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. Courtoy) - 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

B. CELL BIOLOGY – ANIMALS AND PLANTS

C. IMMUNOLOGY - MICROBIOLOGY

D - MOLECULAR BIOLOGY

F. TECHNOLOGICAL PLATFORMS

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.

Representative References

C. Poleunis, C. Rubio, C. Compère, P. Bertrand. *ToF-SIMS chemical mapping study of protein adsorption onto stainless steel surfaces immersed in saline aqueous solutions.* Appl. Surf. Sci. 203-204, 693-697, **2003**.

M. Henry, C. Dupont-Gillain, P. Bertrand. *Conformation change of albumin adsorbed on polycarbonate membranes as revealed by ToF-SIMS.* Langmuir 19, 6271-6276, **2003**.

M. Henry, K. Ulrichs, V. Moskalenko, M. Bonneau, C. Kang, A. Belcourt, P. Bertrand. *Surface analysis of an encapsulation membrane after its implantation in mini-pigs.* Biomedical Materials 2, S78-S89, **2007**.

M. Henry, C. Dupont-Gillain, P. Bertrand. *Characterization of insulin adsorption in presence of albumin by ToF-SIMS and XPS.* Langmuir 24, 458-464, **2008**.

O. Iguerb, P. Bertrand. *Graft photopolymerization of Polyethylene glycol monoacrylate (PEGA) on poly(methyl methacrylate) (PMMA) films to prevent BSA and marine protein adsorption.* Surf. Interface Anal. 40, 386-390, **2008**.

O. Iguerb, C. Poleunis, F. Mazeas, C. Compere, P. Bertrand. *Antifouling properties of PMMA films grafted with Polyethylene glycol monoacrylate (PEGA) and immersed in seawater.* Langmuir 24, 12272-12281, **2008**.

E. Dague, A. Delcorte, J.-P. Latge, Y.-F. Dufrene. *Combined use of atomic force microscopy, X-ray photoelectron spectroscopy and secondary ion mass spectrometry for cell surface analysis.* Langmuir (letters) 24, 2955-2959, **2008**.

G. Legent, A. Delaune, V. Norris, A. Delcorte, D. Gibouin, F. Lefebvre, G. Misevic, M. Thellier, C. Ripoll. *Method for macromolecular colocalization using atomic recombination.* In dynamic SIMS, J. Phys. Chem. B 112, 5534-5546, **2008**.

M. Henry, P. Bertrand. *Surface composition of insulin and albumin adsorbed on polymer substrates as revealed by multivariate analysis of ToF-SIMS data.* Surf. Interface Anal. 41, 105-113, **2009**.

S. Yunus, A. Attout, P. Bertrand. *Controlled aniline polymerization strategies for polyaniline micro- and nano self-assembling into practical electronic devices.* Langmuir 25, 1851-1854, **2009**.

Patents

- J.-L. Dewez, J. B. Lhoest, E. Detrait, P. Bertrand, P. van den Bosch de Aguilar, P. G. Rouxhet. *Biomaterial and method for obtaining it,* Belgian Patent n° 09401022, Nov. 14 (1995); International Patent Application PCT / BE95/00104, Nov. 14, 1995; United states, patent n° 5,962,136, **1998**.
- A. Belcourt, P. Bertrand, G. Legeay, L. Kessler. *Membrane pour chambre d'encapsulation de cellules produisant au moins une substance biologiquement active et organe bio-artificiel comprenant une telle membrane.* Patent FR2820057, **2002**.

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(*) static imaging time-of-flight mass spectrometers (ToF-SIMS)
- Rutherford Backscatering 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 is preventing their expression by genetic engineering (RNA interference).

Representative References

- C. Navarre, M. Delannoy, B. Lefebvre, J. Nader, D. Vanham, M. Boutry. *Expression and secretion of recombinant outer-surface protein A from the Lyme disease agent, Borrelia burgdorferi, in Nicotiana tabacum suspension cells.* Transgenic research 15, 325-335, **2006**.
- M. delannoy, G. Alves, D. Vertommen, J. Ma, M. Boutry, C. Navarre. *Identification of peptidases in Nicotiana tabacum leaf intercellular fluid.* Proteomics 8, 2285-2298, **2008**.
- B. De Muynck, C. Navarre, Y. Nizet, J. Stadlmann, M. Boutry. *Different subcellular localization and glycosylation for a functional antibody expressed in Nicotiana tabacum plants and suspension cells.* Transgenic research 18, (in press), **2009**.
- P. Drake, T. Barbi, A. Sexton, E. McGowan, J. Stadlmann, C. Navarre, M. Paul, J. Ma. *Development of rhizosecretion as a production system for recombinant proteins from hydroponic cultivated tobacco.* FASEB Journal 23 (10), 3581-3589, **2009**.
- B. De Muynck, C. Navarre, M. Boutry. *Production of antibody in plants: status after twenty years.* Plant Biotechnology Journal in press.

Patents

- S. Haunso, J. Carlsen, K. Kjeldsen, T. Johansen, P. Larsen, U. Jensen, S. Fey, M. Boutry, H. Degand. *Markers for organ rejection.* PCT US 5939270, **1999**.
- M. Boutry, Y. Stukkens, S. Grec, M. Jasinski. *Use of NpABC1 transporter and promoter thereof.* PCT/EP03/08137, **2003**.

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 tranformation 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).

Representative References

L. Dreesen, C. Humbert, Y. Sartenaer, Y. Caudano, C. Volcke, A.A. Mani, A. Peremans, P. Thiry, S. Hanique, J.-M. Frère. *Electronic and molecular properties of an adsorbed protein monolayer probed by two-color sum-frequency generation spectroscopy.* Langmuir 20, 7201-7207, **2004**.

L. Dreesen, Y. Sartenaer, C. Humbert, A.A. Mani, C. Méthivier, C.-M. Pradier, P. Thiry, A. Peremans. *Probing ligand-protein recognition with sum-frequency generation spectroscopy: the avidin-biocytin case*. ChemPhysChem 5, 1719–1725, **2004**.

C. Volcke, P. Simonis, P. Thiry, Ph. Lambin, C. Culot, C. Humbert. *Highlighting functional groups in self-assembled overlayers with specific functionalised scanning tunnelling microscopy tips*. Nanotechnology 16, 11, 2596–2600, **2005**.

C. Volcke, S. Pirotton, C. Grandfils, C. Humbert, P. Thiry, I. Ydens, P. Dubois, M. Raes. *Influence of DNA condensation state on transfection efficiency in DNA/polymer complexes : an AFM and DLS comparative study*. J. of Biotechnology 125, 11-21, **2006**.

C. Humbert, I. Dreesen, Y. Sartenaer, A. Peremans, P. Thiry, C. Volcke. *On the protoporphyrin monolayers conformation*. ChemPhysChem 7, 569–571, **2006**.

G. Tourillon, L. Dreesen, C. Volcke, Y. Sartenaer, P. Thiry, A. Peremans. *Total internal reflection sum-frequency generation spectroscopy and dense gold nanoparticles monolayer: a route for probing adsorbed molecules.* Nanotechnology 18, 415301-415308, **2007**.

Y. Sartenaer, G. Tourillon, L. Dreesen, D. Lis, A.A. Mani, P. Thiry, A. Peremans. *Sum-Frequency Generation Spectroscopy of DNA Monolayers.* Biosensors and Bioelectronics 22, 2179-2183, **2007**.

D. Lis, A. Peremans, Y. Sartenaer, Y. Caudano, A.A. Mani, I. Dreesen, P. Thiry, J. Guthmuller, B. Champagne, F. Cecchet. *Self-Assembled Film Organization in Fast Microcontact Printing Investigated by Sum Frequency Generation Spectroscopy.* J. Phys. Chem. C, doi: 10.1021/jp900217d, **2009**.

Patents

A. Peremans, A. A. Mani, P. A. Thiry (inventors). *Device and process for mode-locking a laser.* United States Patent 6928090, issued on August 9, **2005**.

Awards

Economics price of the Namur Province, **1999**.

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 µm) 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 (flavanoïds 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…

Representative References

- S. Bailly, V. Jerkovic, J. Marchand-Brynaert, S. Collin. *Aroma extraction dilution analysis of Sauternes wines; key role of polyfunctional thiols.* J. Agric. Food Chem. 54, 7227-7234, **2006**.
- C. Vermeulen, I. Lejeune, T. T. H. Tran, S. Collin. *Occurence of polyfunctional thiols in fresh lager beers.* J. Agric. Food Chem. 54, 5061-5068, **2006**.
- C. Counet, D. Callemien, S. Collin. *Chocolate and cocoa : new sources of trans-resveratrol and trans-piceid.* Food Chemistry 98, 649-657, **2006**.
- V. Jerkovic, S. Collin. *Fate of resveratrol and piceid through different hop precessing and storage times.* J. Agric. Food Chem. 56, 584-590, **2008**.
- D. Callemien, S. Guyot, S. Collin. *Use of thiolysis hyphenated to RP-HPLC-ESI(-)-MS/MS for analysis of flavanoids in fresh lager beers.* Food Chem. 110, 1012-1018, **2008**.

Awards

- G. Lermusieau. *Interbrew Baillet Latour award,* **1998**.
- C. Counet. *VABA award,* **2002**.
- D. Callemien. *VABA award,* **2002**.
- D. Callemien. *Interbrew Baillet Latour award,* **2002**.
- 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 quanti- fication 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 :

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- 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-, $-SiR_3$, $-PO(OH)_2$…) 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 functionnalisation for toxicity evaluation
- Electrografting for biocompatibilisation

Representative References

- G. Philippin, J. Delhalle, Z. Mekhalif. *Comparative study of the monolayers of CH_3-(CH_2)n-$SiCl_3$ and CH_3-(CH_2)n-$PO(OH)_2$, n= 4 and 13, adsorbed on polycrystalline titanium substrates.* Applied Surface Science, 212-213, 530-536, **2003**.
- C. Arnould, J. Delhalle, Z. Mekhalif. *Multifunctional hybrid coating on titanium towards hydroxyapatite growth : electrodeposition of tantalum and its molecular functionalization with organophosphonic acid films.* Electrochimica Acta, 53, 5632- 5638, **2008**.
- I. Minet, J. Delhalle, L. Hevesi, Z. Mekhalif. *Surface initiated ATRP of PMMA, PS and diblock PS-b-PMMA copolymers from stainless steel modified by 11-(2-bromoisobutyrate)-undecyl-1-phosphonic acid.* Journal of Colloid and Interface Science, 332, 317-326, **2009**.
- D. Aubry, C. Volcke, C. Arnould, C. Humbert, P. Thiry, J. Delhalle, Z. Mekhalif. *Molecular functionalisation of tantalum oxide sur-*

face towards development of apatite growth. Applied Surface Science, 255, 4765-4772, **2009**.

- C. Arnould, C. Volcke, C. Lamarque, P.-A. Thiry, J. Delhalle, Z. Mekhalif. *Titanium modified with layer-by-layer sol-gel tantalum oxide and an organodiphosphonic acid : A coating for hydroxyapaptite growth.* Journal of Colloid and Interface Science, 336, 497 – 503, **2009**.
- J.-P. Piret, S. Detriche, R. Vigneron, S. Vankoningsloo, S. Rolin, J.H. Mejia Mendoza, B. Masereel, S. Lucas , J. Delhalle, F. Luizi, C. Saout, O. Toussaint. *Dispersion of multi-walled carbon nanotubes in biocompatible dipersants.* Journal of Nanoparticle Research, to appear.
- C. Arnould, J. Delhalle, Z. Mekhalif. *Fabrication of 2D ordered Ta2O5 films on a titanium substrate by electrodeposition of Ta from ionic liquid through a polystyrene template.* Journal of the Electrochemical Society, to appear.
- S. Devillers, N. Cuvelier, J. Delhalle, Z. Mekhalif. *Grafting PEG fragments on Phynox® substrates modified with 11-phosphoundecanoic acid.* Journal of the Electrochemical Society, to appear.

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

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- 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 semiconducting, 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

- X. Tang, F. Blondeau, P.-P. Prévot, R. Pampin, E. Godfroid, A. M. Jonas, B. Nysten, S. Demoustier-Champagne, V. Bayot. *Direct Protein Detection with a Nano-Interdigitated Array Gate MOSFET, Biosensors Bioelectron.* In press, **2009**.
- K. Glinel, A. M. Jonas, T. Jouenne, J. Leprince, L. Galas, W. T. S. Huck. *Antibacterial and Antifouling Polymer Brushes Incorporating Antimicrobial Peptide.* Bioconjugate Chem. 20, 71-7, **2009**.
- 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**.
- Z. Hu, B. Muls, L. Gence, D. A. Serban, J. Hofkens, S. Melinte, B. Nysten, S. Demoustier-Champagne, A. M. Jonas. *High-Throughput Fabrication of Organic Nanowire Devices with Preferential Internal Alignment and Improved Performance.* Nano Letters 7, 3639-44, **2007**.
- F. Cecchet, A.-S. Duwez, S. Gabriel, C. Jérôme, R. Jérôme, K. Glinel, S. Demoustier-Champagne, A. M. Jonas, B. Nysten. *Atomic Force Microscopy Investigation of the Morphology and the Biological Activity of Protein-Modified Surfaces for Bio- and Immunosensors.* Anal. Chem. 79, 6488-95, **2007**.
- F. Cecchet, B. De Meersman, S. Demoustier-Champagne, B. Nysten, A. M. Jonas. *One Step Growth of Anti-fouling Surfaces: Self-Assembled Monolayers of Poly (ethylene oxide) (PEO) derivatives on Oxidized Silicon Surfaces or on Hydrogen-Passivated Silicon Surfaces.* Langmuir 22, 1173-81, **2006**.

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 balance 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.

Representative references and patents

- D. Dochain. *Bioprocess Control.* ISTE, London, **2008**.
- J. Harmand, A. Rapaport, D. Dochain, C. Lobry. *Microbial ecology and bioprocess control : opportunities and challenges.* Journal of Process Control 18, 865-875, **2008**.
- A. K. Drame, D. Dochain, J.-J. Winkin. *Asymptotic behaviour and stability for solutions of a biochemical reactor distributed parameter model.* IEEE Trans. Aut. Control, 53 (1), 412-416, **2008**.
- M. Guay, D. Dochain, M. Perrier, N. Hudon. *Flatness-Based Extremum Seeking Control Over Periodic Orbits.* IEEE Trans. Aut. Control 52 (10), 2005-2012, **2007**.
- L. Bodizs, M. Titica, N. Faria, B. Srinivasan, D. Dochain, D. Bonvin. *Oxygen Control for an Industrial Pilot-scale Fed-batch Filamentous Fungal Fermentation.* Journal of Process Control 17, 595-606, **2007**.

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. Pauss, 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 polyadenlation/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'Elevage. 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).

