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FOREWORD

Biocenter Finland (BF) supports frontier research in the life and biomedical sciences by establishing, developing and coordinating state-of-the-art technology services, openly accessible for some 2000 research groups in universities, research institutes and companies. BF operates as a nation-wide research infrastructure, which is distributed to the five biocenters of the country. It is hosted by six of the thirteen Finnish universities, University of Eastern Finland, University of Helsinki, University of Oulu, Tampere University, University of Turku and Åbo Akademi University.

BF’s twelve technology platforms include Bioinformatics, Biological imaging (includes Light microscopy, Electron microscopy and Real-time imaging), Genome editing, Genome-wide methods, Liquid biopsies, Model organisms (includes Mouse models and Non-mammalian model organisms), Proteomics and metabolomics, Single-cell omics, Stem cells, Structural biology, Translational technologies (includes Drug discovery & chemical biology and Biobank technologies) and Viral gene transfer & cell therapy. BF ensures resources for investments into the facilities, mainly from competitive research infrastructure calls of the Academy of Finland – the Finnish Research Council. In the 2018 call BF was awarded the full amount it had applied for, 1.83 M€. The cost of key personnel of all platforms is financed by the host universities. In 2018 their support amounted to 5.79 M€.

BF runs regular user surveys on its platforms’ services. The result of the 2018-2019 survey, answered by 462 principle investigators on behalf of their groups, was positive. The average score was 4.38/5.00. The scores for access to service, quality of service, efficiency and performance of service, staff support and responsiveness, and price/quality ratio varied between 4.24 and 4.48. The comments of the users are essential in order to improve the services.

The choice of new platforms to be established depends on the needs to renew science, build capacity and support implementation of the research strategies of BF’s host universities. BF Board’s decisions to end a platform’s mandate as a BF research infrastructure or include new platforms is informed by evaluations carried out by BF’s scientific Advisory Board.

BF works in close collaboration with the Finnish ESFRI (European Infrastructure Projects) nodes BBMRI (biobanking), EATRIS (translational medicine), ELIXIR (bioinformatics), EU-OPENSCREEN (drug screening), EuroBioImaging, Infrafrontier (mouse models) and Instruct-FI (structural biology). The aim is to ensure knowledge transfer on the opportunities to access pan-European infrastructures, to exchange information on latest technological advances and to avoid redundant investments in equipment. BF is also committed to promote to the Finnish life scientists the use of core facilities, collaboration opportunities and funding that the European Molecular Biology Laboratory EMBL and the European Molecular Biology Conference EMBC offer.

BF features as a major national infrastructure in the Finnish Research Infrastructure Roadmap 2014-2020. According to the criteria of the Roadmap’s mid-term evaluation, level of development, impact and significance, openness and collaborative use, BF is placed in the most advanced category. The Academy of Finland will open in 2020 the call for the next edition of the Finnish Research Infrastructure Roadmap.

BF’s significance as the national technology service provider in the life and biomedical sciences is further highlighted by the creation
of five new national centers: the recently established Cancer Center Finland FICAN, Neurocenter Finland and the Finnish Biobank Cooperative FinBB, and the upcoming Genome Center and national Drug Development Centre. They will form an ecosystem using data from population-wide genomic information to health registers, in order to support maintenance of health, prevention of diseases and provision of clinical care. The services provided by BF are critical for data generation for the centers.

Professor Marja Makarow
Director of Biocenter Finland
**STATISTICS**

**Technology platform funding**

**Figure 1.** BF technology platform funding broken down to direct salary support from the host universities, other host university funding, cost recovery from user fees, and other funding sources. Direct funding from the host universities to BF platforms was 5.1 M€ and total funding of the platforms was 35.7 M€ (+0.9%). Income from user fees increased 9.4%.

**Figure 2.** Distribution of direct host university funding to BF technology platforms in 2018.
Users

Figure 3. Number of research groups
and non-academic customers using BF
technology platform services. Number
of local groups (i.e. same university)
was stable, whereas the number of
national (+25.4%) and international
users (+28.6) increased.

Technology platform personnel

Figure 4. BF technology platform personnel in
full-time equivalents broken down by source of
funding.

Figure 5. BF technology platform personnel by
career stage. Share of technicians and senior
scientists increased while share of PhD students
and post-docs decreased.
HOST UNIVERSITIES, MEMBER INSTITUTES AND FACULTY

Host universities and member institutes

BF is a distributed national research infrastructure that in 2018 consisted of five member institutes hosted by six universities (Fig. 6). The directors of each institute serve as the Governing Board of BF.

From 2019, the new Tampere University will continue the membership of discontinued University of Tampere. The Tampere University member institute changed its name to Faculty of Medicine and Heath Technology.

Helsinki. HiLIFE includes Institute of Biotechnology and Institute for Molecular Medicine Finland FIMM as operational units. At University of Tampere, the Faculty of Medicine and Life Sciences replaced BioMediTech as the member institute from the beginning of 2017.

Biocenter Finland

Figure 6. The host universities and their BF member institutes in 2018.

Faculty to be updated

At the end of 2018, the Biocenter Finland Faculty comprised of 413 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


University of Helsinki


University of Oulu


University of Tampere


University of Turku and Åbo Akademi University

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 five member institutes. The Board meets 5–6 times per year. The governance and organizational structure is depicted in Fig 7.

Figure 7. The governance and organization of Biocenter Finland.

Governing board

The BF Governing Board in 2018 was Professor Tapio Visakorpi (Chair, Faculty of Medicine and Health Technology, TAU), Academy Professor Seppo Ylä-Herttuala (Vice Chair, Biocenter Kuopio, Professor John Eriksson (BioCity Turku, ÅA) and Professor Jyrki Heino (BioCity Turku, UTU, UEF), Professor Johanna Myllyharju (Biocenter Oulu, UO), Professor Tomi Mäkelä (HiLIFE, UH), Professor Olli Silvennoinen (Institute of Biotechnology), and Prof Mark Daly (Institute for Molecular Medicine Finland, UH).

Professor Lauri Eklund (Biocenter Oulu, UO) replaced Johanna Myllyharju from 2019.

Coordination office

Professor Marja Makarow serves as the director, Antti Siltanen is the coordinator, and Ms Anu Taulio the secretary.
The scientific advisory board of Biocenter Finland

The international Scientific Advisory Board of BF evaluates the quality and scientific impact of the BF technology platforms, and prioritizes the community’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
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

The Structural Bioinformatics Laboratory (BCT) was contacted by Adjunct Professor Arto Pullianen at the Institute of Biomedicine, University or Turku to assist on a project involving pertussis toxin and the search for ligands. Pertussis has appeared with increasing frequency in Finland as a serious health issue. The project incorporated one research group at the University of Oulu. In silico screening, structure modeling, docking and then experimental screening were used to arrive at two starting ligands that bind to the toxin, inhibits it, and one even crosses the cell membrane to enter the cell where the toxin exerts its destructive activity. The project relied on the local computing resources within the BF Bioinformatics network and supercomputing at CSC IT Center for Science. One publication is being readied on this research and it will acknowledge the essential contributions from Biocenter Finland that made the research possible.

Medical Bioinformatics Centre (BCT) led by Dr. Laura Elo was involved in a Respiratory Viral DREAM Challenge that is a crowd-sourced effort to bring together a community of international researchers to identify predictive markers of individuals susceptible to getting severe symptoms from acute respiratory viral infection. Laura Elo’s research team was the only top-performing team that achieved nominal significance in the Challenge. By this achievement the team demonstrated that predictive models of symptoms following viral exposure can be built using pre-exposure gene expression. After the competition, multiple teams joined forces to collaborate in the analysis of all the submitted models, their methodologies, and the selected biomarkers to find commonalities between them. Although there was little overlap between the genes selected in the different models, a key finding was their enrichment in the Heme metabolism pathway. The results led to an article in Nature Communications journal which was published on October 24th 2018. https://www.nature.com/articles/s41467-018-06735-8

Label-free mass spectrometry (MS) enables robust detection of thousands of proteins in a single run from multiple complex samples and has developed into an important tool applied in various fields of biological and life sciences. Medical Bioinformatics Centre’s (BCT) research team lead by Dr. Laura Elo conducted an extensive comparison of available popular software workflows to process label free proteomics data. They also evaluated several known imputation methods to deal with the pervasive missing value phenomenon in label free DDA proteomics data. The team concluded that the Progenesis software performed consistently well in the differential expression analysis and produced little to no missing values, while missing values produced by the other software decreased their performance. However, this decrease in performance could be significantly mitigated by using proper data imputation or data filtering methods. Out of the pure imputation methods, the local least squares (lls) regression
imputation was consistently found to improve the performance of the software in the differential expression analysis the most. These comparisons are helpful for the bioscientists in finding the right tools to analyze their label free MS data. The results were published in Briefings in Bioinformatics (https://academic.oup.com/bib/article/19/6/1344/3859191)

The BCO biocomputing core facility was contacted by Prof Lloyd Ruddock with regard to native disulfide bond formation, an essential process in the biogenesis of around one-third of human proteins. In the endoplasmic reticulum, protein disulfide isomerase (PDI) is a key component in both disulfide bond formation and isomerization to the native state. The chemistry of thiol-disulfide exchange during oxidation and isomerization by PDI is highly studied and well understood. However, one fundamental question remains unanswered – how are buried thiols and disulfides in late stage folding intermediates that have stable quasi-native structure accessed? To date this is believed to be directly linked to thiol-disulfide exchange and hence driven by the active site cysteines of PDI. In a long standing project, we have shown that a major part of catalysis of late stage isomerization events can be driven in the absence of thiol-disulfide exchange by PDI. This goes against the assumptions used in the field and has major implications for our understanding of the physiological mechanisms of native disulfide bond formation. Using molecular dynamic simulations and monitoring residue specific hydrogen-deuterium exchange of amide backbone protons in late stage folding intermediates by nuclear magnetic resonance we determined the mechanism by which this occurs. Specifically, PDI induces conformation changes in protein substrates with quasi-native structures. The in silico studies allowed identification of molecular mechanism for this, which is linked to a previously unreported conformational change in PDI.

Electron microscopy

During 2018, BI-EM contributed to an important study related to Type 1 and Type 2 diabetes, which was published in high-impact journal Diabetes. In this study, Danilova et al., reported that the removal of mesencephalic astrocyte-derived neurotrophic factor MANF specifically from beta-cells in adult mice results in the loss of beta-cells in diabetes. This indicates that MANF expression is needed for survival, maintenance and function of pancreatic beta-cells in mice. MANF also protected stressed beta-cells from death and induced beta-cell proliferation in old mice. This discovery suggests that MANF has therapeutic potential for the treatment of Type 1 and Type 2 diabetes, where beta-cell protecting and regenerating therapies are not available.


BCO-EM participated in the identification and characterisation of a novel multi-organ disease, which is fatal in early childhood. This study by Uusimaa et al. was published in high-impact journal Acta Neuropathology and linked variants of highly conserved NHL repeat-containing protein 2 (NHLRC2), function of which is currently unknown, to this early-onset disease. Based on the pathological features including fibrosis, neurodegeneration and cerebral angiomatosis, this disease was named FINCA.

UEF-EM participated in a study related to ophthalmology, which was published in Redox Biology by Felszeghy et al. This study investigated the roles of two transcription factors NRF-2 (nuclear factor-erythroid 2-related factor-2) and PGC-1α (peroxisome proliferator-activated receptor gamma coactivator-1 alpha), and revealed that global double knockout mice exhibited significant age-dependent protein accumulation in retinal pigment epithelium cells. The study has an important role in understanding the histopathological changes involved in development of age-related macular degeneration.


**Light microscopy**

Euro-BioImaging, headed to a large extent by CIC-TBI, is continuously bringing numerous significant advantages to the national research environment by providing open-access to state-of-the-art equipment, facilitating innovation, mobility and training of scientists. Thus, Euro-BioImaging significantly promotes scientific breakthroughs in all areas of life sciences and therefore enables the Finnish light microscopy consortium to produce research at the highest level. Euro-BioImaging also significantly increases the international visibility, impact and influence of the Finnish imaging community, as Finland is the upcoming host of the infrastructure and the developer of some of its key services.

As a whole, the light microscopy platform served a growing number of national and international users, in total more than 1000, coming from almost 400 research groups. These groups have a very significant impact on Finnish life sciences, also regarding its renewal and non-academic partnerships. The whole LM platform instruments or services were used to generate data for a significant amount of scientific peer-reviewed international publications, for example 39 for BIU-LM and 44 for CIC-TBI during 2018.

Business Finland/TEKES FiDiPro fellow project, which boosted the initiation of FIMM-HCA core was finished by the end of 2018. It enabled to develop novel image analysis methods for images acquired at FIMM-HCA, and new open source software tools for researchers. The project created Advanced Cell Classifier software for phenotypic classification of cells and feature space exploration to identify rare or unknown phenotypes. The project also created tools for machine learning based single cell isolation (Brasko et al. Nat Comm.2018) and various methods for cell segmentation in 2/3D advancing the state-of-the-art. These methods were utilized e.g. in studies of tamoxifen resistant breast cancer cells (Hultsch et al. BMC Cancer 2018)

**TIC-BCO** light microscopy was used to investigate cellular phenotypes and mechanism of aggressive prostate cancer due to single nucleotide polymorphism (Gao P et al., Biology and Clinical Implications of the 19q13 Aggressive Prostate Cancer Susceptibility Locus. Cell 174:576-589, 2018).

Concrete example of a scientific breakthrough:
A novel pathway for transporting cholesterol from the plasma membrane to the endoplasmic reticulum in mammalian cells was discovered, using BIU-LM instruments and imaging support. The Aster family of proteins represent the first proteins identified as being responsible for this key step in mammals. The physiological importance of the pathway is highlighted by studies in knockout mice that display defective adrenal cholesterol storage and deficient steroid hormone biosynthesis (Sandhu J et al., Aster Proteins Facilitate Nonvesicular Plasma Membrane to ER Cholesterol Transport in Mammalian Cells. Cell 175:514-529, 2018).
Inhibition of β1-integrin signaling by antibodies or genetic disruption in endothelial cells protected mice from pathological vascular leakage that occurs in several inflammatory diseases. Thus, targeting β1-integrin signaling could provide a novel means of blocking pathological vascular leak. Key data were obtained by confocal and TIRF microscopy with BIU-LM equipment as well as live cell spinning disk confocal at TIC-BCO and traction force microscopy at CIC-TBI (Hakanpaa L et al., Targeting β1-integrin inhibits vascular leakage in endotoxemia. PNAS 115(28): E6467–E6476, 2018).

Mikkola-lab has utilized LMU-BI microscopes for live imaging of mouse skin explants to reveal how hair follicles form during development. All mammal hair springs from hair follicles under the skin. These follicles sit in the dermis, beneath the outermost skin layer, the epidermis. In the embryo, hair follicles develop from unspecialized cells in two tissues, the epithelium and the mesenchyme, which will later develop into the dermis and epidermis, respectively. As development progresses, the cells of these tissues begin to cluster, and signals passing back and forth between the epithelium and mesenchyme instruct the cells what to do. In the mesenchyme, cells called fibroblasts squeeze up against their neighbors, forming patches called dermal condensates. These mature into so-called dermal papillae, which supply specific molecules called growth factors that regulate hair formation throughout lifetime. Fibroblasts in the developing skin respond to a signal from the epithelium called fibroblast growth factor 20 (Fgf20), but we do not yet understand its effects. It is possible that Fgf20 tells the cells to divide, forming clusters of daughter cells around their current location. Or, it could be that Fgf20 tells the cells to move, encouraging them to travel towards one another to form groups. To address this question, Biggs, Mäkelä et al. examined developing mouse skin grown in the laboratory. They traced cells marked with fluorescent tags to analyze their behavior as the condensates formed. This revealed that the Fgf20 signal acts as a rallying call, triggering fibroblast movement. The cells changed shape and moved towards one another, rather than dividing to create their own clusters. In fact, they switched off their own cell cycle as the condensates formed, halting their ability to divide. Dermal papillae control hair growth, and transplanting them under the skin can form new hair follicles. However, these cells lose this ability when grown in the laboratory. Understanding how they develop could be beneficial for future hair growth therapy. Further work could also address fundamental questions in embryology. Condensates of cells from the mesenchyme also precede the formation of limbs, bones, muscles and organs. Extending this work could help us to understand this critical developmental step. (Biggs LC, et al. Elife. 2018 Jul 31;7. pii: e36468. doi: 10.7554/eLife.36468.)

Small animal molecular imaging SPECT/CT

The SPECT/CT laboratory in partnership with the Radiochemistry lab, and along with the customer served, have made a significant contribution on the preclinical imaging technology development, and in applied research, this year specially in development of delivery systems (see references below).

Breakthroughs

Establishing the Helsinki in vivo animal platform (HAIP), along with all in vivo imaging infrastructure of the University and the Helsinki Great area Hospital (HUS).

