PORT for Health: Neuroscience

4–6th September 2023

PORT for Health:
Neuroscience

Ministry of Education and Science
Republic of Poland

PORT for Health is a conference series that brings together scientists, clinicians, and industry professionals, creating a forum of interdisciplinary knowledge exchange to facilitate novel collaborations. These meetings are dedicated to exploring specific topics that are highly relevant to human health, such as neuroscience and oncology. The conferences delve into various themes, including the underlying molecular mechanisms of human diseases, the development of physiological models, the identification of new drug targets, and the advancements in targeted treatments within the field of personalized medicine.

The organizer behind PORT for Health is Łukasiewicz Research Network – PORT Polish Center for Technology Development, located in Wrocław. The Life Sciences and Biotechnology Center at Łukasiewicz – PORT is committed to addressing the most pressing challenges of modern medicine through cutting-edge translational research conducted by teams led by visionary and experienced leaders. Within our Center, the neurobiological branch focuses specifically on unraveling the molecular and cellular foundations of psychiatric diseases, which are among the most significant health and socioeconomic issues in the world today.

This year edition of PORT for Health: Neuroscience 2023 focuses on biological models and computational approaches to understand brain disorders. Participants will have the opportunity to listen to over 20 lectures presenting the latest research findings and achievements in the field of neuropsychiatry, neurodegeneration, and neuro-metabolic disorders.

The PORT for Health: Neuroscience 2023 conference is a part of the SAME-NeuroID project, funded by the Horizon Europe Twinning program. More information about the event and its summary can be found on the website: https://health.port.org.pl/.

Łukasiewicz
PORT
Polish Center
for Technology
Development

Łukasiewicz – PORT Polish Center for Technology Development is a scientific and research institute. Our dedicated team of scientists engages in both fundamental research and the development of innovative technologies for various industries.

The institute's scientific and research endeavors are organized into three centers: Life Sciences and Biotechnology (LS&BC), Population Diagnostics (CPD) and Material Sciences and Engineering (MS&EC). These centers house specialized Research Groups, supported by state-of-the-art measurement laboratories and core facilities. Łukasiewicz – PORT also houses a biobank, Polish National Node (PNN) of the BBMRI-ERIC network.

The Life Science & Biotechnology Center is a forward-thinking institution with a strong focus on research, development, and implementation. It addresses significant societal challenges and cultivates expertise in neurobiology, oncology, and broad biotechnology applications.

Located within the historical Pracze Campus, Łukasiewicz – PORT features architecturally impressive buildings dating back to the turn of the 19th and 20th centuries, enveloped by lush green surroundings. Within these brick walls, modern laboratories equipped with world-class facilities enables both applied research projects and fundamental scientific investigations.

Since 2019, our institute has been a proud member of the Łukasiewicz Research Network, the third-largest research network in Europe. With a collaborative network spanning over 20 institutes across Poland, our shared objective is to foster stronger connections between academia and the business sector.

SAME-NeuroID

STANDARDIZED APPROACHES TO MODELLING AND EXAMINATION OF NEUROPSYCHIATRIC DISORDERS

Project number: 101079181, HORIZON-WIDERA-2021-ACCESS-03-01

The SAME-NeuroID project, a collaborative initiative between **Łukasiewicz – PORT** and leading European neuroscience institutions, including **the Paris Brain Institute, Max Planck Institute for Psychiatry in Munich**, and **Erasmus Medical Center in Rotterdam.** This partnership facilitates the sharing of resources, expertise, and data, accelerating research in neuropsychiatry models and expanding collective knowledge.

The SAME-NeuroID project is funded by the Horizon Europe Twinning Program which enhances networking activities between research institutions of the Widening countries as Poland acting as coordinators, and top-class European counterparts, promoting excellence through knowledge transfer and exchange of best practices.

Neuropsychiatric Research

According to the leading concept of exploring neuropsychiatric disorders it is desired to delineate the neurobiological basis of individual phenotypes associated with disease and investigate them at the respective level (circuit, cell, pathway, gene). The answer to those needs is the collaborative network of laboratories equipped with similar toolbox. This would allow linking drug efficacy with genetic profiles of patients and its consequences for cellular physiology, as well as associating such phenotypes with animal counterparts, largely unachievable given the heterogeneity of tools employed at distinct research units.

In line with the research plan and technology transfer the project hosts various events, including **the Bench-to-Bedside** meeting for senior staff, where experts share insights on translating ideas into medicine, conducting clinical trials, implementing appropriate actions. Additionally, training courses cover topics like grant applications, presentations and publications, regulatory requirements, data management, and gender equality.

To showcase its commitment to innovation and collaboration, SAME-NeuroID organizes the Match Treat Hackathon. This event brings individuals together to collectively address the challenges of neuropsychiatric disorders and develop innovative solutions. The Hackathon represents a unique opportunity to harness collective intelligence and select the best ideas for pre-incubation and product design.

SAME-NeuroID builds a network of commercial and academic collaborators through seminars on project topics and two editions of the PORT for Health: Neuroscience conference. These events encourage interdisciplinary discussions and knowledge sharing, fostering collaboration and scientific synergy among experts, researchers, and industry professionals.

Communication

With the activities and results of the project, we would like to reach not only scientific community but also general public to talk about the societal burden and importance of neuropsychiatric diseases. The scientists need to develop more opportunities for science and policy makers to interact. The European perspective is far from the regional one. We plan to reach the added-value of our project and approach decision makers and stakeholders in the health system and to take full advantage of the collaboration and play a significant role in systemic change in Łukasiewicz – PORT and beyond.

Would you like to give a lecture, become a part of the SAME-Match-TREAT platform, take part in the PORT-Neuroscience conference in 2025 or follow experts talks and discussions on YouTube?

For more information about SAME-NeuroID and its initiatives, please visit: **same-neuroid.eu**

Education

Education is a key pillar of SAME-NeuroID, aiming to increase the availability of experienced researchers and well-trained young talents. Schools for Excellence provide young investigators access to world-class educational programs and opportunities to build international networks of collaborators. The PORT-Neuro Summer School targets talented undergraduate students to inspire curiosity about our research topics.

