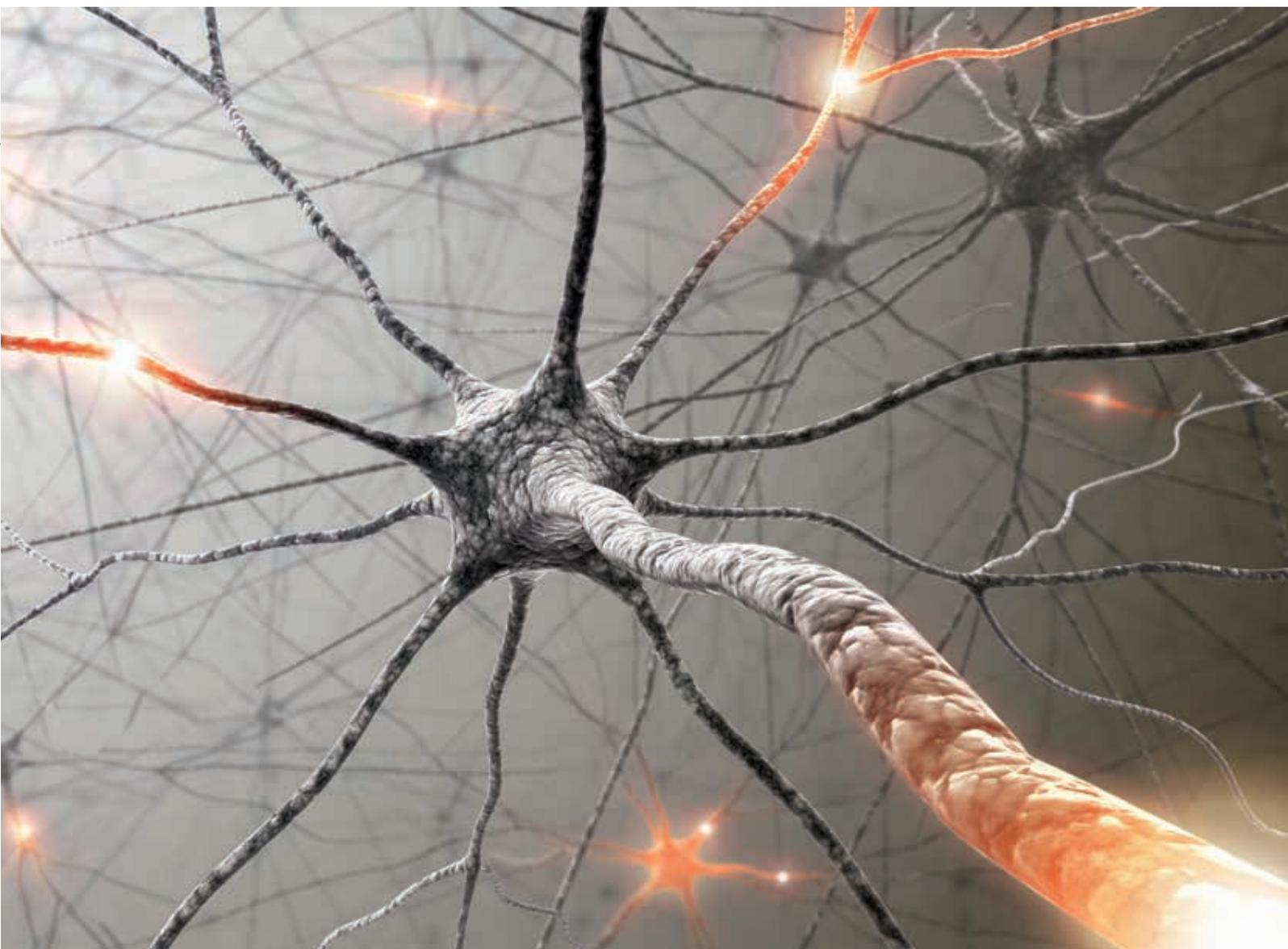


Non-Confidential Information on
Diseases of the CNS
in BioTurku[®]





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

BioTurku® Science 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.

