UNIVERSITY OF HELSINKI

Institute of Biotechnology – Annual report 2010

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Institute of Biotechnology
Annual report 2010

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February

Brachypodium: A small grass with a big role to play

Researchers at the Institute of Biotechnology reported in Nature the sequence of *Brachypodium distachyon*, purple brome grass. This was the first wild grass to be sequenced.

The work represents a breakthrough because the *Brachypodium* genome, which is small like the plant, is organized in much the same way regarding gene content and order as are the large, unsequenced genomes of key crops including wheat, barley, rye, oat, and fodder grasses.

Sequencing and analysis of the *Brachypodium* genome was carried out by a team of 60 researchers. One of the teams, led by **Alan Schulman** of the Institute of Biotechnology and MTT and by Thomas Wicker of the University of Zurich, characterized the transposable elements of the genome.

Courtesy of the John Innes Centre

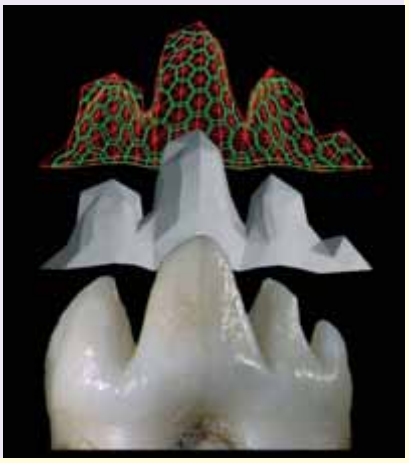
The International Brachypodium Initiative. Genome sequencing and analysis of the model grass Brachypodium distachyon. Nature. 2010; 463: 763–768.

March

The formula for making teeth will soon be found

Academy Professor **Jukka Jernvall** and his team investigate the evolutionary development of mammal teeth. After over 15 years of work, the team has compiled so much data that the main aspects of a formula for making teeth are beginning to be clear. The results were published in Nature.

Salazar-Ciudad I, Jernvall J. A computational model of teeth and the developmental origins of morphological variation. Nature. 2010 Mar 25;464(7288):583–6.



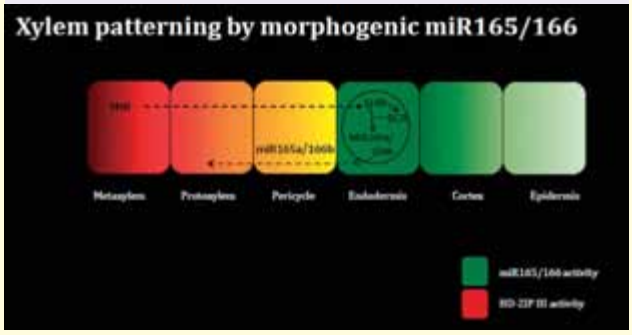
April

Ontogenesis is regulated by moving microRNA molecules

The genes in humans and many other species have been surveyed but their operating principles remain rather unknown. Researchers do not know precisely how genes guide development of various human tissues, or what causes developmental disorders. MicroRNA molecules are recently identified regulatory factors whose ongoing analysis provide more insight into the matter.

Professor **Yrjö Helariutta's** team and colleagues showed in their study the key role of these molecules in chemical communication between plant cells. They showed that microRNAs are capable of moving from cell to cell, and conveying information between them. However, the research findings are universal, since besides plants, these molecules also appear in animal and human tissues, such as in brains. The results were published in Nature.

Carlsbecker A, Lee J-Y, Roberts CJ, Dettmer J, Lehesranta S, Zhou J, Lindgren O, Moreno-Risueno M-A, Vatén A, Thitamadee S, Campilho A, Sebastian J, Bowman J L, Helariutta Y & Benfey PN. Cell signalling by microRNA165/6 directs gene dose-dependent root cell fate. Nature 2010; May 20;465(7296):316–21.



May

Biking and skiing kilometer competitions and other sports

BI staff members took part of the national biking kilometer competition. Winner was **Harri Kangas** from Auvinen lab with more than 3000 kilometers. Inspired by biking kilometer competition Institute's own skiing kilometer competition was organized at December. The competition will go on for as long as there is snow, and there will be small prizes too. Also neck-shoulder-back training and Nordic walking was organized weekly.

A floorball team, **BI Knockouts** has played in a Helsinki area local league organized by the Arena-Center from 1997. In BI Knockouts many foreign researchers have familiarized themselves with a totally new sport.

May

Irma Thesleff as Honorary Doctor at Karolinska Institutet

Irma Thesleff was one of seven honorary doctors appointed by Karolinska Institutet at a ceremony in the Stockholm City Hall 7, May. Professor Thesleff is a world-leading researcher in developmental biology, a field that concerns the growth and development of organisms. From the right: **Irma Thesleff**, business leader **Peter Wallenberg Sr.**, chairman of H&M **Stefan Persson**, and scientists **Andrew Feinberg** and **Tony Pawson**.

June

2010 FEBS Letters Young Group Leader Award

Dr. Hideo Iwai won the 2010 FEBS Letters Young Group Leader Award for his outstanding work and paper entitled "Solution structure of DnaE intein from *Nostoc punctiforme*: structural basis for the design of a new split intein suitable for site specific chemical modification". The prize was presented at the FEBS Congress, 29 June in Sweden.

Hideo Iwai. Interview by Daniela Ruffell. FEBS Lett. 2010 Jun 18;584(12):2494–5.

July

Her Imperial Highness Princess Takamado visited the Institute

HIH Princess **Takamado** of Japan visited the Institute of Biotechnology and Viikki campus on July 2, 2010 as a part of her visit to University of Helsinki. Visit to BI included presentations by Director **Tomi Mäkelä** and Academy Professor **Mart Saarma** and tour to Kinetics and Protein Chemistry laboratories. Princess Takamado was impressed by the craftsmanship of **Ilya Belevitch**'s measuring devices enabling experiments not possible anywhere else in the world.

September

New areas: RNA-binding proteins; cellular reprogramming; stem cell growth dynamics

A open call for new group leaders attracted 57 applications from 12 countries at the beginning of the year, and following a rigorous selection process including interviews, and statements from the SAB and Board three new group leaders were nominated for new tenure-track positions.

Dr. Päivi Ojala has a background in molecular genetics, cell biology, and virology. Ojala aims to decipher molecular mechanisms underlying cellular reprogramming, and transformation by viruses causing cancer such as the Kaposi's Sarcoma herpes virus. Dr. Ojala is currently a Research Professor of the Finnish Cancer Institute in the Genome-Scale Biology Program at Biomedicum Helsinki.

Dr. Ari Pekka Mähönen works in the area of plant biology studying stem cell regulation and growth dynamics in root vascular cambium. The work addresses highly significant questions relating to wood formation and production of renewable energy. Dr. Mähönen has recently completed a post-doctoral period in the group of Ben Scheres at Utrecht University, following a highly awarded PhD at the Institute of Biotechnology.

Dr. Thomas Sandmann was trained as a biochemist, but has since mostly studied regulation of gene expression using genome-wide and computational strategies using the fruit fly as a model system. His current interest is focused on posttransciptional regulation by RNA-binding proteins and miRNAs. Dr. Sandmann works currently as a postdoctoral researcher with Michael Boutros at the German Cancer Research Centre (DKFZ) in Heidelberg.

The potential of CDNF as a Parkinson drug attracts funding

The Michael J. Fox Foundation awarded a $ 515,086 research grant for supporting the research team headed by Professor **Mart Saarma** at the Institute of Biotechnology, who together with **HermoPharma Company** is developing a new Parkinson's disease therapy. The funding will be used to study the therapeutic potential of the neurotrophic factor CDNF in preclinical research on rodent and non-human primate models of Parkinson's disease.

The team involved in the project includes Professors **Raimo K. Tuominen** and **Pekka Männistö**, University of Helsinki, Dr. **Judy Cameron**, University of Pittsburgh, Dr. **Zhiming Zhang**, Udall Parkinson's Disease Research Centers of Excellence, University of Kentucky and Dr. **Richard Penn** University of Illinois & CNS Therapeutics, Inc.

Earlier preclinical research on CDNF, carried out in collaboration with Prof. **Raimo K. Tuominen** has provided highly promising results when comparing the neuroprotective and neurorestorative properties of CDNF with those of other neurotrophic factors, such as glial cell line-derived neurotrophic factor (GDNF). GDNF has been linked to Parkinson´s disease and it has been previously tested in several clinical trials.

The Division for Higher Education and Science from the Ministry of Education learns about the role of the Institute of Biotechnology as part of Biocenter Finland

The Institute of Biotechnology and Biocenter Finland hosted a visit of officials from the Division for Higher Education and Science, the Ministry of Education and Culture, September 21, 2010.

Director **Eero Vuorio** introduced the activities of Biocenter Finland in the restructuring of biological and medical research infrastructure at the national level and Director **Tomi Mäkelä** gave a view to BI as a member institute of Biocenter Finland and as one of the strongest research units of the University of Helsinki. The professor's, postdoctoral researcher's and graduate student's thoughts on BI were heard from the scientists **Sarah Butcher, Frederic Michon** and **Jens Verbeeren**. The visit ended with a tour of several of the technology platform services BI is providing within Biocenter Finland.

October

Genome Biology Research Program starts

The first annual Genome Biology Research Program retreat was organized at Hyytiälä Forestry Field Station with the aim of introducing the member groups of the recently established research program to each other and to find out ways for the members to benefit from the program. 34 participants from **Auvinen**, **Frilander**, **Helariutta**, **Holm**, **Mäkelä** and **Schulman** groups were present. As a result new courses were suggested to be organized and lots of ideas came up concerning the sharing of expertise between groups.

November

The Publication Forum Quality Assessment Project

Professor **Irma Thesleff** nominated as chair of Biosciences II Panel of the Publication Forum Quality Assessment Project. The publication forum quality assessment project has been established from Finnish Universities – Unifi`s initiative in order to assess the quality of publications. The project aims to create a system where the scientific publishing can be assessed quantitatively but also qualitatively. The system is based on the quality assessment of publication channels, namely the scientific journals, series and publishers. Assessment will take place in 23 discipline-specific expert panels.

Mart Saarma co-opted as a member of EMBO Council

EMBO Council co-opted Professor **Mart Saarma** as a member of the Council. Saarma has been EMBO member since 2005. The Council membership is for a three-year period starting in January 2011, with the possibility of one renewal. EMBO Council is the governing body of EMBO, responsible for ensuring the development of the organization. It consists of 15 members. The current Chair of EMBO Council is **Carl-Henrik Heldin.**

December

Group Leader and Principal Investigator winter meeting

Group Leader and Principal Investigator seminar was held on December 10th, in the snowy environment of Kokoushotelli Rantapuisto in Vuosaari.

The main program for the day was a workshop on what Integrative Biology is today and tomorrow at BI facilitated by **Sampsa Hautaniemi** heading a systems biology and bioinformatics group on the Meilahti campus. Participants were divided into five groups that competed against each other in trying to generate competitive programs in Integrative Biology leveraging on current and future expertise at BI. Highly innovative proposals were subsequently evaluated and ranked. The proposal "OxyFly" (**Andressoo, JO**; **Nyman, T**; **Shimmi O**; **Wikström, M**) applying for 500 000 € was rewarded with 1000 "Repe dollars" by a (biased) review panel, where the audience was free to take part to panel discussion and give feedback.

Professor Mart Saarma as a new member of the ERC's Scientific Council

The European Commission appointed **Mart Saarma** together with sex other new members of the Scientific Council, the covering body of ERC. The term of office of the new members runs from 2 February 2011 till the end of 2013.

The Scientific Council, the ERC's governing body, defines the scientific funding strategy and methodologies, and acts on behalf of the scientific community in Europe to promote creativity and innovative research. It is presently chaired by Prof. **Helga Nowotny** and is composed of 22 eminent scientists and scholars, including some Nobel Prize winners.

From the Institute Professors **Tomi Mäkelä** and **Irma Thesleff** have also been members of the ERC's Scientific Council.

New Scientific Advisory Board

The Rector nominated a Scientific Advisory Board for the Institute of Biotechnology for 2011–14: Professor **Joan A . Steitz** (chair), Professor **David Baulcombe**, Professor **Marja Jäättelä**, Professor **Urban Lendahl**, Professor **Annalisa Pastore**, Dr. **Pernille Rørth**, Professor **Kai Simons**, and Professor **John E. Walker** (for details, see page 54).

2010 has been an exciting and busy year at the Institute of Biotechnology. Science at the Institute – or BI – was great and a number of important discoveries got well-deserved attention in top scientific journals and the media. Exciting developments were also taking place in applying new knowledge to the benefit of the society according to our mission for example with the startup of Hermo Pharma Ltd. 2010 was the year when the University of Helsinki was taking its first independent baby steps. This was inevitably strenuous for the entire personnel, but through it all a positive anticipation has been maintained. Execution of BI's strategic plan for 2010–12 started well with a new Board to be followed by an outstanding renewed Scientific Advisory Board nominated at the end of 2010. As part of the plan we initiated a a Genome Biology Research Program and a thematic Integrative Biology Program and made three recruitments to new tenure-track positions. A major development program kicked off in most of our core facilities and research services as part of Biocenter Finland restructuring program.

The new Genome Biology Program touched ground running a nice retreat in October. The Schulman lab took part in the genome sequencing of the first grass plant *Brachypodium*, and figured how its genome is maintained small; an important milestone to get a better hold on important crops such as wheat. The Helariutta gang in turn revealed how cells can communicate using microRNAs as their language. Investigations on regulation of mRNA transcription were also picking up with Frilander lab's identification of a regulator of U12-splicing. The bioinformatics applications of the Holm group are drawing worldwide attention to our servers, and the technology support from the sequencing unit is improving all the time. No wonder there was a lot of excitement doing things together at the retreat. These contributions were complemented by excellent and increasingly collaborative papers from other programs, such as papers e.g. from the Jernvall lab modeling developmental origin of morphological variation, and the solid series of papers from the Structural Biology and Biophysics Program.

A research assessment exercise of the entire University of Helsinki started at the end of the year using a new research information system provided interesting data on BI's scientific output. Considering BI's vision – strengthen its position as an international outstanding research institute in biosciences profiled through high impact research and renowned scientists – it's positive to note that in the majority of high profile papers BI's scientists are the drivers of the research although the great majority of these are international collaborations.

The mission of BI is not only to increase knowledge in biotechnology and integrative biology but also to use this knowledge for the benefit of society. Interesting results on using CDNF to treat Parkinson's disease emerged at BI lead to the quick startup of Hermo Pharma Ltd. With an EPO patent, funding to produce CDNF for preclinical trials, and published success in animal trials the future looks bright, and Mart Saarma's group continues on the preclinical trials at BI with funding from e.g. the Michael J Fox Foundation. There's also been a nice bottom-up initiative in biotechnology with the initiation of a Biotech Club on campus with an ambitious program and excellent steering board with Harvard and Caltech club initiators on board – let's hope the bustle will also stimulate Invention Disclosures still lacking after the legislation change.

A key element in the success of Finland has been investing into R&D. Year 2010 is unfortunately marked as a first year for a long time when public spending into R&D decreased. There are also some other alarming signs of change in the society from a pro-science attitude reflected e.g. in a bill currently in parliament on gene-modified plant production that would cripple research and development in this in Finland. These changes are very hard to understand in the global or European setting where research and innovation are almost universally seen as a key item to develop even in times of financial difficulties to enable growth for future generations. In light of this the recently published guidelines for 2011–15 from the Research and Innovation Council are a turn in the right direction presenting a program for significantly increasing public R&D funding and investing into innovative high quality basic science through making the academic researchers position competitive internationally. This is an opportunity for the Institute of Biotechnology and Biocenter Finland.

Indeed the integration and internationalization of bioscience research through Biocenter Finland sets an example in this regard. In 2010 development of integrated services was in

full speed also at BI in several technology platform areas (e.g. structural biology, imaging, and genome-wide technologies) and significant new restructuring plans e.g. in DNA sequencing were made. Within Biocentrum Helsinki, new frontiers were being mapped at the contact points of biosciences and technology together with Aalto University. Increasing global interest in this area – due largely to biosciences becoming more and more quantitative and exact – is an opportunity Finland should not miss in the coming years, and where stage would be set for a national strong program using the good practices of Biocenter Finland.

Researcher training met with changes in 2010, when naming of Academy of Finland Graduate Schools were changed to Graduate Programs more in line with their primary role as fellowship providers. The active interaction with China in graduate education and science continued and was expanded nationally within Biocenter Finland including a collaborative meeting in Shanghai. Also bachelor's and master's programs on Viikki campus were being reorganized with Sarah Butcher's active participation, and with a decision to continue the HEBIOT program.

In accordance with normal turnover at BI, a highly competitive call for of new group leaders in 2010 led to selection of outstanding scientists with interests integrating well with BI's focus areas as de: Ari-Pekka Mähönen (stem cell regulation in plants), Thomas Sandmann (posttranscriptional regulation by RNA-binding proteins), and Päivi Ojala (cellular reprogramming by Kaposi's sarcoma herpesvirus). Scott Gilbert will spend part of his time at BI within the Finnish Distinguished Professor (FiDiPro) program. In administration we were happy to have Cornelia Thomas's help in grant preparations. Jukka Jernvall started as Academy Professor at the beginning of the year. Juha Partanen took position as the Professor of Genetics at the Faculty of Biological and Environmental Sciences, Pirkko Heikinheimo moved to the Department of Biochemistry and Food Chemistry at the University of Turku, and Claudio Rivera took a position at the Neuroscience Center. Daniel Hirschberg was hired from Sweden as a Senior Researcher to improve services in quantitative proteomics within the Biocenter Finland program. Leevi Kääriäinen ended a fantastic career at BI reminisced at a great seminar and dinner.

Jonathan Knowles finished a record 21-year stint on our Scientific Advisory Board, where his advise has been invaluable – thanks Jonathan! The commitment of Jonathan to science in Finland and elsewhere continues as a FiDiPro professor at FIMM; appropriately his lifetime achievements were acknowledged by the Scrip Lifetime Achievement Award. We are also very pleased with the outstanding new Scientific Advisory Board and Board nominated by the Rector for the coming four years.

Scientists and staff at the Institute of Biotechnology were acknowledged nationally and internationally in many ways some of which are highlighted below. In addition to science accolades, the selection of Mart Saarma to the EMBO Council and the ERC Scientific Council and the active participation of several of us in ERC panels reflect the readiness and interest in international affairs.

I am deeply grateful to all staff members for their continued effort and dedication making the Institute of Biotechnology such a unique place. This is what enables the smiles and achievements seen also on the pages of this Annual Report. Enjoy!

Tomi P. Mäkelä
Director

Signaling in growth and metabolism

- **Nutrient sensing through insulin-like signaling**
- **Sugar sensing mechanisms**

Animals monitor constantly their nutritional status. They use this information to adjust important physiological processes, such as tissue growth and metabolic reactions. Our lab is interested in understanding, how animals perceive their nutritional status and how this information is mediated between different types of cells as well as within the cell. Our main focus is to understand the regulation and physiological consequences of insulin/IGF signaling (IIS), which is the main humoral response to nutrients in multicellular animals.

The nutrient-regulated signaling mechanisms and pathway components currently known are well conserved. Our main model system is the fruit fly *Drosophila melanogaster*, which offers several advantages for research on this topic. Among these are low genetic redundancy, a versatile genetic toolkit for tissue-specific loss- and gain-of-function analyses as well as multitude of assays to monitor the metabolic status and growth of the animal. In parallel, we are using mammalian tissue culture models to test the conservation of our findings and assess their relevance to human metabolic diseases.

At the moment we are performing genetic screens, both *in vivo* and in cell culture. These screens are expected to identify upstream and downstream regulators of IIS. We are also analyzing phenotypes of novel mutants involved in carbohydrate metabolism, aiming to reveal their physiological functions and testing their involvement in IIS and other established metabolic signaling networks.

Selected publications

Hietakangas V, Cohen SM. Regulation of tissue growth through nutrient sensing. Annu Rev Genet. 2009; 43: 389–410.

Szuplewski S, Sandmann T, Hietakangas V, Cohen SM. Drosophila Minus is required for cell proliferation and influences Cyclin E turnover. Genes Dev. 2009; 23: 1998–2003.

Teleman AA*, Hietakangas V*, Sayadian AC, Cohen SM. Nutritional control of protein biosynthetic capacity by insulin via Myc in *Drosophila*. Cell Metab. 2008; 7: 21–32.

Hietakangas V, Cohen SM. Re-evaluating AKT regulation: role of TOR complex 2 in tissue growth. Genes Dev. 2007; 21: 632–637.

Hietakangas V*, Anckar J*, Blomster HA, Fujimoto M, Palvimo JJ, Nakai A, Sistonen L. PDSM, a motif for phosphorylation-dependent SUMO modification. Proc Natl Acad Sci USA. 2006; 103: 45–50.

*equal contribution

Ville Hietakangas

PhD 2004, University of Turku, Finland

Post-doctoral research at EMBL Heidelberg, Germany, 2005–2007

Post-doctoral research at Temasek Life Sciences Laboratory, Singapore, 2007–2009

Group leader at the Institute since 2009

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Group members in 2010

Post-doctoral fellow: Jaakko Mattila

Graduate students: Kiran Hasygar, Essi Lind, Mari Teesalu

Morphological determinants of the endoplasmic reticulum

- **Ratio of ER sheets and tubules changes during cell division and is tightly regulated**

Eija Jokitalo

PhD 1996, University of Helsinki, Finland

Postdoctoral research at Imperial Cancer Research Fund, Cell Biology Laboratory, London, UK, 1997–1999

Researcher at the Institute, 2000–2001

Group Leader at the Institute since 2001

Laboratory Director at the Institute since 2010

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Group members in 2010

Senior scientist: Helena Vihinen, Ilya Belevich (since 1.2.2010), Chun Mei Li (since 1.5.2010)

Graduate students: Merja Joensuu, Maija Puhka, Olli Rämö, Giuseppa Piras (since 1.2.2010)

Technicians: Mervi Lindman, Antti Salminen, Arja Strandell

Undergraduate student: Erika Gucciardo (since 1.3.2010)

Visiting researcher: Agata Zauszkiewicz-Pawlak (1.3.–31.6.2010)

The endoplasmic reticulum (ER) is highly dynamic and complex organelle that hosts fundamental cellular functions such as the synthesis, modification and transport of secretory and membrane proteins and many lipids. ER also has a central role in cell fate decisions as many cell death responses are initiated there. We are studying the sub-compartmental organization and morphogenesis of the ER in mammalian cells. Our main questions are how ER network organization changes during the cell division and what are the regulators of the ER morphology.

