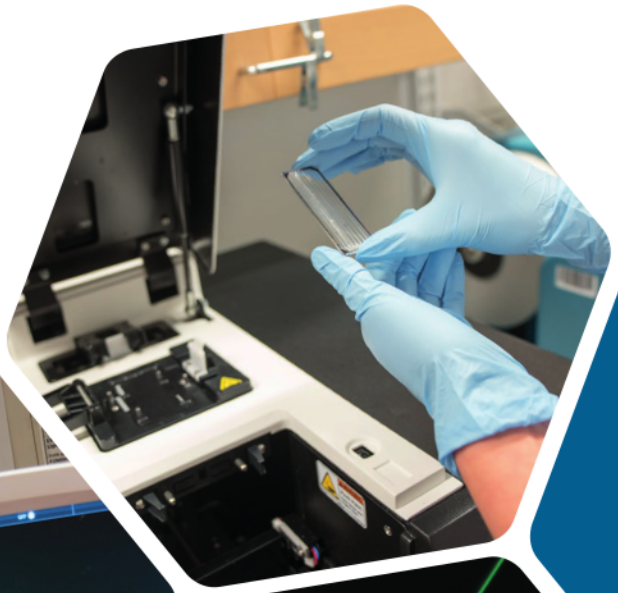
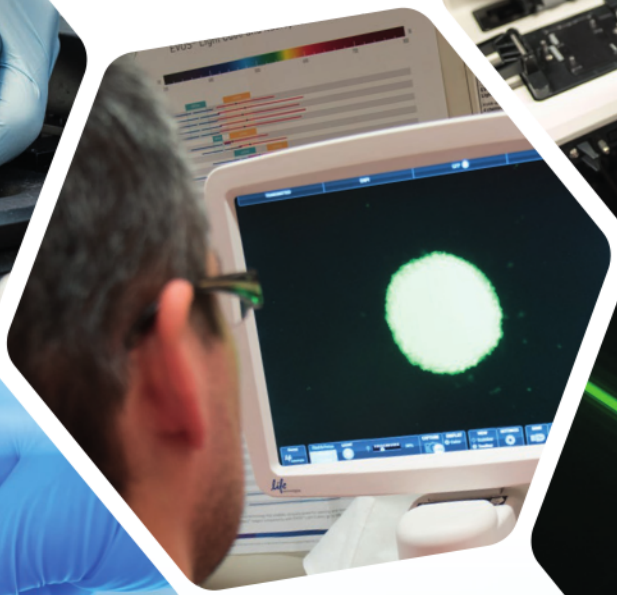
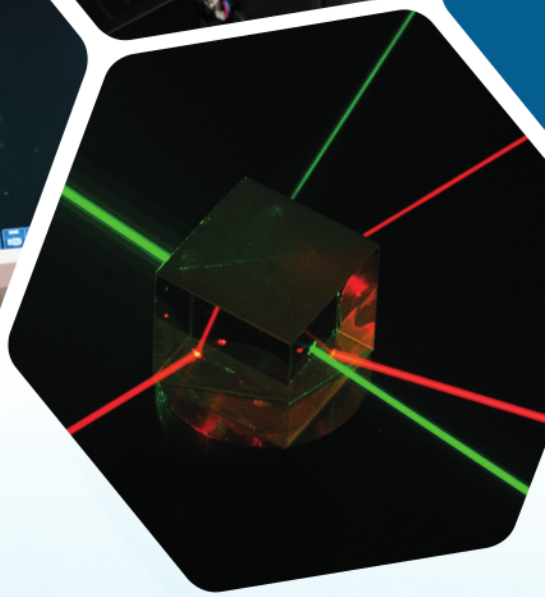
Biocenter Finland

Annual Report 2017







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Biocenter Finland Annual Report 2017

Editor: Antti Siltanen

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

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FOREWORD

The mission of Biocenter Finland is to support frontier research in the life sciences by providing open access technology platforms and services. BF operates as a nation-wide research infrastructure, which is distributed to the five Finnish biocenters. The biocenters and BF are hosted by University of Eastern Finland, University of Helsinki, University of Oulu, University of Tampere, University of Turku and Åbo Akademi University. BF establishes, develops and coordinates state-of-the-art technology services and ensures resources for investments into the facilities. The personnel costs are financed by the host universities. More than 2000 research groups in universities, research institutes and companies in Finland and abroad use the BF technology services annually.

The well-established nine technology platforms of BF, Bioinformatics, Biological Imaging, Genome-wide Methods, Model Organisms, Proteomics and Metabolomics, Stem Cells and Biomaterials, Structural Biology, Translational Technologies and Viral Gene Transfer & Cell Therapy, will be complemented with three new ones, Genome Editing, Liquid Biopsies and Single-cell Omics. The establishment of the new platforms has begun in 2017 with resources that BF obtained from the competitive Research Infrastructure Programme of the Academy of Finland (the Finnish Research Council).

In 2017, the host universities made new investments of about 5 M€, mainly to the Genome-wide methods and to the newly established Single-cell omics platforms. The universities' salary support remained at the 2016 level.

The choice of the platforms to be established or up-graded is crucial. New platforms must support renewal of science, conform to the needs of established scientists as well as the new generation of researchers, and support implementation of the research strategies of BF's host universities. Therefore, BF consulted frontier life scientists such as the directors of Centers of Excellence, Academy professors and ERC Starting Grantees on their needs. The choices were consolidated by BF's Board, where all of its host universities are represented.

The year 2017 was marked by an international mid-term evaluation of the Finnish Research Infrastructure Strategy and Roadmap 2014-2020, where BF is positioned as a major national infrastructure. The criteria of the interim assessment included the level of development, impact and significance, as well as openness and collaborative use of the research infrastructure. BF was placed in the most advanced category, which is a testimony of the success of the BF concept and the quality of the operations.

Since 2017, BF works in close collaboration with the Finnish nodes of the Health and Food domain of the European infrastructure Projects (ESFRI). The Finnish ESFRI nodes are BBMRI (biobanking), EATRIS (translational medicine), ELIXIR (bioinformatics), EU-OPENSCREEN (drug screening), EuroBioImaging, Infrafrontier (mouse models) and Instruct-FI (structural biology).

Not only ESFRI memberships provide access for the Finnish life scientists to research infrastructures not available at home. Finland is also member of the European Molecular Biology laboratory EMBL and the European Molecular Biology Conference EMBC, but the memberships are not taken fully advantage of. BF is committed to promote to the Finnish life scientists' community the use of the core facilities and collaboration opportunities that EMBL offers. EMBC provides funds to the European Molecular Biology Organization EMBO which offers short and long-term fellowships for young researchers and organizes courses, workshops, training and conferences. Raising the awareness of EMBL and EMBC/EMBO started in 2017 with a BF-workshop for PhD candidates and post-docs to showcase what EMBC/EMBO can offer to support their careers.

Professor Marja Makarow
Director of Biocenter Finland

STATISTICS

Technology platform funding

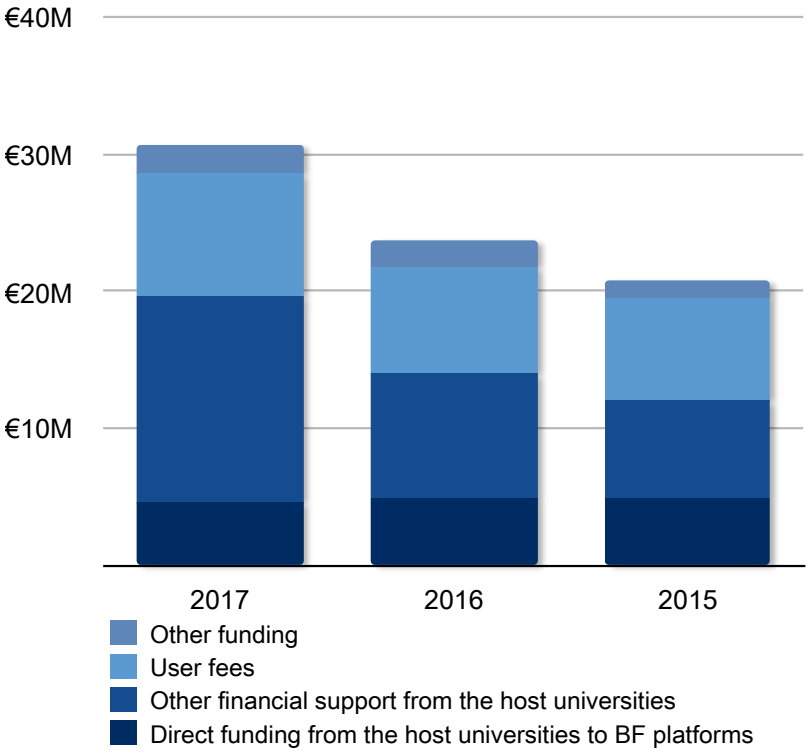


Figure 1. *BF technology platform funding broken down to direct salary support from the host universities, other host university funding, cost recovery from user fees, and other funding sources. The increased other financial support from the host universities was mainly due to increased investments to the Genome-wide methods platform (4M€), and the new Single-cell omics platform (1M€).*

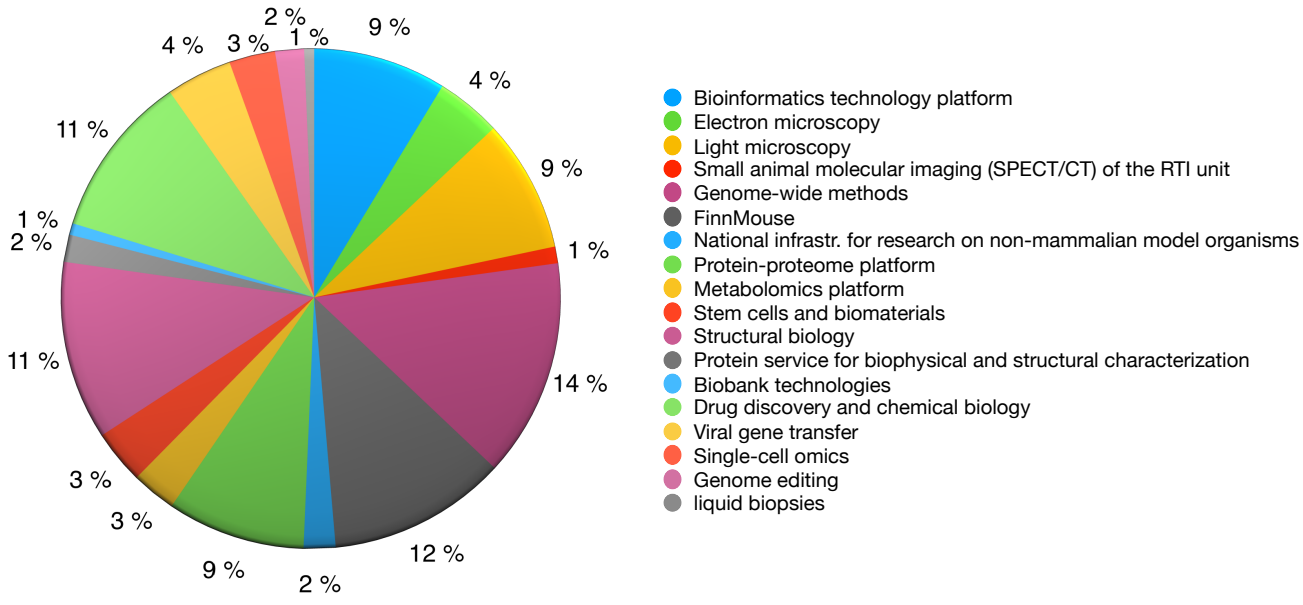


Figure 2*. Distribution of direct host university funding to BF technology platforms in 2017.*

Users

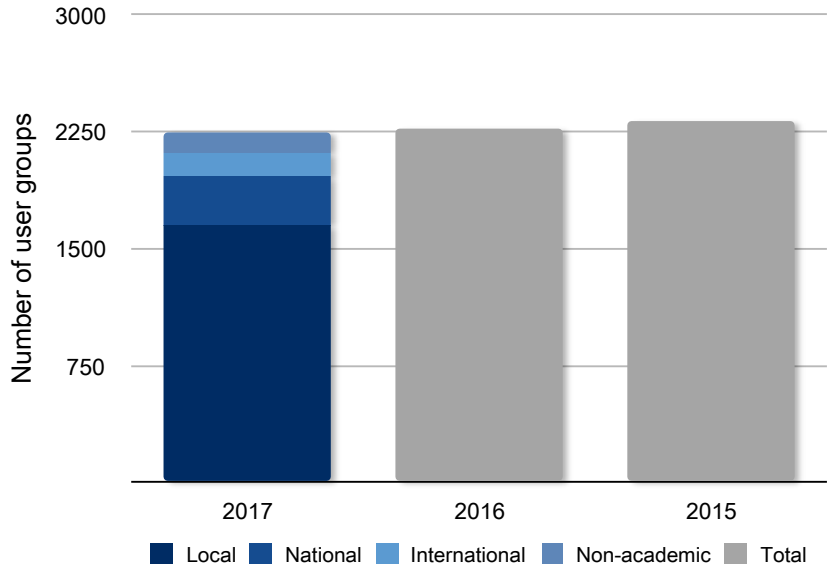


***Figure 3**. Number of research groups and non-academic customers using BF technology platform services.*

Technology platform personnel

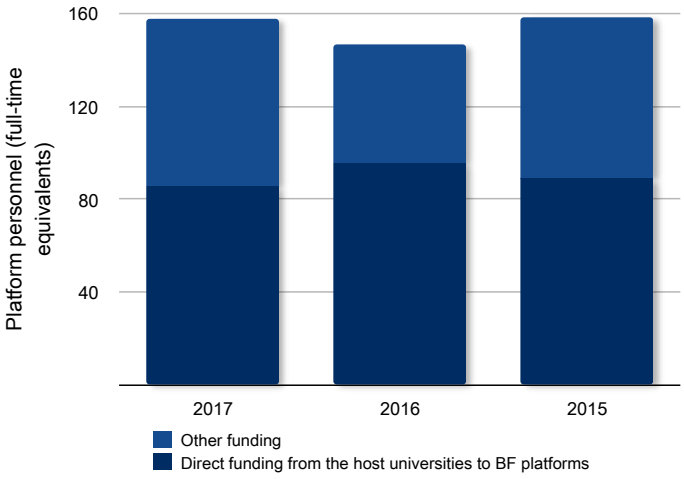


***Figure 4.** BF technology platform personnel in full-time equivalents broken down by source of funding.*

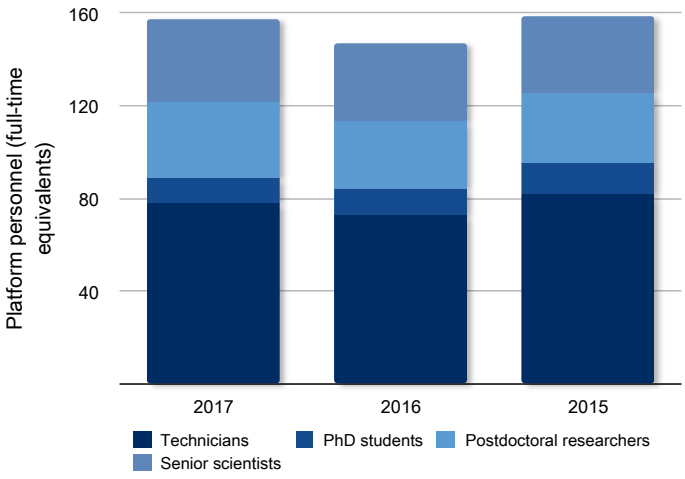


***Figure 5.** BF technology platform personnel by career stage.*

HOST UNIVERSITIES, MEMBER INSTITUTES AND FACULTY

Host universities and member institutes

BF is a distributed national research infrastructure that in 2017 consisted of five member institutes hosted by six universities (Fig. 6). The directors of each institute serve as the Governing Board of BF.

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

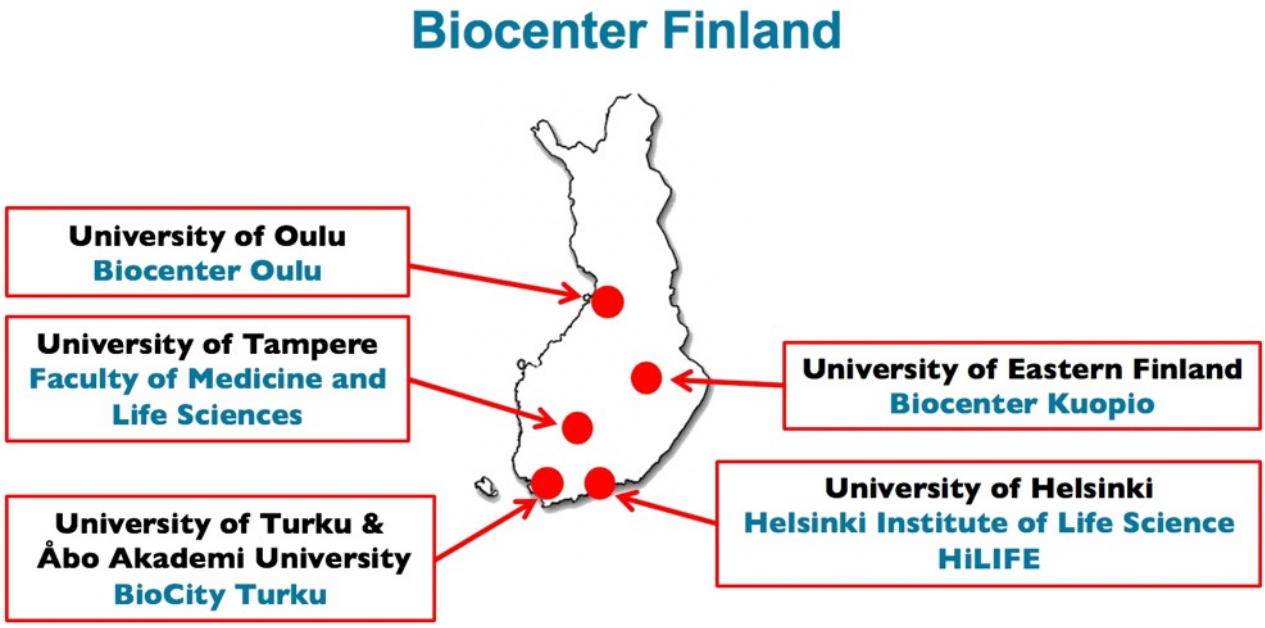


***Figure 6**. The host universities and their BF member institutes in 2017.*

Faculty

At the end of 2017, the Biocenter Finland Faculty comprised of 413 principal investigators listed below. Each member institute has used its own criteria and/or peer review process in assessing the membership (group leaders or principal investigators). In all member institutes, the BF Faculty includes top-tier scientists in each of the scientific fields represented by BF.

University of Eastern Finland

Alhonen L, Auriola S, Carlberg C, Giniatullin R, Goffart s, Gröhn O, Hanhineva K, Heikkinen S, Heinäniemi M, Hiltunen M, Honkakoski P, Ilonen J, Jolkkonen J, Jurvelin J, Jänis J, Kaarniranta K, Kinnunen T, Koistinaho J, Koistinen A, Korhonen R, Kosma VM, Kröger H, Laakso M, Lehto VP, Laitinen J, Levonen AL, Liimatainen T, Mannermaa A, Närväinen A, Paananen J, Palvimo J, Pihlajamäki J, Pitkänen A, Poso A, Pohjoismäki J, Raunio H, Remes A, Rouvinen J, Savinainen J, Sirola J, Tammi M, Tammi R, Tanila H, Tavi P, Töyräs J, Urtti A, Vepsäläinen J, Virtanen T, Ylä-Herttuala S (49).

University of Helsinki

Aaltonen L, Ahtiainen L, Airavaara M, Aittokallio T, Alitalo K, Andressoo JO, Auvinen P, Butcher S, Cerullo V, Castrén E, Claudio R, Daly M, Di-Poi N, Domanskyi A, Dunn C, Fagerholm S, Frilander M, Garcia S, Greco D, Groop L, Hautaniemi S, Heckman C, Helariutta Y, Hemminki A, Hennah W, Hietakangas V, Hiltunen T, Holm L, Horvath P, Huiskonen J, Ikonen E, Iwai H, Jernvall J, Jokitalo E, Kaila K, Kallioniemi O, Kangasjärvi J, Kajander T, Kaprio J, Karhu K, Katajisto P, Kivimäki M, Klefström J, Knip M, Koistinaho J, Kulmuni J, Kuure S, Laine AL, Laiho M, Lappalainen P, Latvala A, Lauri S, Lehesjoki AE, Lehtonen S, Lindström M, Liu D, Lohi H, Lundin J, Löytynoja A, Merilä J, Michon F, Mikkola M, Mustjoki S, Mustonen V, Mähönen AP, Mäkelä T, Niemi M, Ollikainen M, Otonkoski T, Ovaskainen O, Paavilainen V, Palotie A, Palva M, Panula P, Peltomäki P, Pihlatie M, Pirinen M, Primmer C, Poukkula M, Rauvala H, Ripatti S, Saarela J, Saarikangas J, Saarma M, Saharinen P, Salazar-Ciudad I, Santos HA, Schulman A, Sharma V, Shimmi O, Silvennoinen O, Suomalainen-Wartiovaara A, Taipale J, Tian L, Tang J, Thesleff I, Thorogood R, Tyynismaa H, Varjosalo M, Valkonen J, Vattulainen I, Vartiainen M, Verschuren E, Voutilainen M, Vähärautio A, Wennerberg K, Wickström S, Widén E, Zhao H (109).

University of Oulu

Ala-Korpela M, Eklund L, Herzig KH, Hinttala R, Juffer A, Järvelin MR, Karppinen P, Kettunen J, Kursula I, Lehtiö L, Magga J, Manninen A, Myllyharju J, Patanen M, Pihlajaniemi T, Pyhäjärvi T, Reunanen J, Ruddock L, Ruskamo S, Savolainen M, Savolainen O, Sillanpää M, Soininen R, Tapiainen T, Uusimaa J, Vainio S, Wei G, Wierenga R, Winqvist R (29).

University of Tampere

Aalto-Setälä K, Ashorn P, Bova GS, Flodström-Tullberg M, Greco D, Hurme M, Hytönen V, Hyöty H, Isola J, Jaatinen P, Jacobs H, Jämsen E, Järvinen T, Kallioniemi A, Kaltiala-Heino, Kankaanranta H, Karhunen P, Kaukinen K, Kellokumpu-Lehtinen P, Kosunen E, Kulomaa M, Kähönen M, Laurikka J, Lehtimäki T, Lehtimäki L, Lehto M, Leinonen E, Lohi O, Mattila V, Miettinen S, Mikkelsson M, Moilanen E, Mäenpää J, Narkilahti S, Niemelä O, Nikus K, Nikkari S, Nykter M, Oksala N, Paakkala A, Paavonen T, Parikka M, Parkkila S, Peltola J, Peltomäki T, Pesu M, Puura K, Pörsti I, Rautiainen M, Ruusuvuori P, Rämet M, Silvennoinen O, Skottman H, Snellman E, Sumanen M, Tammela T, Visakorpi T, Udd B, Uitti J, Uotila J, Ungureanu D, Uusitalo H, Yli-Hankala A, Ylikomi T, Öhman J (65).

