# Flanders par excellence

## Top scientists hosted by Flemish research institutions

Flemish government

I am proud to present some of Flanders' finest minds: the first Methusalem and Odysseus laureates, as well as the ERC grant holders in Flanders.

Today, more than ever, we have to be prepared for one of the greatest challenges of this century: to guarantee a continuous influx of high quality human capital in order to achieve scientific excellence and keep innovation at the top level.

**Odysseus,** the cunning Greek hero, wandered around the earth for several years before returning to his homeland. Likewise, the Odysseus funding programme offers Flemish scientists occupying a position at a university abroad the opportunity to return to their homeland. Internationally recognised researchers are offered a position at the Flemish institute to set up an own research group or open up a new line of research.

**Methusalem**– Methuselah in English – refers to a well-known biblical patriarch who lived to the age of 969 and gathered vast wisdom and knowledge. Today, every Flemish university has a number of researchers enjoying international recognition. Up till now they strongly depended upon project financing. By giving leading researchers a seven-year period of structural financing, the Methusalem program offers them the means to focus on science rather than on funding.

**The European Research Council Starting Independent Researcher Grants** give financial support to research leaders to conduct a frontier research project hosted by a Flemish research institute.

All these funding programs aim to attract top researchers to Flanders and to provide stable conditions to keep them here. "Bringing great ideas to life" is the motto of the European Research Council. "Bringing and keeping great minds to Flanders" could be that of the Flemish government. The Flemish government's aim is to stimulate scientific excellence by supporting the very best.

I am proud to present to you the very best of the above-mentioned programs in Flanders. Their achievements are impressive; their ambition is promising. I am convinced the grants will contribute substantially to the development of our scientific knowledge and will form the basis of the innovation and economy of the future.

Patricia Ceysens
Flemish Minister for Economy, Enterprise, Science, Innovation and Foreign Trade

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# ERC Starting Independent Researcher Grant

With the slogan "Bringing great ideas to life", the European Research Council is the new flagship of European research. The intention of the ERC is to stimulate scientific excellence by supporting outstanding individual scientists.
With the Starting Independent Researcher Grant, the European Commission seeks to support promising young scientists who pursue frontier research in any field of science, engineering and scholarship and who have the potential to become independent research leaders. Frontier research is defined by the ERC as "the pursuit of questions at or beyond the frontiers of knowledge, without regard for established disciplinary boundaries". Applications can be made in any field of research. Successful candidates are awarded a grant of up to 400.000 euros yearly for a period of five years, in order to set up or consolidate a top research team.
The selection of the candidates is carried out by peer review panels, composed of independent experts, covering all fields of science, engineering and scholarship. Excellence is the only selection criterion for the ERC Starting Grants: excellence of the Principal Investigator, of the proposed research project and of the host institution.

For more information contact the Flemish National Contact Point for Ideas at www.europrogs.be. General information can also be found at erc.europa.eu.

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Eva, of Slovak nationality, was born on December 15, 1969. She has two daughters, Jarmilka and Libuska. She obtained her PhD in 1998 at the Institute of Biophysics Academy of Sciences of the Czech Republic in Brno with a thesis on the "Manipulation of intracellular location of cytokinin specific beta-glucosidase in transgenic tobacco plants as an approach in the investigation of subcellular compartmentation of cytokinin conjugates"). Several postdoctoral fellowships followed in Germany, where she performed research, among others on "The role of auxin and auxin transport in lateral root development", "Specificity of Aux/IAA and ARF interactions in *Arabidopsis* embryo development" and the "Role of hormonal regulation by auxin and cytokinin in lateral root development"). Since August 2007, Eva fulfils a young leader position at the Plant Systems Biology Department at the Flanders Institute for Biotechnology (VIB) in Ghent (Belgium), where she works on "Hormonal cross-talk in plant organogenesis".

## Hormonal cross-talk in plant organogenesis

Plants represent a major life form on the earth. One of the unique features of plants is their extreme developmental flexibility. If we compare the development of plants and animals we will uncover a fundamental difference. Both, plants and animals start life from a single cell called a zygote, and they undergo complex embryonic development in the mothers body. However, whereas animals' including humans' have at the moment of their birth a body of an exactly defined structure with all organs typical for an adult organism formed; plants start their postembryonic life with a simple body that undergoes complex developmental modifications characterised by the formation of many new 'organs' such as leaves, side branches, flowers or lateral roots. The shaping of the plant body continues throughout life and basically, all structures we see on the adult plant are the result of organogenesis that occurred only after the plant seed germinated. This amazing developmental plasticity reflects an important feature of the plant's life strategy. Plant's in contrast to animal's cannot escape dangerous situations, or follow their prey to feed themselves, however, they have evolved another very successful strategies for survival. Rapid modulation of growth and development in reaction to different environmental stimuli, such as availability of nutrients, light, water or temperature fluctuations, are their main survival tactic.

An important role for the regulation and coordination of plant developmental processes is the play of signalling substances (phytohormones) such as auxin, abscisic acid, brassinosteroid, cytokinin, ethylene, gibberellin, and jasmonic acid. Physiological and genetic approaches have been successfully used and, particularly in the model plant *Arabidopsis thaliana*, led to a basic molecular understanding of hormone action in plants. However, at the same time, these studies revealed that hormone action in plants is, determined by complex interactions between hormonal signalling pathways to a much larger extent in plants than in animals. The molecular basis for hormonal cross-talk is largely unknown and its clarification represents a major challenge in the coming years for plant biology research .

In our research we focus on the root system and lateral root formation in Arabidopsis as an experimental model to address molecular mechanism(s) underlying the cross-talk between hormonal signalling pathways.

Root systems perform the essential tasks of providing water, nutrients and physical support to the plants. Roots unceasingly branch throughout the plant's lifetime. The number and placement of new lateral roots are strongly influenced by environmental conditions. The plasticity of a root system represents one mechanism by which plants overcome their inability to move towards nutrients. Hence, lateral root formation is of key agronomic significance because it can greatly affect adaptability of plants to various growing conditions.

Lateral root organogenesis is also exceptional from a developmental point of view because it involves the postembryonic production of an entirely new organ from a small number of already differentiated cells. Lateral roots originate from a few pericycle cells that undergo a series of divisions, and give rise to a few short beginning cells. After initiation, coordinated cell division and differentiation occur, giving rise to lateral root primordia. Primordia continue to grow, emerge through several tissue layers of the primary root and finally a new apical meristem is established that takes over the responsibility for growth of mature lateral roots.

Similarly to other developmental processes, lateral root formation is governed by a complex network of hormonal regulations. The phytohormone auxin dominates this process. Both lateral root initiation and primordia development have been demonstrated to be governed by auxin; for example, an increase of auxin levels results in enhanced lateral root initiation and, on the other hand, mutants impaired in auxin signalling completely fail to initiate lateral roots. A crucial, additional level of regulation of auxin action in lateral root organogenesis is its intercellular distribution. In *Arabidopsis*, the family of influx and efflux carrier (PIN) proteins mediate intercellular auxin transport and, thus, determine auxin distribution within plant tissues. Chemical or genetic interference with this polar auxin transport machinery severely affects lateral root initiation.

Also, during post-initial stages auxin transport-dependent asymmetric distribution (auxin gradient) is crucial for the development of primordia. Polar, subcellular localization of auxin efflux PIN proteins determines the direction of the auxin flow and coordinated changes in PIN localization during lateral root formation play a key role in the formation of the auxin gradient and in lateral root development.

Transport-dependent auxin distribution acts immediately upstream of lateral root formation and has been shown in multiple developmental processes to integrate various signalling pathways. Therefore, some of the hormonal pathways might mediate their effect on organogenesis through modulation of auxin distribution. Recent observations support this hypothesis and also pointed out that other hormonal pathways participate in the regulation of lateral root organogenesis as well. For example, cytokinins effectively counteract the promotive effect of auxin on lateral root initiation and our preliminary data suggest that expression of several members of the auxin transport machinery is tightly regulated by the cytokinin pathway. Another class of plant hormones, brassinosteroids enhance both auxin transport and lateral root initiation, while reduced brassinosteroid biosynthesis results in decreased expression of several auxin efflux carriers. Abscisic acid suppresses both the auxin response in lateral root primordia and the activation of the lateral root apical meristem. Mutations in the *Arabidopsis TIR3* gene disrupt polar auxin transport as well as gibberellin responses, causing characteristic auxin and gibberellin phenotypic defects, such as a reduced number of lateral roots. Altogether, the data indicates that multiple signalling pathways converge in lateral root organogenesis and, in concert with spatial auxin signalling, collectively regulate this developmental process.

Thus, lateral root development in *Arabidopsis* represents an ideal system for studing the mechanisms of plant hormone action, the molecular basis of their interactions, and the role of these interactions in organogenesis.

## FRANKY BOSSUYT

*Left to right: Franky Bossuyt, Ines Van Bocxlaer, Wim Vandebergh, Sunita Janssenswillen, Kim Roelants, Ann Mannaert, Arent Raepsaet.*

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Franky Bossuyt started amphibian research as a hobby while working in a brewery as a biochemical quality engineer. Starting from 1991, he travelled every summer to the Indian subcontinent and was fascinated by the diversity of amphibians there. In 1995, he decided to quit his job and study biology. He obtained his PhD in 2001 with Greatest Distinction. He has built up an impressive publication record and significantly contributed to clarify a number of key issues in amphibian evolution. Additionally, he revealed an unknown adaptive radiation of 120 species of frogs in Madagascar, discovered over 100 new species of frogs in Sri Lanka, described the new frog family Nasikabatrachidae and documented over 20 new species of frogs from India. However, his research has gone beyond bio-discovery *sensu stricto*: For example, in collaboration with Sri Lankan scientists, he published genetic evidence proving Sri Lanka's being a distinct hotspot of biodiversity, and showed that the island is not just the backyard of the Indian mainland. Several of these findings were published in top journals such as Proceedings of the National Academy of Sciences USA, Nature and Science. Franky is now an independent research leader at the FWO and a professor at the Vrije Universiteit Brussel, and he leads a team of researchers that are studying various aspects of amphibian evolution.

### Tracing Antimicrobial Peptides and Pheromones in the Amphibian skin (TAPAS)

Molecular phylogenetic analyses have shown that the present-day species diversity of amphibians arose through a series of explosive radiations that showed a high temporal correlation with major events in earth history. The rapid differentiation from a single lineage has repeatedly led to nearly identical ecomorphs in each independent radiation. These observations raise questions regarding to what extent diversification has been driven by natural or sexual selection. Two general mechanisms that have been proposed to contribute to accelerated speciation in vertebrate radiations are (1) *ecological diversification* (natural selection) and (2) *differentiation of sexual signalling* (sexual selection). The former entails the emergence of specialised traits that sustain niche differentiation within a population and as such lead to reproductive isolation of different ecomorphs. The latter may trigger speciation if sexual signal variation in one of the sexes is linked to divergent sexual preferences in the other.

The Research Project TAPAS aims at studying amphibian skin peptides as an ideal model for testing the relative importance of ecological adaptation and sexual communication in evolutionary radiations. Antimicrobial peptides protect amphibians against a broad diversity of pathogens in their immediate environment, and changes in structure, function and target organisms may have accompanied evolutionary shifts in ecological niche occupation. Upon examination, pheromone peptides have been found to be species-specific in amphibian taxa and therefore likely to have played a key role in the sexual isolation of populations. Moreover, there is interplay between the ecological and sexual functions, since some studies suggest that amphibian pheromones might evolve from antimicrobial peptides.

Because recent studies of amphibian antimicrobial peptides have an explicit pharmacological focus and have been restricted to only a few closely related genera, the origin, diversity, and functional diversification of these molecules remain poorly understood. Furthermore, although multiple behavioural tests indicate chemical communication during courtship in many amphibian species, only a single peptide pheromone has been characterised in anurans (frogs and toads), and only three in caudates (salamanders and newts), and the function of multiple sexual secondary glands (e.g., femoral glands, nuptial pads) in sexual communication has never been investigated.

This project aims at an integration of transcriptome analyses, peptidome analyses, functional assays, and phylogenetic analyses to:

1. Identify and characterize novel antimicrobial and pheromone skin peptides in a representative of all amphibian families.
2. Study the evolution of these molecules by mapping diversity and function in well-supported phylogenies.
3. Determine the relative contribution of different genetic mechanisms to the rise of antimicrobial and pheromone peptide diversity (e.g. recruitment from genes with other functions, tandem duplications, gene conversion etc.,).
4. Test the relative contributions of skin peptide evolution (ecological adaptation and/or sexual signal differentiation) in shaping species diversity in amphibian evolutionary radiations.

## Techniques

Amphibian antimicrobial and pheromone peptides are identified through biochemical analyses of secretion, skin or glands. Analysis of the peptidome is necessary to understand the structure and function of a diversity of peptides secreted by amphibian skin glands. Peptides that are identified as a potential antimicrobial peptide or sex pheromone and of which the full sequence cannot be unambiguously determined by mass spectrometry, are further sequenced. cDNA libraries (based on the mRNA in skin and/or glands) are analysed to (1) rapidly estimate the diversity of expressed peptides, and (2) perform phylogenetic analyses based on the longer mRNA precursors.

Candidate peptides are tested in antimicrobial and toxic assays. Female attraction and molecule specificity are tested with synthesized candidate pheromones (secreted by males only). The timing and relative importance of ecological (antimicrobial) and sexual (pheromone) peptide diversification is estimated by mapping its origin and the loss and functional gain/loss of peptides on an evolutionary tree. Finally, the project aims to estimate evolutionary rate shifts of peptide diversification in amphibian evolution and to test Darwinian selection at the molecular level.

*New horizons:*
The results of this project are expected to throw new light on amphibian defense and chemical communication. This knowledge may be an important contribution to understanding amphibian decline, which is illustrated by two examples:

- Chytridiomycosis, a skin disease caused by the chytrid fungus Batrachochytrium dendrobatidis has been linked with continuing amphibian population declines worldwide. It is intriguing to understand the correlation between resistance to lethal infection by B. dendrobatidis and synthesis of antimicrobial peptides by the host amphibian.
- Systems of chemical communication are especially vulnerable to anthropogenic changes, such as exposure to pesticides, herbicides, and industrial pollutants. Hence, the identification of new pheromones and a better understanding of chemical communication can significantly contribute to the conservation of threatened species.

## CHRISTIAN CLASEN

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Christian Clasen was born in Hamburg, Germany, on the 23rd of February 1973. He is married to Zoë Clasen and has two sons, Henry and Julius.

He obtained his Diploma in Chemistry from Hamburg University in 1999 and conducted his doctoral studies there at the Institute of Technical and Macromolecular Chemistry. He held a postdoctoral position in the Department of Mechanical Engineering at the Massachussets Institute of Technology (MIT) from 2001 to 2002, returning after to Hamburg where he pursued his Habilitation in Technical Chemistry in 2003. He joined the Chemical Engineering Department of K.U.Leuven in October 2006 where he took up a position for Chemical Product Design within the Group of Applied Polymer Processing and Rheology. His research focusses on the investigation of the flow and deformation properties of complex fluids and soft solids in microdimensions and –applications, and the development of required novel experimental techniques and their use within applied problems.

## Complex fluids in microdimensions

The microstructure of a solution or a system in a "soft" state can show a complex behaviour. Determining and controlling the composition of supramolecular structures allows for a specific design of the material properties of a fluid, from purely viscous to highly elastic or even a complex, time-dependent behaviour. Investigation of these phenomena on a microscopic level are even more challenging, not only due to recent interest in fields such as micro reactors or lab-on-a-chip designs. Also naturally occurring flows of polymers as the spinning of protein solutions, filament formation in roller-coating or mastication of food products show a fundamentally different behaviour on a microscopic scale.

Fig. 1: Highspeed imaging of the 'gobbling drop' effect during the jetting from a 150µ m nozzle, caused by traces of polyacrylamid in aqueous solution at a critical flow rate at which the end drop will not detach, but climb up the liquid filament and consume ('gobble') several of the following drops (images acquired with 4000 frames per second).

A main focus of our research is therefore the development of new techniques to determine the deformation and stress profiles of complex fluids in micro time and dimension scales. We focus in, particular, on the investigation of extensional free surface flows as they occur in several natural processes, for example, during the spinning of spider silk, but also in many industrial applications such as inkjet printing or atomization and extrusion processes. In order to investigate those phenomena on the microscale, we have developed novel high-speed imaging and –processing techniques for the investigation of free surface flows, followed by theoretical model development and simulation to evaluate the experimental parameter space and to link the research to the actual design and application of a new techniques and materials.

The clarification of the ingenious structures and properties of natural biopolymers, as for example snail mucus, opens up an immense potential for the development of new polymer fluids and applications (biomimetics). For example, only the microrheological in vivo clarification of the viscoelastic properties of spider silk spinning dope allowed for a correlation with the protein β-sheet formation in the microdimensional spinning canal.

Fig. 2: Ex vivo microrheology of spinning dope from Nephilia clavipes (left). The viscosity and elasticity of 0.7 µl of silk solution, isolated from the spinning gland (right), can be determined over several decades of deformation rate with novel experimental techniques.

Another focus of our research is therefore the development of techniques to probe the actual state of stress of a complex fluid in micro dimensions. We therefore design and develop novel experimental techniques that allow for the detection of the state of stress in micro-volumina and micro-films of liquid and soft solids. We can then follow the effects of the microstructure of a fluid (from micro-particles and gels to weak network structures or self assembling systems) on the changing states of stress that occurs: during the spreading of a skin cream down to micrometer dimensions and relate this to the skin sensation, or with the mechanical properties of the slime film under a snail foot while it is crawling upside down on a wall without falling.

*Electrospinning - The planned research within the ERC project*

The performance and physical attributes of a material and product can be tailored to so far unmatched material strengths and properties by creating new nano fibrous structures from polymers via electrospinning. The electrospinning process uses an electric field to produce charged jets of polymer solutions or melts. Bending instabilities of the jet, caused by surface charge lead to extremely high local extension rates of the jet and produce fibres with diameters of the order on a few nanometers that consist of highly aligned polymer strands.

The biggest unsolved problem of the electrospinning process is the sensitive equilibrium between surface tension, viscosity, elasticity and conductivity of the polymer solutions. These are controlled by molecular parameters as the molar mass, chemical microstructure, conformation in solution or supramolecular structures via intermolecular interactions. The optimal combination of these parameters is, as yet, unknown.

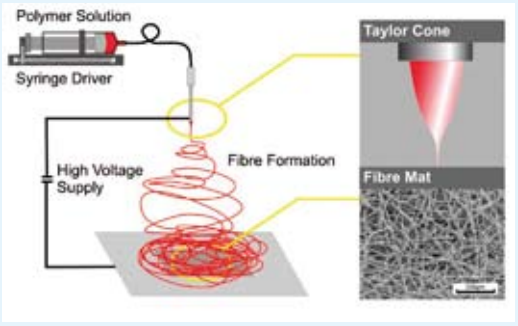


Fig. 3: Electrospinning. A charged droplet of polymer solution produces a thin jet from its tip that is accelerated towards an oppositely charged collector. In order to maximize the distance between charges, the jet extends and bends while solidifying due to solvent evaporation. The endless dry fibre that is collected can reach a diameter of the order of a few nanometers.

Within this project, a novel and unique technical platform will be developed and installed, that is generally capable of imaging and analysing high speed free surface flows in miniaturised dimensions. This platform will then be utilized to analyse electrospinning process parameters and to connect them to the material properties and the molecular structure of the polymer solution. Only such a fundamental understanding of the relation of these properties to the flow and mass transfer phenomena on the micro-time and -dimensional scale will allow to the required structural and material properties of nano-scale fibres for the second part of this project to be designed:

- novel fibre/matrix composites for the creation of ultra-high-strength hydrogel membranes;
- short fibre morphologies created by a novel controlled disruptive spinning process at the boundaries of the parameter space;
- tailoring of fibre properties from renewable resources by modification of the chemical side-chain structure of polysaccharides.

## JAN COOLS

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Jan Cools was born in Ostend on June 5th 1974. He obtained his Bio-engineer degree (cell and gene biotechnology) in 1997 at the K.U.Leuven. After his university studies, he started his career in research as a PhD student at the Center of Human Genetics (K.U.Leuven) under the supervision of Prof. Peter Marynen. He finished his PhD in May 2001, presenting a thesis on the role of ETV6 gene rearrangements in leukemia.

In October 2001 Jan moved with his family to Boston (USA) to continue leukemia research as a postdoctoral researcher in the laboratory of Prof. Gary Gilliland at Harvard Medical School. During this period, Jan discovered a novel oncogene that causes chronic eosinophilic leukemia, a rare form of leukemia that is characterised by the overproduction of eosinophils in the blood. Work on this topic continues and has resulted in the identification of the mechanism that shows how this protein becomes an oncogenic protein. Perhaps the most important results of these studies is that several drugs were identified that can be used to treat this form of leukemia.

In October 2003 Jan returned to Prof. Peter Marynen where he continued his research on oncogenes involved in the pathogenesis of leukemia. During this period he shifted his main focus to the study of T-cell leukemia. Since 2005 he has been a professor at the K.U.Leuven, and since 2008 also a group leader at VIB (Vlaams Instituut voor Biotechnologie). In 2008 he received an ERC Starting Grant from the European Research Council to continue his work on T-cell leukemias. In addition to his research, Jan Cools is also an associate editor of *Haematologica*, the official journal of the European Hematology Association (EHA).

## T-cell leukemia

T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive T-cell malignancy that is most common in children and adolescents. Current treatment for T-ALL consists mainly of multi-agent combination chemotherapy. Improvements of treatment regimens have led to significant increases in survival rates, but come at the cost of significantly severe short-term and potentially long-term side effects. In addition, long-term survival rates for adult T-ALL patients are under 60 years of age still below 40% and are further decreasing in older patients.

Over the past 20 years, the study of the genetics of T-ALL has identified a number of specific defects in the DNA of leukemic cells. Most common abnormalities are: (1) deletions of the gene CDKN2A (also known as p16), (2) DNA rearrangements involving transcription factor genes such as TLX1, TLX3, TAL1, LYL1, and (3) mutations in the NOTCH1 and PTEN genes. In addition, we have identified a NUP214-ABL1 fusion gene and duplication of the MYB gene in a subset of T-ALL patients.

All these DNA defects are acquired defects that initially occur in one single blood cell and then start to divide and gives rise to a large number of progeny, which eventually results in the accumulation of immature T-cells in the body. We now know that just one mistake in the DNA is not sufficient, but that this process requires the accumulation of at least four different types of mutations, resulting in the deregulation of proliferation, survival, differentiation, cell-cycle control, and stem-cell maintenance in the T-cells.

Similar to other types of leukemia, mutations in important signalling proteins such as RAS and tyrosine kinases have been identified in T-ALL, and are believed to account for the abnormal proliferation and survival of leukemic cells. However, in 80% of all cases, the cause of the proliferation and survival advantage of T-ALL cells remains unknown.

The general aim of this project is to generate better insights in to the way the different oncogenes work together to

cause T-ALL and to identify novel targets for therapy. The current therapy does not specifically target leukemic cells, and also affects many normal cells, resulting in severe side effects. A better understanding of the oncogenes and the way they work could result in the identification of novel strategies for specifically targeting leukemic cells and leaving normal cells unaffected. Such novel therapies would specifically target proteins that are present only in leukemic cells or proteins and on which the leukemic cells completely depend for their survival.

In order to identify such proteins, we will perform a molecular genetics analysis of T-ALL, and we will functionally test a large amount of candidate proteins using novel technology (RNAi technology). In addition, we will perform screens with drug libraries to try to identify chemical compounds with a specific activity on the leukemic cells. A special focus will be on signalling pathways that may be involved in the proliferation and survival of the leukemic cells. Based on these results and on our current knowledge of T-ALL we will develop in vitro and in vivo models of T-ALL, in order to study the cooperation of these specific oncogenes, and to determine what type of mutations are required for the development and maintenance of the leukemic cells. These in vitro models will also be used in the functional screens, and will allow us to test the oncogenes/oncoproteins and their signalling pathways as targets for therapy.

While a large number of potential targets for therapy are known, almost all of the new cancer drugs are directed against existing therapeutic targets. This may reflect, in part, for the identification of novel drugable targets, the need for better and larger throughput screens and for further improvement in our understanding of the disease pathogenesis. In the context of T-ALL, there is a strong need to identify the mutations that provide a proliferation and survival advantage to the leukemic cells, since these oncogenes may represent novel drugable targets. To date, the cooperation between different types of oncogenic events has not been addressed or explored for therapeutic application. A further molecular characterization of T-ALL will provide better insight into the critical pathways that are affected in T-ALL, and will allow the generation of better in vitro and in vivo models for the study of the cooperation of the different oncogenes and the study of targeted therapies. Using high resolution genome-wide screens and focussed functional screens, important novel oncogenes and other targets for therapy can be identified, and through our functional studies they can be translated into finding novel therapies.

This study will contribute to the development of novel diagnostic tools and therapies for the treatment of T-ALL. The novel insights into the cooperation of different oncogenic events in T-ALL and the research tools that are generated for this project will also be applicable for the study of other types of cancer.

## ANN HEYLIGHEN

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Ann Heylighen was born in Leuven in 1973. She studied architecture at the K.U.Leuven and ETH Zürich, and obtained her MS in Engineering: Architecture (diploma Burgerlijk ingenieur-architect) in 1996. Since then she has been affiliated with the Architecture, Urbanism & Planning department of the K.U.Leuven, where she studies the design process in architecture and related design domains.

In 2000 she obtained her PhD under the supervision of Prof. Herman Neuckermans, supported by a PhD fellowship from the Research Foundation - Flanders (FWO). Her dissertation investigated the role of design knowledge embedded in concrete design *projects* and resulted in DYNAMO (Dynamic Architectural Memory On-line), a growing collection of building projects that stimulate and support architects' life-long learning from past design experience.

From 2000 untill 2006, she was a Postdoctoral Fellow of the FWO and conducted research at the K.U.Leuven, Harvard University and the University of California-Berkeley. During this period, the focus of her research shifted from design projects to design *processes* as sources of design knowledge.

In 2006 the K.U.Leuven appointed Ann as associate professor of the Bijzonder Onderzoeksfonds (BOF), and in 2007 the European Research Council awarded her a Starting Independent Researcher Grant for the project 'Architectural design In Dialogue with dis-Ability' (AIDA). The grant allows her to establish an interdisciplinary research team that will explore yet another source of design knowledge: the spatial experience of *people* with various capacities and limitations.

Ann is married to Sam Michiels, researcher at the Computer Science department of the K.U.Leuven.

## Architectural design In Dialogue with dis-Ability (AIDA)

*Because of their specific interaction with the built environment, people with particular disabilities are able to appreciate spatial qualities or detect problems that most architects may not even be aware of. The spatial experience of a person who is blind, for instance, is not only critical in designing accessible and comfortable buildings for the actual diversity of people, but may even inspire multi-sensory design solutions that are truly innovative. Yet how can an architect's design process be informed by these valuable experiences from people with disabilities?*

## Design research

On a daily basis, we are confronted with objects, buildings and spaces that have been designed by someone. By consequence, designers have a considerable impact on our lives. They publicly commit to ideas which influence our doings and goings, of which the advantages and disadvantages may only gradually become clear over time. Product designers see their designs eventually disappear from the market, but buildings, and displaying their designers' ideas throughout years. Or, as the American architect Frank Lloyd Wright put it: "*The physician can bury his mistakes, but the architect can only advise his client to plant vines.*"

Given the profound impact that designers have, one of the objectives of design research is to gain insight into how designers think and work—or the nature of design expertise—and to establish those particular strengths and weaknesses. At the base of this relatively recent discipline lays the axiom that there exist forms of knowledge peculiar to the awareness and ability of designers, which clearly distinguish them from scientists or artists. An articulate understanding of these *designerly ways of knowing* is obviously important for design education—which should nurture the development of this ability in the designers of tomorrow—but also for, say, the development of appropriate design software.

## Experiencing what designers see

Key to these *designerly ways of knowing* is the designer's use of models and codes that rely heavily on graphic information. In architecture, as in other design domains, the visual is the mode in which designers know, think and work; their sensorium—that is, the way their senses are organised—is strongly developed through visual input. This bias towards vision, and the suppression of other senses in the way architecture is designed, taught and critiqued can result in a disappearance of sensory qualities. People's experience and assessment of the built environment relies on a combination of multiple senses: the way a space looks is obviously important, but also the way it feels and the sound and smell of the space play a role. Increasingly, however, architecture is produced in consideration of mainly one sense: sight.

This visual way of knowing and working clearly distinguishes designers from, for instance, persons with visual impairment. Because the sensorium of these persons is strongly developed in a tactile and auditory way, they are able to appreciate spatial qualities or detect obstacles that most architects may not even be aware of.

Interestingly, this phenomenon is not limited to sensory disabilities such as blindness, but also holds for certain types of mental disabilities. Mental retardation, for instance, challenges a person's ability to deal with most normally complex environments, highlighting the importance of a clear layout and the signification of orientation and transition from one space into another.

In general, through their specific interaction with buildings and spaces, persons with particular disabilities develop a valuable form of expertise to complement architects' design ability. Key here is the notion of expertise as differentiation or *connoisseurship*, according to which an expert is someone who can perceive and differentiate in body or environment certain variables that are meaningless for a novice. (Think, for instance, of a sommelier who can discern varieties of bitterness in wine.) Because of their specific experience of space, persons with disabilities are the most vulnerable to exclusion as a result of inappropriate design, but at the same time best placed to analyse obstacles and to help find more inclusive solutions. Our research shows that their expertise is not only critical in designing buildings that are accessible and comfortable for the actual diversity of people; but may even inspire genuinely innovative design solutions that expand the overall multi-sensory qualities of the built environment. Therefore, while architects tend to associate disabled persons with accessibility norms that hamper their creativity and design freedom, our research gives these persons the role of experts in the search for innovation in architectural design.

## Dialogue

If we acknowledge that the spatial experience of persons with certain disabilities represents a potential resource that may complement the knowledge and skills of professional designers, the next question that arises is : how can we unlock this resource so that architects can effectively make use of it during the design process?
In other words, how can their specific expertise be valorized to design better spaces for all of us?

In our research, we explore the *dialogue* between architects and persons with disabilities as a way of improving and expanding qualities in the built environment.

On the one hand, we retrospectively analyse the how and why of exceptional, innovative design projects in which disability plays a key role. A case in point is the Glass House for a Blind Man, designed by the Croatian architects Vinko Penezic and Kresimir Rogina. Initially, the dominant feature of glass—transparency and reflection—seems meaningless in the absence of sight. Yet, by juxtaposing glass with blindness, the architects came to realise that the material may provide interesting tactile qualities as well, as it permits the creation of various textures and easily transmits differences in temperature. For exceptional design projects like this, we try to reconstruct how they have been designed, and specifically how the designers gained access to the spatial expertise of persons with disabilities. Moreover, we assess whether the resulting building or space makes a difference for persons with and without disabilities. This will enable us to preliminaily understand how innovative design knowledge is produced in dialogue with disability, and to consider whether this knowledge may be applicable for future design projects.

In addition, we experimentally explore whether dialogue between architects and persons with disabilities can serve as an intentional strategy for triggering innovation in architecture. Real-world design tasks are selected from actual architectural practice in order to test and analyse scenarios for involving people with sensory or mobility disabilities as experts in the design team. At the start of the design process, architects and one or more persons with a disability are teamed up so that the impact of the latter's involvement can be traced and analysed. Unlike the retrospective part of our study, this part is based on real-time in the sense that

it examines the dialogue between architecture and disability in the context of a design process as it unfolds.

## Impact and future research

With this research, we hope to take a significant step towards understanding the multi-sensory spatial experience of people with disabilities—a resource hardly exploited in design so far—and how this experience may provide insights that stimulate innovation in architecture. The initial focus on how sensory or mobility disability may stimulate innovation in architecture should be viewed as a proof-of-concept. Later on we envisage extending the approach by including other disabilities (e.g., mental disabilities such as mental retardation, autism or Alzheimer's disease), other differences (e.g., age, cultural background, education), or by extrapolating towards other design domains (product design, graphic design, material design, software design).

In addition, we anticipate that our research will have a considerable impact on design practies and education—in architecture and other design domains. First of all, the results are expected to make a major contribution to the realisation of Design for All—or Design for More—in architectural practice. So far, efforts in this area are primarily focussed on the development of accessibility criteria, data collection, technology and sensitisation. More recently the focus seems to shift towards the development of 'Accessibility Metrics' and policy issues. Little attention has been paid so far to the role of the designer and the design process in realising the concept of Design for All, which is quite surprising given the profound impact designers may have. Insight into how the multi-sensory experience of people with disabilities made operational in architectural design is an important step towards this realisation.

At least as important, however, is the contribution to innovation in architecture *tout court*. The results of our research can give a powerful impulse to quality improvements in the built environment by stimulating and supporting the development of innovative design concepts. At first sight, viewing a building design as being independent from people might seem to offer architects more creative freedom. However, involving people in the design does not mean that creativity is sacrificed, but that new traditions are created that are both creative and respectful for the human body and brain, and in particular of the diverse ways in which the sensorium may be developed.

*References*


- Cross, N. (1982). Designerly ways of knowing. *Design Studies* 3(4): 221-227.
- Devlieger, P. Renders, F., Froyen, H. & Wildiers, K. (eds.) (2006) *Blindness and the Multi-Sensorial City*. Antwerp: Garant
- Pallasmaa, J. (2005). *The eyes of the skin*. Chichester: John Wiley & Sons.
- Penezic, V. & Rogina K. (1999). *Penezic & Rogina 59-79-99 Tokyo Works*. Zagreb.
- Suwa, M. (2005). Differentiation. *Studying Designers '05*. Sydney: Univ. of Sydney, 33-38.
- Yin, R.K. (2003). (1984). *Case Study Research. Design and Methods*. London: Sage.
- Zeisel, J. (2001). Universal Design to Support the Brain and its Development. In Preiser, W.F.E., Ostroff E (eds) *Universal Design Handbook*, Boston: McGraw-Hill, Chapter 8.

## AERNOUT LUTTUN

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Aernout was born in Roeselare on May 26 1973. After obtaining his high school diploma in classical languages at the Klein Seminarie Roeselare in 1991, he moved on to the K.U.Leuven for his university training at the Faculty of Pharmaceutical Sciences. Upon graduating as a pharmacist in 1996, he decided to join the group of Drs. D. Collen and P. Carmeliet to conduct research on the role of proteinases and angiogenic growth factors in atherosclerosis and rheumatoid arthritis, supported by the Flemish Fund for Scientific Research (FWO). In 2002, he obtained a Doctorate in Pharmaceutical Sciences with a thesis entitled 'Chronic Inflammatory Disease: The Role of Proteolysis and Angiogenesis Revisited. Therapeutic Implications.' During his PhD training, Aernout developed interest in stem cell research. Therefore, supported by the Belgian American Educational Foundation (BAEF) and the American Heart Association (AHA), he went abroad to join the Stem Cell Institute at the University of Minnesota in Minneapolis, USA, as a post-doctoral researcher under the supervision of Dr. C. Verfaillie. There, he focussed on using adult stem cells to generate blood vessels and lymphatic vessels. After three years, in 2006, he was offered a position as principal investigator at the Center for Molecular and Vascular Biology, which is one of the Centers of Excellence at K.U.Leuven. Since then, he has built up a small research unit that studies endothelial differentiation of stem cells. He recently obtained a Starting Grant from the European Research Council (ERC) for a project entitled, 'Integrated Multi-disciplinary Approach to Gain INsight into Endothelial Diversity' ('IMAGINED') that gives him the opportunity to expand his group and conduct research on the phenomenon of endothelial diversity, using stem cells as a central research tool. So far, his research has resulted in having 40 papers published in diverse scientific journals, including *Nature Medicine, Journal of Clinical Investigation, Circulation, Blood and Arteriosclerosis, Thrombosis and Vascular Biology*.

### What is endothelial heterogeneity?

Endothelial cells line the inside ('endo') of blood and lymphatic vessels. Morphological, functional and molecular analyses revealed significant heterogeneity among endothelial cells at different levels within the (lymph) vascular tree. First, arterial, venous or lymphatic endothelial cells clearly have different characteristics. A second level of heterogeneity is seen when comparing vascular beds of different organs. The latter heterogeneity is mostly found at the level of the microvasculature (i.e., the capillary bed), that adapts to the unique needs of the underlying tissue. Finally, endothelial cells have distinct characteristics in different species. This remarkable diversity finds its origin in a combination of factors. On the one hand, each endothelial cell has properties that are intrinsic (independent of external cues) and preserved upon isolation from their in vivo microenvironment. On the other hand, another part of the unique endothelial signature is rapidly lost upon in vitro culture (a phenomenon called 'phenotypic drift') since it is determined by communication with surrounding tissues and by exposure to certain external biomechanical or biochemical stimuli.

### Why is studying endothelial heterogeneity important?

The existence of endothelial heterogeneity has a tremendous clinical impact. It forms the basis of vascular-bed specific diseases (e.g., atherosclerosis, varicosis or lymphedema, restricted to arteries, veins and lymphatics, respectively) and may well contribute to the disappointing results and side-effects obtained with 'broad spectrum' (anti-)angiogenic treatments in patients. In addition, it may determine the vas-

cular tropism of metastasizing tumor cells and be the culprit for vascular-bed-specific manifestations of acquired immunodeficiency syndrome. The existence of vascular-bed specific factors (e.g., endocrine gland vascular endothelial growth factor or EG-VEGF) and inhibitors (e.g., chondromodulin-I) indeed suggests that (anti-)angiogenic therapy with ubiquitous growth factors (e.g., VEGF) or inhibitors may not be an ideal treatment. Also, endothelial cell progenitor-based revascularization approaches have not asked whether the transplanted cells acquire the desired endothelial phenotype once engrafted in a diseased tissue where environmental cues may be absent. In this context, it would be appropriate to have protocols to generate stem cell-derived pre-specialised endothelial cells, which are mostly lacking. Unravelling mechanisms of endothelial heterogeneity should offer the exciting possibility to design tailor-made therapies, which remains the main challenge in curing vessel-related disease. In addition, revealing the 'vascular address' of each vessel, would allow targeting of systemically applied therapeutic agents to the region of interest, thereby minimising the risk for side-effects in other vascular territories.

## How can endothelial heterogeneity be studied?

Despite the early recognition of endothelial heterogeneity in the 1950s, surprisingly little is currently known about the mechanisms that determine it. Only recently have techniques become available allowing a more in-depth study of distinct aspects of endothelial diversity. Morphological diversity is mostly analysed by electron microscopy and vascular casting, thereby focussing on the presence or absence of specialised features. In general, three different endothelial cell types are distinguished morphologically: those lacking fenestrations ('continuous endothelial cells'; e.g., in cardiac muscle, brain), those featuring fenestrations sealed by a diaphragm ('fenestrated endothelial cells'; e.g., in endocrine glands) and those featuring fenestrations without diaphragm ('discontinuous or sinusoidal endothelial cells'; e.g., in liver). Molecular heterogeneity has been studied on the DNA/RNA level by microarray, substractive hybridization or serial analysis of gene expression, or at the protein level using two-dimensional electrophoresis, mass spectrometry or substractive antibody expression cloning. In vivo approaches, most of which are not possible in humans, include specific antigen staining, injection of lectin variants, injection of antibodies, the generation of knock-in reporter mice, in vivo promoter activity analysis, phage display (in which bacteriophages expressing peptides or antibody fragments are injected and specifically retained by certain vascular beds), and most recently, laser capture microdissection. Very few available studies on endothelial heterogeneity have involved stem cells in their methodology and none of them have used an integrated approach as described here in this research programme.

## Which stem cells could be used to study endothelial heterogeneity?

Basically, any stem or progenitor cell with the ability to make endothelial cells is a potential tool for the study of endothelial heterogeneity. Several stem cell types have been considered as potential endothelial precursors, including unfractionated bone marrow cells, embryonic stem cells, mesenchymal stem cells, umbilical cord or peripheral blood mononuclear cells, adipose tissue-derived cells, endothelial progenitor cells, blood outgrowth endothelial cells (BOEC), multipotent adult progenitor cells (MAPC) and mesoangioblasts. Some of the studies, including our own, have demonstrated that there is significant heterogeneity among these progenitors in terms of their phenotypic/functional characteristics, their ability to become incorporated into nascent blood vessels and their potential to be specialised into different subtypes of endothelium.

## How will this research programme study endothelial heterogeneity?

The inherent complexity of endothelial diversity likely requires an integrated multi-disciplinary approach that addresses both endothelial cell-intrinsic and -extrinsic cues. Therefore, this research programme entitled, 'Integrated Multi-disciplinary Approach to Gain INsight into Endothelial Diversity' ('IMAGINED'), proposes to go beyond the state-of-the-art by using an unprecedented and innovative integrated in vitro/in vivo multi-disciplinary approach based on stem/progenitor cells and small animal models and has the following objectives: (i) to expand our knowledge of endothelial cell diversity by obtaining endothelial cell type and vascular-bed specific gene-profiles ('blueprints') which will be validated in vivo; (ii) to exploit that knowledge to design protocols for generating specialised endothelial cells by differentiation from stem cells in order to design specialised vascular therapies for (lymph)vascular disorders. As mentioned earlier, an important aspect is that endothelial signatures may vary among different species, hence the inclusion of four different species in this research programme: mice, rats, zebrafish and humans. Since studying the phenomenon of endothelial heterogeneity encompassing the entire vascular tree presents a tremendous task that cannot be accomplished by one research group in a limited time period, our current programme is concentrated on certain vascular beds: (i) to study heterogeneity at the

macrovascular level (arteries versus veins versus lymphatics); and (ii) at the organ-specific microvascular (capillary) level, there by looking at three organs (liver, heart and brain). As outlined before, numerous stem cell sources could serve as candidates for generating specialised endothelial cells, however, testing all of those would require more time and pairs of hands. Therefore, mainly two stem cell types will be tested: (i) BOEC, which already have an endothelial-restricted phenotype, have been isolated from murine/human (peripheral or cord) blood and have a stable phenotype upon long-term standard culture; and (ii) MAPC, isolated from rodent/human bone marrow that are more primitive – and therefore may feature more plasticity, i.e., be more responsive to inductive signals – and able to be specialised to arterial, venous or lymphatic endothelial cells. The proposed objectives will be achieved in three different work phases: (i) generating endothelial cell type and vascular-bed specific gene-profiles ('blueprints'); (ii) generating specialised endothelial cells with appropriate blueprints from stem cells; and (iii) in vivo validation of the blueprints and stem cell-derived specialised endothelial cells.