SAME-NeuroID introduces the SAME Match Treat platform, connecting young scientists and providing support for idea exchange. It serves as a forum for emerging researchers to connect with mentors, collaborators, and potential career pathways, facilitating networking and knowledge exchange.

Conference Committee

Michał Ślęzak, PhD

Head of the Biology of Astrocytes Research Group

Michal received the PhD at the Louis Pasteur University in Strasbourg (Frank W. Pfrieger's lab) and accomplished postdoctoral training in Inst. Pharmacology PAS in Cracow (Young Investigator Award, Polish MSHE) and in VIB, KU Leuven (Marie-Curie Intra-European Fellowship). In 2016, he won a prestigious competition at BioMed X Institute to lead a team sponsored by Boehringer Ingelheim Pharma. At PORT, his team focuses on the role of astrocytes in brain physiology and pathology.

„In recent years, we discovered aberrations in the molecular program of astrocytes elicited by chronic stress in rodents. Likewise, the transcriptional analysis of post-mortem human brain samples provided evidence for the impairment of fundamental functions of astrocytes in depression. Currently, the team combines genetic manipulations with state-of-the-art functional imaging to investigate the contribution of astrocyte-specific pathways to neurobiological symptoms of psychiatric diseases".

Witold Konopka, PhD

Head of the Neuroplasticity and Metabolism Research Group

Witold received the PhD at Nencki Institute in Warsaw and accomplished postdoctoral training at German Cancer Research Center (DKFZ), Heidelberg (Guenther Schuetz lab). From 2012 he ran the Laboratory of Animal Models and in 2014–2018 he was a deputy director for scientific affairs at the Nencki Institute.

„In the PORT Research Group, we study the precise mechanisms that regulate peripheral metabolism by the brain. We focus on regulation of eating – especially the feeling of hunger and satiety. We are interested in how neurons modify their activity in response to both internal and external signals, informing the brain of such physiological states. Understanding these phenomena will help in the fight against eating disorders such as anorexia and the pandemic of the modern world – obesity".

Tomasz Prószyński, PhD

Head of the Synaptogenesis Research Group

Tomasz received the PhD at the Max Planck Institute in Dresden (Kai Simons' lab) and accomplished postdoctoral training at Harvard University (Joshua Sanes' lab). In 2013-2020, he was leading a Laboratory of Synaptogenesis at the Nencki Institute where he was a member of the Scientific Council for two cadencies. Co-organizer of European Muscle Conference, Neurons in Action, and „Actin and actin-binding proteins in health and diseases 2022". His recent publication (Rojek K. et al., Plos Biology 2019) has been awarded the Konorski Award for the best publication in neuroscience performed predominantly in Poland.

„Laboratory of Synaptogenesis studies molecular mechanisms that regulate neuromuscular junctions in the peripheral nervous system as well as synapses and neuronal organization in the brain. We are particularly interested in understanding the function of the Anigiomotin family of proteins and the Hippo pathway signaling in the central nervous system".

Agnieszka Krzyżosiak, PhD

Head of the Mechanisms of Neurodegeneration Research Group

Agnieszka completed her PhD research at The Institute of Genetics and Molecular and Cellular Biology (IGBMC) in Strasbourg, France and received her cotutelle Ph.D. at the Louis Pasteur University in Strasbourg and Wrocław University of Science and Technology. She next accomplished the EMBO and HFSP funded postdoc at the Medical Research Council Laboratory of Molecular Biology (MRC LMB) in Cambridge, UK followed by the translational development of her scientific research in a spinoff biotech startup. At Łukasiewicz – PORT from February 2023.

"Agnieszka's lab is interested to understand how protein quality control (PQC) deregulation contributes to neurodegeneration. In her research, together with her colleagues, Agnieszka showed that PQC can be targeted for the therapeutic benefit against protein accumulation – an approach currently developed clinically. Building on that, with the use of patient-derived models, the aim of the lab is to scrutinize the PQC pathways in neurodegeneration in the aim to identify novel treatment strategies."

iPSC- and CRISPR-based brain tissue models recapitulate key features of neurodegenerative and neurovascular diseases

Dominik Paquet Keynote Speaker

Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Munich, Germany; Munich Cluster for Systems Neurology (SyNergy), Munich, Germany

Background

Brain research heavily depends on models recapitulating key aspects of human brain physiology and disease pathology. Human iPSCs have great potential to complement existing rodent disease models, as they allow directly studying affected human cell types. In addition, recent developments in CRISPR genome editing revolutionized how impacts of genetic alterations on disease formation can be investigated. Co-culture of disease-relevant iPSC-derived cells with disease-relevant mutations enables studying complex phenotypes involving cellular crosstalk.

Methods

By combining iPSC-, CRISPR- and tissue engineering technologies, we established new brain tissue models for AD and FTD using iPSC-derived cortical neurons, astrocytes, microglia, and oligodendrocytes, as well as a microfluidic model of the neurovascular unit (NVU) based on co-culture of endothelial cells, mural cells and astrocytes.

Results

Our technology provides highly controllable and reproducible 3-dimensional tissues with typical cell morphologies and functional features, including widespread synapse formation, spontaneous and induced electrical activity, network formation, microglial ramification, tiling and phagocytosis, as well as formation of barrier-containing vessels interacting with astrocytic end feet for the NVU model. Interaction between neurons, glia and vascular cells become evident on morphological and functional levels. The models can be long-term cultured in a postmitotic state without proliferation or cell death, thus providing a more controllable, reproducible, and long-lived alternative to cortical organoids currently used for 3D disease modelling.

CRISPR-engineering of disease-causing mutations for AD, FTD, or a neurovascular disease induced characteristic late-stage phenotypes, including protein misfolding and aggregation for AD/FTD models, or barrier impairment for models of the NVU.

Conclusions

We expect that our models will enable studies elucidating novel, potentially human-specific pathomechanisms and provide a human framework for translation and screening.

