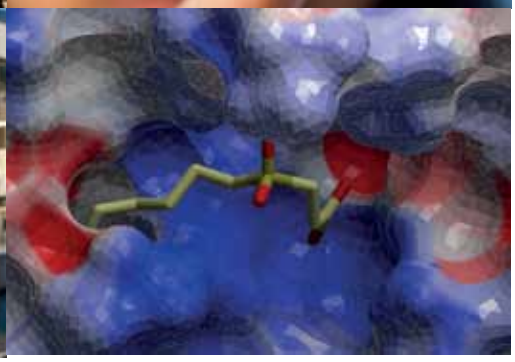
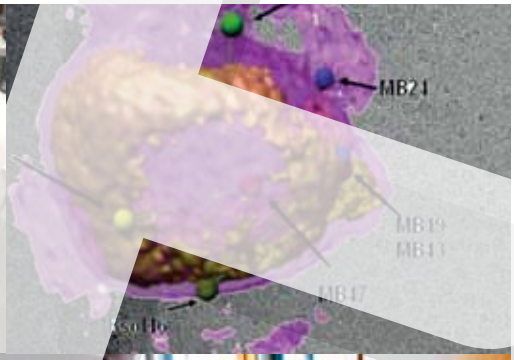


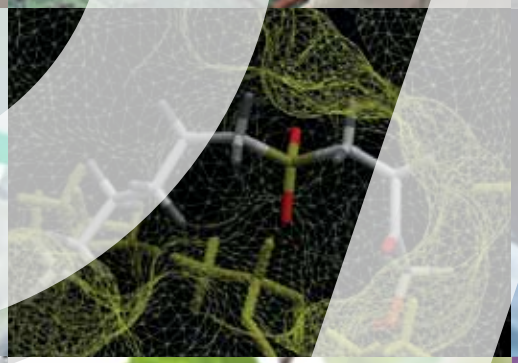


BF Biocenter Finland







ANNUAL REPORT 2011

BF

Biocenter Finland

www.biocenter.fi

Biocenter Finland Annual Report 2011

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Other photos: Veikko Somerpuro (2, 5, 18, 54); Ari Aalto (4, 9); Linda Tammisto (14, Leiomyoma research); Johan Lundin (16, Table screen); Visa Noronen (16, Screen wall); Hanna Oksanen (36); Jari Korhonen, Turku BioImaging (61, BF Infrastructure day); Sanna Leinonen (61, Sino-Finn); Jussi Tiainen (66, Biomedicum Helsinki); Jukka Lehtiniemi (66, Institute of Biomedical Technology).

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Unigrafia Oy 2012

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Painotuote

FOREWORD

In January 2010 when I took office as the director of Biocenter Finland (BF) we had a unique concept at hand to restructure and develop research infrastructures and technology services in life sciences at national level, 45 million € of funds from the Ministry of Education and Culture for three years, and an enthusiastic group of scientists and service providers committed to implement the concept.

Now that a little over two years have passed I am happy to report that all appraisals on Biocenter Finland indicate that it has been a success and exceeded many of the objectives set in the 2010–2012 funding program. All BF networks are in full operation and BF is established as a significant national operator in the area of infrastructures and technology development. BF is becoming a natural one-stop-shop not only for national scientists seeking technology services, but also for international contacts.

The technology services have strengthened the cooperation between universities and simultaneously enabled them to develop their specific focus areas. The infrastructure service platforms have developed transparent pricing models and the revenues of the services are steadily increasing. Biocenter Finland technology platforms have proven to be a success also organizationally providing international visibility, national level integration and quality control. The funding base has been widened although much remains to be done both centrally and at the level of individual technology platforms to provide the best possible services at affordable price for the entire scientific community in Finland and beyond. As can be seen from the user statistics, all biocenters now offer services not only for their own researchers but for those working in other biocenters and elsewhere in academia and industry. The concept works!

Numerical indicators of the success of BF include user statistics as presented in this Annual Report under individual technology platforms, a 32% increase in income from user fees from the previous year, and the success of Finnish life scientists in obtaining funding from international sources, especially from EU and European Research Council. Nearly half (18/40) of Finnish ERC grantees rely on BF technology service platforms in their research. Such success is critical in making Finnish bioscience attractive also for international scientists, companies and investors. Many technology platforms

Continuous support is needed to maintain infrastructures at a level that keeps Finnish research environments attractive for our own scientists and helps recruit international researchers and industry to Finnish biocenters.

report active collaboration with international companies on development of instrumentation. Biocenter Finland technology platforms and infrastructures have also been instrumental in the success of several biotech startups in the Finnish biocenter environments. With the onset of pan-European ESFRI infrastructures it is likely that large international pharmaceutical and diagnostics industry will also turn their eyes on Finland. Biobanks, health registries, well organized health care, large population cohorts and the technology platforms of BF are factors that industry is looking for when developing and implementing the concepts of stratification of diseases, precision drugs and personalized medicine.

Continuous support to research infrastructures is central to creating strong, attractive and competitive research environments. At EU level this is clearly stated in the Horizon 2020 proposal of the European Commission. It is encouraging to note that infrastructures are also mentioned in the program of the new Finnish Government, and to see that an expert group of research infrastructures is being established within the Academy of Finland to coordinate both national and pan-European infrastructures. As BF scientists have played an active role in nearly all biological and medical ESFRI projects during their preparatory phase, Finland can truly claim that our infrastructure networks are ready to join the European activities once the political decisions have been made. In many cases an initial commitment has already been made by the Ministries in charge in the form of a Memorandum of Understanding which has made it possible for Finnish scientists to participate in the shaping of the European research infrastructure landscape. Other positive developments found in the Government program include plans to improve the use of databases and registries for research purposes and a feasibility study for establishment of Comprehensive Cancer Center in Finland. As BF technology platforms are major providers of modern biomedical services and producers of digital data, these developments are also closely linked to future development of BF.

Today, BF is working hard to obtain financial support for its operations from 2013 onwards. Continuous support is needed to maintain infrastructures at a level that keeps Finnish research environments attractive for our own scientists and helps recruit international researchers and industry to Finnish biocenters. Cutting edge equipment and technologies are becoming more and more costly, so joint investments through the BF model are needed to save money. Equally important for efficient operation of BF services is development of a career track model for the technical and service personnel so that they see their work as a true career option with a future. The innovation and technology transfer potential of BF is significant, but we need to improve the technology transfer atmosphere and processes following successful international models.

While reaching out towards future, it is also useful to look back for a while. This Annual Report summarizes the progress made by BF infrastructure networks and their technology platforms during their second year of operation under the current funding scheme. As already discussed above, I believe I can quote our Scientific Advisory Board (SAB) and state that the BF concept has been a success. The work of SAB has been extremely valuable; they not only performed a mid-term evaluation of all our activities, but also gave their expert evaluation of the new proposals for technology services and emerging technologies. I want to express my gratitude to the distinguished scientists who form our SAB for their commitment and expert advice on which the BF Board has based its funding decisions.

I have a large group of individuals to thank for the success of BF in 2011. I start by expressing my gratitude to my two-member staff, scientific coordinator Dr. Tero Ahola and planning officer Sanna Leinonen, M.Sc., and to the Board of BF, which comprises the directors of Finnish biocenters. I also want to acknowledge the help and support of the Universities supporting BF in their own biocenters. Most importantly, however, the success of BF depends on all those individuals who have contributed to BF infrastructure networks and technology platforms. I believe you all have been able to create a new collaborative spirit and the type of enthusiasm needed to get things done and working. I am convinced that also the Government sees that BF is indeed the most effective way to guarantee that Finnish scientists will continue to have access to top-quality research infrastructures also in the coming years.

Eero Vuorio
Director of Biocenter Finland

Commentary

The life sciences are undergoing an important paradigm shift. From being largely descriptive, to the current focus on the molecular level, life sciences are being transformed into quantitative sciences as we attempt to describe new principles and laws of the living world. During the last fifteen years we have seen enhanced collaboration with physics, chemistry, computer science and engineering. Naturally this paradigm shift also requires very significant changes in methods and technologies. Today a life scientist cannot be successful doing experiments solely within his/her own lab, but it is mandatory to use a variety of sophisticated methods and to actively collaborate with multidisciplinary research groups.

Life scientists in Finland face these challenges as much as anywhere else in the world. In order to enhance collaboration between Finnish Biocenters and to develop nation-wide technology platforms and core facilities Biocenter Finland (BF) was established in 2006. During its first years BF was supported mainly by host universities, but for the years 2010–2012 BF received very significant support from the Ministry of Education and Culture. This funding has made it possible for BF to coordinate life science service facilities at national level. After initially challenging negotiations, different core facilities have been placed at the universities where the scientific back-up and expertise has been strongest, thus supporting and strengthening different profiles of the biocenter universities in Finland. This division of activities and specialization has provided efficiency benefits by avoiding duplication of sophisticated and expensive equipment and concentrating talent and expertise around these core facilities. Although BF funds are primarily used for service activities, research in emerging technologies and international recruitment of top technology experts have also been supported. BF has also been successful in supporting and recruiting skilled personnel who are dedicated to the daily running of the core facilities. Such experts are rare and often they must devote most of their time to running the services, resulting in lower scientific productivity. BF has increased the prestige of these practical experts in the scientific community.

I think that BF is a wonderful example for other research areas of how to organize collaboration and the development of a national infrastructure in a small country. BF has been acknowledged internationally as a good model for other European countries for the development of life science infrastructure. Although the first years have been successful and a lot has been achieved many challenges remain. I think that the main challenge of BF is to closely follow the development of modern life sciences in order to implement and develop the most critical technologies and instrumentation. Rapid development in the methods of biological imaging, in transgenic technologies and proteomics and their fast implementation in Finland are just a few examples of crucial BF activities. Another important goal is to enhance BF collaboration with Finnish technological universities and faculties. Finnish biotechnology has suffered from a lack of technological expertise and now there is a historic chance to strengthen this link. Equally important is to offer the services of the technology platforms to all Finnish universities and to industry, to biotech companies. Expanding collaboration between BF, TEKES and life science companies will be hopefully one of the highlights for the coming years. Finally, BF has been an active promoter of international collaboration and now one of the important goals is to facilitate the participation of the Finnish scientific community in ESFRI infrastructure networks. Moreover, with existing collaborative networks and experience in the development of technology platforms BF is ideally suited to be the coordinator of the ESFRI life science infrastructure network in Finland.

Mart Saarma
Academy Professor

INTERNATIONAL EVALUATION BY SCIENTIFIC ADVISORY BOARD

An important element in the success of Biocenter Finland has been the fact that all major funding decisions have been based on the evaluation of proposals by a Scientific Advisory Board (SAB) consisting of eminent international scientists:

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

"BF has been remarkably successful in catalyzing a restructuring of the infrastructure of Finnish life science. This has helped to optimize the operations and to facilitate access to the facilities, and has also prepared the Finnish scientific community for participation in ESFRI infrastructure networks."

- Excerpt from the "Report from the Biocenter Finland Scientific Advisory Board meeting in Helsinki, August 22-24, 2011"

In August 2011 SAB visited Finland with two tasks: to evaluate the performance of the technology services receiving funding since January 2010 and to review proposals for upgrading the current services and for setting up emerging technologies. The laudatory evaluation report stated that SAB was very impressed with what had already been achieved during 2010 and 2011 with BF funding. Based on this mid-term evaluation SAB recommended additional funding to many of the existing technology services for upgrading services. Furthermore, SAB supported funding of proposals from three emerging technologies: Small animal molecular imaging: real-time imaging unit; Proteome-wide profiling of kinase substrates/membrane proteins; and Recombinant antibody generation platform. Another new development was the inclusion of two University of Jyväskylä units in BF technology platforms.

"Modern high quality research cannot be performed without support of well functioning core facilities and BF has proven its capacity to deliver such support. What BF has achieved already after less than two years of operation in terms of national coordination and cooperation stands as a model for other countries to follow when developing their research infrastructures. The SAB therefore strongly recommends the Finnish government to continue the BF effort after 2012 when the current program ends."

- Excerpt from the "Report from the Biocenter Finland Scientific Advisory Board meeting in Helsinki, August 22-24, 2011"

ORGANIZATION OF BIOCENTER FINLAND IN 2011

Biocenter Finland was established in 2006 by the six Finnish Universities housing biocenters, i.e. Universities of Helsinki, Kuopio (now University of Eastern Finland), 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 2011–2012 (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)

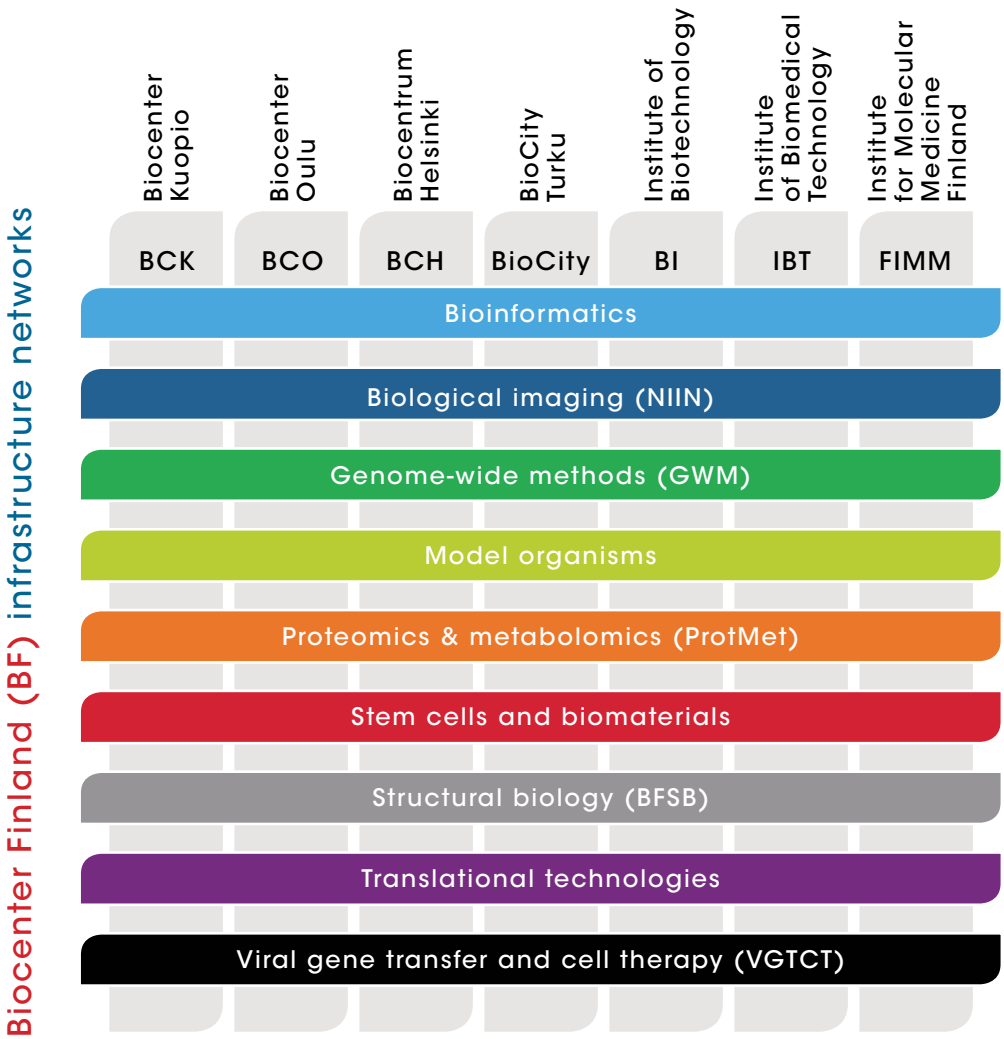
Tomi Mäkelä, Institute of Biotechnology, University of Helsinki (Pekka Lappalainen)

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.

TECHNOLOGY TRANSFER AND BIOCENTER FINLAND

Improving the technology transfer in the field of life sciences in Finland was one of the tasks set for Biocenter Finland in 2009. The original BF proposal called for funding of a small number of proof-of-concept projects to help bridge the gap between academic research and commercial applications. However, EU directives limit the possibility of supporting such research to a limited number of funders. In Finland Tekes has such rights, while budgetary funding from the Ministry of Education and Culture to Biocenter Finland or universities cannot be used for such proof-of-concept funding.

One of the challenges in using the word "Technology Transfer" is that it has several meanings. Wikipedia defines technology transfer as the process of transferring "knowledge, technologies, methods of manufacturing, samples of manufacturing and facilities among governments or universities and other institutions to ensure that scientific and technological developments are accessible to a wider range of users who can then further develop and exploit the technology into new products, processes, applications, materials or services". In this context all BF technology platforms have actively participated in technology transfer between biocenters, research institutions, industry and individual researchers.

Commonly, however, technology transfer is considered as "a process of moving promising research topics into a level of maturity ready for bulk manufacturing or production". Towards this end universities in Finland and elsewhere have set up dedicated technology transfer offices to support researchers in protection and commercialization of their results. In addition to patenting this may involve licensing agreements or joint ventures and partnerships to bring new technologies to market. Users of BF technology platforms get technology transfer support from their home institutions.

The latter type of technology transfer of discoveries made in academic research to industrial applications is not easy. Throughout the European Union academic research institutes are faced with the problem that promising research findings are considered 'too early' to be licensed by commercial partners, yet 'too advanced' to be further nurtured through basic research funding. Internationally, experts often refer to this gap as the "valley of death" as this presents a real obstacle to efficient exploitation of innovations.

Although a lot of effort has been put into smoothening the road from scientific discoveries to commercial exploitation, these efforts have not achieved their goal. Scientists are frequently unhappy because they do not get the type of support they need; e.g. financial support for proof-of-concept validation, technology transfer expertise, advise on intellectual property etc. Although strengthening commercial exploitation of innovations is the leading R&D paradigm of the European Union, statistics show that this culture does not prevail in Europe. The United States has a clear leading edge in this field.

To find solutions to the obstacles of technology transfer in the field of life sciences in Finland BF organized in January 2012 a **Workshop on Innovation: from basic research findings to exploitation and translation.** In the first part of the workshop a representative of the Finnish scientific community (Academy professor Mart Saarma) and a representative of the Finnish drug development community (Dr. Risto Lammintausta) the major obstacles in commercial exploitation of innovations made in academia.

In the second part, a representative from the Ministry of Education and Culture (Dr. Erja Heikkinen) and a representative from Tekes (Dr. Jari Toivo) described how Finland has tried to solve the problem of supporting commercial exploitation of innovations within the legal framework of European Union and national laws. The participants learned of the revised strategy of Tekes aiming to better support of technology transfer and proof-of-concept studies.

For the third part of the workshop BF had the pleasure to hear the experiences of two well known experts representing highly successful technology transfer activities in Europe, Dr. Gabor Lamm (Managing Director of EMBLEM Technology Transfer GmbH, Heidelberg, Germany) and Dr. Rudy Dekeyser (Managing Director at VIB [Vlaams Instituut voor Biotechnologie], Zwijnaarde, Belgium).

Analogous to BF and Finnish biocenters, both EMBL and VIB are networked research organizations with a strong emphasis on excellence in research and infrastructure services. Also the research staff and budgetary funding of these two organizations are comparable with

BF and Finnish biocenters. EMBL organized its technology transfer by establishing in 1999 its fully-owned company EMBLEM. In VIB, founded in 1996, technology transfer is integrated in the overall structure of the institution. The size of EMBLEM staff and VIB technology transfer team are similar, 8-10 full time equivalents. The sole focus of EMBLEM and VIB is on life sciences; therefore most of the technology transfer staff has a PhD in life sciences. Other staff members have legal and entrepreneurial expertise ("toolbox") to cover the entire technology transfer process from recording and evaluating inventions, to protection of IPR, funding of proof-of-concept experiments, raising venture capital, marketing and deal making. The approach to technology transfer is very proactive; the professional EMBLEM and VIB team members participate in seminars and periodically visit all research facilities to discuss with the scientists about their discoveries and potential applications. In both institutions, the technology transfer teams have been so successful that they started to be profitable after five years of operation.

The technology transfer potential of Biocenter Finland is significant. This statement is supported by reports from the infrastructure networks which confirm the importance of technology service platforms for research and development, especially for Tekes-funded projects and for biotech companies in the biocenter environments (e.g. FibroGen Inc, Glycos, Hermo Pharma, MobiDiag and CNS Therapeutics). In 2011 a new spin-off company, Desentum Oy, was established to develop a product line of new hypoallergens to be used as vaccines. Crystallography and the new native mass spectrometry facilities in BCK played a central role in identification of key structures of the allergens, on which the discovery is based. Furthermore, several large EU-funded projects rely of BF technology services and nearly half of Finnish ERC (European Research Council) grantees use them for their research. Recognizing this potential, Biocenter Finland proposes to initiate together with Tekes and the partner universities a technology transfer program in biosciences. The aim is to establish a professional technology transfer team with expertise in life sciences to integrate with the IPR staff of partner universities. The CEO's of EMBLEM and VIB have expressed their interest to initiate an alliance with BF for training of tech transfer professionals with the required expertise. An important part of the program is to ensure that research is not compromised and researchers are not burdened. International experience from EMBL and VIB shows that a professional tech transfer team of well trained scientists can submit an invention disclosure at very short notice so that publication of the original basic research findings is not delayed.

