Questionnaire
Summary of the main activities of a research institute of the Slovak Academy of Sciences

Period: January 1, 2012 - December 31, 2015

1. Basic information on the institute:

1.1. Legal name and address

Institute of Experimental Endocrinology Biomedical Research Center
Slovak Academy of Sciences
Dúbravská cesta 9
845 05 Bratislava
Slovak Republic

Adress till January 1, 2016
Institute of Experimental Endocrinology
Slovak Academy of Sciences
Vlárska 3
833 06 Bratislava
Slovak Republic

1.2. URL of the institute web site

http://www.endo.sav.sk/
http://www.bmc.sav.sk/

1.3. Executive body of the institute and its composition

Directoriat	Name	Age	Years in the position
Director	prof. MUDr. Iwar Klimeš, DrSc.	64	2007-2013
Director	Ing. Štefan Zorad, CSc.	59	2013-
Deputy director	prof. MUDr. Boris Mravec, PhD.	40	2012-
Scientific secretary	Ing. Július Brtko, DrSc.	67	1995-

1.4. Head of the Scientific Board

Mgr. Jozef Ukropec, PhD.

1.5. Basic information on the research personnel

1.5.1. Number of employees with university degrees (PhD students included) engaged in research projects, their full time equivalent work capacity (FTE) in 2012, 2013, 2014, 2015, and average number of employees in the assessment period

	2012		2013		2014		2015		total		
	number	FTE	number	FTE	number	FTE	number	FTE	number	averaged number per year	averaged FTE
Number of employees with university degrees	45,0	29,940	48,0	35,230	49,0	32,980	49,0	33,380	**191,0**	**47,8**	**32,883**
Number of PhD students	13,0	13,000	14,0	14,000	13,0	13,000	14,0	13,000	**54,0**	**13,5**	**13,250**
Total number	58,0	42,940	62,0	49,230	62,0	45,980	63,0	46,380	**245,0**	**61,3**	**46,133**

1.5.2. Institute units/departments and their FTE employees with university degrees engaged in research and development

Research staff	2012		2013		2014		2015		average	
	No.	FTE	No.	FTE	No.	FTE	No.	FTE	No.	FTE
Institute in whole	58,0	42,940	62,0	49,230	62,0	45,980	63,0	46,380	**61,3**	**46,133**
Laboratory of cellular endocrinology	4,0	3,200	3,0	2,200	3,0	2,050	0,0	0,000	**2,5**	**1,863**
Laboratory of developmental genetics	3,0	2,510	3,0	2,510	3,0	2,010	3,0	2,250	**3,0**	**2,320**
Laboratory of diabetes and metabolic derangements - section of genetics	12,0	8,320	10,0	8,550	9,0	7,500	9,0	7,390	**10,0**	**7,940**
Laboratory of diabetes and metabolic derangements - section of obesity	4,0	4,000	5,0	5,000	6,0	6,000	5,0	5,000	**5,0**	**5,000**
Laboratory of functional neuromorphology	4,0	3,200	4,0	3,100	4,0	3,100	5,0	3,130	**4,3**	**3,133**
Laboratory of human endocrinology	3,0	2,480	5,0	3,750	5,0	2,610	5,0	3,100	**4,5**	**2,985**
Laboratory of metabolic regulations	4,0	3,500	5,0	4,000	6,0	5,000	6,0	5,000	**5,3**	**4,375**
Laboratory of molecular endocrinology	7,0	5,200	8,0	6,200	6,0	4,140	8,0	5,150	**7,3**	**5,173**
Laboratory of neurobiology	5,0	2,700	4,0	1,710	3,0	1,570	5,0	2,580	**4,3**	**2,140**
Laboratory of neurohumoral regulations	4,0	2,830	5,0	4,510	5,0	4,150	5,0	4,120	**4,8**	**3,903**
Laboratory of pharmacological neuroendocrinology	6,0	3,900	8,0	5,700	9,0	5,750	10,0	6,660	**8,3**	**5,503**
Laboratory of stress research	2,0	1,100	2,0	2,000	3,0	2,100	2,0	2,000	**2,3**	**1,800**

1.6. Basic information on the funding of the institute

Institutional salary budget and others salary budget

Salary budget	2012	2013	2014	2015	average
Institutional Salary budget *[thousands of EUR]*	601,209	601,003	594,896	580,841	**594,487**
Other Salary budget *[thousands of EUR]*	80,532	101,260	94,349	85,480	**90,405**

1.7. Mission Statement of the Institute as presented in the Foundation Charter

The Institute of Experimental Endocrinology of the Slovak Academy of Sciences (IEE SAS, at this time IEE BMC SAS) is concentrated at basic research in medical, pharmaceutical sciences and neurosciences, with a deep focus toward normal and pathological physiology of the endocrine system with an accent on elucidation of its role in regulation of various physiological functions of the organism, utilising model situations in ontogenesis, in stress, and in relation to the ethiopathogenesis of selected diseases with special emphasis on the induction and development of metabolic, cardiovascular and nervous system diseases.

The Institute performs mechanistic studies of hormone actions, utilising the methodological portfolio of cellular biology, molecular biology, genetics and immunology, with the aim to elucidate the role of hormones in regulation of metabolic processes in the

organism with emphasis to the effect of age, nutrition, sedentary life style as well as to their significance for induction and development of severe, socially important civilisation diseases.

The Institute elaborates new research and/or diagnostic procedures in order to improve the clinical care of endocrine and metabolic diseases throughout the country.

The Institute provides consulting and expertise services which are in harmony with its main activities.

The Institute represents an official training place, fully licensed to carry out the third and highest level of university studies leading to the PhD degree.

The Institute is publishing results of its research activities in periodical and non periodical, domestic and foreign professional scientific journals, books and other standard or electronic press.

1.8. Summary of R&D activity pursued by the institute during the assessment period in both national and international contexts, (recommended 5 pages, max. 10 pages)

The most important R&D activities of the Institute of Experimental Endocrinology contribute to the improvement of human health and quality of life as well as to basic scientific knowledge. Since its founding, the institute has been continually focused on investigation of clinically relevant disease-related problems on molecular, cellular and physiological level in both animal models and clinical settings.

The institute has been awarded the title **"Centre of Excellence of the European Union"**. The award was based on a successful project of the 5th Framework Program which was coordinated by the institute (D. Jezova). Within the four year of project duration, the institute employed PhD students, postdocs, other young scientists as well as internationally accepted senior scientists from other European countries. This had a significant and long-lasting influence on the scientific as well as social environment at the institute. Also during the period of assessment (from 2012 to 2015), the institute was frequently visited by collaborating scientists from abroad creating an international athmosphere for local young researchers.

Activities of the institute are presented in several thematic packages. The list includes laboratories involved in a specified area of research.

1. **Pathophysiology of obesity, metabolic and cardiovascular disease.** *(Obesity Section, Laboratory of Obesity & Metabolic Disease; Laboratory of Human Endocrinology; Laboratory of Metabolic Regulations; Laboratory of Stress Research; Laboratory of Neurobiology)*
2. **Genetics of rare metabolic diseases.** *(Genetic Section, Laboratory of Obesity & Metabolic Disease)*
3. **Pathophysiology of depression and stress response.** *(Laboratory of Pharmacological Neuroendocrinology; Laboratory of Functional Neurobiology; Laboratory of Stress Research)*
4. **Effects of neuropeptides in cell lines and hormonal control of postembryonic morphogenesis in drosophila melanogaster.** *(Laboratory of Neurohumoral Regulation; Laboratory of Developmental Genetics)*
5. **Studies on regulation of tumor growth and progression.** *(Laboratory of Neurobiology; Laboratory of Molecular Endocrinology)*
6. **Nanoparticles in human health.** *(Laboratory of Cellular Endocrinology)*

Detailed description of recent activities

1. Pathophysiology of obesity, metabolic and cardiovascular disease.

Research in the ***Obesity Section, Laboratory of Obesity & Metabolic Disease*** is focused (i) on the role of adipose tissue and skeletal muscle in the pathogenesis of obesity, insulin resistance and type 2. diabetes as well as (ii) on investigating the molecular, cellular and whole body health benefits of exercise, directly thus translating results of intervention studies to clinical practice. Mechanisms dynamically modulating the adipose tissue energy metabolism and storage capacity are directly linked to the development of metabolic disease in obesity. We contributed to the work showing that hypertrophic obesity associated with the activation of hypoxia-induced transcription factor 1α in adipocytes of human visceral adipose tissue determined the obesity-related metabolic disease progression *(Krishnan et al., Genes & Development, 2012)*. Our work with adult growth hormone deficient patients indicated that the level of adipocyte hypertrophy was directly linked with their ability to differentiate (Ukropec et al., JCEM, 2008, Balaz et al., Obesity, 2015a,b). We contributed to work describing l., transcriptional control mechanisms of *de novo* adipocyte differentiation *(Mrosek et al., Mol Metab, 2013)* as well as an intensive cross talk between adipocytes and preadipocytes in regulating the aforementioned process *(Challa, et al., Diabetes 2015)*. We were the first to demonstrate that zinc-α2-glycoprotein, the adipokine with a potent lipolytic and antilipogenic activity, is regulated by growth hormone and mediates the beneficial effects of growth hormone on the adipose tissue and whole-body metabolism in adults with growth hormone deficiency as well as in individuals with obesity & type 2. diabetes *(Balaz et al, Obesity 2014ab; Balaz et al, Adipocyte 2015)*. Comprehensive proteomic analysis of metabolically active human brown fat obtained from peritracheal region of the neck confirmed that mitochondrial creatine kinase represents a completely novel energetically ineffective thermogenic mechanism active in human brown fat in parallel to uncoupling protein 1 *(Mueller, Balaz et al., Sci Rep. 2016)*. We continue studying mechanisms of thermogenic process in the ice water swimmers well acclimated to cold environment. Overall aim is to better understand the many aspects of adipose tissue biology as it offers a great potential for metabolic disease management.

In search for muscle derived factors modulating energy metabolism, we investigated skeletal muscle & adipose tissue FNDC5, a precursor protein of irisin, the putative exercise-induced muscle secretory protein with a proposed beneficial impact on the adipose tissue and whole body energy metabolism *(Kurdiová et al., Journal of Physiology 2014; Peptides 2014)*. We showed that irisin was down-regulated in type 2 diabetes and positively linked to muscle mass, strength & metabolism.

Next, we studied the role of carnosine on glucose metabolism in humans. Carnosine is a naturally present dipeptide abundant in skeletal muscle endowed with an antioxidant capacity and the ability to quench reactive carbonyl species. In our pilot studies we showed that muscle carnosine increases with progressive glucose intolerance in male individuals *(Stegen et al, PlosOne, 2015)* and that its muscle content is related to metabolic and anthropometric phenotypes. Insulin sensitivity and physical activity have been identified as the best predictors of muscle carnosine content *(deCourten et al, PlosOne, 2015)*. In a pilot randomized placebo-controlled double-blind intervention study, we were the first to investigate whether 3-month carnosine supplementation to sedentary individuals with overweight or obesity had a capacity to improve cardiometabolic risk. Our original observations suggest that carnosine supplementation delays the development of insulin resistance and improves glucose tolerance in sedentary, obese, prediabetic individuals *(deCourten et al, Obesity, 2016)*.

One of the research lines in ***The Laboratory of Human Endocrinology*** is focused on dysregulation of metabolism in relationship to inflammation and dysautonomia in newly diagnosed patients with multiple sclerosis. Results clearly showed no differences in glucose tolerance or in many different circulating inflammatory and metabolic parameters but, it impaired insulin sensitivity was found in patients with multiple sclerosis *(Penesova et al., Metabolic Brain Disease,2015).*

Moreover, in research focused on young obese and non-obese patients with hypertension (HT) we demonstrated increased adrenaline concentrations at baseline and during the mental stress test as well as enhanced stress-induced noradrenaline release in HT compared to that in healthy controls. Interestingly, we showed that stress-induced increase of systolic BP was lower in obese compared to lean individuals. Obesity in patients with hypertension did not lead to a different reaction in comparison with lean hypertensive subjects *(Garafova et al., Phys Res 2015)*. Another original finding was that insulin resistance in patients with hypertension was not associated with alterations in concentrations of incretin GLP-1 or circulating adipokines, e.g. visfatin.

In collaboration with Institute of Biochemistry, Nutrition and Health Protection, Department of Nutrition and Food Assessment, Faculty of Chemical and Food Technology of Slovak technical University (STU), we plan to study effects of novel fibre drinks on metabolic heath in humans. Pilot experiments revealed that cereal substrates fermented with *Lactobacillus plantarum* exhibited significantly reduced content of starch, total carbohydrates and lipids *(Mikusova et al., Quality Assurance and Safety of Crops & Foods. 2012)*. Processing of cereal substrates by fermentation was also shown to influence their nutritional and energy values, as well as total polyphenolic content and the antioxidant activities *(Mikusova et al., Asian J Plant Sci, 2013)*.

The Laboratory of Metabolic Regulations is engaged in studies concerning the role of peptide hormones in regulation of glucose and lipid metabolism. The fundamental observation that oxytocin significantly improves adipose tissue cellularity and metabolism *(Eckertova et al., Br J Pharmacol, 2011)* prompted us to look at the specific role of oxytocin in obesity. We have shown that hypooxytocinaemia in obese Zucker rats is caused by elevated oxytocin degradation in liver and adipose tissue *(Gajdosechova et al., J. Endocrinol 2014)*. In addition, we found differential regulation of oxytocin receptor in various adipose tissue depots and fibertype-specific regulation of oxytocin receptor in skeletal muscle of obese Zucker rats *(Gajdosechova et al., Horm Metab Res, 2015)*. Our results imply possibility of using oxytocin for treatment of obesity. Zucker rats represent a model of peripheral insulin resistance, anticipating decrease in insulin sensitivity also in the brain. This was indeed evident by deficient hippocampal insulin signaling paralleled by augmented Tau phosphorylation in obese animals *(Spolcova et al. BMC Neurosc. 2013)*.

In the field of cardiovascular research, our laboratory is focused on renin-angiotensin system (RAS) and protective effect of melatonin. We found that melatonin exerts cardioprotective effects in a model of isoproterenol-induced heart damage. The antiremodeling effect of melatonin may also be of potential benefit to patients with heart failure *(Simko et al. J Pineal Res, 2013)*. Furthermore, we showed that captopril prevented left ventricle hypertrophy development in the continuous light-induced hypertension rat model, while melatonin significantly reduced myocardial fibrosis *(Simko et al., Mediators Inflamm, 2014)*. Currently, we are studying local RAS in skeletal muscle of lean and obese Zucker rats. We observed dysregulation of the functional components of RAS (angiotensinogen, renin, AT1 and AT2 receptors, prorenin receptor, neutral endopeptidase, aminopeptidase A) in skeletal muscle from obese animals.

2. **Genetics of rare metabolic diseases** *(Genetic section, Laboratory of Obesity & Metabolic Disease)*

Research activities of ***The Laboratory of Diabetes and Metabolic Derangements – Genetic Section*** was over the last four years mainly oriented to the genetics of the monogenic diabetes with focus on the identification of mutational spectrum, structure-function studies and the application into the clinical practice in selected monogenic diabetes subtypes.

Monogenic forms of diabetes include a number of diseases, which occur due to mutations in genes involved in insulin secretion and insulin action. Glucokinase diabetes (GCK-MODY) is the most common subtype in many countries. GCK-MODY is caused by heterozygous inactivating mutations in glucokinase gene (GCK) and characterized by stable fasting hyperglycemia. We revealed that GCK-MODY accounts for at least 0.03%

of all diabetic patients in Slovakia, 7 out of 22 (32%) mutations we found were novel so their pathogenicity was further studied. The co-segregation with fasting hyperglycaemia was established in all cases where parental DNA was available. Functional studies have demonstrated the pathogenicity of several GCK mutations due to either lowered kinetic activity or reduced thermal stability *(Valentinova et al., PlosOne, 2012)*. Knowledge of the exact etiology of diabetes and a definitive proof of mutation pathogenicity in functional studies are highly important for clinical practice which has implications for patient treatment and disease management.

We next proposed DG9-glycan index as a new clinical biomarker for distinguishing HNF1A-MODY from other subtypes of diabetes. Recent efforts to improve diagnostic performance by identifying biochemical markers specific for maturity-onset diabetes of the young (MODY) subtypes have met with varying success. A recent genome-wide association study identified the hepatocyte nuclear factor 1α (HNF1A) as a key regulator of fucosylation. The preexisting evidence indicated that loss-of-function HNF1A mutations, causing MODY, displayed altered fucosylation of N-linked glycans on plasma proteins and that glycan biomarkers could improve the diagnostic efficiency of HNF1A-MODY. The aim of our work was to test the hypothesis that HNF1A mutations influence the glycan spectrum (DG9-glycan index) in a larger set of patients. Five European centers provided large patient cohorts for these studies. DG9-glycan index was shown to be markedly lower in HNF1A-induced MODY than in controls or in patients with other diabetes subtypes. It offered a good discrimination tool to differentiate between HNF1A-MODY, type 1 and type 2 diabetes and it enabled to detect 3 previously undetected HNF1A mutations in patients with diabetes. In conclusion, glycan profiles are altered substantially in HNF1A-MODY and the DG9-glycan index has a potential clinical value as a diagnostic biomarker of HNF1A dysfunction *(Thanabalasingham Get al., Diabetes, 2013)*.

3. **Pathophysiology of depression and stress response.** *(Laboratory of Pharmacological Neuroendocrinology, Laboratory of Functional Neurobiology, Laboratory of Stress Research)*

Team of researchers from **The Laboratory of Pharmacological Neuroendocrinology** is interested in investigating many pathophysiological aspects of depression, one of the most serious mental disorders disturbing the health and quality of life of a high number of people. In a preclinical study we have shown for the first time that hormone aldosterone has a causal role in the development of depression-like behaviour. We have brought evidence that aldosterone treatment results in changes in signaling pathways, which are known to be disturbed in depression, such as glutamate neurotransmission, inflammatory processes and brain plasticity *(Hlavacova et al. Int J Neuropsychopharmacol, 2012)*. In the course of the development of depression-like behaviour, the increase in circulating aldosterone precedes the increase in corticosterone, which has been considered to be one of the dominant pathogenetic factors *(Franklin et al., J Psychiatr Res, 2012)*. Modulation of aldosterone release and/or effects may represent a new strategy in the treatment of depression. Almost one third of depressive patients are resistant to the treatment with classic antidepressants. The development of treatment resistant models of depression is in itself problematic because the effectiveness of antidepressants constitutes an important component of the model validation process. We have solved this problem in an original way. We validated a model of depression based on diet-induced tryptophan depletion in male rats and we developed a pharmacoresistant depression-like state using the same model in females. With this new model we have discovered several mechanisms related to pharmacoresistance, such as pro-inflammatory cytokines, the kynurenine pathway, magnesium, the orexin pathway and glutamate neurotransmission *(Franklin et al., Neuroendocrinology, 2015)*. We have shown that memantine, a glutamatergic drug used in the treatment of Alzheimer disease, has an impact on brain plasticity under stress conditions *(Babic et al., J Psychiatr Res, 2012)*. The importance of findings obtained in experimental studies was also confirmed under clinical conditions. We brought evidence that the amount of aldosterone in the saliva of patients with major depression negatively correlated with the outcome of their treatment

with antidepressants *(Buettner et al., J Psychiatr Res, 2015)*. We have demonstrated that an acute increase in state of anxiety contributed to neuroendocrine activation under stress conditions in healthy humans *(Jezova et al., Neuroendocrinology, 2013)*.

Recent work in ***The Laboratory of Functional Neurobiology*** revealed that different antipsychotics may elicit distinct effects on the brain neurons, as revealed by Fos immunohistochemistry *(Kiss et al. J Neurosci Res. 2010)*. In the last few years, we have investigated the effect of asenapine (ASE, a novel atypical antipsychotic drug, approved for the treatment of schizophrenia and bipolar disorder) in the context of 14 days lasting unpredictable variable mild stress (CMS) preconditioning, which mimics the stress environment in a common human life and may interfere with the therapeutic effect of different drugs, including antipsychotics. We have shown that acute asenapine treatment induced a robust Fos expression in neurons of many forebrain structures, including dorsal-lateral striatum, ventral-lateral septum, shell and core of the nucleus accumbens, and medial prefrontal cortex, which however was not modified by 14 days lasting CMS preconditioning (Majercikova et al., Brain Res Bull, 2014). We have also revealed a strong Fos expression after acute ASE treatment in neurons of the Meynert's nucleus (a primary source of acetylcholine for the entire cortex) including the adjacent hypocretin (Hcrt), but not melanin-concentrating hormone neurons. It is important to note that in contrast to forebrain structures, effect of asenapine on the Meynert's nucleus was significantly reduced by the CMS preconditioning (Majercikova & Kiss, Neurol Res, 2016). In the context with CMS, we also studied the effect of asenapine on the Fos expression in Hcrt neurons in medial and lateral portions of the lateral hypothalamus (LH) involved in the food intake regulation. Significant reduction in the number of Fos/Hcrt colocalizations in neurons in the medial, but not lateral LH portion in ASE-treated rats was found. CMS preconditioning did not significantly interfere with this impact of ASE (Majercikova & Kiss, Endocr Regul 2015). These data clearly show that asenapine may reduce activity of the Hcrt cells in the medial LH, which corresponds well with the relatively low weight gain after asenapine treatment in humans. In summary, the present studies indicate that different brain structures activated by acute asenapine administration may have different sensitivity to CMS preconditioning and provide an important comparative background that may broaden the understanding to the effects antipsychotics have on specific brain structures and their responsiveness to CMS challenges.