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Gilles was born in Belgium (Nivelles) in 1974. In 1997, he graduated in Psychology from the University of Louvain (Louvain-la-Neuve). In 1998, he decided to move to Tilburg University (The Netherlands) where he completed a PhD in Neuropsychology (under the supervision of Prof. Beatrice de Gelder), in 2002. His thesis focussed on multisensory integration of emotional signals. He studied how affective information from face (emotional facial expression) and voice (affective prosody of speech) actually combine to yield the strong impression of a unified emotional percept, such as fear, anger or happiness. In 2003, Gilles joined the newly created research laboratory of Patrik Vuilleumier in Geneva University as a post-doctoral fellow to address new scientific questions and augment his knowledge and skills in the Cognitive and Affective Neurosciences. In Geneva, he also had the chance to participate in the 2005 creation of a new research centre for the multidisciplinary study of emotions and affect, headed by Prof. K.R. Scherer. At the University of Geneva, his main research question was to better understand how emotional perception can take place in the human brain in the absence of attention and/or awareness. Among the main results he obtained is that he could show that an emotional facial expression, such as a fearful face revealed very briefly in the visual field at an unattended spatial location, can nevertheless be reliably processed by the human brain and alter behavioural responses of the observer, even if he/she is not actively attending to this specific emotional facial expression.
In September 2008, he joins the Department of Experimental Clinical and Health Psychology at Ghent University, with a research grant from the European Research Council. There he will work on closely studying how anxiety actually transforms and shapes human cognition (with an emphasis on neural/brain effects). His goal is to settle there and lead his own independent research group in psychology and neuroscience.

Besides science and work, he is the father of two lovely children, Manon (6 years old) and Tom (4 years old).

## Anxiety

The main goal of this project (funded for a five-year duration by the European Research Council) is to gain new insight into the neural underpinnings of anxiety and disorders related to anxiety by using modern tools in human brain-imaging. The aim is to shed light on how anxiety transforms and shapes human cognition and what the neural correlates and time-course of this modulatory effect are.

Anxiety disorders are serious medical illnesses that affect millions of adults. According to recent surveys and clinical studies, nearly 25% of all European citizens will experience a clinical level of anxiety within their lifetimes. This makes anxiety one of the most prevalent psychopathological conditions. We all experience brief anxiety episodes caused by stressful events in our everyday life situations. However, these mild anxiety episodes can sometimes grow progressively and eventually lead to psychopathological conditions that require adequate therapeutic treatment. There exists a wide range of anxiety-related disorders, including phobia (either object-based or social), PTSD (post-traumatic stress disorder), OCD (obsessive-compulsive disorder), panic disorder and generalized anxiety disorder. Each of these anxiety disorders has its own distinct features. Nonetheless, a cardinal symptom and shared property of these disorders is that people are overwhelmed by a feeling of anxiety or fear, and are unable to repress this excessive and sometimes irrational dread.

Still, despite the substantial advances of human brain-imaging and the emergence of Affective Neuroscience as a new and distinctive field of research, little is known in fact about the neural bases of anxiety and why this psychopathological condition is so profoundly affects such a vast repertoire of human behaviours (ranging from perception to decision-making). How is anxiety implemented in the

human brain and why does this "state" (or "trait" if anxiety becomes more stable over time) interfere so much with specific aspects of human cognition, including, for instance, selective attention and decision making? It is already known that anxious individuals (even at the sub clinical level) display attentional deficits that are typically manifested by a disproportionate attentional bias towards threat-related or negative stimuli in the environment. Anxious individuals show increased attention towards cues that signal danger. However, little is known about how this phenomenon actually develops and continues, and what its exact neural correlates are.

This project endeavours to tackle this important challenge by uncovering the neural correlates and behavioural repercussions of anxiety by using modern tools in psychophysiology and brain-imaging, such as EEG (Electro-Encephalo-Gram) and fMRI (functional Magnetic Resonance Imaging). The main goal is to better characterise how the brain of (sub clinical) anxious subjects, compared to non-anxious/control subjects actually reacts when processing emotion-laden (and presumably -eliciting anxiety) vs. neutral stimuli in well-controlled experimental laboratory conditions and what the distinctive functional features of anxiety are, in terms of neural networks as well as neurophysiological time-course.

The rationale of this project is to compare anxious vs. non-anxious adult participants, using a variety of classical tasks in psychology (that are designed to test attention, memory or decision-making capacities), while their brain activity is concurrently recorded and the modulatory effect of anxiety is systematically explored. By doing so, we hope to reveal in this project which specific cognitive functions are more likely to be reliably influenced by levels of anxiety and what are the corresponding neural underpinnings and time-course of activation in the human brain. This new line of research is therefore suited to obtain better insight into the range of cognitive impairments and corresponding brain activations that are associated with anxiety disorders. Ultimately, this will allow us to better appraise the repercussions of anxiety disorders in everyday life situations, and by extension, to propose new revalidation schemes aimed at reducing the adverse effects of anxiety on human cognition.

## STEFAAN VAES

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Stefaan Vaes, 32, is a mathematician working in functional analysis. He earned a PhD in Mathematics at K.U.Leuven in 2001. In 2002, he became a research associate of the Centre National de la Recherche Scientifique working at the Jussieu Mathematics Institute in Paris. He returned to K.U.Leuven in 2006 as an associate professor.

The research of Stefaan Vaes deals with operator algebras, ergodic theory of group actions and quantum groups. He teaches undergraduate and graduate courses in mathematical analysis and is an advisor of several PhD students.

Stefaan Vaes is married to Annelies and they have two daughters, Eline and Margot.

## Von Neumann algebras, group actions and discrete quantum groups: Historical background

The roots of functional analysis, a branch of mathematics, lie in the study of spaces of real functions and their transforms (like the Fourier transform) and in the study of differential equations.

It was in the 1920s that functional analysis became a subject in itself, and started to interact with the rest of mathematics. A big impetus came from particle physics, where observables were discovered to behave like operators on a Hilbert space (i.e., a kind of matrices of infinite size), rather than functions on the ground space, with the product corresponding to matrix multiplication. Since matrix multiplication is non-commutative – in general $AB \neq BA$ – these infinite matrices generate non-commutative algebras. This led J. von Neumann to initiate the study of operators on a Hilbert space (e.g., spectral decomposition of operators, generalizing diagonalisation of matrices) and of the algebras they generate (that later would be called von Neumann algebras theory). It also led H. Weyl to study groups of symmetries and the matrix representations of these symmetry groups (group representation theory). The newly developed tools from functional analysis and Hilbert space operators already found use here. The 1920s also saw the emergence of ergodic theory, under the impulse of statistical physics. Here again, von Neumann's proof of the ergodic hypothesis, through his celebrated mean ergodic theorem, gave a new example of the power of his operator algebra methods.

A more intimate connection between von Neumann algebras, group theory and ergodic theory was triggered by the work of Murray and von Neumann in the period 1936-1943, and their so-called group measure space construction. A probability space is a set equipped with a numerical measure of its subsets, like the interval [0,1] with the length measure. The group measure space construction associates a von Neumann algebra M to a group $\Gamma$ of measure preserving symmetries of a probability space X. The isomorphism class of the algebra M depends in subtle ways on the group $\Gamma$ and the nature of its action on X. And vice-versa, some of the most interesting aspects of the dynamics of symmetry groups of probability spaces are revealed by the study of the associated group measure space of von Neumann algebras.

The relation with ergodic theory became more specific in the 1950s, when Singer realized that the isomorphism class of a group measure space von Neumann algebra only depends on the equivalence relation given by the orbits of the symmetry group.

## The early years: classification of amenable von Neumann algebras

Von Neumann algebras that cannot be broken down into a sum of two algebras are called factors. The simplest examples of factors are the matrix algebras and those factors that can be approximated by matrix algebras are called hyperfinite. Murray and von Neumann proved the surprising result that all the hyperfinite tracial factors are isomorphic.

Moreover, Murray and von Neumann divided the factors into three families: type I, type II and type III. The basic building block of an arbitrary factor, is a factor with a finite trace, called factor of type $II_1$.

Von Neumann also singled out a family of groups called amenable groups. Non-amenable groups lie at the heart of the Banach-Tarski paradox: it is possible (but not physically possible, i.e., not in an effective way) to cut an orange into five pieces and to assemble the pieces into two oranges of the same size as the original one!

The research that started from the introduction of amenability and the uniqueness of the hyperfinite $II_1$ factor, culminated with Connes' celebrated theorem (1976) showing that all amenable $II_1$ factors – in particular all group measure space factors associated with amenable groups – are isomorphic. Alain Connes was awarded the Fields Medal (the mathematics Nobel prize) for these and related results in 1982.

## Non-amenable case: breakthrough by Sorin Popa

Understanding non-amenable von Neumann algebras proved to be extremely complex, and for many years progress has been scarce, even after the discovery of the first rigidity phenomena, by Connes in von Neumann algebras and by Zimmer in orbit equivalence ergodic theory (both in 1980). Dramatic progress was obtained in recent years by Sorin Popa in a series of articles published between 2001 and 2007.

Popa developed a method that exploits the tension between deformation properties and rigidity properties to unravel the structure of certain families of von Neumann algebras. This led to the solution of a number of longstanding, unresolved problems, some of them going back to Murray and von Neumann:

The first strong rigidity theorems for a family group measure space $II_1$ factors. The group actions involved are *Bernoulli shifts* of groups having *Kazhdan's property* (T) – a group property entirely opposite to amenability. The associated group measure space von Neumann algebras are shown to be isomorphic if and only if the underlying groups are isomorphic.

The first examples of $II_1$ factors having *a trivial fundamental group* (Popa 2001). The invariant called fundamental group, was introduced by Murray and von Neumann and is a subgroup of the positive real line.

Construction of $II_1$ factors *without symmetries*: every automorphism is inner (Ioana, Peterson, Popa, 2005, Popa, Vaes, 2006).
Factors with *no generalized* (or quantum) symmetries: all finite index bimodules are inner (Vaes, 2007).

## ERC Starting Grant Research Project

Frontier research in mathematics is characterised by international collaboration between several teams. The ERC Starting Grant will fund a post-doctoral researcher on Stefaan Vaes' team at K.U.Leuven, as well as mutual research visits between the team at K.U.Leuven and the teams lead by Popa at UCLA, Skandalis in Paris and Gaboriau in Lyon. Part of the grant will be used to organise a training school for PhD students and an international conference on operator algebras, as well as to contribute towards the organisation of a special trimester devoted to von Neumann algebras and ergodic theory of group actions, in order to gather together all the main specialists in the field during a three-month period at the Institut Henri Poincaré.

The research objectives for the ERC Starting Grant are divided into two parts. The first part focusses on structure and classification results for $II_1$ factors and equivalence relations given by group actions. We would like to answer the following questions:

The *fusion algebra* of a $II_1$ factor is an invariant that synthesises all the invariants discussed above: the fundamental group, the symmetry group and the generalised (or quantum) symmetry group. Which fusion algebras can arise in the world of $II_1$ factors? This research topic is closely related with Jones' subfactor theory, studying the inclusion of one factor into another – research for which Jones was awarded the Fields Medal in 1990.

Popa provided the first examples of $II_1$ factors with trivial fundamental group and even with prescribed countable *fundamental group*. Can *uncountable* proper subgroups of the positive real line arise as a fundamental group?

Are there examples of group actions such that the associated von Neumann algebra entirely remembers the group and the actions that were used to construct it? Such examples would be called *von Neumann superrigid group actions*.

*Quantum groups* and their actions allow the construction of von Neumann algebras, much in the same way that group actions do through the group measure space construction. The major aim of the second part of the research project is to prove the first rigidity and classification results for these

# METHUSALEM

Each Flemish university has research groups that add to the development of scientific knowledge in a substantial way and that meet with the international recognition that they deserve. Eminent researchers who have proven their capacity to develop and manage a research group qualify for the long-term programme funding of the Methusalem programme. Their research should be recognised as high-quality at the international level and there must be ample evidence of adequate fund-raising through existing financing mechanisms. These researchers will receive personal long-term funding.

With the Methusalem programme, full responsibility for the distribution of financial means and the selection of candidates is consigned to the universities. They are responsible for the selection of senior research staff who will receive Methusalem-funding.

An international panel of experts assesses whether the applicants comply with the required international standards of excellence, but it is the board of the university that decides which of the selected candidates will be funded.

These researchers continue to be part of the university, that provides them with the required infrastructure, such as offices, administrative services, etc. and that will continue paying the salary of the team's research director. The selected professor has full responsibility for the research carried out with the Methusalem resources and has to report to the governing body of the university as well as the Flemish government.

The Methusalem financing is paid to the selected candidate as a lump sum that can be applied to the recruitment of staff, the acquisition of equipment or the daily functioning of the research team. The funds come to an end at the superannuation of the selected candidate.

For more information regarding the complete application process and all regulations please contact one of the Flemish universities.

## ROEL BAETS

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Roel Baets was born in 1957. He received a degree "Burgerlijk Elektrotechnisch Ingenieur" from Ghent University, Belgium, in 1980, his MS degree in Electrical Engineering from Stanford University in 1981 and his PhD degree from Ghent University in 1984. Since 1981 he has been with the Department of Information Technology (INTEC) of Ghent University. Since 1989 he has been a professor within the engineering faculty of Ghent University. From 1990 until 1994 he was also a part-time professor at the Technical University of Delft and from 2004 until 2008, at the Technical University of Eindhoven.
The research of Roel Baets focusses on the field of photonics, more specifically, on photonic components and integrated circuits. With about 250 journal publications and 500 conference papers as well as about 15 patents he has made contributions to research on semiconductor optoelectronic components, guided wave and grating devices and to the design and fabrication of photonic integrated circuits, both in III-V semiconductors and in silicon. He leads the Photonics Research Group at Ghent University-INTEC (associated lab of IMEC). This team of 40 researchers focusses on new concepts for photonic components and circuits for optical communication, optical interconnectivity and optical sensing and bio-sensing. Roel Baets has been involved in various European research projects and has been the coordinator of some of them. He currently coordinates the European Network of Excellence ePIXnet, that unites Europe's research forces in the field of photonic ICs. Roel Baets is also co-founder and coordinator of the joint UGent-VUB Master of Photonics Enginering program and its English-thought international Erasmus Mundus variant.

Roel Baets is a member of the Optical Society of America, IEEE-LEOS, SPIE and the Flemish Engineers Association KVIV. He was the chairman of the IEEE-LEOS-Benelux chapter from 1999 to 2001. From 2003 to 2005 he was an elected member of the Board of Governors of IEEE-LEOS. Roel Baets has been awarded with several fellowships and scientific prizes. These include the KVIV-AIG "Isabella van Portugal"prize (1980), a BAEF fellowship (1980), a FWO doctoral fellowship (1981), the FWO-Alcatel-Bell prize (1985), the "Koninklijke Academie"prize (1987), the FWO-Siemens prize (1992) and the SCK-CEN Van Geen prize (1997). He is a Fellow of the IEEE (2007) and an Honorary Professor at the Dalian University of Technology, PR China (2007).

## Smart photonic chips in support of a safe and sustainable world and of a better health care for all

In this Methusalem project a large-scale multidisciplinary research effort will be launched to develop concepts and technologies for smart photonic chips aimed at monitoring a wide variety of systems of critical societal importance (transport, energy, manufacturing, etc.) as well as at diagnosing diseases at an early stage by means of low-cost point-of-care systems.

Photonic chips are similar to microelectronic chips except that they work with light rather than with electrical signals. They consist of a multitude of miniaturised optical components: lasers, detectors, optical switches and filters, amplifiers, etc.

The chips will combine sensing functions with energy provision, communication and information processing functions. A generic technology will be developed and deployed based on the heterogeneous combination of CMOS-compatible silicon-on-insulator nanophotonic circuits with a variety of functional materials including III-V semiconductors, polymers, liquid crystals, nanocrystals and non-linear glasses. The Photonics Research Group of Ghent University plays a

leading international role in the field of photonic chips for telecommunication applications. In recent years the group has successfully explored new application domains outside the strict telecommunication domain. With this project the group will shift its critical mass from telecom to a much broader set of applications, while staying focussed on photonic chips.

## Underlying rationale for the proposed research

The systems of energy provision, communication and information handling, transport, manufacturing, food production and health care have dramatically changed in the past century. The 20th century witnessed the transition from small scale, fine-grained and distributed industrial and economic activity to large scale, coarse-grained and more centralised activity. This transition brought high efficiency in labour and production costs and a high standard of living for many people, at least in the western world.
However, we are now starting to recognize weaknesses with this approach. The two key problems are the non-sustainability and the vulnerability of the current systems. Today's understanding about the world's natural resources and about climate change makes it very clear that it is basically impossible to extrapolate the current systems to the ten billion people of tomorrow's world and to their children and grandchildren. Furthermore, large scale centralised systems have an inherent security problem. A major failure or act of destruction – from natural causes or from a terrorist attack – can lead to unstable runaway effects on a massive scale.

While there are no simple solutions there is an increasing awareness that at least part of the solution is to move towards more widely distributed technical systems with a high degree of energy efficiency, self-organisation, self-reparability and adaptability. This new paradigm is already being explored in diverse areas, including renewable energy, transport and manufacturing systems, peer-to-peer communication networks and medical point-of-care systems. But the introduction of these ideas is very challenging because the cost of such systems is typically much higher than is the case for centralised systems.

From a technical point of view, the key to affordable and sustainable distributed systems is a combination of intelligence and integration. Intelligence means that technical systems should be monitored thoroughly so as to collect information about their status and from that, deduce the most optimal operational mode (lowest energy consumption, least material usage, lowest environmental impact, highest safety, longest lifetime, etc.). Integration means that the four basic functions needed for monitoring -sensing, information processing, communication, energy provisioning- are implemented by means of highly automated design, manufacturing and testing processes thereby allowing for high complexity and high reliability at low cost.

In order to make it happen, there will be a need for interdisciplinary innovation in all engineering fields as well as in fundamental sciences, including in electronics, photonics, RF-technologies, chemistry, material science, nanotechnology, micromechanics, etc. We believe that the role of photonics – and photonics in conjunction with other fields -will become very important. More specifically, we believe that photonic chips will form the heart of many distributed monitoring systems. Examples include: the monitoring of life-threatening chemical substances in the home, in food, in water, etc., the monitoring of safe and reliable operation of power generation systems, of the power grid, of civil constructions etc.; the monitoring of the body and body fluids in terms of early detection and follow-up of diseases. In each case the vision is to focus on compact, energy-efficient low cost systems, that can be deployed at very high volume.

In these photonic chips some or even all of the four basic functions will be combined. The communication function is an obvious match for an optical approach, irrespective of whether the communication is wired by fiber or wireless. The same holds for the energy provisioning function, not only in the context of energy harvesting from ambient light but also through the use of wireless directional energy provisioning beams, thereby exploiting the short wavelength of light. Sensing physical or chemical quantities by means of light is very powerful and most of these sensing functions can, in principle, be miniaturized into optical chips. Finally, information processing is most naturally done by integrating an electronic layer with a photonic layer, but there is an increasing interest in exploring optical information processing approaches, especially in those cases where vast information flows need to be analysed or processed, such as in pattern classification problems.

As the technology matures, these photonic chips will become increasingly powerful and autonomous in their functionality. They will become "smart".

## Objectives

The objective of the proposed research is to develop innovative concepts and technologies for smart photonic chips that can have a strong impact on a wide variety of systems along the lines of the rationale described before. The team

will build upon current know-how and infrastructure to explore new directions of research. They will thereby strengthen and expand our links with complementary research groups within Ghent University as well as with key partners in Belgium and abroad. The timeline for the proposed research is on the order of ten years, but it is likely that some results will be ready for deployment within five years while others may take more than 15 years.
More specifically our research is geared towards:

- new concepts for implementing key functions for distributed sustainable systems in the form of "smart" photonic chips
- photonic chips combining communication functions (wired or wireless), sensing functions, energy provision (wired or wireless) and information processing in a generic technology platform
- wireless communication and energy exchange between chips by means of self-aligning directional optical beams
- sensitive optical sensors for a variety of physical and chemical sensing functions (strain, pressure, temperature, distance, velocity/acceleration, electromagnetic fields (from DC to optical frequencies), concentration of molecules in gases and liquids, etc.
- optical modulation and switching, light emission and amplification at low (or even ultra-low) power levels
- high speed modulation and switching at modest power levels in a compact chip
- non-linear functions and memory functions for optical signal processing

The project will focus on generic technologies that hold the promise of becoming industrially relevant. For this reason Roel Baets will concentrate on mainstream silicon technology derived from microelectronics and combine it heterogeneously with other materials, thereby giving it added value. In view of the importance of microelectronic silicon technology, this project will strongly build on technologies developed by IMEC. The key research challenges at the technological level will be to master the various material interfaces (and the technologies needed to create them) which are of functional importance in a heterogeneous approach.

## BEA CANTILLON

*Back: Tim Van Rie, Ingid Van Zele, Tim Goedemé, Gerlinde Verbist, Sarah Carpentier, Karel Van den Bosch. Middle: Stijn Lefebure, Stijn Rottiers. Front: Veerle De Maesschalck, Kristel Bogaerts, Eva Lefevere, Natascha Van Mechelen, Bea Cantillon, Vincent Corluy, Ive Marx.*

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Bea Cantillon received her MA in Political and Social Sciences from the Katholieke Universiteit Leuven in 1978. From 1985 to 1987 she worked as an Advisor to the Minister of Finance and Scientific Policy. She obtained her PhD in Political and Social Sciences in 1989 at the University of Antwerp (UIA). She was awarded the P.W. Segers Prize for her doctoral thesis entitled, "Socio-demographic changes, income distribution and social security".
Since 1991, she has been the Director at the Center for Social Policy and holds a professorship at the University of Antwerp, specialising in Social Policy, Social Security, Income Distribution and Poverty. In 1999-2000 she was a fellow at the University of Amsterdam (Siswo). Professor Cantillon was elected fellow of the Royal Belgian Academy in 2003. A year later she held the Francqui-chair at the Catholic University in Brussels. Since 2004, she has been the Vice-rector at the University of Antwerp.

She was a senator from 1995 to 1999. She has chairsed the National Administration for Family Allowances since 1995. In 2000-2002 she was the co-president of the Foundation for International Studies on Social Security and presided over the "Commission Cantillon", to which the Minister of Social Affairs assigned the task of reforming Belgian Social Security for independent workers. From 2003 onwards she has been the chair person of the Scientific Committee of the International Social Security Association Conference and the President of the Social Security Association - Belgian Department, of the European Institute for Social Security.

### Social inequalities

Professor Cantillon's research deals with poverty and social inequalities in relation to social security and other forms of institutionalised solidarity within the welfare state. It a) is highly empirical b) builds on a thorough understanding of the formation and content of policy, c) strives for cumulative answers to the question of how an optimal balance can be attained between welfare growth and welfare distribution under changing social, economic and demographic circumstances, and d) is part of the academic tradition of the social policy sciences. It takes a national as well as an international perspective. The purpose is to develop a general theory of social policy and to provide a tool for policy evaluation. This research is embedded in and has contributed to the strong growth of the Herman Deleeck Centre for Social Policy, which Bea Cantillon has led since 1991. The Centre is now part of the European EQUALSOC Network of Excellence that unites the best research centres in the field of social inequality and policymaking.

The core of the research activities consists in developing and interpreting synthetic series of social indicators. This happens on the basis of surveys of large representative samples, which in the developmental phase used to be conducted by the Centre itself but have since been adopted by EUROSTAT and the Directorate-General for Statistics and Economic Information (formerly the National Institute for Statistics – NIS). These many years of experience in the production and processing of survey data have yielded some significant methodological insights. By way of example, we refer to the finding that, contrary to expectations, the measurement of inequality on the basis of annual income (instead of monthly income) results in a higher (rather than a lower) observed inequality (see Cantillon et al. (2003), 'Child poverty à la carte? The effect of measurement period for income on poverty estimates' Bradshaw, J. (ed.), Children and Social Security, Aldershot: Ashgate, p. 63-84).

This expertise in developing and interpreting social indicators

was valorised internationally by her contribution to a book entitled 'Social Indicators. The EU and Social Inclusion', in cooperation with Tony Atkinson, Eric Marlier and Brian Nolan, and published by Oxford University Press in 2002. This book constituted the intellectual foundation for the so-called Laeken Indicators, which currently serve as a guideline in the process of the EU's Open Method of Coordination in Social Inclusion.

With a view to enhancing the measurability of policy impacts, Bea Cantillon has, since the early 1990s, encouraged and enabled the in-house development of simulation models, as a result of which the Centre for Social Policy now also plays a prominent role in the development of the European Microsimulation Model EUROMOD. The application of the microsimulation technique resulted in various relevant policy evaluations (see, for example, Cantillon, B., Kerstens, B., Verbist, G. (2003), 'Les effects redistributifs de la Réforme de l'Impôt des personnes physiques', Cahiers Economiques de Bruxelles, p.71-97) as well as more fundamental insights (e.g., that the "ineffectiveness of social security is connected structurally with its functioning and can therefore only be marginally corrected" (see Cantillon, B. (1992), De verzadigde sociale zekerheid, Berichten / UFSIA, Centrum voor Sociaal Beleid, Antwerpen, November, 31p.). Besides the use of empirical microsimulation models, the application of standard simulation models has also led to new insights, such as the recent observation of a rather general downward trend in Europe in relation to the minimum level of social protection offered; this is a significant finding, as it is contrary to the prevailing assumption that there have been no signs of social dumping in the EU (see Cantillon, B., Van Mechelen, N. and Schulte, B. (2008), 'Minimum Income Policies in Old and New EU Member States', (Routledge Books)).

This research is based on a thorough knowledge of the formation and content of policy in domains such as social security, taxation and education, both in Belgium and at the EU level. Cantillon owes this knowledge in part to several years' experience as a ministerial aide, as a co-opted senator and as a policy advisor (e.g., as the chair of the so-called Cantillon Commission charged with the task of formulating recommendations with regard to the harmonisation of the respective social security regimes for employees and the self-employed). These assignments not only contributed indirectly to her scientific work, they also yielded some crucial insights (e.g., the expert assessment in relation to social security for the self-employed led to the realisation that it is impossible to devise an effective social security system if the distribution of market incomes is inequitable; see Cantillon, B. (2004), 'The failures of Bismarck and Beverigde: The Case of Old-Age Pensions for the Self-Employed in Belgium', in: Overbye, E., Kemp, P. (eds.), Pensions: Challenges and Reforms, Aldershot: Ashgate, p. 131-147).

Professor Cantillon's knowledge of European social policy also yielded valuable input for a publication in cooperation with Marlier, E., Atkinson, T., Cantillon, B. and Nolan, B. (2006), The EU and Social Inclusion: Facing the Challenges, Policy Press).

In terms of content, the central research question in relation to the distribution of wealth within the welfare state encompasses two focal points.

First and foremost, this research looks into (new) social, economic and demographic mechanisms that give rise to inequality. In her doctoral thesis, professor Cantillon examined the impact of female labour participation. Subsequent areas of interest have included the growing impact of schooling on inequalities (see, for example, Cantillon, B., et al. (2001), 'Scholing maakt het verschil: emancipatie in twee snelheden in 13 OESO-landen', Bevolking en Gezin, p. 31-52; this was also the central topic of the interdisciplinary IUAP project on 'The new social question', in cooperation with, among others, Ph. Van Parijs and P. Pestieau).

Additionally, the research sets out to formulate answers to the question of how poverty and inequality can be curbed most effectively through social policy. Effects of policy reform are predicted (see, for example, on the consequences of tax reform in Belgium: Cantillon, B., Kerstens, B., Verbist, G. (2003), 'Les effects redistributifs de la Réforme de l'Impôt des personnes physiques', Cahiers Economiques de Bruxelles, p.71-97) and current policy is analysed (see, for example, Cantillon, B. (1999), De Welvaartsstaat in de kering, Kapellen: Pelckmans, 317 p.). Comparative analysis of the effectiveness of policy under various welfare state models has also provided significant new insights. An important conclusion in the 1990s was, for example, that, if it is at all possible in Europe to achieve a low poverty rate with low public spending, then this has yet to be proven. Cantillon's study into the future of the Dutch welfare state in collaboration with a number of leading European and American sociologists and political scientists deserves mention here: this research yielded the insight that the small and relatively homogeneous European welfare states, unlike in the US, were able to develop so strongly precisely because of their modest scale (see Cantillon, B. (2004), 'What Future for the Dutch Welfare State in Europe? Lessons from American Social Federalism', in: E. de Gier, A. De Swaan, M. Ooijens (eds.), Dutch Welfare Reform in an Expanding Europe. The Neighbours' View. Amsterdam: Het Spinhuis, p. 171-199). This finding now constitutes a basis for reflection on social federalism in Belgium.

## PETER CARMELIET

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Since 1991, Prof. Peter Carmeliet has been studying the molecular basis of neurovascular biology and disease, with a focus on angiogenesis and neurodegenerative disorders.

He has made contributions to the understanding of how blood vessels form (angiogenesis), how they function in normal health and how their abnormal growth or malfunctioning contributes to diseases such as cancer, ischemic heart disease and neurodegeneration. His research efforts utilise a variety of approaches to identify and characterize new factors involved in angiogenesis, and validate therapeutic strategies in relevant in vivo models of human disease. In particular, he studied the role of VEGF, PlGF, hypoxia-signalling and oxygen sensing in angiogenic disorders and vessel growth and investigated how vessel patterning is regulated by guidance molecules. Novel gene candidates, involved in (lymph) angiogenesis and the link between angio/neurogenesis, are studied in (small) animal models, such as zebrafish, Xenopus tadpoles and mouse models. Promising results can be translated to preclinical studies identifying new therapeutic approaches in pathological conditions characterized by vessel growth disregulation.

Dr. Carmeliet was promoted to full professor at the University of Leuven and his laboratory has trained more than 60 pre- and postdoctoral students. He published more than 300 research articles and reviews in peer-reviewed journals.

## Angiogenesis

Over the last 15 years, Peter Carmeliet's research group is focussed on unravelling the molecular basis of angiogenesis (i.e., the formation of blood vessels) and translating these genetic insights into therapeutic concepts. More recently, his research branched out into a new field, the study of an unsuspected link between blood vessels and nerves. This neuro-vascular link, originally discovered 500 years ago by the Belgian anatomist Andreas Vesalius (he recognized the parallel anatomic patterns of vessels and nerves), is of medical relevance for health and disease.

The aim of this Methusalem Group which is part of the Vesalius Research Center (VRC) – is to capitalize on the existing expertise in angiogenesis: by further unravelling its genetic basis; by discovering novel angiogenic genes and studying their function in vivo; by screening, identifying and evaluating the therapeutic potential of novel ("in-house developed") angiogenesis inhibitors preclinically and clinically and, via strategies from the bench to the bedside and back again, improve the overall efficacy of and reduce the resistance to anti-angiogenic treatments. The group will further invest in the more recent initiative of studying the neuro-vascular link: by identifying the molecular mechanisms of, and in particular defining the role of the VEGF family and other angiogenic genes, in the neuro-vascular link in development and neurodegeneration; by developing additional VEGF-based therapeutic strategies preclinically and evaluating the therapeutic potential of VEGF for ALS clinically. By using a gene candidate target-driven approach and an unbiased genome-wide approach the group hopes to discover something novel.

## Neuro-vascular genes and drug candidates.

To achieve these goals, this group will continue to build on its collaborative local (K.U.Leuven, VIB and UZ Leuven) and (inter)national scientific networks; integrate complementary interdisciplinary approaches and novel technologies (bridging genetics to translational medicine); and establish strategic alliances with industry.

To broaden the scope and increase the impact of the ongoing research, collaborations have been set up with three young group leaders in the Biomedical Group at the K.U. Leuven, and with research-oriented clinicians to promote translation of the basic research into clinical practice.

## Anti-plgf treatment of angiogenic disorders

Excessive formation of blood and lymph vessels promotes malignant, inflammatory, infectious and immune disorders. The recent clinical successes with angiogenesis inhibitors for the treatment of cancer and blindness established their place in clinical practice and promise to change the face of medicine in these fields. However, none of the currently available inhibitors of VEGF (a major angiogenic factor) or its receptors (VEGFRs) provide definite cure. On the contrary, they often exhibit unacceptable toxicity by affecting healthy vessels. Thus, additional agents and strategies, with complementary mechanisms and improved safety, are needed to maximize the efficacy and reduce the resistance to current anti-angiogenic drugs.

Through genetic and molecular studies, this research group identified placental growth factor (PlGF) as a "disease-specific" angiogenic factor. PlGF only regulates angiogenesis during disease without affecting healthy vessels. Previous studies indicate that anti-PlGF antibodies (αPlGF) reduce tumor growth, without causing the typical side effects of the VEGF(R) inhibitors, and without evoking anti-angiogenic resistance. The ultimate goal is to develop αPlGF for clinical use – this mandates a better understanding of its molecular mechanisms and preclinical potential. A multi-disciplinary approach "from the bench to the bed, and again to the bench" will be used: from mechanistic studies through preclinical treatment studies to clinical trials.

## Novel research avenues

### 1. Pharmaco-genetic profiling of the response to anti-angiogenic therapy

A fraction of (too many) patients fails to respond to treatment with angiogenic inhibitors, but the reasons remain unknown. Apart from the increasing socio-economic problem related to the increasing costs of biological anti-cancer therapy, some countries (including Belgium) refuse to reimburse angiogenic inhibitors (Avastin), unless "responders" can be identified. Also, most patients, even when initially responding to this therapy, develop acquired drug resistance. This is due in part to tumors that start compensating angiogenic growth factors, a kind of "rescue programme" allowing the tumor to escape from the anti-angiogenic treatment. This escape is likely genetically predetermined. The aim of this project is to investigate whether genetic variations give rise to different responses to drugs. More specifically, the group aims to reveal whether the outcome of angiogenesis inhibitor treatment in cancers is associated with any type of genetic variability, and whether patient who would be the best candidates for a specific therapy could be identified.

### 2. Angiogenic factors and hematological malignancies

Receptor tyrosine kinases (RTKs), receptors for many growth factors such as VEGF, have been shown to have a critical role in the development and progression of many types of cancer. RTKs are often aberrantly activated in hematological malignancies but the role of the VEGF receptors in these diseases has not been studied systematically yet. Emerging evidence supports a possible role for the VEGFR family in the pathogenesis of leukemia. This evidence raises the question of whether VEGF receptors are directly implicated in the development of leukemia and/or whether VEGF or PlGF provide protection to the leukemic cells against the effects of chemotherapy or other treatments. The data obtained in this study may constitute the basis for testing the efficacy of αPlGF treatment on leukemia patients.

### 3. Mechanosensors – regulators of angiogenesis

Endothelial cells (ECs) are exposed to pulsatile blood flow resulting in shear stress, stretch and pressure. Flow importantly determines not only the growth and remodelling of nascent vessels, but also the maintenance of existing vessels. Anti-angiogenic therapy aims at depriving tumors from flow. Hence, understanding the basic mechanisms of how flow affects EC growth and maintenance promises to offer novel therapeutic options to inhibit angiogenesis. The physical signals of flow in ECs are transmitted by specialised ion channels, called mechano- and chemosensors. The roles of many ion channels in vascular remodelling and angiogenesis are poorly understood. Established angiogenesis models will be used, in combination with knockdown genetics in zebrafish and transgenic mice to characterize the role of these channels in angiogenesis in health and disease.

## Neuro-vascular link
## Vessel and axon navigation – common principles and cues

The development and wiring of functional networks of vessels or nerves requires that ECs and axons grow via well-defined routes. Recently, a novel research avenue arose from the realisation that, during evolution, the vascular system coopted signals from the nervous system (f.i. VEGF developed in evolution first as a neuronal signal in primitive avascular organisms,

and later acquired vascular functions in more complex, larger vascularized organisms), and that vessels and axons often use similar guidance signals to navigate to their targets. The group previously documented that axon guidance molecules regulate blood vessel routing during development, while ongoing studies demonstrate that angiogenic molecules, such as VEGF, influence axon guidance across the midline of the spinal cord and neuronal cell migration. Therefore, researchers intend to characterize the molecular mechanisms and discover new genes that regulate the navigation of vessels and axons, by using transgenic mice, tadpoles, zebrafish as well as fruitflies.

## The neuro-vascular link in neurodegeneration

Amyotrophic lateral sclerosis (ALS) is a devastating paralysing disease affecting humans in the middle of their lives. ALS is incurable and fatal in almost all cases. In 10% of those who have it, ALS is inherited, while in the majority of cases, ALS occurs sporadically with its etiology remaining entirely unexplained. A recent analysis of >5,000 individuals (from ten different populations) extends the initial findings that the a VEGF gene variation is significantly associated with an increased risk of ALS in humans and aggravated disease severity, thus identifying VEGF as one of the very few risk factors known to affect sporadic ALS. The group also showed that VEGF gene or protein therapy prolongs survival in rodent models of ALS.

The group will explore the molecular mechanisms underlying the neuroprotective effect of VEGF and its family members and test their therapeutic potential – these studies are likely to yield relevant insights for designing and optimizing VEGF therapy for ALS. More specifically, the group will study the cellular mechanisms of how VEGF affects motoneuron survival, i.e., via vascular and/or neuroprotective effects. They will translate, "from the bench to the bedside", the preclinical data into clinical practice and evaluate the potential of VEGF therapy in ALS patients and, "back to the bench", analyse clinical responses with molecular markers. It will be interesting will be to evaluate whether VEGF has a similar role in other neurodegenerative disorders (Alzheimer, Parkinson, Multiple Sclerosis) and whether angiogenesis inhibitors aggravate neurodegeneration. Also the role of other pathways will be analysed and previous human genetic efforts will be extended to study the neuro-vascular link further by correlating variations in angiogenic genes with neurodegeneration in humans. These genetic studies promise to yield insights relevant to the design of novel and/or the optimization of current VEGF family-based therapies.

## Oxygen sensors – players in neuro-vascular metabolism

A strong stimulus of angiogenesis in numerous disorders is a shortage of oxygen (hypoxia). The group has a long-standing interest in unravelling the molecular basis of the response to hypoxia, evaluating the roles of key molecular players in health and disease and developing novel strategies for the treatment of ischemic disorders like myocardial infarction and stroke. Prolyl-hydroxylases (PHD) are oxygen-dependent enzymes (oxygen sensors), destabilizing the hypoxia-inducible transcription factors (HIFs) and thereby dampening the hypoxia-response. Their role in health and disease, however, remains unknown.

Recently the group generated mice lacking each of the PHDs (PHD1, 2, 3) and is currently generating mice conditionally overexpressing each of these PHDs. By phenotyping mice lacking PHD1, they recently identified an unsuspected link between PHD1, angiogenesis, oxidative stress, and the balance between glucose and fat mitochondrial metabolism in skeletal muscle: PHD1-/- muscle cells were completely protected against ischemic cell death after ligation of the femoral artery. This was in part due by reducing oxygen consumption via a metabolic switch. Initial analysis further revealed that loss of specific PHDs reduces neurodegeneration in ALS and Parkinson disease models. The group intends to study the role of each of the three PHDs in health and disease such as cancer, cardiovascular disorders, neurodegeneration and other disorders with a metabolic component.

## Discovery of novel neuro-vascular genes and drug candidates

Alternative approaches will be necessary for a more efficient and safe treatment of angiogenic and neurodegenerative diseases. The group intends to complement the reverse genetics strategies (outlined above) by forward genetics approaches in order to discover new disease candidate genes. Two distinct but complementary strategies will be used: (i) a gene candidate target-driven approach; and (ii) an unbiased genome-wide approach. Genotyping human DNA samples and (chemo)-genetic screens in animal models are powerful technologies for achieving these objectives. Small aquatic animal models (zebrafish and tadpoles) supersede the mouse in terms of offering the advantage of easy (chemo)-genetic and transgenic manipulation, rapid and relatively inexpensive phenotypic analysis, and superior live imaging – altogether allowing a more rapid analysis of larger sets of genes or drug candidates.

To accelerate the identification of other angiogenic factors and genes involved in neurodegeneration, and to facilitate the screening of novel small chemical anti-angiogenic or neuroprotective drug candidates, the group recently set up genetic zebrafish and tadpole "small animal models" of angiogenesis/lymphangiogenesis and motoneuron degeneration. In a recent multi-disciplinary collaboration with K.U.Leuven scientists, it has been shown that these aquatic models were instrumental in characterizing the biological and pharmacological properties of a novel class of anti-angiogenic agents and chemical compounds improving motoneuron degeneration.

The researchers aim to identify novel disease/therapeutic candidate genes (which will then be studied by reverse genetics) and drugable lead compounds.

## REINHART CEULEMANS

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Reinhart Ceulemans (born in Wilrijk, 1954) is a full professor in the Department of Biology and vice-dean of the Faculty of Sciences at the University of Antwerp. He is spokesman for the research group of Plant and Vegetation Ecology (30 pers.) and the director of the Research Center of Excellence ECO (90 pers.). Reinhart Ceulemans has a background in Biology (PhD. in 1980, Antwerp), with a special emphasis in plant ecology. He has been a visiting Fulbright professor at the University of Washington (Seattle, USA; 1987-1988) and a visiting professor at the Université Paris XI (Orsay-Paris, France; 1989), followed by a permanent faculty appointment in 1990. Since 1978 he has published over 220 articles in international peer-reviewed journals, edited nine scientific volumes and books, and has written more than 50 articles in popularizing journals or volumes. His articles have been cited more than 5000 times; during the period 1999-2005 Reinhart Ceulemans was among the 20 most cited authors in plant science. Under his guidance the research group of Plant and Vegetation Ecology publishes an average of 20 scientific papers per year in international peer-reviewed journals. He is reviewer for over 40 and the editor of two international scientific journals. Reinhart Ceulemans has been a principal investigator of more than 100 research projects (total of ten million euros), including 15 European research contracts. In 1990 he was honoured with the Scientific Achievement Award of the International Union of Forestry Research Organisations (IUFRO), and during the academic year 2006-2007 he was the titular of the Belgian Francqui Chair at the Université Catholique de Louvain-la-Neuve. He has been the supervisor of more than ten successfully completed Phd's and over 40 MS dissertations, and is presently supervising six doctoral students. He is presently a member of the LESC Core Group of the European Science Foundation, a member of the Board of Directors of the Canadian Carbon Flux programme and of the Management Committee of various EC-COST actions and vice-chair of a scientific commission of the Research Foundation-Flanders. In addition, he is an active member of over 20 national committees and international scientific commissions, including IGBP and the Federal Council for Durable Development. Reinhart Ceulemans teaches courses including Ecology, Plant Ecology and Plant Ecophysiology. His main research interests include a.o. global change and terrestrial ecosystems, renewable bio-energy resources, poplar ecophysiology, process modelling, plants unders stress, and biodiversity.

