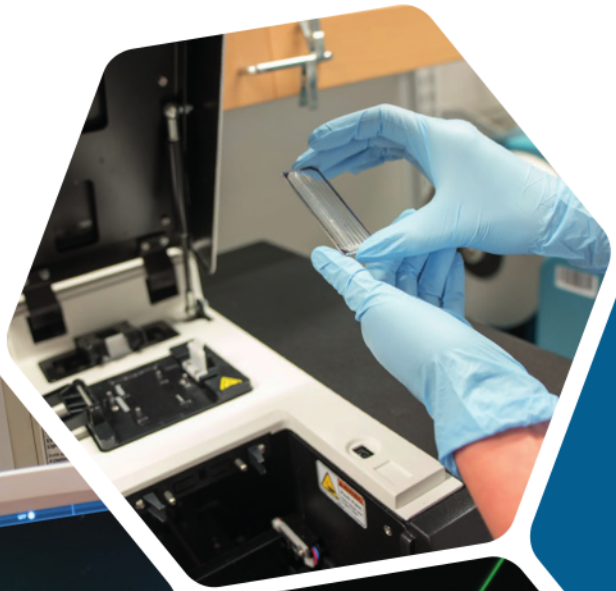
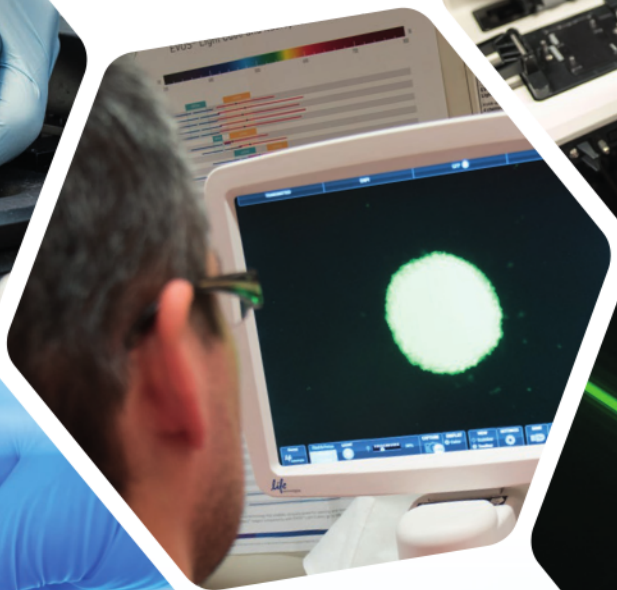
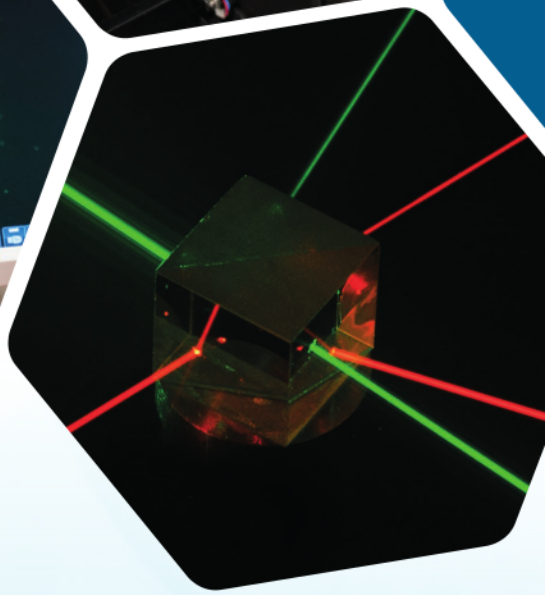
Biocenter Finland

Annual Report 2019







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Biocenter Finland Annual Report 2019

Editor: Antti Siltanen

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

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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 the Finnish community of some 17,000 researchers working in universities, research institutes and companies. BF operates as a nation-wide network of research infrastructures operating in the five Biocenters of the country. It is hosted by University of Eastern Finland, University of Helsinki, University of Oulu, Tampere University, University of Turku and Åbo Akademi University. BF's task is coordination of nationally important RIs for collaboration, division of responsibilities and joint investments.

BF consisted in 2019 of twelve Technology Platforms: 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. Each Platform is composed of 1-5 complementary Nodes operating in different Biocenters. BF evolves constantly due to the Platforms' four-year mandate, subject to renewal based on the assessment of BF's Scientific Advisory Board, according to their ability to support and renew frontier research, national significance, volume of user base and results of user survey. In 2019 the BF Platforms and other RIs prepared their applications for BF's Scientific Advisory Board, scheduled to meet in January 2020 to recommend to the Board the composition of BF's Platform portfolio for the next four years.

BF ensures resources for investments into state-of-the-art equipment mainly from the research infrastructure calls of the Academy of Finland – the Finnish Research Council. The platforms' key personnel's salaries and the Coordination Office are financed by the host universities. In 2019 BF was awarded the full amount requested, 2,7 M€, from the Academy of Finland's FIRI Call. The host universities funded key personnel's salaries with 5,79 M€, and the user fees amounted to 9,83 M€.

BF works in 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 of the opportunities the pan-European infrastructures offer and exchange of information on latest technological advances, as well as to avoid redundant investments in equipment. BF promotes the use of core facilities, collaboration opportunities and funding that the European Molecular Biology Laboratory EMBL and the European Molecular Biology Conference EMBC offer. In November 2019 BF organized with Nature a Master Class on scientific writing for the BF community's PhD candidates and post-docs.

BF features as a major national infrastructure in the Finnish Research Infrastructure Roadmap 2014-2020, and was placed in the most advanced category in the Roadmap's mid-term evaluation in 2018.

Professor Marja Makarow

Director of Biocenter Finland

STATISTICS

Usage

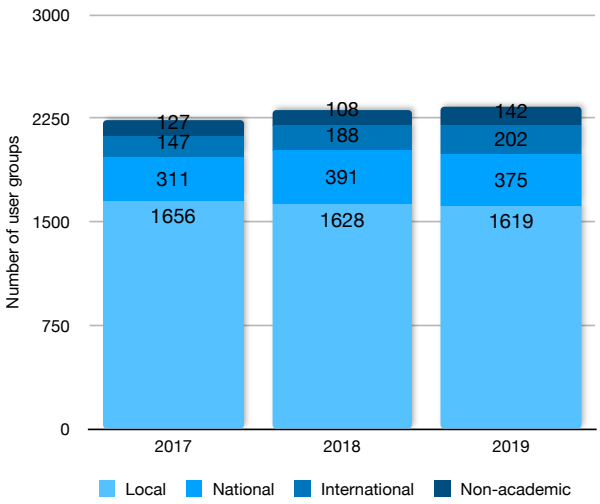


Figure 1. Number of research groups and non-academic customers using BF technology platform services. Total number of user groups in 2019 was 2338.

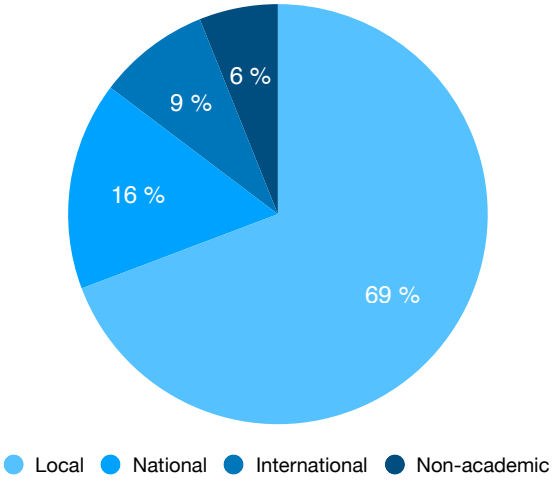


Figure 2. Percent breakdown of user groups into local, national, international, and non-academic users.

Funding

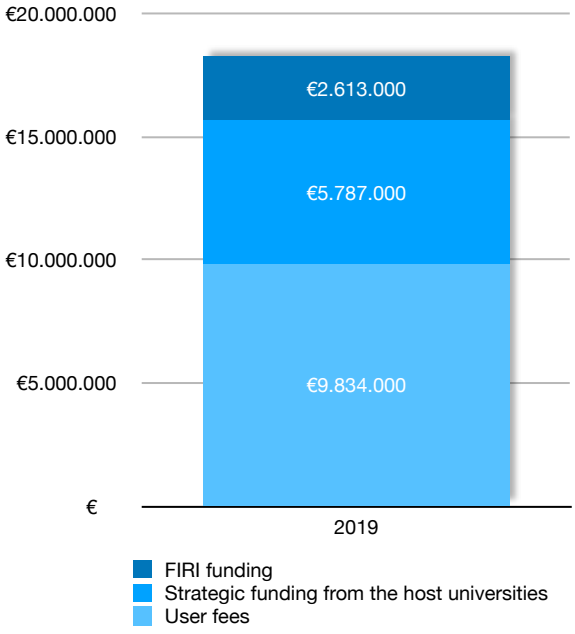


Figure 3. Strategic funding from the host universities for the platform personnel's salary costs was 5,8M€. The platforms collected 9,8M€ of user fees that was used for further salary expenses and small equipment investments. Total Academy of Finland's FIRI funding for instrument investments including host university contributions was 2,6M€.

SCIENTIFIC IMPACT AND SUCCESS STORIES

Bioinformatics

Academician Sirpa Jalkanen discovered a previously undefined role for medullary lymphatic endothelial cells in human immunity. Her findings were facilitated by the BF Genomic-wide methods and BF Bioinformatics Platforms and provide valuable new information with potential to help improving human health and prevent diseases. (Takeda et al. Single-Cell Survey of Human Lymphatics Unveils Marked Endothelial Cell Heterogeneity and Mechanisms of Homing for Neutrophils. Immunity 51(3):561-572.e5, 2019.

Professor Mika Rämet discovered a new molecular component of the signaling network that promotes spontaneous preterm birth, the leading cause of neonatal death and morbidity worldwide. His finding was facilitated by the support provided by the BF Genome-wide methods and BF Bioinformatics Platforms. (Tiensuu et al. Risk of spontaneous preterm birth and fetal growth associates with fetal SLIT2. PLoS Genetics 15(6):e1008107, 2019.

Professor Anna-Liisa Levonen discovered a non-classical activation mechanism in the lethal brain cancer, glioma, providing a rationale to target the Nrf2-regulatory pathway in a subset of patients. The implications of this study on cancer diagnostics are in promoting the wider adoption of multi-omics characterization of patient samples, as the mechanism for oncogenic activity would have been missed by DNA mutation data alone. Data analyses were facilitated by the BF Bioinformatics Platform. (Pölönen et al. Nrf2 and SQSTM1/p62 jointly contribute to mesenchymal transition and invasion in glioblastoma. Oncogene 38(50):7473-7490, 2019.

Electron microscopy

UEF-EM participated in a few studies related to pharmaceuticals and drug development. Hellinen et al. published a study in Scientific Reports using ARPE-19 cells internalized with melanosomes to study drug uptake. Melanin pigment has a significant role in ocular pharmacokinetics, because many drugs bind at high extent to melanin in the retinal pigment epithelial cells. *Hellinen L, Hagström M, Knuutila H, Ruponen M, Urtti A, Reinisalo M. Characterization of artificially re-pigmented ARPE-19 retinal pigment epithelial cell model. Sci Rep. 2019 Sep 24;9(1):13761. doi: 10.1038/s41598-019-50324-8.*

Light microscopy

As imaging is very critical in life science research, the platform has continued to have a central role in several scientific breakthroughs and in solving significant research problems. Some concrete examples:

- Modern laser scanning confocal microscopy at CIC-TBI played a crucial role in Academician Sirpa Jalkanen's research to reveal the structures of lymphatic tissues, unveiling previously undefined functions in human immunity (Single-Cell Survey of Human Lymphatics Unveils Marked Endothelial Cell Heterogeneity and Mechanisms of Homing for Neutrophils. Takeda A. et al. 2019. Immunity, 51: 561-572.)
- FIMM-HCA developed a new software tool for image registration and quantification in spatial tissue analysis, successfully used to analyse oncogenic signalling in lung cancer. (Spa-RQ: An Image Analysis Tool to Visualise and Quantify Spatial Phenotypes Applied to Non-Small Cell Lung Cancer. Bao et al. 2019. Sci Rep, 9: 17613.)
- Several microscopes from BIU-LM, including superresolution imaging, were central in Prof. Elina Ikonen's group's work in developing an improved version of a powerful tool to study protein function.

This work benefits scientists from all domains of cell biological research. (An efficient auxin-inducible degron system with low basal degradation in human cells. Li et al. 2019. Nat Methods, 16: 866-869.)

- The lab of Ari-Pekka Mähönen utilized LMU-BI microscopes to study how plant growth originates, confirming a significant classical theory of plant growth (Sanio 1873). (High levels of auxin signalling define the stem-cell organizer of the vascular cambium. Smetana et al. 2019. Nature, 565: 485-489.)
- A wide range of advanced imaging tools at TIC-BCO played a crucial role in a project where the role of collagen XIII protein in bone remodelling and osteoporosis was characterized. (Collagen XIII-derived ectodomain regulates bone angiogenesis and intracortical remodeling. Koivunen et al. 2019. Matrix Biol, 83: 6-25.)

Small animal molecular imaging SPECT/CT

Demonstration of light-induced release of a cargo from nanoparticles was probably the most impressive research achievement of 2019 in the RTI unit. At the laboratories of Arto Urtti (Division of Pharmaceutical Biosciences, UH) and Dr Tatu Lajunen (Tokyo University) researchers have developed special nanoparticles engineered to deliver the cargo when they are shined with near infrared light. This smart nanodevice makes a drug accessible at the place it is needed, avoiding its dissemination throughout the body and the unwanted side effects most drugs have. This would increase considerably the amount of drug administered, since the dose will not be lost systemically. The nanoparticles were loaded with [^{99m}Tc]HMPAO and administered subcutaneously. Upon NIR irradiation, the nanoparticles disintegrate and the radioactive contents are released resulting in excretion of the radioactivity in urine. Additionally, the RTI unit conducted the **evaluation of two novel drug delivery system scaffolds based on nanocrystalline cellulose and triple-PEGylated PSi** using ^{111}In SPECT with high impact especially for the former to a dual radio- and chemotherapeutic theranostic construct for B-Raf mutated metastatic melanoma (*studies ongoing*).

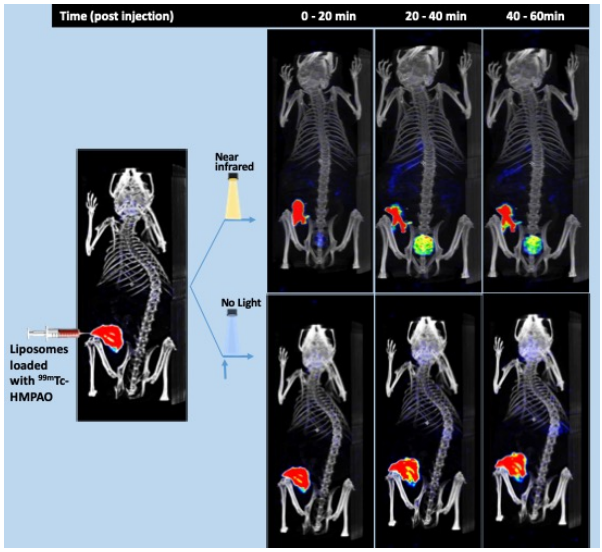


Fig 1. Time resolved SPECT/CT images of cargo (^{99m}Tc-HMPAO) release and distribution from NIR light sensitive liposomes in mice. Shown are representative images of two mice, after radiotracer loaded liposomes injection, and near infrared laser shone to one mice (top panel) but not the other (no light, bottom panel) at the area of injection. Around 4 MBq of ^{99m}Tc-hexamethyl-propyleneamine oxime (HMPAO), were injected in around 10-20 µl of saline. A total of 36 X SPECT images (every 10° from 360°) were recorded during the following 0 to 20, 20 to 40 and 40 to 60 min after injection. Shown are the SPECT signal average during the recording time in each image. The before light SOECT image is a reconstruction of the first 4 (orthogonal) projections (2-4 min) of the "no light" experiment, superimposed to the same CT anatomical reconstruction recorded at the time 120 min after injection. Control free tracer administrated mice showed similar pattern than top images but at slower kinetics (not

Genome-wide methods

A breakthrough study by Prof Sirpa Jalkanen and collaborators examines the role of lymphatic vessels with focus on lymphatic endothelial cells (LEC). The group profiled 33 000 cells and identified 6 LEC subtypes. The study provides comprehensive characterization of LEC heterogeneity and reveals a previously undefined role for medullary LECs in human immunity with implications to cancer metastasis. This study was a cross-platform collaboration between GWM, Single-Cell Omics and Bioinformatics platforms, with GWM providing expertise for

library preparation and next-generation sequencing service for single cell RNA sequencing. *(Takeda A et al. Single-Cell Survey of Human Lymphatics Unveils Marked Endothelial Cell Heterogeneity and Mechanisms of Homing for Neutrophils. Immunity. 2019 Sep 17;51(3):561-572).*

Mouse models

Altogether, several hundred scientists benefit from the FinGMice services in Finland annually. Importantly, the rodent models are essential tools to many of the leading Finnish medical and biomedical research groups led by Academians, Academy professors, and professors at Centres of Excellence of Academy of Finland.

GRACILE syndrome is a severe neonatal metabolic disease of the Finnish disease heritage caused by a point mutation in the nuclear *BCS1L* gene. A mouse model that recapitulates human GRACILE syndrome has been extensively studied in Kallijärvi-Fellman research group at the Folkhälsan Research Center and the University of Helsinki with the help of national and international mouse phenotyping services. Their recent study on GRACILE mouse model, published in the journal Nature Communications, further facilitates the development of diagnostic, prognostic and therapeutic strategies for patients suffering this devastating lethal metabolic disease in neonates and provides a new tool for studies of mitochondrial diseases.

Purhonen J, Grigorjev V, Ekiert R, Aho N, Rajendran J, Pietras R, Truvé K, Wikström M, Sharma V, Osyczka A, Fellman V, Kallijärvi J A Spontaneous Mitonuclear Epistasis Converging on Rieske Fe-S Protein Exacerbates Complex III Deficiency in Mice. Nat Commun. 2020 Jan 16;11(1):322.

Non-mammalian model organisms

In 2019, the group of Osamu Shimmi (Institute of Biotechnology, Helsinki) published a landmark paper in PNAS, describing a major discovery in the field of morphogenesis. Using ModOrgNon's *Drosophila* services, the group demonstrated how changes in tissue shape in 3D affect signaling by morphogens, diffusible substances which establish the specific fates of different cell-types during development, in a gradient fashion. Morphogens not only affect tissue shape, but there is also a feedback mechanism from the 3D architecture to the morphogen gradient itself.

Protein-proteome

CCAAT enhancer–binding protein epsilon (C/EBPε) is a transcription factor involved in late myeloid lineage differentiation and cellular function. The aim of this study was to molecularly characterize the effects of C/EBPε transcription factor Arg219His mutation identified in a Finnish family with previously genetically uncharacterized autoinflammatory and immunodeficiency syndrome. Genetic analysis, proteomics, genome-wide transcriptional profiling by means of RNA-sequencing, chromatin immunoprecipitation (ChIP) sequencing, and assessment of the inflammasome function of primary macrophages were performed. We describe a novel autoinflammatory disease with defective neutrophil function caused by a homozygous Arg219His mutation in the transcription factor C/EBPε. Mutated C/EBPε acts as a regulator of both the inflammasome and interferome, and the Arg219His mutation causes the first human monogenic neomorphic and noncanonical inflammasomopathy/ immunodeficiency. The mechanism, including widely dysregulated transcription, is likely not unique for C/EBPε. Similar multiomics approaches should also be used in studying other transcription factor–associated diseases.

*Göös H, Fogarty CL, Sahu B, Plagnol V, Rajamäki K, Nurmi K, Liu X, Einarsdottir E, Jouppila A, Pettersson T, Vihinen H, Krjutskov K, Saavalainen P, Järvinen A, Muurinen M, Greco D, Scala G, Curtis J, Nordström D, Flaumenhaft R, Vaarala O, Kovanen PE, Keskitalo S, Ranki A, Kere J, Lehto M, Notarangelo LD, Nejentsev S, Eklund KK, Varjosalo *, Taipale J, Seppänen MRJ. J Allergy Clin Immunol. 2019*

Metabolomics

FIMM-Meta has increased its local and international academic and clinical collaborations, and the Unit had 23 projects started or ongoing during 2019. One local academic project with Prof. Anu Wartiovaara (Suomalainen) from University of Helsinki and another one with Prof. Del Chiaro from Karolinska Institute were both published in the high impact journal Scientific Reports, FIMM PI as co-author. The targeted 100 metabolite method (method published 2018 by Velagapudi) was successfully used in both articles. In addition, targeted SCIEX lipidyzer 1000 lipid was combined with the 100 metabolite method to create integrated metabolomics and lipidomics approach.

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

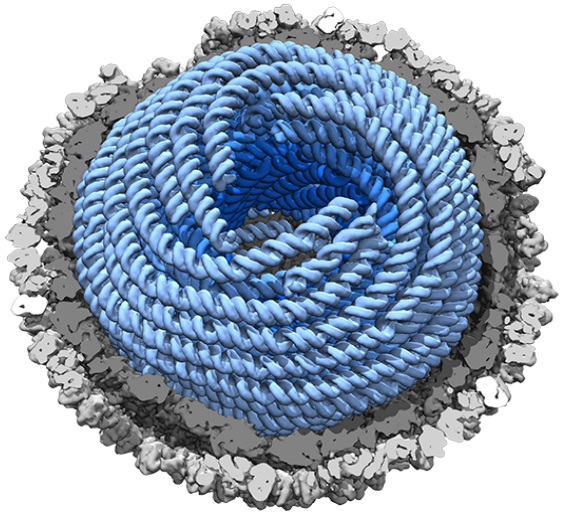
The work at BCK has continued on metabolomics applications for food, health, toxicology, and nutrition studies. The specific topics include the effects of environmental pollutants and alcohol on the offspring or on nutrition effects of nutrition in disease. BCK has been involved in 48 projects in the above-mentioned areas of research. In year 2019 BCK had analyzed over 42,000 samples (20,676 and 22,134 samples in HRMS and QQQ instruments, respectively) involved in these projects. These research results will be and are published in highly reputed international journals. A major deal of the publications is used in PhD theses. BCK was involved in 16 peer-reviewed scientific publications; as a co-author, where analytical services were provided by the unit.

