

Non-Confidential Information on

Diseases of the CNS

in BioTurku®





The key competence areas in BioTurku® are Drug discovery, development and release, Diagnostics and Biomarker development.

BioTurku® Scientific and Business Community

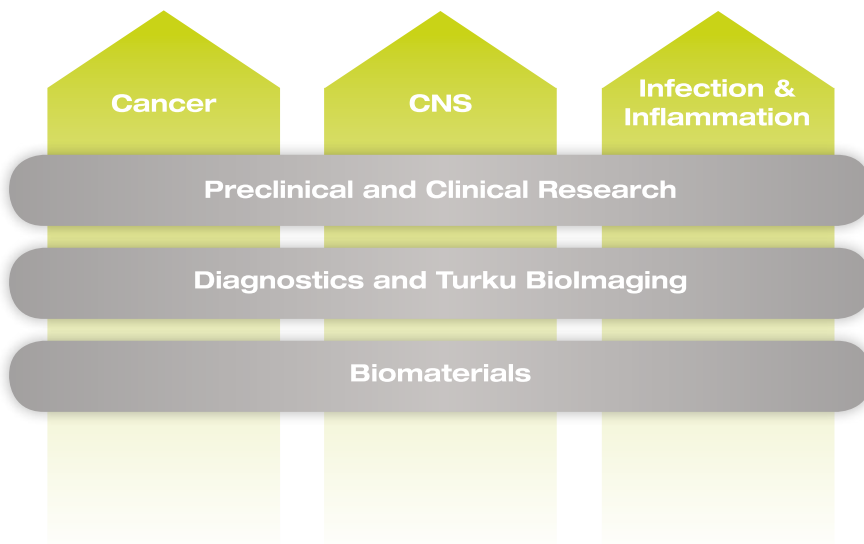
BioTurku® is the leading biotechnology cluster in Finland, an active and dynamic community of bio actors and a centre of top expertise in Northern Europe. Around half of Finland's pharmaceutical and diagnostics industry is located in the Turku region in southwest Finland. The BioTurku cluster comprises about 90 biotechnology companies, two universities as well as several educational and research institutes and the Turku University Hospital. It forms a continuous chain of education, research, product development, production and commercialisation. BioTurku is part of Turku Science Park, one of Finland's oldest and largest science parks.

The key competence areas in BioTurku are preclinical and clinical drug research and development, diagnostics and biomaterials. The three therapeutic areas, within these competence areas, are cancer and hormonal diseases, inflammatory and infectious diseases and diseases of the central nervous system. Close cooperation between academic research groups and companies is an essential element in the practical implementation of the BioTurku strategy.

FinnBIRD, Finnish Brain Injury Research and Development, is the national centre for treatments, research and education of brain injuries. The focus of the research is novel medication for new treatments and biomarkers for diagnosis and treatment follow up.

Further information: www.turkusciencepark.com

BioTurku® – Regional Strengths



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1. RESEARCH INFRASTRUCTURE, PROGRAMMES AND PROJECTS AT BIOTURKU®

The BioTurku cluster builds on a strong scientific basis - the largest single-location Biocampus in Finland is located in Turku, with internationally recognised academic research and education.

The two universities, University of Turku (www.utu.fi) and Åbo Akademi University (www.abo.fi), as well as Finland's largest polytechnic University of Applied Sciences (www.turkuamk.fi) form the main educational structure for the biotechnology research.

In addition to the university faculties and polytechnic, biotechnology research is carried out in a number of research units, institutes and other organisations, e.g.

Turku Centre for Biotechnology (www.btk.fi)

Turku Centre for Biotechnology is an institute of University of Turku and Åbo Akademi University. The Centre provides technical expertise and coordination services for academic and industrial projects in several central areas of biotechnology. Many of the key instruments have been installed at the Centre to create "core facilities" for biotechnical research.

VTT–Technical Research Centre of Finland (www.vtt.fi)

VTT is a multidisciplinary expert organisation on technology and technology-based business research. VTT's special strength is its ability to create new, globally competitive technologies and innovations by combining knowledge and expertise in different fields.

New high-throughput screening methods, biochip technologies and other VTT expertise are developed and applied to the pharmaceutical development process. New technologies are exploited not only to speed up the existing processes, but also to open up entirely new therapeutic opportunities. An RNA interference technique and cell-based screening are used to find and select candidate molecules for the pharmaceutical development pipeline. Systems biology techniques are used to identify biological markers for drug development and diagnostic applications. Such biological markers are enabling better diagnostics, and new generation of diagnostic systems are being created by combining biosciences with microelectronics and information technology.

Turku Clinical Biomaterials Centre (TCBC) (www.biomaterials.utu.fi)

TCBC is a centre with expertise in non-metallic biomaterials in medicine and dentistry. The centre has a core-facility laboratory with a comprehensive range of up-to-date equipment to meet the challenges of research and development of novel biomaterials and implant designs for clinical applications in dentistry, cranio-maxillofacial surgery and orthopaedics. Several facilities are dedicated to particular tasks in fabrication, characterization and biomechanical testing of materials.

Turku Center for Disease Modeling (TCDM) (www.tcdm.fi)

TCDM is a research infrastructure at the Faculty of Medicine, University of Turku, with a guiding principle agreed June 2006. TCDM provides state-of-the-art research facilities and expertise in experimental studies in vivo to support both academic and

industrial associated non-clinical research. The facilities and expertise are also available for contract research.

Turku PET Centre (www.turkupetcentre.fi)

Turku PET Centre is a Finnish National Research Institute for the use of short-lived positron emitting isotopes in the field of medical research, with focus on high quality scientific research and diagnostic service for the whole country. The centre is ranked among the top 5 in the world.