Morphologically ER is composed of two very different forms, flattened sheets and tubules which branch to generate a polygonal network. Sheets are predominant over tubules in the central area of the cell, whereas peripheral areas close to the plasma membrane have long interconnected tubules (Puhka *et al*., 2007). We have combined live cell light microscopy imaging to higher resolution imaging techniques transmission electron microscopy and electron tomography of both chemically fixed and high-pressure frozen specimens to characterize the ER morphology. Our first morphological and quantitative analysis of the ER throughout the cell cycle in CHO-K1 cells revealed that the most abundant interphase ER structures, sheets, are completely lost and transformed into continuous branched tubular network (Puhka *et al*., 2007). We provide mechanistic insight into the inheritance of the ER by showing that similar changes in the ER structure are induced by stripping of ribosomes with puromycin from the interphase ER. This is consistent with the observed loss of ribosomes normally occurring during mitosis.

In continuation to this, we characterized the ER of several other mammalian cell types and found significant variation in the ER morphology between different cell types and cell phase changes. Together, our results fit well with a scheme in which the mitotic conversion of an intact sheet to a tubular network proceeds through appearance and enlargement of fenestrations until the structure resembles a tubular network. The conversion would be caused – directly or indirectly – by the ongoing loss of membrane-bound ribosomes. The starting point (intact vs. fenestrated sheets) and the end point (intact or fenestrated sheets vs. tubules) may vary in a manner that is specific to cell type and ribosomal density.

We are now studying further the maintenance of sheet structures and the transition of ER sheets into tubular network by focusing on the molecular determinants supporting these structures. Our second on-going project aims to examine systematically the role of cytoskeleton in the maintenance and dynamics of the ER morphology.

Selected publications

Ylä-Anttila P*, Vihinen H*, Jokitalo E, Eskelinen E-L. 3D tomography reveals connections between the phagophore and endoplasmic reticulum. Autophagy. 2009; 5: 1180–1185.

Jansen M, Pietiäinen VM, Pölönen H, Rasilainen L, Koivusalo M, Ruotsalainen U, Jokitalo E, Ikonen E. Cholesterol substitution increases the structural heterogeneity of caveolae. J Biol Chem. 2008; 283:4610–4618.

Puhka M, Vihinen H, Joensuu M, Jokitalo E. ER remains continuous and undergoes sheet to tubule transformation during cell division in mammalian cells. J Cell Biol. 2007; 179:895–909.

Mattila PK, Pykäläinen A, Saarikangas J, Paavilainen VO, Vihinen H, Jokitalo E, Lappalainen P. Missing-In-Metastasis (MIM) and IRSp53 deform PI(4,5)P2-rich membranes by an inverse BAR domain like mechanism. J Cell Biol. 2007; 176:953–64.

Uchiyama K*, Totsukawa G*, Puhka M*, Kaneko Y, Jokitalo E, Dreveny I, Beuron F, Zhang X, Freemont P and Kondo H. p37 is a p97 adaptor required for golgi and ER biogenesis in interphase and at the end of mitosis. Dev Cell. 2006; 11:803–816.

*equal contribution

Cell polarity regulation in differentiation and development

Jussi Jäntti

PhD 1995, University of Helsinki, Finland

Docent 2002, University of Helsinki, Finland

Postdoctoral research VTT Technical Research Center of Finland, 1995–1999

Institute of Medical Research, University of Cambridge UK, 1999

Group Leader at VTT Technical Research Center of Finland 2001–2005

Group Leader at the Institute since 2005

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- **Genes, proteins, and interactions regulating cell polarity and exocyst complex function in budding yeast and nematodes**

Correct cellular polarity is a prerequisite for differentiation and development in uni- and multicellular organisms. Polarity generation is intimately linked with molecular machineries that govern transport and targeting of intracellular proteins at the cell surface.

Our previous studies have identified several genes and proteins that function in cell polarity regulation. Using both yeast *S. cerevisiae* and the nematode *C. elegans* as model systems we have continued to investigate these molecular interactions that have been well preserved in evolution. We have recently showed that Mso1p interaction with Sec1p is essential for cell polarity and cell differentiation processes (Weber *et al.*, 2010). Our results show that Mso1p interaction mimics syntaxin N-peptide binding to Sec1p-family proteins and thus reveal a novel type of interaction mode for Sec1p family proteins with their regulators (Weber *et al.*, 2010). Furthermore, we showed that *S. cerevisiae* Sec1p possess a C-terminal domain that is needed for Sec1p protein interaction with SNARE complexes and that this C-terminal domain can alone stimulate SNARE complex assembly both *in vivo* and *in vitro*. We showed that the Sec1p binding protein Mso1p interacts with a GTP-bound rab GTPase Sec4 and that this interaction occurs prior to SNARE complex formation. These results provide novel spatio-temporal resolution on the molecular interactions of a rab GTPase with a Sec1p binding protein in the process of SNARE complex formation (Weber-Boyvat *et al.*, 2010). We have also characterized the contribution of phosphorylation on SNARE complex function in exocytosis in *S. cerevisiae* (Yuan and Jäntti, 2010). Using genetic and biochemical approaches, we are presently identifying in *S. cerevisiae* and in *C. elegans* novel genes and proteins that participate in polarity regulation and investigating how these interactions contribute to cell polarity regulation.

Selected publications

Weber-Boyvat M, Aro N, Chernov KG, Nyman T, Jäntti J. Sec1p and Mso1p C-terminal tails cooperate with the SNAREs and Sec4p in polarized exocytosis. Mol Biol Cell. 2011 Jan;22(2):230–44.

Weber M, Chernov K, Turakainen H, Wohlfahrt G, Pajunen M, Savilahti H, Jäntti J. Mso1p regulates membrane fusion through interactions with the putative N-peptide-binding area in Sec1p domain 1. Mol Biol Cell. 2010 Apr;21(8):1362–74.

Yuan Q, Jäntti J. Functional analysis of phosphorylation on *Saccharomyces cerevisiae* syntaxin 1 homologues Sso1p and Sso2p. PLoS One. 2010 Oct 11;5(10):e13323.

Zhao X, Jäntti J. Functional characterization of the trans-membrane domain interactions of the Sec61 protein translocation complex beta-subunit. BMC Cell Biol. 2009; 10: 76.

Pispa J, Palmen S, Holmberg CI, Jäntti J. *C. elegans* dss-1 is functionally conserved and required for oogenesis and larval growth. BMC Dev Biol. 2008; 8: 51.

Feng D, Zhao X, Soromani C, Toikkanen J, Römisch K, Keränen S, Jäntti J. The trans-membrane domain is sufficient for Sbh1p function and it mediates interactions with Sec61-translocon and Rtn1p. J Biol Chem. 2007; 282: 30618–30628.

Group members in 2010

Postdoctoral fellows: Nina Aro, Konstantin Chernov, Yaming Jiu

Graduate students: Marion Weber, Qiang Yuan

Technician: Anna-Liisa Nyfors (half-time)

Regulation of actin and plasma membrane dynamics in mammalian cells

- **Roles of actin binding proteins in the dynamics of contractile and protrusive actin filament structures**
- **Regulation of the actin cytoskeleton – plasma membrane interplay in cell motility and morphogenesis**

Coordinated polymerization of actin filaments against cellular membranes provides the force for a number of biological processes, including cell morphogenesis, motility, endocytosis, and phagocytosis. In addition, actin filaments together with myosin filaments form contractile structures in muscle and non-muscle cells. Thus, the actin cytoskeleton has a fundamental role in a large number of physiological processes in all eukaryotes. Furthermore, abnormalities in actin-dependent processes, including cell motility and cytokinesis, often occur in cancer cells and many pathogens exploit the actin polymerization machinery of the host cell during the infection process. Thus, elucidating the mechanisms of actin dynamics will also be valuable for understanding these actin-dependent pathological states.

Our laboratory applies a wide range of biochemical, cell biological, and genetic methods to reveal how the structure and dynamics of the actin cytoskeleton are regulated during various cellular and developmental processes. One of our main interests is to examine the roles of actin monomer binding proteins twinfilin and cyclase-associated-protein (CAP) in actin dynamics and to elucidate how these proteins contribute to various motile processes in cells. We also study how assembly and dynamics of contractile actin filament structures in muscle cells (myofibrils) and non-muscle cells (stress fibers) are regulated by different actin binding proteins, and how the actin cytoskeleton contributes to inducible secretion in mast cells. Finally, we aim to reveal how membrane phospholipids regulate actin dynamics, and how the I-BAR domain family proteins deform PI(4,5)P2-rich membranes to coordinate actin and plasma membrane dynamics during cell motility and morphogenesis.

Selected publications

Hotulainen P, Llano O, Smirnov S, Tanhuanpää K, Faix J, Rivera C, Lappalainen P. Defining mechanisms of actin polymerization and depolymerization during dendritic spine morphogenesis. J Cell Biol. 2009; 185: 323–339.

Saarikangas J, Zhao H, Pykäläinen A, Laurinmäki P, Mattila PK, Kinnunen P, Butcher SJ, Lappalainen P. Molecular mechanisms of membrane deformation by I-BAR domain proteins. Curr Biol. 2009; 19: 95–107.

Chereau D, Boczkowska M, Skwarek-Maruszewska A, Fujiwara I, Hayes DB, Renowski G, Lappalainen P, Pollard TD, Dominguez R. Leiomodin is an actin filament nucleator in muscle cells. Science. 2008; 320: 239–243.

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Paavilainen VO, Oksanen E, Goldman A, Lappalainen P. Structure of the actin-depolymerizing factor homology domain in complex with actin. J Cell Biol. 2008; 182: 51–59.

Pekka Lappalainen

PhD 1995, EMBL-Heidelberg, Germany

Post-doctoral research at University of California, Berkeley, USA 1995–1998

Group Leader at the Institute since 1998

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Technician: Anna-Liisa Nyfors (half-time)

Role of ion transporters in neurotransmission

- **KCC2 as a factor synchronizing inhibitory and excitatory synapses and their maturation**
- **Interplay between intracellular chloride regulation and neurotrophic factors in epilepsy and survival by thyroxin**

A central question in neurobiology is the elucidation of the molecular mechanisms orchestrating synaptic maturation in the central nervous system. Alterations in the mechanisms synchronizing inhibitory and excitatory synapses and their maturation may lead to developmentally related disorders including autism, mental retardation and epilepsy. Despite the essential importance of these events very little is known about the molecular mechanisms involved. Our recent data identified the neuron specific K-Cl cotransporter KCC2 as a potential synchronizing factor. This transporter plays a pivotal role in the maturation of inhibitory synapses. Its developmental activation induces a decrease in intracellular chloride that sets the gradual shift in GABA/glycine mediated responses from depolarizing to hyperpolarizing. We found previously that KCC2 also plays a crucial role in the formation of dendritic spines as well as functional glutamatergic synapses. Strikingly, this is independent of its chloride extrusion activity and relies on the interaction of the intracellular domain with the spine protein 4.1N that link it to the regulation of AMPA glutamate receptor trafficking. We have now found additional interacting proteins that mediate a direct regulatory role of KCC2 on the intra-spine actin cytoskeleton.

Because neurotrophic factors are regulated by neuronal activity and can regulate inhibitory and excitatory synapses, they are key molecules to mediate developmental and adult forms of synaptic plasticity. We have previously elucidated part of the mechanisms involved in the interplay between intracellular chloride regulation and neurotrophic factors in clinically important paradigms for epilepsy and CNS injury. From these studies is became clear that a more detailed knowledge of the mechanism regulating KCC2 at the transcriptional level was missing. Now we have defined in more detail the molecular mechanism that mediates the up-regulatory action of BDNF on KCC2 expression in immature neurons. This involves a molecular cascade that is dependent on the expression of MAP-kinase the transcription factor EGR4.

Selected publications

Bespalov MM, Sidorova YA, Tumova S, Ahonen-Bishopp A, Magalhães AC, Kulesskiy E, Paveliev M, Rivera C, Rauvala H, Saarma M. Heparan sulfate proteoglycan syndecan-3 is a novel receptor for GDNF, neurturin, and artemin. Cell Biol. 2011 192(1):153–69.

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Claudio Rivera

PhD 1995, Stockholm University, Sweden

Postdoctoral Fellow of the Swedish Natural Science Research Council performed at the Department of Animal Physiology University of Helsinki, 1996–1998

Docent in Neurobiology, University of Helsinki 2002

Project Leader at the Institute 2002–2007

Group Leader at the Institute 2008–2010

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Technician: Miika Palviainen

Claudio Rivera has moved to the Neuroscience Center (University of Helsinki) in January 2011

Actin as an organizer of gene expression

- **Mechanisms of nucleocytoplasmic shuttling and polymerization of nuclear actin**
- **Roles of novel nuclear actin regulating proteins in actin-regulated gene expression**

The actin cytoskeleton has an essential role in several important cell biological processes, including cell motility and membrane dynamics. These cytoplasmic functions of actin are well characterized, but the role of actin in the nucleus has been less obvious. Recent studies have, however, identified actin as an essential component of several nuclear complexes, including basal transcription machinery and chromatin remodelers. Moreover, nuclear actin can also function as a signal responsive regulator of specific transcription factors. Nuclear actin levels respond to cellular stress, and may therefore play a role in the pathology of different diseases. Hence the functions of actin in the nucleus seem to be as versatile, and as important, as in the cytoplasm. However, the molecular mechanism by which actin functions in the nucleus has remained largely unclear.

To understand how actin is able to contribute to essential nuclear processes our lab is studying several aspects of actin within the nuclear compartment. We are developing several microscopy-based tools to visualize nuclear actin. We are, for example, using live-cell imaging to study nucleocytoplasmic shuttling and polymerization properties of nuclear actin. We have recently shown that the nuclear import of actin occurs by an energy-dependent mechanism, and have identified candidate proteins for mediating this process. Moreover, by using RNAi-based screening, we have discovered novel nuclear actin regulating proteins, and are currently elucidating in molecular detail how they impinge on actin. Two of the most interesting factors are Fbp11, which may function as a general regulator of nuclear actin polymerization, and Phactr-protein family, which seem to sense cellular actin levels to modulate cell morphology. In the future, we aim to apply the knowledge that we have gained from the basic properties of nuclear actin to elucidate the molecular mechanisms by which actin regulates gene expression.

Selected publications

Skarp KP, Vartiainen MK. Actin on DNA-an ancient and dynamic relationship. Cytoskeleton (Hoboken). 2010 Aug;67(8):487–95.

Pawłowski R, Rajakylä EK, Vartiainen MK, Treisman R. An actin-regulated importin α/β-dependent extended bipartite NLS directs nuclear import of MRTF-A. EMBO J. 2010 Oct 20;29(20):3448–58.

Vartiainen MK. Nuclear actin – from form to function. FEBS Letters. 2008; 582(14): 2033–40.

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PhD 2002, University of Helsinki, Finland

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Undergraduate students: Johanna Puusaari, Kaisa Rajakylä

RNA virus replication and its inhibition

RNA viruses cause devastating infectious diseases, and new epidemics continue to emerge. We aim towards deep understanding of RNA virus replication at the molecular level. Through the discovery of basic mechanistic principles, we also hope to develop new and general antiviral strategies. We mainly work with alphaviruses, including Semliki Forest virus. The mosquito-borne alphaviruses can cause large outbreaks, as exemplified by the recent Chikungunya virus epidemic.

The replication of all positive-strand RNA viruses takes place in membrane-associated complexes in the cytoplasm of infected cells. The membrane plays organizing and supporting, as well as protecting and activating roles for the replication complex. The replication complex of alphaviruses and many related viruses is a membrane invagination of 50 nm in diameter. We have shown by electron microscopic tomography that each invagination is connected to the cytoplasm by a narrow neck structure. Thousands of active replication complexes are formed on the inner surface of the plasma membrane and undergo large-scale transport to the outer surface of endo-lysosomal vacuoles. The structure and formation of the replication complexes are studied by advanced electron microscopy and confocal microscopy methods to dissect the roles of viral and cellular components.

We investigate the individual functional domains of the RNA replicase. For the alphavirus protease, we have discovered novel modulation by RNA, and for the macro domain, which is also present in several cellular proteins, we have characterized its interaction with ADP-ribose derivatives. We also study other viruses, including hepatitis E virus and the infamous SARS coronavirus, for which we have discovered one of the RNA capping enzymes. In antiviral studies, we have developed automated screening methods utilizing marker genes inserted in the alphavirus genome. We have discovered antivirally active compounds, whose molecular mechanism of action and efficacy in animal models are currently being pursued.

Group members: Postdoctoral fellows: Kirsi Hellström, Pasi Kaukinen Graduate students: Giuseppe Balistreri, Katri Kallio, Maarit Neuvonen, Leena Pohjala, Pirjo Spuul

Selected publications

Spuul P, Balistreri G, Kääriäinen L, Ahola T. Phosphatidylinositol 3-kinase-, actin-, and microtubule-dependent transport of Semliki Forest virus replication complexes from the plasma membrane to modified lysosomes. J Virol. 2010; 84: 7543–7557.

Chen Y, Cai H, Pan J, Xian N, Tien P, Ahola T, Deyin G. Functional screen reveals SARS coronavirus nonstructural protein nsp14 as a novel cap N7 methyltransferase. Proc Natl Acad Sci USA. 2009; 106: 3484–3489.

Neuvonen M, Ahola T. Differential activities of cellular and viral macro domain proteins in binding of ADP-ribose metabolites. J Mol Biol. 2009; 385: 212–225.

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Tero Ahola
Junior PI

PhD 1997, University of Helsinki, Finland

Postdoctoral research at University of Wisconsin-Madison & Howard Hughes Medical Institute, USA and Pfizer Global Research & Development, Sandwich, UK, 1998–2001

Academy Research Fellow at the Institute 2002–2007

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Developmental genetics of turtle shell development

- **Intercellular communication regulating the formation, patterning, and growth coordination of the scutes, the ectodermal covering of the turtle shell**
- **Molecular and cellular characterization of the plastron mesenchyme as a model for facial dermis and bone formation**

Our research interest is how do the scutes of the turtle shell form and grow, and how is this development related to the formation and growth of structures such as hair, feathers and teeth? Is the formation of sutures in turtle bones directed by the same mechanisms that direct the formation of sutures in the face and skull?

We have localized the scute primordia of the developing turtle, *Trachemys scripta*, and have shown the expression of several paracrine factor genes expressed in these scute primordia. We also have shown by molecular markers that the dermis of the turtle plastron is an ectomesenchyme, and have further evidence that this cell layer is derived from neural crest cells, similar to the origin of the facial dermis.

If the turtle plastron has indeed developed by the re-specification of trunk neural crest cells into cranial (skeletogenic) neural crest cells, this might be the first evidence in vertebrates of evolution by cell re-specification. The mechanisms by which scute development has evolved to coordinate growth on all sides of the developing structure should provide insights into how certain constraints have been circumvented and how the paracrine factor inter-relationships have evolved.

Selected publications

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Scott Gilbert
FiDiPro Professor

PhD 1976, The Johns Hopkins University, USA, Postdoctoral research, molecular biology, developmental biology, University of Wisconsin, 1976–1980

Professorships at Swarthmore College from 1980–, Doctor Honoris Causae, University of Helsinki,
Winner of the Kowalevsky Prize 2004
Viktor Hamburger Prize 2002
Dwight J. Ingle Award 1984
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Fellow, AAAS, St. Petersburg Academy of Science; Education Chair, Society for Developmental Biology;
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Author of Developmental Biology (ninth edition); Bioethics and the New Embryology; Ecological Developmental Biology: Integrating Epigenetics, Medicine, and Evolution.

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Evolution and development

- **Computational and quantitative analyses of patterning**
- **Developmental and evolutionary complexity**
- **The tooth model in life history studies**

Evolutionary developmental biology is a field of biology aiming to uncover how developmental mechanisms and genes have changed in the evolution of phenotypes. Our aim is to construct developmental-based models that are used to predict patterns of phenotypic variation. Our ultimate goal is to discover the logic' that governs the production of the phenotypic variation available for natural selection. Most of our work uses mammalian dentition as a model system in the context of both micro- and macroevolution, and methods ranging from developmental biology experiments to computer models simulating development. Our developmental biology questions include regulation of tooth shape, number, and regeneration.

Tooth phenotypes are invariably complex and difficult to fully characterize, and we are developing approaches to allow fast-throughput' analysis of three-dimensional shapes. To study natural and mutant phenotypes, we have developed a computerized MorphoBrowser database for three-dimensional phenotypes. MorphoBrowser allows the linking of macroevolution level collections on fossils, microevolution level data collected from natural populations, and experimentally changed morphologies of mouse mutants (morphobrowser.biocenter.helsinki.fi/).

Another aim is to understand factors that have contributed to the evolution of longevity in the wild. Dental development is one measure that has been used extensively to estimate maturation rates and ages in mammals, especially in primates. We extend these studies by measuring life-long changes in the structural design of the teeth (dental senescence). The objective is to discover what it means to get old in the smallest-bodied primates, mouse lemurs, in a wild rainforest setting in Madagascar. The tiny 45 gram (1.6 oz) mouse lemurs, which in captivity can live almost ten times longer than mice, bridge work to the biological basis of long lifespan and senescence in humans.

Selected publications

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Evans AR, Wilson GP, Fortelius M, Jernvall J. High-level similarity of dentitions in carnivorans and rodents. Nature. 2007; 445: 78–81.