Stem cells

In 2019 Stem cell platform partners published 33 new research results/technologies related to the iPSC and genome editing for genetic, pharmacology, artificial intelligence, and biomedical research. A concrete example of a solved research problem or a scientific breakthrough provided by each partner of the stem cell consortium is presented below.

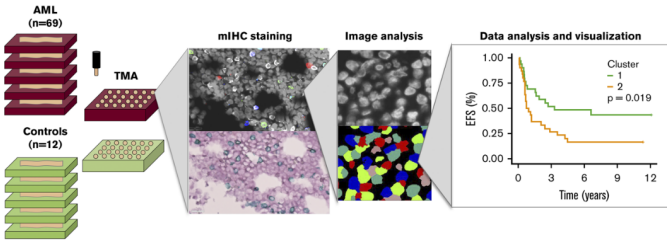
HiLIFE: PMID: 31676859; 31161346; 30728358; 30270471. These publications highlight the advantage of using iPSC derived beta cells and genome editing for modeling pancreatic b-cell pathology and CRISPR activators technology to study cancer.

TAU PMID: 30837492, 31208058, 32079026, 31375001, 31163704. These publications highlight the use of iPS cells to study genetic regulators of hepatic differentiation, epigenetic memory of stem cell derived cells, and heart failure. The important technology



development relates to the machine learning and organ-on-culture studies and their potential application in stem cell research.

BCK PMID: 31522977; 31477693; 31455857, 31016348, 30453390. Differentiation of hiPSC lines into fully functional brain microglia, astrocytes, cortical neurons, and endothelial cells that maintain disease pathology and can be used for transcriptomics, proteomics, and metabolomics analyses with a low number of lines. The studies also demonstrate the advantage of using iPSC-



derived cells of monozygotic twins discordant for a disease for the first time.

Structural biology

Double-stranded (ds) RNA viruses infect a range of hosts, including animals, plants, fungi, and bacteria. Several members of this viral group, such as rotavirus, blue tongue virus, and rice dwarf virus, are associated with deadly and economically damaging diseases. Detailed structural information on these viruses and their assembly intermediates promotes development of antiviral therapies against dsRNA viruses and contributes to the mechanistic understanding of their basic functions.

A collaboration between scientists of Biocomplex unit and Instruct-ERIC Centre UK (joint efforts of sample preparation and cryoEM) has yielded a new structure of the dsRNA bacteriophage phi6 (Cystoviridae family). The genome inside the viral capsid was deciphered in unprecedented detail revealing the double-helical, supercoiled dsRNA spooled in five layers with different liquid-crystalline packing geometries. The highly condensed genome is enclosed in double-shelled protein capsid (depicted in 3.5 Å resolution) comprised of 200 trimers of the other-shell protein and 60 asymmetric dimers of the inner-shell protein.

Figure. Highly condensed dsRNA genome within a viral capsid (Figure: Juha Huiskonen).

In addition to the unique dsRNA genome arrangement, the structure revealed that the phi6 RNA-dependent RNA polymerases responsible for viral RNA replication, detach from the inner capsid shell while the capsid expands during genome packaging and replication. Such information may be exploited in novel gene therapies.

Biobanking technologies

Bruck and others (2020) analysed thirty immunomarkers using multiplexed immunohistochemistry (mIHC) and computerized image analysis at single cell level. Quantitative immunophenotyping distinguished different classes of leukemia (AML, CML, B-ALL) but also revealed distinct prognostic subgroups (Fig 1). Especially, a higher proportion of T regulatory cells (Tregs) predicted inferior survival of patients with acute myeloid leukemia (AML). The results suggest a rationale for including immunologic parameters to improve disease classification and patient risk stratification in AML.

Figure. Flow diagram of the study on multiplexed immunophenotyping combined with image analysis for classification of patients with leukemia

Drug discovery and chemical biology

As a part of long-lasting collaboration between BCK-PCM and University of North-Carolina at Chapel Hill, a systematic study to develop new and specific kinase inhibitors against selected kinases has continued. As an example of results, we were able to develop quantitative structure-activity relationship models and further optimized a series of very selective GAK/SLK/STK10 kinase inhibitors. Some of the key points have been recently published. (1)

Another recent example of BCK-PMC services identification and optimization of CK2 kinase inhibitors together with Prof. Joachmi Jose and his group at University of Münster. A natural ligand, Bikaverin, was identified via virtual screening (using a publicly available ZINC database and CSC taito supercomputer) and this hit compound has now been used as a starting point for a more systematic CK2 inhibitor development project. (2)

Viral gene transfer and cell therapy

VGTCT virus core laboratories have been involved in 180 publications in 2017-2019, many of which have been published in top level peer reviewed journals. Thus, the overall scientific impact of the technologies provided by the VGTCT Virus Core laboratories is very significant.

As examples of the scientific impact, Biocenter Kuopio Virus Core laboratory in A.I.Virtanen Institute has established bioreactor based lentivirus production, which allows generation of highly reproducible homogenous functional viruses for in vitro and in vivo preclinical work.

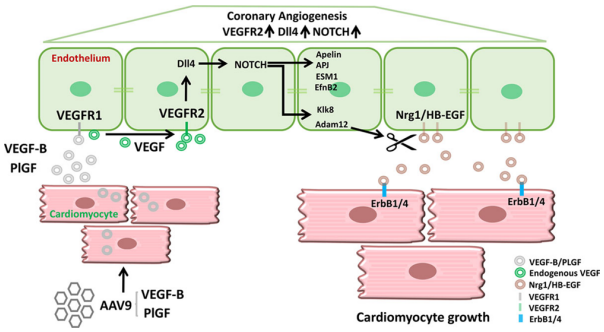


Figure: Example of the use of VGTCT vectors in solving pathophysiological problems (Kivelä et al, 2019).

Oulu Virus Core laboratory has generated novel gene knock-in/knockout technologies in human organoid models which brings patients closer to the laboratory than ever before. Viral vector tools make these approaches feasible to a large group of researchers.

Genome editing

A knockout mouse model was generated to investigate the role of oncogenic transmembrane serine protease hepsin that is commonly overexpressed in breast cancer. GE platform provided in vitro transcribed mRNA based on mouse genome-wide CRISPR/Cas9 gRNA library hosted by Genome editing platform. The hepsin KO mouse model was initiated and housed by Model Organisms platform of BF and F0 generation mice were analyzed by Genome editing platform for gene inactivating mutations. Founder male mouse with 50 bp deletion in the hepsin coding region was used to generate hepsin KO mouse strain. This mouse strain was then crossed with a mouse strain that naturally gives rise to mammary tumors. Remarkable, this new strain where hepsin was knocked out showed decreased in tumorigenesis. Subsequent analyses have shown that this effect involves novel previously undiscovered functions of hepsin oncogene and could facilitate discoveries of new therapeutic interventions targeting hepsin and downstream pathways.

Single cell omics

The last couple of years have seen groundbreaking advances of single cell technologies. Single cell analyses have allowed exploring complexity of tissues at highest resolution, description of development in tissues and organs, identification of cell types that contribute to human diseases, identification of unique cell types for organisms and studying organ evolution. Concrete examples are finding and analyzing rare circulating tumor cells (CTCs) from patients´ blood or studying drug resistant cell populations in cancer patients.

Biocenter Finland sc-omics platform is still a relatively novel infrastructure but it has already been realized that the impact of single cell technologies for Finnish science is going to be huge. In many levels of biomedical research from basic research to personalized medicine single cell analysis methods will be a very important feature of the entire palette of approaches used. This is also reflected in the diversity of user base that the sc omics platform already has.

HOST UNIVERSITIES, MEMBER INSTITUTES AND FACULTY

Host universities and member institutes

BF is a distributed national research infrastructure that in 2019 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, 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 Health Technology replaced BioMediTech as the member institute from the beginning of 2017.

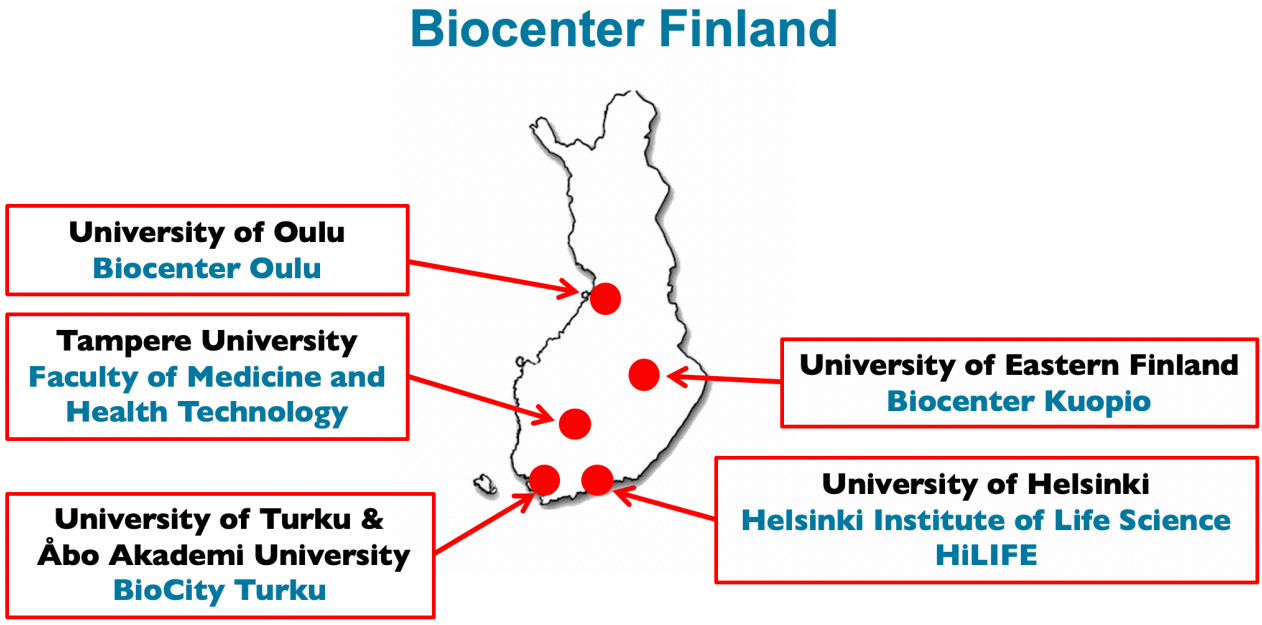


Figure 6. The host universities and their BF member institutes in 2019.

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.

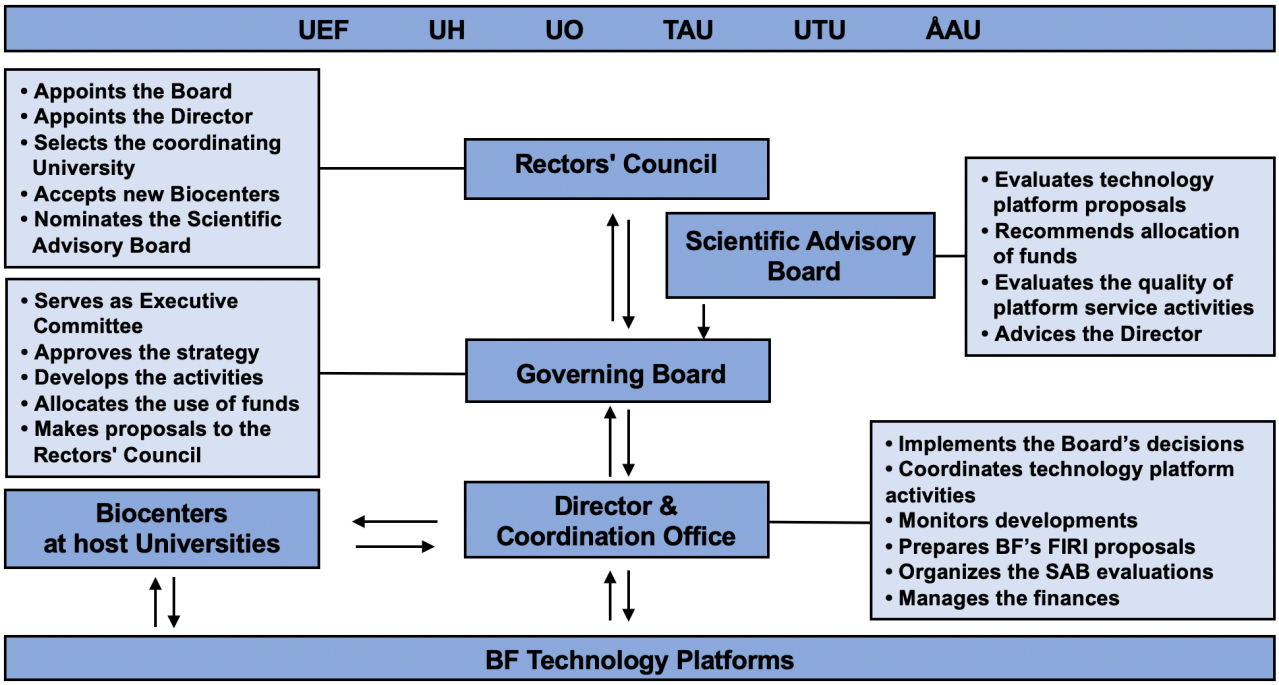


Figure 7. The governance and organization of Biocenter Finland.

Governing board

The BF Governing Board in 2019 was Professor Tapio Visakorpi Chair, TAU, Academy Professor Seppo Ylä-Herttuala Vice Chair, UEF, Professor Lauri Eklund, UO, John Eriksson, ÅA and Professor Jyrki Heino, UTU, Professor Tomi Mäkelä, UH, Professor Olli Silvennoinen, UH, and Prof Mark Daly, UH.

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. A new BF Scientific Advisory Board was nominated in 2019:

Chair: **Professor Carl-Henrik Heldin**, Department of Medical Biochemistry and Microbiology, Uppsala University, Sweden. Chair of the board of the Nobel Foundation and SciLifeLab.

Professor **Frits Thorsen**, Department of Biomedicine, University of Bergen, Norway.

Jussi Helppi Head of Biomedical Services, Max Planck Institute of Molecular, Cell Biology and Genetics, Dresden Germany.

Monica Morales, PhD, Head of Core Facilities, Center of Genomic Regulation, Barcelona, Spain.

Professor **Janne Lehtiö** Department of Oncology-pathology, Karolinska Institute, Sweden. Scientific Director of SciLifeLab

Marjolein Thunnissen, PhD, senior lecturer, Lund University, Life Science Director at MAX IV

Professor **Søren Brunak**, Research director, Novo Nordisk Foundation Center for Protein Research, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

TECHNOLOGY PLATFORMS

The BF technology services are organized by the technology platforms. Each platform is composed of distributed national nodes with complementary expertise and is managed by a board composed of the heads of the nodes and a platform chair (Fig 8).

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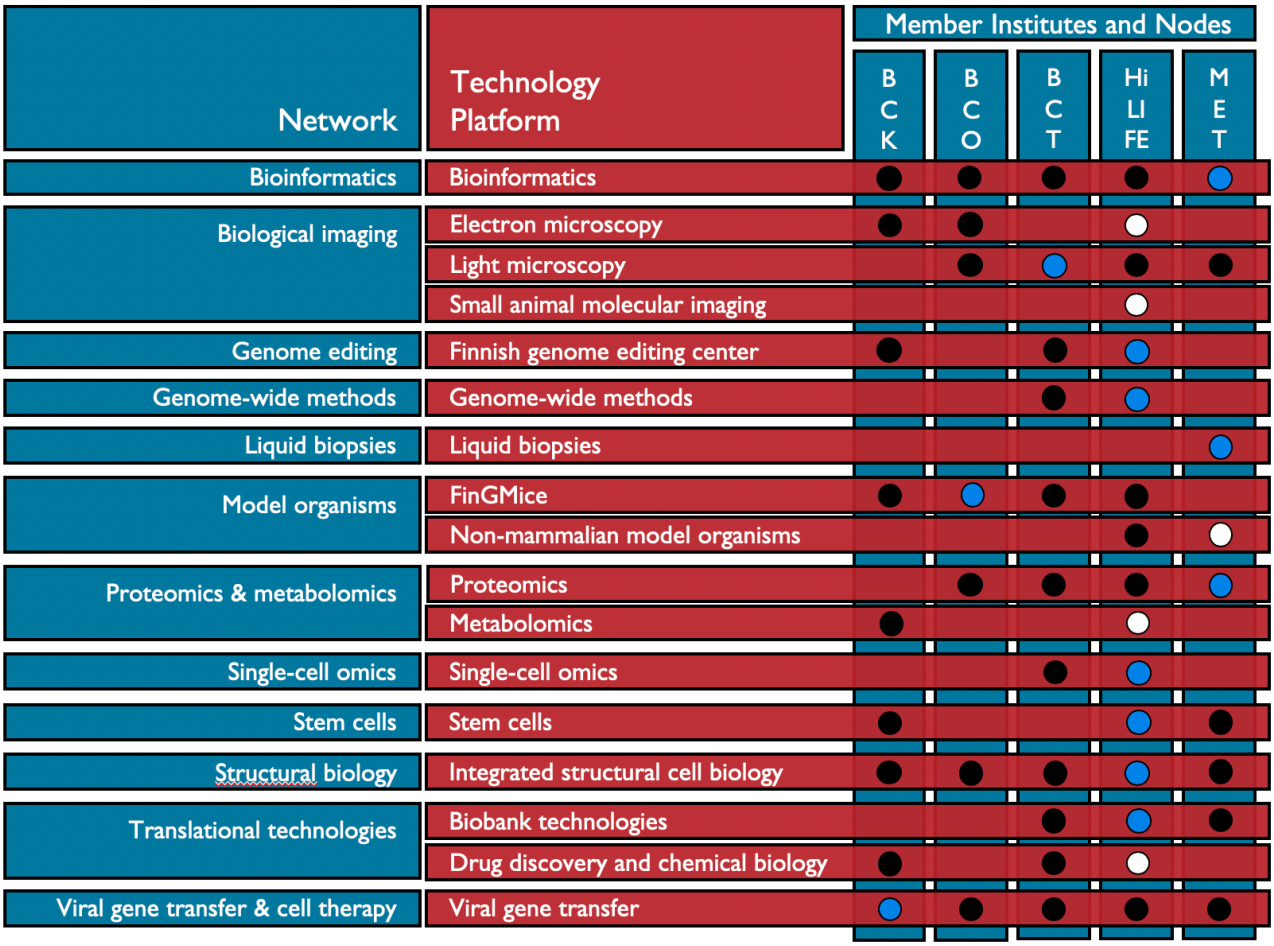

Figure 8. The BF scientific networks, technology platforms and local nodes hosted by the member institutes. The dots indicate in which member institute the nodes are located. Blue dots: network chairmanship, white dots: platform chairmanship. BCK, Biocenter Kuopio (UEF); BCO, Biocenter Oulu (UO); BCT, BioCity Turku (UTU and ÅAU); HiLIFE, Helsinki Institute of Life Science (UH); MET, Faculty of Medicine and Health Technology (TAU).

BIOINFORMATICS

Chair of the platform: Laura Elo, BCT

Node PIs: Matti Nykter, MET; Jussi Paananen, BCK; André Juffer, BCO; Mark Johnson, BioCity; Esa Pitkänen, FIMM-HiLIFE; Liisa Holm, BI-HiLIFE

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

http://bioinformatics.biocenter.fi/

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

Development of technology services

The BF Bioinformatics Platform offers top-level expertise for the analysis of various omics and imaging data and data integration. In addition, the Platform provides support for bioinformatics tools and data management, as well as training and consultation. Nationwide support is provided for both basic and advanced data analysis

While the BF Bioinformatics Platform provides several routine support services, advanced custom-tailored data analysis support has become the most required support type. This is likely due to the decreasing costs of data generation, which has led to increasingly large and complex data sets. At the same time, the measurement technologies are in rapid development, which constantly requires establishment of new data analysis pipelines and workflows. To support the application of new emerging technologies, the development of support services has been started for single-cell data analysis and high content imaging.

Computational infrastructure has been developed to support high-throughput protein sequence analysis and to enable the analysis of hundreds of bacterial genomes and dozens of eukaryotic transcriptomes per day.

Additionally, the role of scientific IT support provided by the BF Bioinformatics Platform has been increasing and it is widely used also by the other BF Platforms that need local expertise in their data management, storage and computing. To address the needs, collaboration with CSC and ELIXIR has been tightened. Changes in the EU privacy regulations and advances in biotechnology that can lead to personal identification from biomolecular data have caused the handling of sensitive data to become an important question, creating further support needs in the form of expert advice and technical assistance.

