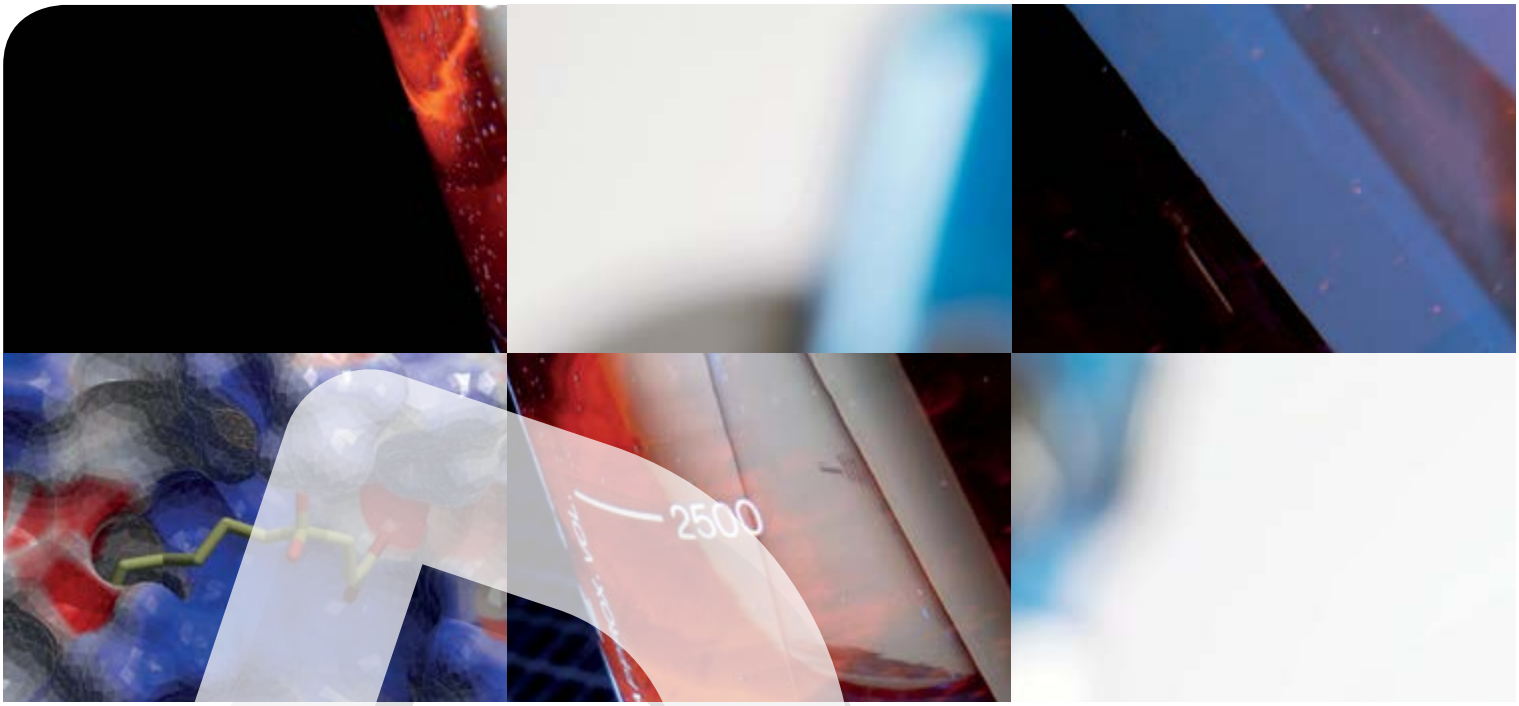

BF Biocenter Finland

ANNUAL REPORT 2012

Biocenter Finland

www.biocenter.fi

Biocenter Finland Annual Report 2012

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Acknowledgements:

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Unigrafia Oy 2013

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FOREWORD

Three years ago I wrote in the foreword to Biocenter Finland (BF) Annual Report about the unique concept we had in our hands to restructure life science infrastructures and technology services at national level. The principles used by BF in the restructuring process were simple; BF was to provide top-of-the line technology services by combining local expertise into a nation-wide knowledge base; to avoid overlapping investments; to provide open access to all services, and to base all funding decisions on periodic evaluation by a high-level international Scientific Advisory Board (SAB). Obviously, this all was made possible through 45 M€ of earmarked funding from the Ministry of Education and Culture (OKM) which was used over a period of three years to purchase equipment, fund salaries of service personnel and some consumables, too. In 2009, proposals from a total of 15 technology consortia were favorably evaluated and subsequently funded to provide technology services to the entire Finnish research community, in academia and industry, and to a limited extent also to users abroad. In 2011, in conjunction to the mid-term review by SAB, the number of technology services was increased to 18. BF also funded research career development and internationalization in Finnish biocenters. Through a combination of a bottom-up process and SAB evaluation, an atmosphere of planning and doing together in a healthy competitive environment was achieved.

In June 2013, the SAB will perform a final evaluation of the funding period 2010-2012 and give their opinion on how BF has performed. Already before their judgment, BF has had to find objective indicators and observations for the ongoing application round for national research infrastructure roadmap update to demonstrate that the BF concept has been successful. Following the principles listed above, the Finnish life science community in charge of providing technology services has found a new spirit of collaboration and networking. User statistics show that BF technology platforms have grown to provide services to the entire biomedical and life science research community in Finnish universities, research institutions and industry. These activities have significantly expanded during the past three years as modern life science research is becoming increasingly dependent

on complex and expensive instrumentation and professional service personnel. Altogether 42 research, training and coordination projects funded by EU under Framework Program 7 and some 25 Finnish ERC awardees have relied heavily on services provided by BF. At least ten of the current Finnish Centers of Excellence and 16 research groups of Academy Professors are users of BF technology services. We also note that implementation of the BF concept has supported host universities and their biocenters to focus on their fields of expertise and to create their unique profile.

The Governance model whereby the director of each biocenter sits on BF Board has functioned well. Business towards host universities and their rectors has been flowing smoothly. For final evaluation of the period 2010-2012 BF conducted a large user survey. With over 350 research groups responding, the survey provided BF and each technology platform with a lot of useful information and feedback, which will be summarized elsewhere in this Annual Report.

A new funding model for BF

Year 2013 marks a moment of truth for BF. Despite a joint effort by all host university rectors, the Ministry decided to stay with its original decision not to extend the earmarked funding beyond 2012. To keep the network operational, all host universities participating in BF endorsed their continuing support to BF for 2013-2016, based on an action plan presented by BF Board. According to this plan, future funding of BF will consist of two major funding streams: the host universities assume responsibilities for *operational and coordination* costs of BF, while investment costs must be primarily sought for from other sources (especially the national FIRI-infrastructure funds). Additional funding to BF will come from user fees and other competitive funding sources.

Will the new funding model provide the sustainability which is a key requirement for provision of technology services? The model had to be tested in a hurry in late 2012, when the rectors of host universities agreed to BF Boards' proposal to fund the salaries of key technology service personnel and some consumables plus the coordination costs of BF with a total of 5.1 M€ in 2013 from their own strategic funds. Although this marked a reduction from the funding level in 2010-2012, this was a very positive sign from the host universities under difficult financial circumstances. This indicates that the new *modus operandi* of BF has been accepted by the host universities.

"Finnish life science community in charge of providing technology services has found a new spirit of collaboration and networking."

The other half of the new funding model will be tested later in 2013. The newly established National Expert group on research infrastructures (FIRI Expert group) is currently organizing the updating of the national research infrastructure roadmap and the evaluation of applications for national infrastructure funds. BF is an applicant in both competitions. The roadmap update is a two-stage process. Our first stage application received very positive evaluation and the second stage application is currently being completed. I trust BF is well positioned to obtain the status of a nationwide research infrastructure, which in the future will be an important criterion for national FIRI funds.

The national FIRI infrastructure funds (15 M€ for 2013) will be allocated to investments based on evaluation by an international review panel (who will also review the roadmap update applications). As the host institutions have already made their commitment for continuation of operational costs, I expect BF infrastructures to be competitive in the FIRI application round, too. In its application BF emphasizes that an annual investment budget is needed to stay at the cutting edge of technology development and lists the most important investments needed. However, only time will show how successfully the BF application will compete against the other infrastructure applications. If the review panel does not approve the large consortium application of BF, this will create a very challenging situation for the future. A horror scenario is that this will force the biocenters and host universities to gradually abandon the coordinated development of BF infrastructure and start competing with each other for FIRI funds and development of life science infrastructures.

International collaboration will increase

By the end of 2013, the six BMS (Biological and Medical Sciences) infrastructures which were included on the 2006 ESFRI (European Strategy Forum on Research Infrastructures) Roadmap will be operational. Through scientists who have represented Finland in five of the ESFRI projects (BBMRI, EATRIS, ELIXIR, Infrafrontier and Instruct) during their planning and preparatory phase, BF Infrastructure networks are closely linked to the national nodes/centers of these infrastructures. Another two BMS infrastructures on the 2008 ESFRI Roadmap (EU-Openscreen and Euro-BioImaging) are equally closely linked to BF infrastructure networks. Close communication between BF and Finnish representatives in ESFRI projects is important so that the national and pan-European developments result in a win-win situation, where ESFRI participation provides Finnish scientists access to pan-European infrastructures and vice versa and helps BF to follow international infrastructure development. The unique network and platform structure of BF services makes life easy for Finnish scientists as the national structures required by BMS ESFRI infrastructures already exist in Finland as BF networks.

Biocenters are among the most international research environments in Finland. This covers all steps of the academic career from visiting (FiDiPro) professors and principal investigators to group leaders, postdocs and doctoral trainees. English is the working language of BF and all biocenters. In 2010-2012, BF spent a small fraction of the earmarked funding to support a highly successful international visitor programme. This brought to Finnish biocenters a total of 60 international doctoral and postdoctoral scientists from 30 countries (from all continents); a majority of them have continued their career in Finland, and nearly all of those who have already left Finland continue to collaborate with Finnish biocenters. This is a living example of the attractiveness of biocenters to young foreign scientists and show how BF has helped in internationalization of Finnish life sciences. With the increasing importance of complex equipment for top-level research in life sciences, BF technology platforms are heavily involved both in provision of services and in researcher training, which has become a key activity of BF technology platforms in each biocenter and nationally.

Acknowledgements

I would like to extend my very best thanks all members of BF SAB, for their immensely valuable work. Their constructive scientific advice has made it possible to develop BF in a balanced way as a national infrastructure. My special thanks go to professor Carl-Henrik Heldin, vice president of ERC Scientific Council, for committing so much of his valuable time to BF as the chair of the SAB since 2009 and for sharing with us his wide knowledge of European science policy. We are very pleased of the fact that all members agreed to continue on the SAB for a second period (2013-2016). Unfortunately, in the end time conflicts prevented Richard Roberts to continue beyond 2012. BF extends a special thanks to Rich for his services to BF, and a warm welcome to the incoming member Gunnar von Heijne from Stockholm University.

The staff of our small coordination office, scientific coordinator Tero Ahola and planning officer Sanna Leinonen, also deserve a big thank you. Often working under immense pressure to produce reports, compiled tables and other documentation at very short notice, they have demonstrated the type of dynamism and creativity that BF needs. With the new funding mode, the workload of the coordination office will probably diminish. Tero Ahola is in the process of leaving us. Fortunately, he will continue his academic career in the Viikki campus, so that we can continue counting on his long institutional memory of BF.

Eero Vuorio
Director of Biocenter Finland

SCIENTIFIC ADVISORY BOARD OF BIOCENTER FINLAND

A rigorous scientific review combined with healthy competition is well known key to success all over the world. BF strongly believes that the high-level international Scientific Advisory Board has been a fundamentally important success factor for BF. Finnish life science community has grown to receive advice and criticism from the world's leading experts and appreciates their judgment. In 2010-2012 nearly all of the 45 M€ of earmarked funding was distributed to technology platforms based on the recommendations of the SAB evaluations in 2009 and 2011. In June 2013, it is up to the SAB to evaluate the overall performance of BF in 2010–2012, and to give advice on future development of BF in 2014–2016 based on the applications received from technology platforms. SAB will also have a possibility to give their opinion on the BF application to the national research infrastructure roadmap and the future development strategy of BF therein.

Composition of BF SAB (2009–2012)*

Chair: **Carl-Henrik Heldin**, Ludwig Institute for Cancer Research, Uppsala
Vice-Chair: **Ole Petter Ottersen**, University of Oslo
Members: **Marja Jäättelä**, Institute of Cancer Biology, Copenhagen
Richard J. Roberts, New England Biolabs, Ipswich, MA
Matthias Wilmanns, EMBL, Hamburg

*The composition of SAB will remain the same in 2013–2016, except for Richard J. Roberts, who will be replaced by Gunnar von Heijne, Stockholm University.

"Biocenter Finland is of utmost importance to assure that Finnish scientists have access to sophisticated infrastructure. It is notable that more than half of the 51 Finnish ERC awardees work in the life science domain and nearly all of them use services provided by BF."
Carl-Henrik Heldin, Chair of SAB

ORGANIZATION OF BIOCENTER FINLAND IN 2012

Biocenter Finland was established in 2006 by the six Finnish Universities housing biocenters, i.e. Universities of Helsinki, Kuopio, Oulu, Tampere and Turku, and Åbo Akademi University. Rectors of these Universities form the highest decision making body of BF. In practice all decisions concerning the operation of BF are made by the Governing Board comprising directors of the seven biocenters. The Board meets 5–6 times per year.

Director

Eero Vuorio

Governing Board in 2012 (deputies in parentheses)

Chairman of the Board:
Seppo Ylä-Herttuala, Biocenter Kuopio, University of Eastern Finland

Vice-Chairman of the Board:
Jyrki Heino, BioCity Turku, University of Turku (Riitta Lahesmaa)

Board members:
Lauri Aaltonen, Biocentrum Helsinki, University of Helsinki (Mart Saarma)

John Eriksson, BioCity Turku, Åbo Akademi (Pia Vuorela)

Olli Kallioniemi, FIMM (Janna Saarela)

Johanna Myllyharju, Biocenter Oulu, University of Oulu (Kalervo Hiltunen)

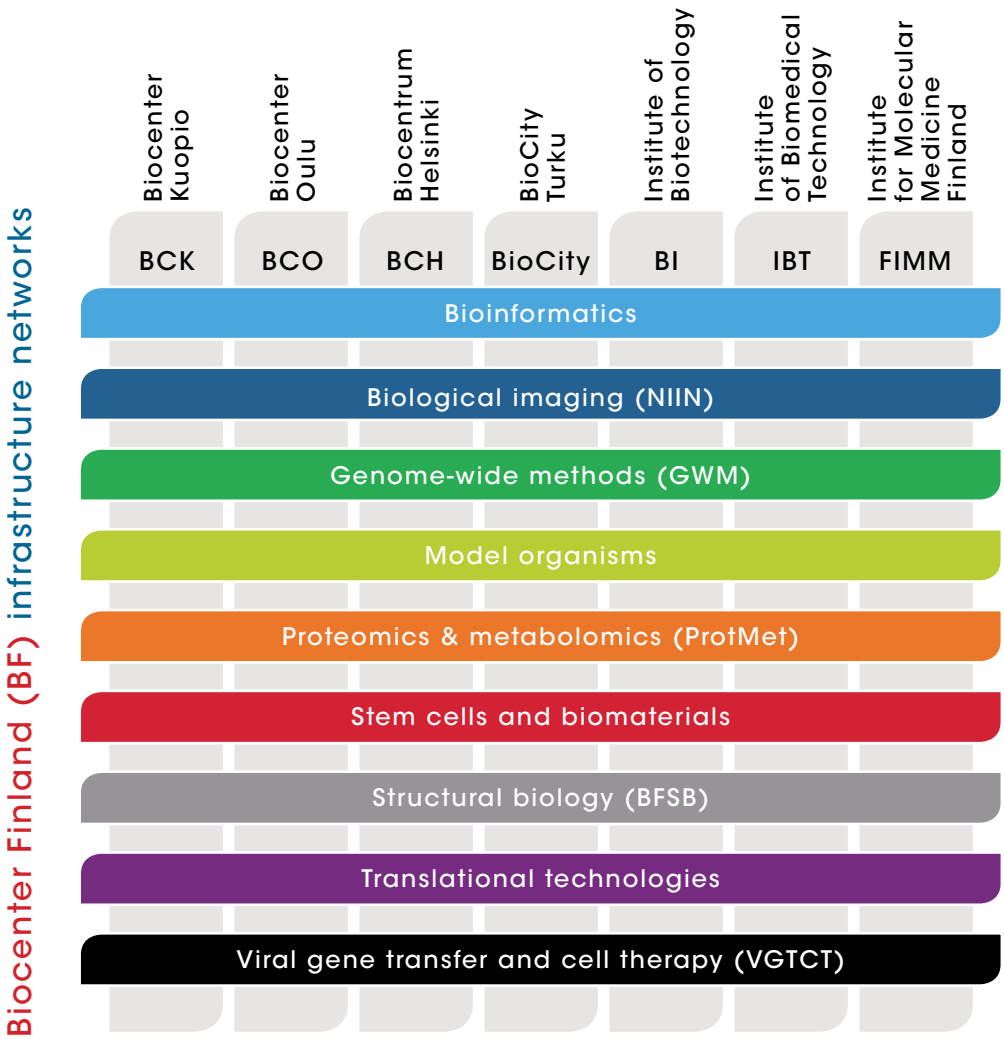
Tomi Mäkelä, Institute of Biotechnology, University of Helsinki (Pekka Lappalainen)

Olli Silvennoinen, Institute of Biomedical Technology, University of Tampere (Tapio Visakorpi)

Biocenter Finland Administration

Research coordinator
Tero Ahola

Planning officer
Sanna Leinonen



Biocenter Finland (BF) member institutes

Please note that Biocenter Finland, its member institutes and the infrastructure networks will be referred to with acronyms/abbreviations as shown in the diagram above. Additional abbreviations frequently used in this Annual report are: CSC, IT Center for Science Ltd; THL, National Institute for Health and Welfare; VTT, Technical Research Centre of Finland.

In its meeting on January 17, 2011 the Board of Biocenter Finland decided to offer scientists working at the University of Jyväskylä a possibility to participate in the activities of BF infrastructure networks. Subsequently the University of Jyväskylä named members to BF infrastructure networks in those scientific fields where the University is actively engaged in research and technology services.

SCIENTIFIC SUCCESS STORIES BASED ON BIOCENTER FINLAND TECHNOLOGY SERVICES

Harnessing anticancer drugs for the future fight against influenza

The Medical Systems Virology group at the Institute for Molecular Medicine Finland (FIMM) at the University of Helsinki, led by Denis Kainov together with its national and international collaborators, developed a new cell screening method that can be used to identify potential anti-influenza drugs utilizing the services of the BF Drug discovery and chemical biology platform (DDCB).

The researchers were able to identify two novel compounds with anti-influenza activity, obatoclax and gemcitabine and prove the efficacy of a previously known drug saliphenylhalamide. Influenza viruses cause significant human morbidity and mortality. To treat the infections, different virus-directed drugs have been developed. However, the currently available drugs are targeting viral proteins and due to a high mutation rate the influenza viruses quickly develop resistance to them. For that reason, next-generation antiviral drugs should be directed towards the host functions. The results of this study provide a foundation for development of next-generation antiviral drugs. Furthermore, these identified compounds can be used as chemical tools when studying the molecular mechanisms of virus-host interactions. The findings were published the Journal of Biological Chemistry. A notable discovery is that the antiviral effects of obatoclax, saliphenylhalamide and gemcitabine, which all are either investigational or approved anticancer agents, are achieved at much lower concentrations than those needed to mediate cancer cell death and further studies are exploring whether these drugs can be clinically tested and applied in influenza infections.

This research project is a good example of repurposing of drugs, i.e. finding new applications for existing drugs and thus saving money and time on drug development.

Denisova OV, Kakkola L, Feng L, Stenman J, Nagaraj A, Lampe J, Yadav B, Aittokallio T, Kaukinen P, Ahola T, Kuivanen S, Vapalahti O, Kantele A, Tynell J, Julkunen I, Kallio-Kokko H, Paavilainen H, Hukkanen V, Elliott RM, De Brabander JK, Saelens X, Kainov DE. 2012. Obatoclax, saliphenylhalamide, and gemcitabine inhibit influenza A virus infection. **J. Biol. Chem.** 287:35324-35332

Dissecting the role of skin microbiota in allergies'

By 2050, two-thirds of the global human population is predicted to live in urban areas with little green space and limited contact with nature and biodiversity. At the same time, an increasing fraction of the urban population is predicted to suffer from chronic inflammatory disorders, of which allergic is a prime example. This is a large study comprising of ecology, immunology and skin 16S metagenome analysis from population of people. Surprisingly a connection between skin microbiota and environmental biodiversity was observed in addition to alteration in immunoresponse. Atopic individuals had lower environmental biodiversity in the surroundings of their homes, and significantly lower generic diversity of gammaproteobacteria on their skin, than healthy individuals. Further IL-10 expression was positively correlated to the abundance of the gammaproteobacterial genus Acinetobacter on the skin (Hanski et al 2012). The expertise of the Institute of Biotechnology DNA sequencing and genomics laboratory (BIDGEN) in metagenome analysis was crucial in this study. Its international reputation was reflected in its choice as one of the ten laboratories in Europe to beta-test FLX+ chemistry and a new software version: also in this test BIDGEN was among the top when compared with other test sites. BIDGEN performed 16S sequencing and data analysis of the community structure

Hanski I, von Hertzen L, Fyhrquist N, Koskinen K, Torppa K, Laatikainen T, Karisola P, Auvinen P, Paulin

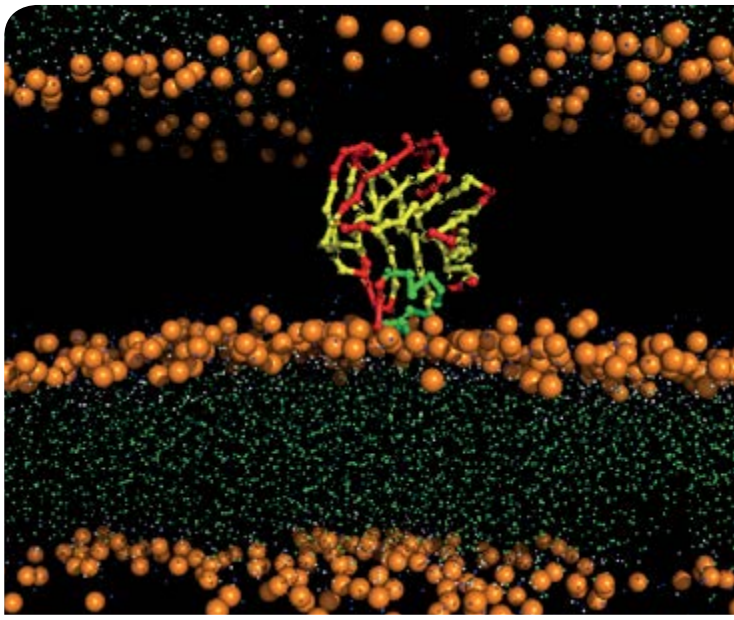
L, Mäkelä MJ, Vartiainen E, Kosunen TU, Alenius H, Haahtela T. Environmental biodiversity, human microbiota and allergy are interrelated. **Proceedings of the National Academy of Sciences U.S.A.** 2012: 109:8334-8339.

Structural biology, *in silico* modeling and self-assembly simulation elucidate self-assembly of myelin protein P2

The myelin protein P2 is a fatty acid binding protein found specifically in the myelin sheath of the vertebrate peripheral nervous system, where it is likely to be involved in the stacking of opposing membranes together, as well as in lipid metabolism. P2 binds phospholipid membranes through its positively charged surface, and monomeric fatty acids inside its barrel-like structure. A multidisciplinary project on the elucidation of structure-function relationships in the human P2 protein was recently completed by the biocomputing group at Biocenter Oulu, and it highlights the complementary nature of structural biology and in silico modeling and simulation.

Along with atomic-resolution structural studies and membrane binding assays both in vitro and in vivo, in silico self-assembly coarse-grained molecular dynamics simulations have been carried out on the association of P2 with membrane surfaces. These combined experiments showed the spontaneous formation of two opposing lipid bilayers in the presence of P2, which is tightly stacked between the membranes. The orientation of P2 would allow for exchange of hydrophobic molecules between the internal binding site in P2 and the membrane interior. Atomistic simulations of P2 have been subsequently carried out, resulting in the most accurate structural view to date on P2, a highly abundant protein of peripheral nerves. The results will be used to guide further experiments, including detailed studies on membrane multilayer formation, structure, and dynamics, as well as lipid transfer between P2 and the membrane (manuscript in preparation).

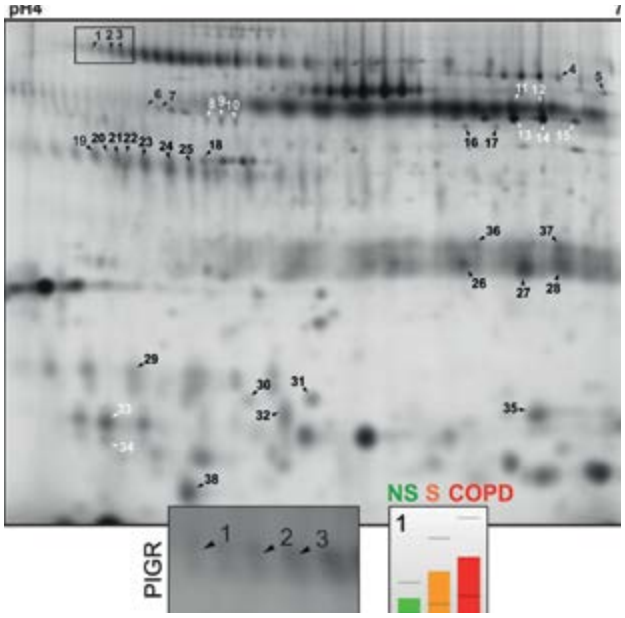
P2 in between opposing lipid bilayers. Water molecules were excluded for clarity, but were part of the simulations.



Proteomics identifies promising biomarkers for chronic obstructive pulmonary disease

A main research focus of the proteomics core facility in Oulu is the study of the smoking-related chronic obstructive pulmonary disease (COPD), which is predicted to become the third leading cause of death by 2030. Current COPD diagnosis is based mainly on pulmonary function tests which results often in late disease detection. Specific biomarkers that could significantly improve treatment and health outcomes are currently lacking. Different proteomic technologies have been applied earlier to screen for promising biomarkers but so far none of these results have been implemented into clinical practice. Therefore, new strategies are asked for to overcome the limitations of these proteomic approaches. In cooperation with Prof. Vuokko Kinnula's research group in Helsinki, one of the leading experts in this field, different sample types of well characterised patient cohorts were analyzed in the proteomics core facility in Oulu to identify potential COPD biomarkers. This research is also promoted by the TEKES/ SHOK programme "Intelligent Monitoring for Health and Well-being (IMO)". A promising target for diagnostic screening represents the noninvasively collected sputum that was investigated by proteomics. Problems caused by e.g. the very low protein amount of high abundant and/or highly glycosylated proteins were solved and human sputum analyzed for the first time with the Difference Gel Electrophoresis (DIGE) technique (Ohlmeier et al., 2012). This resulted in the detection of several promising markers, including e.g. polymeric immunoglobulin receptor (PIGR), which was selected for further validation.

