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 Pharmacology and Toxicology, Slovak Academy of Sciences, Dubravska cesta 9, 841 04 Bratislava, Slovakia (IEPhT or Institute)

1.2. URL of the institute web site

http://www.uef.sav.sk/

1.3. Executive body of the institute and its composition

Directoriat	Name	Age	Years in the position
Director	Michal Dubovicky	49	2012 -
Deputy director	Mojmir Mach	39	2012 -
Scientific secretary	Tatiana Macickova	66	2012 -

1.4. Head of the Scientific Board

Milan Stefek

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	28.0	27.300	31.0	28.800	33.0	29.000	32.0	26.200	**124.0**	**31.0**	**27.825**
Number of PhD students	12.0	12.000	15.0	15.000	16.0	16.000	14.0	14.000	**57.0**	**14.3**	**14.250**
Total number	40.0	39.300	46.0	43.800	49.0	45.000	46.0	40.200	**181.0**	**45.3**	**42.075**

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
Organisation in whole	28.0	27.300	31.0	28.800	33.0	29.000	32.0	26.200	**31.0**	**27.825**
Department of cellular pharmacology	6.0	6.000	7.0	6.600	7.0	6.100	6.0	5.100	**6.5**	**5.950**
Department of biochemical pharmacology	6.0	6.000	7.0	7.000	7.0	6.900	8.0	7.900	**7.0**	**6.950**
Department of pharmacology of inflammation	4.0	4.000	5.0	5.000	6.0	6.000	5.0	2.600	**5.0**	**4.400**
Department of pharmacology of excitable tissues	5.0	4.300	5.0	3.500	5.0	2.400	4.0	2.000	**4.8**	**3.050**
Department of toxicology and breeding of laboratory animals	0.0	0.000	0.0	0.000	1.0	1.000	1.0	1.000	**0.5**	**0.500**
Laboratory of bioorganic chemsitry of drugs	2.0	2.000	2.0	2.000	2.0	2.000	2.0	2.000	**2.0**	**2.000**
Laboratory of developmental and behavioral toxicology	3.0	3.000	3.0	2.700	3.0	2.600	4.0	3.600	**3.3**	**2.975**
Laboratory of cell cultures	2.0	2.000	2.0	2.000	2.0	2.000	2.0	2.000	**2.0**	**2.000**

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]*	545.286	542.076	520.826	551.312	**539.875**
Other Salary budget *[thousands of EUR]*	6.099	4.945	7.336	2.415	**5.199**

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

Article 1 of the Foundation Certificate

Basic Purpose and Subject of Activity

A. The Institute deals with complex basic research mainly in the field of medical and pharmaceutical sciences (pharmacology, pharmaceutical chemistry, normal and pathological physiology, toxicology), further in chemical (biochemistry, bioorganic chemistry and synthesis of new potential drugs) and biological sciences (animal physiology, molecular biology, neurosciences) and other related scientific disciplines.
B. It conducts scientific and research activities in the field of basic and applied research and breeding of laboratory animals (Department of Toxicology and Breeding of Laboratory Animals at Dobra Voda, district Trnava).
C. It conducts scientific education according to general mandatory legal regulations.
D. It pursues scientific and research tasks of the Slovak Academy of Sciences and contributes to the development of science by solving socially significant issues of biomedical research for purposes of pharmacotherapy.

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)

1. Natural compounds and their derivatives in possible treatment of chronic diseases

1.1. Human neutrophils

Neutrophils (neutrophilic polymorphonuclear leukocytes) are not only important cells of the immune system but they participate actively in the initiation and progression of many pathological states such as rheumatoid arthritis, asthma or cystic fibrosis. These conditions are often accompanied by persistent and excessive activation of neutrophils and by delayed apoptosis of these cells which results in tissue damage. We studied effects of synthetic derivatives of natural polyphenols (derivatives of stilbene - resveratrol, pterostilbene, pinosylvin and piceatannol, derivatives of ferulic acid - curcumin and N-feruloylserotonin) on the activity of human neutrophils, with respect to oxidative burst and protein kinase C activation. All substances tested inhibited the production of oxidants in human neutrophils extracellularly as well as intracellularly (Fig. 1). The intracellularly active substances were further analysed for their effect on protein kinase C isoforms alpha and beta II, as these enzymes are involved in the activation of NADPH oxidase and thus in the regulation of oxidant formation. We found that the polyphenols tested inhibited oxidative burst and decreased the phosphorylation of PKC isoforms alpha and beta II. Moreover, these substances induced neutrophil apoptosis (curcumin, resveratrol, piceatannol) and increased activity of caspase-3 (pterostilbene, pinosylvin, curcumin). Similar effect was detected by coumarin derivatives.The results indicated that some natural polyphenols are able not only to inhibit the processes associated with the initiation and development of inflammation, but they can also support resolution by inducing neutrophil apoptosis.

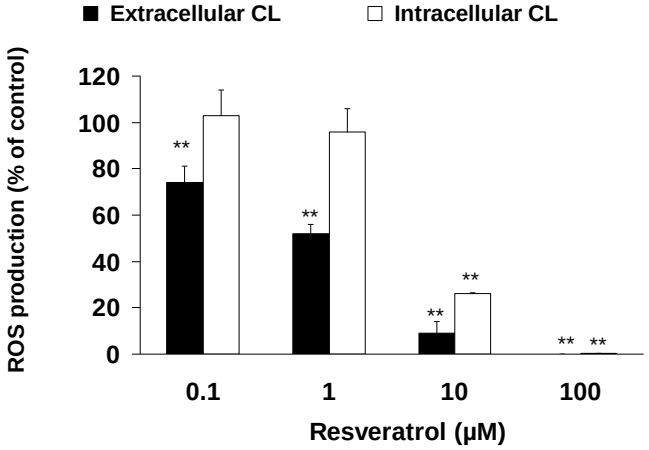


Fig. 1.
Effect of resveratrol on extra- and intracellular formation of reactive oxygen species (ROS) in human neutrophils.

JANČINOVÁ, Viera - PEREČKO, Tomáš - NOSÁĽ, Radomír - HARMATHA, Juraj - ŠMIDRKAL, Jan - DRÁBIKOVÁ, Katarína. The natural stilbenoid pinosylvin and activated neutrophils: effects on oxidative burst, protein kinase C, apoptosis and efficiency in adjuvant arthritis. In Acta Pharmacologica Sinica 2012, vol. 33, no. 10, p. 1285-1292.

DRÁBIKOVÁ, Katarína - PEREČKO, Tomáš - NOSÁĽ, Radomír - HARMATHA, Juraj - ŠMIDRKAL, Jan - JANČINOVÁ, Viera. Study of possible mechanisms involved in the inhibitory effects of coumarin derivatives on neutrophil activity. In Oxidative medicine and cellular longevity, 2013, vol. 2013, 10 p., article ID 136570.

NOSÁĽ, Radomír - DRÁBIKOVÁ, Katarína - JANČINOVÁ, Viera - PEREČKO, Tomáš - AMBROŽOVÁ, Gabriela - ČÍŽ, Milan - LOJEK, Antonín - PEKAROVÁ, Michaela - ŠMIDRKAL, Jan - HARMATHA, Juraj. On the molecular pharmacology of resveratrol on oxidative burst inhibition in professional phagocytes. In Oxidative medicine and cellular longevity, 2014, vol. 2014, article ID 706269, 9 p.

1.2. Serine proteases

Under pathological conditions, serine proteases are responsible for the onset of many diseases, as cancer, cardiovascular diseases, inflammation, multiple sclerosis, etc. A group of 21 polyphenol derivatives was synthesized by the esterification of rutin, phlorizin and aesculin and the ability to

decrease activities of selected protease enzymes - trypsin, thrombin, urokinase and elastase, was analysed. Some derivatives showed a significantly higher inhibitory activity when compared to the activity of the original compounds. QSAR study and cluster analysis of derivatives provided data useful for the synthesis of effective serine proteases inhibitors.

VISKUPIČOVÁ, Jana - DANIHELOVÁ, Martina - MÁJEKOVÁ, Magdaléna - LIPTAJ, Tibor - ŠTURDÍK, Ernest. Polyphenol fatty acid esters as serine protease inhibitors: a quantum-chemical QSAR analysis. In Journal of Enzyme Inhibition and Medicinal Chemistry, 2012, vol. 27, no. 6, p. 800-809.

1.3. Diabetic complications

The invention applied related to semi-synthetic derivatives of quercetin (Fig. 2) useful as bifunctional agents combining antioxidant activity with aldose reductase inhibition ability for treatment or prevention of diseases where oxidative stress and polyol pathway are key etiological factors such as development of diabetic complications including macro- and microangiopathy, atherosclerosis, retinopathy, cataracts, nephropathy and neuropathy, resistance of hepatic cancer to chemotherapy, abnormal proliferation of vascular smooth muscle cells in atherosclerosis and restenosis, inflammatory diseases such as uveitis, sepsis, colon cancer, asthma and periodontitis. The invention also related to pharmaceutical compositions containing the claimed compounds and their use in the treatment of human and animal health problems as mentioned above.

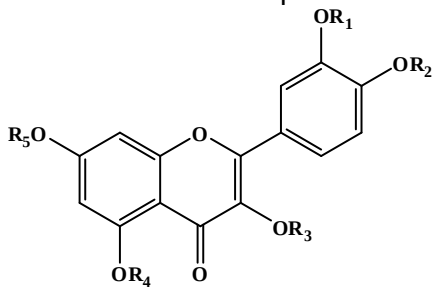


Fig. 2. Structure of quercetin derivatives.

ŠTEFEK, Milan - KOVÁČIKOVÁ, Lucia - MILÁČKOVÁ, Ivana - VEVERKA, Miroslav - ŠVAJDLENKA, Emil - VEVERKOVÁ, Eva. Derivatives of quercetin, its pharmaceutical composition and use. Application number PP 5006-2012 (29.02.2012).

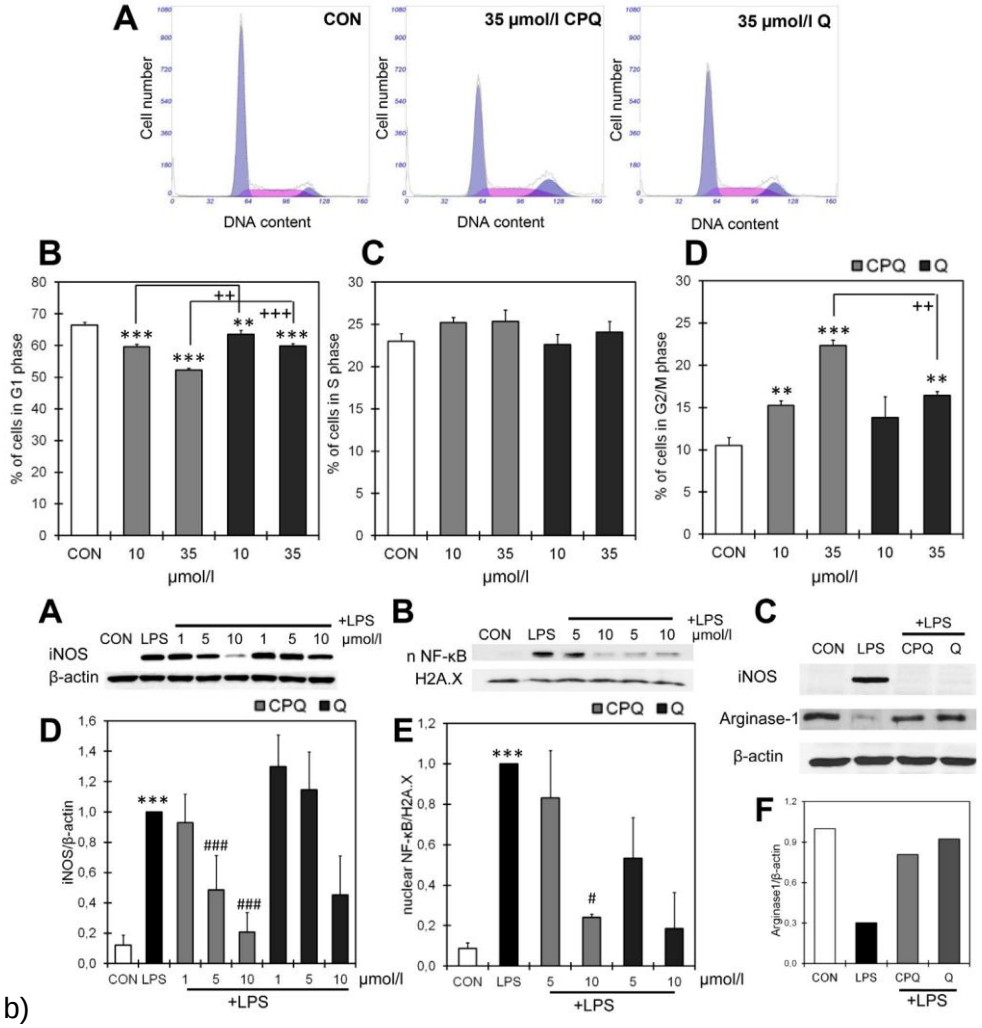
MILÁČKOVÁ, Ivana - ŠOLTÉSOVÁ PRNOVÁ, Marta - MÁJEKOVÁ, Magdaléna - SOTNÍKOVÁ, Ružena - STAŠKO, Michal - KOVÁČIKOVÁ, Lucia - BANERJEE, Sreeparna - VEVERKA, Miroslav - ŠTEFEK, Milan. 2-Chloro-1,4-naphthoquinone derivative of quercetin as an inhibitor of aldose reductase and anti-inflammatory agent. In *Journal of Enzyme Inhibition and Medicinal Chemistry*, 2015, vol. 30, no. 1, p.107-113.

MILÁČKOVÁ, Ivana - RAČKOVÁ, Lucia - MÁJEKOVÁ, Magdaléna - MRVOVÁ, Nataša - ŠTEFEK, Milan. Protection or cytotoxicity mediated by a novel quinonoid-polyphenol compound? In *General Physiology and Biophysics*, 2015, vol. 34, p. 51-64.

1.4. Neuroinflammation

Novel semisynthetic flavonoid, 3′-O-(3-chloropivaloyl) quercetin (CPQ) inhibited production of pro-inflammatory mediators NO and TNFa in BV-2 microglia cell line more effectively than did unmodified quercetin (Fig. 3). These results correlated with inhibition of protein expression of iNOS enzyme and suppression of nuclear translocation of NFkB. CPQ showed also a minor better suppression of PMA-induced generation of superoxide than did quercetin. Flow-cytometric analysis of DNA content confirmed also a more potent inhibitory effect on cell cycle progression. However, antiproliferative effect of CPQ was not associated with drop in either viability, or phagocytosis followed as incorporation of fluorescent particles and bacteria. These data suggest that lipophilic flavonoid CPQ can be a prospective agent with optimized bioavailability in treatment and prevention of neuroinflammatory neurodegenerations.

a)



b)

Fig. 3. Effect of novel flavonoid CPQ on **a)** progression of cell cycle and **b)** protein expression of iNOS (A, D), nuclear translocation of transcription factor NfkB (B, E) and markers of microglia polarization (C, F) in BV-2 microglia cell line stimulated with bacterial lipopolysaccharide.

MRVOVÁ, Nataša - ŠKANDÍK, Martin - KUNIAKOVÁ, Marcela - RAČKOVÁ, Lucia. Modulation of BV-2 microglia functions by novel quercetin pivaloyl ester. In *Neurochemistry International*, 2015, vol. 90, p. 246-254.

1.5. Adjuvant arthritis

Most of the antirheumatics have adverse effects when administered in high doses or during long-term therapy. To achieve better efficacy of rheumatoid arthritis (RA) treatment, the reduced adverse effects antirheumatics are combined together. Beside the standard combinations of antirheumatics and their combinations with biologic drugs, there is a possibility to combine methotrexate (MTX) - antirheumatic drug of first choice with natural non-toxic immunomodulators and antioxidants. Our results evidenced that the combinations of MTX with immunomodulators/antioxidants had a synergic therapeutic potential increasing effect. The treatment of adjuvant arthritis AA with combination of low dose MTX with N-feruloylserotonin was more effective than single treatment with MTX in correcting clinical (arthritic score and hind paw edema) and inflammatory markers (CRP, cytokines: IL-1beta and IL-17, chemokine MCP-1). (Fig. 4). It is a real assumption that the natural N-feruloylserotonin could find in the future a therapeutic use in combination therapy for RA patients. N-feruloylserotonin also showed the ability of reducing the activity of NF-kappa B (key transcription factor of inflammatory conditions) in tissue damaged by AA.

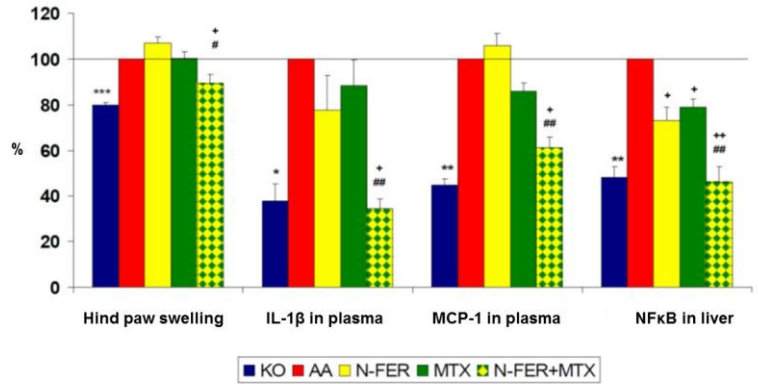


Fig. 4. Effect of N-feruloylserotonin and its combination with MTX in AA on parameters monitored (hind paw edema, IL-1beta, MCP-1 in plasma, and NFκB in liver on day 28). Values are expressed in % calculated on untreated arthritic group (AA-100%): healthy animals without treatment (KO), AA animals treated with N-feruloylserotonin (N-FER), AA animals treated with methotrexate (MTX), AA animals treated with combination of MTX and N-FER (N-FER+MTX). Statistical comparison of untreated arthritic animals with healthy animals (* $p<0.05$, ** $p<0.01$, *** $p<0.001$), and combination of N-FER+MTX (+ $p<0.05$, ++ $p<0.01$) and comparison of MTX treated group with combination of N-FER+MTX ((#$p<0.05$, ##$p<0.01$).

KUNCÍROVÁ, Viera - PONIŠT, Silvester - MIHALOVÁ, Danica - DRÁFI, František - NOSÁĽ, Radomír - ACQUAVIVA, Alessandra - GARDI, Concetta - HARMATHA, Juraj - HRADKOVÁ, Iveta - BAUEROVÁ, Katarína. N-feruloylserotonin in preventive combination therapy with methotrexate reduced inflammation in adjuvant arthritis. In Fundamental & Clinical Pharmacology, 2014, vol. 28, p. 616-626.

GARDI, Concetta - BAUEROVÁ, Katarína - STRINGA, Blerta - KUNCÍROVÁ, Viera - SLOVÁK, Lukáš - PONIŠT, Silvester - DRÁFI, František - BEZÁKOVÁ, Lýdia - TEDESCO, Idolo - ACQUAVIVA, Alessandra - BILOTTO, Stefania - RUSSO, Gian Luigi. Quercetin reduced inflammation and increased antioxidant defense in rat adjuvant arthritis. In Archives of Biochemistry and Biophysics, 2015, vol. 583, p. 150-157.

1.6. Calcium homeostasis

The sensitivity of Ca^{2+}-ATPases (SERCA) to oxidative/nitrosative stress induced by peroxynitrite is associated with regulation of many physiological events and is also included in human pathologies. SERCA may represent a critical target in therapeutic strategies of oxidative stress related diseases or aging. The mechanisms of peroxynitrite induced posttranslational and conformational alterations of SERCA were the foci of our study. Concentration dependent decrease of SERCA was found to be associated with drop of cystein SH-groups, elevation of nitrotyrosine and protein carbonyl levels and with conformational changes in the cytosolic nucleotide (ATP) binding domain of SERCA. In the transmembrane Ca^{2+}-binding sites of SERCA, no conformational alterations induced by peroxynitrite were observed. Quercetin (Q) and its novel derivatives monochloropivaloyl-quercetin (MPQ) and chloronaphthoquinonequercetin (CHQ) were studied in the presence of peroxynitrite as antioxidants and modulators of SERCA activity. Q and MPQ protected SERCA1 activity against peroxynitrite impairment. CHQ, in contradiction, potentiated peroxynitrite-induced enzyme activity decrease, probably due to its most profound prooxidant properties as indicated by strong SH-group decrease, quantum-chemical calculations and slight ability to scavenge peroxynitrite. Furthermore, lipophilic CHQ induced the most significant conformational changes of SERCA in the transmembrane region. The protective effects of Q and MPQ on SERCA against oxidative damage and associated anti-apoptotic efficacy may be useful for prevention and treatment of heart diseases.

We also evaluated the effect of flavonoid rutin and its lipophilic derivatives (acylated with fatty acid chain length of 16–22) on SERCA in the presence/absence of peroxynitrite. Rutin concentration dependently protected $ONOO^-$ induced SERCA1 activity decrease, prevented enzyme from thiol oxidation, tyrosine nitration and protein carbonyl formation after $ONOO^-$ oxidation. Rutin further stimulated SERCA1 activity and induced conformational changes in the cytosol, in the close vicinity of the ATP-binding site, as confirmed also by *in silico* studies (Fig. 5). On the other hand, rutin derivatives caused concentration dependent decrease of SERCA1 activity and significant conformational alterations in the transmembrane region of the enzyme. Upon treatment by

peroxynitrite, rutin derivatives exerted a hormetic effect, i.e. prevented enzyme activity decrease at low concentrations, while additionally inhibited at high concentrations, induced a loss of free sulfhydryl groups, protected the enzyme from protein carbonyl formation, and prevented SERCA from tyrosine nitration. Interaction of rutin derivatives with Glu771, a residue involved in Ca^{2+} binding, is likely to be responsible for the inhibitory effect of the esters.

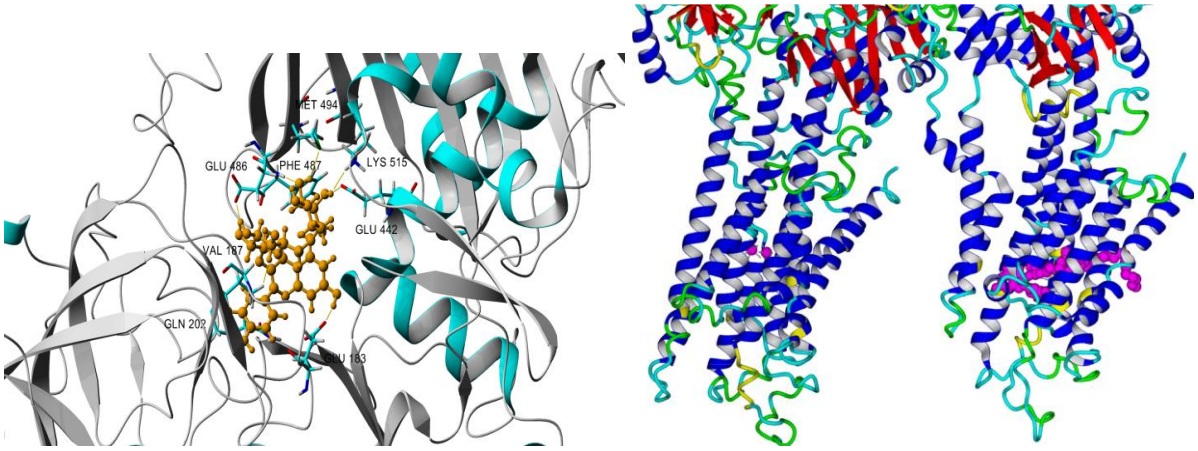


Fig. 5 Rutin binding site in the cytosol (left) and rutin arachidonate binding site in the transmembrane region (right) of SERCA1.