University of Turku and Åbo Akademi University

Airaksinen J, Aitasalo K, Aittokallio T, Alinikula J, Allahverdiyeva-Rinne Y, Aro EM, Aro H, Battchikova N, Belogurov G, Bobacka S, Carpen O, Chen Z, Coffey E, Courtney M, Elenius K, Elo-Uhlgren L, Eriksson J, Fujii H, Ginter F, Goodlett DR, Haataja S, Hannulainen J, He Q, Heino J, Heino T, Holmdahl R, Huhtinen K, Hukkanen V, Hupa L, Hytönen J, Hyötyläinen T, Hänninen P, Härkönen P, Ihalin R, Ivaska J, Ivaska K, Jaakkola P, Jalkanen S, James P, Jartti T, Johnson MS, Julkunen I, Järveläinen H, Kallio M, Kalliokoski K, Kangasjärvi S, Kero J, Kiviranta R, Koskinen P, Knuuti J, Kvarnström C, Kähäri VM, Lahesmaa R, Lahti L, Laitala-Leinonen T, Laitinen K, Laitinen T, Lamminmäki U, Lapinleimu H, Lassila O, Lehtonen J, Lehtonen L, Leino R, Li XQ, Lilius J, Lindfelt M, Lindfors T, Lund R, Lähdesmäki H, Lövgren T, Mattila P, Mattinen J, Meinander A, Meriluoto J, Mertola J, Metsä-Ketelä M, Moritz N, Mulo P, Murzin D, Mäkelä S, Määttä J, Nees M, Niemi J, Niinikoski H, Niiranen T, Nuutila P, Närhi T, Oresic M, Pahikkala T, Papageorgiou T, Parvinen K, , Peltonen J, Peltonen S, Pentikäinen U, Perheentupa A, Pettersson K, Petre I, Posti J, Poutanen M, Pouwels J, Primmer P, Puigpo P, Punkkinen R, Pänkäälä M, Rahman N, Raitakari O, Rautava P, Rautava S, Rekola J, Rintamäki E, Rivero-Muller A, Rogojin V, Roivainen A, Rosenholm J, Sahlgren C, Salakoski T, Salo-Ahen O, Salmi M, Salmi T, Salminen JP, Salminen S, Salminen T, Sandell M, Sandler N, Saraste A, Savolainen J, Savontaus E, Savilahti H, Savukoski T, Scheinin M, Schleutker J, Siitari H, Sillanpää M, Sistonen L, Soukka T, Säämänen AM, Talha S, Tamminen M, Tang J, Tanner J, Tena-Sempere M, Tezvergil-Mutluay A, Toivakka M, Toivola D, Toppari J, Tuomela J, Tyystjärvi E, Tyystjärvi T, Törnquist K, Vallittu P, Virtanen K, Toivakka M, Westermarck J, Wilen CE, Willför s, Wittfooth S, Xiang-Guo L, Xu C, Zavialov A, Zhang H, Österbacka R (161).

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.

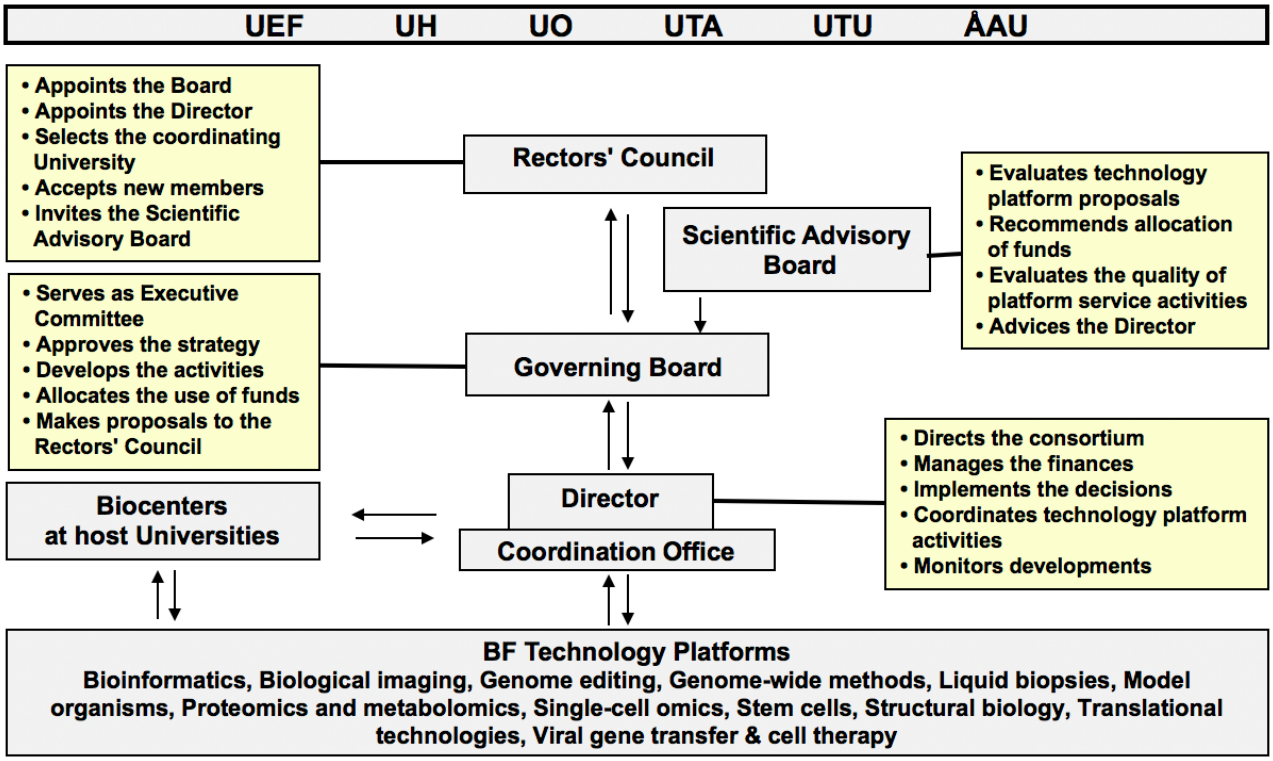


Figure 7. *The governance and organization of Biocenter Finland.*

Governing board

The BF Governing Board in 2017 was Professor Johanna Myllyharju (Chair, Biocenter Oulu, UO), Professor Tapio Visakorpi (Vice Chair, Faculty of Medicine and Life Sciences, UTA), Professor John Eriksson (BioCity Turku, ÅA) and Professor Jyrki Heino (BioCity Turku, UTU), Academy Professor Seppo Ylä-Herttuala (Biocenter Kuopio, UEF), Professor Tomi Mäkelä (HiLIFE, UH), Professor Howard Jacobs (Institute of Biomedicine, UH), and Prof Jaakko Kaprio (Institute for Molecular Medicine Finland, UH).

Coordination office

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

The scientific advisory board of Biocenter Finland

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

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

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

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

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

Professor Matthias Wilmanns, Head of EMBL Hamburg, Germany

SCIENTIFIC SUCCESS STORIES

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

Bioinformatics

The Structural Bioinformatics Laboratory (BCT) was contacted by Professor Juha Kere (Karolinska Institute, Kings College and Biomedicum) for help in identifying the DNA binding sequence for a newly-identified transcription factor (TF) that is responsible for the very early 4-8 cell stage of human embryonic development. The project expanded to include multiple groups in Japan and in 2017 identified a novel target TF that appears to be the key initiator of the events leading to the first 2-3 cell divisions in human life. BF Bioinformatics services were used to model structures, define DNA binding motifs, screen all possible TF binding sites in the human genome, explain biological phenomena associated with mutations (via Decode Genomics) observed in human TFs, and identification of other proteins domains that act in tandem with the TFs to initiate transcriptional control on the early embryo. Structural studies on the TFs are progressing. The project's success relied on our ability to rapidly muster the resources of SBL and the IT infrastructure and programming support provided via BF Bioinformatics especially in 2017.

The Medical Bioinformatics Centre (BCT) worked with Academy Professor Olli Raitakari, Director of the Research Centre of Applied and Preventive Cardiovascular Medicine, to identify markers for improving the prediction of adulthood obesity, known to be an important risk factor for cardiovascular and metabolic diseases. Laura Elo's research group applied machine learning methods on 2262 participants from the Cardiovascular Risk in Young Finns Study, including follow-up information from childhood to adulthood. They discovered a subset of 19 single-nucleotide polymorphisms that improved the prediction of adulthood obesity. The predictive accuracy was highest among young children (3-6 years), whereas among older children (9-18 years) the risk of obesity could be identified using childhood environmental and clinical factors. The developed model can assist in screening children for high risk of developing obesity. The results were published in Circulation: Genomic and Precision Medicine (http://circgenetics.ahajournals.org/content/10/3/e001554.long).

The FIMM NGS bioinformatics unit was an integral part of an international research consortium that established genetic foundations and found potential treatment options for aggressive NK-cell leukemia (ANKL), a highly aggressive form of leukemia leading to death in a couple of months with the current treatment options. The dis-cov-er-ies the team made indicated that ANKL shares a similar genetic background with other NK- and T-cell malignancies and that malignant NK cells are treatable with drugs that inhibit JAK tyrosine kinases and anti-apoptotic BCL family members. The study is available in Nature Communications (Dufva et al., 2018).

Electron microscopy

Autophagy is a regulated, self-degradative process of the cell to balance energy sources during development and in response to nutrient stress. Autophagy also plays a housekeeping role in maintaining healthy cell homeostasis by removing damaged proteins and organelles, as well as eliminating intracellular pathogens. During 2017, NIIN-EM platform was involved in three papers elucidating autophagy functions.

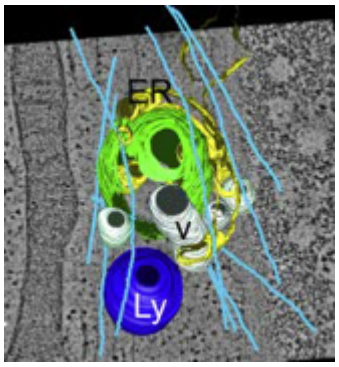
Nascent autophagic membrane, phagophore, nucleates from a subdomain of the endoplasmic reticulum (ER) termed the omegasome. Since the lifespan of the phagophore is only a few minutes and membrane connections and MCSs are very dynamic, capturing these two events requires precision during fixation. In report by Biazik et al., we described our protocol for cryoimmobilization using high-pressure freezing and freeze substitution,

and reported our first findings on phagophore morphology using this approach.

Induction of autophagy leads to the recruitment of lysosomal vesicles onto the chromatoid body, which is a unique germ cell –specific ribonucleoprtein granule playing an important role in compartmentalizing cytoplasmic RNA regulation in haploid round spermatids. In report by Da Ros et al., electron tomography was used to clarify the nature of the chromatoid body associated vesicles and the communication between the chromatoid boby and the autophagosome/lysosome system.

The retinal pigment epithelial (RPE) cells, which are situated between the photoreceptor cells and choroid in the back of the eye, are vitally important for vision by maintaining the viability of photoreceptor cells. In report by Juuti-Uusitalo et al., the functionality of autophagic and proteosomal machinery in the regulation of melanocytic pigmentation were assessed using melanosome-containing human embryonic stem cell –derived retinal pigment epithelial cells. Results revealed that autophagic and proteosomal cleansing co-operatively regulate cellular pigmentation in these cells.

*Figure: 3D model from an APRE-19 cell prepared using high pressure freezing and freeze substitution. A phagophore (depicted in green) is surrounded by vesicles/tubules (V), endoplasmic reticulum sheet (ER), Lysosome (Ly) and microtubulues (light blue). From: Biazik J., **Vihinen H**., **Jokitalo E**. and Eskelinen E.-L. (2017) Ultrastructural characterization of phagophores using electron tomography on cryoimmobilized and freeze substituted samples. Methods in Enzymol. 587:331-349.*



Da Ros M., Lehtiniemi T., Olotu O., Fischer D., Zhang F.-P., Vihinen H., Jokitalo E., Sironen A., Toppari J., and Kotaja N. (2017) FYCO1 and autophagy control the integrity of the haploid male germ cell –specific RNP granules. Autophagy 13:302-321.

Juuti-Uusitalo K., Koskela A., Kivinen N., Viiri j., Hyttinen J.M.T., Reinisalo M., Koistinen A., Uusitalo H., Sinha D., Skottman H and Kaarniranta K., (2017) Autophagy regulates proteasome inhibitor –induced pigmentation in human embryonic stem cell –derived retinal pigment epithelial cells. Int. J. Mol. Sci. 18, 1089; doi:10.3390/ijms10851089

Light microscopy

The light microscopy platform served a growing number of national and international users, in total more than 1000, coming from more than 400 research groups. These groups have a very significant impact on Finnish life sciences, and also science overall. The services of the platform were used in numerous high-impact scientific publications (please see the user statistics report for details). In addition, the Finnish ALM Euro-BioImaging node has served several EuBI international visitors, and the average significance for the scientific impact for the visit was 5/5, as evaluated by the users.

EuBI is bringing numerous advantages to the national research environment by providing open-access to state-of-the-art equipment, facilitating innovation, and training scientists. EuBI will also provide and enhance access to bioimage informatics, a fast-growing new field of science that deals with the processing, visualization and quantitative analysis of biomedical image data. Overall, EuBI will significantly facilitate scientific breakthroughs in all areas of life sciences and therefore enable the Finnish light microscopy consortium to produce state-of-the-art research. Importantly, as the EuBI headquarters will be hosted in Finland and the single access tool of EuBI, the Web Portal, is developed in Finland, EuBI offers unique opportunities for the whole Finnish scientific community to be at the forefront of international development and leadership in imaging.

Small animal molecular imaging SPECT/CT

The SPECT/CT laboratory in partnership with the Radiochemistry lab, and along with the costumer served, have made a significant contribution on the imaging technology development, as well in applied research, especially in the area of cancer (see references below). However, other areas of contribution are in the development of new agents for drug ocular delivery; within the Inovative

Medicines Initiative (EU-IMI) COMPAC project (H2020), where the set goals for SPECT/CT imaging have been met as planned.

Breakthroughs

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

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

Genome-wide methods

With the support of core facility services provided by the BF-GWM technology platform researcher at Hematology Research Unit Helsinki, University of Helsinki, Helsinki University Hospital, Comprehensive Cancer Centre and FIMM were able to show that the somatic mutations play a role also in other human diseases than cancer. Persisting somatic mutations were identified in clonally expanded CD8+ T cells of the newly diagnosed rheumatoid arthritis (RA) patients.

Rheumatoid arthritis (RA) is a common systemic inflammatory disease of autoimmune origin, characterized by chronic inflammation, and T-cell-mediated autoantibody production occurring years before the clinical diagnosis. The study showed that a proportion of RA patients harboured prominent CD8+ T-cell clones. A custom deep-sequencing panel of 986 immune-related genes was developed and utilized in addition to whole exome sequencing to study if the clonal expansion was driven by somatic mutations. In total 30 novel somatic mutations were identified in CD8+ cells of five RA patients, compared to one healthy control harbouring a single mutation in CD8+ cells. The mutations were seen only in the memory-type of CD8+ cell and not in the other blood cell populations. The occurrence of mutations in terminally differentiated T cells may discriminate a benign disorder from a malignant transformation (such as leukaemia or lymphoma), because terminally differentiated effector-memory cells have limited proliferation potential. This study lays the groundwork for future studies seeking to understand the role of somatic mutations in autoimmune diseases and other non-malignant disorders.

Mouse models

A new multi-organ disease named FINCA (Fibrosis, Neurodegeneration and Cerebral Angiomatosis) that is fatal in early childhood was identified in three pediatric patients in Finland by researchers in Oulu University Affected children have previously undescribed formation of connective tissue in the lungs, neurodegeneration and increased vasculature formation in the brain. Mutations in the *NHLRC2* gene with unknown function were detected in FINCA patients. Using genetically modified mouse and zebra fish models, the team discovered that the NHLRC2 protein is essential for normal fetal development and maintenance of multi-organ homeostasis. (Uusimaa J et al. Acta Neuropathol 2018 135:727-742) Further analysis is ongoing in mouse models with patient-specific *Nhlrc2* gene mutations, generated by CRISPR/Cas method.

New findings in the intricate crosstalk between mitochondria, cellular metabolism and the environment have been published by Suomalainen and Tyynismaa research groups. Mitochondrial myopathy (MM) is the most common manifestation of adult-onset mitochondrial disease. The new evidence suggests that a chronic upregulation of anabolic pathways contributes to the disease progression, and rapamycin treatment trials should be considered for adult-type MM. (Khan et al. Cell Metab. 2017 26:419-428). The importance of editing the mitochondrial alanyl-tRNA synthetases for mitochondrial proteostasis was demonstrated by Hilander et al (Nucleic Acids Re 2018, 46:849-860). They showed that tRNA proofreading is essential in mammalian mitochondria and loss of the proofreading activity leads to embryonic lethality in mice.

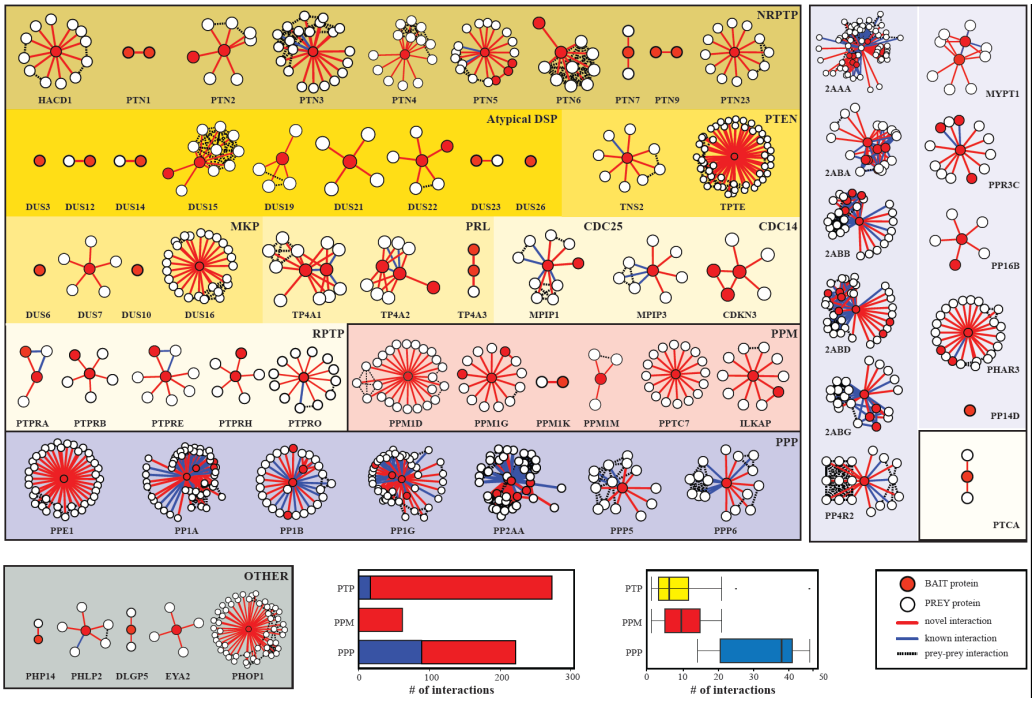
Non-mammalian model organisms

The most important breakthrough is the current standard use of CRISPR-Cas9 method in zebrafish to create targeted mutants that allows for example phenotypic analysis of novel genes associated with certain diseases. Both in the Helsinki and Tampere unit dozens of mutations are created successfully.

Protein-proteome

Example study 1:

Western Diet Deregulates Bile Acid Homeostasis, Cell Proliferation, and Tumorigenesis in Colon



The following paper, done at the Meilahti Clinical Proteomics Unit in Helsinki, was awarded the best article prize for postdoctoral researchers 2017 at the Faculty of Biological and Environmental Sciences at the University of Helsinki.

Denis Dermadi, Satu Valo, Saara Ollila, Rabah Soliymani, Nina Sipari, Marjaana Pussila, Laura Sarantaus, Jere Linden, Marc Baumann and Minna Nyström. *Cancer Res*. 77(12); 3352–63. DOI: 10.1158/0008-5472.CAN-16-2860 Published June 2017

Western-style diet (WD), rich in energy derived from saturated fats of animal origin and scarce of fiber, vitamin D, calcium, and folic acid, is recognized as one of the main risk factors for colorectal cancer. Dietary fat has been implicated to increase colorectal cancer risk, and associations have been found between colorectal cancer incidence, saturated fat intake, and high consumption of red and processed meat. In this paper we performed a long-term diet study in mice to follow tumorigenesis and characterize structural and metabolic changes in colon mucosa associated with WD and predisposition to colorectal cancer by proteomics. WD increased colon tumor numbers, and mucosa proteomic analysis indicated severe deregulation of intracellular bile acid (BA) homeostasis and activation of cell proliferation. WD also increased crypt depth and colon cell proliferation. Despite increased luminal BA, colonocytes from WD-fed mice exhibited decreased expression of the BA transporters FABP6, OSTβ, and ASBT and decreased concentrations of secondary BA deoxycholic acid and lithocholic acid, indicating reduced activity of the nuclear BA receptor FXR. Overall, our results suggest that WD increases cancer risk by FXR inactivation, leading to BA deregulation and increased colon cell proliferation.

The Faculty of Biological and Environmental Sciences nominated this article as best among articles published by early state researchers.

https://www.helsinki.fi/en/news/life-science/best-journal-article-prizes-granted-to-albert-spoljaric-and-denis-dermadi-bebek

Example study 2:

Protein phosphatase interactions

Yadav L, Tamene F, Göös H, van Drogen A, Katainen R, Aebersold R, Gstaiger M, Varjosalo M. "Systematic Analysis of Human Protein Phosphatase Interactions and Dynamics." *Cell Syst*. 2017 Mar 15. (PMID: 28330616)

Affinity purification- and BioID –mass spectrometry were used to identify and characterize molecular interactions for 54 protein phosphatases and 12 of their regulatory subunits. 838 high-confidence interactions were found, of which 631 was novel. With PP1 and PP2 as an example it was shown that this approach captures also spatio-temporal changes in complex composition upon perturbations. Additionally links from phosphatases to several signaling pathways and to human diseases were revealed. This study provided the initial glimpse of the protein phosphatases interaction landscape and their functions in cellular regulation.