Turku Bioluminescence (www.bioimaging.fi)

Turku has genuine traditions in imaging research. The Turku Bioluminescence initiative represents state-of-the-art technologies in the bioscience community in Turku and is highly interdisciplinary, encompassing all areas of imaging, ranging from molecular to cellular, from single molecule to whole animal imaging, and from single cell analysis of sub-cellular events to high-throughput screening (HTS). The initiative also includes proteomics, systems biology, and computational modelling of cellular processes as their own specific modalities of bioimaging.

Turku Clinical Research Centre (Turku CRC) (www.turkucrc.fi)

Turku CRC, a network enterprise between University of Turku and The Hospital District of South-West Finland, offers services and support for the researcher initiated clinical trials and enhances collaboration with the enterprises in research business. The aims of the clinical research centre are to confirm the requirements of successful clinical trial, to ensure the quality of the trial, to relieve the investigators' load in managing the research and to intensify collaboration with the external partners.

Clinical Research Services Turku (CRST) (www.crst.utu.fi)

CRST offers clinical research services for the pharmaceutical industry and other developers of new health care products. The services cover clinical drug development from Phase I to Phase IV and bioanalytical services related to clinical and preclinical trials of pharmaceuticals and other health care products.

Turku University Hospital (www.tyks.fi)

The Turku University Hospital belongs to the Hospital District of South-West Finland. The District is situated in South-West Finland and consists of 58 municipalities. With its 453.000 inhabitants it is the second largest of Finland's twenty-one Hospital Districts. The Turku University Hospital serves its patients within almost 50 medical specialities. It has 828 beds and a staff of about 2200 nurses, 500 doctors and 920 other employees. The Hospital has national centres for Positron Emission Tomography and Hyperbaric Oxygen Therapy. The Hospital offers practice for about 1.500 students in medicine and nursing every year.

National Institute for Health and Welfare (THL) (www.thl.fi)

The National Institute for Health and Welfare (THL) is a research and development institute under the Finnish Ministry of Social Affairs and Health. THL works to promote the well-being and health of the population, prevent diseases and social problems, and develop social and health services. THL is the statutory statistical authority in health and welfare and maintains a strong knowledge base within its own field of operations.

Functional Foods Forum (<http://fff.utu.fi>)

Functional Foods Forum, as an independent special unit of the University of Turku, brings together the multidisciplinary expertise for the research and development of high-quality safe foods to promote human health and well-being. The forum combines leading-edge research expertise in natural, health and medical sciences with technological, legal and business know-how in order to develop and commercialise functional foods for human needs. The activities are independent research Programmes, multidisciplinary expertise in food and health and tailor-made research and development projects.

Academic Research Programmes

The academic research in biosciences carried out in BioTurku is organised under an umbrella organisation - BioCity Turku (www.biocity.turku.fi). BioCity Turku is a multidisciplinary research community consisting of over 80 research groups with some 1000 people: researchers, graduate students and assisting personnel. The research groups are organised under six research programmes:

- Biomaterials Research
- Centre for Reproductive and Developmental Medicine
- Diagnostic Technologies and Applications
- Receptor Research
- Systems Biology Research
- Turku Immunology Centre

In the following a selection of projects related to the area of *Diseases of the Central Nervous System* within relevant research programmes are presented.

1.1 Centre for Reproductive and Developmental Medicine (CREDE) Research Programme

Director: Juha Peltonen, M.D., Ph.D., Professor, Department of Anatomy, Institute of Biomedicine, University of Turku

The centre has actively prompted research in the areas of reproductive, developmental and skeletal research at the University of Turku since 1993. CREDE is composed of 18 research groups, and many of them have participated in CREDE activities during all these years. Hence, there is a long tradition in the research areas of CREDE at the University of Turku. However, new research activities have also been implemented in CREDE and new groups have joined and strengthened the Centre further. The Programme comprises basic, clinical and social science orientations. This comprehensive combination of three orientations has been one of the specific characteristics of CREDE activities from the very beginning. We are committed to further strengthening the interaction between basic and clinical sciences in the future, and keep modern medical care and its development as the

focus of our research. The CREDE Programme aims at problem-oriented, penetrative and systemic research from basic mechanisms to clinical and industrial applications.

The major research topics of the programme fall into three categories:

- Reproductive health and the mechanisms of hormone action
- Developmental mechanisms
- Skeletal research

The basic science projects under the different research topics are highly overlapping in themes such as the mechanisms of development, differentiation and hormone action.

Description of CREDE research projects related to Diseases in the CNS:

1.1.1 Genetics of Rare Hereditary Diseases

Helena Kääriäinen, M.D., Ph.D., Professor of Medical Genetics and Kirsi Huoponen, M.D., Ph.D., Docent, Department of Medical Genetics, University of Turku

Rare hereditary diseases are extremely difficult to diagnose correctly. The starting point in most of the research projects is to first clinically characterize an as uniform patient cohort as possible. This was achieved already years ago in case of some of the diseases investigated in the projects (lysinuric protein intolerance LPI, Leber hereditary optic neuropathy LHON, CADASIL, and some others) and further characterisation of the genetic background and/or pathogenesis is now ongoing. Collecting of the cases has happened more recently in some others (Sotos syndrome, CHARGE syndrome, familial amyotrophic lateral sclerosis FALS, hereditary spastic paraparesis HSP, and some others), and the analysis of mutational background and its correlation to the phenotype is ongoing. The ongoing population genetic projects are directed toward the study of regional differences in the genetic structure of Finns and identification of genetic roots of Finno-Ugric populations. The research group will apply the use of complete mitochondrial DNA (mtDNA) sequences and multiple Y-chromosome polymorphisms. The work will provide insights into primary genetic sources for the founding paternal and maternal lineages of Finno-Ugric populations and it will help to explain some features of the genetics of some rare hereditary diseases like the exceptional mutational background of FALS in Finland. In a European project, EuroGentest, the research group collaborates in a subproject that has as its objective to improve and harmonize the quality of genetic counselling in connection with genetic testing in the EU and in particular