ŽIŽKOVÁ P, VISKUPIČOVÁ J, BLAŠKOVIČ D, ŠTROSOVÁ M, ŽARKOVIČ N, HORÁKOVÁ L. Sarcoplasmic reticulum Ca^{2+}-ATPase from rabbit skeletal muscle modified by peroxynitrite. J Enzyme Inhib Med Chem, 2014 Aug;29(4):563-70.

ŽIŽKOVÁ P, BLAŠKOVIČ D, MÁJEKOVÁ M, ŠVORC L, RAČKOVÁ L, RATKOVSKÁ L, VEVERKA M, HORÁKOVÁ L. Novel quercetin derivatives in treatment of peroxynitrite-oxidized SERCA1. Mol Cell Biochem. 2014 Jan;386(1-2):1-14.

VISKUPICOVA J., MAJEKOVA M., HORAKOVA L. Inhibition of the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA1) by rutin derivatives. J Muscle Res Cell Motil, 2015 Apr;36(2):183-94.

VISKUPICOVA J., STROSOVA MK., ZIZKOVA P., MAJEKOVA M., HORAKOVA L. Rutin stimulates sarcoplasmic reticulum Ca^{2+}-ATPase activity (SERCA1) and protects SERCA1 from peroxynitrite mediated injury. Mol Cell Biochem, 2015 Apr; 402(1):51-62.

1.7. Protection of endothel

Oxidative stress as well as inflammation processes is engaged in diabetic vascular complications. Rosmarinic acid, a natural phenol antioxidant carboxylic acid, was found to have multiple biological activity. By means of streptozocin-induced diabetes in rats, it was found that rosmarinic acid protected aortic endothelial function (Fig. 6) and ultrastructure against diabetes-induced damage. Both antioxidant and anti-inflammatory effects of rosmarinic acid seemed to participate in the mechanism of this protection.

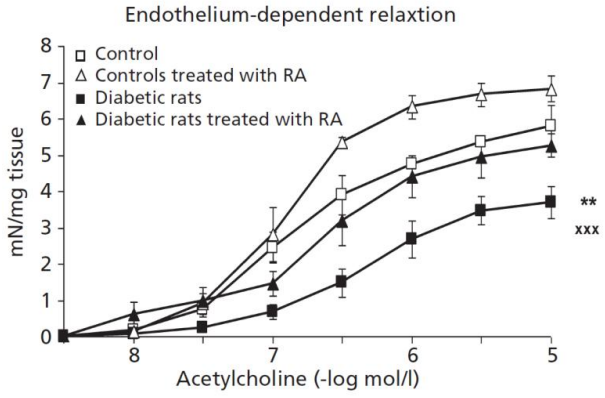


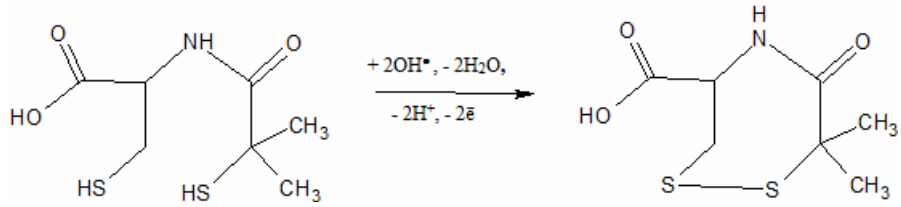
Fig. 6 Responses of the phenylephrine (10-6 mol/l)-precontracted rat thoracic aorta to acetylcholine 10-8–10-5 mol/l), expressed in mN/mg tissue. Rosmarinic acid (RA) administered at 50 mg/kg per day. Data are means SEM of seven experiments. **P < 0.001 vs C; xxxP < 0.0001 vs R.

SOTNÍKOVÁ, Ružena - OKRUHLICOVÁ, Ľudmila - VLKOVIČOVÁ, Jana - NAVAROVÁ, Jana - GAJDÁČOVÁ, Beata - PIVÁČKOVÁ, Lenka - FIALOVÁ, Silvia - KŘENEK, Peter. Rosmarinic acid administration attenuates diabetes-induced vascular dysfunction of the rat aorta. In Journal of Pharmacy and Pharmacology, 2013, vol. 65, no. 5, p. 713-723.

2. Synthetic compounds and their derivatives in possible treatment of chronic diseases

2.1. Synovial fluid

We found that bucillamine, an antirheumatoid drug, acts as a scavenger of reactive oxygen species, namely hydroxyl radical as well as peroxy- and alkoxy-type radicals. Bucillamine is a dithiol donating two atoms of hydrogen ($2H^{\bullet}$) and also a reductant providing two electrons ($2e^{-}$) to form a non-toxic product of a disulfide type (SA981) (Fig. 7). This mechanism as well as kinetics of the antioxidative effect of bucillamine was compared to the findings, when antioxidative properties of several monothiol compounds were studied. The determined values IC_{50} 4±0.4 μM (by ABTS assay) or 9±0.4 μM (by DPPH assay) confirm a high antioxidative effect of bucillamine.



Bucillamine **SA981**

Fig. 7. Reaction of Bucillamine → SA981

BAŇASOVÁ, Mária - VALACHOVÁ, Katarína - RYCHLÝ, Jozef - JANIGOVÁ, Ivica - CSOMOROVÁ, Katarína -MENDICHI, Raniero - MISLOVIČOVÁ, Danica - JURÁNEK, Ivo - ŠOLTÉS, Ladislav. Effect of bucillamine on freeradical-mediated degradation of high-molar-mass hyaluronan induced in vitro by ascorbic acid and Cu(II) ions. In Polymers : Open Access Polymer Science Journal, 2014, vol. 6, no. 10, p. 2625-2644

BAŇASOVÁ, Mária - VALACHOVÁ, Katarína - JURÁNEK, Ivo - ŠOLTÉS, Ladislav. Dithiols as more effective than monothiols in protecting biomacromolecules from free-radical-mediated damage: in vitro oxidative degradation of highmolar-mass hyaluronan. In Chemical Papers, 2014, vol. 68, no. 10, p. 1428-1434.

2.2. Diabetic complications

By application of a ligand-based search in databases of commercially available compounds, novel aldose reductase inhibitors based on carboxymethylated mercapto-triazino-indole scaffold have been designed. Among the novel compounds, 3-mercapto-5H-1,2,4-triazino[5,6-b]indole-5-acetic acid (compound 1, Fig. 8) was the most promising inhibitor, with an IC_{50} in submicromolar range. High selectivity with respect to the closely related aldehyde reductase and AKR1B10 oxidoreductase was recorded. The crystal structure of aldose reductase complexed with 1 revealed an interaction pattern explaining its high afinity (Fig. 9). Physicochemical parameters matching „the rule of five“, along with good water solubility, point to an excellent „drug-likeness“of 1. The ALR2 inhibitory potential of 1 was demonstrated at the organ level in isolated rat eye lenses incubated with high glucose and in vivo in the rat model of experimental diabetes. Currently, compound 1 has been the subject of complex preclinical studies as a prospective agent with a therapeutic potential in the treatment of diabetic complications**.**

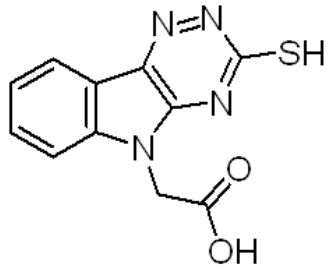


Fig. 8. 3-Mercapto-5H-1,2,4-triazino[5,6-b]indole-5-acetic acid (Compound 1)

ŠTEFEK, Milan - MILÁČKOVÁ, Ivana - DIEZ-DACAL, Beatriz - PÉREZ-SALA, Dolores Gozalo - ŠOLTÉSOVÁ-PRNOVÁ, Marta. Use of 5-karboxymethyl-3-merkapto-1,2,4-triazino-[5,6-b]indoles and pharmaceutical agents with their composition: PP 97-2013. Application number 97-2013, application date 15.10.2013. International patent classification A61K31/00, version: 13, 2013 (Slovak Patent)

ŠTEFEK, Milan - MILÁČKOVÁ, Ivana - DIEZ-DACAL, Beatriz - PÉREZ-SALA, Dolores – ŠOLTÉSOVÁ PRNOVÁ, Marta. Use of 5-carboxymethyl-3-mercapto-1,2,4-triazino-[5,6-B]indoles and their pharmaceutical composition : international publication number WO 2015/057175 A1. International publication date: 23 april 2015 (23.04.2015). International patent classification: A61K 31/53 (2006.01). World Intellectual Property Organization, 2015 (European Patent).

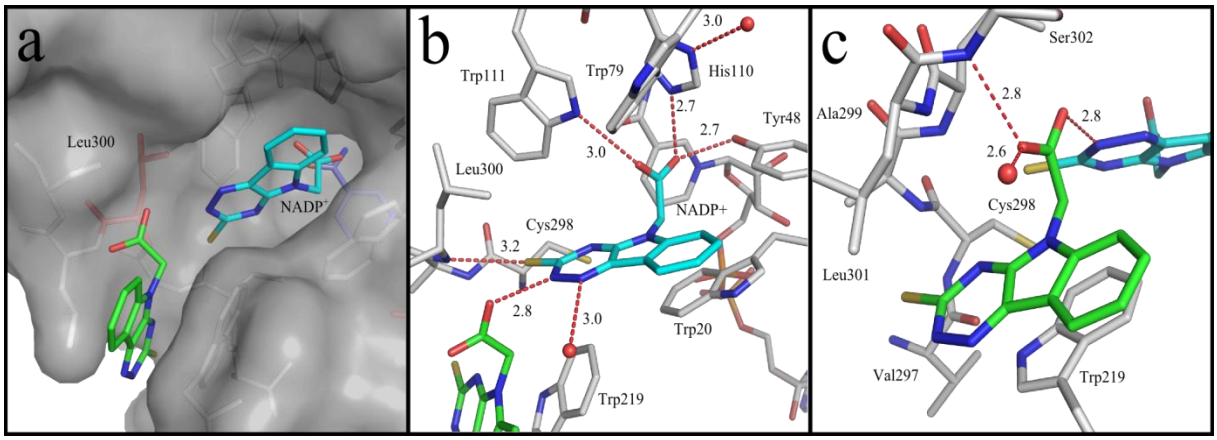


Fig. 9. High resolution X-ray assay of crystal structure of AKR1B1 complexed with compound 1.

ŠTEFEK, Milan - ŠOLTÉSOVÁ PRNOVÁ, Marta - MÁJEKOVÁ, Magdaléna - RECHLIN, Chris - HEINE, Andreas - KLEBE, Gerhard. Identification of novel aldose reductase inhibitors based on carboxymethylated mercaptotriazinoindole scaffold. In *Journal of Medicinal Chemistry*, 2015, vol. 58, no. 6, p. 2649-2657.

ŠOLTÉSOVÁ PRNOVÁ, Marta - BALLEKOVÁ, Jana - GAJDOŠÍKOVÁ, Alena - GAJDOŠÍK, Andrej - ŠTEFEK, Milan. A novel carboxymethylated mercaptotriazinoindole inhibitor of aldose reductase interferens with the polyol pathway in streptozotocin-induced diabetic rats. In *Physiological Research*, 2015, vol. 64, no. 4, p. 587-591.

ŠOLTÉSOVÁ PRNOVÁ, Marta - BALLEKOVÁ, Jana - MÁJEKOVÁ, Magdaléna - ŠTEFEK, Milan. Antioxidant action of 3-mercapto-5H-1,2,4-triazino[5,6-b]indole-5-acetic acid, an efficient aldose reductase inhibitor, in a 1,1′-diphenyl-2-picrylhydrazyl assay and in the cellular system of isolated erythrocytes exposed to tert-butyl hydroperoxide. In *Redox Report*, 2015, vol. 20, no. 6, p. 282-288.

2.3. Trimethyltin animal model of neurodegeneration

Alzheimer disease (AD)-like animal model of trimethyltin (TMT)-induced neurodegeneration, targeting the hippocampus, involves neuronal cell death and cognitive impairment. Effect of the pyridoindole SMe1EC2 and vitamin C was analyzed in the model of TMT-induced neurodegeneration. The study was focused on the effect of the antioxidants tested on learning performance in the Morris water maze (MWM) on days 21–25 after TMT administration, on biochemical variables – malondyaldehyde (MDA) and lysosomal enzyme NAGA in brain cortex and blood serum, and on pyramidal cell number in the CA1 area of the hippocampus on day 31 after TMT administration in adult male Wistar rats. SMe1EC2 apparently preserved pyramidal cell viability in the CA1 area. Both substances tested failed to ameliorate the detrimental effect of TMT on spatial memory. The biochemical and morphometrical findings suggest that reduction of oxidative stress may play a role in AD-like neurodegeneration. Different doses and timing of SMe1EC2 administration might bring improvement in next learning performance.

GÁSPÁROVÁ, Zdenka - STARÁ, Veronika - JANEGA, Pavol - NAVAROVÁ, Jana - SEDLÁČKOVÁ, Natália - MACH, Mojmír - UJHÁZY, Eduard. Pyridoindole antioxidant-induced preservation of rat hippocampal pyramidal cell number linked with reduction of oxidative stress yet without influence on cognitive deterioration in Alzheimer-like neurodegeneration. In *Neuroendocrinology Letters*, 2014, vol. 35, no. 6, p. 454-462.

3. Others

3.1. Enhanced drug delivery

Besides necrotic cells present in a chronic inflamed tissue there are also cells, which are due to their damaged extracellular matrix insufficiently supplied with oxygen (a state of hypoxia). It is known that during hypoxia mitochondria in cells overproduce reactive oxygen species (ROS). ROS such as $O_2^{\bullet-}$ and H_2O_2, of which $^{\bullet}OH$ radicals are produced, are those reactants which damage the tissues. One way of an effective reduction of an adverse flow of ROS from mitochondria is application of the so-called mitochondrially-targeted antioxidants (MTA). The inventors solved the problem (PP 5032-2015) by incorporating an MTA into membranes composed of two biopolymers, namely a high-molar-mass hyaluronan (HA) and chitosan. HA molecules (negatively charged) are components of skin, chitosan is a positively charged biopolymer. By combining the appropriate amounts of chitosan and hyaluronan it is possible to form very firm biofilms with a certain surplus of the negative charge. Incorporation of the MTA into such a biofoil results in a formation of biomembranes, of which MTA is released gradually.

Patent

ŠOLTÉS, Ladislav - TAMER ABD-EL RAZIK, Tamer Mahmoud - VEVERKA, Miroslav - VALACHOVÁ, Katarína - MOHY ELDIN, Mohamed Samir. Self-associated biopolymer membranes as holders of medicinal agents with antioxidant properties and their use: Patent application: PP 5032-2015, International classification: A61L15/00, version MPT: 16, 10.07.2015.

3.2. Mechanism of neurodegeneration

The achieved results confirm the lines of evidence pointing to a link between hypercholesterolaemia and age-related neurodegenerative diseases. Moreover, we discovered a new aspect of neurodegeneration. The incubation of BV-2 microglia with cholesterol and oxysterol influenced cellular functions mediated by membrane proteins, namely p47[phox] subunit of NADPH oxidase complex, scavenger receptor CD36 and membrane-associated form of the cytosolic system, 26S proteasome. The confirmed changes in the distribution of these proteins caused by enrichment of cholesterol in the membrane were suggested as a critical factor contributing to this outcome (Fig. 10). Cholesterol and its oxidized metabolite, cholesterol 5α,6α-epoxide, can modulate neurotoxic potential of microglia in a different way. In particular, either they can augment it (influence by cholesterol), or, contrary, they can mildly mitigate it (in case of influence by cholesterol), as confirmed in a co-culture of PC12 cells with activated BV-2 microglia.

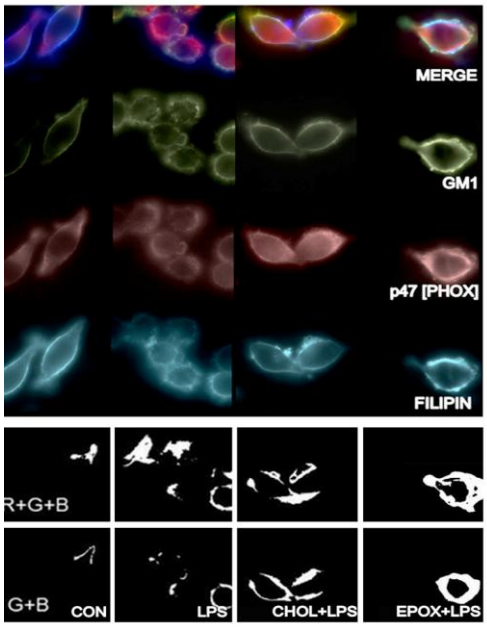


Fig. 10.
Effect of stimulation with lipopolysaccharide (LPS) and influence of cholesterol (CHOL) and cholesterol 5a,6a-epoxide (EPOX) on distribution of the protein p47[phox] (cytosolic component of NADPH oxidase) in membrane of mouse microglia BV-2. Lipid rafts were identified by immunocytochemistry staining with cholera toxin B-fluorescein isothiocyanate, a ligand specific for ganglioside GM1.Cholesterol is labeled with filipin III. The level of co-localization of the individual channels is indicated by white color, scale bar 20 μm.

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3.3. Anti-biofilm activity of dibenzothiepines

The formation of bacterial biofilms connected with the mechanism of *quorum sensing* was found to be one of the reasons of antimicrobial drug resistance of many conventional agents. Although anti-

biofilm agents themselves might not kill the bacteria, they can make them susceptible to conventional antibiotic. New dibenzo[b,e]thiepins were screened for their anti-microbial and anti-biofilm properties. Some of the compounds exhibited good antibiofilm activity against the Gram-negative, non-fermentative bacilli *Pseudomonas aeruginosa* and *Acinetobacter baumanii*, and their possible target was identified as N-acyl-l-homoserine lactone synthase (AHLS) - the enzyme responsible for the synthesis of *quorum sensing* molecules employed by the Gram-negative microorganisms. Molecular modeling study with a model compound – brominate furanone c56 with known inhibition activity - revealed the most probable site for the interaction of dibenzo[b,e]thiepins with AHLS (Fig. 11). The results were then used for docking of the dibenzothiepines and the roles of residues Argl00, Thr14O and Ser143 were confirmed.

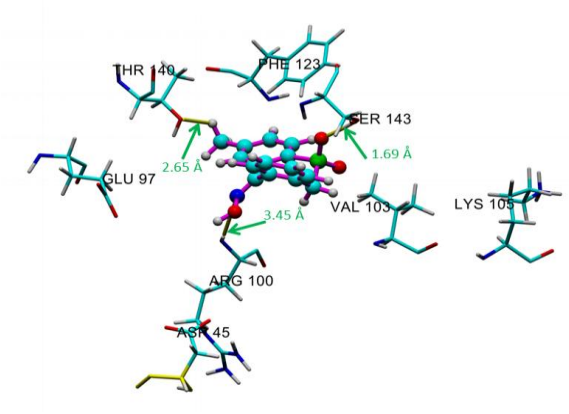

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Fig. 11
Structure of the binding site of l0b.

3.4. Developmental toxicology and hypoxia/ischemia in development

Research in this field is focused on the influence of hypoxia/ischemia, excessive stress and antidepressant treatment during sensitive stages of brain development related to investigation of neonatal injury and rise of neurobehavioral and cardiovascular dysfunctions in adulthood.

Hypoxic-ischemic injury (HII) of neonatal brain induced in new-born rats has a characteristic biphasic course. Energy metabolism failure typically takes place in two stages: primary failure due to the reduced availability of oxygen for OxPhos, while the secondary failure, which often occurs after recovery of the brain due to its reoxygenation, is caused by cell calcium overload. On the contrary to the classical notion, our unique finding is the result that in contrast to the adult brain, there are no specific histological phases of HII in the neonatal brain. It means that necrosis is not characteristic feature only for the first phase and apoptosis for the second one. A relevant finding was a biphasic development of edema. In the primary phase of HII, cytotoxic intracellular edema dominated, while in the secondary stage, it was vasogenic extracellular edema. A significant and clinically relevant is our discovery that in the blood serum of neonatal rats, there was an increased activity of specific matrix metalloproteinases (MMP-2 and MMP-9) in HII brain what indicates functional injury of the blood brain barrier.

Perinatal asphyxia is a major cause of infant mortality and neurological disorders in adulthood. The aim of the study was to assess the effect of sub-chronic prenatal asphyxia (SPA) during the late development in rat fetuses on the behavioral changes and control of blood pressure in adulthood. SPA caused increased anxiety-like behavior in elevated plus maze as well as in the light/dark preferential test. The intensity of climbing in Porsolt´s test was significantly reduced in adult males affected by SPA, which indicates signs of depression-like behavior. The systolic blood pressure and the pulse pressure were significantly increased in SPA rats compared to the controls. The results show that the short interrupted asphyxial period at the end of pregnancy can induce anxiety- and depression-like behaviors and increase blood and pulse pressure in adulthood.

Further, we found that long-term administration of SNRI antidepressant drug venlafaxine (VENF) during pregnancy and lactation caused behavioral changes in the rat offspring. Adult offspring had lower rates of anxiety- and depression-like behaviors in a new unfamiliar environment. They also had higher basal levels of corticosterone and aldosterone. These results indicate that VENF interacts with developmental processes in the brain what in turn results in altered neurobehavioral and neuroendocrine regulations. These changes can not be considered to be serious or adverse. These changes are more in terms of adaptation mechanisms. Animals affected through the mother with VENF were less anxious and depressed in the new environment,

which can be interpreted as a better ability to adapt to novelty. Our study contributes to the knowledge that the VENF compared to other antidepressants is relatively safe drug.

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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/applied research	**85 / 15**
International/regional research	**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

Pharmacology of Inflammation – Animal Models

BAUEROVÁ, Katarína - ACQUAVIVA, Alessandra - PONIŠT, Silvester - GARDI, Concetta - VECCHIO, Daniela - DRÁFI, František - AREZZINI, Beatrice - BEZÁKOVÁ, Lýdia - KUNCÍROVÁ, Viera - MIHALOVÁ, Danica - NOSÁĽ, Radomír. Markers of inflammation and oxidative stress studied in adjuvant-induced arthritis in the rat on systemic and local level affected by pinosylvin and methotrexate and their combination. In *Autoimmunity*, 2015, vol. 48, no. 1, p. 46-56. (2.714 - IF2014). (2015 - Current Contents). ISSN 0891-6934.