Enhancing cellular proteostasis as a strategy against misfolded proteins accumulation

Agnieszka Krzyżosiak

Research Group Mechanisms of Neurodegeneration, Łukasiewicz – PORT, Wrocław

Neurodegenerative diseases (NDDs) are devastating, age-related disorders, which despite substantial efforts remain largely uncurable. The incidence of NDDs rises dramatically in our aging population, which points to an urgent need to tackle these fatal diseases. The deposition of misfolded proteins in a cell is a defining feature of NDDs that points to the deregulation of protein quality control (PQC) pathways in NDDs. With that said, enhancing the PQC systems could serve as an attractive therapeutic strategy. We have validated this concept by identification of PQC-boosting selective phosphatase inhibitors. These eIF2α pathway-targeting small molecules readily crossed the blood-brain barrier and were safe upon chronic administration in vivo. Enhancing cellular proteostasis using those agents prevented the behavioral and molecular deficits in NDD mouse models as well as prevented neurodegenerative phenotypes development in human reprogrammed neurons, derived from patients by direct conversion of fibroblasts, a model retaining the genetic and epigenetic background of the disease. The beneficial effect of boosting PQC was recapitulated upon genetic manipulation of the pathway. This work demonstrates the disease-modifying potential of phosphatase inhibitors and points to the opportunities to identify therapeutic targets in neurodegeneration within the space of the protein quality control.

Modelling non-cell autonomous mechanisms of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) in vitro

Monika Myszczyńska

Dept. Neuroscience, Sheffield Institute for Translational Neuroscience (SITraN), Univ. Sheffield

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterised by motor neuron (MN) death. ALS is predominantly sporadic in origin, with only 10% of cases presenting a clear genetic cause. Of the different genetic mutations associated with ALS, a hexanucleotide repeat expansion in the C9orf72 gene represents the largest proportion of familial ALS patients. Regardless of the causative origin of ALS, 97% of all patients show mislocalisation of a key DNA and RNA-binding protein called TDP-43. TDP-43 and C9orf72 mutations, amongst others, are also present in frontotemporal dementia (FTD), thus putting ALS and FTD on a genetic spectrum.

Although MNs are the cells primarily affected, astrocytes and other glial cells have been shown to play a role in the disease. iAstrocytes show hallmarks of C9orf72 mutation, including a presence of nuclear RNA foci and cytoplasmic dipeptide repeat proteins, as well as TDP-43 proteinopathy. To study the non-cell autonomous mechanism of ALS, we have set up co-cultures of induced astrocytes (iAstrocytes) differentiated from neural progenitor cells (iNPCs), reprogrammed directly from patient fibroblasts, and motor neurons derived from induced pluripotent stem cell (iPSC). Pathophysiologically-relevant assays where astrocytes and neurons are co-cultured, recapitulate the astrocyte toxicity against neurons in both ALS and FTD cases, and can be used to screen drug candidates.

Understanding human brain development in health and disease with brain organoids

Sandra Acosta

Functional Neurogenomics Lab, Univ. Barcelona

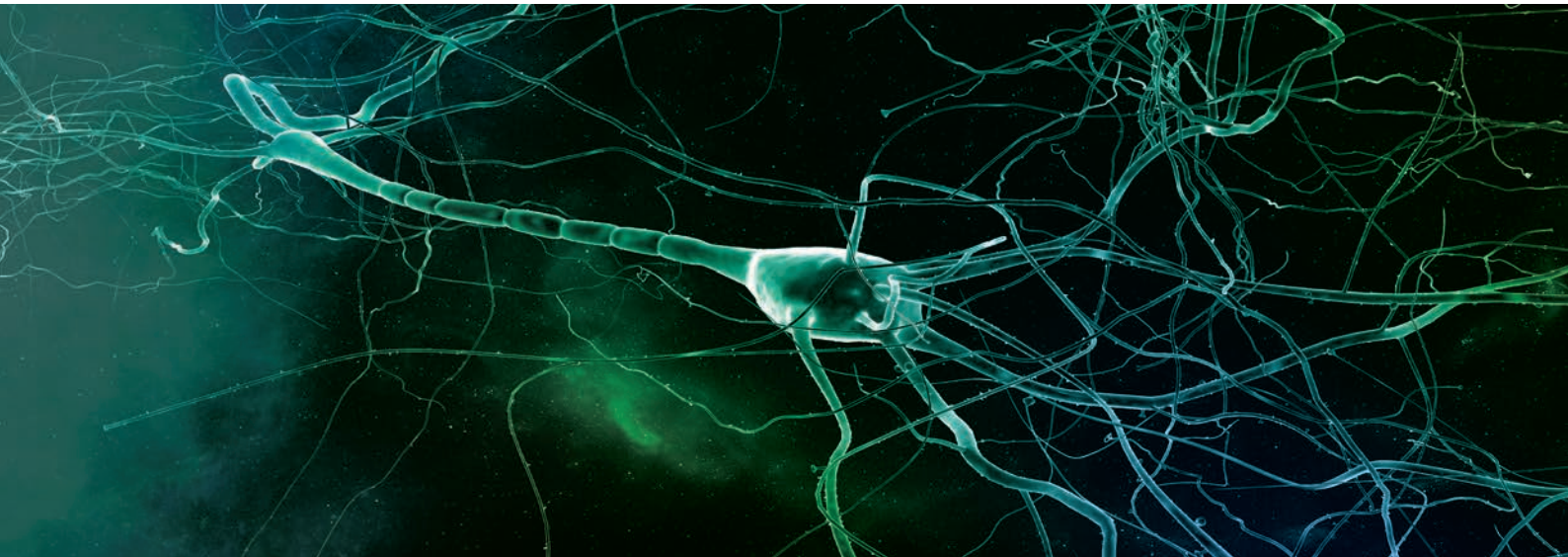
Human brain complexity rises from human-specific gene expression patterns that are tightly controlled. Brain organoids have proven an extraordinary tool to understand aspects of human brain development and evolution that cannot be modeled in non-human models, such cytoarchitectural complexity and its underlaying gene expression and gene regulatory networks. In the last years, there is increasing awareness towards their use in modeling neurological disorders, due to the possibility to use iPSCs derived from patients. However, amongst brain organoids draw backs, inter- and intra-organoid variability. The use of computational tools, such as deep learning is becoming an usual asset to improve the performance of brain organoids analysis. Our deep learning tool, the ImPhenet boosts brain organoids live analysis to circumvent the limitations of brain organoids.