1.1.2 Mitochondrial Dysfunction in Neurodegenerative Diseases

Kari Majamaa, M.D., Ph.D., Professor of Neurology, Department of Neurology, University of Turku

The aims of the research studies on mitochondrial diseases are on Mitochondrial DNA mutations and polymorphisms in neurodegenerative diseases like Parkinson's disease, age-related sensorineural hearing impairment and Alzheimer's disease, on mutations in genes encoding subunits of the OXPHOS Complex I as a cause of childhood encephalomyopathies and on genetic epidemiology of the MTTL1 mutation 3243A>G in the Finnish population.

The studies on neurodegenerative diseases associated with mitochondrial dysfunction are focusing on:

- Genetic epidemiology of early-onset Parkinson's disease in a nationwide ascertainment of cases
- The role of mutations in nine highly conserved genes encoding subunits of the OXPHOS Complex I
- Mutations in genes encoding proteins involved in mitochondrial iron metabolism.

1.2 Diagnostic Technologies and Applications Research Programme

Directors: Kim Pettersson, Ph.D., Docent, Professor in Biotechnology, Department of Biochemistry and Food Chemistry / Biotechnology, University of Turku, and Pekka Hänninen, Ph.D., Professor of Medical Physics, Laboratory of Biophysics, Institute of Biomedicine, University of Turku

The Turku area is a nationally and internationally recognised stronghold in research on in vitro diagnostic technologies both from a scientific and commercial point of view. A central task for the suggested research Programme will therefore be the further development and coordination of the basic and higher education of researchers to promote the interactions within the research community and to the innovative segments of Finnish biotechnological industry.

To cope with an ever increasing number of new and/or clinically improved analytes (nucleic acids for gene detection, gene expression and infectious diseases, growth factors, tumour markers, markers of degeneration, etc.) new approaches and test principles are called for. IVD testing carries great promise as inexpensive and non-invasive means for early diagnosis, risk testing and preventive action thus contributing to the highly needed cost-containment within the health sector. Within this Programme, solutions to these challenges are sought from advanced reporter technologies, new assay formats, improved bioaffinity reagents as well as from creative instrumental solutions and platforms.

Description of Diagnostics research projects related to CNS:

1.2.1 Antibody Engineering and Autoantibodies in Human Diseases

Jukka Hellman, Ph.D. and Urpo Lamminmäki Ph.D., Biotechnology, Department of Biochemistry and Food Chemistry, University of Turku

The research objectives of the group are related to developing tailored reagents for immunorecognition based assays. The focus is on assays intended for clinical diagnostics, food safety, agricultural analytics and applications for high-throughput drug screening. The principal techniques used for the engineering of the recombinant antibodies, include directed evolution methods, structural design guided site-directed mutagenesis and fusion protein techniques. Our group has improved the binding characteristics, stability, labelling, expression levels or immobilisation properties of several recombinant antibodies, including binders against both small molecular compounds as well as protein antigens. These include antibodies against various clinically important disease markers e.g. prostate specific antigen, troponin I and tyrotropin. The generation of a large synthetic recombinant antibody library and the set-up of an automation-assisted screening facility for production binders without immunisation are under construction.

1.2.2 Laboratory of Biophysics

Pekka Hänninen, Ph.D., Professor of Medical Physics, Laboratory of Biophysics, Institute of Biomedicine, University of Turku

The main field of research of the Laboratory of Biophysics is development of fluorescence based methods and technologies to detect interactions at molecular level. The research bases on the use of modern optics methods, imaging, novel approaches for labelling of biomolecules and bioaffinity assays technologies. The current approaches mainly aim for improved two-photon excitation and resonance energy transfer detection technologies in diagnostics and screening assays. Methods for non-specific binding phenomena are also under investigation to understand fundamental limitations in assay performance and development.

1.2.3 Nucleic Acid Technologies

Timo Lövgren, Ph.D., Professor in Biotechnology, Department of Biochemistry and Food Chemistry, University of Turku

The research conducted in this project focuses on the development of novel, homogeneous nucleic acid detection methods based on time-resolved fluorometry, a technique that offers unparalleled performance to various immunoassays and nucleic acid detection schemes. The unique fluorescent properties of certain lanthanide (europium or terbium) chelates enable the detection of a specific nucleic acid sequence in a closed tube (1-4). The advantages of these methods over existing commercial technologies include simpler probe design, lower fluorescent background and reduced reagent costs. Assay throughput and performance are further enhanced by the use of pre-dried PCR reagents so that the actual assay only

consists of sample addition, thermal cycling and real-time or end-point fluorescence measurement and subsequent (or simultaneous) automated data analysis. In short, we aim at bringing the quantitative and qualitative analysis of DNA and RNA into a dimension that is straight forward, reproducible, accurate and cost-effective enough to be exploited in any environment where needed (in a laboratory or out in the field).