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Biochemical Pharmacology – Molecular Modeling

STECOZA, Camelia Elena - MÁJEKOVÁ, Magdaléna - MÁJEK, Pavol - CAPROIU, M.T. - MARUTESCU, Luminita. Novel dibenzothiepins with antibiofilm activity demonstrated by microbiological assays and molecular modeling. In *Current Organic Chemistry*, 2013, vol. 17, no. 2, p. 113-124. (3.039 - IF2012). (2013 - Current Contents). ISSN 1385-2728. APVV SK-RO 0008-10.

VISKUPIČOVÁ, Jana - ŠTROSOVÁ, Miriam - ŽIŽKOVÁ, Petronela - MÁJEKOVÁ, Magdaléna - HORÁKOVÁ, Ľubica. Rutin stimulates sarcoplasmic reticulum Ca2+-ATPase activity (SERCA1) and protects SERCA1 from peroxynitrite mediated injury. In *Molecular and Cellular Biochemistry : an international journal for chemical biology in health and disease*, 2015, vol. 402, iss. 1-2, p. 51-62. (2.393 - IF2014). (2015 - Current Contents). ISSN 0300-8177. ITMS 26240220040, COST Actions CM1001, CM1103, VEGA 2/0038/11, VEGA 2/0033/14.

MILÁČKOVÁ, Ivana - ŠOLTÉSOVÁ PRNOVÁ, Marta - MÁJEKOVÁ, Magdaléna - SOTNÍKOVÁ, Ružena - STAŠKO, Michal - KOVÁČIKOVÁ, Lucia - BANERJEE, Sreeparna - VEVERKA, Miroslav - ŠTEFEK, Milan. 2-Chloro-1,4-naphthoquinone derivative of quercetin as an inhibitor of aldose

reductase and anti-inflammatory agent. In *Journal of Enzyme Inhibition and Medicinal Chemistry*, 2015, vol. 30, no. 1, p.107-113. (2.332 - IF2014). (2015 - Current Contents). ISSN 1475-6366. VEGA 2/0067/11, VEGA 2/0030/11, ITMS 26240220040.

VISKUPIČOVÁ, Jana - DANIHELOVÁ, Martina - MÁJEKOVÁ, Magdaléna - LIPTAJ, Tibor - ŠTURDÍK, Ernest. Polyphenol fatty acid esters as serine protease inhibitors: a quantum-chemical QSAR analysis. In *Journal of Enzyme Inhibition and Medicinal Chemistry*, 2012, vol. 27, no. 6, p. 800-809. (1.617 - IF2011). ISSN 1475-6366

Vascular Pharmacology

SOTNÍKOVÁ, Ružena - OKRUHLICOVÁ, Ľudmila - VLKOVIČOVÁ, Jana - NAVAROVÁ, Jana - GAJDÁČOVÁ, Beata - PIVÁČKOVÁ, Lenka - FIALOVÁ, Silvia - KŘENEK, Peter. Rosmarinic acid administration attenuates diabetes-induced vascular dysfunction of the rat aorta. In *Journal of Pharmacy and Pharmacology*, 2013, vol. 65, no. 5, p. 713-723. (2.033 - IF2012). (2013 - Current Contents). ISSN 0022-3573. ITMS 26240220040, VEGA 2/0108/10, VEGA 1/0981/12, FaF UK 10/2012.

FRIMMEL, Karel - VLKOVIČOVÁ, Jana - SOTNÍKOVÁ, Ružena - NAVAROVÁ, Jana - BERNÁTOVÁ, Iveta - OKRUHLICOVÁ, Ľudmila. The effect of omega-3 fatty acids on expresion of Connexin-40 in Wistar rat aorta after lipopolysaccharide administration. In *Journal of Physiology and Pharmacology : formerly Acta Physiologica Polonica*, 2014, vol. 65, no. 1, p. 83-94. (2.720 - IF2013). (2014 - Current Contents). ISSN 0867-5910. VEGA 2/0108/10, VEGA 2/0065/13.

BROSKOVÁ, Zuzana - DRÁBIKOVÁ, Katarína - SOTNÍKOVÁ, Ružena - FIALOVÁ, Silvia - KNEZL, Vladimír. Effect of plant polyphenols on ischemia-reperfusion injury of the isolated rat heart and vessels. In *Phytotherapy Research*, 2013, vol. 27, p. 1018-1022. (2.068 - IF2012). (2013 - Current Contents).

SOTNÍKOVÁ, Ružena - KAPRINAY, Barbara - NAVAROVÁ, Jana. Rosmarinic acid mitigates signs of systemic oxidative stress in streptozotocin-induced diabetes in rats. In *General Physiology and Biophysics*, 2015, vol. 34, no. 4, p. 449-452. (1.173 - IF2014). (2015 - Current Contents). ISSN 0231-5882. ITMS 26240220040, VEGA 2/0054/15.

Bioorganic Chemistry

VALACHOVÁ, Katarína - BAŇASOVÁ, Mária - TOPOĽSKÁ, Dominika - SASINKOVÁ, Vlasta - JURÁNEK, Ivo - COLLINS, Maurice N. - ŠOLTÉS, Ladislav. Influence of tiopronin, captopril and levamisole therapeutics on the oxidative degradation of hyaluronan. In *Carbohydrate Polymers*, 2015, vol. 134, p. 516-523. (4.074 - IF2014). (2015 - Current Contents). ISSN 0144-8617. VEGA 2/0065/15, VEGA 2/0149/12. DOI: 10.1016/j.carbpol.2015.07.029.

HRABÁROVÁ, Eva - RYCHLÝ, Jozef - SASINKOVÁ, Vlasta - VALACHOVÁ, Katarína - JANIGOVÁ, Ivica - CSOMOROVÁ, Katarína - JURÁNEK, Ivo - ŠOLTÉS, Ladislav. Structural characterisation of thiol-modified hyaluronans. In *Cellulose*, 2012, vol. 19, no. 6, p. 2093-2104. (3.600 - IF2011). (2012 - Current Contents). ISSN 0969-0239. VEGA 2/0083/09, VEGA 1/0529/09, VEGA 2/0056/10, VEGA 1/0145/10, VEGA 2/0011/11, VEGA 2/0147/12, ITMS 26220120054, ITMS 26240220040.

BAŇASOVÁ, Mária - VALACHOVÁ, Katarína - RYCHLÝ, Jozef - JANIGOVÁ, Ivica - CSOMOROVÁ, Katarína - MENDICHI, Raniero - MISLOVIČOVÁ, Danica - JURÁNEK, Ivo - ŠOLTÉS, Ladislav. Effect of bucillamine on free-radical-mediated degradation of high-molar-mass hyaluronan induced in vitro by ascorbic acid and Cu(II) ions. In *Polymers : Open Access Polymer Science Journal*, 2014, vol. 6, no. 10, p. 2625-2644. (2.505 - IF2013). (2014 - Current Contents).

HRABÁROVÁ, Eva - VALACHOVÁ, Katarína - JURÁNEK, Ivo - ŠOLTÉS, Ladislav. Free-radical degradation of high-molar-mass hyaluronan induced by ascorbate plus cupric ions: evaluation of antioxidative effect of cysteine-derived compounds. In *Chemistry & biodiversity*, 2012, vol. 9, no. 2, p. 309-317. (1.804 - IF2011). (2012 - Current Contents). ISSN 1612-1872. VEGA 2/0115/09, VEGA 2/0083/09, VEGA 2/0056/10, VEGA 2/0011/11, ITMS-26220120054, ITMS-26240220040

2.1.3 List of monographs/books published abroad

ALDINI, Giancarlo - VISTOLI, Giulio - ŠTEFEK, Milan - CHONDROGIANNI, N. - GRUNE, Tilman - SEREIKAITE, Jolanta - SADOWSKA-BARTOSZ, Izabela - BARTOSZ, Gregorz. Molecular strategies to prevent, inhibit, and degrade advanced glycoxidation and advanced lipoxidation end products. In *Free Radical Research : official journal of the Society for Free Radical Research - European Region*, 2013, vol. 47, suppl.1 SI, p. 93-137. (3.279 - IF2012). (2013 - Current Contents). ISSN 1071-5762. COST CM1001.

2.1.4. List of monographs/books published in Slovakia

KOŠŤÁLOVÁ, Daniela - FIALOVÁ, Silvia - RAČKOVÁ, Lucia. *Fytoterapia v súčasnej medicíne*. 1. vyd. Martin : Osveta, 2012. 379 s. ISBN 978-80-8063-384-4.

UJHÁZY, Eduard - DUBOVICKÝ, Michal - MACH, Mojmír. *Teratológia : princípy a hodnotenie abnormálneho vývinu* [Teratology]. Bratislava : Slovenská toxikologická spoločnosť SETOX : Ústav experimentálnej farmakológie a toxikológie SAV, 2014. 182 s. VEGA 2/0081/11, VEGA 2/0084/11, VEGA 2/0107/12. ISBN 978-80-969474-6-1.

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

Chapters in scientific monographs published abroad

1. VALACHOVÁ, Katarína - RAPTA, Peter - SLOVÁKOVÁ, M. - PRIESOLOVÁ, Elena - NAGY, Milan - MISLOVIČOVÁ, Danica - DRÁFI, František - BAUEROVÁ, Katarína - ŠOLTÉS, Ladislav. Radical degradation of high-molar-mass hyaluronan induced by ascorbate plus cupric ions: testing of arbutin in the function of antioxidant : chapter 2. In *Kinetics, catalysis and mechanism of chemical reactions. From pure to applied science : Volume 2: Tomorrow and perspectives*. - New York : Nova Science Publishers, 2012, p. 11-27. ISBN 978-1-61470-712-7. VEGA 1/0145/10, VEGA 2/0011/11, VEGA 2/0045/11, APVV 0488-07, APVV 0351-10, ITMS 26220120054.
2. VISKUPIČOVÁ, Jana - ONDREJOVIČ, Miroslav - MALIAR, T. Enzyme-mediated preparation of flavonoid esters and their applications : chapter 10. In *Biochemistry*. - Rijeka: InTech, 2012, p. 263-286. ISBN 978-953-51-0076-8. ITMS 26240220040, APVV-VMSP-II-0021-09.
3. BAŇASOVÁ, Mária - VALACHOVÁ, Katarína - JURÁNEK, Ivo - ŠOLTÉS, Ladislav. Aloe vera and methylsulfonylmethane as dietary supplements: their potential benefits to arthritic patients with diabetic complications. In *Pharmaceutical and medical biotechnology : new perspectives*. - Hauppauge : Nova Science Publishers, 2013, p. 111-128. ISBN 978-1-62618-851-8. VEGA 2/0011/11, VEGA 2/0149/12, APVV 0351-10.
4. VALACHOVÁ, Katarína - BAŇASOVÁ, Mária - MACHOVÁ, Ľubica - JURÁNEK, Ivo - BEZEK, Štefan - ŠOLTÉS, Ladislav. Testing various hexahydropyridoindoles to act as antioxidants. In *Pharmaceutical and medical biotechnology : new perspectives*. - Hauppauge : Nova Science Publishers, 2013, p. 93-110. ISBN 978-1-62618-851-8. *Journal of Information, Intelligence and Knowledge*. - Hauppauge : Nova Science Publishers, 2013, vol. 5, no. 1, p. 15-32. ISSN 1937-7983. VEGA 2/0011/11, VEGA 2/0149/12, ITMS-26240220040.
5. RADOŠINSKÁ, Jana - BAČOVÁ, Barbara - VICZENCZOVÁ, Csilla - EGAN BEŇOVÁ, Tamara - KNEZL, Vladimír - ŽURMANOVÁ, Jitka - SOUKUP, Tomáš - GONCALVESOVÁ, Eva - SLEZÁK, Ján - TRIBULOVÁ, Narcis. Maladaptive myocardial responses to hypertension are attenuated by omega-3 fatty acids and red palm oil

intake. In *Adaptation Biology and Medicine*. Volume 7. New Challenges. - New Delhi : Narosa Publishing House, 2014, p. 19-34. ISBN 978-81-8487-214-9. VEGA 2/0046/12, VEGA 2/207/11, APVV SK-CZ-0027-11, GACR 304/08/0256, AVOZ 50110509, MSM0021620858.

6. ŠOLTÉS, Ladislav - KOGAN, Grigorij. Hyaluronan - an information rich messenger reporting on the physiological and pathophysiological status of synovial joints. In *News in chemistry, biochemistry and biotechnology : state of the art and prospects of development*. - Hauppauge : Nova Science Publishers, 2014, p. 1-26. ISBN 978-1631172731. *Polymers Research Journal*. - Hauppauge : Nova Science Publishers, 2014, vol. 8, no. 1, p. 49-73. ISSN 1935-2530. VEGA 2/0011/11, APVV-0351-10.
7. ŠOLTÉS, Ladislav - KOGAN, Grigorij. Hyaluronan: A harbinger of the status and functionality of the joint. In *Engineering of polymers and chemical complexity, Volume II.: New approaches, limitations and control*. - Toronto : Apple Academic Press, 2014, p. 259-286. ISBN 978-1-926895-87-1.
8. VALACHOVÁ, Katarína - BAŇASOVÁ, Mária - MACHOVÁ, Ľubica - JURÁNEK, Ivo - BEZEK, Štefan - ŠOLTÉS, Ladislav. Practical hints on testing various hexahydropyridoindoles to act as antioxidants. In *Chemistry and physics of modern materials : processing, production and applications*. - Oakville : Apple Academic Press, 2014, p. 137-158. ISBN 978-1-926895-45-1.
9. PAWLUSKI, J.L. - GEMMEL, Mary - CSÁSZÁR, Eszter - STEINBUSCH, H.W. N. - RAYEN, Ine. Developmental fluoxetine exposure and neuroendocrine outcomes : chapter 3. In *Fluoxetine: Pharmacology, Mechanisms of Action and Potential Side Effects*. - Hauppauge : Nova Science Publishers, 2015, p. 43-70. ISBN 978-1-63482-076-9.
10. VALACHOVÁ, Katarína - TAMER ABD-EL RAZIK, Tamer Mahmoud - ŠOLTÉS, Ladislav. Comparison of free-radical scavening properties of glutathione under neutral and acidic conditions : chapter 20. In *Chemistry and chemical biology : methodologies and applications*. - Oakville : Apple Academic Press, CRC Press, 2015, p. 227-245. ISBN 978-1-77188-018-3.

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

No: WO 2015/057175 A1
ŠTEFEK, Milan - MILÁČKOVÁ, Ivana - DIEZ-DACAL, Beatriz - PÉREZ-SALA, Dolores - ŠOLTÉSOVÁ PRNOVÁ, Marta. Use of 5-carboxymethyl-3-mercapto-1,2,4-triazino-[5,6-B]indoles and their pharmaceutical composition: international publication number WO 2015/057175 A1. International publication date: 23 april 2015 (23.04.2015). Applicant: IEPhT (SK). International patent classification: A61K 31/53 (2006.01). World Intellectual Property Organization, 2015 (European Patent)

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

No: 5006/2012
ŠTEFEK, Milan - KOVAČIKOVÁ, Lucia - MILÁČKOVÁ, Ivana - VEVERKA, Miroslav - ŠVAJDLENKA, Emil - VEVERKOVÁ, Eva. Derivatives of quercetine, pharmacological composition with their content and their use. Owner: IEPhT. Patent application: PP 5006/2012.

No: PP 97-2013
ŠTEFEK, Milan - MILAĆKOVÁ, Ivana - ŠOLTESOVÁ, Marta - DIEZ-DACAL, B. - PERÉZ-SALA, Gozalo D. Use of 5-karboxymethyl-3-merkapto-1,2,4-triazino-[5,6-b]indoles and pharmaceutical agents with their composition. Owner: IEPhT. Patent application: PP 97-2013.

No: PP 86-2013
ŠOLTES, Ladislav - VALACHOVÁ, Katarína - VEVERKA, Miroslav - TAMER, M. Tamer - MOHY ELDIN, Mohamed Samir. Complexes of chitosan: their production, use and agents with their composition. Owner: IEPhT, Co-owner: Bel/Novaman International, s.r.o., Patent application: PP 86-2013

No: PP 5032-2015
ŠOLTÉS, Ladislav - TAMER ABD-EL RAZIK, Tamer Mahmoud - VEVERKA, Miroslav - VALACHOVÁ, Katarína - MOHY ELDIN, Mohamed Samir. Self-associated biopolymer membranes as holders of medicinal agents with antioxidant properties and their use. Owner: IEPhT. Patent application: PP 5032-2015.

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	1.0	0.023	0.002	0.0	0.000	0.000	0.0	0.000	0.000	**1.0**	**0.3**	**0.006**	**0.000**
Scientific monographs and monographic studies in journals and proceedings published in Slovakia *(AAB, ABB)*	1.0	0.025	0.002	0.0	0.000	0.000	1.0	0.022	0.002	0.0	0.000	0.000	**2.0**	**0.5**	**0.012**	**0.001**
Chapters in scientific monographs published abroad *(ABC)*	2.0	0.051	0.004	3.0	0.068	0.006	4.0	0.089	0.008	2.0	0.050	0.004	**11.0**	**2.8**	**0.065**	**0.005**
Chapters in scientific monographs published in Slovakia *(ABD)*	0.0	0.000	0.000	2.0	0.046	0.004	0.0	0.000	0.000	0.0	0.000	0.000	**2.0**	**0.5**	**0.012**	**0.001**
Scientific papers published in journals registered in Current Contents Connect *(ADCA, ADCB, ADDA, ADDB)*	13.0	0.331	0.024	16.0	0.365	0.030	20.0	0.444	0.038	27.0	0.672	0.049	**76.0**	**19.0**	**0.452**	**0.035**
Scientific papers published in journals registered in Web of Science Core Collection and SCOPUS *(ADMA, ADMB, ADNA, ADNB)*	20.0	0.509	0.037	15.0	0.342	0.028	14.0	0.311	0.027	6.0	0.149	0.011	**55.0**	**13.8**	**0.327**	**0.025**
Scientific papers published in other foreign journals (not listed above) *(ADEA, ADEB)*	0.0	0.000	0.000	4.0	0.091	0.007	8.0	0.178	0.015	6.0	0.149	0.011	**18.0**	**4.5**	**0.107**	**0.008**
Scientific papers published in other domestic journals (not listed above) *(ADFA, ADFB)*	0.0	0.000	0.000	0.0	0.000	0.000	5.0	0.111	0.010	0.0	0.000	0.000	**5.0**	**1.3**	**0.030**	**0.002**
Scientific papers published in foreign peer-reviewed proceedings *(AEC, AECA)*	4.0	0.102	0.007	0.0	0.000	0.000	8.0	0.178	0.015	3.0	0.075	0.005	**15.0**	**3.8**	**0.089**	**0.007**
Scientific papers published in domestic peer-reviewed proceedings *(AED, AEDA)*	19.0	0.483	0.035	6.0	0.137	0.011	17.0	0.378	0.033	8.0	0.199	0.015	**50.0**	**12.5**	**0.297**	**0.023**
Published papers (full text) from foreign and international scientific conferences *(AFA, AFC, AFBA, AFDA)*	1.0	0.025	0.002	0.0	0.000	0.000	0.0	0.000	0.000	0.0	0.000	0.000	**1.0**	**0.3**	**0.006**	**0.000**
Published papers (full text) from domestic scientific conferences *(AFB, AFD, AFBB, AFDB)*	4.0	0.102	0.007	0.0	0.000	0.000	0.0	0.000	0.000	8.0	0.199	0.015	**12.0**	**3.0**	**0.071**	**0.006**

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

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)	537.0	13.664	504.0	11.507	579.0	12.867	596.0	14.826	**2216.0**	**554.0**	**13.167**
Citations in SCOPUS (1.2, 2.2) if not listed above	108.0	2.748	138.0	3.151	168.0	3.733	155.0	3.856	**569.0**	**142.3**	**3.381**
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)	19.0	0.483	31.0	0.708	21.0	0.467	94.0	2.338	**165.0**	**41.3**	**0.980**
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).

1. KOGAN, Grigorij - ŠOLTÉS, Ladislav - STERN, Robert - GEMEINER, Peter. Hyaluronic acid: a natural biopolymer with a broad range of biomedical and industrial applications. In *Biotechnology Letters*, 2007, vol. 29, no. 1, p. 17-25. (1.134 - IF2006). (2007 - Current Contents). ISSN 0141-5492. Citations: 162
2. STERN, Robert - KOGAN, Grigorij - JEDRZEJAS, Mark J. - ŠOLTÉS, Ladislav. The many ways to cleave hyaluronan. In *Biotechnology Advances*, 2007, vol. 25, p. 537-557. (4.943 - IF2006). (2007 - Current Contents). ISSN 0734-9750. Citations: 70
3. VOLPI, Nikola - SCHILLER, Jürgen - STERN, Robert - ŠOLTÉS, Ladislav. Role, metabolism, chemical modifications and applications of hyaluronan. In *Current Medicinal Chemistry*, 2009, vol.16, iss. 14, p.1718-1745. (4.823 - IF2008). (2009 - Current Contents). ISSN 0929-8673. Citations: 57
4. JURÁNEK, Ivo - BEZEK, Štefan. Controversy of free radical hypothesis: reactive oxygen species - cause or consequence of tissue injury? In *General physiology and biophysics : an international journal*. - Bratislava : Institute of Molecular Physiology and Genetics SAS, 2005, vol. 24, p. 263 - 278. (0.694 - IF2004). (2005 - Current Contents). ISSN 0231-5882. Citations: 53
5. KYSEĽOVÁ, Zuzana - ŠTEFEK, Milan - BAUER, Viktor. Pharmacological prevention of diabetic cataract. In *Journal of diabetes and its complications*. - New York : Elsevier, 2004, vol. 18, p. 129 -140. (2.345 - IF2003). ISSN 1056-8727. Citations: 52
6. ŠOLTÉS, Ladislav - MENDICHI, Raniero - KOGAN, Grigorij - SCHILLER, Jürgen - STANKOVSKÁ, Monika - AMHOLD, Jürgen. Degradative action of reactive oxygen species on hyaluronan. In *Biomacromolecules* [seriál], 2006, vol.7, no. 3, p.659-668. (3.618 - IF2005). (2006 - Current Contents). ISSN 1525-7797. Citations: 42
7. BAUEROVÁ, Katarína - BEZEK, Štefan. Role of reactive oxygen and nitrogen species in etiopathogenesis of rheumatoid arthritis. In *General physiology and biophysics : an international journal*, 1999, vol. 18, focus issue, p.15-20. (0.714 - IF1998). (1999 - Current Contents). ISSN 0231-5882. Citations: 41
8. RAČKOVÁ, Lucia - MÁJEKOVÁ, Magdaléna - KOŠŤÁLOVÁ, Daniela - ŠTEFEK, Milan. Antiradical and antioxidant activities of alkaloids isolated from Mahonia aquifolium. Structural aspects. In *Bioorganic & medicinal chemistry*. - Oxford : Pergamon-Elsevier, 2004, vol. 12, no.17, p. 4709 - 4715. (2.185 - IF2003). (2004 - Current Contents). ISSN 0968-0896. Citations: 35
9. BAUER, Viktor - SOTNÍKOVÁ, Ružena. Nitric oxide - the endothelium-derived relaxing factor and its role in endothelial functions. In *General physiology and biophysics*, 2010, vol. 29, no. 4, p. 319-340. (0.741 - IF2009). (2010 - Current Contents). ISSN 0231-5882. Citations: 34
10. RAČKOVÁ, Lucia - OBLOŽINSKÝ, Marek - KOŠŤÁLOVÁ, Daniela - KETTMANN, Viktor - BEZÁKOVÁ, Lýdia. Free radical scavening activity and lipoxygenase inhibition of Mahonia aquifolium extract and isoquinoline alkaloids. In *Journal of Inflammation* [elektronický zdroj]. - London : BioMed Central Ltd, 2007, vol. 4, article number 15, 7 p. Názov z obrazovky. Požaduje sa acrobat reader. Dostupné na internete: <http://www.journal-inflammation.com/, DOI:10.1186/1476-92255-4-15>. Citations: 32

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.	ŠOLTÉS Ladislav	621
2.	ŠTEFEK Milan	453
3.	BRNOLIAKOVÁ Zuzana	321
4.	NAVAROVÁ Jana	260
5.	RAČKOVÁ Lucia	224

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

In contrast to the previous assessment periods, the full time equivalent work capacity (FTE) of PhD students was also involved to the total number of employees with university degrees engaged in research projects in the assessed period 2012-2015. As a result, both the total number and FTE of the research stuff were increased leading to a significant "dilution" of the research outputs in the period 2012-2015. The PhD students are not institutional employees; officially they are students of the universities, with which we cooperate on PhD study. This should be taken into account in the assessment of the research outputs.

