

# BIOTECHNOLOGY AND BIOMEDICAL APPLICATIONS

2010

This booklet «Biotechnology and Biomedical Applications» has been implemented by the Research Administrations of the Académie universitaire Louvain (FUCAM, FUNDP and UCL) with the precious help of a reading committee composed of Professors MP Mingeot-Leclercq (UCL - Louvain Drug Research Institute), Y. Poumay (FUNDP - Molecular Physiology Unit), Y.J. Schneider (UCL - Institute of Life Sciences) and O. Toussaint (FUNDP - Cellular Biology Unit).

With the contribution of M. Brion (UCL), J. Colin (UCL), A. D'Antonio (FUCAM), M. Dubuisson (UCL), F. Roussel (FUNDP), A. Tondeur (FUCAM).

Cover: Three-dimensional reconstruction of the vascular/glandular interface in mouse embryonic pancreas (green: blood vessels; red: glands - Confocal imaging platform: P. Van Der Smissen & P. J. Courttoy) - A.C. Hick & C. Pierreux (UCL - CELL Unit, de Duve Institute)



## Foreword

The aim of this booklet is to promote the results of research by encouraging their transfer to the private sector. The different topics presented in this brochure highlight the high level of R&D in Biotechnology and Biomedical Applications performed within the Académie universitaire Louvain in order to catalyze the development of scientific research, to support industrial innovation by eliciting the interest of private companies and to encourage inter-partners synergies.

The competences and resources found in the laboratories of the Académie Louvain in “Biotechnology and Biomedical Applications” are broad and range from fundamental research to clinical trials with the final aim of improving the knowledge of biological processes and their potential application in human health.

This booklet presents the topics of interest, recent achievements and current developments of research teams involved in “Biotechnology and Biomedical Applications” for the Académie universitaire Louvain.

These topics are classified in categories, according to the main scientific and/or technological approach:

- ▶ Bioengineering
- ▶ Cell biology :Animals and Plants
- ▶ Immunology - Microbiology
- ▶ Molecular Biology
- ▶ Pharmacology – Pharmacy – Therapy
- ▶ Technological platforms
- ▶ Bioethics

A final annex provides a key-word index.



# Content

## A. BIOENGINEERING

### A.1 - Surface and Interface Characterization

11

P. BERTRAND, A. DELCORTE, S. YUNUS, C. POLEUNIS

### A.2 - Plant Cells As Factories for Pharmacological Proteins

13

M. BOUTRY, M. DELANNOY, C. NAVARRE

### A.3 - Development of Label-Free Biosensors Based on the Intrinsic Detection of Biomolecular Recognition, Using Nonlinear Optical Spectroscopies and Microscopies

15

Y. CAUDANO, A. PEREMANS, P. A. THIRY

### A.4 - Brewing Sciences, Flavour Stability and Polyphenol Chemistry

17

S. COLLIN, V. JERKOVIC, M. MAUDOUX, L. MELOTTE

### A.5 - Electrochemistry and Surface Chemistry of Biomaterials

19

J. DELHALLE, Z. MEKHALIF

### A.6 - Nano-Bio-Sensors Based On Nanowires Of Conjugated Polymers

21

S. DEMOUSTIER-CHAMPAGNE, A. M. JONAS, B. NYSTEN

### A.7 - Process Modeling, Monitoring, Control and Real-Time Optimisation

23

D. DOCHAIN

### A.8 - *In vitro* Production and Cryopreservation of Bovine Embryos

25

I. DONNAY

### A.9 - Design of a Scaffold for Human Isolated Follicle Transplantation

27

J. DONNEZ, M.-M. DOLMANS, C. AMORIM, A. VAN LANGENDONCKT

### A.10 - Physical Chemistry of Biosurfaces

29

CH. DUPONT-GILLAIN, Y. DUFRENE

### A.11 - Electrical Detection of Pathogens

31

D. FLANDRE, L. FRANCIS, Y. NIZET, J. PROOST, P. SOUMILLION

### A.12 - Functional Magnetic Resonance (NMR, EPR) Spectroscopy and Imaging in Small Animals

33

B. GALLEZ, B. JORDAN

### A.13 - Cloning, Modification and Expression of Hydrolases

35

I. HOUSEN

### A.14 - Global Assistance System for Orthognathic Planning and Surgery

37

B. MACQ, B. RAUCENT, H. REYCHLER, R. OLSZEWSKI

## B. CELL BIOLOGY – ANIMALS AND PLANTS

### B.1 - Endocytosis, Epithelial Differentiation and Tissue Remodelling

P. COURTOY, P. HENRIET, E. MARBAIX, C. PIERREUX

### B.2 - Primary Cultures of Neuronal and Glial Cells for the Study of Neurodegenerative Disorders

E. HERMANS, P. KIENLEN-CAMPARD, J.-N. OCTAVE

### B.3 - Mammalian Antioxidant Enzymes

B. KNOOPS, J.-P. DECLERCQ, J.-F. REES

### B.4 - *In Vitro* Evaluation System for Epidermal Function and Treatment

Y. POUMAY, M. HERIN

### B.5 - Reconstructed Human Epidermis for Characterization of Chemicals

Y. POUMAY, M. HERIN

### B.6 - Identification by Mass Spectrometry of Proteins Purified by DNA-Affinity

P. RENARD, M. DIEU, T. ARNOULD

### B.7 - Cell Senescence and Oxidative Stress / Nanotoxicology

O. TOUSSAINT, F. CHAINIAUX

## C. IMMUNOLOGY - MICROBIOLOGY

### C.1 - Molecular Bacteriology Functions

X. DE BOLLE, J.-Y. MATROULE, J.-J. LETESSON

### C.2 - Biotechnological Applications of Lactic Acid Bacteria

P. HOLS

### C.3 - Determination of an Early Immunological Profile Specific of Allergy Development and Its Use In Disease Prevention

E. SOKAL, F. SMETS, C. LOMBARD, P. DUPONT, J.-L. GALA, B. BEARZATTO, C. PILETTE

### C.4 - Rapid Detection of Bacterial Pathogens

P. SOUMILLION

### C.5 - Antibiotic Resistance by Active Efflux

P. M. TULKENS, F. VAN BAMBEKE, M.-P. MINGEOT-LECLERCQ

## D - MOLECULAR BIOLOGY

### D.1 - Engineering Environmental Friendly Plants

H. BATOKO

### D.2 - DNA Fingerprinting for Biodiversity Measurements

F. CHAUMONT, M.-C. FLAMAND

### D.3 - Mechanisms of Cytokine Receptor Dimerization

S. N. CONSTANTINESCU, J.-C. RENAULD

### D.4 - Kidney Diseases, Dialysis, Transplantation

O. DEVUYST, Y. PIRSON, M. JADOUL, É. GOFFIN, K. DAHAN

### D.5 - Protein Docking Using Image Processing and Statistical Tools

J.-L. GALA, B. MACQ

### D.6 - From DNA Transposition and Site-Specific Recombination Mechanisms to the Molecular Biology Toolbox

B. HALLET

### D.7 - Biomarkers Development In Aquatic Organisms to Assess the Ecotoxicological Hazard of Chemicals

F. SILVESTRE, P. KESTEMONT

**D.8 - Directed Evolution of Enzymes**

77

P. SOUMILLION

**D.9 - Molecular and Cellular Regulation of Cardiovascular Metabolism and Function**

79

J.-L. VANOVERSCHELDE, C. BEAULOYE, L. BERTRAND, C. DEPRE, S. HORMAN

**D.10 - Metabolic Basis of Inherited Disorders : Identification of New Enzymes and New Defects**

81

E. VAN SCHAFTINGEN, M. VEIGA-DA-CUNHA

**D.11 - Cleft Lip and Palate : (Epi)Genetic Causes and Development of Genetically Manipulated Animal Models**

83

M. VIKKULA, M. GHASSIBE

**D.12 - Vascular Malformations : (Epi)Genetic Causes and Development of Genetically Manipulated Animal Models**

85

M. VIKKULA, L. BOON, M. AMYERE, P. BROUILLARD, N. LIMAYE

**D.13 - Pathophysiology of Hemangiomas**

87

M. VIKKULA, L. BOON, N. LIMAYE

**E - PHARMACOLOGY - PHARMACY - THERAPY****E.1 - *In vitro* and *in vivo* Evaluation Systems for Cardiovascular Functions**

89

J.-L. BALLIGAND, C. DESSY, O. FERON, P. SONVEAUX

**E.2 - Drug Metabolism and Development of Cell-Based *in vitro* Models In Pharmaco-Toxicological Research**

91

P. BUC CALDERON

**E.3 - Yeast Cells As Therapeutic Agents**

93

J.-P. BUTS

**E.4 - Pathophysiological Mechanisms Underlying Acute and Chronic Renal Failure**

95

N. CARON

**E.5 - Cell Therapy of Central Nervous System Trauma and Pathologies**

97

F. CLOTMAN, E. HERMANS

**E.6 - Cell Therapy of Diabetes**

99

P. COURTOY, D. DUFRANE, P. GIANELLO, P. JACQUEMIN, F. LEMAIGRE, C. PIERREUX

**E.7 - Development of Functional Nutrients for the Control of Gut-Related Metabolic Diseases**

101

N. DELZENNE, P. CANI, A. NEYRINCK

**E.8 - *In vitro* and *in vivo* Pharmacological Evaluation of Anticoagulant and Antiplatelet Agents**

103

J.-M. DOGNÉ, B. MASEREEL, L. POCHET

**E.9 - Regulation of Glial Glutamate Transporters : Influence of Drugs and Diseases**

105

E. HERMANS

**E.10 - Cell Therapy of Liver Disease**

107

P. JACQUEMIN, F. LEMAIGRE, M. NAJIMI, E. SOKAL

**E.11 - Production and Purification of Native or Chimera Proteins for Structure-Based Drug Design**

109

D. LAMBERT, J. POUPAERT

**E.12 - Study of the Pathophysiological Mechanisms and Fundamental Pharmacotherapy In Cystic Fibrosis**

111

T. LEAL, J. LEBACQ, P. LEBECQUE, P. WALLEMACQ, F. HUAUX, E. MARBAIX

**E.13 - Obesity and Metabolic Syndrome : Pathogenic Role of the Liver and Hepatic Complications**

113

I. LECLERCQ, Y. HORSMANS, CH. SEMPOUX, P. CANI

---

**E.14 - Type-I Interferons and Central Nervous System Infections**

115

T. MICHIELS

---

**E.15 - *In Vitro* Models for the Evaluation of the Capacity of Drugs to Induce Lipid Storage Disorders and/or Apoptosis**

117

M.-P. MINGEOT-LECLERCQ, P. TULKENS, F. VAN BAMBEKE

---

**E.16 - *In Vitro* Models for the Biophysical Studies of the Interaction Between Drugs and Membrane Lipids**

119

M.-P. MINGEOT-LECLERCQ, F. VAN BAMBEKE, P. TULKENS

---

**E.17 - *In Vivo* DNA Delivery by Electroporation**

121

V. PREAT, G. VANDERMEULEN

---

**E.18 - Isolation, Structure Determination and Quantification of Bioactive or Antinutritive Metabolites from Plants**

123

J. QUETIN-LECLERCQ, J.-L. HABIB-JIWAN, M.-F. HÉRENT

---

**E.19 - Liver-Derived Progenitor Cells for Regenerative Medicine and Pharmacotoxicology Testing**

125

E. SOKAL, M. NAJIMI, X. STÉPHENNE, D. CAMPARD, F. SMETS

---

**E.20 - *In vitro* Models for the Evaluation of the Cellular Pharmacokinetics and Pharmacodynamics of Antibiotics**

127

P. TULKENS, F. VAN BAMBEKE, M.-P. MINGEOT-LECLERCQ

---

**E.21 - Cell Culture Models for the Study of the Mechanism of Accumulation and Efflux of Drugs in Eucaryotic Cells**

129

F. VAN BAMBEKE, P. TULKENS, M.-P. MINGEOT-LECLERCQ

---

**E.22 - Pulmonary Delivery of Biotech Drugs**

131

R. VANBEVER

**F. TECHNOLOGICAL PLATFORMS****F.1 - Mouse transgene technology platform**

133

Y. ACHOURI, P. JACQUEMIN, F. LEMAIGRE

---

**F.2 - Confocal and Atomic Force Microscopy for Imaging Biological Specimens**

135

H. BATOKO, C. BRAGARD, F. CHAUMONT, Y. DUFRENE, A. LEGREVE

---

**F.3 - Mass Spectrometry and Quantitative Proteomics Adapted to Membrane Proteins**

137

M. BOUTRY, H. DEGAND, P. MORSOMME

---

**F.4 - Statistical Methods, Computation and Software**

139

C. BUGLI, B. GOVAERTS, A. GUILLET, N. LEFÈVRE, C. LEGRAND

---

**F.5 - Cell and Tissue Imaging Platform**

141

P. COURTOY, D. TYTECA, C. PIERREUX, P. VAN DER SMISSEN

---

**F.6 - Protein Crystallography**

143

J.-P. DECLERCQ, A. SMEETS

---

**F.7 - Mycothèque de l'Université Catholique de Louvain**

145

C. DECOCK, S. DECLERCK, F. MUNAUT, F. VAN HOVE, H. M. DANIEL

---

**F.8 - Medicine and Science in Laboratory Animals**

147

J.-P. DEHOUX

---

**F.9 - WINFAB – Technological Platform – Micro- and Nano-Fabrication**

149

R. DELAMARE, M. VANDEN BULCKE, D. FLANDRE, J.-P. RASKIN

---

**F.10 - Bone Bank**

151

C. DELLOYE, O. CORNU, X. BANSE, P.-L. DOCQUIER

---

**F.11 - Detection, Identification and Typing of Bacterial Human Pathogens by Molecular Biology Methods**

153

M. DELMEE, G. GLUPCZYNSKI, J.-L. VAERMAN



**F.12 - Platform for Biochemical Profiling In Small Animals**

155

O. DEVUYST, S. TERRY, Y. CNOPS, S. DRUART

**F.13 - Nanotechnology of Biosurfaces**

157

Y. DUFRÈNE, C. DUPONT-GILLAIN

**F.14 - Data Analysis for High-Throughput Genomic Technologies**

159

P. DUPONT

**F.15 - Identification of Serological and Seric Biomarkers From Proteomic Analysis of Cancer or Cardiovascular Patient Blood**

161

O. FERON, F. DEFRESNE

**F.16 - Electrical Microsensors for DNA Analyses**

163

D. FLANDRE, J.-L. GALA, B. MACQ, S. MELINTE, J.-P. RASKIN

**F.17 - Center for Applied Molecular Technologies**

165

J.-L. GALA

**F.18 - Monoclonal or Polyclonal Antibodies of Rat, Mouse and Human Origin**

167

P. GIANELLO, Y. NIZET

**F.19 - High-Resolution Mass Spectrometry for the Identification of "Small" Molecules (Drugs, Metabolites, Functional Foods, Lipids...)**

169

J. QUETIN-LECLERCQ, J.-L. HABIB JIWAN, P. WALLEMACQ, Y. LARONDELLE

**F.20 - Proteomic and Mass Spectrometry Platform**

171

M. RAES, P. RENARD, C. MICHIELS, T. ARNOULD, O. TOUSSAINT, M. DIEU

**F.21 - Proteomics and Protein Analysis by Mass Spectrometry**

173

M. RIDER, D. VERTOMMEN

**F.22 - Cell Culture Systems as *in vitro* Model of the Intestinal Barrier**

175

Y.-J. SCHNEIDER, Y. LARONDELLE, V. PREAT

**F.23 - Pediatric Clinical Investigation Center**

177

E. SOKAL, F. SMETS, X. STÉPHENNE, C. WANTY, A. BOURGOIS, A. C. DUBOIS, V. LEGROS

**F.24 - Biobank for Vascular Anomalies**

179

M. VIKKULA, L. BOON, M. AMYERE, P. BROUILLARD, N. LIMAYE

**F.25 - Microarray Platform of UCL**

181

M. VIKKULA, M. AMYERE, J.-CH. RENAULD

**F.26 - Drug Analysis and Pharmacokinetic/Dynamic Relationship**

183

P. WALLEMACQ, V. HAUFROID

**G. BIOETHIC****G.1 - Bioethics**

185

M. BOTBOL-BAUM

**G.2 - Bioethics : Biomedical Research With Human Subjects**

187

M.-L. DELFOSSE

**G.3 - Bioethics, Human Rights and Legal Bionorms**

189

M.-L. DELFOSSE, C. BERT

**G.4 - Philosophical and Ethical Thought About Bioethics Issues**

191

M.-L. DELFOSSE

**G.5 - The Human Body and the Law**

193

X. DIJON

**G.6 - Biomedical Anthropology and Ethics**

195

M. DUPUIS

---

**G.7 - Ethical and Societal Stakes of  
Biotechnology**

197

B. FELTZ

---

**G.8 - Capacity Strengthening in Bioethics**

199

L. RAVEZ, C. TILMANS

---

**G.9 - Ethics in Assisted Reproductive  
Technologies**

201

L. RAVEZ, C. TILMANS

---

**G.10 - Medical and Biomedical Law**

203

G. SCHAMPS

---

# Surface and Interface Characterization

## SENIOR SCIENTISTS :

- ▶ Patrick BERTRAND
- ▶ Arnaud DELCORTE
- ▶ Sami YUNUS
- ▶ Claude POLEUNIS

## Research Field and Subjects

- ▶ The research activities concern the physical chemistry of solid surfaces and interfaces. The objective is to develop surface treatments and modifications in order to provide new surface properties for specific applications in materials science. To reach this goal, our approach is based on a control of the surface atomic and molecular composition and structure. The first step required on this road is to be able to characterize the solid surfaces in terms of chemical and functional composition and structure at the nanometer scale. For that purpose, our main expertise has been the development and the use of surface analytical methods based on the ion-solid interaction (Secondary Ion Mass Spectrometry and Ion Scattering Spectrometry – ISS and RBS), in combination with other surface techniques such as AES, XPS and the Near Field Microscopies (AFM, STM).
- ▶ More specifically, for fifteen years, we have been contributing to the development of the static SIMS technique for the molecular characterization of surfaces, with a special emphasis on organic materials such as polymers or proteins. Current developments are geared towards sub-micrometric 3D molecular imaging with C60 ion sources.
- ▶ The surface properties of interest are biocompatibility, specific catalytic activity, gas/ molecule permeability and adhesion. The methods used to modify the surface are based on chemical and physical treatments: plasma treatments, ion beam irradiation, chemical grafting, thin (organic / metallic) layer adsorption.
- ▶ We have studied surface modification protocols aiming to improve adhesive properties and biocompatibility. A special attention was paid to protein adsorption in view of controlling cell adhesion on micro-patterned polymer surfaces or to prevent biofouling. The group has also built a strong expertise in the field of biosensors, from the synthesis of conducting polymers (polyaniline) to the fabrication and characterization of fully integrated devices.
- ▶ The group has a long experience of collaboration with partners from university and industry research centers.

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## Funding

- ▶ European Commission
- ▶ Belgium French Community
- ▶ Belgium Walloon Region

## Partnership

- ▶ Centre Européen d'Etude du Diabète (Strasbourg) bio artificial pancreas
- ▶ IFREMER (Brest) see water biofouling
- ▶ Eppendorf (Namur) biosensor

## Main Equipment

Equipments for surface characterization :

- ▶ Secondary Ion Mass Spectrometry : 2<sup>(\*)</sup> static imaging time-of-flight mass spectrometers (ToF-SIMS)
- ▶ Rutherford Backscattering Spectrometry (using a VDG accelerator) RBS
- ▶ Scanning Auger Microprobe (AES-SAM)
- ▶ Access to AFM, STM, XPS-ESCA, SEM, TEM, XRD, Ellipsometry, static and dynamic contact angles, IR, Raman
- ▶ Access to clean room facilities

## Products and Services

Service provided to companies for practical surface characterization and imaging.

(\*) + a new instrument with automated 3D imaging capabilities at the end of 2009.

## KEY WORDS FOR R&D

Biofouling  
Biomaterials  
Biosensors  
Ion spectrometries  
Protein adsorption  
Surface characterization  
Surface modifications

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# Plant Cells As Factories for Pharmacological Proteins

## SENIOR SCIENTISTS :

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- ▶ Mélanie DELANNOY
- ▶ Catherine NAVARRE

## Research Field and Subjects

Heterologous expression of proteins in various biological systems (microorganisms, animal cells, plant cells) is now feasible. Plant and plant cells are convenient for expressing recombinant pharmaceutical and other proteins because they represent a versatile and inexpensive eucaryotic system.

Our research consists in improving the production of pharmacological proteins (antibodies, interleukins...) in plants and plant cells. Optimization of transformation vectors, transcription promoters and subcellular localization is carried out. To address the problem of degradation by extracellular peptidases secreted in the culture medium or in the leaf intercellular space, our current aim consists in preventing their expression by genetic engineering (RNA interference).

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## Awards

M. BOUTRY, member of the Belgian Academy of Sciences

## Partnership

This group belongs to the Institut des Sciences de la Vie, Louvain-la-Neuve, Belgium.

- ▶ This research is financed by the Région Wallonne (DGTRE) and the European Union.

## Main Equipment

- ▶ All present-day molecular biology and biochemistry equipments
- ▶ Bioreactor 4L

### **Products and Services**

- ▶ Gene cloning and heterologous expression
- ▶ Site-directed mutagenesis
- ▶ Design and transformation vectors
- ▶ Transformation of plant cells and plants for expression of heterologous proteins
- ▶ Follow-up expression
- ▶ Purification of proteins

### **KEY WORDS FOR R&D**

Genetic engineering  
Heterologous expression  
Molecular biology  
Pharmacological proteins  
Plant cells  
Plants  
Subcellular targeting  
Inducible promoter  
Peptidases

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# Development of Label-Free Biosensors Based on the Intrinsic Detection of Biomolecular Recognition, Using Nonlinear Optical Spectroscopies and Microscopies

## SENIOR SCIENTISTS :

- ▶ Yves CAUDANO
- ▶ André PEREMANS
- ▶ Paul A. THIRY

## Research Field and Subjects

- ▶ The biophysical research carried out by the LLS team of the Research Centre in Matter and Radiation Physics (University of Namur, FUNDP) relies on our know-how in the development of novel pulsed laser systems (optical parametric oscillators), tunable in the infrared and in the visible, with picosecond or nanosecond pulse duration. The team uses its strong experience with optical vibrational spectroscopy/microscopy, as well as with local probe microscopy to study nanomaterials, and the organisation of organic and biological molecules at interfaces.
- ▶ In particular, we pursue the development of label-free biosensors, based on the optical detection of the specific recognition occurring between complementary biological molecules. We use nonlinear optical spectroscopies (in particular, sum-frequency generation) and microscopies that do not necessitate the use of (fluorescent) markers.
- ▶ In this context, the team develops research on molecular self-assembly at surfaces, surface fast patterning by micro-contact printing, metallic nanoparticles, carbon nanotubes and fullerenes, biomimetic surfaces, DNA strands recognition, protein adsorption, antibody-antigen recognition. The team is also involved with applied research in dentistry (dental drilling by laser ablation and analysis of fluoride content in teeth).

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## Awards

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## Funding

- ▶ CERUNA-FUNDP
- ▶ EU (projet MIRSURG)
- ▶ FNRS
- ▶ FRFC
- ▶ FRIA
- ▶ RW

## Main Equipment

- ▶ Sum-frequency generation (SFG) spectrometer and microscope.
- ▶ Atomic force microscope (AFM) and scanning-tunnelling microscope (STM).
- ▶ High-resolution electron energy loss spectrometer (HREELS).

## Products and Services

- ▶ Surface and interface analysis by optical (SFG), electronic (HREELS) spectroscopies.
- ▶ Surface and interface analysis by optical (SFG), local probe (AFM-STM) microscopies.
- ▶ Picosecond tunable infrared (2.5-10  $\mu\text{m}$ ) and visible (410-710 nm) lasers.

## KEY WORDS FOR R&D

Biosensor  
Label free  
Optics  
Nonlinear optics  
Sum-frequency generation  
Molecular recognition  
Surface  
Interface  
Laser  
Microscopy  
Spectroscopy  
AFM

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# Brewing Sciences, Flavour Stability and Polyphenol Chemistry

## SENIOR SCIENTISTS :

- ▶ Sonia COLLIN
- ▶ Vesna JERKOVIC
- ▶ Marc MAUDOUX
- ▶ Laurent MELOTTE

## Research Field and Subjects

The team is mainly active in the improvement of flavour stability through ageing (impact of raw materials, manufacturing, processes...). This objective requires the knowledge of all chemical and biochemical pathways leading to food flavours (beer, wine, honey, chocolate...). A large part of the activity is focused on the structures and properties (in vitro activity, health-potential...) of new antioxidants, mainly polyphenols (flavonoïds and resveratrol analogues) and melanoidins. With the aim of having efficient methods for extracting or analyzing aroma, part of our job is also devoted to the mechanisms responsible for aroma retention in food. In the brewing area, other research topics are also investigated : mycotoxins, yeast activity, hop chemistry...

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## Awards

- ▶ G. LERMUSIEAU. *Interbrew Baillet Latour award, 1998*.
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- ▶ V. JERKOVIC. *Interbrew Baillet Latour award, 2003*.
- ▶ J. GROS. *Inbev Baillet Latour award, 2007*.

## Funding

- ▶ FNRS
- ▶ Industrials
- ▶ Region
- ▶ Cooperation

## Partnership

### 1 Industrial partners :

- ▶ Breweries
- ▶ Agro-food
- ▶ Industry
- ▶ Plastic producers

### 2 University partners :

- ▶ Laboratoire de physiologie cellulaire (Prof. B. ANDRÉ, IBMM, Belgium)
- ▶ INAPG (Paris Grignon, France)
- ▶ INRA (Dijon, Nantes, Rennes, France)
- ▶ Faculté d'oenologie de Bordeaux

## Main Equipment

- ▶ Several GC's including on column and split/splitless
- ▶ SPME
- ▶ Static and dynamic headspace injectors
- ▶ FID, NPD, ECD, SCD, PFPD detectors
- ▶ GC-MS
- ▶ GC-olfactometry
- ▶ Several HPLC's including UV, fluorescence, refractometry and electrochemical detection
- ▶ Semi-preparative HPLC
- ▶ HPLC/diode array/MS-MS (ESI and APCI)
- ▶ Micro-brewery
- ▶ Fermentation material (including 30 L and 300 L fermentation vessels)
- ▶ Usual material for malt and beer analyses
- ▶ Various volatile extraction systems
- ▶ Sensory analysis

## Products and Services

- 1 Malt and beer analyses, consulting, new product design (« Centre de référence pour la qualité des malts et de la bière »)
- 2 Extraction, identification and quantification of food flavours and food packaging volatiles
- 3 Polyphenol analysis

## KEY WORDS FOR R&D

Aroma  
Beer  
Cocoa  
Fermentation  
Flavour stability  
Hop  
Mycotoxins  
Polyphenols  
Resveratrol  
*Saccharomyces cerevisiae*  
Sulphur flavours  
Wine

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# Electrochemistry and Surface Chemistry of Biomaterials

## SENIOR SCIENTISTS :

- ▶ Joseph DELHALLE
- ▶ Zineb MEKHALIF

## Research Field and Subjects

The main objectives of our research are the design and elaboration of surface and interfacial materials (thin and ultra-thin organic and inorganic films on metal, oxide and polymer substrates) by chemistry processes (electrochemistry, self-assembly from solutions, sol-gel film deposition...). The general interest is to obtain structured surface materials with new and/or improved properties by resorting to the bottom-up approach which largely depends on the control of the processes and interactions at the molecular level. The major topics are :

*Molecular self-assembly on active metal : from fundamental to application.*

The objectives are to chemically graft on various substrates organic monolayers or multilayers. Achievements have been made possible thanks to our increasing experience and control of the modifications of substrates of noble metal (Au, Ag and Pt) and (re) active metals (Ni, Cu, Zn, Al, Ti and Ta) by bifunctional molecular connectors (X-spacer-Y) where -X is a reactive group (-SH, -SeH, -S-S-, -SiR<sub>3</sub>, -PO(OH)<sub>2</sub>...) selected to preferentially react with the surface substrate. The group -Y is chosen to impart either specific end-properties to the modified substrate (lubrication, anti-wear, corrosion resistance, anti-fouling, controlled wetting...) and/or (re)activity for additional surface processes (chemical anchoring and/or induced growth of one or more additional layers).

*Modern electrochemistry as powerful tools for surface analysis and modification*

Analysis of metallic substrates (in their metallic and oxidised states, before and after modification) is an important part of our research. The routine surface spectroscopic techniques (XPS, AES, ToF-SIMS) provide valuable information of the film structure down to the molecular level, and in some cases information on the elementary steps entering the film formation. Yet, it is also crucial to assess the way these films respond to operational stimuli (voltage, electrochemical potential, pH changes...) and to detrimental effects (corroding atmosphere, mechanical stresses...). This is the reason why we have become increasingly interested in local electrochemical techniques (scanning Kelvin probe or SKP, scanning

vibrating electrode or SVET and scanning electrochemical microscope or SECM) to assess, for example, the quality (resistance to degradation, homogeneity...) of the elaborated films.

*Towards biomaterials*

Our main actual focus is on :

- ▶ Self-assembly of organophosphonic acids and organosilanes on biomaterials.
- ▶ Corrosion investigation of biomaterials in physiological liquid and development of new molecular corrosion inhibitors
- ▶ Surface electrochemical treatment of biomaterials towards M.R.I. visibility
- ▶ Electrodeposition of tantalum and tantalum oxides and composites with CNTs from ionic liquids
- ▶ Molecular structuration of surfaces for hydroxyapatite growth
- ▶ Elaboration of nanobiosensors combining self-assembly chemistry and electrochemistry for fabrication and analysis and read-out of the sensor.
- ▶ Carbon nanotubes fonctionnalisation for toxicity evaluation
- ▶ Electrografting for biocompatibilisation

## Representative References

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## Funding

RW, ESA, EU, Industries

## Partnership

- ▶ Prof. P. SCHMUKI (U. Erlangen, DE)
- ▶ Prof. I. MARKO (UCL)
- ▶ Cardiatis
- ▶ ESA
- ▶ Nanocyl
- ▶ Arcelor

## Main Equipment

- ▶ Potentiostats-Galvanostats
- ▶ Electrochemical Impedance spectrometer (EIS)
- ▶ Electrochemical Quartz Microbalance (EQCM)
- ▶ Scanning Vibrating Electrode Technique (SVET)
- ▶ Scanning Kelvin Probe (SKP)

- ▶ Scanning Electrochemical Microscope (SECM)
- ▶ FTIR PM-IRRAS
- ▶ Infrared microscope
- ▶ Spectroscopic ellipsometer
- ▶ Contact angle measurements
- ▶ Equipment for synthesis (coupling molecules, carbon nanotubes)
- ▶ Access to: XPS, ToF-SIMS, SEM, TEM, XRD, NMR

## Products and Services

- ▶ Design, analysis and modification of surface and interfacial materials.
- ▶ Synthesis of thin and ultra-thin organic and inorganic films on metal, oxide and polymer substrates.
- ▶ Expertise in chemistry processes (electrochemistry, self-assembly from solutions, sol-gel film deposition...).
- ▶ Characterization of surface materials (electrochemical, infrared, ellipsometry...).

## KEY WORDS FOR R&D

Self-assembled monolayer  
Surface and interface  
Local electrochemistry  
Corrosion  
Nanomaterials  
Electrodeposition  
Ionic liquid  
Biomaterials

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# Nano-Bio-Sensors Based On Nanowires Of Conjugated Polymers

## SENIOR SCIENTISTS :

- ▶ Sophie DEMOUSTIER-CHAMPAGNE
- ▶ Alain M. JONAS
- ▶ Bernard NYSTEN

## Research Field and Subjects

We are partners of a large-scale excellence program aiming at developing swarms of bio-sensors capable to communicate with their environment. More specifically, we concentrate on the application of nanotechnologies and nanomaterials for the development of such bio-sensors. In this frame, we investigate methods allowing to produce rapidly sensors based on nanowires of conjugated polymers, either conducting or semi-conducting, grafted with transducing bio-macro-molecules such as antigens, antibodies, chimeric enzymes, or DNA. Different methodologies of nanowire production are explored, including nano-imprint lithography of conjugated polymers, and templated growth of hybrid multi-sequenced nanowires from track-etched membranes or phages. Also investigated are the assembly of the nanowires and the grafting of bio-receptors on them. Different transduction methods are explored in different configurations, including impedance sensors and field-effect transistors.

## Representative references and patents

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- ▶ V. BAYOT, F. BLONDEAU, B. DE MEERSMAN, S. DEMOUSTIER-CHAMPAGNE, A. M. JONAS, B. NYSTEN, X. TANG. *Method and Device for High Sensitivity and Quantitative Detection of Chemical/ Biological Molecules.* European Patent Application EP-07014037.1, **2007**.
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## Funding

- ▶ Wallonia Region (Nanotic-Feeling Excellence Program)
- ▶ Federal Government of Belgium (InterUniversity Attraction Pole "Functional Supramolecular Systems")

## Partnership

- ▶ Prof. P. SOUMILLION (Life Science Institute, University of Louvain)
- ▶ Profs. P. BERTRAND and L. PIRAUX (Institute of Condensed Matter and Nanosciences, University of Louvain)
- ▶ Profs. D. FLANDRE and S. MELINTE (Institute of Information Technology, Communication, Electronics and Applied Mathematics)
- ▶ Prof. J.-L. GALA (Internal Medicine, University of Louvain)

## Main Equipment

- ▶ Clean-rooms facilities
- ▶ E-beam nanolithography
- ▶ Electrochemical analysis & synthesis (chronoamperometry, voltametry...)
- ▶ High-resolution scanning electron microscopy (FE-SEM with EDX)
- ▶ Nano-imprint lithography
- ▶ Scanning probe microscopies (STM, AFM)
- ▶ Spectroscopies: FTIR, Raman, UV-visible
- ▶ Transmission electron microscopy (TEM with EELS & EDX)
- ▶ X-ray diffraction (X-ray reflectometry)
- ▶ Access to surface analysis facilities (XPS, ToF-SIMS, contact angle)

## Products and Services

We offer surface bioconjugation methodologies to graft biomacromolecules on surfaces (including patterned surfaces), advanced analytical tools to characterize such biofunctional interfaces, and nanofabrication methods applied to (bio) macromolecular materials.

## KEY WORDS FOR R&D

Antibodies, antigens  
Bio-sensors  
DNA  
Electroanalysis  
Instrumentation  
Micro- & nano-electronics  
Nanoimprint  
Nanolithography  
Nanotechnologies  
Proteins  
Surfaces

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# Process Modeling, Monitoring, Control and Real-Time Optimisation

SENIOR SCIENTIST :

► Denis DOCHAIN

## Research Field and Subjects

The main area of expertise is related to the mathematical modelling of the dynamics of biological systems, the analysis of the model properties, and the design and application of model-based monitoring, control algorithms and real-time optimisation tools, with application to food, pharmaceutical, environmental and other bioprocesses, as well as to biomedical systems and plant growth.

The need for appropriate monitoring and control tools in order to optimize the on-line operation of biological systems is obvious. Yet the development of such tools has to handle typically two key issues. The first one is related to the difficulty to model the complex dynamics of the biological systems in reliable way. The second difficulty lies in the absence of cheap and/or reliable on-line sensors for the key system variables. These issues are in the core of the expertise developed over the last 25 years.

Well accepted trends in the biotechnology industry require plants to be flexible in order to adapt in real-time to market driven demand and to comply with safety and environmental requirements. This, in turn, translates into the need of integrated tools for wide-plant operation support, that by having full access to plant conditions, are able to predict through reliable models, future scenarios and plant malfunction, and from them to re-adjust in an optimal fashion operation conditions over the different elements of the plant.

The developed approaches are largely based on mass (and energy) balance models. One of the underlying ideas is to incorporate the knowledge about the process dynamics (e.g. basically, the metabolic network and the material balances) in monitoring and control algorithms; moreover the latter are able to deal with process uncertainties (in particular on the reaction kinetics) by introducing, an adaptation scheme.

The monitoring and control strategies are applied to stirred tank reactors (dynamics described by ordinary differential equations) as well as to processes, the dynamics of which are described by partial differential equations, such as plug flow reactors, fixed or fluidised bed reactors or settlers as well as population bal-

ance based models (for processes with size-distributed particles or age-distributed cells). The complexity of the dynamics of the biological systems is also handled by considering possibly complex metabolic networks as well as microbial ecology to emphasize the interactions between the different, possibly competing, species. Monitoring is related in particular to the design of software sensors that are based on the available knowledge on the process dynamics and the limited number of process variables measured on-line in order to reconstruct on-line the values of the unmeasured key process variables. A special attention is also given to the design and implementation of real-time optimisation methods via adaptive extremum seeking control techniques that allow the process to reach a priori unknown optimal operating points, trajectories or profiles. Applications in this field involve also the biomedical field via an on-line optimisation strategy for drug delivery.

Several research projects have been carried out in cooperation with industrial partners. This includes a EC FP7 project "Computer-aided food processes for control engineering" (CAFÉ), and an ESA project (MELISSA) on plant growth.

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## Funding

- ▶ European Commission
- ▶ European Space Agency
- ▶ Walloon Region
- ▶ Private companies

## Partnership

- ▶ INRA  
Dr A. Rapaport. Laboratoire d'Analyse des Systèmes et de Biométrie, Montpellier
- ▶ Dr J. Harmand, Dr J.-Ph. Steyer. Laboratoire de Biotechnologie de l'Environnement, Narbonne
- ▶ Prof. A. Paus, Dr. O. Schoefs. Université de Technologie de Compiègne, Département de Génie Chimique
- ▶ Prof. M. Perrier. Ecole Polytechnique de Montréal, Département de Génie Chimique
- ▶ Prof. M. Guay, Prof. J. Ramsay. Queen's University, Chemical Engineering Department

## Main Equipment

Computers

## Products and Services

- ▶ Dynamical models
- ▶ Software sensors
- ▶ Control algorithms
- ▶ Real-Time Optimisation tools

## KEY WORDS FOR R&D

Modelling  
Monitoring  
Estimation  
Software sensor  
Control  
Real-time optimisation  
Population balance  
Metabolic network  
Microbial ecology

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# *In vitro* Production and Cryopreservation of Bovine Embryos

## SENIOR SCIENTIST :

► Isabelle DONNAY

## Research Field and Subjects

### 1 *In vitro* production of bovine embryos

*In vitro* produced bovine embryos are obtained after *in vitro* maturation, fertilization and culture of embryos up to the blastocyst stage. This technique allows to dramatically increase the number of calves obtained from one female and can be used in breeding programmes or in order to save the genetics of infertile valuable cows.

It represents also an ideal tool for fundamental research on gamete interaction and early embryo development in mammals. The optimization of embryo production implies research on the three main steps of embryo production. It is also necessary to define quality markers for gametes and embryos at different stages of the procedure.

Our laboratory is mainly specialized in the study of :

- The kinetics of development by time-lapse cinematography
- Embryo metabolism, including markers of oxidative stress and apoptosis
- Embryo sexing and gene expression by RT-PCR

### 2 Gene expression in mammalian oocytes and early embryos

Early embryonic development is under the control of proteins and mRNA accumulated in the oocyte before fertilization. mRNA storage or degradation in the oocyte and the regulation of their translation is unique. The major onset of the embryonic genome occurs in the bovine 3 days post-insemination. Few are known about the regulation of the embryonic genome during this onset and the first step of differentiation occurring at the morula/blastocyst stage.

Our current researches in this area are related to :

- The polyadenylation/deadenylation of transcripts and their translation during oocyte maturation
- The kinetics of expression of specific genes (including HOX genes) during oocyte maturation, early embryonic development and the first steps of embryo differentiation

### 3 Cryopreservation and cryobanking (gametes and embryos)

The widespread use of *in vitro* produced embryos is facilitated by their cryopreservation. However, such embryos are more sensitive to cryopreservation than their *in vivo* counterparts. Our research focuses on the improvement of the resistance of bovine IVP blastocysts to cryopreservation, by increasing their quality or by adapting the freezing procedures. Another applied project is related to the resistance to cryopreservation of bovine and equine sperm, in collaboration with the Association wallonne de l'Élevage. We are also involved in a project of creation of a cryobank to preserve the genetics of local breeds of domestic ruminant species in Belgium (in collaboration with Prof. Ph. BARET, Unité de Génétique).

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## **Awards**

*Prize A. Brachet*, from the Royal Academy of Sciences, Belgium, **2007**.

## **Funding**

- ▶ Fonds National de la Recherche Scientifique (FRFC et crédits aux chercheurs)
- ▶ Ministère de la Région wallonne

## **Partnership**

- ▶ Prof. A. VAN SOOM, UGent, Belgium
- ▶ Dr P. MERMILLOD, INRA, France
- ▶ Association wallonne de l'Élevage (AWE), Belgium

## **Main Equipment**

- ▶ IVF laboratory
- ▶ Time lapse cinematography
- ▶ Microinjection
- ▶ RT-PCR
- ▶ Programmed freezing

## **KEY WORDS FOR R&D**

In vitro fertilization  
Gametes and embryo cryopreservation  
Gene expression  
Embryo metabolism  
Embryo sexing  
Cryobanking

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# Design of a Scaffold for Human Isolated Follicle Transplantation

## SENIOR SCIENTISTS :

- ▶ Jacques DONNEZ
- ▶ Marie-Madeleine DOLMANS
- ▶ Christiani AMORIM
- ▶ Anne VAN LANGENDONCKT

## Research Field and Subjects

### Aim

The aim of this project is to design a device or vehicle to graft isolated ovarian follicles or small fragments of ovarian tissue back to the patient after radio-or chemotherapeutic anti-cancer treatment, capable of restoring normal ovarian function with hormone production and fertility.

### Background

Cryopreservation and transplantation of ovarian tissue is a promising approach to preserve fertility of young cancer patients undergoing gonadotoxic treatment. Transplantation of cryopreserved ovarian tissue allows the restoration of ovarian function and fertility. Although safe xenotransplantation of ovarian tissue from lymphoma patients has been reported in SCID mice, the possibility of reintroducing tumour cells into cancer patients by autografting of ovarian tissue cannot be excluded for other indications such as leukemia and breast cancer. To avoid transferring malignant cells, grafting of isolated follicles may be considered. We have recently demonstrated the in vivo growth of isolated human pre-antral follicles up to the antral stage in a SCID mouse model. In order to apply this approach in clinical practice an appropriate matrix needs to be designed as vehicle for isolated follicle grafting and support for their growth. The main goal of the project is thus to develop a 3-dimensional scaffold to graft isolated primordial follicles that could act like a temporary surrogate for native extracellular matrix and allow the formation of an ovary-like structure.

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- ▶ C. A. AMORIM, A. VAN LANGENDONCKT, A. DAVID, M.-M. DOLMANS, J. DONNEZ. *Survival of human pre-antral follicles after cryopreservation of ovarian tissue, follicular isolation and in vitro culture in a calcium alginate matrix*. Human Reproduction 24, 92-9, **2009**.

## Patents

European Patent Application n° 07117661.4-1219 : « Scaffolds for follicle transplantation »

## Partnership

- ▶ Inter-university : Ulg, ULB & UCL
- ▶ CERM Ulg

## Funding

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

## Main Equipment

- ▶ Programmable freezers
- ▶ Facilities for cell and follicle culture

## Products and Services

Scaffold for human ovarian follicle grafting

## KEY WORDS FOR R&D

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

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# Physical Chemistry of Biosurfaces

## SENIOR SCIENTISTS :

- ▶ Christine DUPONT-GILLAIN
- ▶ Yves DUFRENE

## Research Field and Subjects

The laboratory is dedicated to the physical chemistry of colloids and surfaces, and to the application of this discipline, particularly to material science and bioengineering.

The research of this team is focused on the study of interfaces involving bioconstituents and on the understanding of interfacial phenomena (adsorption, adhesion, flocculation, aggregation).

Recent achievements concern :

- 1 The elaboration and, or characterization of organic surfaces (polymer and model surfaces with controlled properties, food constituents).
- 2 The understanding of adhesion between materials.
- 3 The relationships between chemical composition, nanometer-scale organization and properties of biosurfaces (proteins, lipids, microbial cells).
- 4 The supramolecular organization of films of adsorbed proteins and lipids and its dependence on substratum properties and processing factors.
- 5 The understanding and control of interfacial processes (biofilm formation, aggregation) involving microorganisms, in relation with fermentation and environment protection.
- 6 The understanding and control of mammalian cell adhesion (relation with substratum surface properties and protein adsorption, influence of substratum surface heterogeneity at different scales).

