Research objective 4 - Infrastructure for the monitoring of molecular basis of neurological disorders

Activity 1 - Monitoring of neurochemical background of CNS disorders

The aim of this activity is to design and develop new analytical methodologies and biomarker panels for standardized testing of new glutamatergic neurotransmission substances to effectively monitor selected signal molecules (neurotransmitters and their metabolites, amino acids, biomarkers of inflammatory reactions, oxidative stress biomarkers, etc.) in brain tissue, brain microdialysates, blood, and possibly other biological matrices. The aim is to develop standardized methodologies and panels of these biomarkers to ensure rapid and accurate identification of these molecules and allow them to interpret their molecular effects quickly and effectively. This will be achieved by meeting the following steps:

- Using the biomarker fingerprinting and biomarker profiling method to select appropriate biomarkers for early diagnosis, monitoring of pathophysiological processes, monitoring the auspices of applied therapy,
- Validation of developed methods. Preparation of biomarker panels and their testing.
- Validation of methods using test panels.
- Use of developed metabolomic and proteomic panels in model experimental studies.
- Use of developed metabolomic and proteomic panels in clinical trials.
- Development of methods of advanced statistical evaluation.
- Introducing developed biomarker panels into experimental and linear practice.

One of the major concerns of modern society is to identity putative biomarkers that serve as a valuable early diagnostic tool to identity a subset of patients with increased risk to develop neuropsychiatric disorders. Today molecular insight using OMICs (metabolomics, proteomics, transcriptomics, genomics, etc.) approaches have opened new possibilities in diagnostics, pathogenesis and pharmacotherapy monitoring of devastating disorders like neuropsychiatric illnesses. Omics-based technologies for detection and quantification of signalizing molecules have been promising because alterations in protein expression, metabolites concentration levels, change in their structure, or function can be used as indicators of pathological abnormalities prior to development of clinical symptoms of neuropsychiatric disorders. Also the insight on the molecular level of various pathologies allows a personalized approach to the patient. Using mass spectrometry technologies thanks to their extremely high sensitivity allow identifying new biomarkers of these diseases based on the identification of proteins/metabolites in body fluids that is easily available, for example, the serum, plasma, urine, blood, and cerebrospinal fluid. An ideal biomarker is present in the body fluid before the disease is clinically confirmed, have high sensitivity and specificity, and its concentration level determined by the method is reproducible. Despite of advances in the proteomic and metabolomic technologies, it has not yielded significant clinical application in neuropsychiatry research. By means of the proposed activity we would like using overall OMICs approaches create a standardized set of the methods for an experimental and clinical use which will serve for elucidating molecular mechanisms and will be applied for diagnostics, and therapeutics of psychiatrie disorders such as anxiety, depression, Alzheimer's disease, schizophrenia, and bipolar disorder. Our ambition is to postpone the borders and develop the biomarker panels for various pathologic scenarios (neurotransmitters and their metabolites, inflammation, oxidative stress, pharmacs and their metabolites, etc.) of psychiatrie disorders. In addition, we have also discussed issues and challenges regarding the implementation of OMICs approaches as a routine diagnostic tool in the clinical laboratory in context with neuropsychiatric disorders. The aim of the presented activity is also to build up a research infrastructure for the monitoring of molecular basis of neuronal diseases with a focus on early detection and a better understanding of their molecular mechanisms, as well as monitoring the

progress or success of the chosen therapy. The repertoire of biochemicals or small molecules present in cells, tissue, and body fluids known as the proteome and metabolome will be widespread. Today, clinicians utilize only a very small part of the information contained in the proteome and metabolome, as revealed by the quantification of a limited set of analytes to gain information on human health. The proposed activity aims to create a structurally-analytical platform for the detection and quantification of neurologically important molecules and the ability rapidly monitor important biochemical processes. Within this activity, two basic analytical approaches will be combined:

- Instrumental and
- Methodological.