Using hiPSCs to model schizophrenia and related neuropsychiatric disorders

Femke De Vrij

Dept. Psychiatry, Erasmus Medical Center, Rotterdam

Recent developments in human induced pluripotent stem cell (hiPSC) technology offer the unique opportunity to implement lineage-specific human cellular models suitable for uncovering disease-relevant biology and facilitate drug development. We have established a variety of hiPSC models for obtaining defined brain cell types to study the underlying mechanisms of psychiatric and neurodevelopmental disorders. Comparison of control and diseased human brain cells and 3D organoids allows us to study and manipulate human neurobiological mechanisms, focusing on genetic candidate variants for neuropsychiatric disorders, such as schizophrenia.



Unraveling the untapped pathology of schizophrenia: Hypomyelination

Ebru Ercan-Herbst

Team Early Intervention in Psychiatric Diseases, BioMed X Institute, Heidelberg

Schizophrenia is a neurodevelopmental disorder that affects about 1% of the population globally. Despite its high prevalence, the causes of the onset of the disorder remain unknown. Current evidences underline reduction in myelin integrity in the white matter tracts of schizophrenia patients, highlighting a contribution of myelination in the development of the disease. Myelination occurs postnatally and continues until early adulthood which coincides with the pathogenesis of schizophrenia. Myelin changes shape the neuronal circuit function, thus myelin disruption may contribute to the reduced connectivity between brain regions that has been observed in schizophrenia. Therefore, gaining mechanistic insights into the role of myelination in schizophrenia is very important to select an alternative pathway to treat this disorder.

To unravel the hypomyelination pathology of schizophrenia, we explore differentially expressed genes in neurons and oligodendrocytes from brains of schizophrenia patients and healthy controls and as well in iPSC-derived oligodendrocyte lineage cells from schizophrenia patients with hypomyelination pathology and healthy controls. To study the selected candidate targets for their role in myelination, we utilize our established 3D culture platforms of iPSC-derived oligodendrocyte lineage cells and neurons.