The following topics are currently addressed :

- ▶ Nanoscale properties of biosurfaces (see details in topic "Nanotechnology of biosurfaces") : materials, hemocompatibility, thin layers of proteins and lipids, microbial cells, mammalian cells.
- ▶ Influence of adsorption on the activity of enzymes (model systems, environmental systems).
- ▶ Design of smart material surfaces in order to reduce fouling and biofilm formation.

## Representative References

- ▶ Z. KERESZTES, P. G. ROUXHET, Cl. REMACLE, Chr. DUPONT-GILLAIN. *Supramolecular assemblies of adsorbed collagen affect the adhesion of endothelial cells*. J. Biomed. Mater. Res. 76A, 223-233, **2006**.
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- ▶ P. G. ROUXHET, A.-M. MISSELYN-BAUDUIN, F. AHIMOU, M.-J. GENET, Y. ADRIAENSEN, T. DESILLE, P. BODSON, C. DEROANNE. *XPS analysis of food products: toward chemical functions and molecular compounds*. Surf. Interface Anal. 40, 718-724, **2008**.
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- ▶ E. DAGUE, A. DELCORTE, J.-P. LATGE, Y. DUFRÈNE. *Combined use of atomic force microscopy, X-ray photoelectron spectroscopy, and secondary ion mass spectrometry for cell surface analysis*. Langmuir 24, 2955-2959, **2008**.
- ▶ S. CAILLOU, P. A. GERIN, C. J. NONCKREMAN, S. FLEITH, Chr. DUPONT-GILLAIN, J. LANDOULSI, S. M. PANCERA, M.-J. GENET, P. G. ROUXHET. *Enzymes at solid surfaces: nature of the interfaces and physico-chemical processes*. Electrochim. Acta 54, 116-122, **2008**.
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## Patents

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- ▶ Chr. DUPONT-GILLAIN, P. G. ROUXHET. *Method for controlling the morphology of a polymer surface and said obtained polymer surface*. Int. Patent Application n° PCT/EP01/14862, **2001**.

## Funding

- ▶ FNRS
- ▶ Région Wallonne
- ▶ Action de Recherche Concertée
- ▶ Interuniversity pole of attraction program Industrial funding

## Partnership

Companies :

- ▶ AGC
- ▶ THT Research
- ▶ Kitozyme

Partner of :

- ▶ Institut de la matière condensée et des nanosciences (IMCN, UCL)
- ▶ Institut des Sciences de la Vie (ISV, UCL)
- ▶ Wallonia Network for Nanotechnologies (NANOWAL)

## Main Equipment

- ▶ X-ray photoelectron spectrometer (XPS)
- ▶ Atomic force microscope (AFM)
- ▶ Quartz crystal microbalance (QCM-D)
- ▶ Streaming potential measurements
- ▶ Contact angle measurements
- ▶ Dynamic wetting
- ▶ Surface tension measurements
- ▶ Bioadhesion devices
- ▶ Image analysis

## Products and Services

- ▶ Chemical composition of surfaces
- ▶ Wetting properties of surfaces (contact angle, wetting dynamics)
- ▶ Electrical properties of surfaces (zeta potential)
- ▶ Supramolecular organization of surfaces

## KEY WORDS FOR R&D

Adhesion, cells  
Adsorption, proteins, lipids, polymers  
Bioadhesion  
Biocompatibility  
Biomaterials  
Biomembranes  
Enzymes, adsorption, activity  
Lipids, membranes  
Polymers, surfaces  
Proteins, adsorption  
Smart surfaces  
Surfaces

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# Electrical Detection of Pathogens

## SENIOR SCIENTISTS :

- ▶ Denis FLANDRE
- ▶ Laurent FRANCIS
- ▶ Yannick NIZET
- ▶ Joris PROOST
- ▶ Patrice SOUMILLION

## Research Field and Subjects

Rapid, real-time detection of pathogenic microorganisms is an emerging and quickly evolving field of research, especially with regard to microorganisms that pose a major threat to public health. In our laboratories, interdigitated capacitive microsensors covered by metal oxides are investigated for that sake.

In this work, we study the interactions and selections of phages directly with various metal oxides, the latter being synthesised by anodising of thin metal films. The use of phages is believed to be a much more selective and durable alternative to conventional surface functionalisation techniques, both for diagnostic and therapeutic purposes.

Secondly, our sensors have been tested for bacteria detection by coating them with an anti- *Staphylococcus aureus* monoclonal antibody (MoAb), which permits a significant capacitance shift with very good selectivity between a positive sample, here *Staphylococcus aureus*, and a negative one, here *Staphylococcus epidermidis*. Furthermore the capacitance variation appears proportional to the number of bacteria grafted on the chip and compatible with the specific detection of less than 100 bacteria.

Finally, optical measurements in microfluidic platforms are targeted.

## Representative References

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- ▶ O. BULTEEL, P. DUPUIS, S. JEUMONT, L.-M. IRENGE, J. AMBROISE, B. MACQ, J.-L. GALA, D. FLANDRE. *Low-cost miniaturized UV photosensor for direct measurement of DNA concentration within a closed tube container*. European congress for medical and biomedical engineering, Antwerp, Belgium, 23-27 November **2008**.

- ▶ D. MERCIER, R. SANTORO, P. SOUMILLION, J. PROOST. *"Selection of amino acid sequences on metallic oxide surfaces"*. 9th Workshop on Biosensors and bioanalytical microtechniques in environmental and clinical analysis, Montreal, Canada, June **2009**.

## Patents

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## Awards

- D. FLANDRE. « *DNA electrical detection experiments with alumina passivated CMOS sensors* ». "Invited lectures" at Hasselt University, IMEC Research center, Singapore.

## Funding

Région wallonne

## Partnership

NANOTIC – Programme d'excellence de la Région wallonne, 2005-2010.

## Main Equipment

- ▶ The largest research-oriented clean room facilities (1000 m<sup>2</sup>) in Wallonie with the all key technologies required for micro/nano-systems and micro/nano-electronics fabrication.
- ▶ Characterization techniques : optical and electrical in a large range of frequencies and temperature.

## Products and Services

Fabrication and characterization of electrical and optical bio-micro-nano-sensors :

- ▶ Variable capacitive structures
- ▶ Microwave detectors
- ▶ Inorganic nanowires
- ▶ Microfluidic channels
- ▶ Silicon-on-Insulator photodiodes

## KEY WORDS FOR R&D

Electrical detection  
Bacteries, Phages  
Micro-sensors  
UV photodiode

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# Functional Magnetic Resonance (NMR, EPR) Spectroscopy and Imaging in Small Animals

## SENIOR SCIENTISTS :

- ▶ Bernard GALLEZ
- ▶ Bénédicte JORDAN

## Research Field and Subjects

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

Development of sensors for monitoring the oxygen in tissues by EPR  
Selection of paramagnetic materials possessing favourable features for oximetry. Microencapsulation of oxygen sensors in bio-compatible films to improve their performance in vivo and their biocompatibility.

Applications of MR (EPR and NMR) to characterize the micro-environment in tumors and modulate the response to anti-cancer treatments

Use of combination therapies against cancer (vasoactive agents + radiotherapy / antiangiogenesis + radiotherapy / ...) to improve the response of tumors to treatments : characterisation of pO<sub>2</sub>, flow, oxygen consumption, permeability of vessels, nitric oxide ... and correlation with the tumor growth.

Development of predictive biomarkers of tumor response to a treatment

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

## Representative References

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- ▶ N. CROKART, K. RADERMACHER, B. JORDAN, C. BAUDELET, G. O. CRON, V. GRÉGOIRE, N. BEGHEIN, C. BOUZIN, O. FERON, B. GALLEZ. *Tumor radiosensitization by anti-inflammatory drugs : evidence for a new mechanism involving the oxygen effect*. Cancer Res. 65, 7911-7916, **2005**.
- ▶ B. JORDAN, M. RUNQUIST, N. RAGHUNAND, A. BAKER, R. WILLIAMS, L. KIRKPATRICK, G. POWIS, R. GILLIES. *Dynamic contrast-enhanced and diffusion MRI show rapid and dramatic changes in tumor microenvironment in response to inhibition of HIF-1alpha using PX-478*. Neoplasia 7, 475-485, **2005**.

- ▶ R. ANSIAUX, C. BAUDELET, B. JORDAN, N. CROKART, P. MARTINIVE, J. DE WEVER, V. GRÉGOIRE, O. FERON, B. GALLEZ. *Mechanism of reoxygenation after anti-angiogenic therapy using SU5416 and its importance for guiding combined anti-tumor therapy*. Cancer Res. 66, 9698-9704, **2006**.
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- ▶ G. O. CRON, N. BEGHEIN, R. ANSIAUX, P. MARTINIVE, O. FERON, B. GALLEZ. *<sup>19</sup>F NMR in vivo spectroscopy reflects the effectiveness of perfusion-enhancing vascular modifiers for improving gemcitabine chemotherapy*. Magn. Reson. Med.59, 19-27, **2008**.
- ▶ E. VANEA, N. CHARLIER, J. DEWEVER, M. DINGUIZLI, O. FERON, J.-F. BAURAIN, B. GALLEZ. *Molecular EPR Imaging of Melanin in Melanomas: a proof-of-concept*. NMR Biomed. 21, 296-300, **2008**.
- ▶ B. JORDAN, G. O. CRON, B. GALLEZ. *Rapid monitoring of oxygenation by <sup>19</sup>F magnetic resonance imaging : simultaneous comparison with fluorescence quenching*. Magn. Reson. Med. 61, 634-638, **2009**.

## Patents

- ▶ G. POWIS, R. GILLIES, A. BAKER, B. JORDAN. *Method of preselecting for anti VEGF, anti-HIF-1 or anti-Thioredoxin Therapy*. US n°20060104902, **2006**.
- ▶ B. GALLEZ, R. ANSIAUX. *Methods and compositions for the treatment of cancer*. WO/2006/094539, PCT/EP2005/011145, **2005, 2006**.

## Awards

- B. GALLEZ :
  - ▶ *Prix de la Société Belge des Sciences Pharmaceutiques*, **1995**.
  - ▶ *Prix des Alumni de la Fondation Universitaire* (Section : Sciences médicales, pharmaceutiques et vétérinaires), **1998**.
  - ▶ *Prix Paul Van de Velde* (Nouveaux outils diagnostiques ou thérapeutiques), **2000**.
  - ▶ *Young Investigator Award of the International EPR Society*, **2000**.

‣ *Prix Léopold et Marthe Delsaux-Champy* (Prévention, traitement ou physiopathologie de maladies cardiovasculaires ou cancéreuses), **2004**.

‣ *Prix du Concours ordinaire de la 5me section de l'Académie Royale de Médecine de Belgique*, Période **2005-2006**.

B. JORDAN :

‣ *Prix Ishango francophone*, **2003**.

## Funding

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

## Partnership

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

## Main Equipment

- NMR spectrometer and imaging 11.7 T for small animals
- 2 EPR spectrometers (9 GHz, X-Band) for in vitro experiments
- EPR spectrometer (1 GHz, L-Band) for in vivo experiments
- EPR imaging (1GHz and 9GHz)

‣ OxyLite (pO<sub>2</sub> measurements by fluorescence quenching)

‣ OxyFlo (laser-doppler)

## Products and Services

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

## KEY WORDS FOR R&D

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

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# Cloning, Modification and Expression of Hydrolases

## SENIOR SCIENTIST :

Isabelle HOUSEN

### Research Field and Subjects

The research efforts are focused on the isolation of hydrolases from the acidophilic fungus *Scytalidium acidophilum* and on the engineering of hydrolases by mutagenesis.

Potential applications of this research are the transformation of agricultural waste into products with high added-value and the improvement of enzyme activity in an industrial and economic context.

This research area is at the intersection of Molecular Biology and Bioengineering.

**Cloning** of new hydrolases is done through screening of genomic libraries with probes designed by sequence alignments or deduced from peptide fragments identified by mass spectrometry. **Expression** of hydrolases is done in yeast (*Saccharomyces cerevisiae* or *Pichia pastoris*) or in bacteria (*Escherichia coli*). **Modification** of hydrolases is done through random or directed mutagenesis or pentapeptide mutagenesis.

**Characterization** of hydrolases implies purification and activity tests. Sugar profiles are analysed by Dionex and GC chromatography. Crystal structures of some of them have already been obtained.

### Representative References

- ▶ B. AL BALAA, J. WOUTERS, S. DOGNE, C. ROSSINI, J.-M. SCHAUS, E. DEPIEREUX, J. VANDENHAUTE, I. HOUSEN. *Identification, Cloning, and Expression of the Scytalidium acidophilum XYL1 Gene Encoding for an Acidophilic Xylanase*. *Biosci. Biotechnol. Biochem.* 70, 269-272, **2006**.
- ▶ B. AL BALAA, K. BRIJS, K. GEBRUERS, J. WOUTERS, J. VANDENHAUTE, I. HOUSEN. *A Single E141A mutation in the xylanase XYL1 from Scytalidium acidophilum improves its activity at pH 4.0*. In revision in *Bioresource Technology*, **2009**.

### Patents

I. HOUSEN, P. COPPE, E. DEPIEREUX, J. VANDENHAUTE. *Enzyme with xylanase activity at acidic pH*". PCT Int. Appl. WO2004/106510.

### Awards

*Prix Wernaers, 2001*.

### Funding

RW

### Partnerships

- ▶ D. HERMAND, Unité de recherche en biologie moléculaire, FUNDP, Namur
- ▶ X. DE BOLLE, Unité de recherche en biologie moléculaire, FUNDP, Namur
- ▶ J. WOUTERS, Laboratoire de chimie biologie structurale, FUNDP, Namur
- ▶ M. PAQUOT, Unité de Chimie Biologique Industrielle, FUSAGx, Gembloux
- ▶ Cosucra Groupe Warcoing

### Main Equipment

Molecular biology and biochemistry equipments

### Products and Services

- ▶ Cloning of your gene of interest
- ▶ Expression of your protein
- ▶ Molecular analyses of gene of interest

**KEY WORDS FOR R&D**

Genetic engineering  
Cloning  
Mutagenesis  
Protein engineering  
Protein expression  
Protein purification  
Protein crystallisation  
Hydrolases  
Hydrolase activity tests  
Sugar analyses

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# Global Assistance System for Orthognathic Planning and Surgery

## SENIOR SCIENTISTS :

- ▶ Benoît MACQ
- ▶ Benoît RAUCENT
- ▶ Hervé REYCHLER
- ▶ Raphaël OLSZEWSKI

## Research Field and Subjects

The main objective of the research is to develop a global assistance system in order to improve the performances of orthognathic planning and surgery. This kind of surgery consists in correcting the dysmorphoses affecting the skull and face by cutting the bone and repositioning the bony fragments. The system design aims at improving the current planning (cephalometric analysis on lateral radiography for diagnosis and virtual planning, plaster cast model surgery) and the preoperative/intraoperative transfer (acrylic splint).

In this project, the research is declined into 3 main steps :

**1** In the first step, we develop an original three dimensional cephalometric analysis based on a transformation of the 2D Delaire analysis. The method consists in two stages. First, we chose landmarks corresponding to specific anatomical points on the 3D surface models. Second, we construct plans from these point. ACRO3D software is developed in order to perform this cephalometric analysis. ACRO3D is integrated on the MedicalStudio platform. The software guides the user through the manual point-picking procedure in a systematic way. In this way, 22 landmarks are picked on a 3D surface extracted from images dataset of the head of the patient coming from a CT SCAN. Some landmarks are automatically identify and constructed. The software reduce the workload by computing and automatically construct 13 planes from previous identify landmarks. These planes allows to extract information and to compute the correct positioning of the maxillary and the mandibular. The cephalometric analysis is followed of a data-processing simulation of the operation.

**2** The second step concerns the development of extra and intra operative robotic devices for orthognathic and cranio-maxillofacial surgery. A first stage consists in designing an interface between the planning system and the robotized system. This device design guarantees the elaborate system accuracy. The robot architecture is designed under ergonomics and economical constraints. Once the robot architecture is chosen, the design and electric manufacture can begin with the dSpace material. The realization of a dedicated electronic system is then elaborate in order to obtain a complete demonstrator. Then, the fixing system is designed and built in order to join the jawbones and the fragments with the robot.

**3** The third step consists in the production of physical guide for positioning osteosynthesis plates and making osteotomy lines.

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- ▶ R. OLSZEWSKI, K. TRAN DUY, B. RAUCENT, A. HEBDA, H. REYCHLER. « *Communicating a clinical problem to the engineers : towards a common methodology.* » Int J. Oral Maxillofac Surg. 37(3) : 269-74, Mar **2008**.
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- ▶ R. OLSZEWSKI, M. VILLAMIL, D. TREVISAN, L. NEDEL, C. FREITAS, H. REYCHLER, B. MACQ. « *Towards an integrated system for planning and assisting maxillofacial orthognathic surgery.* » Comput Methods Programs Biomed. 91(1) : 13-21, Jul **2008**.

## Patents

R. OLSZEWSKI, K. TRAN DUY, B. RAUCENT, H. REYCHLER, V. NICOLAS.  
«*Method and equipment for the simulation of the operation of maxillofacial surgery and transfer of this planning to the operating room*». EU Patent n°2705051.

## Funding

Wallon Region

## Main Equipment

- ▶ CT-Scan and 3D IRM
- ▶ 3D measurement machine
- ▶ Operating room with optic navigation (optotrack)

## Products and Services

- ▶ Computer aided orthognatic and craniomaxillo-facial surgery
- ▶ Medical software development : ACRO3D

## KEY WORDS FOR R&D

3D cephalometry analysis  
Robot  
Craniomaxillofacial surgery  
Medical imaging  
Software  
Robotic devices

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# Endocytosis, Epithelial Differentiation and Tissue Remodelling

## SENIOR SCIENTISTS :

- ▶ Pierre COURTOY
- ▶ Patrick HENRIET
- ▶ Étienne MARBAIX
- ▶ Christophe PIERREUX

## Research Field and Subjects

The laboratory combines four complementary expertises in cell biology: membrane trafficking, epithelial polarity, paracrine interactions and tissue remodelling. One group is studying the regulation of endocytic membrane trafficking, in particular apical endocytosis and epithelial differentiation *in vitro*, in cultured explants and *in vivo*. We exploit this basic knowledge to address biomedical problems, such as genetic kidney and pancreatic diseases. The other group is addressing the role of matrix metalloproteinases, cytokines and steroid hormones in normal and pathological human tissue remodelling, using the endometrium as a model system.

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## Patent

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## Awards

- P. COURTOY. Chaire Francqui. FUNDP, **2003-2004**.

## Funding

- ▶ FRS/FNRS
- ▶ Télévie
- ▶ FRIA
- ▶ ICP
- ▶ UCL
- ▶ Région bruxelloise
- ▶ Région wallonne
- ▶ Loterie Nationale
- ▶ Actions de recherche concertées
- ▶ Interuniversity attraction poles
- ▶ EU
- ▶ Scientific consulting

## Partnership

- ▶ EU VIth program (EuReGene)
- ▶ EU VIIth program (Eunephron)

## Main Equipments

- ▶ Electron microscopy (transmission, scanning, STEM)
- ▶ Confocal and multiphoton microscopy
- ▶ Live-cell microscopy
- ▶ Multiparametric image analysis
- ▶ Ultracentrifuges and rotors

## Products and Services

- ▶ High-resolution molecular tracking in living and fixed cells
- ▶ Signalling in co-cultures
- ▶ Antibodies specific for mouse collagenase-3 (MMP-13)

## KEY WORDS FOR R&D

Confocal microscopy  
Multiphoton microscopy  
Electron microscopy  
Live-cell imaging  
Endometrium  
Kidney  
Pancreas  
Explants  
Extracellular matrix  
Fractionation  
Matrix metalloproteinases  
Membrane

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# Primary Cultures of Neuronal and Glial Cells for the Study of Neurodegenerative Disorders

## SENIOR SCIENTISTS :

- ▶ Emmanuel HERMANS
- ▶ Pascal KIENLEN-CAMPARD
- ▶ Jean-Noël OCTAVE

## Research Field and Subjects

The research is focused on the study of molecular and cellular mechanisms involved in the development and progression of neurodegenerative disorders. The group develops a series of cell culture models (neurons, astrocytes, microglia) derived from selected regions of the rat brain (cortex, corpus callosum, hippocampus). These in vitro models constitute valuable tools for biochemical and pharmacological studies. In addition, these cultures can also be derived from models of diseases (transgenic or lesions), allowing to characterize the associated cellular dysfunctions. Our principal interest concerns Alzheimer disease, Parkinson's disease, amyotrophic lateral sclerosis and pain.

## Representative References

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## Awards

J.-N. OCTAVE

- ▶ Divry prize, **1989**.
- ▶ IPSEN prize, **1992**.
- ▶ Rene de Cooman prize, **1992**.
- ▶ De Lava prize, **2007**.

E. HERMANS

- ▶ Galenus prize, **2003**.
- ▶ Baron Simonart prize, **2008**.
- ▶ Charcot Foundation prize, **2009**.
- ▶ Prix quinquennal des Sciences Pharmaceutiques de l'Académie Royale de Belgique, **2004-2009**.

## Funding

Research in our groups is funded by :

- ▶ UCL,
- ▶ F.R.S.-FNRS,
- ▶ The Association Belge contre les Maladies Neuro-Musculaires (ABMM)

- ▶ La Région Wallonne
- ▶ La Commission Européenne.

## Partnership

- ▶ Pharmaceutical companies
- ▶ Academic collaborations
- ▶ European Marie-Curie network

## Main Equipment

- ▶ Dynamic fluorescence imaging
- ▶ Cell cultures
- ▶ Immunocytochemistry
- ▶ Molecular biology

## Products and Services

- ▶ Development of primary cultures from rodents
- ▶ Characterization of neuronal and glial cell cultures
- ▶ Expression of recombinant proteins in neural cell models
- ▶ Assays for neural cell toxicity

## KEY WORDS FOR R&D

Neurons  
Astrocytes Microglia  
Primary cultures  
Immunocytochemistry  
Neuroprotection

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# Mammalian Antioxidant Enzymes

## SENIOR SCIENTISTS :

- ▶ Bernard KNOOPS
- ▶ Jean-Paul DECLERCQ
- ▶ Jean-François REES

## Research Field and Subjects

Oxidative stress is a major biological process involved in the development of a number of acute or chronic pathological situations (inflammation, cancer, neurodegenerative diseases, atherosclerosis, lung diseases, aging). Our research projects are focused on the identification and the characterization of enzymes that may play protective roles against cell death (apoptosis and necrosis) caused by oxidative stress. The cytoprotective antioxidant activity is studied in different in vivo and in vitro models such as animal and human cell lines exposed to oxidative or pro-apoptotic compounds. Peroxide and peroxynitrite reductase activities of recombinant proteins are investigated. Tridimensional structure is determined by X-ray crystallography.

The antioxidant enzymes that are currently studied are the peroxiredoxins (PRDXs). The PRDX family is a large family of peroxidases ubiquitously found in bacteria, archaea and eukaryotes. We have cloned and characterized several PRDXs. The crystal structure of animal PRDXs has been solved. Enzymatic activities as well as the pathophysiological implication in cellular protection against oxidative stress have been also explored using recombinant proteins and cell transfection strategies.

## Representative References

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## Patents

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## Funding

- ▶ Fonds national de la recherche scientifique - FNRS
- ▶ Fonds de la recherche fondamentale collective - FRFC
- ▶ Région wallonne

## Partnership

- ▶ Members of the Institut des Sciences de la Vie, Louvain-la-Neuve, Belgium.
- ▶ P. GRESSENS, INSERM, Paris, France.
- ▶ G. MURRELL, St George Hospital Sydney, Australia.
- ▶ W. H. KOPPENOL, ETH, Zurich, Switzerland.
- ▶ R. Radi, CFRBR, Montevideo, Uruguay.

## Main Equipment

- ▶ Cell culture equipment
- ▶ Confocal microscopy
- ▶ Molecular biology equipment

## Products and Services

- ▶ Gene cloning
- ▶ Recombinant proteins
- ▶ Transfection of mammalian cell lines
- ▶ Crystallography

## KEY WORDS FOR R&D

Animal cell culture  
Antioxidant enzyme  
Crystallization  
Peroxidase activity  
Protein purification  
Recombinant protein  
Transfection vectors  
Tridimensional structure

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# *In Vitro* Evaluation System for Epidermal Function and Treatment

## SENIOR SCIENTISTS :

- ▶ Yves POUMAY
- ▶ Michel HERIN

## Research Field and Subjects

The epidermis separates the human body from its environment and creates a cornified barrier by proliferation and terminal differentiation of its main cell the type, namely keratinocytes. Environmental insults and pharmacological compounds influence the homeostasis of the epidermal tissue by the induction or modulation of cellular signaling pathways that control the growing, migrating, or differentiating phenotypes of the keratinocyte.

Primary human epidermal keratinocytes are isolated and grown in the laboratory in serum-free culture conditions, then cultured in autocrine conditions in order to maximally suppress the influence of components of the culture medium on the cell phenotype. In these conditions, no peptide factor is added to the medium, allowing the detection of minute changes induced in the cell phenotype by epidermal growth factors and cytokines, physical agents (UV, temperature), chemical, variations in cellular cholesterol content, or by pharmacological agents.

So far, this system has been successfully utilized for the evaluation of growth factors (EGF-related growth factors, including neuregulins), of prolactin, of retinoic acid and inhibitors of its degradation, of inhibitors of cyclin-dependent kinase, and of cholesterol depletion.

## Representative References

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## **Funding**

FRFC

## **Partnership**

- ▶ Barrier Therapeutics, Geel, Belgium
- ▶ R. GNIADDECKI, Department of Dermatology, Bispebjerg Hospital, Copenhagen, Denmark

## **Main Equipment**

- ▶ Cell culture facility
- ▶ Histology and cell biology facility

## **Products and Services**

- ▶ Production of autocrine keratinocyte cultures
- ▶ Gene expression analysis of keratinocyte cultures

## **KEY WORDS FOR R&D**

Epidermis  
Keratinocytes  
Pharmacology  
Differentiation  
Growth factors  
Cholesterol  
Wound healing

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# Reconstructed Human Epidermis for Characterization of Chemicals

## SENIOR SCIENTISTS :

- ▶ Yves POUMAY
- ▶ Michel HERIN

## Research Field and Subjects

The laboratory is mainly dedicated to the study of human epidermal keratinocytes. This cell type is analyzed as monolayers in serum-free medium in various challenging conditions; however, a model for the reconstruction of the human epidermis in 3 dimension over a polycarbonate filter at the air-liquid interface has also been developed and studied. In the model, the four typical basal, spinous, granular and cornified layers of the epidermis are normally produced, together with the localized expression of specific differentiation markers.

Since this model produces a fully differentiated epidermis, it is suitable for the characterization of tissue response towards exposure of the cornified layer to chemicals, particularly potentially harmful chemicals with sensitizing and/or irritant potency. The measurement of expression and release of specialized epidermal cytokines by the reconstructed tissue allows the identification of the effects produced by certain chemicals on the model, providing an alternative method to the use of animals in cutaneous toxicology.

The model is also adequate in order to evaluate the epidermal metabolism and transepidermal passage of dedicated compounds.

## Representative References

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## Funding

Private funding

## Partnership

- ▶ A. COQUETTE, SGS Belgium SA Life Science Services, Wavre, Belgium
- ▶ Kl.-R. SCHROEDER, Henkel Biological and Clinical Research Department, Duesseldorf, Germany

## Main Equipment

- ▶ Cell culture facility
- ▶ Histology and cell biology facility

## Products and Services

- ▶ Production of reconstructed epidermis
- ▶ Analysis of reconstructed epidermis

**KEY WORDS FOR R&D**

Epidermis  
Keratinocytes  
Sensitization  
Irritation  
Toxicology

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# Identification by Mass Spectrometry of Proteins Purified by DNA-Affinity

## SENIOR SCIENTISTS :

- ▶ Patricia RENARD
- ▶ Marc DIEU
- ▶ Thierry ARNOULD

## Research Field and Subjects

- ▶ We have developed, for several transcription factors, the first ELISA-like DNA-binding activity assay (Renard et al, 2001). This assay has been used for studying transcription factors activation in different research topics (see other references), and is now commercialized by 2 companies, Eppendorf and Active Motif.
- ▶ Although this assay provides a convenient alternative to supershift, it can only address questions related to pre-defined transcription factors. That's why we are developing a method to identify without "a priori" the proteins captured by an immobilised PCR-produced oligonucleotide. The purified proteins are digested with trypsin and the resulting peptides are analysed by strong cation exchange (SCX) followed by nano-LC-MS-MS. We are currently able to identify a hundred of proteins captured by a 300 bp oligonucleotidic regulatory sequence, including several transcription factors and co-activators (manuscript in preparation).

## Representative References

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- ▶ L. MERCY, A. DE PAUW, L. PAYEN, S. TEJERINA, A. HOUBION, C. DEMAZY, M. RAES, P. RENARD, Th. ARNOULD. *Mitochondrial biogenesis in mtDNA-depleted cells involves a Ca<sup>2+</sup>-dependent pathway and a reduced mitochondrial protein import*. FEBS J. Oct; 272(19) : 5031-55, **2005**.

- ▶ S. TEJERINA, A. DE PAUW, S. VANKONINGSLOO, A. HOUBION, P. RENARD, F. DE LONGUEVILLE, M. RAES, Th. ARNOULD. *Mild mitochondrial uncoupling induces 3T3-L1 adipocyte dedifferentiation by a PPAR $\gamma$ -independent mechanism while TNF $\alpha$ -induced dedifferentiation is PPAR $\gamma$ -dependent*. J Cell Sci. Jan 1; 122(Pt 1) : 145-55, **2009**.

## Patents

- ▶ M. ART, J. REMACLE, P. RENARD. *Method and kit for the screening, the detection and/or the quantification of transcriptional factors*. US2004185497, **2004**.

## Funding

- ▶ EU : Specific Target Research or Innovation Project : proposal number 37231 : Systematic Functional Analysis of intracellular parasitism as a model of genomes conflict (Sysco)
- ▶ RW

## Partnership

- ▶ C. VAN LINT, LVM, ULB, Gosselies
- ▶ E. SOKAL, PEDI, UCL, Brussels
- ▶ M. FRANCAUX, IEP, UCL, LLN
- ▶ Partner of the European project : Systematic Functional Analysis of intracellular parasitism as a model of genomes conflict (Sysco)
- ▶ P. RENARD belongs to the Research Unit of Cell Biology (URBC, FUNDP)
- ▶ Eppendorf Assay Technologies
- ▶ Active Motif

### **Main Equipment**

- ▶ MALDI-TOF mass specrometer (Waters)
- ▶ Nano-LC- electrospray ionisation mass spectrometer (Waters)
- ▶ Bidimensional electrophoresis-dependent proteomic platform (2D-DIGE, GE Healthcare)

### **Products and Services**

Identification by electrospray ionisation mass spectrometry of proteins captured by an oligonucleotide sequence produced by PCR (identification of transcription factors and interacting proteins)

### **KEY WORDS FOR R&D**

Transcription factors  
DNA affinity  
Proteomics  
Mass spectrometry

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# Cell Senescence and Oxidative Stress / Nanotoxicology

## SENIOR SCIENTISTS :

- ▶ Olivier Toussaint
- ▶ Florence CHAINIAUX

## Research Field and Subjects

Normal somatic cells proliferate a limited number of times in culture leading to an irreversible growth-arrested phenotype called replicative senescence. This specific phenotype is mainly characterized by a permanent arrest of the cellular divisions, higher resistance to apoptosis and altered gene expression pattern. Senescence can also be induced by exposures to a variety of stress such as oxidative stress or DNA damaging agents ("Stress Induced Senescence") or by overexpression of activated oncogenes ("Oncogene Induced Senescence"). Several reports support the hypothesis that cellular senescence occurs *in vivo*. Moreover, there is evidence that senescent cells can accumulate in tissues with age and in age-related pathologies, such as osteoarthritis and atherosclerosis. Our interests are : Identification of biomarkers of senescence in SIPS in human, deciphering signal transduction in SIPS : role of TGF- $\beta$ 1, p38MAPK, cdc42, etc. Proteomic profilings in replicative senescence (RS) and SIPS, Transcriptomic profilings in RS, SIPS and dermis biopsies, Functional analyses of the role of proteins / genes with changed expression level in RS and/or SIPS, validation of technologies of toxicogenomics and *in vitro* toxicology.

Our *in vitro* facility has expertise in producing and/or handling reconstructed tissue models. We have developed more than ten *in vitro* tests suitable with these tissues, in absence of interactions between the nanoparticles and these tests. These tests allow the determination of cell survival, cell division potential, ROS production, permeability, etc. Moreover RNA in sufficient amount, purity and quality is routinely prepared from these tissues in order to profile gene expression. Three different reconstructed tissues are currently used for nanotoxicological studies and toxicity assessment. The three tissues currently used are fully differentiated reconstructed epidermis, a bronchial epithelium and an intestinal epithelium.

## Representative References

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- ▶ DEBACQ-CHAINIAUX, BORLON, PASCAL, ROYER, NINANE, CARRARD, DE LONGUEVILLE, BOFFE, ELIAERS, FRIGUET, REMACLE, TOUSSAINT. *Repeated exposures of human skin fibroblasts to UVB at subcytotoxic*

*level trigger premature senescence through the TGF- $\beta$ 1 signaling pathway*. J. Cell. Sci. 118, 743-758, **2005**.

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- ▶ ZDANOV, DEBACQ-CHAINIAUX, REMACLE, TOUSSAINT. *Identification of p38MAPK-dependent Genes Involved in H<sub>2</sub>O<sub>2</sub>-induced Premature Senescence of IMR-90 hTERT Human Fibroblasts*. FEBS Lett. 580, 6455-6463, **2006**.

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## Patent

- REMACLE, LONGUEVILLE, ZAMMATTEO, TOUSSAINT, VAN HUFFEL. *Determination of a general three-dimensional status of a cell by multiple gene expression analysis on micro-arrays*. 10/439, 767, applicant EAG US20040229225A1, EP1477571A1, filing date: 16/05/2003, 29/01/2004.

## Awards

Scientific Prizes :

- ▶ *De Cooman*, **1992-1994**.
- ▶ *European Tissue Culture Soc.*, **1994**.

- ▶ *H. Selye Award*, Budapest, **1997**.
- ▶ *De Lava*, **1994-1998**.
- ▶ *Glaxo*, **1999**.
- ▶ *Harwood*, **2000**.

To PhD students under supervision :

- ▶ P. DUMONT. *De Cooman Prize*, **1999-2001**.
- ▶ C. FRIPPIAT. *Novartis Prize*, Paris, **2001**.

To Post-docs under supervision :

- ▶ Fl. CHAINIAUX. *Skin physiology international meeting : Best presentation*, **2008**.

## Funding

- ▶ RW
- ▶ EU
- ▶ FNRS
- ▶ Private

## Partnership

- ▶ 8 EU projects with more than 120 labs
- Pole of excellence Nanotoxicology in collaboration with S. LUCAS (FUNDP) and B. MASEREEL (FUNDP).
- ▶ 2 projects Marshall plan : Walnut-20 (20 partners) and Silicaloy (8 partners).

## Main Equipment

- ▶ Cell biology facility (including a fully automated low O<sub>2</sub> cell culture facility, confocal microscope)
- ▶ Molecular biology
- ▶ Proteomics (including 2D-DIGE, spot picker and MS Q-ToF, MALDI-ToF) and
- ▶ Transcriptomics (microfluidic RT-PCR cards)

## Products and Services

- ▶ Proteomics and transcriptomics services
- ▶ Mass Spectrometry analyses
- ▶ *In vitro* testing of nanoparticles (skin, lung, intestine models)
- ▶ Skin biology in vitro and ex vivo services

## KEY WORDS FOR R&D

Oxidative stress  
 Cell senescence  
 Recruitment of probands  
 Skin biology  
 UVB  
 Gene expression  
 Proteomics  
 Culture at physiological oxygen pressure  
 Transcriptomics

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# Molecular Bacteriology Functions

## SENIOR SCIENTISTS :

- ▶ Xavier DE BOLLE
- ▶ Jean-Yves MATROULE
- ▶ Jean-Jacques LETESSON

## Research Field and Subjects

The molecular bacteriology group is active in the identification of processes that control various aspects of the molecular biology of the bacterial cell, with a particular focus on mechanisms of bacterial pathogenesis. The two organisms currently under investigation are *Caulobacter crescentus*, as a model of asymmetrically dividing bacterium, and *Brucella* spp., as a model of pathogenic bacteria. Various aspects of the host-pathogen relationships are investigated for this bacterial pathogen.

## Representative References

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- ▶ R. Hallez, A.-F. Bellefontaine, J.-J. Letesson, X. De Bolle. *Morphological and functional asymmetry in alpha-proteobacteria*. Trends Microbiol. 12, 361-365, **2004**.
- ▶ D. Fretin, A. Fauconnier, S. Köhler, S. Halling, S. Leonard, C. Nijskens, J. Ferooz, P. Lestrade, R.-M. Delrue, I. Danese, J. Vandenhautte, A. Tibor, X. De Bolle, J.-J. Letesson. *The sheathed flagellum of Brucella melitensis is involved in persistence in a murine model of infection*. Cell. Microbiol. 7, 687-698, **2005**.

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- ▶ R. Hallez, J. Mignolet, V. Van Mullem, M. Wery, J. Vandenhautte, J.-J. Letesson, C. Jacobs-Wagner, X. De Bolle. *The asymmetric distribution of the essential histidine kinase PdhS indicates a differentiation event in Brucella abortus*. EMBO J. 26, 1444-1455, **2007**.

## Patents

- ▶ « *Isolated Brucella antigens-useful for the in vitro diagnosis of Brucella sp. infection, for the detection and/or quantitation of a cellular immune response against a polypeptide and as a vaccine against Brucella sp. infection such as B. abortus B19 or B. melitensis Rev 1 infection.* » Brevet n° W09808951-A1
- ▶ « *Mimotype of a surfacer L3,7,9 LOS of N. meningitidis – for vaccination against serogroup B,C,Y or W-135 meningococci and for the diagnosis of meningococcal infection.* » Brevet n° WO 02/28888 A2

## Funding

- ▶ FNRS
- ▶ CFWB

## Main Equipment

- ▶ Fluorescence microscopy
- ▶ Biological Safety Level 3 Laboratory
- ▶ Flow Cytometry

## Products and Services

The molecular bacteriology research group generated expertise in the manipulation of model bacteria as well as pathogenic bacteria for wild and domestic animals. Several approaches of molecular biology (subcellular localisation, protein-protein interaction assays, recombinant protein production ...) have been set up and are routinely used in the laboratory.

## KEY WORDS FOR R&D

Bacteriology  
Molecular Biology  
Fluorescence Microscopy  
Bacterial Pathogens  
Brucella abortus  
Brucella melitensis  
Caulobacter crescentus

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# Biotechnological Applications of Lactic Acid Bacteria

## SENIOR SCIENTIST :

► Pascal HOLS

## Research Field and Subjects

Research activities are focused on a specific group of Gram-positive bacteria, generically referred to as “lactic acid bacteria” (LAB), which are of major industrial importance in food fermentation. Moreover, some LAB species are natural members of the intestinal microflora of mammals where they play a beneficial health role.

A multidisciplinary range of genomics/post-genomics, biochemical, and biophysical approaches are used to study the function of genes that are involved in **carbon metabolism, cell-wall biosynthesis, and metabolic adaptation to environmental parameters** of different LAB species (*Lactobacillus plantarum*, *Lactococcus lactis*, *Streptococcus thermophilus*, and *Bacillus coagulans*).

In order to improve our knowledge of LAB metabolism, we established the complete **genome sequence of *Streptococcus thermophilus***, a major dairy starter. DNA microarrays are currently exploited for **transcriptomic analyses** in order to study regulatory networks controlling bacteriocin production and natural DNA transformation.

**Metabolic engineering and heterologous gene** expression technologies are used to engineer LAB strains (GMO and non-GMO) to serve as starters in dairy fermentation, as cell factory for the production of lactate isomers, aromas, low calorie sugars, or as host systems for the production and the delivery of specific compounds of food and pharmaceutical interest. This includes the development of *L. plantarum* strains as live vaccine vectors for mucosal immunisation and as second generation probiotics (e.g. immunomodulation, ammonia removal).

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*anti-inflammatory capacity of a *Lactobacillus plantarum* mutant synthesizing modified teichoic acids*. Proc. Natl. Acad. Sci. USA. 102, 10321-10326, **2005**.

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► Y. GILBERT, M. DEGHORAIN, L. WANG, B. XU, P. POLLHEIMER, H. GRUBER, J. ERRINGTON, B. HALLET, X. HAULOT, C. VERBELEN, P. HOLS, Y. DUFRÉNE. *Single-molecule force spectroscopy and imaging of the vancomycin/ D-Ala-D-Ala interaction*. Nano Lett. 7, 796-801, **2007**.

► L. FONTAINE, P. HOLS. *The inhibitory spectrum of thermophilin 9 from *Streptococcus thermophilus* LMD-9 depends on the production of multiple peptides and the activity of BlpG(St), a thiol-disulfide oxidase*. Appl. Environ. Microbiol. 74, 1102-1110, **2008**.

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## Patents

- P. HOLS, M. KLEEREBEZEM, J. HUGENHOLTZ, T. FERAIN, O. KUIPERS, J. DELCOUR, W. M. de Vos. *Process for the production of alanine by recombinant microorganisms*. N°EP19990900710, **1999**.
- C. GRANGETTE, A. MERCENIER, J. DELCOUR, P. HOLS. *Cell wall mutants for delivery of biologically active compounds*. N°EP02447119.5, **2002**.

## Award

Food Ingredients Research Award on « *Efficient 'in-situ' production of L-Alanine sweetener in dairy food products* ». Paris, UCL/ NIZO food research, **1999**.

## Funding

- ▶ Private companies
- ▶ Biotech projects supported by the Walloon Region

National grants :

- ▶ FSR-FNRS
- ▶ ARC
- ▶ FRIA

## Partnership

- ▶ NIZO Food Research, Ede, The Netherlands
- ▶ Top Institute Food and Nutrition, Wageningen, The Netherlands
- ▶ Institut National de la Recherche Agronomique, Jouy en Josas, France
- ▶ Institut Pasteur de Lille, Lille, France

## Main Equipment

- ▶ DNA microarray scanner and bioinformatics servers
- ▶ Nanodrop spectrophotometer
- ▶ Capillary electrophoresis system (Bionalyser)
- ▶ Small scale fermentors (2 L and 10 L)
- ▶ High performance liquid chromatography machines (2) with UV, IR, ELSD detectors

## Products and Services

- ▶ Heterologous gene expression in LAB.
- ▶ Gene knockout in LAB.
- ▶ Transcriptomic analyses using DNA microarrays (Agilent platform).
- ▶ Small-scale fermentation facilities
- ▶ Analysis of fermentation products (sugars, organic acids, lactate isomers, aa ...).

## KEY WORDS FOR R&D

Bacterial genetics  
Lactic acid bacteria  
Dairy products  
Yoghurt  
Cheese  
Probiotics  
Mucosal vaccines  
Metabolic engineering  
Genomics  
Microarrays  
Lactobacillus  
Streptococcus

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# Determination of an Early Immunological Profile Specific of Allergy Development and Its Use In Disease Prevention

## SENIOR SCIENTISTS :

- ▶ Etienne SOKAL
- ▶ Françoise SMETS
- ▶ Catherine LOMBARD
- ▶ Pierre DUPONT
- ▶ Jean-Luc GALA
- ▶ Bertrand BEARZATTO
- ▶ Charles PILETTE

## Research Field and Subjects

Allergy is an immune disorder characterized by an exaggerated response to a normally harmless substance, or allergen. Allergy symptoms usually arise in the newborn in the form of eczema and progress into asthma, followed by allergic rhinitis or hay fever. Although allergic symptoms disappear by the time most people reach adulthood, a non-negligible number of people see these symptoms persist or even worsen, affecting their quality of life and requiring costly treatments.

The risk of developing an allergy is currently assessed from data about the child's environment and his family's medical history, a method which does not allow for an evaluation of each individual's risk and limits medical intervention to therapeutic treatment.

The aim of the CRISTALL study is to determine whether we can define an early immunological profile specific for the development of allergy, in order to establish a strategy for prevention.