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## ECO examines the household of life

The Methusalem-project ECO examines the effects of changes in the abiotic environment on ecosystems and on the condition and health of plants (and animals). Ecology and environment are currently hot topics, primarily because we relate the environment to the disturbances that affect the life of plants, animals and humans. Many of these environmental changes lead directly or indirectly to stress in organisms. Within certain limits, life can adapt to a changing environment and to stress situations, but the changes that have occurred on earth since the middle of the 19th century are more drastic and more far-reaching than ever before. Environmental changes do not all have the same spatial or temporal impact. Some disturbances are limited to the local environment, e.g., a discharge (or drainage) of cadmium in a creek or stream, soil pollution by leakage, eutrophication of a pond or an outbreak of caterpillars. Other disturbances work at the regional level, e.g., air pollution, enhanced concentrations of mercury above an urban setting (agglomeration), elevated tropospheric ozone concentrations, nutrient deposition in the aquatic environment and soil acidification. But there are also global changes such as climate warming, elevated atmospheric $CO_2$ concentration or the atmospheric spread of contaminants. Some of these changes result in immediate responses (seconds, minutes or hours), but others can work for days, weeks, years or even centuries.

The Methusalem-project ECO examines the effects of changes in the abiotic environment on ecosystems and on the condition and health of plants (and animals). Essentially, ECO examines both causes (abiotic changes, disturbance of the living environment, various stress situations) and their consequences, i.e., (eco)physiological and (bio)chemical response processes. Within this overall framework, all hierarchical levels of organisation are being investigated: genes, cells, organisms, populations, ecosystems, landscapes and regions including continents and even on a global scale. The different organizational scales fit spatially and temporally. Researchers from the participating teams within ECO work at different hierarchical scales that are complementary to each other. Plants are the main – but not the only – subjects of this Methusalem-project as they are the basis of each and every ecosystem, and thus of life on earth. In the framework of this long-term project we are looking for mechanistic explanations of the response to environmental disturbance, i.e., trying to understand processes and explain them in relation to the physico-chemical environment.

All life on our planet is part of an ecosystem. Ecosystems are more or less clearly defined units where solar energy is captured and passed on to different organisational life forms, and materials are cycled. An ecosystem consists of the living (or biotic) and abiotic components and the physico-chemical environment of water, soil and air. In the concept

of the ecosystem the biological and physical components of the environment are a single interactive system. The term 'eco' comes from the Greek 'oikos' which means house or household. So, ecology refers to the study of the household of life. As in a household, coherence, cooperation and interactions and the balance between input and output play a key role. An ecosystem interacts with and is affected by the environment, but it can also alter the environment (e.g., in an agricultural ecosystem). Due to the interest in the interactions between the environment and life, ecology became increasingly trendy in the 20th and 21st centuries and earned its position as a scientific discipline.

The Methusalem-funding has been allocated to Prof. Reinhart Ceulemans (spokesman for the research group of Plant and Vegetation Ecology, PLECO) of the University of Antwerp in consortium with Prof. Jaco Vangronsveld (Center for Environmental Sciences, CES) of Hasselt University. Profs. R. Ceulemans and J. Vangronsveld also act as the director, respectively co-director of the Research Centre of Excellence ECO. This research center incorporates – beside the PLECO and CES research groups – the research group of Ecophysiology, Biochemistry & Toxicology (EBT, University of Antwerp; spokesman Prof. Ronny Blust) and the research group of Environmental Analysis MITAC 1 (spokesman Prof. René Van Grieken (University of Antwerp). The total number of full-time researchers in the ECO research center is more than 90, distributed over the University of Antwerp and Hasselt University.

In the study of the effects of environmental changes on plants and ecosystems in the Methusalem project three overall approaches are being used. Firstly, there is the approach of the experimental laboratory and field work with observations, measurements, treatments and analyses. These include a.o. specific experiments (on complex grassland ecosystems and forest trees) with manipulations over multiple years and an integrated suite of measurements that document the range of cellular to organismal to ecosystem responses. Secondly, we are converting our understanding of basic plant, soil and ecosystem processes into a new generation of predictive, process-based models that are being parameterised, validated and tested against further experiments and ongoing field observations. These explicative and predictive models also have some applied value, for example, management or remediation options. Thirdly, we tackle questions on how to scale from smaller plots and landscape studies to a continent and the globe. The integration of large-scale data sets and the synthesis of data from databases lead to an improvement of our understanding of basic ecological principles and ecophysiological responses. The questions that are being asked are critical for our understanding and prediction of ecosystem responses to local, regional or global environmental changes (University of Antwerp). Experimental manipulations combine more than one factor in an effort to see if responses can be predicted from single-factor experiments or if non-linear 'threshold' responses occur. Manipulations include climate warming, elevated $CO_2$, changing biodiversity level, different species combinations, induced stress and extremes (combined, multiple stressors). A suite of measurements including molecular, biochemical, ecophysiological, ecological techniques are being employed. Soil as well as plant responses to multiple drivers are being examined. Amongst several other topics, the study of the effects of global climatic changes and of atmospheric pollution on terrestrial ecosystems will receive particular attention in the Methusalem project. This includes the effects on plant growth, development and physiology, changes in adaptation, in biodiversity, in functionality and stability of ecosystems.

Plant responses and tolerance to combined stress factors are very different from the responses to the individual stressors. Therefore different stress-factors (ozone, heavy metals, organic micro-pollutants) will be applied under controlled conditions with changes in either one stress factor or in combination. Data collection will be performed at different cellular levels and will include: detection of changes in gene and protein expression levels that provide information on the biochemical responses of the tissues and organisms. To provide insight into the underlying mechanisms of the cellular changes, information on the cellular redox state will be collected. The cellular redox state is affected under different stress conditions and plays an important role in the signal transduction that controls the cellular responses. Furthermore intra- and intercellular signalling contribute to a better understanding of the regulation of the cellular responses.

With regard to systems biology (Hasselt University) the aim is to obtain a profound understanding of the synergistic effects between plant-associated microorganisms and their host plant. Focus will be on the association between poplar and its associated rhizosphere and endophytic microorganisms. More specifically we will address the following related scientific questions:
(1) Which environmental factors determine the community structure and diversity of plant-associated microorganisms?
(2) How can rhizosphere and endophytic bacteria help their host plant to obtain sustainable growth on marginal soils, and how can they help their host to overcome environmental stress caused by the presence of contaminants such as heavy metals and organics? The potential role of plant-associated

microorganisms in phytoremediation will also be investigated. Furthermore, microbial populations have key roles in carbon fluxes in soils. However, different functional groups (e.g., bacteria, true degrader fungi, mycorrhizal fungi) exist in the same soil micro-environments and interact with each other.

The synergies between the four composing groups of the Research Center of Excellence coordinated by Profs. R. Ceulemans and J. Vangronsveld will result in an added value for the Research Center. We regard these synergies in several ways. For example, the joint use of common research infrastructure, the use of similar or identical biological models (for exposure to pollution), the development of common research topics and joint applications around existing and new systems, etc. The levels of organisation at which the different research groups of the Center of Excellence are working, are highly complementary: EBT and CES from gene to organism; PLECO from organism to landscape; MITAC 1 environmental chemistry from local to regional. The biotic (both plants and animals) as well as the abiotic environments are receiving equal attention within the Methusalem project ECO.

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Jan Delcour (born 1956, Kortrijk, Belgium) is married to Sabine Vercruysse. The couple have three children: Gil, Eline, and Louis. Jan Delcour was a Youth for Understanding foreign exchange student in Marshall, MN, USA, in 1974-1975 and, subsequently, obtained his BS, MS, and PhD (1985) degrees in food science and technology from the K.U.Leuven. Thanks to a career with the Fund for Scientific Research – Flanders, he later became responsible for the Laboratory of Food Chemistry and Biochemistry in the Faculty of Bioscience Engineering of the K.U.Leuven, a research unit he founded in 1991, that, today is fully equipped based on competitive funding, with 42 staff members, of which 35, based on competitive funding.

As a NATO Research Fellow, he carried a out postdoctoral stay at Kansas State University in 1988 under the supervision of Dr R. Carl Hoseney. This was the starting point for his cereal science and technology career.

With members of his group, Jan Delcour has published around 250 research papers in peer reviewed journals (close to 120 since 2002). In 2005, he obtained the status of ISI highly cited researcher in the field of agricultural science. He and his group have published and/or presented over 250 other scientific communications and/or confidential reports, have filed patents grouped within 16 families, and obtained patents in six of these families. A number of these patent applications have recently been transferred to Fugeia, a K.U. Leuven spinout company founded by Jan Delcour and Willem Broekaert.
Jan Delcour has a track record characterized by numerous long term industrial collaborations with major partners. In addition, he has a track record as partner or coordinator of EU FAIR and Framework V programs, module leader in an ongoing Framework VI Integrated Project programme (Healthgrain, coordinator Dr Kaisa Poutanen, www.healthgrain.org), and major applicant or coordinator of large basic and applied research projects funded by IWT, FWO and the various funding categories of the Research Council of the Katholieke Universiteit Leuven.

He serves as senior editor for Cereal Chemistry and is a member or former member of the Editorial Boards of Journal of the Institute of Brewing (London), Journal of the American Society of Brewing Chemists, and Cerevisia and Biotechnology.

Also, Jan Delcour, who received multiple scientific awards, was also the technical chair of an Annual Meeting of the American Association of Cereal Chemists, a task he fulfilled in Baltimore (1996).

In addition, Jan Delcour was the main organiser of the 3rd European Symposium on Enzymes in Grain Processing which was held in Leuven in September 2002.
Presently, he serves as member of the Board of Directors of AACC International (www.aaccnet.org), and as chairman of the Leuven Food Science and Nutrition Research Centre (LFoRCe).

## Food for the future background

Tomorrow's food needs to meet many criteria, the most predominant ones of which are safety, excellent shelf life, organoleptic and nutritional qualities, and - increasingly important - the capacity to sustain and promote health. An innovative approach to designing tomorrow's foods and, at the same time, to bridging the gap between food processing and nutrition research relies on enzyme science and technology sensu lato. In food processing (including food preservation) as well as in its subsequent storage, endogenous and/or added enzymes play predominant roles. Recent work inter alia shows that especially hydrolytic enzymes can be used to the advantage of in situ or ex situ creation of health promoting constituents, and thus, for the creation of functional foods and/or nutraceuticals. The research group led by Jan Delcour demonstrated that cereal nonstarch polysaccharides can be converted enzymically to prebiotic oligosaccharides. Enzymes are also important in

science-based approaches to evaluate the impact of physical preservation unit operations on food functionality and to use such approaches in process design and optimization, such as investigated by the Laboratory of Food technology. Finally, enzymes such as lysozymes that inactivate bacteria by hydrolyzing their cell wall peptidoglycan, offer promise in natural food bio-preservation and gut health promotion, and are studied at the Laboratory of Food Microbiology.

## Strategic objective

The strategic objective of the Methusalem team, led by Jan Delcour, is to strengthen the established forefront position of the University in academic food science research and to build such position in nutrition research with a specific and unique focus on bridging these two science areas. Starting from the current competences at the Laboratories of Food Chemistry and Biochemistry, Food Technology and Food Microbiology, this will be done by fully mobilizing and further developing basic and applied research capabilities in enzyme, enzyme inhibitor, food technology and nutrition research. In practice, the pluri)disciplinary research programme will cover the complete knowledge chain from basic science to application oriented work.

A major focus will be on enzyme systems and precision processing that allow for unlocking the full potential of raw materials in modulating food properties and creating new functional ingredients. The research targets chosen are, in essence, based on the expertise of the different members of the Methusalem group and can be situated at three different levels, i.e., that of the enzymes and enzyme inhibitors, that of food processes and systems, and that of health related foods (ingredient properties).

The enzyme systems studied are invariably hydrolases. Where relevant, the corresponding plant material endogenous proteinaceous hydrolase inhibitors will be studied as well. The enzyme systems include xylanolytic, β glucanolytic, and pectinolytic enzymes, all of which are active on their target non-starch polysaccharides (dietary fibres), amylolytic enzymes which are active on starch, and muralytic enzymes such as LYS, which are active on peptidoglycan (murein). These enzyme systems are relevant for targeted studies on the specific role of their substrates and/or products in food processing and quality, tailoring sensory quality and/or health related food (ingredient) functionality, and/or natural biopreservation of food.

The food processes chosen primarily include cereal, fruit and vegetable processing. In the particular case of cereal processing, the Methusalem group will increase its capabilities in the areas of bread and especially pasta making, and even more so by introducing both cake and cookie making as models for cereal processing and understanding the role of wheat flour constituents in processing and/or storage. Food systems will thus include bread, pasta, cookies, cakes, and stored and conserved fruits and vegetables. Food processes are either traditional or at the emerging technology stage, they can be aimed at biochemical and physicochemical transformations, food production and/or shelf life procurement. Food properties sought include organoleptic quality (including texture), and shelf life. They need to be studied at different levels of organisation and include micromechanical properties, texture and rheology, gel formation, cloud stability, nutrient availability and digestibility.

The studies of health related food (ingredient) properties particularly target the gastro-intestinal and, in a later stage, the endocrine system. Prebiotic effects exerted by oligosaccharides, as well as their impact on symptoms of intestinal disorders such as irritable bowel syndrome (IBS) will be studied, as will their effects on the gut immune system. This will be done by teams led by the University's Gastro-enterology and Clinical immunology sections. In addition, while the functional characteristics of peptides in food are well known, their physiological effects in the gastro-intestinal tract have remained largely unexplored. In analogy to the research on oligosaccharides, the Methusalem group will study the effects of such peptides on the gut immune system, on modulation of satiety through interactions with the gut, and, in the case of success, on type I and type II diabetes (using the University's large network of insulin and non-insulin treated patients), as both types are linked to overweight.

The above three research lines will not only strengthen food technology researchwork at the University, but also yield groundbreaking insights into the complex structure-activity-functionality relationship of biocatalysts impacting food constituents and systems. The latter will be based on structural, biochemical, and molecular engineering efforts. In addition, the efforts will provide a solid scientific basis for explanatory insights into the health promoting properties of plant- or bacteria- derived oligosaccharides and peptides with particular emphasis on the gut system.

In the work, first and foremost classical routes for dissemination of research results will be followed. In addition, where possible, intellectual property based strategies will be used, as they can generate the interest of major industrial players in partnering with the MG and/or Leuven Food Science and Nutrition Research Centre (LFoRCe).

## Research objectives

The enzyme research-related objectives include the following:

(i) to characterise novel plant or microbial enzymes and their inhibitors through state of the art technologies,

(ii) to identify the parameters and mechanisms governing in vitro and in situ substrate conversion by enzymes and the impact of inhibitors. More specific goals are to quantify substrate conversion processes through hypothesis-driven kinetic analysis of the conversions, to understand substrate specificity and selectivity using structural data, hypothesis-based designed mutants, and subsite mapping, and

(iii) to provide the basis for understanding differences in enzyme and enzyme inhibitor functionality in terms of their stability. More specific goals are to understand and quantify the effects of intrinsic and extrinsic food system parameters on enzyme and inhibitor stability through detailed analysis of their in vitro and in situ inactivation kinetics.

The food processing and food system research-related objectives include the following:

(i) to increase capabilities in the area of food processing by e.g., introducing both cake and cookie making models and by intensifying efforts in the area of pasta making, with the aim of understanding the role of the wheat constituents in such cereal processing and/or product storage,

(ii) to develop, test, and validate hypotheses on enzyme and enzyme substrate functionality in food systems and bioconversions, and

(iii) to use biocatalyst science to the advantage of food (ingredient) production. The enzyme related know-how will be used to create specific food ingredients and their use in modulating food properties throughout the production chain. Studies at different levels of scale will be included.

The food-health research-related objectives include the following:

(i) to study the health promoting properties of enzymically produced plant-derived dietary fibre fractions and oligosaccharides in healthy individuals, and IBS patients. In healthy individuals, the prebiotic potential will be studied, as will inter alia their impact on immunological properties. In IBS patients, similar work will also include investigation of their impact on abdominal symptoms and colon motility. We will equally study the effects of the components on suppression of inflammatory responses triggered by microbiota,

(ii) to study the physiological effects in the gastro-intestinal tract of peptides and muropeptides on the gut immune system. More specific goals are to set up an in vitro assay for immunomodulating activity, to screen protein or murein hydrolysates for and to characterise peptides with such activity, and

(iii) to study the satiety modulation by peptides through interactions with the gut. More specific goals are to identify protein hydrolysate preparations that reduce food intake and that interfere with appetite signalling. If successful, in a later stage, their impact on diabetes will be studied.

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Anne De Paepe is Professor of Human and Medical Genetics and the director of the Center for Medical Genetics at the University of Ghent, Belgium.

She graduated as an MD from Ghent University, completed her residency in internal medicine at the Ghent University Hospital and her fellowship training in medical genetics at Ghent University and the MRC, Dermatology Research Group, Northwick Park Hospital, London, UK. She earned her PhD in human genetics at Ghent University.

Anne De Paepe has conducted research on the clinical aspects and molecular basis of a diverse group of heritable connective tissue disorders, including Marfan syndrome, Ehlers-Danlos syndrome and Osteogenesis imperfecta. She established a research laboratory as well as a clinical service and diagnostic laboratory for heritable collagen diseases and other connective tissue disorders of at Ghent University. She serves actively in different research councils and advisory boards within Ghent University, and at the national and international level. She has been the (co-)organisor of several international research meetings in the field of heritable connective tissue disorders, authored over 250 publications and has been a speaker at many international conferences in this field. She was the first elected female member of the Royal Flemish Academy of Medecine in 1999. She is the recipient of several scientific awards among which the International Antoine Marfan award ( 2007), the M. Vastesaeger prize 2006 from the Belgian Society of Cardiology and the GlaxoSmithKline prize 2004-2006. She recently became a recipient of the Antoine Marfan award. As director of the Center for Medical Genetics she has more than 100 collaborators under her daily supervision.

## Characterisation of the genetic defects and molecular pathways involved in heritable connective tissue disorders

A major area of research in the research group is the study of the causal genes and molecular pathways underlying heritable connective tissue disorders. The heritable connective tissue disorders comprise a heterogeneous group of multisystem diseases affecting diverse organ systems such as the skin, bone and cartilage, cardiovascular and pulmonary systems. Important examples are Marfan syndrome (MFS), Ehlers-Danlos syndromes( EDS) and Osteogenesis Imperfecta (brittle bone disease). These disorders are caused by genetic defects that affect the synthesis or maintenance of different connective tissue (glycol)proteins. Although individually rare, as a group they represent a significant proportion of inherited genetic disorders. The clinical phenotypes of heritable connective tissue disorders are quite diverse and can vary from very mild to life-threatening or severely handicapping disorders, that represent a significant burden on morbidity and mortality of affected patients and families. Identifying the corresponding genes and mutations as well as the underlying disease mechanisms represents an important step towards improving prevention, diagnosis and treatment of these diseases. Moreover, they represent important paradigms for the study of common health problems such as cardiovascular and lung diseases, osteoporosis and degenerative joint disease. Unravelling the causal pathways in these rare disorders can also provide significant insight into the normal function and homeostasis of the connective tissues in the human body.

Over the past decades, several (new) genes have been identified and implicated in these disorders and a whole spectrum of underlying pathogenic mutations have been successfully characterised. These have allowed us to correlate genotypes with corresponding phenotypes. In this way it was possible to illustrate the extensive inter- and intrafamilial clinical variability of many of these conditions and to develop efficient genetic tests that help in providing early diagnosis and for improving prevention and management strategies. This study has also led to important new scientific insights concerning the causal mechanisms underlying the disorders : e.g., perturbation of important cellular signalling cascades that are known to be implicated in normal developmental processes and cellular homeostasis that can

result in the formation of arterial aneurysms or in an abnormal regulation of bone density. Other unexpected discoveries include evidence that a genetic defect in a sugar transporter gene can cause vascular anomalies. This observation is surprising and points to the involvement of a completely new mechanism in these disorders. The importance of these findings is such that they offer opportunities for developing novel therapeutic strategies such as the administration of TGF-β antagonizing drugs to prevent the development of aneurysms.

The major goal of this project is (i) to further increase our understanding of the function of selected genes involved in heritable connective tissue diseases, using both human tissues and animal models (ii) to study the genetic basis underlying the important clinical variation observed in these diseases (iii) to develop and test new therapeutic strategies for these rare and related common disorders based on direct targeting of specific cellular pathways.

One part of the project is dedicated to the study of heritable connective tissue disorders such as Marfan syndrome (MFS) and related disorders, that are associated with vascular anomalies, and in particular, aortic/arterial aneurysms and cardiac valve defects. These disorders represent good models for the study of genes and genetic pathways involved in the development and maintenance of vascular tissues. The causal role of mutations in FBN-1, encoding fibrillin-1, a major component of elastic tissues in the MFS, is now well established. It has been demonstrated that fibrillin-1 deficiency leads to aneurysm formation by the perturbation of a multipotent cytokine, transforming growth factor beta (TGF-ß). The project will explore the effect on TGF-β signalling of mutations in other genes that have been associated with other genetic aneurysm syndromes (related to MFS), such as the TGFBR1&2 genes in the recently identified Loeys-Dietz syndrome ( LDS) or the COL3A1 gene in vascular EDS. To this purpose, specific mouse models will be created that recapitulate the vascular phenotypes of different human aneurismal diseases. The natural history and cardiovascular system will be carefully documented using sophisticated imaging techniques and the ultrastructural characteristics of the elastic tissue in the vascular walls of these mice will also be studied. Where necessary, alternative genetic models such as zebrafish will be used, for example, to explore the role of GLUT 10, a glucose transporter recently implicated in a rare human aneurismal syndrome, in blood vessel formation and maintenance. The project will explore the relationship between genetic variations in these genes and the clinical variability observed in these vascular disorders and investigate whether pathogenetically important polymorphic variants can be identified that can help to predict and refine disease prognosis. Finally, the team will test whether new treatment strategies such as the administration of TGF-ß antagonizing drugs can successfully prevent aneurismal dilatation and rupture in these conditions. Preliminary data have already yielded promising results which have to be confirmed with larger, multi-centre clinical trials.

A second part of the project aims to explore the pathophysiology of another rare but interesting genetic disorder, pseudoxanthoma elasticum, a condition characterised by skin, eye and vascular abnormalities due to progressive fragmentation of the elastic tissue. Affected patients develop inelastic skin folds and retinal problems that can lead to early blindness, and also vascular problems, such as stroke and atherosclerosis, as a result of ectopic calcification. The causal gene, ABCC6, has been identified as a membrane transporter abundantly expressed in liver and kidney, and the mutational spectrum of the gene is well-characterised. However, the substrate of this transporter and the exact mechanism underlying the aberrant calcification is totally unknown. Different mouse models will be used for PXE, including Dyscalc 1 and abcc6 -/-, to explore whether and how active inhibitors of calcification are involved in PXE pathogenesis. Recently a potential link to these proteins was established in another 'PXE-like' disorder associated with a clotting deficiency, and due to mutations in GGCX, encoding a γ-carboxylase important for the activation of vitamin K-dependent proteins, some of which are active calcification inhibitors. Different genes involved in the vitamin K cycle will be tested as candidate 'modifier genes' to explain the significant variability observed in PXE. Based on recent scientific insights, the therapeutic potential of vitamin K and anti-oxidants using human PXE cell cultures as well as animal models will be evaluated.

The third part of the project will focus on bone disorders such as osteopoikilosis (OP) and melorrheostosis (MOS) , which are rare skeletal dysplasias with increased bone density as a common feature. Whereas OP is a benign disorder with autosomal dominant inheritance, MOS is a severe and disabling disease with joint contractures and chronic pain that is usually sporadic. LEMD3 has been identified as the causal gene in families with co-occurrence of OP and MOS, but mutations in this gene are very rare in the sporadic form of MOS. Using different mouse models and expression profiling studies in osteoblast cell cultures in which LEMD3 has been 'knocked –down', the project will explore the cellular pathways and signalling network by which LEMD3 deficiency leads to increased bone density (hyperostosis). These studies are expected to further elucidate the functions of LEMD3 and increase our understanding of the regulation of bone homeostasis and bone density.

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Bart De Strooper is a Professor of Molecular Medicine and head of the department for human genetics at K.U.Leuven as well as being scientific director of the VIB department of Molecular and Developmental Genetics.

He leads a research group of more than 30 researchers coming from over 15 different countries around the world who are investigating the fundamental mechanisms that cause Alzheimer's disease and Parkinson's disease. Their work on the presenilin/gamma-secretase has led them into the area of regulated intramembrane proteolysis, a novel cell signalling pathway. They also collaborate with industry to develop cures.

Dr. De Strooper received his M.D. in 1985 and PhD in 1991 from K.U.Leuven. He did a postdoc in the European Molecular Biology Laboratory of Carlos Dotti (EMBL) in Heidelberg, Germany.

Professor De Strooper is interested in the fundamental molecular processes that underlie neurodegenerative diseases such as Alzheimer's and Parkinson's. His work has also contributed to insights into general physiological mechanisms, in particular, the understanding of regulated intramembrane proteolysis as an important signalling mechanism in health and disease.

## Alzheimer's disease

The working hypothesis is the amyloid hypothesis, i.e., that the amyloid peptide provides the initial trigger of the disease. This peptide is generated by proteolytic processing of the Amyloid Precursor Protein by the consecutive action of a β-secretase and a γ-secretase. Alternatively, a α-secretase cleaves Aβ peptide precluding further Aβ generation. Several questions that are central to the understanding of the disease and can possibly lead to novel cures are tackled.

1. γ-Secretase is in fact a family of at least four different protease complexes. There is evidence that these complexes have different biological and biochemical properties. Biochemical reconstitution assays, drug screens, mutagenesis and other methods are used to unravel structure-function relationships. Also mouse models are used to investigate the role of the individual complexes and their constituents in health and disease models.
2. β-Secretase is a membrane bound aspartyl protease called BACE. Specific monoclonal antibodies are being generated in mice and camels that interfere with its activity in order to explore the possibility of blocking β-secretase activity in the brains of patients.
3. α-Secretase is an underexplored drug target for AD. The project studies pharmacological approaches to modulate this activity in the central nervous system. Furthermore, the team systematically investigates what proteases contribute to this activity in the brain, using knock-out approaches in mice. The working hypothesis is that α-Secretase has a protective effect in the brain.
4. APP biology: although APP was identified 20 years ago, its biological function in the central nervous system is still not fully understood. One of the problems is that two additional homologues of APP exist and can compensate for its function. The triple knock-out mice have a lethal phenotype and can only be generated via complex breeding schemes. The team has therefore derived triple knock-out stem cells that lack all forms and that can now be differentiated into primary neurons in vitro. The project analyses neuronal survival, axonal and dendritic outgrowth, mobility, adhesion, synaptic activity and finally, axonal transport. Phenotypes with APP and APP mutants will be rescued to make a structure-function analysis of APP and its different subdomains. A second line of work is focussed on the identification of the APP receptor postulated many years ago.
5. Sporadic Alzheimer's disease and the microRNA network. Gene dosage is important for the pathogenesis of Alzheimer's disease and therefore that loss of control of gene expression could be an important determinant for the age-related increase in sporadic AD. The team

has analysed micro-RNA expression using micro-array and identified several micro-RNA that are changed in AD and that regulate APP or BACE expression. Work in cell culture and AD brain provides strong evidence that AD could be partially caused by dysregulation of the micro-RNA network in the aging brain. Mouse models are being developed to explore this hypothesis.

6. Oligomer Aβ toxicity: the crucial question to be addressed for the amyloid hypothesis is how Aβ peptides cause neuronal dysfunction and death. In collaboration with the SWITCH group in Brussels a protocol has been developed to generate toxic variants of Aβ oligomers from inert amyloid fibrils ("reversed oligomers"). These species are now used to investigate the mechanism of toxicity analysing the effects on dendritic spines. A second line of research investigates the role of Tau in the observed toxicity (using Tau knock-out neurons and mice).

## Parkinson's disease

The working hypothesis is that mitochondrial dysfunction is an important part of the neurodegenerative process in Parkinson's disease. We approach this hypothesis using a series of mitochondrial assays (fusion-fission, oxygen consumption, cytochrome c release, respiratory chain function, etc.) and evaluating the effects of the loss of functions of proteins involved or potentially involved in PD.

1. Pink-1 is a mitochondrial-located kinase and mutations cause recessive forms of PD. We know very little about the function in the mitochondria, in general, and in neurons, in particular. We have obtained knock-out cells and Drosophila flies and have evidence that Pink-1 regulates oxidative phosphorylation and synaptic activity. We collaborate with Luca Scoranno (Padua, Italy and Geneva, Switzerland) for the mitochondrial biology, and with Patrik Verstreken (Leuven) for the Drosophila work.
2. Lrrk-2 is the major cause of dominant inherited PD. We are generating a recombination cassette exchange protocol to target Lrrk-2 gene in embryonic stem cells. We will use these cells to generate dopaminergic neurons and we will investigate the role of Lrrk-2 and mutants in these neurons, with particular focus on the mitochondrium.
3. Parl-1 is a protease that regulates cytochrome c release from the mitochondrium. We will generate a dopaminergic neuron specific knock-out in mice and investigate the phenotype of these mice.

## Tools and technologies

Mouse models, that are manipulated genetically by over-expression and knock-in and knock-out strategies for most of the genes under investigation are used. Molecular cell biology, confocal and electron microscopy, behaviour and histology are combined. Primary neurons and glia cells are cultured, and ES cells are differentiated to neurons. Excellent detection systems are used for Aβ generation, γ-Secretase biology, Notch signalling and mitochondrial biology.

## HERMAN GOOSSENS

*From left to right: Pierre Van Damme, Herman Goossens, Zwi Berneman.*

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Geert Molenberghs is Professor of Biostatistics at the Hasselt University and the K.U.Leuven in Belgium. He received his BS in Mathematics (1988) and a PhD in Biostatistics (1993) from the University of Antwerp. Geert Molenberghs has published methodological work on surrogate markers in clinical trials, categorical data, longitudinal data analysis and on the analysis of non-response in clinical and epidemiological studies. He served as Joint Editor for Applied Statistics (2001-2004) and as Associate Editor for several journals, including Biometrics and Biostatistics. Since 2007 he has been the Co-Editor of Biometrics. He was President of the International Biometric Society (2004-2005) and is currently the Vice-President (2006). He was elected Fellow of the American Statistical Association and received the Guy Medal in Bronze from the Royal Statistical Society. He is an elected member of the International Statistical Institute and has held visiting positions at the Harvard School of Public Health (Boston, MA). Geert Molenberghs co-authored books on linear mixed models for longitudinal data (Springer, 2000, with Geert Verbeke), on models for discrete longitudinal data (Springer, 2005, with Geert Verbeke), on surrogate marker evaluation in clinical trials (Springer, 2005, with Tomasz Burzykowski and Marc Buyse), and on missing data in clinical trials (Wiley, 2007, with Michael G Kenward). He is a regular short course instructor on the themes of longitudinal and incomplete data, and on surrogate markers. He received the American Statistical Association's Excellence in Continuing Education Award based on short courses on longitudinal and incomplete data at the Joint Statistical Meetings of 2002, 2004, and 2005. He received a Belgian Francqui Chair from the Agricultural Faculty in Gembloux. Geert Molenberghs is founding director of the Center for Statistics (CenStat) Hasselt University and is currently Vice-director of both CenStat and the Biostatistical Centre of K.U. Leuven. In addition, he is the director of the International Institute for Biostatistics and Statistical Bioinformatics (IB2), a joint initiative of both universities.

## Vaccine and Infectious Diseases

The Methusalem Consortium consists of the Vaccine and Infectious Diseases Institute (VIDI) of the University of Antwerp (UA) and the Center for Statistics (CenStat) at Hasselt University (UH).

VIDI consists of the Laboratory of Medical Microbiology (LMM), the Laboratory of Experimental Hematology (LEH), and the Centre for Evaluation of Vaccinations (CEV).

The Laboratory of Medical Microbiology (LMM) is headed by Prof. Herman Goossens and was established in 1995. The LMM has conducted groundbreaking research on antibiotic use and resistance. Research carried out by Surbhi Malhotra and Samuel Coenen, in collaboration with CenStat, clearly showed for the first time the absolute proof that antibiotic use is the main reason for the emergence of antibiotic resistance. This research was published in the lancet in 2007, and extensively covered by newspapers and magazines all over the world. The LMM also developed a standardised methodology to collect data on antibiotic use in the community and hospitals in 34 countries in Europe. This surveillance project on antibiotic use showed that antibiotic prescribing is very high in southern and Eastern Europe, and much lower in northern Europe. This pattern of antibiotic use correlates perfectly well with the pattern of antibiotic resistance, that is indeed much higher in southern and Eastern Europe. These European differences have prompted countries, like Belgium and France to organise awareness campaigns for the general public to reduce antibiotic use. These campaigns have been very successful and have resulted in a spectacular decrease of antibiotic use and resistance in primary care in Belgium. In the LMM, Greet Ieven and Katherine Loens are focussing their research on the development, evaluation and validation of rapid genetic diagnostic tests for the detection of respiratory pathogens in samples from patients with severe lung infections. Finally, Vanessa Vankerchoven is conducting a large research project on the safety of probiotics for human use.

The Laboratory of Experimental Haematology (LEH), headed by Prof. Zwi Berneman, has a track record on the induction of anti-tumoral and antiviral cellular immune responses by a special subset of leukocytes, called dendritic cells. In the coming years LEH will focus on the mechanisms of T cell immunity and tolerance by studying the immunobiology of dendritic cells. More specifically, they want to elucidate the cellular processes and interactions involved in the activation of effector T cells by antigen-presenting cells that are able to destroy tumor cells and virally infected cells or, in case of auto-immunity, normal cells in the body, such as in Multiple Sclerosis. For the latter, modulation of auto-immune effector T cell function by naturally occurring and induced regulatory T cell subsets is one of their primary research interests coordinated by Dr. Nathalie Cools. In collaboration with CEV, LEH will investigate cellular immunity in vaccinees and a possible correlation with the humoral response characterised by antibody formation. They also have a great expertise in phase I therapeutic vaccination programmes in leukaemia, HIV and allotransplant patients using autologous antigen-loaded dendritic cell vaccines. These cellular vac-

cines are produced within the Centre for Cellular Therapy and Regenerative Medicine of Antwerp University Hospital headed by Profs. Berneman and Van Tendeloo. They also run a large research programme on stem cell immunology, headed by Dr. Peter Ponsaerts, in which they are interested in the transplantation effects of autologous and allogeneic adult stem cells in small animal models in order to study the survival, migration and function of transplanted stem cells.

The Centre for Evaluation of Vaccinations (CEV), headed by Prof. Pierre Van Damme, was established in 1994, and has until present conducted more than 120 vaccine trials (Phase 1-4, with all kinds of vaccines and in all age groups) and more than 20 policy research projects related to vaccination. The Centre has been recognised by the World Health Organization as a WHO Collaborating Centre for the control of viral hepatitis since 1996. There is systematic collaboration with the Centre for Statistics (CenStat) at Hasselt University for this research on infectious diseases and vaccination. Evaluation of vaccinations must be considered at large, starting from immunogenicity, effectiveness and safety of a vaccine, the long-term persistence of vaccine-induced antibodies, the impact on the dynamics of an infection, the success of a vaccination programme, and its efficiency (protective efficacy) and economic impact. With regards to technical vaccine research, there is a continuous cooperation with the R&D departments of the major vaccine producers. Regarding policy-oriented research, regional and federal government, and the EU and foreign governmental authorities solicit the expertise of the CEV. For immunological spin-offs there is close collaboration with LEH (immunological memory after vaccination), and for the serological aspects, the expertise of LMM of Prof. Herman Goossens is called upon. At the same time, CEV offers its Phase I vaccine research platform to other research groups inside and outside the University of Antwerp and the University Hospital of Antwerp (e.g., within the framework of therapeutic vaccination as described earlier) in the coming years, the vaccination study platform will be enhanced with a shortened 'bedside-to-bench' delivery time, in order to quickly adjust the vaccine development process.

The passive transfer and presence of maternal antibodies in the long term and in addition the post-vaccination immune memory will receive full attention, since these will have an impact on present and future vaccination policies. The possible interference passive mother-to-child transmission of antibodies is important for the start-up of a vaccination programme for newborns. This research is indeed very timely, because a growing number of women (of childbearing age) have been vaccinated in their childhood, and have never experienced natural infection. This situation will have its effect at the onset of vaccination, and the vaccination of newborns could need to start even earlier. In addition, with support from government attention is given, to further documenting and analysing the safety profiles of vaccines once they have become available on the market.

At the same time, mathematical modelling of infectious diseases and health economic evaluation have become very important topics of research, leading to the inception, as part of the CEV, of the Centre for Health Economics and Modelling Infectious Diseases (CHERMID), led by Prof. Philippe Beutels. This centre continues to expand its research, with further development of basic research in which cellular immunity and the accumulation of maternal and vaccine antibodies are increasingly important themes.

Additionally, the applied analyses of this centre includes very topical infectious diseases, amongst which are pandemic influenza, rotavirus, hepatitis A, human papillomavirus and dengue. The demand for sophisticated mathematical models is very high both nationally and internationally, and all the more so since these models are becoming increasingly essential tools for the economic evaluation of infectious disease prevention. Furthermore, Prof. Philippe Beutels is undertaking research in collaboration with Prof. Herman Goossens on the socioeconomic aspects of antibiotic use. It is expected that these analyses will continue to form a cornerstone in the decision-making processes regarding the reimbursement of pharmaceutical products by Belgian and other European governments.

The main activity of the Center for Statistics (CenStat) at Hasselt University, comprising about 40 researchers, focusses on methodological and collaborative developments in statistics applied broadly to, the biosciences. Here, biosciences should be understood as encompassing and capturing a variety of fields. First, in the area of clinical trials, their design and analysis in general, and the evaluation of surrogate endpoints in particular, are of key interest. Such endpoints allow for the reduction of study length and/or the involvement of fewer study subjects. The gains can be considerable, not only in financial terms but also, and very importantly, in terms of reduction of patient burden. Second, in the field of epidemiology, emphasis is placed on the relationship between the environment and health, including the development of biomonitoring and registration systems. Epidemiological and related studies in infectious diseases are an area of core competence. This includes the development and application of mathematical and statistical models. CenStat members have been

active for over a decade in the dual fields of mental health and psychiatry, from both a clinical-research as well as an epidemiological angle. In particular, CenStat has been active in psychiatric registration for nearly 20 years. A third focal point is risk assessment in the context of the safety of the food chain. The latter area of expertise ties in seamlessly with CenStat's experience in toxicology studies, in particular, in the rat and mouse model. It is also worth mentioning that not only applied areas but also specific methodological foci are discernable in CenStat's competence, such as methodology for repeated and incompletely collected sets of data. Finally, CenStat's proven track record in the fields of bioinformatics and statistical genetics deserves mention.

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Dirk Inzé graduated in 1979 in Zoology at Ghent University and in 1984 he received his PhD in Zoology from the same university with a thesis on the mechanisms by which Agrobacterium tumefaciens causes the proliferation of plant cells. In 1990, he was appointed Research Director of the French National Institute for Agricultural Research (INRA) at the Ghent Joint Laboratory, where he initiated extensive research programmes on cell cycle and cell death in plants. In 1995, he became a professor at Ghent University. In 1998, he founded the biotechnology company CropDesign, currently one of the most active players in high throughput analysis of yield-related genes in cereals. In 1999, he was appointed Deputy Scientific Director of the Department of Plant Systems Biology of the VIB and he became Director of the Department in July 2002. In 2006 CropDesign was acquired by BASF and Dirk Inzé founded Solucel, a biotech company dealing with the production of pharmaceuticals in plants.

Professor Inzé was laureate of the Körber Stiftung Prize in 1994 and in 2003 he became EMBO member. In 2005 he was laureate of the Francqui Prize and became an elected member of the Royal Flemish Academy of Belgium for Science and the Arts. He has served on numerous scientific committees and science advisory boards. Currently he is the Vice Chairman of the European Plant Science Organisation (EPSO).

Prof. Inzé's research focusses on the understanding of the basic cell cycle machinery in plants and on the mechanism of orchestrating plant growth. Prof. Inzé is a member of the editorial or advisory boards of the Journal of Experimental Botany, Plant Physiology, The Plant Journal, Plant Cell Physiology and EMBO Journal. According to a recent ISI survey, he is one of the most cited and influential researchers in his field.

## Yield Booster: towards understanding the molecular basis of plant yield

The global demand for plant-derived products such as feed and food is increasing dramatically, as illustrated by the recent doubling of the price of most commodity crops. Unfortunately, the poorest people on earth will be the first victims of this food shortage and, recently, the United Nations estimated that 37 countries currently struggle with a food crisis. Why do food prices rise so quickly? The first obvious factor is the still exponentionally growing world population. It is hard to fathom, but in the coming decades three billion additional people will have to be fed while less arable land is utilised. Furthermore, the standard of living is anticipated to continue to go up in many developing countries where consumption of animal products is burgeoning, in turn necessitating a larger input of plant-derived feed because, on average, the production of one kilogram of meat requires four to eight kilograms of cereals. High energy prices also make food production more expensive. Last but not least, plants are also starting to play a major role in supplying ever-increasing energy needs. Today, one-third of our energy is provided by oil (of which two-thirds are produced in the MiddleEast) and, in total, 80% of our energy stems from gas, oil, and coal. However, the use of these non-renewable energy sources releases CO2 into the air and causes global warming that consequently limits fresh water availability and crop productivity. The next generation of bio-energy crops might provide a sustainable, CO2-neutral solution. Needless to say, efficient utilisation of bio-energy crops has to be fully compatible and non-competitive with agriculture for food and feed production. It also has to preserve the earth's most precious ecosystems.

How can we deal with these exponentially growing demands for food, feed and bio-energy? How can we cope with the fact that we will have to produce more food on

less arable land, under environmentally more challenging conditions?

There is an obvious and urgent need to further increase crop productivity. Whereas in the sixties the so-called 'green revolution', based on the use of new crop varieties and efficient application of agrochemicals, immensely contributed to increased plant productivity, biotechnological innovations are expected to enhance the ability of plants to capture light energy and convert it into useful products for mankind. One major area for biotechnological improvement is to boost up intrinsic crop yield in a sustainable manner with a minimum input of water, fertilisers, and agrochemicals.

As yield is the most important trait for breeding, a considerable amount of (eco)physiological research has been conducted on the yield performance of crops. In contrast, surprisingly little is known about the molecular networks underpinning crop yield, partly because of the multifactorial nature in which many physiological processes, such as photosynthesis, water and mineral uptake, mobilization of starch and lipid reserves, and stress tolerance determine the resources available to new cells, tissues, and organs of the most vital crops.