1.2.4 Diagnostic Applications (Human and Food)

Kim Pettersson, Ph.D., Docent, Professor in Biotechnology, Department of Biochemistry and Food Chemistry, University of Turku

The project is focusing on the advanced analytical techniques primary from the Diagnostic Programme itself combined with challenges in human and veterinary disease diagnostics and in agricultural and food industry. The methodologies are targeted to routine applications in various test environments but also to basic and translational research. In vitro diagnostics has become an integral part of human disease management. It is increasingly important to find novel markers for common diseases e.g. cardiovascular disease, diabetes, and cancer. In food diagnostics, the research focuses on easy monitoring of food additives, contaminants and central food components.

1.2.5 Biomedical Instrumentation, Detection and Automation Technologies

Juhani Soini, Ph.D., M.Sc.eng., Director of Education, Turku University of Applied Sciences and Medical Physics and Engineering and Department of Anatomy, University of Turku

The research activities are within applications and method development of biomedical instrumentation, biosensors, and, detection and automation technologies. The competence of the group members are highly interdisciplinary, engineering, software and instrument development, signal processing, chemistry and biology, targeted for solving biomedical and biological measurement problems in highly interdisciplinary fashion. The projects are mainly conducted in collaboration with other research groups in fields of technical, biomedical, clinical disciplines. The projects include development of a novel wash free bioaffinity in vitro diagnostics immunoassay platform suitable for bedside and distributed clinical in vitro diagnostics, as well as, scanning flow cytometry, instrumentation for measurement of multi-angle scattering signals from biological particles, such as cells and microbes. Instrumental and statistical methods are developed for improving data stability and measurement repeatability of biological measurements, and, means of signal processing for deriving novel information from measurement data.

1.2.6 Novel Detection Technologies and Assay Formats

Timo Lövgren Ph.D., Professor in Biotechnology, Department of Biochemistry and Food Chemistry, University of Turku

The research is directed to the development of novel photoluminescent reporters, photoluminescence detection systems and advanced photoluminescence-based assay concepts for in vitro diagnostics. The potential applications of the research are improved methods for clinical diagnostics, drug screening, food safety and environmental monitoring, which are developed in cooperation with industrial collaborators.

1.3 The Receptor Research Programme

Directors: Sirpa Jalkanen, M.D., Ph.D., Academy Professor, MediCity Research Laboratory and Department of Medical Microbiology, University of Turku and John Eriksson, Ph.D., Professor, Department of Biology, University of Turku and Turku Centre for Biotechnology

The research programme is focused on how cells receive and process signals. The research projects have a long record of high quality basic research on receptors to cell adhesion molecules, hormones, cytokines, death ligands, and growth factors, as well as cellular receptors for microbes. There is also a strong emphasis on the molecular mechanisms of signal transduction and transcriptional regulation, structure-activity relationships of ligand-receptor interactions, regulation of receptor expression, and on molecular pharmacology. These basic research areas have broad ramifications in different fields of health and disease-related research, including inflammatory, cell stress-related, and degenerative diseases as well as cancer and metastasis. Therefore, many of the individual research groups have active projects aiming at both technology transfer and applying their results to different health-related problems.

The research programme is now comprised of 19 groups. Three quarters of the groups are from the University of Turku. The rest are from the National Institute for Health and Welfare, VTT Technical Research Centre of Finland, and Åbo Akademi University.

Description of Receptor research projects related to Diseases of the CNS:

1.3.1 Protein Kinase Regulation of Brain Development and Disease

Eleanor Coffey, Ph.D., Docent, Academy Research Fellow and Group leader in Molecular and Cellular Biology, Turku Centre for Biotechnology

Neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's disease are characterised by the irreversible loss of nerve cell function. The protein kinases JNK and GSK-3 are recognised as players in a broad range of diseases including stroke and neurodegenerative disease. However exactly how these proteins mediate cell death in the brain remains largely unknown.

Although targeting of JNK and GSK-3 for drug-based therapy is already underway, our understanding of the physiological function of JNK in the brain is in its infancy. Understanding the molecular details of protein kinase effectors and their cellular functions is a pre-requisite to improved drug design.

1.3.2 Organisation of Neuronal Signalling

Michael Courtney, Ph.D., Docent, Research Director of the Molecular Signalling Laboratory and Professor in Cell Signalling, Department of Neurobiology, A.I. Virtanen Institute for Molecular Sciences, University of Eastern Finland

Stress-activated protein kinase pathways are widely accepted to play a significant role in disease progression in and outside the nervous system. However, recent work indicates that these pathways also contribute to development, differentiation, and even survival and proliferation. This suggests that direct stress-activated protein kinase inhibitors may be of only limited therapeutic use. In order to exploit the pathways for the development of novel neuroprotective drugs, it will be necessary to elucidate the mechanisms that organise these pathways into pools with neurodegenerative or physiological functions within the complex structure of neuronal cells.

The Molecular Signalling Laboratory investigates signalling in neuronal cells, with particular emphasis placed on responses to stressful conditions, the impact of stress-signalling on neuronal cell death and the mechanisms cells use to organise signalling proteins thereby ensuring specificity of function and efficiency of signal propagation. The research combines biochemical and molecular biological approaches with single-cell fluorescence methods.

1.3.3 Carbohydrate Receptors and Ligands

Jukka Finne, M.D., Ph.D., Professor of Medical Biochemistry, Department of Medical Biochemistry and Molecular Biology, University of Turku

The goal is to characterise the biological roles cell surface glycoconjugates focusing on the molecular mechanisms of the interactions of carbohydrates with their ligands. The main topics are the role of carbohydrates like polysialic acid in neural cell interactions, and the adhesion of bacteria to host cells. Polysialic acid is a neurodevelopmental carbohydrate antigen shared by the neural cell adhesion molecule NCAM and the capsular polysaccharides of meningitis-causing bacteria. It appears to regulate cell interactions in neural tissue. Its role in the pathogenesis of meningitis is not known. The research group aims at revealing the role of polysialic acid in normal neural tissue and pathological situations like stroke and neural tumours, as well as the development of meningitis. On the other hand meningitis-causing and other pathogenic bacteria attach to their tissue receptors by the binding of their adhesin molecules to specific sugar ligands on cell surfaces.