To this end, each one of the 300 children enrolled in the study will be given regular physical exams from birth to age five and assessed for changes in their environment that could contribute to an allergic response. In addition, the development of allergy will be monitored using skin prick tests and measurements of total and allergen-specific immunoglobulins in the serum.

In parallel, blood samples will be collected throughout the study and used for the isolation of peripheral blood mononuclear cells (PBMCs). The PBMCs' composition, functionality and their activation state will be evaluated and compared between allergic and non-allergic children by flow cytometry and cytokine production analysis by Luminex.

In addition, we will use expression microarray analysis of non-stimulated and allergen-stimulated PBMCs. This technology measures the activity of several thousands of genes in a single experiment. Expression data will be used to identify a subset of genes, or genetic biomarkers, related to the allergic/non-allergic status in a prognosis perspective. If the gene subset, also called a signature, is robust and has a high predictive power, it will be considered as highly informative about the allergic status and

the underlying processes. Multivariate statistical analysis and mathematical optimization techniques are applied to identify candidate biomarkers, to build and to evaluate prognosis models. Specific machine learning techniques can also make use of previous biological knowledge to guide the final signature identification. Such techniques offer an independent validation methodology to confront predicted markers with actual expression data.

Finally, we will measure the amount of aero-allergens found in dust samples collected in the homes of the children participating in the study as well as in the mother's breast-milk to determine whether these allergens can be recovered in breast-milk and whether their presence in breast-milk leads to tolerance.

Together, these data should allow us to determine whether an immunological profile specific of an allergic response can be established early in life and used to prevent the development of allergy in children at risk.

In addition, the techniques developed for this project can be used for the study of many disorders of immune origin.

## Representative References

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- ▶ B. BEARZATTO, S. VAN DER VORST, V. GREGOIRE, J.-L. GALA, A.-F. DEKAIRELLE. *In vitro cellular response of head and neck squamous cell lines exposed to combined docetaxel-radiotherapy*. Abstract for the 7<sup>th</sup> International Conference on Head and Neck Cancer, San Francisco CA, USA, July 19-23, **2008**.
- ▶ T. HELLEPUTTE, P. DUPONT. *Partially Supervised Feature Selection with Regularized Linear Models*. 26<sup>th</sup> International Conference on Machine Learning (ICML), Montreal, Canada, June 14-18, **2009**.
- ▶ O. VOSTERS, S. EVRARD, E. SOKAL, Fr. SMETS. *Deficient production of interferon alpha in neonates rapidly corrected within 2 month of life* (article in preparation).

## Funding

- ▶ Programme d'Excellence universitaire subventionné par la Région wallonne
- ▶ GSK Biologicals

## Partnership

GSK Biologicals

## Main Equipment

- ▶ FACS CANTO II Flow cytometer
- ▶ Luminex
- ▶ Microarray (Laboratory of Jean-Luc Gala)
- ▶ Center for Intensive Computing and Mass Storage (CISM) Computing Grids

## Products and Services

- ▶ Flow cytometry
- ▶ Cytokine profiling by Luminex
- ▶ Genomic Data Analysis
- ▶ Biomarker Identification
- ▶ Prognosis Models Building and Evaluation
- ▶ Experimental Protocol Assessment

## KEY WORDS FOR R&D

Allergy  
Cytokines  
Immune response  
Gene expression  
Biomarkers  
Prognosis  
Feature Selection

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# Rapid Detection of Bacterial Pathogens

## SENIOR SCIENTIST :

► Patrice SOUMILLION

### Research Field and Subjects

► When analysing food samples for the detection of a pathogenic bacterium, the first step is to amplify the pathogen in a culture in order to have enough bacteria for the detection. Two parameters have to be optimised for this step, the culture time and the selectivity of the medium. Obviously, **food analysis has to be rapid**. In general, the required culture time will be short if the medium is rich. On the other hand, a major problem is the difficulty to selectively amplify the target bacterium, i.e the bacterium to be detected. A non selective medium will amplify all the microorganisms in the samples, including non pathogenic ones, and the subsequent detection will be much more laborious and less reliable. Some selective media have been developed by optimizing their composition but they are usually poorly selective and/or poorly nutritive.

► We have developed an innovative method allowing **rapid and selective growth of a target pathogenic bacterium** by the use of a rich medium supplemented with an enzyme-antibody conjugate and an antibiotic. The enzyme is able to degrade the antibiotic (example : the enzyme is a beta-lactamase and the antibiotic is a penicillin) and the antibody recognizes specifically the target bacterium. As the enzyme and the antibody are associated in a conjugate, the enzyme will cover the surface of the target bacterium via the specific antibody recognition. Hence, the bacterium will be protected against the antibiotic and will grow normally whereas all the other bacteria will be sensitive to the antibiotic and will not grow.

► The method was validated for the detection of **salmonellas**: in 8 hours, we were able to detect less than 10 cells of salmonella in a contaminated yogurt sample.

### Patent

P. SOUMILLION, J. FASTREZ. *Method for the selective survival or selective growth of a target cell by the use of a conjugate, its use in therapeutics and/or diagnostics and the preparation of said conjugate*. PCT Int. Appl., WO 01/97854, **2001**.

### Funding

Private company (UCB-Bioproducts), UCL

### Main equipment

Spectrophotometry UV-Vis, protein purification platform.

### Products and Services

Possibility to prepare antibody-enzyme conjugates for testing.

**KEY WORDS FOR R&D**

Selective medium  
Salmonella  
Antibody-beta-lactamase conjugate  
Rapid growth

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# Antibiotic Resistance by Active Efflux

## SENIOR SCIENTISTS :

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- ▶ Françoise VAN BAMBEKE
- ▶ Marie-Paule MINGEOT-LECLERCQ

## Research Field and Subjects

Among resistance mechanisms to antibiotic, active efflux is often neglected, as it often confer low levels of resistance. Yet, by decreasing the antibiotic concentration inside bacteria, this mechanism can select for other, high-level, resistance mechanisms, and also cooperate with them to further increase resistance levels. Moreover, it often confer cross-resistance to several, unrelated antibiotic classes

We are assembling collections of clinical isolates (*S. pneumoniae*, *P. aeruginosa*), in which we specifically examine resistance by efflux, using both phenotypic or genotypic methods that were developed in our laboratory. We then correlate resistance with antibiotic treatments received by the patients. We also examine in vitro how exposure to sub-MIC concentrations of antibiotics can affect the expression of efflux pumps in bacteria.

These studies may help in rationalizing antibiotic use and also in determining the susceptibility to resistance by efflux of new antibiotics.

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- ▶ Fr. VAN BAMBEKE, J. M. PAGÈS, V. J. LEE. *Inhibitors of bacterial efflux pumps as adjuvants in antibiotic treatments and diagnostic tools for detection of resistance by efflux*. Rec. Pat. Anti-Infect. Drug Discov. 1, 157-175, **2006**.
- ▶ N. MESAROS, Y. GLUPCZYNSKI, L. AVRAIN, N. E. CACERES, P. M. TULKENS, Fr. VAN BAMBEKE. *A combined phenotypic and genotypic method for the detection of Mex efflux pumps in Pseudomonas aeruginosa*. J. Antimicrob. Chemother. 59, 378-386, **2007**.

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- ▶ A. LISMOND, P. M. TULKENS, M.-P. MINGEOT-LECLERCQ, P. COURVALIN, Fr. VAN BAMBEKE. *Cooperation between prokaryotic (Lde) and eukaryotic (MRP) efflux transporters in J774 macrophages infected with Listeria monocytogenes. Studies with ciprofloxacin and moxifloxacin*. Antimicrob. Ag. Chemother. 52, 3040-3046, **2008**.

## Funding

Public and private companies

## Partnership

Pharmaceutical industry

## Main Equipment

- ▶ L2 facilities
- ▶ Molecular biology (western-blot, proteomics, PCR, real-time PCR ...)
- ▶ General equipment for microbiological and biochemical assays

## Products and Services

- ▶ Detection of resistance by efflux in clinical isolates (phenotypic and genotypic methods)
- ▶ Collections of clinical isolates with known efflux status.

**KEY WORDS FOR R&D**

Antibiotics  
Resistance  
Efflux  
Streptococcus pneumoniae  
Pseudomonas aeruginosa

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# Engineering Environmental Friendly Plants

## SENIOR SCIENTIST:

Henri BATOKO

## Research Field and Subjects

- ▶ Systematic sequencing programmes cause the focus of plant molecular genetics to shift away from the identification of new genes towards assigning functions to known genes. Our laboratory is using functional genomic tools applied to genetic model plant species to detect and assign functions to key genes involved in plant responses to drought, salinity and cold.
- ▶ To this end, we are concomitantly designing specific tools allowing us to understand the spatio-temporal activities of each gene's promoter, as combined to novel, combinatorial chimeric transcription factors; these will create a spatial and temporal gene regulation system that sufficiently mimic the ideal conditions for in vivo functional studies, and of genuine value to plant biologists.
- ▶ We are also conducting evolutionary analysis of genes of interest, for example comparing the activity or performance of a salinity responsive gene in glycophytes and halophytes, aiming at using the best possible candidates to engineer stress resistant plants.

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- ▶ D. GUILLAUMOT, S. GUILLON, P. MORSOMME, H. BATOKO. *ABA porphyrins and plant TSPO-related protein*, *Plant Signaling & Behavior*. In press, **2009**.

## Awards

The American Society of Plant Biologists' "Young scientist's plant biology paper-of-the-year award", **2001**.

## Funding

- ▶ "Communauté française"
- ▶ EU
- ▶ private companies

## Partnership

- ▶ Member of the Institut des Sciences de la Vie (ISV-UCL)
- ▶ Research collaboration with Desmet Ballestra Group N.V., Belgium

### **Main Equipment**

ZEISS LSM 710 confocal microscope, Standard molecular biology equipments

### **Products and Services**

- ▶ Confocal microscopy expertise
- ▶ Genes mining
- ▶ Genetic tools

### **KEY WORDS FOR R&D**

Plant abiotic stress  
Genetic engineering  
Gene function and regulation  
Tetrapyrroles and signaling  
Organelle biology  
Protein trafficking and subcellular localization  
Protein misexpression and mis-targeting

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# DNA Fingerprinting for Biodiversity Measurements

## SENIOR SCIENTISTS :

- ▶ François CHAUMONT
- ▶ Marie-Christine FLAMAND

## Research Field and Subjects

▶ Our research program is devoted to the development and application of molecular marker methods for the estimation of genetic diversity of forest animals and trees, and river fish populations. In the past twenty years, different techniques have been developed to visualize DNA sequence polymorphisms. The PCR-derived (Polymerase Chain Reaction) techniques such as RAPD (Random Amplified Polymorphic DNA) and microsatellite profiling have been chosen for their facility of use, their reliability and the rapidity to analyse a large number of samples.

▶ First, we have developed the application of the RAPD methodology to study the provenance relationships and clone verification in Norway spruce (*Picea abies*), to identify larch species (*Larix decidua*, *Larix kaempferi* and *Larix X eurolepis*) and estimate hybrid fractions in seed lots of these forest tree species. We then applied the micro-satellite profiling to study the genetic variation of trout (*Salmo trutta*) populations found in the rivers of Belgium and the impact of restocking on the biodiversity. Assignments are currently used to determine the origin of the adult salmon (*Salmo salar*) that are found in our rivers and to choose the better origin for restocking. The impact of entropic barriers on genetic flux between populations of red deers (*Cervus elaphus*) and wild pigs (*Sus scrofa*) as well as the reproductive success of male red deer is also studied.

## Representative References

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## Funding

Région wallonne

## Partnership

- ▶ Members of the "Institut des Sciences de la Vie", Louvain-la-Neuve, Belgium
- ▶ Région wallonne, Département de l'Etude du Milieu Naturel et Agricole de Gembloux (DEMNA) et Service de la Pêche (DNF-DCP)

## Main Equipment

- ▶ Automatic DNA sequencer (Applied Biosystem 3700) and standard molecular biology equipment.
- ▶ PCR thermocycler (Perkin Elmer 9600 and AB Veriti).

## **Products and Services**

- ▶ Microsatellite profiling for biodiversity and reproductive behaviour analysis of animal populations, and to fight poaching.
- ▶ Standardized quick analysis method for the early identification of clones and purity evaluation of seed batches of forest trees during selection and commercialization.
- ▶ The application of these methods can be extended to study the biodiversity of other plant and animal species.

## **KEY WORDS FOR R&D**

Biodiversity  
Forest trees  
Red deers  
Wild pigs  
Salmonids (Trout, Salmon)  
Microsatellites

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# Mechanisms of Cytokine Receptor Dimerization

## SENIOR SCIENTISTS :

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- ▶ Jean-Christophe RENAULD

## Research Field and Subjects

Cytokines bind to transmembrane cell surface receptors which signal through JAK kinases and STAT transcription factors, leading to cell survival, proliferation and differentiation. The common theme of cytokine receptor activation resides in cytokine-induced dimerization/ oligomerization in a conformation productive for cross-activation of JAK protein kinases. Unlike other membrane proteins, cytokine receptors await pharmacologic manipulation in order, for example, to trigger some but not all effects of the cytokines. Researchers at the De Duve Institute have identified a number of “switch” residues located in the juxtamembrane domains of several cytokine receptors. Targeting those “switch” residues, by mutations, leads to receptor activation in the absence of ligand. This is the case for the erythropoietin (EpoR) and thrombopoietin (TpoR) receptor and gives an indication on the precise dimeric conformations competent for signaling. Using coiled coils that induce predictable dimeric orientations, the biologic effects of individual dimeric receptors conformations were probed for EpoR and TpoR, demonstrating the existence of fully active and partially active conformations. On the other hand, inactive receptors (that are not coupled to ligand) were found to adopt preformed homomeric (EpoR, IL2Rbeta, IL90Ralpha, common gamma chain) and heteromeric (IL9Ralpha-gamma chain or IL2Rbeta-gamma chain) complexes that are stabilized by transmembrane sequence interactions. Such interactions are disrupted and transmembrane domains are rotated relative to each others when cytokine binding occurs to the extracellular domains, via a change in position of juxtamembrane “switch” residues. These results are extended to other transmembrane proteins, such as receptor tyrosine kinases (i.e. PDGF receptors).

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## Awards

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

## Funding

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

## Partnership

Ludwig Institute for Cancer Research

## Main Equipment

Microarrays

## Products and Services

- ▶ Identification of novel genetic alterations from patient samples
- ▶ Signal transduction assays

## KEY WORDS FOR R&D

JAK  
STAT  
Cytokine  
Growth factors  
Receptors  
Signal transduction  
Polycythemia vera  
Interleukin

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[www.bru.licr.org/brussels/research/stg/stg.html](http://www.bru.licr.org/brussels/research/stg/stg.html)

# Kidney Diseases, Dialysis, Transplantation

## SENIOR SCIENTISTS :

- ▶ Olivier DEVUYST
- ▶ Yves PIRSON
- ▶ Michel JADOUL
- ▶ Éric GOFFIN
- ▶ Karin DAHAN

## Research Field and Subjects

The kidneys play an essential role in regulating body fluid homeostasis and blood pressure; participate in the complex regulation of vital functions including bone metabolism and hematopoiesis; and ensure the clearance of various drugs and toxic metabolites.

Our research group investigates the mechanisms of various types of kidney diseases, either congenital or acquired, using a multi-disciplinary approach including studies on patients, human and mouse genetics, phenotyping of mouse and cellular models, and cell and molecular biology techniques.

Insights obtained through these investigations are relevant for common conditions such as blood pressure regulation, kidney stones, progression of renal failure, and cardiovascular complications of renal diseases. We also investigate the molecular basis of water and solute transport across the peritoneal membrane, with the aim of improving peritoneal dialysis, a therapeutic modality for patients with end-stage renal disease. These projects include aspects related to the discovery and validation of biomarkers in urine.

## Representative References

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- ▶ EI. CHRISTENSEN, O. DEVUYST, G. DOM, R. NIELSEN, P. VAN DER SMISSEN, P. VERROUST, M. LERUTH, W. B. GUGGINO, P. COURTOY. *Loss of chloride channel CIC-5 impairs endocytosis by defective trafficking of megalin and cubilin in kidney proximal tubules*. Proc. Natl. Acad. Sci. USA 100 : 8472-8477, **2003**.
- ▶ J. NI, J.-M. VERBAVATZ, A. RIPPE, I. BOISDÉ, P. MOULIN, B. RIPPE, A.-S. VERKMAN, O. DEVUYST. *Aquaporin-1 plays an essential role in water permeability and ultrafiltration during peritoneal dialysis*. Kidney Int. 69 : 1518-1525, **2006**.
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*receptor-mediated endocytosis in mouse and human kidney*. J. Am. Soc. Nephrol. 18 : 707-718, **2007**.

- ▶ E. RIVEIRA-MUNOZ, Q. CHANG, N. GODEFROID, J. HOENDEROP, R. BINDELS, K. DAHAN, O. DEVUYST. *Transcriptional and functional analyses of SLC12A3 mutations : New clues for the pathogenesis of Gitelman's syndrome*. J. Am. Soc. Nephrol. 18 : 1271-1283, **2007**.
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## Patents

- ▶ O. DEVUYST, A. PERSU. "Method for diagnosing and treating predisposition for accelerated autosomal dominant polycystic kidney disease." WO 03/074729; PCT/EP02/02505; US 10/506,359
- ▶ O. DEVUYST, F. JOURET, Ph. GAILLY. "Method, device and kit for determining conditions related to a dysfunction of the renal proximal tubule." PCT/EP2008/051690, **2008**.

## Awards

- ▶ *Biennial Prize*, Belgian Society of Nephrology, **2000**.
- ▶ *Lauréat du Concours Ordinaire*, Royal Academy of Medicine of Belgium, **2000**.
- ▶ *Galien Prize*, Belgian Pharmaceutical Industry, **2003**.
- ▶ *Matthys-Bove Award*, UCL Medical School, **2004**.
- ▶ *Biennial Prize of the International Spa Foundation*, **2007**.
- ▶ *Award of the King Baudouin Foundation*, **2005 & 2008**.

## Funding

These research projects are funded through

- ▶ The FNRS
- ▶ FRSM
- ▶ The Communauté Française de Belgique (ARC)
- ▶ An Inter-University Attraction Pole
- ▶ The DIANE project
- ▶ The Fondation Roi Baudouin and
- ▶ The European networks EuReGene
- ▶ EUNEFRON and
- ▶ Genecure

## Partnership

Member/coordinator of EU-funded networks :

- ▶ EuReGene
- ▶ Genecure (<http://www.genecure.eu/>)
- ▶ EUNEFRON (<http://www.eunefron.org/>)

## Main Equipment

- ▶ Dedicated facilities for mouse phenotyping & metabolic studies
- ▶ Platform for biochemical analyses in rodent models ([www.uclouvain.be/md-plateforme.html](http://www.uclouvain.be/md-plateforme.html))
- ▶ Dialysis models in rat and mouse
- ▶ Cell and molecular biology equipment
- ▶ Microdissection, cell culture
- ▶ Quantitative RT-PCR
- ▶ ELISA development
- ▶ Genome, transcriptome and proteome analyses
- ▶ Genome-wide association studies
- ▶ Phenotype and genetic studies of human tubular disorders collected at the EU level
- ▶ Biobanking : cohorts of urine, DNA and plasma samples at EU level

## Products and Services

- ▶ Mouse phenotyping : *in vivo*, *ex vivo*
- ▶ Monitoring : renal function, blood pressure

- ▶ Dedicated platform for biochemical analyses in rodent models
- ▶ Microdissection and primary cell cultures from rodent organs
- ▶ Mouse and rat models of dialysis
- ▶ Water & solute transport, pharmaco-regulation
- ▶ DNA, RNA, Genotyping; ELISA
- ▶ Biomarkers discovery and validation
- ▶ Biobanking: cohorts of urine, DNA and plasma samples at EU level
- ▶ Facilities for pre-clinical studies

## KEY WORDS FOR R&D

Kidney  
Blood pressure  
Dialysis  
Rare diseases  
Cell models  
Mouse models  
Biochemical platform  
Phenotype analysis  
Biomarker  
Urine

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# Protein Docking Using Image Processing and Statistical Tools

## SENIOR SCIENTISTS :

- ▶ Jean-Luc GALA
- ▶ Benoît MACQ

## Research Field and Subjects

Most of the cellular functions are ruled by highly organized proteins assembling. They can be static or temporary.

This research field is becoming really relevant above all for drug design. The modeling of such protein complex is called protein docking.

One of the major difficulty of protein docking is the number of degrees of freedom. Indeed, each molecule potentially included in a complex can be rotated and translated in three dimensions. Moreover, proteins conformation may change after some interactions of a genetic mutation.

In order to reduce the complexity of the problem, simplifications can be considered. For instance, in the case of rigid docking, proteins flexibility is not taken into account. The number of possible solution can also be reduced by discretizing the transformation space or by identifying spots of interest on the protein.

Our work focuses on two points :

- ▶ Protein features extraction using image processing techniques.
- ▶ Statistical analysis of protein features to point out discriminant properties allowing the localization of hot spots on the surface.

## Representative References

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J. GIARD, B. MACQ. *Molecules 3D Delaunay triangulation : a spectral study*. SPIE Medical Imaging 2009, Orlando, FL, USA, 7262, 72622N, **2009**.

## Funding

Walloon Region : Nanotic program

## KEY WORDS FOR R&D

Protein Docking  
Surface description  
Active Site  
Binding Site

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# From DNA Transposition and Site-Specific Recombination Mechanisms to the Molecular Biology Toolbox

## SENIOR SCIENTIST :

► Bernard HALLET

## Research Field and Subjects

Transposition and site-specific recombination are two types of DNA rearrangements that are mediated by specialised enzymes generically referred to as transposases and site-specific recombinases, respectively. Transposition is the process by which genetic elements move at random between different genome locations, whereas site-specific recombination is a reaction in which DNA strands are broken and rejoined at determined positions of two target DNA sequences.

Studies in the laboratory are focused on the transposition and site-specific recombination machinery encoded by the bacterial transposon Tn4430. A multidisciplinary range of genetical and biochemical approaches are used to investigate the molecular interactions involved in the assembly of the transposition / recombination complex and the coordination of the DNA cleavage and rejoining reactions. Both reactions have been reconstituted in vitro using purified components.

Specific features of Tn4430 transposition / recombination mechanisms are also used to develop new tools for genetic engineering and in vitro cloning or mutagenesis technologies.

Pentapeptide scanning mutagenesis (PSM) is a protein mutagenesis method based on Tn4430-mediated insertion of 5-amino acids cassettes at random positions of a target protein. This method was successfully used to study the functional organisation a number of proteins in different laboratories.

DNA site-specific recombination mediated by the Tn4430-encoded tyrosine recombinase Tnpl was demonstrated in a broad range of conditions.

Recombination was also shown to function in different organisms, including mammals, demonstrating its potential for the development of tools in a wide range of biotechnological applications.

## Representative References

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## Patents

A. F. STEWART, Y. ZHANG, B. HALLET. *A new tyrosine recombinase for genetic engineering*. US Patent Application # 09/895.435, **2002**; PCT patent Application # EP02/07176, **2001**.

## Funding

- Fonds UCL et publics
- FRS-FNRS
- FRIA
- FSR
- ARC

## Partnership

Member of the Institut des Sciences de la Vie (ISV), Louvain-la-Neuve, Belgium

Current collaborations :

- ▶ F. CORNET (CNRS-LMGM, Toulouse, Fr)
- ▶ M. CHANDLER (CNRS-LMGM, Toulouse, Fr)
- ▶ D. CHARLIER (VUB, Be)
- ▶ X. DE BOLLE (URBM-FUNDP, Be)
- ▶ J. HOFKENS (KULeuven, Be)
- ▶ P. HOLS (ISV-UCL, Be)
- ▶ R. REZSÖHAZY (ISV-UCL, Be)
- ▶ S. D. COLLOMS (Univ. of Glasgow, UK)

## Main Equipment

Basic molecular biology and biochemistry equipment

## Products and Services

- ▶ Bacterial strains
- ▶ DNA substrates
- ▶ Purified proteins

## KEY WORDS FOR R&D

DNA recombination  
Genetic engineering  
Gene targeting  
Mutagenesis  
Protein engineering  
Site-specific recombination  
Transposition  
Tyrosine recombinase

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# Biomarkers Development In Aquatic Organisms to Assess the Ecotoxicological Hazard of Chemicals

## SENIOR SCIENTISTS :

- ▶ Frédéric SILVESTRE
- ▶ Patrick KESTEMONT

## Research Field and Subjects

Our team is specialized in aquatic ecotoxicology and presents a huge expertise in understanding how chemicals affect organisms at physiological, biochemical, and molecular levels. Beyond fundamental aspects, this research aims at developing highly sensitive processes that could work as early warning signals in order to assess the potential hazard of chemicals found in the natural environment or released by manufacturers. Our team is working with different species of fish, amphibians and invertebrates that are maintained in captivity. It can carry out exposure tests on live animals. Using large scale approaches from systems biology, we can develop proteomic biomarkers and high throughput tests at protein expression level. Such approaches can be useful for manufacturers regarding the REACH legislation from the UE that aims at bringing insurance of the safety of chemicals.

## Representative References

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- ▶ F. SILVESTRE, G. TRAUSSCH, P. DEVOS. *Is HSP70 involved in acclimation to cadmium in the Chinese mitten crab, Eriocheir sinensis ?* *Bull. Environ. Contam. Toxicol.* 78, 432-435, **2007**.
- ▶ V. GILLARDIN, F. SILVESTRE, C. DIVOY, J.-P. THOME, P. KESTEMONT. *Effects of Aroclor 1254 on oxidative stress in developing Xenopus laevis tadpoles*. *Ecotox. Environ. Saf.* 72, 546-551, **2008**.

- ▶ V. GILLARDIN, F. SILVESTRE, M. DIEU, E. DELAIVE, M. RAES, J.-P. THOME, P. KESTEMONT. *Protein expression profiling in the African clawed frog Xenopus laevis tadpoles exposed to the PolyChlorinated Biphenyls mixture Aroclor 1254*. *Mol. Cell. Proteomics* 8, 596-611, **2009**.
- ▶ H. T. TU, F. SILVESTRE, N. T. PHUONG, P. KESTEMONT. *Acetylcholinesterase activity as a biomarker of exposure to antibiotics and pesticides in the black tiger shrimp (Penaeus monodon)*. *Ecotox. Environ. Saf.*, in press.

## Awards

- V. GILLARDIN, C. DIVOY, F. SILVESTRE, M.-C. FORGET, P. KESTEMONT. « *Young Scientist Award* » poster at the 16th SETAC Europe annual meeting Europe, Den Haag (The Netherlands) : « *Effects of the PCBs mixture Aroclor® 1254 on antioxidant systems and protein expression profiles of developing Xenopus laevis tadpoles* », 7-11 may **2006**.

## Partnership

- M. RAES, Research Unit in Cell Biology, University of Namur

## Main Equipment

- ▶ Ettan Dalt 6 unit
- ▶ Criterion Dodeca Cell
- ▶ IPG Phor
- ▶ ImageMaster Platinum

## Products and Services

- ▶ Ecotoxicological tests under GLP standard on aquatic organisms
- ▶ Toxicoproteomics tests
- ▶ ELISA test development for ecotoxicology

**KEY WORDS FOR R&D**

Toxicoproteomics  
Ecotoxicology  
GLP  
Risk assessment  
ELISA  
Pollutant  
REACH  
Aquatic organisms  
Danio rerio  
Xenopus laevis  
Protein assay

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# Directed Evolution of Enzymes

## SENIOR SCIENTIST :

▶ Patrice SOUMILLION

## Research Field and Subjects

Since 1994, our group is developing research projects focusing on the directed evolution of enzymes with the objective of creating artificial biocatalysts endowed with new properties (specificity, catalytic activity or allosteric regulation).

**Engineering allosteric regulation** is of great interest for developing new reporter enzymes that could be used in **bio-sensors**. By introducing degenerated peptides in surface loops of the **phage displayed TEM-1 beta-lactamase**, we are creating large libraries of insertants from which we are selecting clones that have acquired affinity for specific ligands (proteins, ions, small molecules). The activity of most of these hybrid enzymes are up- or down-regulated upon ligand binding. Following activity regulation allows the direct detection of the ligand in solution.

More recently, we initiated a project with the aim of **evolving the substrate specificity** of an enzyme using a new ultrahigh throughput method for protein engineering, the so called **in vitro compartmentalisation technology**. Individual genes of a library can be transcribed-translated in small droplets made by microfluidics devices. With the help of a fluorogenic substrate, droplets containing active enzymes are recovered by a fluorescence activated sorter and the co-selected genes are amplified by PCR. We are applying this "whole in vitro" evolution technique to change the specificity of **penicillin G acylase**. Creating artificial amidases with designed specificities is potentially useful for biocatalysis applications such as deracemization reactions, regio- or enantio-selective hydrolysis, amide synthesis.

## Representative References

- ▶ P. SOUMILLION. *Evolutionary Methods in Biotechnology, Clever Tricks for Directed Evolution. Chapter 6 : Selection of Phage-displayed Enzymes*. S. Brakmann & A. Schwienhorst (eds), Wiley-VCH Verlag GmbH, Weinheim, Germany, pp 47-64, **2004**.
- ▶ P. MATHONET, J. DEHERVE, P. SOUMILLION, J. FASTREZ. *Active TEM-1 beta-lactamase mutants with random peptides inserted in three contiguous surface loops*. *Protein Sci.*, 15, 2323-2334, **2006**.
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- ▶ A. FERNANDEZ-GACIO, A. CODINA, J. FASTREZ, O. RIANI, P. SOUMILLION. *Transforming Carbonic Anhydrase into Epoxide Synthase by Metal Exchange*. *Chembiochem*, 7, 1013-1016, **2006**.
- ▶ C. URBACH, J. FASTREZ, P. SOUMILLION. *A new family of cyanobacterial penicillin-binding proteins. A missing link in the evolution of class A beta-lactamases*. *J. Biol. Chem.*, 283, 32516-32526, **2008**.
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## Patent

- D. LEGENDRE, P. SOUMILLION, J. FASTREZ. *Chimeric target molecules having regulatable activity*. *PCT Int. Appl.*, WO 9823731, **1998**.

## Funding

- ▶ UCL
- ▶ FNRS
- ▶ BSP (Interuniversity Attraction Pole P6/19, PROFUSA)

## Partnership

- ▶ Federal Interuniversity Attraction Poles (IAP) P6/19 PRO-FUSA : PROteins : interactions involved in Folding, FUnction and Supramolecular Assemblies).
- ▶ European Integrated Training Network (ITN) ENEFP (European Network on Evolution of Functional Proteins).
- ▶ Regional NANOTIC program (pôles d'excellence en Région Wallonne): Essais de senseurs intelligents.

## Main equipment

Spectrophotometry UV-Vis, protein purification platform.

## Products and Services

- ▶ Know-how in phage display of proteins and enzyme engineering.
- ▶ Libraries of regulatable beta-lactamases on phage are available for selection on specific targets.

## KEY WORDS FOR R&D

Phage display  
High throughput screening  
Reporter enzymes  
Allosteric regulation  
Beta-lactamase  
Penicillin acylase  
Insertion mutagenesis

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# Molecular and Cellular Regulation of Cardiovascular Metabolism and Function

## SENIOR SCIENTIST :

- ▶ Jean-Louis VANOVERSCHELDE
- ▶ Christophe BEAULOYE
- ▶ Luc BERTRAND
- ▶ Christophe DEPRE
- ▶ Sandrine HORMAN

## Research Field and Subjects

Our research team is studying the intracellular signalling that controls cardiovascular metabolism and function. Our program is mainly focused on protein kinase cascades involved in the regulation of glucose metabolism, of cell growth and architecture and of stem cell differentiation. These aspects are investigated in patho-physiological processes including ischemic injury, hypertrophy and diabetic cardiomyopathy, cardiac remodelling and arterial thrombosis. We are also studying whether the modulation of these signalling events could exert some potential therapeutic effects.

Our research efforts are currently focused :

- ▶ On the evaluation of the protective role of a protein kinase called AMP-activated protein kinase (AMPK) against ischemia, left ventricular hypertrophy and myocardial insulin-resistance.
- ▶ On the use of mesenchymal stem cells for mending the ischemic myocardium. We want to evaluate the effects of tissue hypoxia on the ability of mesenchymal stem cells to home, survive and differentiate into cardiac myocytes and to explore the contribution of AMPK in these phenomena.
- ▶ On the evaluation of the role of AMPK on platelet activation and aggregation.
- ▶ On the evaluation of the role of AMPK on left ventricular remodelling.

## Representative References

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- ▶ D. VANCRAEYNST, X. HAVAU, A.-C. POULEUR, A. PASQUET, B. GERBER, Chr. BEAULOYE, P. RAFTER, L. BERTRAND, J.-L. VANOVERSCHELDE. *Myo-*

*cardial Delivery of Colloidal Nanoparticles using Ultrasound-targeted Microbubble Destruction*. Eur. Heart J. 27, 237-245, **2006**.

- ▶ L. BERTRAND, A. GINION, Chr. BEAULOYE, A. D. HEBERT, B. GUIGAS, L. HUE, J.-L. VANOVERSCHELDE. *AMP-activated protein kinase activation restores the stimulation of glucose uptake in insulin-resistant cardiomyocytes via the activation of protein kinase B*. Am. J. Physiol. Heart Circ. Physiol. 291, 239-250, **2006**.
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- ▶ B. VIOLLET, Y. ATHEA, R. MOUNIER, B. GUIGAS, E. ZARRINPASHNEH, S. HORMAN, J. DEVIN-LECLERC, Chr. BEAULOYE, M. FORETZ, F. ANDREELLI, R. VENTURA-CLAPIER, L. BERTRAND. *AMPK : Lessons from animal models*. Front. Biosci. 14, 19-44, **2009**.

## Awards

- ▶ J.-L. VANOVERSCHELDE. *Prix Camille et Germaine Damman*, **1990**.
- ▶ J.-L. VANOVERSCHELDE. *Prix de la Ligue Cardiologique Belge*, **1992**.
- ▶ J.-L. VANOVERSCHELDE. *Prix Therabel*, 1995.
- ▶ J.-L. VANOVERSCHELDE. *Prix Van Vaerenbergh - de Visccher*, **1996**.
- ▶ J.-L. VANOVERSCHELDE. *Prix Bekales*, 1996.
- ▶ J.-L. VANOVERSCHELDE. *Chaire Astra Foundation*, **1997-1999**.
- ▶ J.-L. VANOVERSCHELDE. *Lecture Bischof*, **2001**.
- ▶ Chr. BEAULOYE. *Young Investigator Award of Belgian Society of Cardiology*, **2001**.
- ▶ L. BERTRAND. *Prix Léopold et Marthe Delsaux-Champy*, **2006**.
- ▶ L. BERTRAND. *Prix Camille et Germaine Damman*, **2007**.

## Funding

- ▶ Fonds National de la Recherche Scientifique (FNRS)
- ▶ Fonds de la Recherche Scientifique et Médicale (FRSM)

## Partnership

Partner in the program Actions de recherche concertées (ARC) on "Beyond myocardial damage : mechanisms of survival and regeneration of the cardiovascular tissue"

## Main Equipment

- ▶ Human and animal cardiac imaging (standard and high resolution echocardiography, SPECT and  $\mu$ SPECT, PET and  $\mu$ PET, MRI, CT)
- ▶ *Ex vivo* system of heart perfusion (for small and big animals)
- ▶ Standard biochemical and cellular biology equipment (1D and 2D electrophoresis, cell culture, immunohistochemistry)
- ▶ Liquid scintillation analyzers, multimodal imaging system (chemiluminescence and fluorescence) and spectrophotometer

## Products and Services

- ▶ Cardiac metabolic and functional measurements including *ex vivo* heart perfusion and primary cultured cardiomyocytes.
- ▶ Human and animal cardiac imaging by (animal)-PET, (animal)-SPECT and echo-cardiography.
- ▶ *In vitro* and *In vivo* protein kinase assay.

## KEY WORDS FOR R&D

Heart metabolism  
Protein phosphorylation  
Platelet  
Diabetes  
Heart failure  
Insulin resistance  
Protein kinase  
Cardiac imaging  
Cardiac remodelling  
Hypertrophy  
Ischemia  
Cell therapy

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# Metabolic Basis of Inherited Disorders : Identification of New Enzymes and New Defects

## SENIOR SCIENTISTS :

- ▶ Emile VAN SCHAFTINGEN
- ▶ Maria VEIGA-DA-CUNHA

## Research Field and Subjects

The general goal of the group is to identify new enzymes involved in the intermediary metabolism and understand their involvement in metabolic disorders (inborn errors of metabolism; diabetes).

The current fields are :

1. The unraveling of the mechanisms of protein deglycation by the study of fructosamine-3-kinase and related enzymes in vitro, in cell culture, in transgenic mice, and by genetic screening of diabetic and/or obese patients.
2. The study of enzymes involved in the synthesis of compounds of neurobiological interest such as N-acetylaspartate and N-acetylaspartylglutamate.
3. The characterization, at the molecular level, of the inherited metabolic disorder L-2-hydroxyglutaric aciduria.
4. The development of enzymatic assays for the diagnosis of inborn metabolic defects.
5. The identification of new enzymes through a database mining approach followed by the characterization of expressed proteins

## Representative References

- ▶ M. VEIGA-DA-CUNHA, P. JACQUEMIN, G. DELPIERRE, C. GODFRAIND, I. THEATE, D. VERTOMMEN, F. CLOTMAN, F. LEMAIGRE, O. DEVUYST, E. VAN SCHAFTINGEN. *Increased protein glycation in fructosamine 3-kinase-deficient mice*. *Biochem J.* 399, 257-64, **2006**.
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- ▶ J. FORTPIED, R. GEMAYEL, D. VERTOMMEN, E. VAN SCHAFTINGEN. *Identification of protein-ribulosamine-5-phosphatase as human low-molecular-mass protein tyrosine phosphatase-A*. *Biochem. J.* 406, 139-45, **2007**.
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- ▶ M. VEIGA-DA-CUNHA, W. VLEUGELS, P. MALIEKAL, G. MATTHIJS, E. VAN SCHAFTINGEN. *Mammalian phosphomannomutase 1 (PMM1) is brain, IMP-sensitive glucose 1,6-bisphosphatase*. *J. Biol. Chem.* 283, 33988-93, **2008**.

## Awards

- E. VAN SCHAFTINGEN. *Van Gysel Award*, **2003**.

## Funding

- ▶ Belgian science policy, Interuniversity Attraction Poles (IAP P6/05)
- ▶ Walloon Region, Programme d'excellence universitaire DIANE
- ▶ FNRS
- ▶ FRSM

## Partnership

J. JAEKEN, Kindergeneeskunde, and G. MATTHIJS, Centrum voor Menselijke Erfelijkheid, KULeuven, Gasthuisberg, 3000 Leuven

## Main Equipment

- ▶ Animal cell technology
- ▶ Biomolecular equipment
- ▶ HPLC and FPLC technology
- ▶ Liquid scintillation analyzers

## Products and Services

- ▶ Transgenic mice
- ▶ Expression vectors
- ▶ Enzymatic assays of inborn errors of metabolism

## KEY WORDS FOR R&D

Intermediary metabolism  
Cell culture systems  
Congenital metabolic disorders  
Diabetes  
Enzymatic assays  
Glycoproteins  
Neurodevelopmental disorders  
Obesity  
Protein glycation  
Protein glycosylation  
Transgenic mice

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# Cleft Lip and Palate : (Epi)Genetic Causes and Development of Genetically Manipulated Animal Models

## SENIOR SCIENTISTS :

- ▶ Miikka VIKKULA
- ▶ Michella GHASSIBE

## Research Field and Subjects

Craniofacial development is one of the most complex events that occurs during embryogenesis. It is coordinated by a series of transcription factors, growth factors and signaling molecules. Disruption of any of these pathways can cause cleft lip with or without palate (CL/P).

Many clinical problems are attributable to this anomaly, from nutritional and dental issues to speech and psychological trouble. This often requires surgical intervention and costly long-term treatment and follow-up. The prevalence of clefts is approximately 1/700 to 1/1000 in Caucasians and varies among populations. Asians are most frequently affected while those of African origin are less frequently so. Clefts are classified into 3 groups: cleft lip, cleft lip and palate, and cleft palate only. Cleft palate only, which occurs without any cleft of the lip, is considered to be etiologically distinct from cleft lip with or without palate. CL/P is isolated in 70% of cases, occurring without any other clinical anomaly. In the remaining 30%, it is a component of one of 500 malformation syndromes, in which the cleft is associated with multiple symptoms. The non-syndromic forms are likely due to gene-environmental interactions, whereas the syndromic forms are mainly due to genetic alterations.

### ▶ Epigenetic causes

We work in close collaboration with the centre labio-palatin of the Saint-Luc hospital. We have studied and characterized several genes implicated in the occurrence of both isolated and syndromic cleft lip and/or palate in patients. Our major achievements in the past six years constitute a dissection of the genetic causes of clefts and they comprise :

1. The determination that IRF6 is a major causative gene for Van der Woude syndrome (VWS) in several populations.
2. The finding that IRF6 is the sole gene causing PPS.
3. The evidence that IRF6 predisposes to cleft occurrence in Belgian patients.
4. The characterization of a new gene responsible for as much as 3% of cleft palate and Pierre Robin sequence.

### ▶ Development of animal models

Embryonic development of the lip and palate are strikingly similar in mice and humans, which makes the mouse a model of choice to study craniofacial development. Thus, current know-

ledge about the etiopathogenesis of clefts has mainly been gathered from this *in vivo* model. Having a mouse facility at the UCL offers us the advantage of creating mouse models of the different genes we identify in the laboratory. Currently, we are phenotyping a mouse model where we knocked-out a new cleft gene. In parallel, we conduct a collaboration with a zebrafish facility in KULeuven, in order to knockdown the same gene and determine if this molecule has the same developmental role across species.

## Representative References

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- ▶ R. L. FERREIRA DE LIMA, S. A. HOPER, M. GHASSIBE, M. E. COOPER, N. K. RORICK, S. KONDO, L. KATZ, M. L. MARAZITA, J. COMPTON, S. BALE, U. HEHR, M. J. DIXON, S. DAACK-HIRSCH, O. BOUTE, B. BAYET, N. REVENCU, C. VERELLEN-DUMOULIN, M. VIKKULA, A. RICHIERI-COSTA, D. MORETTI-FERREIRA, J. C. MURRAY, B. C. SCHUTTE. *Prevalence and nonrandom distribution of exonic mutations in interferon regulatory factor 6 in 307 families with Van der Woude syndrome and 37 families with popliteal pterygium syndrome*. Genet. Med. (Epub ahead of print), **2009**.

## Awards

- ▶ *Eugène de Sommer Scientific Award*. UCL, **2006**.
- ▶ *Pfizer Scientific Award*. Belgium, **2006**.
- ▶ *Pharmacia Scientific Award*. Belgium, **2002**.

## Funding

FRSM 3.4604.06

## Partnership

- ▶ The Centre labio-palatin, Cliniques universitaires St-Luc, Plastic surgery, Brussels, Belgium.
- ▶ The Platform for transgenesis, UCL.
- ▶ The Center for Human Genetics, KULeuven, U.Z. Gasthuisberg, Leuven, Belgium.
- ▶ The Massachusetts General Hospital, Endocrine Unit, Boston, USA.
- ▶ The CHRU Lille, Roger Salingro Hospital, Plastic surgery, Lille, France.
- ▶ The Cleft lip and palate Network of clinicians and centers worldwide.