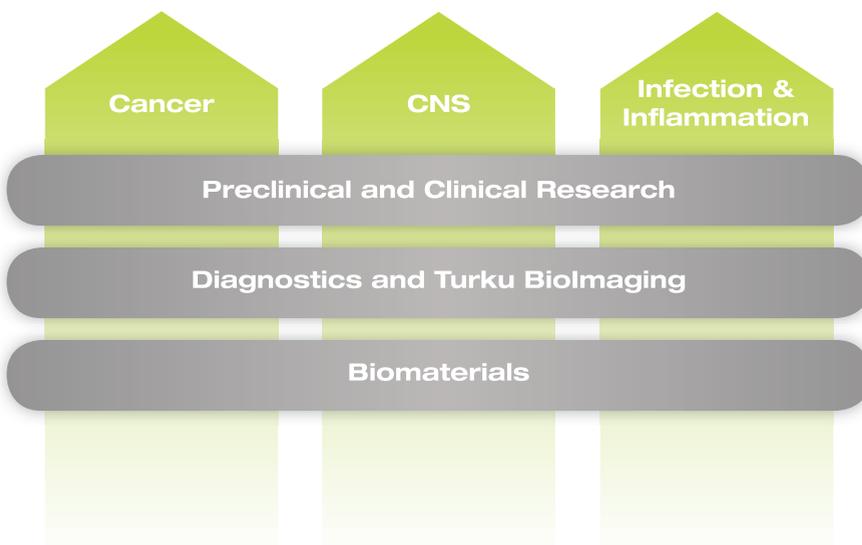
The key competence areas in BioTurku are preclinical and clinical drug research and development, diagnostics and biomaterials. The three therapeutic areas, within these competence areas, are cancer and hormonal diseases, inflammatory and infectious diseases and diseases of the central nervous system. 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.

Turku Brain and Mind Center (TBMC) (www.tbmc.fi) was created in 2011 and gathers twenty research groups from various fields of neuroscience in Turku. TBMC groups are pioneers in systemic neuroscience, molecular neuroscience and brain imaging. A key endeavour of TBMC is to facilitate collaboration with commercial enterprises and pharmaceutical companies, thereby helping to bridge the gap between academic neuroscience research and drug development.

Further information: www.turkusciencepark.com

BioTurku® – Regional Strengths



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1. RESEARCH INFRASTRUCTURE AND PROGRAMMES 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.

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

CRST is a university-based contract research organization (CRO) that conducts clinical, preclinical and bioanalytical studies for the pharmaceutical industry and for other customers. CRST is run by experienced specialists with in-depth understanding of basic and clinical pharmacology and analytical chemistry, especially in therapeutic areas such as disorders of the central nervous system, metabolic diseases and cancer. The services cover clinical drug development from Phase I to Phase IV and bioanalytical and pharmacokinetic services related to clinical and preclinical trials of new pharmaceuticals. Early-phase clinical trials employing imaging (PET and other modalities) and other efficacy biomarkers form the core competence area of CRST.

Functional Foods Forum (FFF) (<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.

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.

Turku BioImaging (www.bioimaging.fi)

Turku has genuine traditions in imaging research. The Turku BioImaging 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 Brain and Mind Center (TBMC) (www.tbmc.fi)

The center was created in 2011 and gathers twenty research groups from various fields of neuroscience in Turku. TBMC groups are from the University of Turku and Åbo Akademi University. We are pioneers in systemic neuroscience, molecular neuroscience and brain imaging. TBMC researchers work in multi-disciplinary teams to explore the mechanisms underlying brain function in health and disease. In addition to scientific research, we provide high-level specialized education (PhD and postdoctoral level) to young scientists with a keen interest to excel in the field of neuroscience. Our teams carry out internationally competitive research and aim to break new horizons in neuroscience. World class academics from the University of Turku, Åbo Akademi University together with our collaborators will help in achieving this goal. A key endeavour of TBMC is to facilitate collaboration with commercial enterprises and pharmaceutical companies, thereby helping to bridge the gap between academic neuroscience research and drug development.

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

TCDM is a research infrastructure at the Faculty of Medicine, University of Turku, providing state-of-the-art facilities and expertise for experimental *in vivo* studies. TCDM focuses on the use of genetically modified mice and tumor xenografts in immuno compromised mice. The center carries out both academic and industry associated non-clinical research, and its facilities are also available for contract research.

Turku Centre for Biotechnology (CBT) (www.btk.fi)

CBT is a joint independent department of the University of Turku and Åbo Akademi University. The Centre provides technical expertise and coordinating services for academic and industrial projects in several central areas of biotechnology. The centre also provides a forum for active interactions between academia and industry. The central areas of research are cell signalling, regulation of gene and protein expression and systems biology focusing on neuroscience, oncology, stem cell research and immunology. CBT has strategically invested in the development of state-of-the-art platforms in areas such as genomics, functional genomics, proteomics, cell imaging and bioinformatics supporting -omics technologies. In addition to serving local needs, based on national profiling of infrastructures, CBT further develops and provides national services in these key areas as well as some other areas (viral vectors, x-ray crystallography) within national infrastructure networks. As a part of CBT's infrastructure, the Central Animal Laboratory serves researchers campus-wide, enabling other functions such as disease modelling.

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

TCBC has special 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 head and neck surgery, cranio-maxillofacial surgery and orthopedics as well as in dentistry. TCBC offers custom-made bioactive composite implants for clinical research purposes. Several facilities are dedicated to particular tasks in the manufacturing, characterization and biomechanical testing of materials.