Instrumental approaches

Within the framework of the instrument approach, the objective is to obtain analytical instruments for the rapid, accurate and reliable detection of significant signal molecules found in complex biological matrices such as blood, cerebrospinal fluid, urine, etc. This approach will use two basic analytical techniques, namely mass spectrometry (MS) which will be responsible for the qualitative and quantitative information and separation techniques high performance liquid chromatography (HPLC), ideally coupling both of them together. In the so-called OMICs field, attention will be paid primarily to the monitoring of small signal molecules from the family of neurotransmitters and their metabolites, such as dopamine, noradrenaline, serotonin, acetylcholine, GABA, glutamate or amino acids, steroids etc. in parallel with a proteomic or genomic approach. To fulfil the activity will be used present equipment as well as intended new apparatus. NIMH is at present equipped with the Triple Quad 6500 System (AS Sciex, Canada) connected to UltiMate™ 3000 HPLC (Dionex, USA). Our intention is to add a new apparatus, mass spectrometry which is complementary to existing one i.e. the TripleTOF 5600 system which is an innovation in LC-MS/MS performance that uniquely integrates comprehensive, qualitative exploration, rapid profiling, and high-resolution quantitation workflows on a single plat form. It combines high-sensitivity detection, high resolution with the fast acquisition speeds.

Featuring:

- MS/MSALL with SWATH Acquisition - enabling comprehensive MS/MS quantitation in proteomics
- Tools for 21 CFR 11 Compliance - in Analyst TF 1.6 and MultiQuant Software, bringing the power of accurate mass to regulated bioanalysis
- Optional SelexION Technology- for an additional dimension of separation
- High resolution at unparalleled speed with 10 msec accumulation time

It will enable in terms of mass spectrometry techniques, two approaches that could be applied - 'Metabolic fingerprinting', i.e. approach not necessarily requiring identification of particular components, which will be used in the first step, in the next step, based on chemometric data, specific compounds - metabolites will be identified/interpreted in terms of metabolic {proteomic) changes. These compounds will be employed as key molecules - biomarkers together with other preselected compounds for' metabolic profiling'.

Untargeted analysis - metabolic fingerprinting. The basis for samples assessment will be set of MS ions and/or fragments together with chromatographic peaks. Their combination and statistical analysis will gain spectral differences among samples, which will allow identifying important biomarkers responsible for differences between experimental (biological) ar clinical samples without their preliminary knowledge. *MS*

Targeted analysis - metabolic profiling. The target analysis will be focused on quantitative analysis of neurotransmitters and their metabolites and biomarkers of oxidative stress (e.g. 8-isoprostane, 4-hydroxy- 2-nonenal, malondialdehyde, aliphatic aldehydes, etc.), biomarkers of nitrative stress (o-nitrotyrosine, etc.), biomarkers of nucleic acids damage (8-hydroxyguanosine, 8-hydroxy-2' -deoxyguanosine, hydroxymethyluracil, etc.), and biomarkers of inflammation (leukotriene 84, cysteiny! leucotrienes, etc.). The attention will be also paid to aminoacids, lipids, saccharides, and other "brain-important" molecules. Furthermore, based on the fingerprinting results, the developed biomarker-panels will be widespread.

Methodological approaches

The overall health status of an individua! is captured by his metabolic state, which is a reflection of what has been encoded by the genome and modified by environmental factors, metabolomics has the potential to have a great impact upon medical practice by providing a wealth of relevant biochemical dat a. Metabolomics promises to improve current, single metabolites-based clinical assessments by identifying metabolic signatures (biomarkers) that embody global biochemical changes in disease, predict responses to treatment or medication side effects (p harmac omet abolomics). State of the art metabolomic analytical platforms and informatics tools are being used to map potential biomarkers for a multitude of disorders including those of the central nervous system (CNS). lndeed, CNS disorders are linked to disturbances in metabolic pathways related to neurotransmitter systems {dopamine, serotonin, GABA and glutamate); fatty acids such as arachidonic acid-cascade; oxidative stress and mitochondrial function. Metabolomics tools are enabling us to map in greater detail perturbations in many biochemical pathways and links among these pathways this information is key for development of biomarkers that are disease -specific.