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Jukka Jernvall

PhD 1995, University of Helsinki, Finland

Postdoctoral research at Stony Brook University, NY, USA, 1996–1997; at University of Helsinki 1997–2000

Group Leader at the Institute since 2000

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Undergraduate students: Tuomas Kankaanpää, Addison Kemp

Regulation of neuronal development in the embryonic brain

- **Differentiation and proliferation of neuronal precursors**
- **Intercellular growth factor signals and cell-type specific transcription factors controlling development**

We are interested in the control of proliferation and differentiation of neural progenitor cells in the developing vertebrate brain, especially the midbrain. Among other neuronal types, the embryonic midbrain gives rise to dopaminergic neurons, which are important for regulation of motor activity and adjustment of the behavioural state of an individual. Degeneration of some of the midbrain dopaminergic nuclei has been associated with the movement disorder Parkinson's disease. Also psychiatric disease like addiction, depression and schizophrenia are thought to be caused by alterations in the activity of neural circuitries in the midbrain and anterior hindbrain.

Our focus has been on the control of midbrain neurogenesis by intercellular growth factor signals and cell-type specific transcription factors. We have characterized how fibroblast growth factor (FGF) signals from the isthmic organizer, a key regulatory signaling center, are received by their target cells and regulate cell survival, neuroepithelial regionalization, neural stem cell activity and maturation of dopaminergic neuron precursors. The function of the dopaminergic neurons is controlled by neural circuitries in the midbrain, including subpopulations of inhibitory GABAergic neurons. Development of the GABAergic neurons in the midbrain is very poorly understood. We have identified transcription networks controlling selection of the inhibitory GABAergic vs. excitatory glutamatergic fate in the post-mitotic midbrain precursor cells. This work has also revealed unexpected heterogeneity in the developmental origins and regulatory mechanisms of the midbrain GABAergic neurons. Recently, we have shown that similar transcriptional networks operate also in some of the other GABAergic neuron populations in the brain.

In brief, our work is focused on the maintenance of neural stem cell properties and transcriptional regulation of differentiating of dopaminergic and GABAergic neuron subpopulations in the developing midbrain. In the long run, we believe that knowledge on the basic developmental mechanisms and their variation will be of importance for understanding and treatment of neurological and psychiatric disorders.

Selected publications

Lahti L, Saarimäki-Vire J, Rita H, Partanen J. Fgf-signaling gradient maintains symmetrical proliferative divisions of midbrain neuronal progenitors. Dev Biol. 2011; 349: 270–282.

Chilov D, Sinjushina N, Saarimäki-Vire J, Taketo MM, Partanen J. beta-Catenin regulates intercellular signalling networks and cell-type specific transcription in the developing mouse midbrain-rhombomere 1 region. PLoS One. 2010; 5:e10881

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Kala K, Haugas M, Lilleväli K, Guimera J, Wurst W, Salminen M, Partanen J. Gata2 is a tissue-specific post-mitotic selector gene for midbrain GABAergic neurons. Development. 2009; 136: 253–62.

Saarimäki-Vire J, Peltopuro P, Lahti L, Naserke T, Blak AA, Vogt Weisenhorn DM, Ornitz D, Wurst W, Partanen J. FGF receptors co-operate to regulate neural progenitor properties in the developing mid- and hindbrain. J Neurosci. 2007; 27: 8581–8592.

Juha Partanen

PhD 1993, University of Helsinki, Finland

Postdoctoral research at Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto (Laboratory of Prof. Janet Rossant), Canada, 1994–1998

Group Leader at the Institute since 1998

Research Director, Laboratory Animal Center, University of Helsinki 1.7.2008–31.12.2008

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Undergraduate students: Sini-Maaria Virolainen, Tanja Wennerström, Mia Åstrand

The inner ear – from development to therapeutic applications

- **Identification of key transcriptional and cell cycle regulators in the inner ear sensory epithelia**
- **Regenerative biology of the inner ear sensory epithelia**
- **Cell polarity in defining the cytoarchitecture of the hearing organ**

The inner ear sensory cells, the hair cells, translate stimuli from sound vibrations and head motions into electrical signals perceived by the nervous system. Due to the lack of hair cell regeneration, cumulative loss of these cells causes progressive, permanent hearing impairment. The advent of regenerative medicine has kick-started the search for biological treatment strategies to restore inner ear function.

We have focused on cell cycle regulation, DNA damage and DNA repair capacity in the inner ear sensory epithelia. In this regard, hair cells serve as excellent models of highly differentiated, postmitotic cells. We have shown that the maintenance of the postmitotic state is crucial for the life-long survival of hair cells. When auditory hair cells are forced into the cell cycle, the DNA damage response pathway is activated, leading to activation of the p53 apoptotic pathway. We have revealed the hypersensitivity of auditory hair cells to p53 induction. Our data, emphasizing the need of keeping p53 in check in hair cells, have clinical implications in connection with stressors such as noise trauma and ototoxic drugs (Sulg *et al*., 2010). We have continued this project by dissecting the role of the primary upstream p53 regulators, Mdm2 and Mdm4, in hair cells.

The long-term aim of our group is to develop a method for hair cell replacement to treat hearing loss. Supporting cells of the inner ear sensory epithelia likely comprise the platform for future regenerative therapies. For efficient regeneration, these postmitotic cells should be triggered to divide and then reprogrammed to functional hair cells. We have found that cyclin D1 underlies the proliferative potential of supporting cells: temporal pattern of this expression closely parallels with the response of supporting cells to mitogens (Laine *et al* 2010). Based on our results, cyclin D1 might serve as a suitable target for hair cell regeneration. This topic is addressed in our ongoing studies.

We have started to study the significance of polarity of auditory supporting cells during development and maturation and to investigate the possible link between cell polarity and regenerative capacity. Our ongoing studies reveal the critical role of the conserved Cdc42/Par3/Par6/aPKC polarity complex in the formation of the cytoarchitecture of the auditory sensory epithelium.

Selected publications

Laine H, Sulg M, Kirjavainen A, Pirvola U. Cell cycle regulation in the inner ear sensory epithelia: Role of cyclin D1 and cyclin-dependent kinase inhibitors. Dev Biol. 2010; 134–146.

Sulg M, Kirjavainen A, Pajusola K, Bueler H, Ylikoski J, Laiho M, Pirvola U. Proliferative potential and p53 sensitivity of the sensory hair cells of the inner ear. J Neurochem. 2010; 112: 1513–1526.

Ulla Pirvola

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Undergraduate student: Tommi Anttonen

Technician: Sari Tynkkynen

Structure, biology and therapeutic potential of neurotrophic factors

- **GDNF family ligands and their receptors in mammalian development, cell death, and in the neurodegeneration of midbrain dopaminergic neurons**
- **Receptors, intracellular signaling, anti-apoptotic effects and therapeutic potential of MANF and CDNF**

Mart Saarma

PhD 1975, University of Tartu, Estonia

Postdoctoral research at the Moscow Institute of Molecular Biology, Russia, 1975; Friedrich Miescher Institute, Basel, Switzerland, 1982

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Group Leader at the Institute since 1990

Director of the Institute 1990–2008

Director of Biocenter Finland 2008–2009

Director of the CoE in Molecular and Integrative Neuroscience Research, 2008

Academy Professor, 2009–

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Our group is interested in the structure, biology and therapeutic effects of neurotrophic factors. We study GDNF family ligands (GDNF, neurturin, artemin and persephin) and their receptors, GFRa1–4 and Ret. We have solved the crystal structure of GDNF in the complex with its receptor GFRa1 and found that one of the GDNF splice isoforms in secreted in the activity-dependent manner. We have also found that heparan sulfate proteoglycan syndecan-3 is a novel receptor for GDNF, neurturin, and artemin. GDNF-syndecan-3 interaction mediates both cell spreading, neurite outgrowth and promotes migration of cortical neurons. To study the biology of GDNF family ligands and their receptors in normal development, cell death and neurodegeneration of the midbrain dopaminergic neurons, we have developed mice enabling conditional deletion of GDNF and GFRa1 from different regions of the nervous system. We have also developed mice over-expressing GDNF from its own locus and found that GDNF regulates midbrain dopamine neurons, but also the development of urogentital tract and kidney much broader than previously known.

Our group has discovered a new neurotrophic factor called cerebral dopamine neurotrophic factor (CDNF) that, together with mesencephalic astrocyte-derived neurotrophic factor (MANF) constitute a novel family of neurotrophic factors. We are currently studying the structure, biology and therapeutic potential of these new factors. We have in collaboration with Structural Biology Program solved the crystal structure of CDNF and MANF, the solution NMR structure of MANF and found that they structurally form a new class of proteins. NMR study reveals that the C-terminal domain of MANF (C-MANF) is homologous to the SAP domain of Ku70, a well-known inhibitor of pro-apoptotic protein Bax. Microinjection studies confirmed that MANF and C-MANF protect neurons from Bax-induced cell death intracellularly as efficiently as Ku70. Thus CDNF-MANF family neurotrophic factors differ from other known neurotrophic factors both in structure and also in their mode of action.

To study the *in vivo* role of these new neurotrophioc factors we have developed conventional and conditional knockout mice of CDNF and MANF. Analysis of the phenotype of these mice is ongoing. Since CDNF and MANF are most potent neurorestorative proteins in rodent models of Parkinson's disease they are, together with GDNF, extremely attractive therapeutic candidates. We are currently making serious efforts to take CDNF to Phase I clinical trials for the treatment of Parkinson's disease.

Group members in 2010

Senior scientists: Johan Peränen, Pia Runeberg-Roos

Postdoctoral fellows: Maxim Bespalov, Jukka Kallijärvi, Maria Lindahl, Päivi Lindholm, Liina Nevalaita, Yulia Sidorova

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Selected publications

Bespalov MM, Sidorova Y A, Tumova S, Ahonen-Bishopp A, Magalhães AC, Kulesskiy E, Paveliev M, Rivera C, Rauvala H, and Saarma M. Heparan sulfate proteoglycan syndecan-3 is a novel receptor for GDNF, neurturin and artemin. J. Cell Biol., 2011; 191 (1): 153–169.

Bryant DM, Datta A, Rodríguez-Fraticelli AE, Peränen J, Martín-Belmonte F, Mostov KE. A molecular network for de novo generation of the apical surface and lumen. Nat Cell Biol. 2010; 12(11):1035–45.

Lonka-Nevalaita L, Lume M, Leppänen S, Jokitalo E, Peränen J, Saarma M. Characterization of the intracellular localization, processing and secretion of two GDNF splice isoforms. J Neurosci 2010; 30(34): 11403–11413.

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New approach to study mammalian gene functions *in vivo*

I have set up an up to date methodology for generating conditional gene knock-out (cKO) and knock-in (cKI) mice at the Institute of Biotechnology. Very recently we have finalized an invention – namely, we have developed a method for overexpressing gene products from their endogenous locus. Patent application is currently underway, thus I unfortunately currently cannot open further details. Publications will follow asap. Besides providing an alternative way to study gene function the new method also enables to screen for drug targets by i.e. crossing mice carrying hypermorphic allele for a potential therapeutic protein to animal models of congenital disease where elevating the therapeutic molecule levels is expected to have an effect.

Next to developing new tools, our research interests cover a broad range of biological phenomena ranging from development and maintenance of various brain neurotransmitter systems to urogenital tract formation and innervation of gastrointestinal system. For example, we have recently developed and are currently analyzing cKO mice for glial cell line-derived neurotrophic factor (GDNF) and its receptor GFR 1. We have also generated hypermorphic allele for GDNF using our new method and an hypomorphic allele for GFR 1. Using the above alleles we have generated mouse models of Hirschprung's disease, congenital anomalies of kidney and urogenital tract (CAKUT); we also address the role of the above molecules in brain dopamine system development and maintenance relevant in Parkinson's disease as well as in memory and learning in young and aging animals. For comprehensive analysis of our unique set of animal models we use both intra lab know how as well national and international collaborations. Examples of the currently used methods include electrophysiology and behavior, HPLC of neurotransmitters, immunohistochemistry, molecular, – and cellular biology.

Group members: Graduate students: Carolina Amberg, Anmol Kumar, Lauriina Porokuokka Undergraduate student: Kärt Varendi

Selected publications

Planken A, Porokoukka L, Tuominen RK, Andressoo JO. Medium-throughput computer aided micro-island method to assay embryonic dopaminergic neuron cultures *in vitro*. J Neurosci Methods. 2010; 194(1): 122–31.

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Neuronal death and survival pathways controlled by neurotrophic factors

We study death/survival pathways in the neurons that depend on the neurotrophic factors. Our studies contribute to the basic knowledge of cell biology but are also essential in developing treatment strategies for the diseases, as neurotrophic factors are good candidates to prevent neuronal degeneration in different neuropathological conditions.

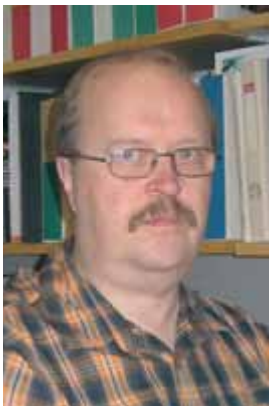
We have found a new, strictly neuron-specific member of the Bcl-2 family, N-Bak that is generated from the pro-apoptotic Bak by alternative splicing. We attempt to block Bak pre-mRNA splicing in the neuroblasts by in vivo electroporation of antisense oligos, i.e. preventing the loss of Bak and appearance of N-Bak in the embryonic neurons. We also study the post-transcriptional regulation of N-Bak mRNA in the neurons.

We study, in collaboration with prof. Mart Saarma, the neurotrophic mechanism of new factors MANF and CDNF that are currently the most potent factors for the treatment of neurodegenerative diseases. However, these factors seem not to work as classical neurotrophic factors. We recently showed that MANF can act as an intracellular antiapoptotic protein that is currently a unique mode of action for a neurotrophic factor. We are currently studying the intracellular neurotrophic mechanism of MANF on the cultured neurons, and its extracellular action on the organotypic brain sections.

Group members: Postdoctoral fellow: Li-ying Yu, Graduate students: Maili Jakobson, Kert Mätlik, Technician: Congjun Zheng

Selected publications

Hellman M, Arumäe U, Yu LY, Lindholm P, Peränen J, Saarma M, Permi P. Neurotrophic factor MANF has a unique mechanism to rescue apoptotic neurons. J Biol Chem. 2011; 286: 2675–2680.



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Patterning and morphological variations regulated by BMP signaling

- **Morphogenesis and post-translational regulation of secreted growth factors**

The Bone Morphogenetic Proteins (BMPs), members of the TGF-ß superfamily, are a family of highly conserved secreted growth factors involved in metazoan developmental processes as diverse as cell proliferation, apoptosis, differentiation, and cell-fate determination. In *Drosophila*, the *dpp* gene is a functional ortholog of vertebrate BMP2/4 and is involved in the processes such as dorsal patterning of the early embryo, patterning and growth of imaginal discs and wing vein formation. The fundamental signaling mechanism employed by BMPs during development is conserved both in vertebrates and invertebrates. This functional conservation suggests that studies of BMP signaling in *Drosophila* will have an impact on our understanding of BMP signaling in mammals.

The TGF-b type signal is regulated by post-transcriptional level such as cleavage of precursor by furin-type proprotein convertases. We have found that cleavage sites of the BMP2/4/*Dpp* family have evolutionarily diversified. We have also found that the *Dpp* precursor is cleaved at three furin sites, and the first cleavage at an upstream furin site is critical and sufficient for long-range *Dpp* signaling, suggesting that the furin cleavage sites in BMP2/4/*Dpp* precursors have adjusted to different systems in diversified species.

Our previous studies suggest that the transport mechanism of BMP ligands is critical for the differentiation of *Drosophila* wing veins as well as axial patterning in the embryos. To understand how spatial distribution of BMP is regulated in *Drosophila* wing development, we established a system in which GFP-tagged *Dpp* can be visualized in the pupal wing. Our results show that *Dpp* distribution is tightly regulated by two distinct mechanisms, the directional (facilitated) transport of ligands and the active retention of ligands. Moreover, our data suggest that differences in the directional *Dpp* transport modulate the spatial ligand distribution and therefore contribute to the variations of wing vein patterns among insects. Since the BMP transport machinery is highly conserved in the animal kingdom, we consider the mechanisms studied in *Drosophila* are widely utilized for developmental processes in vertebrates.

Selected publications

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Regulation of ectodermal organ development

- **Intercellular communication regulating formation and regeneration of ectodermal organs – teeth, hairs,and glands.**
- **Mouse models and organ cultures to analyse the functions of FGF, TGFß Hedgehog, Wnt and Ectodysplasin pathways.**

We explore the mechanisms that regulate the formation of ectodermal organs, including teeth, hairs and glands. We focus on signalling networks mediating intercellular communication, and examine how they regulate the patterns, numbers, sizes, and shapes of organs. The results may have clinical implications in the diagnosis, prevention and treatment of congenital defects as well as in the design of regenerative therapies.

We use mouse models and organ culture techniques to analyse the functions of conserved signal pathways including FGF, TGFß, Hedgehog, Wnt and Ectodysplasin (Eda). Some of the mice are models for human syndromes such as ectodermal dysplasias and tooth agenesis. Our major interest is the formation of placodes initiating the development of all ectodermal appendages. We have shown previously that the Eda pathway stimulates placode formation, and we have identified a number of Eda targets by microarray analysis. Interestingly, these include both positive and negative effectors of other conserved signal pathways. We have shown that Wnt signal activation in the ectoderm induces the formation of extra placodes resulting in continuous tooth formation, and extra whiskers and hairs. Several mouse lines are currently used to examine the integration of Wnt, Eda and the other conserved pathways. We are focusing increasingly in the mechanisms of tooth regeneration. We are continuing studies on epithelial stem cell regulation in a stem cell niche which we discovered in teeth. Our results indicate that the mesenchyme adjacent to the epithelial stem cell niche regulates epithelial stem cell functions via several key signals, and that microRNAs are involved in the regulation of stem cell progeny. We also examine the mechanisms of tooth replacement by using the ferret as model animal. Finally, we continue the long lasting collaboration with clinicians and molecular geneticists at the Institute of Dentistry, University of Helsinki, involving the identification of mutations in syndromes manifesting variations in tooth number.

Selected publications

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Undergraduate student: Xenia Crespo

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Epithelial morphogenesis – from molecular pathways to cellular behavior

Organ development is regulated by an intricate interplay between different tissue types. Although the knowledge on the genetic basis of these inductive tissue interactions has substantially increased during recent years, the challenge is to perceive how this molecular information is translated into changes in cell fate and behavior – proliferation, migration, differentiation, apoptosis – that ultimately shape the developing organ. Dissecting the details of organogenesis will be important for understanding the causes and developing cures when things go awry as seen in developmental disorders or in tumorigenesis, as well as for advancing methods for organ regeneration.

We use hair follicle and mammary gland as model organs, and a combination of mouse models and tissue and cell culture methods to investigate the molecular and cellular basis of epithelial morphogenesis. We have two main interest areas: the early inductive events whereby pluripotent epithelial cells on the surface of the embryo gain hair or mammary gland cell identity instead of epidermal (skin) cell fate; and branching morphogenesis of the mammary gland. We focus on the function of TNF/NF-κB signaling, more commonly associated with immunity and inflammation, in these developmental processes. We have shown that two TNF receptors, Edar and Troy, have redundant functions in hair follicle development. We are currently investigating the functional relevance of several transcriptional targets of Edar/ NF-κB in hair and mammary gland development. More recently, we have initiated studies on Foxi3, a transcription factor mutated in several hairless dog breeds.

Group members: Postdoctoral fellows: Laura Ahtiainen (jointly with Irma Thesleff), Päivi Lindfors Graduate students: Sylvie Lefebvre, Vera Shirokova, Maria Voutilainen, Undergraduate student: Elisa Rysti, Technician: Riikka Santalahti (jointly with Irma Thesleff)

Selected publications

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Genomics and metagenomics

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Biocenter Finland infrastructure: Genome-wide methods

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- **Environmental microbiology and metagenomics in complex surroundings like soil and the Baltic Sea**

In recent years one of our main areas has been on genomics, metagenomics and related bioinformatics. More specifically we have many projects on *de novo* genome sequencing with several collaborations. We have been studying dozens of microbe genomes, some of them also commercially important (Kankainen *et al* 2009, Ojala *et al*., 2010, Kant *et al* 2011, Guo *et al* 2011). The fast development of DNA sequencing technologies has already made it possible, in practice, to sequence genomes of all microbes one works with. In most projects we aim at finished quality genomes which enable studying the effects point mutations and gene order alterations among microbes. We have been sequencing and assembling large eukaryotic genomes utilizing combination of 454, Illumina and SOLiD technologies. In near future our goal in these projects is to finalize the assemblys and start annotation of the genomes.

One of our interests is environmental microbiology and the diversity of microbial communities in complex surroundings like soil, deep subsurface microbe population and the Baltic Sea. We have been working on environmental metagenomics using the 454 platform performing microbe diversity analysis based on 16S sequences and sequencing the entire community DNA. We have also recently initiated collaboration studying human skin microbiome. In conjunction with these environmental sequencing projects we have been successfully developing a relatively simple, sensitive and specific microarray assay for monitoring microbes in environmental samples. Additionally we are utilizing NGS and DNA microarray technologies in functional genomics studies on analysis of transcriptional profiles on tissue and cell samples looking for miRNA and mRNA expression patterns and bioinformatics related to that.

Selected publications

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Regulation of gene expression in eukaryotic systems

- **Post-transcriptional regulation of gene expression by the U12-dependent spliceosome**
- **Genomics of ecological model systems**

Our research has two main foci, both related to eukaryotic gene expression. First, we are studying the mechanism and regulation of eukaryotic gene expression by the U12-dependent spliceosome. We use RNA biochemistry and various model organisms (human cell lines, *Drosophila* and mouse) to investigate the mechanism and regulation of RNA splicing both *in vitro* and *in vivo*. Second, we are developing and using genomic tools for the Glanville fritillary (*Melitae cinxia*) butterfly to study the effect of gene expression on butterfly population structure in the Åland Islands.

