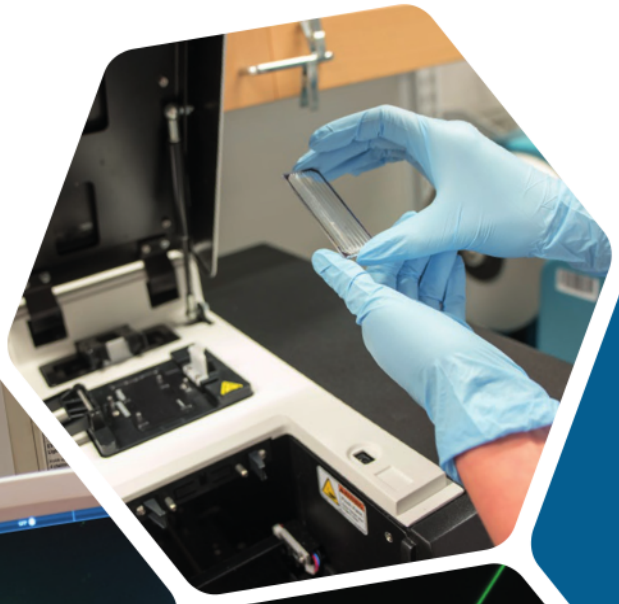
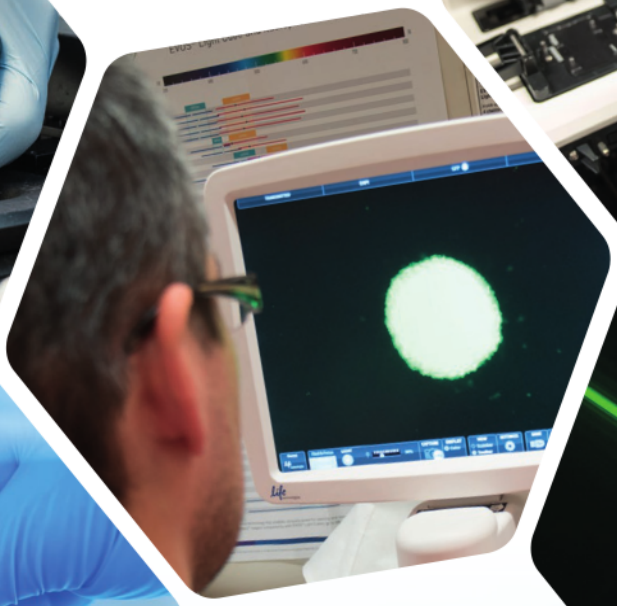
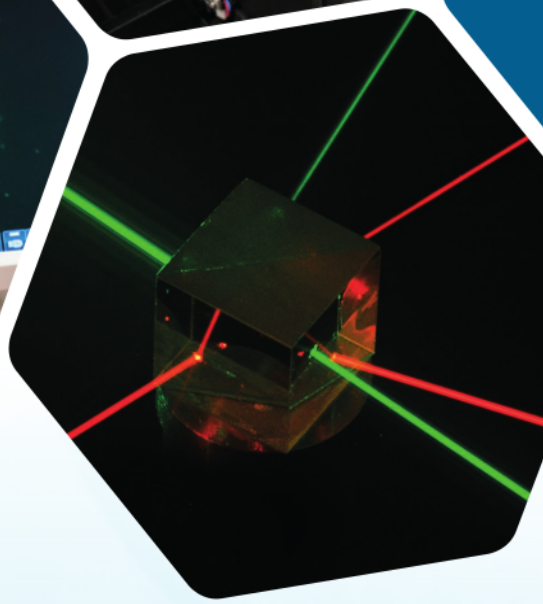
Biocenter Finland

Annual Report 2020







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Biocenter Finland Annual Report 2020

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 developing and coordinating state-of-the-art technology services, openly accessible for the Finnish community of some 17,000 researchers as well as international customers working in universities, research institutes, hospitals and private sector. BF operates as a nation-wide network of around 70 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.

The host universities' Rectors' Council is the highest decision making body of BF. In 2020 the Council made an important strategic decision by signing an agreement to continue to support the Platform personnel's salary costs and the Coordination Office for the years 2021-2024. Despite the challenging general funding situation, the host universities committed to a small increase in funding from the 5,79 M€ in 2020 that ensures continuation and renewal of the infrastructure services to the research community. In addition to the host univerisities' contribution, a key element of BF's funding are the use fees of 9,35 M€.

BF's research infrastructures are organized into 15 thematic BF Technology Platforms: Biobank technologies, Bioinformatics, Biological imaging, Drug discovery & chemical biology, Genome-wide methods, Metabolomics, Mouse models, Non-mammalian model organisms, Plant phenotyping, Proteomics, Real-time imaging, Single-cell omics, Stem cells & Genome editing, Structural biology, and Viral gene transfer & cell therapy. Each Platform is composed of 1-5 complementary Nodes operating in different Biocenters. BF evolves continuously and the Platforms are evaluated every four years by BF's Scientific Advisory Board on their ability to support and renew frontier research, national significance, volume of user base and results of user surveys.

A new Scientific Advisory Board chaired by Professor Carl-Henrik Heldin started its term in 2020. In their first meeting the SAB evaluated applications received via an open call by the existing BF Technology Platforms as well as new Platform openings. Based on the evaluation and Platform interviews, the SAB made a recommendation on the Platforms to be included in BF for the term 2021-2024 and on the salary funding of their personnel. The SAB also gave recommendations for developing individual platforms and BF as a whole. These recommendations were closely followed and led to inclusion of a new Platform for Plant phenotyping as well as some Platform reorganizations that support more integrated services and align the Platforms better with international RI networks such as the Finnish ESFRI nodes.

The Academy of Finland's Roadmap for Finnish research Infrastructures (FIRI) delineates the significant national research infrastructures in Finland. BF has been on the Roadmap since its inception on 2014 with excellent reviews. In 2020, Academy of Finland organized a call for the updated Roadmap 2021-2024, and BF was again selected for the renewed Roadmap with excellent evaluations.

One of the key activities of BF is to apply for funding to maintain, renew and upgrade the instruments and equipment that ensure the professionally operated up-to-date, cutting edge services to researchers. The main source of instrument funding are Academy of Finland's FIRI calls. BF has been highly successful in these calls and in 2020 received a positive funding decision of 2,7 M€ from a previous year's call. During 2020, an additional COVID-19 recovery associated FIRI2020 call was opened that focused on collaboration with the business sector and

industry partners. Due to the existing strong links with the industry, BF´s application received 2,5 M€ funding for instrumentation.

In terms of collaboration, BF works with the Finnish ESFRI (European Infrastructure Projects) nodes BBMRI (biobanking), EATRIS (translational medicine), ELIXIR (bioinformatics), EU-OPENSCREEN (drug screening), EuroBioImaging, Infrafrontier (mouse models) and FInstruct (structural biology). The aim is to ensure knowledge transfer and access to the pan-European infrastructures, and 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.

At the end of the year, BF opened a call for a new director for the term 2021-2026 as Professor Marja Makarow's fixed term was coming to an end. An international call attracted several high quality candidates. The host universities' rectors decided in March 2021 to nominate Professor Olli Silvennoinen, director of Helsinki Institute of Life Sciences as the director of BF for the term 2021-2026. As the new director I am excited and enthusiastic to steer and develop the BF activities in the current landscape where life and biomedical sciences have an increasingly important role for the society and environment.

Professor Olli Silvennoinen

Director of Biocenter Finland

STATISTICS

Usage

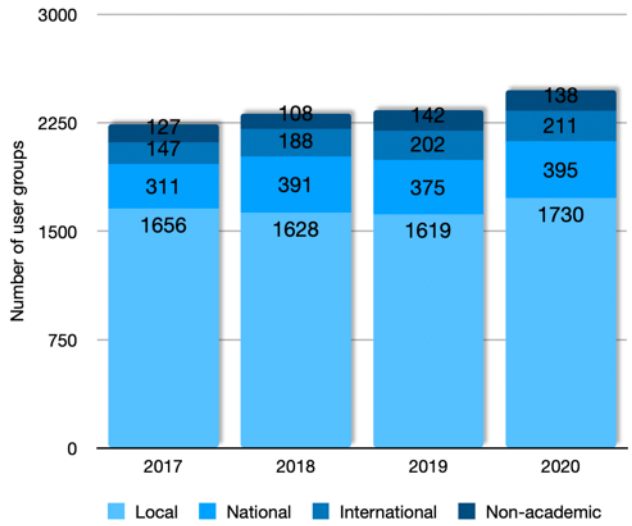


Figure 1. Number of research groups and non-academic customers using BF technology platform services. Total number of user groups in 2020 was 2474.

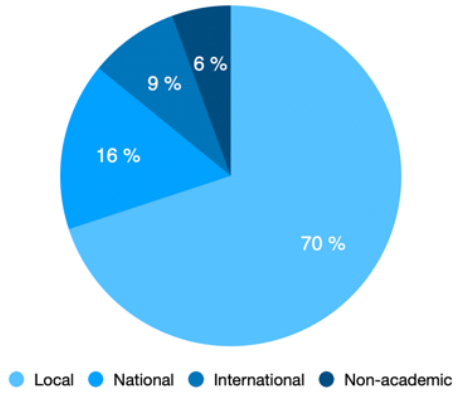


Figure 2. Percent breakdown of user groups into local, national, international, and non-academic users.

Funding

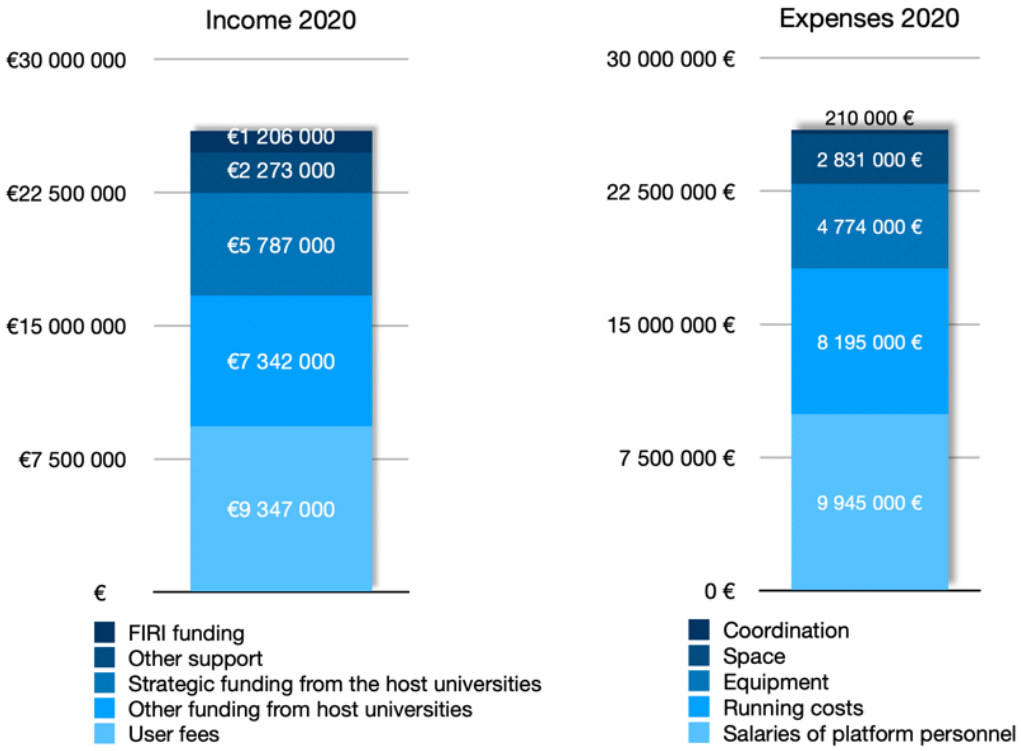


Figure 3. Biocenter Finland's sources of income and expenses in 2020

SCIENTIFIC IMPACT AND SUCCESS STORIES

Biobank technologies

In a recent study within the iCAN project (Machine learning algorithms for superhuman digital diagnostics), it was investigated whether a machine learning algorithm trained with images of tumor tissue morphology only, can predict breast cancer *ERBB2* gene amplification status and whether this prediction is associated with adjuvant treatment efficacy (1). Interestingly, the deep learning algorithm was not only a significant predictor of the *ERBB2* status but also identified patients with *ERBB2*-positive cancer who benefited more from a targeted treatment with trastuzumab (Fig 1). To our knowledge the study is the first to show that morphological features learned by a deep learning algorithm not only predict the molecular status, but also the efficacy of a molecularly targeted treatment.

Figure. A) An AI-algorithm was trained to predict *ERBB2* (HER2) amplification based on tissue morphology B) The AI-algorithm trained based on morphology (AI-HE-*ERBB2*) was a significant predictor of the *ERBB2* status but also identified patients with *ERBB2*-positive cancer who benefited more from trastuzumab and *ERBB2*-negative patients who had a less favorable survival. This indicates that the AI-algorithm can learn morphological patterns that predicts efficacy of anti-*ERBB2* treatment in patients with breast cancer.

Bioinformatics

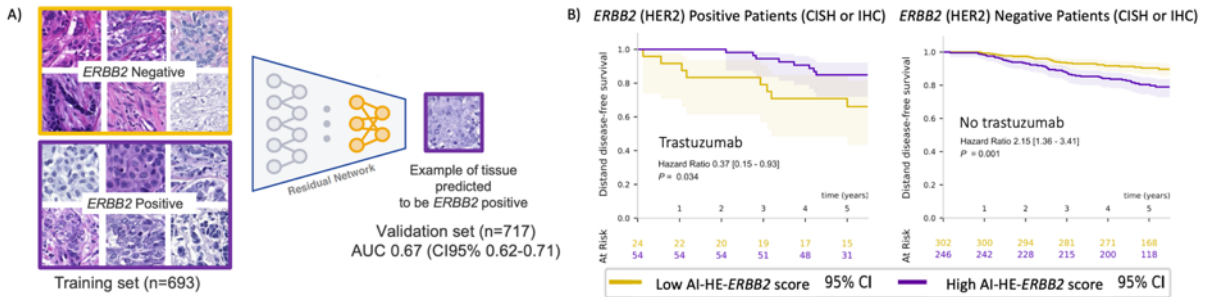
The availability of bioinformatics and data analysis support is a crucial requirement for top international research in life sciences and highly relevant in several strategic profiling areas of all the host universities (UTU, ÅAU, UH, UO, UEF, TAU). Other BF platforms highly rely on the BF Bioinformatics Platform in providing the data analysis and scientific IT/infrastructure support critical for their operation.

Professor Satu Mustjoki investigated how immunological features are linked to hematological cancer subtypes, genetic and epigenetic alterations and patient survival. Understanding factors that shape the immune landscape across hematological malignancies is essential for immunotherapy development. Support provided by the BF Genome-wide methods and BF Bioinformatics platforms were used in the study. (Dufva et al. Immunogenomic Landscape of Hematological Malignancies. Cancer Cell. 2020 Sep 14;38(3):380-399.e13. doi: 10.1016/j.ccell.2020.06.002. Impact Factor (IF) 26.602)

Professor Jukka Westermarck identified a new cancer regulating molecule (UBR5) and studied its implication in the context of breast cancer. The findings were facilitated by the support provided by the BF Genome-wide methods and BF Bioinformatics platforms. (Qiao et al. UBR5 is Coamplified with MYC in Breast Tumors and Encodes and Ubiquiting Ligase That Limits MYC-Dependent Apoptosis. Cancer Res. 2020 Apr 1;80(7):1414-1427. doi: 10.1158/0008-5472.CAN-19-1647. Impact Factor (IF) 9.727.)

BF BioImaging

Wickström-lab utilized BIU-LM and EMBI facilities to demonstrate that cells protect themselves from mechanical stress by



deforming not only the nucleus, but also by softening the genetic material itself. They also demonstrate that cancer cells are less sensitive to mechanical stretch than healthy stem cells, which could contribute to cancer formation.

Nava, M., Miroshnikova, Y., Biggs, L., Whitefield, D., Metge, F., Boucas, J., Vihinen, H., Jokitalo, E., Li, X., Arcos, J., Hoffmann, B., Merkel, R., Niessen, C., Dahl, K., Wickström, S. (2020). Heterochromatin-Driven Nuclear Softening Protects the Genome against Mechanical Stress-Induced Damage. ***Cell*** 181:800-817.

Drug discovery and chemical biology

When the SARS-CoV-2 pandemic started in early 2020, several research groups and core facility units at the University of Helsinki, including the DDCB unit HiLIFE-HTB at FIMM, joined forces and formed a multidisciplinary team to pursue rapid discovery of novel treatment and prevention strategies. We set up a functional drug response profiling platform for SARS-CoV-2 by coupling the state-of-the-art automation platform and data analysis pipeline at FIMM with established BSL3 antiviral testing capabilities against the coronavirus at the Department of Virology. By screening libraries of approved drugs, we have made several interesting findings, which are currently proceeding to *in vivo* studies. This research may lead towards new treatments but will also advance our understanding on SARS-CoV-2 infection.