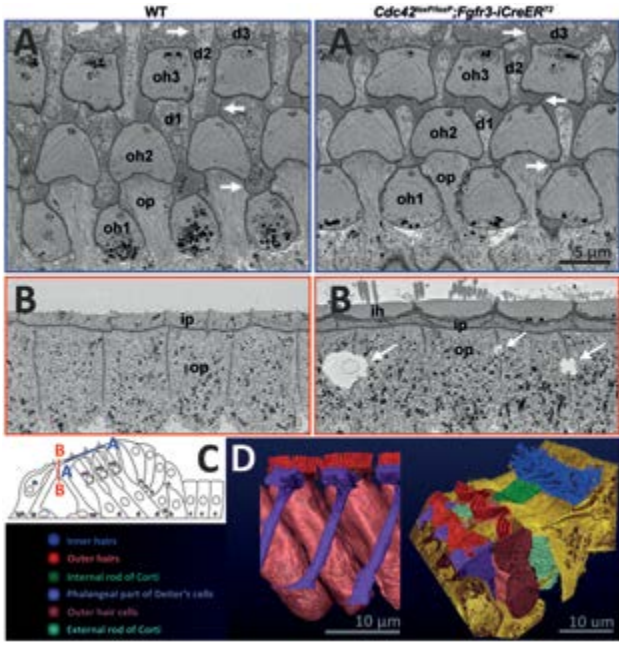
Representative 2-D gel of sputum (5µg) from a characteristic COPD patient (Stage II). Sputum samples of nonsmokers (NS), "healthy" smokers (S) and COPD patients (COPD) were studied by DIGE which detected 38 changed protein spots corresponding to 15 proteins. The selected gel area and expression profile for PIGR are shown as an example.



Ohlmeier S, Mazur W, Linja-Aho A, Louhelainen N, Rönty M, Toljamo T, Bergmann U, Kinnula VL. Sputum proteomics identifies elevated PIGR levels in smokers and mild-to-moderate COPD. **J Proteome Res.** 2012, 11, 599–608.

3-dimensional electron microscopy helps understand organelle structure

The new techniques that have been set up and are now offered to users include two serial section imaging based scanning electron microscope (SEM) techniques, SBF-SEM in Helsinki and FIB-SEM in Oulu. These techniques are used to generate 3D-EM datasets of cells or tissues at reasonably high resolution over large volumes. Typical scientific problems that can be addressed are for instance the phenotypical morphological analysis of transgenic model organisms with affected organelles that require the comparison and examination of many sections. Such an analysis is exceedingly cumbersome by classical TEM sectioning if a similar orientation must be examined from several specimens. Use of SBF-SEM allows the acquisition of large 3D-datasets which can be computationally sliced so that corresponding data can be extracted from different specimens (Figs. A and B). In addition, certain cell types or organelles can be segmented from the dataset to generate 3D-models (Fig. D). Here SBF-SEM was used to analyse the organ of Corti of the mouse cochlea. In this tissue, 3D structural analysis was imperative to understand the complex cellular and subcellular architecture. The results revealed that the GTPase Cdc42 is required for structural remodeling of the developing organ of Corti (Anttonen et al., 2012).



Comparison of supporting cells of loxP/loxP Cdc42; Fgfr3-iCre-T2 ER mice at P10 (10 days old). A: Unelongated adherens junctions and F-actin belts (arrows) in supporting cells of mutant mice. B: Ectopic lumens (arrows) in adherens junctions of mutant mice. C: Schematic representation of the organ of Corti showing the planes of images: panel A in blue, panel B in red. D: 3D reconstruction of the obtained data set.

Anttonen T, Kirjavainen A, Belevich I, Laos M, Richardson WD, Jokitalo E, Brakebusch C, Pirvola U. Cdc42-dependent structural development of auditory supporting cells is required for wound healing at adulthood. **Sci Rep**. 2012. 2:978. doi: 10.1038/srep00978

Gene-modified mouse model to study biological functions of the hypoxia response in erythropoiesis

Hypoxia-inducible transcription factor (HIF) has an important role in the regulation of the expression of the EPO gene and many additional genes influencing erythropoiesis. HIF is regulated by HIF prolyl 4-hydroxylases (HIF-P4Hs) in an oxygen-dependent manner, hypoxia leading to inactivation of these enzymes and concomitant stabilization and activation of HIF. Presently it is well established that HIF-P4Hs 1-3 all have distinct roles in the regulation of erythropoiesis, but the role of a putative fourth HIF-P4H, P4H-TM, in this process has so far been unknown. This paper reported for the first time, using gene-modified mouse lines, that in addition to HIF-P4H-2, P4H-TM is involved in the regulation of EPO production in the kidney but not in the liver, where this function is carried out by HIF-P4Hs 1 and 3.

Studies with HIF-P4H–inhibiting small-molecule compounds have indicated that pharmacologic HIF stabilization appears promising as a strategy for treating diseases associated with acute or chronic hypoxia, such as anemia, myocardial infarction, and stroke, and clinical trials are in progress to evaluate their effectiveness in the treatment of anemia. The present data indicate that a compound inhibiting several HIF-P4Hs would be desirable for the treatment of patients with advanced kidney disease, and a compound inhibiting P4H-TM together with some of the other HIF-P4H isoenzymes could produce a stronger erythropoietic response than that obtained with a HIF-P4H antagonist lacking P4H-TM inhibition.

Laitala A, Aro E, Walkinshaw G, Mäki JM, Rossi M, Heikkilä M, Savolainen E-R, Arend M, Kivirikko KI, Koivunen P & Myllyharju J.(2012) A transmembrane prolyl 4-hydroxylase is a fourth prolyl 4-hydroxylase regulating erythropoietin production and erythropoiesis. **Blood**. 120: 3336–3344.

Researchers benefit from the new methodology that speeds up the protein expression

Exceedingly high mammalian protein expression levels have been achieved with new piggyBac transposition expression methodology in Haartman Institute, which is part of the BF protein production platform coordinated from Tampere protein production facility. This new technique provides about 20–30 fold better expression level of the proteins (and it is faster) than the otherwise well-functioning routine CHO-S cell platform. This will speed up the completion of the customer projects and also cut down significantly costs of getting hundreds of milligrams of correctly folded and bioactive proteins for experimentation of both structure-function and biological activity. The turn over time from cDNA construct design to milligram amount protein production, subsequent purification and in vitro and in vivo characterisation of new recombinant proteins can be cut to just a few weeks from the previous situation that required months of work.

Benefits of the more efficient protein expression become evident in projects where stem cell researchers have been able to generate large amounts of bioactive growth factor ligands as well as molecules modulating cellular growth and differentiation. This can open up completely new possibilities to scale up specific stem cell culture and organoid culture methods. Previously many of the long term stem cell differentiation cultures have been unrealistic due to the high quantities of very expensive bioactive proteins required. Now the experimentation can be done with the availability of milligram amounts of specific growth and differentiation factors produced in our facilities.

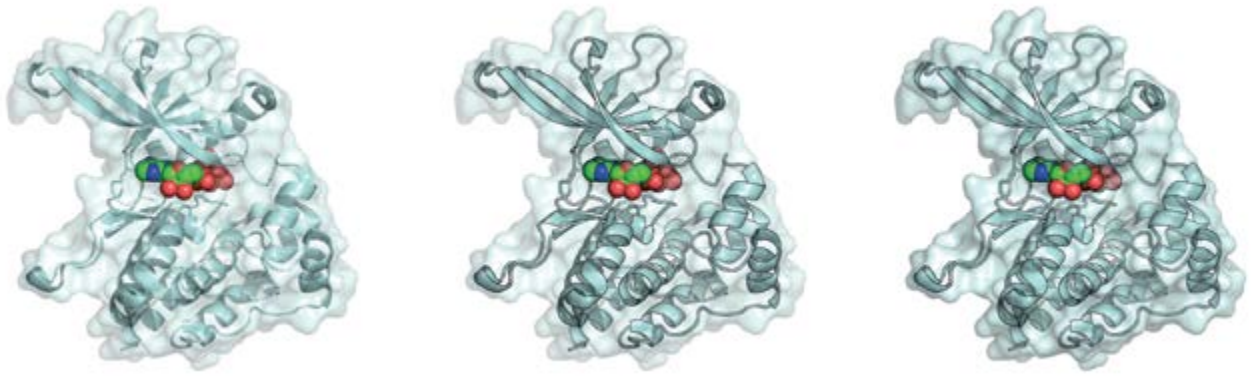
Another protein expression system provided by the protein production platform, a baculovirus expression system, has been successfully used in Tampere to produce proteins that have great significance in cellular signalling. One of the first was a paper describing the crystal structure of JAK2 pseudokinase domain. This story was released on Nat Struct Mol Biol. in 2012.

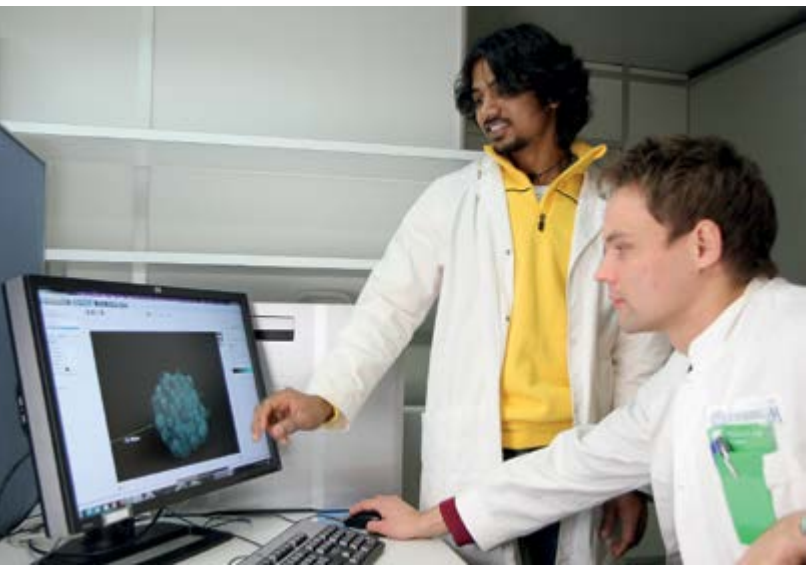
Bandaranayake RM, Ungureanu D, Shan Y, Shaw DE, Silvennoinen O, Hubbard SR. Crystal structures of the JAK2 pseudokinase domain and the pathogenic mutant V617F. **Nat Struct Mol Biol.** (2012) 19(8):754-9.

New general purpose software for global bioimaging use

Since 2006, the BioImageXD open source software platform has been developed in close collaboration between Turku BioImaging and Jyväskylä Imaging facility. BioImageXD has been designed for scientific processing, analysis and visualization of multidimensional images. It was published in a special issue of Nature Methods in 2012, focused on bioimaging (Kankaanpää et al. 2012). The software has enabled many previously impractical applications in bioimaging, such as new, fast and robust motion tracking (Paavolainen et al. 2012), advanced internalization and localization analysis of drug-delivering nanoparticles (manuscript under preparation), and novel 3D quantitative analysis of membrane vesicles

Crystal structure of JAK2 pseudokinase domain with bound ATP (PDB ID: 4FVQ, Bandaranayake et al. 2012).





(Björkbom et al. 2011). The software is downloaded approximately 400 times a month and used worldwide, and the developers have been invited to teach the software on several courses in Finland and USA.

http://www.bioimagexd.net/

Kankaanpää P, Paavolainen L, Tiitta S, Karjalainen M, Päivärinne J, Nieminen J, Marjomäki V, Heino J, White DJ. BioImageXD: an open, general-purpose and high-throughput image-processing platform. **Nature Methods.** 2012, 9(7): 683–689.

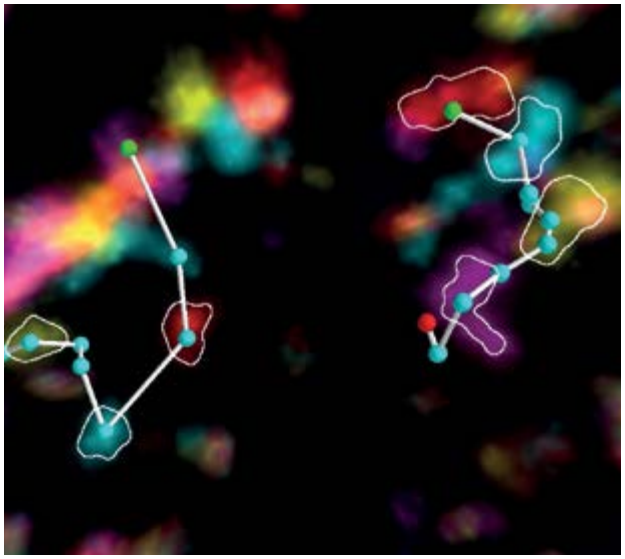
Paavolainen L, Kankaanpää P, Ruusuvuori P, McNerney G, Karjalainen M, Marjomäki V. Application independent greedy particle tracking method for 3D fluorescence microscopy image series. 9th IEEE International Symposium on Biomedical Imaging (ISBI). 2012, 672-675.

Björkbom A, Róg T, Kankaanpää P, Lindroos D, Kaszuba K, Kurita M, Yamaguchi S, Yamamoto T, Jaikishan S, Paavolainen L, Päivärinne J, Nyholm TK, Katsumura S, Vattulainen I, Slotte JP. N- and O-methylation of sphingomyelin markedly affects its membrane properties and interactions with cholesterol. **Biochim Biophys Acta**. 2011, 1808(4):1179-1186

Identifying mechanisms and significance of nuclear actin level control

Actin, the traditional component of the cytoskeleton, has been long known to exist also in the cell nucleus, but its role there has been elusive. Using the BI light microscopic facility and various advanced imaging techniques, the mechanisms by which nuclear actin levels are controlled were identified, and it was demonstrated for the first time that active maintenance of nuclear actin is absolutely critical for the transcriptional activity of the cell. Significantly, this study formed the firm basis for the project "Nuclear actin as a master regulator of nuclear structure and function" by Maria Vartiainen, which was awarded the 1.5 M€ ERC Starting grant in 2012.

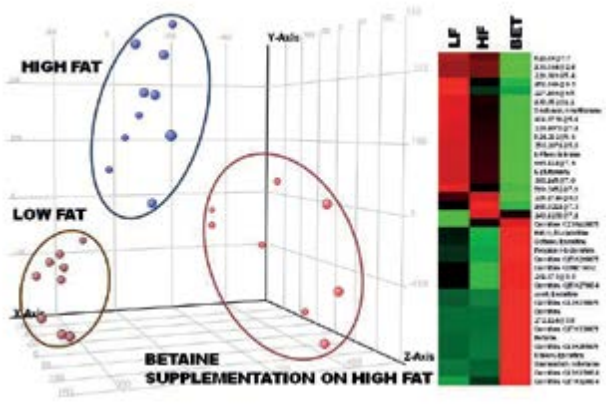
Dopie J, Skarp K-P, Rajakylä EK, Tanhuanpää K, Vartiainen M. Active maintenance of nuclear actin by importin 9 supports transcription. **Proc Natl Acad Sci.** 2012; 109:E544–E552.



Metabolomics helps understand the impact of dietary betaine on metabolism

As an example we include here one of the works performed at the BCK metabolite profiling facility. This is an example of an animal feeding trial, where the impact of dietary betaine on mouse metabolism was investigated. The non-targeted profiling revealed that addition of betaine to the diet increases the amount of various carnitine species in the liver and muscle tissue. This finding is an important link between dietary betaine and possible implication to lipid metabolism, as it known that betaine reduced liver fat accumulation, although the mediated mechanisms have not been clear.

This work nicely demonstrates the novel findings achievable via non-targeted profiling approach, and will appear in "Molecular Nutrition and Food Research": Pekkinen J, Olli K, Huotari A, Tiihonen K, Keski-Rahkonen P, Lehtonen M, Auriola S, Kolehmainen M, Mykkänen H, Poutanen K, Hanhineva K. Betaine supplementation causes increase in carnitine metabolites in muscle and liver in a high-fat diet fed mice as studied by non-targeted LC-MS metabolomics approach.

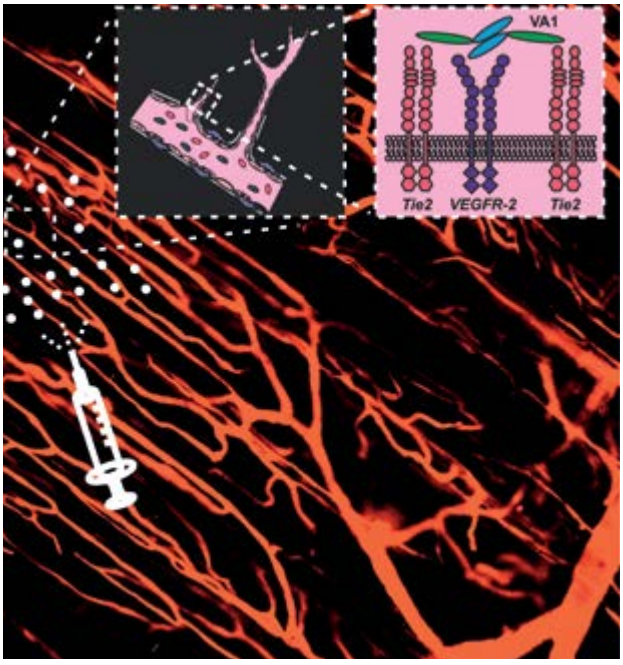


Principal component and hierarchical clustering analyses on the non-targeted metabolite profiling data from the muscle tissue with the HILIC chromatography combined with ESI(+)-MS on features showing significant difference between the dietary groups when compared to the high fat control (ANOVA $p<0.05$).

Promising results in treatment of skeletal muscle ischemia using viral gene transfer of a new chimeric vascular growth factor

Insufficient vascular supply predisposes to tissue ischemia and infarction. The currently used treatments are based on surgical intervention and drugs that do not provide full recovery and may have side effects. We have used AAV gene transfer technology, combined with genetic engineering to show the clinical potential of the new chimeric vascular growth factor, called VA1. VA1 was effective in the treatment of skeletal muscle ischemia in mice induced by ligation of the femoral artery, and it performed significantly better than the parental growth factor VEGF used for comparison. Detailed analysis indicated that VA1 does not induce angioma formation, vascular leakage, or inflammation to the same degree as VEGF. Thus VA1 appears more promising for therapeutic use than VEGF.

A. Anisimov, D. Tvorogov, A. Alitalo, V.M. Leppanen, Y. An, E.C. Han, F. Orsenigo, E.I. Gaal, T. Holopainen, Y.J. Koh, T. Tammela, P. Korpisalo, S. Keskitalo, M. Jeltsch, S. Yla-Herttuala, E. Dejana, G.Y. Koh, C. Choi, P. Saharinen, K. Alitalo, Vascular endothelial growth factor-angiopoietin chimera with improved properties for therapeutic angiogenesis, Circulation 127: 424-434, 2013.



BIOCENTER FINLAND TECHNOLOGY PLATFORM USER SURVEY 2013

BF conducted an extensive user survey in March 2013 as part of the final evaluation of all BF activities in 2010–2012 by SAB. The aim was to get information on the usage and performance of BF technology platforms and to get new ideas about the future development needs of BF.

To fit all the different services in the same survey, a simplified approach had to be selected: instead of listing all specific services provided (they are simply too many for one survey), performance was evaluated at the level of individual units of each technology platform in each biocenter.

On the online form the respondents were asked to evaluate the following five aspects in the performance of the technology platforms with scores from one to five (1 = very poor, 2 = poor, 3 = average, 4 = good, 5 = excellent):

- Access to the service;
- Quality of the service;
- Efficiency / Performance of the service;
- Service staff support & responsiveness;
- Price-quality ratio of the service.

The respondents could specify their answers and give further comments to the service providers to the text boxes next to each question. At the end, some open-ended questions were asked about BF services in general, e.g. which services were considered most important and which services were missing. Answering was completely anonymous.

Distribution of the survey

The survey was directed to research group leaders (principal investigators), but they were encouraged to discuss with their group members on their experience in using these services, and to submit a joint reply. The invitation was distributed by email to approximately 750 group leaders in biocenters and life science faculties of biocenter universities. To reach customers outside universities the service units were asked to distribute the survey invitation to them (the number of these invitations is not known). One reminder about participation in the survey was sent before closing the online form.

Results

Altogether 364 responses were received which corresponds to a response rate of appr. 45 % (Figure 1).

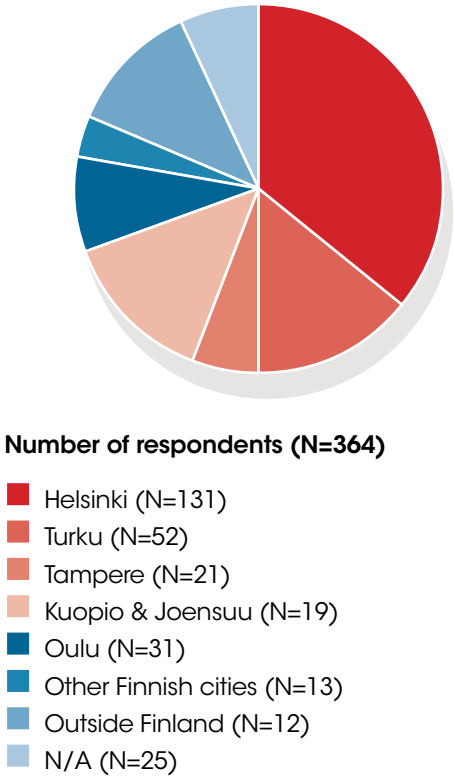
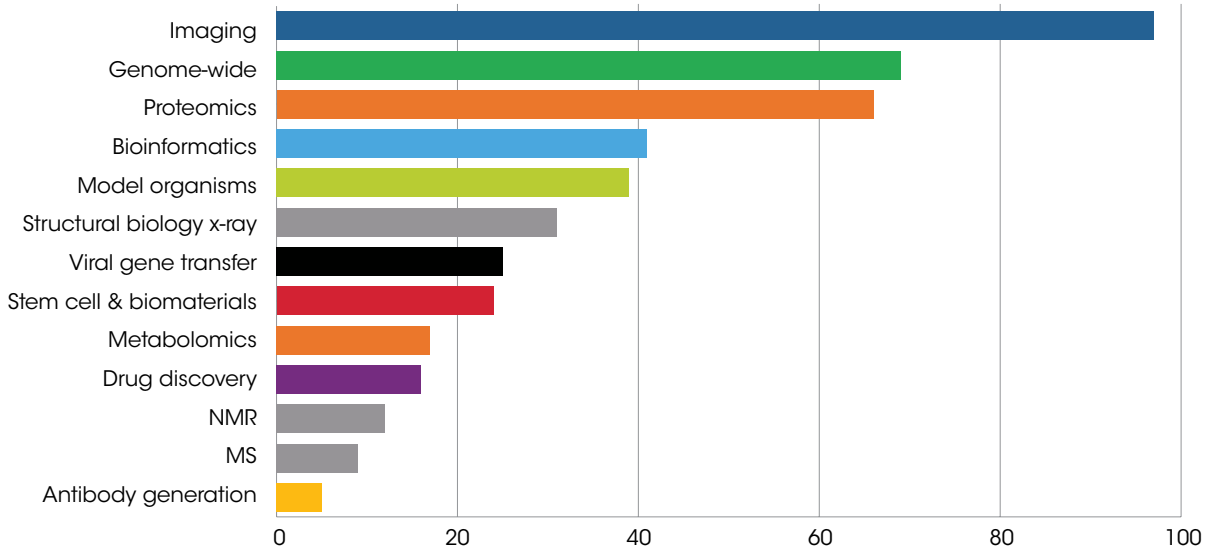


Figure 1. Distribution of the respondents by city (/country).

The average scores given to the different technology platforms varied between 2.5 and 5.0 with an overall average of all aspects of all services of 4.1 (= good). In a country where the word "excellence" is not in much use, this can be considered really quite good. Alternatively such a nice score is a reflection of the increasingly international life science community, who may have brought their values with them. Considerable differences were observed in the number of answers given to the different service provider units as could be expected. A comprehensive survey report is available at www.biocenter.fi.

A direct answer to the question: "Which services you consider most important for your research?" gave

the following distribution (showing how many times services were referred to be the most important ones):



Overall, the survey results give BF Board, the SAB and the technology service providers themselves an indication of how the services are operating and how successful BF and the individual technology platforms have been in making their services known in the scientific community. Answers to questions like "Which services are you missing from BF?" will obviously also help BF and its technology platforms to plan their future. As BF SAB has not commented individual results of the survey, it seems too early for BF to comment them beyond this point.

In the compilation of the general feedback, some important observations could be made. Probably the most important ones are complaints about lack of information about BF services available. Some respondents had apparently gone to visit BF web pages and found many more services than they were aware of. This sends a clear message to everyone participating in BF: despite all our efforts, there are still scientists out there who do not know about us. The same is true of training: although most technology platforms have made major training efforts, they haven't reached the whole community yet. This means we have more infrastructure days, roadshows, seminars, hands-on training and advertising in front of us.

INFRASTRUCTURE NETWORKS & TECHNOLOGY PLATFORM SERVICES

BIOINFORMATICS

NETWORK

Bioinformatics Infrastructure Network

Coordinator of the Network: Sampsa Hautaniemi, BCH

Members: Petri Auvinen, BI; Garry Wong, BCK; André Juffer, BCO; Mauno Vihinen/Matti Nykter, IBT; Mark Johnson, BioCity; Imre Västrik, FIMM; Olli Pentikäinen, University of Jyväskylä

http://www.biocenter.fi/index.php?page=bioinformatics

http://bioinformatics.biocenter.fi/

Advances in measurement technologies, such as microarrays, mass spectrometry, deep sequencing and large-scale screening, have made bioinformatics an integral part of biological and biomedical research. These technologies produce huge amounts of data on gene sequences, mutations, protein structures, human diseases and mouse phenotypes into databanks. Technology platforms for imaging both at microscopic and clinical level also provide increasing amounts of data. The task of bioinformatics is to provide tools, such as in silico modeling and simulation, to translate multidimensional biological data into knowledge and medical benefits. Thus, the productivity of biomedical sciences and related industries is increasingly dependent on computational methodologies and software. Lack of such software or methodologies is seen as a bottleneck for cutting-edge research exploiting the high-quality Finnish biodata and novel measurement technologies. Therefore, the major objective of the Bioinformatics infrastructure network and the corresponding technology platform is to provide services for both bioscientists and bioinformaticians. Although CSC - IT Center for Science Ltd is not officially part of the BF Bioinformatics infrastructure network, they collaborate actively both at national and European level and CSC is invited to all Bioinformatics network meetings.

PLATFORM

Bioinformatics Technology Platform

Chair of the consortium: Sampsa Hautaniemi, BCH, Computational Systems Biology Laboratory

Members: Liisa Holm, BI, Bioinformatics Group; Garry Wong, BCK, Laboratory of Functional Genomics and Bioinformatics; André Juffer, BCO, Biocomputing and Bioinformatics Core Facility; Mauno Vihinen/Matti Nykter, IBT, Bioinformatics Group; Mark Johnson, BioCity, Structural Bioinformatics Laboratory; external member Tommi Nyrönen IT Center for Science, CSC ; Imre Västrik, FIMM

http://bioinformatics.biocenter.fi/

Achievements in development and restructuring of technology services during 2010–2012

The bioinformatics network offers a great variety of services in 13 broad categories (microarray analysis; genotype data management, hosting and analysis; DNA-sequence archiving and analysis; high throughput and high-content screening data management; microscopy image analysis; protein structure analysis; in silico modeling and simulation; pathogenicity of genetic variants; immunology and immunodeficiency knowledge bases; data integration and assorted analysis; proteomics data analysis; bioinformatics software development and Anduril; and server hotel, hosting and scientific IT support). The services in different biocenters have been structured to avoid overlapping activities. All the services have been fully functional and used by the Finnish bioscience community. The consortium has also been in active dialogue with representatives of other BF technology platforms responsible for production of very large amounts of data that require bioinformatics services for interpretation and storage.

As the next generation sequencing service, offered by BF Genome-wide methods network, is the major data producer utilized at close to full capacity, the Bioinformatics network has put a considerable effort into next-generation sequencing (NGS) data processing, analysis and interpretation as well as supporting data and software services for BF Biological imaging, Translational technologies, Proteomics and Structural biology networks. In fact, the Bioinformatics network members have been working closely and integrating their services with the sequencing service providers in their biocenter. The integration creates a "one-stop-shop" for the clients. To cope with the volume of the data we have aimed at creating automated analysis pipelines for the most commonly requested. For example, FIMM has implemented a pipeline for identification and annotation of variants from genome sequence data as this is the main data type produced for the clients of the FIMM NGS unit. Another often used pipeline identifies somatic and possibly tumor-causing mutations from genome sequence of cancer samples. Whereas this is clearly not a clinical diagnostic service, hematologists and oncologists nevertheless have begun to consider such results in support of their treatment decisions in challenging patient cases. According to the division of tasks within the Genome-wide methods network, BioCity Turku focuses on developing technologies in the areas of transcriptomics, its regulation and epigenomics. The bioinformatics team in Turku has developed data analysis pipelines for these tasks, which have already been successfully applied to various projects.