Activities of ***The Laboratory for Stress Research*** were aimed at investigating functional capacity of several peripheral organs (spleen) and tissues (adipose tissues) for *de novo* catecholamine production and responsiveness of this unique catecholamine producing system to various stressors (single and repeated immobilization stress, acute and prolonged cold exposure, combination of cold and immobilization). Catecholamine production in T and B cells isolated from rat spleen in response to stress was associated with apoptosis and suppression of cytokine production including down-regulation of interferon gamma, interleukin 2 and interleukin 4 (Laukova et al., Immunobiology, 2013). Spleen T cells were found to be more vulnerable to stress compared to B cells, which is likely due to increased expression of β1-, β2- and β3 adrenergic receptors, as well as that of pro-apoptotic markers in response to immobilization stress. Moreover, we described immobilization-stress-facilitated translocation of β2-adrenergic receptors from the nucleus to the plasma membrane in T cells (Laukova et al., Neuroimmunomodulation, 2012). We also investigated stress-modulated catecholamine production in four types anatomically, functionally and histologically distinct white adipose tissue depots as well as in rats brown adipose tissue. We found stimulating effect of immobilization and cold stress on catecholamine production in adipocytes and stromal/vascular cell fractions isolated from mesenteric adipose tissue, providing convincing evidence on non-sympathetic source of catecholamine *de novo* production in adipose tissue (Kvetnansky et al., Cell Mol Neurobiol, 2012; Vargovic et al., Stress, 2013).

In addition, we studied response of the central noradrenergic system to stress. We particularly looked at its role in the development of tau pathology in Alzheimer disease, using transgenic rats over-expressing human truncated tau protein. We identified quantitative differences of catecholamine synthesis in brainstem catecholaminergic ascending and descending projecting cell groups and we characterized their response to

single and repeated immobilization stress. Our data support the assumption that brainstem catecholaminergic cell groups represent a functionally differentiated system, which is highly (but specifically) activated in rats exposed to stress (Mravec et al., Eur J Neurosci., 2015). Transgenic rats at age of 6 months which had already developed tau pathology exhibited reduced norepinephrine levels in forebrain neocortical (frontal and temporal association cortices) and hippocampal (cornu ammonis, dentate gyrus) areas and they showed abnormal norepinephrine response to stress in locus coeruleus, as well as reduced plasma levels of norepinephrine and epinephrine *(Lejavova et al., J Alzheimers Dis, 2014)*.

4. **Effects of neuropeptides in cell lines and hormonal control of postembryonic morphogenesis in drosophila melanogaster.** *(Laboratory of Neurohumoral Regulation, Laboratory of Developmental Genetics)*

Research activity of ***The Laboratory of Neurohumoral Regulation*** is focused on the investigation of developmental effects of neuropeptides. Specifically, we looked at the differentiation capacity of neuronal cells and evaluated changes in neuronal cytoskeleton in response to oxytocin. First of all we studied effects of small neuropeptides - thyreoliberin, oxytocin, vasopressin and protein prolactin on neuronal cells using neuroblastoma and glioblastoma cell lines. We have confirmed that oxytocin and vasopressin have pro-proliferative effects; nevertheless thyreoliberin (TRH) and prolactin have more complex influence on neuronal cells. We have proved that prolactin stimulates cytoskeletal proteins nestin and microtubule-associated protein 2 in neuronal-like cells, however no such effect has been observed in astrocyte-like cells. Using different models of oxidative stress, inflammation and apoptosis, no direct neuroprotective effect of aforementioned tested neuropeptides was found. We showed that oxytocin increased proliferation of neuroblastoma and glioblastoma cell lines and protected cells against negative consequences of neurotoxins, damaging dopaminergic neurons *in vitro*, and against negative effects of lipopolysaccharide administration *in vivo* (*Bakos et al., Cell Mol Neurobiol. 2012, Bakos et al., Neuropeptides,* 2014). Our work revealed that ligands of oxytocin receptors specifically modulated gene expression of cytoskeletal proteins related to neurite outgrowth. We have also found that oxytocin affected levels of neurotrophic factors and content cytoskeletal proteins during neuronal development and that these changes are sex-dependent *(Bakos et al., Neuropeptides, 2014)*.

The Laboratory of Developmental Genetics is dealing with hormonal control of postembryonic morphogenesis in Drosophila melanogaster, notably its metamorphosis and associated signaling pathways using molecular and genetic tools, so uniquely available in this species. Two recent achievements of the laboratory can be highlighted;

(1) The atomistic model of juvenile hormone (JH) receptor (JHR), we originally described in 2009 was further elaborated in detail and results were published in *(Ramaseshadri et al., Adv. Insect Physiol, 2012; Farkaš and Polakovičová, CRC Press, 2013)*. Our novel observations are based on a large-scale pharmacophore analysis of >200 JH agonists using a Drosophila morphogenetic bioassay, followed by 3D QSAR (CoMFA and CoMSIA structure-activity relationships) study. In brief, our results provided guidelines and a mechanistic scope for the identification of the steric and electrostatic properties as well as the donor and acceptor hydrogen-bonding interactions of the ligand-binding cavity of a JH target protein. We clearly showed that the active agonist fitting into the ligand binding pocket (LBP) must have an electronegative atom (oxygen or nitrogen) at each of its ends and the distance between these atoms must be between 11.5 Å and 13.5 Å. This analysis also showed that in order for the JH agonist to have high biological activity, it must also have a central electron-deficient moiety. Further, the ligand binding pocket of the JHR has been defined by a group of 8 discontinuous amino acids providing hydrogen bonds between JH's esteratic group and 1.4 Å distant Ser or Tyr, and the second hydrogen bond interactions for the epoxy oxygen of JH with the NH group of Asn or Glu within 1.6 Å distance. All conclusions have been reciprocally verified by FlexiDock docking protocol,

resulting in classification of the LBP by the parameters typical for nuclear receptor superfamily member transducing genomic action of the JH.

(2) Discovery of an apocrine secretion in the late prepupal salivary glands of Drosophila *(Farkaš et al., PlosOne 2014)* is completely novel and was purely unexpected. Since its first presentation by Purkinje in 1883 and description by Schiefferdecker in 1917 there were no data about any mechanistic aspects of apocrine secretion that would allow its better classification. By very detailed developmental genetic, light and electron microscopic as well as laser confocal analysis, by in-depth proteomic approach and other molecular techniques we made crucial reappraisal and definition of the apocrine secretion as novel non-canonical non-vesicular transport and secretory machinery with its own, so far undefined, signaling pathway. Several of these and many other conclusions about, including clear definition of apocrine secretion has been published in seminal review *(Farkaš, Biochim. Biophys. Acta. 2015)*, and also currently are in press in the book by Springer devoted to secretory and excretory products. This type of secretion appears to be common to many, if not all, barrier epithelial tissues including skin derivatives and the epididymis, and is implicated also in lung/bronchi and intestinal epithelium.

5. **Studies on regulation of tumor growth and progression.** *(Laboratory of Neurobiology, Laboratory of Molecular Endocrinology)*

Work in ***The Laboratory of Neurobiology*** was focused mainly on investigation of interactions between the brain and peripherally localized tumors. We investigated mechanisms and pathways responsible for modulatory effect of the brain on proliferation of cancer cells in animal cancer models. We have proved that sympathectomy significantly attenuated progression of solid tumors (e.g. fibrosarcoma, melanoma) but did not affect proliferation of ascitic type of tumor (hepatoma) *(Lackovicova et al., Neoplasma, 2011; Horvathova et al, J Neuroimmunol, 2015)*. Moreover, we have confirmed that tumor cells used in our experiments express beta-adrenergic receptors and that norepinephrine stimulates proliferation of these cells *in vitro*. Comparing to sympathetic nervous system, our experiments investigating the role of parasympathetic nervous system in modulation of tumor growth showed ambiguous effects (Mikova et al, Neurosci Lett, 2015).

Activities in ***The Laboratory of Molecular Endocrinology*** are connected to many biological actions of retinoids including its inhibitory activity for tumor growth and cancer progression. During last four years expression of all retinoic acid receptor subtypes (RARα, RARβ, RARγ) and retinoid X receptor subtypes (RXRα, RXRβ, RXRγ) have been monitored in human papillary thyroid carcinoma (PTC) and renal cell carcinoma (RCC). Human PTC tissue exclusively expressed RXRγ and expressions of RARα and RARγ were significantly higher in PTC than in a healthy thyroid tissue. More importantly, expression of type I iodothyronine deiodinase was either absent or significantly lower in PTC as compared to non-neoplastic tissue *(Macejova et al. Oncol Rep 2013)*. The data from human kidney tissues has shown that all types of RCC cells and healthy kidney cells expressed all subtypes of RARs and also RXRα, RXRβ, and only some of them expressed RXRγ. The mRNA expression of RARγ was enhanced in RCC in comparison to that in intact renal tissue *(Lenko et al. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub, 2013)*. Specific patterns of RAR and RXR subtype expression in various PTCs or RCCs may, together with immunochemical tissue characterization, be used in differential diagnostics of thyroid or kidney neoplasm. Proteomics provides a powerful view on the qualitative and quantitative changes in proteome. Changes in protein composition induced by all-trans retinoic acid, 9-cis retinoic acid and their combination were investigated in human breast cancer cells MCF-7. Results clearly showed significant differences in the expression of proteins affecting cell migration. Interestingly, treatment with combination of retinoic acid isomers was associated with increased amounts of heat shock protein 27, ribonucleoprotein SmD3, and cofilin-1 *(Flodrova et al. Toxicol Lett. 2015).*

6. **Nanoparticles in human health** *(Laboratory of Cellular Endocrinology, Laboratory of Molecular Endocrinology)*

In recent years, nanoparticles (NPs)/nanomaterials (NMs) have been increasingly used in multiple industrial, consumer and medical applications and thereby may pose unknown potential risks to human health. Current data support the notion that different NPs are capable of altering the activity of the endocrine system (Rollerova et al. Endocr Regul, 2011, Reprod Toxicol, 2015). ***The Laboratory of Cellular Endocrinology and Laboratory of Molecular Endocrinology*** therefore investigated effects of polymeric NP PEG-*b*-PLA (a promising tool in a drug delivery, especially for treatment of CNS disorders) and metal NPs (TiO_2, titanium dioxide; Ag, silver) on endocrine (reproductive) and immune system using different *in vivo* and *in vitro* model systems. Results of *in vivo* experiments indicate that neonatal exposure female rats to PEG-b-PLA and TiO_2 NPs may affect hypothalamus-pituitary-ovarian axis in infantile and adult animals. The onset of puberty, oestrus cycle, responsiveness of pituitary, and steroid hormone secretion were altered by the action of tested NPs. In addition, tested NPs induced changes in immune system and oxidative state of female rats neonatally exposed to NPs. Negative effects of tested NPs on gonadotropin and steroid hormone secretion were confirmed *in vitro* using primary cell cultures of rat anterior pituitary cells and porcine ovarian granulosa cells or whole ovaries, respectively (Scsukova et al. Neuroendocrinol Lett 2015). These results may contribute to the safety assessment of therapeutically and commercially used NPs and may be useful for designing new NMs for biological applications.

Doctoral studies and visits of young researchers

IEE SAS performs doctoral studies in three PhD study programmes. With Comenius University in Bratislava, the institute educates PhD students in normal and pathological physiology in cooperation with the Faculty of Medicine, and in animal physiology in cooperation with the Faculty of Natural Sciences. With Slovak Technical University in Bratislava, the institute educates PhD students in biochemistry.

Next to students of Slovak universities, the research topics of the institute attracted. Several of them succeeded to get fellowships from the Slovak Academic Information Agency (SAIA) programme or National Scholarschip Programme. For example, Malgorzata Hasiec, a PhD student from The Kielanowski Institute of Animal Physiology and Nutrition, Polish Academy of Sciences, Jablonna, Poland, spent 3 months in the Laboratory of Pharmacological Neuroendocrinology. She increased her expertise in behavioral physiology by learning how to perform animal models of chronic stress and she helped to broaden the scope of research of the laboratory by transferring the knowledge on plexus choroideus. Snjezana Romic from the Laboratory for Molecular Biology and Endocrinology, Vinca Institute of Nuclear Sciences, University of Belgrade, Belgrade, Serbia, spent 3 months of her PhD study in the Laboratory of Metabolic Regulations. She has increased her knowledge on the olecular mechanisms related to the adipose tissue function. The institute also hosted a master student Marek Paulovic from the University of Vienna for 1 month to initiate his master's thesis on stress associated with the work of interpreters in the Laboratory of Pharmacological Neuroendocrinology.

2. Partial indicators of main activities:

2.1. Research output

2.1.1. Principal types of research output of the institute: basic research/applied research, international/regional (ratios in percentage)

basic research/applied research: 80/20

international/regional: 100/0

2.1.2 List of selected publications documenting the most important results of basic research. The total number of publications listed for the assessment period should not exceed the average number of employees with university degrees engaged in research projects. The principal research outputs (max. 5, including Digital Object Identifier - DOI) should be underlined

1. **BABIC, Stanislav** - **ONDREJČÁKOVÁ, Mária** - **BAKOŠ, Ján** - RAČEKOVÁ, Eniko - **JEŽOVÁ, Daniela**. Cell proliferation in the hippocampus and in the heart is modified by exposure to repeated stress and treatment with memantine. In *Journal of Psychiatric research*, 2012, vol. 46, no. 4, pp. 526-532. (4.664 - IF2011). ISSN 0022-3956.

2. **HLAVÁČOVÁ, Nataša** - WES, P. D. - **ONDREJČÁKOVÁ, Mária** - FLYNN, M. E. - POUNDSTONE, P. K. - **BABIC, Stanislav** - MURCK, Harald - **JEŽOVÁ, Daniela**. Subchronic treatment with aldosterone induces depression-like behaviours and gene expression changes relevant to major depressive disorder. In *The International Journal of Neuropsychopharmacology*, 2012, vol. 15, no. 2, p. 247-265. (4.578 - IF2011). ISSN 1461-1457. DOI 10.1017/S1461145711000368

3. **LAUKOVÁ, Marcela** - **VARGOVIČ, Peter** - CSÁDEROVÁ, Lucia - **CHOVANOVÁ, Lucia** - **VLČEK, Miroslav** - IMRICH, Richard - KRIŽANOVÁ, Oľga - **KVETŇANSKÝ, Richard**. Acute stress differently modulates Beta 1, Beta 2 and Beta 3 adrenoceptors in T cells, but not in B cells, from the rat spleen. In *Neuroimmunomodulation*, 2012, vol.19, no. 2, p. 69-78. (2.383 - IF2011). ISSN 1021-7401.

4. **MRAVEC, Boris**. The brain as a target for development of new class of drugs for the treatment of somatic diseases. In *Expert Opinion on Therapeutic Targets : print*, 2012, vol. 16, no. 5, p. 433-437. (3.716 - IF2011). ISSN 1472-8222.

5. **VALENTÍNOVÁ, Lucia** - BEER, N. L. - **STANÍK, Juraj** - TRIBBLE, N. D. - VAN DE BUNT, M. - **HUČKOVÁ, Miroslava** - BARRETT, Anthony A. - **KLIMEŠ, Iwar** - **GAŠPERÍKOVÁ, Daniela** - GLOYN, A. L. Identification and functional characterisation of novel glucokinase mutations causing maturity-onset diabetes of the young in Slovakia. In *PLoS ONE*, 2012, vol. 7, no. 4, p. e34541. (4.092 - IF2011). ISSN 1932-6203.

6. **BAKOŠ, Ján** - **ŠTRBÁK, Vladimír** - PAULIKOVÁ, H. - KRAJŇÁKOVÁ, L. - **LEŠŤANOVÁ, Zuzana** - **BAČOVÁ, Zuzana**. Oxytocin receptor ligands induce changes in cytoskeleton in neuroblastoma cells. In *Journal of Molecular Neuroscience*, 2013, vol. 50, no. 3, p. 462-468. (2.891 - IF2012). ISSN 0895-8696.

7. BENES, J. - **MRAVEC, Boris** - **KVETŇANSKÝ, Richard** - MYSLIVEČEK, Jaromír. The restructuring of muscarinic receptor subtype gene transcripts in c-fos knock-out mice. In *Brain Research Bulletin*, 2013, vol. 94, pp. 30-39. (2.935 - IF2012). ISSN 0361-9230.

8. **DANEVOVÁ, Veronika** - **KVETŇANSKÝ, Richard** - **JEŽOVÁ, Daniela**. Kinetics of oxytocin response to repeated restraint stress and/or chronic cold exposure. In *Hormone and Metabolic research*, 2013, vol. 45, no. 12, p. 845-848. (2.145 - IF2012). ISSN 0018-5043.

9. **JEŽOVÁ, Daniela** - **HLAVÁČOVÁ, Nataša** - **MAKATSORI, A**. - DUNČKO, Roman - LODER, I. - HINGHOFER-SZALKAY, H. Increased anxiety induced by listening to unpleasant music during stress exposure is associated with reduced blood pressure and ACTH responses in healthy men. In *Neuroendocrinology*, 2013, vol. 98, no. 2, p. 144-150. (3.537 - IF2012). ISSN 0028-3835.

10. **LACKOVIČOVÁ, Ľubica** - GAYKEMA, Ronald P. - BÁNOVSKÁ, Lucia - **KISS, Alexander** - GOEHLER, Lisa E. - **MRAVEC, Boris**. The time-course of hindbrain neuronal activity varies according to location during either intraperitoneal or subcutaneous tumor growth in rats: Single Fos and dual Fos/dopamine β-hydroxylase immunohistochemistry. In *Journal of Neuroimmunology*, 2013, vol. 260, no. 1-2, p. 37-46. (3.033 - IF2012). ISSN 0165-5728.

11. **LAUKOVÁ, Marcela** - **VARGOVIČ, Peter** - **VLČEK, Miroslav** - **LEJAVOVÁ, Katarína** - HUDECOVÁ, Soňa - KRIŽANOVÁ, Oľga - **KVETŇANSKÝ, Richard**. Catecholamine production is differently regulated in splenic T- and B-cells following stress exposure. In *Immunobiology*, 2013, vol. 218, p. 780-789. (2.814 - IF2012). ISSN 0171-2985.

12. **MACEJOVÁ, Dana** - GALBAVÝ, Štefan - PODOBA, J. - **BIALEŠOVÁ, Lucia** - **BRTKO, Július**. mRNA expression pattern of retinoic acid and retinoid X nuclear receptor subtypes in human thyroid papillary carcinoma. In *Oncology Reports*, 2013, vol. 30, no. 5, p. 2371-2378. (2.297 - IF2012). ISSN 1021-335X.

13. **NAGYOVÁ, Eva** - NĚMCOVÁ, Lucie - **MLYNARČÍKOVÁ, Alžbeta** - **SCSUKOVÁ, Soňa** - KALOUS, Jaroslav. Lapatinib inhibits meiotic maturation of porcine oocyte-cumulus complexes cultured in vitro in gonadotropin-supplemented medium. In *Fertility and sterility*, 2013, vol. 99, no. 6, p. 1739-1748. (4.174 - IF2012). ISSN 0015-0282.

14. TKÁČOVÁ, R. - **UKROPEC, Jozef** - SKYBA, P. - **UKROPCOVÁ, Barbara** - POBEHA, P. - **KURDIOVÁ, Timea** - JOPPA, P. - **KLIMEŠ, Iwar** - **GAŠPERÍKOVÁ, Daniela**. Effects of hypoxia on adipose tissue expression of NFjB, IjBa, IKKc and IKAP in patients with chronic obstructive pulmonary disease. In *Cell biochemistry and biophysics*, 2013, vol. 66, no. 1, p. 7-12. (3.743 - IF2012).

