



Institute for Molecular Medicine Finland
Nordic EMBL Partnership for Molecular Medicine

The background of the cover is a white field filled with a pattern of small, elongated oval shapes. These shapes are arranged in a grid-like pattern that tapers towards the right. The colors of the ovals transition from a light blue on the right to a dark orange on the left.

ANNUAL REPORT 2009

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About FIMM

The Institute for Molecular Medicine Finland (FIMM) is an international research institute focusing on building a bridge from discovery to medical applications. FIMM is part of the Nordic EMBL Partnership for Molecular Medicine, together with the European Molecular Biology Laboratory (EMBL), the Centre for Molecular Medicine Norway (NCMM, University of Oslo) and the Laboratory for Molecular Infection Medicine Sweden (MIMS, Umeå University). At the national level FIMM is a joint research institute of the University of Helsinki, the Hospital District of Helsinki and Uusimaa (HUS), the National Institute for Health and Welfare (THL) and the VTT Technical Research Centre of Finland.

FIMM investigates molecular mechanisms of disease using genomics and medical systems biology in order to promote human health. FIMM is a multi-disciplinary institute combining high-quality science with unique patient materials, and state-of-the-art technologies.

1 Review by the Director

I am writing this review as the Institute for Molecular Medicine Finland (FIMM) is preparing to organize its Launch Event on 16-17 March 2010. The decision of the University of Helsinki to launch FIMM as part of the Nordic EMBL Partnership for Molecular Medicine dates back to 2006, as reviewed by the Chair of the FIMM Board, Professor Marja Makarow. However, it is appropriate to organize a launch event now that the institute is well set up. This is illustrated by several highlights from the year 2009 as described below.

The number of employees at the institute grew from roughly 50 in January 2009 to >100 employees in January 2010, and we expect a similar growth to continue in 2010. Therefore, a critical mass of scientists is starting to emerge and significant research progress has already taken place. In 2009, there were around 100 publications, including >30 in high-impact (IF>10) journals, well ahead of expectations for a research institute launched just 2-3 years ago. FIMM has recruited several new group leaders and is now acting as the host institute for more than a dozen full-time group leaders and principal investigators (PI). Four of the PIs are recruited according to the EMBL search criteria, with two more being nominated in early 2010. International recruitment of young group leaders is complemented by two Finland Distinguished Professorships, Joseph D. Terwilliger and Jonathan K.C. Knowles. The recruitment of Professor Knowles has received significant attention (see interview in this report), as he comes to FIMM after stepping down as a leader of the scientific efforts at Hoffman-La Roche in Basel.

Professor Knowles is a globally known pioneer of personalized medicine, and we expect him to help FIMM to become one of the leading institutes in this area.



Research Director of FIMM, Professor Leena Peltonen-Palotie received a rare nomination as an Academician of Science. This is the highest recognition to a scientist in Finland, and is reflecting Professor Peltonen-Palotie's pioneering work on human genetics. This also reflects the tremendous progress in human genetics, which has profoundly changed our understanding of biology and disease and will form the foundation for molecular medicine applications.

The Nordic EMBL Partnership builds upon the significant existing strengths in molecular and clinical medicine in the Nordic countries which together with the strong EMBL background in molecular and cellular biology will provide novel multidisciplinary research opportunities. Collaborative meetings to launch joint research with the Nordic and EMBL partners have now started. Regular meetings of the Nordic EMBL Partnership for Molecular Medicine have taken place including close collaboration in e.g. the joint selection of group leaders and PhD stu-



dents. Research areas of common interest have been identified. For example, all three Nordic nodes as well as EMBL in Heidelberg have an interest in chemical biology.

While the University of Helsinki acts as the primary host to FIMM, the other host institutions, HUS, THL and VTT are also critical to the future success of FIMM. Through these partnerships, FIMM has a much bigger impact nationally, with up to 300 people already associated with FIMM. This provides the ability and opportunity to enrich FIMM research with access to the population-based sample and data resources available at THL, with the disease-oriented biobanks and translational opportunities at HUS and with the state-of-the-art technology development and industrial collaborations that VTT provides. We expect these benefits to be reciprocal, since infrastructures can be shared and multidisciplinary collaborative opportunities increase. At the same time, it will be necessary to further lower the administrative boundaries between these partner institutions that operate under three different ministries. This will be one of the central challenges and opportunities for FIMM.

The FIMM National Network for Molecular Medicine consisting of 15 top Finnish scientists has started its research activities, which will help FIMM to keep up high-profile translational research. At the same time, this represents a national dimension for FIMM as most biocentres in Finland are represented in this network. There are two Academy of Finland Centres of Excellence directly associated with FIMM, as well as

three others via the National Network for Molecular Medicine, providing a unique opportunity for FIMM to link up with the best biomedical research in the country.

Finally, the year 2009 was an expansion phase for the FIMM Technology Centre, whose activities will now include genomics, next-generation sequencing, bioinformatics, high-throughput screening, high-content imaging, biobanking and biomarker technologies. Several new domestic infrastructure grants (collaboration with the Biocenter Finland organization) and European ESFRI infrastructure projects (BBMRI-biobanking, EATRIS-translational research and ELIXIR-bioinformatics) have started at FIMM, together with its partners THL and CSC. For example, FIMM coordinated efforts to raise 1.85 M€ for pilot projects for these three ESFRI projects from the Academy of Finland, with co-funding from the partner institutions. It is important that as an international research institute, FIMM plays a key role in building EU-wide infrastructures for biomedical research.

FIMM is still a growing and developing institute, but a solid foundation has now been achieved on which to build future success. I want to thank all the supporters of FIMM, the significant contribution of the University of Helsinki as well as the other host institutions. Rapid growth and multiple ongoing projects, infrastructures, international collaborations, grants and recruitments have contributed towards a heavy load on every employee at FIMM, including the administrative staff. This is particularly the case in the 2009–2010 transition when the



University's own administrative structures and processes have completely changed. However, most problems have eventually been solved, and the situation hopefully stabilizes in 2010 and onwards as the very rapid early growth phase will be over. Last but not least, I want to thank

the entire staff of FIMM for outstanding work in 2009. I am sure the year 2010 will be equally exciting and wish you all luck and success in this important work.

Professor **Olli Kallioniemi**, Director of FIMM

THE NORWEGIAN NODE OF THE NORDIC EMBL PARTNERSHIP

The overall objective of the Centre for Molecular Medicine Norway (NCMM, www.ncmm.uio.no) is to facilitate translation of discoveries in basic medical research into clinical practice. NCMM will focus particularly on disease mechanisms where Norway has clear strengths and will investigate cancer, cardiovascular and CNS-related disease and immune disorders. NCMM will develop and adapt technologies for personalized medical applications and will be expected to unravel new diagnostic methods and drug targets.

NCMM has three founding partners Drs. Stefan Krauss, Ole Petter Ottersen and Kjetil Taskén that participate with their groups (Ottersen represented by acting group leader Mahmood Amiry-Moghaddam) and have identified the first two new group leaders, Drs. Ian G. Mills and Erlend A. Nagelhus, establishing their groups from the end of 2009. Two new group leader candidates have also been identified for hiring from 2010 and a third call is expected to identify the last 1-2 group leaders that would start in 2011.



In my view, the Nordic EMBL Partnership offers great opportunities and synergies within the Nordic region as we progress towards more molecular and personalized medicine as well as access to a wealth of research and facilities at the EMBL and outstations. Furthermore, as evident at the recent meeting in Heidelberg, there is a lot of enthusiasm around this Nordic alliance with all the new groups starting with vibrant new research programmes. I think we can expect exciting future discoveries for example in the areas of cancer, infection medicine, neurobiology and medical genetics.

Professor **Kjetil Taskén**,
Director of the Centre for Molecular Medicine Norway (NCMM)

2 FIMM addresses research and innovation challenges at Finnish and European levels



Europe is experiencing unprecedented renovations of the national research systems. The reforms realised or planned in most EU Member States provide universities with greater intellectual, financial and administrative autonomy, coupled to full accountability. The aim is to enable universities develop creative environments for education and research, and to engage in partnerships with research institutes and the private sector to address research and innovation challenges at national and European levels. In Finland, a new Act detaching universities from public administration took effect on 1 January 2010.

While the quality of researchers and their projects is recognized as the most important criterion for public funding, relevance is becoming an element of excellence in a number of countries. This is due to the fact that educated citizens and new knowledge are indispensable for

modern society, especially in countries such as Finland, which lacks limitless natural resources and where industry is R&D intensive and global collaboration of vital importance. Moreover, the global Grand Challenges menacing mankind cannot be managed without research. Potential for excellence, in the form of the up-coming researcher generation, is finally gaining attention. The portable Starting Grants of the European Research Council for independent young principal investigators have challenged the old-fashioned career structure of European universities, and are catalysing urgently needed renovations to attract and retain the best young people. State-of-the-art infrastructure, high-quality education and doctoral training, international students and researchers, and cross-border collaboration are recognised as essential characteristics of dynamic and successful research environments.

While Finland's national research policy is largely admired in Europe, the current challenges are a reality. Recent assessments have demonstrated that the upward trend of the quality and impact of research is levelling off, international mobility of fresh PhDs is stagnating, the researcher base is far too domestic, and translation of research findings into applications in the life sciences and medical domains is rare. Fragmentation of research efforts and resources is particularly dangerous in a small country, and lack of sustainable investment in research infrastructure threatens the quality of research and education, and prohibits internationalisation.

