Questionnaire

Summary of the main activities of the Institute of Virology of the Slovak Academy of Sciences

Period: January 1, 2012 - December 31, 2015

Bratislava, July 2016

CONTENTS

1. *Basic information on the institute:*

1.1. Legal name and address

Institute of Virology, Slovak Academy of Sciences (until December 31, 2015)
Biomedical Research Center, Slovak Academy of Sciences (from January 1, 2016)

Dúbravská cesta 9, 84505 Bratislava

1.2. URL of the institute web site

www.virology.sav.sk (until December 2015)
www.bmc.sav.sk (from January 2016)

1.3. Executive body of the institute and its composition

Directoriat	Name	Age	Years in the position
Director	Juraj Kopáček, MVD., DSc.	52	7
Deputy director	Ľudovít Škultéty, DSc.	49	7
Scientific secretary	Tatiana Betáková, DSc.	52	8

1.4. Head of the Scientific Board

Ing. Miroslav Glasa, PhD.

1.5. Basic information on the research personnel

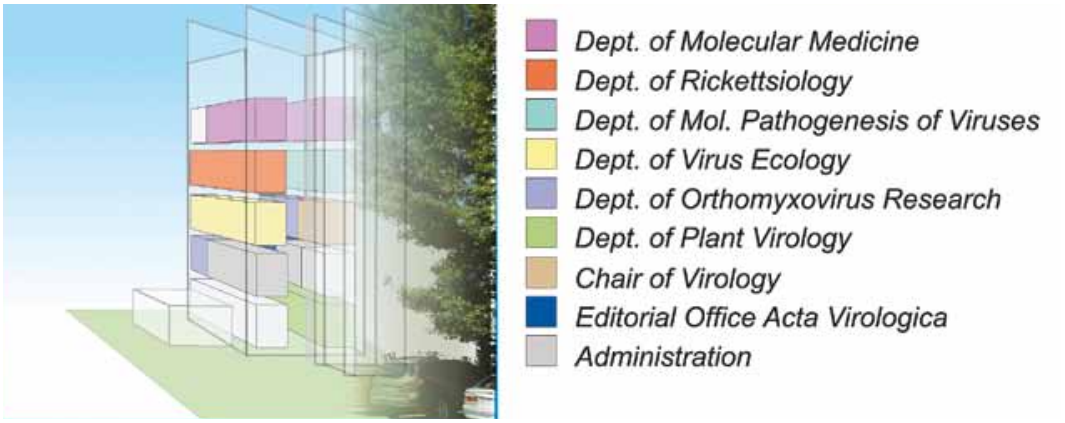
1.5.1. Number of employees with university degrees (PhD students included) engaged in research projects, their full time equivalent work capacity (FTE) in 2012, 2013, 2014, 2015, and average number of employees in the assessment period

	2012		2013		2014		2015		total		
	number	FTE	number	FTE	number	FTE	number	FTE	number	averaged number per year	averaged FTE
Number of employees with university degrees	73.0	50.770	79.0	50.810	76.0	53.350	85.0	56.170	**313.0**	**78.3**	**52.775**
Number of PhD students	21.0	21.000	20.0	20.000	21.0	21.000	16.0	16.000	**78.0**	**19.5**	**19.500**
Total number	94.0	71.770	99.0	70.810	97.0	74.350	101.0	72.170	**391.0**	**97.8**	**72.275**

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

Research staff	2012		2013		2014		2015		average	
	No.	FTE	No.	FTE	No.	FTE	No.	FTE	No.	FTE
Institute in whole	73.0	50.770	79.0	50.810	76.0	53.350	85.0	56.170	78.3	52.775
Department of Virus Ecology	8.0	5.240	9.0	6.330	8.0	6.000	8.0	6.000	8.3	5.893
Department of Molecular Medicine*	27.0	17.570	31.0	18.660	25.0	16.400	34.0	21.330	29.3	18.490
Department of Molecular Pathogenesis of Viruses	10.0	7.220	9.0	6.220	12.0	8.670	11.0	6.880	10.5	7.248
Department of Orthomyxovirus Research	11.0	6.410	11.0	6.680	11.0	6.830	8.0	4.450	10.3	6.093
Department of Plant Virology	5.0	4.330	6.0	5.330	6.0	6.000	5.0	5.000	5.5	5.165
Department of Rickettsiology	12.0	10.000	13.0	7.590	14.0	9.450	13.0	8.230	13.0	8.818
Department of Biotechnological Applications**	0.0	0.000	0.0	0.000	0.0	0.000	6.0	4.280	1.5	1.070

*The number of DMM employees in 2015 includes 6 researchers transiently delimited to the IVSAS from the Institute of Molecular Physiology and Genetics. After the establishment of BMC SAS, these researchers were administratively assigned to the Institute of Clinical and Translational Research BMC SAS.
**Department of Biotechnological Applications is localized in Šarišské Michaľany, Eastern Slovakia.



1.6. Basic information on the funding of the institute

Institutional salary budget and other salary budget

Salary budget	2012	2013	2014	2015	average
Institutional Salary budget *[thousands of EUR]*	972.702	931.426	927.891	961.557	948.394
Other Salary budget *[thousands of EUR]*	182.225	216.371	202.413	268.439	217.362

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

The Institute of Virology was founded in 1953 as a research institution of the Czechoslovak Academy of Sciences with the purpose to accomplish and develop scientific research in virology. In 1969, the Institute was administratively transferred under the guidance of the Slovak Academy of Sciences. According to the Foundation Charter issued by the Presidium of the Slovak Academy of Sciences, the Institute of Virology was a scientific organization with the budgetary form of economy.

The main mission of the Institute is:

- to perform scientific research of biological and molecular properties of human, animal and plant viruses, *Chlamydiae* and *Rickettsiae*,
- to investigate molecular mechanisms of cancer,
- to accomplish scientific education,
- to develop active cooperation with the domestic as well as foreign research institutions and universities,
- to publish the research results in periodic and non-periodic press and edit an international journal Acta virologica in the English language,
- to provide advisory and expert services related to main activities of the Institute.

Since January 1st, 2016, the Institute of Virology of the Slovak Academy of Sciences (IVSAS) has become a part of the newly established Biomedical Research Center of the Slovak Academy of Sciences (BMC SAS), where it has entered together with the Cancer Research Institute, the Institute of Experimental Endocrinology, and the Institute of Clinical and Translational Research SAS. Within the BMC SAS, the Institute of Virology continues to fulfill its original mission and develop close collaborative activities with the other three institutes to strengthen interdisciplinary and translational approaches and to improve research excellence according to the vision and conception described in the chapter 3 of the questionnaire (see page 73).

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

Throughout its history, the Institute of Virology SAS has been consistently focused on investigations of the principal problems of the contemporary virology including the structural composition of the viral particles, functional properties of their components, mechanisms of virus replication, virus-cell-vector-host relationships, genetic variability of viruses, pathogenic mechanisms, immune responses to viral infections as well as ecological aspects of the virus transmission, spreading and maintenance in nature. In addition, the IVSAS has been involved in the basic research of the structure/function relationships of the outer membrane biopolymers of *Rickettsiae* and *Chlamydiae*. During the last two decades, the Institute has also intensified its activity in the field of oncology within the original research topic established and developed at the IVSAS (see below).

During the assessed period (2012 – 2015) we put strong emphasis on research approaches based on modern molecular strategies, techniques an models, including genomics, proteomics, bioimaging and up-to-date methods in virology, microbiology, experimental oncology and cell biology. This attitude was facilitated by our success to attract significant domestic and international grants, particularly from the APVV grant agency, from the EU Structural funds and from the EU Framework programs, which brought funds to build progressive infrastructure, to improve availability of consumables for experimental work, and to attract foreign young researchers and experts to visit our Institute for short- or long-term training and research purposes. This, in turn, created a basis for the development of new research activities and for the increased competitiveness and cooperative potential of the IVSAS in an international dimension. In addition, we developed considerable efforts towards translational research in molecular medicine and biomedical applications by stimulating collaborations with clinical and industrial partners. This is particularly exemplified by our active partnership in the EU Structural funds project resulting in the establishment of the R&D Centre for Immunologically Active Substances with new Biotechnological laboratories in the area of IMUNA PHARM, a.s., a Slovak industrial producer of bioactive substances and materials for clinical use located in Eastern Slovakia. This latter facility operated by the employees of the IVSAS opened new opportunities for the certified (semi)-production of newly identified and/or developed bioactive molecules and for coordinated applied research with the industrial partner(s).

Overview of the R&D activities during the assessment period

The organizational structure of the IVSAS includes seven research departments as main structural units, which develop research activities in the topics traditionally associated with the Institute, but also new topics introduced in conjunction with new discoveries and needs of the society. For the brief overview of the staff and projects in the departments and their R&D activities, see the scheme on page 17.

Department of Plant Virology

Epidemiologically and economically important plant viruses, particularly the RNA viruses of the stone fruit trees, grapevine and cucurbits were studied from several aspects: (1) full-length or partial characterization of virus genomes in order to obtain original data on their genetic variability, relationships and the evolutionary forces shaping this diversity (e.g. recombination) using standard and next-generation sequencing tools, (2) development and optimization of molecular tools for sensitive and specific detection of pathogens infecting stone fruits, grapevine and cucurbits based on the currently available genomic data, (3) study of biological and molecular factors influencing the spread, epidemiology and adaptation of plant viruses, including evaluation of their capability to break the resistance of host plants or assessment of the structure and polymorphism of viral populations in plants, (4) functional genomics to identify genetic determinants involved in pathogenesis of selected viruses, and (5) study of plant/virus

interaction, including analysis of the changes in proteome of plants infected with viral pathogen. The results of these studies have shown direct implications for agricultural practice with the potential to improve the phytosanitary measures aimed to control plant viruses.

The most important results include:

- Identification and characterization of a divergent strain of Plum pox virus naturally infecting cherries (PPV-CR) and development of an RT-PCR assay for its specific detection (*Glasa et al, Phytopathology, 2013*);
- Identification of newly described grapevine viruses (Grapevine Pinot gris virus and Grapevine Syrah virus-1) in Slovakia by next generation sequencing and first assessment of their variability (*Glasa et al, Arch Virol, 2014, Glasa et al, Virus Genes, 2015*);
- Preparation of a Plum pox virus-based vector and its application for transient expression of the heterologous genes in Nicotiana benthamiana, i.e influenza A virus PB1-F2 protein (*Kamencayova et al, Acta Virol, 2014*);
- Mapping of genetic determinants of symptomatology and pathogenicity in the genome of Plum pox virus using chimeric infectious clones (*Nagyova et al, Virus Genes, 2012*);
- Analysis of modifications of the tobacco transcriptome caused by Plum pox virus infection (*Vozárová et al, Acta Virol, 2015)*;
- Proteomic analysis of the cucurbit plants infected with Zucchini yellow mosaic virus, revealing differences in the activation of defence mechanism depending on the genotype susceptibility (*Novakova et al, Front Pl Sci, 2015*);
- First report of Little cherry virus-1 in Slovakia and development of the molecular diagnostic method for the virus monitoring (*Glasa et al, J Plant Pathol, 2015*);
- Evidence of a heterologous population and an intra-isolate variability within Grapevine virus A (*Predajna et al, J Phytopathol, 2016, submitted on 2015*).

Funding: EU 7th Framework program (1 project), European Regional Development Fund (1 project), COST (3 projects), Research and Development Agency (APVV, 3 projects), Scientific Grant Agency of the Ministry of Education and Slovak Academy of Sciences (VEGA, 7 projects). Selected projects:

- Investigation on the Plum pox virus host preference factors in regard to the natural variability of its population in the territory of the Slovak republic (APVV 2011-2014)
- Development of innovative approaches to characterise and control the economically important and emerging virus pathogens of cherry crops in Slovakia (APVV 2013-2017)
- Use of the genome data of economically important grapevine viruses for optimisation of detection tools and development of innovative protection methods against viral infection (VEGA 2013-2015)
- Identification of interactions between plant factors and non-structural viral proteins from genus Potyvirus and their use for understanding the plant natural defence system (VEGA 2012-2014)
- Application of next generation sequencing for the study and diagnosis of plant viral diseases in agriculture (COST 2015-2019)
- SharCo: Containment of sharka virus in view of EU-expansion (7thFP EU 2008-2012)

Department of Rickettsiology

Rickettsiae and rickettsia-like organisms (e.g. *Coxiella burnetii)* comprise a group of microorganisms that phylogenetically occupy a position between bacteria and viruses. The bacteria are usually spread to people through bites of ticks, mites, fleas, or lice, which are the vectors of the infections. However, in the case of *Coxiella burnetii,* the bacterium is usually transmitted from infected animals to humans by the aerosol route or ingestion of raw milk.

In the course of the assessment period, these microorganisms were studied from various angles, in order to: (1) predict and systematically identify protein biomarkers, including surface-associated, virulence-related, and immunoreactive proteins of *C. burnetii*, suitable for diagnosis of Q fever, (2) elucidate the role of the proteins in virulence, pathogenesis, and immunity, (3) elucidate the role of structural variations of lipopolysaccharide antigens in the pathogenicity, (4) monitor *Rickettsia* spp., *Coxiella burnetii* and related microorganisms in natural foci in

connection with the prevalence of human diseases, (5) isolate new species and relate the isolates with vectors and reservoirs (ticks, lice, mites and wild animals), (6) develop cellular and animal models of infection, (7) characterize these organisms by the methods of molecular biology, genomics, serology, and immunology for better understanding of host-parasite interactions, and (8) improve diagnosis of these re-emerging rickettsial infection.

The most important results include:

- Identification of surface-exposed and cell envelope-associated proteins of *Coxiella burnetii* using combined bioinformatics and proteomics strategies, as potential markers of *C. burnetii* infection and targets for future therapies *(Flores-Ramirez et al, Proteomics, 2014);*
- Bioinformatics-based, proteomics-supported prediction of the biosynthetic pathways of the unique *C. burnetii* biomarker virenose *(Flores-Ramirez et al, Proteome Sci, 2012);*
- First evidence of a human case of *Bartonella elisabethae* in Slovakia and the first record of *Rickettsia africae* and *Wolbachia sp*. In *Ceratophyllus garei* fleas from Passerine birds migrated from Africa to Central Europe *(Sekeyova et al, Vector-Borne Zoonot Dis, 2012*);
- First isolation of *Arsenophonus nasoniae* from a nymphal *Ixodes ricinus* and proof that *A. nasoniae* infection of ticks is related to the presence of parasitoid wasps *Ixodiphagus hookeri* emerging from parasitised nymphs (*Bohacsova et al, PLOS one, 2016);*
- Demonstration that *Rickettsia helvetica* is a dominant rickettsia in *I. ricinus* ticks in Slovakia (*Špitalská et al, Ticks Tick-Borne Dis, 2014*);
- Elucidation of the host defense response to *Rickettsia akarii* and its antibiotic resistance variant (RAZC) that target macrophages and endothelial cells and induce cell activation via TLR2 or *TLR4 (Quevedo-Diaz et al, In Int Congr on Rickettsia and other intracellular bacteria 2015);*
- Elucidation of rat cerebrocortical neurons infection by Rickettsia, discovery of specific markers related to infection, and evidence for an involvement of rickettsia in the etiopathogenesis of various neuropathies *(Bohacsova et al, Microbes Infect, 2015)*.

Funding: EU-FP7 (2 projects), bilateral (6 projects), APVV (4 projects), VEGA (12 projects), and 13 other projects. Selected projects:

- Biology and control of vector-borne infections in Europe. EDENext EU 7th FP (2010-2014)
- Profile of the protein response in resistance to tetracycline by *C. burnetii*. European Society of Clinical Microbiology and Infectious Diseases (2014-2015)
- The role of structural variations of lipopolysaccharide antigens in the pathogenicity of Gram-negative bacteria. CNRS-SAS: PICS (2012-2014)
- Development of Lipopolysaccharide-Biopolymer Complex and Conjugates Against the Q Fever Disease For Application Purpose of Vaccine Prototype and Diagnostic Kit. SAS-Turkey (2014–2016)
- Structural characterization and LPS gene cluster annotation of *Coxiella burnetii*. Nationale Forschungsplattform fur Zoonosen, Germany (2016-2017)
- Identification of biomarkers for diagnosis of *Rickettsia* spp., *C. burnetii* and related organisms using immunoproteomic and methods of molecular biology. APVV-0280-12 (2013-2017)
- The function of neuropeptides and their receptors in the regulation of transmission of pathogens from tick to host. APVV-14-0556/15 (2015-2019)

Moreover, research staff of the Department of Rickettsiology operates the core facility for **Proteomics and mass spectrometry** and participates in diverse studies exploiting proteomic approaches mainly related to investigations of adaptive strategies in plants to adverse environmental conditions. These included the proteomics workflow based on a two-dimensional gel electrophoresis to (1) elucidate virus resistance of zucchini and to (2) clarify the mystery behind successful growth of flax in a radio-contaminated environment at Chernobyl. These research activities were supported by the following projects:

- Plant adaptation to heavy metal and radioactive pollution. PlantDNAtoleranc EU 7th FP People (2014-2017)
- Systematic MSE-based quantification of allergenic and other clinically relevant proteins in wheat grains. Syngenta, USA (2011-2012)
- Mechanism of male sterility regulated by DAD1- Activating Factor (DAF), an RIG-finger E3 ligase gene and its agricultural application. SAS-NSC JRP (2013-2016)

- Identification of relevant proteins and characterization of protein-protein interactions of biomarkers associated with regression of malignant diseases. APVV-SK-CZ-2013-0215 (2014-2015)
- Adaptation of plants in the radioactive Chernobyl area and its possible application. APVV-0740-11 (2011–2014)
- Preparation of erythropoietin, the therapeutic hormone affecting the production of red blood cells, by expression in eukaryotic cell system, and its further purification. PEEECS. APVV-14-0474/15 (2015-2018)

Department of Virus Ecology

Zoonotic viral infections remain to be a serious public health concern. The Department of Virus Ecology has been involved in epidemiological and pathogenic studies of tick-born and small mammals-transmitted viruses since its foundation and has made several original contributions mainly to elucidation of arbovirus ecology and hantavirus molecular evolution. During the assessed period, the main emphasis was given to two research lines: (1) establishment and maintenance of the European virus archive (supported by the 7th FP EU project followed by H2020 project expanding to global dimension, described in more detail on page 35), biological and molecular characterization of the deposited viruses (including historical isolates of arboviruses archived previously at the Institute), and collection and identification of new viruses particularly those belonging to the genus Hantavirus, and (2) further development of the concept (co-established by the researchers from our institute) of the non-viraemic transmission of infectious agents by ticks via their saliva whose components weaken or prevent the immune response of the host organism and thereby facilitate infection. The attention was paid to molecular and biological characterization of biologically active substances derived from tick saliva. The aim of these studies is to identify and clone biologically active component(s) of the tick saliva and test their potential use either for development of vaccine protecting humans and animals against feeding ticks and transmission of tick-borne infectious agents (both viruses and microorganisms) or for therapy of various immunologic diseases or cancer.

The most important results include:

- Confirmation of tick mouth part´s length impact on the spectrum anti-growth factors activities in tick saliva and on cell morphology *(Slovák et al., Parasite Immunology 2014)*;
- Detection of inhibitory effect of tick salivary gland extract on TGFβ1 signaling and biological/migratory activities induced by TGFβ1 in different cervical cancer cell lines *(Štibrániová et al., manuscript in preparation)*;
- Elucidation of the protective role of the tick protein subolesin during infection by tick-borne encephalitis virus *(Havlíková et al., Vaccine 2013)*;
- Evaluation of the tick-borne encephalitis virus molecular determinants of non-viraemic transmission of the virus in co-feeding ticks *(Slovák et al., Ticks and tick-borne diseases 2014)*;
- Identification and comprehensive phylogenetic analysis of novel shrew-borne hantaviruses in Central Europe *(Schlegel et al., Virus Genes 2012; Radosa et al., Infection Genetics and Evolution 2013)*;
- Comprehensive analysis of complex molecular evolution and epidemiology of Dobrava-Belgrade virus, the most severe hantavirus in Europe *(Klempa et al., Archives of Virology 2013)*.

Funding: EU-FP7 (2 projects), EU-H2020 (1 project), APVV (2 projects), VEGA (6 projects):

- Structure of the emerging diseases´ natural foci: the role of rodents in urban type of natural foci of diseases (APVV 2011-2014)
- Biological significance and pharmacological features of proteins in tick saliva (APVV 2013-2017)
- Anti-tick Vaccines to Prevent Tick-borne Diseases in Europe – ANTIDotE (EU 7th FP 2013-2018)
- European Virus Archive – EVA (EU 7th FP 2009-2014)
- European Virus Archive goes global — EVAg (EU H2020 2015-2019)

Department of Molecular Medicine

The Department of Molecular Medicine has contributed to molecular studies of viruses through investigation of the lymphocytic choriomeningitis virus (LCMV), particularly its mutual relationships with the host cells during persistent infection. LCMV is a neglected human pathogen, which can have severe consequences for immunosuppressed individuals and developing embryos. We previously identified a new MX strain of LCMV persistently infecting human cells and showed that its extracellular spread can be induced by hypoxia. During the evaluation period, we used our in-house monoclonal antibodies to develop ELISA test for the detection of LCMV nucleoprotein in human serum samples. We also showed that the LCMV infection could be inhibited by the interferon lambda.

However, our major research activities are focused on understading the role of tumor microenvironment (namely hypoxia and acidosis) in cancer progression. This has become our central topic in early 90-ties, following the identification, cloning and characterization of the cancer-associated carbonic anhydrase IX (CA IX) by the researchers of the Institute. At present, CA IX is known worldwide as an intrinsic marker of tumor hypoxia with the clinical value in cancer prognosis, prediction and therapy. Investigations of CA IX at the Institute brought many original data on its distribution in cancer tissues and its functional involvement in adaptation of tumor cells to hypoxia and acidosis. The main efforts were given to study of CA IX regulation, its role in cell adhesion-migration-invasion and pH control in hypoxic tumor cells, and to identification of downstream pathways driven by CA IX. We also produced highly specific monoclonal antibodies for the characterization, detection and therapeutic targeting of CA IX. In addition, research of CA IX gave birth to two other topics, namely (a) expression and regulation of S100P calcium-binding protein in tumor tissues and preparation of S100P-specific monoclonal antibodies, and (b) regulation and role of endosialin gene associated with tumor angiogenesis.

The most important results include:

- Demonstration of the CA IX protein role in cell migration through its catalytic activity and pH regulation, and first direct evidence of in situ interaction of CA IX with bicarbonate transporters in lamellipodia of migrating cells *(Svastova et al, J Biol Chem, 2012)*;
- Dislosure of the functional contribution of the N-terminal proteoglycan-like domain of CA IX to focal adhesion during cell spreading, suggesting its potential role in extravasation and metastatic homing *(Csaderova et al, Front Physiol, 2013*);
- Identification of downstream signaling pathways affected by the suppression of CA IX (e.g. HIF-1 and metabolic pathways, now under completion) and demonstration that the loss of CA IX leads to aberrant focal adhesion and decreased invasion of tumor cells *(Radvak et al, Oncol Reports, 2013, Csaderova et al, Front Physiol, 2013)*;
- Demonstration that CA IX is a clinically significant tissue and serum biomarker associated with renal cell carcinoma *(Takacova et al, Oncol Letters, 2013);*
- Experimental evidence for the crosstalk between RET oncogene and HIF-1 transcription factor resulting in an increased expression of CA IX in medullary thyroid carcinoma, thus providing a rationale for anticancer therapy simultaneously targeting both pathways *(Takacova et al, Am J Pathol, 2014)*;
- Elucidation of the binding specificity, internalization characteristics and therapeutic effects of the CA IX-specific monoclonal antibody G250 in a non-renal cancer model *(Zatovicova et al, Int J Oncol, 2014)*;
- Evidence that a natural dipeptide carnosine inhibits CA IX-mediated extracellular acidosis through disruption of the bicarbonate metabolon *(Ditte et al, BMC Cancer, 2014)*;
- Demonstration that chemotherapy-induced apoptosis leads to increased shedding of CA IX from the surface of dying cells and that the CA IX ectodomain elicits autocrine/paracrine signaling *(Vidlickova et al, BMC Cancer, 2016 – submitted in 2015*);
- Production and characterization of novel monoclonal antibodies specific for CTLD-SSC and sialomucin domains of endosialin, a mural cell marker of tumor vasculature *(Kontsekova et al, Int J Oncol, 2012)*;

- Identification of angiogenesis-related pathways modulated by endosialin in cancer cells (*Kontsekova et al, Neoplasma, 2016, submitted in 2015)*;
- Experimental evidence for the interaction of the cancer-associated calcium-binding protein S100P with p53 tumor suppressor protein and for the ability of S100P to stimulate therapy-induced senescence *(Gibadulionova et al, Oncotarget, 2016, submitted in 2015*).

