Biocenter Finland

ANNUAL REPORT 2013

Biocenter Finland Annual Report 2013

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Cover: iStockphoto

Acknowledgements: We are grateful to BF infrastructure network coordinators and technology platform chairs and members for cooperation in compiling this report.

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FOREWORD

Year 2013 was an exceptionally busy one and full of changes for Biocenter Finland (BF). Much to the disappointment of all those working for BF, the earmarked funding from the Ministry of Education and Culture (OKM) ended and 2013 became the first year BF had to operate without direct support from OKM. Although the host universities came to rescue the salaries of trained BF technology personnel, the new financial situation meant major changes in the operations of BF.

Year 2013 will be remembered as the year of reports and applications. All BF activities during 2010–12 underwent post-hoc evaluation by the Scientific Advisory Board (SAB) of BF. At the same time the SAB also evaluated new proposals drafted by the technology consortia for years 2014–2016. Preparation for SAB evaluation coincided with the updating process of Finnish research infrastructure roadmap and the application for national (FIRI) infrastructure funds. This process also included reporting to the host universities with requests for matching funds. After the SAB review in June the BF Board had to translate the SAB recommendations into a funding request to the rectors of host universities during the summer. And in October 2013 the Academy of Finland decided to perform its own survey of research infrastructures, which resulted in yet another extensive report of current and planned infrastructures.

In many respects year 2013 became a success for BF. First, all host universities agreed to continue their funding towards the operational budget of BF through the 3-year period 2014–2016. Secondly, BF was selected for the national research infrastructure roadmap based on a very positive evaluation. We were able to demonstrate to the rectors of host universities that the BF concept works also without earmarked financial support although discontinuation of such funding hurt many successful BF pilot activities. A sign of the user community's trust in BF is shown by the 31% increase in user fees over 2012.

A major disappointment came at the end of the year with the decision on the distribution of national infrastructure (FIRI 2013) funds. Introduction of a ceiling of 1 MEUR to all funding decisions during the process meant that BF, the largest applicant serving a very wide user community in six major universities suffered most and received considerably less than anticipated.

Year 2013 became an interim phase

As the decision not to grant an extension of the earmarked funding by the Ministry reached us quite late, securing the salaries of the >100 highly trained technical personnel operating the equipment at technology services became our primary goal. With the help of host universities the contracts of most of the key personnel could be extended, but there were no funds for coordinated purchase of equipment in 2013.

Without direct support from OKM, BF had to change its operational mode. Without a common pot of funding many activities that had been judged to be very beneficial had to be drastically cut or discontinued. This reduced the possibility of infrastructure networks and technology platforms to organize their face-to-face meetings which had been considered important in keeping the respective communities together. Also BF support for research career, the international visitor program and other BF international activities had to be discontinued. We had to focus on the very core activities of BF – provision of nationwide technology services to the scientific community.

To keep BF operational, all host universities endorsed their continuing support to coordination and provision of technology services for 2013–2016, based on an action plan presented by BF Board. According to this plan, future funding of BF will consist of three major funding streams: the host universities assume responsibilities for operational and coordination costs of BF, while investment costs must be primarily sought for from other sources (especially the national FIRI-infrastructure funds). The cost of reagents and maintenance of equipment was to be covered by user fees. The increasing importance of BF technology services for the user community is illustrated by the 31% increase in user fees in 2013. In 2013, user fees amounted to 6.5 MEUR! As user fees are typically come from externally funded projects, this increase indirectly demonstrates that projects relying on the availability of BF technology services have been increasingly competitive in obtaining competitive external funding.

Preparations for the new funding period 2014–2016: SAB review and negotiations with the host universities

In June 2013, the SAB came to Finland to perform a post-hoc evaluation of all BF activities supported by the earmarked OKM funding in 2010–12. Preparations for the SAB review included requests for final reports from the technology consortia. At the same time they were invited to write new applications for funding of operational costs and investments for 2014–2016. The SAB stated that the BF program had been very successful during 2010–2012. They were very impressed

with the level of coordination of tasks, efficient specialization and avoidance of duplication of effort, and commended the development of sophisticated and expensive techniques by well-trained experts providing first class service to Finnish scientists. The SAB felt that the user survey organized by the coordination office demonstrated that Finnish scientists generally were very pleased with the service provided by the BF supported core facilities. A comprehensive summary of the user survey can be found at the BF web site (www.biocenter.fi/uploads/documents/BF-User-survey-report-2013.pdf).

In the summer and fall of 2013, BF Board was busy in translating the individual recommendations of SAB into an operational budget of BF for 2014 to be funded by the host universities. Although the financial situation in many universities was very tight, they all agreed to support BF activities at the same level as in 2013 or somewhat higher. This was also the recommendation of the SAB to the host universities. I am very grateful to the leadership of BF host universities for their continued support to BF.

BF included on the national research infrastructure roadmap

The preparation for the SAB review coincided with the two-stage update of the Finnish national research infrastructure roadmap in spring 2013. In the previous infrastructure roadmap of 2008 several pieces of BF, individual infrastructure networks and different local or regional core facilities were listed, but BF as one entity was missing. Therefore it was particularly important for BF to write a clear and concise application to be included in the updated roadmap. This was also one of the recommendations of the 2008 roadmap. The roadmap update was organized by the recently established Finnish Research Infrastructure (FIRI) expert group, where I originally served as a chair, but had to resign when it became obvious that BF would be an applicant for both a roadmap position and national infrastructure funds, "FIRI funds".

The international evaluation panels used for the two-stage roadmap selection process gave very positive statements on BF. The final evaluation ended with the following statements:

> "The committee was deeply impressed by this successful national-scale cooperation. The BF covers with great success key technologies and infrastructure in the biological and biomedical research. In fact, the committee members noted that they do not know of any similar successful national-scale infrastructure in the life sciences elsewhere, and stated that the Finnish experience can serve as a model forother small countries that want to successfully pursue cutting-edge biological and biomedical research…. It is essential to continue and support this proposal as one of the main road map efforts in coming years. It will empower modern cutting-edge research in the life sciences, increase mobility, and the international standing of Finnish life sciences research. It is likely to strongly and positively impact both biotech companies and medicine, and thereby have a strong societal impact. The committee unanimously rated the proposal as outstanding."

Everyone at BF was pleased to read the positive statements of the roadmap evaluation panel which to a considerable extent were in line with those given by BF's own SAB. I am convinced that the rectors of host universities were also pleased to read that the money they had agreed to use for BF was for an excellent cause!

The year ends with a disappointment

The optimism created by the positive SAB and FIRI roadmap panel statements came to a quick end when the results of the FIRI 2013 application round were published. The 1.5 MEUR application of BF was funded at 1.0 MEUR.

In line with the coordinated approach to development of national biomedical infrastructure the Board of BF decided on a joint application strategy to demonstrate the cohesiveness of BF. For the application the BF Board selected what it considered were the most urgent equipment needs based on the application from the technology platforms for 2013–2016. The application focused on equipment only, no salaries or other expenses were included. The selected strategy was obviously wrong: while life sciences and biomedicine as such received over 6 MEUR of FIRI 2013 funding, the share of BF was only about 15% of total infrastructure funding for this domain.

A special challenge for BF in the FIRI 2013 application was the many connections of its technology services to European research infrastructures on the ESFRI Roadmap. Together the 5–6 ESFRI infrastructures received over two-fold more funding than BF. This very disappointing situation was also experienced in host universities which typically received only 50–100 000 EUR of FIRI funds for purchasing new equipment for their very large biomedical research community.

Can the new funding model provide a sustainable foundation for development of BF?

Last year I declared that year 2013 marks a moment of truth for BF. I asked whether the new funding model will provide the sustainability which is a key require-

ment for provision of technology services. The model was tested in 2013. I am very pleased with the decision of the rectors of host universities to BF Boards' proposal to fund the salaries of key technology service personnel and some consumables plus the coordination costs of BF with a total of 5.1 MEUR in 2013 from their own strategic funds. Although this marked a reduction from the funding level in 2010–2012, this was a very positive sign from the host universities under difficult financial circumstances. This indicates that the new modus operandi of BF has been accepted by the host universities. It has also been accepted by the scientific community as shown by the increased user statistics and user fees.

As discussed above, the other half of the new funding model was tested later in 2013. The outside experts gave a very positive evaluation and concluded its statement with the following words:

> "Given the large national scale of BF, the committee notes that a cap of 1.5M/proposal, while sufficiently big for regular infrastructure proposals, is not be big enough for continued BF support. This is particularly true given the much bigger investment in BF in the past, and the fact that except for the host universities, the academy is the only source for infrastructure grants. The committee therefore recommends a special consideration of extra funding for BF. The committee unanimously rated the proposal as outstanding."

But the end result was a disappointment. It is clear that for a national research infrastructure network with an annual budget of over 25 MEUR, an investment budget of 1–2 MEUR does not provide sustainability. The worst case scenario is that the universities are forced to return to the old tradition of sending their own applications without any national coordination to future FIRI calls.

Biocenters are among the most international and attractive research environments in Finland. This covers all steps of the academic career from visiting (FiDiPro) professors and principal investigators to group leaders, postdocs and doctoral trainees. English is the working language of BF and all biocenters. Statistics show that BF technology services are used by nearly half of the Finnish ERC grantees. Also overrepresented among BF customers are Academy professors, Centers of Excellence and EC funded projects. This shows that access to top level instrumentation and technology services is an important success factor. As the need for complex equipment for top-level research keeps increasing, the need for a nationally coordinated open access research infrastructure such as BF remains very high.

During the past 3.5 years I have travelled to a number of European countries to tell about the concept of BF to restructure life science infrastructures and technology services at national level. I am even more convinced now than in the beginning that the successful introduction of the concept in Finland could not have been achieved without the generous start-up support from OKM. This is one area where Finland is ahead of all other European countries. When the special OKM support ended and BF switched to its new operational concept, doubts were raised that this will mark the end of BF. The devoted staff operating the technology services has demonstrated that the new funding model can function. One major challenge remains – funding of equipment. I sincerely hope that we do not need to see the horror scenario where biocenters and host universities gradually abandon the coordinated development of BF infrastructure and start competing with each other for FIRI funds and development of life science infrastructures. This would be a step backwards which Finland cannot afford.

Acknowledgements

Finally, I would like to extend my very best thanks to all members of BF SAB, for their immensely valuable work. Their constructive scientific advice has made it possible to develop BF in a balanced way as a national infrastructure. My special thanks go to Professor Carl-Henrik Heldin, vice president of ERC Scientific Council, for committing so much of his valuable time to BF as the chair of the SAB since 2009 and for sharing with us his wide knowledge of European science policy. Similarly I express my thanks to my Board members whose commitment to BF has been remarkable also under the most difficult times.

With decreasing funding the small coordination office BF has been reduced to two persons, planning officer Sanna Leinonen and myself. The scientific coordinator of BF during 2010–2012, Tero Ahola, continued to help the coordination office up to August 2013, i.e. until the SAB evaluation was finalized. Sanna has consistently demonstrated the type of dynamism and creativity that BF needs, working under considerable pressure to produce reports, compiled tables and other documentation at very short notice. This annual report 2013 is another indicator of her talent. Thank you Tero and Sanna.

Eero Vuorio,
Director of Biocenter Finland

SCIENTIFIC ADVISORY BOARD

The statutes of BF stipulate that major funding decisions should be based on outside evaluation by a high-level international Scientific Advisory Board. BF believes that a rigorous scientific review combined with healthy competition has been an important success factor for BF. Subsequently, in 2010–12 nearly all of the 45 M€ of earmarked funding was distributed to technology platforms based on the SAB evaluations carried out in 2009 and 2011. As 2013 was a particularly important year for post-hoc evaluation of the use of the earmarked funding, the members of SAB were invited to continue for a second four-year period (2013–2016). All but one of them agreed for a second term.

The composition of BF SAB for 2013–2016:

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, **Gunnar von Heijne**, Stockholm University, **Matthias Wilmanns**, EMBL, Hamburg

The SAB visited Helsinki in June 9–11, 2013 to perform a post-hoc evaluation of all BF activities in 2010–2012, and to evaluate a new round of applications for technology platforms for 2014–2016. Prior to their visit, the SAB members has received structured reports from all the technology platforms summarizing their accomplishments, user statistics, finances and other key activities. The SAB had also received new applications, primarily from the same consortia, for further funding of technology services in 2014–2016. During the visit in Helsinki the SAB members listened to the presentations by the technology platform chairs and had a possibility to ask questions about their past performance and their new application.

The following quote from the SAB report summarizes the results of the post-hoc evaluation of the overall performance of BF during the 2010–12 funding period:

> "The SAB is very impressed with what has been achieved by the BF funding. The BF program has encouraged coordination of important core facilities at the national level. The core facilities have been placed where the environment and scientific backup are strongest. This specialization has several advantages; sophisticated and expensive techniques have been placed in the hands of well-trained experts who can provide first class service to Finnish scientists, and the available resources have been used in an efficient manner, avoiding duplications of efforts. A user survey was recently performed, which demonstrated that Finnish scientists generally are very pleased with the service provided by the BF supported core facilities. Thus, the BF program has been very successful and the 45 MEUR set aside for BF funding during 2010–2012 has been well used."

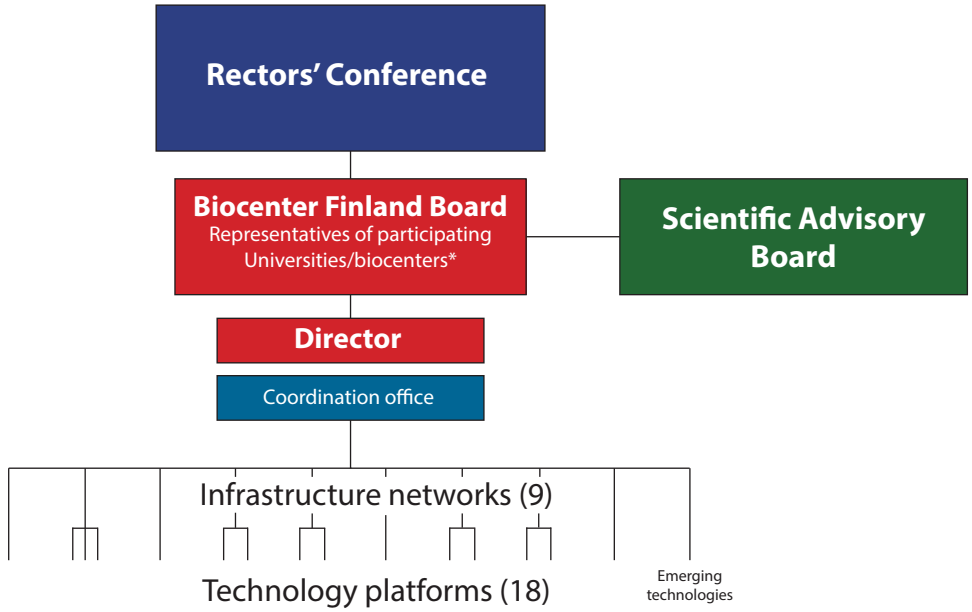
The second part of the evaluation was challenging for the SAB as they were invited to recommend distribution of funds from a virtual pot of money, which the BF Board and Director were then expected to translate into funding recommendations to the Rectors of host universities (for operational expenses) and into an application for the annual calls for national research infrastructure (FIRI) funds by the Academy of Finland (for investments). The SAB proceeded accordingly to recommend operational and other funding for the technology platforms using the same criteria as in 2009 and 2011. The SAB also sent a clear message to the host universities:

> "The SAB recommends that the host universities, at a minimum, support salary costs for key personnel and training costs at the different facilities. Costs for consumables can be covered by user fees. Investment in additional instruments will also be necessary; this may come through FIRI applications, but may in certain cases also need support from the host universities."

ORGANIZATION OF BIOCENTER FINLAND IN 2013

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.

Biocenter Finland Governance Structure



* Participating Universities / biocenters:
University of Helsinki: Biocentrum Helsinki, Institute of Biotechnology, FIMM
University of Tampere: BioMediTech
University of Turku and Åbo Akademi University: BioCity Turku
University of Eastern Finland: Biocenter Kuopio
University of Oulu: Biocenter Oulu

Director

Eero Vuorio

Governing Board in 2013 (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, University of Helsinki (Janna Saarela)

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

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

Tapio Visakorpi, Institute of Biomedical Technology (now BioMediTech), University of Tampere

Governing Board in 2014

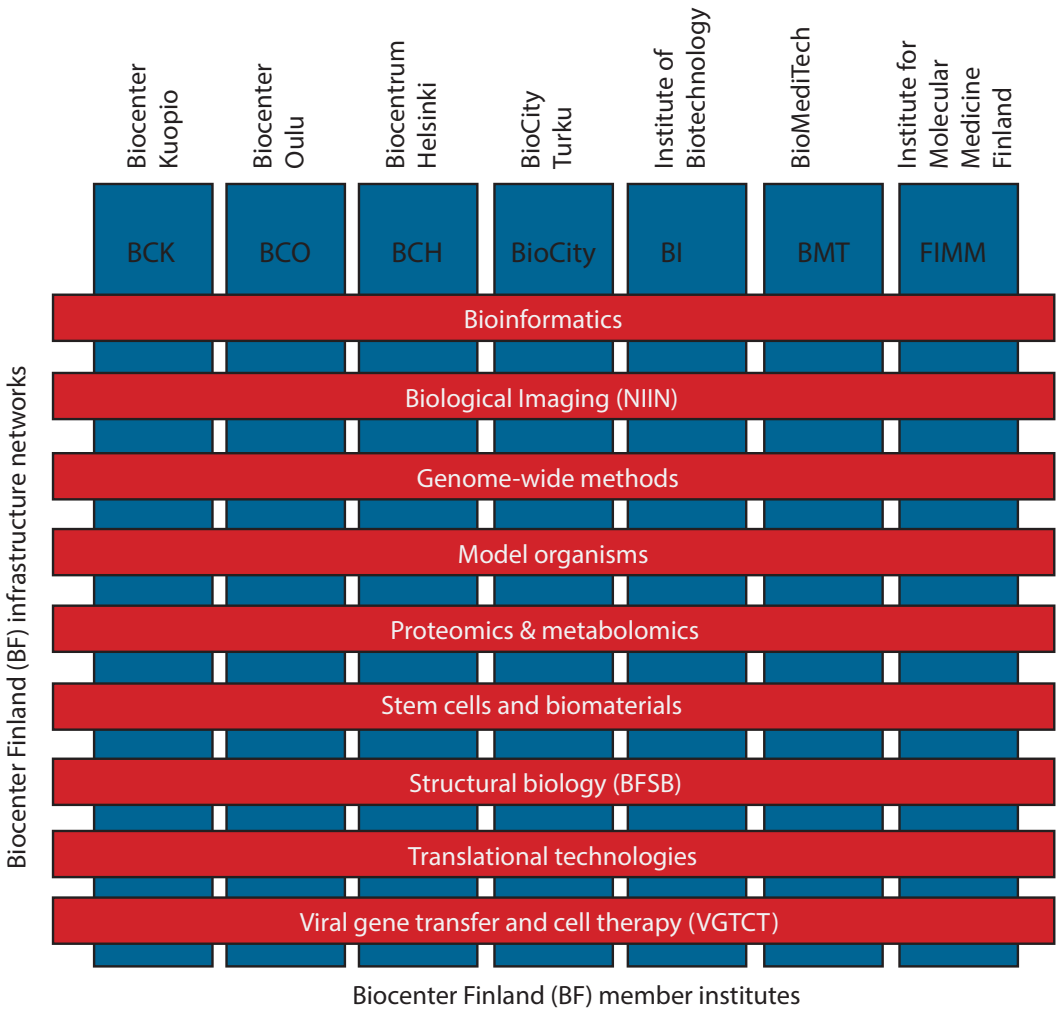
John Eriksson (Chairman of the Board), BioCity, Åbo Akademi;
Johanna Myllyharju (Vice-Chairman of the Board), BCO, University of Oulu (Outi Savolainen);
Jyrki Heino, BioCity, University of Turku (Riitta Lahesmaa);
Olli Kallioniemi, FIMM, University of Helsinki (Janna Saarela);
Pekka Lappalainen, BCH, University of Helsinki (Sampsa Hautaniemi);
Tomi Mäkelä, BI, University of Helsinki;
Tapio Visakorpi, BMT, University of Tampere (Anne Kallioniemi);
Seppo Ylä-Herttuala, BCK, University of Eastern Finland

Biocenter Finland Administration

Research coordinator (part-time)
Tero Ahola (until August 2013)

Planning officer
Sanna Leinonen

Biocenter Finland Member Institutes and Infrastructure Networks



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.

BIOCENTER FINLAND AND THE EUROPEAN RESEARCH INFRASTRUCTURES ON THE ESFRI ROADMAP

Finnish scientists have been actively involved in planning and construction of nine BMS (Biological and Medical Sciences) research infrastructures on the ESFRI (European Strategy Forum for Research Infrastructures) Roadmaps 2006, 2008 and 2010. They have participated in drafting of operational concepts of such infrastructures, their business plans and statutes during the European Commission -funded preparatory phase of these BMS infrastructures.

One indicator of major Finnish participation in the BMS ESFRI infrastructures is that national nodes/centers of seven of them were included in the updated national infrastructure roadmap in 2013. BF scientists and technology platforms are involved in all seven:

- **BBMRI-ERIC** (Biobanking and Biomolecular Resources Research Infrastructure)
- **EATRIS-ERIC** (European Advanced Translational Research Infrastructure)
- **ELIXIR** (European Life Science Infrastructure for Biological Information)
- **EU-Openscreen** (European Infrastructure of Open Screening Platforms for Chemical Biology)
- **Euro-BioImaging** (European Biomedical Imaging Infrastructure)
- **Infrafrontier** (European Infrastructure for Phenotyping and Archiving of Model Organisms)
- **Instruct** (An Integrated Structural Biology Infrastructure for Europe)

A typical feature of all BMS research infrastructures is their distributed structure into different operational sites in participating member states. The distributed nature of BMS infrastructures requires member states to organise their national nodes or centers to build a proper interface with the pan-European ESFRI projects. In Finland the existence of BF infrastructure networks has provided a ready-made solution for the national nodes and user communities for most of the seven BMS infrastructures on the Finnish roadmap. The research community is already well organized, has an updated inventory of equipment, samples and services at hand, and is therefore well prepared to enter the large European research infrastructures. In some fields the BF infrastructure networks correspond almost exactly to ESFRI projects, e.g. in biological imaging (Euro-BioImaging), structural biology (Instruct), mouse biology and model organisms (Infrafrontier) and chemical biology (EU-Openscreen). In the field of bioinformatics (ELIXIR) BF network is involved, but national coordination occurs via CSC. In biobanking and translational research, BF infrastructure networks are involved in the corresponding ESFRI infrastructures BBMRI and EATRIS. In all cases, BF scientists have participated in the preparation of concrete operational plans for the ESFRI projects to guarantee that their voice is heard in Europe when important long-term decisions regarding standardization of technologies, operating procedures, guidelines, access policies and other rules are made. BF and its infrastructure networks are willing to support this process and to function as national level structures for ESFRI projects during their construction phase.

Unfortunately, the close connection between BF and national ESFRI nodes and the services they provide is not only an advantage. In the FIRI2013 call the national ESFRI nodes were encouraged to make their own applications for establishment of the required national node structure. This has caused some confusion both in the host universities and among the wider scientific community as the boundaries between BF technology platforms and national ESFRI nodes have not appeared sufficiently clear. This could have been expected as the goals of ESFRI and BF are very similar, provision of access to world-class research facilities and to overcome fragmentation of the BMS research landscape. Thus BF and the ESFRI nodes ended up competing for the same limited resources in the FIRI2013 call; the national ESFRI nodes were clearly the winners: they received 2.16 MEUR of funding while BF only received 1.0 MEUR. In the future, BF and the national ESFRI nodes need to work hard to clarify their roles both locally and nationally so that a balanced development of life science research infrastructure can be reached in the upcoming years.

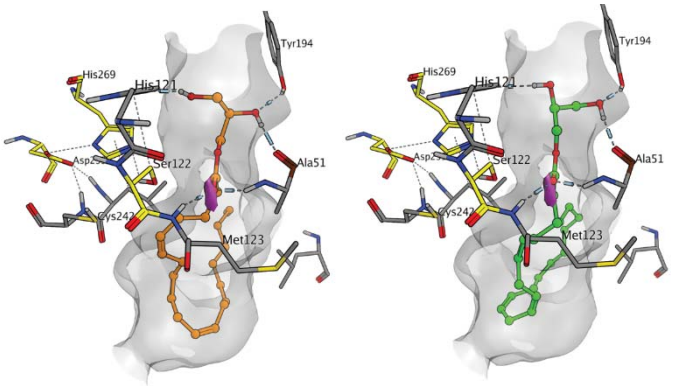
SCIENTIFIC SUCCESS STORIES BASED ON BIOCENTER FINLAND TECHNOLOGY SERVICES

Molecular modeling enhances our understanding on how lipase enzyme works, allowing better design of inhibitors

Molecular modeling and virtual screening combined with follow-up experimental validation are key services of the DDCB platform. Together they provide powerful tools to discover novel bioactive chemicals, and importantly, to understand mechanism of action of existing bioactive small molecules and to identify rational strategies for improving their activities.

Monoacylglycerol lipase has emerged as a promising and druggable target to treat cancer, neurodegenerative diseases, and metabolic disorders. In recent years, considerable progress has been made in developing selective, potent monoacylglycerol lipase inhibitors, but our knowledge regarding determinants that regulate the catalytic activity and substrate preferences of the human enzyme is limited. In this study, molecular modeling of the binding and function of a panel of monoacylglycerol lipase substrates and inhibitors combined with site-directed mutagenesis showed that Cys242 and Tyr194, the two opposing amino acid residues in the catalytic cavity of the enzyme, play important roles in determining the rate and the isomer preferences of monoacylglycerol hydrolysis. The findings may therefore allow for rational design of more potent and selective inhibitors of monoacylglycerol lipases that can be explored as safe and effective drugs to treat a range of different diseases.

Laitinen T. et al. 2014. Mutation of Cys242 of human monoacylglycerol lipase disrupts balanced hydrolysis of 1- and 2-monoacylglycerols and selectively impairs inhibitor potency. Mol. Pharmacol. 85:510-519



Molecular modeling of the role of molecular interactions in the catalytic site of monoacylglycerol lipase.

Placenta growth factor and CNS revascularization

Vascular bypass procedures in the central nervous system (CNS) remain technically challenging, hindered by complications and often failing to prevent adverse outcome such as stroke. Thus, there is an unmet clinical need for a safe and effective CNS revascularization. Vascular endothelial growth factors (VEGFs) are promising candidates for revascularization; however, their effects appear to be tissue-specific and their potential in the CNS has not been fully explored. To test growth factors for angiogenesis in the CNS, we characterized the effects of endothelium-specific growth factors on the brain vasculature and parenchyma. Recombinant adeno-associated virus (AAV) vectors encoding the growth factors were injected transcranially to the frontoparietal cerebrum of mice. Angiogenesis, mural cell investment, leukocyte recruitment, vascular permeability, reactive gliosis and neuronal patterning were evaluated by 3-dimensional immunofluorescence, electron microscopy, optical projection tomography, and magnetic resonance imaging. Placenta growth factor (PlGF) stimulated robust angiogenesis and arteriogenesis without significant side effects, whereas VEGF and VEGF-C incited growth of aberrant vessels, severe edema, and inflammation. VEGF-B, angiopoietin-1, angiopoietin-2, and a VEGF/angiopoietin-1 chimera had minimal effects on the brain vessels or parenchyma. Of the growth factors tested, PlGF emerged as the most efficient and safe angiogenic factor, hence making it a candidate for therapeutic CNS revascularization.

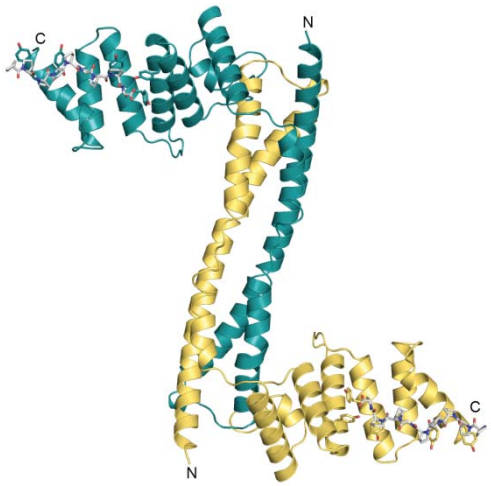
The authors of this study have addressed the important clinical problem of the lack of CNS revascularization therapeutics by using a gene therapy approach in mouse brain. A large part of their analysis of the effects of different VEGF- and angiopoietin growth factors on brain vasculature is based on confocal microscopy of fixed and immunostained tissue (performed on BIU light microscopy instruments). However, the critically important and clinically most relevant aspects of vessel function and therapy side effects were addressed by leakage analysis performed by optical projection tomography of the whole brain, and by contrast-enhanced and unenhanced MRI analysis of brain macroanatomy, blood-brain barrier function, hemorrhaging and edema.

Gaal EI, Tammela T, Anisimov A, Marbacher S, Honkanen P, Zarkada G, Leppänen VM, Tatlisumak T, Hernesniemi J, Niemelä M, Alitalo K. Comparison of vascular growth factors in the murine brain reveals placenta growth factor as prime candidate for CNS revascularization. Blood 2013; 122:658-65, doi: 10.1182/blood-2012-07-441527. IF 9.060. (BIU-BCH)

Crystal structure of collagen prolyl 4-hydroxylase

The crystal structure has been solved of the DD-domain region of the α-chain human collagen prolyl 4-hydroxylase (C-P4H). C-P4H is an $\alpha_2\beta_2$ tetramer. The α-chain consists of an N-terminal domain, a PSB-domain (in the middle) and a catalytic domain at its C-terminus. The crystal structure of the catalytic domain is unknown but the structure of the DD-domain, consisting of the N-terminal domain and the PSB-domain has been solved recently. The crystal structure shows that this domain is a dimer, in which the N-terminal domain is folded as a coiled-coil dimerisation motif, extended by the PSB-domain. The dimer interface is extensive (4000Å^2) and the structure suggests that in the $\alpha_2\beta_2$ tetramer the α_2-dimer will be important for stabilizing the tetrameric assembly. The DD-crystal structure has been determined without and with a bound peptide. The structures of two peptide complexes have been determined, with a substrate peptide $(PPG)_3$ and a polyproline inhibitor peptide (P9). The data of this structure were collected using the new Proteum data collection unit.

Anantharajan J, Koski MK, Kursula P, Hieta R, Bergmann,U, Myllyharju J and Wierenga RK (2013) The unique structural motifs for substrate binding and dimerization of the alfa subunit of collagen prolyl 4-hydroxylase. Structure, 21,2107-2118.



The crystal structure of the DD-domain dimer of human collagen prolyl 4-hydroxylase (C-P4H). (Anantaharajan et al., 2013). The DD-domain concerns the residues 1 to 238 of the α-chain of the $\alpha_2\beta_2$ C-P4H tetramer. The dimer interface is a four helical bundle, which is dominated by an extended antiparallel coiled-coil interface of the residues 8 to 55 of both subunits. Also shown is the bound $(Pro)_9$ inhibitor peptide as a stick model. This peptide binds in an extended groove, lined by 5 tyrosines, which are also shown as stick models. An important peptide-protein interaction is the stacking of the peptide proline side chains with these tyrosine aromatic rings.