Due to the very limited funding targeted for the operations of the BF Bioinformatics Platform,

it has been difficult to develop or expand the provided support service portfolio or meet the level of demand which has been increasing rapidly. In 2019 the total annual BF strategic host university funding for the BF Bioinformatics Platform nodes was ~283kEUR, covering the salary of less than one bioinformatician per node. The lack of funding has severely slowed down the planned developments and hindered the nodes from recruiting permanent support staff. Hence, PhD students have remained in a considerable role in carrying out the support tasks on a part-time basis. As pointed out already by the BF SAB in 2016, this limits the possibilities of building long-term competences and makes the support vulnerable to constantly changing personnel. The latest SAB evaluation performed in spring 2020 also further highlighted the urgent need to substantially increase the funding of the BF Bioinformatics platform in order to serve the scientific community in its great need of additional bioinformatics support.

In order to generate a more solid basis for the developments, several nodes have restructured their services to build more sustainable support models. In particular, user fee-based cost-recovery has been revised, established or is underway in most nodes. However, this cannot compensate for the lack of appropriate host institution funding without making the support unaffordable to a wide community of academic researchers.

While there is a clear imbalance between the demand and the resources available, those users that have received support from the BF Bioinformatics Platform report a high user satisfaction (average score 4.87 out of 5).

User statistics

See table below.

Participation in international, Nordic and European infrastructures

In 2019, the BF Bioinformatics Platform collaborated with or participated in the following international, European and Nordic infrastructures:

- EU-OPENSCREEN: The BF Bioinformatics Platform provides IT support (hardware and software) and input on in silico screening in collaboration with EU-OPENSCREEN, which is a European high-capacity screening network integrating platforms throughout Europe. FIMM, UH, UTU and ÅAU obtained FIRI infrastructure funding supporting the EU-OPENSCREEN ESFRI.
- Instruct-ERIC: BF Bioinformatics Platform is represented in Instruct-ERIC and provides IT expertise and hardware/software support within the network, with the aim to make high-end technologies and methods in structural biology available to all European researchers.

ELIXIR: BF Bioinformatics Platform operates in coordination with ELIXIR/CSC to facilitate efficient utilization of the available

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	inter-national	non-academic	Total
UEF	BCK	Bioinformatics center	29	1	-	-	30
UH	HiLIFE/FIMM	FIMM NGS Unit	31	16	1	3	51
UH	HiLIFE/BI	Viikki campus bioinformatics infrastructure	1	7	1191	83	1282
UO	BCO	Biocomputing	8	1	2	-	13
UTA	BMT	Bioinformatics Facility	7	-	1	-	8
ÅAU	BCT/ÅAU	Structural Bioinformatics Laboratory	25	3	5	-	33
UTU	BCT/UTU	Medical Bioinformatics Centre	19	38	1	-	58
	Total		120	66	1201	86	1475

computational and storage resources available through ELIXIR. The European ELIXIR infrastructure brings together life science resources across Europe, including databases, software tools, training materials, cloud storage, and supercomputers. In addition to heavy utilization of the available computing resources (especially storage and supercomputers), several BF Bioinformatics Platform nodes provide scientific IT support to researchers and other BF Platforms to utilize these resources.

Future perspectives

The BF Bioinformatics Platform aims to continue providing high-level data analysis support, covering the different areas of bioinformatics:

- Transcriptomics
- Genomics
- Epigenomics
- Proteomics
- Metabolomics
- Metagenomics, metatranscriptomics and metaproteomics
- Structural bioinformatics
- Liquid biopsy data analysis
- Screening data analysis
- Imaging related to biomedical research
- Data integration
- Clinical applications
- In silico modeling and simulation of biological systems
- Development of data analysis support for new omics technologies

In addition, scientific IT and infrastructure support is provided to researchers and other BF platforms including for example:

- Data management support (needs especially regarding sensitive data and Open Science)
- Support for accessing and using CSC's services, including computational resources, ePouta Virtual Private Cloud system for the integration of virtual machines and storage resources through local servers/networks, and bioinformatics applications and platforms
- Development and maintenance of web servers
- Implementation of bioinformatics algorithms
- Pipeline development

The Platform also provides consultation and training for research related to the various support areas.

In 2020 the BF strategic host university funding for the BF Bioinformatics Platform remains very limited (covering the salary of less than one bioinformatician per node) and, therefore, the main focus is in attempting to maintain the current level of support. User-fee based cost-recovery system will be further developed to help secure the existing support services in the future in a more sustainable manner. However, very significant increase in the basic funding will be required in the future in order to narrow the gap between the demand and the resources available and build a truly sustainable national bioinformatics infrastructure in Finland.

As the other BF Platforms actively test and set up new high-throughput technologies, the development of new data analysis pipelines and support services to support them is crucial to ensure the access of the research community to these new technologies. Currently there is a foreseeable need to develop new support services especially for single-cell, imaging, and liquid biopsy data. For structural biology research, new pipelines and services are required for the modeling of proteins and membrane systems and for the quality assessment based on database searches.

To enable easy sharing of standardized pipelines across labs, institutions, and biocenters, new Docker container technologies will be important to take into use in the

development and distribution of state-of-the-art bioinformatics pipelines. Additionally, the BF Bioinformatics Platform aims to support training activities of life science researchers to increasingly enable researchers to carry out standardized data analysis tasks also by themselves.

Sensitive data handling is a theme that will need increasingly more support and resources in the future to fulfil the needs of the research community. Training of the researchers on sensitive data management is planned to be developed together with NordForsk Nordic POP.

Plans to further develop the operation of the Platform include, for example, harmonization of the policies and principles of the support and services provided by the Platform nodes. We aim to ensure equal access for researchers across Finland to our support and clearly defined criteria for prioritizing the projects on the basis of feasibility, resources, and scientific excellence. To enable efficient utilization of the BF Bioinformatics Platform, easy-to-find local contact points are needed in all of the BF host universities. It is seen that the local node coordinators will be instrumental for guiding the users to the right level of support and helping to optimally shape the Finnish bioinformatics support in terms of user satisfaction and resource usage.

Major publications supported by the platform services

Takeda A, et al. Single-Cell Survey of Human Lymphatics Unveils Marked Endothelial Cell Heterogeneity and Mechanisms of Homing for Neutrophils. Immunity 2019;51(3):561-572.e5.

Tiensuu H, et al. Risk of spontaneous preterm birth and fetal growth associates with fetal SLIT2. PLoS Genet 2019;15(6):e1008107.

Nykänen AI, et al. Donor Simvastatin Treatment in Heart Transplantation. Circulation 2019;140(8):627-40.

Hanif T, et al. Birch pollen allergen immunotherapy reprograms nasal epithelial transcriptome and recovers microbial diversity. J Allergy Clin Immunol 2019;143(6):2293-2296.e11.

Kuivanen S, et al. Detection of novel tick-borne pathogen, Alongshan virus, in Ixodes ricinus ticks, south-eastern Finland, 2019. Euro Surveill 2019;24(27):< Pagination Error >.

Tan WH, et al. Transcriptomics of monarch butterflies (Danaus plexippus) reveals that toxic host plants alter expression of detoxification genes and down-regulate a small number of immune genes. Mol Ecol 2019;28(22):4845-63.

Pölönen P, et al. Nrf2 and SQSTM1/p62 jointly contribute to mesenchymal transition and invasion in glioblastoma. Oncogene 2019;38(50):7473-90.

Gubina N, et al. Essential Physiological Differences Characterize Short- and Long-Lived Strains of Drosophila melanogaster. J Gerontol A Biol Sci Med Sci 2019;74(12):1835-43.

Lopes de Carvalho L, et al. Evolution and functional classification of mammalian copper amine oxidases. Mol Phylogenet Evol 2019;139:106571.

Mirza MU, et al. In silico structural elucidation of RNA-dependent RNA polymerase towards the identification of potential Crimean-Congo Hemorrhagic Fever Virus inhibitors. Sci Rep 2019;9(1):6809.

BIOLOGICAL IMAGING

2019 was very successful for the platform and to Finnish Bioimaging, as Euro-BioImaging was established by the European Commission as an ERIC (European Research Infrastructure Consortium), with preparations headed by CIC-TBI. During 2019, The Finnish Advanced Light Microscopy Euro-BioImaging Node (FIALM; CIC-TBI, TIC-BCO, BIU-LM and LMU-BI) also received several international Euro-BioImaging users and continued as one of the most popular Nodes in Euro-BioImaging. Overall in 2019, the Light microscopy platform served a high number of national and international users, in total close to 900, coming from over 300 research groups.

Many of the platform core facilities faced similar bottlenecks: lack of resources for image analysis slowing down the use of gained image data, and insufficient instrument resources to meet the image acquisition needs. BMT, LMU-BI and CIC-TBI continued experiencing long ques to confocal microscopes. A general challenge is to utilize limited infrastructure funding to maintain both the basic and the state-of-the-art technologies remains.

As user surveys have highlighted image analysis as a significant bottleneck, training in bioimage informatics has been increased by many units. LMU-BI, BIU-LM, FIMM-HCA and EMBI are extending pre-existing courses, and CIC-TBI has organized an increasing number of one-off courses in collaboration with FIALM.

At CIC-TBI, new instrument reservation and facility management software Open IRIS was implemented in collaboration with the University of Helsinki in 2019.

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

Development of technology services

Imaging technologies have high impact in biomedical research as they allow researchers to visualize, characterize and analyse molecular and cellular functions at high temporal and spatial resolution. The Electron Microscopy Technology Platform consists of three nodes with complementary expertise, each providing services in basic and specific advanced technique. The Helsinki node (BI-EM) focuses on 3D imaging of cells and tissues, correlative light and electron microscopy (CLEM) and image analysis, the Oulu node (BCO-EM) specializes in ultrastructural pathology of human and model organisms and the University of Eastern Finland node (UEF-EM) develops non-destructive imaging techniques to study elemental and chemical composition of biological specimens. For basic EM techniques, each node provides services on specimen preparation in transmission and scanning EM (TEM and SEM) and access to the instruments mainly to local users.

Units have implemented common open-access policies and cost-recovery pricing across three universities of Helsinki, Oulu and Eastern Finland. 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. Our application specialists support users in all steps of their projects, starting from project planning all the way to the image analysis. Training and education are realized in one-on-one contact teaching by core facility personnel; consultation to all microscopy imaging related aspects, from sample preparation to data acquisition and image analysis; and in the form of symposia and courses for graduate and post-graduate students. During 2019, we had 285 users from 167 research groups. About 25% of research groups came outside respective host universities. Combined, Biocenter Finland allocations covered salaries for 50 person

months during 2019, which is 35% of the total 12 FTE. 57% of the personnel are technical staff and 43% researchers (BF funding share 30% and 41%, respectively).

During 2019, our platform was successful in developing its spearhead technologies correlative light electron microscopy and 3D-EM further. To increase the capacity for the correlative light electron microscopy workflow, BI-EM acquired a 120 kV TEM Hitachi HR7800 with a Gatan Rio 9 CMOS camera and several smaller instruments: wide field fluorescent microscope with phase contrast, stereomicroscope with camera, camera for ultramicrotome, Ultra sonic knife with a control unit and CompuStage single-tilt holder for TEM. To increase the capacity for 3D-EM projects, BCO-EM upgraded the UC7 ultramicrotome with ARTOS 3D automated serial sectioning system and SEM with ATLAS 5 hardware and software package for array tomography setup. As part of Biocenter Finland instrument application in FIRI2019 call, BI-EM was granted funding for a focused ion beam scanning electron microscope (FIB-SEM) to bridge the gap between existing 3D-EM options in respect to both volume and resolution, and to increase the capacity. The new FIB-SEM system will open up the technology to new specimen types because of the higher contrast and smaller voxel size gained by the high vacuum system.

User statistics

See table below.

Participation in international, Nordic and European infrastructures

The major international partner for the platform is Euro-BioImaging, which is a pan-European research infrastructure for imaging technologies in biological and medical sciences on the ESFRI Roadmap. The mission of Euro-BioImaging is to create a coordinated plan for organization, utilization, and implementation of advanced biomedical imaging technologies in Europe. During 2019, the Euro-BioImaging ERIC was officially established by the European Commission and the infrastructure launched its full operation. Within the Finnish multimodal Advanced Light Microscopy Node, BI-EM is a partner in Helsinki BioImaging sub-node, and provides several immuno-EM methods, CLEM, two 3D-EM techniques and image analysis. BCO-EM as part of the Oulu Bioimaging network (OBI) forms a mesoscopic imaging platform together with imaging laboratories from Faculty of Technology (Optoelectronics and Machine Vision), Center of Microscopy and Nanotechnology, Institute of Biomedicine and Diagnostics and Biocenter Oulu Tissue Imaging Center and provides morphological and ultrastructural expertize using immunolabelling and FIB-SEM. All sub-nodes are additionally linked together by activities aimed at facilitating image processing, visualization and open-source software production for image analysis. 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. Within UEF, there is close collaboration with Cell and Tissue Imaging unit (light microscopy) and with Biomedical Imaging unit (BIU, in vivo imaging). BIU takes part in e.g. ESFRI network.

BI-EM participates in BIIF, BioImage Informatics Finland, which is a network for bioimage analysts, software developers and

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	inter-national	non-academic	Total
UEF	BCK		24	2	3	2	31
UH	HiLIFE	BI-EM	79	16	6	1	102
UO	BCO	BCO EM Core	27	6	3	0	36
	Total		130	24	12	3	169

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 addition, Finland is a member country in COMULIS (Correlated Multimodal Imaging in Life Sciences), which is an EU-funded COST Action CA 17121. It aims at fueling urgently needed collaborations in the field of correlated multimodal imaging, promoting and disseminating its benefits through showcase pipelines, and paving the way for its technological advancement and implementation as a versatile tool in biological and preclinical research. Eija Jokitalo is a representative of Finland in the Management committee of COMULIS.

Future perspectives

The National imaging infrastructure network has recently undergone major restructuring, as the BF Light microscopy and BF Electron microscopy platforms were merged into a new Biocenter Finland Biological Imaging Infrastructure. Open access services to state-of-the-art equipment and expertise in light microscopy, electron microscopy, high content imaging, mesoscopic imaging and image analysis will be provided to local and national users in a coordinated manner by five BioImaging Nodes: Helsinki, Turku, Oulu, Tampere and Eastern Finland BioImaging. Each Node provides different combinations of services and expertise for distinct applications and methods. Nationally coordinated interaction and collaboration between the Nodes facilitates the best use of limited national resources, both in terms of available instrument funding and expert support personnel as well as foster better integration and synergy between light and electron microscopy communities. To improve communication between the Nodes, and engage core personnel and their expertise in platform operation, the platform will distribute coordination of specific development and management tasks into smaller working groups, which will be chaired by Node PIs or senior staff members across the platform.

BF funding has played a crucial role in enabling Finland to offer the services that most Finnish life scientists require in their research and to rise to the international top in both light and electron microscopy. However, the instrumentation in this field is undergoing very fast development, and without constant instrument and other related investments, there is a substantial risk of quickly falling behind. At the same time, the lifespan of advanced microscopes and their technical support by vendors has become shorter, with numerous new technological innovations becoming available faster. Hence, there are three main scenarios, where BF BioImaging will need significant resources in the near future for instrumentation: 1) renewal of heavily used but aging instruments (e.g. basic confocal and transmission electron microscopes), 2) increased capacity for high-end technologies that have become more common-place (e.g. super-resolution and 3D-EM techniques), and 3) new spearhead technologies that enable previously unforeseen research.

In addition to microscopes, image data analysis and management have recently become a critical area of both LM and EM infrastructure. First, the amount of image data produced by modern instruments is growing exponentially, requiring dedicated solutions so that it can be stored and converted to meaningful scientific information. Second, modern developments in image analysis algorithms, software tools and deep learning enable much more information to be extracted from image data than before. Third, it is increasingly required by e.g. funders and scientific journals that image data and analysis results are available online for re-use by the scientific community. Because of these developments, the scientific community largely sees data management and image analysis becoming one of the most important "instruments" in bioimaging during the next few years. To respond to this need, BF BioImaging will require resources for relevant software and hardware, for instance for data

management and analysis of particularly large files.

Major publications supported by the platform services

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Koivunen J, et al. Collagen XIII-derived ectodomain regulates bone angiogenesis and intracortical remodeling. Matrix Biol 2019;83:6-25.

Danilova T, et al. MANF Is Required for the Postnatal Expansion and Maintenance of Pancreatic β-Cell Mass in Mice. Diabetes 2019;68(1):66-80.

Yan D, et al. Sphingolipid biosynthesis modulates plasmodesmal ultrastructure and phloem unloading. Nat Plants 2019;5(6):604-15.

Salo VT, et al. Seipin Facilitates Triglyceride Flow to Lipid Droplet and Counteracts Droplet Ripening via Endoplasmic Reticulum Contact. Dev Cell 2019;50(4):478-493.e9.

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Hellinen L, et al. Characterization of artificially re-pigmented ARPE-19 retinal pigment epithelial cell model. Sci Rep 2019;9(1):13761.

Arasu UT, et al. Correlative light and electron microscopy is a powerful tool to study interactions of extracellular vesicles with recipient cells. Exp Cell Res 2019;376(2):149-58.

Minkeviciene R, et al. MIM-Deficient Mice Exhibit Anatomical Changes in Dendritic Spines, Cortex Volume and Brain Ventricles, and Functional Changes in Motor Coordination and Learning. Front Mol Neurosci 2019;12:276.

Kozlova N, et al. The Pro-Oncogenic Adaptor CIN85 Acts as an Inhibitory Binding Partner of Hypoxia-Inducible Factor Prolyl Hydroxylase 2. Cancer Res 2019;79(16):4042-56.

Light microscopy technology platform

Chair of the platform: John Eriksson, Turku Bioimaging

Partners: Cell Imaging Core (CIC), Eleanor Coffey and Turku Bioimaging (TBI), John Eriksson, BioCity Turku; Biomedicum Imaging Unit (BIU-LM), Elina Ikonen, HILIFE; Light microscopy unit (LMU-BI), Maria Vartiainen, BI-HiLIFE; High Content Imaging and Analysis at the Institute for Molecular Medicine Finland (FIMM-HCA), Peter Horvath/Vilja Pietiäinen, FIMM-HiLIFE; Tissue Imaging Center, Lauri Eklund, BCO; Institute of Biomedical Technology at the University of Tampere (BMT), Susanna Narkilahti, MET.

Development of technology services

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bioimage informatics has been increased by many units. LMU-BI, BIU-LM, FIMM-HCA and EMBI are extending pre-existing courses, and CIC-TBI has organized an increasing number of one-off courses in collaboration with FIALM.

At CIC-TBI, new instrument reservation and facility management software Open IRIS was implemented in collaboration with the University of Helsinki in 2019.

Widefield and confocal microscopy

LMU-BI: Leica SP8 Upright to meet the urgent demand in confocal imaging. In addition, the GE Deltavision Ultra wide-field microscope for live imaging, with built-in deconvolution, was taken into use.

BIU-LM: Andor Dragonfly 500 spinning-disc confocal microscope, with SRRF-Stream for super-resolution and Borealis for uniform illumination, to answer the growing demand for fast live-cell or large area confocal imaging.

TIC-BCO: Leica SP8 FALCON confocal system for flexible multipurpose usage from cellular studies to organotypic cultures and material sciences. In-built FLIM added a new modality to imaging tools.

BMT obtained funding in the university infrastructure call for upgrading the old spinning disk confocal for live cell imaging purposes.

Super-resolution imaging

LMU-BI: ONI Nanoimager, specialized in localization-based super-resolution microscopy, such as PALM and dSTORM, and very good for single molecule tracking and TIRFM.

Mesoscopic imaging

BIU-LM: LaVision BioTec UltraMicroscope II light sheet microscope especially suited for large cleared samples was used for the first pilot experiments already in the fall 2018. In 2019, the system saw increased use, with cleared mouse and rat organs.

CIC-TBI: M Squared Aurora Airy beam microscope, which is a unique light sheet microscope that provides high resolution imaging of large 3D samples including zebrafish and mice brain.

TIC-BCO: continued to develop a double wavelength, fast scanning optical-resolution photo-acoustic microscopy device for intravital imaging.

High-content and high-throughput imaging

FIMM-HCA: a laser dissection microscope (LEICA LMD7) for Computer assisted laser microdissection.

BIU-LM: Molecular Devices ImageXpress Pico high content imager to replace old equipment. The ImageXpress Pico is an entry point high content microscope that complements the high-end services of **FIMM-HCA.**

BioImage informatics

LMU-BI: new powerful 3D workstation, for 3D image analysis and processing for large data sets, that contains Imaris and Huygens Professional for deconvolution and image fusions.

BMT: Imaris

FIMM-HCA : new workstation for data processing and image analysis for users as well as development of the BIAS software package.

CIC-TBI: an OMERO server was set up for testing purposes for data management and analysis.

User statistics

See table.

Participation in international, Nordic and European infrastructures

CIC-TBI, BIU-LM, LMU-BI, and **TIC-BCO** are partners in FIALM, a Euro-BioImaging Node in Finland that offers open access to biological imaging technologies and services to national and international users from academia and industry. Access is granted based on scientific and technical merit of user

applications submitted in the Euro-BioImaging Web Portal (www.eurobioimaging.eu). FIALM has received international users from Denmark, Sweden, Belgium, Germany, United Kingdom, Russian Federation, India, and Australia. The BF Light microscopy platform also collaborates with Euro-BioImaging ERIC and its headquarters in Turku.

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.

As part of Global BioImaging (GBI, www.globalbioimaging.org), FIALM participates in a Job Shadowing Program that allows staff to visit imaging core facilities across the globe to exchange experience. FIALM has received three international job shadowing participants in 2018 from Singapore, India, and Australia and one participant in 2019 from Australia. (Two **CIC-TBI** staff members have previously visited Australia.) In addition, **CIC-TBI** has been active in participating in workgroups creating various international recommendations in imaging.

CIC-TBI, as part of the Bridging Nordic Microscopy Infrastructures (BNMI) consortium of five Nordic countries, has secured NordForsk 2019 funding to strengthen the competitiveness of Nordic imaging infrastructures and promote the development of advanced microscopy environments by organizing training activities, carrying out a Nordic job shadowing program, and providing short-term imaging mobility grants for researchers.