How does the Institute for Molecular Medicine Finland, FIMM, respond to the challenges of the renovations of the research systems at the Finnish and the European levels? In 2006, the University of Helsinki proposed to the Ministry of Edu-

cation to establish FIMM. The goals were to internationalise the researchers' base in genetics, epidemiology and molecular medicine taking advantage of the unique Finnish registers and biobanks, capitalise on the spearhead research already existing in these research domains, and to translate fundamental research findings into medical practice and innovations. The aim was to support profiling of biomedical research in the Finnish universities according to their individual strengths, while ensuring collaboration via networks. Research infrastructure and doctoral training was to be synergised by sharing responsibilities. Two research institutes, the National Institute for Health and Welfare (THL) and the VTT Technical Research Centre of Finland, and all universities with biocenters were to become founding members together with the University of Helsinki. Public-private partnership was to be realised together with dedicated foundations, the largest Finnish pharmaceutical company, the Hospital District of Helsinki and Uusimaa (HUS) and the City of Helsinki.

The Ministry of Education had just initiated the structural development of the universities, and expected them to pro-actively start identifying their strengths and profile themselves accordingly. As the concept of FIMM was in line with this ambition, the Ministry invited the University of Helsinki to establish FIMM, which was then formally conceived by the University Senate in 2006.

The history of FIMM dates, however, prior to 2006. The concept was created in 2003 by the Nordic Delegates of the Council of the inter-governmental flag ship research institute, the European Molecular Biology Laboratory EMBL. The idea was to establish in several Nordic countries EMBL-type institutes for molecular medicine.

They would be funded nationally, but benefit from a partnership with each other and the EMBL in the form of complementarity of research activities, synergies in doctoral training and access to infrastructure. Indeed, the Nordic EMBL Partnership for Molecular Medicine, including FIMM, the Centre for Molecular Medicine Norway (NCMM) and the Laboratory for Infection Medicine Sweden (MIMS) that were established in parallel with FIMM, was signed on 3 October 2007 by the Director General of EMBL and the Rectors of the Universities of Helsinki, Oslo and Umeå. The structure of FIMM models that of EMBL as an independent laboratory outside of departments and faculties. It was designed to allow facile horizontal collaboration with public, private and regional actors, implementation of international staff recruitment and turnover, and eventual re-orientation of activities according to regular high profile scientific advice.

The initial goals of FIMM, as set out in 2006 for the first three years, have been largely achieved, with the exception of the biocenter universities not wishing to become members of FIMM. Neither is a national doctoral programme in place. However, the first call for PhD candidates, together with the Nordic sister institutes, was carried out in 2009.

The model and ambitions of FIMM matches also the strategic view of a successful European research system developed by the European Research Area Board, an independent advisory body of the EU Commissioner of Research. The recent document lists the following six fundamentals to prepare Europe for a new Renaissance in research. (1) A united European Research Area (ERA) permits ideas, people and resources to move between countries, disciplines and the public and private sectors. (2) A dynamic ERA is

driven by societal needs and addresses Grand Challenges, for instance in public health. (3) The ERA is based on shared responsibility between science, policy and society. (4) An ERA of open innovation between public and private actors strengthens research and innovation and benefits the economy. The universities are autonomous, dynamic "knowledge institutions" fostering excellence and potential. They are open to industry, research institutions with goal-oriented focus and the society at large. (5) The ERA delivers excellence and endures risk. And finally, (6) an ERA of cohesion allows all European actors to take part in the knowledge society. It has been my privilege to take part in the conception of the idea of the Nordic EMBL Partnership for Molecular Medicine as Delegate of Finland for the

Council of EMBL, to have been mandated by the Rector Ilkka Niiniluoto to develop the mission, partnerships, strategy, resources and structure of FIMM in the capacity of Vice-Rector for Research of the University of Helsinki, and finally to promote implementation of the mission of FIMM as Chair of the Board during its first three years.

I wish to thank all decision makers, partners, funders, scientists and experts who have engaged themselves in developing FIMM, and wish it a brilliant future.

Professor **Marja Makarow**,
Chair of the Board of FIMM

THE SWEDISH NODE OF THE NORDIC EMBL PARTNERSHIP

The objective of The Laboratory for Molecular Infection Medicine Sweden (MIMS, www.mims.umu.se) is to strengthen Swedish research and enhance the dynamics in the field of molecular medicine, partly by promoting the career opportunities for young scientists. MIMS has a focus on human infectious diseases and molecular microbial pathogenicity. MIMS is established within the Umeå Centre for Microbial Research (UCMR, www.ucmr.umu.se) that includes researchers active in the fields of molecular and clinical microbiology, molecular biology, chemistry and physics and is closely connected to the university hospital.



MIMS has five founding research groups led by Drs. Sven Bergström, Thomas Borén, Anders Sjöstedt, Bernt Eric Uhlin and Hans Wolf-Watz, respectively. Our three new MIMS group leaders, Drs. Emmanuelle Charpentier, Constantin Urban, Jörgen Johansson, and the two new affiliated group leaders, Drs. Niklas Arnberg and Andrei Chabes, have been recruited during 2008—2009. New group leader candidates have been identified for three positions open for hiring in 2010.

We are very enthusiastic about the opportunities for collaboration and scientific interactions at many levels promoted by the Nordic EMBL Partnership formed together with EMBL, FIMM and NCMM. Our research groups will benefit greatly from the joint scientific meetings and workshops, facilitated access to research facilities, and new contacts with researchers in both complementary and different research areas.

Professor **Bernt Eric Uhlin**,
Director of the Laboratory for Infection Medicine Sweden MIMS

3 Research Groups

Human Genomics

Group Peltonen-Palotie

Academician of Science,
Professor Leena Peltonen-Palotie,
MD, PhD, Research Director, FIMM

Rapidly expanded information of the human genome has facilitated detailed genome-wide analyses of the genetic risk elements in common diseases, representing common health problems. Professor Leena Peltonen-Palotie's group aims to characterize genetic risk factors in cardiovascular and neuropsychiatric diseases. Utilizing unique study samples of Finland we have, in the collaboration with experts in clinical medicine, epidemiology, statistical genetics and biocomputing, identified a multitude of genetic loci associated with hyperlipidemias, cardiovascular diseases, psychiatric diseases and multiple sclerosis. Several of these loci have also been followed up in terms of their functional, biological and clinical impact. In the case of lactose intolerance, familial combined hyperlipidemia and multiple sclerosis, we have been able to identify DNA variants associated with the disease. Many of the studies involve Finnish epidemiological cohorts and collections of disease families. The research is done in close collaboration with the

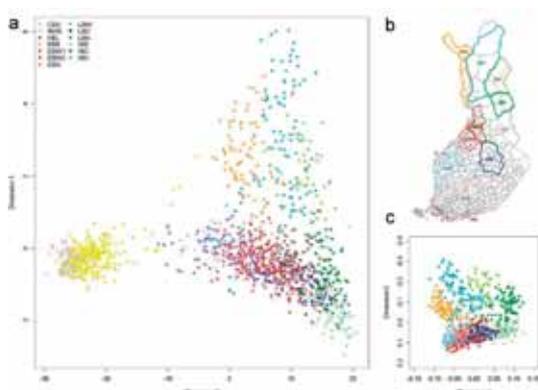
Wellcome Trust Sanger Institute, Broad Institute and other human genetics laboratories across the world. Also, one of the largest International studies is the ENGAGE integrated project, funded by the Seventh Framework Programme (FP7) of the EU (<http://www.euengage.org/>) co-ordinated by Peltonen-Palotie and includes many FIMM investigators. Peltonen-Palotie is also co-ordinator in the Nordic Center of Excellence in Disease Genetics (www.ncoedg.org) and a co-PI in the Academy of Finland Center of Excellence in Complex Disease Genetics (<http://www.ktl.fi/diseasegenetics/>).

Cardiovascular and metabolic traits

In 2009, FIMM investigators coordinated and/or participated in three major genome-wide screening efforts for lipid genes, which were published in the same issue of *Nature genetics* (2009, 41). These studies identified a total of 35 loci associated with total cholesterol, HDL, LDL cholesterol and triglycerides and showed their association with coronary heart disease. The work is now being extended in four ways: 1) to a meta-analysis of over 100 000 individuals across the globe with GWAS data, 2) a joint European genome-wide screen of gene-lifestyle interactions, 3) sequencing efforts to finemap causal mutations of the identified regions, and 4) correlating genome-wide marker data with metabolomic and transcriptomic data to screen for functional variation. Also, the clinical impact of the associated loci are currently being studied in a large-scale genotyping effort of Finnish (Finrisk92, 97, 02 and Health2000) and Southern Swedish prospective cohorts with a total of 50 000 individuals followed up 5-23 years.

Schizophrenia and neuropsychiatric disorders

The Peltonen-Palotie group has followed the leads of the DISC1 pathway and monitored the





allelic diversity of the pathway genes in the Finnish study sample of over 1000 schizophrenia families. Four out of 12 proteins that bind to the DISC1 protein have demonstrated to carry variants in their genes that are associated with schizophrenia (Tomppo et al, *Biol. Psychiatry* 2009). Recently, we have found evidence that variants in DISC1 affect measures of psychosis proneness even at the population level (Tomppo et al, *Archives of General Psychiatry*, 2009).

We are also a partner in the EU SGENE consortium for GWAs on 1433 schizophrenic patients and 33250 controls (<http://www.sgene.eu/>). This analysis has exposed some interesting loci as well as a novel copy number variation on chromosome 22 (Pietilainen et al, submitted), heavily enriched in the high-risk population on the Eastern boarder of Finland. The major joint scientific achievement in the SGENE consortium was the identification of three rare recurrent microdeletions on 1q21, 15q11.2 and 15q13.3 introducing substantial risk for schizophrenia, published in *Nature* (2008).