Characterisation of these molecular interactions sheds light into the pathogenic mechanisms of bacterial diseases, and also enables the development of new vaccines and new types of drugs that interfere with bacterial adhesion. The research group uses libraries of carbohydrates, synthetic inhibitors, enzymes and recombinant proteins to identify and characterise carbohydrate-binding proteins and determine their interaction mechanisms by X-ray crystallography and NMR.

A recent focus of interests has also been the hydrogen peroxide resistance protein Dpr, which also shows carbohydrate-binding activity.

1.3.4 Neurotransmitter Receptors in Nerve Cell Damage and Neuroprotection

Irma E. Holopainen, M.D., Ph.D., Docent, Department of Pharmacology, Drug Development and Therapeutics, University of Turku

The purpose of the research is to clarify molecular processes involved in receptor-mediated nerve cell death, neurogenesis, and synaptic plasticity, and to study the effectiveness of proposed neuroprotective drugs in ameliorating the damage in the developing brain. Better understanding of those complex mechanisms involved in nerve cell death, and on the other hand, neurogenesis, in the immature, plastic brain will offer targets for potential therapeutic interventions to treat paediatric patients suffering from such diseases as epilepsy, hypoxic-ischemic brain damage, and trauma. The research is focused on the hippocampus - the structure of great vulnerability, and of major importance in learning and memory. Current research in the developing hippocampus is focused on the following topics: Importance of GABAA-receptor in the pathogenesis of epilepsy, Signalling pathways involved in nerve cell death and the role of inflammation in epileptogenesis, Seizure-induced neurogenesis and Histaminergic regulation of nerve cell damage and seizure activity.

1.3.5 Molecular Pharmacology of α_2 -Adrenergic Receptors

Mika Scheinin, M.D., Ph.D., Professor of Pharmacology, Department of Pharmacology, Drug Development and Therapeutics, Institute of Biomedicine, University of Turku

The project aims to generate new knowledge on the molecular pharmacology of the three α_2 -adrenoceptor subtypes, a subfamily of the rhodopsin-like G protein coupled receptors. Such knowledge is important for the targeted development of new subtype-selective α_2 -adrenoceptor agonists and antagonists. The research methods of the group include molecular cloning, mutagenesis and recombinant expression systems, cell-based functional receptor assays, transgenic animal models and clinical studies. Current research on α_2 -adrenoceptor subtypes includes the following topics: structural determinants of subtype selectivity, receptor activation mechanisms, receptor trafficking and desensitization, functional cell-based model systems for drug screening, receptor distribution patterns in cells and tissues, receptor functions in transgenic mice, regulation of vascular smooth muscle and human receptor gene polymorphisms.

1.3.6 Systems Biology Research Programme

Director: Riitta Lahesmaa, M.D., Ph.D., Professor, Director of Turku Centre for Biotechnology, University of Turku and Åbo Akademi University

The research programme aims for a system-level understanding of specific biological processes to better comprehend cell signalling and metabolism, and to define the molecular basis of specific biological processes and diseases. The programme has a strong emphasis on data integration, bioinformatics, biomathematics, and computational biology and structural biology and molecular modelling. Common to all the groups focusing on research projects in biology, cell biology, biomedical research or molecular genetics is a devotion to an integrative and holistic approach exploiting and further developing and combining modern technologies in novel ways. This cross-disciplinary combination of research groups has resulted in a unique exchange of approaches and methodologies. Several collaborative research projects, including four research consortia funded by the Academy of Finland or National Technology Agency (TEKES) within the Programme are already ongoing.

Description of System Biology Research projects related to Diseases of the CNS:

1.3.7 Structural Bioinformatics Laboratory

Mark S. Johnson, Ph.D., Professor, Department of Biochemistry and Pharmacy, Åbo Akademi University

The Structural Bioinformatics Laboratory (SBL) has a unique combination of expertise where the independent groups have formed a tight network, sharing the research facilities and infrastructure. The emphasis is on multidisciplinary research aiming to solve complex biological problems related to protein structure and function, molecular interactions, and gene/protein evolution. In addition, there is very strong emphasis on education and research training in the areas of molecular structure determination combining experimental approaches (x-ray crystallography) with computation methods (molecular modelling, computational chemistry and bioinformatics).

1.3.8 Molecular Imaging in Cardiovascular, Metabolic Research and Neuro Research

Juhani Knuutila, M.D., Ph.D., Professor, Turku PET Centre and Juha Rinne, Ph.D., Docent, Professor, Turku PET Centre

The Turku PET Centre has two major functions, high quality scientific research and diagnostic service for the whole country. The scientific research strategy involves four major topics: Cellular energy metabolism, Neurotransmission, Preclinical imaging and drug research and Radiochemistry research. PET is the only noninvasive method to study metabolic pathways in vivo in human tissues and it is well suited to the study tissue metabolism in cardiovascular and endocrinological

diseases and in malignant tumours. The research field has got The National Centre of Excellence status from Academy of Finland for years 2008-2013.