The visibility of "in silico modeling and simulation" has further been improved. There is a clear increase in the number of requests for detailed analysis of enzymes and, more recently, whole genome phylogenetics and protein-membrane systems. Also, as (new) clients realize the potential of such in silico techniques, they usually require additional and more complicated analysis, thus we see a slight increase of returning clients as well. With the recruitment of a second postdoc in December 2011 (salary partly covered by Biocenter Finland in 2012), the level of expertise was also significantly improved, which was one objective for the "in silico modeling and simulation" component of the network.

The Bioinformatics network has presented the services to the biocenter community and established a helpdesk. The questions via helpdesk have been organized so that they can be handled by one of the members. Clearly, the helpdesk needs constant advertising and in the future we will merge our helpdesk with CSC in order to gain more publicity, efficiency and customers.

Biocenter Finland conducted user survey, in which the quality of Bioinformatics services was deemed high together with efficiency (average for the whole network 4/5). We received some critique on the visibility of the services and this is our major focus in the application for 2014–2016.

Participation in international, Nordic and European infrastructures

CSC, the Finnish node of the ELIXIR bioinformatics ESFRI infrastructure, is an observer (and now external member) in the BF Bioinformatics network. As such the CSC's planned service offering in ELIXIR is based on the needs of the BF Bioinformatics network.

Bioinformatics user statistics 2012

	BCH	BI	BCK	BCO	IBT	BioCity	FIMM	Total
Total users	19	6	19	8	224	55	57	388
Local	13	6	5	4	11*	31	11	81
Other domestic	5	0	3	2	11*	14	43	78
International	1	0	2	2	202*	10	3	220
of which non-academic:	0	0	–	0	–	0	3	3
Projects	16	6	10	8	–	55	129	224
Database & server users / requests	–	25 436	0	0	19 212	150 (users)	400*	45 225
Income EUR	50 000	–	0	0	0	40 000	28 882	118 882

* estimated NOTE: BCO and BioCity provide *in silico* modelling services where the time for one project may take months.

Members of the Bioinformatics network use the cloud computing pilot service developed and offered by CSC in preparation for ELIXIR. For example, 80% of the processing power of FIMM compute cluster is actually provided by CSC cloud. Full IaaS services are being implemented at BioCity Turku.

Members of the Bioinformatics network use available grid compute resources - both Finnish Grid Infrastructure (FGI) and European Grids Infrastructure (EGI, http://www.egi.eu/) - and train other platforms to use them as well. BCO and CSC host FGI clusters.

Jointly with CSC and all major universities in Finland, a significant investment was made to create a national scientific computing infrastructure (https://wiki.oulu.fi/display/fgi/Taygeta) based upon the Grid. Users can submit computation requests that can be carried out at any of the participating nodes. This infrastructure provides a stable expandable computing infrastructure that is connected to the European Grid as well, so that users throughout of Europe share a large scale network of computing nodes for in silico modeling and simulation. (http://www.egi.eu/).

Bioinformatics is also in the central role in the EATRIS translational research infrastructure where FIMM leads the Biomarkers services - one of the five service areas of EATRIS. Furthermore, bioinformatics services are also needed to analyse the data produced from samples from the BBMRI biobanking infrastructure.

BIOLOGICAL IMAGING

NETWORK

Biological Imaging Infrastructure Network

Coordinator of the network: John Eriksson, BioCity Turku (with Maritta Löytömäki and Joanna Pylvänäinen)

Members: Elina Ikonen, BCH; Maria Vartiainen, BI; Olli Gröhn, BCK; Sinikka Eskelinen, BCO; Susanna Narkilahti, IBT; Johan Lundin, FIMM; Varpu Marjomäki, University of Jyväskylä

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

Biological imaging ranges from the visualization of ions, molecules, cells and tissues to the non-invasive imaging of full size animals. The importance of imaging has grown tremendously since the development of methods and markers for live cell imaging, such as green fluorescent proteins for confocal microscopy, as well as novel microscopic principles. Different *in vivo* imaging modalities such as computer tomography (CT), single photon emission computer tomography (SPECT) and magnetic resonance imaging (MRI) has given us tools to visualize structure, metabolism and function in a living organism.

Modern imaging requires sophisticated instrumentation for data acquisition and methods of bioinformatics and data handling for their storage and analysis. The prerequisite for live cell imaging is that the equipment is near to the laboratories and animal centers. Therefore, each biocenter has confocal microscopes, video microscopes, and transmission electron microscopes for imaging of cells and tissues. However, in the National Imaging Infrastructure Network of Biocenter Finland (NIIN), different biocenters have been granted specific spearheaded tasks, which are organized under three technology platforms; those for light microscopy, electron microscopy and *in vivo* imaging. In light microscopy, Helsinki and Turku focus on new imaging technologies including high-resolution STED, PALM and STORM microscopy as well as high content screening at cellular and molecular level. Turku Bioimaging hosts some of these most recent technologies and has a high-resolution optical imaging core service at the BF level. In electron microscopy high resolution electron cryo-microscopy, electron tomography and three-dimensional image reconstruction for nanoscale structures are available at the Institute of Biotechnology in the University of Helsinki. *In vivo* imaging platforms include PET instrumentation in Turku, MRI in Kuopio and Helsinki, as well as optical methods in Helsinki and Turku.

Biological imaging emerging technology platform

In addition to electron microscopy, *in vivo* imaging and light microscopy technology platforms BF has funded "Small animal molecular imaging: RTI unit" in 2012. The funding decision was based on the SAB evaluation of applications of new technology platforms in 2011. The activities of this platform are reported in the emerging technology platform chapter (page 62).

PLATFORM

Electron Microscopy Technology Platform

Chair of the consortium: Eija Jokitalo, BI, Electron Microscopy Unit (BI-EM)

Members: Sarah Butcher, BCH, Cryo-EM Facility (BCH-cryoEM); Raija Sormunen, BCO, Electron Microscopy Core Facility (BCO-EM)

Achievements in development and restructuring of technology services during 2010–2012

Each of the three EM units forming this consortium has a long history in providing national services for academia and industry. The main common goal of the units for the funding period 2010–2012 was to restructure and streamline the functioning of the units towards nationally-unique complementary areas. The Helsinki units, BI-EM and BCH-cryoEM focus on 3D imaging and hybrid methods from molecular models to whole cells and tissues, whereas the BCO-EM specializes in the ultrastructural pathology of human and model organisms working closely with the BCO Transgenic mouse core facility. The impact of BF funding has been significant in terms of both renovating the technology platform infrastructure and in retention of highly trained support staff; from Biocenter Finland allocations 75% have been used for instruments and 25% towards personnel costs.

Our analysis at the end of the 3-year funding period indicates a clear improvement in performance and quality of the services evidenced by higher scientific impact. The major instrument investments in this consortium included two 120 kV transmission electron microscopes (BI-EM and BCO-EM) and a field emission gun scanning electron microscope (BI-EM), and in addition, important instrumentation for specimen preparation, image processing and data storage have been realized. New microscopes first of all replaced old ones and thereby guaranteed the continuation of services. Secondly, due to instrument development and the introduction of digital imaging on all of the transmission electron microscopes (TEM), the quality and turn-around of the work have been significantly improved, with the microscopy time required per specimen greatly reduced. Users now have instant access to the recorded data and so can immediately react to the results from a specimen, and improve the data saved. In addition, much support time has been saved as the bottle neck of film development, printing and digitizing has been removed. For very high resolution projects that are typically very data collection intensive however, film still remains the medium primarily in use due to limitation of the CCD technology. The instantaneous access to data at the microscope has dramatically increased the work capacity and lowered the initiation barrier for many researchers and projects. Instrument development has yielded higher resolution and enabled 3D-imaging. For specimen preparation, a common emphasis has been to upgrade instrumentation for advanced EM techniques, and especially in cryo-EM specimen preparation the following purchases are now all in operation: a vitrification robot (at BCH-cryoEM has greatly increased the number of specimens prepared), a fully-automated freeze-substitution device (BCO-EM), an advanced high pressure freezer (BI-EM) and a fluorescent light microscope for examining vitrified specimens (BCH-cryoEM). Increased imaging capacity, especially on 3D-EM projects in each unit has increased the computation and data storage need. BCH-cryoEM set up a suitable computing environment for sub-tomograph averaging and helical reconstruction based on users' project needs, as well as working on methods development in flexible fitting (Seitsonen *et al*, 2012; Pietilä *et al.* 2012). Efforts have been made to build long term data storage solutions that will simultaneously enhance data sharing between the EM units and their users. Overall the workflow has been streamlined to better fit the current and future needs of the research community.

BF funding has made it possible to increase throughput of projects, and to hire new senior scientific staff to develop new advanced EM techniques. These new additions to the technology platform have been very well taken up by the community and this is evident as an upsurge in scientifically demanding projects without increasing the turnover time of the existing services. The new techniques that have been set up and are now offered to users include two serial section imaging based scanning electron microscope (SEM) techniques, SBF-SEM and FIB-SEM, with the first results now being published (Puhka *et al.* 2012; Anttonen *et al.* 2012).

The consortium members have agreed criteria for pricing including a common price category for all academic work, rather than distinguishing between their

User statistics

	BI-EM	BI-cryoEM	BCO-EM	Total
Total number of research groups	81	16	38	135
local academic research groups	59	12	24	95
national academic research groups	16	1	8	25
industrial users	4	0	1	5
international users	5	3	5	13
Microscope usage (hours)	3 739[n]	688	700	5 127
Specimens prepared	735*	556[#]	1 264*	2 555

* Number of specimens that has been embedded *(plastic or cryo),* sectioned *(room temperature or cryo)* and stained *(including immunolabelling),* excluding duplicates of each step;

[#] Number of cryo specimens prepared;

[n] 1354 hours of invoiced TEM & basic FEG-SEM use, and 2622 hours of SBF-SEM use (the proof-of-concept test projects for SBF-SEM were not invoiced, as there were no maintenance expenses to cover during the warranty period)

own university and others. BI-EM and BCH-cryoEM adopted the new pricing scheme from May 2011, and BCO-EM started with the same pricing principles in April 2012. All members have now implemented the same internet-based booking and invoicing system. This makes statistical analysis of the impact of the investments much easier to follow, and as it is fairly automated, has decreased bureaucracy. Standardized laboratory practices such as the reporting and quantification of ultrastructural results have been developed. This has been of utmost importance when widening the services to industrial users. As an example of an industrial application, EM analysis and a quantification method were developed to optimize a protein production bioprocess by BCO-EM, and a similar analysis was published by BCH-cryoEM (Koho *et al.* 2012).

In BI-EM, four projects were selected for proof-of-concept studies to optimize the SBF-SEM technique for cultured cells, plant and animal material. As this setup is among the first of 10 worldwide, it has drawn a lot of interest from outside Finland (with visitors from Ireland and Sweden for instance), but preference is given to national users and projects. The SBF-SEM technology is so new that a lot of development is still going on. As part of the contract, BI-EM agreed to allocate some instrument time to Oxford Instruments Nordiska to host their customer visits and jointly organized workshops. As a result of this agreement, BI-EM and Oxford Instruments Nordiska organised the workshop "Serial imaging in the SEM – a revolution in 3D microscopy". There were 14 participants from 10 countries visiting the EM unit for two days in November 2012. The program consisted of lectures and practical demonstrations on all three aspects of the imaging process: specimen preparation, dataset acquisition, processing and visualization. As the operating software is still under development, we are in active dialog with both FEI and Gatan providing feedback.

Our consortium gained a lot of visibility when BCO-EM organized the annual meeting and three workshops of the Scandinavian Microscopy Society (Scandem 2011). The meeting attracted 240 participants from 16 countries including bio- and material sciences. The extensive commercial exhibition (23 companies) presented the latest equipment and developments in the microscopy field. As part of the program, a workshop in 3D-modeling was jointly organized with BI-EM. BCH-cryoEM has taken part in national roadshow lectures, tutorials and information distribution during 2011 and early 2012 to advertise the technology platform to potential users in Turku, Helsinki, Tampere, Kuopio and Oulu in collaboration with other structural biologists. Since 2010, Helsinki units have organized 15 lecture and practical courses in collaboration with local graduate schools and with Aalto University, and Oulu unit has organised 2 graduate school courses. In 2012, BCH-cryoEM held a successful helical reconstruction workshop in response to user requests from Oulu and Hamburg. In addition, there has been active training and interaction via NIIN (National Imaging Infrastructure Network) of EM staff from Aalto University, Jyväskylä University, University of Eastern Finland, and Turku University.

User statistics 2012

The statistics for the 3-year period and 2008 preceding the formation of the national platform show that the general trend has been an increase of about 30% of research groups overall, and huge increase in the number of samples, instrument hours and the number of publications. It is notable that the services to the research groups require active input from the core personnel as none of the services include off-the-shelf products. Active input is either in the form of instruction and supervision of the use of instruments, sample preparation and/or data interpretation. There is no such commercial service available in Finland or abroad that we are aware of. The majority of the cryoEM users rely on the service staff for data collection and interpretation rather than doing it themselves.

Participation in international, Nordic and European infrastructures

The broad spectrum of techniques that our consortium covers exceeds the boundaries of the European infrastructure calls, and therefore we have split our activities and the units have different connections to a specific ESFRI.

During 2012, Euro-BioImaging ESFRI conducted a series of proof-of-concept studies utilising European advanced biological and biomedical imaging facilities. BI-EM hosted one proof-of-concept project coming from the Technical University of Munich, Germany. BI-EM and BCH-cryoEM has now joined efforts with the BI-Light Microscopy Unit to propose a Correlative Light Electron Microscopy (CLEM) platform in the Finnish Euro-BioImaging node application.

BCO EM belongs to Oulu Bioimaging network (OBI), which joins the biological, biomedical and medical imaging expertise at Biocenter Oulu, Faculty of Medicine and Oulu University Hospital with the machine vision and optoelectronics expertise at the Infotech Oulu Research Center and the Faculty of Technology. OBI is applying to the Finnish Euro-BioImaging node. BI-EM and BCH-cryoEM are members of Helsinki Functional Imaging Center. HFIC is a stakeholder in the preparatory phase of Euro-BioImaging (ESFRI) and a member of the European Light Microscopy Initiative (ELMI) and European Institute of Biomedical Imaging Research (EIBIR).

BCH-cryoEM is part of the ESFRI Instruct National User Group, and is preparing an application for an Instruct National Affiliated Center to cover X-ray (membrane proteins and enzymology), NMR (special labelling techniques and high field NMR), EM (high resolution single particle) and mass spectrometry (ESI Q-FT-ICR and hydrogen-deuterium exchange). BCH-cryoEM is part of the AIROPico FP7 Marie Curie Industry-Academia Partnerships and Pathways with 8 industrial and academic partners that will run from 2014–2018 and includes academic and industrial infrastructure for the development of diagnostics, therapeutics and basic science of picornaviruses.

It is important to note that there is a clear distinction between the two ESFRI calls for development of advanced methods towards international collaboration, and the national Biocenter Finland service platform which is our main priority.

PLATFORM

National *In vivo* Imaging Platform

Chair of the consortium: Olli Gröhn, BCK, Biomedical Imaging Unit and National Bio-NMR Facility

Members: Juhani Knuuti, BioCity, Turku PET Centre and Cell Imaging Core, Turgut Tatlisumak, BCH, Experimental MRI Laborator

Achievements in development and restructuring of technology services during 2010–2012

The aim of this consortium is to create a national multimodal preclinical *in vivo* imaging network, with clear division of the tasks and core expertise area in each of the contributing biocenters. During the funding period, we have completed significant purchases of imaging instruments and established an open access multimodal imaging infrastructure with harmonized user policies and pricing. These investments have made new techniques available for the biomedical research community, and expanded the capacity (both in terms of instrument time and expert service personnel) in each site, so that the quality, quantity and accessibility of the services have significantly improved. The network has reached a fully functional state and is, for example, contributing to the Euro-BioImaging ESFRI as a 'proof-of-concept' site, using a single contact point to redirect service requests to the participating biocenters. When compared to the situation in 2006–2008, before Biocenter Finland, the number of non-local projects (other domestic, international) has increased 38% providing evidence that this activity has opened up the facilities to a wider user community thus leading to significant restructuring of the *in vivo* imaging at the national level.

During the funding period, the following concrete steps have been taken to improve the availability and promote the excellence in different *in vivo* imaging modalities.

The capacity of PET tracer production in Turku PET center has significantly increased. This is the bottleneck for increasing the capacity required for efficient provision of PET imaging services, as the PET imaging systems were already recently upgraded. The PET tracers need to be produced in a dedicated radiotracer synthesis laboratory that is in close proximity to a cyclotron laboratory. The existing synthesis laboratory has the qualified space for the synthesis but the number of synthesis devices was limiting for the availability of tracers for preclinical imaging. In 2011, the establishment of new tracer production devices was successfully finalized. Two synthesis rigs were constructed and tested. In addition, Cu-64 isotope production was developed in order to allow labeling of larger molecules and peptides with slow kinetics. As a result, there is now significantly better access to the various new tracers. Furthermore, as a result of networking of the *in vivo* imaging consortium, Kuopio acquired a preclinical PET imaging system from partner Turku in 2012 (funding for the purchase from University of Eastern Finland). The implementation of the new imaging modality in Kuopio was

greatly facilitated by expertise provided by partner Turku during the process.

By combining BF funding, Academy of Finland Infrastructure funding (FIRI), and some local funding sources MRI instrumentation within the consortium was significantly upgraded. A completely new 7T/16 cm MRI scanner was acquired to replace a 13-year-old 4.7T MRI scanner in Kuopio, and laboratory space was completely rebuilt and modernized. In addition, new multichannel state-of-the-art MRI console was purchased and connected to existing 9.4T/31 cm magnet. As a result, several novel imaging methods became available, especially regarding cardiac imaging and functional brain imaging, and the capacity to perform state-of-the-art preclinical *in vivo* MRI was doubled. The new systems are also significantly more user-friendly and thus serve better external users.

As an indirect consequence of the actions taking place in Kuopio, preclinical MRI also became available in Oulu Biocenter, during 2012. The 4.7T magnet from Kuopio was transferred to Oulu and was upgraded by funding from the University of Oulu to serve as a basic level preclinical MRI instrument for the local research community. MRI services are also provided in Helsinki, with a 4.7T MRI system. During 2011, this was integrated as a part of the multimodal imaging platform, especially in association with optical imaging (see below).

For PET-MRI system in Turku 4 new animal coils were purchased. These coils allow novel small animal studies using combined PET and MRI imaging in the same session. These methods are planned to be mainly used for tumor and inflammation imaging.

During 2011–2012, major advances in optical imaging have taken place in a new dedicated *in vivo* imaging laboratory in Biomedicum Helsinki. These renovated facilities are conveniently located adjacent to the surgery rooms, behavioral analysis and MRI facilities in the laboratory animal unit. The new facilities host the recently acquired intravital multiphoton (MP) microscope with optical parametric oscillator. This allows extended wavelength capabilities that serve the growing use and importance of red shifted fluorescent proteins and tracers in *in vivo* imaging. In addition, a 3D optical projection tomography (OPT) system especially suited for embryonic and mesoscopic imaging has been purchased. Thus, the range of *in vivo* approaches has been expanded to bridge the dimensions from subcellular resolved MP imaging, to small organisms and whole organs with OPT, and to whole animals using optical *in vivo* imaging (IVIS instruments) and MRI platforms. We have also piloted the coregistration of fluorescence molecular tomography (FMT; of e.g. tracer distribution inside tumors) with anatomical detail resolved by MRI. The establishment of a National BioCARS center in Biomedicum Helsinki has taken place in 2012. CARS (coherent anti-Stokes Raman scattering), SHG and THG (second and third harmonic generation) are label-free MP imaging methods that will serve as additional spearhead technologies for *in vivo* optical imaging in Helsinki, offering an important opening also at the international level via the EuroBioImaging ESFRI and EU COST action MicroCoR consortium. Another aim has been to upgrade the optical imaging infrastructure in Turku. Earlier, *in vivo* optical imaging was based on bioluminescence and fluorescence imaging. Tomographic optical imaging with quantitation is expected to improve the usage since it allows to coregister PET, CT or MRI to yield an anatomical and functional hybrid approach. The 3D optical imaging device was purchased in 2012 and has been available for researchers since then.

User statics

Number of research projects (users) in the period 2010–2012.

	Kuopio	Turku	Helsinki
Total number of projects	89	212	64
Local projects	55	137	60
Other domestic projects	14	14	3
International	9	24	1
Non academic projects	12	37	0

Participation in international, Nordic and European infrastructures

The national *in vivo* imaging network participated in the EuroBioImaging ESFRI initiative as one of the European sites for 'proof-of-concept' studies in the 'Multimodal Molecular Imaging' work package. In whole EuroBioImaging, total of five 'proof-of-concept' studies were carried out in this work package, two of which in Finland; a PET study in Turku and an fMRI study in Kuopio. Partner Helsinki is a 'proof-of-concept' site for the 'General Access' work package within this ESFRI. All conducted 'proof-of-concept'

studies in the national *in vivo* imaging network received excellent feedback in user evaluation.

The national *in vivo* imaging network is also linked with other ESFRI initiatives. In EATRIS (European Advanced Translational Research Infrastructure in Medicine) Turku PET Centre is one of the two centers contributing the imaging tracers. Partner Helsinki is a managing committee member in the EU COST action MicroCoR (Chemical Imaging by Coherent Raman Microscopy) that involves all aspects of Coherent Raman microscopy techniques. We are also linked to the Nordic Imaging Network supported by Nordforsk. In collaboration with the Finnish IT Center for Science (CSC), Institute for Molecular Medicine Finland (FIMM), and the University of Helsinki IT Services, the partner Helsinki has established a platform for data management as part of the Ministry of Education and Culture subsidised pilot projects for the ELIXIR ESFRI infrastructure.

PLATFORM

Light Microscopy Technology Platform

Chair of the consortium: John Eriksson, BioCity, Turku BioImaging (CIC-TBI)

Members: Daniel Abankwa, BioCity, Turku BioImaging (CIC-TBI); Elina Ikonen, BCH, Biomedicum Helsinki Imaging Unit (BIU-BCH); Maria Vartiainen, BI, Light Microscopy Unit (LMU-BI); Michael Courtney, BCK, Multimodal imaging Core (MUIC-BCK); Lauri Eklund, BCO, Biocenter Oulu Tissue Imaging Center (TIC-BCO); Susanna Narkilahti, IBT, Tampere IBT Imaging Facility. Also University of Jyväskylä Imaging Facility, Varpu Marjomäki, participates in the Platform activities.

Achievements in development and restructuring of technology services during 2010–2012

In a pan-European survey made by the Euro-BioImaging ESFRI network, Finland had the best open access imaging infrastructure facilities per capita among the participating countries. This has been made possible by funding through BF, host universities and other competitive funding sources. Today Finland is among the leading European nations in terms of available advanced instrumentation. This progress has been made possible by clear national and local division of tasks, and development of core facilities with spear-heading technologies that are among those that are of highest demand Europe, based on the Euro-BioImaging survey.

More specifically, many super-resolution modalities have been developed that surmount the diffraction barrier imposed by wavelength of visible light. Super-resolution centers have been established at the Cell Imaging Core of Turku Bioimaging (CIC-TBI) and in the Biomedicum Imaging Unit (BIU-BCH). These units implement STED and STORM super resolution modalities, respectively. A major unique initiative in Turku is to expand the concept of super-resolution microscopy by combining the unit with other state-of-the-art imaging technologies, including fluorescence lifetime imaging microscopy (FLIM), fluorescence correlation spectroscopy (FCS), and atomic force microscopy, all integrated into the same platform. In addition, LMU at Institute of Biotechnology is operating Bayesian localization microscopy, which enables super-resolution imaging using standard fluorescent markers and microscopes. With STED, PALM, STORM, Bayesian methods, and SIM the BF super-resolution initiative includes all current major super-resolution imaging modalities accompanied with probe-development.

BF investments in 2010–2012 greatly expanded the development of national high-content and high-throughput imaging. Users can now receive expert assistance to use state of the art integrations of imaging, liquid handling, sample incubation instruments and libraries of compounds, RNAis, expression plasmids and even patient-derived stem cells. Critical to this is the active communication with BF networks, in particular Genome-wide methods, Translational technologies, and Stem cell networks for RNAi/plasmid libraries, compound libraries and patient/disease-specific induced pluripotent stem cell lines respectively. Both Biomedicum Imaging Unit and LMU at BI have partnered with the BF Genome-wide methods technology platform to offer complementary high-content imaging services. Close collaboration and job sharing with the Institute for Molecular Medicine Finland (FIMM) RNAi Technology Centre is also important in this context. In addition, LMU and Turku Bioimaging develop Leica SP5 Matrix

platform jointly to enhance complementarity between the two units. BIU-BCH and CIC-TBI also work with CSC to develop solutions for storing large data amounts, and the BioImageXD software platform is being developed to better suit high-content applications.

One of the next big leaps in microscopic imaging will be adopting various label-free techniques. Several units in the network are already on their way to establish imaging modalities based on various label-free principles. Biomedicum Imaging Unit has, during 2012, established a confocal CARS (Coherent Anti-Stokes Raman Spectroscopy) platform, as part of a National BioCARS Centre. In addition to CARS, it offers label-free second and third harmonic generation (SHG, THG) microscopic services suited for label-free visualization of living cells and tissues. This is complemented by Mass spectrometry Imaging (MSI) developed at BCH Proteomics core facility as part of the BF Proteomics and metabolomics platform. Label-free technologies are also the spearhead of the University of Jyväskylä Imaging Facility. Linear Raman signals are already obtained from various biological samples. A new femto-second laser system has been purchased recently. It enables four wave mixing (FWM) based imaging, such as CARS microscopy. Furthermore, a time-resolved 2D-IR spectroscopy setup was developed during 2012. A completely novel label free technique is photo-acoustic microscopy, for which a prototype has been built at TBI in collaboration with Northwestern University, Chicago.

Other special instrumentation and general developments include Multiphoton systems developed at Biomedicum Imaging Unit, LMU at BI, and in Turku BioImaging. At BIU, the platform serves the increasing need for *ex vivo* and *in vivo* intravital microscopy. At LMU, this system has been upgraded with time-domain FLIM and FCS/FCCS, while the Turku multiphoton unit is specially designed for studying the migration of immune and cancer cells in intravital microscopy. LMU has also combined wide-field, TIRF, spinning disc and protein interaction studies on a 3I Marianas platform, which is now capable of very advanced multimodal live-cell imaging applications. Important developments in Oulu BCO-TIC include a spinning disk confocal with TIRF and FRAP units, as well as confocal microscope system, OPT, and a digital holographic microscope for multidimensional imaging of mesoscopic-scale biological specimens such as embryos, organ cultures and tissue biopsies. A collaborative project between the Center for Machine Vision Research at Infotech Oulu and TIC-BCO developed new image analysis services for the various needs of national and international research communities. This collaborative project also included Jyväskylä imaging facility. Tampere Imaging Facility is also focusing on the imaging of mesoscopic objects (3D cell cultures, biomaterials, zebrafish and Drosophila). During 2012 new high-end confocal and long term time lapse imaging systems have been ordered, a new postdoctoral imaging specialist hired, user hours doubled and teaching and collaboration activities significantly increased. Several restructuring and reorganization activities, which provide synergy that has a major positive impact on services and their accessibility, have taken place at various sites. For instance in Helsinki BIU merged three separate core-facilities, in Turku CIC was reorganized to cover nearly all microscopes on the campus, and in Tampere different core technologies were merged.

Post-processing of bioimages is as important as their acquisition. This challenge is being addressed by members of the whole network. An example of this interaction is the open-source software BioImageXD (http://www.bioimagexd.net/), which is being developed as a global collaboration by researchers in Turku, Jyväskylä, and Oulu. This software is intended for versatile and fast processing, analysis and visualization of large amounts of multidimensional bioimaging data, solving several previous bottle-necks in bioimage processing. BioImageXD has already been used for numerous unique bioimaging applications throughout the world, offering opportunities for tailored, novel and high-throughput applications. The software also includes unique built-in validation tools. Future plans include an ongoing project to develop second generation versions of the software, interactive functionality with high-throughput microscopy, interoperability with other open source projects and libraries, and development of new types of image processing algorithms.