Representative References

- G. Leyens, B. Verhaeghe, M. Landmeters, J. Marchandise, B. Knoops, I. Donnay. *Peroxiredoxin 6 is upregulated in bovine oocytes and cumulus cells during in vitro maturation : role of intercellular communication.* Biol Reprod 71, 1646-1651, **2004**.
- J.-M. Traverso, I. Donnay, A. S. Lequarre. *Effect of polyadenylation inhibition of meiosis progression in relation to the polyadenylation status of cyclins A2 and B1 during in vitro maturation of bovine oocytes.* Mol Reprod Dev, 107-114, **2005**.
- F. George, M. Vrancken, B. Verhaeghe, F. Verhoeye, Y. J. Schneider, A. Massip, I. Donnay. *Freezing of in vitro produced bovine embryos in animal protein-free medium containing vegetal peptones.* Theriogenology 66, 1381-1390, **2006**.
- I. Donnay, B. Knoops. *Peroxiredoxins in gametogenesis and embryo development. In: Peroxiredoxin Systems: Structures and Functions.* J.R. Harris and L. Flohé Eds, Springer Verlag, New York, pp. 345-355, **2007**.
- M. Alomar, H. Tasiaux, S. Remacle, F. George, D. Paul, I. Donnay. *Kinetics of fertilization and development and sex ratio of bovine embryos produced using the semen of different bulls.* Anim Reprod Sci 107, 48-61, **2008**.
- F. George, D. Kerschen, A. Van Nuffel, J.-F. Rees, I. Donnay. *Plant protein hydrolysates (plant peptones) as substitutes for animal proteins in embryo culture medium.* Reprod Fert Dev 21, 587-598, **2009**.

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'Elevage (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 :

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- 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.

Representative References

- J. Donnez, M.-M. Dolmans, D. Demylle, P. Jadoul, C. Pirard, J. Squifflet, B. Martinez-Madrid, A. Van Langendonckt. *Livebirth after orthotopic transplantation of cryopreserved ovarian tissue.* Lancet 364, 1405-10, **2004**.
- M.-M. Dolmans, N. Michaux, A. Camboni, B. Martinez-Madrid, A. Van Langendonckt, S. A. Nottola, J. Donnez. *Evaluation of Liberase, a purified enzyme blend, for the isolation of human primordial and primary ovarian follicles.* Human Reproduction 21, 431-420, **2006**.
- M.-M. Dolmans, B. Martinez-Madrid, E. Gadisseux, Y. Guiot, Y. Y. Wu, A. Torre, A. Camboni, A. Van Langendonckt, J. Donnez. *Short-term transplantation of isolated human ovarian follicles and cortical tissue into nude mice.* Reproduction 134, 253-262, **2007**.
- M.-M. Dolmans, Y. Y. Wu, A. Camboni, A. Torre, A. Van Langendonckt, B. Martinez-Madrid, J. Donnez. *Isolated human primordial follicles can develop to the antral stage after xenografting to SCID mice.* Reproductive Biomedicine Online 16,705-711, **2008**.
- 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 Apllication 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**.
- C. Nonckreman, P. G. Rouxhet, Chr. Dupont-Gillain. *Dual radiolabeling to study protein adsorption competition in relation with hemocompatibility.* J. Biomed. Mater. Res. Part A, 81, 791-802, **2007**.
- D. Alsteens, E. Dague, P. G. Rouxhet, A. R. Baulard, Y. Dufrêne. *Direct measurement of hydrophobic forces on cell surfaces using AFM.* Langmuir 23, 11977-11979, **2007**.
- 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**.
- M.-J. Genet, Chr. Dupont-Gillain, P. G. Rouxhet. *XPS analysis of biosystems and biomaterials.* In "Medical applications of Colloids" (E. Matijevic, ed.), Springer Science, ch. 5, 177-307, **2008**.
- E. Dague, A. Delcorte, J.-P. Latge, Y. Dufrêne. *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 physicochemical processes.* Electrochim. Acta 54, 116-122, **2008**.
- K. M. Mc Evoy, M.-J. Genet, Chr. Dupont-Gillain. *Principal component analysis: a versatile method for processing and investigation of XPS spectra.* Anal. Chem. 80, 7226-7238, **2008**.

Patents

- J.-L. Dewez, J.-B. Lhoest, E. Detrait, P. G. Rouxhet, P. Bertrand, Ph. Van Den Bosch De Aguilar. *Biomaterial and method for obtaining it.* U.S. Patent 5, 962, 136, **1999**.
- 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 :

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- 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 bacteries grafted on the chip and compatible with the specific detection of less than 100 bacteries.

Finally, optical measurements in microfluidic platforms are targeted.

Representative References

- L. Moreno-Hagelsieb, B. Foultier, G. Laurent, R. Pampin, J. Remacle, J.-P. Raskin, D. Flandre. *Electrical detection of DNA hybridization : Three extraction techniques based on interdigitated Al/Al2O3 capacitors.* Biosensors & Bioelectronics, 22 (9-10) : 2199-2207, **2007**.
- 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

- D. Flandre (BE), L. Moreno-Hagelsieb (MX), R. Pampin (FR), D. Bourgeois (BE), J. Remacle (BE), P.-E. Lobert (FR). *Method and device for high sensitivity detection of the presence of DNA and other probes.* US2005227373, **2005**.
- R. Pampin (FR), D. Flandre (BE), L. Moreno-Hagelsieb (MX), B. Foultier (FR), J. Remacle (BE). *Insulated Substrate Impedance Transducers.* EP06018835.6, **2006**.

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^2) 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 :

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- 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 biocompatible films to improve their performance in vivo and their biocompatibility.

Applications of MR (EPR and NMR) to characterize the microenvironment in tumors and modulate the response to anticancer treatments
Use of combination therapies against cancer (vasoactive agents + radiotherapy / antiangiogenesis + radiotherapy / …) to improve the response of tumors to treatments : characterisation of pO2, flow, oxygen consumption, permeability of vessels, nitric oxide … and correlation with the tumor growth.

Development of predictive biomarkers of tumor response to a treatment
NMR spectroscopy in vivo, diffusion imaging, contrast agents targeted to cell death…

Representative References

- B. Gallez, C. Baudelet, B. Jordan. *Assessment of tumor oxygenation by EPR oximetry : Principles and applications.* NMR Biomed.17, 240-262, **2004**.
- 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**.
- B. Jordan, N. Christian, N. Crokart, V. Grégoire, O. Feron, B. Gallez. *Thyroid status is a key modulator of tumor sensitivity to irradiation : Determination of the underlying metabolic causes.* Radiat. Res. 168, 428-432, **2007**.
- G. O. Cron, N. Beghein, R. Ansiaux, P. Martinive, O. Feron, B. Gallez. *^{19}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 ^{19}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 (pO2 measurements by fluorescence quenching)
- OxyFlo (laser-doppler)

Products and Services

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

KEY WORDS FOR R&D

Angiogenesis
Biocompatibility
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 Assitance 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 fist 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 craniomaxillofacial 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.

Representative References

- R. Olszewski, F. Zech, G. Cosnard, V. Nicolas, B. Macq, H. Reychler. « *Three-dimensional computed tomography cephalometric craniofacial analysis: experimental validation in vitro.* » Int. Journal Oral Maxillofacial Surg. 36(9) : 828-33, Sep **2007**.
- 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**.
- R. Olszewski, H. Reychler, G. Cosnard, J.-M. Denis, S. Vynckier, F. Zech. « *Accuracy of threedimensional (3D) craniofacial cephalo-metric landmarks on a low-dose 3D computed tomograph.* » Dentomaxillofac Radiol. 37(5) : 261-7, Jul **2008**.
- 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.

Representative References

- E. I. Christensen, O. Devuyst, G. Dom, R. Nielsen, P. Van Der Smissen, P. Verroust, M. Leruth, W. B. Guggino, P.-J. Courtoy. *Loss of chloride channel ClC-5 impairs endocytosis by defective trafficking of megalin and cubilin in kidney proximal tubules.* Proc. Natl. Acad. Sci. USA 100, 8472-8477, **2003**.
- C. Galant, M. Berliere, D. Dubois, A.-C. Verougstraete, P. Lemoine, I. Kokorine, Y. Eeckhout, P.-J. Courtoy, E. Marbaix. *Focal expression and final activity of matrix metalloproteinases may explain irregular dysfunctional endometrial bleeding.* Am. J. Pathol. 165, 83-94, **2004**.
- M. Mettlen, A. Platek, P. Van Der Smissen, S. Carpentier, M. Amyere, L. Lanzetti, Ph. De Diesbach, D. Tyteca, P.-J. Courtoy. *Src triggers circular ruffling and macropinocytosis at the apical surface of polarized MDCK cells.* Traffic 7, 589-603, **2006**.
- M.-F. Van Den Hove, K. Croizet-Berger, D. Tyteca, Ph. De Diesbach, P.-J. Courtoy. *TSH activates GDP/GTP exchange on the rate-limiting endocytic catalyst, Rab5a, in human thyrocytes in vivo and in vitro.* J. Clin. Endocrinol. Metab. 92, 2803-2810, **2007**.
- C. M. Pretto, H. P. Gaide Chevronnay, P. B. Cornet, C. Galant, D. Delvaux, P.-J. Courtoy, E. Marbaix, P. Henriet. *Production of interleukin-1alpha by human endometrial stromal cells is triggered during menses and dysfunctional bleeding and is induced in culture by epithelial interleukin-1alpha released upon ovarian steroids withdrawal.* J. Clin. Endocrinol. Metab. 93, 4126-4134, **2008**.
- C. Selvais, H. P. Gaide Chevronnay, P. Lemoine, S. Dedieu, P. Henriet, P.-J. Courtoy, E. Marbaix, H. Emonard. *Metalloproteinase-dependent shedding of LRP-1 ectodomain decreases endocytic clearance of endometrial MMP-2 and -9 at menstruation and during dysfunctional bleeding episodes.* Endocrinology, in press, **2009**.

Patent

I. Camby, P. Henriet, F. Lefranc, P.-J. Courtoy, R. Kiss. *Use of galectin-1-targeted RNAi-based approach for the treatment of glioma.* United States Patent, US60/670,334, granted 05/09/**2005**.

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
- Scienfific 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

- P. Kienlen-Campard, S. Miolet, B. Tasiaux, J.-N. Octave. *Intracellular amyloid-beta 1-42, but not extracellular soluble amyloid-beta peptides, induces neuronal apoptosis.* J. Biol. Chem. 277, 15666-70, **2002**.
- C. Vermeiren, N. Najimi, J.-M. Maloteaux, E. Hermans. *Molecular and functional characterisation of glutamate transporters in rat cortical astrocytes exposed to a defined combination of growth factors during in vitro differentiation.* Neurochem. Int. 46, 137-147, **2005**.
- C. Vermeiren, N. Najimi, N. Vanhoutte, S.Tilleux, I. De Hemptinne, J.-M. Maloteaux, E. Hermans. *Acute upregulation of glutamate uptake mediated by mGluR5 in reactive astrocytes.* J. Neurochem. 94, 405-416, **2005**.
- N. Pierrot, S. F. Santos, C. Feyt, M. Morel, J.-P. Brion, J.-N. Octave. *Calcium-mediated transient phosphorylation of tau and amyloid precursor protein followed by intraneuronal amyloid-beta accumulation.* J. Biol. Chem. 281, 39907-14, **2006**.
- S. Tilleux, J.-V. Berger, E. Hermans. *Induction of astrogliosis by activated microglia is associated with a down regulation of metabotropic glutamate receptor 5.* J. Neuroimmunol. 189, 23-30, **2007**.
- P. Kienlen-Campard, B. Tasiaux, J. Van Hees, M. Li, S. Huysseune, T. Sato, J. Z. Fei, S. Aimoto, P.-J. Courtoy, S. O. Smith, S. N. Constantinescu, J.-N. Octave. *Amyloidogenic processing but not amyloid precursor protein (APP) intracellular C-terminal domain production requires a precisely oriented APP dimer assembled by transmembrane GXXXG motifs.* J Biol Chem. 283, 7733-44, **2008**.
- 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**.
- S. F. Santos, N. Pierrot, N. Morel, P. Gailly, C. Sindic, J.-N. Octave. *Expression of human amyloid precursor protein in rat cortical neurons inhibits calcium oscillations.* J Neurosci. 29, 4708-18, **2009**.

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

- C. Evrard, A. Capron, C. Marchand, A. Clippe, R. Wattiez, P. Soumillion, B. Knoops, J.-P. Declercq. *Crystal structure of a dimeric oxidized form of human peroxiredoxin 5.* Journal of Molecular Biology, 337 : 1079-1090, **2004**.
- M. Dubuisson, D. Vander Stricht, A. Clippe, F. Etienne, T. Nauser, R. Kissner, W. H. Koppenol, J.-Fr. Rees, B. Knoops. *Human peroxiredoxin 5 is a peroxynitrite reductase.* FEBS Letters, 571 : 161-165, **2004**.
- I. Banmeyer, C. Marchand, A. Clippe. B. Knoops. *Human mitochondrial peroxiredoxin 5 protects from mitochondrial DNA damages induced by hydrogen peroxide.* FEBS Letters, 579 : 2327-2333, **2005**.
- A. Smeets, C. Evrard, M. Landtmeters, C. Marchand, B. Knoops. J.-P. Declercq. *Crystal structures of oxidized and reduced forms of human mitochondrial thioredoxin 2.* Protein Science, 14 : 2610-2621, **2005**.
- M. Trujillo, A. Clippe, B. Manta, G. Ferrer-Sueta, A. Smeets, J.-P. Declercq, B. Knoops. R. Radi. *Pre-steady state kinetic characterization of human peroxiredoxin 5: taking advantage of Trp 84 fluorescence increase upon oxidation.* Archives of Biochemistry and Biophysics, 467: 95-106, **2007**.
- B. Knoops, E. Loumaye. V. Van Der Eecken. *Evolution of the peroxiredoxins (taxonomy / homology / characterization).* In "Peroxiredoxin Systems : Structures and Functions", J. R. Harris & L. Flohé (Eds.). Springer. Subcell. Biochem. 44 : 27-40, **2007**.
- 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**.
- S. De Simoni, J. Goemaere. B. Knoops. *Silencing of peroxiredoxin 3 and peroxiredoxin 5 reveals the role of mitochondrial peroxiredoxins in the protection of human SH-SY5Y cells toward MPP+.* Neuroscience Letters, 433 : 219-224, **2008**.

Patents

B. Knoops, C. Hermans, A. Bernard, R. Wattiez, P. Falmagne. *Peroxisome-associated polypeptide, nucleotide sequence encoding said polypeptide and their uses in the diagnosis and/or the treatment of lung injuries and diseases, and of oxidative stress-related disorders.* WO9909054, **1999**.