Metabolomics

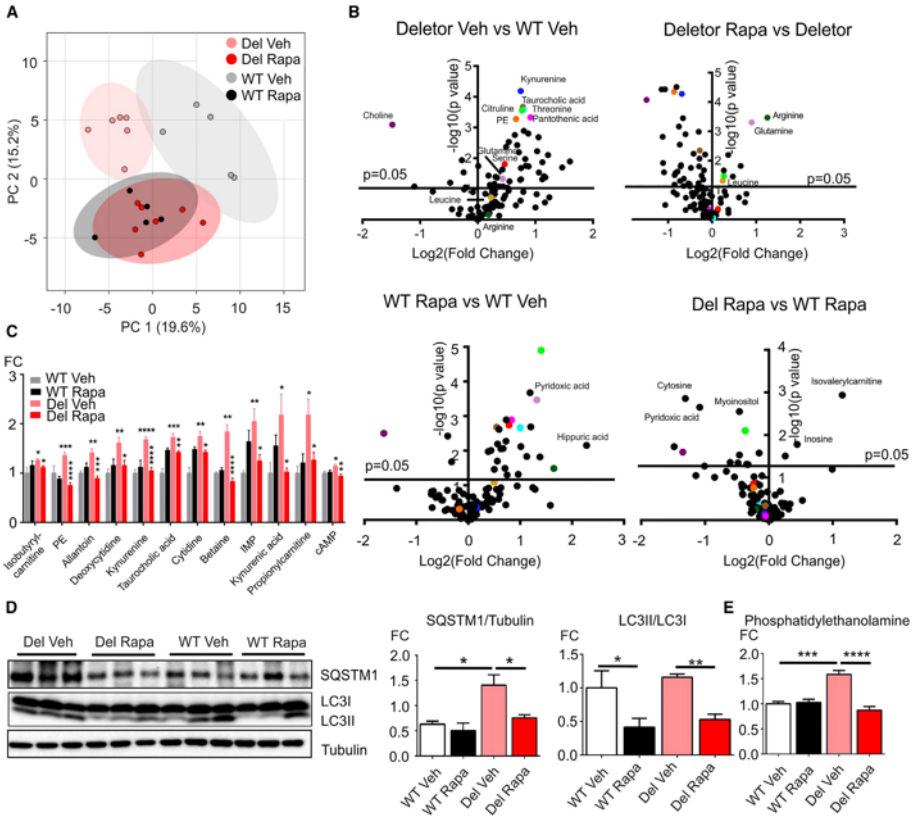
In 2017, FIMM had contributed to an important study related to mitochondrial metabolism and disorders, which was published in a reputed journal "Cell Metabolism". In this study, we reported that mtDNA replication defect activates mTORC1, which drives an integrated mitochondrial stress

response through ATF4 activation, inducing de novo nucleotide and serine synthesis, 1C-cycle, and FGF21 and GDF15 production. Downregulation of this response by rapamycin cured hallmarks of mitochondrial myopathy in mice (Fig 1). FIMM had done all the metabolomics analyses including folate cycle intermediates and also contributed to data analyses and manuscript writing.

Citation: Khan, N.A., Nikkanen, J., Yatsuga, S., Wang, L., Jackson, C., Pessia, A., Riikka Kivelä, Velagapudi, V., Anu Suomalainen. mTORC1 Regulates Mitochondrial Folate Cycle and the Integrated Stress Response in Mitochondrial Disease. *Cell Metabolism*. 2017; 26(2):419-428. PMID:28768179

Figure: *Disease-Associated Metabolic Profile Rescued by mTORC1 Inhibition*

In 2017, ViMU unit started collaboration with the AoF award winning Prof. Helder Santos' research group in Nanomedicine and biomedical engineering by providing the analytical services for pharmacokinetic studies of nanomedicine compared to administration of commonly used medicine. Recent breakthroughs in nanotechnology have paved the way for a new era in medicine. Aim of Prof. Santos' group research is to provide a bridge between medical engineering, pharmaceutical nanotechnology and biomedical research by combining unique techniques, such as microfluidic glass technology to help to build innovative nanomedicines/nanovectors and multidrug loading. To design and test the functionality and efficacy of nanomedicines, ViMU has executed LC-MS based pharmacokinetic analysis for Prof. Helder's group to test the administration of the nanomedicine in vivo and evaluate its metabolic rate.



Stem cells and biomaterials

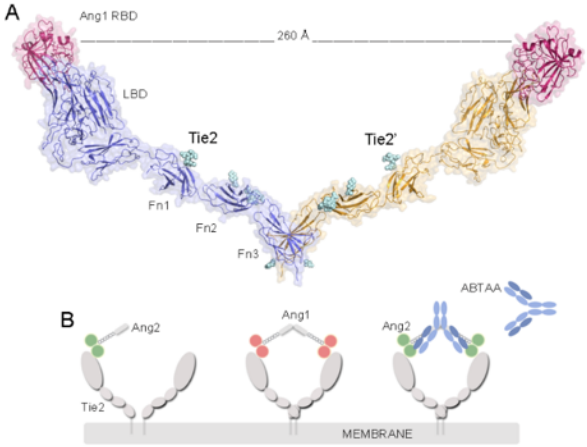
BCH continued services for the derivation of patient-specific iPSCs containing de novo mutation in ATAD3A (ATPase family AAA-domain containing protein 3A). The iPS cells produced from the skin cells were made to differentiate into neuronal cells through a complex in vitro method. Patient-specific iPSCs were used for observation of altered dynamics of the mitochondrial network and increased lysosomes. The practical implication of this study is uncovering of a mechanism of mitochondrial inner membrane AA proteins associated with spasticity (Cooper et al. Hum Mol Genet. 2017; Apr 15;26(8):1432-1443.

BMT has mainly focused on using iPSCs for disease modelling and the improvement of analytical methods. Modelling of cardiac electrophysiological defects has progressed without problems, but cardiomyopathies have proven to be more challenging. The phenotype and functional characteristics of iPSC-derived cardiomyocytes were found to be similar to those observed in patients with hypertrophic cardiomyopathy. This paper also described a wide spectrum of functional assays available in the Core (Ojala M, et al, Stem Cells International 2016, ID 1684792). A lot of emphasis has been put on software improvements and articles relating this been published. Additionally, hepatocytes for studies with lipid metabolism has been set up the detailed lipidomic analysis of those cells have been published (Kiamehr et al, Disease Models and Mech, 2017 Sep 1;10(9):1141-1153). Additionally, reports of combining different analysis software has been published.

BCK has developed methods for differentiation of human iPSC derived cells into a variety of CNS and muscle cells. The differentiation protocols developed are exceptionally broad, extending from specific neuronal subtypes (spinal cord motoneurons and midbrain dopaminergic neurons, astrocytes, oligodendrocytes, microglia) to endothelial and two types of muscle cells. We have shown that specific functional pathologies and clinical phenotypes of CNS diseases, such as Parkinson's disease, Alzheimer's disease, psychopathy, amyotrophic lateral sclerosis and schizophrenia, as well as familial cardiomyopathies can be recapitulated in iPSC-derived cell models. In these studies, the crucial role of astroglia in the pathology of Alzheimer's disease was found (Oksanen et al., Stem Cell Reports 2017, PMID 29153989).

Structural biology

Structural basis of Tie2 activation and Tie2/Tie1 heterodimerization



Tie1 and Tie2 receptor tyrosine kinases are key regulators of blood and lymphatic vessel development, and of pathological processes including tumor angiogenesis, atherosclerosis and vascular leakage in e.g. sepsis. Tie1 is essential for the Tie2 agonist activity of angiopoietins and the activated receptors form heteromeric complexes in endothelial cell-cell junctions. However, little is known about the activation mechanisms of the Tie receptors. The research and structural studies demonstrated that the membrane-proximal domains of Tie2 mediate homotypic interactions, which occur via intermolecular β-sheet formation and are necessary for Tie2 activation. The structural analysis suggests that Tie2/Tie1 heterodimerization occurs by the same mechanism. The crystal structures provide a model for angiopoietin-stimulated Tie2 ectodomain dimerization, clustering and activation, and insights into therapeutic targeting. Crystallization screening and SEC-MALLS characterization were provided by the UH crystallization platform in this study.

Leppänen VM, Saharinen P, Alitalo K. Structural basis of Tie2 activation and Tie2/Tie1 heterodimerization. 2017. Proc Natl Acad Sci U S A. 114:4376-4381.

From homology model to X-ray structure

***Figure**: From homology model to X-ray structure. The diffraction quality of SySPDS crystal was tested with in situ diffraction using PX-Scanner at SBL, BioCity Turku. The X-ray structure of SySPDS (cyan) shows the precise position of the key active site residues (red box), which positions were incorrect in the homology model (grey).*

Spermidine (SPD) is a ubiquitious polyamine synthesized by spermidine synthase (SPDS) from the substrates putrescine and decarboxylated S-adenosylmethionine (dcAdoMet). The 3D structural model for Synechococcus (SySPDS) was first created using X-ray structures of homologous human and parasites SPDSs, which are targets for cancer and antiparasitic therapeutics. The 3D model revealed that the ligand binding residues in human and parasite SPDSs are totally conserved in SySPDS and showed that a proline residue in active site loop defines SySPDS's substrate specificity for short chain polyamines (Pothipongsa et al., 2017). Simultaneously with the structural bioinformatics analysis, SySPDS was produced, purified and crystallized (Guédez et al., manuscript). The X-ray structure of SySPDS revealed a homodimer, which surprisingly has a substrate bound in one active site whereas a product occupies the other one. Due to this feature, the X-ray structure of SySPDS also provides novel information about the catalytic reaction mechanism of SPDSs.

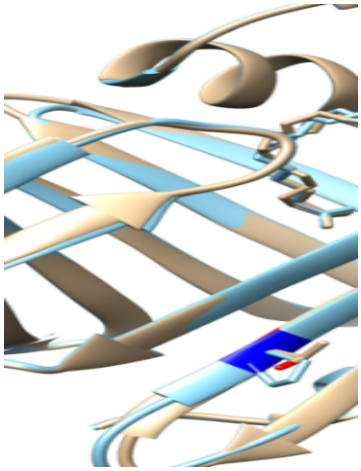
The project started during the 6-month research visit of PhD student Apiradee Pothipongsa (Chulalongkorn University, Thailand) is an illustrative example of the training activities at Structural Bioinformatics Laboratory (BioCity Turku). During her visit, she learned protein sequence analysis, 3D modeling and structural

analysis (structural bioinformatics) but also produced and crystallized SySPDS. Due to the short length of the visit, Dr. Gabriela Guédez at SBL solved the X-ray structure of SySPDS.

Pothipongsa A, Jantaro S, Salminen TA, Incharoensakdi A. 2017. Molecular characterization and homology modeling of spermidine synthase from Synechococcus sp. PCC 7942. World Journal of Microbiology and Biotechnology. 33:72.

Guédez G, Pothipongsa A, Incharoensakdi A, Salminen TA. 2018 Crystal structure of dimeric *Synecochoccus* Spermidine Synthase with bound polyamine substrate and product. Manuscript.

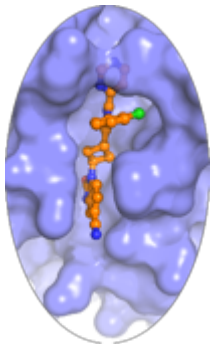
Structural insights into the Charcot-Marie-Tooth neuropathy disease-linked mutations



Charcot-Marie-Tooth (CMT) neuropathy is one of the most common hereditary neurological diseases that affects the peripheral nervous system. Lately, three CMT-associated point mutations (I43N, T51P, and I52T) were found in the peripheral myelin protein P2. The patients with P2-mutations suffer an abnormal myelin compaction and irregular myelin sheaths, leading to reduced nerve conduction velocity, muscle weakness, and atrophy within distal limbs. The mechanisms of CMT-associated disease mutations in P2 were discovered by research groups at the University of Oulu and University of Tampere. None of these mutations affect the overall folding of P2 but the most severe mutation, T51P, at the crystal structure level, has lost one main-chain and one side-chain hydrogen bond. Both experimental and computational methods indicate the opening of the β-barrel in T51P, possibly representing a general functional mechanism in fatty acid-binding proteins. CMT-linked disease mutations also alter aggregation tendency, stability, protein dynamics, fatty acid binding and membrane interactions of P2. Changed biophysical properties and functional dynamics of P2 mutant proteins may give rise to myelin defects in CMT patients.

Ruskamo S, Nieminen T, Kristiansen CK, Vatne GH, Baumann A, Hallin EI, Raasakka A, Joensuu P, Bergmann U, Vattulainen I, Kursula P. 2017. Molecular mechanisms of Charcot-Marie-Tooth neuropathy linked to mutations in human myelin protein P2. Sci Rep. 7:6510.

Development of small molecule inhibitors of tankyrases



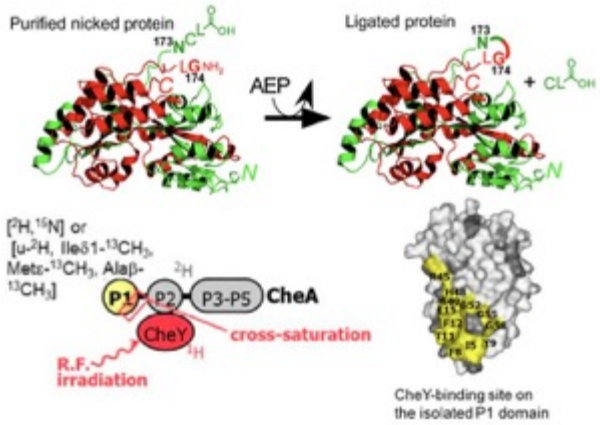
Human tankyrases are protein modifying, ADP-ribosylating enzymes that play a role in multiple cellular signaling pathways by controlling function and stability of multiprotein complexes. A lot of effort has been put in academia and industry for development of potent and specific small molecule inhibitors of tankyrases. International collaboration between University of Oulu, Oslo University Hospital and Berlin Institute of Health reported in 2017 a discovery of a compound which was not only potent, but had also good pharmacological properties and efficacy in cancer models. The team led by professor Stefan Krauss and supported by the research council of Norway funding teamed up with a CRO Mercachem to develop the discovered compound further towards clinical studies. “Protein crystallography has been used throughout the studies and it has facilitated the development of the inhibitors and not only explained the results, but has been a key inspiration for the medicinal chemistry program”, says Professor Krauss.

Anumala UR, Waaler J, Nkizinkiko Y, Ignatev A, Lazarow K, Lindemann P, Olsen PA, Murthy S, Obaji E, Majouga AG, Leonov S, von Kries JP, Lehtiö L, Krauss S, Nazaré M. 2017. Discovery of a novel series of tankyrase inhibitors by a hybridization approach. J Med Chem. 60:10013-10025.

Novel segmental isotopic labeling for NMR

Weak or transient interactions of proteins or domains are examples of protein-protein interactions, which are difficult to investigate because the transient structure is not stable and proteins exist in equilibrium of different forms with various time-scales depending on protein concentrations. By combining segmental isotopic labeling of a domain in the full-length context and NMR spectroscopy, transient domain-domain interactions within a protein have been analyzed (Minato et al., 2017). This approach would not have been possible without segmental isotopic labeling,

opening a new avenue to investigated weak domain-domain interactions within a multi-domain protein.



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

Mikula KM, Tascón I, Tommila JJ, Iwaï H. 2017. Segmental isotopic labeling of a single-domain globular protein without any refolding step by an asparaginyl endopeptidase. FEBS Lett. 591:1285-1294.

Minato Y, Ueda T, Machiyama A, Iwaï H, Shimada I. 2017. Dynamic domain arrangement of CheA-CheY complex regulates bacterial thermotaxis, as revealed by NMR. Sci Rep. 7:16462.

Protein production

Development of target-seeking therapeutic molecules for regenerative medicine

PP has been worked in collaboration with Professor Tero Järvinen to express multi-functional fusion proteins consisting of separate domains for targeting (and tissue penetration) and therapeutic effects. Aim of the research is to develop target tissue specific therapeutics and the expression of model proteins is essential part of the study.

Biobanking technologies

1. Novel multiplex tissue imaging platform.

The paradigm of molecular histopathology is constantly shifting from traditional single-target immunohistochemistry towards novel, multiplexed detection of proteins in order to better understand the complex pathological processes taking place in tissues. The group of Prof. Kallioniemi published a novel platform, which allows for an automatic and quantitative whole-slide analysis of six protein markers with nuclei simultaneously in formalin-fixed human tissues (1).

In the approach they applied multiplexed IHC (mIHC) staining technique coupled with digital image analysis of very large, whole-slide images of tissue sections, enabling automatic classification of all, yet individual, cells in the specific histological context in a quantitative manner. The method enables not only an accurate co-localization analysis of six markers and cell nuclei at the resolution of individual cells but also an automatic classification of cells allowing for a “cytometric” analysis of formalin-fixed tissues. As the system is designed for standard pathology laboratory instrumentation, microscopy, and reagents as well as for open-access image analysis platform, it is possible to implement the system in any laboratory with expertise in histology and microscopy. Furthermore, the system utilizes a fixed set of secondary reagents and unlabeled primary antibodies, which allows for a flexible and user-friendly design and implementation of new marker panels.

As compared to other multiplexing methods currently available, the method does not outweigh the others in terms of the degree of multiplexing, but it is the unique combination of multiplexed detection with flexible implementation of new markers coupled to a quantitative whole-slide analysis that makes the presented system novel.

2. Deep learning techniques

A research team led by Research Director Johan Lundin has shown that deep learning techniques can achieve superhuman performance in prediction of colorectal cancer outcome based on images of cancer tissue samples, without intermediate tissue classification steps. The five-year survival outcome

prediction done by the algorithm outperformed the assessment done by human experts (2).

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

The research team utilized tissue samples from 420 colorectal cancer patients with related disease outcome data that were digitally scanned through the BF supported platform at FIMM.

With this dataset, the team developed and trained a machine learning model to directly predict the five-year disease-specific outcome with only one small tissue image per patient as input. Two deep learning methods, called convolutional and recurrent neural networks, were applied.

The same set of images was then shown to three experienced pathologists from two different institutions. When the researchers then compared the performance of the automated analysis against that of the pathologists they observed that the machine learning based approach outperformed the human observers in categorization of patients into long-term and short-term survivors.

The machine learning-based method also outperformed histological grade, assessed based on conventional microscopy analysis of the whole-slide tumor sample.

The digital risk score is independent of both histological grade and stage of disease. This implies that even a small tissue section contains valuable information about the disease outcome and that artificial intelligence-based methods can be used to extract this information.

Outcome prediction is crucial for patient stratification and disease subtyping to aid the clinical decision-making to achieve a more personalized treatment regimen.

The hypothesis was that training a machine learning classifier supervised by patient outcome instead of expert-defined entities has the potential to identify previously unknown prognostic features. The results suggest that deep learning techniques enable a more accurate outcome prediction as compared to an experienced human observer.

Further research is needed to understand what factors affect the final decision of the classifier and which features drive the predictions, i.e. what the neural networks "see". The suggested model should also be trained on larger tumor tissue areas and evaluated on an extended patient series.

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

Drug discovery and chemical biology

Several research groups in Viikki are developing specialized materials for biomedical applications, such as nanoparticles or functionalized membrane materials. To study biological activities of these kind of materials is not always straightforward and requires many times innovative solutions and development of novel bioassay procedures. The DDCB unit at the Faculty of Pharmacy has supported several projects in this context, and has helped researchers to study for example, antibacterial properties of nanoparticles and anti-biofilm activities of functionalized membranes designed for wound care applications.

Viral gene transfer and cell therapy

Special expertise and strict safety requirements are needed for concentrated viral vector production. In VGTCT network established protocols and procedures are available which guarantee safe and efficient handling of gene transfer reagents for scientists who might not be so familiar with these technologies.

One example of the excellent science is the publication by Antila S et al (Development and plasticity of meningeal lymphatic vessels. J Exp Med. 2017: 214:3645-3667) where plasticity of meningeal lymphatic vessels was demonstrated. AAV encoding VEGF-C/D trap was administered either to newborn pups or at a later time point, and the mice were analyzed in adulthood after several weeks. Under such treatment, the meningeal lymphatic vessels largely regressed.

BIOCENTER FINLAND TECHNOLOGY PLATFORMS

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

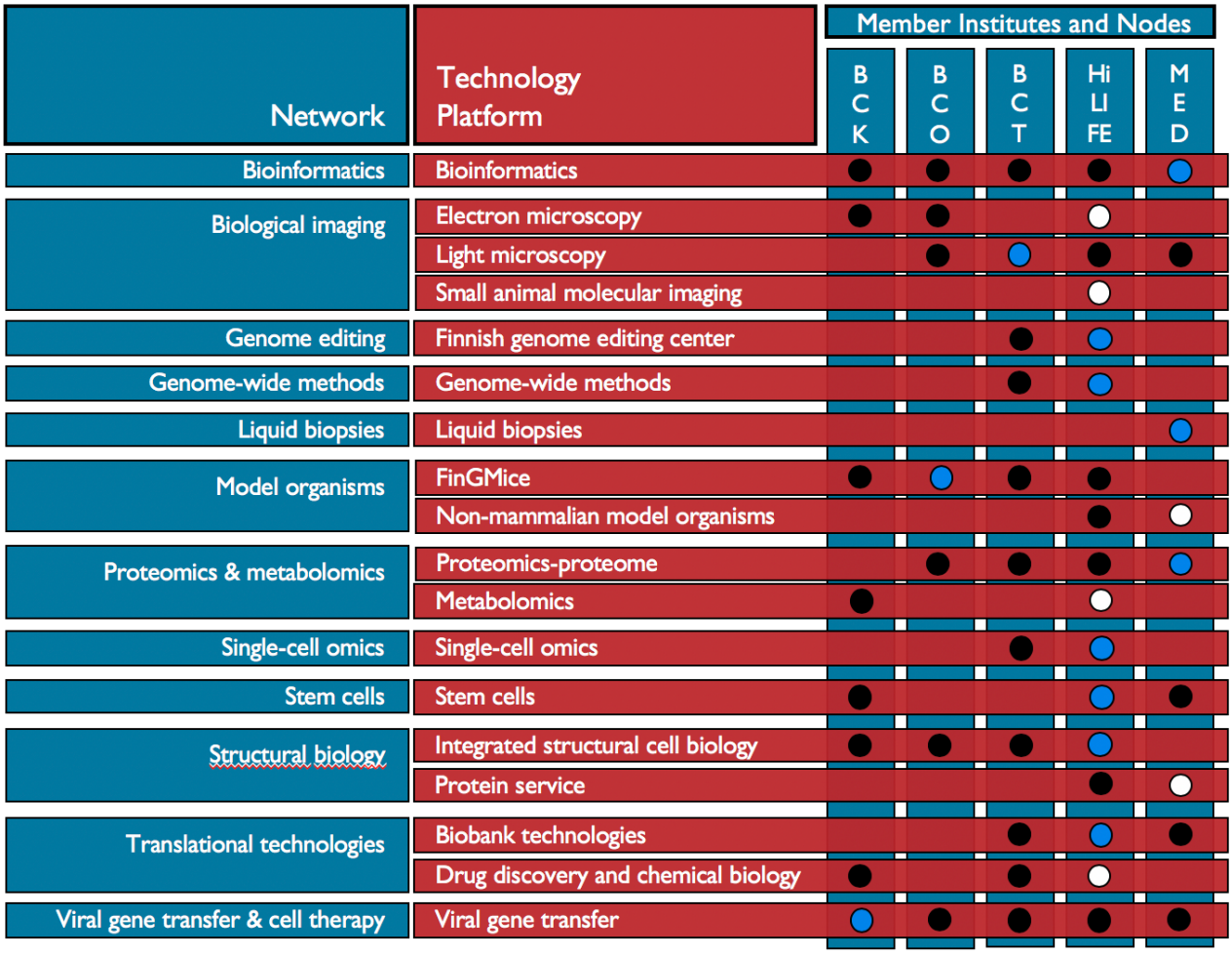


Figure 8. *The BF scientific networks, technology platforms and local nodes hosted by the member institutes. The dots indicate in which member institute the nodes are located. Blue dots: network chairmanship, white dots: platform chairmanship. BCK, Biocenter Kuopio (UEF); BCO, Biocenter Oulu (UO); BCT,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

BIOINFORMATICS

Coordinator: Matti Nykter, MED

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

Bioinformatics technology platform

Chair of the platform: Matti Nykter, MED

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

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

http://bioinformatics.biocenter.fi/

Achievements in development of technology services

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

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

Customer feedback has been positive. After completion of each project we request feedback from the customers. Customers were very pleased with quality of the services. Negative feedback results mostly from the sometimes long wait times due to lack of service staff. Furthermore, it also takes a long time to set up analysis services and workflows for new data types and resources are limited for more tailored analyses. To provide support for the whole national bioscience community, in addition to local contact persons at biocenters, we provide national bioinformatics helpdesk support through email.