On the other hand a new apparatus also allow to use the proteomic approach as well. Proteomics-based technologies for biomarker discovery have been promising because alterations in protein expression and its protein abundance, structure, or function can be used as indicators of pathological abnormalities prior to development of clinical symptoms of neuropsychiatric disorders. We would like to introduce proteomic approaches for elucidating molecular mechanisms and its applicability for biomarker discovery, diagnosis, and therapeutics of psychiatrie disorder s. In addition, we would like also to implement proteomic approaches as a routine diagnostic tool in the clinical laboratory in context with neuropsychiatric disorders.

Statistical data evaluation

The crucial step in this approach will be statistical data analysis. It will be processed by the Principal component analysis (PCA) and Partial least squares Discriminant Analysis (PLS-DA). The spectral data can be understood as a multivariate statistical problem and metabolite concentrations represent the true variables. Spectra will be divided into 'bins' of discrete spectral width (m/z in the case of MS, Rt in the case of HPLC) and the areas under the curve (AUC) in these ' bins' will be integrated and will serve as pseudo- variables. These data will be treated by PCA or PLS-DA. PCA or PLS-DA analyses will be carried aut by available softwares as SIEVE 2.1., AMIX and MATLAB software packages. Individual molecules will be then identified and quantified using online databases (Chemspider, KEGG), Mass Frontier software, and MetWorks software or commercial databases. The resulting infrastructure will be divided into three interdependent parts:

- Laboratory for Metabolomics
- Laboratory for Proteomics
- bMetrology Center

The laboratories (Laboratory for metabolomics and Laboratory for proteomics) will coordinate the establishment of a quality management system in both laboratories and for all developed methods. In parallel, it will strive for the incorporation of all measuring methods into the national metrological system.

The laboratory will be accredited by the Czech institute of accreditation according to the international standard **EN 1S0/IEC 17025:2005 as a testing laboratory No.** 1316.2. The will be also an associated laboratory of the Czech metrological institute according to MRA CIPM (see http:/ / www.bipm .org/ en/ cipm-mra/) which is an agreement under the lnternational Committee for Weights and Measures among national metrological institutes. ln the area of analytical chemistry in the Czech Republic, it has the status of the highest authority in measurement in chemistry. lf the centre proves the highest level in the new area of metrology, it will be integrated into the Czech Metrology Institute as the highest authority in the area of proteomics, metabolomics and some medically attractive markers.

The main objective of the activity is the introduction of bioanalytical methods, based on the use of statacticity should also bring the following specific results, which are briefly summarized in the following points:

- serve to introduce early diagnosis and treatment methods for patients with severe neurological diseases and to design basic research studies in these areas
- allow PhD students to work with state-of-the-art analytical instrumentation
- increase attractiveness for foreign PhD students as well as senior scientists
- the competitiveness of out-of-the-city workplaces to obtain foreign grants will increase
- ensure greater reliability in data interpretation inbiomedicine
- to reinforce the fundamental research in instrumental chemistry, which is not currently very strong in the Czech Republic
- will be able to increase the range of expertise for other sectoral organizations
- the key output at international level is to involve the project in prestigious European research consortia

Affiliates- NIMH, Doc. Ing. Petr Kačer, Ph.D.