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

- R. Jans, G. Atanasova, M. Jadot, Y. Poumay. *Cholesterol depletion upregulates involucrin expression in epidermal keratinocytes through activation of p38.* J. Invest. Dermatol. 123, 564-573, **2004**.
- G. Atanasova, R. Jans, N. Zhelev, V. Mitev, Y. Poumay. *Effects of the cyclin-dependent kinase inhibitor CYC202 (R-roscovitine) on the physiology of cultured human keratinocytes.* Biochem. Pharmacol. 70, 824-836, **2005**.
- E. Nikolova, V. Mitev, F. Minner, C. Deroanne, Y. Poumay. *The inhibition of the expression of the small Rho GTPase Rac1 induces differentiation with no effect on cell proliferation in growing human adult keratinocytes.* J. Cell. Biochem. 103, 857-864, **2008**.
- C. Mathay, S. Giltaire, F. Minner, E. Bera, M. Herin, Y. Poumay. *Heparin-binding EGF-like growth factor is induced by disruption of lipid rafts and oxidative stress in keratinocytes and participates in the epidermal response to cutaneous wounds.* J. Invest. Dermatol. 128, 717-727, **2008**.
- S. Lambert, H. Ameels, R. Gniadecki, M. Herin, Y. Poumay. *Internalization of EGF receptor following lipid rafts disruption in keratinocytes is delayed and dependent on p38 MAPK activation.* J. Cell. Physiol. 217, 834-845, **2008**.
- S. Giltaire, F. Herphelin, A. Frankart, M. Herin, P. Stoppie, Y. Poumay. *The CYP26 iinhibitor R115866 potentiates the effects of all-trans retinoic acid on cultured human epidermal keratinocytes.* Br. J. Dermatol. 160, 505-513, **2009**.

Funding

FRFC

Partnership

- Barrier Therapeutics, Geel, Belgium
- R. Gniadecki, 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 metabolization and transepidermal passage of dedicated compounds.

Representative References

- A. Coquette, N. Berna, A. Vandenbosch, M. Rosdy, B. De Wever, Y. Poumay. *Analysis of interleukin-1alpha and interleukin-8 expression and release in in vitro reconstructed human epidermis for the prediction of in vivo skin irritation and/or sensitization.* Toxicol. In Vitro 17, 311-321, **2003**.
- Y. Poumay, F. Dupont, S. Marcoux, M. Leclercq-Smekens, M. Herin, A. Coquette. *A simple reconstructed human epidermis: preparation of the culture model and utilization in in vitro studies.* Arch. Derm. Res. 296, 203-211, **2004**.
- Y. Poumay, A. Coquette. *Modelling the human epidermis in vitro: tools for basic and applied research.* Arch. Derm. Res. 298, 361-369, **2007**.
- A. Coquette, Y. Poumay. *The reconstructed human epidermis models in fundamental research. In Fundamentals of tissue engineering and regenerative medicine.* (Meyer et al., eds) pp. 967-976, Springer Berlin, **2009**.

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 olinucleotidic regulatory sequence, including several transcription factors and co-activators (manuscript in preparation).

Representative References

Th. Arnould, S. Vankoningsloo, P. Renard, A. Houbion, N. Ninane, C. Demazy, J. Remacle, M. Raes. *CREB activation induced by mitochondrial dysfunction is a new signaling pathway that impairs cell proliferation.* EMBO J. Jan 15; 21(1-2) : 53-63, **2002**.

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 Ca2+-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 PPARg-independent mechanism while TNFa-induced dedifferentiation is PPARg-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 parastism 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 parastism 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-ß1, 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

- De Magalhães, Costa, Toussaint. *HAGR : The Human Ageing Genomic Resources.* Nucl. Acid Res. 33, D537-D543, **2005**.
- 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-ß1 signaling pathway.* J. Cell. Sci. 118, 743-758, **2005**.
- Pascal, Debacq-Chainiaux, Chrétien, Bastin, Dabee, Bertholet, Remacle, Toussaint. *Comparison of replicative senescence and stress-induced premature senescence combining differential display and low-density DNA arrays.* FEBS Lett. 579, 3651-3659, **2005**.
- Zdanov, Debacq-Chainiaux, Remacle, Toussaint. *Identification of p38MAPK-dependent Genes Involved in H2O2-induced Premature Senescence of IMR-90 hTERT Human Fibroblasts.* FEBS Lett. 580, 6455-6463, **2006**.
- Zdanov, Bernard, Debacq-Chainiaux, Martien, Gosselin, Vercamer, Chelli, Toussaint, Abbadie. *Normal or stress-induced fibroblast senescence involves COX-2 activity.* Exp. Cell. Res. 313, 3046-56, **2007**.
- Borlon, Godard, Eskes, Hartung, Zuang, Toussaint. *The usefulness of toxicogenomics for predicting acute skin irritation on in vitro reconstructed human epidermis.* Toxicology 242, 157-66, **2007**.
- Debacq-Chainiaux, Pascal, Boilan, Bastin, Bauwens, Toussaint. *Screening of senescence associated genes with specific DNA array reveals the role of IGFBP-3 in premature senescence of human diploid fibroblasts.* Free Radicals BiolMed. 44, 1817-1832, + Suppl. Mat., **2008**.
- Chrétien, Dierick, Delaive, Larsen, Dieu, Raes, Deroanne, Roepstorff, Toussaint. *Role of TGF-ß1-independent changes in protein neosynthesis, p38alphaMAPK and cdc42 in hydrogen peroxide-induced senescence-like morphogenesis.* Free Radicals Biol. Med. 44, 1732-1751, + Suppl. Mat., **2008**.

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 Nanotoxico in collaboration with S. Lucas (FUNDP) and B. Masereel (FUNDP).
- 2 projects Marshall plan : Walnut-20 (20 partners) and Silicalloy (8 partners).

Main Equipment

- Cell biology facility (including a fully automated low O2 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 probants
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

- J.-Y. Matroule, H. Lam, D. T. Burnette, C. Jacobs-Wagner. *Cytokinesis monitoring during development; rapid pole-to-pole shuttling of a signaling protein by localized kinase and phosphatase in* Caulobacter. Cell 118, 579-90, **2004**.
- A. Dricot, J.-F. Rual, P. Lamesch, N. Bertin, D. Dupuy, T. Hao, C. Lambert, R. Hallez, J.-M. Delroisse, J. Vandenhaute, I. Lopez-Goñi, I. Moriyon, J.-M. Garcia-Lobo, F. J. Sangari, A. P. Macmillan, S. J. Cutler, A. M. Whatmore, S. Bozak, R. Sequerra, L. Doucette-Stamm, M. Vidal, D. E. Hill, J.-J. Letesson, X. De Bolle. *Generation of the* Brucella melitensis *ORFeome version 1.1*. Genome Res. 14, 2201-2206, **2004**.
- 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. Lestrate, R.-M. Delrue, I. Danese, J. Vandenhaute, A. Tibor, X. De Bolle, J.-J. Letesson. *The sheated flagellum of* Brucella melitensis *is involved in persistence in a murine model of infection*. Cell. Microbiol. 7, 687-698, **2005**.
- R.-M. Delrue, C. Deschamps, S. Léonard, C. Nijskens, I. Danese, J.-M. Schaus, S. Bonnot, J. Ferooz, A. Tibor, X. De Bolle, J.-J. Letesson. *A quorum sensing regulator controls expression of both the type fous secretion system and the flagellar apparatus of* Brucella melitensis. Cell. Microbiol. 7, 1151-1161, **2005**.
- M. Dozot, R.-A. Boigegrain, R.-M. Delrue, R. Hallez, S. Ouahrani-Bettache, I. Danese, J.-J. Letesson, X. De Bolle, S. Köhler. *The stringent response mediator Rsh is required for* Brucella *spp. virulence, and regulates expression of the type IV secretion system VirB*. Cell. Microbiol. 8, 1791-1802, **2006**.
- R. Hallez, J. Mignolet, V. Van Mullem, M. Wery, J. Vandenhaute, 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).

Representative References

- P. Hols, F. Hancy, L. Fontaine, B. Grossiord, D. Prozzi, N. Leblond-Bourget, B. Decaris, A. Bolotin, C. Delorme, S. D. Ehrlich, E. Guédon, V. Monnet, P. Renault, M. Kleerebezem. *New insights in the molecular biology and physiology of Streptococcus thermophilus revealed by comparative genomics.* FEMS Microbiol. Rev. 29, 453-463; **2005**.
- C. Grangette, S. Nutten, E. Palumbo, S. Morath, C. Hermann, J. Dewulf, B. Pot, T. Hartung, P. Hols, A. Mercenier. *Enhanced anti-inflamatory capacity of a Lactobacillus plantarum mutant synthesizing modified teichoic acids.* Proc. Natl. Acad. Sci. USA. 102, 10321-10326, **2005**.
- P. Goffin, M. Deghorain, J.-L. Mainardi, I. Tytgat, M.-C. Champomier-Verges, M. Kleerebezem, P. Hols. *Lactate racemization as a rescue pathway for supplying D-lactate to the cell wall biosynthesis machinery in Lactobacillus plantarum.* J. Bacteriol. 187, 6750-6761, **2005**.
- S. De Keersmaecker, K. Braeken, T. Verhoeven, M. Vélez, S. Lebeer, J. Vanderleyden, P. Hols. *Tagging of the probiotic strain Lactobacillus rhamnosus GG with the green fluorescent protein using an optimized electroporation protocol.* Appl. Environ. Microbiol. 72, 4923-4930, **2006**.
- V. Ladero, A. Ramos, A. Wiersma, P. Goffin, A. Schanck, M. Kleerebezem, J. Hugenholtz, E. Smid, P. Hols. *High-level production of the low-calorie sugar sorbitol by Lactobacillus plantarum through metabolic engineering.* Appl. Environ. Microbiol. 73, 1864-1872, **2007**.
- Y. Gilbert, M. Deghorain, L. Wang, B. Xu, P. Pollheimer, H. Gruber, J. Errington, B. Hallet, X. Haulot, C. Verbelen, P. Hols, Y. Dufrêne. *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**.
- C. Nicaise, D. Prozzi, E. Viaene, C. Moreno, T. Gustot, E. Quertinmont, P. Demetter, V. Suain, P. Goffin, J. Devière, P. Hols. *Control of acute, chronic and constitutive hyperammonemia by wild-type and gentically engineered Lactobacillus plantarum in rodens.* Hepatology 48, 1184-1192, **2008**.

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

- S. Burteau, P. Bogaerts, R. de Mendonca, L. Irenge, C. Berhin, J. Hiffe, N. de San, S. Hamels, Y. Glupczynski, M. Struelens, J.-L. Gala, J. Remacle. *Design and validation of a low density array (Nosochip) for the detection of the main pathogenic bacteria and fungi responsible for nosocomial pneumonia.* Eur J. Clin Microbiol Infect Dis. 27(1) : 17-27, Jan **2008**.
- 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 7th 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.* 26th 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.

Representative References

- Fr. Van Bambeke, Y. Glupczynski, P. Plésiat, J.-C. Pechère, P. M. Tulkens. *Antibiotic efflux pumps in prokaryotic cells: occurence, impact on resistance and strategies for the future of antimicrobial therapy.* J. Antimicrob. Chemother. 51, 1055-1065, **2003**.
- 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. Glupczynsk, 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**.
- L. Avrain, M. Garvey, N. Mesaros, Y. Glupczynski, M.-P. Mingeot-Leclercq, L. J. V. Piddock, P. M. Tulkens, R. Vanhoof, Fr. Van Bambeke. *Selection of quinolone resistance in Streptococcus pneumoniae exposed in vitro to sub-inhibitory drug concentrations.* J. Antimicrob. Chemother. 60, 965-972, **2007**.
- 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-blots, 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:

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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.

Representative References

- H. Q. Zheng, L. Camacho, E. Wee, H. Batoko, J. Legen, C. Leaver, R. Malho, P. Hussey, I. Moore. *A Rab-E GTPase mutant acts downstream of the Rab-D subclass in biosynthetic membrane traffic to the plasma membrane.* The Plant Cell, 17, 2020-2036, **2005**.
- C. Baroux, R. Blanvillain, H. Betts, H. Batoko, J. Craft, A. Martinez, P. Gallois, I. Moore. *Predictable activation of tissue-specific expression from a single gene locus using the pOP/LhG4 transactivation system in Arabidopsis.* Plant Biotechnology Journal, 3, 91-101, **2005**.
- E. Zelazny, J.W. Borst, M. Muylaert, H. Batoko, M.A. Hemminga, F. Chaumont. *FRET imaging in living maize cells reveals that plasma membrane aquaporins interact to regulate their subcellular localization.* PNAS, 104, 12359-12364, **2007**.
- M. Frison, J.L. Parrou, D. Guillaumot, D. Masquelier, J. Francois, F. Chaumont, H. Batoko. *The Arabidopsis thaliana trehalase is a plasma membrane-bound enzyme with extracellular activity.* FEBS Letters, 581, 4010-4016, **2007**.
- D. Guillaumot, S. Guillon, T. Deplanque, C. Vanhee, C. Gumy, D. Masquelier, P. Morsomme, H. Batoko. *The Arabidopsis TSPO-related protein is a stress and abscisic acid-regulated, endoplasmic reticulum-Golgi-localized membrane protein.* The Plant Journal, in press, **2009**.
- 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 :

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- 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 salmons (Salmo salar) that are found in our rivers and to chose 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

J. K. J. Houdt, J. Pinceel, M.-Chr. Flamand, M. Briquet, E. Dupont, F.A.M. Volckaert, P. V. Baret. *Migration barriers protect indigenous brown trout (salmo trutta).populations from introgression with stocked hatchery fish.* Conserv. Genet 6 : 175-191, **2005**.

A. C. Frantz, J. T. Pourtois, M. Heuertz, L. Schley, M.-Chr. Flamand, A. Krier, S. Bertouille, Fr. Chaumont, T. Burke. *Genetic structure and assignment tests demonstrate illegal translocation of red deer (Cervus elaphus) into a continuous population.* Mol Ecol 15:3191-203, **2006**.

S. Bertouille, M.-Chr. Flamand, G. Tavier, Ph. Moës, D. Robe. *La structure de la population influence-t-elle la reproduction chez le cerf ?* Forêt wallonne 92 :47-58, **2008**.

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 :

- Stefan N. CONSTANTINESCU
- 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).