## Main Equipment

- ▶ Capillary Sequencing Units
- ▶ Affymetrix whole genome array platform
- ▶ Semi-automated analysis systems for human genome linkage analysis
- ▶ High resolution melting (HRM) PCR system for real-time quantitative PCR and SNP analysis

## Products and Services

- ▶ Tissue, cell line and DNA/RNA/protein biobank
- ▶ Development of genetic tests
- ▶ Transgenic mice
- ▶ Expression constructs and cell-lines
- ▶ Antibodies

## KEY WORDS FOR R&D

Transgenic mice  
Knock-down zebrafish  
Knock-out mice  
Genetics  
Animal model  
Cleft lip  
Cleft palate  
Craniofacial anomaly  
Development  
Etiology  
Mouse model  
Linkage study  
Association study

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# Vascular Malformations : (Epi)Genetic Causes and Development of Genetically Manipulated Animal Models

## SENIOR SCIENTISTS :

- ▶ Miikka VIKKULA
- ▶ Laurence BOON
- ▶ Mustapha AMYERE
- ▶ Pascal BROUILLARD
- ▶ Nisha LIMAYE

## Research Field and Subjects

One of the main interests of our group is to elucidate the factors that orchestrate the processes of lymph/vascular development. A deeper understanding of the precise mechanisms by which genetic alterations mediate developmental defects of the vasculature, and the establishment of good animal models in which to study pathogenicity as well as potential rescue, hold the promise of more effective, targeted therapy of these anomalies. Vascular malformations are localized structural defects that arise during fetal angiogenesis. They are usually present at birth. We have identified the genetic cause of several of the inherited forms and thus shown, for example, that:

- ▶ Glomuvenous malformations (GVMs) are caused by mutations in a gene we named *iglomulin*. These mutations derail vascular smooth muscle cell (vSMC) development towards rounded *iglomus* cells.
- ▶ A rare inherited form of venous malformations (VMs) (Cutaneous mucosal venous malformation) is caused by germline gain-of-function mutations in the gene encoding the angiopoietin receptor TIE2 (TEK). In 2009, we further discovered that half of sporadic VM patients have non-hereditary, somatic TIE2 mutations.
- ▶ Capillary malformation - arteriovenous malformation (CM-AVM) is caused by loss-of-function mutations in *RASA1*, encoding the Ras GTPase activating protein p120RasGAP.
- ▶ Primary lymphedema (LE) is caused by loss-of-function mutations in *VEGFR 3* (*FLT4*). Additional LE genes include the forkhead transcription factor *FOXC2*. LE genes may be involved in cases of unexplained hydrops fetalis, as evidenced by a screen of 12 patients: two had mutations in *VEGFR3* and one in *FOXC2*. Studies on targeted gene deletions in mice show that the molecules implicated in these and other malformations are of central importance in vascular and/or lymphatic development and function. Dissecting their role could therefore yield useful insights relevant to other pathological contexts in which angiogenesis lymphangiogenesis play key roles, including cancer, atherosclerosis, diabetic retinopathy, and transplantation. We are therefore investigating the mechanism by which loss of glomulin causes GVMs, by generating mouse models of the anomaly and dissecting glomulin's function in vSMCs in vitro. This will serve as a model in which to study the effects of gene replacement and/or different therapeutic interventions.

Using gene knock-in technology, we are also creating several mouse models of VMs, and carrying out transcriptional profiling on cells expressing mutant forms of TIE2 in an effort to understand its mode of action and identify therapeutic targets. These models will allow us to study the role of Tie2 in the pathophysiology of VMs, as well as in vascular development and function. They could also prove invaluable in the future, as a source of mutant endothelial cells for in vitro screens of molecules to modify the aberrant Tie2 signaling identified, and for testing the safety and efficacy of such molecules in an in vivo model of the disease.

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### Patents

- ▶ M. VIKKULA. *VMGLOM gene and its mutations causing disorders with a vascular component*. USA Patent n° 2003/0176649.
- ▶ M. VIKKULA. *Medical use of ras antagonists for the treatment of capillary malformation*. International application n° PCT/EP03/02913.

### Awards

- ▶ *Pharmacia Scientific Award*, Belgium, **2002**.
- ▶ *Pfizer Scientific Award*, Belgium, **2006**.
- ▶ *Eugène de Sommer Scientific Award*, UCL, **2006**.

### Funding

FRSM 3.4604.06; ARC 07/12-005; PAI 6/05; NIH P01 AR0485564.

### Partnership

- ▶ The Center for Vascular Malformations, Cliniques Universitaires St. Luc; the Vascular Anomalies Center, Children's Hospital, Boston, USA; the Vascular Anomalies Network of clinicians and centers worldwide.
- ▶ Vascular Anomalies Network of clinicians and centers worldwide.

### Main Equipment

- ▶ Capillary Sequencing Units
- ▶ Affymetrix whole genome array platform
- ▶ Semi-automated analysis systems for human genome linkage analysis
- ▶ High resolution melting (HRM) PCR system for real-time quantitative PCR and SNP analysis

### Products and Services

- ▶ Tissue, cell line and DNA/RNA/protein biobank
- ▶ Transgenic mice
- ▶ Expression constructs and cell-lines
- ▶ Development of genetic tests

### KEY WORDS FOR R&D

Transgenic mice  
 Animal model  
 Vascular malformation  
 Glomuvenous malformation  
 Angiogenesis  
 Lymphangiogenesis  
 Cutaneomucosal venous malformation  
 Lymphedema  
 Capillary malformation-arteriovenous malformation  
 Endothelial/ Smooth muscle cell

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# Pathophysiology of Hemangiomas

## SENIOR SCIENTISTS :

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- ▶ Nisha LIMAYE

## Research Field and Subjects

Hemangiomas are benign tumors of disorganized vasculature, occurring in 5-10% of infants of European ancestry. They are characterized by a proliferative phase that lasts up to about one year of age, followed by a longer involuting phase during which they spontaneously resolve. Depending of size and location, they can cause, for example, visual problems, ulceration, pain, destruction of adjacent tissues, psychological problems, and even high output cardiac failure, when multiple hemangiomas affect the liver.

The etiopathogenic causes of these tumors, as well as the factors that participate in their resolution, have remained elusive, although recent work has implicated the vascular endothelial growth factor (VEGF) signaling pathway in their pathogenesis. We have collected a large panel of blood samples, as well as lesion-derived tissue and endothelial cells from patients with hemangiomas to study involvement of genetic factors. Affymetrix whole-genome high-density mapping arrays (SNP 6.0) are being employed to assay paired blood and tissue samples for any somatic changes (in nucleotide composition or copy number) that occur in the tissue, which may contribute to tumor growth or involution. In addition, we will carry out whole genome mapping on samples from children with PHACEs syndrome (which combines posterior fossa malformations with hemangiomas, arterial anomalies, cardiac/aortic anomalies, eye abnormalities, and sternal clefting), and their unaffected parents, in an attempt to identify genetic changes. Moreover, various hemangioma-derived endothelial cell lines have been generated for further study.

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## Patents

- ▶ M. VIKKULA. *VMGLOM gene and its mutations causing disorders with a vascular component*. USA Patent n° 2003/0176649, **2003**.
- ▶ M. VIKKULA. *Medical use of ras antagonists for the treatment of capillary malformation*. International application n° PCT/EP03/02913, **2003**.

## Awards

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## Funding

- ▶ FRSM 3.4604.06
- ▶ PAI 6/05
- ▶ NIH P01 AR0485564

## Partnership

The Center for Vascular Malformations, Cliniques Universitaires St. Luc; Vascular Anomalies Center, Children's Hospital, Boston, USA; Vascular Anomalies Network of clinicians and centers worldwide.

The Platform for transgenesis, UCL.

## Main Equipment

- ▶ Capillary Sequencing Units
- ▶ Affymetrix whole genome array platform
- ▶ Semi-automated analysis systems for human genome linkage analysis
- ▶ High resolution melting (HRM) PCR system for real-time quantitative PCR and SNP analysis

## Products and Services

- ▶ Tissue, cell line and DNA/RNA/protein biobank
- ▶ Tissue-derived endothelial cell isolation and expansion
- ▶ High-density SNP array-based genotyping

## KEY WORDS FOR R&D

Vascular tumor  
Hemangioma  
PHACES  
Whole-genome SNP arrays  
Endothelial cell  
Expression analysis

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# *In vitro* and *in vivo* Evaluation Systems for Cardiovascular Functions

## SENIOR SCIENTISTS :

- ▶ Jean-Luc BALLIGAND
- ▶ Chantal DESSY
- ▶ Olivier FERON
- ▶ Pierre SONVEAUX

## Research Field and Subjects

The research efforts are focused :

1. On the pharmacology and molecular biology of nitric oxide synthases.

Studies on the transcriptional and post-translational regulation of the three isoforms of NO synthases, are undertaken on both cultured cells *in vitro* and in animal models of cardiovascular diseases. The role of NO in therapeutic angiogenesis is also examined through the study of the regulation of eNOS activity by drugs and protein engineering.

2. On the molecular and cellular pharmacology of adrenergic and muscarinic cholinergic receptors in heart and vascular tissues.

The expression and coupling/ desensitization mechanisms of beta-adrenergic (e.g. beta3-adrenergic), muscarinic cholinergic receptors and other G-protein-coupled receptors are analyzed in models of primary cardiomyocytes from rodents in culture, conductance and resistance vessels, including from humans.

Various agonists and antagonists for these receptors are tested in animal models of cardiomyopathy and on human coronary microvessels.

3. On the study of the alteration of the endothelial phenotype in ischemic/hypoxic conditions.

These studies aim at investigating the mechanisms involved in angiogenesis to identify new therapeutic targets to treat ischemic cardiomyopathies. A part of this project deals with the implication of endothelial progenitor cells and the role of adhesion molecules in their recruitment.

4. On the study of myocardial remodelling in response to hemodynamic and ischemic stress. This includes phenotypic characterization of hemodynamic (telemetry), histologic (hypertrophy, fibrosis) and biochemical (expressional and signalling studies) parameters in mouse models of myocardial infarction and pressure overload. This includes studies on adult cardiac progenitor cells *in vitro* and *in vivo* as part of regenerative processes.

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## Patents

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## Awards

- ▶ J.-L. BALLIGAND. *Prix Vastesaeger-Société Belge de Cardiologie*, **2004**.
- ▶ P. SONVEAUX. *Prix Biennal de la Société Belge des Sciences Pharmaceutiques*, **2005**.
- ▶ J. SALIEZ. *Young Investigator Award, Symposium Mechanisms of Vasodilatation & EDHF*, **2005**.
- ▶ C. DESSY. *Prix Camille et Germaine Damman*, **2005**.
- ▶ F. DESJARDINS. *Orbita Lipidology Award*, **2006**.
- ▶ P. SONVEAUX. *Prix FECS/EJC (Federation of European Cancer Societies)*, **2007**.
- ▶ P. SONVEAUX. *(ESTRO)-VARIAN-Juliana Denekamp Award*, **2007**.
- ▶ J.-L. BALLIGAND. *1<sup>st</sup> European Society of Pharmacology (EPHAR) Lecture*, **2007**.
- ▶ P. SONVEAUX. *Prix Henri Fauconnier*, **2008**.
- ▶ O. FERON. *Prix Eugène De Somer*, **2008**.
- ▶ P. SONVEAUX. *ERC Starting Grant recipient*, **2009**.

## Funding

- ▶ EU: FP6-Integrated Project « EUGeneHeart »
- ▶ Fondation Jean Leducq – International Network of Excellence in Cardiovascular Research
- ▶ Politique Scientifique Fédérale – PAI
- ▶ Communauté Française – ARC
- ▶ FNRS
- ▶ Région Wallonne – BioWin

## Partnership

- ▶ Department of Pathology, Harvard School of Public Health, Boston, USA – Dr. L. KOBZIK.
- ▶ INSERM-U533, Université de Nantes, France – Prof. Ch. GAUTHIER.
- ▶ Laboratory of Cardiovascular Science, National Institute on Aging, Baltimore, USA – Dr. S. SOLLITT.
- ▶ Molecular cardiology laboratory, Medizinische Hochschule Hannover, Hannover, Germany – Dr DREXLER, Prof. D. HILFIKER-KLEINER.
- ▶ Department of Cardiology, University of Gottingen, Germany – Dr G. HASENFUSS.
- ▶ Internal Medicine I, Klinikum Grosshadern, University of Munich, Germany – Prof. P. BOEKSTEGERS and Dr. C. KUPATT.
- ▶ Department of Cardiology, Charité-Universitätsmedizin Berlin, Franz Volhard Klinik, Germany – Dr M. BERGMAN, Dr L. ZELARAYAN.
- ▶ Centre de Recherche INRA, Jouy en Josas, France – Dr. A. SCHWOK.
- ▶ Dipartimenti di Scienze Biomediche e biotecnologie, Università degli Studi di Brescia, Italy – Pr. Dr. R. REZZANI.

- ▶ Département de Pharmacie, FUNDP – Pr. J.-M. DOGNÉ.
- ▶ Department Mol Cell Biology Laboratory Ion Channel Research, KU Leuven, Belgium – Pr. Dr. B. NILIUS.
- ▶ Laboratoire de Biologie des Tissus Conjonctifs, ULG – Dr. A. COLIGE.

## Main Equipment

- ▶ Videomicroscopy systems (edge and fluorescence detection)
- ▶ Hemodynamic measurements of systolic blood pressure and heart rate variability by implantable telemetry in conscious mice
- ▶ Molecular biology equipment including adeno- and lentivirus technology
- ▶ Cell culture (including hypoxic chamber) and isolation (MACS)
- ▶ Histology and immunohistochemistry (Zeiss Axio-Imager), access to laser-capture microscopy
- ▶ Transcriptomics : Access to Affymetrix and Eppendorf platforms
- ▶ Intravital microscopy (Zeiss Axioskop + Hammamatsu EBCD camera)
- ▶ Laser Doppler imaging (Moor)
- ▶ Pressure and wire myographs + videomicroscopy setup
- ▶ Access to on-site MS, FACS, DNA sequencer, EPR and NMR facilities

## Products and Services

*In vitro* and *in vivo* evaluation of cardiovascular drugs on animal and human cell/tissues.

## KEY WORDS FOR R&D

Cardiovascular  
Endothelial cells  
Cardiomyocytes  
Nitric oxide  
Angiogenesis  
Pharmacology

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# Drug Metabolism and Development of Cell-Based *in vitro* Models In Pharmacotoxicological Research

SENIOR SCIENTIST :

▶ Pedro BUC CALDERON

## Research Field and Subjects

Our research group has been actively involved in European networks dealing with the development and validation of *in vitro* methods to be used in pharmacotoxicological research. To this end, two *in vitro* models have been developed, namely isolated rat hepatocytes and precision-cut liver slices (PCLS). The first step of this research was the characterization of major hepatic pathways (ex. protein synthesis), as well as the ability of hepatic cells to metabolize xenobiotics. Afterwards, the influence of some parameters (i.e. hypoxia, cold-temperature, oxidative stress,...) on the survival and metabolic ability of both hepatocytes and PCLS was studied. More recently, we focused our study on different factors affecting the activities of drug metabolizing enzymes. Among them, ageing is an aggravating factor that may lead to alterations in the biotransformation of drugs, and therefore their therapeutic efficacy and safety. We hypothesized that enzyme activities may be affected by modifications at two levels: transcription (for instance, demasculinization and feminization of CYP450 by changes in the GH secretion profile) and post-translation (increased oxidative stress). At present times, we are interested to understand how drug metabolism (via the formation of reactive oxygen species or electrophile intermediates) may influence the intermediary metabolism as well as the adaptive capacity of cells. Since a large proportion of drug candidate fails during clinical development due to toxicity or inefficacy previously unrevealed by cell-based assays or animal testing, and based in our acquired expertise in this field, the aim of the present project is to provide cell-based *in vitro* models of hepatic metabolism for evaluation on new chemical entities. Within this frame, our work will be focused in the evaluation of potential metabolic activities (phase I and phase II) of these *in vitro* differentiated cell types.

## Representative References

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## **Funding**

- ▶ Union Européenne
- ▶ Région Wallonne
- ▶ FSR

## **Partnership**

- ▶ E. SOKAL, PEDI/MD/UCL
- ▶ P. RENARD, FUNDP, Namur, Belgium
- ▶ J.M. NICOLAS, UCB, Belgium
- ▶ J.J. MARIN, U Salamanca, Spain

## **Main Equipment**

- ▶ Tissue slicer
- ▶ Cell culture
- ▶ HPLC
- ▶ Spectrofluorimetry
- ▶ Fluorescent and light microscopes
- ▶ Western blot
- ▶ Ultracentrifuge
- ▶ Luminometer

## **Products and Services**

- ▶ Drug metabolism
- ▶ In vitro toxicity
- ▶ Metabolic profile
- ▶ Cell signaling

## **KEY WORDS FOR R&D**

Ageing  
Cytochrome P450  
Hepatocytes  
In vitro test  
Liver slices  
Oxidative stress  
Xenobiotic metabolism

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# Yeast Cells As Therapeutic Agents

## SENIOR SCIENTIST :

▶ Jean-Paul BUTS

## Research Field and Subjects

Our research program is devoted to the analysis of the effects of « probiotics » or « biotherapeutic agents » which are living organisms administered to promote the health of the host by treating or preventing infections.

*Saccharomyces boulardii* is a non patho-genic yeast, resistant to gastric acidity and proteolysis, able to quickly reach high concentrations in the gastrointestinal tract. It does not translocate easily out of the intestinal tract and, in contrast with all species of bacterial probiotics, it is resistant to all antibiotics. Clinical randomized double-blind trials, conducted in adults and in children, have conclusively demonstrated the efficacy of the oral administration of a lyophilized preparation of *S. boulardii* for the prevention of enterocolopathies and the treatment of gastrointestinal infections.

*S. boulardii* acts by multiple mechanisms converging to eradicate invasive pathogens : interactions with the normal gut flora, antisecretory effects induced by toxins, inhibition of toxin binding to intestinal receptors (*Clostridium difficile*), stimulation of intestinal immunity (secretion of sIgA), trophic effects on the small intestinal mucosa restoring nutrient absorption capacity. In humans and in growing rats, *S. boulardii* enhances the activity of microvillous enzymes and the absorption capacity of D-glucose by endoluminal release of polyamines, mainly spermine and spermidine. A recent project is devoted to the analysis of a secreted metalloprotease which enhances endoluminal hydrolysis of peptides. In addition, *Saccharomyces boulardii* secretes in the intestinal lumen an  $\alpha\alpha$  trehalase and a protein phosphatase able to inhibit the endotoxin LPS from O55B5 *E. coli* by dephosphorylation resulting in a significant decrease of TNF- $\alpha$  levels.

## Representative References

- ▶ J.-P. BUTS, C. STILMANT, P. BERNASCONI, N. DE KEYSER. *Characterisation of alpha alpha trehalase released in the intestinal lumen by the probiotic Saccharomyces boulardii*. Scandinavian J. Gastroenterology, 2008:4312489-1496, **2008**.
- ▶ J.-P. BUTS, N. DE KEYSER, C. STILMANT, E. DELEM, Fr. SMETS, E.M. SOKAL. *Saccharomyces boulardii produces in rat small intestine a novel protein phosphatase that inhibites Escherichia coli endotoxin by dephosphorylation*. Pediatr res 60:24-29, **2006**.
- ▶ J.-P. BUTS. *25 years on trophic effects of Saccharomyces boulardii : updates and perspectives*. Dig. Dis Sc 54: 15-18, **2008**.
- ▶ J.-P. BUTS. *The probiotic Saccharomyces boulardii upgrades intestinal digestive functions by several complementary mechanisms*. Acta Gastroenterologica Belgica vol LXX02, **2009**.
- ▶ J.-P. BUTS, N. DE KEYSER. *Transduction pathways regulating the trophic effects of Saccharomyces boulardii in rat small intestinal mucosa*. Nature prec.10101/NPRE 2009 3061 1., **2009**.

## Funding

Laboratoires Biocodex, Gentilly, France

## Partnership

INSERM.95 NICE, FRANCE

## Main Equipment

- ▶ Protein sequencer
- ▶ Optodensitometer
- ▶ Ultracentrifuge
- ▶ 2 D Electrophoresis
- ▶ HPLC

### **Products and Services**

- ▶ Lyophilized preparation of yeast *Saccharo-mycetes boulardii*
- ▶ Protein sequence analysis
- ▶ Analysis of polyamines (spermine, spermidine, putrescine) by HPLC in biofluids
- ▶ Analysis of intestinal microvillous enzymes in human small bowel biopsies

### **KEY WORDS FOR R&D**

Aminopeptidase  
Enzyme secretion  
Intestinal microflora  
Metalloprotease  
Polyamines  
Probiotic

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# Pathophysiological Mechanisms Underlying Acute and Chronic Renal Failure

## SENIOR SCIENTIST :

► Nathalie CARON

## Research Field and Subjects

Analysis of the regulation of intrarenal hemodynamics and integrated renal function in different animal models of acute and chronic renal failure, including nephrotoxicity, ischemic injury and renal mass reduction. Evaluation of the involvement of paracrine regulation, oxidative and nitrosative stress as well as inflammation mechanisms and mediators in in vivo animal models.

## Representative References

- E. JOLY, R. SEQQAT, B. FLAMION, N. CARON, A. MICHEL, J. D. IMIG, R. KRAMP. *Increased renal vascular reactivity to angiotensin II after unilateral nephrectomy in the rat involves 20-HETE*. American Journal of Physiology, Regulatory, Integrative and Comparative Physiology 291 (4) : R977-R986, **2006**.
- A.-E. DECLÈVES, N. CARON, D. NONCLERCQ, A. LEGRAND, G. TOUBEAU, R. KRAMP, B. FLAMION. *Dynamics of hyaluronan, CD44, and inflammatory cells in the rat kidney after ischemia / reperfusion injury*. International Journal of Molecular Medicine 18 : 83-94, **2006**.
- A. K. AHRABI, S. TERRY, G. VALENTI, N. CARON, C. SERRADEIL-LE GAL, D. RAUFASTE, S. NIELSEN, S. HORIE, J.-M. VERBAVATZ, O. DEVUYST. *Pkd1 haploinsufficiency causes a syndrome of inappropriate antidiuresis in mice*. Journal of the American Society of Nephrology 18(6) : 1740-53, **2007**.
- D. VANSTERTHEM, N. CARON, A.-E. DECLÈVES, S. CLUDTS, A. GOSSIAUX, D. NONCLERCQ, B. FLAMION, A. LEGRAND, G. TOUBEAU. *Label-retaining cells and tubular regeneration in postischaemic kidney*. Nephrol Dial Transplant. 23(12) : 3786-97, **2008**.
- N. MOREL, G. VANDENBERG, A. K. AHRABI, H. DEBAIX, N. CARON, F. DESJARDINS, J.-L. BALLIGAND, S. HORIE, O. DEVUYST. *Altered vascular reactivity and calcium<sup>2+</sup> signalling in Pkd1<sup>+/-</sup> mice*. Pflugers Arch. 457(4) : 845-56, **2009**.

## Funding

Baxter, institution

## Partnership

Collaboration with Baxter R & D Europe

## Main Equipment

*In vivo* hemodynamic evaluation in rodents and rabbits (ultrasound Doppler probes, electromagnetic probes, telemetry, blood pressure transducers)

## Products and Services

- Technical expertise in animal models of renal disease and collection of biological samples.
- *In vivo* hemodynamic evaluation in rodents and rabbits

## KEY WORDS FOR R&D

Animal models  
Acute renal failure  
Chronic renal failure  
Paracrine regulation  
Pharmacology  
Intrarenal hemodynamics  
Inflammation  
Oxidative and nitrosative stress  
Histopathology

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# Cell Therapy of Central Nervous System Trauma and Pathologies

## SENIOR SCIENTISTS :

- ▶ Frédéric CLOTMAN
- ▶ Emmanuel HERMANS

## Research Field and Subjects

- ▶ In case of lesion, degeneration or inflammatory reaction in the central nervous system, grafting of exogenous cells is susceptible to provide with substantial protection of the remaining neurons (neuroprotection) or with replacement of the lost neurons or glial cells (regeneration).
- ▶ The projects developed in our research teams aim (i) to understand the mechanisms that control neuronal and glial differentiation during embryonic development; (ii) to identify the regulatory processes modulating cell differentiation or glial activation in response to traumatic lesions or neurodegeneration in the adult central nervous system; (iii) using this knowledge, to control the differentiation of stem or progenitor cells into specific neuronal or glial populations; (iv) to graft these engineered cells in the spinal cord of rodents after lesion or in the course of a neurodegenerative process, and to assess the resulting benefits in terms of neuroprotection and regeneration.

## Representative References

- ▶ I. DE HEMPTINNE, C. VERMEIREN, J.-M. MALOTEAUX, E. HERMANS. *Induction of glial glutamate transporters in adult mesenchymal stem cells*. J. Neurochem. 91, 155-166, **2004**.
- ▶ I. DE HEMPTINNE, C. BOUCHERIE, R. POCHET, K. BANTUBUNGI, S.N. SCHIFFMANN, J.-M. MALOTEAUX, E. HERMANS. *Endogenous protective responses evidenced in a transgenic rat model of amyotrophic lateral sclerosis*. Neurosci. Lett., 401, 25-9, **2006**.
- ▶ F. CLOTMAN. *The oncut transcription factors HNF-6 and OC-2 control the development of the spinal motor neurons*. Int. J. Dev. Neurosci., 24 (8) p. 532, **2006**.
- ▶ C. BOUCHERIE, A.-S. CAUMONT, J.-M. MALOTEAUX, E. HERMANS. *Altered astroglial differentiation potential of mesenchymal stem cells derived from a transgenic rat model of familial amyotrophic lateral sclerosis (hSOD1G93A)*. Exp. Neurol. 212, 557-561, **2008**.
- ▶ C. FRANCIUS, F. CLOTMAN. *The oncut transcriptional activators hnf-6, oc-2 and oc-3 are required for proper differentiation of the spinal motor neurons*. Int. j. dev. neurosci., 26 (8) 850-851, **2008**.

- ▶ A. ESPANA, F. CLOTMAN. *Roles of the oncut transcription factors in catecholaminergic neuron differentiation*. Int. j. dev. neurosci., 26 (8) p. 875, **2008**.
- ▶ C. BOUCHERIE, E. HERMANS. *Adult stem cell therapies for neurological disorders : benefits beyond neuronal replacement ?* J. neurosci. res. in press, **2009**.
- ▶ C. BOUCHERIE, S. SCHÄFER, P. LAVAND'HOMME, J.-M. MALOTEAUX, E. HERMANS. *Chimerisation of astroglial population in the lumbar spinal cord after mesenchymal stem cells transplantation prolongs survival in a rat model of amyotrophic lateral sclerosis*. J. neurosci. res. in press, **2009**.

## Awards

- ▶ E. HERMANS. Galenus prize, **2003**.
- ▶ F. CLOTMAN. Prix de la Cinquième Section de l'Académie Royale de Médecine de Belgique, **2002-2003**.
- ▶ E. HERMANS. Baron Simonart prize, **2008**.
- ▶ E. HERMANS. Charcot Foundation prize, **2009**.
- ▶ E. HERMANS. Prix quinquennal des Sciences Pharmaceutiques de l'Académie Royale de Belgique, **2004-2009**.

## **Funding**

- ▶ UCL (FSR)
- ▶ FNRS (FRSM, Télévie)
- ▶ ABMM
- ▶ Fonds de soutien Marguerite-Marie Delacroix
- ▶ European Union (Marie Curie Grant)

## **Partnership**

- ▶ These two groups belong to the Institute of Neuroscience (INES).
- ▶ We have collaboration with both academic and industrial partners.

## **Main Equipment**

- ▶ Dynamic fluorescence imaging
- ▶ Cell cultures
- ▶ Molecular biology
- ▶ Video tracking of locomotor activity
- ▶ Microinjection and electroporation unit

## **Products and Services**

- ▶ Chick embryo electroporation
- ▶ Immunohistochemistry/immunofluorescence
- ▶ Cell grafting in the central nervous system (brain & spinal cord)

## **KEY WORDS FOR R&D**

Astroglial cells  
Central nervous system – development  
Mesenchymal stem cells  
Neural differentiation  
Neural stem cells  
Neurodegenerative disease  
Spinal cord injury

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# Cell Therapy of Diabetes

## SENIOR SCIENTISTS :

- ▶ Pierre COURTOY
- ▶ Denis DUFRANE
- ▶ Pierre GIANELLO
- ▶ Patrick JACQUEMIN
- ▶ Frédéric LEMAIGRE
- ▶ Christophe PIERREUX

## Research Field and Subjects

Diabetes, and in particular type I diabetes, is a disease characterized by a functional deficiency of insulin-producing beta cells of the pancreas. Whereas insulin therapy improves the symptoms of the disease, it does not provide a cure. Pancreatic islet allografts is an alternative to insulin therapy but it faces with a shortage of human donors and immunological hurdles. Therefore, the use of xenografts or of cell therapy with in vitro differentiated beta cells constitute additional therapeutic tools. The research groups focus on (i) the identification of the molecular mechanisms that drive pancreatic cell differentiation and pancreas morphogenesis; (ii) the isolation and transplantation of pig islets; and on (iii) in vitro differentiation of islet cells. A Phase 1 clinical trial investigates : " *Type 1 diabetes therapy with Encapsulated human islets allografts*" in view to overcome the immunosuppression required for allo- or xenotransplantation.

## Representative References

- ▶ P. JACQUEMIN, F. LEMAIGRE, G.-G. ROUSSEAU. *The Onecut transcription factor HNF-6 (OC-1) is required for timely specification of the pancreas and acts upstream of Pdx-1 in the specification cascade*. Dev. Biol. 258, 105-116, **2003**.
- ▶ A.-V. POLL, Chr. PIERREUX, L. LOKMANE, C. HAUMAITRE, Y. ACHOURI, P. JACQUEMIN, G.-G. ROUSSEAU, S. CEREGHINI, F. LEMAIGRE. *A vHNF1/TCF2-HNF6 cascade regulates the transcription factor network that controls generation of pancreatic precursor cells*. Diabetes 55, 61-69, **2006**.
- ▶ D. DUFRANE, W. D'HOORE, R.-M. GOEBBELS, A. SALIEZ, Y. GUIOT, P. GIANELLO. *Parameters favouring successful adult pig islet isolations for xenotransplantation in pig-to-primate models*. Xenotransplantation 13, 204-214, **2006**.
- ▶ V. VANHORENBEECK, M. JENNY, J.-F. CORNUT, G. GRADWOHL, F. LEMAIGRE, G.-G. ROUSSEAU, P. Jacquemin. *Role of the Onecut transcription factors in pancreas morphogenesis and in pancreatic and enteric endocrine differentiation*. Dev Biol. 305, 685-694, **2007**.
- ▶ D. DUFRANE, R.-M. GOEBBELS, A. SALIEZ, Y. GUIOT, P. GIANELLO. *Six-month survival of microencapsulated pig islets and alginate biocompatibility in primates : proof of concept*. Transplantation 81, 1345-1353, **2006**.

- ▶ D. DUFRANE, P. GIANELLO. *Pig islet xenotransplantation into non-human primate model*. Transplantation 86, 753-760, **2008** Review.

## Patents

- D. DUFRANE, P. GIANELLO, J. MELVIK. *Monolayer Cellular Device for cellular encapsulation*. United States Patent Application n°20080050417, **2008**.

## Awards

- ▶ F. LEMAIGRE. *Astra-Zeneca/Biothera Prize*, **2003**.
- ▶ P. COURTOY. *Chaire Francqui*, **2003**.

## Funding

- ▶ European Foundation for the Study of Diabetes
- ▶ 6th and 7th European Framework Programs
- ▶ Belgian Science Policy
- ▶ French Community of Belgium

## Partnership

Members of the EU-funded BetaCellTherapy consortium (<http://www.betacelltherapy.org/>)

## **Main Equipment**

- ▶ Cell and molecular biology equipment
- ▶ Cell culture
- ▶ Imaging : confocal and multiphoton microscopy
- ▶ Fluorescence stereomicroscopy

## **Products and Services**

- ▶ Mouse transgenesis.
- ▶ Organ culture
- ▶ Housing of large animals
- ▶ Operating facilities for pre-clinical studies

## **KEY WORDS FOR R&D**

Diabetes  
Beta cell  
Xenograft  
Islet transplantation  
Pancreas differentiation  
Pancreas morphogenesis  
Cell therapy

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# Development of Functional Nutrients for the Control of Gut-Related Metabolic Diseases

## SENIOR SCIENTISTS :

- ▶ Nathalie DELZENNE
- ▶ Patrice CANI
- ▶ Audrey NEYRINCK

## Research Field and Subjects

The development of functional food appears as an interesting way to modulate key metabolic functions in the body, in order to improve health and well-being. Our research group has focused its scientific activities to demonstrate how nutrients which escape the digestion and which are largely fermented in the colon by specific types of bacteria can be helpful in the control of obesity and associated diseases. Experimental models have been developed in vitro and in animals. They allowed us to study how the interaction of nutrients with the microflora creates a metabolic bridge allowing the colon to “dialogue” with the brain, the liver, and the adipose tissue, with relevant effects on the development of obesity and related metabolic diseases (diabetes, liver diseases, inflammation). Specific in vitro models (precision cut liver slices) have been adapted to study the contribution of tissue-fixed macrophages in the metabolic response to nutrients and drugs.

The studies are mostly performed in vitro or in animal models (genetic, pharmacologic or nutritional models of metabolic diseases) but intervention studies are also performed in humans in collaboration with clinicians.

## Representative References

- ▶ P. CANI, C. DAUBIOL, B. REUSENS, C. REMACLE, G. CATILLON, N. DELZENNE. *Involvement of endogenous glucagon-like peptide 1 (7-36) amide on glycemia-lowering effect of oligofructose in streptozotocin-treated rats.* J. Endocrinol, 185 (3), 457-465, **2005**.
- ▶ P. CANI, A. NEYRINCK, N. MATON, N. DELZENNE. *Oligofructose promotes satiety in rats fed a high-fat diet: involvement of glucagon-like peptide-1.* *Obes Res*, 13 (6), 1000-7, **2005**.
- ▶ E. DELMEE, P. CANI, G. GUAL, C. KNAUF, R. BURCELIN, N. MATON, N. DELZENNE. *Relation between colonic proglucagon expression and metabolic response to oligofructose in high fat diet-fed mice.* *Life Sci*, 79 (10), 1007-13, **2006**.
- ▶ P. CANI, C. KNAUF, M. A. IGLESIAS, D. DRUCKER, N. DELZENNE, R. BURCELIN. *Improvement of glucose tolerance and hepatic insulin sensitivity by oligofructose requires a functional glucagon-like peptide 1 receptor.* *Diabetes* 55 (5), 1484-90, **2006**.

- ▶ P. CANI, E. JOLY, Y. HORSMANS, N. DELZENNE. *Oligofructose promotes satiety in healthy human: a pilot study.* *Eur J Clin Nutr*, 60 (5), 567-72, **2006**.
- ▶ P. CANI, S. HOSTE, Y. GUIOT, N. DELZENNE. *Dietary non digestible carbohydrates promote L cell differentiation in the proximal colon of rat.* *Br J Nutr* 98, 32-37, **2007**.
- ▶ P. CANI, A. NEYRINCK, F. FAVA, C. KNAUF, R. BURCELIN, K. TUOHY, G. GIBSON, N. DELZENNE. *Selective increases of bifidobacteria in gut microflora improves high-fat diet – induced diabetes through a mechanisms associated with endotoxemia.* *Diabetologia*, 50 (11), 1374-2383, **2007**.
- ▶ A. NEYRINCK, A. MOUSON, N. DELZENNE. *Dietary supplementation with laminarin, a fermentable marine beta 1-3 glucan, protects against hepatotoxicity induced by LPS in rat by modulating immune response in the hepatic tissue.* *Int. J. Immunopharmacol*, 7 (12), 1497-1506, **2007**.
- ▶ N. DELZENNE, P. CANI, A. NEYRINCK. *Modulation of glucagon-like peptide 1 and energy metabolism by inulin and oligofructose : experimental data.* *J. Nutr* 137 (11), 2547S-2551S, **2007**.
- ▶ P. CANI, N. DELZENNE. *Gut flora as a target for energy and metabolic homeostasis.* *Curr. Opin. Clin. Nutr Metab Care*, 10 (6), 729-734, **2007**.
- ▶ J. URÍAS-SILVAS, P. CANI, E. DELMÉE, G. LÓPEZ MERCEDES, N. DELZENNE. *Physiological effects of dietary fructans extracted from Agave tequilana Gto. and Dasyliirion spp.* *Br J Nutr* 99, 254-261, **2008**.
- ▶ P. CANI, R. BIBILONI, C. KNAUF, A. WAGET, A. NEYRINCK, N. DELZENNE, R. BURCELIN. *Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice.* *Diabetes*, 57(6),1470-81, **2008**.
- ▶ A. NEYRINCK, F. DE BACKER, P. CANI, L. BINDELS, A. STROBANTS, D. PORTETELLE, N. DELZENNE. *Immunomodulatory properties of two wheat bran fractions- aleurone-enriched and crude fractions- in obese mice fed a high fat diet.* *International Immunopharmacology* 8, 1423-1432, **2008**.

## Patents

- ▶ N. DELZENNE, M. ROBERFROID, P. COUSSEMENT. « *Prevention of mammary carcinogenesis and breast cancer treatment* ». N° US 5,721,345, réf : PRAFF 15/US, **1997**.
- ▶ N. DELZENNE, P. CANI, A. FRANCK. « *Composition for suppressing ghrelin and method for same* ». N°EP 03022007.3, **2003**.

## Awards

- ▶ N. DELZENNE. Post-doctoral Award from Danone- Institute, Belgium, **1993**.
- ▶ N. DELZENNE. « *Research Award for the study of carbohydrates* » from International Life Sciences Institute, USA, **1997**.
- ▶ PAINDAVOINE. *Alpro Foundation Award*, **2004**.
- ▶ A. NEYRINCK. Medal from the Royal Academy of Medicine, Belgium, **2005**.
- ▶ P. CANI. *Young Scientist FENS Award* – Federation of the European Nutrition Societies, Paris, France, **2007**.

## Funding

- ▶ UCL
- ▶ F.R.S. – F.N.R.S.
- ▶ Walloon Region
- ▶ European commission
- ▶ Private companies

## Partnership

(see publications)

1 Active intra-UCL collaborations :

C. REMACLE, B. REUSENS, J.-B. DEMOULIN, Y. GUIOT, Y. HORMANS, I. LECLERCQ, J.-P. THISEN.

2 International collaborations – Member of European networks :

- ▶ Prof R. BURCELIN, Dr C. KNAUF INSERM, Toulouse, France
- ▶ Prof G. GIBSON, DR K. TUOHY, Reading, UK
- ▶ Prof P. FERRÉ, Dr F. FOUFELLE, INSERM, Paris, France

## Main Equipment

- ▶ Molecular biology techniques, including q-RT PCR
- ▶ Bioplex technique (multiple immunoquantification of peptides or RNA)
- ▶ Immunohistochemistry
- ▶ Krumdiek slicer and adequate incubation of precision-cut

organ slices

- ▶ Tissue and cell cultures (2 rooms)
- ▶ Spectrophotometer, gas and high performance liquid chromatography (5)

## Products and Services

- ▶ Testing for new ingredients (prebiotics, probiotics, dietary fibers...) prone to interact with gut microflora, in order to assess their interest in the control of inflammation or metabolic diseases
- ▶ Validation of a portfolio of biomarkers related to gut microflora, inflammation (LPS, pro- and anti-inflammatory cytokines), gut peptides controlling food intake and/or metabolism such as glucagon-like peptide 1, PYY, ghrelin....

## KEY WORDS FOR R&D

Prebiotics  
Microflora  
Obesity  
Gut peptides  
Satiety  
Dietary fibers  
Inflammation  
Metabolic diseases  
Diabetes

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# *In vitro* and *in vivo* Pharmacological Evaluation of Anticoagulant and Antiplatelet Agents

## SENIOR SCIENTISTS :

- ▶ Jean-Michel DOGNÉ
- ▶ Bernard MASEREEL
- ▶ Lionel POCHE

## Research Field and Subjects

1. *In vitro* and *in vivo* pharmacological evaluation of anticoagulants. The search for new anticoagulants is a major challenge in medicine. In practice, this involves identifying drugs capable of preventing thrombus formation without increasing the risk of hemorrhage.

The *in vitro* and *ex vivo* studies undertaken include the enzymatic inhibition of the majority of coagulation factors, and mainly the thrombin generation assay validated as a new pharmacological screening test for measuring the anticoagulant behaviour and potency of any molecules (from chemical synthesis or natural products/extracts). *In vitro* and *ex vivo* assays (Activated partial thromboplastin time, prothrombin time, thrombin generation) are also performed.

The *in vivo* effect of anticoagulant molecules is also examined on different venous thrombosis models in rats (i.e. venous thrombosis induced by stasis and activation of thrombosis by ferric chloride).

2. *In vitro* and *in vivo* pharmacological evaluation of antiplatelet agents.

The *in vitro* and *ex vivo* studies undertaken include the platelet aggregation study by the gold standard optical aggregometry. Whole blood impedance aggregometry and PFA-100 can also be used.

The *in vivo* effect of antiplatelet molecules is also examined on specific arterial thrombosis models in rat. The bleeding time in mice and rats can also be performed.

## Representative References

- ▶ J.-M. DOGNÉ, J. HANSON, X. DE LEVAL, Ph. KOLH, V. TCHANA-SATO, L. DE LEVAL, S. ROLIN, A. GHUYSEN, P. SEGERS, B. LAMBERMONT, B. MASEREEL, B. PIROTTE. *Pharmacological characterization of N-tert-butyl-N'-[2-(4'-methylphenylamino)-5-nitrobenzenesulfonyl]urea (BM-573), a novel thromboxane A2 receptor antagonist and thromboxane synthase inhibitor in a rat model of arterial thrombosis and its effects on bleeding time.* J. Pharmacol. Exp. Ther. May; 309(2) : 498-505, **2004**.

- ▶ J.-M. DOGNÉ, S. ROLIN, M. PÉTEIN, V. TCHANA-SATO, A. GHUYSEN, B. LAMBERMONT, J. HANSON, D. MAGIS, P. SEGERS, B. PIROTTE, B. MASEREEL, P. DRION, V. D'ORIO, Ph. KOLH. *Characterization of an original model of myocardial infarction provoked by coronary artery thrombosis induced by ferric chloride in pig.* Thromb. Res. 116(5) : 431-42, **2005**.

- ▶ S. ROLIN, J. HANSON, C. VASTERSAEGHER, C. CHERDON, D. PRATICO, B. MASEREEL, J.-M. DOGNÉ. *BM-520, an original TXA2 modulator, inhibits the action of thromboxane A2 and 8-iso-prostaglandin F2alpha in vitro and in vivo on human and rodent platelets, and aortic vascular smooth muscles from rodents.* Prostaglandins Other Lipid Mediat., **2007**.

- ▶ S. ROBERT, C. BERTOLLA, B. MASEREEL, J.-M. DOGNÉ, L. POCHE. *Novel 3-carboxamide-coumarins as potent and selective FXIIa inhibitors.* J. Med. Chem. Jun 12; 51(11) : 3077-80, **2008**.

- ▶ S. ROBERT, J. GHIOTTO, B. PIROTTE, J.-L. DAVID, B. MASEREEL, L. POCHE, J.-M. DOGNÉ. *Is thrombin generation the new rapid, reliable and relevant pharmacological tool for the development of anticoagulant drugs ?* Pharmacol. Res. Mar; 59(3) : 160-6, **2009**.

## Awards

- ▶ J.-M. DOGNÉ. *Prix Boehringer Ingelheim pour la Recherche Fondamentale sur la Thrombose et l'Hémostase*, **1999**.
- ▶ J.-M. DOGNÉ. *Prix national bisannuel Janssen Research de la Société Royale Belge de Chimie pour la recherche en Chimie Pharmaceutique*, **2001**.
- ▶ J.-M. DOGNÉ. *Prix Servier d'Encouragement à la Recherche*, **2001**.

## Funding

- ▶ Région wallonne
- ▶ FNRS
- ▶ Pharmaceutical firms

## Partnership

- ▶ H. TEN CATE. University of Maastricht (Maastricht, The Netherlands); Laboratory of Clinical Thrombosis and Haemostasis, Cardiovascular Research Institute Maastricht.
- D. Pratico. Temple University (Philadelphia, USA), Department of pharmacology.
- ▶ Th. KINSELLA. University College Dublin (Dublin, Ireland), Department of Biochemistry, Conway Institute of Biomolecular and Biomedical Research
- ▶ Th. KINSELLA. University College Dublin (Dublin, Ireland), Department of Biochemistry, Conway Institute of Biomolecular and Biomedical Research
- ▶ J.-O. DEFRAIGNE, Ph. KOLH. Cardiovascular research center, University of Liège
- ▶ Ch. DESSY. Unit of Pharmacology and Therapeutics, Université catholique de Louvain
- ▶ E. GODFROID. Service de Biologie Moléculaire des Ectoparasites, Institut de Biologie et Médecine Moléculaires, Université Libre de Bruxelles
- ▶ B. CHATELAIN. Hematology Laboratory, Mont-Godinne Hospital

## Main Equipment

- ▶ Platelet aggregometer
- ▶ Microplate fluorometer Fluoroskan Ascent FL, using the Thrombinoscope® software
- ▶ Tissue organ bath system
- ▶ Equipment for small animal surgical procedures and techniques
- ▶ Analytical equipment (HPLC, GC, LC-MS, etc.)