Funding: EU-FP7 (2 projects), COST (1 project), APVV (6 projects), VEGA (13 projects), other (2 projects). Selected projects:

- Identification of the molecular pathways driven by the hypoxia-induced carbonic anhydrase IX in tumor cells (APVV 2011-2014)
- Carbonic anhydrase as a functional component of tumor progression: the role in epithelial-mesenchymal transition and intercellular signaling (APVV 2012-2015)
- Molecular mechanisms of the crosstalk between stress hormones and hypoxia in tumor cells: effect on expression and function of cancer-related protein CA IX (APVV 2012-2015)
- Elucidation of novel pro-metastatic functions of tumor-associated carbonic anhydrase IX and its cross-talk with pro-inflammatory response
- Hypoxia sensing, signaling and adaptation, HypoxiaNet (COST 2010-2014)
- Metastatic tumors facilitated by hypoxic tumor microenvironments (7th FP EU 2009-2014)
- Biomedical engineering for cancer and brain disease development (7th FP EU 2011-2015)
- Role of the CA IX ectodomain in tumor growth and metastasis (US foundation 2015-2016)

Department of Molecular Pathogenesis of Viruses

Research on herpesviruses and influenza viruses has been the integral part of basic and applied research at the Institute of Virology since the early years of its existence.
Herpesviruses represent serious health problem of human and animal populations. Our research is focused on Herpes simplex virus 1 (HSV1) and Murine herpesvirus 68 (MHV-68) that was originally isolated from wild rodents in Slovakia and serves as an experimental model of oncogenic human herpesviruses such as EBV and KSHV. Viruses were studied from several aspects (1) antiviral defense and cell transformation in alfa- and gammaherpesvirus infection; (2) herpesvirus encoded immuno-modulatory proteins; (3) compound of MHV-68 resembling growth factors of some herpesviruses; (4) the role of mutations of murine herpesviruses in latency and reactivation and (5) factors involved in the spread of MHV-68 in nature, including ticks. We also developed assays for detection of mixed infections of herpesviruses commonly transmitted within human populations, such as HSV1+HSV2, HCMV+EBV, and VZV+HSV2. Moreover, a SASPRO fellow joining our team in 2014 has brought a new and attractive research topic of the structural and functional analysis of the human cytomegalovirus (HCMV) protein UL141 mediating virus evasion and/or inhibition of immune effector pathways.

The most important results include:

- Identification of differential antiviral activities induced by IFN-λ1 during infection with highly pathogenic ANGpath and moderately pathogenic KOS strains of HSV-1 (*Lopušná et al., Acta Virol*, 2014);
- Preparation of stable human and mouse cell line transformed by UV irradiated MHV-68 that is suitable for studies of mechanisms of virus-related transformation of cells (*Mrázová et al., Intervirology, 2015);*
- Evidence that the signal sequence and even a single mutation in recombinant M3 protein of MHV-68 prepared in *E. coli* cells can modulate its binding to CCL5, CXCL8, and CCL3 chemokine (*Pančík et al., and Matúšková et al., Acta Virologica, 2013 and 2015);*
- Structural dissection of the interaction of a dimerization-defective mutant of immunomodulatory HCMV protein UL141 with the cell surface TRAIL death receptor and the NK activating protein CD155 suggesting that the Ig-like domain of UL141 is a viral mimic of a T-cell immunoreceptor TIGIT (*Nemčovičová et al., Acta Crystallographica D – Biological Crystallography*, 2014);
- First evidence and characterization of growth factor associated with MHV-68 produced by primary transformed cells and stably transformed S11E cell line (*Šupolíková et al., Acta Virol. 2015);*

- Demonstration that distinct reactivation patterns of murine gammaherpesviruses ex vivo and in vivo are not related to epigenetic modification of RTA (ORF50) promoter (*Lapuníková et al., Acta Virol. 2015);*
- Identification of the genetic variability in the sequences of five proteins of MHV-4556 virus (M4, gB, p43, ORF26, ORF52) that appear to contribute to its different pathogenic and immunogenic properties compared to MHV-68 (*Kúdelová et al., Acta Virol. 2012 and 2013*);
- First detection of MHV-68 infection in three tick species (*Dermacentor reticulatus*, Ixodes ricinus, *Haemaphysalis concinna*) in the territory of Slovakia and of a live virus in tick organs (*Kúdelová et al., Microbial Ecology, 2015);*
- Introduction of cost-saving method for detection of mixed infection with HSV1&HSV2, HCMV&EBV, and VZV&HSV2 in human clinical materials (*Kúdelová&Rajčáni, In: Neuroviral infection, 2013*).

Influenza viruses and other pathogens

During influenza virus A (IAV) infection, multiple factors are likely to influence host immune response to infection. Interferons represent important components of the first line defense against virus. Our research was focused on analysis of immune-signaling pathways and cytokines/chemokines induced in response to influenza virus infection. In addition, we made efforts towards the evaluation and development of new substrates for adaptation of measles and mumps viruses for the subsequent production of vaccines for human use.

The most important results include:

- Demonstration that IFN-ω has significant antiviral activity against highly pathogenic IAV, although lesser than IFN-β1a, IFN-λ1, or IFN-λ2, and that IFN-λ1 and IFN-λ2 are more potent than the type I IFNs *(Skorvanova et al, Acta Virol, 2015)*;
- Evidence that silencing of the NS gene of IAV, mediated by 10 shRNAs used individually and in the mixture, led to decreased virus replication, whereas shRNA targeting of NEP transcript had no effect *(Svancarova et al, Virus Genes, 2015)*;
- Identification of shRNAs suitable for efficient silencing of M1 gene, capable to significantly reduce IAV titers in infected cells and animals *(Svancarova et al, Acta Virol, 2015)*;
- Preparation of adapted measles and mumps virus suitable for production of human vaccines *(Betakova et al, Acta Virol, 2013).*

Funding: ERDF (1 project), bilateral project ÖEAD SK-AT (1 project), APVV (3 projects), VEGA (9 projects), and bilateral projects with industrial partners (1 project). Selected projects:

- Immunomodulation by HCMV and Temporal Viromics to investigate virus/host interactions (ERDF 2013-2016)
- Immune modulation by HCMV and its immunotherapeutic potential (SASPRO 2015-2018)
- Diagnostics of Socially Important Diseases in Slovakia Based on Modern Biotechnologies (ASFEU 2010-2013)
- Imunomod – immune modulation by cytomegalovirus (APVV 2015-2019)
- Murine gammaherpesvirus, a producer of substances exhibiting immunomodulatory and anti-proliferative properties (APVV 2013-2017)
- Characterization of novel motif in M1 protein of influenza A virus and use of NS1 deletion mutants in anti-tumor therapy (APVV 2013-2017)

Department of Orthomyxovirus Research

Influenza A viruses (IAVs) represent serious medical problem, as they cause highly contagious acute respiratory illness in humans, spreading repeatedly in the form of epidemics or even pandemics. Clinical symptoms of disease can range from mild to severe, occasionally resulting in pneumonia and organ failure. At present, infection could be controlled only by seasonal vaccination. However, current influenza vaccines possess narrow specificity for vaccine strains and no cross-protective (so-called universal) influenza vaccine is available. In general, many important problems concerning the efficacy of virus infection and IAV ecology remain to be solved.

At the Institute of Virology, influenza represents continuing research topic of the Department of Orthomyxovirus Research. During the monitoring period (2012-2015), research activities of our group were focused on immunology, pathogenesis and interspecies transmission of IAVs. The main accent was given to the role of PB1-F2 virus protein and IAV fusion activity in the influenza pathogenesis. We also analysed the interaction of mammalian host immune system with IAVs of human and avian origin. The aim was to find out whether avian IAV exposition of the host, previously infected with human viruses, can induce virus-neutralizing antibodies against avian IAV. This is important from the epidemiological point of view for the process of adaptation of avian IAV to mammals, particularly to humans. Another line of our research was the study of effective induction of heterosubtypic immunity. In this aspect, the main problem to solve is that critical conserved IAV antigens are poor immunogens. We focused on two of them, HA2 gp and ectodomain of M2 protein (M2e), and developed delivery systems for antigen presentation, improving its efficacy (particularly recombinant plasmid DNA; adenylate cyclase toxoid derived from Bordetella perthussis toxin; delta-NS1 attenuated influenza A vector virus), and verified their immunogenicity and protectivity. Simultaneously, the large proportion of our research activity was devoted to the 7th FP EU project comprising the design, synthesis, and testing of new antivirals targeting influenza virus polymerase. In the applied research arm, we developed improved diagnostic method for detection of infectious IAVs. Our research interests are supported also by long-lasting collaboration with foreign partners focused mainly on the preclinical animal trials of new forms of influenza vaccines.

The most important results include:

- Introduction of site-directed mutations into the PB1-F2 protein causing its post-translational modification and loss of ubiquitination, resulting in increased PB1-F2 protein stability and aletered IAV virulence and pathogenesis (*Košík et al, PLOS-one, 2015).*
- Identification of new critical amino acids of HA2 protein, substitution of which affected IAV fusion activity with an impact on virus replication (*Kotlárová et al, Acta virologica, 2016)*
- Assessment of virus-neutralizing antibody response of mice to consecutive infection with human and avian IAVs pointing out on original antigenic sin exertion (regarding VN antibodies) and also HA2-specific cross-reactive antibodies (*Janulíková et al, Acta virologica, 2015, Stropkovská et al, Acta virologica, 2015, Kostolanský et al, Acta virologica, 2013).*
- Demonstration by competitive assays with human convalescent sera that antibodies specific to three defined epitopes of HA2 gp (antigenically conserved) were elicited during a natural influenza infection of humans (*Staneková et al, Influenza and Other Respiratory Viruses, 2012, Varečková et al, Biomedfrontiers.org/infection, 2013).*
- Evidence that cross-protective antibody response against influenza was elicited with two distinct regions of HA2 gp (*Janulíková et al, Acta virologica, 2012, Varečková et al, Acta virologica, 2013).*
- Demonstration that insertion of HA2 epitopes into the adenylate cyclase toxoid vector improved heteroprotective immunity against influenza by induction of both B- and T-cell response (*Staneková et al, Antiviral Research, 2013).*
- First evidence that antibodies against the C-terminal region of PB1-F2, obtained by immunization with KLH-PB1-F2 C-terminal peptide or DNA immunization with pC-ter PB1-F2 plasmid, partially protected mice against virus infection (*Košík et al, Archives of Virology, 2012, Košík et al, Acta virologica, 2013, Košík et al, Virology, 2013).*
- Construction of attenuated del-NS1 influenza vector virus presenting conserved IAVs antigens (*cooperation with HSC Development GmbH (Austria) and EF-Bio (Slovakia*).
- *In vivo* screening of newly designed antiviral compounds targeting influenza RNA polymerase and selection one of 100% efficacy comparable to Tamiflu antiviral, but efficient also against Tamiflu-resistant influenza A strains" (*1/ results are the subject of patent processing, 2/ Skaličková et al, Viruses-Basel, 2015).*

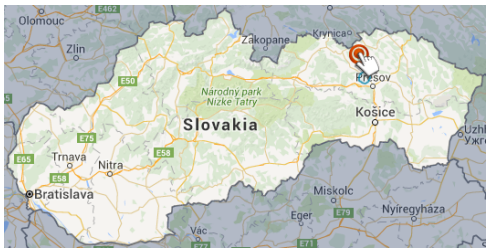
Funding: EU-FP7 (1 project), APVV (2 projects), VEGA (7 projects), and bilateral projects with commercial partners (3 companies). Selected projects:

- Prediction of influenza A virus epidemic/pandemic outcome by identifying dominant markers of viral pathogenesis and transmissibility (APVV 05/2011-10/2014)

- New drugs targeting influenza virus polymerase (7th FP EU and APVV 11/2010-04/2015).
- Bilateral projects with commercial partners: Efficacy of new antivirals (EF-Bio); Antiviral efficacy of Tamiflu derivatives *in vitro* (Synkola), Immunogenicity of new influenza vaccine strains (HSC Development GmbH)

Department of Biotechnology

The Department of Biotechnology was founded only recently, initially in conjunction with the establishment of a common laboratory shared between the Institute of Virology SAS and IMUNA PHARM, a.s., a Slovak pharma company developing and producing biomedical products including antiviral vaccines, and bioactive and immunostimulatory substances. The virtual biotech laboratory was later on materialized through the EU Structural funds project "Centre for Research and Development of Immunologically Active Substances" (ERDF 2014-2015), administered by the Office of the Slovak Academy of Sciences. This project brought funds for the construction of the real building of Biotechnological Laboratories (BTL) with GMP lab spaces equipped with modern biotechnological infrastructure.

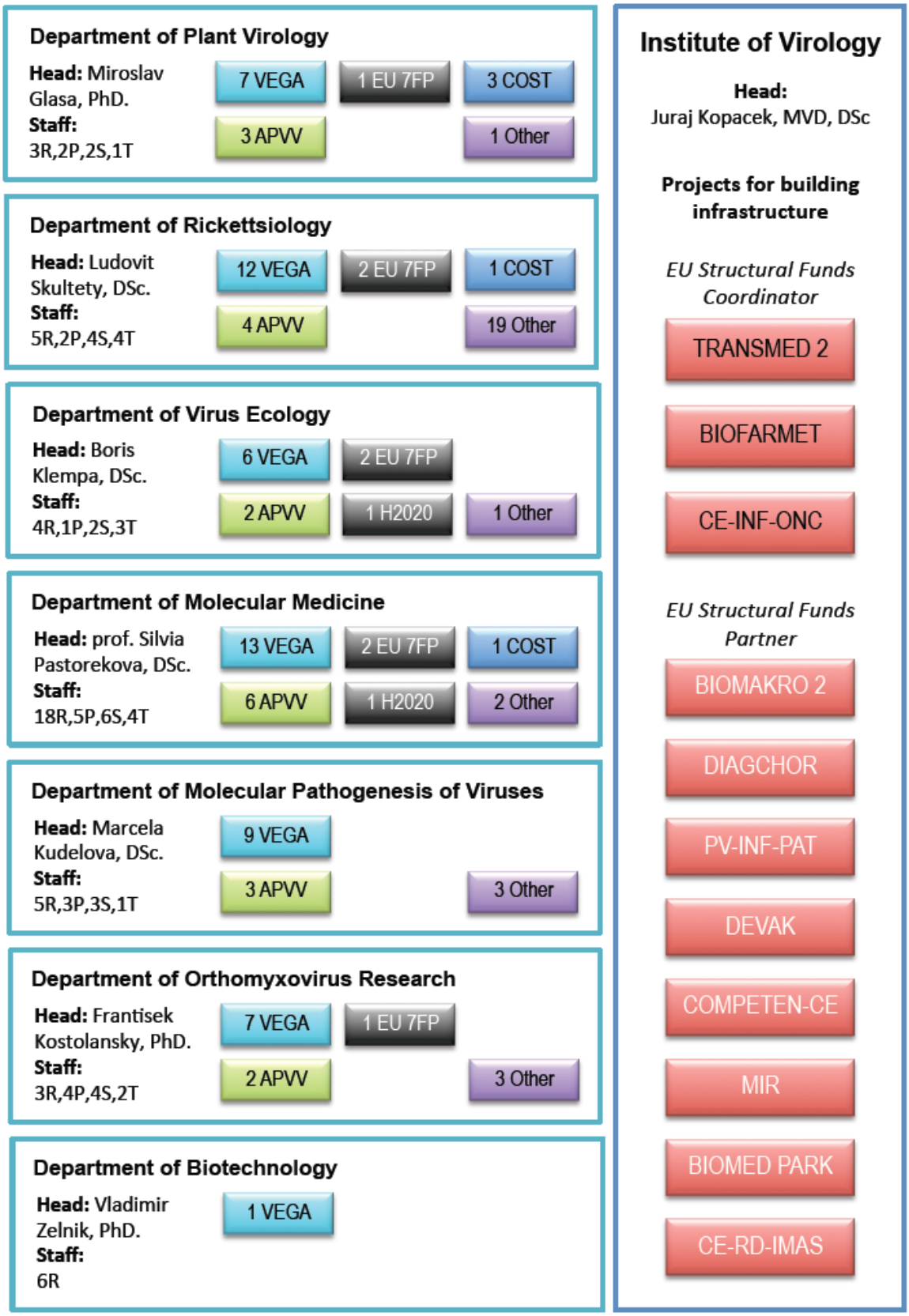


This modern infrastructure, localized in Šarišské Michaľany, Eastern Slovakia, is nowadays actively exploited for the R&D activities including development of new vaccine substrates and procedures, quality testing and other purposes related to the collaboration between IVSAS and IMUNA PHARM, a.s. It is also intended to serve as a core facility for the applied research. In the following years, we plan to broaden the scope of BTL activities to R&D towards new bioactive molecules, research of new applications or repurposing of the traditionally produced substances, and potentially to development of vaccines against new or re-emerging viruses.

Other R&D activities of the Institute of Virology SAS

In the years preceding the assessment period, the Institute of Virology was the principal coordinating organization of the large State program "Biotechnological center of the Slovak Republic" (**BITCET**) with the major aim to build modern infrastructure and distribute advanced biotechnological equipment among 17 R&D academic institutions and universities in the Slovak Republic. This infrastructure is still in use and promotes collaborative research activities.

Later on, we benefited from this unique experience as well as from the large EU project portfolio in successful applications and implementations of several projects funded by the very competitive ERDF program (i.e. EU Structural funds) intended for further building of advanced research infrastructure. In the period 2012-2015, the IVSAS was funded to coordinate 3 projects and participate in 8 projects as partner *(summarized on the scheme on the next page and listed on pages 43-44 and 54).*



Schematic summary of the R&D activities of the IVSAS and its departments illustrated through research projects and staff composition at the departments (left side) and the projects with the participation of the IVSAS as a coordinator or partner (right side, with the project acronyms). The staff personnel include researchers (R), post-docs (P), PhD students (S) and technicians (T).

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)

Our research principally **generates internationally relevant outputs (100%),** which can be also expoited for the regional development strategies. This is due to the worldwide significance of viral infections that we investigate and the importance of cancer molecules that we identified and/or characterized. On the other hand, our studies of the regional distribution of infectious agents can impact on understanding the international epidemiological situation and this is also reflected by the interest of foreign institutions to collaborate with our research teams as described below.

Our research interests were focused not only on the broadening the basic knowledge, but also on its potential applications in diagnostics and/or therapy of viral and cancer diseases. To this end, we have been developing reagents and assays for detection of infectious pathogens and cancer biomarkers, for diagnostics (and potentially therapy) of infectious diseases and cancer as well as for production of vaccines. The **ratio between the basic and applied research** at the Institute of Virology SAS can be only **roughly estimated to be around 80% vs 20%** based on the ratio of funding from the research agencies versus funding from the commercial sources (excluding the EU Structural fund projects for building research infrastructure). Indeed, many basic research activities overlap or inffuse into potential applications, so it is actually impossible to make a clear-cut border between these two types of research activities.

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) are underlined and written in blue

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2.1.3 List of monographs/books published abroad

None during the evaluation period.

2.1.4. List of monographs/books published in Slovakia

None during the evaluation period.

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

We edited and illustrated **the worldwide first monograph on tumor hypoxia**, a phemonenon that significantly affects cancer progression and response to therapy. The monograph consists of chapters written by top world-renowned experts, including discoverers of the hypoxia-inducible factor and key personalities of the recent hypoxia research, such as Peter J Ratcliffe (Oxford), Patrick H Maxwell (London), Roland Wenger (Zurich), Giovanni Melillo (Princeton) and others.

(1) Tumor Hypoxia: Molecular Mechanisms and Clinical Implications. **PASTOREKOVÁ, Silvia** - **KOPÁČEK, Juraj** (eds.). Frankfurt am Main: Veda, SAS Publishing House Bratislava and Peter Lang, GmbH, 2012. 556 pp. ISBN 978-3-631-63991-7.

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(10) **PASTOREKOVÁ, Silvia** - SUPURAN, C.T. Carbonic Anhydrase IX: From Biology to Therapy. In *Hypoxia and Cancer. Biological Implications and Therapeutic Opportunities*. - New York: Humana Press: Springer, 2014, p. 121 - 156. ISBN 978-1-4614-9167-5

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

The patents listed below are related to clinical applications of CA IX, initially named MN, as a biomarker and a therapy target (identified at the Institute of Virology SAS in early nineties) as well as to clinical use of the CA IX-specific antibodies and inhibitors for cancer diagnostics and therapy.

MN gene and protein
Patent Number: US 08759493
Patent Assignee: Institute of Virology Slovak Academy of Sciences
Inventor(s): ZAVADA, J. - **PASTOREKOVA, Silvia** - **PASTOREK, Jaromir**
Official Gazette of the United States Patent and Trademark Office Patents Published: JUN 24 2014
Date Granted: June 24, 2014
Accession Number:BCI:BCI201400766715 ISSN:0098-1133

CA IX-specific inhibitors
Patent Number: US 08628771
Patent Assignee: Institute of Virology Slovak Academy of Sciences
Inventor(s): SUPURAN, C. - SCOZZAFAVA, A. - **PASTOREKOVA, Silvia** - **PASTOREK, Jaromir,** Official Gazette of the United States Patent and Trademark Office Patents
Date Granted: January 14, 2014
Accession Number:BCI:BCI201400214504 ISSN:0098-1133

MN/CA IX-specific monoclonal antibodies generated from MN/CA IX-deficient mice and methods of use
EU Patent Number: EP 1487972 B1
Patent Assignee: Institute of Virology Slovak Academy of Sciences
Inventors: **PASTOREK, Jaromír** - **PASTOREKOVA, Silvia** - **ZATOVICOVA, Miriam** - ZAVADA, J. - GUT, M.O. – ZAVADOVA, Z.
Publication date: August 12, 2015

MN/CA IX-specific monoclonal antibodies generated from MN/CA IX-deficient mice and methods of use
US Patent Application Number: 20150266971
Patent Assignee: Institute of Virology Slovak Academy of Sciences
Inventors: **PASTOREK, Jaromír** - **PASTOREKOVA, Silvia** - **ZATOVICOVA, Miriam** - ZAVADA, J. - GUT, M.O. – ZAVADOVA, Z.
Publication date: September 24, 2015

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

None during the evaluation period.

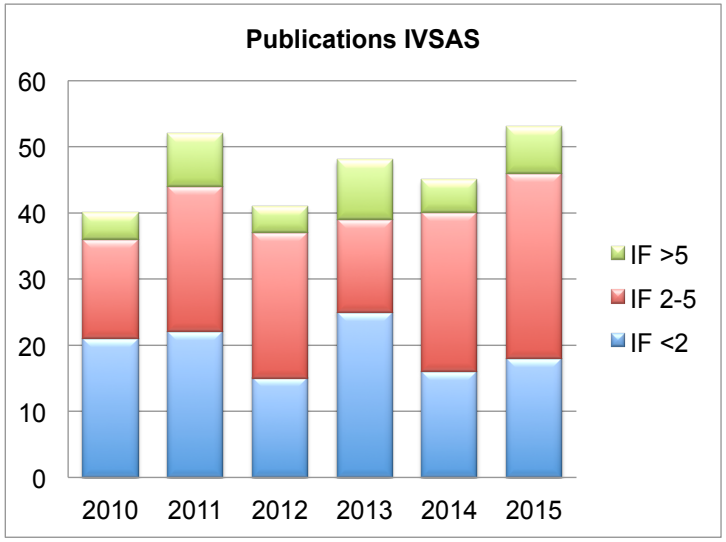
2.1.8. Table of research outputs (as in annual reports).