15. **VARGOVIČ, Peter** - **UKROPEC, Jozef** - **LAUKOVÁ, Marcela** - **KURDIOVÁ, Timea** - **BALÁŽ, Miroslav** - MANZ, B. - **UKROPCOVÁ, Barbara** - **KVETŇANSKÝ, Richard**. Repeated immobilization stress induces catecholamine production in rat mesenteric adipocytes. In *Stress : the international journal on the biologie of stress*, 2013, vol. 16, no. 3, p. 340-352. (3.252 - IF2012). ISSN 1025-3890.

16. **BAKOŠ, Ján** - **LEŠŤANOVÁ, Zuzana** - **ŠTRBÁK, Vladimír** - **HAVRÁNEK, Tomáš** - **BAČOVÁ, Zuzana**. Neonatal manipulation of oxytocin prevents lipopolysaccharide-induced decrease in gene expression of growth factors in two developmental stages of the female rat. In *NEUROPEPTIDES*, 2014, vol. 48, no. 5, p. 281-286. (2.546 - IF2013). ISSN 0143-4179.

17. **BALÁŽ, Miroslav** - VICIAN, Marek - **JANÁKOVÁ, Zuzana** - **KURDIOVÁ, Timea** - **SUROVÁ, Martina** - **IMRICH, Richard** - **MAJERČÍKOVÁ, Zuzana** - **PENESOVÁ, Adela** - **VLČEK, Miroslav** - **KISS, Alexander** -

BELAN, Víťazoslav - **KLIMEŠ, Iwar** - OLEJNÍK, Juraj - **GAŠPERÍKOVÁ, Daniela** - WOLFRUM, Christian - **UKROPCOVÁ, Barbara** - **UKROPEC, Jozef**. Subcutaneous adipose tissue zinc-α2-glycoprotein is associated with adipose tissue and whole-body insulin sensitivity. In *Obesity*, 2014, vol. 22, no. 8, p. 1821-1829. (4.389 - IF2013). ISSN 1930-7381. DOI 10.1002/oby.20764

18. **KURDIOVÁ, Timea** - **BALÁŽ, Miroslav** - VICIAN, Marek - **MÁDEROVÁ, Denisa** - **VLČEK, Miroslav** - VALKOVIČ, Ladislav - SRBECKÝ, Miroslav - **IMRICH, Richard** - KYSELOVIČOVÁ, Oľga - BELAN, Víťazoslav - JELOK, Ivan - WOLFRUM, Christian - **KLIMEŠ, Iwar** - KRŠŠÁK, Martin - ZEMKOVÁ, Erika - **GAŠPERÍKOVÁ, Daniela** - **UKROPEC, Jozef** - **UKROPCOVÁ, Barbara**. Effects of obesity, diabetes and exercise on Fndc5 gene expression and irisin release in human skeletal muscle and adipose tissue: in vivo and in vitro studies. In *Journal of Physiology*, 2014, vol. 592, no. 5, p. 1091-1107. (4.544 - IF2013). ISSN 0022-3751.

19. **KURDIOVÁ, Timea** - **BALÁŽ, Miroslav** - MAYER, Alexander - **MÁDEROVÁ, Denisa** - BELAN, Víťazoslav - WOLFRUM, Christian - **UKROPEC, Jozef** - **UKROPCOVÁ, Barbara**. Exercise-mimicking treatment fails to increase Fndc5 mRNA & irisin secretion in primary human myotubes. In *Peptides*, 2014, vol. 56, p. 1-7. (2.614 - IF2013). ISSN 0196-9781.

20. **MAJERČÍKOVÁ, Zuzana** - ČERNÁČKOVÁ, Alena - **HORVÁTHOVÁ, Ľubica** - **OSACKÁ, Jana** - PEČEŇÁK, J. - **KISS, Alexander**. Effect of acute asenapine treatment on Fos expression in the forebrain structures under normal conditions and mild stress preconditioning in the rat. In *Brain Research Bulletin*, 2014, vol. 108, p. 60-66. (2.974 - IF2013). ISSN 0361-9230.

21. **STANÍK, Juraj** - DUSATKOVA, P. - CINEK, O. - **VALENTÍNOVÁ, Lucia** - **HUČKOVÁ, Miroslava** - **ŠKOPKOVÁ, Martina** - DUSATKOVA, Lenka - **STANÍKOVÁ, Daniela** - PURA, M. - **KLIMEŠ, Iwar** - LEBL, Ján - **GAŠPERÍKOVÁ, Daniela** - PRUHOVA, S. De novo mutations of GCK, HNF1A and HNF4A may be more frequent in MODY than previously assumed. In *Diabetologia : clinical and Experimental Diabetes and Metabolism*, 2014, vol. 57, no. 3, p. 480-484. (6.880 - IF2013). ISSN 0012-186X. DOI 10.1007/s00125-013-3119-2

22. **MRAVEC, Boris** - **LEJAVOVÁ, Katarína** - CUBÍNKOVÁ, Veronika. Locus (coeruleus) minoris resistentiae in pathogenesis of Alzheimer's disease. In *Current Alzheimer Research*, 2014, vol. 11, no. 10, p. 992 - 1001. (3.796 - IF2013). ISSN 1567-2050.

23. **BABIC, Stanislav** - **POKUSA, Michal** - **DANEVOVÁ, Veronika** - DING, S. T. - **JEŽOVÁ, Daniela**. Effects of atosiban on stress-related neuroendocrine factors. In *Journal of Endocrinology*, 2015, vol. 225, no. 1, p. 9-17. (3.718 - IF2014). ISSN 0022-0795.

24. **BALÁŽ, Miroslav** - **UKROPCOVÁ, Barbara** - **KURDIOVÁ, Timea** - **GAJDOŠECHOVÁ, Lucia** - **VLČEK, Miroslav** - **JANÁKOVÁ, Zuzana** - FEDELES, Jozef - PURA, Mikuláš - **GAŠPERÍKOVÁ, Daniela** - SMITH, Steven R. - TKACOVA, Ruzena - **KLIMEŠ, Iwar** - PAYER, Juraj - WOLFRUM, Christian - **UKROPEC, Jozef**. Adipokine Zinc-alpha 2-Glycoprotein Regulated by Growth Hormone and Linked to Insulin Sensitivity. In *Obesity*, 2015, vol. 23, no. 2, p. 322-328. (3.734 - IF2014). ISSN 1930-7381.

25. **BRTKO, Július** - DVOŘÁK, Zdeněk. Triorganotin compounds - ligands for "rexinoid" inducible transcription factors: Biological effects. In *Toxicology Letters : official journal of EUROTOX*, 2015, vol. 234, no. 1, p. 50-58. (3.262 - IF2014). ISSN 0378-4274.

26. **FARKAŠ, Robert** - SLÁMA, Karel. Respiratory metabolism of salivary glands during the late larval and prepupal development of Drosophila melanogaster. In *Journal of Insect Physiology*, 2015, vol. 81, p. 109-117. (2.470 - IF2014). ISSN 0022-1910.

27. **FARKAŠ, Robert**. Apocrine secretion: New insights into an old phenomenon. In *Biochimica et Biophysica Acta : general subjects*, 2015, vol. 1850, no. 9, p. 1740-1750. (4.381 - IF2014). ISSN 0304-4165.

28. **FICKOVÁ, Mária** - **MACHO, Ladislav** - **BRTKO, Július**. A comparison of the effects of tributyltin chloride and triphenyltin chloride on cell proliferation, proapoptotic p53, Bax, and antiapoptotic Bcl-2 protein levels in human breast cancer MCF-7 cell line. In *Toxicology in vitro : the official journal of the European Society for Toxicology in Vitro*, 2015, vol. 29, no. 4, p. 727-731. (2.903 - IF2014). ISSN 0887-2333.

29. FRANKLIN, Michael - **HLAVÁČOVÁ, Nataša** - **BABIC, Stanislav** - **POKUSA, Michal** - BERMUDEZ, Isabel - **JEŽOVÁ, Daniela**. Aldosterone Signals the Onset of Depressive Behaviour in a Female Rat Model of Depression along with SSRI Treatment Resistance. In *Neuroendocrinology*, 2015, vol. 102, no. 4, p. 274-287. (4.373 - IF2014). ISSN 0028-3835. DOI 10.1159/000431152

30. **GAJDOŠECHOVÁ, Lucia** - **KRŠKOVÁ, Katarína** - OLSZANECKI, Rafal - **ZORAD, Štefan**. Differential regulation of oxytocin receptor in various adipose tissue depots and skeletal muscle types in obese zucker rats. In *Hormone and Metabolic research*, 2015, vol. 47, no. 8, p. 600-604. (2.121 - IF2014). ISSN 0018-5043.

31. **HAVRÁNEK, Tomáš** - **ZAŤKOVÁ, Martina** - **LEŠŤANOVÁ, Zuzana** - **BAČOVÁ, Zuzana** - **MRAVEC, Boris** - HODOSY, Július - **ŠTRBÁK, Vladimír** - **BAKOŠ, Ján**. Intracerebroventricular oxytocin administration in rats enhances object recognition and increases expression of neurotrophins, microtubule-associated protein 2, and synapsin I. In *Journal of Neuroscience Research*, 2015, vol. 93, no. 6, p. 893-901. (2.594 - IF2014). ISSN 0360-4012.

32. **HORVÁTHOVÁ, Ľubica** - **TILLINGER, Andrej** - SIVAKOVA, Ivana - **MIKOVÁ, Lucia** - **MRAVEC, Boris** - BUCOVA, Maria. Chemical sympathectomy increases neutrophil-to-lymphocyte ratio in tumor-bearing rats but does not influence cancer progression. In *Journal of Neuroimmunology*, 2015, vol. 278, p. 255-261. (2.467 - IF2014). ISSN 0165-5728.

33. **LEJAVOVÁ, Katarína** - **ONDIČOVÁ, Katarína** - **HORVÁTHOVÁ, Ľubica** - HEGEDUSOVÁ, Noemi - CUBÍNKOVÁ, Veronika - **VARGOVIČ, Peter** - MANZ, Georg - FILIPČÍK, Peter - **MRAVEC, Boris** - NOVÁK, Michal - **KVETŇANSKÝ, Richard**. Stress-Induced Activation of the Sympathoadrenal System is Determined by Genetic Background in Rat Models of Tauopathy. In *Journal of Alzheimer's Disease*, 2015, vol. 43, no. 4, p. 1157-1161. (4.151 - IF2014). ISSN 1387-2877. DOI 10.3233/JAD-141329

34. **MIKOVÁ, Lucia** - **HORVÁTHOVÁ, Ľubica** - **ONDIČOVÁ, Katarína** - **TILLINGER, Andrej** - VANUCCI, Luca E. - BIZIK, Jozef - GIDRON, Yori - **MRAVEC, Boris**. Ambiguous effect of signals transmitted by the vagus nerve on fibrosarcoma incidence and survival of tumor-bearing rats. In *Neuroscience Letters*. - Limerick : Elsevier Science Publishers, 2015, vol. 593, p. 90-94. (2.030 - IF2014). ISSN 0304-3940.

35. **MRAVCOVÁ, Martina** - **CHOVANOVÁ, Lucia** - PAULIKOVA, L. - **VLČEK, Miroslav** - ROVENSKÝ, Jozef - KILLINGER, Z. - WENDL, J. - **IMRICH, Richard**. Genetics of neuroendocrine factors in rheumatoid arthritis. In *Hormone and Metabolic research*, 2015, vol. 47, no. 6, p. 411-417. (2.121 - IF2014). ISSN 0018-5043.

36. **MRAVEC, Boris** - **VARGOVIČ, Peter** - FILIPČÍK, Peter - NOVÁK, Michal - **KVETŇANSKÝ, Richard**. Effect of a single and repeated stress exposure on gene expression of catecholamine biosynthetic enzymes in brainstem catecholaminergic cell groups in rats. In *European Journal of Neuroscience*, 2015, vol. 42, no. 2, p. 1872-1886. (3.181 - IF2014). ISSN 0953-816X.

37. **PENESOVÁ, Adela** - **VLČEK, Miroslav** - **IMRICH, Richard** - **VERNEROVÁ, Lucia** - **MARKO, Andrea** - **MEŠKOVÁ, Milada** - GRUNNEROVA, Lucia - TURČÁNI, Peter - **JEŽOVÁ, Daniela** - KOLLÁR, Branislav. Hyperinsulinemia in newly diagnosed patients with multiple sclerosis. In *Metabolic Brain Disease*, 2015, vol. 30, no. 4, p. 895-901. (2.638 - IF2014). ISSN 0885-7490.

38. **PIRNÍK, Zdenko** - ŽELEZNÁ, Blanka - **KISS, Alexander** - MALETÍNSKÁ, Lenka. Peripheral administration of palmitoylated prolactin-releasing peptide induces Fos expression in hypothalamic neurons involved in energy homeostasis in NMRI male mice. In *Brain Research*, 2015, vol. 1625, p. 151-158. (2.843 - IF2014). ISSN 0006-8993.

2.1.3 List of monographs/books published abroad

N/A

2.1.4. List of monographs/books published in Slovakia

STANÍK, Juraj - **GAŠPERÍKOVÁ, Daniela** - **KLIMEŠ, Iwar**. *Monogénové poruchy sekrécie a účinku inzulínu*. Bratislava : Univerzita Komenského, 2015. 148 s. ISBN 978-80-223-3803-5.

KRAHULEC, Boris - FÁBRYOVÁ, Ľubomíra - HOLÉCZY, Pavol - **KLIMEŠ, Iwar** (Eds.). Klinická obezitológia. 1. vyd. Brno : Facta Medica, 2013. 336 s. ISBN 978-80-904731-7-1.

2.1.5. List of other scientific outputs specifically important for the institute, max. 10 items

1. Partner/contractor: Children diabetological centre of SR at the First children clinic (DFNsP a LF UK).

   Title of application: Identification of patients with monogenic diabetes and pharmacogenomic recomendation of treatment.

2. Partner/contractor: Surgical clinic of Slovak medical university.

   Title of application: The importance of adipose tissue and sceletal muscle in pathogenesis of obesity and insulin resistance

3. Partner/contractor: The National Institute of Cardiovascular Diseases

   Title of application: Sport and Health – the impact of physical activity on metabolic health in man.

4. Partner/contractor: Faculty of natural sciences, Commenius University, Bratislava

   Title of application: Measurement of radioactivity (^{125}I, ^{3}H and ^{14}C) in biological samples.

5. Partner/contractor: The National Institute of Cardiovascular Diseases

   Title of application: Evaluation of adrenergic receptor gene expression in heart.

6. Partner/contractor: Oncological Institute of St. Elizabeth, Bratislava

   Title of application: Replacement of ELISA method for evaluation of diaminooxidase activity by RIA kit for diagnosis of histamin intolerance.

7. Partner/contractor: MED-PED centrum of doc. MUDr. Katarína Rašlová, PhD.

   Title of application: DNA diagnosis of patients with familiar hypercholesteroleamia.

8. Partner/contractor: The First ENT clinic of medical faculty at Commenius University and Faculty hospital, Bratislava.

   Title of application: DNA diagnosis of patients with sensineuronal hearing loss.

2.1.6. List of patents, patent applications, and other intellectual property rights registered abroad, incl. revenues

N/A

2.1.7. List of patents, patent applications, and other intellectual property rights registered in Slovakia, incl. revenues

N/A

2.1.8. Table of research outputs (as in annual reports).

Papers from international collaborations in large-scale scientific projects (Dwarf team, ALICE Collaboration, ATLAS collaboration, CD Collaboration, H1 Collaboration, HADES Collaboration, and STAR Collaboration) have to be listed separately.

Scientific publications	2012			2013			2014			2015			total			
	number	No. / FTE	No. / salary budget	number	No. / FTE	No. / salary budget	number	No. / FTE	No. / salary budget	number	No. / FTE	No. / salary budget	number	averaged number per year	av. No. / FTE	av. No. / salary budget
Scientific monographs and monographic studies in journals and proceedings published abroad *(AAA, ABA)*	0,0	0,000	0,000	0,0	0,000	0,000	0,0	0,000	0,000	0,0	0,000	0,000	**0,0**	**0,0**	**0,000**	**0,000**
Scientific monographs and monographic studies in journals and proceedings published in Slovakia *(AAB, ABB)*	0,0	0,000	0,000	0,0	0,000	0,000	0,0	0,000	0,000	1,0	0,022	0,002	**1,0**	**0,3**	**0,005**	**0,000**
Chapters in scientific monographs published abroad *(ABC)*	1,0	0,023	0,002	5,0	0,102	0,008	1,0	0,022	0,002	0,0	0,000	0,000	**7,0**	**1,8**	**0,038**	**0,003**
Chapters in scientific monographs published in Slovakia *(ABD)*	0,0	0,000	0,000	0,0	0,000	0,000	0,0	0,000	0,000	2,0	0,043	0,003	**2,0**	**0,5**	**0,011**	**0,001**
Scientific papers published in journals registered in Current Contents Connect *(ADCA, ADCB, ADDA, ADDB)*	26,0	0,605	0,043	28,0	0,569	0,047	29,0	0,631	0,049	48,0	1,035	0,083	**131,0**	**32,8**	**0,710**	**0,055**
Scientific papers published in journals registered in Web of Science Core Collection and SCOPUS *(ADMA, ADMB, ADNA, ADNB)*	22,0	0,512	0,037	21,0	0,427	0,035	10,0	0,217	0,017	16,0	0,345	0,028	**69,0**	**17,3**	**0,374**	**0,029**
Scientific papers published in other foreign journals (not listed above) *(ADEA, ADEB)*	0,0	0,000	0,000	2,0	0,041	0,003	0,0	0,000	0,000	0,0	0,000	0,000	**2,0**	**0,5**	**0,011**	**0,001**
Scientific papers published in other domestic journals (not listed above) *(ADFA, ADFB)*	3,0	0,070	0,005	3,0	0,061	0,005	1,0	0,022	0,002	6,0	0,129	0,010	**13,0**	**3,3**	**0,070**	**0,005**
Scientific papers published in foreign peer-reviewed proceedings *(AEC, AECA)*	2,0	0,047	0,003	0,0	0,000	0,000	1,0	0,022	0,002	0,0	0,000	0,000	**3,0**	**0,8**	**0,016**	**0,001**
Scientific papers published in domestic peer-reviewed proceedings *(AED, AEDA)*	0,0	0,000	0,000	2,0	0,041	0,003	4,0	0,087	0,007	5,0	0,108	0,009	**11,0**	**2,8**	**0,060**	**0,005**
Published papers (full text) from foreign and international scientific conferences *(AFA, AFC, AFBA, AFDA)*	3,0	0,070	0,005	0,0	0,000	0,000	1,0	0,022	0,002	0,0	0,000	0,000	**4,0**	**1,0**	**0,022**	**0,002**
Published papers (full text) from domestic scientific conferences *(AFB, AFD, AFBB, AFDB)*	0,0	0,000	0,000	3,0	0,061	0,005	2,0	0,043	0,003	0,0	0,000	0,000	**5,0**	**1,3**	**0,027**	**0,002**

- **Supplementary information and/or comments on the scientific outputs of the institute.**

Most important results documenting international and domestic collaboration of the Institute

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2.2. Responses to the research outputs (citations, etc.)

2.2.1. Table with citations per annum.

Citations of papers from international collaborations in large-scale scientific projects (Dwarf team, ALICE Collaboration, ATLAS collaboration, CD Collaboration, H1 Collaboration, HADES Collaboration, and STAR Collaboration) have to be listed separately.

Citations, reviews	2011		2012		2013		2014		total		
	number	No. / FTE	number	No. / FTE	number	No. / FTE	number	No. / FTE	number	averaged number per year	av. No. / FTE
Citations in Web of Science Core Collection (1.1, 2.1)	869,0	20,238	1025,0	20,821	965,0	20,987	796,0	17,163	**3655,0**	**913,8**	**19,807**
Citations in SCOPUS (1.2, 2.2) if not listed above	161,0	3,749	245,0	4,977	260,0	5,655	209,0	4,506	**875,0**	**218,8**	**4,742**
Citations in other citation indexes and databases (not listed above) (3.2,4.2,9,10)	0,0	0,000	0,0	0,000	0,0	0,000	0,0	0,000	**0,0**	**0,0**	**0,000**
Other citations (not listed above) (3, 4, 3.1, 4.1)	3,0	0,070	0,0	0,000	3,0	0,065	11,0	0,237	**17,0**	**4,3**	**0,092**
Reviews (5,6)	0,0	0,000	0,0	0,000	0,0	0,000	0,0	0,000	**0,0**	**0,0**	**0,000**

2.2.2. List of 10 most-cited publications, with number of citations, in the assessment period (2011 – 2014).

This list includes paper based on research work mainly conducted in the institute with significant contribution of researchers affiliated with the institute. Self citations were excluded.