Representative References

- S. N. Constantinescu, T. Keren, W. P. Russ, I. Ubarretxena-Belandia, Y. Malka, K. Kubatzky, D. M. Engelman, H. F. Lodish, Y. I. Henis. *The Epo receptor transmembrane protein modulates complex formation with viral anemic and polycythemic gp55 proteins.* J. Biol. Chem. 278, 43755-43763, **2003**.
- N. Seubert, Y. Royer, J. Staerk, K. F. Kubatzky, V. Moucadel, S. Krishnqkumar, S. O. Smith, S. N. Constantinescu. *Active and inactive orientations of the transmembrane and cytosolic domains of the erythropoietin receptor dimer.* Mol. Cell. 12, 1239-1250, **2003**.
- F. Chiara, S. Bishayee, C. H. Heldin, J. B. Demoulin. *Autoinhibition of the platelet-derived growth factor beta-receptor tyrosine kinase by its C-terminal tail.* J Biol Chem 279:19732-8, **2004**.
- K. F. Kubatzky, W. Liu, K. Goldgraben, C. Simmerling, S. O. Smith, S. N. Constantinescu. *Structural requirements of the extracellular to transmembrane domain junction for erythropoietin receptor function.* J. Biol. Chem. 280, 14844-14854, **2005**.
- Y. Royer, J. Staerk, M. Costuleanu, P. Courtoy, S. N. Constantinescu. *Janus kinases affect thrombopoietin receptor cell surface localization and stability.* J. Biol. Chem. 280, 27251-27261, **2005**.
- J. Staerk, C. Lacout, T. Sato, S. O. Smith, W. Vainchenker, S. N. Constantinescu. *An amphipathic motif at the transmembrane-cytoplasmic junction prevents autonomous activation of the thrombopoietin receptor.* Blood 107, 1864-1871, **2006**.
- Y. Malka, T. Hornakova, Y. Royer, L. Knoops, J.-Chr. Renauld, S. N. Constantinescu, Y. I. Henis. *Ligand-independent homomeric and heteromeric complexes between interleukin-2 or -9 receptor subunits and the gamma chain.* J Biol Chem. 283:33569-77, **2008**.
- T. Hornakova, J. Staerk, Y. Royer, E. Flex, M. Tartaglia, S. N. Constantinescu, L. Knoops, J.-Chr. Renauld. *Acute lymphoblastic leukemia-associated JAK1 mutants activate the Janus kinase/STAT pathway via interleukin-9 receptor alpha homodimers.* J Biol Chem. 284:6773-81, **2009**.

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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Kidney Diseases, Dialysis, Transplantation

SENIOR SCIENTISTS :

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- 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

- A. Persu, M.-S. Stoenoiu, T. Messiaen, S. Davila, C. Robino, O. El-Khattabi, M. Mourad, S. Horie, R. Wattiez, Y. Pirson, D. Chauveau, X. M. Lens, O. Devuyst. *Modifier effect of ENOS in autosomal dominant polycystic kidney disease*. Hum. Mol. Genet. 11 : 229-241, **2002**.
- 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 ClC-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**.
- F. Jouret, A. Bernard, C. Hermans, G. Dom, S. Terryn, T. Leal, P. Lebecque, J.-J. Cassiman, B. 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**.
- 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**.
- 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**.
- O. Devuyst. *Salt wasting and blood pressure*. Nat. Genet. 40 : 495-496, **2008**.
- S. Biver, S. Belge, S. Bourgeois, P. Van Vooren, M. Nowik, S. Scohy, P. Houillier, 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 rhesus factor.* Nature 456 : 339-343, **2008**.

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

- *Biennal 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**.
- *Biennal 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)
- 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 :

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- 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

J. Giard, P. Rondao Alface, B. Macq. *Fast and accurate travel depth estimation for protein active site prediction.* SPIE Electronic Imaging, San Jose, California, CA, USA, 6812, **2008**.

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 TnpI 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

V. Vanhooff, C. Galloy, H. Agaisse, D. Lereclus, B. Révet, B. Hallet. *Self-control in DNA site-specific recombination mediated by the tyrosine recombinase TnpI.* Mol. Microbiol. 60:617-629, **2006**.

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

Curent 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

- F. Silvestre, J.-F. Dierick, V. Dumont, M. Dieu, M. Raes, P. Devos. *Differential protein expression profiles in anterior gills of Eriocheir sinensis during acclimation to cadmium.* Aquat. Toxicol. 76, 46-58, **2006**.
- F. Silvestre, G. Trausch, 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 **biosensors**. 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**.
- P. Mathonet, H. Barrios, P. Soumillion, J. Fastrez. *Selection of allosteric beta-lactamase mutants featuring an activity regulation by transition metal ions.* Protein Sci., 15, 2335-2343, **2006**.
- A. Fernandez-Gacio, A. Codina, J. Fastrez, O. Riant, 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**.
- P. Minard, A. Urvoas, P. Soumillion. *Protein Engineering Handbook. Chapter 26 : Protein Engineering by Phage display.* S. Lutz & U. Bornscheuer (eds), Wiley-VCH Verlag Gmbh, Weinheim, Germany, pp 563-604, **2008**.

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 PROFUSA : 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): Essaims 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

- E. Zarrinpashneh, K. Carjaval, Chr. Beauloye, A. Ginion, P. Mateo, A.-C. Pouleur, S. Horman, S. Vaulont, J. Hoerter, B. Viollet, L. Hue, J.-L. Vanoverschelde, L. Bertrand. *Role of the alpha2 isoform of AMP-activated protein kinase in the metabolic response of the heart to no-flow ischemia.* Am. J. Physiol. Heart Circ. Physiol. 291, H2875-H2883, **2006**.
- K. Sakamoto, E. Zarrinpashneh, G. R. Budas, A.-C. Pouleur, A. Dutta, A. R. Prescott, J.-L. Vanoverscheld, A. Ashworth, A. Jovanovic, D. R. Alessi, L. Bertrand. *Deficiency of LKB1 in heart prevents ischemia-mediated activation of AMPKalpha2 but not AMPKalpha1.* Am. J. Physiol. Endocrinol. Metab. 290, E780-E788, **2006**.
- D. Vancraeynest, X. Havaux, A.-C. Pouleur, A. Pasquet, B. Gerber, Chr. Beauloye, P. Rafter, L. Bertrand, J.-L. Vanoverschelde. *Myocardial 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**.
- S. Jacquet, E. Zarrinpashneh, A. Chavey, A. Ginion, I. Leclerc, B. Viollet, G. A. Rutter, L. Bertrand, M. S. Marber. *The relationship between p38 mitogen-activated protein kinase and AMP-activated protein kinase during myocardial ischemia.* Cardiovasc. Res. 76, 465-472, **2007**.
- V. Roelants, D. Labar, C. De Meester, X. Havaux, A. Tabilio, S. S. Gambhir, M. Di Ianni, A. Bol, L. Bertrand, J.-L. Vanoverschelde. *Comparison between Adenoviral and Retroviral Vectors for the Transduction of the Thymidine Kinase PET Reporter Gene in Rat Mesenchymal Stem Cells.* J. Nucl. Med. 49, 1836-1844, **2008**.
- L. Bertrand, S. Horman, Chr. Beauloye, J.-L. Vanoverschelde. *Insulin signalling in the heart.* Cardiovasc. Res. 79, 238-248, **2008**.
- B. Violet, 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 Bischop,* **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 tisue"

Main Equipment

- Human and animal cardiac imaging (standard and high resolution echocardiography, SPECT and µSPECT, PET and µPET, 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 scientillation analyzers, multimodal imaging system (chemiluminescence and fluorence) 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**.
- C. Hart, V. Race, Y. Achouri, E. Wiame, M. Sharrard, S. Olpin, J. Watkinson, J. Bonham, J. Jaeken, G. Matthijs, E. Van Schaftingen. *Phosphoserine aminotransferase deficiency : a novel disorder of the serine biosynthesis pathway.* Am. J. Hum. Genet. 80, 931-7, **2007**.
- 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**.
- P. Maliekal, T. Sokolova, D. Vertommen, M. Veiga-da-Cunha, E. Van Schaftingen. *Molecular identification of mammalian phosphopentomutase and glucose-1,6-bisphosphate synthase, two members of the alpha-D-phosphohexomutase family.* J. Biol. Chem. 282, 31844-51, **2007**.
- A. Preumont, K. Snoussi, V. Stroobant, J.-F. Collet, E. Van Schaftingen. *Molecular identification of pseudouridine-metabolizing enzymes.* J. Biol. Chem. 283, 25238-46, **2008**.
- 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 speach 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 knowledge 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

- M. Ghassibe, N. Revencu, B. Bayet, Y. Gillerot, R. Vanwijck, C. Verellen-Dumoulin, M. Vikkula. *Six Families with Van der Woude and/or Popliteal Pterygium Syndrome: all with a mutation in the IRF6 gene.* J. Med. Genet. 41, e15, **2004**.
- M. Ghassibe, B. Bayet, N. Revencu, C. Verellen-Dumoulin, Y. Gillerot, R.Vanwijck, M. Vikkula. *Interferon regulatory factor-6: a gene predisposing to isolated cleft lip with or without cleft palate in the Belgian population.* Eur. J. Hum. Genet. 13, 1239-42, **2005**.
- M. Ghassibe, V. Bernier, L. Boon, M. Vikkula. *A Novel Loss of Function Mutation in the MSX2 Homeobox Gene in a Family with Foramina Parietalia Permagna.* Eur. J. Pediatr. 165, 734-735, **2006**.
- M. Ghassibe, B. Bayet, N. Revencu, L. Desmyter, C. Verellen-Dumoulin, Y. Gillerot, N. Deggouj, R. Vanwijck, M. Vikkula. *Orofacial clefting: update on the role of genetics.* B-ENT. 2, Suppl 4, 20-24, **2006**.
- 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 :

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- 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 ìglomulinî. These mutations derail vascular smooth muscle cell (vSMC) development towards rounded ìglomusî cells.
- A rare inherited form of venous malformations (VMs) (Cutaneomucosal 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 glomulinís 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.

Representative References

- B. A. McIntyre, P. Brouillard, V. Aerts, I. Gutierrez-Roelens, M. Vikkula. *Glomulin is predominantly expressed in vascular smooth muscle cells in the embryonic and adult mouse.* Gene. Expr. Patterns 4, 351-8, **2004**.
- A. Ghalamkarpour, S. Morlot, A. Raas-Rothschild, A. Utkus, J. Mulliken, L. Boon, M. Vikkula. *Hereditary lymphedema type I associated with VEGFR3 mutation : the first de novo case and atypical presentations.* Clin. Genet., 70, 330-335, **2006**.
- P. Brouillard, M. Vikkula. *Genetic causes of vascular malformations.* Hum. Mol. Genet. 16 Spec No. 2:R140-149, **2007**.
- N. Revencu, L. Boon, J. Mulliken, O. Enjolras, M.-R. Cordisco, P. E. Burrows, P. Clapuyt, F. Hammer, J. Dubois, E. Baselga, et al. *Parkes Weber syndrome, vein of Galen aneurysmal malformation, and other fast-flow vascular anomalies are caused by RASA1 mutations.* Hum. Mutat., 29, 959-965 , **2008**.
- N. Limaye, L. Boon, M. Vikkula. *From germline towards somatic mutations in the physiopathology of vascular anomalies.* Hum. Mol. Genet., 18: R65 - R74, **2009**.
- N. Limaye, V. Wouters, M. Uebelhoer, M. Tuominen, R. Wirkkala, J. Mulliken, L. Eklund, L. Boon, M. Vikkula. *Somatic mutations in angiopoietin receptor gene TEK cause solitary and multiple sporadic venous malformations.* Nat. Genet., 41(1) , 118-124, **2009**.
- A. Ghalamkarpour, C. Debauche, E. Haan, N. Van Regemorter, Y. Sznajer, D. Thomas, N. Revencu, Y. Gillerot, L. Boon, M. Vikkula. *Sporadic in utero generalized edema associated with mutations in the lymphangiogenic genes VEGFR3 and FOXC2.* J. Pediatrics., 155(1), 90-93, **2009**.

▸ A. Ghalamkarpour, W. Holnthoner, P. Saharinen, L. Boon, J. Mulliken, K. Alitalo, M. Vikkula. *Recessive primary congenital lymphedema can be caused by a VEGFR3 mutation.* J. Med. Genet., 46(6), 399-404, **2009**.

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, Childrenís 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 :

- Miikka VIKKULA
- Laurence BOON
- 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.

Representative References

- B. Berenguer, J. Mulliken, O. Enjolras, L. Boon, M. Wassef, P. Josset, P. E. Burrows, A.-R. Perez-Atayde, H. P. Kozakewich. *Rapidly involuting congenital hemangioma: clinical and histopathologic features.* Pediatr Dev Pathol, 6(6) : 495-510, **2003**.
- L. Boon, A.-C. Bataille, V. Bernier, C. Vermylen, G. Verellen. *Medical treatment of juvenile hemangiomas.* Ann. Chir. Plast. Esthet., 51(4-5) : 310-20, **2006**.
- A. Dompmartin, L. Boon, D. Labbe. *Infantile hemangiomas: differential diagnosis and associated anomalies.* Ann. Chir. Plast. Esthet., 51(4-5) : 300-9, **2006**.
- M. Jinnin, D. Medici, L. Park, N. Limaye, Y. Liu, E. Boscolo, J. Bischoff, M. Vikkula, E. Boye, B. R. Olsen. *Suppressed NFAT-dependent VEGFR1 expression and constitutive VEGFR2 signaling in infantile hemangioma.* Nat. Med., 14, 1236-1246, **2008**.

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

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

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.

Representative References

- C. Dessy, J. Saliez, P. Ghisdal, G. Daneau, I.I. Lobysheva, F. Frérart, C. Belge, K. Jnaoui, P. Noirhomme, O. Feron, J.-L. Balligand. *Endothelial beta3-adrenoreceptors mediate nitric oxide-dependent vasorelaxation of coronary microvessels in response to the third-generation beta-blocker nebivolol.* Circulation, 112(8) : 1198-205, **2005**.
- E. Sbaa, J. Dewever, P. Martinive, C. Bouzin, F. Frérart, J.-L. Balligand, C. Dessy, O. Feron. *Caveolin plays a central role in endothelial progenitor cell mobilization and homing in SDF-1-driven post-ischemic vasculogenesis.* Circ. Res., 98(9) : 1219-27, **2006**.
- F. Desjardins, B. Sekkali, W. Verreth, M. Pelat, D. De Keyzer, A. Mertens, G. Smith, M.C. Herregods, P. Holvoet, J.-L. Balligand. *Rosuvastatin increases vascular endothelial PPARgamma expression and corrects blood pressure variability in obese dyslipidaemic mice.* Eur. Heart J., (1) : 128-37, **2008**.
- J. Saliez, C. Bouzin, G. Rath, P. Ghisdal, F. Desjardins, R. Rezzani, L.F. Rodella, J. Vriens, B. Nilius, O. Feron, J.-L. Balligand, C. Dessy. *Role of caveolar compartmentation in endothelium-derived hyperpolarizing factor-mediated relaxation: Ca2+ signals and gap junction function are regulated by caveolin in endothelial cells.* Circulation, 117(8) : 1065-74, **2008**.
- F. Desjardins, I. Lobysheva, M. Pelat, B. Gallez, O. Feron, C. Dessy, J.-L. Balligand. *Control of blood pressure variability in caveolin-1-deficient mice: role of nitric oxide identified in vivo through spectral analysis.* Cardiovasc Res., 79(3) : 527-36, **2008**.
- P. Sonveaux, F. Végran, T. Schroeder, M.C. Wergin, J. Verrax, Z.N. Rabbani, C.J. De Saedeleer, K.M. Kennedy, C. Diepart, B.F. Jordan, M.J Kelley, B. Gallez, M.L. Wahl, O. Feron, M.W. Dewhirst. *Targeting lactate-fueled respiration selectively kills hypoxic tumor cells in mice.* J. Clin Invest, 118(12):3930-42, **2008**.
- L. C. Zelarayán, C. Noack, B. Sekkali, J. Kmecova, C. Gehrke, A. Renger, M.P. Zafiriou, R. van der Nagel, R. Dietz, L.J. de Windt, J.-L. Balligand, M.W. Bergmann. *Beta-Catenin downregulation attenuates ischemic cardiac remodeling through enhanced resident precursor cell differentiation.* Proc Natl Acad Sci U S A, 105(50) : 19762-7, **2008**.
- J.-L. Balligand, O. Feron, C. Dessy. *eNOS activation by physical forces: from short-term regulation of contraction to chronic remodeling of cardiovascular tissues.* Physiol Rev., 89(2) : 481-534, **2009**.