Activity 2: Drug delivery systems for new API's dual modulating cholinergic and glutamatergic system

For decades, biomedical and pharmaceutical researchers have worked to develop new and more effective therapeutics to treat diseases affecting the central nervous system. The blood -brain barrier effectively protects the brain, but poses a profound challenge to drug delivery across this barrier. Many traditional drugs cannot cross the blood-brain barrier in appreciable cancentrations, with less than 1% of most drugs reaching the central nervous system, leading to a lack of available treatments for many central nervous system diseases. Due to the ineffective nature of most treatments for central nervous system disorders, the development of novel drug delivery systems is an area of great interest and active research. Multiple novel strategies show promise for effective central nervous system drug delivery, giving potential for more effective and safer therapies in the future. Several novel drug delivery techniques, including intranasal drug delivery, nanoparticles, drug modifications, canvection-enhanced infusion, and ultrasound-mediated drug delivery has been implemented into the pharmaceutical practice. lt also assesses possible clinical applications, limitations, and examples of current clinical and preclinical research for each of these drug delivery approaches. lmproved central nervous system drug delivery is extremely important and will allow for improved treatment of central nervous system diseases, resulting in improved therapies for those who are affected by central nervous system diseases.

In the present activity, drug delivery systems will be addressed due to low drug stability in blood plasma, and the drug delivery system will therefore be used as a protection against a number of enzymatic systems present in the bloodstream. It will try to prepare several transport systems of newly prepared candidate APIs and assess their bioavailability to the CNS. Attention will be paid mainly to liposomes, nanoparticle transport systems and micelles.

Targeted drug transport in the view of nanomedicine is based on a general approach where nanoparticles encapsulate a drug. Instead, the nanoparticles themselves or the recagnition elements on their surface can, on the basis of specific receptors on the cell surface, find the right place for action. The actual realization includes the preparation of nanoparticles, drug capture and attachment of a specific receptor, e.g., antibodies. Although the basic concept of TDD (target drug delivery) is simple, but the transport system must meet a number of conditions. Firstly, nanoparticles must have high capacity for the chosen drug. Furthermore, it must remain stable under physiological canditions, usually in the cardiovascular system. These requirements are well suited for example by liposomes.

Liposomes belong to the lipid bilayers formed by the hydrophilic care. These substances are prepared from various amphiphilic phospholipids. Since their discovery in 1965, Dr. B. Bangham and his colleagues of liposomes have come into pharmaceutical use as carriers in many practical applications. Many liposomal formulations have been prepared and tested, and a large number of them are currently in clinical testing. Liposomes are spherical particles with a hydrophilic care and one or more bilayer lamellae (layers) composed of phospholipids having a diameter of 30 nm to the order of several micrometres. Liposomes can be divided into several subtypes accarding to the size and structure of the layers. Multilamellar liposomes typically have a diameter of from 500 nm to 10 μm, while small unilamellar liposomes usually have less than 50 nm and large unilamellar liposomes are greater than 50 nm. Liposomes are formed when a thin lipid film is hydrated with an aqueous buffer solution followed by sonication or repeated extrusion through a 100nm polycarbonate membrane to reduce their size and reduce the size distribution of liposomes. Physical and chemical properties of liposomes (e.g., surface charge, size and stability) depend on the composition of the liposome. To cantrol the charge on the surface of liposomes, differently charged lipids can be used.The advantage of liposomes is the biocompatibility and the possibility of anchoring into their structure both hydrophilic and lipophilic substances in their aqueous environment or in the membrane. Anchoring hydrophobic drugs within the liposome significantly increases their solubility in aqueous sol utions. The size, surface charge, and surface properties strongly affect the pharmacokinetic profile of the anchored drug. These properties can be varied well depending on the desired properties by adding excipients to the lipid mixture prior to preparation of the liposome or by appropriate adjustment of the reaction conditions. The liposomal formulation used in the clinical practice is formulated from dimyristoylphosphatidylcholine and dimyristoylphosphatidylglycerol (DMPG). Preclinical data showed a different biodistribution and efficacy profile of the liposome as opposed to the original APi.

Polymeric micelles Polymer micelles are aggregating blocks of a copolymer with a care structure into which drug substances can be anchored. The ease of preparing micelles and binding of the active ingredient to the structure together with the ability to change the chemical composition, block copolymer length, control micel size and morphology allows for their broad pharmaceutical use. Polymer micelles assume the accumulation of the drugin its effect.