1. **KVETŇANSKÝ, Richard** - SABBAN, E. L. - PALKOVITS, M. Catecholaminergic Systems in Stress: Structural and Molecular Genetic Approaches. In *Physiological reviews*, 2009, vol. 89, no. 2, p. 535-606.

   115 citations

2. **MONČEK, Fedor** - **DUNČKO, Roman** - JOHANSSON, B.B. - **JEŽOVÁ, Daniela**. Effect of environmental enrichment on stress related systems in rats. In *Journal of neuroendocrinology*, 2004, vol. 16, p. 423-431.

   51 citations

3. **UKROPEC, Jozef** - **RÁDIKOVÁ, Žofia** - **HUČKOVÁ, Miroslava** - **KOŠKA, Juraj** - KOCAN, M. - **ŠEBŐKOVÁ, Elena** - DROBNÁ, Beata - TRNOVEC, Tomáš - SUŠIENKOVÁ, K. - LABUDOVÁ, V. - **GAŠPERÍKOVÁ, Daniela** - **LANGER, Pavel** - **KLIMEŠ, Iwar**. High prevalence of prediabetes and diabetes in a population exposed to high levels of an organochlorine cocktail. In *Diabetologia : clinical and Experimental Diabetes and Metabolism*, 2010, vol. 53, no. 5, p. 899-906.

   39 citations

4. **DUNČKO, Roman** - **KISS, Alexander** - **ŠKULTÉTYOVÁ, I. - RUSNÁK, Martin** - **JEŽOVÁ, Daniela**. Corticotropin-releasing hormone mRNA levels in response to chronic mild stress rise in male but not in female rats while tyrosine hydroxylase mRNA levels decrease in both sexes. In *Psychoneuroendocrinology*, 2001, vol. 26, p. 77-89.

   38 citations

5. **RÁDIKOVÁ, Žofia - KOŠKA, Ján - HUCKOVÁ, M. - KSINANTOVÁ, L. - IMRICH, Richard - VIGAŠ, Milan** - TRNOVEC, Tomáš - **LANGER, Pavel** - **ŠEBŐKOVÁ, Elena** - **KLIMEŠ, Iwar**. Insulin sensitivity indices: A proposal of cut-off points for simple identification of insulin-resistant subjects. In *Experimental and clinical endocrinology and diabetes*, 2006, vol. 114, no. 5, p. 249-256.

   36 citations

6. **MACHO, Ladislav** - **FICKOVÁ, Mária** - **JEŽOVÁ, Daniela** - **ZORAD, Štefan**. Late effects of postnatal administration of monosodium glutamate on insulin action in adult rats. In *Physiological Research*, 2000, vol. 49, suppl. 1, p. S79-S85.

   26 citations

7. **JEŽOVÁ, Daniela** - **ŠKULTÉTYOVÁ, I. - TOKAREV, D. - BAKOŠ, P. - VIGAŠ, Milan**. Vasopressin and oxytocin in stress. In *Annals of the New York Academy of Sciences*, 2006, vol. 771, p. 192-203.

   25 citations

8. **KISS, Alexander** - MIKKELSEN, J.D. Oxytocin - anatomy and functional assignments: A minireview. In *Endocrine Regulations*, 2005, vol. 39, no. 3, p. 97-105.

   25 citations

9. **BAKOŠ, Ján** - **DUNČKO, Roman - MAKATSORI, A.** - **PIRNÍK, Zdenko** - **KISS, Alexander** - **JEŽOVÁ, Daniela**. Prenatal immune challenge affects growth, behavior, and brain dopamine in offspring. In *Annals of the New York Academy of Sciences*, 2004, vol. 1018, p. 281-287. (1.892 - IF2003).

   23 citations

10. **ONDREJČÁKOVÁ, Mária** - RAVINGEROVÁ, Táňa - **BAKOŠ, Ján** - PANCZA, Dezider - **JEŽOVÁ, Daniela**. Oxytocin exerts protective effects on in vitro myocardial injury induced by ischemia and reperfusion. In *Canadian Journal of Physiology and Pharmacology*, 2009, vol. 87, no. 2, p. 137-142. (1.763 - IF2008). (2009 - Current Contents).

    23 citations

2.2.3. List of most-cited authors from the Institute (at most 10 % of the research employees with university degree engaged in research projects) and their number of citations in the assessment period (2011– 2014).

1. Kvetňanský – 1609 citations
2. Ježová – 906 citations
3. Klimeš – 715 citations
4. Gašperíková – 581 citations
5. Kiss – 360 citations
6. Ukropec – 315 citations

- **Supplementary information and/or comments on responses to the scientific output of the institute.**

The research article “Dunčko R., Kiss A., Škultétyová I., Rusnák M., Jezova D.: Corticotropin-releasing hormone mRNA levels in response to chronic mild stress rise in male but not in female rats while tyrosine hydroxylase mRNA levels decrease in both sexes. Psychoneuroendocrinology 26: 77-89, 2001” has been listed among the **Slovak Top 10 Cited Articles** from all scientific disciplines of so called independent research published in 2001-2013 (Fiala and Ho, Current Science, 2016). Term “independent research” means research work conducted solely by researchers affiliated with the home institution without any foreign help.

To underline the long term high quality of the research of the Institute of Experimental Endocrinology we mention the paper published by former researcher of the institute J. Sedlak in 1968 (Anal Biochem. 1968;25(1):192-205). This paper was totally cited 4 007 times (WOS). In the period of 2011-2014 the paper was still cited 885 times.

Two scientists of the IEE SAS belong to the most cited researchers in Slovakia. According to Web of Science, R. Kvetnansky has the total number of citations over 8000 and D. Jezova over 4000.

Citations to selected papers based on international and domestic collaborations

1. SMITH, M.A. - MAKINO, Seiichi - **KVETŇANSKÝ, Richard** - POST, R. M. Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 messenger-rnas in the hippocampus. In *Journal of Neuroscience*, 1995, vol. 15, no. 3, p. 1768-1777.

   208 citations

2. PEARSON, E.R. - FLECHTNER, I. - NJOLSTAD, P.R. - MALECKI, M.T. - FLANAGAN, S.E. - LARKIN, B. - ASHCROFT, F. M. - **KLIMEŠ, Iwar** - CODNER, E. - IOTOVA, V. - SLINGERLAND, A. S. - SHIELD, J. - ROBERT, J. J. - HOLST, J. J. - CLARK, P. M. - ELLARD, S. - SOVIK, O. - POLAK, M. - HATTERSLEY, A. T. - **GAŠPERÍKOVÁ, Daniela** - **STANÍK, Juraj**. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutation. In *New England Journal of Medicine*, 2006, vol. 355, n. 5, p. 467-477.

   127 citations

3. KUO, L. E. - KITLINSKÁ, J. B. - TILAN, J. U. - LI, L. J. - BAKER, S. B. - JOHNSON, M. D. - LEE, E. W. - BURNETT, M. S. - FRICKE, S. T. - **KVETŇANSKÝ, Richard** - HERZOG, H. - ZUKOWSKÁ, Ž. Neuropeptide Y acts directly in the periphery on fat tissue and mediates stress-induced obesity and metabolic syndrome. In *Nature medicine*, 2007, vol. 13, no. 7, p. 803-811.

   122 citations

4. MARTINIOVÁ, Lucia - KOTYS, Melanie S. - THOMASSON, David - SCHIMEL, Daniel - LAI, Edwin W. - BERNARDO, Marcelino - MERINO, Maria J. - POWERS, James F. - RUZICKA, Jan - **KVETŇANSKÝ, Richard** - CHOYKE, Peter L. - PACÁK, Karel. Noninvasive Monitoring of a Murine Model of Metastatic Pheochromocytoma: A Comparison of Contrast-Enhanced MicroCT and Nonenhanced MRI. In *Journal of Magnetic Resonance Imaging*, 2009, vol. 29, no. 3, p. 685-691.

   49 citations

5. SMITH, M.A. - MAKINO, Seiichi - **KVETŇANSKÝ, Richard** - POST, R. M. Effects of stress on neurotrophic factor expression in the rat brain. In *Stress : The international journal on the biologie of stress*, 1995, vol. 771, p. 234-239.

   48 citations

6. KRISHNAN, J. - DANZER, C. - SIMKA, T. - **UKROPEC, Jozef** - WALTER, K.M. - KUMPF, S. - MIRTSCHINK, P. - **UKROPCOVÁ, Barbara** - **GAŠPERÍKOVÁ, Daniela** - PEDRAZZINI, T. - KREK, W. Dietary obesity-associated Hif1α activation in adipocytes restricts fatty acid oxidation and energy expenditure via suppression of the Sirt2-NAD+ system. In *Genes & Development*, 2012, vol. 26, no. 3, p. 259-270.

   47 citations

7. KUO, L. E. - CZARNECKA, M. - KITLINSKA, J. B. - TILAN, J. U. - **KVETŇANSKÝ, Richard** - ZUKOWSKA, Z. Chronic Stress, Combined with a High-Fat/High-Sugar Diet, Shifts Sympathetic Signaling toward Neuropeptide Y and Leads to Obesity and the Metabolic Syndrome. In *Annals of the New York Academy of Sciences*, 2008, vol. 1148, p. 232-237.

   42 citations

8. BARTANUSZ, V. - **JEŽOVÁ, Daniela** - ALAJAJIAN, B. - DIGICAYLIOGLU, M. The blood-spinal cord barrier: Morphology and Clinical Implications. In *Annals of Neurology*. - Hoboken : WILLEY- LISS, 2011, vol. 70, no. 2, p. 194-206. ISSN 0364-5134.

33 citations

2.3. Research status of the institute in international and national contexts

- **International/European position of the institute**

2.3.1. List of the most important research activities demonstrating the international relevance of the research performed by the institute, incl. major projects (details of projects should be supplied under Indicator 2.4). Max. 10 items.

1. Integrated Structural Biology Infrastructure (FP7 211252), 2013-2015, Institute - Robert Farkaš (Investigator)
2. Lipid droplets as dynamic organelles of fat deposition and release: translational research towards human disease (FP7-202272), 2008-2012, Institute - Daniela Gašperíková (Investigator)
3. MEchanisms of Lymphocytes TRansmigration Across the Blood Brain Barrier (NEURON ERA Net II), 2015-2018, Institute - Adela Penesová (Investigator)

2.3.2. List of international conferences (co)organised by the institute.

Of particular importance for the international recognition of the Institute of Experimental Endocrinology was the **world famous symposium on stress**, the *11th* International Symposium on Catecholamines and Other Neurotransmitters in Stress, held in June of 2015. **Since 1975**, the experts in stress research have been gathered every 4 years in Smolenice Castle in Slovakia. This **series of symposia** organized by the researchers of the Institute has become a tradition predating the fall of communism in Eastern Europe, and has witnessed the rich history of truly international stress research. The 2015 meeting included presentations and posters from many countries, featuring international **thought leaders in the area of stress** biology and medicine. The significance of the Smolenice meeting for the future development of stress research is underlined by the fact that about one third of the participants were **PhD students and young scientists**. A special issue of the leading journal in the field "Stress" based on contributions from the 2015 symposium has been published a year thereafter (Jezova D and Herman J.P., 19: 339-340, 2016).

1. International Workshop of 7th framework programme LipidomicNet, Bratislava, Crowne Plaza 16.01.-17.01.2012.
2. Molecular and translational medicine, international conference Bratislava, Slovakia, 26.06.-26.06.2012
3. Endocrine disruptors, international conference, Bratislava, Slovakia, 16.10.-17.10.2012
4. XXIII. Diabetes days, Bratislava, Slovakia, 12.06.-14.06.2013
5. XIII. Slovak obesity days, Trnava, Slovakia, 13.11.-14.11.2015

6. Endocrine disruptors. international conference, Bratislava, Slovakia, 04.06.-05.06.2015
7. 11th Symposium on catecholamines and neurotransmitters in stress (international), Smolenice Castle, Slovakia, 20.06.-25.06.2015

2.3.3. List of edited proceedings from international scientific conferences.

N/A

2.3.4. List of journals edited/published by the institute:

ENDOCRINE REGULATIONS

2.3.4.1. WOS (IF of journals in each year of the assessment period)

NO

2.3.4.2. SCOPUS

YES

2.3.4.3. other databases

PubMed, Excerpta Medica Database (EMBASE), Google Scholar (Indexed Copernicus), The Digital Object Identification (DOI)

2.3.4.4. not included in databases

N/A

- **National position of the institute**

2.3.5. List of selected projects of national importance

1. Molecular-genetic alternations in adipose tissue after change in therapy from ACE inhibitors to AT1 receptor blockers in patients with essential hypertension - ADIRAS (MZ2007/27-SAV-02), 2008-2013**,** Institute - Štefan Zorad (Coordinator)
2. Signal pathway of nitric oxide and hydrogen sulfide, its disturbances and participation in development of hypertension and atherosclerosis (MZ 2012/51-SAV-1), 2011-2016, Institute - Štefan Zorad (Investigator)
3. Genes which are increasing the risk to develop rheumatoid arthritis in the Austrian and Slovak populations (ATMOS N00024; crossboarder collaboration between Austria and Slovakia), 2009-2012, Institute - Daniela Gašperíková (Investigator)
4. Metabolic health and muscle secretory profile in aerobic and resistance trained obese pre-diabetic individuals (European Foundation for the Study of Diabetes), 2010-2013, Institute - Barbara Ukropcová (Investigator)
5. Adipose tissue and skeletal muscle plasticity in metabolic health and in insulin resistance (European Foundation for the Study of Diabetes), 2010-2013, Institute - Jozef Ukropec (Investigator)
6. Effect of exercise on pathophysiology of type 2 diabetes: Focus on magnetic resonance imaging and spectroscopy in skeletal muscle (2013-10-15-0004; Aktion Österreich - Slowakei, Wissenschafts und Erziehungskooperation project), 2014-2015, Institute - Jozef Ukropec (Coordinator)

2.3.6. Projects of the Slovak Research and Development Agency (APVV)

1. The effect of selected endocrine disruptors on the development of mammary gland , prostatic cancer and ovarian dysfunctions (APVV-0147-10), 2011-2014, Institute - Mária Ficková (Coordinator)
2. Interaction of mental, cardiovascular, neuroendocrine and metabolic factors: from animal models to clinical applications (APVV-0028-10), 2011-2014, Institute - Daniela Ježová (Coordinator)

   This project was evaluated as the most successful out of all projects of the grant agency in the field of medical sciences completed in 2014.
3. Developmental effects of neuropeptides (APVV-0253-10), 2011-2014, Institute - Ján Bakoš (Coordinator)
4. Is stress a crucial factor in the process of neurodegeneration accompanying Alzheimer's disease? (APVV-0088-10), 2011-2014, Institute - Richard Kvetňanský (Coordinator)
5. Neurobiology of cancer: the study of the nervous system role in etiopathogenesis of tumor growth and development of metastasis (APVV-0007-10), 2011-2014, Institute - Boris Mravec (Investigator)
6. Antitumour effect of biologically active ligands of nuclear retinoid X receptor heterodimers in tissue carcinoma cell lines (APVV-0160-11), 2012-2015, Institute - Július Brtko (Coordinator)
7. Biosafety of therapeutically and commercially used nanoparticles: focus on reproductive and immune system, oxidative status and prevention of potential risk (APVV-0404-11), 2012-2015, Institute - Soňa Scsuková (Coordinator)
8. Identification of new genetic aspects of monogenic endocrinopathies by next generation sequencing (APVV-0187-12), 2013-2017, Institute - Daniela Gašperíková (Coordinator)
9. Cognitive, personal and psychophysiological factors of the stress in the context of the relationship between anxiety and allergies and their optimalisation (APVV-0496-12), 2013-2017, Institute - Daniela Ježová (Investigator)
10. Possible dual function of P-glycoprotein in leukemia cells: efflux pump and regulatory protein (APVV-14-0334), 2015-2018, Investigator - Július Brtko (Investigator)

2.3.7. Projects of the Scientific Grant Agency of the Slovak Academy of Sciences and the Ministry of Education (VEGA)

1. Protective effects of neuropeptides (2/0132/12), 2012-2014, Institute - Zuzana Bačová (Coordinator)
2. Molecular-genetic and proteomic analysis of developmentally-linked metabolic function of hormonally responsive and obligatory malate dehydrogenases complex in Drosophila melanogaster (2/0109/13), 2013-2016, Institute - Robert Farkaš (Coordinator)
3. Prevalence and mutation spectrum of the most common forms of monogenic obesity (2/0166/14), 2014-2016, Institute - Daniela Gašperíková (Coordinator)

4. Mechanisms of atypical effects of hormones (2/0128/14), 2014-2016, Institute - Nataša Hlaváčová (Coordinator)
5. Interactions of neuroendocrine and metabolic factors in critically ill patients (2/0084/12), 2012-2015, Institute - Richard Imrich (Coordinator)
6. New approaches in identification of individual RAS components and function of ACE2/Ang-(1-7)/MasR and (pro)renin receptor pathways in development of adipose tissue hypertrophy (2/0174/14), 2014-2016, Institute - Katarína Kršková (Coordinator)
7. Regulation of the immune system by activity of sympathoadrenal and adrenocortical systems in mammals exposed to acute and chronic stress (2/0036/11), 2011-2014, Institute - Richard Kvetňanský (Coordinator)
8. Antitumour versus disruption effects of biologically active triaryl-/trialkyl-organometal ligands of retinoid X receptors in tissue cultures of tumour cells (2/0171/14), 2014-2016, Institute - Dana Macejová (Coordinator)
9. Functional relationship between activity of the hypothalamichypophyseal-adrenocortical axis and the effect of selected antipsychotic (2/0069/12), 2012-2014, Institute - Jana Osacká (Coordinator)
10. Effect of Endurance and Strength Training on the Secretory Profile and Molecular Phenotype of Skeletal Muscle and Cultured Primary Human Muscle Cells from Obese Prediabetic Individuals (2/0174/12), 2012-2014, Institute - Barbara Ukropcová (Coordinator)

2.3.8. Projects of SAS Centres of Excellence

Next to the **"Centre of Excellence of the European Union"**, a title awarded by the European Comission to the Institute of Experimental Endocrinology based on a successful project of the 5th Framework Program, researchers of the institute participated on small projects supported by the Slovak Academy of Sciences:

1. Centre of Excellence for the study of metabolic aspects of development, diagnostics and treatment of malignancies (CEMAN), 2011-2015, Institute - Július Brtko (Investigator)
2. Centre of Excellence for the study of metabolic aspects of development, diagnostics and treatment of malignancies (CEMAN), 2011-2015, Institute - Daniela Ježová (Investigator)
3. Centre of excellence for research on the brain (BRAINCENTRUM), 2011-2015, Institute - Alexander Kiss (Investigator)
4. Centre of excellence for research on the brain (BRAINCENTRUM), 2011-2015, Institute - Richard Kvetňanský (Investigator)
5. Centre of excellence for examination of regulatory role of nitric oxide in civilization diseases (NOREG), 2011-2015, Institute - Štefan Zorad (Investigator)

2.3.9. National projects supported by EU Structural Funds

1. Building a Competency Centre for research and development in the field of molecular medicine (26240220071), 2011-2015, Institute - Iwar Klimeš (Partner)
2. Transfer of genetic knowledge of endocrine research into clinical praxis - TRANSENDOGEN (26240220051), 2010-2013, Institute - Iwar Klimeš (Coordinator)

3. Implementation of molecular medicine into diagnostics, therapy and prevention of serious lifestyle diseases (26240220068), 2010-2014, Institute - Iwar Klimeš (Partner)
4. Centre of excellence for translational research in molecular medicine - TRANSMED 2 (26240120030), 2010-2012, Institute - Iwar Klimeš (Partner)
5. University Biomedical Research Park Bratislava (26240220087), 2013-2015, Institute - Daniela Gašperíková (Partner/Investigator), Richard Imrich (Partner/Investigator), Daniela Ježová (Partner/Investigator), Iwar Klimeš (Partner)

2.3.10. List of journals (published only in the Slovak language) edited/published by the institute:

N/A

2.3.10.1. WOS (IF of journals in each year of the assessment period)

2.3.10.2. SCOPUS

2.3.10.3. Other databases

2.3.10.4. Not included in databases

- **Position of individual researchers in an international context**

2.3.11. List of invited/keynote presentations at international conferences, as documented by programme or invitation letter

2012

1. BRTKO J.: Charakter, funkcia a úloha jadrových receptorov biologicky aktívnych derivátov vitamínu A v organizme. International Conference: „Přírodní látky v medicíně“, Faculty of Natural Sciences, Palacky Univerzity, Olomouc, Czech Republic, May 28, 2012.
2. JEZOVA D.: Symposium “Chybějící odměna”, 54. Česko-slovenská psychofarmakologická konferencia, Lazne-Jesenik, Czech Republic, January 4–8, 2012.
3. JEZOVA D.: Players involved in the stress response: what is good and what is bad? International Brain Research Organization Workshop, Szeged, Hungary, January 19–21, 2012. (opening plenary lecture)
4. JEZOVA D.: Oxytocin: an antiobesity and cardioprotective molecule. 17th World Congress on Heart Disease, Toronto, Canada, July 27–30, 2012.
5. JEZOVA D.: Stress and drugs: cardioprotectivite and cardiotoxic effects. Interdisciplinary Toxicology Conference TOXCON 2012: Toxicology at the Crossroad, Stara Lesna, Slovakia, August 29–31, 2012.