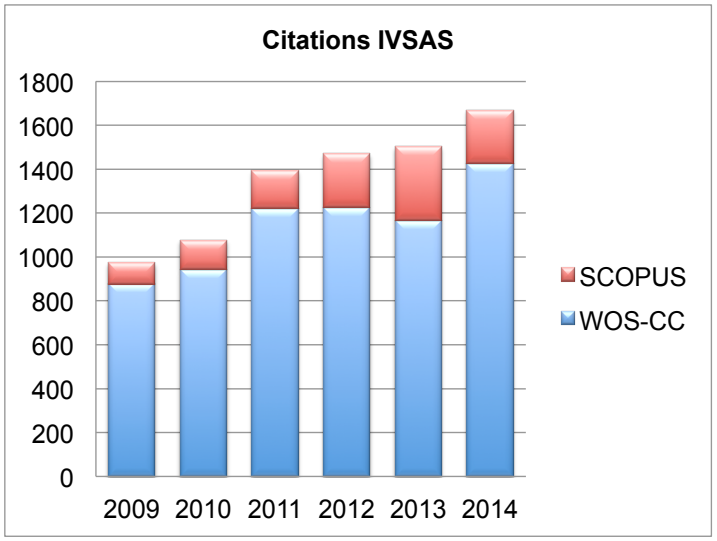
Papers from international collaborations in large-scale scientific projects (Dwarf team, ALICE Collaboration, ATLAS collaboration, CD Collaboration, H1 Collaboration, HADES Collaboration, and STAR Collaboration) have to be listed separately.

Scientific publications	2012			2013			2014			2015			total			
	number	No. / FTE	No. / salary budget	number	No. / FTE	No. / salary budget	number	No. / FTE	No. / salary budget	number	No. / FTE	No. / salary budget	number	averaged number per year	av. No. / FTE	av. No. / salary budget
Scientific monographs and monographic studies in journals and proceedings published abroad *(AAA, ABA)*	0.0	0.000	0.000	0.0	0.000	0.000	0.0	0.000	0.000	0.0	0.000	0.000	**0.0**	**0.0**	**0.000**	**0.000**
Scientific monographs and monographic studies in journals and proceedings published in Slovakia *(AAB, ABB)*	1.0	0.014	0.001	0.0	0.000	0.000	0.0	0.000	0.000	0.0	0.000	0.000	**1.0**	**0.3**	**0.042**	**0.000**
Chapters in scientific monographs published abroad *(ABC)*	5.0	0.070	0.005	2.0	0.028	0.002	3.0	0.040	0.003	1.0	0.014	0.001	**11.0**	**2.8**	**0.038**	**0.003**
Chapters in scientific monographs published in Slovakia *(ABD)*	3.0	0.042	0.003	0.0	0.000	0.000	0.0	0.000	0.000	0.0	0.000	0.000	**3.0**	**0.8**	**0.010**	**0.001**
Scientific papers published in journals registered in Current Contents Connect *(ADCA, ADCB, ADDA, ADDB)*	37.0	0.516	0.038	52.0	0.734	0.056	33.0	0.444	0.036	42.0	0.582	0.044	**164.0**	**41.0**	**0.567**	**0.043**
Scientific papers published in journals registered in Web of Science Core Collection and SCOPUS *(ADMA, ADMB, ADNA, ADNB)*	5.0	0.070	0.005	5.0	0.098	0.005	10.0	0.134	0.011	11.0	0.152	0.011	**31.0**	**7.8**	**0.107**	**0.008**
Scientific papers published in other foreign journals (not listed above) *(ADEA, ADEB)*	0.0	0.000	0.000	3.0	0.042	0.003	1.0	0.013	0.001	1.0	0.014	0.001	**5.0**	**1.3**	**0.017**	**0.001**
Scientific papers published in other domestic journals (not listed above) *(ADFA, ADFB)*	0.0	0.000	0.000	0.0	0.000	0.000	0.0	0.000	0.000	2.0	0.028	0.002	**2.0**	**0.5**	**0.007**	**0.001**
Scientific papers published in foreign peer-reviewed proceedings *(AEC, AECA)*	0.0	0.000	0.000	0.0	0.000	0.000	0.0	0.000	0.000	1.0	0.014	0.001	**1.0**	**0.3**	**0.003**	**0.000**
Scientific papers published in domestic peer-reviewed proceedings *(AED, AEDA)*	18.0	0.251	0.019	21.0	0.297	0.023	19.0	0.256	0.020	26.0	0.360	0.027	**84.0**	**21.0**	**0.291**	**0.022**
Published papers (full text) from foreign and international scientific conferences *(AFA, AFC, AFBA, AFDA)*	1.0	0.014	0.001	0.0	0.000	0.000	1.0	0.013	0.001	1.0	0.014	0.001	**3.0**	**0.8**	**0.010**	**0.001**
Published papers (full text) from domestic scientific conferences *(AFB, AFD, AFBB, AFDB)*	5.0	0.070	0.005	9.0	0.127	0.010	8.0	0.108	0.009	1.0	0.014	0.001	**23.0**	**5.8**	**0.109**	**0.006**

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

The publication strategy of the Institute of Virology SAS is primarily aimed on improving the quality of papers (as judged according to the impact factor upon submission and retrospectively based on the citation output) rather than on their numbers. This is visible throughout the evaluation period in relatively stable yearly numbers of published papers as well as in the trend of publishing in journals possessing higher impact factors. The increase is visible also in the numbers of citations. Two years preceding the evaluation period are included in order to better follow the overall tendency in the scientific outputs of the IVSAS. The graph is based merely on papers published in journals with impact factor.





In 2015, the median impact factor of the IVSAS papers was 2.973, which was slightly above the median IF for the research fields of Virology (2.595) and Oncology (2.827), according to the Essential Science Indicators on July 1st, 2016.

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)	1221.0	17.013	1225.0	17.300	1165.0	15.669	1424.0	19.731	5035.0	1258.8	17.416
Citations in SCOPUS (1.2, 2.2) if not listed above	172.0	2.397	241.0	3.403	338.0	4.546	245.0	3.395	996.0	249.0	3.445
Citations in other citation indexes and databases (not listed above) (3.2,4.2,9,10)	2.0	0.028	1.0	1.175	1.0	0.296	1.0	0.014	5.0	1.3	0.017
Other citations (not listed above) (3, 4, 3.1, 4.1)	56.0	0.780	59.0	1.161	21.0	0.282	45.0	0.624	181.0	45.3	0.626
Reviews (5,6)	0.0	0.000	1.0	0.014	0.0	0.000	0.0	0.000	1.0	0.3	0.003

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

In order to present our genuine research outputs, this selection contains the papers principally generated at the Institute of Virology SAS, without or with contributions of the foreign collaborators. The highly cited papers produced abroad with the contribution of our researchers are included in the Supplementary information below on page 33.

Citation numbers are devoid of self-citations by any of the co-authors.

ŠVASTOVÁ, Eliška - **HULÍKOVÁ, Alžbeta** - **RAFAJOVÁ, Monika** - **ZAŤOVIČOVÁ, Miriam** - **GIBADULINOVÁ, Adriana** - CASINI, A. - CECCHI, A. - SCOZZAFAVA, A. - SUPURAN, C.T. - **PASTOREK, Jaromír** - **PASTOREKOVÁ, Silvia**. Hypoxia activates the capacity of tumor - associated carbonic anhydrase IX to acidify extracellular pH. In *FEBS Letters : Federation of European Biochemical Societies Letters for the Rapid Publication of Short Reports in Biochemistry, Biophysics and Molecular Biology*. - Amsterdam: Elsevier Science Publishers, 2004, vol. 577, no. 3, p. 439-445. (3.609 - IF2003). ISSN 0014-5793.
72 citations

PASTOREKOVÁ, Silvia - PARKKILA, S. - **PASTOREK, Jaromír** - SUPURAN, C.T. Carbonic anhydrases: Current state of the art, therapeutic applications and future prospects. In *Journal of Enzyme Inhibition and Medicinal Chemistry*, 2004, vol. 19, no. 3, p. 199 - 229. (0.775 - IF2003). (2004 - Current Contents).
69 citations

PASTOREK, Jaromír - **PASTOREKOVÁ, Silvia** - CALLEBAUT, I. - MORNON, J.P. - **ZELNÍK, Vladimír** - **OPAVSKÝ, René** - **ZAŤOVIČOVÁ, Miriam** - LIAO, S. - PORTETELLE, D. - STANBRIDGE, E.J. - **ZÁVADA, Jan** - BURNY, A. - KETTMAN, R. Cloning and characterization of MN a human tumor-associated protein with a domain homologous to carbonic anhydrase and a puttative helix-loop-helix DNA binding segment. In *Oncogene*, 1994, vol. 9, no. 10, p. 2877 - 2888. (6.991 - IF1993). ISSN 0950-9232.
52 citations

LABUDA, Milan - TRIMNELL, A.R. - **LIČKOVÁ, Martina** - KAZIMÍROVÁ, M. - DAVIES, G.M. - LISSINA, O. - HAILS, R. - NUTTALL, P.A. An antivector vaccine protects against a lethal vector-borne pathogen. In *PLoS Pathogens*, 2006, vol. 2, no. 4, p. 251 - 259. (9.079 - IF2005). ISSN 1553-7366
37 citations

PASTOREKOVÁ, Silvia - **ZAŤOVIČOVÁ, Miriam** - **PASTOREK, Jaromír**. Cancer-Associated Carbonic Anhydrases and Their Inhibition. In Current Pharmaceutical Design, 2008, vol. 14, p. 685 - 698. (4.868 - IF2007). (2008 - Current Contents). ISSN 1381-6128.
35 citations

STANEKOVÁ, Zuzana - **VAREČKOVÁ, Eva**. Conserved epitopes of influenza A virus as candidates for preparation of universal vaccine. In *Virology Journal*, 2010, vol. 7, no. 1, p. 351. (2.435 - IF2009). (2010 - Current Contents). ISSN 1743-422X.
34 citations

GLASA, Miroslav - PALKOVICS, L. - KOMÍNEK, P. - LABONNE, G. - PITTNEROVÁ, S. - **KÚDELA, Otakar** - CANDRESSE, Thierry - **ŠUBR, Zdeno W.** Geographically and temporally distant natural recombinant isolated of plum pox virus /PPV/ are genetically very similar and form a unique PPV subgroup. In *Journal of General Virology*. - Society for General Microbiology, 2004, vol. 85, p. 2671-2681. (3.036 - IF2003). (2004 - Current Contents). ISSN 0022-1317.
26 citations

KLEMPA, Boris. Hantaviruses and climate change. In Clinical Microbiology and Infection, 2009, vol. 15, no. 6, p. 518 - 523. (3.554 - IF2008). ISSN 1198-743X.
25 citations

KALUZ, Štefan - **KALUZOVÁ, Milota** - **CHRASTINA, Adrian** - OLIVE, P.L. - **PASTOREKOVÁ, Silvia** - **PASTOREK, Jaromír** - LERMAN, M.I. - STANBRIDGE, E.J. Lowered oxygen tension induces expression of the hypoxia marker MN/carbonic anhydrase IX in the absence of hypoxia-inducible factor 1 alpha stabilization: a role for phosphatidylinositol 3-kinase. In *Cancer Research*, 2002, vol. 62, no. 15, p. 4469-4477. (8.302 - IF2001). (2002 - Current Contents). ISSN 0008-5472.
22 citations

IHNATKO, Róbert - **KUBEŠ, Miroslav** - **TAKÁČOVÁ, Martina** - **SEDLÁKOVÁ, Oľga** - SEDLÁK, J. - **PASTOREK, Jaromír** - **KOPÁČEK, Juraj** - **PASTOREKOVÁ, Silvia**. Extracellular acidosis elevates carbonic anhydrase IX in human glioblastoma cells via transcriptional modulation that does not depend on hypoxia. In *International Journal of Oncology*, 2006, vol. 29, no. 4, p. 1025 - 1033. (2.571 - IF2005). (2006 - Current Contents). ISSN 1019-6439.
21 citations

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

	Name	Times cited (2011-2014)	Total No. of citations	H-index
1	Jaromír Pastorek	**1942**	7891	47
2	Silvia Pastoreková	**1655**	6059	44
3	Boris Klempa	**501**	1188	21
4	Miriam Zaťovičová	**333**	999	15
5	Miroslav Glasa	**254**	572	15
6	Adriana Gibadulinová	**232**	837	12
7	Juraj Kopáček	**229**	932	17

The table contains net citation numbers related to the 2011-2014 period without all co-authors' self-citations. Total number of citations and H-index correspond to data from the Web of Science Core Collection on June 1st, 2016.

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

Here we list the selected papers (including their citation numbers in the evaluation period of 2011-2014), to which researchers of the Institute of Virology contributed in the frame of the international projects or through other types of collaboration.
Citation numbers are devoid of self-citations by any of the co-authors.

WYKOFF, C.C. - BEASLEY, N.J. - WATSON, P.H. - CAMPO, L. - CHIA, S.K. - ENGLISH, R. - **PASTOREK, Jaromír** - SLY, W.S. - RATCLIFFE, P. - HARRIS, A.L. Hypoxia-inducible Expression of Tumor-associated Carbonic -Anhydrases. In *Cancer Research* - Birmingham : Amer.Assoc.Cancer Research, 2000, vol. 60, p. 7075-7083. (8.614 - IF1999). (2000 - Current Contents). ISSN 0008-5472.
194 citations

LONCASTER, J.A. - HARRIS, A.L. - DAVIDSON, S.E. - LOGUE, J.P. - HUNTER, R.D. - WYKOFF, C.C. - **PASTOREK, Jaromír** - RATCLIFFE, P.J. - STRATFORD, I.J. - WEST, C.M. Carbonic anhydrase /CA IX/ expression, a potential new intrinsic marker of hypoxia: correlations with tumor oxygen measurements and prognosis in locally advanced carcinoma of the cervix. In *Cancer Research*. - Birmingham : Amer.Assoc.Cancer Research, 2001, vol. 61, p. 6394-6399. (8.460 - IF2000). (2001 - Current Contents). ISSN 0008-5472.
74 citations

CHIA, S.K. - WYKOFF, C.C. - WATSON, P.H. - LEEK, R. - TURLEY, H. - **PASTOREK, Jaromír** - COX, G.J. - RATCLIFFE, P.J. - HARRIS, A.L. Prognostic significance of a novel hypoxia-regulated marker, carbonic anhydrase IX, in invasive breast carcinoma. In *Journal of Clinical Oncology*, 2001, vol.19, p. 3660-3668. (8.773 - IF2000). (2001 - Current Contents).
70 citations

WEISS, S. - WITKOWSKI, P.T. - AUSTE, B. - NOWAK, K. - WEBER, N. - FAHR, J. - MOMBOULI, J.V. - WOLFE, N.D. - DREXLER, J.F. - DROSTEN, C. - **KLEMPA, Boris** - LEENDERTZ, F.H. - KRUGER, D.H. Hantavirus in Bat, Sierra Leone. In *Emerging Infectious Diseases*, 2012, vol. 18, no. 1, p. 159-161. (6.169 - IF2011). (2012 - Current Contents). ISSN 1080-6040
43 citations

GLAZUNOVA, O. - ROUX, V. - FREYLIKMAN, O. - **SEKEYOVÁ, Zuzana** - FOURNOUS, G. - TYCZKA, J. - TOKAREVICH, N.S. - **KOVÁČOVÁ, Elena** - MARIE, T.J. - RAOULT, D. Coxiella burnetii genotyping. In *Emerging Infectious Diseases*, 2005, vol.11, p. 1211-1217. (5.634 - IF2004). (2005 - Current Contents). ISSN 1080-6040.
42 citations

KNÍŽETOVÁ, P. - EHRMANN, J. - HLOBILKOVA, A. - **VANČOVÁ, Iveta** - KALITA, O. - KOLAR, Z. - BARTEK, J. Autocrine regulation of glioblastoma cell cycle progression, viability and radioresistence through the VEGF-VEGFR2 (KDR) interplay. In *Cell Cycle*, 2008, vol. 7, no. 16, p. 2553-2561. (3.314 - IF2007). (2008 - Current Contents). ISSN 1538-4101.
41 citations

ALTERIO, V. - HILVO, M. - DI FIORE, A. - PAN, P. - PARKKILA, S. - SCALONI, A. - **PASTOREK, Jaromír** - **PASTOREKOVÁ, Silvia** - PEDONE, C. - SCOZZAFAVA, A. - MONTI, S.M. - DE SIMONE, G. Crystal structure of the catalytic domain of the tumor-associated human carbonic anhydrase IX. In Proceedings of the National Academy of Sciences of the United States of America, 2009, vol. 106, no. 38, p. 16233 - 16238. (9.380 - IF2008). (2009 - Current Contents). ISSN 0027-8424
38 citations

As of January/February 2016, this **highly cited paper** received enough citations to place it in the top 1% of its academic field based on a highly cited threshold for the field and publication year. *Data from Essential Science Indicators on July 1st, 2016.*

LABUDA, Milan - TRIMNELL, A.R. - **LIČKOVÁ, Martina** - KAZIMÍROVÁ, M. - DAVIES, G.M. - LISSINA, O. - HAILS, R. - NUTTALL, Patricia A. An antivector vaccine protects against a lethal vector-borne pathogen. In PLoS Pathogens, 2006, vol. 2, no. 4, p. 251 - 259. (9.079 - IF2005). ISSN 1553-7366
37 citations

GLASA, Miroslav - PALKOVICS, L. - KOMÍNEK, P. - LABONNE, G. - PITTNEROVÁ, S. - **KÚDELA, Otakar** - CANDRESSE, T. - **ŠUBR, Zdeno W**. Geographically and temporally distant natural recombinant isolated of plum pox virus /PPV/ are genetically very similar and form a unique PPV subgroup. In *Journal of General Virology*. - Society for General Microbiology, 2004, vol. 85, p. 2671-2681. (3.036 - IF2003). (2004 - Current Contents). ISSN 0022-1317.
26 citations

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

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

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

Major international activities of the Institute of Virology SAS have been connected with the participation of its leading researchers in large European consortia of the 7th Framework Program and Horizon 2020.

FP7-INFRASTRUCTURES-228292 (01/2009-03/2015)
European Virus Archive
H2020-INFRAIA-653316 (04/2015-03/2019)
European Virus Archive Goes Global
http://www.european-virus-archive.com/

EVA FP7 project created a European network of high caliber centers with the appropriate expertise to collect, amplify, characterize, standardize, authenticate, distribute and track, mammalian and other exotic viruses. This EVA network was very successful and later expanded to global dimensions counting now 26 institutions. **EVAg** is the first and currently the only 21st century global virus collection conceived as a modern and innovative support organization for scientific research, education and disease control through human and veterinary health programmes. The project objectives meet the needs of scientists, worldwide, by generating a carefully authenticated animal virus collection that is larger than any existing repository, and readily available to all laboratories that meet approved ethical, safety and security standards. EVAg develops a huge number of innovation end points particularly from joint research activities that enhance virus diagnostics and promote the prospects of creating antiviral approaches. The participation in European Network for Diagnostics of "Imported" Viral Diseases and WHO Global Outbrake Allert and Response Network relates EVAg to the international public health laboratory community during outbreaks and in times when novel diagnostic recommendations are being issued because of (re-) emergence of viruses.
The IVSAS group led by Boris Klempa, DSc., contributes to the archive by its historical collection of arboviruses (arthropode-borne viruses). Besides maintenance, characterisation, and distribution of a variety of tick-, mosquito-, and rodent-borne viruses, IVSAS is involved in the joint-research activities, particularly in the fields of viral animal models and novel virus production techniques. Dr. Klempa is also leading the expert group focused on viruses of the family Bunyaviridae.

FP7-HEALTH-INNOVATION-602272
(12/2013-01/2018)
Anti-tick Vaccines to Prevent Tick-borne Diseases in Europe
http://www.antidote-fp7.org/tick-borne-diseases.html

Ixodes ricinus transmits bacterial, protozoal and viral pathogens that cause Lyme borreliosis, babesiosis and tick-borne encephalitis respectively and exceedingly affect Central and Eastern Europe (CEE). During feeding, ticks introduce salivary proteins in the skin that interfere with host defence mechanisms. However, in some animal species, repeated tick infestations as well as vaccination against selected tick proteins can lead to decreased pathogen transmission by inhibiting tick feeding, known as 'tick immunity', or by neutralizing tick proteins that facilitate the transmission of tick-borne pathogens (TBPs). Also humans that are hypersensitive to tick-bites have a lower risk of contracting tick-borne diseases (TBDs). Therefore, anti-tick vaccines encompass an innovative strategy to prevent TBDs in humans, or animals and wildlife to

indirectly reduce the risk of contracting TBDs for humans. Overall objective of the project consortium of 7 partners is to identify and characterize tick proteins involved in 'tick immunity' and TBP transmission and to use this knowledge to develop anti-tick vaccines to prevent multiple human TBDs.
As the main task within the **ANTIDotE** project, the IVSAS group led by Boris Klempa, DSc, is performing mouse experiments with tick borne encephalitis virus (TBEV) transmitted by tick-bite of experimentally infected ticks to test newly identified anti-tick vaccines.

FP7-KBBE-204429
Containment of Sharka virus in view of EU-expansion
(03/2008-08/2012)
https://www.sharco.eu/

The sharka disease is a worldwide serious problem with a severe impact on the productivity and fruit quality of Prunus species. It is caused by Plum pox virus (PPV), a virus against which no chemical or biological curative treatment is available. The current short-term solution is the eradication of infected trees and the plantation of virus-free material. The **SharCo** project was aimed at providing the EU with tools such as marker-assisted selection to speed up the production of PPV-resistant plant materials, guidelines, early warning systems and decision-support system in order to anticipate further PPV outbreaks. The SharCo consortium consisted of 17 partners from 13 countries. The IVSAS group of Miroslav Glasa, PhD. participated in the sequence analysis of the worldwide collected samples, which led to discovery and/or detailed characterization of several PPV strains (*Glasa et al., Phytopathol, 2013*). Thorough mapping of PPV incidence in Slovakia confirmed the spread of three major strains in this area (PPV-D, PPV-Rec and PPV-M) and their preferential appearance in particular host species (*Šubr and Glasa, Acta Virol, 2013*). Genetic diversity of PPV on a single infected tree was evaluated (*Predajňa et al., Virus Res, 2012*). An infectious cDNA clone of PPV-Rec was prepared (*Predajňa et al., Acta Virol, 2012*), simple biolistic transfection of plants was optimized and applied to mapping pathogenic determinants in the PPV genome (*Nagyová et al., Virus Genes, 2012*).

FP7-HEALTH-222741
Metastatic tumours facilitated by hypoxic tumour micro-environments
(02/2009-07/2014)
https://www.metoxia.uio.no/

METOXIA was a five-year research project with 22 partner institutions in 11 EU countries that involved a broad range of expertise, from major cancer clinics, to expert fundamental researchers within biology, chemistry, medicine, physics and electro-engineering. The project was based on the evidence that solid cancers generally contain areas with abnormally low levels of oxygen (denoted as hypoxic) and that the hypoxic microenvironment of tumors is one of the major drivers of metastatic spread of cancer and therapy resistance. Metoxia project was aimed at elucidation the roles and functions of the hypoxic tumor microenvironment in relation to the survival of solid tumors likely to metastasize. The consortium gained new knowledge about molecular mechanisms behind hypoxia-driven metastasis, like the epithelial-mesenchymal transition (EMT) by several routes: (a): mechanisms related to cell growth- and cell proliferation (UPR, mTOR, CA9, HIF, Notch, and VHL), (b): angiogenesis and lymphangiogenesis, (c): metabolism and pH-regulation (d): the handling of reactive oxygen species (ROS). New animal models for the study of the role of hypoxia in metastases were generated, and advanced imaging techniques and biomarkers were identified and developed. The consortium performed proof-of-principle clinical testing of new treatment strategies.
The task of the IVSAS group led by prof. Silvia Pastorekova, DSc., was to investigate the expression, regulation, function and clinical usefulness of CA IX as a key biomarker of hypoxia and acidosis in tumor microenvironment, and provide unique CA IX-related reagents to the other consortium partners. The main contribution of the group was in elucidation of the CA IX role in pH regulation and in cell adhesion-migration-invasion and in understanding of

mechanisms of antibody- and inhibitor-based anticancer strategies targeted to CA IX *(Svastova et al, J Biol Chem, 2012; Csaderova et al, Front Physiol, 2013, Radvak et al, In J Oncol, 2013, Ditte et al, BM Cancer, 2014, Takacova et al, Am J Pathol, 2014, etc.)*

BMBS COST Action TD0901
Hypoxia sensing, signalling and adaptation
(11/2009-11/2013)
http://hypoxianet.com

This COST action allowed for the establishment of the **HypoxiaNet**, an international network of researchers who's work is focussed on developing our understanding of the mechanisms underpinning the cell, tissue and organism response to decreased oxygen levels. Because of the importance of hypoxia in a range of physiologic and pathophysiologic conditions, investigating the potential for targeting these pathways for therapeutic manipulation is also a key objective of the network. HypoxiaNet plays a key role in the organisation of international conferences, which brings the hypoxia research community together to exchange information, ideas and reagents. HypoxiaNet goes beyond the COST action and still continues to organize conferences and other activities for the hypoxia research community. The IVSAS group, represented by prof. Silvia Pastorekova, DSc. (a member of the Management Committee a leader of the Pharmacology Workgroup) contributed to the network by the organization of the first HypoxiaNet conference at the Smolenice castle, Slovakia, in June 2010, by a number of invited lectures, oral and poster contributions to the other HypoxiaNet conferences, and by developing cooperations with other HypoxiaNet members.