The key aim of our research is to understand the role of U12-dependent spliceosome, and more generally, the significance of having two separate spliceosomes in the cells of higher eukaryotes. We (Pessa *et al*. 2006) and others have found that the U12-type introns are spliced more slowly than the normal U2-type introns, but splicing takes place in the nucleus similarly to normal U2-type introns (Pessa *et al*., 2008). This suggests that the primary role of U12-dependent introns could be a regulatory module that provides rate-limiting post-transcriptional control to a defined group of genes at the level of pre-mRNA splicing. Our recent detailed biochemical investigations on the intron recognition have identified a protein component necessary for the 5' splice site recognition (Turunen *et al*., 2008). In a subsequent study we have found that this protein is a target of an evolutionarily ancient regulatory mechanism that adjust the cellular levels of the intron recognition complex (Verbeeren *et al*, 2010). This regulatory mechanism will be the key focus in our future work.

In our ecological genomic project we have recently successfully used massive parallel sequencing methods for the analysis of transcriptomes (Vera *et al*., 2008) which has led to the development of microarrays and related genomic tools for the Glanville fritillary butterfly. Our future research on these organisms will heavily use deep sequencing methods in the analysis of genomes, transcriptomes, and post-transcriptional regulation.

Selected publications

Pessa HKJ, Greco D, Kvist J, Wahlström G, Heino TI, Auvinen P, Frilander MJ. Gene Expression Profiling of U12-Type Spliceosome Mutant Drosophila Reveals Widespread Changes in Metabolic Pathways. PLoS One. 2010; 5(10): e13215.

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Genetic control of wood development

- **Cytokinins and other genetic regulators of stem cell identity in wood and *Arabidopsis***
- **Regulating cell fate through manipulation of the bifunctional kinase-phosphatase cytokinin receptor**

Wood is derived from stem cells that occur as a cylindrical sheet in the trunk of a tree. We investigate how genes regulate these stem cells. We are investigating this process in tree systems and in the more amenable *Arabidopsis*. We have shown that cytokinin phytohormones are important regulators underlying cambial development.

In *Arabidopsis* we have identified two genes (the first CRE1/WOL encodes a cytokinin receptor, the second AHP6 encodes a regulator of cytokinin signalling) which have allowed us to show that cytokinins promote stem cell identity during root development in *Arabidopsis*. Decrease in cytokinin activity causes all vascular cells to differentiate into protoxylem cells. AHP6, an inhibitory protein, counteracts cytokinin signaling in a spatially specific manner thereby allowing protoxylem formation. We have also shown that CRE1/WOL cytokinin receptor is a bifunctional kinase/phosphatase, and elimination of the negatively regulating phosphatase activity of the CRE1/WOL results in stimulation of proliferation of vascular cell files. This indicates that in addition to specifying vascular cell identity, cytokinins have a second role in controlling the rate of proliferation of vascular cell files.

An obvious next question is how much the *Arabidopsis* genetic information applies to economically important plants. We have reduced cytokinin levels endogenously by engineering transgenic poplar trees (*P. tremula* x *tremuloides*) to express a cytokinin catabolic gene, *Arabidopsis* CYTOKININ OXIDASE 2. Transgenic trees showed reduced concentration of a biologically active cytokinin, correlating with impaired cytokinin responsiveness. In these trees, the radial growth and cambial activity was specifically compromised. Together, our results show that cytokinins are major hormonal regulators required for cambial development.

Selected publications

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- **Elucidating functional correlates from sequence and structure**

The complete genomic sequence of over a hundred organisms, including several higher eukaryotes, has been determined. We develop and use a wide range of computational tools to make sense of this book of life. The overall goal is to model evolutionary relationships in sequence and structure data and to elucidate their functional correlates.

Proteins can be clustered based on sequence (or structure) similarities and classified into families which derive from a common ancestor. The members of a family may inherit complex properties from the ancestor. We have for a long time produced evolutionary classifications of all known proteins based on sequence and structure comparisons. The analysis of variation and conservation reveals functional signature motifs which can ultimately lead to an accurate mapping of protein functions.

Our group has gotten involved in the annotation of the genomes of pro-biotic and pathogenic bacteria sequenced on campus, and our tools have been used to analyze functional genomics data generated by collaborating research groups. For example, we have developed tools to locate pilus operons and for rapid function annotation of large protein sets.

A particular focus is on the statistical analysis of differential gene expression data with the aim to detect which functional classes are perturbed in the experiment. We propose a novel test statistic which outperforms existing methods when detecting biological signal. Bayesian statistics and segmentation algorithms applied to genomic datasets have revealed several interesting signal areas.

Selected publications

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Ojala T, Kuparinen V, Koskinen JP, Alatalo E, Holm L, Auvinen P, Edelman S, Westerlund-Wikstrom B, Korhonen TK, Paulin L, Kankainen M Genome Sequence of *Lactobacillus crispatus* ST1. J Bacteriol. 2010; 192, 3547–3548.

Ta XH, Yoon CN, Holm L, Han SK. Inferring the physical connectivity of complex networks from their functional dynamics. BMC Systems Biology. 2010; 2010: 4:70.

Kinase signaling linking metabolism and growth control

- **Signaling by the metabolic regulator and tumor supressor kinase LKB1**
- **Transcriptional regulation by cyclin-dependent kinases Cdk7 and Cdk8 in growth and differentiation**

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Major human diseases such as diabetes and cancer are due to deregulated signaling in target cells. Signaling in pathways and in larger networks typically involves sequential activation of kinases phosphorylating substrates and thus relaying and amplifying signals, which ultimately modulate transcriptional responses in target gene sets. Our longstanding interest is to characterize such pathways and to understand the mechanisms involved in mediating the transcriptional responses and how these are deregulated in human disease.

Two critical mediators of transcriptional responses involved in cancer and metabolism are the transcriptional kinases Cdk7 and Cdk8 mediating signals to RNA polymerase II. We are investigating the molecular mechanisms and *in vivo* functions of Cdk7 and Cdlk8 combining mouse molecular genetics with *Drosophila* knockdown strategies and cell-based screening approaches. Recent results uncovered an critical role for the TFIIH kinase in general transcription as the major kinase responsible for RNA Pol II CTD Ser5 phosphorylation and interestingly revealed a previously unrecognized general stabilization of mRNAs following transcriptional attenuation using analysis of nascent mRNAs. Our goal is to understand the basis for the specificity of transcriptional regulation by metazoan Cdk7 and Cdk8 and their contribution to growth control and differentiation.

One of the rare kinases acting normally to restrict tumor growth is the LKB1serine/threonine kinase critical for activation of several related kinases involved in metabolism and polarity regulation. We are interested in how LKB1 mediates its tumor suppressing function, and recently identified that LKB1 signaling in mesenchymal cells is required for suppression of epithelial hyperproliferation in a mouse polyposis model and likely also in the human Peutz-Jeghers syndrome. We are currently extending investigations of tumor suppression mechanisms of the LKB1 tumor suppressor kinase from hereditary polyposis to sporadic cancer (lung, uterine cervix). For this a combination of tissue- and cell type specific targeting approaches *in vivo* (conditional mouse models) and *in vitro* (2D and 3D RNAi & conditional deletions) of LKB1 and LKB1 substrate mutations will be used with a specific interest in the Nuak2 and AMPK kinases and cytoskeletal regulation.

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Selected publications

Helenius K, Yang Y, Tselykh TV, Pessa HKJ, Frilander MJ, Mäkelä TP. Requirement of TFIIH kinase subunit Mat1 for RNA Pol II C-terminal domain Ser5 phosphorylation, transcription and mRNA turnover. Nucleic Acids Res. in press.

Vallenius T, Vaahtomeri K, Kovac B, Osiceanu AM, Viljanen M, Makela TP. An association between NUAK2 and MRIP reveals a novel mechanism for regulation of actin stress fibers. J Cell Sci in press.

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MTT/BI Plant Genomics Laboratory

- **Retrotransposons as drivers of genomic change**
- **Identification of disease resistance and quality trait genes through functional genomics**

The MTT/BI Plant Genomics Laboratory is a joint laboratory of the Institute of Biotechnology and of MTT Agrifood Research. At MTT, the lab belongs to the Genomics Research programme, which includes plants, animals, and microbes, directed by Prof. Alan H. Schulman within the Department of Biotechnology and Food Research. Plant Genomics has two laboratories, the MTT/BI joint lab at Viikki and a laboratory at Jokioinen, which work together and comprise 25 members. The MTT/BI group studies retrotransposons as drivers of genomic change and as markers for this change, uses these and other marker systems for map-based cloning of genes for disease resistance and quality traits, and analyses the role of candidate genes through the application of functional genomics tools such as microarrays. To support these goals, the Jokioinen lab develops and applies doubled-haploid populations for mapping in barley, rye, oat, and *Brassica* and maps traits in these crops. We also have implemented barley transformation using *Agrobacterium*. Potato di-haploids and fusions have been produced and are being used to develop novel glycoalkaloids as pharmaceutical lead compounds.

The Plant Genomics group has a long-term programme to understand the role of retrotransposons in genome dynamics. These mobile elements replicate in a way similar to retroviruses and create daughter copies that integrate throughout the genome. We are working to establish the details of their lifecycle, the role of cellular regulation of their capacity for enormous copy number increase and mutagenic genome disruption, and their effect on genomic and cellular function. Members of the group are currently studying transcriptional regulation of the barley BARE retrotransposons of barley and the translation, processing and the assembly of virus-like particles. We are also investigating how successful non-autonomous retrotransposons, especially *Cassandra*, parasitize other retrotransposons for needed proteins and evade cellular regulation by using novel pol III transcription.

Selected publications

Vogel JP, Garvin DF, Rokshar D, Bevan MW et al. Genome sequence analysis of the model grass Brachypodium distachyon. Nature. 2010; 463: 763–768.

Schulte D, Close TJ, Graner A, Langridge P, Matsumoto T, Muehlbauer G, Sato K, Schulman AH, Waugh R, Wise RP, Stein N. The International Barley Sequencing Consortium (IBSC) – at the threshold of efficient access to the barley genome. Plant Physiology. 2009; 49: 142–147

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Physical foundations of evolutionary theory

- **Clarification why evolution displays scale-free and non-computable characteristics**
- **Clarification of thermodynamic imperatives in systemic organization**

Evolution by natural selection is the basis of biology. Nevertheless our understanding of nature as a whole has remained obscure because Darwin's tenet, despite its broad scope and central role, is a phenomenological account without a firm physical foundation given in a mathematical form.

It is no new thought that evolution is a manifestation of the 2nd law of thermodynamics. However, this conjecture was proven first when the equation of evolution was derived from statistical physics of open systems. The universal natural law states simply that energy differences will diminish in least time. Species are mechanisms of transduction that acquire energy from their respective surroundings, ultimately from insolation and eventually will transform all of it to dissipation. The flows of energy will naturally select those mechanisms that will level off energy differences most rapidly. These species are said to be the fittest.

The physical portrayal of evolution allows us to understand profound questions and puzzles, most notably: why evolution is a non-deterministic process, why nature organizes itself in a hierarchy of systems within systems and display scaling-laws and small-world patterns, why ecological succession does not necessary terminate at a state of maximum number of species. Moreover, the statistical theory of open systems has given us understanding what a society in its profound meaning is.

The holistic and scale-independent view of nature provided by the 2nd law of thermodynamics, equivalent to the principle of least action, points out that natural selection does not operate only on genes but on all matter. During evolution flows of energy naturally select the steepest descents, equivalent to the paths of least action to even out energy landscape in least time. The thermodynamic theory roots biology via chemistry to physics and widens contemporary discourse on the fundamentals of evolution.

Selected publications

Annila A. All in action. Entropy. 2010; 12: 2333–2358.

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Sharma V, Annila A. Natural process – Natural selection. Biophys Chem. 2007; 127: 123–128.

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Understanding virus evolution through structure

- **Hypothesis on virus evolution and origins: there are only a limited number of ways that a virion can be constructed**
- **Characterization of prokaryotic viruses from ecological niches e.g. human bacterial infections, high saline environments and Baltic Sea to test the hypothesis**

It has been estimated that there are 10^{31}–10^{32} viruses in the biosphere. This number exceeds the number of their host cells by at least one order of magnitude. Consequently practically every organism is constantly under viral attack and viruses may cause the highest selection pressure that cellular organisms encounter. Viruses play an important role as obligate cellular parasites ensuring their own reproduction and modulating their host cells. Due to their adverse effects on the well being of their host organism, the emphasis in virology has focused on detection and prevention of pathogenic viruses infecting humans and domesticated animals and plants. However, how the entire domain of viruses is organized, what is the origin of viruses and how they evolve are deep questions in biology in general and in virology in particular.

Our research has advanced by discovering how viral molecular machines work, what determines the size in certain icosahedral viruses, how a complex infectious viral particle self-assembles from its purified structural constituents, and how RNA dependent RNA polymerases operate. The accumulating information on virus structures has led to a surprising new hypothesis on virus evolution and origins. It is postulated that there are only a limited number of ways that a virion can be constructed.

The underpinning hypothesis is that we can probe deep evolutionary relationships in general and for viruses in particular by combining structural and functional information. We wish to test the hypothesis that prokaryotic viruses are homologues to viruses infecting multicellular eukaryotic organisms. Recognizing such connections will also lead to major revisions in how we classify viruses.

Currently we have combined virology, genetics, biochemistry, biophysics and structural analysis to describe in detail the viral model systems under study (predominantly viruses infecting prokaryotic hosts). We are now also extending to virus ecology by isolating and characterizing prokaryotic viruses from different ecological niches such as human bacterial infections, highly saline and high temperature environments to test our hypothesis and to allow us to search for novel virus types with unknown structural principles.

Selected publications

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Academy of Finland Senior Research Fellow 1983–1991

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Macromolecular structure and function

- **How structure, function and interactions of proteins and lipids influence disease**

Our research interests are primarily focused on the structure, function and interactions of biological molecules, mainly proteins and lipids, and their influence on disease. The majority of current drugs affect membrane proteins and yet there is very little structure-based drug-design on these recalcitrant molecules. We combine electron cryo-microscopy, three-dimensional image reconstruction and X-ray crystallography to image these molecules within large complexes such as viruses and their interaction with cell-surface proteins used for host recognition. Recently we have made significant advances in determining the structures of several membrane-containing viruses, including the X-ray determination of the bacterial virus PM2 (Abrescia *et al*. 2008). We have as well determined the structures of the icosahedrally-symmetric euryarchaeal virus, SH1, the thermophilic viruses P23-77 and STIV2, and several picornaviruses (Happonen *et al*. 2010; Jäälinoja *et al*. 2008; Jaatinen *et al*. 2008; Seitsonen *et al*. 2010). Using electron tomography we have also elucidated the structure of a hantavirus (Huiskonen *et al*. 2010). These studies have shed light on membrane biogenesis, membrane-protein interactions, viral evolution and receptor-host interactions (Abrescia *et al*. 2008; Huiskonen *et al*. 2007; Jäälinoja *et al*. 2008; Jaatinen *et al*. 2008). To complement these studies, we have collaborated with Pekka Lappalainen's group to look at proteins that modulate membrane function in cells such as the I-BAR domain proteins (Saarikangas *et al*. 2009) and furthered the development of nanoparticles for drug development (Paasonen *et al* 2010).

Selected publications

Happonen LJ, Redder P, Peng X, Reigstad LJ, Prangishvili D, Butcher SJ. Familial relationships in hyperthermo- and acidophilic archaeal viruses. J Virol. 2010; 84:4747–4754

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Saarikangas J, Zhao H, Pykäläinen A, Laurinmäki P, Mattila P, Kinnunen P, Butcher SJ, Lappalainen P. Molecular mechanisms of membrane deformation by I-BAR domain proteins. Current Biology. 2009; 19: 95–107.

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Macromolecular Structures Group

- **How membrane-integral and membrane-associated proteins work**
- **Complexes of GDNF with its specific co-receptor, GFRα**

Our goal is to understand the structure and function of various biological systems at the atomic level, in particular membrane-integral and membrane-associated proteins. We wish to understand how they work – whether in transmitting signals, in binding to other proteins, or in pumping protons to conserve energy. We primarily use x-ray crystallography, supplemented with functional, mutagenesis and theoretical studies.

We have solved the structures of two different complexes of GDNF with its specific co-receptor, GFRα, showing that the R171-E62GDNF-R224 triplet at the centre of the complex is supported by different interactions in different GDNF-like ligands (GFLs)-GFRα pairs. Different GFL-GFRα complexes differ because the bend angle between the two monomers in the GFL dimer differs. This changes the relative position of the GFRs and thus how RET positions and signals. We have also solved the structure of another neurotrophic factor, MANF, the first one with an identified *Drosophila* homologue. Its structure explains why MANF can be both cytoprotective and neuroprotective; the N-terminal domain is a SAPLIP; it interacts with membranes, while the unstructured C-terminal domain helps fold proteins in the ER. We are also studying integral membrane proteins, like the *Yersinia* adhesion protein A, a trimeric autotransporter pathogenic protein and its homologues, and have solved the structure of a novel *E. coli* immunoglobulin binding protein. This work aims at understanding the structural basis of adhesion and the mechanism of autotransport. Other work focuses on channels and pumps.

Our goals include complete understanding of the structural basis of the GDNF-GFRα signalling system because it can signal in three different ways through at least two different molecules. The work could lead to new diagnostics and therapeutics. In addition, we intend to study the workings of the other molecules described above, such as YadA, related proteins like the Eibs, KCC2 and pyrophosphatases. Our work links structure and function, design and therapeutics.

Selected publications

Leppänen V-M, Prota AE, Jeltsch M, Anisimov A, Kalkkinen N, Strandin T, Lankinen H, Goldman A, Ballmer-Hofer K, Alitalo K. Structural determinants of growth factor binding and specificity by VEGF receptor 2. Proc Natl Acad Sci U S A. 2010; 107(6):2425–30.

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Protein transport and glycosylation

- **Protein structures as tool to understand molecular basis of hydrolytic lysosomal activity and its hereditary dysfunction**

Lysosomal proteins

Lysosomal Storage Disorders (LSDs) are inherited group of diseases, caused by mutations in individual lysosomal enzymes or in proteins involved in recognition and transport of lysosomal proteins, and carriers of these diseases may be overpopulated in severe diseases of the elderly, such as Parkinson's. A number of LSDs are treated with enzyme replacement therapy (ERT) or small molecules acting as chaperones to increase endogenously produced lysosomal activity. Improvement of the LSD-therapies and selection of suitable therapy for individual patients requires molecular level understanding of the lifecycle and formation of lysosomes and its proteins.

Our overall aim is to increase the structural knowledge of the lumenal lysosomal proteins and their transport by combining X-ray crystallography, structural and proteomic analysis, and cell biology. We seek to understand the structural basis of the lysosomal protein stability and function in low pH as well as their lysosomal targeting. The data will be collected from the overall structural analysis, as well as by studying three structurally novel lysosomal proteins. The hypothesis on the lysosomal protein recognition will be tested on a glycosidase hydrolase family model system.

Structural knowledge so derived can be directly used to stabilise industrial targets with similar folds and to the design of more suitable ERT-proteins, ones with better life time in patients or increased crossing rate for the blood-brain barrier. It benefits individuals suffering from lysosomal storage disorders as it allows design of improved LSD therapies, as well as to choose between ERT and chaperone therapy. Studies of individual lysosomal proteins will increase the understanding of the essentials of lysosomal metabolism and the inherited diseases caused by mutations in their genes. Ultimately, our studies aim to uncover the molecular basis of formation and maintenance of the hydrolytic lysosomal activity essential in all tissues.

Selected publications

Bernon C, Carre Y, Kuokkanen E, Slomianny MC, Mir AM, Krzewinski F, Cacan R, Heikinheimo P, Morelle W, Michalski JC, Foulquier F, Duvet, S. Overexpression of Man2C1 leads to protein underglycosylation and upregulation of ERA pathway. Glycobiology, *in press*

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NMR studies of larger proteins by new labelling technology based on protein splicing

- **Development of protein ligation and segmental isotopic labeling to enhance NMR analysis of multi-domain, membrane and transient protein complexes**

Structural biology increasingly targets larger and more complex systems in order to fully understand biological functions of a biomolecule. Since bimolecular function is intimately coupled with changes in structural organization, it is essential to quantitatively analyze the three-dimensional structures and their dynamics. Nuclear magnetic resonance (NMR) spectroscopy offers unique opportunities to analyze both high-resolution three-dimensional structures of biomolecules and their dynamics in both near physiological and physiological conditions. NMR analysis of larger systems has, however, two major obstacles that are line broadening of NMR signals reducing signal-to-noise ratios and the increased complexity of NMR spectra making NMR analysis difficult and time-consuming. Even though transverse-relaxation optimized NMR spectroscopy (TROSY) has alleviated the line-broadening problem of larger systems, the increased number of atoms in large systems (>30 kDa) inherently increases signal overlaps and remains problematic even with extravagant ultra-high field magnets.

Our group focuses on developing new labeling technology for structural biology, particularly for reducing the complexities of NMR spectra of larger proteins. In the past years, we have advanced protein ligation technology based on protein splicing by further understanding the mechanism and by applying protein-engineering approaches. Especially, we developed a robust segmental isotopic labeling approach with which stable isotopes can be incorporated into a specific region of a protein. This approach not only significantly simplifies NMR spectra but also enables us to apply sophisticated triple-resonance NMR experiments. By advancing the technologies even further, we are aiming to understand structure-function relationships of larger protein systems that have been difficult to analyze, which include large multi-domain proteins containing recurring modular domains, proteins with intrinsically disordered regions, transient complexes, and membrane proteins.

Selected publications

Volkmann G, Iwaï H. Protein trans-splicing and its use in structural biology: opportunities and limitations. Mol Biosyst. 2010, 6: 2110–2121.

Muona M, Aranko AS, Raulinaitis V, Iwaï H. Segmental isotopic labelling of multi-domain and fusion proteins by protein trans-splicing *in vivo* and *in vitro*. Nat Protoc. 2010,5: 574–587.