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.

International projects

1.
Project title: Virtual Physiological Human, Network of Excellence, 7FP WU
Project number: 223920, FP7-ICT-2007-2
Principal investigator: Mária Ďurišová
Duration of the project: 1.5.2009 / 31.12.2012 (42 months)
Role of the organisation: Partner
Coordinator: Professor Peter Coveney, University College London
Number of cooperating institutions: 41: Australia - 1, Belgium -1, Germany - 6, Denmark - 3, Spain - 5, France - 3, UK - 5, Greece - 3, Croatia - 1, Italy - 6, Holland - 2, Norway - 2, New Zealand - 1, Portugal -1, Sweden - 1
The main achieved results: Physiologically relevant mathematical model was developed for studies of the fate of drugs (antibiotics) in body after oral administration. The method description and its application was presented at teleconferences.
Funding for the organisation:
2012: 4000 €

ĎURIŠOVÁ, Mária. Physiologically based structure of mean residence time. In The Scientific World Journal, 2012, vol. 2012, p. 1-4, article number 610631. Doi: 10.1100/2012/610631. ISSN 1537-744X.

ĎURIŠOVÁ, Mária. A physiological view and structures of mean residence times. In General Physiology and Biophysics, 2014, vol. 33, no.1, p. 75-80. (0.875 - IF2013). (2014 - Current Contents). ISSN 0231-5882.

2.
Project title: Detecting evolutionary hot spots of antibiotic resistances in Europe
Project number: ESSEM COST Action TD0803
Principal investigator: Mária Ďurišová
Duration of the project: 23.9.2009 / 22.9.2013 (48 months)
Role of the organisation: Partner
The main objective of the Action: - was to identify and characterize environmental hot spots for antimicrobial resistance emergence and spreading of antibiotics and antibiotic resistance patterns, aiming at the development of measures to control antibiotic resistance evolution. New strategies to combat bacterial resistance. Method to construct mathematical models of structured transport and efflux mechanisms for the development of new strategies against antibiotic resistance has been developed.
Funding for the organisation:
2013: 4000 €
2012: 3000 €
ĎURIŠOVÁ, Mária. Mathematical models of the pharmacokinetic behavior of Cefamandole in healthy adult volunteers after 10 min intravenous administration of Cefamadole. In International Journal of Drug Development and Research : open access, 2015, vol. 7, no. 4, p. 031-034. ISSN 0975-9344.

3.
Project title: Challenging organic synthesis inspired by nature - from natural products to drug discovery.
Project number: COST Action CM1407
Principal investigator: Ľubica Horáková
Duration of the project: 15.3.2015 / 14.3.2019 (48 months)
Role of the organisation: Partner
Coordinator: Prof. Bruno Botta, Sapienza Universita di Roma, Italy
The main objective of the Action: The general aim of this COST Action is to advance the field and to maintain the high level of expertise in natural product (NP) chemistry within Europe by combining synthetic chemistry, computational chemistry, chemical biology, and pharmacology to find new lead structures of pharmaceutical relevance. Since chemistry plays a key role in addressing the industrial requirements for preclinical candidates in terms of physicochemical properties of NP and their analogues, this Action further aims to promote the translation between fundamental academic research and industrial drug discovery by means of NP chemistry
Funding for the organisation:
2015: 1500 €

4.
Project title: Chemistry of non-enzymatic protein modification – modulation of protein structure and function
Project number: COST Action CM 1001
Principal investigator: Ľubica Horáková
Duration of the project: 1.11.2010 / 31.10.2014 (48 months)
Role of the organisation: Partner
Coordinator: Friedrich Schiller Univeristy Jena - Institute of Nutrition, Department of Nutritional Toxicology, Germany
Number of cooperating organisations: 55: Belgium - 4, Czech Rep. - 2, Germany - 3, Denmark - 4, Spain - 3, Finland - 4, France - 5, UK - 1, Greece - 3, Croatia - 1, Hungary - 1, Switzerland - 2, Israel - 2, Israel - 2, Lithuania - 1, Latvia - 1, Macedonia - 1, Holland -1, Poland -3, Portugal - 3, Romania - 1, Serbia - 2, Slovinia - 2, Sweden - 1, Turkey - 2
The main objective of the Action: - was to enhance research on chemical, non-enzymatic protein modifications, integrating European research on bio chemical aspects of such protein modifications and developing methods for their detection and anal yses that will be further disseminated to the broader scientific and technological community. The IEPhT focused mainly on studies of postranslantional modification of SERCA protein (critically involved in calcium homeostasis maintenance) by oxidative damage and its alleviation by the novel prospective compounds.

Funding for the organisation:
2014: 4000 €
2013: 4000 €
2012: 4000 €

HORÁKOVÁ, Ľubica - ŠTROSOVÁ, Miriam - SPICKETT, Corinne M. - BLAŠKOVIČ, Dušan. Impairment of calcium ATPases by high glucose and potential pharmacological protection. In Free Radical Research : official journal of the Society for Free Radical Research -European Region, 2013, vol. 47, suppl. 1, p. 81-92. (3.279 - IF2012). (2013 - Current Contents). ISSN 1071-5762.

ŽIŽKOVÁ, Petronela - VISKUPIČOVÁ, Jana - BLAŠKOVIČ, Dušan - ŠTROSOVÁ, Miriam - ŽARKOVIČ, Neven - HORÁKOVÁ, Ľubica. Sarcoplasmic reticulum Ca2+-ATPase from rabbit skeletal muscle modified by peroxynitrite. In Journal of Enzyme Inhibition and Medicinal Chemistry, 2013, vol. 29, no. 4, p. 563-70. (1.495 - IF2012). (2013 - Current Contents). ISSN 1475-6366

VISKUPIČOVÁ, Jana - ŠTROSOVÁ, Miriam - ŽIŽKOVÁ, Petronela - MÁJEKOVÁ, Magdaléna - HORÁKOVÁ, Ľubica. Rutin stimulates sarcoplasmic reticulum Ca2+-ATPase activity (SERCA1) and protects SERCA1 from peroxynitrite mediated injury. In Molecular and Cellular Biochemistry : an international journal for chemical biology in health and disease, 2015, vol. 402, iss. 1-2, p. 51-62. (2.393 - IF2014).

5.

Project title: An integrated European platform for pancreas cancer
research: from basic science to clinical and public health interventions for a rare disease
Project number: ESSEM COST Action BM1204
Principal investigator: Magdaléna Májeková
Duration of the project: 16.7.2012 / 13.12.2016 **(53 months)**
Role of the organisation: Partner
Coordinator: Spanish National Cancer Research Centre (CNIO), Melchor Fernandez Almagro 3, 28029 Madrid
Number of cooperating organisations: 9: Belgium - 1, Germany - 1, Greece - 1, Hungary -1, Ireland - 1, Israel - 1, Italy - 1, Lithuania - 1, Holland - 1
The main objective of the Action: - is aimed at the creation of a unique European platform to facilitate the collaboration of a broad range of European and international PDAC multidisciplinary research groups to integrate knowledge and experience in a multidisciplinary way "from cell to society".
The main achieved results: International network of scientists in PDAC research has been created with an approach to European databanks with cell cultures from clinical research. Aldose reductase, sorbitol and fructose have been suggested as biomarkers for overall monitoring of PDAC. Inhibitors of AKR1B10, which is responsible for drug resistance, were obtained by drug design and screening.
Funding for the organisation:
2015: 535 €
2014: 797 €
2013: 2000 €

6.
Project title: An integrated European platform for pancreas cancer research: from basic science to clinical and public interventions for a rare disease
Project number: ESSEM COST Action BM1204
Principal investigator: Mária Ďurišová
Duration of the project: 14.12.2012 / 13.12.2016 (48 months)
Role of the organisation: Partner
Funding for the organisation:
2015: 535 €
2014: 2400 €
2013: 4000 €
The main objective of the Action: is aimed at the creation of a unique European platform to facilitate the collaboration of a broad range of European and international PDAC multidisciplinary

research groups to integrate knowledge and experience in a multidisciplinary way "from cell to society".
The achieved results: Methotrexate (MTX) is a drug used for tratment of cancer, but also of other diseases such as psoriasis. Since MTX and its main metabolite 7OH-MTX exert serious adverse effects in treated patients, the time-dependent changes in metabolic processing of MTX were analysed. The results showed that during treatment of patients with MTX: 1) ratio of 7OH-MTX to MTX metabolite remained unchanged; 2) average time of the process of production of metabolite 7OH-MTX from MTX was increasing approx. by 20%; 3) rate of metabolic production of 7OH-MTX from MTX was decreasing approx. by 50%. These findings can be used either for the set up of individual patient therapy with MTX or prevention of its adverse effects.

7.
Project title: Structure-based drug design for diagnosis and treatment of neurological diseases
Project number: COST Action CM1103
Principal investigator: Magdaléna Májeková
Duration of the project: 28.11.2011 / 27.11.2015 (48 months)
Role of the organisation: Partner
Coordinator: Dr. Rona Ramsay, University of St Andrews, UK
Number of cooperating organisations: 39: Austria 1, Belgium - 1, Czech Rep.- 1, Germany - 2, Spain - 5, UK - 2, Croatia - 3, Ireland - 2, Malta - 4, Poland - 1, Portugal - 2, Serbia - 2, Slovakia - 3, Slovinia - 1, Turkey - 4.
The main objective of the Action: - is structure-based drug design, synthetic chemistry and biological characterisation, which will inform the choice of lead compounds to treat select subsets of brain malfunction. COST collaboration can facilitate the cross-disciplinary interaction for discovery of promiscuous drugs for diagnosis and treatment of complex brain diseases.
The main achieved results: A selection of compounds designed or synthetised at our Institute was tested for amine oxidase and cholinesterase inhibition activities. Several compounds with multi-target properties have been identified and porposed for further testing as potential drugs in a treatment of neurodegenerative diseases. Key interactions of these compounds with enzymes used were identified for further design of potential drugs.
Funding for the organisation:
2015 6616 €
2014 979 €
2013 979 €
2012 663 €

CM1103 Action WG1 and WG2 meeting: "Structure-based drug design for diagnosis and treatment of neurological diseases: Dissecting and modulating complex function in the monoaminergic systems of the brain" : 22 - 24 Apri 2014 Smolenice. Local organizer: Magdaléna Májeková.

ŠTEFEK, Milan - ŠOLTÉSOVÁ PRNOVÁ, Marta - MÁJEKOVÁ, Magdaléna - RECHLIN, Chris - HEINE, Andreas - KLEBE, Gerhard. Identification of novel aldose reductase inhibitors based on carboxymethylated mercaptotriazinoindole scaffold. In Journal of medicinal chemistry, 2015, vol. 58, no. 6, p. 2649-2657. (5.447 - IF2014). (2015 - Current Contents). ISSN 0022-2623.

VISKUPIČOVÁ, Jana - ŠTROSOVÁ, Miriam - ŽIŽKOVÁ, Petronela - MÁJEKOVÁ, Magdaléna - HORÁKOVÁ, Ľubica. Rutin stimulates sarcoplasmic reticulum Ca2+-ATPase activity (SERCA1) and protects SERCA1 from peroxynitrite mediated injury. In Molecular and Cellular Biochemistry : an international journal for chemical biology in health and disease, 2015, vol. 402, iss. 1-2, p. 51-62. (2.393 - IF2014). (2015 - Current Contents). ISSN 0300-8177.

VISKUPIČOVÁ, Jana - MÁJEKOVÁ, Magdaléna - HORÁKOVÁ, Ľubica. Inhibition of the sarco/endoplasmic reticulum Ca2+-ATPase (SERCA1) by rutin derivatives. In Journal of Muscle Research and Cell Motility, 2015, vol. 36, p. 183-194. (2.086 - IF2014). (2015 - Current Contents). ISSN 0142-4319.

8.
Project title: Multitarget paradigm for innovative ligand identification in the drug discovery process
Project number: COST Action CA15135
Principal investigator: Magdaléna Májeková
Duration of the project: 4.12.2015 / 29.10.2019 (47 months)

Role of the organisation: Partner
The main objective of the Action: the aim of this COST Action is to join highly-qualified research teams working in disciplines around the field of medicinal chemistry, into a novel network devoted to the multi-target issue in drug discovery.
The choice of this theme is related to its marked multidisciplinary character. The research competencies of the network span around medicinal chemistry, from synthetic chemistry, natural products and biophysics to theoretical chemistry, molecular modelling and biological screening.
The main achieved results: Project has just started.
Funding for the organisation:
2015: mobility

9.
Project title: Recent advances in histamine receptor H4R research
Project number: COST Action BM0806
Principal investigator: Radomír Nosáľ
Duration of the project: 9.4.2009 / 8.4.2013 (48 months)
Role of the organisation: Partner
Coordinator: University of Athens Med. School Dept. of Pharmacology
Number of cooperating organisations: 25: Austria 1, Brasil - 1, Czech Rep.- 1, Germany -3, Spain - 1, Finland - 1, France - 1, UK - 1, Greece - 2, Hungary - 1, Switzerland - 1, Ireland - 1, Israel - 1, Italy - 2, Lithuania - 1, Holland - 1, New Zealand - 1, Poland - 1, Serbia - 1, Slovinia - 1, Sweden - 1
Funding for the organisation:
2013 1300 €
2012 4000 €
The main objective of the Action: The main objective of this Action is to foster a multidisciplinary approach to H4R research, and to focus on the current state of play pertaining to the basic understanding and the huge therapeutic potential of this important new drug target.
The achieved results:
Effect of antagonist of H4 histamine receptors – JNJ 7777120 on activity of human neutrophils. JNJ 7777120 suppressed oxidative burst in isolated human neutrophils stimulated with diverse stimuli (phorbol-myristate-acetate (PMA), opsonized zymozan (OZ), calcium ionophor (A23187) and formylmethionyl-leucyl-phenylalanine (FMLP)) with the strongest effect in FMLP-stimulated cells. An interaction with NADPH oxidase was proposed to be involved in the mechanism of its action

PEREČKO, Tomáš - DRÁBIKOVÁ, Katarína - NOSÁĽ, Radomír - JANČINOVÁ, Viera. The effects of the H4R antagonist JNJ7777120 on the production of reactive oxygen species by human neutrophils. In Inflammation research, 2013, vol. 62, suppl. 1, s10. (1.964 - IF2012). ISSN 1023-3830.

10.
Bilateral projects:
Project title: Phytochemicals in ameliorating rheumatoid arthritis therapy: from preclinical studies to clinical applications
Project number: CNR-SAV 2013
Principal investigator: Katarína Bauerová
Duration of the project: 1.1.2013 / 31.12.2015 (36 months)
Role of the organisation: Partner
Number of cooperating institutions: 3 - Italy
Funding for the organisation:
2012 -2015 mobility
The achieved results:
In a model of adjuvant arthritis in rats, the effects of oral administration of quercetin was studied. Experimental animals were treated with quercetin in a dose 150mg/kg of body weight daily during 28 days. The results showed that quercetin is able to ameliorate all the parameters of inflammation and oxidative stress (OS). In particular, quercetin downregulated levels of IL-1β, CRP and MPC-1 and restored antioxidant activity of plasma. In addition, quercetin inhibited enzymatic activity of pro-inflammatory 12/15-lipoxygenase (LOX) in lungs and liver and up-regulated expression of heme-

oxygenase-1 (HO-1) in joints and lungs of arthritic rats. Quercetin also suppressed the 2-fold increase of activity of NF-kappaB in lungs, liver and joint after induction of arthritis. In arthritic rats, the 28-days monotherapy with pinosylvin (PIN) in a daily oral dose 50mg/kg beneficially modulated activation of NF-kappaB in liver and lungs, HO-1 expression and LOX activity in lungs, MCP-1 levels in plasma (already on 14th day) and plasmatic levels of isoprostanes and TBARS.

BAUEROVÁ, Katarína - ACQUAVIVA, Alessandra - PONIŠT, Silvester - GARDI, Concetta - VECCHIO, Daniela - DRÁFI, František - AREZZINI, Beatrice - BEZÁKOVÁ, Lýdia - KUNCÍROVÁ, Viera - MIHALOVÁ, Danica - NOSÁĽ, Radomír. Markers of inflammation and oxidative stress studied in adjuvant-induced arthritis in the rat on systemic and local level affected by pinosylvin and methotrexate and their combination. In Autoimmunity, 2015, vol. 48, no. 1, p. 46-56. (2.714 - IF2014). (2015 - Current Contents). ISSN 0891 6934.

BAUEROVÁ, Katarína - KUNCÍROVÁ, Viera - GARDI, Concetta - MIHALOVÁ, Danica - DRÁFI, František - PONIŠT, Silvester - VECCHIO, Daniela - NOSÁĽ, Radomír. Two polyphenolic molecules evaluated as potential innovative therapy of rheumatoid arthritis. In 9th World Congress on Polyphenols Applications : ISANH. - Malta : ISANH, 2015, p. 98. ISBN 978-2-35609-073-7. VEGA 2/0044/15, APVV-0052-10, SASCNR.

GARDI, Concetta - BAUEROVÁ, Katarína - STRINGA, Blerta - KUNCÍROVÁ, Viera - SLOVÁK, Lukáš - PONIŠT, Silvester - DRÁFI, František - BEZÁKOVÁ, Lýdia - TEDESCO, Idolo - ACQUAVIVA, Alessandra - BILOTTO, Stefania - RUSSO, Gian Luigi. Quercetin reduced inflammation and increased antioxidant defense in rat adjuvant arthritis. In Archives of Biochemistry and Biophysics, 2015, vol. 583, p. 150-157. (3.017 - IF2014). (2015 - Current Contents). ISSN 0003-9861.

11.

Project title: The characterization and functional effects of quercetin and its derivative CHNQ, a potent aldo keto reductase inhibitor, in colorectal cancer
Project number: 113S006 SAV-TUBITAK
Principal investigator: Milan Štefek
Duration of the project: 1.1.2013 / 31.12.2015 (36 months)
Role of the organisation: Partner
Number of cooperating institutions: 1 - Turkey
Funding for the organisation:
2014-2015 mobility
The achieved results:
Using CRC cell lines HCT-116 and HT-29, we report that synthetically modified quercetin (Q) CHNQ was three-fold more cytotoxic than Q along with a robust induction of apoptosis. As expected from naphthoquinones such as CHNQ, a strong induction of oxidative stress was observed. This was accompanied by reactive oxygen species (ROS) induced autophagy marked by a dramatic increase in the lipidation of LC3, decreased activation of Akt/PKB, acidic vesicle accumulation and puncta formation in HCT-116 cells treated with CHNQ. Interestingly, an incomplete autophagy was observed in HT-29 cells where CHNQ treatment led to LC3 lipidation, but not the formation of acidic vacuoles. CHNQ-induced cytotoxicity, ROS formation and autophagy were also detected *in vivo* in Saccharomyces cerevisiae strain RDKY3615 (WinstonS288C background). Overall, CHNQ can induce cancer cell death through the induction of oxidative stress, and may be examined further as a potential chemotherapeutic drug.

ENAYAT, Shabnam - CEYHAN, Seyma Muserref - TASKOPARAN, Betul - ŠTEFEK, Milan - BANERJEE, Sreeparna. CHNQ, a novel 2-Chloro-1,4-naphthoquinone derivative of quercetin, induces oxidative stress and autophagy both in vitro and in vivo. In Archives of Biochemistry and Biophysics, 2016, vol. 596, p. 84-98. (2.807 - IF2015). ISSN 0003-9861.

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

2014

- WG meeting of COST Action CM1103 Structure-based drug design for diagnosis and treatment of neurological diseases, 22.04.-24.04.2014, Smolenice, SR, Role of IEPhT: Co-organizer
- 19th Interdisciplinary toxicological conference TOXCON 2014, Medziodborová, 23.09.-27.09.2014, Stará Lesná, Vysoké Tatry, SR, Role of IEPhT: Main organizer

2012

- International Symposium on Drugs an Their Action in Pharmacology and Toxicology, Assembly Hall of Slovak Academy of Sciences, Bratislava 31.5.2012, with participation of prof. Y. Ito, Kyushu University, Japan prof. T.B. Bolton, London University, England prof. P. Holzer, University of Graz, Austria prof. E.S. Vizi, Hungarian Academy of Sciences, Budapest, Hungary, Role of IEPhT: Organizer

- 17th Intedisciplinary toxicological conference and Advanced toxicological course TOXCON 2012. Toxicology at the crossrodad: The High Tatras, Slovakia. Stará Lesná - hotel Academia, 27.08.-31.08.2012, Hotel Academia, Stará Lesná, SR, Role of IEPhT: Organizer

2.3.3. List of edited proceedings from international scientific conferences.

- Action WG1 and WG2 meeting: "Structure-based drug design for diagnosis and treatment of neurological diseases: Dissecting and modulating complex function in the monoaminergic systems of the brain" : 22 - 24 Apri 2014 Smolenice. Local organizer, [editor]: Magdaléna Májeková. Bratislava : IEPT SAS, 2014. Non pag. (CM1103 Action WG1 and WG2 meeting: "Structure-based drug design for diagnosis and treatment of neurological diseases: Dissecting and modulating complex function in the monoaminergic systems of the brain")
- TOXCON 2014. Connecting for safer Europe : 19th Interdisciplinary toxicological conference. Programme & abstracts, Interdisciplinary toxicology. - Bratislava : Slovak Toxicology Society SETOX : Institute of Experimental Pharmacology and Toxicology SAS, 2014, vol. 7, suppl. 1 ISSN 1337-6853.
- Drugs: their action in pharmacology and toxicology. Editors Viktor Bauer, Mojmír Mach, Jana Navarová, Ružena Sotníková. Bratislava: Institute of Experimental Pharmacology and Toxicology SAS, 2012, ISBN 978-80-971042-0-7.
- TOXCON 2012. Toxicology at the crossroad: 17th Intedisciplinary toxicological conference and Advanced toxicological course. The High Tatras, Slovakia. Stará Lesná - hotel Academia, August 27-31, 2012. Programme and abstracts, Interdisciplinary toxicology. - Bratislava : Slovak Toxicology Society SETOX : Institute of Experimental Pharmacology and Toxicology SAS, 2012, vol. 5, suppl. 1, ISSN 1337-6853.