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

Turku Clinical Research Centre consists of units of its background organizations, the Hospital District of Southwest Finland and the University of Turku. The work of Turku CRC is aimed at enhancing the prerequisites for investigator initiated clinical research, ensuring a high quality of research, easing the investigators' workload of research administration, and intensifying research collaboration with external partners.

Turku PET Centre (www.pet.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 has 150 staff members and is equipped with e.g. 3 cyclotrons, 19 hot cells for GMP level tracer production, 6 PET or PET/CT scanners, 1.5 T MRI, PET/MRI (3.0T). The centre is ranked among the top 5 in the world. Collaboration between academic researchers and the pharmaceutical industry is active, and the research strategy of the centre involves five major topics: Molecular imaging in cardiovascular and metabolic research, neurotransmission in health and disease, oncology research, preclinical and translational research and PET radiochemistry research.

Turku University Hospital (www.tyks.fi)

The catchment area of highly specialised medical care in western Finland includes Turku University Hospital in the Hospital District of South-West Finland, Satakunta Hospital District and Vaasa Hospital District. The area has some 862 000 inhabitants. University Hospital's role is to coordinate both the medical care and the research and development of new diagnostic and therapeutic methods with other hospital districts and the PET Centre, University of Turku, and the biotech companies in the area.

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

VTT is a multidisciplinary expert organisation on technology development and business. VTT's special strength is its ability to create new, globally competitive technologies and innovations by combining knowledge and expertise in different fields. In VTT Turku, new high-throughput cell based screening methods and biochip technologies are developed and applied in drug development and diagnostics. The new technologies, such as organotypic 3D cell cultures, speed up the existing processes and also open up new therapeutic opportunities. Systems biology techniques are used to identify biomarkers for future diagnostic applications. Such biomarkers enable more precise diagnostics, and can be included in the new generation of diagnostic systems, combining biosciences with microelectronics and information technology.

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 multi-disciplinary research community consisting of over 100 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 Program
- Turku Centre for Systems Biology
- Program for Infection Biology and Infectious Diseases

2. RESEARCH PROJECTS RELATED TO CNS

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

2.1 Anesthesia Mechanisms

*Adjunct Professor (Docent) Harry Scheinin
Turku PET Centre, University of Turku*

The project aims to reveal the effects of anesthetic drugs on cerebral blood flow and metabolism, anesthesia mechanisms and explore the neural correlates of human consciousness. Such knowledge is important in optimizing anesthesia regimens for a compromised brain, in developing new anesthetic treatments and EEG-based methods to monitor the depth of drug-induced anesthesia/hypnosis in humans. The research methods include positron emission tomography (PET), quantitative electroencephalography (EEG) and heart rate variability (HRV). Unconsciousness induced by general anesthesia also constitutes also an excellent platform to study the neural basis of human consciousness. We have recently demonstrated, e.g., that the emergence of consciousness after general anesthesia is associated with the activation of a core network involving subcortical and limbic regions, i.e. phylogenetically old brain structures rather than the neocortex.

2.2 Cognitive control and age

*Professor Heikki Hämäläinen, Fii Takio
Department of Behavioral Sciences and Philosophy, Division of Psychology and Centre for Cognitive Neuroscience, University of Turku*

We have found a spatial perceptual bias (to the right hemifield) in normal subjects, which resembles hemispatial neglect/extinction of the left hemifield. This bias is age-dependent, being evident in children and elderly, and thus is closely related to early development and late decline of frontal cognitive control mechanisms. In future studies this relation of perceptual and cognitive control mechanisms will be studied in different environments, with different participant groups, and also with different brain imaging methods.

2.3 Development and Functioning of Very Low Birth Weight Infants from Infancy to School Age (PIPARI)

*Professor Leena Haataja
Department of Pediatric Neurology and Pediatrics, Turku University Hospital and University of Turku*

Prematurity itself, its causes and related intensive care predispose to brain injury. The neurodevelopmental impairments and learning problems are more frequent among preterm survivors compared to their full term peers. The PIPARI Study is a multidisciplinary follow-up project of a cohort of 232 preterm infants (<32 weeks of gestation or birth weight <1501 g) and 246 full term healthy control infants born at the Turku University Hospital during the years 2001-2006. The follow-up expands from antenatal measurements through neonatal care and imaging to school age.

Our main areas of expertise are neonatal intensive care and obstetrics, brain imaging, the assessment of parent-child interaction, child behavior and neurodevelopment. The aim of the project is to gain a comprehensive understanding of long-term functioning, disability and health of preterm infants and find risk factors as well as protective factors related to the outcome. The detailed knowledge of the pathogenesis and compensating mechanisms of the developing brain are crucial in order to prevent adverse outcomes.