In concert with Professor Inzé's lifelong interest in growth processes in plants, the Methusalem Yield Booster research project deals with understanding the molecular mechanisms underpinning biomass production in the model plants Arabidopsis thaliana and Brachypodium distachyon. Results obtained from this research project not only form the basis for the further yield improvement of food and feed crops, but can also be translated to dedicated bio-energy crops, such as Miscanthus, switch grass, poplar, corn and sugarcane.

Many genes have been described in Arabidopsis that, when mutated or ectopically overexpressed, form larger structures, such as leaves or roots. These "intrinsic yield genes" (abbreviated IYGs), are involved in many different processes whose interrelationship is mostly unknown. Other genes, referred to as "stress tolerance genes" (abbreviated STGs) reduce the negative effects of adverse environmental conditions (such as drought and cold) on plant growth. However, all experiments in which the effects of "yield genes" (both IYGs and STGs) on growth under optimal or stress conditions were measured, were performed in different laboratories worldwide under often very different growth conditions and using different Arabidopsis ecotypes, making comparisons virtually impossible. To this end, a first major goal of the Yield Booster project is to compare the effects of "yield genes" with the same genetic background (Arabidopsis ecotype Col-0), using the appropriate controls, and to analyse the cellular and molecular basis underpinning increased leaf and/or root growth under either optimal conditions and/or drought stress conditions. Drought stress was chosen as the major stress factor to be studied in this project because in future years global warming and, consequently, drought stress, will increasingly have a major impact on plant productivity. In many areas worldwide agriculture already suffers from drought stress and approximately 70% of all fresh water is used for agriculture. The cellular basis of enhanced growth will be studied by kinematic analysis and advanced imaging. Microarray technology will be applied to decipher the transcriptional networks orchestrating the observed growth effects. Changes on proteins will be studied using state-of the art proteomics (iTRACQ) and metabolomics (ICR-FT-MS) methods. Advanced computational biology programmes will be applied to decipher the molecular networks orchestrating growth and biomass production. Novel genes with putative key roles in growth control will be further studied. The long term goal is to construct a scalable model describing growth at the molecular, cellular, tissue and organ levels. In the second part of the project, validated yield genes will be combined to test the hypothesis that stacking yield genes will result in a further increase of the ability of plants to produce biomass under optimal and/or drought stress conditions. It is likely that some yield genes will act synergistically. A third aim is to translate expertise and knowledge obtained from Arabidopsis to Brachypodium, an emerging model plant for agronomically important grasses, including wheat, barley and many temperate grasses that can be used for bio energy production.

The Methusalem Yield Booster project will provide novel insights into the mechanisms orchestrating growth and biomass production in crops and will form the future basis of innovative approaches to improve, by advanced breeding and/or gene engineering, crop productivity worldwide.

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Prof. Dr. Marc Leman (°1958) holds a PhD in Musicology from Ghent University. He is a research professor in systematic musicology and head of the Art, Music and Theatre Studies Department, and Director of UGent-IPEM. He has a record of more than 150 publications in the field of systematic music research (journals: Music Perception, Science, Journal of New Music Research; books: Springer, MIT Press). In 2007 he published a book on Embodied Music Cognition and Mediation Technologies with MIT Press. He was heavily involved in writing a European roadmap for Music and Sound Computing (S2S2, 2007). He won the Methusalemproject prize from the Flemish Government for his project on musical embodiment.

His research focus is on how people engage with music in different signification practices and in particular, how people move to music and what this contributes to experience. He is a pioneer in the areas of epistemological and methodological foundations of (social) embodied music cognition, with implications to cognitive ergonomy for music applications, the development of social music interaction concepts and studies of user feedback.

## EmcoMetecca, a Methusalemproject on Embodied music cognition and Mediation technology for cultural and creative applications

The EmcoMetecca project aims at developing innovative research and applications for the music sector and related cultural/creative industries. Innovation in this field is driven by digital technologies and the user's desire for fascinating experiences. Millions of people are interested in music and they provide a huge potential for the creative deployment and uptake of novel technologies. In this Methusalem-project we cross existing classical boundaries between the natural and human sciences and engineering and artistic research. By doing this, we push musical experience and its supporting technologies to a new level where technology, creation, innovation and enhanced social interaction complement each other in a natural and very appealing way.

## Limitations of technology-driven research

Traditionally, the scientific support for the music industry has been driven by technology, more specifically by digital techniques for audio recording and network-based music distribution. In recent years, this has led to the development of music technologies that have made search and retrieval of music on the basis of musical content possible. Starting from a short audio excerpt one can search the corresponding metadata in large databases. Using similar technologies, one can retrieve audio files from the database by describing the musical content (see Casey et al., 2008).

## Advantages of subject-driven research

Technology is currently driven by the idea that music should be "accessible at all places and at all times". This is a good idea, but current approaches typically address a passive consumer, with an individualized personality and a disembodied mind. The full potential of active involvement, social interaction, and embodied expression is thereby hardly addressed. As a result, technology imposes many restrictions, creating a huge gap between our musical and natural ways of interacting with music on the one hand and on the other hand, the way in which digital instruments allow us to interact with music. The EmcoMetecca project aims to change this situation by exploring more fully the creative potential of technologies. Our mission is to turn technology into something that enhances experiences and social interaction in domains that cover creation, distribution and consumption in such a way that these music technologies become, in themselves, attractive and stimulating. Therefore, our approach is subject-driven, first, and then technology-driven.

Think about the mobile telecom devices that people carry nowadays. These mobiles start to offer services based on content-based search and retrieval of music. What we aim to do is turn these devices into instruments for music-based social interaction. Rather than just listening to your mobile, we

are searching for ways that you can musically interact with your mobile. For example, instead of browsing your files, you could shake the music out of your device, using particular expressive gestures. Or what about making your own music, together with your friends, by using your mobile device as a music instrument? Or what about connecting your device with biometric sensors that sense your mood and provide appropriate music in response? In short, when focussing on the socially active human subject in the creation, distribution and consumption of music, there are many interesting possibilities for new technologies. Dealing with new technologies in creative activities becomes in itself an activity that makes sense, just like music making on the classical guitar. In the EmcoMetecca project, we look for solutions that take into account the multi-modal way in which humans deal with technology. EmcoMetecca aims to study these issues and explore new opportunities for the whole music sector, making this sector a driving force behind creativity and technological innovation.

## Studying human musical capabilities

Our subject-driven approach implies that human musical capabilities are at the focus of our research. We study musical capabilities in relation to different music practices such as performance, listening, search and retrieval, sporting, rehabilitation, dancing and last but not least, social gaming. The technologies are studied from the viewpoint of their role as mediators between human subjects and the music. In that way, our approach is complementary to the technology-driven approach in engineering. By taking the human subject as the starting point, the EmcoMetecca project aims to create a solid base for linking human subjects with technologies that push the music sector and related cultural/creative industries.

## Why important?

There are two obvious reasons why human capabilities in relation to music technologies deserve more attention. The first reason is that the music sector is an important economical sector where user-friendly technologies may contribute to the further development of this booming sector (KEA, 2006, Maenhout, 2006). Indeed, of all "content industries" (film, TV, art, heritage, etc.), music is the one which has been most affected by the digital revolution. Music is pushing broadband development (e.g., Napster and P2P) and mobile networks (GSM/GPRS, UMTS). Music stimulates the uptake of broadband subscription and ICT by mass consumers (e.g. PCs, mobiles), e-business (e.g. iTunes), new management tools (e.g., Digital Rights Management, Audio-fingerprinting, Watermarking) and retrieval methods (Music information retrieval). So, music and ICT are closely connected. The impact of music on media consumption has been huge in recent years and music has been a key driving force behind ICT uptake. There are also signs that music will become a key driving force behind social computing and related web activities. A second reason is perhaps even more important for the viability of our society, namely that music enhances the quality of our lives by adding a value to our daily activities. Indeed, music is known to console, enrich intellectual capacities, stimulate social interaction and provide peak experiences that strongly contribute to our mental stability and health. Music promotes ethical values and therefore there is an intrinsic value in music that justifies its development in connection with new content-based technologies. EmcoMetecca aims at turning music technology into something that contributes to both the sociol-cultural and economic value of music.

Music technology goes hand in hand with human experiences (Kusek and Leonhard, 2005). In a recent European roadmap on sound and music computing (S2S2, 2007), it was concluded that there is a high economic and cultural potential for new and advanced music technologies that focus on this so-called experience economy. However, these technologies should be developed in close interaction with creative research, social interaction, and the rich knowledge about musical experiences that is available in the human sciences. The EmcoMetecca project is fully in line with this roadmap, as it implements one of its core ideas, namely that musicological research should study the mutual relationship between human capabilities and music technologies.

## An experimental and computational methodology

The above description leaves us with an important question: how can human musical capabilities be studied, so that the obtained knowledge provides valid assets? The EmcoMetecca project offers a unique empirical approach that is based on a combined experimental and computational methodology, strongly linked with neuroscience (Leman, 2007).

## Embodied music experiences

The concept is called "embodiment" and is related to notions such as "embodied experiences", "corporeal resonances", "imitation behaviour", "musical empathy", "coupling of perception and action", "enactive music engagement". Thus, rather than limiting research to the perception of mental representations and audio structures, we focus on the entire human body as a mediator of music communication. The

human body is thereby conceived as a biologically designed mediator that links music-related physical energy with engaging experiences, values, and intentions. In this approach, we still include perception and structural analysis, but we expand this analysis with the analysis of other behavioural modalities, such as body movement or bioparametric changes (heart rate, skin conduction, muscle tension, etc.). The idea of the body as mediator offers an extremely promising framework for connecting human experience with music technology. Indeed, if the human body and the music technology are properly hooked to each other, then access to music becomes easier. EmcoMetecca's challenge is to develop ways of making music accessible through technologies that fully comply with our embodied mind and the biomechanics of our body. Similarly, the embodiment of interactive technologies and electronic music making devices provides new and more fluent ways of creating musical content that present new avenues for music-driven social interaction.

## Social music interaction

Embodiment is also at the heart of our work on social music interaction and music-driven social gaming. The research focusses on how people move in response to music, on how people influence each other through synchronization and mirroring. In EmcoMetecca, we develop ways to measure how human bodies synchronize with music and with each other. We use advanced sensing technologies, including custom made and commercial sensors for measuring kinetic movement, all kinds of bioparametric sensors, as well as video recordings. For example, it was found that people walk faster to music than to metronome ticks of the same tempo (Styns et al., 2007). Moving in a group (rather than individually) leads to better synchronization with the music and larger movements (De Bruyn et al., 2008). Based on this, we developed a social gaming system where children can trigger different audio tracks while dancing and in doing this, they learn to socially interact with each other in a way that is enjoyable and enriching. Movement-based triggering systems have high potential for future applications in education and social gaming.

## Implementing research

The EmcoMetecca project provides a full development chain that involves (i) the use, design and development of new hardware (basically in collaboration with other institutes), (ii) the development of associated real-time music software, (i) the development of concepts for social music interaction and gaming, and (iv) the study of how users behave with respect to hardware/software, and social interaction. To activate these potentials, we focus on a deeper understanding and modelling of embodied experiences, developing sensors and platforms, conducting relevant experiments, and engaging in deployment activities related to art, gaming, entertainment and so on.

## Conclusion

In summary, the EmcoMetecca project is about human musical capabilities in connection with novel technologies. Our mission is to transform novel technologies into something that inspires musical experiences, thereby enhancing creativity, innovation, and social networking. Our main focus is on how people interact with music and with each other through movement and how these movements relate to experiences. This subject-driven research, in combination with the use of new technologies, forms the basis of innovative applications for the current traditional music sector and far beyond (such as gaming, rehabilitation, sports, other, etc.).

## References

Casey, M. A., Veltkamp, R., Goto, M., Leman, M., Rhodes, C., & Slaney, M. (2008). Content-based music information retrieval: Current directions and future challenges. Proceedings of the IEEE, 96(4), 668-696.

De Bruyn, L., Leman, M., Demey, M., Desmet, F., & Moelants, D. (2008). Measuring and quantifying the impact of social interaction on listeners' movements to music. Paper presented at the CMMR, Copenhagen.

KEA. (2006). The Economy of Culture in Europe. http://ec.europa.eu/culture/key-documents/doc873_en.htm

Kusek, D., Leonhard, G., & Lindsay, S. G. (2005). The future of music : manifesto for the digital music revolution. Boston: Berklee Press.

Leman, M. (2007). Embodied music cognition and mediation technology. Cambridge, MA: The MIT-Press.

Maenhout, T., De Voldere, I., Onkelinx, J., & Sleuwaegen, L. (2006). Onderzoeksrapport: Creatieve industrie in Vlaanderen Leuven, Gent Vlerick Management School.
S2S2. (2007). A roadmap for sound and music computing. Brussels: The S2S2 Consortium.

Styns, F., Van Noorden, L., Moelants, D., & Leman, M. (2007). Walking on music. Human Movement Science, 26 (5), 769-785.

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Trained in diabetes research as an investigator for the National Fund for Scientific Research (Belgium) and as a Harkness Fellow of the Commonwealth Foundation (New York), at Université Libre de Bruxelles, Washington University, St Louis,USA and the Queen Elisabeth Foundation in Brussels.

As an independent investigator, Daniel Pipeleers initiated a novel research line seeking a cellular basis for the treatment of diabetes. He started his own team on the newly built Medical Campus of Brussels Free University-VUB and progressively developed it into the Diabetes Research Center (DRC) which is currently composed of six research units grouping twelve principal investigators and over 100 collaborators together. His team developed methods to purify and investigate the insulin-producing beta cells that generated new insights in the biology and pathology of these cells. This work helped establish a basis for strategies and clinical trials regarding beta cell therapy that are currently being developed by the JDRF Center for Beta Cell Therapy in Diabetes, a European network of clinical and research departments, associated to reference centers and bioindustry partners (www.betacell-therapy.org). Pipeleers is director of the JDRF Center that is supported by the Juvenile Diabetes Research Foundation (New York) and by the European Union (6th FP). Pipeleers is the author of over 200 original publications in the field of beta cell biology, pathology and therapy in diabetes. He has received several awards and honors, among them the Minkowski Prize of the European Association for the Study of Diabetes, the Merck-Sharp-Dohme Prize for Biomedical Research, the Quinquennial Prize for Biomedical Sciences of the Belgian Research Fund, the Quinquennial Prize for Medical Sciences of the Belgian Government and the International Bial Merit Award in Medical Sciences. He is a member of the Belgian Royal Academy of Medicine and an Honorary Doctor at Upsala University Sweden.

## From Beta Cell Biology to Beta Cell Therapy

Diabetes is a frequently occurring chronic disease that reduces quality of life and increases the risk for life-threatening complications despite current available treatments. Complications can occur acutely or develop as a result of slow and progressive tissue lesions.

The type 1 form of diabetes is caused by the massive loss of insulin-producing beta cells in the pancreas following a process of inflammatory and autoimmune reactions; its cure requires the replacement of destroyed cells, either by transplanting donor beta cells or by endogenous regeneration of beta cells in the pancreas. Type 2 diabetic patients still have a considerable number of beta cells in their pancreas but their mass and functional state have been rendered inadequate for meeting the metabolic needs of the body; in many cases these needs increase in the face of sustained lower sensitivity to the actions of insulin, a condition that is often the consequence of obesity; for a number of type 2 patients, an increase in beta cell mass is also seen as the treatment of choice.

Both forms of diabetes can thus benefit from methods that regenerate a sufficiently large amount of functional beta cells in patients, and for this reason, diabetes is among the major diseases to benefit from cell therapy and regenerative medicine. The goal is not only to restore the number of beta cells but also to establish conditions that preserve their long-term survival and function. The novel beta cell mass is indeed expected to reinstall a tight metabolic control and should therefore exhibit the physiological properties of the normal beta cell population. In addition, it is to be protected against pathologic cell loss and/or dysfunction, as might happen by a recurrence of the disease process, by a (re)activation of inflammatory and autoimmune processes, by rejection of transplanted tissue, or by toxic influences of inadequately controlled glucose or lipid levels.

In general terms, therapeutic strategies should thus aim to replace functional beta cell mass as well as preserve it. We have placed these therapies under the overall name of beta cell therapy for diabetes. With this form of regenerative medicine as our objective, we have chosen a cellular biological approach in which knowledge of the biology and pathology of the beta cells directs and drives the development of methods for the replacement and preservation of insulin-producing beta cell mass in patients. This approach takes advantage of 25 years of laboratory and clinical research at the Diabetes Research Center-DRC of Brussels Free University-VUB. Pipeleers' team was the first one to purify beta cells – first from rodents and then from humans – and to investigate their properties in the absence and/or presence of micro environmental components such as other cell types and their mediators. Regulators of functional beta cell mass were identified in laboratory models which served as the basis for designing and setting up beta cell preparations for the correction of diabetes in rats. The observations, as well as the methodological approach, raised interest for translating the findings into beta cell therapy for diabetic patients. They also indicated areas where complementary expertise and collaborations were needed, where new questions had to be addressed and novel therapies developed.

Over the past 15 years, the VUB-DRC took initiatives to build an international multidisciplinary network of basic and clinical research teams to collaborate towards reaching its objective. A long-term program was outlined in which clinical trials were designed and guided by a biologic platform, and supported by reference centers and bioindustrial partners (Figure). The program and its team have been recognized and supported as a Center of Excellence by the European Union (since 1990) and the US-based Juvenile Diabetes Research Foundation (since 1995). Since 2002 it has formed the core of the JDRF Center for Beta Cell Therapy in Diabetes (www.betacelltherapy.org) with its central unit on the medical campus of VUB and with the DRC as a major partner.

At present, the DRC is composed of six research units that have complementary expertise that ranges from molecular biology to holding clinical trials (Table 1); the units are headed by full-time professors at VUB and bring together a total of 102 scientific, technical and administrative collaborators (see photo). These units undertake three collaborative projects on the roadmap towards beta cell therapy in diabetes for which they interact with the DRC spin-off, BetaCell nv, with the Belgian Diabetes Registry (www.bdronline.be) and with partners of the JDRF Center (Figure). The three projects aim to be translated to clinical applications, where possible directly, and where needed, via further bioindustrial development through BetaCell nv. They translate knowledge of beta cell properties – in particular neogenesis and proliferation, protection and survival mechanisms, insulin production – in order to identify strategies and work out protocols for beta cell transplantation and regeneration. Preclinical models are available to assess and compare the efficacy of the components.

**VUB-Diabetes Research Center**
Director Daniel Pipeleers

| **Research Units** | **Head** |
|---|---|
| 1.Cell Therapy | Daniel Pipeleers |
| 2.Cell Neogenesis | Harry Heimberg |
| 3.Cell Differentiation | Luc Bouwens |
| 4.Experimental Pathology | Miriam Marichal |
| 5.Clinical Biology | Frans Gorus |
| 6.Clinical Trials | Bart Keymeulen |
| **Core Units** | |
| Coordination Core | Christel Hendrieckx |
| Functional Cytomics Core | Geert Stange |
| Gene Expression Core | Harry Heimberg |
| Preclinical Model Core | Daniel Pipeleers |
| **Biobank** | |
| Histopathology Bank | Miriam Marichal |
| Beta Cell Bank | Zhidong Ling |

The clinical trials are undertaken by the JDRF Center. Two long-term trial lines have been set up. Their rationale and experimental design are based on observations of JDRF-associated laboratories, and are conducted by a multidisciplinary team, with major participation by the Belgian Diabetes Registry and its affiliated university and non-university hospitals.

One trial line assesses the effect of an antibody intervention at an early stage of the disease. Using a short course of antiCD3-administration at the time of clinical onset they have shown that the beta cell mass can be preserved for at least 18 months. Patients are followed for longer periods and new protocols are planned to increase the beneficial outcome and extend the findings to younger patients and individuals

at risk for developing the disease. The other trial line aims at replacement through beta cell transplantation in patients with early stage complications. A central Beta Cell Bank receives donor pancreases through an intermediate of the Eurotransplant Foundation, and isolates and characterises diverse pancreatic cell preparations for the transplant trial and its associated research projects. Beta cell grafts that are standardised by cell biologic criteria can correct diabetes in patients. A correlation was demonstrated between the beta cell mass in the graft and metabolic control in the recipients. Conditions for reaching a state where patients can stop administering insulin injections were defined. The functional beta cell mass in the patients who received the transplants was determined and compared with that in normal non-diabetic controls. It was thus found that a larger mass will be needed for further trials.

Further research and development is being carried out at the R&D platform in which European teams collaborate on complementary projects that aim at the programming of cells for beta cell therapy. A major objective is to (re)generate insulin-producing cells in therapeutic quantities. This would provide the potential to produce sufficient beta cells to undertake larger-scale trials and to consider – and further develop – beta cell transplantation as a cure. This could also indicate methods to regenerating a beta cell mass in the pancreas. The R&D consortium undertakes projects to derive a functional beta cell mass from embryonic stem cells, from transdifferentiating endodermal cells and from beta cell(progenitor)s. DRC-units have opened interesting new lines for development in these areas.

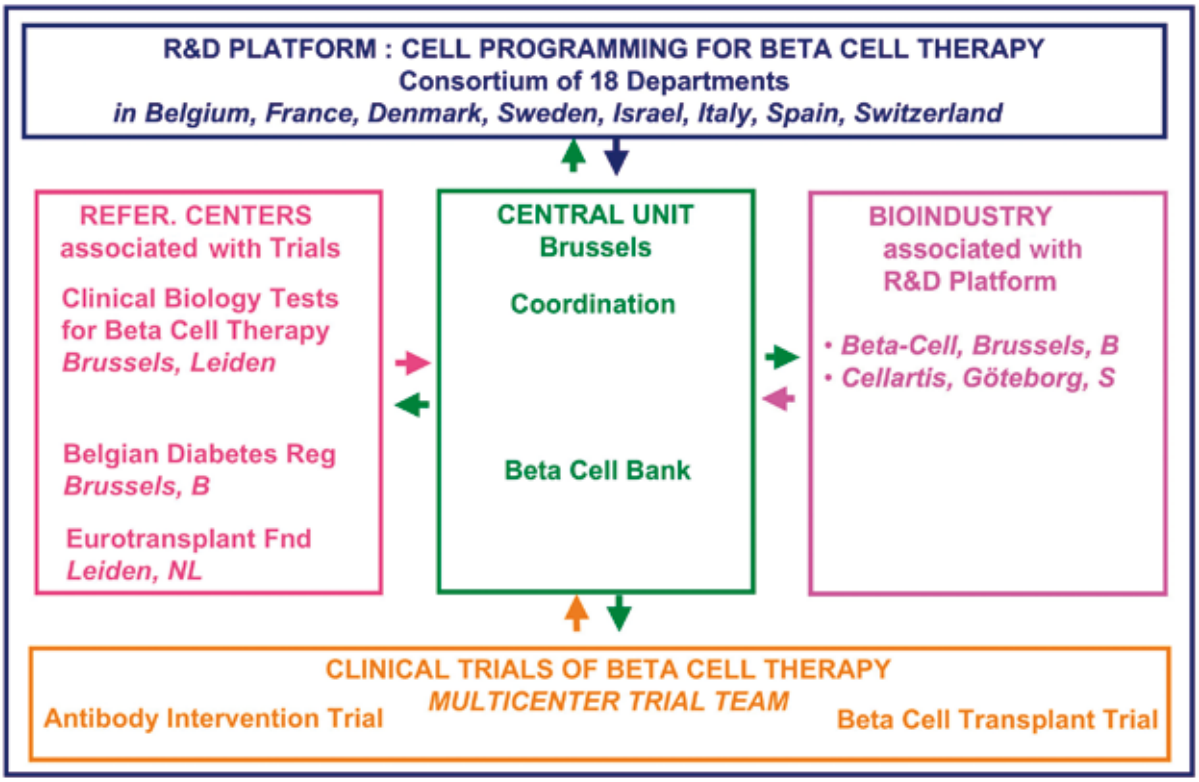


Fig. Composition of JDRF Center for Beta Cell Therapy in Diabetes

## JOHAN SCHOUKENS

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Johan Schoukens (1957) became an electronic and mechanical engineer (Vrije Universiteit Brussel) in 1980, a doctor in engineering (Vrije Universiteit Brussel, 1985), and Geaggregeerde van het hoger onderwijs (Vrije Universiteit Brussel, 1991). For 19 years he was a researcher of the FWO (Fonds voor wetenschappelijk Onderzoek). Since 2000 he has been working full time as a research professor at the Vrije Universiteit Brussel, where he is the head of a research group on System Identification.

Together with Rik Pintelon, he published two books on System Identification, in 1991 and 2001. He is the (co-) promoter of 20 finished doctoral theses.

In 1997 he became a fellow of the International Electric and Electronical Engineering Society (IEEE). The society recognizes unusual distinction within the profession, only one in a thousand members can be elected in a given year. In 2003, he was awarded the IEEE Instrumentation and Measurement Society Distinguished Service Award for technical and professional leadership. In 2007, he held the Belgian Francqui chair at the ULB for the Identification of Linear Systems in the Presence of Nonlinear Distortions: A Frequency Domain Approach. Also in 2007, Johan Schoukens was awarded a Methusalem grant by the Flemish government to set up a "Centre for Data Based Modeling and Model Quality Assessment".

His major research interests are to develop, acquire, and disseminate methods for building models from experimental data, and growing melons and tomatoes in his greenhouse.

### Centre for Data Based Modelling and Model Quality Assessment

The goal of this project is to develop, acquire, and disseminate methods to build models from experimental data.

### Why do we need mathematical models?

Engineers and scientists intensively use mathematical models. For example, to make a weather forecast, the weather evolution is simulated on a computer using a mathematical weather model. Good models will result in better forecasts. Another example is the design of an airplane. The aircraft is simulated for many hours on a computer before it takes off for its first flight. This does not only increase the safety of the test programme, it also significantly speeds up the design process, because changes in the design can be tested without the need to build a new prototype each time. Good mathematical models allow engineers to reduce the number of design cycles, resulting in a reduction in the time-to-market of new or improved products. For that reason, mathematical models are used everywhere: in civil engineering, in the automotive industry, during the design of micro-electronic circuits, etc. Not only engineers need mathematical models.

For example, econometric models provide better insight and understanding of the impact of government actions on the economy. Also, scientists formalize their ideas using mathematical models. For instance, to address the challenges of global change, it is of utmost importance to understand all processes and interactions that affect the's climate earth. Again, this boils down to the development of good mathematical descriptions. Since the quality of the prediction, simulation or theoretical understanding depends directly on the quality of the model, it is clear that we need good methods to build good models.

### What is the problem?

From this short introduction, it is clear that mathematical models are one of the major tools that are used by engineers and scientists. But how can we obtain these models? Because a mathematical model is closely linked to the physical problem that is studied, clearly the specialists in the field will take the lead. They know what aspects are important, and what processes can be neglected. But that is not enough

to arrive at a good model. The model should be tuned such that it matches the reality as well as possible. And this brings us to the essence of each model activity, that can be aligned along the following basic steps and questions:

i) Experimental data are collected. What are the best experiments to perform?
ii) A general model structure is proposed. How do we select from among the different possibilities?
iii) The model and the experimental data should be matched as closely as possible. How do we select the criteria for measuring the quality of the match? What is the quality of the final model?

Although the answers to these questions is very closely linked to the specific goal and application field, it turns out that the tools that can be used to address these questions are very universal. These tools are developed within a statistical framework, and the major goal of our Methusalem project is to contribute to this theory. Below, we will discuss these three general questions in more detail.

**Mathematical modelling: a generic activity.** Our group is not application driven, our results are very generic, and are applied by hundreds of users in widely scattered application fields, from low frequency (modelling of large electrical machines) to high frequency applications (telecommunication problems); from civil engineering (vibration analysis of a bridge), over mechanical (flutter analysis of an air plane) and chemical engineering (electro-chemical reactions), to medical applications (analysis of NMR spectra). We are also involved in the development of environmental (study of mixing water masses in the southern ocean) and climatological modelling tools (reconstruction of the temperature, starting from mussel valves). In all of these examples, our contribution to the modelling effort is not the final goal; we provide only a tool for the optimal extraction of the information from the experimental data. Using good tools provides access to information that is hidden in the experimental data and that would be otherwise lost or unreachable.

This wide but hidden use of our work makes it very difficult for the larger public to get a good feeling for it. We cannot be associated with a single application, and not even with an application field (for example, telecommunication). We provide good paintbrushes to the painter, so that she/he can create a masterpiece. We are not the artist, but offer full scope to her/his creative talent.

**The first main question revisited: collecting experimental data.** In most applications, the mathematical model should reflect a part of the surrounding reality. We call this a system. In order to model this system we should collect information about it. Sometimes we can only observe what happens, but often we can actively ask questions. An astronomer can only look to the sky (wait, watch and see), but an audio engineer can make experiments to design a new loudspeaker (ask questions). Because experiments are often time consuming and expensive, it is important to design them so that they provide maximum information for a minimal cost. The result of these experiments is not perfect, measurements are disturbed by noise. Noise disturbances are unexplained variations that disturb our view on the world, like the way 'television snow' can blur an image. Different balances give different weights for the same person. Due to this noise, we get an imperfect answer to our question. One of the major goals of our research activities is to find methods that eliminate, as much as possible, the impact of the noise on the final result. Bad methods lead to completely wrong results, without any warning the user of this failure. She/he remains unaware of the pitfalls of the model. This is a most dangerous situation.

**The second main question revisited: selecting a model structure.** A model is the mathematical translation of the scientist's and engineer's knowledge. Building a model is closely linked to the application field. The knowledge that is needed to build a model for the climate of the earth is completely different from the know-how that is required to describe an electrical engine.

But it is also possible to create a more general approach. To do so, we introduce the class of linear dynamic systems. First, we briefly explain both terms. *A system is linear* if its response to a combined experiment x+y is given by the sum of the responses of experiment x and experiment y, or to simplify, the sum of one and one is two. The Belgian tax system is not linear: doubling the gross income does not result in a doubled net income. Although most systems are not linear (nonlinear), we can often sufficiently approximate them by using a linear model. *A dynamic system* remembers its past. Its response to an input that is applied in the moment also depends on what happened in the past. If we hit a metal beam, it will oscillate for a few seconds because it 'remembers' that it was hit by a hammer, even when the hammer has been removed for some time. Linear dynamic systems can be used in a very wide range of applications. They are very popular in mechanical, electrical, electronic, chemical, etc., engineering. Also, econometricians make intensive use of these models. General purpose software packages that can be used to model linear dynamic systems are developed. They offer the tools to the engineer and the scientist to obtain the best linear model for his/her

specific application, just like the paint-brush is a tool that an artist uses to create his artwork. Of course, the physical knowledge is still needed for interpreting and using the resulting models. *System identification* is the theory that studies how to obtain dynamic models from noisy experimental data, and this is the topic of our research. At the present time, many groups are intensively looking for methods that can also be applied to nonlinear dynamic systems. These are systems that no longer add up: one plus one does not equal two. The major issue here is to find mathematical descriptions that are as universal as those for linear cases. Although significant progress has been made, we still face many unresolved problems. Nonlinear system identification is the major challenge that we currently face.

**The last main question revisited: matching the data and with the model.** The last major issue to be addressed, once the data and the model structure are available, is to find out how we should match both. If there was no measurement noise, and if our models were perfect (no model errors), it would be a simple task. But in practice, we obtain wrong measurements and we use wrong models. Replacing them with perfect measurements and models is not a solution, because this is an impossible task, for both technical and financial reasons. In the previous century a general statistical theoretic framework was developed to deal with noisy data, and it still informs the actual thinking. The major difference with that era is that we presently have much greater computing power available for transforming these theoretical ideas into practice. Following this approach we end up with more than just a model. We also obtain an estimate of the model's reliability. It is easy to forecast the temperature one year in advance, but it becomes impossible if this has to be done with tight uncertainty bounds. However, the prediction has no value at all without these bounds. Knowing the uncertainty bounds is as important as knowing the value itself.

Within the Methusalem Centre for Data Based Modelling and Model Quality Assessment we continue our work on system identification. Improved identification tools for linear and nonlinear system identification are further developed, with an emphasis on user friendly methods, to make sound modelling techniques accessible to a wide public of engineers and scientists. We make a major effort to disseminate the results. We organise a doctoral school (an intensive one-month training), and invite researchers from other groups for longer periods. This allows them to obtain access to information within their data that was unreachable before, and it gives us strong feedback about the needs in the field that are then used for directing new research.

## CHRISTINE VAN BROECKHOVEN

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Professor Christine Van Broeckhoven obtained her BS in Chemistry in 1973, her MS in Biochemistry in 1975, her PhD in Molecular Biology in 1980, and a doctorate in Molecular Genetics from the University of Antwerp in 1994. She is currently a Professor in Molecular Biology and Genetics at the University of Antwerp. She is Director of the Department of Molecular Genetics at the VIB and group leader of the Neurodegenerative Brain Diseases Group within this department. She is also Research Director of the Laboratory of Neurogenetics at the Institute Born-Bunge. Her team is currently specialised in the molecular genetics, genomics and neuropathology of Alzheimer's disease, frontotemporal dementia and Parkinson's disease. They receive competitive funding from the University of Antwerp, the Fund for Scientific Research Flanders, the Institute for the Promotion of Innovation by Science and Technology Flanders, the Belgian Federal Science Policy Office, the European Commission and charity organisations such as the Foundation for Alzheimer Research Belgium; the Alzheimer Association, American Health Assistance Foundation, the Assosiation for Frontotemporal Dementias and the Michael J. Fox Foundation, USA. They have published over 450 international science articles on their work.

She has been awarded several scientific prizes for her molecular genetics work, among them, the Potamkin Prize for her contribution to the identification of APP as a gene in Alzheimer's disease in 1993. In 1995, she was awarded the five-yearly Joseph Maisin Prize by the Belgian Fund for Scientific Research for her scientific oeuvre in Molecular Genetics. In 2006 she received the International Award for Women in Science by L'Oréal/UNESCO. She is a member of the Royal Flemish Academy of Sciences and the Arts of Belgium. In 2006, she was honoured by the King of Belgium with the title of Grand Officer in the Order of Léopold.

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Piet Stinissen (°1964) is a Professor of Immunology at the Faculty of Medicine and School of Life Sciences (Hasselt University) and guest professor at the University of Antwerp. He is also Director of the Biomedical Research Institute (BIOMED) and head of the Immunology and Biochemistry laboratory at this Institute. BIOMED is a research institute of UHasselt with a staff of 80 researchers and technicians. Piet Stinissen has a strong track record in research on the immune-mediated mechanisms of Multiple Sclerosis and related autoimmune diseases. His team focusses on the mechanisms involved in immune activation, regulation and homeostasis in autoimmunity, the identification of new biomarkers and the development of new immunotherapeutic strategies for Multiple Sclerosis.

He is the author of more than 80 international ly published articles and two patents. He received awards

from the International Foundation Mauro Baschirotto (Italy), the Belgian Royal Academy of Sciences and the Belgian Society of Neurology. He is a board member of the European School for Neuroimmunology (ESNI) and the Belgian WOMS (MS research) foundation. He is also chairman of LifeTechLimburg.be and a board member of NV Life Sciences Development Campus, two organisations that promote and support regional life sciences development.

## An integrated approach towards understanding the pathogenesis of central and peripheral nervous diseases

The Methusalem network brings together researchers specialised in clinical neurology, neuropathology, genetics and genomics, cell biology, mouse modelling and therapeutics. The main expertise is in the field of human molecular genetics with a focus on complex diseases of the central and peripheral nervous system. The main goals are: 1) to identify genes and genetic risk factors, 2) to understand the biological dysfunction of disease genes, 3) to contribute to the development of more effective therapies, and 4) to translate our basic research findings to the clinic.

The network will focus its research activities on neurodegenerative brain diseases such as dementias (Alzheimer's disease and frontotemporal lobar dementia) and Parkinson's disease, as well as on sensory and motor disturbances as in Charcot-Marie-Tooth neuropathy, and neuroinflammatory diseases with an important neurodegenerative component such as Multiple Sclerosis. These debilitating illnesses put an enormous strain on our social system. Although the underlying etiologies remain poorly understood, some common themes in these different diseases are becoming increasingly apparent, and close collaborations between researchers working in these fields might provide major advantages.

All these diseases compromise the nervous system, are characterised by a later age of onset, present with synaptic dysfunction and many of them are characterised by biochemical abnormalities, such as abnormal cellular "inclusions" or accumulation of peptides. From a mechanistic point of view, neuronal function is jeopardised by transport axonal problems, mitochondrial dysfunction, nerve conductance or neurotransmission deficiencies or increased vulnerability to cellular stress resulting in apoptosis. Most forms of neurodegenerative disease are caused by the complex interplay between genes and the environment, but many are purely genetic in nature. The study of the latter has turned out to be extremely fruitful over the years, providing important clues towards the molecular mechanisms underlying both familial and sporadic forms of these diseases. Finally, it is extremely important to translate these novel insights into therapies because at present, no effective treatments are available for patients. Methusalem project is aimed at applying the information provided by the sequencing of the human genome in order to advance our understanding of, and to develop treatments for, these devastating diseases.

The main aim of our Methusalem project is to clarify a series of fundamental questions related to the pathophysiological processes underlying these diseases. More specifically, the elucidation of biological pathways that are linked to these diseases, by identifying novel genes and genetic risk factors, by analysing the functional networks in which the proteins encoded by these genes are operating, and ultimately, by providing novel avenues for early diagnosis, prognosis, prevention and treatment.

In this Methusalem project at the University of Antwerp we specially aim to systematically collect clinically well-documented groups of patients and their families, in case of inherited forms, of neurological diseases. Biological material from these patients/families will be used for genetic (DNA and RNA) and biochemical (proteins and metabolites) research to gain insight into molecular and cellular biological mechanisms that lead to neurodegeneration, for example, through the identification of new disease genes and subsequent cell biology research of the encoded proteins, and by in vitro and in vivo studies of the disease process in transgenic mice models and in situ pathological research in human and mice. We aim to contribute to the development of new therapeutics using cellular and animal models, for example, through the identification of medicines for specific targets or therapeutic approaches aimed at specific cell populations or tissues. We also aim to translate the knowledge obtained from basic research into clinical applications (= translational component), for example, through clinical studies (= clinical trials) of new medicines in clinically well documented groups with a known risk profile.

Dementia is one of the leading causes of morbidity and mortality in the western world as well as in most developing countries. Due to the sharp rise in life expectancy, and coupled with a steady decline in birth rates, the number and proportion of people older than 65 years is growing explosively. As old age is the primary risk factor for dementia (the prevalence increases from 1-to 2% among the population over 65 years old to 25-to 33% among people over 85 years), the number of people suffering from dementia

is rapidly increasing with profound social, economic, and cultural consequences for the healthcare system and society. According to the Delphi consensusstudy, the number of people in 2001 with dementia world wide was 24.3 million. With an estimated 4.6 million new patients each year, the numbers of people living with dementia will almost double every 20 years, to 42.3 million in 2020 and 81.1 million in 2040. There is still no therapy available that can cure or prevent dementia. However, it is to be expected that any intervention that can somehow slow down or postpone the disease will have a major impact on public health. It is therefore essential to invest in scientific research of the causes of dementia.

Neurodegenerative brain diseases are the most common cause of dementia and include Alzheimer's disease, frontotemporal lobar degeneration and Parkinson's disease as the most prevalent diseases. Using molecular genetic approaches, we are searching for novel genes implicated in neurodegenerative brain diseases. These include causal genes associated with Mendelian forms of disease and risk genes associated with disease susceptibility. Such prior studies have been critical for the identification of already known genes and risk factors. Our molecular genetic research strategy will include follow-up of the chromosomal loci identified in previous genome scans and novel genome scans in families segregating Mendelian forms of neurodegenerative brain diseases. This straightforward approach has proven successful and will be further accelerated, thanks to advanced refinement and automation of the applied technologies. Therefore, more time and human resources will become available to establish additional strategies towards identifying susceptibility and protective and modifier genes for complex non-Mendelian forms of neurodegenerative brain diseases. Because these studies require extended and well-characterised patient collections, continued sampling focussing on triad collection and multiplex families will remain of major importance. In addition to extended clinical records, routine collection of serum and plasma will be done to study biomarkers. Doing so, genetic studies will be expanded from disease state as such, to more detailed diagnoses and biological endophenotypes. Furthermore, taking additional clues from human neuropathology, we will continue to decipher pathways and mechanisms involved in neurodegeneration, by utilising in vitro and in vivo mouse models both overexpression and knock-out genetic models.

For instance, for Alzheimer's disease, we will continue to address the mechanism of the formation of Aβ amyloid plaques that are deposited and are toxic. We want to identify molecules that facilitate dense plaque formation at vascular sites as these plaques are the predominant extracellular form of brain Aβ deposited in AD patients and mouse AD models. The targets identified here will be exploited for making better mouse models as well as for therapeutic targeting. For frontotemporal lobar degeneration, we would focus on the recently identified progranulin to show whether and how its loss leads to decreased cell survival.

Inherited peripheral neuropathies belong to the most common neuromuscular disorders and occur worldwide (1/2500 individuals). Of them, the most well-known Charcot-Marie-Tooth disease (CMT), an inherited disorder first described in 1886. Most patients have progressive weakness and wasting of foot and hand muscles. Sometimes patients need walking aids or become wheelchair dependent even at a young age. The clinical variability and genetic heterogeneity often poses difficult diagnostic problems. Treatment is currently supportive (braces and foot surgery)although a therapy that fundamentally alters the course of these diseases is still lacking. A better understanding of the molecular architecture of the peripheral nerve, the functional pathways, the myelination process and the complex interaction between the axon, the myelinating Schwann cells and muscle is crucial to identify targets for therapeutic interventions. The identification of loci, genes and disease-causing mutations involved in the inherited peripheral neuropathies is the first step in this understanding. Over the years, we have assembled a unique collection of unrelated pedigrees, clinical data and DNA samples. Genotype/phenotype correlations are made using clinical, neurophysiological and neuropathological data provided by clinicians and pathologists. The molecular genetic methods used include genome-wide searches and genetic linkage analyses in extended families, identification of novel genes using DNA cloning techniques, gene prediction, mutation analysis of candidate genes and functional analysis of some of the genes. We have been successful in the identification and confirmation of several genes and mutations responsible for various types of inherited peripheral neuropathies.

Although many genes still need to be identified, we have initiated functional studies on selected genes in order to understand the pathomechanism of mutations, the biology of myelination and axonal transport and the differential gene expression in motor and sensory neurons. The current focus is to gain knowledge although distal hereditary motor neuropathies (distal HMN), hereditary sensory and autonomic neuropathies (HSAN) and intermediate types of CMT. One of the pathomechanisms on which we will focus is related to the innate immune response. It starts from the observation that neurodegeneration tends to trigger a strong innate im-

mune response in Schwann cells. Our goal is to understand how innate immune responses are activated in Schwann cells upon neurodegeneration and what the net outcome is on nerve regeneration/degeneration. Understanding the molecular switch between a protective versus a detrimental effect might allow us to fine-tune and stimulate our inherent body's capacity to resolve a neurodegenerative response and allow nerve regeneration. In all our projects it will remain essential to directly correlate the results of our genetic and functional studies with the neurological, neurophysiological and neuropathological observations in patients.