## Products and Services

*In vitro* and *in vivo* pharmacological evaluation of anticoagulant and antiplatelet agents (from chemical synthesis or natural products / extracts).

## KEY WORDS FOR R&D

Cardiovascular  
Platelets  
Coagulation  
Thrombosis  
Pharmacology

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# Regulation of Glial Glutamate Transporters : Influence of Drugs and Diseases

## SENIOR SCIENTIST :

▶ Emmanuel HERMANS

## Research Field and Subjects

The research is focused on the study of molecular and cellular mechanisms involved in the regulation of extracellular glutamate clearance by astrocytes. Considering the role played by excitotoxicity in several insults of the central nervous system, the uptake of glutamate by astrocytes is a major neuroprotective process. The group develops a series of astrocyte culture models (from brain and spinal cord) and study the influence of drugs on the expression, trafficking and activity of glutamate transporters. These studies are also conducted in animal models of diseases (Parkinson's disease, amyotrophic lateral sclerosis and pain).

## Representative References

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- ▶ S. TILLEUX, E. HERMANS. *Neuroinflammation and the regulation of glial glutamate uptake in neurological disorders*. J. Neurosci. Res. 85, 2059-70, **2007**.
- ▶ S. Goursaud, J.-M. MALOTEAUX, E. HERMANS. *Activation of VIP/PACAP type 2 receptor by the peptide histidine isoleucine in astrocytes influences GLAST-mediated glutamate uptake*. J. Neurochem. 105, 1165-1175, **2008**.
- ▶ S. TILLEUX, E. HERMANS. *Down regulation of astrocytic GLAST by microglia related inflammation is abrogated in dibutyl cAMP matured cultures*. J. Neurochem. 105, 2224-2236, **2008**.
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- ▶ S. GOURSAUD, E. KOZLOVA, J.-M. MALOTEAUX, E. HERMANS. *Cultured astrocytes derived from corpus callosum or cortical grey matter show distinct glutamate handling properties*. J. Neurochem. 108(6):1442-52, **2009**.

## Awards

- ▶ *Galenus prize*, **2003**.
- ▶ *Baron Simonart prize*, **2008**.
- ▶ *Charcot Foundation prize*, **2009**.
- ▶ *Prix quinquennal des Sciences Pharmaceutiques de l'Académie Royale de Belgique*, **2004-2009**.

## Funding

Research in our groups is funded by :

- ▶ UCL,
- ▶ F.R.S.-FNRS,
- ▶ The Association Belge contre les Maladies Neuro-Musculaires (ABMM)
- ▶ La Région Wallonne
- ▶ La Commission Européenne.

### **Partnership**

- ▶ Pharmaceutical companies
- ▶ Academic collaborations
- ▶ European Marie-Curie network

### **Main Equipment**

- ▶ Dynamic fluorescence imaging
- ▶ Cell cultures
- ▶ Equipment for radioligand binding assays
- ▶ Molecular biology

### **Products and Services**

- ▶ Primary cultures of glial cells from rodents
- ▶ Measures of glutamate uptake in cell cultures and tissues synaptosomes
- ▶ Recombinant expression of glutamate transporter subtypes
- ▶ Detection and quantification of glutamate transporter expression

### **KEY WORDS FOR R&D**

Astrocytes Microglia  
Primary cultures of astrocytes  
Glutamate transporters  
Excitotoxicity

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# Cell Therapy of Liver Disease

## SENIOR SCIENTISTS :

- ▶ Patrick JACQUEMIN
- ▶ Frédéric LEMAIGRE
- ▶ Mustapha NAJIMI
- ▶ Etienne SOKAL

## Research Field and Subjects

A number of liver diseases can only be cured by liver transplantation. However, the shortage in donor organs indicates that cell therapy is an alternative or complementary strategy. Implementation of this strategy requires that therapeutically efficient hepatocytes or hepatocyte-derived stem/progenitor cells can be generated. The research groups focus on (i) the isolation of stem cells from human organs and their differentiation in vitro; (ii) the identification of the molecular mechanisms that drive liver cell differentiation; and (iii) the treatment of patients by cell therapy.

## Representative References

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- ▶ J.-B. BEAUDRY, C. PIERREUX, G. P. HAYHURST, N. PLUMB-RUDEWIEZ, M.-C. WEISS, G.-G. ROUSSEAU, Fr. LEMAIGRE. *Threshold levels of Hepatocyte Nuclear Factor 6 (HNF-6) acting in synergy with HNF-4 and PGC-1alpha are required for time-specific gene expression during liver development*. *Mol Cell Biol.* 26, 6037-6046, **2006**.
- ▶ X. STÉPHENNE, M. NAJIMI, C. SIBILLE, M.-C. NASSOGNE, F. SMETS, E. SOKAL. *Sustained engraftment and tissue enzyme activity after liver cell transplantation for argininosuccinate lyase deficiency*. *Gastroenterology* 130, 1317-1323, **2006**.
- ▶ M. NAJIMI, D. N. KHUU, P.-A. LYSY, N. JAZOULI, J. ABARCA, C. SEMPoux, E. SOKAL. *Adult-derived human liver mesenchymal-like cells as a potential progenitor reservoir of hepatocytes ?* *Cell Transplant.* 16, 717-728, **2007**.
- ▶ D. CAMPARD, P.-A. LYSY, M. NAJIMI, E. SOKAL. *Native umbilical cord matrix stem cells express hepatic markers and differentiate into hepatocyte-like cells*. *Gastroenterology* 134, 833-848, **2008**.
- ▶ F. SMETS, M. NAJIMI, E. SOKAL. *Cell transplantation in the treatment of liver diseases*. *Pediatr Transplant.* 12, 6-13, **2008** Review
- ▶ Fr. LEMAIGRE. *Mechanisms of liver development: concepts for understanding liver disorders and design of novel therapies*. *Gastroenterology*, in press, **2009** Review

## Patents

M. NAJIMI, E. SOKAL. *Adult derived human liver stem cells*. 0544728.5, Europe, **2005**.

## Awards

Fr. LEMAIGRE. *Astra-Zeneca/Biothera Prize*, **2003**.

## Funding

- ▶ 7th European Framework Programs
- ▶ Belgian Science Policy
- ▶ French Community of Belgium
- ▶ Walloon Region
- ▶ Fondation St Luc
- ▶ Lion's club
- ▶ Private funds

## Partnership

- ▶ Academic Partners in EU-funded
- ▶ Belgian research networks

## Main Equipment

- ▶ Cell and molecular biology equipment
- ▶ Cell culture
- ▶ Imaging : confocal and multiphoton microscopy
- ▶ Cell sorting
- ▶ Flow cytometer

## Products and Services

- ▶ Mouse transgenesis
- ▶ Liver cell isolation (GMP and GCP guidelines)
- ▶ Liver cell transplantation

**KEY WORDS FOR R&D**

Stem cells  
Hepatocytes  
Liver  
Differentiation  
Inborn errors of metabolism  
Cell therapy

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# Production and Purification of Native or Chimera Proteins for Structure-Based Drug Design

## SENIOR SCIENTISTS :

- ▶ Didier LAMBERT
- ▶ Jacques POUPAERT

## Research Field and Subjects

Structure-based drug design is a new way to design new lead compounds based on the tridimensional structure of the target proteins. In this context, our experience in this research field includes :

- ▶ expression / production / purification of native protein and/or modified proteins (mutants, chimeras, fusion proteins)
- ▶ development of pharmacological assays using these purified proteins
- ▶ X-ray determination of the protein structure, docking and in silico design of next lead compounds. The privileged proteins studied by our research team are the enzymes responsible for hydrolysis of endocannabinoids.

## Representative References

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- ▶ C. MICHAUX, G. MUCCIOLI, D. LAMBERT, J. WOUTERS. *Binding mode of new (thio)hydantoin inhibitors of fatty acid amide hydrolase: comparison with two original compounds, OL-92 and JP104.* Bioorg Med Chem Lett. 16, 4772-4776, **2006**.
- ▶ G. LABAR, C. BAUVOIS, G. MUCCIOLI, J. WOUTERS, D. LAMBERT. *Disulfiram is an inhibitor of human purified monoacylglycerol lipase, the enzyme regulating 2-arachidonoylglycerol signalling.* Chem. Bio. Chem. 8, 1293-1297, **2007**.
- ▶ G. LABAR, F. VAN VLIET, J. WOUTERS, D. LAMBERT. *A MBP-FAAH fusion protein as a tool to produce human and rat fatty acid amide hydrolase : expression and pharmacological comparison.* Amino Acids 34, 127-133, **2008**.
- ▶ G. MUCCIOLI, G. LABAR, D. LAMBERT. *CAY10499, a novel monoglyceride lipase inhibitor evidenced by an expeditious MGL assay.* Chembiochem. 9, 2704-2710, **2008**.

## Awards

Vandevelde Prize (UCL), **2004**.

## Funding

- ▶ FNRS-FRSM
- ▶ FNRS-FRFC
- ▶ FNRS-Televie
- ▶ Charcot
- ▶ Foundation, UCL institutional funding

## Partnership

FUNDP Laboratory of Structural Biological Chemistry  
Prof. Wouters

## Main Equipment

- ▶ Cell culture
- ▶ RT-PCR
- ▶ Protein purification
- ▶ Cell harvester
- ▶ Radiochemical synthesis and radioactive assays

## Products and Services

- ▶ Structure-based drug design for enzymes
- ▶ Development of pharmacological assays on purified proteins
- ▶ Drug-target proteins interactions : screening, mode of inhibition, selectivity

**KEY WORDS FOR R&D**

Structure-based drug design  
Protein purification  
Protein crystallisation  
Enzymes  
X-ray  
Drug design  
Pharmacological assays

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# Study of the Pathophysiological Mechanisms and Fundamental Pharmacotherapy In Cystic Fibrosis

## SENIOR SCIENTISTS :

- ▶ Teresinha LEAL
- ▶ Jean LEBACQ
- ▶ Patrick LEBECQUE
- ▶ Pierre WALLEMACQ
- ▶ François HUAUX
- ▶ Etienne MARBAIX

## Research Field and Subjects

The research is focused on the different approaches to stimulate the cAMP-dependant chloride transport pathway, deficient in cystic fibrosis. One approach is the use of therapeutic agonists on animal models, consisting of transgenic mice homozygous for the  $\Delta F508$  mutation.

Another field of interest is the imbalance of inflammatory responses in cystic fibrosis. This topic includes the characterization of the contribution of different cell populations (macrophages, neutrophils ...) in these dysregulated responses and the understanding of the underlying mechanism of action of beneficial effect of azithromycin in cystic fibrosis.

Our team has acquired great expertise in a new, non-invasive in vivo test used to assess the functional activity of the CFTR protein : the nasal potential difference (NPD) test. This test has been routinely used at our center for about 10 years for diagnosis and prognosis purposes in humans. It has been adapted for experiments in spontaneously breathing anaesthetized mice.

## Representative references

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- ▶ T. LEAL, J. LEBACQ, R. VANBINST, Ch. LEDERMAN, M. DE KOCK, P. WALLEMACQ. *Successful protocol of anaesthesia for measuring transepithelial nasal potential difference in spontaneously breathing mice*. *Lab. Anim.* 40 : 43-52, **2006**.
- ▶ T. LEAL, I. FAJAC, H. L. WALLACE, P. LEBECQUE, J. LEBACQ, D. HUBERT, J. DALL'AVA, D. DUSSEY, A.-P. GANESAN, C. KNOOP, J. CUMPS, P. WALLEMACQ, K. W. SOUTHERN. *Airway ion transport impacts on disease presentation and severity in cystic fibrosis*. *Clin. Biochem.* 41 : 764-72, **2008**.
- ▶ B. LUBAMBA, H. LECOURT, J. LEBACQ, P. LEBECQUE, H. DE JONGE, P. WALLEMACQ, T. LEAL. *Preclinical evidence that sildenafil and vardenafil activate chloride transport in cystic fibrosis*. *Am. J. Respir. Crit. Care Med.* 177 : 506-15, **2008**.
- ▶ X. GAVILANES, F. HUAUX, M. MEYER, P. LEBECQUE, E. MARBAIX, D. LISON, B. SCHOLTE, P. WALLEMACQ, T. LEAL. *Azithromycin fails to*

*reduce increased expression of neutrophil-related cytokines in primary-cultured epithelial cells from cystic fibrosis mice*. *J. Cyst. Fibros.* 8 : 203-10, **2009**.

▶ B. LUBAMBA, J. LEBACQ, P. LEBECQUE, R. VANBEVER, A. LEONARD, P. WALLEMACQ, T. LEAL. *Airway Delivery of Low Dose Miglustat Normalizes Nasal Potential Difference in F508del Cystic Fibrosis Mice*. *Am. J. Respir. Crit. Care Med.* 179 : 1022-8, **2009**.

▶ M. MEYER, F. HUAUX, X. GAVILANES, S. VAN DEN BRULE, P. LEBECQUE, S. LO RE, D. LISON, B. SCHOLTE, P. WALLEMACQ, T. LEAL. *Azithromycin Reduces Exaggerated Cytokine Production by M1 Alveolar Macrophages in Cystic Fibrosis*. *Am. J. Respir. Cell. Mol. Biol.* [Epub ahead of print] Feb 24, **2009**.

▶ P. LEBECQUE, A. LEONARD, K. DE BOECK, F. DE BAETS, A. MALFROOT, G. CASIMIR, K. DESAGER, V. GODDING, T. LEAL. *Early referral to cystic fibrosis specialist centre impacts on respiratory outcome*. *J. Cyst. Fibros.* 8 : 26-30, **2009**.

## Funding

Supported by the Department of Pneumology and the Fondation Saint-Luc, Saint-Luc University Hospital, and by the Fonds Scientifique de la Recherche, Université Catholique de Louvain.

## Partnership

- ▶ Association Belge de Lutte contre la Mucoviscidose (ABLM)
- ▶ Bayer Schering Pharma (Berlin, Germany)

## Main Equipment

- ▶ Cell electrophysiology equipment: NPD and Ussing chamber
- ▶ Animal house facility
- ▶ Cell and molecular biology equipment

## Products and Services

- ▶ Experience in handling, anaesthetizing, micro-dissecting organs and tissues in transgenic mice homozygous for the  $\Delta F5068$  mutation and knockout for the CFTR protein.
- ▶ Measurement of NPD test in humans and in mice before/after treatment with potential candidate drugs for the treatment of the disease.
- ▶ Expertise in transepithelial ion transport in excised tissues from mice (nasal mucosa, ileum and colon) mounted in Ussing chamber.
- ▶ Experience in immunohisto- and cytochemistry analyses for membrane and cellular localization of the CFTR protein in mouse and human tissues.
- ▶ Expertise in cell and molecular biology for study of immunoresponses.

## KEY WORDS FOR R&D

Cystic fibrosis  
Cystic fibrosis transmembrane conductance regulator (CFTR)  
Nasal potential difference  
Lung inflammation  
Macrophages  
Transgenic mice

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# Obesity and Metabolic Syndrome : Pathogenic Role of the Liver and Hepatic Complications

## SENIOR SCIENTISTS :

- ▶ Isabelle LECLERCQ
- ▶ Yves HORMSANS
- ▶ Christine SEMPOUX
- ▶ Patrice CANI

## Research Field and Subjects

The prevalence of obesity and metabolic syndrome is rising in our societies and represent serious health concern because they are associated with increased mortality and morbidity including increased cardiovascular risk and increased cancer. All those abnormalities are related to insulin-resistance.

The liver plays a critical role in whole body lipid and glucose homeostasis, and hepatic insulin resistance is a critical component for the progression towards type 2 diabetes. Insulin resistance and obesity are also strongly associated with non-alcoholic steatohepatitis (NASH), a fatty liver disease that can lead to fibrosis, and cancer.

The aim of our research is to progress in the understanding of the pathogenesis of NASH in order to provide diagnostic markers, to identify therapeutic targets and to evaluate therapeutic strategies.

- ▶ J. WANG, I. LECLERCQ, J.-M. BRYMORA, M. RAMEZANI-MOGHADAM, R. M. LONDON, D. BRIGSTOCK, J. GEORGE. *Kupffer cells play a role in leptin-induced liver fibrosis*. Gastroenterology [Epub ahead of print], April 15, **2009**.
- ▶ A. DA SILVA MORAIS, V. LEBRUN, J. ABARCA-QUINONES, S. BRICHARD, L. HUE, B. GUIGAS, B. VIOLLET, I. LECLERCQ. *Prevention of steatohepatitis by pioglitazone: implication of Adiponectin-dependent inhibition of de novo hepatic lipogenesis*. J. Hepatol, 50 : 489-500, **2009**.

## Awards

- ▶ Brohée's prize/ the Royal Belgian Society for Gastroenterology to I Leclercq (2006), to Y Horsmans (1996)
- ▶ Rising star of European Gastroenterology for 2005 (ASNEMGE and UEGW) I Leclercq.

## Representative References

- ▶ I. LECLERCQ, Chr. SEMPOUX, P. STARKEL, Y. HORMSANS. *Limited therapeutic efficacy of pioglitazone on progression of hepatic fibrosis in rats*. Gut, 55 : 1020-1029, **2006**.
- ▶ P. CANI, R. BIBILONI, C. KNAUF, A. WAGET, A. NEYRINCK, N. DELZENNE, R. BURCELIN. *Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice*. Diabetes, 57(6) : 1470-81, June **2008**.
- ▶ I. LECLERCQ, Y. HORMSANS. *Nonalcoholic fatty liver disease: potential role for nutritional management*. (Invited review) Current opinion in clinical nutrition and metabolic care : 11;766-73, **2008**.
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- ▶ N. LANTHIER, Y. HORMSANS, I. LECLERCQ. *The metabolic syndrome : how it may influence hepatic stellate cell activation and hepatic fibrosis*. Current opinion in clinical nutrition and metabolic care, 12 : in press, **2009**.

## Funding

- ▶ Publics :  
University  
FNRS  
Communauté française de Belgique  
Brussels Regio
- ▶ Private benefactors through St Luc Foundation

## Partnership

- ▶ IUAP P6/36
- ▶ IRSIB : project BRUSTEM
- ▶ Collaboration with the University of Sydney, prof J. George.

## Main Equipment

- ▶ Platform for in vivo evaluation of glucose metabolic fluxes in awake mice by the technique of hyperinsulinemic-euglycemic clamp
- ▶ Laboratory for protein and gene expression analysis
- ▶ cell culture facility ( primary and cell lines)

## Products and Services

- ▶ Evaluation of insulin sensitivity in small animals :
  - *In vivo* : hyperinsulinemic-euglycemic clamp (gold standard) to evaluate insulin sensitivity in both whole body or in an organ specific fashion (i.e. liver, adipose tissues, muscles).
  - *In vivo* : dynamic tests for glucose tolerance and insulin sensitivity
  - *Ex-vivo* : evaluation of the sensitivity of intracellular, insulin-dependent signaling pathways.
- ▶ Animal models to study obesity, diabetes, insulin resistance, fatty liver disease, non-alcoholic steatohepatitis and hepatic fibrosis.
- ▶ Surgical and nutritional manipulations of small animals.
- ▶ Isolation of primary cells from murine livers (hepatocytes, hepatic stellate cells, Kupffer and immune cells, liver progenitor cells.
- ▶ In vivo and in vitro (primary hepatic stellate cells and cell lines) models to study hepatic fibrosis, its pathogenesis and the therapeutic efficacy of interventions and compounds.
- ▶ Histological evaluation (including grading, scoring and morphometry), and immunohistochemistry.

## KEY WORDS FOR R&D

Insulin resistance  
Metabolic syndrome  
Non-alcoholic steatohepatitis  
Type 2 diabetes  
Fatty liver  
Hepatic stellate cells  
Adipocytokines  
Adipose tissue  
Leptin  
Adiponectin  
Kupffer cells  
Hyperinsulinemic-euglycemic clamp studies

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# Type-I Interferons and Central Nervous System Infections

## SENIOR SCIENTIST :

▶ Thomas MICHIELS

## Research Field and Subjects

The microbial pathogenesis unit is studying the interplay between the innate immune response and viral infection with focus on the infection of the central nervous system.

Theiler's virus infection is studied as a model. This virus has a striking ability to persist in the central nervous system of the mouse in spite of a strong and specific immune response. Persistence of the virus in the central nervous system and the associated inflammatory response cause demyelinating lesions reminiscent to those of multiple sclerosis.

Our work includes the characterization of viral factors responsible for immune evasion and for inhibition of the interferon response.

Our studies also address some features of the type-I and type-III interferon (IFN) responses :

- ▶ Characterization of the type-I IFN family;
- ▶ Tissue and cell specificity of the response to IFN-lambda;
- ▶ Characterization of the innate immune response in the context of the central nervous system.

## Representative References

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- ▶ C. SOMMEREYNS, S. PAUL, P. STAHELI, Th. MICHIELS. *Interferon lambda (IFN- $\lambda$ ) is expressed in a tissue-dependent fashion and primarily acts on epithelial cells in vivo.* PLoS Pathog. 4 (3) : e1000017, **2008**.

## Awards

Prix « Centre d'étude Princesse Joséphine Charlotte », **2000**.

## Funding

- ▶ Fonds National de la Recherche Scientifique (FNRS/FRSM)
- ▶ Communauté française de Belgique : action de recherche concertée
- ▶ Région wallonne
- ▶ Université catholique de Louvain
- ▶ Fondation Charcot
- ▶ Association pour la recherche sur la Sclérose en plaques (ARSEP).

## Partnerships

- ▶ M. BRAHIC, Stanford Univ., USA
- ▶ Fr. van KUPPEVELD, NCMLS, Radboud University, Nijmegen, the Netherlands
- ▶ P. STAHELI, Univ. Freiburg, Germany

## Main Equipment

Classical equipment for cellular and molecular biology (class-II containment for pathogens and recombinants)

**KEY WORDS FOR R&D**

Central nervous system infections  
Interferons alpha/beta  
Interferon lambda  
Picornavirus  
Theilovirus

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# *In Vitro* Models for the Evaluation of the Capacity of Drugs to Induce Lipid Storage Disorders and/or Apoptosis

## SENIOR SCIENTISTS :

- ▶ Marie-Paule MINGEOT-LECLERCQ
- ▶ Paul TULKENS
- ▶ Françoise VAN BAMBEKE

## Research Field and Subjects

Among the different manifestations of drug-induced cellular toxicities, we are focusing our interest on two specific alterations :

- ▶ Lipid storage disorders, which are mainly induced by drugs accumulating in lysosomes;
- ▶ Cell death by apoptosis, with a particular interest for the role of lysosomes and the cross-talk between organelles.

We study the molecular mechanisms responsible for these toxic effects and the role of the different subcellular organelles in this respect. We also evaluate strategies aimed at reducing them.

We have also set up a series of relevant in vitro models that allow :

- ▶ To measure in vitro of the ability of drugs to inhibit lysosomal phospholipases and bind to membrane lipids;
- ▶ To evaluate the apoptogenic potency of drugs using very limited amounts of drugs (useful for screening).

These studies can thus contribute to characterize the pre-clinical toxicological profile of new drugs.

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## Funding

Public and private companies.

## Partnership

Pharmaceutical industry

## Main Equipment

- ▶ Cell culture facilities
- ▶ General equipment for biochemical and molecular biology assays
- ▶ General equipment for preparing liposomes
- ▶ Material for binding experiments and biophysical techniques (fluorimetry)
- ▶ Microplate reader
- ▶ Fluorescence microscopy

## Products and Services

- ▶ Cellular models for the evaluation of the capacity of drugs to cause lipid storage disorders.
- ▶ Cellular models for the evaluation of the capacity of drugs to induce apoptosis (adapted for screening).
- ▶ *In vitro* models (liposomes) for the evaluation of the capacity of drugs to inhibit phospholipase activity in vitro models.

**KEY WORDS FOR R&D**

Cell culture  
Phospholipids  
Apoptosis  
Drug-membrane interactions  
Liposomes  
Phospholipases  
Lysosomes

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# *In Vitro* Models for the Biophysical Studies of the Interaction Between Drugs and Membrane Lipids

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## Research Field and Subjects

Cell membrane is a key target for many drugs. Drug interaction with membrane may indeed play a critical role in their pharmacological or toxicological activity, and can modulate their pharmacokinetic properties.

To study drug-membrane interactions at the nano-scale level, we use models of membrane (liposomes) mimicking biological membranes or reconstituted from lipids extracted from cells.

We have developed a series of biophysical powerful approaches to study and predict, in a direct and rapid way, the ability of a drug

- ▶ To interact with membrane lipids,
- ▶ To modify the physico-chemical properties of membrane (lateral and transversal heterogeneity, membrane potential, fluidity, permeability, ability to fuse),
- ▶ To alter the activity of enzymes acting on membrane or inserted inside the membrane.

These studies may help rationalizing the pharmacological properties of drugs.

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## Funding

Public and private companies

## Partnership

Pharmaceutical industry

## Main Equipment

- ▶ General equipment for preparing liposomes (MLV, GUV, LUV, SUV).
- ▶ Material for binding experiments and biophysical techniques (fluorimetry).

## Products and Services

- ▶ *In vitro* models (liposomes) and cellular models for the study of drug-membrane interactions and of lipid membrane composition.
- ▶ *In vitro* models (liposomes) for the evaluation of the capacity of drugs to inhibit phospholipase activity.

**KEY WORDS FOR R&D**

Biophysical studies  
Drug-membrane interactions  
Lipids  
Liposomes

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# In Vivo DNA Delivery by Electroporation

## SENIOR SCIENTISTS :

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- ▶ Gaëlle VANDERMEULEN

## Research Field and Subjects

The use of non viral DNA for gene therapy offers several advantages but requires the development of precise, safe and controlled delivery methods. Electroporation is one of the most promising methods of non-viral gene transfer in vivo. This method consists in the injection of plasmid solution in the target organ followed by the application of high voltage pulses to increase cell permeability and promote electrophoresis of negatively charged DNA. Electroporation induces approximately a 2 to 3 log increase of transgene expression.

Our work is focused on the optimization of in vivo DNA electroporation. Several models are studied. First, we study intradermal electroporation for the delivery of DNA vaccine. We optimize the delivery method, the plasmid vector and we study the influence of adjuvants on the immune response. Second, we use electroporation to deliver plasmid encoding antiangiogenic factors for the treatment of solid tumors.

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## Funding

EU: MOLEDA STREP (EC-FP6), ANGIOSKIN STREP (EC-FP6)

## Partnership

- ▶ D. MIKLAVCIC, Ljubljana, Slovenia
- ▶ D. SCHERMAN, Paris-V, France

## Main Equipment

- ▶ Generators and electrodes for electroporation (Cytopulse and Cliniporator systems).
- ▶ Incubator, centrifuge and agarose gel electrophoresis material for production, preparation and quality control of plasmid.

## Products and Services

DNA electroporation into the skin, the muscle and tumors.

**KEY WORDS FOR R&D**

Gene delivery  
Plasmid delivery  
Electroporation  
Electrotransfer  
DNA vaccine

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# Isolation, Structure Determination and Quantification of Bioactive or Antinutritive Metabolites from Plants

## SENIOR SCIENTISTS :

- ▶ Joëlle QUETIN-LECLERCQ
- ▶ Jean-Louis HABIB-JIWAN
- ▶ Marie-France HÉRENT

## Research Field and Subjects

- ▶ The aim of our work is to validate the uses of plants in traditional medicine and find new pharmacologically active natural substances which could constitute new drugs for therapeutic use or be used as models by chemists to improve their properties.
- ▶ We mainly focus our research on the isolation and structure determination of natural compounds with cytotoxic, pro-apoptotic, anti-angiogenic, anti-microbial, anti fungal, antioxidant, anti-inflammatory, anti-trypanosomal, antimalarial or vasorelaxant properties.
- ▶ We also develop methods for quantitative analysis of bioactive or antinutritive compounds in plants and biological extracts, validate these analytical procedures and control the quality of drugs.
- ▶ High resolution UHPLC-MSn-high resolution MS is also used for identification and analysis of natural compounds (MASSMET technological platform) in crude extracts.

## Representative References

- ▶ F. GBAGUIDI, G. ACCROMBESSI, M. MOUDACHIROU, J. QUETIN-LECLERCQ. *HPLC quantification of two isomeric triterpenic acids isolated from Mirtacarpus scaber and antimicrobial activity on Dermatophilus congolensis*. Journal of Pharmaceutical and Biomedical Analysis, 39 : 990-995, **2005**.
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## Funding

- ▶ FNRS, FSR
- ▶ CUD, CGRI, AUF, Belgian cooperation
- ▶ Federal Public Service – scientific research

## Partnership

- ▶ Madagascar : Institut malgache des Recherches Appliquées (IMRA)
- ▶ Bénin : University of Abomey-Calavi (UAC)
- ▶ Maurice : University of Mauritius (UOM)
- ▶ Maroc : University of Fes (USMBA)
- ▶ France : Université Paul Sabatier- Toulouse (UPS)
- ▶ Pérou : Internacional Patato Center (CIP)
- ▶ Bolivie : Université Mayor de San Simon Cochalamba
- ▶ Brésil : Université fédérale de Para (UFPA)
- ▶ Vietnam : Vietnamese Academy of Science and Technology (VAST)
- ▶ Democratic Republic of Congo : university of Kinshasa
- ▶ Rwanda : National University of Rwanda
- ▶ Belgium :
  - University of Liège (ULg)
  - University of Antwerp (UA)
  - Free University of Brussels (VUB)

## Main Equipment

- ▶ Gaz chromatography: MS, FTIR ou FID detection
- ▶ HPLC/UPLC : DAD, UV, SM and high resolution MS<sup>n</sup> (LTQ-Orbitrap) (MASSMET plateform)
- ▶ Fraction collector
- ▶ Preparative MPLC
- ▶ Centrifugal Partition chromatography (CPC)
- ▶ TLC scanning
- ▶ Lyophilisator
- ▶ Overpressure liquid planar chromatography (OPLC)

## Products and Services

- ▶ Quality control of natural extracts or substances (agreed laboratory by the Federal Agency of Medicines and Health Products)
- ▶ Isolation, purification and quantitative determination of biologically active substances from crude extracts
- ▶ Analysis of natural products or vegetable drugs
- ▶ High resolution mass spectrometry (MASSMET Plateform)

## KEY WORDS FOR R&D

Medicinal plants  
Quantitative analysis  
Active natural products  
Isolation  
Structure determination

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# Liver-Derived Progenitor Cells for Regenerative Medicine and Pharmacotoxicology Testing

## SENIOR SCIENTISTS :

- ▶ Etienne SOKAL
- ▶ Mustapha NAJIMI
- ▶ Xavier STÉPHENNE
- ▶ David CAMPARD
- ▶ Françoise SMETS

## Research Field and Subjects

- ▶ Liver regenerative medicine using human adult stem/progenitor cell therapy
- ▶ *In vitro* hepatocytes like cells for pharmacotoxicity (ADME) - testing in the pharma industry, and in research

The lab is owner of the IP from a liver-derived progenitor cell that is being developed for the treatment of inborn errors of liver metabolism, but also as an *in vitro* tool for pharmacology toxicology testing of new medicinal compounds. This development is also made via Promethera Biosciences, a spin off company from the laboratory of pediatric hepatology and cell therapy. Immunologic properties of the cells are also being developed.

## Representative References

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## Patents

- M. NAJIMI, E. SOKAL. Adult derived human liver stem cells. 0544728.5, Europe, **2005**.

## Awards

- ▶ EASL. Best presentation, **2007**.
- ▶ ESPGHAN. Best presentation, **2007**.
- ▶ Société Belge de Pédiatrie. Best presentation, **2009**.

## Funding

- ▶ Walloon region (Waleo, Biowin)
- ▶ Fonds National de la Recherche Scientifique

## Partnership

- Promethera Biosciences, spin-off company of UCL

### **Main Equipment**

- ▶ Cell culture
- ▶ Facs Quanto
- ▶ Luminex
- ▶ Clean rooms

### **Products and Services**

- ▶ Liver cell isolation (GMP and GCP guidelines)
- ▶ Liver cell transplantation

### **KEY WORDS FOR R&D**

Stem cell  
Regenerative medicine  
Cell therapy

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# *In vitro* Models for the Evaluation of the Cellular Pharmacokinetics and Pharmacodynamics of Antibiotics

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## Research Field and Subjects

The recurrent character of several bacterial infections is attributed to the capacity of the microorganism to survive inside eucaryotic cells, where they are protected from the host defense mechanisms and from the action of antibiotics. The treatment of these infections therefore requires the use of antibiotics able to reach the intracellular compartment and to exert their activity intracellularly.

We have developed models of cultured phagocytic (macrophages, PMN) or non phagocytic (keratinocytes, epithelial cells, osteoblasts, endothelial cells) cells, infected or not by intracellular bacteria, for the study of

- ▶ The cellular accumulation of antibiotics
- ▶ The subcellular localization of antibiotics
- ▶ The intracellular activity of antibiotics against bacteria sojourning in different subcellular compartments (*Listeria monocytogenes*, cytosol; *Staphylococcus aureus*, lysosomes; *Legionella pneumophila*, acidic vacuoles)
- ▶ The cooperation between antibiotics and cytokines against intracellular infections.

These studies are helpful in the understanding of the parameters governing the intracellular activity of antibiotics and may serve as first line screening for new molecules for the treatment of intracellular infections

## Representative References

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*and Intracellular Activities (human THP-1 macrophages) of Telavancin vs. Vancomycin against Methicillin-susceptible, Methicillin-resistant, Vancomycin-intermediate and Vancomycin-resistant Staphylococcus aureus.* J. Antimicrob. Chemother 58, 1177-1184, **2006**.

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- ▶ H. A. NGUYEN, O. DENIS, A. VERGISON, A. THEUNIS, P. M. TULKENS, M. STRUELENS, Fr. VAN BAMBEKE. *Intracellular activity of antibiotics in a model of human THP-1 macrophages infected by a Staphylococcus aureus Small Colony Variant isolated from a cystic fibrosis patient.* Antimicrob. Ag. Chemother. 53, 1434-1442 and 1443-1449, **2009**.

## Funding

Public and private companies

## Partnership

Pharmaceutical industry

### **Main Equipment**

- ▶ Cell culture facilities
- ▶ L2 facilities
- ▶ Equipment for assay of drugs by scintillation counting, HPLC, etc.
- ▶ General equipment for biochemical assays

### **Products and Services**

- ▶ Models of cultured phagocytic and non-phagocytic cells, infected or not
- ▶ Measure of cellular concentration and distribution of drugs
- ▶ Measure of intracellular activity of antibiotics

### **KEY WORDS FOR R&D**

Antibiotics  
Cell culture  
Cellular pharmacodynamics  
Cellular pharmacokinetics  
Intracellular infection  
Staphylococcus aureus  
Listeria monocytogenes  
Legionella pneumophila

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# Cell Culture Models for the Study of the Mechanism of Accumulation and Efflux of Drugs In Eucaryotic Cells

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## Research Field and Subjects

The capacity of drugs to enter, distribute and accumulate inside, or cross the cells is an important determinant in their pharmacological activity. In particular, active transporters are recognized today as playing a major role in drug disposition in the organism, by modulating the capacity of drugs to cross biological barriers and to reach their pharmacological target.

We have developed models of cultured cells in which we study :

- ▶ The mechanisms of penetration, subcellular distribution, and accumulation of drugs
- ▶ The implication of active transporters in entry or efflux (in non-polarized cells), or in crossing epithelial barriers (in polarized cells). The transporters involved are characterized by phenotypic, genotypic and proteomic approaches. In parallel, we also develop cell lines resistant to selected drugs by overexpression of efflux transporters and use them to further characterize the role of efflux pumps in the handling of drugs by cells.

These studies may be useful in the early screening of the pharmacokinetic properties of drugs.

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- ▶ H. CHANTEUX, Fr. VAN BAMBEKE, M.-P. MINGEOT-LECLERCQ, P. M. TULKENS. *Accumulation and oriented transport of ampicillin in Caco-2 cells from its pivaloyloxymethyl ester prodrug (PIVA)*. *Antimicrob. Ag. Chemother.* 49, 1279-88, **2005**.
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- ▶ B. MARQUEZ, N. CACERES, M.-P. MINGEOT-LECLERCQ, P. M. TULKENS, Fr. VAN BAMBEKE. *Identification of the efflux transporter of the fluoroquinolone antibiotic ciprofloxacin in murine macrophages : studies with ciprofloxacin-resistant cells*. *Antimicrob. Ag. Chemother.* 53, 2410-2416, **2009**.

## **Funding**

Public and private companies

## **Partnership**

Pharmaceutical industry

## **Main Equipment**

Cell culture facilities

Fluorescence microscopy

Molecular biology (western-blot, proteomics, PCR, real-time PCR ...)

Equipment for assay of drugs by scintillation counting, HPLC ...

General equipment for biochemical assays

## **Products and Services**

Models of cultured cells (including polarized cells)

Determination of drug accumulation levels and subcellular distribution

Identification of efflux pumps involved in drug transport by phenotypic, genetic, and proteomic approaches

## **KEY WORDS FOR R&D**

Cell culture

Cellular pharmacokinetics

Drugs

Subcellular distribution

Efflux pumps

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# Pulmonary Delivery of Biotech Drugs

## SENIOR SCIENTIST :

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## Research Field and Subjects

The large molecular size, hydrophilicity, chemical and enzymatic labilities of peptides and proteins exclude the use of traditional oral dosage forms and injection is currently the most common method for their administration. Our research team aims at optimizing the pulmonary delivery of proteins for a local action in the lungs or for systemic absorption, as alternative to injection. The proteins studied include therapeutic proteins or vaccine antigens.

We optimize the pulmonary administration of proteins by :

- ▶ Designing dry powder aerosols with elevated deep lung deposition.
- ▶ Selecting appropriate excipients.
- ▶ Understanding the biological losses encountered by inhaled macromolecules in the lung. In this regard, we demonstrated in rats that a primary source of elimination of macromolecules following delivery to the lung and prior to absorption into the bloodstream owed to clearance by alveolar macrophages.
- ▶ Targeting the appropriate site of deposition within the respiratory tract. For instance, we showed in mice that the deeper the antigen deposition within the lungs, the stronger the immune response.
- ▶ Modifying chemically the protein.

## Representative References

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## Awards

- R. Vanbever, Named one of the world's top young innovators by Technology Review, Massachusetts Institute of Technology's magazine of innovation, 2003.
- A. Minne, Student Research Award of the International Society for Aerosols in Medicine, 2007.
- A. Minne, Award National Prize of the Belgian Society of Pharmaceutical Sciences, 2009.

## Funding

- ▶ ARC
- ▶ FSR
- ▶ FNRS
- ▶ Walloon Region

### Partnership

- ▶ Kr. HUYGEN, Scientific Institute of Public Health, Uccle
- ▶ GlaxoSmithKline Biologicals
- ▶ UCB Pharma
- ▶ J. VAN SNICK, C. UYTENHOVE, UCL
- ▶ D. CATALDO, Université de Liège
- ▶ F. BUREAU, Université de Liège

### Main Equipment

- ▶ Spray-dryer
- ▶ Sympatec laser diffraction system for particle sizing
- ▶ Pharmacopoeia cascade impactors
- ▶ HPLC with radioactivity detection

### Products and Services

- ▶ Formulation of inhalation dry powders by spray-drying
- ▶ Analysis of aerosols deposition in cascade impactors
- ▶ *In vivo* studies of pulmonary drug absorption and deposition
- ▶ *In vitro* studies of drug transport mechanisms across monolayers of alveolar epithelial cells

### KEY WORDS FOR R&D

Airway hyperractivity  
Antigens  
Bioavailability  
Drug delivery, non-invasive  
Dry powder aerosols  
Immunity  
Lung  
Monoclonal antibody  
Peptides  
Proteins  
Vaccine adjuvant  
Vaccines

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# Mouse Transgene Technology Platform

## SENIOR SCIENTISTS :

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- ▶ Patrick JACQUEMIN
- ▶ Frédéric LEMAIGRE

## Research Field and Subjects

The Université catholique de Louvain has set up a transgene technology platform with the aim to provide scientists of the French Community of Belgium with transgenic mouse models at the lowest possible cost. The facility is housed at the faculty of Medicine in Brussels.

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- ▶ L. HODGE, M. KLASSEN, B.-X. HAN, G. YIU, J. HURRELL, A. HOWELL, G. ROUSSEAU, F. LEMAIGRE, M. TESSIER-LAVIGNE, F. WANG. *Retrograde BMP signaling regulates trigeminal sensory neuron identities and the formation of precise face maps*. Neuron 55, 572-586, **2007**.

## Funding

- ▶ Fonds de la Recherche Scientifique Médicale (FRS-FNRS)
- ▶ Région Wallonne (Projet "DIANE")

## Partnership

Transgene technology platform of the Université Libre de Bruxelles

## Main Equipment

- ▶ Cell culture technology
- ▶ Eppendorf Transferrman NK2
- ▶ Micromanipulator + microscope
- ▶ Mouse breeding facility; mice are bred following FELASA recommendations.

## Products and Services

The platform performs micro-injection of pronuclei with DNA constructs (transgene addition) and injection of blastocysts with recombinant mouse embryonic stem cells (transgenesis by homologous recombination). The platform users are in charge of preparing DNA constructs and have to provide the platform with recombinant ES cells. The platform scientists can provide ES cells, reagents and advice.

**KEY WORDS FOR R&D**

Transgene technology  
Homologous recombination  
Mouse ES cells

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# Confocal and Atomic Force Microscopy for Imaging Biological Specimens

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- ▶ Claude BRAGARD
- ▶ François CHAUMONT
- ▶ Yves DUFRENE
- ▶ Anne LEGREVE

## Research Field and Subjects

Confocal microscopy allows the determination of the cellular and subcellular localization of proteins and biomolecules at high resolution, and to follow their dynamics. This optical imaging technique acquires contrasted images of a single plane of a sample. A laser beam scans the specimen pixel by pixel and line by line and the emitted light is going through a pinhole located in front of the detector to eliminate the light emerging outside that plane. Only the light within the focal plane can reach the detector. The resulting image has a high contrast and resolution. This technique allows the acquisition of images in the X, Y and Z planes of a specimen that can be combined into a 3D representation.

The recent improvement of the equipment and the development of increasing array of fluorescent molecules offer the possibility to detect simultaneously several dyes or fluorophores at high sensitivity and to follow their dynamics in living samples. In addition, combined with appropriate software, this equipment allows obtaining quantitative data on the molecule of interest. The research groups involved have developed facilities for imaging proteins and fluorophores in fixed and living samples including bacteria, fungi, mammal plant, protist, virus and yeast.

Atomic force microscopy (AFM) has recently established as a powerful technique for probing live cells at molecular resolution, complementing optical and electron microscopy techniques. The basic idea behind AFM is to use very small forces acting between a sharp tip and the specimen to generate three-dimensional, high-resolution images of the surface, without depending on an incident beam. In addition, the technique can detect and localize single molecular recognition sites on cell surfaces, such as cell adhesion proteins and membrane sensors. The Dufrene's team has developed a strong expertise in the analysis of single live cells by AFM, providing new insight into the molecular bases of cellular interactions.

## Representative References

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- ▶ Y. Dufrene. Towards nanomicrobiology using atomic force microscopy. *Nature Reviews Microbiology*, 6, 674-680, 2008.
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## Funding

- ▶ Communauté française de Belgique – Actions de Recherches Concertées”
- ▶ FNRS-FRFC
- ▶ Interuniversity Attraction Poles Programme – Belgian Science Policy
- ▶ Région wallonne
- ▶ UCL-FSR

## Partnership

- ▶ H. BATOKO, Chaumont and Dufrêne's teams belong to or are affiliated to the Institute des Sciences de la Vie, Louvain-la-Neuve, Belgium.
- ▶ Cl. BRAGARD and A. LEGREVE's teams belong to the Earth and Life Institute, Louvain-la-Neuve, Belgium.