Busche AEL, Aranko AS, Talebzadeh-Farooji M, Bernhard F, Dötsch V, Iwaï, H Segmental isotopic labelling of a central domain in a multi-domain protein by protein trans-splicing using only one robust DnaE intein. Angew Chem Int Edit. 2009; 48: 6128–6131.

Oeemig JS, Aranko AS, Djupsjöbacka J, Heinämäki K, Iwaï H. Solution structure of DnaE intein from *Nostoc punctiforme*: Structural basis for the design of a new split intein suitable for site-specific chemical modification. FEBS lett. 2009; 583: 1451–1456.

Aranko AS, Züger S, Buchinger E, Iwaï, H. *In vivo* and *in vitro* protein ligation by naturally occurring and engineered split DnaE inteins. PLoS ONE 2009; 4: e5185.

Hideo Iwai

Dr. sc. nat. 1998, ETH-Zürich, Switzerland

Postdoctoral research at University of Zürich, Switzerland, 1998–2003

Assistant Professor, University of Saskatchewan, Canada, 2003–2005

Group leader at the Institute since 2005

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Group members in 2010

Postdoctoral fellow: Gerrit Volkmann

Graduate students: Sesilja Aranko, Jesper Skøttegaard Øemig

Technician: Cathrin Albert

Undergraduate student: Anniina Jaakkonen

Protein Chemistry Research Group

- **Protein chemistry and proteomics approaches to characterize *Lactobacillus* probiotic functions and host-microbe interactions and mutational mechanisms in *Streptococcus* and *Staphylococcus* infections. Many collaborative projects in purification, identification and characterization of proteins from various organisms.**

Nisse Kalkkinen

PhD (biochemistry) 1981, University of Helsinki

Postdoctoral research at Karolinska institutet, Stockholm, Sweden, various periods

PI at the Recombinant DNA Laboratory, University of Helsinki 1985–1989

Group Leader at the Institute since 1989

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Group members in 2010

Senior scientists: Daniel Hirschberg, Kirsi Savijoki

Postdoctoral fellow: Johanna Koponen

Graduate student: Pia Siljamäki

Technicians: Elina Ahola-Iivarinen, Marko Hukka, Gunilla Rönnholm

The Protein Chemistry Research Group was established in June 1982 at the Recombinant DNA Laboratory, and has been a part of the Institute of Biotechnology since 1989. The goal of the laboratory has been from the beginning to adopt, develop, and perform protein chemistry and proteomics analyses to be used in its own research projects as well as in collaborative projects with other academic and industrial partners.

The laboratory is well equipped for modern protein and peptide analysis, including instruments for electrophoresis, chromatography and mass spectrometry. For mass spectrometry a MALDI-TOF/TOF (Bruker Ultraflex) instrument as well as two nanoLC-ESI-Q-TOF (Q-Tof, Micromass and QStar Elite, Applied Biosystems) instruments are available. During 2010 we have performed research on the following consortium projects: "From genomes to probiotic functions: stripping *Lactobacillus rhamnosus* using expression proteomics, host interactomics and immunoproteomics" and "Host-microbe interactions and mutational mechanisms in *Streptococcus* and *Staphylococcus* infections".

In 2010 we have also started with a new service in biological mass spectrometry, hydrogen exchange-mass spectrometry (HX-MS) and native mass spectrometry, both aimed to study higher order structure of proteins and protein complexes. This service has so far been offered as a collaborative service to groups inside BI (kryo-EM and NMR-groups) but will be very soon extended to researchers outside the Institute. In addition to our own research, we serve also as a Core Facility in protein chemistry and are members in the Biocenter Finland infrastructure network (Prot. Met.net). During 2010 we have performed a large number of collaborative as well as commercial protein chemical and proteomics related analyses with other academic as well as industrial groups. These analyses include e.g. identification of proteins and their processing, analysis of protein posttranslational modifications, confirmation of the identity and structure of produced recombinant proteins and mass spectrometric *de novo* sequencing of unknown proteins for e.g. cloning purposes.

Selected publications

Koskenniemi K, Laakso K, Koponen J, Kankainen M, Greco D, Auvinen P, Savijoki K, Nyman TA, Surakka A, Salusjärvi T, de Vos WM, Tynkkynen S, Kalkkinen N, Varmanen P. Proteomic and transcriptomic characterization of bile stress response in probiotic *Lactobacillus rhamnosus* GG. Mol Cell Proteomics. 2010 Nov 15. [Epub ahead of print]

Leppänen VM, Prota AE, Jeltsch M, Anisimov A, Kalkkinen N, Strandin T, Lankinen H, Goldman A, Ballmer-Hofer K, Alitalo K. Structural determinants of growth factor binding and specificity by VEGF receptor 2. Proc Natl Acad Sci U S A. 2010; 107(6):2425–30.

Pulkki MM, Myllymaa S, Pasternack A, Lun S, Ludlow H, Al-Qahtani A, Korchynskyi O, Groome N, Juengel JL, Kalkkinen N, Laitinen M, Ritvos O, Mottershead DG. The bioactivity of human bone morphogenetic protein-15 is sensitive to C-terminal modification: Characterization of the purified untagged processed mature region. Mol Cell Endocrinol. 2010 Oct 16. [Epub ahead of print]

Siigur E, Tõnismägi K, Trummal K, Samel M, Vija H, Aaspõllu A, Rönnholm G, Subbi J, Kalkkinen N, Siigur J. A new tyrosine-specific chymotrypsin-like and angiotensin-degrading serine proteinase from Vipera lebetina snake venom. Biochimie. 2010 Oct 13. [Epub ahead of print]

Tvorogov D, Anisimov A, Zheng W, Leppänen VM, Tammela T, Laurinavicius S, Holnthoner W, Heloterä H, Holopainen T, Jeltsch M, Kalkkinen N, Lankinen H, Ojala PM, Alitalo K. Effective Suppression of Vascular Network Formation by Combination of Antibodies Blocking VEGFR Ligand Binding and Receptor Dimerization. Cancer Cell. 2010; 18(6):630–40.

Quantitative Proteomics to Characterise Cell Signalling Networks

The main goal of my research is to develop quantitative mass spectrometry-based proteomics technologies to enable more efficient and reliable proteome analysis for cell signalling studies. This includes both the analysis of protein expression levels as well as characterisation of proteins' post-translational modifications and protein-protein interactions at the proteome-wide level. As an integral part of these studies novel bioinformatics tools will be developed for large-scale protein identification and quantification as well as analysing protein modifications and variants.

The biological focus of my research is in the detailed characterisation of cell signalling networks activated by viral infection in principal effector cells involved in innate immunity, macrophages and dendritic cells. During the last four years we have characterised protein expression changes in human primary macrophages and in skin epithelial cells upon viral infection using both traditional two-dimensional electrophoresis- as well as advanced mass spectrometry-based subcellular proteomics. In addition, we have developed novel bioinformatics tools for more efficient proteomics data analysis. At present, we are focusing on protein phosphorylation and ubiquitination analysis, as well as on methods to elucidate dynamics of protein complexes.

Group members: Postdoctoral fellows: Tiina Öhman, Minna Korolainen, Graduate students: Niina Lietzén, Juho Miettinen, Maruthibabu Paidikondala

Selected publications

Lietzén N, Natri L, Nevalainen OS, Salmi J, Nyman TA. Compid: A new software tool to integrate and compare MS/MS based protein identification results from mascot and paragon. J Proteome Res. 2010; 9(12): 6795–6800.

Piippo M, Lietzen N, Nevalainen OS, Salmi J, Nyman TA. Pripper: prediction of caspase cleavage sites from whole proteomes. BMC Bioinformatics. 2010; 11(1): 320.

Öhman T, Lietzén N, Välimäki E, Meljchorsen J, Matikainen S, Nyman TA. Cytosolic RNA recognition pathway activates 14-3-3 protein mediated signaling and caspase-dependent disruption of cytoskeleton network in human keratinocytes. J Proteome Res. 2010; 9: 1549–64.

Filén JJ, Filén S, Moulder R, Tuomela S, Ahlfors H, West A, Kouvonen P, Kantola S, Björkman M, Katajamaa M, Rasool O, Nyman TA, Lahesmaa, R. Quantitative proteomics reveals GIMAP family proteins 1 and 4 to be differentially regulated during human T helper cell differentiation. Mol Cell Proteomics. 2009; 8: 32–44.

Öhman T, Rintahaka J, Kalkkinen N, Matikainen S, Nyman TA. Actin and RIG-I/MAVS signaling components translocate to mitochondria upon influenza A virus infection of human primary macrophages. J Immunol. 2009; 182: 5682–92.

Tuula Nyman
Junior PI, Kalkkinen Lab

PhD 2001 University of Helsinki,
Docent 2006 University of Helsinki

Postdoctoral research
at Turku Centre for Biotechnology,
Sept 2001 – Oct 2004

Finnish Institute of Occupational Health,
Oct 2004 – Sept 2006

Senior scientist at the Institute,
Oct 2006 – July 2010

Academy Research Fellow, starting Aug 2010–

Junior PI at the Institute since 2010

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Finnish Biological NMR Center

- **Development and application of biophysical methodologies for studying structure, dynamics and interactions of proteins with focus on transient structures and interactions**
- **Molecular basis of host pathogen interactions**

NMR stands as a unique technique amongst all biophysical tools enabling studies of biomolecular structures at atomic resolution in solution while simultaneously providing also site-specific data on dynamics and molecular interactions that regulate life at the molecular level. Our group seeks to understand protein function through characterization of structure, dynamics and interactions in solution. We mainly focus on proteins and molecular systems whose structures or interactions are dynamic and transient i.e. systems that are difficult to study with the X-ray crystallography.

We boost our efforts in structural and functional studies of biomolecules by participating strongly in NMR method development. We aim to advance and disseminate routines which help to obtain more information with reduced time and effort. Novel assignment strategies and hence new probes developed e.g. for epitope mapping, have had key role in studies of several proteins.

Together with our collaborators, we have performed structural and functional studies of proteins involved in the actin cytoskeleton regulation, pathogenesis, and neuroprotective mechanisms. Twinfilin (Twf), a member of ADF-H family that participates in the regulation of actin, is composed of two ADF-H domains connected by a long linker. We have solved the structure of the C-terminal domain of Twf, which deviated from G-actin binding proteins, but instead showed high similarity to cofilin. Indeed, we demonstrated that TwfC possesses similar depolymerization and severing activities as cofilin. In addition, both domains of Twf are required for capping the filament barbed end albeit domains can be swapped without losing this activity.

We are also interested in SH3 mediated signaling. Initially SH3 domains were classified as a PxxP motif binding proteins but recent studies have revealed that the specificity and cellular functions of SH3s are far more diverse than earlier anticipated. Eps8 mediates downstream signaling by serving as a direct substrate of EGFR. Eps8 has a central role in Rac GTPase activation through its association with Abi1. The SH3 domains of Eps8 family do not bind to canonical PxxP peptides, but instead select targets containing a PxxDY sequence. We have determined the structure of Eps8L1 SH3 domain in complex with the cytoplasmic tail of CD3e, which reveals the structural basis of novel PxxDY binding. We also determined the structure between the bacterial effector EHEC $EspF_U$ and IRTKS SH3 that utilizes novel binding mode to trigger pathogen-driven actin assembly.

On-going work includes aims to understand underlying molecular mechanism in neuroprotection of novel neurotrophic factors MANF and CDNF, structural and functional characterization of several intrinsically disordered proteins, and study the roles of SH3 domains in ligand recognition.

Perttu Permi

PhD 2001, University of Oulu, Finland

Postdoctoral research at NMR laboratory at the Institute of Biotechnology, 2001–2003

Group Leader at the Institute since 2004

Docent 2002, University of Oulu

Head of the Finnish National Biological NMR Center since 2004

Academy Research Fellow since 2009

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Group members in 2010

Postdoctoral fellows: Maarit Hellman, Tero Pihlajamaa, Helena Tossavainen

Graduate students: Olli Aitio, Annika Kyburz, Sampo Mäntylahti, Vytautas Raulinaitis

Technicians: Elina Ahovuo, Tuomas Niemi-Aro

Undergraduate student: Biao Fu

Selected publications

Aitio O, Hellman H, Kazlauskas A, Vingadassalom D, Leong JM, Saksela K, Permi P. Recognition of tandem PxxP motifs as a unique Src homology 3 binding mode triggers pathogen-driven actin assembly. Proc Natl Acad Sci USA. 2010; 107:21743–21748.

Hellman M, Arumäe U, Yu L-y, Lindholm P, Peränen J, Saarma M, Permi P. Neurotrophic factor MANF has a unique mechanism to rescue apoptotic neurons. J Biol Chem. 2010; Nov 3. [Epub ahead of print] doi: 10.1074/jbc.M110.146738.

Mäntylahti S, Aitio O, Hellman M, Permi P. HA-detected experiments for the backbone assignment of intrinsically disordered proteins. J Biomol NMR. 2010; 47: 171–181.

Aitio O, Hellman M, Kesti T, Kleino I, Samuilova O, Pääkkönen K, Tossavainen H, Saksela K, Permi P. Structural basis of PxxDY motif recognition in SH3 binding. J Mol Biol. 2008; 382: 167–178.

Paavilainen V, Hellman M, Bovellan M, Helfer E, Annila A, Carlier MF, Permi P, Lappalainen P. Structural basis and evolutionary origin of actin filament capping by twinfilin. Proc Natl Acad Sci USA. 2007; 104: 3113–3118.

Molecular biophysics of biological energy transduction

- **Real-time recording using single catalytic enzyme turnover of events resulting in transmembrane ion translocation**

Research in the group is focused on understanding of the processes fundamental to biological energy conversion. We concentrate on the molecular basis for the coupling mechanisms through which the energy of an electron transfer turns into a delocalized transmembrane electric potential. Our main tool is real-time recording of a single catalytic enzyme turnover, with the goal of following all of the molecular events that result in transmembrane ion translocation. The main emphasis our group makes is on the understanding of the molecular mechanism of proton pump functioning.

Selected publications

Belevich N P, Verkhovskaya ML, Verkhovsky MI. Electron transfer in respiratory complexes resolved by an ultra-fast freeze-quench approach. In William S. Allison and Immo E. Scheffler, editors: Methods in Enzimology. 2009; Vol. 456, Burlington: Academic Press, pp. 75–93.

Belevich I, Verkhovsky MI. Molecular mechanism of proton translocation by cytochrome c oxidase. Antioxidants & Redox Signaling. 2008; 10(1): 130.

Gorbikova E, Belevich I, Wikström M, Verkhovsky MI. The proton donor for O-O bond scission by cytochrome c oxidase. Proc Natl Acad Sci USA. 2008; 105: 10733–10737.

Belevich I, Bloch DA, Belevich N, Wikström M, Verkhovsky MI. Exploring the proton pump mechanism of cytochrome c oxidase in real time. Proc Natl Acad Sci USA. 2007; 104: 2685–2690.

Belevich I, Borisov VB, Verkhovsky MI. Discovery of the true peroxy intermediate in the catalytic cycle of terminal oxidases by the real-time measurement. J Biol Chem. 2007; 282: 28514–28519.

Belevich I, Verkhovsky MI, Wikström M. Proton-coupled electron transfer drives the proton pump of cytochrome c oxidase. Nature. 2006; 440: 829–832.

Michael I. Verkhovsky

PhD 1981, Moscow State University, Russia

Postdoctoral research at Dept. of Biophysics, Faculty of Biology, Moscow State University 1975–1989; Belozersky Laboratory of Molecular Biology and Bioorganic Chemistry, Moscow State University 1989–1991; Dept. of Medical Chemistry, Faculty of Medicine, University of Helsinki, 1991–1996

Group Leader at the Institute since 2005

Acting professor in Medical Chemistry (changed in 2002 to Physical Biochemistry) University of Helsinki 1996–2006

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Group members in 2010

Senior scientist: Dmitry A. Bloch

Postdoctoral fellows: Elena Gorbikova, Belevich Ilya

Graduate student: Virve Rauhamäki

Undergraduate students: Marko Rintanen, James Evans

Molecular mechanisms of primary energy transduction in biology and medicine

- **Spectroscopic and other biophysical techniques to follow essential electron and proton transfer in cell respiration**
- **Computational techniques to simulate the dynamics and energetics of structural fluctuations essential for catalysis**

The life of all aerobic organisms depends on primary energy transduction in cell respiration. Our research elucidates the molecular mechanisms of oxygen reduction and primary transformation of the liberated energy into an electrochemical proton gradient, subsequently to be used for the synthesis of ATP, the cells' energy currency. An understanding of these essential functions can help in the prevention and diagnosis of several diseases, and may also be valuable in the design of man-made energy transducers on the nanoscale. Recently, we have applied spectroscopic and other biophysical techniques to follow essential electron and proton transfer processes of cell respiration in real time, and computational techniques to simulate the dynamics and energetics of structural fluctuations essential for catalysis. The results of these combined multidisciplinary efforts have given insight into the mechanism of cell respiration on the atomic level, and further work along these lines will lead to a fundamental understanding of these processes.

Selected publications

Kaila VRI, Verkhovsky MI, Hummer G, Wikström M. Glutamic acid 242 is a valve in the proton pump of cytochrome c oxidase. Proc Natl Acad Sci USA. 2008; 105: 6255–6259.

Verkhovskaya ML, Belevich N, Euro L, Wikström M, Verkhovsky MI. Real time electron transfer in Complex I. Proc Natl Acad Sci USA. 2008; 105: 3763–3767.

Belevich I, Verkhovsky MI, Wikström M. Proton-coupled electron transfer drives the proton pump of cytochrome c oxidase. Nature. 2006; 440: 829–832.

Rauhamäki V, Baumann M, Soliymani R, Puustinen A, Wikström M. Identification of a histidine-tyrosine cross-link in the active site of the cbb3type cytochrome c oxidase from Rhodobacter sphaeroides. Proc Natl Acad Sci USA. 2006; 103: 16135–16140.

Wikström M, Ribacka C, Molin M, Laakkonen L, Verkhovsky M, Puustinen A. Gating of proton and water transfer in the respiratory enzyme cytochrome c oxidase. Proc Natl Acad Sci USA. 2005; 102: 10478–10481.

Mårten Wikström

MD, PhD 1971, University of Helsinki, Finland

Postdoctoral research at the University of Amsterdam, The Netherlands (EMBO fellowship), 1971–1972

Visiting professor in physical biochemistry, University of Pennsylvania, Philadelphia, USA, 1975–1976

Professor of Medical Chemistry since 1983; changed in 2002 to Physical Biochemistry

Academy Professor 1996–2006

Research Director of the Program in Structural Biology and Biophysics since 1998

Societas Scientiarum Fennica, Member 1982–

EMBO Member, 1985–

The Royal Swedish Academy of Sciences (chemistry), Member 1992–

Academia Europaea Member, 2010–

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Group members in 2010

Senior scientist: Marina Verkhovskaya

Project researcher: Galina Belevich

Postdoctoral fellow: Ville Kaila

Graduate students: Juho Knuuti, Vivek Sharma

Technicians: Eija Haasanen, Tarja Salojärvi

DNA Sequencing and Genomics Laboratory

Sequencing service

The DNA sequencing service is directed to customers from universities, research institutes and companies. Our services cover a wide area of genomics ranging from single clone sequencing to ***de novo*** whole genome sequencing projects. For the Sanger sequencing an ABI3130 XL 16-capillary sequencer has been used for small scale sequencing samples and an ABI3730 48-capillary sequencer for high-throughput sequencing. These samples include also fragment analysis in addition to Sanger sequencing.

In the large scale sequencing projects we utilize the state of the art technologies. Our laboratory has been pioneering the next generation sequencing in Finland by obtaining the Roche 454 machine in 2006. In 2009 we have updated the 454 platform to the Titanium chemistry with increased read length of up to 400 bp and yield of 300–600x10^6 bp per run. The NGS repertoire was improved in 2008 by obtaining SOLiD 2. Since then SOLiD has been upgraded twice during the last two years; first to SOLiD 3 and later to SOLiD 3plus finally SOLiD4 in 2010. The machine produces ca. 400x10^6 mappable sequences with read length of 50 bp giving out 15–30 Gbp of primary sequence per one slide. Using the Mate-pair or paired-end methods sequence yield will double per analysis.The SOLiD and 454 platforms are used to sequence samples varying from metagenomics and transcriptomics to *de novo* genome sequencing.

The DNA sequencing technologies evolve very rapidly. Along with the new sequencing techniques novel applications using next gen sequencing are arising with increasing speed. The services provided have been broadening in the future and the parallel sequencing technologies can be utilized in several approaches like EST sequencing, SNP discovery, sequence capture, SAGE, miRNA libraries and functional genomic approaches like RNA-seq, methyl-seq and ChIP-seq. During 2010 we analyzed more than 2000 samples with the 454 and SOLiD platforms.

We are also performing more traditional methods like DNA purification in 96 plate format from tissue samples and from plasmid libraries. Our liquid handling robots are performing rearrangement and regrowth of large clone libraries followed by DNA sequencing if nessessary.

Selected publications

Koskenniemi K, Laakso K, Koponen J, Kankainen M, Greco D, Auvinen P, Savijoki K, Nyman TA, Surakka A, Salusjärvi T, de Vos, WM Tynkkynen S, Kalkkinen N, Varmanen P. Proteomic and transcriptomic characterization of bile stress response in *Lactobacillus rhamnosus* GG. Mol Cell Proteomics. 2011; 10:2.

Koskinen K, Hultman J, Paulin L, Auvinen P, Kankaanpää H. Spatially differing bacterial communities in water columns of the northern Baltic Sea. FEMS Microbiol Ecol. 2011; 75:99–110.

Ojala T, Kuparinen V, Koskinen JP, Alatalo E, Holm L, Auvinen P, Edelman S, Westerlund-Wikström B, Korhonen TK, Paulin L, Kankainen K. Genome sequence of *Lactobacillus crispatus* ST1. J Bacteriol. 2010; 192:3547–3548.

Ovaskainen O, Nokso-Koivisto J, Hottola J, Rajala T, Pennanen T, Ali-Kovero H, Miettinen O, Oinonen P, Auvinen P, Paulin L, Larsson KH, Mäkipää R. What is the probability that the best BLAST hit represents the correct species – identifying wood-inhabiting fungi from environmental samples with pyrosequencing. Fungal Ecol. 2010; 3:274–283.

