Biocenter Finland

ANNUAL REPORT 2015-2016

Biocenter Finland Annual Report 2015-2016

Editor: Antti Siltanen

Photos: CanStockPhoto

Acknowledgements: We thank the technology platform chairs and BF board members for cooperation in compiling this report.

www.biocenter.fi

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FOREWORD

Biocenter Finland (BF) is a distributed nation-wide research infrastructure of the seven biocenters hosted by University of Eastern Finland, University of Helsinki, University of Oulu, University of Tampere, University of Turku and Åbo Akademi University. The mission of BF is to support frontier research in life sciences by providing state-of-the-art open access technology services. In 2015 - 2016 the nine technology platforms included Bioinformatics, Biological Imaging, Genome-wide Methods, Model Organisms, Proteomics and Metabolomics, Stem Cells and Biomaterials, Structural Biology, Translational Technologies, as well as Viral Gene Transfer and Cell Therapy, each of them composed of distributed nodes with complementary expertise. BF is charged with coordinating the technology services and fetching resources for investments into the facilities from competitive sources, while the personnel costs are financed by the host universities.

The quality of research enabled by the BF technology platforms has reached global excellence in several domains such as cancer, immunology, neuroscience, human genetics, personalized medicine and structural biology. The scientific significance is evidenced by success in the most competitive national and international calls. Suffice it here to highlight one scientific and one innovation breakthrough delivered by BF's constituency and supported by its technology platforms. Academy Professor Kari Alitalo's group demonstrated that the central nervous system contains lymphatic vessels. The finding was listed a *Break-through of the year 2015 by Science* and a *Notable Advance of 2015 by Nature*. Academician Sirpa Jalkanen's discovery of therapeutic targets for harmful inflammations and cancer was acknowledged by an *EU Innovation Prize for Women in 2015*.

The period 2015-2016 was marked with significant changes in the operational environment that are crucial for the standing of BF, namely the nation-wide focus on universities' research strategies and the implementation of the national research infrastructure strategy through calls issued by the Academy of Finland's (the Finnish Research Council) Research Infrastructure Committee.

In 2015 the Ministry of Education and Culture decided to accelerate the profiling of the 14 Finnish universities by detaching EUR 50 million from their collective block fund of about EUR 2 billion, to be competed back with a smart research strategy and a stringent implementation plan. The management of the universities' profiling programme was entrusted to the Academy of Finland.

Life science evidently is amongst the focus domains of the biocenter universities, and therefore BF needs to be deeply rooted in their research strategies. In the profiling programme's first calls in 2015 and 2016, several of BF's host universities were successful in winning funds for implementation of their long-term life science strategies. In parallel, the host universities' rectors took the decision to support BF's technology platforms' personnel costs for the period 2016-2020.

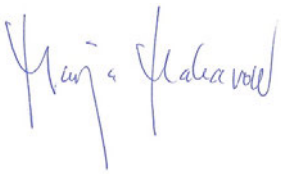
In October 2015, BF conducted a user survey on its technology platform services, in order to obtain information on the clientele's views on the performance of the technology platforms. The feedback has helped to further develop the services. The survey also gave an opportunity to the researchers' community to comment on the BF activities at large. The feedback proved to be very positive.

The research infrastructure calls of the Academy of Finland (FIRI calls) represent currently the only source for investments for the BF platforms. Therefore, success in these calls is vital for BF's existence. BF decided in 2015 to base its future FIRI applications on a long-term strategy, where up-grading of its technology platforms and establishment of

new ones is prioritized according to the needs of renewal of science, and informed by stringent analysis and recommendations by an international scientific advisory board. The board, chaired by professor Carl-Henrik Heldin, met in January 2016 in Helsinki. It emphasized that though BF has been very successful, it is underfunded, risking that it will not be able to maintain and develop the necessary infrastructure in the long run.

The year 2016 closed with excellent news, when BF was granted in full the resources it had applied for from the FIRI 2016 call. The funding will allow BF to expand its technology portfolio to analyses of proteomes and metabolomes including their modifications, and for single cell isolation methods, essential for modern functional systems approaches.

I would like to take this opportunity to thank professor Olli Jänne, who served as interim director of BF from January 2015 till February 2016.



Professor Marja Makarow

Director of Biocenter Finland

HOST UNIVERSITIES, MEMBER INSTITUTES AND FACULTY

Host Universities and Member Institutes

BF is a distributed national research infrastructure that in 2015-2016 consisted of seven member institutes hosted by six universities (Fig. 1). The directors of each institute serve as the Governing Board of BF.

Please note that from 2017 on, Helsinki Institute of Life Science HiLIFE will serve as the member institute at the University of Helsinki. Institute of Biotechnology and Institute for Molecular Medicine Finland will continue as operational units of HiLIFE together with Neuroscience Center as the third unit. At University of Tampere, the Faculty of Medicine and Life Sciences will replace BioMediTech as the member institute from 2017 onwards.

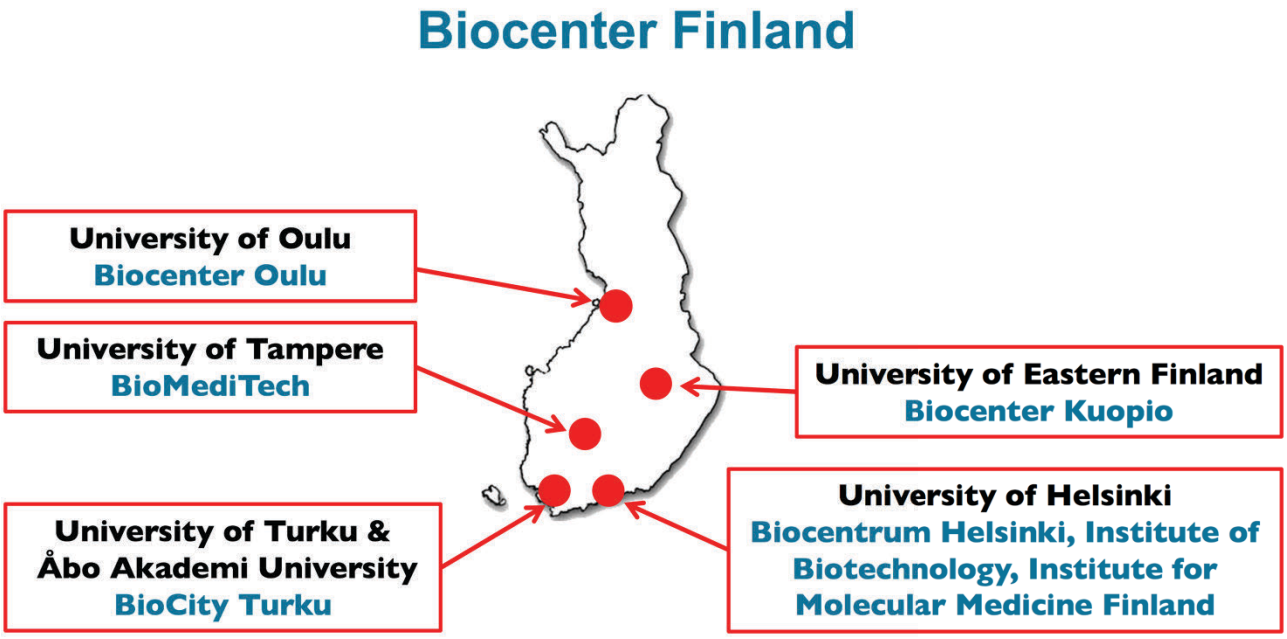


Figure 1. The host universities and their BF member institutes in 2015-2016.

Faculty

At the end of 2016, the Biocenter Finland Faculty comprised of 342 principal investigators listed below. Each member institute has used its own criteria and/or peer review process in assessing the membership (group leaders or principal investigators). In all member institutes, the BF Faculty includes top-tier scientists in each of the scientific fields represented by BF.

University of Eastern Finland

Alhonen L, Auriola S, Carlberg C, Giniatullin R, Goffart s, Gröhn O, Hanhineva K, Heikkinen S, Heinäniemi M, Hiltunen M, Honkakoski P, Ilonen J, Jolkkonen J, Jurvelin J, Jänis J, Kaarniranta K, Kinnunen T, Koistinaho J, Koistinen A, Korhonen R, Kosma VM, Kröger H, Laakso M, Lehto VP, Laitinen J, Levonen AL, Liimatainen T, Mannermaa A, Närväinen A, Paananen J, Palvimo J, Pihlajamäki J, Pitkänen

A, Poso A, Pohjoismäki J, Raunio H, Remes A, Rouvinen J, Savinainen J, Sirola J, Tammi M, Tammi R, Tang J, Tanila H, Tavi P, Töyräs J, Urtti A, Vepsäläinen J, Virtanen T, Ylä-Herttuala S (50).

University of Helsinki

Aaltonen L, Ahtiainen L, Airavaara M, Aittokallio T, Alitalo K, Andressoo JO, Auvinen P, Bamford D, Battersby B, Butcher S, Castrén E, Di-Poi N, Domanskyi A, Fagerholm S, Frilander M, Garcia S, Greco D, Groop L, Hautaniemi S, Heckman C, Helariutta Y, Hemminki A, Hennah W, Hietakangas V, Holm L, Horvath P, Ikonen E, Iwai H, Jacobs H, Jernvall J, Jokitalo E, Kaila K, Kainov D, Kallioniemi O, Kangasjärvi J, Kajander T, Kaprio J, Kaski S, Katajisto P, Kauppi L, Kostiainen M, Kuure S, Laiho M, Lappalainen P, Linder M, Lohi H, Lundin J, Löytynoja A, Michon F, Mikkola M, Mustjoki S, Mähönen AP, Mäkelä T, Ollikainen M, Otonkoski T, Paavilainen V, Palotie A, Peltomäki P, Pirinen M, Poukkula M, Ripatti S, Saarela J, Saarma M, Saksela K, Salazar-Ciudad I, Santos HA, Schulman A, Sharma V, Shimmi O, Tang J, Thesleff I, Varjosalo M, Vartiainen M, Wartiovaara A, Verschuren E, Wennerberg K, Widén E, Zhao H (78).

University of Oulu

Ala-Korpela M, Eklund L, Eskelinen S, Herzig KH, Hiltunen K, Hinttala R, Juffer A, Järvelin MR, Karppinen P, Kettunen J, Kursula I, Lehtiö L, Manninen A, Myllyharju J, Pihlajaniemi T, Pyhäjärvi T, Reunanen J, Ruddock L, Savolainen M, Savolainen O, Sillanpää M, Soininen R, Uusimaa J, Vainio S, Wei G, Wierenga R, Winqvist R (27).

University of Tampere

Aalto-Setälä K, Anderssoo JO, Bova GS, Flodström-Tullberg M, Hytönen V, Isola J, Jacobs H, Kallioniemi A, Kulomaa M, Miettinen S, Narkilahti S, Nykter M, Pesu M, Rämet M, Skottman H Visakorpi T, Ungureanu D (17).

University of Turku and Åbo Akademi University

Abankwa D, Airaksinen J, Airas L, Aittokallio T, Allahverdiyeva-Rinne Y, Aro EM, Aro H, Aronen H, Battchikova N, Belogurov G, Bobacka S, Carpen O, Chen Z, Coffey E, Eerola E, Elenius K, Elo L, Elo-Uhlgren L, Eriksson J, Fujii H, Ginter F, Goodlett DR, Haataja L, Haataja S, Hakanen A, Hannulainen J, Heikkinen T, Heino J, Heino T, Holmdahl R, Huhtinen K, Hukkanen V, Hupa L,Hytönen J, Hyötyläinen T, Hänninen A, Hänninen T, Härkönen P, Ilonen J, Ivaska J, Ivaska K, Jaakkola P, Jalava J, Jalkanen S, James P, Jartti T, Johnson MS, Julkunen I, Järveläinen H, Kallio M, Kalliokoski K, Kangasjärvi S, Kero J, Kiviranta R, Koskinen P, Kotaja N, Knuuti J, Kvarnström C, Kähäri VM, Könönen E, Lahesmaa R, Laitala-Leinonen T, Laitinen K, Laitinen T, Lamminmäki U, Lapinleimu H, Lassila O, Lehtonen J, Lehtonen L, Leino R, Lilius J, Lindfelt M, Lindfors T, Lund R, Lähdesmäki H, Lövgren T, Mattila P, Mattinen J, Meinander A, Meriluoto J, Metsä-Ketelä M, Moritz N, Mulo P, Murzin D, Mäkelä S, Määttä J, Nees M, Niemi J, Niinikoski H, Niiranen T, Nuutila P, Närhi T, Oksi J, Oresic M, Pahikkala T, Papageorgiou T, Parvinen K, Peltola V, Peltonen J, Peltonen S, Perheentupa A, Pettersson K, Petre I, Posti J, Poutanen M, Pouwels J, Primmer P, Puigpo P, Pulliainen A, Pänkäälä M, Qiushui H, Rahman N, Raitakari O, Rautava P, Rautava S, Rekola J, Rintamäki E, Rogojin V, Roivainen A, Rosenholm J, Ruohola A, Saari T, Sahlgren C, Salakoski T, Salo-Ahen O, Salmi M, Salmi T, Salminen JP, Salminen T, Sandler N, Saraste A, Savinainen H, Savolainen J, Savontaus E, Savukoski T, Scheinin M, Schleutker J, Siitari H, Sillanpää M, Sistonen L, Soukka T, Susi P, Syrjänen S, Säämänen AM, Talha S, Tang J, Tanner J, Tauriainen S, Tena-Sempere M, Tezvergil-Mutluay A, Toivakka M, Toivola D, Toppari J, Tuomela J, Tyystjärvi E, Tyystjärvi T, Törnquist K, Vallittu P, Vuopio J, Vuorinen T, Waris M, Westermarck J, Wilen CE, Willför s, Wittfooth S, Xiang-Guo L, Zavialov A, Zhi C, Österbacka R (170).

GOVERNANCE AND ORGANIZATION

The Rectors of the host universities form the highest decision-making body of BF. The decisions concerning the strategy and operations of BF are made by its Governing Board comprised of the directors OF the seven member institutes. The Board meets 5–6 times per year. The governance and organizational structure is depicted in Fig 2.

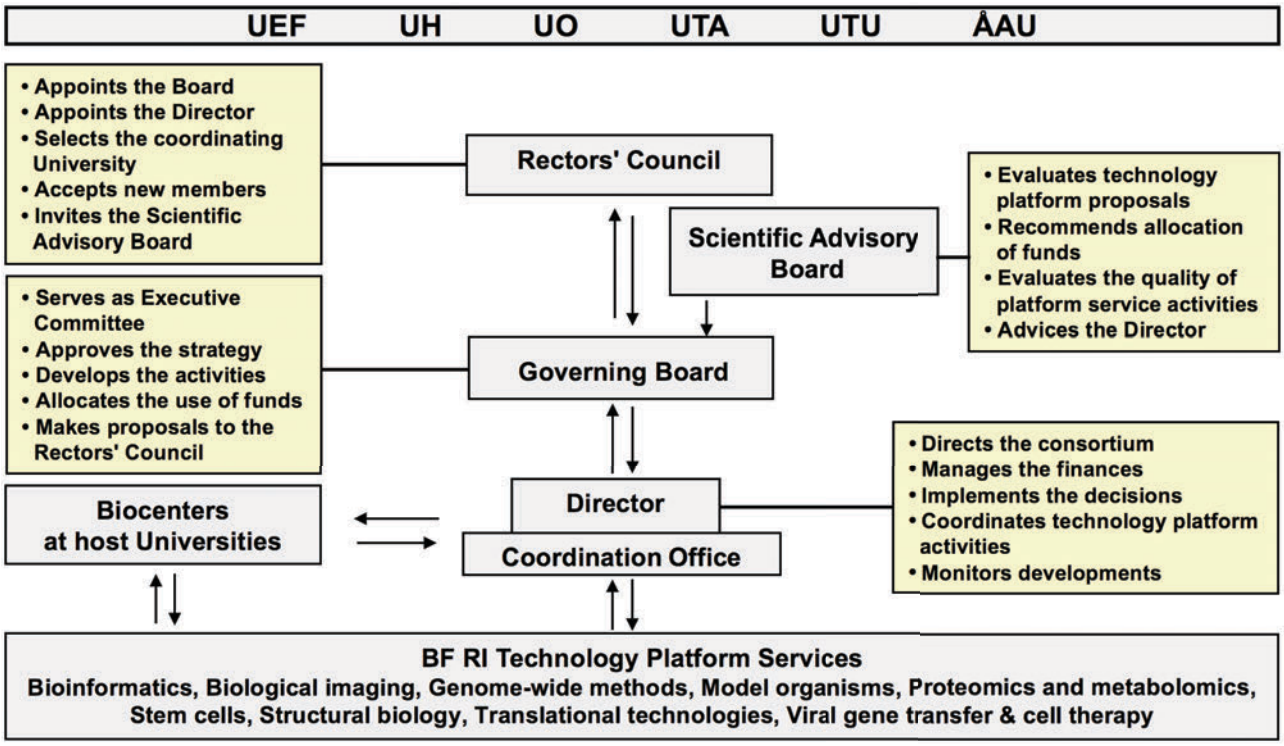


Figure 2. The governance and organization of Biocenter Finland.

Governing Board 2016

The members of the Governing Board of BF in 2016 were Prof Johanna Myllyharju (Chair, Biocenter Oulu, UO, see Fig2), Prof Tapio Visakorpi (Vice Chair, BioMediTech, UTA), Prof John Eriksson (ÅA) and Prof Jyrki Heino (UTU) (BioCity Turku), Academy Prof Seppo Ylä-Herttuala (Biocenter Kuopio, UEF), Prof Tomi Mäkelä (Biocentrum Helsinki, UH), Prof Howard Jacobs (Institute of Biomedicine, UH), and Prof Jaakko Kaprio (Institute for Molecular Medicine Finland, UH).

Governing Board 2015

During 2015 John Eriksson and Johanna Myllyharju served as Chair and Vice Chair, respectively. The Board member for Institute of Biotechnology was Prof Pekka Lappalainen and for Institute for Molecular Medicine Finland Prof Olli Kallioniemi.

Coordination Office

Prof Olli Jänne served as the interim BF director during 1.1.2015-28.2.2016. Professor Marja Makarow serves as the director from 1.7.2016 onwards. Ms. Marianna Jokila was the planning officer until 31.8.2016.

The Scientific Advisory Board of Biocenter Finland 2013-2016

The international Scientific Advisory Board of BF evaluates the quality and scientific impact of the BF technology platforms, and prioritizes the commynity's proposals what concerns updates of existing research infrastructures and establishment of new platforms.

Chair: Professor Carl-Henrik Heldin, Director, Ludwig Institute for Cancer Research, Uppsala, Sweden

Vice-Chair: **Professor Ole Petter Ottersen**, Rector, University of Oslo, Norway

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

Professor Gunnar von Heijne, Director, Center for Membrane Research, Stockholm University, Sweden

Professor Matthias Wilmanns, Head of EMBL Hamburg, Germany

BIOCENTER FINLAND TECHNOLOGY PLATFORM SERVICES

The BF technology services are organized by the technology platforms that are supported by the scientific networks. Each platform is composed of national nodes with complementary expertise and managed by a board composed of the heads of the nodes and a platform chair (Fig 3).

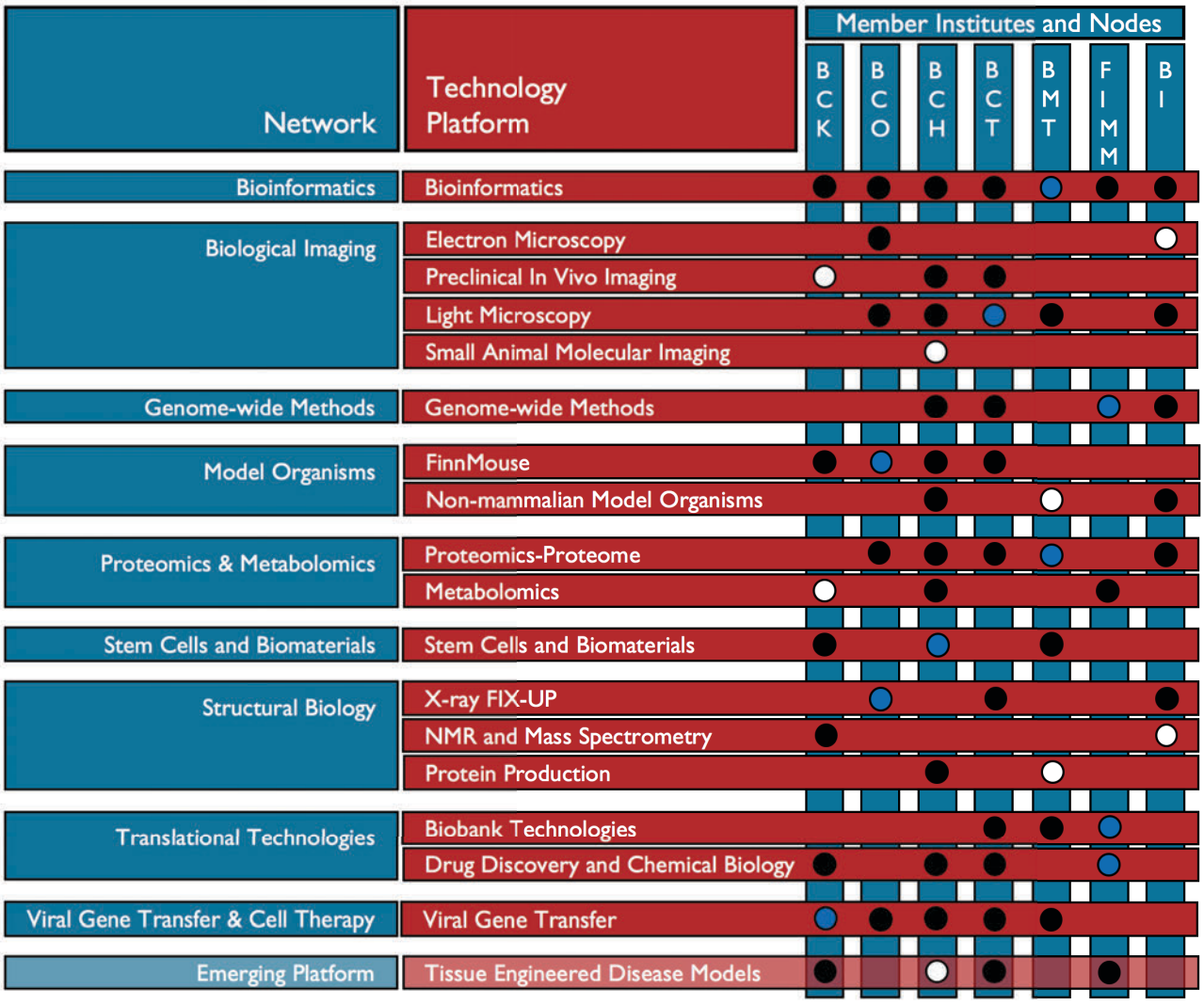


Figure 3. The BF scientific networks, technology platforms and local nodes hosted by the member institutes. The dots indicate in which member institute the nodes are located. Blue dots: network chairmanship, white dots: platform chairmanship. BCK, Biocenter Kuopio; BCO, Biocenter Oulu; BCH, Biocentrum Helsinki; BCT, BioCity Turku; BMT, BioMediTech; FIMM, Institute of Molecular Medicine Finland; BI, Institute of Biotechnology.

BIOINFORMATICS

Coordinator: Matti Nykter, BMT

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 platform: Matti Nykter, BMT

Partners: Jussi Paananen, BCK; André Juffer, BCO; Sampsa Hautaniemi, BCH; Mark Johnson, BioCity; Imre Västrik, FIMM; Liisa Holm, BI;

External members: Tommi Nyrönen, IT Center for Science, CSC; Harri Lähdesmäki, Aalto University

http://bioinformatics.biocenter.fi/

Achievements in development of technology services

Thanks to collaboration between bioinformatics network and CSC - IT Center for Science, major data generation biocenters are now connected to CSC supercomputing via the Lightpath gigabit link, providing fast, efficient moderate-sized data transfers for use of the CSC's ePouta Cloud service, which is sponsored by the Ministry of Education and Culture. 2016 saw complete replacement of the BioMedInfra (BMI) pilot cloud resources with ePouta cloud service. All biocenters are utilizing CSC computing resources to run their analysis pipelines. In addition, bioinformatics network has set up local storage and specialized computing environment to support data generation platforms and we provide generic scientific IT support, hardware and software support, and data analysis to bioscience community.

A successful infrastructure is not based on just equipment. While we have been able to serve a large number of customers with minimal resources, as a result of further cuts in budgets, currently a number of projects are on hold due to personnel shortage and in several biocenters we need to refuse any new projects. Also several services are run in maintenance mode and making any changes to the algorithms would require new personnel. Thus, for a stable and efficient service offering, a commitment to investments in personnel is a must.

Network has focused mainly to supporting next generation sequencing and proteomics analysis while maintaining support also for more more labor intensive areas such as for image analysis, in silico modeling and simulation, and software development services for biomedical research groups. We have also provided consultation on e.g. deep sequence related topics, such as experimental design,

quality control, data analysis and interpretation.

Customer feedback has been positive. After completion of each project we request feedback from the customers. Customers were very pleased with quality of the services. Negative feedback results mostly from the sometimes long wait times due to lack of service staff. To provide support for the whole national bioscience community, in addition to local contact persons at biocenters, we provide national bioinformatics helpdesk support through email.

Bioinformatics network works in close collaboration with ELIXIR Finland node, hosted at the CSC. Services of the network are structured to be complementary to the infrastructure of the ELIXIR; ELIXIR provides access to datasets and databases with necessary IT support while the bioinformatics networks provides services that build on the infrastructure that ELIXIR makes available. Thus, collaboration with ELIXIR has been highly synergistic.

User Statistics

See table below.

Participation in international, Nordic and European infrastructures

Bioinformatics network is actively participating and developing following infrastructures and networks:

ELIXIR ESFRI: we have been a pilot customer for the infrastructure, we have peer-reviewed the proposals for ELIXIR core data resources.

CSC – IT center for science: We have been piloting the ePouta service, CSC cloud resources are in routine use to extend the local bioinformatics infrastructure in each biocenter, we participate in Scientific Customer panel (Hautaniemi).

Horizon 2020 Marie Sklodowska-Curie Innovative Training Network: Training site is hosted within the network

Finnish Cloud and Grid Infrastructure (FCGI): We participate in development and utilization of national distributed computing environment. We have been part of the FIRI 2016 application and obtained funding for new equipments.

Member of the the NordForsk Nordic Center of Excellence on eScience funded by NordForsk.

We participate in analysis working groups international data generation research networks such as the cancer genome atlas and international cancer genomics consortium.

	BCH	BI	BCK	BCO	BMT	BCT	FIMM
Total users	14	5	220	14	7	68	95
a. Local	11	5	190	8	6	40	49
b. Domestic	3	0	25	3	1	15	41
c. International	0	0	5	3	0	13	3
of which non-academic	0	0	2	0	0	0	1
Projects/ Datasets	2	5	180	15	9	119	4833
Database & server users / requests	--	22743	--	--	--	>300	--

We participate COST networks in chemistry of proteins, biomedicine and epigenetics.

EATRIS: We actively collaborating with the European Infrastructure for Translational Medicine (EATRIS) and provide bioinformatics services through infrastructure for its partners.

Future perspectives

From the perspective of bioinformatics, we have a considerable challenge ahead to meet the varying needs of the community we serve. We provide generic scientific IT support, hardware and software support, and data analysis to bioscience community. We also seek to ensure that all bioscience researchers in Finland have access to the computational resources necessary for large-scale data analysis as well as detailed studies on small sets of complex molecules.

Bioinformatics network aims to continue to support the data management and analysis needs of BF Biological imaging, Structural biology, Genome-wide methods, Proteomics, Single-Cell and Liquid biopsies networks. We currently rely upon researchers within bioinformatics groups to provide support to these areas. In addition, there is an urgent need for investments to local highly specialized hardware such as 3D graphics workstations for proteins structure analysis, high memory servers for providing services, as well as for local storage of large datasets generated by other BF networks. The usage of local storage resources has increased rapidly due to BF investments in new data generation instruments (e.g. plate hotel for structural biology and expansion of biological imaging). It should be noted that the local resources in Biocenters and the cloud resources via CSC/ELIXIR are non-competitive and complementary; local nodes serve special use cases and the cloud provides generic computational capacity.

We are constantly developing new analysis pipelines to provide state of the art analysis services for the community. We plan to keep main focus in next generation sequencing and proteomics data analysis. Most recently, we have started to support single cell sequencing and are actively developing services for image analysis. Novel bioinformatics services for *de novo* gene prediction and the detection of sequence contamination will also be made available by the network. For translational research, we are developing quality system for bioinformatics services to support clinical sequencing.

The number of research groups who ask for implementation and use of computational software presented in literature is growing steadily as well as demand for *in silico* modeling and simulation continues. This illustrates that there is a growing demand for more labour-intensive bioinformatics support and to educate researchers to use software tools in their research. The network aims to further increase competence and expertise to offer services to the client through more senior service staff.

We will continue to work in close collaboration and provide guidance for the national ELIXIR node at the CSC. In collaboration with major national data generation initiatives and top level research groups the network aims to support the development of national bioscience research resources towards ELIXIR core data resource status.

Impact on society

In current bioscience research, high throughput instrumentation drives the biological discoveries. To translate these vast datasets into knowledge and biological insights bioinformatics methods are the enabling technologies for discovery. Thus, the services provided by the network are highly valuable for addressing some of the key challenges of the society. For example, more and more structural bioinformatics research is impacting the understanding of human biomolecules, how they misbehave in diseases and the development of new ligands with potential to probe molecular function and to be developed into possible new drug molecules. Biological molecules (e.g. proteins, nucleic acids) based on human sequences are more and more being developed from molecular structural analysis.