MRI helps to estimate efficacy of oncolytic adenovirus treatment

At present, it is not possible to reliably identify patients who will benefit from oncolytic virus treatments. Conventional modalities such as computed tomography (CT), which measure tumor size, are unreliable owing to inflammation-induced tumor swelling. We hypothesized that magnetic resonance imaging (MRI) and spectroscopy (MRS) might be useful in this regard. However, little previous data exist and neither oncolytic adenovirus nor immunocompetent models have been assessed by MRS. Here, we provide evidence that in T2-weighted MRI a hypointense core area, consistent with coagulative necrosis, develops in immunocompetent Syrian hamster carcinomas that respond to oncolytic adenovirus treatment. The same phenomenon was observed in a neuroblastoma patient while he responded to the treatment. With relapse at a later stage, however, the tumor of this patient became moderately hyperintense. We found that MRS of taurine, choline and unsaturated fatty acids can be useful early indicators of response and provide detailed information about tumor growth and degeneration. In hamsters, calprotectin-positive inflammatory cells (heterophils and macrophages) were found in abundance; particularly surrounding necrotic areas in carcinomas and T cells were significantly increased in sarcomas, when these had been treated with a granulocyte–macrophage colony-stimulating factor-producing virus, suggesting a possible link between oncolysis, necrosis (seen as a hypointense core in MRI) and/or immune response. Our study indicates that both MRI and MRS could be useful in the estimation of oncolytic adenovirus efficacy at early time points after treatment.

This study is an excellent demonstration of the basic idea of Biocenter Finland. Researchers in Helsinki needed sophisticated magnetic resonance spectroscopy techniques that are only available in Kuopio through Biocenter Finland. Animals were sent to Kuopio, the study was designed together, the protocols implemented and tested by a staff scientist in Kuopio, and measurements were carried out by a scientist from Helsinki. Results were analyzed and interpreted in collaboration and finally published in a high quality journal.

Hemminki O, Immonen R, Närväinen J, Kipar A, Paasonen J, Jokivarsi KT, Yli-Ollila H, Soininen P, Partanen K, Joensuu T, Parvianen S, Pesonen SK, Koski A, Vähä-Koskela M, Cerullo V, Pesonen S, Gröhn OH, Hemminki A In vivo magnetic resonance imaging and spectroscopy identifies oncolytic adenovirus responders. Int J Cancer. 2013 Nov 18, doi: 10.1002/ijc.28615. Researchers in Haartman Institute, Helsinki sent animals to Kuopio in order to follow the response to oncolytic adenovirus treatment using MRI and MR spectroscopy. IF 6.2 (BIU- Kuopio)

Construction of novel database for data sharing and data analysis

One of the central challenges repeatedly encountered in projects utilizing novel high throughput methods is data storage and analysis. Data sharing when large and complicated data set should need to be seen by many scientists in a flexible manner is major target for research. In this interdisciplinary study a database was generated for stem cell research with advanced features enabling storing, sharing, integrating and analysing genome-wide data produced with Affymetrix and Illumina microarray platforms. This open-access database contains over 1200 samples from pluripotent stem cells and other tissues relevant for stem cell research and provides a valuable tool and solid platform for storing and mining data accumulating from genome-wide studies world-wide (Kong et al., 2013). Designing and building the database and its use to generate part of the data were performed in BioCity Turku by FMSC scientists.

Kong L, Aho KL, Granberg K, Lund R, Järvenpää L, Seppälä J, Gokhale P, Leinonen K, Hahne L, Mäkelä J, Laurila K, Pukkila H, Närvä E, Yli-Harja O, Andrews PW, Nykter M, Lahesmaa R, Roos C, Autio R. ESTOOLS Data@Hand: human stem cell gene expression resource. Nat Methods. 2013 Aug;10(9):814-5.

Activation of T lymphocytes

Activation of T lymphocytes is important in the response to pathogens and it has been unclear how immune cells increase their nutrition uptake to enhance metabolic activity in inflammatory responses. In this study the authors utilized genome-wide Affymetrix gene expression arrays to study the mechanisms regulating the process and highlight that activation of T lymphocytes in response to pathogens and inflammatory cytokines involves System L amino acid transport activity through TCR mediated regulation of Slc7a5 expression, which enables immune-activated T cells to enhance nutrition uptake and metabolic activity and mediate adaptive immune responses (Sinclair et al., 2013). FMSC (BioCity Turku) services were used to define with Affymetrix gene expression arrays and functional assays the mechanisms involved in the process.

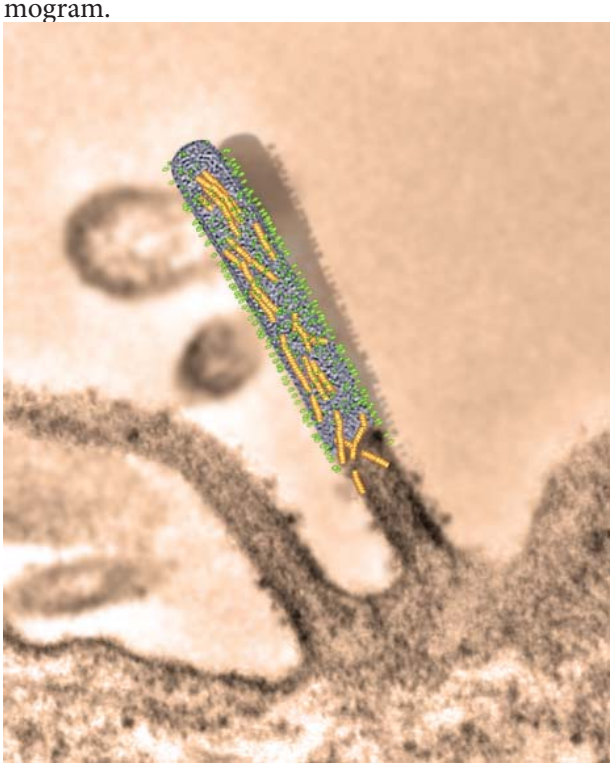
Sinclair LV, Rolf J, Emslie E, Shi YB, Taylor PM, Cantrell DA. Control of amino-acid transport by antigen receptors coordinates the metabolic reprogramming essential for T cell differentiation. Nat Immunol. 2013 May;14(5):500-8. doi: 10.1038/ni.2556.

Three-dimensional structure of respiratory syncytial virus (RSV) solved

Respiratory syncytial virus (RSV) is a common cause of respiratory infection, but there is no vaccine available. It causes flu-like symptoms in healthy adults, but becomes life-threatening in young children and the elderly. It is estimated to cause over 100 000 deaths yearly worldwide. BI-cryoEM in collaboration with Professor Ari Helenius (ETH Zurich) has now solved the three-dimensional structure of RSV.

RSV is related to measles and mumps viruses. All three viruses parasitize human cells, stealing parts of the cell membrane to use as their own. In RSV the resulting virus membranes look likes tubes and spheres, and this shape is controlled by the virus' matrix protein. In addition, two different forms of the fusion protein were observed on the surface. The fusion protein is responsible for attaching the virus to human cells and invading them. This is an important finding because the fusion protein is the key molecule in developing therapeutic antibodies to the virus.

From 2D to 3D in RSV: Transmission electron micrograph of sectioned RSV-infected cells (brown background) with data from an averaged 3D cryo-tomograms of isolated RSV (grey section), showing the distribution of the fusion protein (green), and the nucleocapsids (gold tubes) identified and from that tomogram.



Liljeroos, L. Krzyzaniak, M., Helenius, A., Butcher, S.J. 2013. Architecture of respiratory syncytial virus revealed by electron cryotomography. Proc. Natl. Acad. Sci. (USA) 110:11133-11138.

Transcriptional response to stress

Lea Sistonen's group was studying genome-wide transcriptional program that is rapidly provoked to counteract heat-induced stress and uncovered the broad range of molecular mechanisms that maintain cellular homeostasis under hostile conditions. Heat shock factors (HSFs) are the master regulators of transcription under protein-damaging conditions, acting in an environment where the overall transcription is silenced. Because transcriptional responses are directed in the complex chromatin environment that undergoes dramatic changes during the cell cycle progression, they identified the genome-wide transcriptional response to stress also in cells where the chromatin is condensed for mitotic division. Their results highlight the importance of the cell cycle phase in provoking cellular responses and identify molecular mechanisms that direct transcription during the progression of the cell cycle (Vihervaara et al., 2013). ChIP-seq for heat shock factors HSF1 and HSF2 was performed using next-generation sequencing services by FuGU.

Vihervaara A1, Sergelius C, Vasara J, Blom MA, Elsing AN, Roos-Mattjus P, Sistonen L. Proc Natl Acad Sci U S A. 2013 Sep 3;110(36):E3388-97. doi: 10.1073/pnas.1305275110. Epub 2013 Aug 19. Transcriptional response to stress in the dynamic chromatin environment of cycling and mitotic cells.

LDL cholesterol recycling

BIU-BCH: Low-density lipoprotein (LDL) cholesterol recycles to the plasma membrane (PM) via a Rab8a-Myosin5b-actin-dependent membrane transport route, but the underlying mechanisms have remained obscure. LDL labeled with BODIPY cholesteryl linoleate was employed to identify this pathway in living cells. The BODIPY cholesterol (BC) carriers docked to the cortical actin by a Rab8a- and Myosin5b (Myo5b)-dependent mechanism, typically in the proximity of focal adhesions (FAs). LDL increased the number and dynamics of FAs and stimulated cell migration in an acid lipase, NPC1, and Rab8a-dependent fashion, providing evidence that this cholesterol delivery route to the PM is important for cell movement.

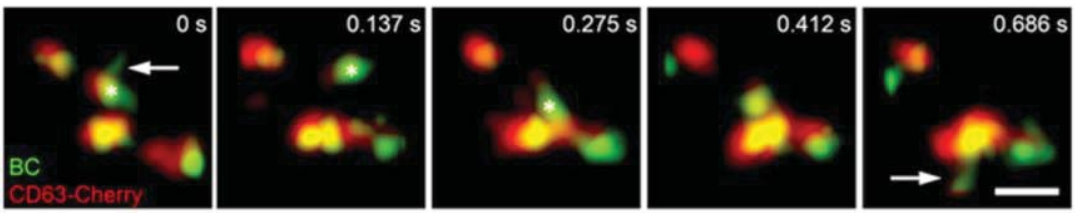
Kanerva et al. Dev Cell 2013; 27:249–262.

Zebrafish models for tuberculosis

Many aspects of tuberculosis 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. Research utilizing the Tampere zebrafish core facility has shown that an intraperitoneal 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. This latent infection can be then reactivated by immunosuppression (Parikka et al. (2012) PLoS Pathogens). 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. During 2013 researchers at Tampere were able to show that new vaccine candidates against tuberculosis can be screened using this model (Oksanen et al. (2013) Vaccine). This will allow efficient identification of novel vaccine antigens guiding thus research efforts to create new - safe and effective - vaccine against tuberculosis.

Oksanen KE, Halfpenny NJ, Sherwood E, Harjula SK, Hammarén MM, Ahava MJ, Pajula ET, Lahtinen MJ, Parikka M, Rämet M. An adult zebrafish model for preclinical tuberculosis vaccine development. Vaccine. 2013 Oct 25;31(45):5202-9.

Parikka M, Vuoksio M, Harjula SK, Halfpenny N, Oksanen K, Lahtinen MJ, Pajula E, Iivanainen A, Pesu M & Rämet M. (2012) Mycobacterium marinum causes a latent infection that can be reactivated by gamma irradiation in adult zebrafish. PLoS Pathogens 8:e1002944.



Images from a high frame-rate recording of fluorescent cholesterol (BODIPY-cholesterol, BC) containing late endosomes stably expressing CD63-Cherry. Cells were labeled with BC-containing low density lipoproteins for 2 h and chased for 2 h. Images represent two-dimensional projections of time-lapse z-stacks. Arrows indicate BC tubules emanating from CD63-positive organelles and asterisks a BC-containing vesicle fusing with another one. Scale bar, 1 µm. Images courtesy of Kristiina Kanerva, Institute of Biomedicine, Anatomy, University of Helsinki.

Technology transfer: pre-clinical prostate cancer model

The validation of a pre-clinical cancer model (VCaP xenografts in castrated immuno deficient mice) together with Orion Pharma was finalized at TCDM. The model has been successfully used in screening novel drugs developed against castration-resistant prostate cancer, and the model has been made available as a service at TCDM in 2013. Using xenograft models of human cells in mice TCDM has carried out 6 projects for Pharma industry.

Furthermore, GM mouse models generated in the Oulu unit have been used in preclinical screenings by Fibrogen Inc. (California, USA).

Knuuttila M, Yatkin E, Kallio J, Savolainen S, Laajala TD, Aittokallio T, Oksala R, Häkkinen M, Keski-Rahkonen P, Auriola S, Poutanen M, Mäkelä S, Castration induces upregulation of intratumoral androgen synthesis and androgen receptor expression in orthotopic VCap human prostate cancer xenograft model. Am. J. Pathology, in press.

Rahtu-Korpela L, Karsikas S, Hörkkö S, Sequeiros RB, Lammentausta E, Mäkelä KA, Herzig KH, Walkinshaw G, Kivirikko KI, Myllyharju J, Serpi R, Koivunen P. HIF prolyl 4-hydroxylase-2 inhibition improves glucose and lipid metabolism and protects against obesity and metabolic dysfunction. Diabetes. 2014 May 1. [Epub ahead of print]

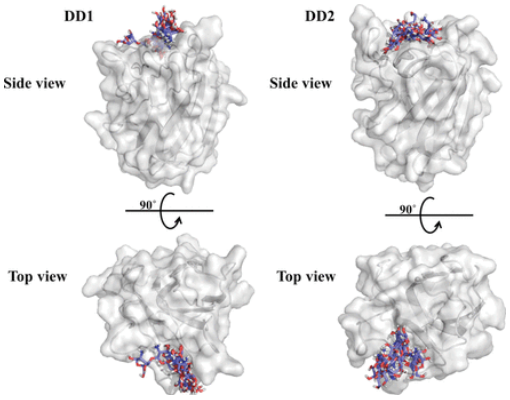
Identification of chitosan-specific binders

BCO has contributed to a study where a combination of calorimetry experiments, nuclear magnetic resonance (NMR), and theoretical protein ligand docking has led to the first identification of carbohydrate binding modules specific to glucosamine (GlcN) polysaccharide chitosan.

Two carbohydrate binding modules (DD1 and DD2) are located at the C terminus of a chitosanase from Paenibacillus sp. Three proteins, DD1, DD2, and the tandem DD1/DD2 (DD1+DD2) were produced, and characterized for their binding ability and transition temperature of thermal unfolding (T_m). The T_m of each protein was elevated by the addition of cello-, laminari-, chitin-, or chitosan-hexamer $(GlcN)_6$. The T_m elevation (ΔT_m) in DD1 was the highest (10.3 °C) upon the addition of $(GlcN)_6$ and was markedly higher than that in DD2 (1.0 °C). A synergistic effect was observed (ΔT_m = 13.6 °C), when $(GlcN)_6$ was added to DD1+DD2. From isothermal titration calorimetry experiments, affinities to DD1 were not clearly dependent upon chain length of $(GlcN)_n$; affinity (ΔGr °) values were −7.8 (n = 6), −7.6 (n = 5), −7.6 (n = 4), −7.6 (n = 3), and −7.1 (n = 2) kcal/mol, and the value was not obtained for GlcN due to the lowest affinity. DD2 bound $(GlcN)_n$ with the lower affinities (ΔGr ° = −5.0 (n = 3) ~ −5.2 (n = 6) kcal/mol). Isothermal titration calorimetry profiles obtained for DD1+DD2 exhibited a better fit when the two-site model was used for analysis and provided greater affinities to $(GlcN)_6$ for individual DD1 and DD2 sites (ΔGr ° = −8.6 and −6.4 kcal/mol, respectively).

From NMR titration experiments, (GlcN)n (n = 2 ~ 6) were found to bind to loops extruded from the core β-sandwich of individual DD1 and DD2, and the interaction sites were similar to each other. To more clearly identify the interaction site, the analysis was extended by conducting docking simulations of (GlcN)2 binding to DD1 and DD2, using varying protonation states of titrating residues relevant to binding. The (GlcN)2 binding sites were found to be restricted to the shallow binding cleft including the residues 14, 33–38, and 121–123 for both DD1 and DD2, see figure below.

In conclusion, the tandem DD1+DD2 is specific to chitosan, and individual modules synergistically interact with at least two GlcN units, facilitating chitosan hydrolysis.



For additional details see: http://www.jbc.org/content/early/2013/08/28/jbc.M113.503243

Reference: Shoko Shinya, Takayuki Ohnuma, Reina Yamashiro, Hisashi Kimoto, Hideo Kusaoke, Padmanabhan Anbazhagan, André H. Juffer and Tamo Fukamizo. The first identification of carbohydrate-binding modules specific to chitosan. J Biol Chem (2013), published online August 28, 2013

Rapid systems medicine analysis for tumor samples

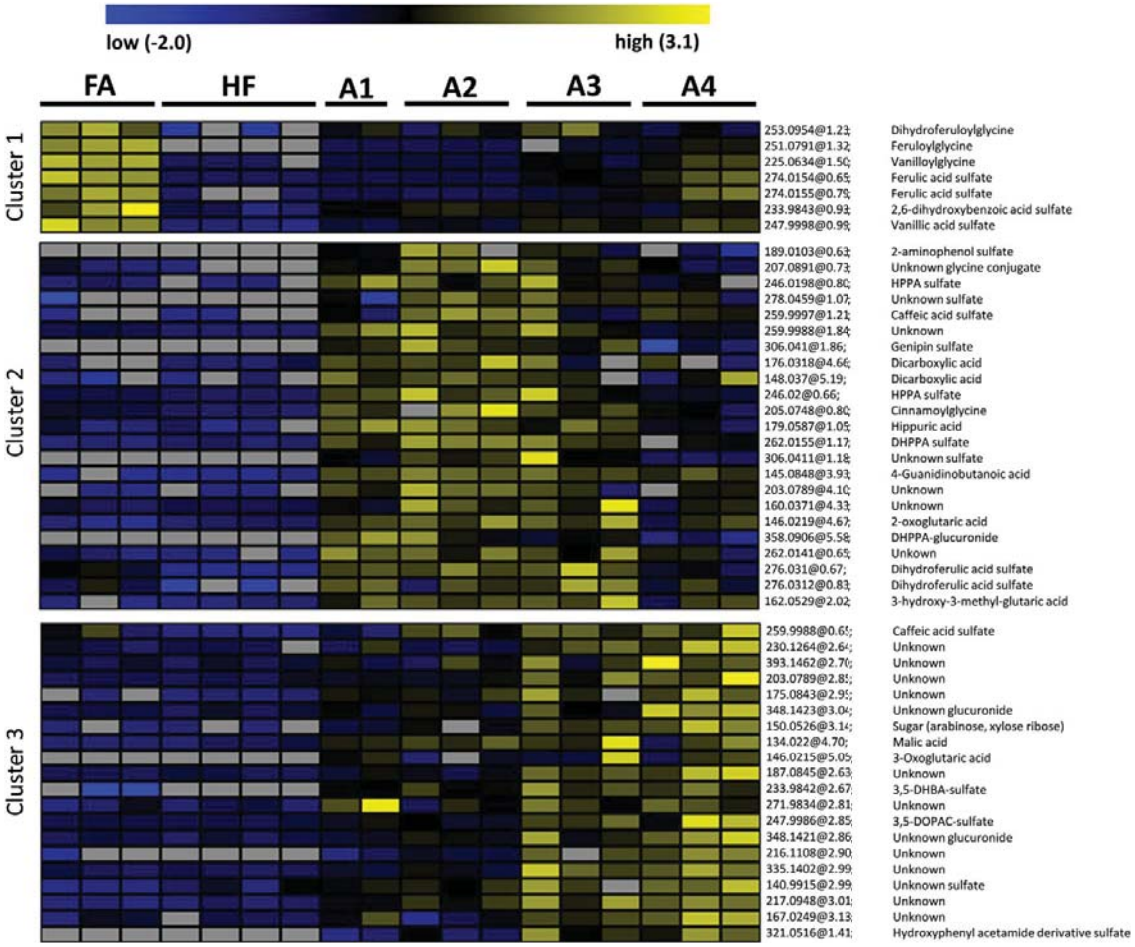
FIMM Technology Center (in a collaboration between the nodes of BF DDCB and BF-Bioinformatics networks as well as several research groups) has set up molecular profiling and drug sensitivity and resistant testing analyses allowing rapid identification of somatic mutations, CNVs and fusion transcripts by genome, exome and transcriptome sequencing as well as drug sensitivity profiling of individual cancer samples. This setup was used to analyse a cohort of patients with chemorefractory acute myeloid leukemia. (Pemovska et al, 2013).

Pemovska T, Kontro M, Yadav B, Edgren H, Eldfors S, Szwajda A, Almusa H, Bespalov MM, Ellonen P, Elonen E, Gjertsen BT, Karjalainen R, Kulesskiy E, Lagström S, Lehto A, Lepistö M, Lundán T, Majumder MM, Marti JM, Mattila P, Murumägi A, Mustjoki S, Palva A, Parsons A, Pirttinen T, Rämet ME, Suvela M, Turunen L, Västrik I, Wolf M, Knowles J, Aittokallio T, Heckman CA, Porkka K, Kallioniemi O, Wennerberg K. Individualized systems medicine strategy to tailor treatments for patients with chemorefractory acute myeloid leukemia. Cancer Discov. 2013 Dec;3(12):1416-29. doi: 10.1158/2159-8290.CD-13-0350.

Metabolomics for bioavailability studies

An animal feeding trial was conducted at the BCK metabolite profiling facility. Differentially processed wheat bran fractions were included in the diet of the black mouse model in order to analyse the impact of technical processing on the bioavailability of the bran-bound phytochemicals. The non-targeted metabolite profiling revealed that the technical processing increased the bioavailability of certain phenolic acids as was evidenced by the different urinary metabolite profiles.

Pekkinen J, Rosa NN, Savolainen OI, Keski-Rahkonen P, Mykkänen H, Poutanen K, Micard V, Hanhineva K: Disintegration of wheat aleurone structure has an impact on the bioavailability of phenolic compounds and other phytochemicals as evidenced by altered urinary metabolite profile of diet-induced obese mice. Nutr Metab (Lond). 2014 Jan 2;11(1):1. doi: 10.1186/1743-7075-11-1.

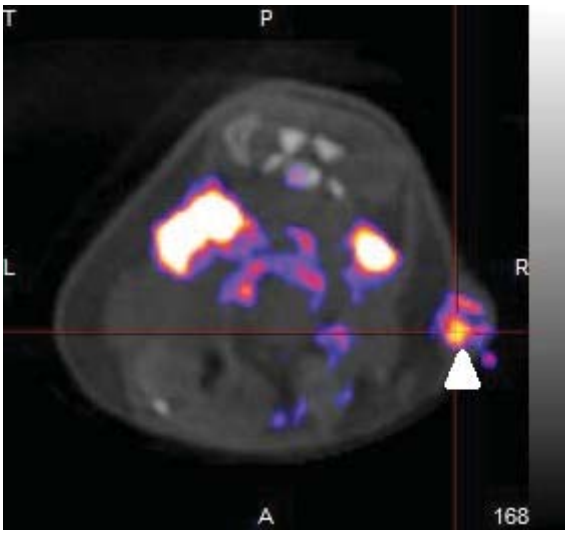


K-means clustering analysis on the 50 significantly increasing ($q < 0.05$) urinary metabolite features after adding FA or one of the aleurone preparations (A1-A4) into the diet when compared to HF control diet. The signal abundances were row-wise normalized and classified into three different clusters. The color-coding scale indicates the abundance within each metabolite: blue: low abundance, yellow: high abundance, gray: not detected. Each replicate is a pool of 2–3 mice on the same diet group.

Imaging the trafficking of ^{111}In labeled lymphatic cells with SPECT/CT

OT-I lymphatic cells were radiolabeled with ^{111}In in a scientific collaboration with Prof. A. Hemminki, Cancer Gene Therapy Group and Academy research fellow Anu Airaksinen, Laboratory of Radiochemistry, University of Helsinki. Trafficking of the radiolabeled OT-I cells were followed by SPECT/CT in C57BL/6 mice bearing B16-OVA tumors. Influence of intratumoral adenovirus treatment on the OT-I tumor accumulation was evaluated.

SPECT/CT imaging allowed follow up of the OT-I cell trafficking in vivo at different time points and up to 7 days. Tumor accumulation of OT-I cells was quantified, which allowed comparison of the adenovirus-treated and non-treated groups, providing valuable information on the efficiency of the adenovirus treatment to influence the OT-I cell trafficking into the treated tumor.

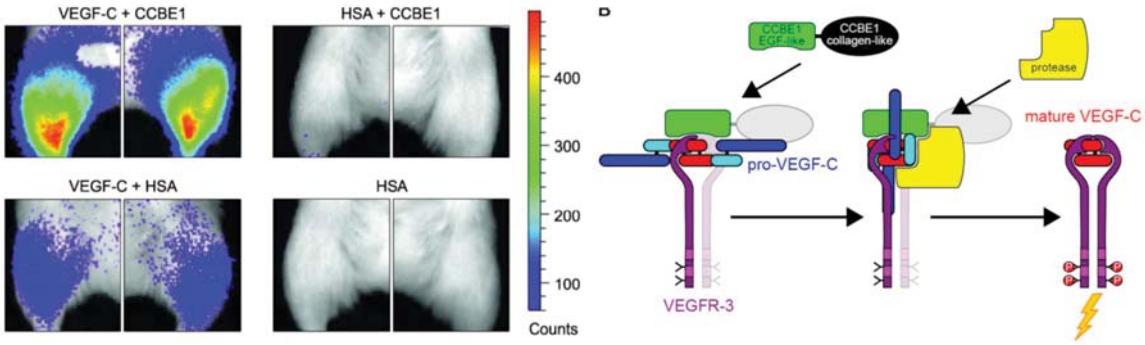


Trafficking and accumulation of 111In labeled OT-I cells into an adenovirus treated tumor 24h after the cell administration (ip.). Arrow indicates location of the tumor.

Gene transfer experiments elucidate VEGF-C action

Hennekam lymphangiectasia–lymphedema syndrome (OMIM 235510) is a rare autosomal recessive disease, which is associated with mutations in the collagen- and calcium-binding EGF domains 1 (CCBE1) gene. Using AAV gene transfer, combined with various molecular biology approaches, the authors were able to identify ADAMTS3 as a VEGF-C activating protease and reveal a novel type of regulation of a vascular growth factor by a protein that enhances its proteolytic cleavage and activation (Figure). The results suggest CCBE1 is a potential therapeutic tool for the modulation of lymphangiogenesis and angiogenesis in a variety of diseases that involve the lymphatic system, such as lymphedema or lymphatic metastasis.

CCBE1 activates VEGF-C. A - VEGFR-3-luciferase reporter signals in mouse skeleteal muscles injected with AAV9 vectors encoding the indicated proteins. B - Schematic view of VEGF-C and VEGFR-3 activation by VEGF-C. Pro-VEGF-C binding to VEGFR-3 is assisted by the N-terminal domain of CCBE1. Pro-VEGF-C is then proteolytically processed in situ and the mature VEGF-C activates VEGFR-3.



INFRASTRUCTURE NETWORKS & TECHNOLOGY PLATFORM SERVICES

BIOINFORMATICS

Bioinformatics Infrastructure Network

Coordinator of the network: Sampsa Hautaniemi, BCH
Members: Petri Auvinen, BI; Garry Wong, BCK; André Juffer, BCO; Matti Nykter, BMT; Mark Johnson, BioCity; Imre Västrik, FIMM

www.biocenter.fi

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

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; Matti Nykter, BMT, Bioinformatics Group; Mark Johnson, BioCity, Structural Bioinformatics Laboratory; Imre Västrik, FIMM
External members: Tommi Nyrönen IT Center for Science, CSC; Samuel Kaski & Harri Lähdesmäki, Aalto University

www.biocenter.fi

http://bioinformatics.biocenter.fi/

Achievements in development and restructuring of technology services during 2013

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

As the next generation sequencing (NGS) service, offered by BF Genome-wide methods network, is the major data producer utilized at close to full capacity, the Bioinformatics network has put a considerable effort into NGS data processing, analysis and interpretation. In fact, the Bioinformatics network members have been working closely and integrating their services with the sequencing service providers in their

biocenters. The integration creates for the clients a "one-stop-shop". This may nevertheless manifest itself in decreased visibility of the bioinformatics network since the users may not be aware of the fact that they are using services of multiple BF networks. To cope with the volume of the data we have aimed at creating automated analysis pipelines for the most commonly requested services. For example, FIMM has implemented a pipeline for identification and annotation of variants from genome sequence data as this is the main data type produced for the clients of the FIMM NGS unit. Another often used pipeline identifies somatic and possibly tumor-causing mutations from the genome sequence of cancer samples. Whereas this is clearly not a clinical diagnostic service, hematologists and oncologists nevertheless have begun to consider such results in support of their treatment decisions in challenging patient cases.

In addition to this, the bioinformatics network has also been supporting data and software services for BF Biological imaging, Translational technologies, Proteomics and Structural Biology. The Bioinformatics network has presented the services to the biocenter communities and established a helpdesk. The questions via the helpdesk have been organized so that they can be handled by one of the members. Clearly, the helpdesk needs constant advertising and in the future we will merge our helpdesk with CSC in order to gain more publicity, efficiency and customers.

The major bottleneck the network sees and foresees is the availability of qualified personnel to conduct computational analysis. Bioinformatics analysis and research is very labor intensive and the number of projects is a strain on the limited personnel.

Biocenter Finland conducted a user survey, in which the quality of Bioinformatics services was deemed high together with efficiency (average for the whole network 4/5). We received some critique on the visibility of the services and this is our major focus in 2014–2016. As an example, BI had 10% of disgruntled customers and a complaint of poor visibility. This will be rectified by putting more focus on developing web services. We note that the services provided by the BMT, in the University of Tampere have been in transition during 2013. Due to the change of personnel, the services have been refactored to reflect the current expertise. During 2013 both the biological database services (IDBases, Immunome KnowledgeBase, KinMutBase, etc.; pathogenicity prediction PON-P) developed earlier and new high throughput data analysis services have been provided in parallel. In future, above mentioned biological databases will not be supported but they are still available for the scientific community through the web pages of Prof. Mauno Vihinen at Lund University.

Participation in international, Nordic and European infrastructures

CSC, the Finnish node of the ELIXIR bioinformatics ESFRI infrastructure, is an external member in the BF Bioinformatics network. As such the CSC's planned service offering in ELIXIR is based on the needs of the BF Bioinformatics network. Members of the Bioinformatics network use the cloud computing pilot service developed and offered by CSC in preparation for ELIXIR. For example, 80% of the processing power of FIMM computer cluster is actually provided by the CSC cloud. Similar arrangements are being implemented at BioCity Turku.

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

BMT works in collaboration with the Cancer Genome Atlas (TCGA) and has provided gene fusion anal-

User statistics 2013

Important: BCO provides in silico modeling and simulation services where the time for one project may take from weeks to months.

	BCH	BI	BCK	BCO	BMT	BioCity	FIMM	Total
Total users	16	9	9	10	14	45	56	159
a) local	10	8	6	7	12	33	38	114
b) domestic	4	1	2	0	2	8	17	34
c) international	2	0	1	3	0	4	1	11
of which non academic	0	0	0	0	0	2	0	2
Projects	21	12	6	10	19	45	203	316
Database & server users / requests	n/a	anonym. / 22 857	n/a	n/a	130	> 200	n/a	> 23 187
Income eur	792	0	0	0	0	44 286	29 500	74 578

ysis for glioblastoma (http://www.ncbi.nlm.nih.gov/pubmed/24120142), endometrial carcinoma (http://www.ncbi.nlm.nih.gov/pubmed/23636398) and prostate cancer (ongoing) analysis working groups.

Bioinformatics is also in the central role in the EATRIS translational research infrastructure where FIMM leads the Biomarkers services - one of the five service areas of EATRIS. Furthermore, bioinformatics services are also needed to analyse the data produced from samples from the BBMRI biobanking infrastructure. Bioinformatics network services are also linked with EC framework program funded projects. For example, the personalized medicine data produced for and used in one of the BioMedBridges project's use case work packages is processed by the bioinformatics pipelines at FIMM.