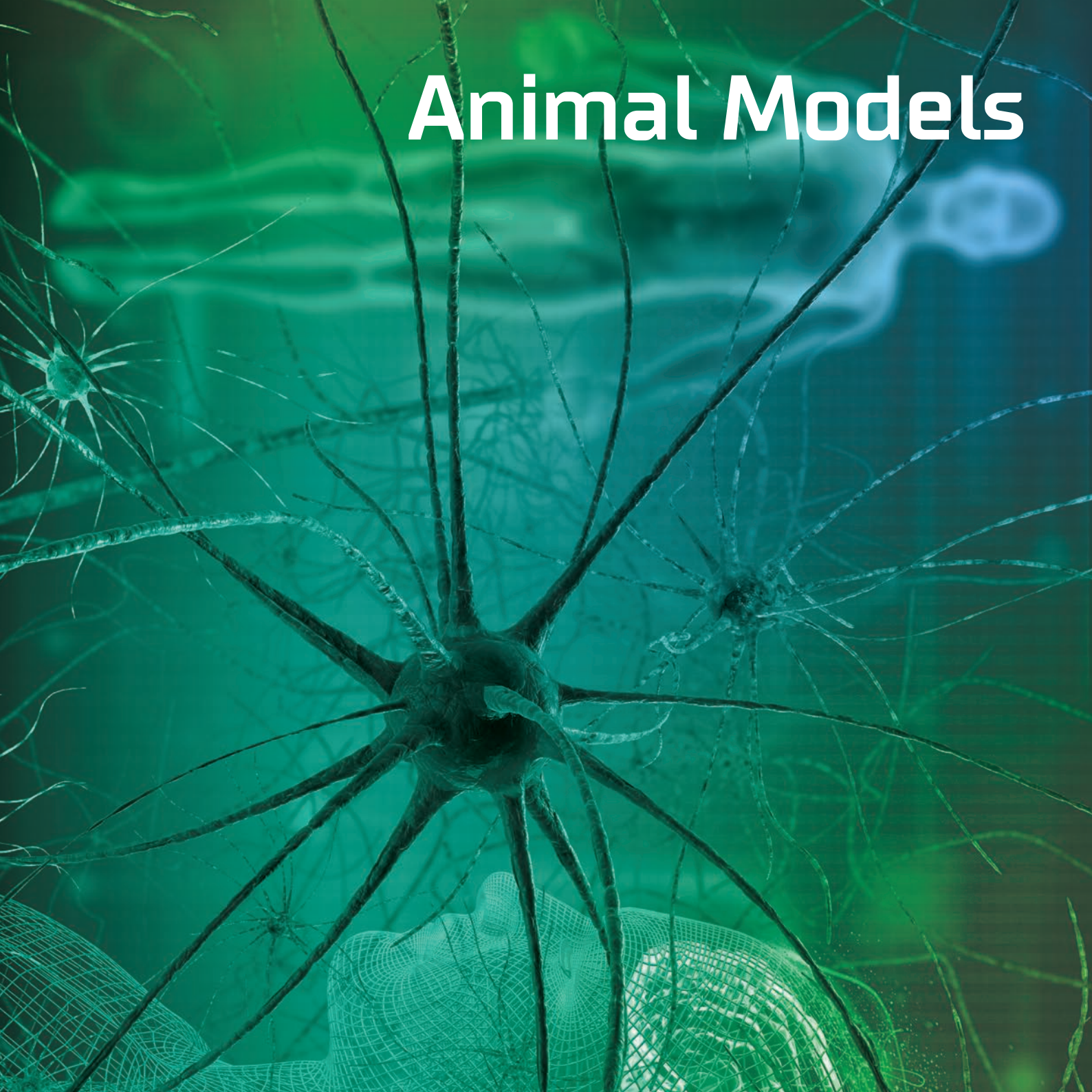
Lessons from modeling mTORopathies

Jacek Jaworski

Laboratory of Molecular and Cellular Neurobiology, IIMCB, Warsaw

mTORopathies are multiorgan diseases that result from excessive mTOR kinase activity. Common characteristics of mTORopathies include developmental alterations in the cerebral cortex anatomy and the presence of benign brain tumors. Clinically, mTORopathies often present as epilepsy, autism spectrum disorders, and neuropsychiatric disorders. One extensively studied mTORopathy is tuberous sclerosis complex (TSC), which occurs due to the loss of function of TSC1 or TSC2 proteins, both of which inhibit mTOR. mTOR is a kinase whose activity is regulated by trophic factors, energy levels, and amino acid levels within the cell. In TSC, this regulation is disrupted, leading to deregulation of numerous mTOR-dependent processes such as translation, lipid and nucleotide biosynthesis, autophagy, and transcription. Currently, patients with TSC receive symptomatic treatment, such as the administration of antiepileptic drugs or mTOR inhibitors like rapamycin. However, there is still a need for new drugs, particularly for TSC-associated neuropsychiatric disorders. In our research, we employ a combination of cellular models (such as in vitro neuron cultures, cells from tumor patients, and induced pluripotent stem cells from patients) and animal models (such as zebrafish and mice) to gain a better understanding of the molecular aspects of neurodevelopment in conditions of mTOR overactivity and to identify new therapeutic targets. This presentation will provide an overview of our team's research in these two areas.

Animal Models

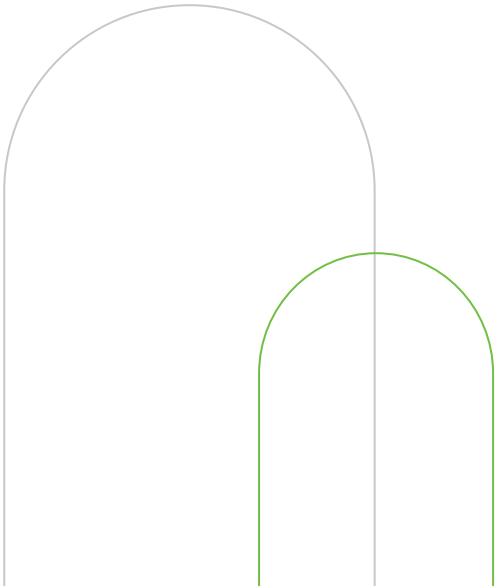


Astrocytes gate the recall of emotional fear memory

Andrew Holmes Keynote Speaker

Laboratory of Behavioral and Genomic Neuroscience, NIAAA, Rockville

Brain systems mediating behavioral responses to previously encountered threats are critical to animals' survival. The basolateral amygdala (BLA) mediates the expression of fear memory, but the contribution of BLA astrocytes to fear remains unclear. Employing in vivo calcium imaging, we found that BLA astrocytes dynamically track behavioral fear state and, using chronic and acute calcium manipulations, causally and bidirectionally link astrocyte-calcium levels with fear expression. In vivo cellular-resolution calcium imaging revealed how neuronal representations of fear are shaped by astrocytes. Our findings reveal that retrieval of fear memory involves a previously unknown degree of functional interaction between BA astrocytes and neurons, redefining current neurocircuit models of an essential survival function.



Overfeeding and Neural Pathways that Regulate Body Weight

Yann Ravussin

L.E.A.N. : Laboratory of Energetics and Advanced Nutrition, Faculty of Science and Medicine, Université de Fribourg

While the escalating public health crisis presented by obesity and adiposity-related metabolic disorders is well-recognized, therapeutic strategies remain few, primarily due to an incomplete comprehension of body weight and adipose mass regulation mechanisms. The importance of discerning peripheral and neuronal circuits modulating caloric intake and energy expenditure cannot be overstated. While extensive research has elucidated the neuronal circuits increasing food consumption following weight loss, the inverse pathways – those curtailing feeding behavior and augmenting metabolic rate during periods of overconsumption – remain comparatively understudied and poorly understood. This gap in knowledge is largely due to a dearth of suitable experimental paradigms.

To address this, we have engineered a gastric intubation procedure facilitating large volume caloric infusion in mice, resulting in rapid weight gain. Upon cessation of overfeeding, a hypophagic period ensues whose length is proportional to the weight gained and returns mice to their weight prior to overfeeding. This observation suggests the existence of an anorectic factor that communicates somatic energy reserves to the brain, subsequently reducing food intake.

We have proposed that the production of this signal emanates from the periphery (potentially the adipose tissue) and acts on the brain to decrease feeding behavior until excess weight is lost. I will present data related to our most recent findings.

The unidentified hormonal defense against weight gain

Jens Lund

Novo Nordisk Foundation Center for Basic Metabolic Research, Univ. Copenhagen

Mammalian energy balance regulation has evolved to keep body fatness within a range that supports survival. During the last three decades, obesity researchers have uncovered key aspects of physiology that prevent fat mass from becoming dangerously low. In contrast, the mechanisms that counteract excessive adipose expansion remain largely unknown. Parabiosis studies dating back to the 1950s suggest the existence of a blood-borne molecule that defends against weight gain. This presentation will highlight the research supporting an "unidentified factor of overfeeding" and theoretical models that explain its role in mammalian body weight homeostasis. Revealing the circulating signaling molecule(s) that defend against weight gain could end a long-lasting enigma of energy balance regulation and facilitate a much-needed breakthrough in the prevention and pharmacological treatment of obesity.