SCIENTIFIC SUCCESS STORIES BASED ON BIOCENTER FINLAND TECHNOLOGY SERVICES

Bioinformatics guides the way towards precision diagnostics of rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, autoimmune disease that seriously affects approximately 1% of the world's population. RA is a painful and often disabling disease. Currently RA cannot be cured although there are several treatments that ease the symptoms and slow down disease progression. In order to initiate such treatments, it is crucial to diagnose RA as reliably as possible. In order to improve the current blood-based diagnosis tools at an early stage, professor Outi Vaarala's group at the National Institute for Health and Welfare (THL) has measured the expression of 15 genes and one housekeeping gene in 74 samples (36 RA cases and 38 controls) using RT-qPCR.

The bioinformatics services at the BCH were used to identify a subset of genes that can most reliably predict the diagnosis of RA samples from normal ones. Several algorithms, such as neural network, linear regression, linear discriminant, decision tree and k-nearest neighbors were used to find the best predictor(s). The performance was measured with cross-validation statistical validation approach. The best predictor was based on the use of 9 genes and produced a mean accuracy of 95%. These results have led to a US patent (Harri Salo, Jarno Honkanen, Outi Vaarala. Method for detection of autoimmune disease. US patent PCT/FI2009/050966).

Structural biology and bioinformatics networks help unravel enzyme action

Bioinformatics services in BCO were used to describe the high resolution crystal structure of an enzyme (thioester dependent racemase) involved in the metabolism of (2-methyl branched) fatty acids and synthesis of bile acids in humans. Studying this enzyme has become important recently, as it has been found that human enzyme levels are a good marker for prostate cancer, although the rationale for this is not clear. The enzyme is found in peroxisomes and mitochondria, complexed with a reaction enolate intermediate, bound in its planar enolate form.

The mode of binding of this enolate is well defined by its electron density map. A detailed QM/MM analysis (see figure) of the complexed active site of this racemase was carried out. The results shed light on 1) the protonation state of the catalytic residues, 2) the oxyanion hole and 3) the planar conformation of the intermediate, in relation to enolization chemistry. It was found that in the complex the calculated intermediate structure is planar and the side chains of His126 and Asp156 are protonated, stabilizing the thioester oxyanion of the enolate intermediate. This story highlights the successful integration of expertise of the BF structural biology and bioinformatics networks to fully characterize a given enzyme. The obtained results are relevant to medicinal chemists developing inhibitors of the prostate cancer therapeutic target human alpha-methylacyl-CoA racemase.

Reference: Sharma S, Bhaumik P, Rajaram V, Hiltunen J-K, Conzelmann E, Schmitz W, Juffer AH, Wierenga RK. The enolisation chemistry of a thioester dependent racemase: the 1.4 Å crystal structure of an enzyme reaction intermediate complex studied by detailed QM/MM-calculations. **J. Phys. Chem. B.** Accepted for publication.

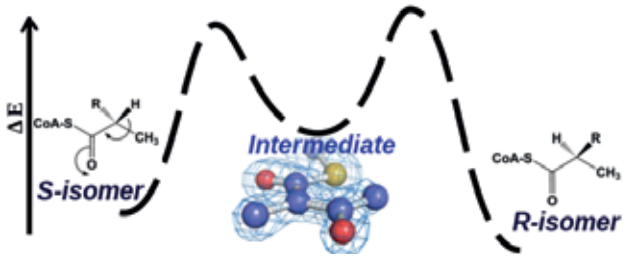


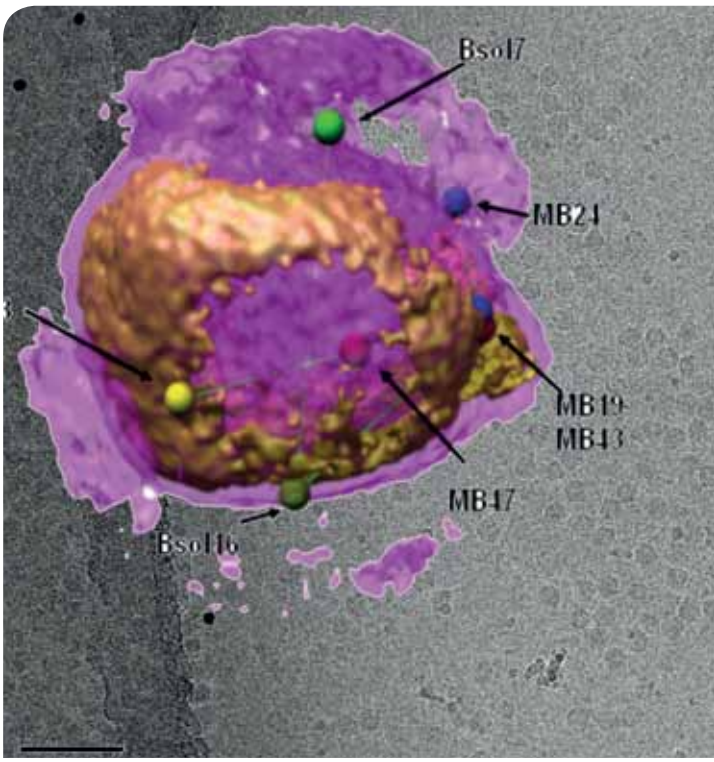
Illustration of the conversion between the substrate's S-isomer and R-isomer form catalyzed by the enzyme racemase.

Electron microscopy platform helps to solve the structure of native lipoprotein particles

Low-density lipoprotein (LDL) particles are the major carriers of cholesterol in the human circulation. They have key roles in both cholesterol physiology and in the development of atherosclerosis. Together with researchers from the Wihuri Research Institute, Aalto University and Oulu University investigators at the BF EM platform have employed three-dimensional cryoEM to characterise the structure of LDL particles at human body temperature to understand the organisation of the lipids and proteins that they are made from. The technology platform was used to optimise samples and to image the particles. There was then transfer of knowhow for the particle processing to the researchers in Aalto University who then carried out the processing. The interpretation of the final structures was again done in the technology platform.

The reconstructions showed that core-forming cholesteryl esters enclosed by a single copy of the huge, non-exchangeable protein, apolipoprotein B-100 become increasingly disordered at 37 °C compared to 6 °C. Segmentation of apoB-100 density, fitting of the lipovitellin X-ray structure, and antibody mapping, jointly revealed the approximate locations of the individual domains of apoB-100 on the surface of native LDL particles. This study provides a molecular background for further understanding of the link between structure and function of native LDL particles at physiological body temperature.

Reference: Kumar V, Butcher SJ, Öörni K, Engelhardt P, Heikkonen J, Kaski K, Ala-Korpela M, Kovanen PT. Three-dimensional cryoEM reconstruction of native LDL particles to 16 Å resolution at physiological body temperature. **PLoS ONE.** 2011; 6(5): e18841. doi:10.1371/journal.pone.0018841.



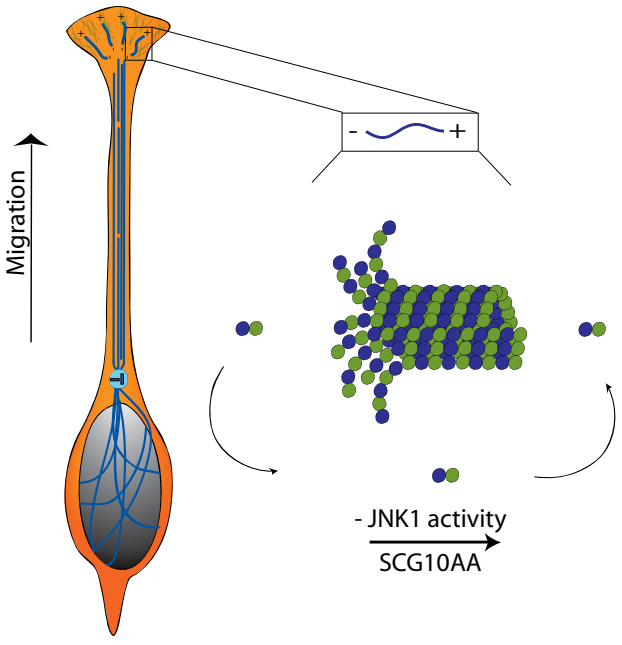
Isosurface representation of the LDL reconstruction at body temperature, shown on a micrograph background of vitrified LDL particles. The transparent violet isosurface is at a threshold of μ+0.7σ (showing mainly the lipid surface of the particles) and the opaque brown high-density isosurface is at a threshold of μ+3σ (showing mainly the rigid structures of apoB-100). Predicted epitope locations of monoclonal antibodies to apoB-100 are indicated as spheres. Adapted from Kumar et al. 2011

JNK1 identified as a major determinant of migration speed of neurons

Incorrect placement of neurons during brain development may leave us at risk for diseases and conditions ranging from epilepsy and mental retardation to schizophrenia and dyslexia. The cortex forms by organized waves of migrating neurons. If a neuron moves too fast during this journey, it may not take the correct route or reach its destination. The way neurons control their speed of migration has not been clear. Westerlund et al. (2011) in a study led by Academy Research Fellow Eleanor Coffey, identified new players that put the brakes on. They showed in mice that lack the star player "JNK1", that newborn neurons spend much less time in the multipolar stage, which is when the cells prepare for

subsequent expedition, possibly choosing the route to be taken. Having hurried through this stage, they move off at elevated speed to reach their final destinations in the cortex days earlier and less precisely than in a normal mouse. The JNK1 effector protein mediating these effects was SCG10, as a normal migration and multipolar phenotype could be rescued by add-back of pseudophosphorylated SCG10 and knockdown of SCG10 indicated a critical function. The authors evaluated the possibility that gene targets of JNK1 contributed to the migration phenotype by carrying out a gene expression analysis using an Illumina array in brains from wild-type and Jnk1-/- mice. Services of the Turku and Kuopio nodes of BF Genome-wide methods platform, the Finnish Microarray and Sequencing Center and the Multimodal imaging core, were critical for this analysis. Gene ontology searches were used to identify genes associated with adhesion or migration. This analysis confirmed the finding that JNK1 regulation of migration during brain development was a nontranscriptional function.

Reference: Westerlund N, Zdrojewska J, Padzik A, Komulainen E, Björkblom B, Rannikko E, Tararuk T, Garcia-Frigola C, Sandholm J, Nguyen L, Kallunki T, Courtney MJ, Coffey ET. Phosphorylation of SCG10/stathmin-2 determines multipolar stage exit and neuronal migration rate. **Nat Neurosci.** 2011; 14: 305–13.



Fluorescence micrograph of the migration pattern in developing cortex.

Defective energy metabolism in stem cells leads to progeroid syndrome in mice

In this study researchers studied two mouse lines that accumulate mtDNA mutations, Deletor (mtDNA deletion accumulation) with a late-onset mitochondrial myopathy with normal lifespan and Mutator (mtDNA point mutations) with progeroid phenotype with anemia, skin thinning, gray hair and osteoporosis. The researchers found that in Mutators, mtDNA mutations accumulated everywhere, including somatic stem cells (SSCs), whereas Deletors had mtDNA mutations only in postmitotic cells. The Mutators developed a dysfunction in somatic stem cells during embryogenesis, with reduced renewal capacity of neural stem cells (NSC) and abnormal lineage differentiation of hematopoietic progenitors (HPC) leading to anemia and lymphopenia. These changes could be ameliorated with antioxidant N-acetyl-cysteine, indicating that SSCs are sensitive to subtle changes in reactive oxygen species (ROS) /redox state. The results indicate that the progeroid manifestation in Mutators can be explained by SSC dysfunction. They also indicate that nutritional supplements, such as antioxidants, can affect behavior of a certain sensitive cell type, and SSCs are especially sensitive to ROS. Furthermore, the results suggest that mitochondrial dysfunction in SSCs can contribute to aging-associated degeneration.

The animals used in this study were maintained in and the experiments performed with the help of the Helsinki University Laboratory Animal Centre. Deletor-mice were generated in the GM unit of the UH Laboratory Animal Center, which is part of the BF Model organism network. These mice ubiquitously overexpress mouse Twinkle cDNA with a dominant human disease mutation, leading to duplication of 13 amino acids (dup353365) in the linker region of mitochondrial Twinkle helicase.

Reference: Ahlqvist KJ, Hämäläinen RH, Yatsuga S, Uutela M, Terzioglu M, Götz A, Forsström S, Salven P, Angers-Loustau A, Kopra OH, Tyynismaa H, Larsson NG, Wartiovaara K, Prolla T, Trifunovic A, Suomalainen (Wartiovaara) A. Somatic progenitor cell vulnerability to mitochondrial DNA mutagenesis underlies progeroid phenotypes in polg mutator mice. **Cell Metab.** 2012; 15:100–9.

Generation of a cell model for a human cardiac disease (long QT syndrome) using iPS cell technology

Long QT syndrome (LQTS) is caused by defective function of cardiac ion channels and is associated with prolonged cardiac repolarization time and increased risk of ventricular arrhythmias and even sudden death (Fig. A). A human disease model for LQTS type 2 was generated with iPS technology using the infrastructure of the BF Stem Cell and Biomaterials Network at the University of Tampere.

The current study investigated whether the electrophysiological characteristics of LQT2 can be recapitulated in vitro using iPS cell technology. Two iPS cell lines derived from an individual with LQT2 carrying the R176W mutation in the KCNH2 (HERG) gene, were differentiated to spontaneously beating cardiomyocytes. Electrophysiological properties of LQT2-specific cardiomyocytes were studied using microelectrode array and patch-clamp, and were compared with control cells derived from healthy individuals.

The results show that the action potential duration of LQT2-specific cardiomyocytes was significantly longer than that of control cardiomyocytes (Fig. 1B), and the rapid delayed potassium channel (IKr) density of the LQT2 cardiomyocytes was significantly reduced. Furthermore, LQT2-derived cardiac cells were more sensitive than controls to potentially arrhythmogenic drugs and demonstrated arrhythmogenic electrical activity. Importantly, these results are consistent with clinical observations, as the LQT2 cardiomyocytes demonstrated a more pronounced inverse correlation between the beating rate and repolarization time compared with control cells. The study demonstrated that the LQT patient-derived cardiomyocytes recapitulate the electrophysiological features of the disorder and these cells could serve as an important platform to study pathophysiological mechanisms and drug sensitivity in LQT2 patients. The results of the study demonstrate that iPS cell technology can be used for generation of functional human disease models to understand the aetiologies of diseases that may also facilitate the development of novel therapeutic interventions.

Reference: Lahti AL, Kujala VJ, Pekkanen-Mattila M, Kerkelä E, Chapman H, Koivisto A-P, Hyttinen J, Kontula K, Swan H, Conklin B, Silvennoinen O, Aalto-Setälä K. Cardiomyocytes derived by iPS cell technology from a long QT syndrome type 2 patient despaly the disease phenotype. **Disease Models and Mechanisms.** doi:10.1242, 2011.

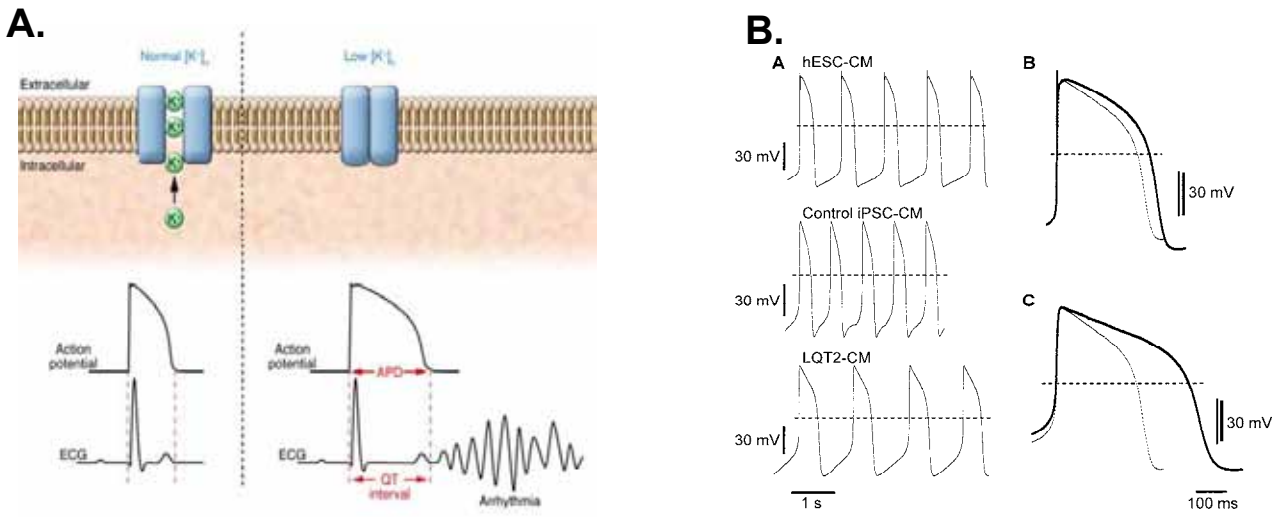


Figure A. Defective function of the hERG channel (K+-channel) prolongs the action potential of cardiac cells and increases the risk of severe cardiac arrhythmias. B. iPS cell derived cardiac cells from a patient having LQTS type 2 (LQT2) demonstrated significantly increased action potential compared to control iPS cell or embryonic stem cell derived cardiac cells.

BF Technology platforms help unraveling the genetic basis of leiomyoma

Lauri Aaltonen's group in Biomedicum Helsinki has made a breakthrough discovery by identifying a key driver mutation in uterine leiomyoma (Mäkinen et al., Science 334:252-255, 2011). This condition affects millions of women causing considerable morbidity. Despite high frequency of leiomyomas worldwide, their molecular genetic background is poorly understood. To study the genetic basis of this tumor type, Aaltonen's group first examined 18 uterine leiomyomas derived from 17 different patients by exome sequencing and identified tumor-specific mutations in the mediator complex subunit 12 (MED12) gene. Mediator complex is 26-subunit transcriptional regulator that bridges DNA regulatory sequences to the RNA polymerase II initiation complex. Through analysis of 207 additional tumors, they determined that MED12 is altered in 70% (159 of 225) of tumors from a total of 80 patients. All mutations resided in exon 2, suggesting that aberrant function of this particular region of MED12 contribute to tumorigenesis. Identification of such an exact mutation site may in the future lead to novel targeted therapies to control the growth of uterine leiomyomas. Gene expression analysis suggested that the mutations may affect global expression profiles of the affected tumors.

The Genome-wide methods network had a central role in the discovery. The gene expression profiling of uterine leiomyomas showing differential expression of mutation-positive and negative cases was performed in BCH/Biomedicum Functional Genomics Unit and exome sequencing in FIMM Technology Center.

Reference: Mäkinen N, Mehine M, Tolvanen J, Kaasinen E, Li Y, Lehtonen HJ, Gentile M, Yan J, Enge M, Taipale M, Aavikko M, Katainen R, Virolainen E, Böhling T, Koski TA, Launonen V, Sjöberg J, Taipale J, Vahteristo P & Aaltonen LA. *MED12,* the *Mediator Complex Subunit 12* gene, is mutated at high frequency in uterine leiomyomas. **Science.** 2011; 334: 252–255.

Zebrafish as a model for human tuberculosis

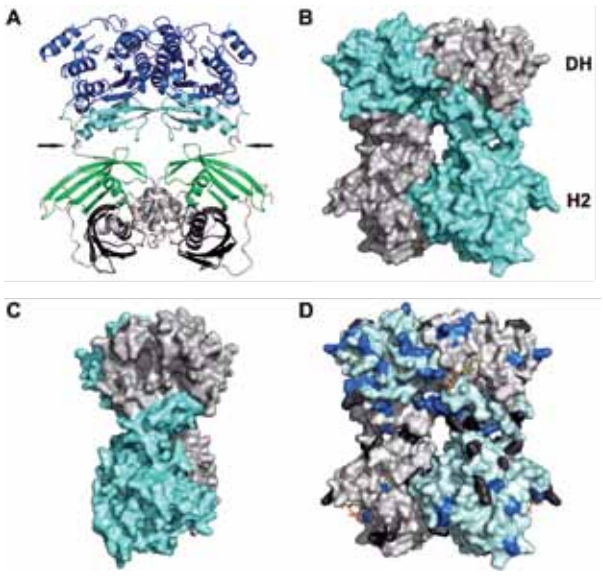
Tuberculosis is caused by *Mycobacterium tuberculosis*, a highly specialized pathogen capable of evading immune defence by various strategies. It has been estimated that a third of the world's population carry the pathogen and to have a chronic, subclinical infection. According to the report of the World Health Organization, tuberculosis caused 1.7 million deaths and 9.4 million infections in 2009.