Neurodegeneration is also important in Multiple Sclerosis (MS), the most common neurological disease in young adults. MS is a chronic inflammatory disease of the central nervous system (CNS) leading to demyelination and nerve cell injury. MS is considered to be an autoimmune disease and becomes clinically apparent in early adulthood (20-40 years). MS has a high prevalence rate (ranging from 50 to 130 in 100,000) among Caucasians living in Europe or Northern America. Females are more commonly affected than males, in a ratio of approximately 2:1. The clinical manifestations of MS include visual and sensory impairment, paralysis and other neurological deficits, sometimes accompanied by considerable cognitive dysfunction. Beside the non-specific immune suppressive agents (corticosteroids) that have been used for a long time to counter the inflammatory reactions and that are still considered to be first line treatment for relapses, five drugs have obtained regulatory approval to modify the course of MS. However, most of these treatments are associated with side effects and still have suboptimal efficacy. Pathologically, MS is characterised by multiple sclerotic lesions or plaques found in the white matter of the CNS. These lesions result from focal loss of CNS myelin and are localized throughout the CNS, predominantly residing within the periventricular regions, optic nerves, brain stem and spinal cord. Sites of active demyelination are characterised by an infiltration of various types of immune cells such as T lymphocytes and macrophages. Many groups including ours at UHasselt have demonstrated the presence and enhanced activation status of myelin-reactive T cells in the blood and cerebrospinal of MS patients. These data support the concept that MS results from a T-cell driven autoimmune process. However, it remains unclear which pathways are important in activating the various components in the immune system that lead to damage to the brain and spinal cord in MS patients. While the inflammatory component is prominent at early stages of the disease, neurodegenerative processes are more important in later stages. Moreover, there is increasing evidence that even in very early stages of the disease, nerve cell damage is prominent and greatly determines clinical outcome. One of the great challenges in MS research is to devise strategies that will promote remyelination and neuroregeneration in the CNS, in addition to therapeutic approaches that will limit inflammatory responses.

However, to reach this goal further information is required on the pathological process, and more particularly at the level of the molecular pathways that are involved in the immune-system and the nervous system. The Methusalem programme at the University of Hasselt will focus on immune mediated processes in neurodegeneration, with a special focus on MS. An integrated approach will be used, applying various powerful molecular technologies to study relevant pathways in vitro, ex vivo and in vivo (animal models). For instance, we will study the molecular mechanisms involved in cell injury to myelin forming oligodendrocytes in culture, and study the effects of neuroprotective molecules belonging to the neurokine family. In addition, we will study the deleterious and/or protective roles of immune cells and related molecules on CNS cells such as nerve cells, astrocytes and oligodendrocytes in relation to neurodegeneration.

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Gustaaf Van Tendeloo (1950) was educated as a physicist at the University of Antwerp and Brussels and graduated from the University of Antwerp in 1974 with a thesis on ordering in alloys under the guidance of Prof. S. Amelinckx. He obtained his habilitation in 1981 from the University of Brussels (VUB). As a solid state physicist and electron microscopist he spent several longer periods at the University of California (Berkeley), University of Illinois (Champaign-Urbana) and the Université de Caen (France). In 1986 he became part time professor at the University of Brussels and since 1994 he has been a full professor at the University of Antwerp. Since 2003 he has been the head of the EMAT laboratory on electron microscopy and since 2006 he has also headed the NANO Centre of Excellence at the University. His major interest is the correlation between the properties and the (atomic) structure of materials. Consequently, EMAT has built up a worldwide reputation.

Van Tendeloo is co-author of over 700 publications in international journals and his work is cited more than 12000 times. He is member of the editorial board of ten international journals and has been invited more than 100 times to international conferences.

## PATRICK WAGNER

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Patrick Hermann Wagner (1967 in Aschaffenburg, Germany) is an experimental solid-state physicist, who obtained his PhD in 1994 from the Technical University Darmstadt with a study on electronic transport properties of high-temperature superconductors. In 1995, he joined the Laboratory for Solid State Physics and Magnetism at the K.U.Leuven where he moved to the field of magnetism, ordering phenomena and colossal negative magnetoresistance in mixed-valency ceramic oxides. These postdoctoral studies were supported by an individual Marie-Curie fellowship of the European Commission and a postdoctoral fellowship of the Research Foundation - Flanders. Research highlights from this period are the unveiling of the anomalous Hall effect in magnetic oxides and the development of the spin-dependent hopping model for magnetotransport in disordered compounds in cooperation with Prof. V.V. Moshchalkov. In 2001, he became Professor of Experimental Physics at Hasselt University, focussing now on the emerging field of biosensors based on novel electronic materials like synthetic diamond and conjugated polymers. The BIOSensor group, currently with ten researchers is specialised in the label-free, real-time

detection of proteins, low-molecular weight species and DNA fragments, reaching sensitivities down to the level of single-nucleotide polymorphisms. In the meantime, the biosensor research was acknowledged with numerous distinctions at international conferences and biosensors also became a key issue in the unique Masters programme on 'Bioelectronics & Nanotechnology' at Hasselt University. Patrick Wagner is involved in several close scientific collaborations with Belgian and foreign universities via projects of the Research Foundation - Flanders, the Interuniversity Attraction Poles Programme, the Methusalem-funded NANO network together with the University of Antwerp and the European Community. During the term 2006-2007, he was president of the Belgian Physical Society and he was vice president in 2005 and 2008.

## NANO Network

The partner groups within the Centre of Excellence (CMT and PLASMANT at the University of Antwerp and IMO at the University of Hasselt) perform very complementary research. The NANO cluster of excellence at Antwerp University has unique experience in high-resolution transmission-electron microscopy, molecular dynamics of plasma-based processes and band-structure calculations in nanoscopic systems. At CMT the structure and properties of new (nano)materials are calculated and compared through experiments. At PLASMANT the growth of thin films is simulated; in this way we hope to optimise the conditions for experimental deposition of thin films. IMO has a long tradition in the preparation of synthetic diamond, electrically conducting polymers, metal-oxide nanoparticles and, more recently, metallic nanoclusters. At IMO nanomaterials are produced; they focus on carbon-based materials and biomaterials and biocompatible materials. The fields of expertises of all the partners are fully complementary and this will allow the project to also tackle the challenging field of hybrid materials: the combinatorial possibilities of mixing two or more different components are practically 'unlimited' and this can bring about completely new, often surprising materials characteristics and insights. In this sense, the seven year-long Methusalem project is like a long journey, as it has provided the freedom to explore new directions in research that can pave the way for future technologies.

## NANO Centre of Excellence

The basic interest of Gustaaf Van Tendeloo is the study of materials at an atomic level. All materials, dead or alive, are built up of atoms or molecules. The properties of inorganic materials (metals, ceramics, semiconductors,etc.) are to a large extent determined by the nature of the atom and the arrangement of these atoms. Whether a material is a conductor or an insulator, magnetic or non magnetic, brittle or ductile, it depends on the kind of atom and the stacking of these atoms to form a real material.

Another important aspect is the perfection of the material. To a large extent, defects occurring in the stacking or missing atoms will determine the final properties. The colour of a diamond for example is determined by missing atoms and the presence of foreign atoms, such as nitrogen. The semiconducting properties of silicon are almost totally dependent on the presence of doping elements.

For all these reasons it is very important to be able to investigate the atomic structure of materials. This means not only to visualise the atomic arrangement, but also to be able to quantify the deviations from perfection. By doing so we will be able to determine and predict the properties of these materials.

Visualisation of the structure of materials down to an atomic scale is done by electron microscopy. The technique was developed in the nineteen-thirties by Ernst Ruska (Nobel Prize in 1986) and the principle is very similar to optical microscopy. However, because the wavelength of light (about 500 nanometer) is way too long to observe atoms with dimensions on the order of 0.2 nanometers we have to replace light source with a source of accelerated electrons. Such electrons, when accelerated to 100000 volts or more, have a wavelength much shorter than the size of the atoms and therefore, are in principle able to image atoms. In practice it requires a lot of technology and skill to build an electron microscope able to resolve the atomic structure. Only a few companies in the world (FEI, Jeol, Hitachi, Zeiss) currently produce high level electron microscopes. The requirement for ultimate resolution not only puts severe restrictions on the mechanical stability, but also on the electronic stability. A major problem is also that the electromagnetic lenses (comparable to the optical lenses) suffer from unavoidable aberrations. Only recently have researcher been able to compensate for these aberrations, representing a significant breakthrough in the development of new instruments.

In 2008 we are able to visualize the atomic configuration in most materials where the atoms are arranged in a regular way. When the arrangement of the atoms is completely chaotic or disordered it still causes a problem for unravelling the structure in three dimensions. The major problem, however, is to understand what we see and to correctly interpret the images. In that respect, the EMAT group has made significant contributions significantly.

One should always keep in mind that whatever one "sees" is not reality, but reality distorted or deformed by the instrument. Along the same lines we can say that our eyes only see reality as perceived by our brains. We all know the effect of optical illusions and the fact that an imperfection of your visual sense (such as a stigmatism or colour blindness) will deform the reality. The same type of distortions take place in an electron microscope. Therefore we have to retrieve reality and to eliminate all artifacts. This is now done worldwide using a method called "through focal series" that was initially developed by the EMAT group.

Another focus of EMAT is to try to retrieve the three dimensional morphology of materials and particles from two dimensional observations. This is called electron tomography. Ultimately the goal is to perform electron tomography at an atomic level. This means being able to determine the position of atoms in three dimensions, rather than in two dimensions.

All these efforts can actually be summarized in one phrase: "Where are my atoms?". Another important question, however, is "Which atom is it?" This question cannot be solved by searching for higher magnifications; one has to investigate secondary effects related to the electron-matter interactions. When the electron beam interacts with the material, X-rays will be emitted and also some electrons will suffer an energy loss because of excitations within the crystal. By correctly analysing the emitted X-rays (EDX) or the electron energy loss (EELS), valuable local information can be collected with respect to the composition. For a long time EELS analysis has been very qualitative, but at EMAT we have developed the EELSMODEL that is able to determine the composition much more correctly and with better precision.
By analysing the fine structure of the EEL spectrum in detail, valuable information can be gathered on the local binding energy of the atoms. Therefore, it is able to provide information for the third question: "What is the electronic state of the atom?" This is neither an easy, nor a straightforward question. Intense collaboration with theoreticians, performing density functional theory, is absolutely necessary in order to be able to interpret the data correct.

For most of the research programmes within EMAT we apply these techniques to study the close relationship between structural properties and physical/chemical properties. The materials studied are very broad, ranging from carbon-based materials such as diamond and nanotubes to ceramic thin films and shape memory alloys.

## Institute for Materials Research IMO

The project on novel functional materials within the Institute for Materials Research IMO of Hasselt University will be a joint endeavour of the materials physics and chemistry teams. The aim of the study is to unveil the formation mechanisms of all these compounds together with the understanding of their electronic, thermodynamic, magnetic and optical properties. Finally, routes will be developed to utilise these materials in innovative high-tech applications like biosensors, molecular electronics, and magnetic data storage.

It is impossible to summarize the 'promises' of today's materials research on three pages, but we will try to give a taste of the potential of three selected materials categories together with typical fields of applications:

**Diamond and graphene for bio- and chemosensors**

Although natural diamond is a highly precious material, it can be readily prepared as thin coatings by chemical vapour deposition: methane gas, CH4, is decomposed by microwaves and, using the right conditions, the carbon atoms condense on a quartz- or silicon substrate as thin diamond layers, see Figure 1.

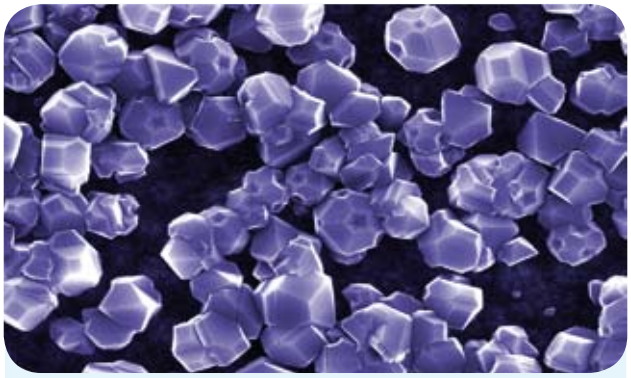

**Fig. 1:** *It's all diamond: micrometer-scaled 'diamondoids' seen in the scanning-electron microscope.*

Adding e.g., boron-containing gasses to the methane, boron atoms will be incorporated into the diamond lattice, giving rise to semiconducting behaviour just like it is done with the silicon technology of microelectronics. With high doping levels, one can achieve metallic conduction and even superconducting behaviour, meaning charge transport without an electric resistance. Special features are also observed right at the surface of the diamond films: there, the carbon atoms do not have four surrounding neighbour-atoms, but only two or three. Therefore, small molecules

like oxygen, hydrogen or the 'acidic' H+ ions will be readily bound to the surface, resulting in specific changes of the electrical surface conductivity. Exploiting this effect, the team recently developed a pH-sensor, which was also modified to an enzymatic biosensor for the detection of penicillin in aqueous solutions.

Since diamond is 'nothing but carbon', it is an ideal, highly inert support for bio molecules, which can be attached simply by adsorption or even better, by surface-chemical routes in order to guarantee a stable, 'covalent' binding. The challenging point is that the bound bio molecules like enzymes, antibodies, and DNA fragments should keep their biological functionality and be able to capture, e.g., metabolites, proteins, or other DNA fragments. The 'fatty acid' route, which was developed at Hasselt University for DNA-immobilisation on diamond layers, is especially simple and efficient. Prototype electronic DNA-sensors based on this technique do not require fluorescent labelling of the patients, DNA like in conventional genetic analyses. Moreover, the coupling between complementary DNA strands can be monitored in real time and the sensor is suitable to repetitive work. Based on this preliminary work, we will use the Methusalem funding to study the stability of DNA-doublets with various types of built-in defects, which also naturally occur in mutations. The 'micromechanics' of DNA hybridisation is also a current hot topic in statistical physics and our work will be right at the interface between theoretical calculations and the daily needs of biomedical research. To study the attractive forces between two complementary DNA fragments or between an antibody and its antigen, we will employ atomic force spectroscopy. This technique is sensitive at the level of individual molecules and allows us to obtain the real, mechanical binding force together with the range of the attractive interaction. Thus, it should become possible to understand and manipulate bio molecular interactions at their own dimension and in their own environment.

Besides diamond, carbon is also known to occur as the football-like 'buckball' molecules built of 60 carbon atoms and carbon nanotubes. This looks like an atomic, wrapped-up sheet of gauze. Less known is graphene: its mother compound, graphite, serves, e.g., in electric contacts, as a lubricant, or in pencils. Graphite can be cleaved down to very thin flakes, and graphene is its ultimate form with just one single layer of hexagonally ordered carbon atoms. Graphene has totally unexpected properties: the electronic charge carriers behave such that they have no measurable mass and their energy increases proportionally to their speed. In a conventional conductor, like copper, electrons have mass and their energy is proportional to the square of their speed like with all other moving bodies in everyday life. If we deposit small molecules like water or ammonia on to a graphene sheet, they have a tendency to transfer either a part of their own electrons to the underlying graphene layer or to extract electrons from it. This has already been utilised for gas sensors and we will develop new biosensing applications. Bio molecules like DNA and proteins are naturally charged and in this sense ideal to design sensors based on the 'charge transfer principle'. Although this sounds 'straightforward', the concept requires considerable experience in nanotechnology and theoretical modelling and it can only work with the combined efforts of the Methusalem team partners.

**Multi-metal oxides for magnetism, superconductivity, and microelectronics**

Oxides like the minerals quartz SiO2 and perovskite CaTiO3 occur naturally in the earth's crust and are known to be electrical insulators. However, the basic perovskite structure shown in Figure 2 allows for plenty of variations: the Ca2+ ions can be partially or fully replaced by trivalent metals and instead of the small Ti4+ ions in the core of the structure, one can use iron, copper, cobalt or manganese.

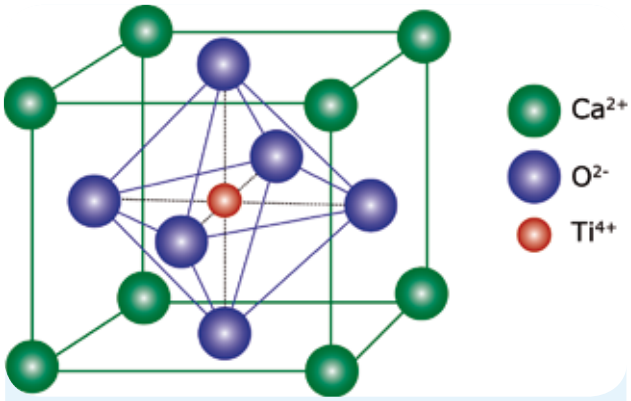


**Fig.2:** *The crystal structure of perovskites with an octahedron of oxygen ions and sites for 'large' and 'small' metal ions.*

Since these synthetic minerals are also electrically neutral, the metal ions will be present in a mixture of valency states such as Cu2+ and Cu3+. The 'mixed-metal crystals' are electrically conducting and this discovery was the basis for high-temperature superconductivity in cuprates and the colossal-negative magnetoresistance in manganese perovskites. Moreover, the metal ions frequently behave as little magnets and their electron shell is not spherical but elongated. These ions are able to 'communicate' with each other along the crystal lattice and this gives rise to long-range

ordering phenomena like ferromagnetism, macroscopic elastic deformations and spontaneous electric polarization. Interestingly enough, all these properties seem to be interrelated and tuning one property with e.g., a magnetic field or a mechanical force will directly influence the other properties. These interplay effects depend very much on the composition and can hardly be predicted beforehand.

To study the properties of multi-metal oxides systematically, we need a combinatorial 'materials designer' approach. Therefore, we will employ a wet chemical synthesis method, in particular the water based solution-gel route, that allows for an environmentally-friendly material synthesis with wide variations of possibilities in composition and stoichiometry. The most challenging step in this synthesis method is to stabilize the different metal ions in an aqueous solution. By complexing the metal ions with the right ligands (e.g., citric acid) and in the right chemical conditions, it is possible, however, to synthesize aqueous precursor solutions of different metal ions that can be simply mixed in the desired ratios to form multi-metal precursor solutions. Upon evaporation of the water, the metal ion complexes chemically link to one another, forming a gel in which the metal ions keep the intimate mixing they had in the solution. This intimate mixing, in particular, allows the formation of phase pure multimetal oxides upon further thermal treatment at relatively low temperatures (typically 500 - 700°C). Besides the compositional control and flexibility, this synthesis method also offers the advantage of morphological versatility, since not only (nano)powders but also thin (< 100nm), ultrathin (< 10nm) or nanostructured layers can be formed by spincoating the tailored precursor solutions before gelation and thermal treatment.

**Metal nanoparticles – from fundamental research to applications**

One of the key requirements for nanotechnology is the availability of powerful methods for the preparation of nanostructures on surfaces with dimensions of ten nm and below. Because conventional top-down techniques like e-beam lithography are approaching their limitations, completely different approaches are currently developed relying on the self-organisation of larger molecules used as building blocks for the resulting nanostructures (bottom-up approaches). Ideally, such a bottom-up technique should allow for the in-situ deposition of ensembles of contamination-free nanostructures of any kind of material with adjustable particle size, interparticle spacing and free choice of the substrate material. One powerful variant of bottom-up approaches exploits the self-organisation of polymer blends, in general or, more specially, of diblock copolymers on top of surfaces, see Figure 3.

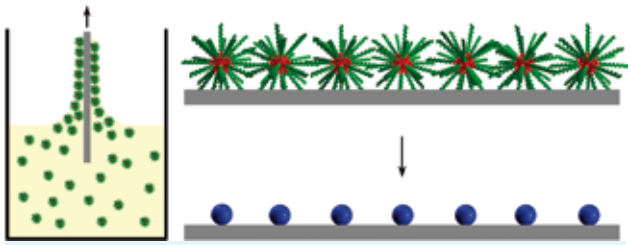

**Fig. 3:** *Illustration of the micellar method for the fabrication of ordered arrays of size-selected metal nanoparticles.*

The basic idea is to use self-assembled, spherical micelles as nanoreactors, that form when a diblock-copolymer consisting of a hydrophilic and a hydrophobic block is dissolved in a solvent such as toluene. The core of such micelles can be loaded with a metal salt ligated to the inner polymer block. In a second step, the loaded micelles are deposited onto a smooth substrate, where they form a hexagonal array due to their spherical shape. The polymer matrix is then removed by means of different plasmas treatments, resulting in an array of well-separated metal nanoparticles of uniform size (1 – 10 nm), that are controlled by the amount of metal salt added to the micellar solution. In addition, the interparticle spacing (20 – 150 nm) can be adjusted via the length of the diblock-copolymers. This way, a perfect platform is available, permitting the study of all fundamental physical and chemical properties at the transition from clusters to solids. In other words, new (nanoscaled) materials can be expected with properties that significantly differ from those of the corresponding bulk materials due to their small size. Such nanostructures are currently being discussed as new building blocks in ultra-high density magnetic recording applications, in single-electron-transistor-based electronic devices, or for example, in heterogeneous catalysis for the oxidation of CO to CO2. Furthermore, metal nanoparticles can also be used as nano-scaled masks in non-conventional lithography for display technology or as catalysts for the growth of ordered carbon-nanotube arrays.

## MARC WAELKENS

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Marc Waelkens was born on April 12, 1948 at Waregem (Belgium). In 1976 he obtained his PhD in Arts and Philosophy (Archaeology) at the University of Ghent. From 1986, he pursued the usual sequential career of professorships at the K.U.Leuven, resulting in becoming 'ordinarius' for Mediterranean Archaeology in 1994. In Leuven he founded the Master of Arts programme "Eastern Mediterranean Archaeology". In 1997-1998 he held the Francqui Chair (Chaire Francqui au titre belge) at the Facultés Universitaires Notre Dame de la Paix, Namur, Belgium. Since 2004 he has been the Director of the Centre for Geo- and Bio-archaeological Sciences and Image Processing in Archaeology (K.U.Leuven) and since 2005 he has been the Director of the Centre for Archaeological Sciences, one of four recognized 'centre of excellence' at the K.U.Leuven (EF programme).

His career has been punctuated with many international experiences. In 1976, for example, he held a Forschungsstipendiat der Alexander von Humboldt-Stiftung" (Bonn, Germany), and he spent the academic year of 1978-1979 as a Junior Fellow of the Centre for Hellenic Studies, Washington D.C., USA. In 1986 he was the "Samuel H. Kress Lecturer of the "Archaeological Institute of America" and in the same year he went to Oberlin College, Ohio, USA as a Visiting Professor of the Archaeological Institute of America". In 2004 he spent two months in Australia, as a visiting professor of the 'Australian Archaeological Institute in Athens.

In 1993 Professor Waelkens was elected Member of the "Koninklijke Academie voor Oudheidkunde en Kunstgeschiedenis van België"and in 1998, of the "Koninklijke Academie voor Wetenschappen, Letteren en Schone Kunsten van België". In addition, since 1985 he has been a Korrespondierendes Mitglied des Deutschen Archäologischen Instituts (Berlin, Germany) and since 1998, a Wirkliches Mitglied des Österreichischen Archäologischen Instituts, Vienna. He is a member of several committees, including the Standing Committee for the Humanities of the ESF, ERIH (European Research Index for the Humanities), the Advisory Board Babesch Monograph Series and the Editorial Board Hesperia (USA).

Professor Waelkens has received several international awards, such as the E.J. Solvay Prize for the Humanities (awarded every five years in Belgium) in 2000; the Altın Kazma (Golden Pick Ax) from the Ministry of Culture of Turkey for the interdisciplinarity of the excavation at Sagalassos and the Üstün Hizmet Madalyasi (Reward for Outstanding Service to the Republic) from the Ministry of Foreign Affairs of Turkey (highest distinction for foreigners in Turkey) in 2002.

Throughout his career Professor Waelkens has focussed (in chronological order) on the following topics, most of which he still studies occasionally, even if most of his attention now is devoted to the multidisciplinary research at Sagalassos and its territory: the study of regional sculpture workshops (basically in the 1970s and the first part of the 1980s), the study of ancient mining and quarrying technology and provenance studies of white marbles used in antiquity (1980 until now), the study of arts and crafts in the Roman West and East, architecture and urban layout in Hellenistic to Early Byzantine Anatolia since 1982 and a holistic approach to classical archaeology.

## Architecture and urban layout in Hellenistic to Early Byzantine Anatolia

Since 1982 Professor Waelkens has produced research on the confrontation between the Hellenistic and Roman building traditions, monumental building types and architectural monuments. After several studies dealing with the introduction of Roman building types and building techniques, he moved towards studying the larger scale of the total urban layout. In 1998 he co-organised an international conference on „Kon-tinuität und Diskontinuität in den Städten des frühkaiserzeitlichen Kleinasien" at Cologne.

During the last two Concerted Actions and Interuniversitary Poles of Attractions the development of rural and urban settlement patterns (including defence, water and street infrastructure, different types of public monuments, subsistence and land use, animal breeding, anthropogenic ecological changes and the effects of the environment on human settlement behaviour, besides elite strategies, economy and trade were studied for two transitional periods with five other Belgian and two European partners covering Northern Gaul, NE Central Italy, C Greece and SW Anatolia:

- The transition from Late Antiquity ( 3rd century AD) to the early Middle Ages (7th/9th AD°)
- The transition from pre-Roman to Imperial societies (2nd century BC to 2nd century AD) and the meaning of the word 'Romanisation'.

## Holistic approach to Classical Archaeology

When Sagalassos became a Belgian excavation site in 1990, and Professor Waelkens its director, he immediately decided to implement a 'holistic approach to classical archaeology', meaning that not only artefacts belonging to the category mentioned above, but also all types of organic remains (pollen, macro botanical remains, anthropological remains, butchering, kitchen and consumption refuse of faunal and vegetational origin; residues impregnated in cooking pots, storage and transport vessels, in lamps, faecal elements) should be studied in detail as they would provide precious evidence for anthropogenic or natural climatic changes, subsistence (to be combined with physico-anthropologcal and faunal studies), land use, the function of isolated farmsteads, villages or large estates producing vegetable oils (walnut, olive), beeswax; vegetable and meat proteins, the composition of which also reflect the prosperity and health of a society at a given moment. In other cases the raw materials mentioned in the previous paragraph may explain the special character or function of a specific settlement (first smelting of ores, stone extraction and prefabrication of stone objects, etc.). As a result, our approach is that every single find, no matter how small it might seem, has value and contributes – combined with architectural elements and decoration – to the identification of, for instance, the changing functions of spaces throughout time (hour of the day, season, year), which is now established by means of 'contextual analysis'. Also the symbolic or economic value of an object might change throughout time, whereas real international transports of bulky goods covering large distances over sea or by land that are 'International' (from port to port) may become 'regional trade' from one port to its hinterland. Conclusions should be based on complementing results from various analyses of different materials.

Moreover, there should be no difference between very carefully conducted prehistoric research and that of classical archaeology: the latter usually contains all traces and types of evidence of the former, even if they are supplemented and therefore, all too often obliterated by 'monumental elements, (buildings, statuary) or very expensive goods (coins, some types of glass, jewellery, etc. From the late Hellenistic period onwards, with its creation of the first Roman provinces and the construction of an excellent road system, this factor also played a major role in the transfer of goods, as did the Imperial annona system (taxes paid in grain, oil, etc. later, as other goods travelled together with cash crops for official use. Therefore, the excavation of a classical site is unthinkable without the active involvement of geomorphologists (and in some regions paleoseismologists) for studying changing landscapes and settlement patterns; paleobotanists for studying climatic change, land use and subsistence; archaeozoologists for identifying faunal remains (role in the economy and in substance; also a source for ecological change); geologists (to study the raw materials used in crafts and industry, identify their provenance and production technology); anthropologists with an experience in both morphological features (skeletons) and genetic characteristics (aDNA), bio-engineers (for the residue analysis of pottery, the identification of faecal markers in manuring, etc.); hydraulic engineers (to understand water maintenance and infrastructure); specialists in various istopes (O, Ca, Nd, etc.) for identifying the provenance of the raw materials for ceramics, glass and metal, also people specialised in strontium isotopes (important for glass, and especially for identifying grazing or working areas for domestic animals that eventual end up in the consumption pattern of the city; specialists in remote sensing, geophysics and more traditional topographical applications; numismatists; epigraphists; ancient historians; statuary specialists and archaeologists specialised in the study of ceramic, glass, metal and bone artifacts; archaeologists who are 'familiar' with more than just 'intensive surveying' and 'off-site archaeology'. And last but not least, there are the archaeologists, who aware of the mass of evidence at their disposal, cannot be careful enough while excavating and identifying loci in the stratigraphy. Famous scientists such as Darwin, and not Indiana Jones, should be their models.

This holistic approach has been applied at Sagalassos since the 1990's: at the start, the only thing we knew was that the city had resisted but eventually was captured by Alexander the Great in 333 BC, that it was punished with an enormous fine by the Roman consul Cn. Manlius Vulso due

to humiliating him in 189 BC, and finally, that under the reign of Augustus, the city belonged to the province of Galatia. By incorporating all of these disciplines and studying all this evidence mentioned above, in less than two decades the Sagalassos team has been able to:

- reconstruct climatic change since the beginning of the Holocene in the 1200 sq. km. territory of Sagalassos
- reconstruct, in detail, the changes in vegetation, deforestations, reforestations and types of land use of most valleys in this territory
- reconstruct and understand the changing settlement patterns from the Epipalaeolithic to the mid-Byzantine period (13th c.)
- identify the mutual dependency between city and hinterland: the former was not a mere 'consumer city', but showed a more diversified picture, including characteristics appropriate for 'producer cities'
- reconstruct the crafts and commercial industries throughout history and analyse changing subsistence and trade patterns
- identify the role of the elite within the urban maintenance and the kinds of competition engaged in for obtaining Imperial grants and privileges.
- locate the city's position in the wider region, Pisidia, for which it became the 'de facto' capital and centre of the Imperial cult. Thanks to an excellent understanding with the current population, onehas been able not only to present the site to the public at large through conservation activities and anastylosis, but also involve the locals in protecting what is their heritage, including the pristine landscape surrounding the site.

In 2006 their activities were recognized as comprising one of the 'centres of excellence' at the K.U.Leuven, by al-lowing us to create the 'CENTRE FOR ARCHAEOLOGIAL SCIENCE', which, under the direction of Professor Waelkens, brought together under one umbrella all archeo-disciplines already present within theuniversity and allowed us to attract top foreign researchers to fill in existing gaps. Moreover, this centre now includes the activities of the archaeological teams at the K.U.Leuven working in Sudan, Egypt, Syria and Belgium. Receiving one of the four METHUSALEM GRANTS of our university, was the highest possible form of recognition for our efforts and approach. As a result, Sagalassos is more and more recognised internationally as being the prototype to follow.

# ODYSSEUS

The Odysseus programme is an important incentive to trigger mobility towards Flanders. The Flemish government has entrusted the practical execution of the funding scheme to the Research Foundation – Flanders.

The purpose of the Odysseus-initiative is to compete in the European Research Area and to expand the Flemish knowledge economy by creating a favourable research climate foster research and knowledge transfer.

Applicants for an Odysseus project are expected to have an excellent research record and to show their potential for becoming world-class leaders in their areas of research. The programme targets **two types of researchers**. The typical **group I applicant, (I)** is an internationally recognised researcher with an established foreign career who will be appointed as leader of a research group with a staff, several postdoctoral researchers and PhD students. **Group II applicant, (II)** are submitted by researchers who possess the potential to become internationally recognised and who have a minimum of 3 years postdoctoral experience in the field of research and strong scientific output to convince their peers that they have the potential to become prominent researchers with a team of several PhD students and one or more postdoctoral researchers.

Selected projects extend over a five-year period, during which a group I project receives a yearly sum of between 400.000 and 1.500.000 euros. For Group II projects a grant of between 100.000 to 200.000 euros per year is set aside. The main criteria for being selected is excellence.

Award recipients are expected to devote their full working time to research and the other activities described in their proposal. To this purpose, applicants receive a full time appointment by the host university to ensure that they can be released from any other commitments.

For more information on the Odysseus programme, see www.fwo.be.

ODYSSEUS
Top science in Flanders

## GUY BOECKXSTAENS(I)

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After finishing his medical training at the University of Antwerp in 1987, Guy Boekxstaens was appointed as a NFWO Research Fellow at the department of Gastroenterology, University Hospital of Antwerp, and obtained his PhD in 1991. In 1994, he finished his clinical training in Internal Medicine/Gastroenterology and left Belgium to accept a staff position in the Department of Gastroenterology & Hepatology at the Academic Medical Center in Amsterdam, The Netherlands, a an internationally recognized group in the area of gastroenterology, then headed by Prof. Tytgat. There he was appointed to set up a GI Motility unit within the division and build up a clinical and experimental research group. In order to obtain expertise in this area, he worked at several leading international centres such as The Mayo Clinic (Rochester MN, USA), Northwestern University (Chicago, USA), and the Royal Adelaide Hospital (Adelaide, Australia). To date, this Motility Center is a leading training centre (nationally and internationally) where patient care and clinical research (establishing phase I and II clinical trials) are performed on a routine basis.

His research has mainly focussed on disease mechanisms. He started several research lines dealing with the pathophysiology of gastroesophageal reflux disease, functional bowel disease (dyspepsia, irritable bowel syndrome) and postoperative ileus. For each research line, animal models and in vitro assays were developed and optimised to evaluate pathophysiological hypotheses. Parallel to this, studies in healthy subjects and patients were performed, testing new treatments based on the findings in animals. This translational approach is of great importance and allowed us to integrate the findings from our animal work rather quickly into clinical practice.

### The brain and the innate immune system

It is well known that our state of mind has a major impact not only on how we feel, but also on our susceptibility to becoming ill. This indirectly implies that there must be an important interaction between our defences against disease or infection and the brain. In previous years, Guy Boeckxstaens provided substantial evidence that there is indeed a dialogue between the brain and the immune system. He showed that on the one hand, the activation of the vagus nerve can control the development of an inflammatory response. The vagus nerve is the largest nerve in the human body in charge of controlling the viscera, including the heart and the gastrointestinal tract. When this nerve is stimulated, it releases acetylcholine, a substance that has been shown to potently reduce the activity of inflammatory cells, in particular macrophages. This finding is of great importance as it provides new possibilities for discovering new drugs to block or prevent inflammation. On the other hand, he showed that psychological stress has a rather detrimental effect, that is, acute psychological stress indeed results in activation of the immune system, which leads to microscopic inflammation and abnormal pain perception in the gut. This finding in animals reflects a common situation that we all experience during stressful situations: stool habits change dramatically and above all, abdominal pain and cramps will sometimes persist for days after this stressful event. The research team discovered that mast cells, another typical cell belonging to the immune system, plays an important role in this process. These cells are well suited to communicate with nerves and thus the brain, and are therefore an important target treating stress-induced disorders, such as irritable bowel syndrome.

The current programme will focus on the interaction between the innate immune system in the gut and the brain. Two main research lines will be developed: 1. The cholinergic anti-inflammatory pathway as hard-wired neural pathway controlling the innate immune system, and 2. The mast cell in functional bowel disorders: could this be the missing link between the brain and the gut?

In the first research line, Boeckxstaens will further investigate the anti-inflammatory effect of the vagus nerve. The intriguing hypothesis has been put forward that the brain integrates vagal immunosensory information and as part of

an inflammatory reflex activates the efferent vagus nerve to locally modulate the immune system. The mediators and receptors involved in the dialogue between the brain (vagus nerve) and the innate immune system (dendritic cells, resident macrophages) will be identified. The outcome of this programme will lead to a new anti-inflammatory approach for inflammatory diseases (ulcerative colitis, postoperative ileus, arthritis).

In the second research line, the role of mast cells in stress-induced abnormalities in gastrointestinal function will be investigated. The hypothesis is that mast cell degranulation, induced by psychological or mechanical stress, leads to increased intestinal permeability and activation of the innate immune system. The mechanisms triggering mast cell degranulation and the processes involved in altering gastrointestinal neuromuscular function will be studied in detail. This knowledge is crucial for the development of drugs to treat disorders such as irritable bowel syndrome and postoperative ileus.

In both research lines, animal models and in vitro models will be developed in parallel to human clinical studies. This translational approach is of great importance for validating and evaluating the clinical relevance of discoveries from these models for human disease.

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Hans-Gerd Boyen (born in 1957 in Oberkirch, Germany) studied physics and mathematics at the Technical University of Karlsruhe (Germany) to become a high-school teacher. This did not happen since, during his studies, he became more attracted towards experimental solid-state physics. He obtained his PhD in this field in1990 with a study on electronic properties of disordered binary alloys. In the same year, he joined the ESCA group in the Institute of Physics at Basel University (Switzerland), where he focussed on surfaces and interfaces investigated by means of electron spectroscopic methods. These postdoctoral studies allowed him to qualify for a teaching post in Experimental Physics in 1996. One year later, he moved to the Solid State Physics group at Ulm University where he became increasingly interested in superhard materials and, especially, in the properties of nanoscaled materials (nanoparticles, nanoclusters, ultrathin films). One research highlight from this period was the unveiling of the extraordinary physical and chemical properties of magic number gold clusters which resulted in the Merckle Research Award in 2004. In April 2007, he became Professor of Experimental Physics at Hasselt University, now focussing on the emerging field of molecular electronics in an Odysseus project. The Nanostructure Physics group currently consists of four researchers and is expected to grow to six researchers by the end of 2008.

## New pathways towards molecular electronics

The evolution of microelectronics into nanoelectronics by continuous reduction of the size of typical features (the so-called top-down approach) will run into big problems within the next two decades due to severe physical limitations. Consequently, by using nature as a role model, alternative strategies have been proposed that try to assemble 'larger' structures with functional properties by taking advantage of the self-organisation of molecular subunits (the so-called bottom-up approach). Examples for such new strategies are field-effect transistors (FETs) based on single nanoparticles, carbon nanotube-based FETs (i.e., electronics based on extended molecular structures) or FETs using short molecules with a length scale in the nanometer range.
As a result, electronics based on molecules ('molecular electronics') has evolved into one of the fastest growing areas in nanoscience because it has the potential to supplement and finally replace well established, silicon-based technology. The idea is that, at the ultimate limit of miniaturization, nanoscaled organic entities (single molecules or small groups of molecules) with tailored physical and chemical properties will act as, electronic switches, for example, as memory cells or sensors for (bio-)molecules. Nanoscaled organic entities can offer the prospect of fabricating ultra-high density electronic circuits as components of molecular computers or can be applied as molecular electronics to detect functional biomolecules at the single-molecule level.

For molecular electronics to become reality, however, all basic factors controlling, e.g., the charge transport across a metal–molecule-metal junction or the interaction between individual molecules in biosensor applications need to be established. Therefore, new experimental and theoretical concepts are required in order to investigate how factors such as metal-molecule coupling, molecule-molecule coupling and the molecular structure and the choice of electrode/support materials finally influence the characteristics of the desired molecular devices.

## Elements and interconnects for molecular electronics

While many of the fascinating electronic properties of molecules could be established even on the single-molecule level, one of the most fundamental factors could not yet be established: the role of the contact between the molecules and the 'outside world' represented by the metal leads (interconnects). Strong chemical bonding to the metal leads induced by appropriate head groups is required in order to achieve

configurations which are stable at room temperature (the operation temperature of future devices). The formation of strong chemical bonds, on theone hand, is well known to affect the electronic structure of the molecules. On the other hand, the attachment of molecules to metal electrodes can also be expected to modify the electronic properties of the metal (at the metal/molecule interface), resulting in large contact resistances well known for many molecular devices. An increased contact resistance, however, might dominate and thus detoriate the performance of a molecular junction especially in case of a high transmission through molecular orbitals (conductive state of the molecule, a 'switched on' state). Due to the importance of such effects for molecular electronics to reach the application level, advanced experimental techniques and modern density functional theory need to be combined to investigate and, finally, optimise molecular junctions with varying basic units (metals, molecules, functional groups).

## Ultra-high density arrays of carbon nanotube-based field effect transistors

The feasibility of fabricating ultra-high density arrays of nanoscaled molecular devices using short carbon nanotubes (<30nm) as semiconducting channels will be explored. Carbon nanotubes will be among the most promising candidates to be applied in nanoelectronic devices in the near future. There is much activity worldwide dedicated to developing new concepts for their controlled growth and application, as, for example, field effect transistors Although offering one of the highest conductivities observed so far for non-su¬perconducting materials, the current which can be passed through single nanotubes is rather limited.
Using a combination of bottom-up (self-organisation of macromolecules) and top-down (conventional lithography) approaches for fabricating ultrahigh-density arrays of nanopores in thin dielectric films, template structures are available that might allow the controlled, nanoparticle-mediated catalytic growth of semiconducting nanotubes within individual nanopores. Gate electrodes could be added as intermediate metal layers to the dielectric film, thereby allowing the design of high-current FETs consisting of ensembles of individual carbon nanotubes in , for example, predefined, templated nanopores. This approach requires the systematic study of conditions regarding how to grow semiconducting single wall nanotubes. Currently, since even noble metal nanoparticles are found to be suitable as catalysts, nanoparticle arrays prepared by a micellar method will offer a perfect platform for the optimisation of growth conditions due to the flexibility for easily exchanging materials (Fe, Co, Ni, Au, Pt, Pd, etc) as well as particle size.

## Applying molecular electronics to functional biomolecules

Modern immuno-sensors used in medical diagnostics are based on highly specific recognition and affinity binding between, e.g., immunoglobulins and their antigens, that are frequently proteins. The binding forces originate from weak, short-ranged electrostatic interactions such as van der Waals forces and hydrogen bridges formed in well-defined geometrical configurations. For sensor applications, the immunoglobulins are immobilized as 'receptors' on suitable, inert substrates and the recognition of target molecules (e.g., specific proteins in blood serum) can be monitored via changes in specific physical properties like the surface impedance. This type of (label-free) sensor can reach sensitivities in the nano- to even attomolar range, depending on the specific antibody-antigen binding constants.
For various applications it is essential to develop strategies, that allow for a regeneration of the sensor by breaking the antibody-antigen coupling in a controlled way. The established technique, rinsing with acidic buffers, usually results in sensitivity loss. Thus, novel routes are required to overcome the attractive, electrostatic forces between complementary biomolecules by, e.g., pulsed electrical fields. The basic requirement for the development of such a method is the systematic study of the 'nanomechanics' between the receptors and the biomolecules to be detected (antibody-antigen, complementary DNA fragments, etc.), that can be accomplished using state-of-the-art atomic force spectroscopy. Thus, it should become possible to understand and to manipulate the interactions between individual molecular units at their own dimension and in their own environment.