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

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

2.3.4.2. SCOPUS

Interdisciplinary Toxicology

The Journal of Institute of Experimental Pharmacology of Slovak Academy of Sciences and Slovak Toxicology Society SETOX

SCImago Journal Rank (SJR) 2015: 0.518

Source Normalized Impact per Paper (SNIP) 2015: 0.897

Impact per Publication (IPP) 2015: 1.520

The Journal publishes Original Papers, Review Articles and Clinical Reports on research relating to the toxicity of chemicals and their mixtures at molecular, cellular, tissue, target organ and whole body level in vivo (by all routes of exposure) and in vitro/ex vivo. Focus is on all aspects of modern toxicology: studies of pharmacotoxicological and metabolic mechanisms, toxicogenomics and proteomics, pharmacokinetics, cytotoxicity, immunotoxicity, organ toxicity, developmental toxicity, carcinogenesis, mutagenesis, environmental toxicity and environmental health concerning humans (including epidemiological studies), predictive toxicology, risk assessment, environmental chemistry of pesticides and dioxins, forensic toxicology and alternative toxicity testing.

2.3.4.3. other databases

2.3.4.4. not included in databases

- ## National position of the institute

2.3.5. List of selected projects of national importance

Project title: Molecular principles of regulation of phagocyte activity and apoptosis. Contribution to new pharmacological strategy for modulation of inflammatory processes
Duration of the project: 1.5.2011 / 31.10.2014 (52 months)
Project number: APVV-0052-10

Project title Research on technology of colloidal dispersion systems with multifunctional effect to the implementation in medical cosmetics
Duration of the project: 1.5.2011 / 31.10.2014 (52 months)
Project number: APVV-0351-10

Project title: Protective effects of natural and synthetic substances against oxidative damage of high-molar-mass hyaluronan, isolated mammal cells and their mitochondria.
Duration of the project: 1.1.2015 / 31.12.2018 (48 months)
Project number: VEGA 2/0065/15

Project title: Gender differences in etiopathogenesis of social stress-related cardiovascular and behavioral disorders in individuals with predisposition to hypertension
Duration of the project: 1.5.2011 / 31.10.2014 (52 months)
Project number: APVV-0523-10

Project title: In silico, in vitro and ex vivo research concerning anti-infective compounds
Duration of the project: 1.1.2011 / 31.12.2012 (24 months)
Project number: APVV SK-RO-0008-10

Project title: Aldo-keto reductases in chronic diseases – in silico modeling of significant enzymes and their complexes with indole derivatives
Duration of the project: 1.1.2014 / 31.12.2017 (48 months)
Project number: VEGA 2/0033/14

Project title: Study of combination of immunosuppressive treatment and substances affecting redox balance of organism on animal models of rheumatoid arthritis
Duration of the project: 1.1.2011 / 31.12.2014 (48 months)
Project number: VEGA 2/0045/11

Project title: Indole-1-acetic acid derivatives as aldose reductase inhibitors: design, synthesis and biological activity
Duration of the project: 1.1.2015 / 31.12.2017 (36 months)
Project number: VEGA 2/0041/15

Project title: Risk factors of cardiovascular and cerebrovascular diseases and pharmacological possibilities of their influence
Duration of the project: 1.1.2015 / 31.12.2018 (48 months)
Project number: VEGA 2/0054/15

Project title Modulation of calcium pumps on the level of sarcoplasmic reticulum (SR), erythrocytes (RBCs) and pancreatic β-cells in relation to diabetes.
Duration of the project: 1.1.2011 / 31.12.2014 (48 months)
Project number: VEGA 2/0038/11

Project title: Prenatal programming of psychiatric diseases: experimental approaches for evaluation of causes and mechanisms of their origin
Duration of the project: 1.1.2012 / 31.12.2015 (48 months)
Project number: VEGA 2/0149/12

Project title: Brain Aging and Neuroprotective Antioxidants: Influence of Glia as Therapeutic Strategy?
Duration of the project: 1.1.2012 / 31.12.2015 (48 months)
Project number: VEGA 2/0031/12

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

Project title: Molecular principles of regulation of phagocyte activity and apoptosis. Contribution to new pharmacological strategy for modulation of inflammatory processes
Principal investigator: Radomír Nosáľ
Duration of the project: 1.5.2011 / 31.10.2014 (52 months)
Project number: APVV-0052-10
Role of the organisation: Coordinator
Number of cooperating institutions: 2 (Czech Republic)
Funding for the organisation:

2014 25425 €
2013 50850 €
2012 50850 €

Project title: Research of the technology of preparing disperse coloide systems with multifunctional effect and using in medicinal cosmetics
Principal investigator: Ladislav Šoltés
Duration of the project: 1.5.2011 / 31.10.2014 (52 months)
Project number: APVV-0351-10
Role of the organisation: Partner
Coordinator: VIPO, Partizánske
Number of cooperating institutions: 1
Funding for the organisation:

2014 4026 €
2013 3028 €
2012 2931 €

Project title: Gender differences in etiopathogenesis of social stress-related cardiovascular and behavioral disorders in individuals with predisposition to hypertension
Principal investigator: Ružena Sotníková
Duration of the project: 1.5.2011 / 31.10.2014 (52 months)
Project number: APVV-0523-10
Role of the organisation: Partner
Funding for the organisation:
2014 3000 €
2013 4242 €
2012 3636 €

Project title: In silico, in vitro and ex vivo research concerning anti-infective compounds
Principal investigator: Magdaléna Májeková
Duration of the project: 1.1.2011 / 31.12.2012 (24 months)
Project number: SK-RO-0008-10
Role of the organisation: Partner
Number of cooperating institutions: 4 - Romania
Funding for the organisation:
2012 252 €

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

Project title: Intervention of inflammation, chronic autoimmune reaction and redox regulation in experimental arthritis using new substances for adjuvant therapy of rheumatoid arthritis
Principal investigator: Katarína Bauerová
Duration of the project: 1.1.2015 / 31.12.2018 **(**48 months)
Project number: VEGA 2/0044/15
Role of the organisation: Coordinator
Funding for the organisation:
2015 12477 €

Project title: Yeasts in protection of endothelial intercellular connections against inflammation-induced injury
Principal investigator: Ružena Sotníková
Duration of the project: 1.1.2013 / 31.12.2015 (36 months)
Project number: VEGA 2/0065/13
Role of the organisation: Partner
Funding for the organisation:
2015 0 €
2014 0 €
2013 0 €

Project title: Gender differences in etiopathogenesis of social stress-related cardiovascular and behavioral disorders in individuals with predisposition to hypertension **Principal investigator:** Ružena Sotníková
Duration of the project: 1.1.2010 / 31.12.2013 (48 months)
Project number: VEGA 2/0084/10
Role of the organisation: Partner
Funding for the organisation:
2013 0 €
2012 0 €

Project title: Pharmacological regulation of phagocyte activity and apoptosis: studies on cellular and molecular levels
Principal investigator: Katarína Drábiková
Duration of the project: 1.1.2013 / 31.12.2016 (48 months)

Project number: VEGA 2/0010/13
Role of the organisation: Coordinator
Funding for the organisation:
2015 6632 €
2014 8744 €
2013 7104 €

Project title: Developmental neurotoxicity of venlafaxine: experimental study of neurobehavioral development and neuroendocrine regulations
Principal investigator: Michal Dubovický
Duration of the project: 1.1.2011 / 31.10.2014 (48 months)
Project number: VEGA 2/0084/11
Role of the organisation: Coordinator
Funding for the organisation:
2014 5045 €
2013 4673 €
2012 4057 €

Project title: Cerebral energy metabolism failure as one of patho-biochemical mechanisms involved in hypoxic-ischemic insult of the neonatal brain
Principal investigator: Ivo Juránek
Duration of the project: 1.1.2012 / 31.12.2015 (48 months)
Project number: VEGA 2/0149/12
Role of the organisation: Coordinator
Funding for the organisation:
2015 5005 €
2014 8382 €
2013 7458 €
2012 4907 €

Project title: Substituted pyridoindoles as potential multi-target-directed ligands in prevention and treatment of chronic diseases - theoretical
Principal investigator: Magdaléna Májeková
Duration of the project: 1.1.2011 / 31.12.2013 (36 months)
Project number: VEGA 2/0030/11
Role of the organisation: Coordinator
Funding for the organisation:
2013 2831 €
2012 2504 €

Project title: Molecular modeling, synthesis and biological activity of substituted pyridoindoles as bifunctional agents in prevention of diabetic complications
Principal investigator: Milan Štefek
Duration of the project: 1.1.2011 / 31.12.2014 (48 months)
Project number: VEGA 2/0067/11
Role of the organisation: Coordinator
Funding for the organisation:
2014 9082 €
2013 9015 €
2012 10905 €

Project title: The study of mechanisms and possible early detection of embryofetal damage caused by intrauterine perinatal hypoxia
Principal investigator: Eduard Ujházy
Duration of the project: 1.1.2011 / 31.10.2014 (48 months)
Project number: VEGA 2/0081/11
Role of the organisation: Coordinator

Funding for the organisation:
2014 10307 €
2013 9860 €
2012 8630 €

Project title: Study of Actions of the Reactive Oxygen/Nitrogen Species on High-Molar-Mass Hyaluronan, Synoviocytes, and Chondrocytes
Principal investigator: Ladislav Šoltés
Duration of the project: 1.1.2011 / 31.12.2014 (48 months)
Project number: VEGA 2/0011/11
Role of the organisation: Coordinator
Funding for the organisation:
2014 8072 €
2013 8012 €
2012 7350 €

2.3.8. Projects of SAS Centres of Excellence

2.3.9. National projects supported by EU Structural Funds

Project title: Centre of excellence for glycomics
Duration of the project: 01/2010 – 12/2014 (48 months)
Project number: ITMS 26240120031
Role of the organisation: Partner
Funding for the organisation: 140 620 €

Project title: Evaluation of natural substances and their selection for prevention and treatment of lifestyle diseases.
Duration of the project: 06/2010 – 05/2013 (48 months)
Project number: ITMS 26240220040
Role of the organisation: Partner
Funding for the organisation: 341 200 €

Project title: Transfer of knowledge and technologies from research and development in toxicology on evaluation of environmental and health risk.
Duration of the project: 01/2010 - 06/2012 (30 months)
Project number: ITMS 26240220005
Role of the organisation: Coordinator
Funding for the organisation: 472 400 €

Project title: University Science Park for Biomedicine
Duration of the project: 08/2013-07/2015 (36 months)
Project number: ITMS 26240220087
Role of the organisation: Partner
Funding for the organisation: 13 050€

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

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

2015

ŠTEFEK, Milan: Cemtirestat a potent aldo-keto reductase inhibitor. Joint Scientific Workshop SAS – TÜBITAK MAM Gebze, 14.-15. 4. 2015

MÁJEKOVÁ, Magdaléna - ŠTEFEK, Milan - ŠOLTÉSOVÁ PRNOVÁ, Marta - BALLEKOVÁ, Jana - RECHLIN, Chris - HEINE, Andreas - KLEBE, Gerhard. Protein-inhibitor interactions in aldo-ketoreductase family. In SSB 2015. 9th International Conference Structure and Stability of Biomacromolecules: book of contributions. Editors: Jaroslav Bágeľová, Diana Fedunová, ZuzanaGažová, Katarína Šipošová. - Košice : Institute of Experimental Physics, Slovak Academy of Sciences, 2015, p. 31-32. ISBN 978-80-89656-08-0.

2014

MACH, Mojmír. Experimental Approaches to Study Origins of Mental Diseases-the Role of Hypoxia during Sensitive Stages of Development. 11th Serbian Congress of Toxicology, Sremski Karlovci, Hotel Dunav, June, 24th -27th 2014

2013

HORÁKOVÁ, Ľubica - LOMENOVÁ, Jana - ŽIŽKOVÁ, Petronela - KLUSOVÁ, Veronika - BLAŠKOVIČ, Dušan. Calcium pumps as a possible therapeutic tool for treatment of oxidative stress related diseases. In First International conference on oncology and anticancer research". "Fourth International conference on recent advances in health and medical sciences". "Twenty second International conference on chelation". - Paphos : Postgraduate Research Institute, 2013, p. 43.

MÁJEKOVÁ, Magdaléna - ŠTEFEK, Milan - ŠOLTÉSOVÁ PRNOVÁ, Marta - MILÁČKOVÁ, Ivana - BALLEKOVÁ, Jana - GÁSPÁROVÁ, Zdenka - JANEGA, Pavol - MÁJEK, Pavol. Bioactivity parameters of indole-type compounds and their relevance to treatment of neurological diseases. Interdisciplinary chemical approaches for neuropathology CM1103, 22.-24.10.2013, Valletta, Malta.

2012

ŠTEFEK, Milan.: “Flavonoids as potential multifactorial anticataract agents” 3rd EuropeannCongress on Preventative Regenerative and Anti-Aging Medicine (ECOPRAM-2012) Istanbul, 28. máj - 1. jún 2012.

JANČINOVÁ, Viera - DRÁBIKOVÁ, Katarína - PEREČKO, Tomáš - NOSÁĽ, Radomír - SVITEKOVÁ, Klára. Farmakologická inhibícia prozápalovej aktivity neutrofilov. In 62. Farmakologické dni : program a zborník abstraktov. Košice, 25. - 27. júna 2012. - Košice : Equilibra, 2012, s. 44. ISBN 978-80-8143-020-6.

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

International interdisciplinary toxicoloigy conferences TOXCON 2012 and TOXCON 2014

Mojmir Mach

Michal Dubovicky

Eduard Ujhazy

Jana Navarova

Ruzena Sotnikova

Tatiana Macickova

Eszter Csaszar

WG meeting of COST Action CM1103 Structure-based drug design for diagnosis and treatment of neurological diseases

Magdalena Majekova

Marta Soltesova-Prnova

Jana Ballekova

International Symposium on Drugs an Their Action in Pharmacology and Toxicology

Viktora Bauer

Michal Dubovicky

Mojmir Mach

Eduard Ujhazy

Jana Navarova

Tatiana Macickova

- **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

2015

ŠOLTÉSOVÁ PRNOVÁ, Marta: Nový inhibítor aldózareduktázy s antioxidačnými vlastnosťami v prevencii diabetických komplikácií. Odborný seminár k otvoreniu „Univerzitného vedeckého parku pre biomedicínu Bratislava“ 14.12.2015

MACH, Mojmír: Farmakologická bezpečnosť liečiv a produkcia hyperimúnnych sér pre biotechnologický priemysel, Odborný seminár k otvoreniu „Univerzitného vedeckého parku pre biomedicínu Bratislava“ 14.12.2015

UJHÁZY, Eduard - NAVAROVÁ, Jana - ZEMÁNEK, Marián - DUBOVICKÝ, Michal - MACH, Mojmír. Twenty-year history of the organization of the international interdisciplinary toxicological conference TOXCON. Interdisciplinary Czech-Slovak Toxicology Meeting TOXCON Brno, Czech Republic, May 27 – 29, 2015 - Opening lecture.

2014

MÁJEKOVÁ, Magdaléna - BALLEKOVÁ, Jana - ŠOLTÉSOVÁ PRNOVÁ, Marta - ŠTEFEK, Milan. Aldo-keto reductases and their inhibitors. In Naše proteíny 2014 - Štruktúra a funkcia. 3. konferencia o proteínoch, Bratislava, Apríl 15-16, 2014, p. 26. ISBN 978-80-971617-0-5.

UJHÁZY, Eduard – DUBOVICKÝ , Michal – NAVAROVÁ, Jana – BRUCKNEROVÁ, Ingrid – SEDLÁĆKOVÁ, Natália - MACH, Mojmír. Experimental approaches to evaluation of prenatal developmental toxicity. Trends in Developmental Toxicology and Teratology Vol. 2, December 9-10, 2014, 3rd Faculty of Medicine CU Prague, Czech Republic

DUBOVICKÝ, Michal – MELICHERČÍKOVÁ, Kristína – UJHÁZY, Eduard - MACH, Mojmír – BRUCKNEROVÁ, Ingrid - CZÁSZÁR, Eszter. Consequences/outcomes/implications of untreated and treated maternal depression on development of fetus and newborn. Trends in Developmental Toxicology and Teratology Vol. 2, December 9-10, 2014, 3rd Faculty of Medicine CU Prague, Czech Republic

CSÁSZÁR, Eszter – DUBOVICKÝ, Michal – PAWLUSKY, Jodi. The effect of prenatal fluoxetine treatment on hippocampal plasticity of juvenile rat offspring. Trends in Developmental Toxicology and Teratology. Trends in Developmental Toxicology and Teratology Vol. 2, December 9-10, 2014, 3rd Faculty of Medicine CU Prague, Czech Republic

MACH, Mojmír – DUBOVICKÝ, Michal – BRUCKNEROVÁ, Ingrid – UJHÁZY, Eduard. Factors influencing prenatal programming of health. Trends in Developmental Toxicology and Teratology Vol. 2, December 9-10, 2014, 3rd Faculty of Medicine CU Prague, Czech Republic

2013

BAUER, Viktor. Voľné kyslíkové radikály, ich patológia a farmakológia. Sviatok maďarskej vedy, 18.11.2013, Komárno

DUBOVICKÝ, Michal. Zmeny funkčného vývinu mozgu a správania v dôsledku pôsobenia prenatálnych a skorých postnatálnych vplyvov. 40. etologická konferencia ČSEtS. 13. - 16. 11. 2013, Košice

2012

NOSÁĽ, Radomír - BAUEROVÁ, Katarína - DRÁBIKOVÁ, Katarína - HARMATHA, Juraj - JANČINOVÁ, Viera - PEREČKO, Tomáš - PONIŠT, Silvester. Účinok prírodných polyfenolov na aktiváciu neutrofilov na modeli adjuvantnej artritídy. Liečivá a ich účinky vo farmakológii a toxikológii, Bratislava, 31.5.2012

PEREČKO, Tomáš - DRÁBIKOVÁ, Katarína - NOSÁĽ, Radomír - HARMATHA, Juraj - JANČINOVÁ, Viera. Účinok derivátov stilbénu na viabilitu ľudských neutrofilov. Liečivá a ich účinky vo farmakológii a toxikológii, Bratislava, 31.5.2012

GÁSPÁROVÁ, Zdenka - JANEGA, Pavol - STARÁ, Veronika - UJHÁZY, Eduard. Neurodegeneration induced by trimethyltin in male Wistar rat hippocampus: electrophysiological and morphological aspects. In 62. Farmakologické dni : program a zborník abstraktov. Košice, 25. - 27. júna 2012. - Košice : Equilibra, 2012, s. 38. ISBN 978-80-8143-020-6.

SOTNÍKOVÁ, Ružena - OKRUHLICOVÁ, Ľudmila - PIVÁČKOVÁ, L. - FIALOVÁ, Silvia - NAVAROVÁ, Jana - VLKOVIČOVÁ, Jana - KŘENEK, Peter. Rosmarinic acid prevents vessels from dysfunction induced by experimental diabetes in rats. In: „Programme and Abstracts of the 62nd Pharmacological Days“ Košice, June 25 - 27, 2012- Košice : Equilibra, 2012, s. 90. ISBN 978-80-8143-020-6.

JANČINOVÁ, Viera - DRÁBIKOVÁ, Katarína - PEREČKO, Tomáš - NOSÁĽ, Radomír - SVITEKOVÁ, Klára. Pharmacological inhibition of neutrophil pro-inflammatory activity. In: „Programme and Abstracts of the 62nd Pharmacological Days“ Košice, June 25 - 27, 2012- Košice : Equilibra, 2012, s. 90. ISBN 978-80-8143-020-6.

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

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

International status

Conferences

Dr. Mojmir Mach is a member of Executive Committee of EUROTOX (Federation of European Toxicologists and European Societies of Toxicology).
The Institute in cooperation with EUROTOX and Slovak Toxicology Society SETOX has been organizing annual conference of EUROTOX 2017 in Bratislava, Slovakia
http://www.eurotox2017.com/

Invited presentations

Štefek Milan: Novel Aldose Reductase Inhibitors Based on Carboxymethylated Mercapto-Triazino-Indole Scaffold, Middle East Technical University, Ankara, Turkey, 2015

Katarína Valachová: Self-associating biopolymeric membranes as carriers of remedies and their use. Polymer Materials Research Department, Advanced Technologies and New Materials Research Institute, City of Scientific Research and Technological Applications (SRTA-City), 21934 Alexandria, Egypt, 2015.

Dominika Topoľská: Effect of mitochondria-targted antioxidant on in vitro model of oxidatively damaged fibroblasts. Polymer Materials Research Department, Advanced Technologies and New Materials Research Institute, City of Scientific Research and Technological Applications (SRTA-City), 21934 Alexandria, Egypt, 2015

Viktor Bauer: Comparison of the effects of activated neutrophils with the action of reactive oxygen species on rat thoracic aorta. Research Division for Life Science, Kumamoto Health Science University, Kumamoto, 861-5598, Japan, 2012

National status

Conferences

In cooperation with the Slovak Biology Society at the Slovak Academy of Sciences, the Institute has established tradition of organizing common meetings of Slovak and Czech toxicologists focus on trends in developmental toxicology and teratology:

Trends in Developmental Toxicology and Teratology II, 2014, Prague, Czech Republic

Trends in Developmental Toxicology and Teratology I, 2013, Bratislava, Slovakia

In 2013, in memory of doyen of Czecho-Slovak pharmacology and toxicology, prof. Helena Raskova, the Institute organized conference "Pharmacology and Toxicology in Slovakia: Heritage of prof. MUDr. Helena Raskova, DrSc."

Invited presentation

BEZEK, Štefan - BRNOLIAKOVÁ, Zuzana - SOTNÍKOVÁ, Ružena - KNEZL, Vladimír. Efficacy and safety of the experimental metabolic syndrome monotherapy. SANECA PHARMACEUTICALS a.s., 2013

National cooperation

The Institute is a founding member of a cluster **Omics4Health** together with the Institute of Chemistry SAS, University of Saint Cyril and Methodius in Trnava, and small and medium enterprises (Saneca Pharmaceuticals a.s., HighChem, s.r.o. and Tau-chem, s.r.o.). Consortium is focused on research and inovations in the field of development and preparation of compounds with pharmacotherapeutic potential.
Aims of cluster:
- establishment of consortium and completing infrastructures of the partner organisations for implementation of research and development between academic and commercial sector in accordance with strategy RIS3, with considering also a financial support from the Operation Program Research and Inovations and projects within the calls of Horizon 2020,
- development of biotechnological and chemical procedures with the aim of industrial acquisition of biologically active compounds or their precursors, either for special pharmaceutical application or as components for nutritional supplements, functional food, nutraceuticals or cosmeceuticals,
- education of experts qualified in research disciplines of biomedical and pharmaceutical research,
- support of innovative small and medium enterprises in the field of biomedical research and pharmaceutical industry.