The purpose of the neurological project part of Turku PET Centre is to study normal ageing, cognitive brain functions and the etiology and pathophysiology and treatment of neurodegenerative diseases. In normal human brain the effect of ageing on neurotransmitter systems and especially the role of brain dopaminergic system in memory and language functions is investigated. Of the neurodegenerative diseases main focus is on Parkinson's disease and Alzheimer's disease.

1.3.9 Regulatory Networks and Natural Language Processing for Bioinformatics

Tapio Salakoski, Ph.D., Professor, Department of Information Technology, University of Turku and TUCS Bioinformatics Laboratory, Turku Centre for Computer Science (TUCS)

Protein-protein and protein-DNA interactions are a key to understand the fundamental mechanisms of biology. The research group is analysing the human genome to identify regulatory networks related to T cell differentiation. The current research is focused on a set of characteristic genomic sequence patterns based on newly identified regulatory sequence modules for transcription factors related to T cell differentiation. The research group is also analysing the protein complexes to find out the interacting cofactors. As a long term goal the research group is building an iterative generate-and-test cycle for two-way exploitation of the mutual information obtained by combining in silico modelling with in vitro and in vivo laboratory experimentation.

1.3.10 Turku Immunology Centre (TIC) Research Programme

Director: Arno Hänninen, Docent, Department of Medical Microbiology, University of Turku

Turku Immunology Centre (TIC) is a research and graduate programme, which was established in 1993 to bring together the research groups working here in the field of immunology, joining the groups of University of Turku, Åbo Akademi University and National Public Health Institute, Department of Turku. The main function of the research programme is to continue and further develop the long traditions of high quality research in basic and clinical immunology in Turku.

Main goals and prospects for the future of TIC include to better understand the development of the immune system from uncommitted stem cells to fully immunocompetent lymphocytes, to elucidate the mechanisms of pathogenesis of autoimmune diseases and allergy, to better comprehend the host-microbe interactions, necessary to provide improved means for effective fight against the infectious diseases, e.g. through vaccine development and to assess the relationships between microbial load, virulence and host tissues in relation to the development and normal function of the immune system, including the following:

- Innate and acquired immunity of the host
- Immune evasion factors and adaptation mechanisms of the microbes
- Microbes belonging to normal microbiota, and the use of probiotics and even prebiotics
- The use of viral vectors for gene therapies of autoimmune and /or infectious diseases

Description of TIC research projects related to Diseases of the CNS:

1.3.11 Targeting of Protein Effectors against Autoimmune CNS Disorder in the Mouse

Ari Hinkkanen, Ph.D., Professor, Department of Biochemistry and Pharmacy, Åbo Akademi University

The research group focuses on the basic replication mechanisms of alphaviruses as well as their potential as tools for central nervous system (CNS) gene delivery and cancer targeting. The group applies neurotropic non-neurovirulent viral vectors for gene delivery (anti-inflammatory lymphokines and protein growth factors) into the central nervous system to inhibit autoimmune inflammation and myelin damage. These studies will provide new information on the factors necessary to activate myelin repair. The research group has shown that avirulent recombinant viral vectors given systematically and expressing IL-4, TGF- β or protease inhibitors are capable of entering CNS, producing effectors proteins and reducing neurological symptoms.

1.3.12 Herpes Simplex Virus Vectors in Gene Therapy

Veijo Hukkanen, M.D., Ph.D., Docent, Academy Research Fellow, Department of Virology, Faculty of Medicine, University of Turku

Herpes simplex virus (HSV) is a ubiquitous alphaherpesvirus, best known as the causative agent of recurrent labial herpes (cold sores). Attenuated neurotropic vectors, derived from herpes simplex viruses (HSV), can be utilised in gene therapy of autoimmune and other diseases of the central nervous system (CNS). The research group has established the use of replicative, neuroattenuated HSV vectors for gene therapy of the experimental autoimmune encephalomyelitis (EAE), as a model for therapy of multiple sclerosis. The research group uses HSV vectors coding for murine Th2 cytokines and develops new HSV vectors carrying genes of other immunoregulatory factors. For the construction of vectors, the research group will apply the bacterial artificial chromosome (BAC) technology. The research aims also to improve the delivery of the HSV vectors into the CNS by developing the routes for vector inoculation, based on the natural routes of HSV for CNS entry. The spread and effects of HSV vectors in the CNS can probably be facilitated in combination with immunomodulating chemotherapy, which the research group studies in the context of EAE therapy. The innate and adaptive responses to HSV and HSV vectors are a subproject topic in the studies, and the research group

searches for the interference of certain HSV immune stealthing genes with the innate host response. The research group study also the latent infection of HSV and vectors derived thereof. The research group has established a model for treatment of cell transformation by human papillomaviruses (HPV) using antisense element-expressing HSV vectors. The research group develops modern molecular methods for detection of herpesviruses and their gene transcripts in tissue samples and in clinical specimens, thus improving the diagnostics of severe herpesvirus infections. The molecular diagnostic techniques are also used to study the relationship of herpesviral infections with certain chronic CNS diseases.

2. BIOTURKU[®] COMPANIES AND THE PRODUCT AND PROJECT PORTFOLIOS

Bayer in Finland (www.bayer.fi)

Company Profile:

Bayer is a global enterprise with core competencies in the fields of health care, nutrition and high-tech materials. The company's products and services are designed to benefit people and improve their quality of life. In Finland Bayer Oy focuses on marketing the product portfolio of Bayer Group in Finland: OTC products of Bayer Consumer Care, equipment for monitoring diabetes therapy from Bayer Diabetes Care, prescription drugs of Bayer Schering Pharma, crop protection products and pesticides from Bayer CropScience as well as materials and chemicals for industry from Bayer MaterialScience. Bayer Schering Pharma Oy focuses on the international business of prescription drugs: research and development, production, and export of products to over 100 countries. The plant in Turku is one of the global pharmaceutical production plants of the Group. In Finland Bayer employs more than 700 persons and their offices are located in Turku and Espoo.