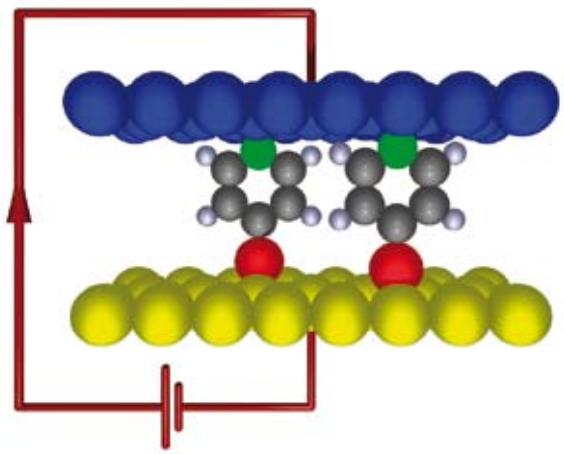

**Fig. 1:** Illustration of a nanoscaled molecular junction consisting of a group of molecules that are sandwiched between appropriate metal electrodes.

## MARC BRYSBAERT (I)

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Marc Brysbaert is a cognitive psychologist who specialises in word and number processing. He obtained his MA (1986) and PhD (1992) at the K.U.Leuven, where he also did postdoctoral research (first financed by the Research Council of the University, then by the Research Foundation - Flanders). In 1997 he was appointed lecturer at Ghent University. In 2001 he moved to Royal Holloway, University of London, where he was appointed senior lecturer and subsequently promoted to Reader (2002) and Professor (2005). In 2007 he was awarded an Odysseus Grant at Ghent University that will start in August 2008.

Marc Brysbaert has published more than 100 journal articles and book chapters, and is the author of four textbooks (three of which are introductory psychology textbooks in Dutch (1998, 2006, 2008), the other is a textbook on Historical and Conceptual Issues in Psychology, co-authored with Kathleen Rastle, to be published in 2009). He is also action editor of Psychologica Belgica, the Quarterly Journal of Experimental Psychology and the European Journal for Cognitive Psychology. He is a member of the editorial board of L'Année Psychologique, Behavior Research Methods, Bilingualism: Language and Cognition, Journal of Experimental Psychology: Learning, Memory, and Cognition, Language and Cognitive Processes, and Psicologica.

Marc Brysbaert was a member of the Committee of the Belgian Association for Psychological Science from 1993 untill 1997 and a member of the Executive Committee of the Experimental Psychology Society from 2002 until 2004. He is currently a local UK officer of the European Society of Cognitive Psychology and starting from the 2008-2009 academic year will be President of the Belgian Association for Psychological Science. In 1996 Marc Brysbaert received the Award of the Research Council of the K.U.Leuven for the best young researcher in the Human Sciences, and in 2002 he was named Laureate of the Royal Belgian Academy for Science and Arts Flanders.

### Centre of excellence on reading research in Flanders

The overall aim is to establish a centre of excellence on reading research in Flanders (Centrum voor Leesonderzoek – Vlaanderen). This centre is expected to have a good international reputation for fundamental research (resulting from a consistent high quality output in the main journals) and to become a point of reference in Flanders with respect to research on reading problems (in particular dyslexia). To achieve these aims, the following three research lines are planned.

### Using atypical brain laterality to obtain insight into reading processes

Ninety-five percent of righthanders and 70% of lefthanders have left hemisphere dominance for language processing (i.e., they use the left half of the brain more for language processing than the right half of the brain). For a long time it was assumed that this had few implications for normal reading, either because information in the centre of the visual field is sent bilaterally to both cerebral hemispheres and/or because interhemispheric communication does not put major constraints on information initially projected to the non-dominant hemisphere. Brysbaert's previous research has shown that this assumption is wrong (e.g., Brysbaert, 1994, 2004). In his most recent work (Hunter & Brysbaert, 2007, 2008), he assessed language dominance with the use of fMRI while participants were generating words (i.e., participants saw a letter and had to generate as many words as possible beginning with the letter). In line with previous research, we saw that in most participants the frontal cortex on the left side was more active (Broca's area), whereas in a few left-handed participants there was either bilateral activation or even a complete reversal of activation to the right hemisphere. Participants with left and right brain dominance subsequently took part in a word naming experiment. We were particularly interested in seeing how their naming latencies would differ as a function of the initial fixation location. The left dominant participants showed the usual word-beginning superiority effect observed in languages read from left to right. That is, they were faster

to name a word when they were allowed to fixate on the beginning of the word than when they were forced to fixate on the end of the word. The word-beginning superiority was substantially attenuated in participants with right hemisphere dominance and even reversed into a word-end superiority effect for short words.

Another recent line of research in collaboration with Nazir (CNRS, Lyon) and Lavidor (Hull, Bar-Ilan) has used atypical brain dominance to obtain insight into the function of the visual word form area (Qing et al., 2008). It has been shown that words visually presented activate a part of the left occipito-temporal cortex, irrespective of the initial projection on the retina (left or right of the fixation location). This has been considered to be the first part of word processing that is lateralized. There may be two reasons why the visual word form area (VWFA) is lateralized to the left in the participants that have been examined thus far. The first is that the VWFA receives feedback input from the higher language centres, in particular from the language production centres (Broca's area). The second reason is that in languages read from left to right, more information is extracted from the right half of the visual field than from the left half. Because information from the right half of the visual field is projected directly into the left cerebral hemisphere, there is more verbal input to the left half of the occipito-temporal cortex than to the right half. To decide between these two possibilities, we examined the laterality of VWFA in participants with known right cerebral dominance for language production (using the same word production task as indicated above) and looked at the lateralization of the VWFA in these participants. It turned out that for them there was much more activity in the right occipto-temporal area than in the left, in line with the hypothesis that the laterality of the VWFA is determined by the laterality of the brain speech areas and not by the reading direction to which the participants have been exposed.

In the coming years this line of research will be extended to get a clearer picture of the extent of laterality at the different stages of word processing (there is quite some behavioral evidence that the right hemisphere capacities are higher than what the available brain imaging data suggest) and to get a better idea of the importance of good interhemispheric communication for normal reading. The former will be done by detailed comparisons of left dominant and right dominant participants on a series of tasks tapping into different aspects of visual word recognition and text comprehension. The latter will be done by looking at the performance of individuals with varying sizes of the corpus callosum and of various levels of reading proficiency. In particular, we want to find out whether or not deficient interhemispheric communication can be a factor that contributes to reading problems, as has been suggested in the past.

## Towards a better understanding of the factors that determine word processing times

The basic factor that is assumed to affect word recognition speed is the frequency with which a word is encountered. Although this frequency effect forms the basis of all models of word processing, it is still far from understood. These are some of the outstanding questions:

1. There is little known about the precise function between word frequency and processing time. We know it is a concave function that is reasonably well approximated by a logarithmic function, but there are indications of systematic deviations from this function. Authors that have looked at these deviations, have proposed different alternative models to account for them.
2. In addition to word frequency, there is also an effect from the age at which a word was acquired. Words that were acquired early in life are processed faster than words that were acquired later (e.g. Brysbaert & Ghyselinck, 2006). Again, the exact relationship between age of acquisition and processing time is not known, nor is the relationship between age of acquisition and occurrence. All we know is that the effect is not due to mere differences in cumulative occurrence (e.g., Ghyselinck et al., 2004).
3. The processing time of a word not only depends on the frequency of the presented word form, but also on the frequencies of related word forms. The English words 'heel' and 'flint' have the same frequency, but 'heel' is processed significantly faster than 'flint', arguably because the frequency of 'heels' is much more frequent then the frequency of 'flints' (New, et al., 2004).
4. The word 'winter' is recognized faster than 'wortel' by Dutch-English bilinguals, and there is good evidence that this is due to the fact that the word 'winter' exists both in English and Dutch.

These are but a few examples of the phenomena that need to be explained. Recent developments indicate that major breakthroughs will take place in the near future. Balota and colleagues have collected naming latencies and lexical decision times for more than 40,000 English words. As a result of this database it is now possible to investigate the impact of several variables on the entire corpus of familiar words and obtain a more accurate picture of the processes that

underlie word recognition. In addition, many of interesting frequency measures are currently available based on automatized analyses of digital databases (e.g., occurrences that take into account the different syntactic roles of word forms, occurrences in spoken language, occurrences for different age ranges and different registers, etc.).

We are currently involved in initiatives to compile databases similar to Balota et al for French and Spanish, so that it will becomes possible to look for convergences and divergences between these languages and English. We also want to include technical improvements to the original database. For instance, the word naming times of Balota et al. are much less useful than the lexical decision times. The reason for this is that the naming times were simply measured with a microphone that detected voice onset times. A much better approach is to store the complete answer and to calculate the voice onset times on the basis of speech waveforms. This not only allows researchers to correct for known problems with sound detection by microphones, but also provides them with much more information about the pronunciation itself.

As part of the present grant project, we will include the Dutch language in this cross-linguistic comparison and look at word processing times in non-native languages. To what extent does English word recognition by a Dutch-English bilingual resemble that of a native speaker? Van Wijnendaele & Brysbaert (2002) showed that the word frequency effect in Dutch word naming is substantially stronger for French-Dutch bilinguals than for Dutch native speakers. However, nothing is known about the precise relationship (the number of stimuli was too small) or about the processes that underlie the difference.

A limitation of corpus analyses (and other correlational analyses) is that different solutions are possible that are equally good (in particular because many characteristics of words are correlated with one another, a problem known as collinearity). Therefore, choices must be made on a theoretical basis. Our previous experiences (in particular, Rastle & Brysbaert, 2006) have taught us, however, that the exact predictions of a theory are error-prone if they are not implemented in a working computational model. A considerable number of convictions and assumptions that researchers have are not confirmed once they are implemented in a working computer model. Therefore, the above corpus part must be accompanied by the implementation in a computational model. The most effectively implemented model currently available is the DRC-model. Improved frequency measures can be directly integrated into the model to see whether they result in a better fit to the human data. A major limitation of this model, however, is that it is a steady-state model that does not learn. Therefore, it does not allow us to directly look at the effects of time of acquisition or frequency of occurrence. A recently-proposed localist model that does make this possible is the SOLAR-model of Davis. We intend to test our English data models (both as first and as second language) in the DRC and the SOLAR-model and to build similar models for the other languages we are testing. Therefore, we will be sure that the explanations we propose also work.

## Applying the knowledge to everyday problems

The final part of the project involves the application of our knowledge to real-world problems. Flanders needs a transfer of knowledge from academics to schools and rehabilitation services. According to the PISA 2003 survey, 8% of the 15-year olds in Belgium do not possess the minimal skills for readinfg; in the Netherlands this figure is only 2%. One of the reasons for this discrepancy is that in the Netherlands much more information about learning problems is available to schools than in Flanders. In Flanders, there are many local initiatives, but there is no real authority that feeds these initiatives with practical information on how to tackle these difficulties. The idea is not to get involved in remedial teaching or rehabilitation ourselves, but to create an information centre that informs practitioners about what to do. An additional task would be to adapt and validate instruments from other countries to Flanders. For instance, in Nijmegen a lot of interesting work is currently being done on reading instruction and dyslexia screening. On the basis of our expertise, we would be extremely well placed to help in the development of these tools and to bring them to Flanders. The applied side is also likely to be welcome to the fundamental research.

Another practical application of some of our research has been recently published by Forbes-McKay et al. (2005). Starting from the hypothesis that the age of acquisition has an influence on the organisation of the semantic system (because concepts that were acquired early have a more central role in the signification system than concepts acquired late), they hypothesised that people with beginning dementia might lose access to late-acquired concepts first. To test this, they compared the performance of control participants to that of participants with a suspicion of beginning Alzheimer's dementia on a category member generation task. Participants were asked to generate as many words as possible referring to animals or fruit in one minute

per category. When the authors subsequently analysed the data, they found that the participants could be diagnosed (95% correctly for the controls and 88% for the patients) on the basis of two variables: the number of words generated and the age of acquisition words generated. Participants with beginning dementia (that could not yet be assessed with a standard clinical interview) generated less words per minute and the concepts they generated had been acquired early (i.e., concepts like apples, pears, and oranges for fruit). Given that we already have valid measures of age of acquisition on the basis of our previous work (Ghyselinck et al., 2003), adapting this test to the Flemish population requires only a limited effort. All that needs to be done is to standardise the data on a representative sample of healthy elderly (and if possible elderly with beginning dementia for further validation) and to look for moderating factors such as education, socio-economic status and age. Once this is done, we will have a simple, inexpensive and easy to use diagnostic that can be used for all patients (e.g., also patients who don't have much experience with reading).

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Igor Douven (Heerlen, The Netherlands, 1963) obtained a Performer's Diploma from the Conservatory of Maastricht (1989, piano), a Master's Degree in Law from the University of Maastricht (1990), an MA in Musicology from the University of Utrecht (1992), and an MA in philosophy, also from Utrecht (1993). He obtained a PhD in Philosophy from the K.U.Leuven (1996). His PhD thesis concerned the scientific realism debate in the philosophy of science. In his later research, he focussed on issues in the philosophy of science (next to the realism debate, the topic of incommensurability and issues in confirmation theory), the philosophy of language (assertion, theories of conditionals, truth), logic (for instance Fitch's paradox), and epistemology (the Gettier problem, contextualism). For the past five to ten years, Igor Douven's research has focussed on issues in what is now commonly referred to as 'formal epistemology'; among others, he developed formal theories regarding coherence and of rational acceptability. He has published on all of the aforementioned topics (and others) in virtually all major journals in the field. Igor Douven is currently Professor of Philosophy at the Institute of Philosophy, K.U.Leuven, where he also heads an Odysseus research group. Earlier he was an assistant professor of philosophy of science at the University of Utrecht and an associate professor of philosophy of science at Erasmus University, Rotterdam. He was a Visiting Research Fellow at Princeton University in 1996.

## Formal epistemology: Foundations and applications

Formal epistemology has largely the same aims as traditional epistemology. It focusses on giving analyses of central epistemological notions such as knowledge and rational acceptability (or justified credibility) and also addresses many of the traditional epistemological questions, such as how knowledge and rational acceptability relate to action, whether knowledge and/or rational acceptability are closed under logical consequence, and what the best methods are for acquiring knowledge. But whereas traditional epistemology aims to give 'ordinary language analyses' of epistemological notions, and typically relies on relatively informal argumentation, formal epistemology uses stronger analytical tools. In particular, the use of probability theory has led to significant results in formal epistemology. It has, for instance, been successfully used in analyzing the notion of coherence, which has figured prominently in epistemology for many decades even though there was widespread agreement among philosophers that an adequate characterisation of the notion was still lacking. The power of the formal and specifically probabilistic approach is well illustrated by the fact that many epistemologically crucial claims involving coherence – such as the claim that coherence is a truth conducive property – which had long been hard to assess, have now been given rigorous mathematical formulations and thereby have become open to formal demonstration (or refutation, as the case may be).

Almost from the very beginnings of epistemology, rational acceptability has been one of the most thoroughly studied notions in the field. Formal epistemologists have also paid great attention to this notion. Even so, satisfactory formal analysis is still missing. One recent result concerning rational acceptability, obtained by Igor Douven and Timothy Williamson, partially explains this fact: the result proves that what to many had seemed the most attractive type of formal analysis of rational acceptability trivialises the notion in that it makes perfect probability (i.e., probability 1) a necessary condition for rational acceptability, something with which few philosophers are willing to live. However, the same result also points to certain directions in which a satisfactory account of rational acceptability may still be found. A main sub-project of Igor Douven's Odysseus project is to develop a formally precise theory of rational acceptability, building on the aforementioned recent result and others obtained by researchers working in the area of Bayesian epistemology and related areas.

Another main subproject deploys the theory of rational acceptability in an account of various kinds of conditionals (that is, sentences of the schematic form 'If p, then q'). Many philosophers as well as linguists currently believe that at least the assertability and acceptability conditions of such sentences must involve some epistemic notion. In previous work, Igor Douven has proposed that for a large class of indicative conditionals, the correct assertability/acceptability conditions are to be stated in terms of rational acceptability. The specific aims of the current project with respect to conditionals are, first, to extend this proposal to other types of conditionals, most notably, 'even if' conditionals and so-called counterfactuals ('If p had been the case, then q would have been the case'), and second, to test the various empirical consequences of the proposal and also of research coming out of work on 'even if' conditionals and counterfactuals.

A third main aim of the current Odysseus project concerns another application of the new theory of rational acceptability, to wit, in an analysis of the nature of antirealist truth. While many antirealists have proposed to analyse truth in terms of rational acceptability – for instance, for what is rationally acceptable in the long run – they have typically done so assuming no more than a loose and informal notion of rational acceptability. It is believed that the new theory of rational acceptability will help to formulate a formally precise theory of antirealist truth, that is still missing from the literature, to date.

Finally, the theory of rational acceptability is also being applied to tackle issues in social epistemology, related to, on the one hand, formal models of judgment aggregation and, on the other, the role of testimony and epistemic authority in moral and other practical contexts.

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Jiri Friml was born on 24 June 1973 in Nedakonice, a small South Moravian village in the Czech Republic. After he obtained his MS degree cum laude in Biochemistry at the Masaryk University in Brno in 1997, he moved to Germany to undertake PhD studies at the Max-Planck Institute of Plant Breeding in Jeff Schell's department. In 2000 he completed his PhD in Biology, summa cum laude, at the University of Cologne, Germany. In 2002 he obtained a PhD in Biochemistry at the Masaryk University, Brno, Czech Republic. From 2002 to 2007 he held a position as independent research group leader at the Centre for Plant Molecular Biology, Tübingen, Germany, during which period he obtained his Habilitation in Genetics (2005).

He was received the following honors and awards: Max Planck Society Award: The Otto Hahn Medal 2000, Volkswagen Junior Researcher Grant; 1.326.000 euros (2002 – 2007), EMBO Young Investigator Award (2004) and the Heinz Maier-Leibnitz Prize 2005.

In 2007 he moved to Belgium where he became a full professor at the VIB Department of Plant Systems Biology, Ghent University, Belgium. He was ranked 1st in the Odysseus Programme call 2007 and was awarded 6.056.473 euros.

## Auxin: how cells make plants

Plants and animals live different lives. Both have to survive in everchanging and often adverse environments but both have evolved different ways of dealing with problems. Whereas animals typically react with a behavioural response such as fighting or running away, rooted plants have evolved a highly adaptive development that allows them to shape their bodies and metabolism according to the specific demands of the environment. Plant developmental plasticity is beautifully demonstrated by a medieval Moravian legend about the linden tree of innocence:

At the margin of the Chriby hills, an old medieval Buchlov castle stands guard over the wide valley of the South Moravian Morava River. There, on the terrace where the tribunal of the hunters court used to be, and where the last farewells with the convicts took place, a famous linden tree of innocence bears witness of a local legend. It is told that early in the 16th century the lord of the castle was deceitfully slain during one of his frequent hunts. A young servant was accused of this murder and imprisoned. After many days of unavailing torture he was condemned to death on the castle terrace. Upon this, the young man rose and pulled out the young linden tree growing nearby. He set it back into the soil, inverted, with the words,"If this small tree is green next year it will be the evidence of a sign from God that you killed an innocent man". And indeed, in the spring, small green leaves flourished from the tree's roots and the young man was set free.

This rather romantic story is a good demonstration of the fascinating plasticity of plant growth that plants evolved as their major adaptation strategy. A plant's repertoire of developmental tricks is extraordinary: permanent stem cell populations (meristems) at both ends of a plant generate growth throughout the plant's entire life. Postembryonic organogenesis enables the formation of new organs such as branches, leaves and flowers at any given time or position, while differential growth allows plantlets to seek light or roots to seek water. Even if plants compete with neighbours for sunlight, for example, they do that by completely reprogramming their own growth rather than by directly fighting with the others. Shade-induced changes in light quality cause a so called shade-avoidance syndrome, a response leading to stem elongation, less branching and earlier flowering that allow plants to outmaneuver their neigbours by getting to the light more rapidly and propagating. Such tailoring of development to the demands of the environment provides plants with unprecedented flexibility in terms of growth and survival.

How do plants coordinate such complex changes in development? Our linden tree had to wait almost 400 years before our curiosity was turned towards the mysterious mechanisms that so strangely affected its fate. At that time, several biologists including Julius Sachs and Charles Darwin proposed that like animals, plants also possess small signalling molecules with hormone characteristics. These substances can act at very low concentrations on physiology and development and their place of action is not necessarily the place of synthesis. As plants lack a cardiovascular system, effective distribution of hormones is an issue and therefore, by and large, plant hormones are not synthesised as locally as their animal counterparts but have are widely produced in different organs. In addition, plants had to evolve specialised systems for short and long range hormone distribution.

The hormone involved almost universally in adaptive plant development is called auxin (from the Greek auxein – to grow) and its discovery dates back to Darwin's studies dealing with plant "movements" and focussing on the problem how small grass plantlets growing towards light. Auxin in this context acts as a signall coordinating the reprogramming of growth in response to unidirectional light. However, the role of auxin in plant development is versatile and occur at multiple levels and ranges, from the regulation of cell elongation, embryonic axis formation and organogenesis to fruit ripening. Almost any modulation of plant growth can be attributed directly or less directly to auxin. It has remained a discomforting mystery for decades how auxin can mediate such a stunning diversity of responses.

Recent discoveries showed that auxin is not distributed equally in plant tissues but accumulates in concentrations in some cells or groups of cells. These spatial differences in auxin concentrations, so called "auxin gradients", accompany important developmental decisions and seem to be important for conveying specific auxin responses. Local manipulation of cellular auxin levels, for example, by application of small auxin droplets or local activation of auxin synthesis, confirms that increased auxin levels in some cells can entirely "reprogram" the fate of the cell and set off developmental changes such as elongation and cell division, differentiation into different cell types triggering different developmental programmes. Thus, one of the crucial questions in plant biology is how these patterns of local auxin accumulation are generated. Studies over the last decade have revealed that an important mechanism is directional, intercellular auxin transport that is mediated by specialised transport proteins. Asymmetric subcellular localisation of these transporters on only one side of the cells determines the direction of auxin movement between cells and can generate auxin accumulation in specific cells.Thus, polar auxin transport provides positional and directional information for many aspects of plant development.

Classical models postulate that polar auxin transport strictly requires the activity of auxin efflux carriers that export auxin out from the cell. Molecular genetic studies in the model plant, a small weed Arabidopsis thaliana, have identified PIN gene family coding for crucial components of auxin efflux. Studies in cultured plant, mammalian and yeast cells showed that indeed, PINs mediate auxin efflux from cells. The PIN gene family in Arabidopsis consists of eight members, and orthologues have been found in other plant species. Different PIN proteins then play an important role in the establishment of auxin gradients during multiple developmental processes including apical organogenesis and phyllotaxis (pattern of organ initiation), gravitropic and phototropic growth, root meristem patterning, vascular tissue development and embryonic axis formation.

The key feature of polar auxin transport – its controlled directionality – is determined, as has been predicted, by the polar subcellular localisation of PIN proteins. The polarity of PIN localisation is developmentally controlled or can be rapidly modulated by environmental stimuli such as light or gravity, thus leading to the redirection of auxin flow between cells. Dynamic changes of PIN polarity in response to environmental and developmental signals have been observed to divert auxin flow during gravitropic response, embryogenesis, postembryonic organogenesis and tissue regeneration. In addition, auxin itself can influence the subcellular distribution of plasma membrane proteins including PINs and thus establish via feedback regulation, its own transport channels through tissues.

These observations revealed that PIN proteins are key components of an intricate auxin distribution network that mediates local auxin gradients in multiple developmental processes.

This fascinating mechanism demonstrates the unique way that plants can change their growth to optimally adapt to the conditions of the place where they are growing. The internal and external signals are thus translated into the fluxes and distribution of the versatile growth regulator auxin, that in turn, reprogram cells where it has accumulated, thus re-arranging plant shape and development.

## BART LAMBRECHT (I)

*Back: Maud Plantinga, Kim Deswarte, Lotte Pyfferoen, Frederic Perros, Bart Lambrecht, Karl Vergote, Filipe Branco-Madeira. Front: Ruth Van Laere, Hamida Hammad, Monique Willart. Not in the picture: Karim Vermaelen, Wendy Toussaint and Philippe Poulliot.*

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Bart N. Lambrecht was born in 1968, is married to Tine Hendrickx and is the father of Louis, Olivia and Maxim. He obtained his MD/PhD degrees from the University of Ghent, Belgium in 1993 and 1999. After obtaining his MD/PhD degrees, he moved first to Sydney, Australia and then to the Netherlands where he specialised in Pulmonary Medicine at Erasmus University Medical Centre Rotterdam. He became Professor of Pulmonary Medicine at ErasmusMC in 2005, holding a special chair in Immunopathology of the Lung and responsible for organising the pulmonary research programme. In October 2007 he was appointed as Professor of Medicine at Ghent University, as part of the Odysseus programme. The group in Ghent now consists 16 international scientists and technicians that perform research on the immunopathology of various lung diseases, in close collaboration with the group in Rotterdam and the various departments at Ghent University that also perform immunological research.

He is the author of over 90 papers dealing with the use of mouse models to study the pathogenesis of asthma, lung infection and cancer-induced immunosuppression. In recent years, he has received several awards, among them the Inbev-Baillet Latour Prize 2008 for clinical research, The Antoine Faes Foundation Prize 2008, The Pharmacia Allergy Research Foundation Award 2004, The NWO VIDI Scholarship, The Schering Plough Respiratory 2000 Award, and the 1998 European Respiratory Society Annual Allergy and Immunology Award. Among his academic activities, he is also a Young Academy member of the Royal Dutch Academy of Arts and Sciences (KNAW), advisory editor of The Journal of Experimental Medicine, associate editor of Mucosal Immunology and a member of the Editorial Board of Clinical and Experimental Allergy. He has organised several international meetings on the topics of immunopathology, including two Keystone symposiums.

The focus of his research group is on the role of antigen presenting dendritic cells in the initiation of the pulmonary immune response that ultimately leads to sensitisation to antigens, as applied to cancer immunotherapy and allergic sensitisation. He is currently the principal investigator on a clinical trial evaluating the safety profile and effectiveness of dendritic cell-based immunotherapy protocol for patients with maliganant mesothelioma.

### The function of dendritic cells to fight disease

Asthma is a chronic inflammatory disease of the airways that affects the lives of millions of people and poses a significant burden on global healthcare costs, approaching five billion euros. The incidence of this disease is steadily increasing in westernised countries. In some European countries, almost one in every three children is allergic and has features of allergic asthma, allergic rhinitis or atopic dermatitis. The reason for this increase in allergic diseases over the last 50 years is unclear, but according to the hygiene hypothesis, allergies are increasing because of an increase in sanitation, changes in lifestyle and diet, and reduced risk of bacterial infections because of vaccination and antibiotic use. All these factors have in common that they are associated with a reduction in infectious pressure on the immune system, possibly leading to a derangement in immune homeostasis. The immunology of asthma has been studied extensively over the last few years. As such, it has become clear that the immune response to inhaled allergens is characterised by an aberrant response of the defence system (a so-called T helper 2 response) that has the potential to cause the features of asthma. In the long run, this chronic immune response leads to irreversible structural changes to the airways called airway remodelling, the severity and speed of which is probably influenced by genetic predisposition. Until

recently, it was unclear how the Th2 response to inhaled allergens was initiated. Over the last 15 years, my group has systematically studied the role of antigen-presenting dendritic cells (DCs) in the pathogenesis of this disease. Dendritic cells are the sensors and controllers of the immune system. They live at the boundaries of our defence system for example, in the airways, on the skin and in the gut, where they sense the presence of foreign invading pathogens, such as microbes and allergens. We have demonstrated that Th2 sensitisation to inhaled allergens is caused by antigen presentation by particular subtypes of DCs, that take up antigen in the lung and present it to naïve T cells in the mediastinal lymph nodes that drain the lung. We have made the crucial observation that myeloid DCs from allergic individuals seem to be uniquely sensitive to the allergens present within house dust mites, explaining why sensitisation to this allergen is so common in Western Europe. It was also shown that certain microbial factors that are associated with 'infectious pressure' on the immune system can indeed suppress the process of Th2 sensitisation through modulation of DC function, explaining why the absence of these factors in clean hygienic circumstances might cause allergy. At the same time, we were able to show that a second subset of DCs called plasmacytoid DCs (PDCs) is able to suppress the process of sensitisation, opening up the possibility that these cells could be exploited for the prevention of allergy. One of the active mechanisms by which microbe exposed myeloid DCs and tolerogenic PDCs reduce sensitisation is by induction of anti-inflammatory T cells with regulatory potential (Treg cells). It has been shown that Treg function in allergic patients is clearly deficient, and this might be due to aberrant function of tolerogenic PDCs or abnormal microbial education of myeloid DCs.

Dendritic cells have functions beyond the sensitisation process. Using the logic of Koch's postulates, we were able to show that DCs also play a crucial role in maintaining chronic inflammation in the airways. First, we showed that mice with experimentally induced asthma and human asthmatics and patients wih allergic rhinitis have more DCs in the airway mucosa within sites of inflammation, and have a clearly activated phenotype, capable of activating memory Th2 cells to cause disease. Next, it was demonstrated that the disease can be fully induced in mice, just by giving a few administrations of DCs to the airways. This leads to all typical features of asthma and even to long term airway remodelling, characteristic of chronic asthma. Finally, and most importantly, we have shown that removal of DCs from the airways of mice with ongoing chronic inflammation cures all the features of the disease, illustrating that targeting the DCs is a novel therapeutic intervention strategy that should be further exploited. Based on the above encouraging results in mouse models that highlighted the essential role of DCs in asthma pathogenesis, our group has started to unravel the mechanisms by which DCs can be manipulated in an attempt to interfere with the natural course of asthma. In this process, we discovered several new therapeutic classes of inhaled drugs that block DC function in the lung and that suppress asthamic inflammation. Several of these new drugs can suppress asthma when given via inhalation by inhibiting the maturation of lung DCs and inducing the formation of regulatory T cells. These compounds are already being developed for other uses and several companies will now initiate trials to address their effectiveness for treating asthma. The immunosuppressant FTY720, as well as its natural analogue, sphingosine-1-P, suppress DC function and experimental asthma. Again, this is a very drugable new pathway for asthma treatment that has generated a lot of interest for further clinical development. Finally, we have found that ATP is released into the broncho-alveolar lavage fluid of patients and mice with asthma and stimulates the function of lung DCs. When ATP or the purinergic receptors were inhibited, all the cardinal features of asthma disappeared. This is an extremely interesting new avenue for future research as the purinergic receptors are very drugable and this could lead to a whole new family of anti-inflammatory compounds for asthma.

One aspect that is unclear at present is whether one can redirect Th2 cells in established inflammation by altering the properties of the DCs, for example, by blocking essential Th2 inducing molecules on the surface of DCs or by administration of tolerogenic DCs, exposed either to microbial products or direct use of tolerogenic PDCs. In order to obtain experience with the production of clinical grade DCs, we are running a clinical programme to grow DCs from a leukapheresis product and have administered DCs to 20 patients with pleural cancer. In the future, we will further develop the use of tolerogenic clinical grade DCs for the treatment of severe asthma. Additionally, we are attempting to distil those factors within microbes that modulate DC function and result in beneficial effects on asthma. These immunomodulators could be used as preventive vaccines when combined with allergen immunotherapy.

Finding new drugs that interfere with asthma and are better than inhaled steroids is a real challenge for the future. We are convinced, however, that by persistently obtaining more basic information about the function of DCs in experimental and human asthma, as well as in cancer and infectious disease, we will come up with a strategy that could really make a difference for asthmatics.

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Jean-Pierre Locquet was born in Tielt (Belgium) on April 5, 1960. He studied Physics at K.U. Leuven. He obtained a PhD in Physics in 1989 for his research on the structural and electrical properties of artificial metallic superlattices. In December 1988, he joined the IBM Research Laboratory Zurich, Switzerland as a research staff member in the team of the Physics Nobel Laureates (1987) J. G. Bednorz and K. A. Müller. His research has focused on the properties of complex oxides such as high temperature superconductors, dielectrics, ferroelectrics and magnetic materials. Both the fundamental understanding of these oxides as well as their synthesis and integration into novel devices has been developed substantially during those years.

From October 2006 to March 2007, Jean-Pierre combined the IBM position with a part-time appointment at the Department of Physics and Astronomy of the K.U. Leuven. In April 2007, he joined this Department for a fulltime position. He obtained an Odysseus Type I grant on the topic of Nanomaterials with controlled functionality, and is currently the chairman of the Leuven Nanocenter.

He is married to Maria Seo, Professor at the Metallurgy and Materials Engineering Department of K. U. Leuven and has two daughters, Sophie and Nathalie.

# Nanomaterials with controlled functionality

## Introduction

Nanomaterials have an immense impact both in science and technology, in areas such as electronics, materials science, catalysis, energy generation and conservation as well as medicine. In recognition of this potential, this project proposes to pursue three main objectives (1) to explore the synthesis -- in an interdisciplinary manner -- of novel nanomaterials; (2) to control precisely the functionality of these materials by atomic scale engineering; and (3) to translate the results into useful devices, tools and systems. This will be applied to three classes of materials, namely heterostructures, nanoparticles and nanosystems, with the latter consisting of combinations of the former including biological substances. The research will rely on several technology platforms (laboratories) namely Nanosynthesis, Lithography, Nanofabrication, Spectroscopy and Microscopy.

Without a question, the development of these activities will considerably enhance the scientific capabilities at the K.U.Leuven and in Flanders. This research requires an in-depth focus on selected areas with a high scientific and innovative potential. It also requires an interdisciplinary approach where experts in the fields of synthesis, lithography, microscopy, spectroscopy, device processing as well as (bio-) materials, tools and system engineering work together in one team.

## Objectives

**Explore the synthesis**
In this part of the project, existing and new synthesis capabilities will be combined. The goal is to extend the experimental parameter space considerably, so that novel and better nanomaterials can be synthesised. This includes combining different deposition methods in one interconnected environment with stringent controls on composition, so that complex compounds can be synthesised with atomic scale precision.

**Control the functionality**
The functionality of nanomaterials is hampered by poorly controllable interface and surface conditions (heterostructures), as well as size, shape, termination and orientation (nanoparticles). To achieve a much better control, novel real-time and in-situ spectroscopy and microscopy methods will be developed. The goal is to measure the main physical properties of interest during synthesis and their nanofabrication. This will provide an extraordinary advantage

compared to the classical approach where the relevant parameters are only accessible after the nanomaterial has been cut and pasted into a full device.

**Translate the results**

The synthesised nanomaterials with their controlled functionality will be used to make devices, components and tools. This includes improved versions of existing nano-electronic, spintronic and optical devices as well as novel exploratory concepts to control charges, spins and photons and their interaction with biological species. As the relevant physical quantities are tightly controlled during synthesis and fabrication, this will quickly lead to optimal devices, components and tools. These will be made in collaboration with partners at the K.U. Leuven, IMEC or the industry.

**Work-packages**

The objectives will be implemented for the three work packages heterostructures, nanoparticles and nanosystems. For each a fundamental question will be answered. First, can the charge and spin density at insulator/semiconductor, semiconductor/metal and ferromagnetic/antiferromagnetic interfaces be controlled? Second, how can size, shape, composition and orientation of catalytic nanoparticles be tuned to control their growth and properties as well as those of nanowires and nanotubes? Finally, how to combine various heterostructures and nanoparticles with biological substances to create multimode tags and intelligent drug delivery systems?

Heterostructures: Any device relies on changing a 'state variable' in a layer, through the application of an external stimulus. This stimulus can be an electric or magnetic field applied through a second layer. Unfortunately, in such heterostructures there are substantial changes in the 'state variables' near the surface and interfaces that dramatically alter the coupling. Furthermore, the elementary excitations (charges, spins, phonons) from both sides of the interface do not terminate sharply but often penetrate over distances up to a nanometer.

Nanoparticles: Most preparation processes for nanoparticles lead to a broad distribution of sizes and shapes. However, when a precise electric, magnetic or optical action on a specific location is desired, a strict control becomes essential. Ultimately, this will require manipulation with atomic level precision. In addition, for a specific functional response the same interface and surface control as mentioned in heterostructures above must be applied.

Nanosystems: The intention is to create combinations of the above two elements, with or without biological elements. One example is the creation of multimode tracers for medical imaging by combining fluorescent and magnetic nanoparticles. Another example is the combination of sensors, electronics, drug molecules and proteins to create an intelligent drug delivery system.

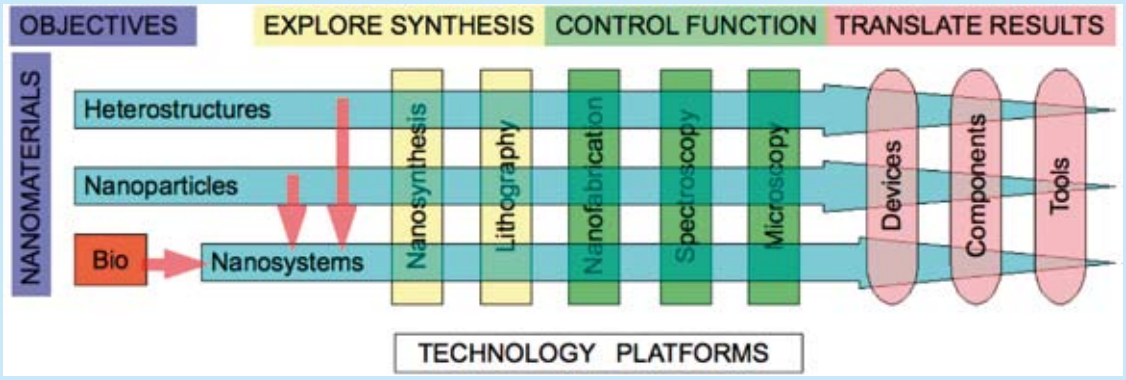


Fig. 1 Project layout

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Filip Meysman (1970) received his MS degree's in Chemical Engineering in 1993 at the K.U.Leuven (Belgium), specialising in waste water treatment technology. Intrigued by the microbial food web that thrives in waste water treatment reservoirs, and the `miraculous´ clean-up of the water by these microbes, he obtained a second MS degree in Biology from Ghent University (Belgium) in 1996, specialising in aquatic ecology. His dissertation on the biogeochemical modelling of algal mats was awarded the best thesis prize by the Royal Society of Natural Sciences. Subsequently, he started a Ph.D on the modelling of biogeochemical processes in marine sediments at the Marine Biology Lab (Ghent University, Belgium), supported by a grant from IWT (Institute for the Promotion of Innovation by Science and Technology in Flanders). His research took him abroad to the CEME-NIOO (Yerseke, the Netherlands) and Dalhousie University (Halifax, Canada). After receiving his PhD in 2001, he became a Research Fellow in the Challenger Division for Seafloor Processes at the Southampton Oceanographic Centre (UK). From 2002 onwards he joined the department of Ecosystem Studies at the Netherlands Institute of Ecology as a post-doc, where he collaborated with Jack Middelburg on the numerical modelling of biogeochemical transformations in ocean floor sediments. In 2006 he was appointed Guest Professor at Ghent University (Belgium), teaching a course on "Ecological Modelling". In 2007 he was the recipient of an Odysseus Grant (FWO Research Foundation - Flanders), and moved to the Chemical Oceanography research group at the Vrije Universiteit Brussel (VUB). At the VUB he has now started a research unit that focuses on carbon cycling and biogeochemistry within the ocean floor.

## Quantifying Darwin's last idea: the influence of bioturbation on the biogeochemistry of marine sediments, and its impact on the global carbon cycle

### Climate mitigation and geo-engineering

In recent years, there has been a strong increase in public awareness and concern about the consequences of climate change. At present, the issue is high on the international political agenda, and as the imprint of climate change becomes ever more tangible, this will remain so in the coming years and even decades. Slowly, society is taking action, and this has spurred new economic activities that involve climate mitigation, that is, preventing the emission of carbon dioxide (CO2) and other greenhouse gases into the atmosphere. Travelers can now "offset" the CO2 emissions of their airplane flights by voluntarily investments in reforestation, and through the Clean Development Mechanism, companies in industrialized nations can receive carbon credits for financing projects that reduce greenhouse gas emissions in developing countries. These are just two examples of the carbon trading markets that soon will be skyrocketing, and actions to curb greenhouse emissions are expected to rapidly accelerate after 2012 (post Kyoto). However, some experts believe that these proposed actions will simply be "too little too late". In their view, the currently initiated transition to a low-carbon economy is occurring at a too slow pace. There are indeed good arguments for this gloomy perspective. Even in the most optimistic projections, that foresee large reductions in fossil fuel consumption, there will still be a substantial increase in atmospheric CO2. In other words, present-day "small-scale" technological fixes to the climate change challenge (like improved energy efficiency, increased wind and solar energy sources, etc.) will not be sufficient to avert the "dangerous" levels of climate change. In response, proposals have been launched that call for a drastic, large-scale approach to reduce atmospheric carbon dioxide levels. The target of these so-called geo-engineering proposals is nothing less than to "adjust" the climate system on a global scale. Not so long ago, such proposals seemed radical and belonging to the realm of science fiction. However, now – faced with the huge consequences of rapid climate change – they are being taken seriously.

## Improving knowledge of the ocean's carbon cycle

The oceans form a large reservoir of carbon, and hence, they play a key role in global carbon cycle and (natural) climate regulation. Therefore, the oceans are given a prominent role in some of the (more credible) geo-engineering proposals, that always involve some method of ocean fertilisation. Central to this are the phytoplankton (single-celled photosynthetic organisms), that are responsible for about half of the carbon fixation on earth. In the surface layer of the ocean, the phytoplankton take up carbon dioxide (CO2) to produce the organic carbon that makes up their cell structure. When these cells die, part of their remains sinks to the deeper layers of the ocean. This biologically mediated transfer of carbon is known as "biological pump", and thus removes CO2 from the atmosphere and stores this in the ocean interior and the ocean floor. This natural form of carbon sequestration has recently received a lot of attention. Indeed, what if we could enhance this natural process in order to remove the greenhouse gas CO2 from the atmosphere?