For autism, we have analyzed genome-wide SNP data for affected individuals from 200 Finnish autism spectrum families. This dataset consists of a subset of individuals diagnosed with autistic disorder, and in addition a subset of families with Asperger syndrome (AS). Association analysis, haplotype sharing analysis and CNV analysis have been performed in these datasets (Rehnström et al manuscript in preparation). When genealogical data was used to identify

common ancestry of the autism families, two large mega-pedigrees (20 and 9 nuclear families respectively) originating from the Central Finland subisolate were identified. We have used both genome-wide SNP data as well as genome-wide transcript profile data to determine whether these distantly related families share genetic susceptibility factors. In accordance with current results suggesting that autism is caused by rare, de novo mutations which are private to nuclear families, we have not been able to identify shared genetic risk factors in these families. The Finnish ASD dataset has also been included in a large international collaboration headed by Dr. Mark Daly at the Broad Institute, which revealed association between autism and common variants on 5p15 (Weiss et al 2009, *Nature*). The Finnish autism spectrum disorder dataset has also been included in an international meta-analysis of neuropsychiatric disorders coordinated by Dr. Mark Daly at the Broad Institute.

Genetic variation in Finland

We have catalogued Finnish common genetic variance in two studies: first by quantifying the east-west and north-south differences in Finnish genomic architecture using genome-wide association scans together with information of the parental origin of individuals, and second by creating a Finnish Hapmap reference data to comprehensively describe the Finnish genetic variation. The Finnish HapMap also allows for precise in silico genotyping of Finnish population-based samples as well as capture of larger structural variants in the Finnish genomes

[Surakka et al, submitted]. This reference dataset has been made available to the research community through the Nordic control database (<http://nordicdb.org/>) and the European Genotyping Archive (EGA) (<http://www.ebi.ac.uk/ega/>).

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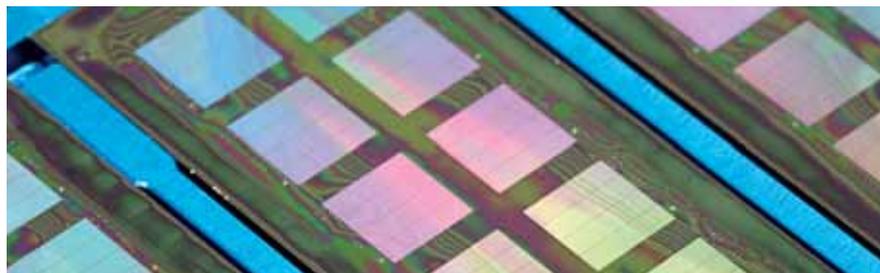
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Group Palotie

Professor Aarno Palotie, MD, PhD, Group Leader in CoE in Complex Disease Genetics



Many common neurological traits such as migraine and multiple sclerosis (MS) have a strong genetic component. However, despite extensive research the detailed molecular background of the genetic suscep-

tibility to these traits has remained relatively unclear.

The overall goal of our group is to improve our understanding of pathogenetic mechanisms underlying common neurological diseases such as migraine and MS. Our strategy has been to combine best possible phenotyping in large samples with cutting edge genetic techniques, including high-throughput genotyping, sequencing and novel tools of statistical genetics. Primarily Finnish clinicians headed by Dr. Mikko Kallela have collected well-phenotyped large study samples with a family history of migraine. Using these unique study samples and extensive international collaborations we aim to identify genes and gene variants contributing to episodic CNS disorders such as migraine and subsequently understand their impact on the disease outcome.

Dr. Palotie's group is attempting to find small variations in the DNA sequence (variants) that commonly arise in these people and to link them to susceptibility to the conditions. These projects are based on the use of large, well-characterised special populations and large family samples. Using family-based studies and subsequent fine DNA mapping strategies the group has been involved in the identification of several new regions of DNA linked to the diseas-

es. In collaboration with international groups, large-scale genetic studies are in progress. The wealth of multiple large study samples enables the group to use different study designs for genome variant identification and verification and for the estimation of the size of the effect contributed by the variants. The strong connection and collaboration with large genome centers such as the Wellcome Trust Sanger Institute and the Broad Institute makes this aims realistic. Dr. Palotie is a faculty member at the Sanger Institute and a visiting faculty at the Broad Institute.

So far, the best insight of underlying genetic alterations causing migraneous symptoms is provided by the Mendelian forms of migraine, Familial Hemiplegic Migraine (FHM), where all identified variants are in genes coding for ion transporters. However, current evidence suggests that variants in these genes do not play a major role in common forms of migraine: migraine with aura (MA) and migraine without aura (MO). Although family studies by us and others have identified several loci linked to migraine with and without aura, no genes have been convincingly associated to these common forms of migraine. We have specifically monitored allelic diversity of 155 known ion transport involved genes in human genome and failed to show a major impact of any of them on common forms of migraine. Our current work is based on a large international effort that has accumulated one of the largest collections of migraine patients in the world (<http://www.headachegenetics.org/index.html>). We have performed a genome-wide association scan to test whether common variants associated to common forms of migraine could be identified in these large study samples of more than 5000 migraine cases.

In multiple sclerosis (MS) the role of the HLA as a susceptibility locus has long been well-established. The role of predisposing non-HLA loci is less well-understood. Our collaborative work with Dr. Leena Peltonen-Palotie's and Janna

Saarela's groups in family-based positional cloning studies have identified the protein kinase A (PRKCA) gene as one susceptibility candidate gene outside the HLA region and recent large international genome-wide association studies identified interleukin-2 receptor - and interleukin-7 receptor -genes as susceptibility genes for MS. These are exciting, new discoveries shedding light on basic mechanism of MS pathogenesis. However, it is evident that non-HLA susceptibility loci identified thus far explain only a very small fraction of the variance of disease susceptibility to MS. It is likely that we need a more comprehensive understanding of the full allelic diversity of susceptibility genes as well as genes involved in these pathways. Our genome-wide association study aims to identify rare alleles enriched in a population isolate of Finland with a high disease prevalence.

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Group Terwilliger

FiDiPro Professor Joseph D. Terwilliger, PhD, FIMM and Columbia University, USA



As a statistical geneticist, the main foci of our research have been development and implementation of statistical methods for inference about human genetics, developing and applying novel study designs using natural experiments to improve the power of human genetic investigations, and organizing and teaching workshops both in Finland and throughout the developing world on "logical reasoning in human genetics".

The primary project we have been involved at FIMM has been the development and implementation of likelihood-based algorithms for inference about linkage and linkage disequilibrium jointly on familial data. While much emphasis in the field has been on the analysis of unrelated individuals in case-control and cohort settings, our emphasis has been based on approaches to analyzing genome-wide SNP and sequence data in collections of families. The primary advantage of the Finnish population in human ge-

netic research has been the ability to construct and ascertain familial data through the use of the well-established registries of medical diagnoses and family structures. In recent years much effort has been invested in attempting to do genome-wide association studies in Finland as elsewhere using "unrelated" subjects, with very little success. The field as a whole is beginning to realize that there are likely to be a significant number of rare variants underlying the risk of most common diseases, and for addressing this problem, a return to analysis of family data has been widely recognized as critically important. Methods for analyzing this sort of data have been lacking because very few studies in recent years have applied the new technologies to large families.

Another aim of our research group has been to explore the likely genetic architecture of complex traits through forward evolutionary simulations under user-specified models of phenotype-based natural selection, mutation, recombination and demographic history. Unlike most existing approaches to this problem, we simulate individuals and their reproduction forward in time over tens of thousands of generations, generate new mutations with simulated effect sizes, and allow natural selection to occur based on phenotypes simulated for each individual in each generation in a biologically natural way. We hope to generate more reasonable hypotheses about the genetic architecture of natural phenotypic variation, now that we have known that there are not many common genetic variants of large effect, as many researchers had been hoping. We hope to thus better understand why gene mapping in complex traits by genome-wide association analysis has been such an overwhelming failure.

Ultimately it is not the statistical analysis method that determines the success or failure of a gene mapping study, but rather the underlying biological truth and the study design used to query the biological reality. Finnish genetics

has been successful over the years because of its emphasis on the use of the natural history of the Finnish population as a natural experiment from which interesting questions could be asked that were impossible in other populations. However, there are many other natural experiments around the world that can be used in an analogous way to answer different questions. Much of our work has involved working with populations in the developing world where many such "natural experiments" can be found, to help the local researchers use their populations in unique and creative ways to ask questions about human biology. Our work in this area at the moment is concentrated on populations in Kazakhstan, Korea and Venezuela, where we are involved in a number of collaborative research projects, to look at interactions between genetic and enviro-cultural factors on normal human variation and health.

Group Saarela

Research Director Janna Saarela, MD, PhD, FIMM Technology Centre



Dr Saarela's research group is focusing on genetics of complex neuropsychiatric diseases using cutting edge genetic technologies. By taking advantage of the well characterized clinical samples from Finnish

population isolates and the large Finnish population cohorts her group has identified novel genes responsible for multiple sclerosis in collaboration with Professor Peltonen's group, Professor Palotie and the International Multiple Sclerosis Genetics Consortium (IMSGC). Additionally her group is actively testing, optimizing and further developing novel genomics and genetics methods and analysis pipelines with the FIMM Technology Centre.

Multiple sclerosis (MS) is one of the most common neurological diseases of young adults with a prevalence of 100-150/100000 in Northern European populations. It is a complex inflammatory disease of the central nervous system with presumed autoimmune etiology. Both environmental and genetic factors are thought to contribute to the development of MS and the genetic risk factors likely include both common and rare risk alleles. The role of the HLA locus and specially the HLA-DRB1*1501 has been established for over a decade, but recent genome-wide association studies (GWAS) and subsequent meta-analysis have identified novel MS loci: IL2RA, IL7R, CLEC16A, CD58, TNFRSF1A, IRF8, and TYK2. Most of these associated variants are common, have small odds ratios and explain only a fraction of the genetic risk. Currently there is no known cure for MS and the diagnosis is often delayed because two separate episodes of neurologic symptoms characteristic of MS are required for a definitive MS diagnosis. Thus, identification of the predisposing genes will shed light to the biological pathways and mechanisms behind MS and will enable functional studies and development of more accurate diagnosis and treatment for the disease.