The platform members have been very active in participating in international events to promote imaging in Finland to researchers abroad, e.g. at annual ELMI (European Light Microscopy Initiative) and GBI conferences. In 2019, **CIC-TBI**, with significant assistance from other platform members, secured ELMI 2021 conference to Turku (to be shifted to 2022 due to effects of COVID-19).

FIMM-HCA is participating as a founding and SG member in the Nordic High Content Screening Network (NHCS), and is active also in the board of the Nordic Microscopy Society SCANDEM and CytoData Society.

For image analysis and data management, several units of the platform collaborated with CSC, and participated in the activities of BIIF (BioImage Informatics Finland) and NEUBIAS (Network of European BioImage Analysts), whose Finnish management committee members are from **FIMM-HCA** and **CIC-TBI. CIC-TBI** also collaborated with the developers of the Open Microscopy Environment (OME) from the University of Dundee, and worked in the EOSC-Life consortium.

Future perspectives

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	inter-national	non-academic	Total
UH	HiLIFE	LMU-BI	71	3	-	1	75
	HiLIFE	BIU-LM	82	12	2	2	98
	FIMM-HiLIFE	FIMM-HCA	34	4	4	2	44
UO	BCO	BCO-TIC	32	4	2	2	40
UTA	MET	BMT	33	0	0	1	34
UTU/ÅAU	BCT	CIC-TBI	43	1	2	1	47
	Total		295	24	10	9	338

In the end of 2019, negotiations were started to combine two successful BF platforms, light and electron microscopy, into a single BF Biological Imaging Infrastructure. The new platform sees several improvements for Finnish imaging, as the light and electron microscopy communities benefit from complementary solutions and expertise. Several new units have also been included, and work packages formed to make concrete progress in practical collaboration. Running the large infrastructure will be challenging, but is expected to provide significant benefits nationally.

In 2020, FIALM aims to expand its services to high throughput microscopy, by seeking in the 2020 Call for Nodes to include **FIMM-HCA** into the Euro-BioImaging Node. At the same time, the medical imaging community in Finland is seeking to establish a Euro-BioImaging Node in Finland. To coordinate all this and various other imaging related activities nationally, and to bring the biological and medical imaging communities closer together, two new Research Manager positions were established at Turku BioImaging in 2019 for biological and medical imaging.

Propelled by both the COVID-19 pandemic and climate change, virtual microscopy and remote access services are foreseen to be increasingly developed and taken into use, in collaboration with Euro-BioImaging. In late 2019, plans for this were started at CIC-TBI, with proof-of- concept studies to follow in early 2020, followed by production-level services.

Data storage, management and analysis solutions will be actively developed, both locally at the various units (e.g. OMERO-server setup at **CIC-TBI**, and a large joint storage setup in Helsinki), and nationally. The latter is done together with CSC, to establish a dual solution consisting of both and OMERO-server and a more generic solution.

Instrumentation will be developed with the aim to both maintain basic services and incorporate the latest state-of-the-art. For example:

LMU-BI obtained funding from FIRI2019 for the purchase of a new generation confocal microscope with fully integrated FLIM. This system, to be installed in 2020, will increase the confocal imaging capacity, offer new features and replace two outdated FLIM systems.

BIU-LM will purchase a high-end confocal microscope with FIRI2019 funding to respond to the continuously growing needs for fast and sensitive live-cell, sub- resolution limit systems, to be installed in 2021.

FIMM-HCA has set up collaboration contracts with Finnish companies and obtained EU-funding to develop an AI-guided SpheroidPicker for high throughput applications, concerning sample preparation and 3D imaging. To be set up in 2020.

TIC-BCO will purchase in collaboration with BCO transgenic unit a high-end stereo fluorescence microscope with 3D imaging capabilities. The unit is also developing a modified light sheet system, which can be used both light sheet and OPT imaging. Personnel will start to evaluate novel mesoscopic imaging systems, which will be purchased in 2022 with FIRI2019 funding.

BMT has acquired funding for upgrading one of the microscopes to an advanced widefield fluorescence live-cell imaging system. Plans are ongoing to renew also other equipment and to hire an additional person to the staff.

Major publications supported by the platform services

Pentinmikko N, et al. Notum produced by Paneth cells attenuates regeneration of aged intestinal epithelium. Nature 2019;571(7765):398-402.

Khoder-Agha F, et al. N-acetylglucosaminyltransferases and nucleotide sugar transporters form multi-enzyme-multi-transporter assemblies in golgi membranes in vivo. Cell Mol Life Sci 2019;76(9):1821-32.

Salo VT, et al. Seipin Facilitates Triglyceride Flow to Lipid Droplet and Counteracts Droplet Ripening via Endoplasmic Reticulum Contact. Dev Cell 2019;50(4):478-493.e9.

Li S, et al. An efficient auxin-inducible degron system with low basal degradation in human cells. Nat Methods 2019;16(9):866-9.

Keeble AH, et al. Approaching infinite affinity through engineering of peptide-protein interaction. Proc Natl Acad Sci USA [published online: December 10, 2019]. 10.1073/pnas.1909653116

Hammarén HM, et al. Janus kinase 2 activation mechanisms revealed by analysis of suppressing mutations. J Allergy Clin Immunol 2019;143(4):1549-1559.e6.

Stubb A, et al. Superresolution architecture of cornerstone focal adhesions in human pluripotent stem cells. Nat Commun 2019;10(1):4756.

Takeda A, et al. Single-Cell Survey of Human Lymphatics Unveils Marked Endothelial Cell Heterogeneity and Mechanisms of Homing for Neutrophils. Immunity 2019;51(3):561-572.e5.

Tervasmäki A, et al. Tumor suppressor MCPH1 regulates gene expression profiles related to malignant conversion and chromosomal assembly. Int J Cancer 2019;145(8):2070-81.

Koivunen J, et al. Collagen XIII-derived ectodomain regulates bone angiogenesis and intracortical remodeling. Matrix Biol 2019;83:6-25.

Small animal molecular imaging (SPECT/CT)

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

Partners: Mirkka Sarparanta and Arturo Garcia, HiLIFE.

Development of technology services

Aside the provision of nuclear imaging studies, the RTI unit has continued to develop its portfolio of services in 2019. New animal models and radiotracer imaging protocols have been validated at the RTI as a result of continuing the studies started in the previous year in collaboration with the Neuroscience Centre and the Division of Pharmaceutical Biosciences. Additionally, the infrastructure of the RadChem node has been expanded to better offer services with iodinated radiotracers as well as with short-lived positron emitters.

Application development

During 2019, the new service protocol for cerebral stroke model was established. In the clinic, 99mTc- hexamethylpropyleneamine oxime (99mTc-HMPAO or Ceretec®) is used to measure brain blood perfusion and was tested in the endothelin-1 mouse model of stroke and the experimental intracerebral haemorrhage (ICH) model in rats. The procedures for the stroke and ICH induction were established and the imaging parameters 99mTc-HMPAO were optimized.

Using the same tracer, a liposome labelling procedure was also validated by RadChem. In order to offer a standard protocol to measure the in vivo stability of nanoparticles having a hydrophobic core isolated with a lipophilic boundary, we set up the method using 99mTc-HMPAO. In this method, the particles are prepared loaded with glutathione, a strong reductant. Thereafter, particles are incubated with the tracer, which after crossing the membrane barrier reacts with glutathione, gets reduced and trapped into the particles. After administration, the radioactivity is only released after the nanocarrier disintegrates in vivo and the release kinetics can be monitored with imaging.

In 2019, the RadChem unit engaged with a significant industrial partner, the Norwegian technology company Nacamed developing a gas-phase production method for porous silicon (PSi) nanoparticles for drug delivery. In the course of this work, a number of radiolabelling techniques for PSi with 111In have been developed and evaluated in murine breast cancer models. Additionally, the radiosynthetic capabilities of the RadChem node were further strengthened by the 0.5 M€ upgrade of the node's IBA Cyclone 10/5 medical cyclotron rendering the instrument at least 10 more useable years as well as the installation of a ventilated glove box for handling volatile radioiodine isotopes.

User statistics

See table below.

Participation in international, Nordic and European infrastructures

The Finnish Infrastructures for Functional Imaging (FiFi) network now includes HAIP, which SPECT/CT and RadioChem nodes are integral part of, and three centres outside of Helsinki: Turku PET Center, Kuopio Biomedical Imaging Unit and Neuroimaging at Aalto University (Espoo) are members. This consortium is a prime opportunity for the RTI lab to develop connections not only nationally, but to make a strong case to join the EuroBioImaging network in the future. This would multiply the technical and scientific contacts, increase mobility and promote our radiosynthesis and imaging services also internationally.

Future perspectives

In 2020, we plan to continue to develop the disease model and comprehensive imaging service portfolio of the RTI unit. Our plan to expand in three different areas: 1) brain imaging, 2) cardiac and lymphatic imaging, and 3) cancer imaging. Since the CNS imaging is well underway with the validation of ^{99m}Tc-HMPAO in stroke, in 2020-2021 the focus is on validating the imaging protocols for cardiac perfusion with [^{201}Tl]TlCl and [^{99m}Tc]tetrofosmin in a myocardial infarct model. For oncology applications, tumour specific tracers targeting the somatostatin receptors (^{111}In-DOTATOC), the prostate-specific membrane antigen (^{111}In-PSMA-617) and the immune checkpoint agonist OX40 (^{111}In-anti-OX40 mAb) for T cell activation will be evaluated in xenograft models.

The funding from the Biocenter Finland is essential for the RTI unit. As the support from the host institution is weakening, additional funds for the salary of one more researcher (around 65 000 € total) is needed in order to be able to cope with everyday imaging, planning and analysis to guarantee maintaining the service at the current level at the SPECT/CT node. RadChem in turn is looking to have one M.Sc. level radiochemist hired permanently for sustained support of tracer development and production.

In addition, the unit has the need to renew the aging camera, and is engaged to gather funding to improve the imaging services by the acquisition of a PET instrument, either a hybrid PET/MRI or triple-mode PET/SPECT/CT. This development plan targeted for the FiRI calls in 2022–2025 would make RTI a comprehensive *in vivo* imaging facility. The RadChem node is already serving a number of academic and industrial customers with tailored radiolabelled PET tracers in Finland. However, the lack of a small animal PET system at UH remains the foremost hurdle to the implementation of small animal nuclear imaging for UH research groups, as PET has far greater selection of receptor ligand and antibody-based radiotracers for example neurodegeneration and oncology than SPECT. Additionally, there is no small animal MRI at UH, despite the highly ranked biomedical research and the unsurpassed advantages of MRI as a functional and anatomical imaging modality. The acquisition of a PET/MRI scanner would be the most suitable way to meet these needs and the RTI unit the logical host for the instrumentation as the support needs shared by all four modalities (PET, SPECT, CT and MRI) have already been established or can be established with the unit's existing expertise. Furthermore, the placement of the instruments under one unit supports the capability for multimodality imaging in a single animal. most of the Finnish research on animal models is made in the University of The Faculties of Pharmacy, Medicine and Biosciences support this ides and they are committed with matching funds.

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	inter-national	non-academic	Total
UH	HiLIFE		11	3	5	1	20

Major publications supported by the platform services

Schmitt M, et al. Intravitreal Pharmacokinetics in Mice: SPECT/CT Imaging and Scaling to Rabbits and Humans. Mol Pharm 2019;16(10):4399-404.

Harloff-Helleberg S, et al. Exploring the mucoadhesive behavior of sucrose acetate isobutyrate: a novel excipient for oral delivery of biopharmaceuticals. Drug Deliv 2019;26(1):532-41.

Imlimthan S, et al. Radiolabeled Molecular Imaging Probes for the In Vivo Evaluation of Cellulose Nanocrystals for Biomedical Applications. Biomacromolecules 2019;20(2):674-83.

Havunen R, et al. Abscopal Effect in Non-injected Tumors Achieved with Cytokine-Armed Oncolytic Adenovirus. Mol Ther Oncolytics 2018;11:109-21.

Huhtala T, et al. Improved synthesis of [18F] fallypride and characterization of a Huntington's disease mouse model, zQ175DN KI, using longitudinal PET imaging of D2/D3 receptors. EJNMMI Radiopharm Chem 2019;4(1):20.

Cervera-Carrascon V, et al. Comparison of Clinically Relevant Oncolytic Virus Platforms for Enhancing T Cell Therapy of Solid Tumors. Mol Ther Oncolytics 2020;17:47-60.

Balasubramanian V, *et al*. Engineered antibody-functionalized porous silicon nanoparticles for therapeutic targeting of pro-survival pathway in endogenous neuroblasts after stroke. *Biomaterials* 2020;227:119556.

Nieminen HJ, *et al*. Localized delivery of compounds into articular cartilage by using high-intensity focused ultrasound. *Sci Rep* 2019;9(1):15937.

GENOME-WIDE METHODS

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: Katja Kivinen, FIMM-HiLIFE

Partners: Outi Monni, FUGU, HiLIFE; Saara Ollila GBU, HiLIFE; Riikka Lund, FFGC-BCT, UTU; Petri Auvinen BIDGEN, BI-HiLIFE; Heini Kallio, Liquid Biopsy MET, UTA.

Development of technology services

Genome-wide methods (GWM) technology platform provides a wide range of services in genomics, gene expression and regulation, metagenomics and de novo genome studies. The platform is growing rapidly with increasing demand for both service capacity and the range of available applications. GWM has one of the largest user base of BF platforms, and continues receiving very good feedback from user surveys.

BMT Cancer Genomics (UTA) has recently joined GWM as a new node to complement the existing services of the platform. The node gives specialized support in cancer genomics by providing circulating tumor DNA (ctDNA) analyses, other GWM nodes will sequence the samples, and UTA node in BF Bioinformatics will perform data processing and analysis.

SERVICES	BioCity Turku (FFGC)			HiLIFE (BIDGEN)			HiLIFE (FIMM)			HiLIFE (FuGU)			HiLIFE (GBU)		
	Samples	Projects	Groups	Samples	Projects	Groups	Samples	Projects	Groups	Samples	Projects	Groups	Samples	Projects	Groups
Resequencing	45	3	3	32 120	29	29	1 248	31	20	28	3	2			
De novo	0	0	0	1 279	16	16	0	0	0	2	2	1			
Metagenomics	648	9	7	2 375	30	30	0	0	0	76	24	11			
Targeted	159 987	162	19	52	3	3	75 298	110	37	68	11	7			
SNP genotyping (QWAS)	0	0	0				25 707	139	27	0	0	0			
Targeted SNP typing	0	0	0				8 969	7	6	0	0	0			
Copy number variation**	0	0	0							2 575	23	2			
Immunoprecipitates (e.g. ChIP-seq)*	385	8	8				944	4	4	8	8	5			
RNA sequencing	1 219	52	29	1 015	21	21	1 228	38	13	668	65	27			
Gene expression microarrays	0	0	0				0	0	0	0	0	0			
Genome-scale reagents	0	0	0										220	77	31
ORF cloning	0	0	0										137	57	15
Nanostring/Fluidigm	0	0	0	348	4	4				180	2	1			
QC only	1 679	21	12				301	12	6	3 056	148	36			
Sequencing only (no. of runs)***	26	16	7				26	66	26						
Automated digital slide scanning	0	0	0				0	0	0				7 770	308	48
CUSTOMERS		Projects	Groups		Projects	Groups		Projects	Groups		Projects	Groups		Projects	Groups
Local		247	35		103	103		291	79		200	69		393	57
Other domestic		11	11		5	5		57	39		50	15		16	11
International		4	3		4	4		12	6		2	2		0	0
Non-academic groups		22	16		14	14		47	3		25	4		7	3
TOTAL		283	65		126	126		407	127		277	90		416	71
BILLING TOTAL (COST RECOVERY)			Total			Total			Total			Total			Total
			602 607			939 949			3 041 889			589 233			75 113

*includes methylation arrays and bisulfite sequencing

**includes genome-wide(CGH) and targeted

***includes also sequencing services provided for other LSRIs

Cost recovery grand total 4 646 184

In 2019, GWM has provided services to 439 research groups and 40 non-academic users with a total cost-recovery of 4,646,184€. Table 1 describes the division of tasks between the individual units of the platform and summarises the range of users across the platform.

Table 1. Services provided by the Genome-wide methods technology platform.

Due to differences in the workload of library preparation methods between the applications, and the increasing amount of sequencing-only services provided by individual units, the numbers of samples listed in the table are not directly comparable.

Platform-wide challenges include:

- the shortage of adequate resources for method and application development,
- increasing demand for single molecule sequencing (to make sequencing of large genomes more affordable and to allow de novo genome assembly for the identification of structural changes),
- full-length mRNA sequencing (to allow direct haplotyping, tissue identification, and identification of RNA splice variants specific to a disease or a developmental stage),
- metagenomic applications, and
- direct analysis of DNA modifications.

GWM works in close partnership with BF Single Cell Analytics platform, which has become one of the largest users of the sequencing capacity. To develop the single molecule long read sequencing applications further, GWM network has secured AoF FIRI funding in 2019 to purchase a long read sequencer (PacBio Sequel II) that will be set up in 2020.

Participation in international, Nordic and European infrastructures

GWM has strong links to international infrastructures enabling rapid and efficient transfer of knowledge and technologies. Nodes provide expertise in international evaluation tasks, e.g. for EU research programs and evaluations of national research infrastructures in Europe.

The platform is a member in EU-Life Core Facilities workgroup (http://eu-life.eu/working-group/core-facilities), European Core Technologies for Life Sciences network (CTLS, http://www.ctls-org.eu/), and the Nordic Alliance for Clinical Genomics (NACG, https://nordicclinicalgenomics.org/).

GWM is also one of the preferred sample analysis sites for BBMRI.fi and the local

biobank nodes. BBMRI uses our expertise in EU-level planning of biomedical infrastructure resources and evaluating research infrastructures internationally. GWM also operates as a national node for EATRIS biomarker platform and is involved in multiple studies in EATRIS Plus initiative.

Future perspectives

Genome approaches have evolved faster than one would anticipate based on how fast any field of biology progresses. The rapid increase in sequencing capacity and quality have enabled the use of NGS approaches in human personalised genomics, population genomics, and single cell assays. GWM will continue to respond to the increasing sequencing capacity needs of large-scale research initiatives aiming to determine functional characteristics at single cell level and to link individual genetic variants to disease risk.

Applications involved in the analysis of challenging samples (liquid biopsies, paraffin-embedded tissue samples, very small volume/concentration samples) is another growing field. GWM platform has the expertise and instrumentation needed to process these types of samples e.g. to track the origin of individuals, estimate the geographical origin of the sample, and to monitor the success of cancer treatments.

Genome-wide studies are supported by state-of-the-art library collections (ORF clones, siRNA and shRNA libraries) provided by the genome scale reagent nodes. Future improvements will include the addition of new species and more coverage, as well as the expansion of the collection of available destination vectors, generation of suitable control constructs and developing customised cloning approaches.

Despite technological challenges associated with single molecule sequencing, the platform sees it as one of the most promising future technologies. GWM has secured AoF FIRI funding to install a new long read sequencer (PacBio Sequel II), and will assess the applicability of Nanopore-based assays to services requested by the platform's end users.

One size fits all -type approach will not work in today's genomics research. GWM will continue to have a key national role in identifying and developing customised methods not available elsewhere, as well as handling challenging sample types. Increasing awareness of what is possible with cutting-edge technologies and helping researchers to choose the right technologies for them will be vital for Finnish research internationally competitive. Although semi-automated data processing and analysis solutions are emerging, increasing the level of available bioinformatics support will also be vital.

Major publications supported by the platform services

Pentinmikko N, et al. Notum produced by Paneth cells attenuates regeneration of aged intestinal epithelium. Nature 2019;571(7765):398-402.

Aho VTE, et al. Gut microbiota in Parkinson's disease: Temporal stability and relations to disease progression. EBioMedicine 2019;44:691-707.

Le Joncour V, et al. Vulnerability of invasive glioblastoma cells to lysosomal membrane destabilization. EMBO Mol Med 2019;11(6):e9034.

Kuony A, et al. Ectodysplasin-A signaling is a key integrator in the lacrimal gland-cornea feedback loop. Development 2019;146(14):dev176693.

Lagström S, et al. TaME-seq: An efficient sequencing approach for characterisation of HPV genomic variability and chromosomal integration. Sci Rep 2019;9(1):524.

Dwivedi OP, et al. Loss of ZnT8 function protects against diabetes by enhanced insulin secretion. Nat Genet 2019;51(11):1596-606.

Takeda A, et al. Single-Cell Survey of Human Lymphatics Unveils Marked Endothelial Cell Heterogeneity and Mechanisms of Homing for Neutrophils. Immunity 2019;51(3):561-572.e5.

Kettunen K, et al. Personalized Drug Sensitivity Screening for Bladder Cancer Using Conditionally Reprogrammed Patient-derived Cells. Eur Urol 2019;76(4):430-4.

Kallionpää H, et al. Early Detection of Peripheral Blood Cell Signature in Children Developing β-Cell Autoimmunity at a Young Age. Diabetes 2019;68(10):2024-34.

Hakonen AH, et al. SLC18A3 variants lead to fetal akinesia deformation sequence early in pregnancy. Am J Med Genet A 2019;179(7):1362-5.

MODEL ORGANISMS

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.

FinGMice technology platform

Chair of the platform: Reetta Hinttala

Node PIs: Heikki Tanila, BCK; Jere Linden HiLIFE, Vootele Voikar, HILIFE; Matti Poutanen, BioCity; Satu Kuure, HiLIFE; Pirjo Laakkonen, HiLIFE, University of Helsinki; Petra Sipilä, BioCity.