FP7-PITN-GA-2010-264417
Biomedical engineering for cancer and brain disease diagnosis and therapy development
(04/2011-08/2015)
http://www.engcabra.eu

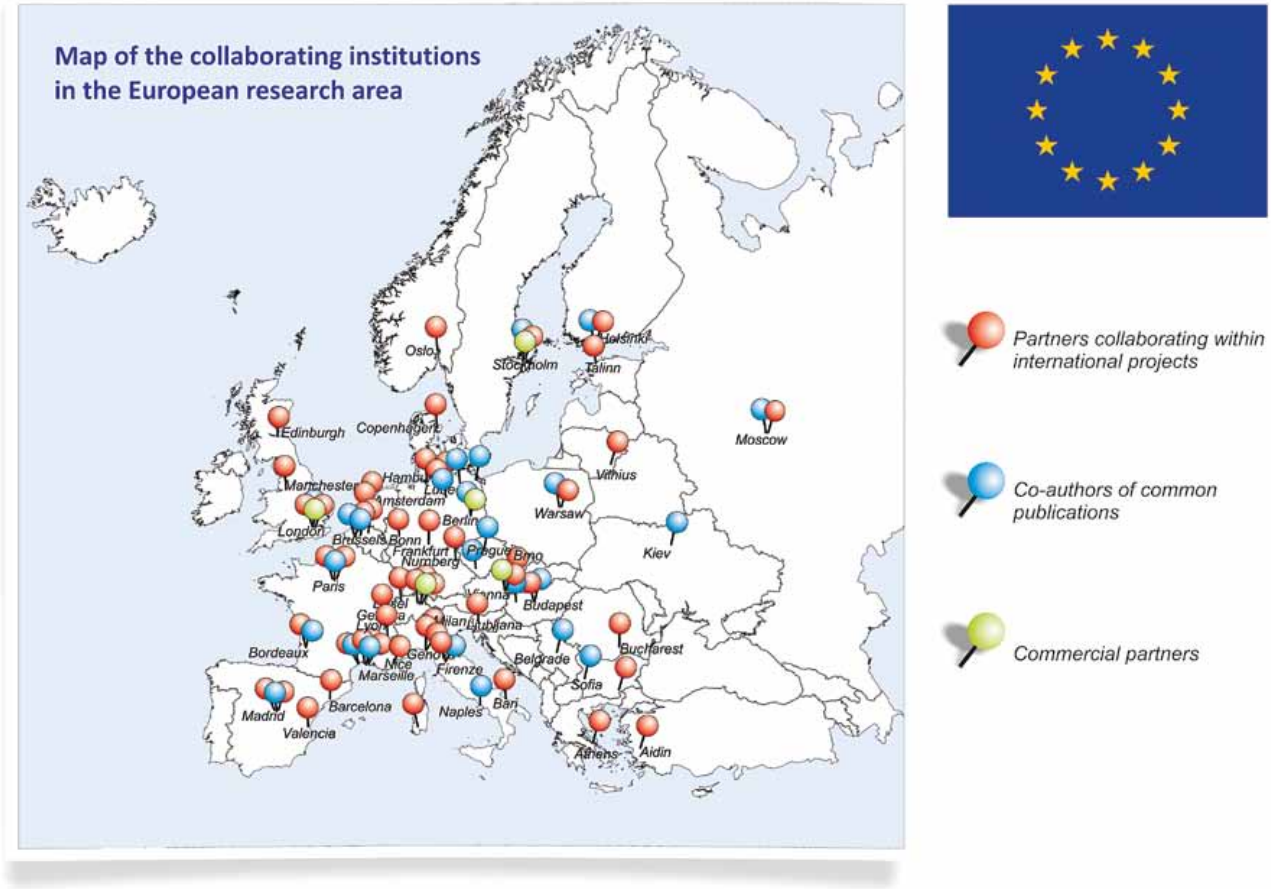
The project was focused on development of novel biosensor and micro/nanochip-based methods and devices for analysis of cellular and molecular mechanisms related to cancer and brain diseases. The main purpose of **EngCaBra** was to conduct training and research in the field of novel bioanalytical methods and tools, which are of great importance for therapy research leading to novel diagnostic and treatment methods. This ITN consortium of 11 partners from 7 countries combined disciplines such as engineering, biotechnology, medicine, and chip-technology and included universities, hospitals and industry. The role of the IVSAS team led by Prof. Silvia Pastorekova, DSc. was to train PhD students and postdocs in biomedical research methods and techniques, provide the other partners models, reagents and expertise in biomedical aspects of their sensor/chip developments, with particular emphasis on tumor hypoxia. This resulted in a number of biological data and technical improvements reported at different technical and biomedical meetings and also in published papers *(Van der Driesch, Sensors and Actuators, 2013, Obacs, Mol Cancer, 2013; Uhlenbrock et al, J Immunol, 2014; Pucciarelli et al, Int J Oncol, 2015; etc.)*

FP7-HEALTH-259751
New drugs targeting influenza virus polymerase
(11/2010-04/2015)
http://flupharm.eu/

The 2009 H1N1 influenza A virus pandemic and the ongoing threat of highly pathogenic H5N1 avian influenza strains have focused attention worldwide on the urgent need for new options of effective anti-influenza drugs, when the public is not protected by vaccination. The need is pressing since several circulating influenza strains are resistant to the currently stockpiled neuraminidase inhibitors. The **FLUPHARM** project exploited recent advances in the detailed elucidation of the structure and function of the viral polymerase to develop new drug candidates that inhibit viral replication (by targeting the PB2 and PA protein domains). Such drugs are

expected to have a reduced risk of resistance development as the viral polymerase in contrast to influenza envelope proteins, is highly conserved among all influenza A strains, and thus could be effective against all influenza A subtypes. The research team of 12 partners from 6 countries included several of the most respected influenza virus research groups working on structure, function, and pathogenesis associated with the viral polymerase, including groups that have generated recent X-ray structures of two functional polymerase domains.
The IVSAS group led by Eva Varečková, DSc., contributed to the project by testing of new designed compounds for *in vitro* and *in vivo* toxicity and antiviral efficacy against influenza A virus. Moreover, several influenza A viruses of different subtypes (including pandemic 2009 virus and Tamiflu-resistant pandemic influenza virus) were adapted to mice and used for development of a lethal pneumonia experimental model. The results obtained by testing of new compounds are to be patented.

In addition to the above-described EU projects, the IVSAS researchers have been involved in other EU projects as well as several bilateral projects and research contracts with foundations and companies (pages 49-50) and have also performed informal collaborative research (see the map below).



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

(1) The International Meeting of the METOXIA Consortium, June 11-15 2012, Bratislava, Slovakia.

(2) The Annual Conference of the Pathobiology Group of the European Organization for the Research and Treatment of Cancer, June 21-24 2012, Smolenice castle, Slovakia.

(3) The International Training course of the EngCaBra consortium: Basics of Cell Biology, September 24-26, 2012, Bratislava, Slovakia.

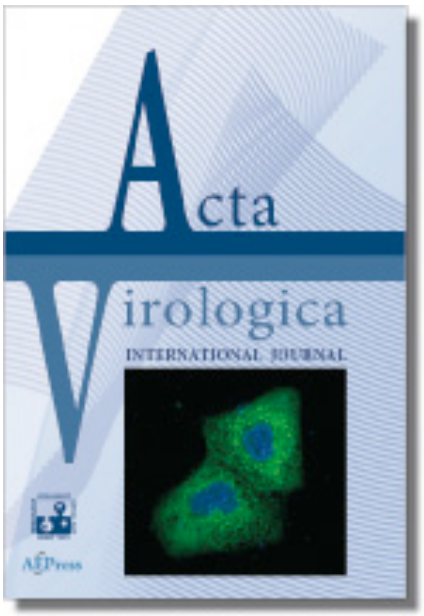
(4) The 1st Meeting of the International Society for Cancer Metabolism and the 5th Meeting of the International Society for Proton Dynamics in Cancer, October 8-11 2014, Smolenice castle, Slovakia. *http://www.iscams.org/meetings*

2.3.3. List of edited proceedings from international scientific conferences.

Book of Abstracts, 1st ISCAM Meeting and 5th ISPDC Meeting on Cancer Metabolism, mechanisms, consequences and therapeutic opportunities, 8-11 October, 2014, Smolenice Castle

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)



Acta virologica is an IVSAS edited international journal publishing papers that report original results of fundamental and applied research mainly on human, animal and plant viruses at cellular and molecular level. As a matter of tradition, also rickettsiae are included. Areas of interest are virus structure and morphology, molecular biology of virus-cell interactions, molecular genetics of viruses, pathogenesis of viral diseases, viral immunology, vaccines, antiviral drugs and viral diagnostics. *http://www.aepress.sk/acta/av.htm*

Chief Editor: **Gustáv RUSS, DSc.**

IF 2011 = 0.682

IF 2012 = 0.759

IF 2013 = 1.037

IF 2014 = 1.280

IF 2015 = 1.222

2.3.4.2. SCOPUS

None during the evaluation period.

2.3.4.3. other databases

None during the evaluation period.

2.3.4.4. not included in databases

None during the evaluation period.

- **National position of the institute**

2.3.5. List of selected projects of national importance

During the evaluation period, the IVSAS national project portfolio was represented by 11 projects supported by the EU Structural Funds, 23 APVV projects, and 50 VEGA projects. Selected projects are listed below and their funding volumes are summarized in the related tables.

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

Below is the selection of the APVV projects coordinated by the principal investigators of the IVSAS (excluding the projects led by the researchers who were transiently delimited to the IVSAS during 2015 and are now at the Institute of Clinical and Translational Research BMC SAS). The projects, in which IVSAS investigators cooperated as partners, are listed below in the Table on page 51.

1. Project title:
Investigation of the Plum-pox virus host preference factors with regard to the natural variability of its population on the territory of the Slovak republic
Project code: APVV-0042-10
Performance period: 05/2011 – 12/2014
Principal investigator: Zdeno Šubr, PhD.

2. Project title:
Prediction of influenza A virus epidemic/pandemic outcome by identifying dominant markers of viral pathogenicity and transmissibility
Project code: APVV-0250-10
Performance period: 05/2011 – 10/2014
Principal investigator: Eva Varečková, DSc.

3. Project title:
Identification of the molecular pathways driven by the hypoxia-induced carbonic anhydrase IX in tumor cells
Project code: APVV-0108-10
Performance period: 05/2011 – 10/2014
Principal investigator: Juraj Kopáček, MVD., DSc.

4. Project title:
Carbonic anhydrase IX as a functional component of cancer progression: the role in epithelial-mesenchymal transition and intercellular signaling
Project code: APVV-0658-11
Performance period: 07/2012 – 12/2015
Principal investigator: Prof. Silvia Pastoreková, DSc.

5. Project title:
Molecular mechanisms of the crosstalk between stress hormones and hypoxia in tumor cells: effect on expression and function of cancer-related protein CA IX
Project code: APVV-0893-11
Performance period: 07/2012 – 12/2015
Principal investigator: Prof. Jaromír Pastorek, DSc., Lucia Csáderová. PhD. (from 2013)

6. Project title:
Biological significance and pharmacological features of bioactive proteins in tick saliva
Project code: APVV-0737-12
Performance period: 10/2013 – 09/2017
Principal investigator: Iveta Štibrániová, PhD.

7. Project title:
Characterization of novel motif in M1 protein of influenza A virus and using NS1 deletion mutants in tumor therapy
Project code: APVV-0676-12
Performance period: 10/2013 – 09/2017
Principal investigator: Tatiana Betáková, PhD.

8. Project title:
Research of diagnostic biomarkers of rickettsiae, Coxiella burnetii and related organisms by the state-of-art immunoproteomic and molecular biologic methods
Project code: APVV-0280-12
Performance period: 10/2013 – 09/2017
Principal investigator: Zuzana Sekeyová, PhD.

9. Project title:
Murine herpesvirus, a producer of substances exhibiting immunomodulatory and antiproliferative properties
Project code: APVV-0621-12
Performance period: 10/2013 – 09/2017
Principal investigator: Marcela Kúdelová, DSc.

10. Project title:
Development of innovative approaches to characterise and control the economically important and emerging virus pathogens of cherry crops in Slovakia
Project code: APVV-0174-12
Performance period: 10/2013 – 09/2017
Principal investigator: Miroslav Glasa, PhD.

11. Project title:
The role of neuropeptides and receptors in regulation of pathogen transfer from ticks to their hosts
Project code: APVV-14-0556
Performance period: 07/2015 – 06/2019
Principal investigator: Eva Špitalská, PhD.

12. Project title:
Immune modulation by cytomegalovirus and its immunotherapeutic potential
Project code: APVV-14-0839
Performance period: 07/2015 – 06/2019
Principal investigator: Ivana Nemčovičová, PhD.

13. Project title:
Elucidation of novel pro-metastatic functions of tumor-associated carbonic anhydrase IX and its cross-talk with pro-inflammatory response
Project code: APVV-14-0816
Performance period: 07/2015 – 06/2019
Principal investigator: Eliška Švastová, PhD.

14. Project title:
Preparation of erythropoietin a therapeutic hormone affecting the production of red blood cells by expression in eukaryotic cell system and its further purification
Project code: APVV-14-0474
Performance period: 07/2015 – 12/2018
Principal investigator: Ľudovít Škultéty, DSc.

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

Here we present the selection of 10 out of 50 VEGA projects, which were implemented during the most part of the evalution period, and which have principal investigators that are not PIs of the other project types. Thereby, we intended to show that the research activities at the IVSAS have a broad range of protagonists.

1. Project title:
Proteomic analysis of cells with modulated expression of calcium-binding protein S100P
Project code: 2/0172/11
Performance period: 01/2011 – 12/2014
Principal investigator: Adriana Gibadulinová, PhD.

2. Project title:
Identification of the cellular proteins affected by persistent infection with lymphocytic choriomeningitis virus
Project code: 2/0128/11
Performance period: 01/2011 – 12/2014
Principal investigator: Jana Tomášková, PhD.

3. Project title:
Molecular determinants of non-viraemic transmission of tick-borne encephalitis between co-feeding ticks
Project code: 2/0191/12
Performance period: 01/2012 – 12/2014
Principal investigator: Sabína Havlíková, PhD.

4. Project title:
Identification of interactions between plant factors and non-structural viral proteins from genus Potyvirus and their use to understand plant natural defense system
Project code: 2/0156/12
Performance period: 01/2012 – 12/2014
Principal investigator: Slavomíra Nováková, PhD.

5. Project title:
Mechanism of Innate Immune responsiveness to Rickettsia akarii and it antibiotic resistance variant
Project code: 2/0193/12
Performance period: 01/2012 – 12/2015
Principal investigator: Marco Quevedo-Diaz, PhD.

6. Project title:
Study of induced reactivation of human oncogenic herpesviruses using the model of mice latently infected with the mouse herpesvirus
Project code: 2/0185/12
Performance period: 01/2012 – 12/2015
Principal investigator: Ingeborg Režuchová, PhD.

7. Project title:
Regulation of carbonic anhydrase IX shedding and biological role of the shed ectodomain in tumor cell-cell interactions
Project code: 2/0134/12
Performance period: 01/2012 – 12/2015
Principal investigator: Miriam Zaťovičová, PhD.

8. Project title:
Elucidation of the mechanisms of persistent infection and spread of the lymphocytic choriomeningitis virus
Project code: 2/0146/12
Performance period: 01/2012 – 12/2015
Principal investigator: Martina Labudová, PhD.

9. Project title:
Structural and functional studies of conservative proteins of influenza viruses in host's environment
Project code: 2/0100/13
Performance period: 01/2013 – 12/2016
Principal investigator: František Kostolanský, PhD.

10. Project title:
Modulation of immunogenicity of HA2 immunogen as potential candidate for preparation of cross-protective influenza vaccine
Project code: 2/0153/14
Performance period: 01/2014 – 12/2017
Principal investigator: Zuzana Staneková, PhD.

2.3.8. Projects of SAS Centres of Excellence

Center of excellence for the study of metabolic aspects of development, diagnostics and treatment of cancer diseases
Period: 07/2011 – 12/2014
Project coordinator: Assoc. Prof. Olga Krizanova, DSc., Intitute of Molecular Physiology and Genetics SAS
Principal investigator at IVSAS: prof. Silvia Pastoreková, DSc.

2.3.9. National projects supported by EU Structural Funds

1. Project title:
Center of Excellence for the Translational Research in Molecular Medicine
Project code: ITMS 26240220030
Performance period: 06/2010 – 05/2012
Project coordinator: Juraj Kopáček, MVD., DSc.

2. Project title:
Center for Innovative Research of Antitumor and Antiviral Strategies
Project code: ITMS 26240220062
Performance period: 05/2011 – 04/2014
Project coordinator: Juraj Kopáček, MVD., DSc.

3. Project title
Development of biopharmaceuticals by modern biotechnologies
Project code: ITMS 26240220045
Performance period: 01/2011 – 12/2013
Coordinator: Ľudovít Škultéty, DSc.

4. Project title:
Industrial research in clinical diagnostics of infectious pathogens
Project code: ITMS 26240220032
Performance period: 05/2010 – 05/2014
Cordinator: Mgr. Peter Kilián, PhD.
PI at IVSAS: Juraj Kopáček, MVD., DSc

5. Project title
Improvement of the Centre of Excellence for the Use of Informational Biomacromolecules in Prevention of Diseases and for Improvement of the Quality of Life
Project code: ITMS 26240120027
Performance period: 06/2010 – 04/2012
Coordinator: Prof. Marta Kollárová, D.Sc., Faculty of Natural Sciences, Comenius University in Bratislava
PI at IVSAS: Juraj Kopáček, MVD., DSc.

6. Project title:
Development of Diagnostic Methods for Detection of Pathogens Transmitted by Ticks and Methods for Preparation of Vaccines against Ticks
Project code: ITMS 26240220044
Performance period: 11/2010 – 10/2013
Coordinator: Dušan Žitňan, DSc., Institute of Zoology, SAS
PI at IVSAS: Boris Klempa, DSc.

7. Project title
Diagnoses of Socially Important Diseases in Slovakia Based on Modern Biotechnologies
Project code: ITMS 26240220058
Performance period: 11/2010 – 10/2013
Coordinator: Assoc. Prof. Ľudevít Kádaši, DSc., Institute of Molecular Physiology and Genetics SAS
PI at IVSAS: Marcela Kúdelová, DSc.

8. Project title:
Development of a Competence Center for the Research and Development in Molecular Medicine
Project title: ITMS 26240220071
Performance period: 10/2011 – 01/2015
Coordinator: Prof. Ján Turňa, PhD., Faculty of Natural Sciences, Comenius University in Bratislava
PI at IVSAS: Juraj Kopáček, MVD., DSc.

9. Project title
Research of oncogenic miR-155 program for diagnostic and prognostic purposes in cancer
Project code: ITMS 26240220074
Performance period: 05/2012 – 10/2014
Coordinator: Dana Jurkovičová, PhD., KRD Technologies, a.s.
PI at IVSAS: Adriana Gibadulinová, PhD.

10. Project title
Centre for the research and development of immunologically active substances
Project code: ITMS 26220220188
Performance period: 03/2014 – 09/2015
Coordinator: Prof. Jaromír Pastorek, DSc., Slovak Academy of Sciences, Bratislava
PI at IVSAS: Juraj Kopáček, MVD, DSc.

11. Project title
University Research Park for Biomedicine in Bratislava
Project code: ITMS 26240220087
Performance period: 09/2013 – 12/2015
Coordinator: Prof. Jaromír Pastorek, DSc., Slovak Academy of Sciences, Bratislava
PI at IVSAS: Vladimiír Zelník, PhD.

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)

None.

2.3.10.2. SCOPUS

None.

2.3.10.3. Other databases

None.

2.3.10.4. Not included in databases

None.

• 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

KLEMPA Boris. Complex of phenotypes and their characteristics. IX.International conference on HFRS, HPS and Hantaviruses, Beijing, Chine June, 2013.

KLEMPA Boris. Molecular evolution and epidemiology of hantaviruses. “Epidemiology and Evolution of Emerging Viruses in Africa”. Lecture Course. Cape Town. South Africa. March 2013.

KLEMPA Boris. Hantaviruses as globally emerging pathogens. In: Symposium on Highly pathogenic agents: “Medical importance and safety issues in Tanzania”. Mbeya. Tansania. 15-16 April 2014.

KLEMPA Boris. Apodemus-borne hantaviruses in Europe: Complex evolution and epidemiology of Dobrava-Belgrade virus. In 14th Rodens et Spatium International Conference on Rodent Biology, Lisboa, Portugal, 2014.

KLEMPA Boris. Hantaviruses got wings. In: German-AfricanWorkshop : “New viruses in bats” within the framework of the “ German-African Collaboration in Infectiology”. Programm of Deutscge Forschungsgemeinschaft (DFG). Skukuza, Kruger National Park. South Africa> Rober Koch Institut/Institut fur Virologie, 2015. Session VI: Expert talks and overview lectures.

KOPÁČEK Juraj. Hypoxia-induced carbonic anhydrase IX as an important component of tumor progression. Institute of Enzyme research, The Tokushima University. Lecture Course. Tokushima, Japan. 5th-9th September 2014.

KÚDELA Otakar. Prevalence of viral and microbial fytopathogens in Slovakia and the influence on quality and safety of plant-derived food. Meeting of the Czech Ministry of agriculture: View accorss the borders on care for heatlhy plants as a prerequisite for safe food. Dolní Dunajovice, April 2012.

NEMČOVIČOVÁ Ivana. HCMV encoding gpUL141 uses specific lock-and-key mechanism to inhibit NK-cell activating ligand CD155. In 5th RECAMO joint meeting: Through cancer research towards applied molecular oncology. Brno 2014.

NEMČOVIČOVÁ Ivana. Advanced methods in macromolecular crystallization VI. In: 1st FEBS-INSTRUCT practical crystallization course in the middle EU (the 6th run of the FEBS practical course). Nové Hrady, June 2014.

PASTOREK Jaromír. Molecular Mechanisms Regulating Expression and Function of Cancer-associated Carbonic Anhydrase IX. In BITs 6th Annual World Cancer Congress (WCC-2013), XI an, China, 2013.

PASTOREK Jaromír. Regulation of the CA IX function by phosphorylation in response to physiological stimuli. In The 9th International Conference on Carbonic Anhydrase. Antalya, Turkey, April 2012.

PASTOREKOVÁ Silvia. Acetazolamide - more than carbonic anhydrase inhibitor. In The 9th International Conference on Carbonic Anhydrase (CA): Antalya, April 2012.

PASTOREKOVÁ Silvia. Carbonic anhydrase IX: Regulation and role in cancer development. In Metabolism and Cancer Progression, 18th Cancer Symposium of Danish Cancer Society - Copenhagen, September 2012.

PASTOREKOVÁ Silvia. CA IX as a hypoxia-directed actor in tumor biology: to be or not to be acidic. In Oxygen 2013, EU COST Action TD0901: Dealing with hypoxia: Regulatory aspects in cells, tissues and organisms. Oulu, Finland, May 2013.

PASTOREKOVÁ Silvia. CA IX role in pH regulation and signaling in cancer – a subcellular context-related view. 4th Annual Meeting of the ISPDC, Munich, October 2013.

PASTOREKOVÁ Silvia. Hypoxia-induced carbonic anhydrase IX as a clinically exploitable component of tumour progression. 7th Conference on Experimental and Translational Oncology. Portorož, 2013.

PASTOREKOVÁ Silvia. Tumor cell adaptations to hypoxia and acidosis. The 6th International Summer School: Modern Approaches to Research and Treatment of Cancer, Piran, April 2013.