Genome-wide methods

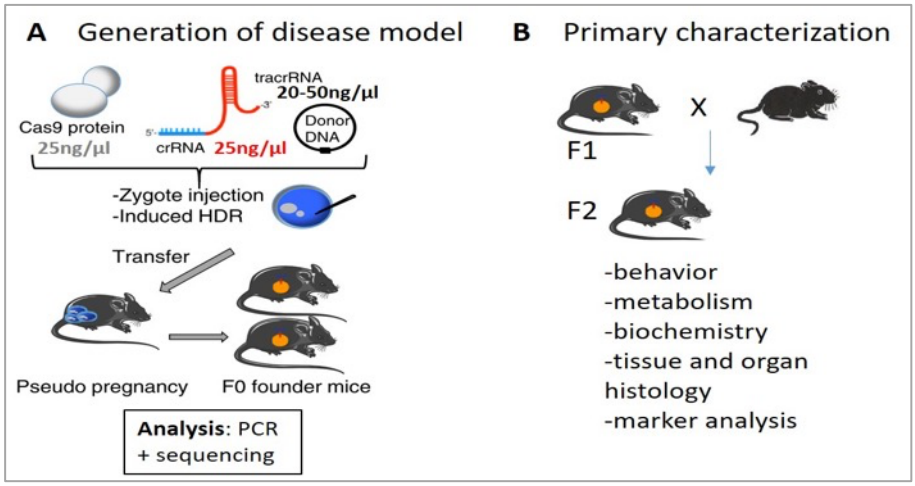
An international collaboration led by Filip Scheperjans and Petri Auvinen studied links between human gut microbiome and Parkinson disease. They found that several risk markers of Parkinson disease are associated with the composition of gut microbiota, and plan further investigations integrating multiomics and clinical data. GWM platform was involved throughout the study including study design, optimisation of several laboratory protocols, and data analysis. *(Heinzel S et al. Gut microbiome signatures of risk and prodromal markers of Parkinson disease. Ann Neurol 2020 Aug; 88(2): 320-331).*

An exciting national partnership led by Merja Heinäniemi and Olli Lohi used single cell RNA-sequencing (scRNA-seq) to characterise B-lineage differentiation in normal and leukemic bone marrow at diagnosis as well as during chemotherapy. Their results paint a detailed picture into transcription factor activities in these tissues and provide ideas for future treatment strategies targeting the immune microenvironment and regulatory network in acute lymphoblastic leukemia. Turku nodes for GWM and Single-Cell Omics worked together to provide expertise in library preparation and next-generation sequencing service for scRNA-seq. *(Mehtonen J et al. Single cell characterisation of B-lymphoid differentiation and leukemic cell states during chemotherapy in ETV6-RUNX1-positive pediatric leukemia identifies drug-targetable transcription factor activities. Genome Med 2020 Nov 20; 12(1): 99).*

A landmark paper by Giuseppe Balistreri, Olli Vapalahti and international collaborators examined the role of neuropilin-1 (NRP1) in Covid-19 infection. Their study discovered that NRP1 significantly strengthens SARS-CoV-2 infectivity and that this effect can be blocked by a monoclonal antibody against NRP1. The data provided insight into the infectivity of SARS-CoV-2 and identified a potential target for antiviral treatment. GWM platform provided library clones for this study. *(Cantuti-Castelvetri L et al. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. Science 2020 Nov 13; 370(6518): 856-860).*

GWM platform also took part in an international effort to examine the distribution of SARS-CoV-2 genetic clades across Europe. The study highlighted the importance of real-time sequencing and data dissemination in a pandemic situation, and laid a foundation for future European genomic surveillance of

SARS-CoV-2. GWM platform provided expertise in library preparation and next-generation sequencing service. *(Alm E et al. Geographical and temporal distribution of SARS-CoV-2 clades in the WHO European Region, January to June 2020. Euro Surveill 2020 Aug; 25(32):2001410).*



FinGMice - Mouse models

The national FinnDisMice project was established in the beginning of February 2020. It focuses on modeling a set of Finnish disease heritage syndromes in mouse. The modelled diseases are selected based on their clinical relevance, active ongoing research and lack of animal model that would faithfully recapitulate the given disease. The goals of the project are to facilitate understanding of disease pathomechanisms that are causative for these rare diseases, provide valuable but currently missing information of the organ and tissue level disease-causative changes necessary for development of therapeutic strategies and generate preclinical validation instruments for potential new therapies.

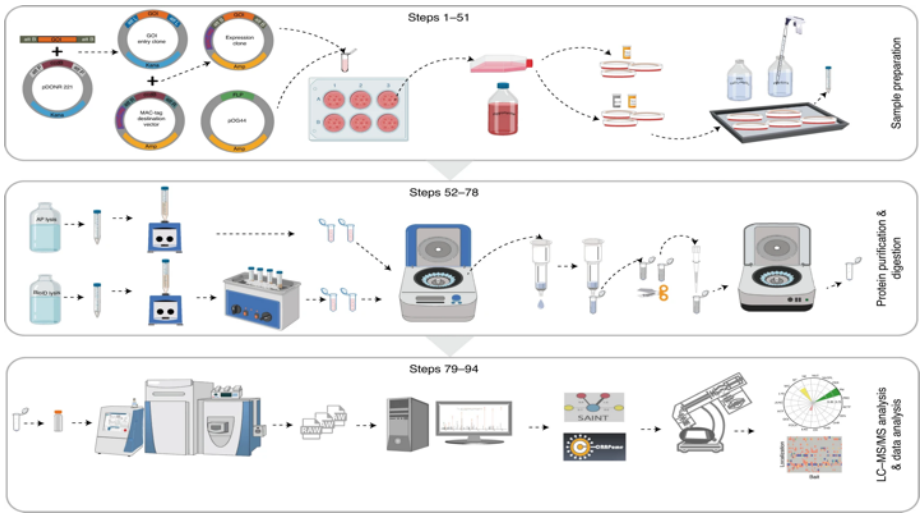
The consortium: Project coordinator: Satu Kuure, GM-Unit, HiLIFE, University of Helsinki. Partners: Reetta Hinttala, TG unit, BCO, University of Oulu and Petra Sipilä, TCDM, University of Turku.

Figure. FinnDisMice project strategy. A) Design of disease mouse model generation utilizes CRISPR/Cas9 genome editing where small gRNA (crRNA-tracrRNA) molecules direct Cas9 protein. Cas9 protein, gRNA and template DNA are micro-injected into fertilized oocytes (zygotes). Upon the cut made by Cas9 and generating double-strand break to the site of mutation in a given gene, donor DNA containing the disease-causing mutation is introduced to the mouse genome via homology directed repair (HDR). Injected zygotes are transferred to foster mothers who give birth to potential founder mice, which fare analyzed for the presence of desired mutation by PCR and Sanger sequencing. B) The confirmed founders will mate with wild type mice to confirm the germ line transmission and set up the new mouse line carrying the disease-causing mutation. Phenotypic characterization including behavioral, metabolic etc. analysis is initiated in F2 generations where homozygote mice can be produced.

Metabolomics

ViMU was involved as a co-author in scientific publications where metabolomics and/or mass spec data and expertise 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).

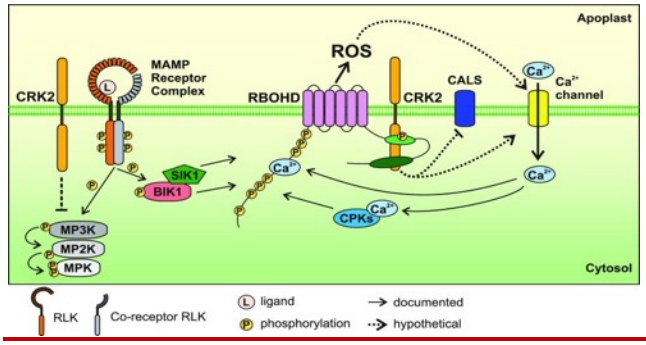
FIMM-Meta has increased its local and international academic and clinical collaborations even though COVID 19 Pandemic situation and the Unit had 28 projects started or ongoing during 2020. FIMM-Meta has been co-author in peer-reviewed high impact publication in article by Prof. Anu Suomalainen in Cell Metabolism, which showed how Vitamin B3/Niacin improves muscle performance in Mitochondrial Myopathy (https://doi.org/10.1016/j.cmet.2020.04.008). Furthermore, FIMM-Meta participated 2020 in SARS-CoV-2 research with Prof. Denis Kainov (Norwegian University of Science and Technology) and Unit PI Anni Nieminen as co-author, currently found as preprint in Biorxiv.



HiLIPID has promoted breakthrough basic research, with the highlight of revealing the mechanisms how growth, energy storage and adipocity are induced as response to nutrient supply (recent EMBO Reports article of Professor Ville Hietakangas group). In human studies, the power of plant stanol ester supplementation to reduce plasma LDL cholesterol concentration as treatment of atherosclerotic cardiovascular disease was proven (recent Arterioscler Thromb Vasc Biol article by a team led by Docent Katariina Öörni)

Supported by business sector collaborators, the platform succeeded in obtaining Academy of Finland FIRI 2020 funding to establish national mass-spectrometry competence center of lipid mediators that starts to serve in HiLIPID laboratory in 2021.

In addition to providing technology for numerous PhD thesis projects, in Helsinki area we yearly coordinate combined effort of 30 omics specialists in offering an extensive course ”Principles of Bioscience Omics” to under- and post-graduate students, and without Biocenter Finland infrastructures such quality education would not be possible.



The work at BCK has continued on metabolomics and lipidomics applications for food, health, toxicology, and nutrition studies. BCK has been involved to 56 projects in above-mentioned areas of research. In year 2020 BCK had analyzed over 61.000 samples.

These research results will be and are published in highly reputed international journals. A major deal of the publications are used in PhD theses. BCK was involved in 15 peer-reviewed scientific publications; as a co-author, where analytical services were provided by the unit.

Protein-proteome

Example study 1: Combined proximity labeling and affinity purification-mass spectrometry workflow for mapping and visualizing protein interaction networks. Liu X, Salokas K, Weldatsadik RG, Gawriyski L, Varjosalo M. Nat Protoc. 2020, 15(10):3182-3211. doi: 10.1038/s41596-020-0365-x. PMID: 32778839

The MAC-tag technology allows an easy way to probe the molecular level localisation of protein of interest. The protocol combines two state-of-the art methods affinity purification - mass spectrometry (AP-MS) and proximity-dependent biotin identification (BioID) to allow rapid identification of protein-protein interactions and more. In this protocol, a detailed three-stage procedure for the MAC-tag workflow was described: (1) cell line generation for the MAC-tagged POI; (2) parallel AP–MS and BioID protein purification followed by MS analysis; and (3) protein interaction data analysis, data filtration and visualization with our localization visualization platform. The developed integrated approach will empower, not only the interaction proteomics community, but also cell/molecular/structural biologists, with

an experimentally proven integrated workflow for mapping in detail the physical and functional interactions and the molecular context of proteins.

Example study 2: CRK2 and C-terminal Phosphorylation of NADPH Oxidase RBOHD Regulate Reactive Oxygen Species Production in Arabidopsis. Kimura S, Hunter K, Vaahtera L, Tran HC, Citterico M, Vaattovaara A, Rokka A, Stolze SC, Harzen A, Meißner L, Wilkens MMT, Hamann T, Toyota M, Nakagami H, Wrzaczek M. Plant Cell. 2020; 32(4):1063-1080. doi: 10.1105/tpc.19.00525. PMID: 32034035

Reactive oxygen species (ROS) are important messengers in eukaryotic organisms, and their production is tightly controlled. Active extracellular ROS production by NADPH oxidases in plants is triggered by receptor-like protein kinase-dependent signaling networks. Kimura and colleagues showed that CYSTEINE-RICH RLK2 (CRK2) kinase activity is required for plant growth and CRK2 exists in a preformed complex with the NADPH oxidase RESPIRATORY BURST OXIDASE HOMOLOG D (RBOHD) in Arabidopsis (Arabidopsis thaliana). The study exploited the protomics facility services of the PPN Turku node and focused especially on the phosphoproteomic analyses.

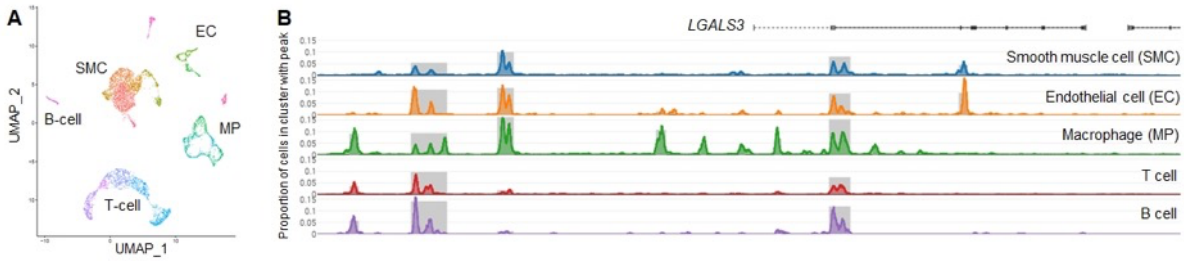
Plant Phenotyping

Image-based method utilizing chlorophyll fluorescence sensors was established to score plant pathogen disease progression and severity in dissected plant organs. https://doi.org/10.3390/plants10010158

Real-time Imaging

RTI unit was hit tremendously by the ongoing world crisis. Projects which were underway in the spring of 2020, had to be suspended, first due to the uncertainty of the availability of animals for imaging from the diverse providers. The projects initially planned for 2020 were all based on the availability of specific mouse or rat strains, of certain genetic characteristics, or specific treatment which would take from, few weeks to several months to develop the phenotype required for study. Some of these animals were being bred abroad. As the personnel was not readily available, and due to travel restrictions, the strains had to be terminated or the treatments suspended. This resulted in imaging services not being done. The uncertainty on the changes of the situation were repeatedly marked after the summer when initiation of activities were planned. Second waves of COVID-19 delayed more the creation of suitable animals for imaging. This crisis brought upon that the continuation of activities to return spring 2021, where we plan to start working on generation of the adequate models for imaging. Other researchers, who might have been needing the services turned down their nuclear imaging projects to second or their priority due to the crisis. The RadChem unit started a few academic service projects in 2020 but due to the present situation, the completion and billing of the projects has been postponed to 2021 and only pilot experiments were carried out in 2020.

The work in the SPECT/CT node of the RTI unit was mainly in validating methods and developing protocols, as specified in the past section. The impact of these new methods are going to be tested in the coming years.



Single cell omics

A landmark study by Depuydt *et al*, provided the first single nuclei chromatin accessibility profile of immune cells in human atherosclerotic lesions to better understand the molecular complexity of disease. This allowed identification of specific transcription factors associated with the myeloid subpopulation and T cell cytokine profiles underlying their activation in atherosclerosis. This study was made possible by a collaboration between the Single-Cell Omics platform nodes providing expertise for generation of single nuclei suspension from highly calcified tissues and library preparation and an international team of collaborators.

Depuydt MA, Prange KH, Slenders L, Örd T, Elbersen D, Boltjes A, de Jager SC, Asselbergs FW, de Borst GJ, Aavik E, Lönnberg T, Lutgens E, Glass CK, den Ruijter HM, Kaikkonen MU, Bot I, Slütter B, van der Laan SW, Yla-Herttuala S, Mokry M, Kuiper J, de Winther MP, Pasterkamp G. Microanatomy of the Human Atherosclerotic Plaque by Single-Cell Transcriptomics. Circ Res. 2020 Sep 28. doi: 10.1161/CIRCRESAHA.120.316770

(A) UMAP projection with automated clustering of 7,000 single-nuclei representing the five major clusters corresponding to smooth muscle cells (SMCs), endothelial cells (ECs), macrophages (MPs), T-cells and B-cells. (B) Loupe browser visualization of snATAC-Seq signal around the LGALS3 gene.

Stem cells & Genome editing

Human-induced pluripotent stem cell (hiPSC)-derived disease-specific cell models, coupled with the progress in genome editing technology, serve as an opportunity to study pathophysiological mechanisms in disease-relevant cell models. Pluripotent stem cells are essential tools in biomedical research, evidenced by the rapidly increasing number of publications and research consortia based on hiPSC models. Life sciences with an emphasis on stem cell research is a priority area of the University of Helsinki and the Tampere University. Health sciences, especially molecular medicine concentrating on cardiovascular, endocrinological, and neurological diseases is one of the three top research areas of the University of Eastern Finland. To make state-of-the-art stem cell and genome editing approaches readily available, Finnish researchers must have access to cost-effective high-quality services tailored to meet national needs. In 2020, Stem cell and Genome editing platform partners published 15 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 this consortium is presented below:

FinGEEC-Helsinki: Translational service project was initiated with UPM Biomedicals related to use of patient-derived materials.

BCH: entered the trusted partnership negotiation with Helsinki biobank.

BCH: PMID: 33164986; 32437855; 33178051, 32442534, 32275861 and 32867368. These publications highlight the advantage of using iPSC derived beta cells, neuronal and endothelial cells and genome editing for modelling pancreatic b-cell, motor neuron diseases, vascular development and CRISPR activators technology to study cancer.

TAU PMID: 31208058, 32494857, 32651186. These publications highlight the use of iPS cells to model genetic diseases and the use and fabrication of various divices for that purpose. Additionally iPSC-derived hepatocytes have been used to study liver lipid metabolism in detail. The iPSC derived cells have also been used as the cell model to fabricate and optimice different divices, e.g. hypoxia related equipment. These technology improvements relate to the machine learning and organ-on-culture studies and their future potential application in stem cell research.

BMT/MED has during the past years submitted four patent applications and one of those got final approval year 2016. Additionally, BMT has created several software for both research groups and companies especially for analysing cardiomyocytes (CardioMDA for electrical analysis, AnamalyExplorer for Ca-transients, CellVisual for mechanical behaviour and CytoSpectre for orientation). All these are freely available for all researchers

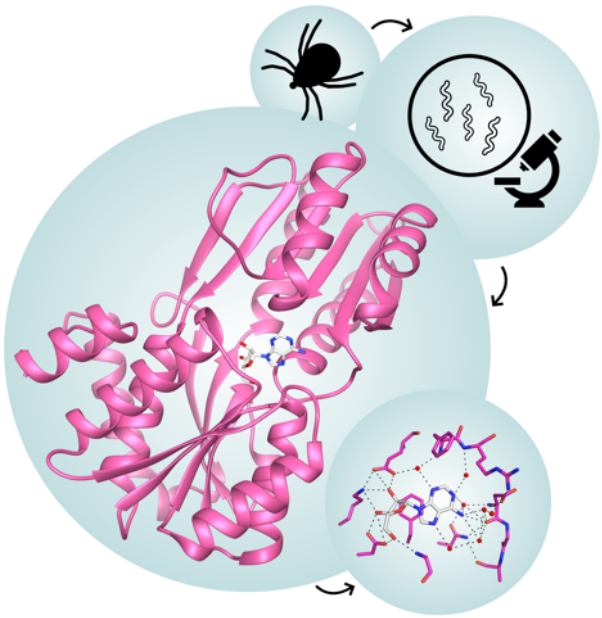
BMT/MED has produced one PhD work related to the core facilities: Disheet Shah. The work was about diseae modelling of dilated cardiomyopathy using iPSC deriveved cardiomyotes from patients.