Dr Saarela's group takes advantage of the population history of Finland and the province of Southern Ostrobothnia, which is an old internal isolate with increased prevalence and familial occurrence of MS, in search for genes predisposing to the disease. We hypothesize that some variants predisposing to MS have either become enriched in Southern Ostrobothnia or can be more easily detected against a homogeneous allelic background using cutting edge genetic technologies like high density SNP screens and targeted next-generation sequencing of the associated loci. We are also utilizing multiplex MS families originating from the high-risk isolate to look for potential rare, even family specific MS variants.



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Group Widén

Academy Research Fellow Elisabeth Widén, MD, PhD

The main focus of the research group is the genetic regulation of pubertal growth and maturation. Most mammals undergo puberty as their postnatal growth is tailing off, but in humans puberty is accompanied by a growth spurt during which the final adult stature and body proportions are attained. The pubertal growth spurt, which is tightly correlated with pubertal sexual maturation, accounts for as much as 15–20 % of final stature and is characterized by a large variation of tempo and timing, both within and between the sexes. Genes and environmental factors contribute to the variation in pubertal growth and maturation, but twin studies indicate that a substantial proportion of the variance is under genetic control.

Little is yet known about the genetic framework regulating puberty. A downward secular trend in the timing of puberty has been apparent during the last century, which potentially might constitute a major public health concern, since early pubertal maturation is associated with long-term adverse health effects, such as increased risk of e.g. obesity and hormone-dependent cancers. We hypothesize that disentangling the genetic architecture controlling the onset of puberty significantly could improve the understanding of the complex interplay of molecular factors regulating pubertal growth and maturation in general, which in turn also might elucidate the mechanisms advancing the onset of puberty.

Our primary aim is to map and characterize genes regulating pubertal growth. To achieve this goal we are conducting both genome-wide mapping studies in population based cohorts, but also have performed genome-wide linkage mapping of genes co-segregating with constitutional delay of pubertal growth and maturation in multiply affected families. Our previous studies of constitutional pubertal delay show that the trait often segregates in an autosomal dominant fashion and we have successfully mapped a gene on chromosome 2 co-segregating with delayed puberty in extended families. The ongoing research activities during 2009 include the genome-wide association mapping of a gene region influencing pubertal growth in the Finnish population. In this study we were able to further identify the presence of two independent genetic effects in the gene region both exerting broad, complex and sex-specific influences on the complete postnatal growth trajectory. In addition we also are involved in ongoing international collaborations on e.g. the genetic mapping of childhood growth related traits and age of menarche. In addition we have pursued the fine-mapping of the gene on chromosome 2, co-segregating with delayed pubertal onset. The results of the research activities of year 2009 are still unpublished, but have so far been summarized in 2 papers under review.

Key publications:

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Medical Systems Biology and Translational Research

Group Kallioniemi

Olli Kallioniemi, MD, PhD, Director, FIMM

In collaboration between FIMM and the VTT Technical Research Centre of Finland our group is carrying out genome-scale cancer biology research in order to facilitate our understanding of the key steps in cancer progression and the identification of novel translational opportunities. The research focusses on breast and prostate cancer, the two most common hormonally regulated cancers.

We have developed a technology to carry out genome-wide gene silencing in a miniaturized cell array format. Up to 20,000 siRNA constructs are reverse-transfected to living cells in an arrayed format (Mousses et al., 2003, Rantala et al., manuscript). This cell spot microarray technology will provide systematic, multi-parametric, high-content readout of the impact of genes on essential cancer cell functions. This miniaturized assay increases the throughput and reduces the cost of large-scale RNAi screening by 100–300-fold as compared to current technologies.

Our group is using new genomic and genome-scale biology technologies to investigate breast and prostate cancers. For example, we have identified genes that are required for the survival of prostate cancer cells in androgen-deficient conditions and micro-RNAs that regulate androgen receptor signaling in prostate cancer and estrogen receptor signaling in breast cancer (Leivonen et al., 2009). These studies are illuminating novel pathways or novel members of previously known pathways that contribute to these cancers.

We are also using high-throughput screening to explore responses of cancer cells to commonly used drugs in order to identify unexpected therapeutic opportunities. In our pilot project on prostate cancer, we identified the antabus-drug Disulfiram as an effective inhibitor of prostate cancer growth at nanomolar concentrations (Iljin et al., 2009). Molecular and genomic studies have then illuminated the mechanisms of the anti-cancer effect. The combination of chemical and genetic/RNAi screens may in the future play a major role in the identification of optimal treatments for individual patients. It will also become possible to apply many of these technologies directly to exploring clinical specimens from cancer patients. This is what we plan to do together with professors Jonathan K. C. Knowles, Kari Alitalo, Leif Andersson and Heikki Joensuu in order to develop strategies for individualized molecular oncology.

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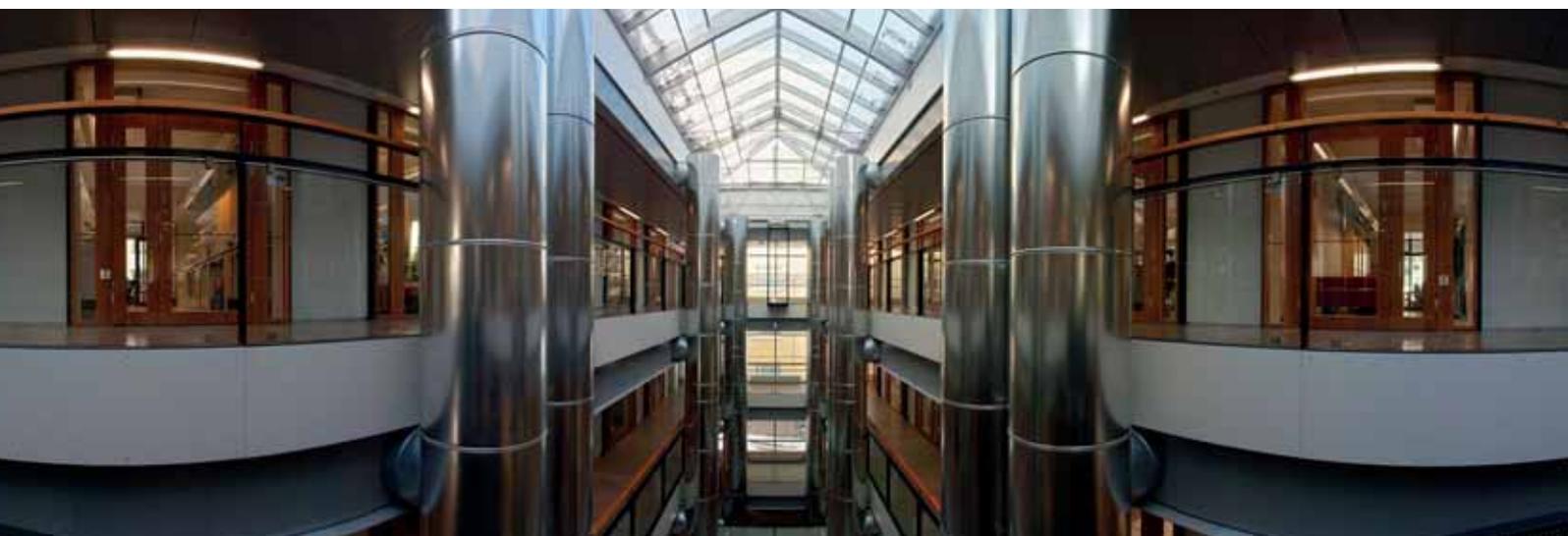
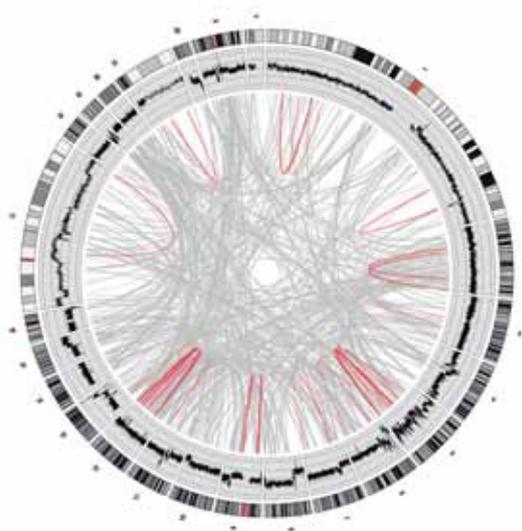
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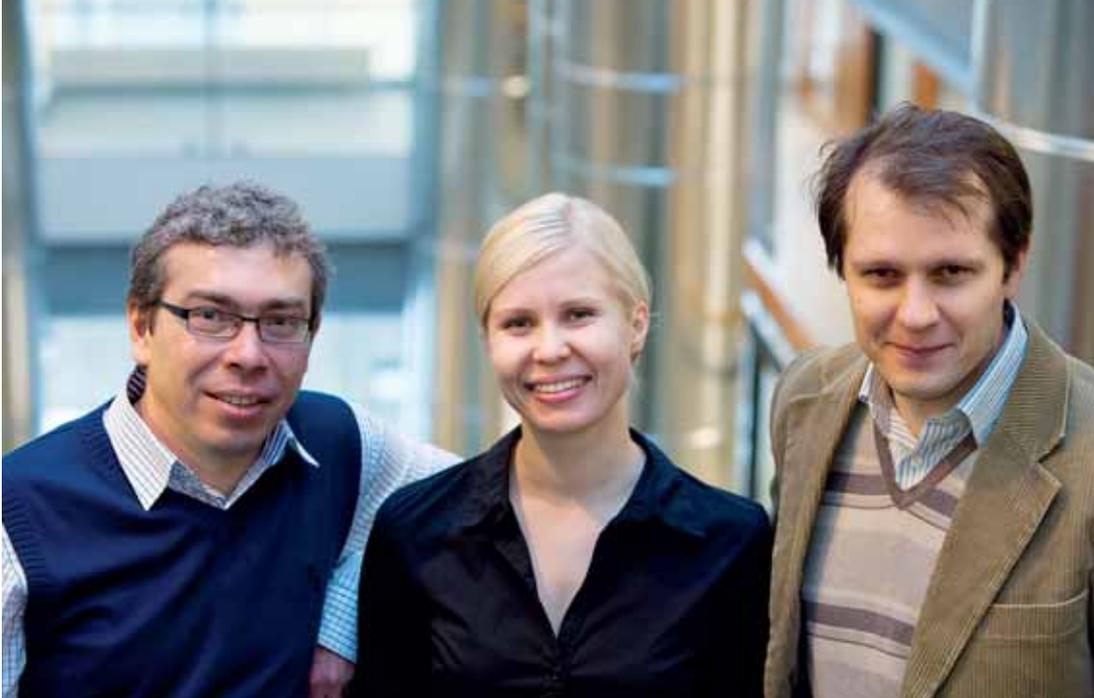
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Group Kainov