2.4 Diagnosis, pathophysiological mechanisms, and neural modulation of neuropathic pain

*Satu Jääskeläinen, M.D., Ph.D., Professor
Department of Clinical Neurophysiology, University of Turku*

The group does both basic and clinical research on human experimental and clinical neuropathic pain utilizing investigations of the whole neuraxis from periphery to the cerebral cortex. Correct diagnosis is the basis for classification of pain, which in turn is the prerequisite for studies on e.g. pathophysiological mechanisms, treatment, risk factors, genetics, brain level mechanisms, and top-down modulation of neuropathic pain. Post-surgical nerve injury with or without pain as well as orofacial pain entities are utilized as clinical models of human neuropathic pain in the projects. The research group has developed and applies a wide range of neurophysiologic, psychophysical, and neuropathological methods for sensitive and accurate diagnosis neuropathy and neuropathic pain. These include ENMG, reflex recordings, and evoked potential techniques for large and small fibre systems, quantitative sensory testing, epithelial nerve fibre density from skin and mucosal biopsies, and navigated transcranial magnetic stimulation (TMS) for cortical mapping. In addition to the neurophysiologic biomarkers of neuropathic pain, the multidisciplinary group has utilized neurotransmitter PET of the brain dopamine and opioid systems, genetic studies, and structured psychiatric and clinical examinations in the evaluation of clinical pain and its risk factors. Most recent studies deal with mechanisms and effects of non-invasive neuromodulatory treatment of pain, depression, and tinnitus with repetitive TMS, enhancing at the brain level the endogenous top-down inhibitory control systems. The ultimate goal is to develop personalized treatment and find new treatment options according to the mechanisms revealed by comprehensive individual neurophysiologic and genetic profiling of the patients.

2.5 Etiology of Schizophrenia spectrum disorders

*Jarmo Hietala, Professor and Chairman
Department of Psychiatry, University of Turku and Turku PET Centre*

There is close local collaboration with Prof. Raimo Salokangas at the Dept. of Psychiatry within psychosis research and core facility researchers at the Turku PET Centre, and networking with groups in the USA, UK, France and Sweden. The group includes 2 post-doctoral researchers and 7 PhD students. The project goal is to advance knowledge on the etiology of diseases belonging to schizophrenia spectrum. In our opinion this is the only way of developing new effective treatments or even prevention of major psychiatric diseases, such as schizophrenia or affective psychoses. We use detailed clinical examination and methods of developmental psychology and neuropsychology in combination with modern structural and

functional brain imaging techniques such as positron emission tomography (PET) and magnetic resonance imaging (sMRI and fMRI). We also utilize the expertise of the high quality Finnish population research in our study designs. The specific neurotransmitter imaging studies within the project are internationally well recognized. They initially focused on dopamine have generated new hypotheses of neural circuitries involved in the biology of schizophrenia and lead to studies in GABA, glutamate, serotonergic and recently also peptidergic systems in patients with schizophrenia patients (e.g. Hietala et al Lancet 1995). The connectivity patterns of these neurotransmitter pathways are explored based on graph theory. This may lead to novel biomarkers and clinical applications within psychiatry. The major funding for the project is from the Academy of Finland, TEKES, EU Biomed and NIMH, USA, EVO-funding.

2.6 FinnBrain Birth Cohort Study

*Hasse Karlsson MA, MD, PhD, Professor of integrative neuroscience and psychiatry
Department of Psychiatry, University of Turku*

We investigate the interplay of genes and the environment in brain development and its relation to childhood neurobiological and psychosocial development and later morbidity, especially major depression, cognitive decline and coronary heart disease. We will collect a birth cohort (N=10000) by recruiting consecutive pregnant women from maternity clinics in Finland. The main hypothesis is that pathways leading to adverse psychosocial and health outcomes have their origin already in pregnancy and early childhood and are mediated by neurodevelopmental factors. This early programming is initiated by the interplay between hereditary and environmental factors, e.g. attachment, quality of care, stressful and traumatic life events and social support. Our multidisciplinary approach includes modern genetic and brain imaging methods in combination with psychiatric assessment of the parents and children, attachment research, assessment of the socio-economic situation and life events, registers and biological parameters to achieve these goals. A subgroup comprising mothers suffering from major depressive disorder, anxiety disorder or severe stress during pregnancy and their healthy controls (N=1000) will be studied especially carefully. Also the children in this subgroup will be in focus of attention and investigated e.g. using functional and structural brain imaging.

2.7 Finnish Brain Injury Research and Development: Traumatic brain injuries

*Olli Tenovuo, Docent of Neurology and Neurotraumatology
University of Turku and Turku University Hospital*

Vision: We aim to do high-level multidisciplinary clinical research, which tries to improve the diagnostics or care of TBIs or to reveal their pathophysiological mechanisms and factors influencing the outcome. The main principles in our research activities are national and international networking, close collaboration between clinical and basic research, continuous connection between clinical care and scientific research, and creation of internationally unique facilities for clinical research of TBIs. Our current research has the following mainstreams: 1) Modern brain imaging and transcranial magnetic stimulation as tools to reveal trauma-induced alterations in brain structure and function, 2) The role of the cholinergic system in TBIs, 3) Mechanisms of fatigue after CNS injury, 4) Depression and sequels of TBI, and 5) Long-term outcome after TBI. In addition, our international

collaboration aims at producing tools for evidence-based individual assessment and treatment planning of TBIs.