Drafting a successful letter of intent to opt for applying for funds from FIRI programme for a PET/MRI new infrastructure.
**Genome-wide methods**

In plants stomatal pores control the intake of atmospheric carbon dioxide in exchange for water loss. The pores are formed by two surrounding guard cells in the epidermis of plant leaves and allow plants to sense and respond to diverse environmental and endogenous stimuli by adjusting the pore opening. The pore decreases in response to drought, low light intensity, low air humidity, elevated intercellular CO₂ concentration, pathogens, and the air pollutant ozone (O₃). An important air pollutant, ozone, has a negative impact on crop yields, how much carbon the plants can bind and thus the climate change. The research group led by Prof Kangasjärvi has previously shown that a plant ion channel gene, SLAC1 (SLOW ANION CHANNEL-ASSOCIATED 1) is critical for stomatal pore closing in response to CO₂, abscisic acid, ozone, light/dark transitions, humidity change, calcium ions, hydrogen peroxide and nitric oxide (Vahisalu et al, 2008). In the recent study the group utilized nine different mutant forms of Arabidopsis thaliana ghr1 (GUARD CELL HYDROGEN PEROXIDE-RESISTANT1) gene to provide further understanding on the its regulatory function in the closure of the pores. By functional analyses and genome sequencing of the mutant forms supported by the core services of the GWM network, they showed that GHR1 is an inactive pseudokinase, which interacts with CPK3 kinase, thus acting as a kinase deficient scaffolding protein regulating SLAC1 activity. By providing detailed understanding of the GHR1 receptor complex, it will be possible to manipulate GHR1 in crop plants, thus modulating gas exchange and water-use efficiency to improve the productivity.


**Mouse models**

Utilization of genetically modified animal models continues to be one of the most central ways to solve research problems tackling basic scientific questions and disease-related mechanisms. In Finland, more than 80 research groups use genetically modified mice in their studies and the use of GM mice as disease models is expected to further increase in future. The research carried out with the genetically modified mice demonstrated the importance of the MAPK signaling for nephron stem cell maintenance and differentiation (Ihermann-Hella et al 2018), revealed clinically relevant differences in distinct brain cell types for mitochondrial dysfunction (Mätlik et al 2018), and contributed to the discovery showing that repair function of neurons in diseased brains can be significantly enhanced by neurotrophic factors (Mätlik et al 2018). The study led by prof. Eklund identified Angiopoietin4 as the first growth factor for venous-specific development and its importance in venous remodeling, retinal fluid clearance and neuronal function (Elamaa et al. 2018).

Hydroxysteroid (17β) dehydrogenases (HSD17Bs) form an enzyme family characterized by their ability to catalyze reactions in steroid and lipid metabolism. In the recent study, Adam et al demonstrated that HSD17B13-knockout (HSD17B13KO) mice, presented with inflammation-associated liver steatosis. The group led by Dr Jaan Olle Anderssoo developed an innovative model of congenital aganglionic megacolon or Hirschsprung’s disease (HSCR) and HSCR-associated enterocolitis (HAEC), the leading cause of mortality in HSCR.

It is foreseen that rare diseases where patient material is limited, as in a new multi-organ disease named FINCA (Fibrosis, Neurodegeneration and Cerebral Angiomatosis) characterized by Dr. Hinttala (Uusimaa et al. 2018), 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, therefore, multidisciplinary expertise is required for phenotype analysis of mutant mice. GM units in Helsinki, Oulu and...
Turku are committed to a nation-wide pilot project aiming to model selected syndromes of the Finnish heritage diseases in mouse. This combined with primary phenotyping provided by FinGMice platform of the newly generated rare disease models is expected to serve as an encouraging pilot project for expanding such approach in utilization of mouse models for analyzing specific disease pathomechanisms. Through a close collaboration with other national infrastructures the aim is to engage more researchers to utilize rodent models as tools to study human diseases.

Non-mammalian model organisms
The most important breakthrough is the efficient use of CRISPR-Cas9 method both in zebrafish and Drosophila to create targeted mutants that allows for example phenotypic analysis of novel genes associated with various diseases. In Helsinki, recent development of single-shot double targeting allows rapid development of mutant lines. Both in the Helsinki and Tampere unit, dozens of mutations have been created successfully.

Protein-proteome

Example study 1:


In this study, a detailed molecular mechanism for the regulation of ErbB2-induced gene expression and invasion was revealed, with implications for breast cancer invasion in vivo. The study utilized phosphoproteomics (see figure above) and protein interactions were studied using proteomics analysis for affinity-purified proteins. The findings increase the understanding of cancer-induced transcriptional activation, and could potentially be used to find ways to control cancer cell invasion and metastasis that is induced by activation of ErbB2 signaling. The study involved PPN network partners from Turku and Helsinki.

Example study 2:

**Protein photochemistry revealed by Fourier transform infrared spectroscopy**

Phytochrome proteins regulate the photoresponse of plants and microorganisms. They absorb red-light photons, traverse through a number of intermediate states, and finally activate a cellular response. In this study, two-color time-resolved Fourier transform infrared spectroscopy (FTIR) was used to resolve the entire photoconversion reaction in the *D. radio*durans* phytochrome. This resulted in the first structural model of the early “Lumi-R” intermediate. The model explains how the structural signal in the protein is generated by photochemistry and how it is then transduced within the protein.

**Metabolomics**

In 2018, FIMM had contributed to an important biomarker study related to mitochondrial metabolism and disorders, which was published in a reputed journal “EMBO Molecular Medicine”. In this study, we investigated a representative group of mitochondrial myopathy and ataxia patients, unaffected MIRAS carriers, as well as patients with inclusion body myositis (IBM) and non-mitochondrial neuromuscular disease by metabolomic analysis. We identified distinct disease-group-specific metabolomic fingerprints in blood and muscle. IBM clustered together with mitochondrial myopathies, proposing important contribution of mitochondrial dysfunction in IBM-related muscle weakness. A novel four metabolite multi-biomarker (sorbitol, alanine, cystathionine and myoinositol) distinguished primary and secondary mitochondrial disorders from other groups.

ViMU was involved in 17 peer-reviewed scientific publications; as a co-author in 2 and acknowledged in 15 articles, where metabolomics and/or mass spec data was provided by the unit. A list of publications linked to ViMU can be seen from Tuhat-database (infrastructures) from University of Helsinki (http://www.helsinki.fi/tuhat/, search for ViMU).

The work at BCK has continued on metabolomics applications for food, health, toxicology, and nutrition studies. The specific topics include the effects of environmental pollutants and alcohol on the offspring or on nutrition effects of nutrition in disease.

**Stem cells and biomaterials**

UH BSCC: Two outstanding PhD theses (Jere Weltner: “Novel Approaches for Pluripotent Reprogramming” and Diego Balboa Alonso: “Human Pluripotent Stem Cells and CRISPR-Cas9 Genome Editing to Model Diabetes”) shared the prize awarded for the best thesis in 2018 in the Faculty of Medicine.

UH BSCC: Weltner J, et al. Nat Commun. 2018;9(1):2643. Pioneering study demonstrated for the first time that human somatic cells can be reprogrammed into iPSCs using only CRISPR activators. In comparison to conventional reprogramming, CRISPR method has a potential for the generation of better iPS cells and for biobank applications.

UH BSCC: Balboa D, et al: Insulin mutations impair beta-cell development in a patient-derived iPSC model of neonatal diabetes. Elife. 2018 Nov 9;7. pii: e38519. doi: 10.7554/eLife.38519. In this pioneering study we have demonstrated the importance of isogenic CRISPR-Cas9 mutation corrected iPS cell line for disease modelling. CRISPR-Cas9 genome editing has become part of the services offered by BSCC core facility.

UH BSCC: Timo Otonkoski together with Pekka Katajisto, Ville Hietakangas and Henna Tyynismaa formed the Center of Excellence in Stem Cell Metabolism, Academy of Finland (2018-2025). The Centre of Excellence in Stem Cell Metabolism focuses on investigating how stem cell function can be modified by regulating their metabolism, and how this information could be applied in regenerative medicine.

UH BSCC: Stem Cells and Metabolism Research Program (STEMM), program director, Timo Otonkoski (2019-2025). STEMM brings together eleven research groups and four associated clinical researchers interested in cellular metabolism as a driving force in tissue homeostasis, cellular differentiation and degenerative diseases. Many of the groups take advantage of the possibilities of stem cell and genome editing technologies to understand molecular disease mechanisms in order to develop innovative treatments. Close ties to pediatric and neurology clinics enable efficient use of our research findings for diagnosis, patient care and counselling.

BCK: Belt H, et al. Temporal Dynamics of Gene Expression During Endothelial Cell Differentiation From Human iPS Cells: A Comparison Study of Signalling Factors and Small Molecules. Front Cardiovasc Med. 2018;5:16. The study provides the first systematic characterization of the most potent signaling factors and small molecules used to generate ECs from human induced pluripotent stem cells, and opens up new protocols for controlling cell fate for regenerative EC therapy.

BCK: Koivumäki JT, et al. Structural Immaturity of Human iPSC-Derived Cardiomyocytes: In Silico Investigation of Effects on Function and Disease Modeling. Front Physiol. 2018 Feb 7;9:80. The study demonstrates how human iPSC-derived cardiomyocytes (CMs) differ from adult CMs and establishes a mathematical platform to
improve the translation of iPSC-CMs to human cardiac diseases.

BCK: Smart Small Molecule Drugs program led by Jari Koistinaho develops and utilizes iPSC-based brain cell models for modern drug development in collaboration with Jari Yli-Kauhaluoma, Department of Pharmacy, UH. TU BMT/MET: Katriina Aalto-Setälä and the Body-on-Chip study consortium from TU was selected by the Academy of Finland to be a center of excellence during 2018-2025. The BoC consortium focuses on creating tissue structures and combining different tissues to each other.

TAU (former UTA) has produced two PhD work related to the core facilities: Chandra Prajapati and Mostafa Kiamehr – one dealing with cardiomyocyte functionality and the other with hepatic differentiation.

TAU most important publications:


Viiri LE, et al. GRO-sequencing identifies transcriptional regulators and ncRNAs important for iPSC to hepatocyte differentiation Sci Rep 2019 Mar 5;9 (1) 3562


### Structural biology

**Structural basis of actin monomer re-charging by cyclase-associated protein.**

Actin polymerization powers key cellular processes, including motility, morphogenesis, and endocytosis. The actin turnover cycle depends critically on "re-charging" of ADP-actin monomers with ATP, but whether this reaction requires dedicated proteins in cells, and the underlying mechanism, have remained elusive. Here it was reported that nucleotide exchange catalyzed by the ubiquitous cytoskeletal regulator cyclase-associated protein (CAP) is critical for actin-based processes in vivo. The structure of the CAP-actin complex was determined, which reveals that nucleotide exchange occurs in a compact, sandwich-like complex formed between the dimeric actin-binding domain of CAP and two ADP-actin monomers. In the crystal structure, the C-terminal tail of CAP associates with the nucleotide-sensing region of actin, and this interaction is required for rapid re-charging of actin by both yeast and mammalian CAPs. These data uncover the conserved structural basis and biological role of protein-catalyzed re-charging of actin monomers. Crystal screening and access to DLS beam time were provided by the UH crystallization platform in this study.

**Novel segmental isotopic labeling for NMR**

Weak or transient interactions of proteins or domains are examples of protein-protein interactions, which are difficult to investigate because the transient structure is not stable and proteins exist in equilibrium of different forms with various time-scales depending on protein concentrations. By combining segmental isotopic labeling of a domain in the full-length context and NMR spectroscopy, transient domain-domain interactions within a protein have been analyzed (Shiraishi et al., 2018). This approach would not have been possible without segmental isotopic labeling, opening a new avenue to investigated weak domain-domain interactions within a multi-domain protein and flexible regions invisible in other structural methods.

Advances in NMR spectroscopy have enabled us to investigate increasingly larger proteins such as membrane proteins. Particularly solid-state NMR spectroscopy is not limited by the molecular size as in solution NMR but limited by NMR signal overlaps due to the increased number of NMR active atoms. Segmental isotopic labeling is an ideal labeling scheme to investigate regions of interests in larger proteins by NMR spectroscopy. However, it has been often challenging to introduce segmental isotopic labeling particularly into single domain globular proteins. The issue is now successfully solved by a novel labeling technology based on an asparaginyl endopeptidase, opening a new possibility to introduce segmental isotopic labeling into proteins. The new technology could attract more scientists to use NMR spectroscopy for studying protein structures and interactions.


**Cells as growth chambers for in vivo virus crystal growth**

Virus particle accumulation within lysis-defective cells and formation of intracellular diffracting nanocrystals. This in vivo single cell virus crystallography could bypass the traditional crystallization approach and facilitate virus structure determination which can provide essential preliminary information relevant to e.g. rational vaccine design. Despite the immense importance and enormous number of viruses, we understand relatively few viruses in atomic detail. This is due to the complexity and large size of virions making them difficult to address using X-ray crystallography. We used bacterial virus
phiX174 as a test system for in vivo crystallography and characterized infected, lysis-defective Escherichia coli cells using electron microscopy, small angle X-ray scattering and X-ray free-electron laser diffraction. We showed that viral condensates, produced within lysis-defective cells, form diffracting nanocrystals, and this in vivo single cell virus crystallography could bypass the traditional crystallization and greatly facilitate structure determination of viruses or other large macromolecular complexes.

Figure above. In vivo production of diffracting nanocrystals of bacteriophage phiX174, which is a small icosahedral ssDNA virus infecting E. coli cells. A. We used thin-section EM to show that, using optimised conditions, phiX174 accumulates within lysis-defective cells forming condensates. B. XFEL technology at the Linac Coherent Light Source (LCLS, Stanford University) confirms that the in vivo made virus particles form diffracting nanocrystals.

This is a collaboration between University of Helsinki, University of Oxford, UK, Diamond Light Source, UK, Lawrence Berkeley National Laboratory, USA, and Howard Hughes Medical Institute, USA, where Biomolecular Complex core facility has been utilized.


**Structural basis for DNA break recognition by ARTD2/PARP2**

ARTD2/PARP2 is one of the human poly-ADP-polymerase enzymes responsible for recognition of a DNA damage and initiation of the repair process. Using multiple biophysical methods we identified that the enzyme binds all DNA oligonucleotides with high affinity, but is only robustly activated by 5’-phosphorylated oligonucleotides. The disordered N-terminal part, unique for ARTD2, appears to be a high affinity DNA binding module, while the following WGR domain is responsible for detection of 5’-phosphorylated DNA and activation of the C-terminal catalytic domain. With help of the crystal structures of the ARTD2 WGR domain with various oligonucleotides and mutagenesis we were able to assign roles for the residues recognizing the DNA damage. The structures revealed a unique binding mode of ARTD2 as it joins and protects loose DNA ends (Obaji et al. 2018). The crystal structures of activating and non-activating DNA break models with and without 5’-phosphate did not reveal how the interaction with the phosphate transmits the signal to the ADP-ribosyltransferase domain and we are therefore now pursuing structural studies of the full-length protein - DNA complexes.

Biobanking technologies


Tumor budding has recently been recognized as an additional prognostic factor for the TNM-8 classification of colorectal cancer, but the standard method of visual scoring of tumor budding is prone to inter-observer variation. The group of Prof. Kallioniemi published a novel platform, which allows for an automatic and quantitative analysis of tumor budding and associated protein markers simultaneously in formalin-fixed human tissues (1).

In the approach they employed multiplex IHC and automated digital image analysis to phenotypically profile tumors using known EMT-associated markers: E-cadherin (adherence junctions), integrin beta 4 (ITGB4; basement membrane), ZO-1 (tight junctions), and pan-cytokeratin in total epithelial clusters and in smaller tumor clusters representing a promising surrogate marker for routine histologically analyzed tumor budding. They showed that in the analysis of tumor budding from small TMA-cores, a combination of epithelial markers rather than a single marker or H&E alone may better reflect the visually assessed tumor budding in the corresponding whole H&E sections. In summary, the results highlight the complex heterogeneous nature of the biology of tumor buds, which can be elaborately studied using digital multiplexed marker analysis of combined object intensity, structure (size), localization, and quantity (bud count).

2. A research team led by Research Director Johan Lundin has shown that artificial intelligence-based models can learn to predict outcome of colorectal and breast cancer based on images of cancer tissue samples, without intermediate tissue classification steps (2-3). The outcome prediction done by the machine learning algorithm reached expert-level in breast cancer (3) and outperformed the assessment done by human experts in colorectal cancer (2).

The main goal of the study was to investigate whether a deep learning algorithm that takes images of small regions of tumor tissue as input can be trained to predict outcome of cancer patients without prior knowledge of the disease or expert guidance.

The machine learning-based method also provided complementary prognostic information to established prognostic indicators, such as tumor size, number of positive lymph nodes, hormone receptor status and histological grade, assessed based on conventional microscopy analysis of the whole-slide tumor sample (3).

Outcome prediction is crucial for patient stratification and disease subtyping to aid the clinical decision-making to achieve a more personalized treatment regimen. The hypothesis was that training a machine learning classifier supervised by patient outcome instead of expert-defined entities has the potential to identify previously unknown prognostic features. The results suggest that deep learning techniques enable a more accurate outcome prediction as compared to an experienced human observer. Further research is needed to understand what factors affect the final decision of the classifier and which features drive the predictions, i.e. what the neural networks “see”. The suggested model should also be trained on larger tumor tissue areas and evaluated on an extended patient series.

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 in a
separate document) where the platform services have contributed to the results and shown scientific impact.

**Drug discovery and chemical biology**

To support analysis of spatiotemporal phenotyping screens, the Turku Screening Unit began to develop algorithms to quantify image sets containing spatially and temporally interconnected events. This was demonstrated for the case of synaptically-connected neuronal cultures exposed to different reagents impacting on connectivity of the cells (Robinson and Courtney, 2018). Such algorithms can be expanded to include multiple independent parameters as new techniques permit the combination of larger number of reporters, facilitating extraction of increasing amounts of information from screens in the future.