Ultimately the availability of the bioinformatics methods to researchers helps to improve the diagnosis, prognosis and treatment of complex diseases, such as diabetes and cancer, by combining computational, experimental and clinical expertise.

Work done by the PIs of the bioinformatics network has led to establishment of several spin-off companies. For example, Genevia Technologies Ltd (Founder Nykter) is providing commercial data analysis for industry and academia widely in Europe and United States.

Significant grants and acknowledgements

PIs of the bioinformatics network have been highly successful in obtaining competitive funding. Examples of recent funding as PI in the application include ERC starting grant (Elo), Academy of Finland Center of Excellence Funding (Hautaniemi), Academy of Finland research grants (Nykter, Elo), Academy of Finland Key Project Funding (Nykter, Hautaniemi, Elo) and Academy of Finland Personalised Health – From Genes to Society pHealth programme funding (Holm, Hautaniemi, Kankainen). Other sources of funding include National Institutes of Health USA (Nykter), TEKES - Finnish Funding Agency for Innovation (Nykter, Kankainen, Elo), Juvenile Diabetes Research Foundation (Elo), and Horizon 2020 project funding (e.g. Hautaniemi coordinator of the HERCULES project, Elo leader of Bioinformatics in the Horizon 2020 Marie Sklodowska-Curie Innovative Training Network ENLIGHT-TEN). In addition network PIs have several smaller grants from foundations (e.g. Cancer Society of Finland, Sigrid Jusélius Foundation, etc).

Major publications supported by the platform services

S. Chul Kwon, Tuan Anh Nguyen, Yeon-Gil Choi, Myung Hyun Jo, Sungchul Hohng, V. Narry Kim, Jae-Sung Woo (2016) Structure of human DROSHA. Cell 164, 81–90.

The Dali server by BI discovered striking structural similarities between Drosha, which is involved in micro-RNA processing, and the downstream ribonuclease Dicer, suggesting an evolutionary relationship.

Heikkinen T, Kämpjärvi K, Keskitalo S, von Nandelstadh P, Liu X, Rantanen V, Pitkänen E, Kinnunen M, Kuusanmäki H, Kontro M, Turunen M, Mäkinen N, Taipale J, Heckman C, Lehti K, Mustjoki S, Varjosalo M, Vahteristo P. Somatic MED12 Nonsense Mutation Escapes mRNA Decay and Reveals a Motif Required for Nuclear Entry. Hum Mutat. 2017 Mar;38(3):269-274.
BCH performed all image analysis that led to the major conclusion that "somatic nonsense mutations in early exons of MED12 may escape NMD by using an alternative translation start site."

De Franceschi N, Arjonen A, Elkhatib N, Denessiouk K, Wrobel AG, Wilson TA, Pouwels J, Montagnac G, Owen DJ, Ivaska J. (2016) Selective integrin endocytosis is driven by interactions between the integrin α-chain and AP2. Nat Struct Mol Biol. 23(2) eISSN: 1545-9985 DOI: 10.1038/nsmb.3161
Structural bioinformatics was used to describe the molecular interactions

Sipilä KH, Ranga V, Rappu P, Torittu A, Pirilä L, Käpylä J, Johnson MS, Larjava H, Heino J. (2016) Extracellular citrullination inhibits the function of matrix associated TGF-β. Matrix Biol. 55 eISSN: 1569-1802 DOI: 10.1016/j.matbio.2016.02.008
Both structural bioinformatics and systems biology approaches were used to explore the role of this post translational modification on proteins observed to be modified in rheumatoid arthritis.

Teppo S, Laukkanen S, Liuksiala T, Nordlund J, Oittinen M, Teittinen K, Grönroos T, St-Onge P, Sinnett D, Syvänen AC, Nykter M, Viiri K, Heinäniemi M, Lohi O Genome-wide repression of eRNA and target gene loci by the ETV6-RUNX1 fusion in acute leukemia. Genome Res 26(11)1468-1477, 2016
BMT provided data analysis support for NGS data and performed the analysis and preprocessing of microarray data.

Välikangas T, Suomi T, Elo LL. A systematic evaluation of normalisation methods in quantitative label-free proteomics. To appear in Brief Bioinform.
BCT performed comparison of proteomic data normalization methods

Jaakkola MK, Seyednasrollah F, Mehmood A, Elo LL. Comparison of methods to detect differentially expressed genes between single-cell populations. To appear in Brief Bioinform.
BCT compared single-cell data analysis methods to develop optimal analysis pipeline

Kaukonen R, Mai A, Georgiadou M, Saari M, De Franceschi N, Betz T, Sihto H, Ventelä S, Elo LL, Jokitalo E, Westermarck J, Kellokumpu-Lehtinen PL, Joensuu H, Grenman R, Ivaska J. Normal stroma suppresses cancer cell proliferation via mechanosensitive regulation of JMJD1a-mediated transcription. Nat Commun. 7:12237, 2016.
BCT performed the analysis of gene expression data.

L. Garma and A.H. Juffer, Comparison of non-sequential sets of protein residues. Computational Biology and Chemistry, 61, 23-39, 2016.
BCO developed new data analysis approach

BIOLOGICAL IMAGING

Coordinator: John Eriksson, BioCity

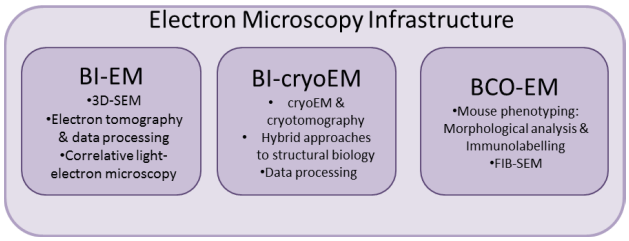
Biological imaging ranges from the visualization of ions, molecules, cells and tissues to the non-invasive imaging of full size animals. e importance of imaging has grown tremendously since the development of methods and markers for live cell imaging, such as green fluorescent proteins for confocal microscopy, 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. e 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 trans-mission electron microscopes for imaging of cells and tissues. However, in the Biological Imaging Infrastructure Network of BF, 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 platform: Eija Jokitalo, BI, Electron Microscopy Unit

Partners: Sarah Butcher BCH/BI CryoEM Unit; Ilkka Miinalainen, BCO Tissue Imaging Center

Achievements in development of technology services during 2016



The main common goal of the three EM units forming this consortium has been to restructure and streamline the functioning of the units towards nationally-unique complementary areas. The Helsinki units, BI-EM and BI-cryoEM focus on 3D imaging and hybrid methods from molecular models to whole cells and tissues, whereas 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 2016 Biocenter Finland allocations covered 6 salaries for a total of 72 person months.

Biocenter Finland funding recommendations to the host universities have been acted on and have resulted in clear improvements in the performance and quality of the services evidenced by higher scientific impact. At the end of 2016, the installation of a new FEI

TALOS Arctica transmission electron microscope with a direct electron detector (Falcon 3) was installed in BI-cryoEM. The instrument was funded by the Academy of Finland (FIRI2015 call for the roadmap infrastructure "Instruct-FI") and supported by the Biocenter Finland SAB. The microscope is especially designed for high resolution cryoelectron microscopy. It provides improved signal-to-noise, greater sensitivity and automated data collection to go on 24/7, due impart to a direct electron detector, a phase plate and a multi-specimen cartilage allowing 10 samples to be loaded together. To make room for the new microscope, an older 120 kV TEM was sold to Denmark, and the location of the other microscopes at BI-EM were rearranged, whilst preserving most of the customer services despite the renovations. Overall, 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 for screening each 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. 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 workflows have 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 utilization of advanced EM techniques, which is evident as an upsurge in scientifically demanding projects without increasing the turnover time of the existing services. The consortium members have agreed 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. 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.* "Basic Course in Light and Electron Microscopy: Across the scales, from electron microscopy to mesoscopic imaging" (BCO EM together with BCO Light Microscopy unit). In March 2016, BCO-EM organized an EM symposia "Electron Microscopy in Science" to honour the retirement of BCO-EM coordinator docent Raija Sormunen and her long career in building up and providing EM expertise in Oulu. The symposium was attended by 100 people, and the program consisted of talks given by national and international experts and researchers using electron microscopic methods in their work.

User statistics

	BI-EM	BI-cryoEM	BCO-EM	Total
total number of research groups	**98**	**14**	**36**	**148**
local academic research groups	74	8	23	**105**
national academic research groups	17	4	7	**28**
industrial users	2		1	**3**
international users	5	2	5	**12**
microscope usage (hours)	**3266**	**429**	**506**	**4201**
specimens prepared	**1483***	**256#**	**1129***	**2868**

* 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

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 BCO-EM are members in Finnish Advanced Light Microscopy Node of Euro-BioImaging (EuBI). EuBI is a pan-European research infrastructure for imaging technologies in biological and medical sciences on the ESFRI Roadmap. The mission

of EuBI is to create a coordinated plan for organization, utilization, and implementation of advanced biomedical imaging technologies in Europe to maintain Europe's leading position and competitiveness in the global research landscape. The Finnish Euro-BioImaging Node is a multimodal Advanced Light Microscopy Node with four different specialties: super-resolution imaging, correlative light and electron microscopy, label free and mesoscopic imaging. These cutting edge technologies are covered in the Finnish EuBI Node by three different sites: Helsinki, Oulu and Turku with a clear national division of tasks. The EuBI infrastructure is now in its Construction Phase and the launching of the EuBI Operation will take place in 2017. Helsinki BioImaging consists of three partners: BI-EM and Light Microscopy units of the BI and Biomedicum BioImaging Unit. BI-EM provides advanced EM techniques such as several immuno-EM methods, correlative light-electron microscopy, two 3D-EM techniques and image analysis. BCO-EM as part of the Oulu Bioimaging network (OBI) forms a mesoscopic imaging platform together with imaging laboratories from Faculty of Technology (Optoelectronics and Machine Vision), Center of Microscopy and Nanotechnology, Institute of Biomedicine and Diagnostics and Biocenter Oulu Tissue Imaging Center. BCO-EM provides for imaging platform morphological and ultrastructural expertize using various EM techniques such as immunolabelling and FIB-SEM. 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 participates in BIIF, BioImage Informatics Finland, which is a network for bioimage analysts, software developers and life scientist who use bioimage informatics as a central toolset and is a partner in EuBIAS (European BioImage Analysis network). EuBIAS is currently preparing a European COST action proposal for getting funding for networking and promoting the organization and development of bioimage informatics in Europe.

BI-cryoEM is part of Instruct-FI which is applying to the ESFRI Instruct as a distributed center covering X-ray, NMR, EM (high resolution single particle) and macromolecular complex production and mass spectrometry. BI-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 and industrial infrastructure for the development of diagnostics, therapeutics and basic science of picornaviruses.

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

Future perspectives

BI-CryoEM has just upgraded the cryoEM imaging system as indicated above. The new system was approved in April 2017, and the first samples are now being imaged. We are working with the manufacturer to optimise data collection with a phase plate and the Falcon 3 camera at 200 kV for very small proteins (90 kDa) at high resolution in a project that will continue for one year. The response from the community has been very promising with 10 groups already wanting to image samples that would not have been possible with older instrumentation. Moreover, the local demand is increasing due to the increasing versatility of the method, especially in combination with other techniques such as light microscopy, X-ray crystallography and small angle X-ray scattering.

This is the only system available to the biological community in Finland, and is one of the few in Europe that is truly open to international users. The BI-cryoEM is now part of the Instruct-FI consortium for integrated structural cell biology and in the future will report as part of that network. We will, in the context of Instruct-FI, vigorously pursue our responsibilities on research, training and outreach to the life science

research community at the national and international level.

BI-EM is aiming to upgrade its current 3D-EM services with a second, high 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 current system has already yielded 8 accepted papers, among them Science and Nature Communications papers from the collaboration project with the Helariutta group (Institute of Biotechnology, University of Helsinki). 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. In addition, we will continue our efforts in developing image analysis tools.

BCO-EM aims to further develop SEM techniques and applications available for users. Our long-term goal is to be able to offer SEM service for 3-D modelling of large tissue samples. We will continue to work closely with BCO Light Microscopy unit to explore the possibilities how our current instrumentation (TEM and SEM) could be linked to the workflow of analysing tissues, organotypic cultures and whole animals using multiphoton microscope.

Major publications

Belevich I, **Joensuu M**, **Kumar D**, **Vihinen H**, **Jokitalo E**. 2016. Microscopy Image Browser: A Platform for Segmentation and Analysis of Multidimensional Datasets. **PLoS Biol.** 14:e1002340.
Around 4 years ago, BI-EM started to develop an own software solution for challenges that the unit was facing with processing of large datasets that the 3D-EM projects produce. In conjunction with the paper, MIB was officially released under the GNU General Public License v2 and is now freely available from mib.helsinki.fi web site.

Jacków J, Schlosser A, **Sormunen R**, Nyström A, Sitaru C, Tasanen K, Bruckner-Tuderman L, Franzke CW. 2016. Generation of a Functional Non-Shedding Collagen XVII Mouse Model: Relevance of Collagen XVII Shedding in Wound Healing. **J. Invest. Dermatol.** 136:516-525.
Immuno-EM was used to analyze the location of collagen XVII in skin and TEM analysis of epidermal architecture revealed altered basement membrane structure in non-shedding collagen XVII mouse.

Kaukonen R, Mai A, Georgiadou M, Saari M, De Franceschi N, Betz T, Sihto H, Ventelä S, Elo L, **Jokitalo E,** Westermarck J, Kellokumpu-Lehtinen PL, Joensuu H, Grenman R, Ivaska J. 2016. Normal stroma suppresses cancer cell proliferation via mechanosensitive regulation of JMJD1a-mediated transcription. **Nature Commun.**7:12237.
SEM was used to analyze the cell-derived matrix produced by the different fibroblast cells in order to investigate the potential effect of matrix on cancer cell proliferation. National academic collaboration project.

Leinonen H, Rossi M, Salo AM, Tiainen P, Hyvärinen J, Pitkänen M, **Sormunen R, Miinalainen I**, Zhang C, Soininen R, Kivirikko KI, Koskelainen A, Tanila H, Myllyharju J, Koivunen P. 2016. Lack of P4H-TM in mice results in age-related retinal and renal alterations. **Hum. Mol. Genet.** 25: 3810-3823.
Renal alterations were studied at the ultrastructural level with TEM. TEM studies of retina revealed defects in retinal pigment epithelial cells and altered photoreceptor recycling.

Li S, Zhu M, Pan R, Fang T, Cao YY, Chen S, Zhao X, Lei CQ, Guo L, Chen Y, **Li CM**, **Jokitalo E**, Yin Y, Shu HB, Guo D. 2016. The tumor suppressor PTEN has a critical role in antiviral innate immunity. **Nature Immunol.** 17:241-249.
Localization of PTEN was analyzed in BI-EM. International collaboration work.

Ohsaki Y, Kawai T, Yoshikawa Y, Cheng J, **Jokitalo E**, Fujimoto T. 2016. PML isoform II plays a critical role in nuclear lipid droplet formation. **J. Cell Biol.** 212:29-38.
Serial block face scanning EM imaging of lipid loaded cells was utilized to analyze lipid droplet formation in cell nucleus. Project was initiated during Dr. Ohsaki's laboratory visit to Prof.

Elina Ikonen's laboratory in Biomedicum, University of Helsinki, and continued as international collaboration between the BI-EM and Fujimoto group, Japan.

Prunskaite-Hyyryläinen R, Skovorodkin I, Xu Q, **Miinalainen I**, Shan J, Vainio SJ. 2016. Wnt4 coordinates directional cell migration and extension of the Müllerian duct essential for ontogenesis of the female reproductive tract. **Hum. Mol. Genet.** 25:1059-1073.

Ultrastructural analysis of Müllerian duct and Wolffian duct was done by TEM and revealed alterations in the basement membrane structure.

Räsänen M, Degerman J, Nissinen TA, **Miinalainen I**, Kerkelä R, Siltanen A, Backman JT, Mervaala E, Hulmi JJ, Kivelä R, Alitalo K. 2016 VEGF-B gene therapy inhibits doxorubicin-induced cardiotoxicity by endothelial protection. **Proc. Natl. Acad. Sci. U.S.A.** 113:13144-13149.

TEM analysis was used to assess the ultrastructural changes in cardiomyocytes caused by doxorubicin treatment and whether gene therapy would protect cardiomyocytes from these changes.

Salo VT, **Belevich I**, Li S, Karhinen L, **Vihinen H**, Vigouroux C, Magre J, Thiele C, Hölttä-Vuori M, **Jokitalo E**, Ikonen E. 2016. Seipin regulates ER-lipid droplet contacts and cargo delivery. **EMBO J.** 35:2699-2716.

Immuno-EM, high resolution 3D EM imaging and modelling was essential for characterization of ER-lipid droplet contact sites and for localization of seipin. Collaboration between Jokitalo and Ikonen groups, University of Helsinki.

Shakeel S, Westerhuis BM, **Domanska A**, Konig RI, Matadeen R, Koster AJ, Bakke, AQ, Beaumont T, Wolthers KC, **Butcher SJ.** 2016. Multiple capsid-stabilizing interactions revealed in a high-resolution structure of an emerging picornavirus causing neonatal sepsis. **Nature Communications** 7:11387. doi: 10.1038/ncomms11387.

The initial screening of the data were carried out in the BI-cryoEM, as were the final data for the high resolution structure of the antibody-bound particle.

National Preclinical *In Vivo* Imaging Technology Platform

Chair of the platform: Olli Gröhn, BCK

Partners: Turgut Tatlisumak, BCH; Juhani Knuuti, BioCity

Achievements in development of technology services during 2015-2016

In vivo imaging consortium continued to serve as a national multimodal preclinical *in vivo* imaging network, with clear division of the tasks and core expertise area in each of the contributing Biocenters. Our open access multimodal imaging infrastructure has now 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.

PET imaging

Improvements in the capacity of PET tracer production in Turku PET center have been achieved. This was the bottleneck for increasing the capacity required for efficient provision of PET imaging services, as the PET imaging systems were already recently upgraded. The PET tracers need to be produced in a dedicated radiotracer synthesis laboratory that is in close proximity to a cyclotron laboratory. The existing synthesis laboratory has the qualified space for the synthesis but the number of synthesis devices was limiting for the availability of tracers for preclinical imaging

Preclinical PET imaging is now available also in Kuopio. Radiotracer production started 2016, and now more comprehensive selection of PET tracers, including also tracer with short life time nuclei, is available for preclinical imaging.

MR Imaging

Kuopio continued to provide MRI services with three MRI systems operating at 7T and 9.4T exploiting both Agilent DirectDrive and Bruker Biospin consoles providing practically all MRI sequences available at the moment for preclinical imaging.

Biomedicum Imaging Unit discontinued MR imaging services at the end of 2014, because of an outdated instrument. The instrument was decommissioned in the spring 2015, coinciding with the move of Prof. Turgut Tatlisumak to the Univ. of Gothenburg. During 2016 also Oulu discontinued activities in the preclinical MRI, making Kuopio only place to provide small animal MRI services with dedicated high filed MRI systems. Turku has capability for basic level small animal MRI using 3T human MRI with dedicated small animal RF-coils.

Optical Imaging

Biomedicum Imaging Unit has continued services in optical in vivo imaging and developed novel intravital modalities, using both multiphoton intravital imaging and two optical in vivo imaging (IVIS) systems. Due to lack of a nominated PI after Prof. Tatlisumak's move, these instruments, User Statistics, personnel, and key publications were reported under the Light Microscopy platform for 2015-2016 (BIU-BCH light microscopy headed by Elina Ikonen). The financial contribution of BIU in vivo imaging was also included in the Light Microscopy platform financial report, but is additionally reiterated here.

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.

Participation in international, Nordic and European infrastructures

Parts of the national preclinical *in vivo* imaging network belong thorugh Euro-BioImaging (EuBI) infrastructure on the Academy of Finland research infrastructure roadmap 2014-2020. In vivo imaging will likely also apply node status in Euro-Bioimaging in the next call. The national preclinical *in vivo* imaging network is also linked with other ESFRI initiatives. In EATRIS ESFRI (European Advanced Translational Research Infrastructure in Medicine) Turku PET Centre is one of the two centers contributing the imaging tracers. Partner Helsinki is a managing committee member in the EU COST action MicroCoR (Chemical Imaging by Coherent Raman Microscopy) that involves all aspects of coherent Raman microscopy techniques. In collaboration with the Finnish IT Center for Science (CSC), Institute for Molecular Medicine Finland (FIMM), and the University of Helsinki IT Services, partner Helsinki has established a centralized platform for data storage, management, visualization, and analysis. The CSC has recently expanded its cloud services to offer cluster computing for the biomedical sector, which is to form a part of the Finnish node in the European life science ELIXIR ESFRI infrastructure. This platform will be hosted in the cloud as one of the Ministry of Education and Culture subsidised pilot projects for the ELIXIR 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.

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 in 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 infrastructure network.

From the beginning of 2017 in vivo imaging is not anymore part of the Biocenter Finland network, however, the same service concept continues to serve Finnish biomedical research community as a part of Finnish Infrastructure for Functional Imaging (FIFI, http://neuro.hut.fi/fifi/), which is on national infrastructure roadmap through EuroBioImaging. The major reason for this change was that in FIFI both small animal and human imaging are in the same consortium, which evokes more interaction and collaboration between in vivo imaging scientists and forms better platform for translational research

Light Microscopy Technology Platform

Chair of the platform: John Eriksson, Turku Bioimaging

Partners: 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.

Achievements in development of technology services

2016 marked the beginning of a new era for Finnish imaging and the Biocenter Finland Light Microscopy consortium. Euro-BioImaging (EuBI) started its Interim Operation in May 2016, with the Finnish Advanced Light Microscopy (ALM) Euro-BioImaging Node being among the 13 of the 1st generation nodes ratified by the EuBI Interim Board in early 2016. The Node is formed by four units of the consortium; TBI-CIC, TIC-BCO, BIU-BCH and LMU-BI. The Node operates at three sites across Finland, Helsinki, Oulu and Turku, with Turku as the coordinator. For its EuBI activities, the node is governed by the Interim EuBI Hub, which in turn interacts closely with the EuBI Interim Board. Finland is the Statutory Seat of the Interim EuBI Hub, lead by Turku.

Services provided by the Finnish EuBI node cover super-resolution imaging and other advanced multidimensional light microscopy (LM) methods, mesoscopic imaging and label free techniques. Importantly, the Finnish node can offer all its services as three-dimensional (3D) packages that cover also the production of quantitative analysis and processing results. Similar services are not provided by other EuBI nodes in an organized manner. By the end of 2016, the Finnish Node was among the most sought-after EuBI Nodes, having received 6 EuBI user applications from Sweden, Germany, United-Kingdom and India.

The investments made to construct the Finnish EuBI Node services have provided also local and national users access to novel, internationally competitive, and cutting-edge techniques not previously available to Finnish scientists. Collaboration between the Finnish imaging facilities has also become stronger, and possible national solutions for instance for image data management and storage are now being planned.

The recent significant funding received from Biocenter Finland (BF) for constructing and strengthening the Finnish EuBI ALM Node has been elemental in enabling the development of Finnish bioimaging to truly international standards. This has also been necessary for Finland to believably assume its position as the head of Euro-BioImaging, and it is crucial to maintain Finland at the international top in bioimaging also in the future.

Based on both BF questionnaire for PIs and local feedback questionnaires, to better meet user's needs and guarantee sufficient service level, new confocal instruments have been acquired: BIU-BCH purchased Leica TCS SP8 X and BMT Tampere, a Nikon A1R with N-SIM, and multiphoton microscopy system in TIC-BCO. In 2017, a new confocal microscope will be also installed at LMU-BI. Platform units have also continued to develop their access policies (including pricing and news about services) to ensure most efficient instrument operation times.

The capacity of the cutting edge imaging technologies will also be increased to further strengthen the services provided by Finnish EuBI ALM node. In 2017 LMU-BI will acquire a STED system, and BIU-BCH a live-cell compatible superresolution microscope.

Recent technological developments at the Finnish imaging centers

Super-resolution imaging:

CIC-TBI_acquired a new Abberior STED system that allows resolutions down to 20-30 nm. This system is customized to have three excitation lasers @488 nm, 532 nm and 640 nm that together with the two depletion lasers @590 nm and 775 nm allow up to three color super-resolution imaging. The instrument also includes the RESCue STED mode that reduces the light dose sent into the sample without compromising resolution and therefore allows STED imaging conditions suitable for live-cell imaging.

BMT-Tampere acquired a Nikon N-SIM super-resolution system (resolution approx. 110nm). The system is equipped with 405 nm, 488 nm, 561 nm and 640 nm lasers, allowing super-resolution imaging with 4 different channels, in living or fixed samples. The system includes also a Nikon A1R LSCM, and the imaging modalities can be easily combined (LSCM + SIM).

BIU-BCH acquired a Leica TCS SP8 X white-light laser confocal. The system was equipped with the HyVolution 2 module, facilitating high-resolution imaging with a lateral resolution of 140 nm with normal confocal samples and fluorescent labels.

High-content and high-throughput imaging:

BIU-BCH: To facilitate larger image sets, the newly acquired Leica TCS SP8 X white-light laser confocal was equipped with the Leica HCS A Matrix Screener module.

Label-free technologies:

TIC-BCO acquired a multiphoton microscope system with tunable 820 nm - 1300 nm femtosecond pulse laser for second and third harmonic generation, which allows label free imaging of various cell types, macromolecular and tissue structures.

BIU-BCH: The national BioCARS Centre offers multiphoton CARS (coherent anti-Stokes Raman scattering) microscopy as well as second and third harmonic generation imaging services suited for label-free sample visualization. BIU-BCH is among the first, if not the first, open access CARS microscopy core facilities in Europe, with users from both EU and non-EU countries (Denmark, Australia, Canada). In addition, the facility fosters collaboration between biological and technical sciences. For example, surface enhanced CARS technique for ultrahigh sensitivity imaging is under development together with a nanotechnology group at Aalto University. University of Helsinki and the Technical University of Lappeenranta, for their part, have initiated a project in the development of label-free analysis of nanoparticle/drug–cell interactions.

Mesoscopic imaging

LMU-BI acquired a Zeiss Lightsheet Z.1 microscope, which permits fast, gentle and long-term imaging of also large samples. The

microscope offers flexible imaging possibilities for samples ranging from 3D cell cultures to embryos and even small organisms, and is, for example, equipped with optics for deep imaging of cleared tissue sections and organs. Z.1 will benefit especially the fields of developmental and neurobiology, which are scientific strongholds of the Viikki campus.

BMT-Tampere acquired a Nikon FN1 upright fluorescence microscope with micromanipulation possibility. The system is equipped with LED fluorescence light source, infrared DIC imaging and reflection imaging. Furthermore, 2 micromanipulators allow simultaneous micromanipulation or patch clamp measurements.

TIC-BCO set up a new multiphoton microscope system that greatly improves 3D imaging of large fluorescent samples, also allowing label-free second/third harmonic generation imaging of biomolecules and tissue structures.

Image analysis and processing

At TIC-BCO a novel joint cell segmentation and tracking method using cell proposals for automated analysis of time-lapse microscopy imaging data was developed (Akram et al IEEE ISBI, 2016). In addition to own custom made solutions for microscopy image data analysis, BCO has also invested in commercial software for allowing better cell tracking, morphological and qualitative analysis of microcopy image data. At CIC-TBI, an automated image quality ranking method for microscopy was developed (Koho and Fazeli et al, 2016), and new types of analyses and methods for high-throughput image analysis were under development based on the BioImageXD software platform.

General bottlenecks

The most frequently used imaging modalities, confocal microscopes, live-cell imaging and time-lapse experiments have continued to be at the top of the list of services in highest demand. Increase in dedicated support personnel is also needed for the efforts to develop novel state-of-the-art imaging technologies and image data analysis that are not yet commercially available. The basic infrastructure funding typically does not cover sufficient amount of personnel costs needed for technique development. On the platform wishlist are e.g. light sheet microscopy for BIU-BCH and a multiphoton system for BMT-Tampere.

User Statistics

See next page.

Participation in international, Nordic and European infrastructures in 2016

The BF light microscopy consortium continued its active participation in the Euro-BioImaging ESFRI (www.eurobioimaging.eu), a pan-European research infrastructure for biological and medical imaging. In 2016, the H2020-funded Euro-BioImaging Preparatory Phase II project was ongoing, with Finland leading the development work of the Euro-BioImaging Web Access Portal. The Interim Operation phase of Euro-BioImaging was started in May 2016, lead by Finland as the future Statutory Seat, and an Interim version of the Web Access Portal was launched (www.eurobioimaging-interim.eu). The Finnish Euro-BioImaging Advanced Light Microscopy Node, consisting of Turku BioImaging, Helsinki BioImaging and Oulu BioImaging, started its operation, coordinated by Turku. A H2020-funded global extension project of Euro-BioImaging, Global BioImaging, also started its operation, with Finland having an active role.

The Bridging Nordic Imaging –network, coordinated by Turku, held its second big international meeting in Gothenburg in the spring, with substantial representation from Finland. The Finnish participants also won the prizes for best oral and poster presentations. The meeting effectively expanded on Nordic imaging collaboration and brought together

	BIU-BCH Helsinki	LMU-BI Helsinki	TIC-BCO Oulu	IBT Tampere	CIC-TBI Turku	Total
Total number of research groups	79	68	40	22	63	**272**
- local groups	63	62	30	22	59	**236**
- other domestic groups	13	4	3	-	1	**21**
- international groups	1	1	5	-	-	**7**
- non-academic groups	2	1	2	-	3	**8**
Total instrument hours	12470	16434	7370	14000	13034	**63308**
Single users	222	212	112	86	339	**971**
Annual financial turnover	171003	168972	38757*	25739	178532	**583003**

*) different cost model

representatives from different imaging-related networks.