Roine E, Kukkaro P, Paulin L, Laurinavicius S, Domanska A, Somerharju P, Bamford DH. New, closely related haloarchaeal viral elements with different nucleic acid types. J Virol. 2010; 84:3682–3689.

Head of the Unit

Petri Auvinen

Ph.D. 1990, University of Turku, Finland

Postdoctoral research at University of Turku, Finland 1990–1993, at EMBL, Heidelberg, Germany, 1993–1996

Senior scientist at the Institute 1996–2000

Group Leader at the Institute since 2001

Laboratory Director at the Institute since 2008

Personnel in 2010

Laboratory engineer: Lars Paulin

Technicians: Heli Ahlsten, Paula Collin-Olkkonen (part of the year), Harri Kangas (part of the year), Päivä Laamanen, Kirsi Lipponen, Lea Merviä, Ritva Rajala (part of the year), Matias Rantanen, Anu Suoranta, Eeva-Maria Turkki, Hanna Turunen (part of the year).

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Biocenter Finland infrastructure: Genome-wide methods

http://www.biocenter.oulu.fi/bf/index3_genomewide.html

Electron Microscopy and CryoEm Unit

Electron microscopy and cryoEM units belong to the Biocenter Finland Biological imaging network, and provide nationwide technology services on advanced electron microscopy techniques.

Electron Microscopy Unit

The Electron Microscopy Unit functions as a central core facility for the whole of the University of Helsinki. Annually we have around 50 projects from bio-, medical and material sciences. About one third of the projects are research collaborations, while the others are on the basis of joint use of instruments and paid services. For new users we provide training for the use of our equipment and guidance for sample preparation. We organize annually practical courses on EM techniques in collaboration with VGSB and MBIOT. We have been actively setting up advanced EM techniques such as electron tomography, correlative light electron microscopy, high pressure freezing and freeze substitution. As part of the Biocenter Finland nationwide technology services, we are establishing a new 3D imaging method based on serial block face imaging on scanning electron micrsocopy.

We encourage everyone to visit our web-pages, where we have collected lot of information about the instruments, methods and practicalities on using the EM facility. There is also a link to our electronic microscopy reservation system and more information about our research.

Currently we have three transmission and one scanning electron microscopes:

- FEI Tecnai 12 Transmission electron microscope
- FEI Tecnai F20 field emission gun Transmission electron microscope
- Jeol 1200 EX II Transmission electron microscope
- FEI Quanta 250 field emission gun Scanning electron microscope (installed in December 2010)

All microscopes are equipped with CCD-cameras, and element analysis can be done on FEI Tecnai 12. Both Tecnai microscopes are equipped for cryoEM, and we have a collection of different holders for room temperature, electron tomography and cryo imaging.

For specimen preparation we have three ultramicrotomes of which one is equipped for cryosectioning and devices for critical point drying, platinum and carbon coating and glow discharge. For cryopreparation we have a high pressure freezing device, freeze substitution units and vitrification robot.

The complete list of instruments including all accessory devices can be found from our web-pages.

Head of the Unit

Eija Jokitalo

PhD 1996, University of Helsinki, Finland

Postdoctoral research at Imperial Cancer Research Fund, Cell Biology Laboratory, London, UK, 1997–1999

Researcher at the Institute, 2000–2001

Group Leader at the Institute since 2001

Laboratory Director at the Institute since 2010

Personnel in 2010

Senior scientist: Helena Vihinen, Ilya Belevich (since 1.2.2010; Biocenter Finland funded position)

Technicians: Mervi Lindman, Antti Salminen, Arja Strandell

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Biocenter Finland infrastructure: Biological Imaging

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CryoEM Unit

For details, see Professor Sarah Butcher's group

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List of methods available

- Plastic embedding
- High pressure freezing, freeze-substitution
- Pre-embedding immunolabelling
- Immunolabelling of cryo-sections (Tokuyasu method)
- Immunolabelling of acrylic sections
- Cytochemical staining of HRP-tagged proteins or endocytosed HRP
- Correlative light electron microscopy
- Electron tomography
- Negative staining
- Specimen preparation for scanning electron microscopy (SEM)
- Element analysis (EDX microanalysis)

Selected publications

Lonka-Nevalaita L, Lume M, Leppänen S, Jokitalo E, Peränen J, Saarma M. Characterization of the intracellular localization, processing, and secretion of two glial cell line-derived neurotrophic factor splice isoforms. J Neurosci. 2010; 30:11403–1413.

Säälik P, Padari K, Niinep A, Lorents A, Hansen M, Jokitalo E, Langel Ü, Pooga M. Protein delivery with transportans is mediated by caveolae rather than flotillin-dependent pathways. Bioconjugate Chem. 2009; 20: 877–887.

Ylä-Anttila P*, Vihinen H*, Jokitalo E, Eskelinen E-L. 3D tomography reveals connections between the phagophore and endoplasmic reticulum. Autophagy 2009; 5: 1180–1185.

Korhonen L, Hansson I, Maugras C, Wehrle R, Kairisalo M, Borgkvist A, Jokitalo E, Sotelo C, Fisone G, Dusart I and Lindholm D. Expression of X-chromosome linked inhibitor of apoptosis protein in mature purkinje cells and in retinal bipolar cells in transgenic mice induces neurodegeneration. Neuroscience. 2008; 156: 515–526.

Mattila PK, Pykäläinen A, Saarikangas J, Paavilainen VO, Vihinen H, Jokitalo E, Lappalainen P. Missing-In-Metastasis (MIM) and IRSp53 deform PI(4,5)P2-rich membranes by an inverse BAR domain like mechanism. J. Cell Biol. 2007; 176:953–64.

*equal contribution

Genome Biology Unit

Scientific Leader: Director Tomi P. Mäkelä

The Genome Biology Unit (GBU) has initiated in 2010 and provides technology platform services and reagent collections related to genome-wide approaches. Among the services available there are integrated two-hybrid screenings and the recently started (January 2011) cloning service. The reagent collection contains full cDNAs (21 000 genes) and in 2010 a new library of full open reading frames (ORFeome) consisting in about 14 000 genes were added to the reagent list. At the end of 2010 GBU and Drug Discovery Unit had joined forces to acquire a High Content Screening (HCS) microscope that is operating trough Light Microscopy Unit. Shortly the unit will start to perform High Throughput cloning of the ORFeome library taking advantage of the Gateway technology. This step, in combination with HCS will speed up genome-wide screenings.

Selected publications

Martinez R. Universal microarray for analysis of breast cancer. PhD thesis (2009) Heidelberg University, Heidelberg, Germany.

Hauser NC, Martinez R, Jacob A, Rupp S, Hoheisel JD, Matysiak S. Utilising the left-helical conformation of L-DNA for analysing different marker types on a single universal microarray platform. Nucleic Acids Res. 2006; 34(18): 5101–5111.

Head of the Unit

Rafael Martinez

PhD: 2009 German Cancer Research Center, Heidelberg, Germany.

Academy Membership: DFG Deutsche Forschungsgemeinschaft (German Research Foundation) 886

Personnel in 2010

Outi Kokkonen: Integrated Two Hybrid Screenings.

Harri Jäälinoja: High-Content Screening microscope (located in Light Microscopy Unit)

E-mail: rafael.martinez@helsinki.fi

http://www.biocenter.helsinki.fi/bi/gbu/

Biocenter Finland infrastructure: Genome-wide methods

http://www.biocenter.fi/index.php?page=genome-wide-methods

Light Microscopy Unit

Scientific Leader: Maria Vartiainen

The light microscopy unit provides high end microscopy systems together with training, consultation, support and equipment management services. All equipment is available to all scientific and commercial users. Larger projects, such as setting up new imaging and analysis systems and methods, are provided as scientific collaboration. We aim to be a facility for high-end data acquisition with a wide range of supported applications, and to keep pace with developing imaging technologies by continuously developing and upgrading our services and instrumentation. As before, our primary goal is to satisfy our customers by offering them well configured and maintained high end light microscopy systems with support ranging from basic user training to advanced methods development.

Currently we have three confocal microscopes, a Leica TCS SP2 AOBS and a Leica TCS SP5 II HCS A high content system with inverted microscopes and a Leica TCS SP5 with an upright microscope. In addition we have a Leica TCS SP5 MP SMD multiphoton and confocal microscope with additional fluorescence lifetime imaging and fluorescence correlation spectrometry detectors. All systems are equipped for live cell imaging; further details can be found on our web pages

Other available systems include a Till Photonics live cell wide field TIRF system and two ChipManTech Cell IQ continuous cell culturing & imaging systems one of which with three channel fluorescence detection in addition to phase contrast. We also have three image analysis workstations, one with off line licenses for microscope software, one for Cell IQ data analysis and one with a full Bitplane Imaris suite and Media Cybernetics Autodeblur deconvolution software. Also backed-up data storage and cell culture facilities are provided.

Selected publications

Hotulainen P, Llano O, Smirnov S, Tanhuanpää K, Faix J, Rivera C, Lappalainen P. Defining mechanisms of actin polymerization and depolymerization during dendritic spine morphogenesis. J Cell Biol. 2009; 185(2): 323–39.

Perttilä J, Merikanto K, Naukkarinen J, Surakka I, Martin NW, Tanhuanpää K, Grimard V, Taskinen MR, Thiele C, Salomaa V, Jula A, Perola M, Virtanen I, Peltonen L, Olkkonen VM. OSBPL10, a novel candidate gene for high triglyceride trait in dyslipidemic Finnish subjects, regulates cellular lipid metabolism. J Mol Med. 2009; 87(8): 825–35.

Shulga A, Blaesse A, Kysenius K, Huttunen HJ, Tanhuanpää K, Saarma M, Rivera C. Thyroxin regulates BDNF expression to promote survival of injured neurons. Mol Cell Neurosci. 2009; 42(4): 408–18.

Lyly A, Marjavaara SK, Kyttälä A, Uusi-Rauva K, Luiro K, Kopra O, Martinez LO, Tanhuanpää K, Kalkkinen N, Suomalainen A, Jauhiainen M, Jalanko A. Deficiency of the INCL protein Ppt1 results in changes in ectopic F1-ATP synthase and altered cholesterol metabolism. Hum Mol Genet. 2008; 17(10): 1406–17.

Uusi-Rauva K, Luiro K, Tanhuanpää K, Kopra O, Martín-Vasallo P, Kyttälä A, Jalanko A. Novel interactions of CLN3 protein link Batten disease to dysregulation of fodrin-Na+, K+ ATPase complex. Exp Cell Res. 2008; 314(15): 2895–905.

Head of the Unit

Kimmo Tanhuanpää

PhD 2001, University of Helsinki, Finland

Postdoctoral research at Department of Molecular Medicine, National Public Health Institute – KTL Helsinki, 2002–2003 and Institute of Biotechnology, University of Helsinki, 2003–2004

Light Microscopy Unit, Institute of Biotechnology, University of Helsinki, since 2004

Personnel in 2010

Postdoctoral fellow: Harri Jäälinoja

Laboratory engineers Marko Crivaro and Mika Molin

www.biocenter.helsinki.fi/bi/lmu/index.htm

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Biocenter Finland infrastructure: Biological Imaging

http://www.biocenter.fi/index.php?page=biological-imaging

Finnish Biological NMR Center

The mission of the National Biological NMR Center is to provide the state-of-the-art NMR instrumentation, methodology and expertise for the use of research groups in the fields of molecular biology, biotechnology and molecular medicine in Finland. The facility houses four high-resolution, top-level NMR spectrometers. The 800 MHz spectrometer is the only one in Finland. Although the facility is specially designed and equipped for biomolecular NMR research, we can, by using broadband probe-heads, measure practically any element.

Biomolecular NMR studies are often regarded as structure determination of proteins or protein-ligand complexes. Fortunately, NMR can go far beyond by enabling studies of features that characterize function of a protein i.e. protein dynamics in timescales ranging from picoseconds to seconds (domain movements, conformational changes, enzyme kinetics, folding), determination of the binding epitope of a ligand and localization of the binding interface on a protein also in the case of weak interaction (Kd ~10–3). Remarkably, NMR based interaction studies do not require development of a system specific assay.

The NMR Lab has also equipment for cloning, expression and purification of proteins e.g. PCR, two Äkta FPLC systems, incubator shakers, centrifuges, French Press, sonicator as well as smaller laboratory equipment.

In addition to NMR equipment, the laboratory also has a VP-ITC microcalorimeter for isothermal titration calorimetry.

Equipment

Varian Inova 800 MHz with 63 mm bore, three RF channels with 2H decoupling capability. Pulsed field gradient capability with Performa X,Y,Z module.
– a 5 mm cryogenically cooled 1H{13C, 15N} probehead with z-axis PFG
– a 5 mm 1H{13C, 15N} probehead with xyz-axis PFGs
– a variable temperature unit

Varian Inova 600 MHz, four RF channels with 2H decoupling capability.
– a 5 mm cryogenically cooled 1H{13C, 15N} probehead with z-axis PFG
– a 5 mm 1H{13C, 15N} probehead with z-axis PFG
– a variable temperature unit

Varian Inova 600 MHz, four RF channels with 2H decoupling capability,
– a 5 mm 1H{13C, 15N} probehead with z-axis PFG
– a 5 mm 1H{13C, 31P, 15N} probehead with z-axis PFG
– a variable temperature unit

Varian Inova 500 MHz, three RF channels with 2H decoupling capability,
– a 5 mm triple-resonance probehead with z-axis PFG
– a 1H{X} nano-probehead with z-axis PFG
– a variable temperature unit

Laboratory has a selection of different probeheads for 500 & 600 MHz spectrometers including 5 & 10 mm broadband probeheads with 1H decoupling.

Selected publications

Nakamura F, Heikkinen O, Pentikäinen OT, Osborn TM, Kasza KE, Weitz DA, Kupiainen O, Permi P, Kilpeläinen I, Ylänne J, Hartwig JH, Stossel TP. Molecular basis of filamin A-FilGAP interaction and its impairment in congenital disorders associated with filamin A mutations. PLoS One. 2009; 4:e4928.

Nuutinen T, Tossavainen H, Fredriksson K, Pirilä P, Permi P, Pospiech H, Syvaoja J. Solution structure of amino terminal domain of human DNA polymerase e subunit B reveals homology to C-domains of AAA+ proteins. Nucleic Acids Res. 2008; 36, 5102–5110.

Head of the Unit
Perttu Permi

PhD 2001, University of Oulu, Finland

Postdoctoral research at NMR laboratory at the Institute of Biotechnology, 2001–2003

Group Leader at the Institute since 2004

Docent 2002, University of Oulu

Head of the Finnish National Biological NMR Center since 2004

Academy Research Fellow since 2009

Personnel in 2010

Paid service in spectroscopy: Olli Aitio

Laboratory engineer: Tuomas Niemi-Aro

www.biocenter.helsinki.fi/bi/nmr/permi

Email: perttu.permi@helsinki.fi

Biocenter Finland infrastructure: Structural Biology

http://www.biocenter.oulu.fi/bf/index3_structuralbiology.html

Rantalainen K, Uversky V, Permi P, Kalkkinen N, Dunker K, Mäkinen K. Potato virus A genome-linked protein VPg is an intrinsically disordered molten globule-like protein with a hydrophobic core. Virology. 2008; 377: 280–288.

Bogachev AV, Bertsova YV, Aitio O, Permi P, Verkhovshy MI. Redox-dependent sodium binding by the Na(+) translocating NADH:Quinone oxireductase from Vibrio harveyi. Biochemistry. 2007; 46: 10186–10191.

Nakamura F, Pudas R, Heikkinen O, Permi P, Kilpeläinen I, Munday AD, Hartwig JH, Stossel T, Ylänne J. The Structure of the GPIb-filamin A complex. Blood. 2006; 107: 1925–1932.

Protein Chemistry Core Facility

The Protein Chemistry Research Group has from its beginning in 1982 served also as a Core Facility (CF) and presently provides analyses for a large number of academic and industrial researchers and research groups. The present Core Facility analyses are connected to different kind of protein purifications, identifications and characterizations by electrophoretic, chromatographic and mass spectromertic methods. Recently also the number of proteomics related analyses have increased. The main instrumentation of the Protein Chemistry Research Group and Core Facility consists of:

- 1D- and 2D-gel electrophoretic separation systems
- Nine different types of liquid chromatographic systems (HPLC) with different protein and peptide separation parameters and column ID:s ranging from 75 µm to 25 mm.
- An Appled Biosystems Procise 494 HT protein/peptide sequencer for N-terminal protein and peptide sequencing.
- A MALDI-TOF/TOF mass spectrometer (Ultraflex TOF/TOF, Bruker Daltonics, Germany), two nanoLC-ESI Q-TOF mass spectrometers (Q-TOF1, Micromass, UK and Applied Biosystems Qstar Elite, Applied Biosystems/Sciex, USA).

Selected publications

Leppänen A, Parviainen V, Ahola-Iivarinen E, Kalkkinen N, Cummings RD. Human L-selectin preferentially binds synthetic glycosulfopeptides modeled after endoglycan and containing tyrosine sulfate residues and sialyl Lewis x in core 2 O-glycans. Glycobiology. 2010; 20(9):1170–85.

Haiko J, Laakkonen L, Juuti K, Kalkkinen N, Korhonen TK. The omptins of *Yersinia pestis* and *Salmonella enterica* cleave the reactive center loop of plasminogen activator inhibitor 1. J Bacteriol. 2010 Jul 16. [Epub ahead of print]

Coleman SK, Cai C, Kalkkinen N, Korpi ER, Keinänen K. Analysis of the potential role of GluA4 carboxyl-terminus in PDZ interactions. PLoS One. 2010; 5(1): e8715.

Tugume AK, Mukasa SB, Kalkkinen N, Valkonen JP. Recombination and selection pressure in the ipomovirus sweet potato mild mottle virus *(Potyviridae)* in wild species and cultivated sweetpotato in the centre of evolution in East Africa. J Gen Virol. 2010; 91(Pt 4):1092–108.

Leppänen VM, Jeltsch M, Anisimov A, Tvorogov D, Aho K, Kalkkinen N, Toivanen P, Ylä-Herttuala S, Ballmer-Hofer K, Alitalo K. Structural determinants of vascular endothelial growth factor-D receptor binding and specificity. Blood. 2011; 117(5):1507–15.

Head of the Unit

Nisse Kalkkinen

PhD (biochemistry) 1981, University of Helsinki

Postdoctoral research at Karolinska institutet, Stockholm, Sweden, various periods

PI at the Recombinant DNA Laboratory, University of Helsinki 1985–1989

Group Leader at the Institute since 1989

Personnel in 2010

Technicians: Elina Ahola-Iivarinen, technician (part time in CF);
Marko Hukka, technician (part time in CF); Gunilla Rönnholm, senior technician

Other Protein Chemistry Research Group members participate part-time in CF according to the need.

www.biocenter.helsinki.fi/bi/protein

Email: nisse.kalkkinen@helsinki.fi

Biocenter Finland infrastructure: Proteomics and Metabolomics

http://www.biocenter.fi

Protein Crystallisation Facility

Our protein crystallisation facility provides low volume crystallisation service in Finland. We use either commercially available screen setups or design novel screens for crystal optimisation. Our customers can also order custom built premixed crystallisation solutions for manual crystallisation. Full crystallisation service includes composition of the crystallisation setup and scheduled imaging of the experiment for up to four months. The crystallisation droplets are set up using our Cartesian MicroSys or Douglas Instruments Oryx nanodrop robots, which can use as little as 100 nl protein per experiment. The small volume is essential in order to save protein in the projects where protein or its complexes are difficult to isolate. In addition our Oryx robot can setup experiments under oil for samples which are sensitive to the air interface or require dedicated seeding experiments. As a result, the scientists receive images from the crystallisation experiments, which follow the maturation of the project over time. At any time point the customer can obviously also pick up the crystallisation plate to mount the crystals for an X-ray experiment. In future we plan to upgrade our system for dedicated methods on membrane protein crystallisation.

Equipment, purpose

Shimadzu/Wyatt HPLC system for protein multicomponent analysis.
Hamilton STAR, liquid Handling robot
Cartesian MicroSys, nanodrop dispenser
Douglas Instruments Oryx 6, nanodrop dispenser
TTP Labtech Mosquito LCP, nanodrop dispenser for membrane protein crystallization
Exploranova Xtal Focus, for imaging at room temperature
Microlab SWAP robotic arm, and
Thermo Rhombix Imager, for imaging at 4°C
700 GB RAID disk system, data storage
Dedicated network server, for image export to end users.

Selected publications

Koutsioulis D, Lyskowski A, Mäki S, Guthrie E, Feller G, Bouriotis V, Heikinheimo P. Coordination sphere of the third metal site is essential to the activity and metal selectivity of alkaline phosphatases. Protein Sci. 2010; 19(1): 75–84.

Parkash V, Goldman A. Comparison of GFL-GFRalpha complexes: further evidence relating GFL bend angle to RET signalling. Acta Cryst. 2009; F65, 551–8.

Parkash V, Lindholm P, Peränen J, Kalkkinen N, Oksanen E, Saarma M, Leppänen V M, Goldman A. The structure of the conserved neurotrophic factors MANF and CDNF explains why they are bifunctional. Protein Eng Des Sel. 2009; 22: 233–41.

Heads of the Unit

Pirkko Heikinheimo
Adrian Goldman

Personnel in 2010

Postdoctoral fellow:
Andrzej Łyskowski (till October);
Robert Kolodziezyk (from October)

Technician: Seija Mäki (50%),
Katja Rosti (50%)

www.biocenter.helsinki.fi/bi/xray/automation

Email: bi-crystallisation@helsinki.fi

Biocenter Finland infrastructure:
Structural Biology

http://www.biocenter.oulu.fi/bf/index3_structuralbiology.html

Careers at BI

The Institute of Biotechnology (BI) offers exciting positions at all levels of your research training and career. Here you will find first class research and state-of-the-art scientific services. As a member of one our groups you will be part of a young international team, using English as your working language. The atmosphere at BI is stimulating, and a distinct pioneering spirit can be felt among our staff. BI housed on the Viikki campus with "a touch of life" offers an inspiring home to about 300 scientists and administrative staff.