Structural biology

Structural and Biomolecular Analyses of *Borrelia burgdorferi* BmpD

Ixodes ticks transmit the spirochaetal *Borrelia* bacteria, the causative agent of tick-borne Lyme borreliosis (LB), to humans. *B. burgdorferi* cannot synthesize nucleosides, needed for e.g DNA/RNA synthesis and, thus, it must obtain them from the host. The BmpD protein has a significant role in this process as a substrate-binding protein that binds to purine nucleosides in the periplasmic space and transports them to a membrane-bound ABC-transporter, which transfers the nucleosides into the cytoplasm of the bacteria. Hence BmpD has an important role in bacterial survival and enables sustaining an infection in the host organism.

The project was done in close collaboration with MSc Mia Åstrand and Dr. Gabriela Guédez from Tiina Salminen's group (Structural Bioinformatics Laboratory, Åbo Akademi University) and MSc Julia Cuellar from Dr. Jukka Hytönen's group (Institute of Biomedicine, University of Turku). During this project two PhD students were trained at SBL: Julia Cuellar in protein purification and ligand-binding studies, and Mia Åstrand in protein crystallization and analysis of crystal structures. The project contributed to Julia Cuellar's PhD thesis (2020) and will be part of Mia Åstrand's PhD thesis (2021).

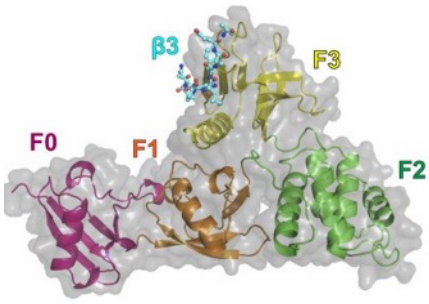


Crystal structure of *Borrelia burgdorferi* BmpD in complex with adenosine (Cover illustration of *Infection and Immunity* (2020) 88(4):e00962-19).

Cuellar J, Åstrand M, Elovaara H, Pietikäinen A, Sirén S, Liljeblad A, Guédez G*, Salminen TA*, Hytönen J.* (2020) Structural and biomolecular analyses of *Borrelia burgdorferi* BmpD reveal a substrate-binding protein of an ABC-type nucleoside transporter family. *Infection and Immunity* 88(4):e00962-19.

Atomic resolution structure of talin bound to integrin explains integrin function.

Structural characterization of the FERM-folded active talin head provides fundamental understanding of the regulatory mechanism of integrin function. Many of the previous mechanistic models based on the talin adapter are likely to be misleading because they were based on the crystal structure of an improperly folded talin head domain. We solved a new structure of a FERM-folded talon head complexed with β3-integrin and confirmed this by transmission electron microscopy. Overall, the results reveal the importance of the FERM-like conformation of the talin head for the coactivation and clustering of integrins.



Crystal structure of talin head in a FERM-folded configuration. (Figure 1 (B) Proc Natl Acad Sci U S A 117(51):32402-32412.).

Zhang, P.,Azizi, L., Kukkurainen, S., Gao, T, Baikoghli, M., Jacquier, M., Sun, Y., Määttä, J.A.E., Cheng, R.H., Wehrle-Haller, B., Hytönen, V.P., Wu, J. (2020) Crystal structure of the FERM-folded talin head reveals the determinants for integrin binding. Proc Natl Acad Sci U S A 117(51):32402-32412.

HOST UNIVERSITIES, MEMBER INSTITUTES AND FACULTY

Host universities and member institutes

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

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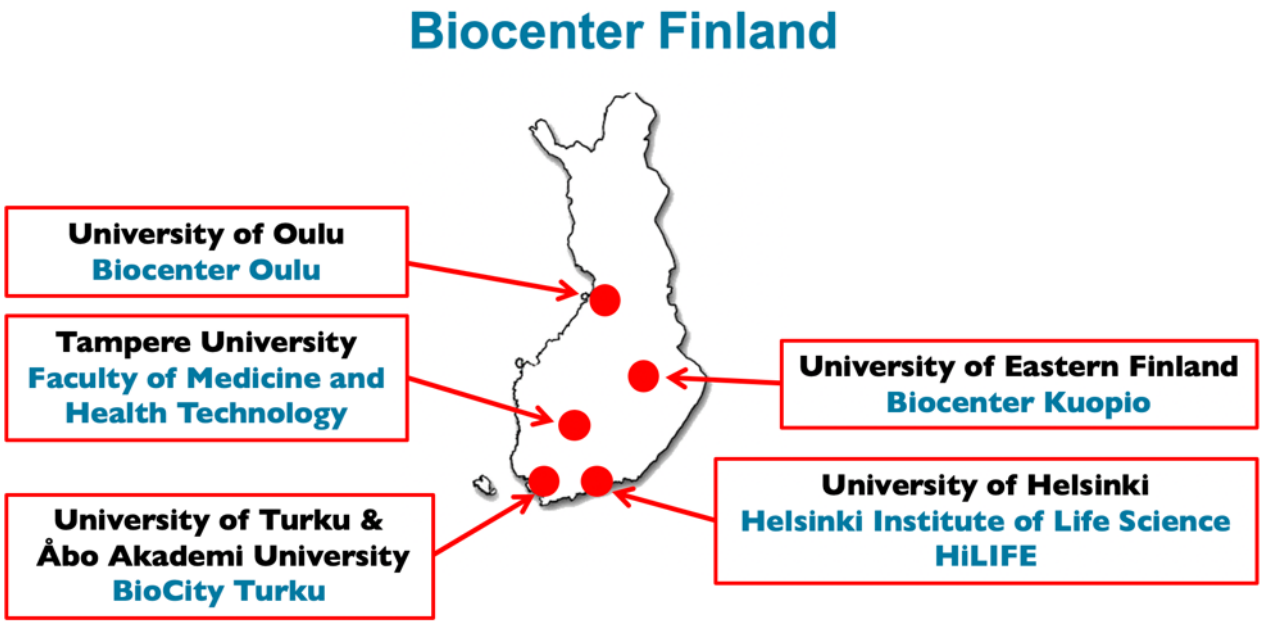

Figure 6. The host universities and their BF member institutes in 2020.

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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.

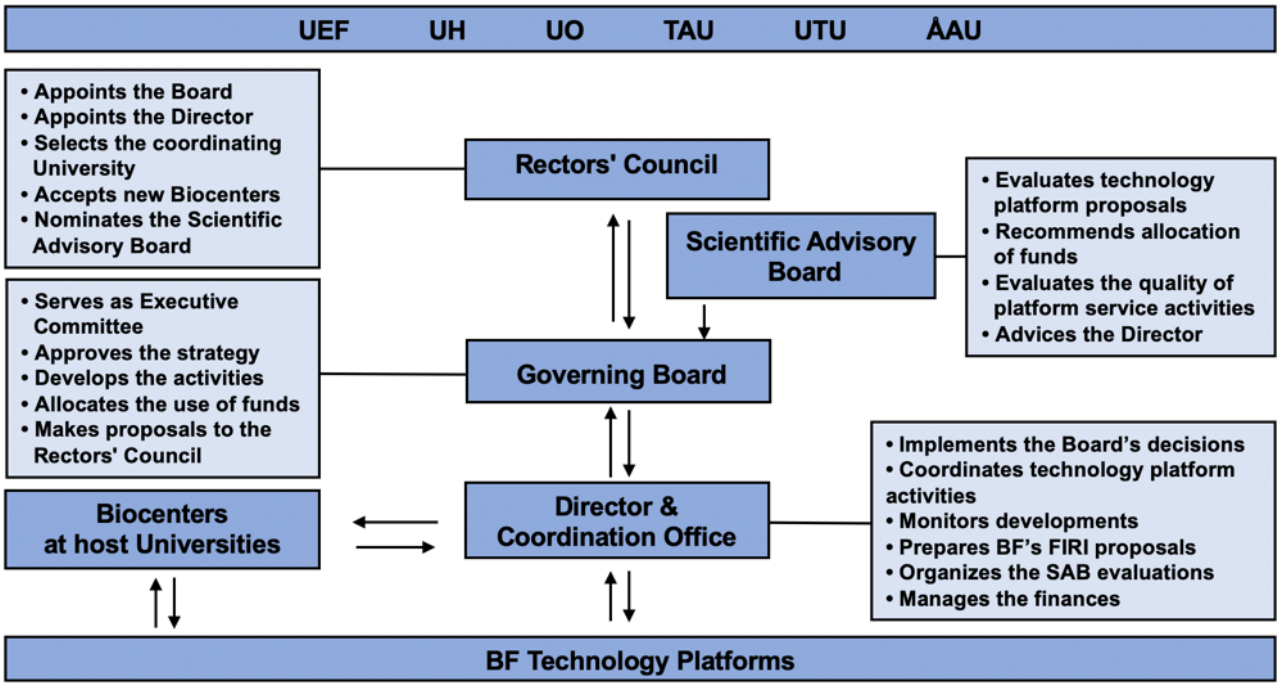

Figure 7. The governance and organization of Biocenter Finland.

Governing board

The BF Governing Board in 2020 was Academy Professor Seppo Ylä-Herttuala Chair, UEF; Professor Mark Daly, UH; Professor Lauri Eklund UO; Professor John Eriksson, ÅAU; Professor Jyrki Heino, Vice-chair, UTU; Professor Tomi Mäkelä, UH, Professor Olli Silvennoinen, UH, and Professor Tapio Visakorpi, TAU.

Coordination office

Professor Marja Makarow served as the director, Antti Siltanen was the coordinator, and Ms Anu Taulio the secretary.

The Scientific Advisory Board of Biocenter Finland 2020-2024

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

Chair: **Professor Carl-Henrik Heldin**, 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).

Each Technology platforms' achievements in 2020 are described on pages 18-72.

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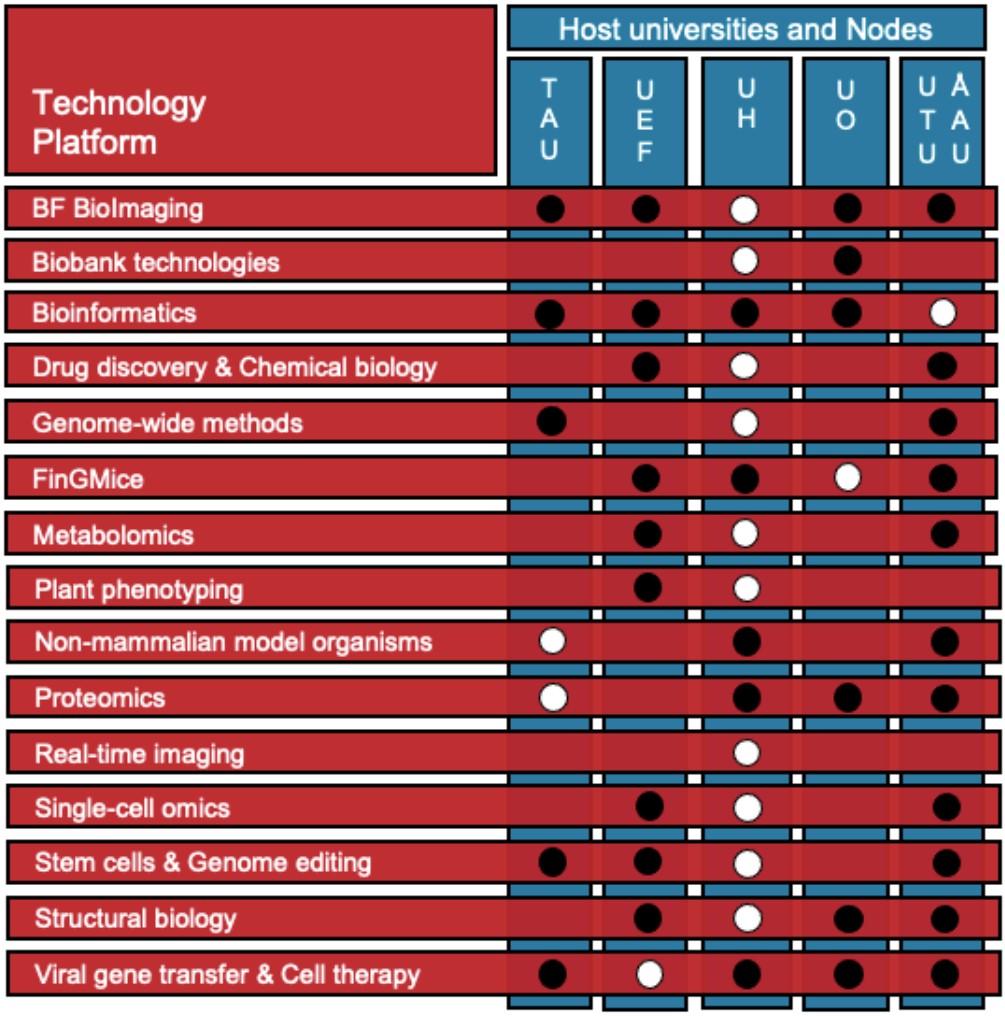

Figure 8. The BF technology platforms and local nodes hosted by the host universities. The dots indicate in which member institute the nodes are located. White dots indicate platform chairmanship. TAU: Tampere University:

BIOBANK TECHNOLOGIES

Chair of the platform: Johan Lundin, UH

Node PIs: Olli Carpen UH, Raisa Serpi UO

http://bioinformatics.biocenter.fi/

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.

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 and has served 24 customers within UH, 12 other academic customers (e.g. within HUS, TTL,

Minerva and Aalto university) and 3 companies.

The unit further has unique capabilities in multiplexed fluorescent immunohistochemistry and provides this as a service and has during 2020 provided services to 24 customers. 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 provided from 2020 onwards.

The nationwide consortium has synergies and has a strong interest in further developing the services. The scientific advisory board of BF in its 2020 evaluation was generally impressed by the developments within the platform and suggested a support of Node 1 with 60 kEU/year, Node 2 with 30 kEUR/ year and Node 3 with 43 kEUR/year. However, only Node 1 received support in 2020 and the total sum granted via HiLIFE was cut by more than 50%. This has hampered the development of the BF platform. All Nodes are continuing their respective operations, but joint novel efforts within BF have been challenging due to the scarce resources.

User statistics

The platform served 17 user groups in 2020.

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-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

The BF SAB found that the type of emerging resource that the platform provides definitely is a strength for the BF effort and that the infrastructure has momentum and a lot of potential, this also relates to the complementarity of the partners. It is essential that the digital resources are set up in a way where secondary use of the digitized records is made possible and facilitated. The SAB also emphasized the importance of harmonizing meta data principles, terminologies and ontologies and the platform will take this feedback into account during 2021-2024.

Tasks of the platform in 2021-24

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 2021-24, we will include image analysis services as well. During the year 2020, we have increasingly included image analysis services. These include 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

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 2021;106(3):718-29.

Pollari M, et al. Adverse prognostic impact of regulatory T-cells in testicular diffuse large B-cell lymphoma. Eur J Haematol 2020;105(6):712-21.

Eineluoto JT, et al. Associations of PTEN and ERG with Magnetic Resonance Imaging Visibility and Assessment of Non-organ-confined Pathology and Biochemical Recurrence After Radical Prostatectomy. Eur Urol Focus 10.1016/j.euf.2020.06.016

Gramolelli S, et al. Oncogenic Herpesvirus Engages Endothelial Transcription Factors SOX18 and PROX1 to Increase Viral Genome Copies and Virus Production. Cancer Res 2020;80(15):3116-29.

Fortino V, et al. Machine-learning-driven biomarker discovery for the discrimination between allergic and irritant contact dermatitis. Proc Natl Acad Sci U S A 2020;117(52):33474-85.

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 is currently 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 is actively ongoing for single-cell data analysis and high content imaging. Computational infrastructure has been further developed to support high-throughput protein sequence analysis and to enable more efficient analysis of bacterial genomes and eukaryotic transcriptomes.

Additionally, the BF Bioinformatics Platform provides scientific IT support which is also widely used by the other BF Platforms that need local expertise in their data management, storage and computing. These operations are organized in collaboration with CSC and ELIXIR. 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 2020 the total annual BF strategic host university funding for the BF Bioinformatics Platform nodes was ~340kEUR, 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 and again in 2020, 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 for it to serve the scientific community in its great need of additional bioinformatics support. Unfortunately this need remains largely unmet in funding term 2021-2024, the BF funding remaining at the level of the previous years in the nodes in UTU and ÅAU and UO, while modest increase is taking place in UEF (from 31k€ to 37k€), in UTA (from 18k€ to 30k€) in BI/UH from (45k€ to 60k€) and FIMM/UH (from 99k€ to 120k€). Notably, similar to previous years, some universities provide significant additional other funding for national level bioinformatics support operations (UH/FIMM, UO, ÅAU, UEF). With the current funding level, the significant strengthening and development of the bioinformatics support, seen critically important by the BF SAB in its evaluation, will unfortunately not be possible but only small developments are annually feasible.

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.

User statistics

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

In 2020, 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.

General		Number of user groups				
Host Univ	Name of core facility	local	national	inter-national	non-academic	Total
UEF	Bioinformatics Center	26	0	0	0	26
UH	BI-BIOINFO	25	15			40
UH	FIMM	72	33	3	10	118
UO	BCO Biocomputing Research Infra	8	3	2	1	14
UTA		6	2	0	0	8
UTU	Medical Bioinformatics Centre	19	8	3		30
ÅAU	Structural Bioinformatics Laborato	24	3	10	1	38
		180	64	18	12	274

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

FGCI - Finnish Grid and Cloud Infrastructure. The BF Bioinformatics Platform participates in FGCI for scientific computing, in particular molecular simulations for proteins and/or membranes. https://research.csc.fi/fgci

Future perspectives

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

- Transcriptomics
- Genomics
- Epigenomics
- Proteomics
- Metabolomics
- Metagenomics, metatranscriptomics and metaproteomics
- Structural bioinformatics
- Liquid biopsy data analysis
- Screening data analysis (e.g. drug sensitivity & resistance screening)
- Imaging related to biomedical research (e.g. digital pathology)
- Data integration
- Clinical applications
- In silico modeling and simulation of biological systems
- Development of data analysis support for new omics technologies

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 continues to provide consultation and training for research related to the various support areas.

Within the platform nodes with no increase in strategic BF funding (UTU, ÅAU and UO), the focus during 2021 will be in attempting to maintain the current level of support. While the user-fee based cost-recovery system will be further developed, this alone cannot secure the development and sustainability of the support services in the future. With the nodes with increase in the budget (UEF, UTA, BI/UH, FIMM/UH), support portfolio will be moderately expanded according to the needs of the support users.

Currently the strongest need for the development of new support services is seen 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. Sensitive data handling issues are also increasingly requiring attention and new solutions.