The COST-funded Network of European BioImage Analysts (Neubias, http://eubias.org/NEUBIAS/) started its operation, with two Finnish representatives in its management board, and the related BioImage Informatics Finland (BIIF) network took its first steps.

Future perspectives

During the next year, the EuBI ERIC is likely to be established, with Finland in the lead as the Statutory Seat. Euro-BioImaging will then officially exist, and strengthening of the Finnish Euro-BioImaging Node will continue with for instance the funding received from Biocenter Finland.

In the near future, EuBI activities are expected to significantly increase the number of international visitors in Finland and the international reputation of Finnish bioimaging. Overall, Finnish bioimaging is likely to become more closely associated with Euro-BioImaging, with the goal of an even better division of tasks and stronger collaboration and harmony between the different imaging facilities in Finland. Common data management and storage solutions should also be developed with the help of CSC. As a whole, Finnish bioimaging is likely to be in a strong international leading position.

Correlation between clinical measures in patients and cellular and molecular mechanisms revealed in preclinical models is likely to be improved, and overall Finland has unique opportunities in bringing medical and biological imaging closer together. Finnish bioimaging will also continue to develop especially its established strongholds, such as multi-dimensional super-resolution, multimodal mesoscopic imaging, hyperspectral imaging and image analysis.

Finland currently has outstanding potential in bioimaging, but realizing and utilizing this potential requires long-term planning, commitment and funding from everyone involved.

Small Animal Molecular Imaging (SPECT/CT)

Chair of the platform: Raimo K. Tuominen, Division of Pharmacology and Toxicology, University of Helsinki

Partners: Anu Airaksinen, BCH.

Achievements in development of technology services during 2016

In 2016 the imaging system got a major upgrade consisting of new work stations, new software Nuclein_Fusion, an improved SPECT camera managing system, 3-D SPECT/CT integration imaging analysis, and automatic and improved reconstruction capabilities. In addition, the system was equipped with an ECG cardiac/respiration gating unit, which compensate the artefacts due to imaging shifts over cardiac/pulmonary movements.

The availability and an upgraded system directly translated into improved service. In 2016, the unit served 10 projects (see Table 1), the double compared to the previous year. Remarkably, in 2016 the service produced a considerable increase of income, the highest in the history of the unit. These achievements are remarkable considering the low number of personnel of the RTI laboratory, lowest since 2013. Compared with 2015, the service provided with a remarkable increase of number scans to 243.

These improvements were reflected in the opinion of the users on the annual BF user survey, which qualified the unit over the "very well" mark (average of 4.3 points out of 5). The main limiting factor for any further improvement was the availability of personnel dedicated to the unit. Furthermore, in the recent BF evaluation, the international scientific advisory board ranked the SPECT/CT services as unique and of high international quality and great scientific importance to the users.

The RTI unit service platform has indeed improved. Technology is now efficiently available for pharmacokinetic and pharmacodynamics studies (e.g. assessment of drug delivery systems; bio-distribution studies). In addition, specific methods to measure neuronal integrity, as dopaminergic, serotoninergic and inflammatory imaging, for research in neurodegeneration models, are available, widening the service in different areas of neuropsychopharmacology.

The RTI unit is member of the newly established infrastructure platform Helsinki in vivo animal imaging platform (HAIP) from the HiLIFE Helsinki Institute of Life Science, which preliminary obtained very good evaluation grades and the provision of start funds

User Statistics

Table shows the service provided by the RTI unit in 2016. Ten projects were provided for 8 different groups, 7 were domestic, 6 of them being local users, one user was from abroad, and two company projects where performed. **In total around 250 scans were performed.** From this work, several articles have been already published where RTI service was essential (see **Major publications**), and more publications are expected to be out soon.

	Tracer	Area	Animals scanned
1	^{111}In-DTPA	Full body bio-distribution	5
2	^{111}In-EDTA	Intraocular bio-distribution	8
3	^{99m}Tc-Hexosomes	Hexosome bio distribution	4
4	^{123}I-β-CIT	GDNF regulation of dopaminergic integrity	4
5	^{111}In-OT-1	Tumour targeting	12
6	^{111}In-DTPA	Full body bio-distribution	15
7	^{123}I-rhCDNF	CNS Biodistribution	2
8	^{99m}Tc-SpmTrien	Hexosomes distribution	
9	^{123}I-CDNF-C	CNS Biodistribution	2
10	^{111}In-T-Cells	Tumour targeting	9

Participation in international, Nordic and European infrastructures

The laboratory is main partner in the COMPACT project (FP7) 2012-2017, and participant partner in the COST action TD1004.

Future perspectives

Having consolidated a variety of applications in our service portfolio it is expected an increase on the demand of the service in the near and midterm future. The good performance of the unit in terms of service provided, has seen an impact in own image, which has attracted more companies to hire the services. We foresee the establishment of at least two big contracts with private companies national and international. The efforts to promote and market the unit, start to give fruitful impact on service development, but also pushes for improvement of service capacity, already feasible in terms of equipment and space.

It is important to note that the funding from the BF (around 25% of the full cost expenses) has been essential for the development of the unit. Since the service needs have increased, we consider that funding from BF should also increase accordingly, at least with additional funds for the salary of one more researcher (around 35 000 €) to be able to cope with everyday imaging, planning and analysis, and in order to guarantee proper service at the current level.

In addition, the laboratory has increased ambition to further expand the area of service to PET imaging. The unit counts with the collaboration of the only non-clinical radiopharmaceutical chemistry laboratory in Finland, at the Radiochemistry Unit in the Department of Chemistry in the Kumpula campus of the University, with the availability of cyclotron facility. The developing of an integral nuclear imaging in Helsinki, would be very welcome by local research community expectations, as particularly reflected in the last BF infrastructure user's survey: most of the Finnish research on animal models is made in the University of Helsinki, and the need for local imaging, nuclear (both SPECT and PET) and that based in magnetic resonance, is essential. The existence of top of the art facilities in locations remote from the metropolitan area, is non ractical, and has delayed or killed essential research on basic science and potentially innovative preclinical research due to local unavailability. The Faculty of Pharmacy has shown good commitment on support applications for these ambitions goals, and would substantially contribute with matching funds in that respect.

GENOME-WIDE METHODS

Coordinator: Janna Saarela, FIMM

Genome-wide methods including DNA sequencing, RNA and epigenetic 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 by the Helsinki biocenters.

It is essential to provide tailored services in the genome-wide methods area to Finnish scientists also in the coming years to maintain at the cutting edge. This development requires both long-term funding to enable recruitment and maintenance of top quality scientists and technical experts as well as continuing investments into new technologies. The BF Genome-wide methods 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, single cell analysis, and the increasing efficiency and speed of DNA sequencing serve as examples of continuous need for new equipment and upgrading of current ones. The fast development 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 platform: Janna Saarela, FIMM

Partners: Outi Monni, Tea Vallenius, BCH; Riitta Lahesmaa, Riikka Lund, BioCity; Petri Auvinen BI

Achievements in development of technology services

As demonstrated by the User Statistics(Table 1) the demand for the services as well as the number of the applications and samples handled by the BF-GWM nodes has steadily increased. Both direct feedback as well as the feedback collected through surveys has indicated that the BF-GWM has been successful in providing high quality, efficient services in reasonable time. Due to high demand for some services, the waiting times have occasionally been unwanted, despite our attempts to reallocate the resources. For example the move of BIDGEN operations to a new building within the Viikki campus during the spring 2016 caused several weeks of down time due to unloading the old facilities and building the new one with 1/3 less space.

With the support from Academy of Finland FIRI and host universities significant developments have been made in implementing the latest cutting edge technologies and establishing single cell analysis services in Finland, including capture, transcriptome analysis and functional characterization of individual cells. However, the insufficient funding for sequencing equipment renewal is significantly hampering the future development and operations of BF-GWM nodes. The existing NGS instruments, supporting the highly utilized established services in addition to the single cell analysis

and other novel services, will be out of the date within a year. The existing high throughput instruments represent expiring technology, which is not developed further by the manufacturer, and can no longer provide the most cost-efficient sequencing services. To temporarily overcome the challenge of providing cost-effective human genome sequencing, the network is collaborating with the SciLife laboratory in Sweden. However, if alternative strategies for securing the funding are not immediately found, the cutting edge NGS services will peter out in Finland. This development would also endanger the goals of the National genome strategy: Finland has an internationally enticing research and business environment for genomics (http://stm.fi/en/article/-/asset_publisher/suomesta-voi-tulla-genomitiedon-hyodyntamisen-mallimaa)

User Statistics

Over 400 research groups have used the services provided by BF-GWM nodes during 2016 with a turnover exceeding 4.7M€ as demonstrated in the Table 1. Most of the users (95 %) were academic. The complementary nature of sharing the tasks between the nodes is evident through comparison of the services in genomics, gene expression, and genome-scale biology (Table 2). Importantly, there is a steady increase in the use of NGS services in 2016 compared to previous years.

Participation in international, Nordic and European infrastructures

The GWM network is in an optimal position to take responsibility as a node for ESFRI level infrastructures, and is one of the preferred sample analysis sites for BBMRI.fi. The expertise of the network is utilized in BBMRI EU level planning of biomedical infrastructure resources. FIMM unit also operates as a national node for EATRIS biomarker platform. Furthermore, the network in collaboration with CSC is developing solutions for the above needs via CSC cloud computing service within the ELIXIR ESFRI program, and is using virtual machine solutions in complex analyses of several pilot projects. These activities are also planned in close contact with the BF-Bioinformatics network. In addition to the national co-operation and collaboration of the infrastructures, BF-GWM has developed strong networks to international infrastructures enabling rapid and efficient transfer of knowledge, technologies and collaboration. FIMM has representative in EU-Life Core Facilities working group which focuses on

Services	BioCity Turku (FFGC)			BI (BIDGEN)			FIMM			BCH (FuGU+GBU)-2016		
	Samples	Projects	Groups	Samples	Projects	Groups	Samples	Projects	Groups	Samples	Projects	Groups
Resequencing	6	1	1	811	19	19	108	33	19	125	5	4
De novo	4	2	1	190	17	17	0	0	0	28	3	1
Metagenomics	263	5	4	2576	31	31	3902	22	6	42	1	1
Targeted	3208	143	71	19	2	2	9053	359	31	184	13	10
SNP genotyping (QWAS)	674	2	2				14647	30	20			
Targeted SNP typing	1681	3	2				40281	16	15			
Copy number variation**	87	13	9							6	2	2
Immunoprecipitates (ChIP-seq etc.)*	50	3	3				2212	6	5	19	7	3
RNA sequencing	1595	52	31	989	32	32	314	45	18	270	29	20
Gene expression microarrays	16	1	1				12	1	1	335	44	19
Targeted RNA analyses, qPCR***				144	1	1	38	3	3	345	4	4
Genome-scale reagents							6	2	2	564	121	35
ORF cloning										83	33	16
High-content analysis (HCA)										4462	178	28
Customers												
					Projects	Groups		Projects	Groups		Projects	Groups
local		199	68		73	80		456	74		375	78
other domestic		27	18		4	3		43	24		35	21
international		11	9		1	3		10	8		3	3
non-academic groups/ units		4	6		8	1		8	7		31	3
TOTAL		241	101		86	87		517	113		444	105
Billing total (Cost recovery)			**Total**			**Total**			**Total**			**Total**
			780,494 €			**610,694 €**			**2,736,882 €**			**604,208 €**

*includes methylation arrays and bisulfite sequencing

**includes genome-wide(CGH) and targeted

*** includes Biomark HD and Nanostring runs

Cost recovery grand total **4,732,278 €**

developing core facilities through information sharing.

Future perspectives

Capability to analyse genome(s) and population of individuals and their functions is an important part of practically all life science research today. Analysing the nature's experiments, the individuals with gene defects, gives both detailed molecular knowledge about the disease, and also improves our understanding of the basic functions of the human body. Furthermore, recent developments in the sequencing technology enable researchers to expand the genome analysis from individuals to populations revealing more subtle genome changes with significant health outcomes in a population level. Taking the next technological step will allow analysis of personal genomes used in precision medicine, and for example cancer care. With this in mind, the BF-GWM network is closely working with the hospitals to enable use of the latest genome analysis technology also in diagnostics.

The same development has been seen in analysis of the microbe genomics, not forgetting other eukaryotic species. Today we are already making population wide analysis of large, so called homemade genomes like birch, Saimaa ringed seal and strawberry, answering basic questions on adaptation, evolution and gene to phenotype correlations, that are relevant also for human biology and diseases. Microbiome sequencing will need much more capacity to enable both targeted approaches like 16S and ITS community analysis, as well as shotgun metagenomics and metatranscriptomics. During the last few years due to the recent advances both in sequencing technologies and development of novel bioinformatic tools, the importance of microbiome in health and diseases has been perceived.

The other end of scale are the single cell approaches, which are being widely used to answer research questions that can not be answered by analysing a group of cell or populations of individuals. BF-GWM network is looking forward in developing the single cell sequencing approaches in collaboration with the Single Cell Analysis network. The development includes optimization of library protocols for single cells and library preparation automation, which need to be adjusted to very small sample volumes. GWM network already has experience in working with very limited sample materials, such as sequencing of only few nanograms of total RNA extracted from tissue slices, sorted rare cell populations or exosome vesicles, which forms a solid basis for development of single cell methodologies. The Helsinki and Turku units have set up single cell transcriptome services in collaboration with the Single Cell analytics units, and Turku unit is currently implementing methods for single cell DNA methylation analysis.

The findings enabled by the current NGS sequencing technologies bring up a need for genome wide and single cell level follow-up methods, which are supported by the library collections (ORF clones, siRNA and shRNA libraries) provided by the genome scale reagent nodes. The current libraries would greatly benefit from an upgrade: new species and more coverage would improve the highly utilized services. Also expanding the collection of destination vectors would be highly relevant as this enables the clones to be applied in various settings. Having the resources for e.g. generating suitable control constructs and developing new approaches, such as customized cloning, would further improve the services.

Although the BF-GWM is one of the largest networks in Biocenter Finland and supporting a very wide research community, it is in a verge of becoming outdated, despite our efforts to maintain state-of-the art sequencing capacity. The altered funding schedule of the FIRI and lack of sufficient resources in maintaining life sciences infrastructures will soon jeopardize further development of the world-class genome research in Finland on brink of new era when due to revolution of technologies and decreased costs, genome research is becoming increasingly popular, important and entering also clinical use. The

newest high throughput and most cost-effective sequencing technologies are lacking in Finland, and compared to for example Sweden and Norway we are already now two-three years behind in the instrument renewal. As a result the BF-GWM network can not fulfil the needs of the newly set up Single Cell Analysis network, nor the development of genome sequencing expertise, unless alternative funding strategies are immediately elaborated.

Major Publications

Andersson, E., Kuusanmaki, H., Bortoluzzi, S., Lagstrom, S., Parsons, A., Rajala, H., van Adrichem, A., Eldfors, S., Olson, T., Clemente, M. J., Laasonen, A., Ellonen, P., Heckman, C., Loughran, T. P., Maciejewski, J. P. & Mustjoki, S. Activating somatic mutations outside the SH2-domain of STAT3 in LGL leukemia May 2016 In : Leukemia. 30, 5, p. 1204-1208.
FIMM: NGS sequencing and data analysis

Balistreri G, Viiliäinen J, Turunen M, Diaz R, Lyly L, Pekkonen P, Rantala J, Ojala K, Sarek G, Teesalu M, Denisova O, Peltonen K, Julkunen I, Varjosalo M, Kainov D, Kallioniemi O, Laiho M, Taipale J, Hautaniemi S, Ojala PM. Oncogenic Herpesvirus Utilizes Stress-Induced Cell Cycle Checkpoints for Efficient Lytic Replication.
PLoS Pathog. 2016 Feb 18;12(2):e1005424.
FuGU: Genome-scale reagents

Hukelmann JL, Anderson KE, Sinclair LV, Grzes KM, Murillo AB, Hawkins PT, Stephens LR, Lamond AI, Cantrell DA. The cytotoxic T cell proteome and its shaping by the kinase mTOR. Nat Immunol. 2016 Jan;17(1):104-12. IF: 19.381.
Biocity Turku (FFGC): gene expression microarray service.

Immanen, J., Nieminen, K., Smolander, OP., Kojima, M., Serra, JA., Koskinen, P., Zhang, J., Elo, A., Mähönen, AP., Street, N., Bhalerao, RP., Paulin, L., Auvinen, P., Sakakibara, H. & Helariutta, Y. 2016. Cytokinin and auxin display distinct but interconnected distribution and signaling profiles to stimulate cambial activity. Current Biology 26, 1990-1997.
BIDGEN: RNA seq from tissue slices and bioinformatic analysis

Kaukonen R, Mai A, Georgiadou M, Saari M, De Franceschi N, Betz T, Sihto H, Ventelä S, Elo L, Jokitalo E, Westermarck J, Kellokumpu-Lehtinen PL, Joensuu H, Grenman R, Ivaska J. Normal stroma suppresses cancer cell proliferation via mechanosensitive regulation of JMJD1a-mediated transcription. Nat Commun. 2016 Aug 4;7:12237. IF: 11.329.
Biocity Turku (FFGC): gene expression microarray service, NGS mRNA-seq service, qPCR service, chromatin immunoprecipitation.

Kumar A, Kopra J, Varendi K, Porokuokka LL, Panhelainen A, Kuure S, Marshall P, Karalija N, Härma MA, Vilenius C, Lilleväli K, Tekko T, Mijatovic J, Pulkkinen N, Jakobson M, Jakobson M, Ola R, Palm E, Lindahl M, Strömberg I, Võikar V, Piepponen TP, Saarma M, Andressoo JO. (2016) GDNF Overexpression from the Native Locus Reveals its Role in the Nigrostriatal Dopaminergic System Function. PLoS Genet. 2016 Jan 11;12(1):e1005808. doi: 10.1371/journal.pgen.1005808. eCollection 2016 Jan. PMID:26752407
BIDGEN: Sequencing, GBU: ORF cloning service

Mehine M, Kaasinen E, Heinonen HR, Mäkinen N, Kämpjärvi K, Sarvilinna N, Aavikko M, Vähärautio A, Pasanen A, Bützow R, Heikinheimo O, Sjöberg J, Pitkänen E, Vahteristo P, Aaltonen LA. Integrated data analysis reveals uterine leiomyoma subtypes with distinct driver pathways and biomarkers
Proc Natl Acad Sci U S A. 2016 Feb 2;113(5):1315-20.
FuGU: NGS

Pehkonen H1, von Nandelstadh P1, Karhemo PR1, Lepikhova T1, Grenman R2, Lehti K1,3,4, Monni O1. Liprin-α1 is a regulator of vimentin intermediate filament network in the cancer cell adhesion machinery. 3. Sci Rep. 2016 Apr 14;6:24486. doi: 10.1038/srep24486.
GBU: ORF cloning service

Robciuc MR1, Kivelä R2, Williams IM3, de Boer JF4, van Dijk TH5, Elamaa H6, Tigistu-Sahle F7, Molotkov D8, Leppänen VM2, Käkelä

R7, Eklund L6, Wasserman DH3, Groen AK9, Alitalo K10.VEGFB/VEGFR1-Induced Expansion of Adipose Vasculature Counteracts Obesity and Related Metabolic Complications. Cell Metab. 2016 Apr 12;23(4):712-24. doi: 10.1016/j.cmet.2016.03.004.

GBU: Digital slide scanning service
Sõber S, Rull K, Reiman M, Ilisson P, Mattila P, Laan M. RNA sequencing of chorionic villi from recurrent pregnancy loss patients reveals impaired function of basic nuclear and cellular machinery. Sci Rep. 2016 Dec 8;6:38439.
FIMM RNA sequencing and data analysis

MODEL ORGANISMS

Coordinator : Raija Soininen, BCO

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

Understanding of gene function and interactions, the impact of environmental factors, and the basic biology of pathways and systems is important for effective treatments of human diseases. 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. They are central tools in the development of diagnostic, prognostic and therapeutic strategies.

Work with GM mice requires high-level technical expertise but also knowledge on regulations related to GM organisms and animal welfare. In Finnish biocenters, GM/transgenic mouse core facilities with experienced personnel were established already in the 1990's to provide high quality service mainly in the generation of GM mice.

Local infrastructure is still essential for providing services and expertise in all aspects of mouse-related issues, especially in customized mutagenesis, re-derivation, and archiving of mutant mouse lines, as well as in counselling and education. In addition, services in analysis ("phenotyping") of mutant mice have become more and more in demand in recent years.

Activities on generation, analysis, and archiving of mutant mice in Finland are organized into the BF FinnMouse technology platform as will be discussed below.

The technology platform on non-mammalian models uses well-characterized, simple organisms, mainly the fruit fly (Drosophila melanogaster) and the zebrafish (Danio rerio) for large-scale genetic analyses of biological regulatory pathways and mechanisms of development. Many important physiological mechanisms are conserved in evolution, therefore, in certain cases, genetically tractable non-mammalian model organisms can be used 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 BF. 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 in 2014.

FinnMouse Technology Platform

Chair of the platform: Raija Soininen

Partners: Heikki Tanila, BCK; Eero Castren, Satu Kuure, Pirjo Laakkonen, Antti Sukura, Vootele Voikar, BCH; Matti Poutanen, BioCity

Eero Castren, Neuroscience Center, University of Helsinki; Satu Kuure, Laboratory Animal Center, University of Helsinki; Pirjo Laakkonen, Laboratory Animal Center, University of Helsinki; Antti Sukura, Finnish Center for Laboratory Animal Pathology, University of Helsinki; Vootele Voikar, Neuroscience Center, University of Helsinki; Matti Poutanen, Turku Center of Disease Modeling, University of Turku; Petra Sipilä, Turku Center of Disease Modeling, University of Turku; Heikki Tanila, Neurophenotypic Core Facility, Biocenter Kuopio, University of Eastern Finland

Achievements In Development Of Technology Services

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 re-derivation of GM mice. In addition to the basic services, the units have special service profiles: The Helsinki GM unit has started to offer the generation of GM rat models using new gene modification techniques, along with rat embryo cryopreservation and re-derivation as a nationwide open access service. 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, cryopreservation and distribution of GM mouse strains, to a world-wide user community. Turku Center for Disease modeling (TCDM) provides services in generation of gene constructs for GM mouse production. Latest addition to the service repertoire in all units is generation of gene-edited mice via the CRISPR/Cas system, which has largely replaced the traditional gene targeting in ES cells. However, ES cells are still used in special projects, especially for *in vitro* differentiation studies.

For phenotypic analyses of mice, Neurophenotyping Centers (NC) in Helsinki and Kuopio (UEF) provide services in automated behavioral phenotyping and in specific neurophenotyping tests both in disease models as well as in analyzing roles of specific factors. New tests and methods are applied based on the requests by users. Testing and monitoring of mouse behavior in home-cage environment is the specific feature of the Helsinki NC facility. The UEF-NC has focused in providing extensive phenotyping test batteries and is the only facility in Nordic countries providing full characterization of the rodent visual system. The Finnish Center for Laboratory Animal Pathology (FCLAP), established 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. TCDM provides services in xenograft studies in immune-deficient mice; also a high-sensitivity steroid profiling in serum and tissues of mice has been established. Biocenter Oulu (BCO) currently focuses on services in analysis of cardiovascular functions, the electron microscopy of mouse tissues, and optical projection tomography (OPT) (reported by the Imaging platform). Also the in vivo imaging system IVIS and basic mouse histopathology services are available.

All service facilities are engaged in education of graduate students and postdocs in laboratory and lecture courses. Visits to partner laboratories and yearly personnel meetings speed up the exchange of best practices and new methods. In 2016, thanks to the funding by NorIMM/NordForsk, several international courses and workshops, fully or partly organized by FinnMouse partners, were organized for both core facility staff and researchers: 'Management of gene-modified mouse colonies' in Oulu, 'Behavioural phenotyping of rodent disease models – Potential and pitfalls' in Tartu, Estonia, 'CRISPR Genome editing' in Copenhagen, and 'Mouse breeding, genetics and colony management' in Stockholm. The meeting of Nordic Transgenic service facility personnel, with participants from all Nordic GM/TG facilities, was organized in Copenhagen in August 2016.

User Statistics

TG/GM UNIT	Local	National	International	Non-academic	Total
GM services					
Helsinki GM Unit	29	3	0	0	**32**
BCO Oulu	22	12	32	0	**66**
TCDM Turku	14	5	4	5	**28**
Total GM units	**65**	**20**	**36**	**5**	**126**
Phenotyping					
FCLAP Helsinki	13	2	1	3	**19**
NC Helsinki	15	0	0	0	**15**
NC Kuopio UEF	3	3	0	1	**7**
TCDM	53	9	3	10	**75**
BCO Oulu	17	0	0	0	**17**
Total phenotyping	**101**	**14**	**4**	**14**	**133**
TOTAL	**166**	**34**	**40**	**19**	**259**

Participation In International And European Infrastructures

University of Oulu represents Finland in the ESFRI project INFRAFRONTIER, the European Infrastructure for Phenotyping and Archiving of Model Mammalian Genomes, is a shareholder in the INFRAFRONTIER GmbH,

established in 2013, a partner in the EMMA network, the FP7-Capasities 2013-2016 project Infrafrontier-I3, and the H2020-INFRADEV-2016 project Infrafrontier2020. The FinnMouse platform is therefore well positioned to coordinate the national activities with those in Europe.

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. All FinnMouse facilities are currently partners in NorIMM.

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 and to full-fill the legal regulations. Dedicated experts are needed to keep in touch with technology development and new innovations in order to maintain the high quality. Funding for instruments and updating current equipment, which in most cases are moderately priced, but have to be up-to-date, should be available. In most cases, it is not possible to charge the customers a fee that covers all costs, therefore continued support by host institutes is essential, on one hand to sustain the quality and reliability of the services, and on the other hand to have the fees affordable to the researchers. In addition, modern animal facilities are essential and have to be properly equipped and managed with excellent health status.

New methods for genome modification, especially the CRISPR/Cas system will speed up the generation of mutant mice, which will also increase the need for archiving the mutant mouse strains. Collaboration of the units is needed in educating personnel and researchers in new techniques and challenges involved in them.

For high-level publications, multidisciplinary expertise is required for phenotype analysis of mutant mice. It is foreseen that rare diseases, where patient material is limited, will be increasingly 'modelled' in mice for therapy applications, and studies on sophisticated models for diseases such as cancer and diabetes will be further advanced.

Major Publications

Havunen R, Siurala M, Sorsa S, Grönberg-Vähä-Koskela S, Behr M, Tähtinen S, Santos JM, Karell P, Rusanen J, Nettelbeck DM, Ehrhardt A, Kanerva A, Hemminki A. Oncolytic Adenoviruses Armed with Tumor Necrosis Factor Alpha and Interleukin-2 Enable Successful Adoptive Cell Therapy. Mol Ther Oncolytics 2016 Dec 31;4:77-86.
The material for histopathological samples was processed and histopathological evaluation of tumour samples was done in FCLAP.

Haugas M, Tikker L, Achim K, Salminen M, Partanen J. Gata2 and Gata3 regulate the differentiation of serotonergic and glutamatergic neuron subtypes of the dorsal raphe. Development 2016 Dec 1;143(23):4495-4508.
GM mice were generated, analyzed and maintained in Helsinki.

Höfling CN. Kulesskaya N, Jaako K, Peltonen I, Männistö PT, Nurmi N, Vartiainen N, Morawski M, Zharkovsky A, Võikar V, Roßner S, García-Horsman JA. Deficiency of prolyl oligopeptidase in mice disturbs synaptic plasticity and reduces anxiety-like behaviour, body weight, and brain volume. Eur Neuropsychopharmacol 2016 Jun 26(6): 1048-61.
Behavioral experiments were carried out by Helsinki-NC.

Kettunen K, Karikoski R, Hämäläinen RH, Toivonen TT, Antonenkov VD, Kulesskaya N, Voikar V, Hölttä-Vuori M, Ikonen E, Sainio K, Jalanko A, Karlberg S, Karlberg N, Lipsanen-Nyman M, Toppari J, Jauhiainen M, Hiltunen JK, Jalanko H, Lehesjoki A-E. Trim37-deficient mice recapitulate several features of the multi-organ disorder Mulibrey nanism. Biol Open 2016 May 15; 5(5):584-95.

The Trim37 KO mouse strain was generated in Oulu, behavioral analysis by Helsinki-NC.

Leinonen H, Rossi M, Salo AM, Tiainen P, Hyvärinen J, Sormunen R, Miinalainen I, Zhang C, Soininen R, Kivirikko KI, Pitkänen M, Koskelainen A, Tanila H, Myllyharju J, Koivunen P. Lack of P4H-TM results in age-related retinal and renal alterations in mice. Hum Mol Gen 2016;25(17):3810-3823.
P4H-TM KO mice were generated in Oulu, analysis in Oulu and UEF-NC.

Morton NM, Beltram J, Carter RN, Michailidou Z, Gorjanc G, McFadden C, Barrios-Llerena ME, Rodriguez-Cuenca S, Gibbins MT, Aird RE, Moreno-Navarrete JM, Munger SC, Svenson KL, Gastaldello A, Ramage L, Naredo G, Zeyda M, Wang ZV, Howie AF, Saari A, Sipilä P, Stulnig TM, Gudnasson V, Kenyon CJ, Seckl JR, Walker BR, Webster SP, Dunbar DR, Churchill GA, Vidal-Puig A, Fernandez-Real JM, Emilsson V, Horvat S Genetic identification of thiosulfate sulfurtransferase as an adipocyte-expressed antidiabetic target in mice selected for leanness. Nature Medicine 2016 Jul;22(7):771-9
Mouse model generated by TCDM.