Data storage, analysis and processing approaches are probably one of the greatest bottlenecks nationally. Data needs to be saved, backed up, distributed, processed, analyzed and visualized reliably, using scientifically sound, distributable, reliable and inexpensive methods capable of dealing also with very large amounts of data. These aspects are in part being addressed in Helsinki by the Bioinformatics network,

in Turku, Jyväskylä and Oulu (with other collaborators) by the BioImageXD team and in Kuopio by the MUIC-BCK team and Bioinformatics network.

User statistics

The user statistics of all facilities from 2012 indicate a clear increase in users and financial turnover for all facilities. Also the numbers of international and other external users are increasing for all facilities. This growth trend illustrates the increasing importance of light microscopic imaging services in biomedical research, and the synergistic effects obtained through national collaboration and organization.

Participation in international, Nordic and European infrastructures

The BF light microscopy consortium participates actively in the pan-European ESFRI Euro-BioImaging (www.eurobioimaging.eu) infrastructure preparatory phase and has excellent possibilities to establish European imaging nodes in Finland. All imaging centers are stakeholders in Euro-BioImaging and the chairmanship of Turku BioImaging (JE) in Work program 12 of Euro-BioImaging provides a direct link of the Finnish imaging community to Euro-BioImaging, and vice versa. The Biomedicum Imaging Unit, the Light microscopy unit of Institute of Biotechnology, the Multimodal imaging core of Biocenter Kuopio, and Turku BioImaging all successfully participated in Euro-BioImaging proof-of-concept studies during the year 2012. The consortium has also been actively involved in Nordic level imaging networks, such as NordForsk supported Nordic Imaging Network.

In the future the Finnish participation in Euro-Bioimaging lies on the strong foundation of the new Finnish BioImaging Network, FiBI, which consists of the technology platform services of the BF biological imaging infrastructure network and medical imaging services which are not part of BF. The application to place Euro-BioImaging onto the updated Finnish Infrastructure roadmap has been prepared by the FiBI network

Turku BioImaging was an active participant at the founding meeting of the Open Bio Image Alliance in 2012, and plans to be actively involved especially through the BioImageXD software platform in this international organization, aimed at providing researchers in life sciences with the highest quality public-domain software and knowledge to analyze and quantify image data reliably and reproducibly. All members are actively engaged in a large number of microscopic societies and imaging alliances. The network of collaboration spans a significant proportion of major imaging communities in the world.

User statistics

	BIU-BCH	LMU-BI	MUIC-BCK	TIC-BCO	IBT	CIC-TBI	Total
Total number of research groups	64	53	15	40	12	104	288
local groups	62	51	9	30	12	83	247
other domestic groups	–	2	2	5	–	13	22
international groups	2	–	2	4	–	6	14
non-academic groups	–	–	2	1	–	2	5
Instrument hours	11 153	11 342	3 244	7 058	348	11 887	45 032
Single users	174	151	54	101	30	313	823
Annual financial turnover	89 744	134 240	7 096	–	8 700	128 702	368 482

GENOME-WIDE METHODS

NETWORK

Genome-Wide Methods Infrastructure Network

Coordinator of the Network: Tomi P. Mäkelä, BI
Members: Outi Monni, BCH; Jorma Palvimo, BCK; Minna Männikkö, Tapio Visakorpi, IBT; Riitta Lahesmaa, BioCity; Janna Saarela, FIMM

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

Opportunities provided by the development of novel technologies such as RNA interference (RNAi) and the increasing efficiency and speed of DNA sequencing are rapidly transforming both basic biological science and biomedicine. This requires rapid adaptation of both researchers and the research environment, where highly specialized and capital-intensive instrumentation and reagent sets are optimally developed as core infrastructures. This is the goal of the nationwide Genome-wide network, which was initiated through integration and focusing of local services 2007–2009, was nationally recognized on the first National Roadmap of Research Infrastructures 2008, and undertook a significant development and restructuring program during 2010–12, where focus was on nodes on the Meilahti and Viikki campuses in Helsinki as well as in Turku.

In 2012 the longstanding development of services in technology platforms in genetics, genomics, and gene expression and regulation in humans and a wide variety of model and non-model organisms was continued. A big effort was placed on cutting edge DNA sequencing and data analysis from the wide variety of applications relating to it. Also services utilizing high-throughput technologies and reagent sets for genome-scale biology were developed. High-content screening services were customized to local research strengths and integrated with imaging and translational technologies. The BF Genome-wide network continues in its role as an expert body to coordinate training efforts, to evaluate the services, to facilitate the use of these services in biocenters throughout Finland, and to integrate these activities internationally.

PLATFORM

Genome-Wide Methods Technology Platform (GWM)

Chair of the consortium: Tomi P. Mäkelä, BI, Genome Biology Unit (GBU)
Members: Outi Monni, BCH, Biomedicum Functional Genomics Unit (FuGU); Petri Auvinen, BI, DNA Sequencing and Genomics Laboratory (BI-DGEN); Jorma Palvimo, BCK, Chromatin and Transcription Laboratory; Riitta Lahesmaa, BioCity, Finnish Microarray and Sequencing Centre (FMSC); Janna Saarela, FIMM, FIMM Technology Center; DNA Sequencing and Genotyping Laboratory; High-throughput Screening Facility

Achievements in development and restructuring of technology services during 2010–2012

Biocenter Finland is in a key position on preserving and developing genome scale biology technologies in Finland. Due to the very rapid development of DNA sequencing (NGS) and other genome-wide applications and novel emerging technologies it is of most importance to secure sufficient funding for personnel and equipment in this field in Finland. The funding agencies in Finland do not usually recognize challenges of running and developing of core units in long term. Without longstanding support it is impossible to keep the very qualified personnel staying in a university environment. Our recruitment policy has been highly successful during the 2010–2012 period but the current situation with uncertainty of sustained funding has resulted in a serious threat that the highly skilled personnel will be leaving the nodes. This would be a significant loss to research and research infrastructure in Finland and waste of Finnish, in particular BF funding.

Genome scale biology is still developing extremely fast. This has a direct impact on the activity and services of this network since continuous technology upgrades require constant method development and rapid introduction of novel equipment and technologies to services in order to keep the services state-of-the-art. The fast pace of development causes constant restructuring as a modus operandi of the platforms. Nodes of BF network are occupied in developing their areas of expertise at a speed needed to provide state-of-the-art services to the Finnish research community in a timely fashion. This

has been achieved by a close collaboration and division of tasks within the network. With the support from BF the Genome-wide methods network has successfully restructured and developed its core infrastructures and now provides several novel NGS based services to the researchers nationally. For example new services available for studies in gene expression and regulation include PAR-CLIP for studying protein RNA interactions, histone modification profiling with ChIP-seq and DNA methylation profiling with several different methods, such as Reduced Representation Bisulfite Sequencing (Hawkins et al. 2013). The data analysis pipelines and computational resources crucial for supporting these new technology platforms have been established and developed accordingly. During 2012 the tech platform services performed a world record in sequencing of a single DNA molecule (30 800 bp) using the PacBioRS single molecule sequencer funded partly by BF. We think that our achievements during the 2010–12 funding period of BF funding have demonstrated the strength, power and competitiveness of such a structure and justify for further funding, subject to regular external evaluation.

The 3-year seed funding from BF has enabled to establish the first version of high-quality national genome-scale reagent collection (Gateway-compatible ORF clones, siRNA and shRNA knockdown libraries). In 2012 the value of high-quality, rapid delivery and reduced costs has been notified in nation-wide on the basis of significantly increased customer numbers and interest towards screening possibilities. The achievement is also the training of skilled personnel, who are now able to respond consultation requests, provide general training, and importantly able to develop further the usage of genome-scale reagents.

The development of the platforms themselves in all the nodes has been rapid due to the BF funding and also supporting funding from the host organisations. GWM-network nodes have been successful in acquiring supporting funding from their host organisations and other sources. Due to the cutting edge research infrastructure developed through BF, the Finnish scientists have been in an excellent position to apply for European Union or other international funding. The Academy of Finland funding is evaluated by external international panels, who in the field of biosciences expect access to cutting-edge infrastructure. This has been made available to the entire Finnish research community through BF-GWM. BF-GWM nodes coordinate their activities aiming at optimising the cost-efficient usage of the funding. The sequencing facilities in Helsinki (FIMM and Institute of Biotechnology) have intensified their collaboration by keeping combined laboratory meetings and further clarifying their division of tasks between medical projects and non-model organism genomics. Tens of project relying on the GWM nodes have been published in prestigious journals between 2010–2012, such as Nature, Nature Immunology, Immunity, Science, PNAS, NEJM, EMBO J.

A number of the bottlenecks evident already from the beginning still remain. In particular, the IT infrastructure needs to be urgently developed to meet the requirements of high-throughput biology. The interaction between the BF networks especially with the Bioinformatics network has been close and crucial. Some of these challenges can be solved through a close collaboration with CSC, utilized by all the nodes. Importantly, since several applications are ideally performed within the data producing units it is essential to reserve funds to develop such local IT infrastructures. This is justified already because transferring large amount of data is expensive not always without complications. Moreover, capacity of CSC is not currently sufficient to accommodate the high demand by our network, though the recent new developments have been making CSC as more suitable producing computing and storage services. Furthermore, with the constant increase in the capacity and through-put of the genome-wide technologies, there is also a pressure for increasing the through-put and automation of the sample preparation process.

User statistics

A total of 318 research groups have used the services provided through BF-GWM nodes during 2012 with a turnover exceeding 2 513 259 € as demonstrated in the table. The restructuring and sharing of tasks is already very evident through comparison of the services in genomics, gene expression, and genome-scale biology. Importantly, there is increase in activities in 2012 compared to 2011, which already was pointed out to be excellent by the external evaluators (see previous report). The number of samples analyzed by the nodes has increased during the entire period of 2010–2012.

Biocenter Finland organized a user survey for all technology platform services, and an early analysis of the results demonstrated that GWM services are widely used; a third of all respondents (99/364) commented on GWM services. Of the various GWM nodes, the

User statistics

	BioCity Turku (FDSC)			BI (BIDGEN & GBU)			FIMM			BCH (FuGu)			BCK		
	Samples	Projects	Groups	Samples	Projects	Groups	Samples	Projects	Groups	Samples	Projects	Groups	Samples	Projects	Groups
Genomics															
Resequensing	8	1	1	2	5	4	120	19	12	27	6	6	–	–	–
De novo	–	–	–	369	9	7	0	0	0	–	–	–	–	–	–
Metagenomics	14	2	1	1 508	23	21	48	1	1	–	–	–	–	–	–
Targeted	402	12	9	–	–	–	2 575	87	36	–	–	–	–	–	–
SNP genotyping (QWAS)	35	2	2	–	–	–	522	18	15	–	–	–	–	–	–
Targeted SNP typing	59	1	1	–	–	–	29 734	41	23	–	–	–	–	–	–
Copy number variation**	–	–	–	–	–	–	1 399	1	1	40	3	3	–	–	–
Gene regulation															
Immunoprecipitates (ChIP-seq etc.)*	146	12	2	–	–	–	224	6	4	131	16	7	50	16	7
RNA sequencing	78	10	8	176	5	5	232	34	12	68	8	7	–	–	–
GENE expression microarrays	1 593	42	26	–	–	–	156	8	4	532	47	31	–	–	–
Cell microarray (384-plate) screening	–	–	–	–	–	–	284	14	14	–	–	–	–	–	–
Genome-scale Biology															
Genome-scale reagents	–	–	–	245	68	27	–	–	–	570	48	19	–	–	–
ORF cloning	–	–	–	122	14	9	–	–	–	–	–	–	–	–	–
Integrated two-hybrid screening	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Pooled & barcode shRNA screen	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
High-content analysis (HCA)	–	–	–	1 432	40	22	180	3	3	–	–	–	2 623	17	13
Customers															
local users		59	25		96	52		154	68		97	43		25	12
other domestic		18	13		8	6		68	48		14	12		5	5
international		3	3		2	2		7	6		9	6		2	2
non-academic groups/ units		–	–		6	6		3	3		8	5		1	1
Total		80	41		112	66		232	125		128	66		33	20
Billing costs		424 131			527 335			1 060 611			454 362			7 095	

* includes methylation arrays
** includes genome-wide (CGH) and targeted

Genome Biology Unit is clearly less known/used than the more established cores, but got good scores. Altogether GWM services received an average score of 4.0 out of 5, which we consider very good. The best average score for the nodes was with the BCH Functional Genomics Unit (4.2). GWM's best scores were in Access and Performance, and worst in Responsiveness and Price/Quality; we will focus to improve the areas of concern also taking into account the more detailed (node-wise) comments.

Participation in international and European infrastructures

The cutting-edge infrastructure developed by the BF funding has made Finnish scientists competitive in obtaining not only national but also international funding (such as ERC grants). The GWM network nodes have contributed among others for example to following EU funded projects: DIABIMMUNE, NANOMMUNE, PEVNET, SYBILLA, ESTOOLS, BioSHaRE-EU, ENGAGE, SYNSYS, PREDECT, Sys-

tems Microscopy Network OF Excellence, and JDRF funded projects, and European infrastructure networks: Biomed Bridges, EATRIS, BBMRI.

There are increasing demands for computing power and for storage and archiving in the field of genome-wide methods. In collaboration with CSC we have been developing solutions for the above needs via CSC cloud computing project within the ELIXIR ESFRI program and in several pilot projects using virtual machines solution in complex analysis. These activities are also planned in close contact with the BF Bioinformatics network. Though cloud computing can be used for certain application the need for local computing and storage capacity near the data production sites does not cease.

Biocenter Finland is in a key position on preserving and developing genome scale biology technologies in Finland. Due to the very rapid development of DNA sequencing (NGS) and other genome-wide applications and novel emerging technologies it is of most importance to secure sufficient funding for personnel and equipment in this field in Finland.

NETWORK

Model Organisms Infrastructure Network

Coordinator of the network: Raija Soininen, BCO
Members: Eero Lehtonen, BCH; Matti Airaksinen, BCH; Heikki Tanila, BCK; Mika Rämet IBT; Matti Poutanen, BioCity; Sergey Kuznetshov FIMM

http://www.biocenter.fi/index.php?page=model-organisms

The Model Organisms network comprises two technology platforms, those on mouse and non-mammalian model organisms.

Genetically modified (GM) mice are currently the key model organisms to understand the molecular basis of health and disease in man and to serve as models for human development and diseases, and are expected to have an important role in the development of new therapeutic approaches. Work with GM mice requires high-level expertise, and specific ethical and regulatory issues have to be followed. In Finnish biocenters GM or "transgenic" mouse core facilities with experienced personnel were established in the 1990's to provide high quality service mainly in the generation of GM mice. Even though large international consortia nowadays systematically produce mutations in genes of the mouse genome, local infrastructure remains essential for providing services and expertise in all aspects of mouse related issues, especially in customized mutagenesis, rederivation, and archiving of mutant mouse lines, as well as in education. Furthermore, in recent years, services in high-level systematic analysis ("phenotyping") of mutant mice have become more and more in demand. Activities on generation, analysis, and archiving of mutant mice in Finland have now been organized into the Biocenter Finland FinnMouse technology platform as will be discussed later.

The technology platform on non-mammalian models uses well characterized, simple organisms such as the fruit fly (*Drosophila melanogaster*), the zebrafish (*Danio rerio*) and the nematode *C. elegans* for large-scale genetic analyses of biological regulatory pathways and mechanisms of development. Their use as model organisms is based on the fact that many of the important physiological mechanisms are conserved in evolution, and therefore it is possible to use genetically tractable model organisms also for studies on human genetic diseases.

PLATFORM

FinnMouse - National Technology Platform for Generation, Analysis and Archiving of Mouse Models

Chair of the consortium: Raija Soininen, BCO, Transgenic Animals Core Facility
Members: Eero Lehtonen & Matti Airaksinen, BCH, Helsinki GM Mouse Unit; Heikki Rauvala, BCH, Neurophenotyping Center (with BCK); Antti Sukura, Finnish Centre for Laboratory Animal Pathology; Heikki Tanila, BCK, Neurophenotyping Center (with BCH); Matti Poutanen, BioCity, Turku Center for Disease Modeling TCDM

http://www.fingmice.org/

Achievements in development and restructuring of technology services during 2010–2012

The mouse is the central model organism for analysis of mammalian gene functions and genetic diseases. Sophisticated genetic tools have been developed to generate mice with specific mutations, and the research subjects range from monogenic to complex diseases, cancer, as well as therapy applications. Currently thousands of new mouse mutants are created each year in individual research laboratories and by large collaborative efforts such as the Complex Trait Consortium (www.complextrait.com) and the International Knockout Mouse Consortium IKMC (www.knockoutmouse.org).

In early days of gene modification experiments, mice were generated by individual research groups and stored in small animal houses. However, it soon became obvious that larger units are the way to go. Special training of researchers and personnel performing the experiments and taking care of animals are required due to regulations on the use of experimental animals and genetically modified (GM) organisms. Core facilities offer possibilities for both reduction of animal numbers used and refining their

life and welfare, following the 3R's principle. Furthermore, in the co-operative, centralized system, the GM animal strains can be used by a large number of researchers. Centralized storing, cleaning and phenotyping are services that reduce the number of animals needed and refine their life.

The FinnMouse technology platform has actively developed GM mouse services, and during 2010–2012 restructuring resulted in three collaborating core facilities (Helsinki, Oulu, and Turku) providing services in GM mouse technologies for all Finnish scientists. Considering long distances it is not possible to centralize all services in one unit. Therefore, all three units provide elementary services, such as generation and rederivation of GM mice. Embryo transfer to a recipient female is the most effective way to get rid of infections or diseases not accepted in the laboratory animals. Furthermore, shipping as embryos instead of living mice between facilities is recommended both considering animal welfare and prevention of contaminations.

In addition to the basic services, the units have special service profiles: the Helsinki GM unit specializes in mouse chimera generation by the morula aggregation method, and the unit plans to start generation of GM rats when the new rodent house is in use. In year 2012 the main effort was in rederivation: About 100 mouse lines were rederived to pathogen-free status to be housed in the new animal facility. The Oulu unit has set up the lentivirus injection method for transgenic mouse production and has special expertise in cryopreservation methods, serving as the Finnish EMMA (European Mouse Mutant Archive, www.emmanet.org) node that provides repository services, including cryopreservation and distribution of GM mouse lines to a world-wide user community. Turku Center for Disease modeling (TCDM) provides services in generation of gene constructs for GM mouse production, tumor xenografts in immunodeficient mice and has collaboration with several pharma and biotech companies.

For phenotypic analyses of mice, specific areas of expertise have been strengthened and services developed. Neurophenotyping Centers In Helsinki and Kuopio (University of Eastern Finland) provide services in automated behavioral phenotyping and in specific neurophenotyping tests with new protocols both in disease models (Alzheimer's disease, epilepsia, schizophrenia and autism -like behavior) as well as in analyzing roles of specific factors. In Biocenter Oulu, current focus areas are services in the electron microscopy of mouse tissues (reported separately) and analysis of cardiovascular functions, with analyses of cardiac structure and special heart failure models being developed. In year 2012, the OPT (optical projection tomography) and basic mouse histopathology services were set up. Turku (TCDM) has put special emphasis on the development of live animal imaging technologies (PET, optical and ultrasound imaging), and new methods for computerized histo-morphometric analyses as well as biomarker studies have been developed. The Finnish Center for Laboratory Animal Pathology (FCLAP), established in 2010 within the Faculty of Veterinary Medicine, University of Helsinki, provides specialist services in laboratory animal pathology, including consultation and diagnostic services. An important part of FCLAP activities is training of veterinary pathologists, but laboratory animal necropsy courses directed to basic researchers have been organized also.

The FinnMouse collaboration has provided benefits that greatly improved the services in all units. The funding made possible the recruitment of new personnel, updating of equipment and setting up new methods. Visits to partner laboratories and personnel meetings (the most recent one held in early 2013) have improved communication and sped up the exchange of best practices and new methods. Information about the FinnMouse services was also delivered to researchers in Roadshows held in all partner universities during 2011–2012.

A web interface, www.fingmice.org, was set up, providing information about services and expertise in generation and analysis of GM mice available in Finland. List of useful reporter and deleter mice available in Finland is included and number of mouse lines there will be gradually increasing.

All service facilities are engaged in education of graduate students and postdocs in laboratory and lecture courses. Workshops on specific subjects have been organized for scientists and technical personnel, most recent ones the workshop 'New advances in genome modification and animal models' in Oulu and the course 'Assesment of Rodent behaviour' in Kuopio. Furthermore, besides the specialist training of veterinarians by FCLAP, a Disease Model Pathology Training Program for researchers is ongoing, with lectures organized in Helsinki, Kuopio, Oulu and Turku, the coordination being by the TCDM, and a web-based training program is being developed.

FinnMouse customers and services 2012

	Research groups/customers				
	Local	National	International	Non-academic	Total
TG/GM unit					
Helsinki	21	2	0	0	23
BCO Oulu	15	6	10	0	31
TCDM Turku	11	8	9	0	28
Total	47	16	19	–	82

Phenotyping					
FCLAP Helsinki	22	1	1	0	24
NC Helsinki	12	1	0	0	13
NC UEF	3	3	1	2	9
TCDM Histol.	18	0	2	0	20
Imaging	23	6	0	1	30
Other	18	6	4	1	29
BCO Histology	15	0	0	0	15
Histopathology	7		1		8
Imaging (IVIS, OPT, Echo)	9	2	2	0	13
Total	127	19	11	4	161

GM services provided	**UHel**	**UTurku**	**UOulu**
Pronuclear injection	0	2	3
ES cell targeting	0	18	3
Consortia ES cell culture	2	0	6
Cryopreservation of 8-cell embryos	13	10	0
Mouse line rederivation	98	30	9
Blastocyst injection	0	7	16
Recovery of cryopres. embryos	5	4	10
Sperm cryopreservation	5	0	39
Genotyping	0	13	14
Husbandry of mouse colonies	0	13	3
Morula aggregation	2	0	0
DNA construct generation	0	6	0
Cryopres. of IVF-derived 2-cell embryos	0	0	39
Other	0	7	6
Total	125	110	148

Phenotyping services provided	
FCLAP Helsinki	Necropsies (84); Immunohistology specimens (837); Paraffin blocks (1 259)
NC Helsinki	Behovioral phenotyping, Testing nociceptive and motor fuctions (in total 15)
NC Kuopio UEF	Brain microinjections; Video-EEG recording; Brain immunohistology; Behavioral testing (in total 10)
TCDM Turku	Hormone and biomarker analyses; Histology and immunohistochemistry; Whole animal imaging
BCO Oulu	Measurements of cardiovascular functions (1 389 animals); *In vivo* imaging; OPT (102 samples); Tissue processing for histology (2 890)

Participation in international and European infrastructures

University of Oulu represents Finland in the ESFRI project Infrafrontier, the European Infrastructure for Phenotyping and Archiving of Model Mammalian Genomes and will be a shareholder in the Infrafrontier GmbH to be established in 2013. University of Oulu is also a partner in EMMA (European Mutant Mouse Archive) network and in the FP7-Capasities 2013–2016 project Infrafrontier-I3. The FinnMouse platform is therefore well positioned to coordinate the national activities with those in Europe. In addition to archiving services, Infrafrontier will provide standardized phenotyping services, which however will not replace the need for highly specialized services at national level but will complement them and provides training.

Universities of Helsinki and Turku are involved in the EU-funded project "International web-based training pathology programme in disease modeling" in collaboration with the University of Glasgow and the German Mouse Clinic. University of Turku is also a partner in the European Advanced Translational research Infrastructure in Medicine (EATRIS).

The NordForsk funded network NorIMM, Nordic infrastructure for Mouse Models, www.norimm.org, established to improve communication between infrastructures for generation and analysis of gene modified mice in Nordic countries, continues its activities.

PLATFORM

Technology Platform for Non-Mammalian Model Organisms

Chair of consortium: Mika Rämet, IBT
Members: Pertti Panula, Neuroscience Center Zebrafish Unit Helsinki, Mataleena Parikka, IBT, Tampere Zebrafish Core Facility; Susanna Valanne, IBT, Tampere *Drosophila* Core facility; Tapio Heino, Ville Hietakangas, Osamu Shimmi, Helsinki *Drosophila* facility

Drosophila is a classic model used in genetics for more than a century, and new genetic tools, such as genome-wide RNAi collections, have made it more versatile than ever before. The infrastructure required is relatively light, mainly consisting of work stations with microscopes, but to be utilized in genetic screens by non-specialists, experts providing consultation and taking care of collections have to be available. In Tampere, a new *Drosophila* Core Facility has been build. This investment was done by the host institute IBT and was supervised by the BF-funded core facility coordinator Dr. Susanna Valanne. The new laboratory includes 12 working stations with stereomicroscopes and carbon dioxide points for anesthetizing flies. This unit is heavily used as it currently hosts e.g. two ERC grant holders and two FiDiPros.

In Helsinki, during the year 2012, three groups (Heino, Hietakangas and Shimmi) have offered *Drosophila* facilities, knowledge and guidance to six groups in the Viikki that do not use fruit fly as their main research model. Furthermore, the Viikki unit has donated flies to secondary schools and hosted a visit of high school students.

New tools for modification of zebrafish genome (e.g. morpholino oligonucleotides, gene knock-out by TILLING) have been developed, resulting in increased use of zebrafish in research projects. In Finland, facilities providing services in major zebrafish methods have been established in Helsinki and Tampere. During 2010–2012, the Tampere Zebrafish core facility has become fully operational after the Phase two expansion of the maintenance system, providing automated systems for maintenance of zebrafishes for research purposes. Tampere Zebrafish laboratory has now capacity to maintain up to 50 000 fishes, allowing large-scale forward genetic screening. Currently, the laboratory employs a full-time coordinator and three technicians, partly supported by Biocenter Finland.

Many researchers from several research teams from the University of Tampere, University of Jyväskylä and University of Oulu have used the facility. Besides ongoing process of creating mutant zebrafish families, zebrafish lines are maintained for scientists, microinjections for production of transgenic zebrafish and for morpholino-based gene silencing are carried out, and assistance in initial phenotype characterization are provided.

In Helsinki, services for generation and maintenance of transgenic and normal zebrafishes, a platform for morpholino-oligonucleotide translation inhibition, fast movement analysis and quantitative locomotor analysis as well as high-resolution confocal microscopy have been provided. The unit has also pro-

duced and used fish mutants generated with the TILLING method, zinc finger nuclease method and most recently established the CRISPr CAS nuclease method for mutant production.

The BF network has organized a week-long hands-on training course 'Non-mammalian model organisms for research in life sciences' in the years 2011 and in 2012, and in Helsinki international courses in zebrafish techniques and neurobiology were organized in 2010, 2011 and 2012.

Participation in international, Nordic and European infrastructures

The consortium partner in Helsinki, professor Pertti Panula, has participated in both of the world-wide strategic zebrafish PI meetings (2011, 2013), and is currently a member of the Management Committee of the EU COST Action EU FishBiomed and the Nordforsk Network BEFINE. He has participated in three NORDFORSK meetings during the 3-year period (Sweden, Finland, Norway), of which he organized one.

User statistics

	local	national	international	total	
Drosophila					
Helsinki	6	–	–	6	
Tampere	9	–	–	9	
Zebrafish					
Helsinki	10	–	4	14	153 service events
Tampere	8	2	4	10	55 510 larvae; 10 574 adult fish

Biocenter Finland Infrastructure Day 2012: Model organisms, Stem cells and biomaterials, and Translational technologies

Organisation of the Biocenter Finland Infrastructure Day in Tampere on August 30, 2012 completed the 3-cycle of presentations by all BF infrastructure networks. During the day the infrastructure networks for Model organisms, Stem cells and biomaterials, and Translational technologies presented their activities and latest developments. In addition to the international keynote lectures in the Model organisms and Stem cells and biomaterials sessions an inspiring guest lecture on the future of bioinformatics was given by Ewan Birney (European Bioinformatics Institute, EBI).