Future perspectives

Given the ambitious plans of other BF networks, especially those of Genome-wide methods, to obtain new equipment producing massive amounts of data, the need for data storage and analysis capacity is going to increase. In practical terms, that means that we are going to need more disk space, more CPUs as well as fast connections between the storage and processors (I/O capacity). Especially the latter is crucial and requires a holistic view of the IT system. We also need the skilled staff – bioinformaticians and IT experts – to develop, maintain and update the processing pipelines and IT systems.

We also note that utilization of publicly available data sources (ENCODE, TCGA, ICGC etc.) in bioscience research is clearly an emerging trend. For this, most bioscience groups will require technical analysis support as well as IT infrastructure for storage and analysis of the data. As a consequence, storage, accessibility and flexible analysis of these vast data collections need to be solved.

Major publications resulting from the Platform services

Radivojac P, Clark W, Oron T, Schnoes A, Wittkop A, Sokolov A, Graim K, Funk C, Verspoor K, Ben-Hur A, Pandey G, Yunes G, Talwalkar A, Repo S, Souza M, Piovesan D, Casadio R, Wang Z, Cheng Z, Fang H, Gough J, Koskinen P, Törönen P, Nokso-Koivisto J, Holm L, Cozzetto D, Buchan D, Bryson K, Jones D, Limaye B, Inamdar H, Datta A, Manjari S, Joshi R, Chitale M, Kihara D, Lisewski AM, Erdin S, Venner E, Lichtarge O, Rentzsch R, Yang H, Romero A, Bhat P, Paccanaro A, Hamp T, Kassner R, Seemayer S, Vicedo E, Schaefer C, Achten D, Auer F, Boehm A, Braun T, Hecht M, Heron M, Honigschmid P, Hopf T, Kaufmann S, Kiening M, Krompass D, Landerer C, Mahlich Y, Roos M, Björne J, Salakoski T, Wong A, Shatkay H, Gatzmann F, Sommer I, Wass M, Sternberg M, Skunca N, Supek F, Bošnjak M, Panov P, Dzeroski S, Šmuc T, Kourmpetis Y, van Dijk A, ter Braak C, Zhou Y, Gong Q, Dong X, Tian W, Falda M, Fontana P, Lavezzo E, Di Camillo B, Toppo S, Lan L, Djuric N, Guo Y, Vucetic S, Bairoch A, Linial M, Babbitt P, Brenner S, Orengo O, Rost B, Mooney S, FriedbergI. A large-scale evaluation of computational protein function prediction. Nature Methods 10, 221-227, 2013. - *Independent evaluation of BI's PANNZER program, which ranked in the top three amongst >50 methods.*

Blokhina OB, Törönen P, Fagerstedt KV. Oxidative Stress Components Explored in Anoxic and Hypoxic Global Gene Expression Data. In J.T. van Dongen and F. Licausi (eds.), Low-Oxygen Stress in Plants, Plant Cell Monographs 21, DOI 10.1007/978-3-7091-1254-0_2, Springer-Verlag Wien 2014. - *BI performed gene set enrichment analysis of microarray experiments.*

Shinya S, Ohnuma T, Yamashiro R, Kimoto H, Kusaoke H, Anbazhagan P, Juffer AH, Fukamizo T. Journal of Biological Chemistry. 288, 30042-30053, 2013. - *All protein modeling and subsequent analysis, e.g. effects of protonation states on binding mode, was carried out by the BCO Biocomputing unit.*

Cancer Genome Atlas Research Network, Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, Shen H, Robertson AG, Pashtan I, Shen R, Benz CC, Yau C, Laird PW, Ding L, Zhang W, Mills GB, Kucherlapati R, Mardis ER, Levine DA. Integrated genomic characterization of endometrial carcinoma. Nature 2;497(7447):67-73, 2013. - *BMT performed the fusion gene analysis for the analysis working group.*

Turpeinen H, Oksanen A, Kivinen V, Kukkurainen S, Uusimäki A, Rämet M, Parikka M, Hytönen VP, Nykter M, Pesu M. Proprotein convertase subtilisin/kexin type 7 (PCSK7) is essential for the zebrafish development and bioavailability of transforming growth factor beta 1a (TGF1a). The Journal of Biological Chemistry, 288(51):36610–36623, 2013. - *BMT performed gene expression data analysis and prepared the corresponding figures to the manuscript.*

Pemovska T, Kontro M, Yadav B, Edgren H, Eldfors S, Szwajda A, Almusa H, Bespalov MM, Ellonen P, Elonen E and others. Individualized Systems Medicine strategy to tailor treatments for patients with chemorefractory acute myeloid leukemia. Cancer discovery 3(12):1416-1429, 2013. - *NGS data was analysed with FIMM bioinformatics pipelines.*

Rajala H, Eldfors S, Kuusanmäki H, van Adrichem A, Olson T, Lagström S, Andersson E, Jerez A, Clemente MJ, Yan Y and others. Discovery of somatic STAT5b mutations in large granular lymphocytic leukemia. Blood 121(22):4541-4550, 2013. - *NGS data was analysed with FIMM bioinformatics pipelines.*

Vihervaara A, Sergelius C, Vasara J, Blom MA, Elsing AN, Roos-Mattjus P, Sistonen L. Transcriptional response to stress in the dynamic chromatin environment of cycling and mitotic cells. Proc Natl Acad Sci USA. 110(36):E3388-97, 2013. - *BioCity provided IT-support and a platform for computational analysis workflow.*

Sittig E, Kauko O, Salmenniemi U, Laiho A, Kairisto V, Johansson J, Itala-Remes M, Westermarck J. Novel molecular markers for acute myeloid leukaemia disease activity. Eur J Cancer 49:S840-S840, 2013. - *BioCity analysed rna-seq data for a project concentrating on novel molecular markers for acute myeloid leukaemia disease activity.*

Gylfe AE, Kondelin J, Turunen M, Ristolainen H, Katainen R, Pitkänen E, Kaasinen E, Rantanen V, Tanskanen T, Varjosalo M, Lehtonen H, Palin K, Taipale M, Taipale J, Renkonen-Sinisalo L, Järvinen H, Böhm J, Mecklin JP, Ristimäki A, Kilpivaara O, Tuupanen S, Karhu A, Vahteristo P, Aaltonen LA. Identification of candidate oncogenes in human colorectal cancers with microsatellite instability. Gastroenterology, 2013, 145(3):540-543.e22. - *BCH conducted all image analyses.*

BIOLOGICAL IMAGING

Biological Imaging Infrastructure Network

Coordinator of the network: John Eriksson, BioCity Turku (with Joanna Pylvänäinen and Petra Miikkulainen)
Members: Elina Ikonen, BCH; Maria Vartiainen, BI; Olli Gröhn, BCK; Sinikka Eskelinen, BCO; Susanna Narkilahti, IBT; Johan Lundin, FIMM; Varpu Marjomäki, University of Jyväskylä

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

Modern imaging requires sophisticated instrumentation for data acquisition and methods of bioinformatics and data handling for their storage and analysis. The prerequisite for live cell imaging is that the equipment is near to the laboratories and animal centers. Therefore, each biocenter has confocal microscopes, video microscopes, and transmission electron microscopes for imaging of cells and tissues. However, in the National Imaging Infrastructure Network of Biocenter Finland (NIIN), different biocenters have been granted specific spearheaded tasks, which are organized under three technology platforms; those for light microscopy, electron microscopy and in vivo imaging. In light microscopy, Helsinki and Turku focus on new imaging technologies including high-resolution STED, PALM and STORM microscopy as well as high content screening at cellular and molecular level. Turku Bioimaging hosts some of these most recent technologies and has a high-resolution optical imaging core service at the BF level. In electron microscopy high resolution electron cryo-microscopy, electron tomography and three-dimensional image reconstruction for nanoscale structures are available at the Institute of Biotechnology in the University of Helsinki. In vivo imaging platforms include PET instrumentation in Turku, MRI in Kuopio and Helsinki, as well as optical methods in Helsinki and Turku. Since 2011, BF has also supported a small animal molecular imaging (SPECT/CT) platform (RTI unit) in Helsinki.

Electron Microscopy Technology Platform

Chair of the consortium: Eija Jokitalo, BI, Electron Microscopy Unit;
Members: Sarah Butcher BCH/BI CryoEM Unit; Raija Sormunen, BCO Tissue Imaging Center

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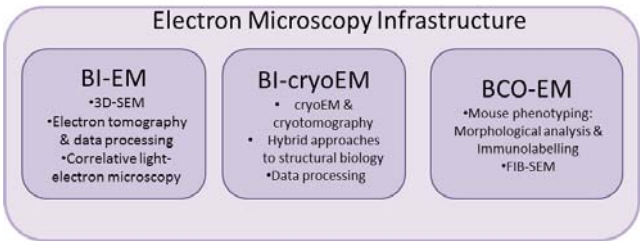
Achievements in development of technology services during 2013

Each of the three EM units forming this consortium has a long history in providing national services for academia and industry. Our main common goal has been to restructure and streamline the functioning of the units towards nationally-unique complementary areas. The Helsinki units, BI-EM and BCH-cryoEM focus on 3D imaging and hybrid methods from molecular models to whole cells and tissues, whereas the BCO-EM specializes in the ultrastructural pathology of human and model organisms working closely with the BCO Transgenic mouse core facility. The impact of BF funding has been significant in terms of both renovating the technology platform infrastructure and in retention of highly trained support staff; During 2013 Biocenter Finland allocations covered 5.5 salaries for a total of 66 person months.



Biocenter Finland allocations have resulted in clear improvements in the performance and quality of the services evidenced by higher scientific impact. The major instrument investments in this consortium included upgrades of three electron microscopes and thereby guaranteed the continuation of basic services. Due to instrument development and the introduction of digital imaging on all of the transmission electron microscopes, the quality and turn-around of the work have been significantly improved, with the microscopy time required per specimen greatly reduced. Users now have instant access to the recorded data and so can immediately react to the results from a specimen, and improve the data saved. In addition, important instrumentation for specimen preparation, image processing and data storage have been realized. For specimen preparation, a common emphasis has been to upgrade instrumentation for advanced EM techniques,

and especially for cryo-EM specimen preparation. Efforts have been made to build long term data storage solutions that will simultaneously enhance data sharing between the EM units and their users. Overall the workflow has been streamlined to better fit the current and future needs of the research community.

BF funding has supported an efficient minimal level of experienced microscopy support staff increasing throughput of projects, and the hiring of new senior scientific staff to develop new advanced EM techniques. These new additions to the technology platform have been very well taken up by the community and this is evident as an upsurge in scientifically demanding projects without increasing the turnover time of the existing services. The new techniques that have been set up and are now offered to users include two serial section imaging based scanning electron microscope techniques for 3D-EM.

The consortium members have agreed on criteria for pricing including a common price category for all academic work, rather than distinguishing between their own university and others. All members have now implemented the same internet-based booking and invoicing system. This makes statistical analysis of the impact of the investments much easier to follow, and as it is fairly automated, has decreased bureaucracy. Standardized laboratory practices such as the reporting and quantification of ultrastructural results have been developed. This has been of utmost importance when widening the services to industrial users. We have remained active in providing training: we have provided personal training for all new users in operation of microscopes and other instruments, supervised specimen preparation and organized lecture and practical courses, e.g. "Recent applications in Biomedical electron microscopy" (Oulu) and "Imaging techniques in biological sciences" (Helsinki).

Participation in international, Nordic and European infrastructures

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

BI-EM and BCH-cryoEM have joined efforts with the Light Microscopy Unit of the BI to propose a Correlative Light Electron Microscopy (CLEM) platform in the Finnish Euro-BioImaging node application. BCO EM belongs to the Oulu Bioimaging network (OBI), which joins the biological, biomedical and medical imaging expertise at Biocenter Oulu, Faculty of Medicine and Oulu University Hospital with the machine vision and optoelectronics expertise at the Infotech Oulu Research Center and the Faculty of Technology and is proposing mesoscopic imaging platform in the Finnish Euro-BioImaging node. All sub-nodes are additionally linked together by activities aimed at facilitating image processing, visualization and open-source software production for image analysis. BI-EM and BCH-cryoEM belong to Helsinki Functional Imaging Center (HFIC), which is a member of the European Light Microscopy Initiative (ELMI) and European Institute of Biomedical Imaging Research (EIBIR).

BCH-cryoEM is part of the ESFRI Instruct National User Group, and the Instruct National Affiliated Center covering X-ray (membrane proteins and enzymology), NMR (special labelling techniques and high field NMR), EM (high resolution single particle), macromolecular complex production and mass spectrometry (ESI Q-FT-ICR and hydrogen-deuterium exchange). BCH-cryoEM is part of the AIROPico FP7 Marie Curie Industry-Academia Partnerships and Pathways with industrial and academic partners that will run from 2014–2018 and includes academic

User statistics 2013

	BI-EM	BCH-cryoEM	BCO-EM	Total
Total number of research groups	83	20	31	134
- local academic groups	57	10	21	88
- national academic groups	17	5	7	27
- industrial users	4	0	0	4
- international users	7	5	3	15
Microscope usage (hours)	3329[n]	837	710	4866
Specimens prepared	764[*]	681[#]	1055[*]	2500

* 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 1621 hours of invoiced TEM & basic FEG-SEM use, and 1708 hours of SBF-SEM use

and industrial infrastructure for the development of diagnostics, therapeutics and basic science of picorna viruses.

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

Future perspectives

Continued staff support is the highest priority for each unit. In addition, we have identified the most urgent needs for further development in each unit. BI-EM is aiming to upgrade its current 3D-EM services with a second, high voltage SEM equipped for serial block face imaging. The current instrument is in constant use, and data series are collected over night and over weekends without breaks. The new system would open up the technology to new type of specimens because of the higher contrast and smaller voxel size gained by the high vacuum system.

A second area of development is the cryo sectioning of vitreous specimens that would allow cryoEM of larger specimens than has been achievable with current technology. For this, a dedicated ultramicrotome equipped for CEMOVIS would serve both BI-EM and BCH-cryoEM units. In the long term, BCH-cryoEM expects a replacement of the high resolution microscope will be required as it comes to the end of its 15 year life time (2016). A future area for development of BCO-EM is focused on SEM methods for life science applications. This is made possible by the purchase of new high resolution SEM (2014). We will work closely with light microscopy section of Biocenter Oulu tissue imaging center to develop and provide correlative light and electron microscopy workflow solutions to researchers. As the new SEM will be compatible with serial block face imaging system, it gives us an option to develop 3D-ultrastructural analysis of large volumes also in Oulu in the future.

Major publications resulting from the Platform services

Aspatwar A, Tolvanen ME, Jokitalo E, Parikka M, Ortutay C, Harjula SK, Rämet M, Vihinen M, Parkkila S. 2013. Abnormal cerebellar development and ataxia in CARP VIII morphant zebrafish. Hum Mol Genet. 22:417-432. - *Morphological analysis of zebrafish brain using TEM complemented histological analysis to understand brain development. National collaboration between Helsinki and Tampere.*

Hendrix A, Sormunen R, Westbroek W, Lambein K, Denys H, Sys G, Braems G, Van den Broecke R, Cocquyt V, Gespach C, Bracke M, De Wever O. 2013. Vacuolar H+ ATPase expression and activity is required for Rab27B-dependent invasive growth and metastasis of breast cancer. Int. J. Cancer 133:843-854. - *This International collaboration utilized BCO´s immunoelectron microscopy services.*

Kallio K, Hellström K, Balistreri G, Spuul P, Jokitalo E, Ahola T. 2013. Template RNA length determines the size of replication complex spherules for Semliki Forest virus. J Virol. 87:9125-9134. - *Correlative light electron microscopy was used to identify the replication complexes in order to analyse their size. National local collaboration.*

Kerkelä R, Karsikas S, Szabo Z, Serpi R, Magga J, Gao E, Alitalo K, Anisimov A, Sormunen R, Pietilä I, Vainio L, Koch WJ, Kivirikko KI, Myllyharju J, Koivunen P. 2013. Activation of hypoxia response in endothelial cells contributes to ischemic cardioprotection. Mol Cell Biol. 33: 3321-3329. - *Transmisson electron microscopy was used for the determination of the capillary structure. This publication involved scientists from Oulu, Helsinki and USA.*

Liljeroos L, Krzyzaniak M, Helenius A, Butcher SJ. 2013. Architecture of respiratory syncytial virus revealed by electron cryotomography. Proc. Natl. Acad. Sci. (USA) 110:11133-11138. - *Transmission cryo-tomography and sub-tomogram averaging of RSV virions and mutants were combined with cell biology to produce the first 3D overview of RSV. International collaboration.*

Nilsson C, Barrios-Lopez B, Kallinen A, Laurinmäki P, Butcher SJ, Raki M, Bergström K, Weng Larsen S, Østergaard J, Larsen C, Urtti A, Airaksinen A, Yaghmur A. 2013. SPECT/CT imaging of radiolabeled cubosomes and hexosomes for potential theranostic applications. Biomaterials 34:8491-8503. - *CryoEM coupled with SPECT/CT and X-ray scattering to develop new in vivo imaging methods. International and national collaboration in Helsinki and Copenhagen.*

Palomäki S, Pietilä M, Laitinen S, Pesälä J, Sormunen R, Lehenkari P, Koivunen P. 2013. HIF-1α is upregulated in human mesenchymal stem cells. Stem Cells 31:1902-1909. - *Transmission electron microscopy was used for the investigation of mitochondrial morphology. National collaboration.*

Pietilä MK, Laurinmäki P, Russell DA, Ko C, Jacobs-Sera D, Hendrix RW, Bamford DH, Butcher SJ. 2013. Structure of the archaeal head-tailed virus HSTV-1 completes the HK97-fold story. Proc. Natl. Acad. Sci. (USA) 110:10604-10609. - *We isolated new archaeal viruses to show for the first time, by sequencing, cryo-electron microscopy, 3D image reconstruction, homology modelling and fitting that an archaeal virus has the same major capsid protein fold as that found in herpes simplex virus and bacteriophage HK97, thus linking viruses infecting organisms from all three domains of life. National and international collaboration within Helsinki and Pittsburgh, USA.*

Rauhamäki V, Wolfram J, Jokitalo E, Hanski I, Dahlhoff EP. 2013. Differences in the Aerobic Capacity of Flight Muscles between Butterfly Populations and Species with Dissimilar Flight Abilities. PLOS One DOI: 10.1371/journal.pone.0078069. - *Quantitative thin-section TEM analysis was used to compare the morphology of flight muscles of butterfly species that flies short or long distances. National and international collaboration between Helsinki and California, USA.*

Shakeel S, Seitsonen J, Kajander T, Laurinmäki P, Hyypiä T, Susi P, Butcher SJ. 2013. Structural and functional analysis of coxsackievirus A9 receptor binding and uncoating. J. Virol. 87:3943-3951. - *CryoEM, cryo-tomography, 3D reconstruction and flexible fitting were used to understand the interaction of integrin with a human pathogen, and to study domain movement during uncoating. National collaboration between Helsinki and Turku.*

National Precilinical *In Vivo* Imaging Technology Platform

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

Members: Juhani Knuuti, BioCity, Turku PET Centre; Turgut Tatlisumak, BCH, Biomedicum Imaging Unit

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Achievements in development of technology services during 2013

This consortium has created a national multimodal preclinical *in vivo* imaging technology platform, with clear division of the tasks and core expertise area in each of the contributing biocenters. During the first three years of operation 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. As a result, in the user survey conducted by Biocenter Finland, *in vivo* imaging received one of the best evaluations receiving either "excellent" or "very good" in all categories. In addition, imaging was most often mentioned, when the need for the individual infrastructures was asked. Also the feedback was excellent from the proof-of-concept studies of the large-scale pan-European Euro-BioImaging ESFRI infrastructure project. The technology platform has reached a fully functional state and during the year 2013 it continued to serve the biomedical scientific community with the personnel funded by the participating universities. In addition, we have also further developed the different imaging modalities and multimodal imaging with other funding sources and the following steps have been taken to improve the availability and promote the excellence in different *in vivo* imaging modalities.

PET imaging

Improvements in the capacity of PET tracer production in Turku PET center have been achieved. This is the bottleneck for increasing the capacity required for efficient provision of PET imaging services, as the PET imaging systems were already recently upgraded. The PET tracers need to be produced in a dedicated radiotracer synthesis laboratory that is in close proximity to a cyclotron laboratory. The existing synthesis laboratory has the qualified space for the synthesis but the number of synthesis devices was limiting for the availability of tracers for preclinical imaging. In 2013, the establishment of new tracer production devices that were purchased in 2012, were successfully finalized. In addition, Cu-64 isotope production is now available in order to allow labeling of larger molecules and peptides with slow kinetics. In addition to this, two novel Fluorine-18 labelling methods for peptides and oligonucleotides were developed and became available. As a result, there is now significantly better access to the various new tracers.

During 2013, preclinical PET imaging was started in Kuopio exploiting the expertise provided by Turku in the implementation of the new imaging modality. Currently, FDG-PET imaging is available for external users, and the first two studies were completed in the end of 2013. Furthermore, Kuopio University Hospital started a three-year project to start radiotracer production in Kuopio 2015–2016, after which a more comprehensive selection of PET tracers will be available also for preclinical imaging.

MR Imaging

Kuopio continues to provide MRI services with three MRI systems. During 2013, we upgraded the electronics of the 9.4T/31cm system and the magnet is now interfaced both to Agilent DirectDrive and Bruker Biospin consoles providing practically all MRI sequences available at the moment for preclinical imaging.

As an indirect consequence of the actions taking place in Kuopio, preclinical MRI has also become available in Oulu. The 4.7T magnet from Kuopio was transferred to Biocenter Oulu and became fully functional during 2013 serving now as a basic level preclinical MRI instrument.

MRI services are also provided in Biomedicum Helsinki, with a 4.7T MRI system. The system is closely integrated as a part of the multimodal imaging platform, especially in association with optical imaging.

Optical Imaging

Advances in optical imaging have taken place in a new dedicated in vivo imaging laboratory in Biomedicum Helsinki. The laboratories were completely renovated in 2013 and they host now the optical imaging systems, including a new multichannel intravital multiphoton microscope, which will allow extended wavelength capabilities in order to serve the growing use of red shifted fluorescent proteins in the phenotypic characterization of genetically modified rodent models. In addition, a new 3D optical projection tomography system was previously purchased. Thus, the range of multimodal in vivo approaches has been expanded from subcellular resolved intravital multiphoton imaging, to small organisms and whole organs with optical projec-

tion tomography, and whole animal imaging using the optical and MRI platforms.

The establishment of a National BioCARS center by partner Helsinki has now been accomplished. Label-free imaging methods, coherent anti-Stokes Raman scattering (CARS), and second and third harmonic generation, will serve as additional spearhead technologies for in vivo imaging, offering an important new opening also at the international level via the EuroBioImaging ESFRI and EU COST action MicroCoR consortium.

Another aim was to upgrade the optical imaging infrastructure in Turku. Earlier, *in vivo* optical imaging was based on bioluminescence and fluorescence imaging. Tomographic optical imaging system was purchased and is now available for the investigators. It allows the co-registration with PET, CT and MRI to yield an anatomical and functional hybrid approach.

User statistics 2013

User statistics and number of research projects (research groups):

	Kuopio	Turku	Helsinki
Total number of projects	30	45	24
Local projects	20	26	19
Other domestic projects	7	5	2
International	3	8	3
Non-academic projects	0	6	0

Participation in international, Nordic and European infrastructures

Parts of the national preclinical in vivo imaging network belong to the Euro-BioImaging (EuBi) ESFRI infrastructure that has now been included in the Academy of Finland research infrastructure roadmap 2014–2020. The national preclinical *in vivo* imaging network has participated in the preparatory phase of Euro-BioImaging ESFRI initiative as one of the European sites for 'proof-of-concept' studies in the 'Molecular imaging' work package. The national preclinical in vivo imaging network is also linked with other ESFRI initiatives. In EATRIS (European Advanced Translational Research Infrastructure in Medicine) Turku PET Centre is one of the two 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 the Finnish IT Center for Science (CSC), Institute for Molecular Medicine Finland (FIMM), and the University of Helsinki IT Services, the partner Helsinki is establishing a centralized platform for data storage, management, visualization, and analysis. This has now been technically tested and the integration into the research projects is currently ongoing. The 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.

Future perspectives

The importance of preclinical *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 the application of the high-end technologies can only be made in dedicated imaging centers harboring the specific expertise, thus justifying the national centers for the most expensive in vivo imaging modalities.

Significant investments have already been made on the instruments. To get the full benefit from these investments the continuity of the personnel and their salaries 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 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 preclinical *in vivo* imaging technologies.

One of the key issues for the 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 GBs and up to TBs. There is a clear need for centralized data management and standardized visualization and analysis tools. Each of the participating imaging centers is currently developing their own solutions for this purpose, thus there is clearly a need for harmonization and more general solutions to allow remote data management and collaboration within partner units of the BF National preclinical in vivo imaging technology platform.

PET

The PET imaging component of the consortium is currently at the 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. During 2013 the coils and other devices for small animal PET-MRI imaging were purchased and tested and are now available for investigators. Despite recent advances in tracer production, the availability and development of new tracers is a continuous challenge and a key issue for the future success. The translational research will require also enough potential to bring novel tracers into GMP level for human applications.

Basic preclinical PET imaging using F-18, Ga-68 and Cu-64 -based tracers (such as FDG), should be established also in other participating Biocenters to make multimodal preclinical imaging more available across the country.

MRI

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 scanner.

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 replacement during 2013-2016.

C13 Hyperpolarized MRI is probably the greatest breakthrough in MRI field within the last decade. It allows 10 000 times increase in signal-to-noise ratio and makes possible of dynamic metabolic studies using C13-labeleld non-radioactive compounds. This kind of instrumentation is not yet available in Finland and the consortium will strongly promote the implementation of this technology to serve the Finnish biomedical research community.

Optical Imaging

In 2013 the animal facility was re-organized at the University of Helsinki due to the completion of the new rodent house at the Viikki Life Science campus. This has affected also the animal logistics due to the differing pathogen status of the units. Both optical multimodal and MRI imaging facilities are concentrated at the Meilahti Academic Medical campus allowing convenient animal transfer between the units and campuses. Further developments include spearheading the CARS and other label-free technologies for preclinical characterization of GM models, and developing the multiphoton platforms for fluorescence life-time molecular imaging. Current pressing needs include also the purchase of a preclinical PET-MRI scanner and a fluorescence molecular tomography system for multimodal cancer research.

Major publications resulting from the Platform services

Hemminki O, Immonen R, Närväinen J, Kipar A, Paasonen J, Jokivarsi KT, Yli-Ollila H, Soininen P, Partanen K, Joensuu T, Parvianen S, Pesonen SK, Koski A, Vähä-Koskela M, Cerullo V, Pesonen S, Gröhn OH, Hemminki A In vivo magnetic resonance imaging and spectroscopy identifies oncolytic adenovirus responders. Int J Cancer. 2013 Nov 18. doi: 10.1002/ijc.28615. - *Researchers in Hartman Institute, Helsinki sent animals to Kuopio in order to follow the response to oncolytic adenovirus treatment using MRI and MR spectroscopy. IF 6.2. (BIU-BCK)*

Sierra A, Laitinen T, Gröhn O, Pitkänen A. Diffusion tensor imaging of hippocampal network plasticity. Brain Struct Funct. 2013 Dec 2 - *Diffusion tensor MRI was used to characterize novel aspects of hippocampal pasticity. IF 7.8 (BIU-BCK)*

Manninen O, Koskenkorva P, Lehtimäki KK, Hyppönen J, Könönen M, Laitinen T, Kalimo H, Kopra O, Kälviäinen R, Gröhn O, Lehesjoki AE, Vanninen R. White matter degeneration with Unverricht-Lundborg progressive myoclonus epilepsy: a translational diffusion-tensor imaging study in patients and cystatin B-deficient mice. Radiology. 2013; 269(1):232-9. - *Researchers in Biomedicum Helsinki sent knock-out mice to Kuopio in order to follow progression of the white matter damage with diffusion tensor imaging. IF 6.3. (BIU-BCK)*

Gaal EI, Tammela T, Anisimov A, Marbacher S, Honkanen P, Zarkada G, Leppänen VM, Tatlisumak T, Hernesniemi J, Niemelä M, Alitalo K. Comparison of vascular growth factors in the murine brain reveals placenta growth factor as prime candidate for CNS revascularization. Blood 2013; 122:658-65. - *Optical projection tomography was used to analyze leakiness of brain neovasculature, and MRI analysis revealed the degrees of integrity of the blood-brain barrier, brain edema and bleeding into the brain caused by the different revascularization therapy candidates. IF 9.0. (BIU-BCH)*

Sarek G, Ma L, Enback J, Järviluoma A, Moreau P, Haas J, Gessain A, Koskinen PJ, Laakkonen P, Ojala PM. Kaposi's sarcoma herpesvirus lytic replication compromises apoptotic response to p53 reactivation in virus-induced lymphomas. Oncogene 2013; 32:1091-8. - *The optical IVIS imaging system was used to follow intraperitoneal growth of luciferase-expressing human primary effusion lymphoma cells in mice, and led to the initial observation that non-responders to p53 reactivation therapy are present in the treatment group. IF 7.4. (BIU-BCH)*

Keränen MA, Tuuminen R, Syrjälä S, Krebs R, Walkinshaw G, Flippin LA, Arend M, Koskinen PK, Nykänen AI, Lemström KB. Differential effects of pharmacological HIF preconditioning of donors versus recipients in rat cardiac allografts. Am J Transplant 2013; 13:600-10. - *Edema in cardiac allografts was determined noninvasively by MRI at different time-points after the procedure, leading to the conclusion that the ischemia-reperfusion injury in the syngeneic model used in this study was transient. IF 6.2. (BIU-BCH)*

Kivelä R, Bry M, Robciuc MR, Räsänen M, Taavitsainen M, Silvola JM, Saraste A, Hulmi JJ, Anisimov A, Mäyränpää MI, Lindeman JH, Eklund L, Hellberg S, Hlushchuk R, Zhuang ZW, Simons M, Djonov V, Knuuti J, Mervaala E, Alitalo K. VEGF-B-induced vascular growth leads to metabolic reprogramming and ischemia resistance in the heart. EMBO Mol Med. 2014 Mar 1;6(3):307-21. - *This was continuation and further study of the effects of VEGF-B induced effects on heart and joint work between Turku and*

Helsinki research groups IF 7.795 (Turku PET)

Li XG, Helariutta K, Roivainen A, Jalkanen S, Knuuti J, Airaksinen AJ. Using 5-deoxy-5-[18F]fluororibose to glycosylate peptides for positron emission tomography. Nat Protoc. 2014 Jan;9(1):138-45. - *See explanation above. IF 7.96 (Turku PET)*

Rissanen TT, Nurro J, Halonen PJ, Tarkia M, Saraste A, Rannankari M, Honkonen K, Pietilä M, Leppänen O, Kuivanen A, Knuuti J, Ylä-Herttuala S. The bottleneck stent model for chronic myocardial ischemia and heart failure in pigs. Am J Physiol Heart Circ Physiol. 2013 Nov 1;305(9):H1297-308. - *This is a joint work with Turku and Kuopio teams validating a novel pig model with ischemia using advanced imaging IF 3.63 (Turku PET)*

Honka H, Mäkinen J, Hannukainen JC, Tarkia M, Oikonen V, Teräs M, Fagerholm V, Ishizu T, Saraste A, Stark C, Vähäsilta T, Salminen P, Kirjavainen A, Soinio M, Gastaldelli A, Knuuti J, Iozzo P, Nuutila P. Validation of [18F]fluorodeoxyglucose and positron emission tomography (PET) for the measurement of intestinal metabolism in pigs, and evidence of intestinal insulin resistance in patients with morbid obesity. Diabetologia. 2013 Apr;56(4):893-900. - *This is a study validating new animal model and new methodology. This is joint work with Finnish and Italian teams IF 6.487 (Turku PET)*

Light Microscopy Technology Platform

Chair of the consortium: John Eriksson, Turku Bioimaging
Members: Cell Imaging Core (CIC), Eleanor Coffey and Turku Bioimaging (TBI), John Eriksson, BioCity Turku; Biomedicum Imaging Unit (BIU-BCH), Elina Ikonen, BCH; Light microscopy unit (LMU-BI), Maria Vartiainen, BI; Multimodal imaging core (MUIC-BCK), Michael Courtney, BCK; Tissue Imaging Center (TIC-BCO), Lauri Eklund, BCO; BMT imaging facility, Susanna Narkilahti, BMT; also University of Jyväskylä Imaging Facility, Varpu Marjomäki participates in the platform activities.