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The IOSCA mouse model was generated in Oulu, analysis in Helsinki, and imaging at TCDM Animal Imaging Unit.

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The aP2-VEGFB mouse model was generated in Oulu.

Tammimaki A, Aonurm-Helm A, Zhang FP, Poutanen M, Duran-Torres G, Garcia-Horsman A, Mannisto PT. Generation of membrane-bound catechol-O-methyl transferase deficient mice with distinct sex dependent behavioral phenotype. J Physiol Pharmacol. 2016 Dec;67(6):827-842.
GM mice were generated, analyzed and maintained in Helsinki.

Movérare-Skrtic S, Wu J, Henning P, Gustafsson KL, Sjögren K, Windahl SH, Koskela A, Tuukkanen J, Börjesson AE, Lagerquist MK, Lerner UH, Zhang FP, Gustafsson JÅ, Poutanen M, Ohlsson C. The bone-sparing effects of estrogen and WNT16 are independent of each other. Proc Natl Acad Sci USA Dec 1; 112 (48):14972-77.
Mouse model was generated by TCDM.

Non-mammalian Model Organisms Technology Platform

Chair of the platform: Mika Rämet, BMT

Partners: Pertti Panula, Neuroscience Center Zebrafish Unit BCH, Mataleena Parikka, Tampere Zebrafish Core Facility; Susanna Valanne, BMT, Tampere *Drosophila* Core facility; Osamu Shimmi, Helsinki *Drosophila* facility BI

Achievements In Development Of Technology Services

During 2015, both zebrafish facilities (Helsinki and Tampere) and Tampere Drosophila unit have succeeded well in providing services for researchers using the model. There were no animal welfare issues or technical problems that could have affected the services.

The first mutants produced using the CRISPR/Cas9 method reached aged stages, which allowed analysis of genes associated with selected genotypes (including degenerative diseases and susceptibility to infections) to be assessed at late adult stages. Targeting techniques, optimized during the

	Groups				Animals Larvae / adult
	Total	Local	Domestic	International	Total
Tampere Zebrafish	8	5	2	1	144 725 / 18 413
Helsinki Zebrafish	12	8	4		
-materials					185 services
-microinjections					66 services
-Behavioral imaging					71 services
Drosophila	7	6	1		~ 500 000

past year were now directed to generation of insertion mutants, which significantly expands the applicability of the methods. Genes which were previously very difficult to target are now accessible.

In general, the feedback received from the users has been positive.

Bottlenecks: In June 2016, Tampere zebrafish facility was translocated to a newly built Arvo-building. The translocation of the facility affected significantly the volume of services that the laboratory was able to provide. The number of fish had to be cut down to less than half of the number that was housed in 2015. Until October 2016, the facility was not able to provide all the requested services to the users (unable to produce enough adult fish for experiments).

The changes in aquarium space in Helsinki resulted in a closure of two smaller stand-alone units temporarily, which prevents currently expansion of services. New facilities have been planned, and expansion can be expected in 2018. The size of the facility is now a serious limiting factor for expansion of services.

User Statistics

Total number of groups that have used the services + volume of the services is depicted in table.

Participation In International, Nordic And European Infrastructures

The organizer of the Helsinki unit has participated in altogether 5 world-wide zebrafish PI meetings 2005-2015 and in 2016 the PI of the Helsinki facility participated in planning of the 7 global strategic ZF meeting, which was held in January 2017 in Asilomar. The Helsinki facility is still an active member of the ZFIN and ZIRC global networks, the international zebrafish society IZFS and in the European Zebrafish Resource Center.

Future Perspectives

Investment on the phenotyping methods (behavior, advanced imaging, fast qPCR in Helsinki) together with successful generation of novel mutants with the CRISP/Cas9 methods in both zebrafish units, including insertion mutagenesis, have already rendered the zebrafish units as very effective and desired avenues for new groups to get involved with zebrafish tools. With the new funding the units will be able to further develop methodological tools and services to foster the use of this advantageous model organism. The BF funding is a necessity for the further developments. The prospect is currently to stay in the forefront of research in particular in the field of basic mechanisms of diseases. We expect the number of groups which use the facility to steadily increase in both units, and to double within the next two years in Helsinki.

Major Publications

Anderl I, Vesala L, Ihalainen TO, Vanha-Aho LM, Andó I, Rämet M, Hultmark D.

Transdifferentiation and Proliferation in Two Distinct Hemocyte Lineages in Drosophila melanogaster Larvae after Wasp Infection. PLoS Pathog. 2016, 12(7):e1005746. doi: 10.1371
The work was carried out using the Tampere Drosophila core facility

Andjelković A, Kemppainen KK, Jacobs HT. Ligand-Bound GeneSwitch Causes Developmental Aberrations in Drosophila that Are Alleviated by the Alternative Oxidase. G3 (Bethesda). 2016 Sep 8;6(9):2839-46. doi: 10.1534/g3.116.030882.

The work was carried out using the Tampere Drosophila core facility

Chen YC, Semenova S, Rozov S, Sundvik M, Bonkowsky JL, Panula P. A novel developmental role for dopaminergic signaling to specify hypothalamic neurotransmitter identity. J Biol Chem. 2016 Aug 18. pii: jbc.M115.697466.

All parts of the study were carried out in the Helsinki zebrafish core, including translation inhibition, HPLC analysis, behavior, gene expression analysis

Gajewski JP, Arnold JJ, Salminen TS, Kaguni LS, Cameron CE. Expression and Purification of Mitochondrial RNA Polymerase and Transcription Factor A from Drosophila melanogaster. Methods Mol Biol. 2016;1351:199-210. doi: 10.1007/978.
The work was carried out in part using the Tampere Drosophila core facility

Kemppainen E, George J, Garipler G, Tuomela T, Kiviranta E, Soga T, Dunn CD, Jacobs HT Mitochondrial Dysfunction Plus High-Sugar Diet Provokes a Metabolic Crisis That Inhibits Growth. PLoS One 2016 Jan 26;11(1):e0145836. doi: 10.1371
The work was carried out using the Tampere Drosophila core facility

Oksanen KE, Myllymäki H, Ahava MJ, Mäkinen L, Parikka M, Rämet M DNA vaccination boosts Bacillus Calmette-Guérin protection against mycobacterial infection in zebrafish. Dev Comp Immunol ;54(1)89-96, 2016. 1371
The work was carried out using the Tampere Zebrafish core facility

Ruokonen SK, Sanwald C, Sundvik M, Polnick S, Vyavaharkar K, Duša F, Holding AJ, King AW, Kilpeläinen I, Lämmerhofer M, Panula P, Wiedmer SK. Effect of Ionic Liquids on Zebrafish (Danio rerio) Viability, Behavior, and Histology; Correlation between Toxicity and Ionic Liquid Aggregation.

Environ Sci Technol. 50:7116-25, 2016. doi: 10.1021/acs.est.5b06107.
The Helsinki zebrafish core provided all zebrafish methods for this crucial study which analyzed in vivo toxic effects of ionic fluids used to produce high-quality fabric fibers from cellulose.

Salminen TS, Rämet M. Pickle Flavors Relish in Drosophila Immunity. Cell Host Microbe 2016; 20(3)273-4,
Invited commentary from the chair of the consortium

Salminen TS, Oliveira MT, Cannino G, Lillsunde P, Jacobs HT, Kaguni LS. Mitochondrial genotype modulates mtDNA copy number and organismal phenotype in Drosophila. Mitochondrion. 2017 Feb 16. pii: S1567-7249(16)30075-7. doi: 10.1016
The work was carried out using the Tampere Drosophila core facility

Schmid MR, Anderl I, Vo HT, Valanne S, Yang H, Kronhamn J, Rämet M, Rusten TE, Hultmark D. Genetic Screen in Drosophila Larvae Links ird1 Function to Toll Signaling in the Fat Body and Hemocyte Motility. PLoS One. 2016 Jul 28;11(7):e0159473. doi: 10.1371
The work was carried out using the Tampere Drosophila core facility

PROTEOMICS AND METABOLOMICS

Coordinator: Vesa Hytönen, BMT

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. The network has 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. BF protein characterization and proteomics core facilities provide access to cutting-edge services and knowledge in mass spectrometry based proteomics and protein characterization techniques. The protein characterization and proteomics platform is expected 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 platform: Vesa Hytönen BMT, Protein Technologies Facility

Partners: Marc Baumann, BCH, Meilahti Clinical Proteomics Core Facility; Kalervo Hiltunen, BCO, Proteomics and Protein Analysis Core Facility; Peter James, BioCity, Epiproteomics Unit; Markku Varjosalo, BI, Proteomics Unit

Achievements/Bottlenecks In Development Of Technology Services

The proteome-proteomics network (PPN) provides access to services in proteomics and protein characterization. All major universities in Finland are part of the network. The services provided differ between the partners, and include proteomics, glycoproteomics, protein arrays, protein quantification, MS imaging, PTM analyses, characterization of protein interactions, membrane protein analysis, organelle proteomics, spectroscopic techniques and biophysical characterization of proteins. The efforts made to avoid unjustified overlap are commendable. The services provided by PPN are important and the number of users is high (189). The services are highly appreciated, as judged from the high scores obtained in the national BF user survey and

further supported by a local Helsinki centred survey in 2016 which reached the score of 4.4 out of 5.

Reflecting its importance, the PPN is overloaded and in need of additional resources in the form of personnel and equipment, in order to be able to provide the necessary services. As already mentioned, the BF-SAB recommends that this platform obtains high priority for funding of new instruments in the next FIRI call and some instruments have been already purchased. User fees brought in 377 kEUR in 2013, 422 kEUR in 2014, 518 kEUR in 2015 and 472kEUR in 2016; however, it is estimated that it will be difficult to increase the user fees much more.

In detail:

The **Turku Proteomics Facility** (CBT) set up a service for large-scale proteomics analysis by data independent acquisition (DIA) based quantification and bought a new mass spectrometer, Q Exactive HF, which is very suitable for DIA analysis. This also reduced the bottleneck in large scale quantitative projects. FIRI funding for a mass spectrometry for Top-down and PTM analysis was achieved.

The **Tampere Protein Technologies** (BMT) moved in year 2016 to new facilities and still managed to increase productivity and reached almost the same number of customers as 2015. Services in both protein characterization and in design and execution of protein production were established in fast schedule. New facilities have increased call of local customers and new organization in the administration of University of Tampere will increase hopefully significance of our service. In addition, new web pages were opened to sell meaningful proteins made in our service unit.

The **Protein analysis core facility of the Biocenter Oulu** (BCO) has its focus on the biophysical analysis of proteins and proteomics based on two-dimensional gel electrophoresis (2-DE). Different techniques of mass spectrometry are used as major tools in both areas. Integrated into the Faculty of Biochemistry and Molecular Medicine in the medical campus it provides service for basic as well as clinical-oriented research.

The **Proteomics Unit of Institute of Biotechnology** (BI) continued providing cutting-edge analysis services including characterization of post-translational modifications as well as label and label-free quantitative and systems-wide proteomics analyses for samples ranging from clinical to cell models. The unit has attracted more customers, both from academia and industry. In the future, the unit will keep further developing the comprehensive quantitative analyses as well start single cell proteomics analyses with BF-SC platform. Biocenter Finland 2016 FIRI-call successfully answered some of the needs and provided funding for new instrument(s), which will even further strengthen this node. Together with the Meilahti Clinical Proteomics Core facility the Unit forms the largest national proteomics hub (The Protein-Proteome network Helsinki).

The **Meilahti Clinical Proteomics Core facility of Biocentrum Helsinki** (BCH) continued to serve its users with comprehensive clinical proteomic analyses starting from planning the sample collection at the hospital, sample storage and analysis, ending in a compact Systems Medicine and Systems Proteomic summary of the results. As a GLP certified proteomics laboratory the unit continued to serve also commercial customers requesting authorised documentation on the GLP level. The Unit also continued to provide MALDI IMS services with a new on-tissue-fragmentation by ISD (in source dissociation) technology, providing absolute identification of the selected ions on-site. The Unit was also granted financial support from the national FIRI call 2016 for to establish new services on large-scale selected-ion-monitoring (SIM). Finally, the Unit closed a strategic alliance with the Helsinki Innovation Service Inc. for the development and manufacturing of second generation micro-chips for clinical diagnostics based on proteomics.

The **Nanoscience center** (NSC) Jyväskylä gives a good balance between high-throughput techniques and "in detail" protein

characterization. NSC offers services in fluorescence spectroscopic and vibrational spectroscopic (Raman and FTIR) techniques for characterization of proteins and other biomolecules. Presently we are addressing the unawareness of the possibilities of spectroscopic tools for protein characterization. This is addressed in the upcoming web pages and clear case-studies. The laser lab NSC is established to widen the perspective of molecular spectroscopic biosciences.

User Statistics

Despite the persisting and significant drop in the funding, PPN network was capable to serve 189 research groups, which is only slightly lower than that reported during 2015 (197). The volume of the services in terms of service hours was extensive (29394 h in total) and the income from the services was 472.304 €, which is 9 % lower as compared to the previous year. Services covered a wide range of expertise ranging from various types of mass spectrometric analysis to detailed protein characterization services to gel separations and protein production. Overall, it is fair to state that PPN network has strong role in protein-focused research in Finland, but the continuous cuts in budget cause a severe threat for the development and maintenance of internationally competitive services. Below is a summary of services for the whole network.

Participation In International, Nordic And European Infrastructures

PPN consortium members are participating in coordination of ISBE (Infrastructure for Systems Biology – Europe) and INSTRUCT (Integrated Structural Biology Infrastructure for Europe) projects which are on (ESFRI) Roadmap.

In addition, the network is involved in various national Centre's of Excellence, FiDiPro projects, several Academy of Finland Professorships as well as national and international funding (FP7 and Horizon 2020). PPN also has a role in the research funded by ERC and private funding organizations such as the Sigrid Jusélius and the Finnish Cancer Foundations.

The consortium also actively contributes to training. For example, **Oulu** facility provided 2 courses in protein characterization (Biochemical methods II). **Tampere** facility has been participating to teaching of MSc students and course focusing on protein production and mutagenesis was carried out during 2016. **Turku** facility gave lectures and other teaching on several university courses, arranged seminars and was actively involved with the Finnish Proteomics Society activities to promote proteomics research. The Protein-Proteome network Helsinki (BI & **BCH)** gave 5 courses on proteomics in 2016 at the undergraduate and graduate student level.

Future Perspectives

We expect even faster development in biophysical methods in protein characterization. Better sensitivity, smaller sample size, faster analyses and better user interfaces will be developed. To meet the demands of high-throughput, low use and maintenance costs, other label-free technologies for binding assays are needed to complement surface plasmon resonance (SPR) technology. In this context, new systems based on e.g. Bio-layer interferometry (BLI) or Corning Epic label-free technology will also improve the analysis of difficult targets or weak biological interactions. We expect also that proteomics methods are becoming more suitable for clinical samples and in the long term for diagnostics. Quantitative proteome-wide analysis methods are emerging. Integration within omics-based methods will be strengthened. Development of protein interaction analysis methods is one of the main streams. SRM and PRM are needed for to replace the time and money consuming large scale immunological measurements conducted today. The verification and evaluation of the large scale proteomic data cannot be done by immunological methods due to the constantly

Research groups	Non-academic groups/units	Local groups	Domestic groups (not at own Uni)	International groups	Volume of the services (hours)
189	21	109	72	17	29394

increasing number of identified proteins with the third-generation mass spectrometers typically reaching already several thousand of proteins in one analysis set.

In proteomics, we aim to characterize protein isoforms and their PTMs, as stated in the 2015 report. In order to open a major bottleneck towards that goal, funding for a new mass spectrometer was granted which will be implemented in 2017. The new instrument will allow sensitive and comprehensive determination of posttranslational modifications and targeted proteomics. As a new service, we have started to set up the analysis of protein interactions and complexes by native gel electrophoresis.

Future development in proteomics and protein characterization will shift towards top-down methods and protein isoform analysis. This will require dedicated instrumentation in the future such as international top-level vibrational spectroscopic tools**.**

Supported by FIRI funding, University of Tampere, BioMediTech (UTA). SPR Navi 420A Surface Plasmon Resonance instrument was purchased and will be installed 2017 for development of biofunctionalized materials, protein interactions and cellular attachment kinetics. JYU Nanoscience center bought Time-gated Raman spectrometer in 2017. Further, sample compartments as well as data analysis improved for in vivo samples. Due to positive FIRI decision, PPN is capable of updating some of the old instruments and continue operational. However, further investments for the instrumentation are important in near future.

Major Publications

Auer S, Azizi L, Faschinger F, Blazevic V, Vesikari T, Gruber HJ, Hytönen VP. Stable immobilisation of His-tagged proteins on BLI biosensor surface using cobalt Sensors and Actuators B: Chemical. 2017, 243:104-113. *Protein production, characterization and biosensor measurements.*

Björling A, Berntsson O, Lehtivuori H, Takala H, Hughes AJ, Panman M, Hoernke M, Niebling S, Henry L, Henning R, Kosheleva I, Chukharev V, Tkachenko NV, Menzel A, Newby G, Khakhulin D, Wulff M, Ihalainen JA, Westenhoff S. Structural photoactivation of a full-length bacterial phytochrome. *Science Advances 2016, 2, e1600920. Time-resolved spectroscopic measurements.*

Ciesielski GL, Hytönen VP, Kaguni LS. Biolayer Interferometry: A Novel Method to Elucidate Protein-Protein and Protein-DNA Interactions in the Mitochondrial DNA Replisome. Methods Mol Biol. 2016;1351:223-31. *Biosensor measurements.*

Gaciarz A, Veijola J, Uchida Y, Saaranen MJ, Wang C, Hörkkö S, Ruddock LW. Systematic screening of soluble expression of antibody fragments in the cytoplasm of E. coli. Microb Cell Fact. 2016 Jan 25;15:22. *Biophysical protein analysis, mass spectrometry*

Haikarainen T, Lehtiö L. Proximal ADP-ribose Hydrolysis in Trypanosomatids is Catalyzed by a Macrodomain. Sci Rep. 2016 Apr 11;6:24213. *Biophysical protein analysis*

Kohtala S, Theilmann W, Suomi T, Wigren HK, Porkka-Heiskanen T, Elo LL, Rokka A, Rantamäki T. Brief Isoflurane Anesthesia Produces Prominent Phosphoproteomic Changes in the Adult Mouse Hippocampus. ACS Chem Neurosci. 2016. Proteomics, PTM analyses

Rantakari P, Patten DA, Valtonen J, Karikoski M, Gerke H, Dawes H, Laurila J, Ohlmeier S, Elima K, Hübscher SG, Weston CJ, Jalkanen S, Adams DH, Salmi M, Shetty S. Stabilin-1 expression defines a subset of macrophages that mediate tissue homeostasis and prevent fibrosis in chronic liver injury. Proc Natl Acad Sci U S A. 2016 Aug 16;113(33):9298-303. *Proteomics (2-DE), mass spectrometry*

Santio NM, Landor SK, Vahtera L, Ylä-Pelto J, Paloniemi E, Imanishi SY, Corthals G, Varjosalo M, Manoharan GB, Uri A, Lendahl U, Sahlgren C, Koskinen PJ. Phosphorylation of Notch1 by Pim kinases promotes oncogenic signaling in breast and prostate cancer cells. Oncotarget. 2016 Jul 12;7(28):43220-43238. *Mass spectrometry, PTM analyses*

Söderholm S, Kainov DE, Ohman T, Denisova OV, Schepens B, Kulesskiy E, Imanishi SY, Corthals G, Hintsanen P, Aittokallio T, Saelens X, Matikainen S, Nyman TA. Phosphoproteomics to characterize host response during influenza A virus infection of human macrophages. Mol Cell Proteomics. 2016 Oct;15(10):3203-3219. *Phosphoproteomics*

Woehlbier U, Colombo A, Saaranen MJ, Pérez V, Ojeda J, Bustos FJ, Andreu CI, Torres M, Valenzuela V, Medinas DB, Rozas P, Vidal RL, Lopez-Gonzalez R, Salameh J, Fernandez-Collemann S, Muñoz N, Matus S, Armisen R, Sagredo A, Palma K, Irrazabal T, Almeida S, Gonzalez-Perez P, Campero M, Gao FB, Henny P, van Zundert B, Ruddock LW, Concha ML, Henriquez JP, Brown RH, Hetz C. ALS-linked protein disulfide isomerase variants cause motor dysfunction. EMBO J 2016 Apr 15; 35(8): 845-865. *Protein characterization*

Metabolomics Technology Platform

Chair of the platform: Seppo Auriola, BCK, Department of Pharmaceutical Chemistry

Partners: Tapio Palva, Teemu Teeri, BCH, Metabolomics Unit; Vidya Velagapudi, FIMM, Metabolomics Laboratory

Achievements In Development Of Technology Services

BCK The work has continued on metabolomics applications for food, health, and nutrition studies. The metabolomics group at UEF has been getting stronger by addition of new doctoral students and two post–docs. Major part of the non-targeted work load consisted of running samples from collaborators, and from our own projects. Key development area was testing and development of data analysis software for metabolomics analysis. The metabolite identification has been enhanced by addition of mainly lipid compounds in our retention time and MS/MS spectrum library. Targeted analysis methods for several new nutrition related biomarkers, and steroids were developed using LC-triple quadrupole mass spectrometers. The sample through put of our laboratory suffered from a lengthy breakdown of the UPLC-Q-tof instrument in 2016, and most of the service income was generated by targeted analysis.

ViMU continues to provide services as previous years but now with a new PI Prof. Teemu Teeri following retirement of Prof. Tapio Palva. The unit continues to focus on plant metabolites but also provides mass spec analysis for synthesis products, novel drugs and their metabolites. The analyses have been performed by UPLC-QTOF/MS and GC-QQQ/MS. At the end of 2016 unit received funding for a new UPLC-QQQ/MS from FIRI 2016 (AoF) so services can be extended to targeted analysis. Beginning of the year 2016 the staff reduction consultations at the University of Helsinki delayed customer negotiations and planning the future. The increased demands of services and a maternity leave of our only technician caused waiting periods for customers accentuated by recruiting prohibition. Nevertheless the unit managed to perform its services almost at the normal level. Recruitment permission of a second researcher in the beginning of 2017, and acquisition of new instrumentation will increase the unit's efficacy in services, and allow development of analyses.

FIMM In BF user survey, our Metabolomics platform had been evaluated very positively and received the highest prioritization for FIRI-2016 call. In BF 2016 user survey, 23 local and 7 external users rated FIMM unit with above cut-off (4.5/5) high score of 4.7/5 in 4/5 fields, and obtained an average of 4.56/5 with very positive open user comments and encouragement. FIMM continued in offering high throughput targeted quantitative metabolomics analyses. FIMM maintained the "self-sustainability" status from the single BF funded LC QQQ-MS instrument in 2016 too. FIMM continued in active research collaborations emerged from the service projects and published in highly reputed international journals. Due to the lack of analytical lab personnel, FIMM continued developing the same targeted method to quantify NAD metabolism intermediates in 2016 too.

The BF metabolomics units have continued teaching various aspects of metabolite analytics and mass spectrometry in their units and internationally. The BF metabolomics units have continued teaching various aspects of metabolite analytics in their units. In UEF,

Prof. Auriola is responsible for education of mass spectrometry and Dr. Hanhineva is lecturing on various courses within university and other national and international schools on topic "Application of non-targeted metabolite profiling in biosciences" as well as educating scientists (2 finished and 4 ongoing PhDs and

2 post-doctoral scientists utilizing metabolomics. FIMM unit continued in teaching "Biomedical Applications of Metabolomics" to medical, Ph.D. and masters students in different courses offered at the University of Helsinki (UH) and also continued organizing the Metabolomics Annual hands-on Workshop with the support of DPBM graduate school at UH. Student's feedback had been over 4.5/5 about the teaching. FIMM is a member of the European Metabolomics Training Coordination Group, http://www.emtrag.eu/training-centres/

BCH unit is responsible for metabolomics and proteomics-part at the Masters and advanced level Genomes courses "Genomes" and/or "From Genomes to Gene Functions".

Bottlenecks

All of the metabolomics units operate with minimal instrumentation. At FIMM the only LC-QQQ-instrument is used for providing services, developing and validating new analytical methods, regular maintenance and also for optimization of protocols for different samples. Even though our Metabolomics platform had been prioritized in the SAB evaluation for FIRI application, due to the lack of internal prioritization within the Units, FIMM Unit was not included in the FIRI-2016 application. Thus, FIMM supported in purchasing used demo instruments (SCIEX 5500 QTRAP MS and AGILENT iFunnel QToF MS) to expand the services. Also the lack of personnel, especially for data analysis and bioinformatics, weakens the availability of the services at all the Units. FIMM also faced the same problem, but due to an increase in demand for services and good revenue projections for 2016, FIMM hired a Biostatistician (Alberto Pessia) in January 2016. All the units have been able to increase the number of instruments and of people working in the metabolomics field.

User Statistics

	Total no. of groups/users 2016
ViMU (BCH)	18/45
FIMM	20
BCK Kuopio	20/20

Total number of research groups (or other customers) that have used the services 2016.
Breakdown of the above user numbers for local, for other domestic and for international users, and the total number of non-academic users is in table 2 below.

Participation In International, Nordic And European Infrastructures

ViMU is associated the Viikki Plant Science Centre, a virtual research center formed by high quality plant research groups at UH and selected by an international board. Unit collaborates with the recently established National Plant Phenotyping infrastructure (NaPPI), where the aim is to integrate non-invasive image data with plant metabolomics data. The unit is part of an EPPN application in plant phenotyping providing metabolomic services for this European network; is part of BF RI; and is associated with NaPPI RI providing metabolomics services in plant phenotyping. No direct Nordic, European or international infrastructure participation for BCH.

Future Perspectives

Units	Campus	National	International	Non-academic	Total no. of samples/Total revenue
ViMU Helsinki (BCH)	13	4	0	1	1900/33,050 €
FIMM	7	7	6	0	2052/242,370 €
BCK	14	3	3	0	5782/120,840 €

BCK FIRI funding enables purchase of a new high resolution instrument for metabolomics analysis. This gives us a possibility to run service samples, and do additional method development. The major analytical challenge of metabolomics analysis of minor sample material, will be addressed by using a micro flow HPLC connected to MS. This will help analysis of minor samples such e.g. purified exosomes, stem cells, or ocular samples. In future, the technique of ion mobility separation will be evaluated to analyze isobaric compounds, such as lipids. The group has added expertise on synthetic chemistry, which enables of development of targeted quantitation of novel biomarkers, not available commercially. Another step will be combination of the excellent capabilities of NMR metabolomics at UEF, with our LC-MS metabolomics services.

ViMU The focus of the unit continues to provide GC-MS and LC-MS analytical services in plant metabolomics and biopharmaceutical analysis. FIRI funding enables the purchase of a high end instrument (UPLC-QQQ/MS) for quantitation of metabolites in plants. The capability to run same samples with variety of instruments (GC-QQQ/MS, UPLC-QQQ/MS and UPLC-QTOF/MS) makes possible to cover vast range of the plant metabolites that have been reported to exist in plant kingdom more than 200 000. Collaboration with high throughput plant phenotyping RI facility (NaPPI RI) will result in increase of demand of analysis of plant primary and secondary metabolites from individual plants, plant organs or organelles.

FIMM Unit's future plans are to install the FIMM supported used instruments, SCIEX 5500 QTRAP MS and AGILENT iFunnel QToF MS; to start developing and optimizing the analytical methods for lipidomics and global metabolomics platforms; and also to set up metabolic flux analyses as users have already expressed their needs to quantify labeled metabolites for their research.

Major Publications

E. Terhonen, N. Sipari, and F.O. Asiegbu. Inhibition of phytopathogens by fungal endophytes of Norway Spruce. **Biological** Control (2016) 53–63. (Non-targeted UPLC-ESI/MS analysis and data analysis)

P. Davidsson, M. Broberg, T. Kariola, N. Sipari, M. Pirhonen and E.T. Palva. Short oligogalacturonides induce pathogen resistance-associated gene expression in Arabidopsis thaliana. BMC Plant Biology (2016) 17:19. (Targeted UPLC-ESI/MS analysis and data analysis)

M. Survila, P. R. Davidsson, V. Pennanen, T. Kariola, M. Broberg, N. Sipari, P. Heino, E. T. Palva, Peroxidase-generated apoplastic ROS impair cuticle integrity and contribute to DAMP-elicited defenses. Frontiers in Plant Science Vol 7 (2016) 1945. (Targeted UPLC-ESI/MS analysis and data analysis)

T. O. Leino, N. G. Johansson, L. Devisscher, N. Sipari, J. Yli-Kauhaluoma and E. A. A. Wallén. Synthesis of 1,3,6-trisubstituted azulenes based on the 1-acyloxyazulene scaffold. European Journal of Organic Chemistry (2016). (UPLC-ESI/MS analysis and method development)

Puurunen J, Tiira K, Lehtonen M, Hanhineva K, Lohi H. Non-targeted metabolite profiling reveals changes in oxidative stress, tryptophan and lipid metabolisms in fearful dogs. *Behav Brain Funct.* (2016) 12:7.