2.8 FucLa, Functional connectivity and Language

Pirjo Korpilahti, Ph.D., Professor of Logopedics, Eira Jansson-Verkasalo, Ph. D., Docent and Marjaana Raukola-Lindblom, Ph. Lic. Logopedics and Center of Cognitive Neuroscience, Department of Behavioral Sciences and Philosophy, University of Turku

The research objectives of this project are related to developing brain imaging methods in diagnostics and rehabilitation of developmental and traumatic deficiencies of communicative skills. The methodologies are targeted to deeper understanding of the connection between auditory processes, executive functions and language related brain activity. We also investigate the fundamental limitations arising both at behavioral level and neural network activity. The main techniques include testing of cognitive and linguistic skills, evaluation of social communication, ERPs (event related potentials) and fMRI of resting state functional connectivity. By using the latest techniques we aim to develop a novel mapping system of neurobiological bases of language and communication. The project is mainly conducted in collaboration with University Hospital of Turku, Imaging laboratory and University Hospital of Oulu, Department of Radiology.

2.9 G-protein coupled receptors in neuro-psychopharmacology

Mika Scheinin, M.D., Ph.D., Professor of Pharmacology, University of Turku and Turku University Hospital

The main focus of the group has been on a subfamily of the G-protein coupled receptors, i.e. the three subtypes of alpha2-adrenoceptors that mediate many of the physiological effects of the neurotransmitter noradrenaline and the adrenomedullary hormone adrenaline. The research interests and technologies of the group range from molecular and cellular studies to clinical trials. Preclinical studies employ gene-targeted mice to investigate the physiological and pharmacological roles of the receptors. Clinical investigations span a broad range of research methods, including mass spectrometric determination of drugs and biomarkers, psychological and physiological assessments and PET imaging.

2.10 Hereditary Diseases with Cognitive Impairment

Matti Viitanen, M.D., Ph.D., Professor of Geriatrics, Hannu Kalimo, M.D., Ph.D., Professor emeritus in Neuropathology Dept. of Clinical Medicine and Dept. of Forensic Medicine, University of Turku

Cognitive impairment often leads to dementia, which is rapidly increasing in an aging population. The familial occurrence of cognitive impairment is increasingly apparent, even if the clinical picture can vary between related individuals. Therefore we try to identify families with cognitive impairment in our out-patient clinics. We examine the patients clinically using blood samples and cerebrospinal fluid and different imaging techniques (MRI and PET scans). We try to verify the histopathological changes in the brain in autopsy. We use different genetic methods to identify possible genetic causes of disease. We investigate protein metabolism in cell lines in order to identify disease mechanisms that could be targeted by

treatments. Our main focus is on cerebrovascular diseases such as Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) and Multi-Infarct Dementia of the Swedish type.

2.11 Herpes simplex virus: host responses and gene therapy applications

*Veijo Hukkanen, MD, PhD, professor
Program for Infection Biology and Infectious Diseases (PIBID)
Department of Virology, University of Turku*

Herpes simplex virus (HSV) is a ubiquitous human virus. It is a promising backbone for gene therapy vector development. We have established the use of replicative, attenuated HSV vectors for gene therapy of the disease model for multiple sclerosis (MS), the autoimmune experimental encephalomyelitis (EAE). We develop novel HSV vectors utilizing the bacterial artificial chromosome (BAC) technology and study the gene therapy of nervous system diseases. We develop new HSV vectors expressing favorable cytokines or neurotrophic factors. We develop means of delivery, targeting, and imaging of the HSV vectors, as well as long-term transgene expression using the HSV latency promoter. HSV with marker transgenes are utilized in the research of viral latency and pathogenesis. We elucidate the cellular responses and innate immunity to HSV and HSV vectors, also in organotypic ganglion cultures and in long-term cultures of neuronal cells. We also study control of HSV infection by RNA interference.