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

User statistics

See table below.

Participation in international, Nordic and European infrastructures

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

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

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

Horizon 2020 Marie Sklodowska-Curie Innovative Training Network: Training sites are hosted within the network

Finnish Cloud and Grid Infrastructure (FCGI): We participate in development and utilization of national distributed computing environment. We have been part of the FIRI application and obtained funding for new equipments for 2019.

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

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

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

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

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

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

EU-OPENSCREEN we contribute analysis tools for high-capacity screening platforms

Future perspectives

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

The bioinformatics network aims to continue to support the data management and analysis needs of BF biological imaging, structural biology, genome-wide methods, proteomics, single-cell and liquid biopsies networks. We currently rely upon researchers within bioinformatics groups to provide support to these areas. In addition, there is an urgent need for investments to local highly specialized hardware such as 3D graphics workstations for proteins structure analysis, high memory servers for providing services, as well as for local storage of large datasets generated by other BF networks. The usage of local storage resources has increased rapidly due to BF investments in new data generation instruments (e.g. plate hotel for

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	international	non-academic	Total
UEF	BCK						0
UH	HiLIFE	Systems Biology Unit	4	0	1	0	5
	BI-HiLIFE	BI-bioinfo	3	9	9990	0	10002
	FIMM-HiLIFE	FIMM NGS Unit	51	9	2	1	63
UO	BCO	Biocomputing Core Facility	6	2	2	0	10
UTA	MED	Bioinformatics Facility	8		1		9
UTU	BCT (ÅAU)	Structural Bioinformatics Laboratory	24	6	13		43
UTU	BCT (TCB)	Medical Bioinformatics Centre - Elo	21	8	3	1	33
	Total		117	34	10012	2	10165

structural biology and expansion of biological imaging). It should be noted that the local resources in Biocenters and the cloud resources via CSC/ELIXIR are non-competitive and complementary; local nodes serve special use cases and the cloud provides generic computational capacity.

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

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

The number of research groups who ask for implementation and use of computational software presented in literature is growing steadily. In addition, the demand for large scale *in silico* modeling and simulation studies of biological systems continues to increase. This clearly illustrates that there is a growing demand for more labour intensive bioinformatics support and to educate researchers to use software tools in their research. The network aims to further increase competence and expertise to offer services to the client through more senior service staff assuming sufficient long term funding is appointed to this.

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

Major publications supported by the platform services

Dufva O, Kankainen M, Kelkka T, et al. Aggressive natural killer-cell leukemia mutational landscape and drug profiling highlight JAK-STAT signaling as therapeutic target. Nat Commun. 2018;9(1):1567.

Savola P, Kelkka T, Rajala HL, et al. Somatic mutations in clonally expanded cytotoxic T lymphocytes in patients with newly diagnosed rheumatoid arthritis. Nature Communications. 2017;8:15869. doi:10.1038/ncomms15869.

Posada IMD, Lectez B, Sharma M, et al. Rapalogs can promote cancer cell stemness in vitro in a Galectin-1 and H-ras-dependent manner. Oncotarget. 2017;8(27):44550-44566. doi:10.18632/oncotarget.17819.

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BIOLOGICAL IMAGING

Coordinator: John Eriksson, BioCity Turku

The year 2017 has been extremely successful for Finnish Bioimaging. On January 19th, 2017 the Euro-BioImaging (EuBI) Interim Board (IB) unanimously approved the submission of the 1st step ERIC application to the European Commission. 12 countries of 17 signatories of the "Memorandum of Understanding (MoU) Concerning the Process of Establishing Euro-BioImaging" have expressed their intention to jointly establish EuBI by submitting the ERIC application to the European Commission. Six founding members (Bulgaria, Czech Republic, Finland, Hungary, Italy and EMBL) have submitted the step-2 ERIC application, which has received unanimous support from the EC's ERIC committee. The new EuBI ERIC is, thus, expected to be formally launched in 2018.

During 2017, several Euro-BioImaging international users visited the Finnish Advanced Light Microscopy Node, and overall the Node is one of the most popular in EuBI, further expanding the network of connections of the imaging facilities in Finland. Also, advances in imaging technologies and services through EuBI, and otherwise in the Finnish light microscopy consortium, have enabled multiple disclosures, patents and patent proposals at each of the participating units.

A New core unit, FIMM-HCA, was established during 2017. FIMM-HCA is one of the three units (with BIU-HILIFE and LMU-BI) that co-founded the HiLIFE Light Microscopy platform, and is offering services in high-content imaging. Additionally, MED-Tampere moved the core activities to a new building, ARVO, allowing novel core facility infrastructure.

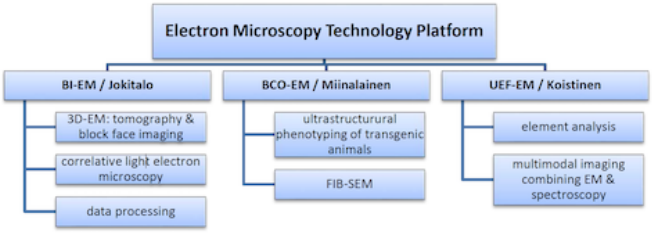
Several units have purchased new instrumentation for national and international use and have widened their national and international infrastructure. Collaboration networks have been established to enhance imaging collaboration and to bring together representatives from different imaging-related networks.

Electron microscopy technology platform

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

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

Achievements in development of technology services



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

The main common goal of the three EM units forming this consortium has been to restructure and streamline the functioning of the units towards nationally unique complementary areas. In Helsinki, BI-EM focus on 3D imaging of cells and tissues and correlative light electron microscopy. In Oulu, BCO-EM specializes in the ultrastructural pathology of human and model organisms working closely with the BCO Transgenic mouse core facility. In University of Eastern Finland, UEF-EM develops non-destructive imaging techniques to

study elemental and chemical composition of biological specimens.

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

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

During 2017, we provided personal training for 37 new users in operation of microscopes and other instruments in our platform. In Oulu, BCO-EM organized an "Advanced Course on Light and Electron Microscopy –Multiphoton and electron microscopy united". In April 2017, BI-EM released the second version of an open-source software Microscopy Image Browser (MIB; http://mib.helsinki.fi/), the MIB 2.0., and after this, we trained new MIB users in two workshops held in the Newcastle University and the Francis Crick Institute, UK. We also participated as teachers in the Annual Microscopy Workshop (theme: Image Analysis and Visualization for Light and Electron microscopy) in Yale University School of Medicine, USA, and EMBO Practical Course: Volume electron microscopy by automated serial SEM in Basel, Switzerland.

User statistics

See table below.

Participation in international, Nordic and European infrastructures

BI-EM and BCO-EM are members in a Finnish multimodal Advanced Light Microscopy Node of Euro-BioImaging (EuBI). EuBI is a pan-European research infrastructure for imaging technologies in biological and medical sciences on the ESFRI Roadmap. The mission of EuBI is to create a coordinated plan for organization, utilization, and implementation of advanced biomedical imaging technologies in Europe. The EuBI infrastructure launched its operation during spring 2017. BI-EM is a partner in Helsinki BioImaging subnode, and provides several immuno-EM methods, correlative light-electron microscopy, two 3D-EM techniques and image analysis. In 2017, a new post-doctoral researcher was recruited with FiRI funding to coordinate the EuBI projects within the Helsinki subnode. BCO-EM as part of the Oulu Bioimaging

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	international	non-academic	Total
UEF	BCK	UEF-EM	35	0	0	4	39
UH	BI-HiLIFE	BI-EM	90	18	7	4	119
	FIMM-HiLIFE						0
	HiLIFE						0
UO	BCO	BCO-EM	22	4	5	0	31
UTA	MED						0
UTU	BCT						0
	Total		147	22	12	8	189

network (OBI) forms a mesoscopic imaging platform together with imaging laboratories from Faculty of Technology (Optoelectronics and Machine Vision), Center of Microscopy and Nanotechnology, Institute of Biomedicine and Diagnostics and Biocenter Oulu Tissue Imaging Center. BCO-EM provides morphological and ultrastructural expertize using immunolabelling and FIB-SEM. All sub-nodes are additionally linked together by activities aimed at facilitating image processing, visualization and open-source software production for image analysis. UEF-EM is part of Biocenter Kuopio, providing a multidisciplinary research network between different actors in the fields of molecular medicine and related drug research and biotechnology.

BI-EM participates in BIIF, BioImage Informatics Finland, which is a network for bioimage analysts, software developers and life scientist who use bioimage informatics as a central toolset and is a partner in NEUBIAS (Network of European BioImage Analysts). NEUBIAS is an action fully funded by European COST (CA15124). In August, BI-EM hosted a staff researcher from EM Research Services at Newcastle University, UK, for 2 weeks on a project "Improving segmentation in challenging 3D-SEM datasets using Microscopy Image Browser" supported by a Short-term scientific mission grant from NEUBIAS.

Future perspectives

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

to increase the capacity for 3D-EM projects, BCO-EM is aiming to get funding to upgrade their SEM platform for serial block face imaging of large tissue samples.

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

Major publications supported by the platform services

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Light microscopy technology platform

Chair of the platform: John Eriksson, Turku Bioimaging

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

Achievements in development of technology services

The year 2017 has been very successful for Finnish Bioimaging. Euro-BioImaging (EuBI) started its Interim Operation in May 2016, and has been successfully continuing this for the whole of 2017. Already during Interim Operation, 28 Node Candidates provide access to their imaging platforms for EuBI users through the EuBI Interim Web Access portal developed in Turku. Development of the EuBI Web Portal that will be in use when the EuBI ERIC is established has also proceeded well. On the European scale, significant progress has also been made in building the EuBI pilot Image Data Resource, a public data repository that stores, integrates and serves image datasets from published scientific studies, and the Image Resource Portal, which lists available software tools for image processing and analysis.

The Finnish Advanced Light Microscopy (ALM) Euro-BioImaging Node is formed by four units of the consortium; TBI-CIC, TIC-BCO, BIU-HILIFE and LMU-BI. Through EuBI, the Finnish ALM Euro-BioImaging Node has received several applications (4 submitted during 2017) and is overall the third most popular Node Candidate during Interim Operation. The successful international visits indicate that the instrumentation and the knowhow in Finland are unique. The EuBI research visits are generally evaluated to be of significant scientific impact by the visitors. For national and local users, the most frequently used imaging modalities were confocal microscopes and live-cell imaging.

A New core unit, FIMM-HCA, was established during 2017. FIMM-HCA is one of the three units (with BIU-HILIFE and LMU-BI) that co-founded the HiLIFE Light Microscopy platform. The unit was officially opened in June. Additionally, recently recruited HiLIFE tenure track principal investigators successfully applied for instrument funding from the faculty of medicine for generally available systems for the research community at the BIU-HILIFE.

Recent technological developments at the Finnish imaging centers

Super-resolution imaging:

In 2017, both CIC-TBI and BIU-HILIFE upgraded to ZEISS LSM 880 Airyscan with "fast mode". The fast mode enables a fourfold increase in image acquisition rate and a fourfold increase in signal to noise ratio in combination with high-resolution imaging with a lateral resolution of 160 nm, with normal confocal samples and fluorescent labels. The fast mode is especially beneficial for live cell imaging.

Two consortium members, CIC-TBI and BIU-HILIFE, both acquired a GE DeltaVision OMX SR structured illumination microscope for fast super-resolution imaging of fixed and live samples using traditional fluorescent dyes. The instrument is capable of 3D SIM with a lateral resolution of 110-160 nm and an axial resolution of 340-380 nm. In addition, the system can be used for 2D SIM, 2D SIM-total internal reflection (TIRF), ring TIRF,

super-resolution localization (STORM, PALM), photokinetic manipulations and widefield imaging.

LMU-BI acquired a Leica TCS SP8 STED for modern confocal and super-resolution imaging. A motorized stage enables multi-point live cell imaging experiments by built-in autofocus. Super-resolution STED imaging can be performed with two colours by careful selection of the dyes.

High-content and high-throughput imaging:

FIMM-HCA purchased a PerkinElmer Opera Phenix spinning-disk confocal high-content screening system. The automated microscope offers confocal and widefield imaging of multi-well plates and slides. The system enables imaging of live samples with environment control and offers the possibility for low resolution pre-scanning of the sample, followed by high-resolution imaging of the selected regions.

LMU-BI acquired a Molecular Devices Nano for automated wide-field imaging of well plates and slides. The system offers several built-in protocols and image analysis algorithms to facilitate simple imaging set-up and analysis.

CIC-TBI purchased the Nikon Eclipse Ti-E, ideal for high-end research and live cell imaging. The instrument functions with both glass bottom dishes and plastic dishes and is especially suited to high-throughput screening applications that involve multi-well plates or larger tissue samples.

Label-free technologies:

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Mesoscopic imaging

MED-Tampere: There have been several upgrades to the Zeiss LSM 780 and an upgrade of Zeiss LSM 700 into a LSM 800. After moving to the ARVO building, the imaging core took over several microscopes originally owned by research groups, and they have been serviced and upgraded to usable level.

TIC-BCO has established a dedicated intravital imaging laboratory, as well as anaesthesia and surgery techniques that allow imaging of living animal tissues at single cell resolution through thinned skull or glass windows.

BIU-HILIFE has acquired a LaVision BioTec UltraMicroscope II light sheet microscope especially suited for cleared larger samples. It thus complements the Zeiss Lightsheet Z.1 microscope at the LMU-BI in both sample size and suitable clearing methods. During 2017 the data handling and analysis capacity at the BIU was upgraded in preparation for the installation of the instrument in June 2018.

Image analysis and processing

At the TIC-BCO, collaboration with the Center for Machine Vision and Signal Analysis has resulted in the development of hyperspectral image data processing and analysis methods. Investments have also been made in commercially available image data analysis software for better post-processing, rendering and deconvolution of thick and often blurry 3D images of mesoscopic scale samples.

MED-Tampere purchased a new analysis computer for time-lapse imaging data (Cell-IQ and Nikon Biostation), a new analysis computer for deconvolution, and an additional license for NIS-Elements software.

FIMM-HCA unit researchers published Advanced Cell Classifier 2.0, open source software for machine learning based phenotypic classification of cells and exploration of 100's-dimensional feature space for new phenotypes. The researchers also developed a method for analysis of multiplexed IHC whole-slide tissue images.

BIU-HILIFE has recently invested in updating data handling and analysis infrastructure as part of the light sheet microscope purchase. Local network connections have been upgraded to optical fiber, and data storage capacity and hardware for advanced virtual image analysis workstations was acquired.

CIC-TBI has continued to develop data management tools both locally and on the national level, with national and international collaborators such as Euro-BioImaging, Global BioImaging and CSC. CIC-TBI has also developed some new image analysis approaches, e.g. for phase-contrast cell screens in drug development and for quantifying nuclear bodies.

User statistics

See table below.

Participation in international, Nordic and European infrastructures in 2016

The BF light microscopy consortium continued its active participation in the Euro-BioImaging ESFRI (www.eurobioimaging.eu). In 2017, the H2020-funded Euro-BioImaging Preparatory Phase II project was ongoing, with Finland leading the development work of the Euro-BioImaging Web Access Portal and overall having a critical role in constructing EuBI for launch of the EuBI ERIC projected for 2018.

During 2017, the H2020-funded Global BioImaging (GBI) project had its Second Exchange of experience meeting in Bangalore, India, with several key representatives and organizers from Finnish BioImaging. Finland also actively participated in the GBI core facilities shadowing programme, hosting a visitor from Australia and sending one to Australia.

The Nordic Imaging network continued networking and discussing about funding possibilities. All participants in the Bridging Nordic Imaging -project (2014-2016), and additionally the newly formed Danish BioImaging network, wanted to continue the expansion of Nordic imaging collaboration and to bring together representatives from different imaging-related networks.

The COST-funded Network of European BioImage Analysts (NEUBIAS, http://eubias.org/NEUBIAS/) continued its operation with three representatives from the Light Microscopy Consortium in its management board. During 2017 two core facility members from Finland participated in the NEUBIAS course for Core facility personnel to extend image analysis service skills. The NEUBIAS related BioImage Informatics Finland network took its first steps including identification of interested collaborators, and making concrete plans such as seminars and workshops.

FIMM-HCA joined and participated the meetings of the European Cell Based -assay interest group (http://eucai.org/index.html), which operates towards shared practises and protocols in cell based screening within member laboratories. It aims at providing cell based screening services and high content analysis solutions for academic translational centres, SMEs and the pharmaceutical industry.

Future perspectives

Step-2 application for EuBI ERIC was submitted by Finland on January 19th, 2018. The ERIC Committee reported on unanimous support for the application already on 9th of February, 2018. This evaluation was timely for the ESFRI landmark evaluation, and contributed to EuBI becoming an ESFRI Landmark project. The new EuBI ERIC is, thus, expected to be formally launched in 2018.

In August 2018, Turku is organising a BioCity Symposium focused on imaging. High profile international researchers, including a Nobel prize winner, will be presenting their latest research in this meeting. Alongside with the BioCity

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	international	non-academic	Total
UH	BI-HiLIFE	LMU-BI	70	4	1	0	75
	FIMM-HiLIFE	FIMM-HCA	7	0	0	2	9
	HiLIFE	Biomedicum Imaging Unit (BIU)	81	12	2	1	96
UO	BCO	Light Microscopy Core Facility	35	3	4	1	42
UTA	MED	Tampere Imaging facility	27	1		1	29
UTU	BCT	Cell Imaging Core	164	1	1	3	169
	Total		384	21	8	8	420

Symposium, a Finnish BioImaging meeting will be organized.

In the plans for possible acquisitions for the near future are e.g. a high-content imaging system for MED-Tampere, as well as computer-assisted microscopy for single cell isolation (CAMI) for FIMM-HCA and a confocal microscope for LMU-BI and TIC-BCO. Retention of existing platform personnel expertise through viable career path advancement options, in addition to an increase of dedicated support personnel via competitive recruitment, is needed for the efforts to develop novel state-of-the-art imaging technologies and image data analysis that are not yet commercially available. Basic infrastructure funding typically does not cover sufficient personnel costs needed for such development.

Major publications supported by the platform services

Zhang K, Myllymäki SM, Gao P, et al. Oncogenic K-Ras upregulates ITGA6 expression via FOSL1 to induce anoikis resistance and synergizes with αV-Class integrins to promote EMT. Oncogene. 2017;36(41):5681-5694.

Saarela U, Akram SU, Desgrange A, et al. Novel fixed -direction (FiZD) kidney primordia and an organoid culture system for time-lapse confocal imaging. Development. 2017;144(6):1113-1117.

Kiamehr M, Viiri LE, Vihervaara T, et al. Lipidomic profiling of patient-specific iPSC-derived hepatocyte-like cells. Dis Model Mech. 2017;10(9):1141-1153.

Turunen S, Joki T, Hiltunen ML, Ihalainen TO, Narkilahti S, Kellomäki M. Direct Laser Writing of Tubular Microtowers for 3D Culture of Human Pluripotent Stem Cell-Derived Neuronal Cells. ACS Appl Mater Interfaces. 2017;9(31):25717-25730.

Caicedo JC, Cooper S, Heigwer F, et al. Data-analysis strategies for image-based cell profiling. Nat Methods. 2017;14(9):849-863.

Piccinini F, Balassa T, Szkalisity A, et al. Advanced Cell Classifier: User-Friendly Machine-Learning-Based Software for Discovering Phenotypes in High-Content Imaging Data. Cell Syst. 2017;4(6):651-655.e5.

Lehtimäki JI, Fenix AM, Kotila TM, et al. UNC-45a promotes myosin folding and stress fiber assembly. J Cell Biol. 2017;216(12):4053-4072.

Liu Y, Mattila J, Ventelä S, et al. PWP1 Mediates Nutrient-Dependent Growth Control through Nucleolar Regulation of Ribosomal Gene Expression. Dev Cell. 2017;43(2):240-252.e5.

Pfisterer SG, Gateva G, Horvath P, et al. Role for formin-like 1-dependent acto-myosin assembly in lipid droplet dynamics and lipid storage. Nat Commun. 2017;8:14858.

Redchuk TA, Omelina ES, Chernov KG, Verkhusha VV. Near-infrared optogenetic pair for protein regulation and spectral multiplexing. Nat Chem Biol. 2017;13(6):633-639.

Small animal molecular imaging (SPECT/CT)

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

Partners: Anu Airaksinen, HiLIFE.

Achievements in development of technology services

After the important upgrade of the SPECT/CT camera performed during 2016, the unit was engaged in initiating a plan for service development. Accordingly, a new electro cardiogram/respirator gating system was set up for cardiac and pulmonary imaging. Additionally, a strategy to validate clinically characterised radiotracers, to be used in animal research, has been set, and collaboration with the Medical Imaging Unit of the Hospital District of Helsinki and Uusimaa (HUS) was established.