Many aspects of the disease progression are still obscure. Especially, the mechanisms leading to latency and reactivation of human tuberculosis are unclear, mainly due to the lack of standardized animal models of latent tuberculosis infection. In the research carried out at the Tampere Zebrafish facility of the BF Non-mammalian model organism platform, researchers lead by M.Sc. Milka Vuoksio developed a Mycobacterial infection model in adult zebrafish that leads to a latent infection that can be reactivated by immunosuppression caused by gamma-irradiation. Following an i.p. infection with a low dose (35 cfu) of *M. marinum* – a natural fish pathogen that is closely related to *M. tuberculosis* – a latent disease develops in most individuals. The infection is characterized by a limited mortality, static bacterial loads after 4 weeks of infection and constant numbers of highly organized granulomas in few target organs. In 5–10% of the cases in human tuberculosis, the disease is reactivated usually as a consequence of immune suppression. In zebrafish model, reactivation can be efficiently induced in infected zebrafish by gamma irradiation that transiently depletes granulo/monocyte and lymphocyte pools. This immunosuppression causes a rapid outgrowth of mycobacteria leading to 88% mortality in four weeks. Thus the adult zebrafish presents itself as a unique non-mammalian vertebrate model for studying the development of latency as well as reactivation of latent tuberculosis. The possibilities of screening for host and pathogen factors affecting the disease progression, as well as for novel therapeutic agents and vaccine targets make the established model especially attractive.

National data collection facility and FinnProCC BAG consortium provide tools to elucidate the mechanism of a metabolic disease-causing bifunctional enzyme MFE-2

A mutation in the human MFE-2 (multifunctional enzyme type-2) gene results in a deficiency of this bifunctional protein, in accumulation of fatty acid metabolites, and in a metabolic condition leading to death at an early age. MFE-2 is a CoA-dependent bifunctional enzyme having two active sites in the same polypeptide: the 2E-Enoyl-CoA hydratase 2 and the 3R-hydroxyacyl-CoA dehydrogenase, being responsible for the 2nd and the 3rd reactions of the b-oxidation spiral of fatty acids, respectively. In order to reveal whether an efficiency-boosting substrate channeling mechanism between the two active sites is in place researchers in the University of Oulu determined the crystal structure of a model MFE-2 protein, the *Drosophila* MFE-2. National data collection facility in the University of Oulu was essential for crystal screening and structure solution, while the ID29 beamline at European Synchrotron Radiation Facility (ESRF) in Grenoble, utilizing the quota of FinnProCC BAG, was used for the high resolution data (Haataja et. al., 2011). The enzyme is an a2-dimer of 598 residues per subunit. The structural assembly of the active sites was totally unexpected, as it did not reveal features that would support a substrate channeling mechanism: the active sites of the enzymes did not face a common space, nor were there spatial or charged paths for the reaction intermediate to channel between the two active sites. Furthermore, when enzyme kinetics were performed both for the full-length MFE-2 and for its enzymes as separate proteins, the catalysis was equally efficient in both cases. The MFE-2 crystal structure is crucial in order to help understanding these kinetics results. Although the question remains why MFE-2 is a multifunctional enzyme *in vivo,* the structure does rationalize how the disease mutations disrupt the function and pave the way towards understanding the disease mechanism.

Reference: Haataja TJ, Koski MK, Hiltunen JK, Glumoff T. Peroxisomal multifunctional enzyme type 2 from the fruitfly: dehydrogenase and hydratase act as separate entities, as revealed by structure and kinetics. **Biochem J.** 2011; 435: 771–781.



Domain organization in the MFE-2 dimer. (A) Standard view revealing the dehydrogenase and the hydratase dimers that are connected via short linkers (black arrows). (B) Surface presentation of the MFE-2 dimer revealing the color-coded monomers. (C) Side view of the hourglass-shaped molecule. (D) Surface presentation of the MFE-2 dimer showing also the substrates of both enzymes in the active sites, thus illustrating their remote positions from each other (Haataja et al., 2011). Reproduced with permission, from Haataja *et al,* 2011, *Biochemical Journal,* **435**:771-781. © the Biochemical Society.

Big size multitouch display turned into a microscope

The multitouch microscope integrates two Finnish innovations and brings new dimensions into teaching and research.

Researchers at the Institute for Molecular Medicine Finland (FIMM) have in collaboration with the Finnish company Multitouch Ltd created a hand and finger gesture controlled microscope. The method is a combination between two technologies: web-based virtual microscopy and a giant size multitouch display.

The result is an entirely new way of performing microscopy: by touching a table- or even wall-sized screen the user can navigate and zoom within a microscope sample in the same way as in a conventional microscope. Using the touch control it is possible to move from the natural size of the sample to a 1000-fold magnification.

Biological samples are digitized using a microscopy scanner and stored on an image server. Samples displayed on the screen are then continuously read from a remote image server over the internet and the size of a single sample can be up to 200 gigabytes.

Multitouch microscopy with a tilted table screen (left), and a 9 MegaPixel screen wall (right).
Video available at http://youtu.be/ihaM3DvyUHE

The developers think that the method will revolutionize microscopy teaching: a group of students can stand around the display together with the teacher and all can examine the same sample. The multitouch microscope can recognize the hands of multiple users at the same time. The multitouch microscope brings a new dimension into interactive teaching and the learning curve is practically zero as compared to conventional microscopy which can be quite challenging for students.

Web-based virtual microscopy was developed a few years ago by the universities of Helsinki and Tampere (the current BF Biobanking Technologies Consortium) and has been well received among students, pathologists and researchers. The multitouch microscope builds upon this webmicroscopy technology and makes it even more useful within teaching. At scientific meetings this technology is excellent in a situation where a group of users need to simultaneously view a microscopy sample, for example when a consensus needs to be reached concerning a new disease entity or a rare case.

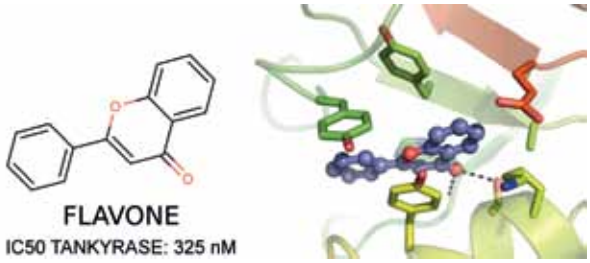
DDCB platform helps researchers to find new inhibitors for PARP enzymes

Small molecule inhibitors of poly(ADP-ribose) polymerase (PARP) enzymes have gained an enormous amount of attention as investigational drugs in recent years. The clinically investigated PARP1 inhibitors show great promise as synthetic lethal-acting drugs in tumors with genetic deficiencies in DNA repair. In addition to PARP1 that is targeted by the mentioned investigational drugs, the PARP family consists of 17 proteins, many of which are very promising therapeutic targets for other diseases, but inhibitors for other family members than PARP1 have not been described due to lack of good assays for screening for chemicals with inhibitory activity. This problem was successfully addressed in a DDCB-supported project lead by Dr. Lari Lehtiö (Biocenter Oulu).

With the assistance of the DDCB network, different novel high throughput screening assays were developed and validated. The first assay was developed to screen for tankyrase-1, a PARP enzyme that is a promising drug target especially in colorectal cancer due to its functions in telomere maintenance and WNT signaling. In this study, one of the natural product subsets of the DDCB-NP collection was screened and flavone was the most potent (IC50= 325 nM) hit found. Flavone derivative apigenin, and isopropyl gallate showed potency on the micromolar range, but displayed over 30-fold selectivity over the other human isoenzymes PARP1 and PARP2, which make them very promising as inspirational leads for the drug design of selective tankyrase-1 inhibitors. The results will be published in Journal of Biomolecular Screening (Narwal et al, 2012). High throughput screening assays for measuring the activity of other less known PARP isoenzymes have also been developed. These fluorescence-based assays have been optimized to measure inhibitory activity and a publication is now being prepared.

Together, these types of assays will open up novel opportunities for developing drug-like chemicals that selectively inhibit different PARP family proteins and allow for testing of their potential as drug targets.

Reference: Narwal M, Fallarero A, Vuorela P, Lehtiö L. Homogeneous screening assay for human tankyrase. **J. Biomol. Screen.** 2012, in press.



Flavone was identified as the most potent hit compound for human tankyrase 1 in the validatory screen. Follow-up studies have now revealed the detailed structural information about the flavone-tankyrase interaction.

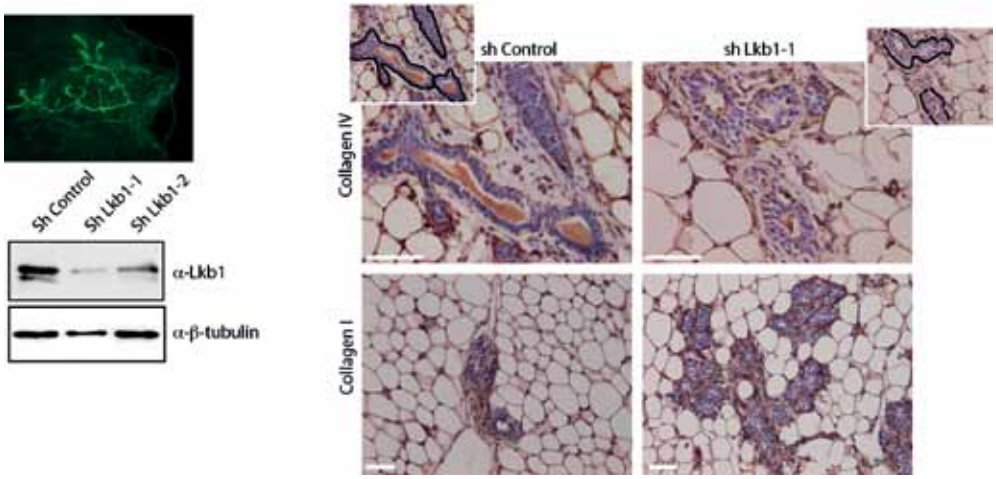
LentiGEMM technology identifies a new targetable protein involved in breast cancer invasion

Cancer researchers in Biocentrum Helsinki using modified viruses to engineer gene function in the mouse mammary gland (equivalent of human breast) have identified a new protein that may help cancer to spread to the neighboring tissues. This process called invasion usually marks the alarming stage when a tumor has started to advance and to become an aggressive and potentially deadly disease for a patient. The study published in Proceedings of the American Academy of Sciences (PNAS) uses a new technology established in the Biocenter Finland's LentiGEMM emerging technology platform.

The LentiGEMM technology, which uses combination of gene inactivating viruses and animal tissue grafting techniques, allowed researchers to inactivate a suspected cancer-protecting gene in living mouse mammary tissue. Further research on the cancer-prone "mouse breast" led to discovery of a new drug-targetable protein involved in cancer spread. The new cell pathway, which the study identifies, may turn out to be a critical target to attack in fight against advanced breast cancer.

The study stresses the importance of studying cancer as a disease of whole tissue rather than only as a disease of the cells. Dr Juha Klefström, the lead researcher and coordinator of LentiGEMM notes "There are many processes in cancer development, which can be studied in cell cultures like abnormal cell division cycles. However, many critical and patient killing processes like cancer spread to neighboring and distant tissues can be effectively studied only in live animals. Therefore, it is important to develop new technologies that on one hand will allow scientists to quickly determine particularly which of the many cancer gene suspects are important for cancer spread and on the other hand, reduce the amount of mice needed for these experiments."

Reference: Partanen JI, Tervonen TA, Myllynen M, Lind E, Imai M, Katajisto P, Dijkgraaf GJ, Kovanen PE, Mäkelä TP, Werb Z, Klefström J.Tumor suppressor function of Liver kinase B1 (Lkb1) is linked to regulation of epithelial integrity. **Proc Natl Acad Sci U S A.** 2012; 109(7):E388–97.



Identifying cell pathways involved in cancer invasion using technologies established in the LentiGEMM platform. The researchers first produced RNAi (gene inactivating element) carrying viruses, which were put in contact with primary mouse mammary epithelial cells. The viruses were able to find rare mammary stem cells hidden among the thousands of epithelial cells and deliver their payload to the stem cells. Researchers placed the cells, now having Lkb1 inactivated, in the mammary glands of young female mice. The stem cells produced new epithelial cells rebuilding new epithelial structures in the mammary gland. The green color shows that the virus payload, RNAi element, is present in most of the cells forming the new mammary gland (upper image on the left). The protein analysis below the image confirms specific knockdown of Lkb1 in the new mammary gland. These experiments led to discovery of an over-activated protein on the surface of tumor-prone epithelial cells. This protein cleaves other proteins, which eventually breaks the basement membrane around the epithelial tissue (pictures on the right show defective breast epithelium structures) and promotes tumor cell invasive properties. Discovery of a invasion promoting protein on tumor cell surface may lead to new therapeutic strategies against advanced breast cancer as drugs targeting the protein could slow down or prevent tumor cell invasion. Photo: Johanna Partanen, reproduced with permission from PNAS.

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, IBT; Mark Johnson, BioCity; Imre Västrik, FIMM; Ulla 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 the 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, IBT, Bioinformatics Group; Mark Johnson, BioCity, Structural Bioinformatics Laboratory; Imre Västrik, FIMM

http://bioinformatics.biocenter.fi/

Development and restructuring of technology services

The Bioinformatics network has heavily engaged in answering the bioinformatics service needs stemming from large data-intensive research, such as next-generation sequencing (NGS) and high-throughput imaging, as well as supporting labor-intensive single molecule studies and IT support. The restructuring has been done at all levels, including dividing tasks within the network and increased visibility of our services via the recently-established bioinformatics helpdesk (http://bioinformatics.biocenter.fi/). We have developed and deployed data analysis pipelines for next-generation sequencing and imaging analysis, upgraded hardware and software to accommodate and manage very large data sets, and we have intensified the collaboration with CSC in multiple ways. CSC has advised us on hardware and software implementations; three groups (BCH, BioCity Turku, FIMM) have tested the CSC cloud pilot computing resources with both very large case studies and computationally-intensive single molecule studies. CSC's emerging cloud service is intended to be used for building topical biomedical science services using public data and biomedical institutes' local data and expertise.

The focus on NGS, imaging and scientific IT support is due to feedback from the wider bioscience community that clearly recognizes bioinformatics services as the major bottleneck in interpreting NGS and imaging data. This is partly due to the complexity of the analysis pipeline and the variety of services needed (ranging from *de novo* genome projects to IT infrastructure, data analysis of patient samples and meta-genomics). Single-molecule studies require long-term investment of effort and, especially in the area of structural simulations, require extensive, up to month-long periods of calculation. There has also been direct consulting and support of other BF infrastructure areas especially concerning hardware, software and data transfer needs.

Future perspectives for 2013–2016

The need for bioinformatics services will grow exponentially in the foreseeable future. The need is in large-scale data management, analysis and, in particular, interpretation. Thus, we envision that services, such as *in silico* modeling and simulation, protein function annotation and prediction, as well as network-based analyses, will be in high demand for at least the next five years. The Bioinformatics network is now well prepared, actively interacting with user groups, and is thus in good shape to answer the future challenges. A nation-wide, coordinated bioinformatics effort of high-quality services and infrastructure implemented by the network and CSC is paramount in order to be able to provide efficient, cost-effective bioinformatics services to Finnish research groups and commercial entities. Without strong investment in bioinformatics there is little sense in investing in the equipment that produce the data in the other infrastructure networks, because the resulting data cannot be processed effectively. Bioinformatics is labor intensive and requires highly skilled individuals – not just hardware and software tools – thus there will be an urgent need for personnel to carry out current services as well as to develop new services.

One of the biggest scientific challenges in the future will be exploiting the exponential growth of biological data and information. We must gain the most from the research that has already been done. In 2012–14 CSC will install computing and data management resources with a budget of 25 million € to serve the scientific communities in Finland, including biology and medicine. European efforts intend to sustain large-scale new data centre facilities that feed research data back to the scientific community. This will also facilitate growth of the Finnish bioinformatics sector. It is important that we work together in order to ensure that we will have enough people with expert skills and career prospects in biological data analysis.

Participation in international and European infrastructures

The Bioinformatics network is active in ESFRI projects ELIXIR (bioinformatics, coordinated by CSC) and ISBE (systems biology). The suggested Finnish ELIXIR Node will provide IT infrastructure (through cloud computing) and storage of large biological data sets for quick computational access. The service is targeted at European biomedical institutes, and technologies are compliant with key European e-Infrastructures. The Bioinformatics network has contributed its expertise and also made extensive use of the cloud computing service that CSC is developing as part of the Biomedinfra consortium formed by Finnish representatives of translational research, biobanking and bioinformatics ESFRI infrastructures. Biocenter Finland and the research institutes supporting national infrastructures for biomedical sciences are the key national stakeholders for the European ELIXIR services, also the ones produced in Finland. With regards to ISBE, the network held a national workshop to inform the Finnish systems biology community on the presence of ISBE. Members of the BF Bioinformatics network are also heavily involved in coordinating NordForsk networks and SocBin (Nordic Bioinformatics Society).

User statistics

	BCH	BI	BCK	BCO	IBT	BioCity Turku	FIMM	Total
Total users	26	39	35	5	520	49	64	737
Local	18	28	30	3	10	30	13	132
Other domestic	6	3	2	0	10	14	46	81
International	2	2	2	2	500	5	5	518
of which non-academic:	0	6	1	0	50	0	0	57
Projects	29	44	5	6	NA	49	64	197
Database & server users / requests	NA	NA / 25 252	NA	NA	25 000 / NA	NA	NA / 500	25 000 / 25 752

BIOLOGICAL IMAGING

NETWORK

Biological Imaging Infrastructure Network

Coordinator of the network: John Eriksson, BioCity Turku

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 body.

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 centres. 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.

PLATFORM

Electron Microscopy Technology Platform

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

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

Development and restructuring of technology services

Each of the three EM units of the consortium has already provided services nationally for academia and industry over a long period. The aim for the funding period 2010–2012 was to restructure the functions towards more specialized areas. The impact of BF funding has been significant in terms of both the technology platform investments and in the running staff. Although the major instrument investments in this consortium were allocated to 2010, due to the long public procurement process they were mostly realized during 2011. These include two microscopes, a field emission scanning electron microscope (FEG-SEM) equipped for automated serial block face imaging (SBF-SEM) in BI-EM and a 120 kV transmission electron microscope (TEM) in BCO-EM, a vitrification robot in BI-cryoEM and a fully-automated freeze-substitution device in BCO-EM. Already now we can see clear improvement in performance and quality of the services resulting in higher scientific impact. The vast majority of FEG-SEM operating time has been used in setting up the 3D-imaging, but we have also seen a growing demand for basic SEM imaging. The new Oulu TEM has significantly improved the image quality, has enabled tomography and increased the uptime. The vitrification robot in BI-cryoEM is now used in all specimen preparation for cryoEM, and users are happy with the simplicity and standardization gained. BF funding has allowed the maintenance of the microscopy support staff for BI-cryoEM, as well as providing a 50% computer programmer shared with the BF crystallization unit in Helsinki. This has significantly streamlined im-

age processing across different platforms and improved the communication with CSC and the university centralized computing services. We are still working on computational restructuring to set up standardized single particle averaging protocols for new projects for all architectures, and to develop new protocols for subtomogram averaging and helical processing. The major computer purchase planned for 2012 will be based on the needs identified during 2010–2011, which are both in data storage and in parallel processing.

The two other units have hired more staff to develop new advanced EM techniques and support new projects. In BCO-EM, a new technician has increased the effectiveness of sample preparation, thus drastically reducing the waiting time for researchers' samples. The recruited postdoctoral researchers have really advanced the 3D-EM techniques. Now the FIB-SEM technique and 3D modeling are available to the community from the BCO-EM unit. Two ongoing projects are utilizing this technology and one project is in the manuscript submission phase. Also 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 technology transfer, electron microscopical analysis and a quantification method were developed to optimize a protein production bioprocess.

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 10 worldwide, it has drawn a lot of interest from outside Finland, but at this stage, 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. We had one visitor from Ireland for two weeks to learn specimen preparation and make some test runs. As the operating software is still under development, we are in active dialogue with the company providing feedback. Our first results were widely appreciated in the Annual meeting of the American Society of Cell Biology 2011, as in addition to our poster presentations, the models were displayed at the company booth throughout the meeting.

The consortium members have sat down to discuss criteria for pricing and have agreed on a common price category for all academic work, rather than distinguishing between their own university and others. BI-EM and BI-cryoEM adopted the new pricing scheme from May 2011, and BCO-EM will start 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.