In the funding term 2021-2024 the co-operation of the platform nodes will be

strengthened according to the available resources to enable efficient utilization of the BF Bioinformatics Platform.

Major publications supported by the platform services

Dufva O, et al. Immunogenomic Landscape of Hematological Malignancies. Cancer Cell 2020;38(3):380-399.e13.

Tiihonen J, et al. Neurobiological roots of psychopathy. Mol Psychiatry 2020;25(12):3432-41.

Kim D, et al. Somatic mTOR mutation in clonally expanded T lymphocytes associated with chronic graft versus host disease. Nat Commun 2020;11(1):2246.

Qiao X, et al. UBR5 Is Coamplified with MYC in Breast Tumors and Encodes an Ubiquitin Ligase That Limits MYC-Dependent Apoptosis. Cancer Res 2020;80(7):1414-27.

Kelkka T, et al. Adult-Onset Anti-Citrullinated Peptide Antibody-Negative Destructive Rheumatoid Arthritis Is Characterized by a Disease-Specific CD8+ T Lymphocyte Signature. Front Immunol 2020;11:578848.

Storey D, et al. Klebsiella pneumoniae type VI secretion system-mediated microbial competition is PhoPQ controlled and reactive oxygen species dependent. PLoS Pathog 2020;16(3):e1007969.

Denesyuk AI, et al. NBCZone: Universal three-dimensional construction of eleven amino acids near the catalytic nucleophile and base in the superfamily of (chymo)trypsin-like serine fold proteases. Int J Biol Macromol 2020;153:399-411.

Ranga V, et al. Immunogenic SARS-CoV-2 Epitopes: In Silico Study Towards Better Understanding of COVID-19 Disease-Paving the Way for Vaccine Development. Vaccines (Basel) 2020;8(3):E408.

Harjula SE, et al. Characterization of immune response against Mycobacterium marinum infection in the main hematopoietic organ of adult zebrafish (Danio rerio). Dev Comp Immunol 2020;103:103523.

Daddali R, et al. CPPED1-targeting microRNA-371a-5p expression in human placenta associates with spontaneous delivery. PLoS One 2020;15(6):e0234403.

BF BIOIMAGING

Chair of the platform: Eija Jokitalo, Helsinki BioImaging, EMBI

Partners:

Helsinki BioImaging: Electron Microscopy unit (EMBI), Eija Jokitalo, BI-HiLIFE; Biomedicum Imaging Unit (BIU-LM), Elina Ikonen, HILIFE and Faculty of Medicine; 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

Turku BioImaging: Turku Cell Imaging Core (CIC-TBI), Pasi Kankaanpää, Turku Bioscience center; Electron Microscopy Unit (EM-TBI), Eeva-Liisa Eskelinen, Institute of Biomedicine; Turku High Throughput Microscopy Unit, Michael Courtney, Turku Bioscience center

Oulu BioImaging: Light Microscopy Core Facility (LM-BCO), Lauri Eklund, Tissue Imaging Center (TIC-BCO); Electron Microscopy Core Facility (EM-BCO, Ilkka Miinalainen, TIC-BCO

Tampere BioImaging: Tampere Imaging Facility (TIF), Teemu Ihalainen, Faculty of Medicine and Health Technology

Eastern Finland BioImaging: Light Microscopy unit (LM-UEF), Kirsi Rilla, School of Medicine; Electron Microscopy unit (EM-UEF), Arto Koistinen, BCK

Development of technology services

The National imaging infrastructure network has recently undergone major restructuring, as the BF Light microscopy (LM) and BF Electron microscopy (EM) platforms were merged into a new Biocenter Finland Biological Imaging Infrastructure (BF BioImaging) at the beginning of 2020. Open access services to state-of-the-art equipment and expertise in LM, EM, high content imaging, mesoscopic imaging and image analysis are 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 LM and EM communities.

The services provided by the BF BioImaging platform are:

1. **Access to microscopes, technologies and applications**: Nodes support, maintain and develop a powerful portfolio of state-of-the-art microscopes and technologies. LM techniques include a wide range of modalities for both fixed samples and live cell and tissue imaging, ranging from super-resolution to mesoscopic scale imaging, and from label-free imaging to high-content microscopy. EM techniques cover various sample preparation techniques, including immunoEM and cryofixation and –processing and transmission and scanning EM imaging at 2D and 3D.
2. **Access to expertise**: Application specialists support users in all steps of their projects, starting from project planning all the way to image analysis.
3. **Training**: 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 and researchers. We also organize microscopy demos for visitors, including pharmaceutical and biotech companies, and road shows and demos with microscope manufacturers.

During 2020, the platform personnel comprised of 14 PIs, 18 researchers/teachers and 22 technical staff (in total 54 persons and 551 working months). To improve communication between the five Nodes and to engage core personnel and their expertise in platform operations, the platform has distributed coordination of specific development and management tasks into work packages (WP). The first platform personnel meeting was organized in early 2020 to kick off the WPs. WP activities have continued on online workspace (Slack), where each WP has their own channel, enabling easy communication and sharing of materials. During 2020, the WP activities were focused on:
- Quality management for services, in line with international requirements; user access and feedback
- Coordinated local and national solutions for image data storage, access and sharing of data
- Coordination of image analysis knowledge sharing and building a community around bioimage analysts, developers and users; organizing image analysis workshops and consultation.

During spring 2020, each Node had to quickly adjust their services and limit their capacity to ensure safe working environment for its personnel and users during the COVID-19 pandemic. One of the main bottlenecks due to restrictions was the contact teaching for new users, which has to be organized on-site in small instrument rooms. Under these special circumstances, the platform provided services to 1206 users from 476 research groups. About 16% of research groups came outside respective host universities. In addition, the Nodes provided in total 1 064 hours of one-to-one instrument training for 520 new users, and had altogether 74 500 registered instrument hours. Nodes have also been actively involved in SARS-CoV-2 research, including image-based drug testing and developing new image-based assays for measurement of immunity.

The core units have very actively participated to training and education. For example, HBI, OBI and TBI units have participated in Master programs and medical student trainings of respective universities by organizing a specific imaging symposium and courses/workshops/presentations on imaging technologies and analysis, OBI participated in H2020 MSCA ITN V.A. Cure PhD training network and EFBI units organized instrument demos and seminars together with company representatives. We have also actively contributed in organization of international network symposia on microscopy and image analysis (e.g Virtual Early Career European Microscopy Congress 2020, CytoData, NEUBIAS Academy at home).

Three larger instrument upgrades were done during 2020. With FIRI2019 funding, LMU-BI acquired a Leica Stellaris 8 multimodal confocal platform for functional imaging of cellular physiology and dynamics. In addition to white light laser for flexible excitation and high-end detectors for sensitive detection, this system has ultrafast Fluorescence Lifetime Imaging (FLIM), opening novel possibilities for tracking dynamic protein interactions and for utilizing biosensors as reporters for cellular metabolic activity. FIMM-HCA purchased a robotic plate handler, which enables high throughput, high-content imaging of tens of 384-well plates with fully automated day and night operation. TBI purchased Arivis AG software to help in analysis of larger data. This production-level OMERO server was set up following earlier proof-of-concept tests, serving test users also in Oulu and Helsinki. Funding for this was obtained from the Academy of Finland in a separate partnership project to develop image analysis services in the coming years (Health Campus Turku 2.0 / Kankaanpää).

User statistics

See table below.

Participation in international, Nordic and European infrastructures

The major international partner for BF BioImaging platform is **Euro-BioImaging**.

General		Number of user groups				
Host Univ	Name of core facility	local	national	inter-national	non-academic	Total
UEF	UEF-LM	37	4			41
UEF	UEF-EM	14	1		2	17
UH	BIU	71	13		3	87
	LMU	64	5			69
	FIMM-HCA	33	2	1	1	37
	EMBI	59	10	5	2	76
UO	BCO-LM	29	4		1	34
UO	BCO-EM	26	6	5	1	38
UTA	TIC	30				30
TU/ÅA	TBI-CIC,EM & TSU	74	7	3	4	88
						0
		400	48	14	14	476

Euro-BioImaging ERIC was recently officially established by the European Commission, and the official launching of Euro-BioImaging operations coincided with the establishment of the new BF BioImaging. Euro-BioImaging is hosted by Finland, with the main Hub located in Turku, and Finland also has a service-providing Node, a multi-sited Advanced Light Microscopy Node coordinated by TBI and hosted by TBI, HBI and OBI. In 2020, FIMM-HCA was accepted as a new core unit within the Euro-BioImaging Advanced Light Microscope node.

The BF BioImaging platform does and will increasingly collaborate with **other national infrastructures**, BF platforms and their ESFRI counterparts, especially Instruct (service and online solution development collaboration), Elixir (collaboration in EOSC development and national data solutions), Infrafrontier (collaboration in EOSC development and image data solutions) and Finnish Biomedical Imaging Node FiBI (recently established multi-modal molecular imaging and medical imaging Euro-BioImaging node). The platform and its Nodes also collaborate with EU-OpenScreen (image-based HC screening of small compounds), EATRIS (imaging in biomarker discovery) and BBMRI (phenotypic screening of patient cells/tissues). Importantly, the platform actively participates in Global BioImaging (a collaboration network of imaging infrastructures from all continents) and EOSC-Life (a new H2020 project developing services related to the European Open Science Cloud).

In addition, Finland is a member in COMULIS (Correlated Multimodal Imaging in Life Sciences), 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.

Development of image analysis methods, data management solutions and the related teaching is topical at every Node, and hence the platform operates actively in BIIF (BioImage Informatics Finland), which is a network for bioimage analysts, software developers and life scientists using bioimage informatics as a central toolset. Similar activities are continued on the European scale in the Network of European Bioimage Analysts (NEUBIAS), an action fully funded by European COST (CA15124), with Finland being one of the member countries. Pasi Kankaanpää (TBI) and Lassi Paavolainen (P. Horvath group, University of Helsinki) are the representatives of Finland in the Management committee of NEUBIAS.

Future perspectives

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, BF BioImaging will continue to need significant resources in the future years to keep at high international level.

The advanced and developed microscopy technologies bring about an increasing amount of high-resolution image data, and therefore the development of large image data management and analytics will be in the focus. We will also continue the development of remote access and virtual microscopy services, which we started during the pandemic to be able to keep the Nodes active and continue our services. Our aim is to cover more applications and modalities in the future, and to develop solutions for issues such as user authentication, network connection speed and responsiveness, safety protocols both at imaging instruments and online, user training, sample shipping and handling protocols, and flexible post-acquisition access to data.

Major publications supported by the platform services

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Nava MM, et al. Heterochromatin-Driven Nuclear Softening Protects the Genome against Mechanical Stress-Induced Damage. Cell 2020;181(4):800-817.e22.

Bernardes JP, et al. Longitudinal Multi-omics Analyses Identify Responses of Megakaryocytes, Erythroid Cells, and Plasmablasts as Hallmarks of Severe COVID-19. Immunity 2020;53(6):1296-1314.e9.

Natunen T, et al. Diabetic phenotype in mouse and humans reduces the number of microglia around β-amyloid plaques. Mol Neurodegener 2020;15(1):66.

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DRUG DISCOVERY AND CHEMICAL BIOLOGY

Chair of the platform: Päivi Tammela, FIMM-HiLIFE, 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, and provides drug discovery and chemical biology expertise and infrastructure for the bioscience community in Finland. DDCB also coordinates national participation to the EU-OPENSCREEN ERIC.

During 2020, DDCB succeeded well in providing services despite the exceptional circumstances and restrictions placed on laboratory access at our units. Services were provided in total for 176 user groups. At all sites, COVID-19 related requirements for remote use has increasingly become the normal mode of operation. Nevertheless COVID-19 restrictions did cause delays in the installation and operator training for new instruments, such as the FIRI-funded liquid handling platform at BCT-TSU, in part because modification and service visits to adapt our acoustic dispenser were required.

Noteworthy, several DDCB units were supporting SARS-CoV-2-focused research initiatives. For example, the High Throughput Biomedicine unit at FIMM (HiLIFE-HTB) established screening workflows jointly with the Department of Virology, Faculty of Medicine, University of Helsinki (UH), to screen FDA-approved drugs for their effects against SARS-CoV-2. We also supported other experimental set-ups in SARS-CoV-2 research by our automation platform and expertise. At BCT-TSU, virtual screening services at ÅAU were provided in a project related to finding novel inhibitors against SARS-CoV-2 as well as docking and interaction analysis in a project aimed at finding new antibacterials in addition to multiple other virtual screening projects that are still mostly ongoing. Meanwhile at UTU, efforts with CIP2A led to a licensing deal with an international pharmaceutical company. The automation site at UTU complemented ÅAU virtual screening projects directed at SARS-CoV-2 with liquid handling and library resources for screening, while developing a novel ultrasensitive assay to bypass limitations of more routine probes for the main protease, Mpro. At HiLIFE-PHAR, the DDCB unit at the Faculty of Pharmacy, UH, our antibacterial screening platform was upgraded with the Omnilog system which allows running various applications, such as microbial identification, characterization, and phenotypic analyses. It also enables automated workflows for antibacterial screening, which allows us to increase the throughput significantly. During 2020, we validated the system for carrying out label-free MIC assays in HTS format.

User statistics

See table below.

Participation in International, Nordic and European infrastructures

The DDCB serves as the Finnish National ESFRI Node of the European infrastructure EU-

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	inter-national	non-academic	Total
UEF	BCK	BCK-PMC	6	5	7	2	20
UH	HiLIFE	HiLIFE-HTB	51	11	17	1	80
UH	HiLIFE	HiLIFE-PHAR	21	6	8	1	36
UTU	BCT	Biocity-TSU	7	4	3		14
ÅAU	BCT	Biocity-TSU	2	8	15	1	26
	Total		87	34	50	5	176

OPENSCREEN (EU-OS) ERIC - the European infrastructure of open screening platforms for chemical biology. EU-OPENSCREEN FI's Roadmap application last year was successful, and we thus received FIRI Roadmap status for 2021-2024. Finnish partner sites in EU-OS ERIC continue to have a central role in developing the services. In 2020, major achievements in this context included establishing workflows for collecting chemical compounds from academic groups for the European Academic Compound Library. This initiative is led by Prof. Tammela, director of EU-OS FI, who also operates as a contact person in Finland. High Capacity Screening Partner Site in EU-OS, the HiLIFE-HTB unit at FIMM, will be hosting one copy of the EU-OS compound library (100 000 compounds) and first parts of this library arrived to us in late 2020. First EU-OS screening project was also initiated at HiLIFe-HTB in 2020 as part of the H2020-funded EU-OS DRIVE project.

The DDCB platform also actively collaborates with similar platforms in the Nordic countries within the Nordic Chemical Biology Consortium (NCBC) and the Nordic High Content Screening Network (NHCSN). These provides us a great way to share expertise and know-how between similar national chemical biology and screening research platforms in Sweden (Chemical Biology Consortium Sweden), Norway (NOR-OPENSCREEN) and Denmark (DK-OPENSCREEN).

Future perspectives

As part of the FIRI2020 application of Biocenter Finland, we received partial funding for purchasing a high-throughput flow cytometer to the DDCB unit at FIMM, HiLIFE-HTB. This will greatly improve our capabilities to develop and expand the Drug Sensitivity and Resistance Testing platform based on flow cytometry (FC) for additional cancer types. Completion of the delayed installation of the FIRI2018-funded automated assay set-up platform at BCT-TSU in early 2021 will allow us to proceed with development of fragment-based screening services. We also aim to develop imaging-based screening services in collaboration with the High Content Imaging and Analysis Unit at FIMM. Only single cell biology has the power to reveal distinct cell-specific mechanisms of action of compounds, so BCT-TSU will establish inter-core services linking live single cell imaging with downstream single cell omics so that dynamic and omic consequences of agents, from tools to clinically used compounds, can be followed at a single cell level.

Furthermore, updated version of the DSRT library at HiLIFE-HTB will be launched in near future. Our aim is also to renew other compound libraries hosted by DDCB, and planning this operation is currently ongoing. Active promotion of the EU-OS Academic Compound Collection Initiative will be relevant during the coming years. We are also renewing our current manual compound storage system in 2021 to a multipod storage system, which allows facilitated handling of compound library plates and improved control of storage conditions.

In the antimicrobial screening services at the HiLIFE-PHAR, the DDCB unit at the Faculty of Pharmacy, UH, we will focus on expanding our service portfolio towards anaerobic bacteria and infection models in small animals. We have also seen increasing interest on providing antibacterial profiling services for natural products and compounds isolated thereof, and emphasis on our capabilities in this context is also included in our future perspectives.

For virtual screening both puhti and mahti supercomputers are at operational stage. The main future topics are preparation for LUMI supercomputer and preparation of ultra-large ENAMINE REALD database for modeling purpose. For LUMI, the main issue is compiling the Desmond MD engine so that AMD GPU-cards can be used. For the ENAMINE database the issue is size of the system, more than 1500 million compounds.

Both projects are already under preparation with collaboration partners (CSC and Orion Pharma).

Major publications supported by the platform services

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Li LL, et al. Resonance energy transfer sensitises and monitors in situ switching of LOV2-based optogenetic actuators. Nat Commun 2020;11(1):5107.

Singha PK, et al. Evaluation of FASN inhibitors by a versatile toolkit reveals differences in pharmacology between human and rodent FASN preparations and in antiproliferative efficacy in vitro vs. in situ in human cancer cells. Eur J Pharm Sci 10.1016/j.ejps.2020.105321

Carabajal MA, et al. Quinazoline-Based Antivirulence Compounds Selectively Target Salmonella PhoP/PhoQ Signal Transduction System. Antimicrob Agents Chemother 2019;64(1):e01744-19.

Böttcher K, et al. AICAR and compound C negatively modulate HCC-induced primary human hepatic stellate cell activation in vitro. Am J Physiol Gastrointest Liver Physiol 2021;320(4):G543-G556.

Bhattacharya M, et al. Release of functional dexamethasone by intracellular enzymes: A modular peptide-based strategy for ocular drug delivery. J Control Release 2020;327:584-94. 4

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GENOME-WIDE METHODS

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.

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.

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. GWM platform has one of the largest user bases in BF and the demand for both service capacity and the range of available applications has continued to grow.