FIMM-EMBL Group Leader
Denis Kainov, PhD

RNA viruses cause severe consequences for human health and global economy. These viruses exist as rapidly evolving quasi-species. The rapid accumulation of mutations in viral genomes enables viruses to develop resistance against commercial antiviral drugs and to evade the immunity developed after previous infections or in response to vaccinations. Therefore, there is an increased demand of novel antiviral therapies.

Our group is studying antiviral drugs that target cellular factors essential for virus replication. In contrast to viral proteins, cellular factors are not prone to rapid mutations. For some of these cellular factors there are existing drugs which were originally developed for cancer treatment etc. We are searching for good drug candidates which can serve as antivirals. Antivirals that will emerge from these studies will be further investigated for their antiviral activities using influenza A viruses, alphaviruses and hantaviruses, representing positive- and negative-sense RNA viruses. Thus, finding of a broad-spectrum antiviral is the main objective of the group.

The group was supported by Jane and Aatos Erko Foundation.

Key publications:

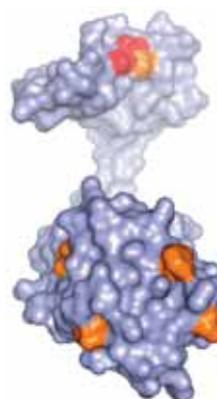
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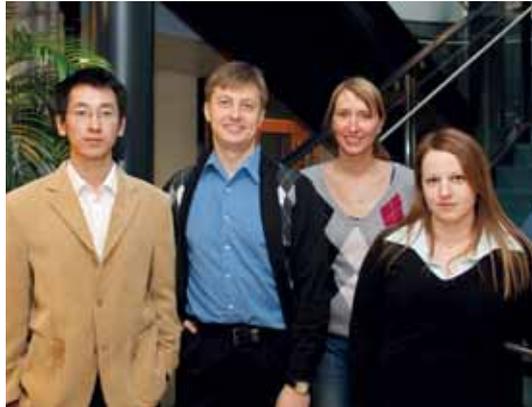
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Group Kuznetsov

FIMM-EMBL Group Leader Sergey Kuznetsov, PhD

Sergey Kuznetsov's research team at FIMM investigates molecular mechanisms of cancer progression. The group aims to identify genes that are critical for development of particular tumor types – genes also known as “drivers” of tumor formation, and distinguish them from “passengers.” To achieve this goal, non-descriptive, functional assays are used. These include high throughput RNA interference (RNAi) screens in cancer cell lines, and forward and reverse genetics approaches in mice. The results are expected to lead to new therapeutic targets and strategies.

Several projects in the group are focused on breast cancer as one of the most common cancer types in women. On the one hand, these are groups of hereditary breast cancer tumors associated with germline mutations in genes such as BRCA1, BRCA2, or CHEK2. Although relatively minor in absolute numbers of affected cancer patients, these tumors are clearly defined by their mutational status in one of these genes. This feature can be used to selectively target mutant cancer cells without harming non-mutated normal tissues. In addition, one project attempts to develop a new in vivo approach that would allow to study any type of breast cancer experimentally. This approach may open unprec-

edented opportunities to study sporadic breast cancer subtypes for which no appropriate animal models have been developed.

The team also continues to study the Rad51c mouse model to answer the fundamental question of why mutations in ubiquitously expressed DNA repair genes lead to tumors of certain tissues but not others. Based on our late finding that mutations in Rad51c promote tumors in specialized sebaceous glands and suppress p53-specific tumor types, tissue-specific roles of Rad51c are investigated in epithelial tissues in mice. Understanding the mechanisms of tissue specificity in cancer may provide another strategy for treatment of certain cancer types.

The group was supported by the Finnish Medical Foundation and Sigrid Jusélius Foundation.

Key publications:

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Group Verschuren

FIMM-EMBL Group Leader

Emmy Verschuren, PhD

Emmy Verschuren's lab is dissecting cellular and biochemical properties of candidate tumour suppressor genes identified in a cellular senescence screen during her postdoctoral work in the lab of Peter Jackson at Genentech Inc. Special focus is on one of the candidates, the EPHA3 receptor tyrosine kinase gene, which is found to be frequently mutated in human lung and colorectal cancers in cancer genome sequencing efforts. The lab is currently studying molecular networks around, and cell system responses to manipulation of EphA3 receptor signalling using a multi-pronged research approach. Technologies we are applying include expression of wild type and tumour-associated point mutation variants and genetic knockdown strategies, and highly efficient dual tag-based protein purification methods. Considering the known role of Eph receptors in cell shape and migration, it will be essential to study its putative tumour suppressive functions in a system resembling *in vivo* architecture. We are therefore setting up primary 3D lung alveolar cyst epithelial culture systems, and aim to develop preclinical mouse lung cancer models applying lentiviral delivery methods directly to the lung tissue. The integration of molecular and epithelial cellular system approaches with genomic profiling will add to our understanding of this new cancer pathway. Importantly, current research objectives are extended to additional candidate tumour suppressors, and reverse genetics-based discovery of new cancer-associated proteins.

The group was supported by Orion-Farmos Research Foundation and Sigrid Jusélius Foundation.



Key publications:

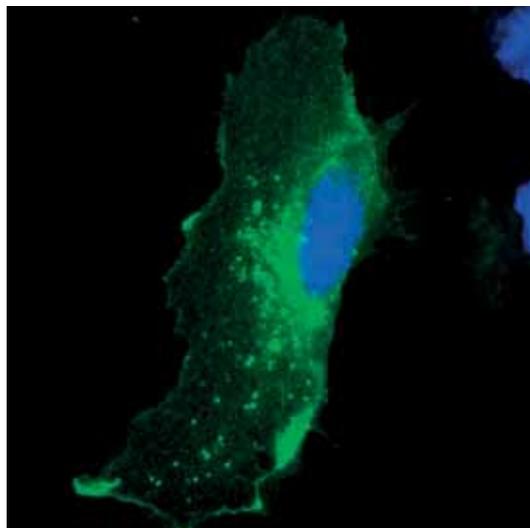
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Group Wennerberg

FIMM-EMBL Group Leader
Kristen Wennerberg, PhD

The Wennerberg lab uses chemical biology approaches to gain fundamental novel understanding of cancers and other major human diseases. The overall goal is to generate novel biological information and molecular probes that ultimately can be used to develop new treatments. The current projects in the lab involve using activity-based profiling technologies to identify putative drug targets as well as the discovery and development of small molecule regulators with new bioactivities.

Activity-based profiling is being performed on putative druggable classes of targets such as adenine and guanine nucleotide-binding and -hydrolyzing proteins to mine their biology and to identify novel molecular drug targets. Cancer as well as infectious disease (*Mycobacterium tuberculosis*) model systems are pursued.

The laboratory is working towards identifying and developing novel drug-like small molecule regulators (small molecule probes) targeted to small G-protein regulators, kinesins as well as nucleotide-binding proteins identified in activity-based profiling. Molecular targets from the mentioned classes involved in cellular transformation, mitosis, cytokinesis and *Mtb* latency are of special interest. Inhibitors and other bioactive regulators are identified through high throughput screening as well as virtual screening approaches in collaboration with cheminformaticians and optimized in collaboration with medicinal chemists. Resulting molecular probes are subsequently used to further probe the biology of the targets and to assess their validity as therapeutic targets.

The group was supported by Jane and Aatos Erkko Foundation.



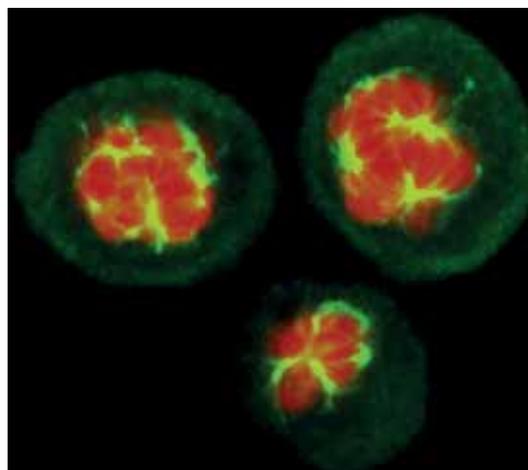
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4 FIMM National Network for Molecular Medicine

Academy Professor **Lauri A. Aaltonen**, University of Helsinki. Group leader in the Centre of Excellence in Translational Genome-Scale Biology

Array-based analysis of paraffin-embedded tissue materials The research of the group focuses on human tumor susceptibility. Particular focus of interest has been hereditary colorectal cancer, where the group has contributed to several key discoveries. The current focus is in utilizing registry-based approaches to identify unique cancer family materials, for identification of new cancer syndromes and genes. The role of FIMM funding for the group is to enable use of archival tissue material in genome-wide approaches, including SNP and expression chips as well as next generation sequencing.