Neurohomeostasis under Stress: Autophagy and Metabolism in stress-related diseases

Nils Gassen

Research Group Neurohomeostasis, Bonn Clinical Centre & Charité Hospital, Berlin

Autophagy is an evolutionary conserved cellular housekeeping process implicated in the surveillance and recycling of cellular proteins and organelles, thereby maintaining cellular homeostasis and functioning. Importantly, autophagy has been centrally linked to stress-related disorders and mental health. Especially in the brain, synaptic autophagy has been shown to regulate synapse remodeling and plasticity, appears critical to neuronal homeostasis and viability, and is directly linked to neuronal functioning and mental disorders. Consequently, genome-wide and proteome-wide association studies have indicated a significant over-representation or impairments of autophagy-related pathways in multiple brain disorders. In line with these findings, autophagic dysfunction has been shown in several stress-related animal models of mental disorders. However, a comprehensive analysis of the role of autophagy during stress and stress-related mental disorders, and an investigation of autophagy-inducing pharmacological and non-pharmacological intervention strategies have not been conducted to date.

In interdisciplinary approaches we aim to improve mental health and stress resilience by targeting the cellular homeostasis and autophagy system. Leveraging a bottom-up approach that combines mechanism-driven neuroscience, clinical studies in patients and healthy subjects and innovative technologies, we uncovered novel mechanisms underlying stress resilience with regard to protein homeostasis and identified solutions to promote mental health. Together, our results unlock the full potential and effective use of biomedical research for the development of health-promoting interventions.

relevant cancer models highlighting the therapeuticpotential of targeting tCDKs.

Basic researchers talk and listen to healthcare professionals: thinking wider together

Laura Cancedda

Brain Development and Disease Laboratory, IIT, Genova

In this talk, I will present recent data from my basic research lab on the development of new animal models for brain disorders, based on chats with medical doctors, psychologists, and nurses.

Mouse models of stress-related emotional pathologies to understand neural circuitry and treatment

Christopher Pryce

Department of Psychiatry, Psychiatric University Clinic and University of Zurich

Stress-related neuropsychiatric disorders present with transdiagnostic pathologies of aversion and/or reward processing. In male mice, chronic social stress (CSS) leads to increased aversion sensitivity and decreased reward sensitivity, as measured in translational behavioural tests. Using various neuroimaging methods (bulk fibre photometry, MRI), the CSS-induced changes in neural circuitry that underlie the behavioural changes can be identified. Ex vivo methods (e.g. laser capture microdissection and RNA-Seq) then allow for molecular target discovery, followed by pharmacological validation. Examples of pharmacological mechanisms validated in the models and now being studied in clinical trials will also be presented.

Brain circuits for fear attenuation

Bianca Silva

Circuits Neuroscience Lab, CNR, Pisa

How are consolidated memories modified on the basis of experience? In this project we aimed to unravel the neural mechanisms at the basis of memory update. Understanding this biological process allows us to decipher how new information is constantly incorporated into existing memory, how a newly formed memory is integrated into previous knowledge and how the fine balance between memory stability and memory flexibility is maintained.

By using fear memory extinction as a model of memory update, we combined neuronal circuit mapping, fiber photometry, chemogenetic and closed-loop optogenetic manipulations in mice, and showed that the extinction of remote (30-day old) fear memories depends on thalamic nucleus reuniens (NRe) inputs to the basolateral amygdala (BLA). We find that remote, but not recent (1-day old), fear extinction activates NRe to BLA inputs, which become potentiated upon fear reduction. Both monosynaptic NRe to BLA, and total NRe activity increase shortly before freezing cessation, suggesting that the NRe registers and transmits safety signals to the BLA. Accordingly, pan-NRe and pathway-specific NRe to BLA inhibition impairs, while their activation facilitates fear extinction.

These findings identify the NRe as a crucial BLA regulator for extinction, and provide the first functional description of the circuits underlying the experience-based modification of consolidated fear memories.

Bridging the Species Gap in Translational Psychiatry

Johannes Passecker Keynote Speaker

Center for Chemistry and Biomedicine, Medical University of Innsbruck

The talk will introduce earlier collaborative work on how prefrontal and hippocampal neuronal activity patterns support and give rise to goal-directed behaviours relevant for higher cognition. Results will further integrate cross-species approaches and computational modelling. The later talk will introduce ongoing work, specifically focusing on unraveling mechanistic symptomatology of psychotic disorders. It will also provide a perspective on how we can enhance translational psychiatry through personalized and multi-modal strategies.

Neuronal correlates of social behavior in health and disease

Ewelina Knapska

Neurophysiology of Mind Laboratory, BRAINCITY, Nencki Institute of Experimental Biology PAS, Warsaw

The current impasse in developing mechanism-based therapies for neuropsychiatric disorders can be overcome by adopting a symptom and circuit-specific approach. The complexity of neuronal circuits involved in controlling behaviors necessitates a focused approach targeting specific brain regions that serve as hubs of high connectivity. One such hub is the central amygdala (CeA), which plays a crucial role in motivation.

We identified specific neuronal circuits within the CeA that are critical for initiating and maintaining social interaction, as well as recognizing negative emotional states in others. We also identified the circuits involved in modulation of food motivation. Interestingly, the social- and food-related circuits only partially overlap. Importantly, our studies have demonstrated the involvement of the human CeA in processing social and food-related stimuli.

These findings provide a promising avenue for developing therapeutic interventions that target specific circuits within the CeA. By focusing on the unique roles of these circuits in various behaviors and emotional processes, researchers can potentially develop circuit-focused treatments for motivation disorders such as depression or autism spectrum disorder.

Translational approach to studying compulsive behaviors: Promise and limitations of animal models in psychiatry

Eric Burguiere

Neurophysiology of Repetitive Behaviors Lab, CNRS, Paris Brain Institute

Our research group has a translational approach, which aim at studying the neurophysiological and behavioral aspects of repetitive behaviors in human and mouse models. We are especially interested in studying how cortico-basal ganglia loops underlie the regulation of these processes in animal models (e.g. SAPAP3-KO mice) and patients (e.g. obsessive-compulsive disorders (OCD), Tourette) suffering from pathological repetitive behaviors. Indeed, repetitive behaviors are the hallmark of these neuropsychiatric disorders, which offer a unique opportunity to explore the neurobiological mechanism underlying their regulation. We aim at probing these neural circuits by using neurophysiological recording and/or modulating their activity with electric or optogenetic neuromodulation. This translational approach is especially promising for better understanding the behavioral dimension and neurophysiological substrates underlying repetitive behaviours, but also to develop innovative therapeutic strategies based on invasive neurostimulation or targeted pharmacological intervention.