One important result from past oceanic research is that the growth of phytoplankton is principally limited by the availability of nutrients such as nitrogen, phosphorus, and iron. Accordingly, when fertilising the ocean through the addition of nutrients, one can stimulate phytoplankton production and the "biological pump". In particular, the idea of iron fertilisation has received a lot of attention in recent years. Since 1993, twelve small-scale ocean experiments have shown that (relatively) small additions of iron could trigger sizeable plankton blooms, and hence, draw more carbon into the ocean. Today, policy makers, economists and even investors have taken notice of the idea. A few companies are already planning ocean iron fertilisation experiments, and are investigating how to commercialize the associated "carbon offset" credits. However, at present, many questions abound. Does ocean fertilisation really work? And if so, how does it work? Putting more carbon into the ocean is one thing. Keeping it there is another. And even more importantly, what would be the possible side effects of large-scale fertilisation efforts? Presently, we have virtually no idea about any unintended consequences of manipulating the ocean ecosystem on such a large scale. Accordingly, there is a strong incentive for improving our understanding of carbon cycling within the ocean system, and this is also the topic of this Odysseus project.

## The Odysseus project: Computer modelling of carbon processing and sequestration in the ocean floor

Critical for the effectiveness of ocean fertilisation schemes is the amount of organic carbon that actually sinks from the surface. A fraction of this carbon falls to the ocean floor, and the main focus in this Odysseus project is to better understand the fate of this organic carbon in the ocean floor. How much is processed by surface sediments and how much is sequestered in deeper sediment layers? How will the biogeochemistry of the sediment ecosystem react to a change in the input of organic matter (e.g., resulting from an ocean fertilisation scheme)? One critical, but poorly understood aspect in the carbon cycle of the ocean floor is the role of burrowing invertebrates. These burrowers populate nearly the entire ocean floor, and they cause a turnover of the sediment (bioturbation), that continuously exposes new sediment material to the oxygenated overlying water. The importance of soil fauna for soil processes was first realised by Charles Darwin, who devoted his last scientific book to the subject. The goal of this Odysseus project is to examine and extend Darwin's "last idea" to the ocean floor. Recent investigations indicate that burrowing fauna can have a major impact on the biogeochemistry of the ocean floor. However, until now, this influence has only been qualitatively examined. Accordingly, one obstacle to improved estimates of carbon cycling in marine sediments is exactly our inability to properly quantify the bioturbation impact of local fauna. In this Odysseus project, the aim is to come up with hard numbers for the impact of marine bioturbation on organic carbon burial and the global carbon cycle. This is done by creating a kind of "virtual ocean floor", a computer-simulation environment of marine sediments, in which we explore the biogeochemical effects resulting from the construction and ventilation of burrow systems. These model simulations will provide quantitative and mechanistic insights into the impact of marine bioturbation on organic matter processing and global biogeochemistry. This will thenlead to improved estimates regarding how much carbon is processed and ultimately sequestered in the ocean floor.

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Vyacheslav Misko (also transliterated as: Veaceslav Misco) was born in 1965 in the eastern (mainly Russian- and Ukrainian-speaking) part of the Moldavian republic of the former USSR ('Republic of Moldova' since 1993). His family is of Ukrainian origin. He graduated (with distinction) from the Kishinev State University (KSU) and obtained his MS degree in Physics in 1989. Between 1989-1992, he was a PhD student at the Institute of Applied Physics (IAP) of the Academy of Sciences of RM. He defended his PhD thesis – on the Bose-Einstein condensation of excitons in low-dimensional semiconductors – at the KSU (with the pre-defence at the Institute for Theoretical Physics in Kiev, Ukraine), and he obtained his PhD in Physics and Mathematics (diploma with distinction) in Moscow in 1993. Until 2003 he was associated with the IAP as a Senior Researcher at the Department of Theory of Semiconductors and Quantum Electronics (head: Academician, Prof. S.A. Moskalenko).

He started his independent scientific research at the University of Antwerp (UIA) in 1996, as a postdoctoral fellow ('Gastprofessor') of NFWO-Belgium. Over the next seven years, he was invited several times as a postdoctoral researcher or visitor in the Department of Physics at the UIA-UA (TFVS group by Prof. J.T. Devreese). His research at the time was mainly focussed on the theoretical study of vortex matter in mesoscopic superconductors within the nonlinear Ginzburg-Landau theory, in collaboration with the VSM group (head: Prof. V.V. Moshchalkov) at the K.U.Leuven. Thus he established himself as an independent researcher in Flanders.

However, challenging, new problems required new expertise and experience, and in 2003 he moved to the Research Centre Jülich (experimental group led by Prof. R. Wördenweber) in Germany, where he studied the guided motion of vortices in high-temperature superconductors. That was the beginning of his 'Odyssey'. At the ESF 'Vortex' 2003 Conference on the island Crete in Greece he met Prof. Franco Nori who invited him to join his group at the University of Michigan (UM), US and at RIKEN in Wako-shi, Japan. In 2004 he moved to Honshu island as a research fellow from the UM. In the Digital Materials Laboratory at RIKEN he studied the dynamics of vortices in periodic and quasiperiodic pinning arrays and the rectification of flux motion. In 2006 he moved to the CMT group led by Prof. François Peeters at the University of Antwerp. At present, he is an EU Marie Curie fellow at the CMT-UA, and hopes that Flanders will become his 'Ithaca' – thanks to the 'Odysseus' Program of the Government of Flanders.
He is a (co)author of about 140 publications including 40 papers in refereed journals (Physical Review Letters, Europhysics Letters, Physical Review B, etc.) and about 100 abstracts and proceedings of international conferences.

### Nonlinear dynamics in nanosystems: flux quanta in nanostructured superconductors, colloids and nanoclusters

Without a doubt, nanotechnology will be the technology of the 21st century. The major industrialized countries have come to recognize this and are comprehensively intensifying their research in communications and material sciences and focussing on the applications of nanotechnology in, life/biotechnology. In the case of superconductors, nanotechnology is used to micro-fabricate materials that exhibit new quantum phenomena leading to new functionalities. Quantum-mechanical principles in nano-structured materials represent one of the most exciting fields of modern physics. In this context, nano-structured superconductors play a special role due to the macroscopic quantum state of the superconducting charge carriers and the appearance of quantized flux lines (vortices), that develop in the presence of an external magnetic field. The proposed research is devoted to the in-depth investigation of the nonlinear dynamics of flux quanta in nano-structured superconductors, the study

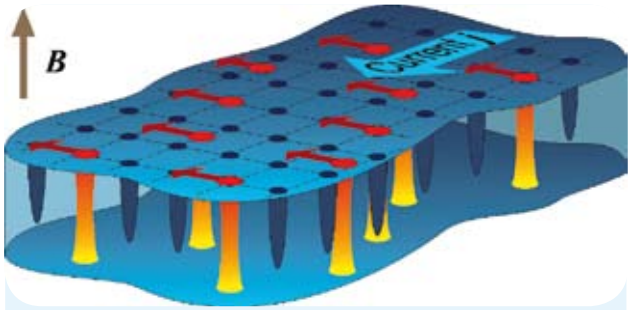
of new mechanisms having effective control of the flux motion and improving the critical parameters of superconductors through their nano-patterning, for creating new materials and devices with desired functionalities. This research also includes several related and interdisciplinary topics (which are spin-offs of the work on superconductivity), i.e., the study of different systems of confined interacting particles, e.g., colloids, atomic clusters, charged metallic particles, etc., where similar theoretical approaches can be used.

## Introduction

Almost a century has passed since the discovery of superconductivity, and since then this phenomenon has been actively investigated. The discovery of so-called high-temperature superconductors and other promising superconducting materials as well as recent progress in their fabrication (including nano-fabrication) have generated a new wave of research activity in this field. Surprisingly, in spite of their unique characteristics (e.g., the absence of resistance to electric current), superconductors are not so widely used in current applications. Mainly, these are superconducting magnets and cables, and some other applications such as ultra-sensitive field detectors based on SQUIDs, etc. One of the main restrictions on using superconducting materials in micro- and nano- electronics is their low critical parameters, i.e., the highest possible magnetic field, temperature and the external current superconductors that can be sustained without deterioration of their properties. During the last two decades, a considerable progress has been reached in improving the critical parameters. Nevertheless, the increase of the critical parameters, in particular the critical current, remains one of the main objectives of applied superconductivity.[1]

Half a century ago, A.A. Abrikosov found that magnetic flux penetrates in (so-called type II) superconductors in the form of vortices, or single quanta of magnetic flux. In 2003, he was awarded the Nobel Prize in Physics for this discovery. While it was a breakthrough in the theory of superconductivity, this discovery revealed one of the major limitations of the applications of superconductors. Under the action of an external current, vortices move that lead to energy dissipation resulting in a considerable decrease of the critical current in superconductors. An efficient way of increasing the critical current is thus to trap the vortices, i.e., in order to prevent their motion. Alternatively, one can think of controlling the motion of flux quanta. These goals can be reached by the nano-patterning of superconductors, i.e., by the creation

*1 See, e.g., materials of the 8th European Conference on Applied Superconductivity (EUCAS'2007), Brussels-Belgium, 16-20 September 2007.*




*Vortices (red-to-yellow tubes/red spots on the top surface) driven by a Lorentz force FL produced by an applied current j in a superconductor with square APS (dark blue bars/dark blue dots on the top surface), placed in an applied magnetic field B (from: V.R. Misko et al., Phys. Rev. Lett. 96, 127004 (2006); Phys. Rev. B 75, 024509 (2007)).*

of artificial vortex traps, or arrays of pinning sites (APS). For example, regular (or random) pinning arrays were used to trap vortices. Recently, it was theoretically demonstrated[2] that using quasiperiodic(QP)[3] pinning arrays leads to a considerable increase of the critical current. These theoretical predictions were experimentally verified[4] by two groups, in Tübingen (Germany) and in K.U.Leuven.
Within this project, we will develop the study on controlling the flux motion in nano-structured superconductors aimed at the enhancement of the critical parameters. This study is also related to possible applications in fluxonics, the design of flux-quantum-based memory, etc. We will also study related interdisciplinary topics including the dynamics of colloids (e.g., binary mixtures), a one-dimensional diffusion in narrow channels, or single-file diffusion (SFD), which is important from both the fundamental research and different applications in physics, biology (e.g., transport in ion channels), medicine (drag release), etc. We will investigate the principles of formation, melting, phase transitions of atomic (or classical) nano-clusters consisting of many interacting particles which could be referred to as "building blocks" of nano-science.

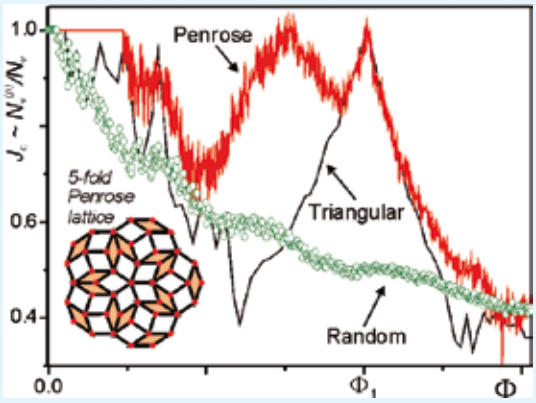
## Controlling the flux motion in nanostructured superconductors

Recent progress in fabrication of nanostructures has provided a wide variety of well-controlled vortex-confinement

*2 V. Misko, S. Savel'ev, and F. Nori, Phys. Rev. Lett. 95, 177007 (2005); Phys. Rev. B 74, 024522 (2006).*
*3 Quasiperiodic structures (or quasicrystals), unlike crystals, do not possess a long-range translational order; their elements are ordered according to local inflation rules (e.g., Penrose tiling).*
*4 M. Kemmler et al., Phys. Rev. Lett. 97, 147003 (2006); A.V. Silhanek et al., Appl. Phys. Lett. 89, 152507 (2006).*

topologies, including different regular pinning arrays[5]. These arrays have been extensively used for studying vortex pinning, dynamics, and commensurability effects[6]. Thus, studying the stochastic transport of fluxons driven by an alternating current (ac), in superconductors with asymmetric channel walls, a non-zero net current (dc), or rectification effect of vortices has been found[7]. These asymmetric channels, or ratchets,[8] would allow, for example the construction of fluxon optics nano-devices. An effective way to control the motion of magnetic flux in high-$T_c$ superconducting thin films has been suggested and experimentally realised[9] using the *guided* motion of vortices via a special arrangement of sub- μm holes, or antidots.

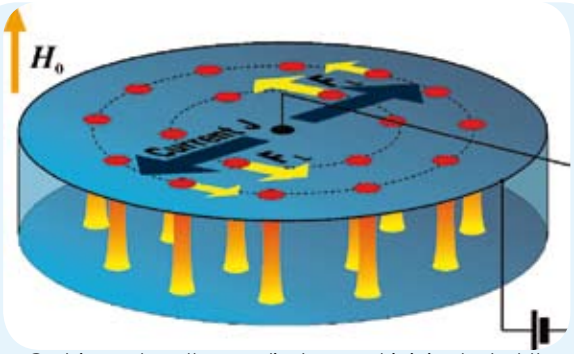
**Enhancement of the critical current in nano-patterned superconductors.** We will study the vortex dynamics, pinning




*The critical current Jc in triangular, random and quasiperiodic Penrose-lattice APS. Inset shows a 46-node fragment of a five-fold Penrose lattice2.*

properties, and the critical current $J_c$ in nanostructured superconductors with various types of APS: (i) Nano-composite superconductors containing non-superconducting phase inclusions; (ii) Disordered superconducting Nb films. We will analyse the finite-size effect on $J_c$ and re-examine the criterion of the "critical current". As recently shown,[2,4] QP APS can enhance $J_c$ as compared to periodic APS. We will analyse Jc and the elastic and pinning energies in various periodic and QP structures – analytically and numerically by solving the Langevin equations and the time-dependent Ginzburg-Landau (GL) equations. In conjunction with the above and in order to understand the dynamics of flux quanta in different types of pinning sites – such as antidots, blind antidots, and magnetic dots, – we will study the Langevin dynamics of interactive massive particles. The use of a simple model for the pinning potential may result in a zero mass term. This fundamental issue will be addressed. The actual potentials will be calculated using the Ginzburg-Landau theory.

**Pinning-induced clusters and giant vortices.** Recently, using the Bitter decoration technique, the first direct observation




*The Corbino setup: the applied current is injected at the centre and removed at the perimeter of the disk to induce a radial current density J. Vortices near the centre experience a stronger Lorentz force FL than near the edge (from: V.R. Misko and F.M. Peeters, Phys. Rev. B 74, 174507 (2006)).*

of rings of vortices in mesoscopic superconducting Nb disks was reported[10]. The circular symmetry led to the formation of concentric shells of vortices, similar to electron shells in atoms. The analysis of different vortex configurations revealed fundamental rules ("periodic law") of shell filling and also "magic-number" configurations.[11] We will study the theories involved in the pinning-induced formation of clusters and giant vortices in mesoscopic disks, triangles and squares, which can be considered as a new mechanism of formation of giant vortices.

**Dynamics of vortices and antivortices.** The possibility of the spontaneous generation of antivortices in symmetrically-confined vortex matter due to the interplay between the C∞-symmetry of the magnetic field and the discrete symmetry of the sample was first predicted,[12] and subsequently

*5 L. Van Look et al., Phys. Rev. B 66, 214511 (2002); A.V. Silhanek et al., Phys. Rev. B 67, 064502 (2003).*
*6 F. Nori, Science 278, 1373 (1996); C. Reichhardt et al., Phys. Rev. Lett. 78, 2648 (1997); Phys. Rev. B 58, 6534 (1998).*
*7 J.F. Wambaugh, C. Reichhardt, C.J. Olson, F. Marchesoni, F. Nori, Phys. Rev. Lett. 83, 5106 (1999).*
*8 J.E. Villegas et al., Science 302, 1188 (2003); S. Savel'ev et al., Phys. Rev. B 71, 214303 (2005); J. Van de Vondel et al., Phys. Rev. Lett. 94, 057003 (2005); C.C. de Souza Silva et al., Nature (London) 440, 651 (2006).*
*9 R. Wördenweber, P. Dymashevski, and V.R. Misko, Phys. Rev. B 69, 184504 (2004).*

*10 I.V. Grigorieva et al., Phys. Rev. Lett. 96, 077005 (2006).*
*11 V.A. Schweigert and F.M. Peeters, Phys. Rev. B 51, 770 (1995).*
*12 L.F. Chibotaru et al., Nature (London) 408, 833 (2000); Phys. Rev. Lett. 86, 1323 (2001).*

the possibility of the appearance of stable vortex-antivortex "molecules" was analysed[13] in type I superconducting mesoscopic triangles. Another effective way to generate vortex states with antivortices is to use magnetic dots[14] placed on top of a superconductor. Several attempts to experimentally observe antivortices in mesoscopic/nanopatterned superconductors were not successful. In this project, we will study an alternative way to experimentally detect antivortices based on the expected different dynamical behaviour of vortices and antivortices under the action of an externally applied current. We plan to study the nonlinear dynamical response of the system of vortices and antivortices to an applied current in: (i) nano-patterned superconducting films; (ii) mesoscopic superconducting Corbino disks.

## The critical parameters in nano-grains and cluster-assembled films

Very recently, the size of a superconductor could be controlled on the nanoscale. Experiments with ultrathin lead films and nanowires gave rise to several fundamental questions: how do the superconducting properties change when decreasing the size of the sample and how are the critical parameters modified at the nano-scale, i.e., in the regime close to the break-down of superconductivity? We will study the size-dependent superconducting properties at the nanometer scale in individual superconducting nano-grains and cluster-assembled films. Thermodynamic properties such as the magnetization and susceptibility of ensembles of particles will be analysed as a function of temperature and magnetic field. We will study theoretically observable manifestations of pairing correlations in thermodynamic properties of ultra-small superconductor grains. The thermodynamic properties (magnetic susceptibility and specific heat) of clusters and cluster-assembled films will be calculated.

## Related interdisciplinary topics

Several of the theoretical techniques used to study the vortex dynamics in superconductors can be transferred to other fields (actually, we employ the methods to study flux dynamics we employ in this research, e.g., the molecular-dynamics simulations are generic and therefore can also be used to study the dynamics of atoms and molecules, cluster formation, diffusion, etc.). An appreciable part of the proposed project will be devoted to such cross-fertilisations.

*13 V.R. Misko et al., Phys. Rev. Lett. 90, 147003 (2003).*
*14 M.V. Miloševic and F.M. Peeters, Phys. Rev. Lett. 93, 267006 (2004); 94, 227001 (2005).*

**Single file diffusion in Wigner rings.** In recent experiments the single file diffusion (i.e., where the mutual exchanges of particles are forbidden) of macroscopic (millimetric) charged metallic balls exhibited subdiffusive behaviour slower than the $t^{1/2}$ behaviour predicted by theory and as has been observed earlier in systems of colloidal particles. To understand this fundamental difference in behaviour (rather a $t^{1/4}$ behaviour was observed instead) we will study theoretically the diffusion of charged massive particles in narrow channels in the presence of a temperature noise.

**Dynamics and self-assembly of colloidal binary-mixture systems.** Recently, there has been a growing interest in studying the self-assembly of various binary mixtures including ionic colloidal crystals. The attractiveness of these systems is explained by the fact that they display the same phase behaviour as atoms or molecules, being of nano- or micrometer size so that they can be observed in real space and at the same time, due to their slow dynamics in time-space. Another attractive feature of colloidal binary-mixture systems is that different types of colloidal interactions can be realised giving rise to equilibrium phases. Within this project, we will study the dynamics and self-assembly of various binary mixtures, that lead to new physics, e.g., new 2D lattice structures, new dynamical properties, melting/freezing behaviour, etc.

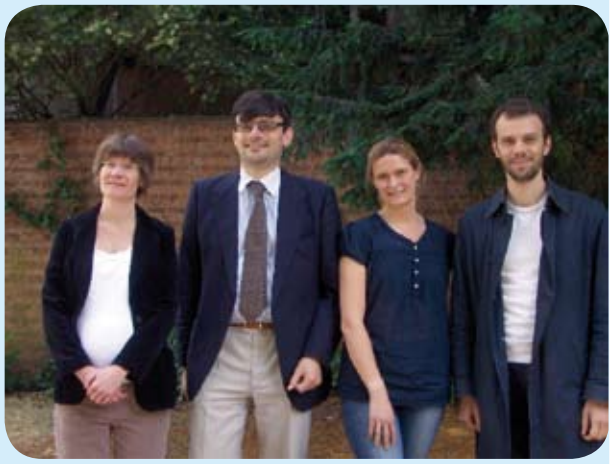
**Formation and growth of nanoclusters.** Nanoclusters are aggregates of atoms or molecules of nanometric size, containing a finite number of constituent particles typically ranging from ~10 to $10^6$. These nano-objects are intermediate between single atoms and molecules and bulk matter. Their properties are often peculiar, qualitatively different from those of their constituent particles (i.e., atoms or molecules) and from those of macroscopic pieces of matter. The study of the formation of nanoclusters, their properties as well as the development of reliable methods to model nanoclusters is a rapidly developing field. In this project, we plan to study the principles and existing methods used for modelling the energetics of nanoclusters, that include ab initio calculations and semi-empirical modeling. Special attention will be paid to the study of the kinetic effects in the formation of nanoclusters, such as, the freezing of liquid nanodroplets and solid-state growth.

## Impact and potential for promoting scientific innovation

The impact of the proposed research is related to the role of nano-science, nano-technologies in science and in contemporary life. The understanding of complex nonlinear

dynamics of the flux quanta and their effective control in superconducting materials and devices is of great importance and remains at present the main objective of several International and European programmes. In this project we propose the implementation of new ways of the nano-structuring of superconducting materials. This would allow us to effectively control the flux quanta and critical parameters in nanostructured superconductors. The practical importance of the results of the study would be that it opens several possibilities for designing new materials with the unique functionalities that are needed for various applications in telecommunications (e.g., high-frequency filters, etc.), medicine (high-sensitive low-noise SQUIDs), quantum computing, etc. The study of the nonlinear dynamics of overdamped and underdamped particles, ratchet effects, etc., has a large impact inside as well as outside the field. It has many common features with several biological systems and, for example, can be used for studying, transport in ion channels, and for developing, different separation techniques of macromolecules in solvents and on membranes. The study of the self-assembly of various binary mixtures, e.g., ionic colloidal crystals and the formation and growth kinetics of nanoclusters has a deep impact on the understanding of the fundamentals of the formation of surfaces and crystalline structures of solids.

## GEORGE PAVLAKOS (II)



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George Pavlakos is a Research Professor in Globalisation and Legal Theory at the Faculty of Laws, University of Antwerp; he also holds a part-time personal Chair in the same field at the School of Law, University fo Glasgow, Scotland. From 2001 to 2007 he was the City Solicitors' Educational Trust Lecturer in Jurisprudence at the School of Law, Queen's University, Belfast. Since 2005 he has been a regular visiting Professor at the chair of Public Law and Legal Theory at the Faculty of Law, University of Kiel, Germany.

George studied Law in Athens, Kiel and Edinburgh. During his studies he received scholarships from the Hellenic State Scholarship Foundation (I.K.Y.) and the Friedrich-Ebert-Foundation. In 1995 he was called to the Bar of Athens where he practiced for a short period. In 2005-2006 George was an Alexander von Humboldt research fellow for 18 months. In September 2008 he was awarded an Odysseus Research Grant by the Research Foundation - Flanders (FWO).

His published work, mainly in the area of legal theory and philosophy, includes two edited collections and a monograph, entitled 'Our Knowledge of the Law', all published by Hart Publishing. Another monograph in German, under the title 'Rechtsontologie und praktische Vernunft', has appeared in early 2008 in Nomos Verlag. In addition he has published over 10 articles in refereed journals and edited volumes.

### The constitution of globalisation

The research conducted under this project undertakes an investigation of the impact of globalisation on the concept of law from the point of view of General Legal Theory and the Philosophy of Law. In addition, extensive use is made of contemporary debates in the Philosophy of Action, Social, Political and Moral Philosophy. Given its interdisciplinary scope, the project focusses on structural as well as substantive aspects of legal orders with an eye to offering an explanatory framework of legal phenomena that lives up to the challenges of the globalised era. Such a framework, it is argued, needs to combine a dynamic understanding of how legal norms and categories evolve in the light of the social, economic and political changes globalisation effects, with an account of the specifically normative structure of law as a source of authority. The two aspects, it is suggested, may be combined through an analysis of the dual character of Law as a system of coordination of action: on one hand, the factual aspect that pertains to legal institutional arrangements; and on the other, the ideal aspect that refers to the claim raised by law of being a legitimate source of normative authority. Research under this programme is being funded by an Odysseus Grant of the Research Foundation - Flanders.

Further details on the project can be found on the website of the Centre for Law and Cosmopolitan Values, Faculty of Laws, University of Antwerp at:
www.lcv.ua.ac.be

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Maurilio Sampaolesi, currently Associate Professor in Translational Hardiomyology at the "Stem Cell Research Institute" of the K.U.Leuven, Belgium, was born on 5 April 1967 in Rome, Italy. He worked on his PhD Degree in Cardiovascular Pathophysiology from 1992-1996 at the University of Rome "Tor Vergata". He held postdoctoral positions in the Department of Molecular Physiology at the National Cardiovascular Center Research Institute, Suita-city, Osaka Japan (1997-1999) and at the Biotechnological Section of the pharmaceutical company, Dompe' SpA, Italy (1999- 2000). From 2000 to 2005 he has been assistant professor at the "Stem Cell Research Institute", H.S. Raffaele, Milan, Italy and from 2005 to the present he was Assistant Professor of Human Anatomy at the University of Pavia in Italy.

His research activities focus on cardio-myogenic cell lineages; cardio-yogenic determination; muscle gene and cell therapy and murltipotency vs. pluripotency of stem cells.

He was awarded the following grants: Minnesota University/K.U.Leuven Wicka Funds n. zkb8720 01/05/2008-30/04/2013; FWO Odysseus Program n. G.0907.08 01/07/2007-30/06/2012STA-JISTEC, JISTEC Japan Grant ID n.197007;TELETHON, Europe Grant ID 463/bi; PRIN-COFIN Ministry of Health, Italy 2006-2007; Luban foundation 2007-2009; CARIPLO Foundation 2007-2009.

### Repairing damage to muscle and cardiac tissues through pharmacological and stem cell treatments

The main goal of the lab is to establish new strategies for repairing damage to muscle and cardiac tissues through pharmacological and stem cell treatments. They focus their efforts on the transplantation of mesodermal stem cells in animal models in order to promote muscle repair for muscular and cardiac dystrophy. The understanding about degenerative and spontaneous regenerative processes is clearly also important for the current extensive research effort to promote long-distance regeneration. Sampaolesi already reported that intra-arterial delivery of wild type mesoangioblasts, a class of vessel-associated stem cells, corrects morphologically and functionally corrects the dystrophic phenotype of virtually all downstream muscles in adult immunocompetent-mice (Sampaolesi et al, Science 2003) and dogs (Sampaolesi et al, Nature 2006) affected by muscular dystrophy.

### Stem Cell therapy for muscular dystrophy

The quest for a therapy for muscular dystrophy has been the driving force behind the past 40 years of advances in this field. Numerous results, such as the identification of satellite cells and gene mutations that are responsible for most forms of dystrophies, advances in gene transfer and modification technology and, more recently, stem cells, have fuelled hopes (Cossu & Sampaolesi Trends Mol Med. 2004; Sampaolesi et al. Arch Ital Biol. 2005). However, administering corticosteroids still remains the only effective treatment available. Several recent advances have uncovered a diversity of possible therapeutic approaches, from pharmacological treatments to gene therapy (exonskipping and adeno-associated viruses) and cell therapy with different types of newly identified stem cells (see Figure A). Most importantly, a combination of these strategies might greatly enhance the possibility of successful therapy. When mesoangioblasts that had been isolated from juvenile dystrophic mice (Sampaolesi et al. Science 2003) and transduced with a lentiviral vector expressing alpha-SG were injected into the femoral artery of dystrophic mice (see Figure C, D), they reconsti-

tuted skeletal muscle in a manner similar to that seen in wild-type cells. In the case of dog experiments the results showed that donor wild-type mesoangioblasts significantly ameliorate many symptoms of canine muscular dystrophy, whereas autologous genetically corrected cells are much less effective. The success of this cell therapy approach using mesoangioblasts is mainly due to widespread distribution of donor stem cells through the capillary network, a distinct advantage of this strategy over previous approaches.
Cells derived from blood vessels of human skeletal muscle (see Figure B) can regenerate skeletal muscle, similarly to embryonic mesoangioblasts. However, adult cells do not express endothelial markers, but instead express markers of pericytes, such as NG2 proteoglycan and alkaline phosphatase (ALP), and can be prospectively isolated from freshly dissociated ALP(+) cells. Unlike canonical myogenic precursors (satellite cells), pericyte-derived cells express myogenic markers only in differentiated myotubes, that they form spontaneously with high efficiency. When transplanted into severe combined immune deficient-X-linked, mouse muscular dystrophy (scid-mdx) mice, pericyte-derived cells colonize host muscle and generate numerous fibres expressing human dystrophin. Similar cells isolated from Duchenne patients, and engineered to express human mini-dystrophin, also give rise to many dystrophin-positive fibres in vivo (Dellavalle Sampaolesi et al. Nat Cell Biol. 2007). Our results qualify mesoangioblasts as candidates for future stem cell therapy for Duchenne patients, however improving ability of cell isolation, cell migration and cell migration is required.

## Stem Cell therapy for chronic cardiac disease

In animal models, several stem and progenitor cells showed potential for improving cardiac regeneration and we recently we identified cardiac stem cells that can efficiently give rise to cardiac myocytes. However, at present there are several aspects to be overcome before cardiac stem cells can be clinically applied. In our lab we are challenging cell therapy approaches using animal models that develop dilated cardiomyopathy, such as beta sarcoglycan KO mice and GRMD (Golden Retriever Muscular Dystrophy) dogs. We succeeded in the identification, clonal expansion and characterisation of self-renewing progenitors that differ from all those previously described for high spontaneous cardiac differentiation. Unique co-expression of endothelial and pericyte markers identify these cells as cardiac mesoangioblasts and allow prospective isolation and clonal expansion from the adult ventricle of mice, dogs and humans.

**Animal models for muscular dystrophy and cardiomyopathy:**

*-Duchenne Muscular dystrophy animal models:*
*mdx mice. Generated by point mutation on exon 23 of dystrophin genetargeted*
*GRMD dog Spontaneus mutation on intron 6. The colony is located at Maison Alfort Vet. School Paris,*
*-Limb girdle muscular dystrophy animal models:*
*alpha-Sarcoglycan KO*
*beta-Sarcoglycan KO*
*-Muscular dystrophy animal models for human cell engraftments:*
*SCID/mdx*
*SCID/alpha-Sarcoglycan KO*
*SCID/beta-Sarcoglycan KO*
*- Transgenic mice for muscular hypertrophy: Tg:MLC1F/MagicF1i (FVB, C57 backgrounds; generated at San Raffaele Institute).*

**Laboratory and Technical Expertise**
We have primary cultures and mesoangioblast stem cell lines established from muscle biopsies and dorsal aorta and at different post-natal ages of the animal disease models, including mice, rat and dog. An established cell bank of several human mesoangioblast clones is also available. Biological assays: cell survival, proliferation, self-renewal, multipotency and cell migration. Cell transduction: lentiviral vectors (LV) expressing reporter genes (i.e., green fluorescent protein, β-galactosidase) and/or therapeutic genes such as alpha and beta- sarcoglycans; mini- microdystrophin are also available. Cell delivery: intra femoral artery, intra tail vein and intra-muscular injection. (see next page)

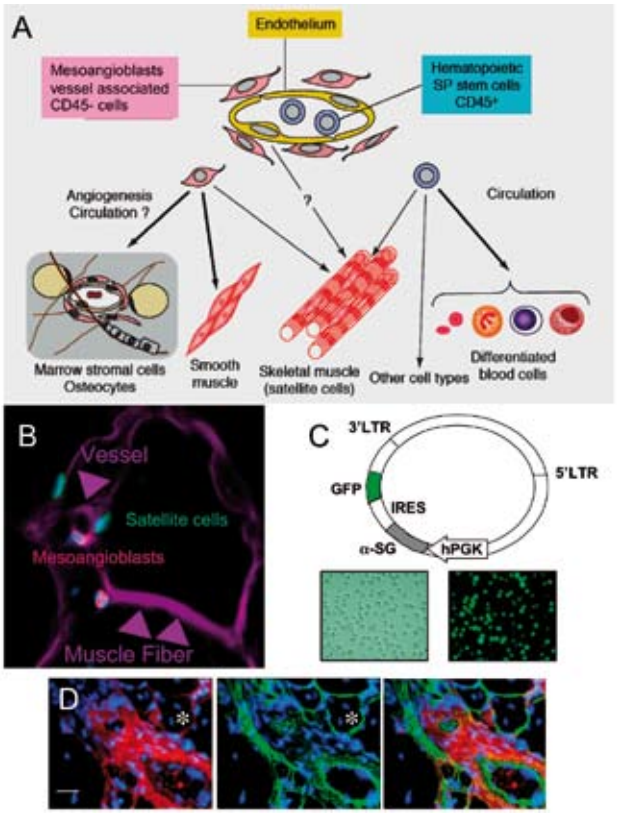


Figure A. Two different progenitors with myogenic potential. The diagram summarises the possible anatomical origin of CD45C hematopoietic (SP) stem cells and of CD45-vessel-associated progenitors (CD45K). SP cells (pale blue) primarily differentiate into blood cells, but might be recruited via the circulatory system to other tissues, including skeletal muscle. Alternatively, CD45K vessel-associated progenitors (pink) are ill-defined, probably heterogeneous cells that primarily form pericytes, vessel smooth muscle layer and bone marrow stromal cells. They might undergo skeletal myogenic differentiation, probably during the angiogenic process that accompanies muscle regeneration. Endothelial cells (yellow) might also undergo skeletal myogenesis during regeneration as they do during embryogenesis.

Figure B. Immunofluorescence of normal human muscle stained with antibodies against M-cadherin recognizing satellite cells (green arrows), laminin (cyan color), and ALP (red color) recognizing pericytes (red arrows), nuclei are stained blue with DAPI.

Figure C. Lentiviral vector construct, carrying the GFP reporter under the control of human PGK promoter (hPGK); in the left panel phase contrast of dystrophic mesoangioblasts infected with the lentiviruses and expressing GFP reporter gene (right panel).

Figure D. Double staining with anti laminin (green) or alpha-SG (red); nuclei in blue (hoechst); several cells expressing alpha-SG are showed after two weeks of being transplanted to the femoral artery; *= regenerating fibers express alpha SG, in the merged panel; bar=50μ.

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Tom Taghon was born in Belgium in 1975. He obtained an MS in Biotechnology in 1997 from Ghent University and completed his PhD studies in Medical Sciences in the lab of Prof. Dr. Georges Leclercq and Prof. Dr. Jean Plum at Ghent University Hospital in 2002. For his postdoctoral work, Tom joined the lab of Prof. Dr. Ellen Rothenberg at the California Institute of Technology in Pasadena, California, where he characterised the molecular events that control the early stages of T cell development in mice. After three years, Tom came back to Belgium, joining his previous lab at Ghent University Hospital, headed by Prof. Dr. Jean Plum.

## Characterisation of molecular pathways that drive human T cell development

The immune system protects the body against invading pathogens, such as bacteria and viruses, as well as against tumor cells. It has the unique property of being able to distinguish malignant and foreign structures from the body's own cells and tissues. One of the critical white blood cells that plays a central role in the immune system are T cells. Like all blood cells, T cells are derived from blood forming stem cells that reside in the bone marrow. But while the bone marrow is also the environment where most blood cells mature, T cells, because of their specific requirements, develop in a unique environment which is called the thymus. In this organ, the cells are guided through their maturation process via well-defined developmental stages that are controlled by various environmental inputs.

In a number of clinical cases, for example, after myelo-ablative therapy and prior to stem cell transplantation or HIV infection, patients have reduced T cell numbers, making them highly susceptible to common infections. Providing such patients with functional T cells would help to strengthen their immune systems, causing a new therapeutic breakthrough. Furthermore, if one could manipulate these T cells in such a manner so that they would specifically recognize tumor cells, this would open up new avenues for specific immunetherapy with multiple applications.

At present, insufficient knowledge is available regarding the differentiation of human stem cells into T cells in order to be able to efficiently generate such immune-competent cells. Recent technical advances, however, make it possible to pursue this goal since a novel in vitro culture system was developed that supports the early stages of human T cell development. In this project, the researchers wish to identify the critical components that are required for T cell development and use these to manipulate the culture system for the generation of functional human T cells.

The Notch signalling pathway is the major driving force for T cell development. It is a highly conserved pathway, comprised of four Notch receptors that can interact with five different ligands and multiple other components that can further modulate the signals that are induced upon receptor-ligand interaction. Based on the essential role for Notch signalling in T cell development, a novel in vitro culture system was developed that also supports human T cell development. In this system, bone marrow stromal cells are genetically manipulated to express the Notch ligand Delta-like-1. Because of this artificial expression, the development of T cells is not optimal, as the precise regulation that normally occurs in vivo is missing. Therefore, it is necessary to carefully characterise the requirements for Notch signalling during human T cell development and use this information to manipulate the in vitro culture system to increase the efficiency of T cell generation. For certain purposes, pharmacological agents are available that alter the Notch pathway. Since uncontrolled Notch signalling is also the major cause of acute T cell leukaemia, knowledge on the normal function of the Notch pathway will provide essential

insights into molecular mechanisms that cause oncogenesis, possibly providing novel therapeutic targets.

Because of its evolutionary conservation, Notch signalling is involved in multiple developmental systems, such as the development of the brain, heart, kidney and other organs. Thus, the decision of a stem cell to become a tissue-specific cell type must also depend on other molecular pathways that define this specificity. For T cell development, some of these pathways involve specific growth factors, Wnt and T cell receptor signalling. Thus, these pathways must very precisely integrate with Notch signalling to efficiently generate T cells. Therefore, the project will investigate how the addition of these signalling events at specific stages of human T cell development will further influence their developmental progression, in conjunction with Notch signalling.

T cell development is initiated when precursor cells from the bone marrow migrate towards the thymus. However, the precursor cells that are responsible for T cell development are poorly characterised, despite being of considerable therapeutic interest. When provided in sufficient numbers, their presence during stem cell transplantations should normally significantly enhance T cell generation in these patients. Furthermore, progenitor cells from adults seem to lose T cell potential compared to those at younger age. Therefore, the aim is also to characterise these early T cell progenitors so that we can examine how to expand this population for therapeutic use.

Overall, the project aims at understanding the molecular mechanisms that control human T cell development so that we can use this information to efficiently generate human T cells in an in vitro culture system.

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Geert van Loo was born in 1971 in Ghent, Belgium. He obtained his Master's in Bioengineering and in Chemistry in 1994, a Master's in Biotechnology in 1996, and a PhD in Biotechnology in 2002, in the Department of Molecular Biology at Ghent University and the Department of Molecular Biomedical research at the VIB.

During his PhD, which he completed in Dr. Peter Vandenabeele's research group, Geert focussed on signalling pathways and molecular mechanisms leading to apoptotic and necrotic cell death, and the involvement of mitochondria in both processes. After his PhD, he moved to Italy for a postdoc at the European Molecular Biology Laboratory (EMBL), Mouse Biology Unit, in the research group of Dr. Manolis Pasparakis, for which he was granted a Marie Curie intra-European fellowship. During this postdoc he used "state of the art" gene targeting technology to genetically dissect in vivo the function of signalling pathways controlling cell survival and death. The main focus of his research concerned the study of NF-κB and apoptotic signalling in central nervous system (CNS) inflammation, with particular emphasis on the autoimmune inflammatory disease multiple sclerosis (MS). In 2006, Geert returned to Ghent University and VIB where he joined the research group of Dr. Rudi Beyaert. His current research is also focussed on in vivo mechanisms regulating inflammation and degeneration using genetically modified mice in combination with mouse models of human diseases. His research was/is financed by a FWO postdoctoral fellowship, a Marie Curie European Reintegration Grant, a grant from the Charcot Foundation and an FWO Odysseus Grant.

### NF - κB inhibitors

Past and present research projects deal with the role of NF-κB in cell survival and cell death in the pathogenesis of inflammatory and degenerative diseases. NF-κB (nuclear factor-kappa B) is a protein complex acting as a transcription factor. NF-κB is found in almost all animal cell types and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, ultraviolet irradiation, bacterial or viral antigens. NF-κB plays a key role in regulating the immune response to infection. Consistent with this role, incorrect regulation of NF-κB has been linked to cancer, inflammatory and autoimmune diseases, septic shock, viral infection, and improper immune development. The NF-κB family is undoubtedly the most-studied collection of eukaryotic transcription factors and although monumental steps in our understanding of the regulation of its activation were made during the last years, we still have little understanding of the in vivo regulation and dynamics of this pathway. As NF-κB activation is so crucial in many biological cellular processes, it is not surprising that a tight regulation of the pathway and the genes induced is an absolute requirement. For this, cells employ a multilayered control system to keep immunity and inflammation in check, and the combined action of different positive and negative regulators helps to fine-tune the immune response.

Because of the essential role of NF-κB signalling and regulation in physiology and disease pathology, many research groups are involved in this study. The research strategy involves the in vivo study of important signalling intermediates through genetic targeting in the mouse. This methodology became much more accessible thanks to the recent completion of the human and mouse genome sequencing projects and provides unique possibilities for the in vivo genetic analysis of pathways with critical functions in normal physiology and in disease pathology.

One critical brake on NF-κB activation is the zinc-finger protein A20, which has been characterised as a dual inhibitor of both NF-κB activation and apoptosis. The critical function of A20 in NF-κB activation was discovered some years ago through the generation of mice lacking A20 in all of the cells in their bodies. A20-deficient mice die prematurely. These mice develop severe inflammation and cachexia,

and are hypersensitive to bacterial products and cytokines, demonstrating the essential role of A20 in controlling NF-κB-dependent inflammation. Very recent studies, mainly using high-throughput screening methods to identify mutations in patients suffering from specific inflammatory diseases, identified A20 as a susceptibility gene for Crohn's disease, inflammatory bowel disease (IBD) and arthritis. As such, studies using mice genetically modified in A20, in combination with well-characterised mouse models for human diseases. are a unique tool for identifing the critical function of A20 in these diseases. Our Odysseus project aims to contribute to this study by generating mice which are deficient in A20 in a conditional way, viz. mice which allow the specific deletion of A20 in a specific tissue or in an inducible way. This conditional approach is essential since the complete (conventional) A20 knockout mouse, as described above, is not viable as it dies shortly after birth. These conditional knockout mice are now used in different mouse models for human diseases, such as in models for rheumatoid arthritis, asthma, multiple sclerosis and IBD. A second important regulatory protein, controlling NF-κB activation and apoptosis, is 'A20-binding inhibitor of NF-κB' (ABIN). It has been proposed that ABINs may function as downstream effectors of A20, switching off NF-κB activation. To resolve the issue of whether ABINs are physiological regulators of NF-κB in vivo, we are generating ABIN-1 conditional knockout mice and studing the role of ABIN-1 in normal tissue physiology and in the context of a pathological condition.