**Viral gene transfer and cell therapy**

In the publication, (Zhang et al (2018) Heterogeneity in VEGFR3 levels drives lymphatic vessel hyperplasia through cell-autonomous and non-cell-autonomous mechanisms. Nat Commun. 9(1):1296) AAV encoding soluble VEGF-C-trap (AAV-Vegfr3-Ig) was used to show that mosaical targeting of VEGFR3 in lymphatic endothelial cells is involved in abnormal lymphatic vessel anastomosis and hyperplasia. These data contribute to our understanding of mechanisms of developmental and pathological tissue growth.
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 8). In 2018 the number of platforms decreased by one as the protein production platform underwent fusion with Instruct platform (integrated structural cell biology).

**Figure 8.** 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 (UEF); BCO, Biocenter Oulu (UO); BCT, BioCity Turku (UTU and ÅAU); HiLIFE, Helsinki Institute of Life Science (UH); MET, Faculty of Medicine and Health Technology (UTA).
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, MED

Partners: Jussi Paananen, BCK; André Juffer, BCO; Samps Haataniemi, HiLIFE; Laura Elo, BioCity; Mark Johnson, BioCity; Matti Kankainen, FIMM-HiLIFE; Liisa Holm, BI-HiLIFE

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. 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 (e.g. IT infra and data management of BCT structural biology’s plate hotel).

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, structural bioinformatics, 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. Furthermore, it also takes a long time to set up analysis services and workflows for new data types and resources are limited for more tailored analyses. 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 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 sites are 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 FIFI application and obtained funding for new equipments for 2019.

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

Member of the Nordic e-Infrastructure Collaboration (NeiC) collaboration for sensitive data.

Participant in the Nordic Alliance for Sequencing and Personalized Medicine (NASPM)

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

We participate COST networks in chemistry of proteins, unstructured 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.

EU-OPENSESCREEN we contribute analysis tools for high-capacity screening platforms
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 (development) support, and data analysis service to the bioscience community. We also seek to ensure that all bioscience researchers in Finland have access to the computational resources and supporting bioinformatics expertise necessary for large-scale data analysis as well as detailed studies on small sets of complex molecules.

The 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.

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 an absolute requirement.

We constantly aim for developing new analysis pipelines to provide state of the art analysis services for the community, however these development activities have been severely limited by lack of funding. 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 have been 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

<table>
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steadily. In addition, the demand for large scale in silico modeling and simulation studies of biological systems continues to increase. This clearly 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 assuming sufficient long term funding is appointed to this.

We will continue to work in close collaboration with and provide guidance to 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.

**Major publications supported by the platform services**


The year 2018 was extremely successful for Finnish Bioimaging. Step-2 application for Euro-BioImaging ERIC was submitted by Finland on January 19, 2018 and The ERIC Committee reported its support on 9th of February 2018. This evaluation was timely and contributed to Euro-BioImaging becoming an ESFRI Landmark. The Euro-BioImaging ERIC, with preparations headed by CIC-TBI, is expected to be formally launched in 2019, with 15 founding members. CIC-TBI also actively participated in the development of open access and data management services on the European scale.

The Finnish Advanced Light Microscopy (ALM) Euro-BioImaging Node (CIC-TBI, TIC-BCO, BIU-LM and LMU-BI) received several international Euro-BioImaging users and overall the Node is one of the most popular in Euro-BioImaging. The successful international visits indicate that the instrumentation and knowhow in Finland are unique.

Turku organized an imaging themed BioCity Symposium with high profile international researchers, e.g. the Nobel prize winner Stefan Hell. Alongside with the symposium, a Finnish BioImaging core personnel meeting was organized in Turku with topics from service development, data and quality management to new reservation systems: Helsinki Institute of Life Science (HiLIFE) Light Microscopy Platform (BIU-LM, LMU-BI and FIMM-HCA) in collaboration with the Electron Microscopy Unit and CIC-TBI all were in the process of implementing the Open Iris reservation system. Oulu and Helsinki organized bioimaging days with speakers from the national imaging network to introduce local and international imaging services.

Several members of the LM-platform participated in these meetings.

Bottlenecks in the core facilities were similar in many consortium members; insufficient staff and instrument resources to meet the needs of the expanding user community. In BMT, the user numbers have been steadily rising and in end of the 2018 a new technical person was finally recruited. Merging of universities has caused delays in development of services. Also, TIC-BCO had a steady increase in the number of users with an occasional long queue for motorized confocal microscopes. Similarly, at LMU-BI, the queues to confocals were long. A general challenge is how to utilize limited infrastructure funding to maintain both the basic and the state-of-the-art technologies.

Regardless of the limitations in resources, several units have managed to purchase instrumentation for national and international use:

**Electron microscopy technology platform**

Chair of the platform: Eija Jokitalo, BI-HiLIFE, Electron Microscopy Unit

Partners: Ilkka Miinalainen, BCO Tissue Imaging Center; Arto Koistinen, BCK

**Achievements in development of technology services**
Biocenter Finland Electron Microscopy Technology Platform presently consists of three units with highly complementary expertise and tasks, and offers unique national services for three-dimensional biological electron microscopy at wide length scale, phenotyping of gene-modified model organisms at the ultrastructural level, hybrid techniques with light microscopy, and correlative structure-composition analysis. The scientists in charge are developers of these areas working closely with other scientists as evidenced by the high number of users and large number of high quality papers published from the platform. Unit heads have clearly defined roles, and have implemented common open-access policies and cost-recovery pricing across three universities of Helsinki, Oulu and Eastern Finland.

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. In Helsinki, BI-EM focus on 3D imaging of cells and tissues and correlative light electron microscopy. In Oulu, BCO-EM specializes in the ultrastructural pathology of human and model organisms working closely with the BCO Transgenic mouse core facility. In University of Eastern Finland, UEF-EM develops non-destructive imaging techniques to study elemental and chemical composition of biological specimens.

Originally, the approved NIIN-EM application for years 2017-2020 comprised four units. To promote coordination and collaboration between BF and national FIRI roadmap research infrastructures in the biological and medical sciences area, one of the founding units of the EM platform, BI-cryoEM, became part of the Instruct-FI consortium, which is integrating structural biology in Finland. Regardless of this restructuring, BI-EM and BI-cryoEM have continued working in close collaboration making sure that our services cover the whole scale of 3D imaging from molecular models to cells and tissues.

Each unit harbors a large variety of sophisticated imaging and specimen preparation instruments that are in heavy use, necessitating continuous user training and assistance as well as maintenance and repairs. In addition to nationally supported specialized techniques, each unit provides support to local users in transmission and scanning EM. For basic EM techniques, we provide services on specimen preparation and access to the instruments. When an EM user wishes to have our scientific input in the project, and in case of more advanced techniques, we make an agreement for scientific collaboration. During 2017, we had nearly 300 users from 189 research groups, and over 3600 samples were embedded and sectioned by our highly skilled staff. Continued staff support is a strategically important undertaking in all three EM core units and has been top of the priority list. Biocenter Finland allocations covered salaries for 50 person months in total in 2017 (including one senior scientist, two technicians and post docs).

During 2017, we provided personal training for 37 new users in operation of microscopes and other instruments in our platform. In Oulu, BCO-EM organized an “Advanced Course on Light and Electron Microscopy –Multiphoton and electron microscopy united”. In April 2017, BI-EM released the second version of an open-source software Microscopy Image Browser (MIB; http://mib.helsinki.fi/), the

### General

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MIB 2.0., and after this, we trained new MIB users in two workshops held in the Newcastle University and the Francis Crick Institute, UK. We also participated as teachers in the Annual Microscopy Workshop (theme: Image Analysis and Visualization for Light and Electron microscopy) in Yale University School of Medicine, USA, and EMBO Practical Course: Volume electron microscopy by automated serial SEM in Basel, Switzerland.

**User statistics**

See table below.

**Participation in international, Nordic and European infrastructures**

BI-EM and BCO-EM are members in a Finnish multimodal 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. The EuBI infrastructure launched its operation during spring 2017. BI-EM is a partner in Helsinki BioImaging subnode, and provides several immuno-EM methods, correlative light-electron microscopy, two 3D-EM techniques and image analysis. In 2017, a new post-doctoral researcher was recruited with FiRI funding to coordinate the EuBI projects within the Helsinki subnode. 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 morphological and ultrastructural expertise using immunolabelling and FIB-SEM. All subnodes are additionally linked together by activities aimed at facilitating image processing, visualization and open-source software production for image analysis. UEF-EM is part of Biocenter Kuopio, providing a multidisciplinary research network between different actors in the fields of molecular medicine and related drug research and biotechnology.

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 NEUBIAS (Network of European BioImage Analysts). NEUBIAS is an action fully funded by European COST (CA15124). In August, BI-EM hosted a staff researcher from EM Research Services at Newcastle University, UK, for 2 weeks on a project “Improving segmentation in challenging 3D-SEM datasets using Microscopy Image Browser” supported by a Short-term scientific mission grant from NEUBIAS.

**Future perspectives**

The impact of BF funding has been significant in renovating the technology platform infrastructure. However, the instrumentation in imaging field is undergoing very fast development, and without constant instrument investments, we are in a risk of falling behind from the international level quickly. To develop the 3D-EM techniques in Finland, our aim is to bridge the gap between existing 3D-EM options in respect to both volume and resolution, and to increase our capacity. For this, firstly, BI-EM is seeking funding for a focused ion beam scanning electron microscope (FIB-SEM) that would allow serial block face imaging for 3D reconstructions of cells and tissue at higher resolution than can provided with the current 3View system and larger volumes than can be achieved with electron tomography. The current 3View instrument at BI-EM is in constant use, collecting data series over 3 nights and weekends without breaks. The new FIB-SEM system would open up the technology to new
specimen types because of the higher contrast and smaller voxel size gained by the high vacuum system. In addition, a cryo transfer platform and cryo imaging chamber can be fitted into this system. To maximize the capacity of the instrument, BI-EM and cryo-EM unit could strengthen their collaboration in developing cryo-CLEM projects to include cryoEM of vitrified sections by using FIB-SEM to mill thin lamella of vitreous specimens for cryo-electron tomographic imaging. Secondly, to increase the capacity for 3D-EM projects, BCO-EM is aiming to get funding to upgrade their SEM platform for serial block face imaging of large tissue samples.

UEF-EM has received external funding for acquiring optical microspectroscopes (FTIR and Raman) that enable imaging of chemical composition of various sample types. In the future, a combinatorial Raman-in-SEM system would improve this unique approach of multimodal imaging capability. Spectroscopic imaging can be used for example to study the effects of drugs in cells or tissues and to make diagnosis at early stages of various diseases.

**Major publications supported by the platform services**


**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; Biomedical Imaging Unit (BIU-HILIFE), Elina Ikonen, HILIFE; Light microscopy unit (LMU-BI), Maria Vartiainen, BI-HILIFE; Multimodal imaging core (MUIC-BCK), Michael Courtney, BCK; Tissue Imaging Center (TIC-BCO), Lauri Eklund, BCO; MED imaging facility, Susanna Narkilahti, MED; also University of Jyväskylä Imaging Facility, Varpu Marjomäki participates in the platform activities.
Achievements in development of technology services

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Regardless of the limitations in resources, several units have managed to purchase instrumentation for national and international use:

1. Widefield and confocal microscopy

BMT upgraded their Zeiss LSM700 Confocal microscope to LSM800 to address the customers’ needs, several automated 2D/3D imaging platforms had demo trials. LMU-BI upgraded a wide-field microscope with Aurox Clarity laser free confocal unit that offers an alternative to traditional confocal imaging for cell and developmental biologists.

TIC-BCO imaging unit purchased a Leica SP8 FALCON equipped with a white light laser, spectral detectors, galvo and resonant scanners, real time adaptive deconvolution and fully integrated fast fluorescence lifetime imaging. TIC-BCO has set up a fully motorized histology microscope, Zeiss Axio Imager.M2m that allows analysis of all sized histological specimens.

CIC-TBI acquired a Leica BMi1 cell culture microscope, IncuCyte S3 Live cell imaging system, and a Carl Zeiss AxioZOOM v16 stereo microscope with Apotome2 to accommodate large sample imaging.

2. Super-resolution imaging
At BIU-LM a GE DeltaVision OMX SR structured illumination microscope for fast super-resolution imaging was installed at the end of 2017. During 2018 the system was used regularly by several different users. CIC-TBI provided a STED imaging and sample preparation workshop to promote user numbers on campus.

3. Mesoscopic imaging
At BIU-LM the LaVision BioTec UltraMicroscope II light sheet microscope suited for cleared large samples was taken into operation. CIC-TBI purchased a DanioVision system for high-throughput tracking of zebrafish embryo behavior. LMU-BI has utilized 3D printing to develop customized sample holders for Zeiss Z.1 light sheet microscope.

4. High-content and high-throughput imaging
FIMM-HCA updated the Harmony software in PerkinElmer Opera Phenix spinning-disk confocal high-content system, for imaging and analysis of spheroids and organoids in 3D. Molecular Devices Nano-system for automated wide-field imaging of well plates and slides was taken into use by LMU-BI. The system offers several built-in protocols and image analysis algorithms to facilitate imaging set-up and analysis.

5. BioImage informatics
FIMM-HCA purchased an image analysis server to provide researchers more computational resources via virtual machines. FIMM-HCA researchers have been involved in the development of Cyto.ai that will provide an open source software for machine learning based phenotypic cell classification. At BIU-LM local network connection upgrades and data analysis and storage capacity extensions have been further extended to handle increasing data requirements. CIC-TBI has continued to develop data management tools both locally and on the national level in collaboration with Euro-BioImaging, Global BioImaging and CSC. Part of this development was an OMERO workshop organized by the Finnish ALM Node. Additionally, CIC-TBI acquired a new powerful computer for ZEISS LSM 880 Airyscan to facilitate image reconstruction and analysis.

User statistics
See table below.

Participation in international, Nordic and European infrastructures
The LM-platform continued its active participation in the Euro-BioImaging ESFRI. Finland continued leading the development work of the Euro-BioImaging Web Portal and having a critical role in preparing the launch of the Euro-BioImaging ERIC.

H2020-funded Global BioImaging (GBI) project had a third Exchange of experience meeting in Sydney, co-organized by CIC-TBI, with several representatives from Finnish BioImaging participating. Finland actively
participated in the GBI core facility shadowing program, hosting visitors from India and Singapore and sent a visitor to Australia.

The Nordic Imaging network met at the European Light Microscopy Initiative (ELMI) meeting in Dublin to make future networking plans. Contact information of the relevant members was collected for a Facebook group and a website. The network will look into possibilities to meet during upcoming imaging events.

The COST-funded Network of European BioImage Analysts (NEUBIAS) management board had three representatives from the LM-platform. One core facility member from Finland participated in NEUBIAS course for Core facility personnel to extend image analysis service skills. CIC-TBI participated in a training development meeting co-organized by NEUBIAS and Euro-BioImaging. Also, BioImage Informatics Finland (BIIF) met for the first time to start activities in national collaboration.

FIMM-HCA was involved in the CytoData Society, an active community around image-based profiling of biological phenotypes and European Cell Based Assay interest group. FIMM-HCA researchers have been involved in the establishment of a Nordic High Content Screening Network. FIMM-HCA is also involved in the successful EraPerMed COMPASS application with multiple European research groups involved in personalized medicine. FIMM-HCA also supports imaging services for drug testing performed at FIMM High Throughput Biomedicine unit, a partner in EU-Openscreen.

**Future perspectives**

The Euro-BioImaging ERIC is expected to launch in 2019 with 15 founding members, its large-scale operations will have a wide reach and impact on the imaging communities in Europe and beyond. Through CIC-TBI coordination, the consortium has submitted a proposal to the H2020 call, a successful proposal will generate opportunities to facilitate trans-national user access to EuBI Nodes, including the Finnish ALM Node, which will further increase visibility on a European level. CIC-TBI also actively participates in the EOSC-Life project (H2020) starting in 2019 developing e.g. training and authentication solutions for various data services.

**BIU-LM** secured funding from the Faculty of Medicine for Andor Dragonfly spinning disk microscope equipped with Borealis Uniform Illumination and dual cameras, to be installed in 2019. The microscope will offer gentle and fast confocal imaging suitable for live and fixed specimens. The system can be used for widefield, total internal reflection and SRRF-Stream super-resolution imaging down to 50 nm resolution.

**FIMM-HCA** will be acquiring a computer-assisted microscopy system for single cell isolation and the unit is involved in the development of microscopy-assisted automatic colony picker technology for the manipulation of spheroids and organoids. The purchase of robotics and incubators for high-content microscopy is planned to maximize the output for 3D DSRT screens.

The **TIC-BCO** is planning to set up emerging technologies that allow imaging of scattering tissue samples using non-diffracting light with high spatio-temporal resolution imaging in a mesoscopic scale.

For 2019 **BMT** got additional personnel resources. Multidisciplinary research has resulted in a need for a multiphoton microscope with 3D cell/material manipulation system. Merge of universities has facilitated better resources for data storage, but the need for suitable imaging analysis tools is urgent.

**Major publications supported by the platform services**


Small animal molecular imaging (SPECT/CT)

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

Partners: Anu Airaksinen, HiLIFE.

Achievements in development of technology services

For its development, and besides the imaging service, during 2018, the unit has been engaged mainly in service development. New radiotracer imaging protocols and animal model were tested to be incorporated in the service portfolio. This was made in collaboration with the Institute of Biotechnology and with the Medical Imaging Unit of the Hospital District of Helsinki and Uusimaa (HUS).