Tovar J, de Mello V, Nilsson A, Johansson M, Paananen J, Lehtonen M, Hanhineva K, Björck I Reduction in cardiometabolic risk factors by a multifunctional diet is mediated via several branches of metabolism as evidenced by non-targeted metabolite profiling approach. *Molecular Nutrition and Food Research* (2016) doi: 10.1002/mnfr.201600552

Koistinen VM, Katina K, Nordlund E, Poutanen K, Hanhineva K (2016) Changes in the phytochemical profile of rye bran induced by enzymatic bioprocessing and sourdough fermentation. In press, *Food Research International.*

Rey, G., Valekunja, U.K., Feeney, K.A., Wulund, L., Milev, N.B., Stangherlin, A., Bollepalli, L., Velagapudi, V., O'Neill, J.S.,

Reddy, A.B. The Pentose Phosphate Pathway Regulates the Circadian Clock. Cell Metabolism. (2016) 24:462-73. (FIMM role: Targeted (semi)quantitative analysis of metabolites and metabolomics data analysis. Manuscript writing and editing including contributions to figures and tables.)

Ahola, S., Auranen, M., Isohanni, P., Niemisalo, S., Buzkova, J., Velagapudi, V., Lundbom, N., Hakkarainen, A., Piirilä, P., Pietiläinen, K., Suomalainen, A. Modified Atkins diet induces subacute selective ragged red fiber lysis in mitochondrial myopathy patients. EMBO Molecular Medicine. (2016). 8:1234-1247. (FIMM role: Targeted (semi)quantitative analysis of metabolites and metabolomics data analysis. Manuscript writing and editing including contributions to figures and tables).

Kolho, K-L§., Pessia, A., Jaakkola, T., de Vos, W., Velagapudi, V.. Fecal and serum metabolomics in pediatric inflammatory bowel disease. *Journal of Crohn's and Colitis.* (2017) 11:321-334. (FIMM role: Designed the clinical study together with the Clinician. Targeted (semi)quantitative analysis of metabolites and metabolomics data analysis. Manuscript writing and editing including contributions to figures and tables).

STEM CELLS AND BIOMATERIALS

Coordinator: Timo Otonkoski, BCH

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, for example, 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 tis- sue 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 platform: Timo Otonkoski, BCH

Partners: Jari Koistinaho, BCK; Katriina Aalto-Setälä, BMT

Achievements In Development Of Technology Services

The overall situation of the nationwide consortium. Platform partners have continued the development of their stem cell services as described below. Coordination activities between the partners have been strengthened by regular activities of The Finnish Stem Cell Network (FSCN). FSCN is pulling together all research groups that are actively using stem cell technologies. The Biocenter Finland Stem Cell Platform is a part of this network, involving those partners who are providing Core Facility services. The annual meetings of the FSCN are held in conjunction with the annual meeting of the Finnish Developmental Biology Society. Annual meeting was held for the second time on November 4-5, 2016, in Pajulahti Sports Institute with active participation from all centers belonging to the Platform (more than 100 participants). Because of exceptional interest, we will continue the annual Finnish stem cell meetings, this time organized by BCK in Kuopio August 31st-September 1st 2017.

Platform partners received a total of 169.000 euros in 2016 for providing stem cell services. This enabled the continuation of the patient iPS cell derivation service by all partners. Platform derived in total 129 iPS lines for 12 customers. The turnover (customer fees) for the platform was 69.440 €. Major scientific progress was made in CRISPR/Cas9 technology which has been applied for efficient genome editing in human pluripotent stem cells, allowing the generation of knockouts or knockins (e.g. for the generation of reporter cell lines), correction or generation of single nucleotide mutations, and transcriptional activation of desired genes. All partners in the consortium have continued with development of genome editing technology creating fluorescently labelled marker cell lines and correction of different

mutations for disease modelling purposes. These are now started to be provided also as Core services.

An increasing interest of customers was to obtain differentiated cells and for assays analysing the functionality of these cells. Besides creating new iPSC lines, BMT (currently MED) has focused in optimizing differentiation methods, functionality assays and various software for cellular analysis. The main cell lines include cardiomyocytes and hepatocytes. Customers have increasingly also been involved in leaning these methods in hands-on trainings. During year 2016, BMT had delays in services due to the moving of the institute to a new building, creating a gap of 3 months in cell culture work.

BCK has established additional differentiation protocols for the following cell types: spinal cord motoneurons, microglia, endothelial cells and pericytes. Setting up differentiation protocols for several other brain cell types is in progress. BCK has also set up more 3D brain cell culture models and is working on cerebral organoid model, blood-brain barrier model (containing endothelial cells, pericytes and astrocytes) and taking the first steps towards 3D bioprinting of iPSC derived brain cells in collaboration with disease model service, imaging service and 3D printing companies.

The Biomedicum Stem Cell Center (BSCC, representing BCH) continued active development of the technologies, following the rapid development of the field. Particular areas of emphasis were: (i) reprogramming using activation of endogenous genes; (ii) generation of iPSC lines for biobanking purposes (iii) genome editing of the stem cells. In 2016 BSCC became part of the GoEditStem platform, part of the Helsinki Institute of Life Sciences (HiLIFE) infrastructure. Biomedicum Functional Genomics Unit (FuGU), also belonging to GoEditStem platform, started providing services for CRISPR-Cas9 genome editing. The first joint service of BSCC and FuGU is the generation of genetic knockouts in human or mouse cells, including pluripotent stem cells.

Bottlenecks in the services provided by the consortium. Comments are presented by each partner of the consortium:

BCH: Generation of iPSC lines as well as genome editing and differentiation services are laborious, time consuming and highly depend on skilled personnel. Development of genome editing and targeted differentiation as routine services would require additional resources for both personnel and space.

BMT: Functional analysis iPSC-derived cardiomyocytes creates large datasets. The bottleneck is usually in the analysis. For this purpose, BMT has been active in creating different software for (semi-automatic data analysis. The software has been created for Ca^{2+} imaging, patch clamp and MEA data, for contraction/relaxation analysis as well as for cellular orientation applicable for any cell type.

BCK: In the field of neuroscience, the need for complex and long-term differentiation of iPSC cells, including 3D models, is rapidly increasing both globally and nationally. However, funding for BCK has remained on the same level (against the recommendations of BF SAB). It is thus evident that the current resources are far too low to meet the requirements for such services in Finland.

Another bottleneck is the lack of funding sources for updating or even maintaining the basic infrastructure/equipment of stem cell core facilities. As there is no internal university funding earmarked for basic equipment, the stem cell cores and BCK in particular is continuously looking for external funding for equipment. This is an extremely difficult challenge as neither TEKES nor AF favour acquisition of equipment by their regular grants.

Comment on the feedback obtained from users and the consequent changes in service provision. Biocenter Finland conducted user survey on its technology platform services in October 2015 in order to obtain information on the use and performance of these services during the period of 2013-2015. Total of 43 users answered the questionnaire for Stem Cells and Biomaterials Platform. Scores for all

questions (access, quality, efficiency, support and price-quality) were excellent for BCH-BSCC, BMT, and BCK. BCH-Viikki (Biomaterial services) scores were poor (score 2 on the scale 1-5). One possible explanation is that BCH-Viikki did not provide services under BF umbrella from 2014. At this time this partner was excluded from the platform. In addition, the respondents mentioned lack of novel gene editing technologies as one of the services missing from BF technology platform. In response to that request BCH-BSCC has increased its activity in exploring novel gene editing technologies for pluripotent stem cells and has partnered with Biomedicum Functional Genomics Unit to form GoEditStem cell platform at HiLIFE. Within the neuroscience as well as local context, the service users (particularly BCK) have expressed need not only for making novel gene editing service more feasible, but also for larger platform for differentiating brain cells in a standardized fashion. This request is reasonable, considering the large range of brain cell types, diseases affecting them and the wealth of neuroscientists in Finland.

Note: BCH has undergone a separate user survey by HiLIFE-RIA (total of 47 respondents) in 2016. Again, BCH got excellent scores for all questions related to the provided services (access, quality, efficiency, price, and relevance). Although the average score was excellent (5), there were few fours (on the scale of 1-5) for access of BCH services. To make access to our services easier for the users, we have scheduled to update protocols, and make the customer instructions more user friendly on our web pages during 2017.

User Statistics

Overall, the service activities of the platform remained at roughly the same level as compared with 2012-15. Consortium produced 129 iPS lines for 12 customers. Teaching and hands on training were provided to 69 users included courses on regenerative medicine for graduate and undergraduate students. Total turnover was 69.440 €

BCH: 2016 turnover was smaller than usual; however, we have signed numerous service agreements for generation of iPSC lines from

Stem cell services provided	iPSC lines				Teaching (courses)				Hands-on training				Cell-IQ imaging/ Electrophysiology			
BSCC, University of Helsinki																
Year	2014	2015	2016	*total*	2014	2015	2016	*total*	2014	2015	2016	*total*	2014	2015	2016	total
Number of customers	6	8	4	39	16	17	38	151	6	1	1	33	6	7	6	47
Academic	5	8	4	37	16	17	38	151	6	1	1	28	6	7	6	47
Non-academic	1			2								5				
Volume	80	98	54	456	16	17	38	151	6	1	1	33	1557	1106	1067	18288
Turnover (EUR), 2014	42,671															
Turnover (EUR), 2015	44,655															
Turnover (EUR), 2016	19,740															
BMT, University of Tampere																
Year	2014	2015	2016	*total*	2014	2015	2016	*total*	2014	2015	2016	*total*	2014	2015	2016	total
Number of customers	5	3	4	12				0	2	2	3	7		1	1	2
Academic	4	3	4	11				0				0		1	1	2
Non-academic	0	0	0	0				0				0				0
Volume	32	8	39	79				0	2	2	3	7		1	1	2
Turnover (EUR), 2014	5000															
Turnover (EUR), 2015	2000															
Turnover (EUR), 2016	3500															
BCK, University of Eastern Finland																
Year	2014	2015	2016	*total*	2014	2015	2016	*total*	2014	2015	2016	*total*	2014	2015	2016	total
Number of customers	6	5	4	26	27	22	24	137	2	3	3	14	0	0	2	4
Academic	5	5	4	24	16	17	24	126	2	3	3	14	0	0	2	4
Non-academic	1	0	0	2	9	0	0	11	0	0	0	0	0	0	0	0
Volume	75	120	36	287	27	22	24	137	2	3	3	14	0	0	2	5
Turnover (EUR), 2014	25,500															
Turnover (EUR), 2015	108,840															
Turnover (EUR), 2016	46,200															

[a] Cell lines; [b] customers; [d] hours

more than 30 patient cell lines scheduled for 2017. This includes reprogramming of biobanked cells from THL Psychiatric Family Collections cohort material. Biobank approval for reprogramming of these cells was granted in 2016 (code: BB2016/56).

BCK: services peaked high in 2015, as reported before, and the activities were counterbalanced in 2016 with were counterbalanced in 2016 with generation of 36 iPSC lines for 4 clients and differentiation of 7 lines into astrocytes and 2 lines into cardiomyocytes. It should be noticed that during the first quarter of 2017 alone, BCK has generated 38 iPSC lines as service, indicating an increasing need for iPSC technology.

Participation In International, Nordic And European Infrastructures In 2016

BCH (Otonkoski) is a partner in one EU (FP7) funded consortium (BETACURE) and in one Horizon 2020/IMI2 funded consortium (INNODIA) with a role in the development of iPSC-based models for pancreatic beta-cell disease modelling and development of in vivo imaging technologies.

BMT (Aalto-Setälä) is a partner in two EU (FP7) funded consortiums (RiskyCAD and AtheroFlux) in the role for development of iPSC-derived hepatocytes for lipidomics and atherosclerosis studies.

UEF (Koistinaho) is a partner in a Horizon 2020-funded consortium (nEUROinflammation) on iPSC-derived models of brain inflammation, coordinates a JPND consortium (MADGIC) on novel iPSC models of Alzheimer's disease, and is a partner and vice coordinator of Scandinavian project on Parkinson's disease (Olav Thon Foundation, Norway), where various iPSC-derived models are developed and used. Koistinaho serves also an external member of the steering group for Danish-Swedish iPSCV consortium BrainStem.

Future perspectives

While generation of 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 pancreatic islet cells, hepatocytes, intestinal cells and lung epithelial 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. Because brain consists of hundreds of different cell types, brain diseases are the burden of Western countries, and neuroscience is one of the strongest research fields in Finland. The need for expertise in differentiation of iPSCs towards brain cells as well setting up 3Dmodels as a service are of utmost importance. Therefore, in addition to differentiation and functional assays of neural cells, 3D cultures, cerebral organoids and 3D bioprinting are on focus of BCK stem cell core.

The need for iPSC biobanks has become obvious, as evidenced for example by large international initiatives sponsored by EC together with pharmaceutical industry. In order for these endeavours to be successful, they have to be based on well-organized national or regional "hubs", centres devoted to the generation and characterization of iPSC collections from defined patient cohorts. The Biocenter Finland Stem Cells Platform is a prime example of these structures. It is essential that the functions of the platform, after a successful start, will be continuously supported through a nationally coordinated program. BCH has been granted permission to obtain cell samples (immortalized B cells) from THL biobank (code: BB2016_56). Blood samples were originally collected from voluntary donors of THL Psychiatric Family Collections cohort. The samples are coded and the identity of the cell donor remains unknown to the investigators. Generated iPSC lines as well as immortalized B cells, will be returned

to original biobank for further research use. Other similar projects in the area of Type 2 diabetes are going to be initiated soon.

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.

Combination of genome editing with patient-specific iPSC derived cells provides endless possibilities for cellular modelling of disease mechanisms. These approaches can be effectively applied to study monogenic diseases using cell types that are otherwise not available for research. However, the approach is not limited to monogenic diseases but can also be used to study the functional effects of disease-associated genetic variants in defined cellular systems. Using CRISPR/Cas9 it is possible to create isogenically controlled experimental systems by either correcting a specific disease-associated mutation or introducing it in a healthy control stem cell line. CRISPR libraries can also be used to functionally dissect enhancers and other regulatory elements.

Major Publications

Kyttälä A, Moraghebi R, Valensisi C, Kettunen J, Andrus C, Pasumarthy KK, Nakanishi M, Nishimura K, Ohtaka M, Weltner J, Van Handel B, Parkkonen O, Sinisalo J, Jalanko A, Hawkins RD, Woods NB, Otonkoski T, Trokovic R: Genetic Variability Overrides the Impact of Parental Cell Type and Determines iPSC Differentiation Potential. Stem Cell Reports. 2016; 6(2):200-12.

One of the first large-scale studies exploring the reasons for variability in iPSC differentiation. Cited 15 times during its year of publication.

Toivonen SC, Malinen M, Küblbeck J, Petsalo A, Urtti A, Honkakoski P, Otonkoski T: Regulation of human pluripotent stem cell derived hepatic cell phenotype by three-dimensional hydrogel models. Tissue Engineering Part A. 2016; 22:971-84.

A collaborative study between UH and UEF developing 3D-hydrogel models for hPSC-derived hepatocytes.

Lund C, Pulli K, Yellapragada V, Giacobini P, Lundin K, Vuoristo S, Tuuri T, Noisa P, Raivio T. Development of Gonadotropin-Releasing Hormone-Secreting Neurons from Human Pluripotent Stem Cells. Stem Cell Reports. 2016 Aug 9;7(2):149-57. doi: 10.1016/j.stemcr.2016.06.007.

BCH platform provided support in stem cell lines and development of methods

Ojala M, Prajapati C, Pölönen R-P, Rajala K, Pekkanen-Mattila M, Larsson K, Aalto-Setälä K. Mutation-specific phenotypes in hiPSC-derived cardiomyocytes carrying either myosin-binding protein C or α-tropomyosin for hypertrophic cardiomyopathy. Stem Cells International 2016, ID 1684792.

Pioneering work for demonstrating mutation specific models for hypertrophic cardiomyopathy and cellular abnormalities present the differentiated cells.

Kuusela J, Kujala VJ, Kiviaho A, Ojala M, Swan H, Kontula K, Aalto-Setälä K. Cardioactive drug effects on human induced pluripotent stem cell – derived long QT syndrome cardiomyocytes. Springerplus. 2016 Feb 29;5:234. doi: 10.1186/s40064-016-1889-y. eCollection 2016.

An important demonstration that iPSC derived cardiomyocytes reproduce clinical findings in their drug responsiveness.

Joutsijoki H, Haponen M, Rasku J, Aalto-Setälä K, Juhola M. Machine Learning Approach to Automated Quality Identification of Human Induced Pluripotent Stem Cell Colony Images. Comput Math Methods Med. 2016.

An automated software to increase the data analysis obtained with Ca2+ imaging. Applicable to any cell type with Ca2+ transients.

Kuusela J., Kim J., Räsänen E., Aalto-Setälä K. The effects of pharmacological compounds on beat rate variations in human long QT syndrome cardiomyocytes. Stem Cell Reviews and Reports 2016, Sep 19.
Demonstration that iPSC derived cardiomyocytes have the same variation in beating rate as observed in the individuals donated the initial sample.

Holmqvist, S.*, Lehtonen, Š.*, Chumarina, M., Puttonen, KA., Azevedo, C., Lebedeva, O., Ruponen, M., Oksanen, M., Collin, A., Goldwurm, S., Meyer, M., Lagarkova, M., Kiselev, S., Koistinaho, J.**, Roybon, L.** 2016 Creation of a library of induced pluripotent stem cells from Parkinsonian patients. Nature publishing Group Parkinsons disease doi:10.1038/npjparkd.2016.9
One of the largest libraries of iPSC models for Parkinson's disease in the world. The paper shows specific pathology in iPSC-derived neurons and astrocytes derived from Parkinson's disease patients carrying a large variety of mutations.

Achuta VS, Grym H, Putkonen N, Louhivuori V, Kärkkäinen V, Koistinaho J, Roybon L, Castrén ML. Metabotropic glutamate receptor 5 responses dictate differentiation of neural progenitors to NMDA-responsive cells in fragile X syndrome. Dev Neurobiol. 2016 Jul 13. doi: 10.1002/dneu.22419.
The study shows that a particular glutamate-induced signalling pathway is responsible for altered neuronal differentiation in Fragile X Syndrome.

STRUCTURAL BIOLOGY

Coordinator: Rik Wierenga, BCO

Structural biology covers a wide range of topics, from protein production and protein characterisation via structure determination to biocomputational analysis. The Biocenter Finland Structural Biology network (BFSB) comprises four major disciplines, all focused on experimental determination of macromolecular structures and elucidation of their mechanisms. They are X-ray crystallography, nuclear magnetic resonance spectroscopy (NMR), high-resolution native mass spectrometry (MS), and cryo electron microscopy (cryoEM). 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, iNEXT and Instruct. Consequently, the BFSB research groups have jointly written an application to become recognized as an Instruct National Affiliate Centre (Instruct-NAC). 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 for the Finnish life science researchers to many expert technologies in Europe, as nicely documented on the Instruct-WWW pages, ranging from biocomputational and molecular biology techniques to large-scale research facilities for example for cryoEM, NMR and X-ray data collection. In general, being an Instruct-NAC will help in building the BFSB units further into a coherent and well-funded research community, which is now preparing an application to the Instruct council to evolve into the Finnish distributed Instruct centre.

The BFSB network also benefits from central resources, such as the CSC – The Finnish IT Center for Science Ltd. and from the BF networks on (i) Bioinformatics and (ii) Proteomics and Metabolomics.

The expert services provided by the BFSB network are organized into several technology platforms, being those for (i) X-ray crystallography, (ii) cryoEM, and for (iii) NMR and MS. In addition BF supports protein production units in Helsinki and Tampere. Four of the biocenters have macromolecular X-ray crystallography facilities (BI, BCK, BCO and BioCityTurku), while BI also has a significant investment in NMR and cryoEM and BCK in MS. BFSB partners have achieved an excellent division of labour, and the BFSB network helps them to communicate efficiently with each other.

NMR Spectroscopy and Mass Spectrometry Technology Platform

Chair of the platform: Hideo Iwai, BI, Finnish Biological NMR Center (FBNMR)

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

Achievements in Development Of Technology Services

NMR spectroscopy: The NMR facility currently consists of three fully operational Bruker NMR spectrometers (600 MHz, 850 MHz and VTT-owned 600 MHz). A new transparent open-access via online-booking system was developed and taken into operation (www.biocenter.helsinki.fi/bi/nmr). The new service using the 850 MHz NMR spectrometer to quantify metabolites from plant extracts was established in 2016 and analyzed hundreds of plant samples. The 850 MHz NMR instrument

owing the very high sensitivity (S/N >11,000) was shown to be very advantageous for metabolite studies. The low throughput of the 24-position sample changer (Sample Case) of the 850 MHz NMR limits the application in metabolomics and could be improved by a new sample exchanger (Sample Jet), which can handle 500 samples at once. New users from material science have utilized the facility to investigate materials dissolved in ionic liquids (ILs), but are limited by only three nuclei (^{1}H, ^{13}C, ^{15}N) in solution states, instead of more desirable solid-state NMR spectroscopy for material sciences. NMR is sensitive to molecular motions such as dynamics in proteins. The facility developed a new service to elucidate protein dynamics by recording ^{15}N backbone relaxation times and analyzed several proteins together with molecular dynamics simulations.

Mass spectrometry: In 2016 FIRI funding was granted to purchase a new ion-mobility mass spectrometer which can be used for analysis of larger protein complexes and it provides a second dimension, shape, in protein separation, allowing for more complex and dynamical systems to be studied. We are currently testing different ion-mobility mass spectrometers.

There has been an increasing interest in the use of high-resolution protein mass spectrometry and native mass spectrometry. New exciting projects have been initiated. Especially encouraging has been a great interest of Finnish industry towards the FT-ICR platform, demonstrated by a number of contract research projects. The platform is also actively involved in the European wide FT-ICR consortium (EU FT-ICR MS Network), which has left an application to the Horizon 2020 INFRAIA-02-2017 (RIA) Integrating Activities for Starting Communities call (second phase).

User Statistics

	Groups 2016	Metrics 2016
NMR Spectroscopy		
local	9	
domestic	1	
international	0	
non-academic	3	
Total	13	
Mass spectrometry		
local	7	
domestic	12	
international	3	
non-academic	3	
Total	25	3296 (measured spectra)

Participation in International, Nordic And European Infrastructures

The platform is part of the National Affiliate Center (Instruct-FI) of ERIC infrastructure Instruct (https://www.structuralbiology.eu). The Nordisk NMR network was established with the NMR core facility. The platform is also involved in Cost Action BM1403: Native Mass Spectrometry and Related Methods for Structural Biology and a partner in the European wide FT-ICR consortium (EU FT-ICR MS Network).

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 (*e.g.* protein dynamics). New developments in this area include the use of solid-state NMR to study, for example, membrane proteins in native cells as well as ion mobility mass spectrometry to study very large biomolecular assemblies such as viruses or DNA. According to our experience, the use of high-resolution mass spectrometry has proven to be very efficient in the analysis of protein materials in respect to heterogeneity and post-translational modifications. The large utilization of these techniques would increase considerably reproducibility of experiments in life sciences, which has been recognized as a major concern in the field. Structural studies by NMR spectroscopy are typically limited by available samples due to low sensitivity of NMR spectroscopy, requiring relatively high concentrations (sub mM concentration) of target proteins. Ultra-high field (1.2GHz

magnet), new probe design, and dynamic nuclear polarization (DNP) techniques would overcome this limitation by enhancing the sensitivity by a factor of 2-1000. Such enormous improvement in the sensitivity would enable us to investigate a wide range of proteins with sub μM concentration and proteins with the limited availability (*e.g.* membrane proteins). In addition, molecular dynamics simulation is expected to complement interpretations of protein dynamics revealed by NMR spectroscopy. This consortium will be a part of the Instruct-FI consortium for integrated structural cell biology. As the part of Instruct-FI, the platform continues to vigorously pursue our responsibilities on research, training and outreach to the life science research community at the national and international level.

Major Publications

Ciragan A, Aranko AS, Tascon I, Iwaï H: Salt-indusible protein splicing in cis and trans by inteins from extremely halophilic archaea as a novel protein-engineering tool. *J. Mol. Biol.* 428: 4573-4588, 2016. This communication describes a patent-pending intein-technology, which was used for segmental isotopic labeling of an energy transducing protein of TonB, and the NMR structure of TonB.

Laitaoja M, Isoniemi S, Valjakka J, Mandity M & Jänis J: Deciphering metal ion preference and primary coordination sphere robustness of a designed zinc finger with high-resolution mass spectrometry. *Protein Sci.* 26: 198-207, 2017. Native mass spectrometry was used to study binding of metals to a designed zinc finger.

Laitaoja M, Tossavainen H, Pihlajamaa T, Valjakka J, Viiri K, Lohi O, Permi P & Jänis J: Redox-dependent disulfide bond formation in SAP30L corepressor protein: Implications for structure and function. *Protein Sci.* 25: 572-586, 2016. High-resolution mass spectrometry was used to study a redox-dependent disulfide formation as a regulatory mechanism of protein function.

X-ray FIX-UP Technology Platform

Chair of the platform: Rik Wierenga, BCO, Protein Crystallography, Oulu X-ray

Partners: Tassos Papageorgiou, BioCity, Protein Crystallography Core Facility; Tommi Kajander, BI, Protein Crystallisation Facility

Achievements In Development Of Technology Services During 2016

The FIX-UP Biocenter Finland Structural Biology (BFSB) technology platform receives BF funding for personnel running the facilities in IB-Helsinki, BCO-Oulu and BCT-Turku. BFSB has been accepted as the Finnish Instruct National Affiliate Center, Instruct-FI, and Instruct-FI has been included in Finland's roadmap for research infrastructures 2014-2020. Consequently, BFSB could apply for equipment funding from the FIRI-2016 call, like in 2015. In this application it was proposed to the FIRI committee to confirm that Finland would join Instruct and in addition it was requested to provide funding for the coordination of a distributed Instruct center. Also in 2015 FIX-UP participated in the 2015 BF evaluation round. For the purpose of this evaluation (for the period 2017-2020, FIX-NMAS) a more extensive platform was proposed including also NMR in Helsinki (Iwai) and native mass spectrometry in Joensuu (Rouvinen, Jänis). Both applications were successful and the effective implementation of these evaluations will be discussed in the Perspective section.

Service Provision

Our goal in service provision is aimed at providing a clear and effective path from a purified protein to a solved crystal structure.

a) We provide protein characterisation (protein stability screening by fluorescence and CD; protein characterization by chromatography/multiple angle light scattering), crystallisation and imaging facilities. Helsinki also provides screens for the other centers. The facility in Helsinki

(http://www.biocenter.helsinki.fi/bi/xray/automation/) provides also advice and training on how to proceed with a crystallisation project. In Oulu a wide range of protein characterisation techniques is offered as a service (http://www.oulu.fi/biocenter/protein-crystallography).

b) We provide a service enabling data collection and structure determination, including crystal testing, in Oulu and in the regional service center in Turku. Remote data collection sessions at Diamond and the ESRF are now routinely organised in each of the centers.

Software Development

The development of the replacement version of xtalPiMS by Ed Daniel (Oulu), has resulted in a new software package, referred to as IceBear ("Integrated crystal-data-tracking, enhancing Biochemistry education and research"). IceBear follows the crystallization experiments by displaying the crystallization drops, together with all relevant information of the actual crystallization conditions. Eventually it will be able to record all the important data of the structure-determination-pipeline, including the sequence information, that is relevant for later publications. It is also aimed to be an educational tool. It is now possible to install this software easily in other homelabs. The current version is now routinely used in Oulu importing the images from Formulatrix drop imaging systems and it will be installed also in Turku. In the Helsinki platform, another imager is used and it is now planned that an importer for this imager will be developed, such that Helsinki can also use IceBear. In this way, a unified platform for following the crystallization experiments will become available in 2017 for the Finnish life science research community.

Training And Outreach

a) Courses at the Masters level on X-ray crystallography and structure interpretation are offered at each University. In Helsinki, the structural biology program has also had outreach activities to high school students, like in Turku and Oulu.

b) We continue to meet yearly as part of FINNBOX (the Finnish Biological Crystallographers), now combined with the national BFSB meetings. In 2016, the meeting was organised in Joensuu by Rouvinen, August 29.

c) The Oulu X-ray core facility is 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). Likewise, the Turku regional data collection center is also part of BioXLabs (http://www.btk.fi/crystallography/cooperation/instruct/bioxlabs, a regional structural biology consortium formed to enhance coordination of activities.

d) The information on the web of each of the platforms is continuously updated. It includes price information and suggestions for how to acknowledge the services provided.

User Statistics

[§] The numbers refer to the number of research groups which have used the core facility infrastructure and expertise. The actual number of users and user projects is much higher. The University teaching activities have not been included in these numbers. See table next page.

Participation In International, Nordic And European Infrastructures

FIX-UP is well connected to Instruct. FIX-UP interacts also with other important EU infrastructure networks like iNEXT. We have good access to the ESRF beamlines through the FinnProCC BAG, and through a similar national BAG at Diamond, coordinated respectively by Kajander, Helsinki and Lehtiö, Oulu. Data collection is also carried out at MAX Lab, DESY and BESSY. We participate in Finnish (FSRUO, Kajander) and European (ESUO, Kajander) synchrotron user organisations on the development of synchrotron radiation for scientific research and transnational access to facilities. Wierenga is a member of the SSP-college on macromolecular crystallography of BESSY,

evaluating twice a year the beamline proposals for data collection using the three beam lines at BESSY. Wierenga is coordinator of the Finnish participation in the Horizon2020 Instruct-ULTRA project. Instruct-ULTRA is aimed at supporting the further expansion of Instruct concerning technologies that are not yet core expertise of Instruct as well as reaching out to countries that are not yet actively engaged in Instruct.