2.12 Neuroendocrine mechanisms in the pathogenesis of obesity and metabolic syndrome

*Eriika Savontaus, MD, PhD, Academy Research Fellow
Research Program: CREDE
Department of Pharmacology, Drug Development and Therapeutics and Turku
Center for Disease Modeling, University of Turku*

Obesity, with its associated metabolic and cardiovascular diseases, is an increasing public health problem, and current therapies for obesity are insufficient. The neuropeptides neuropeptide Y (NPY) and melanocortins play key roles in the regulation of body weight. There is ample evidence both from experimental animals and humans that an overactive NPY system and an inactive melanocortin system leads to obesity. Therefore, these neuropeptides are attractive targets for anti-obesity drug development. We aim to understand the tissue-specific mechanisms of NPY and melanocortins in the regulation of energy balance and cardiovascular functions in order to facilitate drug development for metabolic diseases. We use transgenic mouse models and viral gene delivery combined with pharmacological and dietary interventions. The effects of the interventions on body weight and body composition, feeding behavior, locomotor activity, white and brown adipose tissue morphology and function, glucose and lipid metabolism and obesity biomarkers are investigated. Cardiovascular parameters are monitored with telemetric methods (blood pressure and heart rate), echocardiography and micromyography.

2.13 Neurofibromatosis Research Consortium

*Dr. Juha Peltonen, MD, PhD, Professor and Chair
Department of Cell Biology and Anatomy, University of Turku*

Mutations of the human NF1 gene cause the neurocutaneous-skeletal-ophthalmologic syndrome neurofibromatosis 1 (NF1). The deficiency of NF1 tumor suppressor / histogenesis factor impairs development and cell signaling. Our research penetrates into the question how a single mutation in the NF1 gene can cause the development of tumor masses, skeletal disfigurement, speech defects, and tumors of the eye and the optic pathway. The translational approach from molecules to patients is carried out in an environment that includes the Institute of Biomedicine/Department of Cell Biology and Anatomy and the Department of Dermatology, which hosts the Neurofibromatosis Clinic.

2.14 PET Imaging in Neurology

*Juha Rinne, MD, PhD, Professor
Turku PET Centre*

The purpose of the neurological project of Turku PET Centre is to study normal ageing and cognitive brain functions both in health and disease. Dopamine has been studied in relation to motor and cognitive performance and impulse control disorders. Recently, the important role of brain dopamine in the positive effects of cognitive training was demonstrated in healthy volunteers. Neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease are the main topics in neurological diseases. The research includes multi-tracer and multimodal imaging combined with clinical investigations to enable elucidation of the etiology and pathophysiology of the disorders. In addition, PET has been used to develop new treatments for neurological diseases and to demonstrate their effects in the brain.

2.15 Radio-frequency electromagnetic fields and the human brain

*Professor Heikki Hämäläinen, Myoung Soo Kwon
Department of Behavioral Sciences and Philosophy, Division of Psychology and Centre for Cognitive Neuroscience, University of Turku*

We have applied behavioral, EEG and brain imaging methods to reveal the possible effects of radio-frequency electromagnetic fields (EMFs) emitted by a GSM mobile phone on human cognition and brain activity. Both behavioral and EEG measures show no effects of short term exposures of EMFs on cognition and brain activity in either adults or children, whereas PET studies indicate that exposure duration may play a significant role, longer duration exposures having a decreasing effect of glucose metabolism and blood circulation in the human brain.

2.16 Status epilepticus in the immature brain: Regulators of neuronal damage and neuroprotection

*Irma Holopainen, docent, MD, PhD
Pharmacology, Drug Development and Therapeutics, University of Turku and Medicity Research Laboratory*

Epilepsy, a chronic neurological disorder affecting about 1% of the population, occurs more frequently in children than in adults. Also prolonged seizures, status epilepticus (SE) are more frequent in children than in adults. Albeit this, molecular mechanisms of SE-induced neuronal damage are surprisingly poorly known in the immature brain. The aim of our studies is to find out the contribution of inflammatory processes to neuronal damage in the hippocampus, the seizure-prone temporal lobe structure. Kainate (KA)-induced SE is used as a damage model in rats of different postnatal ages. Organotypic hippocampal slice cultures (OHCs), treated with KA, serve as an *in vitro* model. The supposed beneficial effects of anti-inflammatory and new antiepileptic drugs on neuronal survival will be studied in these models. This project is of high clinical importance, since SE is a significant neurological emergency that may lead to deleterious long-term consequences - chronic epilepsy, developmental delay, and cognitive impairment in children.

3. BIOTURKU® COMPANIES AND THE PRODUCT AND PROJECT PORTFOLIOS

Bayer Oy (www.bayer.fi)

Company Profile:

Bayer is a global enterprise with core competencies in the fields of health care, nutrition, and high-tech materials. Our products and materials are designed to benefit people and improve their quality of life. Our product portfolio in Finland includes Bayer HealthCare prescription medicines, over-the-counter products and tools for monitoring diabetes therapy, Bayer CropScience crop protection agents and control substances as well as industrial materials and chemicals of Bayer MaterialScience. Our international operations in Finland focus on prescription medicines: research and development, production, and export to over 100 countries of products manufactured in Finland. The production plant in Turku is one of the global pharmaceutical supply centers of the Bayer Group. In our research and development, the use of polymers in long-term administration of drugs represents the Finnish expertise. Bayer employs about 750 people in Finland.