The RTI is now fully engaged with the Helsinki in vivo Animal Imaging Platform (HAIP); one of the 23 platforms of HiLIFE. At that point, functions of the RTI laboratory were divided into two different budgeting units: SPECT/CT LSRI and RadChem LSRI. The HAIP platform offers essential infrastructures and expertise for non-invasive dynamic analysis of physiological and pathological processes in animals in vivo. The platform has impact in basic and translational research in life sciences, including neuroscience, cancer research, cardiovascular and metabolic diseases, as well as in veterinary sciences and in drug development. The platform agglutinates the entire in vivo whole animal imaging infrastructures of Helsinki and associates essential services, offers comprehensive animal imaging from small fish to horses, using top-of-the-line technologies from optical
to nuclear imaging. HAIP is the largest and most versatile whole-animal imaging network in Finland.

a) Imaging development

In 2018, the unit undertook projects aimed to develop the portfolio of services. A new radiopharmaceutical in preclinical research, Ceretec, was tested. This tracer assays cerebral blood flow. Also new model of brain infraction was set up to characterise the tracer. This was tested by inducing stereotactic brain vasoconstriction with the aid of endothelin. This peptide was injected at the striatal region, and the blood flow was monitored by Ceretec. This protocol is being refined and is already in the portfolio of SPECT/CT laboratory services.

b) Radiochemistry services

Radiochemistry services (RadChem) of the RTI unit were provided during 2018 in 1) custom radiosynthesis of PET and SPECT radiotracers for imaging and 2) in biological sample preparation for radiometric analyses. In total there were seven projects, from which four were finalized and invoiced in 2018. Majority of all the projects were for investigation of biological properties of new investigational nanomaterials in healthy animals or in disease models of stroke and cancer, and included radiosynthesis development of the investigated nanomaterials before their evaluation in animals. One project was for biological sample preparation for brain autoradiography. Previous projects concerning development and evaluation of new radiotracers for PET and SPECT were published in 2018 (see section 5.).

In general, the RadChem provides services design synthesis and production of SPECT and PET radiotracers, as well as in analysis of biological samples. The facilities locate in the Kumpula campus. Laboratories for synthesis of radiopharmaceuticals are equipped with IBA 10/5 medical cyclotron for production of $^{18}$F and $^{11}$C, Eckert & Ziegler $^{68}$Ge/$^{68}$Ga-generators, lead-shielded hot cells, semi-automatic synthesis units and laboratory instruments for QC. The laboratories are working under radioactive exhaust monitoring system. The facilities include a well-equipped small animal laboratory for housing rodents for evaluation of novel radiotracers by ex vivo autoradiography (Fuji FLA-5100 and Ai4r Le Beaver) for biodistribution studies. This laboratory is approved for radioactivity (Class B), 2 GMO (class2) and adenoviral vector work. As a new addition, a cell culturing laboratory was established enabling cell uptake studies with radiolabelled investigational compounds and materials. Our cyclotron was modernized in a major renovation, which was started in 2018 and completed at the beginning of 2019 and ensures production of short living radionuclides at the Kumpula site for the next 20 years. Both the cyclotron renovation and building of the cell culturing laboratory were funded by the Faculty of Science.

User statistics

See table below.

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.

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<thead>
<tr>
<th>General</th>
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<td>Host Univ</td>
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**Future perspectives**

Infrastructure development. Last year we started the validation of new tracers and protocols to improve the SPECT/CT lab portfolio. These tracers were divided in three groups: **the group a**, brain imaging, in which we had already set the protocols or DATscan tracer in rats and in mice, and last year we started with Ceretec® for blood flow. We will now dedicate time for the **group b**, myocardial imaging, to test cardiac perfusion, and plan to use 201-Thallium, and 99m-Tc-Tetrafosmin, along with setup of the cardiac infraction model. **The group c** which includes tracers for cancer imaging, like OctreoScan, DOTANOC, Octreotide (somatostatin), ProstaScint (prostate cancer), or AB-MECA (breast cancer), would probably be also initiated, mainly setting up first cancer models in our facilities. All this would be coordinated tightly with the radiochemistry laboratory (Anu Airaksinen).

As every year, it is to note that the funding from the Biocenter Finland is essential for the RTI unit. As the support from the host institution is weakening, funding from BF now is of utmost importance, additional funds for the salary of one more researcher (to around 65 000 € total) to be able to cope with everyday imaging, planning and analysis, and in order to guarantee proper service at the current level, is sorely needed.

In addition, the laboratory has ambition to renew its aging camera, and is engaged to apply for funds to improve the facility from the current SPECT/CT camera to a multimodal SPECT/MRI instrument. This is a plan to develop for 2019-2020 which would enable to have a unique in vivo imaging possibilities.

The addition of a MRI imaging in Helsinki, is very welcome by the research community; most of the Finnish research on animal models is made in the University of The Faculties of Pharmacy, Medicine and Biosciences support this idea and they are committed with matching funds.

**Major publications supported by the platform services**

Abscopal Effect in Non-injected Tumors Achieved with Cytokine-Armed Oncolytic Adenovirus

R Havunen, JM Santos, S Sorsa, T Rantapero, D Lumen, M Siurala et al. 2018. Molecular Therapy-Oncolytics 11, 109-121

Efficient cartridge purification for producing high molar activity 18F-glycoconjugates via oxime formation. O Keinänen, D Partelová, O Alalen, M Antopolsky, et.al., 2018 Nuclear medicine and biology 67, 27-35

Delivery of agents into articular cartilage with electric spark-induced sound waves. AG Pérez, HJ Nieminen, M Finnilä, A Salmi, KPH Pritzker, E Lampsijärvi, et. al. Frontiers in Physics 2018

Multimodality imaging of silica and silicon materials in vivo. DŞ Karaman, MP Sarparanta, JM Rosenholm, AJ Airaksinen. 2018 Advanced Materials 30 (24), 1703651

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, Saara Ollila, HiLIFE; Riitta Lahesmaa, Riikka Lund, BioCity; Petri Auvinen BI-HiLIFE

Achievements in development of technology services

In biomedicine similarly as in physics new breakthroughs are often a combination of an idea what to look for and a novel technology making it possible to perform the experiment. The demand for the services as well as the number of different applications and samples handled by the BF-GWM nodes has kept steadily growing. Both direct feedback from users as well as the feedback collected through surveys has indicated that the BF-GWM has been successful in providing high quality, cost-effective services in reasonable time: GWM network is among the ones with the highest number of answers to the survey organized by BF reflecting the extensive use of the services, and received an overall score of 4.4/5. The lowest scores (3.86-4.57; Quality/Price) and the written feedback implicated the need to reduce the prices of the services although the quality of them was considered very good. GWM network had already identified this challenge and applied FIRI funding for the state-of-the-art Illumina NovaSeq instruments, which will enable lowering the prices for samples requiring large amount of sequencing.
for example the human genomes, with 74% of the current prices. The capacity of the new instruments also enables efficient scale-up of

Table 1. Services provided by the Genome-wide methods network.

Due to differences in the workload of library preparation methods between the applications, and some sequencing only services provided by the units, the numbers of samples listed in the table are not directly comparable. The numbers for stand-alone QC analyses are not shown in the table.

support for single cell sequencing, which is in increasing demand. Also, by participating in international consortia we have managed to make better agreements with some of the major reagent providers, and have managed to lower the prices of some of the services, such as GWAS genotyping analyses. This is already seen as slightly lower revenue of some of the units compared to 2017. Due to high request for some services requiring complex library preparation and/or dedicated expertise, the waiting times have occasionally been too long, despite our attempts to restructure the services and reallocate the resources.

In 2018 BF-GWM network has provided services for over 400 national and international research groups, and close to 40 non-academic users with a total cost-recovery of 4,577,057€. Table 1 describes the division of tasks between the individual units of the network.

In addition to single cell sequencing, GWM network expects the next bottle-neck to rise from increased demand for next-generation single molecule sequencing, which enables more affordable sequencing of larger genomes and their de novo assembly for identification of structural changes, full-length mRNA sequencing for direct haplotyping and identification of tissue, development or disease stage-specific RNA splice variants, metagenomic applications, and direct analysis of DNA modifications. To cover these demands GWM network suggests applying FIRI funding for PacBio Sequel II sequencer, which will be available in Q2/2019 and is the most suitable single molecule instrument for core facility operations with significant improvements to current version of the instrument (PacBio RSII), including a 50x increase in data yield with lower price and demand for sample amount.

**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 and the local biobank nodes. The expertise of the network is utilized in BBMRI EU level planning of biomedical infrastructure resources and evaluating the research infrastructures internationally. FIMM unit also operates as a national node for EATRIS biomarker platform.

BF-GWM has also 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 (http://eu-life.eu/working-group/core-facilities), which focuses on developing core facilities through information sharing, as well as in the European Core Technologies for Life Sciences network (CTLs, http://www.ctls-org.eu/). FIMM is also a member of the Nordic Alliance for Clinical Genomics (NACG, https://nordicclinicalgenomics.org/). Most of the nodes provide expertise support in international evaluation tasks, e.g. for EU research programs and evaluations of national research infrastructures in Europe.

Future perspectives

The capacity and quality of the sequencing has increased very rapidly broadening the use of NGS approaches to population genomics, personal genomics of humans and to single cell assays. The core of the developments is that with current technologies we are no longer only sequencing genomes or RNA but using NGS as a measuring device for gene regulation, ribosome function, RNA structure and DNA structure to name a few. The single molecule sequencing was initiated in 2012 in GWM platform. Further development of the initial steps of the single cell analyses, single cell capture and sequencing library preparation, was transferred to the new national network in 2016 and the single cell analysis services are currently being provided to Finnish researchers in collaboration between the Single Cell and GWM networks.

GWM network has also experience in extracting and analyzing low quantity and quality DNA samples for mutation detection from paraffin-embedded tissue samples and liquid biopsies. NGS instrumentation to study variants from low quality and less than 50 picogram amounts of DNA exists in GWM network to track the origin of individuals, estimate the geographical origin of the sample or mix-up of the compromised samples, such as pathology or service laboratories (biopsies and formalin-fixed samples). During the recent years GWM has also set up applications for analyzing cell free DNA from body fluids, and we already see an increasing demand for these services, particularly from the local and national Cancer Centres.

Today we see novel developments in single molecule analysis despite of the challenges of measuring any feature in biology from one single molecule. While the Nanopore-based assays are developing to become mature enough to produce data with quality and quantity on a useful level to implement them in new assays in core facilities, the newest PacBio instrument, Sequel II sequencer, is already available to serve these demands. One size/method fits all -type approach does not work in today’s genome research. Assays and methods used need to be chosen based on the research question in hand. We see our role in introducing and developing new approaches not necessary supplied elsewhere and handling more challenging samples. Furthermore, keeping technology awareness on the level that new groups can meet and get advices on their projects is increasingly important for Finnish research. Only small minority of research groups are self-sufficient in experimental planning, choosing technology or designing how much and what kind of data is necessary to be able to get answers to their research questions. Although semi-automated data processing and bioinformatics solutions are emerging for in depth analysis, bioinformatics support for implementation of new cutting-edge methods for service use is currently not sufficient.

Capability to analyze genome(s) and population of individuals and their functions is an important part of practically all life science research today. Analyzing the nature’s experiments, the individuals with gene defects, gives both detailed molecular knowledge about the disease, and 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. Taking the next technological step will allow routine 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 enhance the use of the latest genome analysis technologies 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, diseases and for example primary production (food, forest). 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 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. Generating suitable control constructs and developing new approaches, such as customized cloning, will further improve the services.

Major publications supported by the platform services


MODEL ORGANISMS

Coordinator: Reetta Hinttala, BCO

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

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

Since special training of researchers and personnel performing the animal experiments as well as taking care of animals are required, and the units have to be managed according to legal regulations on the use of experimental animals and genetically modified (GM) organisms, core facilities are the only choice. They offer possibilities for both reduction of animal numbers used and refining their life and welfare, following the 3R’s principle. Furthermore, in the co-operative, centralized system, the GM animal strains can be shared by a large number of researchers.

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.

FinnMouse technology platform

Chair of the platform: Reetta Hinttala

Partners: Heikki Tanila, BCK; Eero Castren, Satu Kuure, Pirjo Laakkonen, Antti Sukura, Vootele Voikar, HILIFE; 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 FinGMice technology platform has actively developed and maintained up-to-date GM mouse services in Finland in 2018. Platform partners generate, re-derivate, archive and analyse mouse models. Services include generation of GM rodent models by traditional transgenesis and classical targeting and CRISPR/Cas9 method to produce knock-out/knock-in rodent models, pathogen removal, and cryopreservation of mouse as well as rat lines (embryos/sperm). Some of the GM model organism services have been focused on specific units such as transgenic rat models in Helsinki and xenograft models in Turku. The Oulu laboratory functions as the
only Finnish Infrafrontier-EMMA (European Mouse Mutant Archive) node that serves world-wide user community, and it has now taken an active role in several working groups such as technical, communications and quality management working groups. In November 2018, docent Raija Soininen, the coordinator of the TG/EMMA unit in Oulu and the chair of the FinGMice platform, retired and her successor docent Reetta Hinttala was appointed as the new chair.

The phenotypic analyses of mice provided by the FinGMice platform partners have included areas such as Animal Imaging, Bone, Reproductive, Thyroid Biology and Neuroendocrinology by Turku Center for Disease Modelling (TCDM) and automated behavioral phenotyping and specific neurophenotyping tests carried out in the Neurophenotyping Centers in Helsinki and Kuopio (BCK). In 2018, TCDM received funding from the Institute of Biomedicine to develop deep learning–based image analyses together with Aiforia Technologies Company. The first pilot project is to analyze mouse estrus cycle phase from vaginal cytological samples. First versions of the algorithm have been developed and the validation is still ongoing. The goal of the project is to develop an algorithm for estrus cycle determination and offer it as a service via TCDM website.

University of Eastern Finland has undertaken a total renovation of its main laboratory animal unit in 2018. The renovation also included upgrading of key equipment for behavioral studies run by BCK Neurophenotyping Center: video analysis program Ethovision XT14 (Noldus), infrared detection based activity monitor Tru-Scan 2.07 (4 units, Coulbourn Instruments), and metabolic cages (4 units, Phenomaster, TSE). As a part of the Comprehensive Model Organisms (CoMO) platform of HiLIFE Helsinki GM unit has continued to develop joint genome editing activities together with the Biomedicum Stem Cell center and initiated planning of joint phenotyping activities with the Mouse Behavioral Phenotyping Unit.

New tests and methods are applied based on the requests by users. All FinGMice units educate and counsel researcher working with animal models. The facilities are willing to help for example in testing new methods requiring early embryo experience and offer guidance for breeding of complex genetic models. Based on the user survey carried out by BF in 2018, the average value for the services provided by FinGMice platform partners was in the range of 4.17-4.87. In general, the customers were satisfied with the quality of the services and especially with the support provided by the facilities. In some occasions, the efficiency of the service was criticized too slow mainly due to the high workload of the unit. This will be addressed in future by increasing the national collaboration between the FinGMice partners and providing wider repertoire of services especially for phenotyping of mouse models in each unit.

FCLAP, which offers service and consultation on tissue pathology, considers that the amount of personnel as one of the main bottlenecks.

**User statistics**
See table below.

**Participation in international and European Infrastructures**

University of Oulu is a shareholder in the Infrafrontier GmbH that was formed in 2013. Infrafrontier Finland, represented by Biocenter Oulu, was included in the Finnish Research Infrastructure (RI) Roadmap in 2009, and further for 2014-2020. Currently, Infrafrontier GmbH has applied for the ERIC status and the second stage is currently being processed in the German Federal Ministry. Biocenter Oulu is a partner in the Infrafrontier2020 and EC-INFRADEV-3 projects and will host the 3rd Infrafrontier stakeholder meeting co-organized by Infrafrontier2020, International Mouse Phenotyping Consortium (IMPC) and IPAD-MD in Helsinki, Finland, June 3-5, 2019. The EOSC Life project is a new program funded by European Commission, where 13 Biological and Medical research infrastructures join forces to create an open collaborative digital space for life science in the European Open Science Cloud, so that research data, digital services and advanced facilities are Findable, Accessible, Interoperable, Reusable (FAIR) for researchers across scientific disciplines and national boundaries. The project initiated in March 2019 and Infrafrontier GmbH and University of Oulu are among the beneficiaries. Oulu TG unit is involved in the activities of WP1: Publishing FAIR data resources composed of imaging data from mouse models in collaboration with the Finnish ELIXIR node. In addition, other FinGMice platform partners actively participate in the Infrafrontier activities. The Vice Director of the TDMC, Dr. Petra Sipilä, is a member of the Infrafrontier/EMMA Evaluation Committee further facilitating the connections between Infrafrontier ESFRI and FinGMice platform. University of Turku is also a partner in the European Advanced Translational Research Infrastructure in Medicine (EATRIS).

**Future perspectives**

FinGMice platform is dedicated to establish a well-structured pipeline called “Mouse Clinic Finland” for mouse model phenotyping. This will be composed of

1) **primary phenotypic screening** in every platform unit. Currently, FCLAP provides tissue pathology services and Oulu TG unit is investing for further upgrading and expanding the histopathological analyses and facilities for gnotobiological studies. Interest in single-cell analyses is growing rapidly and the single cell analysis techniques are now developing fast for example in the fields of transcriptomics, proteomics and metabolomics. Due to the heterogeneity seen in eukaryotic cell populations, analyzing a single cell makes it possible to discover mechanisms not seen when studying a larger population of cells. The aim is to expand the services offered by TCDM to the single cell analyses from tissue sections from genetically modified animal models.