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Achievements in development and restructuring of technology services during 2013

Biocenter Finland (BF) funding structure has continuously fostered a vast change in the light microscopy scene of Finland towards leading European nations in terms of available advanced instrumentation (Figure). All the units involved in the light microscopy platform are well networked and highly interactive, leading to significant synergistic effects. The clear national and local division into specialized core facilities, with different spearheading technologies, has continued to yield impressive results. The units have also been able to attract new personnel, representing leading experts in their own field of expertise.

The usage of the light microscopy platform has been high. The high numbers are likely due to both excellence in the services and their availability to a larger community through open access, but also because light microscopy methods can be increasingly applied to different research fields. Through participation in the Euro-BioImaging ESFRI project, we expect a significant increase in the amount of international users. The proof-of-concept studies conducted in Finland have attracted several scientists, demonstrating that our infrastructure is competitive and can bring international researchers to utilize our state-of-the-art technologies. The established techniques are clearly of the highest demand among the European countries showing that Finland has taken major steps towards establishing significant European imaging nodes. Thanks to this development, the Finnish imaging units are in many respects exemplary for open access imaging units within the Euro-BioImaging community.

Technology specialization at the Finnish imaging centers

Super-resolution imaging

Super-resolution modalities have been continuously developed with the support from BF, presenting today one of the top super-resolution networks in Europe.

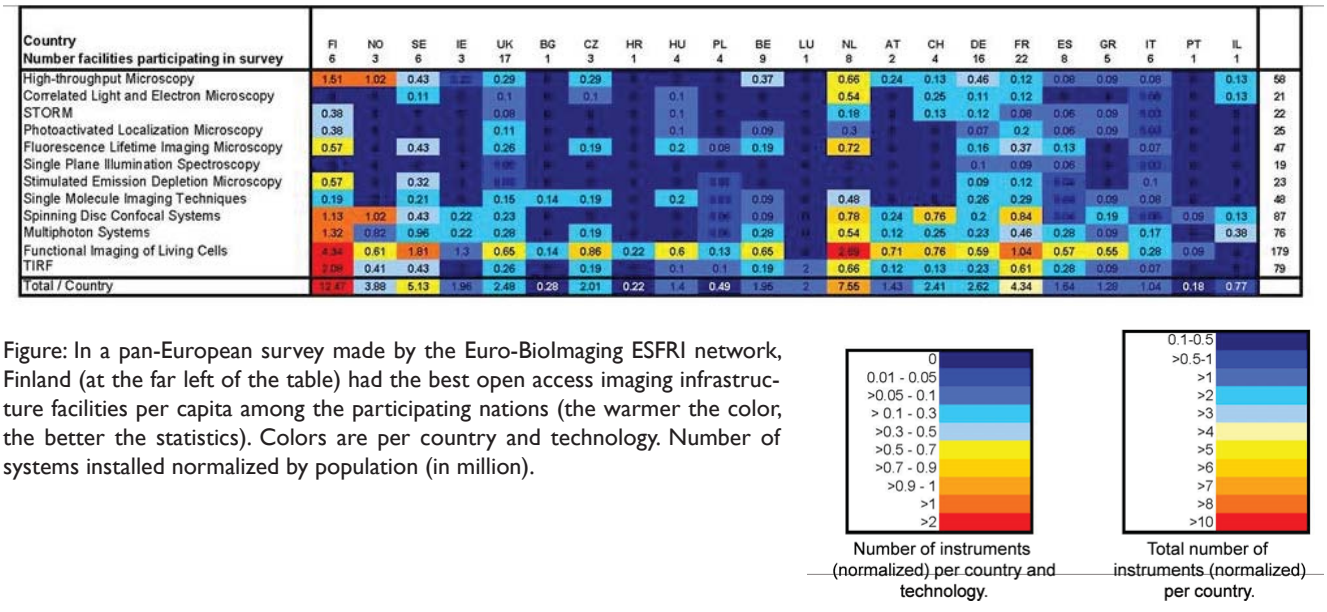

Figure: In a pan-European survey made by the Euro-BioImaging ESFRI network, Finland (at the far left of the table) had the best open access imaging infrastructure facilities per capita among the participating nations (the warmer the color, the better the statistics). Colors are per country and technology. Number of systems installed normalized by population (in million).

Super-resolution centers have been established at the CIC-TBI and BIU-BCH. These units implement STED and STORM super-resolution modalities, respectively. A unique initiative in Turku has been to expand the concept of super-resolution microscopy by successfully combining STED with other imaging technologies. Successful combination of STED with atomic force microscopy has already produced unique data. In addition, fluorescence lifetime imaging microscopy (FLIM) and fluorescence correlation spectroscopy (FCS) will be combined with STED. CIC-TBI has also recently purchased a Zeiss TIRF microscope for more advanced super-resolution applications. LMU-BI is operating Bayesian localization microscopy and is exploring also other techniques that enable super-resolution imaging using standard fluorescent markers and microscopes. A pipeline utilizing the computational resources at CSC aids in this process. The existing BF super-resolution initiative includes all current major super-resolution imaging modalities accompanied with probe-development, all techniques that may then be applied to the research questions and approaches.

High-content and high-throughput imaging

Both BIU-BCH and LMU-BI have partnered with the BF Genome-wide methods technology platform to offer complimentary high-content imaging services. Close collaboration with FIMM RNAi Technology Centre is also important in this context. In addition, LMU and CIC-TBI have developed Leica SP5 Matrix platform to enhance complementarity between the two units. BIU-BCH and CIC-TBI also work with CSC to develop solutions for storing large data amounts, and the BioImageXD software platform (see Image analysis below) is being developed to better suit high-content applications. MUIC-BCK upgraded server capacity and focused on developing integration of recently acquired high-speed imaging and liquid handling devices and novel probes to optimize application of compound/RNAi/cell libraries both local and via established links with national BF resources. LMU-BI utilizes the storage and compute resources available at CSC to create an efficient workflow for image analysis, in particular for medium-sized high-content screening applications. Open source components are used and the work is documented openly, so that it will be possible to replicate the setup at any imaging facility collaborating with CSC.

Label-free technologies

Several units in the network are establishing various label-free principles, most of which are a continuum between cellular and in vivo visualization. BIU-BCH has established a confocal multiphoton CARS (Coherent Anti-Stokes Raman Spectroscopy) platform, as part of a National BioCARS Centre. Additionally, it offers label-free second and third harmonic generation imaging services suited for label-free sample visualization. Label-free technologies are also the spearhead of the University of Jyväskylä, where linear Raman signals can be obtained from various biological samples. A new femto-second laser system has been purchased recently that enables four wave mixing (FWM) based imaging, such as CARS microscopy. Tampere Imaging Facility has purchased Nikon Biostation time lapse imaging system 2013 which together with earlier purchased Cell-IQ system offers versatile tools to study unlabelled cells. A novel label-free technique is photoacoustic microscopy (PAM). A prototype of PAM has been built by the Laboratory of Biophysics in Turku in collaboration with Northwestern University, Chicago. The aim is to utilize the PAM-system in cell-biology research, in correlation with optical imaging methods, e.g. super-resolution STED imaging and in vivo microscopy techniques, primarily multiphoton microscopy.

Mesoscopic imaging

Light sheet microscopy (e.g. selective plane illumination microscopy, SPIM) is an emerging technique that allows exceptionally fast and sensitive imaging of thick living samples. The latest update in mesoscopic imaging at BCO-TIC is a custom-built light sheet microscope, set-up in collaboration between BCO-TIC and Optoelectronics and Measurement Techniques Laboratory (Department of Electrical Engineering, University of Oulu) in Oulu Bioimaging network. Tampere Imaging Facility is also focusing on the imaging of mesoscopic objects (3D cell cultures, biomaterials, zebra fish and Drosophila). During 2013, a new high-end confocal microscope was purchased, a new postdoctoral imaging specialist and a technician were hired, user hours and fees tripled, and teaching and collaboration activities significantly increased. Also, already existing equipment were merged under the Imaging Facility which allowed their open usage.

Image analysis and processing Post-processing of bioimages is as important as their acquisition. Analysis software, BioImageXD (http://www.bioimagexd.net/), has been developed as a collaboration of Turku, Jyväskylä, and Oulu. The usage of BioImageXD has been increasing in Finland and in the whole Europe. In Turku and Jyväskylä, courses and personal assistance with the software and its usage are available throughout the year. The software has been improved in 2013 with updates and reprogramming. Collaborative project between the Center for Machine Vision (CMV) Research at Infotech Oulu and TIC-BCO has led to

the development of novel image analysis tools for 2D and 3D time-lapse microscopy; including a thresholding based local detector (MSER) and Kalman filter based multi-object tracking approach, machine learning-based tools for single cell vs. cluster detection in 3D cultures, and spherical harmonics approach for 3D cell shape analysis.

Other special instrumentation and general development Multiphoton systems have been developed at BIU-BCH, LMU-BI, BCK-MUIC and CIC-TBI. At BIU-BCH, there are two multiphoton platforms that serve the increasing need both for in vitro cellular and intravital in vivo microscopy. At LMU-BI, one stronghold is fluorescence lifetime imaging (FLIM), enabling for example quantitative protein interaction analysis in intact cells and tissues. The frequency-domain FLIM is combined with wide-field, TIRF and spinning disc on a 3I Marianas platform, which is therefore capable of advanced multimodal live-cell imaging applications. CIC-TBI multiphoton unit is specially designed for studying the migration of immune and cancer cells in intravital microscopy.

Major bottlenecks

Data storage, distribution, analysis and processing are major bottlenecks nationally. These aspects are in part being addressed by all the platform units. BMT has purchased a new data server system with data storage up to 100 TB. With BF bioinformatics network funding, Helsinki and Turku have also set up servers for image data storage. To establish common practices in data management and transfer, a well-coordinated national collaboration is required. The planned collaboration between ESFRI infrastructures Euro-BioImaging and ELIXIR could provide a solution also on a national basis.

User statistics 2013

The user statistic summary of all facilities from 2013 indicate a high number of local as well as national, international and non-academic users and financial turnover for all facilities, illustrating the importance of light microscopic imaging services in biomedical research, and the synergistic effects obtained through national collaboration and organization.

Participation in international, Nordic and European infrastructures

The BF light microscopy consortium participates actively in the pan-European Euro-BioImaging (www.eurobioimaging.eu) ESFRI infrastructure preparatory phase and has excellent possibilities to establish European imaging nodes in Finland. All imaging centers are stakeholders in Euro-BioImaging. In 2013 Euro-BioImaging consortium organized two stakeholder meetings, in Vienna and in Heidelberg. Both of these meetings were attended by light microscopy consortium representatives from most of the Finnish units. These meetings lead to the signing of Euro-BioImaging Memorandum of Understanding, Finnish BioImaging was one of the first 7 signatories. Finnish participation in Euro-BioImaging lies on the strong foundation of the Finnish BioImaging Network, FiBI, which consists of the technology platform services from different BF networks. These networks and their services have successfully gone through major restructuring during the Biocenter Finland (BF) funding period of 2010–2012. Under FiBI, Euro-BioImaging organization accepted the Finnish proposal for Node in Biological Imaging. Euro-Bioimaing was also accepted as an ESFRI infrastructure on the Finnish Infrastructure Roadmap.

Plans are also to be actively involved in the international Open Bio Image Alliance organization especially through the BioImageXD software platform. This will provide researchers in life sciences with the highest quality public-domain software and knowledge to analyze image data reliably and reproducibly. All members of the organization are actively engaged in a large number of microscopic societies and thus the network of collaboration spans to all major imaging communities in the world.

	BIU-BCH	LMU-BI	MUIC-BCK	TIC-BCO	BMT	CIC-TBI	Total
Total number of research groups	63	57	9	33	15	76	253
- local groups	63	53	7	29	14	64	230
- other domestic groups		3		2		7	12
- international		1		2	1	4	8
- non-academic			2			1	3
Total instrument hours	12 765	11 016	3 127	8 568	1 785	6 727	43 961
Single users	168	155	24	95	29	197	668
Annual financial turnover	94 393	141 799	6 866	*	26 079	84 704	353 841

* Different costing model.

Future perspectives

During BF funding the quantity of usage and users of the light microscopy platform has steadily increased and the aim is to continue this growth in national and international level. For these reasons the open access availability of services to a larger community has to be maintained. The current technology available is of the highest demand in Europe, but it has to be constantly updated and maintained. Special interest for Light microscopy imaging platform is to develop label free imaging, ultrafast acquisition and super-resolution reconstruction alongside with image analysis and solving the bottlenecks in image analysis and data storage. The main challenge in the forthcoming two years will be the biological imaging Node construction in Euro-Bioimaging. This initiative has been well received by the Ministry of Education and Academy of Finland.

Major publications resulting from the Platform services

Kanerva K, Uronen RL, Blom T, Li S, Bittman R, Lappalainen P, Peränen J, Raposo G, Ikonen E. LDL cholesterol recycles to the plasma membrane via a Rab8a-Myosin5b-actin-dependent membrane transport route. Dev Cell 2013; 27:249-62. - *Widefield, confocal and TIRF time-lapse fluorescence microscopy were used to image BODIPY cholesterol localization, trafficking and colocalization with other molecules in living cells, and quantitative image analysis and rendering was done on the BIU workstations with assistance from BIU staff. IF 12.861. (BIU-BCH)*

Hackman P, Sarparanta J, Lehtinen S, Vihola A, Evilä A, Jonson PH, Luque H, Kere J, Screen M, Chinnery PF, Ahlberg G, Edström L, Udd B. Welander distal myopathy is caused by a mutation in the RNA-binding protein TIA1. Ann Neurol 2013, Epub ahead of print 2013. - *Widefield fluorescence microscopy was used to analyze TIA1 localization and disease induction by the mutant TIA1in patient muscle biopsies: High-content screening microscopy enabled detection of increased stress granule formation in TIA1 mutant cells, and confocal FRAP analysis led to the discovery of a reduction in stress granule-cytoplasm shuttling rate of mutant TIA1. IF 11.193. (BIU-BCH)*

Zhao H1, Michelot A, Koskela EV, Tkach V, Stamou D, Drubin DG, Lappalainen P. Membrane-sculpting BAR domains generate stable lipid microdomains. Cell Rep. 2013 Sep 26;4(6):1213-23. -*The LMU-BI facilities were extensively used for both in vitro and in vivo imaging of lipid dynamics. (LMU-BI)*

Matsuda S1, Blanco J, Shimmi O. A feed-forward loop coupling extracellular BMP transport and morphogenesis in Drosophila wing. PLoS Genet. 2013 Mar;9(3):e1003403. - *The LMU-BI facilities were used for studies on posterior crossvein development in Drosophila wing. IF 8.5 (LMU-BI)*

Castellone MD, Laatikainen LE, Laurila JP, Langella A, Hematti P, Soricelli A, Salvatore M, Laukkanen MO: Brief report: Mesenchymal stromal cell atrophy in coculture increases aggressiveness of transformed cells. Stem Cells. 2013 Jun;31(6):1218-23. - *Collection and assembly of data, data analysis and interpretation was done using CIC instruments. IF 7.7 (CIC-TBI)*

Vihervaara A, Sergelius C, Vasara J, Blom MA, Elsing AN, Roos-Mattjus P, Sistonen L. Transcriptional response to stress in the dynamic chromatin environment of cycling and mitotic cells. Proc Natl Acad Sci USA. 2013 Sep 3;110(36):E3388-97. - *Collection and assembly of data, data analysis and interpretation was done using CIC instruments with assistance of CIC personnel, primarily combining results from genome-wide analysis with advanced FACS analysis and imaging. IF 9.737 (CIC-TBI)*

Li LL1, Ginet V, Liu X, Vergun O, Tuittila M, Mathieu M, Bonny C, Puyal J, Truttmann AC, Courtney MJ. The nNOS-p38MAPK pathway is mediated by NOS1AP during neuronal death. J Neurosci. 2013 May 8;33(19):8185-201. - *This is a substantial translational work from molecular mechanism to disease model, a major theme of BCK. Many figure parts in several of the figures relied on the automated microscopy, liquid handling and image analysis facilities of the core. IF 7.1. (MUIC-BCK)*

Uebelhoer M, Nätynki M, Kangas J, Mendola A, Nguyen HL, Soblet J, Godfraind C, Boon LM, Eklund L, Limaye N, Vikkula M. Venous malformation-causative TIE2 mutations mediate an AKT-dependent decrease in PDGFB. Hum Mol Genet. 2013; 22:3438-3448. - *Confocal microscope analysis of endothelial cells expressing mutated TIE2 receptor tyrosine kinase. IF 7.692 (TIC-BCO)*

Andersson ER, Saltó C, Villaescusa JC, Cajanek L, Yang S, Bryjova L, Nagy II, Vainio SJ, Ramirez C, Bryja V, Arenas E. Wnt5a cooperates with canonical Wnts to generate midbrain dopaminergic neurons in vivo and in stem cells. Proc Natl Acad Sci U S A. 2013; 110:E602-610. - *Light microscopic techniques were used to characterize a novel mouse line. IF 9.737 (TIC-BCO)*

Jing Zou, Ya Zhang, Weikai Zhang, Dennis Poe, Suoqiang Zhai, Shiming Yang, Ilmari Pyykkö. Mitochondria toxin-induced acute cochlear cell death indicates cellular activity-correlated energy consumption. European Archives of Oto-Rhino-Laryngology 2013, Volume 270, Issue 9, pp 2403-2415. - *Confocal imaging was used to study apoptosis and DNA fragmentation. IF 1.29 (IBT)*

Small Animal Molecular Imaging (SPECT/CT)

Chair persons of the consortium: Raimo K. Tuominen, Division of Pharmacology and Toxicology, Anu Airaksinen, Centre for Drug Research

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Achievements in development and restructuring of technology services

Single photon emission computed tomography / computed tomography (SPECT/CT) is a versatile non-invasive molecular and morphological imaging technique that is used regularly in biomedical research and preclinical drug development. With small animal SPECT/CT one can quantify changes in living body such as dissemination and growth of tumors, cardiovascular function, distribution of drug molecules and their delivery systems, and brain function even at level of neurotransmission.

In 2010, the University of Helsinki purchased the first high-resolution small animal SPECT/CT in Finland. It is one of the best in Nordic countries and provides a high spatial resolution at sub millimetre level, which allows e.g. imaging of transgenic mouse brain structures (not possible with the old generation instruments). The SPECT/CT instrument is located in Real-Time Imaging (RTI) unit of the Centre for Drug Research (CDR), Faculty of Pharmacy, University of Helsinki. It provides services to academic research groups in Finland and abroad. In addition, there is a growing interest by drug industry to use this methodology, and part of the costs will be covered by user fees. RTI unit was supported by BF during 2011 and 2012 and again in 2014.

RTI currently provides imaging services including SPECT and CT. In addition, dedicated housing is

available for mice and rats undergoing longitudinal imaging studies. Ancillary facilities and resources of the RTI are devoted to radiopharmacy and image analysis. During 2013 the RTI laboratory dedicated efforts to find new applications, and firmly establish those tested in previous years, and also to the development of translational science supported by external funding.

User statistics 2013

There were 8 projects during 2013 with spans of 2 to 4 weeks each. The projects ranged from establishing a kinetic model for intra-vitreal drug delivery in the mouse eye, to kinetics of radiolabelled cubo- and hexosomes, to monitoring of leukocyte specific migration to tumors in animal models of cancer, and to development of a novel inflammatory marker for diagnosis of neuroinflammation. Total number of animals scanned was 50.

Participation in international, Nordic and European infrastructures

The laboratory is main partner in the COMPACT project (FP7) 2012–2015, and participant partner in the COST action TD1004.

Future perspectives

The immediate perspectives are to crystallise the work form the previous year in a comprehensive and updated list of applications to offer to customers of the imaging facility. The potential of service has grown considerable, and a proper marketing campaign has been designed for 2014 in the frame of new optimised and expanded premises at Biocenter 3 in University of Helsinki Viikki campus. Within the expectations and ambitions of the RTI laboratory, there is a need to upgrade the current system. Negotiations with the nano-SPECT/CT manufacturer have resulted in an upgrade package of around 20 000 €.

Major publications resulting from the Platform services

Raki M, Bergström K, Jolkkonen J. In vivo biodistribution studies and cell tracking in stroke using SPECT imaging. In book: Cell-based therapies in stroke; Edited by Piotr Walczak and Jukka Jolkkonen; Springer-Verlag Wien 2013 - *All imaging made at our facility*

Kerkelä E, Hakkarainen T, Mäkelä T, Raki M, Kambur O, Kilpinen L, Nikkilä J, Lehtonen S, Ritamo I, Pernu R, Pietilä M, Takalo R, Juvonen T, Bergström K, Kalso E, Valmu L, Laitinen S, Lehenkari P, Nystedt J. Transient Proteolytic Modification of Mesenchymal Stromal Cells Increases Lung Clearance Rate and Targeting to Injured Tissue. Stem Cells Transl Med 2013; 2(7):510-20. doi: 10.5966/sctm.2012-0187 - *Clearance rates measured by SPECT/CT in our unit*

Bäck S, Raki M, Tuominen RK, Raasmaja A, Bergström K, Männistö P. High correlation between in vivo [123I]beta-CIT SPECT/CT imaging and post-mortem immunohistochemical findings in the evaluation of lesions induced by 6-OHDA in rats. EJNMMI Research 2013, 3:46 doi:10.1186/2191-219X-3-46. - *Brain strial labelling visualized by SPECT/CT in our unit.*

Nilsson C, Barrios-Lopez B, Kallinen A, Laurinmäki P, Butcher S, Raki M, Weisell J, Bergström K, Larsen SW, Østergaard J, Larsen C, Urtti A, Airaksinen AJ, Yaghmur A. SPECT/CT Imaging of Radiolabeled Cubosomes and Hexosomes for Potential Theranostic Applications. Biomaterials 2013; 34:8491-503. - *All imaging made at our facility*

Barrios-Lopez B, Raki M, Bergström K. Radiolabeled Peptides for Alzheimer's Diagnostic Imaging: Mini Review. Curr Radiopharmaceuticals 2013; 6:181-91. - *Data from previous scanning results in our unit are reviewed here*

Bäck S, Sarparanta M, Raki M, García-Horsman JA, Bergström KA, Wallén EAA, Männistö PT and Airaksinen AJ. Synthesis and biological evaluation of novel 123I-labeled 4-(4-iodophenyl)butanoyl-L-prolyl-(2S)-pyrrolidines for imaging prolyl oligopeptidase in vivo. In press. - *All imaging made at our facility.*

GENOME-WIDE METHODS

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

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Genome-wide methods including DNA sequencing, RNA analyses, and high-throughput genetic screens have rapidly and profoundly changed basic biological science and biomedicine. Because of the highly specialized and capital-intensive nature of genomics instrumentation and reagent sets these technologies have been developed as core infrastructures providing services to researchers nationally. Genome-wide approaches are a focus area of biocenters in Helsinki and Turku: genetics/genomics and genome-scale biology services are primarily developed in Helsinki and gene expression and regulation services in Turku. Cost-effective access to reagents and libraries enabling knockdowns or overexpression as well as high-throughput facilities is provided nationwide as a collaborative effort of Helsinki biocenters. It is essential to provide tailored services in this area to Finnish scientists also in the coming years to maintain the cutting edge. This development requires both long-term funding to enable recruitment and maintenance of top quality scientists and technicians as well as continuing investments into new 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. High-content screening services were customized to local research strengths and integrated with imaging and translational technologies.

Development of novel technologies such as RNA interference (RNAi) and the increasing efficiency and speed of DNA sequencing serve as examples of continuous need for new equipment and upgrading of current ones. 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 providing services to researchers nationally.

Genome-Wide Methods Technology Platform

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); Tea Vallenius, BI, Genome-biology Unit (GBU); Riitta Lahesmaa & Riikka Lund, BioCity, Finnish Microarray and Sequencing Centre (FMSC); Janna Saarela, FIMM, FIMM Technology Center; DNA Sequencing and Genotyping Laboratory; High-throughput Screening Facility

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Achievements in development and restructuring of technology services during 2013

The demand for genome wide technologies, especially NGS sequencing, has steadily increased, and the network has stretched its equipment and personnel resources to respond to the need. At the same time several novel applications have been introduced, the existing technologies have developed rapidly and new single molecule analyzers are approaching mature versions in the coming years. In addition, bioinformatics closely linked to analysis and storage of the omics data has continued developing nearly as fast as the data production in the laboratories. Biocenter Finland is in a key position on providing and developing genome scale biology technologies in Finland. Due to the very rapid development of DNA sequencing (NGS) and other genome-wide applications and novel emerging technologies, it is of most importance to secure sufficient funding for personnel and equipment in this field in Finland.

Long term planning enabled by longstanding support makes keeping of the highly qualified personnel in the university environment possible. Our recruitment policy has been highly successful during the 2010–2013. However, the discontinuation of strategic instrument funding channeled through the Biocenter Finland has already caused the development of genomics infrastructures in Finland to lack behind when compared to the recent developments internationally, for example in Sweden.

Genome scale biology is still developing extremely fast. This has a direct impact on the activity of the network since continuous technology upgrades require constant development of our operations. The fast pace of development causes need for restructuring as a modus operandi of the platforms. Nodes of the BF Genome-wide methods 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. With the support from BF the network has successfully restructured and developed its core infrastructures and now provides several novel NGS based services to the researchers nationally.

The data analysis pipelines and computational resources crucial for supporting these new technology platforms have been established and developed in collaboration with the Bioinformatics network accordingly. We think that our achievements during the first four years of BF funding have demonstrated the strength, power and competitiveness of such a structure and justify for further funding, subject to regular external evaluation. The development of the platforms themselves in all the nodes has been rapid due to the BF funding and also supporting funding from the host organisations and other sources. BF-GWM has been successful in acquiring additional funding. 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 research 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 optimizing the cost-efficient usage of the funding.

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

We found the BF user survey useful and will take the feedback to further improve our services. To make the survey even more inclusive, survey could be sent also to the end users in addition to PIs. Furthermore, including type of service in the questionnaire would further help us to improve specific services. Genome-wide methods technology platform has been successful in coordinating our activities. Currently, the bottleneck in sample handling and sequencing are existing, but the situation will be significantly improved if equipment funding is allocated to these activities. There has been a continuous increase in the usage of the services in our consortia during its existence.

Participation in international, Nordic 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 (including ERC grants). Examples of such funding include participation in European projects (e.g. DIABIMMUNE, NANOMMUNE, PEVNET, SYBILLA, ESTOOLS, CENTER-TBI, EUROHEADPAIN, SYSTUMS, IN-SENS), in JDRF funded projects and European research infrastructures (Systems microscopy, BioMedBridges, European Innovative Medicines Initiatives (IMI) and ESFRI networks (EATRIS, BBMRI, ELIXIR). Nodes are taking part as partners or service providers in several Horizon 2020 applications and NordForsk consortia applications. There are increasing demands for computing power and for storage and archiving in the field of genome-wide methods. The GWM network has prepared two national level roadmaps of infrastructures in this area (2007 and 2009) and is in an optimal position to take responsibility both as a node for ESFRI level infrastructures (such as BBMRI) as well as responsibility for upcoming national infrastructures roadmap. In collaboration with CSC we are developing solutions for the above needs via CSC cloud computing project within the ELIXIR ESFRI program and in several pilot projects using virtual machines solution in complex analysis. These activities are also planned in close contact with the BF-Bioinformatics network. Though cloud computing can be used for certain application the need for local computing and storage capacity near the data production sites does not cease.

User statistics 2013

A total of 407 research groups have used the services provided through BF-GWM nodes during 2013 with a turnover exceeding 3 700 000 € as demonstrated in the table. The restructuring and sharing of tasks is already very evident through comparison of the services in genomics, gene expression, and genome-scale biology. Importantly, there is increase in activities in 2013 compared to 2010–2012, which already was pointed out to be excellent by the external evaluators. The number of samples analyzed by the nodes has increased during the entire period of 2010–2012 and has continued during 2013. The provided services vary among the table below and comparing the numbers directly can be misleading. The amount of work and expertise needed between services might differ even in one cell. This table is only giving a summary of the activities.

Future perspectives

We expect the demand for genome wide technologies to significantly increase. The newly developed applications and improvements in the methods allow especially sequencing to be used in novel areas of genome scale biology and for analyzing even more challenging samples, including single cells. The most urgent needs are listed in our FIRI2014 application, the first being novel DNA sequencers. Technologies are developing and already now we are one to two years behind and cannot follow or make strategic changes in the services according to the new methods appearing and current

	BioCity Turku (FMSC)			BI (BIDGEN & GBU)			FIMM			FuGu		
Services	Samples	Projects	Groups	Samples	Projects	Groups	Samples	Projects	Groups	Samples	Projects	Groups
Resequencing				26	6	4	501	26	13	321	34	16
De novo				302	56	29						
Metagenomics	37	4	4	2728	21	19	270	3	3			
Targeted	6 173	193	83	4	1	1	3 420	129	38	160	11	6
SNP genotyping (QWAS)							5 679	17	15			
Targeted SNP typing	96	1	1				49 902	19	16			
Copy number variation**	38	10	5							30	2	2
Immunoprecipitates (ChIP-Seq etc)*	257	14	6				200	3	3	50	8	2
RNA sequencing	747	33	22	250	9	8	519	72	17	62	6	6
Gene expression microarrays	775	20	15				171	1	5	519	38	31
Cell microarray screening							465	11	11			
Genome-scale reagents				365	86	29				462	28	15
ORF clooning				204	33	12						
Integrated two-hybrid screening												
Pooled & barcode shRNA screens												
High-content analysis (HCA)				1 373	52	21	3	1	1			
Customers												
local		234	82		255	114		199	59		90	49
other domestic		28	20		4	4		64	39		3	4
international		7	6					10	8		4	2
non-academic groups / units		7	5		5	5		1	1		18	9
TOTAL		276	113		264	123		274	107		115	64
Billing total		720 625			631 369			1 917 567			470 576	
	*includes methylation arrays and bisulfite sequencing **includes genome-wide(CGH) and targeted									Billing grand total 3 740 134		

trends elsewhere. The other urgent need includes more automated single cell approaches for RNA and DNA sequencing that should be available in several nodes due to variable needs reflected by the very large spectrum of different samples and approaches utilized across the network, literally ranging from microbes to man. Library preparation needs novel, more current automation. The genome wide reagents including libraries like ORF clones, siRNA libraries, shRNA libraries etc. have been now lacking behind the even more urgent needs of restructuring the DNA sequencing platforms in each node. New species and more coverage to the existing libraries should be added.

One emerging bottle neck already now seen is rising from the need to develop novel applications and methods and at the same time handle an ever increasing number of samples in each node. Development of novel and early adaptation of recently published methods is an important task of the technology platforms. Introduction of more automation to the library preparation would free resources for method development, which should be further enhanced by targeted funding (reagents, equipment, personnel).