Academy Professor **Kari Alitalo**, University of Helsinki, Director of the Centre of Excellence in Cancer Biology

Targeting Prox1 in colorectal cancer progression We have discovered that the homeobox transcription factor PROX1 is overexpressed in approximately 70% of human colorectal carcinomas (CRCs) as well as in mouse models of intestinal cancer with abnormal β -catenin/TCF signaling. Importantly, PROX1 expression marks the transition from benign colon adenoma to carcinoma in situ, and its loss inhibits growth of human colorectal tumor xenografts and intestinal adenomas in Apc(min/+) mice, while its transgenic overexpression promotes colorectal tumorigenesis. Furthermore, in intestinal tumors PROX1 is a direct and dose-dependent target of the beta-catenin/TCF signaling pathway, responsible for the neoplastic transformation. Furthermore, our results demonstrate not only that PROX1 is important for the malignant progression of CRC tumors, but also show the tissue-specific regulation and function of PROX1, and warrant further studies of PROX1 as a potential target of drug

development. We want to develop compounds and dominant negative constructs that inhibit PROX1 activity in CRC and to validate their effect in cultured cells and ultimately in mouse tumor models. We aim to use synthetic lethality high-throughput assays for the identification of compounds that inhibit PROX1 activity or kill PROX1+ cells in CRC and to test them in vivo.

Professor **Akseli Hemminki**, University of Helsinki and HUS

Translational cancer gene therapy for induction of anti-tumor immunity Accumulating evidence indicates that a dynamic cross-talk between tumors and the immune system can regulate tumor growth and metastasis. In this context, a promising approach for improving therapeutic options for tumors currently incurable involves potentiation or redirection of the tumor immune response with oncolytic adenoviruses. This approach is a new concept in cancer gene therapy and it will give the field new insight into understanding the complexity of advanced tumors and their immunobiology.

Assoc. Professor **Iiris Hovatta**, University of Helsinki, Research Fellow of the Academy of Finland

The role of miRNAs in the regulation of anxiety The aim of the group is to understand genetic and molecular factors that regulate normal and pathological anxiety. Functional genomics approaches are used to identify genes and networks involved in anxiety-like behavior. In this project the role of microRNAs in the regulation of anxiety-associated gene networks in the brain is investigated.

Professor **Elina Ikonen**, University of Helsinki

High-throughput screening of sterol distribution in cell membranes: use of fluorescent lipid derivatives The research of the group focuses on the mechanisms



of cellular cholesterol transport and the role of cholesterol-dependent membrane domains in regulating cellular functions. Disturbances in the content or distribution of cholesterol in cells contribute to major health burdens, such as atherosclerosis, stroke, metabolic syndrome and cancer. We utilize cell lines, primary human cells and animal models to gain insight into cholesterol-related pathologies. The rapid development of imaging techniques has motivated us to establish novel compounds and approaches for lipid imaging in cells and tissues.

Professor **Sirpa Jalkanen**, University of Turku and THL, Director of the Centre of Excellence in Host Defence Research

Role of trafficking molecules in cancer spread and harmful inflammations Professor Jalkanen's group is studying mechanisms mediating cell traffic to sites of inflammation and metastatic spread of cancer cells in the body. The final goal of the research is to identify target molecules to be used in drug development against harmful inflammations and cancer spread.

Assoc. Professor **Heli Nevanlinna**, HUS

Novel genes and gene interactions in breast cancer risk and progression Heli Nevanlinna's research project focuses on identification of genes that may modify the risk effect of the breast cancer susceptibility genes BRCA1, BRCA2 or CHEK2, or that may

have an effect on tumour progression and patient survival. The project uses in vitro functional approaches (DNA break repair) in mutation carrier cells for identification of genes related to these pathways as well as targeted siRNA analyses of candidate genes. The project will reveal molecular mechanisms for breast cancer susceptibility and progression and has also clinical significance for more accurate evaluation of breast cancer risks associated with BRCA1 and BRCA2 as well as CHEK2 mutations at individual level or with specific subgroups of patients.

Professor **Matej Oresic**, VTT

Metabolic stress and autoimmunity in health and disease We are investigating how the genetic and environmental factors are imprinted in the metabolome, as well as the mechanisms by which alterations of the metabolome lead to (patho)physiological changes at the systems level. We are relying on metabolomics techniques to characterize the metabolome, combined with systems biology strategies to investigate, e.g., how changes in gene expression or in gut microbial composition alter the metabolic phenotypes.

Professor **Taina Pihlajaniemi**, University of Oulu, Director of Biocenter Oulu and Vice Director of Biocenter Finland

Translational significance of cell-matrix homeostasis The FIMM-project addresses the hypothesis

that the conserved collagens influence epithelial-mesenchymal transformation and other processes in the tumor microenvironment. Bioinformatics analyses will be performed in collaboration with Olli Kallioniemi's group to identify tumor associations and validate the in silico findings by screening selected human tumor materials. Also mechanisms underlying the malignant processes will be addressed. The FIMM project forms a translational pathway including target identification and validation with respect to diagnostic, prognostic and therapeutic value, and development of disease-specific assays and eventually practical applications.

Professor **Anu Wartiovaara**, University of Helsinki, Group leader in the Centre of Excellence in Research on Mitochondrial Disease and Ageing *Mitochondrial function as a risk factor and as a protective trait in metabolic syndrome, cardiovascular events, and neurodegeneration* The major research focus of the group is to study the consequences of disturbed energy metabolism for human health. Variable disease models and human studies are used to gain knowledge on pathogenesis of mitochondrial diseases. These results are generalized to ask related questions on mechanisms of neurodegeneration, metabolic syndrome, obesity and aging-related wasting. The ambitious long-term aim is to utilize the knowledge of pathogenesis to develop means of intervention for disorders of the energy metabolism.

Professor **Jukka Westermarck**,
University of Turku

Identification of novel cancer drug target proteins The goal of this project is to identify novel protein-protein interactions involved in malignant cell growth by characterizing protein complexes associated with proteins previously demonstrated to have an important role in cancer progression. Identification of novel proteins involved in malignant growth may reveal novel possibilities for intervention in the therapy of cancer and other hyperproliferative diseases.

Projects not started yet:

Professor **Willem de Vos**, University of Helsinki and Wageningen University (NL), FiDiPro Professor of the Academy of Finland (Finland Distinguished Professor)

Professor **Heikki Joensuu**, University of Helsinki and HUS, Group leader in the Centre of Excellence in Host Defence Research

Professor **Jaakko Kaprio**, University of Helsinki and THL, Director of the Centre of Excellence in Complex Disease Genetics

Academy Professor **Jussi Taipale**, University of Helsinki and THL, Group leader in the Centre of Excellence in Translational Genome-Scale Biology



5 Aim high – you have what it takes



Jonathan K.C. Knowles, Head of Group Research and Member of the Executive Committee at Hoffman-La Roche, was appointed Professor at the University of Helsinki and FIMM through the Finland Distinguished Professor Programme of the Finnish Funding Agency for Technology and Innovation (Tekes) in September 2009. The professorship has a fixed term of five years.

Professor Knowles is a global opinion leader in personalized medicine. "I've always been interested in how treatment could be targeted so that each individual patient would get exactly the right kind of care. This is what I worked on for twelve years at Roche – my job was to direct the company's research towards personalized medicine. When I retired from there, FIMM offered me the opportunity to continue this work from a slightly different perspective," Knowles explains.

He concedes that there would have been other ways to spend his retirement than starting a new job. "After considering the situation, I decided that this is exactly what I want to do. I am also strongly of the opinion that this is how medicine will develop going forward."

According to Professor Knowles, FIMM and its partners have an excellent opportunity to further the research and development of personalized medicine. "FIMM is a nexus of molecular medicine in Finland, and the University of Helsinki is among the best in Europe in clinical medicine. It has solid research experience and proven competence in this field, and its cooperation with the local hospital district is seamless – FIMM has great potential to become a leading centre in personalized medicine even on a global scale."

In addition to passion for his work, there are personal reasons pulling Professor Knowles to Finland. Before his formidable career in the pharmaceutical industry, he worked as a researcher for the VTT Technical Research Centre of Finland for nearly ten years. "I speak Finnish at home, I'm a Finnish citizen, I like Finland!"

So what will happen in personalized medicine during the next five years? "We are going to revolutionise the treatment of cancer," Knowles states without hesitation. One of his five-year goals is developing diagnostic tests which could detect, for example, cancer of the stomach and kidneys from blood samples at a very early stage.

Cancer touches everyone – even if you do not contract the disease, someone close to you will. Professor Knowles had a close encounter with the disease when his brother died of cancer some years ago. "My goal, my passion, is to improve the treatment of cancer."

According to Professor Knowles, research into personalised medicine is at a very interesting stage, and major strides can be expected in the coming years. And this is the case not just for cancer, but many other illnesses, like Alzheimer's disease.

Professor Knowles also hopes that the coming five years will bridge the gap that in Finland still exists between basic research and innovation, as well as science and treatment. "Finns invest heavily in basic research, and it shows – the research is of a high quality, scientific results are produced and important ideas emerge. But both the scientific acclaim and financial profit go elsewhere because the results are not developed and processed all the way. Society is not getting what it deserves out of the investment. At the same time, there is an increasing gap between rapidly developing medicine and the treatment patients receive. This problem must be solvable in a country as small as Finland – and a solution will be found, if we want it."