2013

1. BRTKO J., MACEJOVA D., GALBAVY S., BIALESOVA L., PODOBA J.: Expression mRNA pattern of retinoic acid and retinoid X nuclear receptor subtypes in thyroid carcinomas. The 4th Congress of the Polish Thyroid Association, Lodz, Poland, March 11–13, 2013.

2. BRTKO J., MACEJOVA D., BIALESOVA L., GALBAVY S.: Expresia podtypov retinoidných a rexinoidných jadrových receptorov a ich koregulátorov v karcinómoch štítnej žľazy. Symposium with international attendance "XXXVI. Endokrinologické dni", Plzen, Czech Republic, October 10–12, 2013.
3. JEZOVA D., HLAVACOVA N.: Ovplyvnenie hormónu aldosterónu – nový smer vo vývoji anxiolytík. Conference 55. česko-slovenská psychofarmakologická konferencia, Lazne-Jesenik, Czech Republic, January 4–8, 2013.
4. JEZOVA D., HLAVACOVA N.: Hyperaldosteronism in an animal model - changes in depression-like behaviour and gene expression relevant to major depressive disorder. 11th World Congress of Biological Psychiatry, Kyoto, Japan, June 23–27, 2013.
5. JEZOVA D., HLAVACOVA N.: Aldosterone-A Bridge Between Cardiovascular and Mood Disorders? 18th World Congress on Heart Disease, Vancouver, Canada, July 26–29, 2013.

2014

1. BRTKO J., DVORAK Z.: Nuclear retinoid/retinoid X receptors and their endogenous and xenobiotic ligands in metabolism, differentiation and cancer treatment. 50th EUROTOX Congress, Edinburgh, Great Britain, September 7-10, 2014.
2. HLAVACOVA N.: Nový pohľad na vzťah renín-angiotenzín-aldosterónového systému k afektívnym poruchám. 56. česko-slovenská psychofarmakologická konferencia, Lazne-Jesenik, Czech Republic, January 8–12, 2014.
3. IZAKOVA I., JEZOVA D., SEGEDA V.: Klinické aspekty hyperaldosteronizmu pri afektívnych poruchách. 56. česko-slovenská psychofarmakologická konferencia, Lazne-Jesenik, Czech Republic, January 8–12, 2014.
4. JEZOVA D.: Receptory aldosterónu ako terč psychofarmakologickej liečby. 56. česko-slovenská psychofarmakologická konferencia, Lazne-Jesenik, Czech Republic, January 8–12, 2014.
5. JEZOVA D., KRIZOVA L., KOLLAR B., SIARNIK P., HLAVACOVA N., PENESOVA A., TURCANI P.: Aldosterone, copeptine and other neuroendocrine markers in patients with stroke. 19th World Congress on Heart Disease, Boston, USA, August 25–28, 2014.
6. JEZOVA D.: Trait and state anxiety: a role in the stress response. IV. Sjezd fiziologov SNG, Soči, Russia, October 8–12, 2014.

2015

1. BRTKO J.: Conditional Nuclear Receptor Heterodimers: Ich úloha vo fyziologických procesoch bunky a v terapii niektorých onkologických ochorení. Faculty of Natural Sciences UP, Olomouc, Czech Republic, April 15, 2014.
2. BRTKO J.: The road to nuclear receptors and their cognate ligands: Insight into physiology and therapy of malignant diseases. 79th Meeting of the Hungarian Physiological Society. Szeged, Hungary, May 27–30, 2015.
3. BRTKO J.: Úloha selenoenzýmov a selenoproteínov na úrovni bunky a v integrovanom organizme. Faculty of Natural Sciences UP, Olomouc, Czech Republic, April 14, 2014.

4. IMRICH R., VLCEK M., PENESOVA A., CHOVANOVA L.: Rheumatoid arthritis: translating genetics to clinical care. 79th Meeting of the Hungarian Physiological Society. Szeged, Hungary, May 27–30, 2015.
5. JEZOVA D.: Pohlavné rozdiely v hormonálnej reaktivite a ich dosah na účinky psychofarmák. 57. česko-slovenská psychofarmakologická konferencia, Lazne-Jesenik, Czech Republic, November 7–11, 2015.
6. HLAVACOVA N., JEZOVA D.: Modulácia mineralokortikoidných receptorov ako možný cieľ psychofarmakologickej liečby. 57. česko-slovenská psychofarmakologická konferencia, Lazne-Jesenik, Czech Republic, November 7–11, 2015.
7. JEZOVA D., HLAVACOVA N., DUNCKO R., SOLARIKOVA P., MARKO M., BREZINA I. Cardiovascular responses to threatful challenges in persons with high trait anxiety. 20th World Congress on Heart Disease, Vancouver, Canada, July 25–27, 2015.
8. JEZOVA D., MAYEROVA M., HLAVACOVA N., CESKOVA E., USTOHAL L.: Aldosterón a schizofrénia. 16. Česko-slovenský psychiatrický sjezd, Brno, Czech Republic, October 21–24., 2015.
9. MRAVEC B., HORVATHOVA L.: The role of neuro-endocrine-immune interactions in cancer. 79th Meeting of the Hungarian Physiological Society. Szeged, Hungary, May 27–30, 2015.
10. STRBAK V.: Thyrotropin releasing hormone and insulin regulatory secretory pathway. 6th Global Diabetes Summit and Medicare Expo, Dubai, UAE, November 2–4, 2015.
11. ZORAD S., KRSKOVA K., GAJDOSECHOVA L.: Is oxytocin a next-generation peptidyl drug target for obesity and diabetes? 79th Meeting of the Hungarian Physiological Society. Szeged, Hungary, May 27–30, 2015.

2.3.12. List of researchers who served as members of the organising and/or programme committees

2012

BRTKO JÚLIUS: Member of the Organising and Programme Committee of the conference “Endocrine Disruptors”, Bratislava, Slovakia, October16, 2012.

GAŠPERÍKOVÁ DANIELA: Member of the Organising and Programme Committee of the “Workshop of LipodomicNet project”, Bratislava, Slovakia, January 16-17, 2012.

IMRICH RICHARD: Chairman of the Organizing Committee of the “Molecular and Translational Medicine Conference 2012”, Bratislava, Slovakia, June 26, 2012.

KLIMEŠ IWAR: Member of the Organising and Programme Committee of the “Workshop of LipodomicNet project”, Bratislava, Slovakia, January 16-17, 2012.

VLČEK MIROSLAV: Scientific secretary of the Organizing Committee of the “Molecular and Translational Medicine Conference 2012”, Bratislava, Slovakia, June 26, 2012.

2014

ZORAD ŠTEFAN: Member of the Scientific Programme Committee of the “FEPS (Federation of European Physiological Societies) Meeting”, Budapest, Hungary, August 27–30, 2014.

2015

BRTKO JÚLIUS: Member of the Scientific Programme Committee of the conference “Endocrine Disruptors”, Bratislava, Slovakia, June 4–5, 2015.

CSANOVÁ AGNESA: Member of the Local Organising Committee of the “11th Symposium on catecholamines and other neurotransmitters in stress”, Smolenice Castle, Slovakia, June 20–25, 2015.

DANEVOVÁ VERONIKA: Member of the Local Organising Committee of the “11th Symposium on catecholamines and other neurotransmitters in stress”, Smolenice Castle, Slovakia, June 20–25, 2015.

HLAVÁČOVÁ NATAŠA: Chairman of the Local Organising Committee of the “11th Symposium on catecholamines and other neurotransmitters in stress”, Smolenice Castle, Slovakia, June 20–25, 2015.

JEŽOVÁ DANIELA: Member of the Scientific Advisory Board, 20th World Congress on Heart Disease, Vancouver, Canada, July 25–27, 2015.

JEŽOVÁ DANIELA: Chairman of the Organising and Programme Committee of the “11th Symposium on catecholamines and other neurotransmitters in stress”, Smolenice Castle, Slovakia, June 20–25, 2015.

POKUSA MICHAL: Member of the Local Organising Committee of the “11th Symposium on catecholamines and other neurotransmitters in stress”, Smolenice Castle, Slovakia, June 20–25, 2015.

PROKOPOVÁ BARBORA: Member of the Local Organising Committee of the “11th Symposium on catecholamines and other neurotransmitters in stress”, Smolenice Castle, Slovakia, June 20–25, 2015.

- **Position of individual researchers in a national context**

2.3.13. List of invited/keynote presentations at national conferences, as documented by programme or invitation letter

2013

1. BRTKO J., BIALESOVA L., LENKO V., MACEJOVA D.: The road to nuclear receptors and their cognate ligands: Insight into physiology and therapy of malignant diseases. Genetic Toxicology and Cancer Prevention Conference, Smolenice Castle, Slovakia, October 13–16, 2013.

2014

1. JEZOVA D.: New direction in anxiolytic drug development. 6th ISMCK, Košice, Slovakia, June 25–27, 2014.

2015

1. BRTKO J., TOPOROVA L., BIALESOVA L., MACEJOVA D.: Triorganotin compounds – environmental contaminants cause their endocrine disruption by binding to retinoid X inducible transcription factors. The Bilateral Czech and Slovak Genetic Toxicology and Cancer Prevention Meeting, Smolenice Castle, Slovakia, June 15–18, 2015.
2. JEZOVA D.: Good and bad players involved in the stress response. XIV. Psychofarmakologické sympózium s medzinárodnou účasťou, Smolenice Castle, Slovakia, November 26–28, 2015.

2.3.14. List of researchers who served as members of organising and programme committees of national conferences

2013

GAŠPERÍKOVÁ DANIELA: Member of the Organising Committee of the national conference with international attendance "XXIII. Diabetologické dni", Hotel DoubleTree by Hilton, Bratislava, Slovakia, June 12–14, 2013.

KLIMEŠ IWAR: Member of the Organising and Programme Committee of the national conference with international attendance "XXIII. Diabetologické dni", Hotel DoubleTree by Hilton, Bratislava, Slovakia, June 12–14, 2013.

STANÍK JURAJ: Member of the Organising Committee of the national conference with international attendance "XXIII. Diabetologické dni", Hotel DoubleTree by Hilton, Bratislava, Slovakia, June 12–14, 2013.

2014

KLIMEŠ IWAR: Member of the Programme Committee of the national conference with international attendance "XXIV. Diabetologické dni", Štrbské Pleso, Slovakia, June 5–7, 2014.

KLIMEŠ IWAR: Member of the Organising and Programme Committee of the national conference with international attendance "XII. Slovenské obezitologické dni", Piešťany, Slovakia, November 7–8, 2014.

2015

KLIMEŠ IWAR: Member of the Programme Committee of the national conference with international attendance "XIII. Slovenské Obezitologické dni", Holiday Inn Trnava, Slovakia, November 13–14, 2015.

UKROPCOVÁ BARBARA: Member of the Organising and Programme Committee of the national conference with international attendance "XIII. Slovenské Obezitologické dni", Holiday Inn Trnava, Slovakia, November 13–14, 2015.

- **Supplementary information and/or comments documenting the international and national status of the Institute**

Among the researchers of the Institute, there are **two excellent teams** identified by an independent agency (ARRA), namely the team of **prof. D. Ježová and S. Zorad** and their co-workers and the team of **prof. I. Klimes and D. Gašperíková**.

Prof. D. Ježová has been invited to be a **member of an ERC panel** in the field strongly related to the basic research performed in the Institute, namely the panel on Physiology, Pathophysiology and Endocrinology.

Doc. Ing. Jana Jurčovičová, PhD. acts as Associate Professor of physiology at Charles University in Prague since 2011. She presents lectures on endocrine physiology at the Third Medical Faculty Charles University to students in English curriculum.

Paper with coauthorship of **R. Farkaš** was selected as **"paper of the year 2014"**, by JBC editorial board in section „protein synthesis and degradation":
Benbahouche N.E.H., Iliopoulos I., Török I., Marhold J., Henri J., Kajava A.V., Farkaš R., Kempf T., Schnölzer M., Meyer P., Kiss I., Bertrand E.E., Mechler B.M. and Pradet-Balade B. (2014) *Drosophila* Spag is the homolog of RNA polymerase II-associated protein 3 (RPAP3) and recruits the heat shock proteins

70 and 90 (Hsp70 and Hsp90) during the assembly of cellular machineries. J. Biol. Chem. 289 (9): 6236-6247. [IF = 4,651].

In addition cover page for the first 2015 issue of Develop. Growth Different. vol. 57 was selected from the paper published by R. Farkaš group:
Farkaš R., Beňová-Liszeková D., Mentelová L., Mahmoodová S., Ďatková Z., Beňo M., Pečeňová L., Raška O., Šmigová J., Raška I. and Mechler B.M. (2015) Vacuole dynamics in the salivary glands of *Drosophila melanogaster* during prepupal development. Develop. Growth Different. 57 (1): 74-96.

Štefan Zorad was appointed as the president of a commission for defending European PhD. at University of Jaen, Jaen, Spain. His commission directed defense of PhD thesis from physiology performed by Dr. Ana Belen Villarejo Villar in 2013.

2.4. Tables of project structure, research grants and other funding resources

- **International projects and funding**

2.4.1. Major projects within the European Research Area and other important project – Framework Programmes of the EU, ERA-NET, European Science Foundation, NATO, COST, INTAS, etc. (here and in items below please specify: type of project, title, grant number, duration, total funding and funding for the institute, responsible person in the institute and his/her status in the project, e.g. coordinator "C", work package leader "W", investigator "I"),

	Project title	Typ / Project number	Duration in months	Funding for the Institute (EUR)	Role of the Institute / Responsible person
2012	Lipid droplets as dynamic organelles of fat deposition and release: translational research towards human disease	FP7-202272	05/2008-10/2012	58670	I
2013	Integrated Structural Biology Infrastructure	FP7 211252	01/2013-12/2015	4000	I
2014	Integrated Structural Biology Infrastructure	FP7 211252	01/2013-12/2015	4000	I
2015	Integrated Structural Biology Infrastructure	FP7 211252	01/2013-12/2015	1400	I
	MEchanisms of Lymphocytes TRansmigration Across the Blood Brain Barrier; NEURON ERA Net II	ERA-NET	08/2015-07/2018	17500	I

2.4.2. Other international projects, incl. total funding and funding for the institute

1. Interaction of nutrients and oxytocin in modulating neuroendocrine, metabolic and cardiovascular functions (SAS-NSC JRP 2010/07), 2011-2013, Institute - Daniela Ježová (Coordinator); funding: 44 000 EUR
2. Developing a rat model of depression based on tryptophan deficiency (Proof of Concept Funding, HEIF 4, HEIF 5, Oxford Brookes University), 2011-2017, Institute - Daniela Ježová (Coordinator); funding: 16 730 EUR
3. Effects of vortioxetine in the tryptophan-depletion model of SSRI-resistant depression in female rats, a research project invited and granted by a

pharmaceutical company, 2014-2018, Institute - Daniela Ježová (Coordinator); funding: 22 001 EUR

4. Skeletal muscle as a mediator of beneficial effects of regular exercise on cognitive functions and metabolism in patients with Alzheimer's disease: the role of muscle myokines and microRNAs (SAS/NSC JRP 2013/17), 2014-2016, Institute - Barbara Ukropcová (Coordinator); funding: 50 000 EUR
5. The effect of a long-term growth hormone supplementation on the whole-body metabolic characteristics and adipose tissue phenotype in growth hormone deficient adults: the 5-yr follow-up (Pfizer Global Investigator Initiated Research Grant WS689054), 2011-2013, Institute - Jozef Ukropec (Coordinator); funding: 33 301 EUR

2.4.3. Other important, international projects and collaborations without direct funding (max. 10 projects)

1. Laboratory of Pharmacological Neuroendocrinology (Prof. D. Jezova) collaborates with Instituto de Investigaciones Biotecnológicas, the SAS-CONICET programme, Buinos Aires, Argentina (Dr. B. Fuchsova) on the subject „Chronic stress impact on neuronal membrane glycoprotein M6a: pathway and regulation analysis“ in the SAS-CONICET programme.
2. Laboratory of Functional Neuromorphology (Dr. A. Kiss) collaborates with Neurobiology Research Unit, University Hospital Copenhagen, Denmark; Department of Translational Neurobiology, NeuroSearch A/S, Ballerup, Denmark (Dr. Jens D. Mikkelsen) on sthe ubject “Mapping of activated neurons in the hypothalamus of rat after acute treatment with Varenicline”.
3. Laboratory for Stress Research (Dr. R. Kvetnansky) collaborates with New York Medical College, Valhalla, USA (Dr. Esther L. Sabban) on the subject “Stressor-specific regulation of catecholamine biosynthetic enzyme gene expression”.
4. Laboratory for Stress Research (Dr. R. Kvetnansky and Prof. B Mravec, MD) collaborates with Pediatric and Reproductive Endocrinology Branch, National Institute of Child and Human Development, NIH, Bethesda, USA (Dr. K Pacak, MD) on the subject “Biomarkers for Early Detection and Therapy of Adrenal Gland Tumors: Molecular Pathogenesis and Clinical Correlates”.
5. Laboratory of Functional Neuromorphology (Dr. A. Kiss) collaborates with Institute of Organic Chemistry and Biochemistry) Prague, Czech Republic (L. Maletinska) on the subject “Effect of new ghrelin analogs with agonist activity on food intake regulation and on the activity of neurons in hypothalamic structures of C57Bl/6 male mice involved in the food intake regulation”.
6. Laboratory of Diabetes and Metabolic Disorders – Obesity section (Dr. J. Ukropec) collaborates with Prof. Wolfrum, ETH Zurich, Switzerland on the subject “Molecular mapping of brown adipose tissue in man & endocrine activity and microRNA profile of sceletal muscle in relation to metabolic health and pathogenesis of diabetes II as well as with Dr. deCourten from Monash University, Melbourne, Australia on “The role of carnosine for metabolic health of man”.
7. Laboratory of Diabetes and Metabolic Disorders – Diabetes section (Dr. D. Gasperikova and Prof. I. Klimes, MD) colaborates with Oxford NIHR Biomedical Research Centre, Churchill Hospital,Oxford, U.K (Prof. A. Gloyn) and a Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, UK (Prof. KR Owen) on the subject “Identification of

8. Laboratory of Molecular Endocrinology (Dr. J. Brtko and Dr. D. Macejova) collaborates with the Institute of Zoology, Laboratory of Molecular Cell Physiology and Endocrinology, Technische Universität, Dresden, Germany (Prof. Dr. Günter Vollmer) on the subject “MNU-activated carcinogenesis of mammary gland in Sprague-Dawley rats".
9. Laboratory of Molecular Endocrinology (Dr. J. Brtko) collaborates with the Department of Cell Biology and Genetics, Faculty of Science, Palacky University, Olomouc; Czech Republic (Prof. Dr. Z. Dvorak) on the subject "The role of natural and xenobiotic agonists of nuclear retinoid X receptors".
10. Laboratory of Diabetes and Metabolic Disorders – obesity section (Dr. J. Ukropec) collaborates with Division of Endocrinology and Metabolism Department of Medicine III Medical University of Vienna & Centre of Excellence High Field MR, Dpt. of Radiology AKH, Austria on three subjects: 1.“The effect of regular excercise on in vivo metabolism of skeletal muscle in relation to metabolic health and diabetes of type II”. 2. “Mapping of neurotransmitter changes in brain of patients with neurodegenerative disease”. 3. “Detection of brown adipose tissue in man with using MRS”.

- **National projects and their funding**

2.4.4. Projects supported by the Slovak Research and Development Agency (APVV)

Role of the Institute e.g. coordinator “C”, investigator “I”.