The involvement of NF-κB in inflammation and disease certainly establishes NF-κB signalling molecules as targets for therapeutics. Indeed, many common synthetic (e.g., aspirin), and traditional (e.g., green tea, turmeric) remedies target, at least in part, the NF-κB signalling pathway, but despite the substantial progress made during the last years in the study of NF-κB and disease pathology, there is still great need for specific and safe therapeutics. Important potential targets in the development of such drugs interfere with the intracellular signal transduction pathways which are activated by inflammatory cytokines, viral and bacterial products and oxidative and chemical stress. Many companies are making great efforts to develop such NF-κB-inhibitors. However, as NF-κB plays a central role in immunity, one fears that a total blockage of NF-κB would lead to substantial side effects. As such, it is important to identify stimulus- and cell-specific inhibitors of the NF-κB pathway. A20 and ABIN proteins, for example, are upstream regulators in the pathway and are thought to be more specific therapeutic targets for interfering with NF-κB signalling. It is likely that our knowledge of the molecular details of these pathways will enable us to develop more specific and potent inhibitors of NF-κB signalling.
The above-described genetically modified mice, depending on the phenotype in specific disease models, can also be useful as new model systems for specific inflammatory and degenerative diseases (for example, in models of multiple sclerosis, atherosclerosis, rheumatoid arthritis, etc.) and for the study of cancer. Moreover, new therapeutics can be tested in such model systems in collaboration with pharmaceutical companies.

To conclude: the study of the in vivo involvement of NF-κB- and apoptosis-signalling molecules that are central to our research projects, will be of considerable interest for the identification of the specific role of these factors and in the design and development of therapeutic drugs needed for the treatment of many important inflammatory and degenerative pathologies. As such, these projects are related to modern medical and societal issues.

## CATHERINE VERFAILLIE (I)

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Catherine Verfaillie received her degree in Medicine from the K.U.Leuven in 1982. She trained as an internist/hematologist at the K.U.Leuven between 1982 and 1987 and then she went to the U. of Minnesota in 1987 for a post-doctoral fellowship. After completing her post-doctoroal fellowship, she was appointed, consecutively, instructor, assistant professor, associate professor and finally full Professor of Medicine in 1998. In 2001, she became the first director of the University of Minnesota's Stem Cell Institute. In 2006, she accepted the position of director of the Interdepartementaal Stamcel Instituut at the K.U.Leuven. She has a longstanding career working in stem cell biology, initially focussing on normal hematopoietic stem cells and leukemic stem cells. Since 1997 she has also focussed extensively on more pluripotent stem cells. In 2002, group described a novel cell population culture from rodent and human bone marrow samples with greater expansion and differentiation potency, named multipotent adult progenitor cells or MAPC. The Verfaillie lab at Leuven is currently focussed on understanding what regulates self-renewal and the differentiation of hematopoietic and adult as well as embryonic pluripotent stem cells, and testing the possible use of stem cell-based and stem cell-derived therapies in animal models of hematopoietic, vascular, liver and metabolic (diabetes) disorders.

## Stem cell research

Stem cells are cells that can undergo self-renewing cell divisions, i.e., a stem cell can generate at least one daughter cell that is identical to the initial cells. The second characteristic of stem cells is that they can generate differentiated or specialised progeny. In most instances a stem cell gives rise to multiple types of differentiated progeny. Notable exceptions are spermatogonial stem cells that give rise to only one type of daughter cells, namely spermatogonia, and corneal epithelial stem cells. A final characteristic of stem cells is that they can functionally repopulate a tissue in vivo.

Stem cells are defined based upon the array of cells that can be generated from them. The fertilised egg is totipotent as these cells can give rise to all cells from the embryo as well as extraembryonic cells. Cells in the inner cell mass of the blastocyst are pluripotent as the cells can give rise to cells of the embryo proper but not extraembryonic cells. Stem cells found in postnatal tissues, such as bone marrow, umbilical cord blood, the brain and almost all organs, are termed multipotent as they give rise to the multitude of cells present in a tissue.

The quintessential stem cell is the embryonic stem cell. Like cells in the inner cell mass wherefrom they are derived, embryonic stem cells are pluripotent as they have the ability to differentiate into all cells of the mouse/human. The second defining characteristic of embryonic stem cells is their ability to proliferate without obvious signs of aging. Due to their ability to generate all cell types of the embryo, embryonic stem cells can be considered the ultimate cell population treating degenerative and genetically acquired diseases.

By contrast, stem cells found in fetal and postnatal tissues have less self-renewal potential and more restricted differentiation potential compared with embryonic stem cells. During development from a fertilised egg to a mouse or human, pluripotent stem cells are specified sequentially to ultimately be specified to one of the 220 cells of the mouse/human.

## Hematopoietic stem cell expansion

The best characterised adult stem cell, and the only one currently and routinely used in the clinical setting, is the blood (hematopoietic) stem cell. Existence of the hematopoietic stem cell was first demonstrated more than 50 years ago. Blood stem cells can be harvested from bone marrow and also from peripheral blood, following treatment of the donor with a blood growth factor, and in umbilical

cord blood. Aside from the inherent greater potency of umbilical cord blood stem cells, the immune cells present in cord blood are naive, and cause less graft versus host disease, making cord blood stem cells perhaps the best source of cells for allogeneic hematopoietic cell transplantation. One impediment for more broad based use of umbilical cord blood stem cells in adult recipients is the fixed, relatively limited number of stem cells that can be collected.

Therefore, at the Stamcelinstituut, the group of Dr. Verfaillie together with members of the Division of Hematology at the K.U.Leuven, the University of Antwerp, and VIB, is searching for methods that would allow expansion of blood stem cells such that sufficient cord blood stem cells could be generated to graft into an adult patient. These studies focus on the effect of proteins and other molecules, produced by cells harvested from tissues wherein blood stem cells reside at different stages of development, on blood stem cell expansion. In addition, we have evaluated the genes expressed in human blood stem cells, tested their possible role in blood production of the zebrafish as a model-organism, and are now testing whether manipulating the expression of these genes in mouse and human blood stem cells will result in stem cell expansion.

## "Pluripotent stem cells"

Stem cells can also be found in many other tissues/organs. As discussed above, these are multipotent, i.e., they generate cells from the tissue to which they belong, but not cells from other tissues, and they undergo senescence after many cell divisions. Since the 1990s however, a large series of studies have since suggested that multipotent stem cells may, under certain circumstances, have more pluripotent characteristics.

Now in one very large series of studies investigators have demonstrated cells harvested from bone marrow, or other tissues, can acquire features of cells from totally unrelated tissues such as from the liver, lung or brain upon transplantation in a diseased animal. This field has been designated as "stem cell plasticity". The extent of such phenomena, and the underlying mechanisms are still unclear. However, the efficiency with which one stem cell appears to acquire the phenotype of a tissue cell different from the tissue of origin, whether via fusion or direct, is limited; and it remains to be determined if this would have clinical relevance.

A second series of observations revolves around the apparent greater potency of cells from cultures of post-embryonic tissues. In 2002, our group described the isolation of cells with near pluripotent features from murine and rat bone marrow. These cells were termed multipotent adult progenitor cells or MAPCells, and were characterised by the ability to expand the cells extensively without obvious senescence and differentiation in vitro to cells of the three germ layers (mesoderm, ectoderm and endoderm). Since the description of MAPCells, many other similar cell populations have been described, derived from marrow, umbilical cord blood, liver, cardiac tissue and amniotic fluid (USSC, BSSC, MASC, AFS, VSEL, pre-MSC cells, among others). All these populations appear to have the ability to differentiate into cells of tissues different from the tissue of origin and can be expanded extensively, features thought to be present only in embryonic stem cells. It should also be noted that the majority of the cell lines, generated express some of the key genes (transcription factors) thought to be responsible for the pluripotent nature of embryonic stem cells, specifically the POU-factor POU5F1 or OCT4, and for some of the cell lines also NANOG and SOX2. We recently showed that for MAPC, they also express additional genes relatively specifically expressed in embryonic stem cells and known to play a role in the pluripotency of embryonic stem cells, including SALL4 and TBX3, among others. However, despite the expression of some of the genes known to be responsible for embryonic stem cells pluripotency none of the cell populations described above have the same potential as embryonic stem cells.

Almost all the cell populations described above were derived from cultured cells from somatic or germline origin. Hence, it is possible that the acquisition of greater potency occurs via the culture method, we believe in specific subpopulations of somatic cells. That induction of greater potency is possible follows from a number of studies. "Dolly", generated from a reprogrammed skin cell, was one of the first examples. Several recent studies have demonstrated that mere transduction of four transcription factors, OCT4, SOX2, KLF4 and c-MYC can reprogram mouse and human fibroblasts to an embryonic stem cell state. The latter cells are termed induced pluripotent stem cells or iPS. It should be noted that MAPCells, described by us, also express KLF4 and nMYC at levels found in embryonic stem cells, or iPS. Obviously the ability to generate from the tissue of an adult, cells with many (MAPcells) or most (iPS cells) features of embryonic stem cells, is a remarkable biological feat, and may make generations of patient-specific stem cells possible without the need for therapeutic cloning.

Within the Stamcelinstituut the following areas of study are ongoing using (more) pluripotent stem cells:

1. Studies aimed at understanding the mechanism(s) underlying the MAPCell phenotype: do the cells exist in vivo, or are they created, like iPS cells? If the latter, what is the mechanism underlying the generation of MAPcells, and once we understand these mechanisms, can the induction be increased? If the cells exist and are not a culture-induced phenomenon, where are they located in the body, and can we activate their functions in vivo?
2. Studies aimed at inducing tissue specific differentiation of MAPCells, iPS cells and embryonic stem cells.
   - In collaboration with the department of neurology at the K.U.Leuven, MOZAIEK (imaging consortium) at K.U.Leuven, and the Universities of Antwerp, Ghent and Hasselt, we are testing whether MAPCells, iPS cells or embryonic stem cells can be differentiated towards brain or spinal cord stem cells and neurons; whether these cells can be grafted in the brain or spinal cord in the contexts of stroke, spinal cord injury and other neural disorders. Using different types of imaging procedures including MRI, CT, PET and BLI, we are following the fate of the cells after they have been grafted into an animal, and evaluating the effect of the grafted cells on the cells in the host tissues.
   - In collaboration with the division of Endocrinology at the K.U.Leuven and the Diabetes Research Center at the VUB, we are testing whether MAPCells, iPS cells or embryonic stem cells can be induced to differentiate towards functional insulin-producing beta cells that reverse diabetes in animal models.
   - In collaboration with the division of Hepatology and Pathology at the K.U.Leuven, we are testing whether MAPCells, iPS cells or embryonic stem cells can be induced to differentiate towards functional liver cells that can cure animals with liver disease. In addition, we are testing whether such stem cell-derived liver cells would be suitable for toxicity studies in the context of developing new drugs.
   - In collaboration with the division of Rheumatology at the K.U.Leuven, we are testing whether MAPCells and other stem cells such as bone- or joint-derived mesenchymal stem cells, can be induced to differentiate towards bone tissue (and cartilage tissue) that could then be used to treat patients with non-healing fractures.
   - In collaboration with the division of Cardiology, the Centrum voor Molecular and Vascular Biology at the K.U.Leuven, and VIB, we are testing whether MAPCells and other stem cells such as mesenchymal stem cells, or heart-derived stem cells can be used to regenerate heart tissue, which could then be applied in patients with heart infarcts. In addition, we are testing whether MAPCells can generate the necessary cells for producing blood vessels (endothelium and smooth muscle), to be used in patients with blocked arteries, problems with the lymphatic drainage system, or even for generating blood vessels using bioreactors.
   - In collaboration with Dr Sampaolesi, K.U.Leuven, who was recently recruited Odysseus funds, we are testing whether MAPCells might be a good source of cells for the treatment of muscular diseases, specifically muscular dystrophy.

3. In collaboration with the Division of Experimental Transplantation and Division of Clinical Immunology, studies are being done that are aimed at testing the immunological consequences of transplanting stem cells or their progeny in vivo, and methods to curtail cell rejection are being developed.

4. In collaboration with the Department of Human Genetics, we plan to develop human iPS lines from patients with genetic disorders to use as tools for studying different disorders, including genetic blood disorders and genetic brain disorders.

## KEVIN VERSTREPEN (II)

*Bena Chan, Bianca Calderon, Scott Smukalla, Kevin Verstrepen, Ted Pak, Marcelo Vinces, Chris Brown, Matthieu Legendre, Chen Yan. Not in the picture, but also part of the group: Marina Caldara, Aaron New.*

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Kevin Verstrepen studied biological engineering at the Catholic K.U.Leuven. During his studies, Verstrepen volunteered as an intern in the REGA institute, where he took his first, shaky steps in scientific research under the skilful (and patient) guidance of Guy Froyen. For his MS thesis, Verstrepen joined Isak Pretorius' group at Stellenbosch University, South Africa. Here, Verstrepen shifted from human cell lines to the model eukaryote and biotechnology workhorse Saccharomyces cerevisiae, the common baker's and brewer's yeast. Verstrepen's research focussed on the genetic mechanisms underlying the clumping of yeast cells. Realising just how much fun it is to combine fundamental and applied research, Verstrepen continued in the same vein and started doctoral research as a research assistant of the Research Foundation - Flanders (FWO) under the guidance of Freddy Delvaux at K.U.Leuven. Here, Verstrepen characterised yeast genes involved in flavor formation during fermentation. After obtaining his PhD, Verstrepen was awarded a BAEF fellowship to join the lab of genetics pioneer Gerald Fink at the Massachusetts Institute of Technology (MIT) in Cambridge, USA. Revisiting the topic of his MSc thesis, Verstrepen discovered that the genes responsible for flocculation contain arrays of highly unstable repeats in their DNA sequence. After spending two years at MIT, Verstrepen joined Harvard University where he now heads a multinational team of researchers and students dedicated to investigating unstable genetic phenomena. In 2007, Verstrepen was promoted to lecturer and started teaching a course on industrial fermentation and genetics to Harvard freshmen. Verstrepen is now transferring his team back to his Alma Mater in Leuven, where he will continue his research with financial support from the Odysseus programme.

### Systems biology… of yeast cells?

Verstrepen and his team use a combination of mathematics, informatics, engineering and biological experiments to study how living cells work. This combination of different disciplines to understand and model biological processes is called "systems biology". Their research revolves mainly around how heritable information is stored, processed, interpreted and changed. While the research is fundamental and aimed at improving our understanding of basic genetics, it also has applications in various fields, ranging from genetic improvement of microbes for food production to generating insight into pathogens and human genetic diseases such as cancer and Huntington's disease.

The common brewer's yeast Saccharomyces cerevisiae is used as a model system. This single-cell organism shares many properties with human cells, but is much easier to manipulate and investigate. In fact, much of today's genetic, medical and cellular research is carried out in yeast cells. Yeast cells have provided basic insight into various diseases and processes, including providing insight into the mechanisms and principles of cells, cancer, Parkinson's and even Alzheimer's disease. Moreover, apart from being a good model for human cells, yeast cells are important for several industrial applications, including food production (bread, beer, wine), bio-ethanol and several of today's most important drugs and vaccines.

### Studying "evolvability"

Currently, the group mainly focusses on one basic biological question: Why and how do some heritable biological characteristics and traits change more rapidly than others?

It is well known that living organisms can change and evolve. These changes are often very slow and take many hundreds or even thousands of generations. However, some properties of some living organisms change much more rapidly. When they infect the body, some pathogenic

microbes are able to constantly change their outer cell surface. This enables them to elude the immune system, which is still mounting an attack to the previous outer layer. The proteins that coat these pathogens seem to change rapidly between a seemingly endless reservoir of different variants. Yet, these small microbes simply do not have enough DNA to carry enough information for so many different proteins. Similarly, in just a few thousand years, humans were able to breed very different dogs, ranging from poodles to shepherds, from dachshunds to Afghan hounds. Yet, similar breeding efforts with cats or cattle did not result in a similar wide variety in morphology. Is there something that makes the dog shape easier to change? Less obvious, but perhaps even more importantly, some proteins in human cells have acquired very different functions throughout evolution, while others remained virtually unchanged. Is there something that makes these proteins change more rapidly?

There are many more examples of biological traits that evolve more quickly than others. The research focusses on three specific examples of such highly unstable, "evolvable" phenotypes. These examples are used to understand why certain traits are more unstable, which mechanisms underlie the variability and how we can employ these new insights for practical applications.

## Three specific topics

To understand these intriguing questions, three related specific topics are taken under consideration.

**1. Genes "at the edge".** Telomeres (i.e., the end of chromosomes) are some of the most dynamic and unstable regions in genomes. Genes located near the telomeres are subjected to unusually high recombination frequencies, as well as chromatin-dependent epigenetic effects. A S. cerevisiae gene family located near the telomeres is being studied to investigate how their unique location allows the genes to evolve much quicker and benefit from both genetic and epigenetic inheritance for coordinating their regulation. Such mechanisms may allow parent cells to pass on information about recent growth conditions to their progeny. Stochastic silencing and desilencing of the telomeric genes allow some cells to "escape" this epigenetic regulation and explore alternative lifestyles. Moreover, DNA itself also changes more rapidly near telomeres, allowing the swift development of new genes with novel functions.

**2. The swift evolution of yeast "stickiness".** Yeast cells show an amazing capacity to adhere to various abiotic surfaces as well as other living cells. However, closely related yeast strains vary widely in their adherence phenotypes, indicating that this trait evolves very quickly. The research shows that this swift evolution is explained by the fact that the genes underlying adherence contain internal tandem repeat sequences. These repeats are unstable and generate frequent mutation events, leading to altered adherence phenotypes. This might allow pathogens to adhere to novel materials used in today's medical devices. Moreover, since the variable adhesion proteins are located at the cell surface, the mechanism may also allow cells to elude the host's immune system.

**3. "Junk" DNA as an accelerator of genetic change.** About 50% of the human genome consists of so-called "repetitive DNA", stretches of DNA sequence that are repeated multiple times within the genome. These repeats are traditionally believed to be useless "junk" DNA. However, the research shows that these repeat regions are highly variable, with the numbers of repeated units changing at exceptionally high frequencies (at least 100-fold higher than normal point mutation rates). Some of these changes affect the function or activity of nearby genes or regulatory loci. As such, tandem repeats may represent a common but much ignored mechanism of genetic change, besides the much more widely studied single nucleotide polymorphisms (SNPs) and copy number variations (CNVs). Using the S. cerevisiae genome as a model, we use comparative genomics and genetic engineering to explore the physiological role of all tandem repeats in the yeast genome. In addition, through various collaborations, we also explore the importance of repeats in other organisms, including pathogens, plants and humans.

Through various collaborations, the team is now also starting to look at different organisms, ranging from pathogenic microbes to plants and humans. First, a number of researchers use our bioinformatics analyses to study repeats in various organisms. Pardis Sabeti (Harvard) and Manuel Llinas (Yale) work with them to study the role of variable repeats in the malaria pathogen Plasmodium falciparum. Christine Queitsch (Washington University) studies repeats in the model plant Arabidposis thaliana. And finally, Jean-Paul Latgé (Institute Pasteur), Carol Munro (Aberdeen University), Patrick Van Dijck (K.U.Leuven), Chris Michiels (K.U.Leuven) and Jozef Anné (K.U.Leuven) study repeats in microbial pathogens.

Apart from these three current fundamental topics, the team also focusses on possible applications of their work. Their results allow us to design and develop yeast strains that are better suited for industrial use (e.g., beer brewing or bioethanol production), or to help understand and fight human diseases.

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Professor Johan W.S. Vlaeyen is Professor of Behavioural Medicine at the K.U.Leuven, Belgium and also holds a Chair at the Maastricht University, Netherlands. In 2007, he obtained an honourary doctorate from the University of Orebro, Sweden for his scientific contributions in the area of the psychology of pain.

Body tissue damage due to injury most often leads to pain and suffering. However, there are many instances in which the association between injury and pain is weak. Sometimes there is pain without a somatic origin, and tissue damage without pain. There is accumulating evidence that pain is an ambiguous stimulus that needs to be disambiguated by contextual information. For example, numerous studies have shown that fear of pain is more disabling than the pain itself. In other words, the same nociceptive stimulus can have different responses depending on the threat value of the context in which it occurs. Johan Vlaeyen's main interests are the contextual influences on nociceptive information, and how these can produce or worsen chronic disabling pain conditions.

His experimental work has highlighted the role of the threat value of pain in the engagement of defensive responses such as increased physiological arousal, hypervigilance and escape/avoidance behaviours. One of the questions that he currently addresses is how anxiety influences pain, and how primary defense responses can be inhibited by higher goals. He and his team are currently examining the paradoxical situation where a negative mood leads to persistence rather than avoidance behaviour, and the behavioural responses of individuals who are faced with pain-related goal conflicts.

Johan Vlaeyen and his team have also developed exposure-based treatments for fear-reduction and they have utilised randomised controlled trials as well as replicated single-case experimental designs to evaluate the effects of behavioural interventions for patients with chronic pain.

Johan Vlaeyen has published more than 130 papers in peer-reviewed international journals. He also serves on the editorial boards of the journal Pain, the European Journal of Pain, the Clinical Journal of Pain, and Cognitive Behaviour Therapy. He co-edited the book "Understanding and Treating Fear of Pain" published by Oxford University Press. He received the Pain Award of the Dutch Chapter of the International Association for the Study of Pain (IASP). He is currently a member of the scientific committee of the IASP.

## Odysseus Psychology of Pain and Disability Research Programme

**Acute and chronic pain**
Pain is a universal experience that affects human beings across their life span, and serves an important protective function. Acute pain urges us to interrupt ongoing activity, to escape the source of threat to the body and to withdraw for healing to take place. Chronic pain, however, persists beyond the healing time. It ceases to serve a protective function, and can severely disrupt daily life activities, thereby prolonging suffering and disability. As there is no immediate and definitive solution available for the pain problem, it also is a vexing frustration for health care professionals and a challenge for modern health care, too.

**Fear of pain**
Increasing evidence has indicated the important role of negative emotions in the individual's experience and response to pain. Initially, researchers examined the role of depressive mood as a consequence of persistent pain, but more recently, the focus of scientific attention has shifted to the reciprocal relationship between negative emotions and pain, and to the relationship between fear and pain,

in particular. A major breakthrough was the introduction of the Fear Avoidance (FA) model of chronic pain, which presents a plausible pathway by which people get caught in a downward spiral of increasing avoidance, disability and pain. In essence, if a person catastrophically (mis)interprets pain (for example: "the pain in my back means that I am in danger of becoming paralysed"), fear of pain develops and initiates al least two forms of so-called safety behaviours: escape/avoidance behaviour and selective attention to pain. Paradoxically, rather than reducing the pain problem, in the long term, safety behaviours prevent fear from diminishing and contribute to deconditioning and disability, which in turn, reinforce further pain experiences, negative expectancies and avoidance (Vlaeyen & Linton, 2000). In sum, pain-related fear has been shown to be associated with (1) increased pain reports (2) attentional interference and difficulty to disengage from pain (3) impaired physical performance and increased self-reported disability (4) future disability and weak health status. In addition, the reduction of pain-related fear by cognitive-behavioural treatment is associated with improved functioning, increased physical activity and decreased pain severity.

Although research evidence supporting the FA model is accumulating, there are unresolved issues that merit further scientific attention:

**First,** most of the research on the FA-model has been based on the assumption that fear responses are elicited by discrete conditioned stimuli, such as particular movements and work-related activities. In some cases of chronic pain, however, no such stimuli can be recognized by the individual; pain and associated pain-related fear is unpredictable, and appears to come from out of the blue. Rather than cued pain-related fear, more generalized pain anxiety is at stake then.

**Second,** the FA-model, in its current application, doesn't tell us about the social dimension of the pain. Social cueing effects may enhance or inhibit pain expression. Inhibition of expressive behaviour is known to have repercussions, and usually leads to a rebound of pain later on. The social environment may also enhance or inhibit the threat value of pain via contextual safety and danger signals.

**Third,** pain-related fear cannot be approached without the broader context of other motives and threats. So far, there is a paucity in the literature regarding the effects and resolution of conflicting goals. Escaping from painful situations can be considered a primary (avoidance) goal that may compete with higher order goals such as reward seeking (avoidance-approach conflict) and the prevention of social rejection (avoidance-avoidance conflict).

## Research theme 1: Contextual and interoceptive pain-related fear

The development of pain-related fear can best be understood in terms of learning theory. When an association between a previously neutral but relevant stimuli (e.g., a movement) and pain as an unconditioned stimulus (UCS) is learned, the neutral stimulus becomes a conditioned stimulus (CS) eliciting a conditioned response (CR) that includes physiological arousal, escape/avoidance behaviour and selective attention towards the source of threat. Optimal learning requires the detection of both the presence (CS+) and the absence (CS-) of these co-occurrences. When the individual is exposed to the CS+ in the absence of the UCS, extinction of pain-related fear takes place. In the last decade, pain researchers have mainly focussed on proprioceptively cued pain-related fear, such as fear of movement or "kinesiophobia". This line of research has therapeutically been quite fruitful, as exposure to the feared movements has shown to decrease fear and associated disability levels. However, modern learning theory has recognized that the origins of pathological behaviour are much more complex, involving both individual differences and contextual factors. In this research theme, we will examine two elaborations of conditioned pain-related fear in which contextual factors play a key role; "contextual" fear and "interoceptive" fear.

The FA-model does not explicitly make a distinction between "fear" and "anxiety". While fear is an immediate response to present threat, anxiety is a future-oriented emotion characterised by apprehensive anticipation of potential threat. The idea is that both kinds of fear result from a different acquisition process. A key distinguishing factor is the unpredictability of the UCS. In the absence of discrete cues indicating when, for how long, or how intensely the aversive event will occur, fear will be conditioned to the background context, resulting in contextual fear. Cue-specific, predictable fear shares the characteristics of a "phobia", while contextual fear is more analog to "generalized anxiety".

Interoceptive fear occurs when the conditioned stimulus is not an external discrete cue but a cue within the body, such as a muscle spasm, bowel movements, etc. To our knowledge, interoceptive conditioning has never been examined in relation to pain-related fear. The "fear of pain" construct is probably more relevant in cases of chronic pain where the musculoskeletal system is less involved, such as facial, abdominal and pelvic pain. Beside having theoreti-

cal importance, the findings may also lead to different therapeutic interventions. For example, "interoceptive exposure" has been reported as an effective treatment in patients with panic disorder, assumed to be mediated by interceptive fear conditioning.

## Research theme 2: Social threat hurts: The influence of safe and unsafe social contexts and their influence on the threat value of pain.

Although the conditioning theory has a strong appeal, it is basically supported by animal research. In humans, traumatic conditioning is neither necessary nor sufficient to explain the origins of fears and phobias, and theorists concluded that there is more than one pathway to fear. Two other (indirect) pathways have been proposed: instructional learning (or transmission of verbal information) and vicarious (or observational) conditioning. The idea that fears can be acquired by hearing or reading frightening information about some object or situation has received only weak support. Instructional learning experiences may lead to the development of mild and probably transient fears in children. However, there is stronger evidence for an observational learning pathway to the development of fears. These pathways have not yet been studied in the area of pain-related fear.

Traditionally, the role of social responses has been framed in the operant conditioning processes, and a number of studies have investigated how social responses influence overt expression of pain. These studies seem to suggest that punishing responses are associated with inhibited expression of verbal and non-verbal pain behaviour, while empathic responses increase the magnitude of pain behaviour. More recently, researchers have examined the social context in relation to emotional distress, and conceptualized pain catastrophizing is a way of eliciting empathic responses from others. From this perspective, pain expression is elicited in the presence of an observer of high pain catastrophisers only. This findings are, however, in contrast with previous investigations showing that the presence of a potential communication partner may produce expressive inhibition. Of interest, however, is that these studies have not controlled for the threat value of the painful stimulus. It is quite likely that the influence of social presence is dependent on both the experience threat value of pain and the meaning of the observer. Such a position would be in line with the idea that reciprocal influences of both the individual in pain and the observer influence behavioural responses.

Up to now, there is also no information on the effect of the threat/safety value of the observer. We hypothesize that the interaction effects between the threat value of pain and the observer are even stronger when the subject is faced with a cooperative vs. a competitive observer, or an observer who is fearful himself as compared to a non-fearful observer. We will examine the intriguing assumption that social threats "hurt". This might be particularly important in the context of work environments characterised by competition among workers, or health care setting in which health care providers induce fear by virtue of their own pain-related fears.

## Research theme 3: Pain in the face of goal conflicts.

Another type of social context that is quite relevant in chronic pain is the environment in which certain achievement goals are expected from the individual. We have recently begun to examine the psychological mechanisms that might explain the seemingly paradoxical situation that in some patients with chronic pain, task persistence rather than avoidance occurs. Although this is a neglected research area, so far, there are at least two theoretical accounts for the observation that individuals persist in task performance despite pain: the "mood-as-input" and "active avoidance learning".

The basic tenet of the Mood-as-Input model is that task persistence is a function of the interaction between mood and the stop-rule used. When individuals adopt an explicit or implicit "As-Many-As-Can (AMAC)" stop rule (they persist until satisfaction is reached in dealing with the task), negative mood will facilitate task persistence, while positive mood will inhibit task persistence. In the AMAC condition, the negative mood signals to the individual that not enough progress on the task has been made, leading to continuation of the task. Using the "Feel-Like-Discontinuing (FLDC)" stop rule, the opposite pattern is found. A negative mood here signals that continuing with the task is no longer appropriate, and therefore the subject disengages from the task. Thus, with different stop-rules, the same mood can have different motivational effects. A pertinent question is what role pain severity plays in determining the predicted stop-rule - mood interaction. In our preliminary study, we induced both mood and goals before assigning a weight lifting task to patients with fibromyalgia. The predicted relationships between goals and mood were observed only in the patients with relatively high current levels of pain. In those with lower pain levels, subjects receiving the AMAC stop-rule performed much better as compared to those receiving the FLDC stop-rule. A number of studies are planned in healthy subjects

and pain patients with Work-Related Upper Extremity Pain (WRUEP), in whom stop rules and mood are induced before they are requested to perform a task. One of the questions addressed is whether the stop-rules, and associated goal pursuit, occur without conscious awareness. Additionally, early studies showed that if goal-directed behaviour ceases, leaving a task unfinished, a state of psychological tension exists that keeps the goal and goal-related thoughts activated in the memory. Analogue to these findings, we also will test the assumption that after being interrupted by increased pain, task performance increases in individuals primed with high achievement goals.

Active avoidance occurs during fear learning when the display of certain behaviour postpones or averts the UCS when confronted with a CS. In contrast to passive avoidance learning (e.g., freezing), active avoidance learning increased the frequency and magnitude of certain behaviours. Active avoidance has been almost exclusively studied almost exclusively in animal behaviour, and there is evidence that it is associated with fear-induced conditioned analgesia. Active avoidance is performed in anticipation of threat, and therefore resistant to extinction. Translated to chronic pain, it is quite conceivable that fear of negative evaluation, of even social rejection in the workplace may instigate active avoidance learning, leading to task persistence despite pain. Whether such persistence is associated with reduced pain sensitivity is an intriguing question. If so, there might be a cost, as suppression is usually followed by increased pain sensitivity after task termination (rebound effects). To the best of our knowledge, this line of thought has never been examined systematically. In one of our previous studies, chronic low back pain patients were requested to perform a lifting task, after receiving success or failure manipulation. Of interest was that patients receiving failure feedback performed longer than those with success feedback. Although there is ample literature on active avoidance learning of fear in animals, there is a need for a confirmable paradigm that enables us to examine active avoidance and task persistence in humans.

In the daily life context, individuals with chronic pain may be faced with multiple goals and threats. A particularly stressful situation occurs in ambiguous situations in which pain-related fear coincides with other fears (e.g fear of social rejection). In such cases, one single CS may elicit opposing behavioural responses. What happens when individuals are faced with such an (active) avoidance- (passive) avoidance goal conflict? The situation may be extra pregnant as recent studies revealed that social rejection itself is associated with increased pain sensitivity. Early theorists predicted that in approach-approach conflicts, once an individual starts approaching either goal, that goal quickly becomes dominant and a choice is readily made. In contrast, in an avoidance-avoidance conflict, either response weakens once it is started, whereas its competitive goal is strengthened. Thus, movement toward either goal inhibits that movement, resulting in oscillation. This process might be responsible for the sawtooth-like pattern that is often observed in chronic pain patients' activity profiles.

## Conclusion

Task performance in patients with chronic pain occurs as the result of a dynamic interplay among current pain levels, current mood, contextual safety and threat cues, and higher order goals.

The results of the experimental studies that will be carried out in this Odysseus PPD research program should contribute to a better understanding of the impact of (chronic) pain, and will be likely to produce novel and more customized cognitive-behavioral treatment approaches for individuals suffering from chronic disabling pain conditions.

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Currently, Arjen van Witteloostuijn (1960) is Research Professor of Economics and Management at the University of Antwerp in Belgium, Professor of Institutional Economics at Utrecht University in the Netherlands and Professor of Strategy at the University of Durham in the United Kingdom. In the 1980s and 1990s, he was affiliated with the University of Groningen and University Maastricht (both in the Netherlands), and he visited New York University (in the US) and Warwick Business School (in the UK). He holds degrees in business, economics and psychology. In 1996-1998, he was Dean of the Maastricht Faculty of Economics and Business Administration. He is founder of the University Maastricht's Netherlands Institute of Business Organization and Strategy Research (NIBOR), co-establisher of the Star Numan Institute (SNI), founder of the research institute of international economics and business (SNI Research) and (former) member of the editorial board of the Academische boekengids, Academy Management Journal, Bedrijfskunde: tijdschrift voor modern management, British Journal of Management, Economisch statistische berichten, Filosofie in bedrijf, Industrial and Corporate Change, Journal of International Business Studies, M&O: tijdschrift voor organisatiekunde en sociaal beleid, Organization Studies, Strategic Organization and Tijdschrift voor bedrijfsadministratie (in 2001 renamed into Accounting). Additionally, he was/is member of the Executive Committee of the European Association for Research in Industrial Economics (EARIE), President of the Dutch-Flemish Academy of Management (NVAM), Chairman of the Board of the Council for Economic, Social and Regional Sciences (ESR) of the Dutch National Science Foundation (NWO) and member of the Economic Advisory Council of the Dutch Parliament. Apart from many (chapters in) books, and articles in Dutch dailies and journals, he has published widely in such international journals as the Academy of Management Executive, Academy of Management Journal, Academy of Management Review, Accounting, Organizations & Society, American Sociological Review, Economica, Economics of Education Review, European Journal of Political Economy, History of Political Economy, Journal of Business Ethics, Journal of Economic Behavior and Organization, Journal of Economic Psychology, Journal of International Business Studies, Journal of Management Studies, Management Science, Metroeconomica, International Journal of Industrial Organization, Organization Studies, Personality and Individual Differences, Strategic Management Journal and Weltwirtschaftliches Archiv. In 1999, he published a critical analysis of the Dutch "poldermodel": De anorexiastrategie: over de gevolgen van saneren (Amsterdam / Antwerpen: De Arbeiderspers) for which he received the Book of the Year 2000 Prize of the Dutch Society of Management Consultants (Ooa) and the Reader Prize 2000 of the Dutch Association of Consultancy Firms (Roa). On a regular basis, he is involved in consultancy and training activities for private and public organizations. His research interests range from international macroeconomics and personality psychology to industrial economics and organizational behavior. Examples of current research projects are "The Performance Effect of Organizational Change", "Trust and Team Performance", "CEO Personality, Entrepreneurial Behaviour and Organisational Excellence", "Foreign Direct Investment and International Trade", "The Ecology of Political Parties" "The Downsides of Downsizing and Flexibility", "Measuring Societal Corporate Performance", "A Game Theory of Human Resource Management" and "The Evolution of Market Structures".

## Antecedents and consequences of demographic diversity

This project deals with the antecedents and consequences of demographic diversity in the realm of teams, organisations, industries, networks and communities. Demographic diversity refers to groups of people or organisations. Both can be more or less diverse in terms of, e.g., age, gender and personality (people) or age, size and strategy (organisations). The key questions are where this extent of diversity comes from and what it implies for the behaviour and per-

formance of the social entities involved. At the team level, for instance, the metabolism of executive boards of corporate enterprises will be studied. What types of managers enter into and leave such boards, and what is the impact of this turnover and the implied (change in) demographic diversity on the organisation's strategy and performance?

At the community level, for example, the focus is on the origin and effect of a city's population diversity (age, ethnicity, religion, etc.). Why is, say, Antwerp more or less diverse than Rotterdam, and what does this imply for these cities' social cohesion and economic performance? The proposed research programme is groundbreaking because it pushes the demographic diversity of social entities to centre stage. Moreover, it is unique in its multi-method, multidisciplinary and multi-level approach. First, a theory will be developed by building models that use mathematical, logical and simulation techniques, while empirical studies will analyse novel panel datasets by applying advanced multivariate statistical tools. Second, insights from different behavioural, economic and social science disciplines will be combined and integrated, notably economics, public administration, economic geography, political science, psychology and sociology. Third, the multi-level perspective will be explored systematically, implying that interactions across different levels of analysis will be investigated. Fourth, a key aspect of the programme is the ecological angle. That is, all research will be dynamic in nature, focussing on evolutionary processes over time. In so doing, processes of entry, growth, change, decline and exit will be explored, offering ample opportunities to study the underlying chain of causality. So, the key questions are: (1) How does human and organisational demographic diversity evolve?; (2) Which are the forces behind its increase or decrease?; and (3) What are its implications for how social entities behave and perform? Since the early work of sociologists, these questions have attracted the attention of a wide array of scholars in fields as diverse as strategic management, institutional theory, and organisational ecology. Such questions are important because demographic diversity represents the dynamo of evolutionary change upon which selection operates. Demographic diversity has important implications at different levels of analysis. Diversity impinges on individuals' career opportunities, affects the innovation potential of organizations, stimulates learning at the level of the general population, and determines the adaptive capacity of teams, organisations, industries, networks and communities by setting the limit to the available alternatives. Notwithstanding its major theoretical and empirical importance, the number of studies that explicitly focus on diversity as the major variable of interest is limited. In the research programme proposed here, theories are systematically developed and tested regarding the dynamics of the antecedents and consequences of demographic diversity at different levels of analysis.

Social entities at different levels of analysis are collectives of people. Hence, people are key drivers of their behaviour and performance. However, social entities do not operate in isolation, they interact with their environment and other social entities. In management, psychology and sociology, different and separate research traditions have emerged that focus precisely on these people – behaviour – performance nexus in the context of the broader environment. Three examples may bring this point home:

1. In **management**, upper echelon studies have revealed how the behaviour and performance of top management teams (TMTs) and their organisations can, to a large extent, be explained with reference to the demographic features of TMT members, such as their educational background and tenure distribution, contingent upon environmental and competition.
2. In **psychology**, group research focusses on a wide array of issues related to the psychological drivers, such as attitudes and personalities, group behaviour and performance, as well as the psychological determinants of group composition through processes of selection and self-selection, dependent upon the characteristics of the tasks involved.
3. In **sociology**, homophily theory argues that people self-select into 'demographically similar' groups, such as private organisations and social movements, that in turn reflect specific types of behaviour and levels of performance, since human beings generally prefer to be among similar rather than dissimilar others. Such processes determine the macro-level structure of social entities at higher levels of aggregation.

Of course, the above three examples serve illustrative purposes only. In all three disciplines, other examples abound. For instance, the so-called attraction-selection-attrition (ASA) theory in social psychology claims, and provides evidence, that people with similar traits self-select into specific types of organisations. That is, field work has revealed that the organisation 'dummy' explains much within-organisation trait similarity (vis-à-vis between-organisation trait dissimilarity). For example, particular types of personalities that self-select into accountancy, newspaper or theatre organisations. Another prominent example is organisational ecology, which is a Darwinian theory of the evolution of organisations and their populations. Here, the focus is not on human demo-

graphics, but rather on its corporate counterpart. Organizations have demographic features as well, such as age and size. The survival odds of an organisation are argued to critically depend upon such demographic features.

Key to the above examples of theories and the research programme proposed here is the concept of demographic diversity. Take the examples of teams and industries, the members of a team are bound to have different demographic features. However, the extent to which this is the case varies across teams. Some teams are relatively homogeneous, with members of the same gender, of roughly the same age, from similar educational backgrounds, with shared attitudes, etc. Other teams are relatively heterogeneous, both males and females, spanning a wide variety of ages, multidisciplinary backgrounds, conflicting attitudes, and so on and so forth. From (psychological) group research, we know that this degree of diversity may well affect the teams' behaviour and performance. For instance, highly diverse teams are very creative but highly inefficient, while extremely homogeneous teams are trapped in routine-driven behaviour but are very efficient. In a similar vein, industries feature different degrees of organisational diversity. In some industries, look-alike firms compete for clients' favour. For example, one energy producer is not very different from the other. In other industries, demographic diversity is high. Similarly, small, young independent brewpubs operate next to old, corporate-like mass producers in the US beer industry. What explains the emergence of such different degrees of demographic diversity? How is diversity at different levels of analysis related? What are the implications for the behaviour and performance of the social entities involved? This three-fold question as to the antecedents and consequences of demographic diversity in social entities is at the heart of the research programme proposed here.

The key aim of this Odysseus programme is to apply this type of demographic logic in economics, specifically, and the behavioural and social sciences, in general. Note that here economics is defined in the 'Germanic' tradition, and not in the Anglo Saxon one, implying that both business and general economics (in Dutch: algemene en bedrijfseconomie) are included. In so doing, a demographic perspective for behavioural, economic and social issues will be developed. As a by-product, we will integrate insights from theories that have, to date, lived their scientific lives in isolation. Note that this is not to say that demographic perspectives are non-existent in these disciplines – they are not. For example, the extensive demography-like research traditions in economic geography and industrial economics offer counterevidence against such a strawman-type of claim. However, the nature of the demographic approach suggested here and the list of behavioural, economic and social issues that will be tackled in the context of the proposed Odysseus programme imply entry into new ground. Specifically, we will develop a comprehensive multi-level and multidisciplinary approach emphasising an ecological perspective. Moreover, the programmed set of projects offers ample opportunities to work on groundbreaking theory development and innovative empirical studies. This will not only contribute to fundamental knowledge accumulation, but also inform relevant societal issues. A final up-front remark relates to method: although multi-method triangulation will guide both theory building and empirical work, the emphasis is clearly on quantitative methodologies.

## COLOPHON

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