BI's research groups are well funded to support a number of pre- and post-doctoral positions. There is a strong tradition to encourage traveling and participation in meetings and courses. BI also participates in organizing international meetings and courses every year especially within the graduate program curricula. The Viikki Biocenter Lectures (see Table, page 53) is a weekly high profile research seminar series organized by the Viikki Research Group Organization in Molecular Biosciences.

If you come to work at BI, we also recognize your private needs and try to make relocation as smooth as possible. For newcomers, there are short-term housing possibilities. Our administrative staff is helpful in your legal requirements including visas, work permits, health insurance and family matters. Finland is an outstanding country for parent with young kids with world-class public day-care and education, and Helsinki offers a range of foreign language schooling options. We are also very aware that many of our new employees are accompanied by spouses looking for qualified positions, and in some cases can help secure positions. BI has a program to support your efforts to learn the local languages and we have several possibilities for team and personal exercise.

Detailed information on career opportunities is available below and at www.biocenter.helsinki.fi/bi/careers

Undergraduate and Master's Programs (HEBIOT & MBIOT)

BI offers and excellent surrounding for undergraduate training on the Viikki campus in collaboration with the University of Helsinki faculties and the Neuroscience Center. The education coordinator at BI is **Professor Sarah Butcher**. Researchers in the Institute are directly responsible for B.Sc. and M.Sc. training in the **Helsinki region biotechnology educational programme (HEBIOT)**, which has expanded undergraduate training in the fields of developmental biology, virology, and neurobiology to systems biology and structural biology. HEBIOT is a joint initiative in interdisciplinary education by the University of Helsinki and the Aalto University. In the University of Helsinki, the Faculties of Agriculture and Forestry, Pharmacy, and Medicine, and the Institute of Biotechnology and the Neuroscience Center participate in education.

BI contributes significantly to an **International Master's Degree Programme in Biotechnology (MBIOT)**, which is a collaboration with the Faculty of Biosciences and the Faculty of Agriculture and Forestry. Within the regions of their expertise, the cell biotechnology, structural biology and developmental biology researchers at BI are responsible for providing essentially all the courses and training, as well as supervision of M.Sc. theses.

Many BI researchers also participate in other undergraduate teaching programs at the University. The active role that the BI is taking in basic teaching promotes contact with undergraduate students, teaching at the cutting edge of research and the possibility of grooming potential Ph.D. students. Moreover, the group leaders of BI can compete on pedagological grounds when applying for faculty positions. The BI staff is a valuable teaching resource, providing highly trained expertise in their fields which has now been mobilized to promote biotechnology education in the Helsinki metropolitan area.

Students wishing to pursue post-graduate studies can thus readily join research groups at an early stage in their education and can also participate in the educational programs of the graduate schools prior to completing their Master's degrees. There are about 30 undergraduate and master's students rotating in BI groups and preparing their Master's theses.

Graduate Training and Doctoral Programs

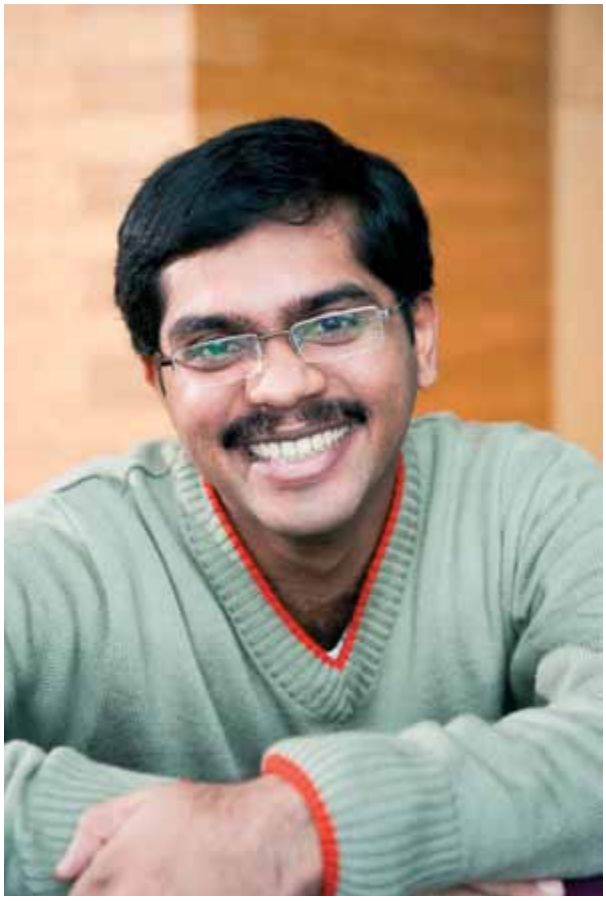
Graduate training within BI groups and number PhD graduate programs is a critical element for the success of BI integrating training and research. Graduate students join BI through a number of PhD programs available both within nationally funded and internationally recognized doctoral programs and within the faculties of the University of Helsinki. Calls for applications for funded positions in the graduate programs go out annually or every other year, with contracts typically lasting 4 years. There are typically about 80 graduate students from all over the world working at BI.

The Finnish doctoral programs have attracted significant international attention as a model for enabling structured high-quality PhD training, and provide an exciting opportunity for international students warmly welcome within the BI groups. Training is nationally coordinated through FinBioNet – Finnish Graduate School Network in Life Sciences, a national network of doctoral programs in biosciences and health sciences (www.finbionet.fi).

The four major nationally funded doctoral programs BI researchers are affiliated with are:

- **Helsinki Graduate Program in Biotechnology and Molecular Biology (GPBM)**
  Director: Professor Pekka Lappalainen
  www.biocenter.helsinki.fi/biotechgs
- **Viikki Doctoral Programme in Molecular Biosciences (VGSB)**
  Director: Professor Dennis Bamford
  www.biocenter.helsinki.fi/viikkigs
- **Finnish Graduate School of Neuroscience (FGSN)**
  Director: Professor Kai Kaila
  www.helsinki.fi/fgsn
- **National Doctoral Programmes in Informational and Structural Biology (ISB)**
  Director: Professor Mark S. Johnson
  www. abo.fi/isb

Together with our colleagues from the Faculty of Biosciences, the Faculty of Science, the Faculty of Pharmacy, and the Faculty of Medicine, we organize lectures and practical courses for these doctoral programs. Annually, researchers at the Institute are involved in the organization of 60–90 ECTS credits for Ph.D. students.



Kiran Hasygar works as a PhD student at Hietakangas lab. He is analyzing various signaling pathways involved in insulin production using *Drosophila melanogaster* (fruit fly) as a model system. He hopes to identify novel proteins regulating insulin secretion. As variations in the levels of insulin may have severe effects on the physiology leading to diseases like diabetes mellitus, obesity and aberrations in growth, a thorough understanding of insulin production and all the genes involved in it will help to develop methods to prevent or treat these diseases. Kiran says: "Institute of Biotechnology provides encouraging atmosphere for research with state of the art facilities and inspiring scientists".

Post-doctoral Training at BI

Postdoctoral scientists are highly valued at BI demonstrated by the nationally very high ratio of postdocs to graduate students and with an exceptionally high number of international postdocs. BI recruits postdoctoral scientists worldwide and offers an excellent environment for young scientists at a critical point in their careers. The Research Programs organize journal clubs and discussion forums, and mentoring of postdoctoral students is an acknowledged responsibility of group leaders. A structured post-doctoral training program is included in the strategy of the BI for 2010–12.

Tenure Track at BI

One of the keys to the success of BI has been the ability to offer independent Group Leader positions to young scientists with strong track records in the focus areas of BI demonstrated by a successful postdoctoral period in an international setting. Group Leader contracts have been renewable 5 year contracts pending successful evaluations by a top-level Scientific Advisory Board and the Board. During 2009 this model has been developed to further clarify and enhance the attractiveness of the Group Leader positions, and in the 2010 spring call the Institute for the first time announced Tenure Track positions for new Group Leaders. Further information is available at www.biocenter.helsinki.fi/bi/recruit/

Graduate and advanced courses given by the researchers of the Institute

Viikki Doctoral Programme in Molecular Biosciences (VGSB) courses, Spring 2010

Course	ECTS	Time	Number of participants average per lecture
Viikki Biocenter Monday Lectures Spring 2010 Seminar series (once a week, org. Doc. Ville Hietakangas)	1,0	Monday 15.15–16.00	70
Virus Club Seminar series (once a month, org. Doc. Tero Ahola)	0,5	Thursday 15.30–17	30–40
Next Generation Genomics** (org. Petri Auvinen, Yrjö Helariutta, Liisa Holm, Mikko Frilander, Tomi Mäkelä)	1,5 – 4,0	14.–15.1.	90
Imaging Techniques In Biological Sciences** Practical course (org. Eija Jokitalo & Maria Vartiainen)	3,0	1.2.–30.4.	15
From Cell To Organism – Developmental Biology* Lecture course (contact Doc. Tapio Heino)	3,0	8.3.–19.4. Mon–Tue 10–12	40
Practical Course In Electron Microscopy Practical course (org. Eija Jokitalo)	5,0	9.–19.3.	12
Developmental Biology Practical Course* Practical course (org. Juha Partanen)	4,0	26.4.–7.5.	14
The 3rd Finnish Cell Biology Symposium Symposium (org. Doc. Eija Jokitalo & Doc. Jussi Jäntti)	1,0	22.–23.4.	60

Viikki Doctoral Programme in Molecular Biosciences (VGSB) courses, Fall 2010

Viikki Biocenter Monday Lectures Fall 2010 Seminar series (once a week, org. Doc. Ville Hietakangas)	1,0	Mon 15.15–16.00	70
Virus Club Seminar series (once a month, org. Doc. Tero Ahola)	0.5	Thursday 15.30–17	30–40
Genome Club Seminar series (once a month, org. Doc. Mikko Frilander)	0.5	Thursday 15.15–16.45	30–40
Double-Stranded Rna Production For Plant Biotechnology Practical course (org. Dennis Bamford, Peter Sarin, Antti Aalto)	1,5	18.–20.10. & 15.–17.11.	8
Stem Cells And Organogenesis* Lecture course (org. Doc. Ulla Pirvola)	3,0	13.9.–25.10. Mon–Tue 10–12	20
Transcriptomics And Resequencing*** Lecture course (org. Prof. Alan Schulman)	1,0 – 3,0	25.–28.10.	20
Fret Workshop: A Tool To Study Biological Interactions** Practical course (org. Maria Vartiainen and Light Microscopy Unit LMU)	2,0	13.–15.12	12

* Together with MBIOT Program ** Together with GPBM Doctoral Program *** Together with FGSPB Doctoral Program

Helsinki Graduate Program in Biotechnology and Molecular Biology (GPBM)

Advanced PhD Training Course: Next Generation Genomics Practical course (Org. Doc. Petri Auvinen)	4	14.–15.1.	60
Imaging Technologies in Biological Sciences (Org. Doc. Eija Jokitalo and Maria Vartiainen)	4	1.2.–30.4.	16
GSBM Steering Day - Introduction to New PhD Students (Org. Prof Pekka Lappalainen and Erkki Raulo		17.2.	
Membrane Cell Biology and Biophysics Lecture course (org. Prof Pekka Lappalainen)	2	12.–16.4.	40
Analysis of Proteomics Data Using R Practical course (Org. Doc. Tuula Nyman)	1	20.–21.9.	15
Mass Analyzers in Biological Mass Spectrometry Practical course (Org. Doc. Tuula Nyman)	1	4.–5.11.	15

HEBIOT/MBIOT Courses

Course	ECTS	Time	Number of participants average per lecture
Analytical protein chemistry Lecture course (org. Doc. Nisse Kalkkinen)	1	30.11.–3.12.	14
Short lab course on structural biology and biophysics Laboratory course (org. Prof. Sarah Butcher)	6	27.9.–15.10.	8
Lecture and exercise course on electron microscopy and image construction Lecture and exercise (org. Prof. Sarah Butcher)	3	5.11.–19.11.	6
Johdanto viruksiin Lecture course (Org. Prof Dennis Bamford)	3–4	1.11.–15.12.	98
mRNA processing in Eucaryotes Lecture course (org. Doc. Mikko Frilander)	3	18.3.–6.5.	35
Indroduction to structural biology and biophysics Laboratory course (org. Prof. Sarah Butcher)	3		
Growth factors and their receptors Lecture course (Org. Prof. Mart Saarma)	3		
Advanced course in Structural Biology and Biophysics Practise course (Org. Prof. Sarah Butcher)	10		1

The Finnish Graduate School of Neuroscience FGSN

Advanced protein characterisation and crystallisation course Lecture and practical course (Org. Doc. Adrian Goldman)	2	2.–6.5.	

Viikki Biocenter Monday Lectures, Spring 2010

Organised by Doc. Ville Hietakangas, Institute of Biotechnology

Drosophila as a model to study immune response Mika Rämet, Institute of Medical Technology (IMT), University of Tampere, Finland (Host: Jussi Jäntti)	11.1.
Metabolic engineering and systems biology in production of biofuels with yeasts Merja Penttilä, VTT Biotechnology, Espoo, Finland (Host: Jussi Jäntti)	18.1.
Cytoskeletal intermediate filaments as signaling determinants John Eriksson, Department of Biology, Åbo Akademi University, Turku, Finland (Host: Jussi Jäntti)	25.1.
Mass spectrometry beyond proteomics Carol Robinson, Physical & Theoretical Chemistry Laboratory, University of Oxford, UK (Host: Adrian Goldman)	1.2.
The cell biology of lithium: prolyl oligopeptidase and inostiol phosphate signalling Adrian Harwood, Cardiff School of Biosciences, Cardiff University, Cardiff, UK (Host: Arturo García-Horsman)	8.2.
Visualizing mRNP assembly and transport in the Drosophila oocyte Anne Ephrussi, EMBL, Developmental Biology Unit, Heidelberg, Germany (Host: Jussi Jäntti)	15.2.
An atomic model of adenovirus deduced by electron cryo-microscopy and image reconstruction Hong Zhou, Electron Imaging Center for Nanomachines and Department of Microbiology, Immunology and Molecular Genetics, UCLA, Los Angeles, USA (Host: Sarah Butcher)	1.3.
Trafficking pathways which control mammalian autophagy Sharon Tooze, Cancer Research UK, London Research Institute, London, UK (Host: Eeva-Liisa Eskelinen)	8.3.
The structure and function of cation pumps Poul Nissen, The Centre for Membrane Pumps in Cells and Disease, Department of Molecular Biology, Aarhus University, Denmark (Host: Mikko Frilander)	15.3.
Cholesterol distribution and transport in cell membranes Elina Ikonen, Institute of Biomedicine/Anatomy, University of Helsinki, Finland (Host: Jussi Jäntti)	22.3.
Search of genetic background of schizophrenia Maria Karayiorgou, Department of Psychiatry, Columbia University Medical Center, New York, USA (Host: Pekka Männistö)	29.3.
Canine models of human inherited diseases Hannes Lohi, Department of Basic Veterinary Sciences, University of Helsinki, Finland (Host: Jussi Jäntti)	12.4.
Cytoplasmic oxysterol-binding proteins: At the crossroads of lipid metabolism, membrane trafficking and cell signaling Vesa Olkkonen, The Minerva Foundation Medical Research Institute, Helsinki, Finland (Host: Jussi Jäntti)	19.4.
Prospects for X-rays in Biology David Stuart, Division of Structural Biology, Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK (Host: Dennis Bamford)	26.4.
Autophagy and lysosomes as targets for cancer therapy Marja Jäättelä, Apoptosis Department and Centre for Genotoxic Stress Research, Institute of Cancer Biology, Danish Cancer Society, Copenhagen, Denmark (Host: Carl Gahmberg)	3.5.
Cyanobacterial photosynthesis – implication for production of SolarFuels Eva-Mari Aro, Laboratory of Plant Physiology and Molecular Biology University of Turku, Finland (Host: Jussi Jäntti)	10.5.

Viikki Biocenter Monday Lectures, Autumn 2010

The ubiquitin proteolytic system: From basic mechanisms thru human diseases and onto drug targeting. Aaron Ciechanover, Cancer and Vascular Biology Research Center, Technion-Israel Institute of Technology, Haifa, Israel. Nobel laureate in Chemistry in 2004. (Host: Carl Gahmberg)	6.9.
Ecological implications of plant communication Ariel Novoplansky, Mitrani Dept of Desert Ecology, Institutes for Desert Research, Ben-Gurion University of the Negev, Israel. (Host: Pedro Aphalo)	13.9.
Polarity proteins in morphogenesis and metastasis Ian Macara, Center for Cell Signaling, University of Virginia, Charlottesville, USA. (Host: Jussi Jäntti)	20.9.
Hijacking of cellular protein interaction networks by pathogens Kalle Saksela, Department of Virology, Haartman Institute, University of Helsinki. (Host: Jussi Jäntti)	27.9.
Intercellular transfer of homeoprotein transcription factors: a novel signaling mechanism in the developing and adult nervous system Alain Prochiantz, Collège de France, Paris, France. (Host: Eero Castren)	4.10
Retrotransposons and genome dynamics in plants Alan Schulman, Genomics Research, MTT & Institute of Biotechnology, University of Helsinki (Host: Ville Hietakangas)	11.10.
Enzymes as oxygen sensors in the hypoxia response Johanna Myllyharju, Department of Medical Biochemistry and Molecular Biology, Institute of Biomedicine, Faculty of Medicine, University of Oulu. (Host: Ville Hietakangas)	18.10.
Novel players in human RNA metabolism: RNA-kinases and RNA-ligases come to light Javier Martinez, Institute of Molecular Biotechnology, Vienna, Austria (Host: Mikko Frilander)	25.10.
Sculpting cell membranes: Understanding pathways of endocytosis and exocytosis Harvey McMahon, MRC Laboratory of Molecular Biology, Cambridge, UK (Host: Pekka Lappalainen)	1.11.
Molecular mechanisms of the biological energy transduction Michael Verkhovsky, Institute of Biotechnology, University of Helsinki (Host: Ville Hietakangas)	8.11.
Pharmacogenetics to Pharmacogenomics Richard Weinshilboum, Division of Clinical Pharmacology, Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Minnesota, USA. (Host: Moshe Finel)	15.11.
SUMOylation in transcriptional regulation Jorma Palvimo, Department of Medical Biochemistry, University of Eastern Finland, Kuopio. (Host: Ville Hietakangas)	22.11.
A gene-specific requirement of RNA polymerase II CTD phosphorylation for sexual differentiation in s. pombe Damien Hermand, Laboratoire de Genetique Moleculaire, The University of Namur, Belgium. (Host: Tomi Mäkelä)	29.11.
Analysis and integration of large-scale data in cancers Sampsa Hautaniemi, Institute of Biomedicine, Genome-Scale Biology Research Program, Faculty of Medicine, Biomedicum Helsinki, University of Helsinki. (Host: Ville Hietakangas)	13.12.

The program is available at www.biocenter.helsinki.fi/Viikki_lectures.html

Board (Jan 1 – Jul 31, 2010)

Board of the Institute
(March 18, 2009 – July 31, 2010;
term of office became shorter in consequence of the modification in the Institute's Regulations)

Chair:

Professor Esko Ukkonen
Department of Computer Science, Faculty of Science

Members:

Academy Professor Lauri Aaltonen
Vice-Chair,
Haartman Institute, Faculty of Medicine

Professor Kielo Haahtela
Department of Biosciences, Faculty of Biological and Environmental Sciences

MD, PhD, CEO Markku Jalkanen
Faron Pharmaceuticals Ltd

Professor Kai Kaila
Department of Biosciences, Faculty of Biological and Environmental Sciences

PhD, Academy Research Fellow
Marja Mikkola
Institute of Biotechnology;
representative of staff

Research Technician Miika Palviainen
Institute of Biotechnology;
representative of staff

Research Professor Merja Penttilä
VTT Technical Research Centre of Finland

Professor Vieno Piironen
Department of Food and Environmental Sciences, Faculty of Agriculture and Forestry

Director

Professor Tomi P. Mäkelä, MD, PhD.

Administration Director

Arto Halinen, M.Pol.Sc.

Board (Aug 1, 2010 – Mar 31, 2014)

According to the Regulations of the Institute the Board is appointed by the Rector for a term of four years. The Board comprises nine members, each of whom has a personal deputy. Two members must be chosen from amongst the Institute's staff.