Patents

- O. Feron; J.-L. Balligand. *Use of compound or pharmaceutical composition for the prevention and/or the treatment of*

ischemic heart and peripheral vascular diseases, tumour development and for wound healing, n° 99870171.8-2107, **2000**.

- C. Dessy; J.-L. Balligand. *Use of agonists and antagonists of beta-adrenoceptors for treating arterial diseases,* US Provisional Patent Application n° 60/600,093, **2004**.

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. *1st 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. Sollott.
- 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, Universita 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 Pharmaco-Toxicological 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 pharmaco-toxicological research. To this end, two in vitro models has 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

- V. Wauthier, R.K. Verbeeck, P. Buc Calderon. *Age-related changes in the protein and mRNA levels of CYP2E1 and CYP3A isoforms as well as in their hepatic activities in Wistar rats. What role for oxidative stress ?* Arch. Toxicol. 78, 131-138, **2004**.
- V. Wauthier, R.K. Verbeeck, P. Buc Calderon. *The use of precision-cut liver slices from male Wistar rats as a tool to study age related changes in CYP3A induction and in formation of paracetamol conjugates.* Toxicol. in Vitro 18, 879-885, **2004**.
- V. Wauthier, R.K. Verbeeck, P. Buc Calderon. *Decreased CYP3A2 expression and activity in senescent male Wistar rats. Is there a role for HNF4α ?* Exp. Gerontol. 41, 846-854, **2006**.
- V. Wauthier, V. Schenten, R.K. Verbeeck, P. Buc Calderon. *Ageing is associated with increased expression but decreased activity of CYP2E1 in male Wistar rats.* Life Sci. 79, 1913-1920, **2006**.
- V. Wauthier, P. Dubois, R.K. Verbeeck, P. Buc Calderon. *Induction of CYP2C12 expression in senescent male rats is well correlated to an increase of HNF3β expression, while the decline of CYP2C11 expression is unlikely due to a decrease of STAT5 activation.* Biochem. Pharmacol. 73, 923-933, **2007**.
- S. Cuesta de Juan, M.J. Monte, R.I.R. Macias, V. Wauthier, P. Buc Calderon, J.J.G. Marin. *Ontogenic development and effect of weaning on the expression of enzymes, transporters and nuclear receptors involved in rat bile acid homeostasis.* J. Lipid Res. 48, 1362-1370, **2007**.
- V. Wauthier, R.K. Verbeeck, P. Buc Calderon. *The effect of ageing on cytochrome P450 enzymes; consequences for drug biotransformation.* In elderly Curr. Med. Chem. 14, 745-757, **2007**.

Funding

- Union Européenne
- Région Wallonne
- FSR

Partnership

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- 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 :

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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-αlevels.

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-myces 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. Terryn, 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 calcium² signalling in Pkd1+/- 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 onecut 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 onecut 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 onecut 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. Daubioul, 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 homesostasis.* 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 Dasylirion 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. Thissen.

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 :

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- Bernard MASEREEL
- Lionel POCHET

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. Pochet. *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. Pochet, 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
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- 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 chirurgical 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

- C. Vermeiren, N. Najimi, N. Vanhoutte, S. Tilleux, I. De Hemptinne, J.-M. Maloteaux, E. Hermans. *Acute upregulation of glutamate uptake mediated by mGluR5 in reactive astrocytes.* J. Neurochem. 94, 405-416, **2005**.
- 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 dibutyryl cAMP matured cultures.* J. Neurochem. 105, 2224-2236, **2008**.
- N. Vanhoutte, E. Hermans. *Glutamate-induced glioma cells proliferation is prevented by functional expression of the glutamate transporter GLT-1.* FEBS Lett 582, 1847-1852, **2008**.
- N. Vanhoutte, J. Abarca-Quinones, B. Jordan, J.-M. Maloteaux, E. Hermans. *Enhanced expression of the high affinity glutamate transporter GLT-1 in C6 glioma cells delays tumour progression in rat.* Exp. Neurol. In press, **2009**.
- 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

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- 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

- F. Clotman, P. Jacquemin, N. Plumb-Rudewiez, C. Pierreux, P. Van Der Smissen, H. Dietz, P. Courtoy, G.-G. Rousseau, Fr. Lemaigre. *Control of liver cell fate decision by a gradient of TGF beta signaling modulated by Onecut transcription factors.* Genes Dev. 15, 19,1849-1854, **2005**.
- 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 endocannabinoïdes.

Representative References

- Y. Sun, K. Tsuboi, L. Zhao, Y. Okamoto, D. Lambert, N. Ueda. *Involvement of N-acylethanolamine-hydrolyzing acid amidase in the degradation of anandamide and other N-acylethanolamines in macrophages.* Biochim Biophys Acta. 1736 : 211-220, **2005**.
- 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 :

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- 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 ΔF508 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

- R. Legssyer, F. Huaux, J. Lebacq, M. Delos, E. Marbaix, P. Lebecque, D. Lison, B. Scholte, P. Wallemacq, T. Leal. *Azithromycin reduces spontaneous and induced inflammation in DeltaF508 cystic fibrosis mice.* Respir. Res. 7 : 134, **2006**.
- 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. Dusser, 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 Recheche, 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 ΔF5068 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 immuno-responses.

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 HORSMANS
- 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.

Representative References

- I. Leclercq, Chr. Sempoux, P. Starkel, Y. Horsmans. *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. Horsmans. *Nonalcoholic fatty liver disease: potential role for nutritional management.* (Invited review) Current opinion in clinical nutrition and metabolic care : 11;766-73, **2008**.
- P. Cani, S. Possemiers, T. Van de Wiele, Y. Guiot, A. Everard, O. Rottier, L. Geurts, D. Naslain, A. Neyrinck, D. Lambert, G. Muccioli, N. Delzenne. *Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability.* Epub ahead of print, Gut., Feb 24, **2009**.
- N. Lanthier, Y. Horsmans, 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**.
- 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.

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 remiscent 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

- V. Van Pesch, O. Van Eyll, Th. Michiels. *The leader protein of Theiler's virus inhibits immediate-early alpha/beta interferon production.* J. Virol. 75, 7811-7817, **2001**.
- V. Van Pesch, Th. Michiels. *Characterization of the murine alpha interferon gene family.* J. Virol. 78, 8219-8228, **2004**.
- M. Brahic, J.-Fr. Bureau, Th. Michiels. *The geentics of the persistent infection and demyelinating disease caused by Theiler's viruss.* Annu. Rev. Microbiol. 59, 279-298, **2005**.
- S. Delhaye, Th. Michiels. *Neurons produce type-I interferon during viral encephalitis.* Proc. Natl. Acad. Sci. USA 103, 7835-7840, **2006**.
- C. Sommereyns, S. Paul, P. Staeheli, Th. Michiels. *Interferon lambda (IFN-l) 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
- Univerité 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. Stäheli, 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.

Representative References

- H. Servais, P. Van Der Smissen, G. Thirion, G. Van Der Essen, F. Van Bambeke, P. Tulkens, M.-P. Mingeot-Leclercq. *Gentamicin-induced apoptosis in LLC-PK1 cells: involvement of lysosomes and mitochondria.* Toxicol. Appl. Pharmacol. 15, 321-333, **2005**.
- F. Van Bambeke, J. Saffran, M.-P. Mingeot-Leclercq, P. Tulkens. *Mixed lipid storage disorder induced in macrophages and fibroblasts by oritavancin (LY333328), a new glycopeptide antibiotic with exceptional cellular accumulation.* Antimicrob. Ag. Chemother. 49, 1695-1700, **2005**.
- H. Servais, Y. Jossin, Fr. Van Bambeke, P. Tulkens, M.-P. Mingeot-Leclercq. *Gentamicin causes apoptosis at low concentrations in renal LLC-PK1 cells subjected to electroporation.* Antimicrob. Ag. Chemother. 50, 1213-1221, **2006**.
- H. Servais, A. Ortiz, O. Devuyst, S. Denamur, P. Tulkens, M.-P. Mingeot-Leclercq. *Renal cell apoptosis induced by nephrotoxic drugs: cellular and molecular mechanisms and potential approaches to modulation.* Apoptosis 13, 11-32, **2008**.
- S. Denamur, Fr. Van Bambeke, M.-P. Mingeot-Leclercq, P. Tulkens. *Apoptosis induced by aminoglycosides in LLC-PK1 cells: comparison between neomycin, gentamicin, amikacin, and isepamicin using electroporation.* Antimicrob. Ag. Chemother. 52, 2236–2238, **2008**.
- M. Barcia-Macay, F. Mouaden, M.-P. Mingeot-Leclercq, P. Tulkens, Fr. Van Bambeke. *Cellular pharmacokinetics of telavancin, a novel lipoglycopeptide antibiotic, and analysis of lysosomal changes in cultured eukaryotic cells (J774 mouse macrophages; rat embryonic fibroblasts).* J. Antimicrob. Chemother. 61, 1288-1294, **2008**.

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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- Françoise VAN BAMBEKE
- Paul TULKENS

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.

Representative References

- J. Piret, A. Schanck, S. Delfosse, Fr. Van Bambeke, B. K. Kishore, P. Tulkens, M.-P. Mingeot-Leclercq. *Modulation of the in vitro activity of lysosomal phospholipase A1 by membrane lipids.* Chem. Phys. Lipids 133, 1-15, **2005**.
- N. Fa, S. Ronkart, A. Schanck, M. Deleu, G. Gaigneaux, E. Goormaghtigh, M.-P. Mingeot-Leclercq. *Effect of the antibiotic azithromycin on thermotropic behavior of DOPC or DPPC bilayers.* Chem. Phys. Lipids 144, 108-16, **2006**.
- N. Fa, L. Lins, P. Courtoy, Y. Dufrêne, P. Van Der Smissen, R. Brasseur, D. Tyteca, M.-P. Mingeot-Leclercq. *Decrease of elastic moduli of DOPC bilayers induced by a macrolide antibiotic, azithromycin.* Biochim. Biophys. Acta 1768, 1830-1838, **2007**.
- R. Brasseur, N. Braun, K. El Kirat , M. Deleu, M.-P. Mingeot-Leclercq, Y. Dufrêne. *The biologically important surfactin lipopeptide induces nanoripples in supported lipid bilayers.* Langmuir 23, 9769-9772, **2007**.
- H. Bensikaddour, N. Fa, I. Burton, M. Deleu, L. Lins, A. Schanck, R. Brasseur, Y. Dufrêne, E. Goormaghtigh, M.-P. Mingeot-Leclercq. *Characterization of the interactions between fluoroquinolone antibiotics and lipids: a multitechnique approach.* Biophys. J. 94, 3035-3046, **2008**.
- H. Bensikaddour, K. Snoussi, L. Lins, R. Brasseur, F. Van Bambeke, P. Tulkens, E. Goormaghtigh, M.-P. Mingeot-Leclercq. *Interactions of ciprofloxacin with DPPC and DPPG: Fluorescence anisotropy, ATR-FTIR and 31P NMR spectroscopies and conformational analysis.* Biochim. Biophys. Acta 1778, 2535-2543, **2008**.
- G. Francius, O. Domenech, M.-P. Mingeot-Leclercq, Y. Dufrêne. *Direct observation of Staphylococcus aureus cell wall digestion by lysostaphin.* J. Bacteriol. 190, 7904-7909, **2008**.
- Fr. Van Bambeke, M.-P. Mingeot-Leclercq, M. Struelens, P. Tulkens. *The bacterial envelope as a target for novel anti-MRSA antibiotics.* Trends Pharmacol. Sc. 29, 124-134, **2008**.

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

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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.

Representative References

- N. Pavselj, V. Preat. *DNA electrotransfer into the skin using a combination of one high- and one low-voltage pulse.* Journal of Controlled Release 106:407-415, **2005**.
- G. Vandermeulen, E. Staes, M. Vanderhaeghen, M. Bureau, D. Scherman, V. Preat. *Optimisation of intradermal DNA electrotransfer for immunisation.* Journal of Controlled Release, 124: 81-87, **2007**.
- N. Pavselj, V. Preat, D. Miklavcic. *A numerical model of skin electropermeabilization based on in vivo experiments.* Annals of Biomedical Engineering 35:2138-2144, **2007**.
- F. Andre, J. Gehl, G. Sersa, V. Preat, P. Hojman, J. Eriksen, M. Golzio, M. Cemazar, N. Pavselj, M. Rols, D. Miklavcic, E. Neumann, J. Teissie, L. Mir. *Efficiency of high and low voltage pulse combinations for gene electrotransfer in muscle, liver, tumor and skin.* Hum Gene Ther., **2008**.
- G. Vandermeulen, L. Daugimont, H. Richiardi, M. Vanderhaeghen, N. Lecouturier, B. Ucakar, V. Wascotte. *Effect of tape stripping and adjuvants on immune response after intradermal DNA electroporation.* Pharmaceutical Research, 26:1745-1751, **2009**.
- G. Vandermeulen, H. Richiardi, V. Escriou, J. Ni, P. Fournier, V. Schirrmacher, D. Scherman, V. Preat. *Skin-specific promoters for genetic immunisation by DNA electroporation.* Vaccine, 27:4272-4277, **2009**.