Future Perspectives

In 2016 the structural biology research infrastructure landscape in Finland has seen a significant transformation, following the 2015 Biocenter Finland evaluation and following the FIRI-2016 decisions of the Academy of Finland. Both evaluations were positive and the FIRI-2016 decisions confirmed that Finland should join Instruct. These developments have prompted the BF board to transform the BFSB network into the Instruct-FI network having as its mission the fostering of structural biology research in Finland, including that Finland joins Instruct and that a distributed Instruct center will be established in Finland. Once Finland has joined Instruct then the Finnish life science researchers will have funded access to the expertise of the Instruct centers, located elsewhere in Europe. The FIX-UP partners will provide essential expertise for this new distributed Instruct-FI Instruct center. The Instruct-FI coordination hub will be in Helsinki with shared responsibilities for each of the four current major structural biology platforms. Helsinki will add its intein expertise (on protein splicing) for NMR studies as well as its cryoEM expertise to the proposed Instruct-FI distributed Instruct center, whereas Turku will contribute with its expertise in bioinformatics based structural drug discovery research, Oulu will develop further its structural biocatalysis research and Joensuu its native mass spectrometry expertise. These developments are very well in line with the funding decisions concerning the FIRI-2015 equipment grant allowing further profiling of the four major structural biology centers. Turku will expand its crystallization capacity through the purchase of two Formulatrix imagers. Joensuu will purchase new native mass equipment and Helsinki has purchased modern cryoEM equipment. Oulu considers to renovate its crystallization equipment as well as expand its biocatalysis expertise with the purchase of a state-of-the-art stopped flow device to be able to ensure that its structural biocatalysis setup remains competitive internationally and to be able to fulfil its role in Instruct-ULTRA. Helsinki is able to obtain a new X-ray data collection unit which is now being planned. Through these developments we aim to keep our expertise internationally competitive, and at the same time we are able to deliver better support for the Finnish life science research

	Number of research groups[§]		
	IB Helsinki	BCO Oulu	BCT Turku
Campus	10	12	3
Local University	1	-	3
Other Universities	3	-	4
Non-academic	1	2	-
International	-	-	6
	Other metrics		
Number of publications in which services have been used	3	7	4
Estimated number of 96-well plates used in crystallization experiments	205	1400	200
Number of deposited PDB-entries	4	15	6

community. Structural biology research is expensive. A bottle neck for the efficient exchange of information between the structural biology platforms and the life science research community is the lack of funding available in the life science research groups for travel and for contributing to the consumable costs related to structural biology research. The FIX-UP units actively interact also with the biotech research community. This is seen as very important given the large potential of structural biology expertise for profitable and highly desirable applications that can be developed in the bioeconomy sector. Cutting edge research efforts elsewhere demonstrate the great potential of these approaches. This includes both drug discovery research as well as the engineering of new enzymes for obtaining much more sustainable production protocols of high value chemicals, including pharmaceuticals that improve the human health. The FIX-UP research units are now part of the Instruct-FI network for integrated structural cell biology and in the future they will report as part of that network. We will, in the context of Instruct-FI, vigorously pursue our responsibilities on research, training and outreach supporting the life science research community at the national and international level.

Major Publications

Li KM, Wilkinson C, Kellosalo J, Tsai JY, Kajander T, Jeuken LJ, Sun YJ, Goldman A. (2016) Membrane pyrophosphatases from Thermotoga maritima and Vigna radiate suggest a conserved coupling mechanism. Nat Commun. 6, 13596.
BF Helsinki robot crystallization facility; FinnProCC and Diamond BAG consortium. International collaboration.

Paatero A, Rosti K, Shkumatov AV, Sele C, Brunello C, Kysenius K, Singha P, Jokinen V, Huttunen H, and Kajander T. (2016) Crystal Structure of an Engineered LRRTM2 Synaptic Adhesion Molecule and a Model for Neurexin Binding. Biochemistry. 55, 914-926.
BF Helsinki robot crystallization facility; data collection via FinnProCC BAG consortium.

Obaji, E., Haikarainen, T. & Lehtiö, L. (2016) Characterization of the DNA dependent activation of human ARTD2/PARP2. Sci. Rep. 6:34487.
Data were collected at synchrotrons via FinnProCC and Diamond BAG consortium.

Haikarainen, T. & Lehtiö, L. (2016) Proximal ADP-ribose Hydrolysis in Trypanosomatids is Catalyzed by a Macrodomain. Sci. Rep. 6:24213.
Crystallization was done at the Oulu facility and data were collected at synchrotron via Diamond BAG consortium.

Harijan, R. K., Mazet, M., Kiema, T. R., Bouyssou, G., Alexson, S., Bergmann, U., Moreau, P., Michels, P.A.M., Bringaud, F. and Wierenga, R. K. (2016) The SCP2-thiolase-like protein (SLP) of Trypanosoma brucei is an enzyme involved in lipid metabolism. PROTEINS, 84, 1075-1096.
Initial studies and structure refinements were done at the Oulu Data collection Center and data collection via FinnProCC consortium at the ESRF. International collaboration.

Meriläinen G, Koski MK, Wierenga RK. The extended structure of the periplasmic region of CdsD, a structural protein of the type III secretion system of Chlamydia trachomatis. (2016) Protein Sci. 25, 987-998.
Initial studies, data collection and structure refinements were done at the Oulu Data collection Center and data collection was also done via FinnProCC at the ESRF, at Diamond, Oxford and at EMBL-Hamburg, DESY.

Blazevits, O., Mideksa, Y., Solman, M., Ligabue, A., Ariotti, N., Nakhaeizadeh, H., Fansa,E., Papageorgiou, A.C., Wittinghofer, A., Ahmadian, M., and Abankwa, D. (2016). Galectin-1 dimers can scaffold Raf-effectors to increase H-ras nanoclustering. Sci. Rep. 6:24165
Turku computing facilities. Departmental and international collaboration.

Axarli, I., Muleta, A.W., Vlachakis, D., Kossida, S., Kotzia, G., Maltezos, A., Dhavala, P., Papageorgiou, A.C. and Labrou, N.E. (2016). Directed evolution of tau class glutathione transferases reveals a site that regulates catalytic

efficiency and masks cooperativity. Biochem. J. 473, 559-570
Turku data collection and synchrotrons (ESRF BAG and EMBL-Hamburg c/o DESY). International collaboration.

Perveen, S., Rashid, N. and Papageorgiou, A.C. (2016) Crystal structure of a phosphoribosyl anthranilate isomerase from the hyperthermophilic archaeon Thermococcus kodakaraensis. Acta Cryst F72, 804-812
Turku data collection. ESRF BAG. International collaboration.

Protein Services Technology Platform

Chair of the consortium: Juha Määttä (BMT)

Partners: Olli Ritvos (BCH/HiLIFE), Michael Jeltsch (HiLIFE, starting 2017)

Achievements In Development Of Technology Services

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

Tampere Protein Technologies offers protein expression in *E. coli* and *Spodoptera frugiperda* (baculovirus expression system, BV) cells. In addition, service 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 2016, Tampere Protein facility has continued to serve existing users and also new customers. The number of customers who used our baculovirus expression system increased from previous year and charged income increased still 13% from 2015, which was previous record year (both ProtMet and Structural Biology parts taken into account). Protein technologies made headway in virus like particle (VLP) expression and purification, which will be one of the main focus also in the future.

The Helsinki protein production facility at Haartman Institute complements the Protein production platform by offering services for generating recombinant protein expressing mammalian CHO-S and HEK293 cell lines. 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.

During 2016, the customer base of the Helsinki facility was same as previous year and number of cell lines decreased from 26 to 20. Customers usually need both cell line generation and scale up protein production services, but now also 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.

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.

An important part of the operation in both Tampere and Helsinki has been training of the personnel who need larger scale protein production in their studies. In the Tampere and Helsinki facility, all services are working

under the leadership of head scientists Dr. Juha Määttä and Dr. Olli Ritvos, respectively. This mode of operation and coordination ensures high quality of the work, and makes it possible to start new projects fluently. However, BF funding is not sufficient but can be to a certain extent complemented through incomes from non-academic customers.

Major bottleneck is the lack of employees. The number of service users has been steady several years in a row mainly because units work at the maximum level of projects. Therefore, the lack of personnel funding is limiting the number of projects that can be handled per year. However, services have regular customer base that have been satisfied and who will turn over and over again to use our service. Few technicians would make possible to increase projects per year and decrease waiting times.

User Statistics

Our vision: PP could become a network providing broad methodology to screen and express novel proteins in most efficient way and by that 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.

Service has managed to keep regular clientele and volume. However, incomes have increased 44% (total incomes in 2016: 34057 €). Total volume of service hours increased dramatically because HPLC instrument have been utilized for protein preparation more efficiently (over 4000 h/year) in Tampere unit.

Participation In International, Nordic And European Infrastructures In 2016

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 during 2011-2016. Our service is part of BF Structural Biology platform (BFSB) which has set up Instruct Finland (Instruct-FI) platform that aims to serve as a community for all structural biology researchers in Finland but also internationally.

We also joined EU level network named P4EU (Protein Production and Purification Partnership in Europe) that is established to have a platform for the exchange of information, know-how and materials between core facility labs in the field of protein expression and purification. P4EU have 77 members at the moment.

Future Perspectives

In year 2016 Tampere unit moved to new facilities and had to establish protein expression and purification service again. However, after successful move, service has been able start operation on wheels. Since then, already several baculovirus and *E.coli* expressions (both small scale and fermentations) have been made successfully. In addition, the number of expressions of viruses made in mammalian cells has been increased and their use as vaccine will be studied in mouse models. Tampere unit will also start using mammalian cells for protein expressions and the University of Tampere has purchased appropriate CO shakers for this purpose. This will increase flexibility and productivity of PP service.

Tampere unit established new web service to sell overexpressed proteins that could have general interest

Research groups	Non-academic groups/units	Local groups	Domestic groups (not at own Uni)	International groups	Volume of the services (cell lines and hours)
25	4	8	20	4	20 cell lines 5876 h

http://biomeditech.fi/Protein_Shop/, which could bring more incomes and will be easy way to market new protein products also in the future.

The Helsinki University core facility services are in 2016-2017 under an ongoing major reorganization and restructuring process which affects broadly all Biocenter Finland core facilities in Helsinki including the Helsinki BF PP services node run by Dr. Ritvos. Once the process has been completed in late 2017 it is anticipated that the current Helsinki BF PP activities will be expanded in terms of their ability to provide recombinant protein expression and purification services and recombinant antibody generation services.

In connection to the restructuring of the Helsinki University core facility services during 2016-2017 the Biocentrum Centrum Helsinki (BCH) infrastructure is being transformed to become part of the new Helsinki Institute of Life Sciences (HiLife). Consequently, most of the Biocenter Finland affiliated BCH core facilities will become restructured as HiLife core facilities after the transition during 2017-2018 has happened.

During 2016-2017 a two phase HiLife core facility application round has been organized and an evaluation process of the core facilities selected of the first round of application is ongoing during the spring and summer of 2017. The current Helsinki node of the Biocenter Finland PP service is now organizationally part of a the new HiLife 3P (protein production and purification) unit jointly headed by Dr. Michael Jeltsch and Dr. Olli Ritvos which was selected in 2016 from the first application round to the ongoing second round of evaluation to be become HiLife funded during 2017-2020. The HiLife 3P service will include the current Helsinki BF node of PP services with the CHO-S and HEK293 protein expression services but now also include stable insect S2 cell based protein expression services and protein purification services provided previously as a separate core facility unit at the Medical Faculty campus in Helsinki. This will broaden the service portfolio of the Helsinki BF node and develop the service to a unit operationally run by Dr. Arja Pasternack and a technician funded by the Helsinki University as a HiLife core facility instead of being a BCH core facility.

Academy researcher Michael Jeltsch's group has been offering in 2016 protein expression and purification services which starting from 2017 will as part of the HiLife 3P unit increase the number of service projects made in the Helsinki BF PP service node. Michael Jeltsch has received very recently substantial funding for the development of novel Crispr/Cas-based antibody generation and optimization technologies, which will be incorporated into the services as soon as they can be deployed on a routine basis.

The vision of Drs Ritvos and Jeltsch is to develop the HiLife 3P services to a core facility platform not only providing stable mammalian (CHO-S and HEK293) and S2 insect cell protein expression and purification services but also to a platform providing *E.coli* and eukaryotic cell expressed recombinant scFv-Fc and full IgG antibodies. The continued close co-operation of the Tampere and Helsinki PP nodes of non-overlapping services co-ordinated by Dr Juha Määttä will provide a basis for expanded future Biocenter Finland protein expression and recombinant antibody services serving academic and local industry clients at the national level in Finland.

To improve our protein expression optimization and purification methods, we like to have JANUS® BioTx Automated workstation with GXII Touch 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. The price of 276 000 eur is supported by recent quote and with 24% VAT.

PP is now part of the Instruct-FI consortium for integrated structural cell biology and in the future, will report as part of that network. We will, in the context of Instruct-FI, vigorously pursue our responsibilities on research, training and outreach to the life science

research community at the national and international level.

Major Publications

10 Major publications are provided. The role of the PP facility is described with italics. Names highlighted in bold are the authors who are working in the Tampere Protein Facility or in Haartman Institute Protein Production Service.

FNDC4 acts as an anti-inflammatory factor on macrophages and improves colitis in mice. Bosma M, Gerling M, Pasto J, Georgiadi A, Graham E, Shilkova O, Iwata Y, Almer S, Söderman J, Toftgård R, Wermeling F, Boström EA, Boström PA. Nat Commun. 2016 Apr 12;7:11314. *6His-Fc-FNDC4 and 6His-Fc protein production in CHO-S cells.*

Artificial Avidin-Based Receptors for a Panel of Small Molecules. Lehtonen SI, Tullila A, Agrawal N, Kukkurainen S, Kähkönen N, Koskinen M, Nevanen TK, Johnson MS, Airenne TT, Kulomaa MS, Riihimäki TA, Hytönen VP. ACS Chem Biol. 2016 Jan 15;11(1):211-21. *Protein production and characterization*

Stable immobilisation of His-tagged proteins on BLI biosensor surface using cobalt - Auer Sanna, Azizi Latifeh, Faschinger Felix, Blazevic Vesna, Vesikari Timo, Gruber Hermann J., Hytönen Vesa P. Sensors and Actuators B: Chemical. 2017 May 243:104-113. *Protein production, characterization and biosensor measurements*

Systemic blockade of ACVR2B ligands prevents chemotherapy-induced muscle wasting by restoring muscle protein synthesis without affecting oxidative capacity or atrogenes. Nissinen TA, Degerman J, Räsänen M, Poikonen AR, Koskinen S, Mervaala E, Pasternack A, Ritvos O, Kivelä R, Hulmi JJ. Sci Rep. 2016 Sep 26;6:32695. *ActRIIBFc protein production in CHO-S cells*

Enhanced exercise and regenerative capacity in a mouse model that violates size constraints of oxidative muscle fibres. Omairi S, Matsakas A, Degens H, Kretz O, Hansson KA, Solbrå AV, Bruusgaard JC, Joch B, Sartori R, Giallourou N, Mitchell R, Collins-Hooper H, Foster K, Pasternack A, Ritvos O, Sandri M, Narkar V, Swann JR, Huber TB, Patel K. Elife. 2016 Aug 5;5. pii: e16940. *ActRIIBFc protein production in CHO-S cells*

Inhibition of Activin Signaling Slows Progression of Polycystic Kidney Disease. Leonhard WN, Kunnen SJ, Plugge AJ, Pasternack A, Jianu SB, Veraar K, El Bouazzaoui F, Hoogaars WM, Ten Dijke P, Breuning MH, De Heer E, Ritvos O, Peters DJ. J Am Soc Nephrol. 2016 Dec;27(12):3589-3599. *ActRIIBFc protein production in CHO-S cells*

Effects of muscular dystrophy, exercise and blocking activin receptor IIB ligands on the unfolded protein response and oxidative stress. Hulmi JJ, Hentilä J, DeRuisseau KC, Oliveira BM, Papaioannou KG, Autio R, Kujala UM, Ritvos O, Kainulainen H, Korkmaz A, Atalay M. Free Radic Biol Med. 2016 Oct;99:308-322. *ActRIIBFc protein production in CHO-S cells*

TRANSLATIONAL TECHNOLOGIES

Coordinator: Johan Lundin, FIMM

The network coordinates two technology platforms: (i) Drug Discovery and Chemical Biology (DDCB) for discovery and proof-of-concept validation of therapeutic molecules, and (ii) 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 platform: Johan Lundin, FIMM

Partners: Jorma Isola, BMT; Olli Carpen, BioCity

Achievements In Development Of Technology Services

The main goal of the technology platform is to support incorporation of digital microscopy in medical tissue biobanking projects and biomarker research. The consortium also provides know-how for best phenotypic 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, clinical databases and computational environments for image analysis.

Services Provided

1. *Whole-slide cell- and tissue sample scanning services*. Scanning instruments are available at FIMM (https://www.fimm.fi/en/services/technology-centre/digital-microscopy-and-molecular-pathology-unit), IBT 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 5-25 €/slide. Volume prices for larger series.

2. *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.

3: *Access to computational tools, image analysis, 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 http://fimm.webmicroscope.net/research/testimmune and for clinical informatics.

The current BF funding only allows 1-2 part time employed persons (one at FIMM and one at IBT) to handle the services and therefore some waiting times can occur. Especially scans that require a long scanning time (e.g. cytological samples and samples that require fluorescent imaging) are challenging with the current equipment and personnel. For example, scanning a whole-slide sample in the fluorescence mode at high resolution (40x-63x) can easily take up to 12 hours per sample, as compared to brightfield histology slides that can be scanned in 5-10 minutes.

Overall situation of the nationwide consortium: Activities in this field has increased substantially and we foresee that a high demand for sample digitization. Biocity Turku has now also established similar infrastructure as those at FIMM and IBT 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 and Kuopio Universities have acquired microscopy scanners and introduced whole-slide scanning and webmicroscopy related to biobank activities, and are future potential partners of the platform.

User Statistics

1) Total number of research groups who have used the services in 2015-16: 80+

2)Breakdown of users (research groups): FIMM local: 26+, domestic: 8+, international: 30+, non-academic: 10+ IBT local: 10, domestic: 1, international: 1

3) Metrics:
FIMM: Total number of scanned slides 2015-2016 approx. 5.000 that constitute ~ 40.000.000 individual digital images and a data amount of ~150.000 gigabytes of data

IBT: Total number of scanned slides 2015-2016 approx. 5.000. The ImmunoRatio software developed at IBT has been used to analyze more than 256,000 images and ImmunoMembrane more than 21,000 images since introduction.

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 granted for the time period 2014-2016 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.

The services have also been advertised through the Biomarker Product Group of the European Advanced Translational Research Infrastructure in Medicine (EATRIS) which is one of the ESFRIs.

Last year the FIMM part of the platform was in 2016 proposed to become a research infrastructure (RIA) of the newly established Helsinki Institute for Life Sciences (HiLife) and this was accepted by the Board of HiLife. In the proposal, it was also suggested how the service could be improved to support HiLife even better, but so far no additional budget in addition to the BF budget has been provided by HiLife.

Future Perspectives

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

Tasks of The Consortium 2017-18

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. readout 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

Hemminki O, Parviainen S, Juhila J, Turkki R, Linder N, Lundin J, Kankainen M, Ristimaki A, Koski A, Liikanen I, Oksanen M, Nettelbeck DM, Kairemo K, Partanen K, Joensuu T, Kanerva A, Hemminki A. Immunological data from cancer patients treated with Ad5/3-E2F-Delta24-GMCSF suggests utility for tumor immunotherapy. Oncotarget 2015;6:4467-81.
-this article presents results on a collaborative immuno-oncological study between FIMM and a pharmaceutical company Oncos Therapeutics that used both tissue slide scanning of tumor biopsies combined with automated readout of immunohistochemical stainings
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-the article presents results of tumor samples obtained from patients treated with a novel oncolytic therapy and used digital whole-slide scanning coupled with image analysis for quantification of the immune cell invasion in the tumors before and after treatment.

Luhtala S, Staff S, Barok M, Tanner M, Isola J. Comparison of Antibodies for Immunohistochemistry-based Detection of HER3 in Breast Cancer. Appl Immunohistochem Mol Morphol. 2016 Jul 6.

-software developed at IBT (ImmunoMembrane) used for automated quantification of HER3 expression

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-immunostained tissue samples stained scanned at IBT

Drug Discovery and Chemical Biology Technology Platform

Chair of the platform: Krister Wennerberg, FIMM, High Throughput Biomedicine Unit

Partners: Antti Poso, BCK, Drug Design and Synthesis Laboratory; Matthias Nees, BioCity, Drug Discovery of Natural Products Laboratory; Arto Urtti, Adyary Fallarero, BCH, Centre for Drug Research (CDR); Olli Kallioniemi, FIMM (co-chair)

Achievements In Development Of Technology Services

FIRI-AoF funding supported purchase of several instruments like a Biotek microplate multi-mode dispenser and stacker, a Biotek Cytation5 plate reader for cell imaging, a Thermo Cytomat 10 series plate hotel for increased assay capacity in drug screening automation systems and an automated multiwell plate cell culture incubator (Thermo Cytomat 10 series) for improved capacity in cell-based screening.

A “Clinical DSRT” (drug sensitivity and resistance testing) service established 2014 fall was used for 75 fresh primary leukemia patient samples during year 2015. The oncology drug collection used for DSRT was updated and 66 new compounds were added.

Host institutes supported purchases of new instruments such as microplate readers (BMG

Labtech Pherastar FS and Thermo Varioskan LUX), a plate labeler to provide more capacity and efficiency to screening projects, and a BioTek Multiflo liquid dispenser. In addition, a ChemiDoc MP imager was purchased with an external grant of the host group at CDR

A "Clinical DSRT" (drug sensitivity and resistance testing) service established 2014 was used for 80 fresh primary leukemia patient samples during year 2016. This service is highly acknowledged among local clinicians and new patient samples have been received also outside Helsinki from other national or international (mostly Nordic) hospitals. The DSRT platform was a key component in several collaborative projects with pharmaceutical companies.

- iQue high throughput flow cytometry was used for one user drug screening project (>40 000 compounds). Currently, DDCB is relying on host institute's (non-open access) instrument as it was not yet able to get funding for its own iQue. However, there may be more requests for the use of iQue usage for different screening purposes e.g. clinical leukemia samples to study more detailed drug responses.

-Specialized screening assay development and consultation were provided for users studying biomaterials and nanoparticles

- LC/MS analysis services have been provided in the fields of drug and peptide analysis, and chemical purity.

- DDCB staff generated and published a database covering predictive modeling ADMET and adverse effect data on approved drugs that is publicly available for the scientific community (http://idaapm.helsinki.fi).

- Methods for performing and analyzing drug combination testing has actively been developed and a publicly available web site for these types of analyses has been generated (https://synergyfinder.fimm.fi/)

- Funding support for the group at Åbo Akademi University ended in 2015.

User Statistics

Drug sensitivity and resistance testing services were used for four pharmaceutical company-funded research studies involving two new companies. See table.

	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 res. groups	50	20	0	52	122
-local	38	9	0	27	74
-national	9	2	0	13	24
-international	3	9	0	12	24
-Non-academic (incl. above)	1	2	0	14	17
Service revenue	3488	9826 €	0	485 422 €	498 736 €
Key metrics	4 screening / follow-up projects, 2 virtual screens 4 in silico ADME projects 6 LC-MS projects	20 screening projects, of which 9 international projects		> 4600 DSRT plates made. > 870 custom drug plates made. > 200 compound aliquots provided	

Participation In International, Nordic And European Infrastructures

The DDCB 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. Second, we are also actively taking part of the work of the Small Molecules product platform of the EATRIS translational ESFRI roadmap (www.eatris.eu). Third, DDCB services will link to the high throughput microscopy core of the Finnish node of the Euro-BioImaging ESFRI (http://www.eurobioimaging.eu).

During year 2016, EU-OPENSCREEN work mainly focused on upgrading the potential Finnish EU-OPENSCREEN partner site platforms, preparing for a potential national participation as a founding member of EU-OPENSCREEN and applying for funding for further upgrades and future coordination. FIRI-application was submitted in 2016 and granted in 2017. EU-OPENSCREEN operations, which are scheduled to start in 2018, 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.

The members of the DDCB have played active roles in setting up and running a Nordic Chemical Biology Network between key chemical biology infrastructures in the Nordic countries. This network has also received NordForsk funding for its activities since 2014, but the funding will end 2017. The network aims to share knowledge, services and best practices between the infrastructure units through workshops, joint meetings and staff exchanges. I addition, the network is aiming to establish a Nordic academic compound collection with unique chemistries from academic laboratories that will be available to screen and use for other researchers. During 2016, the network held two joint meetings (in Oslo and Copenhagen) and two staff members from infrastructures in other Nordic countries visited the DDCB platform to learn from our expertise and infrastructures. Three visits to chemical biology infrastructures in other Nordic countries have been planned for DDCB staff during 2017.

Future Perspectives

Medicinal Chemistry Support

A bottleneck in probe development projects within DDCB has been a lack of medicinal chemistry support to optimize screening hits into high potency, selective, stable and ideally bioavailable leads. Moreover, the void of medicinal chemistry resources was identified as a lacking resource in the 2013 Biocenter Finland Technology Platform User Survey. In view of that, we believe that medicinal chemistry services should be integrated into the DDCB service platform using available expertise within the BCK-PMC group at UEF and the BCH-PharmDD group at UH. Incorporation of these two sites would make it possible to have a seamless integration of screening, follow-up bioassays, molecular modeling and synthetic medicinal chemistry to support the development of new bioactive compounds for both chemical biology and drug discovery purposes. Also, it would allow access to unique chemotypes synthesized in Finland that will enrich DDCB's chemical libraries. It is ideal if services (modeling and synthesis) are located in same laboratories to speed up the design and synthesis process. It must also be emphasized that this type of research cannot be replaced with normal organic chemistry work, as the critical question is to design and synthesize biologically stable and active, and ideally *in vivo* active compounds.

Advanced Cell Models

For ideal optimization and validation as well as translational discoveries on bioactive molecules, it is widely accepted that more advanced models than conventional in vitro "2D" tissue culture plastic culture can be extremely beneficial or even essential. For this

reason, we are actively expanding our capacity for advanced cell models such as 3D culture, organoid cultures, co-culture methods, cells under shear stress followed by appropriate readouts, often based on high content imaging. A new high throughput open access high content/high throughput confocal microscope is being set up at FIMM in a new infrastructure unit that is closely collaborating with the High Throughput Biomedicine unit. From 2017, we had also proposed to include the BCT-HCSLab at the University of Turku to strengthen this aspect and provide users the best possible services in phenotypic studies of 3D and co-culture cell growth in cancer models and beyond. However, the inclusion of this unit has been complicated by the fact that the leader of that unit left University of Turku and we need to sort out how we can go forward.

Multiplexed Readout Miniaturized Bioassays

The bioscience community requires more and more advanced bioassays to allow for increasingly deeper understanding of responses to drugs and drug-like molecules. A challenge is that more advanced and multiplexed bioassays typically are expensive and therefore often become cost-prohibitive for the user in screening or profiling settings. Therefore, our platform is continuously working on identifying and adapting technologies that allow for the maximal data output per invested euro. The acoustic dispensing capabilities at FIMM-HTB allows for ultra-miniaturization and thereby reduced reagent costs. Reverse-phase protein arrays for antibody-based detection of biomarkers in a screening setting is an ultra-low cost method that is being established at HTB. Finally, miniaturized high throughput flow cytometry by IntelliCyt's technology allows for both low cost multiplexed cell based screening and highly multiplexed antibody-bead detection of protein markers in cell supernatants and lysates at a fraction of the cost of competing technologies such as Luminex technologies. Two HTS flow cytometers are currently available at FIMM, UH but these are unfortunately not set up as full open access instruments and availability of instrument time is often limited. For this reason, funding for acquiring another open access instrument has been sought in a UH infrastructure application.

Establishment Of A National And Nordic Academic Compound Collection

DDCB will lead the efforts to build a national and Nordic academic compound collection. DDCB will benefit with 1) larger access to academic compounds from other Nordic collections; 2) access to Nordic experts that can support other assay technologies, or further synthetic medicinal chemistry efforts.

Informatics

An important aspect of the DDCB services is to provide users the tools to analyze and visualize the data generated. We have already been supporting the work to establish such public databases as well as analysis and visualization tools (some of them mentioned in section 1) and we will continue to develop these tools so that users more effectively can explore, understand and disseminate their data.

Biologics

The Biocenter Finland Scientific Advisory Board commented in their latest evaluation that antibody-based approaches are missing from DDCB services. Antibody-based and other biologics based profiling and screening services could be of great value to the research community in Finland and linking it to the DDCB platform would be a logical extension of the current operations. Open access infrastructures for providing these types of services do not currently exist in Finland and the DDCB will continue to explore how these types of services could be provided in the future.

Major Publications

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Mpindi JP, Yadav B, Östling P, Gautam P, Malani D, Murumägi A, Hirasawa A, Kangaspeska S, Wennerberg K, Kallioniemi O, Aittokallio T. Consistency in drug response profiling. *Nature*. **2016** 540:E5-E6 [*DDCB provided DSRT and bioinformatics services.*]

Tervonen, T. A.; Belitskin, D.; Pant, S. M.; Englund, J. I.; Marques, E.; Ala-Hongisto, H.; Nevalaita, L.; Sihto, H.; Heikkila, P.; Leidenius, M.; Hewitson, K.; Ramachandra, M.; Moilanen, A.; Joensuu, H.; Kovanen, P. E.; Poso, A.; Klefstrom, J. Deregulated hepsin protease activity confers oncogenicity by concomitantly augmenting HGF/MET signalling and disrupting epithelial cohesion. *Oncogene* **2016**, 35:1832-1846. [*DDCB provided virtual screening, assay development support and cell-based screening services*.]