At first the activities of the Translational technologies infrastructure network and its technology platforms were presented by Johan Lundin (FIMM), Krister Wennerberg (FIMM) and Jorma Isola (IBT). Also the links the network has to the ESFRI's were discussed.

Michael Hagn (Helmholtz Zentrum München, Germany) continued with the European perspective by introducing Infrafrontier, the European infrastructure for phenotyping and archiving of model mammalian genomes. Raija Soininen (Biocenter Oulu) gave an introduction to the national model organisms infrastructure. The introduction was followed by scientific talks by Peppi Karppinen on the use of mouse models (University of Oulu) and by Dan Hultmark (IBT & Umeå University) on Drosophila models.

Kenji Osafune (Center for iPS Cell Research and Application, Japan) gave a keynote speak for the stem cells and biomaterials session on the iPS cell technology-based research towards regenerative medicine for kidney diseases. Timo Otonkoski (University of Helsinki) and Katriina Aalto-Setälä (University of Tampere) continued the session with their talks on the iPS-cell technologies.


400
200

NETWORK

Proteomics and Metabolomics Infrastructure Network

Coordinator of the network: Garry Corthals, BioCity Turku

Members: Marc Bauman, BCH; Markku Varjosalo, BI; Antti Poso, BCK; Kalervo Hiltunen, BCO; Vesa Hytönen, IBT; Vidya Velagapudi, FIMM; Janne Ihalainen, University of Jyväskylä

www.protmet.net

www.biocenter.fi/index.php?page=proteomics-and-metabolomics

The Proteomics and Metabolomics network, ProtMet.net, comprises two technology platforms, one in proteomics and protein characterization, and the other one in metabolomics. Together these platforms represent a large group of skilled researchers offering a diverse range of services, methodologies and applications covering all areas of life science.

In establishing the network we embarked on an ambitious plan to link independently operating national service laboratories, combining experience and resources to offer a coordinated national technology platform. The broad field of proteomics is an essential technology in biosciences that underpins strategically important areas in academia and biotechnology, enabling characterization and temporal and spatial quantitation of proteins at various locations in practically all biological systems. It also affords measurement and discovery of post-translational protein modifications, protein-protein interactions and protein properties, which are amongst the most sought after applications.

Metabolomics is a rapidly emerging discipline dedicated to the global study of metabolites in biological systems, their dynamics, composition, interactions, and responses to interventions. The metabolome can be studied as an intermediate phenotype linking the genotype and the environment.

Proteomics and metabolomics emerging technology platform

In addition to proteomics and protein characterization, and metabolomics technology platforms BF has funded "Proteome-wide profiling of kinase-substrates" platform in 2012. The funding decision was based on the SAB evaluation of applications of new technology platforms in 2011. The activities of this platform are reported in the emerging technology platform chapter (page 62).

PLATFORM

Proteomics and Protein Characterisation Technology Platform

Chair of the consortium: Garry Corthals, BioCity, Turku Proteomics Facility

Members: Marc Baumann, BCH, Meilahti Clinical Proteomics Core Facility; Markku Varjosalo, BI, Proteomics Unit; Kalervo Hiltunen, BCO, Proteomics and Protein Analysis Core Facility; Vesa Hytönen, IBT, Protein Technologies Facility

http://www.protnet.net

Achievements in development and restructuring of technology services during 2010–2012

At the inception of the funding period in 2010, scattered facilities with unique expertise operated throughout Finland, where neither services nor expert personnel were accessible at the national level. In three years time this situation has dramatically improved. A large overhaul of the facilities has taken place and this Biocenter Finland infrastructure is now equipped with modern instrumentation providing access to cutting-edge services and knowledge in mass spectrometry based proteomics and protein characterisation. Importantly the facilities are now connected and experts from various teams collectively use our knowledge that extends beyond state-of-the-art instruments. For example, where previously there was a void, there are now coordinated efforts in protein science between facilities in Oulu and Tampere offering services in protein characterisation using a range of biochemical and biophysical methods including calorimetric methods (ITC, DSC) to study ligand binding and thermal stability of proteins and their complexes. Additionally novel biosensors technology (BLI) and updated SPR instrument are to obtain information about binding kinetics and binding affinity.

We have recently expanded the network to Jyväskylä to include light scattering and spectroscopic methods that e.g. can be used to characterise protein behaviours in solution, or to screen for protein formulation. Similarly in the field of proteomics major investments in instrumentation and new personnel have ushered in a new era for the field in Finland. All laboratories offering services in quantitative MS are in consultation about best practices and offer joint courses, using identical computational approaches. Thus, other facilities nationally have taken up what one laboratory has spearheaded. This has been the case for post-translational modification analyses, label and label-free quantitative analysis and systems-wide analyses. Similarly, the Turku facility in early 2012 initiated targeted SRM, provided training and knowhow; now other labs will follow and begin to offer similar services.

Importantly we have also brought in a wide range of new instruments, none of which are identical, but that offer similar capabilities in terms of coverage and sensitivity. The difference of the instruments is found in the performance and ultimately the molecular content they provide creating detailed 'niche' characterisation analyses for virtually any biological sample. Additionally trained personnel in emerging fields of protein network analyses have been recruited as well as experienced operators using SRM technology.

The goals for the Proteomics & protein characterisation consortium (PPCC) were to be achieved within three years. The tasks and responsibilities were divided between the facilities, whilst being mindful to maintain a national capacity for services and training. A website was created to promote the ProtMet.net and its goals and to provide immediate and open access to the entire network of researchers for our services, researchers and scientific events including workshops, courses, training and seminars. The website continues to serve as a single location for all information about services. Throughout the funding period detailed information on seminars, courses, workshops, ProtMet meetings and presentations, symposia, new positions and updates on new instruments and new services have been posted on the website (www.ProtMet.net).

Concerning the actual goals of the ProtMet.net, starting in 2010 with the national coordination of services for protein analysis and proteomics the following areas were instigated: 1) protein identification and quantitation in cells, fluids and tissues; 2) protein modification analysis; 3) data analysis and proteomics bioinformatics; 4) protein kinetics; and 5) biophysical characterization of proteins and interaction analyses. Additionally in the first year educational services were initiated through the training of both the facility staff and the user community. In 2011 SRM analysis was established through the strategic recruitment of personnel to Turku, and in 2012 the first SRM instrument was purchased and services were added as planned. It is noteworthy to highlight that throughout the period from 2010–2012 we had as goals to implement, innovate and maintain cutting-edge science, through the adoption of newly published methods, staff training and development of new tools and methods used for protein and proteome analysis, several of which are in our publication list, as well as on our ProtMet website.

While the whole network offers services in virtually all areas of protein science, a particular strength of the network's protein research is its special focus on a range of biochemical and biophysical methods and the characterisation of protein interactions. Our advanced methods now include calorimetric methods (ITC, DSC) to study ligand binding and thermal stability of proteins and their complexes. Modern biosensors are available (SPR, BLI) to obtain information about binding kinetics and binding affinity. Because many protein characterization methods consume a substantial amount of high-quality protein, services are available to support protein production and purification as well. The protein production systems include *E. coli* and *Spodoptera frugiperda* (baculovirus expression system). Furthermore we have upgraded to state-of-the-art instruments isothermal titration microcalorimetry (ITC200), surface plasmon resonance (Biacore T200 and a multiparametric-SPR Navi220A), and circular dichroism spectroscopy (CD) (AppliedPhotophysic Chirascan Plus with stopped-flow accessory and autotitrator).

For proteome based research there is now a continuum of services on offer. Instruments for discovery research and protein identification and biological mass spectrometry have been installed in all facilities, including an LTQ Orbitrap Elite and an LTQ Orbitrap Velos Pro in Helsinki and Turku, three SYNAPT G2 HDMS instruments of which two in Helsinki and one in Oulu. Furthermore two UltrafleXtreme MALDI-Tof-Tof instruments have been installed, where one offers services for general biological mass spectrometry in Oulu and recently a new installation

was completed for Helsinki specifically for services in imaging MS. Turku also installed two additional instruments: a Q Exactive specifically used for phosphorylation and targeted MS workflows and a triple quadrupole (TSQ) specifically for SRM analyses.

A field that is now dominated by mass spectrometry has witnessed a significant growth in the usage of computational approaches to understand and represent data in a humanly interpretable format. To keep up with national demand three facilities now offer systems-wide quantitative proteome analysis, one in Turku and two in Helsinki. More than 25 training events have been organized in 2012 for personnel, graduate schools and new users.

User statistics

The transition of the PPCC has been dramatic: from a selection of facilities offering protein characterisation and identification services in the past to becoming a network providing broad and tightly integrated program of services, methods and training to quantitate protein interactions and dynamics of the biological systems. Proteomic and protein analyses now support practically all research activities across the whole life sciences field. Covering both fundamental and applied sciences, service applications include areas pertaining to health and disease in cell biology, pre-clinical, clinical medicine, quality of life and health, improving health through better diagnostics,

	BCH Helsinki	BI Helsinki	BCO Oulu	IBT Tampere	CBT Turku
Total number of research groups*	33	54	34	23	29
Total number of non-academic groups/units	3	10	3	3	3
Local research groups*	27	39	24	3	21
Domestic research groups*	4	13	4	18	7
International research groups*	2	2	6	2	1
Volume of services (instrument time in hrs)	Mass spec: 3150 h [a,b] Gels: 36 [c]	Mass spec: 2390 h [a,b] N-seq: 420 h [b]	Mass spec: 1700 h [a] Gels: 313 [b] Characterisation: 2592 h [c]	DSC: 130 h Octet: 40 h ÄKTA: 359 h Fermentor: 230 h	Mass spec: 4479 h
Specifications *Research groups (or other customers) who have used the services. ** For proteomics, only MS instrument times recorded; Sample preparation and IT-services, peptide- and protein purification not included. *** For protein production and characterization, experiment design, service coordination and data analysis are not recorded except for non-academic groups.	**a: Mass spectrometry**** MALDI-Tof/Tof, 450 h Q-Tof, 1 890 h IonTrap, 360 h **b: MS glycoproteomics**** Q-Tof, 450 h **c: 2-DE gel-based proteomics** 36 gels, 100 h	**a: Mass spectrometry**** LTQ-Orbitrap Elite, 2 350 h MALDI-Tof/Tof, 40 h **b: Edman** sequencing, 420 h	**a: Mass spectrometry**** MALDI-Tof/Tof Q-Tof Total, 1700 h **b: 2-DE gel-based proteomics** 313 gels, 2330 h **c: Protein characterisation***** ITC, 230 h CD, 636 h SPR (Biacore), 1726 h	**a: Protein production***** expression, 230 h preparation, 359 h **b: Protein characterisation***** BLI, 40 h DSC, 130 h	**Mass spectrometry**** LTQ-Orbitrap Velos, 2 139 h Q-Exactive, 1 392 h Q-Tof, 457 h TSQ Vantage, 455 h MALDI-Tof/Tof, 36 h

evolutionary genetics, animal health, as well as areas as diverse as agroscience, ecoscience and biofuels and crop research.

In terms of numbers there was for the third year in a row a measureable growth, with 153 research groups engaging in professional services, which was a modest rise of 15% on the number of actual groups in the previous year. When compared to when the network first started, the upward trend continued. The significant success that restructuring enabled is reflected in the 100% increase of research services, when compared to the first year (end 2010), which was a success in itself. A year on year comparison reveals a 25% growth in research services between 2011 and 2012. Interestingly all facilities reported many new instrument installations and significant long services breaks in 2012, effectively lowering the number of months in operation of the instrumentation. Thus while the number of groups grew modestly by 15%, the volume of research services grew by 25%. This is reflects what we noticed in a rising number of research projects, where many groups have shifted their focus from analysis of a small number of proteins to systems-wide analysis, -omics analysis, which follows a global trend from the past years. Thus the developments of novel services, acquisition of new instrumentation, combined with the expertise of our personnel is now having a major impact on Finnish sciences.

Participation in international, Nordic and European infrastructures

The further development of services and training are enabling the Facilities to strengthen their impact on sciences nationally. Significant funding has been awarded to the consortia's affiliated researchers in need of new services through several Nordforsk funded programs, several existing and applied for Centre's of Excellence, three FiDiPro, several Academy Professorships as well as national and international funding (FP7, COST). The network is currently also engaged in future activities of the ESFRI ISBE, by heading one of the WPs, and is involved in the consultation of proteomics for Horizon 2020.

PLATFORM

Metabolomics Technology Platform

Chair of the consortium: Seppo Auriola, BCK, Department of Pharmaceutical Chemistry
Members: Tapio Palva, BCH, Metabolomics Unit; Vidya Velagapudi, FIMM, Metabolomics Laboratory

www.protmet.net

Achievements in development and restructuring of technology services during 2010–2012

During 2011 the BF Metabolomics technology platform continued to take shape, as the last instruments were purchased and installed. The year 2012 was the period for very intensive method development, expansion of customer base, and final structuring of the services, which all are now up and running. All the units in BF metabolomics consortium utilize MS-based analytics with varying targets in terms of metabolite groups and/or sample types analysed.

The BCK unit performs non-targeted metabolite profiling with a one-step metabolite extraction capturing semi-polar metabolites as well as part of the hydrophilic and hydrophobic compounds from any biological sample. The liquid chromatography is performed with a two column approach (HILIC and RP) to maximize the separation capacity of the analytes, and additionally the ionization for MS is performed in both positive and negative modes to further widen up the window of detectable metabolites.

The general profiling is suitable for non-targeted examination of the metabolite pool, and has potential to bring out unexpected findings. Downside of the non-targeted profiling approach is the extensive data-analysis with heavy bioinformatics and chemometrics requirements as well as often laborious metabolite identification, which require multiple working hours that are difficult to estimate in beforehand, since each of the analysed sample sets are unique. Presently the analysis price constitutes the extraction, analysis, raw data collection and preliminary statistics, but the rest of the work is performed as collaborative activities with the customers under our guidance. The general profiling assays can be com-

plemented with the analytics in the FIMM unit offering high-throughput targeted quantitative metabolomics analyses for biomedical applications. Method for quantitative analysis has been developed on LC-QQQ and a robotic system for extraction and quantification of 94 endogenous polar metabolites from 15 different metabolite classes using multiple reaction monitoring (MRM) strategy within a single chromatographic run (HILIC, 15 minutes/run, i.e., 96 samples in 24 h). An in-house metabolome database has been developed. The method validation and testing has been carried out using quality control (QC) sample in inter-laboratory and inter-platform cross validation (local laboratories and NMR facility in Kuopio, commercial kit). The relative error for most of the metabolites is less than 20%, which shows the credibility of the method.

The BCH unit focuses particularly on plant and microbial metabolite analysis. This is very important part of the BF metabolomics consortium, since the metabolite repertoire present in plants/microbes is multiple when compare to mammalian metabolites, and therefore units mainly analysing samples of human or animal origin won't be able to cover those in terms of metabolite identifications. BCH funding together with that of the host university removed the serious bottlenecks encountered in 2010 due to equipment limitations. In addition to the LC-qTOF/MS funded by BF, the University of Helsinki financed a new GC-MS from its infrastructure funds and it became operational in April. The BCH services were restarted in the second half of 2011 and the unit is now fully functional providing improved high throughput metabolic services to its customers. Unit offers both targeted and non-targeted analysis using UPLC-Q-tof and GC-MS techniques mainly for plant and microbial applications. Main area of analysis is plant metabolomics (e.g. hormones, waxes, phenolics or glucosinolates in plants), including metabolite identification. Unit provides also analysis of small peptides (i.e. cyanobacteria toxins), synthesis products and drug metabolites.

All the metabolomics units have been actively contributing to education and training in various aspects of metabolite related analytics, as they provide education both for the graduate students and researchers. The FIMM unit has been responsible for teaching clinical metabolomics as part of the Master's degree program in Translational Medicine, and BCH unit has been responsible for metabolomics at the Masters level Genomes course. In Kuopio the metabolomics training has been included in various lectures and practical courses at the Department of Clinical Nutrition and School of Pharmacy. In August 2012 the unit personnel was responsible for organizing a one week course "Nordic Graduate School Course on Metabolomics", which was a great success with over 30 participants from 5 countries.

User statistics

During 2012 samples from altogether 19 research projects were analysed in Kuopio facility. The scientific context in the projects was diverse, including various nutrition research related projects like dietary biomarkers of Nordic diet and intervention studies with various setups like whole grains, different berries in both human studies and animal feeding trials. Other setups have pertained issues e.g. the effect of smoking or alcohol/drug abuse during pregnancy. Out of those projects, 10 have been from the UEF, 4 projects from Finnish collaborators, and 4 projects from foreign collaborators from Sweden and Spain, and one company customer from France. When including the host department projects, altogether ca. 15 000 sample injections were performed during 2012 (note: two column approach with two ionization techniques means that most of the samples were analysed with four injections). Additionally several thousand of other metabolite samples were analyzed using other HPLC and mass spec techniques that are available at the facility. Out of the performed analyses >10 publications are expected to be submitted 2013.

The number of groups using services in Helsinki in 2011 was 16 of which 14 were local, and 2 domestic. The services have been expanded during 2012 to include also international academic collaborations (see Table 1). The focus of the projects has been mainly on analysis of plant hormones and other plant primary and secondary metabolites including phenolic compounds and waxes but includes also drug analysis (synthesis products) and identification of unknown signal transduction metabolites (pathogens).

At FIMM two projects, one from FIMM and the other from University of Helsinki, were finished by end of 2012. There are already several projects in pipeline and 4 of them were finished in the beginning of 2013. Out of these projects, 10 projects are from Finnish collaborators (Viikki campus, Turku, Kuopio, Meilahti hospital, FIMM and Biomedicum Helsinki), 4 from foreign collaborators (UK and Spain),

and one commercial project from Helsinki is under negotiations. The diversity of scientific projects is very wide including metabolite profiling of human dietary intervention studies, human mitochondrial dysfunctional study, population based studies and so on. The applicability of our method is extended to different biological sample types including biofluids (serum, plasma and cell culture supernatants); tissues (brain and liver) from both human and mouse origin; cells (adherent and suspension cultures); and *C.elegans*. From the collaborative studies, we have already submitted one manuscript and several are in pipeline to be submitted by end of 2013.

Table 1: Metabolomics consortium user base and income in 2012.

	BCK	FIMM	BCH	Total
Campus	10	1	9	20
National	4	1	1	6
International	5	–	3	8
Service income, e	47 100	12 350	30 090	89 540

Participation in international, Nordic and European infrastructures

The BF metabolomics consortium is not part of any European infrastructure networks. Instead, all centers have international collaborative projects where the facility services have been used. BCK has hosted scientists visiting from Sweden (NordForsk project) and Spain (Spanish governmental grant) to conduct metabolite profiling of samples from nutritional study setups. Additionally, a French food company has used our services on a large sample set from animal feeding trial. BCH has collaborated with Wood Buffalo Environmental Association (WBEA), Canada and Umeå Plant Science Center, Sweden on metabolite profiling of plant natural products and plant hormones and non-targeted analysis of root leachates with Ben-Gurion of the Negev, Israel. FIMM has many international ongoing collaborative projects from University of Cambridge (UK), Sanger Institute (UK), and University of Rey Juon Carlos (Spain) and few more are in pipeline, which shows the demand and applicability of the FIMM metabolomics services at international level.

During 2011 the BF Metabolomics technology platform continued to take shape, as the last instruments were purchased and installed. The year 2012 was the period for very intensive method development, expansion of customer base, and final structuring of the services, which all are now up and running.

STEM CELLS AND BIOMATERIALS

NETWORK

Stem Cells and Biomaterials Infrastructure Network

Coordinator of the network: Timo Otonkoski, BCH
Members: Olli Silvennoinen, IBT, Ulla Pirvola, BI; Mikko Lammi, BCK; Seppo Vainio, BCO; Olli Lassila, BioCity

http://www.biocenter.fi/index.php?page=stem-cells-and-biomaterials

Stem cell research is a rapidly developing area of biomedicine. Recent stem cell technologies have opened up several novel avenues for biomedical research, such as developing disease models, drug development, tissue regeneration and development of functional organoids.

The efforts of the BF network are directed to obtain knowledge and protocols to generate stem cells from different sources. The network aims also to develop adult stem cell-based tissue engineered biomaterial implants and organoids. A special emphasis is put to develop techniques to generate and use the so called induced pluripotent cells (iPS) from committed permanently differentiated cells. The discovery that somatic cells can be reprogrammed into pluripotency via only a few developmental control genes has opened new horizons for stem cells in e.g. derivation of patient specific cellular disease models for basic and applied research. Propagation of pluripotent cells from patients permits for the first time detailed studies on the molecular biology of human disease mechanisms and the use of such cells for development of novel therapeutics. In the long term the iPS cells should provide a unique way to develop technologies for obtaining immunologically tolerated cells for cell and tissue transplantation.

The main challenges of the network are: 1) how to channel and validate stem cells to specific cell lineages and functional cell types, 2) how to use these in tissue engineering and regeneration, and 3) how to use these as models for drug screening and organoid development.

PLATFORM

Stem Cells and Biomaterials Technology Platform

Chair of the consortium: Timo Otonkoski, BCH, Biomedicum Stem Cell Center (BSCC)
Members: Olli Silvennoinen, IBT; Marjo Yliperttula, Faculty of Pharmacy, Viikki Facility; Mikko Lammi, Jari Koistinaho, BCK, Stem Cell Center

Achievements in development and restructuring of technology services during 2010–2012

The Stem cells and biomaterials technology platform was established in 2010 to provide induced pluripotent stem cell (iPSC) technology and biomaterial expertise to the scientific community. Biocenter Finland funding for the consortium was extremely timely as it allowed to develop the iPSC activities in three Universities into technology service operation, and thereby enabled Finnish researchers to implement this technology early on for derivation of disease models from valuable patient samples. The main activities of the platform has been derivation of human iPSC lines from patient samples, development of human disease models and integration of novel xenon free biomaterial with iPS and hSC. These activities involve the development and provision of differentiation and analytical protocols and services, where all biocenters have their own focus and specialization areas. In addition, various types of training is provided.

Biocenter Finland funding was instrumental in establishing the national service platform. During the first year the emphasis of the platform was to set up the facilities and technologies, and during 2nd and 3rd year the activities have been directed to expand services provided for the clients, and optimization of the production of iPSC lines with genome non-integrating methods, which is now available in all units of the consortium. The profiling and development of unique differentiation protocols and analytical services continued in different biocenters, which involved close interaction between the platforms and subsequently resulted in a comprehensive scientific publication comparing the differentiation capacity of embryonal stem cells and iPSC (Toivonen, Ojala et al. 2013).

The services of the platform include provision of well-characterized human pluripotent stem cell lines upon request, reprogramming of primary cells provid-

ed by the clients using integrative (retroviruses) or non-integrative (Sendai viruses) methods, teratoma generation, differentiation of iPSCs into the desired cell type, longterm visualization of cultured cells and analysis platform using Cell-IQ, electrophysiological, Ca-imaging and functional analysis of differentiated cells, and training courses and tailored training packages for researchers. Helsinki has established differentiation protocols for hepatocytes, pancreatic islet cells and intestinal stem cells, Tampere for cardiomyocytes, peripheral neurons and retinal pigment epithelial cells, and Kuopio for GABA-ergic, dopaminergic

User statistics

Stem cell services provided	iPSC lines		Teaching (courses)		Hands-on training		Teratoma		Cell-IQ imaging		Electro-physiology laboratory	
	2012	Total 2010 -2012	2012	Total 2010 -2012	2012	Total 2010 -2012	2012	Total 2010 -2012	2012	Total 2010 -2012	2012	Total 2010 -2012
BSCC, University of Helsinki												
Number of customers	6	16	16	56	6	17	4	9	10	10		0
Academic	3	15	16	56	6	12	4	9	10	10		0
Non-academic	0	1	0		0	5	0	0	0	0		0
Volume	81[a]	179	16[b]	56	6[b]	17	37[c]	89	4348[d]	4348		0
Turnover	2012: 41 632 EUR (2010: 7 788 EUR; 2011: 27 865 EUR)											
University of Tampere												
Number of customers	7	20	15	35	0	0					1	2
Academic	5	13	15	35	0	0					0	1
Non-academic	2	7	0	0	0	0					1	1
Volume	65[a]	92	15[b]	35	0	0					1[b]	2
Turnover	2012: 8 520 EUR (2010: 10 000 EUR; 2011: 14 000 EUR)											
University of Eastern Finland												
Number of customers	3	10	0	64	3	6	1	2	1	3	0	4
Academic	3	9	0	62	3	6	1	2	1	3	0	4
Non-academic	0	1	0	2	0	0	0	0	0	0	0	0
Volume	15[a]	41	0[b]	64	3[b]	6	2[c]	3	20[d]	40	0[b]	4
Turnover	2012: 9 500 EUR (2011: 6 000 EUR)											
[a] cell lines, [b] customers, [c] tumors, [d] hours												
Stem cell biomaterials services provided	Biomaterials testing with SC		Teaching biomaterials interactions with cells		Hands-on training		3D imaging		Biomaterials cell printing			
Viikki BC, University of Helsinki												
Number of customers	6	12	25	75	8	19	4	9	4	7		
Academic	6	11	25	66	6	16	4	9	4	7		
Non-academic	0	1	0	9	2	3	0	0	0	0		
Turnover	2012: 8 000 EUR (2011: 3 500 EUR)											

and glutamatergic neurons and astrocytes as well as striatal muscle cells and chondrocytes. In addition, the platform has performed quality control and development projects on the storage time and conditions of donor samples including blood and skin biopsy that will be important for future biobanking applications. Biomaterial library and toxicity test with SC/iPSC as well as 3D imaging with gene delivery nanoparticles have been established and offered to clients. Annually a 30 hours course "Biomaterials interactions with stem cells" has been established and about 25 scientists have passed the course every year.

The number of iPSC lines generated has been steadily increasing. In 2012 the platform units have produced 161 iPSC lines, which is an increase of 50% compared to 2011. In total 312 iPSC lines were generated by the units in the period from 2010 to 2012. These lines have been subjected to various differentiation protocols. Most of the lines have entered the experimental phase, where the molecular and cellular pathogenetic events are studied in a variety of disease-specific cellular models. The disease models that have been developed or are being developed include Amyotrophic lateral sclerosis (ALS), retinopathy associated with long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, hepatic insulin resistance and liver failure in monogenic diseases enriched in Finland (MULIBREY and GRACILE), neonatal diabetes associated with known and unknown gene mutations, congenital hyperinsulinism, disorders of sexual development including Kallman syndrome, colorectal cancer in familial adenomatous polyposis of colon, familial Alzheimer's disease, lysosomal storage disease (PLO-SL), genetic cardiac diseases such as long QT syndrome (LQTS), hypertrophic cardiomyopathy, dilated cardiomyopathy, familial conduction defect, familial ventricular tachycardia (CPVT), and atherosclerosis, peripheral neuropathy, Kashin-Beck disease (KBD), familial Parkinson's disease, familial epilepsy and ALS and lysosomal storage disease PLO-SL. Several new control iPSC lines from healthy individuals were generated also by clients' request. In addition to dermal fibroblasts, other cell types such as myoblasts and peripheral blood T-cells were used to generate iPSC lines. In collaboration with National Health Institute (THL), Helsinki unit of the platform (BSCC) has successfully established the generation of iPSC from banked blood samples using non-integrative methods. However, platform had to turn down a request for generation of iPSC lines from hundreds client provided donor cells due to the limited processing capacity. There is a clear need for the development and adaptation of automatization processes for generation of iPSC lines.

The platform funding has allowed the development of analytical services and purchase of critical instruments for e.g. cellular electrophysiology laboratory. The broader scientific community has been increasingly using services for teratoma analysis and long-term imaging of cell cultures. From 2010 to 2012, all biocenters have provided training including hands-on training in human pluripotent stem cell related methods (total 23 participants), and courses for stem cell technologies and biomaterials (total 155 participants).