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 – 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, work package leader, investigator),

Start	Project title	Project number	Duration in months	Funding for theOrganisation (EUR)	Role of the Organisation
2012	An integrated European platform for pancreas cancer research: from basic science to clinical and public interventions for a rare disease	ESSEM COST Action BM1204	48	6 935	Partner
2013	Structure-based drug design for diagnosis and treatment of neurological diseases	COST Action CM1103	24	7 595	Partner
2014					
2015	Challenging organic synthesis inspired by nature - from natural products to drug discovery	COST Action CM1407	48	1 500	Partner
	Multitarged paradigm for innovative ligand identification in the drug discovery process	COST Action CA15135	47	Mobilty costs	Partner

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

Bilateral projects:
Project title: Phytochemicals in ameliorating rheumatoid arthritis therapy: from preclinical studies to clinical applications
Project number: CNR-SAV 2013
Principal investigator: Katarína Bauerová
Duration of the project: 1.1.2013 / 31.12.2015 (36 months)
Role of the organisation: Partner
Number of cooperating institutions: 3 - Italy
Funding for the organisation:
2015 mobility
2014 mobility
2013 mobility

Project title: Role of the systemic inflammatory processes in the development of oxidative stress in the brain of arthritic subjects. Evaluation of experimental therapy based on new carnosine preparations
Project number: RAMS-SAV 2013
Principal investigator: Katarína Bauerová
Duration of the project: 1.1.2013 / 31.12.2015 (36 months)
Role of the organisation: Partner
Number of cooperating institutions: 1 - Russia
Funding for the organisation:
2015 mobility
2014 mobility
2013 mobility

Project title: In silico, in vitro and ex vivo research concerning anti-infective
Project number: SK-RO-0008-10
Principal investigator: Magdaléna Májeková
Duration of the project: 1.1.2012 / 31.12.2012 (12 months)
Role of the organisation: Partner
Number of cooperating institutions: 1 - Romania
Funding for the organisation:
2012 mobility

Project title: Regulation of cytokine synthesis during inflammation develoment in brain and other tissues
Project number: RAMS-SAV 2010
Principal investigator: Katarína Bauerová
Duration of the project: 1.1.2010 / 31.12.2012 (36 months)
Role of the organisation: Partner
Number of cooperating institutions: 1 - Russia
Funding for the organisation:
2012 mobility

Project title: The characterization and functional effects of quercetin and its derivative CHNQ, a potent aldo keto reductase inhibitor, in colorectal cancer
Project number: 113S006 SAV-TUBITAK
Principal investigator: Milan Štefek
Duration of the project: 1.1.2013 / 31.12.2015 (36 months)
Role of the organisation: Partner
Number of cooperating institutions: 1 - Turkey
Funding for the organisation:
2015 mobility
2014 mobility
2013 mobility

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

The IEPhT has established several collaborations with national and foreign partners in order to strengthen the research and development area, to exchange the experience and expertise, and to increase its funding attractiveness at both national and international level.

In the period 2012-2015, IEPhT was collaborating without direct funding with the following partners:

National cooperation

1. Assoc. prof. Andrej Bohac, Department of Organic Chemistry, Faculty of Natural Sciences, Comenius University in Bratislava; IEPhT partner: Dr. Majekova, Department of Biochemical Pharmacology; cooperation in design, synthesis, and analysis of new drug candidates.

2. Assoc. prof. Peter Weisman, Medical Faculty, Comenius University in Bratislava; IEPhT partner: Dr. Gasparova, Department of Pharmacology of Excitable Tissues; cooperation in histological analysis of liver tissue and abdominal aorta.

International cooperation

1. Prof. Gerhard Klebe, Department of Pharmaceutical Chemistry, Philipps-University Marburg, Marburg, Germany; IEPhT partner: Dr. Majekova, Department of Biochemical Pharmacology; cooperation in X-ray and computational analysis of inhibitor-protein complexes.

2. Mercedes Unzeta, Departament de Bioquímica i Biologia Molecular, Facultat de Medicina, Institut de Neurociències, Universitat Autònoma de Barcelona, Spain; IEPhT partner: Dr. Majekova, Department of Biochemical Pharmacology; cooperation in enzymatic assays and molecular modeling studies of the interaction between inhibitors and enzymes.

3. Assoc. prof. Eva Kmonickova, Institute of Pharmacology and Toxicology and Biomedical Center, Faculty of Medicine in Pilsen, Charles University in Prague, Pilsen, Czech Republic; IEPhT partner: Dr. Lomenova and Dr. Rezbarikova, Department of Biochemical Pharmacology; cooperation in the study of the effects of thapsigargin and its structural analogue on the induction of NO production and on the activity of Ca-ATPase from sarcoplasmic reticulum.

4. Dr. Tamer Mahmoud Tamer, Polymer Materials Research Department, Advanced Technologies and New Materials Research Institute (ATNMRI), City of Scientific Research and Technological Applications (SRTA-City), Alexandria, Egypt; IEPhT partner: Dr. Soltes, Dr. Valachova, and Ing. Topolska, Laboratory of Bioorganic Chemistry of Drugs; cooperation in preparation of membranes composed of hyaluronan, chitosan and an antioxidant with the aim to enhance healing of skin wounds.

5. Prof. Vladimir Havlicek, Institute of Microbiology of the Czech Academy of Sciences, Prague, Czech Republic; IEPhT partner: Dr. Juranek, MSc. Luptakova, Laboratory of Molecular Pharmacology; cooperation in the study of biomarkers localization in hypoxic-ischemic brain of newborn rats by mass spectrometry imaging.

6. Dr. Juraj Harmatha, Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, Prague, Czech Republic; prof. Jan Smidrkal, Department of Dairy and Fat Technology, University of Chemistry and Technology, Prague, Czech Republic; IEPhT partner: Dr. Jancinova, The Department of Cellular Pharmacology; cooperation in the study of biological effect of natural compounds and their synthesized analogues.

7. Prof. Çimen Karasu, Department of Medical Informatics, Faculty of Medicine, Gazi University, Ankara, Turkey; IEPhT partner: Dr. Rackova, The Laboratory of Cell Cultures; cooperation in evaluation of the natural compounds in the cellular models of pathologies associated with oxidative stress and inflammation.

8. Prof. Jodi Pawluski, University of Renne, France; IEPhT partner: Dr. Michal Dubovicky, Eszter Csaszar, MSc., Laboratory of Developmental and Behavioral Toxicology; cooperation in the field of antidepressant treamtment in pregnancy and lactation, experimental studies on laboratory animals.

- **National projects and their funding**

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

Start	Project title	Project number	Duration in months	Funding for theOrganisation (EUR)	Role of the Organisation
2012					
2013					
2014					
2015					

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	12	12	12	12
Funding in the year (EUR)	89.051	92.769	103.434	93.657

- **Summary of funding from external resources**

2.4.6. List of projects supported by EU Structural Funds

2.4.6. List of projects supported by EU Structural Funds

Project title: Centre of excellence for glycomics
Duration of the project: 01/2010 – 12/2014 (48 months)
Project number: ITMS 26240120031
Role of the organisation: Partner
Funding for the organisation: 140 620 €

Project title: Evaluation of natural substances and their selection for prevention and treatment of lifestyle diseases.
Duration of the project: 06/2010 – 05/2013 (48 months)
Project number: ITMS 26240220040

Role of the organisation: Partner
Funding for the organisation: 341 200,00€

Project title: Transfer of knowledge and technologies from research and development in toxicology on evaluation of environmental and health risk.
Duration of the project: 01/2010 - 06/2012 (30 months)
Project number: ITMS 26240220005
Role of the organisation: Coordinator
Funding for the organisation: 472 400,00€

Project title: University Science Park for Biomedicine
Duration of the project: 08/2013-07/2015 (36 months)
Project number: ITMS 26240220087
Role of the organisation: Partner
Funding for the organisation: 13050€

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

Year	Project title	Project number	Duration in months	Funding for the Organisation (EUR)	Role of the Organisation
2012					
2013	University scientific park for biomedicine Bratislava	ITMS 26240220087	28	13050	Partner
2014					
2015					

External resources	2012	2013	2014	2015	total	average
External resources (milions of EUR)	366.258	111.677	148.320	28.536	**654.791**	**163.698**
External resources transfered to coooperating research organisations (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**

Within the accreditated period, 4 EU SF projects, 10 international projects, and 17 national projects were successfully completed. Their outcomes include:

- generation of new critical knowledge addressing the needs of current society,
- the data applicable in medical and pharmaceutical practice,
- education of a great number of students and young researchers,
- creation of a strong research platform for the present as well as the future national and international cooperation (including the commercial sector).

In 2013, the project ITMS 26240220040 "Evaluation of natural substances and their selection for prevention and treatment of lifestyle diseases" was successfully completed. The implementation of the project, integrating Slovak Academy of Sciences with Slovak Technical University, released a set of natural compounds prospective for their health benefits in prevention and therapy as well as their further investigation. The project also contributed to the establishment of standard approaches in analysing the compounds of interest. The output is represented by more than 20 CC and 30 non-CC publications, more than 70 contributions at the national and international conferences, and 5 patents.
In 2014, IEPhT has become a member of the Centre of Excellence for Glycomics (CEG), allowing the Institute to use the unique equipment of CEG and to develop and conduct the joint research activities within CEG.

The new EU SF integrative project, University Science Park for Biomedicine Bratislava (ITMS 26240220087), is aimed to take the advantage of the existing equipment infrastructure and, especially, the concentration of human research potential of the participating research organisations including IEPhT. Scientific research of the project is focused on 3 main areas: basic research, clinical research and translational/applied research. Their interconnection brings better diagnostics, using molecular-based techniques, and leads to the development of new therapies. The new University Science Park will become the workplace for scientists from the SAS, Comenius University in Bratislava and the University of Economics in Bratislava.

The received funds from mostly national projects (along with the modern equipment purchased from the EU Structural Funds ITMS 26240120031 and ITMS 26240220040 in a previous accreditated period) served for the establishment of the up-to-date methodologies for the assessment of markers of the main pathological processes studied at the Institute, i.e. oxidative stress, inflammation and metabolic dysfunction. Furthermore, national projects also supplied funds to purchase the material necessary for the equipment provided from the EU SF project ITMS 26240220005 "Transfer of knowledge and technologies from research and development in toxicology on evaluation of environmental and health risk." The national projects also helped to develop cooperation within the COST Actions listed above.

The selected national projects converge to the actual research focus of the Institute, which is in line with the up-to-date emerging research priorities (reflected also by Horizon2020 priorities). The prevalence of chronic diseases is alarmingly increasing because of such factors as the increased life expectancy and cumulative effects of unhealthy lifestyles. Therefore, the development of relevant therapeutic and preventive strategies is highly needed. Thus, the projects of the Institute solved in 2012-2015 focused on studies of the main pathological mechanisms in these diseases, namely the oxidative stress and inflammation, and their potential pharmacological modulation. The studies also included the animal models of diabetes (VEGA 2/0041/15), rheumatoid arthritis (VEGA 2/0045/11), and metabolic syndrome with its cardiovascular and cerebrovascular complications (VEGA 2/0054/15, APVV-0523-10). In addition, the developmental origin of the diseases was considered (VEGA 2/0149/12). The inflammatory and oxidative processes and their potential modulation were also studied at the level of cell culture (VEGA 2/0038/11, VEGA 2/0031/12) and cell-free systems (VEGA 2/0065/15). Furthermore, *in silico* modeling studies of interactions of the key enzymes with the drugs of interest were performed (VEGA 2/0033/14, APVV SK-RO-0008-10).

In 2015, the Institute applied for financial support from **APVV agency**. Four project proposals have been successful and will be supported from the second half of 2016:

Institutional projects:

Molecular-pharmacology approaches to innovative therapy of rheumatoid arthrithis evaluated in experimental conditions in vivo and in vitro (Principal investigator: Katarina Bauerova).

Pharmacological intervention in glucose-toxicity in type 2 diabetes (Principal investigator: Magdalena Majekova)

In cooperation:

Prenatal and postnatal effects of ligands of δ and μ opioid receptors on development and function of hippocampus (Institute of Molecular Physiology and Genetics SAS).

Investigation of anatomical-functional differences between the effects of aripiprazole and quetiapine, atypical antipsychotics with similar therapeutic indications, but different impact on brain dopaminergic receptors, in experimental animals (Institute of Experimerntal Endocrinology BMC SAS).

However, the funding from national grant agencies is still unsatisfactory with regard to the current demands on scientific and technological excellence of modern research reflected also by costs of consumable materials. Nevertheless, the research outcomes and existing cooperations of the Institute show a remarkably good quality considering the persisting limitations in financial support.

2.5. PhD studies and educational activities

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

1. **4.1.22 biochemistry**; validity: May 2005 – present; in coordination with Faculty of Chemical and Food Technology, Slovak University of Technology, Bratislava
2. **4.1.22 biochemistry**; validity: May 2005 – present; in coordination with Faculty of Natural Sciences, Comenius University, Bratislava
3. **7.3.2 pharmacology**; validity: April 2006 – present; in coordination with Jessenius Faculty of Medicine, Comenius University, Martin

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 thesis, 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	11.0	2.0	0.0	15.0	1.0	0.0	15.0	3.0	0.0	13.0	2.0	0.0
External	2.0	1.0	0.0	1.0	0.0	0.0	1.0	0.0	1.0	1.0	0.0	0.0
Other supervised by the research employees of the institute	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Foreign students accepted for study visits at IEPhT in the period 2012-2015

Year	Student	Study	IEPhT host	Number of days	Institution
2013	Ondrej Vasicek	PhD	V. Jančinová	11	Faculty of Medicine, Masaryk University, Brno, Czech Republic
2014	Muserref S. Ceyhan	PhD	M. Štefek	14	Department of Biological Sciences, Middle East Technical University, Ankara, Turkey
2014	Tereza Skopova	MSc	V. Jančinová	14	Faculty of Medicine, Masaryk University, Brno, Czech Republic
2014	M.P. Montes Lourido	PhD	Z. Gasparova	90	Faculty of Medicine and Dentistry, University of Santiago de Compostela, Santiago de Compostela, Spain
2015	Katarina Vorcakova	PhD	M. Majekova	30	Department of Analytical Chemistry, University of Pardubice, Faculty of Chemical Technology, Czech Republic
2015	Tamara Chachibaia	PhD	M. Majekova	105	D.Tvildiani Medical University, Tbilisi, Georgia

2.5.3. Summary table on educational activities

Teaching	2012	2013	2014	2015
Lectures (hours/year)[3]	45	38	54	50
Practicum courses (hours/year)[3]	1460	1020	780	1140
Supervised bachelor thesis (in total)	2	0	4	4
Supervised diploma thesis (in total)	17	14	9	10
Supervised PhD thesis (in total)	13	16	16	14
Members in PhD committees (in total)	7	3	3	5
Members in DrSc. committees (in total)	1	1	1	0
Members in university/faculty councils (in total)	0	0	0	0
Members in habilitation/inauguration committees (in total)	1	1	0	0

2.5.4. List of published university textbooks

2.5.5. Number of published academic course books

CORSINI, Emanuela - KANĎÁROVÁ, Helena - SEDLÁK, Ján - PASTOREK, Michal. Advances in toxicology : textbook for advanced toxicology course. Vol. 2. Editor Mojmir Mach. Autors Emanuela Corsini, Helena Kandárová, Ján Sedlák, Michal Pastorek. Bratislava : Slovenská toxikologická spoločnosť SETOX, 2012. 152 p. ISBN 978-80-969474-5-4.

2.5.6. List of joint research laboratories/facilities with universities

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

Education and training of students at all levels belong among the important interests of IEPhT. Besides supervising the diploma and doctoral theses, IEPhT also cooperates closely with several faculties in Slovakia in education.
The Institute is involved in the following educational activities:

Lectures:

- Design of biomolecules, Faculty of Chemical and Food Technology, Slovak University of Technology in Bratislava
- Doping control, Faculty of Physical Education and Sport, Comenius University in Bratislava
- Pharmacokinetic parameters, Faculty of Pharmacy, Comenius University in Bratislava
- Selected chapters from pharmacology, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava
- Selected chapters from psychopharmacology, Ethology in developmental neurotoxicology, Behavioural pharmacology, Basics of experimental teratology, Basics of neurobehavioural toxicology, Faculty of Natural Sciences, Comenius University in Bratislava

Courses and seminars:

- Practical courses from biology, Practical courses from microbiology, Faculty of Chemical and Food Technology, Slovak University of Technology in Bratislava
- Doping control, Faculty of Physical Education and Sport, Comenius University in Bratislava
- Pharmacology, Faculty of Pharmacy, Comenius University in Bratislava
- Seminar in pharmacology, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava
- Basics of experimental teratology, Faculty of Natural Sciences, Comenius University in Bratislava

In addition to teaching activities, IEPhT established a unique annual Miniconference of PhD. Students in 2012. The Conference is organized exclusively by the doctoral students who are in the last year of their doctoral study. Thus, it provides doctoral students the opportunity not only to gain the experience in presenting their results in English in front of a diverse scientific audience, but also to get a hands-on experience with organizing a scientific event. The quality of the conferences has been increasing, as documented by the printed abstract books and several sponsors supporting the Conference in 2015.

Foreign research visits of the IEPhT PhD. students in the period 2012-2015

Year	Student	Number of days	Country
2012	Marta Soltesova	6	Greece
2012	Viera Kuncirova	9	Italy
2012	Ivana Milackova	42	Spain
2013	Katerina Placha	90	Estonia
2013	Viera Kuncirova	10	Italy
2014	Natalia Sedlackova	60	Austria
2014	Romana Koprdova	60	Austria
2014	Katerina Placha	90	Estonia
2014	Romana Koprdova	60	Germany
2014	Jana Ballekova	7	Greece
2014	Petronela Zizkova	7	Greece
2014	Jana Ballekova	28	Spain
2014	Marta Soltesova-Prnova	42	Turkey
2015	Natalia Sedlackova	60	Austria
2015	Dominika Luptakova	30	Czech Republic
2015	Petronela Rezbarikova	90	Czech Republic
2015	Dominika Topolska	10	Egypt
2015	Romana Koprdova	150	Germany
2015	Romana Koprdova	40	Greece
2015	Eszter Csaszar	60	Hungary
2015	Kristina Melichercikova	6	Poland
2015	Jana Ballekova	42	Turkey

2.6. Social impact

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

Patent applications

ŠOLTÉS, Ladislav - TAMER ABD-EL RAZIK, Tamer Mahmoud - VEVERKA, Miroslav - VALACHOVÁ, Katarína - MOHY ELDIN, Mohamed Samir. Self-associating biopolymer membranes as carriers of the remedies with antioxidative properties and their application. Slovak Patent Application PP 5032-2015 (2015) priority date July 10th 2015. Applicant: IEPhT (SK).

ŠOLTES, Ladislav - VALACHOVÁ, Katarína - VEVERKA, Miroslav - TAMER, M. Tamer - MOHY ELDIN, Mohamed Samir. Complexes of chitosan: their production, use and agents with their composition. Owner: IEPhT, Co-owner: Bel/Novaman International, s.r.o., Patent application: PP 86-2013

The inventions relate to mitochondrially targeted antioxidant (MTA) incorporated into two polymers, namely high-molar-mass hyaluronan (HA) and chitosan. Molecules of HA (negatively charged) are components of skin, chitosan is positively charged polymer. By combination of appropriate contents of HA and chitosan, the generation of very compact bio-foils can be achieved with a certain abundance of of negative charge. MTA is released from the polymer carrier by a sustaned delivery mode. The preparation can be used for treatment of chronically inflammed tissue.

ŠTEFEK, Milan - MILÁČKOVÁ, Ivana - DIEZ-DACAL, Beatriz - PÉREZ-SALA, Dolores - ŠOLTÉSOVÁ PRNOVÁ, Marta. Use of 5-carboxymethyl-3-mercapto-1,2,4-triazino-[5,6-B]indoles and their pharmaceutical composition: international publication number WO 2015/057175 A1. International publication date: 23 april 2015 (23.04.2015). Applicant: IEPhT (SK).

The invention relates to the use of 5-carboxymethyl-3- mercapto-1,2,4-triazino-[5,6-b]indoles and their pharmaceutically acceptable salts hydrates and solvates thereof for the use in treatment, control and prevention of human and veterinary diseases in which activities of aldo- keto reductases AKR1B1 and AKR1B10 are key etiological factors for their development and progress such as the development of diabetic complications (macro-, microangiopathy, atherosclerosis, retinopathy, cataracts, nephropathy, neuropathy, bone mass loss and atherosclerosis), inflammatory diseases (uveitis, sepsis, periodontitis, asthma and colorectal cancer), abnormal proliferation of vascular smooth muscle cells in atherosclerosis and restenosis, lung carcinoma in smokers, and several types of cancer, diseases of the female reproductive system (menstrual disorders and fertility problems), timing of parturition, mood disorders, psychiatric and neurological diseases.

ŠTEFEK, Milan - MILÁČKOVÁ, Ivana - DIEZ-DACAL, Beatriz - PÉREZ-SALA, Dolores - ŠOLTÉSOVÁ PRNOVÁ, Marta. Použitie 5-karboxylmetyl-3-merkapto-1,2,4-triazino-[5,6-b]indolov a farmaceutický prostriedok s ich obsahom : PP 97-2013. Application number 97-2013, application date 15.10.2013. International patent classification A61K31/00, version: 13. Name and adress of applicant: IEPhT.

This is the national patent preceding the international one of ŠTEFEK, Milan - MILÁČKOVÁ, Ivana - DIEZ-DACAL, Beatriz - PÉREZ-SALA, Dolores - ŠOLTÉSOVÁ PRNOVÁ, Marta.

ŠTEFEK, Milan - KOVÁČIKOVÁ, Lucia - MILÁČKOVÁ, Ivana - VEVERKA, Miroslav - ŠVAJDLENKA, Emil - VEVERKOVÁ, Eva. Novel quercetin derivatives, their preparation, pharmaceutical compositions containing them and their use. Patent application No. 5006-2012.

The invention relates to novel quercetin derivatives and pharmaceutically acceptable salts, hydrates, and solvates and dimers thereof; a process for the preparation of the novel quercetin

derivatives and pharmaceutically acceptable salts, hydrates, and solvates and dimers thereof; and pharmaceutical compositions comprising the same that are useful for the treatment of various disorders.

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

2013

Experts´ report of the studies:
"Prenatal Developmental Toxicity Study of the substance DUSANTOX L", and "Two-Generation Reproductive Toxicity Study of the substance DUSANTOX L" for the purposes of the Centre for chemical substances and preparations, Ministry of Economy (Mojmir Mach and Eduard Ujhazy).