Major publications resulting from the Platform services

Glerup S, Lume M, Olsen D, Nyengaard JR, Vaegter, CB, Gustafsen C, Christensen EI, Kjolby M, Hay-Schmidt A, Lande AD, Madsen P, Saarma M, Nykjaer A and Petersen CM. (2013) SorLA controls neurotrophic activity through sorting of GDNF and its receptors GFRα1 and RET. Cell Reports 3(1):186-99. - *Sequencing service at BIDGEN was used.*

Ovaskainen, O., Schigel, D., Ali-Kovero, H., Auvinen, P., Paulin, L., Nordén, B., & Nordén, J. 2013. Combining high-throughput sequencing with fruit body surveys reveals contrasting life-history strategies in fungi. The ISME Journal 7: 1696-1709. - *Metagenome sequencing of ITS regions using NGS sequencing by BIDGEN*

CCRK depletion inhibits glioblastoma cell proliferation in a cilium-dependent manner. Yang Y, Roine N, Mäkelä TP. EMBO Rep. 2013 Aug;14(8):741-7. doi: 10.1038/embor.2013.80. Epub 2013 Jun 7. - *GBU ORFeome clone and cloning service used.*

Kong L, Aho KL, Granberg K, Lund R, Järvenpää L, Seppälä J, Gokhale P, Leinonen K, Hahne L, Mäkelä J, Laurila K, Pukkila H, Närvä E, Yli-Harja O, Andrews PW, Nykter M, Lahesmaa R, Roos C, Autio R. ESTOOLS Data@Hand: human stem cell gene expression resource. Nat Methods. 2013 Aug;10(9):814-5. - *FMSC services have been used to generate part of the data for the database.*

Sinclair LV, Rolf J, Emslie E, Shi YB, Taylor PM, Cantrell DA. Control of amino-acid transport by antigen receptors coordinates the metabolic reprogramming essential for T cell differentiation. Nat Immunol. 2013 May;14(5):500-8. doi: 10.1038/ni.2556. IF: 26.199 - *FMSC services with Affymetrix gene expression arrays and functional assays.*

Paakinaho V, Kaikkonen S, Makkonen H, Benes V, Palvimo JJ. SUMOylation regulates the chromatin occupancy and anti-proliferative gene programs of glucocorticoid receptor. Nucleic Acids Res. 2013 Nov 4. IF: 8.278. - *The gene expression array service provided by FMSC was utilized in the study.*

Vihervaara A1, Sergelius C, Vasara J, Blom MA, Elsing AN, Roos-Mattjus P, Sistonen L. Proc Natl Acad Sci U S A. 2013 Sep 3;110(36):E3388-97. doi: 10.1073/pnas.1305275110. Epub 2013 Aug 19. Transcriptional response to stress in the dynamic chromatin environment of cycling and mitotic cells. - *ChIP-seq services were used from FuGU.*

Nieminen AI1, Eskelinen VM, Haikala HM, Tervonen TA, Yan Y, Partanen JI, Klefström J. Proc Natl Acad Sci U S A. 2013 May 14;110(20):E1839-48. doi: 10.1073/pnas.1208530110. Epub 2013 Apr 15. Myc-induced AMPK-phospho p53 pathway activates Bak to sensitize mitochondrial apoptosis. - *Lentiviral shRNA constructs were used from FuGU*

Andersson EI, Rajala HL, Eldfors S, Ellonen P, Olson T, Jerez A, Clemente MJ, Kallioniemi O, Porkka K, Heckman C, Loughran TP Jr, Maciejewski JP, Mustjoki S. Novel somatic mutations in large granular lymphocytic leukemia affecting the STAT-pathway and T-cell activation. Blood Cancer J. 2013 Dec 6;3:e168. doi: 10.1038/bcj.2013.65. - *Exome sequencing, data analysis, and variant validation were conducted at the FIMM Technology Centre.*

Mäki-Nevala S, Kaur Sarhadi V, Tuononen K, Lagström S, Ellonen P, Rönty M, Wirtanen A, Knuuttila A, Knuutila S. Mutated ephrin receptor genes in non-small cell lung carcinoma and their occurrence with driver mutations-targeted resequencing study on formalin-fixed, paraffin-embedded tumor material of 81 patients. Genes Chromosomes Cancer. 2013 Dec;52(12):1141-9. doi: 10.1002/gcc.22109. - *Agilent custom capture enrichment, sequencing, data analysis and mutation validation were conducted at the FIMM Technology Centre.*

Pemovska T, Kontro M, Yadav B, Edgren H, Eldfors S, Szwajda A, Almusa H, Bespalov MM, Ellonen P, Elonen E, Gjertsen BT, Karjalainen R, Kulesskiy E, Lagström S, Lehto A, Lepistö M, Lundán T, Majumder MM, Marti JM, Mattila P, Murumägi A, Mustjoki S, Palva A, Parsons A, Pirttinen T, Rämet ME, Suvela M, Turunen L, Västrik I, Wolf M, Knowles J, Aittokallio T, Heckman CA, Porkka K, Kallioniemi O, Wennerberg K. Individualized systems medicine strategy to tailor treatments for patients with chemorefractory acute myeloid leukemia. Cancer Discov. 2013 Dec;3(12):1416-29. doi: 10.1158/2159-8290.CD-13-0350. - *Exome, transcriptome and amplicon sequencing of patients' tumor DNA & RNA and germline DNA, primary data analysis, somatic variant calling and in vitro drug sensitivity and resistance testing was conducted at the FIMM Technology Centre.*

MODEL ORGANISMS

Model Organisms Infrastructure Network

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

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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 are 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.

Emerging technology platform for tissue engineered disease models (TEDM) complements the services of the mouse model, viral gene transfer and drug discovery platforms of Biocenter Finland. TEDM-platform is a sequel to LentiGEMM platform developing lentiviral technologies for tissue transductions funded by BF in 2010–2012. In 2013 funding was not available for TEDM platform, but the activities are being supported again in 2014.

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 and Petra Sipilä, BCH, Helsinki GM Mouse Unit; Eero Castren, 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

www.biocenter.fi

www.fingmice.org

Achievements in development of technology services during 2013

One of the key research tools in understanding mammalian gene function is the laboratory mouse. The scientific community has taken advantage of its fundamental similarity to humans at the genetic level (>95% at the gene level), similar physiology and anatomy, its relatively low cost compared to other mammals, and nearly 100 years of genetic study. An extensive toolkit for the manipulation of the mouse genome and the generation of new disease models has been generated.

In the early days of gene modification experiments, genetically modified (GM) mice were generated by individual research groups and stored in small animal houses. However, it soon became obvious that larger units are the only choice, since special training of researchers and personnel performing the experiments and taking care of animals are required, and the facilities have to be managed according to regulations on the use of experimental animals and GM organisms. Core facilities offer possibilities for both reduction of animal numbers used and refining their life and welfare, following the 3R's principle. Furthermore, in the co-operative, centralized system, the GM animal strains can be used by a large number of researchers. Centralized storing, cleaning and phenotyping are services that reduce the number of animals needed and refine their life.

The FinnMouse technology platform has actively developed GM mouse services, and restructuring resulted in three collaborating core facilities (Helsinki, Oulu, and Turku) providing services in GM mouse

technologies for all Finnish scientists. All three units provide elementary services, such as generation and rederivation of GM mice. In addition to the basic services, the units have special service profiles: the Helsinki GM unit specializes in mouse chimera generation by the morula aggregation method, and is launching the generation of GM rats. The Oulu unit has special expertise in embryonic stem (ES) cells and cryopreservation methods, serving as the Finnish Infrafrontier-EMMA (European Mouse Mutant Archive, www.infrafrontier.eu) node that provides repository services, including cryopreservation and distribution of GM mouse lines to a world-wide user community. Generation of ES cell lines, sperm freezing and IVF are new services being provided in Oulu. Turku Center for Disease modeling (TCDM) provides services in generation of gene constructs for GM mouse production, tumor xenografts in immunodeficient mice and has collaboration with several pharma and biotech companies.

For phenotypic analyses of mice, specific areas of expertise have been strengthened and services developed. Neurophenotyping Centers (NC) in Helsinki and Kuopio, University of Eastern Finland, provide services in automated behavioral phenotyping and in specific neurophenotyping tests both in disease models (Alzheimer's disease, epilepsia, schizophrenia and autism-like behavior) as well as in analyzing roles of specific factors. In 2013, the Mouse Behavioural Phenotyping Facility as a core unit was established in the newly renovated Laboratory Animal Center in University of Helsinki, and in Kuopio, electroretinography techniques for a full assessment of mouse retina were optimized. In Biocenter Oulu (BCO), current focus areas are services in the electron microscopy of mouse tissues (reported separately) and analysis of cardiovascular functions. Furthermore, the optical projection tomography (OPT) and basic mouse histopathology services are available. TCDM has furnished operation rooms at the animal facility for use of the 3T MRI for animal imaging and established the technology for culturing and inoculating patient-derived cells into immune deficient mice. 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, and trains veterinary pathologists.

Visits to partner laboratories and yearly personnel meetings speed up the exchange of best practices and new methods. A web interface www.fingmice.org provides information about services and expertise in generation and analysis of GM mice available in Finland. All service facilities are engaged in education of graduate students and postdocs in laboratory and lecture courses. Workshops on specific subjects have been organized for scientists and technical personnel; most recent ones were a 2-day Intensive Course on Neuropathology organized by Kuopio NC in May 2013, a Laboratory Animal Necropsy Course in Oulu in February and a NorIMM workshop 'Microenvironmental Cues in Regeneration, Aging, and Inflammation' in Oulu in December 2013. A 5-day PhD course "Experimental and Laboratory Animal Pathology" was organized by FCLAP, and a web-based course on "Basics in Mouse Modeling and Pathology" has been developed by TCDM together with Institute of Pathology, TU München, College of Medical, Veterinary and Life Sciences, Glasgow University, and Palmenia Centre for Continuing Education, Helsinki University. During 2013 a pilot course for 30 international students was carried out.

Participation in international, Nordic and European infrastructures

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

The NordForsk funded network NorIMM, Nordic infrastructure for Mouse Models, www.norimm.org, established to improve communication between GM mouse generation and phenotyping infrastructures in Nordic countries, is coordinated by Oulu University.

Future perspectives

The FinnMouse core facilities are and will be in a key position to provide knowledge and services in GM mouse models to the Finnish research community, and permanent staff is essential for reliable services. Co-operation in purchase and updating of equipment and training personnel is of major importance. Also animal facilities have to be properly equipped and managed. It is important to keep up-to-date in the technology development and the huge amount of new information being produced in large international

User statistics 2013

Research groups / other customers in 2013					
TG/GM unit	Local	National	International	Non-academic	Total
Helsinki	34	0	0	0	34
BCO Oulu	12	5	17	0	34
TCDM Turku	18	10	5	1	34
total GM units	64	15	22	1	102
Phenotyping					
FCLAP Helsinki	17	2	2	1	22
NC Helsinki	11	2	0	0	13
NC UEF	3	1	0	2	6
TCDM Histology	22	1	2	0	25
- Imaging	14	6	3	3	26
- Xenocraft stud.	4	0	0	2	6
- Other	31	11	6	2	50
BCO Histology	15	0	0	0	15
- Histopathology	9		0		9
- Imaging (IVIS, OPT, Echo)	9	2	2	0	13
Total Phenotyping	135	25	15	10	185
TOTAL	199	40	37	11	287
GM Services			Univ. Helsinki	Univ. Turku	Univ. Oulu
Pronuclear injection			1	6	8
ES cell targeting			0	12	11
Consortia ES cell culture			0	0	11
Cryopreservation of 8-cell embryos			17	12	0
Mouse line rederivation			73	3	5
Blastocyst injection			0	10	16
Recovery of cryopres. embryos			5	0	13
Sperm cryopreservation			11	0	32
Genotyping			0	16	22
Husbandry of mouse colonies			0	20	5
Morula aggregation			4	0	0
DNA construct generation			0	6	0
Cryopres. of IVF-derived 2-cell embryos			0	0	32
Other			0	6	3
Total			111	91	157

Phenotyping services provided	
FCLAP Helsinki	Necropsies (41); Immunohistology specimens (533); Paraffin blocks (2 335)
NC Helsinki	Behavioral phenotyping (25 in total)
NC Kuopio UEF	Brain microinjections; Video-EEG recording; Brain immuno-histology; Behavioral testing (in total 10)
TCDM Turku	Biomarker analyses; Histology and immunohistochemistry; whole animal imaging; Xenografts in mice; Organ-specific expertise for Adipose tissue, Bone, Cardiovascular, Intestine, Reproduction, Thyroid
BCO Oulu	Measurements of cardiovascular functions (1 233 animals); In vivo imaging; OPT (200 samples); Tissue processing for histology (4 506)

consortia. New methods for genome modification, e.g. the TALENs and the CRISPR/Cas system will speed up the generation of mutant mice. It is foreseen that rare diseases, where patient material, is limited, will be increasingly 'modelled' in mice for therapy applications. Studies on sophisticated models for diseases such as cancer and diabetes will be further advanced.

Major publications resulting from the Platform services

Aikio M, Hurskainen M, Brideu G, Hägg P, Sormunen R, Heljasvaara R, Gould DB, Pihlajaniemi T (2013) Collagen XVIII short isoform is critical for retinal vascularization, and overexpression of the Tsp-1 domain affects eye growth and cataract formation. Invest Ophthalmol Vis Sci 54: 7450-62. - – GM mice were generated and analyzed in Oulu.

Huh SH, Närhi K, Lindfors PH, Häärä O, Yang L, Ornitz DM, Mikkola ML. (2013) Fgf20 governs formation of primary and secondary dermal condensations in developing hair follicles. Genes Dev. 27:450-8. - GM mice were generated in the Helsinki GM unit and the analysis was a collaboration of research groups in Helsinki and USA.

Kerkelä R, Karsikas S, Szabo Z, Serpi R, Magga J, Gao E, Alitalo K, Anisimov A, Sormunen R, Pietilä I, Vainio L, Koch WJ, Kivirikko KI, Myllyharju J, Koivunen P. (2013) Activation of hypoxia response in endothelial cells contributes to ischemic cardioprotection. Mol Cell Biol 33:3321-9. – GM mice were generated and analyzed in Oulu.

Kulesskaya N, Võikar V, Peltola M, Yegutkin GG, Salmi M, Jalkanen S, Rauvala H. (2013) CD73 is a major regulator of adenosinergic signalling in mouse brain. PLoS One 8: e66896. - Behavioural phenotyping carried out at the Neurophenotyping Center Helsinki

Laine CM, Joeng KS, Campeau PM, Kiviranta R, Tarkkonen K, Grover M, Lu JT, Pekkinen M, Wessman M, Heino TJ, Nieminen-Pihala V, Aronen M, Laine T, Kröger H, Cole WG, Lehesjoki AE, Nevarez L, Krakow D, Curry CJ, Cohn DH, Gibbs RA, Lee BH, Mäkitie O (2013) WNT1 mutations in early-onset osteoporosis and osteogenesis imperfecta. N Engl J Med. 368:1809-16 - The mouse studies included in the study were carried out at the Bone biology Unit at TCDM.

Lotinun S, Kiviranta R, Matsubara T, Alzate JA, Neff L, Lüth A, Koskivirta I, Kleuser B, Vacher J, Vuorio E, Horne WC, Baron R. (2013) Osteoclast-specific cathepsin K deletion stimulates S1P-dependent bone formation. J Clin Invest. 123:666-81. - GM mice were generated at TCDM and phenotyped in an international collaboration between TCDM and Harvard School of Dental Medicine.

Rinne P, Nordlund W, Heinonen I, Penttinen AM, Saraste A, Ruohonen ST, Mäkelä S, Vähätalo L, Kaipio K, Cai M, Hruby VJ, Ruohonen S, Savontaus E (2013) α-Melanocyte-stimulating hormone regulates vascular NO availability and protects against endothelial dysfunction. Cardiovasc Res. 97:360-368. - GM mice were produced at TCDM and phenotyped at the Cardiovascular Physiology Unit at TCDM.

Rantamäki T, Kemppainen S, Autio H, Stavén S, Koivisto H, Kojima M, Miettinen PO, Kärkkäinen E, Karpova N, Vesa L, Lindemann L, Hoener MC, Tanila H, Castrén E. (2013) The impact of Bdnf gene deficiency to the memory impairment and brain pathology of APPswe/PS1dE9 mouse model of Alzheimer's disease. PLoSOne 8:e68722. – This study is a collaboration of Neuroscience Center, Helsinki and the BCK Neurophenotyping Center, where all behavioral neurotyping and immunohistology was done.

Rolova T, Puli L, Magga J, Dhungana H, Kanninen K, Wojciehowski S, Salminen A, Tanila H, Malm T, Koistinaho J. (2013) Complex regulation of acute and chronic neuroinflammatory responses in mouse models deficient for nuclear factor kappa B p50 subunit. Neurobiol Dis. 64C:16-29. - All behavioral phenotyping was done at BCK Neurophenotyping center.

Zilberter M, Ivanov A, Ziyatdinova S, Mukhtarov M, Malkov A , Alpar A, Tortoriello G, Botting CH, Fülop L, Osypov AA, Pitkänen A, Tanila H, Harkany T, Zilberter Y. (2013) Dietary energy substrates reverse early neuronal hyperactivity in a mouse model of Alzheimer's disease. J Neurochem 125:157-71. - All video-EEG and immunohistology was done at BCK Neurophenotyping center.

Non-mammalian Models Technology Platform

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

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Achievements in development of technology services during 2013

During the restructuring process of national technology services, Tampere (BioMediTech) became particularly invested to develop research infrastructure for non-mammalian models (namely *Drosophila melanogaster* and zebrafish *Danio rerio*) rather than for mammalian models during the past 5 years. Nation widely, adequate infrastructure and knowhow in Helsinki related to both *Drosophila* and zebrafish is important to provide service locally and to enhance quality of Finnish biomedical research in general. Currently, the most important investments to equipment related to routine maintenance of both *Drosophila* and zebrafish have been done both in Helsinki and in Tampere.

Zebrafish

During 2013, the Tampere Zebrafish core facility has been fully operational after investments in 2010–2012. Currently, the laboratory employs a full-time coordinator and three technicians. Researchers from several teams from the Universities of Tampere, Jyväskylä and Oulu have so far used the facility. Besides on-going process of creating mutant zebrafish families, 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 network has organized twice a week-long in-hands training course for the use of non-mammalian model organisms for research in life sciences in 2011 and 2012. The major obstacle for providing services to the community in 2013 was renovation of the laboratory (10/2013-1/2014) due to moisture damage and subsequent problems in the air quality. Renovation was completed in January 2014 and thereafter zebrafish facility has operated normally. In the nationwide user survey performed by Biocenter Finland we got feedback from 4 users of our facility, two from our own University and two from elsewhere in Finland. All the feedback was considered positive, ranging from 4 to 5 (out of 6).

During 2013, the Helsinki zebrafish facility has

been fully operational. Due to cuts in internal funding, one technician's position was discontinued despite the need, and the postdoc who had been responsible for user guidance with demanding techniques has also helped in practical procedures and contributed essentially to the maintenance. One technician has been funded by University of Helsinki. Most users have been from the University of Helsinki or nearby institutions (Minerva, Folkhälsan, FIMM), one from University of Turku. The unit maintains fish lines, carries out microinjections and other procedures. As planned for division of work between the Tampere and Helsinki units, Helsinki unit has started targeted zebrafish mutagenesis projects using the CRISP-R/Cas method (reverse genetics). The Viikki backup facility has been closed because of renovation since April 2013, and will need a new space for this second large-scale facility soon since the current one will be taken to other purposes. The main facility in Biomedicium 2 has been operating without obstacles throughout the year 2013.

Drosophila

In Tampere, a new *Drosophila* Core Facility has been built in 2012. This investment was done by the host Institute and was supervised by the BF-funded core facility coordinator Dr. Susanna Valanne. The new laboratory includes 12 working stations with stereomicroscopes and carbon dioxide points for anesthetizing flies. This unit is heavily used as it currently hosts – for instance – two ERC grant holders and two FiDiPros.

Participation in international, Nordic and European infrastructures

Our consortium (Tampere) has not been formally involved in Nordic or European infrastructures in 2013. However, Pertti Panula from the University of Helsinki has been actively involved in related international, European and Nordic networks. He has been a member of the Management Committee of EuFishBioMed (COST Action BM0804), which ended in 2013. A publication of this action and its significance was published in the journal Zebrafish (Strähle et al. Zebrafish 2012; 9: 90–93). He was also a member of the management group of the Nordforsk network BIFINE (Integrative Fish Behavioural Neuroscience Network) 2010–2013. This network included active groups from all 4 Nordic countries and organized 4 meetings (one in each country) during the grant period, and a number of visits of young scientists between the labs. Panula has also participated in all the five international Strategic Conferences of Zebrafish Investigators in 2005-2013.

Future perspectives

Based on support from the Biocenter Finland, our consortium has successfully developed research infrastructure (and knowhow) related to use of non-mammalian model organisms in Finland. The most important investments have been carried out both in Tampere and in Helsinki allowing high-quality services to be provided to the scientific community. Currently there are many researchers and teams that are using the facilities. The main challenge in the future is to maintain skilled personnel to run these operations as the funding situations in general related biomedical research is worrisome for the next years.

Major publications resulting from the Platform services

All these papers are carried out primarily using model organisms provided by our consortium at Tampere, Helsinki and Viikki.

Aspatwar A, Tolvanen M, Jokitalo E, Parikka M, Ortutay C, Harjula SK, Rämet M, Vihinen M & Parkkila S. Altered cerebellum development and motor dysfunction in CARP VIII morphant zebrafish embryos. Human Molecula Genetics 2013, 22:417-32.

Havula E, Teesalu M, Hyötyläinen T, Seppälä H, Hasygar K, Auvinen P, Orešič M, Sandmann T, Hietakangas V. (2013) Mondo/ChREBP-Mlx-regulated transcriptional network is essential for dietary sugar tolerance in Drosophila. PLoS Genet. 4:e1003438

User statistics 2013

	Groups				Animals Larvae / adult	
	Total	Local	Domestic	International	Total	Domestic
Zebrafish						
Tampere	6	4	2		22 450 / 16 364	- / 800
Helsinki	13	10	1	2	55 946 / 112	500 / 0
Drosophila					~ 500 000	
Tampere	8	8			~ 1 000 lines	
Helsinki	7	7	7		2 500 stocks	

Hölttä-Vuori M, Salo VT, Ohsaki Y, Suster ML, Ikonen E. Alleviation of seipinopathy- related ER stress by triglyceride storage. Human Molecular Genetics 22:1157-1166, 2013.

Jõers P, Lewis S, Fukuoh A, Parhiala M, Ellilä S, Holt IJ, Jacobs HT (2013) Mitochondrial transcription terminator family members mTTF and mTerf5 have opposing roles in coordination of mtDNA synthesis PLoS Genet. 9, e1003800

Kemppainen KK, Rinne J, Sriram A, Lakanmaa M, Zeb A, Tuomela T, Popplestone A, Singh S, Sanz A, Rustin P, Jacobs HT (2013) Expression of alternative oxidase in Drosophila ameliorates diverse phenotypes due to cytochrome oxidase deficiency. Human Molecular Genetics, Doi: 10.1093

Matsuda S, Blanco J, Shimmi O. (2013) A feed-forward loop coupling extracellular BMP transport and morphogenesis in Drosophila wing. PLoS Genet. 9:e1003403

Reimer, M.M., Norris, A., Ohnmacht, J., Patani, R., Zhong, Z., Dias, T.B., Kuscha, V., Scott, A.L., Chen, Y.C., Rozov, S., Frazer, S.L., Wyatt, C., Higashijima, S.I., Patton, E.E., Panula, P., Chandran, S., Becker, T., Becker, C.G..: Dopamine from the Brain Promotes Spinal Motor Neuron Generation during Development and Adult Regeneration. Developmental Cell doi:10.1016/j.devcel.2013.04.012, 2013

Sundvik, M., Chen, Y.-C., Panula, P.: Dynamic regulation of zebrafish histaminergic neuron population and behavior by presenilin 1. J. Neuroscience 33: 1589-1597, 2013.

Turpeinen H, Oksanen A, Kivinen V, Oksanen A, Kukkurainen S, Uusimäki A, Rämet M, Parikka M, Hytönen V, Nykter M & Pesu M. Proprotein Convertase Subtilisin/Kexin Type 7 (PCSK7) is essential for the zebrafish development and bioavailability of Transforming Growth Factor Beta 1a (TGFβ1a). Journal of Biological Chemistry, 2013,288:36610-23.

Zhang W, Hietakangas V, Wee S, Lim SC, Gunaratne J, Cohen SM. (2013) ER stress potentiates insulin resistance through PERK-mediated FOXO phosphorylation. Genes Dev. 27:441-449

Tissue Engineered Disease Models (TEDM)

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

Members: Emmy Verschuren (FIMM) (co-chair); Jukka Westermarck (BioCity) (co-chair); Pipsa Saharinen (BCH); Sergey Kuznetsov (FIMM); Johanna Ivaska (BioCity); Petri Mäkinen (BCK)

www.biocenter.fi

LentiGEMM, an emerging technology platform, was established to develop methods and train researchers for use of lentiviral technologies in context of challenging *in vivo* tissue transductions. LentiGEMM was operational during 2010–2012. However, during the past five years, there has been an increasing interest in complex *ex vivo* models and transplantation-based tissue models of diseases as well as surge of chemical biology methods as tools to address different biological and biomedical questions. Therefore, in 2013, LentiGEMM extended and refocused its activities to meet the new demands from research community. The sequel of LentiGEMM is called The Tissue Engineered Disease Models (TEDM), which is a new emerging technology platform focusing on development of complex *ex vivo* and *in vivo* tissue models compatible with genetic and chemical biology approaches. The targeted tissues are mammary gland and lung epithelial organs, and vascular and lymphoid systems. Technology development will focus on systemic, intraductal, and orthotopic somatic cell-based transplantation methods using donor cells from GEMMs or human diseases, direct virus-mediated engineering of cells in animal tissues and ex vivo organoid surrogates. TEDM will restructure this fast developing technology area by bringing leading Finnish groups together to create significant synergy.

In Biocenter Finland, TEDM's focus complements existing virus, drug discovery and animal models networks. TEDM will strongly interact with the existing core facilities to create new rechargeable services for them. This model was already successful during the period 2010–2012, and given the increasing number of Finnish scientists working on complex biological models, we foresee a solid user base for new TEDM services.

PROTEOMICS AND METABOLOMICS

Proteomics and Metabolomics Infrastructure Network

Coordinator of the network: Garry Corthals, BioCity Turku

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

www.ProtMet.net and www.biocenter.fi

The Proteomics and Metabolomics network comprises two technology platforms, one in proteomics and protein characterization, and the other one in metabolomics. Together these platforms represent a large group of skilled researchers offering a diverse range of services, methodologies and applications covering all areas of life science. In establishing the network we embarked on an ambitious plan to link independently operating national service laboratories, combining experience and resources to offer a coordinated national technology platforms.

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.

Successful proteomics requires both expensive and constantly evolving infrastructures, and a critical mass of expertly trained personnel with skills covering the areas of biochemistry, biomedicine, chemistry and bioinformatics. Biocenter Finland protein and proteomics core facilities provide access to cutting-edge services and knowledge in mass spectrometry based proteomics and protein characterisation. We expect the protein-proteome platform to enable the scientific community to take a wide range of societal challenges of a biological and medical nature.

Metabolomics is a rapidly growing field of small molecule analytics, which has applications in different sectors of bio-, health-, and medical sciences. Wide range of metabolites in biofluids and tissues can be currently measured by using metabolomics platforms based on LC-MS, GC-MS or NMR. However, analysis of many important compounds is still challenging, which means that there is a need for major analytical method development in the field of metabolomics in the coming years. The metabolomics analytics within BF network have been welcomed with high interest in national and international scientific forum, which is evidenced by rapidly increasing customer base in each of the facilities.

Protein-Proteome 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

www.ProtMet.net and www.biocenter.fi/

Achievements in development of technology services during 2013

The Protein characterisation and Proteomics Network (PPN) of the ProtMet infrastructure is a network of facilities focusing on the application and development of research services and training at the national level. In 2013 the network continued its strategy to develop and provide cutting-edge protein research services nationally through the strategic implementation of instrumentation, attract and retain highly skilled personnel, develop services through collaborative research projects, and to hold numerous regional and national courses, workshops and scientific meetings. The overriding objective was and is to ensure and enable the wide and appropriate use of services in protein-based life scientific research. The supranational coordination of has resulted in nation-wide access to cutting-edge services in proteomics such as quantitative proteomics, PTM analysis, pathway analysis and a unique spectrum of requested protein characterisation tools.

Overall picture

The successful provision of high quality services has been a key goal for the infrastructure and was maintained on several fronts. First, the consortium continued its web portal that displays information about the services in proteomics (and metabolomics) within the ProtMet network. Furthermore it contains information on activities related to entire network, such as courses, workshops, training and other relevant news, such as new instrument purchases. In such, it has provided a rich source of information and has acted as a one-stop 'front office' for new researchers to the facility and existing customers. Second, a closer collaboration between the individual facilities has resulted in the building of a national capacity for specific 'high

demand' services. Turku and Helsinki have specifically focused on proteome-based services, whereas the facilities in Tampere and Oulu have further developed their support for services in protein characterisation. Furthermore, the unique services in 2-DE for Oulu and a protein production facility in Tampere have been maintained and services have grown in these areas as well. According to this national division of services several highlights achieved are worth mentioning. For example, for the most sought after applications including proteome-wide identification and quantitation is now also available in both Helsinki facilities, in addition to existing service in Turku. Due to this high demand of services users now experience similar analytical performance in both Helsinki and Turku facilities. Additionally the time between data requests and data acquisition has been significantly shortened. To achieve this, the role of re-training and education in method development has been critical.

Nationwide survey

The ProtMet eagerly took part in and encouraged the BF nationwide survey. Participation in the survey was high, indicating the level of activity and interest in the ProtMet services and training. The survey was in many ways useful for the network as it obliged both interested customers and facility staff to evaluate key areas of operation related to our services. In the first instance it showed how well the facility was operating: overall the network enjoyed very high scores with an average positive rating of 4.2 out of 5. An important achievement we took from the survey was that our staff support and responsiveness were highly rated, and that both access to the service and the quality of service both scored high. Key metrics for the successful operation of the facilities within our infrastructure were to perform analysis in a systematic, accurate and reproducible manner. Overall we conclude that this has been achieved. The overall lowest scoring in the survey was the price of the services, for which little can be done without further financial stimulus, as the facilities run under University directives and are run on a full cost model.

It should be noted that the network also experienced setbacks, and has solved these now. In particular three facilities had problems with either inadequate or inoperable mass spectrometers. After negotiations with instrument vendors the MS instruments were either replaced (Turku) and upgraded (Helsinki) or repaired (Helsinki) by the vendors. By the end 2013 all MS instruments acquired through BF funding were in full operation.

Ongoing developments for the network

As stated in our plan for 2014–2016 the facilities have undergone development and we have identified key and emerging areas where all Finnish facilities need to further develop in line with emerging trends and requests from leading research groups and consortia. Whilst the network initially sought to provide technologies for the identification and quantitation of proteins, recently the field has grown and diversified to enable the analysis of interaction networks. The new goals and subsequent developments that now must take place require capacities to analyse at speed and in depth any given biological system and characterise any protein interaction network, or trace its quantitative profile. Complementary tools for measuring specific protein interactions in high-throughput fashion are also provided to quantitate binding affinities and binding kinetics. This is also enabled by support in protein production.

User statistics 2013

For the fourth year in a row a significant growth for the network was witnessed: A 21% rise in the total number of services to research groups rose from 153 to an additional 32 groups (185). Services covered a wide range of expertise ranging from various types of mass spectrometric analysis to detailed protein characterisation services to gel separations and protein production. The increased research activity with an emphasis on protein-focused research can be attributed to the successful integration of the network into the national scientific skill-base and the continued growth in research funding in this field. More researchers are asking specif-ic questions about biological phenomena that require a both a rise in services and new sophisticated tools in proteomics. In mass spectrometry alone there was a 22% increase in the number of user hours from approximately ~11,700 to ~14,300 hrs. As occurred last year, the Facilities reported many new instrument installations but also, unfortunately, significant long services breaks, together lowering the number of months in operation of new and repaired instrumentation. Nevertheless, the new services developed and made available through ongoing training and dissemination by our Facilities, together with the deployment of new instrumentation continues to impact on Finnish sciences.