Participation in international, Nordic and European infrastructures

Active participation in international networks is an important function of the platform. Platform members representing University of Helsinki participated in the LIV-ES consortium of the EU 7 FP, aiming to develop optimal methods for the differentiation of hepatocytes. Platform members representing IBT participate in EU 7 FP (RISKYCAD), aiming at understanding different types of coronary atherosclerosis. BSCC and IBT both have participated in the ISCBI (International Stem Cell Banking Initiative) consortium that creates quidelines for translational requirements for pluripotent stem cell production, banking, testing and use. During year 2012 the consortium focused on setting quality standards for iPS cell production. Platform members representing BCK participated in ARISE consortium of FP7 and PROTEA ERANET consortium, aiming at understaning ischemic brain insults with iPS-derived cell models. In 2013, BSCC is participating in a large European IMI Call within the consortium "European iPS Cell Bank", and BCK in FP7 Call coordinating the consortium StemTreatAD and also a partner in a large international MarieCurie ITN program nEUROinflammation where iPSC-derived cell models are on focus.

NETWORK

Structural Biology Infrastructure Network (BFSB)

Coordinators of the network: Adrian Goldman, BI and Rik Wierenga, BCO

Members: Sarah Butcher, BI; Juha Rouvinen, BCK; Markku Kulomaa, IBT; Tiina Salminen, BioCity; Denis Kainov, FIMM; Jari Ylänne, University of Jyväskylä

http://www.biocenter.fi/index.php?page=structural-biology

Structural biology and biophysics cover a wide range of topics, from protein production via structure determination to biocomputational analysis. Biocenter Finland Structural Biology network (BFSB) comprises four major disciplines, all focused on experimental determination of macromolecular structures and elucidation of mechanisms by various time-resolved techniques. They are X-ray crystallography, nuclear magnetic resonance (NMR) spectroscopy, other time-resolved biophysical techniques, including high-resolution mass spectrometry equipment, and electron microscopy. This network also benefits from central resources, such as CSC – IT Center for Science Ltd. and from the BF Bioinformatics network.

The expert services provided by the network are organized into two technology platforms, those for X-ray crystallography and for NMR spectroscopy and mass spectrometry. Four of the biocenters have macromolecular x-ray crystallography facilities (BI, BCK, BCO and BioCity), while BI has a significant investment in nuclear magnetic resonance (NMR) spectroscopy, cryo-electron microscopy and novel three-dimensional methods and time-resolved optical spectroscopy (TROS), and BCK in high-resolution mass spectrometry. BFSB-partners have achieved an excellent division of labor and the BF network helps them to communicate efficiently with each other.

Structural biology emerging technology platform

In addition to X-ray crystallography and NMR and mass spectrometry technology platforms BF has funded "Gateways to structures: Filling the gap in protein production" platform in 2012. The funding decision was based on the SAB evaluation of applications of new technology platforms in 2011. The activities of this platform are reported in the emerging technology platform chapter (page 63).

PLATFORM

NMR Spectroscopy and Mass Spectrometry Technology Platform

Chair of consortium: Perttu Permi, BI, Finnish Biological NMR Center (FBNMR)

Member: Juha Rouvinen, BCK, High-resolution Mass Spectrometry Facility

Achievements in development and restructuring of technology services during 2010–2012

Molecular biosciences, as we recognize it today, is a composition of interdisciplinary techniques trying to characterize molecular interactions in varying level and scale. Both NMR and native high-resolution mass spectrometry are major and emerging technologies which have great potential to advance research in different branches of biomedicine and biotechnology. The NMR and mass spectrometry consortium stands unique in Finland, not solely due to rare, yet expensive, instrumentation but also to immense potential of these techniques in the field of bio- and material sciences and their interface. The characteristic features are versatility, high resolution and sensitivity which are important to increase accuracy and reliability of research when working with large and complicated biomolecules and heterogeneous media. Owing to very expensive instrumentation, high running costs as well as limited availability of dedicated operating personnel, the most efficient mode of action for ultra-high field NMR and MS systems is a core facility. The consortium is convinced that investments put into development of high field NMR spectroscopy and mass spectrometry technologies will increase scientific competitiveness of Finnish molecular biosciences and beyond.

The NMR laboratory of the Institute of Biotechnology is a national facility, since 2001 National Biological NMR Center (FBNMR). One of the four spectrometers in the facility, a 600 MHz NMR system, has

been upgraded in 2011 by our partner, VTT technical research centre of Finland. This instrument has the latest 1H,13C{15N/31P) cryogenically cooled probehead and electronics (e.g., digital receiver), and is also fully equipped for protein NMR studies. In addition, it has fully automatic sample changer with a capacity of 510 samples for metabo(l/n)omics studies. The majority of the funding provided by Biocenter Finland is used to purchase a completely new 850 MHz NMR spectrometer, equipped with the latest generation NMR console and cryogenically cooled probehead. Electronics and cryogenically cooled probehead of another 600 MHz spectrometer will be upgraded to digital NMR console and the next generation cryo-cooled probehead. Due to the serious financial and administrative issues the purchase order had to be postponed to the beginning of 2013. Consequently, installation of the new 850 MHz instrument and upgrade of 600 MHz spectrometer will take place at the end of 2013. In addition to superior resolution, the new 850 MHz instrument enables studies of more dilute samples and offers superior sensitivity for salty samples.

In 2010–12 the focus of NMR facility has been in the development of protein production for NMR studies. Protein production service provided to customers includes design of expression construct for NMR studies that increases expression levels and solubility, which in turn translates to decreased material costs and increased success rate. In NMR service development emphasis has been put especially on dynamical systems i.e. proteins that either lack a well-defined three dimensional structure (intrinsically disordered proteins) or display elevated dynamics between structural domains, or interact transiently with their binding partners. As a result, services provided by FBNMR have been instrumental in studies of several proteins and complexes that were not amenable to high resolution studies by X-ray crystallography.

While it is possible to utilize streamlined and automated protein structure determination protocols, these are rarely useful when trying to meet customers' needs. Therefore, human intervention is often required to address specific scientific questions and usually this person is structural biologist in FBNMR. Despite the needs for NMR-driven structural characterization of proteins and their interactions are steadily increasing within the scientific community in Finland, a lack of experts in the field is becoming a rate limiting step. It is then of utmost importance to provide sufficient support for core units to warrant breadth of customer service.

During 2010–2012, FBNMR received several requests for service in the field of solid state NMR. Given the growing interest both nationally and internationally to the expanding field of biosolid state NMR, we reckon that fitting one of the spectrometers up with solid state NMR capacity is justified in terms of facility development.

User statistics

	2010		2011		2012	
	Groups	Metrics	Groups	Metrics	Groups	Metrics
NMR Spectroscopy						
local	11		11		11	
domestic	13		15		12	
international					2	
industry	2		2		1	
Total	26		28		26	44[1] /350[2] /3 000[3]
Mass Spectroscopy						
local			4		6	
domestic			16		18	
international			3		2	
industry						
Total			23	2 200[4]	26	2 720[4]

Metrics NMR:

[1] Number of isotopically labeled proteins produced in FBNMR in 2010-2012; [2] Number of spectra recorded for structure determination of proteins (estimate) in 2010-2012; [3] Number of spectra recorded in total (estimate) in 2010-2012

Metrics MS:

[4] Approximate number of measured spectra

The high-resolution mass spectrometry facility is located at Biocenter Kuopio, Department of Chemistry, University of Eastern Finland. FT-ICR mass spectrometry was installed in 1996. It was upgraded in 2005–2007, excluding the 4.7 Tesla magnet. The majority of the funding provided by Biocenter Finland was used for purchasing of a new 12 T superconducting magnet which installation was completed in January 2011. The new magnet provided dramatic improvement both in resolution and sensitivity, especially when measuring larger proteins and complicated mixtures. The high-resolution mass spectra from different protein samples provided by a number of laboratories have showed the significance of high-resolution analysis. A large number of protein variants and unexpected modifications, not observable with conventional methods have been found. There are now only six laboratories in Europe with this level of instrumentation. In 2011 Biocenter Finland provided additional 150 k€ funding for supplementary items. In December 2011, a new ionization robot (Triversa Nanomate, Advion) was installed. It allows fully automated sample handling and provides very gentle ionization, thus it will be exclusively used for native mass spectrometry (native MS) measurements. Additional items purchased include an atmospheric pressure photoionization source, which allows mass analyses of less polar/hydrophobic biomolecules; the acquisition of a nano/micro-LC system (which implementation has been delayed because of problems in software); and desorption electrospray ionization source (Prosolia) to detect biological molecules from the sample surface. In autumn 2011, a project, supported by TEKES and biotechnology companies, was initiated in order to utilize FTICR technology in the analysis of industrially significant protein materials like immunoglobulins and enzymes.

Both the high-resolution mass spectrometry instrumentation at the Structural Biology Center and instrumentation at the Finnish National Biological NMR center represent unique world-class facilities, thus promoting specialization as a part of restructuring of scientific research in Finland. On one hand, the high-resolution NMR and MS spectrometry consortium establishes techniques that are complementary to other high-resolution, but static, techniques. On the other hand, they are mutually complementary to each other by enabling studies of dynamics, protein interactions, and kinetics with high sensitivity and resolution.

Participation in international, Nordic and European infrastructures

As a member of the BF Structural biology infrastructure network, the platform has followed the development of Instruct, the ESFRI infrastructure for structural biology in which both NMR and mass spectrometry are included. Our next step is to become National Affiliate Center of Instruct in order to strengthen our community further.

PLATFORM

X-ray Crystallography Technology Platform

Chair of the consortium: Adrian Goldman, BI, Protein Crystallisation Facility

Members: Rik Wierenga, BCO, Protein Crystallography, Oulu X-ray; Tassos Papageorgiou, BioCity, Protein Crystallography Core Facility

Achievements in development and restructuring of technology services during 2010–2012

The FIX-UP BFSB (Biocenter Finland Structural Biology) technology platform received funding through the BF-infrastructure funding scheme for upgrading and expanding X-ray equipment in Finland, and the upgrades of equipment and infrastructure have been implemented according to our proposal. The new equipment has very much enhanced the X-ray infrastructure for the benefit of life sciences in Finland. Our plan was to partition the work so that Oulu would become the chief data collection centre in Finland and provide a gateway to remote data collection that Turku would become a regional centre, and that Helsinki would become the national characterisation and crystallisation centre. We have successfully achieved this, and the achievements are listed under four headings: equipment upgrades, service provision, software development, and user training.

Over the last three years, all of the available equipment money has been spent on the following major pieces of equipment:

i. Purchase of Wyatt/Shimadzu system for semi-micro SEC/MALS including UV/Vis, multiple-

wavelength static light scattering, fluorescence, and refractive index detectors (2010) (Helsinki).

ii. Purchase of a TTP Labtech Mosquito LCP robot for growing crystals of membrane protein lipidic cubic phase (2011) (Helsinki).

iii. Purchase of a Rigaku Desktop Minstrel UV for examination of crystals, including those grown in lipidic cubic phases (2012) (Helsinki).

iv. Purchase and installation of a Bruker microfocus Microstar X-ray generator, equipped with Helios mirrors, the X8 PROTEUM -kappa goniometer and a CCD PT[135] area detector (2011/2012) (Oulu).

v. Purchase and installation of a Rigaku microfocus micromax 007 HF generator with Varimax optics, part-funded by local funds (2011/operational in 2012) (Turku).

Our goal in service provision has been to provide a clear and effective pathway from a purified protein/macromolecule to a solved structure. To that end:

a. We provide protein characterisation (unfolding studies measured by fluorescence; protein aggregation and sizing by chromatography/ multiple angle light scattering) crystallisation and imaging facilities. These have been used by over 30 different groups in Finland and worldwide on 109 different crystallisation projects, and we provide advice and training on how to proceed with a crystallisation project.

b. Another important service we provide is the provision of random screens for crystallisation at cost-effective prices: these screens are in use in Helsinki, Turku, Jyväskylä and Oulu; and we also provide services to design new screens based on hits within these screens. This service provides an important complement to our crystallisation services.

c. We provide a service enabling data collection and also advice on data collection strategies, including crystal testing, in Oulu and in the regional service in Turku leading to 36 completed structures (2010-present).

One of the reasons why x-ray crystallography is a dominant force in solving structures has been the ready availability of high-quality, free software to simplify and automate tasks. We are involved in two software development efforts.

a. We have developed new web-based imaging software, PiXray with a simple modular architecture to allow visualising crystallisation experiments. PiXray is capable of taking images from three different imaging platforms (Thermo Rhombix, ExploraNova and Rigaku Minstrel) and present them in a platform-independent way for scoring using MySQL as a database. The images are tagged with screen information from the three platforms to allow design of new crystallisation conditions in the Rhombix or Minstrel software.

b. We have added new modules to the PiMS data-tracking package, one providing the possibility to view and annotate the results of crystallization experiments. The annotation option allows us to document the subsequent crystal handling and structure determination process (including the PDB-entry code) for a selected crystal of each drop of a 96 well crystallization plate. This module also facilitates discussions on the crystallographic experiments between students and supervisors. The PiMS IT-infrastructure will in the future allow remote access to its database. This project is setup in the context of Instruct, in collaboration with staff at the STFC in Daresbury, UK and Diamond in Oxford, UK.

The two national centres (Helsinki and Oulu) have both organised international courses in their respective specialities at the EMBO course level. Helsinki has organised week-long advanced courses in crystallisation and characterisation in 2010, 2011 and 2012. They have had typically 16-20 students at the Ph.D. to postdoctoral level from Finland, the Nordic countries, and further afield. The international lecturers have included Martin Caffrey (Trinity, Dublin), Janet Newman (CSIRO, Australia) and Vadim Cherezov (Scripps, USA). The courses, including a mixture of practicals, demonstrations and lectures have been very well-received by the students.

Oulu has organised an international course focussing on data collection and data processing, including remote data collection, in 2012. The course, supported by Biocenter Finland and by FP7 program Biostruct-X, has been very well-appreciated and has disseminated important knowledge around Finland. Remote data collection at Diamond has been included. The new data collection setup has increased training possibilities for inexperienced users and was so used during the most recent international course as well as for several local courses.

We have prepared brochures and posters providing information on the expertise in each of the

centres and we organised a series of roadshow lectures, posters and tutorial events on our expertise in Turku, Helsinki, Tampere, Kuopio and Oulu in November 2011 to February 2012. These roadshows increased awareness of our expertise in the Biocenters. We also continue to meet yearly as part of FinnBox (the Finnish Biological Crystallographers), which has been combined with the national BFSB meetings.

The Turku regional data collection centre is also part of BioXLabs (www.sci.utu.fi/projects/biokemia/bioxlabs/), a regional structural biology consortium formed to enhance coordination of activities. Courses at the Masters level on X-ray crystallography and structure interpretation are offered at each University. Further courses are currently in preparation at a more advanced level.

User statistics

	BI Helsinki	BCO Oulu	BioCity Turku
Campus	9	6	2
Local University	8	2	2
Other Universities	11	2	3
Non-academic	2	1	2
International	2	2	3

*By group leader: the total number of projects and users would be about three fold higher.

Crystallisation has been performed on 109 different protein/macromolecule systems, with a total of over 200,000 crystallisation experiments (2010-present), leading to over 40 structures deposited. With the Proteum X8 system (2011-present) 40 data sets were collected, 29 structures were solved, and 6 structures have been deposited, while with the Rigaku micromax (2012-present), 15 data sets have been collected and seven structures deposited. We expect these numbers to grow by about 25% over the next three years, as the technology platform was not fully operational until 2012.

Participation in international, Nordic and European infrastructures

The Finnish biological community in general and the crystallographers in particular are actively involved in the European synchrotron institutions. We have very good access to the ESRF beamlines through the FinnProCC BAG, coordinated by Goldman, Helsinki and through a similar one at Diamond, coordinated by Kajander, Helsinki. Data collection is also carried out at MAX Lab, DESY and BESSY. In addition to data collection, SAXS and SRCD experiments are routinely performed. FIX-UP collaborates with important EU infrastructures including the EU Biostruct-X training initiative, the EU ESFRI Instruct activities, and the development of the new MAX IV synchrotron setup in Lund as well as the European Spallation Source that is being built there. The BFSB network currently has User Group status with Instruct, and will apply to become an Instruct National Associate Centre in the summer, thus extending the involvement of Finnish structural biologists with Instruct. We participate in Finnish (FSRUO) and European (ESUO) synchrotron user organisations on the development of synchrotron radiation for scientific research, as well as being actively involved in the guidance of the ESRF (Goldman is Head of Delegation for Nordsync in 2012). For the future it will be important for the Finnish user community to remain actively in contact with both current and future large European infrastructures.

TRANSLATIONAL TECHNOLOGIES

NETWORK

Translational Technologies Infrastructure Network

Coordinator of the Network: Olli Kallioniemi, FIMM
Members: Kalle Saksela, BCH; Mart Saarma, BI; Asla Pitkänen, BCK; Robert Winqvist, BCO; Jorma Isola, IBT, Noora Kotaja, BioCity; Krister Wennerberg, FIMM; Olli Pentikäinen, University of Jyväskylä

http://www.biocenter.fi/index.php?page=translational-technologies

The network coordinates two technology platforms: those on Drug Discovery and Chemical Biology (DDCB) for discovery and proof-of-concept validation of therapeutic molecules, and Tissue Biobanking for biobanking and biomarker research. The DDCB platform focuses on drug discovery and development, and is linked to the European EATRIS and EU-Openscreen infrastructures, coordinated in Finland by FIMM. This platform will further develop several existing strong capabilities in Finland, such as chemoinformatics/structural biology, high-throughput screening, as well as in vivo testing. The aim is to facilitate the capabilities for discovering inhibitors to interesting targets, and to carry out proof-of-concept testing in vivo. This platform should optimally bridge the gap between academic research and industrial interests to drug discovery.

Finland is well-positioned to play a major role globally in the development of biobanks and biomarker capabilities. Systematic large-scale biobanking activities are ongoing at a few sites, such as at the University of Tampere (with Tampere University Hospital) and in Helsinki (Institute for Health and Welfare (THL), University of Helsinki/FIMM and HUS, Helsinki University Hospital). The focus of the BF Tissue Biobanking technology platform is on development of virtual microscopy based methods particularly for cancer biobanking. The BF platform is linked through FIMM and THL to the European-level biobanking infrastructure (Biobanking and Biomolecular Resources Research Infrastructure, BBMRI). The Finnish BBMRI node comprises not only the large scale Finnish population cohorts, but also numerous investigator-initiated sample collections and clinical data sources and the BF biobanking technology platform. In the future, automation of sample acquisition and fractionation technologies, as well as generation of arrayed tissue and molecular resources will be developed together with demographic and clinical annotation of the samples.

Translational technologies emerging technology platform

In addition to Drug discovery and chemical biology and Tissue biobanking technology platforms BF has funded "Recombinant antibody generation" platform in 2012. The funding decision was based on the SAB evaluation of applications of new technology platforms in 2011. The activities of this platform are reported in the emerging technology platform chapter (page 64).

PLATFORM

Tissue Biobanking Technology Platform

Chair of the consortium: Jorma Isola, IBT
Members: Johan Lundin, FIMM

Achievements in development and restructuring of technology services during 2010–2012

A translational technology platform with focus on web-based access to digitized tissue samples and associated clinical/phenotypic data has been jointly implemented by the Universities of Tampere (IBT) and Helsinki (FIMM). Through the platform we can now provide services of whole-slide tissue digitization, web-based viewing of scanned gigapixel-size tissue samples and quantitative microscopy readout of tissue stainings (brightfield immunohistochemical and fluorescence) as well as automated, pattern recognition based morphological classification.

The platform serves as a national core facility offering services for microscope specimen scanning, networked virtual microscopy, image analyses and linking of results to clinical and phenotypic data. FIMM and IBT have jointly provided these services. Recently, also BioCity Turku has joined the consor-

tium and introduced a network node with scanning capabilities, webmicroscopy, biomarker analytical services and access to the almost 400 000 diagnostic tissue specimens stored at the local Auria Biobank.

The platform has also brought resources from a European level through a recent funding from the world's largest public-private partnership IMI, to establish a similar platform for the PREDECT project developing advanced, transferable in vitro models for breast, prostate and lung cancers.

User statistics

Webmicroscopy is used in the Helsinki area by 19 research groups in BCH, FIMM and Helsinki University Central Hospital working in diverse fields. In Turku, eight research groups use services of the platform. They are also used in Tampere by several groups as well as in Oulu and Kuopio. Virtual slides stored on the platform's servers are used in all Finnish medical faculties in cell biology, microscopic anatomy and pathology teaching.

Participation in international, Nordic and European infrastructures

The translational technology platform is used within the IMI-funded PREDECT project between 9 academic, 3 SME and 7 EU pharmaceutical partners, developing target validation models for breast, prostate and lung cancer with a total budget of approx 20 million euro (predect.webmicroscope.net). The webmicroscopy portal is provided as a platform for data sharing also within the EU funded projects BioMedBridges (biomedbridges.webmicroscope.net) and Systems Microscopy. Webmicroscopy software is also in use at Karolinska Institutet, University of Oslo and VU University Medical Center in Amsterdam, and by the European disease model program (http://pathpath.eu/).

New improved virtual microscopy techniques have been developed and provided as a service also to commercial customers and to the organizers of the European Congress of Pathology. More than 400 European labs have participated in webmicroscopy-based external quality assurance rounds during 2012, and in yearly large-scale virtual slide seminars (>2000 participants).

PLATFORM

The Drug Discovery and Chemical Biology Technology Platform (DDCB)

Chair of the consortium: Olli Kallioniemi, FIMM

Members: Krister Wennerberg, FIMM, Chemical Biology Lab (co-chair); Antti Poso, BCK, Drug Design and Synthesis Laboratory; Pia Vuorela, BioCity, Drug Discovery of Natural Products Laboratory; Arto Urtti, BCH, Centre for Drug Research (CDR); Olli Pentikäinen, University of Jyväskylä, Computational Bioscience Laboratory

Expert members: Antti Pursula, CSC, Merja Perälä, VTT

http://ddcb.fi/en

Achievements in development and restructuring of technology services during 2010–2012

The Drug Discovery and Chemical Biology plaform (DDCB) was set up to coordinate and integrate the significant infrastructure and expertise in drug discovery and chemical biology that exist in Finland and make it available to the scientific community with the ultimate goal of providing users with the tools to enable world class chemical biology research and eventually facilitate the translation of academic discoveries to clinical application. Within DDCB, each partner contributes with complementary expertise and service and each partner provides expertise in complementary target classes and biological systems. In addition to the five funded partners (at BCH Helsinki, BCK Kuopio, Biocity Turku, FIMM and the Biocenter-affiliated University of Jyväskylä), two additional non-biocenter partners, VTT Medical Biotechnology and CSC, add significant value, expertise and outreach to the platform.

With the support of Biocenter Finland funding and participating institutions, we built the DDCB platform and its national services during the years 2010–2012. It is important to note that the involved sites were not set up to provide open access national infrastructure services prior to the funding as individual sites or as a consortium and it was only through Biocenter Finland support this was made possible. Numerous new services were established:

- Four screening sites provide their services to the platform with different sets of expertise and edge competencies.
- The system of using an advisory panel that can help guide projects and users to the best strategies and services continued to be used and was successful in that many projects within the platform utilized coordinated services from several DDCB partners.
- A DDCB Technology Transfer Advisory Board consisting of national experts of biotech and pharma drug discovery and -development as well as venture capital, investment banking and market analysis was established to aid the transfer of projects and discoveries with commercial potential to IP protection, licensing and further development.
- Consortium meetings were held on a quarterly basis where we also invited users to present and discuss their projects.
- As an indication of the successful building of the service infrastructure, user support doubled on an annual basis: 18 user-initiated projects were supported in 2010, 35 in 2011, and 71 in 2012.
- A platform web site was been set up as a common user interface: www.ddcb.fi
- Olli Pentikäinen, University of Jyväskylä was recruited to the consortium, adding unique expertise in molecular modeling and virtual screening for protein-protein interaction modulators as well as modeling and chemistry expertise towards developing fluorescent small molecule biosensors.
- The national screening collection (>140 000 compounds) is now available for all biocenter researchers in Finland, both for projects run at DDCB sites as well as in assay-ready formats for multiwell plates that can be used in the researcher's own laboratory. A searchable web interface linked to compound request submission is being established will be publicly available in the second half of 2013. The natural products database (2500 compounds) is also available in an OpenOffice database format and can be used for in silico screening.
- The national compound collection has been used in combination with virtual screening after which hit compounds can be cherry-picked for confirmatory testing in an efficient and affordable manner.
- A novel drug sensitivity and resistence platform that allows users to profile cellular model systems and ex vivo clinical samples against an annotated set of signal transduction inhibitors and approved oncology drugs was established and has already been used for more than 400 screens by the user community with more than 10 publications being published, under review or in preparation as a result.
- More than 300 known bioactive compounds, primarily signal transduction inhibitors, are available in a unique proof-of-principle experiment volumes for researchers upon request.
- An integrated service allowing for validation of small molecule compound integrity by mass spectrometry has been established and actively used in screening projects to confirm the identity of screening hit compounds before further optimization and followup testing was done.

Multiple upgrades of instrumentation and infra-structural capacities:

- Three acoustic nanoliter dispensers with complementary capabilities and a dedicated robotic platform have been aquired for DDCB services. These dispensers allow for distribution of the national chemical collection in user-defined formats and importantly for new screening technologies where ultra-minaturized assay formats can be run and drastically cut reagent costs for users in high throughput screens. This development has also resulted in a collaborative development agreement with Labcyte, the company making the dispensers.
- A confocal HCS instrument was installed for use in 2011 to provide services in second stage screening with complex cell models.
- A multi-well plate dynamic light scattering instrument was installed and is available for quality checking of the libraries in terms of solubility.
- A Bioflux 200 instrument was added at Biocity Turku to allow for label-free high throughput imaging of cells under flow and sheer conditions.
- High quality compound management and storage systems were established at the operational sites.
- A state-of-the-art multilabel a plate reader was acquired and made available as an open access instrument for the user community.
- A quadrupole mass spectrometer was purchased to assist compound integrity and metabolism testing.
- A plate washer for washing of live cells in screening assays was installed and is operational since early 2012
- An Incucyte FL live cell monitoring microscope was acquired and is now available for the user community.

User statistics

	BCH/CDR	BCK	BioCity / ÅAU	FIMM	University of Jyväskylä	Total
Total user research groups	31	11	5	23 (3 jointly with UEF, 1 with CDR)	5	71
Local	24	3	2	14	0	
National	6	6	1	5	3	
International	1	1	0	1	0	
Non-academic	0	1	0	1	0	
Service revenue 2012 (€)	2 000 (most service costs covered by BF and internal funds)	20 000 (industrial project)	2 000 (supply costs)	79 000 (supply costs and equipment usage)	0 (service costs covered by BF and internal funds)	

As examples of metrics, assay development support and HTS optimization was provided for 26 projects, 250 high throughput screens were performed (including DSRTs) and virtual screening and molecular modeling for 17 projects.

Participation in international, Nordic and European infrastructures

As a part of the buildup of DDCB, our platform also built strong ties to similar research infrastructures in other Nordic countries so that expertise and access to technologies are shared between the countries. These collaborations now mean that researchers in Finland can access specialized chemical biology technologies that may exist in other Nordic countries but not in Finland, and vice versa, that users from other countries can access the technologies and expertise in Finland. We have been sharing compound acquisitions with Sweden to access more and diverse chemical collections and have supported several projects.

Our platform is directly linked to two emerging ESFRI roadmap initiatives. First, we are coordinating the plans for technologies and screening centers with the preparatory phase of EU-OPENSCREEN, a European research infrastructure with very similar goals as DDCB; open access infrastructures for high throughput screening, chemical biology and small molecule probe development. EU-OPENSCREEN operations, which are scheduled to start in 2015 are expected to be highly supplementary with the ongoing operations within DDCB and the infrastructures that now are supporting the national platform will also serve the larger European research communities for EU-OPENSCREEN projects. Second, we are also actively taking part of the work of the Small Molecules product platform of the EATRIS translational ESFRI roadmap. In addition, CSC and FIMM are involved in the work of BioMedBridges and ELIXIR, ESFRI roadmap projects focusing on the coordination and management of biological information. Furthermore, members of the platform were involved in the preparation of the "European Lead Factory" EU FP7 IMI project call (www.imi.europa.eu), are participating in the buildup of an International Chemical Biology Society (www.chemicalbiology.org) and one project initially developed with DDCB services and infrastructures was approved as a project under the NIH Roadmap Molecular Libraries Program (mli.nih.gov) in the USA.