PASTOREKOVÁ Silvia. Hypoxia-induced phosphorylation of carbonic anhydrase IX and its impact on pH regulation and cell migration. Meeting of the COST action TD0901 HypoxiaNet, Bilbao, 2012.

PASTOREKOVÁ Silvia. Cell migration and invasion in cancer: the role of pH regulating machinery and beyond. Symposium on Membrane Biology and Transport, Kaiserslautern, September 2013.

PASTOREKOVÁ Silvia. Tumor cell adaptations to hypoxia and acidosis: role of the carbonic anhydrase IX and opportunities for its clinical exploitation. 4th RECAMO joint meeting – Through cancer research towards applied molecular oncology. Brno, October 2013.

PASTOREKOVÁ Silvia. Carbonic anhydrase IX – a catalytic component of ion transport machinery in cancer. Annual Meeting of the German Physiological Society, Mainz, March 2014.

PASTOREKOVÁ Silvia. Adaptive responses of cancer cells to hypoxia and acidosis in tumor microenvironment. XXI.Biological days. Advances and challenges in current cancer biology (Pokroky a výzvy současné nádorové biologie). Brno, September 2014.

PASTOREKOVÁ Silvia. Carbonic anhydrase IX as a driver and regulator of acidosis in tumor microenvironment. First International Munich ROS Meeting of COST Action BM 1203. Munich, April 2015.

PASTOREKOVÁ Silvia. Carbonic anhydrase IX: Past, present and future. The 10th International Carbonic anhydrase conference, Maastricht, April 2015.

PREDAJŇA Lukáš. Impact of the diversity of plant viruses on their effective diagnostics. TOMÁŠKOVY DNY 2015, XXIV. Conference of young microbiologists Brno, 2015.

REŽUCHOVÁ Ingeborg. The role of epigeninetic regulation immurine gammaherpesvirus latency and reactivation. Discussion Forum 2014 “Host Pathogen Interaction”. Hradec Králové, May 2014.

ŠKULTÉTY Ľudovít. Identification of Coxiella burnetii cell envelope related proteins using a combined bioinformatics plus proteomics strategy. In: Friedrich-Loeffler Institut. Jena, Germany March 31, 2014.

ŠVASTOVÁ Eliška. The role of CA IX in cell migration and invasion. The 9th International Conference on Carbonic Anhydrase, April 2012, Antalya.

ŠVASTOVÁ Eliška. CA IX – multitasking component of the metastatic cascade. 1st ISCAM Meeting and 5th ISPDC Meeting on Cancer Metabolism, mechanisms, consequences and therapeutic opportunities, October, 2014, Smolenice Castle.

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

PASTOREKOVÁ Silvia, Program Committees:
The 9th International Conference on Carbonic Anhydrase, April 2012, Antalya.
The 10th International Carbonic anhydrase conference, Maastricht, April 2015.
2nd Meeting of the International Society of Cancer Metabolism - Metabolism and microenvironment in cancer plasticity. Venice, September 2015.
1st ISCAM Meeting and 5th ISPDC Meeting on Cancer Metabolism, mechanisms, consequences and therapeutic opportunities, October, 2014, Smolenice Castle.

ŠVASTOVÁ Eliška, TAKÁČOVÁ Martina, ONDRISKOVÁ Elena, DEBREOVÁ Michaela, Organizing Committee:
1st ISCAM Meeting and 5th ISPDC Meeting on Cancer Metabolism, mechanisms, consequences and therapeutic opportunities, October, 2014, Smolenice Castle.

• 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

GLASA Miroslav. Virus pathogens threatening cherries and sour cherries in Slovakia and prospects for their. Symposium on cultivation of stone fruits. National center of agriculture, Research Institute of plant production. July, 2014, Piešťany.

LABUDOVÁ Martina. Interaction of the lymphocytic choriomenigitis virus with infected cell and its consequences. Organ tramsplantations and virus infections, Symposium on actual problems of current transplantology. April 2014, Bratislava.

PASTOREKOVÁ Silvia. Hypoxia, an important factor of progression and therapeutic resistance of colorectal tumors. XVII. Congress of natural medicine with interdisciplinary participation. October 2014, Šamorín – Čilistov.

PASTOREKOVÁ, Silvia. Tumor microenviroenment in colorectal carcinogenesis: its central role in disease progression and implication for clinical practice. 69th Surgical day of Kostlivy, December 2015, Bratislava.

PASTOREKOVÁ, Silvia. Carbonic anhydrase IX - key component of pH regulation and signalling in tumors. XXIV. Biochemical meeting of SSBMB a ČSBMB. September 2014, Bratislava.

TOMÁŠKOVÁ Jana. Lymphocytic choriomenigitis virus – a neglected human pathogen. Organ transplantations and virus infections, Symposium on actual problems of current transplantology. April 2014, Bratislava.

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

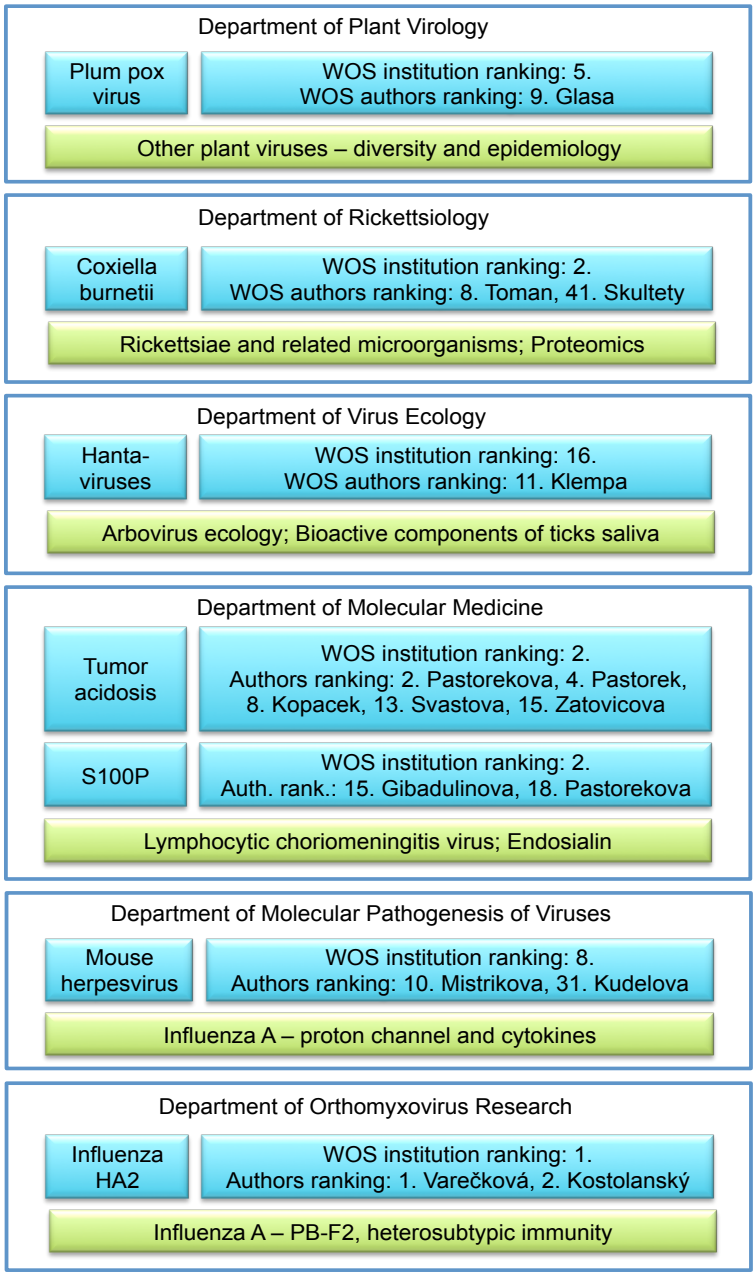
PASTOREKOVÁ Silvia: Symposium on actual problems of current transplantology. April 2014, Bratislava.

KOCIANOVÁ Elena: Labuda's Days (Conference of young researchers dedicated to the memory of the renowned Slovak virologist and zoologist Milan Labuda), Bratislava, 2013

ŠPITALSKÁ Eva, ŠTEFANIDESOVÁ Katarína: Labuda's Days, Bratislava 2015

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

IVSAS main research topics and WOS ranking



Here we provide the schematic summary of the research topics of the IVSAS departments and the corresponding ranking of the authors and the institution according to the Web of Science Core Collection (based on the numbers of published papers). The search procedure included the selection of research topics and time period (for broader topics it was 2012-2015, for more specific topics it was 2000-2016 in order to evaluate a sufficiently large collection of papers). The search was then submitted to the action "Analyse results" and ranking category was chosen (Author, Organization). This procedure generated the list of top 10-50 authors/institutions for each topic.

The Department of Molecular Medicine was designated as the "Top research team of SAS" according to the evaluation of ARRA (independent Academic Rating and Ranking Agency, Slovakia) in 2011.

The international and/or national status of the IVSAS can be also demonstrated by the engagement of its researchers in the international organizations, boards and bodies, e.g.:

Boris KLEMPA, delegate of the Slovak Republic in the European Network for Diagnostics of "Imported" Viral Diseases (ENIVD).

Silvia PASTOREKOVÁ, delegate of the Slovak Republic in the European Molecular Biology Conference (EMBC), elected member of the Pathobiology Group of the European Organization for Research and Treatment of Cancer (EORTC), elected scientific board member of the International Society of Cancer Metabolism (ISCAM).

Jaromír PASTOREK, elected member of the European Academy of Science and Arts.

Rudolf TOMAN, board member of the European Working Group on Rickettsiae, Coxiella and Ehrlichiae.

Additional international memberships are described in the annual reports of the IVSAS.

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

- **International projects and funding**

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

	Project title	Type / Project number	Duration in months	Funding for the Institute (EUR)	Role of the Institute / Responsible person
2012	European Virus Archive (EVA)	FP7-228292	01/2009 12/2012	2012: 112.639,00 € 2013: 84.110,00 €	W / Boris Klempa
	Metastatic tumours facilitated by hypoxic tumour microenvironments (METOXIA)	FP7-222741	02/2009 01/2014	2012: 130.018,00 € 2013: 44.878,00 € 2014: 1.456,00 €	W / Silvia Pastoreková
	Containment of sharka virus in view of EU-expansion (SHARCO)	FP7-204429	03/2008 08/2012	2012: 9.048,00 €	W / Miroslav Glasa
	New drugs targeting influenza virus polymerase (FLUPHARM)	FP7-259751	11/2010 04/2015	2012: 59.568,00 € 2013: 63.432,00 € 2014: 52.279,00 € 2015: 15.530,00 €	W / Eva Varečková
	Biomedical engineering for cancer and brain disease diagnosis and therapy development (EngCABRa)	FP7-264417	04/2011 08/2015	2012: 51.225,00 € 2013: 46.629,00 € 2014: 69.481,00 € 2015: 17.125,00 €	W / Silvia Pastoreková
	Plant virus control employing RNA-based vaccines: A novel non-transgenic strategy	COST-FA0806	05/2009 03/2013	2012: 4 000€ 2013: 1 000€	W / Miroslav Glasa
	Hypoxia sensing, signalling and adaptation (HypoxiaNet)	COST-TD0901	11/2010 10/2013	2012: 4.000,00 € 2013: 3.667,00 €	W / Silvia Pastoreková
	Combined innovative methods to improve the health status and the qualityof regional fruit production	HUSK0901 /1.2.1/0126	02/2011 01/2013	2012: 26.406,00 € 2013: 54.887,00 €	W / Miroslav Glasa
2013	Anti-tick Vaccines to Prevent Tick-borne Diseases in Europe (ANTIDotE)	FP7-602272	12/2013 11/2018	2014: 37.283,00 € 2015: 47.474,00 €	W / Boris Klempa
	Sustainable production of high-quality cherries for the European market	COST FA1104	04/2013 03/2016	2013: 3.000,00 € 2014: 4.000,00 € 2015: 8.000,00 €	W / Miroslav Glasa
2014	Biochemical and structural characterization of HCMV immune modulators and F-actin capping muscular proteins	SAIA-AKTION-6-IN	09/2014 02/2015	2014: 6.000,00 € 2015: 9.000,00 €	C / Ivana Nemčovičová
2015	Application of next generation sequencing for the study and diagnosis of plant viral diseases in agriculture	COST FA1407	03/2015 02/2019	2015: 6.666,00 €	C / Miroslav Glasa
	Building-up Centre of Excellence for dvanced materials application (CEMEA)	Project No. 664 337 CSA/SGA	06/2015 05/2016	2015: 0,00 €	W / Silvia Pastoreková
	European virus archive goes global	H2020-653316	04/2015 03/2019	2015: 1.963,00 €	W / Boris Klempa

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

Project title: ***Association of the hypoxia-induced carbonic anhydrase IX with drug response, miRNA profile and oncogenic pathways: from integrative analysis of the NCI60 cancer cell panel to cancer patients***
Project type: Interacademic agreement between the Slovak Academy of Sciences and the Ministry of Science and Technology in Taiwan
Project code: SAS-MOST-JRP-2014/10
Performance period: 01/2015 – 12/2017
Principal investigator: Prof. Silvia Pastoreková, DSc.
Funding for 2015: 25,000.00 €

Project title: ***Application of the next-generation sequencing analyses for the detection and characterization of important viral pathogens of cherries.***
Project type: APVV, bilateral Slovak-French
Project code: SK-FR-2013-0021
Performance period: 01/2014 – 12/2015
Coordinating institution: Institut Nationale de la Recherche Agronomique
Principal investigator at IVSAS: Miroslav Glasa, PhD.
Funding for 2015: 2,560.00 €

Project title: ***Identification of relevant proteins and characterization of protein-protein interactions of biomarkers of malignant diseases regression.***
Project type: APVV, bilateral Slovak-Czech
Project code: SK-CZ-2013-0215
Performance period: 01/2015 – 12/2015
Principal investigator: Ľudovít Škultéty, DSc.
Funding for 2015: 2,300.00 €

Project title: ***Role of the CA IX ectodomain in tumor growth and metastasis***
Project type: Leona Lauder and George Schwab Foundation, USA
Performance period: 11/2014 – 12/2016
Principal investigator: Prof. Silvia Pastoreková, DSc.
Funding for 2015: 33,000.00 €

2.4.3. Other important, international projects and collaborations without direct funding

Project title: ***Symptomatology of the Arabis mosaic virus infection***
Project type: bilateral Slovak-Austrian
Performance period: 01/2013 – 12/2014
Coordinator: RLP Agroscience, AlPlanta, Neustadt
Principal investigator at IVSAS: Miroslav Glasa, PhD.

Project title: ***Biomarkers for Early Detection and Therapy of Adrenal Gland Tumors: Molecular Pathogenesis and Clinical Correlates***
Project type: bilateral NIH-SAS
Performance period: 01/2009 – 12/2014
Coordinator: prof. Karel Pacak, DSc., National Institute of Child Health and Human Development, NIH, Bethesda
Principal investigator: Juraj Kopáček, MVD., DSc.

- **National projects and their funding**

2.4.4. Projects supported by the Slovak Research and Development Agency (APVV) Role of the Institute e.g. coordinator “C”, investigator “I”.

	Project title	Type / Project number	Duration in months	Funding for the Institute (EUR)	Role of the Institute / Responsible person
2012	Identification of the molecular pathways driven by hypoxia-induced carbonic anhydrase IX in tumor cells	APVV-0108-10	05/2011 10/2014	2012: 63.996,00 € 2013: 71.244,00 € 2014: 53.067,00 €	C / Juraj Kopáček
	Molecular mechanisms of the crosstalk between stress hormones and hypoxia in tumor cells: effect on expression and function of cancer-related protein CA IX	APVV-0893-11	07/2012 12/2015	2012: 33.903,00 € 2013: 56.306,00 € 2014: 51.091,00 € 2015: 62.577,00 €	C / Jaromír Pastorek, Lucia Csáderová
	Carbonic anhydrase IX as a functional component of cancer progression: the role in epithelial-mesenchymal transition and intercellular signaling	APVV-0658-11	07/2012 12/2015	2012: 20.364,00 € 2013: 38.965,00 € 2014: 35.569,00 € 2015: 38.965,00 €	C / Silvia Pastoreková
	Investigation on the Plum pox virus host preference factors in regard to the natural variability of its population on the territory of Slovak republic	APVV-0042-10	05/2011 12/2014	2012: 30.129,00 € 2013: 30.129,00 € 2014: 0,00 €	C / Zdeno Šubr
	Prediction of influenza A virus epidemic/pandemic outcome by identifying dominant markers of viral pathogenesis and transmissibility	APVV-0250-10	05/2011 10/2014	2012: 74.794,00 € 2013: 74.794,00 € 2014: 44.397,00 €	C / Eva Varečková
	Structure of foci and emerging diseases with emphasis on role of rodents in urban type of natural foci of diseases	APVV-0267-10	05/2011 10/2014	2012: 8.000,00 € 2013: 7.950,00 € 2014: 6.900,00 €	I / Boris Klempa
	Understanding of plant adaptation in the radioactive Chernobyl area	APVV-0740-11	07/2012 12/2015	2012: 6.418,00 € 2013: 9.206,00 € 2014: 8.240,00 € 2015: 4.654,00 €	I / Ľudovít Škultéty
2013	Characterization of novel motif in M1 protein of influenza A virus and using NS1 deletion mutants in tumor therapy	APVV-0676-12	10/2013 09/2017	2013: 17.520,00 € 2014: 41.474,00 € 2015: 47.600,00 €	C / Tatiana Betáková
	Development of innovative approaches to characterise and control the economically important and emerging virus pathogens of cherry crops in Slovakia	APVV-0174-12	10/2013 09/2017	2013: 1.000,00 € 2014: 29.977,00 € 2015: 43.273,00 €	C / Miroslav Glasa
	Murine gammaherpesvirus a producent of substances exhibiting immunomodulatory and antiproliferative properties	APVV-0621-12	10/2013 09/2017	2013: 1.600,00 € 2014: 26.011,00 € 2015: 32.303,00 €	C / Marcela Kúdelová
	Research of biomarkers for diagnosis of rickettsiae, C. burnetii and related organisms by state-of-art immunoproteomic and molecular biologic methods	APVV-0280-12	10/2013 09/2017	2013: 19.894,00 € 2014: 58.074,00 € 2015: 6.081,00 €	C / Zuzana Sekeyová
	Biological significance and pharmacological features of bioactive proteins in tick saliva	APVV-0737-12	10/2013 09/2017	2013: 0.00 € 2014: 39.803,00 € 2015: 39.327,00 €	C / Iveta Štibrániová
2014	No call				
2015	Functional analysis of newly identified DNA variants in genes responsible for cystic fibrosis and fenylketonuria.	APVV-0240-12	10/2013 09/2017	2015: 23.360,00 €	C / Ľudevít Kádaši*
	IP3 receptors, their modulation and function in cancer cells	APVV-0045-11	07/2012 12/2015	2015: 28.900,00 €	C / Oľga Križanová*
	Study of molecular mechanisms of H2S biological effects	APVV-0074-11	07/2012 12/2015	2015: 32.44,00 0€	C / Karol Ondriaš*
	Immune modulation by cytomegalovirus and its immunotherapeutic potential	APVV-14-0839	07/2015 06/2019	2015: 22.661,00 €	C / Ivana Nemčovičová
	Elucidation of novel pro-metastatic functions of tumor-associated carbonic anhydrase IX and its cross-talk with pro-inflammatory response	APVV-14-0816	07/2015 12/2019	2015: 32.465,00 €	C / Eliška Švastová
	Preparation of erythropoietin a therapeutic hormone affecting the production of red blood cells by expression in eukaryotic cell system and its further purification	APVV-14-0474	07/2015 12/2019	2015: 26.000,00 €	C / Ľudovít Škultéty
	Graphene-based nanoplatform for detection of cancer	APVV-14-0120	07/2015 06/2019	2015: 6.658,00 €	I / Silvia Pastoreková
	The role of neuropeptides and receptors in regulation of pathogen transfer from ticks to their hosts	APVV-14-0556	07/2015 06/2019	2015: 0,00 €	I / Eva Špitalská
	Biochips and biosensors for glycorecognition, their development, prepararion and application in cancer research	APVV-14-0753	07/2015 06/2019	2015: 2.875,00 €	I / Martina Takáčová
	Effective diagnostics of viruses threatening the production of tomato in Slovakia	APVV-0055-14	07/2015 06/2019	2015: 13.625,00 €	I / Miroslav Glasa

*PIs were transiently delimited to IVSAS in 2015, but currently work at the Institute of Clinical and Translational Research, BMC SAS

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	28	24	25	28
Funding in the year (EUR)	173,710	186,477	190,182	218,567

- **Summary of funding from external resources**

2.4.6. List of projects supported by the EU Structural Funds

Project title: ***Center of Excellence for the Translational Research in Molecular Medicine 2 (TRANSMED 2)*** ITMS 26240220030, 06/2010 – 05/2012
Project coordinator: Juraj Kopáček, MVD., DSc.

TRANSMED 2 was a continuation of the earlier TRANSMED project. Both projects were aimed at building infrastructure and networking of national institutions in the biomedical area with the purpose of strengthening translational research. The projects involved 5 partner institutes of the Slovak Academy of Sciences (Institute of Endocrinology, Cancer Research Institute, Institute of Molecular Biology, Institute of Molecular Physiology and Genetics, and Institute of Biochemistry and Genetics of Animals) and two faculties of the Comenius University (Faculty of Medicine and Faculty of Natural Sciences). The main emphasis was given on equipment needed for translational biomedical research using cell and animal models, human tissue specimens and body fluids, including the hypoxic workstation, personal flow cytometer, supplementary equipment for confocal microscope (motorized sample platform), isolation boxes with ventilation system for animal housing, eletroporator, system for optical imaging in vivo, beta counter, HPLC system, automatic DNA, RNA and protein analyser, microscope for cytogenetic analysis and related software packages. The equipment was allocated to participating institutions and is available to all the other project partners. This allowed us to strengthen our domestic collaboration, to create seeds for building core facilities within the national academic environment and increase our international competitiveness.

Project title: ***Development of biopharmaceuticals by modern biotechnologies (BIOFARMET)*** ITMS 26240220045, 01/2011 – 12/2013
Coordinator: Ľudovít Škultéty, DSc.

BIOFARMET was focused on development of technological procedures and platforms for production of specific bioactive compounds using modern methods based on eukaryotic expression systems. This project enabled us to build cell cultivation unit with a small-scale fermentation containers and fully automatic system for purification of bioactive molecules and for production of different recombinant molecules for diagnostic and therapeutic applications.

Project title: ***Center for Innovative Research of Antitumor and Antiviral Strategies***
ITMS 26240220062, 05/2011 – 04/2014
Project coordinator: Juraj Kopáček, MVD., DSc.

CE-INF-ONC was established within the collaborative project between the Institute of Virology as a coordinator and the SME Bioscience Slovakia, ltd., as a partner. This project enabled us to obtain and/or upgrade the infrastructure for the development of diverse diagnostic assays and reagents for biomedical applications, including the platform for real-time measurements of cell viability, proliferation, adhesion and cytotoxic effects of drugs, complex system for HPLC, and several advanced softwares for acquisition, processing and storage of data from proteomic, bioimaging and bioinformatic analyses.

The projects listed below, where IVSAS participated as a partner, provided further resources that brought additional important equipment *(described and illustrated in more detail on pages 70-71).*

Project title: ***Industrial research in clinical diagnostics of infectious pathogens***
ITMS 26240220032, 05/2010 – 05/2014
Cordinator: Peter Kilián, PhD.
PI at IVSAS: Juraj Kopáček, MVD., DSc

Project title: ***Improvement of the Centre of Excellence for the Use of Informational Biomacromolecules in Prevention of Diseases and for Improvement of the Quality of Life***
ITMS 26240120027, 06/2010 – 04/2012
Coordinator: Prof. Marta Kollárová, D.Sc., Faculty of Natural Sciences,
Comenius University in Bratislava
PI at IVSAS: Juraj Kopáček, MVD., DSc.

Project title: ***Development of Diagnostic Methods for Detection of Pathogens Transmitted by Ticks and Methods for Preparation of Vaccines against Ticks***
ITMS 26240220044,11/2010 – 10/2013
Coordinator: Dušan Žitňan, DSc., Institute of Zoology, SAS
PI at IVSAS: Boris Klempa, DSc.