Participation in international, Nordic and European infrastructures

The network is involved in various national Centre's of Excellence, three FiDiPro, several Academy of Finland Professorships as well as national and international funding (FP7 and COST actions), and importantly underpins our best young research talents in the ERC

User statistics 2013

	BCH Helsinki	BI Helsinki	BCO Oulu	BMT Tampere	CBT Turku
Total number of research groups*	41	53	37	25	29
Total number of non-academic groups/units	3	2	2	3	3
Local research groups*	29	40	26	8	24
Domestic research groups*	6	8	4	22	5
International research groups*	6	5	5	3	0
Volume of services (instrument time in h)	5887 h Mass spec: 5687 h[a, b] Gels: 73, 200 h[c]	3635 h Mass spec: 3240 h[a] N-seq: 395 h[b]	6078 h Gels: 2628 h[a] MS: 1200 h[b] Protein characterization: 2250 h[c]	3490 h Protein production: 1050 h[a] Protein characterization: 2440 h[b]	3817 h Mass spec: 3817 h
Specifications					
* Research groups (or other customers) who have used the services. ** For proteomics, only MS instrument times recorded; Sample preparation and IT-services, peptide- and protein purification not included. *** For protein production and characterization, experiment design, service coordination and data analysis are not recorded except for non-academic groups.	[a] Mass spectrometry** MALDI-Tof/Tof 550 h Q-Tof 2190 h IonTrap 300 h [b] MS glycoproteomics** Q-Tof 2647 h [c] 2-DE gel-based proteomics 73 gels 200 h	[a] Mass spectrometry** LTQ-Orbitrap Elite 3200 h MALDI-Tof/Tof 40 h [b] Edman sequencing 395 h	[a] 353 2D gels: 2628 h [b] MS h (Ultraflex, Synapt): 1200 [c] ITC 570 h CD: 576 h Biacore: 1104 h	[a] Protein production*** Fermentor (expression) 150 h ÄKTA (preparation) 900 h [b] Protein characterization *** BLI 330 h DSC 1450 h ITC 30 h Spectrofluorometer 630 h	Mass spectrometry** LQT-Orbitrap Velos: 1399 h Q-Exactive: 1795 h QSTAR Elite: 181 h TSQ Vantage: 442 h

programs and various privately funding organisations such as the Sigrid Jusélius and the Finnish Cancer Foundations. The network is currently also engaged in future activities of the ESFRI ISBE, by heading one of the WPs, and is involved in the consultation of proteomics for Horizon2020.

Major publications resulting from the Platform services

Kummu O, Turunen SP, Prus P, Lehtimäki J, Veneskoski M, Wang C, Hörkkö S. Human monoclonal Fab and human plasma antibodies to carbamylepitopes cross-react with malondialdehyde-adducts. Immunology 2013, 141, 416–430. - *Biophysical protein analysis*

Szambowska A, Tessmer I, Kursula P, Usskilat C, Prus P, Pospiech H, Grosse F. DNA binding properties of human Cdc45 suggest a function as molecular wedge for DNA un-winding. Nucleic Acids Res. 2014 Feb;42(4):2308-19. - *Biophysical protein analysis*

Anantharajan J, Koski MK, Kursula, P, Hieta R, Bergmann U, Myllyharju J, Wierenga RK.The Structural Motifs for Substrate Binding and Dimerization of the α Subunit of Collagen Prolyl 4-Hydroxylase. Structure 2013, 2107-2118. - *Mass spectrometry*

Lehtonen MT, Takikawa Y, Rönnholm G, Akita M, Kalkkinen N, Ahola-Iivarinen E, So-mervuo P, Varjosalo M, Valkonen JP. Protein secretome of moss plants (*Physcomitrella patens*) with emphasis on changes induced by a fungal elicitor. J Proteome Res. 2014 Feb 7;13(2):447-59. - *Proteome-wide analysis (MS) of the moss secretome.*

Scifo E, Szwajda A, Dębski J, Uusi-Rauva K, Kesti T, Dadlez M, Gingras AC, Tyynelä J, Baumann MH, Jalanko A, Lalowski M. Drafting the CLN3 protein interactome in SH-SY5Y human neuroblastoma cells: a label-free quantitative proteomics approach. J Proteome Res. 2013 May 3;12(5):2101-15. - *Mass spectrometry analysis performed and interactomics experiments.*

Tamminen JA, Parviainen V, Rönty M, Wohl AP, Murray L, Joenväärä S, Varjosalo M, Leppäranta O, Ritvos O, Sengle G, Renkonen R, Myllärniemi M, Koli K. Gremlin-1 asso-ciates with fibrillin microfibrils in vivo and regulates mesothelioma cell survival through transcription factor slug. Oncogenesis. 2013 Aug 26;2:e66. - *Mass spectrometry based glycoproteomics.*

Talin-bound NPLY motif recruits integrin-signaling adapters to regulate cell spreading and mechanosensing. Pinon P, Pärssinen J, Vazquez P, Bachmann M, Rahikainen R, Jacquier MC, Azizi L, Määttä JA, Bastmeyer M, Hytönen VP, Wehrle-Haller B. J. Cell Biol. In press. - *Protein production, interaction analyses by Biolayer interferometry.*

Kinetics of bioconjugate nanoparticle label binding in a sandwich-type immunoassay. Näreoja T, Ebner A, Gruber HJ, Taskinen B, Kienberger F, Hänninen PE, Hytönen VP, Hinterdorfer P, Härmä H. Anal Bioanal Chem. 2014 Jan;406(2):493-503. - *Interaction analyses Biolayer interferometry.*

Kannaste O, Suomi T, Salmi J, Uusipaikka E, Nevalainen O, Corthals GL. Cross-correlation of spectral count ranking to validate quantitative proteome measurements. J Proteome Res. 2014 Mar 10. - *All Mass spectrometry and development of new label-free quantitative analysis pipeline.*

Sjöqvist M, Antfolk D, Ferraris S, Rraklli V, Haga C, Antila C, Mutvei A, Imanishi SY, Holmberg J, Jin S, Eriksson JE, Lendahl U, Sahlgren C. PKCζ regulates Notch receptor routing and activity in a Notch signaling-dependent manner. Cell Res. 2014 Apr;24(4):433-50. - *All Mass spectrometry and phosphorylation analysis.*

Metabolomics Technology Platform

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

www.biocenter.fi

Achievements in development of technology services during 2013

Three units of the BF metabolomics consortium have all been intensively functioning during 2013 and the consortium holds logic, complementary niche within the field as evidenced by the high number of samples analyzed in each unit. BCK focuses on large-scale non-targeted profiling with LC-MS, FIMM on high-throughput targeted quantitative LC-MS metabolomics, and BCH on plant metabolite analyses with LC- and GC-MS approaches.

BCK unit has performed non-targeted profiling analyses on various sample types extending from plasma to food products, and has revealed metabolite level alterations in all the studies. The dual column approach (hilic and RP) has proven very powerful enabling concomitant monitoring of the levels of thousands of metabolic features in practically any biomaterial.

BCH unit focuses on plant metabolites, but due to growing demand of analytical services at Viikki, BCH services have been extended to different biological sample types including biofluids (serum, plasma and cell cultures) and tissues (muscle and liver) from both human and mouse origin. The analyses have been done using either UPLC-qTOF-MS funded by BF or GC-MS/MS funded by UH infrastructure funds. Both equipment have been operational most of the year and have been used full time for analytical services and methods development. Windows 7 update has forced to update also the equipment software, causing extra costs for the unit and made small pauses to the services. Last few years BCH unit has been responsible for metabolomics and proteomics-part at the Masters level Genomes course.

The year 2013 was the first year of providing services in full swing in the FIMM unit. FIMM was able to set up customer base and finished 16 projects (1000 samples) and also participated in research activities, where FIMM was involved in analyzing the results together with the principal investigator of the project and contributed in writing the publications as well. For the last few years, FIMM unit has been teaching "Basics in Clinical Proteomics and Metabolomics" as part of the Masters level Translational Medicine course.

All the units received high scores in the BF-user survey: BCK: 4.50; FIMM: 3.76; and BCH: 3.96. The feedback based on the survey has been useful for the improvement of services, for example for FIMM unit one of the suggestions was that the metabolome coverage could be broader; FIMM took this positive suggestion into account and is developing targeted method for quantification of 45 acylcarnitines (under validation).

Key bottlenecks are identified both in personnel resources, as well as in instrumentation. For example, the non-targeted profiling analyses in BCK are carried out in a manner that the sample preparation, analytical runs, and raw data collection have been performed at the facility, followed by collaborative work on the data analysis between the coordinator together with scientist responsible for the study. However, the metabolomics data analysis including statistical evaluation and metabolite identification is a demanding scientific task, and it is clear that the supervision from the unit should be more intensive to ensure that the project is carried out efficiently all the way to interpretation and publication of the results. This is the major bottleneck for the services, and results from the fact that there is no dedicated full-time personnel due to lack of funds. Due to long waiting time (>6 months) two industrial customers have withdrawn their samples. Partial salaries for technical personnel and coordinator have been covered solely based on the user fees and the BF-linked support from the university, but no positions have been funded by UEF, in contrary to for example FIMM, where the lab coordinator position is partially funded by FIMM. Similarly, in BCH the major bottleneck in the analysis is inadequate personnel, the number of services has been stayed the same during last two years due to limited number of staff.

FIMM received feedback from BF survey about long waiting time. Being a new and small unit, FIMM needs to take care of development and validation of the analytical methods along with getting customer projects, providing services including regular maintenance of the unit, and analyzing the data and documentation until publishing the results. Thus providing a quick service is not always an easy task with limited human resources.

The BCK and BCH units operate at the moment with one qTOF-MS instrument for the metabolite profiling services. At BCK the same instrument is used for the MS/MS analyses for the structural elucidation of the biomarker candidates, as well as for any adjustments, optimizations and tests for analytical conditions. At the BCH all the analysis are performed by qTOF-MS even though for the routine (hormone) analysis a QQQ-instrument would fit much better. FIMM has only one QQQ-instrument, which is used for providing services, developing and validating analytical methods, regular maintenance and also for opti-

misation of protocols for different samples.

Limited number of human resources and instruments cause long waiting periods for all the units, and if there is down time due to instrument malfunction, it will inevitably delay analysis.

User statistics 2013

Metabolomics consortium user base and income in 2013.

	Units			
Users	BCK	FIMM	BCH	Total
Campus	7	10	11	28
National	1	3	2	6
International	8	3	2	13
Total no. of projects	16	16	15	47
Service income (eur)	46 320	102 236	30 650	179 206
Total no. of samples	1 400	1 000	1 900	4 300

Since the onset of the services at BCK five full research papers have been published based on the results obtained with the non-targeted metabolite profiling services, and five papers have been submitted or are under revision, together with several manuscripts in preparation. The results have been presented in several scientific meetings.

FIMM unit has one article accepted for publication; second one is under revision and several others in pipeline.

Eight publications from BCH unit were submitted (7 published, 1 under review) during year 2013 out of the performed metabolite analysis.

Participation in international, Nordic and European infrastructures

The BF metabolomics consortium is not part of any European infrastructures. Instead, all units have international collaborative projects where the facility services have been used.

Future perspectives

The BCK metabolomics unit will expand the services within the targeted quantitative analyses of biomarker molecules found in the non-targeted profiling assays and a QQQ-MS instrument is being purchased during 2014. Also, for the reasons mentioned under "bottlenecks", new qTOF-MS instrument that will be dedicated solely for the analytical runs of the true sample sequences needs to be purchased.

BCH has streamlined its services, including an increase in technical personnel funded by the Department of Biosciences, University of Helsinki, focused on plant secondary metabolites. There is, however, a dramatic increase in the demand of particularly targeted quantitative analysis of plant primary and secondary metabolites such as hormones, phenolics, flavonoids and waxes that has created a serious bottle neck with long waiting times for the high throughput analytical services. This situation will be drastically accentuated by the establishment of the National Plant Phenotyping Infrastructure (NaPPI; part of the current national infrastructure roadmap) in Viikki by the end of next year, which will create a very substantial increase in the demand of plant metabolic services. This will require a substantial increase in the capacity of our metabolic analysis services and these demands clearly necessitate urgent purchase of a high end QQQ-MS, which is best suited for such high throughput targeted analysis. Future development of the BCH analysis capacity (2015-) involves ambient MS techniques such as DESI, LAESI or DAPPI that provide direct analysis of analytes form biological surfaces such as plants without any sample preparation.

Currently FIMM offers services in polar metabolite quantifications. There is a pressing need to have global lipidomics facility as soon as possible for biomedical applications as the Metabolomics facility at VTT has been shut down a couple of months ago. There is no laboratory in Finland that can provide global non-polar metabolomics analyses to academic groups for a low price. Most of the current academic customers are utilizing this service from abroad, which is not always easy. For this purpose, FIMM would need a QToF instrument. FIMM had applied for this instrument in FIRI2013 call but couldn't get it and is trying again in FIRI2014 call, hoping to establish a global lipidomics platform soon to serve Finnish and international academic community.

Major publications resulting from the Platform services

Hanhineva K, Pedret A, Lankinen M, Schwab U, Kolehmainen M, Paananen J, De Mello V, Sola R, Lehtonen M, Poutanen K, Uusitupa M, Mykkänen H: Non- targeted metabolite profiling discriminates diet-specific biomarkers for consumption of whole grains, fatty fish and bilberries – a randomized trial (Sysdimet). In revision in the American Journal of Clinical Nutrition. - *Non-targeted LC-MS work conducted at the BCK unit.*

Hanhineva K, Keski-Rahkonen P, Lappi J, Pekkinen J, Savolainen O, Mykkänen H, Poutanen K: Benzoxazinoid-derived phenylacetamide-sulfates are among the most discriminative post-prandial plasma markers after rye bread consumption. In revision in the Journal of Nutrition. - *Non-targeted LC-MS work conducted at the BCK unit.*

Bondia-Pons I., Savolainen O, Torronen R, Martinez JA, Poutanen K, Hanhineva K (2014) Metabolic profiling of Goji berry extracts for discrimination of geographical origin by non-targeted liquid chromatography coupled to quadrupole time-of-flight mass spectrometry. Food Res. Int. In press. - *Non- targeted LC-MS work conducted at the BCK unit.*

Pekkinen J, Rosa N, Savolainen O, Mykkänen H, Poutanen K, Micard V,

Hanhineva K (2014) Wheat aleurone processing changes the urinary metabolite profile of mice fed a high-fat diet. Nutr. Metab. 11:1. *-Non-targeted LC-MS work conducted at the BCK unit.*

Nahid A Khan, Mari Auranen, Ilse Paetau, Eija Pirinen, Liliya Euro, Saara Forsström, Lotta Pasila, Vidya Velagapudi, Christopher J Carroll, Johan Auwerx, and Anu Suomalainen (2014). Effective Treatment of Mitochondrial Myopathy by Nicotinamide Riboside, a Vitamin-B3. EMBO Molecular Medicine (In press). - *This work includes quantitative analysis of polar metabolites at FIMM Unit.*

L.O. Morales, M. Brosché, J. Vainonen, N. Sipari, A.V. Lindfors, Å. Strid, and P.J. Aphalo. Are solar UV-B- and UV-A-dependent gene expression and metabolite accumulation in Arabidopsis mediated by the stress response regulator RADICAL CELL DEATH1? Plant, Cell and Environment (2013) In press. - *This work includes analysis of flavonoids and organic acids in Arabidopsis by UPLC-MS.*

Morales Suarez, L. O. , Brosché, M. , Vainonen, J. , Jenkins, G. I. , Wargent, J. J. , Sipari, N. , Strid, A. , Lindfors, A. V. , Tegelberg, R. and Aphalo, P. J. (2013) Multiple Roles for UV RESISTANCE LOCUS 8 in Regulating Gene Expression and Metabolite Accumulation in Arabidopsis under Solar UV Radiation. Plant Physiology 161 (2013) 744-759. - *This work includes analysis of flavonoids and organic acids in Arabidopsis by UPLC-MS.*

Li JZ, Besseau S, Sipari N, Törönen P, Holm L and Palva ET (2013) Defense related transcription factors WRKY70 and WRKY54 control stomatal aperture and osmotic stress tolerance in plants. New Phytologist 200 (2013) 457–472. - *This work includes analysis of plant hormones by GC-MS.*

M. Brosche, T. Blomster, J. Salojärvi, Fuqiang Cui, N. Sipari, J. Leppälä, A.Lamminmäki, G. Tomai, S. Narayanasamy, R. Reddy, M. Keinänen, K. Overmyer and J. Kangasjärvi. Transcriptomics and Functional Genomics of ROS-Induced Cell Death Regulation by RADICAL-INDUCED CELL DEATH1. PLOS Genetics (2014) 10 (2) 1-16. - *This work includes analysis of plant hormones by GC-MS.*

K. Karppinen, E. Hirvelä, T. Nevala, N. Sipari, M. Suokas and L. Jaakola. Changes in the abscisic acid levels and related gene expression during fruit development and ripening in bilberry (Vaccinium myrtillus L.). Phytochemistry 95 (2013) 127-134. - *This work includes analysis of plant hormones by UPLC-ESI-MS.*

F. Cui, M. Brosché, N. Sipari, S.Tang and K. Overmyer. Regulation of ABA dependent wound induced 1 spreading cell death by MYB108. New Phytologist (2013) rapid report 1-7. - *This work includes analysis of plant hormones by UPLC- ESI-MS.*

S.M. Siipola, T. Kotilainen, N. Sipari, L.O. Morales, A.V. Lindfors, T.M. Robson, and P.J. Aphalo. Epidermal UV screening and whole-leaf flavonoid composition respond more to solar blue than solar UV radiation. Plant Cell and Environment (2013) submitted. - *This work includes analysis of flavonoids and organic acids in Arabidopsis by UPLC-MS.*

Pasanen, M., Laurila, J., Brader, G., Palva, E. T., Ahola, V., van der Wolf, J., Hannukkala, A. & Pirhonen, M. (2013) Characterisation of Pectobacterium wasabiae and Pectobacterium carotovorum subsp. carotovorum isolates from diseased potato plants in Finland. Annals of Appl Biol. 163, 403–419. - *MS analysis of microbial homoserine lactone signal molecules*

STEM CELLS AND BIOMATERIALS

Stem Cells and Biomaterials Infrastructure Network

Coordinator of the network: Timo Otonkoski, BCH
Members: Katriina Aalto-Setälä, BMT; Ulla Pirvola, BI; Mikko Lammi, BCK; Seppo Vainio, BCO; Olli Lassila, BioCity Turku

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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 into development of 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.

Stem Cells and Biomaterials Technology Platform

Chair of the consortium: Timo Otonkoski, BCH, Biomedicum Stem Cell Center (BSCC)
Members: Katriina Aalto-Setälä, BMT; Marjo Yliperttula, Faculty of Pharmacy, University of Helsinki, Viikki Facility; Jari Koistinaho, BCK, Stem Cell Center

www.biocenter.fi

Achievements in development of technology services during 2013

Since the Ministry of Education funding to BF platforms ended at the end of 2012, the support provided to platform partners through their own universities became disparate. This made the development of coordinated services difficult. Also, the lack of any designated coordination budget for the platform meant that joint meetings were discontinued. Each partner continued the development of their services in their own areas. The emphasis was in iPS cell based approaches for disease modelling and in the development of the technologies needed for larger scale biobanking activities.

Financial support from the University of Helsinki to BCH enabled the continuation of the patient iPS cell derivation service, developed during the previous three years. In addition, the technologies were actively developed, following the rapid development of the field. Particular areas of emphasis are: (i) chemical reprogramming without genetic manipulation; (ii) genetic integrity during reprogramming (iii) development of automated methods for the early isolation of reprogrammed cells and (iv) genome editing of the stem cells. All of these topics are of utmost importance for the scaling up of the services to allow large scale cellular biobanking activities. Several improved methods will soon be ready to be provided as Core Facility services for clients.

Financial support from the University of Tampere to BMT was sufficient to maintain patient iPS cell derivation service with current methods but did not allow further optimization for the technology. The main interest of customers has still been on control iPS cell lines for differentiation analysis. Additionally, an increasing interest of customers was to obtain differentiated cells and for assays analyzing the functionality of the cells (cardiomyocytes, neuronal cells, hepatocytes, endothelial). With current funding these services are only partially possible to fulfil.

In BCK the host university funding was not sufficient for maintaining services to produce iPSC lines. The nationwide BF user survey and also the feedback from laboratories abroad in spring 2013 was encouraging for BCK and confirmed that the quality and the time lines for producing iPSC lines was excellent during the previous years. The equipment and facilities for producing iPSC lines have remained excellent. However, a major need is in providing high-quality differentiation of iPSC-derived lines as well as their characterization. For these purposes the lack of appropriate technologies/equipment has been a limiting factor.

Viikki facility did not obtain any funds from the University of Helsinki to support the biomaterial services in 2013. Consequently, there were only few services provided under the BF umbrella in 2013 by this partner.

User statistics 2013

Overall, the service activities remained of the platform remained at roughly the same level as compared with 2012 in BCH and BMT, whereas the service activities of BCK and BCH/BI were significantly decreased. BCH produced 45 iPSC lines for 5 clients in 2013 and provided training in pluripotent stem cell methods to 24 individuals at courses and 8 individuals through hands-on training. BMT obtained twenty new patient samples during 2013 and the total number of iPS cells lines produced during 2013 was 63. BCK provided services only for one international research group: 3 patients, 5 lines from each donor produced. BCH/Bihas organized the "Biomaterials interactions with cells" course, passed by 23 students from various faculties of the University of Helsinki. Detailed user statistics are provided in the table.

Participation in international, Nordic and European infrastructures

BCH (Otonkoski) is a partner in one EU (FP7) funded consortium (BETACURE) with a role in the development of iPSC-based models for pancreatic beta-cell hyperfunction and imaging. UEF (Koistinaho) is a partner in two EU-funded consortia (ERANET PROTEA; Neuroinflammation Marie Curie ITN program) proving iPSC-derived models for the projects. BMT (Aalto-Setälä) is a partner in two EU-funded consortia

Table. Stem cells and biomaterials technology platform user statistics 2013.

Stem cell services provided	iPSC lines		Teaching (courses)		Hands-on training		Teratoma		Cell-IQ imaging		Electro-physiology	
	2013	Total 2010-2013	2013	Total 2010-2013	2013	Total 2010-2013	2013	Total 2010-2013	2013	Total 2010-2013	2013	Total 2010-2013
BSCC, University of Helsinki												
Number of customers	5	21	24	80	8	25	2	11	6			0
Academic	5	20	24	80	8	20	1	10	6			0
Non-academic	0	1	0	0	0	5	1	1	0			0
Volume	45[a]	224	24[b]	80	8[b]	25	21[c]	110	2819[d]	15651		0
Turnover	2013: 37 840 EUR (2012 41 632 EUR; 2010 7 788 EUR; 2011 27 865 EUR)											
BMT, University of Tampere												
Number of customers	9	29	0	35							2	2
Academic	7	20	0	35							1	1
Non-academic	2	9	0	0							1	1
Volume	63	143	0	35							7	9
Turnover	2013 9 000 EUR (2012 8 520 EUR ;2010 10 000 EUR; 2011 14 000 EUR)											
University of Eastern Finland												
Number of customers	1	10	0	64	0	6	0	2	0	3	0	4
Academic	1	9	0	62	0	6	0	2	0	3	0	4
Non-academic	0	1	0	2	0	0	0	0	0	0	0	0
Volume		41[a]	0	64[b]	0	6[b]	0	3[c]	0	40[d]	0	4[b]
Turnover	2013 3 000 EUR (2012 9 500 EUR; 2011 6 000 EUR)											

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

(Risky-CAD and Atero-Flux) providing iPSC-based models for atherosclerosis studies.

Future perspectives

While generation iPSC lines is becoming a routine technology, it still requires special expertise, experience and facilities. At the same time, know-how and technology development for differentiating cells to true models of human cells and tissues is becoming a bottleneck for taking the full advantage of iPSC methodology. Therefore, the BF Stem cell platform services need to focus more on technologies of differentiation and functional analysis of the differentiated iPSCs. BCH focuses mainly on endodermal differentiation to derive functional hepatocytes and pancreatic islet cells. BMT focuses on the differentiation of cardiomyocytes as well as retinal pigment epithelial cells and neurons. The emphasis of stem cell services of BCK is towards neural and muscular cells and diseases.

The iPS cells are ideal cells for biobanking purposes because of their unlimited growth capacity and potential to generate other cell types. Therefore, one area of emphasis needs to be in developing coordinated programs to add the banking of iPS cells in current Finnish biobanking initiatives. The BF Stem Cell Platform should play an instrumental role in this.

Due to the challenges in obtaining fully functional and mature cells from pluripotent stem cells, an increasingly important trend in this field is the direct reprogramming (i.e. transdifferentiation) of somatic cells into functional cells and their expandable progenitors. Therefore, one area of focus at BCH will be the development of direct reprogramming approaches for the generation of endodermal progenitors which could be used as a reliable source for hepatocytes, pancreatic islet cells and intestinal cells. Direct differentiation of mature cells into cardiomyocytes will be a focus of BMT in collaboration with both national and international collaborators. Other cell types could also be a target in the future. Transdifferentiation of neuronal cells is pursued by BCK.

New nanofibrillar cellulose based material has been developed for the use in 3D SC culture and the method to release the spheroids from the biomaterial were developed. The material is still available via BCH/BI.

Major publications resulting from the Platform services

Hämäläinen RH, Manninen T, Koivumäki H, Otonkoski T, Suomalainen A: iPS-derived heteroplasmic human tissues with mtDNA MELAS-A3243G disease mutation. Proc Natl Acad Sci U S A. 2013; 110:E3622-30. - *MELAS patient iPS cell lines derived at BCH were used to elucidate the mechanisms of tissue heterogeneity in pathologies caused by mitochondrial mutations*

Kärkkäinen V, Pomeshchik Y, Savchenko E, Dhungana H, Kurronen A, Lehtonen S, Naumenko N, Tavi P, Levonen AL,Yamamoto M, Malm T, Magga J, Kanninen KM, Koistinaho J. Nrf2 regulates neurogenesis and protects neural cells against Aβ toxicity. Stem Cells, in press. - *Novel tests for investigating neurogenesis on stem cells directed to neural cells were set up and an effect of gene transfer as well Alzheimer pathology was tested on these models*

Lou YR, Kanninen L, Kuisma T, Niklander J, Noon LA, Burks D, Urtti A, Yliperttula M.: The use of nanofibrillar cellulose hydrogel as a flexible three-dimensional model to culture human pluripotent stem cells. Stem Cells Dev. 2014 Feb 15;23(4):380-92. - *New biomaterial optimized for 3D stem cell culture.*

Mikhailova, A., Ilmarinen, T., Uusitalo, H., Skottman, H. Small molecule induction promotes corneal epithelium cell differentiation from human induced pluripotent stem cells. Stem Cell Reports, 2014. Feb 6;2(2):219-31. - *Control iPS cell lines were successfully differentiated towards limbal stem cell type cells and future towards corneal epithelial like cells.*

Mikkola M, Toivonen S, Tamminen K, Alfthan K, Tuuri T, Satomaa T, Natunen J, Saarinen J, Tiittanen M, Lampinen M, Valmu L, Partanen J, Otonkoski T: Lectin from Erythrina cristagalli supports undifferentiated growth and differentiation of human pluripotent stem cells. Stem Cells Dev 2013;22:707-716. - *A novel defined matrix developed for hESC and hiPSC.*

Noisa P, Lund C, Kanduri K, Lund R, Lähdesmäki H, Lahesmaa R, Lundin K, Chokechuwattanalert H, Otonkoski T, Tuuri T, Raivio T: Notch signaling regulates neural crest differentiation from human pluripotent stem cells. J Cell Sci. 2014 Feb 25. - *An efficient protocol developed for pre-migratory neural crest differentiation of hESC and hiPSC.*

Pradhapan, P., Kuusela, J., Viik, J., Aalto-Setälä, K. and Hyttinen J. Cardio Drug Analysis Software (CardioDAS) – A novel field potential data analysis software for pluripotent stem cell derived cardiomyocytes PLoS One 2013 Sep 19;8(9):e73637. doi: 10.1371/journal.pone.0073637. - *An automated assay to analyze electrical properties of iPSC derived cardiomyocytes*

Puttonen KA, Ruponen M, Kauppinen R, Wojciechowski S, Hovatta O, Koistinaho J. Improved method of producing human neural progenitor cells of high purity and in large quantities from pluripotent stem cells for transplantation studies. Cell Transplant. 2013; 22:1753-66. - *A novel model for a large-sclae production of neural stem cells suitable for transplantation was developed.*

Qu C, Puttonen KA, Lindeberg H, Ruponen M, Hovatta O, Koistinaho J, Lammi MJ. Chondrogenic differentiation of human pluripotent stem cells in chondrocyte co-culture. Int J Biochem Cell Biol. 2013;45:1802-12. - *A method of inducing speficic chondrogenic differentiation by using co-culture of hESCs or hiPSCs with primary chondrocytes was developed.*

Toivonen S, Ojala M, Hyysalo A, Ilmarinen T, Rajala K, Pekkanen-Mattila M, Äänismaa R, Lundin K, Palgi J, Weltner J, Trokovic R, Silvennoinen O, Skottman H, Narkilahti S, Aalto-Setälä K, Otonkoski T: Comparative analysis of targeted differentiation of hiPSC and hESC reveals variability associated with incomplete transgene silencing in retrovirally derived hiPSC lines. Stem Cells Transl Med, 2013; 2:83-93. - *The variability between human iPSC lines and its association with transgene silencing was studied in collaboration between BCH and BMT.*

STRUCTURAL BIOLOGY

Structural Biology Infrastructure Network (BFSB)

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

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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. The BFSB activities are continuously aimed at ensuring good facilities for these powerful but expensive technologies. The research activities of the BFSB units are of major importance for the expert teaching and training activities of the next generation of Finnish structural biologists as also highlighted in the annual reports of the respective platforms. In addition it fosters the development of structure based biotech activities.

Many of the BFSB research groups interact with the European structural biology networks, like Biostruct-X and Instruct. Consequently, the BFSB research groups have jointly written an application to become recognized as an Instruct National Affiliate Centre (Instruct-NAC). In February 2013 this application has been approved by the Instruct-council. Simultaneously, the FIRI committee of the Academy of Finland has provided the funding for Finland to join Instruct. This will open the much needed funded access to many expert technologies in Europe, as nicely documented on the Instruct-WWW pages. Negotiations to implement Finland officially joining Instruct are under way. In general being an Instruct-NAC will help in building the BFSB units further into a coherent and well-funded research community. It will also provide the Finnish life science community with good access to the impressive expertise for structural biology research in the EU, ranging from biocomputational and molecular biology techniques to the large scale facilities for example for EM, NMR and X-ray data collection.

This BFSB 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 BFSB 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.

In addition to X-ray crystallography and NMR and mass spectrometry technology platforms BF has funded protein service for biophysical and structural characterization since 2012.

NMR Spectroscopy and Mass Spectrometry Technology Platform

Chair of the consortium: Perttu Permi, BI, Finnish Biological NMR Center (FBNMR)
Member: Juha Rouvinen, BCK, High-resolution Mass Spectrometry Facility

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Achievements in development of technology services during 2013

Major refurbishment of the Finnish Biological NMR Center (FBNMR) instrumentation will be completed during the summer 2014. In March 2014, one of the 600 MHz spectrometers in the Center was upgraded to the Bruker Avance III HD NMR console with three RF channels and integrated NMR "thermometer" which minimizes problems associated with sample heating effects due to RF radiation. The 600 MHz spectrometer will also be equipped with the latest cryo-cooled probe technology i.e. $^{1}H\{^{13}C,^{15}N\}$ TXI cryoprobehead. These upgrades offer significant sensitivity improvement in attainable signal-to-noise ratio as well as minimize problems associated with aging electronics in a 15 years old NMR console. The new system has been operative since March 2014. Upgrade of the NMR Center instrumentation will be finalized in August 2014 as the first 850 MHz NMR spectrometer in Finland will be installed to the premises of FBNMR. Although the magnetic field strength corresponds to 20 T, the advanced shielding technology utilized in the system enables housing the magnet in the NMR Center. The new

850 MHz system is equipped with the similar Bruker Avance III HD NMR console and inverse detected $^{1}H,\{^{13}C,^{15}N\}$ cryoprobe. The 850 MHz spectrometer will then provide the highest signal-to-noise ratio and resolution available for biological samples in Finland.