VIRAL GENE TRANSFER AND CELL THERAPY

NETWORK

Viral Gene Transfer and Cell Therapy Network

Coordinator of the network: Seppo Ylä-Herttuala, BCK
Members: Akseli Hemminki, BCH; Kari Alitalo BCH; Aki Manninen, BCO; Eric Dufour, IBT; Eleanor Coffey, BioCity; Emmy Verschuren, FIMM; Maija Vihinen-Ranta, University of Jyväskylä

http://www.biocenter.fi/index.php?page=viral-gene-transfer

Gene transfer techniques are an important tool in studies of gene function as well as in the clinical evaluation of new treatments. In research the most important impact of efficient transient and stable gene transfer methods is the generation of new cell lines or animal models for the basic research of protein functions. Many of these methods are based on utilization of viruses as means to target and deliver genes into appropriate cells. More recently, advances in the RNAi-methodology enable the same delivery method to be used to efficiently silence specific genes in cells.

Successful work with the sophisticated viral methods requires special expertise and strict safety considerations both of which are found in all biocentres in Finland. In particular, the A.I. Virtanen Institute in BCK, specializing in gene transfer methods for drug development, has a long-standing experience with strict regulations and requirements essential for gene therapy based approaches for human patients. Some of their products are already in clinical trials. The AIV Institute is responsible for coordinating the development and production of gene transfer vectors at national level in Finland.

Viral gene transfer and cell therapy emerging technology platform

In addition to viral gene transfer and cell therapy platform BF has funded "LentiGEMM - Lentiviral platform for creating genetically engineered mouse models" in 2010–2012. The funding decision was based on the SAB evaluation of applications of new technology platforms in 2009. The activities of this platform are reported in the emerging technology platform chapter (page 65).

PLATFORM

Viral Gene Transfer and Cell Therapy Technology Platform

Chair of the consortium: Seppo Ylä-Herttuala, BCK, National Virus Core Facility, A. I. Virtanen Institute
Members: Kari Alitalo, Akseli Hemminki, Juha Klefström, BCH, Helsinki Virus Vector Core Facilities; Aki Manninen, BCO, Virus Vector Core Facility; Eric Dufour, IBT Virus Vector Facility; Eleanor Coffey, Ketlin Adel, BioCity, Viral Vector Facility; Maija Vihinen-Ranta, University of Jyväskylä

Achievements in development and restructuring of technology services during 2010–2012

Before the establishment of the VGTCT network, several "private" virus facilities existed. These small labs were located in many places in different Biocenters, often in inadequately equipped lab spaces with no quality control systems in place. No standardized protocols or techniques were used but many researchers were developing their own approaches for the production of viral vectors. It was recognized that it is totally unreasonable for every researcher to implement his/her own viral production laboratory because of high operational risks and prohibitively high costs, in addition to heavy burden and workload caused by various permissions required by national and EU control agencies. VGTCT network was established to solve the above disorganized situation because it was widely recognized in all biocenters that there is a rapidly increasing need for high quality viral vectors in almost every field of modern biomedical research.

VGTCT is an excellent example of well-functioning Biocenter Finland network now providing established vector services to a large number of domestic and international researchers and biotech companies. In addition to the production of high quality vectors and standardization of the methods, the mission of VGTCT network has been to promote the use of viral gene transfer methods in Finland and to support development of novel gene delivery vectors and applications. VGTCT has created a consortium of all biocenters strengthening their collaboration and supporting their specific profiles.

BF funding has been vital for the establishment, maintenance and development of VGTCT network services. Currently, recombinant viral particles are sold in miniscale (100 ul) and midiscale (1,5 ml). Larger volumes are also available (>6 ml) by individual requests. The current VGTCT network now allows us to produce, quantify and functionally test several different virus preps simultaneously within 2–3 weeks waiting time for researchers with competitive prices. Compared to VGTCT services, for example in AAV production commercial suppliers produce AAV of lower titer and for about fourfold higher price with production time at least twice as long as in the VGTCT network. Non-commercial academic affiliated AAV Core facilities provide similar service as we do, but for a higher price, and, compared to the VGTCT, the production time is considerably longer. Similar situation exists with adenoviral, lentiviral and baculoviral vectors. VGTCT network uses state-of-the-art technology to serve customers in Finland, Northern Europe and other countries.

Scientific development of the viral vectors has also been carried out in the VGTCT network. In various research projects we have tested many different recombinant adenovirus, lentivirus and AAV vectors in vitro and *in vivo* in order to provide researchers with better tools for their applications. For example VGTCT Helsinki core has optimized conditions, which work best for gene transfer in cultured cells of different origin and in most mouse tissues in vivo. Tissue specificity is achieved through using tissue-specific regulatory promoter elements. VGTCT Helsinki core has provided a large number of glycerol stocks of TRC shRNA lentiviral backbones as a new service and VGTCT Turku core has developed FACS-based services for the analyses of transduced cells and AIV Kuopio core has further developed large-scale production services and baculoviral vectors for gene transfer applications.

Oulu core has set up a service where transgenic mice can be generated with lentiviruses injected into the perivitelline space of mouse eggs to generate transgenic animals. The lentitransgenics-service is an efficient tool to screen for possible embryonic phenotypes prior to making traditional transgenic animals. Based on clients demand, VGTCT Tampere core has included virus-based iPS generation in their services. In 2011 the network has also expanded its operations to University of Jyväskylä to include live viral vector imaging services.

In addition to virus production, VGTCT network offers biosafety training, reagents for recombinant virus production and biosafety tests to exclude replication competent virus. Training of new users is a key component of the operation in each vector core. At the international level, VGTCT network organized an "EMBO Course in Viral Vectors" in AIV Kuopio core in 2011 and a practical "Retrovirus-mediated RNA interference" in 2012 in Oulu core where participants got hands-on introduction to RNAi methodology and its viral applications.

Considerable extra effort has also been devoted to assist users in the preparation of Gene Technology Law applications and risk assessments of new viral vector projects. There have been several incidents before our coordinated actions where new virus vector users have failed to acknowledge the Gene Technology Law requirements. However, the situation has now been significantly improved due to coordinated actions of the VGTCT network.

User statistics

	2010	2011	2012
Customers			
local	75	91	129
domestic	27	29	22
international	29	28	38
non academic	7	12	14
Volume/number of preps	630	712	785
Income, e	26 446*	51 036	64 840

* Helsinki (Klefström) and Oulu income are not available for 2010.

For years 2013 onwards, clinical grade full GMP virus vector production in AIV National Virus Vector Laboratory has been removed from the VGTCT network since operating environment and facilities for clinical GMP gene therapy vector production are very different from standard research grade vector production facilities in VGTCT network. GMP facilities include very significant costs for the operation, maintenance and continued microbiological and environmental controls, quality assurance and release tests for materials used for the GMP production. Therefore, these operations are not any more included in the VGTCT network.

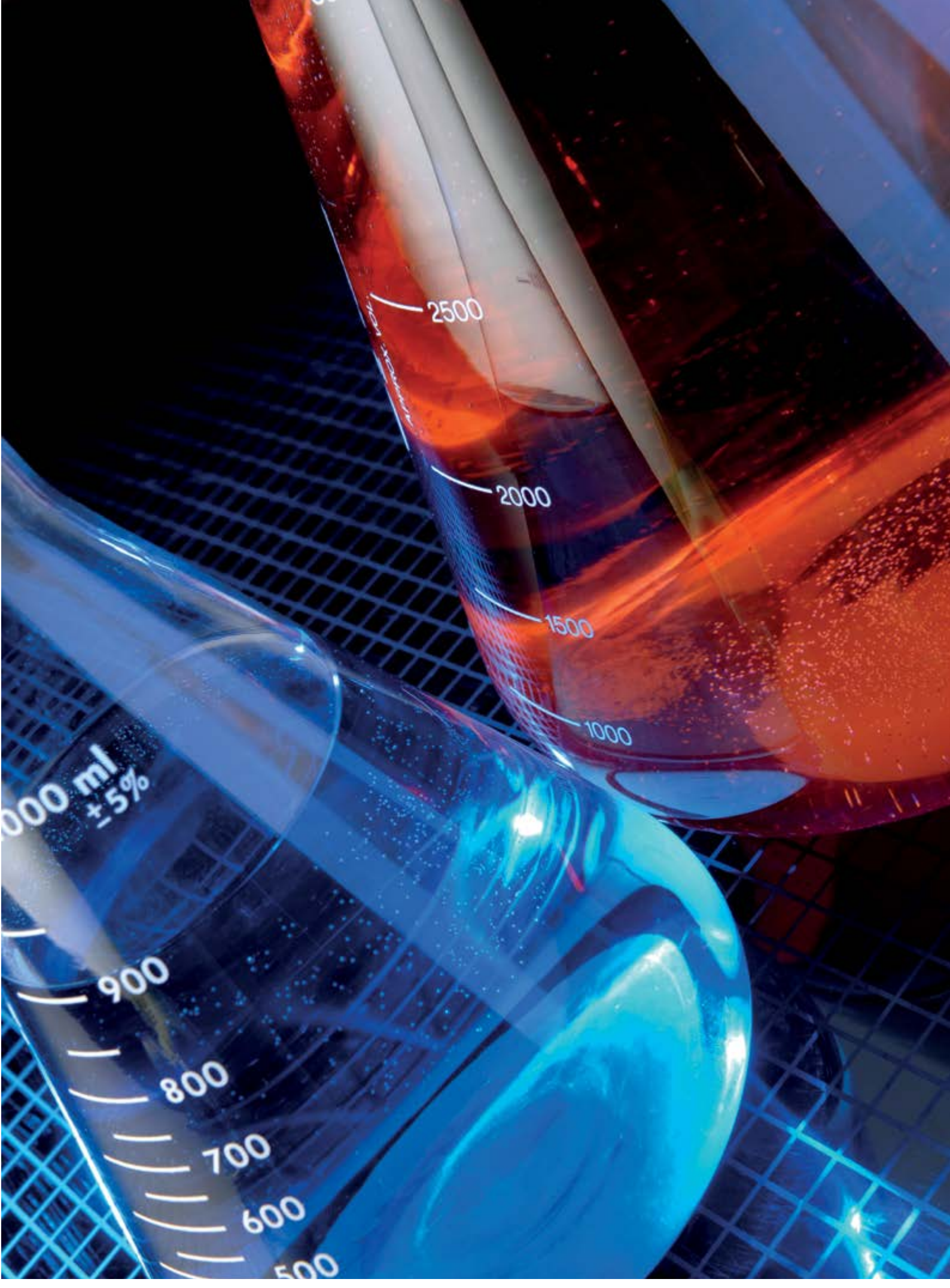
User statistics

VGTCT network has successfully served both the scientific community and biotech companies with high quality viral vectors. It is clear that there is a significant demand for this kind of services in Finland and abroad. Table on the previous page shows number of customers and viral preps produced in the VGTCT network. It is anticipated that the proportion of customers from abroad will increase steadily in the coming years in addition to continuously increasing demands from the domestic users of virus vector technology.

Participation in international, Nordic and European infrastructures

VGTCT AIV Kuopio virus core has participated in five EU FP7 programs (CliniGene, Baculogenes, BAMI, Biomagscar and AdVance) and is a member of EATRIS network. Also, it has been designated as a core facility of virus vector production for a Transatlantic Leducq Research Network. VGTCT Helsinki virus core participates in EU & EFPIA Innovative Medicines Initiative –PREDECT which aims to the development of services lowering the bar for Finnish academic- global pharma industrial collaborations in the area of virus gene transfer services. ■■■

In addition to virus production, VGTCT network offers biosafety training, reagents for recombinant virus production and biosafety tests to exclude replication competent virus. Training of new users is a key component of the operation in each vector core.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PLATFORM

Small animal molecular imaging: RTI unit

Chair of the consortium: Kim Bergström, Faculty of Pharmacy, University of Helsinki
Member: Raimo K. Tuominen, Faculty of Pharmacy, University of Helsinki

Achievements in development and restructuring of technology services during 2011–2012

Real-Time Imaging (RTI) unit was established in University of Helsinki Viikki campus in 2009. RTI unit obtained a top-of-the-line single photon emission computed tomography / computed tomography (SPECT/CT) imaging instrument in January 2010 and became a BF-facility in October 2011. The unit has increased its throughput significantly after getting support from BF in 2012. The unit has served 12 national customers during 2012, including one client from industry, and one international customer from Europe. Average SPECT/CT days during 2012 has been 6.3 days per month. There is a capacity to increase the throughput if necessary support will be provided.

Small animal SPECT/CT is a versatile non-invasive molecular and morphological imaging technique that is used regularly in biomedical research and preclinical drug development. SPECT/CT equipment is an important addition to the imaging technologies in Helsinki; E.g. 90% of transgenic animals in Finland are located in Helsinki region, and SPECT/CT is used in longitudinal imaging studies of the transgenic rodents. SPECT/CT is also part of the Helsinki Functional Imaging Center (http://www.hfic.helsinki.fi/). RTI is an operational service unit and is offering efficient and wide-spread services of the latest small animal imaging technology in Finland.

User statistics

	2011–2012
domestic customers	12
international customers	1
SPECT/CT Project days/ month	6,3
Comments	2011: October-December

Participation in international, Nordic and European infrastructures

SPECT/CT unit has participated in the following infrastructures during 2011–2012: COST TD1004 (http://www.cost.eu/domains_actions/cmst/Actions/TD1004) and Innovative Medicines Initiative (IMI) COMPACT project (http://www.compact-research.org/).

PLATFORM

Proteome-Wide Profiling of Kinase-Substrates

Eleanor Coffey, Turku Centre for Biotechnolgy, BioCity Turku

Achievements in development and restructuring of technology services during 2012

We optimized KSID technology to bypass the need for 2D gels and tested its efficacy using kinases with known substrate binding motifs for assay validation. The phospho-peptide purification strategy was modified to maximise phosphopeptide detections by including acidic and basic eluates and pooling of fractions. Efforts to stably label phosphopeptides using a non-hydrolysable ion raised unexpected technical issues and the strategy was modified accordingly and successfully. The work was carried out with Peter James's lab at the University of Lund where the required mass spectrometry time was available for method development.

In parallel with successful methods development a screen of phosphopeptide loss in WT and JNK-/- brain was compared (over a lifetime). This analysis yielded 25,000 unique phosphopeptides. Importantly methods were used to ensure that the phosphopeptide analysis was quantitative (i.e. TMT labelling and Progenesis tools were incorporated). Among these, 40% of KSID-derived substrate phosphopeptides were down-regulated or completely lost in knockout brains. This provided proteome-wide, in vivo validation of the substrates and hence the technology.

Bioinformatics tools development

An important addition to the project was a postdoc from McGill to advance the computational aspects in identifying kinase substrates and motifs. Novel motif finding requires a large number of input sequences, while minimizing false positives of non-biological relevance, such as sequences detected due to downstream kinase signalling and maximizing the machine learning classification sets. For these analyses an open-source Python analysis program was used. Compared to javascript or other scripting languages more commonly applied to web development, Python has been adopted by the scientific community. This means that scripting has been optimized for scientific questions and datasets typically resulting from scientific experiments. These approaches are applied to automated data extraction, compression, ratiometric determinations and motif prediction, and make it possible to assemble data ready for further data mining using tools such as MetaCore for pathway analysis and disease prediction.

User statistics

Three research groups (2 local, 1 international) have initiated KSID screens during 2012. One local group has expressed an interest in carrying out a screen. We have not yet invested in hard-core broad advertising of the method, but instead continue to develop on a collaborative basis for interested groups. This will continue in cooperation with the University of Lund until additional instrumentation is secured by the Proteomics platform at Turku Centre for Biotechnology.

Participation in international, Nordic and European Infrastructures

An important collaboration was set up with Amos Bairoch (University of Geneva) who is profiling proteome-wide kinase substrate data for the neXtProt database. The technique is part of a FP7 MC-ITN project commencing in September 2013 (coordinated by Coffey). We are interested to cooperate with ESFRI (e.g. INSTRUCT) via the local proteomics unit.

PLATFORM

Gateways to Structures: Protein Production for Biophysical and Structural Characterization

Chair of the consortium: Pirkko Heikinheimo, BioCity
Members: Markku Kulomaa, Juha Määttä, IBT, Protein Service Facility; Olli Ritvos, BCH, Haartman Institute Protein Production Service

The protein service platform of the Structural biology and biophysics network aims to become a platform providing broad methodology to screen and express novel proteins in most efficient way. This requires continuous development of processes making it possible to easily transition from screening phase to sufficient size of scale up taking advantage of the most appropriately chosen protein expression methodology. This work also requires developing, streamlining and perfecting the methodology approaches in protein overexpression and purification.

Achievements in development and restructuring of technology services during 2010–2012

Tampere Protein Service facility offers services in protein production and characterization. *E. coli* and *Spodoptera frugiperda* (baculovirus expression system) cells are used for protein expression. The facility has special focus on protein interactions. The customers are from universities and companies from Finland (90%) and abroad (10%). Virtually all Finnish universities are represented within the customers.

During the period 2010–12, Tampere Protein facility has established wide user base and there has been constantly increasing need for the services: the number of customers during 2012 tripled as compared to 2011 and there was also significant increase in the charged income. With the support from BF, Council of Tampere region and University of Tampere, the facility has been equipped with top-quality instruments enabling biophysical characterization of proteins and upgraded cell culturing facilities.

Helsinki protein production facility at Haartman Institute complements the Protein services platform by offering services for generating recombinant protein expressing mammalian CHO-S and HEK293 cell lines and their use in protein expression scale up. Helsinki facility has its focus on expressing and purifying secretory mam-

malian proteins in native form or as fusion molecules in milligram to gram quantities. The coordination between the Tampere and Helsinki protein expression platforms offers the choice of three robust protein expression platforms that the clients can use for satisfying their specific protein expression needs. Guidance, counselling and planning aid is provided to help the customers to decide whether to use in parallel several expression methods or to choose the most appropriate recombinant protein expression approaches for their research subject. During 2011–2012 the customer base of the Helsinki facility has increased to over 12 with both local, nationwide domestic and international clients.

An important part of the operation in both Tampere and Helsinki has been training of the personnel. At the moment, the Tampere facility is operated with dedicated laboratory technicians, who are trained and supervised by the coordinator of the facility (Määttä). In the Helsinki facility a full time protein service dedicated bioengineer technician has been thoroughly trained and is supervised by the facility staff scientist and coordinators. This mode of operation and coordination ensures high quality of the work, and makes it possible to start new projects fluently. During 2010–12, our mode of operation has been significantly improved towards scrutinized project tracking and reporting. Some of the customers have technically participated to the laboratory work as visitors.

User statistics

User statistics: research groups (or other customers) who have used the services.

	BHC	IBT Tampere	Total
Total number of research groups	12	7	19
local	4	0	4
domestic	8	7	15
international	4	0	4
Instrument hours	47 cell lines	22 virus constructs	45 032
Annual financial turnover	33 540	7 073	40 613

Participation in international, Nordic and European infrastructures

With focus on our national mission we have not yet officially networked our activities with other Scandinavian or European initiatives but discussions have been initiated. Prof Ritvos is currently in discussions with a network of academic protein expression service providing units in Sweden coordinated by Drs Helena Berglund and Tomas Nyman (SciLifeLab and Karolinska institute, Protein Science Facility, psf.ki.se). Planning meetings are being held to explore the possibilities to facilitate especially recombinant protein expression needs of numerous Finnish-Swedish research collaborations and cooperation to researcher training in this area.

PLATFORM

Recombinant Antibody Generation Platform

Urpo Lamminmäki, University of Turku, Department of Biochemistry and Food Chemistry

Achievements in development and restructuring of technology services during 2012

Biocenter Finland started its funding to the platform in 2012. A major effort was made to streamline the operational practices of the antibody generation platform. First of all, measures were taken to optimize the antibody expression and purification procedures. The developed approach combining bottle scale bacterial cultures and rapid affinity purification steps gives yields from 1 to 10 mgs of pure antibody and is currently used in a routine manner. To speed up the phage display selection process, we developed a rapid technique for quantification of the phage particles during the selections (Lehmusvuori et al., Biotechniques. 2012, 53:301-3). With our homogeneous assay technique phage can be quantified in 20 min while the conventional plating method requires o/n incubation and is laborious. Considering future possibilities, a very interesting technological step was taken related to use of high-throughput sequencing tools for the readout of the library selection outputs (performed in collaboration with sequencing facility in Center of Biotechnology, Turku). Our single framework library is especially well-suited to the use current NGS technologies (such as Illumina's) with fairly limited read-length. Owing to the single framework design all the clones can be amplified with a single pair of primers. Sequencing of the extremely divergent CDR-H3 region of the antibodies in the library enables identification of the clones as well as PCR based retrieval of

the clones of interest (= showing enrichement). Bioforte BLItz biosensor instrument was acquired by the host department to facilitate the determination of the binding affinities/kinetics of the developed antibodies. Work aiming to develop a rapid affinity maturation procedure based on our proprietary highly powerful mutagenesis technology (Huovinen et al., PLoS One. 2012;7(2):e31817) was started and is on-going. As an indication of the performance of our library technology, we were in 2012 contacted by MRC-T (Medical Research Council-Technology), one of the pioneers in the field of antibody therapeutics, and signed a Plan-of-Intent concerning the use of our antibody library platform for the development of novel therapeutic antibodies. The first pilot project in this context has already been successfully completed from our behalf.

User statistics

Number customers: 11 (9 academic, 2 industrial)
Number of target antigens: 16
Number of local users 8, international 3 (currently there are 3 on-going projects involving altogether 4 targets with academic users in Helsinki and Tampere).

Participation in international, Nordic and European infrastructures

Our host unit (Department of Biochemistry and Food Chemistry / Biotechnology) is a partner in Biomarker platform of EATRIS. Within the EATRIS network, the principal role of our host unit will be to provide services related to assay development. By enabling the development of tailor-made high quality affinity reagents, the recombinant antibody generation platform is expected to be in a central role in the future EATRIS-activities at our unit.

PLATFORM

Emerging Technology Platform: Lentiviral Platform for Creating Genetically Engineered Mouse Models (LentiGEMM)

Chair of the consortium: Juha Klefström, Institute of Biomedicine and Genome-Scale Biology Program, BCH

Members: Emmy Verschuren (FIMM) (vice-chair); Jukka Westermarck (BioCity) (vice-chair); Iiris Hovatta (BCH); Pipsa Saharinen (BCH); Sergey Kuznetsov (FIMM); Mikko Laukkanen (BioCity); Kari Airenne (BCK)

http://www.biocenter.fi/index.php?page=emerging-technologies

Achievements in development and restructuring of technology services during 2010–2012

LentiGEMM develops new virus-aided gene transfer technologies to generate transgenic animal tissue models of human diseases, especially in neurological diseases and cancer. These methods will enable researchers to introduce disease genes or gene function altering components directly into the animal tissue or alternatively, use stem-cell technologies to recreate gene function altered tissues in a live animal. The technology has broad applications in life sciences and pharmaceutical research. LentiGEMM integrates lentiviral gene transfer (Lenti) and genetically engineered mouse model (GEMM) methods to establish genetically modified mouse tissues and tissue explants within a time frame of months. By enabling targeted genetic modification of the mouse tissue of interest without a need to establish transgenic breeding colonies, the technology will reduce animal costs and the number animals needed. This lowers the bar for use of transgenic and knockdown in vivo models for studies on basic biology and disease mechanisms.

The service model of LentiGEMM is to primarily focus on new technology development to be offered to the scientific community through technology transfer and outsourcing of technology to existing core facilities/infrastructures. The LentiGEMM service model gives research groups an active role in developing and modernizing research infrastructures, for example virus and animal facilities. This service model is dynamic and customer-oriented, allowing rapid transfer of latest science technologies from individual laboratories to core facilities. A division of tasks has been agreed upon based on the expertise of eight research groups in four biocenters. These include a novel lentivirus generation platform in BCK based on the baculovirus technology to meet the needs of larger animal and clinical trials, a methodology for lentivirus-mediated gene transfer to specific regions of the mouse brain (BCH),

a procedure for the isolation and culture of mouse embryonic allantois membranes and establishment of a mouse endothelial cell culture system for testing of the efficacy of shRNA lentiviruses and a lentiviral delivery to mouse allantois ex vivo (BCH). In the field of cancer biology, LentiGEMM technology using a combination of gene inactivating viruses and animal tissue grafting techniques, allowed researchers to inactivate a suspected cancer-protecting gene in living mouse mammary tissue (BCH). In FIMM a procedure for isolation and lentiviral transduction of primary mouse mammary epithelial cells with their subsequent transplantation into a mammary fat pads of recipient mice and a set of lentiviral vectors to combine fluorescent/bioluminescent imaging with germline Cre-mediated gene activation, and cDNA/shRNA expression were developed. In BioCity Turku, development has focused on optimization of mesenchymal stem cell transplantation and cell survival as well as on lentiviral production, transduction and lymphoma transplantation protocols.

During June 2010 – December 2012, LentiGEMM created and transferred five new technologies to core facilities. The specific needs for LentiGEMM type of infrastructure were also considered in local animal facilities and new instrumentation has been installed per requests. Furthermore, LentiGEMM has brought individual research groups together to discuss on harmonization of biosafety procedures and the network has organized training on lentiviral gene transfer and animal techniques through graduate schools.

User statistics

During 2010–2012, LentiGEMM platforms generated five new services which are currently available through core facilities for academic and industrial customers. The numbers of customers and services provided are shown in the table. These services brought in user fees totaling 87.2 k€. Furthermore the LentiGEMM platform generated 225 k€ of income for animal and virus core facilities in Helsinki, Kuopio and Turku.

Table 1: LentiGEMM established services and revenues in 2011–2012.