2) **customized primary phenotyping** incl. eg. basic behavioral testing, specific IHC stainings...
and sample collection, performed at each home university but using data analysis expertise among the FinGMice partners, and

3) secondary, more specialized, phenotyping carried out in the platform units with the appropriate expertise, including (but not limited to) the expertise on mouse modelling, imaging and protein sciences (UO), on endocrinology and reproduction (UTU), on mouse modelling, neurophenotyping (UH) and on neurophenotyping (UEF). These services are made accessible to all researchers in Finland.

Altogether routine digitalization of slides and use of artificial intelligence may lead to marked changes in the tissue pathology services provided by FinGMice platform: 1) The pathologist’s role in slide reading may decrease and researchers may “directly” utilize the rapidly emerging and developing “Artificial intelligence (AI) analysis systems”. 2) Sampling, sample quality and sample representativeness will be of utmost importance since automatized analysis may lead to unforeseen and imperceptible biases. This results in strong need of expertise in sampling and of high technical (laboratory) quality. 3) The AI systems employed in non-AI related research are generally commercial which requires funding allocation, expertise in whether to use and which system to choose, and how to organize long term data and model storage.

**Major publications supported by the platform services**


Non-mammalian model organisms
technology platform

Chair of the platform: Mika Rämet, MED

Partners: Pertti Panula, Neuroscience Center Zebrafish Unit HILIFE; Matalena Parikka, Tampere Zebrafish Core Facility; Susanna Valanne, MED, Tampere Drosophila Core facility; Ville Hietakangas BL-HiLIFE, HiFly

Achievements in development of technology services

During 2018, both zebrafish facilities (Helsinki and Tampere) and Tampere Drosophila unit have maintained their status as trusted providers for required services for researchers using these models. The services were not affected by any animal welfare issues or any significant technical problems during the reporting period.

For zebrafish research, the production of mutants using the CRISPR/Cas9 method has become routine, which allows disease modeling for several phenotypes (including degenerative diseases and susceptibility to infections). In addition, a new social behavior and shoaling analysis methods were developed and published in Helsinki.

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

Bottlenecks: In June 2016, Tampere zebrafish facility was translocated to a newly constructed Arvo-building. During the translocation, the volume of services that the laboratory was able to provide decreased temporarily. During 2018, all the facilities have been fully operational.

The overall situation with the national services are adequate with recently renovated spaces both in Tampere and Helsinki, provided that the new space finished in 2019 in Helsinki can be properly equipped. The Helsinki unit acutely needs a live imaging light-sheet microscope (about 100 000 euro), as an update for the current dedicated confocal microscope. The microscope core facilities do not have such an instrument.

User statistics

See table below.

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. The Helsinki facility is an active member of the ZFIN and ZIRC global networks, the international zebrafish society IZFS and in the European Zebrafish Resource Center. PI of the Helsinki facility participated in a world-wide zebrafish neuroscience technology meeting in Brighton in 2018.

Future perspectives

With recently renovated infrastructure, steady investment on the different phenotyping methods (for example behavior, advanced imaging, fast qPCR in Helsinki) and highly trained personnel, zebrafish units in both locations have become a routine model for many teams. With the steady funding the units will be able to further develop methodological tools and services to foster the use of both the zebrafish and Drosophila models. However, the BF funding is a necessity for the further developments. The prospect is currently to stay

<table>
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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 all units. The Helsinki facility has during 2018 optimized double-targeting CRISPR/Cas method and produced about 30 fish lines, which need enhanced phenotyping using a new dedicated microscope.

**Major publications supported by the platform services**


PROTEOMICS AND METABOLOMICS

Coordinator: Vesa Hytönen, MET

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 MET, Protein Technologies Facility

Partners: Marc Baumann, HILIFE, Meilahti Clinical Proteomics Core Facility; Lloyd Ruddock, BCO, Proteomics and Protein Analysis Core Facility; Peter James, BioCity, Epiproteomics Unit; Markku Varjosaalo, BI, Proteomics Unit

The year 2018 showed a positive trend for Protein characterization and Proteomics Network (PPN) in terms of services provided. The network served 214 research groups (2% increase compared to 2017) and the income from the user fees increased by 31% corresponding to 664 809 €. This was the first year when the Tampere Protein Technologies facility started to provide also proteomics services which partially explains the increase in annual income. The network also received
more financial support from the host universities as compared to 2017: BF funding for salaries increased as compared to previous year by 31% and the other financial support from the local universities increased by 27%.

**Achievements 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 (214 research groups reported as users during 2018). The services are highly appreciated, as judged from the high scores obtained in the national BF user survey (average score 4.49/5, n = 193). Notably, the number of answers was highest among the BF platforms, reflecting the significant role of the PPN network.

Although PPN is well-established, it is evident that substantial investments would be needed to maintain the internationally competitive setting. The quality of the services provided is absolutely dependent on skilled personnel, but also the instrumentation has to be up to date.

**In detail**

The Turku Proteomics Facility (CBT) continued providing services including characterization of post-translational modifications and large-scale proteomics analysis by data independent acquisition (DIA) and DDA based quantification methods. The facility set up an automated sample preparation workflow for large clinical sample sets. A new mass spectrometer, Orbitrap Fusion Lumos with UVPD, was bought with FIRI funding. The new instrument enables top-down and middle-down mass spectrometry analysis of intact proteins and offers therefore advantages for characterization of biotherapeutics like antibodies. Cross-linking mass spectrometry analyses of protein-protein interactions is also provided as a new service.

The Tampere Protein Technologies facility has established its functions in new facilities in ARVO building. Services in both protein characterization and in design and execution of protein production were provided. For the first time, the proteomics services were provided as a part of the Biocenter Finland activity and this led to increase in the number of users and in the collected user fees. The proteomics services are provided by team consisting of Prof. Hannu Uusitalo, MSc Janika Nättinen, Dr. Juha Määttä, Dr. Ulla Aapola and laboratory technicians Saara Lähdekorpi and Niklas Kähkönen. From the beginning of 2019, University of Tampere and Tampere University of Technology have been a part of the new Tampere University.

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. 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 GLP documentation. 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. During 2018, the unit closed a strategic alliance with Orion Corp. and they now have a fully automated robot for sample preparation coupled to an Q-Exactive Plus MS instrument being able to serve the customers with the SISCAPA technology in MRM and PRM for high-throughput biomarker validation.

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 tools for biosciences.

**User statistics**

PPN network served 214 research groups, which is slightly more than that reported during 2017 (209). The volume of the services in terms of the income from the services was 664 809€, which is 31% higher 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. 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 INSTRUCT (Integrated Structural Biology Infrastructure for Europe) and EPTRI (European Pediatric Transnational Research Infrastructure) projects which are on ESFRI Roadmap.

<table>
<thead>
<tr>
<th>Host Univ</th>
<th>Biocenter</th>
<th>Name of core facility</th>
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<td>15</td>
<td>16</td>
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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 is carried out as a part of the MSc curriculum. Moreover, Tampere facility organizes a summer course in collaboration with BioNavis company focusing on SPR biosensor techniques. 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 2018 at the undergraduate and graduate student level.

Future perspectives

We expect that the importance of proteomics and protein characterization services are becoming even more important for the researchers. The establishment of novel methods for interactomics will also reflect to the target molecules to be inspected thoroughly with biophysical methods. Better sensitivity, smaller sample size, faster analyses and better user interfaces will be developed. We expect also that proteomics methods are becoming more suitable for clinical samples and in the long term for diagnostics. The research conducted in Tampere for the eye samples is an example of such development. Quantitative proteome-wide analysis methods are emerging. Integration within omics-based methods will be strengthened. Methods such as Parallel reaction monitoring 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 increasing number of identified proteins with the third-generation mass spectrometers typically reaching already several thousand of proteins in one analysis set.

In proteomics, PPN will continue to provide services to characterize protein isoforms and their PTMs. The analysis of protein interactions and their complexes are now provided by multiple units within the network, and those services will be developed further. Also, 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 top-level vibrational spectroscopic tools.

MS-Imaging (MSI), a technology for direct ion monitoring and identification at the tissue level, without prior labelling or the need for any antibodies, has internationally entered to a new level with the 3rd generation MSI instrumentation. With a speed of analyses of less than 20 minutes for a complex tissue slice sample with a resolution of a few micrometer spatial rastering and direct ion fragmentation scanning, provides a future possibility for ultra-high resolution tissue 3D Smart-Beam laser imaging. Such technology is already in test use at several research laboratories and will hopefully soon also get hold in our consortium and the National Center for MSI in Meilahti, Helsinki.

Single cell proteomics is taking steps towards the reality and will have a first-ever European Single Proteomics Conference in Vienna later this year, where some of our network partners have been selected to be presenting their first single-cell experiments for the public.
We are happy to see that the universities are investing more for the services provided by the PPN network. Heavy investments for the instrumentation are important in near future due to ageing of some of the key instruments. Simultaneously, it is good to recognize that the quality of the services is highly dependent on the skilled personnel.

**Major publications supported by the platform services**


Kauko O, O’connor CM, Kulesskiy E, et al. PP2A inhibition is a druggable MEK inhibitor resistance mechanism in KRAS-mutant lung cancer cells. Sci Transl Med. 2018;10(450)


**Metabolomics technology platform**

Chair of the platform: Vidya Velagapudi, Metabolomics Unit FIMM-HiLIFE

Partners: Seppo Auriola, Department of Pharmaceutical Chemistry, BCK; Teemu Teeri, Viikki Metabolomics Unit, HiLIFE

**Achievements in development of technology services**

FIMM, ViMU and BCK Units together as a single entity offers very broad coverage of analytical services in various fields of metabolomics both nationally and internationally. Most importantly we have a nice complementary niche. The BF metabolomics units have continued services in their key analytical focus areas in the year 2018 too.

FIMM unit has been successfully offering high throughput targeted and (semi)quantitative metabolomics and lipidomics, and isotope enrichment analyses as
services. We continued in active research collaborations emerged from the service projects and published in highly reputed international journals. In addition, we had published our developed methods about analysis of polar metabolites and folate cycle intermediates in analytical journals. Our Unit’s focus has been mainly clinical and biomedical applications, early biomarker discovery, (pre)-clinical trials, and precision medicine. For e.g. in 2018, we had analysed 1000 clinical samples from Meilahti hospital, Helsinki to identify biomarkers for acute kidney injury. For the global metabolomics analysis, we started creating an in-house standard library of hundreds of pure compounds. We continued to maintain the “self-sustainability” status since 2014, and generated the highest revenue of around 306,000 € in 2018. In the BF user survey, 36 customers evaluated and rated very well with 4.22/5 score with quite encouraging positive comments. We have obtained good reputation and great visibility at international level. We were invited to participate in an international inter-lab ring trial for lipidomics analyses, where FIMM PI is one of the leading investigators. FIMM PI also lead a subtask group in Precision Medicine and Pharmacometabolomics group of The International Metabolomics Society, USA about biobanking and preanalytical issues in metabolomics and published a White paper as a leading author. We were also invited to podcast and as experts for Q&A session in the same Clinical Chemistry journal. FIMM PI is the Finnish Ambassador for Metabolomics community at ELIXIR, where our proposed work flow for fluxomics got funded and also FIMM PI is leading one of the WPs.

**ViMU** (Viikki Metabolomics Unit) has been functional service unit for 10 years (2008–) and continues to provide analytical services mainly for the Finnish plant community and Pharmacy. The unit is focused on the plant primary and secondary metabolites from different plant species and organs (root, shoot), but also provides pharmacokinetic and mass spectrometry analysis for pharmaceutical synthesis products, novel drugs and their metabolites. The focus of the ViMU continues to provide GC-MS and LC-MS analytical services in plant metabolomics, microbiology, biopharmaceutical analysis and pharmacokinetics. The mass spectrometry-based analyses are performed by three instruments; UPLC-QTOF/MS, GC-QQQ/MS and UPLC-QTRAP/MS. Both targeted (quantitative) and untargeted metabolomic studies were performed in the unit. In the BF user survey, 16 customers evaluated ViMU and obtained a high score of 4.34/5.

**BCK** has continued providing non-targeted metabolomics services using UPLC-Q-ToF methodology. The installation of second high resolution instrument, Thermo Q-exactive orbitrap, in 2017 markedly increased the sample capacity. The technology allows for a better combination of screening the known compounds, and non-targeted metabolomics in same sample acquisition. The main non-targeted metabolomics applications include nutrition, health, environmental and toxicology studies. The LC-MS Metabolomics Center has also developed methods for targeted quantitative analyses of various compounds, the most important the methods published in 2018 for simultaneous measurement for up to 22 steroids. The center (in co-operation with the Institute of public health and clinical nutrition and School of Pharmacy) started lipidomics funded by EAKR. The EAKR funding was used to purchase a second Orbitrap instrument, and to hire a post-doc for setting up the analytical services. Because of the high customer demand for analysis of other than serum or plasma samples, the Kuopio laboratory has been developing sample preparation methods for hair, tissue and saliva samples among others. Another continuously important part under development has been the pre-study counselling services for the research groups, optimization of the work-flow, as well as instruction of the researchers in the use of data analysis software. These tasks have been performed by Dr Marko Lehtonen, who was
hired as a laboratory manager to further develop the core laboratory services. The instrumentation in the Kuopio laboratory is in major part at adequate level.

**Bottlenecks**

From May 2018, ViMU has again had only one analytical researcher (N.Sipari) and no technical staff working in the unit due to reorganization of the staff in the new Faculty and two research programs. FIMM also suffered from lack of enough human resources as a results development work was hampered. For BCK, the main bottlenecks being the slow process of non-targeted metabolomics data analysis.

**Education and training**

The metabolomics results obtained from all the Units have been used in many Ph.D and post-doc projects and collaborations resulted in joint publications with the staff. The BF metabolomics Units have continued teaching various aspects of metabolite analytics in their Units. FIMM continued in offering hands-on workshops and training to young researchers and students. FIMM PI has been organizing Precision Medicine workshops at the International Metabolomics Society’s Annual Conferences. In June 2019, ViMU will be part of organizing NOVA University Network (The NOrdic forestry, Veterinary and Agricultural University Network) PhD course series: Phenotyping technologies in plant environment interactions: -image based phenotyping with Kristiina Himanen (NaPPI) and Prof. Markku Keinänen (UEF) from National Plant Phenotyping infrastructure (NaPPI). ViMU will be responsible of MS-based metabolomic plant phenotyping with GC-MS, UPLC-MS and MS-based imaging part of the course.

**User statistics**

See table below.

**Participation in international, Nordic and European infrastructures**

FIMM is part of the EATRIS network. ViMU collaborates with the National Plant Phenotyping infrastructure (NaPPI), where the aim is to integrate non-invasive image data with plant metabolomics data, and the unit is part of an EPPN application in plant phenotyping. The Kuopio laboratory is participating in NordForsk funded Nordic POP program, which deals with the development of new innovative medicinal products relying on a combination of diagnostic tools and personalized dose.

**Future perspectives**

The future vision of our metabolomics technology platform would be offering services in metabolite imaging technology. The specific goals of each unit are given below. In future, FIMM will focus on setting up global metabolomics platform. As a long-term goal, we plan to set up a national core facility for “Spatial Metabolomics” (metabolite imaging). The aim of ViMU is to develop more analytical methods for targeted, quantitative metabolomics. The long-term future aim of the unit is to offer MS-based imaging services to investigate surface and volatile plant metabolites, and to integrate MS-based imaging data with the imaging data (e.g. RGB/visible, fluorescence, NIR/SWIR data

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Biocenter Finland – Annual Report 2018
from NaPPI) and metabolomic profiling data (LC-MS, GC-MS) for plant phenotyping research. For further development, the BCK will expand services to MALDI imaging mass spectrometry in drug, peptide and metabolite analysis. Some new application areas will include methods for leachables in food and drug formulations, and analysis of contaminants bound to plastic waste. In addition, automation of sample preparation will be developed to increase sample throughput in the laboratory.

**Major publications supported by the platform services**


STEM CELLS AND BIOMATERIALS

Coordinator: Timo Otonkoski, HILIFE

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 tissue transplantation.

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

Stem cells and biomaterials technology platform

Chair of the platform: Timo Otonkoski, BCH

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

Achievements in development of technology services

The overall situation of the nationwide consortium.

The BF stem cells platform annual meeting was held for the fourth time in conjunction with the Joint Meeting of Finnish Developmental Biology Society & Finnish Stem Cell Network (FSCN) from October 26th to 27th, in Murikanranta, Teisko, Tampere with active participation from all centres belonging to the BF stem cells platform (more than 100 participants). FSCN is pulling together all research groups that are actively using stem cell technologies. The BF stem cells platform is a part of this network, involving those partners who are providing Core Facility services. Present were representatives of all three national stem cell Core Facilities from University of Eastern Finland, University of Tampere and Helsinki University. Important issues related to the coordination of activities between BF stem cells platform partners were discussed including the organization of the next year joint meeting of Finnish Developmental Biology Society & FSCN. Because of the exceptional interest, we decided to continue the annual meeting, this time organized by University of Helsinki on October 11th-12th, 2019, in Kiljavanranta in Nurmijärvi. BF stem cells platform partners have continued the development of their stem cell services as described below. Meeting memo was produced
after the annual meeting and sent to BF representative.