In terms of user service, the NMR Centre has been fully operational during 2013. In the NMR service development emphasis has been put especially on dynamical systems i.e. proteins that either lack a well-defined three-dimensional structure (intrinsically disordered proteins) or display elevated dynamics between structural domains, or interact transiently with their binding partners. It is evident that the research community is becoming more aware of highly dynamic nature of functional proteins as vast majority of our customers approach us with proteins that can be characterized as intrinsically disordered. In 2013, several projects were initiated where NMR is employed together with X-ray crystallography, small-angle X-ray scattering or other biophysical methods in an integrative manner to solve more challenging molecular targets.

The high-resolution FTICR mass spectrometry facility has been fully operational except a 2.5-month break in May-July when the instrument was relocated because of the total renovation of the departmental building. In January 2014, the instrument was moved back to the original room. There was an increase in the number of groups and projects which used the facility as compared to the last year. We were finally able to install online nano/micro-LC system in Autumn. The system now al-lows analysis of complicated mixtures from very low concentrations/sample volumes. In addition, the usage of a new ionization robot (Triversa Nanomate) has been developed and now it is possible to measure automatically up to 384 samples overnight. This is a useful option, for example, in direct ligand screening. In addition, in parallel TEKES project we have developed IgG antibody analytics, especially direct amino acid sequencing of a protein, and automated ligand screening of proteins using a small molecule library of 400 compounds. The installation of a direct surface sam-pling/ionization technique (desorption electrospray ionization, DESI) is ongoing. The DESI method allows analysis of peptides, proteins and other biomolecules almost from any surface (e.g., plants, tissue sections etc.) without any sample preparation.

Participation in international, Nordic and European infrastructures

As a member of the BF Structural biology infrastructure network (BFSB), the platform has followed the development of Instruct, the ESFRI infrastructure for structural biology in which both NMR and mass spectrometry are included. A recent FIRI grant for Instruct activities is a major step forward in this area. A next step forward for BFSB and the NMR/MS consortium therein, is to become Instruct National Affiliate Center (NAC) that provides support to the structural biology community in Finland and will act as key portal to facilities, training and networking through Instruct supported programs.

User statistics

	Groups	Metrics
NMR Spectroscopy		
local	17	
domestic	13	
international	-	
non-academic	1	
Total	31	
Mass spectrometry		
local	8	
domestic	13	
international	2	
non-academic	8	
Total	31	3 175 (number of measured spectra)

Future perspectives

The structural studies of biological macromolecules in solution are an essential part of modern structural biology. Both NMR and native MS offer such information which cannot be obtained with any other method. For instance, NMR enables studies of intrinsically disordered proteins which play pivotal role in cellular processes and disease related biology. The new instrumentation at the NMR facility is very well suited for these studies. On the other, emergence of integrative approaches where NMR is employed together with e.g., X-ray crystallography to study molecular systems that are attainable with neither of these techniques alone is evident. New developments in this area include the use of solid state NMR to study, for example, membrane proteins as well as ion mobility mass spectrometry to study very large biomolecular assemblies such as viruses. According to our experience the use of high-resolution mass spectrometry has proven to be very efficient in analysis of protein material in detecting heterogeneity and modifications. The large utilization of these tech-niques would increase considerably the reproducibility of experiments in life sciences which has been recognized as a major concern in the field.

Major publications resulting from the Platform services

Pihlajamaa T, Kajander T, Knuuti J, Horkka K, Sharma A, Permi P. Structure of Plasmodium falci-parum TRAP (thrombospondin-related anonymous protein) A domain highlights distinct features in apicomplexan von Willebrand factor A homologues. Biochem J., 450:469-76, 2013. - *The NMR data collection and analysis was carried out in FBNMR.*

Leikoski N, Liu L, Jokela J, Wahlsten M, Gugger M, Calteau A, Permi P, Kerfeld CA, Sivonen K, Fewer DP. Genome mining expands the chemical diversity of the cyanobactin family to include highly modified linear peptides. Chem Biol., 20:1033-43, 2013. - *The NMR data collection was car-ried out in FBNMR.*

Fewer DP, Jokela J, Paukku E, Österholm J, Wahlsten M, Permi P, Aitio O, Rouhiainen L, Gomez-Saez GV, Sivonen K. New structural variants of aeruginosin produced by the toxic bloom forming cyanobacterium Nodularia spumigena. PLoS One, 8:e73618, 2013. - *The NMR data collection was carried out in FBNMR.*

Aranko AS, Oeemig JS, Kajander T, Iwaï H. Intermolecular domain swapping induces intein-mediated protein alternative splicing. Nat Chem Biol., 9:616-22, 2013. - *The NMR data collection was carried out in FBNMR.*

Bhattacharjee A, Oeemig JS, Kolodziejczyk R, Meri T, Kajander T, Lehtinen MJ, Iwaï H, Jokiranta TS, Goldman A. Structural basis for complement evasion by Lyme disease pathogen Borrelia burgdorferi. J Biol Chem., 288:18685-95, 2013. - *The NMR data collection was carried out in FBNMR.*

Sethi R, Seppälä J, Tossavainen H, Ylilauri M, Ruskamo S, Pentikäinen OT, Pentikäinen U, Permi P, Ylänne J. A Novel Structural Unit in the N-terminal Region of Filamins. J Biol Chem. 289:8588-98, 2014. - *The NMR data collection and analysis was carried out in FBNMR.*

Lee TC, Kalenius E, Lazar AI, Assaf KI, Kuhnert N, Grün CH, Jänis J, Scherman OA & Nau WM. Chemistry inside molecular containers in the gas phase. Nature Chem. 5 (2013) 376-382. - *FTICR mass spectrometry facility was used to measure mass spectra.*

Safdar M, Spross J & Jänis J: J. Mass Spectrom. Microscale enzyme reactors comprising gold na-noparticles with immobilized trypsin for efficient protein digestion. 48 (2013) 1281-1284. - *FTICR mass spectrometry facility was used to measure mass spectra.*

Leppiniemi J, Meir A, Kähkönen N, Kukkurainen S, Määttä JA, Ojanen M, Jänis J, Kulomaa MS, Livnah O & Hytönen VP. The highly dynamic oligomeric structure of bradavidin II is unique among avidin proteins. Protein Sci. 22 (2013) 980-994. - *FTICR mass spectrometry facility was used to measure mass spectra.*

Taskinen B, Zmurko J, Ojanen M, Kukkurainen S, Parthiban M, Määttä JA, Leppiniemi J, Jänis J, Parikka M, Turpeinen H, Rämet M, Pesu M, Johnson MS, Kulomaa MS, Airenne TT, Hytönen VP. Zebavidin - an avidin-like protein from zebrafish. PLoS One 10 (2013) e77207. - *FTICR mass spectrometry facility was used to measure mass spectra.*

X-ray FIX-UP Technology Platform

Chair of the consortium: Rik Wierenga, BCO, Protein Crystallography, Oulu X-ray
Members: Tommi Kajander, BI, Protein Crystallisation Facility, Tassos Papageorgiou, BioCity, Protein Crystallography Core Facility

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Achievements in development of technology services during 2013

In 2013 the FIX-UP BFSB (Biocenter Finland Structural Biology) technology platform received BF-funding for personnel running the facilities in BI-Helsinki and BCO-Oulu.

In Helsinki there has been a change in management: Prof. Adrian Goldman has stepped down because of his transfer to the University of Leeds. The PI of the BI FIX-UP platform is now Dr. Tommi Kajander. Another change concerns the Oulu BCO X-ray setup, which will be moved from the Linnanmaa campus to the Kontinkangas campus in summer of 2014, placing the BCO X-ray core facility close to all other BCO core facilities.

There have not been equipment upgrades in 2013. We have developed our centers further, taking also into account the feedback from the BF-survey. We have improved the information on our internet pages, and included information on expertise related to biophysical characterisation. The service provision, software development and outreach activities of the three centers are listed in the following.

Service provision

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

- We provide protein characterisation (protein stability screening by fluorescence; protein characterization by chromatography/multiple angle light scattering) crystallisation and imaging facilities. The facilities in Helsinki (http://www.biocenter.helsinki.fi/bi/xray/automation/) have been used by 19 different groups on ca. 40 different crystallisation projects. The facility also provides advice and training on how to proceed with a crystallisation project.

- Another important service is the provision of random screens for crystallisation: these screens are in use in Helsinki, Turku, Jyväskylä and Oulu; and we also provide services to design new screens based on hits within these screens.

- We provide a service enabling data collection and also advice on data collection strategies, including crystal testing, in Oulu and in the regional service in Turku. In Oulu three successful remote data collection sessions to Diamond have been organised.

Software development

We are involved in two software development efforts.

In Helsinki we have further developed the web-based imaging software, PiXray with a simple modular architecture to allow visualising crystallisation experiments. The images are tagged with screen information from the three platforms to allow design of new crystallisation conditions in the Minstrel software. We are also implementing new software to operate communication between Rigaku screen design software and our Hamilton screen preparation robot.

In Oulu we have further developed the xtalPiMS

data-tracking package, for viewing and annotating the images of crystallisation experiments generated by Formulatrix imagers. The xtalPiMS IT-infrastructure allows remote access to its database. A new module to facilitate the shipment of crystals-on-pins to Diamond is now ready. This project is setup in the context of Instruct, in collaboration with staff at the STFC in Daresbury, UK and Diamond in Oxford, UK, and is now continued in collaboration with Diamond.

Training and outreach

- Courses at the Masters level on X-ray crystallography and structure interpretation are offered at each University.

- Oulu has organised an international X-ray course focusing on data collection and data processing, including in-house and remote data collection, in September 2013. The Oulu data collection setup is being used regularly for educational purposes. Helsinki has also had outreach activities to schools, and in the spring 2013 we had local 4th graders visiting the facility. A 4-day course was organised in Turku together with the Proteomics core facility on Protein complexes and networks.

- We continue to meet yearly as part of FINNBOX (the Finnish Biological Crystallographers), which has been combined with the national BFSB meetings.

- The Oulu X-ray core facility is now an integral part of the local Strucbiocat initiative, which is being developed as a multidisciplinary core facility including not only X-ray but also enzymology and biophysical characterisation (http://www.oulu.fi/biocenter/strucbiocat). This Strucbiocat initiative reaches out also to the wider life science academic and biotech community in Finland and abroad.

- Likewise, the Turku regional data collection centre is also part of BioXLabs (www.sci.utu.fi/projects/biokemia/bioxlabs/), a regional structural biology consortium formed to enhance coordination of activities.

User statistics 2013

Number of users*			
	BI Helsinki	BCO Oulu	Biocity Turku
Campus	13	7	3
Local University	1	1	4
Other Universities	3	4	2
Non-academic	-	-	2
International	3	2	5

*By group leader: the total number of projects and users would be about two fold higher. The educational activities have not been included in these numbers.

In Helsinki crystallisation has been performed on 40 different protein/macromolecule systems, with a total of 160 crystallisation experiments during 2013. With the Oulu Proteum system data sets have been collected for 22 projects. 6 PDB-entries of Proteum data sets have been described in 2013 publications. The Proteum system is also much used for user training and teaching purposes, including for master student courses. During the Oulu international X-ray course each of the 16 students collected their own dataset using the Proteum system. At the Turku regional data collection center the Rigaku micromax has been used on a regular basis for research and educational purposes. Data sets for 18 projects have been collected and 9 structures have been deposited.

Participation in International, Nordic and European infrastructures

We have good access to the ESRF beamlines through the FinnProCC BAG, coordinated by Kajander/Goldman, Helsinki and through a similar national BAG at Diamond, coordinated by Kajander, Helsinki. We also have access to the Biostruct-X synchrotron facilities via a BAG, coordinated by Glumoff, Oulu. Data collection is also carried out at MAX Lab, DESY and BESSY. In addition SAXS and SRCD experiments are performed at several synchrotrons. FIX-UP interacts with important EU infrastructure networks including the EU Biostruct-X training initiative, the EU ESFRI Instruct activities, and the development of the new MAX IV synchrotron setup in Lund; Wierenga is a member of the advisory committee of the new PX-beam line of MAX IV. We participate in Finnish (FSRUO, Kajander) and European (ESUO, Kajander) synchrotron user organisations on the development of synchrotron radiation for scientific research, as well as we are actively involved in the guidance of the ESRF (Goldman is Head of Delegation for Nordsync in 2013/2014).

Future perspectives

Protein crystallography continues to be a crucial method for better understanding of how proteins and enzymes work, as for example highlighted in a recent special issue of Science (March 7, 2014, “Going from Strength to Strength”). This knowledge is also of key importance for developing structure-based biotech applications. In order for Finland to remain competitive in structural biology research and in its derived biotech applications it is of key importance that the four protein crystallography centers remain well supported. Three of these centers are involved in the FIX-UP project but active interactions with the Joensuu center are maintained via FINNBOX- and BFSB-meetings, as

well as via collaborations. The topical interest of each of these centers is different, for example in Helsinki there is a focus and specialised expertise on membrane protein studies and protein crystallisation, in Oulu on data collection and structural enzymology studies, in Turku on a combination of protein crystallography and bioinformatics and in Joensuu on a combination of protein crystallography and mass spectrometry. A unifying and supportive initiative will be the implementation and further development of the Finnish Instruct-NAC, which has been approved by the Instruct council in February 2014. This initiative of the BFSB network has also great potential to improve the communication between the Finnish protein crystallography and life science communities.

In the 2013 FIX-UP upgrade plan it has been noted that there is a significant need to upgrade existing equipment and in addition there are costs related to deferred maintenance. In the 2014 equipment investment plan therefore new equipment has been requested for BI-Helsinki (replacement of old generator system and a new crystallization plate scanner) and for Turku (replacement of old detector). For Oulu a modern plate scanner has been proposed, also related to the ongoing xtalPiMS development.

Major publications resulting from the Platform services

Kasaragod P, Schmitz W, Hiltunen JK, Wierenga RK (2013) The isomerase and hydratase reaction mechanism of the crotonase active site of the multifunctional enzyme (type-1), as deduced from structures of complexes with 3S-hydroxy-acyl-CoA. FEBS J., 280, 3160-3175. - *Data collection via FinnProCC BAG consortium; international collaboration.*

Venkatesan R, Wierenga RK (2013) Structure of mycobacterial beta-oxidation trifunctional enzyme reveals its altered assembly and putative substrate channeling pathway. American Chemical Society-Chemical Biology, 8, 1063-1075. - *Data collection via FinnProCC BAG consortium.*

Harijan RK, Kiema TR, Karjalainen MP, Janardan N, Murthy MR, Weiss MS, Michels PA, Wierenga RK (2013) Crystal structures of SCP2-thiolases of Trypanosomatidae, human pathogens causing widespread tropical diseases: the importance for catalysis of the cysteine of the unique HDCF loop. Biochem J., 455, 119-130. - *Data collection at the Oulu Data collection Center and via FinnProCC BAG consortium; international collaboration.*

Anantharajan J, Koski MK, Kursula P, Hieta R, Bergmann U, Myllyharju J and Wierenga RK (2013) The unique structural motifs for substrate binding and dimerization of the alfa subunit of collagen prolyl 4-hydroxylase. Structure, 21, 2107-2118. - *Data collection at the Oulu Data collection Center and via FinnProCC BAG consortium; intercampus collaboration*

Bligt-Lindén E, Pihlavisto M, Szatmári I, Otwinowski Z, Smith DJ, Lázár L, Fülöp F, Salminen TA. (2013) Novel Pyridazinone Inhibitors for Vascular Adhesion Protein-1 (VAP-1): Old target - New Inhibition Mode. Journal of Medicinal Chemistry, 56, 9837-9848. - *Data collection via FinnProCC BAG consortium; use of data collection facility at Biocity Turku; industry and international collaboration.*

Jendrossek D, Hermawan S, Subedi B, Papageorgiou AC (2013). Biochemical analysis and structure determination of poly(3-hydroxybutyrate) (PHB) depolymerase PhaZ7 muteins reveal the PHB binding site and details of substrate-enzyme interactions. Mol. Microbiol., 90, 649-664. - *Use of data collection facility at Biocity Turku; international collaboration.*

Haikarainen T, Frioux C, Zhnag LQ, Li DC, Papageorgiou AC (2014) Crystal structure and biochemical characterization of a manganese superoxide dismutase from Chaetomium thermophilum. Biochim. Biophys. Acta, 1844, 422-429. - *Use of data collection facility at Biocity Turku; international collaboration.*

Bhattacharjee J, Oeemig JS, Kolodziejczyk R, Meri T, Kajander T, Lehtinen MJ, Iwaï H, Jokiranta TS, Goldman A. (2013) Structural basis for complement evasion by Lyme disease pathogen Borrelia burgdorferi. J. Biol. Chem. 288,18685-18695. - *BF robot crystallization facility; data collection via FinnProCC BAG consortium; intercampus collaboration.*

Aranko AS, Oeemig JS, Kajander T, Iwaï H. (2013) Intermolecular domain swapping induces intein-mediated protein alternative splicing. Nat. Chem. Biol., 9, 616-622. - *BF robot crystallization facility; data collection via FinnProCC BAG consortium.*

Happonen LJ, Oksanen E, Liljeroos L, Goldman A, Kajander T, Butcher S.J. (2013) The structure of the NTPase that powers DNA packaging into Sulfolobus turreted icosahedral virus 2. J. Virol., 87, 8388-8398. - *BF robot crystallization facility; data collection via FinnProCC BAG consortium.*

Protein Services Technology Platform

Chair of the consortium: Juha Määttä, BMT, Tampere Protein Facility
Member: Olli Ritvos, BCH, Haartman Institute Protein Production Service

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Achievements in development of technology services during 2013

Protein production for biophysical and structural characterization in Tampere and Helsinki is essential supplement for Structural Biology platform services. Protein expression in several organisms offers a suitable system for any recombinant protein that is needed with proper scale-up possibility.

The Tampere Protein facility offers services in protein production and characterization. *E. coli* and *Spodoptera frugiperda* (baculovirus expression system) cells are used for protein expression. The facility has special focus on protein interactions. The customers are mainly from universities and virtually all Finnish universities are represented within the customers.

During the period 2012/2013, Tampere Protein facility has continued to serve existing users and also new customers. The number of customers who used our baculovirus expression system was the same as previous year, but the charged income increased with +25% (both ProtMet and Structural Biology parts taken into account). With the support from BF, Council of Tampere region and University of Tampere, the facility has been equipped with top-quality instruments enabling biophysical characterization of proteins and upgraded cell culturing facilities. However, protein expression systems would benefit significantly from new equipment (costing less than 100 k€) and it should be taken into account.

The Helsinki protein production facility at Haartman Institute complements the Protein Services platform coordinated by the Tampere facility by offering

services for generating recombinant protein expressing mammalian CHO-S and HEK293 cell lines and their use in protein expression scale up. The Helsinki facility has its focus on expressing and purifying secretory mammalian proteins in native form or as fusion molecules in milligram to gram quantities. The coordination between the Tampere and Helsinki protein expression platforms offers the choice of three robust protein expression platforms that the clients can use for satisfying their specific protein expression needs. Guidance, counselling and planning aid is provided to help the customers to decide whether to use in parallel several expression methods or to choose the most appropriate recombinant protein expression approaches for their research subject. During 2012–2013 the customer base of the Helsinki facility has increased to over 12 with both local, nationwide domestic and international clients. Customers usually need both cell line generation and scale up protein production services but now we have also in several customer contacts served as a provider of suspension culture cell culture scale up services from customers own existing cells lines. We have also noticed that several customers need repeated scale up productions of their preferred proteins from cell lines we have previously generated for them. While we are continuously getting new interested customers with a specific protein expression need many of our "old" customers need new batches of freshly produced and purified proteins for their specific needs. We have been also requested to provide scale up productions of mouse monoclonal antibodies in chemically defined serum free media from customers hybridoma cells. Our BF-funded orbital shaker incubators are well suited for that and this activity also fits well to our expertise as we are also expressing and purifying recombinant human IgG and scFv-Fc antibodies for academic and commercial customers.

An important part of the operation in both Tampere and Helsinki has been training of the personnel and also training of PhD students who need larger scale protein production in their studies. At the moment, the Tampere facility is operated by a dedicated laboratory technician (Niklas Kähkönen), who is trained and supervised by the coordinator of the facility, Dr. Juha Määttä. In the Helsinki facility a full time protein service dedicated bioengineer technician (Ulla Tienhaara) has been thoroughly trained and is supervised by the facility head scientist Dr. Olli Ritvos and the coordinator of customer projects, Dr. Arja Pasternack. This mode of operation and coordination ensures high quality of the work, and makes it possible to start new projects fluently. During 2012/2013, our mode of operation has been significantly improved towards scrutinized project tracking and reporting. Some of the customers have technically participated to the laboratory work as visitors.

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

Based on nationwide BF user survey, we have managed to offer high quality service. However, we like to improve our service all the time and offer more reliable, faster and satisfying service. To see how we are doing in this aim, we are happy to see similar surveys in future.

User statistics 2013

	BCH	BMT	Total
Total number of research groups*	11	25	36
Local research groups*	4	8	12
Domestic research groups*	7	14	21
International research groups*	4	3	7
Volume of services (cell lines)	38	6	44
Volume of services (hours)	500	1 018	1 518

*Research groups (or other customers) who have used the services regrdless of expression system.

Specification	BMT	BCH
Protein production	118	not estimated
Protein Purification with FPLC	900	app 500

Participation in international, Nordic and European infrastructures

So far it has been important to spread awareness of the possibility to use these protein expression services in the Biocenter Finland context on a national scale. We have not yet officially networked our activities with other Scandinavian or European units. Dr. Ritvos is currently in discussions with representatives of units providing protein expression services in Sweden (Karolinska institute, Protein Science Facility, psf.ki.se; and the novel SciLifeLab Drug and Discovery and Development (DDD) platform infrastructure in Stockholm and Uppsala). Interactions with the Swedish and Finnish National infrastructures within the protein

expression area would likely facilitate numerous Finnish-Swedish research collaborations and cooperation to researcher training in this area.

Future perspectives

To offer more valuable services and a scale-up system that is not limited by our current capacity we like to purchase WAVE Bioreactor System. It would more easily allow larger scale upstream operations by making cell culture faster, flexible, and more cost-effective. It is suitable for both insect and mammalian cells. So far we have been forced to reject customers asking high volume scale ups. WAVE bioreactor would make possible to offer large scale productions and then improve our service.

To improve our protein expression optimization and purification methods, we would need a JANUS® BioTx Automated workstation that enables consistent small scale protein purification and sample prep for analytical protein characterization required to support quality by design experimentation in both upstream and downstream processes.

Major publications resulting from the Platform services

Pinon P, Pärssinen J, Vazquez P, Bachmann M, Rahikainen R, Jacquier MC, Azizi L, Määttä JA, Bastmeyer M, Hytönen VP, Wehrle-Haller B. J. Talin-bound NPLY motif recruits integrin-signaling adapters to regulate cell spreading and mechanosensing. Cell Biol. accepted for publication. - *Protein production, interaction analyses by BLI, Tampere Protein Facility.*

Taskinen B, Zmurko J, Ojanen M, Kukkurainen S, Parthiban M, Määttä JA, Leppiniemi J, Jänis J, Parikka M, Turpeinen H, Rämet M, Pesu M, Johnson MS, Kulomaa MS, Airenne TT, Hytönen VP. Zebavidin - an avidin-like protein from zebrafish. PLoS One. 2013 Oct 24;8(10):e77207. - *Protein production and characterization, Tampere Protein Facility.*

Ylilauri M, Mattila E, Nurminen EM, Käpylä J, Niinivehmas SP, Määttä JA, Pentikäinen U, Ivaska J, Pentikäinen OT. Molecular mechanism of T-cell protein tyrosine phosphatase (TCPTP) activation by mitoxantrone. Biochim Biophys Acta. 2013 Oct;1834(10):1988-97. - *Interaction analyses using ITC, Tampere Protein Facility.*

Leppiniemi J, Meir A, Kähkönen N, Kukkurainen S, Määttä JA, Ojanen M, Jänis J, Kulomaa MS, Livnah O, Hytönen VP. The highly dynamic oligomeric structure of bradavidin II is unique among avidin proteins. Protein Sci. 2013 Jul;22(7):980-94. - *Protein production and characterization, Tampere Protein Facility.*

Tossavainen H, Helppolainen SH, Määttä JA, Pihlajamaa T, Hytönen VP, Kulomaa MS, Permi P. Resonance assignments of the 56 kDa chimeric avidin in the biotin-bound and free forms. Biomol NMR Assign. (2013) 7(1):35-8. - *Protein production, Tampere Protein Facility.*

Hulmi JJ, Oliveira BM, Silvennoinen M, Hoogaars WMH, Ma H, Pierre P, Pasternack A, Kainulainen H, Ritvos O. Muscle protein synthesis, mTORC1/MAPK/Hippo signaling, and capillary density are altered by blocking of myostatin and activins. Am J Physiol Endocrinol Metab. (2013) 304: E41–E50. - *ActRIIBFc protein production in CHO-s cells, Haartman Institute Protein Production Service.*

Tamminen JA, Parviainen V, Rönty M, Wohl AP, Murray L, Joenväärä S, Varjosalo M, Leppäranta O, Ritvos O, Sengle G, Renkonen R, Myllärniemi M, Koli K. Gremlin-1 associates with fibrillin microfibrils in vivo and regulates mesothelioma cell survival through transcription factor slug. Oncogenesis. (2013) 26;2:e66. - *hGrem1 and hGrem2 protein production in CHO-S cells, Haartman Institute Protein Production Service.*

Hulmi JJ, Oliveira BM, Silvennoinen M, Hoogaars WM, Pasternack A, Kainulainen H, Ritvos O. Exercise restores decreased physical activity levels and increases markers of autophagy and oxidative capacity in myostatin/activin-blocked mdx mice. Am J Physiol Endocrinol Metab. (2013) 305:E171-82. - *ActRIIBFc protein production in CHO-S cells, Haartman Institute Protein Production Service.*

Wiener Z, Band AM, Kallio P, Högström J, Hyvönen V, Kaijalainen S, Ritvos O, Haglund K, Kruuna O, Robine S, Louvard D, Ben-Neriah Y, Alitalo K. Oncogenic mutations in intestinal adenomas regulate Bim-mediated apoptosis induced by TGFβ. Proc Natl Acad Sci U S A. 2014 May 27;111(21):E2229-36. - *Rspo1 protein production in CHO-S cells, Haartman Institute Protein Production Service.*

TRANSLATIONAL TECHNOLOGIES

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, BMT, Noora Kotaja, BioCity; Krister Wennerberg, FIMM; Olli Pentikäinen, University of Jyväskylä

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

Finland is well-positioned to play a major role globally in the development of biobanks and biomarker capabilities. Systematic large-scale biobanking activities are ongoing at several sites, such as at the University of Tampere (with Tampere University Hospital) and in Helsinki (Institute for Health and Welfare (THL), University of Helsinki/FIMM and HUS, Helsinki University Hospital) and the 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-ERIC). The Finnish BBMRI node comprises not only the large scale Finnish population cohorts, but also numerous investigator-initiated sample collections and clinical data sources and the BF biobanking technology platform. In the future, automation of sample acquisition and fractionation technologies, as well as generation of arrayed tissue and molecular resources will be developed together with demographic and clinical annotation of the samples.

Tissue Biobanking Technology Platform

Chair of the consortium: Johan Lundin, FIMM
Members: Jorma Isola, BMT; Olli Carpen, BioCity

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Achievements in development of technology services during 2013

The main goal of the technology platform is to support incorporation of virtual microscopy in medical tissue biobanking projects and biomarker research. The consortium also provides know-how for best histological characterization of biobanked samples and for automated assessment of tissue sample stainings. The platform has been improved further to enable seamless integration of whole-slide images with biobank samples and clinical databases.

The platform provides the following services:

- Whole-slide cell and tissue sample scanning services. Scanning instruments are available at FIMM, BMT and BioCity Turku. Service is charged for per project or according to a pay-per-slide principle, including the digitization process and data storage. Price per project or slide varies according to volume demands and sample type. Typical price for smaller series (<100) histological slides in the range of 25–40 €/slide.

- Access to an online platform for virtual microscopy. The consortium maintains webmicroscopy platforms (fimm.webmicroscope.net, turku.webmicroscope.net, predect.webmicroscope.net, jvsmicroscope.uta.fi). Service for management, storage and access provided on a project basis and charged for (per working day) according to a cost-recovery principle.

- Access to computational tools, image analysis and clinical informatics. Development and tailoring of image analysis and clinical informatics tools and access to pathologist' consultation services on a project basis charged for (per working day) according to a cost-recovery principle. The consortium has implemented analytical tools for image annotation, image analysis (e.g. jvsmicroscope.uta.fi/immunoratio/, jvsmicroscope.uta.fi/immunomembrane/) and for clinical informatics. In 2013 a new fluorescence and brightfield combination scanning for immunohistochemistry together with new image analysis software was developed by BMT. In addition, reporting tools are provided for biomarker analytics.

According to the BF user survey 2013, the users were quite pleased with the provided services (average scores in the range of 4.00–4.83 on a scale from 1–5).

The most common request was a faster throughput of slide scanning services and the consortium applied for an additional scanning instrument through the FIRI applications of the Academy of Finland. The outcome of this application is still to be confirmed. The scanning instrument access has been the most important bottleneck at one of the centers (Helsinki) and since the service at the Meilahti Campus relies on a single instrument, the service is sensitive to instrument malfunction or many concurrent requests. Also, the current BF funding only allows 1–2 part time employed persons (one at FIMM and one at BMT) to handle the services and therefore longer waiting times can occur.

Activities in this field have increased substantially and we foresee that a high demand for sample digitization and the establishment of new biobanks in Finland will create a need to expand the consortium. Already for several years, Biocity Turku has expressed interest in establishing similar services as those at FIMM and BMT and has been promoting the biobank technologies by acquiring a whole-slide scanner and by proposing expansion of the sample digitization related to the activities of the BBMRI/ESFRI. For example, Auria Biobank aims to provide an access point between hospital-based biobanks and digital image acquisition, storage, analysis and webmicroscopy. Also, Oulu University has expressed and interest in the introduction of whole-slide scanning and webmicroscopy related to biobank activities.

User statistics 2013

Total number of research groups who have used the services in 2013: 80+

Breakdown of users (research groups): FIMM local: 20+, domestic: 10+, international: 30+, non-academic: 10+; IBT local: 10, domestic: 1, international: 1

Metrics:

FIMM: Total number of scanned slides approx. 5.000 that constitute ~ 40.000.000 individual digital images and a data amount of ~150.000 gigabytes of data;
BMT: Total number of scanned slides approx. 14.000. The ImmunoRatio software developed at BMT has been downloaded over 3,000 times and ImmunoMembrane downloaded over 500 times. The ImmunoRatio web application is frequently used: over 100,000 images analyzed during 2011–2013.

Participation in international, Nordic and European infrastructures

The translational technology platform is also used internationally, and has exceptionally strong links to EU level initiatives. For example a grant of 660k € was recently granted to develop a platform for the world's largest private-public partnership, the IMI-funded PREDECT project between 9 academic, 3 SME and 7 EU pharmaceutical partners, developing target validation models for breast, prostate and lung cancer, and with a total budget of approx 20 million euro (predect.webmicroscope.net).

Also, the webmicroscopy portal is provided as a platform for data sharing within the EU funded projects BioMedBridges (biomedbridges.webmicroscope.net) and Systems Microscopy. In addition, the webmicroscopy portal is used by the European Society of Pathology for arranging yearly large-scale, virtual slide seminars (>2 000 particpants) (ecp25.webmicroscope.net). The platform was also recently installed at the University of Oslo and VU University Medical Center in Amsterdam.