BMT Cancer Genomics (TAU) joined GWM as a new node in 2020 to complement the existing services. The node will focus on circulating tumor DNA (ctDNA) analyses in support of cancer genomics. Other GWM nodes will sequence the samples and TAU node in BF Bioinformatics will perform the associated data processing and analysis.

2020 was a challenging year with Covid-19 epidemic resulting in widespread disruptions in the availability of laboratory consumables and delays in instrument repairs and set up of new workflows. While host universities increased pressure to shut down research services as non-critical activities, many BF platforms reorganised their services around global research efforts to develop new diagnostic tests, monitor the spread of new virus variants, identify genetic risk factors for hospitalisation, and screen for effective treatments.

Despite several disruptions to workflows, GWM technology platform provided research services to 527 academic and 32 non-academic

groups with a total cost-recovery of 4,460,229€. Table 1 summarises the task division between GWM nodes and user groups across the platform.

	UTU-FFGC			UH-BIDGEN			UH-FIMM			UH-FuGU			UH-GBU		
SERVICES	Samples	Projects	Groups	Samples	Projects	Groups	Samples	Projects	Groups	Samples	Projects	Groups	Samples	Projects	Groups
Resequencing	59	4	3	18881	22	22	4079	82	69	68	6	6	0	0	0
De novo	0	0	0	227	15	15	0	0	0	264	3	2	0	0	0
Metagenomics	1645	18	10	15406	25	25	3120	19	11	21	12	7	0	0	0
Targeted	105136	156	22	35	2	2	62512	63	43	106	5	5	0	0	0
SNP genotyping (GWAS)	0	0	0	0	0	0	5370	46	22	0	0	0	0	0	0
Targeted SNP typing	0	0	0	0	0	0	5780	21	12	0	0	0	0	0	0
Copy number variation**	0	0	0	0	0	0	0	0	0	621	4	3	0	0	0
Immunoprecipitates (ChIP-seq etc.)*	374	11	5	0	0	0	24	1	1	25	6	2	0	0	0
RNA sequencing	1650	51	32	859	23	23	1382	49	49	2041	68	38	0	0	0
Genome-scale reagents	0	0	0	0	0	0	0	0	0	0	0	0	122	54	25
ORF cloning	0	0	0	0	0	0	0	0	0	0	0	0	46	25	14
Automated digital slide scanning	0	0	0	0	0	0	0	0	0	0	0	0	8186	326	42
Nanostring/Fluidigm Biomark	0	0	0	132	3	3	0	0	0	342	6	4	0	0	0
QC only	1207	22	12	0	0	0	0	0	0	3505	115	44	0	0	0
CUSTOMERS		Projects	Groups		Projects	Groups		Projects	Groups		Projects	Groups		Projects	Groups
Local		217	43		73	73		144	170		184	90		341	48
Other domestic		9	9		7	7		48	42		35	17		49	18
International		4	2		0	0		9	7		1	1		0	0
Non-academic		32	16		10	10		8	3		5	3		0	0
TOTAL		284	70		90	90		209	222		225	111		390	66
COST RECOVERY			TOTAL			TOTAL			TOTAL			TOTAL			TOTAL
			886 585			627 783			2 263 199			602 599			80 063

*includes methylation arrays and bisulfite sequencing
**includes genome-wide(CGH) and targeted

GRAND TOTAL 4 460 229

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

NB: 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.

Participation in international, Nordic and European infrastructures

GWM platform 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 programmes and evaluations of national research infrastructures in Europe. The platform is a member of EU-LIFE (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 platform is also a 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. Additionally, GWM platform operates as a national node for EATRIS biomarker platform and is involved in multiple studies in the EU-funded EATRIS+ initiative.

Future perspectives

The rapid increase in both quality and quantity have enabled the use of sequencing applications in personalised medicine, population genomics, and single cell assays. Large-scale research initiatives will necessitate a major acceleration in both pre-sequencing workflow and post-sequencing data processing pipelines, and automating these steps will be our focus in the next 12 months. The needs for bioinformatics support will also continue to grow and we will join forces with BF Bioinformatics platform, CSC and ELIXIR Finland to identify ways to overcome these challenges.

Applications to process high-end samples (liquid biopsies, paraffin-embedded tissue samples, very small volume/concentration samples) will be another focus area. TAU node will provide expertise in liquid biopsies for cancer genomics, and GWM platform will work closely with others to secure consistently high-quality starting materials from other challenging sample types.

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.

We see single molecule sequencing as one of the most exciting future technologies in our research field. To this end, GWM platform purchased a new long read sequencer (PacBio Sequel II) in 2020, and plans to assess the applicability of Nanopore-based assays.

No single technology or approach works for all users. GWM platform will continue to developing customised methods not available elsewhere and providing services tailored to each research group's needs. Two important activities that we will continue, will be to act as consultants to help research groups choose the best technology and approach for their research question, and to continue to take part in international benchmarking exercises to identify future gold standard laboratory and data processing methods.

Major publications supported by the platform services

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FINGMICE – MOUSE MODELS

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.

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.

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 (www.fingmice.fi), 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, are closely interlinked with the research community. Services are openly available to all researchers for a fee, and altogether, several hundred scientists (138 research groups in 2020) 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 timeline 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.

Biennial seminar series (BF Model Organisms RoadShow) was planned for 2020 but had to be cancelled due to Covid-19 pandemic. Instead, to increase awareness and knowledge in GM models FinGMice organized one-day webinar entitled "Boost your research - national mouse clinic network" on November 20th. The full program can be found here: https://www.biocenter.fi/images/images/FinG

Mice_Webinar_201120.pdf. In this webinar, the revamped FinGMice webpage and the FinnDisMice project were launched to the scientific community. The overall aim of the event was to provide information 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. The webinar attracted altogether 160 registered participants.

Based on the most recent user report, each of the core facility has ~10-50 user groups yearly (depending on their service repertoire). The user fees cover the running costs. Along with the establishment of FinGMice, the know-how exchange and interaction between units has improved, allowing recognition of strengths in each unit, which has facilitated their specialization in high-level technologies. There is a complementarity between the different nodes and the division of tasks is rational and cost-effective. If the desired service is not available in one unit, customers are directed to another facility.

In order to increase the visibility, FinGMice platform has launched an up-dated webpage www.fingmice.fi including information about the nodes, the services they provide and special expertise available by each core facility in March 2020. In addition, Twitter (@fingmice) is used as a social media channel to announce news and events related to FinGMice.

The services are up-to-date and core facilities with skillful technical personnel can quickly adapt 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.

During 2020, technical developments have been carried out with FIRI2019 funding for the mouse phenotyping services that are the most frequently enquired by the customers. New equipment 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) are being purchased. In addition, Laser micro dissection system (UTU) enables 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.

User statistics

See table above.

Participation in international and European Infrastructures

FinGMice actively participated and reported on the virtual TT2020 meeting organized by Weizmann Institute of Science, Israel in

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

Transgenic Research (Hinttala & Kuure 2021). Next, Finland will be hosting TT2022 meeting of the International Society of Transgenic Technologies (https://www.transtechsociety.org/) after an application process through which coordinators Kuure and Hinttala of FinGMice TG units in Helsinki and Oulu were selected as the next local organizers of the meeting. Practical arrangements for organizing a hybrid meeting together with international TT and scientific committees to Levi, Lapland, in Spring 2022 are taking place in 2021.

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). University of Oulu represents Finland in the INFRAFRONTIER ESFRI and as a partner and a chair (since March 2021) of 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.

Future perspectives

GM animal models remain important tools to study biological and physiological phenomena at the organism level. During following years, the FinGMice platform will be focusing on generation of human disease specific mutations in mouse and rat, and 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, increasing the efficiency in the use of *in vivo* models. 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.

With the FIRI2020 funding, FinGMice is developing specific and sensitive mass spectrometric metabolite profiling which is an important approach for phenotyping of preclinical animal models to be implemented for pharmacological drug testing. A sensitive complementary LC-MS/MS system will boost throughput of small molecule profiling focused on bioactive lipid metabolites. The Biocity Turku Node is focused on analyzing steroids, sterols and bile acids from animal models created by the FinGMice Platform.

In 2020 Biocenter Oulu Transgenic and Tissue Phenotyping Core Facility (TTP) (former Transgenic core facility) successfully extended its service repertoire from transgenics in histology including high-resolution digital imaging of histology sections using brightfield slide scanner (which doubled the customer base of the core facility). Whole slide scanning provides numerous benefits to researchers such as safe digital archives of tissue specimens, alleviated transfer, and sharing of the image data among national mouse clinic nodes. Machine learning and artificial intelligence (AI) are powerful tools for automating identification of structural features in tissue samples. FIRI2021 funding is applied for fluorescent scanning of tissue specimens and for updating the image analysis software with the AI module to provide further engineered high-throughput quantitative tissue phenotyping analyses (UO). This will essentially facilitate the analysis of extensive and complicated image data sets and make the quantitative digital histopathological analysis easily accessible for scientists, achievement of quantitative data faster and output more precise.

Major publications supported by the platform services

Lerche M, et al. Integrin Binding Dynamics Modulate Ligand-Specific Mechanosensing in Mammary Gland Fibroblasts. iScience 2020;23(3):100907.

Messina A, et al. Neuron-Derived Neurotrophic Factor Is Mutated in Congenital Hypogonadotropic Hypogonadism. Am J Hum Genet 2020;106(1):58-70.

Natunen T, et al. Diabetic phenotype in mouse and humans reduces the number of microglia around β-amyloid plaques. Mol Neurodegener 2020;15(1):66.

Lensu S, et al. Prebiotic Xylo-Oligosaccharides Ameliorate High-Fat-Diet-Induced Hepatic Steatosis in Rats. Nutrients 2020;12(11):E3225.

Hiltunen AE, et al. Variant in NHLRC2 leads to increased hnRNP C2 in developing neurons and the hippocampus of a mouse model of FINCA disease. Mol Med 2020;26(1):123.

Heikelä H, et al. Hydroxysteroid (17β) dehydrogenase 12 is essential for metabolic homeostasis in adult mice. Am J Physiol Endocrinol Metab 2020;319(3):E494-E508.

Voikar V, Gaburro S. Three Pillars of Automated Home-Cage Phenotyping of Mice: Novel Findings, Refinement, and Reproducibility Based on Literature and Experience. Front Behav Neurosci 2020;14:575434.

Mennesson M, et al. Kainate Receptor Auxiliary Subunit NETO2-Related Cued Fear Conditioning Impairments Associate with Defects in Amygdala Development and Excitability. eNeuro 2020;7(4):ENEURO.0541-19.2020.

Gao Y, et al. LKB1 Represses ATOH1 via PDK4 and Energy Metabolism and Regulates Intestinal Stem Cell Fate. Gastroenterology 2020;158(5):1389-1401.e10.

Johansson P, et al. A Patient-Derived Cell Atlas Informs Precision Targeting of Glioblastoma. Cell Rep 2020;32(2):107897.

METABOLOMICS

Chair of the platform: Teemu Teeri, HiLIFE

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

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.

Development of technology services

The ViMU, FIMM, HiLIPID, BCK and TMC units together, as a single entity, offer broad coverage of MS-based analytical services in various fields of metabolomics both nationally and internationally. Since the initiation of the infrastructure platform 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 was added to the platform in 2019 to increase both the capacity and technologies available for the scientific community and HiLIPID joined to increase the versatility and know-how even more.

Currently, the metabolomics platform has initiated a clear roadmap to expand MS-based imaging technology in Finland, as there is no such technology dedicated for small molecule analysis. The future aim is to increase the MS-imaging platform to cover all the customer research bases in the metabolomics platform in the next few years. BCK already got funding for a MALDI-imaging instrument, which will be specifically utilized for drug metabolism studies including localization of pharmaceutical agents within tissues. ViMU has started to develop MS-based imaging techniques in collaboration with Faculty of Pharmacy (University of Helsinki) with Laser ablation electrospray ionization/ atmospheric pressure photoionization techniques.

ViMU continues to provide analytical services for the Finnish plant community and pharmaceutical research, but a growing need for analytical expertise has led to development of methods for molecular biology, e.g. for RNA research. The focus of the ViMU will remain to provide MS-based analytical services in plant metabolomics, microbiology, biopharmaceutical analysis and pharmacokinetics, but in addition, the unit offers a method for over 50 nucleoside modifications in RNA (archaea, bacteria, eucarya). The unit has also collaborated with the MS-group in the Faculty of Pharmacy to develop a high-resolution MS-based imaging protocol for plants at single-cell level. All MS-based analyses are performed by three existing instruments; UPLC-QTOF/MS, GC-QQQ/MS and UPLC-QTRAP/MS, but to develop MS-based imaging further, the unit needs a HDMS instrument in the future so that it can develop and provide MS-based imaging also for the customers.

FIMM-Meta has successfully offered high throughput targeted metabolomics and lipidomics, and isotope enrichment analyses for academic research, (pre-)clinical and biomedical applications, early biomarker discovery, and precision medicine. The Unit has increased its internal, national and

international academic research collaborations emerged from the service projects and published in highly reputed international journals. During year 2020, the Unit has developed multiple needed methods with high-resolution (Q-Exactive orbitrap) LC-MS instrumentation purchased in 2018. These methods include targeted biomarker screening using 500 metabolites standardized library suitable for various sample types (patient and animal blood/serum and white blood cells, isolated stem cells from tissues, nanovesicles from human gut bacterial and milk). Most significant development has been taken with the isotope tracer (C^{13}, N^{15}, H^{d}) fluxomics analysis serving now academic research groups. In addition, Unit has successfully developed and performed new LC-MS (Xevo TQ-S) services for clinical trial by international pharmaceutical company Abliva. Furthermore, a great developmental step has been taken when HiLIFE-funded core facility service portal iLAB was implemented to coordinate the Unit workflow.

HiLIPID has established lipidomics services for mechanistic biomedical and ecological research. Currently HiLIPID develops towards a national competence center in the analysis of ”lipid mediators” (polyunsaturated fatty acid–derived signaling molecules), which was supported by AoF FIRI funding in 2020 that allowed to purchase a highly sensitive QTRAP LC-MS/MS system dedicated for this purpose. The other development focus has been on ”dynamic lipidomics”, where the rates of synthesis, turn-over as well as the metabolic pathways are determined for a large number of individual lipid species by using deuterated lipid precursors.

We have tried to maintain the previous level of customer satisfaction that in HiLIFE RIA user survey 2019 gave the average rank 4.37/5, the numbers being especially high for HiLIPID (4.56) and ViMU (4.51). To keep our high ”quality” and ”staff support” grades high also in future, HiLIFE Metabolomics continues to invest in skilful staff; FIMM has recruited Dr Anni Nieminen to lead FIMM-Meta, and HiLIPID hired its laboratory coordinators Minna Holopainen and Hanna Ruhanen, who defended their PhD theses in 2020, as postdoctoral staff scientists for 2021-2024.

In year 2020 BCK has provided non-targeted metabolomics and lipidomics services using three UPLC-HRMS instruments. The main applications include nutrition, health, environmental and toxicology studies. The laboratory has also provided targeted analyses of steroids, drugs, and betaines. Because of the high demand for analysis of other than serum samples, BCK has continued to develop sample preparation methods for hair, tissue and saliva samples. Another important part has been the pre-study counselling services for customers, optimization of the work-flow, as well as instruction of the researchers in the use of data analysis software. The instrumentation of BCK is in major part at adequate level, the main bottlenecks being the lack of sample preparation automation and non-targeted metabolomics data analysis.

Turku Metabolomics (UTU) has expanded the number of targeted and untargeted assays available to customers. This includes expanding our endocannabinoid assay to cover more related compounds as well as the metabolites of cannabidiol (CBD) which will be used over the next two years in a major clinical trial run by Kings College London (UK). We have also finalised our fecal metabolomics assay and used in a major project measuring 1000+ samples in the local birth cohort. The TMC has taken part in two ring trials, this included our recent fecal metabolomic assay which was run by NIST. The second trial was of our ceramide assay. The results of these will be published shortly. The TMC has also been heavily involved the planning of a bile acid ring trial which is in the pilot phase as of early 2021. During 2020 Dr Alex Dickens, the coordinator of the TMC started a new job in Turku heading up the instrument centre in the Department of Chemistry. The aim is to unite the measuring of small molecules in Turku thus opening up different analytical services to the Metabolomics platform.

The BF metabolomics platform, as whole, is the main national provider of lipidomics services from biomedicine to ecology. Both high-throughput clinical studies and small-scale mechanistic studies are supported. New technology investments obtained in 2020 (lipid mediator analysis) and applied for 2021 (mass spectrometric spatial imaging of tissue lipids) will strengthen our role nationally and internationally. From 2020 BF platform can now nationally provide fluxomics analysis for research groups.

Bottlenecks

The largest bottleneck in developing HiLIFE lipidomics services with HiLIPID has been the lack of a highly sensitive mass spectrometer, which the platform succeeded to obtain in AoF FIRI 2020 call. The restrictions due to pandemics and periodical floor vibrations, caused by building a tram route nearby, hampered providing services on Helsinki Viikki campus (ViMU and HiLIPID) in 2020, and these challenges continue in 2021.

In 2019-2020 FIMM-Meta was without head and TC research director Katja Kivinen acted as an interim head of the unit for a while. From May 2020 all developments with Q-Exactive orbitrap have been led by the new head Anni Nieminen-Viheriäranta. Pandemic restriction has affected on the customer amounts and efficacy of the work, even though the Unit was able run the samples all the time during 2020.

The lack of high resolution instruments in Turku has been a bottle neck in 2020 as we would like to develop new profiling metabolomics assays in Turku. The other main bottle neck in the TMC remains staff to perform data processing. Efforts have been made to improve this but it remains slow for larger projects.

Education and training

The metabolomics results obtained from all units have been used in many PhD and post-doc projects and collaborations resulted in joint publications. The BF metabolomics units have continued teaching various aspects of metabolite analytics, remotely for most part of 2020.

User statistics

See table below.

Participation in international, Nordic and European infrastructures

ViMU collaborated 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. In 2020 FIMM-Meta was part of the EATRIS and EPTRI networks. BF Metabolomics personnel from FIMM, HiLIPID and TMC takes part as chair and national board members in Pan-European Network in Lipidomics and EpiLipidomics. BCK is participating in NordForsk funded Nordic POP program, and Metabolomics community at ELIXIR.