Dr. Mojmir Mach
Member of the Advisory body of Chief veterinarian, the State veterinary and food administration of the Slovak Republic

Dr. Mojmir Mach
Member of the training of team of the State veterinary and food administration of the Slovak Republic

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

2015

Production of hyperimmune sera in rabbits.
Partner: BioVendor Laboratorní medicina, a.s. Brno, Czech R.
Sum of acquired funds: **43 000 EUR**

Verification of antiadhesive agents' efficacy in rats.
Partner: Contipro Biotech, spol. s. r. o., Dolní Dobrouč, Czech R.
Sum of acquired funds: **3 550 EUR**

Production of laboratory animals and feed diets
Partners: Organisations of SAS, universities and others.
Sum of acquired funds: **54 000 EUR**

2014

Production of hyperimmune sera in rabbits.
Partner: BioVendor Laboratorní medicina, a.s. Brno, Czech R.
Sum of acquired funds: **30 470 €**

Production of hyperimmune eggs in hens.
Partner: Sciotec GmbH, Tulln, Austria
Sum of acquired funds: **15 000 €**

Repeated dose ocular tolerance testing – 28 days in rabbits
Partner: Unipharma s.r.o. Bratislava, SR
Sum of acquired funds: **7 000 €**

Production of laboratory animals and feed diets
Partners: Organisations of SAS, universities and others.
Sum of acquired funds: **56 700 €**

2013

Production of hyperimmune eggs in hens.
Partner: Sciotec GmbH, Tulln, Austria
Sum of acquired funds: **28 546 €**

Production of hyperimmune sera in rabbits.
Partner: BioVendor Laboratorní medicina, a.s. Brno, Czech R.
Sum of acquired funds: **39 935 €**

Production of laboratory animals and feed diets
Partners: Organisations of SAS, universities and others.
Sum of acquired funds: **42 060 €**

Evaluation of skin irritability of fabric conditioner BUPI BABY and BUPI BABY AVIVÁŽ, PALMA a.s. Račianska 76, Bratislava

2012

Production of hyperimmune eggs in hens.
Partner: Sciotec GmbH, Tulln, Austria
Sum of acquired funds: **10 726 €**

Production of hyperimmune sera in rabbits.
Partner: BioVendor Laboratorní medicina, a.s. Brno, Czech R.
Sum of acquired funds: **48 078 €**

Production of laboratory animals and feed diets
Partners: Organisations of SAS, universities and others.
Sum of acquired funds: **23 840 €**

Prenatal developmental toxicity of the compound ATLEN.SK
Partner: Hameln, rds, Modra
Sum of acquired funds: **4 100 €**

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

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

The results of applied research relate to patent applications. In future, these inventions could be used pharmaceutical practice, particularly in the topical treatment of chronic inflammatory leisures (Slovak Patent Application PP 5032-2015), in the therapies, control and prevention of diabetic complications, inflammatory diseases, cancer, diseases of female reproductive system, psychiatric and neurological diseases (WO 2015/057175 A1).
In 2014, the research cluster Omics4Health was established with partners: IEPhT SAS, Institute of Chemistry SAS Bratislava; Ss. Cyril and Methodius University, Trnava; Saneca Pharmaceuticals a.s.; HighChem, s.r.o. and Tau-chem, s.r.o. The aim of cluster is to join universities, SAS institutions and SMEs focused on research and inovations in the field of development and preparation of compounds with pharmacotherapeutic potential.
The applied research activities also involved annual production of hyperimmune sera in rabbits (BioVendor, CZR), production of hyperimmune eggs in hens (Sciotec GmbH, Tulln, Austria|) and

production of laboratory animals and feed diets. The hyperimmune sera from rabbits (BioVendor, CZR) are used for the production of diagnostic kits, which are exploited in clinical practice.
The final reports of the studies “Verification of antiadhesive agents’ efficacy in rats (Contipro Biotech, spol. s. r. o., Dolní Dobrouč, Czech Republic)” and “Repeated dose ocular tolerance testing – 28 days in rabbits (Unipharma s.r.o. Bratislava, SR)” are parts of complete documentations submitted to relevant Authorities for drug registrations.
The results of the IEPhT researchers reported in 2 publications (Rackova et al., J Med Chem 2006; 49:2543–2548 and Rackova et al., Bioorg Med Chem 2005; 13:6477–6484) were used for the elaboration of the prediction equations for the activity of 22 pinoline derivatives (1,2,3,4-tetrahydro-b-carbolines). These results were published by Durand et al., J Enz Inhib Med Chem 2007; 22(5): 556-562.

2.7. Popularisation of Science (outreach activities)

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

1. Eduard Ujházy, Public lecture, How to study the adverse effects of drugs? Toxicology and teratology, European week of science and technology, November 2015
2. Viktor Bauer, TV, Alopatia/homeopatia, Hungarian TV broadcast, June 2015
3. Viktor Bauer, TV, Natural drugs - problem with the China natural medicine, Hungarian TV broadcast, July 2015
4. Magdaléna Májeková**,** Public lecture, The Journey of a New Drug, Researchers' night 2014, Bratislava, September 2014
5. Lucia Račková**,** Press, In vino veritas: Health benefits of red wine and grapes, Bio&Life: bio-eco-nature-Magazine with a content, October 2014
6. Lucia Račková**,** Press, Evening primrose and premenstrual syndrome, Bio&Life: bio-eco-nature-Magazine with a content, August 2014
7. Magdaléna Májeková, Press, The Journey of a New Drug, Science.sk, Slovak Science Popularization Portal, Ed. Frédérique Hazéová, 26. 09. 2014; http://science.dennikn.sk/clanky-a-rozhovory/ziva-priroda-a-chemicke-vedy/lekarstvo/5103-cesta-noveho-lieku
8. Michal Dubovický, TV, Toxicity of formaldehyde, TV Markíza, TV News, March 2013
9. Silvester Poništ, Public lecture, Novel prospectives of combined therapy of rheumatoid arthritis, 11th Days of Young Pharmacists of Slovakia, June 2013
10. Viktor Bauer, Broadcasting, Drugs, their use, adverse effects and the ways of abuse, Radio Patria, March 2013
11. Viktor Bauer, Broadcasting, Prospectives of Science, Hungarian TV broadcast, February 2012
12. ViktorBauer, Broadcasting, Scientist and his life career, Radio Patria, December 2012
13. ViktorBauer, Broadcasting, Scientist pharmacologist, Radio Regina, September 2012
14. MichalDubovický, TV, Toxicity of spreading salt, Interview for TV JOJ, March 2012
15. Magdaléna Májeková, Public lecture, Modeling of drugs and chemical structures, European week of science and technology, November 2012
16. Lucia Račková, Book, Phytotherapy in current medicine, Bookstore Martinus (Ed. Osveta Martin), November 2012
17. Ružena Sotníková, Broadcasting, Briefing, Radio Regina, December 2012

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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 Organization	3	0	8	0	11
Appearances in telecommunication media popularising results of science, in particular those achieved by the Organization	9	1	1	2	13
Public popularisation lectures	6	4	8	4	22

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

Besides the most important popularisation activities listed in 2.7.1., the IEPhT employees also actively participate in a wide variety of other popularization events during the period 2012-2015. More specifically, they regularly participated in educational or specialized TV and radio discussions. Several public lectures were also organized by IEPhT during the period 2012-2015, such as “What is teratology”, or “The structure and function of the autonomic nervous system” in 2012 and 2014, respectively.
Further, several IEPhT researchers have been members of committees and reviewers of different student scientific events, particularly the Biology Olympiads for students 2012-2015 and TUDOK competition of young students 2013 and 2015.
Each year during the period 2012-2015, several IEPhT researchers participated at the preparation and realization of the scientific festival “European Week of Science and Technology” in the form of specialized popularization lectures and open door days with a significant number of attendees, mainly coming from secondary schools.
Finally, IEPhT also focuses on popularization activities to motivate young talented students from primary and secondary schools to study medicine and science. In this respect, public lectures held by IEPhT established researchers were realized in the year 2012 and 2014 dealing with the topics “What is pharmacology?” and “Mental health from the view of a biologist.”, respectively. In 2012, IEPhT was also involved in a “Career day” organized at a primary school in Bratislava.

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	56.0	58.0	56.0	55.0
Research employees from Tab. Research staff	28.0	31.0	33.0	32.0
FTE from Tab. Research staff	27.300	28.800	29.000	26.200
Average age of research employees with university degree	51.9	50.7	50.5	49.9

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. [5]							1		1
II.a / Assoc. prof. [6]	2	1	1	2			2	1	3
Other researchers PhD./CSc.	1	2						1	
doc. / Assoc. prof.									

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. [5]						1			2
II.a / Assoc. prof. [6]		1	2	1	1	2			2
Other researchers PhD./CSc.		1							
doc. / Assoc. prof.									1

2.8.2. Postdoctoral and mobility scheme

2.8.2.1. Postdoctoral positions supported by national and international resources

2.8.2.2. Postdoctoral positions supported external funding

2.8.2.3. SAS stipends and SASPRO stipends

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

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

The infrastructure of the Institute was obtained mostly thanks to 3 projects supported by Structural Funds of EU. It is intensively used not only by IEPhT, but also by other institutes of SAS and universities.

Laboratory of Cell Culture. The research staff of the laboratory has the appropriate qualification and expertise in a range of techniques for the study of pathological processes in cells associated with oxidative stress, inflammation and ageing. The Laboratory utilises a spectrum of standard cellular and molecular biology methods such as fluorescence-based methods for assessment of oxidative stress and cytotoxicity assisted by the fluorescence microscopy and flow cytometry, colorimetric cytotoxicity tests, ELISA and western blot analysis. The laboratory disposes modern standard equipment necessary for the work with cell cultures. Supplementary equipment, such as spectrophotometer TECAN and system for electrophoresis and western blot, serve for the biochemical processing of cultured cells. Based on cooperation with Institute of Chemistry SAS within the Centre of Excellence for Glycomics ITMS 26240120031 and other projects the Laboratory can utilise also Droplet Digital PCR (BioRad) and flow cytometer Beckman Coulter FC500.

Department of Pharmacology of Excitable Tissues. The research staff of the department has the appropriate qualification and expertise in a range of techniques for the study of pathological processes in the heart, brain and vessels associated with metabolic syndrome, oxidative stress, degeneration and ageing. The department utilises a spectrum of specified methods to determine function deficits of organs and tissues, such as perfusion of isolated heart under Langendorff method, measurement of smooth muscle tension of vessels under isometric conditions, the non-invasive method of blood pressure measurement, extracellular electrophysiological measurement of electrically evoked potentials in hippocampal slices, as well as a spectrum of standard biochemical laboratory methods for determination of biochemical variables playing role in metabolic syndrome, oxidative stress, aging, etc. The department disposes equipment for this techniques such as the McIllwain tissue chopper, the Grass stimulator, the DigiData 1332A (Molecular Devices), the Tektronix osciloscope, the AxoScope software, cold centrifuge, plate reader etc. Based on cooperation with Medical Faculty of Comenius University, there is possibility to analyse morphological changes in stained tissue preparates from brain/hippocampus, liver, abdominal aorta, heart etc. Based on the cooperation with Pharmaceutical Faculty CU, there is possibility to determine changes in expression of pro-inflammatory markers in tissue due to RT PCR method and Western blot analysis. Based on cooperation with Faculty of Chemical and Food Technology, Slovak University of Technology we can determine proton nuclear magnetic resonance (1H-NMR) spectra of brain metabolites measured on the 600 MHz Varian VNMRS spectrometer in nano-probe of hippocampal extracts *in vitro*. Further, based on the co-operation with the above mentioned faculty there is possibility to determine volume changes of hippocampus, ventricle and whole brain connected with trimethyltin-induced neurodegeneration measured by non-invasive method of magnetic resonance imaging (MRI) as well as determine proton magnetic resonance spectra (MRS) from dorsal hippocampus *in vivo.*

Laboratory of Bioorganic Chemistry of Drugs. The research staff is focused on studying oxidative degradation of a high-molar-mass hyaluronan induced by cupric ions and ascorbate. We assess protective effects of various drugs and antioxidants to prevent hyaluronan degradation. As a method we use rotational viscometry, which allows monitoring time-dependent changes in dynamic viscosity of hyaluronan solutions. Radical scavenging capacity of examined antioxidants/drugs is assessed by ABTS assay, DPPH assay, site- and non-site specific hydroxyl radical-mediated 2-deoxy-d-ribose degradation. The laboratory is equipped with two rotational viscometers LVDV Brookfield Pro-II and spectrophotometer UV-Vis 1800.

Department of Biochemical Pharmacology. The research of our department focuses on the etiology and possible prevention of diabetic complications as well as on the maintenance of calcium homeostasis from the point of view of sarcoplasmic reticulum Ca^{2+}-ATPase function (SERCA). Our staff has the appropriate qualification and expertise in a range of techniques for the

study of interactions of drugs/xenobiotics with proteins. The department utilizes a spectrum of standard enzymology methods at the level of isolated enzymes. The complex questions of biological activity/bioavailability and toxicity of drugs under study are solved by applying standard pharmacological approaches both at cellular and isolated organ levels as well as in intact animals. *In silico* methods comprise the molecular modeling from the quantum-chemical DFT level through docking to full optimization of protein-ligand complexes by means of molecular dynamics and simulated annealing. These methods are used for interpreting of experimental results and drug design, together with ADMET prediction and advanced QSAR techniques. *Equipment used with methods:* 3 HP PCs with the remote access to the HPC Aurel at the Computing Centre of SAS. Available software: Spartan08 (quantum-chemical and conformational calculations), Yasara (docking and ligand-complex optimization, molecular dynamics), Dragon (molecular descriptors, activity prediction), Pymol (visualization), Statistica (advanced statistical methods), NMAD (large scale molecular dynamics). Spectrophotometer Specord 40 (measurement of aldose reductase activity and inhibition; determination of SERCA activity and its enzyme kinetics); FluoroMax-4 spectrofluorometer (evaluation of conformational changes of SERCA). In the laboratory of cell cultures we utilise a spectrum of fluorescence and colorimetric methods and flow cytometry (Beckman Coulter FC500) for determination of cytotoxicity of pancreatic ß-cells induced by oxidative stress or methylglyoxal. To the standard methods of the laboratory belongs also the electrophoresis, ELISA, western blot used for evaluation of impaired SERCA and pancreatic ß-cells as well as standard antioxidant tests (DPPH, AAPH, DOPC lipid peroxidation). For *in vivo* experiments we used animal rat models of diabetes and colitis.

Department of Cellular Pharmacology. The research team of the department is experienced in pharmacological studies concerning the effects of drugs and biologically active substances on functions of immune and inflammatory cells. Studies are concentrated on human phagocytes (control and from patients with rheumatoid arthritis) and on phagocytes of rats with adjuvant arthritis. Modern molecular-biologic approaches are applied to the identification of cellular and molecular mechanisms participating in the effects studied: chemiluminescence methods (formation of reactive oxygen species in blood, neutrophils and in tissues e.g. joint, spleen, blood vessels), SDS-PAGE, western blotting and immunodetection with phosphospecific antibodies (phosphorylation of PKC isoforms and NADPH oxidase subunits), flow cytometry (oxidative burst, phagocytic activity, apoptosis, calcium mobilisation), ELISA (caspase-3 and PKC activity, concentration of cytokines), fluorescence microscopy (formation of neutrophil extracellular traps). The department possesses its own devices (luminometers, spectrophotometer, equipment for gel electrophoresis and western blotting, lumiaggregometer, laminar box, CO_2 incubator, haematological analyser) and can share the utilisation of another devices needed (flow cytometer, fluorimeter, fluorescent and confocal microscope).

Department of Developmental and Behavioral Toxicology. The broad area of research interest in our department involves studies to elucidate mechanisms of hypoxia during sensitive stages of development and involvement of drug during organogenesis and “fine tuning” of central nervous system. Using a variety of animal models of human diseases in conjunction with biochemical, histology and behavioral methods of analysis, we seek to determine the extent to which these early influences can change the quality of later life. Screening for new prospective psychoactive drugs is also one of the research focuses. The Department utilises a spectrum of standard toxicological and behavioral methods such as screening for developmental anomalies, neurodevelopmental analysis, imunohistochemical-based assessment, anxiety- and depression-like behaviour observations, cognition and social behaviour evaluation. The department disposes modern equipment necessary for teratological and behavioural studies (ActiTrack and ANYmaze systems for recording of animal movement).

Department of Pharmacology of Inflammation. The pharmacological research is focusing on new therapeutic combinations of the classical immunosuppressive treatment (represented by methotrexate - MTX) with immunomodulators and compounds affecting redox homeostasis for treatment of rheumatoid arthritis (RA). In particular, natural substances capable to improve standard therapy of RA by MTX and minimize the administration of biological therapy are studied in the animal model of adjuvant arthritis. Moreover, elucidation of the mechanism of action of these substances in treatment of chronic inflammatory diseases could bring them into the evidence-

based medicine. For this purpose, the studies are focused on the connection between systemic and local oxidative stress and inflammatory processes in the organism. The laboratory is equipped for measurement of markers of oxidative stress (malondialdehyde, 4-hydroxynonenal, protein carbonyls, heme oxygenase-1 and F2-isoprostanes) and inflammation (CRP, TNF-alpha, IL-1beta, MCP-1, IL-17, MMP-9, IL-6, oxidative burst and phagocytosis of neutrophils and monocytes) in plasma and different tissues using ELISA, Western blot, flow cytometry and spectrophotometry methods.

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

The Evaluation Panel of the previous assessment suggested and recommended:

1. *not to add to the number of research topics, but rather to expand existing research projects promoting additional internal and external partnerships,*
2. *to narrow some of the future projects to more specific, hypothesis-driven, well defined scientific questions,*
3. *to continue publishing in high quality journals,*
4. *to improve the effort towards more profuse external funds,*
5. *to increase the number of younger DrSc. investigators,*
6. *to strengthen collaboration with clinical departments anywhere,*
7. *to increase the number of popularization articles and expand the activities to internet based media,*
8. *to improve infrastructure of molecular biology laboratories.*

1. Rather than expanding the research to new research topics, the Institute has concentrated the research interest on investigation of serious chronic diseases related to life style. In particular, the emphasis is put on their main unifying pathological mechanisms of these diseases, namely inflammatory processes, oxidative stress, metabolic disorders and developmental aspects. Individual research teams within the Institute are studying these pathogenic mechanisms more in depth while developing more intensive cooperation under the common projects/grants supported by VEGA and APVV grant agencies. The inter-institutional cooperation and cooperation with universities is highly supported. The cooperating institutions within the current scientific projects include the Institute for Heart Research, the Institute of Normal and Pathological Physiology, the Institute of Molecular Physiology and Genetics, the Institute of Experimental Endocrinology, Commenius University and Slovak Technical University.
2. The individual projects are more specific and better defined. The scientific hypotheses are focused on the individual aspects of the main research interests of the Institute, particularly on potential pharmacological and nutritional interventions that could defeat serious lifestyle diseases. The examples of such projects are as follows:
    - two scientific projects funded by APVV grant agency: “Molecular-pharmacology approaches to innovative therapy of rheumatoid arthrithis evaluated in experimental conditions in vivo and *in vitro*”, and “Pharmacological intervention in glucose-toxicity in type 2 diabetes”
    - the common SAS-TUBITAK JRP (Turkey) 2015/7 project “Targeting Molecular Pathways of Glucolipotoxicity by a Novel Carboxymethylated Mercaptotriazinoindole Inhibitor of Aldo-Keto Reductase AKR1B1 iIn Diabetes, Inflammation and Age-related Neurodegeneration”.
3. We continue in publishing the original results obtained in higher ranking peer-reviewed international scientific journals in the field of pharmacology, biochemistry, toxicology and other related disciplines.

4. We also try to gain the external resources of financing, mostly within the cooperation with private sector (BioVendor, UnimedPharma, toxicity studies).
5. During the assessed period 2012-2015, two middle-aged scientists received the degree Doctor of Science (Drs. Katarina Bauerova and Ivo Juranek).
6. We intensively cooperate within VEGA projects with the Department of Neonatology, Faculty of Medicine, Commenius University in research of consequences of perinatal asphyxia, and with the Centre for Biological Treatment in Rheumatology, 5th Department of Internal Medicine, School of Medicine, Comenius University, University Hospital, Ružinov on activity of blood phagocytes obtained from patients suffering from rheumatoid arthritis. We communicate with clinical departments mostly in the field of exploitation of our original results from the experimental studies of adjuvant arthrithis in reumathological practice.
7. Since we concentrated our effort on conception of the Institute, transformation process, searching for contacts with private sector and revitalization of the department at Dobra Voda, we did not succeed in increasing our popularization activities in the assessed period. We concentrated our popularisation activities mostly to period of Week of Science a Technique. Within this week we organized the Days of Open Doors for students from secondary school in Bratislava. These events involve lectures and excursions of individual laboratories.
8. To improve our molecular biology infrastructure, two new laboratories have been established. The scientific team led by Dr. L. Horakova established up-to-date laboratory of post-translational changes of proteins thanks to financial support from Structural Funds of EU. In 2016, the independent laboratory of molecular pharmacology has been established headed by Dr. I. Juranek. Among others, the laboratory will study the effect of hypoxia/ischemia on both the gene expression of selected calcium channels and the distribution of intracellular calcium in neuronal cells and brain slices of rat pups. In close cooperation with the Chemical Institute of SAS within the Centre of Excellence for Glycomics (a project funded by Structural Funds of EU), we have built up a common workplace equipped with modern molecular biology techniques (PCR, mass spectroscopy, ^{1}H NMR, next generaton sequencing and others). Several groups of the Institute have strengthened their focus on studies of the cell signalling pathways with the application of up-to-date cell and molecular biology methods.

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

The long-term strategy of the Institute is to delegate the young and middle-age researchers to the management positions. In this regard, 2 researchers (Dr.Valachová and Dr. Račková) of age <40 became the head of laboratories/research groups. In 2012 and in 2016, two young scientists (Dr. Poništ and Dr. Lomenová, respectively) became the members of the Scientific Comittee. The full time position of scientists in pensionary age has been gradually decreasing what enables to save finances and accept young scientists after PhD study.

The funds from SF EU projects (ITMS 26240220005, 26240220040, 26240120031) and national projects realized in the period 2012-2015 helped to establish the up-to-date methodologies in the laboratories (Laboratory of Cell Cultures, Laboratory of Biochemistry and Cell Biology) such as fluorescence-based flow cytometry methods for assessment of oxidative stress, cytotoxicity and surface protein expression, as well as western blot-based analyses, ELISA and immunocytochemistry of the protein expression in cellular systems. These techniques are routinely used also by other departments for the purpose of assessment of inflammatory profile of human blood cells and tissues from the animal inflammatory models (Department of Pharmacology of Inflammation, Department of Cellular Pharmacology). The establishment of studies of the expression of target genes by using the digital PCR technique has been in progress since 2015 (Department of Pharmacology of Inflammation, Laboratory of Cell Cultures, Laboratory of Biochemistry and Cell Biology). Several departments/laboratories strengthened their focus on studies of modulation of signalling pathways in cells and tissues. The studied target proteins include predominantly those involved in inflammatory and oxidative stress pathways.