A pilot study has been proposed to the Biomarker Product Group of EATRIS, an ESFRI infrastructure for translational research. The intention is to assess whether the virtual microscopy methods 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.

Future perspectives

The global trend towards digital whole-slide microscopy is likely to increase the demand for slide scanning and webmicroscopy services during the next years.

Tasks of the consortium 2014–16

1. To maintain and improve the high-performance platform for digital microscopy and associated analytical tools established during 2010–13, including image servers, software for managing the image data, biomarker analysis functionality, linking of image data to clinical/phenotypic data and return of analysis results to the user. To develop and provide tools for linking the morphological analysis platform to the (hospital) biobanks and integrating the databases.

2. To implement analytical tools for translational research, such as a) computerized analysis of digitized tissue and cell samples, i.e. segmentation of the tissue into compartments (i.e. epithelium, stroma, blood vessels, fat tissue, immune response) including quantification of each compartment b) clinical informatics tools to enable and promote translational research, biomarker validation, cross-linking of data from several network platforms and model organisms (animal model, human samples), patient outcome analysis (prognostic tools).

3. Combining the computerized morphological analysis with other image analysis processes, i.e. read-

out of immunohistochemical or fluorescence staining within specific compartments of the segmented tissue (e.g. quantification of immunostaining in epithelial cells only), with special focus on robust detection and quantification of signals from the novel molecular detection methods developed.

Major publications resulting from the Platform services

Ojansivu V, Linder N, Turkki R, Rahtu E, Pietikäinen M, Lundin M, Konsti J, Joensuu H, Lundin J. Automated classification of breast cancer morphology in histopathological images. Diagnostic Pathology 2013; 8, Suppl. 1, p. S29 4 p. - *Samples scanned using the whole-slide scanning instrument at FIMM and the webmicroscopy platform was used for access to images of digitized breast cancer samples.*

Walliander M, Turkki R, Linder N, Lundin M, Konsti J, Ojansivu V, Meri T, Holmberg V, Lundin J. Automated segmentation of blood cells in Giemsa stained digitized thin blood films. Diagnostic Pathology 2013, 8 37: doi:10.1186/1746-1596-8-S1-S37. - *Samples scanned using the whole-slide scanning instrument at FIMM and the webmicroscopy platform was used for access to images of digitized blood smear samples.*

Turkki R, Linder N, Turkki R, Rahtu E, Pietikäinen M, Lundin M, Konsti J, Lundin J. An open-source, MATLAB-based annotation tool for virtual slides. Diagnostic Pathology 2013, 8 37: doi:10.1186/1746-1596-8-S1-S37. - *An annotation tool was developed for the purpose of developing image analysis algorithms that then can be applied on digitized whole-slide samples.*

Linder E, Grote A, Varjo S, Linder N, Lebbad M, Lundin M, Diwan V, Hannuksela J, Lundin J. On-Chip imaging of schistosoma haematobium eggs in urine for diagnosis by computer vision. PLoS Negl Trop Dis 2013; 7(12): e2547. doi:10.1371/journal.pntd.0002547. - *A novel, miniaturized microscopy imaging technology was developed that can provide an alternative way of sample digitization in the future.*

Drug Discovery and Chemical Biology Technology Platform

Chair of the consortium: Krister Wennerberg, FIMM, Chemical Biology Lab
Members: Olli Kallioniemi, FIMM (co-chair); Antti Poso, BCK, Drug Design and Synthesis Laboratory; Adyary Fallarero, BioCity, Drug Discovery of Natural Products Laboratory; Arto Urtti, BCH, Centre for Drug Research (CDR);
Affiliated expert members: Antti Pursula, CSC; Merja Perälä, VTT; Olli Pentikäinen, University of Jyväskylä, Computational Bioscience Laboratory

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http://ddcb.fi/en

Achievements in development of technology services during 2013

To be able to provide world-class services to users in the Biocenter community and beyond, the most important support the Drug Discovery and Chemical Biology (DDCB) infrastructure platform receives is definitely the salary support for service staff. Without this support, it will be very challenging to maintain the highly specialized expert staff at our operational units and services to users would not only get more costly but also likely be of lower quality. With this in mind, the new phase of Biocenter Finland funding that started in 2013 did not massively affect the Drug Discovery and Chemical Biology infrastructure platform because we were fortunate enough to receive continued salary support from 4 of 5 biocenters involved in the platform. Only the University of Eastern Finland/Biocenter Kuopio was not able to continue salary support at levels we had previously received. With the continued support from host universities 2014–2016, we are confident that we will be able to continue to provide top-level services and build and adapt to evolving user community demands.

The much-reduced availability of funds for instrument purchases is a challenge that all Biocenter Finland technology platforms have to face. DDCB did not receive any BF funding for instrumentation and upgrades in 2013, to advance capabilities and services two major instruments were bought last year with host institute funding: a LabCyte 525 acoustic dispenser that enhances our capacity to miniaturize and multiplex bioassays and an IncuCyte Zoom high throughput live cell incubator microscope giving our users new capacity to study live cells with two fluorescence channels.

Finally, we continued to enhance our capacity for follow-up studies of chemical compounds and drugs used in experiments, including providing dynamic light scattering and LC/MS analysis. These types of analyses have proven extremely important to verify results with drugs and drug-like molecules and quality controlling our specialized chemical compound collections.

User statistics 2013

User statistics are presented in a table next page. User statistics highlights:

- Increased revenue: Although our revenue is still relatively modest (most of the services provided by DDCB come with very little costs for the user other than supplies and many of the services are in silico services), it more than doubled from last year and is expected to continue to grow in 2014.

- DDCB assay development services and high throughput screening capacity led to a collaborative project between UH and an international pharmaceutical company.

- Two industrial collaborations focused on technological improvement of equipment and detection methods.

- Drug sensitivity and resistance testing services resulted in two pharmaceutical company-funded research studies.

Table: DDCB user statistics 2013.

	CDR/BCH	UEF/BCK	ÅAU/BioCity Turku	FIMM	Platform total
PI	Arto Urtti	Antti Poso	Pia Vuorela & A. Fallarero	K. Wennerberg & O. Kallioniemi	
Total user research groups	27	12	14	31 (1 jointly with UEF, 1 with CDR)	82
- local	19	6	6	21	48
- national	5	1	2	6	14
- international	3	5	5	2	5
- non-academic			1	2	3
Service revenue	4 000 e (supply costs)	0 e (in silico work only)	30 000 e (supply costs)	196 574 e (supplies & equipment)	230 574 e
Key metrics		13 virtual screens / molecular modeling projects performed		More than 400 screens performed and supported with 392 DSRT plate sets provided	

Participation in international, Nordic and European infrastructures

Our platform has since the start built strong ties to similar research infrastructures in other Nordic countries so that expertise and access to technologies are shared between the countries. These collaborations now mean that researchers in Finland can access specialized chemical biology technologies that may exist in other Nordic countries but not in Finland, and vice versa, that users from other countries can access the technologies and expertise in Finland. We have been sharing compound acquisitions with Sweden to access more and diverse chemical collections and have supported several projects. An active ongoing effort among the Nordic countries is to build a Nordic academic compound collection that could help spark collaborations and discoveries between the Nordic countries where the DDCB coordinated an application to NordForsk in early 2014 for fording for this Nordic infrastructure effort.

Our platform is directly linked to three ESFRI roadmap initiatives. First, we are coordinating the national participation and plans for construction and operation of EU-OPENSCREEN (www.eu-openscreen.eu), a European research infrastructure focused on the open access development of small molecule "tool compounds" with novel bioactivities. EU-OPENSCREEN operations, which are scheduled to start in 2015 are expected to be highly complementary to the ongoing operations within DDCB and some of the physical infrastructures that now are supporting the national platform will also serve the larger European research communities for EU-OPENSCREEN projects. Second, we are also actively taking part of the work of the Small Molecules product platform of the EATRIS (www.eatris.eu). Third, FIMM will serve as the high throughput microscopy core of the Finnish node of the Euro-BioImaging ESFRI (http://www.eurobioimaging.eu). In addition, CSC and FIMM are involved in the work of BioMedBridges (http://www.biomedbridges.eu) and ELIXIR (www.elixir-europe.org), focusing on the coordination and management of biological information produced by the ESFRI infrastructures.

Future perspectives

The DDCB infrastructure platform was formed in 2010 and during the first four years of operation, the services that the platform provides and the user demand for services have been constantly evolving. Initially, a relatively heavy focus was put on traditional drug discovery services such as high throughput screening, but with time, a key trend has been that services matching future visions biomedical research and biomedicine now are the dominant services of the DDCB platform and they continue to grow. A few examples are:

- Personalized medicine approaches such as drug sensitivity testing, personalized drug responses, drug repositioning, and studies of individualized drug metabolism and drug transport.

- Increasingly advanced assay readouts to generate more profound biological knowledge from a bioassay such as imaging as well as multiplexed biomarker detection and importantly, novel methods for automated analysis of these complex readouts.

- Specialized bioassays such as microbial biofilm assay technologies, label-free screening detection and complex mammalian cell-based assays (co-cultures, 3-dimensional cell culture) in high throughput-capable formats.

- Integration of phenotypic bioassay data with molecular profiling data such as next-generation sequencing to identify personalized drug response biomarkers.

We expect that more "traditional" high throughput screening projects to an increasing extent will be handled by recently established and emerging European infrastructure efforts such as EU-OPENSCREEN, EATRIS, and to a minor degree the European Lead Factory IMI. However, none of these infrastructures will provide assay development, optimization and validation services and for Finnish researchers to get their projects considered and accepted into these pipelines in European competition, local support will be highly important. Therefore, although not a major national service, the expertise of the DDCB staff and the access to automation equipment for validation is expected to be a key factor in making Finnish research competitive in these European projects.

As indicated, the DDCB provides a number of services that are not covered by other infrastructures and will complement the European initiatives. These services include a unique computational-experimental service platform based on virtual screening followed by picking hits from the extensive DDCB chemical collection and confirmatory follow-up testing. The unique aspect of this service is that there is no need for the user to re-purchase compounds for the experimental validation, which otherwise can cost tens of thousands of euros. With the DDCB service, this can instead be offered for a few hundred euros. The proof-of-concept compound distribution is another unique service that is quickly growing and is expected to keep growing. In 2013 we already provided over 300 of these aliquots to researchers. Similarly, the service to profile and quality control compounds with mass spectrometry has been critical for many projects and we aim to extend this service to NMR analysis.

To handle the future services we expect to continue to build on the technological platforms that exist within the network, including an NMR spectrometer, miniaturization and multiplexing using acoustic dispensing, enhanced label-free detection and enhanced high throughput imaging of live and fixed cells.

Major publications resulting from the Platform services

del Amo E. M. et al. 2013. Applying Linear and Non-Linear Methods for Parallel Prediction of Volume of Distribution and Fraction of Unbound Drug. PLoS ONE 8:e74758. - *Expertise in ADME modeling provided by DDCB.*

Laitinen T. et al. 2014. Mutation of Cys242 of human monoacylglycerol lipase disrupts balanced hydrolysis of 1- and 2-monoacylglycerols and selectively impairs inhibitor potency. Mol. Pharmacol. 85:510-519. - *Molecular modeling provided by DDCB.*

Manner S. et al. 2013. Systematic exploration of natural and synthetic flavonoids for inhibition of Staphylococcus aureus biofilms. International Journal of Molecular Sciences. 14:19434-19451. - *Expertise in chemical screening and chemical libraries provided by DDCB.*

Narwal M. et al. 2013 Screening and structural analysis of flavones inhibiting tankyrases Journal of Medicinal Chemistry.. 56:3507-3517. - *Expertise in chemical screening and chemical libraries provided by DDCB.*

Nybond S. et al. 2013. Antimicrobial assay optimization and validation for HTS in 384-well format using a bioluminescent E. coli K-12 strain. European Journal of Pharmaceutical Sciences 49:782–789. - *DDCB compound libraries, liquid handling and detection instrumentation were used in the project.*

Pemovska T. et al. 2013. Individualized Systems Medicine strategy to tailor treatments for patients with chemorefractory acute myeloid leukemia. Cancer Discovery 3:1416-1429. - *Method development, design and use of custom-made compound collections, drug sensitivity and resistance testing provided by DDCB.*

Salo H. S. et al. 2013. Identification of novel SIRT3 inhibitor scaffolds by virtual screening Bioorg Med Chem Lett. 23, 2990-2995. - *Virtual screening and chemical collections provided by DDCB.*

Stylianou M. et al. 2014. Antifungal application of non-antifungal drugs. Antimicrob. Agents Chemother. 58:1055-1062. - *Assay design and guidance, Chemical compound access, chemical screening provided by DDCB.*

Tang J. et al. 2013. Target Inhibition Networks: Predicting Selective Combinations of Druggable Targets to Block Cancer Survival Pathways. PLOS Computational Biology 9: e1003226. - *Drug sensitivity and resistance testing provided by DDCB.*

Venkannagari H et al. 2013. Activity-based assay for human mono-ADP-ribosyltransferases ARTD7/PARP15 and ARTD10/PARP10 aimed at screening and profiling inhibitors. European Journal of Pharmaceutical Sciences. 49:148-156. - *Assay design and guidance, expertise in assay development, chemical screening as well as chemical libraries provided by DDCB.*

VIRAL GENE TRANSFER AND CELL THERAPY

Viral Gene Transfer and Cell Therapy Infrastructure Network

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

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

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

In addition to viral gene transfer and cell therapy platform, BF has funded "LentiGEMM - Lentiviral platform for creating genetically engineered mouse models" in 2010–2012. For the 2013 SAB evaluation the platform changed its name into Tissue Engineered Disease Models (TEDM). The SAB recommended funding to TEDM and recommended its inclusion in the Model Organism infrastructure network. Therefore the technology services of the Tissue Engineered Disease Models are now listed under model organisms.

Viral Gene Transfer and Cell Therapy Technology Platform (VGTCT)

Chair of the consortium: Seppo Ylä-Herttuala, BCK, National Virus Core Facility, A. I. Virtanen Institute
Members: Kari Alitalo, BCH, AAV Gene Transfer and Cell Therapy Core Facility; Akseli Hemminki, BCH, Oncolytic vector core facility; Juha Klefström, BCH, Functional Genomics Unit (FuGu); Aki Manninen, BCO, Virus Vector Core Facility; Eric Dufour, BMT Virus Vector Facility; Eleanor Coffey, BioCity, Viral Vector Facility.
External member: Maija Vihinen-Ranta, University of Jyväskylä

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Achievements in development of technology services during 2013

Biocenter Finland's funding has been vital for maintenance and development of the AAV Gene Transfer and Cell Therapy Core Facility. Core Facility produces recombinant AAVs for internal and external customers. Currently the Core is able to produce four high-quality fully-tested AAV preps for both *in vitro* and *in vivo* applications within 10–12 days, with concentration of 10^{12}–10^{13} viral particles per prep. Recombinant AAV preps are generated based on the vectors either available in the stock or provided by the customer. Because of the long-time expertise and successful operation of the Core we are now offering a library of the useful AAV vectors, which can be used for AAV production as such, without any further modifications.

Biocenter Finland's funding has been vital for maintenance and development of Biomedicum Functional Genomics Unit's (FuGU) lentiviral and eco/amphotropic retroviral particles production services. Currently, recombinant viral particles are sold in microscale (500 ul), miniscale (1,5 ml), midiscale (6 ml) or maxiscale (20 ml). We have streamlined production of high-titer concentrated lentivirus particles for stem cell and in vivo transduction purposes. The vectors for virus production originate either from customer or from the genome-scale mouse and human TRC1 shRNA libraries licensed for and housed in FuGU. The core offers biosafety training, reagents for recombinant virus production, virus titer analysis and biosafety tests to exclude replication competent virus. FuGU has been providing large number of glycerol stocks corresponding to TRC1 shRNA lentiviral backbones as a new service within genome-wide methods network and tightened up collaboration with Genome Biology Unit in UH Viikki campus to improve access to cDNA

encoding lentivirus preparations.

FuGU has excellent and functional facilities and equipment for recombinant viral services. In the past few years, we have also launched RT-qPCR based gene expression knockdown validation service, which has increased the amount of customer orders. FuGU's daily routines are labour-intensive and the major bottleneck lies more in the lack of sufficient staff than in equipments. Due to lack of manpower, delivery times vary a lot. TRC1 shRNA constructs have been FuGU's most sold product for several years. However, in some cases the library does not meet the needs of all customers since the constructs of interest are only included in the newer versions of the TRC library.

Oncolytic vector core has been involved in several preclinical and clinical studies during 2013 with vector produced in their facilities.

During 2013 production of viral vectors (lenti, adeno and retro-virus) preps continued at Turku Core Facility. We implemented changes in the organization of the core to better facilitate user flow. Thus, an electronic reservation was implemented for each of the three sterile workstations in the BSL2 lab. This was implemented mid-way through 2013 and we have 571 hours of registered and paid BSL2 usage since that time. We imposed a small fee for facility usage, to cover the costs associated with maintenance of the lab e.g. waste removal, provision of sterile gloves, overshoes and tips.

Demand for one-to-one training on production of Lenti vectors continued to increase during 2013, charged on an hourly basis. We added a FACS sorting aerosol filtration unit, thereby expanding the reporter assay repertoire. This helped maintain user number.

Virus Core Facility in Tampere ran as a service cofounded by Biocenter Finland & BMT. The facility has produced approximately four virus productions or cell-line infections per month. The service was provided at no cost for the "clients". By the end of 2012/ beginning 2013, only few local research groups were still working in their own laboratories for virus production and most had transferred it to the common virus facility.

During the past three years, and based on clients demand, the facility has undergone major development to include retrovirus production, virus-clearance certification and iPS generation while providing access to plasmid repository and standardized protocols. Most significant bottleneck is that there is some uncertainty whether university will continue to support Core Facility in the future.

In Oulu the number of virus preparations produced at the BCO Virus Core laboratory increased 35% in 2013. In particular, preparation of lentiviral vectors has more than doubled since 2012 (from 70 to 176).

In 2013, University of Oulu funding was downscaled from 1.5 to 0.5 post doctoral positions which may affect the operations in the future. Biocenter Oulu funding continued providing salaries for a technician and a M.Sc. level researcher.

During 2013, National Virus Vector Laboratory, Kuopio (NVVL), has further developed its viral vector production methods, upgraded downstream purification methods for large-scale chromatography based techniques and validated some release assays for adenoviral and lentiviral vectors. Additional technical staff has been trained for GMP-compliant operations and vector production work has been carried out for several domestic and international customers.

To meet the demand of downstream purification of GMP vectors, we will need new chromatography and TFF units in the next 12 months in order to keep up with the increased need of vectors.

Based on the survey in spring 2013, the customers are satisfied with the services of the VGTCT. Compared to companies, such as Sirion Biotech GmbH or outside AAV Core facilities, the pricing for academic users is very moderate indeed.

The average grade of all the FuGU's viral services was 3.92. The highest score (4.10) was achieved from Service-staff Support-responsiveness and the lowest score (3.81) from Price- Quality-Ratio of the Service. To improve FuGU's services, frequently asked questions were added to our website and the prices were adjusted considering the price-quality-ratio.

Customer feedback from the services provided by NVVL was very positive in 2013 and both quality and pricing were appreciated by the customers. Also, according to the survey, speed of the services was also generally very good.

User statistics 2013

VGTCT provided well-defined services to a large number of customers during 2013. Other core labs served mainly their local communities in the production of basic vectors. Break-down to various core facilities is shown in a table next page.

Also other services were provided: FuGU provided 462 TRCI library vectors to national and international customers. Oncolytic Core laboratory provided FACS assays for immunological cells: 1210 samples; ELISA: 350 samples; ELISPOT: 335 samples; Neutralizing antibodies: 205 samples; Production of T-cells for adoptive transfer in mice: 6 experiments, cells grown for a total of 200 mice, a total of $650x10^6$ cells.

Table: Viral gene transfer and cell therapy user statistics 2013.

	Helsinki			NVVL	BCO	BMT	BioCity	Total
	AAV	Oncolytic	FuGu	Kuopio	Oulu	Tampere	Turku	
Customers	6	15	36	40	9	7	24	137
local	2	6	27	8	9	4	21	77
domestic	1	4	5	15			2	27
international	3	4	2	13		3		25
non academic		1	2	4			1	8
Volume*	54	20	75	85	394	41		669
Financial turnover	12 456 e	NA	28 773 e	62 600 e	10 511 e	NA	4 518 e	118 858 e

Participation in international, Nordic and European infrastructures

NVVL belongs to the EATRIS-ERIC infrastructure network and is responsible for ATMP viral vector production for domestic and European customers. NVVL is also an integral part of Centre of Excellence awarded by the Academy of Finland and for EU FP7 funded research consortia in the area of gene therapy and vascular biology. AAV and FuGU belong to Academy of Finland Centre of Excellence in Helsinki.

Juha Klefström is a founding member and a work package leader in EU & EFPIA Innovative Medicines Initiative –PREDECT (2011-2015). Development of services in the PREDECT project should help to lower the bar for Finnish academic - global pharma industrial collaborations in the area of virus gene transfer services.

Future perspectives

Requests for the production of high-quality GMP-level preclinical and clinical vectors has increased steadily in NVVL over the last years. Currently, it is predicted that the use of viral vectors will be doubled among European research community in the next 3-5 years. Therefore, production capacity of high-quality GMP vectors will be critical for Finnish and European translational medical research and biotechnology applications. In 2013, an increasing number of biotech companies have also searched for places to produce phase I/II clinical material for various types of gene and cell therapy clinical applications.

Currently the capacity of the AAV gene transfer technology is limited to about 4.7 kb of transgene DNA. We are developing a modification of the technology, which would allow to increase the length of the transgenic DNA, which can be transferred by AAV particles. This is important considering the rapid development of therapeutic applications and clinical trials using AAV-based gene-transfer technology (http://regenxbio.com/nav_therapeutics/clinical_trials/ and http://www.the-scientist.com/?articles.view/articleNo/33166/title/Gene-Therapy-Arrives-in-Europe/).

FuGU viral services continue to find cheaper options for virus production, especially concentrated viruses, to save costs and provide affordable virus products to customers. Also PhD student and postdoctoral training will be organized for graduate schools to promote use of viral techniques. In addition, FuGU continues to develop RT-qPCR services to estimate knockdown efficacies in different cell types.

Since glycerol stocks are the major selling point of FuGU, the purchase of updated versions of TRC shRNA library should be considered. These libraries include the MISSION® shRNA library (versions TRC1.5 and 2.0) and additional 88 000 clones targeting 4 000 new human and 5 000 mouse genes.

BCO VirusCore has launched a new project that aims at utilizing lentiviral vectors to employ the CRISPR-based genome editing technology. This technology will be used to create gene knockout cell lines as well as variable mutated cell clones.

Major publications resulting from the Platform services

Jeltsch M et al. CCBE1 Enhances Lymphangiogenesis via ADAMTS3-Mediated VEGF-C Activation. Circulation. 2014 Feb 19. doi: 10.1161/ CIRCULATIONAHA.113.002779. - *Virus vectors produced in Helsinki Virus Core*

Gaál EI et al. Comparison of vascular growth factors in the murine brain reveals placenta growth factor as prime candidate for CNS revascularization. Blood. 2013 Aug 1;122(5):658-665. - *Virus vectors produced in Helsinki Virus Core*

Koski A, Ahtinen H, Liljenback H, Roivainen A, Koskela A, Oksanen M, Partanen K, Laasonen L, Kairemo K, Joensuu T, Hemminki A. [(18)F]-fluorodeoxyglucose positron emission tomography and computed tomography in response evaluation of oncolytic adenovirus treatments of patients with advanced cancer. Hum Gene Ther. 2013;24(12):1029-41. - *Virus vectors produced in Helsinki Virus Core*

Liikanen I, Ahtiainen L, Hirvinen ML, Bramante S, Cerullo V, Nokisalmi P, Hemminki O, Diaconu I, Pesonen S, Koski A, Kangasniemi L, Pesonen SK, Oksanen M, Laasonen L, Partanen K, Joensuu T, Zhao F, Kanerva A, Hemminki A. Oncolytic adenovirus with temozolomide induces autophagy and antitumor immune responses in cancer patients. Mol Ther. 2013;21(6):1212-23. - *Virus vectors produced in Helsinki Virus Core*

Savontaus M. Intracardiac injection of a capsid-modified Ad5/35 results in decreased heart toxicity when compared to standard Ad5. Virol J. 2012; 29;9;296. - *Virus vectors produced in Turku Vector Core*

Sullivan L, Martinez E, Mullen AR, Nguyen H, Dufour E, Sudarshan S, Yang Y, Linehan WM, Licht JD, Deberardinis RJ & Chandel NS. The proto-oncometabolite fumarate binds glutathione to amplify ROS dependent signalling. Mol. Cell. 51(2):236-48. - *Tampere Virus Facility produced lentivirus used in this study*

Teräväinen, T.P., Myllymäki, S.M., Friedrichs, J., Strohmeyer, N., Moyano, J.V., Wu, C., Matlin, K.S., Muller, D.J., Manninen, A. aV-integrins are required for mechanotransduction in MDCK epithelial cells. PLoS One. 2013, 8(8):e71485. - *Virus vectors produced in BCO Virus Core*

Huang, Q., Whitington, T., Gao, P., Lindberg, J.F., Yuehong Yang, Y., Sun, J., Väisänen, M.R., Szulkin, R., Annala, M., Yan, J., Egevad, L.A., Zhang, K., Lin, R., Jolma, A., Nykter, M., Manninen, A., Wiklund, F., Vaarala, M.H., Visakorpi, T., Xu, J., Taipale, J. and Wei GH. A prostate cancer susceptibility allele at 6q22 increases RFX6 expression by modulating HOXB13 chromatin binding. Nature Genetics. 2014, 46: 126–135. - *Virus vectors produced in BCO Virus Core*

Westphal, M., Ylä-Herttuala, S., Martin, J., Warnke, P., Menei, P., Eckland, D., Kinley, J., Kay, R., Ram, Z.; ASPECT Study Group. Adenovirus-mediated gene therapy with sitimagene ceradenovec followed by intravenous ganciclovir for patients with operable high-grade glioma (ASPECT): a randomised, open-label, phase 3 trial. Lancet Oncol. 14; 823-833, 2013. - *Virus vector for phase 3 trial was produced in NVVL in Kuopio*

Turunen, M.P., Husso, T., Musthafa, H., Laidinen, S., Dragneva, G., Laham-Karam, N., Honkanen, S., Paakinaho, A., Laakkonen, J.P., Gao, E., Vihinen-Ranta, M., Liimatainen, T., Ylä- Herttuala, S. Epigenetic Upregulation of Endogenous VEGF-A Reduces Myocardial Infarct Size in Mice, PLoS One 9; e89979, 2014. (doi:10.1371/journal.pone.0089979). - *Virus vector produced in NVVL in Kuopio*

STATISTICS

Statistics confirm the commitment of host universities

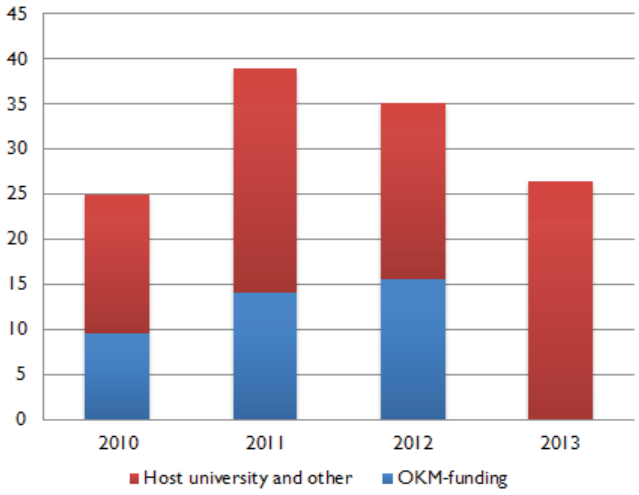
Since 2010, the BF coordination office has been collecting reports from the technology platforms on their use of earmarked OKM funds and of other funds that they have received from the host universities and other sources towards provision of technology services to the scientific community. Despite consistent instructions and reporting forms used to address the technology platforms this type of reporting has obvious problems as it may not be easy to decide what funds are used for services and related research activities. Differences exist particularly in reporting host university contribution. Yet, as the reporting instructions and forms have remained essentially the same through the four-year reporting period the data should give some reasonably reliable estimates of the development of BF technology service funding at national level.

Graph A shows the total funding of BF technology services as reported by the technology platforms. The effect of the three-year earmarked funding from OKM is evident, but the graph also shows how the host universities were able to compensate for the discontinuation of targeted OKM funding in 2013. Yet, the 32 % reduction of total BF funding from 2011 to 2013 made it impossible to continue all BF international activities. On the positive side, increased host university funding made it possible to continue support to the most important BF resource – the trained technical personnel.

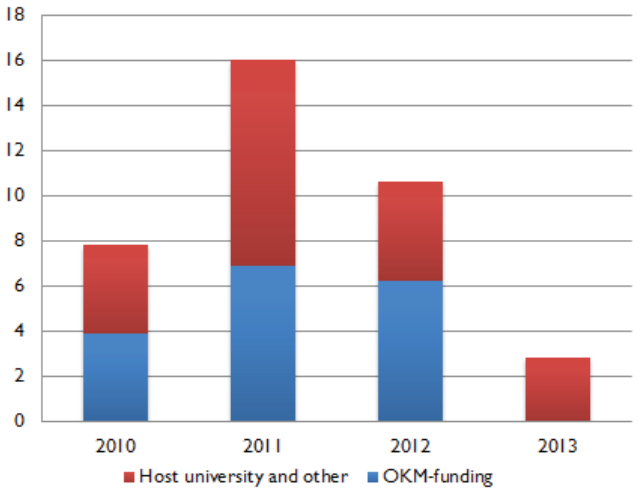
Graph B illustrates the drastic annual changes in funding for BF equipment. In 2011 and 2012 earmarked OKM and national FIRI funds were supplemented with host university support to purchase equipment. Against this background year 2013 with no targeted OKM or FIRI support became almost a disaster as total equipment funding dropped by >80 % of the level in 2012. And year 2014 promises to be nearly as difficult, as the 1 MEUR of FIRI2013 funds and universities' matching funds are clearly insufficient for BF to maintain its top-of-the-line equipment and services for the Finnish life science community.

Graph C summarizes the development of user fees received by BF technology platforms for their services. User fees for academic researchers primarily cover the cost of reagents and maintenance of equipment. The 31 % increase reported in user fees from 2012 to 2013 is an indication of the importance of these services and also of the success of research groups using these services in obtaining external funding for their research. In 2013, user fees amounted to 6.5 MEUR, which corresponds to 25 % of the total budget of technology platforms.

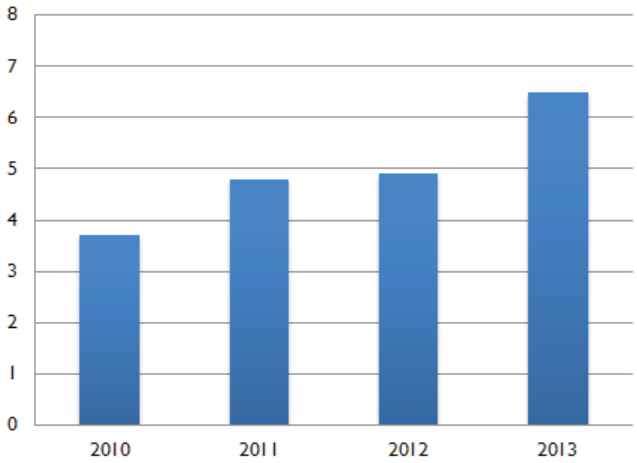
A: BF technology platforms, total funding (MEUR)



B: BF technology platforms, equipment funding (MEUR)



C: BF technology platforms, user fees (MEUR)



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