Year	Project title	Type/ Project number	Duration in months	Funding for the Institute (EUR)	Role of the Institute/ Responsible person
2012	Developmental effects of neuropeptides	APVV-0253-10	05/2011-05/2014	35 311	C
	Antitumour effect of biologically active ligands of nuclear retinoid X receptor heterodimers in tissue carcinoma cell lines	APVV-0160-11	07/2012-12/2015	19 440	C
	Changes in the cell metabolism developed by overexpression of the drug transporter – P-glycoprotein in leukemic cells	APVV-0290-10	07/2011-12/2014	10 215	I
	The effect of selected endocrine disruptors on the development of mammary gland , prostatic cancer and ovarian disfunctions	APVV-0147-10	05/2011-10/2014	55 566	C
	Application of proteomic techniques for monitoring of biologically active retinoid receptors ligands effects explitable for therapy of breast cancer	APVV-SK-CZ-0211-11	07/2012-12/2015	1 755	C
	Interaction of mental, cardiovascular, neuroendocrine and metabolic factors: from animal models toclinical applications	APVV-0028-10	05/2011-12/2014	71 867	C
	Neurobiology of cancer: the study of the nervous system role in etiopathogenesis of tumor growth and development of metastasis	APVV-0007-10	05/2011-10/2014	14 637	I
	Screening of hereditary hearing disorders in Slovakia by DNA analysis	APVV-0148-10	05/2011-10/2014	67 650	I
	Is stress a crucial factor in the process of neurodegeneration accompanying Alzheimer's disease?	APVV-0088-10	05/2011-10/2014	40 000	C

	Advanced polymer technologies in biomedicine: Polymer microcapsules for immunoprotection of transplanted pancreatic islets in diabetes treatment	APVV-0468-10	05/2011-10/2014	14 770	I
	Biosafety of therapeutically and commercially used nanoparticles: focus on reproductive and immune system, oxidative status and prevention of potential risk	APVV-0404-11	07/2012-12/2015	6 000	C
2013	Developmental effects of neuropeptides	APVV-0253-10	05/2011-05/2014	30 311	C
	Antitumour effect of biologically active ligands of nuclear retinoid X receptor heterodimers in tissue carcinoma cell lines	APVV-0160-11	07/2012-12/2015	38 879	C
	Changes in the cell metabolism developed by overexpression of the drug transporter – P-glycoprotein in leukemic cells	APVV-0290-10	07/2011-12/2014	10 215	I
	The effect of selected endocrine disruptors on the development of mammary gland , prostatic cancer and ovarian disfunctions	APVV-0147-10	05/2011-10/2014	58 089	C
	Application of proteomic techniques for monitoring of biologically active retinoid receptors ligands effects explitable for therapy of breast cancer	APVV-SK-CZ-0211-11	07/2012-12/2015	1 755	C
	Interaction of mental, cardiovascular, neuroendocrine and metabolic factors: from animal models toclinical applications	APVV-0028-10	05/2011-12/2014	91 899	C
	Neurobiology of cancer: the study of the nervous system role in etiopathogenesis of tumor growth and development of metastasis	APVV-0007-10	05/2011-10/2014	14 761	I
	Screening of hereditary hearing disorders in Slovakia by DNA analysis	APVV-0148-10	05/2011-10/2014	66 400	I
	Is stress a crucial factor in the process of neurodegeneration accompanying Alzheimer's disease?	APVV-0088-10	05/2011-10/2014	73 390	C
	Advanced polymer technologies in biomedicine: Polymer microcapsules for immunoprotection of transplanted pancreatic islets in diabetes treatment	APVV-0468-10	05/2011-10/2014	14 770	I
	Biosafety of therapeutically and commercially used nanoparticles: focus on reproductive and immune system, oxidative status and prevention of potential risk	APVV-0404-11	07/2012-12/2015	51 000	C
	Identification of new genetic aspects of monogenic endocrinopathies by next generation sequencing	APVV-0187-12	10/2013-05/2017	11 557	C
	Molecular-genetic research with pharmacogenetic consequences in children with hyperinsulinemic hypoglycemia	APVV-0107-12	10/2013-05/2017	17 833	I
	Cognitive, personal and psychophysiological factors of the stress in the context of the relationship between anxiety and allergies and their optimalisation	APVV-0496-12	10/2013-09/2017	4 463	I
2014	Developmental effects of neuropeptides	APVV-0253-10	05/2011-05/2014	23 578	C
	Antitumour effect of biologically active ligands of nuclear retinoid X receptor heterodimers in tissue carcinoma cell lines	APVV-0160-11	07/2012-12/2015	34 602	C
	Changes in the cell metabolism developed by overexpression of the drug transporter – P-glycoprotein in leukemic cells	APVV-0290-10	07/2011-12/2014	8 122	I
	The effect of selected endocrine disruptors on the development of mammary gland , prostatic cancer and ovarian disfunctions	APVV-0147-10	05/2011-10/2014	35 584	C

	Application of proteomic techniques for monitoring of biologically active retinoid receptors ligands effects explitable for therapy of breast cancer	APVV-SK-CZ-0211-11	07/2012-12/2015	1 755	C
	Interaction of mental, cardiovascular, neuroendocrine and metabolic factors: from animal models toclinical applications	APVV-0028-10	05/2011-12/2014	46 733	C
	Neurobiology of cancer: the study of the nervous system role in etiopathogenesis of tumor growth and development of metastasis	APVV-0007-10	05/2011-10/2014	12 043	I
	Screening of hereditary hearing disorders in Slovakia by DNA analysis	APVV-0148-10	05/2011-10/2014	22 777	I
	Is stress a crucial factor in the process of neurodegeneration accompanying Alzheimer's disease?	APVV-0088-10	05/2011-10/2014	44 020	C
	Advanced polymer technologies in biomedicine: Polymer microcapsules for immunoprotection of transplanted pancreatic islets in diabetes treatment	APVV-0468-10	05/2011-10/2014	11 996	I
	Biosafety of therapeutically and commercially used nanoparticles: focus on reproductive and immune system, oxidative status and prevention of potential risk	APVV-0404-11	07/2012-12/2015	45 390	C
	Identification of new genetic aspects of monogenic endocrinopathies by next generation sequencing	APVV-0187-12	10/2013-05/2017	73 126	C
	Molecular-genetic research with pharmacogenetic consequences in children with hyperinsulinemic hypoglycemia	APVV-0107-12	10/2013-05/2017	28 531	I
	Cognitive, personal and psychophysiological factors of the stress in the context of the relationship between anxiety and allergies and their optimalisation	APVV-0496-12	10/2013-09/2017	21 056	I
2015	Antitumour effect of biologically active ligands of nuclear retinoid X receptor heterodimers in tissue carcinoma cell lines	APVV-0160-11	07/2012-12/2015	41 094	C
	Biosafety of therapeutically and commercially used nanoparticles: focus on reproductive and immune system, oxidative status and prevention of potential risk	APVV-0404-11	07/2012-12/2015	43 610	C
	Application of proteomic techniques for monitoring of biologically active retinoid receptors ligands effects explitable for therapy of breast cancer	APVV-SK-CZ-0211-11	07/2012-12/2015	1 755	C
	Identification of new genetic aspects of monogenic endocrinopathies by next generation sequencing	APVV-0187-12	10/2013-05/2017	27 612	C
	Molecular-genetic research with pharmacogenetic consequences in children with hyperinsulinemic hypoglycemia	APVV-0107-12	10/2013-05/2017	32 058	I
	Cognitive, personal and psychophysiological factors of the stress in the context of the relationship between anxiety and allergies and their optimalisation	APVV-0496-12	10/2013-09/2017	28 510	I
	Interaction of nitrergic, neurotrophic and endocrine signaling in the etiopathogenesis of schizophrenia	APVV-14-0840	07/2015-06/2019	10 994	I
	Possible dual function of P-glycoprotein in leukemia cells: efflux pump and regulatory protein	APVV-14-0334	07/2015-12/2018	1 287	I

2.4.5. Projects supported by the Scientific Grant Agency of the Slovak Academy of Sciences and the Ministry of Education (VEGA) for each year, and their funding

VEGA	2012	2013	2014	2015
Number	19	17	17	17
Funding in the year (EUR)	92084	91308	111995	115783

[1]

- ## Summary of funding from external resources

2.4.6. List of projects supported by EU Structural Funds

1. Building a Competency Centre for research and development in the field of molecular medicine (26240220071), 2011-2015, Institute - Iwar Klimeš
2. Transfer of genetic knowledge of endocrine research into clinical praxis - TRANSENDOGEN (26240220051), 2010-2013, Institute - Iwar Klimeš
3. Implementation of molecular medicine into diagnostics, therapy and prevention of serious lifestyle diseases (26240220068), 2010-2014, Institute - Iwar Klimeš
4. Centre of excellence for translational research in molecular medicine - TRANSMED 2 (26240120030), 2010-2012, Institute - Iwar Klimeš
5. University Biomedical Research Park Bratislava (26240220087), 2013-2015, Institute - Daniela Gašperíková, Richard Imrich, Daniela Ježová, Iwar Klimeš

2.4.7. Summary of external resources of the EU Structural Funds (ERDF/ESF)

Role of the Institute in the project, e.g. coordinator “C”, work package leader “W”, investigator “I”.

[1] Excluding projects for the popularisation of science

Year	Project title	Project number	Duration in months	Funding for the Institute (EUR)	Role of the Institute
2012	Transfer of genetic knowledge of endocrine research into clinical praxis TRANSENDOGEN	26240220051	11/2010-08/2013	8 056	W
	Build a competency centre for research and development in molecular medicine KCMOLMED	26240220071	10/2011-10/2015	0	I
	Centre of excellence for translational research in molecular medicine TRANSMED2	26240120030	11/2010-05/2012	16 056	I
2013	Transfer of genetic knowledge of endocrine research into clinical praxis TRANSENDOGEN	26240220051	11/2010-08/2013	282 248,65	W
	Build a competency centre for research and development in molecular medicine KCMOLMED	26240220071	10/2011-10/2015	2 216,76	I
	University Biomedical Research Park Bratislava	26240220087	07/2013-12/2015	0	I
2014	Transfer of genetic knowledge of endocrine research into clinical praxis TRANSENDOGEN	26240220051	11/2010-08/2013	49 594,14	W
	Build a competency centre for research and development in molecular medicine KCMOLMED	26240220071	10/2011-10/2015	3 765,09 €	I
	University Biomedical Research Park Bratislava	26240220087	07/2013-12/2015	0	I
2015	Build a competency centre for research and development in molecular medicine KCMOLMED	26240220071	10/2011-10/2015	13107,41	I
	University Biomedical Research Park Bratislava	26240220087	07/2013-12/2015	35185,86	I

External resources	2012	2013	2014	2015	total	average
External resources (milions of EUR)	0,024	0,284	0,053	0,048	**0,410**	**0,103**
External resources transfered to coooperating research institute (milions of EUR)	0,000	0,000	0,000	0,000	**0,000**	**0,000**

- **Supplementary information and/or comments on research projects and funding sources**

2.5. PhD studies and educational activities

2.5.1. List of accredited programmes of doctoral studies, period of validity

4.2.10 Animal physiology – Faculty of Natural Sciences, Comenius University Bratislava, since 2005 – without the time limit

4.1.22 Biochemistry – Faculty of Chemical and Food Technology, Slovak Technical University, Bratislava, since 2005 – without the time limit

7.1.3 Normal and pathological physiology – Medical faculty Comenius University, Bratislava, since 2005 – without the time limit

2.5.2. Summary table on doctoral studies (number of internal/external PhD students; number of foreign PhD students, number of students who successfully completed their theses, number of PhD students who quit the programme*)*

PhD study	31.12.2012			31.12.2013			31.12.2014			31.12.2015		
Number of potential PhD supervisors												
PhD students	number	defended thesis	students quitted	number	defended thesis	students quitted	number	defended thesis	students quitted	number	defended thesis	students quitted
Internal	13,0	2,0	0,0	14,0	2,0	0,0	13,0	4,0	1,0	14,0	4,0	0,0
External	3,0	0,0	1,0	3,0	0,0	0,0	5,0	0,0	0,0	3,0	1,0	1,0
Other supervised by the research employees of the institute	5,0	0,0	0,0	7,0	0,0	0,0	6,0	0,0	1,0	10,0	3,0	0,0

2.5.3. Summary table on educational activities

Teaching	2012	2013	2014	2015
Lectures (hours/year)[2]	481	287	316	313
Practicum courses (hours/year)[2]	558	672	542	484
Supervised bachelor theses (in total)	14	14	10	13
Supervised diploma theses (in total)	20	22	19	23
Supervised PhD theses (in total)	24	26	30	36
Members in PhD committees (in total)	7	15	8	6
Members in DrSc. committees (in total)	3	11	3	3
Members in university/faculty councils (in total)	4	2	3	4
Members in habilitation/inauguration committees (in total)	2	4	1	2

2

2.5.4. List of published university textbooks

DOBROTA, Dušan - BRECHTLOVÁ, M. - DRGOVÁ, A. - GUZY, J. - HALČÁK, L. - **JEŽOVÁ, Daniela** - KAPLÁN, Peter - KRIŽANOVÁ, Oľga - KRON, I. - LEHOTSKÝ, Ján - LÍŠKA, B. - MAREKOVÁ, Mária - PECHÁŇ, Ivan - PODHRADSKÝ, J. - RAČAY, P. *Lekárska biochémia : vysokoškolská učebnica* [Medical biochemistry: University textbook]. 1. slov. vyd. Martin : Osveta, 2012. 723 s. ISBN 978-80869-293-9.

MRAVEC, Boris. *Nervový systém: patofyziológia* [Nerve system: pathophysiology]. 132 s. Bratislava : Slovak Academic Press, 2013. ISBN 978-80-89607-08-2.

2.5.5. Number of published academic course books

N/A

2.5.6. List of joint research laboratories/facilities with universities

N/A

- **Supplementary information and/or comments on doctoral studies and educational activities**

  One of the research topics investigated at the IEE was included into the topics of **Children University** organised by Comenius University in Bratislava in summer 2015. Prof. D. Ježová was invited to give a lecture entitled „Why is sugar a poison?“. In front of about 300 children she explained that sugar is a poison only if misused or wrongly metabolised. Her PhD students B. Prokopová and M. Pokusa practically demonstrated handgrip exercise tests used in research as the physical exercise is an effective “antidote”.

[2] Do not include time spent with bachelor, diploma or PhD students during their supervising

Doc. Jana Jurčovičová acts as Associate Professor of physiology at Charles University in Prague since 2011. She presents lectures on endocrine physiology at the Third Medical Faculty Charles University to students in English curriculum. Several researchers of the institute perform teaching activities for both pre- and post-graduate students, often without being paid for it. The most intensive teaching has been performed at the Comenius University in Bratislava at the Faculty of Medicine (6 persons; Institute of Pharmacology and Clinical Pharmacology, Institute of Physiology, Institute of Pathophysiology) and Faculty of Natural Sciences (1 person; Department of Genetics). Employees of the institute (4 persons) contribute to the teaching also at the Faculty of Medicine and the Faculty of Public Health of the Slovak Medical University in Bratislava. One researcher is teaching at the Institute of Human and Clinical Pharmacology, University of Veterinary Medicine and Pharmacy in Košice.

Dr. Štefan Zorad was appointed as the president of a commission for defending European PhD. at University of Jaen, Jaen, Spain. His commission directed defense of PhD thesis from physiology performed by Dr. Ana Belen Villarejo Villar in 2013.

List of study stays of PhD students abroad:

Baláž Miroslav, study stay at the ETH Zürich, Switzerland, 26 days, 2012

Babic Stanislav, study stay at the National Taiwan University Taipei, Taiwan, 30 days, 2012

Gajdošechová Lucia, study stay at the National Taiwan University Taipei, Taiwan, 30 days, 2012

Pokusa Michal, study stay at the National Taiwan University Taipei, Taiwan, 17 days, 2012

Chovanová Lucia, study stay at Institute of Immunology and Infection Research, University of Edinburgh, Edinburgh, Great Britain, 180 days, 2012

Kurdiová Timea, study stay at the ETH Zürich, Switzerland, 120 days, 2012

Gajdošechová Lucia, study stay at the University of Jaén, Jaén, Spain, 30 days, 2012

Baláž Miroslav, study stay at the ETH Zürich, Switzerland,184 days, 2013

Bialešová Lucia, study stay at the Department of Cell Biology and Genetics, Faculty of Science, Palacky University, Olomouc; Czech Republic, 31 days, 2013

Prokopová Barbora, study stay at the Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary, 21 days, 2013

Csánová Agneša, study stay at the Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary, 21 days, 2013

Pokusa Michal, study stay at the National Taiwan University Taipei, Taiwan, 16 days, 2013

Danevová Veronika, study stay at the National Taiwan University Taipei, Taiwan, 16 days, 2013

Gajdošechová Lucia, study stay at the Department of Pharmacology, Jagiellonian University Krakow, Poland, 20 days, 2014

Csánová Agneša, study stay at the Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary, 30 days, 2014

Balagová Lucia, study stay at the Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary, 14 days, 2015

Buzgóová Katarína, study stay at the Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary, 14 days, 2015

Csánová Agneša, study stay at the Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary, 13 days, 2015

Chmelová Magdaléna, study stay at the Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary, 18 days, 2015

Lešťanová Zuzana, study stay at the Nova Southeastern University College of Pharmacy, Ford Lauderdale, Florida, USA, 90 days, 2015

2.6. Social impact

2.6.1. List of the most important results of applied research projects. Max. 10 items

Research on stress and depression resulted in the development of a unique animal model of depression resistant to the treatment with classical antidepressants. The model has brought the attention of several pharma companies and has already led to a commercially supported on-going project (Laboratory of Pharmacological Neuroendocrinology).

The results obtained in the Institute significantly contributed to the finding that “DG9-glycan index” is a new clinical biomarker for distinguishing HNF1A-MODY from other subtypes of diabetes. It has been demonstrated that individuals with HNF1A-MODY diabetes have low levels of C-reactive protein and that this parameter helps to discriminate between HNF1A-MODY subtype and both type 2 and HNF4A-MODY diabetes (Laboratory of Diabetes and Metabolic Derangements).

An appropriate methodological background has been developed enabling DNA analysis for patients in the whole territory of Slovakia focusing on unknown mutations (Laboratory of Diabetes and Metabolic Derangements).

2.6.2. List of the most important studies commissioned for the decision-making authorities, the government and NGOs, international and foreign institutes

N/A

2.6.3. List of contracts and research projects with industrial and other commercial partners, incl. revenues

Collaboration contract between Attoquant Diagnostics GmbH, Vienna, Austria and Institue of experimental endocrinology SAS has been established. This contract enabled us to have free access to patented MAS spectrometry metod RAS FINGERPRINTING to evaluate 10 diferent angiotensin peptide in a single sample of blood or tissue (Laboratory of Metabolic Regulations).

Research project entitled “Effects of vortioxetine in the tryptophan depletion model of SSRI-resistant depression in female rats” with financial grant of the pharmaceutical company Lundbeck. The aim of the project is to test the efficacy of vortioxetine, a new antidepressant drug of this company. It is an on-going project and the results obtained show new mechanisms of vortioxetine action and clearly demonstrate its higher effectivity compared to that of currently clinically used antidepressant drugs (Laboratory of Pharmacological Neuroendocrinology).

2.6.4. List of licences sold abroad and in Slovakia, incl. revenues

N/A

2.6.5. List of most important social discourses under the leadership or with significant participation of the institute (max. 10 items)

2.6.6. Summary of relevant activities, max. 300 words

There is an on-going collaboration with Imuno TT s.r.o., Trnava, Planeat s.r.o., Bratislava Slovakia related to studies in patients and healthy volunteers as well as to the use of professional nutritional software PLANEAT for running clinical studies (Laboratory of Human Endocrinology).

The DNA analysis is available for selected monogenic disorders (e.g. monogenic diabetes, monogenic hypoglycemia, monogenic obesity and dyslipidemia, glycogenosis, familial hearing loss and selected monogenic endocrinopathies) which include the DNA analysis of more than 35 genes using the Sanger sequencing and/or next generation sequencing methodology. Moreover, the whole exome sequencing approach is carrying out for purpose of identification of new variants responsible for aforementioned selected monogenic disorders (Diabgene Laboratory and Laboratory of Diabetes and Metabolic Derangements).

There is an on-going collaboration with the Vittateq Biotechnology GmbH, Innsbruck, Austria and with Flamma S.p.A. Italy, focused on vitamin E binding protein and on bioactive peptides (Laboratory of Diabetes and Metabolic Derangements).