Total support for the BF stem cells platform partners was 262 360 € in 2018. This enabled the continuation of the existing services and development of the new stem cell services by all partners. Stem cell services were provided for 23 user groups of which 17 local and five internationals. BF stem cells platform partners have derived 58 fully characterized and 184 early passage uncharacterized human induced pluripotent stem cell (hiPSC) lines. In general, the need for new hiPSC lines was limited, but has been steady. 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. As a new service development platform has generated 13 genome edited hiPSC lines. Those included generation of isogenic hiPSC lines and cell type specific reporter lines with CRISPR/ Cas9 technology. Isogenic hiPSC lines have been made with increasing interest. Fluorescent-labelled reporter stem cell lines were produced for the pluripotent state and for pancreatic, cardiac and hepatocyte applications. BF stem cells platform partners have put an effort on improving pancreatic, hepatic, cardiac and neuronal differentiations including 3D brain cell cultures. Training was provided to total of 281 students/ researchers. This includes the hands-on training for individual researchers on basic hiPSC production but also for genome editing with CRISPR/ Cas9. Several lectures have also been provided on these issues including active participation by graduate students. The total turnover (customer fees) for the BF stem cells platform was 81 360 €.

In 2018 BF conducted the life science research infrastructure user survey. Responses by life science principal investigators totalled 515. The survey has asked participants to give a numeric score, on the scale from 1 to 5, describing: access, quality, efficiency/ performance, staff support and price/ quality of each core facility. BF stem cells platform received a total of 24 evaluations, the average score was 4,7. BF stem cells platform users have not given written feedback. Services and service development provided by each partner of the stem cell consortium are presented below.

During 2018, the iPSC core at the Tampere University has created isogenic lines and cell type specific reporter lines using CRISPR/ Cas9 technology. The need for new iPSC lines has been steady, and additionally isogenic lines have been made with increasing interest. Fluorescent-labelled marker cell lines were created for cardiac applications having different fluorescent labels. Additionally, three different types of hepatocyte specific reporter lines have been designed with two of them functional at the moment. The core also put a great effort in improving hepatic differentiation and now the system is fairly robust. The know-how of the core for cardiac applications is still the major task for providing differentiated cells. The main aim with the fluorescent lines is to provide cell type - specific lines especially for co-culturing and tissue model studies. Training was mainly hand-on training for individual researchers on the basic hiPSC production but also for the genome editing using CRISPR/ Cas9. Several lectures have also been provided on these issues to different researcher groups.

BCK has established additional differentiation protocols for the following cell types: spinal cord motoneurons, microglia, endothelial cells and pericytes. BCK has also set up more 3D brain cell culture models and is working on a cerebral organoid model, a blood-brain barrier model (containing endothelial cells, pericytes and astrocytes) and taking the first steps
towards 3D bioprinting of hiPSC derived brain cells in collaboration with companies having disease models, imaging services and 3D printing in their portfolios. Electrophysiological characterization of hiPSC-derived neurons has become more automated. The future profile of BCK stem cell core includes specialization in hiPSC models of mitochondrial diseases. During 2018 iPSC lines from four patients for two customers and astroglial differentiation for two customers were provided. The service also included electrophysiological characterization of neurons derived from 9 hiPSC lines for one customer.

The Biomedicum Stem Cell Center (BSCC, representing BCH) provided previously produced fully characterized human pluripotent stem cell lines to four clients. Derivation and characterization of new hiPSC lines was provided for eight clients to derive 33 fully characterized hiPSC lines. For the projects in the area of Type 2 diabetes, hiPSC were derived from 15 donors for the National Institute for Health and Welfare Biobank (THL Biobank). The samples are coded and the identity of the cell donor remains unknown to the investigators. This will be added to the 10 hiPSC lines already deposited in the THL Biobank. BCH has continued active technological development and developed a novel reprogramming system based on the activation of cells own pluripotent genes, using CRISPR activators only (CRISPRa). This is a new technology for the generation of hiPSCs with important biobanking potential. BCH has been granted permission to obtain cell samples (immortalized B cells) from THL biobank. Blood samples were originally collected from voluntary donors of THL Psychiatric Family Collections cohort. hiPSC lines from six donors were produced using the novel CRISPRa reprogramming system.

BCH has continued active development of genome editing services. Reporter hiPSC lines for OCT4 and SOX2 expression have been produced and these are actively demanded by the international community (Balboa et al. PMID: 28952927 and 28925359). From 1.4.2018 BSCC has partially employed Fuping Zhang, MD, PhD to facilitate development of the genome editing services. Fuping has a long experience in genome editing and has been one of the key people for genome editing services in Turku Centre for Disease Modeling (TCDM). As a result, BCH has initiated three genome editing projects, one for the generation of a knockout hiPSC lines and two for the introduction of a point mutation for three clients. As a part of GoEditStem platform, part of the Helsinki Institute of Life Sciences (HiLIFE) infrastructure, we have offered the provision of validated CRISPR-Cas9 gRNA library and training in the field of genome editing for doctorate students. Hand-on training was provided to eight researchers. In addition, BCH has organized a minisymposium on genome editing and participated in the pluripotent stem cell courses organized by the Faculty of Medicine, UH; Master’s Programme – Translational Medicine, UH; and Doctoral Programme in Biomedicine (DPBM), UH. Those were very popular with active participation of 263 students and researchers. In addition, BCH has promoted human pluripotent stem cells to high school students by taking active part in the Medical Faculty’s educational program. In 2018 BCH has not provided any continuous visualization of live cells services due to the malfunction in CellIQ, that has been broken beyond repair. At the end of 2018 BSCC has secured funding from the Faculty of Medicine, UH, to acquire the IncuCyte S3, an automated cell culture and analysis system. IncyCyte will replace the CellIQ, from 2019 enabling us to provide stem cell live imaging services to the clients.

**Bottlenecks in the services provided by the consortium.**

Comments are presented by each partner of the consortium:

**BCH:** Generation of hiPSC 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/MET: Functional analysis hiPSC-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 Ca2+ imaging, patch clamp and MEA data, for contraction/relaxation analysis as well as for cellular orientation applicable for any cell type. Additionally, the genome editing processes are labour-intensive and requires usually more time and recourses initially expected.

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 stem cell score remains low 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 Business Finland nor AF favour acquisition of equipment by their regular grants.

Overall, the service activities of the platform remained at roughly the same level as compared with 2012-15. Consortium provided services to 28 user groups and have produced 111 iPS lines. Teaching and hands on training were provided to 95 users included courses on regenerative medicine for graduate and undergraduate students. Total turnover was 117 500 €

BCH: 2017 turnover was 54 200€. This includes reprogramming of biobanked cells from THL Biobank. In addition, BCH has provided two validated genome edited iPS lines for two customers and organised training for medical and transmed doctorate students. BCK: 2017 turnover was 55 000€. This includes generation of iPS lines, their differentiation into brain cells and their thorough characterization. BCK organized the annual meetings of the FSCN with over 100 participants. Detailed user statistic is provided in the separate table.

**Participation in international, Nordic and European infrastructures**

BSCC (Otonkoski) is a partner in a 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/MED (Aalto-Setälä) participates in the Nordis Organ-on-Chip consortium as well as in the European Organ-on-Chip consortium for combining different tissues to each other and creating research consortiums for future funding options.

**User statistics**

<table>
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<th>Biocenter</th>
<th>Name of core facility</th>
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</tr>
</tbody>
</table>
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 hiPSC lines has become 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 hiPSC methodology. Therefore, the BF stem cells platform services need to focus more on technologies of differentiation and functional analysis of the differentiated hiPSCs. BCH has focused mainly on endodermal differentiation to derive functional pancreatic islet cells, hepatocytes, intestinal cells and lung epithelial cells. BMT/ MED focuses on the differentiation of cardiomyocytes as well as hepatocytes, retinal pigment epithelial cells and neurons. As Jari Koistinaho, who has been running the stem cell core in BCK from the very beginning, is gradually moving to Neuroscience Center at UH in 2018-2019, BCH is considering to enlarge the profile to include differentiation of brain cells. BCK continues to have emphasis on differentiation and functional analysis on brain and muscle cells and to further concentrate on models and assays of mitochondrial diseases, the expertise area of Dr. Riikka Martikainen who will be in charge of the stem cell core of BCK after 2019.

The need for hiPSC 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 hiPSC collections from defined patient cohorts. The BF 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. Blood samples were originally collected from voluntary donors of THL Psychiatric Family Collections cohort. Other similar projects in the area of Type 2 diabetes have been completed, and iPSC derived from 15 donors for the THL Biobank. The samples are coded and the identity of the cell donor remains unknown to the investigators. BCH has started collaborative project with UH and University of Turku together with biobanks within one of pilot project of National Centre for Neuroscience to generate hiPSC lines from desired material stored in a biobank and returning them for general use.

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 hiPSC 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. CRISPR technology is used in addition to create marker cell lines having fluorescent labels under the promotor of cell type specific promoter. This enables detection of different cell types in co-cultures while the cells are still viable. Generation of the knockout human pluripotent stem cell lines has become a routine procedure and this is now provided as a service by BCH. Reporter hiPSC lines will also be made available for distribution through core service web pages.

**Major publications supported by the platform services**


Aalen RB, Gundersen WB. Molecular characterization and comparison of plasmid
STRUCTURAL BIOLOGY

Coordinator: Sarah Butcher, BI-HiLIFE

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.

Instruct-Fi, Integrated structural cell biology platform

Chair of the platform: Sarah Butcher, BI-HiLIFE, Cryo-Electron Microscopy

Partner: X-ray Crystallography Tommi Kajander, BI-HiLIFE, Tassos Papageorgiou, Biocity, Tiina A. Salminen, Biocity Turku, Åbo Akademi University (ÅAU), Rik Wierenga, Biocenter Oulu, University of Oulu (UO), Lari Lehtiö, Biocenter Oulu, University of Oulu (UO)

Nuclear Magnetic Resonance: Hideo Iwai, BI-HiLIFE

Mass Spectrometry: Juha Rouvinen, BCK
Achievements in development of technology services

We support state-of-the-art research in protein and biomolecular complex production, purification and characterization; high-resolution cryo-electron microscopy (cryoEM); nuclear magnetic resonance spectroscopy (NMR); native mass spectrometry (MS); structural bioinformatics; and X-ray crystallography (Table 1).

In 2017, the Instruct-FI UH units (Instruct-HiLIFE) were evaluated by the HiLIFE RI Assessment (international evaluation panel) and graded outstanding. Based on the positive evaluation Biocomplex was included in Instruct-HiLIFE from 2018 onwards and therefore Biocomplex is now also included in the Instruct-FI annual 2018 BF report. In the BF 2017 user survey we obtained very good ratings with average of >4/5 in all areas (access, efficiency/performance, staff, price/quality, support/responsiveness). We aim to keep our services dedicated to the users, discussing with them on a case-by-case basis to try to support their scientific questions fully. The services are used extensively by biotechnology companies, and local, national and international academic users.

The national service providers in X-ray crystallography are currently in three geographical locations each with its own specialization, down from five in 2014 (UEF and University of Jyväskylä, now primarily local). Instruct-FI benefitted from the appointment of coordinators on BF and FIRI funding. Minna Poranen was nominated as a voting member of the Steering group representing University of Helsinki and provide expertise in purification of complexes. The Instruct-FI steering group met eight times during 2018 to develop common activities including strategic objectives and targets, and reports to host organizations, the BF Board, Instruct-ERIC, Ministry of Education and Culture (MinEdu) etc.

The primary activities of the Instruct-FI Coordination Hub and Instruct-FI Consortium Members have been:

The Instruct-FI Coordination Hub in Helsinki is operational and works for the whole network;

The establishment of clear Instruct-FI steering group protocols;

Regular steering group meetings with distributed minutes;

Organisation of the annual structural biology user group FINNBOX-meeting jointly with the Finnish Synchrotron Radiation Users Organisation (FSRUO) meeting (Oulu, November 2018);

Preparation of the Instruct Centre Finland application that was submitted by the Ministry...
of Education and Culture to the Instruct-ERIC Council 2018;

Positive review reports by external experts set by the Instruct-ERIC administration on the Instruct Centre Finland application in 2018;

Consultation for the Ministry of Education and Culture in preparation of the governmental documents (U-letter) for the Finnish membership in the Instruct-ERIC. Preparations for membership application have been almost completed in the government.

New web pages and updating of the existing ones;

Pilot scheme for user policies and user access ongoing in UH with the four UH units of Instruct-FI;

Open communication channels to the stakeholders: the MinEdu, the Finnish ESFRI directors, Academy of Finland and the Instruct-ERIC Hub.

We obtained significant new instruments for the network through successful funding from the host universities and the Academy of Finland FIRI2015 and FIRI2016 calls, and Horizon 2020 calls, because Instruct-FI is on the Finnish roadmap for infrastructure.

**Developments and Bottlenecks**

The new transmission electron microscope with a direct electron detector, phase plate and multiple sample holder designed for high resolution cryoEM has now had a full operational year, with 33 projects started. The prices had to be re-calculated as the service costs are in the range of 63 000 € for the minimum contract, more than 3 times the contract on the old machine, and are primarily covered by the user fees. The new instrument provides improved signal-to-noise, greater sensitivity and automated data collection. There has been a significant expansion of the user base and improvement in the data quality, with several users reporting structures going to 3.4 Å resolution and better (manuscripts in preparation). Having only one microscope has caused some bottlenecks as it has not been as reliable as the old one, and we have had significantly more downtime than we expected. We are making better usage of international facilities as the grids can easily be screened and then transferred to Krios microscopes e.g. in Diamond.

The NMR unit currently consists of Bruker NMR spectrometers (600 MHz, 850 MHz and VTT-owned 600 MHz) equipped with cryogenically cooled probes. A new method for determining rotational diffusion of anisotropic proteins has been developed. The metabolite studies have been further developed from insect metabolites to milk metabolites. The lack of a high-throughput sample changer currently limits the number of metabolite samples recorded. A new RT broad-band probe is about to be installed to widen the application of NMR spectrometer to other nuclei, especially fluorine. A new CIDNP device is under construction to enhance the sensitivity of the RT probe.

The crystallization facilities provide advice on protein production and purification, and services in protein characterization, as part of the upstream processing prior to crystallization screening. The centers are critical for national service in providing the crystallization and structure solution services and in coordinating the synchrotron beam time to Diamond Light Source (DLS) (Lehtio, Oulu), ESRF and MAX IV (Kajander, Helsinki). A major effort has been the development and implementation of the Icebear software used for crystal data management, together with the DLS, UK and Weizmann Institute, Israel within the H2020 Instruct-ULTRA project. We have also initiated discussions and tests with Bruker towards implementing the Icebear software for in-house diffractometers. The crystallization units around Finland have actively worked to deploy the same software, so that all users will
benefit from these developments, this has now been implemented in all three centers. A state-of-the-art, in-house diffractometer and detector for data collection and in-situ screening of crystals directly from 96-well plates has been recently installed in Helsinki (Rigaku XtalLab Synergy-S with photon counting detector), and a similar detector setup is planned in Turku to replace a 17-year old imaging plate detector. Renewal of crystal imaging systems is planned currently in Helsinki (imaging instruments are close to end of life time) and Oulu, where the imaging unit needs an upgrade to increase the capacity of the plate hotels. A high-throughput liquid handling all-in-one platform is required in Turku to allow fully robotic crystallization trials. Overall the centers continue to serve the national structural and molecular biology community very successfully, enabling high-end research and high throughput when applicable, while critical instrument upgrades are necessary to maintain and develop these functions.

The current native mass spectrometry research infrastructure consists of two state-of-the-art mass spectrometers. 1) Ultra-high resolution ESI FT-ICR Mass Spectrometer consisting of Bruker Solarix-XR mass spectrometer and 12-Tesla superconducting magnet providing ultra-high mass resolution and sensitivity. 2) A new ion-mobility mass spectrometer Bruker timsTOF (Academy FIFI-funding) was installed in December 2018. This is a major, new, unique instrument in Finland that can separate molecular ions based on their size and shape enabling detection of isomers and even major conformers.

**Biocomplex** is nationally unique core facility which provides services for the purification of large macromolecular complexes for functional and structural studies. The available separation technologies are monolithic anion exchange chromatography, preparative ultracentrifugation, and asymmetrical flow field-flow fractionation (AF4). Biocomplex has successfully served both national and international academic and industrial users in the field of life sciences. The major initiatives during 2018 have been the setting up of transparent user policy, service catalogue, and invoicing system, and service fees for national and international academic as well as industrial users. Invoicing of the users has been implemented since fall 2018. A new preparative ultracentrifugation rotor type with larger volumetric capacity (requested by the users) is now included in the service catalogue. In addition, AF4 service was updated with an autosampler and a preparative separation channel increasing the capacity and enabling high-throughput preparative sample loading. To increase the separation capacity of AF4 and develop new services allowing more efficient separation of macromolecular complexes, a new electrical flow field flow fractionation technology coupled to size-and charge-based separation is our next development project as a new opening. A bottleneck for the maintaining and further development of AF4 service is the renewal of the nine years old instrument. The preparative centrifugation platform (3 high-speed centrifuges, 6 ultracentrifuges, and ~30 rotors) needs frequent updating and the most urgent need is the replacement of obsolete ultracentrifuges. The critical instrument replacements, upgrades, and new openings are essential for maintaining and developing the core facility services and are applied in the FIFI 2019 call.