Funding

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

Partnership

- D. Miklavcic, Ljubljana, Slovenie
- 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 :

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- 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-trypanosomial, antimalarial or vaso-relaxant 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 plateform) 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**.
- S. Hoet, C. Stévigny, M.-Fr. Hérent, J. Quetin-Leclercq. *Antitrypanosomal compounds from the leaf essential oil of Strychnos spinosa.* Planta Medica, 72 : 480-482, **2006**.
- C. Baccelli, I. Navarro, S. Block, A. Abad, N. Morel, J. Quetin-Leclercq. *Vasorelaxant activity from Croton zambesicus and synthetic trachylobanes and their structure-activity relationships.* J. Nat. Prod. 70(6) : 910-917, **2007**.
- H. Mavar-Manga, M. Haddad, L. Pieters, C. Baccelli, A. Penge, J. Quetin-Leclercq. *Anti-inflammatory compounds from leaves and root bark of Alchornea cordifolia (Schumach. & Thonn.) Müll. Arg.* Journal of Ethnopharmacology 115, 25-29, **2008**.
- B. Portet, N. Fabre, R. Rozenberg, J.-L. Habib-Jiwan, C. Moulis, J. Quetin-Leclercq. *Analysis of minor flavonoids in Piper hotmannianum var. berbicense using liquid chromatography coupled with atmospheric pressure ionization mass spectrometry.* Journal of Chromatography A, 1210, 45-54, **2008**.
- C. Rivière, T. H. V. Nguyen, L. Pieters, B. Dejaegher, Y. Vander Heyden, M. Chau Van, J. Quetin-Leclercq. *Polyphenols isolated from antiradical extracts of Mallotus metcalfianus.* Phytochemsitry 70, 91-99, **2009**.
- J. Bero, H. Ganfon, M. Jonville, M. Frédérich, F. Gbaguidi, P. De Mol, M. Moudachirou, J. Quetin-Leclercq. *In vitro antiplasmodial activity of plants used in Benin in traditional medicine to treat malaria.* Journal of Ethnopharmaco-logy 122, 439-444, **2009**.

Funding

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

Partnership

- Madagascar : Institut malgache des Recherches Appliquées (IMRA)
- Bénin : University of Abomey-Calavi (UAC)
- Maurice : University of Maurtius (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^n (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

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- 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 pharmaco toxicity (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

- 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(7):717-28, **2007**.
- P. A. Lysy, Fr. Smets, C. Sibille, M. Najimi, E. Sokal. *Human skin fibroblasts : From mesodermal to hepatocyte-like differentiation.* Hepatology 46(5):1574-85, Nov **2007**.
- X. Stéphenne, M. Najimi, D. K. Ngoc, F. Smets, L. Hue, B. Guigas, E. Sokal. *Cryopreservation of human hepatocytes alters the mitochondrial respiratory chain complex 1.* Cell Transplant. 16(4):409-19, **2007**.
- P. Sancho-Bru, M. Najimi, M. Caruso, K. Pawelyn, T. Cantz, S. J. Forbes, T. Roskams, M. Ott, U. Gehling, E. Sokal, C. Verfaillie, M. Muraca. *Stem and progenitor cells for liver repopulation : can we standardize the process from bench to bedside ?* Gut. [Epub ahead of print], Dec 17, **2008**.
- P. A. Lysy, M. Najimi, X. Stephenne, A. Bourgois, Fr. Smets, E. Sokal. *Liver cell transplantation for Crigler-Najjar syndrome type I : update and perspectives.* World J. Gastroenterol. 14(22):3464-70. Review Jun 14, **2008**.
- P. A. Lysy, Fr. Smets, M. Najimi, E. Sokal. *Leukemia inhibitory factor contributes to hepatocyte-like differentiation of human bone marrow mesenchymal stem cells.* Differentiation, 2008 Dec, 76(10):1057-67; Epub Jun 13, **2008**.
- D. Campard, P. A. Lysy, M. Najimi, E. Sokal. *Native umbilical cord matrix stem cells express hepatic markers and differentiate into hepatocyte-like cells.* Epub 2007 Dec 23. Gastroenterology 134(3):833-48, March **2008**.
- P. A. Lysy, D. Campard, Fr. Smets, M. Najimi, E. Sokal. *Stem cells for liver tissue repair : current knowledge and perspectives.* World J. Gastroenterol. 14(6):864-75. Review, Feb 14, **2008**.
- P. A. Lysy, D. Campard, Fr. Smets, J. Malaise, M. Mourad, M. Najimi, E. Sokal. *Persistence of a chimerical phenotype after hepatocyte differentiation of human bone marrow mesenchymal stem cells.* Cell Prolif. 41(1):36-58, Feb **2008**.

Patents

M. Najimi, E. Sokal. Adult derived human liver stem cells. 0544728.5, Europe, **2005**.

Awards

- EASL. Best presentation, **2007**.
- ESPGHAN. Best presenttaion, **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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- Françoise VAN BAMBEKE
- Marie-Paule MINGEOT-LECLERCQ

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

- S. Carryn, S. Van De Velde, Fr. Van Bambeke, M.-P. Mingeot-Leclercq, P. M. Tulkens. *Impairment of growth of Listeria monocytogenes in THP-1 macrophages by granulocyte macrophage colony-stimulating factor : release of tumor necrosis factor-alpha and nitric oxide.* J. Infect. Dis. 189, 2101-2109, **2004**.
- M. Barcia-Macay, C. Seral, M.-P. Mingeot-Leclercq, P. M. Tulkens, Fr. Van Bambeke. *Pharmacodynamic evaluation of the intracellular activity of antibiotics against Staphylococcus aureus in a model of THP-1 macrophages.* Antimicrob. Ag. Chemother 50, 841-851, **2006**.
- M. Barcia-Macay, S. Lemaire, M.-P. Mingeot-Leclercq, P. M. Tulkens, Fr. Van Bambeke. *Evaluation of the Extracellular 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**.
- Fr. Van Bambeke F, M. Barcia-Macay, S. Lemaire, P. M. Tulkens. *Cellular pharmacokinetics and pharmacodynamics of antibiotics: current views and perspectives.* Cur. Op. Drug Discov. Devel. 9, 218-230, **2006**.
- S. Lemaire, Fr. Van Bambeke, M.-P. Mingeot-Leclercq, Y. Glupczynski, P. M. Tulkens. *Role of Acidic pH in the Susceptibility of Intraphagocytic Methicillin-Resistant Staphylococcus aureus Strains to Meropenem and Cloxacillin.* Antimicrob. Ag. Chemother 51, 1627-1632, **2007**.
- 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**.
- S. Lemaire, K. Kosowska-Shick, K. Julian, P. M. Tulkens, Fr. Van Bambeke, P. C. Appelbaum. *Activities of antistaphylococcal antibiotics towards the extracellular and intraphagocytic forms of S. aureus isolates from a patient with persistent bacteraemia and endocarditis.* Clin. Microb. Infect. 14, 766-777, **2008**.
- 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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- Marie-Paule MINGEOT-LECLERCQ

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.

Representative References

- C. Seral, J.-M. Michot, H. Chanteux, M.-P. Mingeot-Leclercq, P. M. Tulkens, Fr. Van Bambeke. *Influence of P-glycoprotein inhibitors on accumulation of macrolides in J774 murine macrophages.* Antimicrob. Ag. Chemother. 47, 1047-1051, **2003**.
- Fr. Van Bambeke, S. Carryn, C. Seral, H. Chanteux, D. Tyteca, M.-P. Mingeot-Leclercq, P. M. Tulkens. *Cellular pharmacokinetics and pharmacodynamics of the glycopeptide antibiotic oritavancin (LY333328) in a model of J774 mouse macrophages.* Antimicrob. Ag. Chemother. 48, 2853-2860, **2004**.
- J.-M. Michot, Fr. Van Bambeke, M.-P. Mingeot-Leclercq, P. M. Tulkens. *Active efflux of ciprofloxacin from J774 macrophages through an MRP-like transporter.* Antimicrob. Ag. Chemother. 48, 2673-2682, **2004**.
- J.-M. Michot, C. Seral, Fr. Van Bambeke, M.-P. Mingeot-Leclercq, P. M. Tulkens. *Influence of efflux transporters on the accumulation and efflux of four quinolones (ciprofloxacin, levofloxacin, garenoxacin, and moxifloxacin) in J774 macrophages.* Antimicrob. Ag. Chemother. 49, 2429-2437, **2005**.
- 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**.
- J.-M. Michot, M. Heremans, N. Caceres, M.-P. Mingeot-Leclercq, P. M. Tulkens, Fr. Van Bambeke. *Cellular accumulation and activity of quinolones in ciprofloxacin-resistant J774 macrophages.* Antimicrob. Ag. Chemother. 50, 1689-1695, **2006**.
- S. Lemaire, Fr. Van Bambeke, M.-P. Mingeot-Leclercq, P. M. Tulkens. *Modulation of the Cellular Accumulation and Intracellular Activity of Daptomycin towards phagocytized Staphylococcus aureus by the P-glycoprotein (MDR1) Efflux Transporter in human THP-1 macrophages and Madin-Darby canine kidney cells.* Antimicrob. Ag. Chemother. 51, 2748-2757, **2007**.
- 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-blots, 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

- C. Bosquillon, P. Rouxhet, F. Ahimou, D. Simon, C. Culot, V. Preat, R. Vanbever. *Aerosolization properties, surface composition and physical state of spray-dried protein powders.* J. Control. Release 99 : 357-367, **2004**.
- C. Bosquillon, V. Preat, R. Vanbever. *Pulmonary delivery of growth hormone using dry powders and visualization of its local fate in rats.* J. Control. Release 96 : 233-244, **2004**.
- V. Codrons, F. Vanderbist, B. Ucakar, V. Préat, R. Vanbever. *Impact of formulation and methods of pulmonary delivery on absorption of parathyroid hormone (1-34) from rat lungs.* J. Pharm. Sci. 93 : 1241-1252, **2004**.
- C. Lombry, D. A. Edwards, V. Préat, R. Vanbever. *Alveolar macrophages are a primary barrier to pulmonary absorption of macromolecules.* Am. J. Physiol. Lung Cell Mol Physiol. 286 : L1002-L1008, **2004**.
- A. Minne, J. Louahed, S. Mehauden, B. Baras, J.-C. Renauld, R. Vanbever. *The delivery site of a monovalent influenza vaccine within the respiratory tract impacts on the immune response.* Immunology 122 : 316-325, 2007.
- A. Minne, F. Huaux, J. Jaworska, R. D. Rha, E. Hamelmann, R. Vanbever. *Safety evaluation of pulmonary influenza vaccination in healthy and "asthmatic" mice.* Vaccine 26 : 2360-2368, 2008.
- J. Ducreux, D. Tyteca, B. Ucakar, T. Medts, P. Crocker, P. Courtoy, R. Vanbever. *PEGylation of anti-sialoadhesin monoclonal antibodies enhances their inhibitory potencies without impairing endocytosis in mouse peritoneal macrophages.* Bioconjugate Chem. 29 : 295-303, **2009**.

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. Uyttenhove, 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.

Representative References

- F. Clotman, P. Jacquemin, N. Plumb-Rudewiez, P. Van der Smissen, C. Pierreux, H. Dietz, P. Courtoy, G. Rousseau, F. Lemaigre. *Control of liver cell fate decision by a gradient of TGFß signaling modulated by Onecut transcription factors.* Genes. Dev. 19, 1849-1854, **2005**.
- 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, 257-264, **2006**.
- V. Vanhorenbeeck, M. Jenny, J.-F. Cornut, G. Gradwohl, F. Lemaigre, 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**.
- 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 Transferman 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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- 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 Dufrêne'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

- E. Zelazny, J. Borst, M. Muylaert, H. Batoko, M. Hemminga, Fr. Chaumont. FRET imaging in living maize cells reveals that plasma membrane aquaporins interact to regulate their subcellular localization. Proc. Natl. Acad. Sci. USA, 104, 12359-12364, 2007.
- Y. Dufrene. Towards nanomicrobiology using atomic force microscopy. Nature Reviews Microbiology, 6, 674-680, 2008.
- B. Dieryck, G. Otto, D. Doucet, Ph. Delfosse, A. Legreve, C. Bragard. Seed, soil and vegetative transmission contribute to the spread of pecluviruses in Western Africa and the Indian sub-continent. Virus research, 181, 184-189, 2009.
- D. Müller, J. Helenius, D. Alsteens, Y. Dufrene. Force probing surfaces of living cells to molecular resolution. Nat. Chem. Biol. 5, 383-390, 2009.
- E. Zelazny, U. Miecielica, J. Borst, M. Hemminga, Fr. Chaumont. An N-terminal diacidic motif is required for the trafficking of the maize aquaporins ZmPIP2;5 and ZmPIP2;4 to the plasma membrane. Plant. J. 57, 346-355, 2009.
- D. Guillaumot, S. Guillon, T. Deplanque, C. Vanhee, C. Gumy, D. Masquelier, P. Morsomme, H. Batoko. The Arabidopsis TSPO-related protein is a stress and abscisic acid-regulated, ER-Golgi-localized membrane protein. Plant. J. In Press, 2009.

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. Legrève'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

SENIOR SCIENTISTS :

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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 subcellular 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**.
- E. Loumaye, A.C. Andersen, A. Clippe, H. Degand, M. Dubuisson, F. Zal, P. Morsomme, J.F. Rees, B. Knoops. *Cloning and characterization of arenicola marina peroxiredoxin 6, an annelid two-cysteine peroxiredoxin highly homologous to mammalian one-cysteine peroxiredoxins*. Free Radic Biol Med., 15, 482-93, **2008**.
- H. Degand, A.M. Faber, N. Dauchot, D. Mingeot, B. Watillon, P. Van Cutsem, P. Morsomme, M. Boutry. *Proteome analysis of the chicory root identifies proteins involved in cold acclimation.* Proteomics, 9, 2903-07, **2009**.
- B. De Muynck, C. Navarre, Y. Nizet, J. Stadlmann, M. Boutry. *Different subcellular localization and glycosylation for a functional antibody expressed in Nicotiana tabacum plants and suspension cells.* Transgenic Research, 18, 467-82, **2009**.

Patents

- S. Haunso, J. Carlsen, K. Kjeldsen, T. Johansen, P. Larsen, U. Jensen, S. Fey, M. Boutry, H. Degand. *Markers for organ rejection.* PCT US 5939270, **1999**.
- M. Boutry, Y. Stukkens, S. Grec, M. Jasinski. *Use of NpABC1 transporter and promoter thereof.* PCT/EP03/08137, **2003**.

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

SENIOR SCIENTISTS :

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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 desease 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**.
- V. Lorant, C. Depuydt, B. Gillain, A. Guillet, V. Dubois. *Involuntary commitment in psychiatric care: what drives the decision ?* Soc. Psychiatry Psychiatr Epidemiol., 42 (5) : 360-5, **2007**.
- B. Govaerts, W. Dewé, M. Maumy, B. Boulanger. *Pre-study analytical method validation : comparison of four alternative approaches based on quality level estimation and tolerance intervals.* Quality and reliability Engineering, 24, 667-680, **2008**.
- R. Rousseau, B. Govaerts, M. Verleysen, B. Boulanger. *Comparison of chemometrics tools for in metabonomics biomarkers identification.* Chemometrics and Intelligent Laboratory Systems, 91, 54-66, **2008**.
- N. Vriamont, B. Govaerts, C. De Bellefon, O. Riant. *Simulated evolution of a new library of chiral catalysts for asymmetric hydrogen transfer.* Chemistry, an European Journal, Vol. 15 Issue 25, 6267-6278, **2009**.