Functional Ultrasound for the In Vivo Monitoring of Pharmacological Effects

Tudor Ionescu

CNS Diseases, Boehringer Ingelheim Pharma

Over the last couple of decades, functional magnetic resonance imaging has emerged as the gold-standard method to investigate brain activity and functional connectivity in vivo and at whole-brain level in both humans and animals. While fMRI is undoubtedly driving forward our understanding of brain function, it does suffer from the convoluted, incompletely understood nature of its blood-oxygenation-level-derived (BOLD) signal and from its poorer sensitivity compared to other imaging methods. More recently, functional ultrasound (fUS) has emerged as a powerful alternative to fMRI. While not yet fully translational, fUS has shown great promise to outperform fMRI with regards to spatiotemporal resolution and sensitivity. Being also easier to handle, house and much less expensive than MRI, could fUS be a better option than fMRI for functional brain imaging in the future?

The lecture will cover the principles of fUS, present direct comparisons with fMRI, as well as applications of fUS to monitor pharmacological effects of different classes of compounds, thus aiming to provide a comprehensive picture of the present and a glimpse into the future of this promising new imaging technology.

Implicit and explicit learning in psychotic disorders

Dorota Frydecka

Dept. of Psychiatry, Wroclaw Medical University

Humans learn how to behave both through rules and instructions (explicit learning) as well as through environmental experiences (implicit learning). It has been shown that instructions can powerfully control people's choices, often leading to a confirmation bias. Difficulty to flexibly and adequately adapt to environment conditions due to deficits in motivation and learning are considered to be core negative symptoms domain of psychotic disorders. Given the complexity of neural circuits involved in reinforcement and instruction-based learning, it becomes difficult to capture the possible interactions of these circuits, and particularly how they are disrupted in schizophrenia. In order to explore reinforcement learning and confirmation bias both in schizophrenia patients and in healthy controls, we employed Probabilistic Selection Task (PST) and Instructed Version of Probabilistic Selection Task (IPST). The data was analyzed computational models taking under account interactions between prefrontal cortex (PFC) responsible for explicit learning and basal ganglia (BG) playing mainly role in implicit learning. This approach allows to assess the relevance of different neural circuits in psychotic disorders in comparison to healthy controls and to capture the essence of the proposed mechanisms of cognitive processing based on behavioral data of the participants with respect to their symptomatology and genetic underpinnings of PFC-BG system.

Brain Graph networks between biomarkers, graph convolutional networks, and causality

Alessandro Crimi

Brain and More, Sano Centre for Computational Medicine

Brain connectivity refers to the approach of representing different aspects of the brain (structural connections, correlation of blood concentration, gene expressions, etc). As a biomarker, brain connectivity provides valuable insights into the brain. By mapping and analyzing the intricate network of connections between different brain regions, researchers can identify aberrant connectivity patterns associated with various neurological disorders such as Alzheimer's disease, schizophrenia, and autism spectrum disorders. These findings aid in early detection, diagnosis, and monitoring of these conditions, allowing for targeted interventions and personalized treatment strategies.

Furthermore, the advent of graph convolutional networks has revolutionized the field of brain connectivity analysis. GCNs utilize graph theory and deep learning techniques to extract meaningful features from brain connectivity data. By leveraging the rich information encoded in brain networks, GCNs enable accurate classification, prediction, and understanding of brain-related phenomena. They have been successfully applied in tasks such as brain image segmentation, functional connectivity analysis, and brain network comparison, providing novel insights into the complex dynamics of the human brain.

Moreover. the complex and nonlinear nature of brain dynamics often makes it difficult to establish direct causal links. Researchers must carefully consider confounding factors, such as network topology and feedback loops, to ensure the validity of their models. Advanced statistical and computational methods, such as Bayesian networks and structural equation modeling, are employed to address these challenges.

Let's discuss together whether novel artificial neural networks can help shedding a light in this context.

The invaluable role of machine learning methods at different stages of drug design pipelines

Sabina Podlewska

Dept. Medicinal Chemistry, Maj Institute of Pharmacology PAS, Cracow

Computer-aided methods are nowadays an essential component of the drug discovery workflow, providing useful tools various stages of this expensive and time-consuming process. Their service starts at the very beginning, when computational tools are applied to identify new compounds with potentially desirable biological profiles. However, in silico evaluation is not only limited to the assessment of the activities of the investigated molecules towards considered targets but also involves analysis of their physicochemical and pharmacokinetic properties and potential toxicities, as well as generation of new potential drug candidates.

The presentation will summarize the areas of application of machine learning methods in projects implemented in the Department of Medicinal Chemistry Maj Institute of Pharmacology Polish Academy of Sciences. They involve both methodological initiatives aimed at the development of novel machine-learning-based algorithms, as well as projects oriented at the search of structurally novel ligands of selected G protein-coupled receptors (mostly serotonin and opioid receptors). In addition, the on-line platforms allowing the usage of the constructed tools by wide community will be presented. They refer mostly to the prediction of compound ADMET properties and indication of chemical moieties influencing to the highest extent the value of the considered parameter.

Pioneering the Future of Mental Healthcare: Leveraging Research in Emerging Digital Technologies and Computational Psychiatry

Brian Wallace

Co-Founder Calmsie Therapeutics, Inc.