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 and TAMOFEN®, a product for the treatment of breast cancer.

Biotie Therapies Corp. (www.biotie.com)

Company Profile:

Biotie is a specialized drug development company focused on the development of drugs for neurodegenerative and psychiatric disorders (e.g. Parkinson's disease, Alzheimer's disease and other cognitive disorders, alcohol and drug dependence (addiction) and post traumatic stress disorder), and inflammatory and fibrotic liver disease. The company has a strong and balanced development portfolio with several innovative small molecule and biological drug candidates at different stages of clinical development. Biotie's products address diseases with high unmet medical need and significant market potential. Partnerships with top-tier pharmaceutical partners are in place for several programs as well as a strategic collaboration with UCB Pharma S.A. The Marketing Authorization Application for Biotie's most advanced product, Selincro™ (nalmefene) for alcohol dependence was filed in the EU by our partner H. Lundbeck A/S and was accepted for review by the European Medicines Agency in December 2011. Biotie shares are listed on NASDAQ OMX Helsinki Ltd.

Product and project Portfolio:

Selincro™ (nalmefene) – alcohol dependence, opioid antagonist is in commercial phase (H.Lundbeck Oy AB). Tozadenant (SYN115) – Parkinson's disease, adenosine A_{2a} antagonist is in Phase II (moving to Phase III, licensed by UCB Pharma). SYN120 – AD/cognitive disorders, 5-HT₆ antagonist is ready for Phase II (seeking partner, option agreement with Roche). VAP-1 antibody – inflammatory/fibrotic disease, VAP-1 antagonist fully human, is ready for Phase II (seeking partner for further development, Asia-Pacific rights licensed to Seikagaku). Nepicastat (SYN 117) – ¹cocaine dependence DBH inhibitor and ²PTSD (¹ Start Phase2 in Q1 2013, ² PTSD did not meet endpoint). Seeking partner for

development of Ronomilast – COPD, PDE4 inhibitor and Nitisinone (SYN 118) – movement disorders, HPPD inhibitor.

- 1) ¹⁾US National Institute on Drug Abuse (NIDA) to fund clinical study
- 2) ²⁾Post Traumatic Stress Disorder; clinical study conducted by US Department of Defense

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

Company Profile:

Oy H. Lundbeck Ab, first founded in 1928, is the Finnish subsidiary of H. Lundbeck A/S, an international pharmaceutical company established in 1915. Its focus is on the research, development, production and marketing of medicines for the treatment of psychiatric and neurological diseases.

Product and Project Portfolio:

Lundbeck is specialized in medicines for the central nervous system and neurology, e.g. schizophrenia, depression, bipolar disorder and Alzheimer's and Parkinson's disease. Our product portfolio currently consists of Sycrest, Azilect, Serdolect, Cipralext, Ebixa, Cipramil, Sepram, Cisordinol, Cisordinol-Acutard, Fluanxol, Noritren and Truxal. We are continuously bringing new, more efficacious innovative treatments into market.

HyTest Ltd (www.hytest.fi)

Company Profile:

Hytest Ltd, founded in 1994, offers innovative solutions for assay development and re-search 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 also offers extensive customer services and has a certified ISO 9001:2000 quality system.

Product and Project Portfolio:

Immunological reagents.

Montisera Ltd (www.montisera.com)

Company Profile:

Montisera develops bioactive compounds and sells them onwards for commercialization. Mission is to make molecule development more efficient and to offer high-value, low-risk investment opportunities. Projects bring together investors, candidate molecule owners, contract research organizations and drug & biotechnology companies. Lean organization with experienced professionals. Founded in March 2012.

Product and Project Portfolio:

Montisera makes molecule development more efficient and offers higher-value, lower risk investment opportunities. Our mission is to provide our customers with a fast and cost-effective way to develop lead molecules from discovery through clinical proof of concept.

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 two therapeutic areas are CNS (Central Nervous System) and OCC (Oncology & Critical Care).

Orion has dedicated research teams and tools to identify and characterise novel compounds. The research has yielded several novel and innovative lead candidates that deserve further characterisation to relieve their full potential.

Orion's early phase research has also yielded a number of highly potent antagonists for certain steroid-dependent pathways. Basic research over the years has confirmed that pathways inhibited by these compounds play a critical role in certain hormone-dependent and -refractory cancers (e.g. prostate cancer).

Novel and innovative cancer 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 platforms of nuclear receptors enzyme inhibition, G-protein coupled receptors and, ion channels, approaches will be leveraged to discover additional medically relevant druggable targets in the treatment of humans and animals.

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.