Development of technology services

Gene modified (GM) mice and more recently also rats are the key model organisms to understand the molecular basis of health and disease in man and to serve as in vivo models for human development and diseases. They are also central tools in the development of diagnostic, prognostic and therapeutic strategies. FinGMice, the national technology platform for generation, analysis and archiving of mouse models is a consortium composed of four nodes that have jointly developed their services in Finland already for two decades. Finland is known for excellence in biomedical research and the aim of the FinGMice platform is to guarantee that Finnish scientists can fully exploit the research models generated nationally and internationally. At the same time, through active research careers of the node PIs, we aim to maintain and to further develop the national infrastructure for customized mutagenesis, disease modeling and phenotypic analyses in rodent models.

FinGMice is in a key position to provide knowledge about current developments in the field of GM rodent models and, driven by the scientific needs in the field, is closely interlinked with the research community. Services are openly available to all researchers for a fee, and altogether, several hundred scientists benefit from the FinGMice services in Finland annually. Recent new methods for genome editing have speed up the generation of GM rodents and the expected time-line not only for services but also for education and consultation in generation, validation and analysis of the models have increased. As the

availability of animal models is increasing, a wider research community, where the scientific background may vary from a basic scientist to clinician, will benefit from the models as tools in the research projects. Full utilization of new genome editing era in animal models requires professional counseling and education, which is provided by FinGMice partners. Special training of researchers, personnel performing the experiments and taking care of the animal models is required due to regulations on the use of experimental animals and GM models.

Based on the previous annual reports, each of the core facility has a large number of customers yearly. Along with the establishment of FinGMice, the exchange of know-how and interaction between units has improved, allowing recognition of strengths in each unit, which has facilitated their specialization to high-level technologies. The services are up-to-date and core facilities with skillful technical personnel can quickly adapt to new methodologies. It is important that the personnel can continue to develop the well-established laboratories so that further improvement and development of the services can continue. Since the facilities are closely interlinked with the research community, services can and are adapted to fulfill the needs of the researchers. In general, the customers have been satisfied with the quality of the services and especially with the support offered for research. In some occasions, the efficiency of the service has been criticized too slow, deriving mainly from the high workload of the unit. Addressing this in the future requires further increase in the national collaboration between the FinGMice partners, better resourcing of the platform, and wider repertoire of services especially for phenotyping of mouse models in each unit. Thus, the amount of personnel in many of the nodes (e.g. GM-unit and FCLAP, UH) appears as the main bottleneck that hamper the improvement of user satisfaction. The recent evaluation by SAB strongly recommended continuation of the FinGMice platform.

In order to increase the visibility, the FinGMice platform has launched an up-dated web page (www.fingmice.fi) including information about the nodes, the services they provide and special expertise available by each core facility. Furthermore, biennial seminar series (BF Model Organisms RoadShow) to increase awareness and knowledge in GM models will be organized during Fall 2020 in each home university (UH, UTU, UEF, UO) and at the University of Tampere in collaboration with the Non-mammalian model organism platform (ModOrgNon). During these one-day seminars, information will be provided on generation, availability and phenotypic analyses of GM models in order to highlight the possibilities and enhance the best utilization of each GM model, and ultimately to maintain high-level cutting-edge research in Finland. Twitter (@fingmice) is used as a social media channel to announce news and events related to FinGMice.

User statistics

See table above.

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	inter-national	non-academic	Total
UEF	BCK	BCK neuropheotyping ctr	-	3	1	-	4
UH	HiLIFE	FCLAP	8	2	2	2	14
UH	HiLIFE	GM-Unit	34	4	1	9	39
UH	HiLIFE	MBPF	11	-	-	-	11
UO	BCO	TG core facility	24	10	19	-	53
UO	BCO	Histopathology	9	-	-	-	9
UTU	BCT	TCDM	16	5	5	4	30
	Total		102	24	28	15	160

Participation in international and European Infrastructures

GM unit at University of Helsinki through the director of Laboratory Animal Centre is a member of the LERU's Thematic Group "Animals Used for Scientific Purposes" (ANI). TCDM is part of the Turku Bioimaging (the Biological imaging platform), which is hosting the Euro-BioImaging ERIC (European Research Infrastructure Consortium) recently established by The European Commission. TCDM is also a partner in European infrastructure for translational medicine (EATRIS), which belongs to the Finnish research infrastructure (RI) roadmap 2014-2020. University of Oulu represents Finland in the ESFRI project INFRAFRONTIER, which was included in the Finnish RI Roadmap 2014-2020. The University of Oulu is representing Finland as a partner in the legal entity, Infrafrontier GmbH. Finnish participation in INFRAFRONTIER facilitates harmonization of procedures and data on work with mutant mice according to European standards. One of the ongoing EC funded projects involving Infrafrontier and BCO TG core facility is EOSC Life, providing an open collaborative space for digital biology in Europe, that initiated in March 2019. Thirteen Biological and Medical ESFRI RIs join forces in the project 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 EOSC-Life project is carried out by INFRAFRONTIER FI node in UO in collaboration with the Biocenter Oulu EM core, the Turku BioImaging and the Finnish ELIXIR nodes. The cloud deployment of the datasets collected in UO via EOSC-Life will support various laboratory and computational workflows which are present in several ESFRI entries.

Future perspectives

GM animal models remain important tools to study biological and physiological phenomena at the organism level. Knock-out models have greatly advanced understanding of essential genetic requirements for life, but seldomly recapitulate the phenotype of human patients. Next, the GM modeling field is focused on creating knock-in models by creating specific disease-causing mutations to animals, which is foreseen as the major future perspective during the following years.

To better support the use of GM models in Finland, the FinGMice platform is focused on creation of a well-structured pipeline, called "Mouse Clinic Finland", combining and developing the phenotyping services available in each host university. More sophisticated and centralized phenotyping analyses will further reduce the number of GM animals used, thus complying well with 3R principles by increasing the efficiency in the use of in vivo models. With the FIRI 2019 funding, FinGMice will improve the mouse phenotyping services that are the most frequently enquired by the customers. New equipment is needed for upgrading the tissue sample preparation for histological analysis in high spatial resolution (UO) and for 3D stereoimaging of genetic fluorescent reporter mouse lines to detect structural abnormalities in large mouse specimens (i.e. embryos, organs, tissue biopsies) (UO, UH) and to prepare defined regions of interest from 3D fluorescent specimen (i.e. genetically labelled group of cells, defined anatomical region within an organ). In addition, Laser micro dissection system (UTU) will enable single cell isolation from mouse tissue sections. All the instruments complement each other by enabling the preparation of high-quality specimens, and the precise analysis of the target area either from tissue sections or from 3D tissue samples.

Altogether, there are no indications that service requests would decrease, instead, by making the generation and phenotyping services of GM models more visible and accessible to researchers and by providing also consultation in gene editing design, the FinGMice aims to increase the amount of service requests in the next years. The FinGMice platform has

remained as a relatively compact network that continues collaborating and sharing expertise with each other and with researchers and students by consulting and organizing educational courses in all partner universities.

Major publications supported by the platform services

Misiewicz Z, et al. Multi-omics analysis identifies mitochondrial pathways associated with anxiety-related behavior. PLoS Genet 2019;15(9):e1008358.

Forsgård RA, et al. Two-Week Aflibercept or Erlotinib Administration Does Not Induce Changes in Intestinal Morphology in Male Sprague-Dawley Rats But Aflibercept Affects Serum and Urine Metabolic Profiles. Transl Oncol 2019;12(8):1122-30.

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Leinonen H, et al. Null mutation in P4h-tm leads to decreased fear and anxiety and increased social behavior in mice. Neuropharmacology 2019;153:63-72.

Koivunen J, et al. Collagen XIII-derived ectodomain regulates bone angiogenesis and intracortical remodeling. Matrix Biol 2019;83:6-25.

He Q, et al. The Cdh5-CreERT2 transgene causes conditional Shb gene deletion in hematopoietic cells with consequences for immune cell responses to tumors. Sci Rep 2019;9(1):7548.

Zhang FP, et al. Lack of androgen receptor SUMOylation results in male infertility due to epididymal dysfunction. Nat Commun 2019;10(1):777.

Kettunen K, et al. Personalized Drug Sensitivity Screening for Bladder Cancer Using Conditionally Reprogrammed Patient-derived Cells. Eur Urol 2019;76(4):430-4.

Rajendran J, et al. Alternative oxidase-mediated respiration prevents lethal mitochondrial cardiomyopathy. EMBO Mol Med 2019;11(1):e9456.

Kivelä R, et al. Endothelial Cells Regulate Physiological Cardiomyocyte Growth via VEGFR2-Mediated Paracrine Signaling. Circulation 2019;139(22):2570-84.

Non-mammalian model organisms technology platform

Chair of the platform: Howard Jacobs, MET

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

Development of technology services

ModOrgNon provides services and facilities on three sites for scientists to use Drosophila and zebrafish in research. The major users are from the host biocenters, but the facilities are available to the entire Finnish bioscience community and, in principle, to international or even private-sector partners as well. How to make use of these services is described on the webpages of our host universities, and are linked to/from the Biocenter Finland pages.

Facilities

(i) Flies: Drosophila-related services are provided in both Tampere and Helsinki, under operational principles adopted from other units with high volume Drosophila research, such as EMBL. In 2019, both sites were able to provide high-quality supplies of fly food to order, whilst stock maintenance and project guidance, already established in Tampere, will shortly be fully operational in Helsinki. To give an indication of scale, each unit supplied at least 15-20,000 vials of fly food in 2019. At present, adequate laboratory space is available on both sites, although some basic hardware, notably fly incubators with integrated heating, cooling, internal lighting and humidity control, are near the end of their useful life and will need to be renewed soon in order to sustain services.

(ii) Fish: A new zebrafish unit was inaugurated in Helsinki, expanding local capacity and serving as a back-up in case of failure of the main aquarium system. The new unit has larger aquaria, allowing maintenance of higher numbers of fish where fast maturation and growth is required. In Tampere, a separate

pathogen-free unit was installed in December 2019, with capacity for 10,000 adult fish. A colony health-monitoring program has been established in the facility, to ensure that fish stocks remain pathogen-free, and facilitating transfers to/from other units with similar, certifiable pathogen-free status. A separate quarantine laboratory is now in use, for fish lines acquired from other facilities without such status.

New methods and services

Within the limit of our resources, we have continued to take up new methods, concepts and techniques to meet researcher needs. For example, to study hypoxia in flies, we have tested several hypoxic O2 concentrations and recovery conditions. We have also developed a method to collect hemolymph from adult flies so as to measure circulating sugar levels for metabolic studies. At the end of 2019, an additional service node was incorporated into our platform, the zebrafish unit from Turku Bioscience. This expands the provision of basic zebrafish culture and genetic manipulation services nationally, but also brings in collaborative expertise and facilities for drug screening, as well as access to cancer models. We are also now able to offer the turquoise killifish as an additional model organism, which will prove highly useful as a short-lived vertebrate model for the study of ageing.

Feedback and service issues

To develop and shape our services according to the needs of our users we depend heavily on their feedback, both as regards the facilities and services provided, and our theoretical and hands-on guidance on their projects. Feedback has been mainly very positive on all sites. The fly units in both Tampere and Helsinki, for example, have acted as flexible service partners whenever scientists had special needs related to the quality, quantity or composition of fly food.

User statistics

See table below.

Participation In International, Nordic and European infrastructures

ModOrgNon is affiliated with various international consortia for the co-ordination of zebrafish research and the development of its infrastructures, notably ZFIN (Zebrafish Information Network), ZIRC (Zebrafish International Resource Center), EZRC (European Zebrafish Resource Center), and IZFS (the International Zebrafish Society). One of the key platform members (Pertti Panula) participated in the global strategic zebrafish PI meeting in Asilomar, CA in January 2019, and in the strategic PI meeting of zebrafish neuroscientists in Cold Spring Harbor in December 2019. There is no formal international body for orchestrating research resources for Drosophila. Instead the community relies on stock centres in each continent and resource collections developed within individual institutes, plus a global database of genomic information (Flybase), funded by NIH and by subscriptions. We interact regularly with these bodies. In 2019, platform leader Howy Jacobs became editor-in-chief of Fly, the main specialized journal of the field, which gives us additional reach within the worldwide Drosophila community. Inside Finland we are part of the FinnFly intranet, which promotes collaboration and

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	inter-national	non-academic	Total
UH	HiLIFE	Hi-Fly	10				10
UH	HiLIFE	NC-ZebrafU	7	2			9
TAU	MET	Tampere Drosophila Facility	3	1	1		5
TAU	MET	Tampere Zebrafish Facility	7	3			10
	Total		27	6	1	0	34

exchange among Drosophila labs nationally, ensuring that our services are well known and properly used.

Future perspectives

During 2020-2024 ModOrgNon will extend Drosophila strain maintenance services across both fly nodes, and develop an integrated database of stocks held. Note that, in line with best practice, many commonly used strains will be duplicated in both Tampere and Helsinki. We will also harmonize and develop guidance and training procedures for potential new Drosophila users. Longer term we will explore the possibilities of developing services for RNA sequencing, e.g. single cell sequencing of hemocytes, or hemocyte populations separated by flow cytometry. On the zebrafish side, although all nodes will maintain core services, such as housing of adult fish, embryo/larval cultures and CRISR/Cas9 genetic modification, each will deploy skills in line with local partnerships and expertise, which will be offered nationally. These include infection biology, neurological disease and cancer models, live imaging (provided a custom-built light-sheet microscope can be acquired) and drug-screening capabilities. We will also introduce additional fish models, notably the small fish medaka (Oryzias latipes), which will facilitate comparative analyses and GWAS studies using inbred strains. However, further service expansion at the existing sites may be limited by the availability of laboratory space. We plan to strengthen interactions and harmonize services between the nodes of the platform by organizing annual platform PI meetings, which will be linked to topic-oriented mini-symposia in which different user groups and external speakers will participate. We will also incorporate groups offering other models into our platform, notably C. elegans and Arabidopsis, initially as associate members, and intensify collaboration with FinGmice, so as to provide an integrated advisory service on how to apply a customized pipeline approach to the use of model organisms.

Major publications supported by the platform services

Gui J, et al. Coupling between dynamic 3D tissue architecture and BMP morphogen signaling during Drosophila wing morphogenesis. Proc Natl Acad Sci USA 2019;116(10):4352-61.

Gungor B, et al. HSP70 induces liver X receptor pathway activation and cholesterol reduction in vitro and in vivo. Mol Metab 2019;28:135-43.

Valanne S, et al. Immune-inducible non-coding RNA molecule lincRNA-IBIN connects immunity and metabolism in Drosophila melanogaster. PLoS Pathog 2019;15(1):e1007504.

George J, et al. Mitochondrial dysfunction generates a growth-restraining signal linked to pyruvate in Drosophila larvae. Fly (Austin) 2019;13(1-4):12-28.

Caldwell LJ, et al. Regeneration of Dopaminergic Neurons in Adult Zebrafish Depends on Immune System Activation and Differs for Distinct Populations. J Neurosci 2019;39(24):4694-713.

Leinonen JT, et al. LIN28B affects gene expression at the hypothalamic-pituitary axis and serum testosterone levels. Sci Rep 2019;9(1):18060.

Sahu MP, et al. Neurotrophin receptor Ntrk2b function in the maintenance of dopamine and serotonin neurons in zebrafish. Sci Rep 2019;9(1):2036.

Ojanen MJT, et al. Intelectin 3 is dispensable for resistance against a mycobacterial infection in zebrafish (Danio rerio). Sci Rep 2019;9(1):995.

Al-Samadi A, et al. PCR-based zebrafish model for personalised medicine in head and neck cancer. J Transl Med 2019;17(1):235.

Saari S, et al. Alternative respiratory chain enzymes: Therapeutic potential and possible pitfalls. Biochim Biophys Acta Mol Basis Dis 2019;1865(4):854-66.

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 Varjosalo, BI, Proteomics Unit

The year 2019 showed a positive trend for Protein characterization and Proteomics Network (PPN) in terms of services provided. The network served 255 research groups (19% increase compared to 2018) and the income from the user fees increased by 13% corresponding to 751,805 €. Whereas the network received slightly more financial support to BF activity related salaries from the host universities (3% increase compared to 2018), the other financial support from the local universities decreased by 61%. Main reason to the drop was the lack of big investments to the infrastructure (130,258 € compared to 820,400 € in year 2018). Details are provided in the attachment.

Development of technology services

PPN provides access to services in proteomics and protein characterization. The services 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 (246 research groups reported as users during 2019).

The SAB evaluation performed early 2020 led into following conclusion: "In view of the importance of proteomics and protein analyses for the Finnish researcher community and the increasing user demands, the SAB recommends that the PPN continues within BF."

In detail:

The Turku Proteomics Facility (CBT) provides services including characterization of post-translational modifications, large-scale quantitative proteomics analysis by DIA or DDA based methods and targeted protein quantitation by a PRM method. Top-down and middle-down mass spectrometry (MS) analysis of intact proteins and protein-protein interactions by cross-linking MS are also available. The facility set up an automated sample preparation workflow and Evosep One was bought to improve robustness and sample throughput in large clinical studies. Turku node will recruit a tenure track group leader for the core facility starting from the beginning of year 2021.

The Tampere Protein Technologies facility provides services in protein design, protein production and protein characterization. From the beginning of 2019, University of Tampere and Tampere University of Technology have been a part of the new Tampere University (TAU). Tampere organized during summer 2019 an advanced course focusing on the use of surface plasmon resonance technology in collaboration with BioNavis company.

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.

PPN Helsinki

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 together with the Meilahti Unit single cell proteomics analyses, partially in collaboration with the BF- Single Cell platform and Instruct-ERIC. These will be further strengthened by instrument acquisitions in 2020. PPN-Helsinki is devoted to continue its world-class level of services.

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 mass-spectrometry imaging (MSI) services with a new on-tissue-fragmentation by ISD (in source dissociation) technology, providing absolute identification of the selected ions on-site. The Unit started to serve its customers with immuno-mass-spectrometry (IMS) analyses using 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 Biological Nanoscience (Bio-Nano) 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, both in cell environment and in vitro conditions. Our work has focused to the development of proteins with new type of functions and a detailed characterization of them.

User statistics

PPN network served 246 research groups, which is slightly more than that reported during 2018 (214). The volume of the services in terms of the income from the services was 751,805 €, which is 13% 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, European and Nordic infrastructures

PPN nodes BI and Oulu participate in INSTRUCT-ERIC (Integrated Structural Biology Infrastructure for Europe) project which is on the ESFRI Roadmap. Turku hosts headquarters for newly established Euro-BioImaging ERIC, and acts as one of the three Euro-BioImaging hubs. Recently, BCH became a part of a Horizon 2020 neuroproteomics consortia and in the proteomics-chip development FP7 consortium. Moreover, BCH is a member of the EPTRI consortium and contribute to the Cooperative Action in Science and Technology (COST) in Mass Spectrometry Imaging. PPN is involved in various national Centre's of Excellence, FiDiPro projects, several Academy of Finland Professorships as well as national and international funding (FP7, MC-ITN, IMI and COST actions). For example, BCH facility has been a partner in two continuing COST actions for using IMS technology to analyze chemically modified proteins, and is now a full partner in 3 EU coordinated programs (JPND, ERANET and RISE). BI as a member of AoF Strategic Centres for Science, Technology and Innovation on developing diagnostic and therapeutic approaches for host-pathogen interactions.

PPN also has an important role in the research funded by ERC, EU-Horizon 2020, and private funding bodies such as the Sigrid Jusélius and the Finnish Cancer Foundation. BCO is part of one MC-ITN network, which includes Lonza, UCB, Boehringer and Gideon Richter. TBC is part of two MC-ITN networks and a new IMI program.

Future perspectives

Our goal is to maintain an infrastructure that will provide access to services, which are comparable to technologies used by world-leading scientists with the most advanced tools and knowledge. The infrastructure is expected to

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	inter-national	non-academic	Total
UH	HiLIFE	Viikki Proteomics Unit	41	17	9	4	71
UH	HiLIFE	Meilahti Clinical Proteomics Unit	36	6	3	3	48
UO	BCO	Proteomics and Protein Analysis	42	4	7	5	58
TAU	MET	Protein Service	3	1	1	11	16
TAU	MET	Mass Spectrometry Facility	10	2		1	13
UTU	BCT	Turku Proteomics Facility	27	9	3	1	40
JYU	BIO-Nano	Biospectroscopy	4	1	2	2	9
	Total		163	40	25	27	255

support Life Scientists involved in new Nordic initiatives as well as pan-European projects such as Horizon 2020, and ESRFI's such as Instruct, EPTRI, ISBE, EATRIS, ELIXIR and BBMRI and EU-OPENSCREEN.

Proteomics is developing fast with rapid increases in speed and coverage and is soon matching NGS in data acquisition and depth. Single Cell Proteomics in PPN is linked to total protein content analysis of a cell with a few thousand of proteins and their possible modifications to be measured in one shot, independent of available antibodies or metal labels. Furthermore, PPN has started to implement 4D protein analyses to allow in-depth proteome coverage of model organisms, tissues or cells lines enabling up to 12,000 proteins to be identified and 10,000 post-translational modifications to be analyzed and quantified, in a manner similar to RNA profiling by next-generation sequencing. This will also allow studies of protein-drug interactions, defining structural changes in complexes and separation of isobaric molecules.

For the clinical proteomics, sample quality and adequate sample processing are the key factors for reliable results. PPN will together develop uniform clinical sample processing guidelines and procedures, including use of operating theatre sample processing equipment. User training in clinical proteomics methods will be also increased through planned network-wide workshops.