Turku A, Borrel A, Leino TO, Karhu L, Kukkonen JP, Xhaard H. Pharmacophore Model To Discover OX1 and OX2 Orexin Receptor Ligands. *J Med Chem*. **2016** 59:8263-8265. [*DDCB provided physical access to ~400 cherry-picked compounds, expert advice with screening and with computational studies, and helped set up the computational infrastructure around the project.*]

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VIRAL GENE TRANSFER & CELL THERAPY

Coordinator: Seppo Ylä-Herttuala, BCK

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- and CRISPR 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 and track record with production and strict regulatory 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 funded initially "LentiGEMM - Lentiviral platform for creating genetically engineered mouse models" in 2010–2012. The platform changed its name into Tissue Engineered Disease Models (TEDM) in 2013, and the SAB recommended its inclusion in the Model Organism infrastructure network.

Viral Gene Transfer Technology Platform

Chair of the platform: Seppo Ylä-Herttuala, BCK, National Virus Core Facility, A. I. Virtanen Institute

Partners: Kari Airenne, BCK; Aki Manninen, BCO, Virus Vector Core Facility; 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); Eleanor Coffey, BioCity, Viral Vector Facility; Eric Dufour, BMT, Virus Vector Facility.

Achievements In Development Of Technology Services During 2016

VGTCT network has successfully coordinated virus vector production and also helped to develop specific profiles in different biocenters for vector production. In Kuopio, A.I. Virtanen Institute viral vector facility has focused on large scale high quality adenoviral, lentiviral, AAV and baculovirus vector production whereas other biocenters smaller scale local production activities have been developed in such a way that AAV vectors are mainly produced in Buomedicum (Prof. Alitalo), oncolytic vectors in Haartman Institute (Prof. Hemminki), lentiviral and retroviral vectors in Biomedicum (Docent Juha Kleftström), siRNA vectors in University of Oulu (Docent Aki Manninen) and adenoviral and lentiviral vectors and CRISPR-products in BioCity Turku (Docent Eleanor Coffey). Small volume virus and cell preparations and sendaiviruses are produced in Tampere (Dr. Erik Dufour).

Last year VGTCT core facilities and researchers were heavily involved in European Society of Gene and Cell Therapy Annual Congress which was organized in Helsinki in Finlandia Hall in September. During the meeting several high level contacts between researchers from all parts of the world and biotech companies were formed and Finnish scientific level of vector production was widely acknowledged. This scientific congress was very useful for the interchange of information and also opened doors and access to several other research groups and vector producing facilities worldwide.

Biocenter Finland funding has been of a key significance for the maintenance and development of VGTCT services. At the moment, small scale vector production is usually in the range of 10^8-10^{12} viral particles whereas large scale production can nowadays extend up to 10^{16} viral particles based on large volume bioreactor methods. Significant advantages have been made in vector purification and required QC/QA analyses. Core facilities have also been involved in helping researchers to use viral vectors, provided standard operating procedures and helped in regulatory permission applications. In all centers, prices for the production of vectors are affordable and greatly help Finnish researchers to use these modern biotechnology tools in their research.

A.I. Virtanen Institute core facility has established not only suspension cell culture bioreactor methods, but also new adhesion based iCELLIS bioreactors which allow even more efficient lentivirus and AAV production. Downstream purification has been upgraded to be able to handle 20-50 l original virus volumes, which will yield 10^{16} viral particles. AAV Core Facility in Helsinki has successfully continued to provide services to the customers. Currently the AAV Core provides purified and fully characterized AAV preps of 4 serotypes (2, 6, 8 and 9), which allow efficient transduction of virtually all tissues in the animals. These preps include viruses, which can be used as a negative control, as well as AAVs, encoding widely used fluorescent proteins, such as GFP. Availability of these AAV preps further reduce waiting time for the customers. In 2016, the AAV Core continued to provide consultative help to the customers. The customers were interested in AAV vector redesign to improve target specificity and in packaging of the longer genes, which are not permitted by the current available AAV vectors.

Biomedicum functional genomics unit (FuGU) provides lentiviral and retroviral production and also hosts mouse and human TRC1 shRNA libraries licensed for and housed in FuGU. FuGU has so far provided large numbers of glycerol stocks containing shRNA vector backbones as a new service to several research groups.

Turku core facility has established CRISPR technology for the development of gene modified cell lines using lentivirus and retrovirus vectors. They have also established large scale screening systems for CRISPR/Cas9 gene editing technologies. Oulu vector core facility has focused on siRNA and lenti-CRISPR vector design and production. They also organize practical courses on RNAi methods and how to use vectors in real wet lab conditions. In Tampere core facility new laboratory space has been taken into use in a new BioMediTech-building and the laboratory has now significantly improved operating conditions for vector production at BSL2 and in the future also BSL3 level. Sendaivirus vector production has also been fully established in 2016.

Most Significant Bottlenecks

VGTCT network is quite well equipped and ready in its operations in all participating biocenters. However, increasing demand of the high quality vectors will require further developments especially in the purification methods and QC/QA testing so that the produced gene transfer tools will meet the highest possible quality in all biocenters. A.I. Virtanen Institute core facility is leading the development of established SOPs for these assays, which can then be used in all participating biocenters. A constant bottleneck is the lack of sufficient funds to pay staff scientists and technicians in all core facilities so that the highly developed methods could be kept in the hands of the most skilled people.

User Statistics

See table below.

	Helsinki			AIV core	BCO	BioMediTech	BioCity	Total
	AAV	Oncolytic	FuGu	Kuopio	Oulu	Tampere	Turku	
Customers	9	5	44	35	14	5	32	144
• **local**	4	3	31	11	14	4	29	57
• **domestic**	1	1	11	8	-	-	1	21
• **internatio nal**	3	1	1	13	-	1	2	21
• **non academic**	-	-	1	2	-	-	1	4
Volume*	88	16	85	98	326	19	57	689
Financial turnover/€	36 787	NA	NA	35 050	7811	NA	NA	79 648

*number of virus preps produced

Participation In International, Nordic And European Infrastructures In 2016

A.I. Virtanen Institute core facility is an integral part of Finnish Academy Centre of Excellence and participates in three EU FP7 funded research consortia. AAV core facility and FuGU in Helsinki belong to Finnish Academy Centre of Excellence and also participate in several EU FP7 consortia.

Future Perspectives

It is anticipated that the need for viral vectors will further increase in the coming years. In A.I. Virtanen Institute core facility large scale production capacity and purification of viral vectors will be further developed using affinity column and chromatography methods and in other core facilities methods for the production and purification of the vectors will also be brought to higher standards. Here we will utilize QC/QA methods developed in A.I. Virtanen Institute core facility. We envision big potential in the development of genome editing technologies using CRISPR and AAV. In humans and animals, AAV can transduce multiple cell types, especially heart, liver, lung and skeletal muscle, making it possible to use CRISPR most efficiently in these target organs. In Tampere move into the new building and core facility laboratory space will significantly improve capacity for the vector work especially in the area of sendaivirus production for vaccine development. In Turku core facility lenti CRISPR/Cas9 editing services will be further developed for in vitro applications.

Major Publications

Merentie M, Lottonen-Raikaslehto L, Parviainen V, Huusko J, Pikkarainen S, Mendel M, Laham-Karam N, Kärjä V, Hedman M, Ylä-Herttuala S. Efficacy and safety of myocardial gene transfer of adenovirus, adeno-associated virus and lentivirus vectors in mouse heart. **Gene Ther.** 23:296-305, 2016. (doi: 10.1038/gt.2015.114)
Succinct description: Vectors produced in core facility.

Gallini R, Huusko J, Ylä-Herttuala S, Betsholtz C, Andrae J. Isoform-Specific Modulation of Inflammation Induced by Adenoviral Mediated Delivery of Platelet-Derived Growth Factors in the Adult Mouse Heart. **PLoS One.** 2016 Aug 11;11(8):e0160930. (doi: 10.1371/journal.pone.0160930. eCollection 2016.)
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Whitington T, Gao P, Song W, Ross-Adams H, Lamb AD, Yang Y, Svezia I, Klevebring D, Mills IG, Karlsson R, Halim S, Dunning MJ, Egevad L, Warren AY, Neal DE, Grönberg H, Lindberg J, Wei GH, Wiklund F. Gene regulatory mechanisms underpinning prostate cancer susceptibility. **Nat. Genet.** 48, 387-397, 2016.
Succinct description: Vectors produced in core facility.

EMERGING PLATFORM: TISSUE ENGINEERED DISEASE MODELS

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

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

Tissue Engineered Disease Models (TEDM) develops complex ex vivo and in vivo tissue models compatible with genetic and chemical biology approaches, to benefit biomedical research. The disease focus is in breast and lung cancers and cardiovascular disease. Technology development will focus on systemic, intraductal, and orthotopic somatic cell-based transplantation methods using donor cells from GEMMs (syngrafts) 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. The focus of TEDM does not overlap with technologies in other BF networks, but complements the existing virus, drug discovery and animal models networks. TEDM will interact with these infrastructures, not by establishing its own core facilities, but by supporting existing core facilities by creating new rechargeable services. This model was already successful in the period 2010–2012, and given the increasing number of Finnish scientists working on complex biological models, TEDM anticipates a solid user base for new TEDM services.

Achievements In Development Of Technology Services During 2015-2016

The core element in TEDM is development of complex *ex vivo* and *in vivo* tissue models compatible with genetic and chemical biology approaches, to benefit biomedical research. 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 (syngrafts) 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. TEDM's focus does not overlap with technologies already presented in other BF networks, but complements existing virus, drug discovery and animal models networks. TEDM will interact with these, not by establishing its own core facilities but building on existing core facilities by creating new rechargeable services for them. Given the increasing number of Finnish scientists working on complex biological models, we foresee a solid user base for new TEDM services.

FinGEEC *in vivo* platform, which has been coordinated at University of Turku has generated a platform capable of handling and expanding genome edited cells lines for the new state-of-the art mouse intraductal orthotopic breast cancer model (MIND). The MIND model is unique for its ability to reliably model human ductal carcinomas and the fact that this model is amendable also for hormone-dependent cancer types (Cancer Cell, 2016 Vol. 29, Issue 3, p407–422). The methodology for this advanced orthotopic intraductal transplantation of tumor cells via nipple injections was succesfully optimized during the TEDM project. There were no major bottlenecks in the method development and the model has proven to be robust and provide reproducible results. In concert with the original project plan, and in order to make the model accessible to all BF customers, Turku partners have already initiated transition of the technique to be provided as a research service under Turku Center for Disease Modelling (http://www.tcdm.fi). In addition, U.Turku has

provided consultation to the oncology R&D unit of Orion with regards to use of intraductal models in drug discovery. Another line of in vivo model development, which also includes ex vivo tumor model development has taken place in FIMM. FIMM has developed, and routinely applies, a SOP for robust intranasal delivery of adenoviral-Cre particles, using isoflurane anesthetics, to target the somatic murine lung epithelium. This permits the versatile creation of mouse models for studies related to lung disease, such as cancer. The method has been fine-tuned, using titration of progenitor cell-directed adenoviruses and use of the mT/mG reporter, to target equivalent numbers (0.8% of total cells) of lung progenitor cells; distal airway located SPC+ alveolar cells require higher $2.5x10^9$ pfu Ad5-SPC-Cre and more proximal CC10+ bronchiolar cells lower Ad5-CC10-Cre infection rates. Furthermore, FIMM optimised a method for the *ex vivo* culture and study of non-small cell lung tumours from AdCre-infected mice carrying conditional lung cancer predisposition alleles. This SOP consists of precision-cutting of tumour slices using a vibratome, and culture of 200 um slices on rotating media-dipping incubating units under 20% oxygen. This culture method ensures tissue viability up to four days of culture, while oncogenic signalling mimics the *in situ* tissue for 24h. **FinGEEC *ex vivo* platform** has focused on two different areas of technology development. The UEF (Kuopio) service has increased the use of lentiviral vectors and flow cytometry based analysis and sorting in multiple research areas, including cardiovascular diseases and neurosicences. As a new method year 2016, sorting of LV-CRISPR/Cas9-modified cells into 96-well plates for single cell analysis has been performed. In the coming years, when more and more research is focusing on single cell level, where TEDM-Kuopio flow cytometry service offers a valid tool for creating single-cell samples with high purity and sensitivity. The U.Helsinki partners have focused on the development of vascular biology models and recently, especially on development of breast cancer explant platform for studies of breast and solid tumors in general. These patient-derived explant (PDEx) models, which preserve the heterogeneity and the cell identity of the original patient's tumor, offer unique research tools for wide range of personalized oncology projects. The platform has been used (as yet with no cost recovery) by number of academic and industry partners form the Finnish biocenters and abroad. The main cost recovery for TEDM services in Helsinki (BCH) currently comes from RT-PCR services, offered for customers working on different human or animal in vivo or ex vivo models of human disease.

User Statistic

During 2015-2016, the development TEDM platforms generated new services, which are currently available through core facilities for biocenter and industry customers. The revenues from user fees:

2015 Tot. 10.676 € (BCH)

2016 Tot 21443 € (BCH 6443€, AIV 15000€)

The services have been provided for 15 different customers (Helsinki, Kuopio), including one Finnish company

During 2015-2016, the development of TEDM platforms has generated income for animal and virus core facilities from TEDM partners. For example, in Turku a single MIND (mammary intraductal transplantation) service generated 3300€ income for mouse facility and 6000€ income for virus core facility, 300 € for imaging facility and 530€ for histology services. These numbers are given as example of how BF support of emerging technology services widely benefits and invigorates the local life science infrastructures. The MIND model and technology is currently being transferred to Turku mouse facility (negotiations underway). AIV has successfully established a state-of-the-art flow cytometry core, which reported income for 2016. BCH has succeeded in establishing a disease model geared qRT-PCR expression and knockdown/knockout validation services, which have generated steady income during 2015-2016. FIMM has invested its efforts

mainly to technology development and do not report yet income from the services.

Participation In International, Nordic And European Infrastructures

The development of the technology platforms within BF have been closely tied with a public-private Innovative Medicines Initiative consortium effort, PREDECT. Activities particularly included the co-development of slice culture methods for tumours of different epithelial origins, with collaborators at the IKP in Stuttgart, Erasmus University Rotterdam and AstraZeneca UK.

Future Perspectives

The discussions within the platform have pointed out several different Future perspectives for TEDM:

One is related to need of new infrastructures to lower bar for Finnish groups to capture the rapidly developing CRISPR/Cas9 gene editing technology. Currently, a new emerging technology platform, Finnish Genome Editing Center (FinGEEC) drives development in this area. It is also envisioned that infrastructure around clinical tumour samples obtained via biopsies or as resected surgical samples would be in need. They provide unique samples with precision medicine-related diagnostic value. For solid tumour samples, this requires a method that preserves the architecture, viability and functional characteristics of the original tumour. Extrapolation of organotypic culture methods from murine to patient tumour tissue are thus foreseen. TEDM also endorses the importance of single cell based analytics fot future research. For example, flow cytometry has consolidated its role as a key research platform in AIV-institute in Kuopio. This has partly led to acquisition in Kuopio a state of the art imaging flow cytometer, Amnis Flowsight, which can microscopically image every cell at speed of 2000 cells/s. In addition, a new laser for the FACSAria Cell Sorter will be purchased later 2017. Therefore, this widens the possibilities to use flow cytometry in more complicated and advanced studies in the future.

Major Publications

FIMM: Nagaraj, A.S., Lahtela, J., Hemmes, A., Pellinen, T., Blom S., Devlin, J.R., Salmenkivi, K., Kallioniemi, O., Mäyranpää, M.I., Närhi, K. and Verschuren, E.W. (2017). Cell of origin links histotype spectrum to immune microenvironment diversity in non-small-cell lung cancer driven by mutant *Kras* and loss of *Lkb1*. *Cell Rep.* 18: 673-684.
Application of AdCre delivery method (FIMM service platform 1) to identify an important role for the progenitor cell in establishing non-small cell lung cancer histopathology spectra.
Davies, E.J.*, Dong, M.*, Gutekunst, M.*, Närhi, K.*, van Zoggel, H.*, Blom, S., Nagaraj, A., Metsalu, T., Oswald, E., Erkens-Schulze, E., Turkki, R., Wedge, S., af Hällström, T.M., Schueler, J., van Weerden, W., Verschuren, E.W., Barry, S.T., van der Kuip, H. and Hickman, J.A. (2015). Capturing complex tumour biology *in vitro*: histological and molecular characterisation of precision cut slices. *Sci. Rep.* 5: 17187.
Development of organotypic tissue slice culture methodology, FIMM service platform 2.
AIV: Babu M, Durga Devi T, Mäkinen P, Kaikkonen M, Lesch HP, Junttila S, Laiho A, Ghimire B, Gyenesei A, Ylä-Herttuala S. Differential Promoter Methylation of Macrophage Genes Is Associated With Impaired Vascular Growth in Ischemic Muscles of Hyperlipidemic and Type 2 Diabetic Mice: Genome-Wide Promoter Methylation Study. Circ Res. 2015. 117:289-99. doi: 10.1161/CIRCRESAHA.115.306424. Flow Cytometric analysis on inflammatory cells.

Kotimaa AA, Zainana A-M, Huusko J, Stedt H, Heinonen SE, Kholová I, Mäkinen P, Lesch HP, Alhonen L, Ylä-Herttuala S. Knockdown of endogenous VEGF-D in mice with lentiviral short-hairpin RNA technology leads to reduced lifespan and increased incidence of malignancies. Manuscript. 2015. Flow Cytometric analysis of TG mouse organs/cells.

Laham-Karam N, Lalli M, Leinonen N, Ylä-Herttuala S. Differential Regulation of Vascular Endothelial Growth Factors by Promoter-targeted shRNAs. Mol Ther Nucleic Acids. 2015. 4:e243. doi: 10.1038/mtna.2015.16. Flow Cytometric analysis cell produced by lentivirus technology.

BCH: E. Marques, J.I. Englund, T. Tervonen, E. Virkunen, M. Laakso, M. Myllynen, A. Mäkelä, M. Ahvenainen, T. Lepikhova, O. Monni, S. Hautaniemi, J. Klefström. Par6G suppresses cell proliferation and is targeted by loss-of-function mutations in multiple cancers, 2016, Oncogene, Mar 17;35(11):1386-98.

Large shRNA screen (> 200 constructs). qPCR combined with 3D mammary epithelial culture enabled validation of shRNA knockdown. Viral particles were provided by FuGU. In this paper transgene vectors were virally delivered and integrated for long-term transgene expression and knockdown efficacy was validated in hard-to-transfect mammary epithelial cells.

T. Tervonen, D. Belitškin, S.M. Pant, J.I. Englund, E. Marques, H. Ala-Hongisto, L. Nevalaita, H. Sihto, P. Heikkilä, M. Leidenius, K. Hewitson, M. Ramachandra, A. Moilanen, H. Joensuu, P.E. Kovanen, A. Poso, J. Klefström. Deregulated hepsin protease activity confers oncogenicity by concomitantly augmenting HGF/MET signalling and disrupting epithelial cohesion, 2016, Oncogene, Apr 7; 35(14): 1832-46.
qRT-PCR was used to validate all genetic manipulation with dox-inducible hepsin construct in this study. shRNAs and viral particles were provided by FuGU.

SCIENTIFIC SUCCESS STORIES

A significant share of the following distinctions, covering all scientific, scholarly and artistic research domains in Finland, have been awarded to researchers for whose science the BF technology services have been instrumental: Academy professors (currently 15/41), Centers of Excellence (6/18 in 2008-2013; 7/18 in 2012-2017; 6/14 in 2014-2019) and Academicians of Science (3/7 since 2014). The BF-community has fetched from the EU Framework Programme 7 and Horizon 2020 over 40 research, coordination and training projects. Half of the 115 ERC awards fetched so far to Finland have been granted to life scientists using BF facilities.

Bioinformatics

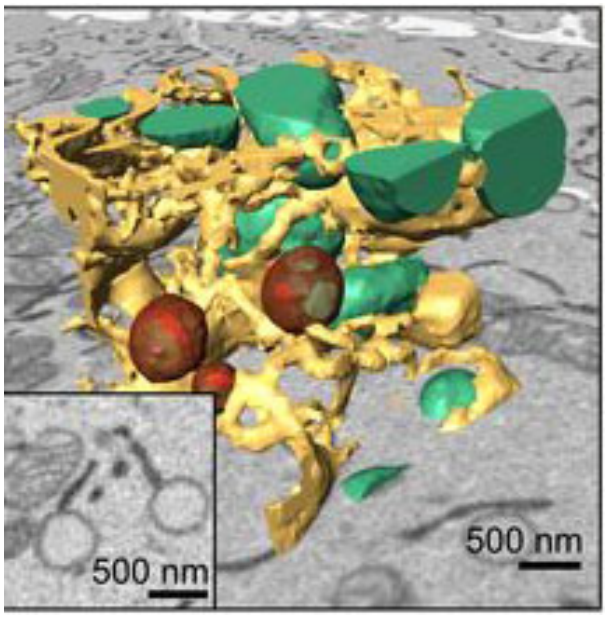
Recently, Structural Bioinformatics Laboratory (BCT) was contacted by Professor Juha Kere (Karolinska Institute, Kings College and Biomedicum) for help in identifying the DNA binding sequence for a newly-identified transcription factor (TF) that is responsible for the very early 4-8 cell stage of human embryonic development. The DNA sequence was identified using bioinformatics means, model structures were made and demonstrated the most likely residues involved and supported the studies on mutations made on Leutx based on genetic variation in the Icelandic human population (via Decode Genomics). Structural studies on the TF have begun and studies have expanded now to other TFs in early development that were also reported by Juha Kere's consortium on 9 international laboratories. A manuscript on the genomic studies and modeling have been submitted for publication. The project's success relied on our ability to rapidly muster the resources of SBL and the IT infrastructure of BCT provided via BF support in 2016.

In an another example Panu Jaakkola (oncologist at Turku University Hospital) was looking for novel prognostic biomarkers in renal cell cancer study. Analyses conducted in the group of Laura Elo (BCT) based on 442 ccRCC patients provided by The Cancer Genome Atlas (TCGA) revealed a list of 152 genes playing role in prediction of survival outcomes. The findings were validated using an independent Japanese dataset of 100 patients. Remarkably, novel markers include for example a number of proteins that function in transporting different chemical between cells and extracellular space. The work highlights the importance of joining expertise across clinical, experimental and computational experts. The article was recently published in Nucleic Acids Research journal:

http://nar.oxfordjournals.org/content/early/2015/08/11/nar.gkv806.full

Electron microscopy

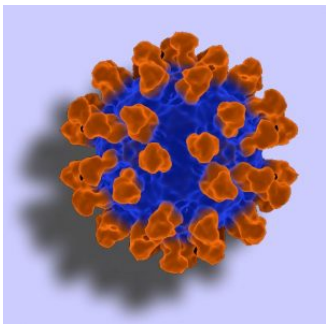
Lipid droplets (LDs) are ubiquitous cellular organelles that function in regulating lipid metabolism by storing lipids at times of excess and releasing them upon demand. In a collaboration project between University of Helsinki research groups of Elina Ikonen (Department of Anatomy, Faculty of Medicine) and Eija Jokitalo (Institute of Biotechnology), we showed that Seipin, mutated in severe congenital lipodystrophy (BSCL2), is an ER–lipid droplet contact protein, regulates the extent of ER–LD contacts and facilitates incorporation of lipid and protein cargo into maturing LDs. Seipin deficiency increases the heterogeneity of ER–LD contacts, resulting in completely missing, rudimentary, or very extensive contacts. Seipin is required during LD formation for the targeting of ER-derived fatty acid-activating enzyme ACSL3 to LDs. In seipin deficiency, the fatty acid flux to neutral lipids becomes



3D-EM model of LDs (red) and surrounding ER (yellow) and mitochondria (green) profiles shown on top of a block face image.

compromised when LD formation has been initiated.

Salo VT, Belevich I, Li S, Karhinen L, Vihinen H, Vigouroux C, Magre J, Thiele C, Hölttä-Vuori M, Jokitalo E, Ikonen E. 2016. Seipin regulates ER-lipid droplet contacts and cargo delivery. EMBO J. 35:2699-2716.



Human parechovirus type 3 is a picornavirus that can cause severe infections in humans, resulting in sepsis and central nervous system disease in newborns. So far the most promising anti-picornaviral drug candidates do not have any effect on the parechovirus, therefore new effective means have to be found. Researchers in the University of Helsinki have determined a high-resolution structure of the human parechovirus type 3. The three-dimensional model was created by collecting thousands of images of virus with an electron microscope under -190 °C. The images were then computationally aligned and combined. "The virus genome is a single-stranded RNA, which is encapsidated in a protein shell. About a quarter of the genome is in close contact with the capsid proteins, leading to highly ordered RNA. This has not been seen in other picornaviruses," describes Postdoctoral Researcher, Dr Shabih Shakeel in the Institute of Biotechnology. The atomic model of the virus shows a distinct way of how viral proteins interact with each other to stabilize the capsid. The best studied anti-picornaviral drug pleconaril and its derivatives work well against enteroviruses, large group of picornaviruses. The parechovirus type 3 structure demonstrates that pleconaril binding place is blocked in parechoviruses and therefore does not work against this virus group.

Marie Curie Postdoctoral Research Fellow, Dr Ausra Domanska worked on the structure of the same virus in complex with antibody fragments recognising parechovirus type 3. "In the absence of antiviral drugs, developing broadly neutralising monoclonal antibodies as therapeutic antibodies against this virus is one of the most promising treatment options for clinicians in the near future," she says.

Shakeel S, Westerhuis BM, Domanska A, Konig RI, Matadeen R, Koster AJ, Bakke, AQ, Beaumont T, Wolthers KC, Butcher SJ. 2016. Multiple capsid-stabilizing interactions revealed in a high-resolution structure of an emerging picornavirus causing neonatal sepsis. Nature Communications 7:11387. doi: 10.1038/ncomms11387.

Light Microscopy

The light microscopy platform served a growing number of users, nearly 1000, coming from more than 270 research groups, and continued to have a very significant impact on Finnish life sciences. The services of the platform were used in numerous high-impact scientific publications, a small selection of which is listed below. The contributions of the platform include both routine imaging, advanced imaging and protocol development, and bioimage informatics.

Small Animal Molecular Imaging SPECT/CT

The unit has offered a record service level accounting with an income of around 25 000 € in 2016, this is in part due to the efforts of previous years on public relationships in promoting and publicising the unit, and also for the support of the Faculty of Pharmacy on the upgrade of the SPECT/CT camera, as well as partially covering service contract expenses.

Efforts of this unit, along with the Radiochemistry Unit, have crystallised in the foundation of the Helsinki *in vivo* animal platform (HAIP), which would provide a more versatile environment and a better situation on the national infrastructure development, and give more international projection.

Genome-wide Methods

With the support of core facility services provided by the BF-GWM technology platform, Academy Prof. Johanna Ivaska's research team made breakthrough novel findings on how surrounding tissue influences growth and malignancy of the cancer cells. The study published by Riina Kaukonen et al. 2016 in Nature Communication revealed that the stiffness of both tumor and the surrounding tissue affects largely expression of the genes in cancer cells and increases the malignancy of the cancer. Importantly, Kaukonen et al. were able to prevent the growth of the tumour by returning stiffness of the surrounding tissue into the normal level found in healthy tissues. Mediator of these effects in cancer cells was found to be an epigenetic regulator JMJD1A enzyme. In collaboration with the medical doctors at University Hospitals in Turku and Helsinki, the group also found that this JMJD1A is expressed at higher levels in those cancers which were surrounded by tissue with higher density. The results by Prof. Ivaska's group open completely new insights and into the mechanisms how surrounding tissues contribute to the development of cancers. Novel therapies targeting also tissues surrounding the tumor may improve the efficiency of cancer treatments.

Mouse Models

The NC-UEF is the only laboratory in Nordic countries able to perform combined electroretinogram (ERG) and visual evoked potential (VEP) recordings in mice. These techniques were employed to assess the question whether degenerative brain diseases manifest in the retina of the eye, which is developmentally part of the brain. Indeed, in two genetically modified mouse lines, one modeling Huntington's disease, and one cerebral neurolipofuscinosis (CLN5), functional ERG changes preceded motor symptoms at an early stage of the disease. Retinal changes were progressive, allowing follow-up studies over several months. On the other hand, the possibility suggested in the literature that progressive impairment in spatial navigation in Alzheimer model mice might be caused by the progressively impaired vision was ruled out: the ERG and VEP responses were intact in middle-aged APP/PS1 mice with documented spatial memory impairment. (Leinonen H, Lipponen A, Gurevicius K, Tanila H. Normal amplitude of ERG and VEP responses in APP/PS1 mice. J Alzheimer's Dis 2016; 51(1):21-26.)

These findings encourage the use of ERG and VEP in preclinical treatment trials in mice modelling neurodegenerative diseases. They also suggest that ERG, combined with automated fundoscopy, as a minimally invasive and low-cost method could be used as a screening tool for common brain diseases in the risk group of aged individuals.

Non-mammalian Model Organisms

The most important breakthrough is the current standard use of CRISPR-Cas9 method in zebrafish to create targeted mutants that allows for example phenotypic analysis of novel genes associated with certain diseases. Both in

the Helsinki and Tampere unit dozens of mutations are created successfully.

Protein-Proteome

Biocenter Finland SAB evaluated all the platforms and PPN was ranked very high in the evaluation. Furthermore, the user survey indicated the impact of PPN to be high and we received the highest score among the BF platforms. Therefore, it is clear that PPN represents widely recognized source of scientific services. The PPN consortium is well-established and several important contributions were made during 2016. We decided to highlight two success stories, reflecting the technologies important also for the future development.