Our consortium gained a lot of visibility as BCO-EM organized and hosted the Annual Meeting of Scandinavian Microscopy Society (Scandem 2011) in June. 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. The BI-

User statistics

	BI-EM	BI-cryoEM	BCO-EM	Total
Total number of research groups	73	13	38	124
local academic research groups	53	6	25	84
national academic research groups	12	5	7	24
industrial users	4	0	1	5
international users	4	2	5	11
Microscope usage (hours)	3634[n]	788	600	5022
Specimens prepared	508*	529[#]	1204*	

* 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] 1 539 hours of invoiced TEM & basic FEG-SEM use, and 2 095 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).

cryoEM has been taking 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. During 2011, Helsinki units organized four lecture and practical courses in collaboration with local graduate schools and with Aalto University.

Future perspectives for 2013–2016

The most significant impact of Biocenter Finland has been in strengthening the work force in the technology platforms. The best utilization of the platform comes when it is properly supported by specialists. This investment must be secured for the future to meet the expanding needs of the community.

BI-cryoEM and BI-EM aim to set up together the sectioning of high-pressure frozen, vitrified specimens to aid correlated light and electron microscopy studies as a new technology service. This will need a dedicated room, equipment and personnel (estimated costs 500,000 €) and a better high pressure freezer that can vitrify the thicker specimens appropriate to these techniques (estimated costs 300,000 €). There has been a major breakthrough in TEM digital camera development during the past year with the appearance on the market of direct electron detector cameras (DEDC). Such a camera would improve both cryoEM and electron tomography imaging significantly. The estimated cost of a new DEDC for the BI-cryoEM Tecnai F20 is ~500,000 €. In BCO-Oulu, all SEM analysis is done using the instrument in the Center of Microscopy and Nanotechnology, which is heavily booked. There is an increasing interest for SEM-based analysis in biomedical research, and a purchase of a new instrument equipped with a cryostage would both reduce the long waiting times and allow development of new technology platform services (estimated costs 350,000 €).

Participation in international and European infrastructures

BCO-EM belongs to Oulu Bioimaging network (OBI), which joins the biological, biomedical and medical imaging expertise with the machine vision and optoelectronics expertise. The OBI network has one FiDiPro professor, five spin off companies and is integrated with the Euro-BioImaging ESFRI network. BI-EM and BI-cryoEM are members of Helsinki Functional Imaging Center which is a stakeholder in the preparatory phase of Euro-BioImaging and a member of the European Light Microscopy Initiative (ELMI) and European Institute of Biomedical Imaging Research (EIBIR).

From January to July 2012 Euro-BioImaging conducts a series of proof-of-concept studies and therefore offers free access to European advanced biological and biomedical imaging facilities. BI-EM will host one Proof-of-concept project coming from the Technical University of Munich, Germany.

PLATFORM

National *In vivo* Imaging Platform

Chair of the consortium: Olli Gröhn, BCK, Biomedical Imaging Unit and National Bio-NMR Facility
Members: Juhani Knuuti and Cecilia Sahlgren, BioCity, Turku PET Centre and Cell Imaging Core, Turgut Tatlisumak and Anu Wartiovaara, BCH, Experimental MRI Laboratory

Development and restructuring of technology services

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 2011, 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 both the quality and quantity of the services have significantly improved. The network has now 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, non-academic) has increased by 32% providing evidence that this activity has opened up the facilities to a wider user community thus leading to significant restructuring of *in vivo* imaging at the national level.

In 2011, the following steps have been taken to improve availability and promote excellence in different *in vivo* imaging modalities.

The capacity of PET tracer production in Turku PET centre has significantly increased. This was 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 are currently being 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, networking of the *in vivo* imaging consortium has created a scenario where preclinical PET imaging can also start in Kuopio in 2012, using the expertise provided by partner Turku in the implementation of the new imaging modality.

A new 7T MRI scanner was acquired to replace 13-year-old 4.7T MRI scanner in Kuopio. As a result, the capacity to perform state-of-the-art preclinical *in vivo* MRI was doubled. In addition, we have ordered a unique custom designed gradient set for 9.4T/31cm MRI system (delivery spring 2012), which was developed in a collaborative project with Agilent Technologies and International Electronics (IECO, Espoo, Finland). The new gradient set has an extremely high duty cycle and extra strong 3rd order shimming, allowing faster imaging with higher resolution, making possible more demanding diffusion MRI and fMRI as well as high quality MR spectroscopy.

As an indirect consequence of the actions taking place in Kuopio, preclinical MRI will also become available in Oulu during 2012. The 4.7T magnet from Kuopio has been transferred to Biocenter Oulu and will be upgraded with funding from the University of Oulu to serve as a basic level preclinical MRI instrument. MRI services are also provided in Biomedicum Helsinki, with a 4.7T MRI system. During 2011, this was closely integrated as a part of the multimodal imaging platform, especially in association with optical imaging.

During 2011, major advances in optical imaging have taken place in a new dedicated *in vivo* imaging laboratory in Biomedicum Helsinki. This will host new optical imaging systems, including an intra-vital multiphoton (MP) microscope with optical parametric oscillator, which will allow extended wavelength capabilities in order to serve the growing use and importance of red shifted fluorescent proteins in the phenotypic characterization of genetically modified rodent models. In addition, a new 3D optical projection tomography (OPT) system has been purchased. Thus, the range of *in vivo* approaches will be expanded to bridge the dimensions from subcellular resolved MP imaging, to small organisms and whole organs with OPT, and whole animal imaging using the optical and MRI platforms. The purchase of a 3D fluorescence molecular tomography (FMT) system especially suited for multimodality and co-registration with MRI or CT will take place in spring 2012.

The establishment of a National BioCARS center by partner Helsinki will take place during 2012. Label-free imaging methods, Coherent anti-Stokes Raman Scattering (CARS), SHG and THG, will serve as additional spearhead technologies for *in vivo* imaging, offering an important new opening also at the international level via the Euro-BioImaging ESFRI and EU COST action MicroCoR consortium.

Another aim has been to upgrade the optical imaging infrastructure in Turku. Currently, *in vivo* optical imaging has been based on bioluminescence and fluorescence imaging. Tomographic optical imaging with quantitation would improve the usage since it allows the co-register of PET, CT or MRI to yield an anatomical and functional hybrid approach. The optical device purchase process was delayed, but currently the quotations are under evaluation and the purchase decision will be made in January 2012.

User statistics

Number of research projects (research groups) in 2011.

	Kuopio	Turku	Helsinki
Total number of projects	30	46	22
Local projects	17	27	21
Other domestic projects	5	5	1
International	2	8	0
Non academic projects	6	6	0

Future perspectives 2013–2016

The importance of *in vivo* imaging as a major research tool in translational medicine is increasing. Two general trends can be seen in technological development: Basic level imaging equipment is becoming more economically feasible making it possible to establish several multimodal preclinical *in vivo* imaging centers in Finland. On the other hand, the state-of-the-art instruments are becoming increasingly expensive and application of the high-end technologies can only be made in dedicated imaging centers harboring the specific expertise, thus justifying national centers for the most expensive *in vivo* imaging modalities.

Significant investments have already been made on the instruments. To get full benefit from these investments the continuity of the personnel has to be guaranteed. This is especially important as the running of these imaging facilities requires highly specialized experts and any gap in funding may result in losing these key personnel. The current levels of staffing are essential for the sustainability of our services to the large user community with increasing needs for sophisticated *in vivo* imaging technologies.

One of the key issues for future success is the availability of animal models for human diseases. In each of the three contributing Biocenters a large variety of rodent models are available. For translational imaging larger animal models, such as swine are also needed.

Rapid advances in imaging technologies generate large multidimensional data sets typically of the order of gigabytes and up to terabytes. There is a clear need for centralized data management and standardized visualization and analysis tools. Each of the participating imaging centers are currently developing their own solutions for this, thus there is clearly a need for harmonization and more general solutions to allow remote data management and collaboration with partner units of the National Imaging Infrastructure Network.

The PET imaging component of the consortium is currently at a world class level. The newest development in this field is a hybrid imaging system that combines both PET and MRI. This hybrid system was installed in Turku in 2011. The main challenge is to get these novel systems to run effectively and to establish dedicated toolboxes for preclinical imaging. The availability and development of new tracers is a continuous challenge and a key issue for the future success. Basic preclinical PET imaging using F-18 -based tracers (such as FDG), should be established also in other participating Biocenters to make multimodal imaging more easily available across the country.

Overall, the situation regarding MRI instrumentation in the consortium is at the top European level with the most advanced instrumentation located in Kuopio. However, the MRI field is rapidly developing and, for example, new advances in parallel transmit RF technique are becoming available in preclinical MRI scanners in a few years time, requiring upgrades to maintain the availability of the state-of-the-art techniques. MRI microscopy (mice *in vivo*, and *ex vivo* tissue samples) is currently done on a 9.4T MRI system in Kuopio (magnet purchased 1995, console upgrade 2002). This should be replaced during the next 3 year period with a high field (11.7–14.4 T) MRI microscopy system. Basic preclinical MRI should also be developed in different Biocenters to provide multimodality at the local level. In particular the 4.7T MRI system in Helsinki, purchased in 2002, needs a major upgrade or replacement during 2013–2016

In 2013–2014 the animal facilities will be re-organised at the University of Helsinki due to the completion of the new rodent house at the Viikki campus. This will affect also the animal logistics due to the differing microbial pathogen status of the units. Both optical multimodal and MRI imaging facilities are concentrated at the Meilahti campus allowing animal transfer between the units. Further developments include spearheading the CARS technology for preclinical diagnostics of GM models, and developing the MP platform for fluorescence life-time molecular imaging. Current pressing needs include also the purchase of a preclinical micro-CT X-ray scanner for high-resolution 3D FMT-CT multimodality, especially required for cancer research.

Participation in international and European infrastructures

The national *in vivo* imaging platform participates in the Euro-BioImaging ESFRI initiative as one of the European sites for 'proof-of-concept' studies in the 'Molecular imaging' Work Package. Two *in vivo* imaging studies have been selected to be performed in 2012; 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.

The national *in vivo* imaging platform is also linked with other ESFRI initiatives. In EATRIS, Turku PET Centre is one of the two centres 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.

In collaboration with CSC, FIMM and the University of Helsinki IT Services, partner Helsinki is establishing a platform for data storage, management, visualization, and analysis. CSC has recently expanded its cloud services to offer cluster computing for the biomedical sector, which is to form a part of the emerging Finnish node in the European life science ELIXIR ESFRI infrastructure. This platform will be hosted on the cloud as one 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 (TBI)

Members: Daniel Abankwa, BioCity, Turku BioImaging (TBI); Elina Ikonen, BCH, Biomedicum Helsinki Imaging Unit (BIU); Maria Vartiainen, BI, Light Microscopy Unit (LMU); Michael Courtney, BCK, Multimodal imaging core of Biocenter Kuopio (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.

Development and restructuring of technology services

Thanks to BF funding the light microscopy scene of Finland has entirely changed. From being a country with relatively modest microscopy facilities, Finland is now among the leading European nations in terms of available advanced instrumentation. In a recent pan-European survey made by the Euro-BioImaging ESFRI network, Finland had the best open access imaging infrastructure facilities per capita among the participating Euro-BioImaging nations.

The clear national and local division of tasks, with different core facilities spear-heading technologies that are closest to their expertise area, has yielded impressive results. The BF-linked imaging units are now developed based upon common principles, offering nation-wide completely open access services with harmonized user policies that are published on the web pages of the involved units. These units are well networked and highly interactive, leading to significant synergistic effects. The units have also recruited new personnel, representing leading experts in their own fields. Thanks to this development, the Finnish units are in many respects exemplary for open access imaging units within the Euro-BioImaging community. Importantly, the established techniques are clearly those that are in highest demand among the European countries (unpublished Euro-BioImaging survey results). Finland has clearly taken significant steps towards establishing true European imaging nodes with imaging techniques that are in high demand.

The funding from BF has taken Finland into the lead among super-resolution imaging centers in Europe. Super-resolution center has been established at the Cell Imaging Core of Turku BioImaging and one is being developed at Biomedicum Imaging Unit. In Turku the stimulated emission depletion (STED) super-resolution platform was in general use already in the summer of 2010. A significant development was the installation of the second channel in 2011. Currently both channels are operational and have been successfully employed by local and visiting researchers. The site is a Euro-BioImaging proof-of-concept site on Working Program "Access to Innovative Technologies". Ten proof-of-concept studies from both Europe and the United States have been approved to take place during January–June 2012. A major unique initiative 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. The aim is to have all these imaging modalities combined with the STED unit, which will yield us unique possibilities to assess molecule quarternary structure, behavior, and turnover, by using completely different imaging techniques integrated into the same platform. Moreover, Turku will purchase a live-cell total internal reflection microscopy (TIRF)-microscope, which provides very high resolution in the z-dimension. A single-molecule localization super-resolution platform (photo-activated localization microscopy; PALM) is planned to be placed on the same instrument.

Super-resolution techniques are also developed within Biomedicum Light Microscopy Core. One of the spear-heads of this unit is high-end confocal and super-resolution imaging using single molecule techniques. The establishment of sub-diffraction super-resolution techniques will continue in collaboration with Turku BioImaging, and

Biomedicum Imaging Unit will establish a national reference site for multichannel 3D stochastic optical reconstruction microscopy (STORM) unit in partnership with Nikon Instruments Europe B.V. The latter has been constructed on an operational TIRF microscopy platform. With STED, PALM and STORM, the BF super-resolution initiatives will include all major super-resolution imaging modalities.

Approaches to develop high-content and high-throughput imaging had been made already before BF was established, but following specific investments in these technologies, significant advances have been made in the past two years, with increased national availability of High Content Analysis (HCA) type instruments. There are very good possibilities to interact with other BF infrastructure networks, for example those for Genome-wide Methods and Translational Technologies.

During 2011, the restructuring greatly improved the range and flexibility of HCA facilities available to users in Finland. 2011 has seen several instrumentation-related improvements at the Multimodal Imaging Core in Kuopio (high-content imaging with live-cell incubator option including high-throughput imaging of model organisms as *in vivo* disease models). The Multimodal Imaging Core has also made agreements with BF DDCB/Translational Technologies Network for user access to cell-ready library plates (compounds or siRNA). The development of the unit also facilitated the attraction of a strategic grant from University of Eastern Finland and was involved in an EU application. Moreover, improvements in data handling, as well as instrument set ups and further HCA assay development are actively pursued. The unit participates in EuroBioImaging proof-of-concept studies.

Biomedicum Light Microscopy Center has provided complementary imaging services to partners in the BF Genome-wide Methods technology platform. A partnership between the Biomedicum Bioimaging Unit and the FIMM RNAi Technology Centre has been established based on offering complimentary HCS services on confocal and widefield platforms.

In BI, the LMU is also actively developing its HCA capacity, especially on its recently purchased, Leica SP5 Matrix platform. The overall goal of the unit is to provide a toolbox to study protein dynamics and interactions in living cells and tissues. This goal can be adapted to fit the high-content imaging platform, especially on the Leica SP5 Matrix platform. The same Leica SP5 platform has also been purchased for Turku BioImaging. Attempts are being made to develop these two units in a concerted effort with joint activities and complementarity between the two units. Both Helsinki Light Microscopy Unit and Cell Imaging Core of Turku BioImaging participate in proof-of-concept studies related to advanced light microscopy techniques that could be adopted on the SP5 high-content imaging platform.

The next big leap within microscopic imaging will be adopting various label-free techniques. Several units of the network are already on their way to establish imaging modalities based on various label-free principles. On a European scale these initiatives could be truly consequential.

In order to establish the National BioCARS Centre in 2012, the Biomedicum Imaging Unit will combine BF finances with Academy of Finland FIRI2010 infrastructure funding for a major investment on a confocal CARS (Coherent Anti-Stokes Raman Spectroscopy) platform with additional facilities for Raman microspectroscopy. The Biomedicum Imaging Unit participates in the Academy of Finland 'Photonics and Modern Imaging Techniques' program (2010–2013; as part of the 'Advanced Nonlinear Imaging of Molecular Structures' consortium that also involves Jyväskylä Nanoscience).

Label-free technologies are also the spearhead of the University of Jyväskylä Imaging Facility (Varpu Marjomäki), participating in the National Imaging Infrastructure Network activities. 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. The approach in Jyväskylä is somewhat different compared with Helsinki; CARS signal is obtained in time-domain, which lowers the non-resonant background. Furthermore, a time-resolved 2D-IR spectroscopy setup will be developed during 2012.

The LMU of BI previously purchased a state-of-the-art multiphoton system, which was upgraded with FCS during 2011. While the Helsinki unit is suitable for general purposes, Turku BioImaging has purchased a multiphoton unit specially designed for studying the migration of immune and cancer cells in intravital microscopy. LMU at BI aims to provide a toolbox to study protein dynamics and interactions in living cells and tissues. In 2011, LMU acquired with BF funding a new wide-field system, which permits fast live-cell imaging experiments. During 2012, this system will be further upgraded with a spinning disc confocal and frequency-domain Fluorescence lifetime imaging.

Oulu BCO-TIC has purchased new equipments including a system for advanced live cell imaging (spinning disk confocal with TIRF and FRAP units) and, importantly, a digital holographic microscope. BF and University of Oulu funded collaborative project between the

Center for Machine Vision Research at Infotech Oulu and BCO-TIC has started aiming at developing of new type of image analysis services, with additional funding from ERDF (European Regional Development Fund)

Data analysis approaches may be one of the greatest bottlenecks nationally, though this is being addressed in Helsinki by the Bioinformatics Network, in Turku and Jyväskylä by the BioimageXD team and in Kuopio by the MUIC team and Bioinformatics Network.

Future perspectives 2013–2016

The National Imaging Infrastructure Network will provide a highly efficient tool to restructure and further improve the Finnish imaging landscape and to establish interactions with other infrastructure networks. A major asset is the human resources and the facilitated intellectual and technical interactions. Some national spearheads that can be employed to establish European nodes of excellence have been identified. The super-resolution stronghold will clearly be a platform to build upon, with already demonstrated European impact. Label-free imaging technologies comprise a nation-wide development platform with broad ramifications into different application areas. These technologies often represent a continuum from *in vivo* imaging technologies and they can benefit from highly specialized expertise within chemistry, physics, and engineering way beyond the existing imaging core facilities. While CARS microscopy is already featured (Helsinki and Jyväskylä), there is interest both in Helsinki and Turku for Stimulated Raman Scattering (SRS) microscopy to enable background free and quantitative vibrational imaging. A novel label-free imaging modality at the crossroads between *in vivo* and cellular imaging is photo-acoustic imaging, will be built by Turku BioImaging biophysicists by the end of 2012.

High-content imaging is also developing fast with a good division of task between Helsinki, Kuopio, and Turku, and with excellent interactions of Helsinki and Kuopio with the Genome-wide Methods network and Translational technologies network. The key components of HCA in the future will be integration, scalability and adaptability. Light microscopy is extremely diverse and ultimately only the on-site staff are sufficiently competent to carry out an integration that maximizes the benefits to users.

The different imaging facilities link to expertise areas that can become highly consequential for future development, including various forms of data and image analysis technologies, data management, computer and machine vision, holographic technologies, photonics, and nanotechnologies as well as material science. Especially Oulu has well established interactions with technology developers interested in photonics and visualization technologies. The special technology ramifications provide an excellent national platform for interdisciplinary development of imaging technologies and future development in diagnostics and technology transfer.

Beyond 2012, a major bottleneck will be personnel salary costs as they derive from external sources with fixed term. Considering the major investments in sophisticated instrumentation, it is essential that the salary costs of key support personnel will be secured in the long term.

Participation in international and European infrastructures

The BF light microscopy consortium participates actively in Euro-BioImaging 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 Package 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 participate in the proof-of-concept studies of Euro-BioImaging.

User statistics

	BCH	BI	BCK	BCO	IBT	BioCity	Total
Total number of customers	81	46	15	26	11	82	261
local users	80	45	13	20	10	78	246
other domestic users	1	1	1	4		3	10
international users			1	2	1		4
non-academic users						1	1
Instrument hours	11 250	8 162	3 102	3 900	684	7 601	34 699

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 initiated through Integration and focusing of local services 2007–2009, was nationally recognized on the Roadmap of National Research Infrastructures 2008, and is undertaking a significant development and restructuring program during 2010–12, where focus is on nodes on the Meilahti and Viikki campuses in Helsinki as well as in Turku.

The 2010–12 program continues 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. A big effort is 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 are developed. High-content screening services are 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

Development and restructuring of technology services

Biocenter Finland is in a key position to maintain and develop genome scale biology technologies in Finland. Due to the very rapid development of next-generation DNA sequencing (NGS) and other genome-wide applications and novel emerging technologies it is of utmost 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 the long term. Without longstanding support it is impossible to keep the highly qualified personnel staying in a university environment. Our recruitment policy has been highly successful during the 2010–2011 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 in Finland and waste of Finnish, in particular BF funding.