## Main Equipment

- ▶ Zeiss LSM 710 confocal microscope fitted with 7 laser lines (405, 440, 458, 488, 514, 543 and 633 nm) and a scanning module including 34 spectral detection channels.
- ▶ Zeiss LSM 5 exciter confocal microscope fitted with 4 laser lines (458, 488, 514, 543 nm).
- ▶ Multimode AFM (Veeco Metrology Group, Santa Barbara, CA).
- ▶ Workspaces station equipped with Zen Software as a user interface for image acquisition, analysis and quantification.
- ▶ All present-day molecular biology, microbiology and biochemistry equipments

## Products and Services

- ▶ Live cell imaging
- ▶ Multifluorescence
- ▶ Co-localization
- ▶ 3D and 4D imaging
- ▶ Spectral imaging
- ▶ Fluorescence recovery after photobleaching (FRAP)
- ▶ Fluorescence lost in photobleaching (FLIP)
- ▶ Förster resonance energy transfer (FRET)
- ▶ Nanoscale surface imaging (AFM)
- ▶ Single-molecule manipulation and imaging (AFM)

## KEY WORDS FOR R&D

Bacteria  
Confocal microscope  
Fluorescent dyes  
Fluorophores  
Fungi  
Mammals  
Protein localization  
Protein dynamics  
Single molecules  
Plant  
Protists  
Virus  
Yeast

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# Mass Spectrometry and Quantitative Proteomics Adapted to Membrane Proteins

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- ▶ Hervé DEGAND
- ▶ Pierre MORSOMME

## Research Field and Subjects

In conjunction with the growing number of genome sequences that are available in databases, mass spectrometry (MS) can be used to investigate the proteome, i.e. to identify the most abundant proteins, of a biological sample, from whole tissues to sub-cellular fractions. This can be conveniently performed either by analyzing spots from 2-D gels by MALDI-MS-MS or by LC-MS-MS ('gel-free proteomics'). Moreover, information on changes in protein expression can be obtained by measuring changes in spot intensities in 2-D gels between different samples (2D-DIGE technology) coupled to protein identification and by differential isotopic tagging or labeling of peptides prior to LC-MS-MS.

Mass spectrometry (MS) has flourished over the last years with the advent of 'soft' ionization techniques to measure the molecular masses of proteins and peptides. The principal technique used in our group is matrix-assisted laser-desorption ionization mass spectrometry (MALDI-MS), allowing rapid, high-throughput analysis of digests of protein spots from 2-D gels. This technique allows mass measurement of intact proteins and acquisition of sequence information from peptide fragmentation spectra for protein identification

This research group has developed facilities for systematic protein analysis by 1D or 2D gel electrophoresis, HPLC and mass spectrometry. Quantitative proteomics (DIGE, ITRAQ) as well as gel-free approaches have been used and adapted for **membrane proteins** characterization. Our current projects aim at identifying genes and proteins that are differently expressed according to the cell type and the environmental factors in model and **non-model** species.

## Representative References

- ▶ M. STAWIECKA-MIROTA, W. POKRZYWA, J. MORVAN, T. ZOLADEK, R. HAGUENAUER-TSAPIS, D. URBAN-GRIMAL, P. MORSOMME. *Targeting of Sna3p to the endosomal pathway depends on its interaction with Rsp5p and MVB sorting on its ubiquitylation*. Traffic, 8, 1280-1296, 2007.

- ▶ M. DELANNOY, G. ALVES, D. VERTOMMEN, J. MA, M. BOUTRY, C. NAVARRE. *Identification of peptidases in Nicotiana tabacum leaf intercellular fluid*. Proteomics, 8:2285-98, 2008.
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## Patents

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## Awards

- M. BOUTRY. *Member of the Belgian Academy of Sciences*.

## Funding

- ▶ Région Wallonne
- ▶ FRS-FNRS
- ▶ European Union

## Partnership

This group belongs to the Institut des Sciences de la Vie, Louvain-la-Neuve, Belgium.

## Main Equipment

- ▶ Applied Biosystems 4800 MALDI-TOF-TOF (“matrix-assisted laser desorption ionization – Time of flight”) mass spectrometer for MS and MSMS analysis.
- ▶ 2D-nano and capillary LC (Ultimate3000, Dionex) + Microfraction collector and MALDI spotting system (Probot, Dionex) for off-line 1D- or 2D-LC-MS.
- ▶ Bioinformatics workstation for protein identification and quantification: Mascot, GPS explorer, Protein Pilot v2.0.
- ▶ 2D-gels electrophoresis: IPGPhor + Ettan Dalt 6 (Amersham), Image scanner Labscan + Image Master 2D Platinum + Ettan DIGE Imager + Decyder v7.0 software.
- ▶ All present-day molecular biology and biochemistry equipments.

## Products and Services

- ▶ Measurement of masses of intact proteins for quality control.
- ▶ Gel-purified protein identification by peptide mass fingerprinting and peptide fragmentation.
- ▶ De novo sequencing of peptides for protein identification.
- ▶ Quantification of differential protein expression by 2D-differential gel electrophoresis (DIGE).
- ▶ Quantification of differential protein expression by gel-free proteomics and 2D-LC-MS (iTraq, ICAT...).

## KEY WORDS FOR R&D

Function analysis  
Plant  
Protein analysis  
Proteome  
Yeast  
Membrane proteins  
Maldi  
Gel-free  
Mass spectrometry  
Quantitative proteomics

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# Statistical Methods, Computation and Software

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- ▶ Bernadette GOVAERTS
- ▶ Alain GUILLET
- ▶ Nathalie LEFÈVRE
- ▶ Catherine LEGRAND

## Research Field and Subjects

The SMCS is a UCL university service in “statistical methodology and computing”. Its mission is to help researchers from the university and members of public or private companies in the statistical problems they encounter in their work: design of experiment, statistical data analysis, data management, use of statistical software ...

It also spreads new statistical methodology in collaboration with the Institute of Statistics of the UCL in order to solve statistical questions in a modern and innovative way.

## Representative References

- ▶ C. LEGRAND, L. DUCHATEAU, R. SYLVESTER, P. JANSSEN, J. VAN DER HAGE, C. VAN DE VELDE, P. THERASSE. *Heterogeneity in disease free survival between centers: lessons learned from an EORTC early breast cancer trial*. Clinical Trials, 3, 1-9, **2006**.
- ▶ C. BUGLI, P. LAMBERT. *Functional ANOVA with random effects: an application to event-related potentials modeling for electroencephalograms analysis*. Statistics in Medicine, 25, 3718-3739, **2006**.
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## Funding

- ▶ University budget
- ▶ Research and consulting contracts

## Partnership

The SMCS develops short and long terms partnerships or collaborations with other university groups, software companies, industrial companies and public services: SAS-Belgium, Belgian Red-Cross, IDDI, Sanofi ...

## Main Equipment

- ▶ One “statistical computation” server for time-consuming statistical analyses or data management of big databases.
- ▶ Project of a second server to give access to statistical software that are needed very seldom.

## Products and Services

- ▶ Statistical consulting: design of experiments or surveys, data management, statistical data analysis in various fields of application: industry, research or analytical laboratory, business...
- ▶ Training in statistical software and statistical methods.
- ▶ Development of customized statistical computing applications.

**KEY WORDS FOR R&D**

Statistics  
Design of experiment  
Survey  
Quality control  
Data management  
Training  
Computation

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# Cell and Tissue Imaging Platform

## SENIOR SCIENTIST :

- ▶ Pierre COURTOY
- ▶ Donatienne TYTECA
- ▶ Christophe PIERREUX
- ▶ Patrick VAN DER SMISSEN

## Research Field and Subjects

This research Unit has built since several decades a tradition of excellence and collaboration in advanced methods of cell and tissue imaging. This goal led us to assemble a collection of sophisticated instrumentation and methods. Topics of particular interest for us is the study of endocytosis and membrane trafficking, epithelial differentiation, paracrine interactions and translational research. We are happy to share expertise in scientific projects addressing defined questions which can benefit from electron microscopy (Refs 1 and 2), e.g. analysis of liposomes, scanning electron microscopy (Ref.3); ultrastructural cytochemistry (Ref.1); autoradiography, immunolabelling and in situ hybridization in serial sections (Ref.4); high-throughput confocal microscopy and live-cell imaging (Ref.3); multiphoton microscopy (Ref.5) including vital tissue and organ imaging for several hours without damage (Ref.5) and multiparametric analyses such as 3-D reconstruction, objective co-localization, in situ measurement of ionic environment and proteolytic processing, protein : protein interactions by FRET (Ref.6), etc...

## Representative References

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- ▶ A. CAPLANUSI, K. PARREIRA, W. LIMA, B. MARIEN, P. VAN DER SMISSEN, P. DE DIESBACH, O. DEVUYST, P. COURTOY. *Intraviral multi-photon*

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## Awards

- P. COURTOY. *Chaire Francqui*, FUNDP, **2003-2004**.

## Funding

- ▶ de Duve Institute
- ▶ FRS/FNRS
- ▶ Télévie
- ▶ FRIA
- ▶ ICP
- ▶ UCL
- ▶ «Région wallonne»
- ▶ «Région bruxelloise»
- ▶ National lottery
- ▶ Concerted research actions
- ▶ Interuniversity attraction poles
- ▶ EU Frameworks VI and VII
- ▶ Scientific consulting

## Partnership

- ▶ EU VIth program (EuReGene)
- ▶ EU VIIth program (Eunephron)

## **Main Equipment**

- ▶ Electron microscopy (transmission and scanning)
- ▶ Confocal and multiphoton microscopy
- ▶ Live-cell imaging microscopy
- ▶ Fluorescent dissection stereomicroscopy
- ▶ Cell culture
- ▶ Ultracentrifuges

## **Products and Services**

- ▶ Sophisticated methods for preparation of biological samples
- ▶ High-resolution molecular tracking in fixed and living cells and tissues
- ▶ Advanced image analysis (including deconvolution and morphometry)
- ▶ Ratiometric microscopy and protein interactions in situ
- ▶ Lipid domains
- ▶ Ultrastructural analysis of particles (large protein complexes, viruses, liposomes)

## **KEY WORDS FOR R&D**

Confocal microscopy  
Multiphoton microscopy  
Electron microscopy  
Live-cell imaging  
Explants  
Liposomes

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# Protein Crystallography

## SENIOR SCIENTISTS :

- ▶ Jean-Paul DECLERCQ
- ▶ Aude SMEETS

## Research Field and Subjects

X-ray diffraction analysis by mono-crystals leads to the knowledge of the three-dimensional structure of the molecules. From the diffraction data, it is possible to build a picture of the electron density in the crystal and this picture provides an accurate access to the molecular geometry. Such structural data are often extremely important for understanding chemical and biochemical properties at a molecular level.

In the field of protein crystallography, the results achieved during the last five years concerned the following topics : crystallization under micro-gravity conditions, macromolecular crystallography at atomic resolution, structures of new enzymes.

## Representative References

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- ▶ L. TOUSSAINT, L. BERTRAND, L. HUE, R. CRICHTON, J.-P. DECLERCQ. *High-resolution X-ray structures of human apoferritin H-chain mutants correlated with their activity and metal-binding sites*. J. Mol. Biol. 365, 440-452, **2007**.
- ▶ C. EVRARD, D. MAES, I. ZEGERS, J.-P. DECLERCQ, C. VANHEE, J. MARTIAL, L. WYNS, C. VAN DE WEERDT. *TIM crystals grown by capillary counterdiffusion: statistical evidence of quality improvement in microgravity*. Crystal Growth and Design, Volume 7, number 11, 2161-2166, **2007**.
- ▶ D. MAES, K. DECANNIERE, I. ZEGERS, M. SLEUTEL, R. WILLAERT, C. VAN DE WEERDT, J. MARTIAL, J.-P. DECLERCQ, C. EVRARD, F. OTALORA, J.-M. GARCIA-RUIZ. *Protein crystallization under microgravity conditions: what did we learn on TIM crystallization from the Soyuz missions*. Microgravity Science and Technology XIX-5/6, 90-94, **2007**.
- ▶ A. SMEETS, E. LOUMAYE, A. CLIPPE, J.-F. REES, B. KNOOPS, J.-P. DECLERCQ. *The crystal structure of the C45S mutant of annelid Arenicola marina peroxiredoxin 6 supports its assignment to the mechanistic typical 2-Cys subfamily without any formation of toroid-shaped decamers*. Protein Science, 17, 700-710, **2008**.

- ▶ A. SMEETS, C. MARCHAND, D. LINARD, B. KNOOPS, J.-P. DECLERCQ. *The crystal structures of oxidized forms of human peroxiredoxin 5 with an intramolecular disulfide bond confirm the proposed enzymatic mechanism for atypical 2-Cys peroxiredoxins*. Archives of Biochemistry and biophysics, 477, 98-104, **2008**.
- ▶ A. SMEETS, B. KNOOPS, J.-P. DECLERCQ. *Crystal growth of C45S mutant of Arenicola marina peroxiredoxin 6 in microgravity environment. An unexpected benefice of convection on crystal quality*. J. Jpn. Soc. Microgravity Appl., 25, 603-606, **2008**.
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## Partnership

- ▶ European Space Agency (ESA)
- ▶ Prof. B. KNOOPS, ISV-BANI, UCL
- ▶ Prof. P. SOUMILLION, ISV-BANI, UCL
- ▶ Prof. R. R. CRICHTON, BIOC, UCL
- ▶ Prof. J.-F. COLLET, BCHM, UCL

## Main Equipment

- ▶ Rotating anode generator Rigaku Ultra X18
- ▶ Imaging plate detector MAR345
- ▶ Oxford Cryosystem
- ▶ Dynamic light scattering

## Products and Services

- ▶ Crystallization of proteins
- ▶ Structure determination by X-ray diffraction

**KEY WORDS FOR R&D**

Crystallization  
Structure  
X-ray diffraction

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# Mycothèque de l'Université Catholique de Louvain

## SENIOR SCIENTISTS :

- ▶ Cony DECOCK
- ▶ Stéphane DECLERCK
- ▶ Françoise MUNAUT
- ▶ François VAN HOVE
- ▶ Heide Marie DANIEL

## Research Field and Subjects

Hosted by the mycological laboratory, the «Mycothèque de l'Université catholique de Louvain» (MUCL), belongs to the Belgian Coordinated Collection of Microorganisms consortium (BCCM) supported by the Prime Minister's Services, Scientific, Technical and Cultural affairs (SSTC). BCCM is a partner of the European network of Culture Collection (ECCO) and of the World Network of Culture Collections (WFCC). BCCM/MUCL is also recognised as an «International Depositary Authority» (IDA) under the Budapest Treaty for patented strains and safe deposits.

Belonging to the BCCM consortium, MUCL is an active partner in major ongoing bio informatics projects in the field of microbiology. The BCCM databases are continuously updated and optimised and can be consulted on Internet. MUCL holds more than 26,000 alive strains. The SSTC supports the collection maintenance, strain preservation, updating of the database, preparation of the catalogue, execution of the services for industry, university, public and private organisms. The valorisation of MUCL is enforced by the development of research projects of agro-industrial interests, especially in food and environmental microbiology, which contribute to innovative tools in biotechnology. These projects undertaken in the mycological laboratory develop an expertise in yeasts, filamentous fungi and endomycorrhiza using morphological, physiological, biochemical, biophysical and molecular methods.

## Representative References

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- ▶ S. DECLERCK, H. DUPRÉ DE BOULOIS, C. BIVORT, B. DELVAUX. *Extraradical mycelium of the mycorrhizal fungus Glomus lamellosum can uptake, accumulate and translocate radiocesium under root-organ culture conditions*. Environmental Microbiology 5 : 510-516, **2003**.
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- ▶ H. KAUSERUD, K. SHALCHIAN-TABRIZI, C. DECOCK. *Multi-locus sequencing reveals multiple geographically structured lineages of Coniophora arida and C. olivacea (Boletales) in North America*. Mycologia 99 : 705-713, **2007**.
- ▶ C. DECOCK, S. HERRERA FIGUEROA, G. ROBLEDO, G. CASTILLO. *Fomitiporia punctata (Basidiomycota, Hymenochaetales) and its presumed taxonomic synonyms in America : taxonomy and phylogeny of some species from tropical / subtropical area*. Mycologia 99(5) : 733-752 (1.574), **2007**.
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## Partnership

- ▶ Chinese Academy of Science, Beijing, China
- ▶ Institut d'Ecologie et Systématique (IES), La Havane, Cuba
- ▶ Institut de recherche en Ecologie Tropical, Gabon
- ▶ Madagascar (IMRA, Institut Malgache de Recherches Appliquées)

## Main Equipment

- ▶ Automatic Sequencer
- ▶ Capillary electrophoresis (CE)
- ▶ Freezers (-130°, -80°)
- ▶ Gas chromatography
- ▶ Lyophilisator
- ▶ Microplates Reader
- ▶ Pulse-Field Gel Electrophoresis (PFGE)
- ▶ Scanning Electron Microscopes (SEM)
- ▶ Spectrophotometer
- ▶ Thermal Gradient Cycler

## Products and Services

- ▶ Identification and numeration of fungi that decay paint, paper, plastics, electronics, wood and wood products.
- ▶ Bioassays of fungicides and fungistatic compounds.
- ▶ Monitoring of fungal fermenting or contaminating fungi in food, animal feed and industrial environments and advice for improvement of production conditions and stock preservation.
- ▶ Rapid identification of yeasts through the BCCM/ALLEV 2.0 automated identification system.
- ▶ Classical and molecular characterisation of fungal strains by a range of techniques including DNA-fingerprinting and DNA sequencing.
- ▶ Identification and quantification of myco-toxins by capillary electrophoresis.
- ▶ Training in techniques of systematic and applied mycology at technician and postgraduate level.

## KEY WORDS FOR R&D

Cryopreservation  
Culture collection  
Endomycorrhiza  
Filamentous fungi  
Lignolytic enzymes  
Mycotoxins  
Phylogenetic systematics  
Primary metabolites  
Secondary metabolites  
Taxonomy  
Yeast

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# Medicine and Science In Laboratory Animals

## SENIOR SCIENTIST :

▶ Jean-Paul DEHOUX

## Research Field and Subjects

Medicine and science of laboratory animals :

- ▶ Immunology
- ▶ Surgery
- ▶ Anesthesiology
- ▶ Animal behavior

## Representative References

- ▶ J.-P. DEHOUX, P. GIANELLO. *The importance of large animal models in transplantation*. *Frontiers in Bioscience* 12, 4864-4880, **2007**.
- ▶ E. MARBAIX, S. DEFRERE, K. HO MINH DUC, J.-C. LOUSSE, J. SQUIFFLET, J. DONNEZ, J.-P. DEHOUX. *“Non-gestational malignant placental site trophoblastic tumour of the ovary in a 4-year-old rhesus monkey”*. *Vet. Pathology*, 45(3) : 375-8, **2008**.
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- ▶ C. BOUDRY, J.-P. DEHOUX, J. WAVREILLE, D. PORTETELLE, A. THEWIS, A. BULDGEN. *Effect of a low bovine colostrum supplementation on growth performance, faecal Escherichia coli population and systemic immune response of piglets at weaning*. *Animal*, 2 : 730-737, **2008**.
- ▶ C. BOUDRY, A. BULDGEN, D. PORTETELLE, A. COLLARD, P. GIANELLO, A. THEWIS, J.-P. DEHOUX. *Effects of oral supplementation of bovine colostrum on weaned piglets immunity*. *Res. Vet. Sci.* 83(1) : 91-101, **2008**.
- ▶ J.-P. DEHOUX, P. GIANELLO. *Accommodation in xenotransplantation*. *Transplant immunology* 21, 106-110, **2009**.

## Awards

*Euroliver Fund Award*, for the work : Development of rat monoclonal antibodies to prevent hyperacute and acute rejection of vascularized xenograft in a pig-to-baboon model. **2002**.

## Funding

Various (DGTRE, UCL)

## Partnership

- ▶ More than 35 units from UCL, Faculty of medicine
- ▶ Ulg, MD, Biological development unit
- ▶ Ulg, agronomical faculty of Gembloux, animal husbandry unit
- ▶ Institute of Primatology Research, Kenya

## Main Equipment

Animal house facilities : rearing and housing, surgery (small and large animals), anesthesiology equipment.

## Products and Services

Medicine and science of laboratory animals (small and large animals) : research and formation support, housing.

**KEY WORDS FOR R&D**

Laboratory animals  
Animal husbandry  
Animal house facilities  
Experimental surgery  
Experimental anesthesiology  
Immunology  
Rodents  
Primates  
Swine  
Rabbits

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# WINFAB – Technological Platform – Micro- and Nano-Fabrication

## SENIOR SCIENTISTS :

- ▶ Romain DELAMARE
- ▶ Mathieu VANDEN BULCKE
- ▶ Denis FLANDRE
- ▶ Jean-Pierre RASKIN

## Research Field and Subjects

WINFAB (Wallonia Infrastructure Nano Fabrication) is the technological platform of UCL active in micro and nano-fabrication. It is an inter-institute platform from the Sciences and Technology Sector. Main research activities include SOI (Silicon-on-Insulator)-CMOS integrated circuit processing, Micro(Nano) Electromechanical Systems (MEMS/NEMS), nanoelectronics, organic electronics, photovoltaics and biosensors.

Besides processing, activities are also carried out on materials development and characterization.

The infrastructure avails of about 1000 m<sup>2</sup> of clean environment (ISO 5), distributed over two levels and 13 zones.

Overall process line is based on 3 inches silicon wafers, but some equipments can accommodate smaller and larger wafer sizes, as well as glass slides. The panel of available equipments allows the users to experiment standard and non standard micro-nano-fabrication process steps, applied on various substrates, but also more applications oriented processing aiming at modifying or adding properties to selected materials.

## Funding

Funding from the Walloon Region and EU, through several programs or projects :

- ▶ NANOTIC – Programme d'excellence de la Région wallonne, 2005-2010
- ▶ FEDER, programme compétitivité, portefeuille MINATIS
- ▶ SKYWIN and MECATECH, Pôles de compétitivité
- ▶ NANOSIL, European Network of excellence
- ▶ TRIADE, FP7 Aero project ...

Funding from the Belgian National Fund for Scientific Research (FNRS)

## Partnership

▶ As technological platform, WINFAB is open to partnership with any research center of UCL, but also opens its infrastructure to external users from university or industry. Current active internal partners include groups from the Information and Communication Technologies, Electronics and Applied Mathematics institute (ICTEAM), the Institute of Mechanics, Materials and Civil Engineering (IMMC), the Mathematics and Physics Institute (IMAP), and the Institute of Condensed Matter and Nanosciences (IMCN).

▶ External users from Mons and Namur Universities also benefit from WINFAB infrastructure.

▶ Technical training for teachers, workers, students, and unemployed via Technifutur ([www.technifutur.be/formation\\_entreprise.asp](http://www.technifutur.be/formation_entreprise.asp)).

## Main Equipments

- ▶ Cleanroom Environment
- ▶ Characterization (microscopy, ellipsometry, profilometry...)
- ▶ Wet Benches (substrate cleaning, wet etch...)
- ▶ UV Lithography (Spin coating, Exposure, Development)
- ▶ E-beam nanolithography
- ▶ Nano-imprint lithography
- ▶ Furnaces (Oxidation, LP CVD Nitride and PolySi, Anneal...)
- ▶ Plasma (RIE, DRIE, PE CVD Nitride and Oxide...)
- ▶ Metallization (sputtering, evaporation, reactive sputtering...)
- ▶ Ion Implanter
- ▶ Glove boxes
- ▶ MEMS release (CPD)
- ▶ Pre- / Post processing (wafer grinding, CMP...)
- ▶ Packaging (Dicing, wire bonding...)

## **Products and Services**

- ▶ Clean work environment
- ▶ Available process steps (cleaning, etching, lithography, characterization...)
- ▶ MEMS, Sensors and SOI CMOS Processing
- ▶ Education and training

## **KEY WORDS FOR R&D**

Cleanroom  
Microelectronics  
Nanoelectronics  
CMOS  
SOI  
MEMS  
Sensors  
Organic electronics  
Photovoltaics

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# Bone Bank

## SENIOR SCIENTISTS :

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

## Research Field and Subjects

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

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

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

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

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

## Representative References

- ▶ O. CORNU, X. LIBOUTON, B. NAETS, B. GODTS, J. VAN TOMME, C. DELLOYE, X. BANSE. *Freeze-dried irradiated bone brittleness improves compactness in an impaction bone grafting model*. Acta Orthop Scand, 75, 309-314, **2004**.
- ▶ C. DELLOYE AND G. BANNISTER. *Impaction Bone Grafting in Revision Arthroplasty*. 456pp, illustrated, Index. Dekker Inc, New-York. ISBN: 0-8247-4799-2, **2004**.
- ▶ P. DOCQUIER, C. DELLOYE. *Treatment of aneurysmal bone cysts by introduction of demineralized bone and autogenous bone marrow*. J Bone Joint Surg, 87A, 2253-2258, **2005**.
- ▶ C. DELLOYE, X. BANSE, B. BRICHARD, P.L. DOCQUIER, O. CORNU. *Pelvic reconstruction with a structural pelvic allograft after resection of a malignant bone tumor*. J Bone Joint Surg (Am) 89A: 579-587, **2007**.
- ▶ C. DELLOYE, O. CORNU, V. DRUEZ, O. BARBIER. *Bone allografts: what they can offer and they cannot*. J Bone Joint Surg (Br), 89B: 574-579, **2007**.
- ▶ L. PAUL, P.L. DOCQUIER, O. CARTIAUX, O. CORNU, C. DELLOYE, X. BANSE. *Inaccuracy in selection of massive bone allograft using template comparison method*. Cell Tissue Bank, 9: 83-90, **2008**.
- ▶ O. CARTIAUX, P.L. DOCQUIER, B.G. PAUL, L. FRANCO, O. CORNU, C. DELLOYE, B. RAUCENT, B. DEHEZ, X. BANSE *Surgical inaccuracy of tumor resection and reconstruction within the pelvis: an experimental study*. Acta Orthop. 79:695-702, **2008**.

## Products and Services

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

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

### Main Equipment

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

### Awards

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

### Funding

- ▶ TELEVIE-FNRS
- ▶ Salus Sanguinis foundation.

### Partnership

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

### Staff

Total : 20

### KEY WORDS FOR R&D

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

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# Detection, Identification and Typing of Bacterial Human Pathogens by Molecular Biology Methods

## SENIOR SCIENTISTS :

- ▶ Michel DELMÉE
- ▶ Gerald GLUPCZYNSKI
- ▶ Jean-Luc VAERMAN

## Research Field and Subjects

Our laboratory is devoted to the diagnosis of bacterial human infections, surveillance of the epidemiology and detection of antimicrobial resistance.

Since 1994, multiple R & D programs have been carried out for implementing molecular biology approaches in these fields.

Epidemiological investigation of most hospital outbreaks are now performed by using molecular methods like pulsed field gel electrophoresis (PFGE) of restriction fragments of chromosomal DNA or randomly amplified polymorphic DNA (RAPD).

Ribotyping and toxinotyping have been developed for typing of *Clostridium difficile*. The laboratory is now the Belgian reference center for *C. difficile* and, on an annual basis, more than a thousand strains from about 100 laboratories in Belgium are typed for epidemiological purpose.

Detection of antimicrobial resistance mechanisms is obtained by PCR amplification of known resistance genes. This allows the rapid identification of major hospital pathogens like glycopeptide-resistant-*enterococci*, or methicillin-resistant *Staphylococcus aureus* (MRSA).

Macrolide resistance in *Helicobacter pylori* is linked to single point mutations in the 23S RNA which are now diagnosed by PCR amplification followed by a set of enzyme restrictions giving specific patterns for each known resistance. New mutations are studied by 23S RNA sequencing.

When classical phenotypic methods fail, identification of bacteria can be performed by complete sequencing of the 16S rDNA.

## Representative References

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- ▶ P. van DIJCK, M. DELMÉE, H. EZZEDINE, A. DEPLANO, M.-J. STRUELENS. *Evaluation of pulsed-field gel electrophoresis and rep-PCR for*

*the epidemiological analysis of Ochrobactrum anthropi strains*. European Journal of Clinical Microbiology and Infectious Diseases; 14: 1099-1102, **1995**.

- ▶ P. van DIJCK, V. AVESANI, M. DELMÉE. *Genotyping of Outbreak-Related and Sporadic Isolates of Clostridium difficile Belonging to Serogroup C*. Journal of Clinical Microbiology; 34:3049-3055, **1996**.

- ▶ J.-S. BRAZIER, M.-E. MULLIGAN, M. DELMÉE, S. TABAQCHALI, G. L. ONEILL, D. N. GERDING, J. SILVA, Y. TANG, P. GUMERLOCK, R. KWOK, M. WILKS, T. V. RILEY. *Preliminary findings of the international typing study on Clostridium difficile*. Clinical Infectious Diseases, 25 Suppl. 2:S199-S201, **1997**.

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- ▶ T. KARJALAINEN, N. SAUMIER, M.-C. BARC, M. DELMÉE, A. COLLIGNON. *Clostridium difficile genotyping based on slpA variable region in S-Layer gene sequence : an alternative to serotyping*. Journal of Clinical Microbiology, 40: 2452-8, **2002**.

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- ▶ P. D. GHISLAIN, S. WOESTYN, D. TENNSTEDT, J.-M. LACHAPPELLE, G. BIGAIGNON, M. DELMÉE. *Borrelia afzelii evidenced by polymerase chain reaction in a biopsy of nipple lymphocytoma*. British Journal of Dermatology, 148 (2):377-379, **2003**.

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- ▶ S. WOESTYN, N. OLIVÉ, G. BIGAIGNON, V. AVESANI, M. DELMÉE. *Study of genotypes and virB4 secretion gene of Bartonella henselae strains from patients with clinically defined cat scratch disease*. Journal of Clinical Microbiology, 42:1420-1427, **2004**.

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*sanguinis* sp. Nov. Journal of Clinical Microbiology, 42 (6):2829-2832, **2004**.

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► B. G. STARE, M. DELMÉE, M. RUPNIK. *Variant forms of the binary toxin CDT locus and tcdC gene in Clostridium difficile strains*. Journal of Medical Microbiology 56:329-35, **2007**.

### Awards

M. DELMÉE. *Georges Brohée Award*, **1986-1987**.

### Funding

- SPF Santé publique
- European Center for Disease Prevention and Control

### Partnership

- Université de Liège, faculté vétérinaire
- European Study Group *Clostridium difficile*
- Hôpital Saint-Antoine, Paris

### Main Equipment

- Pulsed field gel electrophoresis
- ICycler
- RAPD
- RT – PCR
- DNA Sequencer

### Products and Services

- Outbreak investigations for hospital infection control teams
- Bacterial strain collection
- Identification of bacterial isolates

### KEY WORDS FOR R&D

Bacterial pathogens  
Genotyping  
Molecular biology

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# Platform for Biochemical Profiling In Small Animals

## SENIOR SCIENTIST :

- ▶ Olivier DEVUYST
- ▶ Sara TERRYIN
- ▶ Yvette CNOPS
- ▶ Sébastien DRUART

## Research Field and Subjects

Conventional and genetically-manipulated murine models represent a tool that is increasingly used in biomedical research. The biochemical investigation of these models is hampered by the small plasma volume (< 1ml). This limitation is even more critical in case of iterative procedures *in vivo*, or repeated measurements during a single experiment. Most of the existing systems for biochemical profiling in animal models are limited in parameters, require large volume samples and expensive reagents (dry chemistry), and do not have adequate calibration. To overcome these limitations, our unit has acquired a platform of biochemical profiling dedicated to small animals. Like in clinical analyses performed in man, the platform is based on liquid chemistry technologies, which allow to obtain a large array of reliable biochemical analyses in minimal volumes (usually < 10-15 microl), with a high throughput (> 200 analyses per h) and an automated calibration system. The platform includes a biochemical analyser (Beckman Synchron CX5), an acid-base monitoring system (Radiometer ABL 77), a micro-titrator (Mettler – Toledo) and a Fiske osmometer, allowing to analyze multiple biochemical and toxicological parameters in a large variety of biological fluids (plasma, urine, CSF,...) in small volumes.

We also provide expert advice on the sampling techniques of rodent models.

## Representative References

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- ▶ J. NI, J.-M. VERBAVATZ, A. RIPPE, I. BOISDÉ, P. MOULIN, B. RIPPE, A.-S. VERKMAN, O. DEVUYST. *Aquaporin-1 plays an essential role in*

*water permeability and ultrafiltration during peritoneal dialysis*. Kidney Int. 69 : 1518-1525, **2006**.

- ▶ F. JOURET, A. BERNARD, C. HERMANS, G. DOM, S. TERRYIN, T. LEAL, P. LEBECQUE, J.-J. CASSIMAN, B. J. SCHOLTE, H. DE JONGE, P. COURTOY, O. DEVUYST. *Cystic fibrosis is associated with a defect in apical receptor-mediated endocytosis in mouse and human kidney*. J. Am. Soc. Nephrol. 18 : 707-718, **2007**.
- ▶ H. BELGE, P. GAILLY, B. SCHWALLER, J. LOFFING, H. DEBAIX, E. RIVEIRA-MUNOZ, R. BEAUWENS, J.-P. DEVOGELAER, J. HOENDEROP, R. BINDELS, O. DEVUYST. *Renal expression of parvalbumin is critical for NaCl handling and response to diuretics*. Proc. Natl. Acad. Sci., USA, 104 : 14849-14854, **2007**.
- ▶ S. BIVER, S. BELGE, S. BOURGEOIS, P. VAN VOOREN, M. NOWIK, S. SCOHY, P. HOULLIER, J. SZPIRER, C. SZPIRER, C. A. WAGNER, O. DEVUYST, A.-M. MARINI. *Impaired ammonium excretion, renal tubular acidosis and decreased male fertility in mice lacking the Rhcg receptor factor*. Nature 456 : 339-343, **2008**.

## Awards

- ▶ *Biennial Prize*, Belgian Society of Nephrology, **2000**.
- ▶ *Lauréat du Concours Ordinaire*, Royal Academy of Medicine of Belgium, **2000**.
- ▶ *Galien Prize*, Belgian Pharmaceutical Industry, **2003**.
- ▶ *Matthys-Bove Award*, UCL Medical School, **2004**.
- ▶ *Biennial Prize of the International Spa Foundation*, **2007**.
- ▶ *Award of the King Baudouin Foundation*, **2005 & 2008**.

## Funding

This platform is funded by grants from the :

FNRS

FRSM

The CFB (Diane Network)

The European networks (EuReGene and EUNEFON)

## Partnership

- ▶ EU VIth program (EuReGene)
- ▶ EU VIIth program (Genecure, EUNEFRON)
- ▶ Industry : Baxter, Danone

## Main Equipment

- ▶ Biochemical analyzer Synchron CX5 Beckman
- ▶ Blood gases analyzer Radiometer ABL77
- ▶ Fiske osmometer
- ▶ Micro-titrator Mettler Toledo T50M
- ▶ Temperature-controlled cryo-storage (-80°C)

## Products and Services

- ▶ Dedicated methods for sampling biological fluids in mouse & rats
- ▶ Ultrasmall volume analyses for most biological parameters in all types of biological fluids
- ▶ High throughput, robust quality control
- ▶ Development of ELISA
- ▶ Biobanking

## KEY WORDS FOR R&D

Biochemical analyzer  
Osmometer  
Micro-titration  
Blood gases  
Biological fluids  
Biomarkers  
Sampling animal models  
Biobanking  
ELISA development

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# Nanotechnology of Biosurfaces

## SENIOR SCIENTISTS :

- ▶ Yves DUFRÈNE
- ▶ Christine DUPONT-GILLAIN

## Research Field and Subjects

The research activity deals with nanobiotechnology, i.e. the design and investigation of biological systems on the nanometer scale. This includes the control of interactions between living cells and their environment, the creation of nanobiomimetic structures by self-assembly and by scanning probe devices, the manipulation of single biomolecules and the development of high-sensitivity biosensors.

Recent achievements concern :

- 1 The elaboration and, or characterization of materials surfaces (polymers, metals, adsorbed layers) with properties (topography, chemical composition) controlled on the  $\mu\text{m}$ -nm scale.
- 2 The supramolecular organization of adsorbed proteins and its dependence on substratum properties and processing factors.
- 3 The supramolecular organization of supported lipid membranes.
- 4 The development of methods and the modification of AFM probes to investigate the surface properties (relief; electrostatic, macromolecular, specific interactions; mechanical properties) of microbial cells on the nanometer scale.

The following topics are currently addressed :

- 1 Structure and interactions of biomolecules at solid surfaces : adsorbed proteins, self-assembled monolayers, grafted layers, single molecule experiments.
- 2 Nanoscale properties of lipid membranes: molecular organization of mixed monolayers and bilayers, physical properties and molecular interaction forces using functionalized AFM tips, drug-membrane interactions, biomedical applications.
- 3 Surface properties of living cells at the nanometer level: visualization of surface ultrastructure, real time analysis of dynamic processes, mapping of physical properties, single molecule force spectroscopy, design and use of chemically and biologically functionalized AFM tips.

## Representative References

- ▶ F. DENIS, A. PALLANDRE, B. NYSTEN, A.-M. JONAS, Chr. DUPONT-GILLAIN. *Alignment and assembly of adsorbed collagen molecules induced by anisotropic chemical nanopatterns*. *Small* 1, 984-991, **2005**.
- ▶ E. GURDAK, Chr. DUPONT-GILLAIN, J. BOOTH, C. J. ROBERTS, P. G. ROUXHET. *Resolution of the vertical and horizontal heterogeneity of adsorbed collagen layers by combination of QCM-D and AFM*. *Langmuir* 21, 10684-10692, **2005**.
- ▶ P. HINTERDORFER, Y. DUFRÈNE. *Detection and localization of single molecular recognition events using atomic force microscopy*. *Nature methods* 3, 347-355, **2006**.
- ▶ V. DUPRES, C. VERBELEN, Y. DUFRÈNE. *Probing molecular recognition sites on biosurfaces using AFM*. *Biomaterials* 28, 2393-2402, **2007**.
- ▶ E. DAGUE, Y. GILBERT, C. VERBELEN, G. ANDRE, D. ALSTEENS, Y. DUFRÈNE. *Towards a nanoscale view of fungal surfaces*. *Yeast* 24, 229-237, **2007**.
- ▶ M.-P. MINGEOT-LECLERCQ, M. DELEU, R. BRASSEUR, Y. DUFRÈNE. *Atomic force microscopy of supported lipid bilayers*. *Nat. Protocols* 3, 1654-1659, **2008**.
- ▶ G. FRANCIUS, S. LEBEER, D. ALSTEENS, L. WILDING, H. J. GRUBER, P. HOLS, S. DE KEERSMAECKER, J. VANDERLEYDEN, Y. DUFRÈNE. *Detection, localization, and conformational analysis of single polysaccharide molecules on live bacteria*. *ACSNano* 2, 1921-1929, **2008**.
- ▶ Y. DUFRÈNE. *Towards nanomicrobiology using atomic force microscopy*. *Nature Reviews Microbiology*, 6, 674-680, **2008**.
- ▶ J. LANDOULSI, C. J. ROY, Chr. DUPONT-GILLAIN, S. DEMOUSTIER-CHAMPAGNE. *Synthesis of collagen nanotubes with highly regular dimensions through membrane-templated layer-by-layer assembly*. *Biomacromolecules* 10, 1021-1024, **2009**.
- ▶ D. J. MÜLLER, M. KRIEG, D. ALSTEENS, Y. DUFRÈNE. *New frontiers in atomic force microscopy: analyzing interactions from single-molecules to cells*. *Curr. Opin. Biotechnol.* 20, 4-13, **2009**.

## Funding

- ▶ FNRS
- ▶ Région Wallonne
- ▶ Action de Recherche Concertée
- ▶ Interuniversity pole of attraction program
- ▶ Industrial funding

## Partnership

- ▶ Institut de la matière condensée et des nanosciences (IMCN, UCL)
- ▶ Institut des sciences de la vie (ISV, UCL)
- ▶ Wallonia network for nanotechnologies (NANOWAL)

## Main Equipment

- ▶ Atomic force microscope (AFM).
- ▶ X-ray photoelectron spectrometer (XPS).
- ▶ Quartz crystal microbalance (QCM-D)
- ▶ Streaming potential measurements.
- ▶ Wetting measurements.
- ▶ Cell adhesion devices.

## Products and Services

- ▶ Nanofabrication of biointerfaces
- ▶ Nanocharacterization of biointerfaces
- ▶ Chemical composition of surfaces
- ▶ Wetting properties of surfaces
- ▶ Electrical properties of surfaces

## KEY WORDS FOR R&D

Bioadhesion  
Biocompatibility  
Biomaterials  
Biomedicine  
Biomembranes  
Biosensors  
Biosurfaces  
Drugs  
Lipids, membranes  
Microbiology  
Nanobiomimetic, devices  
Nanobioscience  
Nanobiotechnology  
Nanocharacterization  
Proteins, adsorption  
Self-assembly  
Surfaces, cells

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# Data Analysis for High-Throughput Genomic Technologies

## SENIOR SCIENTIST :

► Pierre DUPONT

## Research Field and Subjects

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

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

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

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

We also develop dedicated machine learning techniques to make use of prior biological knowledge in the form of candidate genetic biomarkers. Those candidate markers guide the final gene signature identification. In addition to knowledge about candidate markers, our techniques can also extract information from other available data produced in different but related contexts to enhance the quality of the identified signatures. For example, knowledge can be automatically acquired on publicly available data sets and transferred on data of interest, generally leading to a higher robustness and predictive power of the model.

Such techniques offer an independent validation methodology to confront predicted markers with actual expression data.

## Representative References

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- J. LOUAHED, S. GAULIS, T. HELLEPUTTE, P. DUPONT, O. GRUSELLE, A. SPATZ, W. KRUIT, B. DRENO, F. LEHMANN, V. BRICHARD. *Clinical response to the MAGE-3 immunotherapeutic in metastatic melanoma patients is associated with a specific gene profile present prior to treatment*. In : 33th European Society for Medical Oncology (ESMO) Congress, Stockholm, Sweden, **2008**.
- T. HELLEPUTTE, P. DUPONT. *Partially Supervised Feature Selection with Regularized Linear Models*. 26th International Conference on Machine Learning (ICML), Montreal, Canada, **2009**.
- T. HELLEPUTTE, P. DUPONT. *Feature Selection by Transfer Learning with Linear Regularized Models*. European Conference on Machine Learning (ECML), Bled, Slovenia, **2009**.

## Patents

UK and US Patents Pending

## Funding

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

## Partnership

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

## Main Equipment

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

## Products and Services

- ▶ Genomic Data Analysis
- ▶ Gene Profiling/Biomarker Identification
- ▶ Pro/Diagnosis Models Building and Evaluation
- ▶ Experimental Protocol Assessment
- ▶ Independent Validation of Biological or Clinical Markers

## KEY WORDS FOR R&D

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

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# Identification of Serological and Seric Biomarkers From Proteomic Analysis of Cancer or Cardiovascular Patient Blood

## SENIOR SCIENTISTS :

- ▶ Olivier FERON
- ▶ Florence DEFRESNE

## Research Field and Subjects

Biomarkers may fulfil different goals : to detect diseases at early stages, to classify diseases so that the patient can receive the most appropriate therapy and to monitor diseases progression, regression and recurrence. In addition, biomarkers can be used to assess response to therapy.

The ease with which the blood can be sampled makes it a logical choice for biomarker applications. Among the blood components that may provide an indication of cancer or cardiovascular disease status or response to treatments, we focus our attention on serum auto-antibodies (directed against tumor-associated or dysfunctional endothelium antigens, respectively), peptides associated with plasma macro-proteins and circulating progenitor cells. We use a variety of techniques including 2D-DIGE and SERPA (serological proteome analysis) to identify and validate biomarkers from plasma and serum of cancer or cardiovascular patients (or mouse models recapitulating such diseases). Correlations with circulating or micro-dialysed end-products of metabolism (including nitrites and lactate) are also evaluated.

## Representative References

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- ▶ F. FRÉRART, P. SONVEAUX, G. RATH, A. SMOOS, A. MEQOR, N. CHARLIER, B. F. JORDAN, J. SALIEZ, A. NOËL, C. DESSY, B. GALLEZ, O. FERON. *The acidic tumor microenvironment promotes the reconversion of nitrite into nitric oxide : towards a new and safe radiosensitizing strategy*. *Clin. Cancer Res.*; 14(9) : 2768-74, **2008**.
- ▶ P. SONVEAUX, F. VÉGRAN, T. SCHROEDER, M.-C. WÉRGIN, J. VERRAX, Z. N. RABBANI, C.-J. DE SAEDELEER, K. M. KENNEDY, C. DIEPART, B. F. JORDAN, M.-J. KELLEY, B. GALLEZ, M.-L. WAHL; M. W. DEWHIRST, O. FERON (co-last author). *Targeting lactate-fueled respiration selectively kills hypoxic tumor cells in mice*. *J. Clin. Invest.*; 118(12) : 3930-42, **2008**.
- ▶ F. DEFRESNE, C. BOUZIN, C. GUILBAUD, M. DIEU, E. DELAIVE, C. MICHIELS, M. RAES, O. FERON. *Identification by multiplex serological proteome analysis of GRP78 auto-antibody as biomarker of tumor progression and response to treatment*. *Proteomics* **2009**.