Professor Knowles believes that both FIMM and Finns in general should set their sights higher, be bolder. "I don't mean be more arrogant or boastful, but just have a belief in your own competence. You have to aim high. You may not get there, but it's worth it to try. Sometimes you succeed. Let's revolutionise cancer treatment!"

Interview by **Päivi Lehtinen**, University of Helsinki

6 FIMM Technology Centre

Dr Janna Saarela, Research Director

The FIMM Technology Centre is a local, national and international infrastructure and service facility developing new technologies and serving the user community with state-of-the-art technologies. The Technology Centre was listed as one of the eight existing bio- and biomedical research infrastructures of national importance in the report of the Finnish Research Infrastructure Survey and Roadmap project. The FIMM Technology Centre is focusing on genomics, sequencing, bioinformatics, high-throughput RNAi screening, and translational technologies. The Technology Centre employed 25 people at the end of 2009, and this number is expected to go up to 35 during 2010, as a result of recent grants from the Biocenter Finland and the European ESFRI Infrastructure funding.

In 2009, FIMM Technology Centre produced 1.5 Billion genotypes, and 130 Gb of DNA sequence data.

Genomics

Dr Päivi Lahermo

The genotyping facility is the only nationwide genotyping centre and offers high-throughput genotyping services. During 2009 it more than doubled its SNP genotyping capacity by investing in a new Illumina iScan System. The genotyping services were continued to be offered also on Illumina BeadStation, Sequenom MassArray, Affymetrix GeneChip, and ABI 3730 platforms. In addition RT-PCR based genotyping was also set up on Roche Light Cycler 480 II instrument in the end of 2009. The facility also offered gene-expression and methylation analysis services.

In 2009, the unit produced 1470 million genotypes and carried 35 collaborative projects with approximately 25 group leaders from six Finnish universities and research institutes. In addition to providing research groups with high quality and high-throughput laboratory services, the



genomics unit offers expertise in project planning, data handling, and analysis. In addition to research collaborations, the staff of the Genomics unit is also active in own research projects, especially in genetics of complex traits, including e.g. IBD, migraine and diabetes, as well as genetic structure of populations.

Next generation sequencing (NGS)

Head of Laboratory Pekka Ellonen

The Sequencing facility is one of the two national centers providing capillary and "next-generation" sequencing (NGS). In 2009 the Sequencing facility set up of the Illumina Genome Analyzer II services and processed 24 sequencing runs producing 129 gigabases of sequence for 15 research groups from Finland and abroad. The applications included RNA, miRNA, CHIP, genome sequencing. The early access agreement with Roche Nimblegen allows the facility to offer targeted genome sequencing with two different capture methods (Agilent Sure select and Roche Nimblegen), covering either the whole exome or custom selected chromosomal regions.



To help the clients and improve the results the services were extended to include also the sample preparation steps. Sample preparation is a key part of any successful NGS experiment. Continuous optimization and method development is part of all NGS projects within the Sequencing laboratory. The aim is to reduce the amount of nucleic acid starting material and to develop more feasible and robust methods. Ligation based and PCR-based multiplexing strategies were developed and set up to fully utilize the capacity of the GAII platform. To optimize sequencing yields a qPCR assay was developed for library quantification. Sample preparation protocol for RNA sequencing is being optimized and a novel DNA saving transposome-based library preparation method is under evaluation. The sequencing facility operates in close collaboration with the Sanger Institute and many of the Nordic centers (Uppsala, Oslo and Tartu as part of the Joint Nordic Use of Research Infrastructure 2007-project) to facilitate the technology development and sharing as well to standardize laboratory and analysis protocols.

The sequencing facility also continued to offer capillary sequencing service producing 209 000 capillary sequencing reads corresponding to 90 Mb of sequence and 5 % increase compared to 2008. In August 2009, after six years of operation, the facility produced the millionth capillary sequencing read. The lucky client was awarded a diploma and some sparkling wine.



Bioinformatics

Dr Imre Västriik and IT Designer Timo Miettinen With the advance of novel measurement technologies, numerous of which are available at FIMM Technology Centre, as well as the need to integrate information from multiple sources, bioinformatics has become an integral part of bioscience. To serve the needs of the biomedical scientists better the Technology Centre has tripled its computational processing power and increased the storage capacity by 30 %. The latest IT tools, such as virtualization and scale-out storage technologies (IBM GPFS cluster file system), are utilized to provide a robust and scalable platform for doing data intensive science. The computing environment is geared towards solving questions in bioinformatics, molecular medicine, genetics as well as related fields and FIMM Technology Centre maintains over hundred physical and virtual servers used for host-

ing bioinformatics databases and other applications. The unit also offers fast and personal user support.

Bioinformatics is also an important component of most of the services offered by the FIMM Technology Centre. As such the offering covers e.g. data management, hosting, archiving and analysis of genotyping and sequencing data. For example, we have developed automated analysis pipelines for "next-generation" sequencing based gene expression analysis, identification of fusion genes and for identification and annotation of genomic variants. Also data integration from multiple resources, such as reference databases, to extract knowledge from the data, is an increasingly relevant capability.



High-Throughput Screening Centre

Dr Maxim Bespalov

The High Throughput Screening Centre (HTC) provides researchers with access to high throughput screening of chemical libraries (in total about 90 000 compounds, including chemical diversity, natural compound, known bioactive and approved drug collections), a genomic siRNA library, a cDNA ORFeome library and other screening collections. The screening centre operates two facilities; a new fully automated ultra-high throughput (uHT) facility as well as a self-service facility.

The fully automated uHT facility was built in 2009. This state-of-the-art system is one of the most powerful academic high-throughput screening systems in Europe. The system can process up to 250 000 data-points in a single day and is suited for mammalian cell-based experiments but can also handle any standard biochemical assay format.

The second high-throughput facility is a self-service centre serving mainly the local research community as a part of Biocentrum Helsinki organization. It is operated jointly between FIMM and Biomedicum Helsinki. The facility contains the equipment to perform smaller chemical and genomic screens in a semi-automated manner.

In addition to performing and assisting with the screening, the staff of the HTC can consult and assist researchers on various other aspects surrounding chemical biology and drug discovery, such as assay development and optimization as well as advice on screening and drug discovery strategies. We also have a network of cheminformaticians, medicinal chemists and other drug development experts.

The HTC operates as a national infrastructure on the national level within the Biocenter Finland Drug Discovery and Chemical Biology (DDCB) network. On the European level FIMM is a partner in the EU-OPENSREEN and EATRIS ESFRI

Consortia. EU-OPENSREEN aims to integrate high-throughput screening and chemical biology infrastructure across Europe, facilitating the exchange of chemical resources and simplifying the access for the researchers. EATRIS aims to build up a translational research infrastructure network, including early drug discovery capacities.

Gene silencing facility:

Cell microarrays for genome-scale RNAi screens

In 2010, FIMM will collaborate with VTT to undertake the production of siRNA-cell microarrays for genome-scale and targeted cell biological analyses. This uHTS platform is based on an Aushon high-throughput microarrayer and Olympus Scan-R high-content imaging system that were purchased in 2009.

Biobanks

Dr Kimmo Pitkänen

Biobanks, professionally managed archives of human derived samples, are an essential asset for modern biomedical research. Some of the most important national biobanking resources



are located on the Meilahti campus. The long tradition and extensive biobanking know-how of National Institute for Health and Welfare (THL), the diagnostic patient samples and data of Hospital District of Helsinki and Uusimaa (HUS) and the world-class science of the University of Helsinki, combined with the systems biology and bioinformatics expertise of FIMM, make the campus the most important hub for biobanking in Finland.

FIMM has been responsible for coordinating the development of Meilahti biobanking activities. During 2009, the first concrete steps towards centralized biobanking on the campus were taken by setting up an expandable, liquid nitrogen based storage system for 335 000 samples. The facility has dedicated professional staff and detailed operating, as well as safety, procedures. Also automated sample storage systems have been considered and are still in process of being evaluated.

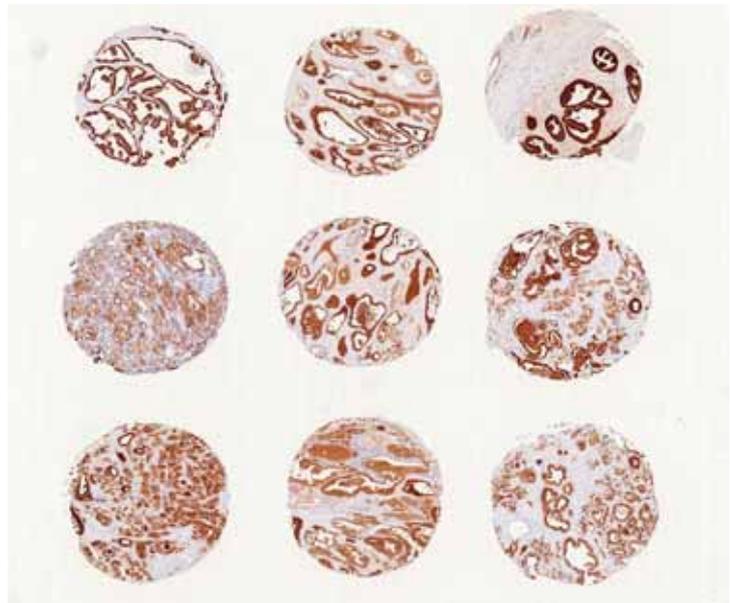
Tissue microarray infrastructure and clinical informatics

Dr Johan Lundin and Dr Juha Turunen

The tissue microarray (TMA) facility was developed in co-ordination with HUS and HUSLAB Department of Pathology. HUSLAB has more than 4 million paraffin-embedded tissue blocks in its archive and also many important collections with associated clinical data which have been utilized during building this infrastructure.