Future perspectives

The aim of ViMU is to develop more analytical methods for targeted, quantitative metabolomics, but also identify novel metabolites with plant-descent, which are numerous and still mostly unidentified. Another aim is to participate in RNA research with Peter Sarin's group by providing analytical methods for understanding RNA modifications especially during oxidative stress. The long-term future aim is to offer MS-based

General		Number of user groups				
Host Univ	Name of core facility	local	national	inter-national	non-academic	Total
UH	ViMU	14	3		2	19
UH	FIMM-Meta	9	9	8	2	28
UH	HiLIPID	7	9	3		19
UEF	BCK	32	17		7	56
UTU	TMC	5	1	2		8
		67	39	13	11	130

imaging services to investigate surface and/or cell-specific plant metabolites, and to integrate MS-based imaging data with the imaging data (e.g. RGB/visible, fluorescence, NIR/SWIR from NaPPI) and metabolomic profiling data for plant phenotyping research.

The FIMM-Meta will continue its national and international collaborations to further develop the targeted high-throughput biomarker discovery method and aims to start research collaborations on larger disease- and genetic background-related metabolomics projects such as FinnGen. FIMM-META aims to publish the new fluxomics method provided to research groups in Finland and internationally in high-impact journals. In future, unit aims to increase their customer-base by developing new methods like lipid fluxomics with already existing SCIEX instrumentation and bioinformatics in the area of fluxomics via increased collaboration with other metabolomics HiLIFE units and academic research groups. In addition, FIMM-Meta aims to increase its collaboration with hospitals and precision medicine via offering targeted metabolomics and in the long term MALDI metabolite imaging.

In lipidomics, the platform opens new services supporting breakthrough science and requested for long by academic and business center. National competence centers are developed in Helsinki, Turku and Kuopio, which coordinate services and support the activities of each other. Significant developments are currently seen in fluxomics, analyses of signaling lipids and spatial imaging of lipids.

At BCK methods will be developed for analysis of leachables in food and medicine and for contaminants bound to plastic waste. MS imaging services will be set up for pharmacokinetic studies, and laboratory automation will be developed to increase sample through-put.

The TMC will be collaborating with the Turku Centre for Disease modelling and the Instrument Centre to develop novel steroid analytics. This will also be in collaboration with UEF to complement their existing services. The main aim will be to develop novel highly sensitive measures of a broad range of steroid and steroid related molecules. This will be possible thanks to FIRI funding awarded to the Turku Centre for Disease modelling which will allow for the purchase of an ultra-sensitive QqQ instrument. Hopefully, the next FIRI funding from BF will be successful and this will allow us to develop metabolic imaging focusing on lipids in UTU. This will require the purchase of new instrumentation for ion mobility MS combined with MALDI and DESI imaging sources. This will be used to develop metabolic imaging for the whole metabolomics platform.

Major publications supported by the platform services

Jaiswal A, et al. Multi-modal meta-analysis of cancer cell line omics profiles identifies ECHDC1 as a novel breast tumor suppressor. Mol Syst Biol 2021;17(3):e9526.

Gregorova P, Sipari NH, Sarin LP. Broad-range RNA modification analysis of complex biological samples using rapid C18-UPLC-MS. RNA Biol 10.1080/15476286.2020.1853385

Palviainen M, et al. Cancer Alters the Metabolic Fingerprint of Extracellular Vesicles. Cancers (Basel) 2020;12(11):E3292.

Pirinen E, et al. Niacin Cures Systemic NAD+ Deficiency and Improves Muscle Performance in Adult-Onset Mitochondrial Myopathy. Cell Metab 2020;31(6):1078-1090.e5.

Hasygar K, et al. Coordinated control of adiposity and growth by anti-anabolic kinase ERK7. EMBO Rep 2021;22(2):e49602.

Leclercq JF, et al. Results of electrical fulguration in arrhythmogenic right ventricular disease. Am J Cardiol 1988;62(4):220-4.

Palviainen M, et al. Cancer Alters the Metabolic Fingerprint of Extracellular Vesicles. Cancers (Basel) 2020;12(11):E3292.

Noerman S, et al. Associations of the serum metabolite profile with a healthy Nordic diet

and risk of coronary artery disease. Clin Nutr 10.1016/j.clnu.2020.10.051

Dickens AM, et al. Dysregulated Lipid Metabolism Precedes Onset of Psychosis. Biol Psychiatry 2021;89(3):288-97.

McGlinchey A, et al. Prenatal exposure to perfluoroalkyl substances modulates neonatal serum phospholipids, increasing risk of type 1 diabetes. Environ Int 2020;143:105935..

NON-MAMMALIAN MODEL ORGANISMS

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

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.

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 and private-sector partners as well.

Services and their development

As in other sectors, the work of the platform was seriously disrupted by the coronavirus pandemic in 2020, due to the strict sanitary procedures put in place throughout the Finnish biocenters. We were able to continue basic services for animal maintenance, since these were considered essential, but the requirements for social distancing and mask wearing hampered the delivery of all services. For some periods, notably at the start of the pandemic (March-June), normal research activities were not possible. Ongoing and planned experiments had to be abandoned or postponed, and were only able to resume with restrictions in place for the remainder of the year. For our platform this was a serious handicap since, by their nature, the services we provide support long-term experiments. The disruption will likely be reflected in decreased productivity in 2021/2022.

1) Flies: Our Drosophila services use operational principles adopted from other high-volume units, such as EMBL. These include supplies of high-quality fly food to order, plus stock maintenance, project guidance and training (fully operational in Tampere, establishment of stock maintenance in Helsinki delayed due to Covid-19). To give an indication of scale, Hi-Fly supplied approximately 200,000 vials of fly food in 2020. 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. In addition to basic services, we now provide metabolic analyses of mitochondrial function in larvae and adults, specifically concentrating on blood cells. Methods include measuring mitochondrial membrane potential, and analyzing different metabolites and reactive oxygen species, using both flow cytometry and fluorescence microscopy.

2) Fish: Fish services now operate on three sites, with the establishment of node 5 in Turku, focusing on cancer, cardiovascular biology, drug research and screening, whilst the nodes in Tampere and Helsinki focus mostly on infectious disease and neuroscience, respectively. This subdivision enables us to channel users to the most appropriate site for services and collaborations. Genome-modified

fish lines are also supplied, and phenotyping services provided to users who need them. In addition to the pathogen-free unit established in Tampere in 2019, housing up to 10,000 adult zebrafish, a second, larger unit was sanitized in 2019-2020. Pathogen-free zebrafish lines were procured from the European Zebrafish Research Center to re-establish all stocks. A comprehensive colony-health monitoring program is now in place. This ensures that stocks remain pathogen free, enabling safe transfer to/from other facilities, promoting improved health and welfare of experimental animals and high service quality. In addition, we have established a separate quarantine laboratory to house fish lines arriving from facilities without reliable health monitoring programmes, whenever necessary (e. g. unique non-commercial fish lines). The Covid-19 pandemic has reduced the use of some services, due to the restrictions on access needed to ensure the safety of our personnel and researchers. Nevertheless, the user base has actually increased slightly, and billing was on a similar level as in 2019.

Feedback and changes enacted

Despite the disruptions caused by the coronavirus pandemic, feedback has mostly been positive on all sites. The fly units have continued to address scientists' special needs, such as related to the quality, quantity or composition of fly food. No specific changes were implemented based on feedback, and the need for strict working conditions during the Covid-19 pandemic was widely understood and accepted, though obviously slowed down many projects. The health situation for personnel, users and animals remained good and no adverse issues were reported.

User statistics

See table below.

Participation In International, Nordic and European infrastructures

We have continued to participate actively in international zebrafish networks, including ZFIN (submitting data on new mutant fish lines), ZIRC and EZRC (supplying and procuring mutant fish lines). Pertti Panula has remained an active member of the International Zebrafish Society, despite its physical meeting being cancelled in 2020. We maintain links with the major *Drosophila* stock centres (DGRC in Bloomington and VDRC in Vienna) for strain deposition and acquisition, contribute data to Flybase, and serve the global *Drosophila* community via platform leader Howy Jacobs' editorship of *Fly*.

Future perspectives

In concert with key researchers we will continue to develop new *Drosophila* disease models, notably for mitochondrial disease, making these available to the scientific community, depending on our ability to maintain basic infrastructure (see above) Future development of zebrafish services will include the establishment of a sperm cryopreservation service, enabling storage of zebrafish lines, and the introduction of a comprehensive animal data management system. However, our aquarium facilities are now operating at close to their maximum capacity. Service expansion would require new facilities, such as the refurbishment of an existing large automated Aquatic Habitats unit in Helsinki, that is currently stored dry. The need of a dedicated light-sheet microscope for live

General		Number of user groups				
Host Univ	Name of core facility	local	national	inter-national	non-academic	Total
UEF						0
UH	Hi-Fly	10				10
UH	NC-Zebrafish Unit	7	2			9
TAU	Tampere Drosophila Facility	3	1	2	0	6
TAU	Tampere Zebrafish Facility	7	1	1	0	9
UTU	Turku Zebrafish Core	17	1	0	1	19
		44	5	3	1	53

imaging of zebrafish larvae also remains urgent. It would greatly facilitate the use of our facilities for cutting-edge research and contribute to high-quality publications. As a future development, a turquoise killifish (*Nothobranchius furzeri*) aging model is being developed to enable work on aging-related disorders – a major health issue of contemporary society. However, these plans have been delayed because of restrictions due to Covid-19 and to funding constraints.

Major publications supported by the platform services

Yalgin C, et al. Effects on Dopaminergic Neurons Are Secondary in COX-Deficient Locomotor Dysfunction in Drosophila. iScience 2020;23(8):101362.

Heliste J, et al. Genetic and functional implications of an exonic TRIM55 variant in heart failure. J Mol Cell Cardiol 2020;138:222-33.

Chen YC, et al. Cerebral Dopamine Neurotrophic Factor Regulates Multiple Neuronal Subtypes and Behavior. J Neurosci 2020;40(32):6146-64.

Liu Y, Mattila J, Hietakangas V. Systematic Screen for Drosophila Transcriptional Regulators Phosphorylated in Response to Insulin/mTOR Pathway. G3 (Bethesda) 2020;10(8):2843-9.

Qiao X, et al. UBR5 Is Coamplified with MYC in Breast Tumors and Encodes an Ubiquitin Ligase That Limits MYC-Dependent Apoptosis. Cancer Res 2020;80(7):1414-27.

Hasygar K, et al. Coordinated control of adiposity and growth by anti-anabolic kinase ERK7. EMBO Rep 2021;22(2):e49602.

Valanne S, et al. Osa-Containing Brahma Complex Regulates Innate Immunity and the Expression of Metabolic Genes in Drosophila. J Immunol 2020;204(8):2143-55.

Vesala L, Hultmark D, Valanne S. Editorial: Recent Advances in Drosophila Cellular and Humoral Innate Immunity. Front Immunol 2020;11:598618.

Aspatwar A, et al. Toxicity evaluation of sulfamides and coumarins that efficiently inhibit human carbonic anhydrases. J Enzyme Inhib Med Chem 2020;35(1):1765-72.

Frischmeyer-Guerrerio PA, Milner JD. Editorial overview: Collusion between genes and environment in the pathogenesis of allergic disease. Curr Opin Immunol 2019;60:iii-v.

PLANT PHENOTYPING

Chair of the platform: Kurt Fagerstedt, UH

Node PIs: : Jari Koistinaho, UH, Johanna Ivaska, UTU, Katriina Aalto-Setälä, UTA, Petri Mäkinen, UEF, Riikka Martikainen UEF.

Development of technology services

For nation-wide added value, RI has advanced the state-of-the-art Finnish plant science by providing access to specialized imaging instruments for monitoring photosynthesis and other important plant traits. In this regard, in the autumn of 2020 a shared effort between UEF and UH nodes was done through testing a shared **hyperspectral** imaging system, thereby allowing expanding UH activities with UEF expertise and vise versa.

In 2020, HiLIFE SAB recommended that NaPPI imaging activities would be integrated more closely to the daily operations of Viikki greenhouses (ViGOR). To promote this, in November 2020 Viikki Plant Science center (HiLIFE GC 2018-2021 V) granted NaPPI funding that will allow ViPS PIs to test NaPPI plant phenotyping facility with no cost. Time series imaging of sample plants with or without chosen pretreatments will be organized for ViPS PIs. They will obtain both image data from 1-to-3 sensors as well as the numeric data of plant size, morphology and physiological status at the chosen time points. ViPS researchers will obtain pilot data for future grant applications. When writing grant proposals, utilization of novel research instruments such as the NaPPI multisensor imaging facility, can be challenging to justify if no pilot data can be shown. In reverse, it might be challenging for funding agencies to estimate the value of such new data if no pilot data is shown.

User statistics

The Platform served 5 user groups in 2020.

Participation in international, Nordic and European infrastructures

Nordic level: Together with Nordic universities (UCPH Denmark, SLU Sweden, LU Sweden, UiT Norway, UH Finland), NaPPI won a 16 million NOK grant from Nordforsk to build a NordPlant university hub (http://www.nordplant.org/) for shared plant research infrastructures, and associated researcher mobility and education (Alexandersson et al., 2018, Chawade et al., 2018).

European level: NaPPI has engaged with two major European projects to guarantee success of NaPPI development activities. Since May 2017, NaPPI has been a partner in the 10M€ Horizon2020 project EPPN2020 that aims at providing European researchers from both public and private sectors with transnational access to a wide range of state-of-the-art facilities, techniques and methods for plant phenotyping under controlled conditions. EPPN2020 aims at excellence in the whole phenotyping pipeline, involving sensors and imaging techniques, data analysis in relation to environmental conditions, data interpretation in a biological context and meta-analyses of experiments carried out at different scales of plants. EPPN2020 project will end in October 2021 but many tools and practices generated by the project will remain in the use of the plant phenotyping community.

The importance of plant phenotyping as a key bottleneck for advancements in plant and agricultural sciences has also been recognized by the European Strategy Forum for Research Infrastructures (ESFRI) that actively supports and facilitates RI development and EC policy making. In 2016, the ESFRI project EMPHASIS was listed on the ESFRI Roadmap as a pan-European Plant Phenotyping

Research Infrastructure, which will provide an important basis for the development of science-based solutions as well as for generating basic knowledge about plants and their interaction with the environment. The Europe-wide development of such a unique infrastructure will sustain the leading role of Europe in a key technology for plant sciences, breeding and agricultural systems. In 2020, the EMPHASIS project is in its' implementation phase. NaPPI has the National Mandate to represent Finland and the Finnish plant science community as EMPHASIS support partner but unfortunately, the Academy of Finland has not shown interest in supporting EMPHASIS at any level. The cost of being actual partner in EMPHASIS has not been defined yet but can be in the range of 50 to 100 k€ per year.

International level: NaPPI has established contacts with intercontinental colleagues in North America and Canada (Oak Ridge National Laboratory prof. Jacobson, and Qubit Systems prof. Hunt, respectively). To establish its status as an international player, NaPPI has been associated with the International Plant Phenotyping Network (IPPN), a network that provides workshops and education, but unfortunately NaPPI cannot afford the membership fee of 3000 €.

Future perspectives

Personnel situation

NaPPI infra personnel budgets have been based on HiLIFE budget for coordination and project budgets for technical, IT and experimental design and data processing activities. In 2021, all project funding but for IT will end and NaPPI activities will remain as sole responsibility of the coordination. In this situation it will be difficult to accept external commercial clients who request full service from experimental design, execution of the assays and data reporting. Because the technical assistance at the RI is demanding in load and time the originally assigned UH personnel has stepped out from the RI functions. The prospected situation is hardly viable for growing services.

Development of a "Green Deal Assay Portfolio"

European commission Green Deal aims at implementing the UN Sustainability Development Goals through Farm to Fork (F2F) initiatives on sustainable and resilient food systems. To support research on sustainable agriculture research at the Faculty of Agriculture and Forestry and Faculty of Biological and Environmental Sciences, the National Plant Phenotyping Infrastructure (NaPPI) has the ambition to establish a "Green Deal Assay Portfolio" that will allow experimentation towards F2F aims, such as:

i) "Reduction in fertilizer use by 20% by 2030"

ii) "Reduction in pesticide use by 50% by 2030"

iii) "Ensuring food security, nutrition and public health"

Development of this assay portfolio will allow expanding the user base of NaPPI and will strengthen the role of NaPPI in related EC grant proposals.

Progress in Data Management Activities

Similarly to molecular omics data, image-based phenotyping at NaPPI generates valuable knowledge and data. It should be taken well care of as an asset and resource, that creates value for the research community both on the short and the long term, especially in terms of future open science data. During 2020, data management practices were supported by a part time (project funded) IT specialist who has followed the Horizon2020 EPPN2020 and ESFRI EMPHASIS recommendations for FAIR phenomics data standards. These projects develop and provide tools for automation of the data management practices such as URI generation and PHIS database for plant phenotyping data. In addition, the NordForsk project NordPlant has

committed to establish a Nordic phenotyping data structure that would allow combination of environmental data, metadata with the phenotyping data utilizing the same PHIS system. These activities are supported by a service contract that has been signed between INRAE, UCPH and UH for implementation of PHIS installation at the two Nordic universities during 2021.

Integrated molecular omics and metabolomics development plan

A natural direction for developing phenotyping approaches in the field would be to combine hyperspectral imaging not only with physiological assays, but also with detailed and comprehensive chemical analysis from the same material, i.e., metabolomics. Metabolomics laboratories are associated with both Nappi nodes already, but complete integration of the established protocols and workflows is not fully developed. Ideally, this would be complemented with ambient imaging mass spectroscopy to gain insight in localized chemical alterations. This is especially pertinent for plant chemical defense and stress responses, because many of the defensive secondary metabolites induced in response to various external stimuli are either fluorescent or contain characteristic chemical bonds in their structure, and typically accumulate in large quantities in affected areas, all of which make them ideal chemical imaging targets. For shorter term development at the UEF NaPPI, purchase of a very high spectral resolution hyperspectral imaging station would enable much more detailed characterization of reflectance spectrum, which would be very useful in photosynthesis related studies and organic material characterization.

UH NaPPI special instruments for chlorophyll fluorescence

At UH one development area is the improvement of chlorophyll fluorescence equipment. Integration of the photosynthesis analysis tools available at the campus will continue to make a valuable contribution to the NaPPI services. We estimate that researchers from at least 10 research groups in Viikki campus, including those specialized in plant environmental interactions (Dr M. Robson), stress biology and ecophysiology (Prof. A. Porcar), will benefit from the new research possibilities provided by this novel instrument, furthermore, additional chlorophyll fluorescence instruments are available in these groups.