The **Protein Service** (PS) is the only open access academic provider for recombinant protein production in Finland. PP offers services for academic and industrial partners at the national and international level. Protein expression in several organisms offers suitable system for any recombinant protein that is needed with proper scale-up possibility. The lack of personnel is the main reason that is limiting the projects that could be carried out yearly. Moreover, instrumentation like single-use ReadyToProcess WAVE™ 25 bioreactor system would easy work load by helping with scale-up with both insect and mammalian
cells. PS has already invested to equipment to increase *Escherichia coli* expression volumes (2018) and have got new instrumentation for protein purification (2019), but still instrumentation for throughput should be increased.

**User statistics**

**Participation in International, Nordic and European infrastructures**

Instruct-FI coordinates an effort to join the ESFRI Instruct-ERIC. Instruct-FI interacts also with other EU infrastructure networks like Instruct-ULTRA and iNEXT, and UO is organizing iNEXT training courses in 2019. We coordinate access through block allocation groups to ESRF, the Diamond Light Source, and MAX IV. We also collect data collection at DESY and BESSY. We participate in Finnish (FSRUO) and European (ESUO) synchrotron user organisations to develop synchrotron radiation for scientific research and transnational access. We collaborate with several other international research institutes and networks e.g. the Laboratory for Molecular Infection Medicine Sweden (MIMS) in a joint Swedish Research Council grant (Butcher), CalipsoPlus, EMBL-Hamburg, and European XFEL. We participate in the Nordisk NMR network, organizing NMR courses for students and postdocs. The Protein production core is part of the European vide Protein Production and Purification Partnership in Europe (P4EU). The Structural Bioinformatics Laboratory (ÅAU) is a member in the NordForsk Nordic POP (promoting patented solutions in the pharmaceutical sciences), ELIXIR for computational IT, and have obtained Academy of Finland (FIRI 2018) funding (2019-2022) within the ESFRI EU OPENSCREEN. Importantly, we are part of the 3Dbioinfo community.

Professor Emeritus Rik Wierenga (X-ray crystallography, OU), is a member of the Bessy SSP-college on macromolecular crystallography. Butcher is in the wwPDB Scientific Advisory Council. Wierenga is a project leader in the Horizon2020 Instruct-ULTRA project. The native MS service is a member of EU FT-ICR MS (European Network of Fourier-Transform Ion-Cyclotron-Resonance Mass Spectrometry Centers), H2020 supported project (www.eu-fticr-ms.eu).

ÅAU and UH are members in the CMST COST Action CM1306 Understanding Movement and Mechanism in Molecular Machines (2014-2018). Tiina A. Salminen is a
Management Committee (MC) member of COST Action CM1306 Understanding Movement and Mechanism in Molecular Machines (2014–2018) and a MC member and Short-term Scientific Mission coordinator of COST Action CA17139 EUTOPIA (2019–2022) and Steering group member of 3D-BioInfo Community initiative of ELIXIR (2018–). UO is a member in the COST Action CM15135 Multi-target paradigm for innovative ligand identification in the drug discovery process (MuTaLig) (2016–2020). Instruct-FI has close links to Finnish ESFRI nodes that provide complementary data and services or are dependent on structural cell biology results (ELIXIR, Euro-BioImaging, EATRIS, EU-OPENSCREEN). Butcher is a Work Package leader in the H2020-WIDESPREAD-2018-03 IMpaCT project to bring cryoEM to Portugal, and a project leader in H2020-MCSA-ITN-2017 Vibrant to train PhD students in viral structural biology.

**Future perspectives**

In 2017, the Finnish RI Committee recommended membership of the Instruct-ERIC. The application process is ongoing and coordinated by the MinEdu. On April 25, 2019 the Finnish Government gave the mandate to the Ministry of Education and Culture to submit the membership application to the Instruct-ERIC. The Instruct-ERIC Council will decide on the Membership application in its meeting on May 31, 2019. Selected Instruct-FI structural biology services will be open for users coming through the Instruct-ERIC Access. This strategic move will boost the international research profile of the Instruct-FI platform.

In native mass spectrometry, proteins and other biopolymers are analyzed in their native state, thus enabling MS studies of protein higher-order structures and folding, dynamics, protein-protein and protein-ligand/metal ion interactions providing in many cases unique information. There is now a clear growing interest in utilization of this technology both in academia and industry.

Through Instruct-ULTRA project we have been able to develop IceBear-software, which is used for crystal tracking and transfer of sample information from home laboratories to the synchrotrons. The development is continuing and we have initiated discussions with CSC for hosting the software for all the Instruct-FI structural biology nodes.

The most significant technological advances in the field include stronger in-house X-ray sources, the use of shielded NMR magnets incorporating biosolid technology. Ultra-high field (1.2GHz magnet), new probe design, and dynamic nuclear polarization techniques would enhance the sensitivity by a factor of 2-10000. We anticipate a joint application with Euro-BioImaging for a 300 kV cryoelectron microscope, improvements to data management, data storage and computation improving access and investment in training. Biocomplex is continuously enriching its AF4 service catalogue by including analytical detectors and new separation technologies.

**Major publications supported by the platform services**


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, MED; 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-and-molecular-pathology-unit), IBT and BioCity Turku. Service is charged 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 3.50-40 €/slide. Volume prices for larger series.

2. Access to an online platform for virtual microscopy. The consortium maintains webmicroscopy platforms (fimm.webmicroscope.net, http://jvsmicroscope.uta.fi/?q=virtual_slides. 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.

4. Seven-plex immunofluorescence. During 2018, we included multiplexed immunohistochemical (IHC) tissue staining and imaging into the service pipeline. Now, we have upgraded the system to allow seven-marker detection using fluorescence. This technology is based on the work by group Kallioniemi and led by senior researcher Teijo Pellinen. The original methodology and instrumentation used is described in a recent article (1). The system takes advantage of the high-resolution/high-speed imaging instrumentation, for which we have three different scanners. All the scanners have been updated to include five spectrally different fluorescent channels with filters and a special light source. We have also installed a near-infrared fluorescent channel in the instruments. This allows the use of one extra channel as compared to the conventional default set up. The scanners have different properties, and this is a crucial advantage when dealing with different types of samples (e.g. FFPE whole tissue sections, tissue microarrays, blood smear samples, macro tissue sections). We have gained several new customers especially due to the multiplex imaging capabilities. The feedback has been very positive. The services have not yet included the image analysis, and this needs to be implemented in the pipeline in the near future.

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 several hours per sample, as compared to brightfield histology slides that can be scanned in 3-10 minutes.

Overall situation of the nationwide consortium: Activities in this field has increased substantially and we foresee that a high demand for sample digitization. For whole slide imaging (WSI) the old scanners at IBT were upgraded and a new scanner (Hamamatsu) was purchased. This has increased the use of the scanners.

For example, fluorescence and deep z-stacks has been used for large scale imaging of developmental markers in Drosophila embryos and in detection of organoid morphology and their protein-of-interest disposition. High-throughput capability and reliability has also been proven to be essential for many projects. The use of WSI technologies is expected to grow steadily. The, large generated datasets pose challenge for data management and server infrastructure. These issues need to be resolved.

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**

See table below.

**Participation in international, Nordic and European infrastructures**

The translational technology platform is also used internationally and has strong links to EU level initiatives. For example, the services is advertised through the Biomarker Product Group of the European Advanced Translational Research Infrastructure in Medicine (EATRIS) which is one of the ESFRIs (https://eatris.eu/infrastucture/product-platforms/biomarkers/).

The FIMM part of the platform is a research infrastructure (RIA) of the newly established Helsinki Institute for Life Sciences (HiLIFE) as part of a joint infrastructure entitled Histotechnology and Laboratory Animal Pathology (HiLAPS; https://www.helsinki.fi/en/infrastuctures/histotechnology-and-laboratory-animal-pathology). In the proposal to HiLIFE, it was also suggested how the service could be improved to support HiLIFE even better but so far no additional unit-specific budget in addition to the BF budget has been provided to the RIA 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 2019-20**

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

<table>
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Biocenter Finland – Annual Report 2018
4. Multiplex tissue imaging. Our current set up for fluorescent imaging is seven different channels. This means that seven different markers can be co-stained from the same sample. We are now upgrading the technology to achieve 8-9 marker detection from the same sample. We are in the phase of publishing this upgrade, and we hope to include this novel 8/9-plex system as a service pipeline as soon as possible.

Multiplex imaging generates a lot of digital data, which often needs to be analyzed using computer-aided digital analysis. Thus far the multiplex image analysis has not been part of the service platform. During the year 2019, we will include image analysis services as well. These will include the basic machine vision-based analysis using non-commercial software such as CellProfiler, but also advanced machine learning such as deep convolutional neural networks.

**Major publications supported by the platform services**


**Drug discovery and chemical biology technology platform**

Chair of the platform: Päivi Tammela, 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, HILIFE, Centre for Drug Research (CDR); Olli Kallioniemi, FIMM (co-chair)

**Achievements in development of technology services**

The Drug Discovery and Chemical Biology (DDCB) platform consists of four units located in Helsinki, Kuopio and Turku, providing complementary expertise in various technologies related to chemical biology and early drug discovery. DDCB is also coordinating national participation to the EU-OPENSCREEN ERIC, which was established in April 2018. Two DDCB units are nominated partner sites in the EU-OPENSCREEN ERIC.

With AoF FIRI funding received for 2018, the High Throughput Biomedicine (HTB) Unit at UH-FIMM renewed the dated high throughput screening (HTS) automation platform during the autumn 2018. Our new A-cell system from HighRes Biosolutions is compact, modular and flexible enabling different combinations of hardware for various applications. All the dispensers, reader, plate sealer, plate hotels and centrifuge were transferred from the old system to the new one, and a new plate peeler was included. The system has two dock positions where a device on a cart can be integrated very easily. Any new device can be
put on a similar cart to be docked just as easily. Currently we have four devices on carts: acoustic dispenser for DMSO solutions, acoustic dispenser for aqueous solutions, automated plate hotel and an automated incubator. The new system is capable of similar HTS operations as the old one, and in addition acoustic dispensing and multiple operations can be run in parallel, and it allows improved flexibility in setting up customised screening programmes. The controlling software is naturally more advanced than the old one, allowing dynamic scheduling, more advanced error handling and runtime control.

The “Clinical DSRT” (drug sensitivity and resistance testing) service at the HTB Unit continued being very popular in 2018, and there was a great demand for customized DSRT and combination plates. This was becoming a bottleneck according to received user feedback, so during 2018 we re-organised our operations to direct additional personnel resources for compound management activities. Furthermore, we initiated developing the DRST platform further to integrate high-throughput flow cytometry as a read-out for studying the response of \textit{ex vivo} patient samples. This service is foreseen to be ready in validated format in autumn 2019.

At the UH-PHAR site, several new instruments were purchased 2017 and during 2018, these have been taken into full use. The Cytation 5 imaging plate reader has expanded the unit’s capacity particularly in detection technologies, allowing the use of imaging-based readout in cell-based assays. In 2018, we utilized this instrument in specialized customer projects studying e.g. cellular delivery by liposomes. Our screening unit operates mostly as a self-service unit, providing access to screening instruments, such as plate readers, which are in heavy use (>100 registered users). The LC-MS unit at UH-PHAR had a very active year, and seven projects were completed. These included 15 quantitatively measured compounds (over 6000 injections) and 162 identified compounds from the chemical libraries. Regarding our ability to conduct virtual screens and computational follow-up studies at UH-PHAR, we have continued our data mining and database integration efforts (see \url{http://idaaspm.helsinki.fi/}). We were also developing further our skills to conduct machine-learning based predictive modeling in particular using deep-learning.

The DDCB unit in Turku was reorganised during in 2017-2018 with the establishment of the Turku Screening Unit. This umbrella now offers expertise and facilities provided in laboratories specialising in a large portion of the DDCB mandate, encompassing virtual screening, medicinal chemistry, structural bioinformatics, laboratory automation, screening assays and complex cell-based models. In late 2018, the automation platforms were moved to a new site. User feedback indicated service provision was found to be open, excellent, fast and on budget with expert support. Bottlenecks are limitations to service provision and has come from insufficient automation and integration of devices (obtained FIRI2018 funds partly address this), lack of siRNA libraries that have been requested by potential users, and down-time during repairs of cell-based screening instrumentation.

The DDCB platform initiative, the Finnish Compound Collection, was continued in 2018 by developing further the procedures for collecting compounds from academic groups into this collection. In collaboration with CSC, a data sharing platform was created for storing efficiently data related to the compounds. Similar activities at European level are ongoing within the EU-OPENSSCREEN DRIVE project, and our platform chair, Dr. Tammela, is leading a work package focused on academic compound acquisition into the EU-OPENSSCREEN compound collection. At national level, our aim is to follow the progress made in the EU-OPENSSCREEN initiative to ensure compatibility and synergy with our national activities.
**User statistics**

See table below.

**Participation in International, Nordic and European infrastructures**

The DDCB platform has strong ties to similar research infrastructures in other Nordic and European countries. We are active members in the Nordic Chemical Biology Network (NCBN), which meets annually to discuss activities and joined initiatives in the Nordic platforms. NCBN is organizing the third Nordic Chemical Biology Symposium in Gothenburg in May 2019 (previous symposia have been organized in 2015 and 2017) and the programme includes presentations from all the Nordic screening sites. This shows that collaborative efforts continue and the ties of DDCB to the Nordic Chemical Biology Network are tight. Furthermore, the DDCB partner in Turku is in the steering group of the newly established Nordic High-Content Screening Network.

Our platform is also linked to several European-level initiatives. Most importantly, we are coordinating the national participation to EU-OPENSSCREEN ERIC (www.eu-openscreen.eu), which was founded in April 2018 by seven European countries, including Finland. EU-OPENSSCREEN integrates high-capacity screening platforms throughout Europe, which jointly use a rationally selected compound collection, comprising up to 140,000 commercial and proprietary compounds collected from European chemists. EU-OPENSCREEN operations are starting in 2019, and the DDCB platform is actively involved in planning the operations. Two of the DDCB sites have partner site status in EU-OPENSSCREEN ERIC: The High Throughput Biomedicine Unit at UH-FIMM as a high-capacity screening site and the DDCB unit at the Faculty of Pharmacy, UH, as a specialist screening site. The DDCB unit in Turku received funding from FIRI 2018 call for upgrading facilities to be competitive as an applicant specialised screening site to EU-OPENSCREEN at the next opportunity.

**Future perspectives**

Besides small molecule screening, the HTB Unit at UH-FIMM has been offering functional genomics capabilities in the past. However, our genome-wide siRNA library has become dated and partially depleted over the years. Now we are planning to expand our functional genomics services by establishing CRISPR/Cas9-based services in three main formats. First, a pooled CRISPR/Cas9 library screening format would allow for comprehensive investigation of functional consequences of gene knock-out or activation at a genome-wide scale. This approach will greatly benefit from the high-throughput sequencing capabilities available at FIMM, but somewhat limited by the need for cell selection. The second format is an arrayed CRISPR/Cas9-based screening in multi-well plates. Due to the high reagent costs, this approach would allow for functional profiling of a limited number of genes at a time (up to several 100s) but, in contrast to the pooled approach, would enable microscopic imaging as an assay readout. Third, we plan to offer CRISPR/Cas9-mediated custom gene targeting and generation of isogenic cell line services.

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At UH-PHAR, the screening unit obtained FIRI2018 funding to enhance the capabilities and throughput in antimicrobial screening, which will allow the unit to develop antibacterial profiling services by utilising the in-house collection of bacterial strains (including multidrug resistant strains). Antimicrobial screening is one of the specialties of this unit also as the EU-OPENSCREEN partner site.

The DDCB unit in Turku is aiming to develop fragment-based screening approaches, coupling wet-lab screens with virtual screening and fragment joining techniques. This will be supported by the FIRI2018 funding and is considered highly complementary to the activities of the other DDCB sites and a potential basis for EU-OPENSCREEN participation in the future. Another aim is to further extend the multiplexing of dynamic single-cell signalling assays, combining cell-based screening instrumentation, analysis algorithms and computational facilities, as well as corresponding virally delivered probe panels. This would greatly enhance the power of cell-based screens and target-engagement assays for newly developed chemical biology tools.

**Major publications supported by the platform services**


**Kauko O, O’connor CM, Kulesskiy E, et al.** PP2A inhibition is a druggable MEK inhibitor resistance mechanism in KRAS-mutant lung cancer cells. Sci Transl Med. 2018;10(450)


VIRAL GENE TRANSFER & CELL THERAPY

Coordinator: Seppo Ylä-Herttuala, BCK

Gene transfer is an invaluable tool for studies of gene function, gene regulation and generation of new disease models both in cell cultures and in experimental animals. Viral vectors are currently the most efficient tools to deliver transgenes or constructs that block gene expression in cell cultures and in animal models. Also, stable long-term expression in the host cells can be achieved with integrating vectors. Some cell types, such as iPSCs or progenitor cells are typical targets for ex vivo gene transfer. In the clinics, six gene therapy drugs have been recently approved for clinical use. Thus, it is not surprising that the demand of gene transfer vectors has increased significantly over the last few years.

VGTCT platform has established and developed well-functioning gene transfer and viral vector production services in Finland which can be used by academic researchers and biotech companies with affordable prices. Biocenter Finland support to VGTCT platform has been essential for the maintenance and development of core vector services in all Biocenters.

Viral gene transfer technology platform

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

Partners: Tommi Heikura, BCK; Aki Manninen, BCO, Virus Vector Core Facility; Kari Alitalo, HILIFE, HelVi; Akseli Hemminki, HILIFE, Oncolytic vector core facility; Topi Tervonen, HILIFE, Functional Genomics Unit (FuGu); Eleanor Coffey, BioCity, Viral Vector Facility; Eric Dufour, MET, Virus Vector Facility.