Project title: ***Diagnoses of Socially Important Diseases in Slovakia Based on Modern Biotechnologies***
ITMS 26240220058,11/2010 – 10/2013
Coordinator: Prof. Ľudevít Kádaši, DSc., Institute of Molecular Physiology and Genetics SAS
PI at IVSAS: Marcela Kúdelová, PhD.

Project title: ***Development of a Competence Center for the Research and Development in Molecular Medicine***
ITMS 26240220071, 10/2011 – 01/2015
Coordinator: Prof. Ján Turňa, PhD., Faculty of Natural Sciences, Comenius University in Bratislava
PI at IVSAS: Juraj Kopáček, MVD., DSc.

Project title: ***Research program of miR-155 oncogene for diagnostic and prognostic purposes in cancer***
ITMS 26240220074, 05/2012 – 10/2014
Coordinator: Dana Jurkovičová, PhD., KRD Technologies, a.s.
PI at IVSAS: Adriana Gibadulinová, PhD.

Project title ***Centre for the research and development of immunologically active substances***
ITMS 26220220188, 03/2014 – 09/2015
Coordinator: Prof. Jaromír Pastorek, DSc., Slovak Academy of Sciences, Bratislava
PI at IVSAS: Juraj Kopáček, MVD, DSc.

Project title: ***University Research Park for Biomedicine in Bratislava***
ITMS 26240220087, 09/2013 – 12/2015
Coordinator: Prof. Jaromír Pastorek, DSc., Slovak Academy of Sciences, Bratislava
PI at IVSAS: Vladimiír Zelník, PhD.

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

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

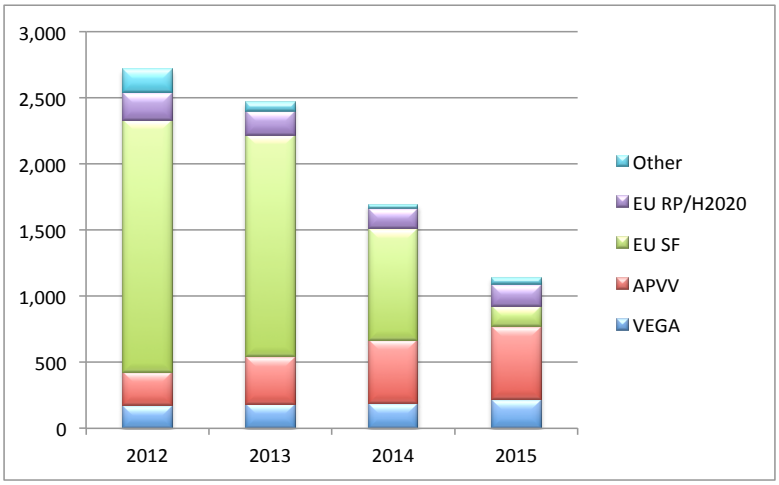
Year	Project title	Project number	Duration in months	Funding for the Institute (EUR)	Role of the Institute
2012	Centre of Excellence for the Translational Research in Molecular Medicine	26240220030	06/2010 05/2012	2012: 699.514,00 €	C
	Development of Biopharmaceuticals by Modern Biotechnology	26240220045	01/2011 12/2013	2012: 502.796,00 € 2013: 110.609,00 €	C
	Centre for Innovative Research of Antitumor and Antiviral Strategies	26240220062	05/2011 04/2014	2012: 872,00 € 2013: 674.884,00 € 2014: 202.391,00 € 2015: 162.872,00 €	C
	Diagnostics of Socially Important Diseases in Slovakia Based on Modern Biotechnologies	26240220058	11/2010 10/2013	2012: 12.613,00 € 2013: 17.285,00 €	W
	Development of Diagnostic Methods for Detection of Pathogens Tramsmitted by Ticks and Methods for Preparation of Vaccines against Ticks	26240220044	11/2010 10/2013	2012: 86.670,00 € 2013: 149.982,00 €	W
	Industrial Research in Clinical Diagnostics of Infectious Pathogens	26240220032	05/2010 05/2014	2012: 589.778,00 € 2013: 18.141,00 € 2014: 105.123,00 €	W
	Competency Center for the Research and Development in Molecular Medicine	26240220071	10/2011 01/2015	2012: 25.744,00 € 2013: 31.153,00 € 2014: 347.774,00 € 2015: 111.702,00 €	W
	Advancement of the Centre of Excelence for the Use of Informational Biomacromolecules in Prevention of Diseases and for the Improvement of the Quality of Life	26240120027	06/2010 04/2012	2012: 1.400,00 € 2013: 8.010,00 €	W
	Research of the Oncogenic miR-155 Program for Diagnostic and Prognostic Applications in Cancer	26240220074	05/2012 10/2014	2012: 0,00 € 2013: 47.305,00 € 2014: 146.607,00 € 2015: 178.189,00 €	W
2013	University Research Park for Biomedicine in Bratislava	26240220087	09/2013 12/2015	2013: 0,00 € 2014: 4.210,00 € 2015: 26.075,00 €	W
2014	Centre for Research and Development of Immunologically Active Substances	26220220188	03/2014 09/2015	2014: 20.926,00 € 2015: 26.950,00 €	W

External resources	2012	2013	2014	2015	total	average
External resources (milions of EUR)	1.907	1.675	0.842	0.155	4.579	1.145
External resources transfered to coooperating research institute (milions of EUR)	0.000	0.000	0.000	0.000	0.000	0.000

External funding obtained by the IVSAS from the EU Structural Funds was completely executed at the IVSAS through the public prosecutions, and the relevant infrastructure was then allocated to the cooperating research institutes (thus, no transfer of resources was made).

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

In order to provide better view on the IVSAS overall project structure and funding sources, see the graph below. It shows the volume of the IVSAS funding from both national and international sources during the evaluation period divided according to the project types (numbers on y axis show the funding in thousands of Euro). It is evident that the VEGA and EU FP7/H2020 projects represented relatively stable component of the project portfolio of the IVSAS, whereas the funding from the APVV projects displayed increasing trend. This was a very positive phenomenon, since the APVV projects are very competitive at the domestic research scene and are reasonably well funded.



The projects supported by the EU Structural Funds were of strategic importance for the Institute of Virology SAS (and its project partners), as they represented a unique opportunity to build and improve research facilities, to keep in touch with methods and techniques of up-to-date biomedical research, and to improve our competitiveness. This was possible also thanks to a highly qualified and dedicated research personnel capable to implement the projects (which was both time- and energy-consuming task associated with excessive administration) and, even more importantly, operate the infrastructure, transfer this knowledge to other active users in-house, and also to provide advises and support to researchers from other institutions, as evident from a number of collaborations and resulting publications.

In 2015, the first ERDF program period ended and all the EU Structural funds projects were completed, leading to drastically reduced resources (see the graph above). However, the built infrastructure now urgently needs a continuous support for the stabilization of the highly qualified personnel and for the maintenance and/or upgrade of the equipment to ensure its sustainable development. Such situation calls for further project funds from the currently opened EU structural funds program period. This, however, might be very challenging due to the significantly restricted proportion of resources that can be allocated to institutions localized in the Bratislava district, where more than 80% of the Slovak research activities are ongoing. Nevertheless, the IVSAS, now being a part of the Biomedical Research Center SAS, will make strong efforts to elaborate and submit collaborative projects to this new funding scheme.

2.5. PhD studies and educational activities

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

The IVSAS is accredited to accomplish PhD education in the following programs:
Virology – 4.2.13 – Faculty of Natural Sciences, Comenius University in Bratislava, and University of Veterinary Medicine and Pharmacy, Košice
Guaranting expert: Marcela Kúdelová, DSc.
Microbiology – 4.2.7. – Faculty of Natural Sciences, Comenius University in Bratislava
Guaranting expert: Juraj Kopáček, MVD., DSc.
Molecular Biology – 4.2.3. – Faculty of Natural Sciences, Comenius University in Bratislava
Guaranting expert: Prof. Jaromír Pastorek, DSc.
Oncology – 7.1.15. – Faculty of Medicine, Comenius University in Bratislava
Guaranting expert: Prof. Silvia Pastoreková, DSc.

All these programs have received an unlimited period of validity, if accomplished in accordance with the corresponding law (i.e. if the age of the guarantying experts is below 65 years). This gives 7-14 years period of validity to the programs of Microbiology, Molecular biology and Oncology, but only 3 years to the program of Virology. Thus, in the near future, we will focus on the nomination of a new candidate that fulfils the criteria for this expert position out of several younger colleagues who recently received the Doctor of Science title.

All four PhD programs are very important from the point of view of the increasing interest of graduate students, whose number regularly exceeds the number of available PhD positions at the IVSAS. Although this creates a "selective pressure" in favour of best applicants, we would welcome if there is a space to accommodate more PhD students as they are often the main driving force of new experimental approaches.

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

PhD study	12/31/12			12/31/13			12/31/14			12/31/15		
Number of potential PhD supervisors	33			33			36			37		
PhD students	number	defended thesis	students quitted	number	defended thesis	students quitted	number	defended thesis	students quitted	number	defended thesis	students quitted
Internal	21.0	6.0	0.0	20.0	6.0	1.0	21.0	2.0	1.0	16.0	5.0	2.0
External	3.0	0.0	1.0	3.0	0.0	0.0	3.0	0.0	0.0	2.0	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

2.5.3. Summary table on educational activities

Teaching	2012	2013	2014	2015
Lectures (hours/year)[2]	98	117	118	89
Practicum courses (hours/year)[2]	48	122	74	142
Supervised bachelor theses (in total)	5	8	9	8
Supervised diploma theses (in total)	10	15	17	14
Supervised PhD theses (in total)	24	24	25	24
Members in PhD committees (in total)	7	5	7	7
Members in DrSc. committees (in total)	2	0	2	5
Members in university/faculty councils (in total)	3	3	3	1
Members in habilitation/inauguration committees (in total)	1	1	2	2

2.5.4. List of published university textbooks

GOLAIS, F. - **KABÁT, Peter**. *GENERAL, CELLULAR AND MOLECULAR VIROLOGY* [electronic version]. 1st Edition, Publishing house of the Comenius University in Bratislava, 2013. ISBN 978-80-223-3452-5.

2.5.5. Number of published academic course books

None during the evaluation period.

2.5.6. List of joint research laboratories/facilities with universities

Laboratory spaces and facilities at IVSAS shared with the Chair of Microbiology and Virology, Faculty of Natural Sciences, Comenius University in Bratislava
– used for education of pre-graduate and post-graduate students of virology (since 1968).

Joint research facility of the new Pavillon of Medical Sciences built as a part of the University research park for biomedicine in Bratislava (BIOMED park)
– the building constructed with the support of the EU Structural funds project (with IVSAS as a project partner) provides laboratory, technical and clinical unit spaces to several SAS institutes and Faculty of Medicine, Comenius University in Bratislava.

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

We believe that doctoral studies and educational activities are very important for the IVSAS future. Through the experience-based lecturing and presentations of our research topics, we can attract the most talented students to join our teams and perform research in our laboratories. The series of lectures and seminars on virology, molecular biology of the cell, and cancer biology that we have been giving over more than two decades especially at the Faculty of Natural Sciences, Comenius University in Bratislava, are very well accepted and largely attended by the faculty students, who are then keen to apply for practical studies at the Institute. Indeed, majority of the young researchers at the IVSAS is represented by our previous students, who acquired skills and knowledge during the diploma- or PhD-related experimental work at the IVSAS. Therefore, we intend to support and develop these activities.

Moreover, we continuously stimulate our PhD students to gain new experiences and skills through visits of excellent laboratories abroad. These visits often open new opportunities for collaborations and in some cases also for postdoctoral stays as exemplified below:

- Martin Benej, PhD student at the Department of Molecular Medicine (until 2015)
  2-moths visit at the University of Napoli, Italy (03-04/2012), in the team of Prof. Zambrano, to learn proteomic techniques, specifically DIGE
  5-months visit at the State University of Ohio, USA (01-06/2015), in the team of Prof. Denko, to get skills in real-time analysis of cell metabolism, which resulted in the post-doc position starting from 09/2015.
- Petra Bullova, PhD student at the Department of Molecular Medicine
  4-years stay at NIH Bethesda (2012-2015), USA in the team of Prof. Pacak, to investigate mechanisms of pheochromocytoma progression.
- Elena Ondriskova, PhD student at the Department of Molecular Medicine
  7-months stay at Free University of Brussels, Belgium (11/2014-05/2015), in the ERC project team of Prof. Sonveaux, to get skills for study of cancer metabolism.
- Radivojka Vulić, PhD student at the Department of Rickettsiology and Chamydiology
  1-month visit at the Institute of Microbiology, Czech Academy of Sciences in Prague (10-11/2015) to get skills in advanced proteomics.
- Lenka Berthova, PhD student at the Department of Rickettsiology and Chamydiology
  2-months visit at Northumbria University, UK (10-12/2012), Prof. Saparagano, to learn about approaches to investigation of ecology of ticks and tick-transmitted infections
  1-week practical course on diagnosis of arthropod-borne viruses in Marseille (03/2014)
- Monika Bohacsova, PhD student at the Department of Rickettsiology and Chamydiology,
  1-month visit in Marseille, France (11-12/2015), to investigate inrracellular bacteria based on project collaboration woth Prof. Raoult.
- Róbert Szabó, PhD student at the Department of Virus Ecology
  1-year stay at the University of Cagliari (09/2015-08/2016).

On the other hand, the IVSAS hosted many foreign PhD students for short or long-term stays, mostly with the EU project consortia, who came to learn from our experts.

2.6. Social impact

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

(1) Development of diagnostic assays of mixed herpesvirus infections

We elaborated and introduced a sensitive duplex PCR-based method suitable for the concurrent detection of herpes simplex viruses 1 and 2, which are transmissible in human population via direct contact and contaminated saliva. The new method allows for detection of mix infections in clinical materials, such as sputum, mucosal and skin swabs. Differential diagnostics of the HSV2 virus causeing genital herpes enables early, sensitive and fast virus detection and early intervention using suitable antivirus therapy. It can be also useful for prevention of herpetic infections including congenital infections. We also implemented a duplex PCR method for detection of human cytomegalovirus and Epstein-Barr virus in clinical samples of immunocompromised patients. The assays are described in detail in the agenda of the DEVAC project supported by EU Structural funds.

(2) Identification and characterization of novel rodent-borne viruses and evaluation of their impact on human heath.

Within a broad international collaboration with the partners in Germany, Russia and several African countries, we contributed to identification and characterization of new hantaviruses and arenaviruses. Retrospective analysis of patients suffering from hemorrhagic fever with renal syndrome from the coastal region of the Black sea in Russia allowed for the first complex clinical survey of the recently identified Sochi hantavirus and showed it life-theatening potential with 14.5% of recognized fatal cases. In the same region, we identified a new hantavirus transmitted by Microtus majori voles, which was genetically determined as a novel genotype of Tula virus, present also in Slovakia. We also participated on genetic characterization of new arenaviruses identified in rodents in Namibia. These studies were accompanied by the development of detection tools and assays for the future diagnostics and surveillance of these new viruses.

Kruger DH, Tkachenko EA, Morozov VG, Yunicheva YV, Pilikova OM, Malkin G, Ishmukhametov AA, Heinemann P, Witkowski PT, Klempa B, Dzagurova TK. Life-Threatening Sochi Virus Infections, Russia. Emerg Infect Dis. 2015 Dec;21(12):2204-8.

Tkachenko EA, Witkowski PT, Radosa L, Dzagurova TK, Okulova NM, Yunicheva YV, Vasilenko L, Morozov VG, Malkin GA, Krüger DH, Klempa B. Adler hantavirus, a new genetic variant of Tula virus identified in Major's pine voles (Microtus majori) sampled in southern European Russia. Infect Genet Evol. 2015 Jan;29:156-63.

Witkowski PT, Kallies R, Hoveka J, Auste B, Ithete NL, Šoltys K, Szemes T, Drosten C, Preiser W, Klempa B, Mfune JK, Kruger DH. Novel Arenavirus Isolates from Namaqua Rock Mice, Namibia, Southern Africa. Emerg Infect Dis. 2015 Jul;21(7):1213-6.

(3) Assessment of the molecular variability and genetic determinants of the pathogenicity of Plum pox virus for the development of effective control strategies.

Plant RNA viruses are characterised by a dynamic genetic structure of populations resulting in the substantial intra-species and intra-isolate molecular variability. Plum pox virus (PPV) is an RNA virus belonging to the most economically important pathogens of the fruit trees. We have mapped the genetic determinants of the symptoms of PPV infection by the study of intra-strain infectious chimeras and the site-directed mutagenesis. We found that even one amino acid substitution in the non-structural viral protein can lead to the change of the virus pathotype. A high intrahost molecular variability of PPV in a single natural host (plum, *Prunus domestica*) was observed 7 years post controlled inoculation by a characterised PPV isolate. Evolution led to the

generation of dominant and a number of minor variants of the isolate, however, without their clear-cut structuration in relation to the tree architecture. Although the comparison of the consensus sequence with the original source isolate showed no difference at the aminoacid level, the observed heterogenous RNA population within a tree constitutes a high adaptation potential of the virus. A polyvalent RT-PCR has been developed based on the available viral sequences, able to intercept all known PPV strains, which can be applied in the effective routine detection of the virus.

Nagyová A, Kamencayová M, Glasa M, Šubr Z. The 3'-proximal part of the Plum pox virus P1 gene determinates the symptom expression in two herbaceous host plants. Virus Genes, 2012, vol. 44, no. 3, p. 505-514.

Predajňa L, Šubr Z, Candresse T, Glasa M. Evaluation of the genetic diversity of Plum pox virus in a single plum tree. Virus Research, 2012, vol. 167, p. 112-117.

(4) Identification and characterization of a new divergent cherry-adapted strain of Plum pox virus (PPV) and development of molecular tool for its detection

The vast majority of the Plum pox virus (PPV) isolates are unable to infect cherries and so far, rare PPV isolates adapted to cherry hosts have been assigned to the PPV-C (cherry) strain. We discovered unusual PPV isolates from sour cherry trees in the Volga river basin of Russia, not reliably recognised by conventional detection tests. Comparison of the complete genome sequences has shown only 77.5-83.5% nucleotide identity with other PPV strains. Phylogenetic analyses clearly assigned the unusual isolates to a distinct cluster, most closely related to the PPV-C and, to a lesser extent, PPV-W strain. Based on the biological properties (natural infection of sour cherry trees) and genome characterization, these PPV isolates represent a new highly divergent strain of PPV, for which the name PPV-CR (Cherry Russian) was proposed. The unique amino acids conserved among PPV-CR and PPV-C cherry-infecting isolates are mostly distributed within the central part of P1, NIa and the N-terminus of the CP, making them potential candidates for genetic determinants of the ability to infect cherry species or of adaptation to these hosts. The variability observed within PPV-CR isolates (0-2.6% nucleotide divergence in partial CP sequences) and the identification of these isolates in different localities and cultivations suggest the efficient establishment and competitiveness of the PPV-CR in the environment. As this strain represent a potential emerging pathogen for the EU territory, a specific RT-PCR has been developed/validated based on the available viral sequences. It is able to intercept the isolates of PPV-CR strains, which can be applied in the effective routine detection.

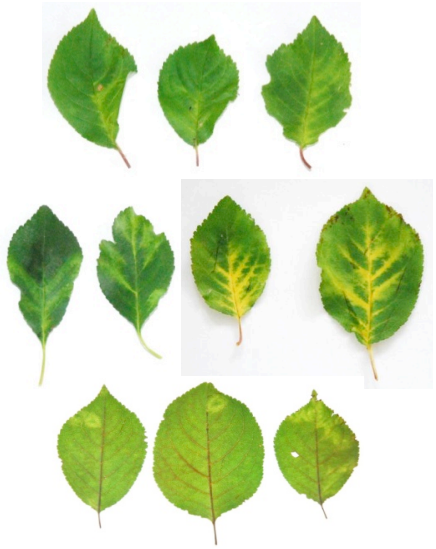


Figure on the left shows the symptoms caused by the Plum pox virus (strain PPV-CR) on the sour cherry tree.

Glasa M, Prikhodko Y, Predajňa L, Nagyová A, Shneyder Y, Zhivaeva T, Šubr Z, Cambra M, Candresse T. Characterization of sour cherry isolates of Plum pox virus from the Volga basin in Russia reveals a new cherry strain of the virus. Phytopathology, 2013, vol. 103, no. 9, p. 972- 979.

Šubr Z, Glasa M. Unfolding the secrets of Plum pox virus: from epidemiology to genomics. Acta Virologica, 2013, vol. 57, no. 2, p. 217-228.

(5) Development of RT-PCR for detection of grapevine Syrah virus-1 and first evidence for this virus in Central Europe

By the application of new generation sequencing (NGS) we have found for the first time in Central Europe the presence of vine Syrah virus-1 (GSyV-1) and subsequently we confirmed its considerable intraspecific molecular heterogeneity. Based on the determined full and partial genome sequences of GSyV-1 isolates we have developed a reliable and specific RT-PCR.

Surprisingly we found the prevalence of this virus pathogen so far overlooked in the vineyards of Slovakia.

Glasa M, Predajna L, Šoltys K, Sabanadzovic S, Olmos A. (2015). Detection and molecular characterisation of Grapevine Syrah virus-1 isolates from Central Europe. In Virus Genes, 2015, vol. 51, no. 1, p. 112-121.

(6) Evaluation of the impact of ticks and tick-borne pathogens in Slovakia on human and animal health using molecular detection methods

We performed an epizootological study of ticks and tick-borne pathogens in different areas of Slovakia in order to evaluate their potential impact on human and animal health and develop methods for diagnostics of tick-borne diseases. We noted the presence of pathogenic species of rickettsiae, namely *Rickettsia helvetica* and *R. monacensis* in *Ixodes ricinus* ticks and *R. slovaca*, *R. raoultiii* in *Dermacentor reticulatus* ticks. In addition, we detected protozoal parasite pathogens such as *Babesia canis* and *Babesia venatorum* in both commonly occurring species of ticks. Circulation of these pathogens in urban (cemeteries, city parks), semi-urban (forest parks) and natural areas pointed out that humans and animals are exposed to high risk of infection.

Špitalská E, Boldiš V, Derdáková M, Selyemová D, Rusňáková-Tarageľová V. Rickettsial infection in Ixodes ricinus ticks in urban and natural habitats of Slovakia. In Ticks and Tick-Borne Diseases, 2014, vol.5, no.2, p.161-165.

Švehlová A, Berthová L, Sallay B, Boldiš V, Sparagano O.A.E. Špitálska E. Sympatric occurrence of Ixodes ricinus, Dermacentor reticulatus and Haemaphysalis concinna ticks and Rickettsia and Babesia species in Slovakia. In Ticks and Tick-Borne Diseases, 2014, vol. 5, p. 600-605.

(7) Development of immunodiagnostic approaches to detection of human toxocariosis

In collaboration with the HPL laboratory of the microbiologic diagnostics in Bratislava, we elaborated a method for immunodiagnostics of human toxocariasis. Currently, there is no assay for discrimination between acute and chronic form of infection by larvae of the roundworm Toxocara. We found 15.3% seroprevalence of toxocariasis in the Slovak population. IgG antibodies of low eosinophilic avidity were often detected in the patients, with the significantly higher eosinophilia in children compared to adults. We observed a slight correlation between the number of eosinophils and avidity index of IgG antibodies. Evidence of low avidity IgG antibodies may be useful for determination of acute toxocariasis, but this test has to be evaluated in correlation with other immunological markers, as well as epidemiological and medical history of patients' data.

Boldis V, Ondiska F, Špitalska E, Reiterova K. Immunodiagnostic approaches for the detection of human toxocarosis. Experimental Parasitology, 2015, vol. 159, p. 252-258.

(8) Routine diagnostics of Coxiella burnetii, production of the vaccination antigen and development of new biomarkers and diagnostic approaches

C. burnetii is an intracellular bacterium that is an etiologic agent of severe disease called Q fever. Infectious potential of this bacterium enabled its classification among bioteroristic agents listed in bio-safety level 3. *C. burnetii* is an air-transmittable microorganism that causes dangerous zoonoses or serious human epidemics. Acute form of the disease in human usually starts as a mild flu-like illness, which may evolve into a life threatening chronic disease. This severe form of Q fever may be accompanied by various complications, such as hardly detectable Q fever endocarditis, mostly with complicated treatment, and many times with fatal end. Therefore it is clear that reliable diagnostic is crucial for fast and effective treatment.

Our Institute is the only one in Slovakia where the diagnostic tests, based on C. burnetii specific proteins and lipopolysaccharides, are being developed and routinely used with the application of the most recent e.g. immuno-proteomic approach.