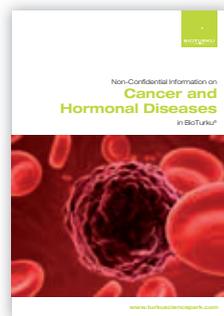
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- 5500 university students
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- 100 new Doctors (PhD/MD) annually

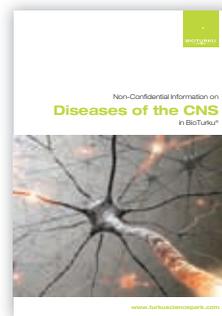
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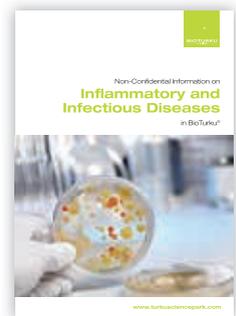
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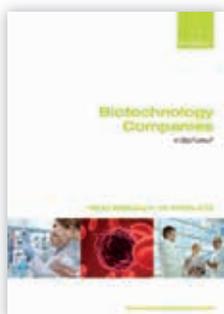


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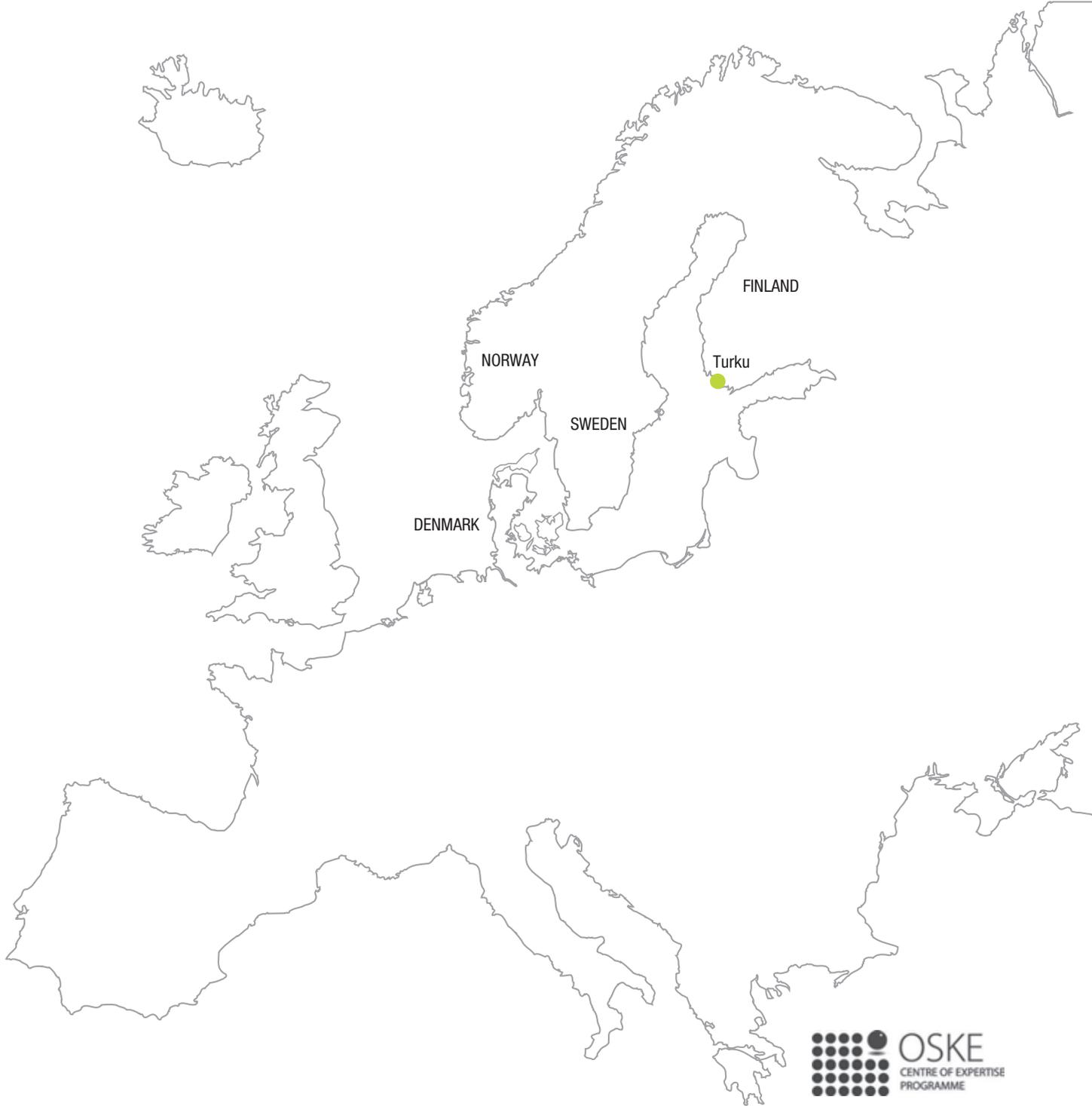


Inflammatory and
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