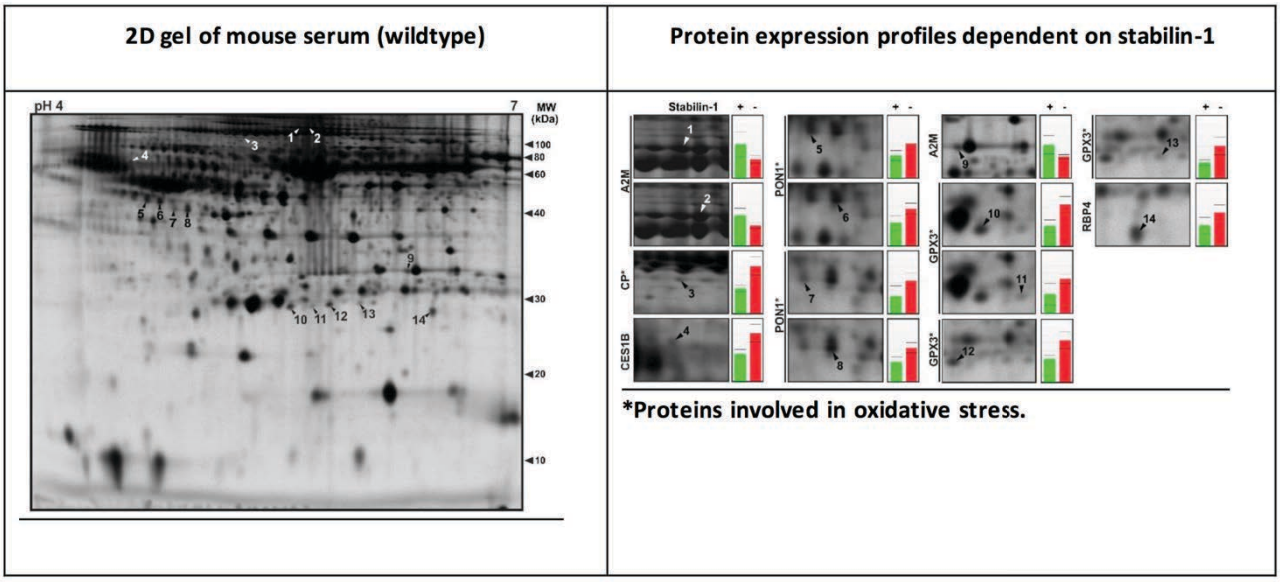
Example study 1: A subset of stabilin-1-expressing macrophages prevents fibrosis in chronic liver injury

Rantakari P, Patten DA, Valtonen J, Karikoski M, Gerke H, Dawes H, Laurila J, Ohlmeier S, Elima K, Hübscher SG, Weston CJ, Jalkanen S, Adams DH, Salmi M, Shetty S. Stabilin-1 expression defines a subset of macrophages that mediate tissue homeostasis and prevent fibrosis in chronic liver injury. Proc Natl Acad Sci U S A. 2016, 113(33):9298-303.

A consortium of national (Oulu, Turku) and international (United Kingdom) research groups has studied organ fibrosis, a major cause of global morbidity and mortality. The disease is driven by oxidative stress and chronic inflammation, but beyond a critical involvement of macrophages little is known about its mechanism. Stabilin-1, expressed in specific subpopulations of macrophages, has been suspected as a potential key player. In this study, BCO's protein analysis core facility has contributed gel-based proteomics (2-DE) and mass spectrometry to analyze serum of stabilin-$1^{-/-}$ and wildtype mice. This revealed increased levels of several oxidative stress-related proteins upon stabilin-1 deficiency. Further studies showed that stabilin-1^{+} macrophages were induced at sites of cellular injury. Upon uptake of MDA-LDL, an oxidative stress product, stabilin-1 downregulates the profibrogenic chemokine CCL3 and prevents excessive collagen deposition. These results suggest that stabilin-1 is a protective factor against oxidative tissue damage.

Example study 2: Anesthesia and Prominent Phosphoproteomic Changes

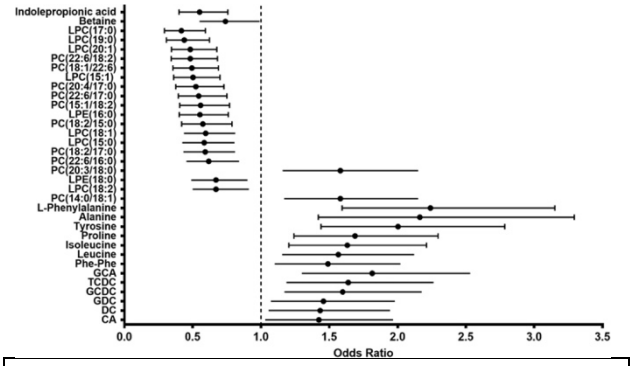
Kohtala S, Theilmann W, Suomi T, Wigren HK, Porkka-Heiskanen T, Elo LL, Rokka A, Rantamäki T. Brief Isoflurane Anesthesia Produces Prominent Phosphoproteomic Changes in the Adult Mouse Hippocampus. ACS Chem Neurosci. 2016 15;7(6):749-56.



F1000 Prime recommendation for publication: Brief Isoflurane Anesthesia Produces Prominent Phosphoproteomic Changes in the Adult Mouse Hippocampus

"The publication by Kohtala et al. offered the first quantitative assessment of general anesthetic-induced global changes in protein phosphorylation within the hippocampus. The article by Kohtala et al. leads to greater appreciation of the complex molecular mechanisms that are associated with general anesthesia. "

Metabolomics



Identified metabolites and their association with the development of T2D in the DPS (N = 200). Closed bars: FDR-P < 0.05 Opened bars: P < 0.05. Phe: phenylalanine GCA: Glycocholic acid TCDC: Taurochenodeoxycholic acid GCDC: Glycochenodeoxycholic acid GDC: Glycodeoxycholic DC: Deoxycholic acid CA: Cholic acid.

BCK Group published an article reporting novel discoveries related to metabolism of type 2 diabetes, including discovery of microbiota-produced compound indolepropionic acid and its protective role against type 2 diabetes, thereby providing direct link between gut microbiota and the disease. The publication gained wide national and international media visibility, *e.g.*: https://www.sciencedaily.com/releases/2017/04/170411090159.htm

http://www.laakarilehti.fi/ajassa/ajankohtaista/suolistobakteerit-voivat-suojata-diabetekselta/

http://www.hs.fi/hyvinvointi/art-2000005168506.html?share=0f3bde0640623644a60ade5636f0833a

Original article: *de Mello V, Paananen J, Lindström J, Lankinen MA, Shi L, Kuusisto J, Pihlajamäki J, Auriola S, Lehtonen M, Rolandsson O, Bergdahl IA, Nordin E, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Landberg R, Eriksson JG, Tuomilehto J, Hanhineva K, Uusitupa M* (2017) Indolepropionic acid and novel lipid metabolites are associated with a lower risk of type 2 diabetes in the Finnish Diabetes Prevention Study. *Nature Scientific Reports,* doi: 10.1038/srep46337.

Stem Cells and Biomaterials

BCH continued further optimization of reprogramming technology with particular focus on biobanking. We showed that fully reprogrammed iPS cells have similar differentiation propensities regardless of the cell-type of origin. The practical implication of this finding is that bona-fide iPS cell lines derived from different tissues can be combined in the biobank repositories (Kyttälä et al. Stem Cell Reports 2016; 6(2):200-12).

BMT has mainly focused on using iPSCs for disease modelling and the improvement of analytical methods. Modelling of cardiac electrophysiological defects has progressed without problems, but cardiomyopathies have proven to be more challenging. The phenotype and functional characteristics of iPSC-derived cardiomyocytes were found to be similar to those observed in patients with hypertrophic cardiomyopathy. This paper also described a wide spectrum of functional assays available in the Core (Ojala M, et al, Stem Cells International 2016, ID 1684792).

BCK has developed methods for differentiation of human iPSC derived cells into a variety of CNS and muscle cells. The differentiation protocols developed are exceptionally broad, extending from specific neuronal subtypes (spinal cord motoneurons and midbrain dopaminergic neurons, astrocytes, oligodendrocytes, microglia) to endothelial and two types of muscle cells. We have shown that specific functional

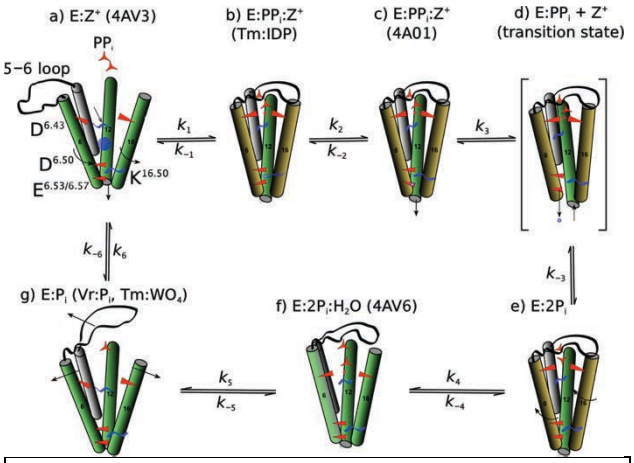
pathologies and clinical phenotypes of CNS diseases, such as Parkinson's disease, Alzheimer's disease, psychopathy, amyotrophic lateral sclerosis and schizophrenia, as well as familial cardiomyopathies can be recapitulated in iPSC-derived cell models. While most of these results have so far been published only at the abstract level, an example for Parkinson's disease has been published (https://www.nature.com/articles/npjparkd201 69). Another important example of successful exploitation of the results is the identification and validation of IL-33 for therapeutic application in neurodegenerative disease. After patenting the discovery (WO 2014128254 A1), the finding was verified with human iPSC-derived models and licenced by the University of Eastern Finland to an US-based company with a deal worth 10 million euros.

X-RAY FIX-UP

The research expertise of FIX-UP is a critical component of modern life science research. Our researchers continuously engage in exchanges in discussions with the life science research community. A highlight in this respect has been the EMBO symposium on biocatalysis organized in Oulu, June 12-16, 2016, focusing on fundamental and applied aspects of biocatalysis, with an emphasis on the impact that enzyme research has at the interface of biology and chemistry. The meeting was attended by166 participants who enjoyed the 32 talks by experts in the field. A selected set of papers has been published in a special issue of PEDS (March 2017).

Structural and Functional Studies of Membrane Pyrophosphatases

Membrane pyrophosphatases (M-PPases) occur in organisms ranging from plants and protozoan parasites to prokaryotes. They are associated with low-energy stress: overcoming saline or drought conditions in plants or rapid changes in pH or osmotic pressure in protozoan parasites. M-PPases couple pyrophosphate hydrolysis to the pumping of sodium ions and/or protons across the inner membrane of prokaryotes or the vacuole/acidocalcisome membranes of plants/parasites. There are no analogues in mammals, so M-PPases are an important potential drug target. Continuing from our initial M-PPase structure (Kellosalo et al, *Science*, 2012) using X-ray crystallography, we are completing a model of the catalytic cycle using additional structural and biochemical data. We have solved two new structures of the M-PPase of the thermophilic bacteria: *Thermotoga maritima* (Tm-PPase) in different catalytic states. Combining this data with previously solved structures of this protein and of a related protein from the plant: *Vigna radiata* (Vr-PPase) we have generated a plausible model of the complete catalytic cycle that covers all the major catalytic states (Figure).



Overview of the catalytic cycle model proposed for membrane pyrophosphatases based on structural information obtained via X-ray crystallography. Only key helices and residues are shown for the sake of clarity (Li, K-M., Wilkinson, C., Kellosalo, J., Tsai, J-Y., Kajander, T., Jeuken, L.J.C., Sun, Y-J. and Goldman, A. (2016) Membrane pyrophosphatases from Thermotoga maritima and Vigna radiata suggest a conserved coupling mechanism. Nat. Commun. 7:13596).

Nuclear Magnetic Resonance and Mass Spectrometry

Weak or transient oligomers of proteins are examples of protein-protein interactions,

which are difficult to study because the quaternary structure is not stable and protein exist in equilibrium of different forms depending on protein concentrations. Native mass spectrometry is a new effective tool to study mixtures, which consist of different protein species. This methodology has been efficiently used to reveal that inherent feature of allergens is their ability to form transient oligomers (Niemi *et al. Sci Rep.* 5 (2015) 13841). This is key information in the development hypoallergenic variants of allergens, which can be used in specific immunotherapy of allergic diseases.

Biobanking Technologies

The FIMM partner in the consortium has set up a webmicroscopy portal (predect.webmicroscope.net) through which partners in the PREDECT project (predect.eu) funded by Innovative Medicines Initiatives (IMI) of the European Union can access a common repository of digitized tissue samples. More than 28 laboratories around Europe, including 9 pharma companies participate in this 20 million Euro project that is one of the largest public-private partnerships within the biomedical research domain.

The aim of the project is to find better models for cancer drug discovery by integration and comparison of information retrieved from a large series of cancer model (2D and 3D cell culture, mouse xenografts, ex vivo tissue culture and human cancer samples).

All samples are made available on-line for visual inspection, comparisons and quantitative digital image analysis with cloud-based computing support through the portal maintained by FIMM (Figure). Linking the image data from the PREDECT TMAs directly to the sample metadata enables users to assess and antibody staining and tissue morphology.

Interface for PREDECT WebMicroscope database (http://predect.webmicroscope.net) with more than 30,000 scanned tissue samples

The image analysis tools developed at FIMM and IBT can support biomarker research and provide reproducible and high-throughput readout of protein expression and automated morphological characterization of tissue samples. A large number of studies have been published (selected publications reported below) where the platform services have contributed to the results and shown scientific impact.

Drug Discovery and Chemical Biology

In a joint project between researchers at the University of Eastern Finland and Eberhard Karls University Tübingen in Germany, a new molecular level mechanism to prevent growth of hepatocellular cancer (HCC, liver cancer) has been identified. In the study, it was revealed that HCC with p53 deficiency is depending on interaction between the kinase Aurora A and MYC. Inhibition of Aurora A with specific inhibitors can prevent this interaction and further kills the HCC cells. Molecular modeling (provided by DDCB) could explain and predict how Aurora A inhibitors should interact with their target and

this information is now used to design new anti-cancer compounds. Given that MYC plays a vital role in most types of cancer, these findings are likely to have a broad impact on cancer in general. (Dauch et al, *Nat. Med.* 2016, 22:744-753)

Viral Gene Transfer and Cell Therapy

A new nonviral integrating vector system based on transposons (Sleeping Beauty Transposon system) has been established in A.I. Virtanen Institute virus core facility. This vector system would avoid risks associated with viral gene carriers since it is based on plasmid constructs and it would also be easier to produce due to the simple bioreactor methods available for plasmid production in E. coli suspension cultures. The method was used for liver gene transfer in hypercholesteremic mice using LDL receptor and VLDL receptor transposon constructs. Results revealed a significant decrease in plasma cholesterol levels for extended periods of time after only a single application of the Sleeping Beauty transposon in the liver (Turunen TA et al. Mol Ther. 24:620-35, 2016.).

Tissue Engineering and Disease Modelling

TEDM wish to highlight as one story FIMM's efforts to develop a lung cancer model, which allows simultaneous ex vivo and in vivo experimentation. These types of approaches are great examples of new enabling technologies as parallel ex vivo/in vivo experiments will enable genetic or pharmacological tractability, will save money and time as well as reduce the amount of mice needed for the experiments (3R principle).

While distinct roles for different progenitor cells in the actuation of lung adenocarcinomas had been described, the role of the cell-of-origin in GEMMs with mixed histopathology spectrum disease, including squamous and adenosquamous pathology, was unknown. Using intranasal AdCre delivery to comparatively target alveolar and bronchiolar progenitors, we addressed how the cell-of-origin defines non-small cell lung cancer pathology and microenvironmental disease heterogeneity in the conditional *Kras;Lkb1* GEMM. Bronchiolar progenitors were shown to actuate faster and more aggressive lung tumours, including large adenosquamous tumours, and the latter exhibited a unique immunosuppressive microenvironment. This suggests a major contribution of progenitor cell- and/or niche-specific factors in disease outcome, and underscores that the clinical profiling of oncogenetic driver allelel should be assessed in a pathology-specific context.

IMPACT ON SOCIETY

The quality of research enabled by the BF research infrastructure has reached the global excellence level in domains such as cancer, immunology, neuroscience, human genetics and personalized medicine. The high scientific significance of life science research at large is evidenced by the success in the most competitive calls in Finland and Europe (Academy of Finland, Finnish Innovation Agency TEKES and EU Framework Programmes). Building on scientific excellence, the BF reserchers' community has delivered impact at large on society, as detailed below.

The Finnish Growth Strategy of Health Sector's Research and Innovation Activities (commissioned by the ministries of Education & Culture, Social Affairs & Health, Employment & Economy) aims at boosting new business and research partnerships with companies, and improved health care. The Strategy with its Roadmap highlights the potential of top-quality research and research infrastructure in attracting private funding and international business to Finland, and identifies BF as a prime enabler of top-quality research and provider of impact through its RI platforms.

Examples of strategic framework collaborations of the BF community include agreements in cancer precision medicine and in genomics with many leading pharma companies, as well as agreements between university, academic hospital and companies.

Finland has attracted international big pharma companies such as AstraZeneca, Bayer Pharma, GE Health Care, IBM, Pfizer, Philips, Roche and ThermoFisher to invest in Finland. They have recently intensified their presence in the research and innovation scene by establishing companies and initiating strategic collaborations. The reasons to drive innovation and business in Finland is the high quality of life sciences spear-headed by the BF-community, the national biobanks and health registers, and RI such as the BF technology platforms.

BF's researcher community has delivered impact on society in the form of disclosed inventions, patented innovations, spin-off companies, new technologies, disease risk estimation tools based on genetic data, diagnostic microchips and high-throughput tools, genome-sequencing methods for diagnostics in the clinic, cancer treatments, treatment strategies for neurodegeneration, drug delivery tools, new clinical practices, open access software solutions and commercial data analysis.

Finland has become one of the three largest Health technology economies world-wide and has the highest density of Health start-ups in the world. Health technology is one of Finland's fastest growing export sectors with a 10% increase in export in 2016.

Selected Success Stories Of Impact Supported By BF Technology Platforms

Biocenter Kuopio, University of Eastern Finland

Professor Seppo Ylä-Herttuala discovered gene therapy for treatment of malignant brain tumors, based on virus vectors produced in the BF's Viral Gene Transfer and Cell Therapy platform. The treatment has reached clinical trial Phase 3, ongoing in 35 centers in Europe and Israel.

Institute of Biotechnology, University of Helsinki

Professor Mart Saarma discovered a neurotrophic factor that repairs degenerated dopamine neurons in animal Parkinson's disease models. He co-founded Herantis Pharma Plc to commercialize the treatment, which was recently authorized to enter Phase 1-2 clinical trials in Karolinska University Hospital Stockholm, supported by a multimillion EU grant.

Institute for Molecular Medicine Finland, University of Helsinki

Development of a webmicroscopy and digital microscopy interface including a large-size touchscreen for visualization of digitized microscopy samples and establishment of the spin-off company Fimmic Oy for its commercialization.

Biocenter Oulu, University of Oulu

Collaboration with FibroGen Ltd. in development of therapeutics affecting the hypoxia response pathway. The first one is in Phase 3 clinical trials for treatment of anaemia of chronic kidney disease. FibroGen had a 146 M$ initial public offering in 2014. The Finnish Innovation Fund SITRA made its biggest revenue on a single investment, 18.3 M€ in 2015 by selling its equity in FibroGen.

BioMediTech, University of Tampere

Professor Howard Jacobs and Dr Eric Dufour developed a unique approach to alleviate mitochondrial dysfunction, which have resulted in breakthroughs in cancer metabolism and signalling, inflammation and xenogeneic gene therapy. Their achievements, facilitated by the BF Viral Gene Transfer and Cell Therapy platform, place UTA at the core of an international effort to develop a delivery system for the treatment of mitochondrial diseases.

BioCity Turku, University of Turku

Academician Sirpa Jalkanen discovered unique molecular mechanisms regulating cell trafficking in human inflammation and demonstrated the value of several molecules as drug targets to treat inflammatory diseases and cancer. Some targets are in pre-clinical phase, and two are in clinical Phase 2 (UK) and Phase 3 trials in 60 centers in Europe, supported partially by a multimillion EU grant. She has co-founded the biotech companies BioTie Therapies and Faron Pharmaceuticals, both listed in New York and London stock exchanges.

BioCity Turku, Åbo Akademi University

Professor Cecilia Sahlgren discovered several mechanisms that regulate stem cell function and fate during tissue regeneration and disease progression. In collaboration with material scientists, she developed smart biomaterials for targeted control of cell function in cancer and regenerative therapies. Co-affiliated in the Eindhoven University, she is engaged in the Dutch Center of Excellence on Materials-Driven Regeneration, which was recently rewarded 25 million € for development of these novel regenerative technologies.

FUNDING AND PERSONNEL - STATISTICS

Funding of Biocenter Finland in 2015-2016

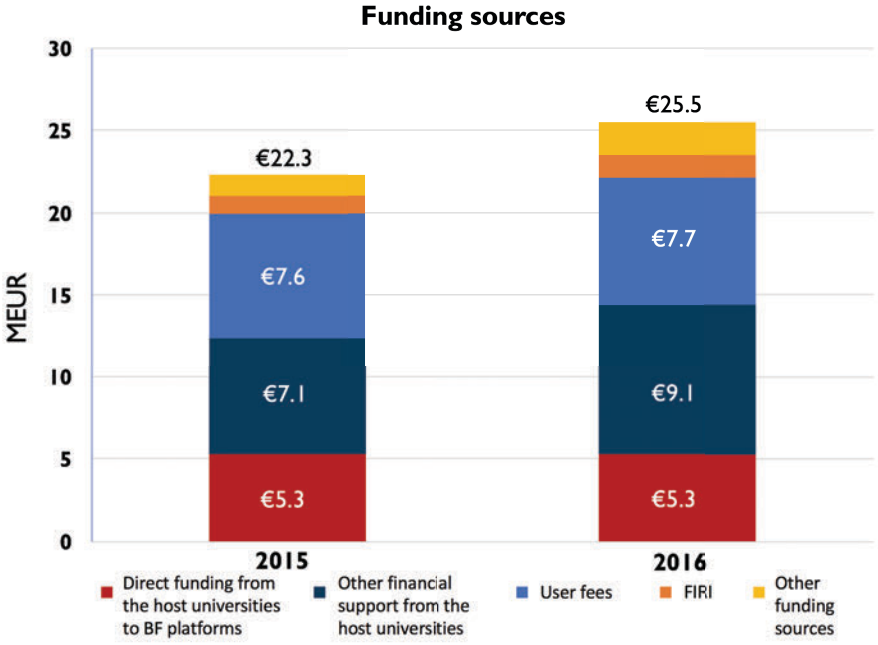


Figure 4. Funding of BF technology platforms and services. FIRI, the Research Infrastructure calls of the Academy of Finland.

Allocation of Funding to the Technology Platforms in 2016

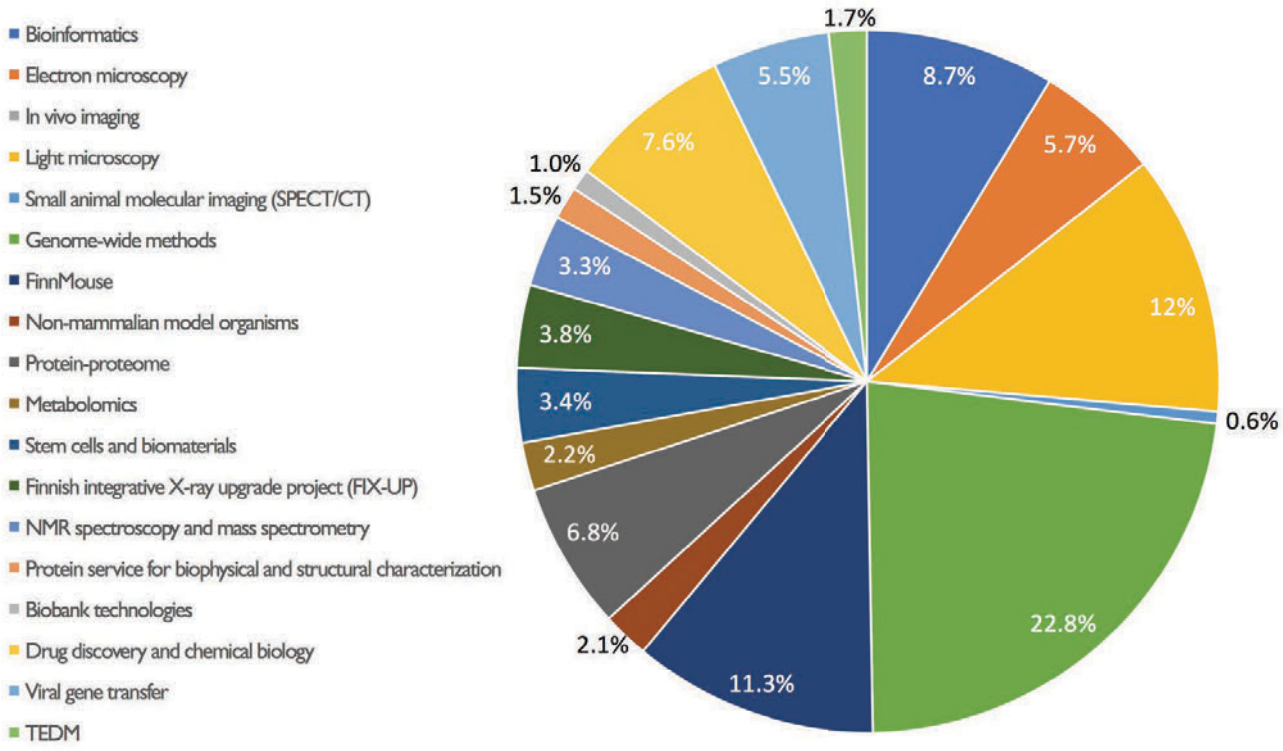


Figure 5. Relative distribution of the total funding between the platforms. The figures for the In vivo imaging platform were unavailable.

Personnel

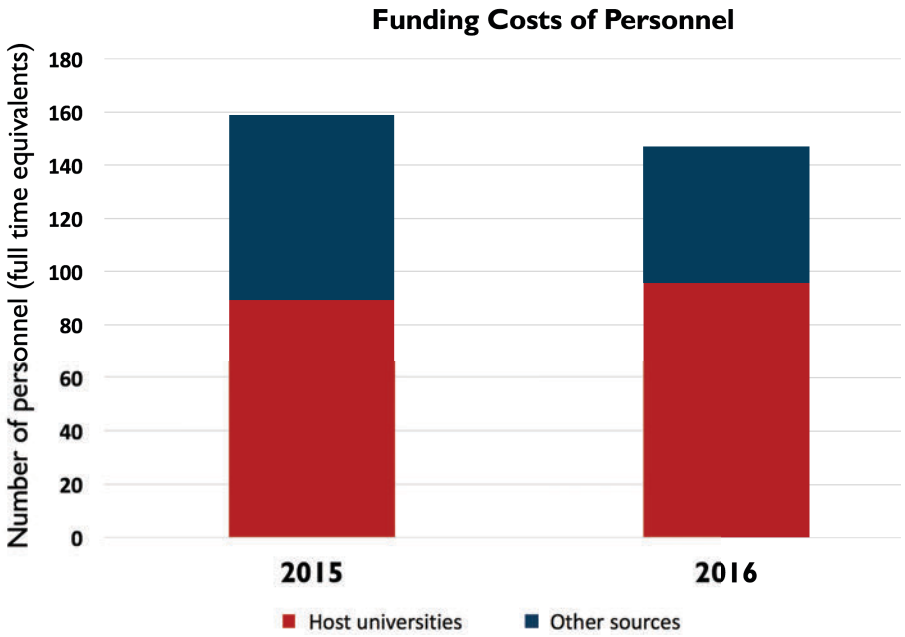


Figure 6. The technology platforms' service personnel in full time equivalents. The majority of personnel funding came as direct support from the host universities.

Personnel by Career Stage

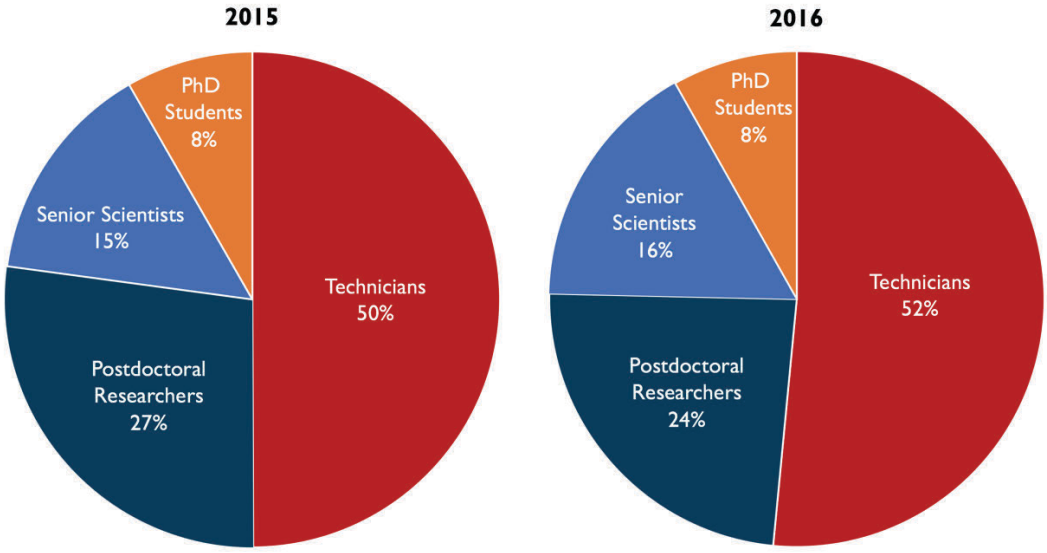


Figure 7. Personnel working in the technology platforms providing BF services.

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