11/2010
Durée de validité : 15 jours

Catalogue : UNIV-LILLE1
Client : Université de Lille 1

ADRESSE DE LIVRAISON

GEPV - CNRS FRE3268
Bâtiment SN2 2eme étage porte 107bis
Université des Sciences et Technologies de Lille 1
59655 Villeneuve d'Ascq Cedex FRANCE

ADRESSE DE FACTURATION

Bâtiment A3 - Service facturier
Cité Scientifique
59655 Villeneuve d'Ascq

VOS INFORMATIONS

Votre référence : GEPV - Xavier Vekemans

Contact : Xavier Vekemans

Téléphone : 03.20.43.67.53

Adresse mail : xavier.vekemans@univ-lille1.fr

VOTRE COMMERCIAL / SON ASSISTANT(E)

Didier BRAUNE
Tel : 03 20 41 54 50 / Fax :03 20 41 54 55
EMail : didier_braune@topinfo.fr

Jessica SALAMONE
Tel : 03 20 41 54 50 / Fax :03 20 41 54 55
EMail : jessica_salamone@topinfo.fr

LISTE DES ARTICLES

Référence	Article	Marque	Prix unitaire	Quantité	Total Ligne
FX465AV	HP Z800 Xéon E5504 QC/2GB/SANS OS/SANS DD NI CARTE GRAPHIQUE/3 Ans site J+1	HP	1080.00 € HT	1	1080.00 € HT
NF126AV	Upgrade Processeur Xeon E5530 Pour Z600/Z800	HP	372.00 € HT	1	372.00 € HT
NF149AA	Processeur Xeon E5530 CPU-2 Pour Z600/Z800	HP	635.00 € HT	1	635.00 € HT
FX621AA	Barrette mémoire 1 x 4GB pour Z800	HP	178.45 € HT	8	1427.60 € HT
VH997AA	Disque Dur 1,5 To SATA pour Z400, Z600, Z800	HP	198.37 € HT	5	991.85 € HT
U7943E	Extension de Garantie à 5 ans site J+1pour Z400/Z600/Z800	HP	163.10 € HT	1	163.10 € HT
FY945AA	NVIDIA Quadro FX 580 512 Mo pour Z400/Z600/Z800	HP	135.00 € HT	1	135.00 € HT
NM360AT	Ecran TFT 19" LA1905wg	HP	144.40 € HT	1	144.40 € HT
MCT1063F3	linux pour 6000Pro/6005Pro/dc7900	REDHAT	60.00 € HT	1	60.00 € HT
	MONTANT TOTAL HT TVA (19.6%)				5008.95 € HT 981.75 €
	MONTANT TOTAL TTC				**5990.70 € TTC**

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DESCRIPTIONS LONGUES DES ARTICLES DU DEVIS

Référence	Description Longue
FX465AV	HP Z800 MiniTour Bi-Processeur 1 x Intel Xéon E5504 2,00GHz 4 MB/800 QC 2 Go DDR3-1333 MHz ECC **SANS Disque Dur** Ethernet Gigabit intégré Controleur video : **SANS CARTE GRAPHIQUE** Graveur DVD 16X Supermulti SATA AUDIO : Realteck ALC262 connecteurs : à l'arriere 6 ports USB 2,0 1 entrée/sortie audio,1 entrée micro, 2 PS/2, 1 RJ45 Gigabit, a l'avant : 3 ports USB 2,0 1 entrée micro, 1 sortie casque, en interne : 3 USB 2,0 **SANS OS** Clavier USB, souris 2 boutons + molette USB Garantie : 3 ans site J+1 **ATTENTION CETTE MACHINE N'A PAS D'OS, MERCI DE PENSER A COMMANDER UN OS EN SUS**
NF126AV	Upgrade Processeur Xeon E5530 Pour Z600/Z800
NF149AA	Processeur Xeon E5530 CPU-2 Pour Z600/Z800
FX621AA	Barrette mémoire 1 x 4GB DDR3-1333 ECC reg pour Z800
VH997AA	Disque dur 1,5 To SATA 3 Gb/s NCQ
U7943E	Extensionde Garantie à 5 anssur site J+1 pour Z400/Z600/Z800
FY945AA	NVIDIA Quadro FX 580 512 Mo Graphics pour Z400/Z600/Z800
NM360AT	LCD 19" wide matrice active TFT Format 16:10 Pitch 0,283 temps de réponse 5 ms Ratio contr 1000:1 luminosité 250 nits, angle de vue : 160°Horiz /160°Vertic Interface VGA/DVI-D/Display Port, Résolution native 1440 x 900 Ecran réglable en hauteur, pivotable à 90°, 2 ports USB Consommation < 33 W Garantie 3 ANS sur site "0 pixel défectueux" J+1
MCT1063F3	RED HAT Enterprise linux desktop 3 ans (tranche 1 à 99)