Achievements in development of technology services

BCK core facility in A.I. Virtanen Institute has established new iCellis bioreactors which allow efficient large scale production of lentiviruses and AAV vectors. Upstream and downstream methods have been scaled up so that large quantities of viruses can now be produced yielding up to $10^9$ viral particles per production run. Previously, suspension cell based bioreactors have been established for large scale production of adenoviral vectors. BCK core facility also offers training courses, biosafety training and help in regulatory issues regarding the use of viral vectors and gene transfer technology.

HiLIFE AAV core facility has been renamed to HelVi as part of the reorganization of the operations in Helsinki. HelVi has successfully continued providing AAV vector production services of four serotypes which can be used in cell cultures and in animal experiments. HelVi also produces a number of control AAVs encoding fluorescent proteins (EGFP mCherry) which can be used for cell tracking studies and as control vectors. HelVi also provides consultative help for vector design and the use of AAV vectors. Biocenter Finland funding has been of key importance for the maintenance and development of HelVi services.

HiLIFE functional genomics unit (FuGu) now operates under GoEditStem platform in HiLIFE infrastructure and has provided lentiviral and retroviral production services and distributed mouse and human TRC1 shRNA and CRISPR/Cas9 gRNA libraries for research groups. FuGu has also received University of Helsinki funding for 2018-2020 for their operations. FuGu provides off-the-shelf products, which are recombinant viral particle preparations at two production scales.
FuGu also offers biosafety training, virus titer analysis and biosafety tests to exclude replication competent viruses. Biocity Turku core facility has changed its name to Turku Genome Editing Core to reflect its new range of services which include CRISPR services, shRNA services as well as vector production for cell transductions. Biocenter Oulu has developed siRNA constructs for gene transfer in various vector backbones and has also been involved in lentivirus CRISPR vector design and production. Tampere BioMediTech has specialized for sendaivirus based vector production and also offers facilities for researchers to conduct gene transfer studies ex vivo.

Most significant bottlenecks

Lack of permanent positions for staff is a constant challenge in all viral core facilities. In FuGu yearly personnel funding from University of Helsinki has gone down nearly 20% although the core facility still employs the same number of personnel as in 2017 and has managed to maintain the same level of production capabilities. Also, TRC1 libraries need to be rejuvenated from bacterial glycerol stocks so that FuGu can provide these clones only as DNA mini preps in the future. In Turku a need for a new VIPS all-in-one system for single cell cloning has emerged and funding is currently searched for this equipment.

BCK test runs of the next generation solid phase bioreactors are ongoing and there is a need to upgrade equipment in the next 1-2 years. Funding is currently searched for the new bioreactor equipment. Utilizing lentiviral genome-wide gene editing resources as coherent services has provided to be challenging and very time consuming.

Development of the technology services

In general, VGTCT is a well-performing platform to offer vector services with clearly developed profiles and expertise in each core facility. Virus core facilities also offer biosafety training, reagents for recombinant virus production, virus titer analysis and biosafety tests to exclude replication competent virus as well as maintains BSL2 cell culture space for researchers to work with their recombinant viral vectors and transduced cells. We have noticed that increased marketing of VGTCT infra would make these valuable services better known to local and national scientists.

User feedbacks from VGTCT services have been very favorable underscoring the fast and reliable service and useful consultative help. So far, the production of recombinant viral vectors did not require any additional high-cost or specific equipment. All necessary equipment and reagents are currently available. However, as indicated above, there is a need to upgrade bioreactors and some other key equipment in the next 1-2 years. The cost of consumables has been covered by the collected fees for selling of the viral preps to the customers.

User statistics

See table below.
Participation in international, Nordic and European infrastructures

BCK core facility is an integral part of EU EATRIS research infrastructure for large scale vector production in EU. Core facility also participates in three EU Horizon2020 consortia as the place for vector production. AAV core facility and FuGu in Helsinki participate in several EU funded consortia. A.I. Virtanen core facility and AAV core facility are also parts of Transatlantic Leducq Foundation Research Consortia.

Future perspectives

VGTCT estimates that there is a continuous increased need for viral vector production services in Finland and elsewhere with affordable prices. It has been brought to our attention from several sources that commercial companies providing similar services do not have production slots available but only after 1-2 years waiting time. This type of delays will be very harmful for top level research programs and therefore VGTCT will fulfill a significant unmet need for viral gene transfer vectors and related technologies. With current funding we will continue to arrange educations courses organized by member biocenter universities as part of their doctoral training programs. New vectors and serotypes will be taken to the production schedules as they appear in published literature and when available with reasonable licensing terms.

Upgrade of equipment in VGTCT network will be needed in BCK and Turku Genome Editing Core since bioreactor technology and cloning systems continuously develop to become more cost-effective. Also, obtaining standardized reference materials for viral vectors will become important in the future. Further interactions with platforms like stem cell technologies and drug development are foreseen. With the recent approvals of clinical products based on viral vectors a need to get involved into translational and preclinical services in imminent.

Major publications supported by the platform services


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*FuGU and HelVi combined


Downes NL, Laham-karam N, Kaikkonen MU, Ylä-herttuala S. Differential but Complementary HIF1\( \alpha \) and HIF2\( \alpha \) Transcriptional Regulation. Mol Ther. 2018;26(7):1735-1745.

NEW PLATFORMS

Single-cell omics technology platform

Chair: Pirkko Mattila, FIMM-HiLIFE, UH

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

Achievements in development of technology services

2018 was the second year single cell operations were included in Biocenter Finland technology platforms. The basic activities of the Single-Cell omics (SC omics) platform on droplet based assays including single cell RNA sequencing, single cell proteomics and single cell bioinformatics services are now well established in UH and at Turku Bioscience (UTU and ÅA) with increasing user base.

Sc omics integrates and complements the existing national research infrastructures. Especially, sc omics network is very closely collaborating with sequencing infrastructure (GWM) to provide seamless NGS services downstream to single cell capturing and sequencing library preparation. Single cell omics infrastructure has had a great benefit on the newly funded high capacity state-of-the-art sequencing instrument, NovaSeq 6000 allowing cost effective sequencing also for sc omics platform.

The mass cytometer at Turku Bioscience have been highly appreciated for immune profiling applications and diagnostics. We have analysed samples for basic research and clinical trials. Two workshops have been organised with invited speakers and protocols for sample preparation optimized by core staff. For mass cytometry, we initiated use of SPADE and viSNE softwares for analysis and visualisation of multidimensional data and training is offered to users so that they can perform data analysis themselves. After a pilot phase the full service was launched in 2018.

Development of instrumentation

To further strengthen single cell services sc omics platform has invested in two new instruments to enable single cell capture and analysis for various downstream applications (microscopy, sc-proteomics, sc-genomics) on plate based assays. The new services based on these instruments are applicable for low cell amounts when droplet -based systems cannot be used. Both equipments listed below are located at Meilahti campus (FIMM).

CellenONE by Scenion (FIRI2015 funding)
- capturing of one single cell per one well of any type of plate
- applicable for NGS, sc proteomics, HT screenings etc.

Mosquito HV by TTP Biotech (FIRI2015 funding)
- liquid handler for analyses downstream to cell capture
- miniaturization of single cell RNA-seq method on plate format to provide cheaper assays for samples with low cell counts

In addition to purchasing above mentioned new instruments we have used FIRI 2015 funding also to upgrade disk space for single cell data storage.

Implementation of new assays

In 2018 sc omics platform has successfully implemented several new methodologies to service portfolio:

1. New droplet based single cell sequencing techniques
   - CITE-seq for simultaneous epitope and transcriptome measurement in single
cells (also enabling sample multiplexing and increased cell throughput)
- ATAC-seq to study chromatin accessibility
- immune profiling services for T-cell and B-cell receptors
- single cell CNV analysis

2. New slide based single cell sequencing techniques
   - Portable sc-RNA-seq assays for SeqWell
3. New 96/384 plate format protocols
   - Index sorting methods for FACS sorted single cells
     (in house modified 3’ tagging method)
4. Single cell methods currently under development
   - piloting and optimizing methods for single cell DNA methylation analysis
   - development of workflows so that fixed cells instead for living cells could be used for SC RNA-seq

Overall, in 2018 the user base has been growing and often we are not able to serve our customers in reasonable time due to long queues. It is already evident that since we are working with living cells it is extremely important to start processing the cells immediately when they come to the lab to ensure best results. This makes tight scheduling necessary, presenting challenges in some cases, e.g. when analyzing newborn mice or clinical samples from hospital. Currently, the successful completion of certain experiments has relied on the availability of independently funded postdocs and operational and administrative support from Genome-wide methods platform, which is not a sustainable solution long-term. Budgeting sufficient resources for personnel to run the first steps of single cell workflow would increase the capacity.

For mass cytometry, the instruments have been under warranty up till now and no instrument service costs have been included in user fees. AH Diagnostics charges for annual service package is 48k€. It will require that current service fees of 70€ per hour will be tripled in order to cover this very high cost.

For Polaris instrument (system allowing to choose environmental condition for single cells for up to 24 hours and to measure each cell’s acute response transcriptionally via next generation sequencing) service cost are ca. 38 k€ which cannot be covered by the user fees in 2019.

**User statistic**

See table below.

**Participation in international, Nordic And European infrastructures**

SC omics infrastructure collaborates and interacts with large national and international networks. Especially, collaboration with CSC, the scientific computing center in Finland, has been active. CSC has installed single cell omics infrastructure collaborates and interacts with large national and international networks. Especially, collaboration with CSC, the scientific computing center in Finland, has been active. CSC has installed single cell...
analysis tools to the user-friendly Chipster NGS analysis platform freely available for academic researchers. CSC also organizes R courses regularly in collaboration with sc omics platform. Through collaboration with CSC, sc omics platform is also linked with ELIXIR, the European life-sciences infrastructure for biological information.

**Future perspectives**

We expect the single cell research field to grow further with increasing demand for new services. Single cell technologies will be developing fast with emerging novel equipments. For these reasons the network is constantly monitoring for emergence of next-generation single cell analysis instruments. Recently, there has been rapid growth of demand for **spatial transcriptomics**, i.e. the analysis of gene expression in relation to tissue architecture. The single cell genomics services currently provided by single-cell omics platform are based on capturing and analyzing cells in single cell suspension, which is optimal for blood cells but represents a compromise for solid tissue samples. When solid tissues are dissociated into single cell suspension the spatial information i.e. the knowledge of the neighbouring cells is lost. For this reason with the FIRI2019 funding application we will apply resources to set up services for spatial transcriptomics. There is an urgent need for instrumentation that allow high throughput measurements of RNA from samples that preserve spatial architecture. Single cell technologies are developing fast and there are already a couple of upcoming cutting edge technologies for spatial transcriptomics expected to be mature enough for core lab use by the end of 2019.

**Major publications supported by the platform services**


**Genome editing**

Chair of the platform: Juha Klefström, HiLIFE, UH

Partners: Jukka Westermarck & Johanna Ivaska, Centre for Biotechnology, UTU & ÅAU; Pipsa Saharinen, HiLIFE, UH; Emmy Verschuren, FIMM-HiLIFE, Petri Mäkinen, A.I. Virtanen Institute for Molecular Sciences, UEF.

**Achievements in development of technology services**

Finnish genome editing center (FinGEEC) is a new platform to facilitate capture and development of novel genome editing technologies to generate knockout and sequence-specific gene expression control systems in cell lines, patient-derived cells & tissue models, and in ES cells/fertilized oocytes for rapid generation of genetically engineered rodents. FinGEEC integrate, provide support and spread the use of genome editing activities across Finnish biocenters. FinGEEC captures the latest genome editing technologies and via establishment of better infrastructures and services (see Fig.1) aims to lower the bar for research groups to access new disruptive technology in genetic analysis.
FinGEEC Strategy: HiLIFE (Helsinki): FinGEEC platform coordination and development, genomic resources, & services. Coordination via TEDM with other FinGEEC nodes in Helsinki, Turku, Kuopio and Oulu Biocenters.

FinGEEC-HiLIFE has taken major efforts to build synergy within HiLIFE through GoEditStem platform. The platform currently organizes biweekly meetings with FinGEEC, Biomedicum Stem Cell Center (BSCC), Genome Biology Unit (GBU) and Helsinki Virus Services (HelVi). These actions have generated synergy across related technologies and also new core facility marketing potential, joint CRISPR and stem cell courses for graduate school curriculum and general inspiration among the platform participants. Younger PI’s have had opportunities to strengthen their independent profile. FinGEEC-HiLIFE has also collaborated with Helsinki Laboratory Animal Center to establish CRISPR-mediated mouse knockout platform, the pilot projects serving four different research groups. Parallel to these efforts, the network has established LAGO imaging in collaboration with HiLIFE in vivo imaging unit to support imaging of KO mouse phenotypes.

FinGEEC - Kuopio has focused on flow cytometric analysis of gene edited cells. Sorting of CRISPR/Cas9-modified cells into 96-well plates for single cell analysis has consolidated its role. In addition, during 2018, technically demanding plate sorting option to 384-well plate has been successfully established. Moreover, incorporation of violet laser has increased the multicolor sorting possibilities. 2017 acquired Beckman Coulter S flow analyzer serves now large user population. Also, Amnis Flowsight Imaging Flow Cytometer had been set up for advanced imaging analysis. Two new cytometers have been acquired to AIV-Institute at 2017 (Amnis Flowsight Imaging Flow Cytometer and Beckman Coulter Cytoflex S analyzer). Also, a new violet laser was installed to FACSAria III sorter. New machinery has increased and widened the capabilities to use flow cytometry. When more and more research is focusing on single cell level, flow cytometry offers a valid tool for creating single-cell samples with high purity and sensitivity. Flow cytometry has been used together with various researchers and research groups studying cardiovascular disease, neurosciences and exosome research. Also, non-academic collaboration has been done. Funding has supported in part the possibility to organize specialized flow cytometry course to increase the knowledge and usage of Flow Cytometry.
**User statistics**

See table.

**Participation in international, Nordic and European infrastructures**

The FinGEEC Turku has been in close contact with the EuBI (Euro-Bioimaging) European Infra initiative. The European Hub and a national EuBI node are in Turku and Ivaska has been involved in planning how the FinGEEC services are optimally integrated into the imaging pipe-lines developed at Turku as part of the starting EuBI functions.

**Future perspectives**

The network synergy will be improved especially since different biocenters have clearly focused areas in genome editing research. Locally, Helsinki plans to deepen cooperation with Helsinki and other national Laboratory Animal Centers to spread the use of CRISPR KO’s. Alternatively, these services could be provided in a centralized fashion from Helsinki. These options will be discussed. Furthermore, co-developing & testing of CRISPR-mediated gene activation systems together with BSCC is currently evolving process. The third anticipated development includes development of CRISPR applications for genetic analysis of patient-derived organoids. This initiative is closely related to other similar initiatives with similar goals, for example, iCAN Flagship in Helsinki. In flow cytometry, the future plans include strengthening Amnis FlowSight image analysis capabilities. Also, more complex sorting protocols will be carried out with emphasis on single cell sorting. In Turku, the efforts include deepening collaboration with the Turku Centre for Disease modelling in applying lentivirally transduced and genome edited cell lines in mouse xenografts. Co-developing and testing endogenously tagging (CRISPR-mediated genome editing to tag endogenous proteins with fluorescent imaging tags like GFP) in different cell types, including human induced pluripotent stem cells and cancer cells. Co-developing and testing zebra fish embryo xenografts of genome edited cells for live-cell microscopy and drug screening (in collaboration with the new, currently not BF funded zebra-fish core facility at Turku Centre for Biotechnology).

**Major publications supported by the platform services**


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**Liquid biopsies technology platform**

Chair of the platform: Tapio Visakorpi

**Development of technology services**

Liquid biopsy platform is a new emerging service. Two main assay are developed in the platform 1) detection and analysis of circulating tumor cells (CTC), and 2) detection and analysis of circulating tumor DNA (ctDNA). In 2018, the platform set-up and validated qRT-PCR based assay detection of prostate cancer derived CTCs. The assay is based on Fluidigm qPCR technology. In addition, an equipment to enrich CTCs, Parsortix system, was purchased. Currently, testing of the system (sensitivity, specificity etc) is ongoing. For downstream analysis of the enriched CTCs, Droplet Digital™ PCR (ddPCR™) system as well as 10x Genomics Platform for single-cell sequencing were purchased.

In terms of the ctDNA analysis a method to detect mutations and copy number changes in 76 prostate cancer specific genes was developed. The genes in the panel fall into several pathways and categories, such as hormonal signaling, DNA repair (BRACAness), PI3K pathway, WNT pathway and cell cycle. To improve the accuracy of computational analysis, designed custom unique molecular identifiers (UMIs) that are compatible with sequencing library construction workflow (SeqCap EZ HyperCap, Roche) were utilized. The panel has also been tested in ovarian cancer to identify BRACAness mutations.

The key part of the ctDNA assays is the data analysis. It has actively been developed with the Bioinformatics platform of BF.

**Future perspectives**

The ctDNA BRACAness/Prostate cancer panel is now ready to be used. The platform can develop other panels for ctDNA analysis upon needs. The main weakness of current ctDNA analyses is poor sensitivity. Current methods cannot detect ctDNA, for example in oligometastatic disease. Thus, methods to increase the sensitivity of the assay will be tested. Also, assays for DNA methylation will be set-up. Current technologies to enrich CTCs are in general poor. Thus, testing and developing new tools for CTC analyses will also continue.

**Major publications supported by the platform services**

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