Major publications supported by the platform servicestions

Guinea Diaz M, et al. Two chloroplast thioredoxin systems differentially modulate photosynthesis in Arabidopsis depending on light intensity and leaf age. Plant J 2020;104(3):718-34.

PROTEIN – PROTEOME NETWORK

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 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.

Development of technology services

PPN provides 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. PPN is devoted to continuing its world-class level of services for high number of users (184 research groups reported as users during 2020).

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:

Turku Proteomics facility provides a wide range of services including protein identification, protein interactions, analysis of post-translational modifications, large-scale quantitative proteomics analysis, and targeted protein quantification. The analyses are increasingly based on data independent acquisition (DIA), and the unit strives to provide access to newest acquisition methods requested by users. The unit has implemented multidimensional and high-throughput front-end separation techniques, and this will be further strengthened by the recent acquisition of FAIMS and ZipChip interfaces. The unit has supported the analysis of large cohorts of plasma samples, including projects from Centre for Population Health Research, Turku University Hospital, and InFLAMES flagship programme. Turku node has recruited a new head for the proteomics facility: Dr. Otto Kauko, M.D., Ph.D. has started in the tenure track position from the beginning of 2021.

The **Tampere Protein Technologies** facility provides services in protein design, protein production and protein characterization and proteomics services are also provided to a small number of customers. There has been constant increase for the needs of services in protein production, and the facility is the only academic service provider in this field. In addition to academic customers, the facility has provided services to Finnish biotech companies, which has positively reflected to financial outcome and supports the collaboration between academy and industry.

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. Different MS techniques 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. Usage of all areas of the facility increased significantly, with a 51% increase in overall usage compared with 2019. The proportion of usage by external users also significantly increased from 23.6% to 34.2% of total usage. Oulu introduced the iLab service, which allows online booking of equipment and services and facilitates smooth invoicing. Group leaders can pre-assign spending limits to individuals by project number and can see constantly updated usage information broken down to individual group members and equipment/service. In parallel to this, protein related core-facilities in Oulu launched a joint multi-facility service model, to provide a seamless service between BF nodes in Oulu.

The **Proteomics Unit of Institute of Biotechnology** (BI) continues to provide 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. During 2020, the unit developed further the clinical and structural proteomics analyses to respond the large number for SARS-CoV-2 related samples. 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 strengthened by the timsTOF Pro instrument acquisition in 2021.

The **Meilahti Clinical Proteomics Core facility** (BCH) offers comprehensive clinical proteomic analyses from planning the sample collection at the hospital, storage and analysis, ending in a compact Systems Medicine and Systems Proteomic summary of the results. The unit is the national center for glycoproteomics and the only GLP certified proteomics laboratory in the country, serving commercial customers requesting authorised GLP documentation. The unit provides MALDI mass-spectrometry imaging (MSI) services as the national MSI center with an on-tissue-fragmentation by ISD (in source dissociation) technology, providing absolute identification of the selected ions on-site. To serve the needs of its clinical customers, immuno-mass-spectrometry (IMS) analyses using a fully automated robot for sample preparation are available, coupled to an Q-Exactive Plus MS instrument, enabling the SISCAPA technology in MRM and PRM for high-throughput clinical large scale biomarker validation.

The **Biological Nanoscience** (Bio-Nano) **Jyväskylä** gives a good balance between high-throughput techniques and "in detail" protein characterization. It 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 184 research groups, which is less than that reported during 2019 (246). Accordingly, the income from the services was 17% lower (625,938 €) as compared to the previous year (751,805 €). These numbers reflect the exceptional year due to Covid-19 pandemics; laboratories were partially closed, and pandemics made it difficult to organize the actions, reflecting for example into number of international customers. 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 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. 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, Horizon 2020, MC-ITN, IMI and COST actions). For example, BCH is 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 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. Three Covid-19 related projects have been initiated in 2020 in PPN and two special FIRI grants received in UTU and UH during 2020.

Future perspectives

Our goal is to offer an infrastructure and services, which are comparable to those used by world-leading scientists with the most advanced tools and knowledge. The infrastructure is expected to 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. The new 4D protein analysis technology allows 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. Single Cell Proteomics, one of the recently funded FIRI special projects, will link PPN nodes to total protein content analysis of a cell

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

with a few thousand of proteins and their possible modifications to be measured in one shot, independent of available antibodies or metal labels. Studies of protein-drug interactions, defining structural changes in complexes and separation of isobaric molecules with ever increasing ultra-high precision will be possible in the near future.

Clinical proteomics will benefit of better sample quality and adequate sample processing guidelines for reliable results. PPN will together develop uniform clinical sample processing guidelines and procedures, including the use of operating theatre for sample processing by top equipment such as FAIMS and PASEF. 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 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 better 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 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 technologies.

Major publications supported by the platform servicestions

Mustonen V, et al. Crystal and solution structure of NDRG1, a membrane-binding protein linked to myelination and tumour suppression. FEBS J 10.1111/febs.15660

Hiltunen AE, et al. Variant in NHLRC2 leads to increased hnRNP C2 in developing neurons and the hippocampus of a mouse model of FINCA disease. Mol Med 2020;26(1):123.

Kimura S, et al. CRK2 and C-terminal Phosphorylation of NADPH Oxidase RBOHD Regulate Reactive Oxygen Species Production in Arabidopsis. Plant Cell 2020;32(4):1063-80.

Grebe S, et al. Specific thylakoid protein phosphorylations are prerequisites for overwintering of Norway spruce (Picea abies) photosynthesis. Proc Natl Acad Sci U S A 2020;117(30):17499-509.

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Kumari R, et al. Tropomodulins Control the Balance between Protrusive and Contractile Structures by Stabilizing Actin-Tropomyosin Filaments. Curr Biol 2020;30(5):767-778.e5.

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Xie Y, et al. Epicardial transplantation of atrial appendage micrograft patch salvages myocardium after infarction. J Heart Lung Transplant 2020;39(7):707-18.

Kukkurainen S, et al. The F1 loop of the talin head domain acts as a gatekeeper in integrin activation and clustering. J Cell Sci 2020;133(19):jcs239202.

Zhang P, et al. Crystal structure of the FERM-folded talin head reveals the determinants for integrin binding. Proc Natl Acad Sci U S A 2020;117(51):32402-12.

REAL-TIME IMAGING

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

Partners: Mirkka Sarparanta and Arturo Garcia, HiLIFE.

Single photon emission computed tomography (SPECT) is a versatile functional imaging technique with high translational potential. It is based on the detection of gamma radiation emitted by radioactive isotopes distributed in the body according to the nature of their carrier vector (radiotracer). These tracers are administered usually at sub-pharmacological concentrations, allowing for high sensitivity, low radiation exposure, and unlimited tissue depth. Depending on their chemical character, tracers can bind specific targets in the body or distribute otherwise by physiological parameters. The radioactivity distribution is then followed in real time using non-invasive imaging and conclusions can be drawn about target affinity, kinetics, distribution and disposition. SPECT is able to quantify tumour dissemination and growth, changes in cardiovascular function, and brain activity at the neurotransmitter level, or for example the tissue distribution and elimination kinetics of radiolabelled drug delivery systems can be studied. This can be done longitudinally in a single animal; an unmatched advantage compared with ex vivo methods, which employ large number of animals, and pose post-mortem or tissue dissection artefacts. SPECT imaging is non-invasive, statistically inexpensive, and fulfils the principle of 3R, reducing considerably the number of animals. The SPECT camera is combined with an x-ray computed tomography (CT) detection system to confer anatomical context for SPECT images.

The RTI unit was established in 2010 with the acquisition of the nanoSPECT/CT system at the Faculty of Pharmacy, partnered with the Tracers in Molecular Imaging (TRIM) Group at the Department of Chemistry at the Faculty of Science. The group established in 1995 has extensive experience in radiotracer development, quality control and biological evaluation for SPECT and positron emission tomography (PET) with state-of-the-art radiopharmaceutical chemistry facilities. This collaboration made the RTI a unique facility in Finland and rare in Europe, with the capability to offer custom radiotracer synthesis and evaluation tailored to the needs of a specific research and less commonly explored targets such as nanoscale drug delivery systems.

The RTI unit has grown significantly after getting support from BF in 2012. The RTI is part of the Helsinki Functional Imaging unit (2016–), and part of Helsinki in vivo Animal Imaging Platform (HAIP, 2017–), one of the infrastructure platforms of the Helsinki Institute of Life Science (HiLIFE), which gathers all modalities of whole-animal in vivo imaging in the Helsinki metropolitan area. At HAIP, the RTI laboratory is split into two different budgeting units: the RadChem (LSRI2) and SPECT/CT (LSRI3) but still keeps an identity of an integrated nuclear imaging facility.

Development of technology services

Despite 2020 was a year full of issues derived from the consequences of restrictions due to COIVD-19 pandemic, RTI could develop few developments in its service portfolio. The RTI unit has continued to develop its portfolio of services in 2020. New imaging protocols have been developed 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. In 2020, RadChem continued to provide radiochemistry services to one major industrial customer, Norwegian nanotechnology company Nacamed, and added HUS and the Helsinki University Central Hospital in the list of customers with a radiolabelling development project completed in December 2020. The collaboration with HUS expected to continue in 2021.

Application development

During 2020, the protocol for cerebral stroke model, validated in 2019 was extended to a second model or stroke. Previously, in 2019, ^{99m}Tc- hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO or Ceretec®) was used to image brain blood perfusion, testing mainly endothelin-1 mouse model of stroke. We have modified the method for rat stroke model using collagenase induced haemorrhage in rats. In this setup, we went ahead and tested neurotrophic factor CDNF to validate the method. The results of these manipulation validated the method, and provided more tools that can be used for the study of stroke, and be incorporated into RTI unit service.

On the other hand, the protocol to quantify brain dopamine receptors (DAT), and serotonin receptors (SERT) using one tracers, [123]-I-β-CIT, has been tested. We have developed a model, based on dynamic tracer binding potential were we are able to dissect DAT and SERT levels during the same experiment. This has a high potential impact in neuroscience research since parallel quantification of these important neurotransmitter modulators is central during behaviour responses to stimuli. This would provide an attractive tool for many behavioural scientists.

User statistics

See table below.

Participation in international, Nordic and European infrastructures

The **Finnish Biomedical Imaging Node (FiBI)** was recently established. This is a multi-sited **research infrastructure** offering open access to a wide selection of advanced in vivo imaging technologies. It comprises of the four leading Finnish in vivo imaging facilities: **Turku PET Centre (TPC**; UTU,ÅAU,TYKS), **Kuopio Biomedical Imaging Unit (BIU**; UEF,KYS), NEUROIMAGING Research Infrastructure (NI; AU,HU,HUS) and RTI unit parent organization **Helsinki In vivo Animal Imaging Platform (HAIP**; **UH)**, with each partner having a different spearhead specialization. Tight collaboration within the FiBI Node together with identified specialization areas of each partner enable *strategic national coordination*, effective development of *joint services*, and utilization of *synergies across the multi-disciplinary imaging field*. This minimizes unnecessary overlaps while ensuring efficient technological transfer and dissemination of expertise between the partners, and ultimately, strengthens and expands the biomedical research environment and opportunities across Finland. **The FiBI Node is on the Roadmap for National Research Infrastructures 2021–2024 as part of Euro-BioImaging Finland,** and thus the RTI unit can be benefited within this umbrella for further development.

Future perspectives

As a result of the previous BF evaluation of the platform, and based on SAB comments, the BF board recommended to look into the possibility of making the platform more robust and less vulnerable, suggesting a merge with other infrastructures, as BF BioImaging or BF FinGMice platforms. Both possibilities were considered. As differences in the scope, technical background, and incompatibility of the RedChem node with general BF Bioimaging background, this merge was not supported. On the other hand, negotiations with BF FinGMice have taken place. As RTI platform goes well beyond of being a first line phenotyping technology, and as a good

General		Number of user groups				
Host Univ	Name of core facility	local	national	inter-national	non-academic	Total
UH	SPECT/CT lab	2	1			3
UH	RadChem	4		1	2	7
		6	1	1	2	10

proportion of the projects carried out in RTI are done in wild type animals, it has been hard to justify properly a merge between the platforms. However, and despite having not reach any decision, these negotiations continue with the feedback from BF board. Alternatively, incorporating other research infrastructure(s) dealing with in vivo real time animal imaging is being also consider in order to increase the critical mass of the RTI platform. We plan to have a conclusion in this matter in 2021.

As we experienced a significant setback due the global situation. The plans for 2021 are very similar to those planned for 2020 that could not be developed. Thus, in 2021, we plan to expand our services on 1) brain imaging, 2) cardiac and lymphatic imaging, and 3) cancer imaging. On CNS imaging we will 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, and 2020 was not a good year to increase the funding, we are still with the expectative to obtain 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 still looking to have one M.Sc. level radiochemist hired permanently for sustained support of tracer development and production for 2022 and further.

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 multimodal instrument, such as a hybrid PET/SPECT/Optical tomography system. This development plan has been materialised in 2021 with targeted FiRI call in 2021. Accordingly, a letter of intent has been submitted to the UH council, via FiBI as part of EuroBioimaging. Thus, plans are well in the way to expand the imaging capacity of the unit.

Major publications supported by the platform services

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.

Alitalo O, Rantamäki T, Huhtala T. Digital autoradiography for efficient functional imaging without anesthesia in experimental animals: Reversing phencyclidine-induced functional alterations using clozapine. Prog Neuropsychopharmacol Biol Psychiatry 2020;100:109887.

SINGLE CELL OMICS

Coordinator: Pirkko Mattila, FIMM-HiLIFE

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

Development of technology services

2020 was the fourth year single cell operations were included in Biocenter Finland technology platforms. Overall, the user base has increased as judged by number of user groups (50 and 59 user groups in 2019 and 2020, respectively). However, the number of processed samples has strongly decreased (933 and 296 processed samples in 2019 and 2020, respectively) reflecting smaller sample batches. This is probably due to exceptional circumstances and the new service types implemented 2020. Many laboratories were closed long times during 2020 and as freshly isolated cells are typically used, less projects have been able to proceed with their experiments due to the restrictions in universities. The decrease in sample numbers was compensated with development in methods and lab processes i.e implementation of project management software, Agilent iLab in some of the SC omics nodes.

The basic activities of the Single-Cell omics (SC omics) platform on droplet based assays using 10XGenomics Chromium platform are well established in all Biocenter Finland nodes. User demand for different multiomics approaches especially for gene expression + cell surface protein detection and gene expression + chromatin accessibility is increasing. To meet the growing user demand for single cell services, SC omics platform is currently implementing automation for Chromium (Chromium Connect) with FIRI2020 funding. Droplet based DNA analyses on Tapestri technology platform have also been set up in 2020.

Spatial transcriptomics has been selected as method of the year for 2020 by Nature Methods. SC omics network has already reacted to this novel technology by implementing Visium spatial transcriptomics system by 10XGenomics. Adapting this method has been challenging due to expertise needed not only for NGS (GWM) but also for histology, IT and RNA isolation. In spatial transcriptomics SC omics collaborates with all relevant BF platforms.

SC omics platform ended up in sharpening task division regarding sc proteomics services based on Helios CyTOF instrument. From the beginning of 2021 sc proteomics services are only available in BCT (UTU/ÅAU) node. To develop the service repertoire further, the node is in the process of acquiring a Fluidigm Hyperion imaging mass cytometer funded by FIRI2020.

User statistics

See table below.

Participation in international, Nordic and European infrastructures

For single cell bioinformatics training SC omics platform is linked to ELIXIR via

General		Number of user groups				
Host Univ	Name of core facility	local	national	inter-national	non-academic	Total
UEF	Single Cell Genomics	9	3	1	1	14
UH	sc ProtGen BI	3				3
UH	Single-Cell Analytics FIMM	25	3			28
TU/ÅA	Single Cell Omics	14	0	0		14
		51	6	1	1	59

collaboration with CSC. Via EU-LIFE SC omics been in contact with other tech centres like VIB to discuss strategies of building up functional (virtual) sc core facilities.

Future perspectives

Spatial transcriptomics represent the next frontier in single cell technologies allowing a groundbreaking way to measure all the gene activity in a tissue sample and map where that gene activity is occurring. Several nodes within the Single Cell Omics platform are already looking into options to purchase next-generation spatial transcriptomics platforms (e.g. Nanostring and Resolve Biosciences) in 2021-2022 to fill the needs of the researchers and to keep Finnish research institutes at the leading edge of this technology. With the emergence of spatial transcriptomics and solutions for single-cell analyses of samples preserved by fixation, more diverse types of samples can be subjected to single cell omics measurements. This will lead to increasing adoption of single cell omics in clinical research and immuno-oncology.

Single cell omics approaches will eventually evolve to nearly the same plurality as NGS methods have done since 2005 after 454 sequencing instrument was launched. Spatial analytics will be an important new avenue but also technologies i.e long read transcriptomics is just waiting for projects for which it would give new perspectives. Similarly DNA level analytics like ATAC-seq and other epigenomics solutions will be more widely utilized limited mostly by budget of the project. One important feature will be development of technologies that would allow conversion rate of libraries to increase, making sc sequencing able to capture transcripts with lower expression level to be properly analyzed. Single cell analytics will also be more broadly used for species outside of human/mouse axis. We have already some published methods for scRNAseq for microbes, which will be changing our views on microbe/microbiome activities as the sc analytics of human cell types has already done.

Major publications supported by the platform services

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Mehtonen J, et al. Single cell characterization of B-lymphoid differentiation and leukemic cell states during chemotherapy in ETV6-RUNX1-positive pediatric leukemia identifies drug-targetable transcription factor activities. Genome Med 2020;12(1):99.

Kelkka T, et al. Adult-Onset Anti-Citrullinated Peptide Antibody-Negative Destructive Rheumatoid Arthritis Is Characterized by a Disease-Specific CD8+ T Lymphocyte Signature. Front Immunol 2020;11:578848.

Depuydt MAC, et al. Microanatomy of the Human Atherosclerotic Plaque by Single-Cell Transcriptomics. Circ Res 2020;127(11):1437-55.

Kim D, et al. Somatic mTOR mutation in clonally expanded T lymphocytes associated with chronic graft versus host disease. Nat Commun 2020;11(1):2246.