Product and project Portfolio:

Products from the plant in Turku: MIRENA[®] - hormonal intrauterine system, JADELLE[®] - contraceptive implant, NOVA T[®] and NOVA T[®] 380 copper intrauterine devices, BONEFOS[®], a product for supportive cancer therapy, RECOFOL[®], a short-acting anaesthetic and TAMOFEN[®], a product for the treatment of breast cancer.

Biotie Therapies Corp. (www.biotie.com)

Company Profile:

Biotie is a drug discovery and development company focused on central nervous system and inflammatory diseases. It has a broad range of innovative small molecule and biological drug candidates at different stages of clinical and pre-clinical development. Biotie's products address diseases with high unmet medical need and significant market potential, including addiction and psychotic disorders, rheumatoid arthritis, psoriasis and chronic obstructive pulmonary disease (COPD). The most advanced product, nalmefene for alcohol dependence, is currently in phase III clinical development by licensing partner H. Lundbeck A/S. The commercial value of the pipeline has been demonstrated through existing alliances with top-tier global pharmaceutical companies such as Lundbeck, Roche and Pfizer. Biotie has operations in Turku, Finland and Radebeul, Germany. Shares are listed on NASDAQ OMX Helsinki Ltd.

Product and project Portfolio:

Biotie's lead product, the opioid receptor antagonist nalmefene, is in phase III clinical trials for the treatment of alcoholism. The Company has licensed worldwide marketing and development rights to Lundbeck, a leading CNS company. Also in the CNS field, Biotie is developing phosphodiesterase 10 (PDE-10) inhibitors for schizophrenia; Pfizer has licensed certain rights to this programme, and a research collaboration between the companies has recently identified a clinical drug candidate. In the inflammatory disease area, Biotie is developing both a monoclonal antibody and a small molecule inhibitor of the VAP-1 protein; Roche has options to license both of these programmes. The VAP-1 mAb is currently in clinical trials in rheumatoid arthritis and psoriasis. A phosphodiesterase 4 (PDE-4) inhibitor is also in

clinical trials, and is a potential treatment for chronic obstructive pulmonary disease (COPD) and other inflammatory diseases. Biotie also has several discovery and early development projects in different stages from hit discovery to lead optimization underway, including PDE-2 inhibitors and $\alpha 2\beta 1$ integrin inhibitors.

H.Lundbeck Oy Ab (www.lundbeck.fi)

Company Profile:

Oy Lundbeck Ab, founded in 1985, is the Finnish subsidiary of H. Lundbeck A/S, an international pharmaceutical company established in 1915. Its focus is on the research, development and marketing of medicines for the treatment of psychiatric and neurological diseases. The company is the market leader in the field of depression medicines.

Product and Project Portfolio:

Lundbeck is specialized in medicines for the central nervous system and neurology, e.g. depression (Cipralex[®]), schizophrenia (Serdolect[®]), Alzheimer's disease, dementia and amnesia (Ebixa[®]) and Parkinson's disease (Azilect[®])

HyTest Ltd (www.hytest.fi)

Company Profile:

HyTest Ltd., founded in 1994, offers innovative solutions for assay development and research applications by providing high-quality immunological reagents in such areas as cardiac markers, infectious, neuroscience and autoimmune disease reagents. HyTest is a leading provider of several reagents such as antibodies and antigens of the troponin I and troponin complex. HyTest offers also extensive customer services and has a certified ISO 9001:2000 quality system.

Product and Project Portfolio:

Immunological reagents.

Orion Corporation, Orion Pharma (www.orion.fi)

Company Profile:

Orion is a pharmaceuticals and diagnostics company dedicated to treating and preventing disease by discovering and developing innovative medicinal treatments and diagnostic products for global markets. Orion is engaged in human and veterinary drugs, active pharmaceutical ingredients and diagnostic tests. Orion's corporate headquarters and most of the supply chain and R&D operations are located in Finland. The company's own marketing organisation is almost European-wide. Partnerships and networking are one of the key elements in Orion's business strategy. Orion is listed on the NASDAQ OMX Helsinki stock exchange. Corporate homepage www.orion.fi/en

Product and Project Portfolio:

Orion Pharma is the pharmaceuticals business division of the Orion Group. Its businesses consist of proprietary and generic medicines for humans and animal health, as well as active pharmaceutical ingredients. Orion's pharmaceutical research operations mainly engage in the first phases of the research process, the preclinical research aiming at creating new drug molecules for the subsequent clinical trials in patients. The prioritised therapeutic areas are CNS (Central Nervous System) and OCC (Oncology & Critical Care).

Joint cross-organisational work and collaboration within Orion Pharma has markedly contributed to the extensive knowledge on role of $\alpha 2C$ adrenoceptors in the

functions of the central nervous system. This knowledge is being leveraged to harness the use of selective antagonists at alpha_{2C} receptors to treat various psychiatric and neurological diseases still coping with major unmet medical needs. Furthermore, the deep cutting-edge understanding held by Orion of the handling of perorally taken dopamine precursor in the periphery and the brain is being used for the optimisation of this most potent treatment of Parkinson's disease, one of the major movement disorders in humans.