Chair:

Professor Esko Ukkonen (Department of Computer Science, Faculty of Science)

Members
(personal deputies in parentheses):

Professor Sarah Butcher
Institute of Biotechnology;
representative of staff
(Postdoctoral researcher Tommi Kajander,
Institute of Biotechnology;
representative of staff)

Professor Kielo Haahtela, Vice-Chair
Department of Biosciences, Faculty of Biological and Environmental Sciences
(Professor Jaakko Kangasjärvi,
Department of Biosciences, Faculty of Biological and Environmental Sciences)

Dr., CEO Markku Jalkanen
Faron Pharmaceuticals Ltd
(Dr., Project Leader Jari Helin,
Glykos Finland Ltd)

Professor Airi Palva
Faculty of Veterinary Medicine
(Professor Hannes Lohi,
Faculty of Veterinary Medicine & Faculty of Medicine)

Research technician Miika Palviainen
Institute of Biotechnology;
representative of staff
(Research technician Anne-Mari Narvanto
Institute of Biotechnology;
representative of staff)

Professor Merja Penttilä
VTT Technical Research Centre of Finland
(Dr., PI Laura Ruohonen,
VTT Technical Research Centre of Finland)

Professor Kalle Saksela
Haartman Institute, Faculty of Medicine
(Professor Anna-Elina Lehesjoki,
Haartman Institute, Faculty of Medicine, and Neuroscience Center)

Professor Raimo Tuominen
Faculty of Pharmacy
(Professor Arto Urtti,
Faculty of Pharmacy)

Scientific Advisory Board (Jan 1, 2006 – Dec 31, 2010)

Chair:

Professor Jonathan Knowles, F. Hoffman – La Roche Ltd., Basel, Switzerland

Members:

Dr. Marius Clore, Chief of Protein NMR Section, Laboratory of Chemical Physics, NIDDK, National Institutes of Health, USA

Professor Urban Lendahl, Department of Cell and Molecular Biology (CMB), Karolinska Institutet, Stockholm, Sweden

Professor Ralf F. Pettersson, Ludwig Institute of Cancer Research, Stockholm, Sweden

Dr. Pernille Rørth, Temasek Life Sciences Laboratory (TLL), National University of Singapore, Singapore

Professor Kai Simons, Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany

Professor Joan A. Steitz, Howard Hughes Medical Institute, Yale University, USA

Professor John E. Walker, Medical Research Council, Mitochondrial Biology Unit, Cambridge, UK

Scientific Advisory Board (Jan 1, 2011 – Dec 31, 2014)

Chair:

Professor Joan A. Steitz, Howard Hughes Medical Institute, Yale University, USA

Members:

Professor David Baulcombe, Department of Plant Sciences, University of Cambridge, UK

Professor Marja Jäättelä, Institute of Cancer Biology, Copenhagen, Denmark

Professor Urban Lendahl, Department of Cell and Molecular Biology (CMB), Karolinska Institutet, Stockholm, Sweden

Professor Annalisa Pastore, MRC National Institute for Medical Research, London, UK

Dr. Pernille Rørth, Institute of Molecular and Cell Biology, Singapore

Professor Kai Simons, Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany

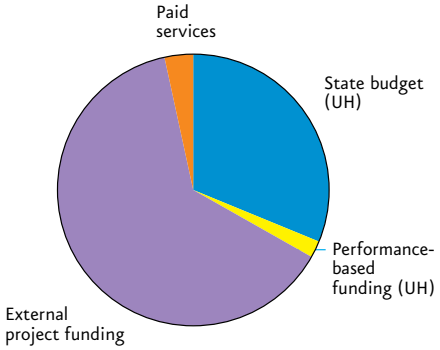
Professor, Sir John E. Walker, MRC Mitochondrial Biology Unit, Cambridge, UK

Funding of the Institute of Biotechnology in 2010

Total Funding

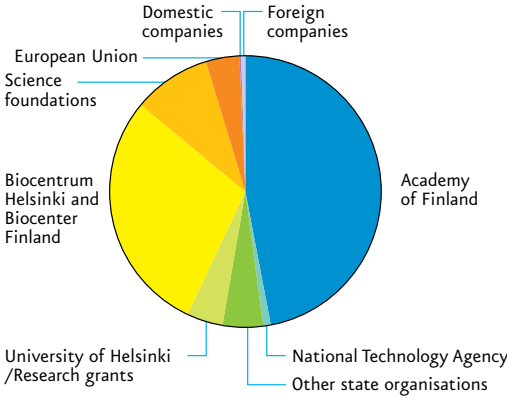
	In 1000 Euros	Percentage
State budget funding (UH) *	6 914	31.2
Performance-based funding (UH)	423	1.9
External project funding	14 038	63.4
Paid services	762	3.4
Total	22 137	100

* Includes basic funding, wage increase funding, and space rents.
UH = University of Helsinki.



External project funding

	Granted (in 1000 Euros)	Percentage
Academy of Finland	6 595	47.0
National Technology Agency	126	0.9
Other state organisations	675	4.8
University of Helsinki/Research grants	600	4.3
Biocentrum Helsinki and Biocenter Finland	4 076	29.0
Science foundations	1 306	9.3
European Union	564	4.0
Domestic companies	24	0.2
Foreign companies	72	0.5
Total	14 038	100



Paid Services

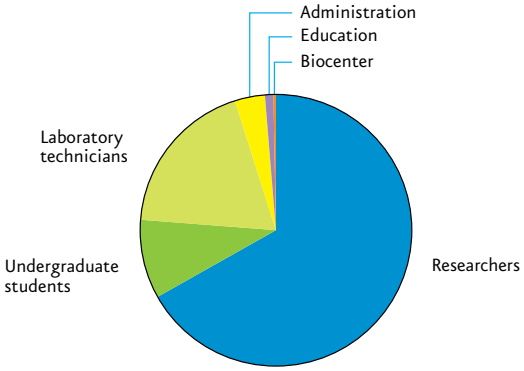
Laboratory	Funding (in 1000 Euros)
DNA sequencing	505
Electron microscopy	83
Light microscopy	100
NMR	5
Protein analysis	69
Total	762

Personnel of the Institute of Biotechnology in 2010

Personnel in person years

	Person years	Percentage
Researchers*	206	66.9
Undergraduate students	29	9.4
Laboratory technicians	58	18.9
Administration	11	3.5
Education	3	1.0
Biocenter	1	0.3
Total	308	100

* Including graduate students (doctoral students)



PhD's
Proportion of PhD's in the category researchers: 50%.

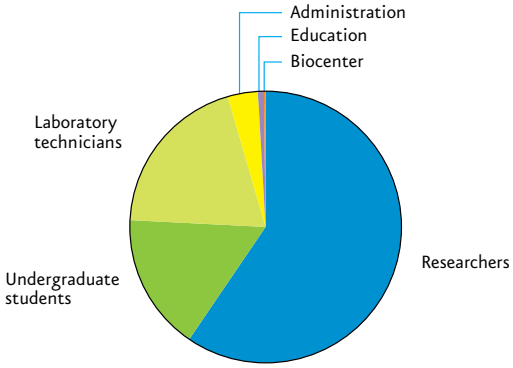
Women
Proportion of women in the category researchers: 51,6% and in students: 61,8%.
Proportion of women in the whole staff: 57%.

Foreign researchers
49% of all researchers; from 32 countries.

Personnel (total)

	Number	Percentage
Researchers*	248	59.5
Undergraduate students	68	16.3
Laboratory technicians	82	19.7
Administration	15	3.6
Education	3	0.7
Biocenter	1	0.2
Total	417	100

* Including graduate students (doctoral students).



Undergraduate students in 2010
18 undergraduate students preparing their Master's thesis.
3 Master's theses were completed.

Proportions of staff categories (%) in person years since 1992

	2010	2009	2008	2007	2006	2005	2004	2003	2002	2001	2000	1998	1996	1994	1992
Researchers *	66.9	66.8	67.6	67.9	66.5	61.3	59.8	61.1	64.9	60.8	61.9	64.5	63.1	63.7	60.3
Undergrad. students	9.4	7.8	7.0	7.2	8.4	11.4	11.5	10.3	9.0	10.0	9.0	6.4	8.4	4.6	7.0
Lab. technicians	18.9	20.4	20.6	18.8	18.7	20.4	21.3	19.9	17.4	21.5	21.7	21.9	21.0	22.1	22.8
Administration **	3.5	3.7	3.5	5.1	5.4	5.9	6.1	6.4	6.6	6.5	6.1	5.7	6.3	8.6	9.1
Education	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.7	1.7	0.7	0.4	0.3	0.6	1.0	0.8
Viikki Biocenter	0.3	0.3	0.3	0.0	0.0	0.0	0.3	0.6	0.2	0.5	0.9	1.2	0.6	0.0	0.0
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
(N)	(308)	(292)	(286)	(293)	(299)	(304)	(296)	(283)	(288)	(299)	(301)	(229)	(177)	(103)	(88)

* Including graduate students (doctoral students).
** Including computing and maintenance.

Staff members

Principal Investigators

Annila, Arto
Auvinen, Petri
Bamford, Dennis
Butcher, Sarah
Frilander, Mikko
Goldman, Adrian
Heikinheimo, Pirkko
Helariutta, Yrjö
Hietakangas, Ville
Holm, Liisa
Iwai, Hideo
Jernvall, Jukka
Jokitalo, Eija
Jäntti, Jussi 1
Kalkkinen, Nisse
Lappalainen, Pekka
Mäkelä, Tomi
Partanen, Juha
Permi, Perttu
Pirvola, Ulla
Rivera, Claudio
Saarma, Mart
Schulman, Alan
Shimmi, Osamu
Thesleff, Irma
Vartiainen, Maria
Verkhovsky, Michael
Wikström, Mårten

Other Researchers

(including junior PIs, staff scientists, postdoctoral fellows and graduate students)

Aalto, Antti
Achim, Kaia
Ahola, Tero
Ahtiainen, Laura 2
Aitio, Olli
Aivelo, Tuomas 2
Alatalo, Rauno
Amberg, Carolina
Andressoo, Jaan-Olle
Aro, Nina Kaarina
Arumäe, Urmas
Balistreri, Giuseppe
Belevich, Galina
Belevitch, Ilya
Belevitch, Nikolai
Bespalov, Maxim
Bishopp, Anthony
Blokh, Dmitry
Bruckmann, Chiara 2
Buivydas, Andrius 2
Carter, Kathrine
Chang, Wei 2
Chernov, Konstantin
Corfe, Ian
Cvirkaite, Virginija 2
Danilova, Tatiana 2
Dettmer, Jan
Dopie, Joseph
Doungous, Oumar
Eesmaa, Ave
Elo, Annakaisa
El-Showk, Sedeer
Evans, James 2
Gao, Yajing
Gateva, Gergana
Gorbikova, Elena 2
Greco, Dario
Happonen, Lotta
Harjunmaa, Enni
Hasygar, Kiran
Hattula, Katarina
Helenius, Katja
Hellman, Maarit
Hellström, Kirsi
Help, Hanna
Hirschberg, Daniel 2
Huet, Guillaume
Hultman, Jenni 2
Häärä, Otso
Immanen, Juha
Jakobson, Maili
Jiang, Miao
Jiu, Yaming 2
Joensuu, Merja
Jurvansuu, Jaana
Jussila, Maria
Juuri, Emma
Jäälinoja, Harri 2
Jääskeläinen, Marko
Kajander, Tommi
Kalendar, Ruslan
Kallijärvi, Jukka
Kallio, Katri 2
Kankainen, Matti 3
Kaukinen, Pasi 2
Kellosalo, Juho
Kirjavainen, Anna
Knuuti, Juho
Kolodziejczyk, Robert 2
Koponen, Johanna
Korolainen, Minna
Koskinen, Kaisa
Koskinen, Patrik
Kovacs, Bianca 2
Kremneva, Elena
Krupovic, Mart 2
Kumar, Anmol
Kunnapuu, Jaana
Kuokkanen, Elina
Kuuluvainen, Emilia
Kvist, Jouni 2
Kyburz, Annika 2
Laajanen, Kaisa
Lackman, Petri
Lahti, Laura 2
Lefebvre, Sylvie 2
Lehesranta, Satu
Leo, Jack 2
Leppänen, Satu
Li, Chun-Mej 2
Lichtenberger, Raffael
Lietzen, Niina
Liljeroos, Lassi
Lind, Essi
Lindahl, Maria
Lindfors, Päivi
Lindholm, Päivi
Lioudvig, Anastasia
Llano, Olaya
Loponen, Heidi
Lume, Maria
Lyskowski, Andrzej
Magalhaes, Ana
Makkonen, Maarit
Manole, Violeta
Marshall, Pepin
Martinez-Gallegos, Rafael
Matsuda, Shinya
Mattila, Jaakko
Michon, Frederic
Miettinen, Juho
Mikkola, Marja
Miyashima, Shunsuke
Moisy, Cedric
Moringlane, Denise
Moustakas, Jacqueline 2
Munne, Pauliina
Mähönen, Ari Pekka
Mäntylahti, Sampo 2
Mätlik, Kert
Neuvonen, Maarit
Nevalaita, Liina
Niemelä, Elina
Nyman, Tuula
Närhi, Katja 1
Oemig, Jesper
Oksanen, Hanna
Ollila, Saara
Ora, Ari-Juha
Pace, Marcelo 2
Paidikondala, Maruthibabu 2
Palm, Erik
Paramonova, Natalia 2
Paulin, Lars
Peltopuro, Paula
Peränen, Johan
Pessa, Heli
Pihlajamaa, Tero
Piras, Giuseppa 2
Pitkäranta, Miia
Planken, Anu 2
Pljusnin, Ilja 2
Pohjala, Leena 1
Poranen, Minna
Porokuokka, Leena 2
Poukkula, Minna
Priyadarshi, Pushkar 2
Puhka, Maija
Puusaari, Johanna
Pykäläinen, Anette
Qian, Kui
Rajakylä, Eeva
Rauhamäki, Virve
Raulinautis, Vytautas
Ravantti, Janne
Renvoise, Elodie
Repo, Heidi
Rice, Ritva 3
Ritari, Jarmo
Roine, Elina
Roland, Kardos 2
Romanovskaya, Alesia 2
Rosenström, Päivi
Runeberg-Roos, Pia
Ruzicka, Kamil
Rämö, Olli
Saarikangas, Juha
Saarimäki-Vire, Jonna
Saito, Kan
Sarin, Peter
Sarkhel, Sanjay
Savijoki, Kirsi
Schürmann, Sabine 2
Seitsonen, Jani
Serlachius, Eva
Sharma, Vivek
Shilov, Dmitri
Shirokova, Vera
Shulga, Anastasia
Sidorova, Yulia
Siljamäki, Pia 1
Sinjushina, Natalia
Skarp, Kari-Pekka
Smirnov, Sergei
Somervuo, Panu 2
Spuul, Pirjo 2
Sulg, Marilin
Suoranta, Anu
Ta, Xuan Hung
Tanhuanpää, Kimmo
Tanskanen, Jaakko
Teesalu, Mari 2
Tojkander, Sari
Tossavainen, Helena
Tummers, Mark
Turunen, Janne
Törönen, Petri
Ursache, Robertas
Vaahtomeri, Kari
Wartiovaara, Kirmo

1 worked part-time
2 worked part of the year
3 worked part-time and part of the year

Vaten, Anne
Weber-Boyvat, Marion 2
Verbeeren, Jens
Verkhovskaia, Marina
Vihinen, Helena
Volkmann, Gerrit
Voutilainen, Maria
Yadav, Shri
Yan, Yan
Yang, Ying
Yaniv, Elitsur
Yu, Liying
Yuan, Qiang
Zauszkiewicz-Pawlak, Agata 2
Zeng, Zhao
Zhang, Jing
Zhao, Hongxia
Zheng, Congjun 2
Zohdy, Sarah
Öhman, Tiina

Laboratory Technicians

Ahlsten, Heli
Ahola-Iivarinen, Elina
Ahovuo, Aura 1
Albert, Cathrin
Al-Sharefi, Arif 3
Bansfield, Danielle
Basaran, Zeren 2
Bjerstedt, Lotta
Broberg, Raija
Bågman, Anne-Maarit 2
Collin-Olkkonen, Paula
Crivaro, Marko
Faber, Christina
Haasanen, Eija 1
Harvey, Stephen
Haukanniemi, Johanna 2
Heikkinen, Mari 1
Herpola, Mikko
Hukka, Marko
Hämäläinen, Tuulia 3
Ihamäki, Riitta
Janssen, Edda 2
Jyrkinen, Sirkka
Kainulainen, Katja
Kangas, Harri 2
Kestilä, Veli-Pekka 2
Koivunen, Eija
Kokkonen, Outi
Korhonen, Sari
Kärkkäinen, Tarja
Laamanen, Päivi
Laine, Pia
Laukka, Mari
Laurinmäki, Pasi
Lipponen, Kirsi
Lounela, Olli
Lukka, Anneli
Löflund, Benita
Lönnqvist, Ursula
Mattila, Rauli
Merviä, Lea
Molin, Mika
Mäki, Seija 1
Mäkinen, Merja
Mäkinen, Tuukka 2
Narvanto, Anne-Mari
Niemi-Aro, Tuomas
Nokso-Koivisto, Jussi 2
Numers von, Maria 1
Nyfors, Anna-Liisa 1
Palonen, Jenny 2
Palviainen, Miika
Peltonen, Marja-Leena
Pietilä, Tuuli
Plewe, Daniel 2
Rajala, Ritva 3
Rantanen, Lauri
Rehn, Maria
Rosti, Katja
Ruusulampi, Saana
Rönnholm, Gunilla
Salminen, Antti
Salojärvi, Tarja
Santalahti, Riikka
Savolainen, Raija
Savolainen, Tuomo 2
Schlinkheider, Alina 2
Shimmi, Risa
Siipola, Lilia
Storman, Satu
Strandell, Arja
Suoranta, Anu
Tarkiainen, Riitta
Thome, Jonas 2
Turkki, Eeva-Marja
Turunen, Hanna
Tynkkynen, Sari 2
Vesanen, Eevakaisa 2
Viren, Krista 1
Wiss, Susanna
Åkerberg, Satu

Undergraduate Students

Ahde, Antti 2
Anttila, Jani 2
Anttonen, Tommi 2
Aranko, Aino
Bhowmik, Subhanjan 2
Bunn, Jonathan 2
Cederlöf, Sari 2
Crespo Yanez, Xenia
Demir, Hande 2
Di Girolamo, Salvatore 2
Dumont, Vincent 2
Fu, Biao
Gucciardo, Erika 2
Helin, Kristel
Hunter, Kerri 2
Hyvönen, Hanna 2
Jaakkonen, Anniina 2
Kankaanpää, Tuomas 2
Karja, Sami 2
Kemp, Addison
Kivioja, Jarno 2
Koskela, Essi
Kumar, Ajay 2
Kuoppala, Mario 2
Kähärä, Juhani 2
Laari, Liina 2
Laitinen, Ville 2
Latvala, Mervi 3
Lindelöf, Anna-Emilia 2
Lindfors, Sonja 2
Linge, Ayubah 2
Lintulahti, Anu 2
Mahonen, Minna 2
Mikkonen, Elisa 2
Mikula, Kornelia 2
Mohammadi, Omid 2
Mäntylä, Eemi 2
Mönttinen, Heli 2
Nurmi, Maria 2
Nurmi, Visa 2
Ojala, Teija 2
Orasmaa, Saila 2
Piccinini, Elisa 2
Pirttiniemi, Anniina 2
Rintanen, Marko 2
Rysti, Elisa 2
Saarekas, Maiju 2
Saarikangas, Niina 2
Sahal-Estime, Michelle 2
Salminen, Laura 2
Sepponen, Kirsi 2
Seppälä, Netta 2
Sevilem, Iris 2
Sihvo, Sanna 2
Sonck, Matti 2
Soni, Shetal
Sova, Satu
Sumuvuori, Carl-Mikael 2
Syedbasha, Mohammed 2
Troberg, Johanna 2
Varendi, Kärt
Venkannagari, Harikanth 2
Wennerström, Tanja
Virolainen, Sini-Maaria 2
Väänänen, Juho 3
Åstrand, Mia 1

Administration

Bjerstedt, Kristiina
Dart, Pauli
Halinen, Arto
Kauko, Hannu
Leikkonen, Tuomas 2
Leinonen, Sanna 2
Lepistö, Maija
Mäntymaa, Ville 2
Nieminen, Tommi
Oja, Minna
Peltomaa, Reijo
Salo, Iikka
Ranta, Anssi 2
Sankkila-Forsström, Satu
Tossavainen, Atro

Education/Doctoral Programmes

Tienhaara, Anita
Raulo, Erkki
Falck, Sandra

Biocentrum Helsinki

Smahl-El Hamraui, Riitta

Publications

(Authors from BI in bold)

Original articles

1. **Aalto AP**, **Poranen MM**, Grimes JM, Stuart DI, **Bamford DH**. *In vitro* activities of the multifunctional RNA silencing polymerase QDE-1 of *Neurospora crassa*. *J Biol Chem*. 2010; 285: 29367–29374.

2. Airavaara M, Chiocco MJ, Howard DB, Zuchowski KL, **Peränen J**, Liu C, Fang S, Hoffer BJ, Wang Y, Harvey BK. Widespread cortical expression of MANF by AAV serotype 7: Localization and protection against ischemic brain injury. *Exp Neurol*. 2010; 225(1): 104–113.

3. **Aitio OMA**, Hellman M, Kazlauskas A, Vingadassalom D, Leong J M, Saksela K, **Permi P**. Recognition of tandem PxxP motifs as a unique Src homology 3-binding mode triggers pathogen-driven actin assembly. *Proc Natl Acad Sci USA. 2010*; 107(50): 21743–21748.

4. Aittamaa M, Somervuo P, Laakso I, **Auvinen P**, Valkonen JP. Microarray-based comparison of genetic differences between strains of *Streptomyces turgidiscabies* with focus on the pathogenicity island. *Mol Plant Pathol*. 2010; 11(6): 733–746

5. Ambrosino C, Tarallo R, Bamundo A, Cuomo D, Franci G, Nassa G, Paris O, Ravo M, Giovane A, Zambrano N, Lepikhova T, Jänne OA, Baumann M, **Nyman TA**, Cicatiello L, Weisz A. Identification of a hormone-regulated dynamic nuclear actin network associated to estrogen receptor alpha in human breast cancer cell nuclei. *Mol Cell Proteomics*. 2010; 9(6): 1352–1367.

6. **Annila A**. All in action. *Entropy*. 2010; 12: 2333–2358.

7. **Annila A**, Salthe S. Cultural Naturalism. *Entropy*. 2010; 12: 1325–1343.

8. **Annila A**, Salthe S. Physical foundations of evolutionary theory. *J Non-Equilib. Thermodyn*. 2010; 35: 301–321

9. Baskin TI, Peret B, Baluška F, Benfey PN, Bennett M, Forde BG, Gilroy S, **Helariutta Y**, Hepler PK, Leyser O, Masson PH, Muday GK, Murphy AS, Poethig S, Rahman A, Roberts K, Scheres B, Sharp RE, Somerville C. Shootward and rootward: peak terminology for plant polarity. *Trends Plant Sci*. 2010; 15(11): 593–594.

10. **Belevich I**, **Gorbikova E**, **Belevich NP**, **Rauhamäki V**, **Wikström M**, **Verkhovsky MI**. Initiation of the proton pump of cytochrome c oxidase. *Proc Natl Acad Sci U S A*. 2010; 107(43): 18469-18474.

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