The exact identification of C. burnetii species and the combination of various diagnostic methods provides a clear picture concerning the infection and possible future progression of the disease. Accurate diagnostics enables recommendation of the right antibiotic application. In this manner, possible treatment errors due to sensitivity or resistance of studied bacteria are hampered. Constant search for specific markers in order to distinguish different stages of Q fever is a key momentum for development of suitable and reliable vaccine in the future.

Moreover, the IVSAS routinely produces C.burnetii antigens for the diagnostic purposes and the vaccination against Q fever.

(9) Diagnostics and confirmation of the prevalance of important Proteobacteria species in the clinical samples from patients in Slovakia.

Using serological and molecular biological methods we confirmed bacterial origins of diverse diseases caused by pathogens of Rickettsia, Bartonella, Borrelia, Coxiella, Anaplasma, and Franciscella sp. in serum samples of patients hospitalized in the various regions of Slovakia with serious clinical symptoms designated as of “an unknown etiology”.

Presence of the recently identified microorganism Bartonella elisabethae was for the first time confirmed in Slovakia. Other two unique bacteria, Arsenophonus nasoniae (endosymbiont of the wasp Nasonia vitripennis) a Ehrlichia muris were detected for the first time in Europe. Rickettsia Africae, also detected for the first time in Slovakia, was apparently transmitted in conjunction with the traveling birds.

Sekeyova Z, Geetha S; Mediannikov O; Quevedo Diaz M; Nyitray, A; Blaskovicova H; Raoult, D.: Evaluation of clinical specimens for Rickettsia, Bartonella, Borrelia, Coxiella, Anaplasma, Franciscella and Diplorickettsia positivity using serological and molecular biology methods. FEMS Immunol Med Microbiol 64 (2012) 82–91. IF: 2,494

Sekeyová Z, Mediannikov O, Roux V, Subramanian G, Eva Špitalská, Jano Kristofík, Alžbeta Darolová, Didier Raoult: Identification of Rickettsia africae and Wolbachia sp. in Ceratophyllus garei fleas from a passerine birds migrated from Africa. Vector Borne Zoonotic Dis. 2012 Jul;12(7):539-43.

Sekeyová Z, Mediannikov O, Subramanian G, Kowalczewska M, Quevedo-Diaz M, Kocianová E, Raoult D.: Isolation of Rickettsia helvetica from ticks in Slovakia. Acta Virol. 2012;56(3):247-52.

Mediannikov O, Subramanian G, Sekeyova Z, Bell-Sakyi L, Raoult D.: Isolation of Arsenophonus nasoniae from Ixodes ricinus ticks in Slovakia. Ticks Tick Borne Dis. 2012 Dec;3(5-6):367-70.

Subramanian G, Sekeyova Z, Raoult D, Mediannikov O.: Multiple tick-associated bacteria in Ixodes ricinus from Slovakia. Ticks Tick Borne Dis. 2012 Dec;3(5-6):406-10.

(10) PB1-F2 antibodies confering protection effect against lethal influenza virus infection

PB1-F2 is a small influenza A virus (IAV) protein encoded by an alternative reading frame of the PB1gene. Despite PB1-F2 is nonstructural protein, during IAV infection, antibodies toPB1- F2 proteins are induced. Detailed immunological maps as well as biological relevance of the anti PB1-F2 antibodies were elusive. To reach such goal, we performed extensive study to found out above-mentioned enigmas. Mostly N-terminal specific antibodies were detected in polyclonal sera raised to complete PB1-F2. Passive and active immunization revealed that antibodies recognizing the N-terminal part of the PB1-F2 molecule have no remarkable effect on the course of IAV infection, whereas antibodies against the C-terminal region of PB1-F2 possess protection potential in mice against virus infection suggesting their potential application in anti-influenza strategies.

Kosik I, Krejnusova I, Práznovská M, Russ G. The multifaceted effect of PB1-specific antibodies on influenza A virus infection. In Virology, 2013, vol. 447, no. 1-2, p. 1-8.

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

The Institute of Virology SAS is an official partner of the Central Controlling and Testing Institute in Agriculture (ÚKSÚP) of the Slovak Republic with the expertise in virus infections of plants; and a member of the Global Outbreak Alert and Response Network, which works under the auspices of the World Health Organization.

2012
Contribution to the expert report for EU authorities
STEFANOFF, P. - PARDA, N. - POLKOWSKA, A. - D'ANCONA, F. - ANDA, P. - RIZZOLI, A. - ESCUDERO, R. - **KOCIANOVÁ, Elena** - DONOSO-MANTKE, O. - KAZIMÍROVÁ, M. - FERENCZI, E. - SERRANO, L.P.S. - ZAJKOWSKA, J. - RANDOLPH, S.. *Epidemiological situation of tick-borne encephalitis in the European Union and European Free Trade Association countries* = ECDC Technical Report. Herve Zeller, Wim Van Bortel (eds). Stockholm : European Centre for Disease Prevention and Control (ECDC), 2012. 54 p. ISBN 978-92-9193-384-6.

2013
Expert report for the Ministry of agriculture and regional development of the Slovak Republic
Title: Detection of virus pathogens.
Author: Miroslav Glasa, PhD.
Description: Detection of virus pathogens in cherries' pollen imported from the USA using molecular methods (RT PCR) and expert opinion on risk evaluation.

Expert reports for the Slovak National Accreditation Service (SNAS)
Title: Accreditation, reaccreditation and supervision in medical laboratories in the Slovak Republic
Author: Marcela Kúdelová, DSc.
Description: Evaluation and expert assessment of the performance of accredited diagnostic methods (10-times)

Expert reports for the Slovak National Accreditation Service (SNAS)
Title: Expert assessment of the Laboratory "State expert center" of the Ministry of Health in Kiev, Ukraine.
Author: Zuzana Sekeyová, PhD.
Description: On-site evaluation of the laboratory.

2014
Expert reports for the Slovak National Accreditation Service (SNAS)
Title: Accreditation, reaccreditation and supervision in medical laboratories in the Slovak Republic
Author: Marcela Kúdelová, DSc.
Description:
Expert assessment of the performance of accredited tests at reaccreditation of medical laboratories (5-times);
Expert assessment of the performance of accredited tests at supervision of medical laboratories (4-times);
Expert assessment of the performance of accredited tests at supervision of probationary laboratoriy (1);

2015
Expert activities and reports of a member of the National Reference Center for the surveillance and laboratory diagnostics of Rickettsiae at the Regional Office of Public Health in Banská Bystrica
Author: Zuzana Sekeyová, PhD.
Description: Surveillance of rickettsial infection in human population of the Slovak Republic

Expert activities and reports in virology and microbiology for the Slovak National Accreditation Service (SNAS)
Author: Zuzana Sekeyová, PhD.
Description: SNAS expert in virology and microbiology, involved in the implementation of the Slovak National Program of Good Laboratory Practice.

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

New cultivation substrates for the preparation of antivirus vaccines.
Grant number: CD-2009-36912/39534-1:11
Industrial partner: IMUNA PHARM, a.s.
Duration: 12/2009 – 10/2012
Funding: 49.000,00 €
Principal investigator: Tatiana Betáková, DSc.

Industrial Research in Clinical Diagnostics of Infectious Pathogens
Grant number: ITMS 26240220032
Industrial partner: BioScience Slovakia, s.r.o
Duration: 06/2010 - 05/2013
Funding: EU Structural funds: 319.446,00 €
Principal investigator: Juraj Kopáček, MVD., DSc.

Center for Innovative Research of Antitumor and Antiviral Strategies
Grant number: ITMS 26240220062,
Industrial partner: BioScience Slovakia, s.r.o
Duration: 05/2011-04/2014
Funding: EU Structural funds: 1.180.000,00 €
Principal investigator: Juraj Kopáček, MVD., DSc.

Research program of miR-155 oncogene for the purposes of diagnosis and prognosis of cancer diseases
Grant number: ITMS 26240220074
Industrial partner: KRD Molecular Technologies, s.r.o
Duration: 05/2012 - 10/2014
Funding: EU Structural funds: 400.301,00 €
Principal investigator: Adriana Gibadulinová, PhD.

Testing of an antiviral potential of new drugs targeted against influenza viruses on the mouse model of influenza.
Contract No: 268/0300/09
Industrial partner: EF-Bio, s.r.o.
Duration: 01/2009 – 12/2015
Funding: 40.000,00 €
Principal investigator: Eva Varečková, DSc.

Genetic characterization of the vaccination strains of Mumps and Measles viruses.
Contract No: 45/15
Industrial partner: IMUNA PHARM, a.s.
Duration: 01/2015-12/2015
Funding: 39.600,00 €
Principal investigator: Vladimír Zelník, PhD.

Cultivation of Measles and Mumps viruses on chicken embryo fibroblasts.
Contract No: 46/15
Industrial partner: Bohemia Pharmaceuticals s.r.o.

Duration: 01/2015-12/2015
Funding: 39.000,00 €
Principal investigator: Vladimír Zelník, PhD.

***In vivo* testing of antiviral properties of eye drops on rabbit HSV-1 model.**
Contract No: 24/14
Industrial partner: Unimed Pharma s.r.o.
Duration: 2014.
Funding: 5.501,00 €
Principal investigator: Ingeborg Režuchová, PhD.

Definition of antiviral properties of newly synthesized compounds with specific effect against influenza viruses.
Contract No: 5/15
Industrial partner: Synkola s.r.o.
Duration: 01/2015-12/2015
Funding: 4.800,00 €
Principal investigator: Eva Varečková, DSc.

Testing of antiviral properties of potassium and sodium iodide using the cell culture model of HSV-1 infection.
Contract No: 439/0300/2013
Industrial partner: Unimed Pharma s.r.o.
Duration: 2014 – 2015
Funding: 2.898,00 €
Principal investigator: Ingeborg Režuchová, PhD.

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

None in the evaluation period.

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

None in the evaluation period.

2.6.6. Summary of relevant activities, max. 300 words

In summary, the IVSAS activities with the social impact are principally focused on:

- The research and development of diagnostic reagents and methods suitable for detection of viral, rickettsial, chlamydial and other microbial infections in humans, animals and plants with potential health, social and economic benefits.
- R&D of reagents and methods for diagnosis and/or prognosis of cancer and prediction of therapy outcome.
- R&D of vaccines, their components, substrates for cultivation, genetic and biologic characterization.
- Preclinical evaluation of potential drugs and bioactive compounds for their antiviral or antimicrobial properties.
- Expert reviews, evaluations and surveillance activities for the public offices, institutes or bodies for health or agriculture.

Moreover, IVSAS researchers are members of boards and/or commissions of grant agencies and commissions of the Slovak Academy of Sciences, which make decisions on funding of national research projects, on qualification degrees etc.:

- Prof. Silvia Pastoreková, DSc., chairman of the Board for medical sciences of the APVV Slovak Research and Development Agency
- Tatiana Betáková, DSc., Juraj Kopáček, DSc., Prof. Jela Mistríková, DSc., Ľudovít Škultéty, DSc., Zdeno Šubr, PhD., members of the Evaluation commissions of the VEGA grant agency
- Juraj Kopáček, DSc., Ján Košovský, PhD., Prof. Silvia Pstoreková, DSc., Miroslav Glasa, PhD, Ľudovít Škultéty, DSc., members of SAS commissions for Schwarz PHD fund, environment, research qaulifications, foreign affairs, and infrastructure.

In addition, Prof. Jaromir Pastorek, DSc., was the President of the Slovak Academy of Sciences (till December 2014) and from January 2015 serves as the Plenipotentiary of the Government of the Slovak Republic for research and innovations.

2.7. Popularisation of Science (outreach activities)

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

Active participation at the European Researcher´s Nights
The European Researchers' Nights are the events dedicated to science popularization and fun learning. They represent a unique opportunity for public to meet researchers, talk to them, and find out what they *really* do for society, in interactive and engaging ways. This can be through hands-on experiments, science shows, learning activities for children, guided visits of research labs, science quizzes, games, competitions with researchers and more. The European Researchers' Night takes place every year all over Europe and neighbouring countries the last Friday of September and the researchers of the Institute of Virology regularly participate at these events to present and explain interesting topics of their research to lay public. These presentations are always met with enournous interest especially of children and young people who join diverse connected activities, such as virus drawing, virtual excursion from molecules through viruses to humans etc.
Participating IVSAS researchers: Ivan Košík (2012, 2013,2014), Sivia Pastoreková (2012), Martina Takáčová (2012), Martina Labudová (2012), Jaroslav Hollý (2013), Margaréta Práznovská (2013), Zuzana Staneková (2013), Eva Varečková (2013), Iveta Štibrániová- (2014), Eva Špitalská (2014)

Active participation at the Week of Science and Technology in the Slovak Republic, organized by the Ministry of Education, Science, Research, and Sports of the Slovak Republic in 2013 in order to increase awareness of the public about Slovak science and technology and their practical realizations and to attract the interest of young people in R&D.
Expositions and active presentations were accomplished by the young researchers of the influenza virus team: Ivan Košík, Jaroslav Hollý, Lucia Kotlárová, Margaréta Práznovská and were positively evaluated by visitors.

Documentary film of the series "Spectrum of Science" on research of viruses, their vectors and hosts entitled "Live againt live" with casting and commentaries of Boris Klempa, Sabina Havlíková, and Martina Ličková, performed at the Slovak Radio and TV on October 2012.

Radio interviews in the series "Night pyramid" broadcasted by the Slovak Radio and TV for public with representatives of various professions, by Ivan Košik, in 2012 and 2013.

Series of interviews, articles and reports for TV, radio and newspapers on actual topics, mainly related to threatening epidemics of virus infections, including
Ebola epidemics: Tatiana Betáková for Plus 7 dní, Pravda newspapers (2014), Fedor Čiampor for Slovak Radio and TV, TA3 television, SRO1 radio, TASR press agency, SME and UJSZÓ newspapers (2014), Ivan Košík for Markíza and JOJ TVs (2014), Boris Klempa for Slovak radio (2014);
MERS epidemics: Boris Klempa, interviews on coronavirus causing MERS for PRAVDA newspaper (2015), Fedor Čiampor, Threat of MERS infection, interview for the Slovak radio (2014);

Influenza epidemics: Ivan Košík, Revival of The Spanish influenza, presentation for students and public (2012), Fedor Čiampor, Influenza - Past and Present, articles in journals "Space", vol. 91(2012), interview on Influenza virus H7N9 for TA3 TV (2013), Influenza is serious, article for SME newspaper (2013)

Many additional activities are described in the annual reports of the Institute of Virology SAS and summarized in the Table below.

2.7.2. Table of outreach activities according to institute annual reports

Outreach activities	2012	2013	2014	2015	total
Articles in press media/internet popularising results of science, in particular those achieved by the Institute	7	11	15	3	36
Appearances in telecommunication media popularising results of science, in particular those achieved by the Institute	9	14	20	4	47
Public popularisation lectures	4	14	19	4	41

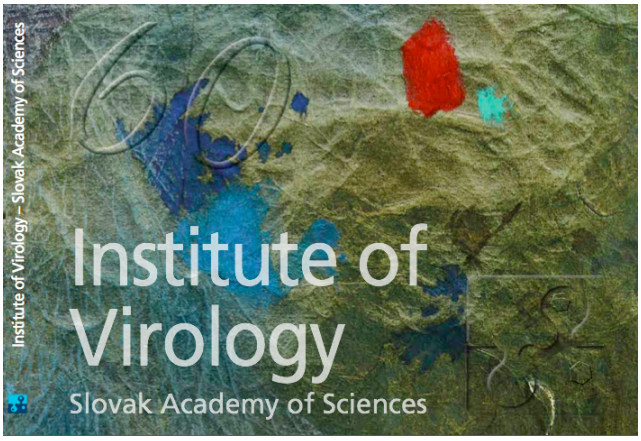
- **Supplementary information and/or comments on popularisation activities, max. 300 words**

In summary, popularisation activities of the Institute of Virology were concentrated on three main areas:

Informations about the scientific activities and results of investigation achieved by the Institute – films for STV 2 (Slovak Television Channel 2) for the Spectrum of Science in Slovakia, interviews for press media and telecommunication media and articles for press media.

Comments, reactions, recommendations and advices in the actual emerging situations in viral infections - bird influenza, SARS, swine influenza, pandemic influenza, hantaviruses, tick born encephalitis, boreliosis etc. – for press media, and news in telecommunication media.

Public popularisation lectures and articles – for citizens of Slovakia (e.g. vaccination against influenza), lectures for the students of High Schools, lectures and articles for physicians and pharmaceutical community. All of them were positively accepted and contributed to increased public awareness on and credibility of the IVSAS research.



In order to disseminate and popularize the activities of the Institute of Virology among the collaborators and guests of the Institute, we assembled and edited a richesly illustrated booklet on the IVSAS history and ongoing research. The booklet was printed at the occasion of the 60th anniversary of the IVSAS establishment, but we plan its re-edition in the updated form possibly as a part of a larger information bulleting of the Biomedical Research Center SAS.

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

The organization, management structure and the internal operational rules are specified in the Organization manual of the IVSAS. In brief, the research activities are performed in seven departments (as described on pages 6-14 of this document). Economic department, Department of law and organization, and Technical department are responsible for the administrative activities. Additional units, such as Animal facility and Washing/Cleaning unit accomplish the research-supporting activities. The IVSAS also possesses specialized laboratories for Proteomics and Biomaging, run by the experts in the fields.

Managing board of the IVSAS bears responsibility for operative, staff and strategic decisions. Its personal composition in the period of 2012-2015 was as follows:
Basic body:
Director: Juraj Kopáček, MVD, DSc.
Vice-director: Ľudovít Škultéty, DSc.
Scienific secretary: Tatiana Betáková, DSc.
Head of the Scientific board: Miroslav Glasa, PhD.
Head of the Economic department: Hana Krasoňová, Bc.
Head of the Department of law and organization: Iveta Šárniková, JUDr.
Head of the Technical unit: Kornel Dobročka
Extended body:
Head of the Department of Plant Virology: Miroslav Glasa, PhD.
Head of the Department of Rickettsiology: Ľudovít Škultéty, DSc.
Head of the Department of Virus Ecology: Boris Klempa, DSc.
Head of the Department of Molecular Medicine: Prof. Silvia Pastoreková, DSc.
Head of the Department of Molecular Pathogenesis of Viruses: Marcela Kúdelová, DSc.
Head of the Department of Orthomyxovirus Research: Eva Varečková, DSc.
Head of the Department of Biotechnology: Vladimír Zelník, DSc.

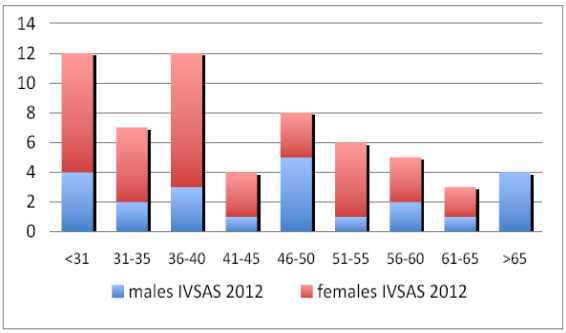
Scientific board is an academic staff-elected body responsible for the supervision and strategic planning of the research activities of the IVSAS, selection of PhD topics and students, organization of academic events, preparation of research reports etc. Its personal composition in the period of 2012-2015 was as follows:
Internal members:
Miroslav Glasa, PhD, Chairman
Marcela Kúdelová, DSc., Vice-chairman
Eva Špitalská, PhD., Secretary
Tatiana Betáková, DSc.
Boris Klempa, DSc.
Ľudovít Škultéty, DSc.
Eliška Švastová, PhD.
Zuzana Sekeyová, PhD.
Prof. Silvia Pastoreková, DSc.
External members:
Assoc. prof. Helena Bujdáková, PhD., Faculty of Natural Sciences, Comenius University
Prof. Oľga Križanová, DSc., Institute of Molecular Physiology and Genetics, SAS
Ladislav Roller, PhD., Institute of Zoology, SAS
Ján Sedlák, DSc., Cancer Research Institute, SAS

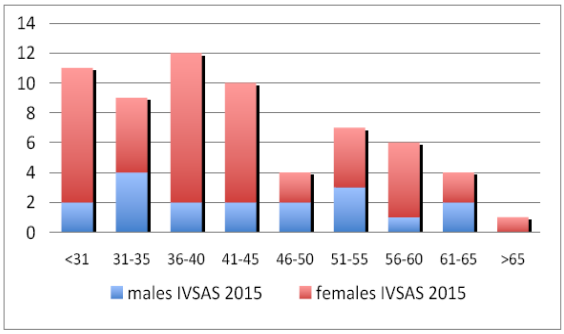
Principles of the management of the academic and administrative activities at IVSAS include an open communication, transparent decisions, a friendly atmosphere, an academic freedom linked with a strong responsibility towards the Institute, support of pro-active efforts to project proposing, developing perspective topics, application activities, educational activities (including lecturing and supervisions of both pre- and post-graduate students) and all other undertakings leading to progress of the Institute and benefit of the entire society.

The main emphasis oh the Management borad is on ensuring the best possible infrastructure and working conditions for the researchers of the Institute as a prerequisite for excellent research results and for their personal carrier development connected with an overall success of the Institute. The Management and Scientific boards support study and working stays abroad that allow for acquisition of new skills and experiences, useful for further development of the home research. They also support qualification upgrade and all avalilabe types of rewards for the extra research activities and outstading performances. These principles will be maintained and further developed also in the future, within the new Biomedical research center SAS.

Human resources

The IVSAS research staff consists of a relatively well-preserved continuum of generations of scientists, including the experienced, still active senior scientists and a solid middle generation of project leaders, who have a strong drive for further development, advance and innovation of the recent research topics. This middle generation has got potential successors in a large pool of young scientists, who are expected to overtake the lead in the future.





The graphs on the left side show the gender and age structure of the research staff of the IVSAS at the beginning and at the end of the evalution period. It is clearly visible that the IVSAS has got more female researchers and a strong young generation, which continuously replaces the oldest senior researchers. This is facilitated by the temporally limited working contracts of research personnel, which create both pressure and motivation for better performance.

This structure of the human resources resulted from a long-lasting staff-building policy of the Institute, which is done with an intention to support the expansion of the most successful teams engaged in the international project and motivate the most active PIs to submit new projects, build collaborations with the relevant partners at home and abroad, increase their qualification and transfer the skills and knowledge to younger colleagues.

Implementation of recommendations from the previous assessment

See the explanation below on pages 71-72.

2.8.1. Summary table of personnel

Personnel	2012	2013	2014	2015
All personnel	114.0	119.0	114.0	125.0
Research employees from Tab. Research staff	73.0	79.0	76.0	85.0
FTE from Tab. Research staff	50.770	50.810	53.350	56.170
Average age of research employees with university degree	43.6	44.2	43.2	42.2

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.						2	1	2	1
II.a / Assoc. prof.		1	3	6	2		3		
Other researchers PhD./CSc.	7	3	7	4	3				
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.					1	1	1	2	1
II.a / Assoc. prof.	2		1	2	1	3		2	
Other researchers PhD./CSc.	2	2	3						
doc. / Assoc. prof.						1			

2.8.2. Postdoctoral and mobility scheme

2.8.2.1. Postdoctoral positions supported by national and international resources

Filippo Iuliano, PhD., Department of Molecular Medicine, EU FP7 project METOXIA

2.8.2.2. Postdoctoral positions supported by external funding

Ivan Košík, NIH Bethesda, USA (from 01/2015)
Martin Benej, the State University of Ohio, USA (from 09/2015)

2.8.2.3. SAS stipends and SASPRO stipends

Tereza Golias, PhD., Department of Molecular Medicine, SASPRO
Ivana Nemčovičová, PhD., Department of Molecular Pathogenesis of Viruses, SASPRO

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

Monika Baráthová, PhD., 05/2008 – 04/2012
Martina Labudová, PhD., 05/2010 – 04/2014
Zuzana Staneková, PhD., 05/2013 – 04/2017
Ivan Košík, PhD., 05/2014 – 04/2018
Lukáš Predajňa, PhD., 05/2015 – 04/2019

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

During the last decade, the Intitute has gradually made significant investments into the equipment infrastructure. This was initially facilitated by the State Program of Research and Development: Biotechnological center of the Slovak Republic (BITCET), aimed at building modern infrastructure and distribution of advanced biotechnological equipment among the R&D institutions of the Slovak Republic. The investments into the equipment infrastructructure of the IVSAS then further continued through several Structural Funds Projects (see page 54). The primary emphasis was given on development of bioimaging techniques, proteomic approaches and animal experimentations.