The permeation through the membranes can be controlled by the effective micelles diameters that are prepared from 20 to 100 nm. Polymer micelles can thus protect the APi from degradation and achieve controlled delivery of the substance to the site of action. Polymer micelles in various drug compositions were investigated for parenteral, oral, nasal and ophthalmic applicatio ns. Many of these studies have shown clear

benefits, including increasing bioavailability or reducing adverse eff ects. The most commonly used copolymers for pharmaceuticals are polyamine acids (e.g., poly (aspartic acid) or poly (glutamic acid)). Kataoka and his colleagues first described complexation of APi with PEG-PAsp copolymer, which led to the spontaneous formulation of a stable polymeric micelle with a high binding capacity for API's.

An example of polymer micelles as a transport system for APi is a PEG block copolymer and poly(glutamic acid) block copolymer. The hydrophilic PEG chain is located on the outside of the micelle and the PGlu-API complex chain fills the inner care of the micelle. The molecular weight of PEG-PGlu in the sodium salt form is 18 kDa with an APi content of 19.6-47.6% depending on the time of preparati on. Clinical trials have shown a better tolerance (i.e. less adverse effects) than the APi alone (particularly toxicity). Currently, this system is in the third phase of clinical testing.

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Nanoparticles

Gold nanoparticles have long been widely used for catalysis, bioassay and imaging techniques. The advantage of gold nanoparticles is their inertness, negligible toxicity, biocompatibility and ease of preparation. Gold nanoparticles can also be easily modified by targeted transport groups to improve bioavailability, and thus have a great potential in targeted drug transport. The entry of gold nanoparticles into cells is mediated by endocytosis. At present, several types of gold nanoparticles with different APIs have been prepared, where the platinum complex has been embedded on the surface of the gold nanoparticles that occurred in the form of Au-Au2S. The preparation of different sizes of gold nanoparticles ranging from 13-60 nm is feasible by reducing the gold salts in water. This makes it possible to achieve a large APi binding surface.

Iron magnetic nanoparticles are a promising carrier for targeted drug delivery to the site of action because they have the ability to deliberately drive the drug to a biological target using a magnetic field. This property of magnetic nanoparticles is already used in magnetic resonance imaging, where magnetic nanoparticles are used as a contrast medium. In addition, the nanoparticle surface may be modified by various targeted transport agents, such as monoclonal antibodies, peptides or small molecules capable of

facilitating the entry of magnetic nanoparticles into the brain. Surface modification of the so-called superparamagnetic iron oxide (SPION) is one of the variants for the drug carrier, which achieves biocompatibility, biodegradability and ability to form dispersion solutions while retaining magnetic properties, thus achieving more accurate transport to the desired compartment between the bilayer in the hydrophobic environment or inside the core In a SiO2 matrix. These conjugates also form stable dispersion conjugates and their relative size is relatively large (about 200 nm) over other inorganic c nanoparticles. Substances of such dimensions may be eliminated from the body by the reticuloendothelial system. Au- Fe3Q4 nanoparticles with a diameter of 32 nm were used as a multifunctional platform for the specific targeted transport of other APIs.

Titanium dioxide nanoparticles - One of the possible potential pathways appears to be the preparation of titanium based nanoparticles. Porous titanium dioxide (TiO2) offers many possibilities for use dueto high photocatalytic activity or a specific surface capable of various modifications. Titanium dioxide is a typical semi-conductive material that has a wide range of applications such as photocatalysis, sensory, energy storage, or medicine (e.g. anticancer drug and implants). TiO2 nanoparticles exhibit chemical stability, negligible toxicity and excellent biocompatibility. At present, polyethyleneimine (PEl)-based hybrid nanoparticles have been prepared with an anchored drug on the surface where release of the drug is prevented by creating a hydrophilic PEi layer. Subsequent use of UV radiation results in the destruction of the hydrophilic PEi layer by OH radicals, thereby enabling the release of the drug. This path appears to be potential for targeted transport.