The most important networking development in 2017 was the participation in the creation of an infrastructure platform: The Helsinki in vivo Animal Imaging Platform (HAIP); one of the 23 platforms of HiLIFE. At that point, functions of the RTI laboratory were divided into two different budgeting units: SPECT/CT LSRI and RadChem LSRI. The HAIP platform offers essential infrastructures and expertise for non-invasive dynamic analysis of physiological and pathological processes in animals in vivo. The platform has impact in basic and translational research in life sciences, including neuroscience, cancer research, cardiovascular and metabolic diseases, as well as in veterinary sciences and in drug development. The platform agglutinates the entire in vivo whole

animal imaging infrastructures of Helsinki and associates essential services, offers comprehensive animal imaging from small fish to horses, using top-of-the-line technologies from optical to nuclear imaging. HAIP is the largest and most versatile whole-animal imaging network in Finland.

a) Imaging development

In 2017, the unit undertook projects aimed to develop the portfolio of services. This included experiments to set Terbium-155 as an new emerging SPECT radioisotope, in response to the lack of suitable SPECT radionuclides matched for diagnosis and therapeutics using (pseudo-) radiolanthanides, This isotope has suitable physical properties for SPECT imaging, a half-life of 5.6 d, and better chemical properties than iodine or indium 155Tb is a superb candidate. Preliminary test were performed, and further characterization and prove of concept experiments are being planned.

A new area of research was opened in the SPECT/CT unit with the tests on plant imaging. A group at the Radiochemistry Unit (M. Lusa), studies bacterial-plant interactions where selenium is up taken. An isotope of this element (75Se) is suitable to SPECT imaging, thus can be applied to image infector-host interactions. Preliminary work was initiated in this field.

b) Radiochemistry services

Radiochemistry services of RTI unit were provided during 2017 in two different modes: custom radiosynthesis of SPECT radiotracers via the SPECT/CT imaging core facility (radiochemistry lab) and by the LSRI in radiopharmaceutical chemistry (RadChem; radiochemistry laboratory and radiosynthesis facilities). From 2018, all radiochemistry services are provided by the RadChem infrastructure under HAIP.

In general, the RadChem provides services design synthesis and production of SPECT and PET radiotracers, as well as in analysis of biological samples. The facilities locate in the Kumpula campus. Laboratories for synthesis of radiopharmaceuticals are equipped with IBA 10/5 medical cyclotron for production of 18F and 11C, Eckert & Ziegler 68Ge/68Ga-generators, lead-shielded hot cells, semi-automatic synthesis units and laboratory instruments for QC. The laboratories are working under radioactive exhaust monitoring system. The facilities include a well equipped small animal laboratory for housing rodents for evaluation of novel radiotracers by ex vivo autoradiography (Fuji FLA-5100 and ai4r Le Beaver) for biodistribution studies. This laboratory is approved for radioactivity (Class B), 2 GMO (class2) and adenoviral vector work.

In 2017, RadChem carried services in both of our main activities: Two projects for academic customers from the University of Helsinki included radiosynthesis development for T-Cell and functionalized exosomes labelling with In-111 and one project for an industrial customer of on-line digital autoradiography analysis of biological samples. Synthesis of SPECT radiotracers for specific SPECT/CT projects was performed. Previous projects concerning development and evaluation of new radiotracers for PET and SPECT were published in 2017 (see section 5.).

User statistics

See table below.

Participation in international, Nordic and European infrastructures

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

Future perspectives

Infrastructure development. In order to improve the SPECT/CT lab portfolio, several new tracers will be validated and added to the services provided by the facility, besides the already validated (b-CIT, DATscan). Our plan is to validate three different groups of tracers: the group a, brain imaging, includes CLINDE® for neuroinflammation; NEUROLite® and Stabilised Ceretec® for blood flow. The group b, myocardial imaging, includes 201-Thallium, and 99m-Tc-Tetrafosmin for cardiac efficiency/ischemia. The group c will include tracers for cancer imaging: OctreoScan, DOTA-NOC, Octreotide (somatostatin), ProstaScint

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	international	non-academic	Total
UH	HiLIFE	RTI unit	3	3		1	7
	Total		3	3	0	1	7

(prostate cancer), and AB-MECA (breast cancer). Animal models for these tracers are available. For stroke in rats, from the Institute of Biotechnology (M. Airavaara). Neuroinflammation models (LPS, hepatic encephalopathy, or autoimmune encephalopathy) from the Division of Pharmacology, Faculty of Pharmacy (García-Horsman). A model of myocardial infraction will be from the Faculty of Pharmacy (H. Ruskoaho). Cancer models will come from Biomedicum Helsinki (Hemminki/Joensuu), the Faculty of Pharmacy (V. Cerullo), and the Department of Chemistry (A. Airaksinen).

It is important to note that the funding from the BF (~ 20% of RTI expenses) is essential for the unit. As the service needs increased, funding from BF should also increase accordingly, at least with additional funds for the salary of one more researcher (to around 65 000 € total) to be able to cope with everyday imaging, planning and analysis, and in order to guarantee proper service at the current level.

In addition, the laboratory has ambition to expand the area of service to PET imaging. HAIP is applying for preclinical PET/MRI system to Academy of Finland's FIRI call. The Rector of the University of Helsinki has ranked the application as number 1 among those from the University. PET/MRI and SPECT/CT would be located in the same laboratory, which would enable unique *in vivo* imaging possibilities. Development to PET/MRI imaging in Helsinki, is very welcome by the research community; most of the Finnish research on animal models is made in the University of Helsinki, and imaging, nuclear (both SPECT and PET) and the one based in magnetic resonance, would be essential. The Faculties of Pharmacy, Sciences, Medicine and Biosciences support this application and they are committed with matching funds.

Major publications supported by the platform services

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El-Kawy OA and García-Horsman JA. 99mTc-roxifiban: a potential molecular imaging agent for the detection and localization of acute venous thrombosis. Journal of Radioanalytical and Nuclear Chemistry. Vol 311, Issue 3, pp 1719–1728

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GENOME-WIDE METHODS

Coordinator: Janna Saarela, FIMM

Genome-wide methods including DNA sequencing, RNA and epigenetic analyses, and high-throughput genetic screens have rapidly and profoundly changed basic biological science and biomedicine. Because of the highly specialized and capital-intensive nature of genomics instrumentation and reagent sets these technologies have been developed as core infrastructures providing services to researchers nationally. Genome-wide approaches are a focus area of biocenters in Helsinki and Turku: genetics/genomics and genome-scale biology services are primarily developed in Helsinki and gene expression and regulation services in Turku. Cost-effective access to reagents and libraries enabling knockdowns or overexpression as well as high-throughput facilities is provided by the Helsinki biocenters.

It is essential to provide tailored services in the genome-wide methods area to Finnish scientists also in the coming years to maintain at the cutting edge. This development requires both long-term funding to enable recruitment and maintenance of top quality scientists and technical experts as well as continuing investments into new technologies. The BF Genome-wide methods network continues in its role as an expert body to coordinate training efforts, to evaluate the services, to facilitate the use of these services in biocenters throughout Finland, and to integrate these activities internationally. High-content screening services were customized to local research strengths and integrated with imaging and translational technologies.

Development of novel technologies such as, single cell analysis, and the increasing efficiency and speed of DNA sequencing serve as examples of continuous need for new equipment and upgrading of current ones. The fast development requires rapid adaptation of both researchers and the research environment, where highly specialized and capital-intensive instrumentation and reagent sets are optimally developed as core infrastructures providing services to researchers nationally.

Genome-wide methods technology platform

Chair of the platform: Janna Saarela, FIMM

Partners: Outi Monni, Saara Ollila, HiLIFE; Riitta Lahesmaa, Riikka Lund, BioCity; Petri Auvinen BI-HiLIFE

Achievements in development of technology services

In biomedicine similarly to other fields of science new important insights are often a combination of an idea what to look after and novel technologies making us able to perform the experiment. The demand for the services as well as the number of the applications and samples handled by the BF-GWM nodes has kept steadily growing. Both direct feedback as well as the feedback collected through surveys has indicated that the BF-GWM has been successful in providing high quality, efficient services in reasonable time. Due to high demand for some services, the waiting times have occasionally been too long, despite our attempts to restructure the services and reallocate the resources.

In 2017 BF-GWM network has provided services for 400 national and international research groups, and close to 40 non-academic users with a total cost-recovery of 5,002,689€. Table 1. describes the division of tasks between the individual units of the network.

The insufficient funding for sequencing equipment renewal has been a significant thread for the future development and operations of BF-GWM nodes. In 2017 Biocenter Finland made a decision to apply Academy of Finland FIRI funding for novel, state-of-the-art sequencing instrument. FIRI

Services	BioCity Turku (FFGC)			BI (BIDGEN)			FIMM			BCH (FuGU)			BCH (GBU)		
	Samples	Projects	Groups	Samples	Projects	Groups	Sample	Projects	Groups	Samples	Projects	Groups	Samples	Projects	Groups
Resequencing	483	9	7	843	31	31	1623	47	42	25	3	3			
De novo				528	17	17									
Metagenomics	550	11	8	7839	44	44	50	2	2	10241	9	3			
Targeted (incl WES)	1460	76	25	41	2	2	12991	572	50	276	11	7			
SNP genotyping (GWAS)							13624	38	25						
Targeted SNP typing							15672	11	9						
Copy number variation**	53	8	5												
Immunoprecipitates (ChIP-seq)*	815	10	8				534	4	4	136	9	4			
RNA sequencing	1480	62	33	1239	27	27	629	47	47	803	65	29			
qPCR based assays				372	3	3				528	7	5			
Gene expression microarrays										142	29	7			
Genome-scale reagents										111	21	15	302	96	31
ORF cloning													167	53	20
High-content analysis (HCA)													4289	234	30
Customers															
		Projects	**Groups**		**Project**	**Groups**		**Project**	**Groups**		**Projects**	**Groups**		**Project**	**Groups**
local		133	39		102	102		419	55		110	56		369	55
other domestic		15	10		4	4		225	41		19	8		25	6
international		6	4		4	4		53	6		3	3		0	0
non-academic groups/ units		22	13		14	14		24	4		24	5		1	1
TOTAL		176	66		124	124		721	106		156	72		395	62
Billing total (Cost recovery)			**Total**			**Total**			**Total**			**Total**			**Total**
			817,346 €			774,000 €			2,736,139 €			640,137 €			35,067
*includes methylation arrays and bisulfite sequencing															
**includes genome-wide(CGH) and targeted									**Cost recovery grand total**			**5,002,689 €**			

funding would enable setting up cost-efficient

human genome scale sequencing first time in Finland. With the new instrumentation BF-GWM network would be able to support novel technologies, such as single cell and liquid biopsy analyses, the national Genome and Cancer Centers, in addition to enabling researchers to expand the genome analysis from individuals to populations. Insufficient bioinformatics support will remain a bottleneck for core facilities in development and implementation of new services and supporting increasing user base.

Participation in international, Nordic and European infrastructures

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

Future perspectives

Since the launch of the first NGS platform 454 in 2005 the trajectory of genomics, metagenomics and related bioinformatics changed completely. Smaller samples could be used due to no need to clone anything. The capacity was considered enormous from the beginning when compared to the clone based approaches. Today one can obtain 6 000 000 000 000 sequences in two days. The capacity and quality of the sequencing has increased very rapidly broadening the use of NGS approaches to population genomics, personal genomics of humans and to single cell assays. The core of the developments is that with current technologies we are no longer only sequencing genomes or RNA but using NGS as a measuring apparatus to gene regulation, ribosome function, RNA structure and DNA structure to name a few. The single molecule sequencing was initiated 2012 in our platform. Today we see novel developments also in single molecule analysis despite of the challenges of

measuring any feature in biology from one single molecule. Nanopore-based assays are coming to be mature enough to produce data with quality and quantity on a useful level to implement them to new assays in core facilities. One size/method fits all -type approach does not work in today's genomics research. Assays and methods used need to be chosen based on the research question in hand. We see our role in introducing and developing new approaches not necessary supplied elsewhere, handling more challenging samples, and also keeping technology awareness on the level that new groups can meet and get advices on their project is increasingly important for Finnish research. Only small minority of research groups are self-sufficient in experimental planning, choosing technology or designing how much and what kind of data is necessary to be able to get answers to the research questions.

Capability to analyse genome(s) and population of individuals and their functions is an important part of practically all life science research today. Analysing the nature's experiments, the individuals with gene defects, gives both detailed molecular knowledge about the disease, and also improves our understanding of the basic functions of the human body. Furthermore, recent developments in the sequencing technology enable researchers to expand the genome analysis from individuals to populations revealing more subtle genome changes with significant health outcomes. In parallel the cost of sequencing has consistently decreased and with the emerging sequencing platforms is anticipated to reach 100 dollars per genome in the near future. Taking the next technological step will allow routine analysis of personal genomes used in precision medicine, and for example cancer care. With this in mind, the BF-GWM network is closely working with the hospitals to enable use of the latest genome analysis technology also in diagnostics.

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

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

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

Major publications supported by the platform services

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MODEL ORGANISMS

Coordinator: Raija Soininen, BCO

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

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

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

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

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

FinnMouse technology platform

Chair of the platform: Raija Soininen

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

Achievements in development of technology services

The FinnMouse technology platform has actively developed GM mouse services, and restructuring resulted in three collaborating GM core facilities (Helsinki, Oulu, and Turku) providing elementary services such as generation and re-derivation of GM mice, and some unit-specific services, for all Finnish scientists. Latest addition to the service repertoire in all units is generation of gene-edited mice via the CRISPR/Cas system. The Oulu laboratory serves as the Finnish Infrafrontier-EMMA (European Mouse Mutant Archive, www.infrafrontier.eu) node that provides repository services, cryopreservation and distribution of GM mouse strains to a world-wide user community, and is involved in development of new technology in the field, the latest additions being oocyte vitrification and IVF using cryopreserved materials.

For phenotypic analyses of mice, Neurophenotyping Centers (NC) in Helsinki and Kuopio (BCK) provide services in automated behavioral phenotyping and specific neurophenotyping tests both in disease models as well as in analyzing roles of specific factors. New tests and methods are applied based on the requests by users, such as a new behavioral test for Alzheimer model mice by BCK-NC, and a new fear conditioning system set up in the Mouse Behavioural Phenotyping Facility (MBPF) of Helsinki NC. Testing and monitoring of mouse behavior in home-cage environment is the specific feature of MBPF, whereas BCK-NC has focused in providing extensive phenotyping test batteries and

is the only facility in Nordic countries providing full characterization of the rodent visual system.

The Finnish Center for Laboratory Animal Pathology (FCLAP), established within the Faculty of Veterinary Medicine, University of Helsinki, trains veterinary pathologists and provides pathological consultation and diagnostic services in laboratory animal pathology. To further improve the services, digitized slides and image analysis in sample assessment are being set up.

Turku Center for Disease Modeling (TCDM) provides a wide range of services by experts in the field. Xenograft studies in immune-deficient mice are provided, and in 2017, TCDM started to perform Chick Chorioallantoic Membrane assays for researchers for tumor growth and invasion studies that can often precede the xenograft studies. A high-sensitivity steroid profiling in serum and tissues of mice is also available. A new high-resolution ex-vivo micro-CT is being set up in the TCDM.

Biocenter Oulu has focused on services in analysis of cardiovascular functions, the electron microscopy of mouse tissues, *in vivo* imaging system IVIS, and optical projection tomography. In 2017, a laboratory for small-animal intra-vital microscopy and multimodal sensor system was established for live animal experiments. The imaging devices include a state-of-the art multiphoton microscope for imaging of label-free and fluorescently labeled objects. Further, a photoacoustic microscope for *e.g.* imaging of oxy/deoxyhemoglobin content in different-sized blood vessels is being assembled in the laboratory.

All FinnMouse service facilities are engaged in education of graduate students and postdocs in laboratory and lecture courses and counsel researchers at all levels. Visits to partner laboratories and personnel meetings speed up the exchange of best practices and new methods.

User statistics

See table below.

Participation in international and European Infrastructures

University of Oulu represents Finland in the ESFRI project INFRAFRONTIER, the European Infrastructure for Phenotyping and Archiving of Model Mammalian Genomes, is a shareholder in the INFRAFRONTIER GmbH, established in 2013, and a partner in the H2020-INFRADEV-2016 project INFRAFRONTIER 2020.

University of Turku is a partner in the European Advanced Translational Research Infrastructure in Medicine (EATRIS).

The NordForsk funded network NorIMM, Nordic infrastructure for Mouse Models, coordinated by Oulu University, was established in 2008 to improve communication between GM mouse generation and phenotyping infrastructures in Nordic countries. All FinnMouse facilities were partners in the third NordForsk grant period that ended in 2017.

Future perspectives

The use of GM mice as disease models is expected to further increase in future. It is foreseen that rare diseases, where patient material is limited, will be increasingly 'modelled' in mice for therapy applications, and studies on sophisticated models for diseases such as cancer and diabetes will be further advanced, therefore, multidisciplinary expertise is required for phenotype analysis of mutant mice. A rapidly increasing research approach is also to use a GM mouse line as a basis and combine that with inactivation or overexpression of a gene of interest in the adult

General			Number of user groups/customers				
Host Univ	**Biocenter**	**Name of core facility**	**local**	**national**	**international**	**non-academic**	**Total**
UEF	**BCK**	Neurophenotyping Center	4	1		1	6
UH	**HiLIFE**	FCLAP	10	2		2	14
	HiLIFE	MPBF	14				14
	HiLIFE	GM Core	39				39
UO	**BCO**	Histopathology	59				59
	BCO	TG Core	13	11	20		44
UTU	**BCT**	TCDM	64	11	5	13	93
	Total		**203**	**25**	**25**	**16**	**269**

animal either systemically or locally in the tissue of interest by viral vector mediated gene transfer.

The FinnMouse core facilities are and will be in a key position to provide knowledge and services in GM mouse models to the Finnish research community, and permanent staff is essential for reliable services and to full-fill the legal regulations. Dedicated experts are needed to keep in touch with technology development and new innovations in order to maintain the high quality. Funding for instruments and updating equipment has to be available also for equipment with moderate prices. In addition, modern animal facilities with excellent health status are essential and have to be properly equipped and managed.

Collaboration of the FinnMouse units is important in educating personnel and researchers in new techniques and challenges involved in them. New methods for genome modification, especially the CRISPR/Cas system will speed up the generation of mutant mice, which will also increase the need for services in analysis and storage of the mutant mouse strains. Knowledge in mouse genetics is required to understand the effects of genetic background, additional mutations and husbandry conditions, and expertise has to be available for consultation on mouse background selection and breeding schemes.

The role of microbiome in health and disease progression has gained increasing interest in recent years. Animal models are needed to decipher the complex interactions between microbes and host, and to infer causal relationships. Studies using germ-free (axenic) mice infected with specific microbiota require specific isolators to ensure their continued sterility, or if colonized with specific microbiota, to ensure that no other species are introduced (or spread from the mice). Facilities for generation and analysis of germ-free mice are not yet available in Finland.

MBPF plans to combine existing methods with optogenetics, a wireless optogenetic stimulation in home cage and other behavioral settings. In general, neurophenotyping is developing into automated, data intensive home cage monitoring. This will require investment on the new technology in all Finnish Biocenters. To make this happen in a coordinated manner should be a high priority for Biocenter Finland, since harmonization of the technology, data storage and analysis methods would allow the possibility to conduct multi-center studies in GM mice in the same way as human clinical studies. With automated home cage monitoring the animals can stay in their units, only data is transferred and shared.

To widen the mouse services further, expansion to specific phenotyping services will be planned in the FinnMouse network. A catalogue of services available in FinnMouse facilities was generated a few years ago, but further work is needed to include more specialist services and make the services more visible, the idea being to form a distributed Finnish Mouse Clinic, which is planned to be a facility for specialized, secondary phenotype analyses provided by experts within Finland.

Major publications supported by the platform services

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Non-mammalian model organisms technology platform

Chair of the platform: Mika Rämet, MED

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

Achievements in development of technology services

During 2017, both zebrafish facilities (Helsinki and Tampere) and Tampere Drosophila unit have succeeded well in providing services for researchers using these models. The services were not affected by any animal welfare issues or any significant technical problems during the reporting period.

For zebrafish research, the production of mutants using the CRISPR/Cas9 method has become routine, which allows disease modeling for several phenotypes (including degenerative diseases and susceptibility to infections).

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

Bottlenecks: In June 2016, Tampere zebrafish facility was translocated to a newly constructed Arvo-building. During the translocation, the volume of services that the laboratory was able to provide decreased temporarily. Until October 2016, the facility was not able to provide all the requested services to the users (unable to produce enough adult fish for experiments). During 2017, the facility has become again fully operational.

The changes in aquarium space in Helsinki resulted in a closure of two smaller stand-alone units temporarily, which prevents currently expansion of services. In addition, the second large facility closed in 2016 has not been opened yet but waits for new space. New facilities have been planned, and expansion can be expected in late 2018. The size of the facility is now a serious limiting factor for expansion of services. In addition, maintenance of fish in quarantine is limited.

The overall situation with the national services are adequate with recently renovated spaces both in Tampere and Helsinki, but the future development requires that the new space will be available in Helsinki in 2018.

User statistics

See table below.

Participation In International, Nordic and European infrastructures

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

Future perspectives

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

Major publications supported by the platform services

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PROTEOMICS AND METABOLOMICS

Coordinator: Vesa Hytönen, MED

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

The broad field of proteomics is an essential technology in biosciences that underpins strategically important areas in academia and biotechnology, enabling characterization and temporal and spatial quantitation of proteins at various locations in practically all biological systems. It also affords measurement and discovery of post-translational protein modifications, protein-protein interactions and protein properties, which are amongst the most sought after applications.

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

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

Protein-proteome technology platform

Chair of the platform: Vesa Hytönen MED, Protein Technologies Facility

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

The year 2017 showed positive trend for Protein characterization and Proteomics Network (PPN) both financially and in terms of services provided. BF funding for salaries increased 21% and the support from the local universities 9% as compared to previous year. Furthermore, the other financial support was 5-fold higher as compared to 2016. PPN served more than 200 research groups and the income from the user fees increased by 8% corresponding to 509.313 €. PPN contributed for user training and teaching of undergraduate and graduate students. PPN members had a strong role in international activities.

Achievements in development of technology services

PPN provides access to services in proteomics and protein characterization. All major universities in Finland are part of the network. The services provided include proteomics, glycoproteomics, protein arrays, protein quantification, MS imaging, PTM analyses, characterization of protein interactions, membrane protein analysis, organelle proteomics, spectroscopic techniques and biophysical characterization of proteins. The efforts made to avoid unjustified overlap are commendable. The services provided by PPN are important and the number of users is high (209 research groups reported as users during 2017). The services are highly appreciated, as judged from the high scores obtained in the national BF user survey

and further supported by a local Helsinki centred survey in 2016.

In detail:

The Turku Proteomics Facility has applied data independent acquisition (DIA) based protein quantification method for several large-scale projects. Selected Reaction Monitoring (SRM) method originally used for protein quantification has been set up also for small molecules to provide services for wider range of customers. The newest method development field has been metaproteomics where active work has been done in close collaboration with a bioinformatics group. A new Orbitrap Fusion Lumos instrument will be installed soon. It enables protein analysis by top-down proteomics methods which will be future focus of Turku.

The Tampere Protein Technologies (MED) has established new facilities in ARVO building. Services in both protein characterization and in design and execution of protein production were provided. From 2019 onwards, University of Tampere and Tampere University of Technology will merge, which may open possibilities for enhancing the visibility of the services. Tampere facility installed novel SPR biosensor BioNavis Ilves 420, financially supported via FIRI. The mass spectrometry facility services are being incorporated to BF network.