Bioimaging unit

The main equipment of the Bioimaging unit at the IVSAS consists of a single-photon confocal laser-scanning microscope, a universal fluorescence workstation with camera, and a cell observer for the time-lapsed microscopy with incubation chambers allowing for control of gasses (oxygen and carbon dioxide) in the athmosphere. In addition, the unit involves the lab for processing cell samples and tissue specimens, including automated systems for tissue embedding, sectioning and immunohistochemical staining. This constellation has been recently supplemented with a modern *in vivo* IVIS chamber for CT analysis and optical imaging of small animals. This complex bioimaging equipment allows for a broad scale of analyses of biological processes and their molecular components from the subcellular level to the entire organism including investigation of in vivo infections and/or growth of xenografted tumors as well as detection of metastatic spread of cancer cells.

Proteomic and Mass Spectrometry Unit

The facility provides accurate molecular mass determination of biomolecules, identification of proteins, sequence characterization of peptides, separation and purification of proteins and peptides by liquid chromatography, gel electrophoresis, robotic excision of gel spots or bands, analysis of post-translational modifications, bioinformatic interpretation of proteomic datasets.

The unit contains up-to-date equipment for the protein purification and analysis (such as HPLC devices), isolelectric focusing and 2D electrophoretic unit (including DIGE), mass spectrometers (ESI-Q-TOF, MALDI, ESI-Q-TRAP), imaging systems and data analysis sotwares.

Animal facility

The Institute has built a state-of-the-art animal facility including the Bioafety Level 3 unit with the sterile barrier area, which is suitable for manipulating highly pathogenic infections (e.g, with hantavirues or influenza A viruses, left). Small experimental animals are housed in ventilated racks with integration of individually ventilated caging units in the central ventilation system (right). The primary responsibility of the facility is the housing of laboratory animal during the experiments, keeping the strict compliance to national and EU recommendations regarding the use and care of animals in research. This BSL3 unit also represents a core facility housing a part of the European Virus Archive built in the frame of EVA / EVAg projects. The institute uses a high-level Operational Concept and the Health Management of the Laboratory Animals, which have been approved by the State Veterinary and Food Administration of the Slovak Republic (SVFA Approval number SK P 400011)

Biotechnological laboratories with GMP certificate

The laboratories localized in Šarišské MIchaľany (see page 16) contain clean spaces containing modern equipment for cultivation of eukaryotic cells and bacteria, for protein separation, purification and analysis and for other biotechnological procedures needed for the development, preparation and final production of the therapeutic and diagnostic products, bioactive molecules, and vaccines.

Other facilities

Overall, the IVSAS has a 3000 m^2 area of state-of-the-art lab facilities (Biosafety levels 1 and 2), including laboratories for **cell culture** (equipped with laminairs, hypoxia workstations, CO_2 incubators and plaforms for real-time measurement of cell growth and pericellular environment), **molecular biology and biochemistry** (with microarray spotter and reader, PCR and gradient PCR machines, fluorimeters, ELISA readers, bacteria incubators, DNA and protein electrophoreses and blotters), well as low temperature storage rooms, deep-freezer spaces etc.

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

According to the previous assessment, the IVSAS was accredited in category A, with evaluation of 92.88%.

Conclusions from the previous assessment of the IVSAS include the following statements:

"The research being performed at the institute is of high quality. Although the number of publications did not change substantially, when compared to the previous evaluation period, the ranking of the journal has grown from average IF 3:0 to 3.5. The Opirion of the Evaluation Panel is that the publication potential of the Institute has not been fully used."

To improve the publication input, we introduced new rules of internal evaluation of the researchers, which included the requirements for the minimum number of papers per person published during a certain time period. However, this did not lead to further increase in the number of publications suggesting that the publication potential of the IVSAS has been almost fully used. We believe that this is due to the fact that our researchers were engaged in a significant number of large international consortia and robust national projects with research agenda that required extensive time and energy. Much effort was also invested into writing of proposals for numerous projects, which were submitted to EU FP calls and also to domestic grant agencies and which unfortunately did not succeed. We are of course aware that the future of the Institute relies both on scientific renome, which is built on quality of reseach outputs, and on projects' funding, which is needed to cover reseach expenses, so we aim at making balance between these two activities.

"The number of citations has a raising trend (from 600 to over 900/year) with contribution from all departments".

As shown above on pages 30-31, we noticed further increase in the number of citation per annum to about 1400 in 2015, indicating that our work is well accepted and recognized by the international research community.

"The national and international standing of the Institute is strong. The Institute has established a large number of collaboratve exchanges inside as well as outside of the country…."

We continued to employ this strategy of building and maintaining the collaborations also during the period of 2012-2015.

"The structure of the Institute forms a sizeable research entity with diverse focus on plant, animal and human virology, proteomics and microbiology to cancer research. The Institute was also able to attract high level of external funding resources".

The range of research focus and attraction of funding remained the main strategic goals also during the past four years.

"The overall pedagogical activity and PhD education are excellent. The average age of program sponsors is favorable for the stability of the programs."

We continued these activities.

"The Panel recognizes the potential of the institution to expand the socio-economic outputs, including 6 patents. The Institute has established close collaboration with clinical departments and ongoing partnerships with industry."

Applications and translation of knowledge to clinical practice remained in the core of our professional interests.

"The Panel appreciates the various forms of popularization of research activities of the Institute".

We understand the social impact of the popularization activities, which are becoming even more important with newly emerging virus infections that threaten the human population and therefore, we have been always ready to react to the actual epidemiological situation and comment/explain it to lay public.

"The panel acknowledges the rich infrastructure of the Institute and the successful recovery after the fire in 2010. The personnel and the management maintain a good spirited atmosphere in the Institute. The Panel recognizes thet the Institute has the largest number of researchers, when compared to other medical institutes of SAS. Therefore, the Panel thinks that the Institute has the responsibility to raise more nationally and internationally recognized leaders in science."

The number of internationaly recognized leaders at the Institute has expanded as demonstrated by the spectrum of invited speakers at international conferences and by the list of the most cited researchers, which has shifted to younger generation and includes now new names compared to the previous assessment period. In addition, three representatives of the middle generation (from 40-50 years), including Boris Klempa, Ľudovít Škultéty and Tatiana Betáková have received a Doctor of Science grade, which is the highest scientific grade in the Slovak Republic awarded to outstanding research personalities.

Overall evaluation:

"The main strengths of this institute are: very good infrastructure, stimulating atmosphere, good level of translational research, cooperation inside the institute, very good in raising external funds, strong participation of investigators. The Institute has a very good potential for further improvement of its research output."

We agree that the improvement of the research output is still necessary and are doing continuous efforts towards this aim. Our strategy for improvement includes closer cooperation with the partner institutes that we joined in the newly established Biomedical Research Center SAS, particularly through combining expertise, models / reagents and topics.

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

No further comments.

3. Research strategy and future development of the institute for the next five years (2016-2020)

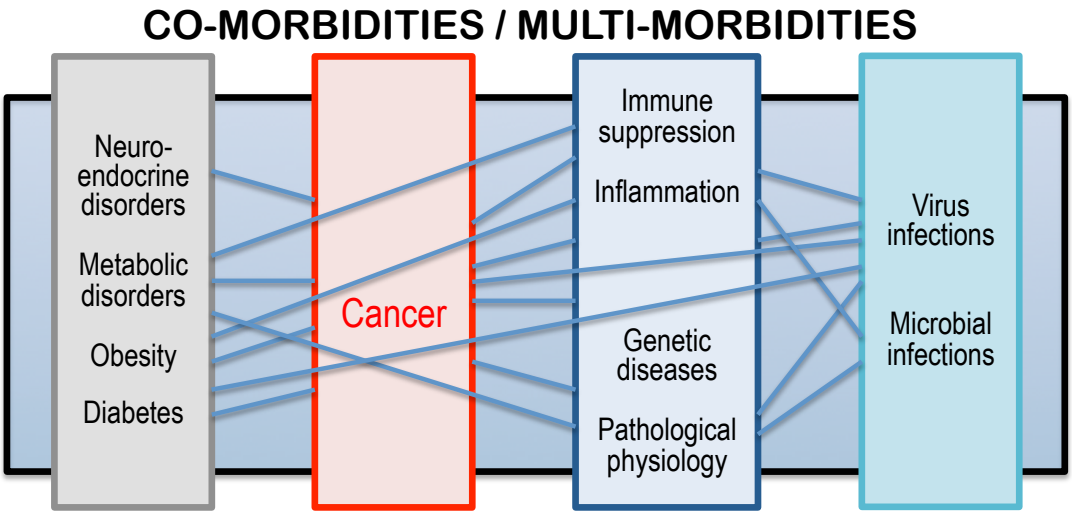
From January 1st, 2016, the Institute of Virology has become an integral part of the Biomedical Research Centre of the Slovak Academy of Sciences (BMC SAS), together with three other SAS institutes, namely the Cancer Research Institute, the Institute of Experimental Endocrinology and the former Centre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

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

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

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

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



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

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

VIRAL and MICROBIAL INFECTIONS
Institute of Virology

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

Worldwide awareness of this threatening situation is associated with intensive developments of approaches and methods for rapid detection of infectious agents, new therapeutic strategies based on inhibition of molecular pathways important for multiplication of viruses and bacteria, production of recombinant vaccines and anti-viral compounds. Simultaneously, molecular changes in the cells and organisms, which host or transmit infection, are investigated with the purpose to understand genetic, epigenetic and physiological processes contributing to spread of infection and/or manifestation of pathologies.

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

The research staff of the Institute of Virology BMC SAS includes several internationally recognized researchers that built their reputation through excellent research achievements, such as discoveries of new hantaviruses, elucidation of the genetic diversity of economically

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

CANCER

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

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

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

Similar shift in paradigm can be observed also in translational and clinical cancer research, where much emphasis is now given to patient-centric approach based on trials examining biology, developing biomarkers, and bringing together a range of health and scientific disciplines to work with patients. This is underlined by the recent success of new immunotherapy targeting immune checkpoint molecules co-opted by cancer cells to escape immune responses. Technological advances including new devices for multi-parametric analyses allow now for massive and detailed genomic, proteomic and immunologic profiling of tumor tissues, liquid biopsies, and tumor-bearing patients, uncovering common molecular and physiological drivers of different types of cancer. Deeper knowledge of tumor biology has recently promoted “basket clinical studies” that address different tumor types documented to be driven by the same molecular alterations. This strategy in turn further highlights the critical role of academic groups in acquisition of new knowledge on molecular mechanisms of oncogenesis and cancer progression and in development of pre-clinical models indicating which drug will be effective for which cancer type.

In line with these advances in the field of oncology, cancer researchers of the BMC SAS investigate key aspects of cancer biology and use up-to-date research approaches, including molecular and cellular mechanisms of tumor-stroma crosstalk (CRI), mechanisms of chemoresistance (CRI), DNA damage responses, genetic and epigenetic traits of cancer development and progression (CRI), advanced multiparametric immunophenotyping of leukemia patients (CRI), hypoxia and acidosis as critical physiologic factors of tumor microenvironment affecting tumor biology, metastatic propensity and response to therapy (IV), ion transport and signaling in cancer cells (ICTR), neuroendocrine mechanisms of cancer (IEE), effects of obesity and metabolism on tumor phenotype and progression (IEE), etc. as described in the questionnaires of the BMC institutes. Many of our achievements are at the forefront of the current cancer research and are well recognized by the international community. Some of them are being translated to clinical applications in the form of new biomarkers, detection assays for

diagnostic, prognostic and predictive purposes (including the non-invasive formats) and of promising new therapeutic strategies. This international dimension of the cancer research at BMC SAS is documented by a number of EU and other international projects, patents, invited talks at the international meetings, collaborations with universities and clinics, and highly cited publications.

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

STRESS, NEUROENDOCRINE DISORDERS, AND DEPRESSION

Institute of Experimental Endocrinology

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

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

Researchers at the IEE BMC SAS investigate stress responses at the molecular and cellular levels as well as at the level of the entire organism using current state-of-art approaches. Studies of catecholamines at IEE are known worldwide similarly as the research focusing on psychopharmacology. The IEE regularly organizes international meetings of the world-leading endocrinologists and its scientists contributed to this area by a number of highly cited papers, some of which can be considered seminal for the development of this field.

METABOLIC DISORDERS, OBESITY AND DIABETES

Institute of Experimental Endocrinology and Institute of Clinical and Translational Research

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

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

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

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

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

GENETIC AND INFLAMMATORY DISEASES

Institute of Clinical and Translational Research and Institute of Experimental Endocrinology

The rapid advance of genomic technologies have led to improved understanding of the genetic bases of diseases. Recent approaches encounter shift from targeted analyses of specific genes based on particular symptoms or family histories to sequencing of an entire genome or exome. Targeted approaches characteristically have a high yield for penetrant monogenic conditions; whole genome approaches have the potential to unravel a much larger proportion of genetic disease burden. Both directions can provide predictions about diagnoses, or susceptibilities to conditions with important implications for the affected person as well as for her/his relatives.

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

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

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

CO-MORBIDITIES / MULTI-MORBIDITIES

One of the main advantages of the BMC SAS resides in the strong human infrastructure creating the critical mass of internationally recognized experts in research of diverse human diseases. These experts can now join forces in order to take a complex approach to understanding of human diseases with their co-morbidities. Up til now, both basic and clinical research has focused predominantly on single disease and episode, often with a focus on mortality as the main endpoint. Nowadays, the concept of co-morbidities (or multi-morbidities) is gaining more and more importance with increasing awareness that healthcare needs to address the management of persons with multiple coexisting diseases, who are now the norm rather then exception. The costs of management of multi-morbid patients are growing exponentially as the number of chronic conditions increases. Moreover, standard treatment protocols used for

individual diagnoses may not work due to co-existing pathologies. Co-morbidity can impact on a range of outcomes, including mortality and health-related quality of life. Etiological relationships between diseases may involve direct causation, associated risk factors, heterogeneity and independence. Co-occurrence of certain pathologies seems obvious, such as obesity linked with diabetes, cardiovascular problems, hormonal imbalance, cancer (particularly hormone-dependent tumors), and depression. However, current research helped to uncover the obesity connection to inflammation and increased sensitivity to infections (such as influenza virus). On the other hand, adenovirus 36 was recently identified as one of the factors contributing to the obesity. From the clinical point of view, the treatment of obese patient with cancer would surely lead to different outcome as the same treatment of the lean person and this may be true for other pathologies. Moreover, co-morbidity may include the situation in which treatment for the one disease causes another condition, such as immunosuppressive chemotherapy may increase the permissiveness of cancer patient to virus infections. And vice versa, virus or microbial infections can cause inflammation, which may support cancer progression.

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

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

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

The first strategic step was made in the course of 2015, when four biomedical institutes of the Slovak Academy of Sciences, namely

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

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

The first period of the BMC SAS was characterized by complex legal and administrative arrangements of the new institution (according to the law of the Slovak Republic, these could be accomplished only after the legal entity was officially established). This included all documents related to identification, accounting and financial operations, registration for VAT, social/health

insurances, public prosecutions, status of research institution, transfer of projects, approvals of biosafety, approvals for work with GMO etc. Moreover, three of the institutes (except IV) had to undertake a time- and energy-consuming moving from the old buildings to the new Pavilion of Medical Sciences in the main campus of the SAS. However, that brought the BMC institutes to close proximity, which now facilitates the communication and operation inside the BMC SAS.

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

The **Managing board of the BMC SAS** consists of the representatives of all four founding institutions:
Director: prof. Silvia PASTOREKOVÁ, DSc.
Deputy Director and Scientific Director of the IV BMC: Juraj KOPÁČEK, MVD., DSc.
Scientific Director of the CRI BMC: Lucia KUČEROVÁ, PhD.
Scientific Director of the IEE BMC: Štefan ZÓRAD, PhD.
Scientific Director of the ICTR BMC: Miroslav VLČEK, MD., PhD.
Scientific Secretary: Jozef UKROPEC, PhD.
Scientific Secretary: Miroslav CHOVANEC, PhD.
Head of the Scientific Board: Richard IMRICH, MD., DSc.
Head of the Economic Unit: Hana KRASOŇOVÁ
Head of the Legal and Organizational Unit: Iveta ŠÁRNIKOVÁ, JUDr.
Head of the Project Evidence and Administration Unit: Erika CHUDĚJOVÁ
Head of the Technical Unit: Kornel DOBROČKA

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

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

Compatibility of topics

All institutes of the BMC SAS perform research in biomedical area, and are principally aimed at elucidation of molecular and physiological mechanisms of human diseases, their epidemiology, and possibilities of better prevention, diagnostics and therapy. They investigate the human organism from different points of view in order to bring deeper understanding of metabolic, neuroendocrine, autoimmune disorders, cancer, and infections. These chronic diseases represent major socio-economic burden and health-care expenses also in Slovakia, and

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

Complementarity of infrastructure

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

Concentration of excellent research teams and experts

The merge of the institutes in the BMC SAS brought together several groups that were recently listed among the top research teams of the Slovak Academy of Sciences
according to ARRA, an independent ranking and rating agency, 2011,
(http://www.sav.sk/uploads/Spickove_vedecke_timy_a_osobnosti_SAV.pdf).
These teams continuously and successfully perform excellent research in the following areas:

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

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

Critical mass of projects and capacities

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

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

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

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

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

Coordinated approach to challenges of sustainable development

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

Construction and management of the budget

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

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

Consolidation of personnel

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

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

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

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

Convergence and optimization of supporting units

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

Common interests

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

Nevertheless, these common interests have to be first recognized and adopted by the people creating the community of the BMC SAS, and this can be made possible through building their

collaborations, friendships, and feeling of responsibility for the future development of the BMC SAS. It is now the role of the BMC SAS governance to create conditions for such an empathic environment, particularly via open communications, transparent and helpful decisions, and also via personal positions, opinions, knowledge and activities that are worth to follow.

Conclusion

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

4. Other information relevant for the assessment

This is the supplementary information related to past project submission activities of the Institute of Virology in the assessment period of 2012-2015 demonstrating efforts and networking potential of its researchers as the starting point for the future development within the BMC SAS.

2012

FP7-HEALTH-2013-INNOVATION-1
FP7 Health.2013.2.3.4-1: Neglected infectious diseases of Central and Eastern Europe

1. **Anti-tick Vaccines to Prevent Tick-borne Diseases in Europe (ANTIDotE)**, Coordinator: Joppe WR Hovius, University of Amsterdam, The Netherlands, PI at IVSAS: Boris Klempa, funded project
2. **Neglected tick-borne pathogens along a Central and Eastern European transect (TICK-TRANS),** Coordinator: Rainer G. Ulrich, Fridrich-Loeffler Institute, Grefswald-Insel Riems, Germany, PI at IVSAS: Boris Klempa
3. **Tackling tick-borne encephalitis: from TBE virus epidemiology to innovative point-of-care diagnostics (TackTick),** Coordinator: Gerhard Dobler, Institut für Mikrobiologie der Bundeswehr, Munich, Germany, PI at IVSAS: Boris Klempa
4. **TBEV Biology, Pathogenesis and diagnostics in eastern Europe (TBE BioPath),** Coordinator: Mathias Niedrig, Robert Koch Institute, Berlin, Germany, PI at IVSAS: Boris Klempa
5. **Parasites and tick-borne pathogens of Central and Eastern Europe: a novel toolbox for the surveillance and prevention of neglected infectious diseases (PATH),** Coordinator: Annapaola Rizzoli, Fondazione Edmund Mach, San Michele all'Adige, Italy PI at IVSAS: Boris Klempa
6. **Electronic Encyclopaedia of Virology, application to emerging viruses of economic or health threat to Europe (EEV),** Coordinator: Tamara Gritsun, University of Reading, Reading, UK, PI at IVSAS: Boris Klempa
7. **Uncovering Tick-Borne Bacteria in the human body: new insights to improve direct detection** Coordinator: Dr. Paula García, Applied Research using Omic Sciences, S.L. (AROMICS), Spain, PI at IVSAS: Eva Špitalská
8. The biological activity and pathogenesis of emerging tick-borne pathogens, Coordinator: Dr. Ali Mirazimi, Linkopings Universitet, Sweden, PI at IVSAS: Zuzana Sekeyová

   HEALTH.2013.2.3.0-1: Innovation in vaccines. FP7-HEALTH-2013-INNOVATION-1.
9. Development of a cross-protective vaccination strategy against seasonal and pandemic influenza virus infection (uniFLU) Coordinator: Helmut Schmutz, HSC Development GmbH, Austria, PI at IVSAS: Eva Varečková

   ERA-NET – Translational Cancer Research (TRANSCAN)
10. Biomarkers for anti-angiogenic therapy in colorectal cancer, Coordinator: prof. Stefano Indraccolo, Instituto Oncologico Veneto, Padova, Italy, PI at IVSAS: Silvia Pastoreková
11. Molecular and Sero-epidemiology of Crimean Congo Hemorrhagic fever in Animals, PI at

IVSAS: Zuzana Sekeyová

European Research Council Advanced Grants (ERC)

12. Redefining tumor microenvironment as a crossroad of stress factors, Coordinator: Silvia Pastoreková

2014

1. ***Graphene Flagship Competitive Call 2014***
   Antibody-mediated graphene-based sensing and detection of hypoxic tumor cells, Coordinator at SAS: Jaromír Pastorek, PI at IVSAS: Silvia Pastoreková
2. ***Health, demographic change and wellbeing, PHC-10:***
   Lab-on-chip for fast antibiotic resistance determination and therapy monitoring, Coordinator: Prof. Vellekoop, University of Bremen, PI at IVSAS: Silvia Pastoreková
3. ***H2020-PHC-01-2014***
   Cancer, Obesity and MicroMilieu driven molecular pathways in an Ageing population, Coordinator: prof. Agnes Gorlach, Technical University Munich, PI at IVSAS: Silvia Pastoreková
4. ***H2020-MSCA-ITN-2014-ETN***
   Deciphering the hypoxia pathways in human health and diseases, Coordinator: Edurne Berra, Taéchnological park Bilbao, PI at IVSAS: prof. RNDr. Silvia Pastoreková
5. ***H2020-MSCA-ITN-2014-ETN***
   Rapid Blood Allergy Test, Coordinator: Winnie E. Swendsen, Danish Technical University Nanotech, PI at IVSAS, Silvia Pastoreková

2015

1. ***H2020-PHC-2014-Stage 2*** Health, demographic change and wellbeing: Lab-on-chip for fast antibiotic resistance determination and therapy monitoring, Coordinator: Prof. Vellekoop, University of Bremen, Germany, PI at IVSAS: Silvia Pastoreková
2. ***H2020-PHC-01-2015***
   Cancer, Obesity and MicroMilieu driven molecular pathways in an Ageing population. Coordinator: Prof. Agnes Görlach, Technical University Munich, Germany, PI at IVSAS: Silvia Pastoreková
3. ***H2020-MSCA-ITN-2015***
   Deciphering the hypoxia pathways in human health and diseases. Coordinator: Edurne Berra, Téchnological park Bilbao, Spain, PI at IVSAS: Silvia Pastoreková
4. ***H2020-MSCA-ITN-2015***
   Rapid Blood Allergy Test, Coordinator: prof. Winnie E. Swendsen, Danish Technical University Nanotech, Denmark, PI at IVSAS: Silvia Pastoreková
5. ***H2020, SFS-7-2014/2015***
   European Fruit Resources Diversity Network. Coordinator: JM Audergon, INRA Avignon, France, PI at IVSAS: M. Glasa

ERA-NET – Translational Cancer Research (TRANSCAN-2)

6. European Digital Pathology Image Analysis Initiative Against Breast Cancer Recurrence. Coordinator: prof. Dr. Niels Grabe, National Center for Tumor Diseases, Heidelberg, Gemany, PI at IVSAS: Silvia Pastoreková
7. Tracing the origins of metastasis in primary ovarian cancer: Identification of novel refined biomarker panels and therapeutic targets. Coordinator: Prof. Robert Zeilinger, Medical University of Vienna, Austria, PI at IVSAS: Silvia Pastoreková
8. Tracking spatial and temporal intratumor heterogeneity to better predict breast cancer response to neoadjuvant therapies. Coordinator: prof. Andrea Rocca, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola, Italy, PI at IVSAS: Silvia Pastoreková

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