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 :

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- 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

- E. Christensen, O. Devuyst, G. Dom, R. Nielsen, P. Van Der Smissen, P. Verroust, M. Leruth, W. Guggino, P. Courtoy. *Loss of chloride channel ClC-5 impairs endocytosis by defective trafficking of megalin and cubilin in kidney proximal tubules.* Proc. Natl Acad. Sci. USA 100, 8472-8477, **2003**.
- F. Clotman, P. Jacquemin, N. Plumb-Rudewiez, Chr. Pierreux, P. Van Der Smissen, H. Dietz, P. Courtoy, G. Rousseau, F. Lemaigre. *Control of liver cell fate decision by a gradient of TGFβ signalling modulated by Onecut transcription factors.* Genes Dev. 19, 1849-1854, **2005**.
- C. Pretto, H. Gaide Chevronnay, P. Cornet, C. Galant, D. Delvaux, P. Courtoy, E. Marbaix, P. Henriet. *Production of interleukin-1α by human endometrial stromal cells is triggered during menses and dysfunctional bleeding and is induced in culture by epithelial interleukin-1α released upon ovarian steroids withdrawal.* J. Clin. Endocrinol. Metab. 93, 4126-4134, **2008**.
- A. Caplanusi, K. Parreira, W. Lima, B. Marien, P. Van Der Smissen, P. de Diesbach, O. Devuyst, P. Courtoy. *Intraviral multi-photon microscopy reveals several levels of heterogeneity in endocytic uptake by mouse renal proximal tubules.* J. Cell. Mol. Med. 12, 351-354, **2008**.
- N. Demotte, V Stroobant, P. Courtoy, P. Van Der Smissen, D. Colau, I. Luescher, C. Hivroz, J. Nicaise, J.-L. Squifflet, M. Mourad, D. Godelaine, T. Boon, P. van der Bruggen. *Restoring the association of the T cell receptor with CD8 reverses anergy in human tumor-infiltrating lymphocytes*. Immunity 28, 414-424, **2008**.

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
- Scienfific 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 :

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- 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

- A. Smeets, C. Evrard, M. Landtmeters, C. Marchand, B. Knoops, J.-P. Declercq. *Crystal structures of oxidized and reduced forms of human mitochondrial thioredoxin 2.* Protein Science 14, 2610-2621, **2005**.
- 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.* Microgavity 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**.
- C. Urbach, C. Evrard, V. Pudzaitis, J. Fastrez, P. Soumillion, J.-P. Declercq. *Structure of PBP-A from Thermosynechococcus elongatus, a penicillin-binding protein closely related to class A β-lactamases.* J. Mol. Biol., 386, 109-120, **2009**.

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

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- 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 alife 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

- C. Guyard, P. Evrard, A-M. Corbisier, E. Dei-Cas, F. Menozzi, L. Polonelli, J-C. Cailliez. *Neutralization of a Williopsis saturnus var. mrakii killer toxin (WmKT) by an anti-Pichia anomala killer toxin (PaKT) monoclonal antibody.* Medical Mycology, 39 : 395-400, **2001**.
- 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**.
- C. Decock, J. Stalpers. *Studies in Perenniporia : Polyporus unitus, Boletus medulla-panis, and the nomenclature of Perenniporia, Poria, and Physisporus, with a note on the European Perenniporia taxa with a resupinate basidiome.* Taxon 55 : 759-778, **2006**.
- 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**.
- C. Decock, S. Huret, C. Bivort. *Anamorphic fungi from French Guyana. Septomyrothecium maraitianum sp. nov. and Septomyrothecium setiramosum comb. nov. (Ascomycota, anamorphic Hypocreales).* Cryptogamie Mycologie 29(4), 321-331, **2008**.
- Lu Quan, C. Decock, X. Y. Zhang, H. Maraite. *Ophiostomatoid fungi (Ascomycota) associated with Pinus tabuliformis and Dendroctonus valens (Coleoptera) in northern China and assessment of their pathogenicity on mature trees.* Antonie van Leeuwenhoek : in press, **2009**.

Partnerschip

- 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**.
- S. Defrere, J. Squifflet, J.-C. Lousse, A. Van Langendonckt, R. Gonzalez-Ramos, J.-M. Foidart, C. Jerome, L. Delattre, J. Donnez, J.-P. Dehoux. *"Unsuccessful induction of endometriosis in female rhesus macaques (Macaca mulatta)".* Gynecologic and Obstetric Investigation 66(2) : 84-90, **2008**.
- 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 :

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- 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 m2 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).

Main Equipments

- Cleanroom Environment
- Characterization (microscopy, ellipsometry, profilometry…)
- Wet Benches (susbtrate 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. Francq, 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 fundation.

Partnership

- Royal Military School - Engineering (Prof Van Thomme), Bruxelles, Belgium
- University of Toronto – Phospho-calcic metabolism Lab (Prof Grynpas), 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 DELMEE
- 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

F. Barbut, N. Mario, M. Delmée, J. Gozian, J.-C. Petit. *Genomic fingerprinting of Clostridium difficile isolates by using a random amplified polymorphic DNA (RAPD) assay.* FEMS Microbiology Letters, 114:161-166, **1993**.

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**.

M. Rupnik, V. Avesani, M. Janc, C. Von Eichel-Streiber, M. Delmée. *A novel toxinotyping scheme and its correlation to serogrouping of Clostridium difficile isolates.* Journal of Clinical Microbiology ; 36:2240-2247, **1998**.

M. Delmée, I. Ramboer, J. Van Broeck, C. Suetens. *Epidemiology of clostridium difficle toxinotype III, PCR-ribotype 027 associated disease.* In Belgium Euro surveillance, 11 (9):p.E060914.2, **2006**.

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**.

S. Johnson, S. P. Sambol, J. S. Brazier, M. Delmée, V. Avesani, M. M. Merrigan, D. N. Gerding. *International typing study of toxin A-negative, B-positive Clostridium difficile variants.* Journal of Clinical Microbiology, 41:1543-1547, **2003**.

P. D. Ghislain, S. Woestyn, D. Tennstedt, J.-M. Lachapelle, 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**.

G. Wauters, V. Avesani, K. Laffineur, J. Charlier, M. Janssens, B. Van Bosterhaut, M. Delmée. *Brevibacterium lutescens sp. Nov. From human and environmental samples.* International Journal of Systematic Evolutionary Microbiology. 53 (5):1321-1325, **2003**.

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**.

G. Wauters, G. Haase, V. Avesani, J. Charlier, M. Janssens, J. Van Broeck, M. Delmée. *Identification of a novel Brevibacterium species isolated from humans and description of Brevibacterium*

sanguinis sp. Nov. Journal of Clinical Microbiology, 42 (6):2829-2832, **2004**.

- I. Poilane, Ch. Humeniuk-Ainouz, I. Durand, C. Janoir, Ph. Cruaud, M. Delmée, M. Popoff, A. Colignon. *Molecular characterization of Clostridium difficile clinical isolates.* In a geriatric hospital Journal of medical Microbiology, 56: 386-390, **2007**.
- 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 :

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- Sara TERRYN
- 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 troughput (> 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 microtitrator (Mettler – Toledo) and a Fiske osmometer, allowing to analyze multiple biochemical and toxical 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

- S. Wang, O. Devuyst, P. Courtoy, T. Wang, H. Wang, Y. Wang, R. Thakker, S. Guggino, W. B. Guggino. *Mice lacking renal chloride channel, CLC-5, are a model for Dent's disease, a nephrolithiasis disorder associated with defective receptor-mediated endocytosis.* Hum. Mol. Genet. 9 : 2937-2945, **2000**.
- E. I. Christensen, O. Devuyst, G. Dom, R. Nielsen, P. Van Der Smissen, P. Verroust, M. Leruth, W. B. Guggino, P. Courtoy. *Loss of chloride channel ClC-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**.
- F. Jouret, A. Bernard, C. Hermans, G. Dom, S. Terryn, 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. Houillier, 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 rhesus factor.* Nature 456 : 339-343, **2008**.

Awards

- *Biennal 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**.
- *Biennal 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 EUNEFRON)

Partnership

- EU VIth program (EuReGene)
- EU VIIth program (Genecure, EUNEFRON)
- Industry : Baxter, Danone

Main Equipment

- Biochemical analyzer Synchron CX5 Beckman
- Blood gazes 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 gazes
Biological fluids
Biomarkers
Sampling animal models
Biobanking
ELISA development

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Nanotechnology of Biosurfaces

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- 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 µm-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. Dufrêne. *Detection and localization of single molecular recognition events using atomic force microscopy.* Nature methods 3, 347-355, **2006**.
▶V. Dupres, C. Verbelen, Y. Dufrêne. *Probing molecular recognition sites on biosurfaces using AFM.* Biomaterials 28, 2393-2402, **2007**.
▶E. Dague, Y. Gilbert, C. Verbelen, G. Andre, D. Alsteens, Y. Dufrêne. *Towards a nanoscale view of fungal surfaces.* Yeast 24, 229-237, **2007**.
▶M.-P. Mingeot-Leclercq, M. Deleu, R. Brasseur, Y. Dufrêne. *Atomic force microscopy of supported lipid bilayers.* Nat. Protocols 3, 1654-1659, **2008**.
▶G. Francius, S. Lebeer, D. Alsteens, L. Wildling, H. J. Gruber, P. Hols, S. De Keersmaecker, J. Vanderleyden, Y. Dufrêne. *Detection, localization, and conformational analysis of single polysaccharide molecules on live bacteria.* ACSNano 2, 1921-1929, **2008.**
▶Y. Dufrêne. *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. Dufrêne. *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

- T. Helleputte, P. Dupont. *A Comparative Study of Normalization and Feature Selection Techniques for Breast Cancer Prognosis from Gene Expression.* In : Benelux Bioinformatics Conference (BBC), KUL, Leuven, Belgium, **2007**.
- 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

- E. Sbaa, J. Dewever, P. Martinive, C. Bouzin, F. Frérart, J.-L. Balligand, C. Dessy, O. Feron. *Caveolin plays a central role in endothelial progenitor cell mobilization and homing in SDF-1-driven postischemic vasculogenesis.* Circ. Res.; 98(9) : 1219-27, **2006**.
- F. Frérart, P. Sonveaux, G. Rath, A. Smoos, A. Meqor, N. Charlier, B. F. Jordan, J. Saliez, A. Noël, C. Dessy, B. Gallez, O. Feron. *The acidic tumor microenvironment promotes the reconversion of nitrite into nitric oxide : towards a new and safe radiosensitizing strategy.* Clin. Cancer Res.; 14(9) : 2768-74, **2008**.
- P. Sonveaux, F. Végran, T. Schroeder, M.-C. Wergin, J. Verrax, Z. N. Rabbani, C.-J. De Saedeleer, K. M. Kennedy, C. Diepart, B. F. Jordan, M.-J. Kelley, B. Gallez, M.-L. Wahl; M. W. Dewhirst, O. Feron (co-last author). *Targeting lactate-fueled respiration selectively kills hypoxic tumor cells in mice.* J. Clin. Invest.; 118(12) : 3930-42, **2008**.
- 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

SENIOR SCIENTISTS :

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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

- L. Moreno-Hagelsieb, B. Foultier, G. Laurent, R. Pampin, J. Remacle, J.-P. Raskin, D. Flandre. *Electrical detection of DNA hybridization : Three extraction techniques based on interdigitated Al/Al2O3 capacitors.* Biosensors & Bioelectronics, 22 (9-10) : 2199-2207, **2007**.
- 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**.

Patents

- D. Flandre (BE), L. Moreno-Hagelsieb (MX), R. Pampin (FR), D. Bourgeois (BE), J. Remacle (BE), P.-E. Lobert (FR). *Method and device for high sensitivity detection of the presence of DNA and other probes.* US2005227373.
- 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^2) 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

SENIOR SCIENTIST :

- Jean-Luc GALA

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 ProgensaTM) 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 form 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).

Representative References

- F. Lecouvet, L.-M. Irenge, B. Vandercam, A. Nzeusseu, S. Hamels, J.-L. Gala. *The etiologic diagnosis of infectious discitis is improved by amplification-based DNA analysis.* Arthritis & Rheumatism, 9 : 2985-94, **2004**.
- A.-F. Dekairelle, B. Tombal, J.-P. Cosyns, J.-L. Gala. *Assessment of the transcriptional activity of p53 improves the prediction of recurrence in superficial transitional cell carcinoma (TCC) of the bladder.* Clinical Cancer Research, 11 : 4724-32, **2005**.
- J.-F. Durant, P.-A. Fonteyne, P. Richez, L. Marot, B. Vandercam, D. Tennstedt, J.-L. Gala. *Real-time PCR and DNA sequencing for detection an identification of Trichophyton rubrum infection in a case of culture negative chronic dermatophytosis.* Medical Mycology, 46:1-7, **2008**.
- B. Vandercam, S. Jeumont, O. Cornu, J.-C. Yombi, F. Lecouvet, V. Druez, L. Irenge, J.-L. Gala. *Amplification-Based DNA Analysis in the Diagnosis of Prosthetic Joint Infection.* Journal of Molecular Diagnostics, 10 : 537-43, **2008**.
- L.-M. Irenge, K. Walravens, M. Govaerts, J. Godfroid, V. Rosseels, K. Huygen, J.-L. Gala. *Rapid detection and specific identification M. avium subsp. paratuberculosis in fecal samples from experimentally infected, subclinically affected cattle by a triplex real-time PCR : comparison with conventional methods.* Vet Microbiol, ahead of print http://dx.doi.org/10.1016/j.vetmic. 2008.09.087, **2008**.
- 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**.
- S. Burteau, P. Bogaerts, R. de Mendonca, L. Irenge, C. Berhin, J. Hiffe, N. de San, P. Beyne, S. Hamels, Y. Glupczynski, M. Struelens, J.-L. Gala, J. Remacle. *Design and validation of a low density array (Nosochip) for the detection and identification of the main pathogenic bacteria and fungi responsible for nosocomial pneumonia.* European Journal of Clinical Microbiology & Infectious Diseases, 27: 17-27, **2008**.
- 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 MYCOSERV, 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

SENIOR SCIENTISTS :

- Pierre GIANELLO
- 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

- B. Machiels, L. Gillet, S. Brito, P. Drion, C. Delforge, Y. Nizet, C. Bona, B. Costes, N. Markine-Gorianoff, A. Vanderplasschen. *Natural antibody-complement dependent neutralization of Bovine herpesvirus 4 by human serum.* Microbes and infection 14: 1530, **2007**.
- A.-J. Poncelet, Y. Nizet, J. Vercruyse, A.-L. Hiel, A. Saliez, P. Gianello. *Inhibition of humoral response to allogeneic porcine mesenchymal stem cell with 12 days of tacrolimus.* Transplantation 15; 86(11) : 1586-95, **2008**.
- B. De Munck, C. Navarre, Y. Nizet, J. Stadmann, M. Boutry. *Different subcellular localization and glycosylation for a functional antibody expressed in Nicotiana tabacum plants ans suspension cells.* Transgenic Res. 18 : 467-482, **2009**.
- L. Moreno-Hagelsieb, Y. Nizet, X. Tang, J.-P. Raskin, D. Flandre, L. Francis. *CMOS Compatible Anodic Al2O3 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…)