Genome scale biology is developing extremely fast. This has had a direct impact on the activity of this network since continuous technology upgrades make 'online' development of our operations necessary. The fast pace of development causes constant restructuring as a modus operandi of the platforms. Nodes of BF network are occupied in developing their assigned areas 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. We think that our achievements during the first two years of BF funding

have demonstrated the strength, power and competitiveness of such a structure and justify further funding, subject to regular external evaluation.

Platform development in all GWM nodes has been rapid due to funding from BF and the host organisations and other sources, thereby broadening the funding base. 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. Restructuring is continuing also in the 2012 following a decision to join DNA sequencing facilities in Helsinki at least for FIMM and Institute of Biotechnology. Altogether the BF-GWM has been made of use in more than 70 publications during 2011 (such as Nature Immunology, Immunity, and Science).

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. Moreover, capacity of CSC is not currently sufficient to accommodate the high demand by our network.

User statistics

A total of 286 research groups have used the services provided through BF-GWM nodes during 2011 with a turnover exceeding 2 760 000 €. 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 a significant increase in activities in 2011 compared to 2010, which already was pointed out to be excellent by the external evaluators.

Future perspectives for 2013–2016

Genomic research is developing very rapidly worldwide and computational biology will play a crucial role in the analyses and storage of genomic data, which urgently need further investments. Strong and fruitful collaboration with the Bioinformatics network should continue and be further strengthened. BF-GWM has been very active and successful both in developing new services and dividing the tasks between the units. This activity will continue with the same pace in future. Whole genome sequencing of human and other mammalian genomes will become feasible for many researchers (1000$ / genome) already during 2012. The human genome is only a measure for the ability of the technologies but this development will radiate more widely to all organisms. The high rate of technology development will open new avenues for studying populations and even sequencing individual patient genomes if necessary. DNA sequencing is likely to be transferred also to clinical work in hospitals in the next few years. Biocenters in BF-GWM network now have ten years' experience in providing microarray services for the whole scientific community. During this time the nodes have built a very large customer base. Despite the advances in the development of next-generation sequencing technologies, so far there has been no decline in the request for microarray services supporting the continued importance of these activities as well.

The BF-GWM has a strong know how on de novo genome sequencing, re-sequencing, sequence capture technologies and related bioinformatics which we are aiming at enhancing and developing further. There is

	BioCity Turku (FMSC)		BI (BIDGEN & GBU)		FIMM		BCH (FuGu)		BCK	
	Projects	Groups	Projects	Groups	Projects	Groups	Projects	Groups	Projects	Groups
Local	40	25	76	62	93	63	97	57	5	5
Other domestic	31	23	20	6	24	18	6	6	2	2
International	7	6	6	4	10	10	3	2	1	1
Non-academic groups/units	1	1	6	6	3	2	6	3		
Total	79	55	108	78	130	93	112	68	8	8

still need for de novo genome assembling even in cases when a reference genome exists. Novel structural variants cannot always be observed if only mapping reads to reference genome is performed independent whether one is sequencing DNA or RNA samples. This is even more true with metagenomes when only parts of the genomes can be covered by sequencing and in which reference data is often lacking completely or is very scarce.

Many applications focusing on the functional features of the genomes are most likely to be even more important in the future. RNA-seq is already commonly used with model species and groups working on non-model species are adopting this approach though the analysis is much more difficult when one lacks annotated reference genome. Metatranscriptomics is an obvious development hindered mostly by the difficulties in isolating relevant samples from complex environments and more CPU heavy analysis.

Transcriptome analysis is likely to transform very rapidly during the next few years. In addition to the already conventional RNA-seq approach there is an entire family of applications that can deepen our understanding of the function and regulation of genomes. Gro-seq is used to detect actively transcribed RNAs, analysis of the RNA complexes via RNA-seq methods such as CLIP-seq and PAR-CLIP will unravel miRNA/mRNA complexes responsible for regulation of gene activity. Frac-seq for analysing structures of RNA and ribosome profiling localizing ribosomes on mRNAs are other new applications. All these existing and all forthcoming novel applications need special focus on technology development so that services can be rapidly provided in such novel applications as soon as possible. Epigenetic markers have already been very efficiently analysed using NGS methods. Epigenomics has become an attractive approach to answer important questions not previously possible. The research activity in this area is increasing at a high speed to investigate the role of DNA modifications and DNA binding proteins in the regulation of gene activity. 3rd generation solutions for a range of applications will be established and further developed closely following the emerging technologies in the field. Automation of sample handling and library preparation will be further implemented. One cannot forget the development of other gene scale reagents produced and distributed via the network.

In the worst scenario, if the direct Ministry of Education infrastructure support to Biocenter Finland would be discontinued, the efforts and results achieved by BF funding so far would be lost. This in turn would result in a rapid downsizing and downgrading of Finnish infrastructures and inevitable drop in competitiveness of Finnish biomedical research. Therefore, it is of central importance that the support for personnel and equipment will be continuing. One important pricing issue is the service costs which are rather large in complex technologies and have a direct effect on the pricing. The excellent BF-GWM has been one of the key factors for high quality research in Finland and if the infrastructure network will be ramped down, it will have severe effects for the quality of Finnish research. In the future GWM network needs to invest in cutting edge technologies/equipment in order to provide such research services to the Finnish researchers. Compared to large sequencing centers we can provide onsite local sequencing service with tailor-made solutions, unique handling for all samples, several different applications (DNA, RNA, Methyl, ChIP, metagenomics etc seq from the same sample) and data integration. A key to our success is to continuously train the Finnish researchers to know the rapidly emerging state-of-the-art technologies available and how to best apply such tools for their specific research questions. Tailored solutions integrating different types of genome wide methods and their computational analysis are essential to be able to solve a range of research questions in an innovative fashion.

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. Examples of such funding include participation in European projects (e.g. DIABIMMUNE, NANOMMUNE, PEVNET, SYBILLA) or European infrastructures, e.g. EU projects: Systems microscopy, BioMedBridges, Innovative Medicines Initiative (IMI) and ESFRI networks (EATRIS, BBMRI).

There are increasing demands for computing power and for storage and archiving in the field of genome-wide methods. FMSC, FIMM and BCH are developing in collaboration with CSC solutions for the above needs via a cloud computing project within the ELIXIR ESFRI program. The GWM network has prepared two national level roadmaps of infrastructures in this area (2007 and 2009) and is in a optimal position to take responsibility both as a node for ESFRI level infrastructures (such as BBMRI) as well as responsibility for a upcoming national infrastructures roadmap.

MODEL ORGANISMS

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 & Juha Partanen/ 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/

Development and restructuring of technology services

Gene modified (GM) mouse strains are increasingly used in biomedical research. Use of specific animal strains provides possibilities to study human diseases or other conditions from a gene to the living animal, and they are also remarkable tools for basic research. Controlled use and efficient production of mouse models are essential parts of modern biomedical research. Core facilities offer possibilities for both reduction of animal numbers used and refining their life and welfare. 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.

Following restructuring of activities for 2010–2012, generation of genetically modified (GM) mouse models has been centralized to Biocenter Finland service facilities in Helsinki, Oulu, and Turku that provide services in transgenic and gene targeting technologies. An essential activity in all units is also the assistance in transfers of mouse lines between facilities in Finland as well as abroad. Instead of living mice, mice are shipped as embryos, which prevents stress to animals and also helps to avoid spreading of pathogens. Animal health and microbiological quality are of utmost importance in the modern research. Embryo transfer to a recipient female is the most effective way to get rid of the infections or diseases not accepted in the laboratory animals.

The FinnMouse collaboration has greatly improved the exchange of best practices and new methods, and the net-

work has initiated standardization of procedures in the core facilities through technology workshops. In specific technologies a high level of specialization has been achieved: The Helsinki unit specializes in mouse chimera generation by the morula aggregation method; the Turku unit provides services in generation of gene constructs and tumor xenografts in immunodeficient mice; the Oulu unit has set up the lentivirus injection method and is involved in development of cryopreservation technology. The units have special service profiles, Turku Center for Disease modeling (TCDM) having links to several pharma and biotech companies, Oulu unit is serving as the EMMA (European Mouse Mutant Archive, www.emmanet.org) node that provides repository services, including cryopreservation and distribution of GM mouse lines to a wide user community. In Helsinki, ongoing restructuring of animal facilities is expected to improve the services and reduce costs. The Helsinki unit also plans to start generation of GM rats in future.

The FinnMouse technology platform has set up a web interface, www.fingmice.org, which provides information about services and expertise in generation and analysis of GM mice available in Finland. New features, such as a database containing the services and tests available in mouse phenotyping, are being developed and will be added to the web page.

For phenotypic analyses of mice, specific areas of expertise are being strengthened and tests and services developed and validated. Neurophenotyping Centers in Helsinki and Kuopio provide services in automated behavioral phenotyping and in specific neurophenotyping tests with new protocols under development both in disease models (Azheimer'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 and analysis of cardiovascular functions, with analyses of cardiac structure and special heart failure models being developed. TCDM has put special emphasis on the development of live animal imaging technologies. In addition, two new phenotyping units (intestinal disease and thyroid biology) have been established, and new methods in pharmacokinetic and biomarker studies are being 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.

All core facilities are engaged in education of graduate students and postdocs in laboratory and lecture courses. Workshops on specific subjects are organized for scientists and technical personnel. In addition to 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. A web-microscopy infrastructure is being developed, where BF has provided funding.

The BF funding has made it possible for all units to recruit new personnel, which has improved the quality and widened the repertoire of services. Well-trained personnel is of special importance in animal experiments. Pricing of established tests and services are being calculated if not in use yet. An important item is the increase in the exchange of know-how and the awareness of special expertise in other service laboratories, and the information is and will be distributed to the large user community in special occasions.

User statistics

	Research groups/customers				
	Local	National	International	Non-academic	Total
TG/GM unit					
Univ. Helsinki	30	3	-	-	33
BCO Univ. Oulu	20	6	14	-	40
TCDM Univ. Turku	20	5	9	1	35
Phenotyping					
FCLAP Univ. Helsinki	26	0	0	0	26
NC Univ. Helsinki	7	1	0	0	8
NC Univ. Eastern Finland Kuopio	4	3	-	-	7
TCDM Univ. Turku	60	20	8	9	97
BCO histology	17	-	-	-	17
BCO *in vivo* imaging (echo, IVIS)	6	-	-	-	6

Future perspectives for 2013–2016

Large European and more recently also global consortia for generation (www.knockoutmouse.org) and phenotyping of mouse models (www.mousephenotype.org) have been formed, which reflects the importance of mouse models in modern biomedical research. The availability of targeted embryonic stem cells for generation of mutant mouse lines and embryos from repositories will increase the use of mouse models especially in preclinical translational medicine. New tools for genome editing, increased use of miRNAs, and production of complex tumor models with GM mice as a starting material include manipulation of mouse embryos. Sustained funding for GM core facilities is essential to maintain the high quality of services, which is guaranteed by permanent, well-trained personnel. FCLAP represents one of the few facilities in Europe dedicated to the training of veterinary pathologists in laboratory animal pathology, and appointment of a fully trained laboratory animal pathologist on a long term basis is essential to provide service and allow training. Combination of research techniques to improve phenotyping and modeling human diseases will also increase, and national and international collaboration will be extended.

Upgrading of animal facilities with high-level hygiene status, and building specific quarantine and isolation units is required. Due to huge increase in information about mouse genome and phenotypic characteristics, data management is becoming extremely important for utilization of the data produced. The core and animal facilities must be equipped with proper equipment and data programs. In general, collaboration with other BF technology platforms (e.g. imaging, bioinformatics, and viral gene transfer) is likely to be increasing.

Participation in international and European infrastructures

University of Oulu has represented Finland in the ESFRI project Infrafrontier, the European Infrastructure for Phenotyping and Archiving of Model Mammalian Genomes, during the preparatory phase which will end in 2012. Finland signed the Memorandum of Understanding on preparing a European Mouse Phenotyping and Archiving Infrafrontier in July 2011, and negotiations on its legal status are ongoing. Oulu is also a partner in the EMMA network and in the FP7-Capasities proposal Infrafrontierscale that was submitted in October 2011. 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 provide training. Joining in Infrafrontier will thus guarantee Finnish scientists an access to services and newest information in the field on one hand, on the other hand it provides Finnish researchers an opportunity to present their expertise, increase scientific collaboration, and participate in technology development.

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 Unversity of Glasgow and the German Mouse Clinic.

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: Mataleena Parikka, IBT, Tampere Zebrafish Core Facility; Susanna Valanne, IBT, Tampere *Drosophila* Core facility; Tapio Heino, Helsinki *Drosophila* Core Facility

Development and restructuring of technology services

Tampere has focused primarily to develop research infrastructure for non-mammalian models (namely *Drosophila*) and zebrafish. In addition, infrastructure and knowhow in Helsinki related to both *Drosophila* and zebrafish is important to provide service locally. Biocenter Finland funding has been essential to carry out the expansion of the Tampere Zebrafish Core facility. In addition, the funding has been vital to for the routine maintenance of the system including salary for one technician. Besides BF, the routine maintenance of the system is secured by funding from other sources to technician and facility manager. For the Tampere *Drosophila* Core facility, BF funding has enabled to hire a

50 % coordinator who devoted her time to establish a new, centralized space for the facility.

By the end of 2011, the Tampere Zebrafish core facility is fully operational after the Phase two expansion of the zebrafish maintenance system, which was purchased from Aquatics Habitats, the leading company providing automated systems for maintenance of zebrafish for research purposes. Tampere Zebrafish laboratory has now capacity to maintain up to 50,000 zebrafish allowing large-scale forward genetic screening. Currently, the laboratory employs a full-time coordinator and three technicians. Numerous researchers from several research teams from the University of Tampere, University of Jyväskylä and University of Oulu have used the facility. Besides on-going process of creating mutant zebrafish families (very recently, the first F3 generation mutant fish were obtained), we maintain zebrafish lines for scientists in the facility, carry out microinjections for production of transgenic zebrafish and for morpholino-based gene silencing, and provide assistance in initial phenotype characterization. Furthermore, our platform organized a week-long hands-on training course for the use of non-mammalian model organisms for research in life sciences in September 2011.

In Tampere, a new *Drosophila* Core Facility has been built. This investment was done by the host institute IBT. The new laboratory includes 12 working stations with stereomicroscopes and carbon dioxide points for anesthetizing flies. In the next room, a new fly food kitchen is built with facilities to cook, cool, refrigerate and store the food and ingredients. Users of the Core Facility currently include a total of eight research teams from the IBT as well as international collaborators including FiDiPro Dan Hultmark's laboratory members in Umeå, Sweden and Professor M. Williams's research group in Aberdeen, UK.

In Helsinki, during the year 2011 the three groups (Heino, Hietakangas and Shimmi) have offered *Drosophila* facilities, knowledge and guidance to six groups in the Viikki Biocenter that do not use fruit fly as their main research model. The Viikki unit has also donated flies to several secondary schools in Finland.

Future perspectives for 2013–2016

Demand for ethically acceptable animal models will steadily increase towards 2016. Thus it is easy to envision that there is increasing number of consumers for zebrafish and *Drosophila* core facilities both in Helsinki and in Tampere. The basic infrastructure for both zebrafish and *Drosophila* research is currently at an appropriate level and also the knowledge to run core facilities is appropriate. The major challenge for the years 2013–2016 is to maintain current and well-trained personnel at each core facility. Thus the major need for future funding will be salary costs to ensure that trained personnel that run the facilities can be maintained. On the other hand, there will be more and more users of all four non-mammalian model organism core facilities and thus expenses can be partially/substantially covered through user fees. However, Biocenter Finland infrastructure funding will be necessary to maintain the best possible core facility managers by allowing long-term contracts.

In conclusion, access to state-of-the-art non-mammalian model organism core facilities is extremely valuable for the scientific community as these platforms allow generation of high quality *in vivo* data with large numbers of organisms. In addition, powerful genetic tools allow such innovative genetic experiments that may be impossible in mammalian systems.

As a new emerging technology in the field the zinc finger nuclease methodology will be developed to produce gene knock-out fish (reverse genetics). This development is planned by Helsinki Zebrafish Core facility led by Professor Pertti Panula and will be funded tentatively through another Biocenter network.

User statistics

	Groups			Animals *Larvae/adult		
	Total	Local	Domestic	Total*	Local*+ Domestic	International
Tampere						
Zebrafish	9	6	3	155 376 / 6 091	122 169 / 10 519	
Drosophila	9	8	1	~ 1 000 000		
				~1 000 lines		
Helsinki						
Drosophila	9	9		~3 500 independent lines		

PROTEOMICS AND METABOLOMICS

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; Jean-Christophe Yorke, 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 life science areas.

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.

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.ProtMet.net

Development and restructuring of technology services

In 2011 all facilities of platform reported an increase in use of new technologies and research services nationally. Many newly funded instruments became available in 2011 and had a striking effect on the overall activity of the network. A near doubling of services was reached in 2011, even without the full-time operation of most instruments. Approximately 50% of the customers are from outside our own institutes. Thus the model of a national network is catching on and growing. The overall increase is further noticed in all metrics with significant growth in volume of the total number of research groups – local, domestic and international – and in the overall volume of services, which has also served to increase the annual turnover and publications from year to year.

The strategic prioritising of instrumentation purchases nationally has had a significant effect and has ushered in new activities around new measurements. Several large-scale projects have now been intiated in the network that owes this success to the new technologies and skills. Without the impulse provided through BF, it would not have been possible to attract the top tier experts that are required to conduct and lead research services and innovation.

The Proteomics and Protein Characterisation consortium now includes two nodes in Helsinki, and one facility in Oulu, Tampere and Turku. Proteome analyses, which are most in demand throughout the country, are present in Helsinki, Oulu and Turku. Helsinki also provides services in Glycoproteomics at the Medical Faculty. A diverse number of services

in protein characterisation are provided both at Oulu and Tampere, with both sites focusing on unique service areas. Several discussions and meetings have involved researchers at the facilities at Jyväskylä to evaluate how their protein characterisation services can be used by Finnish bioscientists. We are pleased to report that overall the consortium has made significant strides in catching up with our Nordic and European partners, in terms of analytical capability and capacity. In restructuring the activities of the consortium we have been mindful in strengthening local expertise, using existing and newly available resources, and followed the strategies of the individual Biocenters. Where needed, critical services have been duplicated, using similar but not identical technologies, enabling niche technologies to cover 'all angles'. Needless overlaps in services do not exist in the network.

Helsinki, which has two facilities, continued restructuring its campus-wide activities by further focusing Biocentrum Helsinki Facility's (BCH) efforts on clinical proteomics due to its location in the Meilahti Medical Campus (Meilahti Clinical Proteomics Core Facility). A success of this ongoing development and restructuring has been observed by the increase in consultation and project planning in biomedical projects for the facility, including large-scale projects for protein identification by MS. Additionally label-free and labeled quantitation based on dimethylation was introduced and is now offered as a service. To facilitate these services a full-time technician was recruited. Interest in imaging MS (IMS) continues to grow and BCH facility is now part the FP7 DEM-CHILD project started in 2011. Additionally it became a partner in the European COST action on Imaging MS. The BCH node also oversees services in Glycoproteomics, which successfully finished its own software development for fully automated combined peptide identification and glycan structural analysis. New instrument upgrades are planned for early 2012 for both IMS and the Glycoproteomics node. In 2011 a senior scientist expert in glycoprotein analysis was hired on a part-time basis.

The Institute of Biotechnology (BI) has undergone major changes as it is now under the new direction of Dr. Varjosalo who has expanded its activities from protein sequencing and MS services to omics-scale PTMs and quantitative and systems-wide analyses. Respectively, renaming the facility to Proteomics Unit gives a more up to date picture of the current activities. Restructuring the activities at the BI has involved the hiring of one technician (half-time) and three senior scientists. New analyses for the Unit include PTM analysis, label and label-free quantitative and systems-wide analyses. The adaptation and development of these analyses has been greatly facilitated through the acquisition of the Orbitrap Elite Hybrid MS and data analysis software and workflows for quantitative MS analyses, shared with the Turku Facility. Offering wide range of PTM analyses has become possible by recruited PTM-expert and a new lab manager is responsible for the Unit´s day to day services.

Biocenter Oulu has further strengthened its emphasis in biophysical analysis of proteins and 2-DE with the acquisition of new instruments and developments in biophysical protein analysis led by a senior scientist recruited through BF funding. Specifically methods for isothermal titration microcalorimetry, surface plasmon resonance and CD spectropolarimetry have been used in several pilot projects with local, domestic and international researchers. Proteomics and protein characterisation has been bolstered through a BF funded new MALDI-TOF-TOF that has been employed in numerous and diverse projects. Small molecule work analysis on full-length proteins has been enabled through the use of a newly installed Synapt G2 mass spectrometer.