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

The Proteomics Unit of Institute of Biotechnology (BI) has continued to provide cutting-edge services including characterization of post-translational modifications as well as label and label-free quantitative and systems-wide proteomics analyses for samples ranging from clinical to cell models. The unit has attracted more customers, both from academia and industry. In the future, the unit will keep further developing the comprehensive quantitative analyses as well start single cell proteomics analyses with BF-SC platform, which naturally will require appropriate instrumentation and personnel. In 2017, with the Academy of Finland and the BI support (FIRI 2016), we successfully underwent a purchase of TripleTOF 6600 system. Especially the purchase strengthened the clinical quantitative proteomics analyses, allowing now performing SWATH (DIA) analyses and quantitation.

The Meilahti Clinical Proteomics Core facility of Helsinki Institute of Life Science (HiLife) and Faculty of Medicine continued to serve its users with comprehensive clinical proteomic analyses starting from planning the sample collection at the hospital, sample storage and analysis, ending in a compact Systems Medicine and Systems Proteomic summary of the results. As a GLP certified proteomics laboratory the unit continued to serve also customers requesting authorized documentation. With the support of BF-FIRI-AKA-HiLife funding the Unit extended its services to include Selected Ion Monitoring (SIM) analyses as well as upstream Targeted Proteomics analyses by SWATH. In 2017 a new LCM (laser capture microdissection) device was installed and targeted MS analyses upgraded by a COFRADIC sample preparation station.

The Nanoscience center (NSC) Jyväskylä offers services in fluorescence spectroscopic and vibrational spectroscopic (Raman and FTIR) techniques for characterization of proteins and other biomolecules. The laser lab NSC organization widens the perspective of molecular spectroscopic tools for biosciences. We have updated our web pages and further improvements are in progress. The time-gated Raman set up, particularly suitable for protein characterization, waits for an update by the provider.

User statistics

PPN network was capable to serve 209 research groups, which is slightly higher than that reported during 2016 (189). The income from the services was 509.313 €, which is 8% higher as compared to 2016. Services ranged from various types of MS analysis to detailed protein characterization services to gel separations and protein production. Overall, it is fair to state that PPN network has strong role in protein-focused research in Finland, but the development and maintenance of internationally competitive services would require substantial financial investments.

Participation in international, Nordic and European infrastructures

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

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

PPN actively contributes to training. Oulu facility provided one 10 ECTS course in protein characterization (Biochemical methods II). Tampere facility participated to teaching of MSc students and two courses focusing on protein production, mutagenesis methods and protein characterization were organized. Turku facility organized two courses focusing on proteomics and contributed to teaching on courses organized by Medical School, arranged seminars and was actively involved with the Finnish Proteomics Society activities to promote proteomics research. The Protein-Proteome network Helsinki (BI & Clinical Proteomics Meilahti) gave 4 courses on proteomics at the undergraduate and graduate student level and two courses for the medical students. Jyväskylä organized a 3 ECTS course "Where are the protons" along the well-known Jyväskylä Summer School for graduate students and post docs. The course concentrated to investigate protonation states of proteins both computationally as well as by means of NMR and IR spectroscopy.

Future perspectives

The proteomics and protein characterization methods are developing towards more precise quantitation. Small sample size and high sensitivity are essential for successful methods. Overall, we envision closer communication between biophysics and proteomics in the future.

PPN has already strong position in the analysis of clinical samples and this will become even stronger. For example, Turku Proteomics Facility is implementing a high-throughput serum sample preparation, digestion and non-isobaric multiplexing for large cohorts in cooperation with Auria biobank and TYKS hospital. Samples will be analysed by data independent mass spectrometry analysis (DIA-MS) with co-temporal parallel reaction monitoring (SWATH-PRM) of standard serum biomarkers. Overall, we expect that proteomics methods are becoming more suitable for clinical samples and in the long term for diagnostics.

Especially in proteomics, data analysis has an important role. Therefore, new bioinformatics processing pipelines will be created to handle massive scale data acquisition, storage and analysis.

While the consortium is gratefully acknowledging the substantial support for new instrumentation leading to new services granted in 2017 from the AKA-FIRI 2016-2017 call, several of the older instruments of the consortium partners are slowly reaching their end and need to be replaced in the near future. Due to the fact that our technology platform depends on costly instrumentation, there should be a nationwide and local long-term planning for renewing of instruments. AKA-FIRI funding is insufficient to cover the needs of our consortium on the long run.

Major publications supported by the platform servicestions

Ruskamo S, Nieminen T, Kristiansen CK, et al. Molecular mechanisms of Charcot-Marie-Tooth

General		Number of user groups				
Host Univ	Biocenter	local	national	international	non-academic	Total
UH	BI-HiLIFE	35	16	5	4	60
	HiLIFE	36	4	2	3	45
UO	BCO	43	8	3	3	57
UTA	MED	4	5		1	10
UTU	BCT	23	10		1	34
	Total	141	43	10	12	209
JYU		2			1	3

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Metabolomics technology platform

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

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

Achievements in development of technology services

FIMM, ViMU and BCK Units together as a single entity offers very broad coverage of analytical services in various fields of metabolomics both nationally and internationally. Most importantly we have a nice complementary niche. The BF metabolomics units have continued services in their key analytical focus areas. Since 2017, FIMM PI Vidya Velagapudi has been acting as a Platform Chair.

FIMM unit has been successfully offering high throughput targeted and (semi)quantitative metabolomics analyses. In addition, FIMM had installed the institute supported demo QTRAP 5500 instrument and started offering high throughput targeted and (semi)quantitative lipidomics services for biofluids at the end of 2017 (one user from University of Turku, Finland) and has also been optimizing the protocols for non-biofluid samples (e.g. tissues, cells etc.), which is a major development at the unit. Furthermore, FIMM started developing isotope enrichment analyses using tracer studies and metabolic flux analyses with the support of institute funded post-doc, which is another significant development at the unit where FIMM had finished two pilot projects from KI, Sweden and CECAD, Germany. FIMM continued in active research collaborations emerged from the service projects and published in highly reputed international journals. FIMM maintained the "self-sustainability" status from the single BF funded LC QQQ-MS instrument since 2014. In the Helsinki Institute of Life Sciences (HiLIFE) user survey, 63 users evaluated and rated very well with 4.44/5 score. Out of 63, 25 were University of Helsinki (UH) PIs, where they rated with high score of 4.64/5 in efficiency and access of FIMM services. FIMM also got excellent relevance of the offered services to UH researchers (4.56/5).

ViMU (Viikki Metabolomics Unit) continues to provide analytical services mainly for the plant community with Prof. Teemu Teeri in charge after Prof. Tapio Palva's retirement. The unit continues to focus on plant primary and secondary metabolites but also provides mass spectrometry analysis for pharmaceutical synthesis products, novel drugs and their metabolites. The analyses have been performed by three instruments; UPLC-QTOF/MS,

GC-QQQ/MS and/or the newly purchased, highly-sensitive UPLC-QTRAP ABSCIEX 6500+. At the end of 2016 unit received funding for a new UPLC-QQQ/MS from FIRI 2016 from the Academy of Finland (AoF) and the new instrument was installed in June/August 2017. Immediately method development and optimization of instrumentation for new analysis was started and during the fall 2017, services were extended for targeted and quantitative analysis. Recruitment of a second researcher, Dr. Jenna Lihavainen (April 2017) improved the situation with the shortage of personnel and the unit managed to perform its services at the normal level while performing method development simultaneously for the new equipment. In the HiLIFE user survey, 33 customers evaluated ViMU and obtained a high score of 4.32/5.

BCK has continued on metabolomics applications for food, health, toxicology, and nutrition studies. The LC-MS Metabolomics Center has developed methods for targeted quantitative analyses of various compounds. The methods available at the center (in co-operation with School of Pharmacy) are based on long-term experience in the analysis of specific compounds or compound groups with wide range of instrumentation (LC-MS/MS, GC-MS, HPLC-UV/DAD, HPLC-ECD). The development and validation of these methods follows the international quality guidelines. Major part of the non-targeted work load consisted of running samples from collaborators, and from our own projects. Key development area was testing and development of data analysis software for metabolomics analysis. The metabolite identification has been enhanced by addition of mainly lipid compounds in our retention time and MS/MS spectrum library. Targeted analysis methods for several new nutrition related biomarkers, and steroids were developed using LC-triple quadrupole mass spectrometers. The sample throughput of our laboratory was increased compared to 2016, as the problems with the UPLC-Q-ToF instrument were mostly solved. In addition, installation of the Orbitrap LCMS in the end of 2017 markedly increased the sample capacity of the laboratory. Dr Marko Lehtonen was hired as a new laboratory manager to further develop the core laboratory services.

Bottlenecks

All of the metabolomics units operate with minimal personnel support. Due to the lack of analytical lab personnel, FIMM had paused the most demanded targeted method development to quantify NAD metabolism intermediates. During 2017 ViMU had two analytical researchers working in the unit for the first time, which ensured the almost continuous supply of the offered services even during holiday season and obligatory maintenance brakes of the instruments. The end of year 2017, the extra manpower was mainly used to method development of quantitative methods for units new UPLC-QTRAP ABSCIEX 6500.

Education and training

The BF metabolomics units have continued teaching various aspects of metabolite analytics in their units. FIMM unit continued in teaching "Biomedical Applications of Metabolomics" to medical, Ph.D. and masters students in different courses offered at the UH and also continued organizing the Metabolomics and Clinical Lipidomics Annual hands-on Workshop with the support of DPBM graduate school at UH. Student's feedback had been over 4.5/5 about the teaching and training. FIMM is also a member of the European Metabolomics Training Coordination Group, (http://www.emtrag.eu/training-centres/). In BCK, Prof. Auriola is responsible for education of mass spectrometry. The work at BCK has continued on metabolomics applications for food, health, toxicology, and nutrition studies. The studies done at the metabolomics laboratory have been an integral part of several PhD theses. Some of the work has been an integral part in drug development and health studies. At ViMU, Several PhD theses in plant sciences have benefited from the services and collaboration and included joint publications with the ViMU staff.

User statistics

See table next page.

Participation in international, Nordic and European infrastructures

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

Future perspectives

The future vision of our metabolomics technology platform would be offering services in metabolite imaging technology, and also to combine NMR and LC-MS analytical platforms to increase the coverage. The specific goals of each unit are given below.

As reported in 2016, FIMM had successfully installed the institute supported used instruments, in 2017; and started developing and optimizing the analytical methods for lipidomics and metabolic flux analyses. In future, we will continue this development work and also focus on setting up global metabolomics platform and NAD method development. As a long-term goal, FIMM plans to set up a national core facility for "Spatial Metabolomics" (metabolite imaging). Thus, FIMM requested a FT-ICR MS instrument in the last FIRI round but didn't get the funding.

ViMU aims to develop methods with the newest high-end MS, which was crucial as the concentration of the signalling molecules (e.g. phytohormones) tend to accumulate in near-detection-limit and the sample sizes are limited. The capability to run the same samples with variety of instruments and features (e.g. highest sensitivity, resolution/exact mass, polarity switching) makes possible to cover a vast range of metabolites. The increasing demand for compartmentalized metabolomics has put the units' future emphasis on sample pretreatment and development of non-aqueous fractionation protocols. The long-term goal is to offer imaging services to investigate surface and volatile plant metabolites, and to integrate MS-based imaging data with the imaging data (e.g. RGB/visible, fluorescence, NIR/SWIR, thermal) from NaPPI facility.

At BCK, the major analytical challenge is metabolomics analysis of minor sample material, which will be addressed by using a micro flow HPLC connected to MS. This will help analysing minor samples e.g. purified exosomes, stem cells, or ocular samples. The group has added expertise on synthetic chemistry, which enables development of targeted quantitation of novel biomarkers, not available commercially. As NMR metabolomics is very strong field at UEF, we aim to combine this technology with our LC-MS metabolomics services. There is also a constant need of education in advances and possibilities of the methodology.

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Davidsson P, Broberg M, Kariola T, Sipari N, Pirhonen M, Palva ET. Short oligogalacturonides induce pathogen resistance-associated gene expression in Arabidopsis thaliana. BMC Plant Biol. 2017;17(1):19.

Dermadi D, Valo S, Ollila S, et al. Western Diet Deregulates Bile Acid Homeostasis, Cell

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	international	non-academic	Total
UEF	BCK	BCK	8	8	2	0	18
UH	FIMM-HiLIFE	FIMM	5	5	4	0	14
	HiLIFE	ViMU	20	2	1	0	23
	Total		33	15	7	0	55

Proliferation, and Tumorigenesis in Colon. Cancer Res. 2017;77(12):3352-3363.

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STEM CELLS AND BIOMATERIALS

Coordinator: Timo Otonkoski, HILIFE

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

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

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

Stem cells and biomaterials technology platform

Chair of the platform: Timo Otonkoski, BCH

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

Achievements in development of technology services

The overall situation of the nationwide consortium.

Platform partners have continued the development of their stem cell services as described below. Coordination activities between the partners have been strengthened by regular activities of The Finnish Stem Cell Network (FSCN). FSCN is pulling together all research groups that are actively using stem cell technologies. The Biocenter Finland Stem Cell Platform is a part of this network, involving those partners who are providing Core Facility services. The annual meetings of the FSCN are held in conjunction with the annual meeting of the Finnish Developmental Biology Society. Annual meeting was held for the third time on 31.8.-1.9.2017, in Rauhalahti, Kuopio with active participation from all centres belonging to the Platform (more than 100 participants). Because of exceptional interest, we will continue the annual FSCN, this time organized by BMT, University of Tampere on October 26-27, 2018, at Hotel Murikanranta near Tampere.

Platform partners received a total of 157 495 euros in 2017 for providing stem cell services. This enabled the continuation of the patient iPS cell derivation service by all partners, provided for 28 user groups. Platform has derived 111 fully characterized and 99 early passage uncharacterized iPSC lines. In addition, platform has differentiated 18 lines into astroglia for one client. As a new service platform has provided genome edited iPS cells to five clients. The turnover (customer fees) for the platform was 117 500 €. Major scientific progress was made in CRISPR/Cas9 technology which has been applied for efficient genome editing in human pluripotent stem cells, allowing the generation of knockouts or knockins (e.g. for the generation of reporter cell lines), correction or generation of single nucleotide mutations, and transcriptional activation of desired genes. All partners in the consortium have continued with development of genome editing technology creating fluorescently labelled marker cell lines and correction of different mutations for disease modelling purposes. These are now started to be provided also as Core services.

During 2017 MED at the University of Tampere set up systems to create isogenic lines and cell type specific reporter lines with CRISPR-CAS9 technology. The need for new iPSC lines was not

much, but isogenic lines were contracted for two mutation specific iPSC lines. Additionally, fluorescent-labelled marker cell line was done for cardiac applications. Additionally, 3 different types of hepatocyte specific reporter lines were initiated. One was finished during 2017 having fluorescent label under the promoter of HNF4A gene and lines having the marker under the promoters of AFP or albumin were initiated. The core also put a great effort in improving hepatic differentiation and now the system is fairly robust. Training was mainly hand-on training for individual researchers. Equipment purchased for iPSC production (Nucleofector 4D, EVOS-microscope) were also used for various purposes by different groups of MED.

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

The Biomedicum Stem Cell Center (BSCC, representing BCH) continued active development of the technologies, following the rapid development of the field. Particular areas of emphasis were: (i) reprogramming using activation of endogenous genes; (ii) generation of iPSC lines for biobanking purposes (iii) genome editing of the stem cells. In 2017 BSCC has started to actively search for suitable candidates to facilitate development of the genome editing services. As a part of GoEditStem platform, part of the Helsinki Institute of Life Sciences (HiLIFE) infrastructure, we have offered the provision of validated CRISPR-Cas9 gRNA library and training in the field of genome editing for doctorate students. During 2017 Cell-IQ, an automated cell culture and analysis system has broken down and could not be repaired. BSCC has started a process to replace the live cell analysis imaging system.

Bottlenecks in the services provided by the consortium.

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

BMT/ MED: Functional analysis iPSC-derived cardiomyocytes creates large datasets. The bottleneck is usually in the analysis. For this purpose, BMT has been active in creating different software for (semi-automatic data analysis. The software has been created for Ca2+ imaging, patch clamp and MEA data, for contraction/relaxation analysis as well as for cellular orientation applicable for any cell type.

BCK: In the field of neuroscience, the need for complex and long-term differentiation of iPSC cells, including 3D models, is rapidly increasing both globally and nationally. However, funding for BCK has decreased compared to previous years (against the recommendations of BF SAB). It is thus evident that the current resources are far too low to meet the requirements for such services in Finland. Another bottleneck is the lack of funding sources for updating or even maintaining the basic infrastructure/equipment of stem cell core facilities. As there is no internal university funding earmarked for basic equipment, the stem cell cores and BCK in particular is continuously looking for external funding for equipment. This is an extremely difficult challenge as neither TEKES nor AF favour acquisition of equipment by their regular grants.

User statistics

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

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

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	international	non-academic	Total
UEF	BCK	BCK	3	1	0	0	4
UH	HiLIFE	BSCC	14	1	1	0	16
UTA	MED	iPSC core	4	1	3	0	8
	Total		21	3	4	0	28

Participation in international, Nordic and European infrastructures in 2017

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

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

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

Future perspectives

While generation of iPSC lines is becoming a routine technology, it still requires special expertise, experience and facilities. At the same time, know-how and technology development for differentiating cells to true models of human cells and tissues is becoming a bottleneck for taking the full advantage of iPSC methodology. Therefore, the BF Stem Cell Platform services need to focus more on technologies of differentiation and functional analysis of the differentiated iPSCs. BCH focuses mainly on endodermal differentiation to derive functional pancreatic islet cells, hepatocytes, intestinal cells and lung epithelial cells. BMT/ MED focuses on the differentiation of cardiomyocytes as well as hepatocytes, retinal pigment epithelial cells and neurons. The emphasis of stem cell services of BCK is towards neural and muscular cells and diseases. Because brain consists of hundreds of different cell types, brain diseases are the burden of Western countries, and neuroscience is one of the strongest research fields in Finland, the need for expertise in differentiation of iPSCs towards brain cells as well setting up 3Dmodels as a service are of utmost importance. Therefore, in addition to differentiation and functional assays of neural cells, 3D cultures, cerebral organoids and 3D bioprinting are on focus of BCK stem cell core.

The need for iPSC biobanks has become obvious, as evidenced for example by large international initiatives sponsored by EC together with pharmaceutical industry. In order for these endeavours to be successful, they have to be based on well-organized national or regional "hubs", centres devoted to the generation and characterization of iPSC collections from defined patient cohorts. The Biocenter Finland Stem Cells Platform is a prime example of these structures. It is essential that the functions of the platform, after a successful start, will be continuously supported through a nationally coordinated program. BCH has been granted permission to obtain cell samples (immortalized B cells) from THL biobank. Blood samples were originally collected from voluntary donors of THL Psychiatric Family Collections cohort. Other similar projects in the area of Type 2 diabetes are initiated, and fibroblasts from 15 donors have been received from THL Biobank. The samples are coded and the identity of the cell donor remains unknown to the investigators. BCK starts collaborative project together with biobanks within one of pilot project of National Centre for Neuroscience to generate iPSC lines from desired material stored in a biobank and returning them for general use.

Due to the challenges in obtaining fully functional and mature cells from pluripotent stem cells, an increasingly important trend in this field is the direct reprogramming (i.e. transdifferentiation) of somatic cells into functional cells and their expandable progenitors. Therefore, one area of focus at BCH will be the development of direct reprogramming approaches for the generation of endodermal progenitors which could be used as a reliable source for hepatocytes, pancreatic islet cells and intestinal

cells. Direct differentiation of mature cells into cardiomyocytes will be a focus of BMT in collaboration with both national and international collaborators. Other cell types could also be a target in the future. Transdifferentiation of neuronal cells is pursued by BCK.

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

Major publications supported by the platform servicestions

Sepponen K, Lundin K, Knuus K, et al. The Role of Sequential BMP Signaling in Directing Human Embryonic Stem Cells to Bipotential Gonadal Cells. J Clin Endocrinol Metab. 2017;102(11):4303-4314.

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Saarimäki-vire J, Balboa D, Russell MA, et al. An Activating STAT3 Mutation Causes Neonatal Diabetes through Premature Induction of Pancreatic Differentiation. Cell Rep. 2017;19(2):281-294.

Cooper HM, Yang Y, Ylikallio E, et al. ATPase-deficient mitochondrial inner membrane protein ATAD3A disturbs mitochondrial dynamics in dominant hereditary spastic paraplegia. Hum Mol Genet. 2017;26(8):1432-1443.

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Vuorenpää H, Penttinen K, Heinonen T, et al. Maturation of human pluripotent stem cell derived cardiomyocytes is improved in cardiovascular construct. Cytotechnology. 2017;69(5):785-800.

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STRUCTURAL BIOLOGY

Coordinator: Sarah Butcher, BI-HiLIFE

Structural biology covers a wide range of topics, from protein production and protein characterisation via structure determination to biocomputational analysis. The Biocenter Finland Structural Biology network (BFSB) comprises four major disciplines, all focused on experimental determination of macromolecular structures and elucidation of their mechanisms. They are X-ray crystallography, nuclear magnetic resonance spectroscopy (NMR), high-resolution native mass spectrometry (MS), and cryo electron microscopy (cryoEM). The BFSB activities are continuously aimed at ensuring good facilities for these powerful but expensive technologies. The research activities of the BFSB units are of major importance for the expert teaching and training activities of the next generation of Finnish structural biologists as also highlighted in the annual reports of the respective platforms. In addition it fosters the development of structure based biotech activities.

Many of the BFSB research groups interact with the European structural biology networks, like Biostruct-X, iNEXT and Instruct. Consequently, the BFSB research groups have jointly written an application to become recognized as an Instruct National Affiliate Centre (Instruct-NAC). This application has been approved by the Instruct council. Simultaneously, the FIRI committee of the Academy of Finland has provided the funding for Finland to join Instruct. This will open the much needed funded access for the Finnish life science researchers to many expert technologies in Europe, as nicely documented on the Instruct-WWW pages, ranging from biocomputational and molecular biology techniques to large-scale research facilities for example for cryoEM, NMR and X-ray data collection. In general, being an Instruct-NAC will help in building the BFSB units further into a coherent and well-funded research community, which is now preparing an application to the Instruct council to evolve into the Finnish distributed Instruct centre.