## Awards

- ▶ *Prize Belgian Soc. Pharm. Sci.*, **1997**.
- ▶ *Prize Galien*, **1999**.
- ▶ *Prize Eugène De Somer*, **2008**.

## Funding

- ▶ FNRS
- ▶ FRSM
- ▶ Télévie
- ▶ Fondations Maisin & Saint-Luc
- ▶ Fondation belge contre le cancer
- ▶ Communauté française : ARC
- ▶ Private companies

## Partnership

- ▶ C. CHANTRAIN, J.-P. MACHIELS, V. GRÉGOIRE, Y. HORSMANS, Cliniques Saint-Luc
- ▶ M. DE RIDDER, S. SERMEUS, AZ VUB
- ▶ M. RAES, FUNDP, Namur
- ▶ J.-L. BALLIGAND, C. DESSY, UCL

## Main Equipment

- ▶ Ettan IpgPhor III (GE) [1st dim-electroph]
- ▶ Ettan DALT6 (GE) [2nd dim-electroph]
- ▶ TE77 transfer units (GE)
- ▶ Ettan DIGE Imager (GE)
- ▶ Decyder analysis software (GE)
- ▶ SE600 large gels electrophoresis unit (GE)
- ▶ SG100 gradient maker (GE)
- ▶ Ettan Spot Picker (GE)
- ▶ Home-made ELISA kit development
- ▶ Microplate reader & injectors (Victor 5, PE)
- ▶ Microscale liquid chromatography
- ▶ Access to Mass Spectrometry for protein identification

► The above proteomic platform is completed with various pre-clinical imaging technologies (*in vivo* bioluminescence detection, laser Doppler, intravital microscopy set-up) and high-standard molecular biology/biochemistry and cell biology equipments.

### **Products and Services**

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

### **KEY WORDS FOR R&D**

Proteomic  
2D-DIGE  
Auto-antibody  
Tumor-associated antigens  
Cancer  
Ischemic diseases  
Hypertension  
Endothelial dysfunction  
Biomarker  
Prognostic  
Predictive  
Treatment monitoring

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# Electrical Microsensors for DNA Analyses

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- ▶ Jean-Luc GALA
- ▶ Benoît MACQ
- ▶ Sorin MELINTE
- ▶ Jean-Pierre RASKIN

## Research Field and Subjects

The analysis of DNA by electronics means appears of major interest in view of the miniaturisation of bioanalytic systems such as labs-on-chip, for low-cost diagnosis or point-of-care applications. This still presents numerous scientific and technical challenges, especially with regards to problems of compatibility between integrated electronics circuits and biochemical species in aqueous and ionic solutions, as well as to the extreme levels of sensitivity and specificity to be achieved.

Our research targets the electrical detection of DNA hybridization by on-chip microsensors (with ultimate limit of detection down to the atto-mole level) and on the measurement of DNA/RNA concentration in assay tubes by UV light and specific photodiodes (with better sensitivity than existing lab equipment). In addition to the fabrication of the sensors, our group carries out their biological experimentation and the statistical data processing of the electrical results.

## Representative References

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## Patents

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- ▶ R. PAMPIN (FR), D. FLANDRE (BE), L. MORENO-HAGELSIEB (MX), B. FOULTIER (FR), J. REMACLE (BE). *Insulated Substrate Impedance Transducers*. EP06018835.6.

## Awards

- D. FLANDRE. « *DNA electrical detection experiments with alumina passivated CMOS sensors* ». "Invited lectures" at Hasselt University, IMEC Research center, Singapore.

## Funding

Région wallonne

## Partnership

NANOTIC – Programme d'excellence de la Région wallonne, 2005-2010.

## Main Equipment

- ▶ The largest research-oriented clean room facilities (1000 m<sup>2</sup>) in Wallonie with the all key technologies required for micro/nano-systems and micro/nano-electronics fabrication.
- ▶ Characterization techniques : optical and electrical in a large range of frequencies and temperature.
- ▶ Technological platform for molecular genetic analyses

## Products and Services

Fabrication and characterization of electrical and optical bio-micro-nano-sensors :

- ▶ Variable capacitive structures
- ▶ Microwave detectors
- ▶ Inorganic nanowires
- ▶ Microfluidic channels
- ▶ Silicon-on-Insulator photodiodes
  
- ▶ Optimization of pre-analytical procedures
- ▶ R&D
- ▶ Validation in the clinical setting and valorization
  
- ▶ Statistical data set analysis
  
- ▶ Bioinformatic analysis

## KEY WORDS FOR R&D

DNA hybridization  
DNA/RNA concentration  
Micro-sensors  
UV photodiode

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# Center for Applied Molecular Technologies

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## Research Field and Subjects

The Center for Applied Molecular Technologies (CTMA) is a mixed military-academic technological plate-form.

The main goal of CTMA is to develop and validate dual-use molecular and genetic tools and methods, for diagnostic and prognostic purposes.

The laboratory is particularly active in the fields of cancer genomic, pharmacogenetic and infectious diseases. This led to fruitful industrial partnerships for the set up and development of protocols, methods, and innovative diagnostic kits. For example, CTMA is the first laboratory in Belgium to have set up the new detection method (PCA3 Progensis™) for identifying the presence of prostate cancer cell in the urine of patients with unconfirmed suspicion of prostate cancer.

CTMA is especially in charge with the issues related to Biological Threats and develops its expertise through a synergistic partnership between the university and the Defense Laboratories Department (BE Armed Forces). Accordingly, this plate-form hosts at the same location researchers appointed by the Belgian Ministry of Defense, the UCL and its associated academic hospital.

Detection methods are validated and directly applied both on human samples collected for presumed infected patients presenting in hospitals with a difficult diagnosis (failure of conventional microbiologic methods, need for a very rapid diagnosis) or from environmental samples collected from operational theaters where a potential risk has been identified or is feared. Cancer patients and pharmacogenetic patents take also profit from the innovative technologies.

Aside of the current genetic methods, new emerging genetic and molecular technologies, such as nanotechnologies, are indeed designed and validated to produce innovative operational tools enabling us to better detect known and unknown threatening infectious agents as well as cancer or inflammatory diseases. In that respect, a mobile fieldable laboratory for molecular genetic identification of life-threatening agents has been successfully deployed in Kananga RDC, in May 2009.

From 2002, CTMA has constituted several tissue banks (DNA, RNA, plasma, serum).

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▶ N. TAJEDDINE, I. MILLARD, Ph. GAILLY, J.-L. GALA. *Real-time RT-PCR quantification of PRAME gene expression for monitoring minimal residual disease in acute myeloblastic leukaemia.* Clinical Chemistry and Laboratory Medicine, 44 : 548-55, **2006**.

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▶ S. VAN DER VORST, A.-F. DEKAIRELLE, I. IRENGE, A. ROBERT, M. HAMOIR, J.-L. GALA. *Automated cell disruption is a reliable and powerful method to isolate RNA from fresh snap frozen normal or malignant oral mucosa samples.* Clinical Chemistry and Laboratory Medicine, in press, **2009**.

## Patents

International patents jointly hold by the Belgian Defense and the University

## Awards

- ▶ *9e Edition of the Baudouin Elleboudt Awards*, attributed to Th. HELLEPUTTE for his work on to the "Analysis of Microarray signals using a multiple scanning approach" (Promotor : J.-L. GALA and P. DUPONT), **2006**.
- ▶ *Lecturers Award in Laryngology and Head & Neck Pathology 2008* of the Société Royale Belge d'ORL et de Chirurgie Cervico-Faciale, attributed to S. VANDERVORST (Promotor : J.-L. GALA), **2008**.

## Funding

- ▶ Belgian Defense
- ▶ Walloon Region
- ▶ FNRS
- ▶ European projects
- ▶ Televie
- ▶ Fondation Saint-Luc, Salus sanguinis
- ▶ Private companies

## Partnership

- ▶ International military networks (e.g. European Defence Agency/Database of B-agents, NATO/JCP/SIBCRA) and bilateral military partnerships
- ▶ Co-chairman of the Integrated Mission Group Security (IMGS) network
- ▶ International academic networks (COSTB28/Emergarray, PASR/Bio3R)
- ▶ KUL, Gasthuisberg (human genetics and detection of prostate cancer)
- ▶ CTMA leads the workpackage "Biomedical Application" in the NANOTIC consortium within the framework of the Marshall plan

## Main Equipment

- ▶ Equipment for nucleic acids purification and quantification (Nano-Drop ND-1000 spectrophotometry system, Agilent 2100 Bioanalyzer, Fastprep-24 instrument, BioRobot EZ1, MiniMAG DNA extractor)
- ▶ PCR equipment: (Fast system 9800, PCR System 2700 and 2720, Gene Amp PCR system 2400)
- ▶ Real-time amplification equipment (Taqman Fast Real Time 7900HT 96 well, Light Cycler 480 Real time PCR – 96 and 384 wells)
- ▶ DNA Engine Tetrad 2 Thermal cycler
- ▶ Material for nucleic sequence analysis (Sequencer 3130, Pyrosequencer PSQ96 system GenProbe DTS 400 system)

- ▶ Microarrays equipment (Scanner Microarrays Genepix AXON 4200 AL, Scanner Array WoRx eAuto, Affimetrix platform, GeneChip Fluidics Station 450, GeneChip Hybridization oven 640, PamStation@4, Piezorray, Non-contact Microarraying System, Hybridization Station 4-Bay,
- ▶ TECAN Freedom EVO 100 DTS (Direct Tube Sampling) System
- ▶ Microscopes (Axiovert 40 CFL, Axioplan + camera, Eclipse 80i with caméra DS-2M and logiciel Imaging software NISE, Stéréomicroscope MZ7.5)
- ▶ Biosafety lab (BSL2)

## Products and Services

- ▶ Production, analysis and interpretation of microarrays
- ▶ Identification of genetic pathologies
- ▶ Development of new molecular assay / innovative technologies for pathogen detection in the clinical setting
- ▶ Research projects have led to the creation of several spin off activities (Eppendorf Array Technology active in the development of low density microarrays; EONIX, involved in tracability of biological and clinical data and geolocalisation; and MYCOS-ERV, dealing with environmental quantitative and qualitative monitoring of pathogenic fungi).

## KEY WORDS FOR R&D

Genetics & Genomics  
Pharmacogenetic  
Cancer diseases  
Infectious diseases  
Microarrays  
ProteinChips  
Detection, Identification & monitoring (DIM)  
Pathogen  
Diagnostic  
Prognostic

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# Monoclonal or Polyclonal Antibodies of Rat, Mouse and Human Origin

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- ▶ Yannick NIZET

## Research Field and Subjects

The research field is devoted to the development of new techniques of production of specific antibodies. In the past, efforts have been focused on the rat and mouse models in order to obtain monoclonal antibodies against immunoglobulins from various species and human leucocyte antigens.

New efforts are directed on :

- ▶ New systems of immunization of rodents and human cells in vivo and in vitro (depending on the species).
- ▶ Immunization by use of transfected B lymphocyte cell lines expressing polypeptides proteins at their surfaces.
- ▶ New methods of characterization of monoclonal antibodies
- ▶ Production of monoclonal antibodies by in vitro systems.
- ▶ Production of monoclonal antibodies directed against molecules implicated in neurodegeneratives disorders
- ▶ Development of immunodetection methods to detect bacteria.

## Representative References

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- ▶ L. MORENO-HAGELSIEB, Y. NIZET, X. TANG, J.-P. RASKIN, D. FLANDRE, L. FRANCIS. *CMOS Compatible Anodic Al<sub>2</sub>O<sub>3</sub> Based Sensors for Bacteria Detection*. Procedia Chemistry. In press, **2009**.

## Patents

H. BAZIN, Y. NIZET. *Method for preparing and selecting antibody*. EP 1373320, WO 02/081523.

## Partnership

DIANE – programme d'excellence de la region wallonne 2008-2013  
Unisensor  
Eurogentec

## Main Equipment

Laminar flows  
Chromatography  
Flow cytometry

## Products and Services

This methodology could be applied for the development of new hybridoma cell lines secreting requested monoclonal antibodies. Fields of applications: cytotoxicity by targeting specific cells or modulation of immune response in transplantation, cancer and auto-immunity; diagnosis or therapy of infectious diseases.

**KEY WORDS FOR R&D**

Antibodies  
Antigen presenting cell  
B lymphocyte  
Chimeric antibody  
Human  
Humanized antibody  
Immunization  
Immunoglobulins  
Monoclonal antibody  
Mouse  
Rat  
T helper  
Human, rat, mouse immune cells

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# High-Resolution Mass Spectrometry for the Identification of “Small” Molecules (Drugs, Metabolites, Functional Foods, Lipids...)

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## Research Field and Subjects

High resolution mass spectrometry is becoming a tool of major importance for the identification of “small” molecules in numerous fields like identification of metabolites or active compounds in plants used in traditional medicine, toxicology, study of functional foods or pharmacological properties of new compounds, ...

Due to this high importance, a research facility has been created around a LTQ-Orbitrap-XL, a high resolution and high accuracy mass spectrometer which is coupled to a high performance liquid chromatography (UHPLC) system.

This mass spectrometer has a resolution up to 100 000 and a mass accuracy < 3ppm. Furthermore, due the presence of the linear LTQ trap in front of the Orbitrap, it is possible to perform MS<sub>n</sub> experiments with determination of the exact mass of all the observed fragments. This is an unvaluable tool for the identification of unknown compounds or metabolites. Higher energy fragmentation experiment is also possible thanks to the presence of an extra collision cell.

The (U)HPLC coupling allows to perform all these experiments in complex mixture without preliminary purification and to perform quantitative analysis.

## Representative references

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## Funding

- ▶ FNRS
- ▶ FSR
- ▶ Brussels region
- ▶ International cooperation

## Partnership

► This research equipment is the core of a technological platform devoted to the chemical analysis of small molecules called MASSMET.

MASSMET belongs to the *Louvain Drug Research Institute* and to the *Institut des Sciences de la Vie*.

► The equipment was financed by the FRS-FNRS and the Université catholique de Louvain (FSR and Secteur des Sciences de la Santé).

## Main Equipment

► HPLC/UPLC: DAD, UV, SM and high resolution MSn (LTQ-Orbitrap-XL)

► GC-MS (low resolution)

► HPLC-MS (ion trap low resolution)

Several HPLC-DAD systems

## Products and Services

► Low and High resolution mass spectrometry

► Determination of elementary composition of "small" molecules

► Identification of "small" molecules

► Quantitative and qualitative LC-MS analysis

► GC-MS analysis

► Metabolites identification

## KEY WORDS FOR R&D

Mass spectrometry

Quantitative analysis

Structure determination

Exact mass

Elementary composition

Identification

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# Proteomic and Mass Spectrometry Platform

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- ▶ Carine MICHIELS
- ▶ Thierry ARNOULD
- ▶ Olivier TOUSSAINT
- ▶ Marc DIEU

## Research Field and Subjects

The proteomic and mass spectrometry platform is located in the URBC and is open for users from inside and outside the FUNDP. The platform of the URBC has a 2D-DIGE facility including various equipments for running 1D and 2D gels (IPGPhor, Ettan Dalt, 2D Opimizer for gradient gels ...) and analyzing the gels in fluorescence using the Typhoon confocal scanner and the DeCyder 2D Software (GE-Healthcare). A Spotpicker allows the picking of selected spots for mass spectrometry (MS) analysis. Proteins are cleaved (generally using trypsin) in a white room and then analyzed by MS. The MS platform combines a MALDI-TOF mass spectrometer (Waters) and two tandem mass spectrometers : an ion-trap with ETD (Bruker) and in autumn 2009, an ultra high resolution Q-TOF (maXis, Bruker) coupled to a Dionex Ultimate 3000 2D-LC system. A central bioinformatics platform for storage and processing of MS data completes our proteomic platform (MASCOT, Matrix Science server integrated in Protein-Scape, Bruker). The MALDI-TOF allows the protein identification with high throughput by peptide mass fingerprints, while the tandem MS/MS identifies proteins by sequencing derived peptides.

## Representative References

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## Funding

- ▶ FRFC & FUNDP (for the mass spectrometers Typhoon and Spotpicker)
- ▶ Walloon Region
- ▶ & FUNDP for the white room

## Partnership

- ▶ URBM, URBO, URPhYM, URBV, Dpt of Chemistry (FUNDP)
- ▶ Laboratory of Molecular Parasitology and Service de Chimie Pharmaceutique Organique (ULB)
- ▶ CRA, Gembloux
- ▶ Cellular and Molecular Pharmacology and Unité de pharmacocinétique, métabolisme, nutrition et toxicologie (UCL)
- ▶ CRP, Luxembourg

## Main Equipment

- ▶ Typhoon confocal scanner (GE-Healthcare) and DeCyder 2D Software
- ▶ MALDI MX (Waters)
- ▶ HCT ultra with ETD II (Bruker) coupled to a Dionex Ultimate 3000 nanoLC system
- ▶ maXis (Bruker) coupled to a Dionex Ultimate 3000 2D-LC system
- ▶ ProteinScape (Bruker), MASCOT (Matrix Science)

## Products and Services

This platform has been used successfully to run 2D-DIGE gels and identify proteins from gels, but also in the context of gel-independent proteomics.

## KEY WORDS FOR R&D

2D-DIGE  
Fluorescence Confocal Scanner  
Mass spectrometry  
MALDI-TOF  
Tandem MS/MS  
Expression profiling  
Protein identification  
Peptide mass fingerprinting  
Peptide sequencing  
Gel-independent proteomics

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# Proteomics and Protein Analysis by Mass Spectrometry

## SENIOR SCIENTISTS :

- ▶ Mark RIDER
- ▶ Didier VERTOMMEN

## Research Field and Subjects

Control of cellular functions by reversible protein phosphorylation with particular emphasis on the insulin and AMP-activated protein kinase (AMPK) cascades. Quantitative protein expression, protein and peptide identification. Identification of sites of post-translational modification and covalent modification by chemical reagents of proteins by electrospray ionization mass spectrometry including nanospray and 2D-LC-MS with peptide fragmentation by CID or ETD. Identification and quantification of potential biomarkers in cerebro-spinal fluid and serum of patients with neurodegenerative diseases.

## Representative References

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- ▶ D. VERTOMMEN, J. VAN ROY, J.-P. SZIKORA, M. RIDER, P. MICHELS, F. OPPERDOES. *Differential expression of glycosomal and mitochondrial proteins in the two major life-cycle stages of Trypanosoma brucei*. Mol. Biochem. Parasitol. 158, 189-201, **2008**.

## Awards

M. RIDER, V. DUPRIEZ. *Prix Robert et Maggy de Hovre* (Immunology, joint award), **1997**.

## Funding

- ▶ De Duve Institute
- ▶ Interuniversity Attraction Poles Program
- ▶ Belgian Science Policy (P6/28)
- ▶ The Directorate General Higher Education and Scientific Research
- ▶ French Community of Belgium
- ▶ The Fund for Medical Scientific Research (Belgium) and
- ▶ The EXGENESIS Integrated Project (LSHM-CT-2004-005272) from the European Commission

## Partnership

- ▶ IUAP P6/28 network 'Signal Integration Mechanisms in Health and Disease' and the EU FP6 'EXGENESIS' consortium on the beneficial effects of exercise to counteract the metabolic syndrome
- ▶ Partners with the laboratory of P. MORSOMME (Unité de Biochimie Physiologique, ISV-UCL, B-1348 Louvain-la-Neuve) in running the platform for proteomics and protein analysis by mass spectrometry (MASSPROT)
- ▶ Member of the proteomics platform for the consortium 'DIANE'

## Main Equipment

- ▶ ThermoScientific LTQ XL electrospray ionization linear ion trap mass spectrometer fitted with CID and ETD fragmentation with possibilities of performing nano-electrospray ionization analysis or peptide analysis by coupling to a Dionex capillary HPLC system for on-line 1D- or 2D-LC-MS
- ▶ Bioinformatics workstation for protein identification and label-free quantification :  
Proteome Discoverer  
BioWorks  
Sieve  
Biomass  
Sequest

## Products and Services

- ▶ Measurement of masses of intact proteins for quality control
- ▶ Gel-purified protein identification by peptide mass fingerprinting and peptide fragmentation
- ▶ De novo sequencing of peptides for protein identification
- ▶ Quantification of differential protein expression by gel-free proteomics and 2D-LC-MS
- ▶ Identification of sites of covalent modification by collision-induced dissociation (CID)
- ▶ Fragmentation of peptides or by electron transfer dissociation of peptides (ETD)

## Technological Platforms

Platform for proteomics and protein analysis by mass spectrometry (MASSPROT) along with the team of M. BOUTRY, H. DEGAND, P. MORSOMME.

## KEY WORDS FOR R&D

Proteomics  
Electrospray (ESI)  
Mass spectrometry (MS)  
Nanospray, ESI-MS  
2D-LC-MS  
Phosphorylation  
Post-translational modification  
Covalent modification

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[http://www.deduveinstitute.be/control\\_of\\_cell\\_function\\_by\\_protein\\_phosphorylation.php](http://www.deduveinstitute.be/control_of_cell_function_by_protein_phosphorylation.php)

# Cell Culture Systems as *in vitro* Model of the Intestinal Barrier

## SENIOR SCIENTISTS :

- ▶ Yves-Jacques SCHNEIDER
- ▶ Yvan LARONDELLE
- ▶ Véronique PREAT

## Research Field and Subjects

The research is focused on developing and using cell culture systems as *in vitro* models of the intestinal barrier. Cell culture systems are indeed increasingly used to investigate the transport as well as the interactions of various substances, nutrients, drugs, xenobiotics, with the cell physiology.

In particular, in the case of the intestinal barrier, cultured Caco-2 cells allow to set up *in vitro* models of the human intestinal barrier that are widely used in pharmaco-toxicology. Such systems have been validated and serve now to evaluate the absorption of substances across the intestinal barrier and to predict their bioavailability as well as possible toxic effects, drug interactions... More recently, the experimental conditions have been adapted to also set up a model of the M cells, characteristic of the FAE (follicle-associated epithelium).

The systems based on Caco-2 cells are currently used :

- ▶ To perform mechanistic studies, at the cellular and molecular level, of the passage of nutrients, drugs or xenobiotics across the human intestinal barrier
- ▶ To determine the modulation of the expression of the genes and of the activities of proteins related to biotransformation, efflux and apoptosis by drugs and xenobiotics in human intestinal cells
- ▶ To target nanoparticules to human M cells, for a more selective delivery of therapeutic proteins or antigens

## Representative References

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- ▶ A. des RIEUX, V. FIEVEZ, M. MOMTAZ, C. DETREMBLEUR, M. ALONSO-SANDE, J. VAN GELDER, A. CAUVIN, Y.-J. SCHNEIDER, V. PRÉAT. *Helodermin-loaded nanoparticles: characterization and transport across an in vitro model of the follicle-associated epithelium*. J. Control Release. 118(3):294-302, **2007**.
- ▶ F. MATHOT, A. des RIEUX, A. ARIËN, Y.-J. SCHNEIDER, M. BREWSTER, V. PRÉAT. *Transport mechanisms of mmePEG750P(CL-co-TMC) polymeric micelles across the intestinal barrier*. J. Control Release. 124(3):134-43, **2007**.
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## Funding

- ▶ Walloon regional government (DGO 6)
- ▶ Federal Belgian Science Policy (BELSPO)
- ▶ Fondation Louvain
- ▶ Fonds de la Recherche Scientifique (FNRS)
- ▶ Industrial partnership

## Partnership

- ▶ Y.-J. SCHNEIDER, Y. LARONDELLE. Partner of Institut des Sciences de la Vie (ISV), Louvain-la Neuve, Belgium
- ▶ V. PREAT. Partner of the Louvain Drug research Institute

## Main Equipment

- ▶ Animal cell technology
- ▶ Equipment for cell biochemistry
- ▶ Access to mass spectrometry and laser scanning confocal microscopy

## Products and Services

- ▶ Cell culture system as *in vitro* model of the human intestinal barrier in normal and inflammatory situations
- ▶ *In vitro* testing of intestinal permeability and biotransformation of substances
- ▶ *In vitro* evaluation of drug interaction and intestinal gene regulation by xenobiotics

## KEY WORDS FOR R&D

Cell culture systems  
Drug delivery  
Food safety  
Intestinal barrier  
*In vitro* toxicology

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# Pediatric Clinical Investigation Center

## SENIOR SCIENTISTS :

- ▶ Étienne SOKAL
- ▶ Françoise SMETS
- ▶ Xavier STÉPHENNE
- ▶ Catherine WANTY
- ▶ Annick BOURGOIS
- ▶ Anne Catherine DUBOIS
- ▶ Véronique LEGROS

## Research field and subjects

The Pediatric Clinical Investigation Center (PCIC) is part of the Paediatric Research Institute at the Cliniques Universitaires Saint-Luc, Université Catholique de Louvain. The Centre is aiming to provide an efficient platform for high quality clinical investigations in accordance to ICH/GCP rules. The importance of the PCIC is highlighted by the European regulation which aims to promote a secure use of drugs in the paediatric population (new European regulation on Medicinal Products for Paediatric Use adopted in 2007). The PCIC is not only conducting phase I, II & III paediatric drug trials, but also informative and epidemiological studies to create new information on diseases history. The PCIC also benefits from a fully equipped bench research laboratory and organises basic research targeting clinical problems, i.e. translational research.

The Centre brings together the strengths of all paediatric specialties : cardiopediatry, endocrinology, gastroenterology, neonatology, onco-hematology, neuropediatrics, emergency unit, onco-hematology, pediatric intensive care, anesthesia, genetics, pediatric radiology, pathology, pharmacists, toxicology and drug monitoring.

The platform works with external collaborators in order to facilitate patient recruitment for clinical studies, and to give them access by this way to innovative treatments even before their availability on the market.

Our personnel, including physicians, research nurses, pharmacists and technicians is highly qualified and has a long-lasting experience in trial organisation, protocol, data management and administrative follow-up.

The PCIC can recruit and take care of patients for clinical trials of every phase for drug trial. Depending of the design of the study, the patients are followed during hospitalisation, in the day-care centre, in the specialised outpatient clinics or within the network of associated paediatricians.

The PCIC has already conducted many randomised control trials and is familiar with electronic CRF, collaboration with CRO, investigator meetings, audits ...

## Funding

Self supported

## Partnership

- ▶ Close collaboration with the ethical committee of the teaching hospital.
- ▶ Belgian Pediatric Drug Network (BPDN)

## Main equipment

- ▶ The PCIC has its own clinical and research fully equipped facility: Centrifuges, monitored refrigerators, -20° and -80°C freezers.
- ▶ The blood samples can be received, processed and stored 7 days/7 and 24 h/24. Express shipments to the reference laboratories are well known procedures.
- ▶ The Center has access to all facilities at the Cliniques St Luc.

## Product and services

- ▶ Pediatric pharmacologic studies
- ▶ Pharmacokinetics
- ▶ Phase I & II studies

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# Biobank for Vascular Anomalies

## SENIOR SCIENTISTS :

- ▶ Miikka VIKKULA
- ▶ Laurence BOON
- ▶ Mustapha AMYERE
- ▶ Pascal BROUILLARD
- ▶ Nisha LIMAYE

## Research Field and Subjects

Vascular anomalies are localized defects of lymph/vascular development that usually affect a limited number of vessels in a restricted area of the body. They are subdivided into vascular tumors and vascular malformations. The most frequent vascular tumors are hemangiomas, whereas malformations can affect any vessel type, and thus are classified as capillary, venous, lymphatic and arteriovenous malformations. They can also be combined. Although most malformations are sporadic and present with a single lesion, inheritance is encountered, in which case multiple lesions are observed. The last decade has seen unraveling of several causative genes (most of which by our group) and beginning of elucidation of the pathophysiological pathways involved in the inherited forms (Brouillard and Vikkula 2007; Limaye et al., 2009). Moreover, precise clinical diagnosis is of great importance, as lesions may mimic each other for an unexperienced clinician, and wrong categorization of samples would render molecular studies inefficient. Conversely, identification of the causative genes help to define and refine the criteria for precise (differential) diagnosis (Boon et al 2004; Revencu 2008). For this, it is crucial to obtain a large number of samples from patients affected by these lesions.

In collaboration with numerous Vascular Anomalies centers worldwide, and especially with the Center for Vascular Malformations, Cliniques universitaires St-Luc, Brussels, Belgium, we are continuously collecting blood and tissue samples as a source for DNA, RNA, cDNA and proteins, and derived cell lines, from patients and their family members with vascular anomalies. We collect clinical data and pedigree information using specialized clinico-genetic questionnaires. The pedigree data and all other sample-related and genetic data are coded and collected in a proprietary database. Analyses of this data and the families can be used e.g. for evaluation of inheritance patterns, penetrance and expressivity of vascular anomalies. We also collect venous blood samples, and for some index patients, we establish Epstein-Barr virus transformed lymphoblast cell lines, as a source for RNA. When a patient is operated, vascular anomaly tissue is snap-frozen in liquid nitrogen, or embedded in O.C.T. with or without prior formalin fixation. We also derive endothelial and non-endothelial cell lines from pieces of freshly resected vascular anomalies. So far, we have collected information on about 1500 families, and 750 tissues for 115 of which cell lines have also been derived.

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## Patents

M. VIKKULA. *VMGLOM gene and its mutations causing disorders with a vascular component*. USA Patent n° 2003/0176649.

M. VIKKULA. *Medical use of ras antagonists for the treatment of capillary malformation*. International application n° PCT/EP03/02913.

## Awards

- ▶ *Eugène de Sommer Scientific Award*. UCL, **2006**.
- ▶ *Pfizer Scientific Award*. Belgium, **2006**.
- ▶ *Pharmacia Scientific Award*. Belgium, **2002**.

## Funding

- ▶ FRSM 3.4604.06
- ▶ NIH P01 AR0485564
- ▶ ARC 07/12-005
- ▶ PAI 6/05
- ▶ EU LSHG-CT-2004-503573

## Partnership

- ▶ The Platform for transgenesis, UCL
- ▶ The Center for Vascular Malformations, Cliniques Universitaires St. Luc
- ▶ The Vascular Anomalies Center, Children's Hospital, Boston, USA
- ▶ The Vascular Anomalies Network of clinicians and centers worldwide

## Main Equipment

- ▶ Capillary Sequencing Units
- ▶ Affymetrix whole genome array platform
- ▶ Semi-automated analysis systems for human genome linkage analysis
- ▶ High resolution melting (HRM) PCR system for real-time quantitative PCR and SNP analysis

## Products and Services

Tissue, cell line and DNA/RNA/protein biobank

### KEY WORDS FOR R&D

Vascular anomaly  
Vascular malformation  
Glomuvenous malformation  
Venous malformation  
Cutaneomucosal venous malformation  
Lymphedema  
Capillary malformation-arteriovenous malformation  
Hemangioma  
Endothelial cell  
Smooth muscle cell

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# Microarray Platform of UCL

## SENIOR SCIENTISTS :

- ▶ Miikka VIKKULA
- ▶ Mustapha AMYERE
- ▶ Jean-Christophe RENAULD

## Research Field and Subjects

The microarray platform (Affymetrix) is located in Human Molecular Genetics laboratory (de Duve Institute 5th floor) and is open for users from de Duve Institute, Uclouvain, and the Belgian French community.

The platform of UCLouvain is able to use all available Affymetrix Chips for Whole-Transcript Gene Expression & Alternative Splicing, 3' Gene Expression, SNP Genotyping & CNV Analysis, Genome-Wide Association, and Copy Number Analysis. Data generated by the system can be analysed using specific software for SNP copy number analysis, LOH, autozygosity mapping, uniparental disomy, linkage analysis and expression profiling. The integrated genomics solution combines copy number data from the SNP Array 6.0 and expression information from the Human Exon 1.0 ST Array to deliver the most comprehensive view of the genome. This approach may accelerate the discovery and validation of candidate genes associated with a disease. Using this strategy, we have successfully identified a causative gene and several new disease-linked regions for various diseases.

## Representative References

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G. VERBEKE, T. D'HOOGHE, Y. MOREAU, J. VERMEESCH. *Chromosome instability is common in human cleavage-stage embryos*. Nat. Med., 15(5), 577-583, **2009**.

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## Awards

- ▶ *Pharmacia Scientific Award*, Belgium, **2002**.
- ▶ *Pfizer Scientific Award*, Belgium, **2006**.
- ▶ *Eugène de Sommer Scientific Award*, UCL, **2006**.

## Funding

- ▶ FRSM 3.4613.07
- ▶ FRSM 3.4560.08

## Partnership

The Center for Vascular Malformations, Cliniques Universitaires St. Luc; Vascular Anomalies Center, Children's Hospital, Boston, USA; Vascular Anomalies Network of clinicians and centers worldwide.

## Main Equipment

- ▶ GeneChip® Scanner 3000 7G System with GeneChip® AutoLoader System
- ▶ GeneChip® Fluidics Station 450
- ▶ Two GeneChip® Hybridization Oven 640
- ▶ Three workstations for data mining and data analysis with all package software needed
- ▶ GeneChip® Scanner 3000 Targeted
- ▶ Genotyping System

### **Products and Services**

This platform has been used successfully to complete more than 2000 hybridizations by various groups in de Duve Institute, UCL Louvain-la-Neuve, Cliniques universitaires St-Luc, Belgian French Community groups (FUNDP), as well as investigators in KULeuven, Harvard Medical School and University of Regensburg, Germany.

### **KEY WORDS FOR R&D**

Genechip  
Microarray  
Copy Number Analysis (CNA)  
Loss-of-Heterozygosity (LOH)  
Uniparental Disomy (UPD)  
Pathway analysis  
Expression profiling  
miRNA  
Linkage analysis  
Statistical analysis

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# Drug Analysis and Pharmacokinetic/Dynamic Relationship

## SENIOR SCIENTISTS :

- ▶ Pierre WALLEMACQ
- ▶ Vincent HAUFROID

## Research Field and Subjects

The research is focused on the different approaches accessible both to optimize drug efficacy and to minimize toxicities. Individualization of therapies is the major objective for potent but potentially toxic drugs such as immunosuppressive, antiretroviral, antibiotics, antifungal, cytotoxic agents....

Development of sensitive and specific analytical methods (e.g. LC-MS/MS) is one of the critical approaches. Applied pharmacokinetics (including population pharmacokinetics) and pharmacogenetics are others. The study of the genetic polymorphism of the proteins involved in the transport (P-gp) or metabolism (CYP3A) of the drugs would allow clinicians to anticipate any further dosage adjustments. Similar approaches are used in the field of toxicology (analytical, toxicokinetic, toxicogenetic), involving drugs or drugs of abuse in a medical or medico-legal context.

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- ▶ P. WALLEMACQ, R. VANBINST, S. ASTA, D. COOPER. *High-throughput liquid chromatography-tandem mass spectrometric analysis of sirolimus in whole blood*. Clin. Chem. Lab. Med., 41, 921-5, **2003**.
- ▶ V. HAUFROID, M. MOURAD, V. VAN KERCKHOVE, J. WAWRZYNIAK, D. LISON, J.-P. SQUIFFLET, P. WALLEMACQ. *The effect of CYP3A5 and MDR1 polymorphisms on cyclosporine and tacrolimus dose requirements and trough blood levels in stable renal transplant patients*. Pharmacogenetics, 14, 147-54, **2004**.
- ▶ L. ELENS, A. CAPRON, M. MOURAD, J. LERUT, P. WALLEMACQ, V. HAUFROID. *1199G>A and 2677G>T/A polymorphisms of ABCB1/ independently affect tacrolimus concentration in hepatic tissue after liver transplantation*. Pharmacogenetics and Genomics. 17, 873-83, **2007**.

- ▶ L. ELENS, S. VERITER, V. DIFAZIO, R. VANBINST, D. BOESMANS, P. WALLEMACQ, V. HAUFROID. *Quantification of 8 HIV-Protease Inhibitors and 2 Nonnucleoside Reverse Transcriptase Inhibitors by Ultra-Performance Liquid Chromatography with Diode Array Detection*. Clin. Chem., 55, 170-4, **2009**.
- ▶ P. WALLEMACQ, V. ARMSTRONG, M. BRUNET, V. HAUFROID, D. HOLT, A. JOHNSTON, D. KUYPERS, Y. LE MEUR, P. MARQUET, M. OELLERICH, E. THERVET, B. TOENSHOFF, N. UNDRÉ, L. WEBER, I. WESTLEY, M. MOURAD. *Opportunities to optimize tacrolimus therapy in solid organ transplantation: report of the European Consensus Conference*. Ther. Drug Monit., 31 : 139-52, **2009**.
- ▶ A. CAPRON, F. MUSUAMBA, D. LATINNE, M. MOURAD, J. LERUT, V. HAUFROID, P. WALLEMACQ. *Validation of a Liquid-chromatography Mass Spectrometric Assay for Tacrolimus in Peripheral Blood Mononuclear Cells*. Ther. Drug Monit., 31 : 178-86, **2009**.

## Awards

- ▶ V. HAUFROID. ECETOC (European Center for Ecotoxicology and Toxicology of Chemicals). *Scientific award*, **2003**.
- ▶ V. HAUFROID. *Prix Bauchau*, **2007**.

## Funding

- ▶ FNRS + FRSM funding
- ▶ FRIA
- ▶ Bauchau funds
- ▶ Industrial partnerships

## Partnership

- ▶ Number of Pharmaceutical Companies
- ▶ P. WALLEMACQ is Chairman of the Immunosuppressive Drug Committee of the IATDMCT (Intern Assoc Therap Drug Monit and Clin Toxicol).

### **Main Equipment**

- ▶ HPLC-UV
- ▶ GC-FID, NPD, ECD
- ▶ GC-MS (ion-trap and quadrupole)
- ▶ LC-MS/MS (triple quadrupole)

### **Products and Services**

- ▶ Xenobiotics quantitative analysis by immunoassays or different chromatographic methods
- ▶ Drugs analysis in different biological matrices (blood, urine, hair, human tissues...)
- ▶ Normal PCR and RFLP
- ▶ Real time PCR
- ▶ CaCo-2 cells culture and MDR1 knock-out mice

### **KEY WORDS FOR R&D**

Analytical toxicology  
Clinical pharmacokinetics  
Drug analysis  
Pharmacogenetics  
Therapeutic drug monitoring

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# Bioethics

## SENIOR SCIENTIST :

- ▶ Mylène BOTBOL-BAUM

## Research Field and Subjects

Bioethics  
Public Health Ethics (responsible of HELESI)  
Gender Ethics  
Philosophy of Medicine

## Representative References

- ▶ M. BOTBOL-BAUM (co-author). "Promoting the integration of Continuous Care in the hospital". *The Palliative Care mobile support team as a means to convey the philosophy of Continuous and Integrated Care. Analysing medical practice and research in new integration strategies*. "The Fifth Framework Programme 1998-2002; Quality of Life and living resources", EU publications, **2004**.
- ▶ M. BOTBOL-BAUM. "Bioéthique dans les pays du Sud. Récits de médecins africains". L'Harmattan, Paris, mars **2006**.
- ▶ M. BOTBOL-BAUM. "Health-related biotechnology transfer in Africa : a Critique from a Capability Approach". In "Special Issue on Bioethical Technology Health-related in Africa", African Journal of Medicine and Medical Sciences, Lagos (Nigeria), 36, p.49-54, Suppl **2007**.
- ▶ M. BOTBOL-BAUM. "La pluralité des modes d'argumentation du discours bioéthique : entre pragmatisme et recherche d'objectivité du jugement". In "Argumentation et Narration", p.163-177, Coll. Philosophie et Société, Ed. de l'Université de Bruxelles, **2007**.
- ▶ M. BOTBOL-BAUM, H. ATLAN. "Des embryons et des hommes". PUF, Paris, avril **2007**.
- ▶ M. BOTBOL-BAUM. "Rôle de l'éthique narrative comme condition d'un projet thérapeutique cohérent". In "Narration et identité. De la philosophie à la bioéthique", dir. M.-G. PINSART, Vrin, Paris, janvier **2009**.
- ▶ M. BOTBOL-BAUM. "Les visions plurielles de la maternité et la position des femmes face à la différence des sexes". In "Ed. de l'Université des Femmes", Bruxelles, janvier **2010**.

## Awards

- ▶ *International Research Ethics Education And Curriculum Development Award* - Fogarty International Center
- ▶ "Strengthening Bioethics Capacity and Justice in Health", for the NIH international program. Grant R25-TW 7098, 2004-2008, renewed for **2008-2012**.

## Partnerships

- ▶ A. DECCACHE, G. SCHAMPS, M.-C. CLOSON, J.-P. COBBAUT. Members of HELESI, IRSS, UCL
- ▶ H. ATLAN, EHSS, Paris
- ▶ E. HIRSCH, APHP, Paris
- ▶ Fr. BEHETS, Chapel Hill University, NC, USA
- ▶ Mb. KYOMBO, Ecole de Santé Publique, Kinshasa, RDC
- ▶ Ch. BOUESSEAU, WHO, Geneva, CH
- ▶ J. SOLBAKK, Oslo University, Norway

## Products and Services

Member of the Belgian National Ethics Committee

## KEY WORDS FOR R&D

Bioethics  
Global Ethics  
Ethics of Research  
Philosophy of Techniques  
Ethics of Public Health  
Epistemology

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# Bioethics : Biomedical Research With Human Subjects

## SENIOR SCIENTIST :

- ▶ Marie-Luce DELFOSSE

## Research Field and Subjects

Biomedical research with human subjects (adults, children, developing countries) and topics related, especially :

- ▶ Legal, deontological and ethical norms and Guidelines
- ▶ Ethical committees

## Representative References

- ▶ M.-L. DELFOSSE. *L'encadrement éthique et juridique de l'expérimentation médicale sur l'être humain : histoire d'une collaboration. Autour de la Déclaration d'Helsinki*. In Liber amicorum Michel Coipel, Bruxelles, Kluwer, 21-36, **2004**.
- ▶ M.-L. DELFOSSE. *Réflexions sur l'utilisation du placebo dans la recherche internationale*. In Journal international de bioéthique vol.18, n° 4, 59-67, **2007**.
- ▶ M.-L. DELFOSSE, M.-H. PARIZEAU, J.-P. AMANN (éds). *La recherche clinique avec les enfants : au carrefour de l'éthique et du droit*. Belgique, France, Québec; Québec, Presses de l'Université Laval; Louvain-la-Neuve, Anthemis, 350p., **2009**.
- ▶ M.-L. DELFOSSE. *Un cadre éthique pour les essais cliniques de médicaments : histoire et enjeux*. In Revue des questions scientifiques, 180, 3, 141-164, **2009**.

## Partnership

- ▶ M.-H. PARIZEAU, chaire de bioéthique, Université Laval, Québec
- ▶ J.-P. AMANN, INSERM, Comité consultatif de bioéthique de Belgique

## Products and Services

- ▶ Expertise on ethic related issues
- ▶ Pediatric research
- ▶ Human research
- ▶ Biomedical research
- ▶ Ethical norms
- ▶ Deontology

## KEY WORDS FOR R&D

Biomedical research with human subjects  
Ethics and Law  
Ethics committees  
Vulnerable populations  
Placebo

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# Bioethics, Human Rights and Legal Bionorms

## SENIOR SCIENTISTS :

- ▶ Marie-Luce DELFOSSE
- ▶ Catherine BERT

## Research Field and Subjects

Bioethics, human rights and legal bionorms:  
Compendium of official texts :

- ▶ General texts about bioethics and human rights : ONU, African Union, Organization of American States, ASEAN, Conseil de l'Europe, Organization of the Islamic Conference and League of Arab States;
- ▶ International ethics texts, European legal texts, national legal texts (Belgium and France) about specific issues :
  - Patient's rights,
  - Use of elements and products of the human body,
  - Human experimentation,
  - Research on embryo and human cloning,
  - Assisted procreation,
  - Genetics,
  - Palliative care and euthanasia.