2.7. Popularisation of Science (outreach activities)

2.7.1. List of the most important popularisation activities, max. 20 items

- **The Hipocampus and Brain Development**. Interview, television „Markíza“ - 13.3. 2012 (*Prof. Daniela Ježová, PharmD., DSc.*)
- **Depression and Stress – Do we know how to resist?** A 60 min lecture for general public. Centre of Slovak Christian Inteligence „Quo vadis“, Bratislava - 5.3.2013 *(Prof. Daniela Ježová, PharmD., DSc)*
- **Stress and Depression** – Interview, Czech radio, Czech Republic, programme “The day according to Barbora Tacheci” - 8.1.2014 *(Prof. Daniela Ježová, PharmD., DSc)*
- **Why is Sugar a Poison?** Children University of Comenius University in Bratislava, Theatre Arena - 12.8.2015 *(Prof. Daniela Ježová, PharmD., DSc)*
- **Health and Medicine of Future**, A long discourse of experts in front of general public, The Night of Researchers - 25.9.2015 *(Prof. Daniela Ježová, PharmD., DSc)*
- **Stress and Adaptation. Interview,** Radio RTVS, programme The Night Pyramid - 11.9.2015 *(RNDr. Richard Kvetňanský, DrSc.)*
- **Stress Research.** Television TA3, Discussions through the Midnight - 4.9.2015, *(RNDr. Richard Kvetňanský, DrSc.)*
- **Science in the CENTER: New trends in research & therapy of monogenic diabetes**, Centrum vedecko-technických informácií SR - 28.6.2012 *(prof. MUDr. Iwar Klimeš, DrSc.)*
- **Adipose tissue metamorphosis: another way to solve obesity problem,** *http://www.mediportal.sk - 2013 (MUDr. Barbara Ukropcová, PhD.)*
- **20th European Obesity Congress in a city of Beatles, Liverpool, England,** Diabetes a obezita, vol. 13, no. 26, p.105-108, 2013. *(MUDr. Barbara Ukropcová, PhD)*
- **Effect of exercise on the brain and cognitive function**, Memory centrum - 27.2.2014 *(MUDr. Barbara Ukropcová, PhD)*
- **Effect of regular exercise on the brain and metabolism**, Aula FTVŠ – 2014 *(MUDr. Barbara Ukropcová, PhD)*.
- **Lean about our fitness and live healthier lives,** The Night of Researchers - 25.9.2015 *(MUDr. Barbara Ukropcová, PhD).*
- **Regular exercise brain and metabolism,** Aula FTVŠ - 14.10.2015, *(MUDr. Barbara Ukropcová, PhD)*.
- **Topics of heart failure, dyslipidemia and metobolic syndrome,** Lekárske listy 2015. *(prof. MUDr. Fedor Šimko, CSc)*
- **Let`s motivate patients to move: The role of physical activity for human health, obesity prevention and treatment**, Via practica 2015 *(MUDr. Barbara Ukropcová, PhD)*.
- **Personalised physical activity diagnostics, education and prescription,** Via practica 2015 *(MUDr. Barbara Ukropcová, PhD)*.

2.7.2. Table of outreach activities according to institute annual reports

Outreach activities	2012	2013	2014	2015	total
Articles in press media/internet popularising results of science, in particular those achieved by the Institute	2	7	2	4	15
Appearances in telecommunication media popularising results of science, in particular those achieved by the Institute	2	3	3	6	14
Public popularisation lectures	5	2	4	5	16

- **Supplementary information and/or comments on popularisation activities, max. 300 words**

  Our outreach activities towards general public (including children, students and seniors), health care professionals and scientific community were aimed at presenting results of our work in a context of the state-of-the-art scientific knowledge to show importance of biomedical scientific research progress for the everyday life of humans in the modern society.

  It is important to say that we not only presented the results of scientific research and its possible translational aspects towards health care practice. We also conveyed many different messages about (i) excitement one can feel while making scientific discovery, (ii) importance of collaboration within as well as outside the scientific community, (iii) pathways we pursue in an effort to develop strategies aimed at modifying morbidity/mortality risk associated with obesity, diabetes, depression, chronic disease states and stress, (iv) significance of a continuous education of students, professionals and general public on the role of healthy lifestyle in prevention and treatment of chronic diseases.

  Press, internet, telecommunication media or direct personal contacts within (i) ”Children's University” at Comenius university in Bratislava, (ii) “The European Researchers' Night” a scientific festival aimed at increasing awareness of research and innovation in a society, (iii) popular presentations for foreign university students in the frame of Erasmus program, as well as (iv) for general public in a frame of the exercise-intervention studies we perform to learn the mechanistic details of regular exercise benefits for human health.

  We hope that our concentrated effort might bring a bit of light to general understanding of important societal/health problems such as obesity, metabolic disease, depression, or pitfalls of stress response. We however, are also aiming to find global solutions (preventive measures) in providing complex information and structural capacity to emphasize importance of healthy diet and regular exercise for healthy life and ageing.

2.8. Background and management. Human resources and implementation of recommendations from previous assessment

2.8.1. Summary table of personnel

Personnel	2012	2013	2014	2015
All personnel	106,0	100,0	105,0	99,0
Research employees from Tab. Research staff	58,0	62,0	62,0	63,0
FTE from Tab. Research staff	42,940	49,230	45,980	46,380
Average age of research employees with university degree	40,0	39,0	40,0	40,0

2.8.1.1. Professional qualification structure (as of 31.12. 2015) FEMALE

FEMALE	AGE								
Number of	< 30	31 - 34	35 - 39	40 - 44	45 - 49	50 - 54	55 - 59	60 - 64	> 65
DrSc. / prof.	0	0	0	0	1	0	0	0	1
II.a / Assoc. prof.	0	1	5	4	1	0	0	0	0
Other researchers PhD./CSc.	3	2	1	0	0	0	0	0	0
doc. / Assoc. prof.	0	0	0	0	0	0	0	0	1

2.8.1.2. Professional qualification structure (as of 31.12. 2015) MALE

MALE	AGE								
Number of	< 30	31 - 34	35 - 39	40 - 44	45 - 49	50 - 54	55 - 59	60 - 64	> 65
DrSc. / prof.	0	0	0	2	0	0	0	1	5
II.a / Assoc. prof.	0	1	3	2	0	0	4	0	0
Other researchers PhD./CSc.	3	1	3	0	0	0	0	0	0
doc. / Assoc. prof.	0	0	1	0	0	0	0	1	0

2.8.2. Postdoctoral and mobility scheme

2.8.2.1. Postdoctoral positions supported by national and international resources

N/A

2.8.2.2. Postdoctoral positions supported by external funding

N/A

2.8.2.3. SAS stipends and SASPRO stipends

N/A

2.8.2.4. Internal funding - the Slovak Academy of Sciences Supporting Fund of Stefan Schwarz

N/A

2.8.3. Important research infrastructure *(max. 2 pages)*

The tissue culture laboratories appropriate for acute and chronic *ex vivo* cultivation of biological material. The laboratory has all necessary basic equipment (laminar box, UV lamps, CO2 incubators, refrigerators, freezers, cell counter and inverse microscope etc.).

Morphological and immunohistochemical laboratory is equipped by infrastructure (cryostat, microtome, different types of microscopes) allowing neuroanatomical and immunohistochemical investigations in cooperation with other adequately equipped institutes from SAS or Comenius University.

Biochemical and molecular-biological devices: ultracentrifuge, different types of re-frigerated centrifuges, Dynamic Spectro and Fluorometer, ELISA readers for normal light and fluorescence signals, automatic biochemical analyser at the electrochemiluminiscence principle, biochemical analyzer at the immunochemical principle, spectrophotometer, photodocumentary and camera equipments, equipment for PCR /thermocyclers/ and two instruments for real-time PCR (Rotor Gene and ABI 7900 HT) ,

DNA diagnostic laboratory as the Member of the European Molecular Genetics Quality Network is equipped for screening for mutations by dHPLC (Transgenomic, USA), direct sequencing (ABI 310, ABI-Hitachi 3130, ABI 3500) and next generation sequencing (Ion PGM system) equipped with appropriate softwares, automatic gradient PCR machines, DNA and RNA concentration measurement device for direct measurements in small sample volumes, microfluidics-based platform for the analysis of DNA, RNA, proteins and cells.

The radioisotopes department is equipped with a new apparatus for measuring radioisotopes by beta and gamma radiation. In the department is also available a laminar box for handling radioactive and biological hazards.

During 2012-2015 IEE provided 17 778 $^{3}H/^{14}C$ and 5 954 ^{125}I measurements for external institutions.

The IEE SAS had two facilities for breeding laboratory animals - one for the rats, the other for the genetically modified mouse. Both devices are equipped with an automatic air spraying and air conditioning as well as tracking devices to neuroendocrine responses to acute and chronic stress loads, on the assessment of the behavior and mental disorders in animals.

Clinical approach includes 2 independent clinical-physiological rooms equipped with twin beds, ECG and blood pressure monitor, automatic defibrillation system and apparatus enabling the assessment of the degree of stress and anxiety conditions, euglycemic hyperinusulinemic clamp system (including glucose

analyzer for a very quick and precious assessment of glucose level), indirect calorimetry apparatus and microdialysis apparatus. The body composition analysis, oral glucose tolerance test, Stroop test, modified Shellong orthostatic test, hypertonic saline infusion test abdominal adipose tissue biopsies are performed on routine basis by trained clinicians.

2.8.4. Description of how the results and suggestions of the previous assessment were taken into account

1. Research outputs

Research activity for the evaluated period meets high standards. However, in several selected papers in highly ranked journals the Institute investigators played only subsidiary role.

The Institute continues publishing original research articles in highly ranked journals. During the period 2012-2015 the ratio of "domestic" and collaborative papers improved to approximately 1:1.

2. Response to the scientific outputs

There is a clear increase in the number of citations in particular in the last year with an increase almost by 200.

Recommendation: The citation table provides controversial results, which will have to be clarified.

During the evaluated time period, the Institute recorded the number of citations very precisely to avoid any controversial results.

3. Research status of the organization within international and national context

The Institute continues to have an excellent national and international scientific reputation.

During the evaluated time period, the Institute continued to keep an excellent national and international scientific reputation.

4. Projects structure, research grants and other external funding resources

Project structure, research grants and external funding of the Institute are excellent.

The Evaluation Panel appreciates the upgrading of selected laboratories (diabetes oriented programs) and now expects providing equal development opportunities for other scientific groups.

The higher number of research grants enabled development of research opportunities for a higher number of scientific groups working in different areas of endocrinology.

5. Organization of PhD education and other pedagogical activities

The Institute is approved for three PhD study programs but has to support strongly qualification promotion of young researchers to secure the programs for the future (motivation for DrSc.).

The Institute keeps three PhD study programs. During the evaluated period, two relatively young scientists in age ranging from 41 to 47 successfully defended their DrSc. thesis.

6. Socio-economic outputs

The Institute is equipped with a broad spectrum of diagnostic devices, moreover, it has a long standing history of translating research into clinical practice and society. The panel sees a good potential to increase socio-economic output by taking advantage of the infrastructure and scientific capacity of the institution.

The Institute continued in the long standing history of translating original results of basic research into clinical practice and society.

7. Popularizations and outreach activities

The Panel appreciates the popularization activities of the Institute.

During the evaluated time period, the Institute kept the performance of popularization activities.

8. Background and management: infrastructure and personal development

The infrastructure of the Institute is very good. However, the personal policy of the institute is suboptimal, especially for the middle age group.

The Institute significantly improved personal policy of the organization, which can be documented by a decrease in average age of researchers at the Institute (IEE) by approximately 4 years.

The Panel requests clarification of the legal status of Diabgene.

The legal status of DIABGENE (joint laboratory of IEE and National Institute of Endocrinology and Diabetes in Lubochňa, Slovakia) has already been clarified.

- **Supplementary information and/or comments on management, research infrastructure, and trends in personnel development**

3. Research strategy and future development of the institute for the next five years (2016-2020) (Recommended 3 pages, max. 5 pages)

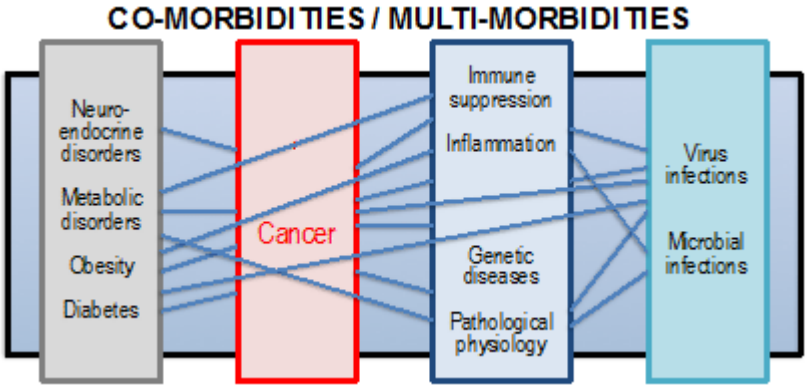
From January 1st, 2016, the Institute of Experimental Endocrinology has become an integral part of the Biomedical Research Centre of the Slovak Academy of Sciences (BMC SAS), together with three other SAS institutes, namely the Cancer Research Institute (CRI), the Institute of Virology (IV), and the former Centre for Molecular Medicine (now renamed as the Institute of Clinical and Translational Research, ICTR).

The BMC SAS is currently the largest Slovak institution (>350 employees) devoted to basic and applied research in biomedical sciences, with the former SAS institutes representing its main structural units.

From this reason, the research and management strategy for the future development of the Institute of Experimental Endocrinology is described in the context of the BMC SAS and the Part 3 of the Questionnaire is common for all four BMC SAS institutes.

3.1. Present state of the art in both the national and the international contexts

Present state of the art in the biomedical research can be viewed both "vertically" in relationship to particular research areas central to the BMC institutes and "horizontally" as the intersection of these research areas towards understanding the cross-talk of diseases often simultaneously affecting the same human organism (also called co-morbidities or multi-morbidities). Establishment of the BMC SAS has created excellent conditions for both approaches, via combining interests, skills, knowledge and infrastructures.



The scheme depicts the types of diseases sharing common/similar underlying mechanisms (vertical groups) and evidence-based horizontal relationships and/or dependencies (due to primary or secondary effects). These relationships significantly influence progression of diseases and therapeutic responses.

The "vertical view" on the present state of the art

VIRAL and MICROBIAL INFECTIONS

Institute of Virology

Recent era faces the emergence of new infections and reappearance of old infectious agents with altered pathogenic properties, which occur due to civilization-related penetrations of humans into intact natural environment, increased travelling and climate changes. The pathogens often escape from vaccination barriers and the prevalence of persistent infections is growing. It is highly probable that the humans, animals and plants will be more often confronted with new types of infections in the near future.

Worldwide awareness of this threatening situation is associated with intensive developments of approaches and methods for rapid detection of infectious agents, new

therapeutic strategies based on inhibition of molecular pathways important for multiplication of viruses and bacteria, production of recombinant vaccines and anti-viral compounds. Simultaneously, molecular changes in the cells and organisms, which host or transmit infection, are investigated with the purpose to understand genetic, epigenetic and physiological processes contributing to spread of infection and/or manifestation of pathologies.

Research activities at the Institute of Virology BMC SAS, the only Slovak institution consistently performing research on viruses, rickettsiae and chlamydiae, follow the trends mentioned above reaching the international level, particularly in the research of infectious agents and host cells/organisms at the molecular levels using state of the art technologies, and in the development of new vaccines.

The research staff of the Institute of Virology BMC SAS includes several internationally recognized researchers that built their reputation through excellent research achievements, such as discoveries of new hantaviruses, elucidation of the genetic diversity of economically important plant viruses, ecology of old but underestimated and/or emerging zoonoses, identification of new diagnostic markers of *Coxiella burnetii*-caused Q fever, clarification of immune responses to influenza virus etc. Most of these middle-aged leaders have also demonstrated their networking abilities and collaborative potential through participation in several EU consortia including the European Virus Archive which reached global dimensions and is not just a bio-bank facility, but also performs breaking-through research in virology. In the national context IV BMC SAS plays an important role in epidemiological studies and surveys of diverse infections, development of reagents and methods for detection of viruses, rickettsiae and chamydiae, and in collaboration with healthcare institutions and domestic pharmaceutical industry.

CANCER

Cancer Research Institute (CRI), Institute of Experimental Endocrinology (IEE), Institute of Clinical and Translational Research (ICTR), and Institute of Virology (IV)

Civilization-associated demographic changes (increased age of the human population), altered life style (quality and composition of food, increased speed of life, more stresses), and increased exposition to environmental carcinogens lead to increasing frequency of cancer as well as of social and economic burden accompanying this devastating disease. On the other hand, we are witnessing a real revolution in our understanding of mechanisms underlying cancer initiation, development and progression, going hand-in-hand with enormous technological advances and shifts in clinical translations and therapeutic strategies.

Cancer cell-centric model dominating in tumor biology in the past century is now supplemented by the microenvironmental model that appreciates important roles of diverse tumor-associated cell types and subpopulations (such as mesenchymal stem cells, stromal fibroblasts and immune cells) as well as a complex secretome and physiological milieu of tumor tissue (including hypoxia, acidosis, extracellular matrix signalling etc), which altogether generate intratumoral heterogeneity now perceived as the one of the major factors of treatment failure. Thus, the attention of the basic cancer research community focuses a lot of attention on investigating the above-mentioned phenomena and on their possible implications for the clinic.

Similar shift in paradigm can be observed also in translational and clinical cancer research, where much emphasis is now given to patient-centric approach based on trials examining biology, developing biomarkers, and bringing together a range of health and scientific disciplines to work with patients. This is underlined by the recent success of new immunotherapy targeting immune checkpoint molecules co-opted by cancer cells to escape immune responses. Technological advances including new devices for multi-parametric analyses allow now for massive and detailed genomic, proteomic and immunologic profiling of tumor tissues, liquid biopsies, and tumor-bearing patients,

uncovering common molecular and physiological drivers of different types of cancer. Deeper knowledge of tumor biology has recently promoted “basket clinical studies” that address different tumor types documented to be driven by the same molecular alterations. This strategy in turn further highlights the critical role of academic groups in acquisition of new knowledge on molecular mechanisms of oncogenesis and cancer progression and in development of pre-clinical models indicating which drug will be effective for which cancer type.

In line with these advances in the field of oncology, cancer researchers of the BMC SAS investigate key aspects of cancer biology and use up-to-date research approaches, including molecular and cellular mechanisms of tumor-stroma crosstalk (CRI), mechanisms of chemoresistance (CRI), DNA damage responses, genetic and epigenetic traits of cancer development and progression (CRI), advanced multiparametric immunophenotyping of leukemia patients (CRI), hypoxia and acidosis as critical physiologic factors of tumor microenvironment affecting tumor biology, metastatic propensity and response to therapy (IV), ion transport and signaling in cancer cells (ICTR), neuroendocrine mechanisms of cancer (IEE), effects of obesity and metabolism on tumor phenotype and progression (IEE), etc. as described in the questionnaires of the BMC institutes. Many of our achievements are at the forefront of the current cancer research and are well recognized by the international community. Some of them are being translated to clinical applications in the form of new biomarkers, detection assays for diagnostic, prognostic and predictive purposes (including the non-invasive formats) and of promising new therapeutic strategies. This international dimension of the cancer research at BMC SAS is documented by a number of EU and other international projects, patents, invited talks at the international meetings, collaborations with universities and clinics, and highly cited publications.

With this reputation, BMC SAS represents the leading institution of the basic and translational cancer research in the Slovak Republic, activities of which fully conform to the current global trends in oncology and also respond to unmet needs of the home country which faces increasing prevalence of cancer and calls for concentration of experts and efforts to develop new treatment strategies taking into account specific characteristics of our population and the healthcare system.

STRESS, NEUROENDOCRINE DISORDERS, AND DEPRESSION

Institute of Experimental Endocrinology

Stress has been termed the “Health Epidemic of the 21st Century” by the World Health Organization. The effect of stress on human emotional and physical health can be devastating and negatively impacts on social relationships and work productivity leading to enormous economic losses. Stress is associated with increased rates of heart attack, hypertension, obesity, addiction, anxiety, depression and other disorders.

Recent stress research focuses on hypothalamic-pituitary-adrenal (HPA) axis, which plays a central role in the adaptive response to numerous stressors. This system has a strong influence on the brain and its major functions, such as cognition, memory, behavior, and mood. In addition, this system affects the general homeostasis of the human organism a may result in deterioration of diverse organs and tissues. Thus, the main challenge is to obtain complex understanding of the mechanisms mediating adaptive responses to stress, elucidate consequences of their abnormal activation and develop pharmacological, mental and exercise-based strategies for their normalization.