SENIOR SCIENTISTS :

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- Jean-Louis HABIB JIWAN
- Pierre WALLEMACQ
- Yvan LARONDELLE

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 MSn 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

- R. Rozenberg, N. L. Ruibal-Mendieta, G. Petijean, P. Cani, D. L. Delacroix, N. Delzenne, M. Meurens, J. Leclercq-Quetin, J.-L. Habib Jiwan. *Phytosterol analysis and characterisation in spelt (Triticum aestivum ssp. Spelta L.) and wheat (T. aestivum L.) lipids by LC/APCI-MS.* Journal of Cereal sciences, 38, 189-97, **2003**.
- C. Stevigny, J.-L. Habib Jiwan, R. Rozenberg, E. de Hoffmann, J. Leclercq-Quetin. *Key fragmentation patterns of aporphine alkaloids by direct inlet ESI multistage mass spectrometry.* Rapid Commun. in Mass Spec. 18, 523-528, **2004**.
- N. L. Ruibal-Mendieta, R. Rozenberg, D. L. Delacroix, G. Petijean, A. Dekeyzer, C. Baccelli, C. Marques, N. Delzenne, M. Meurens, J.-L. Habib Jiwan, J. Leclercq-Quetin. *Spelt (Triticum spelta L.) and winter wheat (T. aestivum L.) wholemeals have similar sterol profiles as determined by quantitative liquid chromatography and mass spectrometry analysis.* Journal of Agricultural and Food Chemistry 52, 4802-4807, **2004**.
- B. Stenuit, L. Eyers, R. Rozenberg, J.-L. Habib Jiwan, S. N. Agathos, J. P. Jones. *Aerobic growth on 2,4,6-trinitrotoluene (TNT) as sole nitrogen source by Escherichia coli and evidence of TNT denitration with whole cells and cell-free extracts.* Appl. Environ. Microbiol. 72, 7945-48, **2006**.
- H. Cabana, J.-L. Habib Jiwan, R. Rozenberg, V. Elisashvili, M. Penninckx, S. N. Agathos, J. P. Jones*Ingredient Triclosan using Enzyme Preparation from the White Rot FungusCoriolopsis polyzona.* Chemosphere 67, 770-778, **2007**.
- S. Hoet, L. Pieters, G. G. Muccioli, J.-L. Habib Jiwan, Fr. R. Opperdoes, J. Quetin-Leclercq. *Antitripanosomal activity of triterpenoids and sterols from the leaves of Strychnos spinosa and related compounds.* Journal of Natural Products, 70(8), 1360-1363, **2007**.
- B. Portet, N. Fabre, R. Rozenberg, J.-L. Habib-Jiwan, C. Moulis, J. Quetin-Leclercq. *Analysis of minor flavonoids in Piper hotmannianum var. berbicense using liquid chromatography coupled with atmospheric pressure ionization mass spectrometry.* Journal of Chromatography A, 1210, 45-54, **2008**.
- C. Rivière, T. H. V. Nguyen, L. Pieters, B. Dejaegher, Y. Vander Heyden, M. Chau Van, J. Quetin-Leclercq. *Polyphenols isolated from antiradical extracts of Mallotus metcalfianus.* Phytochemsitry 70, 91-99, **2009**.
- J. Bero, H. Ganfon, M.-C. Jonville, M. Frédérich, F. Gbaguidi, P. De Mol, M. Moudachirou, J. Quetin-Leclercq. *In vitro antiplasmodial activity of plants used in Benin in traditional medicine to treat malaria.* Journal of Ethnopharmacology 122, 439-444, **2009**.

Funding

- FNRS
- FSR
- Brussels region
- International cooperation

Partnership

- This research equipment is the core of a technological platform devoted 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

SENIOR SCIENTIST :

- Martine RAES
- Patsy RENARD
- 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 ProteinScape, 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

- C. Gustin, E. Delaive, M. Dieu, D. Calay, M. Raes. *Upregulation of pentraxin-3 in human endothelial cells after lysophosphatidic acid exposure.* Arterioscler Thromb. Vasc. Biol., 28 : 491-97, **2008**.
- A. Chrétien, E. Delaive, M. Dieu, C. Demazy, N. Ninane, M. Raes, O. Toussaint. *Upregulation of annexin-A2 in H2O2-induced premature senescence as evidenced by 2D-DIGE proteome analysis.* Exp. Gerontol. 43 : 353-59, **2008**.
- B. Vanhollebeke, G. De Muylder, M.-J. Nielsen, A. Pays, P. Tebabi, M. Dieu, M. Raes, S. K. Moestrup, E. Pays. *A haptoglobin-hemoglobin receptor conveys innate immunity to Trypanosoma brucei in humans.* Science, 320 : 677-681, **2008**.
- M. Dewez, F. Bauer, M. Dieu, M. Raes, J. Vandenhaute, D. Hermand. *The conserved Wobble uridine tRNA thiolase Ctu1-Ctu2 is required to maintain genome integrity.* Proc. Natl. Acad. Sci. USA 105, 5459-64, **2008**.
- V. Gillardin, F. Silvestre, M. Dieu, E. Delaive, M. Raes, J.-P. Thomé, P. Kestemont. *The African clawed frog Xenopus laevis tadpole proteome during exposure to the PCBs mixture Aroclor 1254.* Mol. Cell. Proteomics, 8 : 596-611, **2009**.

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 fuctions 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 chemcal 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

- S. Horman, D. Vertommen, R. Heath, D. Neumann, V. Mouton, A. Woods, U. Schlattner, T. Walimann, D. Carling, L. Hue, M. Rider. *Insulin antagonizes ischemia-induced Thr172 phosphorylation of AMP-activated protein kinase alpha-subunits in heart via hierarchical phosphorylation of Ser485/491*. J. Biol. Chem. 281, 5335-5340, **2006**.
- 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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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

- A. des Rieux, V. Fievez, I. Théate, J. Mast, V. Préat, Y.-J. Schneider. *An improved in vitro model of human intestinal follicle-associated epithelium to study nanoparticle transport by M cells.* Eur J. Pharm Sci. 30(5):380-91, **2007**.
- 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: characteri-zation 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**.
- J. Van De Walle, B. Romier, Y. Larondelle, Y.-J. Schneider. *Influence of deoxynivalenol on NF-kappaB activation and IL-8 secretion in human intestinal Caco-2 cells*. Toxicol Lett. 177(3):205-14, **2008**.
- T. Sergent, L. Ribonnet, A. Kolosova, S. Garsou, A. Schaut, S. De Saeger, C. Van Peteghem, Y. Larondelle, L. Pussemier, Y.-J. Schneider. *Molecular and cellular effects of food contaminants and secondary plant components and their plausible interactions at the intestinal level.* Food Chem Toxicol. 46(3):813-41, **2008**.
- R. Chalghoumi, A. Théwis, Y. Beckers, C. Marcq, D. Portetelle, Y.-J. Schneider. *Adhesion and Growth Inhibitory Effect of Chicken Egg Yolk Antibody (IgY) on Salmonella enterica Serovars Enteritidis and Typhimurium In Vitro.* Foodborne Pathog Dis., **2009**.
- B. Romier-Crouzet, J. Van De Walle, A. During, A. Joly, C. Rousseau, O. Henry, Y. Larondelle, Y.-J. Schneider. *Inhibition of inflammatory mediators by polyphenolic plant extracts in human intestinal Caco-2 cells.* Food Chem Toxicol. 47(6):1221-30, **2009**.
- T. Sergent, I. Dupont, C. Jassogne, L. Ribonnet, E. van der Heiden, M.-L. Scippo, M. Muller, D. McAlister, L. Pussemier, Y. Larondelle, Y.-J. Schneider. *CYP1A1 induction and CYP3A4 inhibition by the fungicide imazalil in the human intestinal Caco-2 cells-comparison with other conazole pesticides.* Toxicol Lett. 184(3):159-68, **2009**.

Funding

- Walloon regional government (DGO 6)
- Federal Belgian Science Policy (BELSPO)
- Fondation Louvain
- Fonds de la Recherche Scientifqiue (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 spectometry 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

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- 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 subspecialties : cardiopediatry, endocrinology, gastroenterology, neonatology, onco-hematology, neuropediatry, 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 pae-diatricians.

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
- Pharmacocinetics
- Phase I & II studies

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Biobank for Vascular Anomalies

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- 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.

Representative References

- L. Boon, J. Mulliken, O. Enjolras, M. Vikkula. *Glomuvenous malformation (glomangioma) and venous malformation: distinct clinicopathologic and genetic entities.* Arch. Dermatol. 140, 971-976, **2004**.
- P. Brouillard, M. Ghassibe, A. Penington, L. Boon, A. Dompmartin, K. Temple, M. Cordisco, D. Adams, F. Piette, J. Harper, S. Syed, F. Boralevi, A. Taïeb, S. Danda, E. Baselga, O. Enjolras, J. Mulliken, M. Vikkula. *Four common glomulin mutations cause two thirds of glomuvenous malformations ("familial glomangiomas") : evidence for a founder effect.* J. Med. Genet. 42(2):e13, **2005**.
- P. Brouillard, M. Vikkula. *Genetic causes of vascular malformations.* Hum. Mol. Genet. 16 Spec No. 2:R140-149, **2007**.
- N. Revencu, L. Boon, J. Mulliken, O. Enjolras, M. Cordisco, P. Burrows, P. Clapuyt, F. Hammer, J. Dubois, E. Baselga *et al. Parkes Weber syndrome, vein of Galen aneurysmal malformation, and other fast-flow vascular anomalies are caused by RASA1 mutations.* Hum. Mutat. 29, 959-965, **2008**.
- M. Jinnin, D. Medici, L. Park, N. Limaye, Y. Liu, E. Boscolo, J. Bischoff, M. Vikkula, E. Boye, B. R. Olsen. *Suppressed NFAT-dependent VEGFR1 expression and constitutive VEGFR2 signaling in infantile hemangioma.* Nat. Med. 14, 1236-1246, **2008**.
- N. Limaye, L. Boon, M. Vikkula. *From germline towards somatic mutations in the physiopathology of vascular anomalies.* Hum. Mol. Genet. 18 : R65 - R74, **2009**.
- N. Limaye, V. Wouters, M. Uebelhoer, M. Tuominen, R. Wirkkala, J. Mulliken, L. Eklund, L. Boon, M. Vikkula. *Somatic mutations in angiopoietin receptor gene TEK cause solitary and multiple sporadic venous malformations.* Nat. Genet. 41(1) , 118-124, **2009**.
- A. Ghalamkarpour, C. Debauche, E. Haan, N. Van Regemorter, Y. Sznajer, D. Thomas, N. Revencu, Y. Gillerot, L. Boon, M. Vikkula. *Sporadic in utero generalized edema associated with mutations in the lymphangiogenic genes VEGFR3 and FOXC2.* J. Pediatrics. 155(1), 90-93, **2009**.
- A. Ghalamkarpour, W. Holnthoner, P. Saharinen, L. Boon, J. Mulliken, K. Alitalo, M. Vikkula. *Recessive primary congenital lymphedema can be caused by a VEGFR3 mutation.* J. Med. Genet. 46(6), 399-404, **2009**.

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

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- 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 successfuly identified a causative gene and several new disease-linked regions for various diseases.

Representative References

- I. Gutierrez-Roelens, T. Sluysmans, M. Jorissen, M. Amyere, M. Vikkula. *Localization of candidate regions for a novel gene for Kartagener syndrome.* Eur. J. Hum. Genet., 14(7) : 809-15, **2006**.
- B. Lorenz-Depiereux, M. Bastepe, A. Benet-Pages, M. Amyere, J. Wagenstaller, U. Müller-Barth, K. Badenhoop, S. M. Kaiser, R. S. Rittmaster, A. H. Shlossberg, J.-L. Olivares, C. Loris, F. J. Ramos, F. Glorieux, M. Vikkula, H. Jüppner, T. M. Strom. *DMP1 mutations in autosomal recessive hypophosphatemia implicate a bone matrix protein in the regulation of phosphate homeostasis.* Nat. Genet., 38 : 1248-50, **2006**.
- I. Balikova, K. Martens, C. Melotte, M. Amyere, S. Van Vooren, Y. Moreau, D. Vetrie, H. Fiegler, N. P. Carter, T. Liehr, M. Vikkula, G. Matthijs, J.-P. Fryns, I. Casteels, K. Devriendt, J. Vermeesch. *Autosomal-dominant microtia linked to five tandem copies of a copy-number-variable region at chromosome 4p16.* Am. J. Hum. Genet., 82 : 181-7, **2008**.
- E. Vanneste, T. Voet, C. Le Caignec, M. Ampe, P. Konings, C. Melotte, S. Debrock, M. Amyere, M. Vikkula, F. Schuit, J.-P. Fryns, 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**.
- L. Knoops, M. Amyere, D. Selleslag, J. Van Hees, M. Girardot, L. Michaux. *Analysis of the progression of JAK2 V617F positive myeloproliferative neoplasms by single-nucleotide polymorphism array does not reveal a strong chromosomal instability.* Cancer. Genet. Cytogen., 192(2), 102-104, **2009**.

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 succesfully 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 metabolisation (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.

Representative References

- P. Wallemacq, R. Verbeeck. *Comparative clinical pharmacokinetics of tacrolimus in paediatric and adult patients.* Clin. Pharmacokinet., 40, 283-95, **2001**.
- M. Mourad, J. Malaise, D. Chaib Eddour, M. De Meyer, J. König, R. Schepers, J.-P. Squifflet, P. Wallemacq. *Correlation of mycophenolic acid pharmaco-kinetic parameters with side effects in kidney transplant patients treated with myco-phenolate mofetil.* Clin. Chem., 47, 88-94, **2001**.
- 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. VanKerckhove, 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 I 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. Undre, 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 ressources", 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.

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

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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…

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

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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 Wydzial 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 Civilta´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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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 Universite 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-strenghtening

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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

SENIOR SCIENTISTS

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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 leds, 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**.
- G. Schamps. *Les réglementations belge et européenne relatives aux expérimentations sur la personne humaine et les mesures de protection des personnes vulnérables : les mineurs, les majeurs incapables et les personnes en situation d'urgence.* In La recherche clinique avec les enfants : à la croisée de l'éthique

et du droit. Belgique, France, Québec, M.-L. Delfosse, M.-H. Parizeau, J.-P. Amann (Ed.), Québec, Les Presses de l'Université Laval, Louvain-la-Neuve, Anthémis, 159-265, **2009**.

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 [Switserland], 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, Switserland)
- Faculté de droit de l'Université de Genève (Switserland)
- Fondation Brocher (Genève, Switserland)
- 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.
- Presidence 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