LentiGEMM service	Service opening date	Services available (core/lab)	Price/unit (example volumes)	Revenues 2010–2012	Customers 2011–2012
Concentrated lentivirusparticles	06/2010	FuGU/Klefström	899€/1x380µl 2 075€/4x380µl 4x380µl	2010: 19,2 k€ 2011: 9,3 k€ 2012: 4,1 k€ Tot. 32,6 k€	12 research groups: 10 local, 2 domestic, 1 industry; 69 virus preparations
Sucrose-cushion purified lentivirusparticles	12/2011	FuGU/Hovatta	1128€/160µl	2011: 2,2 k€ 2012: 4,2 k€ Tot. 6,4 k€	4 research groups (local); 17 virus preparations
RT-PCR virus construct validation service	12/2011	FuGu/Klefström (pilot exp.)	1171€/5 constructs for 1 gene	2011: 2,2 k€ 2012: 3,8 k€ Tot. 6,0 k€	3 research group; 2 local, 1 domestic 19 validations
Mouse speed-backcrossing service (syngrafts)	06/2012	FuGu/Klefström	Custom	2012: 41,9k€	1 industry 331 mice

Table 2: LentiGEMM pilot services and revenues in 2011–2012

LentiGEMM produced service	Service opening date	Services available (core/lab)	Price/unit (example volumes)	Revenues 2010–2012	Customers 2011–2012
Ex vivo vascular culture model (mouse embryonic allantois membrane)	2012	FuGU/ Saharinen	400€/prep	2012: 0,25 k€	1 research groups: 1 domestic

OTHER ACTIVITIES

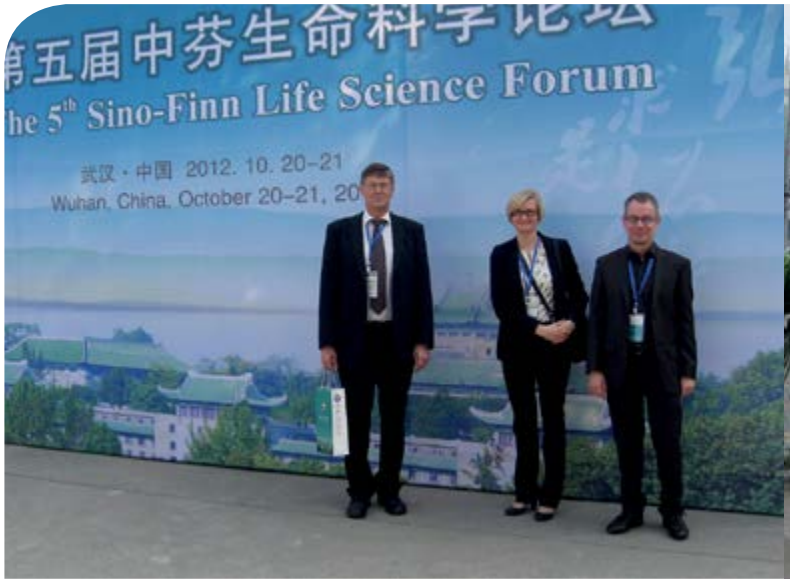
Provision of personalized support to research career development

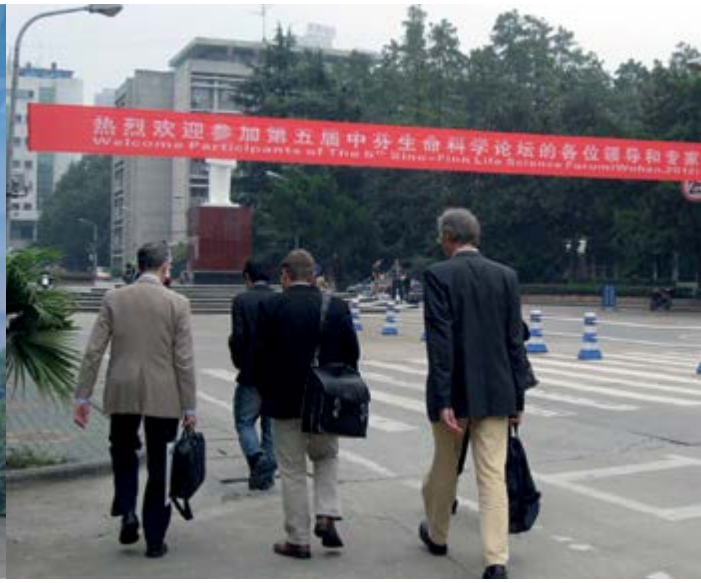
In summer 2010, Biocenter Finland opened a call for personalized support to research career development in areas that also serve to strengthen the technology platforms of Biocenter Finland. Two types of research career schemes were funded: (1) talented young principal investigators with excellent track records whose fixed-term appointments are coming to their end, and (2) returning scientists living abroad to bring expertise in novel technologies to Finland in key areas where gaps in expertise currently exist. To make sure that the applicants integrate into partner biocenters, the applications were invited through the partner biocenters which were also to provide part of the funding and a suitable working environment for the applicant.

In the end, funds were used to support nine young scientists to enter the next step of their research career. The program brought in one Finnish and two foreign scientists from abroad, and funded another two foreigners and four Finns to continue their career in Finnish biocenters. Based on their final reports, all funded scientists considered this type of support very important during the difficult transition from the first principal investigator (group leader) position to the next position that requires financial commitment from the organization and permits a successful principal investigator to continue his/her work. After BF funding ended, all but one have secured a position corresponding to their scientific level and all remain in Finland. One scientist took a position in pharma industry. All those funded through the program felt this type of a funding scheme is much needed in Finland to allow talented and highly motivated scientists to continue their career in research and service.

Sino-Finn Collaboration

Wuhan University hosted the 5th Sino-Finn Life Science Forum, on October 20–21, 2012. Altogether 11 principal investigators from Finnish biocenters, the staff of Biocenter Finland and a representative of SalWe Ltd participated in this 2-day seminar with Finnish and Chinese speakers. From China, the following institutions were represented: School of Medical Sciences, College of Life Sciences and Zhognan Hospital of Wuhan University, Sun Yat-sen University and Institute of Biophysics, Chinese Academy of Sciences and Huazhong University of Science and Technology. Finnish Ambassador Lars Backström from the Embassy of Finland, Beijing, honoured the Forum opening with his presence. After the Forum the Finnish delegation visited Shanghai Institutes for Biological Sciences (SIBS) to introduce current activities in Finnish biocenters and to explore possible future collaborations.





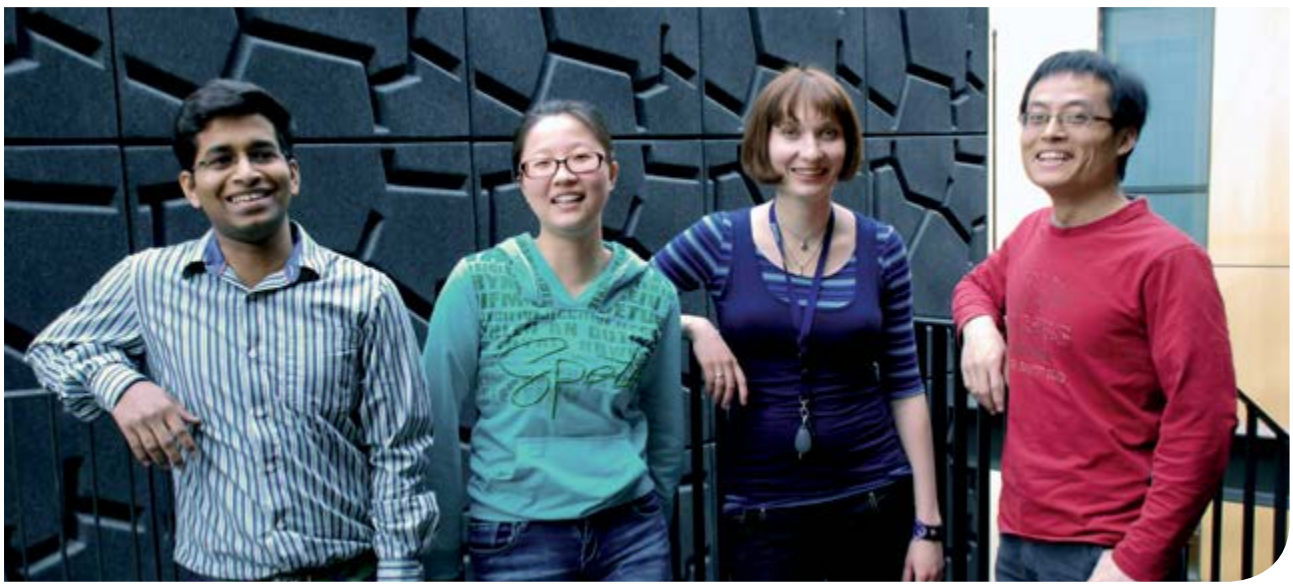
Biocenter Finland International Visitor Program

The first Biocenter Finland international visitor program was launched in 2010. The aims of this novel program were (1) to recruit high-quality students to enter doctoral training programs and (2) to recruit foreign postdoctoral researchers to Finnish biocenters. The start-up program was designed not to compete with the graduate schools/doctoral training programs in the biocenter campuses, but to provide them a possibility to screen potential international graduate students and postdocs. Funding was targeted to support short (6 month – 1 year) visits of prospective doctoral trainees and postdocs from abroad who were interested in conducting research in Finnish biocenters.

The program turned out to be a real success and was repeated and enlarged in 2011. The statistics of the international visitor program are impressive: with an investment of 1.1 M€, BF partner biocenters recruited a total of 28 prospective doctoral trainees and 32 postdoc to Finnish biocenter universities. These 60 internationally mobile doctoral students and postdocs moved to Finland from 12 European and 14 non-European countries. They were citizens of 29 different countries (14 European and 15 non-European): (number of visitors in parenthesis): Brazil (1), Cameroon (1), China (8), Cuba (1), Egypt (1), Eritrea (1), Estonia (1), France (1), Germany (6), Hungary (1), India (11), Iran (1), Italy (1), Japan (1), Macedonia (1), Malaysia (2), Nepal (1), Poland (2), Portugal (1), Russia (4), Singapore (1), Spain (1), Sri Lanka (1), Sweden (1), Switzerland (2), UK (2), Ukraine (1) and USA (2). In addition two Finnish postdocs returning from Japan and Canada were supported.

These statistics clearly indicate that Finnish biocenters can offer internationally competitive working environments that attract doctoral trainees and postdocs from East, South and West. Even more encouraging is the fact that 45 of the 60 international visitors have continued their career (doctoral training or postdoc) in Finland through other funding. Essentially all of the 15 visitors who returned to their home country or moved elsewhere, also report continuing collaborations with their Finnish host laboratory.

Happy portrait of four researchers supported in BF visitor program in Biocenter Oulu. In total, ten visitors were funded in the program in Oulu. From left to right: Mr. Umamaheshwaran Panneerselvam (originally from India), received his Master's degree at Nottingham Trent University, UK, and is currently working as a PhD student in Professor Johanna Myllyharju's group; Ms. Qi Xu came to visit Professor Seppo Vainio's group and has started her PhD training in Oulu in 2013; Ms. Nadiya Byts, originally from Ukraine, finished her PhD at University of Göttingen, Germany and works now in Myllyharju group; Qilai Huang, PhD, Nanjing University, China, ended up to Oulu through collaboration between Nanjing University and Gonghong Wei group at Biocenter Oulu.



BIOCENTER FINLAND ON NATIONAL AND EUROPEAN RESEARCH INFRASTRUCTURE ROADMAPS

In 2012 the Ministry of Education and Culture gave the Academy of Finland the task of establishing a high-level expert group on research infrastructures. Immediate tasks of this expert group ("FIRI expert group") nominated in April 2012 were (1) to update the national research infrastructure roadmap of 2009, (2) to make recommendations on distribution of annual FIRI funds to support national research infrastructures and Finnish participation in international research infrastructures particularly those on the ESFRI (European Strategy Forum for Research Infrastructures) roadmaps, and (3) to obtain a comprehensive picture of the research infrastructure scene in Finland. Obviously the FIRI expert group will be making several important decisions with direct consequences to BF.

Update of the national research infrastructure roadmap of 2009

The first national research infrastructure roadmap was based on information available in early 2008 at the time the first pan-European ESFRI roadmap was published. Although BF had been established in 2007, the infrastructure networks and technology platforms as they exist today were not yet fully organized for the first national roadmap. Since then the ESFRI roadmap has been updated twice, in 2008 and 2010, which has had a clear structuring effect on national infrastructures. From BF's perspective the update is a highly welcomed process as it gives us a possibility to present to the Finnish scientific community and international evaluators a fully functional nationwide research infrastructure which brings together essentially all national life science infrastructures. The principles of BF technology platforms, national-level specialization, avoidance of overlapping investments, and provision of top-quality services, technological support, open access to all services and transparent participation and pricing rules, are characteristics which were recommended by the international experts who evaluated the applications to the first roadmap. Although the new roadmap will not be a funding instrument *per se*, it will serve as a guide for future funding of research infrastructures at national level. The roadmap update process was initiated in late 2012. All host universities have included BF in their prioritized lists of infrastructures they support, so we remain optimistic that BF will be found on the revised national research infrastructure roadmap which will be published by the end of 2013.

Finnish participation in ESFRI infrastructures

Another timely task of the FIRI expert group is to make recommendations to Ministries and Government regarding Finland's participation in ESFRI infrastructures that are becoming operational in 2012–2013. The ESFRI process initially raised a lot of enthusiasm and optimism among the participating scientists, but their slow establishment as legal entities has become a source of considerable frustration. Many of the ESFRI infrastructures plan to seek for the ERIC (European Research Infrastructure Consortium) legal entity drafted for this purpose, but others have started operations as limited liability companies (Ltd or GmbH) or as a special project of an existing intergovernmental organization (EMBL).

Biocenter Finland scientists have been involved in all of the six BMS (Biological and Medical Sciences) Research Infrastructures on the first ESFRI Roadmap published in 2006. They participated in drafting of operational concepts of such infrastructures, their business plans and statutes. The European Commission provided funding for the Preparatory Phase of each BMS infrastructure and has also supported their further development through other funding instruments. Despite all this preparatory work the European governments have found it very difficult to agree on the terms of their participation in BMS research infrastructures. Major problem areas include the principles for determining national contributions towards joint budget, voting rights and the principles

of operation. Thus, seven years after publishing the first Roadmap only a few of the BMS ESFRI Infrastructures have started their operations. Finland has not yet become an official partner in any of the BMS ESFRI infrastructures.

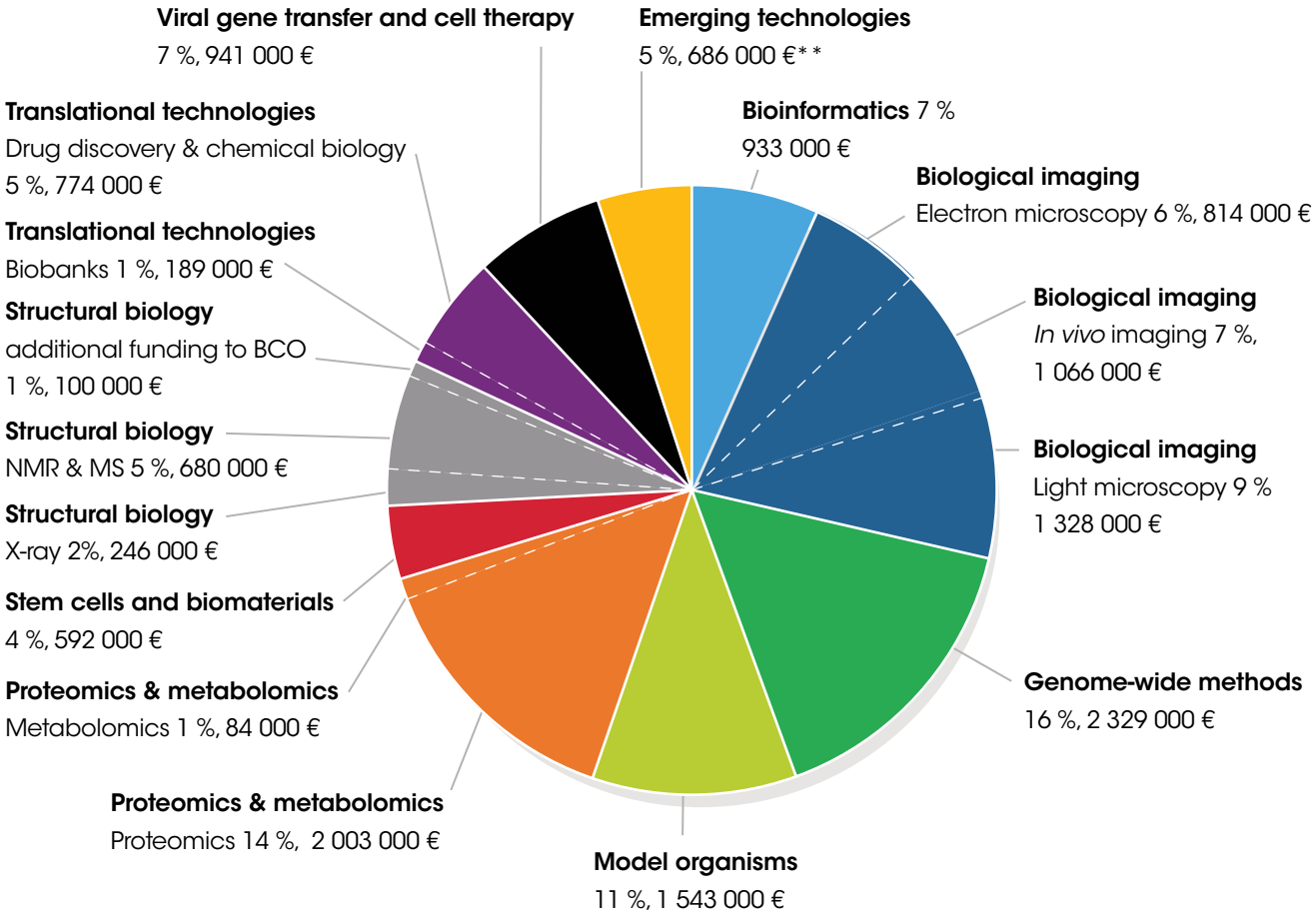
A typical feature of all BMS research infrastructures is their distributed structure into different operational sites through participating member states. The distributed nature of BMS infrastructures requires member states to organise their infrastructures into national nodes to build a proper interface with the pan-European ESFRI projects. In Finland the existence of BF infrastructure networks has provided a ready-made solution for the national node structures for essentially all nine BMS infrastructures where Finland is an active partner (Table). The research community is already well organized, has an updated inventory of equipment, samples and services at hand, and is therefore well prepared to enter the large European research infrastructures. In some fields the BF infrastructure networks correspond almost exactly to ESFRI projects, e.g. in biological imaging (Euro-BioImaging), structural biology (Instruct) and mouse biology and model organisms (Infrafrontier). In the field of bioinformatics (ELIXIR) BF network is involved, but national coordination occurs via CSC. In other fields the terminology of BF infrastructure networks does not correspond so well with the ESFRI Roadmap. However, even here the infrastructure networks provide natural links to BMS infrastructures; thus genome-wide methods, proteomics and metabolomics and translational research technologies (including biobanks) contain the same elements than BBMRI, EATRIS and EU-Openscreen, while those of stem cells and biomaterials and viral gene transfer and cell therapy have clear links to ECRIN. In all cases, BF scientists have participated in the preparation of concrete operational plans for the ESFRI projects to guarantee that their voice is heard in Europe when important long-term decisions regarding standardization of technologies, operating procedures, guidelines, access policies and other rules are made. BF and its infrastructure networks are willing to support this process and to function as national level structures for ESFRI projects during their construction phase. However, in the national research infrastructure roadmap update process, each ESFRI project was encouraged to make its own application for establishment of the required national node structure and for getting ESFRIs also on the national roadmap. As the goals of ESFRI and BF are very similar, provision of access to world-class research facilities and to overcome fragmentation of the BMS research landscape, we expect close collaboration between BF and the BMS ESFRIs to continue in the upcoming years.

Table. Summary of BMS ESFRI projects where Biocenter Finland scientists are involved

Roadmap 2006	
BBMRI	Biobanking and Biomolecular Resources Research Infrastructure
EATRIS	European Advanced Translational Research Infrastructure in Medicine
ECRIN	European Clinical Research Infrastructures Network
ELIXIR	European Life Science Infrastructure for Biological Information
Infrafrontier	European Infrastructure for Phenotyping and Archiving of Model Mammalian Genomes
Instruct	An Integrated Structural Biology Infrastructure for Europe
Roadmap 2008	
EU-Openscreen	European Infrastructure of Open Screening Platforms for Chemical Biology
Euro-BioImaging	European Biomedical Imaging Infrastructure
Roadmap 2010	
ISBE	Integrated Systems Biology in Europe

STATISTICS

Allocation of BF funding to technology platforms in 2012. Total funding for technology platforms in 2012 was 14,3 M€.



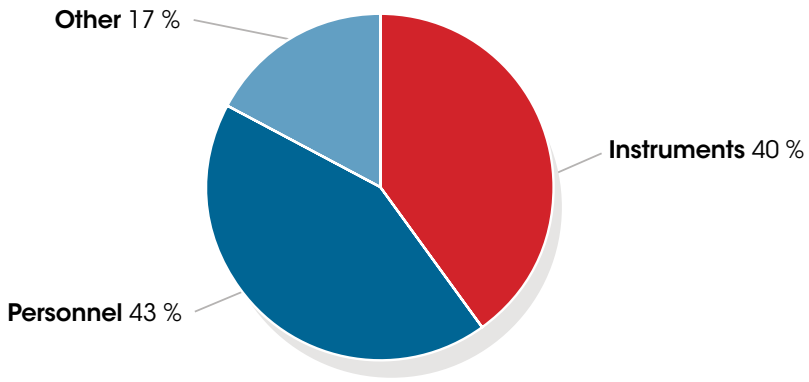
* BF Board allocated an additional 100 000 e grant for structural biology activities (instruments) in Biocenter Oulu.

** LentiGEMM 246 000 e, RTI 90 000 e, Proteome-wide profiling of kinase substrates/membrane proteins 70 000 e, Gateways to structures; protein production 200 000 e, Recombinant antibody generation 80 000 e.

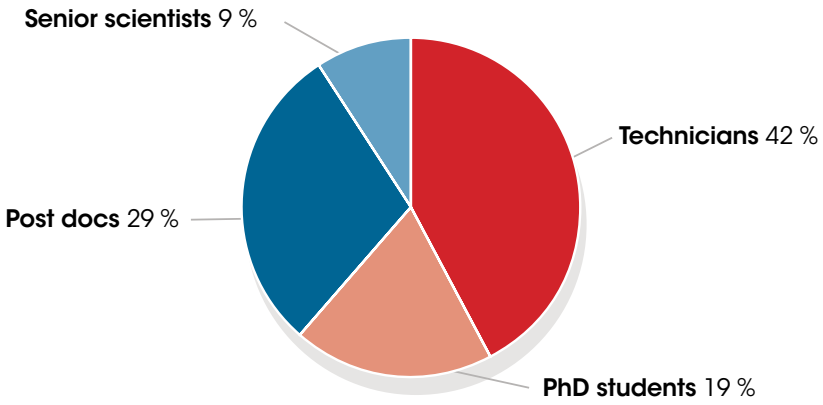
Allocation of BF funding to other activities in 2012

Research career development program 440 000 e; International visitor program 555 000 e. BF Board has also financially supported the coordination and training activities of the infrastructure networks in 2012.

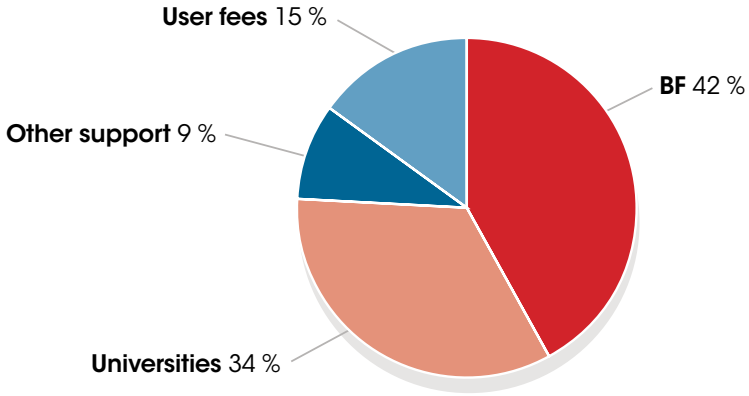
Distribution of BF funds used by technology platforms in 2012.
Category "Other" include small instruments (< 25 000 e), reagents and maintenance.



Breakdown of BF funding to technology platform personnel.
In total 1 785 person months, 149 full time equivalents.



The total funding of technology platforms by funding source.



MEMBER INSTITUTES

Biocenter Kuopio

Director: Professor Seppo Ylä-Herttuala

www.uef.fi/bck

Biocenter Kuopio (BCK) is an umbrella organization for research groups active in molecular medicine, biotechnology and pharmaceutical research at the University of Eastern Finland. In addition Kuopio University Hospital and six companies are members of BCK. The research profile of BCK is on molecular medicine of major diseases of high importance for health care, including cardiovascular diseases, neurodegenerative diseases and metabolism-related diseases. The strong areas are molecular and cellular mechanisms of the diseases, disease modeling, prevention and therapy of the diseases, gene and cell-based therapy, and pharmaceutical intervention as well as *in vitro* and *in vivo* imaging.

Biocentrum Helsinki

Director: Professor Lauri Aaltonen

www.helsinki.fi/biocentrum

Biocentrum Helsinki (BCH) is a large umbrella organization hosted by the University of Helsinki and Aalto University coordinating the multidisciplinary research in molecular biology, experimental biomedicine, biotechnology and bioinformatics. The research activities range from human molecular genetics to plant biotechnology and data analysis. The mission of BCH is to foster high quality research and collaboration between UH and Aalto campuses as well as to support the development and operation of research core facilities.

Biocenter Oulu

Director: Professor Johanna Myllyharju

www.biocenter.oulu.fi

Biocenter Oulu (BCO) is an umbrella organization which aims to enhance international, high-level research in the focus area of biosciences and health of the University of Oulu. BCO currently consists of 10 research projects and 3 junior investigator projects selected for fixed terms after international evaluation, 6 coordinator projects, 9 infrastructure core facilities and a doctoral program of about 110 students. The staff is ca. 270. BCO has a strong international research profile in extracellular matrix biology, structure-based biocatalysis, lipid metabolism and metabolic syndrome, organogenesis, and evolutionary and cancer genomics. The core facilities provide a continuum for studying the structure and function of proteins, the function of normal and diseased cells, and control of genes and physiological processes. Within Biocenter Finland the BCO infrastructure profile is focused on gene-modified mice, ultrastructural pathology of model organisms and X-ray crystallography.

BioCity Turku

Director: Professor Jyrki Heino

www.biocity.turku.fi

BioCity Turku is an umbrella organization supporting and coordinating life science and molecular medicine related research in the University of Turku and in the Åbo Akademi University. The two universities share one campus area which additionally houses the Turku University Central Hospital, the VTT (Technical Research Centre of Finland) Medical Biotechnology Unit and the THL (National Institute for Health and Welfare) Turku unit. The research groups working in these organizations are also active members in the six BioCity Turku research programs: Systems biology, Receptor research, Microbiology, Reproductive and developmental medicine, Diagnostics and Biomaterials. BioCity Turku core laboratories and research services provide top-of-line technology services in biological imaging, genomics, proteomics and disease models.

Institute for Molecular Medicine Finland FIMM

Institute of Biomedical Technology

Biocenter Oulu

BioCity Turku

Biocentrum Helsinki

Institute of Biotechnology

Biocenter Kuopio

Institute of Biotechnology

Director: Professor Tomi Mäkelä

www.biocenter.helsinki.fi/bi

The Institute of Biotechnology (BI) at the University of Helsinki is an independent research institute with a mission to increase knowledge in biotechnology and integrative biology and use this for the benefit of society. BI has research programs in Molecular cell biology, Developmental biology, Genome biology, and Structural biology & biophysics, and integrative programs in Quantitative biology and Patterning dynamics. BI has state-of-the-art facilities in imaging, model organisms, proteomics, genomics, bioinformatics, crystallography, and NMR. These are shared both locally as well as nationally as part of Biocenter Finland.

UNIVERSITY OF HELSINKI
INSTITUTE OF BIOTECHNOLOGY

Institute of Biomedical Technology

Director: Hannu Hanhijärvi

www.uta.fi/ibt

The Institute of Biomedical Technology (IBT) of Tampere University is dedicated to excel in basic and translational research and education in the fields of biomedicine. Its research activities cover diverse areas, including cancer, immunology, cellular biology, bioinformatics, biotechnology and stem cell-based regenerative medicine with a common aim of developing personalized medicine via new diagnostic and treatment methods. IBT also houses FinMIT, the Academy of Finland Centre of Excellence in research on mitochondrial genetics, disease and ageing. IBT is part of BioMediTech, a joint institute of University of Tampere (UTA) and Tampere University of Technology (TUT). The collaboration between the universities has enabled a unique research and educational environment. In the autumn 2012 UTA and TUT launched a single degree program with the objective to educate top-level experts in life sciences and medical technology.

UNIVERSITY OF TAMPERE

Institute for Molecular Medicine Finland FIMM

Director: Professor Olli Kallioniemi

www.fimm.fi

The Institute for Molecular Medicine Finland (FIMM) is an international research institute focusing on building a bridge from discovery to medical applications. FIMM investigates molecular mechanisms of disease using genomics and medical systems biology in order to promote human health. The three research focus areas are i) human genomics, ii) medical systems biology and iii) translational research. FIMM combines high-quality science with unique patient and biobank materials, and state-of-the-art technologies. The FIMM Technology Centre is focusing on genomics, sequencing, bioinformatics, high-throughput chemical and RNAi screening, and translational research technologies. FIMM operates a biobank infrastructure as part of the BBMRI.FI network, and is participating as a national node in EATRIS and EU Openscreen ESFRI networks. FIMM is part of the Nordic EMBL Partnership for Molecular Medicine with Heidelberg, Umeå and Oslo and is operated by the University of Helsinki, in collaboration with THL, HUS and VTT.

FIMM
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Nordic EMBL Partnership for Molecular Medicine

BF

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