Silica nanoparticles

The application of porous nanomaterials-carriers for targeted transport is currently a field of prime interest. One of the other possible methods is the use of mesoporous silicon nanoparticles which exhibit excellent chemical-physical properties, which are suitably volume to surface, with nanoparticles of up to 700-1000 $m^2 \cdot kg\text{-}1$, with a large number of pores up to O, 9 $cm3 \cdot g^{-1}$. Other advantages of silicon nanoparticles include high thermal, chemical and mechanical stability, homogeneous stability, negligible toxicity, biodegradability and biocompatibility, which have been demonstrated in both in vitro and in vivo assays. ln SiO2 nanoparticles, as withtitanium, gold and magnetic nanoparticles, nanoparticles canrange in size from a dozen nanometers to hundreds of nanometers and modify their surface for targeted use in pharmacy. lmmobilization of the drug can occur either within the nanoparticle structure by non-pulling forces or on the surface of the modified SiO 2 nanoparticles by covalent bonding through the polymeric chain. Drug release typically occurs when the nanoparticle is degraded by erosion, desorption, diffusion, or in a lower pH environment.

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EVROPSKÁ UNIE
Evropské strukturální a investiční fondy
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Institutions involved

- **NIMH, Doc. Ing. Petr Kačer, Ph.O.**

Activity 3 - Introduction of GLP / GMP for drug synthesis

The aim of the activity is to build a laboratory for Good Manufacturing Practice {GMP) and its certification by the State Institute for Drug Control (SÚKL). In particular, these are the following objectives:

- Building and equipping a laboratory corresponding to the GMP requirements for the preparation of pharmaceuticals {synthesis, formulation, packaging) and parts for drug analysis according to the pharmacopoeia
- Certification of the workplace and equipment by the State Institute for Drug Control, production authorization {synthesis, formulation, packaging) and manufacturing authorization in the scope of quality control {raw materials and pharmaceuticals analysis, quality control).
- Development of the procedure for the preparation of the organic synthesis of selected potential drugs, preparation of 3 batches (necessary for approval by SÚKL), obtaining certification for production of the given drugs

The research of new drugs and products for diagnostics of diseases is supported in the Czech Republic by many grants and centers, the output of which is a number of promising substances, but the overwhelming majority of them end in the stage of basic research. For transfer from academic research into practice, it is necessary to go through several phases of clinical studies preceded by a so-called preclinical study. If these are to be performed, it is necessary to supply a substance of a pharmacopoeia quality (or produced under SVP, certified by the State Institute for Drug Control after inspection, renewal (with inspection) every 2 years). The GMP defines Decree 2003/94 / EC, the Drug Act, the VYR-32 regulation on the SÚKL website and its aim is to ensure quality assurance in pharmacy, especially air quality controlled rooms, qualified (validated, calibrated) , Staff training system, prescription and recording documentation, control of inputs and raw materials of output products (according to pharmacopoeia).

In the case of CNS drugs, it is essential that the manufacturer of this substance in a pharmacopoeia quality also has a right to handle OPLs. No drug manufacturer in the Czech Republic has this right, in the EU only one company (THC Pharm), which specializes only in cannabinoids. This greatly limits the possibilities of advanced phases of clinical trials that cannot be dealt without GMP. NIMH, as one of the few workplaces that is licensed to handle OPLs, is the ideal place to build your own lab under good manufacturing practice. This will facilitate the shift of research from academic to practical use.

The aim of the project here is to build and equip the laboratory with the requirements of SVP for the preparation of medicaments with classical synthetic equipment, the size of batches in tens to hundreds of grams. The amount produced is sufficient for both preclinical and clinical studies. Part of the project is the development of the procedure for the preparation of the organic synthesis of selected drugs, the preparation of 3 batches (necessary for SÚKL approval) and the obtaining of certification for the production of these CNS drugs

Institutions involved

- National Institute of Mental Health - Jakub Rak, PhD