In 2016, independent laboratory of molecular pharmacology has been established. It is headed by Dr. Juranek. The laboratory will study the effect of hypoxia/ischemia on the gene

expression of selected calcium channels together with the monitoring of intracellular levels and distribution of calcium in neuronal cells and brain slices of rat pups subjected to hypoxic-ischaemic brain injury. The studies will be conducted by young researcher, Dr. Hodurova.

Foreign postdoc researchers accepted for research visits at IEPhT in the period 2012-2015

Year	Student	IEPhT host	Period/Number of days	Institution
2012	Alessandra Acquaviva	K. Bauerova	30	Department of Molecular and Developmental Medicine, University of Siena, Siena, Italy
2013/2014	Tamer M. Tamer	L. Soltes	270	Polymer Materials Research Department, Advanced Technologies and New Materials Research Institute, City of Scientific Research and Technological Applications, Alexandria, Egypt
2014	Shabnam Enayat	M. Štefek	40	Department of Biological Sciences, Middle East Technical University, Ankara, Turkey
2014	Ondrej Vasicek	V. Jančinová	27	Faculty of Medicine, Masaryk University, Brno, Czech Republic
2014	Ahmed M. Omer	L. Soltes	90	Polymer Materials Research Department, Advanced Technologies and New Materials Research Institute, City of Scientific Research and Technological Applications, Alexandria, Egypt
2015	Ondrej Vasicek	V. Jančinová	18	Faculty of Medicine, Masaryk University, Brno, Czech Republic
2015	Daniel da Silva	M. Majekova	60	Research Institute for Medicines, Faculty of Pharmacy, University of Lisbon, Portugal
2015	Joy H. Hoskeri	I. Juranek	180	Department of Biotechnology, Oxford College of Science, Bangalore, India
2015	Zuzana Hodurova	I. Juranek	15	Department of Pharmacology, Faculty of Medicine, University of Tartu, Tartu, Estonia

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

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

The Institute focuses its scientific effort on research of **civilization ("life-style") diseases**. The main goal is to study mechanisms involved in the etiology and progression of the pathologies, as well as possibilities to prevent and treat these disorders with the final aim to reveal **novel therapeutic approaches**. In this respect, the main effort is devoted to the study of inflammatory processes, reactive oxygen species (ROS)-mediated pathologies, metabolic disorders as well as developmental aspects of chronic diseases. Moreover, commercial toxicity studies in compliance with Good Laboratory Practice (GLP) can be conducted in cooperation with a private sector.

Inflammatory processes (chronic inflammation)

Decreased activity and enhanced apoptosis of neutrophils as a part of therapy of chronic inflammation. Activated neutrophils release reactive oxygen species (ROS) to the extracellular environment, which is important in the elimination of infection in tissues. However, they are also considered to be the agents causing tissue injury and transition of an acute inflammation into a chronic one. From this point of view, pharmacological intervention aimed to decrease ROS release from neutrophils represents a prospective way of supporting therapy in chronic inflammatory diseases, such as rheumatoid arthritis and allergies. On the other hand, findings from recent years indicate that ROS rising inside the neutrophils on granular membranes have anti-inflammatory effects. Regarding both the pro- as well as the antinflammatory effects of oxidants arising in the neutron, it is important to differentiate extra- and intra-cellular actions of antioxidants. Thus, in pharmacotherapy it is significant to prefer substances which inhibit potentially dangerous extracellular oxidants and at the same time retain regulatory radicals inside the neutrophils (*Bjorkman et al., Arthritis & Rheumatism 58 (10), 2008, 2931-2935*).

Evaluation of pharmacological effects of natural substances in experimental model of arthritis and translation of the results obtained to rheumathological practice. Rheumatoid arthritis (RA) is a chronic autoimmune disease affecting approximately 1% of the worldwide population. Resistance and adverse effects frequently occur during antiarthritic therapy. There is thus an urgent need for the introduction of new substances into medical practice. Based on our own experimental experience as well as that of other authors, we suggest that oxidative stress plays an important role in the pathogenesis of RA (*Bauerova et al., Autoimmunity, 2015, 48(1), 46-56)*. Combinations of classical immunosuppressive therapies with natural immunomodulators or antioxidants have been used very rarely as yet. Elucidation of the relationship between immune mechanisms and redox homeostasis in the organism and search for substances able to control these processes in RA is inevitable. Contemporary treatment is insufficient because there are several serious unfavorable side effects.

Pharmacology of chronic disease (role of ROS)

Acute and chronic injury of the brain. Aging and age-related increase in ROS plays an important role in neurodegenerative diseases. Accumulated ROS injure the cell nucleus, mitochondria, lipids and proteins. An increase of mitochondrial mutations was found in neurodegenarative diseases. Lipid peroxidation is a frequent marker of oxidative stress which increases with age. Moreover, the intensity of protein carbonylation is increased and levels of modified oxidated proteins correlate with the cognitive deficit. Further, degeneration of synaptic endings and death of neurons are characteristic features of neurodegenerative diseases. In Alzheimer disease, the most affected neurons are located in the hippocampus, which is associated with learning and memory processes. Neuroinflammation is a common feature in neurodegenerative diseases and brain ischemia. Local inflammation of so-called "residential cells" (mostly microglia) and infiltration of leukocytes from the peripheral blood are further characteristics of neurodegeneration (*Sugama et al., Inflamm Alergy Drug Target, 2009, 8, 277-284*). Neurodegenarative diseases are commonly treated by non-steroid anti-inflammatory drugs. However, neurodegeneration is a multifactorial process and therefore it significantly affects several pathologies. One of the ways is to inhibit production and remove ROS which are out of control of natural regulatory mechanisms (*Gasparova et al., Neuroendocrinol Lett, 2014, 35(6), 454-462*).

Injury of the brain due to pre- and perinatal hypoxia/ischemia. Reactive metabolites can injure also the developing organism which is not sufficiently protected against oxidative stress. Searching for early markers of oxidative stress due to hypoxia/ischemia of the developing body is therefore very significant. Structural and functional alterations in the developing organism can be studied by using relevant animal models of intrauterine and/or perinatal hypoxia/ischemia (*Ujhazy et al., Food and Chem. Toxicol. 2013, 61, 233-239*). Functional and neuroendocrine changes can occur in later postnatal development in the form of mental and behavioral disorders.

Effects of pharmacologically active substances on injury of the cardiovascular system. Due to aging of the population and marked changes in life style in developed countries, there is a significant increaase in so-called „life-style-related" diseases, which involve also cardiovascular diseases, such as hypertension and atherosclerosis. These diseases frequently present in other diseases, such as diabetes, where the presence of hyperglycemia, hypertension and dyslipidemia increase the risk for further development of cardiovascular diseases. In experimental models of hypertension, excessive production of ROS by cells of vessel endothelium and smooth muscle was found (*Cuzzocrea et al., FASEB, 2004, 18, 94-101*). Epidemiological studies showed that increased supply of natural phenolic antioxidants in food is associated with reduction of cardiovascular diseases and cancer. Therefore, at present, there is increased interest in studying pharmacological effects of polyphenolic substances in cardiovascular and other chronic diseases (*Sotnikova et al., J Pharmacy Pharmacol,, 2013, 65(5),713-723*).

Damage of the cartilage with emphasis on the role of hyaluronic acid. Hyaluronan (HA) is a polysaccharide present in many tissues of vertebrates. One milliliter of synovial fluid (essential constituent of the joint) contains 2-3 mg of HA with molar mass reaching in healthy humans values in megaDaltons. However, in a case of joint inflammation, the mean molar mass of HA is significantly reduced. This decline is accompanied by marked decrease of viscoelasticity of HA, which in turn affects unfavorably the lubrication properties of synovial fluid. Low resistance of HA against oxidants is a very suitable characteristic, which can be used in assessing the degradation activity of oxidants and/or antioxidant properties of various substances (*Valachova et al., Carbohydrate Polymers, 2015, 134, 516-523*).

Molecular design, synthesis and biological activity of substituted pyridoindoles and indole-1- acetic acids as multifunctional agents in prevention of diabetic complications. Diabetics are susceptible to development of chronic health complications, which are responsible for significant increase in their morbidity and mortality. The understanding of mechanisms by which glucose exerts its toxicity is of utmost importance for rational pharmacological interventions to treat diabetic complications (DCs) and β-cell dysfunction. The etiology of DCs is multifactorial – multiple hyperglycemia-dependent mechanisms contribute to their development. Oxidative and glycation stress as well as the polyol pathway are considered to have a key role in the etiology of DCs. An innovative „multi-target" strategy in prevention of DCs is oriented on the rational design of chemical entities able to affect simultaneously multiple key mechanisms. This approach increases the chance of successful therapeutic intervention, decreases the risk of side effects and is economical. Recently designed and synthesized carboxymethylated pyridoindoles at the Institute, structural analogues of stobadine originally developed at the Institute three decades ago, were characterized as bifunctional agents with combined antioxidant and aldose reductase inhibitory (AO/ARI) activities. The design of the novel generations of the carboxymethylated pyridoindoles as well as indole-1-acetic acids is based on computer-aided modeling of the interaction of the "inhibitor-enzyme", with the main stress on maximalization of the inhibitory effect and selectivity along with optimization of the biological availability with preservation of high antioxidant activity (*Soltesova-Prnova et al., Physiol, Res. 2015, 64(4),587-591*).

Modulation of calcium pumps at the level of sarcoplasmatic reticulum, erythrocytes and pancreatic β-cells in diabetes and adjuvant arthritis. Hyperglycemia in diabetes mellitus increases cytosolic Ca2+ and induces oxidative stress in erythrocytes as well as in pancreatic β-cells, resulting in eryptosis and apoptosis, respectively. Calcium regulating Ca-ATPase from sarco/endoplasmic reticulum (SERCA) represents a model protein with known structure for studying the correlation between enzyme function and its conformational modifications. Flavonoids are able to bind to proteins, including SERCA and ion channels, thus changing their function and conformational properties. Directly targeted flavonoid derivatives were synthesized with modulating effects on SERCA activity and may thus represent a pharmacological tool to reduce both eryptosis and β-cell apoptosis. The results of *in silico* structural analysis clarified the interaction of compounds with SERCA and indicated new ways of efficient substitution (*Horakova et al. Free Rad Res - Eur Reg, 2013, 47(l), 81-92*).

Metabolic (and cognitive) syndrome

Risk factors of metabolic syndrome and ways of treatment by using hereditary hypertriglyceridemic rats. Metabolic syndrome (MetS) is applied to the clustering of risk factors as atherogenic dyslipidemia, elevated blood pressure, elevated plasma glucose, a prothrombotic and a proinflammatory state, often accompanying obesity and is associated with increased risk for both atherosclerotic cardiovascular and cerebrovascular diseases and stroke. The prevalence of MetS in the whole population of Slovakia is according to the National Center of Health Information around 30%, reaching in the elderly more than 60%. In the year 2005, the prevalence of MetS was found to be 31 % in the 25-64-year-old population and 38.1 % in the population 18 years and older (*Mokáň et al., Diabetes a obezita 2006, 6, 10–16, in Slovak)*. Therapy of MetS is based on evaluation of global clinical manifestations and risk factors of the patient and based on WHO recommendations, NCEP ATP III for each individual risk factor. Recently, the approved medications for the treatment of MetS concern only the therapy of individual risk factors: antihypertensive agents, antithrombotic agents, lipid-lowering medication for hyperglycemia and weight loss. At present, preference lies on the search for effective compounds that could simultaneously affect all risk factors. However, so far all

efforts to find the active substance affecting a complete metabolic syndrome have failed. This is a challenge for research and and calls for an increase of the efforts in searching for the active substance or combination of substances which would be effective in reducing hypertension, hyperglycemia, dislipidemia, and other risk factors.

Metabolic-inflammatory axis in neurodegeneration associated with aging. A growing body of epidemiological evidence has suggested that the metabolic syndrome (MetS) and Mets components, such as impaired glucose tolerance, hypertension, hypertriglyceridemia, and reduced high-density lipoprotein cholesterol, are important in the development of age-related cognitive decline, mild cognitive impairment, vascular dementia, and Alzheimer's disease.. These suggestions proposed the presence of a "metabolic-cognitive syndrome", i.e. a MetS plus cognitive impairment of degenerative or vascular origin in these patients (*Panza et al., J Alzheimers Dis. 2012, Suppl 2, S31-75*).

Developmental toxicology

Developmental toxicity as a risk factor for development of mental disorders in adulthood („Developmental Origin of Adult Diseases"). The concept of "developmental programming" and Developmental Origins of Adult Diseases has become well accepted because of the compelling animal studies that have precisely defined the outcome of specific exposures (*Kermack et al., J Dev Orig Health Dis, 2015, 6(5), 415-24*). The environmental pollutants and other chemical toxicants may influence crucial cellular functions during critical periods of fetal development and permanently alter the structure or function of specific organ systems. Developmental epigenetics is believed to establish "adaptive" phenotypes to meet the demands of the later-life environment. Resulting phenotypes that match predicted later-life demands will promote health, while a high degree of mismatch will impede adaptability to later-life challenges and elevate disease risk. The rapid introduction of synthetic chemicals, environmental pollutants and medical interventions may result in conflict with the programed adaptive changes made during early development and explain the alarming increases in some diseases (*Bezek et al.,Interdisc Toxicol, 2008, 1(1), 29-31*).

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

There are several important strategy points/plans which are inevitable for the further development of the Institute:

- The Institute of Experimental Pharmacology and Toxicology is in the pre-period for transformation of the Slovak Academy of Sciences into public research institutes. Transformation of the Institute from the budgetary to a new form of economy will facilitate the financial funding from various sources, including the private sector. In the form of a public research center, the Institute will own all its properties, which will provide better conditions for mutual cooperation with small and medium-sized enterprises (SME).

- Our plan is to create a spin off in the cooperation with SME at Dobra Voda (Department of Toxicology and Breeding of Laboratory Animals) where we provide our scientific experience and know-how in toxicity studies and breeding of small laboratory animals (2017-2018).

- Financial support from SME will help us to revitalize the Department of Toxicology and Breeding of Laboratory Animals at Dobra Voda (especially breeding and toxicology units).

- The management of the Institute realizes the need of concentrated research and development with bigger compact scientific centers within the Slovak Academy of Sciences and plans to create together with partner institutes a center for the research of life style diseases. The common scientific centre established mostly from the institutes located in the newly built Pavilion of Medical Sciences at the campus of the Slovak Academy of Sciences at Patronka in Bratislava will have excellent conditions and a great potential for integrative research of life- style related diseases with strong aspiration to create an up-to-date "core facility" and smart flexible "brain trust" at one place (*Memorandum of Understanding, attachment in the chapter 4*).

The research strategy of the Institute is based on the experience of knowledgeable researchers, on scientific infrastructure and on its own "know-how" in the field of basic and applied pharmacology, biochemistry, *in silico* pharmacology, toxicology and related subjects. In basic research, the focus will be on the following scientific issues.

Inflammatory processes (chronic inflammation)

Decreased activity and enhanced apoptosis of neutrophils as part of the therapy of chronic inflammation. Research will be focused on pharmacological effects on the activity and apoptosis of neutrophils, on mechanisms of action of the tested substances and on the activity of neutrophils in inflammation (animal model of adjuvant arthritis in rats, patients with arthritis). Chemilumenescence, ELISA,

flow cytometry, flourescence microscopy, Western blot and gene expression approaches and methods will be exploited in individual experiments.

Evaluation of pharmacological effects of natural substances in experimental model of arthritis and translation of the results obtained to rheumatological practice. The scientific team plans to study effects of natural substances of herbal origin (chemically defined extracts from green tea, pine, red grapes and unique herbs from African flora) as well as animal origin (derivatives of carnosine, substances from honey bee and snake venom). Focus will be also on extra joint manifestations of the disease and other health complications. Animal models will be used in the studies (*Mycobacterium butyricum* injection, or collagen, caragen or capsaicine induced arthritis). Molecular biology approaches will be used, such as ELISA, flow cytometry, to establish production of ROS in monocytes and neutrophils, DNA damage of helper and regulatory T-lymphocytes.

Role of reactive oxygen species in etiology of chronic diseases

Acute and chronic injury of the brain. Research will be concentrated on the study of neuroprotective substances in acute and chronic injury of the CNS. Acute injury will be investigated by means of i*n vitro* induced ischemia of the nervous tissue (hypoxia/hypopglycemia). To model chronic injury of the brain, trimethyltin induced neurodegeneration in rats will be exploited. Studies will be conducted at various levels: functional (electrophysiology), morphological (morphometry, immunohistochemistry), biochemical (markers of oxidative damage, Western blot), behavioral (water maze), spectroscopy and imaging of magnetic resonance.

Injury of the brain due to pre- and perinatal hypoxia/ischemia. Effects of hypoxia/ischemia on neonatal rat brain will be studied using the Rice-Vannucci model combining unilateral carotid artery ligation with exposure to hypoxia in rat pups. Non-invasive *in vivo* MRI/MRS (brain damage, profile of key neurotrasmitters and their metabolites), histochemistry, respiratory activity in mitochondria (OxPhos), changes in the level and distribution of calcium in brain slices and gene expression of the selected calcium channels will be investigated to assess the rate and mechanisms of the developing brain injury.

Effects of pharmacologically active substances on injury of the cardiovascular system. The aim is to study effects of pharmacologically active substances on cardiovascular injuries (animal models of life style diseases). Evaluation of functional changes in heart and vessels (Langendorff method, plethysmography), selected biochemical variables (NO, NOS) and electron microscopy of vessels will be performed.

Damage of the cartilage with emphasis on the role of hyaluronic acid. Effects of pharmacologically active substances originating from the drugs intended to reduce acute and chronic inflammation will be studied. The substances under current interest are classified as mitochondrially targeted antioxidants. Several *in vitro* and *in vivo* models will be used in which the ROS will be generated by the so called Weissberger biogenic oxidative system consisting of ascorbate plus cupric ions. The *in vitro* model will operate with on line monitoring of changes of the molar mass of HA. The *in vivo* model will use the counting of survival of cells originated from human and laboratory animal tissues.

Molecular design, synthesis and biological activity of novel multitarget-oriented agents in prevention of diabetic complications. The Department of Biochemical Pharmacology utilizes modern medicinal chemistry approaches which allow sophisticated drug design and structure-activity relationships (QSAR) studies of drugs. The main goal is to intensify pharmacodynamic effects, maximizing selectivity of action, optimizing bioavailability and attenuation of toxic side-effects by structure alteration of already known chemical entities of high biological activity. Derivatives with the most appropriate pharmacological properties and low toxicity are forwarded for further research under experimental *in vitro* and *in vivo* conditions

Modulation of calcium pumps at the level of sarcoplasmatic reticulum, erythrocytes and pancreatic β-cells in diabetes and adjuvant arthritis. Flavonoids and original synthetic compounds will be tested for their modulatory activity on altered function of Ca-ATPase from sarco/endoplasmic reticulum (SERCA) and pancreatic β-cell due to pathological conditions using various biochemical approaches (e.g. fluorescence probes and markers, Western blot, flow cytometry). Thorough molecular dynamics computer study will be performed in order to assess the conformational changes of SERCA initiated by flavonoids and their derivatives.

Metabolic (and cognitive) syndrome

Risk factors of metabolic syndrome and ways of treatment by using hereditary hypetriglyceridemic rats. Cardioprotective, antihypertensive, hypoglycemic and hypocaloric effects of the substance SMe1EC2 in experimental model of hereditary hypetriglyceridemia in rats will be studied at various levels: blood pressure, isolated heart, reactivity of vessels, glycemia, aterogenic lipids, inflammation and oxidative stress.

Metabolic-inflammatory axis in neurodegeneration associated with aging. The future strategy of the laboratory will focus on the investigation of molecular mechanisms of the compounds (of natural and synthetic origin) with pleiotropic potential in prevention and treatment of age-related diseases. In particular,

the primary interest will be put on the agents simultaneously downregulating oxidative stress and inflammatory pathways while upregulating antioxidant mechanisms and metabolic functions. Relevant cellular models will be used (e.g. brain macrophages, connective tissue cells, metabolic cells).

Developmental toxicology

Developmental toxicity as a risk factor for development of mental disorders in adulthood („Fetal Origin of Adult Diseases", FOAD). Focus will be on the effect of hypoxia/ischemia, excessive stress and the antidepressant venlafaxine during sensitive developmental stages on neurobehavioral development of the rat offspring. Expected changes will be studied at behavioral (tests of emotional, social and cognitive functions), neurochemical (brain monoamines), and morphological (immunohistochemistry) levels.

Project proposals submited to 7RP or H2020	2012	2013	2014	2015
Institute as coordinator	0	0	0	0
Institute as participant	0	0	1	0

Bratislava, August 4, 2016

Dr. Michal Dubovicky, PhD.
Director

4. Other information relevant for the assessment

Attachment:

Translated text of the Memorandum of Understandig

Memorandum of Understanding

among

Institute for Heart Research SAS, Dúbravská cesta 9, 840 05 Bratislava,
Institute of Experimental Pharmacology and Toxicology SAS, Dúbravská cesta 9,
841 04 Bratislava
and
Institute of Normal and Pathological Physiology SAS, Sienkiewiczova 1,
813 71 Bratislava

The Institute for Heart Research (hereafter IHR), the Institute of Experimental Pharmacology and Toxicology (hereafter IEPT) and the Institute of Normal and Pathological Physiology (hereafter INPP) being aware of the need to concentrate multidisciplinary and interdisciplinary research in the field of medical and life sciences and gradually build larger compact scientific units within the Slovak Academy of Sciences (hereafter SAS) decided to sign the Memorandum.

1. After the anticipated transformation of SAS into public research institutions, stabilization of the individual institutes within the new legislature, and assessment of the functioning of the already existing "pilot" scientific centers of SAS, the following institutes, i.e. IHR, IEPT, INPP and INB, express their willingness to be integrated in a compact unit.
2. In the event of a consensus, the institutes will create a scientific Center of SAS focused on research of life style diseases. This Center will deal with integrated research of causes, mechanisms of development, and possibilities to prevent and treat socially significant lifestyle diseases, with emphasis on diseases of the cardiovascular and nervous system, metabolic disorders, as well as diseases that originate in the prenatal and early postnatal period of development. Research will be carried on *in silico, in vitro, ex vivo* and *in vivo* with the aim to transfer the acquired knowledge into clinical practice. An integral part of the scientific efforts of the Center will be the assessment of effects of natural compounds and their derivatives and of original synthetic substances with pharmacotherapeutic potential using animal models of human diseases, as well as the study of adverse side and toxic effects of the substances tested.
3. The process of integration and functioning of the future Center will be a subject of further negotiations after general agreement of the institutes willing to create the Center has been reached.
4. Signing of the Memorandum does not bind any institution to join the planned center.

The above draft was prepared in Bratislava on July 14, 2016

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RNDr. Miroslav Barančík, DrSc.
Director of the IHR SAS

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RNDr. Michal Dubovický, CSc.
Director of the IEPT SAS

.....
Assoc. Prof. RNDr. Oľga Pecháňová, DrSc.
Director of the INPP SAS