In 2011 the IBT in Tampere expanded services to include protein production and characterization, with a special focus on protein interactions via calorimetric analyses of proteins and their interactions. Two new instruments housed in the IBT have increased capacity in the quality and throughput for protein characterisation. Several developments worth mentioning are installation of a ForteBio Octet RED 384 instrument equipped with 16 parallel biosensors, to provide high throughput analyses on protein quantitation on 384-well plates (1hr), and kinetic screening and characterization on 384-well plates (2hrs). The DSC instrument installed in 2010 has been actively used in approximately 1200 scans in 2011. BF funding has also allowed us to hire a coordinator to this project, taking over responsibilities for calorimetric analyses and chromatographic services, and design of protein expression constructs as well as expression and purification experiments prior to scale-up in our pilot scale fermenter.

Finally, the Turku facility has largely focussed on the further development of national services on proteome-wide quantitation, targeted quantitation and large-scale analysis of protein phosphorylation and

validation methods. These elaborate methods involve an integrated workflow from sample to validation of results spanning many skills from post-doctoral scientists as well as many sophisticated technologies. New methods, allowing single-step quantitative analysis of 1000s of phosphorylation sites, developed in our facility, are now in use by Finnish researchers nationally. In parallel with other researchers at the Facility computational methods now exist that enable the automated validation of such measurements. Unique to Turku is the parallel targeted quantitative MS analysis, known as SRM analysis. A new senior scientist recruited in mid 2011 to spearhead these developments has evaluated five instruments for targeted quantitative analysis, and has set-up a computational framework for design and analysis of SRM experiments.

The installation of the new instruments and allied technologies will take place in early 2012. A measurable interest was observed for MS services and a record number of instrument hours was achieved for a single MS instrument, the LTQ OrbiTrap Velos MS (BF funded), in 2011 despite the installation and further downtime due to instrument repairs and updates. An upgrade to a LTQ OrbiTrap Velos PRO will take place early in 2012. The impact of the instrument can be witnessed by the central role it plays in several high-impact grants such as the recently funded Academy of Finland Centre of Excellence and a FiDiPro (TEKES) in proteomics. Furthermore the Facility will now co-chair a new European COST action on Biomedical imaging in Mass Spectrometry that involves the BCH arm as well.

Continued development of methods and services has again been achieved by all platform nodes: since the inception of BF, our publication list now spans (~150 peer reviewed publications). 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 Centre's of Excellence, FiDiPro, and Academy of Finland Professorships as well as national and international funding (FP7, COST).

Again outreach activities were emphasised in 2011. Numerous workshops and training courses have been organised in several different forms. The elaborate activities of the network's researchers start with the role of these facilities in teaching at under-graduate and graduate schools. More than 10 graduate schools received teaching from the network, and several hands-on courses were organized throughout the country. The annual Summer School in mass spectrometry was also continued. Furthermore it should be noted that a wide scope of bioinformatics courses were held in specific proteomics niche areas, as well as several more general methods including programming and statistics. Additionally, the network was actively involved in training in Master's programs, and training of Master's and PhD students. Most of the courses offered are not funded directly through BF, and have been funded through national organisations or international agencies including ESF, NordForsk and EMBO. The personnel from our facilities are however the backbone to these activities and are of critical essence for the continuation of outreach activities.

The www.ProtMet.net website continues to act as a primary medium for the promotion of our activities, as well as serving as a single location for all information about platform services. Besides information on seminars, courses, workshops etc. it also provides a direct means to information and developments about services and responsibilities within the national network (including metabolomics). In addition the website promotes research competence within the overall ProtMet network, the associated Biocentres, and in doing so highlights Finland as an attractive place to conduct research. The promotion of the services and operations of the ProtMet.net to the Biocenter Universities, other Finnish universities, national and local life science organisations and industry have taken place at national and international conferences, and have been promoted at the national Users Days.

User statistics

A dramatic increase in activities was noted for 2011 by almost a doubling of service projects and a large-increase in the number of outreach activities. For 2011 the network has performed collaborative research services for more than 17,250 hrs (from 10,000), servicing 142 (from 120) research groups. A true measure of success of the national scope of the network can be found in the ratio of local to national customers. Overall, 81 (57%) local research groups sought services from local facilities, whereas 62 (43%) groups required services from a network facility outside their host institution. In outreach activities this ratio is even higher. Fourteen research groups from outside Finland required our services. In 2012 we expect an increase in overall national and international activity, due to international projects and the dissemination of activities.

	BCH	BI	BCO	IBT	BioCity
Total number of research groups	28	43	29	10	32
Local	22	15 (BI)	20	2	22
Domestic	4	39	4	8	7
International	2	4	5	0	3
Volume of services (instrument time in hrs)	2790[a,b,c]	3200[d,e,f]	6100[g,h,i]	729[j,k,l]	4433[m,n,o,p ,#]

Specifications

a: MS proteomics: 1850 hrs. MS analysis and sample handling for clinical proteomics/non-clinical proteomics and peptide screening-profiling.

b: MS glycoproteomics: 670 hrs. MS analysis and sample handling for glycoproteomics analysis.

c: 1D-2D-GE, LC analysis: 270 hrs

d: MS: 1700 h

e: Edman sequencing: 1200 h

f: Protein/peptide purification LC: 300 h

g: 416 2D gels, estimated instrument use: 3100h

h: MS, estimated instrument use: 1600h (Ultraflex, Synapt, Q_ Tof2)

i: ITC: 200h,CD: 420h, Biacore: 794h

j: Calorimetry: 178 h

k: Protein production: 417 h

l: Chromatography and others: 134 h

m: LTQ Orbitrap Velos: 2321 h

n: QSTAR Elite: 1728 h

o: QSTAR Pulsar: 108 h

p: Ultraflex: 276 h

Only instrument times recorded. IT-services, peptide- and protein purification not included

Table. Research groups (or other costumers) who have used the services

Future perspectives for 2013–2016

Biocenter Finland funding to our network has ushered in a new era of research in proteomics and metabolomics Finland, of which the full impact is only witnessed scarcely in this report. The new stimulus has prompted nationally coordinated economical decisions and acquisition of critical instrumentation. This has enabled scientists to extend their view on increasingly intricate detail and complexity. Through new instrumentation and acquired skills our researchers can now compete, internationally, and generate unpredictable new ideas and opportunities. In particular the new instruments and technologies, that are increasingly sophisticated and accurate, have allowed us to learn and build new materials and procedures. Now scientists with the right tools will continue to respond to ideas and opportunities with new skills and inventions. Exact instrument requests for the future are therefore not known, but the elements required for success are clear in that current hurdles we face can only be tackled through new technologies. It is envisaged that the amount of funding for personnel and instrumentation remain the same, albeit and increase in dedicated computationally trained personnel will be required.

Participation in international and European infrastructures

Several nodes of the network have been actively involved in enabling nation-wide access to international and European networks and infrastructures and several grant applications are underway. With the final implementation of BF funding, we expect to see an increase in international activities for 2012 and 2013. Noteworthy projects are new areas such as the participation of the imaging mass spectrometry community in two individual COST Actions, recognising our expertise in this area. Furthermore, the network was invited to the ESFRI 'Infrastructure for Systems Biology' (ISBE) preparatory phase application. Other active areas for the network have been coordinating three Nordic networks, and involved in several Nordic networks as active members. The platform supports projects supported by FP7, ERC and other international grants.

PLATFORM

Metabolomics Technology Platform

Chair of the consortium: Seppo Auriola, BCK, Department of Pharmaceutical Chemistry
Members: Tapio Palva, BCH, Metabolomics Unit; Jean-Christophe Yorke, FIMM, Metabolomics Laboratory; Matej Orešič, FIMM/VTT

www.ProtMet.net

Development and restructuring of technology services

During 2011 the Metabolomics Technology Platform continued to take shape, as the last instruments were purchased and installed. The year 2011 was the period for very intensive method development and analytical optimization, as well as final structuring of the services to be provided in each center.

The Metabolomics unit of BCH specializing in plant metabolic profiling has offered services since 2004 supported by the mass spectrometry (MS) group at the Faculty of Pharmacy. Since then, services have expanded their focus from mainly plant metabolomics to both targeted and nontargeted analysis of microbial metabolites. The new UPLC-q-TOF/MS became operational in March 2011 even though during the whole year 2011 Waters had to replace several parts and reinstall software before instrument became fully operational. Furthermore the University of Helsinki financed a new GC-MS from its infrastructure funds, which became operational in April 2011. Testing and method development was continued during and after summer holidays until the end of year. BF funding together with that of the host university removed the serious bottlenecks encountered in 2010 due to equipment limitations. Thus the unit is now fully functional and capable of providing improved high throughput metabolomics services to its customers.

The FIMM metabolomics unit focuses on targeted quantitative analyses of endogenous metabolites in high throughput manner. A list of metabolites has been created in January 2011. Different classes of metabolites that were included in the list were, sugars, nucleotides, nucleosides, nucleobases, organic compounds, bile acids, amino acids, central carbon metabolites, TCA cycle, urea cycle and neurotransmitter metabolic intermediates, enzyme cofactors, etc. All the available information about these metabolites was retrieved from the Human Metabome DataBase (HMDB, www.hmdb.ca). An in-house database has been developed covering the details of HMDB ID, chemical formula, molecular weight, structure, CAS, KEGG, METLIN & pubchem IDs, water solubility, concentration ranges etc for about 150 polar metabolites in autumn 2011.

A Waters Xevo TQ-S triple quadrupole mass spectrometer (UPLC-MS/MS system) has been installed in May 2011. An analytical method for the extraction of some of the endogenous polar metabolites has been developed during the summer 2011 that includes fast and simple preparation techniques (protein precipitation), separation of a mixture of basic, neutral and acidic molecules within a single chromatographic run (Hydrophilic interaction liquid chromatography, Hilic) in short run time (15 minutes/run, i.e., 96 samples in 24 h).

One pilot study with human plasma samples coming from the Red Cross was run in December 2011 to assess the performance of the developed method. At present we are calculating the concentration levels of the metabolites in the samples. Sample extraction method for rest of the 1/3rd of the compounds still needs to be developed and optimized. The robot from Hamilton, MicroLab Star has been installed in June 2011 followed by a training session in July 2011. We have programmed the developed sample extraction protocol into the software and successfully implemented. We have also utilized the robotic system to make serial dilutions of pure compounds in order to make calibration curves.

The unit in Kuopio focuses on non-targeted metabolite profiling experiments. The installation of the LC-qTOF-MS instrument was initiated in May 2011. Testing and run-in was continued after summer and prolonged until the end of the year, as there were several issues with the instrumentation that required visits from the Agilent service.

Within the method development special emphasis was laid on the optimization of the extraction of various metabolite species (both hydrophilic and hydrophobic) and development of several liquid chromatographic separation methods. We have optimized the separation of polar constituents for Hilic-chromatography (developed in collaboration with FIMM to offer compatible and complementary results from both platforms), and the analysis

of semi-polar and non-polar metabolites in reversed phase column. Both chromatographic approaches are followed by qTOF-MS with positive and negative electrospray ionization. The subsequent peak picking and alignment for generation of raw data files for each of the analyzed samples are performed at the moment with vendor's software, but other possibilities (freeware such as MZmine) are also examined. Preliminary data-analysis for elimination of noise and adducts, and general checking for the data quality will be performed by various chemometrics and bioinformatics approaches. The sample sets are delivered to customers including the annotation of identified metabolites as well as key statistics such as fold changes with significance between the study groups for each of the metabolite markers. In addition, heat maps and correlation graphs will be provided for visualization of the data. The identification of the unknown metabolite markers (if not included in our database of earlier identified metabolites) will be customized in each case. Additionally, a vast set of metabolite reference compounds have been purchased and are presently processed to constitute a quality control mix to be included in the analytics.

Furthermore, one of the largest metabolomics conferences, the Metabomeeting, was held in Helsinki in August 2011 organized jointly by several institutions including members of the BF-metabolomics technology platform and the Metabolic Profiling Platform (UK).

User statistics

In BCH the number of groups using the services during 2011 was 16; of these 14 were local, and 2 other domestic. All users were academic. The units in BCK and FIMM were not yet operational in 2011. However, both biocenters have faced a growing list of potential customers for their respective special fields; BCK for non-targeted metabolomics analyses of sample collections from large cohorts pertaining link between diet and health; FIMM from a large number of groups and cohort studies and some samples from clinical studies.

Future perspectives for 2013–2016

Metabolomics is a diverse field which requires customized solutions for metabolite analyses depending on biological questions asked and sample types analyzed. The BF platform is set up to cover a broad range of applications, from microbiology and plant biology to medical applications, from targeted quantitative methods to untargeted discovery-driven profiling. The BF platform, as currently shaping, will establish complimentary methodologies at different centers and will also support the cooperation between the facilities, both in terms of method developments as well as offering a comprehensive service.

The key areas where further support will be required include both instrumentation and personnel. Special focus areas will be targeted lipidomics platform (planned at FIMM, analyses of specialized lipid species such as eicosanoids). Another area that will be developed is fluxomics. The fluxomic analyses can be performed using LC-MS/MS as set up at FIMM (and VTT) as well as complemented by GC-MS and NMR based methods (Viikki and VTT). In order to offer fluxomics as a service, the activities related to fluxomics at different centres must be better coordinated. Much of the resources needed for successful metabolomics analyses are related to data processing. The proper handling of metabolomics data involves both statistical treatment requiring bioinformaticians as well as spectral interpretations necessitating skillful and experienced mass spectroscopists. At this level, we foresee that cooperation between the centers and VTT will much improve the quality of metabolomics analyses and will also assure the data acquired are most comparable, to the extent the analytical platforms allow. Metabolite identification is another challenging area, particularly for the untargeted methods. In the future, we will seek better integration of multiple platforms that can facilitate de novo metabolite identification, including NMR facilities (Viikki, Kuopio) as well as the Orbitrap at VTT (used specifically for metabolite identification). Additionally the new FT-mass spectrometer at University of Eastern Finland Joensuu campus can be used for structural studies.

Participation in international and European infrastructures

Metabolomics has not been to date a major infrastructure involved in ESFRI. Instead, a number of major national initiatives have emerged, among them the biggest being the Netherlands Metabolomics Centre. Similar applications are being planned in France and Germany, at least.

STEM CELLS AND BIOMATERIALS

NETWORK

Stem Cells and Biomaterials Infrastructure Network

Coordinator of the network: Olli Silvennoinen, IBT
Members: Timo Otonkoski, BCH, 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: Olli Silvennoinen, IBT
Members: Timo Otonkoski, BCH, Biomedicum Stem Cell Center; Marjo Yliperttula, Faculty of Pharmacy, Viikki Facility; Mikko Lammi, BCK, Stem Cell Center

Development and restructuring of technology services

The main service of the Stem Cells and Biomaterials platform is to derive induced pluripotent stem (iPS) cell lines from human cells. This activity is closely linked to the development and provision of differentiation and analytical protocols and services, where each Biocenter have their own focus and specialization areas. Additional services include provision and testing of biomaterials and different training functions.

During year 2011 the emphasis of the platform was directed to expand services provided for the clients and optimization of the production of iPS cell lines with genome non-integrating method. Currently, the non-integrating method is available in all centers of the consortium. The profiling and development of unique differentiation protocols and analytical services continued in different Biocenters, which resulted in closer interaction between the platforms.

During 2011, all of the platform functions expanded from the previous (first) year. The number of iPS cell lines derived from human somatic cells increased by 108% (over 100 iPS cell lines for 21 clients). These lines have been subjected to various differentiation protocols and 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 insulin gene mutations, defective development of GnRH neurons associated with Kallman syndrome, familial Alzheimer's disease, lysosomal storage disease PLOSL, Long-QT syndrome, ventricular tachycardia,

hypertrophic cardiomyopathy and peripheral neuropathy. As part of international networking, iPS cell line from chondrocyte-specific Kashin-Beck disease (KBD) is under generation. Several new control iPS cell lines from healthy individuals were generated. In addition to dermal fibroblasts also other cell types such as myoblasts and peripheral blood T-cells were used to generate iPS cell lines in Biocenters.

The analytical services were significantly improved by purchases of new equipments in the cellular electrophysiology laboratory and by implementing new methods such as calcium imaging. With these developments the cellular electrophysiology laboratory is now fully operational for service functions and the first clients were served during year 2011. Services for teratoma analysis and provision of long-term imaging of cell cultures increased by 330% and 35% respectively, compared to the previous year. The library for the screening of biomaterials for stem cell applications has been established and functional screening has been carried out. In addition, the Nanoplotter for nanoplotting of biomaterials on glass sides has been adopted for testing and screening of the cell differentiation. The biomaterials for the maintenance of stem cells have been tested, and the novel nanofibrillar cellulose, Growdex ™ is now in regular use in 2D and 3D cell culture systems. Material has been distributed to Kuopio, Tampere and Helsinki Biomedicum, and the training has been provided. All Biocenters provided training activities including personal training in human pluripotent stem cell related methods, courses for stem cell technologies and biomaterials. These training activities received more than 80 participants. Turnover of the platform's functions provided to customers increased by 169% compared to the previous year.

Future perspectives for 2013–2016

The iPS cell technology enables to generate cells or tissues that recapitulate human genetic diversity, physiology and pathology. The most important foreseeable application of this technology is the generation of validated iPS cell biobanks consisting of selected donors representing genetically and clinically characterized cohorts of patients or healthy individuals. Such biobanks will be instrumental for the study of pathogenetic processes, for drug discovery and for prediction of drug safety. The pharmaceutical industry has great interest towards this possibility, as evidenced by the recent call of the Innovative Medicines Initiative, looking for the establishment of iPS cell biobanks. In Finland, we have several large well-characterized genetic biobanks; through collaboration between the various national infrastructure networks we have an excellent possibility to establish iPS cell biobanks for various diseases.

User statistics

Stem cell services provided in 2011	iPSC lines	Teaching (courses)	Hands-on training	Teratoma	Cell-IQ imaging	Electro-physiology laboratory
BSCC, University of Helsinki						
Number of customers	9	3	6	3	6	
Academic	8	3	1	3	6	
Non-academic	1		5			
Volume	63[a]	3[b]	6[b]	42[c]	4242[d]	
University of Tampere						
Number of customers	6	20				1
Academic	3	20				1
Non-academic	3					
Volume	15[a]	20[b]				1[b]
University of Eastern Finland						
Number of customers	6	52	3	1	2	2
Academic	5	50	3	1	2	2
Non-academic	1	2				
Volume	24[a]	52[b]	3[b]	1[c]	20[d]	2[b]

[a] cell lines, [b] customers, [c] tumors, [d] hours

iPS cell technologies have developed rapidly and it is now feasible to generate stem cell lines using methods that do not involve genomic integration. Such non-integrating methods are now in use in all Biocenters of the consortium. In order to enable the generation of biobanks consisting of tens of fully characterized cell lines, efforts must be targeted towards automating the derivation, culture and differentiation processes.

There is a growing need for more physiological cell and tissue models where scaffolding or actively supporting biomaterials play a key role. The platform will provide new cell culture systems (2D, 3D and co-culture) with new biomaterials in their services. In addition, nanoparticles research will be combined more tightly into the biomaterial services through international collaborations.

Participation in international and European infrastructures

Active participation in international networks is an important function of the platform. During 2011, 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. In addition, BSCC and University of Tampere both participated in the ISCBI (International Stem Cell Banking Initiative) consortium that creates guidelines for translational requirements for pluripotent stem cell production, banking, testing and use. During year 2012 the consortium will focus on setting quality standards for iPS cell production. BSCC, University of Helsinki and University of Tampere participated in the International Stem Cell Initiative, where the aim of the next collaborative project is to validate major differentiation protocols.

The iPS cell technology enables the generation of cells or tissues that recapitulate human genetic diversity, physiology and pathology. The most important foreseeable application of this technology is the establishment of validated iPS cell biobanks consisting of selected donors representing genetically and clinically characterized cohorts of patients or healthy individuals. Such biobanks will be instrumental for the study of pathogenetic processes, for drug discovery and for prediction of drug safety.

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.

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

Development and restructuring of technology services

Both the high-resolution mass spectrometry instrumentation at the Structural Biology Center and instrumentation at the Finnish National Biological NMR center represent world-class unique facilities, thus promoting specialization as a part of restructuring of scientific research in Finland.

In 2011, NMR Center has focused on improving the capacity of protein production. This resulted in over 30 proteins targets that have been successfully produced in the facility and also led to further breakthroughs in NMR studies of challenging targets, larger modular proteins as well as highly dynamic intrinsically disordered systems. The facility has been fully active in terms of sample production, data collection and analysis. For instance, over 250 samples for Glykos Finland Ltd. have been analyzed in 2011.

One of the four spectrometers in the facility, a 600 MHz NMR system, has been upgraded in 2011 by a partner, VTT technical research centre of Finland. This instrument has the latest ^{1}H, ^{13}C {$^{15}N/^{31}P$} cryo-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.