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

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

Instruct-FI, Integrated structural cell biology platform

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

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

Nuclear Magnetic Resonance: Hideo Iwai, BI-HiLIFE

Mass Spectrometry: Juha Rouvinen, BCK

Achievements in development of technology services

Unit	Service
CryoEM (UH) ♣♦	Single particle cryoEM; correlative light and cryoEM tomography
NMR (UH) ♣♦	Specialized labelling techniques, 600 and 850 MHz data collection
X-ray crystallography (UH) ♣♦	Membrane protein crystallization and analysis
X-ray crystallography, biocatalysis (UO) ♣	Biocatalysts, IceBear data management development
X-ray crystallography (Biocity Turku, UTu & ÅAU) ♣	Soluble proteins; Structure-based drug design
MS (UEF) ♣	Native mass spectrometry
Protein services (UTa & UH) ♣ ♦	Protein production, purification and characterization

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

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

The Protein Production service, UH, did not pass the HiLIFE RI Assessment in 2017, and operated as part of Instruct-FI until the end of 2017. The national service providers in X-ray crystallography are currently in three geographical locations each with its own specialization, down from five in 2014 (UEF and University of Jyväskylä, now primarily local). CryoEM was moved to the network. Instruct-FI benefitted from the appointment of coordinators on BF and FIRI funding. The Instruct-FI steering group met five times, to develop common activities including strategic objectives and targets, and reports to host organizations, the BF Board, Instruct-ERIC, Ministry of Education and Culture (MinEdu) etc.

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

The establishment of the Instruct-FI Coordination Hub in Helsinki for the whole network in 2017;

The establishment of clear Instruct-FI steering group protocols;

Regular steering group meetings with distributed minutes;

Organisation of the annual structural biology user group FINNBOX-meeting jointly with the Finnish Synchrotron Radiation Users Organisation (FSRUO) meeting (Turku, December 2017);

Preparation of the Instruct Centre Finland application;

New web pages;

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

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

Developments and bottlenecks

The new transmission electron microscope with a direct electron detector, phase plate and multiple sample holder designed for high resolution cryoEM was delivered to UH in late 2016 (FIRI2015 call funding) and fully operational since 12.2017. The troublesome installation caused a significant backlog in projects as the old microscope was decommissioned already in December 2016. The new instrument provides improved signal-to-noise, greater sensitivity and automated data collection. There has been a significant expansion of the user base and improvement in the data quality, with several users reporting structures going to 4 Å resolution or beyond (manuscripts in preparation).

The NMR unit currently consists of Bruker NMR spectrometers (600 MHz, 850 MHz and VTT-owned 600 MHz) equipped with cryogenically cooled probes. The facility developed new services to investigate protein dynamics by combining 15N backbone relaxation times and molecular dynamics simulations. Metabolite studies have been extended from plant extracts to caterpillar and butterfly extracts. The lack of a high-throughput sample changer currently limits the number of metabolite samples recorded. A new RT broad-band probe was purchased to widen the application of NMR spectrometer to other nuclei, especially fluorine. A new CIDNP device is under construction to enhance the sensitivity of the RT probe. The effect of high magnetic field on protein crystals was investigated to improve the quality of protein crystals.

The crystallization facilities provide advice on protein production and purification, as part of the upstream processing prior to crystallization screening. The major changes have been in the development of software used for crystal data management, IceBear, together with the Diamond Light Source, UK and Weizmann Institute of Science, Israel within the H2020 Instruct-ULTRA project. The crystallization units around Finland are working to deploy the same software so that all users will benefit from these developments. Instrument upgrades in Turku support the demands of users for screening and there is an ongoing

purchase for a state-of-the-art, in-house diffractometer and detector for data collection and in-situ screening of crystals directly from plates in Helsinki. Two units are working at maximum capacity and need upgrades to increase the capacity plate hotels. Similarly, state-of–the art pipetting robots are needed, and an upgrade to the detector in Turku to broaden its functionality. Staffing is a particular pressing issue in Turku, where the 2016 BF recommendations were not implemented. The activities planned within the Turku Instruct-FI units (coordination of teaching and guidance in structural biology) and offering of high quality services would benefit from additional staff.

Native MS unit has successfully offered services for national and international users. There is an increasing interest to utilize modern MS platforms in life sciences. Especially delightful has been the use of services by Finnish industry. The current bottle-neck is in describing both the size and shape of molecules tested. This will be solved by the purchase of a new ion-mobility mass spectrometer (FIRI2015 awarded funding) and the model to buy is currently under consideration.

User statistics

See table below.

Participation in International, Nordic and European infrastructures

Instruct-FI coordinates an effort to join the ESFRI Instruct-ERIC. Instruct-FI interacts also with other EU infrastructure networks like iNEXT. We coordinate access through block allocation groups to ESRF and the Diamond Light Source. We also collect data collection at MAX IV, 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), CalipsoPlus, EMBL-Hamburg, and European XFEL. We participate in the Nordisk NMR network, organizing NMR courses for students and postdocs.

Wierenga is a member of the Bessy SSP-college on macromolecular crystallography. Butcher is in the wwPDB Scientific Advisory Council. Wierenga is a project leader in the Horizon2020 Instruct-ULTRA project. UEF is participating in the "European Network of Fourier-Transform Ion-Cyclotron-Resonance Mass Spectrometry Centers". ÅAU and UH are members in the CMST COST Action CM1306 Understanding Movement and Mechanism in Molecular Machines.

Instruct-FI has close links to Finnish ESFRI nodes that provide complementary data and services or are dependent on structural cell biology results (ELIXIR, Euro-Bioimaging, EATRIS, EU-OPENSCREEN).

Future perspectives

In 2017, the Finnish RI Committee recommended membership of the Instruct-ERIC. The application process is ongoing and coordinated by the MinEdu. Selected BF structural biology services (10% of the capacity) will be open for users coming through the Instruct-ERIC Access. This strategic move will boost the international research profile of the platform.

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	international	non-academic	Total
UEF	**BCK**	**Native MS**	9	13	4	3	29
UH	**BI-HiLIFE**	**CryoEM**	18	2	0	0	20
UH	**BI-HiLIFE**	**NMR**	10	0	1	11	22
UH	**BI-HiLIFE**	**X-ray**	10	1	0	2	13
UO	**BCO**	**Protein crystallography**	14	2	0	2	18
ÅAU	**BCT**	**Structural Bioinformatic Laboratory**	6	2	4	0	12
UTU	**BCT**	**Protein Crystallography**	5	3	8	0	16
	Total		72	23	17	18	130

The most significant technological advances in the field include stronger in-house X-ray sources, the use of shielded NMR magnets incorporating biosolid technology. Ultra-high field (1.2GHz magnet), new probe design, and dynamic nuclear polarization techniques would enhance the sensitivity by a factor of 2-10000. We anticipate a joint application with Euro-BioImaging for a cryoFIB-SEM apparatus and a 300 kV cryoelectron microscope, improvements to data management, data storage and computation improving access, investment in training, and developing single cell proteomics services. Through these developments we aim to keep our expertise internationally competitive, and provide high-quality service and support for the Finnish life and natural science research communities.

Major publications supported by the platform services

Leppänen VM, Saharinen P, Alitalo K. Structural basis of Tie2 activation and Tie2/Tie1 heterodimerization. Proc Natl Acad Sci USA. 2017;114(17):4376-4381.

Perveen S, Rashid N, Tang XF, Imanaka T, Papageorgiou AC. Anthranilate phosphoribosyltransferase from the hyperthermophilic archaeon shows maximum activity with zinc and forms a unique dimeric structure. FEBS Open Bio. 2017;7(8):1217-1230.

Anumala UR, Waaler J, Nkizinkiko Y, et al. Discovery of a Novel Series of Tankyrase Inhibitors by a Hybridization Approach. J Med Chem. 2017;60(24):10013-10025.

Rahman MM, Andberg M, Thangaraj SK, et al. The Crystal Structure of a Bacterial l-Arabinonate Dehydratase Contains a [2Fe-2S] Cluster. ACS Chem Biol. 2017;12(7):1919-1927.

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Agrawal N, Määttä JAE, Kulomaa MS, Hytönen VP, Johnson MS, Airenne TT. Structural characterization of core-bradavidin in complex with biotin. PLoS ONE. 2017;12(4):e0176086.

Shakeel S, Dykeman EC, White SJ, et al. Genomic RNA folding mediates assembly of human parechovirus. Nat Commun. 2017;8(1):5.

Protein Services Technology Platform

Chair of the consortium: Juha Määttä, MED

Partners: Olli Ritvos, HiLIFE, Michael Jeltsch HiLIFE

Achievements in development of technology services

Protein production (PP) is open access recombinant protein expression, purification and characterization service for Finnish academy and for national and international industry partners. Protein expression in several organisms offers suitable system for any recombinant protein that is needed with proper scale-up possibility.

Tampere Protein Technologies offers protein expression in *E. coli*, *Spodoptera frugiperda* cells (baculovirus expression system, BV) and in mammalian cells (CHO, HEK293T, stable and transient). Protein purification with traditional methods (affinity, IEX and SEC) is offered as straightforward continuum for protein expression. In addition, service has special focus on protein interactions.

During the period 2017, PP had to reorganize its service as Helsinki unit was not supported by university and mammalian cell expression was started to offer at Tampere. PP has continued to serve existing users and also new customers and charged income increased 32% from 2016, which was previous record year (both ProtMet and Structural Biology parts taken into account). Mayor

reason for increased income was collaboration with industry partners. PP made headway in virus like particle (VLP) expression and purification, which will be one of the main focus also in the future.

The PP offers the choice of three robust protein expression platforms that the clients can use for satisfying their specific protein expression needs. Guidance, counselling and planning aid is provided to help the customers to decide whether to use in parallel several expression methods or to choose the most appropriate recombinant protein expression approaches for their research subject.

All services are working under the leadership of head scientist Dr. Juha Määttä. This mode of operation and coordination ensures high quality of the work, and makes it possible to start new projects fluently. Although, BF funding is not sufficient for full time commitment, we have been able to complement it with a certain extent through incomes from non-academic customers.

Major bottleneck is the lack of employees. The number of service users has been steady several years in a row mainly because units work at the maximum level of projects. Therefore, the lack of personnel funding is limiting the number of projects that can be handled per year. However, services have regular customer base that have been satisfied and who will turn over and over again to use our service. Greater number of technicians would make possible to increase projects per year and decrease waiting times. However, also instrumentation like single-use ReadyToProcess WAVE™ 25 bioreactor system would easy work load by helping with scale-up with both insect and mammalian cells. PP has already invested to equipment to increase *E. coli* expression volumes.

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

User statistics

See table below.

Participation in International, Nordic and European infrastructures

So far it has been important to spread awareness of the possibility to use these protein expression services in the Biocenter Finland context on a national scale during 2011-2017. Our service is part of Instruct Finland (Instruct-FI, Integrated Structural Biology Infrastructure for Europe) platform that aims to serve as a community for all structural biology researchers in Finland but also internationally. Moreover, it is on ESFRI Roadmap.

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

Future perspectives

The Helsinki University core facility service underwent major reorganization and restructuring process which affects broadly all Biocenter Finland core facilities in Helsinki including the Helsinki BF PP services node run by Dr. Ritvos. Process was completed in late 2017 and current Helsinki BF PP activities wasn't supported and Helsinki has no more ability to provide recombinant protein expression and purification services and recombinant antibody generation services.

These services will be offered therefore from Tampere. Protein expression in stable mammalian cells were performed already in 2017 in Tampere from constructs made in Helsinki and first transient expression has been made in the beginning of 2018. Moreover, several baculovirus and *E.coli* expressions (both small scale and fermentations)

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	international	non-academic	Total
UH	HiLIFE	B3P	-	-	-	-	0
UTA	MED	Protein Services	2	4	0	4	10
	Total		2	4	0	4	10

have been made successfully. In addition, the number of expressions of viruses made in mammalian cells has been increased and their use as vaccine will be studied in mouse models.

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

Moreover, funding for single-use ready to Process WAVE™ 25 bioreactor and automated PEAQ-ITC instrument was applied in FIRI2018 application to improve service scale-up possibilities with insect and mammalian cells.

PP works in close collaboration with Proteomics and Metabolomics and therefore protein characterization is also natural continuum of protein expression and important part of quality control (MS). Use of AB Sciex TripleTOF™ 5600 System with Nano LS and access to MicroLC-MSTrap Sciex Qtrap 6500+ will be valuable addition to the methods that are available in Tampere.

Major publications supported by the platform services

Agrawal N, Määttä JAE, Kulomaa MS, Hytönen VP, Johnson MS, Airenne TT. Structural characterization of core-bradavidin in complex with biotin. PLoS ONE. 2017;12(4):e0176086.

Hankaniemi MM, Laitinen OH, Stone VM, et al. Optimized production and purification of Coxsackievirus B1 vaccine and its preclinical evaluation in a mouse model. Vaccine. 2017;35(30):3718-3725.

Kalliokoski S, Piqueras VO, Frías R, et al. Transglutaminase 2-specific coeliac disease autoantibodies induce morphological changes and signs of inflammation in the small-bowel mucosa of mice. Amino Acids. 2017;49(3):529-540.

TRANSLATIONAL TECHNOLOGIES

Coordinator: Johan Lundin, FIMM

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

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

Tissue biobanking technology platform

Chair of the platform: Johan Lundin, FIMM

Partners: Jorma Isola, MED; Olli Carpen, BioCity

Achievements in development of technology services

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

Services provided

1. *Whole-slide cell- and tissue sample scanning services*. Scanning instruments are available at FIMM (https://www.fimm.fi/en/services/technology-centre/digital-and-molecular-pathology-unit), IBT and BioCity Turku. Service is charged for per project or according to a pay-per-slide principle, including the digitization process and data storage. Price per project or slide varies according to volume demands and sample type. Typical price for smaller series (<100) histological slides in the range of 3.50-40 €/slide. Volume prices for larger series.

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

3. *Access to computational tools, image analysis, clinical informatics*. Development and tailoring of image analysis and clinical informatics tools and access to pathologist' consultation services on a project basis charged for (per working day)

according to a cost-recovery principle. The consortium has implemented analytical tools for image annotation, image analysis (e.g. jvsmicroscope.uta.fi/immunoratio/, jvsmicroscope.uta.fi/immunomembrane/ and http://fimm.webmicroscope.net/research/testimmune and for clinical informatics.

4. *Multiplexed immunohistochemistry*. During 2017, we have included multiplexed immunohistochemical (IHC) tissue staining and imaging into the service pipeline. This technology is based on the work by group Kallioniemi and led by senior researcher Teijo Pellinen. The methodology and instrumentation used is described in a recent article (1). The system takes advantage of the high-resolution/high-speed imaging instrumentation, for which we have three different scanners. All the scanners have been updated to include 5 spectrally different fluorescent channels with filters and a special light source. We have also installed a near-infrared fluorescent channel in the instruments. This allows the use of one extra channel as compared to the conventional default set up. The scanners have different properties, and this is a crucial advantage when dealing with different types of samples (e.g. FFPE whole tissue sections, tissue micro-arrays, blood smear samples, macro tissue sections). We have gained several new customers especially due to the multiplex imaging capabilities. The feedback has been very positive. The services have not yet included the image analysis, and this needs to be implemented in the pipeline in the near future.

The current BF funding only allows 1-2 part time employed persons (one at FIMM and one at IBT) to handle the services and therefore some waiting times can occur. Especially scans that require a long scanning time (e.g. cytological samples and samples that require fluorescent imaging) are challenging with the current equipment and personnel. For example, scanning a whole-slide sample in the fluorescence mode at high resolution (40x-63x) can easily take several hours per sample, as compared to brightfield histology slides that can be scanned in 3-10 minutes.

Overall situation of the nationwide consortium: Activities in this field has increased substantially and we foresee that a high demand for sample digitization. Biocity Turku has now also established similar infrastructure as those at FIMM and IBT and has been promoting the biobank technologies by acquiring a whole-slide scanner and by proposing expansion of the sample digitization related to the activities of the BBMRI/ESFRI. For example, Auria Biobank aims to provide an access point between hospital-based biobanks and digital image acquisition, storage, analysis and webmicroscopy. Also, Oulu and Kuopio Universities have acquired microscopy scanners and introduced whole-slide scanning and webmicroscopy related to biobank activities and are future potential partners of the platform.

User statistics

See table below.

Participation in international, Nordic and European infrastructures

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

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

General			Number of user groups				
Host Univ	**Biocenter**	**Name of core facility**	**local**	**national**	**international**	**non-academic**	**Total**
UH	**FIMM-HiLIFE**	**FIMM Digital microscopy and molecular pathology unit**	7	2	1	2	12
UTA	**MED**	**Histocore UTA**	5				5
	Total		12	2	1	2	17

Future perspectives

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

Tasks of the consortium 2018-19

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

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

3. Combining the computerized morphological analysis with other image analysis processes, i.e. readout of immunohistochemical or fluorescence staining within specific compartments of the segmented tissue (e.g. quantification of immunostaining in epithelial cells only), with special focus on robust detection and quantification of signals from the novel molecular detection methods developed

4. Multiplex tissue imaging. Our current set up for fluorescent imaging is 5 different channels. This means that 5 different markers can be co-stained from the same sample. We are now upgrading the technology to achieve 8-9 marker detection from the same sample. We are in the phase of publishing this upgrade, and we hope to include this novel 8/9-plex system as a service pipeline as soon as possible.

Multiplex imaging generates a lot of digital data, which often needs to be analyzed using computer-aided digital analysis. Thus far the multiplex image analysis has not been part of the service platform. During the year 2018, we will include image analysis services as well. These will include the basic machine vision-based analysis using non-commercial software such as CellProfiler, but also advanced machine learning such as deep convolutional neural networks.

Major publications supported by the platform services

Nagaraj AS, Lahtela J, Hemmes A, et al. Cell of Origin Links Histotype Spectrum to Immune Microenvironment Diversity in Non-small-Cell Lung Cancer Driven by Mutant Kras and Loss of Lkb1. Cell Rep. 2017;18(3):673-684.

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Lokman U, Erickson AM, Vasarainen H, Rannikko AS, Mirtti T. PTEN Loss but Not ERG Expression in Diagnostic Biopsies Is Associated with Increased Risk of Progression and Adverse Surgical Findings in Men with Prostate Cancer on Active Surveillance. Eur Urol Focus. 2017;

Bychkov D, Linder N, Turkki R, et al. Deep learning based tissue analysis predicts outcome in colorectal cancer. Sci Rep. 2018;8(1):3395.

Holmström O, Linder N, Ngasala B, et al. Point-of-care mobile digital microscopy and deep learning for the detection of soil-transmitted helminths and Schistosoma haematobium. Glob Health Action. 2017;10(sup3):1337325.

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TGFβ signalling from tumour-suppressive to oncogenic in prostate cancer. Sci Rep. 2018;8(1):2338.

Drug discovery and chemical biology technology platform

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

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

Achievements in development of technology services

The "Clinical DSRT" (drug sensitivity and resistance testing) service established in 2014 at the High Throughput Biomedicine (HTB) Unit at FIMM was used for 89 fresh primary leukemia and 43 myeloma patient samples during year 2017. The current version of the DSRT compound set includes 528 approved and investigational oncology drugs or drug combinations. Altogether 669 DSRT assay plate sets, 1000 customised plates, and 400 commercial compound plates for customers were prepared by the HTB unit in 2017. Due to the high interest, supplying the DSRT and compound plates in requested capacity is becoming a bottleneck, which we hope to resolve by training additional personnel for compound management. We are also developing the DRST platform further by using e.g. the iQue high-throughput flow cytometry for studying in depth the response of *ex vivo* patient samples towards the drugs in the DSRT set. This aim is, however, hampered by the fact that the HTB unit does not have an iQue instrument available for the core facility services full-time.

At the DDCB-PHAR site, several new instruments were purchased in 2017, including Cytation 5 with integrated Biospa incubator and MultiFlo FX dispenser-washer. Cytation 5 expands the unit's capacity particularly in detection technologies, allowing the use of imaging-based readouts. In addition, the main automated liquid handler of the unit, over 15 years' old Biomek FX, was replaced by purchasing Biomek i7 with 96- and 384-channel pipetting heads in HEPA-filtered enclosure, providing flexibility and better suitability for e.g. long-term cell-based assays. These purchases were supported by FIRI-AoF funding as well as by the host institute, Faculty of Pharmacy.

Regarding our ability to conduct virtual screens and computational follow-up studies at DDCB-PHAR, we have continued our data mining and database integration efforts (see http://idaapm.helsinki.fi/). We have also developed computational models, e.g. to understand transporter specificity. We are also developing our skills to conduct machine-learning based predictive modeling in particular using deep-learning.

In 2017, the DDCB actively advanced the Finnish Compound Collection by establishing legal framework as well as procedures for collecting compounds from academic groups into this collection. We visited several chemistry groups at different universities to promote this initiative and also published a commentary article in the Kemia magazine to attract more interest towards the collection. This activity was supported by FIRI-AoF funding.

User statistics

See table below.

Participation in International, Nordic and European infrastructures

Our platform has since the start built strong ties to similar research infrastructures in other Nordic and European countries so that expertise and access to technologies are shared between the countries. The pan-Nordic initiatives were supported by a grant from NordForsk from 2014 to 2017. Although the grant has expired, Nordic Chemical Biology

General		Number of user groups				
Host Univ	Biocenter	local	national	international	non-academic	Total
UEF	BCK	7	8	9	4	28
UH	FIMM-HiLIFE	34	13	17	5	69
	HiLIFE	24	7	6		37
	Total	65	28	32	9	134

community meetings are held yearly and exchange of information is active (e.g. ~10 researcher visits to Nordic sites from Finland and vice versa in 2017, and several collaborative projects). The third Nordic Chemical Biology Symposium is being organised (in Gothenburg in May 2019; previous symposia organized in 2015 and 2017). DDCB members have been involved in the organization of every symposium. This shows that collaborative efforts continue and the ties of DDCB to the Nordic chemical biology consortia are tight.

Within DDCB, FIMM is now preparing a NordForsk application together with the Karolinska Institute and the University of Copenhagen to support Nordic collaborative efforts that aim to develop further personalized cancer treatments. FIMM's position in this joint application is strong since the Drug Sensitivity and Resistance Testing (DSRT) platform that is in the core of the application was developed at FIMM and the extensive data that has been acquired from the DSRT's done at FIMM will be a valuable reference point for any new data produced.

Our platform is directly linked to two ESFRI roadmap initiatives. First, we are coordinating the national participation in EU-OPENSCREEN (www.eu-openscreen.eu), a European research infrastructure focused on open access development of small molecule "tool compounds" with novel bioactivities. Finland has always had an active role in EU-OPENSCREEN and it recently joined EU-OPENSCREEN as a founding member. EU-OPENSCREEN operations, scheduled to start in 2019, are expected to be highly complementary to ongoing DDCB operations and some of the physical infrastructures that now are supporting the national platform will also serve the larger European research communities for EU-OPENSCREEN projects. Second, FIMM will serve as the high throughput microscopy core of the Finnish node of the Euro-BioImaging ESFRI (http://www.eurobioimaging.eu). In addition, CSC and FIMM are involved in the work of BioMedBridges (http://www.biomedbridges.eu) and ELIXIR (www.elixir-europe.org), ESFRI roadmap projects focusing on the coordination and management of biological information.