PPN aims to provide services in near-field nanospectroscopy and imaging to allow spectroscopic studies and imaging of materials down to 10 nm resolution. This is significant because the characteristic scale for functional biological molecules is on the order of 10 nm. This allows detection of chemical reactions and dynamics of molecular interactions during molecular lifetimes, from femtoseconds to milliseconds. To address the needs for interactomics, PPN will implement fluorescence-based approaches, e.g. TS-FITGE for the identification of drug-binding proteins. To facilitate determination of protein interactions in demanding environment such as in clinical samples PPN aims to introduce novel microfluidics-based protein interactions technology.

Major publications supported by the platform servicestions

Keeble AH, et al. Approaching infinite affinity through engineering of peptide-protein interaction. Proc Natl Acad Sci USA https://doi.org/10.1073/pnas.1909653116

Lietzén N, et al. Coxsackievirus B Persistence Modifies the Proteome and the Secretome of Pancreatic Ductal Cells. iScience 2019;19:340-57.

Trotta A, et al. The Role of Phosphorylation Dynamics of CURVATURE THYLAKOID 1B in Plant Thylakoid Membranes. Plant Physiol 2019;181(4):1615-31.

Göös H, et al. Gain-of-function CEBPE mutation causes noncanonical autoinflammatory inflammasomopathy. J Allergy Clin Immunol 2019;144(5):1364-76.

Cortes E, et al. Tamoxifen mechanically reprograms the tumor microenvironment via HIF-1A and reduces cancer cell survival. EMBO Rep 2019;20(1):e46557.

Arasu UT, et al. HAS3-induced extracellular vesicles from melanoma cells stimulate IHH mediated c-Myc upregulation via the hedgehog signaling pathway in target cells. Cell Mol Life Sci https://doi.org/10.1007/s00018-019-03399-5

Rumfeldt JA, et al. UV-Vis Spectroscopy Reveals a Correlation Between Y263 and BV Protonation States in Bacteriophytochromes. Photochem Photobiol 2019;95(4):969-79.

Metabolomics technology platform

Chair of the platform: Teemu Teeri, HiLIFE

Partners: Seppo Auriola, BCK; Anni Nieminen-Viheriäranta, FIMM- HiLIFE; Matej Orešič, BCT

Development of technology services

The ViMU, FIMM, BKC and TMC units together, as a single entity, offer broad

coverage of analytical services in various fields of metabolomics both nationally and internationally. Since the initiation of the infrastructure platforms a decade ago, all units have managed to get a strong foothold within the scientific community by providing high-level, versatile MS-based services on various chemical analyses. TMC (Turku Metabolomics Centre) was added to the platform in 2019 in order to increase both the capacity and technologies available for the scientific community. However, as a nonvoting member, TMC is not included in this report.

ViMU (Viikki Metabolomics Unit) continues to provide analytical services mainly for the Finnish plant community and Pharmacy. The unit is focused on plant primary and secondary metabolites from different plant species and organs (roots, shoots), 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-based analytical services in plant metabolomics, microbiology, biopharmaceutical analysis and pharmacokinetics. In addition, unit has developed a method for over 50 nucleoside modifications in RNA (archaea, bacteria, eucarya) as well as a MS-based imaging protocol for plants with high-resolution (in collaboration with the MS-group in the Faculty of Pharmacy). The mass spectrometry-based, both targeted (quantitative) and untargeted, analyses are performed by three instruments; UPLC-QTOF/MS, GC-QQQ/MS and UPLC-QTRAP/MS.

FIMM-Meta (FIMM Metabolomics 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. During year 2019, the Unit has developed a new targeted and quantitative analysis method for TCA Metabolites. The method was recently published (Rathod et al. 2020). Another development step was taken with the targeted method for NAD metabolome to meet the specific UH research groups demand.

FIMM-Meta has been again focusing on clinical and biomedical applications, early biomarker discovery, (pre)-clinical trials, and precision medicine. During year 2019 our Unit has started upgrading its service to meet the criteria to perform clinical trials with pharmacological companies. The process has been started with NeuroVive Pharmaceuticals AB to analyze samples from patients undergoing clinical trial. Furthermore, a great developmental step has been taken with the statistical Bioinformatics analysis in the Unit, since FIMM personnel has been attending at courses on R-programming that has enabled an increase in the service capacity for metabolomics data analysis. The head of FIMM-Meta Vidya Velagapudi left the unit close to the end of 2019 and the unit is now headed by Anni Nieminen-Viheriäranta. Before leaving the Unit, Velagapudi was internationally active in many metabolomics societies.

In year 2019 BCK (Biocenter Kuopio Metabolomics Center) has continued providing non-targeted metabolomics services using UPLC-HRMS methodology. The installation of second and third high resolution instruments, Thermo Q-exactive orbitraps, in 2017 and 2018 markedly increased the sample capacity. 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, such as steroids and betaines. Because of the high customer demand for analysis of other than serum or plasma samples, the Kuopio laboratory has continued to develop 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 workflow, 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, the main bottlenecks being the lack of sample preparation automation and laborious process of non-targeted metabolomics data analysis.

Bottlenecks

ViMU has had in 2019 only one analytical researcher (Nina Sipari) and no technical staff has been working in the unit. A second analytical researcher could increase the capacity of the unit markedly.

From Sep 2019, FIMM-Meta was without head and TC research director Katja Kivinen acted as an interim head of the unit for a while. There has been a partial change in other personnel as well since one postdoc left. Therefore, the development of new method for fluxomics using new instrument Q-Exactive has been delayed and was not immediately started upon its installation. The new head PhD Anni Nieminen-Viheriäranta started in May 2020.

Education and training

The metabolomics results obtained from all the Units have been used in many PhD 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.

In June 2019, ViMU participated in organizing the NOVA University Network PhD course Phenotyping technologies in plant environment interactions together with Dr. Kristiina Himanen and Prof. Markku Keinänen from the National Plant Phenotyping infrastructure (NaPPI). ViMU was responsible for MS-based metabolomic plant phenotyping with GC-MS, UPLC-MS and MS-based imaging part of the course.

2019 FIMM continued in offering hands-on workshops and training to young researchers and students. The Unit organized spring workshop for "Targeted Metabolomics and its applications in precision medicine Biomarker identification and clinical field". Simultaneously, the Unit kept an introduction on basic principles and software overviews of the lipidomics workflow on SCIEX lipidyzer. The new head of the Unit will be also actively teaching at the courses for Master students at the University of Helsinki.

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

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	inter-national	non-academic	Total
UH	HiLIFE (ViMU)	Viikki Metabolomics Unit	14	2	0	1	17
UH	HiLIFE (FIMM)	FIMM Metabolomics Unit	12	1	4	0	17
UEF	BCK	BCK Metabolomics Center	28	9	1	3	41
	Total		54	12	5	4	75

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 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 through-put in the laboratory.

Major publications supported by the platform services

Shapiguzov A, et al. Arabidopsis RCD1 coordinates chloroplast and mitochondrial functions through interaction with ANAC transcription factors. Elife 2019;8:e43284.

Peivastegan B, et al. Effect of wet storage conditions on potato tuber transcriptome, phytohormones and growth. BMC Plant Biol 2019;19(1):262.

Gaiser RA, et al. Integrated targeted metabolomic and lipidomic analysis: A novel approach to classifying early cystic precursors to invasive pancreatic cancer. Sci Rep 2019;9(1):10208.

Heikkinen N, et al. Changes in the serum metabolite profile correlate with decreased brain gray matter volume in moderate-to-heavy drinking young adults. Alcohol 2019;75:89-97.

Gupta R, et al. Epigenome-wide association study of serum cotinine in current smokers reveals novel genetically driven loci. Clin Epigenetics 2019;11(1):1.

Reid AM, et al. In Vitro Human Metabolism and Inhibition Potency of Verbascoside for CYP Enzymes. Molecules 2019;24(11):E2191.

Pikkarainen A, et al. Gender- and dose-related metabolome alterations in rat offspring after in utero and lactational exposure to PCB 180. Toxicol Appl Pharmacol 2019;370:56-64.

Noerman S, et al. Metabolic Profiling of High Egg Consumption and the Associated Lower Risk of Type 2 Diabetes in Middle-Aged Finnish Men. Mol Nutr Food Res 2019;63(5):e1800605.

Kärkkäinen O, et al. Heart specific PGC-1α deletion identifies metabolome of cardiac restricted metabolic heart failure. Cardiovasc Res 2019;115(1):107-18.

STEM CELLS

Chair of the platform: Timo Otonkoski, BCH

Node PIs: Jari Koistinaho, BCK; Katriina Aalto-Setälä, MET

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

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

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

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 11th to 12th, in Kiljavanranta, Nurmijärvi, 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. Representatives of all three national stem cell Core Facilities from the Universities of Eastern Finland, Tampere and Helsinki were present. Important issues related to the coordination of activities between BF stem cells platform partners were discussed including the stem cell platform Biocenter Finland application for the year 2021-2024. BF stem cells platform partners have continued the development of their stem cell services as described below. A meeting memo was produced after the annual meeting and sent to the BF representative.

The total support for the BF stem cell platform partners was 181 717 € in 2019. 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 44 user groups of which 34 local and 10 internationals. BF stem cells platform partners produced 132 human induced pluripotent stem cell (hiPSC) lines. In general, the need for the derivation of new hiPSC lines was limited but has been steady. Major scientific progress was made in the development of CRISPR/Cas9 genome editing technology, which has been applied for efficient genome editing in human pluripotent stem cells for disease modelling purposes. Isogenic hiPSC lines have been made with increasing interest for pancreatic, hepatic, cardiac, and neuronal disease modelling applications. Furthermore, the BF

stem cells platform partners have put effort into improving pancreatic, hepatic, cardiac, and neuronal differentiations including 3D brain cell and cardiac muscle cultures. BF stem cell platform partners provided the training to 206 students/researchers. This includes hands-on training for individual researchers on basic iPSC cell culture and genome editing with CRISPR/Cas9. Furthermore, the stem cell platform partners organized several lectures on stem cells and genome editing, with the active participation of graduate students. BF stem cell platform total turnover (customer fees) was 108 219 €.

In 2019 HiLIFE conducted the University of Helsinki shared-use Life Science Research Infrastructure (LSRI) user survey. The total number of respondents was 593, including 211 principal investigators. Respondents were requested to rate each LSRI on a scale of 1 to 5, describing: access, quality, efficiency/performance, staff support, and price to quality. Biomedicum stem cell center (BSCC, BCH) received a total of 31 evaluation, the average score was 4,7. The action was taken in response: BSCC has included the provision of two reporter lines (OCT4 and SOX2) generated using the CRISPR/Cas9 knock-in strategy. BSCC started offering CRISPR-mediated gene editing in stem cells as a service (generation of the knockout hPSC line). Services and service development provided by each partner of the stem cell consortium are presented below.

During 2019, 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 was smaller than previously during 2019, but increasing interest has been towards isogenic lines. Fluorescent-labelled marker cell line for cardiac application has been a success and a great interest towards that been received nationally and internationally and this line is now available for customers. Additionally, three different types of hepatocyte specific reporter lines have been constructed. These lines are also ready to be delivered to customers. The core also put an effort in improving hepatic differentiation in addition to cardiac differentiation. 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 groups ranging from high school students to scientists. BMT is also aiming at providing technologies and cellular applications for Organ-on-Chip technologies and co-cultures of different cell types have been successfully applied and new technologies designed in collaboration with technical groups at MET, TAU and these will be provided for customers in the future, but most likely in collaboration form.

BCK has renewed and improved differentiation protocols for microglia and endothelial cells. BCK has also set up more 3D cardiac muscle and 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.

The Biomedicum Stem Cell Center (BSCC, representing BCH, www.helsinki.fi/bscc) provided services to 28 user groups. BCH derived 60 new iPSC lines and provided three frozen iPSC lines to eight clients. BCH signed a licensing agreement with Glycos Oy for the use of hESC lines derived in Helsinki. From the beginning of 2019, BCH provided automated live-cell imaging service to 49 users from 23 groups.

BCH continued active technological development of the CRISPR/Cas9 genome editing technology. BCH developed a novel reprogramming system, based on the activation of the cell's pluripotent genes, using CRISPR activators only (Weltner et al., PMID: 29980666). This is a new technology for the generation of iPSCs with important biobanking potential. iPSC lines from six donors were produced, using this novel reprogramming system, and returned to the biobank for broader use. Furthermore, BCH continued the development of isogenic iPSC-based models for diabetes research (e.g. Balboa et al., PMID: 30412052 and Balboa et al., PMID: 31161346). BSCC provides services based on this special expertise. Together with the Faculty of Medicine, BCH has organized genome editing and stem cells mini-symposium and courses. Those were very popular with the active participation of more than 200 students and researchers. Besides, BCH has promoted genome editing and human pluripotent stem cells to high school students by taking an active part in the Faculty of Medicine educational program.

Bottlenecks in the services provided by the consortium.

Comments are presented by each partner of the consortium:

BCH: Generation of hiPSC lines, genome editing, and differentiation services are laborious, time-consuming, and highly depend on skilled personnel. Further development of the genome editing and targeted differentiation as routine services requires additional resources for both personnel and space.

BMT/MED: 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 than initially expected. Orga-on-Chip technology is new and thus it is currently time and money consuming and is not ready to be provided for customers.

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.

User statistics

See table below.

Participation in international, Nordic and European infrastructures

BCH (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. . Since 2019, Otonkoski is also a member in the EMBL working group setting up the principles for human embryo and embryonic stem cell work at the EMBL.

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.

UEF (Koistinaho) is a partner in a Horizon 2020-funded consortia (nEUROinflammation and ENTRAN) on iPSC-derived models of brain inflammation, coordinates a JPND consortium (MADGIC) on novel iPSC models of Alzheimer's disease, is a partner in another JPND consortium PMG-AD, iPSC-derived microglia in AD) 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 the 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 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. BMT/ MED focuses on the differentiation of cardiomyocytes as well as hepatocytes as well in setting up new technologies for Organ-on-Chip technology and its applications. As Jari Koistinaho, who has been running the stem cell core in BCK from the very beginning, has started as the director of the Neuroscience Center at UH, BCH has applied for funding to enlarge the profile to include Neural iPSC Services. This significantly expands the services provided by BSCC to the large neuroscience community of the Helsinki area and whole Finland by offering differentiation of iPSC lines into various neuronal types, microglia, astrocytes, brain endothelial cells, cerebral organoids, and in vivo models of iPSC-derived brain cells. In addition to establishing the differentiation protocols Koistinaho group has contributed to the standardization of iPSC-derived brain cell models for both neurological and psychiatric diseases. BCK continues to have emphasis on differentiation and functional analysis on brain and cardiac 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 is obvious, as evidenced for example by large international initiatives sponsored by EC together with the pharmaceutical industry. 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 obtained cell samples from THL Biobank and generated iPSC from 20 donors for the THL Biobank. BCH expects an increase in the need for hiPSCs for biobank purposes and has started the trusted partnership negotiation with Helsinki biobank. This is based on the expressed interest from PIs recently recruited to the HiLIFE tenure track program and Neuroscience center and the start of negotiations with Orion Corporation, for the production of disease-specific iPSC lines.

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	inter-national	non-academic	Total
UEF	BCK	Stem Cell Center*	3	2	5	1	11
UH	HiLIFE	BSCC	25		2	1	28
UTA	MET	TAU	4		1		5
	Total		32	2	8	2	44

BCK 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.

A 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. Progress in CRISPR technology enabled the creation of controlled isogenic 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. Besides, the CRISPR technology is used to create marker cell lines having fluorescent labels under the promotor of cell type-specific promoter. This enables the detection of different cell types in co-cultures while the cells are still viable. Reporter iPSC lines generated by BCH researchers (Balboa et al., PMID: 28952927 and 28925359) are now available to the broader scientific community through core facility web pages. Generation of the knockout human pluripotent stem cell lines has become a routine procedure and this is provided as a service by BCH. BCH has close collaboration and coordinates its functions with the BF Genome Editing platform (FinGEEC) chair Topi Tervonen.

Major publications supported by the platform servicestions

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Stubb A, et al. Superresolution architecture of cornerstone focal adhesions in human pluripotent stem cells. Nat Commun 2019;10(1):4756.

Kiamehr M, et al. Compromised Barrier Function in Human Induced Pluripotent Stem-Cell-Derived Retinal Pigment Epithelial Cells from Type 2 Diabetic Patients. Int J Mol Sci 2019;20(15):E3773.

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Oksanen M, et al. Astrocyte alterations in neurodegenerative pathologies and their modeling in human induced pluripotent stem cell platforms. Cell Mol Life Sci 2019;76(14):2739-60.

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STRUCTURAL BIOLOGY

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), Lari Lehtiö, Biocenter Oulu, University of Oulu (UO);

Nuclear Magnetic Resonance: Hideo Iwai, BI-HiLIFE

Mass Spectrometry: Juha Rouvinen, BCK

Development of technology services

The platform has benefitted from the regular meetings of the Instruct-FI steering group (4 meetings in 2019) and the work of the Instruct-FI Coordination Hub to develop and meet common national and international strategic objectives and targets. We have open communication channels to the stakeholders: BF Board, Ministry of Education and Culture,

Finnish ESFRI directors, Academy of Finland and Instruct-ERIC Hub.

The feedback of the BF user survey 2018 was positive. The overall grade was 4.5/5 and grades for access, quality, efficiency/performance, staff support, and price/quality varied from 4.33 to 4.53. The survey contained minor feedback, noting a capacity lack in UO which has been taken into account in the equipment renewal plans. 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. From 2018 onwards, Biocomplex has been included in Instruct-HiLIFE (HiLIFE RI Assessment 2017) and reported annually as part of the Instruct-FI.

Main milestones in 2019

- Organisation of the annual structural biology user group FINNBOX-meeting in Helsinki;
- Finland joined Instruct-ERIC in July 2019;
- Instruct-ERIC Centre Finland was approved in October 2019 and services were opened in February 2020;
- Platform successfully evaluated in BF2020 call for 2021-2024; UH units positively evaluated in HiLIFE RIA2020 (pending);
- New instruments installed for the network through successful funding from the host universities and the Academy of Finland FIRI2015 and FIRI2016 calls;
- Significant funding (FIRI2019 call) for new instruments and coordination for 2020-2021 (a total of 2.6 M€) for the network - Instruct-FI being on the Finnish roadmap for infrastructure.

Developments and Bottlenecks

CryoEM had a fully operational year in 2019 with good increase in the overall use, and the first publications appearing using the Talos Arctica installed in 2017. The lack of tomography software was a bottleneck which will be addressed in 2020 with installation of academic software, serialEM. An increasing number of projects are using the facility to screen samples which are then sent to international centers for 300 kV data collection which gives higher resolution data for three-dimensional image reconstruction.

The **NMR** facility provides measurements of various molecules in solution, for elucidation of chemical structures and 3D-dimensional structures of proteins and nucleic acids, including dynamics and interactions. The facility also provides isotope-labeled samples and segmental labeling as the unique service, which will be further developed as the I-ERIC service. The 20-years old 600 MHz magnet has large magnetic field drifts and will be inoperable due to stray magnetic fields of the new tramline. The high-field 850 MHz can be detrimental to some nuclei like ^{31}P because of chemical shift anisotropy.

Crystallography facilities provide protein sample characterization, crystallization and structure solution services nationally. 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. 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. X-ray detectors have been updated to a photon counting models in Helsinki and Oulu allowing also in situ crystal testing in Helsinki. A similar detector setup with serial crystallography data collection capabilities will be installed in Turku in near future. A renewal of crystal imaging systems is currently in progress in Helsinki and Oulu. 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.

Native mass spectrometry unit 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 FIRI-funding; installed in December 2018) is a unique instrument in Finland and can separate molecular ions based on their size and shape enabling a detection of isomers and even major conformations. Bruker timsTOF shows potential for higher ion-mobility resolution but is sensitive for measurement conditions which must be tuned for native protein studies. Ion-mobility mass spectrometer allows also the measurement collision cross-section which correlates closely with the three-dimensional structure of proteins. This promotes integration of native mass spectrometry with three-dimensional structure information.

Biocomplex provides services for macromolecular complex purification. In 2019, a superspeed centrifuge with three rotors and an ultracentrifuge were replaced to support the highly used centrifugation service (FIRI2016 funding). Also, a new chromatography equipment was installed to guarantee the monolithic anion exchange chromatography service. Currently, the most urgent task is the installation of new electronic asymmetrical flow field-flow fractionation equipment with online light scattering detectors (FIRI2019). A bottleneck for the service is the continuous need to replace obsolete centrifugation instruments (ultracentrifuges, rotors and fractionation instrument).

Protein Service provides recombinant protein production, purification and characterization 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. FIRI 2019 funded WAVE™ 25 bioreactor system will be installed in summer 2020 enabling scale-up of insect and mammalian cell based productions in GLP like environment. Protein Service have got equipment to increase *Escherichia coli* expression volumes (2018) and new tangential flow filtration together with chromatographic instrumentation for protein purification (2019), but still instrument upgrades and addition of personnel are necessary to maintain and develop these functions. In overall, Protein Service has served the national structural and molecular biology community very successfully enabling high-end research.

User statistics

See table on previous page.

Participation in International, Nordic and European infrastructures

We coordinate the ESFRI Instruct-ERIC Centre Finland with leading edge technologies that are available to all national BF and international users, who can apply supported access through the Instruct-ERIC. We are actively enhancing collaboration within the EU infrastructure networks like Instruct-

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	international	non-academic	Total
UEF	BCK	Native-MS	13	12	7	4	36
UH	HiLIFE	CryoEM	20	4	0	1	25
UH	HiLIFE	NMR	14	0	0	6	20
UH	HiLIFE	Crystallization	11	1	1	2	15
UH	HiLIFE&FacBES	Biocomplex	15	8	9	3	35
UO	BCO	Protein Crystallography	16	1	0	2	19
TAU	MET	Protein Services	0	6	0	1	7
UTU	BCT	Protein Crystallography	7	3	8	0	18
ÅAU	BCT	SBL/Structural Biology	12		10		22
	Total		108	35	35	19	197

ULTRA and iNEXT and other Instruct and structural biology related projects e.g iNEXT-Discovery, CORBEL, Instruct-ULTRA, Open-Sesame, Transvac2, AARC2, EOSC-Life, ERIC-Forum, RI-VIS. 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).