Investment in ultra-high field 900 MHz NMR spectrometer is the most important upgrade and of first priority as it is a prerequisite for further development of FBNMR towards highly competitive, *state-of-the-art* NMR facility, which can tackle the most challenging problems encountered in the era of molecular systems biology. In fall 2011, positive development for purchasing such an ultra-high field NMR system has taken place and we foresee to release invitation to tender in February 2012. Site survey and planning has taken place during 2011 in order to prepare NMR facility for installation of new magnet technology.

This development will ultimately translate into a unique NMR facility, where the most challenging problems in NMR-driven structural biology can be addressed with ultra-high field NMR instrumentation and NMR-optimized sample production service. Additional equipment optimized for NMR metabo(l/n) omics studies ensures a wide spectrum of services to the customers.

The installation of a new 12 T superconducting high-field magnet on the FTICR mass spectrometer was completed successfully 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 Spectrometry Facility at the Structural Biology Center of BCK has now the most high-grade mass spectrometry instrumentation in Northern Europe. Together, there are now only six laboratories in Europe with this level of instrumentation. In December 2011, a new ionization robot (Triversa Nanomate, Advion) was installed. The robot uses the latest microchip technology combined with microfluidistics. It allows fully automated sample handling and measurements from a well-plate with considerably less material required for protein sample analyses. In addition, ionization robotics is especially useful in a high throughput screening of a ligand binding to macromolecules. Samples from different wells can be mixed and incubated at a desired temperature and infused automatically. The ionization robot 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 is currently underway. In autumn 2011, a new project, supported by TEKES, was initiated in order to utilize FTICR technology in the analysis of industrially significant protein materials.

Future perspectives for 2013-2016

After modernization of NMR instrumentation, the biggest challenge will be in dissemination of good practices and procedures while simultaneously trying to develop and utilize great potential of NMR for *in-cell* NMR studies, intrinsically disordered proteins or structure determination of larger (membrane) proteins/complexes, to name a few. We envisage extending our footprint beyond the national level and become internationally well-recognized NMR facility. To that end, we propose that the BF funding in 2013–2016 should be targeted to following objects to ensure maintenance and further development of FBNMR's key functions:

1) It is imperative that also the highly dedicated and trained personnel are supported through stable funding. This not only ensures that new, most efficient and appropriate tools are implemented for structural studies but also allows FBNMR serve as an innovation platform for new methodological breakthroughs. Such development

User statistics

NMR spectroscopy: Total number of research groups in 2011: 28

Institution	Groups	Institution	Groups
University of Helsinki	11	University of Eastern Finland	3
Aalto University	1	University of Oulu	1
University of Tampere	2	FIMM	1
University of Turku	3	VTT	2
University of Jyväskylä	1	THL	1
		Industry	2

Mass spectrometry: Total number of research groups in 2011: 23

Institution	Groups	Institution	Groups
Tampere University of Technology	1	VTT (Espoo)	2
University of Eastern Finland	4	VTT (Turku)	1
University of Helsinki	5	FIOH (TTL)	1
University of Tampere	3	THL	1
International	3	Industry	2

is not possible without long-term input from skilled personnel, and this in turn necessitates stronger financial commitment to the key supporting individuals – first class science requires first class expertise.

2) Funding should also be reserved for cryogenics, repairs costs and minor upgrades of auxiliary but essential devices such as probeheads, NMR consoles and robotics in sample production. This warrants better service as delicate instrumentation of FBNMR is running continuously, and expands our possibilities to study highly challenging membrane proteins.

3) Funds should also be allocated to arrange training for our customers on-site. To disseminate best practices and routines calls for nationwide, practical level, hands-on courses. The highest throughput can be obtained by division of labour, considering substantial amount of customers, it is not possible to offer turn-key approach for everyone.

Native MS represents an emerging technology in the field of structural biology. It is especially useful when performed with high-resolution instruments. It can be used, for example, to study protein–protein and protein–ligand interactions without any labeling or covalent immobilization needed. In addition to small and average sized, well soluble (globular) proteins, recent technological developments have allowed native MS to be used also for characterization of extremely large protein complexes, viral capsids and membrane proteins. Our vision is to be a leading laboratory in Northern Europe which utilizes state-of-the-art MS techniques for structural biology studies. This would require further development of our current FTICR facilities. In addition, ion mobility spectrometry (IMS) combined with MS has drawn a vast interest during recent years as being a very useful tool to investigate conformations and dynamics of large biomacromolecular assemblies. When combined with time-of-flight (TOF) mass analyzers, its mass range is virtually unlimited allowing studies of even intact viral capsids with embedded DNA. An IMS-TOF MS instrumentation together with the existing high-resolution FTICR MS facility would constitute a unique technology platform for structural biology studies. Dedicated personnel for maintaining, developing and user training should also be supported to guarantee the functionality of this core facility.

Participation in international and European infrastructures

As a member of the BF Infrastructure Network on Structural Biology, the platform has followed the development of Instruct, the ESFRI infrastructure for structural biology in which both NMR and mass spectrometry are included.

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

Development and restructuring of technology services

The BFSB X-ray technology platform (Finnish Integrative X-ray Upgrade Project, FIX-UP) has received funding through the BF-infrastructure funding scheme for upgrading and expanding the X-ray equipment in Finland. The developments in 2011, as listed below, are in line with the plan we presented to Biocenter Finland in 2009.

In BI Protein Characterisation and Crystallization Unit the purchase of a Wyatt/Shimadzu system for semi-micro SEC/MALS including UV/Vis, multiple-wavelength static light scattering, fluorescence, and refractive index detectors has been completed in 2011. The tendering procedure for a UV/Vis imager has been initiated and this will be completed in 2012. A major bottleneck has been the integration of the various hardware platforms into a single user interface. The development of a crystal image viewing system (PICView) for remote access via (mobile) browser is being continued. More than 300 service crystallization screens were carried out in 2011, for research groups in various places in Finland. In May 2011 an international crystallization workshop was organized with Finnish and foreign participants.

In Oulu National Protein Crystallography Datacollection Centre a new microfocus X-ray generator has been installed, which will considerably increase the data collection efficiency and quality. It concerns the Bruker Microstar, equipped with Helios mirrors, the X8-PROTEUM kappagoniometer and a CCD PT^{135} area detector. The data collection and the data processing package is the PROTEUM2 package. The training of new users will soon start. Considerable efforts are

being directed to achieve a user friendly computing environment. In 2011 a programmer has been recruited to work on the installation of PiMS/xtalPiMS of the Instruct ESFRI program. This package is now being developed such that it will be used routinely for monitoring the results of the crystallization experiments via internet. Subsequently, a module for data tracking of the crystal handling protocols including the exchange of metadata between synchrotrons and home labs will be implemented. In January 2012 an international X-ray course ("From Data to Structures") will take place on protein crystallography data collection and data processing. This course is part of the EU-Biostruct-X project.

In Turku Regional Data Collection Centre a new generator and optics (Rigaku micromax 007 HF) were purchased and installed at the end of 2011, according to schedule. Complementary funding was obtained from the University of Turku Infrastructure funds. Training for users is planned in January/February 2012 and use by groups will start as soon as the Finnish Radiation Authority has given permission. The regional data collection center is also involved in BioXLabs in Turku aimed to improve the pipeline of structural biological studies.

At the national level, the Finnish protein crystallographers meet yearly at the FINNBOX meetings to discuss joint future developments. In 2011 our meeting was in Joensuu. Regionally, the structural biology groups in Turku formed a structural biology consortium, BioXlabs Turku, to enhance coordination of activities. Courses at the Masters level on X-ray crystallography and structure interpretation are offered at each University. We have prepared brochures and posters providing information on the expertise in each of the centers and we have organized roadshow lectures, posters and tutorial events on our expertise in Turku, Helsinki, Tampere, Kuopio and Oulu. These roadshows have increased the awareness of our expertise.

User statistics

User statistics by group leader (total projects & users would be about 3 fold higher).

	BI Helsinki	BCO Oulu	BioCity Turku
Campus	7	6	2
University	2	2	2
Other University	7	1	3
Other Finland	1	1	

Future perspectives for 2013–2016

High quality protein crystal structures will remain absolutely essential for improving our understanding of the functional properties of proteins, *in vitro* and *in vivo*, at the molecular and atomic level. Our structural biology research is aimed at a quantitative description of these properties, including not only the structures, but also the biophysical and enzymological characterization. Excellent setups for accurate characterization of the studied macromolecules on-site are essential. This high-tech expertise, available in Helsinki, Oulu, Turku and Joensuu remains a vital technology for every drug and biocatalysis discovery project. Important for this research is also efficient high-throughput cloning, expression and purification technology in prokaryotic and eukaryotic systems. Structure based directed evolution and translational research will require further investments. The Biocenter Finland supported centers are continuously developing their infrastructure and expertise to provide optimal support for the researchers of the Finnish biochemical and medical research community. We constantly strive to enhance also the availability and quality of the structural biology services and training for research groups having an interest, but lacking expertise, in the field of structural biology.

Participation in international and European infrastructures

The Finnish protein crystallographers have very good access to the ESRF beamlines through the FinnProCC BAG, coordinated by BI. Data collection is also carried out at MAX Lab, DESY, DIAMOND, BESSY and other European synchrotron radiation facilities. In addition to protein crystallography data collection, also SAXS and SRCD experiments are routinely performed. Collaborative efforts with ILL and ESS on neutron methods have been initiated. The Oulu X-ray setup is part of the EU Biostruct-X training initiative and contributes also to the EU ESFRI Instruct activities. The protein crystallographers in Oulu are also involved in the developmental planning of the new MAX IV synchrotron setup in Lund. The Finnish protein crystallographers are participating in Finnish (FSRUO) and European (ESUO) synchrotron user organisations on the development of synchrotron radiation for scientific research. 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.

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

This network coordinates two technology platforms: (1) Drug Discovery and Chemical Biology (DDCB) for discovery and proof-of-concept validation of therapeutic molecules, and (2) Tissue Biobanking for biobanking and biomarker research. The DDCB platform focuses on drug and chemical probe discovery, 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 and high-throughput screening, as well as ex-vivo drug testing. The aim is to facilitate discovery of inhibitors to interesting targets, and to carry out proof-of-concept testing of compounds and drugs in cell models and ex-vivo samples from patients. 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 at the University of Helsinki/FIMM (with Institute for Health and Welfare (THL) and Helsinki University Hospital (HUS)), as well as at University of Turku (with Turku 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). Currently, 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.

PLATFORM

Tissue Biobanking Technology Platform

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

Development and restructuring of technology services

The Tissue biobanking technology platform has continued to work on new improved virtual microscopy based methods, which will have a central role in cancer specimen biobanking.

Virtual microscopy techniques have been further developed and provided as a service also to commercial customers, such as LabQuality Inc. In 2011 The WebMicroscope virtual microscopy administration portal has been adapted for medical tissue biobanking functions and a first version has been installed on a new, dedicated server, for use at FIMM and other networked departments.

The processing capacity for computer vision analysis of the huge amount of image data is crucial for virtual microscopy. In 2011 the WebMicroscope biobanking portal was connected to comprehensive computer grids at FIMM and CSC. Reading image data from the WebMicroscope servers, the computing grid at FIMM (with 500 node cores) was able to reduce the calculating time for a Matlab whole slide algorithm from three hours to just three minutes. The collaboration with CSC and the Finnish company Techila Technologies Ltd. will continue during 2012. Starting from 2012 collaboration with Microsoft for utilizing the powerful MS Azure cloud services, available worldwide, has been initiated.

All Finnish medical faculties use our virtual slides in cell biology, microscopic anatomy and pathology teaching and the WebMicroscope administration system is used at the universities of Helsinki, Turku, Kuopio and Oulu. The virtual microscopy portal was highly noticed in the European Congress of Pathology in Helsinki in August 2011 where more than 2000 pathologists and researchers received logins to the WebMicroscope portal.

The new tissue block preparation system has been carefully tested at the University of Tampere. Using the new molecular fixative, we can, for the first time,

prepare paraffin-embedded tissue blocks which retain protein antigenicity, DNA and mRNA as well as in deep-frozen tissue samples. The new system will be implemented in the Fimlab laboratory for research sample collection during 2012.

The image analysis web application softwares ImmunoRatio and ImmunoMembrane are in full use via University of Tampere virtual slide servers. The softwares give diagnostic aid for personnel trained to score immunostained samples. Over 25.000 images have been analyzed thus far (in one year). In addition, the numerous researchers have downloaded our software for their own use (over 7.000 downloads).

User statistics

The virtual microscopy internet web pages of the platform are world famous. In 2011 the main customers of the WebMicroscope virtual microscopy platform have been LabQuality Inc, FIMM, Tampere University Laboratory Centre (Fimlab Inc), European Society for Pathology and medical student teaching organizations in all.

Examples of larger research consortia utilizing the virtual microscopy platform (via a local portal in Turku) are the SyTra Translational biomarkers for hormonal cancer project, and the world's largest private-public partnership, the PREDECT European Consortium (from December 2011 on). PREDECT is an IMI-funded partnership between nine academic, three SME and seven EU pharmaceutical partners, developing advanced, transferable models for breast, prostate and lung cancers. Our virtual microscopy portal was also recently installed at the University of Oslo and VU University Amsterdam Medical Center.

Over 25,000 images have been analysed using ImmunoRatio and ImmunoMembrane web softwares and numerous researchers have downloaded the softwares for their own use (over 7,000 downloads).

Future perspectives 2013–2016

The main goal of the technology platform is to support incorporation of virtual microscopy in medical tissue biobanking projects and biomarker research. Thus, the platform has plans to provide know-how for best histological characterization of biobanked samples and for automated assessment of tissue sample stainings. The systems will be developed further to enable seamless integration of virtual microscopy information to biobank sample and clinical databases.

Participation in international and European infrastructures

A pilot study has been proposed to the Biomarker Product Group of EATRIS which is one of the ESFRIs. The intention is to assess whether the virtual microscopy methods partly developed within the BF project could be used for biomarker validation and standardization of readout of immunohistochemical staining. Five EATRIS centers have expressed their interest in participation and the WebMicroscope platform has been installed at VU University Amsterdam Medical Center as described above.

PLATFORM

The Drug Discovery and Chemical Biology Technology Platform (DDCB)

Chair of the consortium: Olli Kallioniemi, FIMM

Members: Krister Wennerberg, FIMM, Chemical Biology Lab; 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

http://ddcb.fi/en/

Development and restructuring of technology services

The Drug Discovery and Chemical Biology consortium (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 together with the support from the participating institutions, we continued to build our national platform during 2011. A platform website www.ddcb.fi has been set up as a major user interface. Consortium meetings were held on a quarterly basis and users were also invited to present and discuss their projects. The use of an advisory panel to guide projects and users to best strategies and services was continued and was successful in that many projects within the platform utilized coordinated services from several DDCB partners. A total of 35 projects/users were supported in 2011, up from 18 in 2010.

A new advisory body DDCB Business Opportunity Board was established to aid the transfer of projects and discoveries with commercial potential to IP protection, licensing and further development. This Board consists of national experts of biotech and pharma drug discovery and -development as well as venture capital, investment banking and market analysis experts.

The national screening collection (>130 000 compounds) is now available, 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 will be established during 2012. An increasing number of known bioactive compounds, primarily signal transduction inhibitors, are available in proof-of-principle volumes for researchers upon request. An integrated service allowing for validation of small molecule compound integrity by mass spectrometry has been established. This compound profiling capacity will be further enhanced by the purchase of a high throughput-capable mass spectrometry.

A new robotics platform and an operational upgrade to the acoustic dispenser were ordered and they were delivered in January 2012. These upgrades will allow for distribution of the chemical collection in user-defined formats and importantly new screening capacities where nanoliter-scale volume assays can be run and drastically cut reagent costs for users in high throughput screens. Confocal HCS instrument was installed for use in 2011 to provide services in second stage screening with complex cell models. Likewise, multi-well plate dynamic light scattering instrument is being ordered for quality checking of the libraries in terms of solubility. A Bioflux 200 instrument was added at Biocity Turku to allow for high throughput imaging of cells under flow and sheer conditions.

The consortium collaborates with University of Jyväskylä. In 2011 Dr. Olli Pentikäinen (Computational Bioscience Laboratory) 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 small molecule biosensors.

Future perspectives for 2013–2016

We believe that world-class research services go beyond the basic infrastructure. In addition to the core infrastructure support the platform should help the

User statistics

	BCH/CDR	BCK/UEF	BioCity / ÅAU	FIMM	Total
Total user research groups	7	10	4	17 (three projects jointly with BCK/UEF)	35
Local	3	3	2	11	
National	4	6	1	3	
International		1	1	2	
Non-academic		1			

As examples of metrics, assay development support and HTS optimization was provided for 14 projects, 97 high throughput screens were performed and virtual screening and molecular modeling for 11 projects. The resources and expertise of the group of Olli Pentikäinen/University of Jyväskylä were added only in October and this group did therefore not have time to get involved in new user projects during 2011.

user link the right research services to his or her specific project. The goal of the DDCB consortium is to operate as one functional unit that is separated over several sites at different Biocenters covering a broad range of expertise and services within one field. The addition of an associated Business Opportunity Board is taking over where the Biocenter Finland infrastructure services end to help researchers at Finnish Biocenters take their findings towards translation. The services provided within one infrastructure platform could in turn very often be further strengthened by the expertise in other infrastructure platforms. It is important to note that these types of service platforms and -networks will not easily be established at level of each university and a national initiative such as Biocenter Finland will only become increasingly important for Finnish research in the future. We expect that the DDCB platform in the coming years will continue to integrate services connected to chemical biology and from other disciplines as well as other countries (primarily through ESFRI initiatives).

Participation in international and European infrastructures

Our platform is directly linked to two ESFRI roadmap initiatives. First, we are coordinating the plans for technologies and screening centers with the preparatory phase of EUOPENSCREEN, a research infrastructure with the same goals as DDCB; open access infrastructures for high throughput screening, chemical biology and small molecule probe development. We expect that the operations of EU-OPENSCREEN, which are expected to start in 2014 will be highly aligned with the ongoing operations within DDCB and that the infrastructures and research services that now are available through the national platform will be able to serve also the larger European research communities.

Second, we are also actively taking part of the work of a small molecule product group of the EATRIS translational ESFRI roadmap. CSC and FIMM are also involved in the buildup work of ELIXIR, an ESFRI roadmap project for biological information that will be an important link for DDCB. Furthermore, members of the platform are have been involved in the preparation of the "European Lead Factory" EU FP7 IMI project call and are participating in the buildup of an International Chemical Biology Society and one project initially developed with the help of DDCB infrastructures have been approved as a project under the NIH Roadmap Molecular Libraries Program in the USA.

The aim of DDCB platform is to facilitate the discovery of inhibitors to interesting targets, and to carry out proof-of-concept testing of compounds in cell models and *ex-vivo* samples from patients. This platform should optimally bridge the gap between academic research and industrial interests to drug discovery.

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 co-ordinating the development and production of gene transfer vectors at national level in Finland.

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;
Eleanor Coffey, BioCity, Viral Vector Facility,
Eric Dufour, IBT, Virus Vector Facility

Development and restructuring of technology services

Viral Gene Transfer and Cell Therapy Network (VGTCT) has significantly improved technology services and helped to restructure Biocenter profiles and services available in Finland for the use of gene transfer and cell therapy researchers. In general, very high quality, high titer viral vectors produced using good manufacturing practice techniques are available from A. I. Virtanen Institute Virus Vector Laboratory, whereas smaller quantities of adenoviral, lentiviral, retroviral and AAV vectors are available from local vector core facilities in different Biocenters. In addition, special knowledge of AAV vectors is available in Helsinki together with special knowledge of oncolytic vectors (BCH Helsinki), lentiviral transgenesis and RNAi vectors in Oulu (BCO) and siRNA libraries (BCH). In addition, BioCity Turku and IBT Tampere have developed small-scale methods to produce the most commonly used viral vectors. Overall, viral vector services are now available in all Biocenters with tailor-made technologies to produce both small and large-scale vector preps for basic research, translational research and clinical studies. It can be concluded that VGTCT Network has greatly helped to profile and restructure Biocenters and to improve virus vector availability and related services in Finland with prices affordable to researchers and biotech companies. Vectors produced by VGTCT Network have been used in more than 50 publications in 2011 by both domestic and international collaborators and the increasing value of *ex vivo* and *in vivo* gene transfer technologies has been acknowledged worldwide in several international meetings and top-class peer-reviewed publications.

For cell therapy applications, vector backbones have been developed and harmonized in the VGCTC Network. Reprogramming of somatic cells into induced pluripotent stem cells (iPS) has been achieved in A. I. Virtanen Institute Vector Core Laboratory with lentiviral and mRNA vectors and using AAV technology in BCH. Knowledge in viral transduction and high quality validated vectors will be essential in order to achieve repeatable and reliable results in cell therapy, reprogramming and iPS research.