The samples for TMA blocks are chosen carefully by an expert pathologist to make sure that the most representative sample areas will be studied. TMA blocks are prepared with a semi-automated instrument that allows making of 8 replica blocks at a time. One TMA block can contain 100 to 500 samples.

TMA blocks are sectioned with a fully motorized microtome attached to a section transfer system which allows an accurate sectioning. Sectioned slides can further be stained with e.g. immuno-



histochemistry or in situ hybridisation. Stained slides can be screened and analyzed traditionally by microscope or they can be scanned and analysed on computer screen. Staining analysis can further be correlated with clinical follow-up data.

A 2009 started pilot project, jointly run and financed by FIMM and HUS, has developed standard procedures for utilization of human tissue samples, particularly in the form of tissue microarrays. The project brings together clinicians, pathologists and researchers.

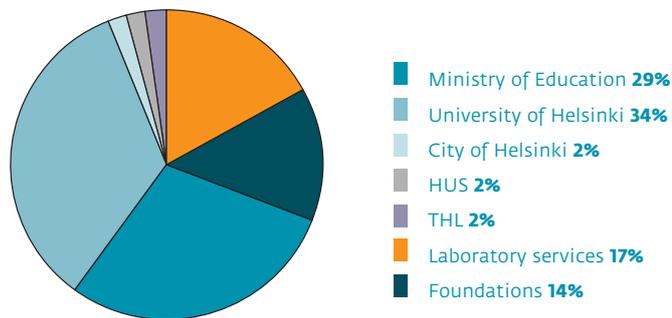


7 Private foundations supporting FIMM and finances

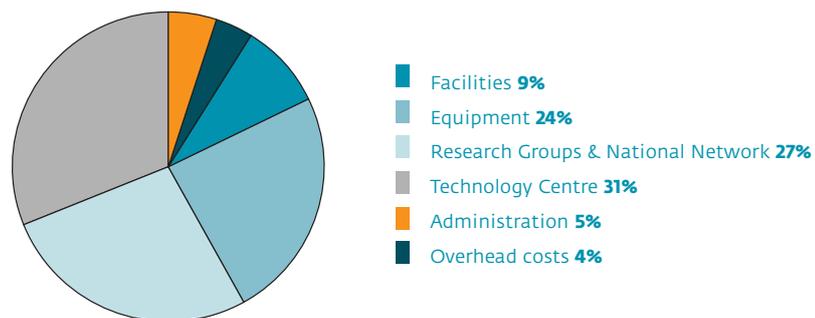
The Jane and Aatos Erkko Foundation, the Sigrid Jusélius Foundation, the Finnish Medical Foundation and the Orion-Farmos Research Foundation have committed to provide significant support for FIMM for the initial five-year period. Their support has been allocated to the new FIMM-EMBL groups to cover the salaries of the group leaders, members of the groups as well as consumables and other laboratory costs. The three year direct support from the Ministry of Education has provided FIMM the opportunity to start to build up a world-class research infrastructure which is essential in successful international recruitments.



FIMM SOURCES OF FUNDING 2009 (7,66 M€)



FIMM EXPENSES 2009



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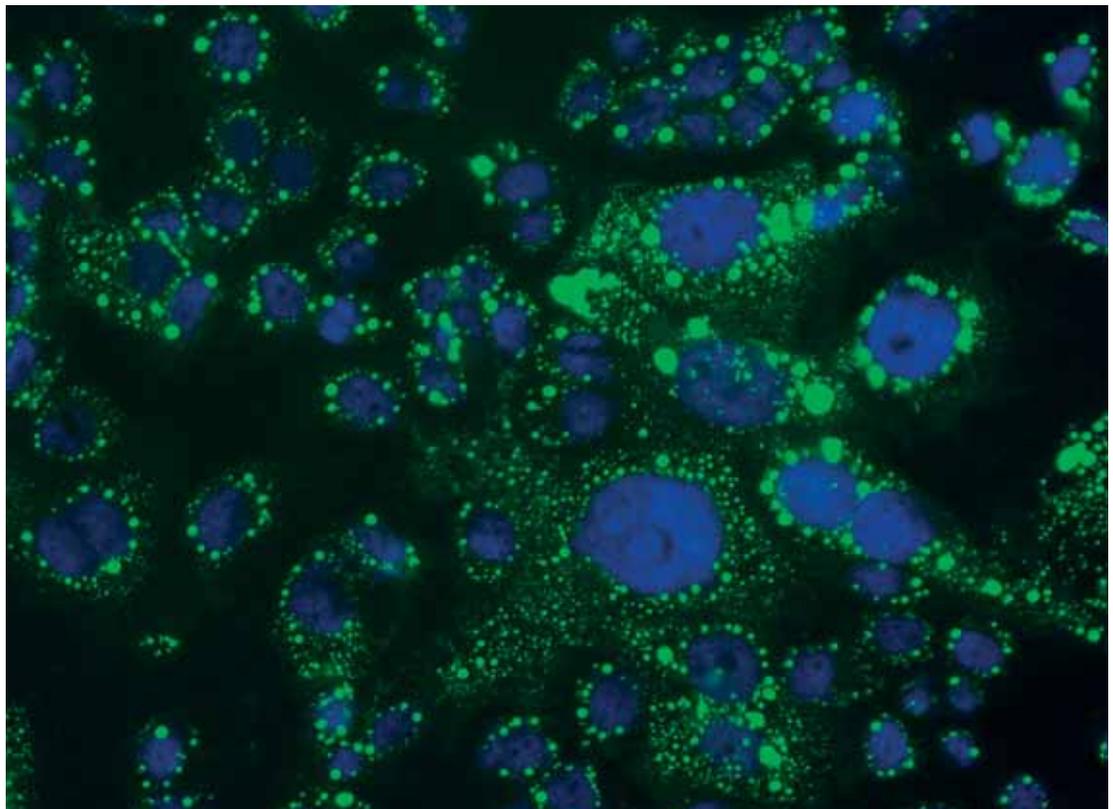
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9 Personnel

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(As February 2010)



10 Publications by FIMM scientists in 2009—2010

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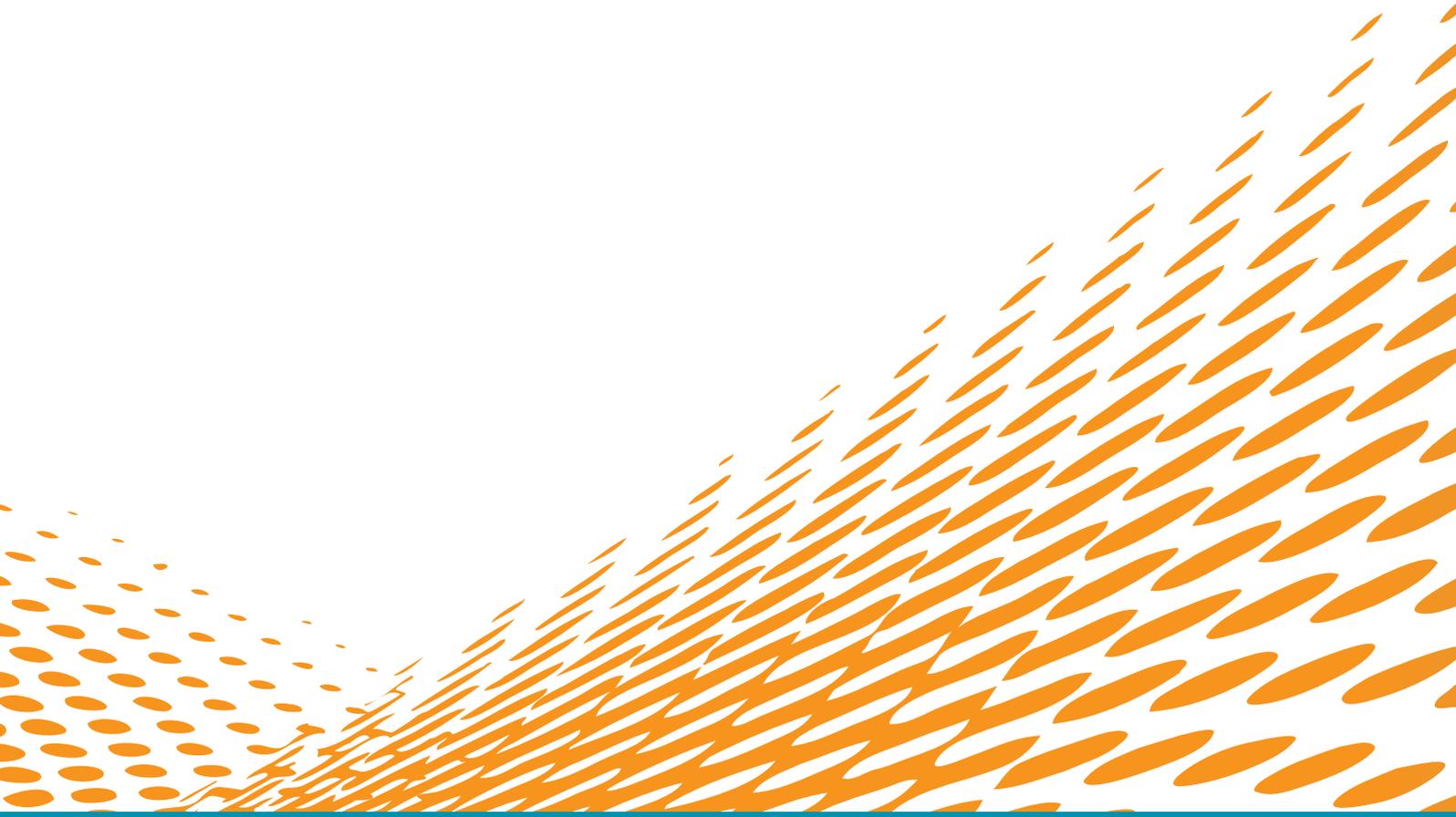
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