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## Representative References

M.-L. DELFOSSE, C. BERT. *Bioéthique, droits de l'homme et biodroit*. Textes internationaux, régionaux, belges et français; Bruxelles, Larcier, 1e éd., 555p., 2005; Codes commentés Larcier, 2e éd., revue et augmentée, 574 p., 2009.

## Products and Services

- ▶ Expertise on bioethics
- ▶ Human rights
- ▶ Bionorms



# Philosophical and Ethical Thought About Bioethics Issues

## SENIOR SCIENTIST :

► Marie-Luce DELFOSSE

## Research Field and Subjects

Philosophical and ethical thought about various bioethical issues, notably autonomy, integrity, human body...

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## Representative References

- M.-L. DELFOSSE. *Directives anticipées : quels choix éthiques en Belgique ?* In Bulletin de la Société des sciences médicales, n° 3, 299-304, **2008**.
- M.-L. DELFOSSE. *L'évolution de la signification des directives anticipées dans l'éthos médical.* In Bulletin de la Société des sciences médicales, n° 3, 383-394, **2008**.
- M.-L. DELFOSSE. *Au cœur des directives anticipées : l'intégrité.* In Bulletin de la Société des sciences médicales, n° 3, 451-469, **2008**.

## Products and Services

Expertise on ethics  
Ethics and philosophy  
Bioethics





# The Human Body and the Law

## SENIOR SCIENTIST :

► Xavier DIJON

## Research Field and Subjects

Since antiquity, the relationship between man and its own body has always been extensively studied. Starting from the 19th century, science got involved in biology, thus allowing the extensive exploration of the secret workings of the human body in order to benefit human well-being. Our research aims at positioning this bio-medical effort in the context of human destiny, first from the philosophical point of view in order to determine how the human subject can realize what can be called its "reconciliation" with data issued from its own body, and second, from a juridical point of view in order to identify reference marks which will allow legislating on euthanasia, organ graft, handicap prevention, medically assisted procreation, and more generally all matters where society is looking to legislate on the human body.

## Representative References

- X. DIJON. « *La contribution de la morale catholique à la formulation démocratique des lois bioéthiques.* » Revue générale de droit médical, n° 13, pp.183-195, 2004; et Forum Iuridicum (Papieski Wydział Teologiczny, Sekcja Bobolanum, Varsovie), n° 2, pp. 61-74, **2003**.
- X. DIJON. « *Vers un commerce du corps humain ?* » Journal des tribunaux, n° 6233, pp. 501-504, **2006**.
- X. DIJON. « *Les mutations du droit de la famille en Belgique, réflexion éthique sur les enjeux de la loi.* » Etudes, décembre 2006, pp. 609-620. Traduit : « I cambiamenti del diritto di famiglia in Belgio, una riflessione etica. » La Civiltà cattolica, n° 3758, pp. 140-150, Janvier **2007**.
- X. DIJON. « *Science biologique et tradition chrétienne* ». Nouvelle revue théologique, pp. 402-418, **2007**.
- X. DIJON. « *Les miroirs de l'engendrement homosexuel* ». Revue interdisciplinaire d'études juridiques, n° 58, pp. 31-62, **2007**.
- X. DIJON. « *L'autre de la différence : la loi à l'épreuve de l'homoparentalité* ». Bulletin Freudien, revue de l'Association Freudienne de Belgique, n° 54, **2009**.

## Funding

Public fundings

## Products and Services

- Expertise on bioethics
- Natural law
- Human rights

## KEY WORDS FOR R&D

Bioethics  
Natural law  
Human rights

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# Biomedical Anthropology and Ethics

## SENIOR SCIENTIST :

- ▶ Michel DUPUIS

## Research Field and Subjects

Theory of care  
Hermeneutics and narrative approach of medicine  
Phenomenological medical anthropology  
Ethical leadership in care organizations and management  
Christian medical ethics

## Representative References

- ▶ M. DUPUIS. *Culture et entreprise : quelle 'valeur' ajoutée ?* In R. de Borchgrave (ed.), *Le philosophe et le manager. Penser autrement le management*, Bruxelles, De Boeck, 150-155, **2006**.
- ▶ M. DUPUIS. *Recherches sur les cellules souches et santé des femmes : questions éthiques*. In F. Cailleau (ed.), *Cellules souches et santé des femmes*, Louvain-la-Neuve, Antémis, 93-100, **2007**.
- ▶ M. DUPUIS. *New Technologies and Bioethics : A Short Reflection*. In Ch. Gastmans, K. Dierickx, H. Nys, P. Schotsmans (eds), *New pathways for European Bioethics*, Anvers, Intersertia, **2007**.
- ▶ M. DUPUIS. *L'écriture : visage ou masque de l'émotion ?* In *Perspective soignante*, 31, 6-16, **2008**.
- ▶ M. DUPUIS. *Éthique et morale dans les métiers de service*. In *Perspective soignante*, 34, 6-29, **2009**.
- ▶ M. DUPUIS. *La gloire de la Vie ?* In J.-M. Brohm, J. Leclercq (eds), *Michel Henry, Lausanne, L'Age d'Homme*, 451-456, **2009**.
- ▶ M. DUPUIS. *'Etre-à-chaque-fois', souci et sens clinique (Heidegger, 1923)*. In J.-Ph. Pierron (ed.), *Herméneutique et médecine*, Lyon (forthcoming)
- ▶ M. DUPUIS. *Dignité humaine*. In E. Gaziaux, L. Lemoine, D. Müller (eds), *Dictionnaire d'éthique chrétienne*, Paris, Cerf (forthcoming)

## Funding

- ▶ Saint-Luc Foundation (Brussels): 2004, 2007-2009 (ethics of home health care)
- ▶ Fondation Roi Baudouin (Brussels): 2002 (ethics of genetic counseling)

## Partnership

- ▶ P. Schotsmans, Centre for Biomedical Ethics and Law, Leuven
- ▶ J. Walter, The Bioethics Institute of Loyola Marymount University, Los Angeles
- G. Virt, M. Beck, Wien

## Main Equipment

Specialized Documentation Center

## Products and Services

- ▶ Vice-president (2004-2007; 2008-2009) and president (2007-2008) of the Belgian Bioethics Committee
- ▶ Co-founder of the GEFERS (see web site)

## KEY WORDS FOR R&D

Applied phenomenology  
Medical anthropology  
Ethics of management  
Ethics of care  
Narrativity  
Christian ethics

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<http://www.gefers.fr>



# Ethical and Societal Stakes of Biotechnology

## SENIOR SCIENTIST :

- ▶ Bernard FELTZ

## Research Field and Subjects

Ethical stakes of biotechnology  
Ethical stakes of sustainable development  
Societal stakes of darwinism

## Representative References

- ▶ B. FELTZ (Dir.) et al. *Ethique, technique et démocratie*. Academia Bruylant, Louvain-la-Neuve, **2007**.
- ▶ G. EGGERMONT, B. FELTZ. *Ethics and Radiological Protection*. Academia Bruylant, Louvain-la-Neuve, **2008**.
- ▶ B. FELTZ. *Théories de l'évolution, religions et modernités*. In Wolfs, J.L. (Dir.), *Sciences et croyances en éducation, Education comparée*, vol. 1, AFEC, 33-46, **2008**.
- ▶ B. FELTZ, P. DEFOURNY (Dir.). *Expertise, patrimoine naturel et développement local en Afrique*. Le Parc national des Virunga, *Revue des questions scientifiques*, 179 (1), **2008**.
- ▶ B. FELTZ (Dir.). *Darwin entre science et société*. *Revue Philosophique de Louvain*, 107, 3, août **2009**.

## Funding

FNRS, O. SARTENAER :

- ▶ Mandat d'aspirant, 2009-2011
- ▶ Soutien à divers colloques internationaux
- ▶ Soutien à participations à colloques internationaux

FSR (UCL), Q. DELVAL :

- ▶ bourse de doctorat, 2005-2009

CGRI :

- ▶ Convention Wallonie-Bruxelles – Maroc, 2006-2008 et 2009-2011 : Faculté de Droit Cadi Ayyat, Marrakech

CCD (Commission pour la coopération au développement, UCL) :

- ▶ Convention de coopération avec la Faculté de philosophie de l'Université catholique du Congo, Kinshasa, 2003-2008.

## Partnership

- ▶ G. EGGERMONT, UGent, SCK/CEN (Centre Electronucléaire)
- ▶ P. SMEESTERS. (Federal Agency for Nuclear Control (FANC)
- ▶ P. DEFOURNY. (Laboratoire de géomatique, UCL)
- ▶ M. MALKI. (Université Caddi Ayyad, Marrakech)
- ▶ M. HADDAD. (Université de Tunis)
- ▶ St. LEYENS. (Sciences, philosophies, sociétés, FUNDP)
- ▶ ESST (European Sciences, Society, Technology)

## Products and Services

- ▶ Member of Ethical commissions
- ▶ Member of the board of the Université Catholique du Congo (UCC)

## KEY WORDS FOR R&D

Ethics  
Environment  
Technology  
Radiological protection  
Expertise  
Darwinism  
Religion  
Society

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# Capacity Strengthening in Bioethics

## SENIOR SCIENTISTS :

- ▶ Laurent Ravez
- ▶ Chantal Tilmans

## Research Field and Subjects

- ▶ Capacity strengthening in bioethics for professionals in healthcare through the design and implementation of a Master training program in bioethics.
- ▶ The aims are the strengthening of competencies of bioethics committees (IRB) initially in Democratic Republic of Congo and later in Western Africa. And the strengthening of competencies in clinical ethics (daily ethics in dealing with patients) for physicians and nurses.

## Representative References

- ▶ L. RAVEZ. « *De la possibilité d'universaliser les valeurs en éthique clinique : questions et enjeux* ». In Journal international de bioéthique, vol.18, n°3, p.17-23, **2007**.
- ▶ L. RAVEZ. « *Les valeurs traditionnelles de la bioéthique face au défi de la multiculturalité* ». In Ethica Clinica n°49, p. 12-15, **2008**.

## Funding

EDCTP (European and Developing Countries Clinical Trials Partnership)

## Partnership

- ▶ Centre Interdisciplinaire de Bioéthique pour l'Afrique Francophone (CIBAF) à l'Université de Kinshasa (Ecole de Santé Publique)
- ▶ Prof. Stuart RENNIE, University of North Carolina at Chapel Hill (Bioethics, Social Justice and Global Health Project)

## Products and Services

- ▶ Design and implementation of training programs in developing countries.
- ▶ Training in clinical ethics for physicians and nurses in developing countries.

## KEY WORDS FOR R&D

Bioethics  
Clinical  
Ethics capacity-strengthening

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# Ethics in Assisted Reproductive Technologies

## SENIOR SCIENTISTS :

- ▶ Laurent RAVEZ
- ▶ Chantal TILMANS

## Research Field and Subjects

(ART) : counseling for physicians, nurses, researchers, politics, etc.

The main questions in these field are : ethics problems with pre-implantation genetic diagnosis (PGD) or screening (PGS), surrogate motherhood, frozen embryos, embryo selection, oocyte donations.

## Representative References

- ▶ L. RAVEZ. « *L'amour : continent oublié de l'assistance médicale à la procréation* ». In *Ethique & Santé*, Paris, Vol. 2, n°1, p. 9-13, **2005**.
- ▶ L. RAVEZ. *Les amours auscultées. Une nouvelle éthique pour l'assistance médicale à la procréation*. Editions du Cerf, Paris, **2006**.
- ▶ L. RAVEZ. « *Prendre le temps de repenser la relation procréative* ». In S. A. ALDEEB ABU-SAHLIEH, D. BLOEM, Th. GERGELY, et al., *Médecine et Droit. Questions d'actualité en droit médical et en bioéthique*, Anthémis, Louvain-la-Neuve, **2007**.
- ▶ L. RAVEZ. « *Autorité, désir d'enfant et assistance médicale à la procréation* ». In *Ethique & Santé*, accepté, à paraître, Patents, **2009**.

## Products and Services

**Expertise in** ethics of assisted reproductive technologies

## KEY WORDS FOR R&D

ART  
Ethics  
Assisted reproductive technologies

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# Medical and Biomedical Law

## SENIOR SCIENTIST :

► Geneviève SCHAMPS

## Research Field and Subjects

Medical Law and Biomedical Law  
 Biomedicine and human rights  
 Bioethics  
 Patient's Rights  
 Patient's Autonomy  
 Mediation  
 Regulation of biobanking  
 Regulation of Genetic Testing  
 Health professions  
 Health institutions  
 Federal State and health care  
 Electronic Health Records  
 Health Records  
 Clinical trials  
 Human Research Subjects Rights  
 Research on embryo's in vitro  
 Store and use of human Tissue  
 End of life (Euthanasia; palliative Care)  
 In vitro Fertilisation  
 Surrogate Mother  
 Organ Transplant  
 Telemedicine  
 Patient Privacy and Confidentiality  
 Civil Liability  
 Criminology and Criminal Law  
 No-fault Compensation for medical Damage

The progress of biotechnology leads, with others, to a deep evolution of medicine, more and more characterized by new or renewed practices, by a technicization of the health structures and by a specialization of the health professionals. Law is particularly engaged in these evolutions, at the Belgian as to the European and international levels : a body of law rules and jurisdictional decisions, constantly on the move, develops on this matter.

The Center for medical and biomedical law submits this vast body to a critical and constructive analysis in order to contribute to its harmonious development and to an effective implementation of the applicable rules.

## Representative References

- J.-M. HAUSMAN. *Tests et banques de données ADN en matière pénale : modes de régulation et de contrôle*. Rev. dr. pén. crim., vol. 85, n° 4, 387-400, **2005**.
- M. VAN OVERSTRAETEN. *État fédéral et bioéthique : le système belge de répartition des compétences à l'épreuve du défi biomédical*. In "En hommage à Francis Delpérée. Itinéraires d'un constitutionnaliste", Bruxelles, Bruylant, Paris, L.G.D.J., 1587-1598, **2007**.
- J.-M. HAUSMAN. *Le droit d'accès direct au système d'information Santé organisé par le décret du 16 juin 2006 de la Communauté flamande*. In G. Schamps (Dir.), *Evolution des droits du patient, indemnisation sans faute des dommages liés aux soins de santé : le droit médical en mouvement*, Paris, L.G.D.J., Bruxelles, Bruylant, 187-247, **2008**.
- M. VAN OVERSTRAETEN. *Une manifestation particulière du droit du patient au consentement libre et éclairé : la faculté de rédiger une déclaration anticipée*. In G. Schamps (Dir.), *Évolution des droits du patient, indemnisation sans faute des dommages liés aux soins de santé : le droit médical en mouvement*, Bruxelles, Bruylant, Paris, L.G.D.J., 83-153, **2008**.
- M. VAN OVERSTRAETEN. *Belgian Act on Euthanasia : alterations to be expected ?* In Actes du 17ème Congrès mondial de droit médical, Pékin, World Association for Medical Law, China Health Law Society, 1-7, **2008**.
- M.-N. DERESE. *Mediation in the Belgian healthcare sector : the "complainant" conception, the mediator's independence and training*. Actes du 17ème Congrès mondial de droit médical, Pékin, World Association for Medical Law, China Health Law Society, 1-7, **2008**.
- G. SCHAMPS (Dir.). *Évolution des droits du patient, indemnisation sans faute des dommages liés aux soins de santé*. Le droit médical en mouvement, Bruxelles, Bruylant, Paris, L.G.D.J., 600 p., **2008**.
- G. SCHAMPS, M.-N. DERESE. *L'anonymat et la procréation médicalement assistée en droit belge. Des pratiques à la loi du 6 juillet 2007*. In *Procréation assistée et Anonymat*. Panorama international, B. Feuillet (Ed.), Bruxelles, Bruylant, 128-152, **2009**.
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### Awards

- ▶ *Prix quinquennal Baron E. VAN DIEVOET*, **1999**.
- ▶ *Prix quinquennal de la Revue Critique de Jurisprudence Belge*, **2001**.

### Partnership

- ▶ HELESI, Institut de recherche Santé et Société (UCL, Belgium)
- ▶ CIDES, Facultés Universitaires Notre-Dame de la Paix (Namur, Belgium)
- ▶ CRID, Facultés Universitaires Notre-Dame de la Paix (Namur, Belgium)
- ▶ Centre for Biomedical Ethics and Law (University of Leuven, Belgium)
- ▶ International Academic Bioethics Network (members of the University of Caxias do sul – UCS [Brasil], the University of Coimbra [Portugal], the University of Columbia [New York, United States], the University of Central Europe [Budapest ; Hungria], the University of Genève [Switzerland], the University of Kyoto [Japan], the University of Navarre [Soaub], the University of Pirée [Greece], the University of de Reading [Grande-Bretagne], the Université de Rennes I [France], the the University of Rome II [Italia], the University of la Sarre [Saarbrücken, Germany], d the University of Tunis III [Tunisie] et the University of Utrecht [The Netherland])
- ▶ Groupe de recherche en droit de la santé de l'Université de Sherbrooke (Canada)
- ▶ Federal University of Pelotas (Brasil)
- ▶ Centre de droit médical (Université de Poitiers, France)
- ▶ Centre européen d'études et de recherche droit et santé (Université de Montpellier, France)
- ▶ Université Paul Sabatier Toulouse III (France)
- ▶ Centre de recherche juridique et judiciaire de l'Ouest (Université de Rennes, France)
- ▶ Institut de droit de la santé (Faculté de droit de l'Université de Neufchâtel, Switzerland)
- ▶ Faculté de droit de l'Université de Genève (Switzerland)

- ▶ Fondation Brocher (Genève, Switzerland)
- ▶ Institute for European Tort Law (Vienne, Austria)
- ▶ Office national d'indemnisation des accidents médicaux (Paris, France)

### Products and Services

- ▶ The Center for medical and biomedical law offers to the public authorities, the health professionals and health institutions as well as to the citizens an expertise likely to enlighten them about the – sometimes difficult to appreciate – content and reach of the pertinent rules and jurisdictional decisions. It also brings out indications likely to help the preparation or the revision of the statutes.
- ▶ Presidency of the Federal Commission Patient's Rights
- ▶ Member of the Ethics Committee of the Cliniques universitaires St Luc (UCL)
- ▶ Expertise for Belgian or foreign parliamentary assemblies, institutions, National Science Foundations, etc.
- ▶ Member of scientific reviews' committees

### KEY WORDS FOR R&D

Medical and Biomedical Law  
Health Care Dispute - Mediation  
Patient's rights  
Regulation of biobanking  
Regulation of Genetic Testing  
Civil and criminal Liability  
Reproductive Technologies  
Bioethics  
Professional orders in Health Care  
Human rights  
Comparative Law  
Governmental Studies  
Technology and Society

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# Key Words Index

2D-DIGE	<b>F15, F20</b>	Association study	<b>D11</b>
2D-LC-MS	<b>F21</b>	Astrocytes Microglia	<b>B2, E9</b>
3D cephalometry analysis	<b>A14</b>	Astroglial cells	<b>E5</b>
Active natural products	<b>E18</b>	Auto-antibody	<b>F15</b>
Active Site	<b>D5</b>	Autologous cell therapy	<b>F10</b>
Acute renal failure	<b>E4</b>	B lymphocyte	<b>F18</b>
Adhesion, cells	<b>A10</b>	Bacteria	<b>F2</b>
Adipocytokines	<b>E13</b>	Bacterial genetics	<b>C2</b>
Adiponectin	<b>E13</b>	Bacterial pathogens	<b>C1</b>
Adipose tissue	<b>E13</b>	Bacterial pathogens	<b>F11</b>
Adsorption, proteins, lipids, polymers	<b>A10</b>	Bacteries	<b>A11</b>
AFM	<b>A3</b>	Bacteriology	<b>C1, F10</b>
Ageing	<b>E2</b>	Beer	<b>A4</b>
Airway hyperactivity	<b>E22</b>	Beta cell	<b>E6</b>
Allergy	<b>C3</b>	Beta-lactamase	<b>D8</b>
Allografts	<b>F10</b>	Binding Site	<b>D5</b>
Allosteric regulation	<b>D8</b>	Bioadhesion	<b>A10, F13</b>
Aminopeptidase	<b>E3</b>	Bioavailability	<b>E22</b>
Analytical toxicology	<b>F26</b>	Biobanking	<b>F12</b>
Anatomopathology	<b>F10</b>	Biochemical analyzer	<b>F12</b>
Angiogenesis	<b>A12, D12, E1</b>	Biochemical platform	<b>D4</b>
Animal cell culture	<b>B3</b>	Biocompatibility	<b>A10, A12, F13</b>
Animal house facilities	<b>F8</b>	Biodiversity	<b>D2</b>
Animal husbandry	<b>F8</b>	Bioethics	<b>G1, G10, G5, G8</b>
Animal model	<b>D11, D12, E4</b>	Biofouling	<b>A1</b>
Antibiotics	<b>C5, E20</b>	Biological fluids	<b>F12</b>
Antibodies	<b>F18, A6</b>	Biomarker	<b>C3, D4, F12, F15, F14</b>
Antibody-beta-lactamase conjugate	<b>C4</b>	Biomaterials	<b>A1, A10, A12, A5, F13</b>
Antigen presenting cell	<b>F18</b>	Biomechanic	<b>F10</b>
Antigens	<b>A6, E22</b>	Biomedical research with human subjects	<b>G2</b>
Antioxidant enzyme	<b>B3</b>	Biomedicine	<b>F13</b>
Apoptosis	<b>E15</b>	Biomembranes	<b>A10, F13</b>
Applied phenomenology	<b>G6</b>	Biophysical studies	<b>E16</b>
Aquatic organisms	<b>D7</b>	Biosensor	<b>A1, A3, A6, F13</b>
Aroma	<b>A4</b>	Biosurfaces	<b>F13</b>
ART	<b>G9</b>	Blood gazes	<b>F12</b>
Arteriovenous malformation	<b>D12, F24</b>	Blood pressure	<b>D4</b>
Artificial ovary	<b>A9</b>	Bone induction	<b>F10</b>
Assisted reproductive technologies	<b>G9</b>	Bone remodeling	<b>F10</b>

Brucella abortus	<b>C1</b>	Confocal microscope	<b>F2</b>
Brucella melitensis	<b>C1</b>	Confocal microscopy	<b>B1, F5</b>
Cancer	<b>A12, F15</b>	Congenital metabolic disorders	<b>D10</b>
Cancer diseases	<b>F17</b>	Control	<b>A7</b>
Capillary malformation	<b>F24</b>	Corrosion	<b>A5</b>
Capillary malformation	<b>D12</b>	Covalent modification	<b>F21</b>
Cardiac imaging	<b>D9</b>	Craniofacial anomaly	<b>D11</b>
Cardiac remodelling	<b>D9</b>	Craniomaxillofacial surgery	<b>A14</b>
Cardiomyocytes	<b>E1</b>	Cryobanking	<b>A8</b>
Cardiovascular	<b>E1, E8</b>	Cryopreservation	<b>A9, F7</b>
Caulobacter crescentus	<b>C1</b>	Crystallization	<b>B3, F6</b>
Cell culture	<b>E15, E20, E21</b>	Culture at physiological oxygen pressure	<b>B7</b>
Cell culture systems	<b>D10, F22</b>	Culture collection	<b>F7</b>
Cell models	<b>D4</b>	Cutaneomucosal venous malformation	<b>D12, F24</b>
Cell senescence	<b>B7</b>	Cystic fibrosis	<b>E12</b>
Cell therapy	<b>D9, E6, E10, E19</b>	Cystic fibrosis transmembrane conductance regulator (CFTR)	<b>E12</b>
Cellular pharmacodynamics	<b>E20</b>	Cytochrome P450	<b>E2</b>
Cellular pharmacokinetics	<b>E20, E21</b>	Cytokine	<b>C3, D3</b>
Central nervous system – development	<b>E5</b>	Dairy products	<b>C2</b>
Central nervous system – infections	<b>E14</b>	Danio rerio	<b>D7</b>
Cheese	<b>C2</b>	Darwinism	<b>G7</b>
Chemotherapy	<b>A12</b>	Data management	<b>F4</b>
Chimeric antibody	<b>F18</b>	Delayed-union	<b>F10</b>
Cholesterol	<b>B4</b>	Design of experiment	<b>F4</b>
Christian ethics	<b>G6</b>	Development	<b>D11</b>
Chronic renal failure	<b>E4</b>	Diabetes	<b>D9, D10, E6, E7</b>
Civil and criminal Liability	<b>G10</b>	Diagnosis	<b>F14</b>
Cleanroom	<b>F9</b>	Diagnostic	<b>F17</b>
Cleft lip	<b>D11</b>	Dialysis	<b>D4</b>
Cleft palate	<b>D11</b>	Dietary fibers	<b>E7</b>
Clinical	<b>G8</b>	Differentiation	<b>B4, E10</b>
Clinical pharmacokinetics	<b>F26</b>	DIM (Detection, Identification & monitoring)	<b>F17</b>
Cloning	<b>A13</b>	DNA	<b>A6</b>
CMOS	<b>F9</b>	DNA affinity	<b>B6</b>
CNA (Copy Number Analysis)	<b>F25</b>	DNA hybridization	<b>F16</b>
Coagulation	<b>E8</b>	DNA recombination	<b>D6</b>
Cocoa	<b>A4</b>	DNA vaccine	<b>E17</b>
Comparative Law	<b>G10</b>	DNA/RNA concentration	<b>F16</b>
Computation	<b>F4</b>	Drug analysis	<b>F26</b>

Drug delivery	<b>F22</b>	Ethics of care	<b>G6</b>
Drug delivery, non-invasive	<b>E22</b>	Ethics of management	<b>G6</b>
Drug design	<b>E11</b>	Ethics of Public Health	<b>G1</b>
Drug-membrane interactions	<b>E15, E16</b>	Ethics of Research	<b>G1</b>
Drugs	<b>E21, F13</b>	Etiology	<b>D11</b>
Dry powder aerosols	<b>E22</b>	Exact mass	<b>F19</b>
Ecotoxicology	<b>D7</b>	Excitotoxicity	<b>E9</b>
Efflux	<b>C5</b>	Experimental anesthesiology	<b>F8</b>
Efflux pumps	<b>E21</b>	Experimental surgery	<b>F8</b>
Electrical detection	<b>A11</b>	Expertise	<b>G7</b>
Electroanalysis	<b>A6</b>	Explants	<b>B1, F5</b>
Electrodeposition	<b>A5</b>	Expression analysis	<b>D13</b>
Electron microscopy	<b>B1, F5</b>	Expression profiling	<b>F20, F25</b>
Electroporation	<b>E17</b>	Extracellular matrix	<b>B1</b>
Electrospray (ESI)	<b>F21</b>	Fatty liver	<b>E13</b>
Electrotransfer	<b>E17</b>	Feature Selection	<b>C3, F14</b>
Elementary composition	<b>F19</b>	Fermentation	<b>A4</b>
ELISA	<b>D7</b>	Fertility preservation	<b>A9</b>
ELISA development	<b>F12</b>	Filamentous fungi	<b>F7</b>
Embryo metabolism	<b>A8</b>	Flavour stability	<b>A4</b>
Embryo sexing	<b>A8</b>	Fluorescence Confocal Scanner	<b>F20</b>
Endometrium	<b>B1</b>	Fluorescence Microscopy	<b>C1</b>
Endomycorrhiza	<b>F7</b>	Fluorescent dyes	<b>F2</b>
Endothelial cell	<b>D13, E1, F24</b>	Fluorophores	<b>F2</b>
Endothelial dysfunction	<b>F15</b>	Follicle isolation	<b>A9</b>
Endothelial/ Smooth muscle cell	<b>D12</b>	Food safety	<b>F22</b>
Environment	<b>G7</b>	Forest trees	<b>D2</b>
Enzymatic assays	<b>D10</b>	Fractionation	<b>B1</b>
Enzyme secretion	<b>E3</b>	Fracture	<b>F10</b>
Enzymes	<b>E11</b>	Free radicals	<b>A12</b>
Enzymes, adsorption, activity	<b>A10</b>	Function analysis	<b>F3</b>
Epidermis	<b>B4, B5</b>	Functional imaging	<b>A12</b>
Epistemology	<b>G1</b>	Fungi	<b>F2</b>
EPR	<b>A12</b>	Gametes and embryo cryopreservation	<b>A8</b>
Estimation	<b>A7</b>	Gel-free	<b>F3</b>
Ethics	<b>G7, G9</b>	Gel-independent proteomics	<b>F20</b>
Ethics and Law	<b>G2</b>	Gene delivery	<b>E17</b>
Ethics capacity-strengthening	<b>G8</b>	Gene expression	<b>A8, B7, C3</b>
Ethics committees	<b>G2</b>	Gene function and regulation	<b>D1</b>

Gene Profiling	<b>F14</b>	Immunity	<b>E22</b>
Gene targeting	<b>D6</b>	Immunization	<b>F18</b>
Genechip	<b>F25</b>	Immunocytochemistry	<b>B2</b>
Genetic engineering	<b>A2, A13, D1, D6</b>	Immunoglobulins	<b>F18</b>
Genetics	<b>D11, F17</b>	Immunology	<b>F8</b>
Genomics	<b>C2, F17</b>	<i>In vitro</i> fertilization	<b>A8</b>
Genotyping	<b>F11</b>	<i>In vitro</i> test	<b>E2</b>
Global Ethics	<b>G1</b>	<i>In vitro</i> toxicology	<b>F22</b>
Glomovenous malformation	<b>D12, F24</b>	Inborn errors of metabolism	<b>E10</b>
GLP	<b>D7</b>	Inducible promoter	<b>A2</b>
Glutamate transporters	<b>E9</b>	Infection	<b>F10</b>
Glycoproteins	<b>D10</b>	Infectious diseases	<b>F17</b>
Governmental Studies	<b>G10</b>	Inflammation	<b>E4, E7</b>
Growth factors	<b>B4, D3</b>	Insertion mutagenesis	<b>D8</b>
Gut peptides	<b>E7</b>	Instrumentation	<b>A6</b>
Health Care Dispute - Mediation	<b>G10</b>	Insulin resistance	<b>D9, E13</b>
Heart failure	<b>D9</b>	Interface	<b>A3</b>
Heart metabolism	<b>D9</b>	Interferon lambda	<b>E14</b>
Hemangioma	<b>D13, F24</b>	Interferons alpha/beta	<b>E14</b>
Hepatic stellate cells	<b>E13</b>	Interleukin	<b>D3</b>
Hepatocytes	<b>E2, E10</b>	Intermediary metabolism	<b>D10</b>
Heterologous expression	<b>A2</b>	Intestinal barrier	<b>F22</b>
High Throughput Screening	<b>D8</b>	Intestinal microflora	<b>E3</b>
High Throughput Technologies	<b>F14</b>	Intracellular infection	<b>E20</b>
Histopathology	<b>E4</b>	Intrarenal hemodynamics	<b>E4</b>
Homologous recombination	<b>F1</b>	Ion spectrometries	<b>A1</b>
Hop	<b>A4</b>	Ionic liquid	<b>A5</b>
Human	<b>F18</b>	Irritation	<b>B5</b>
Human rights	<b>G5, G10</b>	Ischemia	<b>D9</b>
Human, rat, mouse immune cells	<b>F18</b>	Ischemic diseases	<b>F15</b>
Humanized antibody	<b>F18</b>	Islet transplantation	<b>E6</b>
Hydrolase activity tests	<b>A13</b>	Isolation	<b>E18</b>
Hydrolases	<b>A13</b>	JAK	<b>D3</b>
Hyperinsulinemic-euglycemic clamp studies	<b>E13</b>	Keratinocytes	<b>B4, B5</b>
Hypertension	<b>F15</b>	Kidney	<b>B1, D4</b>
Hypertrophy	<b>D9</b>	Knock-down zebrafish	<b>D11</b>
Identification	<b>F19</b>	Knock-out mice	<b>D11</b>
Imaging	<b>A12</b>	Kupffer cells	<b>E13</b>
Immune response	<b>C3</b>	Label free	<b>A3</b>



Laboratory animals	<b>F8</b>	Metabolic engineering	<b>C2</b>
Lactic acid bacteria	<b>C2</b>	Metabolic network	<b>A7</b>
Lactobacillus	<b>C2</b>	Metabolic syndrome	<b>E13</b>
Laser	<b>A3</b>	Metalloprotease	<b>E3</b>
Legionella pneumophila	<b>E20</b>	Microarray	<b>C2, F17, F25</b>
Leptin	<b>E13</b>	Microarray Data	<b>F14</b>
Lignolytic enzymes	<b>F7</b>	Microbial ecology	<b>A7</b>
Limb salvage	<b>F10</b>	Microbiology	<b>F13</b>
Linkage analysis	<b>F25</b>	Microelectronics	<b>A6, F9</b>
Linkage study	<b>D11</b>	Microflora	<b>E7</b>
Lipids	<b>E16</b>	Microsatellites	<b>D2</b>
Lipids, membranes	<b>A10, F13</b>	Microscopy	<b>A3</b>
Liposomes	<b>E15, E16, F5</b>	Micro-sensors	<b>A11, F16</b>
Listeria monocytogenes	<b>E20</b>	Micro-titration	<b>F12</b>
Live-cell imaging	<b>B1, F5</b>	miRNA	<b>F25</b>
Liver	<b>E10</b>	Mis-targeting	<b>D1</b>
Liver slices	<b>E2</b>	Modelling	<b>A7</b>
Local electrochemistry	<b>A5</b>	Molecular Biology	<b>A2, C1, F11</b>
LOH (Loss-of-Heterozygosity)	<b>F25</b>	Molecular recognition	<b>A3</b>
Lung	<b>E22</b>	Monitoring	<b>A7</b>
Lung inflammation	<b>E12</b>	Monoclonal antibody	<b>E22, F18</b>
Lymphangiogenesis	<b>D12</b>	Mouse	<b>F18</b>
Lymphedema	<b>D12, F24</b>	Mouse ES cells	<b>F1</b>
Lysosomes	<b>E15</b>	Mouse model	<b>D4, D11</b>
Macrophages	<b>E12</b>	MRI	<b>A12</b>
Maldi	<b>F3</b>	Mucosal vaccines	<b>C2</b>
Maldi-Tof	<b>F20</b>	Multiphoton microscopy	<b>B1, F5</b>
Mammals	<b>F2</b>	Mutagenesis	<b>A13, D6</b>
Mass Spectrometry (MS)	<b>B6, F19, F3, F20, F21</b>	Mycotoxins	<b>A4, F7</b>
Matrix metalloproteinases	<b>B1</b>	Nanobiomimetic, devices	<b>F13</b>
Medical and Biomedical Law	<b>G10</b>	Nanobioscience	<b>F13</b>
Medical anthropology	<b>G6</b>	Nanobiotechnology	<b>A6, F13</b>
Medical imaging	<b>A14</b>	Nanocharacterization	<b>F13</b>
Medicinal plants	<b>E18</b>	Nanoelectronics	<b>A6, F9</b>
Membrane	<b>B1</b>	Nanoimprint	<b>A6</b>
Membrane proteins	<b>F3</b>	Nanolithography	<b>A6</b>
MEMS	<b>F9</b>	Nanomaterials	<b>A5</b>
Mesenchymal stem cells	<b>E5</b>	Nanospray, ESI-MS	<b>F21</b>
Metabolic diseases	<b>E7</b>	Narrativity	<b>G6</b>

Nasal potential difference	<b>E12</b>	Pharmacological assays	<b>E11</b>
Natural law	<b>G5</b>	Pharmacological proteins	<b>A2</b>
Neural differentiation	<b>E5</b>	Pharmacology	<b>A12, B4, E1, E4, E8</b>
Neural stem cells	<b>E5</b>	Phenotype analysis	<b>D4</b>
Neurodegenerative disease	<b>E5</b>	Philosophy of Techniques	<b>G1</b>
Neurodevelopmental disorders	<b>D10</b>	Phospholipases	<b>E15</b>
Neurons	<b>B2</b>	Phospholipids	<b>E15</b>
Neuroprotection	<b>B2</b>	Phosphorylation	<b>F21</b>
Nitric oxide	<b>E1</b>	Photovoltaics	<b>F9</b>
Nitrosative stress	<b>E4</b>	Phylogenetic systematics	<b>F7</b>
NMR	<b>A12</b>	Picornavirus	<b>E14</b>
Non-alcoholic steatohepatitis	<b>E13</b>	Placebo	<b>G2</b>
Nonlinear optics	<b>A3</b>	Plant	<b>A2, F2, F3</b>
Obesity	<b>D10, E7</b>	Plant abiotic stress	<b>D1</b>
Optics	<b>A3</b>	Plant cells	<b>A2</b>
Organelle biology	<b>D1</b>	Plasmid delivery	<b>E17</b>
Organic electronics	<b>F9</b>	Platelet	<b>D9, E8</b>
Orthopaedic	<b>F10</b>	Pollutant	<b>D7</b>
Osmometer	<b>F12</b>	Polyamines	<b>E3</b>
Ovarian tissue	<b>A9</b>	Polycythemia Vera	<b>D3</b>
Oxidative stress	<b>B7, E2, E4</b>	Polymers, surfaces	<b>A10</b>
Oxygen	<b>A12</b>	Polyphenols	<b>A4</b>
Pancreas	<b>B1</b>	Population balance	<b>A7</b>
Pancreas differentiation	<b>E6</b>	Post-chemotherapy	<b>A9</b>
Pancreas morphogenesis	<b>E6</b>	Post-translational modification	<b>F21</b>
Paracrine regulation	<b>E4</b>	Prebiotics	<b>E7</b>
Pathogen	<b>F17</b>	Predictive	<b>F15</b>
Pathway analysis	<b>F25</b>	Primary cultures	<b>B2</b>
Patient's rights	<b>G10</b>	Primary cultures of astrocytes	<b>E9</b>
Penicillin acylase	<b>D8</b>	Primary metabolites	<b>F7</b>
Peptidases	<b>A2</b>	Primates	<b>F8</b>
Peptide mass fingerprinting	<b>F20</b>	Probiotic	<b>C2, E3</b>
Peptide sequencing	<b>F20</b>	Professional orders in Health Care	<b>G10</b>
Peptides	<b>E22</b>	Prognosis	<b>C3, F14</b>
Peroxidase activity	<b>B3</b>	Prognostic	<b>F15, F17</b>
PHACES	<b>D13</b>	Protein adsorption	<b>A1</b>
Phage display	<b>D8</b>	Protein analysis	<b>F3</b>
Phages	<b>A11</b>	Protein assay	<b>D7</b>
Pharmacogenetic	<b>F17, F26</b>	Protein crystallisation	<b>A13, E11</b>

Protein Docking	<b>D5</b>	Reporter enzymes	<b>D8</b>
Protein dynamics	<b>F2</b>	Reproductive Technologies	<b>G10</b>
Protein engineering	<b>A13, D6</b>	Resistance	<b>C5</b>
Protein expression	<b>A13</b>	Resveratrol	<b>A4</b>
Protein glycation	<b>D10</b>	Risk assessment	<b>D7</b>
Protein glycosylation	<b>D10</b>	Robot	<b>A14</b>
Protein identification	<b>F20</b>	Robotic devices	<b>A14</b>
Protein kinase	<b>D9</b>	Rodents	<b>F8</b>
Protein localization	<b>F2</b>	<i>Saccharomyces cerevisiae</i>	<b>A4</b>
Protein misexpression	<b>D1</b>	Salmonella	<b>C4</b>
Protein phosphorylation	<b>D9</b>	Salmonids (Trout, Salmon)	<b>D2</b>
Protein purification	<b>A13, B3, E11</b>	Sampling animal models	<b>F12</b>
Protein trafficking	<b>D1</b>	Satiety	<b>E7</b>
ProteinChips	<b>F17</b>	Scaffold	<b>A9</b>
Proteins	<b>A6, E22</b>	Secondary metabolites	<b>F7</b>
Proteins, adsorption	<b>A10, F13</b>	Selective medium	<b>C4</b>
Proteome	<b>F3</b>	Self-assembled monolayer	<b>A5</b>
Proteomic	<b>B6, B7, F15, F21</b>	Self-assembly	<b>F13</b>
Protists	<b>F2</b>	Sensitization	<b>B5</b>
<i>Pseudomonas aeruginosa</i>	<b>C5</b>	Sensors	<b>F9</b>
Quality control	<b>F4</b>	Signal transduction	<b>D3</b>
Quantitative analysis	<b>E18, F19</b>	Single molecules	<b>F2</b>
Quantitative proteomics	<b>F3</b>	Site-specific recombination	<b>D6</b>
Rabbits	<b>F8</b>	Skin biology	<b>B7</b>
Radiological protection	<b>G7</b>	Smart surfaces	<b>A10</b>
Radiotherapy	<b>A12</b>	Smooth muscle cell	<b>F24</b>
Rapid growth	<b>C4</b>	Society	<b>G7</b>
Rare diseases	<b>D4</b>	Software	<b>A14</b>
Rat	<b>F18</b>	Software sensor	<b>A7</b>
REACH	<b>D7</b>	SOI	<b>F9</b>
Real-time optimisation	<b>A7</b>	Spectroscopy	<b>A3, A12</b>
Receptors	<b>D3</b>	Spin trapping	<b>A12</b>
Recombinant protein	<b>B3</b>	Spinal cord injury	<b>E5</b>
Recruitment of probants	<b>B7</b>	<i>Staphylococcus aureus</i>	<b>E20</b>
Red deers	<b>D2</b>	STAT	<b>D3</b>
Regenerative medicine	<b>E19</b>	Statistical analysis	<b>F25</b>
Regulation of biobanking	<b>G10</b>	Statistics	<b>F4</b>
Regulation of Genetic Testing	<b>G10</b>	Stem cell	<b>E10, E19</b>
Religion	<b>G7</b>	<i>Streptococcus</i>	<b>C2</b>

Streptococcus pneumoniae	<b>C5</b>	Transfection vectors	<b>B3</b>
Structure	<b>F6</b>	Transgene technology	<b>F1</b>
Structure determination	<b>E18, F19</b>	Transgenic mice	<b>D10, D11, D12, E12</b>
Structure-based drug design	<b>E11</b>	Transplantation	<b>A9, F10</b>
Subcellular distribution	<b>E21</b>	Transposition	<b>D6</b>
Subcellular localization	<b>D1</b>	Treatment monitoring	<b>F15</b>
Subcellular targeting	<b>A2</b>	Tridimensional structure	<b>B3</b>
Sugar analyses	<b>A13</b>	Tumor	<b>A12</b>
Sulphur flavours	<b>A4</b>	Tumor-associated antigens	<b>F15</b>
Sum-frequency generation	<b>A3</b>	Type 2 diabetes	<b>E13</b>
Surface	<b>A3</b>	Tyrosine recombinase	<b>D6</b>
Surface and interface	<b>A5</b>	UPD (Uniparental Disomy)	<b>F25</b>
Surface characterization	<b>A1</b>	Urine	<b>D4</b>
Surface description	<b>D5</b>	UV photodiode	<b>A11, F16</b>
Surface modifications	<b>A1</b>	UVB	<b>B7</b>
Surfaces	<b>A6, A10</b>	Vaccine adjuvant	<b>E22</b>
Surfaces, cells	<b>F13</b>	Vaccines	<b>E22</b>
Surgery	<b>F10</b>	Vascular anomaly	<b>F24</b>
Survey	<b>F4</b>	Vascular malformation	<b>D12, F24</b>
Swine	<b>F8</b>	Vascular tumor	<b>D13</b>
T helper	<b>F18</b>	Venous malformation	<b>F24</b>
Tandem MS/MS	<b>F20</b>	Virus	<b>F2</b>
Taxonomy	<b>F7</b>	Vulnerable populations	<b>G2</b>
Technology	<b>G7</b>	Whole-genome SNP arrays	<b>D13</b>
Technology and Society	<b>G10</b>	Wild pigs	<b>D2</b>
Tetrapyrroles and signaling	<b>D1</b>	Wine	<b>A4</b>
Theilovirus	<b>E14</b>	Wound healing	<b>B4</b>
Therapeutic drug monitoring	<b>F26</b>	Xenobiotic metabolism	<b>E2</b>
Thrombosis	<b>E8</b>	Xenograft	<b>E6</b>
Toxicology	<b>B5</b>	Xenopus laevis	<b>D7</b>
Toxicoproteomics	<b>D7</b>	X-ray	<b>E11</b>
Training	<b>F4</b>	X-ray diffraction	<b>F6</b>
Transcription factors	<b>B6</b>	Yeast	<b>F2, F3, F7</b>
Transcriptomics	<b>B7</b>	Yoghurt	<b>C2</b>