Significant bottlenecks still exist, which include high cost related to the maintenance of good manufacturing practice environment, continuous monitoring of microbiological and particle concentrations/contaminants and quality testing of raw materials and final viral vector products used for experimental purposes and in clinical research. Also, the demand for viral gene transfer in basic and preclinical research has grown dramatically in all Biocenters during the past three years. Therefore, increased capacity for vector production and for example production of validated, function-tested control vectors to be used in all Biocenters is required in the future. Also, knowledge and protocols for animal testing with biosafety level 2 environment needs to be further developed so that research groups can have first experience from their vector constructs in animal models, even if required facilities are not available in their own research institutes or biotech companies.

User statistics

User statistics from Biocenters and their viral vector laboratories show a continuously increasing demand of viral vectors for biological, preclinical and clinical experiments.

Future perspectives for 2013–2016

VGTCT Network has clearly demonstrated that its services are required in Finland and that these services should be maintained also in the coming years. Further resources are needed in the development of regulated vector backbones and vectors that can provide tissue-specific gene expression. Production of knockdown cell lines will be an important new area, as well as generation of iPS cell lines together with gene transfer-based cell reprogramming technology. Also, continuously increasing need of viral vectors will demand higher production capacity and larger production volumes at least in some Biocenters.

The needs of the VGTCT Network in the future focus on maintaining the level of services from the existing virus vector core facilities. VGTCT network needs support for salaries of the expert staff and to cover at least part of the costs of the numerous environmental controls, biosafety requirements, microbiological controls and quality testing of both raw materials and final vector products. Support for salaries of the trained expert researchers and technicians is a key to keep the cost of the vector preparation affordable to researchers and biotech companies. Special support is also needed for vectors produced with clinical grade good manufacturing practices, since in this area vector facilities, such as A. I. Virtanen Institute Vector Core, can serve several customers also outside Finland. Another new area will be translational experiments in validated animal models, where establishment of protocols and guidance to biosafety level 2 animal procedures with existing imaging services, characterization of the phenotype, and safety and toxicology testing need to be developed in at least some Biocenters. In this area a fruitful collaboration is also foreseen between the vector producing core facilities, experimental animal centers familiar to gene transfer experiments and imaging

	BCH [KA/AH/JK*]	BCK	BCO	IBT	BioCity	Total
Customers						
local	8 [2/1/5]	30	8	3	26	75
domestic	4 [2/1/1]	8		0	3	15
international	15 [2/12/1]	10	1	3	0	29
non academic	9 [0/9/0]	2		0	0	11
Volume*	472 [68/60/344]	52	194	44	115	877

* KA = Kari Alitalo, AH = Akseli Hemminki, JK = Juha Klefström

centers within the Biocenter Finland network. Extending the testing to the first human clinical trials with the new products produced in the VGTCT network is also an important further development of the services.

Participation in international and European infrastructures

VGTCT Network has participated in several EU FP7 networks, including ADVance Marie Curie ITN (A. I. Virtanen Institute and BCH), CliniGene EU Network (A. I. Virtanen Institute and BCH), IMI-PREDECT (BHC), IMI-SUMMIT (A. I. Virtanen Institute), Biomagscar EU FP7 (A. I. Virtanen Institute), BAMI EU FP7 (A. I. Virtanen Institute), ERC Advanced Grant program (A. I. Virtanen Institute and BCH), ERC Starting Grant (BCH), Leducq Transatlantic Research Network (A. I. Virtanen Institute and BCH). Also, negotiations are actively proceeding in order to involve VGTCT Network to ESFRI programs at the European Union level infrastructures.

Vectors produced by VGTCT Network have been used in more than 50 publications in 2011 by both domestic and international collaborators and the increasing value of *ex vivo* and *in vivo* gene transfer technologies has been acknowledged worldwide in several international meetings and top-class peer-reviewed publications.

EMERGING TECHNOLOGIES: LENTIGEMM

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, Biocentrum Helsinki

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

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

Development and restructuring of technology services

LentiGEMM, the first Biocenter Finland funded emerging technology platform, develops new virus-aided gene transfer technologies to generate a suite of transgenic animal tissue models of human diseases, especially in neurological diseases and cancer. The new 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 new technology will save both animals and animal costs having 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 of animals needed. This should lower the bar for use of transgenic and knock-down *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 will give research groups an active role in developing and modernizing research infrastructures, for example virus and animal facilities. This service model is very dynamic and customer-oriented, allowing rapid transfer of latest science technologies from individual laboratories to core facilities. A clear division of tasks has been agreed upon based on the expertise of the 8 research groups, representing 4 biocenters, involved.

Over the period of June 2010 – December 2011, the network has transferred three technologies to Helsinki-based core facility Biomedicum Functional Genomics Unit (FuGU). These new technologies, concentrated virus particles, sucrose-cushion purified virus particles and shRNA validation, are now available for Biocenters as non-profit fee-based services from the core facility. 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

User statistics

LentiGEMM established services and users.

LentiGEMM service	Service open	Services available (core/lab)	Price/unit (example volumes)	Customers
Concentrated lentivirusparticles	06/2010	FuGU/Klefström	899€/1x380µl 2075€/4x380µl	6 research groups: 5 local, 1 domestic; 46 virus preparations
Sucrose-cushion purified lentivirusparticles	12/2011	FuGU/Hovatta	1128€/160µl	2 research groups (local); 4 virus preparations
RT-PCR virus construct validation service	12/2011	FuGu/Klefström (pilot exp.)	1171€/5 constructs for 1 gene	1 research group (local); 9 validations

procedures and the network has organized training on lentiviral gene transfer and animal techniques through graduate schools. In September 2011, LentiGEMM organized a minisymposium "Tissue mosaic mouse models of human disease", which featured both international experts and LentiGEMM members as speakers.

The restructuring component of LentiGEMM has been obvious: it has restructured and developed Finnish life science infrastructure by bringing together local expertise for joint development of new services at the interface of genomic technologies, virus production and animal model development. LentiGEMM has promoted collaboration between biocenters and further developed and upgraded existing core facilities. LentiGEMM has thereby increased the use of BF-supported services on virus production and genetically modified mice.

Future perspectives for 2013–2016

LentiGEMM is a research-centered emerging technology platform in which future services are currently under active development. During the next four years, LentiGEMM strives to take a role as a central network creating new services at the interface of genomics, virus and animal technologies. The new services, service packages and solutions will be transferred to existing Biocenter genomics, virus and animal core facilities for nationwide distribution. LentiGEMM will also continue to investigate possibilities to reduce the costs of the newly created services through alternative methods or finding cheaper reagent options. The following new mouse tissue engineering services will be launched in 2012: Mouse mammary epithelial tissue: mammary epithelial cell isolation, transplantation and gene engineering services (Klefström, FuGU/BCH); Brain tissue: stereotactic virus injection and gene transfer services (Hovatta, FuGU-LAC/BCH); Endothelial tissue: lentiviruses, gene transfer methods and allantois membrane tissue culture for functional analysis of vascular network formation (Saharinen, FuGU/BCH; Lung epithelial tissue: intranasal lenti- and adenoviral gene delivery techniques to lung epithelium (Verschuren, FuGU-LAC/BCH).

For 2013 onwards, a number of other service types are being created for example, for genetic engineering and transplantation of lymphoid cells (BioCity Turku) and novel methods for gene engineering of brain endothelium (BCK). However, components of the LentiGEMM technologies as well as expertise is already available in the partners laboratories and the advances and pre-publication results are disseminated through LentiGEMM organized symposia and training sessions.

During 2013–2016, LentiGEMM efforts will spearhead access to reverse genetics tools in Finland and improvement of preclinical research platforms. Importantly, LentiGEMM emerges when preclinical studies in both academia and industry experience an increasing shift to apply genetically-engineered mouse models for co-clinical trials or target validation approaches, to better model accurate drug efficacy in eventual patient trials. Sophisticated methods to manipulate cells in their natural, heterogeneous, context are therefore of imminent importance. LentiGEMM's pliable next-generation technologies should increase opportunities for academia-industry collaborations, while reducing animal breedings and therefore cost and time, and are expected to culminate in high-profile exposure of Finnish academic research.

Participation in international and European infrastructures

LentiGEMM is highly compatible with large number of EU-funded consortia established to advance and reshape the life science infrastructures at the European level. While the current first priority of LentiGEMM as a Finnish network is to translate the newly developed technologies in the partner'slaboratories to services that can be distributed nationally, the individual LentiGEMM partners are engaged in international network supporting activities. For example, members Emmy Verschuren (FIMM) and Juha Klefström (BCH) have coordinator duties (EV is a main coordinator) in EU & EFPIA Innovative Medicines initiative PREDECT, which has taken a center stage in Europe in developing new disease models for pharmaceutical target validation. These collaborations are expected to lower the bar for Finnish academic and global pharma industrial collaborations in the areas represented by LentiGEMM.

OTHER ACTIVITIES

Sino-Finn collaboration

As a continuation to the events building scientific collaboration between Finnish biocenters and Chinese universities and research institutes the 4th Sino Finn Life Science Forum was organized together with Sino-Finn Summer School in Turku and Helsinki in August 17–24, 2011. Ten principal investigators from Shanghai Institutes of Biological Sciences (SIBS) and Wuhan University participated in the Forum. The Summer School for Chinese students co-organized by Graduate Program in Molecular Biology and Biotechnology (University of Helsinki and Biocentrum Helsinki) and Biocenter Finland attracted sixteen students from Shanghai Jiao Tong University and Wuhan University to Finland. The one week visit of the Chinese guests started with following the BioCity Turku Symposium on cellular movements and continued with scientific talks from both Chinese and Finnish Forum participants.

In September 2011 University of Helsinki and University of Wuhan agreed to further strengthen their scientific and educational exchange and research collaboration in life sciences. Biocenter Finland was co-signatory to this agreement thus extending the academic collaboration agreement to cover other member biocenters, too.

Biocenter Finland International Visitor program

Biocenter Finland international visitor program (initiated in 2010) supports the recruitment of international students and postdoctoral researchers into Finnish graduate schools and biocenters. Based on the good experiences in the first call the Board of Biocenter Finland decided to continue the program, and the call for applications was opened again in 2011. In the second call, a total of 19 prospective graduate students and 21 postdocs were selected for funding.

A total of 54 internationally mobile doctoral students and postdocs have received support from the visitor program. Countries represented are (number of visitors in parenthesis): Australia (1), Brazil (1), China (7), Cuba (1), Egypt (1), Eritrea (1), Estonia (1), France (2), Germany (4), Hungary (1), India (9), Iran (1), Israel (1), Japan (1), Kamerun (1), Malaysia (1), Nepal (1), Poland (2), Portugal (2), Russia (2), Singapore (3), Spain (1), Sri Lanka (1), Switzerland (1), UK (2), Ukraine (1) and USA (2). In addition two Finnish postdocs returning from Japan and Canada have been funded.

Biocenter Finland Infrastructure Day

In 2011 the annual Biocenter Finland Infrastructure Day concentrated on topical questions in biological imaging, proteomics and metabolomics, and structural biology. Besides the national technology platform presentations, the international views on research infrastructures were heard. The keynote lectures by international infrastructure-oriented scientists were given by Jan Ellenberg (EMBL, Heidelberg), Rob Moritz (Institute for Systems Biology, ISB, Seattle), and David Stuart (STRUBI - The Division of Structural Biology, University of Oxford). The Infrastructure Day was organized in Turku in October 2011.


When Life is Art


SKUS


When life

BIOCENTER FINLAND SCIENTISTS PARTICIPATE ACTIVELY IN EUROPEAN RESEARCH INFRASTRUCTURES ON THE ESFRI ROADMAPS

While the ESFRI (European Strategy Forum for Research Infrastructures) process has raised a lot of enthusiasm and optimism in Europe during the past ten years, the slow establishment of individual Research Infrastructures has become a source of considerable frustration among participating scientists. 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 created a new Community legal framework (ERIC, European Research Infrastructure Consortium) for pan-European Research Infrastructures. 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, six years after publishing the first Roadmap none of the BMS ESFRI Infrastructures has started its operation.

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. Particularly in the Nordic Countries the establishment of national infrastructures has proceeded much faster than the European process which has provided a head-start for Nordic collaboration in many ESFRI fields. In Finland the existence of BF infrastructure networks has provided a ready-made solution for the national node structures for essentially all BMS infrastructures where Finland is an active partner. 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. Furthermore, the goals of ESFRI and BF are very similar; both aim to provide researchers access to world-class research

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

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

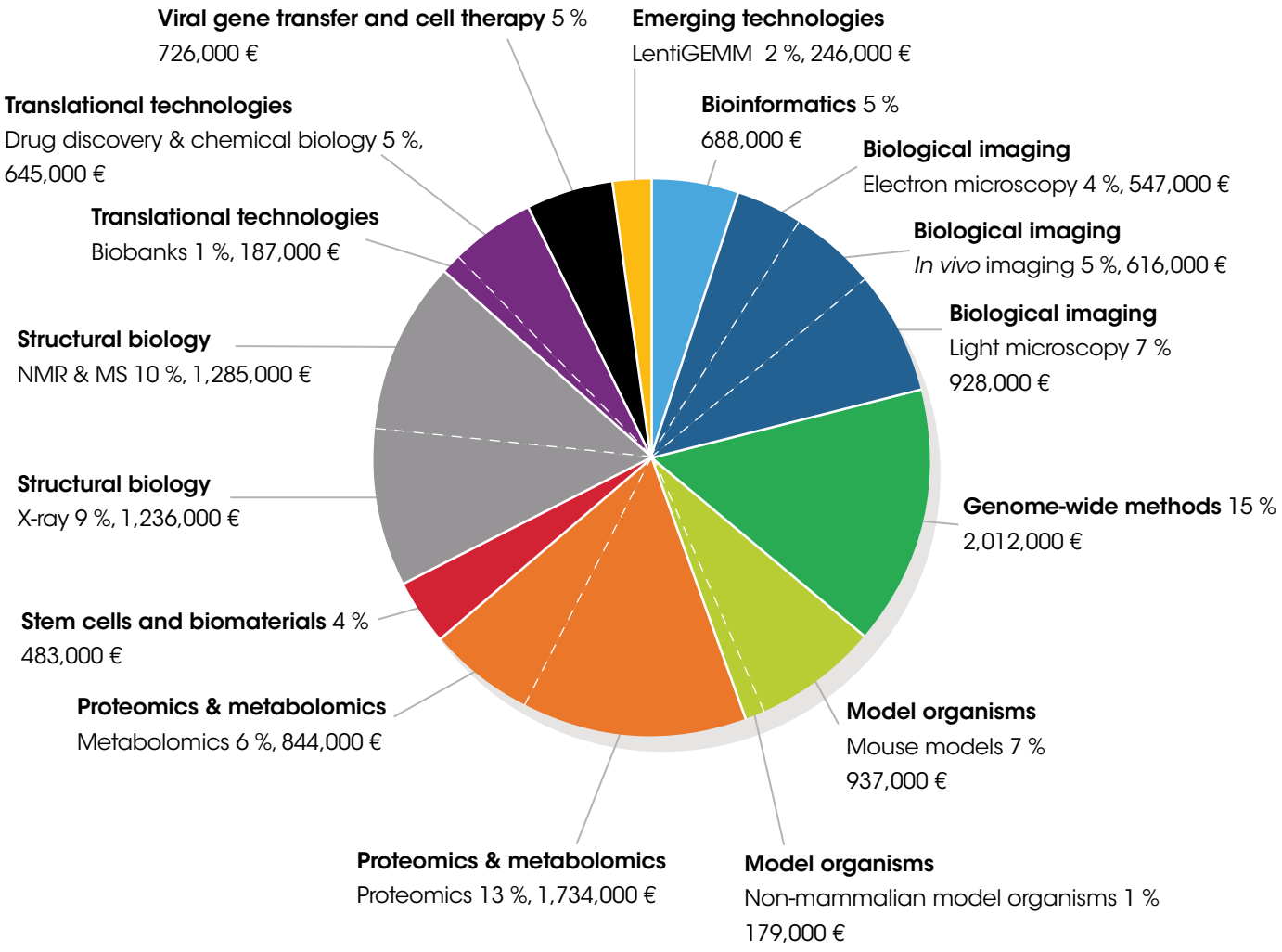
facilities and to overcome fragmentation of the BMS research landscape at European/national level.

In October 2011, Biocenter Finland organized a one-day seminar on Finnish participation in BMS ESFRI infrastructures. During this meeting it became apparent that BF scientists have been actively involved in nine of the 13 BMS ESFRI projects (Table). 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 when they enter the construction phase.

In Finland the existence of BF infrastructure networks has provided a ready-made solution for the national node structures for BMS infrastructures. 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.

STATISTICS

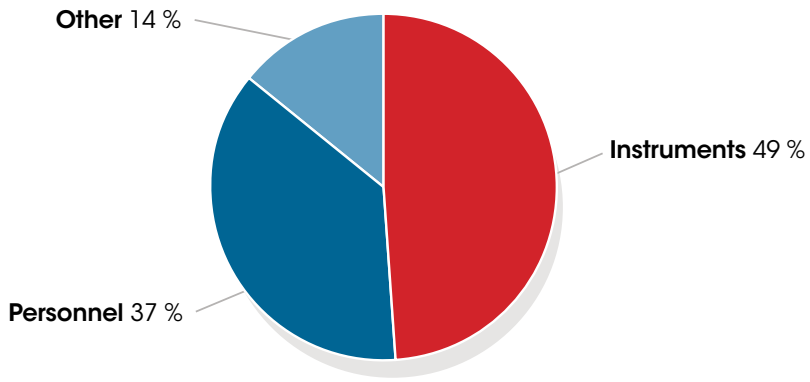
Allocation of BF funding to technology platforms in 2011.
Total funding for technology platforms in 2011 was 13,3 M€.



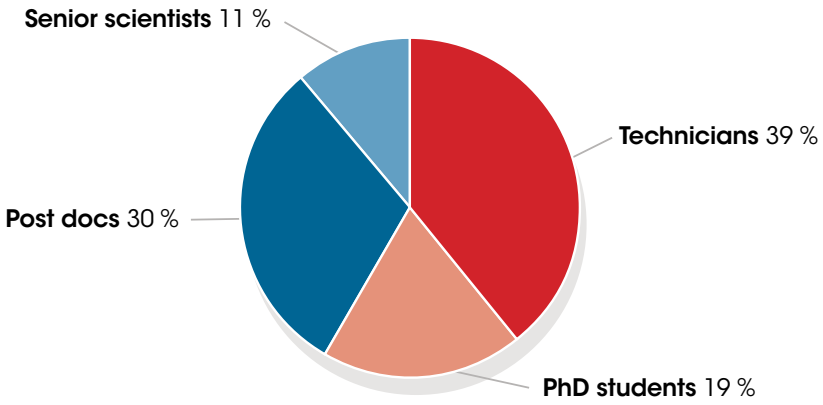
Allocation of BF funding to other activities in 2011

Research career development program 500 000 e; International visitor program 600 000 e. BF Board has also financially supported the coordination and training activities of the infrastructure networks in 2011.

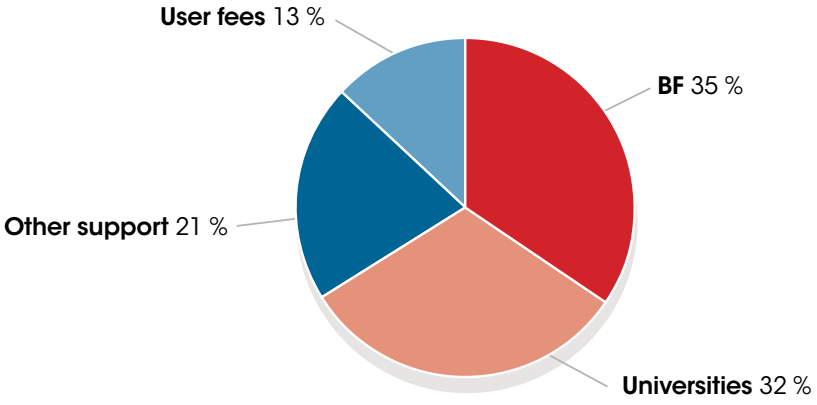
Distribution of BF funds used by technology platforms in 2011.
Category "Other" includes small instruments (< 25 000 e), reagents and maintenance.



Breakdown of BF funding to technology platform personnel.
In total 1 436 person months, 120 full time equivalents.



The total funding of technology platforms by funding source.




Institute of Biotechnology

Biocenter Kuopio


Biocentrum Helsinki


Biocenter Oulu


BioCity Turku


Institute for Molecular Medicine Finland FIMM


Institute of Biomedical Technology

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.

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 120 students. The total number of personnel in 2011 was about 260. 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.

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, molecular medicine, 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.

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 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 life sciences and 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 the joint institute of Tampere University of Technology and University of Tampere, BioMediTech. The collaboration between the universities has enabled a unique research and educational environment. In 2012 BioMediTech will launch a single degree program with the objective to educate top-level experts in life sciences and medical technology.

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) personalized medicine. 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
Institute for Molecular Medicine Finland
Nordic EMBL Partnership for Molecular Medicine

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