Future perspectives

With FIRI-AoF funding for 2018, the HTB unit at FIMM is upgrading its ultra high throughput robotic system, which is unique in Finland. The previous system was established in 2009 and upgrading the core robotic system and software to maintain full performance is needed. The new system to be installed in Autumn 2018 is Cellario-driven ACell from HighRes Biosolutions, designed to be very flexible and to allow future upgrades as needed. An important instrument in terms of developing the technology services in the future, would be to obtain an iQue high-throughput flow cytometer dedicated for the core facility services, allowing development of multiplexed readouts for the DSRT platform and other cell-based screens. In addition, obtaining a solenoid valve based nanoliter-microliter scale multichannel dispenser would enable accurate and higher throughput dispensing of cells in cell-based screens.

At DDCB-PHAR, the screening unit focuses on antimicrobial screening along with in vitro ADME-Tox and follow-up assays. This unit has a comprehensive panel of bacterial strains (incl. multidrug resistant strains) that would allow extensive antibacterial profiling of novel compounds, but the current capacity in carrying out antibacterial screening is limited and would require additional instrumentation to enhance the capabilities in offering antibacterial profiling services. Funding for acquiring key instruments to improve this capacity have been sought from the FIRI-AoF call. To enhance computational resources at DDCB-PHAR, we will access Schrödinger Maestro over the 2018-2019 period and have purchased licences for a new set of software, Grid/Pentacle/Vosurf+ in particular. The computational modelling group is also developing to take advantage of its expertise in data integration and state-of-art machine learning using deep-learning, which will make it well connected to industrial needs. Furthermore, this should allow to decrease the dependency on commercial software licences.

Recently established screening and medicinal chemistry site at Biocity Turku joined our platform meetings as an affiliated member, and in the future this site could be integrated into the platform. This would bring in medicinal chemistry expertise to the DDCB as well as expertise in advanced cell models such as 3D culture, organoid cultures, and in high content imaging.

Within the DDCB platform, the current status and quality of the compound libraries available have been extensively discussed. Some of the compound libraries are getting old and depleted, and to ensure the availability and quality of supplied compounds for future screens, plans for renewing the libraries

should be initiated. We are also currently checking the integrity of selected compounds by LC-MS, which should provide a better view of the current status of the libraries and required actions. During the next few years, we also anticipate to be able to set up the first version of the Finnish Compound Collection and to include the compounds submitted by chemists into screens carried out at the screening sites.

Previously, we have created tools to analyze and visualize data generated, for example, from the DSRT analyses, and supported the work to establish such public databases as well as analysis and visualization tools. Development of these tools will continue so that users can explore, understand and disseminate their data more effectively. Our plan is also to create a data sharing platform for the DDCB, which would allow the partners to share data within DDCB projects in secured and functional manner. Aim with this initiative would also be to store data related to the compounds of the Finnish Compound Collection efficiently, which would allow efficient communication of results between compound-submitting chemists and researchers carrying our screens with the compounds.

Major publications supported by the platform services

Bonabi A, Cito S, Tammela P, Jokinen V, Sikanen T. Fabrication of concave micromirrors for single cell imaging controlled over-exposure of organically modified ceramics in single step lithography. Biomicrofluidics. 2017;11(3):034118.

Haltia UM, Andersson N, Yadav B, et al. Systematic drug sensitivity testing reveals synergistic growth inhibition by dasatinib or mTOR inhibitors with paclitaxel in ovarian granulosa cell tumor cells. Gynecol Oncol. 2017;144(3):621-630.

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Christensen JR, Meng-lund H, Grohganz H, et al. Surface area, volume and shape descriptors as a novel tool for polymer lead design and discovery. Eur J Pharm Sci. 2017;102:188-195.

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Asquith CRM, Laitinen T, Bennett JM, et al. Identification and Optimization of 4-Anilinoquinolines as Inhibitors of Cyclin G Associated Kinase. ChemMedChem. 2018;13(1):48-66.

Wissel G, Deng F, Kudryavtsev P, et al. A structure-activity relationship study of ABCC2 inhibitors. Eur J Pharm Sci. 2017;103:60-69.

Saeed K, Rahkama V, Eldfors S, et al. Comprehensive Drug Testing of Patient-derived Conditionally Reprogrammed Cells from Castration-resistant Prostate Cancer. Eur Urol. 2017;71(3):319-327.

VIRAL GENE TRANSFER & CELL THERAPY

Coordinator: Seppo Ylä-Herttuala, BCK

Gene transfer technology has become an invaluable tool for studies of gene function, gene regulation and generation of new disease models both in cells and in gene modified animals. Researchers consider recombinant virus vectors as the most efficient and often the only means to deliver transgenes to achieve stable long-term expression in the host. Also, therapeutic applications based on gene and cell therapy have progressed rapidly during the last few years with approval of the first gene therapy products for clinical use in EU and USA. Thus, it is not surprising that the demand for gene transfer vectors has increased significantly over the last few years. VGTCT platform has very successfully developed and established well-functioning gene transfer and viral production services that researchers in Finland and elsewhere can use for their experiments with affordable prices. Biocenter Finland support has been vital for the maintenance and development of core vector services in all Biocenters.

Viral gene transfer technology platform

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

Partners: Kari Airenne, BCK; Aki Manninen, BCO, Virus Vector Core Facility; Kari Alitalo, HILIFE, AAV Gene Transfer and Cell Therapy Core Facility; Akseli Hemminki, HILIFE, Oncolytic vector core facility; Topi Tervonen, HILIFE, Functional Genomics Unit (FuGu); Eleanor Coffey, BioCity, Viral Vector Facility; Eric Dufour, MED, Virus Vector Facility.

Achievements in development of technology services

A.I. Virtanen Institute core facility at BCK has brought into full operation new iCELLIS bioreactors, which allow efficient large scale lentivirus and AAV production. Downstream purification can now handle up to 100 liters original virus volumes, which will yield up to 1015 viral particles. Suspension cell-based bioreactors have been set up previously for large scale production of adenoviral vectors. Core facility also offers training courses and biosafety training regarding the produced vectors.

HiLIFE AAV Gene Transfer and Cell Therapy Core Facility (AAV Core facility) has successfully continued providing services to the customers by providing fully purified and characterized AAV preps of four serotypes, which allow efficient transduction of virtually all tissues in the animals, as well as a wide range of cultured cell lines. The AAV Core facility has also produced a number of control AAVs and AAVs encoding fluorescent proteins (EGFP, mCherry etc), which are used for cell tracking studies in vivo.

HiLIFE Functional Genomics Unit (FuGU) has provided lentiviral and eco/amphotropic retroviral production services. Recombinant viral particles are sold in MINIscale (1,5 ml) and MIDIscale (6 ml) volumes. We offer production of high-titer concentrated lentivirus particles in two different volumes (180 ul and 380 ul) for hard to transfect cells and in vivo transduction purposes with specially purified vectors. The vectors for virus production can originate from the customer or from the genome-scale arrayed mouse and human TRC1 shRNA or CRISPR/Cas9 gRNA libraries licensed for and housed in FuGU. The core offers biosafety training, reagents for recombinant virus production, virus titer analysis and biosafety tests to exclude replication competent virus.

Biocity Turku core facility has further developed gene editing technologies based on CRISPR/Cas9 technologies and Biocenter Oulu has developed lenti- CRISPR vectors and constructs for siRNA gene transfers. In Tampere BioMediTech special expertise is available for sendai virus based vector production.

Most significant bottlenecks:

Even though basic production methods have been established in all Biocenters there is a continuous need to develop especially purification methods, other downstream technologies and robust quality control tests for viral vectors. Also, next generation more efficient solid phase bioreactors are entering the field of viral production and there is a need to upgrade key equipment for large scale vector production in the next 2-3 years. A constant bottleneck is the lack of sufficient funds to pay staff scientists and technicians who maintain and operate virus production facilities in all Biocenters. Utilizing the lentiviral genome wide editing resources as coherent services has proved to be challenging and time consuming.

User statistics

See table below.

Participation in international, Nordic and European infrastructures

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

Future perspectives

The foreseeable development is an increased need for the vector production services in Finland and elsewhere with affordable prices. We also need to set up lentiviral genome wide editing services. With current funding, we will continue to arrange education through courses organized by members of the VGTCT network. In HiLIFE, there will be a jointly acquired new equipment (IncuCyte S3), which is going to be in shared use by several labs. The AAV Core facility is planning to use it for the purposes of screening the transduction efficiency of new serotypes and uncommon AAV preps.

Considering the successful development of various gene transfer techniques and several ongoing clinical trials worldwide, we envision a rapid increase in the number of our customers who would like to use gene transfer techniques in their research. There is clearly a need to develop more efficient solid-phase bioreactor methods for largescale vector production. We also anticipate a growing need to adapt additional viral serotypes for the recombinant virus production and the need to develop better adenovirus-, lentivirus- and AAV-CRISPR vectors for efficient and safe genome editing.

Major publications supported by the platform services

Gao P, Xia JH, Sipeky C, et al. Biology and Clinical Implications of the 19q13 Aggressive Prostate Cancer Susceptibility Locus. Cell. 2018;174(3):576-589.e18.

Raykhel I, Moafi F, Myllymäki SM, et al. BAMBI is a novel HIF1-dependent modulator of TGFβ-mediated disruption of cell polarity during hypoxia. J Cell Sci. 2018;131(10)

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Mäntylä E, Salokas K, Oittinen M, et al. Promoter-Targeted Histone Acetylation of Chromatinized Parvoviral Genome Is Essential for the Progress of Infection. J Virol. 2016;90(8):4059-4066.

Hartikainen J, Hassinen I, Hedman A, et al. Adenoviral intramyocardial VEGF-DΔNΔC gene transfer increases myocardial perfusion reserve in refractory angina patients: a phase I/IIa study with 1-year follow-up. Eur Heart J. 2017;38(33):2547-2555.

Antila S, Karaman S, Nurmi H, et al. Development and plasticity of meningeal lymphatic vessels. J Exp Med. 2017;214(12):3645-3667.

Rademakers T, Van der vorst EP, Daissormont IT, et al. Adventitial lymphatic capillary expansion impacts on plaque T cell accumulation in atherosclerosis. Sci Rep. 2017;7:45263.

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	international	non-academic	Total
UEF	BCK	BCK	20	8	8	2	38
UH	BI-HiLIFE	AAV Core	5	2	1	0	8
	FIMM-HiLIFE						0
	HiLIFE	FuGu	29	4	2	1	36
UO	BCO	VirusCore	11				11
UTA	MED	Tampere Virus Facility	7	0	0	0	7
ÅAU	BCT		9			1	10
	Total		81	14	11	4	110

Laham-karam N, Laitinen P, Turunen TA, Yläherttuala S. Activating the Chromatin by Noncoding RNAs. Antioxid Redox Signal. 2018;29(9):813-831.

Vuorinen EM, Rajala NK, Rauhala HE, Nurminen AT, Hytönen VP, Kallioniemi A. Search for KPNA7 cargo proteins in human cells reveals MVP and ZNF414 as novel regulators of cancer cell growth. Biochim Biophys Acta. 2017;1863(1):211-219.

Ahola A, Pölönen RP, Aalto-setälä K, Hyttinen J. Simultaneous Measurement of Contraction and Calcium Transients in Stem Cell Derived Cardiomyocytes. Ann Biomed Eng. 2018;46(1):148-158.

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NEW PLATFORMS

Single-cell omics technology platform

Chair: Pirkko Mattila, FIMM-HiLIFE, UH

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

Achievements in development of technology services

2017 was the first year single cell operations were included in Biocenter Finland technology platforms. The activities of the Single-Cell omics (SC omics) include capture and processing of individual cells for transcriptome, epigenome and protein expression profiling. Single-cell omics infrastructure has been funded in FIRI2015 (SC-Infra) and FIRI2016 (Biocenter Finland) calls for single cell genomics and single cell proteomics, respectively. With this funding four instruments have been purchased in 2016 for single cell capturing and processing for NGS applications, and two instruments for proteomic applications in 2017.

The equipments enabling cutting edge SC technologies and their locations are listed below:

University of Helsinki (Meilahti Campus):
Chromium by 10XGenomics (FIRI2015)

single cell RNA sequencing and targeted assays

Drop-Seq by Dolomite-Bio (FIRI2015)

single cell RNA sequencing, high throughput microfluidics and assay development

University of Helsinki (Viikki Campus):
Polaris by Fluidigm (FIRI2015)

single cell selection, perturbations and RNA sequencing

CyTOF (Helios) by Fluidigm (FIRI2016)

single cell proteomic profiling

University of Turku (Turku Centre for Biotechnology):
Chromium by 10XGenomics (FIRI2015)

single cell RNA sequencing and epigenomics

CyTOF (Helios) by Fluidigm (FIRI2016)

single cell proteomic profiling

With the above mentioned instrumentation the following services have either been set up (SC transcriptomics) or currently being developed (SC proteomics)

Single-cell RNAseq services
3´counting expression assays

SC sorting, perturbations and transcriptional analysis

custom expression assays on plate format

Single-cell proteomics services
profiling of cells with focused panel of metal-tagged antibodies - services under development

Single-cell bioinformatics services
since fall 2017 bioinformatic supervision has been available and educational network meetings arranged for customers

A lot of method development work has already been done. SC Polaris platform has so far been used in development work of the protocols. We have obtained promising results and ca 80% cells give enough data for analysis. Library protocol is using Smart system aiming at entire transcript coverage which is finally made suitable for sequencing using Nextera approach. To our surprise in several samples (cells) we got data from nearly 9000 genes which is really high number. The analysis of the data from Polaris cannot be performed using conventional methods. We have constructed scripts that be used in the primary and secondary analysis. The same SmartSeq -system has also been used to process single cells in plate format. This is applicaple for low cell amounts when microfluidics -based systems cannot be used.

SC -omics network collaborates very closely with Biocenter Finland technology platform Genome-wide methods. While single cell capturing for NGS and library preparations are provided by SC Network the sequencing services in the end of the single cell NGS -workflow are provided by Genome-wide methods. Data analysis for SC NGS applications is specific for single cell data and single cell data analysis services have been set up and developed further.

We expect the single cell research field to grow fast with increasing demand for new services. This includes an overall increase in the number of samples, a tendency for increasing numbers of cells per sample, and more diversity in sample types,

tissues, and experimental designs. We also expect the demand for bioinformatics services to grow accordingly. Overall, the user base has already been large and the customers have welcomed the new services so well that occasionally we are not able to serve our customers in reasonable time due to long queues. It is already evident that since we are working with living cells and for the best results it is extremely important to start processing the cells immediately when they come to the lab. This makes tight scheduling necessary and in some cases the scheduling is very difficult i.e when analysing newborn mice or clinical samples from hospital. Currently, the successful completion of certain experiments has relied on the availability of independently funded postdocs and operational and administrative support from Genome-wide methods platform, which is not a sustainable solution long-term. Budgeting sufficient resources for personnel to run the first steps of single cell workflow would increase the capacity.

Single cell technologies will be developing fast with emerging novel equipments. For these reasons the network will monitor for emergence of next-generation single cell analysis instruments, and plans to upgrade and/or supplement the current instrumentation during 2018-2021. At the same time, it is crucial to maintain sufficient availability and internationally competitive pricing of sequencing capacity within the Genome-wide methods platform.

User statistic

See table below.

Participation in international, Nordic And European infrastructures

As a young consortium we don´t have international infrastructure related activities yet.

Future perspectives

While during the year 2017 the basic services on single cell transcriptomics were set up the next couple of years will be a period for development and implementation of new (customized) assays and protocols. The new methodology to be implemented contains at least the following:

- piloting and optimizing methods for single cell DNA methylation analysis
- development of portable sc-RNA-seq assays (e.g. SeqWell)
- developing novel library protocols for Polaris instrument
- miniaturization of single cell RNA-seq method on plate format to provide cheaper assays for samples with low cell counts
- implementation of immune profiling services for T -cell and B-cell receptors
- development of workflows so that fixed cells instead for living cells could be used for SC RNA-seq
- implementation of new single cell sequencing techniques like CITE-seq for simultaneous epitope and transcriptome measurement in single cells (also enabling sample multiplexing and increased cell throughput), and ATAC-seq to study chromatin accessibility

Launching of single cell proteomics services took place in early 2018 and the facilities are currently up and running.

We will also strengthen our single cell bioinformatics services by implementing new analysis methods and developing analysis pipelines.

The collaboration strategy of the consortium on single cell infrastructure is to divide developmental tasks based on prior expertise and existing research

General			Number of user groups				
Host Univ	**Biocenter**	**Name of core facility**	**local**	**National**	**International**	**non-academic**	**Total**
UH	**BI-HiLIFE**	Single-cell proteomics and genomics	0	0	0	0	0
	FIMM-HiLIFE	Single-cell analytics	7	0	1	0	8
	HiLIFE	Single cell microfluidics service lab	2	0	0	0	2
UTU	**BCT**	Functional Single Cell Genomics and SC proteomics	5	3	0	0	8
	Total		14	0	1	0	15

focus areas and enable specialization to certain applications in each research center to provide nationally a strong and wide technical single cell expertise.

In addition to Genome-wide methods SC -omics network will be more closely connected to at least the following Biocenter Finland networks: Proteomics and metabolomics, Translational technologies, Bioinformatics and Biological imaging. Furthermore all nodes located in Helsinki are Life Science Research Infrastructures (LSRIs) in Helsinki institute of Life Science (HiLIFE).

In addition SC omics infrastructure collaborates and interacts with large national and international networks. For example collaboration with CSC, the scientific computing center in Finland, has been active. CSC has already started installation of single cell analysis tools to the user-friendly Chipster NGS analysis platform freely available for academic researchers.

Major publications supported by the platform services

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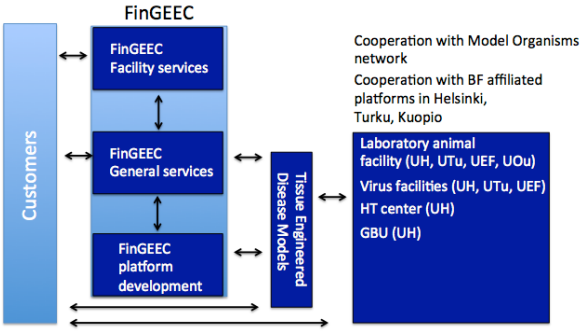
Genome editing

Chair of the platform: Juha Klefström, HiLIFE, UH

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

Achievements in development of technology services

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



***FinGEEC Strategy**: HiLIFE (Helsinki): FinGEEC platform coordination and development, genomic resources, & services. Coordination via TEDM with other FinGEEC nodes in Helsinki, Turku, Kuopio and Oulu Biocenters.*

FinGEEC - HiLIFE:

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

FinGEEC - Turku has continued providing gene-editing lentivirus services to researchers interested in using these in the in vivo animal models developed in the project earlier. The main aim of the FinGEEC in Turku has in the previous years been to set-up an intra-ductal inoculated xenograft model for human breast cancer in immunocompromised mice. This succeeded well, the technology was transferred to the TCDM core-facility in Turku starting 1.1.2018 and has been successfully used the by customers testing their lentivirally transduced and edited human breast cancer cell lines for in vivo tumorigenicity. Currently, the main focus has been to develop and expand the virus transduction services to enable customers to efficiently and in a timely manner to generate their edited cell lines. A new technical person was hired to the virus facility to provided expanded services and cut down of waiting times. This was in response to increasing customer volume and feedback. In addition, several new gene-editing approaches have been set-up and are currently being developed by the core personnel.

FinGEEC - Kuopio has focused on flow cytometric analysis of gene edited cells. Sorting of CRISPR/Cas9-modified cells into 96-well plates for single cell analysis has consolidated its role. Two new cytometers have been acquired to AIV-Institute at 2017 (Amnis Flowsight Imaging Flow Cytometer and Beckman Coulter Cytoflex S analyzer). Also, a new violet laser was installed to FACSAria III sorter. New machinery has increased and widened the capabilities to use flow cytometry. When more and more research is focusing on single cell level, flow cytometry offers a valid tool for creating single-cell samples with high purity and sensitivity. Flow cytometry has been used together with various researchers and research groups studying cardiovascular disease, neurosciences and exosome research. Also, non-academic collaboration has been done. Funding has supported in part the possibility to organize specialized flow cytometry course to increase the knowledge and usage of Flow Cytometry.

User statistics

See table.

Participation in international, Nordic and European infrastructures

The FinGEEC Turku has been in close contact with the EuBI (euro-Bioimaging) European Infra intiative. The European Hub and a national EuBI

General			Number of user groups				
Host Univ	Biocenter	Name of core facility	local	national	international	non-academic	Total
UEF	BCK	Genome editing	8	1		2	11
UH	HiLIFE		20	1	1	1	23
UTU	BCT		1	1		2	4
	Total		29	3	1	5	38

node are in Turku and Ivaska has been involved in planning how the FinGEEC services are optimally integrated into the imaging pipe-lines developed at Turku as part of the starting EuBI functions.

Future perspectives

The network synergy will be improved especially since different biocenters have clearly focused areas in genome editing research. Locally, Helsinki plans to deepen cooperation with Helsinki and other national Laboratory Animal Centers to spread the use of CRISPR KO's. Alternatively, these services could be provided in a centralized fashion from Helsinki. These options will be discussed. Furthermore, co-developing & testing of CRISPR-mediated gene activation systems together with BSCC is currently evolving process. The third anticipated development includes development of CRISPR applications for genetic analysis of patient-derived organoids. This initiative is closely related to other similar initiatives with similar goals, for example, iCAN Flagship in Helsinki. In flow cytometry, the future plans include setting up Amnis FlowSight imaging cytometer for advanced analysis. Another current direction includes expanding the FACSAria-sorting capabilities to 384-well plate format for more robust single cell analysis possibilities. In Turku, the efforts include deepening collaboration with the Turku Centre for Disease modelling in applying lentivirally transduced and genome edited cell lines in mouse xenografts. Co-developing and testing endogenously tagging (CRISPR-mediated genome editing to tag endogenous proteins with fluorescent imaging tags like GFP) in different cell types, including human induced pluripotent stem cells and cancer cells. Co-developing and testing zebra fish embryo xenografts of genome edited cells for live-cell microscopy and drug screening (in collaboration with the new, currently not BF funded zebra-fish core facility at Turku Centre for Biotechnology).

Major publications supported by the platform services

Marques E, Peltola T, Kaski S, Klefström J. Phenotype-driven identification of epithelial signalling clusters. Sci Rep. 2018;8(1):4034.

Merentie M, Rissanen R, Lottonen-raikaslehto L, et al. Doxycycline modulates VEGF-A expression: Failure of doxycycline-inducible lentivirus shRNA vector to knockdown VEGF-A expression in transgenic mice. PLoS ONE. 2018;13(1):e0190981.

Liquid biopsies technology platform

Chair of the platform: Tapio Visakorpi

Achievements in development of technology services

FIRI2016 funding was granted to purchase equipment for enrichment and analysis of circulating tumor cells (CTC) from blood. Currently, one equipment is under testing and the purchasing will take place in Fall 2018.

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