Researchers at the IEE BMC SAS investigate stress responses at the molecular and cellular levels as well as at the level of the entire organism using current state-of-art approaches. Studies of catecholamines at IEE are known worldwide similarly as the research focusing on psychopharmacology. The IEE regularly organizes international meetings of the world-leading endocrinologists and its scientists contributed to this area

by a number of highly cited papers, some of which can be considered seminal for the development of this field.

METABOLIC DISORDERS, OBESITY AND DIABETES

Institute of Experimental Endocrinology and Institute of Clinical and Translational Research

Similarly, metabolic disorders, obesity and diabetes are designated as pandemics of the 21st century, due to their continuously and rapidly increasing prevalence and incidence.

About 415 million people around the world have diabetes (9% of adults). Over the next decade, this number is predicted to increase to 642 million people (according to WHO reports). Given that diabetes is a major cause of mortality, morbidity, and health care expenditures, addressing this chronic disease represents one of the greatest global health challenges of our time. Approximately 90% of the total diabetes burden is represented by the type 2 diabetes, which is determined by genetic factors and closely linked to obesity, unhealthy diet and physical inactivity.

IEE researchers contributed to this expanding global health problem by discovering new mutations responsible for the monogenic forms of diabetes. In addition to performing basic research in this area, they also accomplish genetic analyses to identify mutations driving the early onset of diabetes that are useful for diagnostic purposes with direct impact on clinical decisions. Thanks to their achievements, they have participated in large EU consortia and have established strong international cooperations.

Obesity is a major health-compromising problem not only worldwide, but also in Slovakia, where around 20% of population suffers from morbid obesity and about 50% people (including children) are overweighed. This situation has constant health, societal and economic impact and is thus perceived as one of the most prominent challenges that urgently need solutions.

The obesity research at IEE is focused on adipose tissue and muscle metabolism, on the prevention of obesity through optimizing caloric intake, and on elucidation of effects of some food constituents such as flavonoids and mycotoxins on the development of obesity and metabolic disorders. In addition, its essential part is the study of atypical obesity hormones such as oxytocin, angiotensin peptides and aldosteron with respect to their role in mechanisms of fat tissue enlargement. Both IEE and ICTR researchers continuously develop translational and clinical studies on the importance of the physical activity in prevention of diabetes, treatment of neurodegenerative diseases, and improvement of cardiorespiratory fitness.

GENETIC AND INFLAMMATORY DISEASES

Institute of Clinical and Translational Research and Institute of Experimental Endocrinology

The rapid advance of genomic technologies have led to improved understanding of the genetic bases of diseases. Recent approaches encounter shift from targeted analyses of specific genes based on particular symptoms or family histories to sequencing of an entire genome or exome. Targeted approaches characteristically have a high yield for penetrant monogenic conditions; whole genome approaches have the potential to unravel a much larger proportion of genetic disease burden. Both directions can provide

predictions about diagnoses, or susceptibilities to conditions with important implications for the affected person as well as for her/his relatives.

The BMC SAS researchers focus on identification of new mutations and mapping of genetic diseases with high prevalence in Slovak non-Romany inhabitants and specifically in Slovak Romany inhabitants, which is a genetically isolated population of almost 100% endogamy suffering from one of the highest phenylketonuria incidences in the world as well as from other monogenic disorders. The researchers who are currently based at BMC SAS have contributed to characterization of the genetic basis of alkaptonuria in non-Romany population, and monogenic hearing impairments and primary congenital glaucoma in Romany population in the Slovak Republic. They also participate in the National Screening Program and genetic testing of monogenic (ICTR), metabolic (IEE) and oncologic (CRI) disorders, using state of the art genomic technologies. The BMC researchers also develop international activities through participation in EU networks aimed at characterization of monogenic disorders.

Using state of the art genetic approaches, the BMC researchers also helped to uncover the impact of polymorphisms in genes of the hypothalamic-pituitary-adrenal (HPA)-axis regulation on the pathophysiology of rheumatoid arthritis (ICTR) and also brought new knowledge on neuroendocrine and inflammation-related factors contributing to this chronic disease. As in the case of other important topics investigated at BMC SAS, the ICTR researchers have been invited to large EU network, where they collaborate with renowned domestic and foreign clinics and research institutions.

The “horizontal view” on the present state of the art

CO-MORBIDITIES / MULTI-MORBIDITIES

One of the main advantages of the BMC SAS resides in the strong human infrastructure creating critical mass of internationally recognized experts in research of diverse human diseases. These experts can now join forces in order to take complex approach to understanding of human diseases with their co-morbidities. Up until now, both basic and clinical research has focused predominantly on single disease and episode, often with a focus on mortality as the main endpoint. Nowadays, the concept of co-morbidities (or multi-morbidities) is gaining more and more importance with increasing awareness that healthcare needs to address the management of persons with multiple coexisting diseases, who are now the norm rather the exception. The costs of management of multi-morbid patients are growing exponentially as the number of chronic conditions increases. Moreover, standard treatment protocols used for individual diagnoses may not work due to co-existing pathologies. Co-morbidity can impact on a range of outcomes, including mortality and health-related quality of life. Etiological relationships between diseases may involve direct causation, associated risk factors, heterogeneity and independence. Co-occurrence of certain pathologies seems obvious, such as obesity linked with diabetes, cardiovascular problems, hormonal imbalance, cancer (particularly hormone-dependent tumors), and depression. However, current research helped to uncover the obesity connection to inflammation and increased sensitivity to infections (such as influenza virus…). On the other hand, adenovirus 36 was recently identified as one of the factors contributing to the obesity. From the clinical point of view, treatment of obese patient with cancer would surely lead to different outcome as the same treatment of the lean person and this may be true for other pathologies. Moreover, co-morbidity may include the situation in which treatment for the one disease causes another condition, such as immunosuppressive chemotherapy may increase the permissiveness of cancer patient to virus infections. And vice versa, virus or microbial infections can cause inflammation, which may support cancer progression.

The BMC SAS is well predisposed to address the above-described problems mainly thanks to the renowned researcher leaders as well as excellent young researchers, who are now keen to closely cooperate. This will be facilitated by the availability of unique in vitro and in vivo models, modern infrastructure, up-to-date methodical portfolio and broad spectrum of academic and clinical partners. Our initial effort will be focused on prevention, risk stratification, treatment and overall mechanistic understanding and management of obesity and obesity-related comorbidities in the Slovak population, including cancer, neurologic, endocrine, immune and infectious diseases, with the vision to improve our healthcare and quality of life.

This brief overview shows that the research activities at BMC SAS, which are largely focused on chronic non-communicable diseases accounting for almost three quarters of deaths worldwide, correspond to the most recent state of the art in the biomedical field and react to global as well as national challenges of healthcare and society. At present, the BMC SAS stands at the crossroad that converges all experiences, skills and infrastructure, interconnects networks of existing collaborations, but also opens new directions for interdisciplinary approaches towards more complex knowledge on human diseases translatable to practice. As the most robust institution of this type in Slovakia, the BMC SAS is now becoming increasingly attractive to clinical partners, which already expressed their interest for more close cooperation in areas that urgently need solutions in our country and which have far reaching implications for basic knowledge.

3.2. Research strategy of the institute in the national and the international contexts, objectives and methods

In the course of 2015, four biomedical institutes of the Slovak Academy of Sciences, namely

- The Cancer Research Institute,
- The Institute of Clinical and Translational Research (formerly Centre for Molecular Medicine)
- The Institute of Experimental Endocrinology,
- The Institute of Virology,

represented by their managing and scientific boards decided to merge into a bigger entity named “Biomedical Research Center of the Slovak Academy of Sciences” (BMC SAS). By the end of the year, this decision was supported by the execution of the Memorandum of Understanding, signed by the directors and heads of scientific boards, which provided a framework for future co-existence and functioning of the institutes within the BMC SAS. Subsequently, the BMC SAS was **officially established on January 1st, 2016 by the Presidium of the Slovak Academy of Sciences**.

The first period of the BMC SAS was characterized by complex legal and administrative arrangements of the new institution (according to the law of the Slovak Republic, these could be accomplished only after the legal entity was officially established). This included all documents related to identification, accounting and financial operations, registration for VAT, social/health insurances, public prosecutions, status of research institution, transfer of projects, approvals of biosafety, approvals for work with GMO etc. Moreover, three of the institutes (except IV) had to undertake a time- and energy-consuming moving from the old buildings to the new Pavilion of Medical Sciences in the main campus of the SAS. However, that brought the BMC institutes to close proximity, which now facilitates the communication and operation inside the BMC SAS.

The initial period of the BMC existence was also employed for the arrangement of the managing board, election of the scientific board, merging and reorganization of administrative and other supporting units and settlement of the overall structure of the BMC SAS, in which the institutes retain their internal academic life besides contributing to the common interests of the BMC SAS.

The **Managing board of the BMC SAS** consists of the representatives of all four founding institutions:

Director: prof. Silvia PASTOREKOVÁ, DSc.

Deputy Director and Scientific Director of the IV BMC: Juraj KOPÁČEK, MVD., DSc.

Scientific Director of the CRI BMC: Lucia KUČEROVÁ, PhD.

Scientific Director of the IEE BMC: Štefan ZÓRAD, PhD.

Scientific Director of the ICTR BMC: Miroslav VLČEK, MD., PhD.

Scientific Secretary: Jozef UKROPEC, PhD.

Scientific Secretary: Miroslav CHOVANEC, PhD.

Head of the Scientific Board: Richard IMRICH, MD., DSc.

Head of the Economic Unit: Hana KRASOŇOVÁ

Head of the Legal and Organizational Unit: Iveta ŠÁRNIKOVÁ, JUDr.

Head of the Project Evidence and Administration Unit: Erika CHUDĚJOVÁ

Head of the Technical Unit: Kornel DOBROČKA

The principal mission of this novel research center is to foster research excellence, develop interdisciplinary approaches, and stimulate innovative potential for the improvement of our knowledge on human diseases, its better translation to clinic and more effective practical use for the benefit of patients and the entire society.

The strategy for the future development of the BMC SAS stems from the historical backgrounds, infrastructures, human capacities and existing project portfolio of the institutes as its main pillars and takes advantage of the following attributes:

Compatibility of topics

All institutes of the BMC SAS perform research in biomedical area, and are principally aimed at elucidation of molecular and physiological mechanisms of human diseases, their epidemiology, and possibilities of better prevention, diagnostics and therapy. They investigate the human organism from different points of view in order to bring deeper understanding of metabolic, neuroendocrine, autoimmune disorders, cancer, and infections. These chronic diseases, known worldwide as non-communicable diseases

(NCD), represent major socio-economic burden and health-care expenses also in Slovakia, and therefore, their control and management requires both basic research and translational approaches. Moreover, these pathologic situations, so far perceived as individual entities, often co-occur in the same organism and indeed, global biomedical research of the 21st century faces co-morbidities (or multi-morbidities) as one of the key challenges of the human health and quality of life improvement. It is becoming more apparent that viruses readily infect humans, which are obese or suffer from cardiovascular or metabolic problems, that virus infection can even contribute to obesity and vice versa, that obesity facilitates progression of cancer and development of metabolic and cardiovascular disorders etc. This complex view on co-occurring disease, on their cross-talk (e.g. how infections develop in obese organism, how obesity modifies response to anticancer therapy, how neuroendocrine imbalances affect cardiovascular system etc.) opens a new space for the closer collaborations inside the BMC SAS, using existing models, methodical approaches and knowledge. This inter-institutional cooperation will receive a maximum support of the Managing board of the BMC SAS.

Complementarity of infrastructure

These collaborative efforts can be facilitated by the complementary infrastructure of the BMC SAS that was brought together by the merged institutes (as described in more details in their quests). Thus, the BMC SAS researchers have to disposition modern robust setups for genomics, proteomics, metabolomics, cytoanalytics, cell and animal bioimaging, biotechnological procedures, animal facilities for preclinical research (for highly contagious agents and immunodefficient animals), and small clinical research and health-care unit. The infrastructure is operated by the highly qualified, technically skilled and imaginative BMC researchers and is effectively used by the intramural personnel but also by external experts. In the near future, these infrastructures will receive the status of the BMC core facilities, which can be utilized not only for the basic research but also for the service purposes. This will, however, require investments and intesive care for the sustainable development of this infrastructure as discussed below.

Concentration of excellent research teams and experts

The merge of the institutes in the BMC SAS brought together several groups that were recently listed among the top research teams of SAS (according to ARRA, an independent ranking and rating agency, 2011). These teams continuously and successfully perform excellent research in the following areas:

- Hypoxia and acidosis in tumor microenvironment
- Signal transduction pathways in cancer cells
- Stem cells and gene therapy
- Genetic and metabolic factors of diabetes and obesity
- Neuroendocrine mechanisms of stress and depression
- Cell signaling mediated by calcium, hydrogen sulfide and catecholamines

Leading personalities of these teams, but also additional younger generation researchers, who grew up from the institutes, are now becoming the BMC “torch holders” whose main commitment is to maintain and further develop excellent research activities. In accord with this vision, preliminary individual research personnel assessment accomplished in June 2016 revealed that the BMC SAS concentrates a number of superb experienced researchers and young talents with a great potential for the future growth.

Critical mass of projects and capacities

In conjunction with the concentration of experts and teams, the BMC SAS has received a large project portfolio, composed mainly of the relatively high number of projects funded by the very competitive national grant agency APVV (including the new grants awarded this year). In addition, the portfolio contains several international projects comprising the highly prestigious EU FP7 and H2020-funded projects, albeit their number is lower than in the past. The projects funded by the EU Structural funds in the first program period were completed last year and are currently not active.

Thus, the BMC is now at the starting point of the competition for new projects. The rich project history as well as excellent research capacities and topics relevant for H2020 strategy and national RIS3 strategic priorities represent good prerequisites for the new project proposals, which are currently in the process of elaboration and submission by the leading BMC scientists.

The governance bodies of the BMC SAS will strongly support all activities leading to acquisition of new projects. That would require excellent research outputs, which in turn need reasonable funding of experimental work and other components of the research. This vicious cycle can be driven only through increased personal engagement and activities of the BMC researchers. The main task of the Managing board will be to create the best possible conditions for all the activities leading to excellent research outputs and new projects. In addition, researchers that are members of the managing and scientific boards are expected to develop great personal initiatives in all these activities in order to serve as a positive example for their colleagues.

Here we can build on past experiences and networking capabilities, which were demonstrated by a number of EU project proposals submitted during the assessment period by the institutes of the BMC SAS (see the table below).

BMC SAS institute	**Project proposals submitted to 7RP or H2020**	**2012**	**2013**	**2014**	**2015**
Cancer Research Institute	Institute as coordinator	0	0	0	**1**
	Institute as participant	**1**	0	**1**	**3**
Institute of Experimental Endocrinology	Institute as coordinator	0	0	0	0
	Institute as participant	0	**1**	**2**	0
Institute of Clinical and Translational Research	Institute as coordinator	0	0	0	0
	Institute as participant	0	0	0	0
Institute of Virology	Institute as coordinator	0	0	**1**	**3**
	Institute as participant	**12**	0	**4**	**5**

Coordinated approach to challenges of sustainable development

In realization of all the above-mentioned plans and strategies of sustainable development, the BMC SAS governance will face several serious limitations and obstacles. Successful passing of these hurdles would require enormous coordinated efforts within each aspect of the BMC SAS life, especially in the following areas:

Construction and management of the budget

The BMC SAS operates on a contributory budget basis, with the contribution allocated by the Presidium of the SAS and covering the most part of the personnel costs and the minor part of the operational costs such as energy, water, heating etc. (up to one third of the yearly expenses). Remaining costs, including the research, administration, maintenance of the buildings and infrastructure etc. has to be covered from the projects, contracts and other external sources. Thus, an attraction of new project funds and a good economic management are key for the sustainable development and motivation of the most active personnel. Additional strategic direction towards the active budget-building is the use of core facilities for service purposes as well as the stimulation and support of spin-off and start-up facilities.

Currently, the BMC budget is derived from the historical situation (four independent institutes, old infrastructure) and does not reflect the actual costs and requirements of the newly built infrastructure. It is composed of a common portion, allocated to the supporting units performing activities necessary for all partner institutions (economic operations, elaboration, administration and posting of documents, legal support, evidence and administration of project documents, technical support and repairs, transportations, housing of animals, etc.). The other part of the budget is broken down into four parts allocated to the institutes for the research purposes and internal activities. Future budget management strategy will be constructed taking into account experiences from the first year of the BMC SAS, in order to achieve more coherence, optimize income and expenses and facilitate the convergence of the institutes.

Consolidation of personnel

The initial assessment indicates that despite excellent personalities, the individual performance of the BMC researchers needs consolidation in order to improve the research outcomes. This can be done by positive or negative motivation of the current personnel and/or by restructuring its composition.

Positive motivation of the best-performing individuals is complicated due to the limited resources related to salaries, especially with the intent to accept and stabilize new postdocs and young scientists. One possibility is to give a personal salary bonus on the basis of the active participation in the key projects (which has to be carefully planned by PIs upon the project proposal submission).

Negative motivation is also problematic, because most of the salaries are at the very basic level. Moreover, the institutes have got permanent contracts with some researchers (enabled by past legislation), and this creates legal disadvantages for any contractual changes. The situation can be solved by the step-wise restructuring of the research groups, through the staffing policy taking into account personal interaction and mutual benefit. However, this intervention is very case-sensitive due to big number of contracted running projects that require continuous research work and capacities to reach the goals.

Thus, we intend to keep eye on the performance of the research personnel through annual evaluations and regular reviews of the researchers in order to stimulate them to higher activity.

Convergence and optimization of supporting units

It is also necessary to optimize the structure and functioning of the supporting units of the BMC SAS, which have been assembled from the staff of the partner institutes, who were traditionally using quite diverse working procedures. Therefore, we intend to accomplish an external evaluation of the administrative personnel, its working processes, communications, and flow of the documents to achieve their harmonization and improved efficacy.

Common interests

The accomplishment of all the intended activities and strategic decisions will follow the common interests of the BMC SAS, mainly the support and development of research excellence, translation of the basic knowledge to applications and clinical practice, and increasing the awareness of the public about the BMC activities and principally about the importance and meaningful social role of the scientific research in our country and worldwide. One of the most prominent activities in this respect is the cross-institutional cooperation in drafting, elaborating and submission of common project proposals representing a horizontal intersection of the BMC topics.

Nevertheless, these common interests have to be first recognized and adopted by the people creating the community of the BMC SAS, and this can be made possible through building their collaborations, friendships, the feeling of responsibility for the future development of the BMC SAS. It is now the role of the BMC SAS governance to create conditions for such an empathic environment, particularly via open communications, transparent and helpful decisions, and also via personal positions, opinions, knowledge and activities that are worth to follow.

Conclusion

The Biomedical Research Center of the Slovak Academy of Sciences is at the beginning of its existence and faces many challenges. Our main goal is to stabilize and then strengthen the position of the BMC SAS in the national R&D context and to build and fix its reputation in the international research community through its excellent research and renowned personalities.

4. Other information relevant for the assessment

IEE main research focus within BMC

Last year an increase in number of publications in impacted journals by more than 60% as well as an increased success rate in competition for APVV grants made a solid base for further research achievements in IEE BMC.

We also partially succeeded to reduce topic fragmentation of the institute by decreasing the number of laboratories from 12 to 8. We assume further reduction of the number of laboratories on the basis of similar topics or common methods used. This process might happen not only in IEE BMC but also throughout the whole BMC. The main goal of the common laboratories is to increase the chances of research groups in competition for great domestic and external grants.

From a scientific point of view the main topic of IEE BMC seems to be obesity and diabetes (J. Ukropec, Š. Zorad, D. Gašperíková, D. Ježová). The obesity has very tight relation to development of cancer (Dr. Brtko, B. Mravec), neurological disorders (R. Kvetňanský, D. Ježová, J. Bakoš), high blood pressure, depression (R. Imrich, D. Ježová, Š. Zorad) as well as immune and infection disorders.

For the future we see of very importance prevention of obesity through optimizing caloric intake as well as studying impact of some food constituents such as flavonoids and mycotoxins on the development of obesity and metabolic disorders.

Further topic is evaluation of influence of energetic expenditure on prevention of obesity, metabolic, neurodegenerative, oncological and immune disorders.

BMC including IEE has an ideal personal and technical conditions for complex research in the field of obesity and related disorders. Therefore breakthrough results might be expected in the near future.

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