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Lokka E, et al. Generation, localization and functions of macrophages during

the development of testis. Nat Commun 2020;11(1):4375.

STEM CELLS & GENOME EDITING

Chair of the platform: Timo Otonkoski, BCH

Vice Chair: Topi Tervonen, UH

Node PIs: : Jari Koistinaho, UH, Johanna Ivaska, UTU, Katriina Aalto-Setälä, UTA, Petri Mäkinen, UEF, Riikka Martikainen UEF.

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 year 2020 was shadowed by COVID-19 that variably reduced the overall functionality of the platform's units by inhibiting service production, and on the other hand, reducing the number of possible clients. During this time, the Stem cell platform and Genome editing platform completed fusion as suggested by the BF board. As a result, the united Stem cell & Genome editing platform was formed. The platform provided services for 35 user groups of which 27 were local, five national and three non-academics. The major scientific progress of the platform was in the CRISPR/Cas9 genome editing technology for efficient genome editing in human pluripotent stem cells, immortalized cell lines and mouse models for disease modelling purposes. The platform partners have put effort into improving pancreatic, hepatic, cardiac, and neuronal differentiation, including 3D brain cell and cardiac muscle cultures. Furthermore, the platform was active in organizing training and teaching. Services and service development provided by each partner of the Stem cells & Genome editing platform are presented below:

The iPSC core at Tampere University has created isogenic lines and cell type-specific reporter lines using CRISPR/Cas9 technology. Also, new iPSC lines were created, although the interest was smaller than previously. Reporter lines for cardiac and hepatocyte application have been a success. Reporter lines are an important asset particularly for co-culturing and tissue model studies. These lines are now available for customers. The core also put effort into improving hepatic differentiation, in addition to cardiac differentiation, which is the core's major task. The training was mainly hands-on training for individual researchers on hiPSC production and genome editing using CRISPR/Cas9. BTM provided several lectures to different groups ranging from high school students to scientists. BMT is also aiming at providing

Organ-on-Chip technologies in collaboration with technical groups at MET, TAU. BMT will provide this to customers in the future, initially as scientific collaboration.

In 2020, the COVID-19 pandemic caused some disruptions to the BCK Stem cell centre services, including a 2-month closure of the centre. Despite this, the centre provided services for five local users and derived three new iPSC lines. BCK started a large patient cohort collection in collaboration with Kuopio University Hospital and the Biobank of Eastern Finland, which will continue during 2021. BCK has set up improved differentiation protocols for endothelial cells, skeletal muscle cells and cerebral organoids. BCK started the development of gene-editing tools targeting mitochondrial DNA heteroplasmy levels. The planned symposiums and courses were postponed due to the pandemic.

The Biomedicum Stem Cell Center (BSCC, representing BCH, www.helsinki.fi/bscc) provided services to 17 user groups. BCH derived 21 new iPSC lines and provided five iPSC lines to six clients. BCH provided an automated live-cell imaging service to 11 users. BCH continued active technological development of the CRISPRa-based reprogramming technology, as a promising new method for reliable and rapid generation of iPSC for biobanking. Furthermore, BCH continued the development of isogenic iPSC-based models for diabetes research. BCH has organized a genome editing and beta-cell differentiation course involving 23 international participants. Also, BCH organized Genome Editing and Stem Cells course and journal club (DPBM-147 HiLIFE) for 20 PhD students. These were organized remotely in compliance with the University of Helsinki COVID-19 recommendations.

In 2020, FinGEEC-Helsinki launched several new services, however, their establishment and public reach was hampered by the pandemic. Nevertheless, FinGEEC-Helsinki started several new projects offering analytic services such as SURVEYOR analysis, Sanger sequencing, and TOPO TA clone analysis from edited genomic DNA samples. Several cell line pilot projects were started during 2020, however, they were still unfinished when the year ended. Regardless the hardship that COVID-19 brought last year, FinGEEC-Helsinki managed to negotiate a valuable service project with a Finnish biotechnology company.

FinGEEC-Turku provided consultation, model design, and reagent generation for CRISPR editing of cell lines. Customers were helped in generation of cell lines where endogenous proteins were tagged with fluorescent tags (Stubb et al., 2020 Nano Letters). This enabled live cells light microscopy imaging of endogenous proteins. Customers were also assisted in design of gene knockout strategies to deplete genes of interest in cell lines for functional studies (Kauko et al., 2020 J. Biol. Chem.). The platform customers have also been provided with help and consultation on non-viral genome editing (CRISPR/Cas9 knockout) on a method based on cell electroporation with ribonuclear protein complexes (RNP) of Cas9 protein with bound gRNAs (Bagati et al, 2021, Cancer Cell). This has been successfully piloted by Prof. Ivaska's team and will now be provided as a consultation service to platform users.

FinGEEC-Turku also provided consultation on CRISPR screens as a service. 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.

FinGEEC-Kuopio's isolation and analytics of gene edited cells at single cell level to

potentiate new discoveries by state-of-the-art flow cytometry has been one of the platform's focus areas. In UEF the platform houses and maintains FACS Aria III Sorter, FlowSight imaging cytometer, and CytoFLEX S analyzer instruments that are used to provide full hands-off services and support for BF community. Unfortunately, this facility (FinGEEC-Kuopio) didn't get any salary support from the host university (UEF) during 2020.

In summary, Stem cell platform and Genome editing platform continuously follows new developments in pluripotent stem cells and genome editing research and technology, and translates them into state-of-the-art services for BF research community.

User statistics

See table below.

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 (EATRIS network at ESFRI).

FinGEEC-Turku (Ivaska) 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.

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 Nordic 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.

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 cell and Genome editing platform services need to focus more on technologies of differentiation and functional analysis of the differentiated hiPSC. BCH focuses mainly on endodermal differentiation to derive functional pancreatic islet cells. BMT/MED focuses on the differentiation of cardiomyocytes and hepatocytes as well as setting up Organ-on-Chip technology and its applications. Analyzing the functionality of cardiomyocytes is still a high priority and the request of many customers. 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,

General		Number of user groups				
Host Univ	Name of core facility	local	national	inter-national	non-academic	Total
UEF	BCK stem cell center	5				5
UH	BSCC	17				17
UH	FINGEEC-HELSINKI	1	1		1	3
UTA	iPSC core	4	4		2	10
		27	5	0	3	35

brain endothelial cells, pericytes, cerebral organoids, blood-brain barrier 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 an emphasis on differentiation and functional analysis on the brain and cardiac muscle cells. BCK concentrate on models and assays of mitochondrial diseases.

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 expects an increase in the need for hiPSC for biobank purposes and has established a trusted partnership with Helsinki biobank.

New inducible CRISPR KO system has been piloted in FinGEEC-Helsinki. This service is collaboration with local VGTCT node and relies on stable lentivirally introduced expression of inducible Cas and stable lentivirally mediated expression of gRNA in a cell line. Second piloted service has been validation of gRNAs in easely transfectable cell lines also by FinGEEC-Helsinki. Both services will be included in the services portfolio of Stem cells and Genome editing platform in 2021. As genome editing field is evolving rapidly, Stem cell and Genome editing platform is exited to capture and disseminate any widely usable genome editing technology that becomes available. There are already several genome editing technologies around that might be possible to translate into service entities, if there is an unmet need (for example, base editing and prime editing).

We acknowledge that certain Instruments would improve stem cell and genome editing services such as microscopy assisted picking of single cells or clusters by CellCelector (ALS Automated Lab Solutions GmbH), single cell multiplex editing by Fluid FM BOT BIO (CYTOSURGE), and sensitive and accurate detection of editing events by Droplet digital PCR system (Bio-Rad) Stem cells and genome editing platform continues to seek funding for these or any novel instrument applicable for stem cell and genome editing through AoF FIRI calls and local host university equipment calls.

Major publications supported by the platform servicestions

De Franco E, et al. YIPF5 mutations cause neonatal diabetes and microcephaly through endoplasmic reticulum stress. J Clin Invest 2020;130(12):6338-53.

Elbasani E, et al. Kaposi's Sarcoma-Associated Herpesvirus Reactivation by Targeting of a dCas9-Based Transcription Activator to the ORF50 Promoter. Viruses 2020;12(9):E952.

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Sonninen TM, et al. Metabolic alterations in Parkinson's disease astrocytes. Sci Rep 2020;10(1):14474.

Oksanen M, et al. NF-E2-related factor 2 activation boosts antioxidant defenses and ameliorates inflammatory and amyloid properties in human Presenilin-1 mutated Alzheimer's disease astrocytes. Glia 2020;68(3):589-99.

Shah D, et al. Modeling of LMNA-Related Dilated Cardiomyopathy Using Human Induced Pluripotent Stem Cells. Cells 2019;8(6):E594.

Zelnik ID, et al. Different rates of flux through the biosynthetic pathway for long-chain versus very-long-chain sphingolipids. J Lipid Res 2020;61(10):1341-6.

Kauko O, et al. Phosphoproteome and drug-response effects mediated by the three protein phosphatase 2A inhibitor proteins CIP2A, SET, and PME-1. J Biol Chem 2020;295(13):4194-211.

Oikari LE, et al. Altered Brain Endothelial Cell Phenotype from a Familial Alzheimer Mutation and Its Potential Implications for Amyloid Clearance and Drug Delivery. Stem Cell Reports 2020;14(5):924-39.

STRUCTURAL BIOLOGY

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

Platform partners:

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);

Biomolecular complex purification Minna Poranen, HiLIFE,

Nuclear Magnetic Resonance: Hideo Iwai, BI-HiLIFE

Mass Spectrometry: Juha Rouvinen, BCK

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.

Development of technology services

The name of the national consortium, which provides the platform for structural biologists at BF, was changed to the Structural Biology Finland (FINStruct) after Finland joined the Instruct-ERIC consortium. The platform has benefitted from the regular meetings of the FINStruct steering group (6 meetings in 2020) and the work of the RI 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.

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.

Main milestones in 2020

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 were successfully evaluated in HiLIFE RIA2020;

Significant funding was awarded in 2020 for both the FIRI2019 and the FIRI2020 calls for coordination, instrument upgrades and membership of the Instruct-ERIC.

New instruments installed for the network through successful funding from the host universities and the Academy of Finland FIRI2015 and FIRI2019 calls;

Upgrade of the Bruker X-ray detector (installed in 2019) to the photon counting PHOTON III version / UO (FIRI2015, 250 480 €)

Hybrid photon counting detector and new goniometer /UTU (FIRI2019, 383 796 €)

Biowave reactor /TUNI (FIRI2019, 66 935 €)

Eclipse Neon field flow fractionator with multiple detectors / UH (FIRI2019, 317 885 €)

Fluorescence detector for Eclipse Neon / UH (host funding, 10 327 €)

T-1270 rotor for ultracentrifuges / UH (host funding, 21 443 €)

Integrated Structural Biology (FINStruct) and the Instruct-ERIC Centre FI were selected for the Finnish roadmap for infrastructures for 2021-2024.

We supported 62 publications, 29 theses, and 253 user groups in 2020.

Developments and Bottlenecks

Although onsite access was severely restricted due to the COVID pandemic from March 2020 to present, we instead developed mail-in services for remote access. CryoEM had a fully operational year in 2020 with good increase in the overall use. We also held two pilot remote cryoEM sample preparation workshops, one for Oulu University and one for the Horizon2020 Impact project. The latter took advantage of the Digicampus possibilities with help from Tiina Salminen in ÅAU. Academic cryo electron tomography software (serialEM) was successfully installed and the first user projects started. This is the same software used for room temperature electron tomography in the BF Biological imaging which eases user transition between electron microscopes and modalities. 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, e.g. through supported Instruct ERIC access or through the Swedish cryoEM block allocation group. With user meetings held three times a year, we have been responding to requests and suggestions on improvements of service provision and types, including putting in place a clear training programme for independent usage of the microscope, with the first users taking advantage of this. Data management and smooth transfer of data to the CSC data containers still needs some more optimisation, and would benefit from institutional IT support that is currently lacking.

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 is now offered as an I-ERIC service. Scarless segmental isotopic labeling developed at the NMR facility offers segmentally isotope-labeled proteins without any mutation. Fully automated-resonance assignment and structure

determination of proteins is currently under development for broader users. The 20-years old 600 MHz magnet having large magnetic field drifts is at the high risk of quenching at any time. Multinuclear experiments at 600 MHz such as 31P will not be feasible when the new tramline is operational (from 2024).

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 Diamond Light Source, UK and the Weizmann Institute, Israel within the H2020 Instruct-ULTRA project. IceBear is currently being implemented in a cPouta cloud environment at CSC within an EOSC-Life project. The crystallization units around Finland have actively worked to deploy IceBear software, so that all users benefit from these developments. X-ray detectors have been updated to photon counting models in Oulu and Turku. Now in situ imaging from crystallization plates can now be done in all three cities. In 2021, a renewal of crystal imaging systems is expected in Helsinki and Oulu, and a high-throughput liquid handling platform will be purchased 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 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. A new Thermo Scientific Q Exactive ultra-high mass range hybrid quadrupole-orbitrap mass spectrometer will be purchased in 2021. It is especially designed for the measurement of large protein complexes such as viruses of molecular weight up to 20 MDa.

Biocomplex provides services for macromolecular complex purification. In 2020, a new device for asymmetrical flow field-flow fractionation (AF4; Eclipse NEON) was installed (FIRI2019 funding). This is the very first new-generation Wyatt FFF-MALS installed in Europe. The premium setup has multiangle (DAWN) and dynamic light scattering (QELS) detectors as well as UV, refractive index (Optilab dRI) and fluorescence detectors. A bottleneck for the Biocomplex service is the continuous need to replace obsolete centrifugation instruments (ultracentrifuges and rotors) which may become a safety risk in the near future. A major obstacle for the service provision in 2020 has been the restrictions in the use of vibration sensitive instruments due to the construction work of the Raide Jokeri tram line through the Viikki Campus area. This was especially affecting the ultracentrifugation service which was closed several months in 2020.

Protein Service provides recombinant protein production, purification and characterization services for academic and industrial partners at the national and international level. Scaled-up of protein expression has been improved with a FIRI 2019-funded WAVETM 25 bioreactor system, which came online in 2020 enabling large scale insect and mammalian cell based productions in GLP like environment. Protein service activities were transferred in January 2021 to the BF proteomics platform.

User statistics

See table on below.

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. Instruct-ERIC decision-making bodies and committees have a broad Finnish representation and representatives are in the Council (Butcher, UH), Executive Committee (Butcher, Varjosalo, UH), Access Committee (Oksanen, UH), Data Management and Computational Committee (Lehtiö, UO), Training Committee (Kajander, UH), and R&D review panel (Rouvinen, UEF) enabling RI development at the forefront of Europe.

We are actively enhancing collaboration within the EU infrastructure networks and other Instruct and structural biology related projects e.g iNEXT-Discovery, Instruct-ULTRA, EU-LAC ResInfra, TRANSVAC2, TRANSVAC-DS, EOSC-Life, ERIC Forum, RI-VIS. The RI has close links to Finnish ESFRI nodes that provide complementary data and services or are dependent on structural cell biology results (ELIXIR, Euro-Bioimaging, EU-OPENSCREEN). Our efforts are tightly linked to the European Open Science Cloud for developing large scale data management

We coordinate access through block allocation groups to ESRF, the Diamond Light Source, MAX IV and Swedish cryoEM. 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. Importantly, we are part of the 3DBioInfo community of ELIXIR.

Professor Emeritus Rik Wierenga (X-ray crystallization, UO), is a member of the Bessy SSP-college on macromolecular crystallography. Wierenga was a project leader in the Horizon2020 Instruct-ULTRA project that ended in 2020. 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 Synergy Board Leader 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

General		Number of user groups				
Host Univ	Name of core facility	local	national	inter-national	non-academic	Total
UEF	High-resolution Mass Spectrometr	7	4	6	5	22
UH	Biocomplex	54	12	11	9	86
UH	CryoEM	9	6	18	3	36
UH	NMR	12	0	1	8	21
UH	Crystallization	12	1	2	1	16
UO	BCO Protein Crystallography Core	12	3	0	6	21
UTA	Protein Service	0	2	1	0	3
UTU	Protein Structure and Chemistry C	12	5	8	1	26
ÅAU	Structural Bioinformatics Laborato	12	0	10	0	22
		130	33	57	33	253

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

Finnish membership in the Instruct-ERIC was ratified in July 2019. Following that, the Instruct Centre Finland was approved in October 2019, and the Centre has been open for applications since February 2020 through Instruct-ERIC supported access. This move is boosting the international research profile of the platform, 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 spectrometer. 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 FINStruct nodes and internationally through the EOSC Life project.

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 2021, with cryo capacity anticipated in 2022. We are testing the current cryoEM setup to see if it is suitable for microelectron diffraction, and if it is, this will be offered as a complementary service for crystallization experiments from 2022. We are working with CSC to improve data management, data storage and computation. New instrumentation will be installed in 2021 to allow blotting-free vitrification in collaboration with a small startup company called CryoSol from the Netherlands. This should improve the speed, ease and reproducibility of grid preparation, especially for industrial users.

Biocomplex has enriched its AF4 service catalogue by including analytical light scattering and concentration detectors to allow data collection on absolute mass, size, and size distribution. 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

De S, et al. Association of host protein VARICOSE with HCPro within a multiprotein complex is crucial for RNA silencing suppression, translation, encapsidation and systemic spread of potato virus A infection. PLoS Pathog 2020;16(10):e1008956.

Laurinmäki P, et al. Structure of Nora virus at 2.7 Å resolution and implications for receptor binding, capsid stability and taxonomy. Sci Rep 2020;10(1):19675.

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Leppänen VM, et al. Characterization of ANGPT2 mutations associated with primary lymphedema. Sci Transl Med 2020;12(560):eaax8013.

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Kukkurainen S, et al. The F1 loop of the talin head domain acts as a gatekeeper in integrin activation and clustering. J Cell Sci 2020;133(19):jcs239202.

Madar Johansson M, et al. The binding mechanism of the virulence factor Streptococcus suis adhesin P subtype to globotetraosylceramide is associated with systemic disease. J Biol Chem 2020;295(42):14305-24.

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Storey D, et al. Klebsiella pneumoniae type VI secretion system-mediated microbial competition is PhoPQ controlled and reactive oxygen species dependent. PLoS Pathog 2020;16(3):e1007969.

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