Novel and innovative CNS disorder mechanisms and models are being investigated while also performing chemistry and in vitro optimisation of the most promising compound families both in Orion and within collaboration network. In future, the platform of alpha_{2C} adrenoceptors and other G-protein coupled receptors, ion channels, nuclear receptors and enzyme inhibition approaches will be leveraged to discover additional medically relevant druggable targets in the treatment of humans and animals.

Turku Imanet Oy (www.imanet.com)

Company Profile:

Turku Imanet Oy is part of GE Healthcare's Global Imaging Network/Imanet working in collaboration with Turku PET Centre. Turku Imanet provides pharmaceutical companies with imaging solutions to accelerate and facilitate development of novel therapeutics.

Product and Project Portfolio:

Identification of new molecules or techniques for diagnostic use, development of new PET tracers and preclinical and clinical studies for the pharmaceutical industry.

Vitabalans Oy (www.vitabalans.fi)

Company Profile:

Vitabalans Oy was founded in 1980 and employs 160 people. The company develops, manufactures and markets prescription pharmaceuticals, self-care preparations, health food supplements and health care products for animals.

Product and Project Portfolio:

Pharmaceutical development, manufacturing and marketing of pharmaceuticals, e.g. pain killers, infection medication, nutraceuticals, etc.

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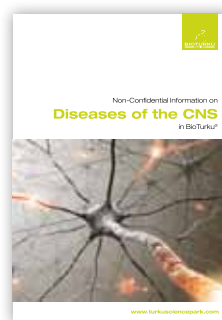
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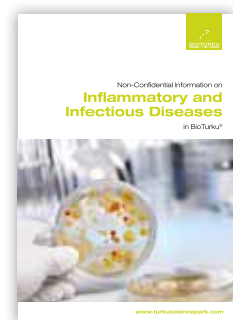
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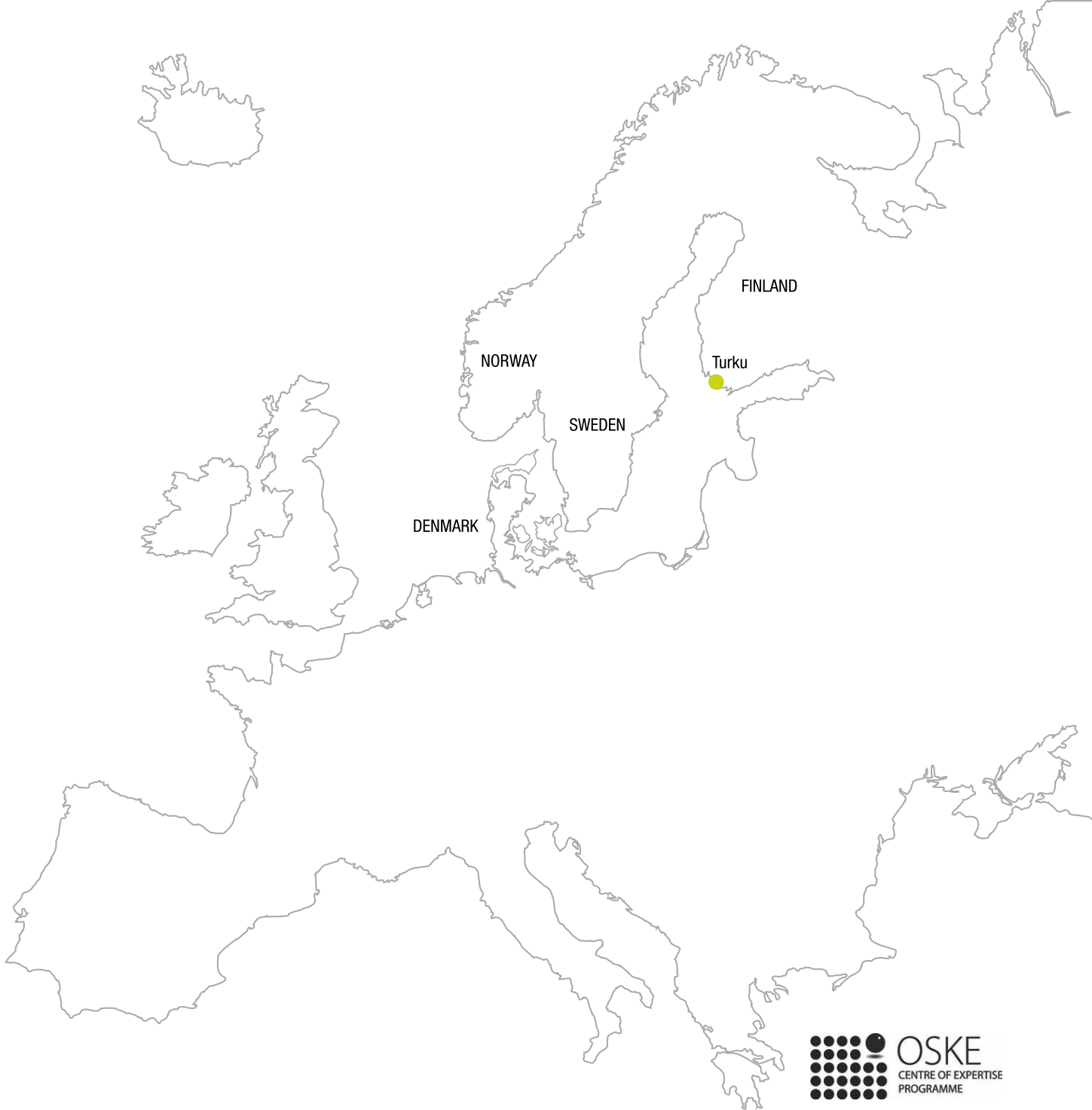


Inflammatory and
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