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 e.g. by organizing NMR courses. The Protein Service is part of the 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 crystallization, 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 H2020 EU FT-ICR MS (European Network of Fourier-Transform Ion-Cyclotron-Resonance Mass Spectrometry Centers). Salminen is a Management Committee 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. UO is a member in the COST Action CM15135 Multi-target paradigm for innovative ligand identification in the drug discovery process (MuTaLig) (2016-2020). Butcher is a Work Package leader in the H2020-WIDESPREAD-2018-03 IMpaCT project to bring cryoEM to Portugal, and in H2020-MCSA-ITN-2017 Vibrant to train PhD students in viral structural biology.

Future perspectives

The Finnish membership in the Instruct-ERIC was ratified in July 2019. Following that, the Instruct Centre Finland was approved in October 2019 and we have now opened the selected Instruct-FI structural biology services in February 2020 for users coming through the Instruct-ERIC Access. This strategic move will boost the international research profile of the Instruct-FI platform. We are working towards expanding the user base internationally. There will be important equipment renewals, which will start to be seen in scientific output in the coming years. We are achieving better focus and coordination within the network.

Native mass spectrometry studies on protein or other biopolymers higher-order structures and folding, dynamics, protein-protein and protein-ligand/metal ion interactions provides unique information. Academia and industry are increasingly interested in this technology. We have currently two state-of-the-art instruments, Bruker FTICR and timsTOF instruments. The new FIRI funding allows us to buy the third instrument, high-mass range mass spectometer. Therefore, we will have an international-level instrumentation which offers wide possibilities to serve the research community in native mass spectrometry. Through the Instruct-ULTRA project we have developed further the IceBear-software, which is used for crystal tracking and transfer of sample information from home laboratories to the synchrotrons (Implemented for DLS,

planning with ESRF and MAXIV). To continue development supported by FIRI2019 funding we have set up a proof-of-concept server at CSC for hosting the software for all the Instruct-FI nodes and internationally through EOSC Life project (proposal submitted).

NMR technique has been continuously improving its relatively low sensitivity and spectral resolution. Ultra-high field (up to 1.2GHz magnet), new probe designs, high speed magic angle spinning, and dynamic nuclear polarization techniques have contributed to NMR spectroscopy expanding application possibilities. A shielded NMR magnet replacing the current 600 MHz spectrometer plan to introduce the solid-state capability for biological solid materials such as membrane proteins and biomaterials. CryoEM will develop in house methodology along with EMBI for sample preparation using Focused Ion Beam Scanning Electron Microscope (FIB-SEM) that will be purchased in UH during 2020, with cryo capacity anticipated in 2021. We are working with CSC to improve data management, data storage and computation.

Biocomplex is enriching its AF4 service catalogue by including analytical light scattering and concentration detectors and new separation technologies to allow data collection on absolute mass, size, size distribution, zeta potential, and net charge. Also automated sample analysis and data collection is taken into use to increase instrument capacity. Protein service is actively participating in vaccine development and research. Moreover, development of recombinant protein expression and purification practises that meet GMP standards for therapeutic proteins are improved. The RI also plans to promote utilization of structural biology within fields where it has been rare in Finland e.g. sustainable development, bioenergy and green chemistry. In Turku, the bioinformatics platform at SBL has an integral role in maintaining and planning the IT infrastructure of the nodes (e.g. IceBear software). New all-in-one crystallization platform will enhance reliability and capacity for setting up crystallization trials. In situ diffraction and serial crystallography data collection setups will contribute in improving the functionalities of the IceBear software for effective crystal tracking.

Major publications supported by the platform services

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Thangaraj SK, et al. Thermokinetic Analysis of Protein Subunit Exchange by Variable-Temperature Native Mass Spectrometry. Biochemistry 2019;58(50):5025-9.

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El Omari K, et al. The structure of a prokaryotic viral envelope protein expands the landscape of membrane fusion proteins. Nat Commun 2019;10(1):846.

TRANSLATIONAL TECHNOLOGIES

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-HiLIFE

Node PIs: Raisa Serpi, UO; Olli Carpen, UH

Development of technology services

Biobank technologies provides digital microscopy scanning services, advanced tissue profiling and artificial intelligence-based analytics for medical tissue biobanking projects, pre-clinical studies and biomarker research. The platform provides know-how for best phenotypic characterization of biobanked samples and for automated assessment of tissue sample stainings. The services enable seamless integration of multiplexed immunohistochemistry, whole-slide imaging, computational environments for image analysis, tools for biomarker discovery and linking of results to clinical data and patient outcomes.

Activities in this field has increased substantially and we foresee that a high demand for sample digitization. The FIMM Digital microscopy and molecular pathology unit has increased the services in histopathological lab work since 2018 (multiplexed fluorescent immunohistochemistry) and this service is expected to expand even further due to high demand. In 2019 a licence for Aiforia image analysis software (Aiforia Technologies Oy) was purchased and we expect to expand the services in image analysis with aid of this software the coming years.

The platform has been active since 2010 and previously included Auria Biobank in Turku and Institute of Biosciences and Medical Technologies (BioMediTech) at Tampere University. Dr. Olli Carpen who has been PI of

the Turku node has moved to Helsinki and therefore a new node has been established at the University of Helsinki starting in 2020, including some new RNA in situ services. The Tampere node has decided to discontinue its participation in the platform due to the fact that the former PI Jorma Isola has moved to the industry. Instead the Northern Finland Biobank Borealis in Oulu, with similar services as in Tampere has joined from 2020 as a second new node. The division of tasks is as follows:

Node 1 – the Digital Microscopy and Molecular Pathology unit at FIMM, UH provides high throughput whole-slide scanning services and has top-level expertise in digital microscopy and image-based diagnostics. The node operates three different high-end microscopy scanners that are capable of both brightfield and fluorescence scanning.

The unit further has unique capabilities in multiplexed fluorescent immunohistochemistry and provides this as a service. Also, the node now plans to include advanced artificial intelligence analytics as a service in the future, to enable more efficient and faster translational research projects related to tissues and cells.

Node 2 – the RNA In Situ Hybridization and Imaging Service at UH (New) provides a small-scale core facility for RNA in situ hybridization (RNA-ISH) in Olli Carpén's group. The node provides access to novel RNAscope and Basescope technologies (Advanced Cell Diagnostics) for detecting single RNA molecules within intact cells and within the actual morphological context of clinical specimens. The probe and assay design allow highly specific and sensitive signal amplification and background suppression simultaneously, while preserving tissue morphology.

The RNA-ISH core facility also provides a high-quality imaging platform using a Nikon Eclipse Ni-E motorized scanning microscope compatible with both brightfield and fluorescent microscopy, and automated scanning. The unit also provides user training for using the scanning microscope. The use of these novel services is expected to increase considerably during the next few years

Node 3 – Northern Finland Biobank Borealis at OUH (New) provides high throughput whole-slide scanning services and has top-level expertise in digital microscopy both at the OUH Pathology Department and at the Univ of Oulu, Machine Vision and Signal analysis group. The node operates one high-end microscopy scanner that is capable of brightfield scanning.

Biobank also offers the planning and production of tissue microarray (TMA) blocks as part of the digital pathology service package. OUH has joined as a new node, but already has provided services for 3-4 years. The user base is expected to show slow steady growth, mostly with academic partners. Service to scan macroslides is planned to be developed from 2020 onwards.

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/infrastructure/product-platforms/biomarkers/). EATRIS is a non-

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	inter-national	non-academic	Total
UH	FIMM-HiLIFE	Digital microscopy and molecular pathology u	8	7	1	1	17
	Total		8	7	1	1	17

profit European Research Infrastructure Consortium (ERIC). Researchers can approach EATRIS to provide guidance related to drug, vaccine or diagnostic development projects. Subsequently, EATRIS will match the need with the capabilities within the infrastructure, facilitate collaboration among academics, physicians, and developers, as well as provide fast, tailored access to cutting-edge enabling technologies in translational research.

The FIMM part of the platform is a research infrastructure (RIA) of the Helsinki Institute for Life Sciences (HiLIFE) as part of a joint infrastructure entitled Histotechnology and Laboratory Animal Pathology (HiLAPS; https://www.helsinki.fi/en/infrastructures/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.

All biobanks are linked to BBMRI-ERIC http://www.bbmri-eric.eu/ as well as on the national level to FinBB-biobank Co-operative https://finbb.fi/ Borealis also has links to CSC-run infrastructure node ELIXIR https://elixir-europe.org/about-us

Future perspectives

Tasks of the platform in 2020-24

1. To maintain and improve the high-performance platform for digital microscopy and associated analytical tools, 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

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.

During the year 2020-24, we will include image analysis services as well. During the year 2019, we have included image analysis services as pilot projects, as the methods need to be better standardized for the service. We will continue to work on this and include as a service in the near future. 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 (e.g. Aiforia Create by Aiforia Technologies and similar).

Major publications supported by the platform services

Turkki R, et al. Breast cancer outcome prediction with tumour tissue images and machine learning. Breast Cancer Res Treat 2019;177(1):41-52.

Holmström O, et al. Detection of breast cancer lymph node metastases in frozen sections with a point-of-care low-cost microscope scanner. PLoS ONE 2019;14(3):e0208366.

Saeed K, et al. Clonal heterogeneity influences drug responsiveness in renal cancer assessed by ex vivo drug testing of multiple patient-derived cancer cells. Int J Cancer 2019;144(6):1356-66.

Hohtari H, et al. Immune cell constitution in bone marrow microenvironment predicts outcome in adult ALL. Leukemia 2019;33(7):1570-82.

Blom S, et al. Fibroblast as a critical stromal cell type determining prognosis in prostate cancer. Prostate 2019;79(13):1505-13.

Talwelkar SS, et al. Receptor Tyrosine Kinase Signaling Networks Define Sensitivity to ERBB Inhibition and Stratify Kras-Mutant Lung Cancers. Mol Cancer Ther 2019;18(10):1863-74.

Bao J, et al. Spa-RQ: an Image Analysis Tool to Visualise and Quantify Spatial Phenotypes Applied to Non-Small Cell Lung Cancer. Sci Rep 2019;9(1):17613.

Karihtala K, et al. Prognostic Impact of Tumor-Associated Macrophages on Survival Is Checkpoint Dependent in Classical Hodgkin Lymphoma. Cancers (Basel) 2020;12(4):E877.

Brück O, et al. Immune profiles in acute myeloid leukemia bone marrow associate with patient age, T-cell receptor clonality, and survival. Blood Adv 2020;4(2):274-86.

Autio M, et al. Immune cell constitution in the tumor microenvironment predicts the outcome in diffuse large B-cell lymphoma. Haematologica https://doi.org/10.3324/haematol.2019.243626

Drug discovery and chemical biology technology platform

Chair of the platform: Päivi Tammela, FIMM, High Throughput Biomedicine Unit

Node PIs: Antti Poso, BCK; Matthias Nees, BioCity, Laboratory; Arto Urtti, HILIFE

Development of technology services

The Drug Discovery and Chemical Biology (DDCB) platform consists of four nodes located in Helsinki, Kuopio and Turku. DDCB provides drug discovery and chemical biology expertise and infrastructure for the bioscience community in Finland with the goal of providing world-class services in research involving discovery and exploration of drugs, natural products and small molecules. DDCB also coordinates national participation to the EU-OPENSCREEN ERIC.

During 2019, we have made very good progress in developing our technology services specifically in medicinal chemistry, advanced cell models, multiplexed miniaturised bioassays, and in the academic compound collection initiative. Medicinal chemistry support is now strengthened by the involvement of Professor Olli Pentikäinen, and by the extensive network of medicinal chemistry collaborators of the chair and node PIs. In addition, in December 2019 Dr. Piia Kokkonen joined the Biocenter Kuopio, BCK-PMC unit via a PROFI-funded position. Services with advanced cell models and multiplexed bioassays have been developed at several DDCB nodes.

DDCB offers high-end integrated laboratory automation systems for high throughput screening (HTS) including acoustic and other liquid dispensing instrumentation and multimode readers. Recently, we have expanded the Drug sensitivity and resistance testing (DSRT) service available at HiLIFE-FIMM High Throughput Biomedicine Unit with the first flow cytometry-based readout option for acute myeloid leukemia (AML), which allows in-depth subpopulation analysis of drug responses. The unit provides on average 4500 assay-ready and/or customised compound plates per year. Our services at HiLIFE-PHAR include *in vitro* screening specialised on antimicrobial targets and we have recently obtained new equipment that significantly increases throughput in our antibacterial screening capabilities and will open new service opportunities for users.

DDCB offers molecular modeling and virtual screening including chemoinformatics, protein modeling and QSAR, and provides access to drug discovery software licenses,

supercomputing capacity and training related to chemical biology and drug discovery both for specialists in the DDCB platform as well as for users at various levels of expertise. The main virtual screening and drug design software offered by CSC has been switched to Maestro-suite from Schrödinger Inc., which replaces Discovery Studio. Our leading research in Finland in the area of computer-aided drug design, MD simulations and computational chemistry is also internationally highly recognized.

Latest approaches in the DDCB network include library wide or cherry-picked RNAi and compound delivery, in addition to range of standard assays. Also available are parallel libraries of gene transfer vectors (AAV), compounds and targeted RNAis. The High Content Screening Laboratory in Turku contributes advanced 3D organotypic culture models for oncology with tailored high-content analysis solutions to extract biologically relevant parameters indicative of tumour progression and invasion. Although our DDCB platform has good capabilities in providing services based on advanced cell models, certain limitations and lack of instrumentation exist. For example, at HiLIFE-HTB unit, we do not yet have a high-content screening imager integrated to our automation platform. BCT-TSU unit in Turku has a mature integrated imaging solution providing high capacity. However, the resolution is limiting for some applications, so we plan to coordinate with the Bioimaging platform to integrate a high resolution high-content imaging device. Meanwhile BCT-TSU unit will improve the integrated liquid handling capacities.

User statistics

User statistics 2019 not available.

Participation in International, Nordic and European infrastructures

The DDCB platform is one of the four founding pillars of the Nordic Chemical Biology Consortium (NCBC), along with similar national chemical biology research platforms in Sweden (Chemical Biology Consortium Sweden), Norway (NOR-OPENSCREEN) and Denmark (DK-OPENSCREEN). In Oct 2019, the NCBC together with the Nordic High Content Screening Consortium submitted a proposal to the NordForsk Nordic Research Infrastructure Hub Call and applied support for our collaborative activities specifically in networking and training.

The DDCB serves as the Finnish National ESFRI Node of the European infrastructure EU-OPENSCREEN ERIC - the European infrastructure of open screening platforms for chemical biology, which is on the FIRI Roadmap 2014-2020. The national DDCB platform provides an excellent network for disseminating information about EU-OPENSCREEN activities and opportunities, and leads to increased national value. In February 2019, the EU-OS DRIVE project (funded by H2020) was started to support the EU-OS activities. During the first year of the DRIVE project, an MTA (material transfer agreement) has been constructed for academic compound donations. This sets frames for the workflow describing the compound donation process. Last autumn, Small Molecule Screening Call was launched by EU-OS and received 53 project proposals, of which 13 were selected. Noteworthy is that one accepted user project is from the University of Oulu, Finland. One of the selected projects will be carried out at FIMM-HTB unit. The projects have undergone a two-step scientific evaluation process by external evaluators and all of the partner sites, and are now ready for screening.

Future perspectives

Development and expansion of the DSRT platform based on flow cytometry (FC) will be optimized for other cancer types. HTS flow cytometer dedicated to core facility services would be needed as the current instruments at FIMM are within the research groups and heavily used. We will also develop imaging-based DSRT protocols using high-content fluorescence microscopy and AI to facilitate

the expansion of DSRT testing to solid tumors. Furthermore, updated version of the DSRT library shall be created during the next period.

In the antimicrobial screening services, we will focus, for example, on creating bioreporter strains amenable for HTS, and on establishing infection models in small animals. We aim also to improve our readiness level to provide tailored services for biological activity testing of various kinds of materials, such as nanoparticles, textiles, medical materials as well as 3D-printed materials.

Compound libraries will be renewed, for example, by creating new library sets in-house and by actively promoting the Academic Compound Collection Initiatives both at the national level as well as through EU-OPENSCREEN. In addition, our aim is to renew our current manual compound storage system to a multipod storage system, which will allow facilitated handling of compound library plates and improved control of storage conditions.

After June 2020 the main effort in virtual screening will be to fully utilize the new computing environment of CSC, especially recently launched "Puhti" and at the end of 2020 operational "Mahti" supercomputers. This work is especially needed for molecular dynamics simulations and a more efficient use of induced-fit docking algorithms.

Major publications supported by the platform services

Tang J, et al. Network pharmacology modeling identifies synergistic Aurora B and ZAK interaction in triple-negative breast cancer. NPJ Syst Biol Appl 2019;5:20.

Pulkka OP, et al. Anagrelide for Gastrointestinal Stromal Tumor. Clin Cancer Res 2019;25(5):1676-87.

Ianevski A, et al. Prediction of drug combination effects with a minimal set of experiments. Nat Mach Intell 2019;1(12):568-77.

Kilpeläinen TP, Tyni JK, Lahtela-Kakkonen MK, Eteläinen TS, Myöhänen TT, Wallén EAA. Tetrazole as a Replacement of the Electrophilic Group in Characteristic Prolyl Oligopeptidase Inhibitors. ACS Med Chem Lett 2019;10(12):1635-40.

Cortes E, et al. Tamoxifen mechanically deactivates hepatic stellate cells via the G protein-coupled estrogen receptor. Oncogene 2019;38(16):2910-22.

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Asquith CRM, et al. Investigation of the Pentathiepin Functionality as an Inhibitor of Feline Immunodeficiency Virus (FIV) via a Potential Zinc Ejection Mechanism, as a Model for HIV Infection. ChemMedChem 2019;14(4):454-61.

Nassa G, et al. Inhibition of histone methyltransferase DOT1L silences ERα gene and blocks proliferation of antiestrogen-resistant breast cancer cells. Sci Adv 2019;5(2):eaav5590.

Mirza MU, Vanmeert M, Froeyen M, Ali A, Rafique S, Idrees M. In silico structural elucidation of RNA-dependent RNA polymerase towards the identification of potential Crimean-Congo Hemorrhagic Fever Virus inhibitors. Sci Rep 2019;9(1):6809.

VIRAL GENE TRANSFER & CELL THERAPY

Coordinator: Seppo Ylä-Herttuala, BCK

Gene transfer technology has very important applications in studies dealing with gene function, gene regulation, generation of new disease models and development of new therapeutic approaches. Viral vectors can be used both in cell culture studies and in experimental animals and are currently the most efficient tool to deliver transgenes or constructs to block gene expression. Also, new applications based on gene editing have become available. In addition, cell therapy approaches and iPSCs or progenitor cell applications often require ex vivo gene transfer. Thus, it is not surprising that the demand of gene transfer vectors has increased significantly over the last few years.

VGTCT platform has developed and established 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 the core vector services in all Biocenters.

Viral gene transfer technology platform

Chair of the platform: Seppo Ylä-Herttuala, BCK

Partners: Tommi Heikura, BCK; Aki Manninen, BCO, Kari Alitalo, HILIFE, Topi Tervonen, HILIFE; Eleanor Coffey, BioCity, Eric Dufour, MET

Development of technology services

Biocenter Kuopio core facility located in A.I. Virtanen Institute has developed bioreactor-based technologies for the production of adenoviruses, lentiviruses and AAV vectors. Upstream and downstream purification methods have also been scaled up and can now produce vectors yielding up to 10e15 viral particles per production run. Also, suspension cell-based bioreactor methods are available especially for adenoviral vector production. Vector plasmids and tested backbones have been shared between VGTCT laboratories, thus making sure that the production of viral vectors within the VGTCT platform have the highest possible quality.

HelVi (Helsinki Virus) Virus Cores laboratories consists of two integrated parts, the AAVC (AAV Core Facility) and the BVC (Biomedicum Virus Core Facility). The HelVi is located in Biomedicum-1, as a part of the University of Helsinki. AAVC provides manufacturing of recombinant AAV preps of four different serotypes from the customer's gene-encoding plasmids. HelVi also keeps a collection of ready-made rAAV preps immediately available upon request. Generation of CRISPR rAAV preps for genome editing is a new service established in AAVC in 2019. BVC provides Biosafety level 2 laboratory, basic equipment and technology for lentiviruses and retroviruses.

Functional Genomic Unit (FuGU) of the University of Helsinki has been funded by HiLIFE infrastructure platform based on the Biocenter Finland's recommendations for 2018-2020 funding period. This support from BF has been vital for the continuation of FuGU's lentiviral and retroviral particle production services and BSL2 cell culture facility. In 2019, FuGU viral vector services and BSL2 cell culture facility operated under GoEditStem platform in HiLIFE infrastructure network of the University of Helsinki. FuGU provided off-the-shelf products, which are recombinant viral particle preparations at two production scales as well as high-titer concentrated lentivirus particles in two different volumes for hard to transfect cells (such as stem cells) and in vivo transduction purposes. The vectors for virus production originated from the customer or from the

genome-scale arrayed mouse and human TRC1 shRNA or CRISPR/Cas9 gRNA libraries licensed for and housed in FuGU. These libraries are significant and an unique in-house resource that can easily be reached by academic community within BF. In 2019 Maria Salmela, PhD, replaced Dr. Topi Tervonen as FuGU Libraries representative in VGTCT network. She has been operating FuGU Libraries since 2017. As a new service, the core has produced lentivirally transduced cell lines for customers.