Innovative digital technologies and AI-driven solutions in Computational Psychiatry and related disciplines offer transformative possibilities for revolutionizing mental healthcare access and delivery. These emerging technologies provide personalized mental health solutions, necessitating rigorous research to establish their safety, effectiveness, and engagement. To fully harness the potential of these advancements, robust multidisciplinary research supporting safe data management, clinical efficacy, and health economic outcomes is paramount. This level of evidence instils confidence among healthcare providers, driving adoption and paving the way for regulatory approval. Recognizing the indispensable role of applied research in shaping the future of mental healthcare, the talk will explore collaborative efforts and strategic research partnerships to unlock the full potential of computational Psychiatry and usher in a new era of personalized value-based care solutions.

Timetable

MONDAY 4.09.2023

13:00 – 14:00	Lunch
14:00 – 14:15	Official opening (**Alicja Bachmatiuk**, Director of Łukasiewicz – PORT) & presentation of SAME-NeuroID project (**Witold Konopka**)

CELLULAR MODELS IN NEURODEGENERATION

Chair Agnieszka Krzyżosiak (Łukasiewicz – PORT)

14:15 – 14:50	**Agnieszka Krzyżosiak** (Research Group Mechanisms of Neurodegeneration, Łukasiewicz–PORT, Wroclaw)
14:50 – 15:25	**Monika Myszczyńska** (Dept. Neuroscience, Sheffield Institute for Translational Neuroscience (SITraN), Univ. Sheffield)
15:25 – 16:00	**Sandra Acosta** (Functional Neurogenomics Lab, Univ. Barcelona)
16:00 – 16:30	Coffe break
16:30 – 17:30	Łukasiewicz–PORT Young Investigators (FlashTalks)
17:30 – 18:30	**KEYNOTE LECTURE: Dominik Paquet** (Laboratory of Neurobiology, Univ. Hospital, LMU, Munich & Munich Cluster for Systems Neurology (SyNergy)
18:30	Get together at Łukasiewicz – PORT
21:00	Transfer to the hotel

TUESDAY 5.09.2023

8:00	Transfer hotel – PORT

CELLULAR MODELS IN NEUROPSYCHIATRY

Chair Femke De Vrij (Erasmus Medical Center)

09:00 – 09:35	**Femke De Vrij** (Dept. Psychiatry, Erasmus Medical Center, Rotterdam)

9:35 – 10:10	**Ebru Ercan-Herbst** (Team Early Intervention in Psychiatric Diseases, BioMed X Institute, Heidelberg)
10:10 – 10:45	**Jacek Jaworski** (Laboratory of Molecular and Cellular Neurobiology, International Institute of Molecular and Cellular Biology, Warsaw)
10:45 – 11:15	Coffe break

NEUROMETABOLIC DISORDERS

Chair Witold Konopka (Łukasiewicz – PORT)

11:15 – 11:50	**Yann Ravussin** (L.E.A.N. : Laboratory of Energetics and Advanced Nutrition, Dept. Medicine, Univ. Fribourg)
11:50 – 12:25	**Jens Lund** (Novo Nordisk Foundation Center for Basic Metabolic Research, Univ. Copenhagen)
12:25 – 13:00	**Nils Gassen** (Research Group Neurohomeostasis, Bonn Clinical Centre & Charité Hospital, Berlin)
13:00 – 13:50	Lunch
13:50 – 14:50	**MATCHMAKING:** part I (3 x 20 min) "Meet the Speakers"

ANIMAL MODELS IN NEUROPSYCHIATRY

Chair Tomasz Prószyński (Łukasiewicz – PORT)

15:00 – 15:35	**Laura Cancedda** (Brain Development and Disease Laboratory, Italian Institute of Technology, Genova)
15:35 – 16:10	**Christopher Pryce** (Preclinical Laboratory, Univ. Zurich & ETH, Zurich)
16:10 – 16:45	**Bianca Silva** (Circuits Neuroscience Lab, CNR, Pisa)
16:45 – 17:15	Coffe break
17:15 – 18:15	**KEYNOTE LECTURE: Andrew Holmes** (Laboratory of Behavioral and Genomic Neuroscience, NIAAA, Rockville)
18:15	Transfer to the hotel
19:30 – 22:00	Dinner

WEDNESDAY 6.09.2023

8:00	Transfer hotel – PORT

COMPUTATIONAL NEUROPSYCHIATRY I

Chair Mathias Schmidt (Max Planck Institute for Psychiatry)

9:00 – 9:35	**Ewelina Knapska** (Neurophysiology of Mind Laboratory, BRAINCITY, Nencki Institute of Experimental Biology PAS, Warsaw)
9:35 – 10:10	**Eric Burguiere** (Neurophysiology of Repetitive Behaviors Lab, CNRS, Paris Brain Institute)
10:10 – 10:45	**Tudor Ionescu** (CNS Diseases, Boehringer Ingelheim Pharma)
10:45 – 11:15	Coffe break

COMPUTATIONAL NEUROPSYCHIATRY II

Chair Michał Ślęzak (Łukasiewicz – PORT)

11:15 – 11:45	**Dorota Frydecka** (Dept. of Psychiatry, Wroclaw Medical University)
11:45 – 12:15	**Alessandro Crimi** (Brain and More, Sano Centre for Computational Medicine)
12:15 – 12:45	**Sabina Podlewska** (Dept. Medicinal Chemistry, Maj Institute of Pharmacology PAS, Cracow)
12:45 – 13:15	**Brian Wallace** (Co-Founder Calmsie Therapeutics, Inc.)
13:15 – 14:00	Lunch
14:00 – 15:00	**KEYNOTE LECTURE: Johannes Passecker** (Center for Chemistry and Biomedicine, Medical University of Innsbruck)
15:00 – 15:15	Final Remarks & Official Closing (Michał Ślęzak & Witold Konopka)
15:20 – 16:20	**MATCHMAKING:** part II (3 x 20 min) "PORT for Health: Neuroscience meets International Symposium on Integrative Bioinformatics"
16:20 – 16:30	Coffe break
16:30	**17th INTERNATIONAL SYMPOSIUM ON INTEGRATIVE BIOINFORMATICS** **ib2023.port.org.pl**

Łukasiewicz
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Łukasiewicz Research Network – PORT Polish Center for Technology Development

147 Stabłowicka Street
54-066 Wrocław, Poland

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