University of Oulu Virus Core laboratory has further developed its lentivirus-mediated CRISPR/Cas9 genetic engineering services and is now, in addition to CRISPR/Cas9-knockouts providing consultation for the generation of CRISPR/Cas9 knock-in cell lines.

In 2019, Tampere Virus Core laboratory provided local researchers lentivirus, retrovirus and Sendai virus production and cell transduction services. The facility generated more than 30 transduced cell lines including iPSCs and Sendai virus-transduced cells. We observed a clear increase in CRISPR work, half of the projects involving CRISPR/Cas9 strategy. To respond to the increased demand for local viral-gRNA solutions, we decided to make available to the national community, through the VGTCT platform, the gRNA libraries that are hosted in Tampere. This library will complement the FuGu lenti-array human library, increasing the amount of gRNAs from 2 per target gene to 5 – 6. As gRNA effectiveness is difficult to predict, such increase should be really valuable. We have also started planning coordinated services with the BF Stem Cell Core (prof. K. Aalto-Setälä) which will allow to streamline the production of differentiated stem cells with viral vector technologies.

Turku Virus Core laboratory (now called Genome Editing Core Facility) provides vectors for CRISPR/Cas9 genome editing, shRNA knockdown, transgene over-expression and immortalization of primary cells. Turku Virus Core has also recently established methods for T-cell transduction.

Jyväskylä Virus Core laboratory will provide tools to study intracellular events of therapeutic virus vectors. Laser scanning confocal microscopy will be used to image viral transport processes in living cells with high temporal resolution. Fluorescence lifetime imaging will be used to expand imaging modalities to observe lifetimes of fluorophores in local cellular environments and fast molecular interactions which will be studied by Förster Resonance Energy Transfer. To analyze nuclear diffusion and active transport of viral capsids, we can create 3D reconstructions of cells and use our existing models to analyze viral dynamics. Notably, as far as we know we are the only microscopy unit in Finland where imaging of infective viruses in living cells is possible. Also, a new Leica SP8 Falcon confocal microscope was purchases in Fall 2019.

All VGTCT Virus Core laboratories provide training for researchers for the use of gene transfer methods, design of vectors and consulting regarding useful fluorescent markers, tags, methods to increase expression level and bioavailability. In many cases, VGTCT has helped to adapt the best possible techniques to the client needs. Troubleshooting of potential problems in study design and for unexpected outcomes is also available from all VGTCT laboratories.

VGTCT core laboratories have a large number of customers who value our reliable, fast and cost-effective services and use them regularly. We have repeatedly obtained very positive feedback from Biocenter Finland user surveys. It is important to note that based on the most recent Evaluation in 2020 of the Biocenter Finland's Technology Platforms, the VGTCT platform got favorable comments from the SAB: "The overall user satisfaction is very high. The platform has contributed to a large number of publications (180 during 2017-2019), including several contributions in high impact journals." On the other hand, we have recognized that our services are still unknown

for many researchers in academia and we are working towards better visibility and marketing plan.

Most significant bottlenecks

In all VGTCT Virus Core laboratories there is a continuous need for salary support from host Universities to keep expert staff scientists in the core units and to quarantee the high quality of services. In some laboratories shortage of space has been problematic: Due to the new space allocations in Research Programs Unit at the University of Helsinki our BSL2 lab space was temporarily unavailable. At the moment Biomedicum Virus Core (BVC) is sharing the lab space with Biomedicum Stem Cell Center (GoEditStem, HiLIFE) using space allocated for STEMM program. In the near future BVC would definitely need more space to be able to serve the community efficiently.

User statistics

See table below.

Participation in international, Nordic and European infrastructures

VGTCT Virus Core laboratories have participated in several ERC, EU Horizon2020, Leducq Foundation and other international grants. Based on the user feedback from past 5 years (2015-2019), the VGTCT platform was credited the assessment value "good" or "excellent" for all measured parameters, especially for "Quality of the service".

Future perspectives

VGTCT will continuously develop its services based on customer demands and new vector technologies becoming available to the research community. In Biocenter Kuopio A.I.Virtanen institute Virus Core laboratory, more emphasis will be put on the bioreactor-based production methods, upstream and downstream processes and qualified release and safety assays of the produced vectors.

HelVi Virus Cores laboratories will provide services to the research groups in the iCAN Digital Precision Cancer Medicine Platform and by broadening the user base at national and international scale. HelVi-AAVC will include gene targeting service, as the users often ask for this and prime editing vectors in its future technologies. By optimizing vector design and selection of a suitable promoter with tissue-specific expression characteristics it is possible to improve significantly specificity of transgene expression. To this end, a range of regulatory elements, such as transcriptional enhancers or inserted miRNA elements can further improve tissue-specificity of AAV transduction and expression.

In FuGu, retroviral and lentiviral gene transfer vectors continue to be important tools to achieve stable long-term transgene expression in the host cells extending from cell lines to primary cells in vitro and in vivo. Novel techniques like CAR T cell technology or large scale CRISPR screens heavily rely on lentiviral gene transfer. Since foreseeable future sees even a further increased need for services around recombinant lentiviral and retroviral technologies, the core facility will continue to provide these services.

Biocenter Oulu Virus Core laboratory is developing a digital holographic microscopy-

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	inter-national	non-academic	Total
UEF	BCK		23	10	7	4	44
UH	BI-HiLIFE	FuGu	52	15	2	0	69
	HiLIFE	HelVi	0	0	0	0	0
UO	BCO	BCO VirusCore	9	3	0	0	12
UTA	MET		4	0	0	0	4
UTU	BCT	Turku VirusCore	7	1	1	0	9
	Total		95	29	10	4	138

based imaging platform for automated label-free 3D morphological imaging of organoids (also suitable for regular cell culture). Recently, a faculty supported acquisition of a motorized stage was made allowing development of semi-high throughput imaging pipelines. This platform has been developed to allow fluent integration of 3D organoid culture models, a crucial basis for novel drug discovery pipelines, their transduction with viral expression/KO libraries and label-free imaging to record drug responses.

Turku Virus Core laboratory will further develop CRISPR/Cas-based genome editing technology, shRNA knockdown vectors, stable cell line production and T-cell transduction with viral vectors.

The existing therapy applications usually require high virus doses for efficient treatments. This poses a challenge both for vector production and restriction of the immune responses. In Jyväskylä Virus Core laboratory service focus is in the characterization of intracellular transit of viruses, especially cellular entry and nuclear import. Comprehension of intracellular transit mechanisms of viruses will contribute to the development of novel strategies to improve virus-mediated gene therapy. State-of-the-art imaging techniques, such as Fluorescence Lifetime Imaging and Förster Resonance Energy Transfer will be offered for studies regarding imaging of viral entry and characterization of fast molecular interactions.

Major publications supported by the platform services

Hytönen E, et al. Bile-duct proliferation as an unexpected side-effect after AAV2-LDLR gene transfer to rabbit liver. Sci Rep. 9: 6934, 2019.

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Song et al. VEGF-C-driven lymphatic drainage enables immunosurveillance of brain tumours. Nature. 2020. 577(7792):689-694.

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Pietilä M et al. SORLA regulates endosomal trafficking and oncogenic fitness of HER2. Nat Commun. 2019 May 28;10(1):2340.

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NEW PLATFORMS

Single-cell omics technology platform

Chair: Pirkko Mattila, FIMM-HiLIFE, UH

Node PIs: Minna Kaikkonen-Määttä, BCK; Eleanor Coffey and Tapio Lönnberg, BioCity; Pekka Katajisto, HiLIFE.

Development of technology services

2019 was the third 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 transcriptomics, sc epigenomics, sc proteomics and sc bioinformatics services are well established in UH and at Turku Bioscience (UTU and ÅA) with ever increasing user base. UEF joined sc omics platform as a new node 2019 because of increased local user demand in University of Eastern Finland. As the newest technological development, services for plate based assays relying on CellenONE instrument have been set up.

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 in-house developed Pool-seq method for 96-well based sequencing of FACS sorted single cells has become as a popular cost-efficient bulk RNAseq method, and also Functional Genomics Unit (FuGU/GWM) has adapted it from RPU-HTSC lab to serve the increasing locally and national customer base.

The mass cytometer has been highly appreciated for immune profiling applications and diagnostics. We have analysed samples for basic research and clinical trials, however, the small salary support has somewhat hindered the development. At Turku Bioscience 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.

Development of instrumentation

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 transcriptomics services currently provided by the 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 Single cell omics platform participated in the BF FIRI2019 funding application where we applied funding to set up services for spatial transcriptomics in UH and UTU/ÅAU. However, the funding granted was only partial and currently we are looking for options to find the rest of the funding for both of the instruments.

With Faculty and partial research funding (granted in 2018), RPU-HTSC lab set up in 2019 a fully equipped cleanroom with soft lithography fabrication instruments for microfluidic chip design and prototyping, suitable also for many single cell chips.

Implementation of new assays

In 2019 sc omics platform has successfully implemented the following new methodologies to service portfolio:

1. Single cell services based on CellenONE -instrument
   - applicable for sc NGS assays as well as for sc proteomics, HT screens etc.

2. TCR/BCR protocol for in-house Pool-seq 96-well format for single cells and bulk RNAseq

for T cell / B cell clonotype sequencing along with whole transcriptome, mainly in immunology, infection and immuno-oncology studies

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 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.

Sc omics has also actively participated in fund raising with other nordic single cell infrastructures to get funding for cooperation and to be better connected. Because FIMM is member of EU-LIFE sc omics is also connected to LifeTime, an EU initiative for revolutionizing healthcare by tracking and understanding human cells during disease. https://lifetime-fetflagship.eu/index.php/the-initiative/

Future perspectives

Immediate access to single cell technology is an urgent and in extreme demand. In the following years the user base is expected to explode further since the new emerging single cell technologies for single cell genomics and spatial transcriptomics are already available. Budgeting sufficient resources for recruiting personnel to provide consultancy in optimization of sample quality and running the first steps of single cell workflow would increase the efficiency and capacity. The increase of personnel could be balanced with robotics i.e by updating of Chromium (10XGenomics) with Chromium Connect - an automated system for sc capture and sample preparation for scRNAseq.

Until recently most of the single cell technologies commercially available and robust enough for core facility use have been either for sc transcriptomics applications or sc proteomics applications. Now there is the first instrument, Tapestri (MissionBio), available for single cell genomics. With Tapestri gene panels can be used to study copy number variations (CNV), single nucleotide variants SNV and co-occurrence of mutations in single cells. Tapestri instrument is useful when the researcher is interested in studying either clonal evolution on single cell resolution or detection of rare cell populations relevant i.e in hematological cancers.

Single cell proteomics (UTU/ÅAU) plans to add mass cytometry imaging (e.g.Hyperion, Fluidigm) to its technology platform (please see instrument plan). Highly multiplexed, epitope-based imaging of tissues provides a powerful means to extract high-dimensional data while retaining spatial information. This

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	inter-national	non-academic	Total
UEF	BCK	Single Cell Genomics	6	0	0	1	7
UH	HiLIFE	sc ProtGen	5	1	1	0	7
UH	HiLIFE	Single-Cell Analytics FIMM	21	3	1	1	26
UH	HiLIFE	RPU HTSC	2	0	0	0	2
UTU/ÅAU	BCT	Single Cell Omics	7	1	0	0	8
	Total		41	5	2	2	50

systems-level view of diseased and healthy tissues has added a valuable new dimension to biomarker analysis and drug discovery pipelines in addition to basic research. It is the device most requested from local pharma from us in recent years. The importance of cellular tissue topography and microenvironment is now appreciated and actively studied across fields of cancer, immunology and neurobiology. Mass cytometry imaging is equally applicable to animal and human tissues and utilizes commercially validated antibodies while facilitating custom antibody labeling using MaxPar kits. The Fluidigm device is an add-on to the Helios mass cytometer, however unlike the Helios, it is operator-free once the samples are loaded and thus imaging applications can run over the weekend. Meanwhile the Single cell proteomics (UH) plans to focus on blood sample and biobank sample analyses, which critically due to large sample numbers require automated sample preparation before mass cytometry analyses. Additionally, with biobank samples we need to clean the samples from variable amounts of dead cell and cell debris. For these we are applying for funding for an automated sample handling robotic platform and HT-microfluidics system for cell separation, respectively.

Major publications supported by the platform services

Kaasinen E, et al. Impact of constitutional TET2 haploinsufficiency on molecular and clinical phenotype in humans. Nat Commun 2019;10(1):1252.

Konki M, et al. Peripheral blood DNA methylation differences in twin pairs discordant for Alzheimer's disease. Clin Epigenetics 2019;11(1):130.

Kallionpää H, et al. Early Detection of Peripheral Blood Cell Signature in Children Developing β-Cell Autoimmunity at a Young Age. Diabetes 2019;68(10):2024-34.

Takeda A, et al. Single-Cell Survey of Human Lymphatics Unveils Marked Endothelial Cell Heterogeneity and Mechanisms of Homing for Neutrophils. Immunity 2019;51(3):561-572.e5.

Jäppinen N, et al. Fetal-derived macrophages dominate in adult mammary glands. Nat Commun 2019;10(1):281.

Keskitalo S, et al. Dominant TOM1 mutation associated with combined immunodeficiency and autoimmune disease. NPJ Genom Med 2019;4:14.

Genome editing

Chair of the platform: Topi Tervonen, HiLIFE, UH

Partners: Jukka Westermarck & Johanna Ivaska, Centre for Biotechnology, UTU & ÅAU; Petri Mäkinen, A.I. Virtanen Institute for Molecular Sciences, UEF.

Development of technology services

Genome editing (GE) platform aims to maintain and systematically build resources and services for in vitro and in vivo genome editing purposes. Furthermore, GE platform aims to maintain physical facilities enabling wide use of the resources across the Finnish biocenters, provide faculty services, platform services and develop beyond-the-state-of-art genome editing technologies with partners from Helsinki, Turku and Kuopio.

In 2019, GE platform leadership changed when docent Topi Tervonen became the chair of the platform. T. Tervonen has had more than 10 years of experience in recombinant viral technologies and 5 years of experience in genome editing technology. He has been working in a university core unit for more than 5 years and have been leading the way for genome editing technology in UH by driving the purchase of lentiviral genome-wide arrayed CRISPR/Cas9 gRNA libraries and setting up novel genome editing services as well as participating in international GE networks. Tervonen was previously a partner in VGTCT network of BF. In 2019, GE platform started to focus its efforts toward more specific service entities.

One of the Genome editing platform's aims has been housing and maintaining genome editing resources that would be too expensive for

individual research groups to obtain and maintain. To this end, Genome editing platform's services included distribution of clones from human and mouse arrayed genome-wide lentiviral CRISPR/Cas9 sgRNA libraries (Merck/Sigma-Aldrich) as bacterial glycerol stocks, DNA preparations, and recombinant lentiviral particles. This service enables fast and affordable way to obtain pre-designed gRNA constructs for gene KO purposes in several different formats within BF. Furthermore, already more than 50 gRNAs from this library have been validated in cell lines in projects initiated and co-funded by client researchers.

To do efficient CRISPR genome editing in cell lines and animal models the function and efficacy of used gRNAs need to be validated beforehand to avoid loss of money, time and effort. Therefore, Genome editing platform has managed to setup, pilot and launch three services aimed to analyze gRNA efficacy and editing outcomes in the end of 2019. The first of these services is SURVEYOR analysis to overall detect gRNA-specific editing events and editing efficacy in polyclonal cell populations. The second is edited sequence analysis by Sanger sequencing to detected overall editing events in clonal cell populations and mouse strains. Third service is TOPO TA clone analysis to detect exact alterations in all alleles, which is ideal for edited cell line or mouse strain characterization.

Cell line editing service has been established and opened after conducting successful pilot projects. This service enables generation of tagged cell lines, as well as knockout and knock-in cell lines. Creation or reversion of pathogenic mutations and cellular systems to facilitate genetic screening and drug screening will also be possible. Furthermore, validation of hits from screens, and generation of isogenic cell lines for isogenic disease models can be done. For example, Prof. Ivaska has set up methodology for genome editing of endogenous proteins to carry fluorescents tags for live cell imaging and the methodology has been used successfully for cancer cells, normal somatic cells and iPSC. Also, docent Tervonen has initiated pilots of generating CRISPR KOs with several cell lines and different target genes. GE platform will place genome edited cell technologies on the reach of BF client researchers that would otherwise by too difficult, tedious and expensive to master. Because the highly customizable nature of this service, the pilot phase is still ongoing.

Genome editing platform provided consultation, model design, and reagent generation for CRISPR mouse models generation in collaboration with Model Organisms technology platform of BF. For example, an animal model for breast cancer research that is fully compatible with genome-editing methods was successfully established and was recently used with virus-edited cells to test oncogene dependence of breast cancer (Pietilä et al., 2019 Nat Communs).

A new service that Genome editing platform successfully piloted in 2019 was pooled CRISPR screen. Pooled CRISPR screens are extremely versatile tool for making genome-scale discoveries. Practically any phenotype that allows cell separation can be queried. For example, essential genes, drug resistance and drug sensitivity genes, novel genes and pathways involved in cell differentiation can be discovered. These CRISPR screens can be performed in cell lines, stem cells or primary cells. Pooled CRISPR screens currently mostly rely on lentiviral gene transfer; therefore, this service is closely coordinated together with local VGTCT partners of BF. The pilot pooled CRISPR screen was conducted with genome-wide kinase gRNA library in the end of 2019 by Prof. Ivaska and Prof. Westermarck jointly. The service was still at pilot stage at the end of 2019.

One of the platform's focus areas has been isolation and analytics of gene edited cells at single cell level to potentiate new discoveries by state-of-the-art flow cytometry. Genome editing platform houses and maintains FACS Aria III Sorter (Becton Dickinson), FlowSight imaging cytometer (Merck Millipore), and CytoFLEX S analyzer (Beckman-Coulter) instruments that are used to provide full hands-

off services and support for BF community. During 2019, highly sensitive iPSC sorting protocol was set up, and new previously unused fluorochromes were used for sorting purposes. The instruments have been used by large population of academic customers and collaborators, and also by a nonacademic company.

Genome editing platform has put an effort on disseminating advances in genome editing research and technology in academic community by organizing (together with HiLIFE through GoEditStem platform, UH) joint CRISPR and stem cell symposium and practical course for graduate school curriculum and general academic audience in Helsinki with speakers representing international genome editing core facilities was again success drawing audience of more than 150 researchers interested in genome editing.

Currently, genome editing services rely more on the knowhow of skilled personnel than large equipment. Therefore, lack of sufficient long-term funding for core personnel is definitely an anticipated bottleneck in the future as cell line editing and CRISPR screen services become more and more popular. Also, many genome editing services need to be highly customizable to fit everybody's needs, therefore, projects might need to be selected based on difficulty and success factor. This selection creates obvious bottlenecks, since every project needs to be pre-evaluated.

In summary, Genome editing platform aims to continuously follow new developments in genome editing research and technology, and translate them into state-of-the-art services for BF research community.

User statistics

See table.

Participation in international, Nordic and European infrastructures

FinGEEC-Kuopio partner, P. Mäkinen, holds a position as lentiviral vector responsible person at National Virus Vector Laboratory, providing a direct link and collaboration potentials to EATRIS network at ESFRI. J. Ivaska (FinGEEC-Turku) has been involved in planning how the FinGEEC services are optimally integrated into the imaging pipelines developed at Turku as part of the starting EuBI (euro-Bioimaging) functions.

Future perspectives

Instruments that would have been designed for genome editing are practically non-existing. However, one instrument that would facilitate sensitive isolation of single edited cell clones is microscopy assisted cell selector (CellCelector, ALS Automated Lab Solutions GmbH). The instrument would automatize edited single cell clone selection and improve the survival of selected clones, therefore, make cell line editing service more efficient. Also, while more and more users are using flow cytometry on gene edited cells, and single-cell isolation for RNA analysis seem to gain interest, therefore, a new cell sorter would be needed to increase both safety and performance of the sorting.

Genome Editing platform will further develop newly opened analytical services, and cell line editing services, and make them available and known for BF community. Pooled CRISPR screening will be established and launched to serve BF community. As genome editing field is evolving rapidly, Genome editing platform is exited to capture and disseminate any widely usable genome editing technology that

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	inter-national	non-academic	Total
UEF	BCK	FinGEEC-Kuopio	8	1		2	11
UH	HiLIFE	FinGEEC-Helsinki	2				2
UTU	BCT	FinGEEC-Turku	6				6
	Total		16	1	0	2	19

becomes available. There are already several genome editing technologies around that might be possible to translate into service entities, provided that there is an unmet need (for example, CRISPR off-target analysis).

Major publications supported by the platform services

Haikala HM, et al. Publisher Correction: Pharmacological reactivation of MYC-dependent apoptosis induces susceptibility to anti-PD-1 immunotherapy. Nat Commun 2019;10(1):932.

Arasu UT, et al. HAS3-induced extracellular vesicles from melanoma cells stimulate IHH mediated c-Myc upregulation via the hedgehog signaling pathway in target cells. Cell Mol Life Sci https://doi.org/10.1007/s00018-019-03399-5

Pietilä M, et al. SORLA regulates endosomal trafficking and oncogenic fitness of HER2. Nat Commun 2019;10(1):2340.

Mäkelä E, et al. Arpp19 Promotes Myc and Cip2a Expression and Associates with Patient Relapse in Acute Myeloid Leukemia. Cancers (Basel) 2019;11(11):E1774.

Stubb A, et al. Superresolution architecture of cornerstone focal adhesions in human pluripotent stem cells. Nat Commun 2019;10(1):4756.

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